The Total Synthesis of the Glycosylated Antibiotic Fidaxomicin

and

Methionine-Derived Iminium Lactones

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Prof. Dr. Jörg Schibler
Dekan

Für Jacqueline

und meine Familie

Phantasie ist wichtiger als Wissen, denn Wissen ist begrenzt.

Albert Einstein

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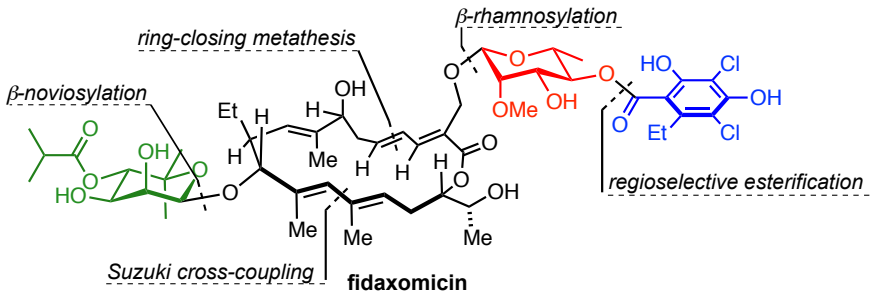
Abstract

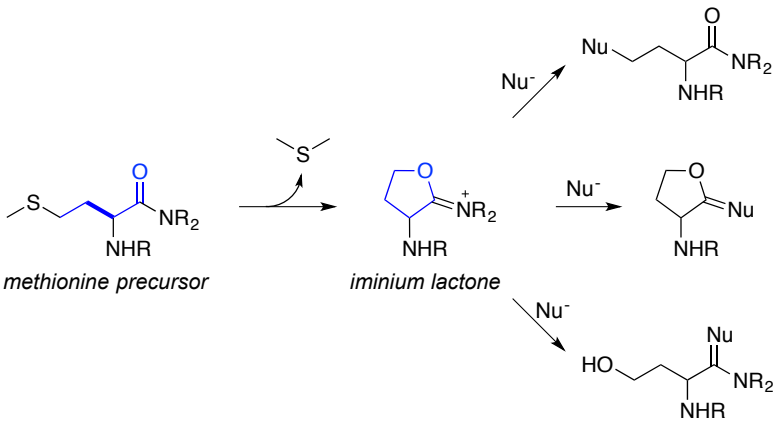
This thesis is divided into two chapters, describing two organic chemistry projects, both born from fundamentally different motivations. The main part of this work was application-driven research, in which a specific “real-world”-problem was approached, targeting a goal with a direct impact on our society. In the contrary, the second chapter describes a curiosity-driven project, based on a simple idea not having a direct application for society that is obvious.

In **Chapter 1** the stereoselective total synthesis of the antibiotic, fidaxomicin, is described. The chapter starts with an introduction about the history and origin of antibiotics, and the increasing threat of multidrug-resistant pathogens. The promising bioactivity of fidaxomicin against many pathogens and the shortcomings of the natural product as therapeutic make the natural product an interesting synthetic target. The goal of this project was the development of a new antibiotic, based on the fidaxomicin lead structure, with improved pharmacological profile. Synthetically, six main fragments were prepared and assembled in the end-game, leading to a highly convergent and flexible route, required for prospective structure-activity relationship studies. The key features of the total synthesis were the first ever β-selective noviosylation, a Suzuki cross-coupling of sterically demanding substrates, a ring-closing metathesis and a challenging, β-selective rhamnosylation. Furthermore, semisynthetic studies were performed, intercepting a late-stage intermediate of the total synthesis. The synthetic route is currently used to produce diverse analogues of fidaxomicin for biological evaluation in our group.



The genesis of the project in **Chapter 2** was created from the idea, to apply methionine derivatives as precursors for 1,3-oxazines, making use of the thioether as triggerable leaving group. In the course of the studies, the focus of the project changed as we discovered a novel methodology for the preparation of isolable iminium lactones from methionine. The synthetic

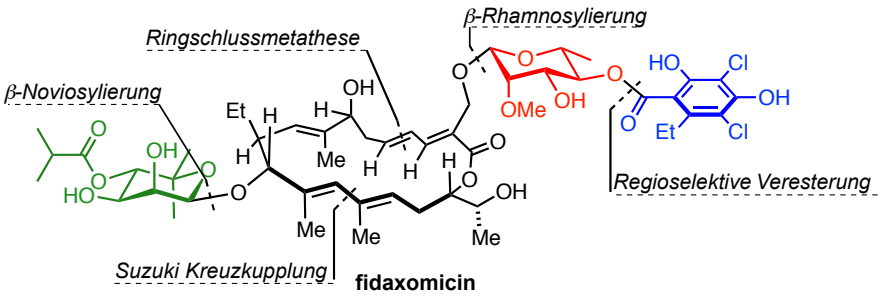
utility of the methionine-derived iminium lactones as electrophiles was explored. Despite the interesting features of the transformation that may find its use in the synthesis of unnatural amino acids and peptidomimetics, the method has a major drawback that the cyclisation leads to racemic products. To make synthetic use of the methionine-derived iminium lactones, future studies will have to address this issue.



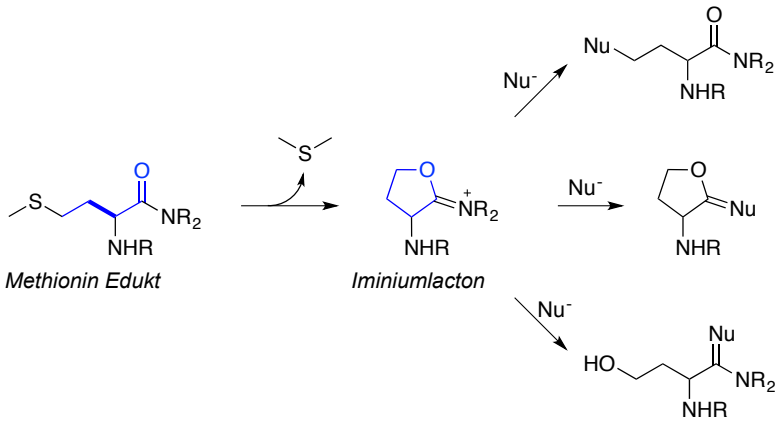
Zusammenfassung

Die hier vorliegende Doktorarbeit ist in zwei Kapitel unterteilt, beide beschreiben ein organisch chemisches Projekt, denen jedoch eine unterschiedliche Motivation zugrunde liegt. Der Hauptteil dieser Arbeit umfasste eine anwendungsorientierte Forschung, in der ein spezifisches Problem aus der "realen Welt" angegangen wurde, mit einer direkten Auswirkung auf unsere Gesellschaft. Im zweiten Kapitel hingegen ist ein Projekt beschrieben, welches von Neugier getrieben war und auf einer einfachen Idee basierte ohne, dass eine direkte Anwendung im Vordergrund gestanden hätte.

In **Kapitel 1** ist die erste, stereoselektive Totalsynthese des Antibiotikums, Fidaxomicin beschrieben. Das Kapitel beginnt mit einer Einleitung über die Geschichte und Herkunft von Antibiotika und die immer grösser werdende Gefahr die von multiresistenten Pathogenen ausgeht. Fidaxomicins vielversprechende biologische Aktivität gegen verschiedene Pathogene, sowie dessen ausbaufähigen Eigenschaften als Therapeutikum, machen den Naturstoff zu einem attraktiven Syntheseobjekt. Das Ziel dieses Projekts war die Entwicklung eines neuen Antibiotikums mit verbessertem pharmakologischen Profil basierend auf der Fidaxomicin Grundstruktur. Unsere Totalsynthese begann mit der Herstellung von sechs Hauptfragmenten die in der Endphase zusammengesetzt wurden, was zu der notwendigen, höchst konvergenten und flexiblen Route für künftige Struktur-Aktivitätsbeziehungs Studien führte. Die Schlüsselelemente der Synthese waren die erste β-selektive Noviosylierung, eine Suzuki Kreuzkupplung sterisch gehinderter Substrate, eine Ringschlussmetathese und die anspruchsvolle β-selektive Rhamnosylierung. Weiter wurden semisynthetische Studien durchgeführt die Zugang zu einem späten Intermediat der Totalsynthese erlaubten. Unsere Route wird momentan für die Herstellung unterschiedlichster Fidaxomicin Analoge verwendet, um sie dann auf ihre biologische Aktivität zu prüfen.



Der Anstoß zum Projekt im **Kapitel 2** war die Idee, Methionin Derivate als Ausgangsmaterial für die Herstellung von 1,3-Oxazinen zu verwenden, dabei sollte der Thioether als aktivierbare Abgangsgruppe dienen. Während unseren Untersuchungen änderte sich der Fokus des Projekts als wir eine neue Methode, um stabile Iminiumlactone aus Methionin herzustellen, entdeckten. In der Folge untersuchten wir den synthetischen Nutzen der Methionin abgeleiteten Iminiumlactone als Elektrophile. Die gefundene Transformation könnte ihre Anwendung in der Synthese unnatürlicher Aminosäuren und Peptidomimetika finden. Allerdings hat die Methode den Nachteil während der Zyklisierung zu razemischen Produkten zu führen. Der Herausforderung, eine enantioselektive Variante zu entwickeln, werden sich künftige Studien stellen müssen.



General Introduction

Generally, there are two fundamental scientific approaches that thrive science; application-driven and curiosity-driven research.[1] The motivation of application-driven science is a defined goal with a concrete utility, having immediate impact for economy and society. Curiosity-driven science (also referred as basic or blue skies research) stands in contrast to applied science, in that it does not have a defined goal with a specific utility. The uncertainty of the output and significance of such projects is expressed in the difficulty to find financial support for basic research. The funding of application-driven projects is comprehensibly easier, as the output is measurable and a return of investment is anticipated. This leads to the pressure to formulate a defined goal, even if a project is purely curiosity-driven at the core.[1a] That aspect is highly controversial. In fact, Prof. Dr. Dieter Seebach's seminars are often covering the conflict between curiosity-driven science and the pressures of the current model of publication and funding, which are followed by extensive discussions among scientists.[2]

During my doctoral studies I was involved in two projects, each covering one of the above-mentioned scientific approaches. In Chapter 1, an application-driven project is described, in which we aimed for a new antibiotic to act against the increasing threat of drug-resistant pathogens. Antibacterial research was neglected by the free market in the last decades and, thus, has become a task for academia. In the second Chapter, a curiosity-driven project was approached. At the outset, a purely chemical question was formulated and the project came without boundaries. Throughout the studies, an interesting observation shifted our attention from the original idea to another, which led to the discovery of a new chemical methodology.

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1 a) B. Linden, *J. Biomed. Discov. Collab.* **2008**, *3*, 3; b) P. Balaram, *Curr. Sci.* **1999**, 76, 5–6.

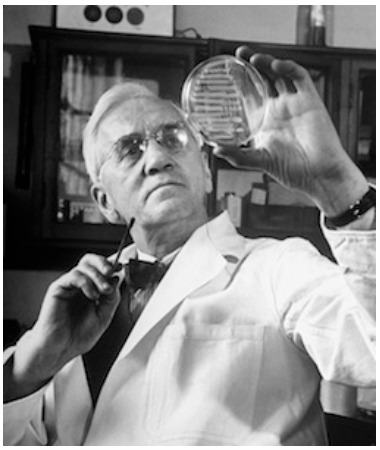
2 http://inspiringchemistry.reaxys.com/conference2014; accessed: 16.01.2015.

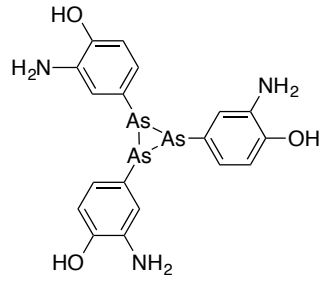
1 Total Synthesis of the Antibiotic Fidaxomicin

1.1 Introduction

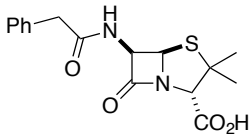
1.1.1 The Antibiotic and the Post-Antibiotic Era

With the discovery of the antibiotics a new era in medicine began.[3] Salvarsan, an arsenic compound, was one of the first modern chemotherapeutic agents against syphilis, but suffered from difficult administration (air-sensitivity) and severe side effects (Figure 1.1). The breakthrough came with the discovery of penicillin (1928, Fleming) and prontosil (1932, Domagk), which had much less side-effects. Suddenly, many live threatening bacterial infections became curable.[4] As a cut with a knife could become a doom due to inflammation, it turned that seemingly all bacterial diseases could be defeated. Not least, owing to the discovery and development of antibiotics, the life expectancy of humankind increased dramatically after World War II.

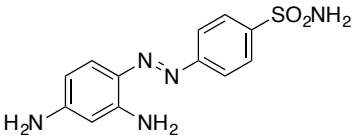




salvarsan (Ehrlich, Berlheim 1909)



penicillin (Fleming, 1940)



prontosil (Domagk, 1932)

Figure 1.1: Left: Alexander Fleming the godfather of penicillin. Right: The first marketed antibiotics.

The huge significance and demand of antibiotics encouraged industrial and academic laboratories to discover new antibiotics. As a consequence, a gold rush in antibiotic development took place in the following years and decades. Drugs like streptomycin (1944), erythromycin (1952), isoniazid (1950`s), tetracycline (1955), vancomycin (1955), metronidazole (1960), doxycycline (1966), rifampicin (1967) and ciprofloxacin (1987) are

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[3] A. Fleming, *Brit. J. Exp. Pathol.* **1929**, *10*, 226.

[4] J. Li, E. J. Corey, *Drug Discovery*, John Wiley & Sons, **2013**.

only a few antibiotics on the WHO model list of essential medicines, which rose from this period.[5]

Bacteria are the oldest, simplest and most successful live form on our planet and owing to their high plasticity, it is not surprising that these microorganisms evolved resistance to our antibiotics. Alexander Fleming predicted already in 1948 that no antibiotic would ever be able to compete with the power of evolution.[6] This phenomenon has been recognized very soon after introduction of antibiotic therapy. The first drug resistant strains emerged from hospitals – e.g. sulphonamide resistant *Streptococcus pyogenes* in the 30's and penicillin resistant *Staphylococcus aureus* in the 40's.[6] It was not until the 50's that the first multiple drug resistant (MDR) bacteria were found, and physicians were faced with a novel, severe problem. Ignoring these alarming signs, antimicrobial resistance was enhanced through expanding misuse of antibiotics in humans, food animals and crop protection. Nowadays, the situation has become a global concern not only in hospitals but also in the society. In the WHO report on antimicrobial resistance in 2014, therapeutics with critical levels of effectiveness were identified.[7] Among the concerned infections are common pathogens like *Mycobacterium tuberculosis* (TB), *Plasmodium falciparum* (malaria), methicillin resistant *staphylococcus aureus*[8] (MRSA) or *Escherichia coli*[9]. The swissnoso[10] estimated that 70`000 drug resistant infections cause about 2000 deaths per year in swiss hospitals.[11] In the US, the FDA stated two million infections of which 99`000 were deadly in 2002.[11] Keiji Fukuda (assistant director general health security, WHO) paints a dark picture, of a future threatened by "a post-antibiotic era – in which common infections and minor injuries can kill".[7]

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5 World Health Organization, *19th WHO Model List of Essential Medicines* **2015**, April.

6 a) M. Barber, M. Rozwadowska-Dowzenko, *The Lancet* **1948**, 641–644. b) S. B. Levy, *The Lancet* **1982**, 83–88. c) S. B. Levy, B. Marshall, *Nat. Med.* **2004**, *10*, 122–129.

7 World Health Organization, *Antimicrobial Resistance: Global Report on Surveillance* **2014**.

8 MRSA is a main issue in surgery as *staphylococcus aureus* is the most common cause of postoperative wound infections.

9 *E. coli* is the most common cause for bloodstream and urinary tract infections as well as foodborne infections.

10 Swissnoso is a group of Swiss medical doctors in leader positions at hospitals and at the Swiss federal agency of health (BAG).

11 S. Gross, Trendwende bei Antibiotikaforschung, in: *Tages Anzeiger* **2014**, *Dez. 03.*

After the golden age of antibiotic drug discovery, the numbers of approved antibiotic pharmaceuticals decreased remarkably (Figure 1.2).[12] Many pharmaceutical companies ceased their investigations on antibiotic drug development during the 90's. This is in stark contrast to the above-mentioned increasing threat of resistant bacteria strains. The question rises why there is such an imbalance between supply and demand. One reason is that research on antibiotics is not profitable anymore. Marijn Dekkers from Bayer stated in an interview with "Der Spiegel" that a new antibiotic would need to be around six times more expensive than an existing one, to have economical relevance.[13] In addition, novel anti-infective agents should be used as little as possible to prevent resistance and to keep them as a reserve for patients suffering from drug resistant pathogens.

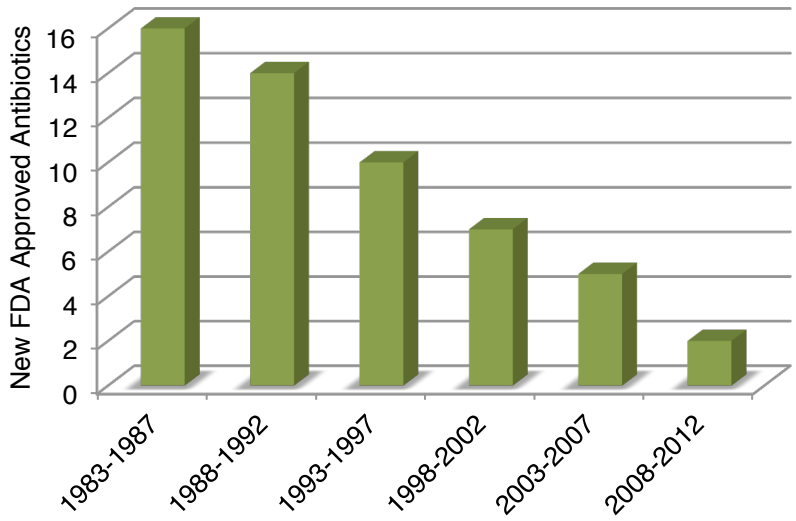

Figure 1.2: Approved systemic antibiotics by the US Food and Drug Administration in the recent years.[12]

These reasons are preventing profit-oriented institutions to invest in this field. Hence, there is an increasing call for political stimulation of antibiotic development. In this context, Piddock et al. assessed funding, promoting antibiotic research in the UK,[14] and found that 0.7% (95 million £) of research funding available, was awarded to antibiotic research. Compared with the importance and urgency of the global problematic, this is a seemingly small amount. To approach the increasing threat, the US launched the so-called GAIN

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[12] H. W. Boucher, G. H. Talbot, D. K. Benjamin, J. Bradley, R. J. Guidos, R. N. Jones, B. E. Murray, R. A. Bonomo, D. Gilbert, *Clin. Infect. Dis.* **2013**, *56*, 1685.

[13] C. Pauly, F. Dohmen *Der Spiegel* **2015**, *22*, 74-76.

[14] E. C. Bragginton, L. J. V. Piddock, *The Lancet Infectious Diseases* **2014**, *14*, 857–868.

(Generating Antibiotic Incentives Now) programme in 2012, which secures to new antibiotics a five-year market restriction of drugs with the same profile. In addition, the FDA approval of such pharmaceuticals will be accelerated.[11] This topic was also discussed at the G-7 meeting in Elmau 2015 and it was agreed to stimulate fundamental research and the development of antimicrobials.[15] Moreover, the EU has announced that the issue should play a prominent role in the agenda of 2016.[16]

[15] *Annex to the Leader's Declaration of G7 Summit* **2015**, *Jun. 06*, 1-15.

[16] K. M. Smolka, Wenn kein Antibiotikum mehr hilft in: *Frankfurter Allgemeine Zeitung* **2015**, *Sept. 07*, 22.

1.1.2 Antibiotics – Origin and Development

Most of the antibiotics available are natural products or natural product derived molecules.[4] However, the pioneers under the antibiotics were fully synthetic and simple compounds. One of the first antibiotics arose from the dye industry. Paul Ehrlich's search for the "magic bullet"[17] together with the company Bertheim, brought up a range of organoarsenic compounds, one of which was salvarsan, the first therapeutic against syphilis (Figure 1.3).

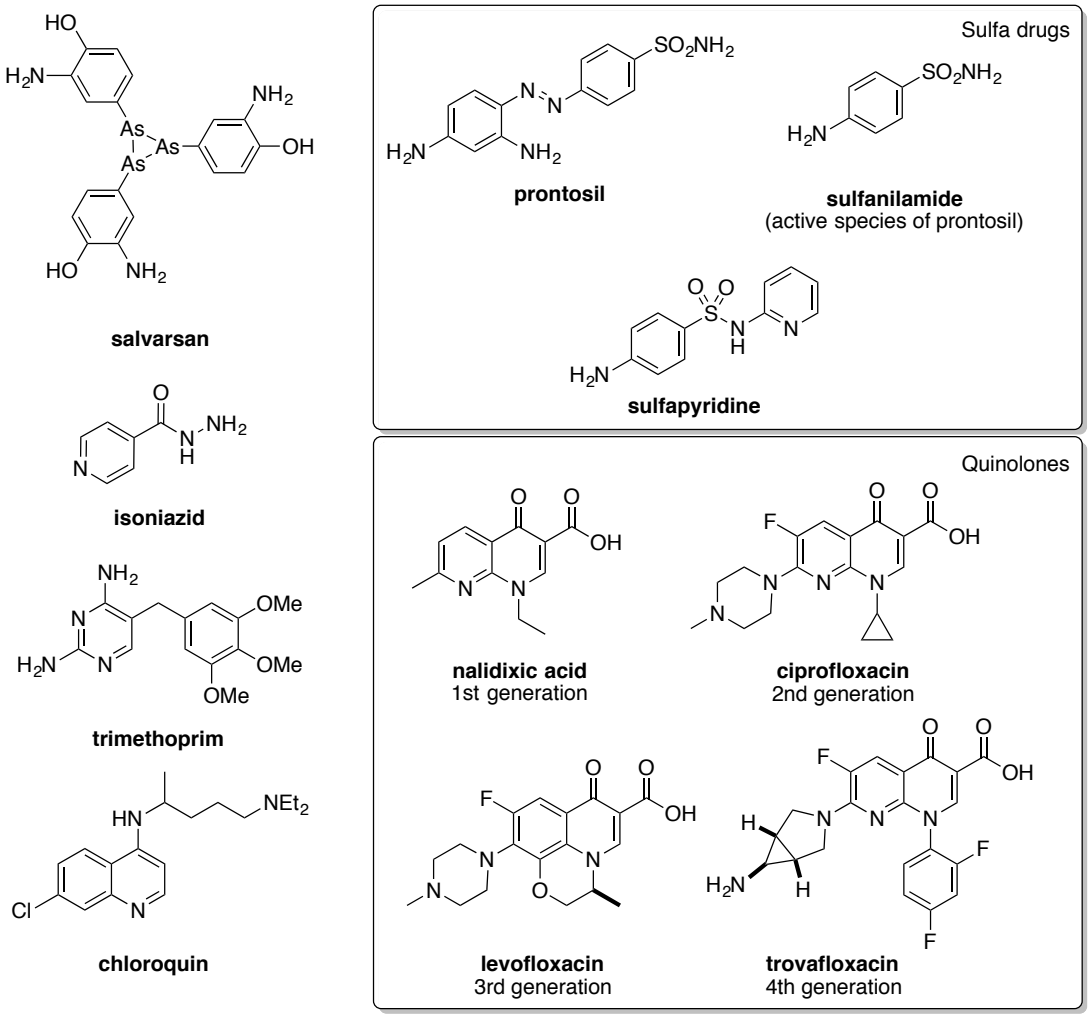

Figure 1.3: Fully synthetic antibiotics.

[17] With the magic bullet Paul Ehrlich meant chemical compounds capable to combat pathogens.

The sulfa drugs have their origin in the dye industry as well. The company I.G. Farben, together with Gerhard Domagk discovered prontosil, to be effective against streptococci.[18,19] Later, it was discovered that prontosil was simply a prodrug, and the active species the sulfanilamide. In further elaborative studies, around 5000 variants of sulfanilamide have been synthesized and tested of which some, such as sulfapyridine, made it to market. Another success story was the discovery of the quionolones,[20] which was isolated as a byproduct during a synthetic approach towards the antimalarial chloroquine. Based on this structure, four generations of antibiotics have been developed, evolving from gram negative activity to broad spectrum activity.[21,19] George Hitching and co-workers followed a more rational approach in antibiotic development, trying to prevent DNA synthesis by interrupting the incorporation of purines in the strand. Thus, they were looking into purine-mimicking molecules that would block DNA chain grow. Along this line, trimethoprim, a pyrimidine-based antibiotic was developed, which is of particular importance in developing countries due to its low costs.

Natural products are a valuable source of inspiration in drug discovery. In contrast to fully synthetic anti-infectives they have a very broad spectrum of complexity (Figure 1.4). In some cases, the natural products itself made it to market (e.g. penicillin, fosfomycin, streptomycin, erythromycin, vancomycin, chlorotetracycline), in others semisynthetic modifications or *de novo* synthesized analogues led to new therapeutics (e.g. 2-nitroimidazole (metronidazole), thienamycin (carbapenems), cephalosporin C (cephalosporins), rifamycin SV (rifampicin)).[19] In the following section a few examples from antibiotic drug discovery by 1) semisynthetic and 2) fully synthetic means are described.

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[18] J. E. Lesch, *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine*, Oxford University Press, New York, **2007**.

[19] P. M. Wright, I. B. Seiple, A. G. Myers, *Angew. Chem. Int. Ed.* **2014**, *53*, 8840–8869.

[20] G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey, R. P. Brundage, *J. Med. Pharm. Chem.* **1962**, *5*, 1063-1065.

[21] V. T. Andriole, *Clin. Infect. Dis.* **2005**, *41*, 113–119.

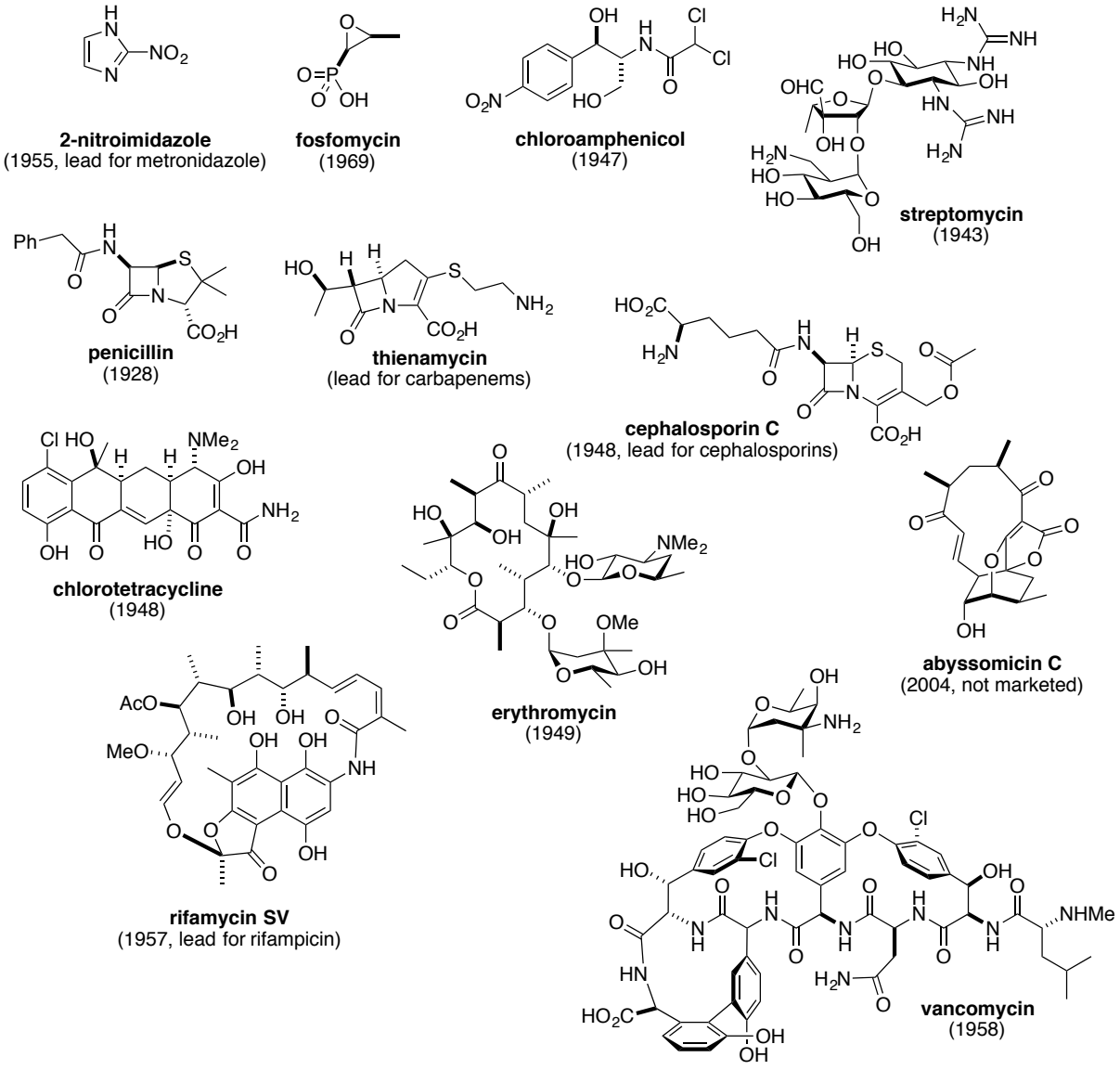

Figure 1.4: The beautiful diversity of natural products with antimicrobial activity, serving as lead structures for drug development. Dates in brackets refer to the year marketed or isolated.

A success story of antibiotic development by semisynthetic means, are the simple modifications of tetracycline (natural product analogue of chlorotetracycline), which brought up a range of new antibiotics (Figure 1.5). It was discovered that removal of the benzylic alcohol led to more stable compounds while maintaining their biological activity. Thus, modifications under more forcing conditions could be performed, especially, electrophilic substitution at the aromatic portion brought up new antibiotics.

The erythromycin-based anti-infectives are another successful example of semisynthetic drug discovery. The ketone in the macrolide is prone to react with the tertiary alcohol in γ-position to give an anhydrohemiketal. Protection of the alcohol as the methylether

(clarithromycin, six steps from erythromycin), or complete removal of the ketone (azithromycin, four steps from erythromycin) led to more stable therapeutics (Figure 1.5).

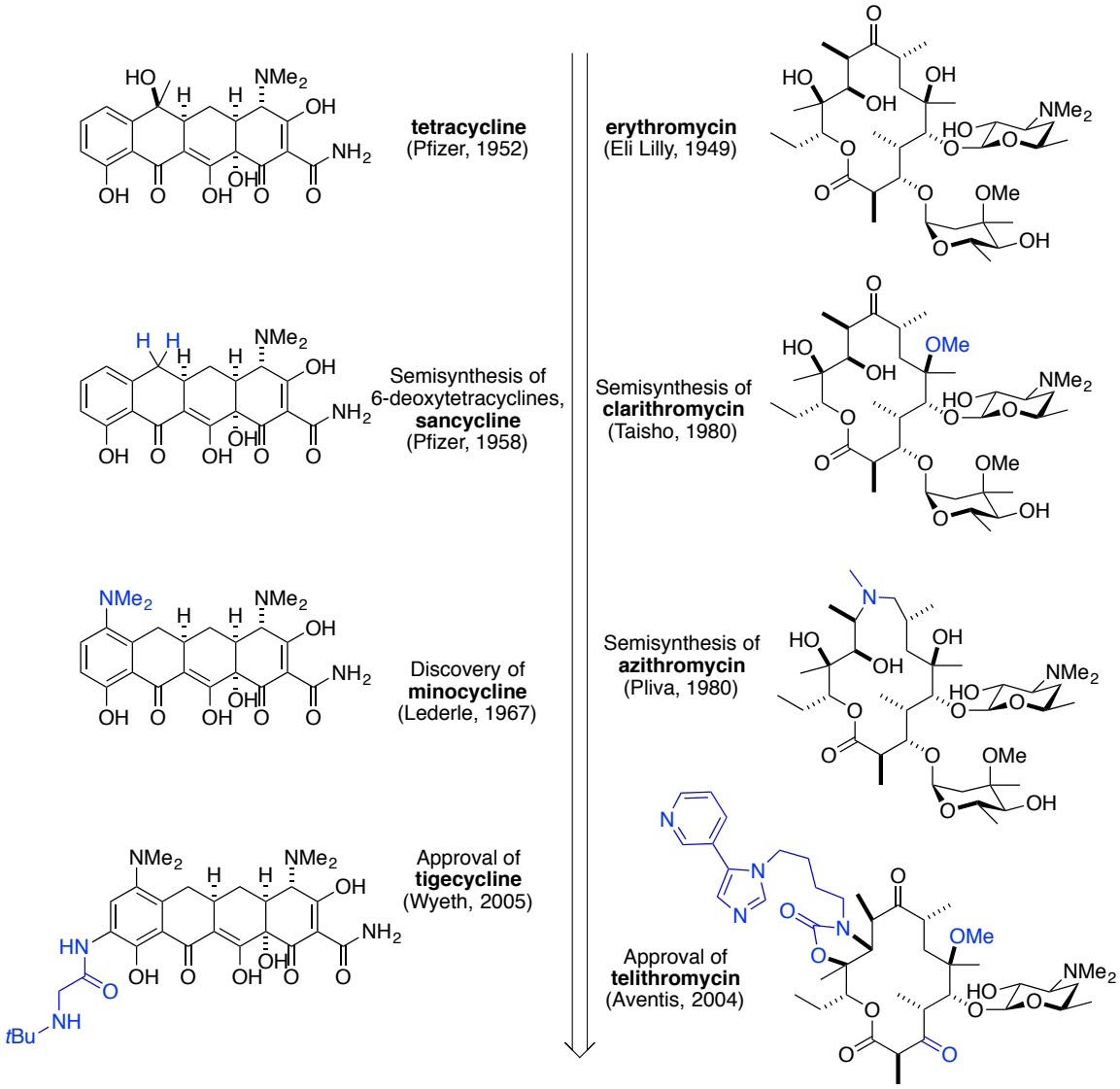

Figure 1.5: Semisynthetically developed antibiotics from the parental natural compounds tetracycline and erythromycin. The blue portions highlight the semisynthetic modifications. The figure was adapted from reference[19].

Semisynthetically, the variation of the lead structure is limited by the stability of the compounds and in addition certain transformations are not doable in a selective manner, and for a long time, fully synthetic antibiotics were very simple molecules with no chiral centre. With the development of the fully synthetic β-lactams (e.g. cephalosporin, thienamycin) in the 80's, a huge step was taken. Suddenly, a wide variety of antibacterial molecules with high complexity could be manufactured (Figure 1.6). Non-trivial modifications by semisynthetic strategies, like the replacement of the sulphur by oxygen or methylene in cephalosporin (Figure 1.4), were achieved fully synthetically and gave rise to new antibiotics. Thienamycin,

a very promising broad-spectrum antibiotic, was highly unstable due to intermolecular attack of the primary amine on the lactam. Here, semisynthetic studies led to imipenem, which was significantly more stable while retaining the high bioactivtity (Figure 1.6). Since the isolation and purification of thienamycin was very challenging, imipenem was manufactured using a fully synthetic route. Along the successful total synthesis and therapeutic utility of imipenem, the antibiotic has been further developed, resulting in meropenem – introduction of a methyl group α to the thioether improved the pharmacokinetics – and more recently, ertapenem (Figure 1.6).

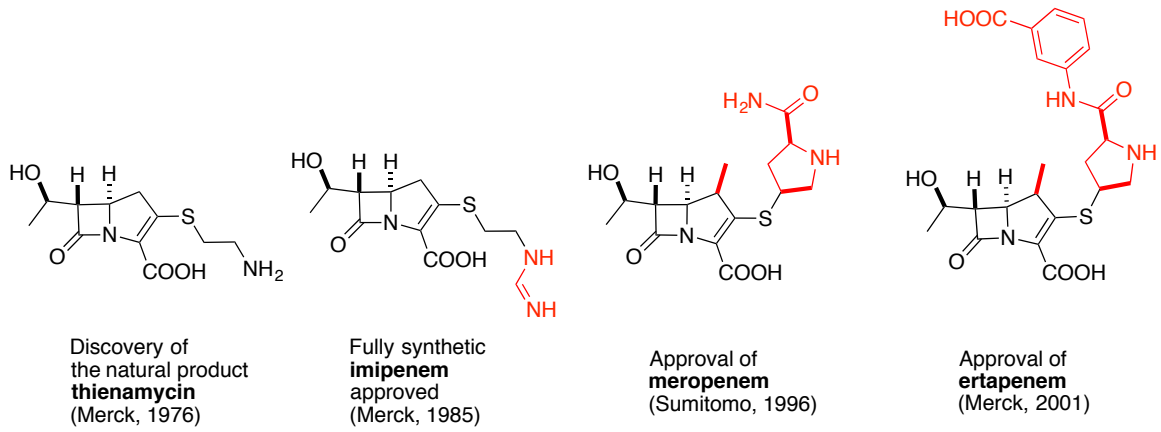

Figure 1.6: Fully synthetic β-lactams based on the parent thienamycin. The portions in red highlight the fully synthetic modifications compared to the lead structure. The figure was adapted from reference[19].

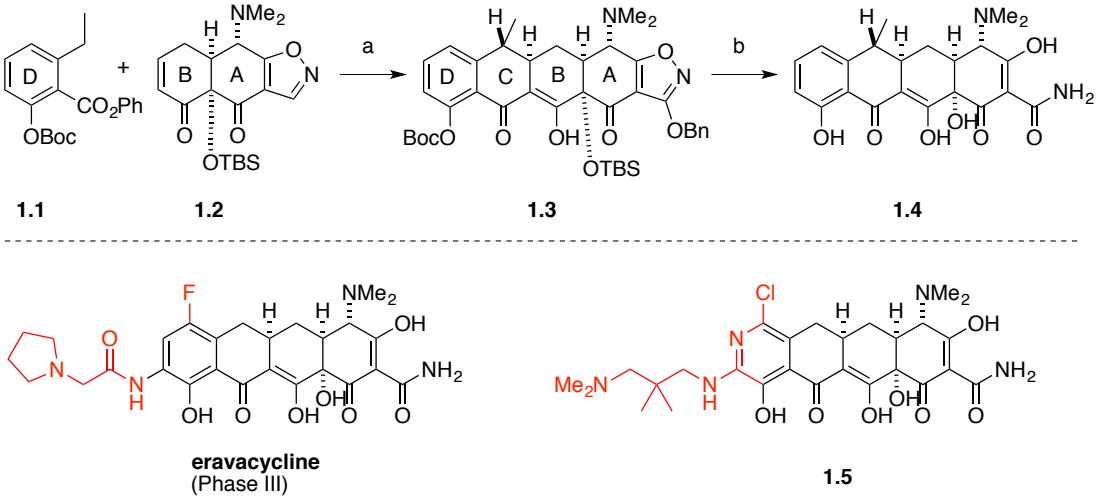

Figure 1.7: Top: Fully synthetic approach towards tetracyclines. Bottom: Selected examples of fully synthetic tetracycline analogues derived from the approach above. The figure was adapted from reference [19].

Another example that shows the advantage of fully synthetic versus semisynthetic approach was the development of eravacycline and other tetracycline derived antibiotics. Due to a lack of possible chemical transformations, semisynthetic changes on tetracycline were

limited to only three positions in the molecule (Figure 1.5). The total synthesis of tetracycline by Myers and co-workers, contributed an important tool for the synthesis of diverse analogues, such as **1.5**. In their synthesis, the A-ring is introduced at a late stage of the synthesis (Figure 1.7).[22] This was of particular interest since modifications at this site is widely tolerated for the antibiotic activity. Thereof a huge number of tetracycline analogues were synthesized and tested and finally resulted in the discovery of eravacycline, which is currently in the phase III clinical trial against urinary tract infections.

1.1.3 Lipiarmycins, Tiacumicins, Clostomicins and Fidaxomicin

In 1975, Parenti et al. published the isolation of a new compound isolated from a soil sample, which was collected in India on the 29th February in 1972, a leap year.[23] Thereof the isolate from the strain *Actinoplanes deccanensis,* lipiarmycin. The compound was found to be active against Gram-positive bacteria and more interestingly, against strains, resistant to commercially available antibiotics (e.g., rifampin, streptomycin, tetracycline, erythromycin). It took until 1987 to realize that the isolated sample indeed was a mixture of two compounds in a 3:1 ratio, which were termed lipiarmycin A3 and A4.[24]

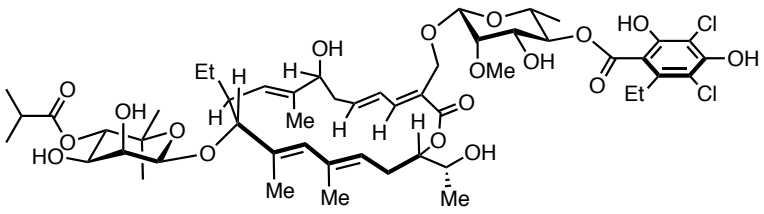

Figure 1.8: The antibiotic macrolide fidaxomicin, also known under the names lipiarmycin A3, tiacumicin B and clostomicin B1.

[22] a) M. G. Charest, D. R. Siegel, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 8292–8293; b) C. Sun, Q. Wang, J. D. Brubaker, P. M. Wright, C. D. Lerner, K. Noson, M. Charest, D. R. Siegel, Y.-M. Wang, A. G. Myers, *J. Am. Chem. Soc.* **2008**, *130*, 17913–17927.

[23] C. Coronelli, R. J. White, G. C. Lancini, F. Parenti, *J. Antibiot.* **1975**, 253–259.

[24] A. Arnone, G. Nasini, B. Cavalleri, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1353–1359.

Independently, in 1986, the isolation of the clostomicins from a new strain collected in Japan called *Micromonospora chinospora* was reported.[25] One of them, clostomicin B1, was identified to be identical with lipiarmycin A3. In addition, the group of McAlpine reported the isolation of the tiacumicins A-F in 1987, of which "B" was found to be the same compound as lipiarmycin A3.[26] Despite the early discovery of these antimicrobially active compounds, it was not until the end of the 90's that their therapeutic potential was recognized. The investigations on tiacumicin B by Optimer Pharmaceuticals paid off, and the FDA approved the antibiotic under its tradename Dificid® and generic name Fidaxomicin in 2011 for the treatment of *Clostridium difficile* infections (CDI).[27]

Fidaxomicin consists of a central 18-membered polyketide macrolide with high unsaturation and five stereocenters, which is glycosylated at two sides with an unusual D-noviose and a D-rhamnose. The rhamnose moiety on his part, is linked to a chlorinated resorcylate unit (Figure 1.9). It should be mentioned that the assignment of all stereocenters in fidaxomicin (and the lipiarmycins, clostomicins and tiacumicins), in particular the configuration at C18, remained unclear for a long time. The stereocenters were unambiguously assigned by X-ray crystal structure analysis in 2006 for the first time.[28] Optimer Pharmaceuticals presents in the same patent their studies on the isolate (OPT-80) from *Dactylosporangium auantiacum,* containing mainly C18-(*R*)-tiacumicin B and in minor quantities lipiarmycin A4, as well as, what they call "C19-ketone" (clostomicin D). Reduction of the C18 ketone in C19-ketone/clostomicin D afforded (*S*)-tiacumicin B. As the (*S*)-tiacumicin B (bearing an ethyl group at resorcylate) appeared spectroscopically identical to lipiarmycin A4 (bearing a methyl group at resorcylate), the stereocenter of the latter was assigned as (*S*)*,* too. By that, the C18 configuration of lipiarmycin A3 and its co-identity with tiacumicin B was questionable again. Late, in 2014, degradation studies by Serra *et al*. proofed that lipiarmycin A3 is identical to tiacumicin B.[29] Though the co-identity of tiacumicin B, clostomicin B1, lipiarmycin A3 and fidaxomicin is clear, the configuration of

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[25] S. Omura, N. Imamura, R. Oiwa, H. Kuga, R. Iwata, R. Masuma, Y. Iwai, *J. Antibiot.* **1986**, *39*, 1407–1412.

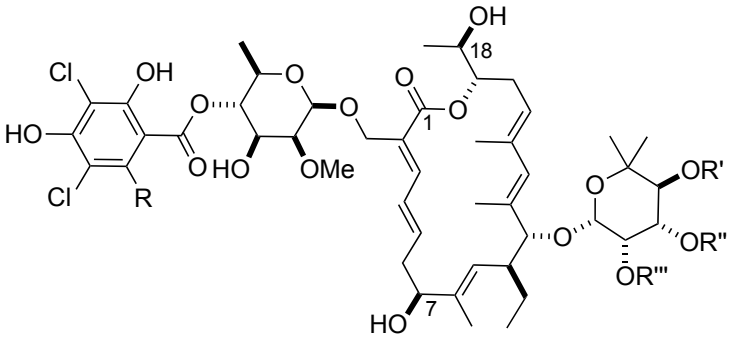
[26] J. E. Hochlowski, S. J. Swanson, L. M. Ranfranz, D. N. Whittern, A. M. Buko, J. B. McAlpine, *J. Antibiot.* **1987**, *40*, 575–588.

[27] W. Erb, J. Zhu, *Nat. Prod. Rep.* **2013**, *30*, 161.

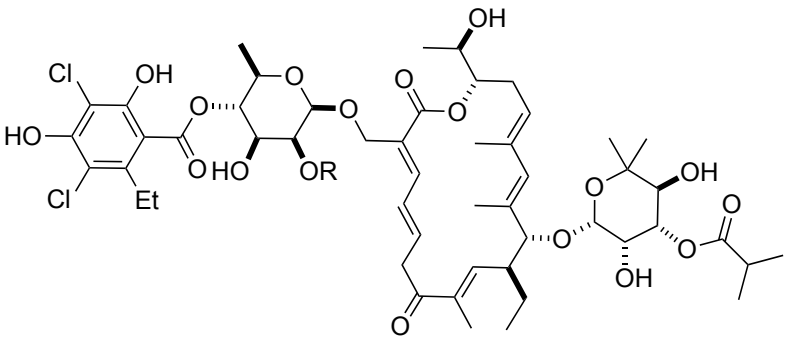
[28] Y.-K. Shue, C.-K. Hwang, Y.-H. Chiu, A. Romero, F. Babakhani, P. Sears, F. Okumu **2006**, *WO2006/085838*.

[29] A. Bedeschi, P. Fonte, G. Fronza, C. Fuganti, S. Serra, *Nat. Prod. Commun.* **2014**, *9*, 237-240.

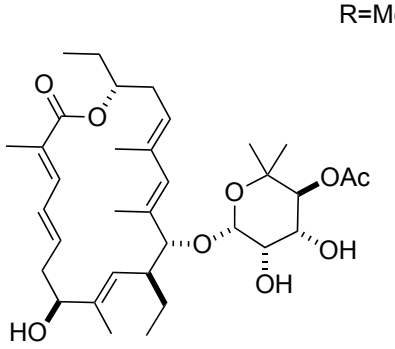
other analogues is still unsure. So far, no unambigious analytical proof of any (*S*)-configured natural product in the fidaxomicin family was given.



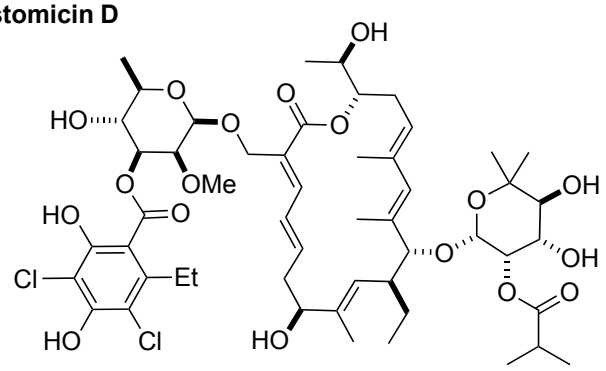
R	R'	R''	R'''	
Et	CO*i*Pr	H	H	**lipiarmycin A3, clostomicin B1, tiacumicin B, fidaxomicin**
Et	H	H	CO*i*Pr	**lipiarmycin B3, clostomicin B2, tiacumicin C**
Et	H	H	COEt	**tiacumicin E**
Et	H	CO*i*Pr	H	**tiacumicin F, clostomicin A**
Me	CO*i*Pr	H	H	**lipiarmycin A4** putative (*S*)-C18
Me	H	H	CO*i*Pr	**lipiarmycin B4**



R=H **clostomicin C**
R=Me **clostomicin D**



tiacumicin A



tiacumicin D

Figure 1.9: The isolated natural products having the central macrolactone in common. The configuration at C18, shown here as *R*-configured, is not terminally determined, except for fidaxomicin and synonyms.

1.1.4 Fidaxomicin – Biological Activity and Mode of Action

Fidaxomicin is a narrow-spectrum antibiotic against Gram-positive bacteria with minimal systemic absorption. Owing to its potent activity against the Gram-positive bacteria *C. difficile* (MIC = 0.012 μg/mL (0.011 nmol/mL)), it was introduced to the market in 2011 for the treatment of *Clostridium difficile* infections (CDI).[30] CDI is a nosocomial (hospital acquired) disease, causing diarrhea. Compared to vancomycin, treatment with fidaxomicin shows comparable cure rates but decreased recurrence. Further, broad-spectrum antibiotics such as metronidazole or vancomycin are prone to promote resistance of *Enterococci*, which is not the case with fidaxomicin.[31] Fidaxomicin also showed promising activity against MDR strains of *Mycobacterium tuberculosis* (MTB) (MIC < 0.1 mg/mL (<0.1 nmol/mL)).[32] This result is especially interesting as MDR-MTB is one of the growing public health concerns worldwide.[7] For CDI the minimal oral systemic bioavailability is highly advantageous as it results in fewer adverse effects. On the other hand, the antibiotic is not suitable as therapeutic for systemic diseases like tuberculosis. In addition, fidaxomicin and semisynthetic derivatives showed good IC_{50} values (5.56–4.04 μg/mL) in breast cancer cells, comparable with the values of Tamoxifen® (5.50 μg/mL).[33]

The RNA-polymerase (RNAP) is essential to all organisms, and responsible for the transcription of DNA to RNA. The bacterial RNAP consists of five subunits (α_I, α_{II}, β, β', ω), which form a pincer-like structure between the β, β'-subunits. The so formed channel serves as the active site where the DNA-strand fits and a Mg^{2+} ion is complexed (Figure 1.10). The β'-subunit plays a special role in this enzyme as it is a mobile part which opens and closes the access to the active site and it constitutes the docking site for the σ-cofactor to form the active holoenzyme. The σ-cofactor is responsible for the recognition of the promoter in the DNA sequence (Figure 1.10). When the holoenzyme-DNA complex is formed, the DNA is opened to single strands and the transcription to RNA is started. Once the first ten RNA-nucleotides are synthesized the σ-cofactor is released and the transcription goes on until the termination

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30 A. A. Venugopal, S. Johnson, *Clin. Infect. Dis.* **2012**, *54*, 568–574.

31 W. N. Al-Nassir, A. K. Sethi, Y. Li, M. J. Pultz, M. M. Riggs, C. J. Donskey, *Antimicrob. Agents Chemother.* **2008**, *52*, 2403-2406.

32 M. Kurabachew, S. H. J. Lu, P. Krastel, E. K. Schmitt, B. L. Suresh, A. Goh, J. E. Knox, N. L. Ma, J. Jiricek, D. Beer, M. Cynamon, F. Petersen, V. Dartois, T. Keller, V. Sambandamurthy, *J. Antimicrob. Chemother.* **2008**, *62*, 713–719.

33 M. C. Wu, C. C. Huang, Y. C. Lu, W. J. Fan, US 20090110718 A1, **2009**.

signal is reached. Often this terminal signal results in the formation of a β-hairpin in the synthesized RNA, which destabilizes the complex to release DNA and RNA.

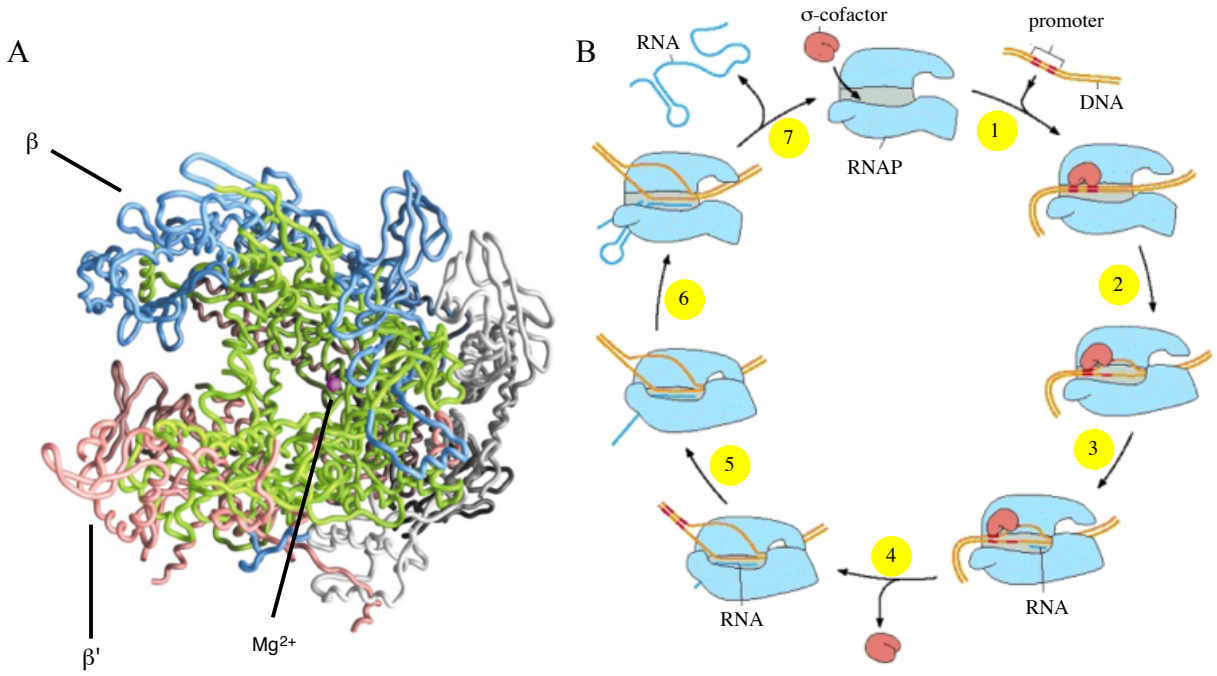

Figure 1.10: A: Backbone worm diagram of bacterial RNAP. [34] The two α and ω subunits are coloured in white. The blue part assigns the β- and the pink the β'-subunit. The complexed Mg^{2+}-ion in the active pocket is in magenta. In green, evolutionarily highly conserved regions of the β-units are highlighted. **B:** The transcription cycle of bacterial RNAP. In the first step the σ-cofactor binds to the polymerase forming the holoenzyme. Specific bindings between the σ-cofactor and the promoter on the DNA are formed (1) and the double helix is unwound (2). Now transcription into RNA starts (3) and the σ-unit is released (4) while the polymerase tightens around the DNA. Now transcription goes on until the termination signal on the sequence is reached (6) and the RNA and DNA are released from the complex (7). Adapted from reference[35].

Although many compounds have been found to inhibit bacterial RNAP, only a few have been approved as antibiotics, e.g., the rifamycins and fidaxomicin. While it was shown that the rifamycins bind to the β-subunit and block the elongation of the RNA,[36] the mode of action of fidaxomicin is not fully understood yet and the published studies are often contradictory.

Already along with the isolation-paper of lipiarmycin, it was found that the inhibition pattern was very similar to that of rifampicin.[23] The RNA synthesis was completely inhibited

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[34] Illustration used with permission of Elsevier from: S. A. Darst, *Current Opinion in Structural Biology* **2001**.

[35] B. Alberts, A. Johnson, J. Lewis, D. Morgan, M. Raff, K. Roberts, P. Walter, *Molecular Biology of the Cell*, Garland Science **2015**, *4th Ed.*

[36] E. A. Campbell, N. Korzheva, A. Mustaev, K. Murakami, S. Nair, A. Goldfarb, S. A. Darst, *Cell* **2001**, *104*, 901–912.

when the isolate was added prior to the RNAP-DNA association. When added after the complex formation, RNA synthesis was only gradually inhibited.[37]

The group of Sonenshein showed for *B. subtilis*, that the inhibition did not result from the interaction with the σ-cofactor but more likely with the holoenzyme.[38] Furthermore, lipiarmycin resistant strains incorporated mutations in the gene coding for the β-subunit of the RNAP.

Much later, in 2006, the group of Leonetti showed that mutations of the gene in *B. subtilis*, coding for the β'-subunit, led to resistance against fidaxomicin.[39] Later, Sambandamurthy *et al*. and Leonetti *et al.* showed on different strains (*M. tuberculosis* and *E. faecalis*), that mutations in the genes, coding for the β- and β'-subunits in the region of the RNA-exit-channel, caused resistance.[32,40] Leonetti and co-workers then investigated the mode of action of fidaxomicin on *E. coli* as a model,[41] and found that, indeed, two sites are targeted, the σ^{70} 3.2 region and the switch-2 element on the β'-subunit. The switch-2 unit is responsible for the clamping of the promoter DNA in the active pocket of the RNAP, while the σ^{70}-region stimulates the RNA synthesis. As the two regions are essential for the DNA fitting into the active site, it was reasoned that fidaxomicin blocks this process to inhibit transcription.

Referring on unpublished results, the group of Ebright, could not verify the interaction with the σ-cofactor.[42] They located the binding site of fidaxomicin in the switch-2 to switch-3 region of the β'-subunit (Figure 1.11). The site of binding, strongly suggests fidaxomicin to interfere with the RNAP switch-region or the RNA-exit channel or both.

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[37] S. Sergio, G. Pirali, R. White, F. Parenti, *J. Antibiot.* **1975**, *28*, 543–549.

[38] a) A. L. Sonenshein, H. B. Alexander, D. M. Rothstein, S. H. Fisher, *J. Bacteriol.* **1977**, *132*, 73–79; b)A. L. Sonenshein, H. B. Alexander, *J. Mol. Biol.* **1979**, *127*, 55–72.

[39] M. Gualtieri, P. Villain-Guillot, J. Latouche, J.-P. Leonetti, L. Bastide, *Antimicrob. Agents Chemother.* **2006**, *50*, 401–402.

[40] M. Gualtieri, A. Tupin, K. Brodolin, J.-P. Leonetti, *Int. J. Antimicrob. Agents* **2009**, *34*, 605–606.

[41] A. Tupin, M. Gualtieri, J.-P. Leonetti, K. Brodolin, *EMBO J* **2010**, *29*, 2527–2537.

[42] A. Srivastava, M. Talaue, S. Liu, D. Degen, R. Y. Ebright, E. Sineva, A. Chakraborty, S. Y. Druzhinin, S. Chatterjee, J. Mukhopadhyay, Y. W. Ebright, A. Zozula, J. Shen, S. Sengutpa, R.R. Niedfeldt, C. Xin, T. Kaneko, H. Irschik, R. Jansen, S. Donadio, N. Connell, R. H. Ebright, *Curr. Opin. Microbiol.* **2011**, *14*, 532–543.

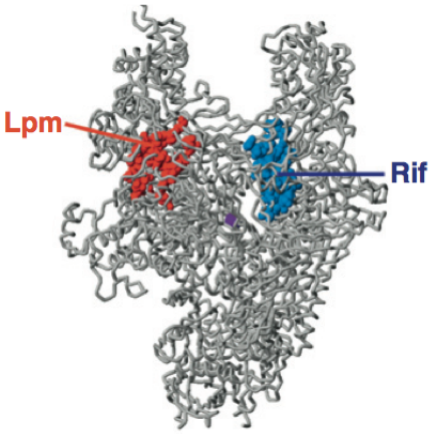

Figure 1.11: The binding sites in bacterial RNAP of rifamycins (Rif) and fidaxomicin (= lipiarmycin, Lpm). Fidaxomicin binds to the switch-2 region of the β'-subunit, the rifamycins on the other hand, bind to the β-subunit, which is in agreement with no cross-resistance between the antibiotics. The illustration is used with permission from reference [42].

In 2012, researchers from Optimer Pharmaceuticals published results, showing that fidaxomicin inhibits the transcription in *C. difficile* and *E. coli* upon holoenzyme formation, but necessarily before opening of the complex for DNA fitting.[43] They compared the results between fidaxomicin in their tests and the results from Leonetti[41], using a fermentation mixture from *A. deccanensis*, stated as lipiarmycin (of which the authors believed to have the C18-(*S*)-configuration). In contrast to Leonetti, in their tests, the activity of fidaxomicin was not dependant on alterations of the σ-cofactor. Though, they found different results than Leonetti, it is declared that this observation might origin from differing analysis methods.

To sum up, fidaxomicin is a RNAP inhibitor with no cross-resistance to rifamycins (a RNAP inhibitor itself) and it inhibits the holoenzyme better then the core RNAP. It is very likely that inhibition occurs in the opening of the protein complex for DNA docking, which would be a new mechanism of transcription inhibition.

[43] I. Artsimovitch, J. Seddon, P. Sears, *Clin. Infect. Dis.* **2012**, *55*, 127–131.

1.1.5 Biosynthesis of Fidaxomicin

The group of Zhang has investigated the biosynthesis of fidaxomicin in the *D. aurantiacum* strain, from which tiacumicin B was isolated originally.[44] Extensive DNA-sequence analysis and knockout experiments resulted in the identification of 31 open reading frames putatively involved in the fidaxomicin biosynthesis. Specific genes have been inactivated, and the metabolites of the mutants identified. In this way, the functions of a halogenase (TiaM), two glycosyltransferases (TiaG1, TiaG2), a sugar C-methyltransferase (TiaS2), an acyltransferase (TiaS6) and two cytochrome P450s (TiaP1, TiaP2) were identified. Together with bioinformatic comparison of identified enzymes, and established knowledge from polyketide biosynthesis, the following pathway was suggested (Figure 1.12).

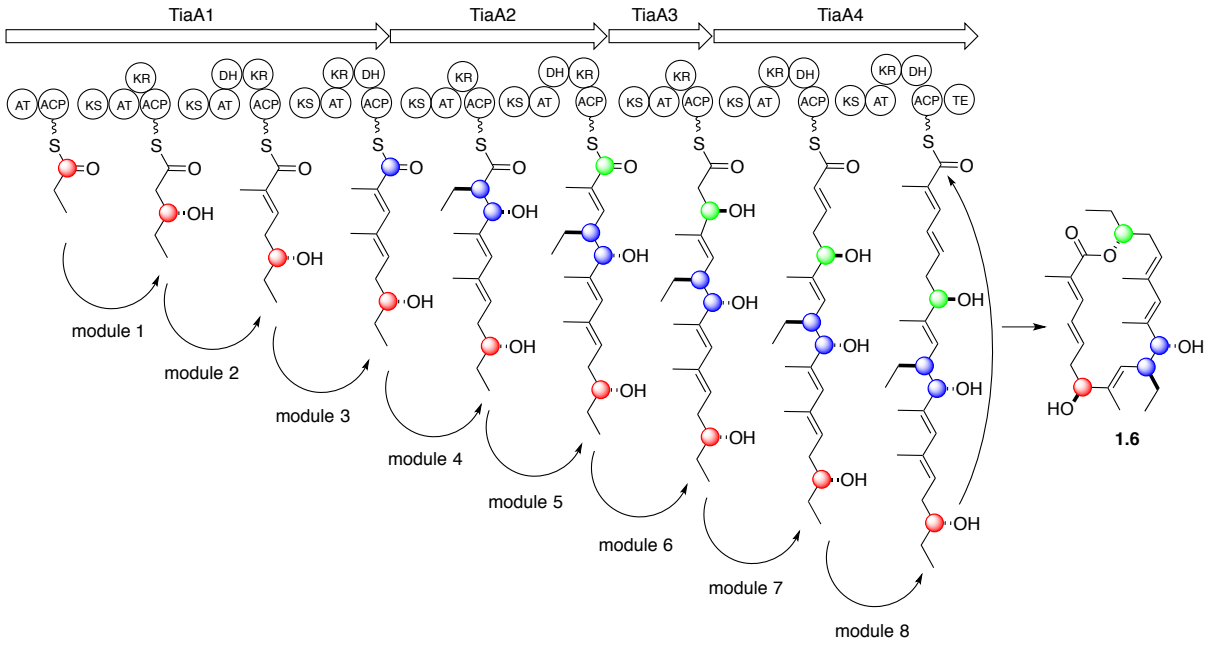

Figure 1.12: Biosynthetic pathway of the central macrolide of fidaxomicin. Only four of the final five stereocenters are introduced, yet. ACP = acyl carrier protein; AT = acyl-transferase; DH = dehydratase; KR = keto-reductase; KS = keto-synthase; TE = thio-esterase. The *tiaA1* to *tiaA4* encode the TiaA1 to TiaA4 modular type I polyketidesynthases (PKS).[44]

The central aglycon **1.6** is synthesized by a modular type I polyketide synthase (PKS). PKS are very large multi domain enzymes, mainly occurring in bacteria, plants and fungi, that produce polyketides. Typically, polyketide synthesis starts with the loading module, in which step the acyl group is bound to the acyl carrier protein (ACP) domain, in this case promoted

[44] a) Y. Xiao, S. Li, S. Niu, L. Ma, G. Zhang, H. Zhang, G. Zhang, J. Ju, C. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1092–1105; b) T. Hu, S. Li, Y. Xiao, L. Ma, G. Zhang, H. Zhang, X. Yang, J. Ju, C. Zhang, *ChemBioChem* **2011**, *12*, 1740-1748.

by TiaA1. Successively, acyl-transferase (AT) and keto-synthase (KS) modules are responsible for chain elongation and the dehydrogenase (DH) and keto-reductase (KR) modules are required for the chain decoration. The sequence is terminated with the cyclization and releasing through the thioesterase (TE).

The biosynthesis of the homo-orsellinic acid unit **1.10** commences with the PKS TiaB, which incorporates AT, KS and ACP domains, required for the synthesis of the linear polyketide **1.9** from propionyl-CoA **1.7** and three malonyl-CoA **1.8 (**Figure 1.13**)**. Spontaneous cyclization and aromatization then leads to the non-halogenated resorcylate unit **1.10**.

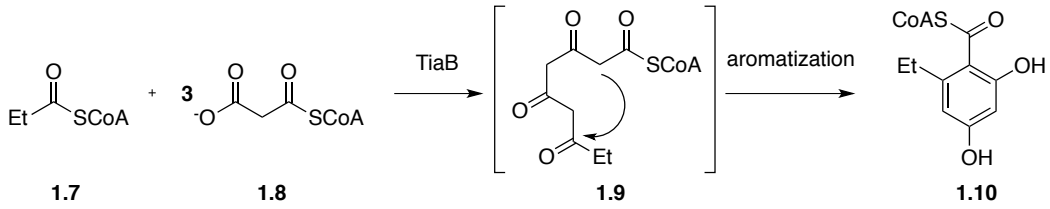

Figure 1.13: The biosynthesis of the homo-orsellinic acid moiety **1.10**. TiaB is a polyketide synthase containing active KS, AT and ACP domains. The sequence starts with the rather unusual propionyl-CoA.

The two carbohydrate units of fidaxomicin are suggested to derive from GDP-mannose **1.11 (**Figure 1.14**)**. Three genes *tiaS1*, *tiaS3* and *tiaS4* have been found to share high sequence similarity to GDP-mannose-4,6-dehydratase encoding genes (GmD). Although no required GDP-4-keto-6-deoxymannose reductase (Rmd) has been found, they propose that at least one of the GmD's is bifunctional as a RmD. Thus, the ketone **1.12** was suggested as an intermediate in the biosynthesis before transformation to the GDP-rhamnose **1.13** occurs. TiaS2, a *C*-methyltransferase and TiaS6 an isovaleryltransferase are most probably responsible for the biosynthesis of the C4 acylated GDP-noviose **1.14**. The TiaS5, an *O*-methyltransferase is responsible for the transformation to the 2*O*-methyl rhamnose **1.15**.

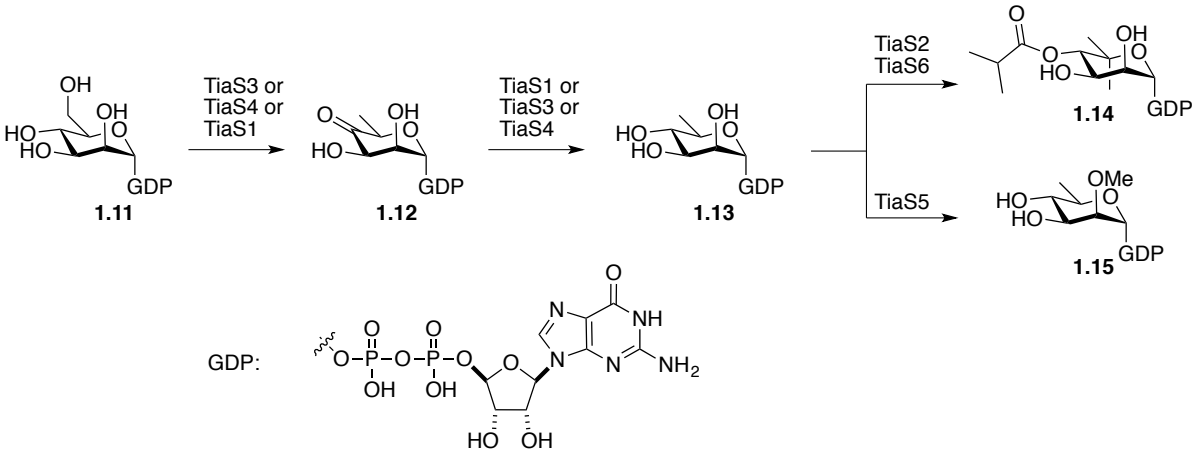

Figure 1.14: Biosynthesis of the GDP-noviose and the GDP-rhamnose starting from GDP-mannose. TiaS1, TiaS3 and TiasS4 are putatively GDP-mannose-4,6-deoxygenases (GmD) of which at least one is supposed to contain a GDP-4-keto-6-deoxymannose reductase (Rmd).

In the final steps of the proposed biosynthesis, TiaP2 and TiaP1 (cytochrome P450 enzymes) are responsible for the oxidation to the primary alcohol and the C18 alcohol. Sequential insertion of the glycosides (TiaG1, TiaG2) renders the fully glycosylated macrolide. Further acylation (TiaF) of the rhamnoside with the resorcylate, and chlorination (TiaM) finally gives fidaxomicin (Figure 1.15).

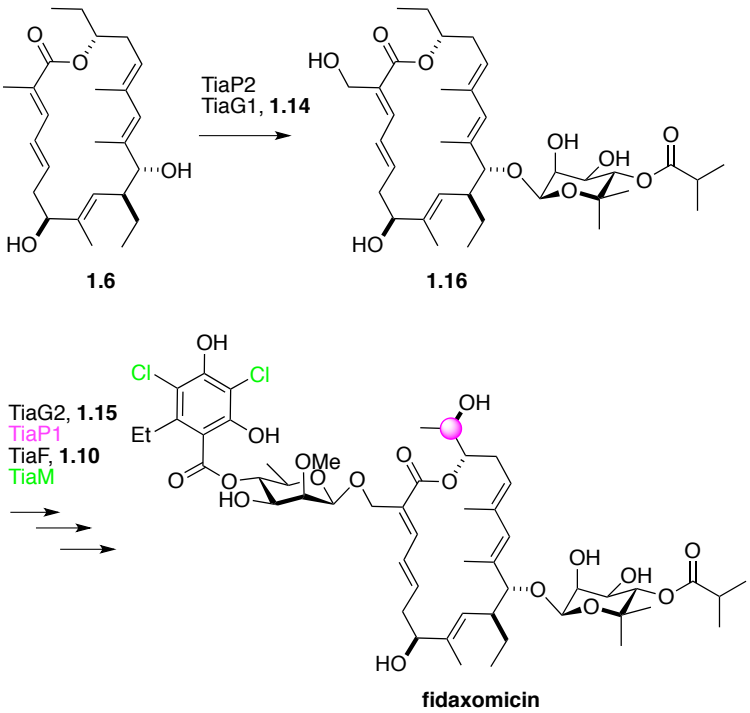

Figure 1.15: The final steps of the fidaxomicin biosynthesis. TiaG1, TiaG2 = glycosyltransferases; TiaP2, TiaP1 = Cytochrome P450 enzymes; TiaF = acyltransferase; TiaM = halogenase.

1.1.6 Structure-Activity-Relationship Studies

So far, there exists only limited knowledge about the structure activity relationship (SAR) of fidaxomicin. The available data are often not comparable between different publications due to differences in the bioassays, and unsystematic modifications of the compounds. The reported biological activities of fidaxomicin analogues so far originate from the isolation of similar natural products,[23-26] the patents around fidaxomicin and the biosynthesic studies.[44] Nevertheless some statements can be made.

Results of Zhang *et al.* [44] as well as from the thesis of Glaus[45] in the group of Altmann showed that the bioactivity was lost when a carbohydrate or resorcylate moiety was missing. This is also in agreement with the low bioactivity of the natural product analogue tiacumicin A, which lacks the rhamnosyl-resorcylate unit (Figure 1.9).[46]

Modifications on the resorcylate part are to some extend tolerated. The exchange of the chlorines against hydrogens led to a small MIC value increase.[44] Brominated variants from feeding experiments with NaBr, showed higher MIC values for some strains, except for *C. difficile* the activity was mostly preserved (Table 1.1, Entry 13–16).[47] Substitution of the phenolic groups by methyl was not tolerated at all and showed an 8–16 fold loss of activity.[48] The phenolic groups of fidaxomicin are also responsible for the lower bioyctivity at higher pH values (8 to 16 fold increase of MIC, from pH 6 to pH 8.1).[49] This can be explained by deprotonation of the phenols, leading to a charged molecule, which hinders the permeation through bacterial membranes. The alkyl-substituent (ethyl or methyl) on the aromatic ring seems to play a minor role for the bioactivity (Entry 1 *vs.* 5).

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[45] F. D. Glaus, Total Synthesis and SAR Investigations of Natural Products Inhibiting Bacterial RNA Polymerase: Ripostatin B and Tiacumicin B. ETH-Zürich **2015**. http://dx.doi.org/10.3929/ethz-a-010422569 online accessed 26.11.2015.

[46] R. J. Theriault, J. P. Karwowski, M. Jackson, R. L. Girolami, G. N. Sunga, C. M. Vojtko, L. J. Coen, *J. Antibiot.* **1987**, *40*, 567–574.

[47] J. Hochlowski, M. Jackson, R. Rasmussen, A. Buko, J. Clement, D. Whittern, J. McAlpine, *J. Antibiot.* **1997**, *50*, 201–205.

[48] J. B. McAlpine, J. E. Hochlowski (Abbott Laboratories), WO9635702 A1 **1996**,.

[49] P. Sears, S. L. Miller-Shangle, R. B. Walsh, Y.-K. Shue, F. Babakhani, T. J. Louie (Optimer Pharmaceuticals) US 20070105791 **2007**.

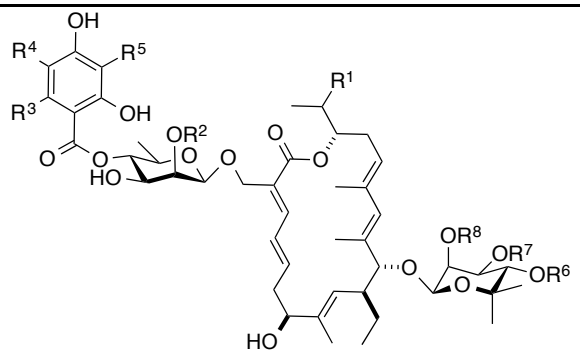
The major metabolite of fidaxomicin, OP-1118, is missing the isobutyric ester, which results in a dramatic loss of antibiotic activity (Entry 6).[50] Also migrations of the ester to adjacent alcohols (Entry 17-20) and exchanges with propionic and acetyl esters (Entry 9-11) have an adverse effect on the biological activity.

The impact of the C18 substituent is unclear. From a patent of Optimer Pharmaceuticals, it can be depicted that the C18 configuration has a high impact on the activity.[51] Their fidaxomicin isolate showed around 4-8 fold lower MIC values in *C. difficile* strains than the semisynthetic (*S*)-tiacumicin B (Entry 2). At the same time, lipiarmycin A4, with the putative (*S*)-C18 configuration and a methyl substituent at the resorcylate, and the C18 ketone (Clostomicin D) showed only small changes of the MIC values (Entry 3,5). Compounds without substitution at C18 showed also similar biological activities (Entry 4).

[50] Y. Ichikawa, Y.-H. Chiu, Y.-K. Shue, F. K. Babakhani (Optimer Pharmaceuticals), WO 2009070779 **2009**.

[51] Y. K. Shue, C. K. Hwang, Y. H. Chiu, A. Romero, F. Babakhani, P. Sears, F. Okumu (Optimer Pharmaceuticals) US20080269145 A1, **2008**.

Table 1.1: Biological Activities of Selected Fidaxomicin Analogues.



Ref: 44,51	R^4, R^5= Cl; R^8,R^7=H				MIC [µg/mL]		
	R^1	R^2	R^3	R^6	*C. difficile*	*E. faecalis*	*S. aureus*
1	(*R*)-OH	Me	Et	*i*PrCO	0.5	2-4	8
2	(*S*)-OH	Me	Et	*i*PrCO	1	8	64
3	=O	Me	Et	*i*PrCO	0.5	–	–
4	H	Me	Et	*i*PrCO	–	4	8
5	(*S*)-OH[52]	Me	Me	*i*PrCO	0.5	2	8
6	(*R*)-OH	Me	Et	H	4	16-64	>64
7	(*R*)-OH	H	Et	*i*PrCO	–	4	16
8	H	Me	Et	H	–	32	128
9	H	H	Et	*i*PrCO	–	1	2
10	H	H	Et	EtCO	–	2	4
11	H	H	Et	MeCO	–	4	8

Ref:47	R^2= Me; R^3=Et; R^7=H					MIC [µg/mL]		
	R^1	R^4	R^5	R^6	R^8	*C. difficile*	*C. perfringens*	*S. aureus*
12	(*R*)-OH	Cl	Cl	*i*PrCO	H	0.06-0.12	0.06	0.78
13	(*R*)-OH	Br	Cl	*i*PrCO	H	0.06	0.03	6.2
14	=O	Br	Cl	*i*PrCO	H	0.25-1.0	0.015	50
15	(*R*)-OH	H	Br	*i*PrCO	H	0.12-0.5	<0.06	6.2
16	(*R*)-OH	H	Br	H	*i*PrCO	0.5-2.0	0.06	50

Ref:46	R^1=(*R*)-OH; R^2= Me; R^3=Et; R^4,R^5=Cl			MIC [µg/mL]		
	R^6	R^7	R^8	*E. faecium*	*S. epidermis*	*S. aureus*
17	*i*PrCO	H	H	6.2	12.5	6.2
18	H	*i*PrCO	H	16.2	12.5	12.5
19	H	H	*i*PrCO	100	25	50
20	H	H	EtCO	12.5	12.5	25

[52] putative and not proven.

1.1.7 Synthetic Studies Towards the Total Syntheses of Fidaxomicin

Despite the interesting biological activity and the unique structure of fidaxomicin, no total synthesis of fidaxomicin or related products were published until 2015. The single fragments, on the other hand, have been approached before. Grassot and Erb in the group of Jieping Zhu described efforts towards the putative lipiarmycin A4 central aglycon in their Ph.D. theses.[53] In addition synthetic studies towards the carbohydrates[54,55] and the homo-orsellinic acid,[56] mainly for structure elucidation purposes, have been published (discussed in the respective chapters). It took until early 2015, when independently Altmann[57] and our group[58] published the first total synthesis of the fidaxomicin aglycon, back-to-back. At the same time, Zhu and coworkers[59] reported their synthesis of the C18 epimeric aglycon of fidaxomicin. In the following sections the synthesis of Zhu and Altmann are summarized.

Zhu's Aglycon Synthesis of Putative Lipiarmycin A4

Zhu's approach towards the protected aglycon **1.17** is based on the synthesis of a main fragment, incorporating all the stereogenic centers, and a dienoic acid, which are combined by Yamaguchi esterification and a ring closing metathesis (Figure 1.16). The main fragment's five stereocenters are defined by a Brown alkoxyallylation, an Evans aldol reaction and a Brown allylation.

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53 J. M. Grassot, Ph. D. Thesis, Université de Paris-Sud XI **2007**; W. Erb, Ph. D. Thesis, Université de Paris-Sud XI **2010**.

54 a) A. Lipták, *Carbohydr. Res*. **1982**, *107*, 300–302; b) A. Lipták, I. Czégény, J. Harangi, P. Nánási, *Carbohydr. Res.* **1970**, *15*, 327–331.

55 a) A. Klemer, M. Waldmann, *Liebigs Ann. Chem.* **1986**, 2, 221–225; b) E. Walton (Merck & Co), US 2938900, **1960**.

56 M. Alexy, H.-D. Scharf, *Liebigs Ann. Chem* **1991**, 1363–1364.

57 F. Glaus, K.-H. Altmann, *Angew. Chem. Int. Ed. Engl.* **2015**, *54*, 1937–1940.

58 H. Miyatake-Ondozabal, E. Kaufmann, K. Gademann, *Angew. Chem. Int. Ed. Engl.* **2015**, *54*, 1933–1936.

59 W. Erb, J.-M. Grassot, D. Linder, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed. Engl.* **2015**, 1929–1932.

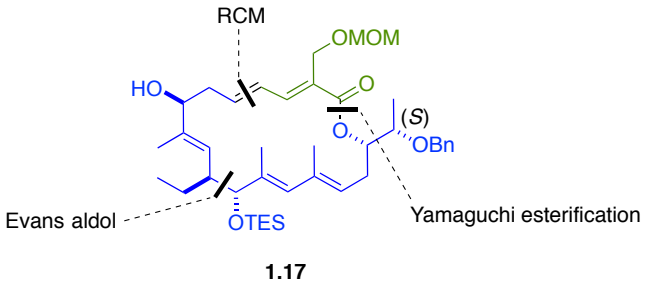
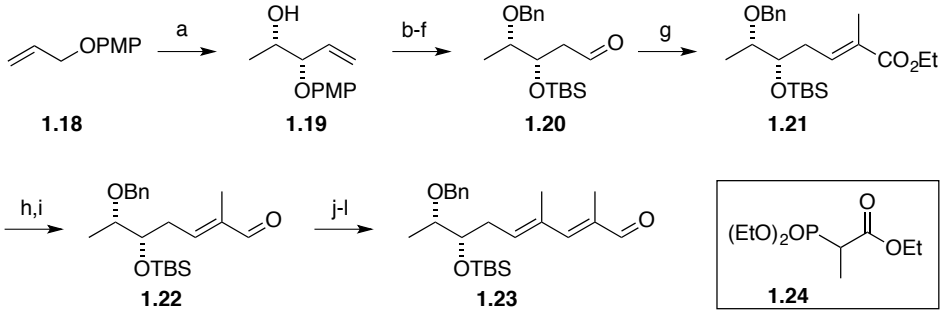


Figure 1.16: Zhu's approach towards the putative liparmycin A4 aglycon. RCM = ring closing metathesis.

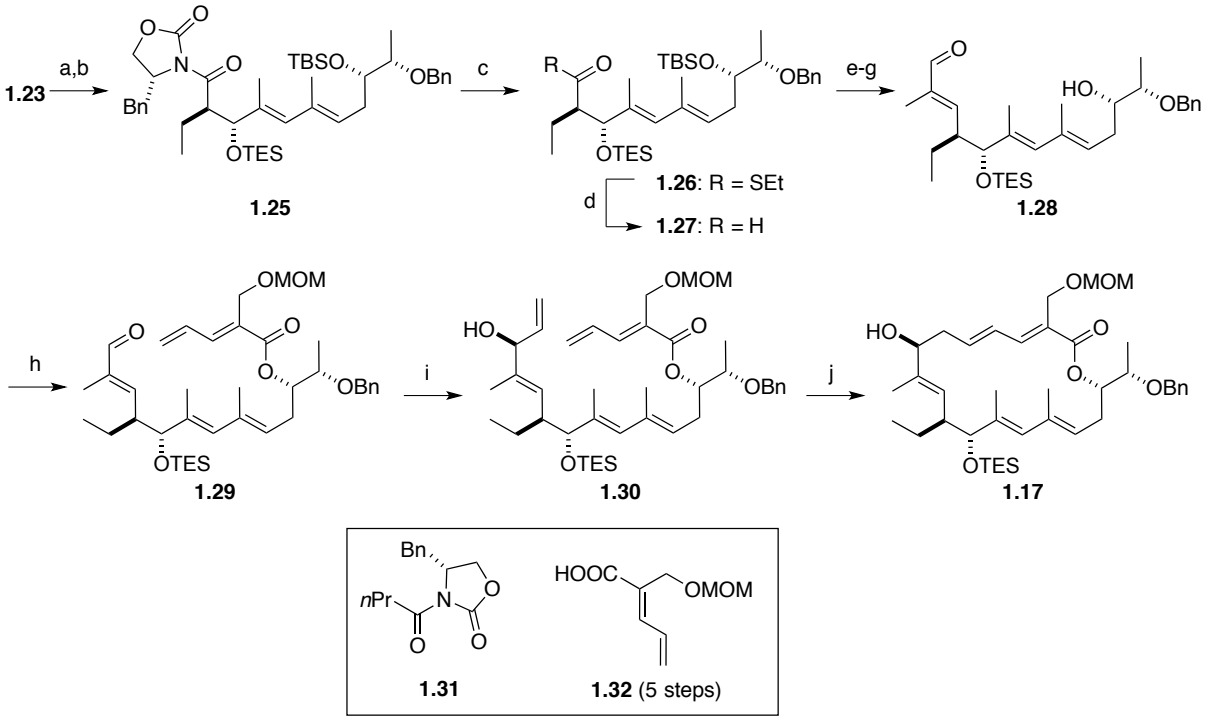
The synthesis commences with the stereoselective Brown alkoxyallylation of the PMP protected allylalcohol **1.18** to furnish the two first stereocenters in **1.19** (Scheme 1.1). Unfortunately, the corresponding TBS-protected allylalcohol was unreactive towards acetaldehyde in this reaction. Thus, the benzyl protecting group was installed and the PMP group was swopped to TBS. Hydroboration of the terminal alkene and Swern oxidation yielded the suitable aldehyde **1.20**. A Horner Wadsworth Emmons (HWE) olefination gave the *trans*-enoate ester **1.21**, which was transformed to the aldehyde **1.22**, by reduction with DIBAL-H and oxidation using manganese dioxide. The same sequence, HWE-reduction-oxidation, gave the α,β-unsaturated aldehyde **1.23**.



Scheme 1.1: a) *s*BuLi, THF, –78°C, 30 min, then (+)-Ipc$_2$BOMe, –78°C, 60 min, then $BF_3{\cdot}OEt_2$, –78°C, then acetaldehyde, –78°C, 3 h, then H_2O_2, NaOH, –78°C to RT, 18 h, 80%, *ee* 92%; b) NaH, DMF, 0°C, 1 h, then BnBr, 0°C to RT, 18 h, 81%; c) CAN, CH_3CN, H_2O, 0°C, 15 min, 81%; d) TBSCl, imidazole, DMF, RT, 18 h, 90%; e) Cy_2BH, THF, 0°C, 2 h, then H_2O_2, NaOH, 0°C, 4 h, 73%; f) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, then Et_3N, –78°C to RT, 1 h, 99%; g) **1.24**, NaH, THF, 0°C, 20 min, then **1.22**, 0°C, 2 h, 92%, E/Z=7:1; h) DIBAL-H, toluene, –78°C, 1 h, 93%; i) MnO_2, THF, RT, 2 h; j) **1.24**, NaH, THF, 0°C, 20 min, then **1.23**, 0°C, 2 h, 78%, *E*:*Z* = 4:1; k) DIBAL-H, toluene, –78°C, 1 h, 59%; l) MnO_2, THF, RT, 2 h.

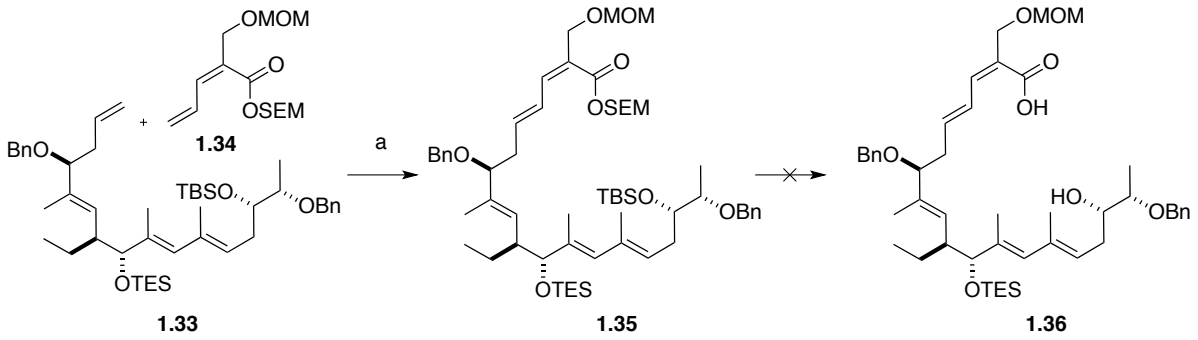
An Evans aldol reaction with the oxazolidinone **1.31** and the dienal **1.23** followed by TES protection of the secondary alcohol furnished the intermediate **1.25** in good yield (Scheme 1.2). Cleavage of the auxiliary with the lithium thiolate gave the corresponding thioester **1.26**, which was then reduced directly to the aldehyde **1.27**. Now, another HWE-reduction-oxidation sequence gave the aldehyde **1.28**. Interestingly and fortunately, the TBS-ether was chemoselectively cleaved during the reduction with DIBAL-H. Zhu *et al.* suggest a chelating

effect of the adjacent benzyl ether to be responsible for this unexpected chemoselectivity. Yamaguchi esterification of the secondary alcohol **1.28** with the dienoate **1.32** then gave the advanced intermediate **1.29**. The last stereocenter was formed during the following Brown allylation. A ring closing metathesis (Grubbs II) between the terminal olefin and the dienoate moiety of **1.30** was performed. In this way, the macrolide **1.17** with an *E:Z* selectivity of 2:1 was reached with a longest linear sequence of 21 steps.



Scheme 1.2: a) **1.31**, *n*Bu_2BOTf, Et_3N, CH_2Cl_2, 0°C, 30 min, then **1.23**, –78°C to RT, then H_2O_2, MeOH, buffer pH 7.0, 10°C to RT, 1 h, 86% (2 steps); b) TESCl, imidazole, DMF, 0°C, 20 min, 73%; c) EtSH, *n*BuLi, THF, 0°C, 5 min, then **1.25**, THF, RT, 10 min, 85%; d) DIBAL-H (1.0 M in hexane, 2 equiv), toluene, –78 °C, 20 min; e) **1.24**, NaH, THF, 0°C, 2 h, then crude aldehyde **1.28**, 0°C, 2 h, 65% (2 steps), *E:Z* = 4:1; f) DIBAL-H (1.0 M in hexane, 5 equiv), CH_2Cl_2, –78°C, 1 h, 71%; g) MnO_2, THF, RT, 2 h; h) **1.32**, 1,3,5-trichloro-benzoyl chloride, Et_3N, toluene, RT, 1 h, then **1.29**, DMAP, RT, 4 h, 53% (2 steps); i) (–)-Ipc_2BAllyl, THF, –78°C, 1 h, then H_2O_2, NaOH, –78°C to RT, 3 h, 42%; j) Grubbs II (20mol%), toluene, 100°C, 43%, *E:Z* = 2:1.

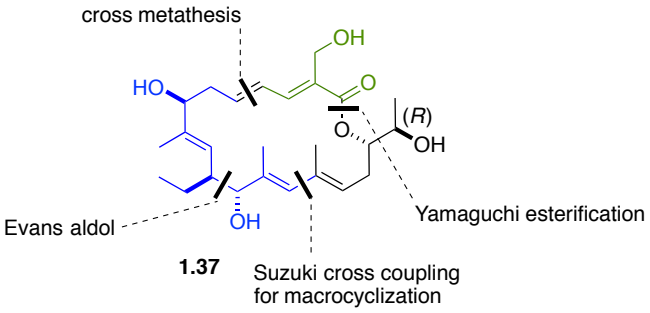
It should be mentioned that Zhu *et al.* first attempted to perform a macrolactonization with the linear precursor **1.36** (Scheme 1.3). Thus, a cross metathesis between **1.33** and **1.34** was performed, which furnished the protected intermediate **1.35** in low yield (*E:Z* selectivity not given). Unfortunately, the deprotection of the carboxylic acid and TBS ether cleavage gave complex mixtures and the product **1.36** could not be isolated.



Scheme 1.3: Zhu`s macrolactionization attempt failed due to troublesome hydrolysis of the ester and the TBS silyl ether. a) Hoveyda-Grubbs II (25 mol%), toluene, 100°C, µw, 15 min, 38%.

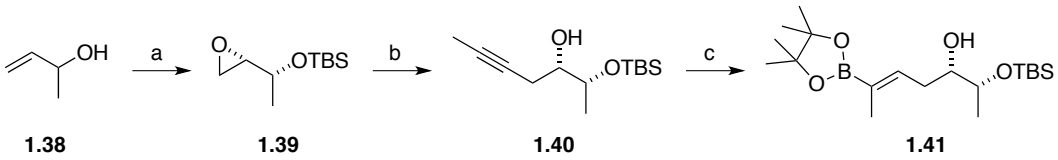
Altmann's Fidaxomicin Aglycon Synthesis

In the approach of Altmann[57] and Glaus the aglycon is built up through an assembly of three fragments *via* successive cross metathesis, Yamaguchi esterification and a Suzuki cross coupling for ring closure (Scheme 1.4).



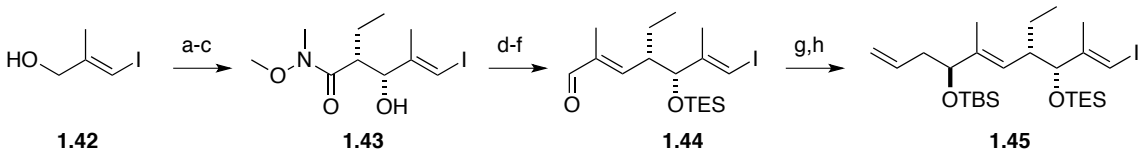
Scheme 1.4: Altmann's approach towards the central aglycon of fidaxomicin.

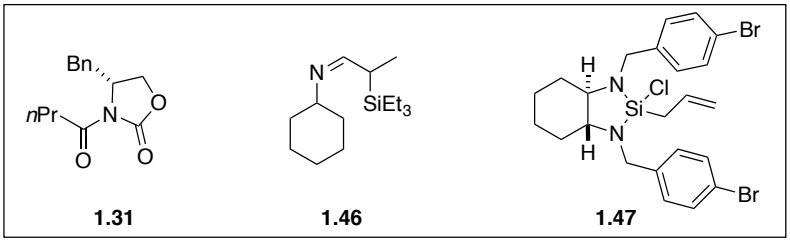
The boronic ester fragment **1.41** was synthesized from the racemic allyl alcohol **1.38**, which was submitted to kinetic resolution using Sharpless epoxidation and *in situ* TBS protection. Opening of the epoxide **1.39** with propyne and *n*BuLi gave **1.40**, further hydroboration furnished the boronic ester **1.41** with high regioselectivity (Scheme 1.5).



Scheme 1.5: a) $Ti(OiPr)_4$, (–)-DIPT, *t*BuOOH (0.45 equiv), m.s. 3Å, CH_2Cl_2, –20°C, 39 h; then TBSCl, imidazole, CH_2Cl_2, –20°C to RT; then RT, 16 h, 21%; b) *n*BuLi, propyne, $BF_3{\cdot}OEt_2$, THF, –78°C, 3.5 h, 75%; c) bis(pinacolato)diboron, CuCl (5 mol%), KO*t*Bu (20 mol%), PPh_3 (6 mol%), THF/MeOH, RT, 3.5 h, 79%.

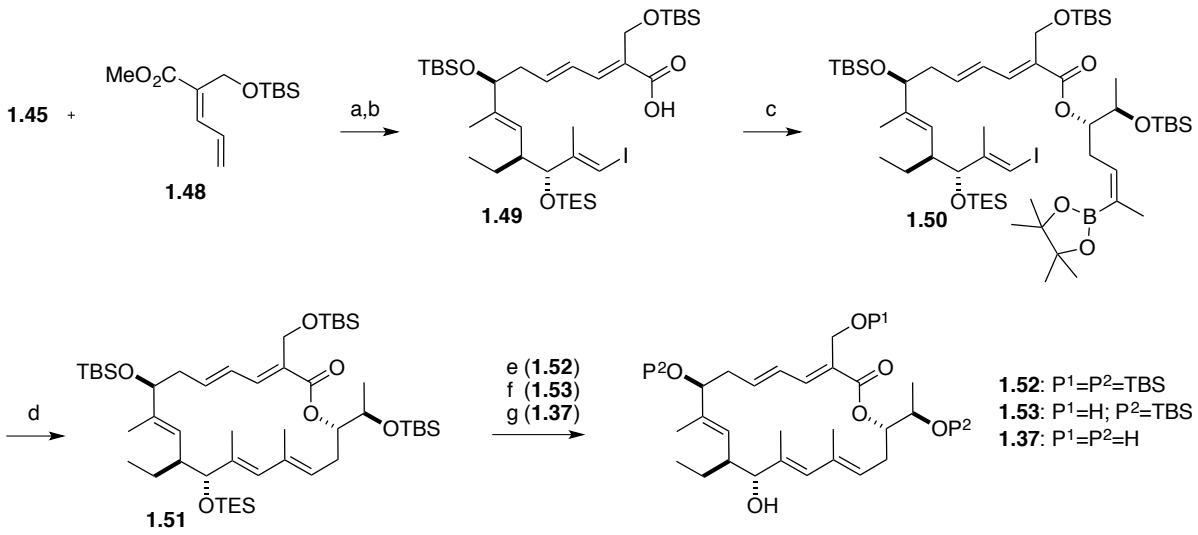
The western part was synthesized from the known alcohol **1.42** (Scheme 1.6), which was transformed to the aldehyde by allylic oxidation with manganese dioxide. Then, an Evans aldol reaction with **1.31** furnished the *syn*-product with high diastereoselectivity (20:1), cleavage of the auxiliary with MeONHMe·HCl gave the corresponding Weinreb amide **1.43**. After TES-protection and direct reduction to the aldehyde, a Peterson olefination with imine **1.46** was performed to give the enal **1.44** with excellent *E:Z*-selectivity (20:1). The aldehyde **1.44** was stereoselectively allylated using Leighton's silacycle **1.47,** and the resulting secondary alcohol was protected as TBS silyl ether to give the fragment **1.45**.





Scheme 1.6: a) MnO_2, m.s. 3Å, CH_2Cl_2, RT, 75 min; b) **1.31**, *n*Bu_2BOTf, Et_3N, CH_2Cl_2, –78°C, 2.5 h; then 0°C, 1.5 h; then pH 7 buffer, MeOH, H_2O_2, 0 °C, 1 h ; c) MeONHMe·HCl, $AlMe_3$, THF, 0 °C, 2 h, 53% (3 steps); d) TESCl, imid, CH_2Cl_2, RT, 30 min, 94%; e) DIBAL-H, THF, –30°C, 1 h; then –20°C, 1 h, 94%; f) **1.46**, *s*BuLi, THF, –20°C, 2 h; then PhSH, –20°C, 2 h; then sat. aq. NaH_2PO_4, RT, 4 h, *E:Z* = 20:1, 81%; g) **1.47**, $Sc(OTf)_3$, CH_2Cl_2, –35°C to –20°C, 30 min; then –20°C, 2.5 h; then 1M HCl, RT, 7 min, 83%, *d.r.* > 20:1; h) TBSCl, imid, CH_2Cl_2, RT, 22 h, 93%.

With all the fragments in hands, the cross metathesis of the terminal olefin **1.45** with the dienoate **1.48** (synthesis not shown) was performed (Scheme 1.7). The cross metathesis was highly challenging, especially homo-dimerization of the dienoate was a problem. However, Altmann and Glaus managed to reach a good yield and high *E:Z*-selectivity (6.7:1) with the Hoveyda-Grubbs II catalyst.



Scheme 1.7: a) Hoveyda–Grubbs II (15 mol%), EtOAc, RT, 3.5 h, 56%, *E:Z* 6.7:1; b) LiOH, *t*BuOH/H_2O 3:1, 33°C, 48 h, 69%; c) **1.41**, 2,4,6-$Cl_3H_2C_6COCl$, Et_3N, DMAP, toluene, RT, 5.5 h, 81%; d) [$Pd(PPh_3)_4$] (20 mol%), TlOEt, THF/H_2O 3:1, RT, 25 min, 73%; e) $Et_3N{\cdot}3HF$, CH_3CN/THF 7:3, –15°C, 4 h; then –25°C, 15 h; then –15°C, 7 h, 70%; f) $Et_3N{\cdot}3HF$, CH_3CN/THF 6:4, –15°C to 5°C, 2 h; then 5°C, 5 h; then 15°C, 27 h, 54%; g) $Et_3N{\cdot}3HF$, CH_3CN, 0°C to RT, 1 h; then RT, 8 h; then 50°C, 86 h, 47%.

Hydrolysis of the methylester afforded the carboxylic acid precursor **1.49** for the subsequent Yamaguchi esterification with the boronic ester **1.41**. A rapid intramolecular Suzuki coupling of the resulting compound **1.50** affected the macrocyclization to give the fully protected macrolide **1.51** in 73% yield. Conveniently, silyl ether cleavage at different temperatures gave access to the differently protected macrolides **1.52**, **1.53** and **1.37**. The TES group was found to be the most labile followed by the primary and finally the two secondary TBS ethers. This highly efficient and convergent approach furnished the fully deprotected aglycon **1.37** in 13 steps (longest linear sequence).

1.2 Goal of the Study and Retrosynthetic Considerations

The aim of this project was to develop a total synthesis of fidaxomicin, in order to enable the synthesis of a second-generation antibiotic, based on the fidaxomicin lead structure, with improved pharmacokinetics and increased or maintained biological activity against nowadays multidrug resistant pathogens. This shall be reached either by semisynthetic or fully synthetic means. By the total synthesis of the antibiotic, insights into the chemistry of fidaxomicin should be gained. In reference to diversified fully synthetic analogues we aimed for a total synthesis, which a) is highly convergent, b) allows a flexible assembly and c) is easily modifiable at a late stage.

The total synthesis of fidaxomicin should derive from four main fragments: 1) the central polyketide macrolide, 2) the rare carbohydrate novioside, 3) the 2*O*-methyl rhamnoside and 4) the resorcylate fragment (Figure 1.17). Considering the protecting group-strategy, we aimed for orthogonally and easily cleavable hydroxyl-masks. Thus, we planned to protect the alcohols on the core macrolide and the rhamnoside C3 alcohol as the TBS ether (Figure 1.17). A cyclic carbonate-protecting group seemed to be a convenient protecting group of the *cis*-diol in the novioside portion. Importantly, the electron-withdrawing nature of the carbonate supports the selectivity of the β-noviosylation (Chapter 1.6.4). For the phenols, we chose an allyl ether protection since it offers mild cleavage conditions. In this protecting group-strategy the different groups are all orthogonal to each other allowing for a high flexibility in the end-game of the synthesis. To satisfy the challenges of the total synthesis of the antibiotic fidaxomicin we decided to share the tasks between Dr. Hideki Miyatake Ondozabal and me. Thus, Dr. Miyatake Ondozabal was approaching the synthesis of the central aglycon, while I was engaged in the synthesis of the carbohydrate moieties, the resorcylate unit, as well as the demanding *cis*-selective rhamnosylation and noviosylation. Since the main focus of my work was on the carbohydrates, our synthesis of the macrolide is not discussed in full detail in this thesis.

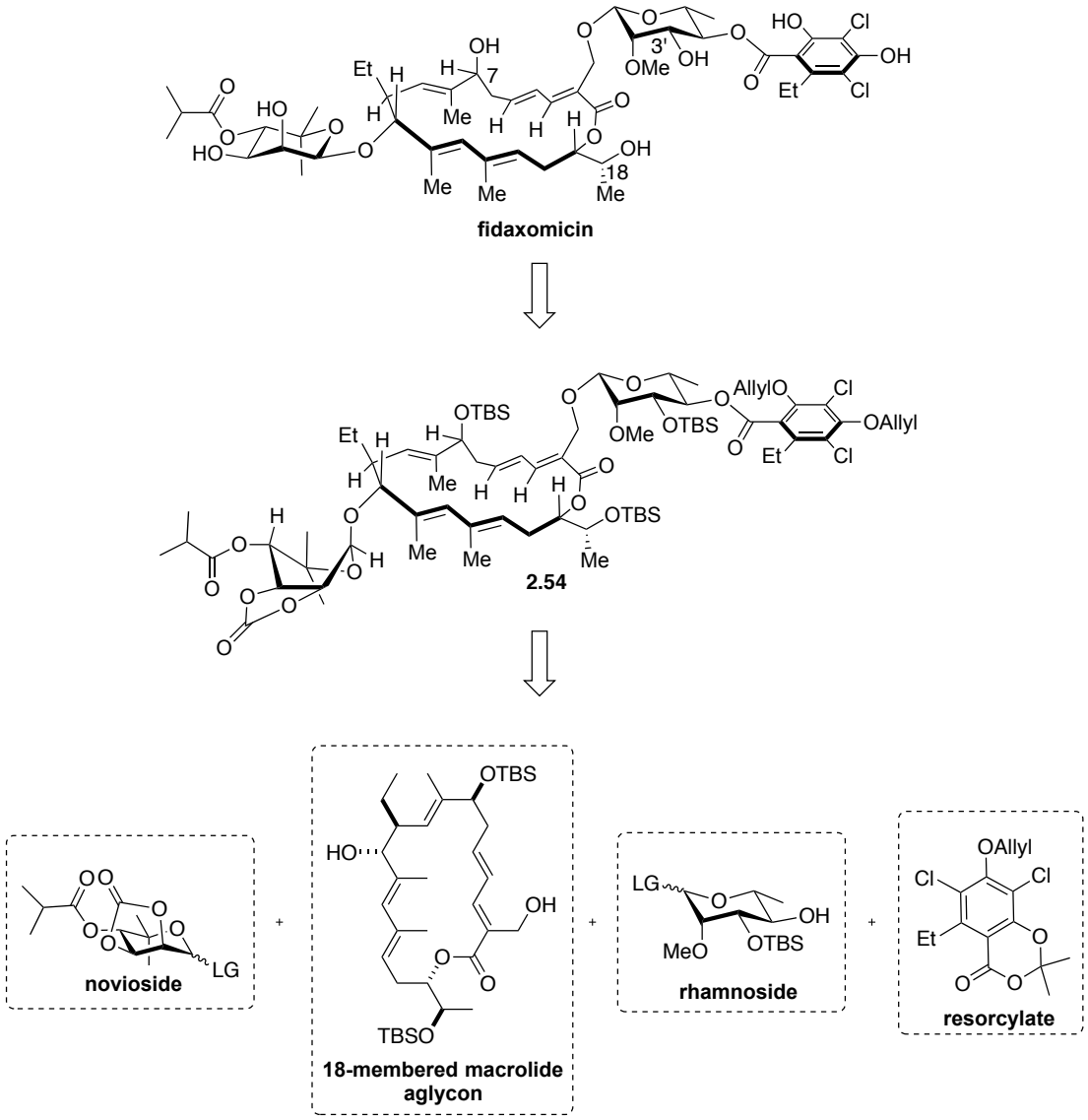


Figure 1.17: Retrosynthetic strategy leading to four main fragments.

1.3 The Synthesis of the Aglycon

As mentioned before, the studies towards the core aglycon in this chapter were mainly conducted by Dr. Hideki Miyatake Ondozabal during his post-doctoral studies in our group. The accomplished synthesis of the macrolide was published[58] in *Angewandte Chemie* back to back with the syntheses of Altmann[57] and Zhu[59]. The key steps of our aglycon **2.53** synthesis were a ring closing metathesis (RCM), a Yamaguchi esterification, a Stille coupling and a vinylogous Mukaiyama aldol reaction (VMAR). Our retrosynthetic analysis led to three main fragments, the iodide **2.45**, the dienoic acid **2.55** and the stannane **2.56**.

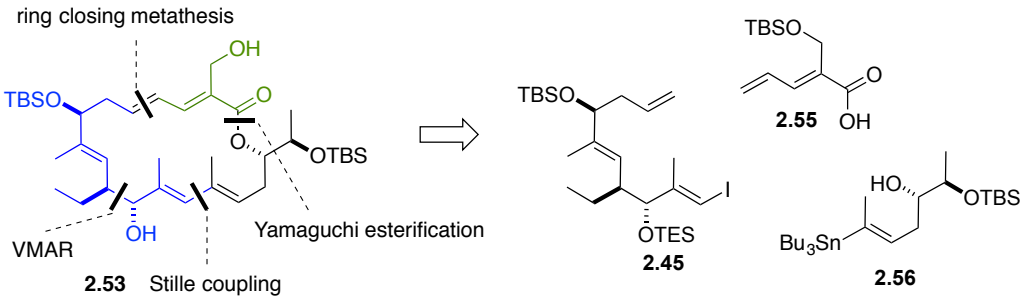


Figure 1.18: Retrosynthetic plan towards the protected aglycon.

The known compound **2.57** (2 steps)[60] served as the starting material for our synthesis of the fragment **2.45**. In the first step, the Mukaiyama aldol precursor **2.58** was synthesized by γ-deprotonation of **2.57** using NaHMDS and trapping of the enolate with TBSCl (Scheme 1.8). A vinylogous Mukaiyama aldol reaction (VMAR) of the silyl ether **2.58** and the aldehyde **2.63**, mediated by $TiCl_4$, gave the *trans*-product **2.59** in high diastereoselectivity (*d.r.* > 20:1).[61] To the best of our knowledge, Kobayashi's VMAR has so far never been conducted with a larger substituent than a methyl in γ-position. Nonetheless, the reaction gave 47% yield of the desired compound **2.59** and a considerable amount of the desilylated starting material **2.57** was recovered (35%). The rationale behind the trans selectivity of the reaction is shown in Figure 1.19.

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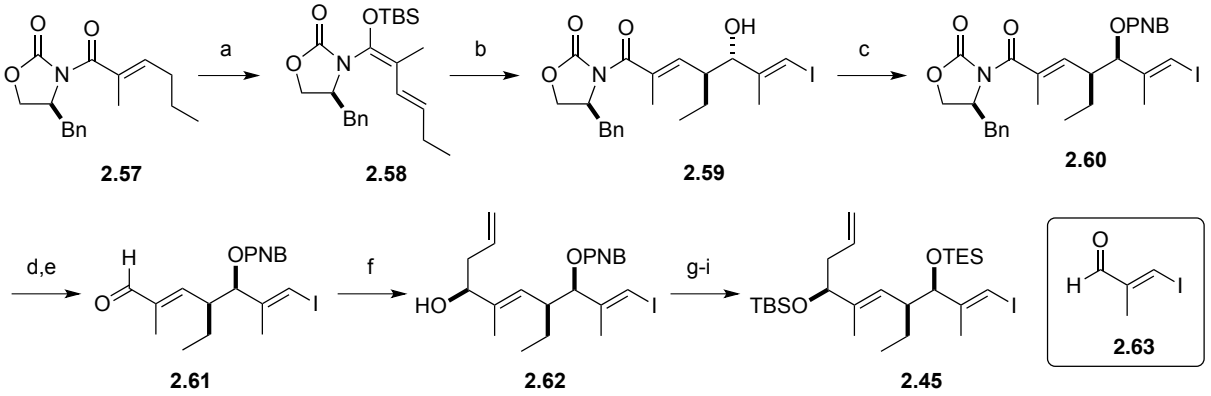
[60] a) K. Ohata, S. Terashima, *Chem. Pharm. Bull.* **2009**, *57*, 920-936; b) D. J. Ager, D. R. Allen, D. R. Schaad, *Synthesis* **1996**, 1283-1285

[61] a) S.-I. Shirokawa, M. Kamiyama, T. Nakamura, M. Okada, A. Nakazaki, A. Seijiro Hosokawa, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605; b) M. Kalesse, M. Cordes, G. Symkenberg, H.-H. Lu, *Nat. Prod. Rep.* **2014**, *31*, 563–594.



Scheme 1.8: Synthesis of the eastern iodide fragment: a) NaHMDS, THF, −78°C then TBSCl, 97%; b) **2.63**, $TiCl_4$, CH_2Cl_2, −78°C to −30°C, 47%, *d.r.* > 20:1; c) *p*-nitrobenzoic acid, DEAD, PPh_3, THF, 0°C, 78%; d) $NaBH_4$, THF/H_2O; e) MnO_2, CH_2Cl_2, 76% (2 steps); f) (−)-Ipc_2B(allyl), Et_2O, −78°C then aq. $NaBO_3$, 70%, *d.r.* = 20:1; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 93%; h) K_2CO_3, MeOH/H_2O; i) TESOTf, 2,6-lutidine, CH_2Cl_2, 95% (2 steps).

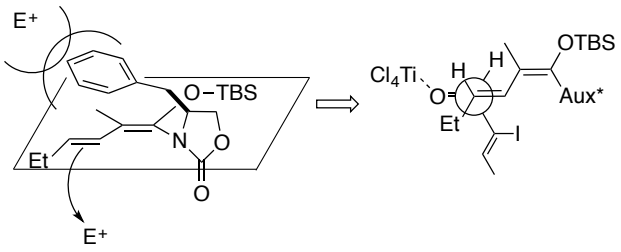


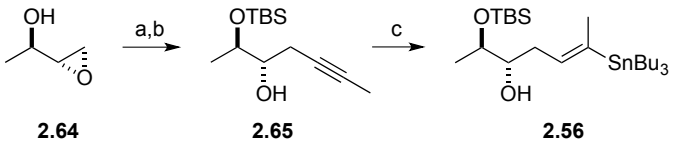
Figure 1.19: Stereochemical rational for the vinylougous Mukaiyama aldol reaction.

The required *syn*-product **2.60** was achieved by a Mitsunobu inversion under standard conditions using *para*-nitrobenzoic acid as nucleophile (Scheme 1.8). Cleavage of the Evans auxiliary was performed selectively over the PNB-ester using $NaBH_4$ and the resulting primary allyl alcohol was oxidized successively with MnO_2 to give aldehyde **2.61**. A Brown allylation was chosen to introduce the last stereocenter of this fragment, which gave good yield and high diastereoselectivity (70%, *d.r.* = 20:1). The resulting secondary alcohol was protected as the TBS-ether using TBSOTf and lutidine with good yield (93%). Since, the Stille-coupling with benzoyl ester **2.62** was not successful, a protecting group swap from the ester to the triethylsilyl ether was performed to give the final fragment **2.45**.

The stannane fragment **2.56** was synthesized in only three steps, starting from enantiopure epoxide **2.64** (Scheme 1.9).[62] First, the TBS-protecting group was installed, then the epoxide was regioselectively opened with propynyl lithium and $BF_3{\cdot}Et_2O$. Unfortunately, the

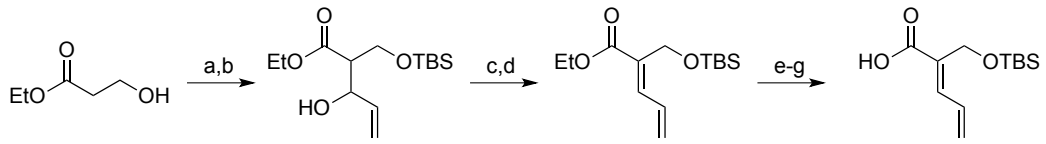
[62] J. D. White, M. Kang, B. G. Sheldon, *Tetrahedron Lett.* **1983**, *24*, 4539–4542.

regioselectivity during the following hydrostannylation of alkyne **2.65** was only poor, thus stannane **2.56** was isolated in moderate yield (51%).



Scheme 1.9: Synthesis of the stannane fragment: a) TBSCl, imid, CH_2Cl_2, 93%; b) propyne, *n*BuLi, $BF_3{\cdot}Et_2O$, THF, −78°C to 0°C, 90%; c) $Pd(OAc)_2$, PCy_3, Bu_3SnH, hexane, 51%.

The third and final fragment, the dienoic acid **2.55**, was synthesized from the commercially available β-hydroxy propanoate **2.66** (Scheme 1.10). An aldol reaction with acrolein was performed, followed by monoselective silyl ether protection of the primary alcohol mediated by dimethyltin chloride, to furnish the allylic alcohol **2.67** in 75% yield over two steps. Next, acylation and DBU induced elimination gave the dienoate **2.68** with good *E:Z*-selectivity (5.5:1). As the ester hydrolysis under standard conditions (LiOH, NaOH) was troublesome, mainly due to silyl ether cleavage, a reduction-oxidation sequence was performed to access the final building block **2.55** in 70% yield.

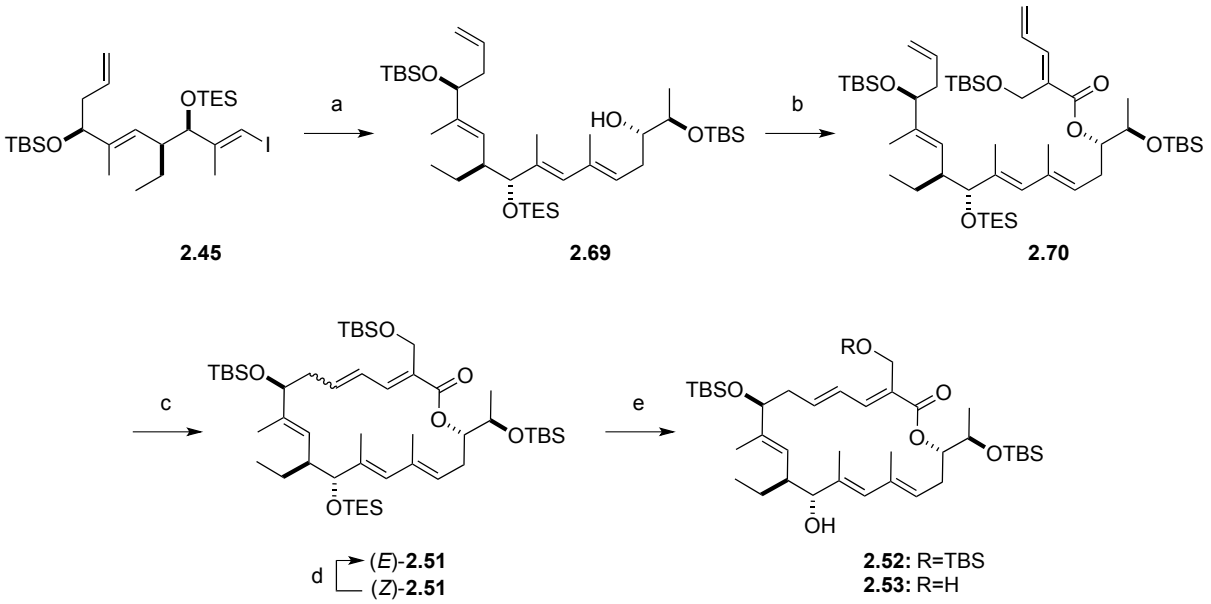


Scheme 1.10: Synthesis of the dienoate: a) LDA, THF, −78°C then acrolein, −78°C; b) Me_2SnCl_2 (10 mol%), TBSCl, Et_3N, 75% (2 steps); c) Ac_2O, Et_3N, DMAP, CH_2Cl_2; d) DBU, CH_2Cl_2, 72% (2 steps), *E*:*Z* = 5.5:1; e) DIBAL-H, CH_2Cl_2, −10°C; f) MnO_2, CH_2Cl_2; g) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 70% (3 steps).

As all the required building blocks have been synthesized, we moved on to their assembly (Scheme 1.11). The Stille coupling between the stannane **2.56** and iodide **2.45** was performed first. As expected, the reaction was exceptionally challenging due to the bulky nature of the two fragments. Nevertheless, we found that Fürstner's conditions[63] using thiophene-2-carboxylate Cu(TC), tetrabutylammonium diphenylphosphonate and $Pd(PPh_3)_4$ gave the diene **2.69** in good yield (77%). The secondary alcohol **2.69** was then condensed with dienoic acid **2.55** using Yamaguchi esterification conditions to furnish the linear compound **2.70**. Ring

[63] A. Fürstner, C. Nevado, M. Tremblay, C. Chevrier, F. Teplý, C. Aïssa, M. Waser, *Angew. Chem. Int. Ed.* **2006**, *45*, 5837-5842.

closing metathesis between the terminal olefins of **2.70** was conducted with the second generation Grubbs catalyst. This furnished macrocycle **2.51** smoothly even at room temperature, although only the *Z* isomer was formed in this case. By increasing the temperature, the *E*:*Z* ratio could be optimized in favour of the *E*-isomer (40°C, 2:3; 100°C, 2:1). Further *E*-macrolide **2.51** was obtained by recycling of (*Z*)-**2.51**. In this way, after one cycle a yield of 80% of the desired fully protected fidaxomicin aglycon **2.51** was reached. The final task was the cleavage of the primary *tert*-butyl dimethysilyl ether and the triethylsilyl ether. Thus the macrolide **2.51** was treated with $3HF \cdot Et_3N$ at room temperature. To avoid over-deprotection, the reaction was stopped after a certain time to isolate the desired aglycon **2.53** in 65% and the mono deprotected macrolide **2.52** in 35% yield.



Scheme 1.11: a) **2.56**, CuTC, $[Pd(PPh_3)_4]$, $[Bu_4N]^+[Ph_2PO_2]^-$, DMF, 77%; b) **2.55**, $Cl_3C_6H_2COCl$, Et_3N, DMAP, toluene, 86%; c) Grubbs cat. II (15 mol%), toluene, 40°C (μw), 10 min, *E*:*Z* = 2:3, then 100°C, 18 h, *E*:*Z* = 2:1, 90%; d) Grubbs cat. II (15 mol%), toluene, 100°C, 18 h, *E*:*Z* = 2:1, 92%; e) $Et_3N \cdot 3HF$, THF/MeCN 1:1, 0°C to 23°C, **2.53**:65%, **2.52**:32%.

In this chapter the synthesis of the protected fidaxomicin aglycon **2.51** in a highly convergent fashion from three main fragments was described. The longest linear sequence of the synthesis from compound **2.57** was only 14 steps. The aglycon **2.53** serves as the appropriate precursor for the total synthesis of the glycosylated fidaxomicin.

1.4 Synthesis of the D-Novioside – an Unusual Carbohydrate

1.4.1 Occurrence and Previous Synthetic Contribution

Fidaxomicin and the related natural products bear a β-linked D-(–)-novioside fragment, which is unique in nature (Figure 1.20). So far, the glycosylated macrolide is the only known natural source of this enantiomer. Similarly, the L-(+)-antipode is also only sparely occurring in natural products. The family of the aminocoumarins (e.g. novobiocin, clorobiocin, coumermycin A1, coumabiocin A) are the only natural products incorporating the L-(+)-novioside, which is exclusively α-linked to a coumarine system and all bear a methoxy function at C4 (Figure 1.20). Novobiocin, clorobiocin and coumermycin A1 are potent bacterial DNA gyrase inhibitors of the type II topoisomerase.[64] Special interest gained novobiocin, which was available for a short time as a broad-spectrum antibiotic in combination with tetracycline under the tradename Albamycin T.[65] Further it was used in anticancer therapy,[66] and caught attention as an effective compound for MRSA treatment.[67]

To the best of our knowledge, eleven different synthetic studies towards the noviose can be found in literature. Most of them are targeting the 4-*O*-methyl L-(+)-novioside, only three reports furnished the 4-*O*-methyl D-(–)-novioside. Except for one publication,[68] the entire published syntheses target the methylated noviose, and generally the alkyl substituent is introduced in an early step. In the following, I want to discuss the key features of the reported novioside syntheses in chronological order.

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64 a) D. C. Hooper, J. S. Wolfson, G. L. McHugh, M. B. Winters, M. N. Swartz, Antimicrob. Agent. Chemother. **1982**, 22, 662–671; b) R. J. Lewis, O. M. P. Singh, S. V. C, T. Skarzynski, A. Maxwell, A. J. Wonacott, D. B. Wigley, *EMBO J* **1996**, 15, 1412.

65 Canadian Medical Association Journal **1960**, 82, 30.

66 M. V. Blagosklonny, *Leukemia* **2002**, *16*, 455–462.

67 T. J. Walsh, H. C. Standiford, A. C. Reboli, J. F. John, M. E. Mulligan, B. S. Ribner, J. Z. Montgomerie, M. B. Goetz, C. G. Mayhall, D. Rimland, *Antimicrob. Agent. Chemother.* **1993**, *37*, 1334–1342.

68 A. Klemer, M. Waldmann, *Liebigs Ann. Chem.* **1986**, *2*, 221–406.

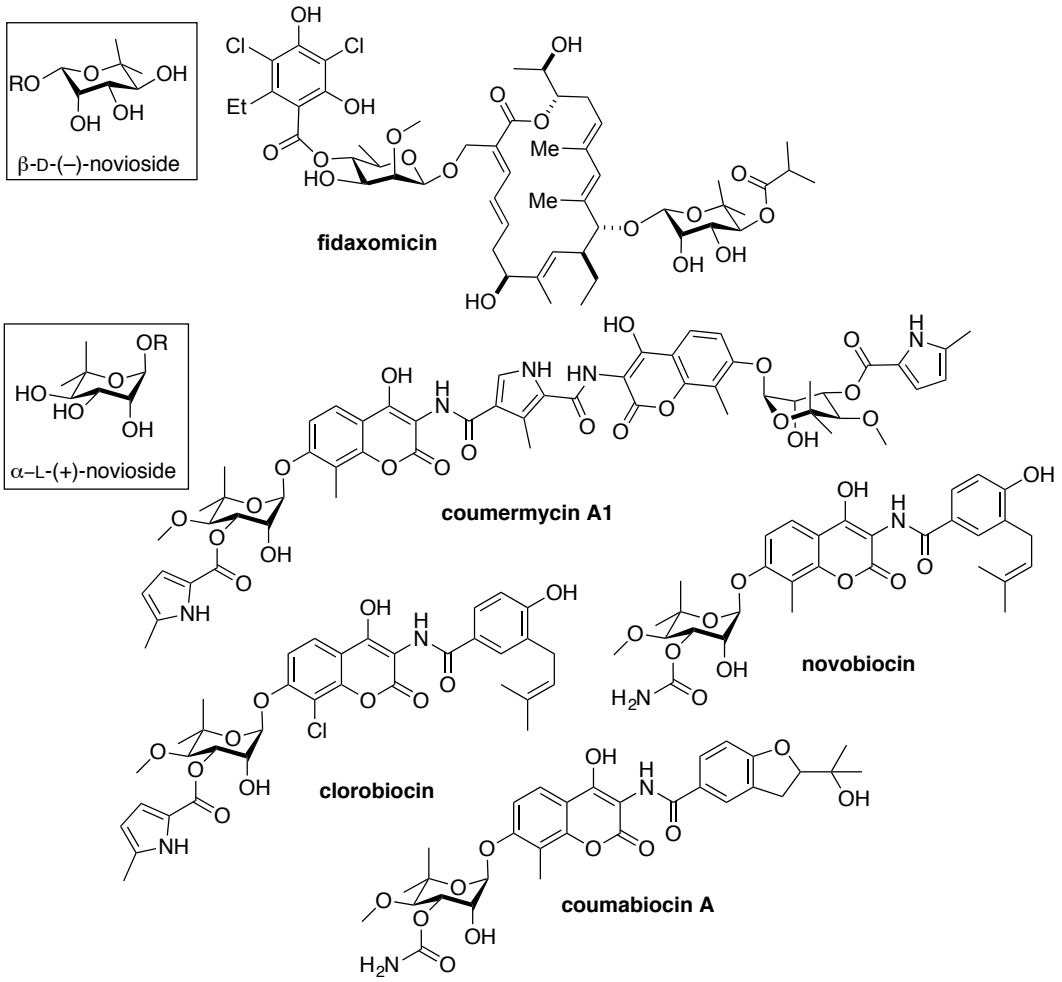
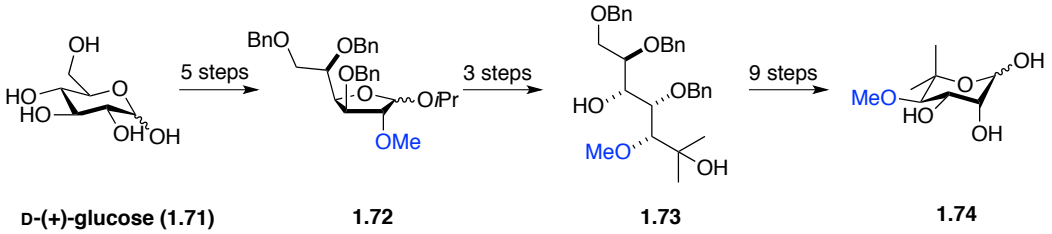


Figure 1.20: The aminocoumarins and the fidaxomicin family constitute the two only natural sources of the carbohydrate noviose.

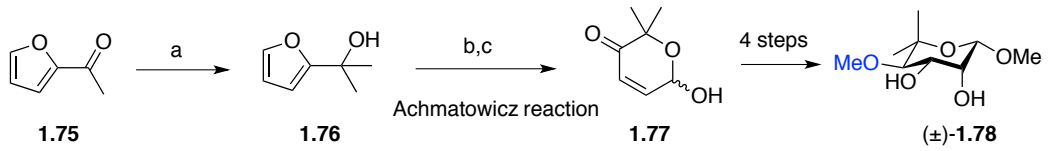
The earliest synthesis of the noviose dates back to 1964.[69] Spiegelberg's approach commenced with glucose **1.71**, which was transformed to the glucofuranose **1.72** having the methoxy-function already installed. Hydrolysis and oxidation at the anomeric position served the lactone, which was methylated twice using methyl Grignard to give the linear intermediate **1.73**. In the last nine steps elaborate protection/deprotections, an oxidative cleavage using $Pb(OAc)_4$ and a base catalysed epimerization at C3 were carried out to furnish the noviose **1.74**.

[69] J. Kiss, H. Spiegelberg, *Helv. Chim. Acta* **1964**, *47*, 398–407.



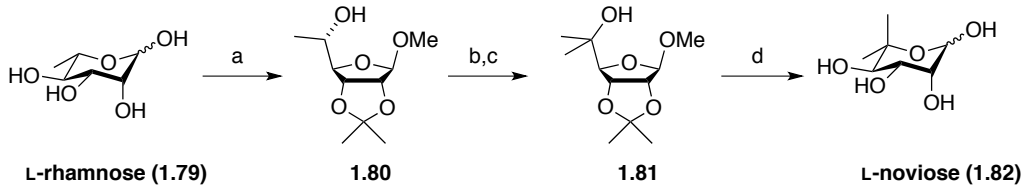
Scheme 1.12: The first noviose synthesis by Spiegelberg *et al.* in 1964 commencing from glucose.[69]

In 1975 Achmatowicz and co-workers[70] reported the synthesis of the racemic 4-*O*-methyl β-novioside **1.78** from 2-acetylfuran **1.75** (Scheme 1.13). Key to the synthesis is a ring expansion – nowadays referred as Achmatowicz reaction – which transforms the furfuryl alcohol **1.76** into the dihydropyran **1.77**. Subsequent insertion of the 4-*O*-methyl group and a dihydroxylation of the corresponding 1,4-trans intermediate gave the desired (±)-novioside **1.78** in total seven steps.



Scheme 1.13: Achmatowicz's synthesis of the β-D,L-novioside.[70] a) MeMgBr, Et_2O; b) Br_2, MeOH, Et_2O, –35°C, 97%; c) H_2SO_4 1% aq., 2 h, 98%.

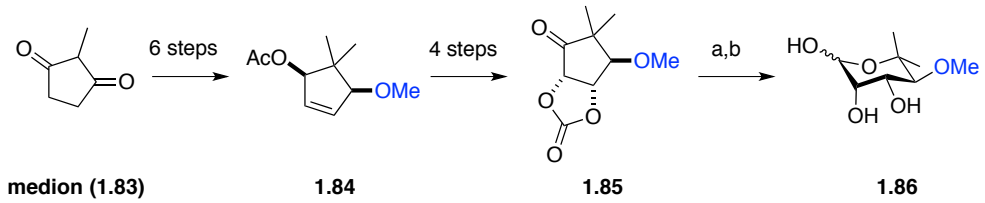
Up to date, the only synthesis of the unsubstituted L-noviose **1.82** was reported by Klemer in 1986 (Scheme 1.14).[68] They started with the natural L-rhamnose **1.79**, which was isomerized to the furanoside **1.80**. The C5 hydroxy group was then oxidized and reacted with methyl Grignard to give the novio-furanoside **1.81**. Aqueous acidic hydrolysis then gave the desired L-noviose. This protocol is the shortest (4 steps) and highest yielding (76% over all) reported in literature.



Scheme 1.14: Synthesis of the L-noviose by Klemer *et al.* a) MeOH, 2,2-DMP, *p*TsOH, 65°C, 8 h, 89%; b) CrO_3, py, CH_2Cl_2, 94%; c) MeMgI, Et_2O, 35°C, 95%; d) H_2SO_4 0.5 M aq., 80°C, 2 h, 95%.

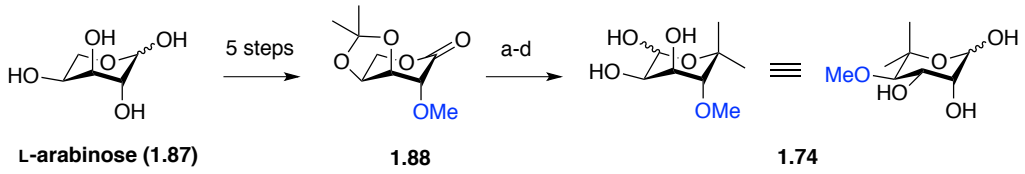
[70] O. Achmatowicz Jr., G. Grynkiewicz, B. Szechner, *Tetrahedron* **1976**, *32*, 1051–1054.

Kreiser et al. were the first to describe a stereoselective total synthesis of the 4*O*-methyl-D-noviose **1.86** (Scheme 1.15).[71] Starting from readily available medion (**1.83**) a desymmetrization approach with lipase gave the enantiopure precursor **1.84** in six steps. Then dihydroxylation, acetate hydrolysis, carbonate protection and oxidation served the ketone **1.85**. To finalize the synthesis a Baeyer-Villiger oxidation to the lactone and a reduction using DIBAL-H was conducted.



Scheme 1.15: The first stereoselective synthesis of D-noviose. a) *m*CPBA, CH_2Cl_2, 3 d, RT, 74% b) DIBAL-H, CH_2Cl_2, –78°C, 78%.

The synthesis of Musicki[72] and co-workers started with L-arabinose **1.87** as the chiral pool precursor and followed the strategy of Spiegelberg (*vide supra*). Their route also goes *via* oxidation of the anomeric position to the lactone **1.88**. Then dimethylation using Grignard conditions gave the linear diol, which is then oxidized and deprotected to give the desired carbohydrate **1.74**.



Scheme 1.16: Total synthesis of the 4*O*-methyl-L-noviose by Musicki.[72] a) MeMgBr, THF, 0°C, 86%; (b) PCC, CH_2C1_2, RT, 66%; (c) DIBAL-H, THF, 0°C, 63%; (d) H_2SO_4 aq., 65°C, 95%.

D-Ribose **1.89** served as precursor in the synthesis by the group of Wilson (Scheme 1.17).[73] In the first four steps the C5 methyl groups were installed. Hydrolysis of the anomeric position was undertaken to reductively open up the ring using LAH and protection of the

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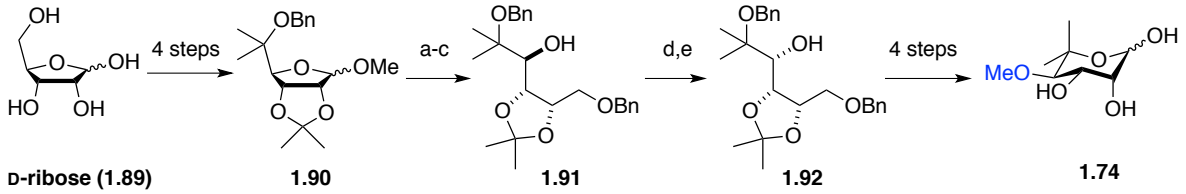
[71] a) W. M. Pankau, W. Kreiser, *Helv. Chim. Acta* **1998**, *81*, 1997–2004; b) W. M. Pankau, W. Kreiser, *Tetrahedron Lett.* **1998**, *39*, 2089–2090; c) W. Kreiser, A. Wiggermann, A. Krief, D. Swinnen, *Tetrahedron Lett.* **1996**, *37*, 7119-7122.

[72] P. Laurin, D. Ferroud, M. Klich, C. Dupuis-Hamelin, P. Mauvais, P. Lassaigne, A. Bonnefoy, B. Musicki, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2079–2084.

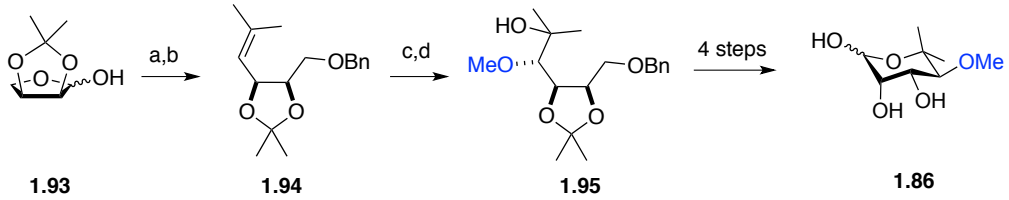
[73] D. W. Gammon, R. Hunter, S. Wilson, *Tetrahedron Lett.* **2002**, *43*, 3141–3144.

resulting primary alchohol to give **1.91**. An oxidation/reduction sequence of the C4 hydroxy group was performed to interconvert the stereogenic center and furnish **1.92**. In the final steps, the methoxy group at C4 was introduced and the pyranose **1.74** was formed by cleavage of the benzyl groups and reoxidation of the C1-carbon.



Scheme 1.17: Wilson's synthesis of 4*O*-methyl-L-noviose: a) i. HCl 1M aq., dioxane, 60°C; ii. acetone, H_2SO_4, 0°C, 62%; b) LAH, THF, 0°C, 84%; c) NaH, benzyl bromide, THF, RT, 98%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 85%; e) K-selectride®, toluene, 0°C to RT, 72%.

Another synthesis serving 4*O*-methyl-D-noviose **1.86**, *via* a similar intermediate **1.95** as Wilson **1.92**, was reported by Blagg *et al*. (Scheme 1.18). Here, the previously reported furanose **1.93** served as the starting material to reach the olefin **1.94** by a Wittig reaction. Key to their approach was the dihydroxylation of the olefin to give the right diastereomer **1.95** in modest selectivity (*d.r.* = 2:1). Further standard transformations accomplished the synthesis to obtain the D-noviose **1.86**.[74]



Scheme 1.18: Synthesis of 4*O*-methyl-D-noviose by Blagg *et al.*[74] a) $Ph_3P^+CH(CH_3)_2$, *n*BuLi, 91%; b) NaH, BnBr, 95%; c) OsO_4, NMO, 84% *d.r.*=2:1; d) KO*t*Bu, MeI, 86%.

The starting point of the synthesis by Reddy *et al.*[75] was the olefin **1.96** (Scheme 1.19). Key transformations in their synthesis were a RCM, a stereoselective dihydroxylation and a Baeyer-Villiger oxidation to access the target molecule **1.86** in overall 14 steps. This synthesis was later further developed, such that both enantiomers could be prepared using the same approach.[75b]

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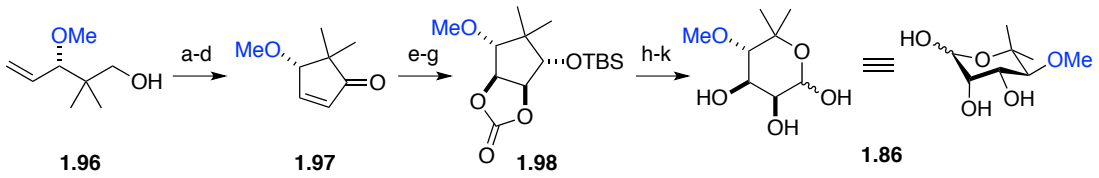
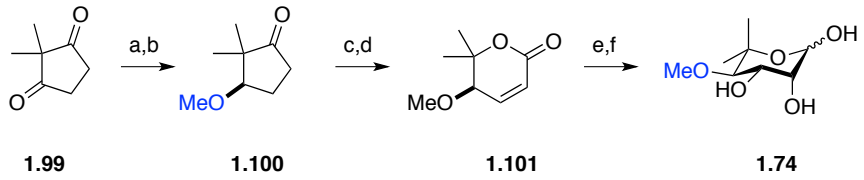
[74] X. M. Yu, G. Shen, B. S. J. Blagg, *J. Org. Chem.* **2004**, *69*, 7375–7378.

[75] a) D. S. Reddy, G. Srinivas, B. M. Rajesh, M. Kannan, T. V. Rajale, J. Iqbal, *Tetrahedron Lett.* **2006**, *47*, 6373–6375; b) B. M. Rajesh, M. V. Shinde, M. Kannan, G. Srinivas, J. Iqbal, D. S. Reddy, *RSC Adv.* **2013**, *3*, 20291–20297.



Scheme 1.19: Synthesis of 4*O*-methyl-D-noviose by Reddy and co-workers. a) $(COCl)_2$, DMSO, Et_3N, –78°C, 96%; b) $CH_2CHMgBr$, 0°C, 82%; c) Grubb's catalyst (5 mol%), RT, 91%; d) Jones' oxidation, 86%; e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0°C, 96%; f) TBSCl, imid, 0°C, 83%; f) OsO_4, NMO, acetone, H_2O, *t*BuOH, rt, 89%; g) triphosgene, 0°C to RT, 92%; h) TBAF, THF, 94%; i) Swern or PDC; j) *m*CPBA, CH_2Cl_2, 3 d, RT, 90% (2 steps); k) DIBAL-H, CH_2Cl_2, –78 °C, 60%.

The most efficient synthesis of the novioside **1.74** starting from achiral starting material was reported by Hanessian in 2008.[76] Within only six steps from **1.99**, the 4*O*-methyl-L-noviose **1.74** was reached using a CBS-reduction-desymmetrization approach combined with an established Baeyer-Villiger, dihydroxylation end-game (Scheme 1.20). Thereby, the C4 methoxy group is installed at the very beginning of the synthesis.



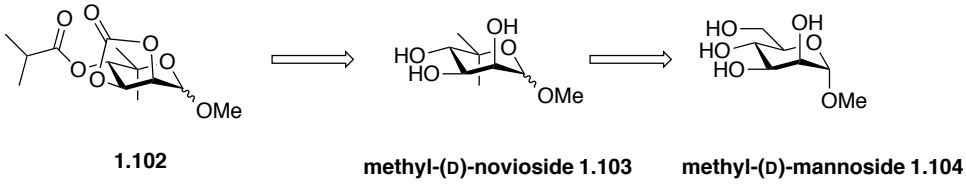
Scheme 1.20: Synthesis of Hanessian and co-workers.[76] a) CBS, borane-*N*,*N*-diethylaniline complex, THF, 0°C, 78%, 96% *ee*; b) MeI, Ag_2O, reflux, 5 d, 88%, c) *m*CPBA, $Sc(OTf)_3$ (5 mol%), CH_2Cl_2, 99%; d) LHMDS, TMSCl, THF, –78°C, then $Pd(OAc)_2$, MeCN, 0°C to RT, 72%; e) DIBAL-H, CH_2Cl_2, –78°C; f) OsO_4, NMO, H_2O, acetone, 0°C, 55% (2 steps).

1.4.2 Novel Synthetic Route Towards D-Novioside

For our total synthesis of fidaxomicin and in respect to the synthesis of analogues we aimed to synthesize the novioside fragment **1.102** *via* the unsubstituted novioside **1.103** (Scheme 1.21). This approach allows us to the the O4 substituents at a late stage of the synthesis, which is of special interest with regard to the decreased biological activity of fidaxomicin's major metabolite (OP1118) – lacking the isobutyric ester at the noviose. We planned to use the carbonate-protecting group to reach a high degree of S_N2-like character during the glycosylation (*vide infra*). Most of the reported syntheses (Chapter 1.6.4) insert a methoxy group at C4 in an early stage. Unfortunately, these strategies are not only

[76] S. Hanessian, L. Auzzas, *Org. Lett.* **2008**, *10*, 261–264.

incompatible with an ester substituent but also limit the flexibility of the substitution pattern. Furthermore, the rare examples that serve the D-noviose require many synthetic steps. However, the synthesis by Klemer *et al*. would be the most suitable to address our requirements (chapter 1.4.1). For us, a simultaneous synthesis was not possible since the unnatural D-rhamnose is not commercially available. In addition, we aimed for the sake of convenience towards the methyl-novioside **1.103** rather than the noviose. Due to these considerations, we decided to developed a new route towards this unusual carbohydrate. We figured that the natural and commercially readily available D-mannoside **1.104** would be a logical precursor for this purpose as it unites all the required stereochemical information (Scheme 1.21).



1.102 **methyl-(D)-novioside 1.103** **methyl-(D)-mannoside 1.104**

Scheme 1.21: Retrosynthetic plan towards the desired substituted novioside.

Our approach commenced with the transformation of the primary C6-alcohol in **1.104** to the iodide **1.105** under Garegg-Samuelson conditions and protection of the *cis*-diol using 2,2-dimethoxypropan to give the dimethylacetal **1.106**.[77] A Bernet-Vasella fragmentation gave the furanose **1.107**. The procedure we used is a variant of the originally applied condtions.[78] Generally, this reaction needs acidic preactivation of zinc or the addition of TMSCl. also vitamin B_{12} was used as activator.[79] In our case, the addition of NH_4Cl was sufficient to initiate the reaction.

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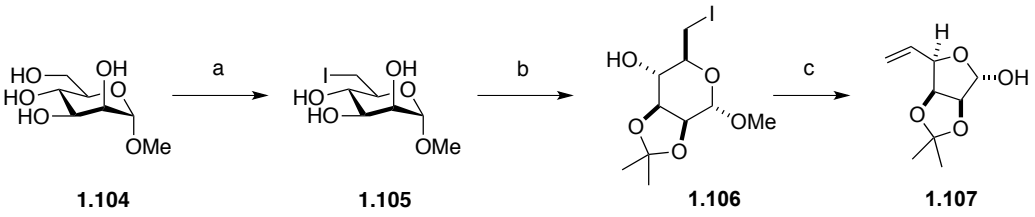
[77] H. Kumamoto, K. Deguchi, T. Wagata, Y. Furuya, *Tetrahedron* **2009**, *65*, 8007-8013.

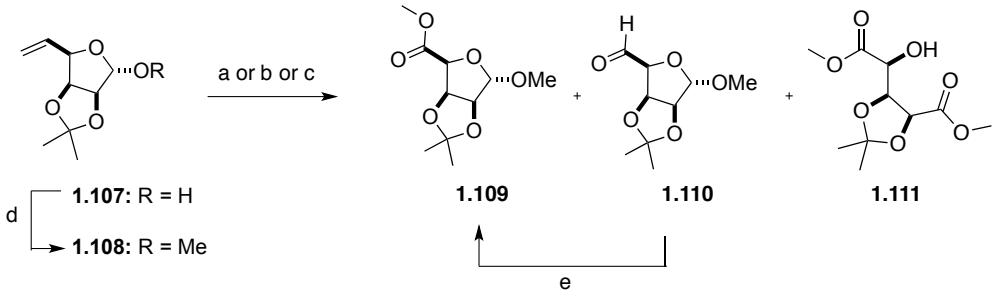
[78] B. Bernet, A. Vasella, *Helv. Chim. Acta* **1979**, *62*, 1990–2016; B. Bernet, A. Vasella, *Helv. Chim. Acta* **1984**, *67*, 1328–1347.

[79] a) P. R. Skaanderup, L. Hyldtoft, R. Madsen, *Chem. Month.* **2002**, *133*, 467–472; b) M. Kleban, U. Kautz, J. Greul, P. Hilgers, R. Kugler, H.-Q. Dong, V. Jäger, *Synthesis* **2000**, *7*, 1027–1033; c) A. Fürstner, H. Weidmann, *J. Org. Chem.* **1989**, *54*, 2307–2311.



Scheme 1.22 Garegg-Samuelson iodination and Bernet-Vasella fragmentation: a) I_2, PPh_3, imid, THF, reflux, 80%; b) 2,2-DMP, TsOH, acetone, RT, 93% (2 steps); c) Zn (10 equiv), NH_4Cl (0.4 equiv), MeOH, 60°C, 91%.

The oxidative cleavage of the terminal olefin was performed by Marshall's ozonolysis in the presence of sodium hydroxide and methanol which gave direct rise to the desired methyl ester (Scheme 1.23).[80] It was important to protect the anomeric position first as the furanoside **1.108** – which has a nice, sweet smell – as otherwise the hemiacetal in **1.107** is oxidized to the methylester **1.111** to some extend. After acetal formation, Marshall's protocol furnished the previously reported[81] methylester **1.109**, along with a small amount of the known corresponding aldehyde **1.110**.[82] Alternatively, simple ozonolysis to the aldehyde followed by bromine-mediated oxidation in methanol gave the ester **1.109** in about the same overall yield (66%). The conditions reported by Borhan and co-workers using oxone in methanol[83] to oxidize aldehydes to esters gave only very poor yield in this case.



Scheme 1.23: Oxidative cleavage of the terminal olefin: a) i. **1.107**, O_3, 2.5M methanolic NaOH, CH_2Cl_2, −78°C; ii. Amberlyst IR120H$^+$, 2,2-DMP, MeOH, 55°C, 30% **1.109**, 10% **1.111**; b) **1.108**, O_3, 2.5M methanolic NaOH, CH_2Cl_2, −78°C, 62% **1.109**; c) **1.108**, O_3, MeOH, CH_2Cl_2, −78°C, then Me_2S, 72% **1.109** d) CSA, 2,2-DMP, MeOH, 55°C, quant; e) Br_2, $NaHCO_3$, MeOH, H_2O, 40°C, 92%.

Treatment of the methylester with methyl Grignard in ether at reflux inserted the C5 methyl groups with quantitative yield. At this point, we crossed the synthesis of the L-noviose by Klemer *et al.*[68] in which the enantiomeric compound was synthesized and then fully

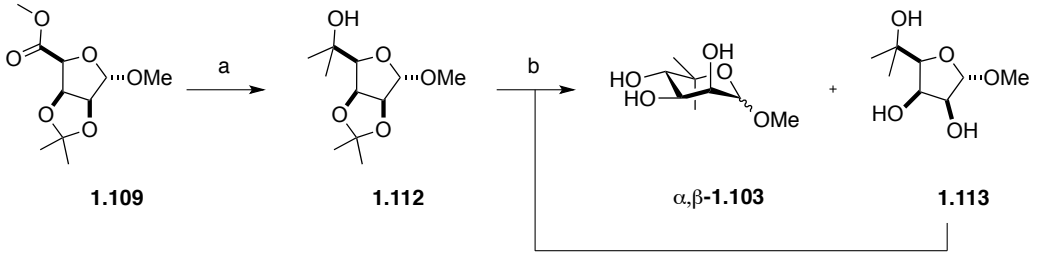
[80] J. A. Marshall, A. W. Garofalo, R. C. Sedrani, *Synlett* **1992**, 643–645.

[81] R. R. Schmidt, P. Hermentin, *Chem. Ber.* **1979**, *112*, 2659–2671.

[82] J. M. J. Tronchet, B. Gentile, A. P. Bonenfant, O. R. Martin, *Helv. Chim. Acta* **1979**, *62*, 696–699.

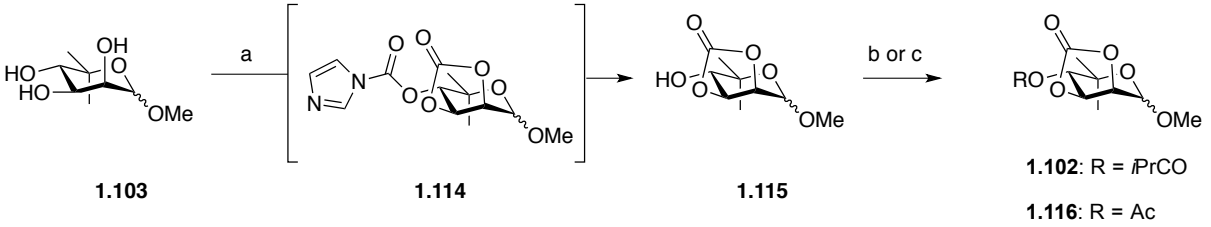
[83] B. R. Travis, M. Sivakumar, G. O. Hollist, B. Borhan, *Org. Lett.* **2003**, *5*, 1031–1034.

hydrolysed and isomerized to the pyranose. In contrast, we aimed to keep the anomeric position protected as the methyl acetal **1.103**. Thus, the hydrolysis of the acetal was performed in presence of methanol. Heating the furanoside **1.112** in methanol and Amberlyst IR120H$^+$ at 50°C for 2 days gave a 2:1 ratio of the pyranoside (60%) to furanoside (30%). This ratio corresponds to the thermodynamic equilibrium and does not change by prolonged reaction time. Hence, we decided to recycle the furanoside **1.113** to increase the output. We then changed to more forcing conditions, in order to lower the reaction time. Treating the tertiary alcohol **1.113** with trifluoroacetic acid in methanol at 100°C in the microwave gave the same 2:1 ratio after 1 h. Recycling of the furanoside **1.113** two times served the desired methyl-D-novioside **1.103** in good yield (81%) as an inseparable anomeric mixture (α:β = 2:1).



Scheme 1.24: C5 Methylation and isomerization to the D-novioside: a) MeMgBr (2.4 equiv), Et_2O, reflux, 99%; b) TFA, MeOH, 100°C (μw), 1 h, 81% (3 cycles), α:β = 2:1.

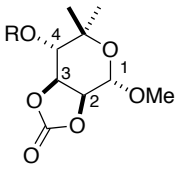
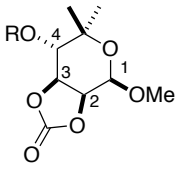
The *cis*-selective protection of the C2,C3-hydroxyl groups was achieved by the addition of 1,1-carbonyldiimidazole (CDI) (Scheme 1.25). In an initial approach we added CDI (freshly recrystallized) portion wise to a solution of **1.103** in DCE at reflux until complete consumption. The crude material was then used directly in the acylation step with isobutyryl chloride to give the desired product **1.102** in 67% yield over the two steps. Unfortunately, the carbonate protection is not easy to control and in certain batches the yield dropped dramatically due to over dosing or under dosing of CDI. We thus tried to improve the protocol. Triphosgene in dichloromethane and pyridine at –78°C to room temperature, gave only poor yield (30%) of the desired carbonate **1.115**. On the other hand, treatment of the novioside **1.103** with an excess of CDI in THF and subsequent hydrolysis of the intermediate **1.114** in aqueous HCl (6M) gave the desired carbonate **1.115** in 88% yield (Scheme 1.25). This procedure is significantly easier to conduct, as tedious reaction control is not required anymore. In regard to the synthesis of analogues, in particular the natural product tiacumicin A, the acetylated novioside equivalent **1.116** was synthesized as well (Scheme 1.25). Acetic anhydride/pyridine furnished the desired product **1.116** in moderate yield.



Scheme 1.25: Carbonate protection and acylation: a) CDI (3.5 equiv), THF, 50°C, 3 h, then HCl 6M aq., RT 1 h, 88%; b) from **1.103,** CDI, DCE, reflux, 3 h; then *i*PrCOCl, Et_3N, CH_2Cl_2, RT 67% **1.102** (2 steps); c) Ac_2O, pyridine, RT, 1 h, 67% **1.116**.

Even though irrelevant to advance further, the anomers were separable by column chromatography on the acetylated stages. The α- and β-epimers were isolated in a 2:1 ratio and the stereochemistry was assigned by NMR (NOESY) and X-ray analysis. The coupling constants and the chemical shifts of the anomers are highly characteristic (Table 1.2). The coupling constants of the α epimers are in agreement with a flattened $^1C_4$ ring conformation according to the Karplus and Bothner-By equation. The signals of the β-novioside do not show distinct coupling patterns and the H2 and H3 signals are superimposed. The most likely explanation for this observation is the slow interconversion of one into another ring conformation, slower than NMR measuring time scale. Thus, a distinct ring conformation can not be assigned to this molecule. Remarkably, the β-H4 (5.8-5.7 ppm) is significantly down field shifted compared with the α-H4 (5.1 ppm). These characteristics simplified the identification of the anomeric ratio in the later noviosylations substantially (chapter 1.6.4).

Table 1.2: ^{1}H-NMR chemical shifts of the α- and β-anomers in $CDCl_3$. d = duplet; dd = duplet of duplet; t = triplet; m = multiplet.

	 α		 β	
	R = *i*PrCO	R = Ac	R = *i*PrCO	R = Ac
H no.	δ_H/ppm, (*J*/Hz)	δ_H/ppm, (*J*/Hz)	δ_H/ppm, (*J*/Hz)	δ_H/ppm, (*J*/Hz)
1	4.85, d (7.7)	4.91, d (3.0)	4.79–4.75, m	4.86–4.82, m
2	4.62, dd (7.8, 2.9)	4.68, dd (7.8, 3.0)	4.73–4.70, m, 2H	4.81–4.74, m, 2H
3	4.72, t (7.7)	4.78, t (7.7)		
4	5.06, d (7.6)	5.11, d (7.7)	5.73–5.66, m	5.80–5.72, m

In addition to the NOESY correlation the relative stereochemistry of the β-novioside **1.102** was confirmed by X-ray crystallographic analysis (Figure 1.21). Remarkably, the compound crystallized in a boat conformation (^{1,4}B), placing the anomeric oxygen in the axial position and allowing the stabilization by the anomeric effect.

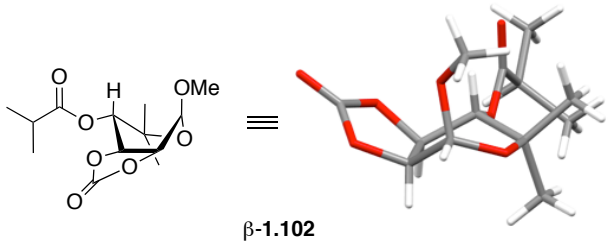


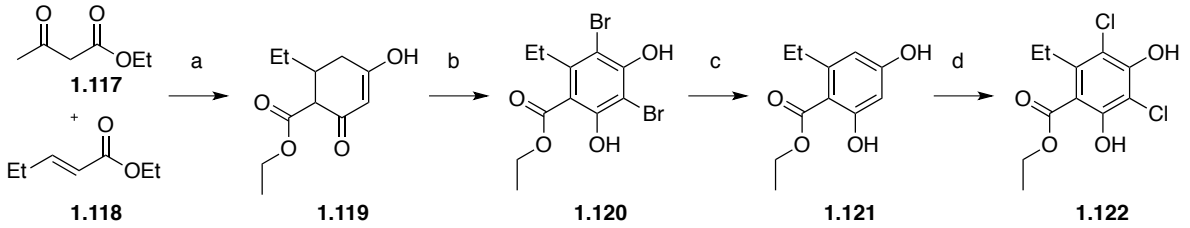
Figure 1.21: X-ray crystallographic analysis of β-novioside. grey = carbon; red = oxygen; white = hydrogen.

To sum up, we developed a new synthetic route to prepare D-novioside **1.103** in only six steps, which is the shortest synthesis reported so far for this enantiomer. Carbonylation and acylation of the carbohydrate gave then the desired precursor **1.102** for the total synthesis of fidaxomicin. The investigations of the β-selective noviosylation are described in Chapter 1.6.4.

1.5 Synthesis of the Resorcylate-Rhamnoside Fragment

1.5.1 Previous Synthetic Contributions and Retrosynthetic Analysis

Fidaxomicin is β-linked to a 2*O*-methyl-D-rhamnoside, which is substituted with a resorcylate unit – sometimes referred as homodichloro orsellinic acid. The previous synthetic studies of these fragments are limited to the separate units. Scharf and co-workers described the preparation of the dichloro resorcylate **1.122** in 1991, in order to verify the structural motif in fidaxomicin. (Scheme 1.26).[84] The synthesis commenced with the intermolecular cyclization of ethyl acetoacetate **1.117** and ethyl pentenoate **1.118** under basic conditions. Then aromatization and bromination of **1.119** in anhydrous acetic acid was conducted to get to the homodibromo-orsellinate **1.120**. To exchange the bromides with chlorides a two-step sequence was conducted. First, a reduction using Raney-Nickel in aqueous sodium hydroxide furnished the homo-orsellinate **1.121** and finally chlorination using sulfuryl chloride in ether gave the resorcylate **1.122**.



Scheme 1.26: The resorcylate synthesis by Scharf:[84] a) Na, EtOH, 94%; b) Br_2, AcOH, 40°C, 16 h, 65%; c) Raney Nickel, NaOH 1M aq., 0–5°C, 4 h, quant; d) SO_2Cl_2, Et_2O, reflux, 10 min, 86%.

Lipták et al. reported so far the only synthesis of the 2*O*-methyl-D-rhamose **1.126** in 1982.[85] They commenced with the acetalization of methyl-D-mannoside **1.104** using α,α-dimethoxy toluene and *para*-toluenesulfonic acid in DMF (Scheme 1.27). Then the regioselective opening of the five-membered acetal **1.123** with LAH and $AlCl_3$ gave the O3-benzylated intermediate, which was methylated at O2 using methyl iodide and Ag_2O to give compound **1.124**. After a regioselective opening of the six-membered acetal using LAH/$AlCl_3$, the free primary alcohol was tosylated and reduced to give the dibenzylated rhamnoside **1.125**. Hydrogenolysis of the benzyl ethers and subsequent acidic hydrolysis furnished the 2*O*-methyl-D-rhamose **1.126** in overall eight steps.

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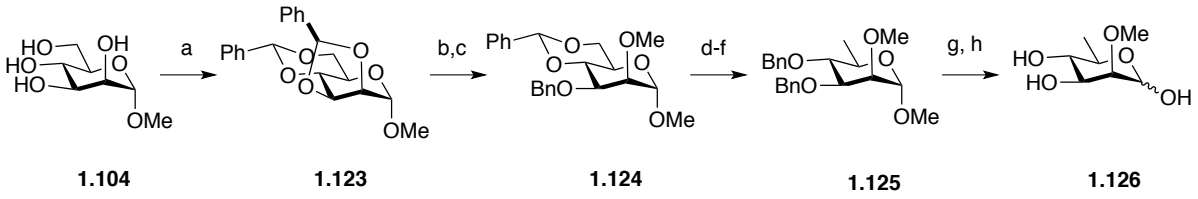
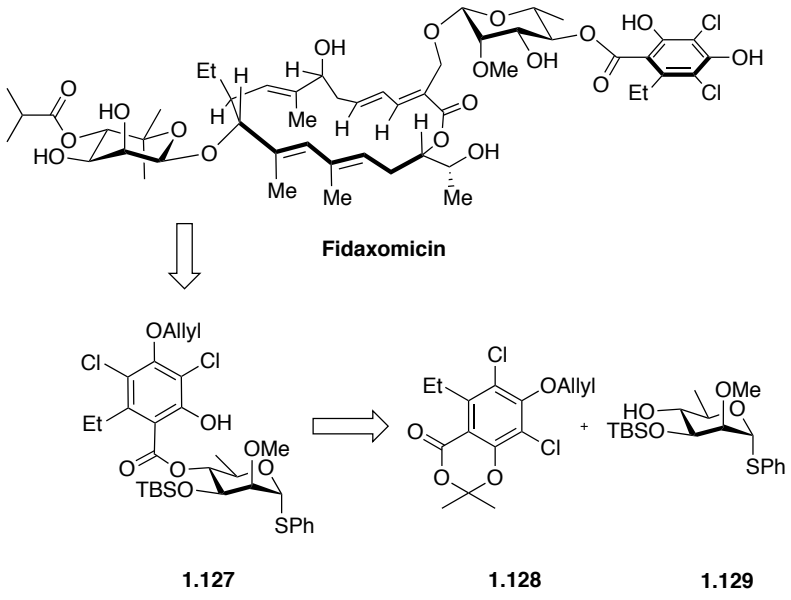
[84] M. Alexy, H.-D. Scharf, *Liebigs Ann. Chem.* **1991**, 1363–1364.

[85] a) A. Lipták, *Carbohydr. Res.* **1982**, *107*, 300–302; b) A. Lipták, I. Czégény, J. Harangi, P. Nánási, *Carbohydr. Res.* **1979**, *73*, 327–331.



Scheme 1.27: Synthesis of the 2*O*-methyl-D-rhamnose by Liptàk et al.:[85] a) $PhCH(OCH_3)_2$, *p*TSA, DMF, 95%; b) LAH, $AlCl_3$, Et_2O, CH_2Cl_2, 67%; c) MeI, Ag_2O, DMF, 90%; d) LAH, $AlCl_3$, Et_2O, CH_2Cl_2, reflux, 67%; e) tosylation (not described); f) LAH, benzene, Et_2O, reflux, 86%; g) Pd/C, AcOH, EtOH, 88%; h) aq. H_2SO_4, 100°C, 6 h, 76%.

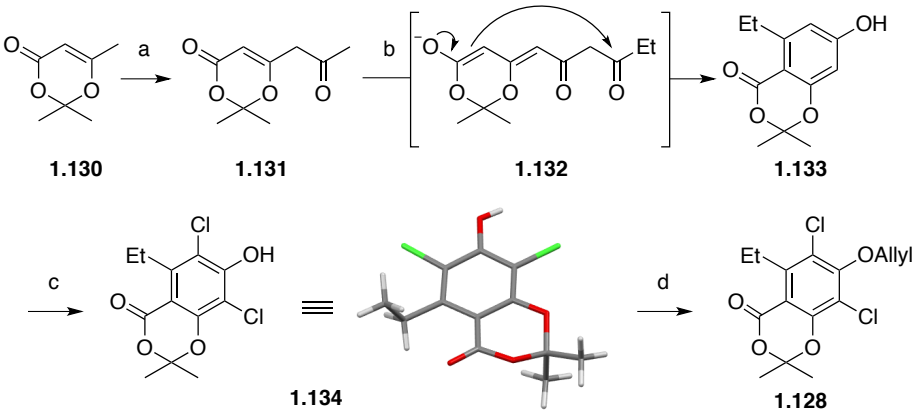
Since thio-glycosides are common donors, which are generally stable under acidic conditions and still can be easily converted into other leaving groups, our synthetic target was the thio-rhamnoside **1.127**. The flexibility was of special interest as β-selective rhamnosylations are a challenging task and not easy to predict (Chapter 1.6.2). TBS silyl ether protection of the C3 hydroxyl group in the rhamnoside should simplify the final global deprotection, as the core macrolide is silyl ether protected as well. These considerations led to the resorcylate-rhamnoside fragment **1.127**, which could derive from the resorcylate unit **1.128** and the appropriately protected rhamnoside **1.129** (Scheme 1.28).



Scheme 1.28: Retrosynthetic analysis for the resorcylate-rhamnoside donor.

1.5.2 Biomimetic Synthesis of the Resorcylate Fragment

To prepare the homodichloro-orsellinate, we imagined performing a biomimetic aromatization as elaborated by Barrett *et al.* (Scheme 1.29).[86] In analogy to the existing procedures, the dioxinone **1.130** was acylated.[86f] Then the resulting product **1.131** was two-fold deprotonated and acylated with propionyl imidazole. The intermediate diketodioxinone **1.132** was then treated with Et_3N to mediate aromatization to the homo orsellinate **1.133**.



Scheme 1.29: Biomimetic synthesis of the resorcylate fragment: a) LHMDS, THF, then AcCl, –78°C, 61%; b) LDA (2.1 equiv), propionyl imidazole (0.5 equiv), THF, −78°C then Et_3N, 57%; c) SO_2Cl_2, CH_2Cl_2, reflux, 98%; d) K_2CO_3, allyl bromide, DMF, 50°C, 95%.

The aromatic compound was then efficiently chlorinated using sulfuryl chloride[84] (98%) and the resulting homodichloro orsellinate **1.134** was protected as the allyl ether using K_2CO_3 and allyl bromide (95%). In this way, the required resorcylate **1.128** was achieved in only four steps.

1.5.3 The Synthesis of the 2*O*-Methyl-D-rhamnoside – 1st Approach

As depicted in Scheme 1.28 we targeted the O2 methylated and O3-TBS protected rhamnoside **1.129** in the first attempt. Thus, we started from commercially available methyl-D-mannoside **1.104** and protected the C6-C4 hydroxyl groups as the six-membered cyclic

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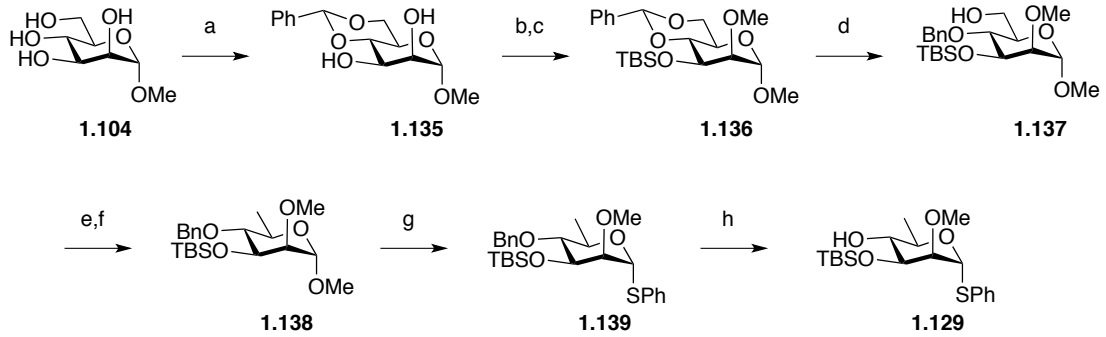
[86] a) B. H. Patel, A. M. Mason, H. Patel, R. C. Coombes, S. Ali, A. G. M. Barrett, *J. Org. Chem.* **2011**, *76*, 6209–6217; b) I. Navarro, C. Pöverlein, G. Schlingmann, A. G. M. Barrett, *J. Org. Chem.* **2009**, *74*, 8139–8142; c) B. H. Patel, A. M. Mason, A. G. M. Barrett, *Org. Lett.* **2011**, *13*, 5156–5159; d) K. Anderson, F. Calo, T. Pfaffeneder, A. J. P. White, A. G. M. Barrett, *Org. Lett.* **2011**, *13*, 5748–5750; e) M. Fouché, L. Rooney, A. G. M. Barrett, *J. Org. Chem.* **2012**, *77*, 3060–3070; f) B. H. Patel, S. F. A. Heath, A. M. Mason, A. G. M. Barrett, *Tetrahedron Lett.* **2011**, *52*, 2258–2261.

benzylidene acetal. Various one step protocols using α,α-dimethoxy benzaldehyde in combination with e.g., ionic liquids,[87] trichlorotriazine (TCT),[88] HBF_4,[89] or *p*TSA at 200 mbar,[90] are described in literature. The reported yields range from 40 to 99%, in our hands the yields were always lower than described in the literature. The only protocol that gave reliable yields was the method by Leino and co-workers: Stirring of the mannoside **1.104** in DMF with an equivalent dimethoxy benzaldehyde and catalytic *p*TSA at 200 mbar and 60°C, to remove formed methanol, furnished the product **1.135** in 53% yield.



Scheme 1.30: 1st Approach of the synthesis of the 2*O*-methyl-D-rhamnoside: a) $PhCH(OCH_3)_2$, *p*TSA, DMF, 60°C, 200 mbar, 2 h, 53%; b) nBu_2SnO, MeOH, reflux, 1 h, then TBSCl, TBAI, DMF, CH_2Cl_2, 16 h, 80%; c) NaH, MeI, THF, 0°C to RT, 82%; d) $BH_3 \cdot THF$, TMSOTf, CH_2Cl_2, RT, 45 min, 91%; e) I_2, PPh_3, imid, toluene, 100°C, 7 h, 85%; f) LAH, THF, 60°C, 6 h, 82%; or Pd/C, H_2 (50 bar), Et_3N, MeOH, 68%; g) TMSSPh, ZnI_2, TBAI, DCE, 65°C, 79%; h) DDQ, CH_2Cl_2/H_2O 10/1, RT, 82%.

To distinguish between O2 and O3 the stannylidene acetal method was applied.[91,92] Thus the tethered mannoside **1.135** was refluxed with dibutyltin oxide in methanol to give the dialkylstannylene acetal. Then the solvent was exchanged from methanol to DMF/CH_2Cl_2 and the stannane was reacted with TBSCl to give the selectively O3 TBS protected mannoside. Methylation of the O2 position was performed under standard conditions using sodium hydride and iodomethane to furnish the mannoside **1.136** (Scheme 1.30).

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87 J. Zhang, A. J. Ragauskas, *Carbohydr. Res.* **2005**, *340*, 2812–2815.

88 M. Tatina, S. K. Yousuf, D. Mukherjee, *Org. Biomol. Chem.* **2012**, *10*, 5357–5360.

89 H.-S. Cheon, Y. Lian, Y. Kishi, *Org. Lett.* **2007**, *9*, 3323–3326.

90 a) M. Poláková, M. U. Roslund, F. S. Ekholm, T. Saloranta, R. Leino, *Eur. J. Org. Chem.* **2009**, 870–888; b) F. Ekholm, M. Poláková, A. Pawłowicz, R. Leino, *Synthesis* **2009**, 567–576.

91 a) T. B. Grindley, *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17–142; b) T. B. Grindley, R. Thangarasa, *Can. J. Chem.* **1990**, *68*, 1007–1019; c) N.-C. Reichardt, M. Martín-Lomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 4674–4677.

92 E. Bedini, A. Carabellese, G. Barone, M. Parrilli, *J. Org. Chem.* **2005**, *70*, 8064–8070.

The next sequence aimed for the reduction of the primary alcohol, the transformation of mannoside to rhamnoside. Selective, reductive opening of the benzylidene acetal **1.136** using borane THF complex and TMSOTf as Lewis acid furnished the O4 benzyl protected and O6 deprotected compound **1.137**.[93] The primary alcohol was converted to the iodide using Garegg-Samuelsson conditions with iodine, triphenylphosphine and imidazole at reflux.[94] The reduction of the iodide using lithium aluminiumhydride proofed to be superior over hydrogenation with Pd/C and triethylamine to furnish the rhamnoside **1.138**.

In order to have a flexible handle at the anomeric position we exchanged the anomeric acetal to the thioacetal using trimethylsilyl thiophenol, zinc iodide and tetrabutylammonium iodide in dichloroethane.[95,96] This procedure gave the fully protected thio-rhamnoside **1.139** in pleasant yield. At this stage the benzyl ether deprotection was the last task towards the selectively O4 deprotected carbohydrate **1.129**. Confusingly, the deprotection using Pd/C in methanol or ethyl acetate even at 100 bar hydrogen pressure for two days did not show any conversion of the starting material **1.139**. As we suspected the thioacetal to be interfering during the hydrogenation these conditions were also applied before thiophenol insertion on compound **1.138**, but without success. Finally, we found DDQ in a CH_2Cl_2/water mixture to conduct the benzyl ether cleavage to give the desired thiorhamnoside **1.129**.[97]

1.5.4 Resorcylate-Rhamnoside Coupling – Take 1

Having the appropriately protected rhamnoside **1.129** and the homodichloro orsellinate **1.128** in hand we moved to the coupling of the two fragments (Scheme 1.31). Surprisingly, treating of the two fragments with sodium hydride in THF gave a mixture of the two constitutional isomers **1.127** and **1.140**. Obviously, the silyl ether migrates faster from O3 to O4 than esterification with the resorcinol takes place. Wondering if migration of substituents at O3 occurs in general, we cleaved the silyl ether of **1.140** using TBAF and treated the O3

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93 a) K. Daragics, P. Fügedi, *Tetrahedron Lett.* **2009**, *50*, 2914–2916; b) R. Johnsson, D. Olsson, U. Ellervik, *J. Org. Chem.* **2008**, *73*, 5226–5232.

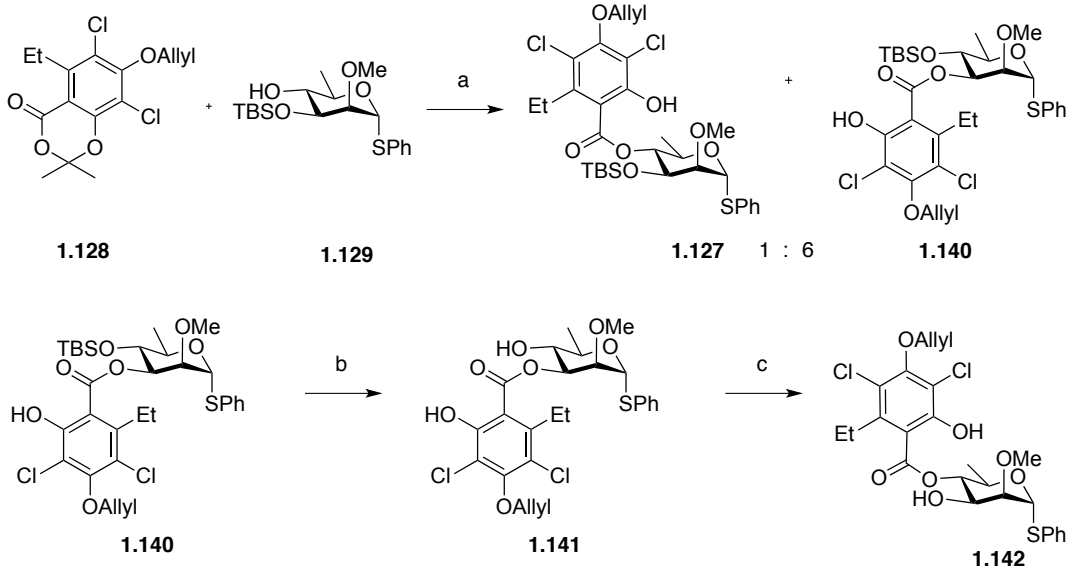
94 P. J. Garegg, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866–2869.

95 a) S. Hanessian, S. Hanessian, S. Hanessian, Y. Guindon, Y. Guindon, Y. Guindon, *Carbohydr. Res.* **1980**, *86*, 3-6. b) D. A. Evans, B. Trotter, P. J. Coleman, B. Côté, L. C. Dias, *Tetrahedron* **1999**, *55*, 8671-8726.

96 I. Paterson, T. Paquet, *Org. Lett.* **2010**, *12*, 2158–2161.

97 D. Crich, O. Vinogradova, *J. Org. Chem.* **2007**, *72*, 3581–3584.

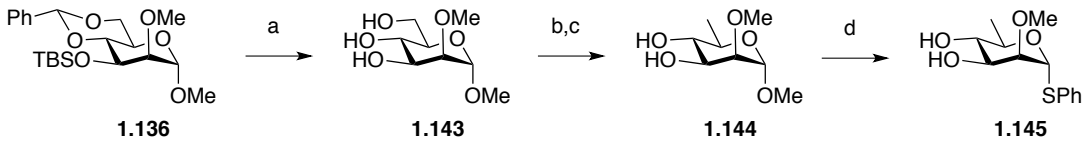
substituted rhamnoside **1.141** with sodium hydride again. Indeed, ester migration underwent smoothly to give the O4 substituted rhamnoside-resorcylate fragment **1.142**.



Scheme 1.31: Rhamnoside-resorcylate coupling, an unexpected migration. a) NaH, THF, RT, 4 h, 10% **1.127**, 59% **1.140**; b) TBAF, THF, 2 h, 81%; c) NaH, THF, 18 h, 0°C to RT, clean conversion, % n.d.

1.5.5 The Synthesis of the 2*O*-Methyl-D-rhamnoside – 2nd Approach

As a logical consequence, of the observations above, a protecting group at O3 was obsolete. Esterification of the diol **1.145** with the resorcylate **1.128** should indeed give the O4 substituted product **1.142**, too. To proof our assumption, we synthesized the thioglycoside **1.145** starting from the O2 methylated intermediate **1.136**. Acidic hydrolysis of the benzylidene acetal and the silyl ether was conducted first to give the triol **1.143**, followed by selective removal of the pimary alcohol using a mild Garegg Samuelsson iodination and a hydrogenolysis using $Pd(OH)_2$ and triethylamine as HI-quencher under hydrogen atmosphere. The thiophenol **1.142** was then synthesized from the diol **1.144** using the same procedure as in the previous sequence.

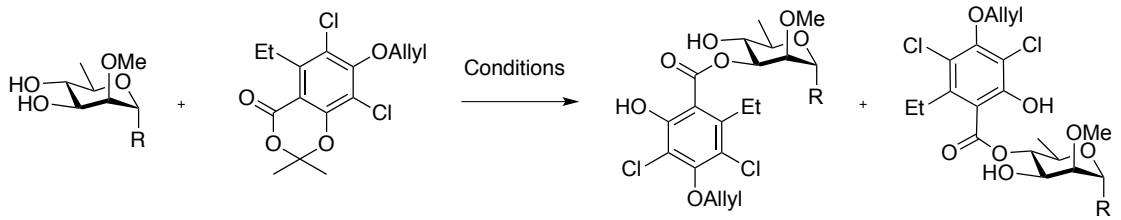


Scheme 1.32: Synthesis of the unprotected thiorhamnoside: a) aq. HCl 1M, MeOH, H_2O, quant.; b) I_2, PPh_3, imid, THF, 65°C, 1.5 h, 58%; c) $Pd(OH)_2$, H_2 (atm.), Et_3N, MeOH, RT, 6 h, 97%; d) TMSSPh, ZnI_2, TBAI, DCE, 65°C, 70%.

1.5.6 Resorylate-Rhamnoside Coupling – Take 2

Having the diol **1.145** in hand, we examined the regioselective esterification with the resorcylate **1.128** (Table 1.3). Pleasantly, under the same conditions previously used, a high regioselectivity (10:1) and good yield (83%) was achieved (Entry 1). Interestingly, initially within the first 30 minutes the O3 isomer **1.141** is formed, exclusively (Entry 8). A prolonged reaction time (18 h) is required until the equilibrium in favour of the O4 isomer **1.142** is reached. The same observation was made with the reactions in Entry 2, 4, 6-7. In DMF (Entry 3) the reaction quickly reached its equilibrium (1:1 ratio) within 30 minutes. On the other hand, lithium hydride (Entry 5) mediated the reaction very slowly. Full conversion was reached after 14 h and heating of the reaction was required to initiate migration of the resorcylate unit.

Table 1.3: Examination of the regioselective resorcylate ester couplings.



1.145: R=SPh
1.144: R=OMe

1.128

1.141: R=SPh
1.146: R=OMe

1.142: R=SPh
1.147: R=OMe

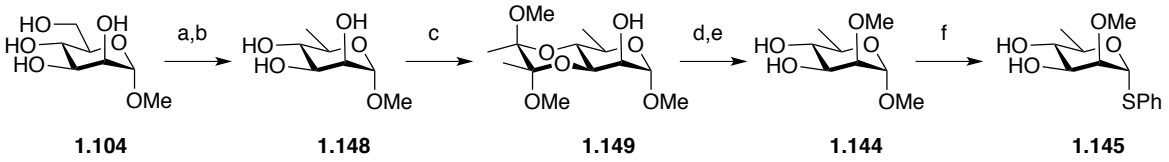
Entry	R	Solvent	Base (equiv)	O3:O4	Yield
1	SPh	THF	NaH (5.0)	1 : 10	83% **1.142**
2	SPh	Et_2O	NaH (5.0)	1 : 10	66% **1.142**
3	SPh	DMF	NaH (5.0)	1 : 1	n.d.
4	SPh	toluene	NaH (5.0)	1 : 17	50% **1.142**
5[a]	SPh	THF	LiH (5.0)	1 : 1	n.d.
6	OMe	THF	NaH (5.0)	1.4 : 1	22% **1.146**, 16% **1.147**
7	OMe	toluene	NaH (5.0)	1 : 11	50% **1.147**
8[b]	SPh	Et_2O	NaH (5.0)	1 : 0	72% **1.141**

Conditions: 18 h, 0°C to RT. [a] Carried out at RT for 24 h then 50°C for 24 h. [b] Carried out at RT for 0.5 h.

Clearly, using apolar solvents (Entry 4, 7) gives higher selectivity towards O4 substitution. Comparing Entry 1, 6 and Entry 4, 7 respectively, a remarkable difference of the O3:O4 ratios becomes apparent. Obviously, the methyl-rhamnoside **1.144** gives lower selectivity than the thioacetal **1.145**.

1.5.7 The Synthesis of the 2*O*-Methyl-D-rhamnoside – 3rd and Final Approach

Encouraged by the results for the resorcylate coupling, we targeted a new, shorter synthesis of the diol **1.145**. The elaborate protecting group strategy as in the first strategy was not necessary anymore and thus the route could be reduced dramatically (Scheme 1.33).



Scheme 1.33: Final version of the thio-rhamnoside synthesis: a) I_2, PPh_3, imid, THF, reflux, 95%; b) $Pd(OH)_2$, H_2 (atm.), Et_3N, MeOH, RT, 3.5 h, quant.; c) $HC(OMe)_3$, $(CH_3CO)_2$, CSA, MeOH, 90°C; d) NaH, MeI, THF, 0°C to RT; e) CH_2Cl_2, TFA/H_2O 9:1, RT, 72% (3 steps); f) TMSSPh,TBAI, ZnI_2, DCE, 60°C, 73%.

Again the starting point of our synthesis was methyl-D-mannoside **1.104** and the first step was, in analogy with the novioside synthesis (Chapter 1.4.2), the Garegg Samuelsson iodination. Next, the iodide was reduced using $Pd(OH)_2$ and Hünig's base to give methyl-D-rhamnoside **1.148**. Key to this approach was to introduce the trans-selective butane-2,3-diacetal (BDA) protecting group.[98] Thus the triol **1.148**, 2,3-butadione, orthoformate and camphersulfonic acid was heated in a pressure tube at 90°C in methanol to give the O3/O4 BDA-protected product **1.149**. O2–Methylation was effected using sodium hydride and methyl iodide. Then BDA cleavage with TFA/water in CH_2Cl_2 gave the previously synthesized rhamnoside **1.144**. The three steps (BDA protection, methylation, BDA deprotection) could be conveniently conducted without purification of the intermediates and afforded **1.144** in excellent overall yield (72%).

To conclude, a straightforward synthesis of the 2*O*-methyl rhamnoside **1.145** was developed and a biomimetic aromatization approach furnished the homodichloro orsellinate **1.128**. The two fragments could be selectively coupled by an unexpected and simple esterification to give convenient access to the resorcylate-rhamnoside fragment **1.142**.

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[98] a) S. V. Ley, D. R. Owen, K. E. Wesson, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2805–2806; b) A. Hense, S. V. Ley, H. Osborn, D. R. Owen, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2023–2031.

1.6 Glycosylations

1.6.1 Introduction

In glycosylation reactions, a sugar molecule is attached to another molecule by a covalent linkage. Biosynthetically, this procedure by which saccharides are linked to lipids, proteins or other biomolecules is catalyzed by enzymes. In synthetic organic chemistry, problems arise due to the need to control the stereochemical outcome of the glycosylation reaction, which often cannot be reliably predicted by theoretical reasoning. The practical challenge lies in the combination of the many parameters that influence the attack at the anomeric position. These factors include the conformation of the glycosyl donor (dependent of the substitution pattern), its configuration, neighbouring-group effects of substituents, the leaving group on the anomeric center, the reactivity and steric demand of the acceptor, the promoter, the solvent and the reaction temperature. In natural product total synthesis, the choice of the carbohydrates' substitution pattern is often limited, such that directing groups cannot be used and post-glycosylative modifications are not compatible with the structural motif. These circumstances make the total syntheses of complex glycosylated natural products highly challenging and the yields and selectivities are in many cases far from ideal.[99]

Figure 1.22 shows the general outline of *O*-glycosylation reactions by formation of an ether bond between the saccharide's anomeric carbon atom and an alcohol (ROH). In the first step, a promoter (EX) reacts with the sugar to activate the leaving group on the glycosyl donor.[100] Depending on the parameters mentioned above, activated and covalently bound donors or ion pairs with varying proximity are formed (CIP, SSIP or oxocarbenium ion) this either with the original leaving group, the solvent or anions present in the reaction mixture. Each of these states can be attacked by the acceptor (ROH) and thus the abundance and kinetic preference of a species determines the stereochemical outcome of the reaction. Tuning of the reaction conditions can direct to one or the other intermediates. Obviously, the polarity of the solvent has influences on the conformation and the stabilization of the oxocarbenium

[99] Y. Yang, X. Zhang, B. Yu, *Nat. Prod. Rep.* **2015**, *32*, 1331–1355.

[100] X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 1900–1934.

ion and may even engage in weak covalent bonds (*cf.* the nitrile effect[101]). The lesser the solvents ability to separate/stabilize charges, the more favoured are intermediates featuring covalent bonds and contact ion pairs (CIP), which will then preferentially undergo an S_N2 or S_N2-like reaction with the acceptor.

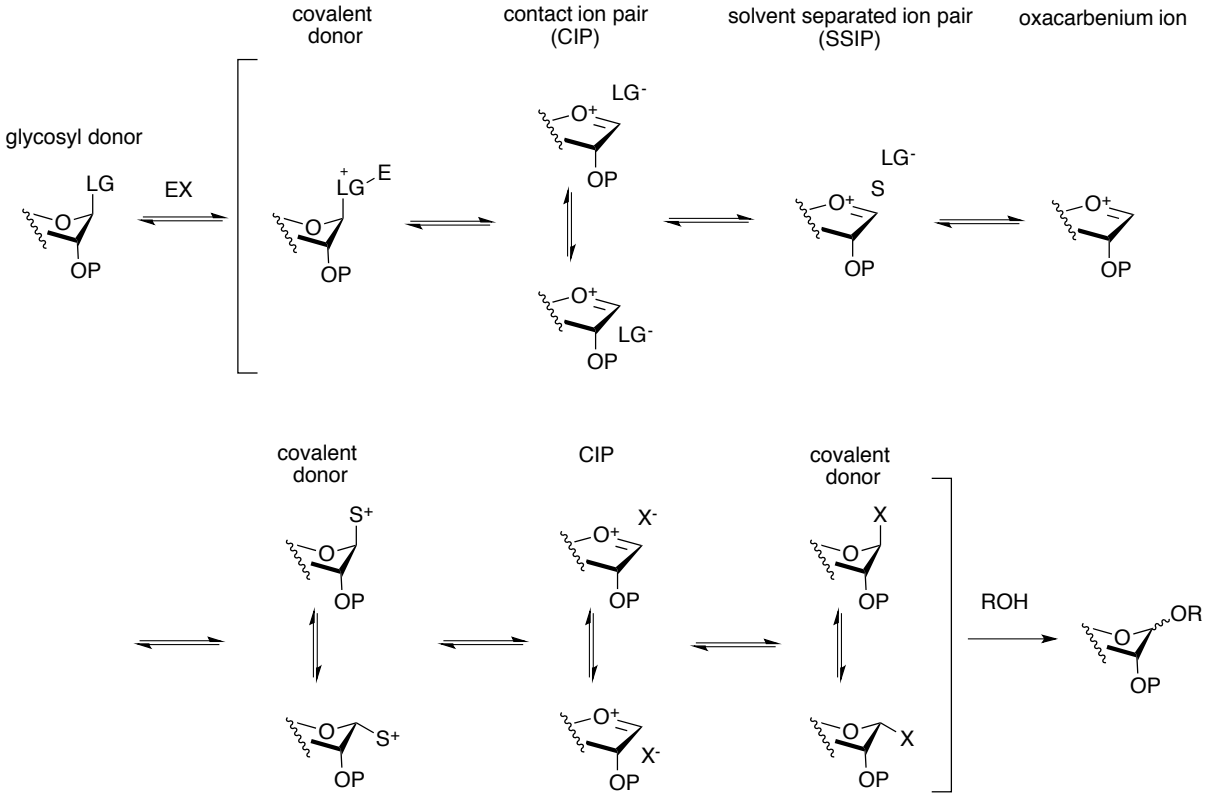

Figure 1.22: Intermediates that have an influence on the stereochemical outcome of the glycosylation reaction LG = leaving group; EX = Promoter (electrophile and leaving group), S = solvent; P = nonparticipating substituent.

Clearly, the characteristics of the leaving group also determine the character of the nucleophilic substitution; the better the leaving group the more probable is an S_N1-type reaction mechanism. The promoter (EX) plays a major role at this point, as it tunes the character of the leaving group. Furthermore, the nucleophilicity and streric bulk of the couneterion (X^-) has a crucial effect on the reaction mechanism due to its plausible interaction with the oxocarbenium intermediate.

[101] a) J.-R. Pougny, P. Sinaÿ, *Tetrahedron Lett.* **1976**, *17*, 4073–4076; b) A. J. Ratcliffe, B. Fraser-Reid, *J. Chem. Soc., Perkin Trans. 1* **1990**, 747–750; c) I. Braccini, C. Derouet, J. Esnault, C. H. E. de Penhoat, J. M. Mallet, V. Michon, P. Sinaÿ, *Carbohydr. Res.* **1993**, *246*, 23–41; d) R. R. Schmidt, M. Behrendt, A. Toepfer, *Synlett* **1990**, 694–696; e) D. Crich, M. Patel, *Carbohydr. Res.* **2006**, *341*, 1467–1475.

The reactivity of the oxocarbenium ion is also heavily influenced by the substituents of the carbohydrate. In 1988 Fraser-Reid *et al.* recognized that donors bearing benzyl protecting groups react substantially faster than the equivalent acetylated donors. To characterize their relative reactivity they termed them "armed" and "disarmed" donors.[102] Electron-withdrawing groups reduce the reactivity of the glycosyl donor as they destabilize the transition state of bond dissociation between the anomeric carbon and the leaving group with its partial positive charge on the anomeric carbon. Later, the group of Fraser-Reid reported on the "arming" effect of cyclic groups like acetals.[103] Glucosides, mannosides and galactosides, forced to adapt a twist conformation through the cyclic protecting group, reacted two to ten times faster than the non-tethered carbohydrates. Bols et al. went even further and developed so-called "superarmed" donors with bulky silyl groups that force the substituents in axial position. These conformationally armed donors did not only show much faster reaction rates but also higher diastereoselectivities.[104] The use of this concept has become an important strategy in carbohydrate chemistry, and is especially useful in oligosaccharide one-pot-synthesis, as the reactivity of co-existing carbohydrate donors in can be controlled by protecting group decoration.[105]

1.6.2 The 1,2-*cis* Problem

The preparation of 1,2-*cis* configured rhamnosides and mannosides is generally difficult as they are sterically and electronically unfavourable. Thus, β-selective rhamnosylation is a challenging and widely recognized as an unsolved task in preparative carbohydrate chemistry.[106] A breakthrough in β-mannosylation was Crich's method to tether the O6-O4 by a benzylidene acetal (**1.150**) (Figure 1.23).[107] The conformational restriction and the use of triflate-forming promoters leads to highly reactive intermediates bearing a triflate in α-position (**1.151**), which readily react in an S_N2-type with acceptors to give mannosides with high β-selectivity.

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[102] D. R. Mootoo, P. Konradsson, U. Udodong, B. Fraser-Reid, *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.

[103] B. Fraser-Reid, Z. Wu, C. W. Andrews, *J. Am. Chem. Soc.* **1991**, *113*, 1434–1435.

[104] C. M. Pedersen, N. Lars Ulrik, M. Bols, *J. Am. Chem. Soc.* **2007**, *129*, 9222–9235.

[105] Review: C.-H. Hsu, S.-C. Hung, C.-Y. Wu, C.-H. Wong, *Angew. Chem. Int. Ed.* **2011**, *50*, 11872–11923.

[106] E. S. H. El Ashry, N. Rashed, E. S. I. Ibrahim, *Tetrahedron* **2008**, *64*, 10631–10648.

[107] a) D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 4506–4507; b) D. Crich, S. Sun, *J. Org. Chem.* **1997**, *62*, 1198–1199; c) D. Crich, S. Sun, *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223; d) D. Crich, M. Smith, *Org. Lett.* **2000**, *2*, 4067–4069.

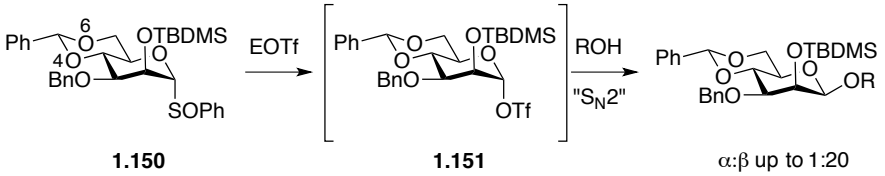
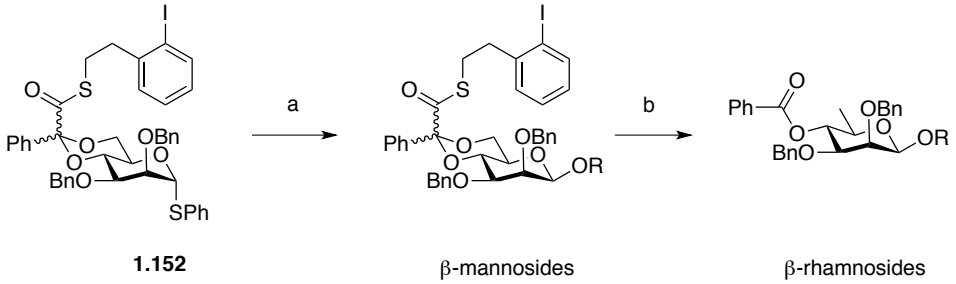


Figure 1.23: β-Selective mannosylation developed by the group of Crich. Tethering of the O6-O4 position and promoters of general formula EOTf give intermediate triflates, which are attacked by the acceptor from the β-side in an S_N2-like fashion.[107]

This strategy is not directly applicable to the preparation of β-rhamnosides, as the C6-position is not oxygenated. Thus, Crich and co-workers developed a benzylidene acetal bridge that can be reductively cleaved to give the C6 deoxygenated rhamnosides after mannosylation (Scheme 1.34).[108]



Scheme 1.34: Crich`s approach for the highly selective preparation of β-rhamnosides.[108] a) BSP, TTBP, Tf_2O, CH_2Cl_2, –60°C, 10 min, then ROH, –60°C to RT, 3 h, 71–94%, β-only; b) Bu_3SnH, AIBN, toluene, reflux, 74–80%.

Though this method furnished the β-mannosides in good yield and high diastereoselectivity, the method is not very practical for applications in total synthesis. The preparation of the acetal **1.152** is not straightforward and not many complex natural products would tolerate the chemoselective radical cleavage of the acetal using tributyltin hydride in boiling toluene.

Most publications on rhamnosylations feature the more abundant and so-called natural L-series. Unfortunately, the donors reported to give high β-selectivities and yields in literature are not compatible with the rhamnosyl donor suitable for the total synthesis of fidaxomicin (Figure 1.24). As post-glycosylative modifications should preferentially be avoided, the only modifiable sites in the rhamnosyl donor for the synthesis of fidaxomicin are the leaving group, the O3 substitution and the two phenolic groups at a considerable distance from the

[108] D. Crich, Q. Yao, *J. Am. Chem. Soc.* **2004**, *126*, 8232–8236.

pyranoside ring. Thus, the ulosyl bromide (**A**) strategy reported by Lichtenthaler[109] and the approaches with a non-participating sulfonate at C2-position (**B**) by Schuerch[110] (1981, LG = Cl) and Crich[111] (2003, LG = SPh) cannot be used as precursors for the total synthesis. Also cyclic protecting groups (**C**–**E**) cannot be applied, so the precursor of general structure **F** is the only option left.

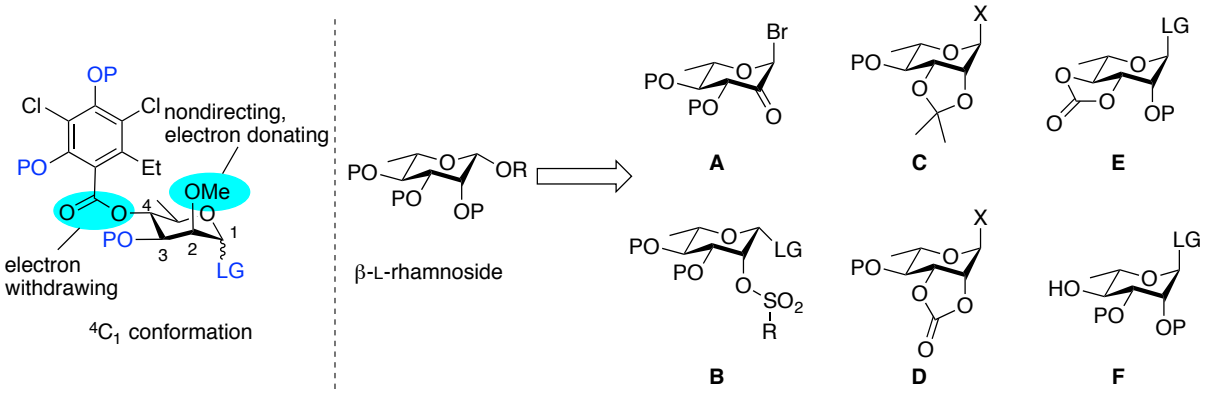


Figure 1.24: Left: Rhamnosyl donor for the total synthesis of fidaxomicin; in blue: adaptable groups; right: Precursors giving the highest β-selective rhamnosylation in the L-series as reported in literature. P = protecting group; X = halogen; LG = leaving group.

There are only few examples that give good 1,2-*cis* rhamnosylation results, using the general structure formula **F**. In general, Königs-Knorr glycosylations using heterogeneous catalysts gave good β-selectivities.[112] Though this method is promising, the generation of the glycosyl halides often require harsh conditions.

Interestingly, Inazu and co-workers found that rhamnosyl donors with an ester substituent at the C4-position (**1.154**, **1.155**) showed increased β-selectivity compared to the benzyl ether **1.153** (Scheme 1.35).[113] They suggest that the oxocarbenium ion is intercepted by the ester in

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[109] a) F. W. Lichtenthaler, T. Schneider-Adams, S. Immel, *J. Org. Chem.* **1994**, *59*, 6735–6738; b) F. W. Lichtenthaler, T. W. Metz, *Tetrahedron Lett.* **1997**, *38*, 5477–5480; c) F. W. Lichtenthaler, T. Metz, *Eur. J. Org. Chem.* **2003**, *16*, 3081–3093.

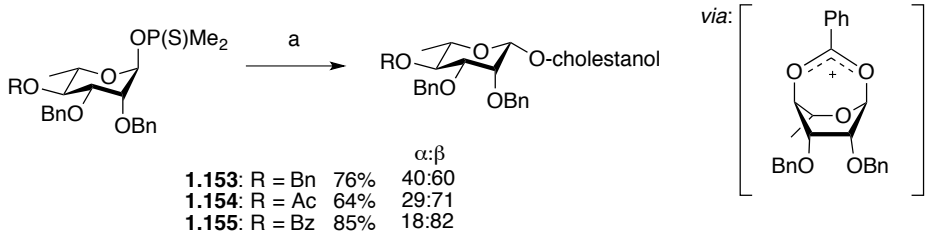
[110] V. K. Srivastava, C. Schuerch, *J. Org. Chem.* **1981**, *46*, 1121–1126.

[111] a) D. Crich, J. Picione, *Org. Lett.* **2003**, *5*, 781–784; b) D. Crich, T. K. Hutton, A. Banerjee, P. Jayalath, J. Picione, *Tetrahedron: Asymm.* **2005**, *16*, 105–119.

[112] a) H. Paulsen, W. Kutschker, O. Lockhoff, *Chem. Ber.* **1981**, *114*, 3233–3241; b) A. M. P. van Steijn, J. P. Kamerling, J. F. G. Vliegenthart, *J. Carbohydr. Chem.* **1992**, *11*, 665–689; c) E. Eichler, H. J. Jennings, D. M. Whitfield, *J. Carbohydr. Chem.* **1997**, *16*, 385–411.

[113] T. Yamanoi, K. Nakamura, H. Takeyama, K. Yanagihara, T. Inazu, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1359–1366.

an intramolecular reaction, forming a 7-membered cyclic intermediate (Scheme 1.35). The incoming aglycon attacks this cyclic intermediate by an S_N2-attack, thus forming the desired β-anomer. Although this reaction is carried out under rather harsh condition (iodine), the high yield and good diastereomeric ratio of α:β = 1:4 encouraged us to first look into the reactivity and selectivity of our thiophenyl-donor **1.142** in hand.



Scheme 1.35: The influence of the C4-substituent on the stereoselectivity found by Inazu.[113] a) iodine (1 eq), $TrtClO_4$ (5mol%), 3β-cholestanol, benzene, m.s. 4Å, RT.

It needs to be mentioned that the described neighbouring group effect (anchimeric assistance) with ester substituents on C4 is exceptional and has not been observed with other leaving groups or different substituents on C2 and C3. On the contrary, the reaction even proceeds with exclusive α-selectivity when structural parameters are changed.[106,114]

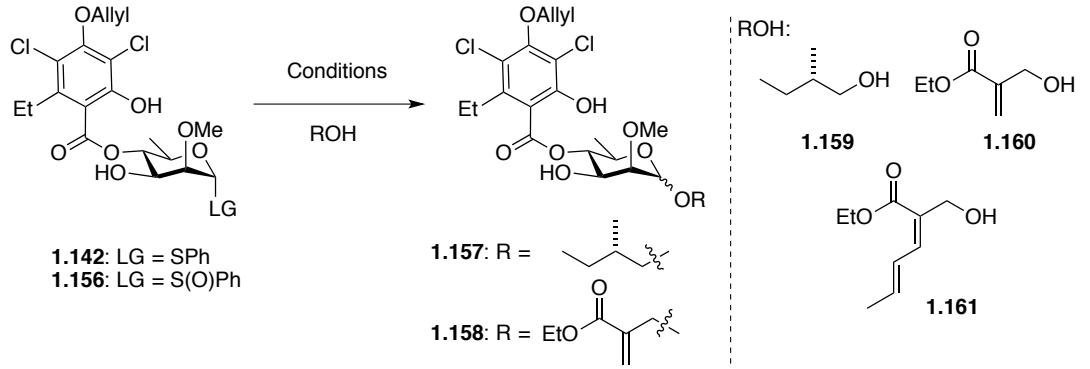
In summary, there are only very few examples of rhamnosyl donors reported in literature that might be suitable for the total synthesis of fidaxomicin. The most reliable β-selective reactions known are the ones using glycosyl halides and heterogeneous promoters/scavengers. These glycosyl halides are unfortunately not easy to prepare due to their instability and the required conditions are typically harsh (*vide supra*). As changes regarding the choice of the substituents can have an unforeseen impact on the selectivity and no donors with the same rhamnoside substitution pattern as in fidaxomicin have been reported, we were not able to predict the stereochemical outcome of the glycosylation with our donor **1.142**. As a consequence, we had to test its reactivity, and the stereochemistry of the glycosylation product.

[114] a) D. E. Long, P. Karmakar, K. A. Wall, S. J. Sucheck, *Bioorg. Med. Chem.* **2014**, *22*, 5279–5289; b) Y. Liu, N. Ding, H. Xiao, Y. Li, *J. Carbohydr. Chem.* **2006**, *25*, 471–489; c) J. Boutet, C. Guerreiro, L. A. Mulard, *Tetrahedron* **2008**, *64*, 10558–10572; d) D. Crich, M. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.

1.6.3 β-Rhamnosylation – Screening

For a start, we tested donor **1.142** in standard glycosylation reactions with different glycosyl acceptors, without installing additional protecting groups (Table 1.4). To our delight, the selectivity with the simple alcohol **1.159** was in favour of the desired β-anomer (Entry 1, 2). The configuration of the products was determined by the coupling constant $^1J_{CH}$ = 152 Hz for the β-anomer, which is close to the value in fidaxomicin ($^1J_{CH}$ = 156 Hz)[115] and is in the characteristic range of β-rhamnosides (β: $^1J_{CH}$ = 152.9–159.8 Hz; α: $^1J_{CH}$ = 167.2–172.3 Hz).[111a,116]

Table 1.4: Screening of reaction conditions for rhamnosylation using the unprotected glycosyldonor.



Entry	LG	ROH	Conditions	Yield/Conv.	α : β
1	SPh	**1.159**	NIS, TfOH (cat.), CH_2Cl_2, –78°C to RT	63% conv.	1 : 2
2	SPh	**1.159**	NBS, CH_2Cl_2, 40°C	40% conv.	1 : 2
3	SPh	**1.159**	Tf_2O, BSP, TTBP, CH_2Cl_2, –60 to –50°C	0% conv.	–
4	SPh	**1.160**	NBS, CH_2Cl_2, RT	0% conv.	–
5	SPh	**1.160**	NIS, AgOTf (cat.), CH_2Cl_2, –78°C to RT	58%	1 : 2
6	SPh	**1.161**	NIS, TfOH (cat.), CH_2Cl_2, –78°C to RT	0%[a]	–
7	S(O)Ph	**1.161**	Tf_2O, DTBMP, CH_2Cl_2, –78°C to –35°C	0%[b]	–

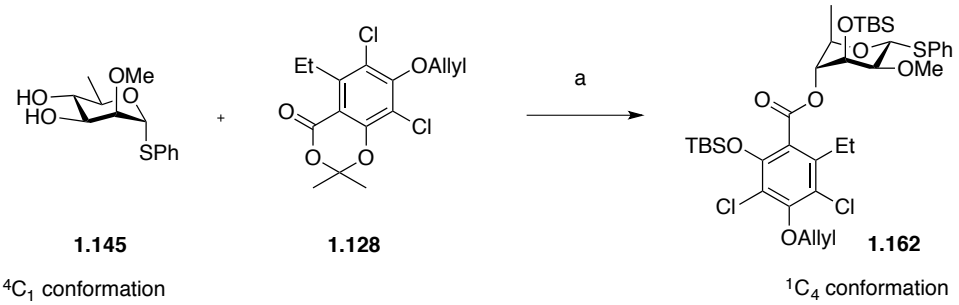
The reactions were carried out under careful exclusion of water and in the presence of m.s. 3Å. Conversion was determined after quenching by ^{1}H-NMR. [a] The acceptor was fully converted; [b] A complex mixture was obtained.

[115] A. Arnone, G. Nasini, B. Cavalleri, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1353–1359.

[116] K. Bock, C. Pedersen, *J. Chem. Soc., Perkin Trans. 2* **1974**, 293–297.

Unfortunately, the thioglycoside donor is unreactive and there was no sufficient conversion with the more sophisticated acceptors **1.160** and **1.161**. Unlike with **1.159**, the reaction with Nicolaou`s method[117] did not proceed with substrate **1.160** and the donor was recovered (Entry 4). The more activating promoter system NIS/AgOTf[118], on the other hand, furnished the glycosylated product in sufficient yield (58%) and with the same anomeric ratio as with acceptor **1.159** (Entry 5). However, this method failed with the more authentic acceptor **1.161** (Entry 6). In this case, the donor was not converted, but the dienoate **1.161** was completely degraded. Not surprisingly, these conditions are not compatible with alkene functionalities. Thus, we also applied the method reported by Crich *et al.* using 1-benzenesulfonyl piperidine (BSP) and trifluoromethanesulfonic acid as activator. Surprisingly, even with this method, which is reported to promote even highly deactivated donors, thioglycoside **1.142** did not react with the acceptor (Entry 3). As the thioglycoside **1.142** seemed very unreactive, we oxidized the thioether to the sulfoxide **1.156** using *m*CPBA. Kahne's glycosylation method using sulfoxide, is especially useful in cases of very unreactive donors.[119] Indeed, this method efficiently converted the donor **1.156**, but no desired glycosylated product could be isolated. We figured that in this case the free alcohol groups in the donor are competing with the acceptor and thus a complex mixture was obtained.

As a consequence, we protected the resorcylate moiety as well as the C3-alcohol. From retrosynthetic perspective, protection as silyl ether made most sense, and thus we trapped the alkoxide from the resorcylate-rhamnoside esterification with TBSOTf to obtain thioglycoside **1.162** (Scheme 1.36).



1.145 **1.128** **1.162**

$^4C_1$ conformation $^1C_4$ conformation

Scheme 1.36: Synthesis of the TBS-protected donor: a) NaH, THF, 0°C to RT, 16 h, then TBSOTf, 3 h, RT, 54%.

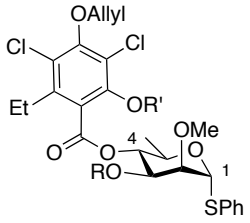
[117] K. C. Nicolaou, S. P. Seitz, D. P. Papahatjis, *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434.

[118] P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313–4316.

[119] D. Kahne, S. Walker, Y. Cheng, D. Van Engen, *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882.

Interestingly, the ^{1}H-NMR coupling constants of **1.162** indicate a tendency towards a $^1C_4$ conformation of the pyranose ring (Table 1.5). The ring flip from the $^4C_1$ conformation in the unprotected donor **1.142** to the $^1C_4$ conformation of the protected donor **1.162** is the result of the clash of the bulky *tert*-butyldimethylsilyl ether at C3 with the resorcylate moiety, which forces them to adopt the transaxial conformation. Table 1.5 illustrates that the TBS group in the ring, but also the protecting group in the resorcylate is required to induce the ringflip. The ^{1}H-NMR of the mono-silylether protected sugar **1.141** does only show a slight decrease of the coupling constant $^3J_{H3,4}$. The significant drop of the coupling constant can only be observed, when in addition, the phenolic hydroxyl group is protected as the allyl ether (**1.165**) or silyl ether (**1.162**). Though, the conformation of the TBS-protected donor **1.162** does not correspond to a perfect $^1C_4$-chair – the coupling constants do not show according values – but rather a distorted ring, for representational reasons the donor will be drawn in this conformation.

Table 1.5: Coupling constants of the pyranose ring with different protecting group decoration.



1.142: R=R`=H
1.162: R=R`=TBS
1.163: R=R`=SEM
1.164: R=H; R`=Allyl
1.141: R=TBS; R`=H
1.165: R=TBS; R`=Allyl

^3J [Hz]	**1.142**	**1.162**	**1.163**	**1.165**	**1.141**	**1.165**
$H_{1,2}$	0.7	0	0	1.2	1.8	2.5
$H_{2,3}$	3.6	–	–	3.6	–	3.0
$H_{3,4}$	9.8	6.4	9.4	9.8	9.5	8.7
$H_{4,5}$	9.8	6.7	9.7	9.8	9.5	8.7

This ring flip to a axial rich conformation was of special interest to us, since these pyranoses are known to be "superarmed" and the conformational change might also influence the anomeric selectivity in the subsequent glycosylation step.[120] The common explanation for the higher reactivity is the decreased electron withdrawing effect of axial substituents, which

[120] a) H. Yamada, T. Ikeda, *Chem. Lett.* **2000**, 432–433; b) T. Ikeda, H. Yamada, *Carbohydr. Res.* **2000**, *329*, 889–893; c) C. M. Pedersen, N. Lars Ulrik, M. Bols, *J. Am. Chem. Soc.* **2007**, 9222–9235; d) M. Heuckendorff, C. M. Pedersen, M. Bols, *J. Org. Chem.* **2012**, *77*, 5559–5568; e) M. Heuckendorff, H. D. Premathilake, *Org. Lett.* **2013**, *15*, 4904–4907; f) Review: H. Satoh, S. Manabe, *Chem. Soc. Rev.* **2013**, *42*, 4297–4309.

reduces the destabilization of a partial positive charge in the ring. Confusingly, Bols et al. found the β-selectivity in glycosylations with rhamnosides featuring electron-withdrawing substituents in axial positions to be lower compared to their counterparts with the same electron-withdrawing substituents in equatorial positions,[120c,d] whereas Yamada and co-workers[120a,b] describe the expected increase in β-selectivity. Thus we were conducting a set of reactions using the TBS-protected sugar **1.162** (Table 1.6). We first applied Nicolaou's conditions, which had also been employed by Yamada[120a] for the glycosylation of thiorhamnosides with electron-withdrawing substituents in axial positions. On contrast to the reaction with the unreactive glycosyl donor **1.142**, the desired glycoside **1.167** was furnished using the donor **1.162** and NBS as activating agent in dichloromethane (Table 1.6, Entry 1-5). Also, the diastereoselectivity was reversed in favour of the α-rhamnoside. Thus, we screened other solvents, but in hexane, toluene and ether only insufficient conversion or no reaction at all were observed (Entry 2-4). In acetonitrile, the reaction took place smoothly even at 0°C, though the solvent did not change the diastereoselectivity (Entry 5). The α-anomer was even more preferred at lower temperature using NIS/AgOTf in CH_2Cl_2 (α:β = 4:1, Entry 6). The Ph_2SO/Tf_2O promoter system developed by van der Marel and co-workers[121] mainly resulted in cleavage of the allyl ether (Entry 7). Nevertheless, some glycosylated product was isolated in a ratio of α:β = 4:1. We then examined the sulfoxide leaving group and thus oxidized the thioglycoside **1.162** using a standard procedure to obtain **1.166**.[119] Kahne's protocol, in which the sulfoxide is first activated with triflic anhydride to give the intermediate glycosyl triflate prior to addition of the glycosyl acceptor, furnished the product in good yield (quant., α:β = 4:1, Entry 8). Thus we used the protocol developed by Crich in which the acceptor and donor are premixed before adding triflic anhydride. In this procedure, the alcohol is supposed to intercept the formation of the glycosyl triflate and thus invert the selectivity.[122] In our case, we did indeed observe a slight shift towards β-selectivity (α:β = 3:1), but the effect was much less pronounced than anticipated (Entry 9). Additionally, glycosylation under Königs-Knorr conditions were examined. Though it is expected that glycosyl chlorides would adopt an axial position at the anomeric centre, Bols reported a slight β-selectivity with their axially enriched rhamnosyl chloride.[120d] Unfortunately, under the same conditions our system only furnished the expected α anomer (Entry 10).

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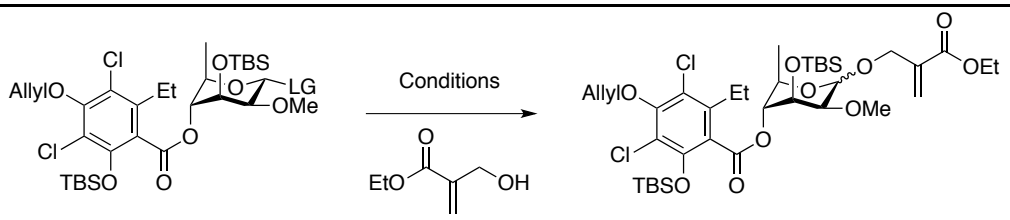
[121] J. D. C. Codée, R. E. J. N. Litjens, R. den Heeten, H. S. Overkleeft, J. H. van Boom, G. A. van der Marel, *Org. Lett.* **2003**, *5*, 1519–1522.

[122] a) D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 4506–4507; b) D. Crich, S. Sun, *J. Org. Chem.* **1997**, *62*, 1198–1199.

Table 1.6: Screening of reaction conditions using rhamnosyl donors with axial rich conformation.



1.162: LG = SPh
1.166: LG = S(O)Ph

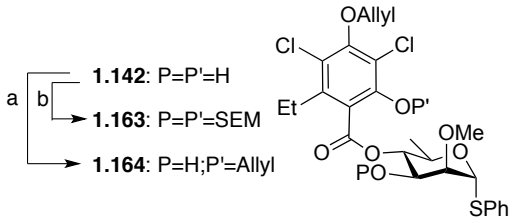
1.160

1.167

Entry	LG	Conditions[a]	Yield/Conv.[b]	α : β[c]
1	SPh	NBS, CH_2Cl_2, 0°C to RT	full conv./bp.	1.7 : 1
2	SPh	NBS, hexane, 0°C to RT	0% conv.	–
3	SPh	NBS, toluene, 0°C to RT	0% conv.	–
4	SPh	NBS, Et_2O, 0°C to RT	low conv.	–
5	SPh	NBS, MeCN, 0°C	full conv.	2 : 1
6	SPh	NIS, AgOTf (cat.), CH_2Cl_2, –78 to –30°C	68%	4 : 1
7	SPh	Tf_2O, $SOPh_2$, TTBP, CH_2Cl_2, –60 to RT	de-allylation	4 : 1
8	S(O)Ph	Tf_2O, DTBMP, CH_2Cl_2, –78°C, then **1.160**	quant.	4 : 1
9	S(O)Ph	**1.160**, DTBMP, CH_2Cl_2, –78°C, then Tf_2O	full conv.	3 : 1
10	SPh	i) ICl, $CDCl_3$ ii) **1.160**, Ag_2CO_3, CH_2Cl_2, 60°C, 2 d	50% conv.	1 : 0

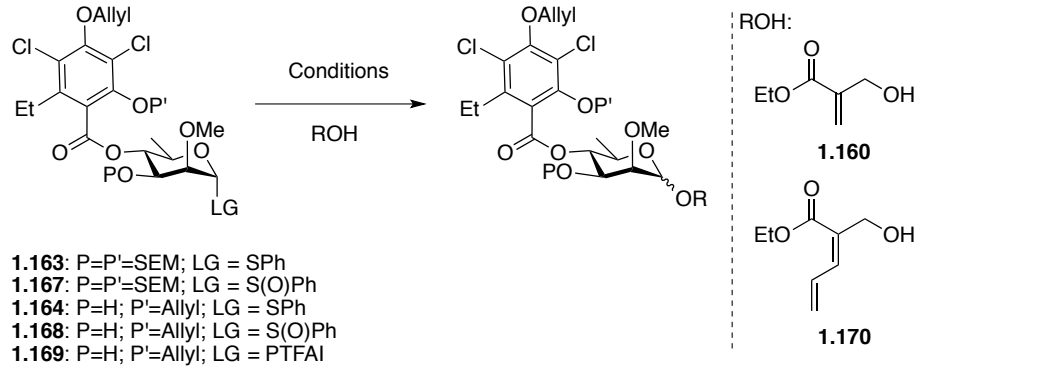
[a] The reactions were carried out under careful exclusion of water and in presence of m.s. 3Å. [b] The screening was performed with small amounts, thus the yield was not always determined, but the conversion was monitored by ^{1}H-NMR analysis. [c] The anomers were inseparable, thus a silyl ether deprotection was performed to obtain 1.158 in order to determine the identity of α and β.

From the two screenings with the unprotected donor **1.142** and the conformationally armed donor **1.162** it follows that the $^1C_4$ conformation of the D-rhamnoside is more reactive than the $^4C_1$, but only at the expense of a lower β-selectivity. This is aggravated by the fact that the anomeric effect in the $^1C_4$ conformation directs nucleophiles, such as triflate to the β-face, resulting in retention by the subsequent attack of the glycosyl acceptor. As a consequence, we decorated the donor with sterically less demanding protecting groups in order to retain the $^4C_1$ conformation. We reasoned that the trimethylsilylethoxymethyl acetal (SEM) protected donor **1.163** might be suitable, as SEM is linear and can eventually be cleaved along with the other silyl ethers at the end of the total synthesis. Furthermore, we decided to protect the phenolic hydroxyl groups as the allyl ether, hoping that the C3 hydroxyl group of glycosyl donor **1.164** would be too hindered to undergo self-condensation in presence of the primary acceptor alcohol (Scheme 1.37). Indeed, the two donors **1.163** and **1.164** showed coupling constants in the expected range for a $^4C_1$ pyranose conformation (Table 1.5).



Scheme 1.37: Synthesis of protected thiophenyl-donors: a) allyl bromide, K_2CO_3, DMF, 50°C, 96%; b) NaH, SEMCl, DMF 0°C to RT, 48%.

Table 1.7: Screening of protected, rhamnosyl donors.



Entry	Donor	ROH	Conditions[a]	Yield/Conv.[b]	α : β[c]
1	**1.163**	**1.160**	NBS, CH_2Cl_2, 0°C to RT	0% conv.	–
2	**1.163**	**1.160**	NBS, MeCN, 0°C to RT	0% conv.	–
3	**1.163**	**1.160**	NIS, AgOTf (cat.), CH_2Cl_2, –78 to –20°C	deprotection	3 : 2
4	**1.163**	**1.160**	NIS, AgOTf (1 eq.), DTBMP, CH_2Cl_2, RT	full conv.	3 : 2
5	**1.167**	**1.160**	Tf_2O, DTBMP, CH_2Cl_2, –78°C, then ROH	decomp.	–
6	**1.164**	**1.160**	NIS, AgOTf (cat.), CH_2Cl_2, RT	77%	5 : 6
7	**1.164**	**1.160**	NIS, AgOTf (1 eq.), DTBMP, CH_2Cl_2, 0°C	full conv.	2 : 3
8	**1.168**	**1.170**	Tf_2O, DTBMP, CH_2Cl_2, –78°C, then ROH	full conv.	1 : 2
9	**1.169**	**1.170**	TBSOTf, CH_2Cl_2, –78°C to –55°C	full conv.	1 : 3

[a] The reactions were carried out under careful exclusion of water and in presence of m.s. 3Å. [b] The screening was performed with small amounts, thus the yield was not always determined, but conversion was monitored by ^{1}H-NMR analysis. [c] In the case of the SEM-protected rhamnosides, the anomeric ratio was determined by the characteristic shifts in the ^{1}H-NMR spectrum (α: 5.0-4.8 ppm; β: 4.5-4.6 ppm).

The SEM-protected donor **1.163** was inert under Nicolaou's conditions[117] with NBS in CH_2Cl_2, and even in acetonitrile the reaction did not take place (Table 1.7, Entry1-2). The phenolic SEM-group, proofed to be very labile under various reaction conditions. For instance, NIS/AgOTf at –20°C already effected deprotection and a complex mixture of starting materials and glycosylated products was obtained. Nevertheless, the anomeric ratio was determined after deprotection (Entry 3). The undesired deprotection during glycosylation

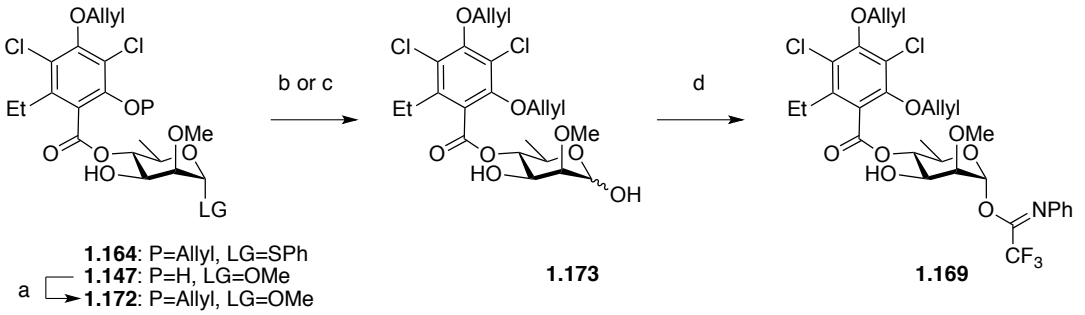
was avoided by addition of the bulky base di-*tert*-butyl-methylpyridine (DTBMP) and indeed the same diastereomeric ratio (α:β = 3:2) was obtained (Entry 4). Also Kahne's sulfoxide method resulted in decomposition and the formation of a complex mixture (Entry 5). As the protected donor **1.163** showed preference for forming the α-anomer and as the SEM group turned out to be labile, we decided to cease further investigations.

Next, we examined the double allyl-protected donor **1.164** using the Fraser-Reid activator (NIS, AgOTf)[118], in order to compare the behaviour with the other donors (**1.142**, **1.162**, **1.163**). Finally, we reached a higher preference for the β-anomer again (α:β = 5:6, Entry 6). With these results, we came to a conclusive analysis: Reactivity of the rhamnosyl donor increases with the steric bulk of the protecting groups employed. The TBS protected donor **1.162** already reacts at a low –30°C (Table 1.6, Entry 6); the less hindered SEM protected rhamnoside **1.163** requires –20°C to proceed (Table 1.4, Entry 3) and the unprotected **1.142** (Table 1.4, Entry 5) and allyl-protected donors **1.164** (Table 1.7, Entry 6) require 25°C for a prolonged time. Further, the more twisted the pyranoside, the lower the preference for β-selective rhamnosylation.

The selectivity with donor **1.164** was slightly improved by the use of stoichiometric amounts of silver triflate (Table 1.7, Entry 7). With Kahne's glycosylation method, we reached full conversion and a diastereomeric ratio of α:β = 1:2 (Entry 8). We then applied a β-rhamnosylation protocol[123] using the *N*-phenyltrifluoroacetimidiate (PTFAI) as a leaving group, developed by the group of Yu.[124] With this donor α:β ratios of 1:1 to 1:2.5 was reached. We thus hydrolysed thiophenol **1.164** using NBS in acetone/water to give pyranose **1.173** as a α:β = 5:1 mixture of the two anomers (Scheme 1.38). Later, we synthesized the pyranose **1.173** from the donor **1.147**, which was first allylated and then hydrolysed under acidic conditions. This sequence is shorter by one step, though, the overall yield is lower. The PTFAI was then installed using $ClC(NPh)CF_3$ and potassium carbonate in wet acetone to furnish donor **1.169** (Scheme 1.38).

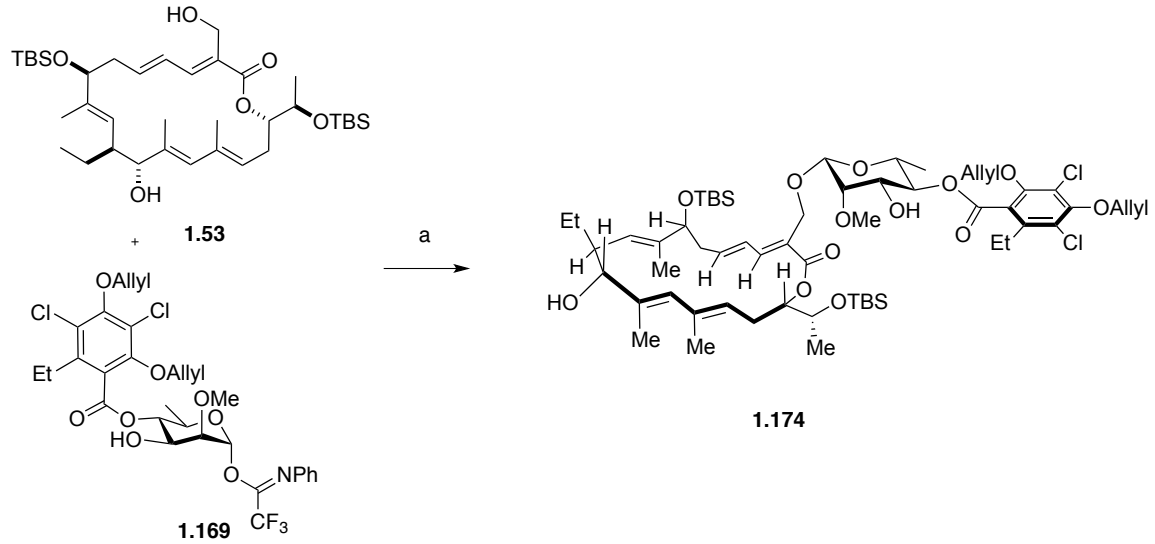
[123] A. E. Christina, D. van der Es, J. Dinkelaar, H. S. Overkleeft, G. A. van der Marel, J. D. C. Codée, *Chem. Commun.* **2012**, *48*, 2686–2688.

[124] a) B. Yu, H. Tao, *Tetrahedron Lett.* **2001**, *42*, 2405–2407; b) B. Yu, H. Tao, *J. Org. Chem.* **2002**, *67*, 9099–9102; c) Review: B. Yu, J. Sun, *Chem. Commun.* **2010**, *46*, 4668–4679.



Scheme 1.38: Introduction of PTFAI as leaving group: a) allyl bromide, K_2CO_3, DMF, 92%; b) **1.164**, NBS, acetone/H_2O 10:1, 0°C to RT, 95%, α:β = 5:1; c) **1.172**, AcOH, HCl aq. 1M, H_2O, 120°C, 3.5 h, 55%, α:β = 5:1; d) $ClC(NPh)CF_3$, K_2CO_3, acetone, 78%.

Rhamnosylation of alcohol **1.170** with donor **1.169** using TBSOTf resulted in a good diastereomeric ratio of α:β = 1:3 and high conversion (Table 1.7, Entry 9). As this donor gave such promising results we moved on to test it on the fidaxomicin aglycon **1.53** (Scheme 1.39). As the macrolide **1.53** was only available in small amounts at that stage of the project, control of the equivalents was very difficult to achieve. Ideally, the macrolide **1.53** and the imidate **1.169** should be used in equimolar amounts, since excess of imidate resulted in twofold glycosylation (confirmed by ESI-MS). On the other hand, if an excess of the macrolide was used the excess aglycon was difficult to separate from the glycosylated products. Thus, only low yields of β-rhamnosylated product **1.174** were obtained.

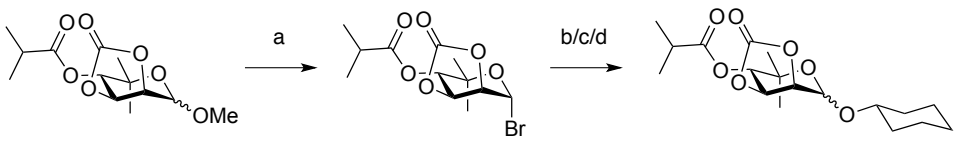


Scheme 1.39: Rhamnosylation of the macrolide: a) TBSOTf (cat.), CH_2Cl_2, –78°C to –20°C, 16%, α:β = 1:3.

At this time, we decided to introduce the rhamnoside moiety later, and after successful noviosylation, due to the results of our studies described in Chapter 1.6.4. The final rhamnosylation of the advanced noviosylated macrolide is described in the next chapter.

1.6.4 β-Noviosylation – a Novelty

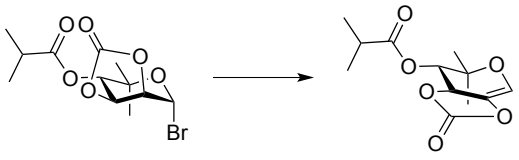
As described in Chapter 1.4, besides the fidaxomicin family, the noviobiocins are the only molecules that have been found to contain a novioside carbohydrate, however, α-linked to a phenol group. As a consequence, no β-selective noviosylation has been attempted so far, to the best of our knowledge. Nevertheless, the structural similarity of noviose and rhamnose allows conjectures about the reactivity of this rare carbohydrate. We thus based the design of the noviosyl donor on the knowledge gained from 1,2-*cis* rhamnosylations, as discussed in chapter 1.6.2. We opted for the introduction of the cyclic *O*-2,3 carbonate as the most promising protecting group strategy. Deprotection does not require acidic conditions that would most probably destroy the central macrolide. In addition, the cyclic carbonate is highly deactivating the noviose due to its strong electron-withdrawing effect, which is beneficial for high β-selectivity. Generally, Königs-Knorr glycosylations result in a high degree of S_N2-like glycosylation under mild conditions. We thus prepared glycosyl bromide **1.175** from novioside **1.102** by reaction with hydrogen bromide in acetic acid. The labile glycosyl bromide **1.175** was then immediately used in the following Königs-Knorr glycosylation with cyclohexanol. We were pleased to find that the reaction with the heterogeneous silver oxide and silver carbonate catalysts gave exclusively the β-anomer **1.176**. As expected, the use of soluble silver triflate resulted in the loss of S_N2-type character of the reaction giving the glycosylated product in a diastereomeric ratio of α:β = 10:1 (Scheme 1.40). Though we could not obtain any spectroscopic evidence, the results obtained, strongly indicate that the intermediate noviosyl bromide is exclusively formed as the α-anomer **1.175**.



1.102 **1.175** **α/β-1.176**

Scheme 1.40: β-Noviosylation using noviosyl bromide: a) HBr (33 wt% in AcOH), CH_2Cl_2, 0°C to RT; b) cylcohexanol, Ag_2O, m.s. 4Å, CH_2Cl_2, RT, clean conversion, β only; c) cylcohexanol, Ag_2CO_3, m.s. 4Å, CH_2Cl_2, 81%, β only; d) cylcohexanol, AgOTf, m.s. 4Å, CH_2Cl_2, clean conversion, α:β 10:1.

Encouraged by these preliminary results, we moved on to the noviosylation of the central macrolide. Unfortunately, under Königs-Knorr conditions with silver oxide and silver carbonate neither the aglycon acceptor **1.52** nor the rhamnosylated macrolide **1.174** were glycosylated. Even with silver oxide freshly prepared from silver nitrate and sodium hydroxide, no reaction was observed. Instead, the glycosyl bromide was mostly consumed through elimination of HBr to give the enolether **1.177** (Figure 1.25). This elimination competes with the glycosylation reaction, meaning that the acceptor is not reactive enough.



1.175 **1.177**

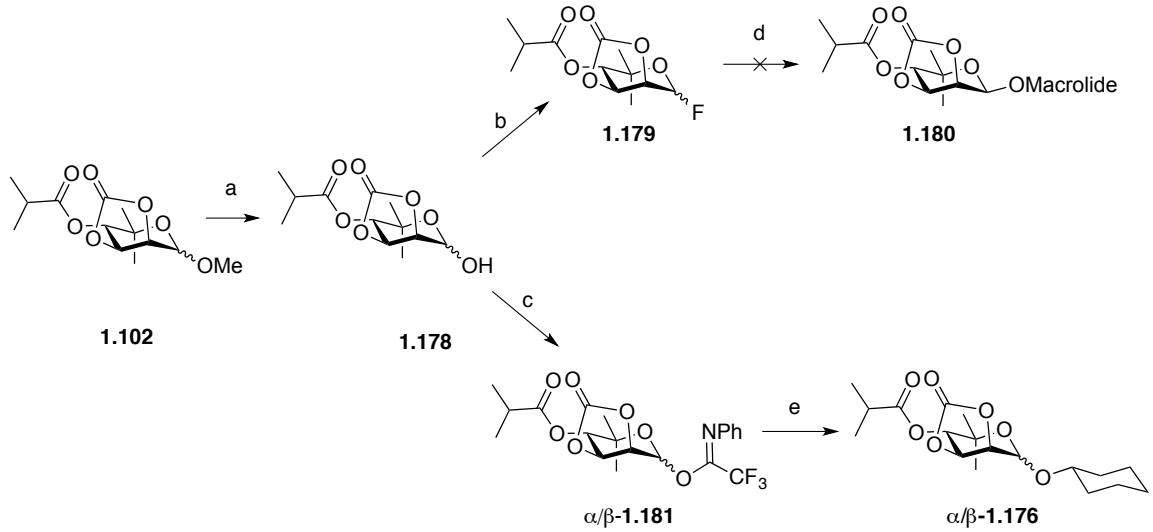
Figure 1.25: Attempted Königs-Knorr noviosylation with macrolide acceptors using Ag_2O and Ag_2CO_3 only resulted in elimination of HBr to give enolether **1.177**.

We then synthesized the fluoride- **1.179** and PTFAI-substituted donor **1.181** in order to increase the reactivity of the donor. Thus the methyl-novioside **1.102** was hydrolized in wet hydrogen bromide/acetic acid giving noviose **1.178** as an inseparable anomeric mixture of α:β = 2:1. Treating pyranose **1.178** with diethylaminosulfurtrifluoride (DAST) cleanly furnished noviosyl fluoride **1.179**, which was used without purification in the glycosylation step (Scheme 1.41). The PTFAI donor was synthesized from noviose **1.178** using phenyltrifluoroacetimidate chloride and potassium chloride in wet acetone to obtain the chromatographically separable anomers **1.181** in good yield.

The projected Mukaiyama glycosylation of the rhamnosylated macrolide **1.174** with fluoride donor **1.179** with an excess of tin dichloride did not give any conversion (Scheme 1.41).[125] The PTFAI-donor was first tested in the glycosylation of cyclohexanol. Interestingly, the α- and the β-imidate **1.181** both cleanly furnished the product **1.176** with the same diastereoselectivity of α:β = 3:2, using TBSOTf as the activator (Scheme 1.41). When the less bulky promoter TMSOTf was used the ratio shifted in favour of the α-product **1.176** (α:β = 3:1). This finding is in accordance with the results obtained with Schmidt's

[125] a) T. Mukaiyama, K. Takeuchi, H. Jona, H. Maeshima, T. Saitoh, *Helv. Chim. Acta* **2000**, *83*, 1901–1918; b) K. C. Nicolaou, H. J. Mitchell, R. M. Rodríguez, H. Suzuki, *Chem. Eur. J.* **2000**, *6*, 3116–3148; c) Review: K. Toshima, *Carbohydr. Res.* **2000**, *327*, 15–26.

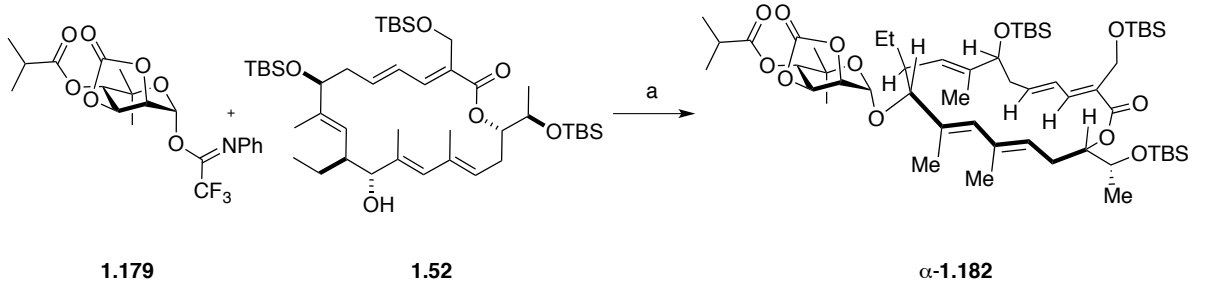
trichloroacetimidate donor.[126] It indicates that the electrophile (silyl) must be involved in the transition state of the selectivity determining nucleophilic attack. Thus, neither the glycosyl triflate CIP nor the covalent triflate intermediate is formed. As the leaving group can obviously migrate from one to the other face, a CIP between the donor and leaving group is likely.



Scheme 1.41: Synthesis of the fluoride- and PTFAI-donor: a) HBr (in AcOH 33wt%), CH_2Cl_2, H_2O RT then NaOH aq., 47%, α:β = 2:1; b) DAST, CH_2Cl_2, 0°C, quant.; c) $ClC(NPh)CF_3$, acetone, K_2CO_3, 88%, α:β = 4:3; d) **1.174**, $SnCl_2$, CH_2Cl_2, m.s. 4Å, 0°C to RT, 0% conv.; e) α-**1.181**, cyclohexanol, TBSOTf, CH_2Cl_2, m.s. 4Å, –78°C, full conversion, α:β = 3:2; or β-**1.181**, cyclohexanol, TBSOTf, CH_2Cl_2, m.s. 4Å, –78°C, full conversion, α:β = 3:2; or α-**1.181**, cyclohexanol, TMSOTf, CH_2Cl_2, m.s. 4Å, –78°C, full conversion, α:β = 3:1.

Though the anomeric selectivity was not in favour of the desired diastereomer, we intended to test the imidate donor **1.181** on the aglycon **1.52**, since the imidate donor has a high reactivity. On contrast to cyclohexanol, the aglycon was not consumed at –78°C. Thus, the reaction was allowed to slowly warm to room temperature, whereupon a complex mixture was obtained. After elaborative preperative TLC purification, we were able to isolate small amounts of the α-**1.182** novioside product; the β-**1.182** epimer could not be identified in the product mixture.

[126] T. Ikeda, H. Yamada, *Carbohydr. Res.* **2000**, *329*, 889–893.



1.179 **1.52** **α-1.182**

Scheme 1.42: α-Noviosylation of the fidacomicin aglycon: a) TBSOTf, CH_2Cl_2, m.s. 4Å, –78°C to RT, yield not determined, α-only.

Since, none of the noviosylations with the macrolide were successful and as only the α-anomer was isolated, we concluded that the macrolide acceptor was too unreactive to undergo efficient β-noviosylation. We thus approached a new strategy towards the total synthesis of fidaxomicin, in which the novioside is introduced at an earlier stage (chapter 1.6.5).

1.6.5 Step Back to Step Further – The Final Glycosylations

As a consequence of the low reactivity of the macrolide towards noviosylation (chapter 1.6.4), we decided to introduce the novioside on a linear, more flexible fragment at an early stage of the total synthesis. We chose the iodide fragment **1.184** as a suitable acceptor for this task. Thus intermediate **1.183** was deprotected using DIBAL-H in quantitative yield (Scheme 1.43).[127,128] The secondary alcohol **1.184** was submitted to Königs-Knorr glycosylation conditions with noviosyl bromide **1.175** to give the desired β-anomer **1.185** exclusively, but in low yield (20%). Encouraged by this result, we aimed to optimize the yield. We thus, lowered and increased the temperature, slowly added the donor to the acceptor and inverse, and added an excess of the glycosyl bromide. Unfortunately, all these variations did not lead to improved yields. Thus, we changed the promoter to silver carbonate, which worked as good as the reaction with silver oxide (Scheme 1.43). Employing conditions reported by Helferich[129] with mercury oxide and catalytic amounts of mercury bromide to mediate the reaction gave 63% yield of noviosylated fragment **1.185**, but not exclusively as the β-anomer, though still in good anomeric ratio (α:β = 1:3).

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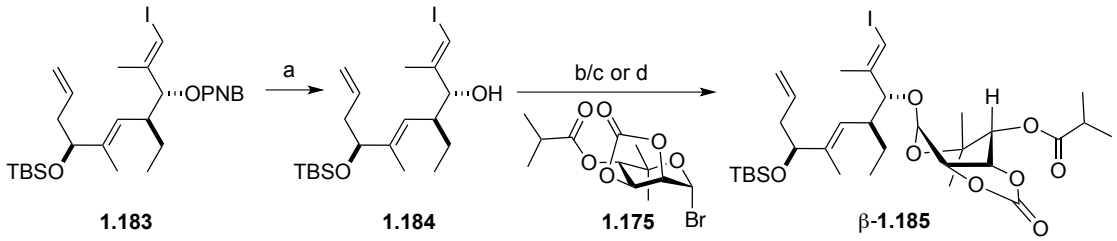
[127] The previous method using K_2CO_3/MeOH was troublesome for purification reasons as the PNB-acid was not separable from alcohol **1.184**.

[128] The reaction was performed by M.Sc. Hiromu Hattori, PhD-Student at the University of Basel/Zurich.

[129] a) B. Helferich, K. F. Wedemeyer, *Liebigs Ann. Chem.* **1949**, *563*, 139-145; b) L. R. Schroeder, J. W. Green, *J. Chem. Soc. C* **1966**, 530. c) Y. Chen, M. J. Heeg, P. G. Braunschweiger, W. Xie, P. G. Wang, *Angew. Chem. Int. Ed.* **1999**, *38*, 1768-1769.



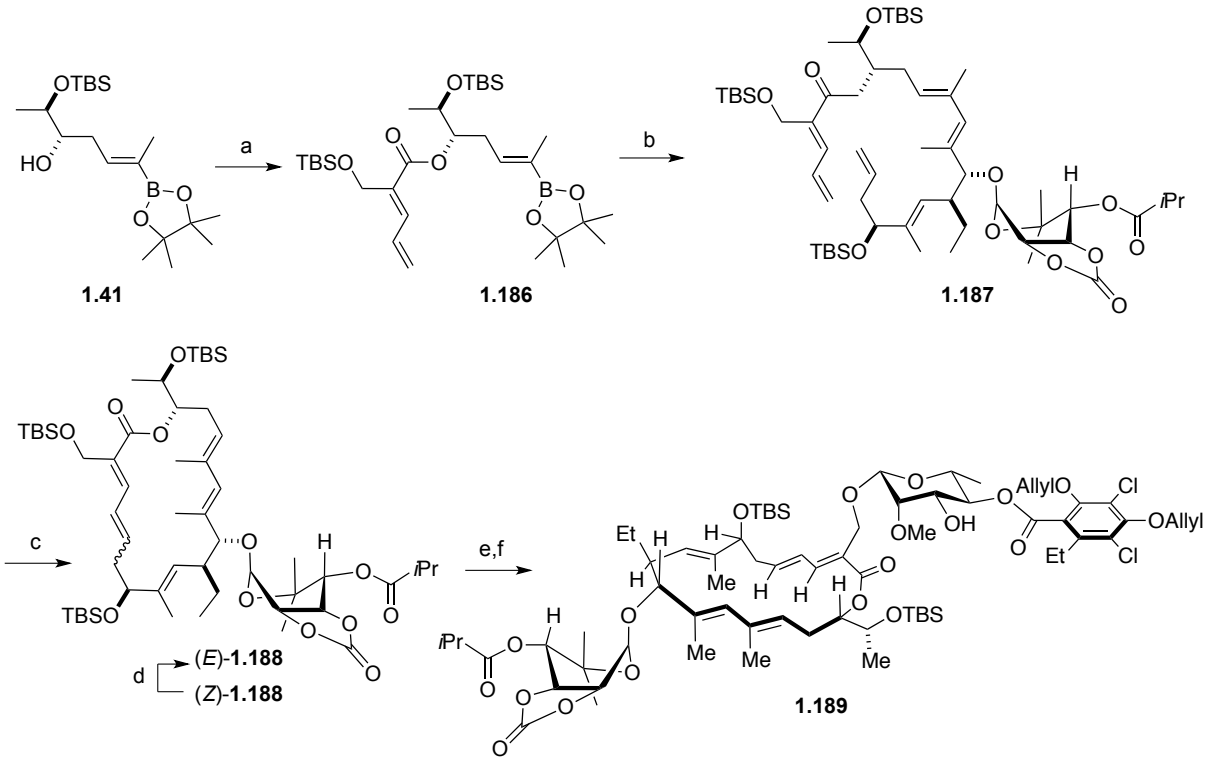
1.183 **1.184** **1.175** **β-1.185**

Scheme 1.43: β-Noviosylation of the linear iodide fragment: a) DIBAL-H, CH_2Cl_2, −78 to 0°C, quant.; b) HgO (6 equiv.), $HgBr_2$ (0.1 equiv.), m.s. 4Å, CH_2Cl_2, 63%, α:β = 1:3; c) Ag_2O, m.s. 4Å, CH_2Cl_2, RT, 20%, β-only; d) Ag_2CO_3, m.s. 4Å, CH_2Cl_2, 20%, β-only.

With the novioside installed, we moved on to the assembly of the remaining parts. Fragment **1.186** was prepared from the known precursor **1.41**[130] by Yamaguchi esterification (61%) with dienoic acid **1.55** (Scheme 1.44).[128] The following Suzuki cross coupling of the boronate **1.186** and noviosylated iodide **1.185** was highly effective and furnished product **1.187** in good yield.[128] Fortunately, the basic conditions ($[Pd(PPh_3)_4]$, TlOEt in THF/H_2O), also used by Altmann and Glaus in their aglycon synthesis,[130] did affect neither the base labile carbonate nor the ester moiety, which can be attributed to the very short reaction time (less than 30 min).[131] As in the synthesis of the aglycon (chapter 1.3), treatment of linear fragment **1.187** with the second generation Grubbs catalyst (20 mol%) for one hour at 100°C gave the macrolide with an (*E*/*Z*) ratio of 2:1 in 75% yield (54% of *E*-**1.188**).[128] Chromatographic separation of the *E*/*Z* isomers, allowed for a subsequent recycling of the (*Z*)-isomer. As a result, the overall yield of (*E*)-**1.188** in this transformation was increased to 63%. Selective deprotection of the primary TBS-ether was achieved with trihydrogenfluoride triethylamine in moderate yield (Scheme 1.44). The last step in fragment assembly was the rhamnosylation, which we had examined earlier on the aglycon **1.189** (chapter 1.6.3). Under the conditions that were found to work best in our screening with the PTFAI-rhamnosyl donor and TBSOTf as catalytic promoter, we reached the desired fidaxomicin precursor **1.189** in good yield (62%) and excellent anomeric ratio (α:β = 1:4). Finally, as all the fragments were successfully assembled, the last task was the global deprotection to furnish fully synthetic fidaxomicin for the first time (chapter 1.7.2).

[130] F. Glaus, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 1937–1940.

[131] S. A. Frank, H. Chen, R. K. Kunz, A. M. J. Schnaderbeck, W. R. Roush, *Org. Lett.* **2000**, *2*, 2691–2694.



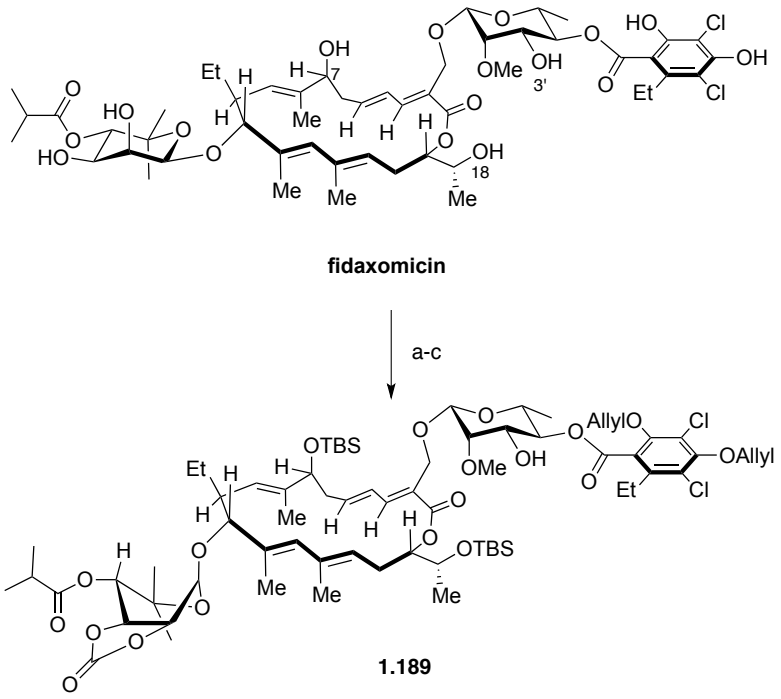
Scheme 1.44: Final assembly of the fragments and rhamnosylation: a) **1.55**, 2,4,6-$Cl_3H_2C_6COCl$, Et_3N, DMAP, toluene, RT, 61%; b) **1.185**, $[Pd(PPh_3)_4]$ (20 mol%), TlOEt, THF/H_2O 3:1, RT, 77%; c) Grubbs II (20 mol%), toluene, 100°C, 1 h, 75%, *E:Z* = 2:1; d) Grubbs II (20 mol%), toluene, 100°C, 11 h, 44% of (*E*)-**1.188**; e) 3HF·Et_3N, THF/CH_3CN 1:1, RT, 8 h, 49%; f) **1.169**, TBSOTf (20 mol%), CH_2Cl_2, –78 to –30°C, 62%, α:β = 1:4.

1.7 Global Deprotection and Relay Synthesis

In order to test our protecting group strategy as well as to get insights into the behaviour and stability of the advanced intermediates, we aimed to synthesize the appropriately protected compound **1.189** from commercially available fidaxomicin. In this chapter the relay-synthesis to the fully protected fidaxomicin and the global deprotection of semisynthetic and fully synthetic material is discussed.

1.7.1 Fidaxomicin Protection – Relay Synthesis

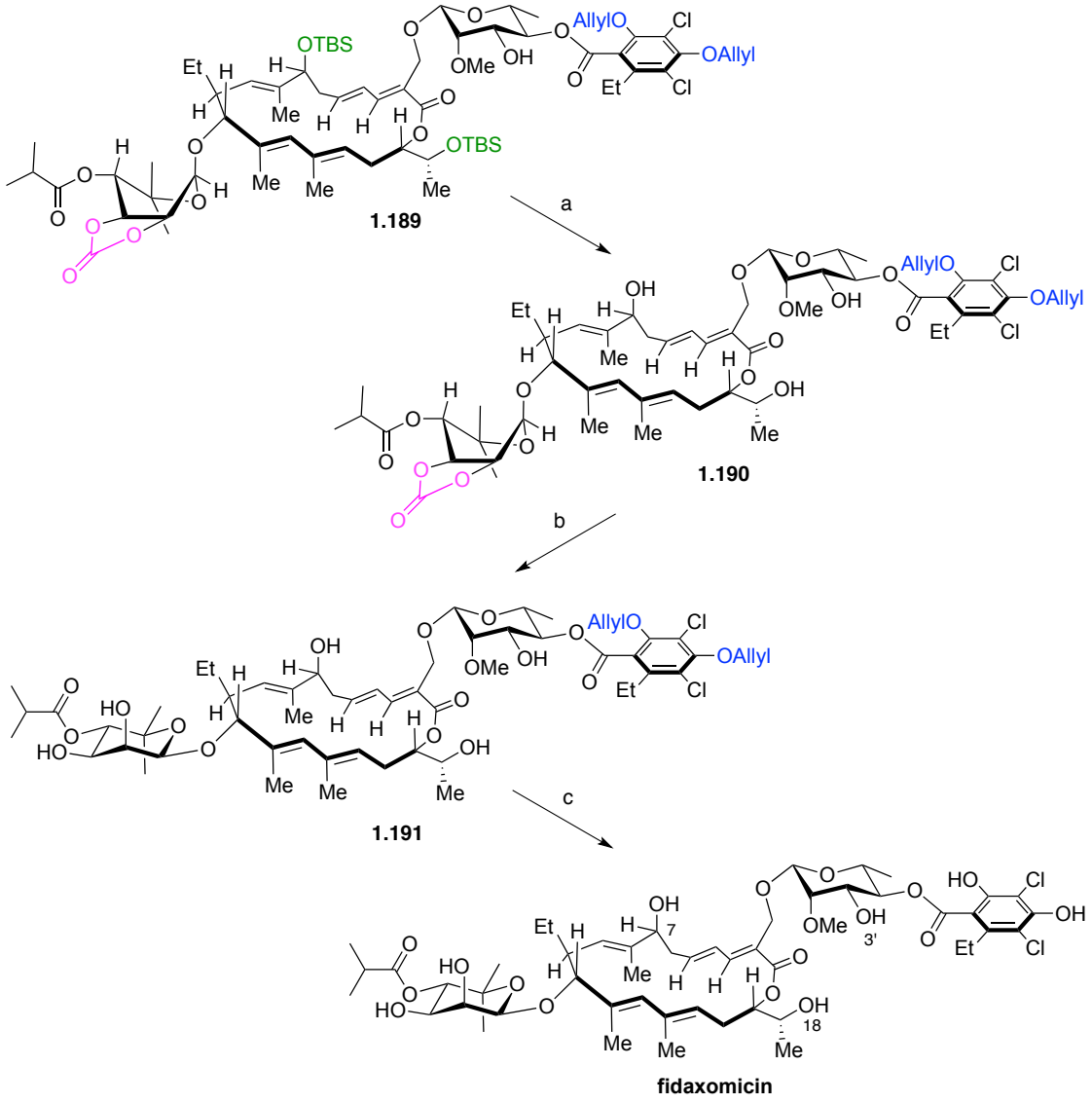
To selectively decorate the natural product, we first approached the allyl-protection of the phenols on the resorcylate unit using allyl bromide and potassium carbonate in DMF to furnish the desired diallyl-protected fidaxomicin **1.191** in good yield (89%, Scheme 1.45). We also tried to mono-protect the resorcylate by simply reducing the amount of allyl bromide to 1.0–1.5 equivalents. Thereby, we found that the phenolic OH group *para* to the ester reacts first, which was unambigiously identified by the characteristic signal at around 10 ppm corresponding to the phenol-group in *ortho*-position. The following carbonate-protection of the *cis*-diol proved to be sluggish. Repetitive addition of carbonyl diimidazole was required throughout the reaction, while carefully monitoring conversion by TLC. An excess of the reagent resulted in reaction with the free hydroxyl groups. The use of triphosgene/pyridine for the carbonylation was low-yielding and decomposition of the starting material was observed. We then protected the hydroxyl groups on the core macrolide as the TBS-ether, without affecting the free alcohol at the rhamnoside moiety (C3'-OH). Conveniently, the three hydroxyl groups reacted with very different rates (C18-OH > C7-OH >> C3'-OH). Thus, the protection using TBS-triflate could be controlled by the choice of the reaction time, the concentration and equivalents of the reactants. In this way, we achieved the desired late stage intermediate **1.189** of our total synthesis in 50% overall yield.



Scheme 1.45: Relay synthesis of the advanced protected intermediate of the total synthesis: a) allyl bromide, K_2CO_3, DMF, 45°C, 3 h, 89%; b) $(imid)_2CO$, Et_3N, CH_2Cl_2, RT, 24 h, 90%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to RT, 5 h, 63%.

1.7.2 The Global Deprotection Towards Fidaxomicin

With the intermediate **1.189** in hand, we examined the conditions for the projected deprotection reactions of our protecting group strategy. We planned to perform the global deprotection in the reverse order as the protection. Thus, we exposed the silyl ether **1.189** to trihydrogenfluoride triethylamine in THF (Scheme 1.46). As already recognized in the TBS-protection, the reaction rate of the two silyl ethers differs substantially. While the 1st silyl ether at position C18 was already cleaved at room temperature after few hours, the silyl ether at C7 required much harsher conditions (50°C, 24 h). In this way, the carbonate/allyl-protected fidaxomicin **1.190** was isolated in good yield (88%). It should be mentioned, that the yield using fully synthetic starting material – probably due to its lower purity – was lower (60%).

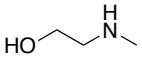


Scheme 1.46: a) 3HF·Et_3N, THF, 50°C, 24 h, 88%; b) NaH (0.04 mol%), ethylene glycol, THF, 0°C, 15 min, 46% (53%brsm); c) morpholine, [$Pd(PPh_3)_4$] cat., THF, 0°C, 30 min, 86%.

The carbonate cleavage was highly challenging, mainly due to competing hydrolysis and isobutyrate ester-migration to adjacent positions. To find the optimal conditions with the best selectivity and conversion, we screened different bases and nucleophiles (Table 1.8). The quality of the deprotection was determined by NMR spectroscopy since the desired product **1.191** was inseparable by column chromatography from the products bearing the ester at C2" and C3". No conversion was observed using DBU in dry CH_2Cl_2 (Entry 1), but in wet solvents (Entry 2,3), a rather complex mixture of hydrolized and migrated products with some desired products were formed. DMAP in CH_2Cl_2/CH_3OH showed only little conversion and seemed to stop, even addition of more base did not push the reaction to completion (Entry 5). Triethylamine in methanol, on the other hand, was very unselective and induced migration of the ester to a large extent (Entry 6,7). Even less selective was the secondary amine 2-

(methylamino)-ethanol, giving a 1 : 1 mixture of fully hydrolysed to mono esterified products, while starting material was still present (Entry 8). Astonishingly, the rather harsh conditions reported in Entry 9 to 11 did not lead to any conversion of the starting material. We were very pleased to find Barton's base to be sufficiently selective, if the reaction was stopped as soon as the formation of fully hydrolysed byproduct was monitored (Entry 12). Purification of this reaction by column chromatography gave 16% of recovered starting material and 54% of the desired product **1.191** along with inseparable byproducts. This material was directly subjected to the next deprotection step using tetrakis(triphenylphosphine) palladium (0) and morpholine at 0°C. This furnished fidaxomicin smoothly within 30 minutes. Purification first by column chromatography and then RP-HPLC gave only 10% yield over the two steps (conducted with semisynthetic and fully synthetic material).

Table 1.8: Screening of conditions for the carbonate deprotection.

	Reagent ([v/v])	Solvent/Temp. [°C]	time	Observation
1	DBU (0.02)	dry CH_2Cl_2; RT	18 h	no conv.
2	DBU (0.02)	wet CH_2Cl_2; RT	16 h	13% p./bp
3	DBU (0.02)	wet THF; RT	0.5 h	p. + many bp.
4	DABCO cat.	wet CH_2Cl_2; RT	2 h	no conv.
5	DMAP cat.	CH_2Cl_2/CH_3OH; RT	18 h	low conversion
6	Et_3N (0.1)	MeOH; RT	12 h	p. + many bp. + s.m.
7	Et_3N (0.1)	MeOH; 40°C	4 h	p. + many bp. + s.m.
8	 (0.02)	Hex/CH_2Cl_2; RT	18 h	p:bp 1:1 + s.m.
9	K_2CO_3 (0.07 g/mL)	H_2O/THF; 50°C	1.5 h	no conv.
10[a]	–	H_2O/THF; 150°C	0.5 h	no conv.
11[a]	DIBAL-H	CH_2Cl_2; –40°C		no conv.
12[a]	Barton's base (0.02)	wet CH_2Cl_2; RT	5 h	54% p./minor bp.+16% s.m.
13	NaH (cat.)	THF/MEG; 0°C	15 min	55% p./minor bp.+13% s.m.

p. = product; bp. = byproduct (mainly fully hydrolized and migrated ester); s.m.= starting material;
[a] experiments conducted by Dr. Hideki Miyatake Ondozabal, post doctoral researcher at Univ. of Basel.

Though, we could not conclusively figure out the reason for the low yield of the last two steps in the deprotection sequence, we further investigated on the carbonate deprotection step. We found that catalytic amount of sodium hydride in THF/ethylene glycol (10/1) efficiently furnished the desired product with only a minimum amount of byproducts (Entry 13). Purification by column chromatography and subsequent RP-HPLC gave 46% yield of

allylated fidaxomicin **1.191**. This material was further deprotected to obtain fidaxomicin in 86% yield without the need for another elaborate RP-HPLC purification (Scheme 1.46). To illustrate the differences of Entry 3, 12 and 13 (Table 1.8), the ^{1}H-NMR spectra of the reactions after column chromatography are shown in Figure 1.26. The reaction using NaH/ethylene glycol gives a ratio of product to inseparable byproducts of around 5:1. The deprotections using DBU and Barton's base, on the other hand, led to formation of inseparable byproducts in substantial amounts. Further, the overall yield of the two last steps using Barton's base was only 10% and the one using NaH/ethylene glycol 40%. Thus the global deprotection sequence using the latter carbonate deprotection is the route of choice.

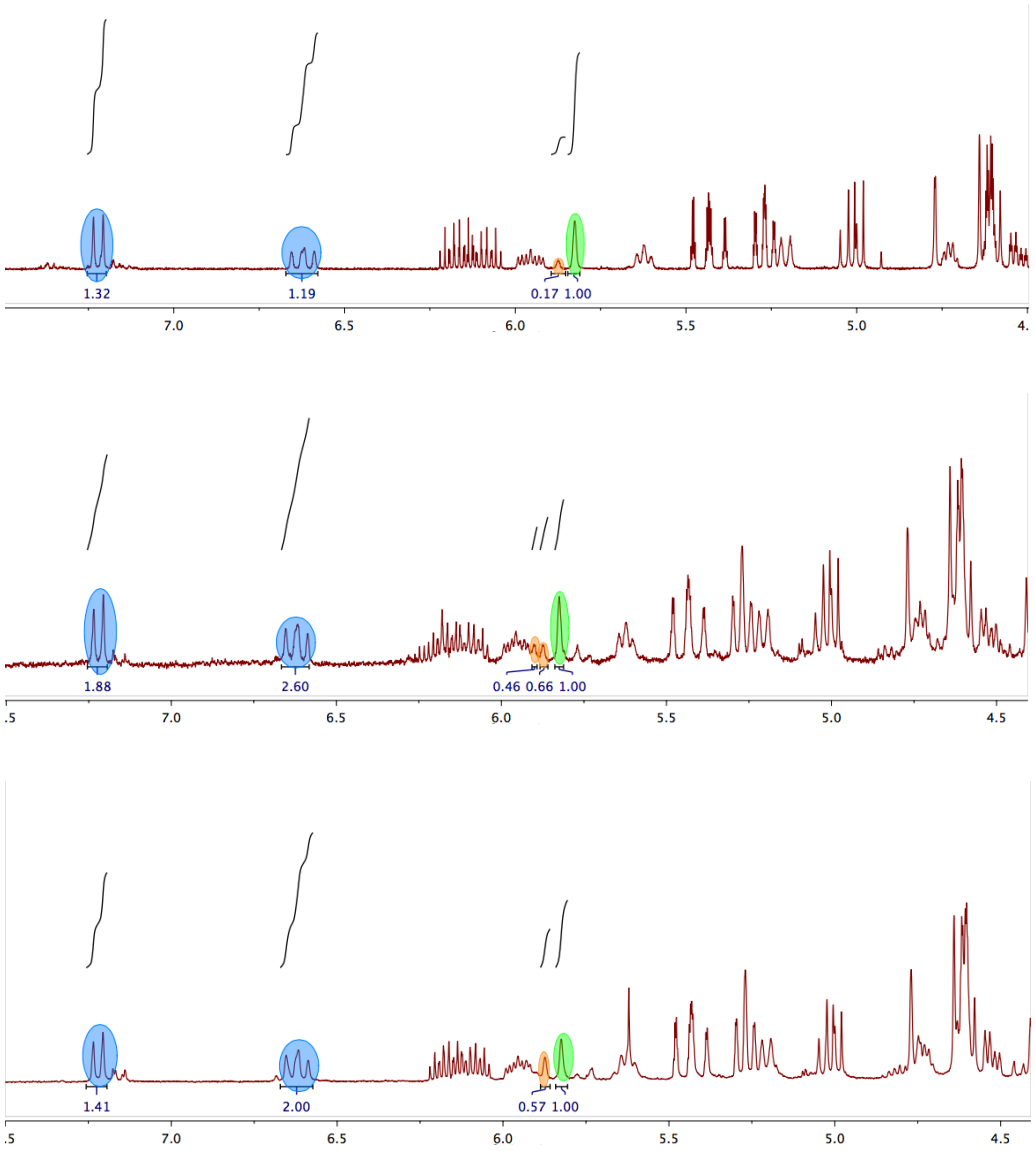


Figure 1.26: ^{1}H-NMR spectra of the carbonate deprotection after column chromatography. Green: product peak; orange: byproduct peaks; blue: superimposed product and byproduct peaks. Top: NaH (cat.), ethylene glycol, THF, 0°C, 15 min; middle: Barton's base, wet CH_2Cl_2, RT, 5 h; bottom: DBU, wet CH_2Cl_2, RT, 18 h.

Confusingly, after global deprotection and RP-HPLC purification of fully synthetic fidaxomicin, the ^{1}H-NMR-spectra did not fully match with the spectra of natural fidaxomicin (Figure 1.27). The signals of the resorcylate-rhamnosyl part were shifted, whereas the signals from the macrolide and the novioside were identical with the corresponding signals of the authentic fidaxomicin sample.

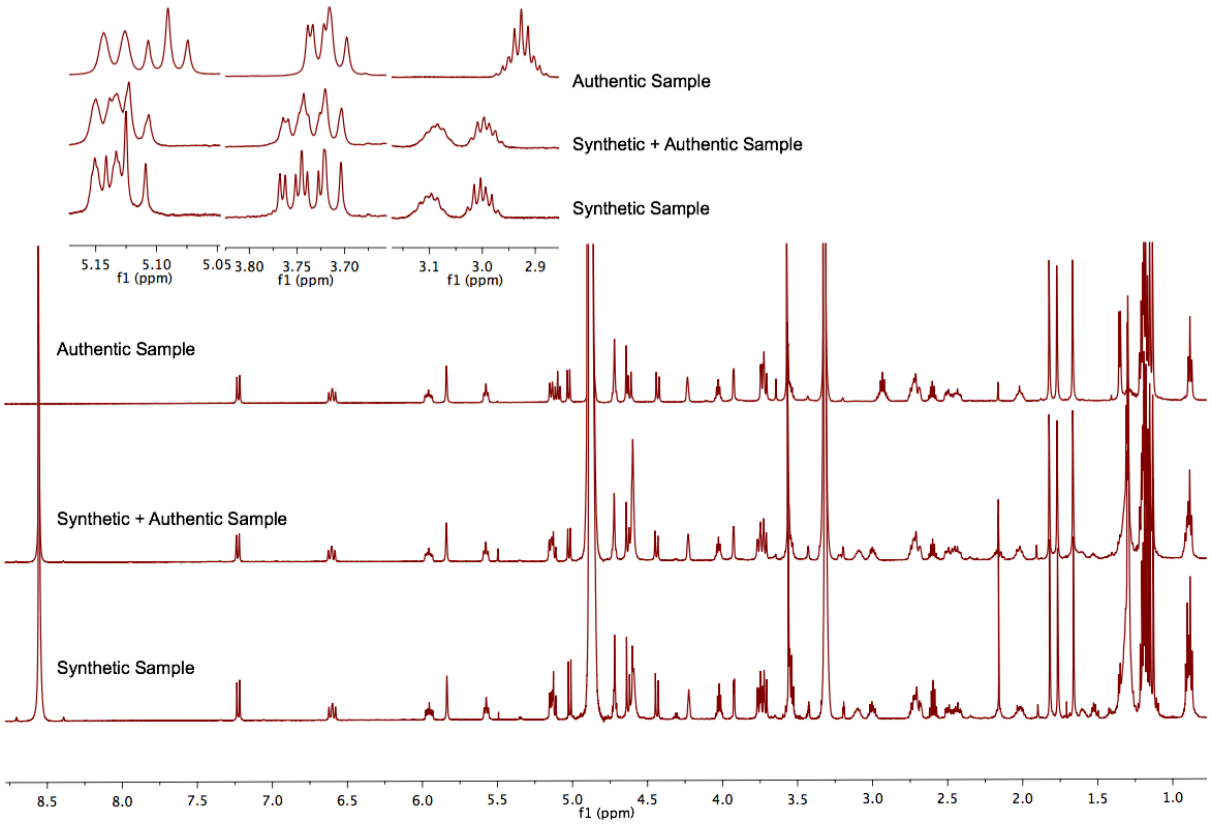


Figure 1.27: Proof of co-identity of the natural and fully synthetic (containing formate) fidaxomicin in CD_3OD.

We figured that the acidic phenol groups of the resorcylate might be shifted due to the formate salt present in the fully synthetic sample. This assumption was confirmed by equimolar mixing of the authentic with the fully synthetic sample. The spectra of this mixed sample showed only one set of signals, which proofs the co-identity of the fully synthetic and natural fidaxomicin. Further proof was gained by addition of ammonium formate to an authentic sample and comparison with the spectra under neutral conditions. Also in this case the signals of the resorcylate-rhamnosyl part were shifted (Figure 1.28).

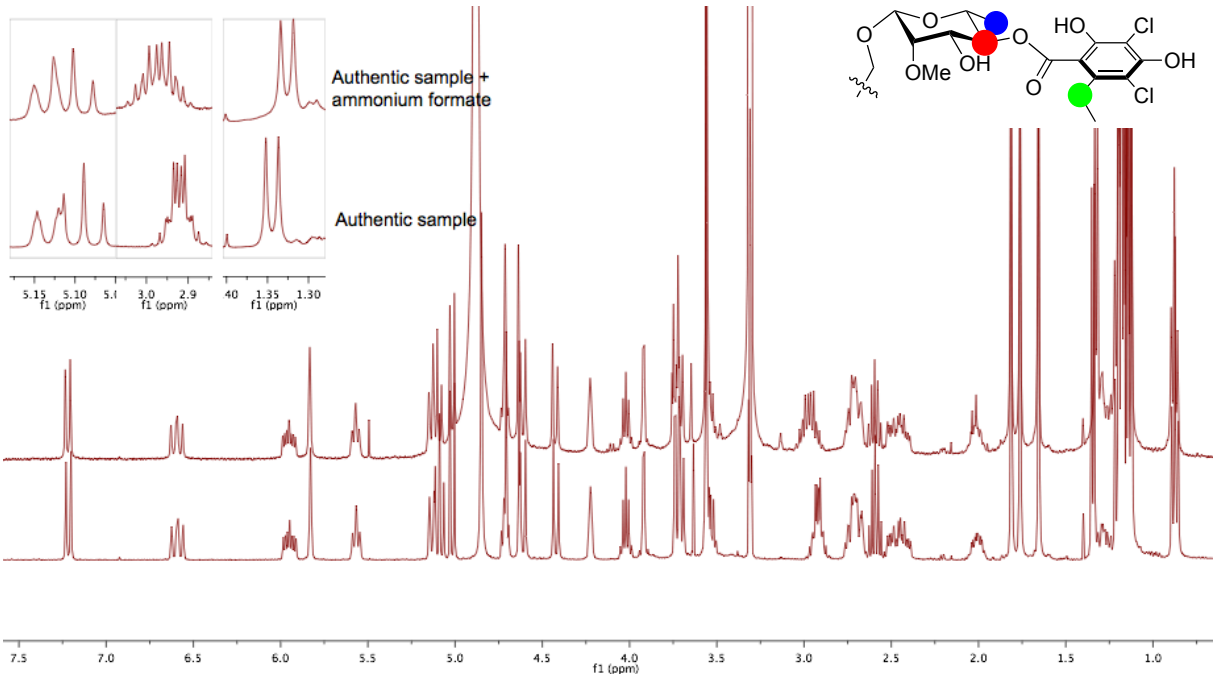


Figure 1.28: Comparison of the chemical shifts of pure fidaxomicin and a sample treated with ammonium formate. Depicted regions are highlighted: red, δ 5.10 ppm: CH4' triplett of rhamnosyl part; green, δ 2.92 ppm methlyene substituent at resorcylate; blue, δ 1.35 ppm CH6' methyl group of rhamnosyl part.

Further proof of the co-identity was obtained by co-injection of fully synthetic and natural fidaxomicin on an RP-HPLC instrument (Figure 1.29).

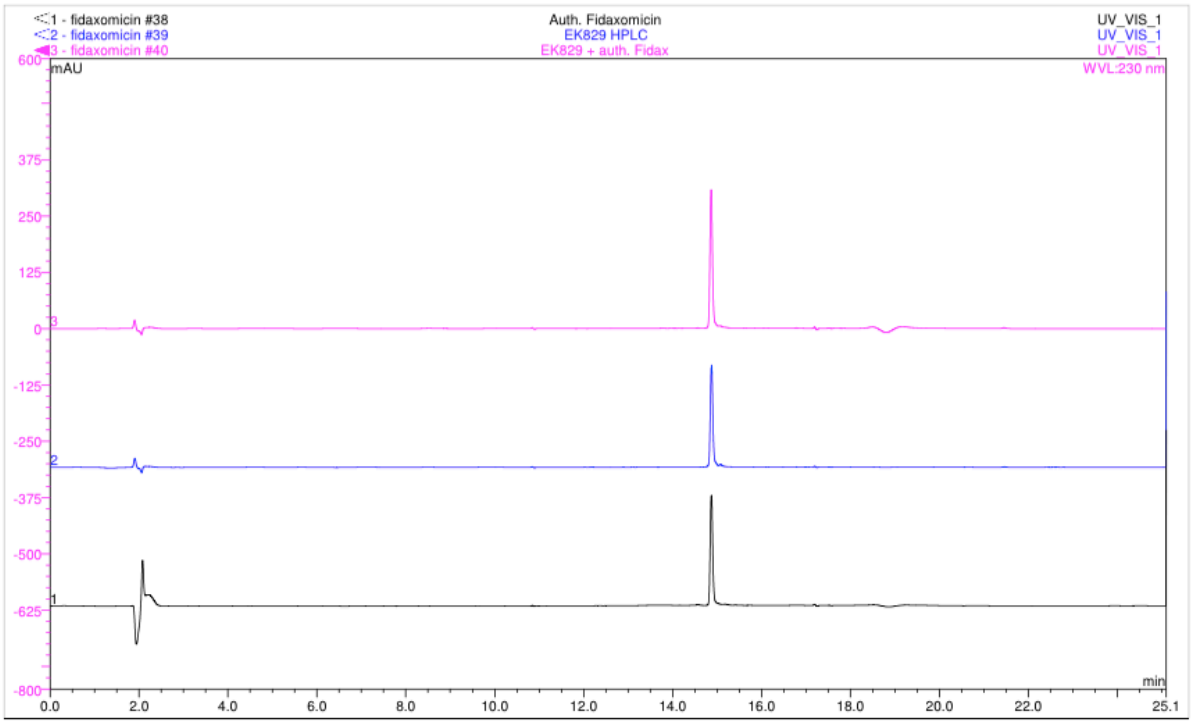


Figure 1.29: RP-HPLC co-injection of the authentic and synthetic compound. Black = authentic sample; blue = fully synthetic sample; pink = mixture of authentic and fully synthetic sample.

1.8 Conclusion and Outlook

In this project, we accomplished the first total synthesis of the antibiotic fidaxomicin. The natural product is a novel therapeutic for the treatment of *Clostridium difficile* infections (CDI) in the gastrointestinal tract. Besides the advantageous activity against CDI, the natural product is active against various other pathogens, most strikingly against multidrug-resistant strains of *Mycobacterium tuberculosis*. Unfortunately, the pharmacological properties of the natural product are not suitable for the treatment of systemic diseases. Thus, structural modifications of the antibiotic are highly desirable in order to improve its pharmacokinetic characteristics.

Fidaxomicin consists of a central macrolide attached to a D-noviose and a D-rhamnose-resorcylate fragment. The unusual D-novioside **1.103** was prepared by a novel and short synthetic approach (six steps). The resorcylate unit **1.128** was synthesized using a biomimetic aromatization approach (four steps), and a regioselective esterification with the rhamnoside **1.144** (five steps) furnished the resorcylate-rhamnoside fragment in a very straightforward way. The synthesis of the central macrolide was based on three main fragments, assembled by a Stille cross-coupling, a vinylogous Mukaiyama aldol reaction and a ring-closing metathesis (14 steps). Attempts to introduce the novioside at the central macrolactone failed due to the low reactivity of the macrolide acceptor. Thus, noviosylation was performed on a linear fragment **1.184** before assembly of the macrolide, constituting the first β-selective noviosylation reported. The connection of the remaining fragments feature a Suzuki cross-coupling of sterically demanding substrates and a ring-closing metathesis. The challenging β-rhamnosylation has been elaborated by systematic variation of the donor-conformation and screening of leaving groups, to finally reach high diastereomeric ratio with the PTFAI-donor **1.169** in the $^4C_1$ conformation. Subsequent global deprotection furnished fully synthetic fidaxomicin for the first time. NMR and HPLC measurements unambiguously established the co-identity of the synthetic material and an authentic sample of the natural product. The reported total synthesis is highly convergent (six fragments) and the longest linear sequence is only 16 steps.

The total synthesis as well as the results of the semisynthetic studies pave the way for the generation of structurally diverse analogues. In our laboratories, investigations using fully synthetic and semisynthetic strategies are on-going, to address the shortcomings of the pharmaceutical.

2 Methionine-Derived Iminium Lactones

2.1 Introduction

The inception of this project was the idea of a distinct chemical transformation. The application of the transformation or its product was only vague at that time. Thus, the aim of the project was very flexible and the project purely curiosity-driven. Along the study of this venture, a sudden observation shifted our attention to a different objective. This introducing chapter, thus, starts with the general idea, followed by some background information, which also applies for the second objective.

The initial idea of this project was a simple and unusual chemical transformation. In this reaction a peptidic methionine building block should be transformed to a 5,6-dihydro-4*H*-1,3-oxazine (Figure 2.1). To initiate the reaction, an electrophile should convert the thioether into a leaving group and a subsequent 6-*exo*-*tet* cyclisation by the attack of the amide portion should take place.

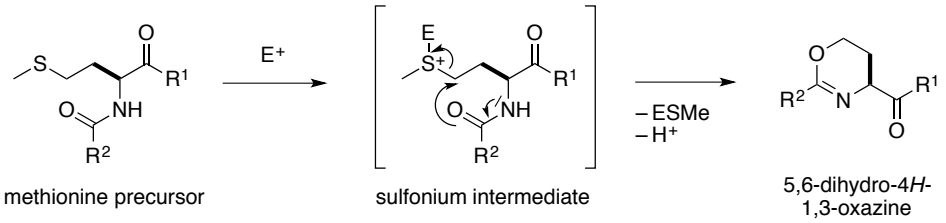


Figure 2.1 The general concept: Transformation of methionine to a 1,3-oxazine by electrophilic activation and subsequent attack of the amide portion.

This transformation is interesting since it yields functionalized 1,3-oxazines from relatively cheap, chiral starting materials in a straightforward way. Furthermore, 5,6-dihydro-4*H*-1,3-oxazines are valuable synthetic intermediates and present in molecules with interesting bioactivities (Chapter 2.1.2). Also, the oxazines could be an interesting motif in peptidomimetic research (Chapter 2.3.3). In the following sections, background to related synthetic contributions in literature, 5,6-dihydro-4*H*-1,3-oxazines and peptide drugs are given.

2.1.1 Related Synthetic Contributions

The transformation of thioethers to leaving groups through electrophilic activation is a common concept. Mostly, methyl iodide or 2-iodo acetates are used as alkylating agent to obtain the corresponding sulfonium ions. So far only five-membered rings and no six-membered rings have been synthesized in this way. In the following section, several examples of intramolecular cyclisations using the thioether as triggerable leaving group are mentioned.

Methionine is a frequently used precursor for homoserine lactones, such as **2.2**. It can be easily prepared by the treatment of **2.1** with an alkylating agent in acidic aqueous media (equation 1, Scheme 2.1).[132] Similarly, boiling hydroxylamide **2.3** with methyl iodide and subsequent addition of base gave the cyclized hydroxylimino ether **2.4** (equation 2).[133] Alkylation and subsequent base treatment of methionine linked by a secondary amide at the C-terminus, such as **2.5** gave γ-lactam **2.6** (equation 3).[134] The concept was also recognized as a useful too for peptide sequencing and identification by peptide bond cleavage C-terminal to methionine, using cyanogen bromide (equation 4).[135] In addition, 1,3-oxazolidines **2.12** (equation 5) have been prepared from thioether **2.11** and dimethyl(methylthio)sulfonium fluoroborate (DMTSF).[136]

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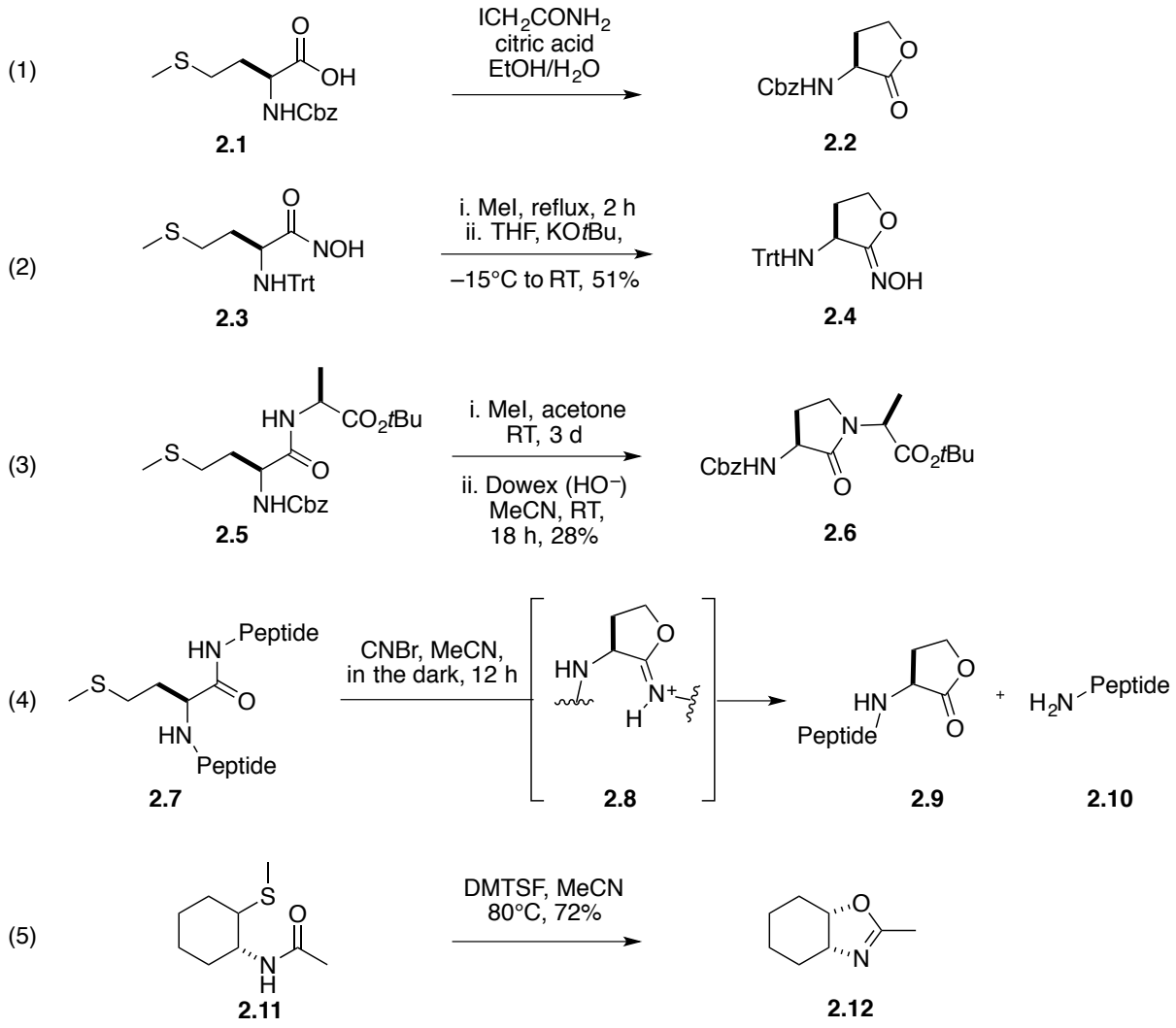
[135] a) E. Gross, B. Witkop, *J. Am. Chem. Soc.* **1961**, *83*, 1510–1511; b) W. B. Lawson, E. Gross, C. M. Foltz, B. Witkop, *J. Am. Chem. Soc.* **1962**, *84*, 1715–1718; c) R. Kaiser, L. Metzka, *Anal. Biochem.* **1999**, *266*, 1–8.

[136] a) B. M. Trost, T. Shibata, *J. Am. Chem. Soc.* **1982**, *104*, 3225–3228.

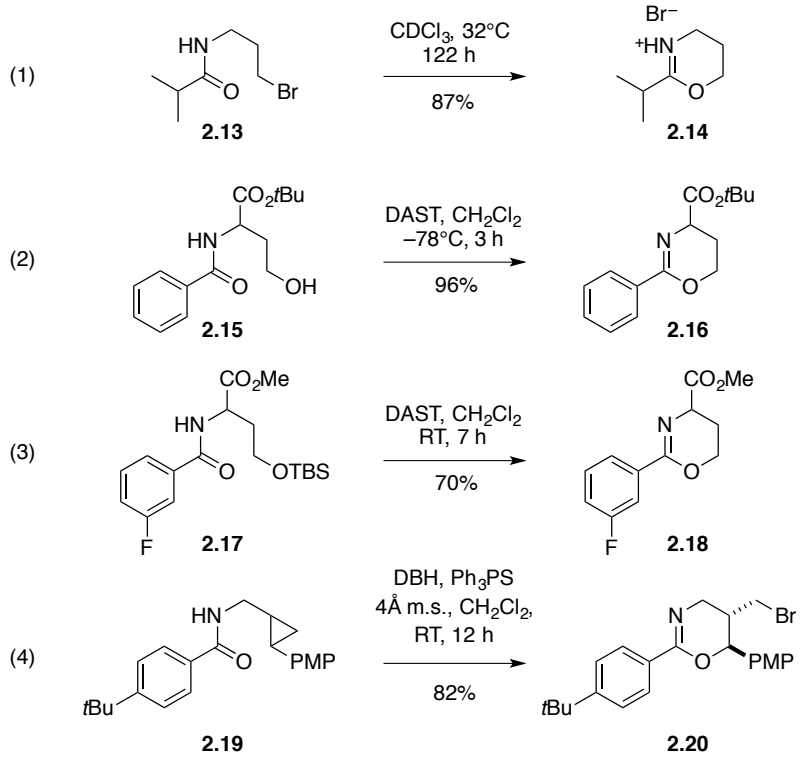


Scheme 2.1: Selected methionine activation/cyclization reactions.

In contrast, the 6-*exo*-*tet* cyclisations to prepare 5,6-dihydro-4*H*-1,3-oxazines with other leaving groups than trialkylsulfonium ions has been widely applied, and some are depicted in Scheme 2.2. Probably the most common among them feature a halogen as leaving group. The reaction can be enhanced with silver salts, but also takes place spontaneously as shown by Prabhakaran *et al.* (equation 1).[137] Various conditions for the activation of hydroxy groups,

[137] a) D. N. Reddy, E. N. Prabhakaran, *J. Org. Chem.* **2011**, *76*, 680–683; b) P. Deslongchamps, P. Soucy, *Tetrahedron* **1981**, *37*, 4385–4390; d) T. Nishikawa, D. Urabe, K. Yoshida, T. Iwabuchi, M. Asai, M. Isobe, *Org. Lett.* **2002**, *4*, 2679–2682.

followed by cyclisations have been reported.[138] In equation 2, a functionalized homoserine **2.15** was treated with (diethylamino)sulfur trifluoride (DAST) to give the 1,3-oxazine **2.16** in high yield. Also, silyl ether protected alcohols have been activated using DAST (equation 3).[139] In a recent example, 1,3-oxazine **2.20** was furnished by cyclopropane ring-opening of **2.19**, induced by bromination with 1,3-dibromo-5,5-dimethyl-hydantoin (DBH) and catalytic amounts of Ph_3PS as activator.[140]



Scheme 2.2: Selected 6-*exo*-*tet* cyclisations with internal amide bond to form 1,3-oxazines.

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[138] a) T.-S. Kim, Y.-J. Lee, K. Lee, B.-S. Jeong, H.-G. Park, S.-S. Jew, *Synlett* **2009**, *2009*, 671–674; b) M.-F. Pouliot, L. Angers, J.-D. Hamel, J.-F. Paquin, *Tetrahedron Letters* **2012**, *53*, 4121–4123; c) T. Sauvaître, M. Barlier, D. Herlem, N. Gresh, A. Chiaroni, A. D. Guenard, C. Guillou, *J. Med. Chem.* **2007**, *50*, 5311–5323; d) J. Huber, J. Wölfling, G. Schneider, I. Ocsovszki, M. Varga, I. Zupkó, E. Mernyák, *Steroids* **2015**, *102*, 76–84.

[139] a) B. B. Metaferia, B. J. Fetterolf, S. Shazad-Ul-Hussan, M. Moravec, J. A. Smith, S. Ray, M.-T. Gutierrez-Lugo, C. A. Bewley, *J. Med. Chem.* **2007**, *50*, 6326–6336; b) T. Kline, N. H. Andersen, E. A. Harwood, J. Bowman, A. Malanda, S. Endsley, A. L. Erwin, M. Doyle, S. Fong, A. L. Harris, *et al*., *J. Med. Chem.* **2002**, *45*, 3112–3129.

[140] Y.-C. Wong, Z. Ke, Y.-Y. Yeung, *Org. Lett.* **2015**, *17*, 4944–4947.

2.1.2 5,6-Dihydro-4*H*-1,3-oxazines

5,6-Dihydro-4*H*-1,3-oxazines are abundant structural motifs in bioactive compounds, such as choline acetyl transfer inhibitors,[141] acetylcholine-esterase inhibitors,[138c] cytostatics[138d] and β-secretase inhibitors for clinical evaluation against Alzheimer's disease.[142]

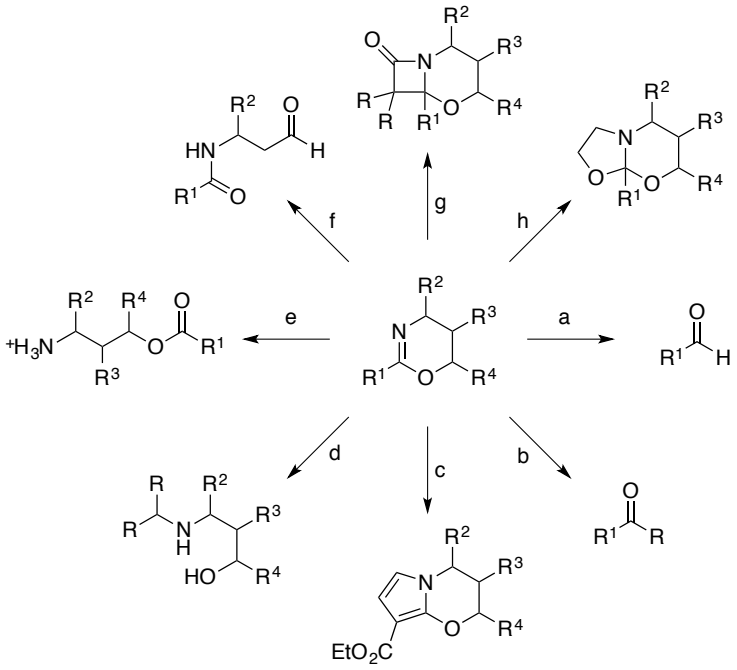

Figure 2.2 5,6-Dihydro-4*H*-1,3-oxazines as versatile synthetic precursor. a) i. $NaBH_4$, THF/EtOH/H_2O, ii. aq. oxalic acid, 60-70%;[143] b) i. MeI, RT ii. RMgX, ether, iii. aq. oxalic acid, 22-85%;[144] c) R^1=CH_2CO_2Et, NaH, $ICH_2CH(OEt)_2$, DMSO, RT then TFA, toluene, reflux;[145] d) R_2CO, H_2 (50 atm.), Pd/C, RT, 30-91%;[148] e) HCl or HBr, H_2O, % n.d.;[147a] f) R^1=Ph; R^2=Ph; R^4=OR, Amberlyst, acetone, H_2O, RT, quant;[146a] g) R^1=Ar, $R_2CH_2CO_2Tos$, Et_3N, CH_2Cl_2, RT, 48h;[149a] h) ethylene oxide, 120-200°C, 27–61%.[149b]

The heterocycle also gained attention as valuable synthetic intermediate for aldehydes,[143] ketones,[144] pyrroles,[145] β-amido aldehydes,[146] β-amino esters,[147] aminoalcohols[148] and

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[141] N. B. Mehta, D. L. Musso, H. L. White, *Eur. J. Med. Chem.* **1985**, *20*, 443-446.

[142] H. Hilpert, W. Guba, T. J. Woltering, W. Wostl, E. Pinard, H. Mauser, A. V. Mayweg, M. Rogers-Evans, R. Humm, D. Krummenacher, T. Muser, C. Schnider, H. Jacobsen, L. Ozmen, A. Bergadano, D. W. Banner, R. Hochstrasser, A. Kuglstatter, P. David-Pierson, H. Fischer, A. Polara, R. Narquizian, *J. Med. Chem.* **2013**, *56*, 3980–3995.

[143] a) A. I. Meyers, A. Nabeya, H. W. Adickes, *J. Am. Chem. Soc.* **1969**, *91*, 763–764; b) A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, *J. Am. Chem. Soc.* **1969**, *91*, 764–765.

[144] A. I. Meyers, E. M. Smith, *J. Org. Chem.* **1972**, *37*, 4289–4293.

bicycles[149] (Figure 2.2). The cyclic imidate is stable in water and cold basic media, but hydrolyses under acidic aqueous conditions.

Further, it was found those terminal 1,3-oxazine in peptides are able to force a peptide bond into a natively disallowed conformation (cf. the Ramachandran map) (Figure 2.3).[137a,150] This behaviour might be useful to stabilize secondary structures in peptides and is thus of special interest for the design of peptidomimetics.

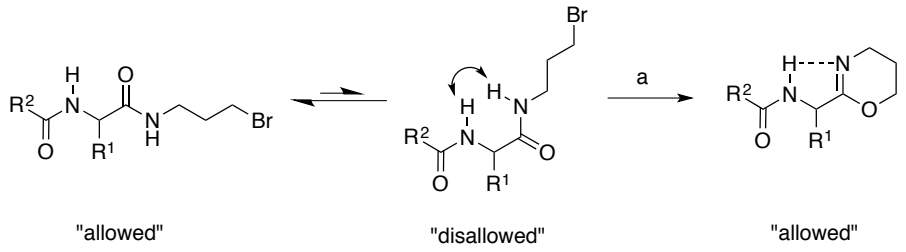

Figure 2.3 The amide to imidate modification gives access to an otherwise disallowed conformation.[137a] a) NaH, THF, 0°C to RT, 97% to quant.

[145] T. A. Narwid, A. I. Meyers, *J. Org. Chem.* **1974**, *39*, 2572–2574.

[146] a) P. Gizecki, R. Dhal, L. Toupet, G. Dujardin, *Org. Lett.* **2000**, *2*, 585–588; b) S. H. Kang, C. M. Kim, J. H. Youn, *Tetrahedron Lett.* **1999**, *40*, 3581–3582.

[147] a) S. Gabriel, *Liebigs Ann. Chem.* **1915**, *409*, 305–327; b) P. Wipf, G. B. Hayes, *Tetrahedron* **1998**, *54*, 6987–6998.

[148] A. Balazs, Z. Szakonyi, *J. Heterocycl. Chem.* **2007**, *44*, 403–406.

[149] a) M. Miykae, N. Tokutake, M. Kirisawa, *Synthesis* **1983**, 833–835; b) W Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, H. Hellmann, *Angew. Chem. Int. Ed.* **2015**, *5*, 875–888.

[150] a) D. N. Reddy, R. Thirupathi, S. Tumminakatti, *Tetrahedron* **2012**, *53*, 4413–4417; b) D. N. Reddy, R. Thirupathi, E. N. Prabhakaran, *Chem. Commun.* **2011**, *47*, 9417–9419.

2.1.3 The Peptide and Protein Architecture

Proteins and peptides are essential for all the living species on our planet.[151] They are fulfilling a range of diverse functions in living organisms in the form of enzymes, signalling molecules, toxins, antibodies or structural proteins. Nature has twenty proteogenic amino acids on hand to build these peptides by linear covalent amide bond connections (primary structure) during translation. Various post-translational modifications increase the range of diversity of proteins even further.[152]

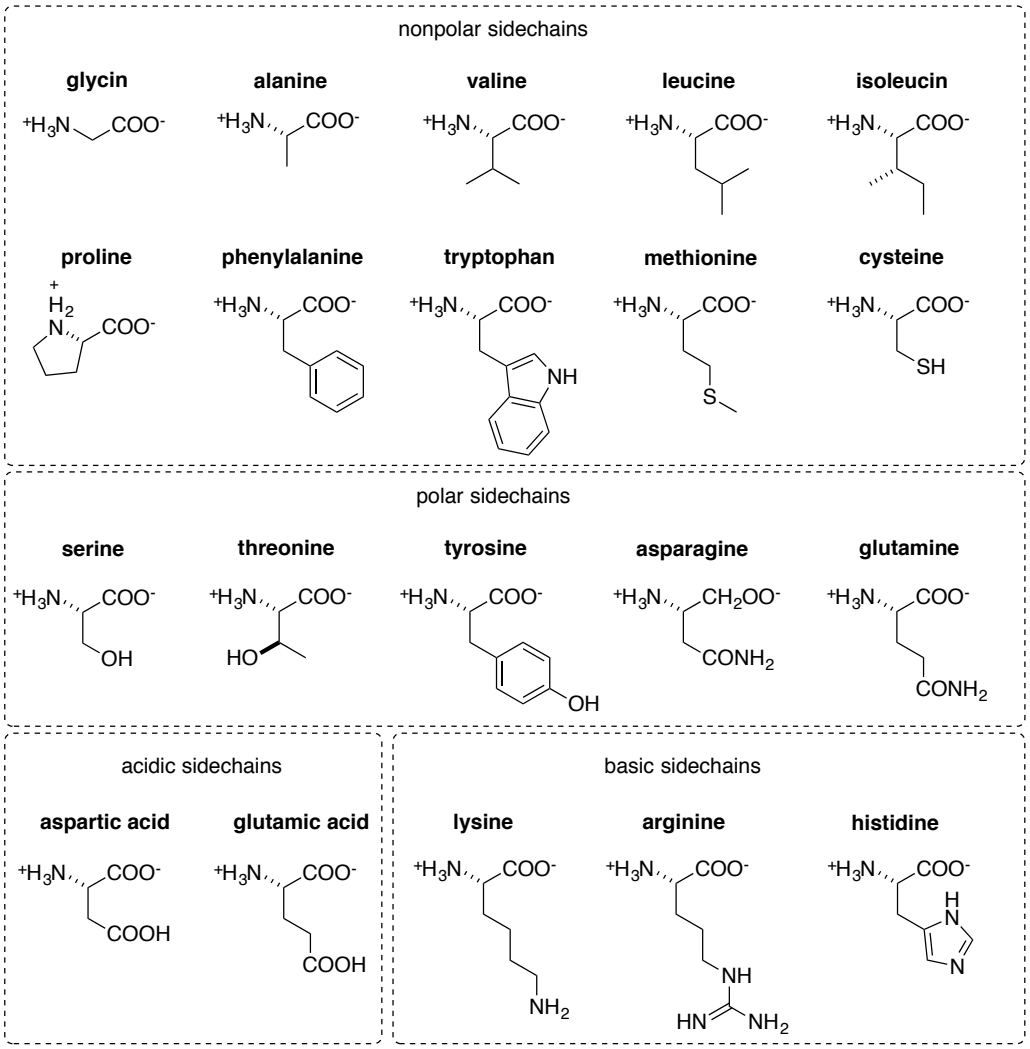

Figure 2.4: The proteogenic amino acids encoded by RNA codons.

The peptide chains arrange in a distinct, yet flexible and three-dimensional shape (e.g. α-helices, β-sheets) with high complexity (secondary and tertiary structure). Thereby, the side

[151] J. Reece, L. A. Urry, N. Meyers, M. L. Cain, *Campbell Biology*, Pearson Benjamin Cummings, **2011**.

[152] D. Voet, J. G. Voet, C. W. Pratt, *Fundamentals of Biochemistry*, John Wiley & Sons Incorporated, **2006**.

chains of the amino acids, which interact with each other by covalent (disulfide bridges) or noncovalent bonds, such as ionic interactions, hydrogen bonds or Van der Waals interactions, determine the folding of the protein (Figure 2.5).[153] Also, hydrophobic/hydrophilic interactions play an important role for the arrangement of the proteins in the physiological, aqueous media. The three dimensional structure of enzymes usually bear an active pocket where a certain substrate binds. This pocket is formed by folding of the linear chain, and is highly important for the biological function of proteins. Denaturation or unfolding of the peptide results in loss of the catalytic activity and is a major challenge for peptide-drug development.

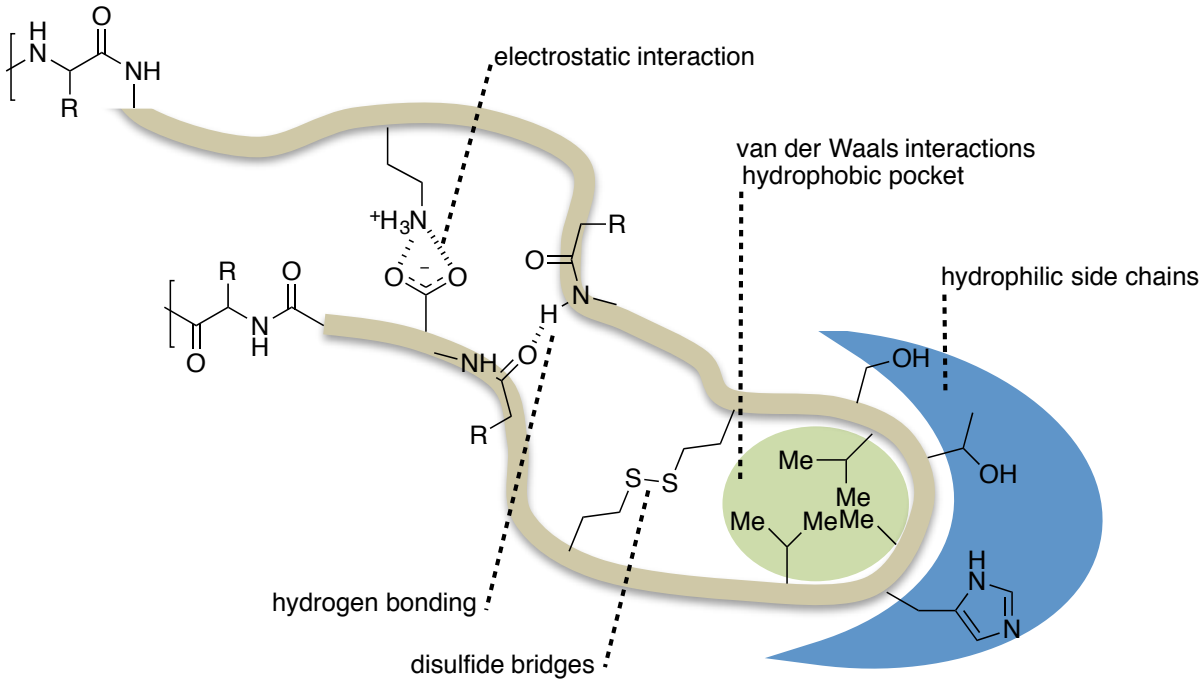

Figure 2.5: Important amino acid interactions for the peptide folding.

[153] B. Alberts, A. Johnson. J. Lewis, D. Morgan, M. Raff, K. Roberts, P. Walter, *Molecular Biology of the Cell*, Garland Science, **2015**, *6th Ed.*

2.1.4 Peptidomimetics – Chemically Modified Peptides

Proteins, peptides or so-called peptidomimetics made up one third of the top 100 prescription drugs in the US in 2013.[154] In the development of new drugs, scientists in medical research are faced with some shortcomings of natural peptides, such as rapid metabolization by proteases, fast hydrolysis and denaturation in the stomach or low membrane permeability.[155] A further disadvantage is the high conformational flexibility of peptides, which may result in nonspecific bindings to different targets, and thus undesired side effects of a drug can occur. Since peptides are only rarely suitable drug candidates, especially considering the low oral bioavailability, scientists aim to develop small molecules – so called peptidomimetics – that retain the biological activity but overcome the shortcomings of the parent compounds. These peptidomimetics are compounds that should imitate the structure of a peptide in its receptor-bound conformation.[155] To reach this challenging and time-consuming goal, manifold strategies have been developed. Mainly, increasing rigidity of the active conformer and, thus, optimizing the selectivity has been tried, while avoiding recognition by proteolytic enzymes (cf. amide bond isosteres e.g azapeptides, oligoureas, phoshphonopeptides) to reach higher bioavailability.[156] Generally the lead-structure is found through structure-activity studies of the protein-ligand interaction, X-ray analysis, and also computational chemistry.[157] In this way, the important pharmacophoric groups and the three-dimensional conformation can be elicited. While the computational models are highly advanced, they are still not sufficient and laborious experimental work is required (trial and error). Chemists have developed various chemical modules to avoid recognition by proteolytic enzymes, to increase rigidity, to make a peptide more lipophilic, or to induce a distinct secondary structure such as helices, sheets or β-turns (Figure 2.6).

A simple idea was the incorporation of D-enantiomeric amino acids into peptides, which became useful to prevent proteolytic recognition, but also for the modulation of secondary structures (e.g. D-Pro-L-Pro induces a β-turn).[158] The α,α-dialkylamino acids have been

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[154] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348–1349.

[155] N. Sewald, H.-D. Jakubke, *Peptides: Chemistry and Biology*, Wiley-VCH, **2009**.

[156] V. J. Hruby, *Drug Discovery Today* **1997**, *2*, 165–167.

[157] J. Gante, *Angew. Chem.* **1994**, *106*, 1780–1802.

[158] a) J. A. Robinson, *J. Pept. Sci.* **2013**, *19*, 127–140; b) C. M. Nair, M. Vijayan, Y. V. Venkatachalapathi, P. Balaram, *J. Chem. Soc., Chem. Commun.* **1979**, 1183–1184.

successfully applied to induce and stabilize helixes in small peptides.[159] Especially, 2-aminoisobutyric acid (Aib) exhibits a strong helix induction in peptides.[159c-f]

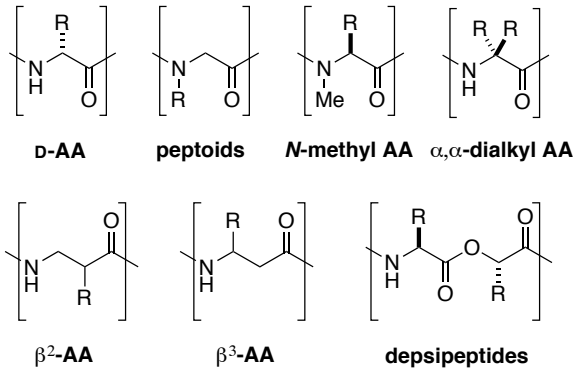

Figure 2.6: Selected examples of chemical modules to influence the structural properties of a peptide. AA = amino acids.

Also, the β-amino acids contributed a powerful tool for the definition of secondary structures such as β-turns and 3_{14} helices[160] and they have been applied to increase proteolytic stability of peptides.[161] Oligoglycins with the sidechain attached to the amide nitrogen instead of the α-carbon, the so-called peptoids, have been designed to inhibit the formation of α-helices and β-sheets.[162] These peptoids are achiral along the backbone and the hydrogen bonding interactions are suppressed. Also, *N*-methylation of the peptide backbone reduces the hydrogen donor capacity, as well as the proteolytic recognition, and is a common method to increase lipohilicity or alter the conformation of peptides.[163] *N*-methylated amino acids

[159] a) K.-H. Altmann, E. Altmann, M. Mutter, *Helv. Chim. Acta* **1992**, *75*, 1198–1210; b) E. Altmann, K.-H. Altmann, K. Nebel, M. Mutter, *Int. J. Pept. Protein Res.* **1988**, *32*, 344–351; c) M. Mutter, K.-H. Altmann, A. Flörsheimer, J. R. Herbert, *Helv. Chim. Acta* **1986**, *69*, 786–792; d) F. R. Carbone, B. S. Fox, R. H. Schwartz, Y. Paterson, *J. Immun.* **1987**, *138*, 1838–1844; e) I. L. Karle, J. L. Flippen-Anderson, K. Uma, P. Balaram, *Int. J. Pept. Prot. Res.* **1988**, *32*, 536–543; f) D. Seebach, B. Jaun, R. Sebesta, R. I. Mathad, O. Flögel, M. Limbach, H. Sellner, S. Cottens, *Helv. Chim. Acta* **2006**, *89*, 1801–1825; g) C. Toniolo, E. Benedetti, *Macromolecules* **1991**, *24*, 4004–4009.

[160] a) K. Gademann, T. Kimmerlin, D. Hoyer, D. Seebach, *J. Med. Chem.* **2001**, *44*, 2460–2468; b) D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, L. Oberer, U. Hommel, R. Amstutz, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 2043–2066.

[161] M. Rodriguez, A. Aumelas, J. Martinez, *Tetrahedron Lett.* **1990**, *31*, 5153–5156.

[162] R. N. Zuckermann, T. Kodadek, *Curr. Opin. Mol. Ther.* **2009**, *11*, 299–307.

[163] a) L. Aurelio, R. T. C. Brownlee, A. B. Hughes, *Chem. Rev.* **2004**, *104*, 5823–5846; c) D. P. Fairlie, G. Abbenante, D. R. March, *Curr. Med. Chem.* **1995**, *2*, 654–686.

(NMA's) are also abundant structural motifs in bioactive natural products like vancomycin and cyclosporine.

Another tool used is depsipeptides bearing at least one ester in the backbone in place of an amide (Figure 2.6). This is a common feature in natural products, but also caught the attention as a feature in peptidomimetics, especially in the so-called switch-peptides.[164] The secondary structures of switch-peptides are convertible from one distinct shape to another by exterior influences. The depsipeptides can be triggered to induce an *O*-to-*N* acyl-migration, thereby transforming the ester with a random coil chain into a regular peptide, forming α-helices or β-sheets.[164a,165] These transformations have become of particular interest in neurodegenerative disease research.

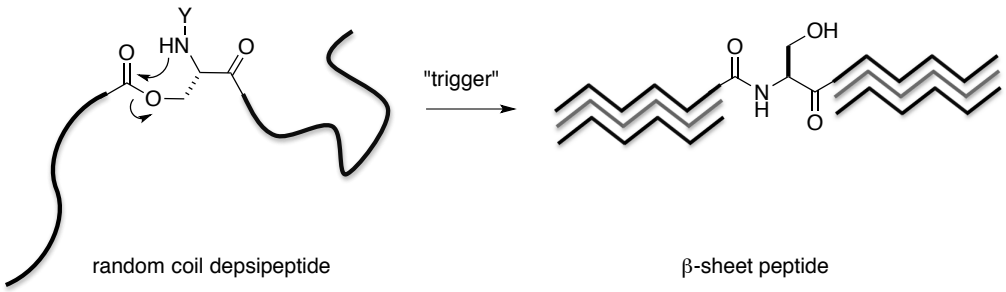

Figure 2.7: Switch peptide concept: A depsipeptide having a random coil shape is triggered by deprotection of the *N*-protecting group (Y). The free amine then undergoes an *O*-to-*N* acyl migration to give a regular peptide backbone. The new peptide then folds into a new shape (e.g β-sheet) and coagulates.

A disadvantage with the above mentioned unnatural amino acids (Figure 2.6) is that they still have rotational freedom around their bonds and thus the secondary structure is not easy to predict. To address this challenge, amino acid mimetics and dipeptide mimetics with fixed conformations have been developed (Figure 2.8) – so-called secondary structure mimetica. The most abundant shapes successfully mimicked are the β- and γ-turns.[166] In the following section some selected examples are given.

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[164] a) M. Mutter, A. Chandravarkar, C. Boyat, J. Lopez, S. Dos Santos, B. Mandal, R. Mimna, K. Murat, L. Patiny, L. Saucède, G. Tuchscherer, *Angew. Chem. Int. Ed.* **2004**, *43*, 4172–4178; b) M. Mutter, *Chimia* **2013**, *67*, 868–873.

[165] N. Nepomniaschiy, V. Grimminger, A. Cohen, S. DiGiovanni, H. A. Lashuel, A. Brik, *Org. Lett.* **2008**, *10*, 5243–5246.

[166] Review: A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303–1326.

Tetrahydroisochinolinecarboxylic acid (Tic) is a bridged unnatural amino acid, which has been used to mimic phenylalanine in opioid antagonists (Figure 2.8).[167] Tic has limited conformational freedom in the side chain and the *N*-bridged peptide bond is forced into a *Z* configuration. The Freidinger lactam is a dipeptide turn-mimetic that was successfully used in biologically active compounds.[168] Also *E*-locked motifs, such as the aza-lactam have been developed.[169] The bicyclic dipeptide β-turn mimetic found application as an analogue of a dopamine receptor modulating-peptide.[170]

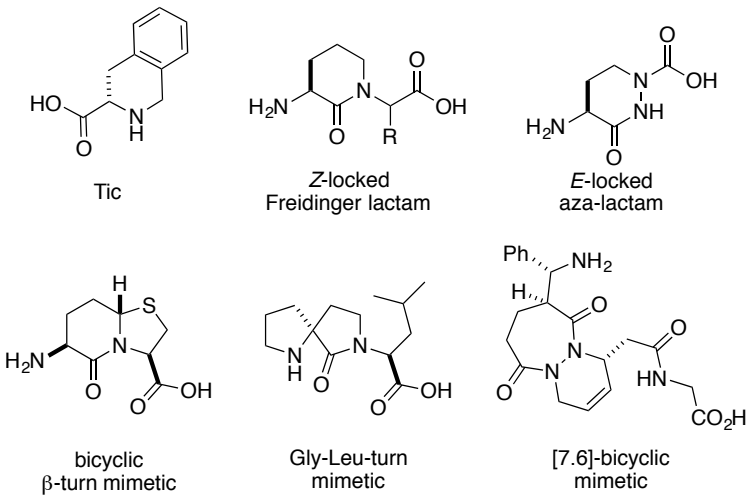

Figure 2.8: Selected building blocks that give fixed secondary structures.

Another bicyclic motif is the Gly-Leu-turn mimetic, which gave rise to a potent neurokinin antagonist.[171] Also, more complex building blocks like the [7.6]-bicycle were developed as shape mimetic and found application in a protease inhibitor.[172]

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[167] W. Kazmierski, V. J. Hruby, *Tetrahedron* **1988**, *44*, 697–710.

[168] a) R. M. Freidinger, D. F. Veber, D. S. Perlow, J. R. Brooks, R. Saperstein, *Science* **1980**, *210*, 656–658; b) R. M. Freidinger, D. S. Perlow, D. F. Veber, *J. Org. Chem.* **1982**, *47*, 104–109; c) J. D. Aebi, D. Guillaume, B. E. Dunlap, D. H. Rich, *J. Med. Chem.* **1988**, *31*, 1805–1815.

[169] P. A. Ottersbach, J. Schmitz, G. Schnakenburg, M. Gütschow, *Org. Lett.* **2013**, *15*, 448–451.

[170] a) U. Nagai, K. Sato, *Tetrahedron Lett.* **1985**, *26*, 647–650; b) N. L. Subasinghe, R. J. Bontems, E. McIntee, R. K. Mishra, R. L. Johnson, *J. Med. Chem.* **1993**, *36*, 2356–2361.

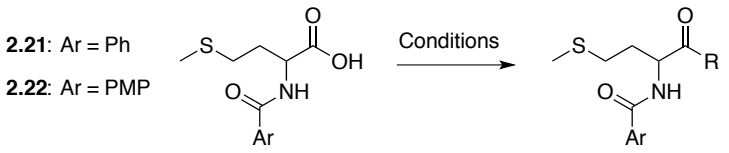
[171] a) M. G. Hinds, N. G. J. Richards, J. A. Robinson, *J. Chem. Soc., Chem. Commun.* **1988**, 1447–1449; b) P. Ward, G. B. Ewan, C. C. Jordan, S. J. Ireland, R. M. Hagan, J. R. Brown, *J. Med. Chem.* **1990**, *33*, 1848–1851; c) M. G. Hinds, J. H. Welsh, D. M. Brennand, J. Fisher, M. J. Glennie, N. G. J. Richards, D. L. Turner, J. A. Robinson, *J. Med. Chem.* **1991**, *34*, 1777–1789.

[172] H. Nakanishi, R. A. Chrusciel, R. Shen, S. Bertenshaw, M. E. Johnson, T. J. Rydel, A. Tulinsky, M. Kahn, *Proc. Nat. Ac. Sc. USA* **1992**, *89*, 1705–1709.

2.2 Towards Methionine-Derived 1,3-Oxazines

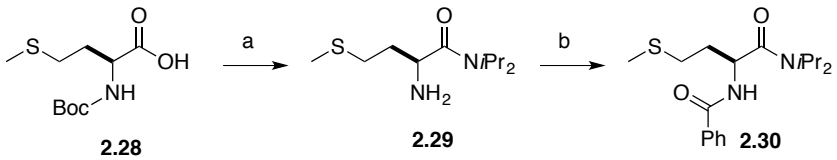
We decided to start with a *C*- and *N*-terminus amide bond linked methionine model system. Since *C*-terminal secondary amides undergo 5-*exo*-*tet* cyclisations to give γ-lactams (Scheme 2.1), we blocked the nitrogen with an alkyl group. Thus, we synthesized the benzoylated tertiary amides **2.23**-**2.27** from the known, racemic benzoylated precursors **2.21**[173] and **2.22**,[174] using standard peptide coupling reactions (Table 2.1).

Table 2.1: Preparation of methionine tertiary amide precursors.



Ar	Amine	Conditions	Product	Yield
Ph	Et_2NH	BOP, Et_3N, THF, 0°C to RT	**2.23**: R = NEt_2	56%
Ph	piperidine	EDC·HCl, DMAP, CH_2Cl_2, RT	**2.24**: R = piperidine	quant.
Ph	pyrrolidine	EDC·HCl, DMAP, CH_2Cl_2, RT	**2.25**: R = pyrrolidine	96%
Ph	morpholine	EDC·HCl, DMAP, CH_2Cl_2, RT	**2.26**: R = morpholine	92%
PMP	piperidine	EDC·HCl, DMAP, CH_2Cl_2, RT	**2.27**: R = piperidine	56%

The peptide coupling with the sterically demanding diisopropylamine using the procedure above, did not furnish the desired amide **2.30**. Most likely the issue was a competing intramolecular attack of the benzoyl moiety. Thus, peptide coupling of the Boc-protected methionine **2.28** and hydrolysis of the Boc group was performed to get the amine **2.29**. The desired amide **2.30** was synthesized using benzoyl chloride (Scheme 2.3).



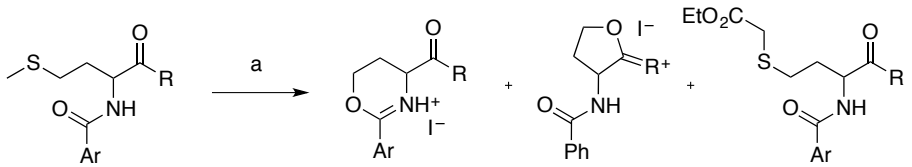
Scheme 2.3: Synthesis of the sterically demanding amide **2.30**: a) i. BOP, Et_3N, THF, diisopropylamine, 0°C to RT; ii. HCl aq. conc., MeOH, RT, 26%; b) PhCOCl, Et*i*Pr_2, CH_2Cl_2, RT, 79%.

[173] H. L. Holland, P. R. Andreana, R. Salehzadeh-Asl, A. van Vliet, N. J. Ihasz, F. M. Brown, *Chem. Month.* **2000**, *131*, 667–672.

[174] S. Benvenuti, F. Severi, L. Costantino, G. Vampa, M. Melegari, *Farmaco* **1998**, *53*, 439–442.

To begin with, the alkylations were performed using iodo-ethylacetate (Table 2.2). The reactions were monitored by UPLC-MS and the isolated compounds were purified by triturations or short column chromatography using aprotic solvents. Indeed we found cyclized and eliminated products under these reaction conditions. Unexpectedly, the morpholine amide **2.26** did not show any product formation. Alarmed by that fact, we realized that instead of 6-exo-tet cyclisations, forming 1,3-oxazines **A**, 5-*exo-tet* cyclisations took place, to give iminium lactones **B**. This was unambiguously confirmed by X-ray crystal structure analysis of the diisopropyl compound **2.35**.

Table 2.2: Methionine activation with iodo-acetate furnishing iminium lactones.



Amide	Ar	R	Yield of B
2.23	Ph	NEt_2	29%, **2.31**
2.24	Ph	piperidine	29%, **2.32**
2.25	Ph	pyrrolidine	n.d.[a], **2.33**
2.26	Ph	morpholine	0%[b] **2.34**
2.30	Ph	N*i*Pr_2	63%, **2.35**
2.27	PMP	piperidine	n.d.[c], **2.36**

Conditions: a) ICH_2CO_2Et, MeCN, 50°C, 1 d. [a] Decomposed during HPLC purification, UPLC-MS showed a single product. [b] Elimination did not occur, alkylation occurred. [c] UPLC-MS showed *m/z* of the product along with starting material and alkylated product.

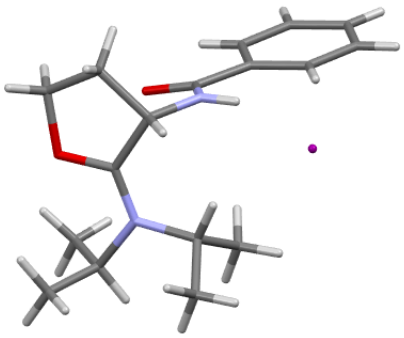


Figure 2.9: X-ray crystal structure of iminium ether **2.35**. grey = carbon; white = hydrogen; red = oxygen; blue = nitrogen; magenta = iodine.

The conversion of the reactions were generally very low. During the reaction, initially product **B** is exclusively formed and with prolonged reaction time, the alkylated compounds **C** were observed. A reasonable explanation for this observation is shown by the equilibrium in Figure 2.10. In the first, step alkylation takes place to give the sulfonium species **A**, then the cyclisation to the iminium lactone **B** takes place by releasing of ethyl 2-(methylthio) acetate. The cyclisation is reversible as the thioether can attack the iminium lactone to reform **A**. The sulfonium species might also react with the iodide to form methyl iodide and the corresponding thioether **C**. Since the methyl iodide is volatile, slow accumulation of product **C** occured.

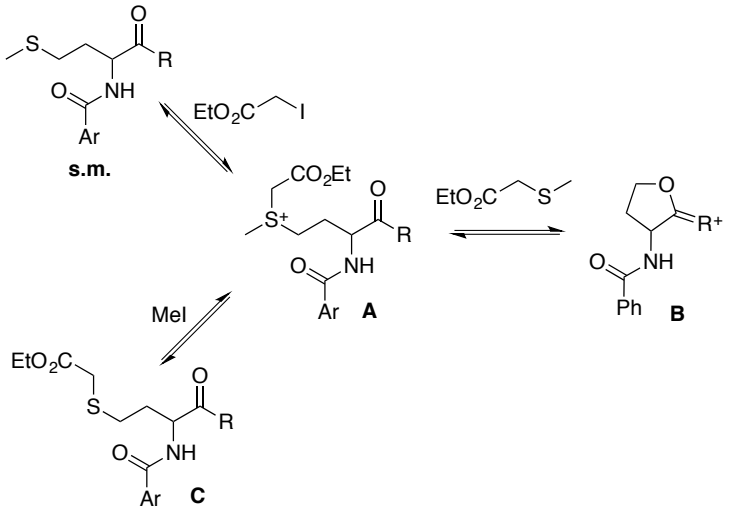
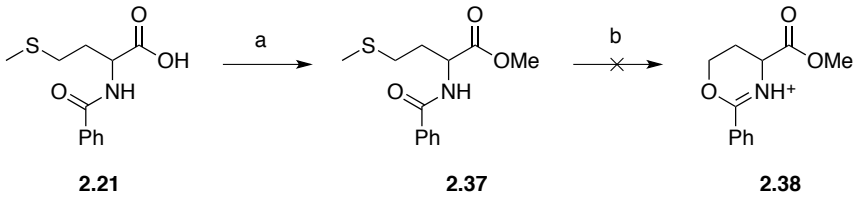


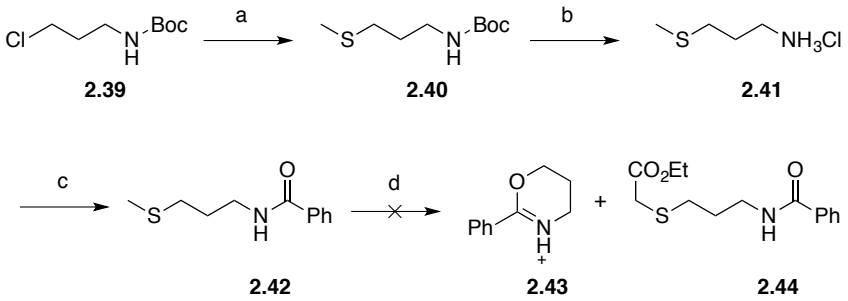
Figure 2.10: Proposed equilibrium of the methionine alkylation reaction.

As a consequence of the competing iminium ether formation, we wanted to eliminate the amide moiety at the *C*-terminus. Thus, the carboxylic acid **2.21** was treated with thionyl chloride in methanol (Scheme 2.4) and the resulting methyl ester **2.37** was then treated with iodo-ethylacetate. The reaction was stirred for 2 days, without observing any 1,3-oxazine **2.38** formation. Instead, the corresponding alkylated product **C** (Figure 2.10) was detected by UPLC-MS.



Scheme 2.4: a) $SOCl_2$, MeOH, 0°C to RT, 55%; b) ICH_2CO_2Et, MeCN, 60°C, 2 d, 0%.

As an ultimate test, we synthesized the unfuctionalized thioether **2.42** (Scheme 2.5). Nucleophilic exchange of the chloride in the Boc protected amine **2.39** by methanethiolate and subsequent aqueous acidic deprotection furnished the ammonium salt **2.41**. Next, amidation with benzoic anhydride gave the desired decarboxy-methionine substrate **2.42**. Again, treatment with iodo-ethylacetate and stirring at 60°C for 2 days did not furnish the desired 1,3-oxazine **2.43**, but the alkylated byproduct **2.44** was found.



Scheme 2.5: Synthesis of the unfunctionalized thioether **2.42**: a) NaSMe, EtOH, 50°C, 18 h, 85%; b) HCl aq. conc., THF, 50°C, 45 min., 96%; c) benzoic anhydride, MeCN, toluene, 60°C, 5 h, 66%; d) ICH_2CO_2Et, MeCN, 60°C, 2 d, 0% **2.43**.

Though the desired transformation could be more elaborated (e.g. addition of base, other alkylating agents, solvent), with this experiment we ended our investigations on the methionine-derived 1,3-oxazines. The observed iminium ether formation (Table 2.2) caught our attention, and is the topic of the next Chapter 2.3.

2.3 Methionine-Derived Iminium Lactones

2.3.1 Introduction

Iminium ethers **I** have been found to be useful electrophiles in medicinal chemistry[175] and also as ambident intermediates[176] (Figure 2.11).

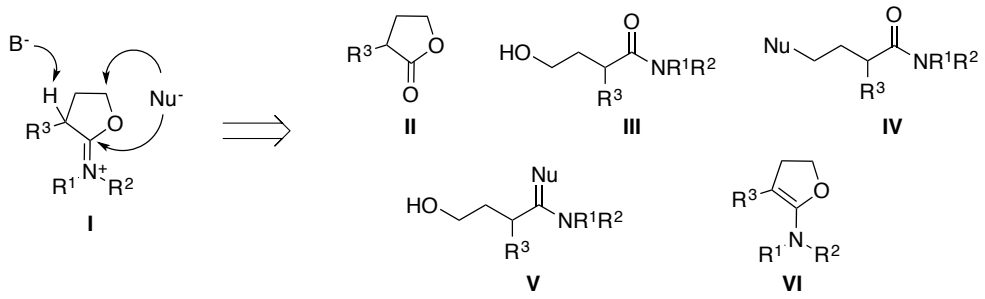


Figure 2.11: Iminium lactones are valuable electrophlic intermediates. B = base; Nu = nucleophile.

Generally, iminium lactones are prone to hydrolysis and in aqueous media homoserine lactones **II** and homoserine-amides **III** are equally formed.[177] The lactone **II** can be selectively synthesised by hydrolysis on wet silica[178] or in aqueous, slightly basic media.[179,180] Interestingly, in strongly basic media the hydroxy amide **III** is favourably formed.[180] Interestingly, iminium ethers show an ambident behaviour with nucleophiles. Soft nucleophiles (e.g. secondary amines, PPh_3, N_3^-, RS^-) react at the sp^3 carbon to form amides **IV**, whereas hard and small nucleophiles (e.g. H^-) rather react at the sp^2 carbon, followed by ring-opening to give alcohols **V**.[179] Furthermore, iminium ethers can be deprotonated in α-position to obtain enamines **VI**, which are very useful as nucleophiles to prepare α-functionalized iminium ethers.[179,181]

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[175] a) M. Wang, M. Gao, Q.-H. Zheng, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5259–5263; b) R. A. Stokbroekx, J. Vandenberk, A. H. M. T. Van Heertum, G. M. L. W. Van Laar, M. J. M. C. Van der Aa, W. F. M. Van Bever, P. A. J. Janssen, *J. Med. Chem.* **1973**, *16*, 782–786.

[176] Review: S. Hünig, *Angew. Chem.* **1964**, *76*, 400–412.

[177] P. Deslongchamps, S. Dubé, C. Lebreux, *Can. J. Chem.* **1975**, *53*, 2791–2807.

[178] . Felix, U. M. Kempe, A. Eschenmoser, *Helv. Chim. Acta* **1972**, *55*, 2198–2205.

[179] B. Peng, D. H. O'Donovan, I. D. Jurberg, N. Maulide, *Chem. Eur. J.* **2012**, *18*, 16292–16296.

[180] M. V. Zlokazov, V. V. Veselovsky, *Russ. Chem. Bull., Int. Ed.* **2009**, *58*, 322–326.

[181] a) R. J. Sundberg, B. C. Pearce, *J. Org. Chem.* **1985**, *50*, 425–432; b) T. M. Ugurchieva, A. V. Lozanova, M. V. Zlokazov, V. V. Veselosky, *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 1544–1549.

As in our case, the vast majority of iminium lactone **I** syntheses follow an *exo-tet* cyclication mechanism (Figure 2.12). γ-Halo-amides **VII** have been found to be in equilibrium with iminium lactones **I** in solution. The higher the positive inductive effect (+I) of R^1 and R^2, better the leaving halogenide (Cl<Br<I), and more polar the solvent, the more is the equilibrium shifted to **I**.[182] Other common precursors are the γ,δ-unsaturated amides **VIII**, which can be activated by bromine[183] or by sulfonyl azides to furnish intermediate aziridines **X**[184]. Also, cylopropane ring-opening by mesyl activation of the adjacent alcohol **IX** furnished functionalized iminium ethers **I** at RT.[180]

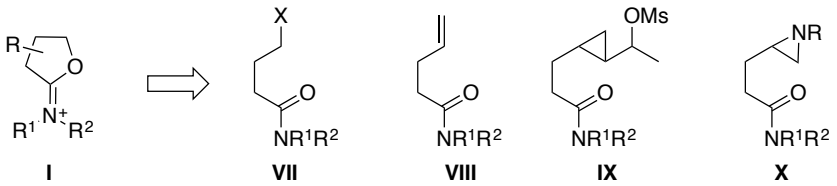
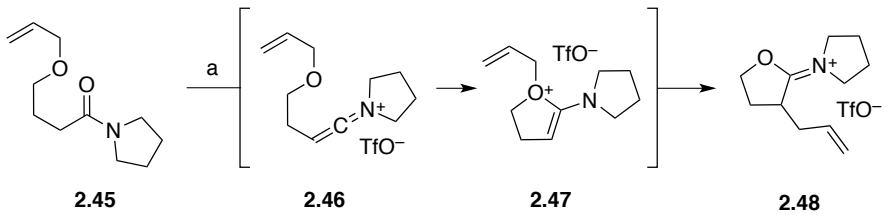


Figure 2.12: Preparation of iminium lactones.

Another approach was developed by Maulide and co-workers (Scheme 2.6). In their synthesis, the γ-allylether amide **2.45** was activated using triflic anhydride, which gave the ketene iminium salt **2.46**. Attack by the ether furnished the oxonium species **2.47** that underwent a [3,3]-sigmatropic rearrangement to give the isolable α-allyl iminium ether **2.48**.



Scheme 2.6: Maulides approach towards iminium ether **2.48**: a) Tf_2O, 2,4,6-collidine, 120°C, CH_2Cl_2, μw, 5 min, 61%.

[182] M. V. Zlokazov, A. V. Lozanova, V. V. Veselovsky, *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 547–550.

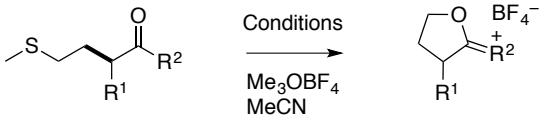
[183] a) P. N. Craig, *J. Am. Chem. Soc.* **1952**, *74*, 129–131; b) A. V. Lozanova, T. M. Ugurchieva, M. V. Zlokazov, A. V. Stepanov, V. V. Veselovsky, *Mend. Comm.* **2006**, *16*, 15–16; c) T. M. Ugurchieva, A. V. Lozanova, M. V. Zlokazov, *Russ. Chem. Bull., Int. Ed.* **2008**, *57*, 657–659

[184] I. V. Tkachenko, I. N. Tarabara, S. V. Shishkina, O. V. Shishkin, L. I. Kas'yan, *Russ. J. Org. Chem.* **2009**, *45*, 1143–1148.

2.3.2 Substrate Scope

As a first task, we aimed to push the equilibrium towards the desired product (Figure 2.10, Chapter 2.2). One way to do so, was to remove the leaving group from the reaction mixture and thus prevent the possibility of the back reaction. As a logical consequence, we changed our alkylating agent from iodo-ethylacetate to the trimethyloxonium tetrafluoroborate (Meerwein's salt), which led to the volatile dimethylsulfide as leaving group. Indeed, this change was successful, the sulfonium ion was formed immediately after addition of Meerwein's salt and the conversion went to completion. We then evaluated the scope of the reaction by changing the substituents at the *C* and *N*-terminus of methionine (Table 2.3). The syntheses of the substrates **2**.**49**–**2.54** have been performed using standard peptide coupling conditions, and are described in detail in the experimental part of this thesis (BOP or EDC; 52–99%).

Table 2.3: Substrate scope of the iminium ether formation.



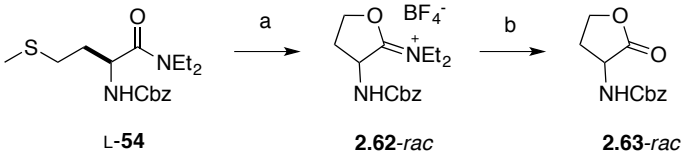
Substrate	R^1	R^2	Yield	Conditions
2.23-rac.	BzNH	NEt_2	47%[a], **2.55**	130°C, μw, 0.5 h
2.24-rac.	BzNH	piperidine	quant., **2.56**	80°C, 18 h
2.30	BzNH	N*i*Pr$_2$	51%[b], **2.35**	130°C, 0.5 h, μw, then NaI
2.49-rac.	BzNH	N(Me)Ph	full conv.[c], **2.57**	130°C, μw, 0.5 h
2.50-rac.	BzNH	N(Me)OMe	0%, **2.58**	80°C, 18 h
2.51-rac.	BzNH	N(Me)AlaBoc	0%, **2.59**	130°C, μw, 0.5 h
2.52	BocNH	NEt_2	70%[a], **2.60**	80°C, 18 h
2.53	Boc(Me)N	NEt_2	50%[a], **2.61**	80°C, 18 h
2.54	CbzNH	NEt_2	91%, **2.62**	130°C, μw, 0.5 h

[a] After purification by column chromatography [b] The yield corresponds to the iodide salt. [c] The conversion was determined by UPLC-MS.

Concerning the yield, the major issue of the reaction is purification. The best yields were obtained when the iminium lactone was purified by trituration (**2.56**, **2.62**). Unfortunately the yield dramatically dropped if a column chromatography of the product had to be performed (**2.55**, **2.60**, **2.61**). Clearly, the amide substituents have great influence on the reactivity of the amide, which becomes apparent by the nonreactive electron-poor amides **2.50** and **2.51**. It

should be mentioned here that the high temperatures of 130°C effected Boc-deprotection of **2.52** and **2.53**.

Unfortunate but not unexpected, racemisation is occurring during the reaction. This was proved by chiral HPLC analysis of the homoserinelactone **2.63**, synthesized from L- and *rac*-methionine (Scheme 2.7).

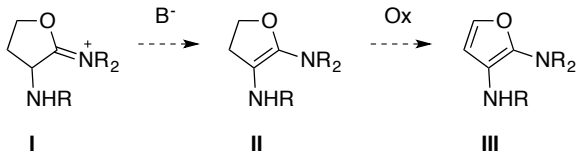


L-**54** **2.62**-*rac* **2.63**-*rac*

Scheme 2.7: The racemisation of the α-carbon was determined by chiral HPLC of **2.63**. a) Me_3OBF_4, MeCN, 130°C, μw, 0.5 h, 91%; b) SiO_2, H_2O, MeOH, 50°C, 18 h, 47%.

2.3.3 The Synthetic Utility of Methionine-Derived Iminium Lactones

In this chapter, our investigations of the synthetic value of the methionine-derived iminium lactones as intermediates are described. As mentioned in Chapter 2.3.2, the iminium ether is prone to racemise, meaning that its α-proton is acidic. We thus envisioned deprotonation in α-position of **I** and then oxidation of the formed enamine **II** to get access to 2,3-amino furan **III** (Figure 2.13). Commonly the deprotonation of iminium ethers can be easily achieved using various bases (Chapter 2.3.1), while the oxidation of enamines similar to **II** instead has been reported only once.[185]



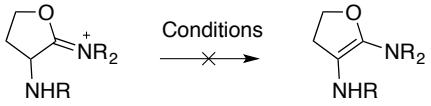
I **II** **III**

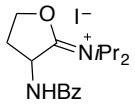
Figure 2.13: Envisioned transformation of the iminium lactone **I** to the 2,3-aminofuran **III**.

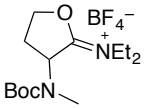
[185] C. Funke, A. M. Es-Sayed, A. Meijere, *Org. Lett.* **2000**, *2*, 4249–4251.

Unfortunately, we were not able to prepare the desired enamine with various bases (Table 2.4). In most cases the starting material was re-isolated and in other cases the hydrolysed homoserine product was found. Even the *N*-methylated derivative **2.61**, which doesn`t bear any other removable proton, did not furnish the enamine. Most likely, the deprotonation of our starting material bearing the α-nitrogen substituent led to unstable enamines that cannot be isolated.

Table 2.4: Iminium lactone deprotonation experiments.

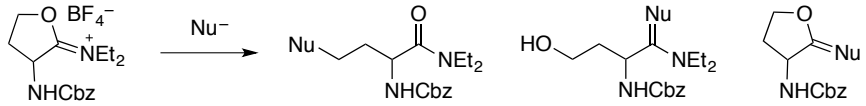


Entry	Starting material	Conditions
1		DMAP, MeCN
2	**2.35**	NaH, MeCN
3		*n*BuLi, THF, –78°C
4		DBU, MeCN
5		CaH_2, THF, 45°C
6	**2.60**	Cs_2CO_3, MeCN
7		NaHMDS, Et_2O
8		KO*t*Bu, THF
9	**2.61**	NaH, MeCN

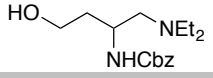
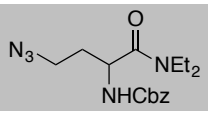
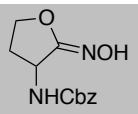
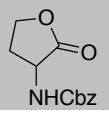
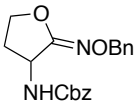
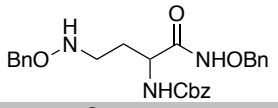
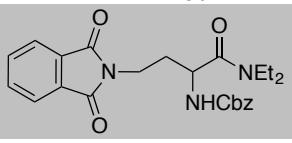


We then moved on to investigate the reactivity of the iminium ether towards various nucleophiles (Table 2.5). We first examined some nucleophiles that have already been reported to react with iminium lactones ($NaBH_4$, NaN_3, KCN).[179] The reduction to the tertiary amine **2.64** using $NaBH_4$ in methanol was the highest yielding reaction in our screening (81%). The reaction with sodium azide gave only low yield of the amide **2.65** (35%) and potassium cyanide did not convert the starting material, even at elevated temperatures. In contrast to sodium azide, hydroxylamine reacted at the sp^2-center to give the hydroxylactam **2.66** along with the homoserinelactone **2.63** – a consequence of the aqueous media. On the other hand, the benzyloxyamine reacted at the sp^2-carbon and sp^3-carbon to form the lactam **2.67** and the benzyloxyamine **2.68** to equal extents. The reaction with potassium phthalate gave only poor yield of the amide **2.69** and the primary alanine amine did not react with the iminium lactone at all.

Table 2.5: Reactivity of the methionine-derived iminium lactone towards nucleophiles.

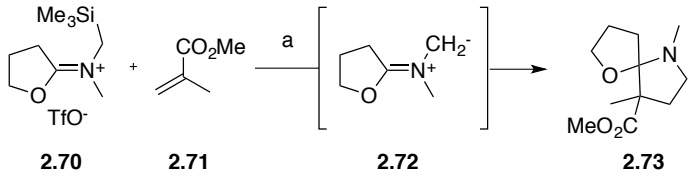


2.62

Nucleophile	Conditions	Product	Yield
$NaBH_4$	MeOH, RT, 16 h		81%, **2.64**
NaN_3	MeCN, RT, 24 h		35%, **2.65**
KCN	MeCN, 130°C, µw, 1.5 h	—	0%
NH_2OH (aq.)	MeCN, RT, 24 h	 	22%, **2.66** 17%, **2.63**
NH_2OBn	MeCN, RT, 48 h	 	36%, **2.67** 35%, **2.68**
K-Phtalimide	MeCN, RT, 2 h		19%, **2.69**
H_3N^+-Ala-OMe	Et_3N, MeCN, 130°C, µw, 5 h	—	0%

The last experiment approached, arose from the idea to increase the nucleophilicity of the amide moiety, which eventually would prohibit the racemisation of the iminium lactone. We wanted to make use of the β-silyl effect, which is stabilizing positive charges in β-position of the silicon. This silyl iminium lactone might then be used as an azomethine ylide-precursor for a 3+2 dipolar cycloaddition, as decribed by Fishwick *et al.* (Scheme 2.8).[186]

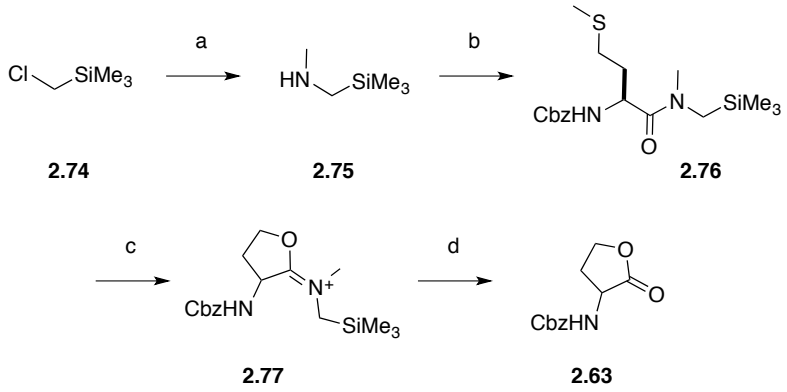
[186] a) A. Alanine, C. Fishwick, C. Szantay Jr., *Tetrahedron Lett.* **1989**, *30*, 6573–6576; b) A. Alanine, C. Fishwick, C. Szantay Jr., *Tetrahedron Lett.* **1989**, *30*, 6777–6780; c) C. Fishwick, R. J. Foster, R. E. Carr, *Tetrahedron Lett.* **1996**, *37*, 5163–5166.



2.70 **2.71** **2.72** **2.73**

Scheme 2.8: Iminium lactone derived azomethine ylide for 3+2 dipolar cycloadditions (Fishwick *et al.*[186a]): a) CsF, DME, –70°C to RT, 65%.

Thus, we first synthesized the silyl amine **2.75** using a known protocol[187] followed by a standard peptide coupling using BOP to get the methionine substrate **2.76** (Scheme 2.9). As we expected, the cyclization of the silyl amide **2.76** using Me_3OBF_4 was much faster (90°C, 0.5 h) than with the previously used tertiary amides (130°C, 0.5 h; 80°C 18 h). Unfortunately, also in this case racemisation occurred, as chiral HPLC analysis of the hydrolysed iminium lactone **2.77** showed, and we did not pursue this reaction further.



2.74 **2.75** **2.76** **2.77** **2.63**

Scheme 2.9: Synthesis of the silyl-iminium lactone **2.77**: a) $MeNH_2$ aq. (40%), 80°C, 5 h, μw, 59%; b) CbzMetOH, BOP, Et_3N, THF, diethylamine, 0°C to RT, 75%; c) Me_3OBF_4, MeCN, 90°C, μw, 0.5 h 84%, d) CsF (wet), MeCN, RT, 24 h, 36%.

[187] B. P. Roberts, A. R. Vazquez-Persaud, *J. Chem. Soc., Perkin Trans. 2* **1995**, 1087–1095.

2.4 Conclusion and Outlook

In this project, we examined intramolecular cyclisations of methionine substrates using the thioether moiety as a triggerable leaving group. Thereby, we developed a new straightforward methodology that gives access to iminium γ-lactones. In our experiments, we found 6-*exo*-*tet* cyclisations to be unfavourable, and the initially expected 1,3-oxazines were not formed. Instead, 5-*exo*-*tet* cyclisations of the prepared methionine substrates bearing *C*-terminal tertiary amides was observed, and readily gave access to isolable iminium lactones upon alkylation of the thioether with Meerwein's salt. Unfortunately, under the reaction conditions applied, racemisation of the enantiopure starting material occurred. We then investigated on the utility of these novel iminium lactones and tested their reactivity towards various nucleophiles. In our tests we found an ambident behaviour of the electrophile, depending on the nature of the nucleophile. Though we found racemisation, α-deprotonation of the iminium ethers to obtain the corresponding enamines could not be affected using various bases. This is likely due to instability of the formed enamines with the particular nitrogen substituent.

Future work will include an elaborate screening of reactivity of the iminium ether towards nucleophiles, deprotonation in presence of electrophiles for α-functionalization, and solvent screening in the cyclisation step. But the biggest challenge to make synthetic use out of the methionine-derived iminium lactones, would be to overcome racemisation; an enantioselective version of this process is highly desirable. One possibility to overcome that issue would be the introduction of chiral amide substituents at the *C*-terminus, which induces a preferential configuration at the α-carbon (Figure 2.14).

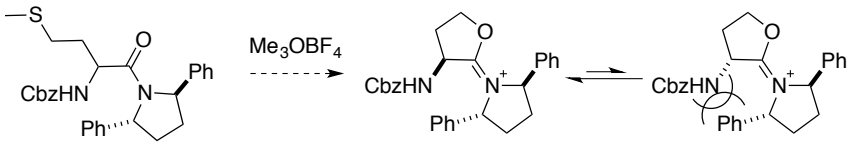


Figure 2.14: Inducement of enantioselectivity by a chiral amide substituent.

Even if the racemisation problem can not be circumvented by this measure, our approach could be a useful tool for the design of α,α-dialkyl amino acids. In combination with

Bannwarth's[188] cleavable bispicolylamide, additional practicability would be gained in respect to further peptide couplings and incorporation in peptidomimetics (Figure 2.15).

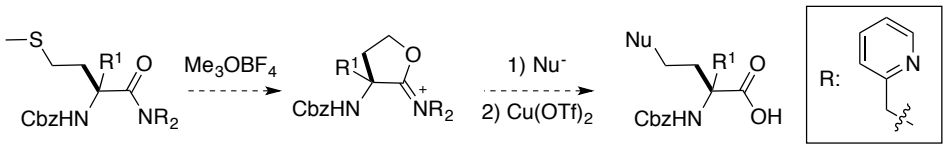


Figure 2.15: Application of our elaborated method for the synthesis of α,α-dialkyl amino acids, equipped with the readily, cleavable bispicolylamide.

[188] M. C. Bröhmer, S. Mundinger, S. Bräse, W. Bannwarth, *Angew. Chem. Int. Ed.* **2011**, *50*, 6175–6177.

3 Conclusion

This thesis, entitled *Total Synthesis of the Glycosylated Antibiotic Fidaxomicin and Methionine-Derived Iminium Lactones*, describes two distinct organic chemical research projects.

Chapter 1 was dedicated to the achievement of the first total synthesis of fidaxomicin, an FDA- and EMA- approved antibiotic against *Clostridium difficile* infection (CDI). The natural product exhibited potent biological activity against multi-drug resistant pathogens e.g., *Mycobacterium tuberculosis*. Unfortunately, poor pharmacokinetics prohibit its use as a treatment for this type of infections. The understanding of the macrolides chemical behaviour is crucial in respect to its bioactivity and thus total synthesis was essential. Fidaxomicin consists of a central 18-membered macrolide attached to a noviose and a rhamnose-resorcylate fragment. Key features of the described synthetic route include a rapid access to the rhamnosyl side-chain, the first ever β-selective noviosylation, followed by Suzuki cross-coupling, a ring-closing metathesis of complex noviosylated precursors, and a β-selective rhamnosylation. In particular, the stereo-selective 1,2-*cis* instalments of both β-linked carbohydrate units constitutes a notable feature of the approach. This total synthesis contributes to a detailed understanding of the chemistry of fidaxomicin and paves the way for the generation of analogues addressing some of the shortcoming of the natural product.

In Chapter 2, we explored methionine derivatives as synthetic precursors of 5,6-dihydro-4*H*-1,3-oxazines. The 6-*exo*-*tet* cyclisation was approached by alkylation of the thioether moiety to generate a leaving group. Though this desired reaction could not be enforced, a new 5-*exo*-*tet* cyclisation leading to isolable iminium lactones was explored and elaborated instead. A screening revealed the ambident behaviour of the electrophilic methionine-derived iminium lactones, depending on the nature of the nucleophile. The interesting synthetic utility of the discovered transformation is hampered through racemisation, occurring during the cyclisation. All over, we established a good base of fundamental research for the synthesis of iminium lactones from methionine. Further experimental investigations are required to overcome the stereochemical challenge, and to potentially provide a new and useful tool in peptidomimetic research.

4 Experimental Part

General Methods and Materials

All reactions were performed in oven-dried round-bottomed flasks using anhydrous solvents and under an argon atmosphere unless otherwise stated. The following anhydrous reaction solvents were obtained by filtration and passing through activated anhydrous alumina columns (Innovative Technology solvent purification system); THF, CH_2Cl_2, Et_2O, toluene. All other solvents (DMF, MeOH, MeCN, $CHCl_3$) and reagents were obtained from commercial suppliers and used without further purification. Syringes or stainless steel cannula were used to transfer air and moisture sensitive liquids and solutions. Analytical thin layer chromatography (Merck silica gel 60 F_{254} plates) was utilized for monitoring reactions and the spots were visualized by UV light (254 nm and 350nm) or by staining using p-anisalhdehyde or ceric ammonium molybdate (CAM) followed by gentle heating with a heat gun. Flash Chromatography was performed using SiliCycle silica gel 60 (230-400 Mesh) and the R_f values of compounds are indicated. Preparative thin layer chromatography (preparative TLC) was performed using Merck TLC silica gel 60 F_{254} or Merck PLC silica gel 60 F_{254}, 0.5 mm plates. Reversed-phase high-performance liquid chromatography (RP-HPLC) for analytical and separation purposes was performed on a Dionex HPLC equipped with a P680 HPLC Pump, an ASI-100 automated sample injector, a PDA-100 photodiode array detector, a MSQ-ESI mass spectrometric detector and a Gemini NX 3 µm 150x4.6 mm (Phenomenex) column and the respective retention times (t_R) are indicated. ESI-MS were measured on a ultra high performance liquid chromatography with Mass Spectrometry (UHPLC-MS) Agilent 1290 Infinity instrument equipped with an Eclipse Plus C18 column and an Agilent 6130 ESI-MS detector using a formic acid buffered MeCN/H_2O gradient. Chiral high performance liquid chromatography (Chiral HPLC) analysis was performed on a Dionex HPLC equipped with a UV-detecor and a Chiralpak IA or ODH column, using isocratic *n*hexane/*i*PrOH eluents. NMR spectra were recorded on Varian Gemini Bruker DPX 400 MHz (^{1}H) & 101 MHz (^{13}C) & 128 MHz (^{11}B), Bruker DRX 500 MHz (^{1}H) & 126 MHz (^{13}C) or a Bruker Bruker Avance III 600 MHz proton frequency equipped with a cryogenic 1.7 mm TCI cryoprobe at 298K in the indicated deuterated solvent, unless otherwise stated. Chemical shifts (δ) are quoted in parts per million (ppm) and the multiplicity is reported as follows: s = singlet; d = duplet; dd = duplet of duplet (etc.); t = triplet; q = quartet; quin = quintet; hept = heptet; m = multiplet or unresolved signal; the prefix ap = apparent is stated wherever further multiplicity could not be

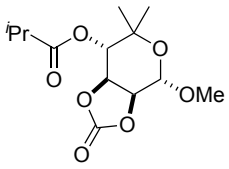
determined; the prefix br = broad is statet where the signal is not sharp. The ^{1}H-NMR spectra were referenced to the residual solvent peak (δ 7.26 ppm for $CHCl_3$; δ 2.05 ppm for acetone; δ 3.31 ppm for methanol), ^{13}C-NMR spectra were recorded with ^{1}H-decoupling and referenced to the residual solvent peak (δ 77.16 ppm for $CHCl_3$; δ 29.84 ppm for acetone; δ 49.00 ppm for methanol). Melting points (M.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Varian 800 FT-IR ATR spectrometer and data are reported in terms of frequency of absorption (ν, cm^{-1}). Optical rotations $\mathbf{[\alpha]_D}$ were recorded at 24.5°C on a Jasco P-2000 digital polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g/100 mL. All mass spectra (HRMS-ESI) were recorded by Dr. Heinz Nadig at University of Basel on a Bruker maXis 4G QTOF ESI mass spectrometer. Intermediates that are not labelled in the theoretical part but in the experimental part are labelled with **Xb** (afterwards in synthetic order).

4.1 Total Synthesis of Fidaxomicin

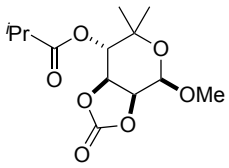
4.1.1 Novioside Substrates

(3a*S*,4*S*,7*S*,7a*S*)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (1.102)

To a solution of novioside **1.103** (106 mg, 0.55 mmol) in 1,2-dichloroethane (5.0 mL), 1,1'-carbonyldiimidazole (98 mg, 0.61 mmol) was added and the reaction mixture was stirred at reflux for 3 h. Then, 1,1'-carbonyldiimidazole was added in portions until TLC indicated full consumption of the starting material. The reaction was quenched with aq. HCl (1 M, 10 mL), and extracted with CH_2Cl_2 (3x10 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. This residue was dissolved in CH_2Cl_2 (4.0 mL), and Et_3N (0.39 mL) and subsequently isobutyryl chloride (0.17 mL, 1.65 mmol) were added dropwise. After stirring for 1 h at RT the mixture was quenched with H_2O (10 mL) and HCl (1 M, 10 mL). The aq. layer was extracted with CH_2Cl_2 (3x10 mL) and the org. layers washed with aq. $NaHCO_3$ (20 mL), combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/2 to Et_2O) afforded the two anomers (α-**1.102**: 66 mg, 42%; β-**1.102**: 40 mg, 25%) as white solids.



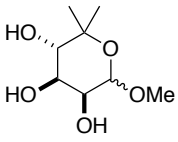
α-**1.102**: R_f = 0.63 (Et_2O/pentane 1/1); **M.p.** = 89.0–90.0°C; $[\alpha]_D$ = +18.5° (*c* = 0.3, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.06 (d, *J* = 7.6 Hz, 1H), 4.85 (d, *J* = 2.9 Hz, 1H), 4.72 (pt, *J* = 7.7 Hz, 1H), 4.62 (dd, *J* = 7.8, 2.9 Hz, 1H), 3.40 (s, 3H), 2.56 (qq, *J* = 7.0 Hz, 1H), 1.22 (s, 6H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 175.6, 153.2, 97.3, 76.6, 75.4, 74.7, 72.0 56.1, 34.1, 26.9, 23.2, 19.0, 18.8; **HRMS ESI** calcd. for $[C_{13}H_{21}O_7]^+$ $[M+H]^+$: 289.1282; found: 289.1281; **IR** ν = 2988, 1793, 1737, 1464, 1392, 1340, 1127, 1087, 1026, 969, 818 cm^{-1}.



β-**1.102**: R_f = 0.3 (Et_2O/pentane 1/1); **M.p.** = 134.0–137.0°C; $[\alpha]_D$ = –101.9° (*c* = 0.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.73–5.66 (m, 1H), 4.79–4.75 (m, 1H), 4.73–4.70 (m, 2H), 3.45 (s, 3H), 2.61–2.49 (qq, *J* = 7.0 Hz, 1H), 1.21 (s, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.14 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 175.2, 153.9, 95.8, 75.7, 75.0, 72.3, 71.9, 56.2, 34.1, 28.7, 24.3, 19.1, 18.8; **HRMS ESI** calcd. for $[C_{13}H_{21}O_7]^+$ $[M+H]^+$: 289.1282;

found: 289.1281; **IR** ν = 2984, 1790, 1740, 1472, 1394, 1355, 1148, 1048, 962, 807, 774 cm^{-1}.

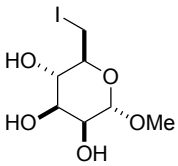
(3*S*,4*S*,5*S*)-6-methoxy-2,2-dimethyltetrahydro-2*H*-pyran-3,4,5-triol (1.103)



To a solution of furanoside **1.112** (210 mg, 0.90 mmol) in MeOH (2.0 mL), TFA (1.0 mL) was added. The colourless solution was heated in the microwave to 100°C for 3 h. The reaction mixture was diluted with toluene (10 mL), evaporated under reduced pressure and the residue was submitted to column chromatography (CH_2Cl_2/MeOH 20/1 to 10/1) to afford the desired pyranoside **1.103** and a mixture of deprotected furanoside **1.113** with starting material **1.112**. The same protocol was used twice to convert this mixture to the pyranoside **1.103**. In this way the desired compound **1.103** (141 mg, 81%) was obtained as a mixture of two inseparable anomers.

R_f = 0.28 (CH_2Cl_2/MeOH 10/1); **^{1}H-NMR** (400 MHz, CD_3OD, α:β 2:1) δ 4.57 (d, J = 1.5 Hz, 1H), 4.54 (d, J = 1.0 Hz, 0.5H), 3.85 (dd, J = 3.0, 1.0 Hz, 0.5H), 3.83–3.78 (m, 1H) 3.81 (s, 1H), 3.63 (d, J = 9.1 Hz, 1H), 3.57 (dd, J = 10.0, 3.1 Hz, 0.5H), 3.52 (d, J = 10.0 Hz, 0.5H), 3.45 (s, 1.5H), 3.37 (s, 3H), 1.29 (s, 1.5H), 1.28 (s, 6H), 1.18 (s, 1.5H); **^{13}C-NMR** (101 MHz, CD_3OD, α:β 2:1) δ 104.1, 98.4 (0.5C), 79.0, 76.2 (0.5C), 74.8 (0.5C), 74.7, 72.8, 72.5 (0.5C), 71.9 (0.5C), 69.3, 56.9 (0.5C), 55.8, 29.2, 28.7 (0.5C), 22.7, 18.5 (0.5C); **HRMS ESI** calcd. for $[C_8H_{16}NaO_5]^+$ $[M+Na]^+$: 215.0890; found: 215.0890; **IR** ν = 3377, 2981, 2925, 2361, 1673, 1445, 1369, 1193, 1135, 1065, 1037, 979, 803, 736 cm^{-1}.

(2*S*,3*S*,4*S*, 5*S*, 6*S*)-2-(iodomethyl)-6-methoxytetrahydro-2H-pyran-3,4,5-triol (1.105)



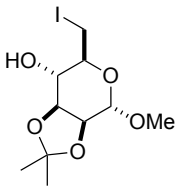
To a solution of methyl α-D-mannopyranoside (**1.104**, 5.00 g, 25.7 mmol) in THF (45 mL), triphenylphosphine (9.46 g, 36.0 mmol) and imidazole (3.51 g, 51.5 mmol) were added and the mixture was heated to reflux. A solution of iodine (9.15 g, 36.0 mmol) in THF (15 mL) was added slowly via dropping funnel (the dark orange color of iodine fades immediately). The light yellow suspension was kept at reflux until complete consumption of the starting material (2.5 h). Then the solution was cooled to RT, eventually formed solids were filtered off and the THF was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with aq. sat.

$Na_2S_2O_3$ solution and brine. The water layers were reextracted each with EtOAc (6x). The organic layers were combined, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 15:1) and the desired product **1.105** was obtained as white crystals (5.60 g, 72%).

The analytical data matched those reported in the literature: P. R. Skaanderup, C. S. Poulsen, L. Hyldtoft, M. R. Jørgensen, R. Madsen, *Synthesis* **2002**, 1721–1727.

R_f = 0.1 (CH_2Cl_2/MeOH 10/1); **M.p.**: 122–123°C; $[\alpha]_D$ = +60.7° (c = 0.4, H_2O); **^{1}H-NMR** (400 MHz, D_2O) δ 4.74 (d, J = 1.7 Hz, 1H), 3.94 (dd, J = 3.5, 1.7 Hz, 1H), 3.77 (dd, J = 9.5, 3.4 Hz, 1H), 3.65 (dd, J = 11.0, 2.2 Hz, 1H), 3.58 (pt, J = 9.4 Hz, 1H), 3.49–3.45 (m, 1H), 3.45 (s, 3H), 3.38 (dd, J = 10.9, 7.0 Hz, 1H); **^{13}C-NMR** (101 MHz, D_2O) δ 101.1, 71.5, 70.6, 70.1, 69.9, 55.0, 6.2.

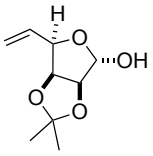
(3a*S*,4*S*,6*S*,73a*S*,7a*S*)-6-(iodomethyl)-4-methoxy-2,2-dimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-ol (1.106)



To a suspension of iodinated mannopyranoside **1.105** (1.00 g, 3.3 mmol) in 2,2-dimethoxypropane (5 mL), ca. 100 mg Amberlite IR120 hydrogen form (washed with methanol and diethyl ether before use) was added (suspension turns slowly into a solution). The reaction mixture was stirred for 3 h at RT, then it was filtrated and evaporated under reduced pressure. The crude product was treated with Et_2O/pentane 1/3 then more pentane was added, such that a white precipitate was formed. The suspension was filtrated and the filter washed with pentane. The yellow filtrate was evaporated under reduced pressure, the residue suspended in pentane and filtrated again, yielding white crystals. The combined solid parts were dried under reduced pressure affording the desired acetonide-protected product **1.106** (1.10 g, 94%) as a white powder.

R_f = 0.2 (Et_2O/pentane 1/3); **M.p.** = 110–111°C; $[\alpha]_D$ = +44.9° (c = 1.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.15–4.10 (m, 2H), 3.59 (dd, J = 10.6, 2.6 Hz, 1H), 3.57–3.46 (m, 5H), 3.31 (dd, J = 10.5, 7.1 Hz, 1H), 2.38 (d, J = 4.3 Hz, 1H), 1.52 (s, 3H), 1.35 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 109.8, 98.5, 78.2, 75.7, 73.2, 69.3, 55.6, 28.0, 26.1, 6.6.

(3a*S*, 4*S*, 6*R*,6a*S*)-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (1.107)

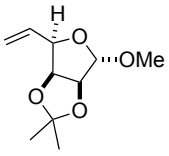


This procedure is a modified version of a Vitamine B_{12}-catalyzed Vasella-Bernet fragmentation: M. Kleban, U. Kautz, J. Greul, P. Hilgers, R. Kugler, H.-Q. Dong, V. Jäger, *Synthesis* **2000**, *7*, 1027–1033. To a solution of iodo-mannopyranoside **1.106** (4.42 g, 12.8 mmol) in MeOH (40 mL), zinc powder (8.40 g, 128 mmol) was added and the grey suspension was heated to 60°C. Solid NH_4Cl (0.150 g, 2.80 mmol) was added and it was stirred for 30 minutes. Then another portion of solid NH_4Cl (0.150 g, 2.80 mmol) was added. After stirring for 90 minutes the mixture was allowed to cool to RT. The grey suspension was filtered through Celite, the filtercake washed with CH_2Cl_2 (3x20 mL) and the solvent was evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/3) afforded the desired furanose **1.107** (2.20 g, 91%) as a colourless oil which crystallized at –20°C.

The analytical data matched those reported in the literature: M. Kleban, U. Kautz, J. Greul, P. Hilgers, R. Kugler, H.-Q. Dong, V. Jäger, *Synthesis* **2000**, *7*, 1027–1033.

***R*$_f$** = 0.6 (Et_2O/pentane 1/1); **M.p.** = 58.0–59.0°C; **[α]$_D$** = –28.7° (*c* = 0.54, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 17.6, 10.4, 7.4 Hz, 1H), 5.42 (ddd, *J* = 17.4, 1.6, 1.1 Hz, 1H), 5.41 (d, *J* = 2.3 Hz, 1H), 5.34 (ddd, *J* = 10.4, 1.6, 0.8 Hz, 1H), 4.73 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.64 (d, *J* = 5.8 Hz, 1H), 4.62–4.59 (m, 1H), 2.69 (d, *J* = 2.3 Hz, 1H), 1.49–1.46 (m, 3H), 1.32 (d, *J* = 0.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 132.2, 119.3, 112.7, 101.1, 85.8, 81.6, 26.1, 24.9.

(3a*S*,4*S*,6*R*,6a*S*)-4-methoxy-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxole (1.108)



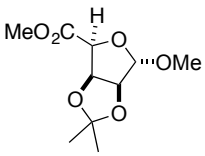
To a solution of furanose **1.107 (**1.00 g, 5.45 mmol) in MeOH (10 mL) and 2,2-dimethoxypropane (5 mL), 10-camphorsulfonic acid (250 mg, 1.10 mmol) was added. The solution was heated to 55°C for 18 h. Then, the dark solution was neutralized with Et_3N turning into a bright yellow solution and the solvents were carefully evaporated under reduced pressure. The residue was treated with H_2O (100 mL) and the aq. layer extracted with Et_2O (3x50 mL). The combined org. layers were dried ($MgSO_4$),

filtered and evaporated under reduced pressure. Purification by Kugelrohr distillation afforded product **1.108** (1.08 g, 99%) as a colourless liquid.

The analytical data matched those reported in the literature: K. Bock, C. Pedersen, *Acta Chem. Scand*. **1977**, *B31*, 248–250.

***R*$_f$** = 0.6 (Et_2O/pentane 1/3); **B.p. =** 130°C (5.6 mbar); **[α]$_D$** = +24.3° (*c* = 0.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) *δ* 5.99 (ddd, *J* = 17.3, 10.1, 7.4 Hz, 1H), 5.42 (ddd, *J* = 17.4, 1.7, 1.1 Hz, 1H), 5.34 (ddd, *J* = 10.4, 1.5, 0.8 Hz, 1H), 4.91 (s, 1H), 4.68 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 1H), 4.39 (dd, *J* = 7.4, 3.7 Hz, 1H), 3.35 (s, 3H), 1.47 (s, 3H), 1.31 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) *δ* 132.3, 119.1, 112.6, 107.2, 85.3, 81.5, 81.1, 54.7, 26.1, 24.9.

methyl (3a*R*,4*S*, 6*S*, 6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (1.109)



A solution of furanoside **1.108** (1.03 g, 5.14 mmol) in CH_2Cl_2 (20 mL) and methanolic NaOH (5.0 mL, 2.5 M) was cooled to –78°C. Then ozone was bubbled through the solution. The solution turned orange and faded to yellow after a while, after 1 h it turned deep blue. After 8 h, again methanolic NaOH (5.0 mL, 2.5 M) was added (solution turns yellow and turbid again which faded again after 45 minutes). Additional methanolic NaOH (2.5 M) was added until full conversion to the ester (monitored by TLC). Then, oxygen was bubbled through the solution for 15 minutes before it was diluted with CH_2Cl_2 (50 mL) and H_2O (20 mL). The reaction mixture was allowed to warm to RT then aq. sat. NH_4Cl (30 mL) was added. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (4x50 mL). The org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/3 to 1/2) afforded the desired ester **1.109** (0.740 g, 62%) as a colourless fluid.

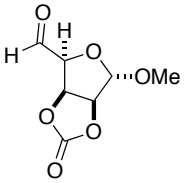
Or

To a solution of aldehyde **1.110** (795 mg, 3.9 mmol) in MeOH (24 mL) and water (4 mL) at RT, $NaHCO_3$ (5.30 g, 63 mmol) was added. Under vigorous stirring bromine (0.65 mL, 13 mmol) was added and the mixture was heated to 40°C. After stirring for 3 h again bromine (50 μL, 1.0 mmol) was added and it was stirred for another 1 h. The reaction mixture was

quenched with aq. sat. $Na_2S_2O_3$ (50 mL) and the reaction mixture was diluted with water (50 mL), and extracted with EtOAc (3x70 mL). The org. layers were washed with water (50 mL) and brine (50 mL), dried (MgSO4), filtered and evaporated under reduce pressure. This afforded the ester **1.109** (0.840 g, 92%) as a colourless fluid.

R_f = 0.17 (Et_2O/pentane 1/3); $[\alpha]_D$ = +23.5° (*c* = 0.65, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.98 (dd, *J* = 5.8, 4.3 Hz, 1H), 4.60–4.55 (m, 2H), 3.81 (s, 3H), 3.35 (s, 3H), 1.42 (s, 3H), 1.31–1.27 (m, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 167.9, 113.4, 107.5, 84.0, 80.6, 79.5, 55.1, 52.2, 25.9, 25.1; **HRMS ESI** calcd. for $[C_{10}H_{16}NaO_6]^+$ $[M+Na]^+$: 255.0839; found: 255.0840; **IR** ν = 2990, 2942, 2839, 1769, 1739, 1439, 1374, 1208, 1095, 1061, 967, 860, 775, 613 cm^{-1}.

(3a*S*,4*S*,6*S*,6a*S*)-6-methoxy-2-oxotetrahydrofuro[3,4-d][1,3]dioxole-4-carbaldehyde (1.110)

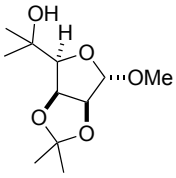


A solution of olefin **1.108** (1.10 g, 5.5 mmol) in CH_2Cl_2 (20 mL) and MeOH (5 mL) was cooled to –78°C. Then ozone was bubbled through the solution until it turned blue. The solution was purged with O_2, and then DMS (2 mL) was added. The colourless solution was allowed to warm to RT and the solvent was evaporated under reduced pressure. Purification by column chromatography (EtOAc/*c*Hex 1/4 to 1/1) yielded the desired aldehyde **1.110** (798 mg, 72%) as colourless oil.

The analytical data matched those reported in the literature: J. M. J. Tronchet, B. Gentile, A. P. Bonenfant, O. R. Martin, *Helv. Chim. Acta* **1979**, *62*, 696–699.

R_f = 0.1 (Et_2O/pentane 1/3); $[\alpha]_D$ = +44.5° (*c* = 1.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.2 Hz, 1H), 5.09 (s, 1H), 5.07 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 1H), 4.37 (d, *J* = 4.3 Hz, 1H), 3.36 (s, 3H), 1.43 (s, 3H), 1.29 (d, *J* = 0.7 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 197.9, 113.7, 108.0, 84.7, 84.1, 81.0, 55.2, 26.0, 24.7.

2-((3a*S*,4*S*,6*S*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-propan-2-ol (1.112)



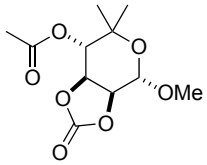
To a solution of ester **1.109** (735 mg, 3.2 mmol) in Et_2O (28 mL), MeMgBr (3 M solution in Et_2O, 3.2 mL, 9.5 mmol) was added dropwise at RT and the mixture heated to 35°C for 30 minutes. The reaction was cooled to RT and carefully quenched with aq. sat. NH_4Cl (10 mL) Then H_2O (30 mL) was added and the mixture was extracted with Et_2O (3x20 mL). The org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure, giving the pure title compound **1.112** (721 mg, 99%) as colourless oil.

The analytical data matched those reported for its enantiomer in the literature: A. Klemer, M. Waldmann, *Liebigs Ann. Chem.* **1986**, *2*, 221–406.

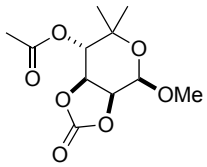
R_f = 0.4 (Et_2O/pentane 1/1); $[\alpha]_D$ = +84.0° (*c* = 1.15, MeOH); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.86 (dd, *J* = 5.9, 3.4, Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 1H), 3.71 (d, *J* = 3.3 Hz, 1H), 3.56 (s, 1H), 3.35 (s, 3H), 1.52 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 112.8, 106.6, 85.2, 82.9, 80.7, 70.9, 54.5, 27.3, 27.3, 25.8, 24.2; **IR** ν = 3525, 2979, 2937, 1465, 1374, 1209, 1153, 1092, 1031, 964, 881, 854 cm^{-1}.

(3a*S*,7*S*,7a*S*)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl acetate (1.116)

To a solution of novioside **1.103** (47 mg, 0.25 mmol) in THF (2.5 mL) at 50°C, 1,1'-carbonyldiimidazole (140 mg, 0.86 mmol) was added over a period of 3 h. Then the mixture was cooled to RT and quenched with aq. HCl (6 M, 0.6 mL), and the mixture was stirred for 1 h. EtOAc was added and the THF was evaporated under reduced pressure. The residual solution was then washed with brine, reextracted with EtOAc and the org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was dissolved in pyridine (0.7 mL) and acetic anhydride (0.7 mL). The colourless solution was stirred for 1 h at RT. The solvents were evaporated under reduced pressure and azeotropized with toluene. Purification by column chromatography (EtOAc/toluene 1/8) afforded the two anomers (α-**1.116**: 24 mg, 38%; β-**1.116**: 9 mg, 14% and a mix-fraction of α-/β-**1.116**: 10 mg, 16%) as white solids.

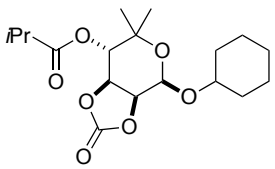


α-**1.116**: R_f = 0.61 (EtOAc/toluene 1/3); $[\alpha]_D$ = +21.6° (*c* = 0.82, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.11 (d, *J* = 7.7 Hz, 1H), 4.91 (d, *J* = 3.0 Hz, 1H), 4.78 (pt, *J* = 7.7 Hz, 1H), 4.68 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.46 (s, 3H), 2.13 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H); **^{13}C-NMR** (63 MHz, $CDCl_3$) δ 169.6, 153.2, 97.3, 76.7 75.4, 74.7, 72.4, 56.1, 26.7, 23.1, 20.9; **HRMS ESI** calcd. for $[C_{11}H_{16}NaO_7]^+$ $[M+Na]^+$: 283.0788; found: 283.0790; **IR** ν = 2987, 2945, 2848, 1827, 1809, 1748, 1374, 1223, 1174, 1130, 1082, 1035, 883, 768 cm^{-1}.



β-**1.116**: R_f = 0.44 (EtOAc/toluene 1/3); $[\alpha]_D$ = –91.6° (*c* = 1.10, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.80–5.72 (m, 1H), 4.86–4.82 (m, 1H), 4.81–4.74 (m, 2H), 3.52 (s, 3H), 2.14 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.2, 153.9, 95.8, 75.7, 75.0, 72.6, 71.9, 56.2, 28.7, 24.2, 21.0; **HRMS ESI** calcd. for $[C_{11}H_{16}NaO_7]^+$ $[M+Na]^+$: 283.0788; found: 283.0793; **IR** ν = 2983, 2940, 2849, 1806, 1745, 1371, 1223, 1171, 1075, 1042, 770 cm^{-1}.

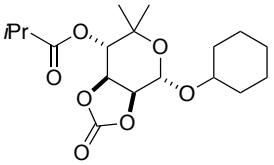
(3a*S*,4*R*,7*S*,7a*S*)-4-(cyclohexyloxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (β-1.176)



To a solution of novioside **1.102** (2.5 mg, 9 μmol) in CH_2Cl_2 (0.2 mL) at 0°C and protected from light, HBr (33% in AcOH, 0.2 mL) was added and the solution was stirred for 2 h at RT. The solution was cooled to 5°C and diluted with CH_2Cl_2 (3 mL). The reaction was quenched with ice and H_2O. The layers were separated and the org. layer was washed with aq. sat. $NaHCO_3$ (8 mL) The aq. solutions were extracted with CH_2Cl_2 (2x3 mL) and the combined org. layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure at RT. The residual glycosyl bromide **1.175** was dissolved in CH_2Cl_2 (0.1 mL) and added dropwise to a suspension of cyclohexanol (1.1 μL, 10 μmol), Ag_2CO_3 (120 mg, excess), and powdered molecular sieves (3Å, 100 mg) in CH_2Cl_2 (0.1 mL). The suspension was stirred for 1.5 h. Then it was diluted with CH_2Cl_2 (2 mL), quenched with Et_3N (0.05 mL), filtered through Celite, the filter was washed with CH_2Cl_2 (2 mL) and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/*c*Hex 1/4) to give the product β-**1.176** (2.5 mg, 81%).

R_f = 0.27 (EtOAc/cHex 1/4); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.96 (d, J = 6.6 Hz, 1H), 5.05 (d, J = 3.1 Hz, 1H), 4.82–4.72 (m, 2H), 3.73 (tt, J = 8.4, 3.5 Hz, 2H), 2.62 (dt, J = 14.0, 7.0 Hz, 1H), 1.94–1.83 (m, 1H), 1.83–1.65 (m, 3H), 1.60–1.20 (m, 6H), 1.24 (s, 3H), 1.21 (d, J = 7.0 Hz, 6H), 1.18 (s, 3H); **HRMS ESI** calcd. for $[C_{18}H_{28}NaO_7]^+$ $[M+Na]^+$: 379.1727; found: 379.1725.

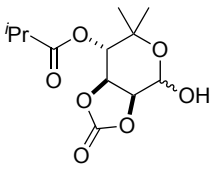
(3a*S*,4*S*,7*S*,7a*S*)-4-(cyclohexyloxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (α-1.176)



To a solution of novioside **1.102** (2.5 mg, 9 μmol) in CH_2Cl_2 (0.2 mL) at 0°C and protected from light, HBr (33% in AcOH, 0.2 mL) was added. and the solution was stirred for 2 h at RT. Then solution was cooled to 5°C and diluted with CH_2Cl_2 (3 mL). The reaction was quenched with ice and H_2O. The layers were separated and the org. layer was washed with aq. sat. $NaHCO_3$ (8 mL) The aq. solutions were extracted with CH_2Cl_2 (2x3 mL) and the combined org. layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure at RT. The residual glycosyl bromide **1.175** was dissolved in CH_2Cl_2 (0.1 mL) and added dropwise to a suspension of cyclohexanol (1.1 μL, 0.01 mmol), AgOTf (22.3 mg, 0.086 mmol), and powdered molecular sieves (3Å, 100 mg) in CH_2Cl_2 (0.1 mL). The suspension was stirred for 1 h then it was diluted with CH_2Cl_2 (2 mL), quenched with Et_3N (0.05 mL), filtered through Celite, the filter was washed with CH_2Cl_2 (2 mL) and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/*c*Hex 1/8) to give the product α-**1.176** (n.d., quant. conv.).

R_f = 0.5 (EtOAc/cHex 1/4); **$[\alpha]_D$** = +19.2° (c = 0.19, $CHCl_3$); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.14 (s, 1H), 5.13 (d, J = 4.1 Hz, 1H), 4.79 (t, J = 7.9 Hz, 1H), 4.67 (dd, J = 7.9, 3.7 Hz, 1H), 3.68 (td, J = 9.1, 4.5 Hz, 1H), 2.62 (hept, J = 7.0 Hz, 1H), 1.95–1.84 (m, 2H), 1.78–1.70 (m, 2H), 1.56–1.50 (m, 2H), 1.45–1.35 (m, 1H), 1.35–1.27 (m, 1H), 1.28 (s, 6H), 1.25–1.20 (m, 2H), 1.21 (d, J = 1.6 Hz, 3H), 1.20 (d, J = 1.6 Hz, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 175.5, 153.3, 93.3, 77.0, 76.0, 75.5, 74.5, 71.9, 34.0, 33.1, 31.0, 26.6, 25.5 (2C), 24.0, 23.7, 18.9, 18.7; **HRMS ESI** calcd. for $[C_{18}H_{28}NaO_7]^+$ $[M+Na]^+$: 379.1727; found: 379.1725; **IR** ν = 2937, 2859, 1791, 1736, 1467, 1375, 1348, 1184, 1129, 1063, 1029, 984, 956, 899, 793, 770 cm^{-1}.

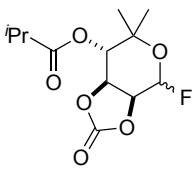
(3a*S*,7*S*,7a*S*)-4-hydroxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (1.178)



To a solution of novioside **1.102** (19 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL, wet) at RT, HBr (33% in AcOH (wet), 0.4 mL) was added. The slightly orange solution was then stirred at RT for 0.5 h. Then it was diluted with CH_2Cl_2 (2 mL) and quenched with NaOH (1 M, 2 mL). The layers were separated and the aq. layer extracted with CH_2Cl_2 (2x3 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/CyHex 1/4 to 1/1) gave the desired noviose **1.178** (8.5 mg, 47%) as an inseparable anomeric mixture (α:β = 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$, major/minor anomer 2/1) δ 5.50 (d, J = 5.3 Hz, 1H), 5.39 (d, J = 3.6 Hz, 0.5H), 5.22 (d, J = 2.0 Hz, 1H), 5.16 (d, J = 7.2 Hz, 0.5H), 4.85–4.80 (m, 1.5H), 4.76 (dd, J = 8.5, 2.3 Hz, 1H), 4.70 (dd, J = 8.0, 3.6 Hz, 0.5H), 3.62 (br s, 1H), 3.49 (br s, 0.5H), 2.70–2.56 (m, J = 7.0 Hz, 2H), 1.36 (s, 3H), 1.30 (s, 1.5H), 1.30 (s, 1.5H), 1.25–1.16 (m, 12H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 175.6 (minor), 175.2, 153.6, 153.4 (minor), 90.8 (minor), 88.2, 76.8 (minor), 76.1, 75.3 (minor), 75.0, 75.0 (minor), 73.5, 71.4 (minor), 70.3, 34.12, 34.10 (minor), 28.6, 26.8 (minor), 24.5 (minor), 23.1, 19.1, 19.0 (minor), 18.9, 18.8 (minor).

(3a*S*,7*S*,7a*S*)-4-fluoro-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (1.179)



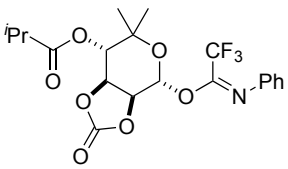
To a solution of noviose **1.178** (3 mg, 0.01 mmol) CH_2Cl_2 (0.5 mL) at 0°C, diethylaminosulfur trifluoride (a drop) was added. The reaction was stirred for 30 minutes at this temperature then it was quenched with aq. sat. NaHCO3 (2 mL). The aq. layer was extracted with Et2O (3x2 mL), the combined org. layers dried ($MgSO_4$), filtered and evaporated under reduced pressure. This furnished the title compound **1.179** (3 mg, quant.) in high purity.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.75 (d, J = 50.7 Hz, 1H), 5.11–5.07 (m, 1H), 4.82–4.79 (m, 2H), 2.56 (dq, J = 14.0, 7.0 Hz, 1H), 1.25 (s, 3H), 1.18 (s, 3H), 1.16 (d, J = 1.6 Hz, 3H), 1.14 (d, J = 1.5 Hz, 3H).

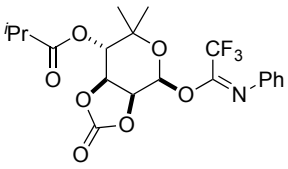
(3a*S*,4*S*,7*S*,7a*S*)-6,6-dimethyl-2-oxo-4-((*E*)-2,2,2-trifluoro-1-(phenylimino)ethoxy)-tetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (α-1.181);

(3a*S*,4*R*,7*S*,7a*S*)-6,6-dimethyl-2-oxo-4-((*E*)-2,2,2-trifluoro-1-(phenylimino)ethoxy)-tetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (β-1.181)

To a solution of noviose **1.178** (7.1 mg, 26 μmol) in acetone (0.6 mL) at RT, K_2CO_3 (14 mg, 0.10 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (9 μL, 50 μmol) were added and the mixture was stirred at RT for 1 h. Then it was filtered and the solvents were evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/4 to 1/2 to 1/0) gave the two anomers **1.181** (α-**1.181** 5.8 mg, 50%; β-**1.181** 4.4 mg, 38%) as colourless resins.



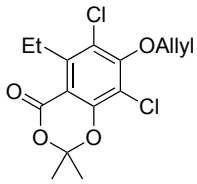
α-**1.181**: R_f = 0.5 (EtOAc/cHex 1/4); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.17–7.10 (m, 1H), 6.86–6.81 (m, 2H), 6.50 (br s, 1H), 5.23 (d, J = 5.8 Hz, 1H), 4.97–4.89 (m, 2H), 2.64 (hept, J = 7.0 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.22 (d, J = 7.0 Hz, 6H); **IR** ν = 2986, 1794, 1725, 1720, 1598, 1469, 1325, 1155, 1115, 1074, 1040, 940, 774, 695 cm^{-1}.



β-**1.181**: R_f = 0.25 (EtOAc/cHex 1/4); **^{1}H-NMR** (400 MHz, Acetone-d_6) δ 7.42–7.33 (m, 2H), 7.18–7.12 (m, 1H), 6.90 (d, J = 7.5 Hz, 2H), 6.60 (br s, 1H), 5.74 (d, J = 7.3 Hz, 1H), 5.45 (dd, J = 9.0, 3.2 Hz, 1H), 5.26 (dd, J = 8.9, 7.3 Hz, 1H), 2.72 (hept, J = 7.0 Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.21 (d, J = 3.2 Hz, 3H), 1.20 (d, J = 3.2 Hz, 3H); **IR** ν = 2983, 1794, 1738, 1549, 1452, 1376, 1241, 1146, 1115, 1078, 1025, 756 cm^{-1}.

4.1.2 Rhamnoside-Resorcylate Substrates

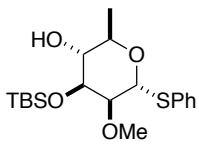
7-(allyloxy)-6,8-dichloro-5-ethyl-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (1.128)



To a suspension of resorcylate **1.134** (492 mg, 1.7 mmol) and K_2CO_3 (701 mg, 5.1 mmol) in DMF (5.0 mL), allyl bromide (0.44 mL, 5.1 mmol) was added and the reaction mixture was stirred at RT for 4 h. The reaction mixture was then quenched with H_2O (50 mL) and aq. sat. $NaHCO_3$ (50 mL) The aq. layer was extracted with Et_2O (3x50 mL), the org. layers washed with H_2O (50 mL) and brine (50 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the allyl-protected resorcylate **1.128** (534 mg, 95%) as a beige, crystalline compound.

R_f = 0.74 (pentane/Et_2O 3/1); **M.p. =** 93.5-94.5°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.15 (ddt, J = 17.1, 10.3, 6.0 Hz, 1H), 5.45 (ddd, J = 17.1, 1.4, 2.9 Hz, 1H), 5.32 (ddd, J = 10.3, 2.4, 1.1 Hz, 1H), 4.63 (dt, J = 6.0, 1.3 Hz, 2H), 3.30 (q, J = 7.4 Hz, 2H), 1.74 (s, 6H), 1.21 (t, J = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 158.5, 156.9, 152.7, 146.2, 132.5, 124.9, 119.3, 115.9, 109.9, 105.9, 74.6, 25.6 (2C), 24.5, 13.4; **HRMS ESI** calcd. for $[C_{15}H_{16}Cl_2NaO_4]^+$ $[M+Na]^+$: 353.0318; found: 353.0312; **IR** ν = 2990, 2943, 1733, 1573, 1380, 1277, 1231, 1204, 1112, 1047, 911, 787 cm^{-1}.

2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-ol (1.129)

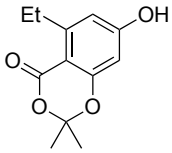


To a solution of thioglycoside **1.139** (18 mg, 38 µmol) in CH_2Cl_2 (1.0 mL) and H_2O (0.1 mL) under vigorous stirring, DDQ (86 mg, 0.38 mmol) was added. The resulting brown mixture was stirred at RT for 5 h, then additional DDQ (34 mg, 0.15 mmol) was added, and stirred for another 2.5 h. Then it was quenched with aq. sat. $NaHCO_3$ (20 mL) and the reaction mixture was extracted with CH_2Cl_2 (4x10 mL). The combined org. layers were dried ($MgSO_4$), filtrated and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/3) gave the desired alcohol **1.129** (12 mg, 82%) as colourless oil.

R_f = 0.32 (Et_2O/pentane 1/3); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 2H), 7.35–7.20 (m, 3H), 5.54 (d, J = 1.0 Hz, 1H), 4.11 (dq, J = 9.3, 6.2 Hz, 1H), 3.85 (dd, J = 9.3, 3.1 Hz,

1H), 3.64 (dt, *J* = 3.2, 1.5 Hz, 1H), 3.61 (dd, *J* = 9.3, 2.6 Hz, 1H), 3.47 (s, 3H), 2.10 (d, *J* = 2.7 Hz, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 0.95 (s, 9H), 0.18 (s, 3H), 0.18 (s, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 134.9, 130.9 (2C), 129.1 (2C), 127.2, 85.4, 82.7, 73.9, 73.1, 69.5, 58.8, 25.9 (3C), 18.9, 17.7, –4.29, –4.61.

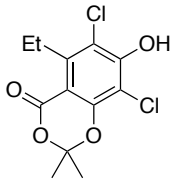
5-ethyl-7-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (1.133)



To a solution of diisopropylamine (0.35 mL, 2.5 mmol) in THF (25 mL) at –78°C, *n*BuLi (1.6 M in hexane; 1.57 mL, 2.5 mmol) was added slowly. The solution was stirred for 40 minutes before keto-dioxinone **1.131** (221 mg, 1.2 mmol) in THF (1.5 mL) was added. The resulting orange reaction mixture was stirred for 100 minutes at –78°C. Then propionyl imidazole (74 mg, 0.60 mmol) dissolved in THF (1.1 mL) was added. After stirring the reaction mixture for 2.5 h at –78°C, the reaction was quenched with aq. sat. NH_4Cl (20 mL) The medium was adjusted to pH 3 using aq. HCl (1 M), extracted with EtOAc (3x50 mL) and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The yellow residue was dissolved in CH_2Cl_2 (15 mL) and Et_3N (2 mL, excess). After stirring for 16 h, the mixture was acidified to pH 1 using aq. HCl (1 M) and the aq. layer was extracted with CH_2Cl_2 (3x50 mL), the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/2 to 2/1) afforded the isopropylidene-protected resorcylate **1.133** (76 mg, 57%) as a yellow crystalline solid.

R_f = 0.45 (Et_2O/pentane 1/2); **M.p.** = 138.0–140.0°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 3.05 (q, *J* = 7.4 Hz, 2H), 1.68 (s, 6H), 1.22 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 163.2, 161.8, 159.3, 152.1, 112.6, 105.1, 103.8, 101.7, 27.8, 25.5 (2C), 14.9; **HRMS ESI** calcd. for $[C_{12}H_{15}O_4]^+$ $[M+H]^+$: 223.0965; found: 223.0967; **IR** ν = 3224, 3000, 2955, 2870, 1688, 1608, 1499, 1442, 1294, 1213, 1154, 1048, 915, 840, 704 cm^{-1}.

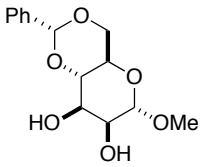
6,8-dichloro-5-ethyl-7-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (1.134)



To a solution of resorcylate **1.133** (500 mg, 2.3 mmol) in CH_2Cl_2 (25 mL) at RT, sulfuryl chloride (0.43 mL, 5.3 mmol) was added dropwise. The resulting yellow solution was heated to reflux for 1.5 h and subsequently the solvent was evaporated under reduced pressure. The yellow residue was triturated with pentane (3x7 mL). The remaining solid was dried under HV to afford the title compound **1.134** (639 mg, 98%) as beige solid.

R_f = 0.25 (pentane/Et_2O 3/1); **M.p.** = 172.5-173.5°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 3.30 (q, J = 7.4 Hz, 2H), 1.75 (s, 6H), 1.21 (t, J = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 158.6, 153.3, 152.9, 145.9, 116.5, 107.2, 106.3, 105.9, 25.6 (2C), 24.5, 13.3; **HRMS ESI** calcd. for $[C_{12}H_{11}Cl_2O_4]^+$ $[M+H]^+$: 289.0040; found: 289.0037; **IR** ν = 3287, 3001, 2974, 2950, 2881, 1716, 1584, 1561, 1437, 1280, 1192, 1044, 786, 621 cm^{-1}.

(2*R*,4a*R*,6*S*,7*S*,8*R*,8a*S*)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (1.135)



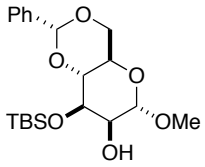
This procedure was adopted from F. Ekholm, M. Poláková, A. Pawłowicz, R. Leino, *Synthesis* **2009**, 567–576. Methyl α-D-mannopyranoside **1.104** (100 mg, 0.50 mmol), benzaldehyde dimethyl acetal (80 µL, 0.50 mmol) and *para*-toluenesulfonic acid monohydrate (10.0 mg, 0.50 mmol) were dissolved in DMF (2.5 mL). The reaction mixture was rotated in a rotary evaporater at 200 mbar at 60°C for 2 h. The reaction mixture was then quenched with H_2O (50 mL), extracted with EtOAc (3x50 mL), the combined org. layers were dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. Purification by column chromatography (EtOAc/pentane 1/2 to pure EtOAc) yielded the title compound **1.135** (78.0 mg, 53%) as a white solid.

The analytical data are in good agreement with the literature: P. S. Kumar, G. D. K. Kumar, S. Baskaran, *Eur. J. Org. Chem.* **2008**, *63*, 6063–6067.

[α]$_D$ = +65.3° (c = 1.0, $CHCl_3$); **M.p.** = 144.4–144.3°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 1H), 7.41–7.35 (m, 2H), 5.55 (s, 1H), 4.71 (d, J = 1.2 Hz, 1H), 4.33 – 4.21 (m, 1H), 4.03 (dd, J = 9.5, 3.5 Hz, 1H), 3.97 (d, J = 3.5 Hz, 1H), 3.89 (t, J = 9.2 Hz, 1H), 3.86–3.78

(m, 2H), 3.38 (s, 2H), 2.94 (br s, 1H), 2.90 (br s, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 137.2, 129.3, 128.4, 126.3, 102.3, 101.3, 78.9, 70.9, 68.8, 68.6, 62.9, 55.1; **IR** ν = 3562, 3000, 2928, 2856, 1463, 1381, 1253, 1120, 1075, 1099, 1048, 860, 836, 781, 697 cm^{-1}.

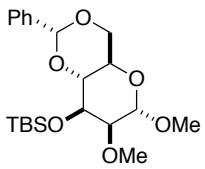
(2*R*,4a*R*,6*S*,7*S*,8*R*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (1.135b)



4,6-Benzylidene acetal-protected compound **1.135** (2.00 g, 7.1 mmol) and dibutyltin oxide (2.12 g, 8.5 mmol) were suspended in MeOH (50 mL) and heated to reflux. After stirring for 1 h, the suspension turned into a slightly turbid solution. The volatiles were evaporated under reduced pressure and the residue was dried under high vacuum for 2 h. The resulting oily residue was dissolved in DMF (40 mL) and evacuated to 0.2 mbar until bubbling ceased. Then a solution of TBSCl (2.45 mL, 14.0 mmol) and TBAI (52.3 mg, 0.14 mmol) in CH_2Cl_2 (3 mL) was added and the reaction was stirred for 16 h. The reaction mixture was quenched with MeOH (2.5 mL), diluted with water (200 mL), and extracted with Et_2O (3x100 mL), the org. layers were washed with brine (200 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/3) afforded the TBS-protected product **1.135b** (2.24 g, 80%) as a colourless oil.

R_f = 0.57 (pentane/Et_2O 1/1); $[\alpha]_D$ = +24.8° (*c* = 0.59, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.39–7.32 (m, 3H) 5.55 (s, 1H), 4.79 (d, *J* = 1.2 Hz, 1H), 4.29–4.23 (m, 1H), 4.07 (dd, *J* = 9.1, 3.8 Hz, 1H), 3.87 (dd, *J* = 5.6, 3.9 Hz, 1H), 3.86–3.75 (m, 3H), 3.39 (s, 3H), 2.82 (br s, 1H), 0.88 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 137.5, 128.9, 128.1 (2C), 126.1 (2C), 101.9, 100.9, 79.1, 72.0, 69.8, 68.9, 63.0, 55.0, 25.7 (3C), 18.1, –4.4, –5.0; **HRMS ESI** calcd. for $[C_{20}H_{33}O_6Si]^+$ $[M+H]^+$: 397.2041; found: 397.2040; **IR** ν = 3562, 3000, 2928, 2856, 1463, 1381, 1253, 1120, 1075, 1099, 1048, 860, 836, 781, 697 cm^{-1}.

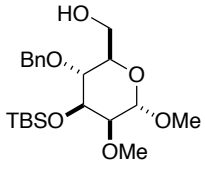
tert-butyl(((2*R*,4a*R*,6*S*,7*S*,8*S*,8a*R*)-6,7-dimethoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)oxy)dimethylsilane (1.136)



To a solution of TBS protected mannose **1.135b** (105.0 mg, 0.27 mmol) in THF (1 mL) at 0°C, sodium hydride (31.5 mg, 0.80 mmol, 60 % dispersion in oil) was added and the mixture was stirred for 40 minutes at 0 °C. MeI (0.04 mL, 0.66 mmol) was then added and the mixture was stirred for 30 minutes at 0 °C. The reaction mixture was warmed to RT, stirred 8 h and the reaction mixture was diluted with EtOAc (2 mL) and quenched with water (2 mL). The layers were separated, the aqueous layer reextracted with EtOAc (3x5 mL), the combined org. layers washed with aq. sat. NH_4Cl (5 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/5) yielded the 2*O*-methylated mannose **1.136** (89.0 mg, 82%) as colourless oil.

R_f = 0.27 (pentane/Et_2O 5/1, CAM, UV); $[\alpha]_D$ = +32.0° (*c* = 1.14, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.38–7.32 (m, 3H), 5.56 (s, 1H), 4.72 (d, *J* = 1.5 Hz, 1H), 4.23 (dd, *J* = 10.0, 4.6 Hz, 1H), 4.13 (dd, *J* = 9.7, 3.3 Hz, 1H), 3.91 (t, *J* = 9.5 Hz, 1H), 3.83 (t, *J* = 10.2 Hz, 1H), 3.74 (dd, *J* = 9.5, 4.6 Hz, 1H), 3.59 (s, 3H), 3.45 (dd, *J* = 3.3, 1.6 Hz, 1H), 3.38 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 137.7, 128.8, 128.1 (2C), 126.2 (2C), 101.9, 100.5, 81.9, 79.2, 70.5, 68.9, 64.1, 60.8, 54.9, 25.8 (3C), 18.3, –4.4, –4.9; **HRMS ESI** calcd. for $[C_{21}H_{34}NaO_6Si]^+$ $[M+Na]^+$: 433.2017; found: 433.2013; **IR** ν = 2928, 2967, 2856, 1463, 1386, 1251, 1126, 1100, 1055, 1024, 975, 864, 836, 779, 697 cm^{-1}.

((2*R*,3*R*,4*S*,5*S*,6*S*)-3-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-5,6-dimethoxytetrahydro-2*H*-pyran-2-yl)methanol (1.137)

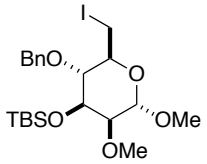


To a solution of acetal **1.136** (88 mg, 0.21 mmol) in CH_2Cl_2 (2.5 mL), borane THF complex (1M, 1.18 mL, 1.2 mmol) and TMSOTf (0.7 µL, 40 µmol) were added and the colourless solution was stirred at RT for 45 minutes. The reaction mixture was quenched with Et_3N (0.3 mL) followed by slow addition of MeOH (1 mL). The reaction mixture was then evaporated under reduced pressure, the residue dissolved in MeOH (3 mL) and evaporated again. Purification by

column chromatography (Et_2O/pentane 1/2 to Et_2O) gave the primary alcohol **1.137** (80 mg, 91%) as colourless oil.

R_f = 0.3 (Et_2O/pentane 1/1); $[\alpha]_D$ = +74.0° (*c* = 0.94, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.24–7.19 (m, 4H), 7.16 (dq, *J* = 6.8, 4.0 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 1.7 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 3.95 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.67 (ddd, *J* = 11.6, 5.4, 2.8 Hz, 1H), 3.61 (t, *J* = 9.5 Hz, 1H), 3.60–3.54 (m, 1H), 3.45 (ddd, *J* = 8.6, 4.2, 2.3 Hz 1H), 3.42 (s, 3H), 3.26 (dd, *J* = 3.1, 1.9 Hz, 1H), 3.23 (s, 3H), 2.01 (t, *J* = 6.5 Hz, 1H), 0.84 (s, 9H), 0.01 (d, *J* = 8.2 Hz, 6H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 138.6, 128.4 (2C), 127.8 (2C), 127.7, 99.0, 81.5, 75.9, 75.2, 73.2, 72.3, 62. 4, 60.0, 54.9, 26.1 (3C), 18.2, –4.3, –4.5; **HRMS ESI** calcd. for $[C_{21}H_{37}O_6Si]^+$ $[M+H]^+$: 413.2354; found: 413.2352; **IR** ν = 3482, 2929, 2857, 1383, 1252, 1191, 1125, 1097, 1057, 866, 836, 776, 734, 697 cm^{-1}.

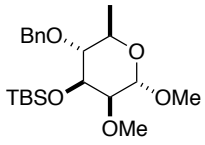
(((2*S*,3*R*,4*S*,5*S*,6*S*)-3-(benzyloxy)-2-(iodomethyl)-5,6-dimethoxytetrahydro-2*H*-pyran-4-yl)oxy)(tert-butyl)dimethylsilane (1.137b)



To a solution of the primary alcohol **1.137** (100 mg, 0.24 mmol) toluene (2 mL), iodine (92 mg, 0.36 mmol), imidazole (97 mg, 1.4 mmol) and triphenylphosphine (184 mg, 0.70 mmol) were added. The orange solution was heated to 100°C, becoming a colourless solution, and stirred for 7 h at this temperature. Then the solvent was evaporated under reduced pressure. Purification by column chromatography (pentane to Et_2O/pentane 1/7, dry loading) yielded the iodide **1.137b** (107 mg, 85%) as a colourless oil.

R_f = 0.75 (Et_2O/pentane 1/2); $[\alpha]_D$ = +55.7° (*c* = 0.48, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.73 (d, *J* = 1.7 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.05 (dd, *J* = 8.7, 3.2 Hz, 1H), 3.56–3.45 (m, 3H), 3.53 (s, 3H), 3.41 (s, 3H), 3.37 (dd, *J* = 3.2, 1.8 Hz, 1H), 3.25–3.18 (m, 1H), 0.95 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 138.2, 128.4 (2C), 127.7, 127.7 (2C), 98.6, 81.4, 79.6, 75.4, 72.9, 71.6, 59.7, 55.1, 26.0 (3C), 18.1, 6.96, –4.43, –4.60; **IR** ν = 2954, 2929, 2856, 1462, 1408, 1253, 1194, 1124, 1061, 967, 865, 836, 776, 733, 697 cm^{-1}.

(((2*R*,3*R*,4*S*,5*S*,6*S*)-3-(benzyloxy)-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-4-yl)oxy)(tert-butyl)dimethylsilane (1.138)



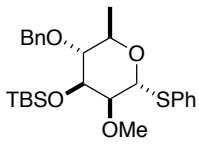
To a solution of iodide **1.137b** (16 mg, 30 µmol) in THF (1 mL) at RT, LAH (1 M in THF, 90 µL, 90 µmol) was added. The reaction mixture was then heated to 60°C and stirred for 6 h. MeOH (1 mL) and silica gel (ca. 200 mg) were added and the suspension was evaporated under reduced pressure. The residue was filtrated over silica using Et_2O and the solvent was evaporated under reduced pressure yielding the rhamnoside **1.138** (10 mg, 82%) as colourless oil.

Or

To a solution of iodide **1.137b** (107 mg, 0.21 mmol) in MeOH (1.0 mL), Et_3N (0.06 mL, 0.41 mmol) and Pd/C (10%, 25 mg) were added. The black suspension was then stirred in an autoclave for 2 h at RT and 50 bar hydrogen atmosphere. The reaction mixture was filtrated over Celite washed with Et_2O (10 mL) and evaporated under reduced pressure. The residue was purified by column chromatography (Et_2O/pentane 1/3) to yield the rhamnoside **1.138** (55 mg, 68%) as colourless oil.

R_f = 0.45 (Et_2O/pentane 1/3); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25–7.14 (m, 5H), 4.80 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 1.8 Hz, 1H), 4.48 (d, J = 11.3 Hz, 1H), 3.91 (dd, J = 9.2, 3.2 Hz, 1H), 3.52 (dq, J = 9.5, 6.3 Hz, 1H), 3.44 (s, 3H), 3.31 (d, J = 9.4 Hz, 1H), 3.26 (dd, J = 3.3, 1.9 Hz, 1H), 3.23 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), –0.00 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 138.7, 128.3 (2C), 127.7 (2C), 127.5, 98.6, 81.6, 81.4, 75.3, 73.0, 67.9, 59.7, 54.7, 26.0 (3C), 18.1, 18.0, –4.42, –4.57; **HRMS ESI** calcd. for $[C_{21}H_{36}NaO_5Si]^+$ $[M+Na]^+$: 419.2224; found: 419.2222.

(((2*R*,3*R*,4*S*,5*S*,6*R*)-3-(benzyloxy)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-4-yl)oxy)(*tert*-butyl)dimethylsilane (1.139)



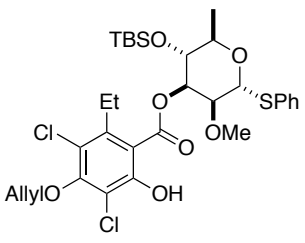
To a solution of pyranoside **1.138** (55 mg, 0.14 mmol) in DCE (1.0 ml) at RT, TMSSPh (0.13 mL, 0.69 mmol), ZnI_2 (133 mg, 0.42 mmol) and tetrabutlyammonium iodide (77 mg, 0.21 mmol) were added and the mixture was stirred at 65°C for 2 h. The reaction mixture was quenched with aq. sat. $Ba(OH)_2$ (10 mL), diluted with CH_2Cl_2 (10 mL), the layers were separated and the aq. layer extracted

with CH_2Cl_2 (3x10 mL). The combined org. layers were dried ($MgSO_4$), filtrated and evaporated under reduced pressure. Purification by column chromatography (adsorbed on silica, Et_2O/pentane 1/10) yielded the thioglycoside **1.139** (52 mg, 79%) as a colourless solid.

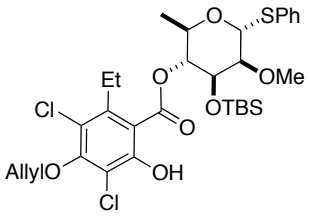
***R*$_f$** = 0.35 (Et_2O/pentane 1/10); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.26–7.12 (m, 9H), 5.44 (d, *J* = 1.4 Hz, 2H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.04 (dq, *J* = 9.4, 6.2 Hz, 1H), 3.93 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.56 (dd, *J* = 3.1, 1.8 Hz, 1H), 3.42 (s, 3H), 3.40 (t, *J* = 9.3 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 138.6, 135.1, 130.9 (2C), 129.0 (2C), 128.3 (2C), 127.8 (2C), 127.6, 127.2, 85.2, 83.3, 81.5, 75.5, 73.5, 69.4, 58.9, 26.0 (3C), 18.2, 17.9, –4.47 (2C); **ESI-MS** *m/z* = 497.3 $[M+Na]^+$; **IR** ν = 3059, 2952, 2930, 2884, 2858, 1471, 1386, 1255, 1127, 1099, 1075, 1032, 867, 833, 764, 736, 694, 670 cm^{-1}.

(2*R*,3*R*,4*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)-tetrahydro-2*H*-pyran-4-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.140)

To a solution of TBS-protected thioglycoside **1.129** (12 mg, 30 μmol) and resorcylate **1.128** (16.5 mg, 50 μmol) in THF (1.0 mL), NaH (60% dispersion in mineral oil, 6.2 mg, 0.16 mmol) was added and the reaction mixture was stirred at RT for 4 h. Then the mixture was diluted with Et_2O (3 mL) and quenched with aq. sat. NH_4Cl (2 mL), the layers were seperated, and the aq. layer was extracted with Et_2O (3x3 mL). The combined org layers were dried ($MgSO_4$), filtrated and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/20) afforded the title compound **1.140** (O3, 12 mg, 59%) and its regioisomer **1.127** (O4, 2 mg, 10%).

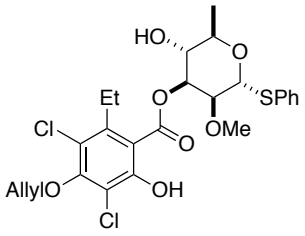


1.140 (O3): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 11.44 (s, 1H), 7.43–7.39 (m, 2H), 7.28–7.18 (m, 3H), 6.07 (ddt, *J* = 17.2, 10.3, 6.0 Hz, 1H), 5.53 (d, *J* = 1.7 Hz, 1H), 5.40 (t, *J* = 9.5 Hz, 1H), 5.36 (dq, *J* = 17.5, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.3, 1.2, Hz, 1H), 4.54 (ddd, *J* = 6.0, 1.3, 1.3, Hz, 2H), 4.30 (dq, *J* = 9.8, 6.2 Hz, 1H), 4.03 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.63 (dd, *J* = 3.0, 1.9 Hz, 1H), 3.42 (s, 3H), 3.08 (dq, *J* = 12.8, 7.3 Hz, 1H), 2.91 (dq, *J* = 12.9, 7.3 Hz, 1H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.19 (t, *J* = 7.3 Hz, 3H), 0.70 (s, 9H), 0.00 (s, 3H), –0.17 (s, 3H).



1.127 (O4): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.54–7.49 (m, 2H), 7.37–7.27 (m, 3H), 6.16 (ddt, J = 17.2, 10.3, 5.9 Hz, 1H), 5.64 (d, J = 1.4 Hz, 1H), 5.44 (dq, J = 17.2, 1.5 Hz, 1H), 5.36–5.26 (m, 3H), 4.62 (ddd, J = 5.9, 1.3, 1.3 Hz, 2H), 4.22 (dq, J = 9.0, 6.2 Hz, 1H), 4.05 (dd, J = 3.5, 1.7 Hz, 1H), 3.85 (t, J = 9.1 Hz, 1H), 3.44 (s, 3H), 3.12 (dq, J = 12.9, 7.4 Hz, 1H), 2.87 (dq, J = 12.9, 7.3 Hz, 1H), 1.32 (d, J = 6.2 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H), 0.80 (s, 9H), 0.04 (s, 3H), –0.18 (s, 3H); **ESI-MS** *m/z* = 679.2 (681.2, 680.2) $[M+Na]^+$.

(2*R*,3*R*,4*S*,5*S*,6*R*)-3-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-4-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.141)



To a solution of the rhamnose **1.145** (163 mg, 0.60 mmol) and the resorcylate **1.128** (200 mg, 0.60 mmol) in THF (6 mL) at 0°C, NaH (60% dispersion in mineral oil, 121 mg, 3.0 mmol) was added in portions. The grey turbid mixture was stirred at RT for 0.5 h. The reaction was quenched with aq. sat. NH_4Cl (10 mL) and the aq. layer was extracted with *t*BME (3x10 mL), the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (*t*BME/pentane 1/5) afforded the desired title compound **1.141** (272 mg, 83%) as colourless oil.

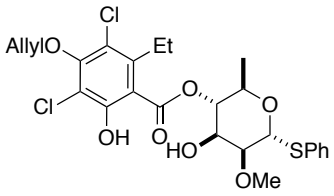
Or

To a solution of silyl ether **1.140** (12 mg, 18 µmol) in THF (1.0 mL) at RT, TBAF (1M in THF, 18 µL, 18 µmol) was added. The solution was stirred for 2 h, then quenched with aq. sat. NH_4Cl, and the THF was evaporated under reduced pressure. The residue was extracted with Et_2O (3x), the combined org. layer were dried ($MgSO_4$) filtered and evaporated under reduced pressure, giving the title compound **1.141** (8 mg, 81%).

R_f = 0.24 (*t*BME/pentane 1/5); $[\alpha]_D$ = +58.0° (c = 0.78, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.49–7.39 (m, 2H), 7.32–7.20 (m, 3H), 6.09 (ddt, J = 17.2, 10.3, 5.9 Hz, 1H), 5.56 (d, J = 1.5 Hz, 1H), 5.38 (ddd, J = 17.1, 1.5, 1.5 Hz, 1H), 5.26 (dd, J = 9.9, 3.4 Hz, 1H), 5.23 (ddd, J = 10.3, 1.2, 1.2 Hz, 1H), 4.53 (dt, J = 5.9, 1.3 Hz, 2H), 4.20 (dq, J = 9.4, 6.2 Hz,

1H), 4.00 (dd, *J* = 3.4, 1.6 Hz, 1H), 3.83 (t, *J* = 9.6 Hz, 1H), 3.34 (s, 3H), 3.02 (qd, *J* = 7.4, 2.0 Hz, 2H), 2.03 (br s, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.18 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 168.7, 155.9, 155.8, 143.4, 134.1, 132.8, 131.5, 129.3, 127.8, 122.0, 119.2, 115.9, 112.1, 84.0, 79.7, 76.2, 74.5, 71.1, 69.7, 58.1, 25.9, 17.6, 14.2; **HRMS ESI** calcd. for $[C_{25}H_{28}Cl_2NaO_7S]^+$ $[M+Na]^+$: 565.0825; found: 565.0827; **IR** ν = 3387, 2978, 2936, 1735, 1659, 1582, 1547, 1453, 1393, 1301, 1220, 1104, 1071, 988, 966, 812, 748, 691 cm^{-1}.

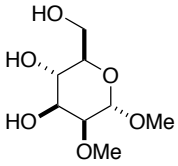
(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.142)



To a solution of the rhamnose **1.145** (163 mg, 0.60 mmol) and the resorcylate **1.128** (200 mg, 0.60 mmol) in THF (6 mL) at 0°C NaH (60% dispersion in mineral oil, 114 mg, 2.84 mmol) was added in portions. The grey turbid mixture was stirred at RT for 16 h. The reaction was quenched with aq. sat. NH_4Cl (10 mL) and the aq. layer was extracted with Et_2O (3x10 mL), the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (*t*BME/*c*Hex 1/3) afforded the desired title compound **1.142** (272 mg, 83%) as pale yellow oil.

R_f = 0.1 (Et_2O/pentane 1/3); $[\alpha]_D$ = +138.4° (*c* = 1.25, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.44–7.40 (m, 2H), 7.30–7.22 (m, 3H), 6.09 (ddt, *J* = 16.3, 10.3, 5.9 Hz, 2H), 5.60 (d, *J* = 0.7 Hz, 1H), 5.39 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.24 (ddd, *J* = 10.3, 2.5, 1.1 Hz, 1H), 5.19 (dd, *J* = 9.8, 9.8 Hz 1H), 4.54 (ddd, *J* = 5.9, 1.2, 1.2 Hz, 2H), 4.31 (dq, *J* = 9.8, 6.1 Hz, 1H), 3.96–3.87 (m, 1H), 3.78 (dd, *J* = 3.6, 1.3 Hz, 1H), 3.44 (s, 3H), 3.02–2.94 (m, 2H), 2.47 (d, *J* = 10.9 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.20 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.2, 155.5, 155.4, 142.5, 133.9, 132.7, 131.2 (2C), 129.2 (2C), 127.7, 121.7, 119.1, 115.6, 112.4, 83.8, 81.6, 76.8, 74.3, 69.9, 66.9, 58.0, 26.0, 17.5, 14.0; **HRMS ESI** calcd. for $[C_{25}H_{28}Cl_2NaO_7S]^+$ $[M+Na]^+$: 565.0825; found: 565.0825; **IR** ν = 2980, 2936, 2878, 1737, 1664, 1583, 1549, 1392, 1311, 1222, 1099, 998, 840, 764, 742, 691 cm^{-1}.

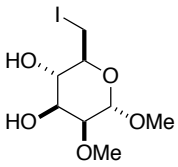
(2*R*,3*S*,4*S*,5*S*,6*S*)-2-(hydroxymethyl)-5,6-dimethoxytetrahydro-2*H*-pyran-3,4-diol (1.143)



To a turbid mixture of acetal-protected compound **1.136** (967 mg, 2.4 mmol) in MeOH (20 mL) and H_2O (1 mL), 1 M HCl (2 mL) was added and the solution was heated to 55°C for 1.5 h. Then it was quenched with aq. sat. $NaHCO_3$ until pH 7 then the solvent was evaporated under reduced pressure and the residue was azeotropized three times using acetonitrile. The residual crude product was filtrated through a short plug of silica and the cake was washed with CH_2Cl_2/MeOH (10/1). After evaporation under reduced pressure product **1.143** (491 mg, quant.) was obtained as colourless oil.

***R*$_f$** = 0.24 (CH_2Cl_2/MeOH 10/1); **[α]$_D$** = +50.6° (*c* = 0.35, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) *δ* 4.80 (d, *J* = 1.2 Hz, 1H), 3.87–3.83 (m, 2H), 3.81–3.68 (m, 2H), 3.57–3.51 (m, 1H), 3.48 (s, 3H), 3.49–3.46 (m, 1H) 3.38 (s, 3H), 3.31 (d, *J* = 2.9 Hz, 1H), 2.90 (d, *J* = 9.2 Hz, 1H), 2.57 (t, *J* = 6.3 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) *δ* 97.7, 80.1, 71.6, 71.5, 68.8, 62.4, 59.0, 55.0; **HRMS ESI** calcd. for $[C_8H_{16}NaO_6]^+$ $[M+Na]^+$: 231.0839; found: 231.0840; **IR** ν = 3371, 2935, 2837, 1647, 1135, 1104, 1041, 963 cm^{-1}.

(2*S*,3*S*,4*S*,5*S*,6*S*)-2-(iodomethyl)-5,6-dimethoxytetrahydro-2*H*-pyran-3,4-diol (1.143b)

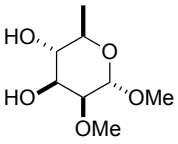


To a solution of methyl mannopyranoside **1.143** (254 mg, 1.2 mmol), triphenylphosphine (480 mg, 1.8 mmol,) and imidazole (168 mg, 2.4 mmol) in THF (10 mL), iodine (403 mg, 1.5 mmol) was added. The orange solution was heated to reflux for 1.5 h turning into a white suspension. Then the solvent was evaporated under reduced pressure and the residue was dissolved in Et_2O (25 mL), extracted with aq. sat. NH_4Cl (25 mL) and the org. layer was dried ($MgSO_4$), filtrated and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/3 to Et_2O) afforded the desired compound **1.143b** (226 mg, 58%).

***R*$_f$** = 0.28 (Et_2O); **[α]$_D$** = +45.1° (*c* = 0.95, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) *δ* 4.88 (d, *J* = 1.0 Hz, 1H), 3.74 (ddd, *J* = 10.9, 8.8, 3.8 Hz, 1H), 3.54–3.44 (m, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 3.29 (dd, *J* = 10.6, 8.1 Hz, 1H), 2.45 (d, *J* = 2.1 Hz, 1H), 2.37 (d, *J* = 10.8 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) *δ* 97.3, 79.9, 72.5, 71.4, 71.3, 58.8, 55.3, 6.5; **HRMS ESI** calcd. for

$[C_8H_{15}INaO_5]^+$ $[M+Na]^+$: 340.9856; found: 340.9856; **IR** ν = 3398, 2930, 2910, 2832, 1439, 1414, 1379, 1190, 1132, 1102, 1050, 962, 874, 808 cm^{-1}.

(2*R*,3*S*,4*S*,5*S*,6*S*)-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-3,4-diol (1.144)



To a solution of D-rhamnoside **1.148** (494 mg, 2.8 mmol) in MeOH (28 mL), 2,3-butadione (0.29 mL, 3.3 mmol), trimethyl orthoformate (1.17 mL, 10.6 mmol) and 10-camphorsulfonic acid (41.1 mg, 0.16 mmol) were added. The mixture was heated in a sealed tube to 90°C for 24 h. Then the reaction mixture was neutralized with Et_3N and the solvent was removed under reduced pressure, yielding the protected intermediate which was used in the next step without further purification.

To the protected intermediate in THF (17 mL) at 0°C, NaH (223 mg, 5.6 mmol, 60 % dispersion in mineral oil) was added in portions. The mixture was allowed to warm to RT and was stirred for an additional 1 h. Then MeI (0.19 mL, 3.1 mmol) was added dropwise and the mixture was stirred for 3.5 h at RT. The reaction was quenched with aq. sat. NH_4Cl (20 mL), the volatiles was removed under reduced pressure and the remaining aq. suspension was diluted with H_2O (40 mL). The mixture was extracted with CH_2Cl_2 (3x50 mL) and the org. layers were washed with brine (30 mL), combined, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The methylated intermediate was used in the next step without further purification.

To a solution of methylated intermediate in CH_2Cl_2 (30 mL), a mixture of TFA/H_2O (9/1, 2.4 mL) was added. The reaction was stirred for 1 h while the mixture turned slightly yellow. The reaction was quenched with Et_3N (2.5 mL), diluted with toluene (10 mL), and the solvents were removed under reduced pressure. Azeotropic removal of Et_3N was carried out twice with toluene (5 mL). Purification by column chromatography (Et_2O) afforded the desired product **1.144** (356 mg, 72% over three steps) as a colourless oil.

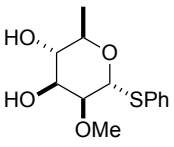
Or

To a solution of iodomannopyranoside **1.143b** (174 mg, 0.55 mmol) in Et_3N/MeOH (1/10 1.1 mL), $Pd(OH)_2$ (20wt% on activated carbon, 115 mg, 0.16 mmol) were added. The dark turbid mixture was degassed with argon during 10 minutes, then hydrogen was bubbled through the suspension for 0.5 h, and the reaction mixture was subsequently stirred under a

hydrogen atmosphere for 6 h. The hydrogen atmosphere was exchanged by argon and the solution was filtered through Hyflo. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography (Et_2O) to yield the rhamnoside **1.144** (102 mg, 97%) as a colourless oil.

R_f = 0.18 (Et_2O); $[\alpha]_D$ = +40.2° (c = 0.48, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.75 (d, J = 1.1 Hz, 1H), 3.72–3.65 (m, 1H), 3.59 (dq, J = 9.3, 6.2 Hz, 1H), 3.47 (s, 3H), 3.45 (dd, J = 3.9, 1.5 Hz, 1H), 3.37 (s, 3H), 3.38–3.32 (m, 1H) 2.50 (d, J = 2.7 Hz, 1H), 2.43 (d, J = 10.4 Hz, 1H), 1.31 (d, J = 6.2 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 97.2, 80.2, 74.0, 71.5, 67.5, 58.8, 54.8, 17.5; **HRMS ESI** calcd. for $[C_8H_{16}NaO_5]^+$ $[M+Na]^+$: 215.0890; found: 215.0889; **IR** ν = 3426, 2976, 2935, 2905, 2832, 1540, 1378, 1190, 1136, 1104,1046, 966, 836, 807 cm^{-1}.

(2*R*,3*S*,4*S*,5*S*,6*R*)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3,4-diol (1.145)



To a solution of pyrannoside **1.144** (240 mg, 1.3 mmol) in DCE (10 mL), tetrabutylammonium iodide (692 mg, 1.9 mmol), zinc iodide (1.19 g, 3.8 mmol) and trimethyl(phenylthio)silane (1.14 g, 6.2 mmol) were added. The white turbid mixture was heated to 65°C for 2.5 h. Then it was cooled to RT and a solution of TFA/H_2O (9/1, 3 mL) was added. After stirring for 30 min, toluene (5 mL) was added and evaporated under reduced pressure. The residue was treated with Et_2O (10 mL) and the biphasic mixture was stirred for 5 minutes. The ethereal extract was decanted and the remaining oil was reextracted twice in the same manner. The combined etheral extracts were evaporated under reduced pressure and purified by column chromatography (Et_2O) to afford the title compound **1.145** (247 mg, 73%) as yellowish oil.

R_f = 0.3 (Et_2O); $[\alpha]_D$ = +184.4° (c = 0.47, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.35–7.30 (m, 2H), 7.30–7.27 (m, 1H), 5.62 (ap s, 1H), 4.13 (dqd, J = 9.4, 6.2, 0.6 Hz 1H), 3.77–3.70 (m, 2H), 3.48–3.43 (m, 1H), 3.46 (s, 3H), 2.41 (d, J = 10.0 Hz, 1H), 2.39 (d, J = 2.6 Hz, 1H), 1.32 (d, J = 6.2 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 134.4, 131.3 (2C), 129.1 (2C), 127.4, 84.0, 81.7, 74.3, 72.1, 68.9, 58.1, 17.4; **HRMS ESI** calcd. for $[C_{13}H_{18}NaO_4S]^+$ $[M+Na]^+$: 293.0818; found: 293.0817; **IR** ν = 3523, 3296, 2976, 2932, 2898, 2831, 1581, 1478, 1438, 1355, 1141, 1099, 1055, 1021, 839, 740, 690 cm^{-1}.

(2*R*,3*R*,4*S*,5*S*,6*S*)-3-hydroxy-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-4-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.146)

(2*R*,3*S*,4*S*,5*S*,6*S*)-4-hydroxy-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.147)

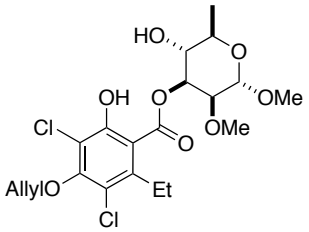
To a solution of rhamnoside **1.144** (40 mg, 0.21 mmol) and resorcylate **1.128** (69 mg, 0.21 mmol) in THF (2 mL) at 0°C, NaH (60 % dispersion in mineral oil, 42 mg, 1.0 mmol) was added in portions. The white turbid mixture was then slowly warmed to RT and stirred for 24 h. The reaction was diluted with *t*BME (8 mL), quenched with aq. sat. NH_4Cl (20 mL). Then the layers were separated, the aq. layer extracted with *t*BME (20 mL) and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/*c*Hex 1/3) gave the two inseperable regioisomers **1.146** and **1.147** (36 mg, 47%) in a 1.4:1 ratio.

Or

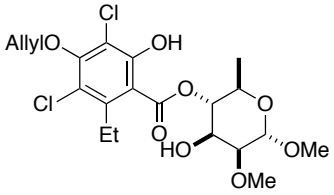
To a solution of rhamnoside **1.147** (32 mg, 68 µmol) in toluene (3 mL) at 0°C, NaH (60 % dispersion in mineral oil, 11 mg, 0.28 mmol) was added. The white turbid mixture was warmed to RT and then heated to 40°C for 48 h. The reaction was diluted with *t*BME (4 mL), quenched with aq. sat. NH_4Cl (4 mL), the layers were separated and the aq. layer was extracted with *t*BME (2x3 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/*c*Hex 1/3) gave the O4 isomer **1.147** (24 mg, 75%) as a colourless oil.

Or

To a solution of rhamnoside **1.144** (233 mg, 1.2 mmol) and resorcylate **1.128** (401 mg, 1.2 mmol) in toluene (5 mL) at 0°C, NaH (60 % dispersion in mineral oil, 242 mg, 6.1 mmol) was added in portions. The white turbid mixture was then slowly warmed to RT and then heated to 40°C for 48 h. The reaction was diluted with *t*BME (20 mL), quenched with aq. sat. NH_4Cl (30 mL) and the layers were separated. The aq. layer was extracted with *t*BME (20 mL) and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/*c*Hex 1/3) gave the desired regioisomer **1.147** (282 mg, 50%).

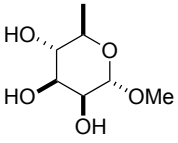


1.146 (O3): R_f = 0.29 (EtOAc/*c*Hex 1/3); **[α]$_D$** = +11.0° (*c* = 0.8, $CHCl_3$); **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 10.42 (s, 1H), 6.15 (ddt, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.45 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.33 (dd, *J* = 9.2, 3.6 Hz, 1H), 5.30 (ddd, *J* = 10.0, 1.2, 1.2 Hz, 1H), 4.80 (d, *J* = 1.7 Hz, 1H), 4.60 (dt, *J* = 5.9, 1.3 Hz, 2H), 3.86–3.68 (m, 3H), 3.43 (s, 3H), 3.42 (s, 3H), 3.09 (qd, *J* = 7.3, 2.0 Hz, 2H), 1.91 (br s, 1H), 1.38 (d, *J* = 5.8 Hz, 3H), 1.24 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 168.9, 155.9, 155.7, 143.4, 132.9, 121.9, 119.2, 115.8, 112.2, 97.5, 78.2, 76.3, 74.5, 71.0, 68.4, 58. 9, 55.2, 25.9, 17.7, 14.1; **HRMS ESI** calcd. for $[C_{20}H_{26}Cl_2NaO_8]^+$ $[M+Na]^+$: 487.0897; found: 487.0892; **IR** ν = 3376, 2979, 2937, 2834, 2363, 2340, 1736, 1660, 1582, 1548, 1452, 1393, 1302, 1247, 1224, 1131, 1107, 1059, 968, 812, 766 cm^{-1}.



1.147 (O4): R_f = 0.19 (EtOAc/*c*Hex 1/3); **[α]$_D$** = +27.5° (*c* = 0.48, $CHCl_3$); **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 10.45 (s, 1H), 6.16 (ddt, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.45 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.30 (ddd, *J* = 10.3, 1.2, 1.2 Hz, 1H), 5.17 (t, *J* = 9.9 Hz, 1H), 4.82 (d, *J* = 1.4 Hz, 1H), 4.59 (dt, *J* = 5.9, 1.3 Hz, 2H), 3.95 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.83 (dq, *J* = 9.9, 6.2 Hz, 1H), 3.55 (dd, *J* = 3.7, 1.5 Hz, 1H), 3.52 (s, 3H), 3.41 (s, 3H), 3.03 (qd, *J* = 7.4, 2.0 Hz, 2H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.7, 155.5, 142.6, 132.9, 121.7, 119.2, 115.8, 112.6, 97.2, 80.3, 77.4, 74.4, 69.5, 65.7, 58.9, 55.4, 26.1, 17.7, 14.1; **HRMS ESI** calcd. for $[C_{20}H_{26}Cl_2NaO_8]^+$ $[M+Na]^+$: 487.0897; found: 487.0898; **IR** ν = 3419, 2982, 2937, 2835, 2361, 1737, 1665, 1583, 1453, 1413, 1392, 1376, 1313, 1293, 1244, 1224, 1131, 1107, 1068, 1003, 970, 802, 766 cm^{-1}.

(2*S*,3*S*,4*S*,5*S*,6*R*)-2-methoxy-6-methyltetrahydro-2*H*-pyran-3,4,5-triol (1.148)



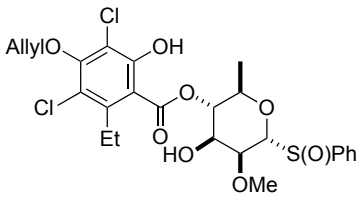
To a solution of iodomannopyranoside **1.105** (3.59 g, 12 mmol) in MeOH (42 mL), *N*,*N*-diisopropylethylamine (6.19 mL, 35 mmol) and $Pd(OH)_2$ (20wt% on activated carbon, 0.83 g, 1.2 mmol) were added. The dark turbid mixture was degassed with argon during 10 minutes, then hydrogen was bubbled through the suspension for 0.5 h, and the reaction mixture was subsequently stirred under a hydrogen atmosphere for 3 h. The hydrogen atmosphere was exchanged by argon and the solution was filtered through Hyflo. The filtrate was evaporated under reduced pressure and purified by

column chromatography (MeOH/CH_2Cl_2 1/10) to yield the rhamnoside **1.148** (2.19 g, quant.) as a colourless oil.

The analytical data matched those reported in the literature: P. Wang, G. J. Shen, Y. F. Wang, Y. Ichikawa, C.-H. Wong, *J. Org. Chem.* **1993**, *58*, 3985–3990.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.56 (d, J = 1.7 Hz, 1H), 3.78 (dd, J = 3.5, 1.7 Hz, 1H), 3.61 (dd, J = 9.4, 3.5 Hz, 1H), 3.57–3.48 (m, 1H), 3.38 (pt, J = 9.5 Hz, 1H), 3.35 (s, 3H), 1.27 (d, J = 6.2 Hz, 3H); **^{13}C-NMR** (101 MHz, CD_3OD) δ 102.8, 74.0, 72.4, 72.2, 69.6, 55.1, 18.0.

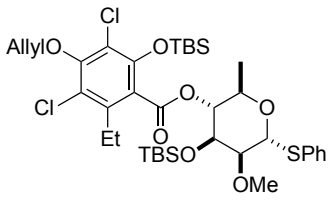
(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-((*S*)-phenylsulfinyl)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.156)



The sulfoxide was prepared following the representative procedure for **1.168**. Purification by column chromatography (MeOH/CH_2Cl_2 1/10) afforded the sulfoxide **1.156** (5 mg, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.20 (br s, 1H), 7.69–7.64 (m, 2H), 7.63–7.56 (m, 3H), 6.16 (ddt, J = 17.2, 10.3, 5.9 Hz, 1H), 5.48 (q, J = 1.5 Hz, 1H), 5.44 (q, J = 1.5 Hz, 1H), 5.33 (q, J = 1.2 Hz, 1H), 5.30 (q, J = 1.2 Hz, 1H), 5.28 (t, J = 9.9 Hz, 1H), 4.61 (dt, J = 6.0, 1.3 Hz, 2H), 4.58 (br s, 1H), 4.35 (dd, J = 10.0, 4.0 Hz, 1H), 4.28 (dq, J = 9.6, 6.1 Hz, 1H), 4.06 (dd, J = 4.0, 1.3 Hz, 1H), 3.26 (s, 3H), 3.04 (qd, J = 7.4, 4.8 Hz, 2H), 1.31 (d, J = 6.1 Hz, 3H), 1.26 (t, J = 7.4 Hz, 3H).

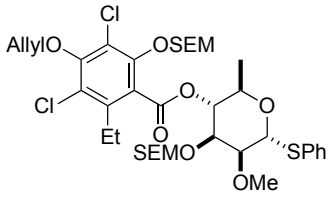
(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((tert-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)-tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-2-((tert-butyldimethylsilyl)oxy)-3,5-dichloro-6-ethylbenzoate (1.162)



To a solution of the rhamnoside **1.145** (102 mg, 0.38 mmol) and resorcylate **1.128** (125 mg, 0.38 mmol) in THF (2.5 mL) at 0°C, NaH (60% dispersion in mineral oil, 76 mg, 1.9 mmol) was added and the mixture was slowly warmed to RT in 30 minutes and stirred for 16 h. TBSOTf (63 µL, 1.5 mmol) was then added dropwise. The resulting beige suspension was stirred for 3 h then it was quenched with aq. sat. NH_4Cl, and extracted with Et_2O (5x). The combined org. layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography (Et_2O/pentane 1/10) gave the desired product **1.162** (157 mg, 54%) as a colourless oil.

R_f = 0.71 (Et_2O/pentane 1/8); $[\alpha]_D$ = +63.7° (*c* = 0.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.53–7.47 (m, 2H), 7.31–7.23 (m, 3H), 6.15 (ddt, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.44 (dq, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.39 (br s, 1H), 5.30 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1H), 4.90 (t, *J* = 6.4 Hz, 1H), 4.55 (dt, *J* = 6.0, 1.3 Hz, 2H), 4.25–4.15 (m, 2H), 3.44 (s, 3H), 2.76 (dq, *J* = 14.1, 7.2 Hz, 1H), 2.64 (dq, *J* = 14.5, 7.5 Hz, 1H), 1.46 (d, *J* = 6.7 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.4 Hz, 3H), 0.99 (s, 9H), 0.89 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (101 MHz, C_6D_6, HMBC) δ 165.9, 153.8, 149.4, 139.2, 135.5, 133.4, 131.6 (2C), 129.3 (2C), 127.4, 125.0, 123.0, 120.2, 118.3, 84.4, 81.4, 77.8, 74.2, 71.2, 69.8, 58.2, 26.7 (3C), 26.2 (3+1C), 19.4, 19.2, 18.6, 14.5, –2.28, –2.60, –4.49, –4.57; **HRMS ESI** calcd. for $[C_{37}H_{56}Cl_2NaO_7SSi_2]^+$ $[M+Na]^+$: 793.2555; found: 793.2564; **IR** ν = 2954, 2932, 2887, 2858, 1741, 1560, 1469, 1409, 1239, 1112, 1086, 1006, 969, 835, 779, 741, 690 cm^{-1}.

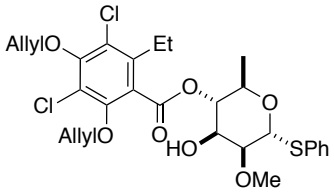
(2*R*,3*R*,4*S*,5*S*,6*R*)-5-methoxy-2-methyl-6-(phenylthio)-4-((2-(trimethylsilyl)ethoxy)-methoxy)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-((2-(trimethyl-silyl)ethoxy)methoxy)benzoate (1.163)



To a solution of the diol **1.142** (73 mg, 0.13 mmol) in DMF (1.0 mL) at 0°C, NaH (60% dispersion in mineral oil, 12 mg, 0.30 mmol,) was added and the mixture was stirred for 30 minutes at RT. To the resulting orange solution SEM-Cl (71 µL, 0.40 mmol) was added dropwise and the beige suspension was stirred for 1.5 h. Then it was diluted with *t*BME (5 mL) and quenched with water (20 mL). The layers were separated and the organic layer was washed with water (20 mL) and brine (20 mL). The aq. layers were reextracted with *t*BME (20 mL) and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (*t*BME/*c*Hex 1/10) gave the desired product **1.163** (52 mg, 48%) as a colourless oil.

R_f = 0.24 (Et_2O/pentane 1/8); $[\alpha]_D$ = +116.6° (*c* = 0.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.53–7.44 (m, 2H), 7.35–7.24 (m, 3H), 6.16 (ddt, *J* = 16.3, 10.4, 5.9 Hz, 1H), 5.63 (s, 1H), 5.45 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.37 (t, *J* = 9.4 Hz, 1H), 5.31 (ap dd, *J* = 10.3, 1.3 Hz, 1H), 5.17 (s, 2H), 4.85 (d, *J* = 7.1 Hz, 1H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.55 (dt, *J* = 5.9, 1.1 Hz, 2H), 4.32 (dq, *J* = 9.7, 6.1 Hz, 1H), 3.95 (s, 1H), 3.96–3.77 (m, 4H), 3.57–3.50 (m, 1H), 3.49 (s, 3H), 2.75 (ddq, *J* = 28.2, 13.4, 7.4 Hz, 2H), 1.41 (d, *J* = 6.2 Hz, 3H), 1.39 (m, 3H), 1.19 (t, *J* = 7.4 Hz, 3H), 1.05–0.86 (m, 4H), 0.01 (s, 9H), 0.01 (s, 9H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.6, 153.2, 149.1, 139.0, 134.7, 133.0, 131.2 (2C), 129.2 (2C), 127.6, 127.5, 125.7, 121.9, 119.0, 98.8, 95.8, 84.2, 81.0, 76.3, 74.5, 74.4, 68.5, 68.0, 65.9, 58.0, 25.3, 18.5, 18.3, 18.0, 14.3, –1.25 (3C), –1.27 (3C); **HRMS ESI** calcd. for $[C_{37}H_{56}Cl_2NaO_9SSi_2]^+$ $[M+Na]^+$: 825.2453; found: 825.2451; **IR** ν = 2952, 2892, 1739, 1568, 1389, 1245, 1095, 1031, 935, 901, 861, 834, 765, 745, 692 cm^{-1}.

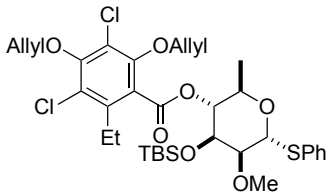
(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.164)



To a suspension of the rhamnose **1.142** (90 mg, 0.17 mmol) and K_2CO_3 (69 mg, 0.50 mmol) in DMF (2.0 mL), allyl bromide (22 µL, 0.25 mmol) was added and the suspension was heated to 50°C for 3 h. It was subsequently diluted with Et_2O (5 mL), quenched with aq. sat. NH_4Cl (50 mL) and extracted with Et_2O (3x20 mL). The org. layers were washed with brine (40 mL), combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the double allyl-protected product **1.164** (93 mg, 96%) as a colourless oil.

R_f = 0.3 (Et_2O/pentane 1/3); $[\alpha]_D$ = +111.1° (*c* = 0.54, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.26–7.17 (m, 3H), 6.07 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 2H), 5.97 (ddt, *J* = 17.2, 10.3, 5.9, 1H) 5.57 (d, *J* = 1.2 Hz, 1H), 5.36 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.30 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.22 (ddd, *J* = 10.3, 2.6, 1.1 Hz, 1H), 5.17 (ddd, *J* = 10.3, 2.6, 1.1 Hz, 1H), 5.10 (dd, *J* = 9.7, 9.7 Hz, 1H), 4.52 (dddd, *J* = 11.6, 5.9, 1.4, 1.4 Hz, 1H) 4.48 (ddd, *J* = 5.9, 1.3, 1.3 Hz, 2H) 4.42 (dddd, *J* = 11.5, 6.0, 1.3, 1.3 Hz, 1H), 4.22 (dq, *J* = 9.8, 6.2 Hz, 1H), 3.85 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.73 (dd, *J* =3.6, 1.4 Hz, 1H), 3.42 (s, 3H), 3.39 (q, *J* = 7.0 Hz, 2H) 2.83–2.66 (m, 2H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.14 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.5, 153.3, 151.1, 139.2, 134.1, 132.9, 132.9, 131.4 (2C), 129.3 (2C), 127.7, 127.3, 125.7, 121.7, 119.1, 113.0, 84.2, 81.9, 76.6, 75.9, 74.4, 70.2, 67.2, 58.3, 25.3, 17.6, 14.1; **HRMS ESI** calcd. for $[C_{28}H_{34}Cl_2NaO_7S]^+$ $[M+Na]^+$: 605.1138; found: 605.1130; **IR** ν = 3548, 2978, 2936, 2883, 1736, 1570, 1402, 1314, 1246, 1099, 998, 929, 841, 742, 692 cm^{-1}.

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)-tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.165)

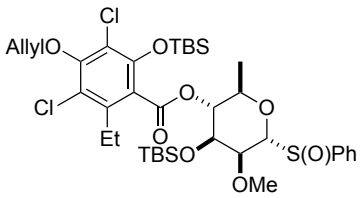


To a solution of thiorhamnoside **1.141** (6.0 mg, 91 µmol) and K_2CO_3 (1.3 mg, 91 µmol) in DMF (0.5 mL) at RT, allyl bromide (one drop) was added. The reaction mixture was stirred for 30 minutes then it was diluted with Et_2O (3 mL) and brine (6 mL), and the layers were separated. The aqueous layer was reextraced with Et_2O (4x3 mL) and the

combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure yielding the title compound **1.165** (7.0 mg, quant.).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44–7.36 (m, 2H), 7.29–7.20 (m, 3H), 6.04 (dddt, J = 33.3, 17.2, 10.4, 5.8 Hz, 2H), 5.46 (d, J = 2.5 Hz, 1H), 5.37 (dq, J = 8.7, 1.5 Hz, 1H), 5.33 (dq, J = 8.8, 1.5 Hz, 1H), 5.23 (dq, J = 10.3, 1.2 Hz, 1H), 5.18 (dq, J = 10.4, 1.3 Hz, 1H), 5.16 (t, J = 8.7 Hz, 1H), 4.58–4.45 (m, 4H), 4.16 (dq, J = 8.7, 6.3 Hz, 1H), 4.03 (dd, J = 8.6, 3.0 Hz, 1H), 3.57 (br s, 1H), 3.42 (s, 3H), 2.75 (dq, J = 13.2, 7.4 Hz, 1H), 2.51 (dq, J = 13.1, 7.3 Hz, 1H), 1.31 (d, J = 6.4 Hz, 3H), 1.14 (t, J = 7.4 Hz, 3H), 0.82 (s, 9H), 0.00 (s, 2H), 0.00 (s, 1H), -0.07 (s, 1H), -0.10 (s, 2H).

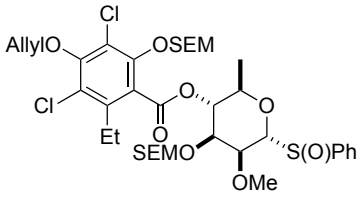
(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-((*S*)-phenylsulfinyl)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-3,5-dichloro-6-ethylbenzoate (1.166)



The sulfoxide was prepared following the representative procedure for **1.168**. Purification by column chromatography (MeOH/CH_2Cl_2 1/20) afforded the sulfoxide **1.166** (15 mg, 80%) as a mix of epimers (1:4, calcd. from ^{1}H-NMR).

***R*$_f$** = 0.33 (Et_2O/pentane 1/3); **^{1}H-NMR** (400 MHz, $CDCl_3$, major epimer) δ 7.64–7.58 (m, 2H), 7.53–7.43 (m, 3H), 6.15 (ddt, J = 17.3, 10.3, 5.9 Hz, 1H), 5.44 (dq, J = 17.1, 1.5 Hz, 1H), 5.30 (dq, J = 10.4, 1.2 Hz, 1H), 4.87 (t, J = 4.6 Hz, 1H), 4.73 (d, J = 7.1 Hz, 1H), 4.55 (dt, J = 6.0, 1.3 Hz, 2H), 4.29 (dd, J = 4.4, 2.8 Hz, 1H), 4.22–4.15 (m, 1H), 3.71 (dd, J = 7.1, 2.8 Hz, 1H), 3.22 (s, 3H), 2.69–2.55 (m, 2H), 1.47 (d, J = 6.8 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H), 0.98 (s, 9H), 0.87 (s, 9H), 0.21 (s, 3H), 0.21 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H); **IR** ν = 2931, 2885, 2858, 1737, 1561, 1472, 1408, 1239, 1119, 1090, 1043, 970, 836, 779, 748, 690 cm^{-1}.

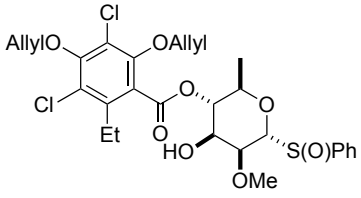
(2*R*,3*R*,4*S*,5*S*,6*R*)-5-methoxy-2-methyl-6-((*R*)-phenylsulfinyl)-4-((2-(trimethylsilyl)ethoxy)methoxy)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-((2-(trimethylsilyl)ethoxy)methoxy)benzoate (1.167)



The sulfoxide was prepared following the representative procedure for **1.168**. Purification by preperative TLC (Et_2O/pentane 1/1) afforded the sulfoxide **1.167** (5 mg, 82%) as a single of epimer.

***R*$_f$** = 0.57 (Et_2O/pentane 1/1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.68–7.61 (m, 2H), 7.59–7.51 (m, 3H), 6.16 (ddt, *J* = 16.5, 10.3, 5.9 Hz, 1H), 5.46 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.37 (dd, *J* = 9.4, 9.4 Hz, 1H), 5.31 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.16 (s, 2H), 4.84 (d, *J* = 7.0 Hz, 1H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.56 (dt, *J* = 5.9, 1.3 Hz, 2H), 4.53 (d, *J* = 1.9 Hz, 1H), 4.33 (dd, *J* = 9.3, 3.4 Hz, 1H), 4.24–4.15 (m, 2H), 3.94–3.71 (m, 3H), 3.58–3.46 (m, 1H), 3.28 (s, 3H), 2.83–2.64 (m, 2H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H), 1.02–0.82 (m, 4H), 0.02 (s, 9H), –0.01 (s, 9H).

(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-((*S*)-phenylsulfinyl)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.168)

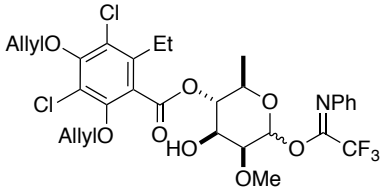


To a solution of thioglycoside **1.164** (105 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) at –78°C, *m*CPBA (34.0 mg, 0.20 mmol) was added. The solution was stirred at this temperature for 1.5 h and then slowly warmed to –50°C and stirred for 3 h. At this temperature the reaction mixture was quenched with aq. sat. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3x20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/*c*Hex 1/2) to yield the epimers (1:20, calcd. from ^{1}H-NMR) of sulfoxide **1.168** (96.0 mg, 89%) as colourless oil.

***R*$_f$** = 0.21 (EtOAc/*c*Hex 1/2); **^{1}H-NMR** (400 MHz, $CDCl_3$, major epimer) δ 7.67–7.60 (m, 2H), 7.61–7.22 (m, 3H), 6.16 (ddt, *J* = 17.0, 10.3, 5.9 Hz, 1H), 6.04 (ddt, *J* = 16.3, 10.4, 6.0 Hz, 1H), 5.45 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.38 (ddd, *J* = 17.2, 2.8, 1.4 Hz, 1H), 5.31 (ddd, *J* = 10.3, 2.2, 1.1 Hz, 1H), 5.25 (ddd, *J* = 10.4, 2.8, 1.4 Hz, 1H), 5.19 (dd, *J* = 9.8, 9.8 Hz, 1H), 4.61 (dddd, *J* = 11.6, 5.9, 1.2, 1.2 Hz 1H), 4.56 (ddd, *J* = 6.0, 1.1, 1.1 Hz, 2H),

4.54 (s, 1H), 4.48 (dddd, *J* = 11.5, 6.1, 1.2, 1.2 Hz, 2H), 4.25 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.19–4.06 (m, 2H), 3.33 (s, 3H), 2.91–2.74 (m, 2H), 1.31 (d, *J* = 6.1 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$, HMBC) δ 166.4, 153.4, 151.1, 139.3, 132.9, 132.9, 131.8, 129.6 (2C), 127.1, 125.8, 124.5 (2C), 121.7, 119.1, 119.0, 100.1, 95.0 (HMQC), 77.4, 75.9, 75.3, 74.5, 72.8, 70.1, 58.3, 25.3, 18.0, 14.2; **HRMS ESI** calcd. for $[C_{28}H_{32}Cl_2NaO_8S]^+$ $[M+Na]^+$: 621.1087; found: 621.1085; **IR** ν = 3359, 3084, 2977, 2938, 2879, 1736, 1569, 1444, 1402, 1314, 1247, 1124, 1103, 1039, 998, 932, 747, 691 cm^{-1}.

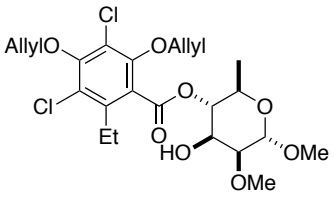
(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-((*E*)-2,2,2-trifluoro-1-(phenylimino)-ethoxy)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.169)



To a solution of rhamnose **1.173** (4.5 mg, 9.2 µmol) in acetone (0.3 mL, techn.), K_2CO_3 (5.0 mg, 0.40 mmol) was added. The white suspension was cooled to 0°C and $ClC(NPh)CF_3$ (1.7 µL, 10 µmol) in acetone (0.1 mL) was added dropwise. Then the reaction mixture was stirred at RT for 3 h. The suspension was diluted with toluene (1 mL), filtered and evaporated under reduced pressure. Purification by preparative TLC (EtOAc/cHex 1/4) afforded the imidate **1.169** (6.0 mg, 98%) as a colourless oil.

R_f = 0.5 (EtOAc/cHex 1/4); $[\alpha]_D$ = +20.2° (*c* = 0.07, $CHCl_3$); **^{1}H-NMR** (400 MHz, Acetone-d_6) δ 7.42–7.32 (m, 2H), 7.18–7.12 (m, 1H), 6.99–6.89 (m, 2H), 6.24 (br, 1H), 6.23–6.02 (m, 2H), 5.46 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.40 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.31–5.23 (m, 2H), 5.19 (dd *J* = 10.0, 10.0 Hz, 1H), 4.68–4.58 (m, 3H), 4.54 (dddd, *J* = 11.8, 5.7, 1.4, 1.4 Hz, 2H), 4.20 (d, *J* = 9.4, 1H), 4.04–3.88 (m, 2H), 3.83 (br, 1H), 3.50 (br, 3H), 2.92–2.75 (m, 2H), 1.35–1.26 (m, 3H), 1.17 (t, *J* = 7.4 Hz, 3H); **HRMS ESI** calcd. for $[C_{30}H_{32}Cl_2F_3NaO_8]^+$ $[M+Na]^+$: 684.1349; found: 684.1348; **IR** ν = 3546, 2981, 2937, 1737, 1569, 1454, 1404, 1330, 1316, 1249, 1211, 1164, 1118, 1024, 2012, 975, 929, 777, 752, 695 cm^{-1}.

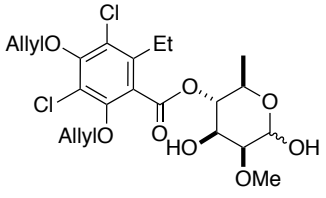
(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.172)



To a suspension of the rhamnose **1.147** (32.0 mg, 68 µmol) and K_2CO_3 (14.3 mg, 0.10 mmol) in DMF (0.4 mL), allyl bromide (9 µL, 0.10 mmol) was added and the suspension was heated to 50°C for 1 h. Then it was diluted with *t*BME (2 mL), quenched with aq. sat. NH_4Cl (5 mL) and extracted with *t*BME (3x5 mL). The org. layers were washed with brine (2x10 mL), combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the double allyl-protected product **1.172** (32.0 mg, 92%) as a colourless oil.

R_f = 0.53 (EtOAc/*c*Hex 1/2). $[\alpha]_D$ = +9.9° (*c* = 1.07, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.14 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1H), 6.04 (ddt, *J* = 17.3, 10.3, 6.0 Hz, 1H), 5.43 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.37 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.29 (ddd, *J* = 10.3, 1.2, 1.2 Hz, 1H), 5.24 (ddd, *J* = 10.3, 1.2, 1.2 Hz, 1H), 5.07 (t, *J* = 9.8 Hz, 1H), 4.79 (d, *J* = 1.5 Hz, 1H), 4.58 (ddt, *J* = 11.5, 5.9, 1.5 Hz, 1H), 4.54 (dt, *J* = 5.9, 1.4 Hz, 2H), 4.48 (ddt, *J* = 11.5, 6.0, 1.3 Hz, 1H), 3.88 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.75 (dq, *J* = 9.8, 6.3 Hz, 1H), 3.53–3.50 (m, 1H), 3.51 (s, 3H), 3.36 (s, 3H), 2.91–2.72 (m, 2H), 2.33 (br s, 1H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.19 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.5, 153.2, 151.1, 139.2, 132.9, 132.9, 127.4, 125.6, 121.6, 119.0, 118.9, 97.4, 80.5, 76.6, 75.9, 74.4, 69.7, 65.8, 59.1, 55.1, 25.3, 17.7, 14.1; **HRMS ESI** calcd. for $[C_{23}H_{30}Cl_2KO_8]^+$ $[M+K]^+$: 543.0949; found: 543.0948. **IR** ν = 3508, 2979, 2937, 2835, 1735, 1569, 1460, 1403, 1316, 1249, 1134, 1107, 1067, 1005, 973, 931, 803, 748 cm^{-1}.

(2*R*,3*S*,4*S*,5*S*)-4,6-dihydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.173)



To a solution of thioglycoside **1.164** (17.5 mg, 30 µmol) in acetone (1.0 mL) and H_2O (0.1 mL) at 0°C, NBS (5.9 mg, 30 µmol) was added. The orange reaction mixture was stirred at 0°C for 15 minutes then it was warmed to RT. The colourless solution was treated with NBS in the same manner until full consumption of the starting material was observed by TLC. The reaction mixture was quenched with aq. sat. $NaHCO_3$ (10 mL) extracted with CH_2Cl_2 (3x10 mL), and the combined org. layers were dried

($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/cHex 1/4 to 1/2) gave the desired pyranose **1.173** (14.0 mg, 95%, α:β = 5:1) as a colourless oil of inseparable anomers.

Or

A solution of the rhamnoside **1.172** (277 mg, 0.55 mmol) in acetic acid (12.0 mL), HCl (1M, 5 mL) and water (2.5 mL) was heated to 120°C in a μw-oven for 3 h. Then it was diluted with water (40 mL), and extracted with *t*BME (2x40 mL), washed with aq. sat. $NaHCO_3$ (40 mL), and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (*t*BME/*c*Hex 1/1) gave the title compound **1.173** (140 mg, 52%, 57% brsm) as colourless oil.

R_f = 0.18 (EtOAc/cHex 1/2); **^{1}H-NMR** (400 MHz, $CDCl_3$, major anomer) δ 6.15 (ddt, J = 16.4, 10.4, 5.9 Hz, 1H), 6.05 (ddt, J = 16.4, 10.4, 6.0 Hz, 1H), 5.44 (ddd, J = 17.1, 1.4, 1.4 Hz, 1H), 5.39 (ddd, J = 17.1, 1.4, 1.4 Hz, 1H), 5.35 (s, 1H), 5.32 (ddd, J = 10.3. 1.2, 1.2 Hz, 1H), 5.27 (ddd, J = 10.4, 1.3, 1.3 Hz, 1H), 5.09 (dd J = 9.8, 9.8 Hz, 1H), 4.60 (dddd, J = 11.5, 5.9, 1.3, 1.3 Hz, 1H), 4.57 (ddd, J = 6.0, 1.3, 1.3 Hz, 2H), 4.51 (dddd, J = 11.5, 6.1, 1.3, 1.3 Hz, 1H), 4.03 (dq, J = 9.8, 6.2 Hz, 1H) 3.99 (dd, J = 9.8, 3.7 Hz, 1H), 3.58 (dd, J = 3.6, 1.5 Hz, 1H), 3.53 (s, 3H), 2.89–2.73 (m, 2H), 1.30 (d, J = 6.2 Hz, 3H), 1.20 (t, J = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$, major anomer) δ 166.6, 153.2, 151.1, 139.2, 132.9, 132.9, 127.4, 125.7, 121.7, 119.1, 119.0, 91.1, 80.7, 75.6, 75.9, 74.5, 69.3, 66.1, 59.2, 25.3, 17.8, 14.1; **HRMS ESI** calcd. for $[C_{22}H_{28}Cl_2NaO_8]^+$ $[M+Na]^+$: 513.1053; found: 513.1052; **IR** ν = 3442, 2936, 1734, 1567, 1460, 1403, 1315, 1248, 1100, 1065, 1041, 995, 930, 798, 748 cm^{-1}.

4.1.3 Glycosylations and End-Game

General procedure for the rhamnosylation using NIS:

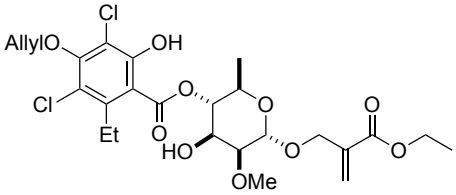
To a solution of the thioglycoside (1.0 eq) and ethyl 2-(hydroxymethyl)acrylate (1.0 eq) in CH_2Cl_2 (0.05 M), powdered m.s. 3Å (50 mg/mL) was added. The white suspension was stirred for 0.5 h and then cooled to –78°C. *N*-Iodosuccinimide (1.2 eq) and AgOTf (0.1 eq) was added and the mixture was stirred for 1 h at that temperature. The white suspension was slowly warmed to 0°C (or –30°C) and was kept at that temperature until TLC indicated full conversion (reaction mixtures turn orange to red). The reaction mixture was then diluted with CH_2Cl_2, quenched with aq. sat. NH_4Cl and aq. sat. $Na_2S_2O_3$ and the layers were separated, the aq. layer was reextracted with CH_2Cl_2, the org. layer was dried ($MgSO_4$), filtered and evaporated. The crude products were purified as described in the specific procedures.

(2*R*,3*S*,4*S*,5*S*,6*S*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyl-tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (α-1.158)

(2*R*,3*S*,4*S*,5*S*,6*R*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyl-tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (β-1.158)

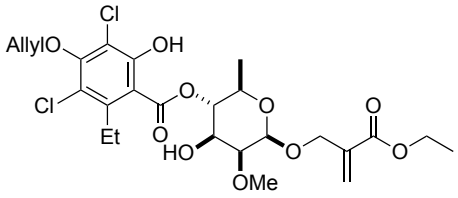
The glycosylation with the donor **1.142** was performed following the general procedure (see above). Purification by column chromatography (EtOAc/*c*Hex 1/4) gave an anomeric mixture of **1.158** (3.9 mg, 94%, α:β = 1:2) as a colourless oil.

For further characterization the anomeric mixture was separated by preparative TLC (*t*BME/*c*Hex 1/1).



α-**1.158**: R_f = 0.37 (*t*BME/*c*Hex 1/1); $[\alpha]_D$ = +12.2° (*c* = 0.35, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 6.33 (d, *J* = 1.3 Hz, 1H), 6.16 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.45 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.30 (dq, *J* = 10.4, 1.1 Hz, 1H), 5.18 (t, *J* = 9.8 Hz, 1H), 5.02 (d, *J* = 1.2 Hz, 1H), 4.59 (dt, *J* = 5.9, 1.2 Hz, 2H), 4.46 (dt, *J* = 13.5, 1.3 Hz, 1H), 4.29–4.17 (m, 3H), 4.05–3.94 (m, 1H), 3.90 (dq, *J* = 9.7, 6.2 Hz, 1H), 3.59 (dd, *J* = 3.7, 1.5 Hz, 1H), 3.52 (s, 3H), 3.09–2.94 (m, 2H), 2.45 (br d, *J* = 11.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz,

3H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.22 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.3, 165.6, 155.6, 155.5, 142.5, 136.9, 132.9, 126.5, 121.7, 119.2, 115.8, 112.7, 95.8, 80.3, 76.8, 74.4, 69.5, 66.1, 66.1, 61.1, 59.0, 26.1, 17.7, 14.4, 14.1; **HRMS ESI** calcd. for $[C_{25}H_{32}Cl_2NaO_{10}]^+$ $[M+Na]^+$: 585.1265; found: 585.1265; **IR** ν = 3416, 2981, 2931, 2361, 2342, 1715, 1665, 1582, 1550, 1459, 1412, 1392, 1372, 1310, 1269, 1213, 1189, 1129, 1106, 1068, 1053, 1001, 965, 802, 766, 745, 718 cm^{-1}.

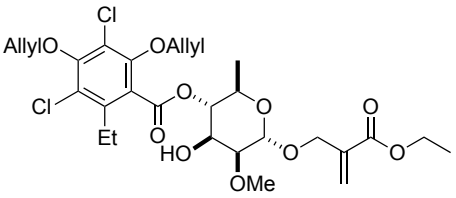


β-**1.158**: R_f = 0.45 (*t*BME/*c*Hex 1/1); **[α]$_D$** = –39.4° (*c* = 0.31, $CHCl_3$); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 6.34 (q, *J* = 1.4 Hz, 1H), 6.15 (ddt, *J* = 16.6, 10.3, 5.9 Hz, 1H), 5.89 (q, *J* = 1.7 Hz, 1H), 5.45 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.30 (dq, *J* = 10.2, 1.2 Hz, 1H), 5.15 (t, *J* = 9.4 Hz, 1H), 4.65 (dt, *J* = 13.9, 1.5 Hz, 1H), 4.62 (s, 1H), 4.59 (dt, *J* = 5.9, 1.3 Hz, 2H), 4.31 (dt, *J* = 14.0, 1.5 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 3.74–3.68 (m, 2H), 3.51 (dq, *J* = 9.4, 6.1 Hz, 1H), 3.01 (p, *J* = 7.5 Hz, 2H), 2.60 (br d, *J* = 11.1 Hz, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.32 (t, *J* = 7.4 Hz, 3H), 1.22 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.3, 165.7, 155.7, 155.5, 142.4, 136.8, 132.9, 126.2, 121.7, 119.2, 115.8, 112.6, 101.5, 80.4, 76.7, 74.5, 71.9, 70.1, 68.3, 62.3, 61.0, 26.1, 17.7, 14.4, 14.1; **HRMS ESI** calcd. for $[C_{25}H_{32}Cl_2NaO_{10}]^+$ $[M+Na]^+$: 585.1265; found: 585.1264; **IR** ν = 3421, 2981, 2917, 2849, 2360, 2341, 1713, 1665, 1582, 1550, 1455, 1392, 1371, 1307, 1266, 1213, 1198, 1178, 1108, 1071, 1020, 965, 855, 802, 768, 745 cm^{-1}.

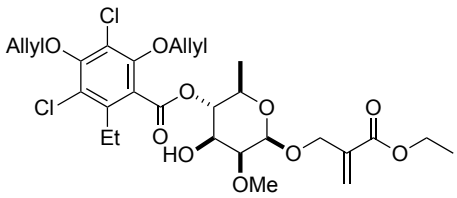
(2*R*,3*S*,4*S*,5*S*,6*S*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (α-1.164b)

(2*R*,3*S*,4*S*,5*S*,6*R*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (β-1.164b)

The glycosylation with the donor **1.164** was performed following the general procedure (see above). Purification by column chromatography (*t*BME/*c*Hex 1/3) gave the partially separated anomers (16 mg, 77%, α:β = 5:6) as a colourless oil.



α-**1.164b**: R_f = 0.33 (*t*BME/*c*Hex 1/1); $[\alpha]_D$ = +6.0° (*c* = 0.23, $CHCl_3$); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 1.2 Hz, 1H), 6.17 (ddt, *J* = 17.1, 10.3, 5.9 Hz, 1H), 6.06 (ddt, *J* = 17.0, 10.4, 6.0 Hz, 1H), 5.82 (q, *J* = 1.5 Hz, 1H), 5.46 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.39 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.32 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.27 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.11 (t, *J* = 9.8 Hz, 1H), 5.01 (d, *J* = 1.3 Hz, 1H), 4.60 (ddt, *J* = 11.5, 6.0, 1.2 Hz, 1H), 4.57 (dt, *J* = 5.9, 1.2 Hz, 2H), 4.50 (ddt, *J* = 11.5, 6.1, 1.2 Hz, 1H), 4.42 (dt, *J* = 13.7, 1.3 Hz, 2H), 4.27–4.18 (m, 3H), 3.95 (br s, 1H), 3.83 (dq, *J* = 9.9, 6.3 Hz, 1H), 3.58 (dd, *J* = 3.7, 1.5 Hz, 1H), 3.54 (s, 3H), 2.90–2.75 (m, 2H), 1.36–1.28 (m, 6H), 1.22 (q, *J* = 7.5, 7.0 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.5, 165.7, 153.2, 151.1, 139.2, 136.9, 133.0, 132.9, 127.4, 126.3, 125.67, 121.7, 119.1, 119.0, 96.1, 80.5, 76.5, 75.9, 74.5, 69.8, 66.3, 66.0, 61.0, 59.2, 25.3, 17.7, 14.3, 14.1; **HRMS ESI** calcd. for $[C_{28}H_{36}Cl_2NaO_{10}]^+$ $[M+Na]^+$: 625.1578; found: 625.1578; **IR** ν = 3493, 2979, 2934, 1718, 1636, 1568, 1462, 1402, 1370, 1353, 1313, 1276, 1248, 1178, 1130, 1106, 1066, 995, 973, 931, 802, 748, 721 cm^{-1}.

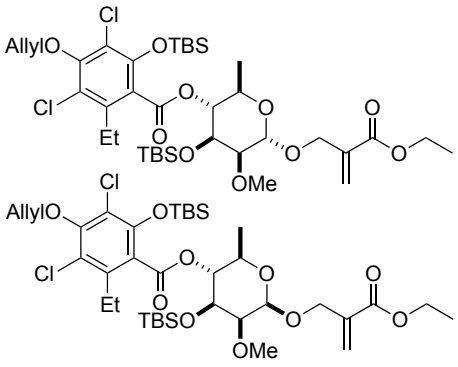


β-**1.164b**: R_f = 0.40 (*t*BME/*c*Hex 1/1); $[\alpha]_D$ = –37.3° (*c* = 0.45, $CHCl_3$); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.33 (q, *J* = 1.2 Hz, 1H), 6.15 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1H), 6.04 (ddt, *J* = 17.0, 10.4, 6.0 Hz, 1H), 5.89 (q, *J* = 1.6 Hz, 1H), 5.44 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.30 (dq, *J* = 10.4, 1.1 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.06 (t, *J* = 9.5 Hz, 1H), 4.65 (dt, *J* = 14.1, 1.6 Hz, 1H), 4.58 (ddt, *J* = 11.4, 5.6, 1.3 Hz, 1H), 4.56 (s, 1H), 4.55 (dt, *J* = 5.9, 1.2 Hz, 2H), 4.47 (ddt, *J* = 11.5, 6.1, 1.2 Hz, 1H), 4.29 (dt, *J* = 14.1, 1.4 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 3.66 (d, *J* = 3.6 Hz, 1H), 3.63 (br s, 1H), 3.42 (dq, *J* = 9.6, 6.2 Hz, 1H), 2.87–2.74 (m, 2H), 2.60 (br s, 1H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* =

7.5 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.4, 165.8, 153.3, 151.1, 139.2, 136.9, 133.0, 132.9, 127.3, 126.0, 125.7, 121.7, 119.1, 101.4, 80.6, 76.4, 75.9, 74.5, 72.2, 70.3, 68.2, 62.3, 61.0, 29.9, 25.3, 17.6, 14.4, 14.1; **HRMS ESI** calcd. for $[C_{28}H_{36}Cl_2NaO_{10}]^+$ $[M+Na]^+$: 625.1578; found: 625.1576; **IR** ν = 3497, 2971, 2932, 1733, 1707, 1648, 1572, 1457, 1403, 1372, 1310, 1251, 1201, 1166, 1141, 1110, 1082, 1038, 1022, 992, 932, 856, 776, 751 cm^{-1}.

(2*R*,3*R*,4*S*,5*S*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((2-(ethoxycarbonyl)allyl)oxy)-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-3,5-dichloro-6-ethylbenzoate (α-1.167)

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((2-(ethoxycarbonyl)allyl)oxy)-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-3,5-dichloro-6-ethylbenzoate (β-1.167)



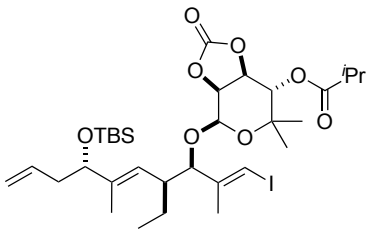
The glycosylation with the donor **1.162** was performed following the general procedure, the reaction was warmed to –30°C and was kept for 30 minutes at this temperature before workup. Purification by column chromatography (*t*BME/*c*Hex 1/10) gave the anomers **1.167** as an inseparable mixture (14 mg, 68%, α:β = 5:1).

For further structural confirmation the anomeric mixture was deprotected and compared with α-**1.158** and β-**1.158**:

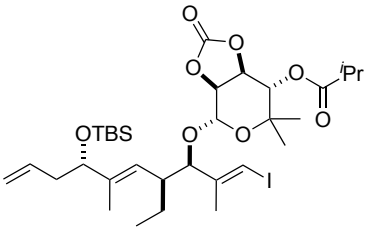
To a solution of the TBS-protected anomeric mixture of **1.167** (14 mg, 18 μmol) in THF (0.4 mL), $Et_3N{\cdot}3HF$ (60 μL, excess) was added. The colourless solution was heated to 50°C for 6 h. Then the yellow solution was poured on aq. sat. $NaHCO_3$ (5 mL) and extracted with *t*BME (2x2 mL). The org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure giving an anomeric mixture of α-**1.158** and β-**1.158** (7 mg, 70%, α:β = 4.5:1).

(3a*S*,4*R*,7*S*,7a*S*)-4-(((1*E*,3*R*,4*S*,5*E*,7*S*)-7-((tert-butyldimethylsilyl)oxy)-4-ethyl-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (1.185)

To a solution of novioside **1.102** (50.0 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) at 0°C and protected from light, HBr (33% in AcOH, 1.0 mL) was added. The solution was stirred for 2 h at RT before it was cooled to 5°C and diluted with CH_2Cl_2 (3 mL). The reaction was quenched with ice and H_2O. The layers were separated and the org. layer was washed with aq. sat. $NaHCO_3$ (8 mL) The aq. solutions were extracted with CH_2Cl_2 (2x3 mL) and the combined org. layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure at RT. The residual glycosyl bromide **16** was dissolved in CH_2Cl_2 (0.5 mL) and added dropwise to a suspension of alcohol **1.184** (50.0 mg, 0.11 mmol), HgO (152 mg, 0.70 mmol), $HgBr_2$ (5.8 mg, 20 µmol) and powdered molecular sieves 3Å (100 mg) in CH_2Cl_2 (0.6 mL) over 20 minutes. The orange suspension was stirred for 50 minutes before it was diluted with $CHCl_3$ (2 mL), filtered through silica gel and washed with $CHCl_3$ (2 mL). The filtrate was evaporated under reduced pressure and the residue was suspended in $CHCl_3$ (0.4 mL) and filtered through cotton. The filtrate was diluted with $CHCl_3$ (5 mL), washed with aq. sat. $NaHCO_3$ (5 mL), dried (Na_2SO_4), filtrated and evaporated under reduced pressure. Purification by column chromatography (EtOAc/cHex 1/10) afforded the anomer β-**1.185** (37 mg, 48%) and further purification by column chromatography (Et_2O/pentane 1/10) yielded the other anomer α-**1.185** (12 mg, 15%).

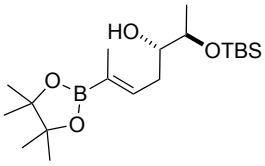


β-**1.185**: R_f = 0.38 (EtOAc/cHex 1/4); $[\alpha]_D$ = –23.1° (*c* = 0.22, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 0.9 Hz, 1H), 5.79 (ap dd, 4.0, 2.9 Hz, 1H) 5.75–5.62 (m, 1H), 5.03–4.97 (m, 3H), 4.86 (d, *J* = 10.5 Hz, 1H), 4.79–4.76 (m, 2H), 3.94 (dd, *J* = 6.1, 6.1 Hz, 1H), 3.82 (d, *J* = 9.3 Hz, 1H), 2.62 (hept, *J* = 7.0 Hz, 1H), 2.58–2.48 (m, 1H), 2.27–2.14 (m, 2H), 1.92–1.78 (m, 1H), 1.78 (d, *J* = 0.9, 3H), 1.57 (d, *J* = 1.2, 3H), 1.21 (d, *J* = 6.9, 6H), 1.16 (s, 3H), 1.14 (s, 3H), 0.87 (s, 9H) 0.81 (t, *J* = 7.4, 3H), 0.01 (s, 3H), –0.03 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 175.2, 153.8, 147.6, 140.0, 135.6, 123.6, 116.5, 95.3, 89.8, 81.6, 75.7, 75.1, 72.1, 71.8, 42.6, 42.0, 34.1, 28.0, 26.0 (3C), 25.6, 28.8, 24.3, 19.8, 19.1, 18.8, 18.3, 12.8, 11.2, –4.2, –4.7; **HRMS ESI** calcd. for $[C_{32}H_{53}INaO_8Si]^+$ $[M+Na]^+$: 743.2447; found: 743.2445; **IR** ν = 2954, 2929, 2856, 1818, 1749, 1468, 1389, 1253, 1145, 1091, 1074, 1034, 915, 837, 775 cm^{-1}.



α-**1.185:** R_f = 0.56 (EtOAc/cHex 1/4); **[α]$_D$** = +31.6° (*c* = 0.8, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.23 (d, *J* = 1.0 Hz, 1H), 5.70 (dddd, *J* = 17.2, 10.2, 7.1, 7.1 Hz, 1H), 5.13 (d, *J* = 8.3 Hz, 1H), 5.04–4.98 (m, 2H), 4.90 (ap d, *J* = 10.5 Hz, 1H), 4.78 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.78 (d, *J* = 5.2 Hz, 1H), 4.66 (dd, *J* = 8.4, 5.2 Hz, 1H), 4.06 (d, *J* = 9.2 Hz, 1H), 3.95 (dd, *J* = 6.1, 6.1 Hz, 1H), 2.63 (hept, *J* = 7.0 Hz, 1H), 2.53–2.45 (m, 1H), 2.27–2.15 (m, 2H), 1.85–1.76 (m, 1H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.57 (d, *J* = 1.3 Hz, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.21 (d, *J* = 1.3 Hz, 3H), 1.20 (d, *J* = 1.3 Hz, 3H), 1.18–1.10 (m, 1H), 0.88 (s, 9H), 0.80 (t, *J* = 7.4 Hz, 3H), 0.01 (s, 3H), –0.02 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 175.5, 153.2, 145.4, 139.8, 135.5, 123.7, 116.4, 91.8, 83.9, 82.3, 77.5, 76.6, 75.6, 74.8, 72.0, 41.9, 41.5, 33.9, 25.9 (3C), 25.8, 25.0, 23.8, 18.9, 18.7, 18.7, 18.2, 12.5, 10.9, –4.28, –4.85; **HRMS ESI** calcd. for $[C_{32}H_{53}INaO_8Si]^+$ $[M+Na]^+$: 743.2447; found: 743.2451; **IR** ν = 2954, 2931, 2858, 1831, 1748, 1468, 1389, 1253, 1138, 1080, 1037, 914, 837, 777 cm^{-1}.

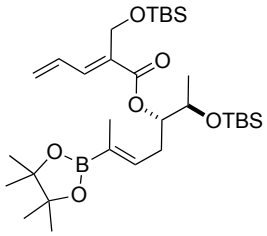
(2*R*,3*S*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-ol (1.41)



This compound was synthesized and characterized by Hiromu Hattori. CuCl (15.6 mg, 0.15 mmol, 5 mol%), PPh_3 (46.0 mg, 0.18 mmol, 6 mol%) and KO^{t}Bu (67 mg, 0.59 mmol, 20 mol%) were dissolved in THF (8.0 mL) and stirred at RT for 30 min, forming a brown solution. $(Bpin)_2$ (824 mg, 3.25 mmol) in THF (10.0 mL) was added and the reaction mixture was stirred for additional 10 minutes before it was cooled to 0°C and a solution of alkyne **1.65** (714 mg, 2.95 mmol) and MeOH (240 µL, 5.90 mmol) in THF (6.0 mL) were added dropwise in 5 minutes. The reaction mixture was warmed to RT and stirred for 26 h. Then it was filtered through Celite, washed with Et_2O (30 mL) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (Et_2O/pentane 1/8 to 1/6 to 1/4) yielding the boronic ester **1.41** (867 mg, 79%) as a colourless oil. The product should be purified immediately by silica gel chromatography to avoid slow decomposition of boronate under air.

$\mathbf{R_f}$ = 0.35 (Et_2O/pentane 1/4); $\mathbf{[\alpha]_D}$ = –13.2° (*c* = 0.62, $CHCl_3$). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.37 (tq, *J* = 6.7, 1.5 Hz, 1H), 3.77 (qd, *J* = 6.2, 3.8 Hz, 1H), 3.64–3.59 (m, 1H), 2.26 (ap d, *J* = 10.0 Hz, 1H), 2.24 (ap d, *J* = 10.0 Hz, 1H), 2.12 (d, *J* = 3.5 Hz, 1H), 1.69 (s, 3H), 1.24 (s, 12H), 1.09 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 142.1, 128.3, 83.3 (2C), 74.9, 71.2, 31.7, 25.9 (3C), 24.9 (4C), 18.2, 17.5, 14.3, –4.3, –4.7; **HMBC** (δ_H: 1.69 ppm, δ_C: 128.3 ppm); **^{11}B-NMR** (128 MHz, $CDCl_3$) δ 29.85; **HRMS ESI** calcd. for $[C_{19}H_{39}BNaO_4Si]^+$ $[M+Na]^+$: 393.2603; Found: 393.2604; **IR** ν = 3479, 2977, 2956, 2931, 2888, 2858, 1633, 1463, 1369, 1310, 1254, 1214, 1143, 1083, 975, 833, 775, 667 cm^{-1}.

(2*R*,3*S*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-yl (*E*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)penta-2,4-dienoate (1.186)

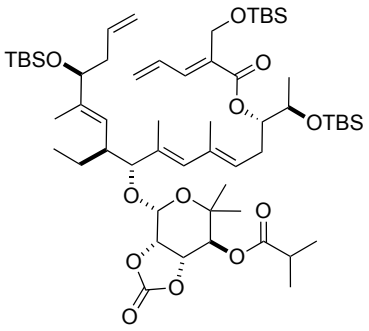


This compound was synthesized and characterized by Hiromu Hattori. To a stirred solution of carboxylic acid **1.55** (40 mg, 0.17 mmol) in benzene (1.5 mL) at RT, Et_3N (49 µL, 0.35 mmol) and 2,4,6-trichlorobenzoyl chloride (29 µL, 0.18 mmol) were added and stirred for 1.5 h. To this mixture, alcohol **1.41** (51 mg, 0.14 mmol) and DMAP (17 mg, 0.14 mmol) in PhH (1.5 mL) were added and stirred for 7 h at RT. The reaction was quenched with aq. sat. NH_4Cl (10 mL) and the aq. layer was extracted with Et_2O (3x10 mL). The org. layers were washed with aq. sat. $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by silica gel chromatography (Et_2O/pentane 1/40 to 1/30 to 1/20) gave the desired ester **1.186** (50 mg, 61%) as a colourless oil.

$\mathbf{R_f}$ = 0.40 (Et_2O/pentane 1/12); $\mathbf{[\alpha]_D}$ = –43.5° (*c* = 1.08, $CHCl_3$); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 11.4 Hz, 1H), 6.92 (ddd, *J* = 16.9, 11.5, 10.0 Hz, 1H), 6.33 (ddt, *J* = 7.1, 5.3, 1.8 Hz, 1H), 5.56 (ddd, *J* = 16.9, 1.8, 0.8 Hz, 1H), 5.48 (dd, *J* = 10.0, 1.8 Hz, 1H), 4.88 (dt, *J* = 7.9, 4.6 Hz, 1H), 4.49 (d, *J* = 1.5 Hz, 2H), 3.97 (qd, *J* = 6.3, 4.0 Hz, 1H), 2.58–2.44 (m, 2H), 1.69 (s, 3H), 1.22 (s, 12H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 166.9, 141.6, 141.4, 132.6, 131.3, 129.3, 125.6, 83.2 (2C), 77.8, 69.4, 57.9, 28.6, 26.0 (3C), 25.9 (3C), 24.92 (2C), 24.89 (2C), 20.1, 18.5, 18.1, 14.2, –4.30, –4.7, –5.1 (2C); **HMBC** (δ_H: 1.69 ppm, δ_C: 129.3 ppm); **^{11}B-NMR** (128 MHz, $CDCl_3$) δ 29.60; **HRMS ESI** calcd. for $[C_{31}H_{59}BNaO_6Si_2]^+$ $[M+Na]^+$:

617.3835; Found: 617.3839; **IR** ν = 2930, 2887, 2858, 1706, 1634, 1370, 1305, 1370, 1145, 1072, 834, 775, 668 cm^{-1}.

(5*R*,6*S*,8*E*,10*E*,12*R*,13*S*,14*E*,16*S*)-16-allyl-13-ethyl-12-(((3a*S*,4*R*,7*S*,7a*S*)-7-(isobutyryl-oxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yl)oxy)-2,2,3,3,5,9, 11,15,18,18,19,19-dodecamethyl-4,17-dioxa-3,18-disilaicosa-8,10,14-trien-6-yl (*E*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)penta-2,4-dienoate (1.187)

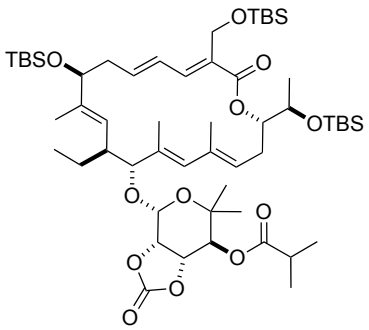


This compound was synthesized and characterized by Hiromu Hattori. A water stock solution of TlOEt was prepared as follows: To a vial under Ar, TlOEt (12.0 mg) and degassed H_2O (120 µL) were added and stirred until the residue was completely dissolved. To a solution of iodide **1.185** (16.5 mg, 23 µmol) and boronate **1.186** (22.5 mg, 34 µmol) in degassed THF (600 µL) and degassed H_2O (150 µL), $Pd(PPh_3)_4$ (5.4 mg, 20 mol%) was added and stirred for 5 minutes at RT. Then the stock solution of TlOEt (45 µL, ca. 4.5 mg, 18 µmol) was added dropwise for 2 minutes. After stirring for 30 minutes at the same temperature, the reaction mixture was diluted with Et_2O (5 mL) and quenched with brine (5 mL) and aq. sat. NH_4Cl (5 mL). The aq. layer was extracted with Et_2O (3x10 mL). The combined org. layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/6 to 1/4) gave alkene **1.187** (20 mg, 82%) as a colourless oil.

R_f = 0.43 (EtOAc/cHex 1/4); **$[\alpha]_D$** = –48.5° (*c* = 0.57, $CHCl_3$); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 11.4 Hz, 1H), 6.92 (ddd, *J* = 16.9, 11.4, 9.9 Hz, 1H), 5.85–5.79 (m, 1H), 5.74 (s, 1H), 5.69 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.56 (dd, *J* = 16.8, 1.0 Hz, 1H), 5.50 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 1.7 Hz, 1H), 4.97 (dd, *J* = 17.2, 2.2 Hz, 1H), 4.93–4.92 (m, 1H), 4.92 (dd, *J* = 19.2, 2.2 Hz, 1H), 4.89–4.81 (m, 1H), 4.76 (d, *J* = 1.2 Hz, 1H), 4.75 (d, *J* = 1.9 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 3.98–3.90 (m, 2H), 3.66 (d, *J* = 8.9 Hz, 1H), 2.65-2.56 (m, 1H), 2.56–2.37 (m, 3H), 2.18 (t, *J* = 6.9 Hz, 2H), 1.86–1.77 (m, 1H), 1.74 (d, *J* = 1.3 Hz, 3H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.62–1.56 (m, 1H), 1.56 (d, *J* = 1.3 Hz, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 1.15 (d, *J* = 5.0 Hz, 3H), 1.12 (s, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.80 (t, *J* = 7.4 Hz, 3H), 0.07 (s, 3H), 0.07 (s,

3H), 0.03 (s, 3H), 0.02 (s, 3H), –0.03 (s, 3H), –0.09 (s, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 175.2, 166.8, 153.9, 141.5, 138.8, 135.8, 134.3, 133.8, 133.6, 132.5, 131.3, 126.5, 125.7, 124.8, 116.3, 94.1, 92.1, 78.1, 77.7, 75.8, 74.9, 72.3, 72.0, 69.5, 57.9, 42.3, 42.0, 34.1, 28.4, 28.2, 26.1 (3C), 26.0 (3C), 25.9 (3C), 24.7, 24.3, 20.0, 19.1, 18.8, 18.5, 18.3, 18.1, 17.2, 13.8, 12.7, 11.3, –4.3, –4.5, –4.7, –4.9, –5.10, –5.12; **HRMS ESI** calcd. for $[C_{57}H_{100}NaO_{12}Si_3]^+$ $[M+Na]^+$: 1083.6415; Found: 1083.6417; **IR** ν = 2954, 2929, 2856, 1818, 1747, 1468, 1254, 1146, 1091, 1035, 837, 777, 668 cm^{-1}.

(3a*S*,4*R*,7*S*,7a*S*)-4-(((2*S*,4*E*,6*E*,8*R*,9*S*,10*E*,12*S*,14*E*,16*E*)-12-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-17-(((*tert*-butyldimethylsilyl)oxy)methyl)-9-ethyl-5,7,11-trimethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (1.188)



This compound was synthesized and characterized by Hiromu Hattori. To a degassed solution of alkene **1.187** (5.5 mg, 52 µmol) in benzene (1.0 mL), Grubbs-II catalyst (0.9 mg, 10 µmol, 20 mol%) was added using Schlenk technique and the resulting mixture was heated to 100°C in a pre-heated oil bath for 75 minutes. After cooling to RT, the reaction mixture was diluted with Et_2O (3 mL) and H_2O (3 mL). The layers were separated and the aq. layer was extracted with Et_2O (3x8 mL). The combined org. layers were dried (Na_2SO_4), filtered and concentrated. ^{1}H-NMR analysis of the crude mixture revealed the desired product formation as a 2:1 (*E*/*Z*) mixture at C4-C5 olefin. Purification by prep. TLC (Et_2O/pentane 1/4) gave the desired (*E*)-**1.188** (2.9 mg, 54%) as a colourless oil. In addition, (*Z*)-**1.188** (1.1 mg, 21%) was also obtained as an impure mixture.

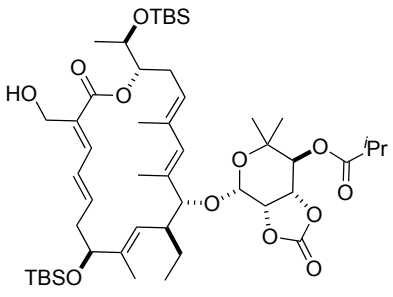
Isomerization of (*Z*)-**1.188** to (*E*)-**1.188**:

To a degassed solution of (*Z*)-**1.188** (7.9 mg, 7.5 µmol) in PhMe (1.5 mL), Grubbs-II catalyst (1.3 mg, 1.5 µmol, 20 mol%) was added using Schlenk technique and the resulting mixture was heated to 100°C in a pre-heated oil bath for 11 h. After cooling to RT, the reaction mixture was diluted with Et_2O (3.0 mL) and H_2O (3.0 mL). The org. layer was separated and the resulting aq. layer was extracted by Et_2O (2x10 mL). The combined org. layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. ^{1}H-NMR analysis revealed the

desired product formation as a 2:1 (*E*/*Z*) mixture at C4-C5 olefin. Purification by prep. TLC (Et_2O/pentane 1/4, 3 times) gave the desired (*E*)-**1.188** (3.5 mg, 44%) as a colourless oil.

R_f = 0.20 (Et_2O/pentane 1/4); **$[\alpha]_D$** = –42.5° (*c* = 0.41, $CHCl_3$); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 11.5 Hz, 1H), 6.48 (ddd, *J* = 14.8, 11.4, 1.4 Hz, 1H), 5.85–5.80 (m, 2H), 5.71 (ddd, *J* = 14.8, 10.0, 4.5 Hz, 1H), 5.44 (t, *J* = 8.3 Hz, 1H), 5.11–5.03 (m, 2H), 4.80–4.74 (m, 2H), 4.68–4.62 (m, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.16 (br, 1H), 4.10 (p, *J* = 6.1 Hz, 1H), 3.67 (d, *J* = 9.8 Hz, 1H), 2.82–2.72 (m, 1H), 2.69–2.62 (m, 1H), 2.66–2.58 (m, 1H), 2.55 (dt, *J* = 15.0, 2.4 Hz, 1H), 2.32–2.22 (m, 2H), 1.89 (dt, *J* = 7.4, 4.5 Hz, 1H), 1.83 (s, 3H), 1.76 (s, 3H), 1.60 (m, 1H), 1.59 (s, 3H), 1.22–1.20 (m, 9H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.13 (s, 3H), 0.88 (s, 18H), 0.85 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), –0.02 (s, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 175.3, 167.9, 154.0, 142.6, 140.4, 135.8, 135.4, 133.1, 128.2, 127.8, 126.9, 125.7, 124.0, 93.6, 93.1, 77.1, 75.7, 75.0, 73.2, 72.4, 72.1, 68.4, 57.6, 42.0, 37.5, 34.1, 28.4, 26.9, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.4, 24.2, 20.8, 19.1, 18.8, 18.5, 18.3, 18.1, 17.0, 15.1, 13.4, 10.9, –4.1, –4.5, –4.9, –5.0, –5.1, –5.2; **HRMS ESI** calcd. for $[C_{55}H_{96}NaO_{12}Si_3]^+$ $[M+Na]^+$: 1055.6102; Found: 1055.6104; **IR** ν = 2930, 2857, 1820, 1751, 1703, 1645, 1465, 1252, 1145, 1072, 1004, 838, 776 cm^{-1}.

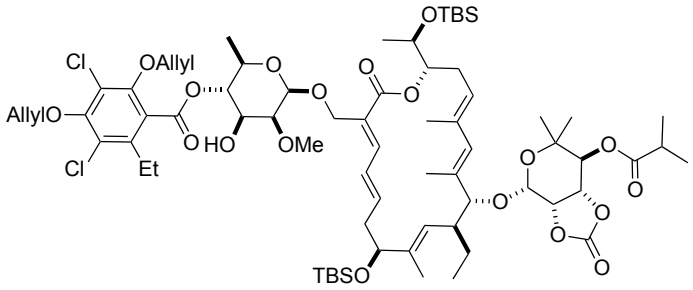
(3a*S*,4*R*,7*S*,7a*S*)-4-(((2*S*,4*E*,6*E*,8*R*,9*S*,10*E*,12*S*,14*E*,16*E*)-12-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-9-ethyl-17-(hydroxymethyl)-5,7,11-trimethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (1.188b)



To a solution of macrolide **1.188** (8.0 mg, 7.7 µmol) in THF/MeCN 1/1 (1.0 mL) at 0°C, trihydrogenfluoride triethylamine (50 µL, 0.31 mmol) was added dropwise. The reaction mixture was stirred at RT for 8 h, then it was quenched with aq. sat. $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3x2 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by preparative TLC (EtOAc/cHex 1/4) afforded the alcohol **1.188b** (3.5 mg, 49%) as a colourless oil which was used without further purification in the next step.

***R*$_f$** = 0.24 (EtOAc/cHex 1/4).

(2*R*,4*S*,5*R*)-6-(((3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-8-((*tert*-butyldimethylsilyl)oxy)-18-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-11-ethyl-12-(((4*R*,7*S*,7a*R*)-7-(isobutyryloxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yl)oxy)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.189).



To a solution of alcohol **1.188b** (2.8 mg, 3.1 μmol) and acetimidate **1.169** (3.0 mg, 3.1 μmol) in CH_2Cl_2 (0.3 mL) molecular sieves (4Å, 30 mg) was added and the white suspension was stirred for 30 minutes at RT. Then, it was cooled to –78°C and TBSOTf (0.15 mL, 20 mol%) in CH_2Cl_2 (50 μL) was added dropwise. The reaction mixture was warmed to –50°C and subsequently warmed to –30°C over 1 h. The reaction mixture was diluted with CH_2Cl_2 (1 mL), quenched with a drop of Et_3N, filtered, washed with toluene and evaporated under reduced pressure. Purification by preparative TLC (EtOAc/cHex 1/4) afforded the desired anomer **1.189** (β-**1.189**: 3.3 mg, 62%; α:β 1:4, calculated by ^{1}H-NMR of the crude reaction mixture) containing a minor inseparable impurity.

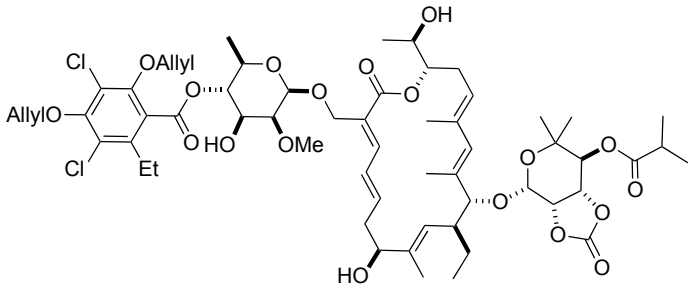
Or:

To a solution of carbonate protected fidaxomicin **1.190** (23 mg, 18 μmol) in CH_2Cl_2 (0.5 mL) at 0°C, 2,6-lutidine (20 μL, 0.18 mmol) and TBSOTf (24 μL, 90 μmol) were added. The solution was stirred at RT for 5 h. Then it was quenched with aq. sat. NH_4Cl (5 mL) and extracted with EtOAc (3x3 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (Et_2O/pentane 1/1) gave the protected fidaxomicin **1.1.189** (13 mg, 52%).

R_f = 0.32 (EtOAc/*c*Hex 1/4), 0.45 (Et_2O/pentane); $[\alpha]_D$ = –45.3° (*c* = 0.6, MeOH); **^{1}H-NMR** (400 MHz, acetone-d_6) δ 7.19 (d, *J* = 11.5 Hz, 1H), 6.64–6.56 (m, 1H), 6.23–6.05 (m, 2H), 5.95 (s, 1H), 5.92 (ddd, *J* = 14.8, 10.3, 4.5 Hz 1H), 5.77 (d, *J* = 7.0 Hz, 1H), 5.55 (dd, *J* = 8.3, 8.3 Hz, 1H), 5.49–5.37 (m, 2H), 5.31–5.23 (m, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 5.17 (ap d, *J* =

11.0 Hz 1H), 5.12–5.05 (m, 2H), 5.03 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.67–4.56 (m, 4H), 4.64 (s, 1H), 4.52 (dddd, *J* = 11.7, 5.9, 1.4, 1.4 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.36–4.34 (m, 1H), 4.27–4.20 (m, 1H), 3.90 (d, *J* = 10.1 Hz, 1H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.69 (ddd, *J* = 9.7, 9.7, 3.3, Hz, 1H), 3.55 (d, *J* = 3.5 Hz, 1H), 3.54–3.47 (m, 1H) 3.52 (s, 3H), 2.92–2.76 (m, 3H), 2.75–2.63 (m, 3H), 2.40 (ddd, *J* = 14.8, 10.3, 4.5 Hz, 1H), 2.32 (ddd, *J* = 13.8, 7.6, 4.1 Hz, 1H), 2.02–1.94 (m, 1H), 1.91 (ap s, 3H), 1.87 (ap s, 3H), 1.71 (ap s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.22–1.14 (m, 19H), 0.91 (s, 9H), 0.88 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H); **^{13}C-NMR** (101 MHz, acetone-d_6) δ 175.8, 167.9, 166.5, 154.7, 153.9, 152.0, 145.2, 142.9, 140.0, 136.7, 136.5, 136.0, 134.5, 134.2, 134.1, 128.7, 128.6, 127.8, 126.0, 125.4, 124.8, 122.3, 118.8, 118.7, 102.2, 95.1, 93.4, 81.8, 77.9, 77.5, 76.4, 76.4, 75.4, 75.0, 74.0, 73.2, 73.0, 72.4, 70.8, 69.2, 63.2, 61.7, 42.9, 38.1, 34.6, 28.8, 27.1, 26.3, 26.2, 26.0, 25.6, 24.1, 20.9, 19.2, 19.0, 18.8, 18.6, 18.4, 17.3, 15.2, 14.4, 13.9, 11.3, –4.1, –4.2, –4.8, –4.9; **HRMS ESI** calcd. for $[C_{71}H_{108}Cl_2NaO_{19}Si_2]^+$ $[M+Na]^+$: 1408.6739; found: 1408.6725; **IR** ν = 2928, 2856, 2361, 1819, 1741, 1643, 1566, 1462, 1371, 1324, 1249, 1094, 1069, 1018, 1003, 938, 836, 774 cm^{-1}.

(2*R*,3*R*,6*S*)-6-(((3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-11-ethyl-8-hydroxy-18-((*R*)-1-hydroxyethyl)-12-(((3a*S*,4*R*,7*S*,7a*S*)-7-(isobutyryloxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yl)oxy)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.190).



To a solution of the macrolide **1.189** (4 mg, 2 µmol) in THF (0.5 mL), trihydrogenfluoride triethylamine (120 µL, excess) was added dropwise. The solution was stirred for 24 h at 50°C before it was quenched by the addition of aq. sat. $NaHCO_3$ (3 mL) The aq. layer was extracted with EtOAc (4x2 mL) and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by preparative TLC (acetone/pentane 2/3) yielded the triol **1.190** (2.8 mg, 88%).

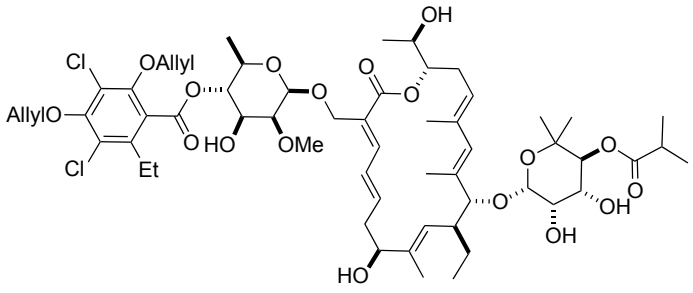
Or

To a solution of allyl protected fidaxomicin **1.191** (130 mg, 0.11 mmol) in CH_2Cl_2 (5.0 mL) at RT, Et_3N (0.32 mL, 2.3 mmol) and 1,1'-carbonyldiimidazole (28 mg, 0.17 mmol) were added and the mixture was stirred for 24 h. Then it was quenched with aq. sat. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (1x10 mL). The combiner org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (Et_2O) gave the desired carbonate protected fidaxomicin **1.190** (120 mg, 90%).

R_f = 0.85 (acetone/pentane 2/3); $[\alpha]_D$ = –55.3° (c = 0.02, MeOH); **^{1}H-NMR** (400 MHz, acetone-d_6) δ 7.19 (d, J = 11.4 Hz, 1H), 6.63 (dd, 14.4, 12.0 1H), 6.17 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 6.09 (ddt, J = 17.1, 10.4, 5.8 Hz, 1H), 6.00–5.90 (m, 1H) 5.93 (s, 1H), 5.74 (d, J = 6.9 Hz, 1H), 5.61 (dd, J = 8.1, 8.1 Hz, 1H), 5.43 (ap ddq, J = 20.4, 17.2, 1.6 Hz, 1H), 5.31–5.23 (m, 2H), 5.21–5.16 (m, 2H), 5.18 (d, J = 3.2 Hz, 1H), 5.12–4.99 (m, 3H), 4.72–4.67 (m, 1H), 4.64 (s, 1H), 4.64–4.57 (m, 4H), 4.53 (dddd, J = 11.7, 5.8, 1.4, 1.4 Hz, 1H),

4.39 (d, *J* = 11.5 Hz, 1H), 4.29–4.24 (m, 1H), 4.07–4.00 (m, 2H), 3.86 (d, *J* = 10.1 Hz, 1H), 3.80 (d, *J* = 9.8 Hz, 1H), 3.75 (d, *J* = 4.2 Hz, 1H), 3.73–3.66 (m, 1H), 3.55 (d, *J* = 3.3 Hz, 1H), 3.55–3.50 (m, 1H), 3.52 (s, 3H), 2.92–2.62 (m, 6H), 2.50 (ddd, *J* = 14.7, 9.6, 4.4 Hz, 1H), 2.40 (ddd, *J* = 13.7, 8.3, 4.4 Hz, 1H), 1.96–1.90 (m, 1H), 1.89 (ap s, 3H), 1.79 (ap s, 3H), 1.68 (ap s, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.25–1.12 (m, 19H), 0.82 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, acetone-d_6) δ 176.0, 168.1, 166.5, 154.7, 153.9, 152.0, 145.1, 143.1, 140.0, 137.3, 136.0, 135.5, 134.7, 134.1, 134.1, 128.7, 128.4, 127.5, 126.0, 125.6, 123.8, 122.3, 118.8, 118.7, 101.9, 95.3, 93.0, 81.9, 78.5, 77.5, 76.4, 76.4, 75.4, 75.0, 73.3, 73.1, 72.9, 72.4, 70.7, 66.1, 63.5, 61.8, 42.8, 37.4, 34.6, 28.5, 28.4, 26.0, 25.6, 23.9, 20.4, 19.2, 19.0, 18.3, 17.4, 15.3, 14.4, 13.8, 11.2; **HRMS ESI** calcd. for $[C_{59}H_{80}Cl_2NaO_{19}]^+$ $[M+Na]^+$: 1185.4563; found: 1185.4570; **IR** ν = 3461, 2976, 2935, 2878, 2360, 2324, 2231, 2167, 2049, 1814, 1737, 1701, 1642, 1565, 1459, 1400, 1370, 1319, 1246, 1066, 1041, 1024, 933, 902, 769 cm^{-1}.

(2*R*,3*R*,6*S*)-6-(((3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-12-(((2*R*,3*S*,4*R*,5*S*)-3,4-dihydroxy-5-(isobutyryloxy)-6,6-dimethyltetrahydro-2*H*-pyran-2-yl)oxy)-11-ethyl-8-hydroxy-18-((*R*)-1-hydroxyethyl)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)-methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.191)



To a solution of the protected macrolide **1.190** (8 mg, 7 mmol) in THF (0.2 mL) at 0°C, a solution of sodium hydride in ethylene glycol (20 µL, 0.5 mg/mL) was added. The mixture was stirred vigorously for 15 minutes and quenched with aq. sat. NH_4Cl (2 mL) and EtOAc (3 mL) was added. The layers were separated and the aq. layer was extracted with EtOAc (2x3 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/toluene 2/3 to 1/1 to 3/2) gave the carbonate-deprotected intermediate along with minor a minor byproduct and starting material (1.0 mg, 13%). The compound was further purified by RP-HPLC (A: H_2O+0.1%

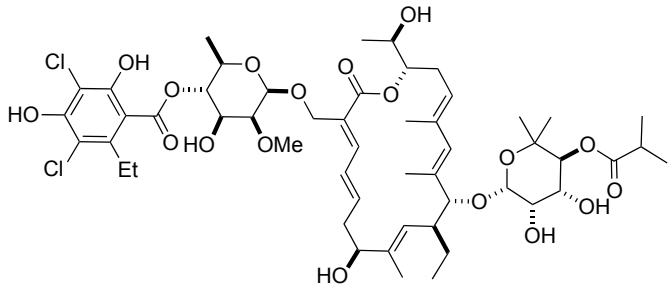
HCOOH; Solvent B: CH_3CN+0.1% HCOOH; 1 mL/min; T = 20°C; B[%] (t_R [min])= 65 (0 to 3); 90 (15); 100 (16)). The impure allylated fidaxomicin was dissolved in CH_3CN (0.15 mL) and separated in portions (100 µL). The product **1.191** eluted at t_R = 14.0 minutes and the solvents were evaporated under reduced pressure to give pure **1.190** (3.6 mg, 46%, 53% brsm) as an amorphous solid.

or

To a solution of fidaxomicin (400 mg, 0.38 mmol) in DMF (10 mL), K_2CO_3 (209 mg, 1.51 mmol) was added. To the suspension allyl bromide (82 µL, 0.95 mmol) was added and the colourless reaction mixture was stirred at 45°C for 3 h. The orange-red reaction mixture was quenched with aq. sat. NH_4Cl and the mixture was extracted with EtOAc (3x). The organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (acetone/pentane 2/3) gave the allylated fidaxomicin **1.190** (384 mg, 89%) as a colourless resin.

^{1}H-NMR (400 MHz, acetone-d_6) δ 7.22 (d, J = 11.4 Hz, 1H), 6.62 (dd, J = 15.2, 11.5 Hz, 1H), 6.13 (dddt, J = 32.0, 17.2, 10.4, 5.8 Hz, 2H), 5.96 (ddd, J = 14.7, 9.6, 4.7 Hz, 1H), 5.83 (s, 1H), 5.62 (t, J = 8.2 Hz, 1H), 5.43 (ddq, J = 20.4, 17.2, 1.6 Hz, 2H), 5.33–5.23 (m, 2H), 5.21 (dt, J = 10.5, 1.6 Hz, 1H), 5.02 (t, J = 9.7 Hz, 1H), 4.99 (d, J = 10.1 Hz, 1H), 4.77 (d, J = 1.3 Hz, 1H), 4.76–4.69 (m, 1H), 4.64 (d, J = 0.8 Hz, 1H), 4.63–4.58 (m, 4H), 4.53 (ddt, J = 11.8, 5.8, 1.4 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.26 (br s, 1H), 4.02 (p, J = 6.4 Hz, 1H), 3.95 (dd, J = 3.4, 1.2 Hz, 1H), 3.75–3.66 (m, 3H), 3.59 (ddd, J = 3.1, 2.3, 1.3 Hz, 1H), 3.55 (dd, J = 3.6, 0.8 Hz, 1H), 3.52 (s, 3H), 2.94–2.59 (m, 6H), 2.56 (p, J = 7.0 Hz, 1H), 2.52–2.38 (m, 1H), 1.99–1.87 (m, 1H), 1.81 (d, J = 1.4 Hz, 3H), 1.73 (d, J = 1.4 Hz, 3H), 1.66 (dd, J = 1.4, 0.7 Hz, 3H), 1.33 (d, J = 6.1 Hz, 3H), 1.30–1.21 (m, 1H), 1.19–1.12 (m, 15H), 1.09 (d, J = 0.6 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H).

Fidaxomicin (Tiacumicin B, Lipiarmycin A3)



To a solution of the protected macrolide **1.190** (0.9 mg, 0.8 μmol) in CH_2Cl_2 (0.2 mL), a drop of Barton's base and a drop of H_2O were added. The mixture was stirred vigorously for 1.5 h before it was diluted with EtOAc (2 mL) and quenched with aq. sat. NH_4Cl (2 mL) The layers were separated and the aq. layer was extracted with EtOAc (3x2 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by preparative TLC (MeOH/toluene 1/5) gave the carbonate deprotected intermediate **1.190** (0.4 mg) with minor impurities.

To a solution of the crude allyl-protected intermediate **1.191** in THF (0.2 mL) at 0°C morpholine (0.3 mL, 3.6 mmol) in CH_2Cl_2 (10 mL) and $Pd(PPh_3)_4$ (0.14 mg, 10 mol%) were added and the reaction mixture was stirred at this temperature for 20 minutes. The reaction mixture was quenched with aq. sat. NH_4Cl (2 mL), extracted with EtOAc (4x2 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by preparative TLC (MeOH/CH_2Cl_2 1/10) yielded fidaxomicin (0.4 mg) as a colourless oil with minor impurities.

The compound was further purified by RP-HPLC (A: H_2O+0.1% HCOOH; Solvent B: MeCN+0.1% HCOOH; 1 mL/min; T = 20°C; B[%] (t_R [min])= 50 (0 to 3); 65 (15); 100 (16)). The impure fidaxomicin was dissolved in MeCN (0.15 mL) and separated in portions (3x50 μL). Fidaxomicin (**1**) eluted at t_R = 12.3 minutes and the solvents were evaporated under a constant stream of nitrogen yielding fidaxomicin contaminated with formate (ca. 0.1 mg 10% over 2 steps, calculated from a UV-standard curve of an authentic sample of fidaxomicin by linear regression analysis).

Or

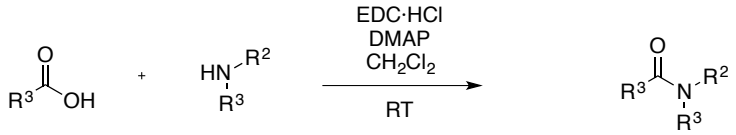
To a solution of the pure allyl-protected intermediate **1.191** (3.0 mg, 2.6 μmol) in THF (0.5 mL) at 0°C morpholine (0.5 mL in 10 mL THF) and $Pd(PPh_3)_4$ (0.3 mg, in 0.1 mL THF)

were added and the reaction mixture was stirred at this temperature for 30 minutes. The reaction mixture was diluted with EtOAc (2 mL) and quenched with aq. sat. NH_4Cl (2 mL). The Layers were separated and the aq. layer was extracted with EtOAc (3x2 mL), the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (acetone/pentane 2/3 to 1/1) yielded pure fidaxomicin (2.4 mg, 86%).

R_f = 0.44 (MeOH/CH_2Cl_2 1/10); $[\alpha]_D$ = –7.6° (*c* = 0.96, MeOH) **^{1}H-NMR** (600 MHz, CD_3OD, containing $HCOO^-$) δ 7.23 (d, *J* = 11.5 Hz, 1H), 6.60 (dd, *J* = 14.9, 11.8 Hz, 1H), 5.95 (ddd, *J* = 14.7, 9.5, 4.8 Hz, 1H), 5.83 (s, 1H), 5.57 (ap t, *J* = 8.2 Hz, 1H), 5.14 (ap d, *J* = 10.7, 1H), 5.13 (dd, *J* = 9.7 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.74–4.70 (m, 1H), 4.71 (s, 1H), 4.64 (s, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.22 (ap s, 1H), 4.02 (p, *J* = 6.3 Hz, 1H), 3.92 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.75 (ddd, *J* = 13.9, 10.2, 3.3 Hz, 1H) 3.71 (d, *J* = 9.7 Hz 1H), 3.58–3.52 (m, 2H) 3.54 (s, 3H), 3.15–3.06 (m, 1H), 3.04–2.95 (m, 1H), 2.76–2.66 (m, 3H), 2.60 (hept, *J* = 7.0 Hz, 1H), 2.49 (ddd, *J* = 14.9, 9.5, 4.4 Hz, 1H), 2.43 (ddd, *J* = 13.8, 8.8, 4.5 Hz, 1H), 2.05–1.98 (m, 1H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.76 (ap s, 3H), 1.66 (ap s, 3H), 1.32–1.27 (m, 4H), 1.22–1.15 (m, 12H), 1.15 (s, 3H), 1.13 (s, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, CD_3OD) δ 178.4, 169.7, 169.1, 154.6, 153.9, 146.2, 143.7, 141.9, 137.0, 137.0, 136.4, 134.6, 128.5, 126.9, 125.6, 124.6, 114.8, 112.7, 108.8, 102.2, 97.2, 94.3, 82.5, 78.6, 76.9, 75.9, 74.5, 73.5, 73.2, 72.8, 71.6, 70.6, 68.3, 63.9, 62.2, 42.5, 37.3, 35.4, 28.7, 28.4, 26.9, 26.4, 20.3, 19.5, 19.1, 18.7, 18.1, 17.5, 15.4, 14.5, 13.9, 11.3; **^{1}H-NMR** (400 MHz, acetone-d_6) δ 7.24 (dd, *J* = 11.5, 0.8 Hz, 1H), 6.63 (dddd, *J* = 14.8, 11.6, 2.0, 1.0 Hz, 1H), 5.96 (ddd, *J* = 14.6, 9.3, 4.6 Hz, 1H), 5.83 (s, 1H), 5.71–5.54 (m, 1H), 5.22 (dt, *J* = 10.6, 1.5 Hz, 1H), 5.10 (t, *J* = 9.8 Hz, 1H), 5.00 (d, *J* = 10.1 Hz, 1H), 4.77 (d, *J* = 1.3 Hz, 1H), 4.75–4.71 (m, 1H), 4.68 (d, *J* = 0.8 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.26 (s, 1), 4.05–3.99 (m, 1H), 3.95 (dd, *J* = 3.4, 1.2 Hz, 1H), 3.80 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.75–3.73 (m, 1H), 3.73–3.70 (m, 1H), 3.65–3.60 (m, 1H,), 3.59 (d, *J* = 2.5 Hz, 1H), 3.52 (s, 3H), 3.01 (qd, *J* = 7.4, 2.0 Hz, 2H), 2.76 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.72–2.67 (m, 1H), 2.67–2.60 (m, 1H), 2.56 (sept, *J* = 7.0 Hz, 1H), 2.53–2.46 (m, 1H), 2.46–2.38 (m, 1H), 1.93 (qdd, *J* = 10.5, 6.3, 1.9 Hz, 1H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.73 (d, *J* = 1.5 Hz, 3H), 1.65 (dd, *J* = 1.4, 0.7 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.29–1.24 (m, 1H), 1.22 (t, *J* = 7.4 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.16–1.12 (m, 9H), 1.09 (s, 3H), 0.83 (t, *J* = 7.5 Hz, 3H); **HRMS ESI** calcd. for $[C_{52}H_{74}Cl_2NaO_{18}]^+$ $[M+Na]^+$: 1079.4144; found: 1079.4151; **IR** ν = 3452, 2974, 2933, 2363, 2327, 2189, 1703, 1643, 1584, 1370, 1312, 1242, 1199, 1146, 1068, 1024, 900, 797, 762 cm^{-1}.

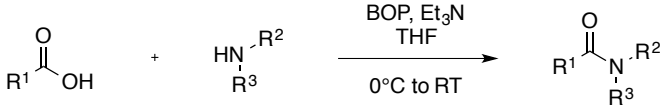
4.2 Methionine-Derived Iminium Lactones

General procedure for the amide coupling using EDC·HCl



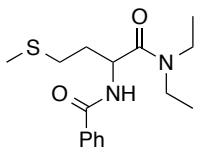
To a solution of the carboxylic acid (1.0 eq), DMAP (0.50 eq) and EDC·HCl (1.5 eq) in CH_2Cl_2 (c = 0.2 mol/L) at RT, the amine (1.0 eq) was added. The solution was stirred at RT until full conversion was indicated by TLC. The reaction was quenched with aq. sat. $NaHCO_3$, and the layers were separated. The org. layer was washed with aq. HCl (1M), the aq. layers were reextracted with CH_2Cl_2 (2x) and the combined org. layers were dried ($MgSO_4$ or Na_2SO_4), filtered and evaporated under reduced pressure. The products were further purified by column chromatography.

General procedure for the amide coupling using BOP.



To a solution of the carboxylic acid (1.0 eq) and the amine (1.0 eq) in THF (c = 0.15-0.4 mol/L) at RT, Et_3N (2.0 eq) was added. The solution was cooled to 0°C and BOP (1.3 eq) was added portion-wise. The mixture was stirred at 0°C for further 2 h before it was warmed to RT and stirred until TLC indicated full conversion. The reaction was quenched with water and THF removed by evaporation under reduced pressure. The aq. residue was extracted with CH_2Cl_2 (3x), and org. layers were washed with aq. sat. $NaHCO_3$, combined, dried ($MgSO_4$ or Na_2SO_4), filtered and evaporated under reduced pressure. The products were further purified by column chromatography.

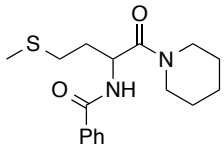
***N*-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.23)**



The reaction was performed according to the general procedure using BOP. Purification by column chromatography (EtOAc/pentane 1/2 to 1/1) yielded the title compound **2.23** (78 mg, 56%) as a white solid.

***R*$_f$** = 0.36 (EtOAc/pentane 1/1); **M.p.** = 126.0°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.86–7.80 (m, 2H), 7.53–7.47 (m, 1H), 7.46–7.40 (m, 2H), 7.22 (br d, J = 8.1 Hz, 1H), 5.25 (td, J = 8.1, 4.4 Hz, 1H), 3.62–3.48 (m, 2H), 3.42 (dq, J = 14.4, 7.1 Hz, 1H), 3.27 (dq, J = 14.1, 7.1 Hz, 1H), 2.68–2.51 (m, 2H), 2.15–2.05 (m, 1H), 2.11 (s, 3H), 2.05–1.93 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.9, 167.0, 134.0, 131.9, 128.7, 127.3, 48.8, 42.2, 40.7, 33.7, 30.4, 15.9, 14.7, 13.0; **HRMS ESI** calcd. for $[C_{16}H_{25}N_2NaO_2S]^+$ $[M+Na]^+$: 331.1451; found: 331.1451; **IR** ν = 3327, 2968, 2919, 1662, 1616, 1531, 1490, 1462, 1431, 1365, 1306, 1263, 1218, 1138, 1083, 955, 807, 715, 632 cm^{-1}.

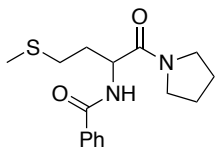
***N*-(4-(methylthio)-1-oxo-1-(piperidin-1-yl)butan-2-yl)benzamide (2.24)**



The reaction was performed according to the general procedure using EDC·HCl. Purification by recrystallization from *t*BME yielded the desired title compound **2.24** (410 mg, quant.).

***R*$_f$** = 0.18 (EtOAc/pentane 1/1); **M.p.** = 123.0°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.86–7.80 (m, 2H), 7.55–7.47 (m, 1H), 7.46–7.40 (m, 2H), 7.35 (br d, J = 7.2 Hz, 1H), 5.30 (ddd, J = 7.8, 4.2, 4.2 Hz, 1H), 3.67–3.50 (m, 4H), 2.69–2.48 (m, 2H), 2.19–2.09 (m, 1H), 2.10 (s, 3H), 1.99–1.86 (m, 1H), 1.73–1.52 (m, 6H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.6, 167.0, 134.1, 131.8, 128.7, 127.2, 48.7, 46.8, 43.6, 33.4, 30.3, 26.7, 25.7, 24.6, 15.8; **HRMS ESI** calcd. for $[C_{17}H_{24}N_2NaO_2S]^+$ $[M+Na]^+$: 343.1451; found: 343.1447; **IR** ν = 3302, 2941, 2858, 1631, 1536, 1467, 1442, 1307, 1246, 1138, 1086, 1011, 695, 652 cm^{-1}.

_N_-(4-(methylthio)-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)benzamide (2.25)

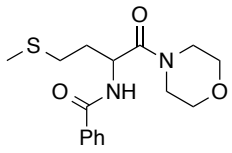


The reaction was performed according to the general procedure using EDC·HCl. No column chromatography was necessary. In this way the title compound **2.25** (116 mg, 96%) was isolated as a white solid.

The analytical data matched those reported in the literature: J. Gardiner, A. D. Abell, *Org. Biomol. Chem.* **2004**, *2*, 2365–2370.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.54–7.48 (m, 1H), 7.47–7.41 (m, 2H), 7.27 (br d, J = 7.7 Hz, 1H), 5.13 (ddd, J = 7.9, 5.1, 5.1 Hz, 1H), 3.78 (ddd, J = 10.2, 6.6, 6.6 Hz, 1H), 3.64–3.43 (m, 3H), 2.70–2.53 (m, 2H), 2.23–2.11 (m, 1H), 2.12 (s, 3H), 2.10–1.96 (m, 3H), 1.97–1.86 (m, 2H).

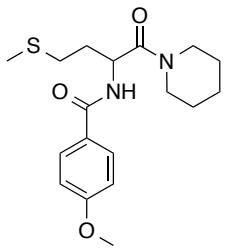
_N_-(4-(methylthio)-1-morpholino-1-oxobutan-2-yl)benzamide (2.26)



The reaction was performed according to the general procedure using EDC·HCl. No column chromatography was necessary. In this way the title compound **2.26** (110 mg, 92%) was isolated as a white solid.

***R*$_f$** = 0.15 (EtOAc/cHex 1/1); **M.p.** = 128.0°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H), 7.55–7.49 (m, 1H), 7.48–7.41 (m, 2H), 7.19 (br d, J = 7.7 Hz, 1H), 5.30 (ddd, J = 7.9, 4.6, 4.6 Hz, 1H), 3.80–3.57 (m, 8H), 2.70–2.51 (m, 2H), 2.17–2.06 (m, 1H), 2.11 (s, 3H), 2.03–1.91 (m, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.2, 167.1, 133.9, 132.0, 128.7, 127.2, 66.9, 66.8, 48.3, 46.3, 42.8, 33.2, 30.4, 15.9; **HRMS ESI** calcd. for $[C_{16}H_{22}N_2NaO_3S]^+$ $[M+Na]^+$: 345.1243; found: 345.1240; **IR** ν = 3271, 3058, 2973, 2920, 2857, 1655, 1619, 1533, 1435, 1351, 1302, 1241, 1115, 1070, 1033, 865, 697, 669 cm^{-1}.

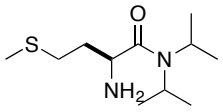
4-methoxy-*N*-(4-(methylthio)-1-oxo-1-(piperidin-1-yl)butan-2-yl)benzamide (2.27)



The reaction was performed according to the general procedure using EDC·HCl. Purification by column chromatography (EtOAc/pentane 1/2) yielded the title compound **2.27** (78 mg, 56%) as a white solid.

***R*$_f$** = 0.24 (EtOAc/pentane 1/1); **M.p.** = 143.8°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.84–7.75 (m, 2H), 7.20 (br d, J = 7.6 Hz, 1H), 6.97–6.88 (m, 2H), 5.27 (td, J = 7.8, 4.2 Hz, 1H), 3.85 (s, 3H), 3.68–3.50 (m, 4H), 2.68–2.49 (m, 2H), 2.16–2.06 (m, 1H), 2.10 (s, 3H), 1.96–1.85 (m, 1H), 1.63 (m, 6H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.7 166.48, 162.4, 129.1, 126.4, 113.8, 55.5, 48.6, 46.7, 43.5, 33.4, 30.3, 26.6, 25.7, 24.5, 15.8; **HRMS ESI** calcd. for $[C_{18}H_{26}N_2NaO_3S]^+$ $[M+Na]^+$: 373.1556; found: 373.1556; **IR** ν = 3286, 2942, 2855, 1610, 1543, 1504, 1463, 1440, 1298, 1249, 1180, 1139, 1107, 1015, 954, 845, 771, 658 cm^{-1}.

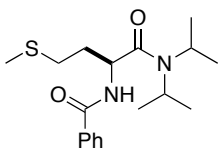
(*S*)-2-amino-*N*,*N*-diisopropyl-4-(methylthio)butanamide (2.29)



The reaction was performed according to the general procedure using BOP and Boc-L-Met-OH. Purification by column chromatography (EtOAc/pentane 1/3) yielded the Boc protected amide, which was dissolved in MeOH (1 mL). To the solution aq. HCl conc. (few drops) was added and the reaction was stirred at RT for 3 h. The reaction mixture was neutralized with NaOH 1M and extracted with CH_2Cl_2 (3x5 mL). The combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the title compound **2.29** (52 mg, 26%).

***R*$_f$** = 0.18 (CH_2Cl_2/MeOH 20/1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.01 (p, J = 6.6 Hz, 1H), 3.71 (dd, J = 8.7, 3.4 Hz, 1H), 3.44 (br s, 1H), 2.70–2.50 (m, 2H), 2.05 (s, 3H), 1.86 (br s, 2H), 1.74 (dddd, J = 14.0, 8.2, 7.2, 3.7 Hz, 1H), 1.61 (dddd, J = 14.1, 8.8, 7.1, 5.2 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H) 1.16 (d, J = 7.6 Hz, 7H); **IR** ν = 3368, 292966, 2929, 1630, 1441, 1369, 1327, 1210, 1135, 1040, 958, 920, 873, 847 cm^{-1}.

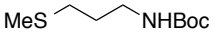
(*S*)-*N*-(1-(diisopropylamino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.30)



To a solution of amine **2.29** (200 mg, 0.86 mmol) in CH_2Cl_2 (3 mL) *N,N*-diisopropylethylamine (0.18 mL, 1.1 mmol) was added. To the colourless solution benzoyl chloride (0.12 mL, 1.0 mmol) was added dropwise. The mixture was stirred at RT for 18 h. Aq. citric acid (1M) was added and the mixture was extracted with CH_2Cl_2 (3x). The org. layers were washed with water, aq. sat. $NaHCO_3$ and the combined org. layers were dried ($MgSO_4$), filtrated and evaporated under reduced pressure. Purification by recrystallization from EtOAc/pentane 1/4 and Et_2O/pentane gave the desired product **2.30** (230 mg, 79%) as a white powder.

***R*$_f$** = 0.24 (EtOAc/pentane 1/4); **M.p.** = 141.4°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.87–7.82 (m, 2H), 7.54–7.47 (m, 1H), 7.46–7.40 (m, 3H), 5.19 (td, *J* = 7.5, 3.8 Hz, 1H), 4.16 (p, *J* = 6.6 Hz, 1H), 3.56–3.44 (m, 1H), 2.63 (ddd, *J* = 13.1, 9.6, 6.6 Hz, 1H), 2.53 (ddd, *J* = 13.1, 9.7, 5.1 Hz, 1H), 2.18–2.08 (m, 1H), 2.10 (s, 3H), 1.91 (dddd, *J* = 14.3, 9.6, 7.6, 5.1 Hz, 1H), 1.41 (d, *J* = 3.1 Hz, 3H), 1.40 (d, *J* = 3.1 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.9, 166.8, 134.2, 131.8, 128.7, 127.3, 49.8, 48.7, 46.5, 33.7, 31.8, 30.1, 21.4, 20.8, 20.3, 15.9, 11.3; **IR** ν = 3256, 3068, 2973, 2935, 1652, 1616, 1546, 1473, 1438, 1368, 1337, 1325, 1295, 1210, 1157, 1136, 1088, 1044, 801, 737, 690, 658, 610 cm^{-1}.

***tert*-butyl (3-(methylthio)propyl)carbamate (2.40)**

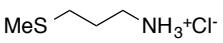


To a solution of *tert*-butyl (3-chloropropyl)carbamate (**2.39**, 165 mg, 0.85 mmol) in EtOH (2 mL) sodium methanethiolate (153 mg, 2.0 mmol) was added and the white suspension was heated to 50°C and stirred for 18 h. Then it was filtrated over silica, washed with Et_2O and evaporated under reduced pressure to yield the desired thioether **2.40** (148 mg, 85%).

The analytical data matched those reported in the literature: Y. Yoshimi, T. Itou, M. Hatanaka, *Chem. Commun.* **2007**, 5244–5246.

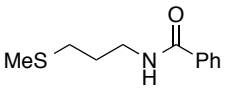
^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.62 (s br, 1H), 3.22 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.78 (p, *J* = 7.0 Hz, 2H), 1.44 (s, 9H).

3-(methylthio)propan-1-aminium chloride (2.41)



To a solution of thioether **2.40** (140 mg, 0.68 mmol) in THF (3 ml) aq. conc. HCl (1 mL) was added and the mixture was heated to 50°C for 45 minutes. The clear solution was evaporated under reduced pressure to yield the ammonium salt **2.41** (93 mg, 96%), which was used without further purification in the next step.

***N*-(3-(methylthio)propyl)benzamide (2.42)**

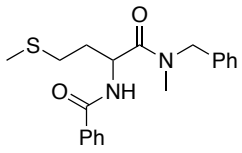


To a suspension of the ammonium salt **2.41** (93 mg, 0.66 mmol) in toluene (2 mL), MeCN (1 mL) and Et_3N (0.4 mL) at 50°C, benzoic anhydride (312 mg, 1.31 mmol) was added and the reaction was stirred for 5 h at 60°C. The MeCN was evaporated under reduced pressure and the residue was treated with water and basified with aq. conc. NaOH, extracted with Et_2O (3x). The org. layers were washed with aq. HCl (1M), and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatrography (Et_2O/pentane 1/3 to pure Et_2O) gave the desired amide **2.42** (90 mg, 66%).

The analytical data matched those reported in the literature: J. Barluenga, F. Foubelo, F. J. Fañanás, M. Yus, *Tetrahedron* **1989**, *45*, 2183–2192.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80–7.74 (m, 2H), 7.51–7.38 (m, 3H), 6.53 (br s, 1H), 3.58 (q, J = 6.4 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 2.12 (s, 3H), 1.94 (ap, J = 6.8 Hz, 2H).

***N*-(1-(benzyl(methyl)amino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.49)**

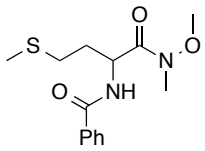


The reaction was performed according to the general procedure using EDC·HCl. Purification by column chromatography (EtOAc/pentane 1/3) yielded the desired title compound **2.49** (75 mg, 53%).

^{1}H-NMR (400 MHz, $CDCl_3$, major/minor rotamer 2/1) δ 7.89-7.79 (m, 3H), 7.56-7.49 (m, 1.5H), 7.48-7.41 (m, 3H), 7.40-7.27 (m, 4.5H), 7.25-7.21 (m, 3H), 7.19 (br d, 1H) 5.41 (ddd, J = 8.1, 4.0, 4.0 Hz, 0.5H), 5.35 (ddd, J = 7.9, 4.4, 4.4 Hz, 1H), 4.77 (d, J = 16.4 Hz, 1H), 4.74 (d, J = 14.6 Hz, 2H), 4.70 (d, J = 16.4 Hz, 1H), 4.50 (d, J = 14.6 Hz, 1H), 3.10 (s, 3H),

2.97 (s, 1.5H), 2.70-2.47 (m, 3H), 2.22-2.11 (m, 1H), 2.10 (s, 3H), 2.04 (s, 0.5H), 2.05-1.93 (m, 1H).

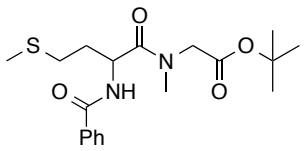
_N_-(1-(methoxy(methyl)amino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.50)



The reaction was performed according to the general procedure using EDC·HCl. No column chromatography was necessary. In this way the title compound **2.50** (50 mg, 52%) was isolated as a white solid.

R_f = 0.39 (EtOAc/cHex 1/1); **M.p.** = 91.7°C; **^{1}H-NMR** (400 MHz, $CDCl_3$, major/minor rotamer 5/1) δ 7.86–7.79 (m, 2.4H), 7.53–7.46 (m, 1.2H), 7.46–7.40 (m, 2.4H), 7.16 (br d, J = 8.3 Hz, 1H), 7.07 (br d, J = 7.4 Hz, 0.2H), 5.38–5.27 (ddd, J = 8.1, 4.8, 4.8 Hz, 1H), 4.88 (ddd, J = 7.1, 5.2, 5.2 Hz, 0.2H), 3.84 (s, 3.6H), 3.24 (s, 3.6H), 2.60 (pt, J = 7.5 Hz, 2.4H), 2.23–2.12 (m, 1.2H), 2.10 (s, 3H), 2.09 (s, 0.6H), 2.07–1.93 (m, 1.2H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.0, 172.2, 167.4, 134.0, 131.9, 128.8, 128.7, 127.3, 62.0, 52.4, 49.3, 32.3, 30.4, 15.7; **HRMS ESI** calcd. for $[C_{14}H_{20}N_2NaO_3S]^+$ $[M+Na]^+$: 319.1087; found: 319.1086; **IR** ν = 3292, 3061, 2911, 1731, 1632, 1538, 1488, 1315, 1188, 1076, 974, 713, 691 cm^{-1}.

***tert*-butyl *N*-(benzoylmethionyl)-*N*-methylglycinate (2.51)**

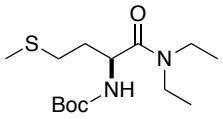


The reaction was performed according to the general procedure using BOP. Purification by column chromatography (EtOAc/pentane 1/2) yielded the title compound **2.51** (310 mg, 69%) as a white solid.

R_f = 0.35 (EtOAc/pentane 1/2); **M.p.** = 112.7°C; **^{1}H-NMR** (400 MHz, $CDCl_3$, major/minor rotamer 3/1) δ 7.86–7.77 (m, 2.6 H), 7.54–7.47 (m, 1.3H), 7.47–7.40 (m, 2.6H), 7.18 (br d, J = 7.8 Hz, 1H), 7.12 (br d, J = 7.5 Hz, 0.3H), 5.36 (td, J = 7.8, 4.5 Hz, 1H), 5.17 (td, J = 7.8, 4.6 Hz, 0.3H), 4.39 (d, J = 18.2 Hz, 0.3H), 4.33 (d, J = 17.1 Hz, 1H), 4.03 (d, J = 18.2 Hz, 0.3H), 3.74 (d, J = 17.1 Hz, 1H), 3.22 (s, 3H), 3.00 (s, 0.9H), 2.70–2.52 (m, 2.6H), 2.27–2.14 (m, 1.3H), 2.12 (s, 3H), 2.09 (s, 0.9H), 2.00 (dq, J = 14.1, 7.9 Hz, 1.3H), 1.46 (s, 11.7H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.3 (0.3C), 172.1, 167.9 (0.3C), 167.7, 167.0, 166.9 (0.3C), 133.9, 133.8 (0.3C), 131.8 (0.3C), 131.8, 128.6 (2.6C), 127.2 (0.6C), 127.2 (2C), 83.0 (0.3C),

82.2, 52.2 (0.3C), 50.6, 48.7, 48.5 (0.3C), 36.6, 35.2 (0.3C), 32.7 (0.3C), 32.6, 30.2 (0.3C), 30.1, 28.1 (3C), 28.1 (0.9C), 15.7, 15.7 (0.3C); **HRMS ESI** calcd. for $[C_{19}H_{28}N_2NaO_4S]^+$ $[M+Na]^+$: 403.1662; found: 403.1666; **IR** ν = 3292, 3047, 2979, 1733, 1651, 1623, 1528, 1489, 1447, 1403, 1366, 1318, 1291, 1227, 1151, 1116, 1029, 846, 800, 725, 691 cm^{-1}.

tert-butyl (_S_)-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (2.52)

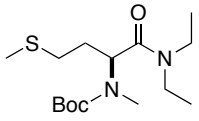


The reaction was performed according to the general procedure using BOP. Purification by column chromatography (EtOAc/pentane 1/1) yielded the title compound **2.52** (665 mg, quant.) as colourless oil.

The analytical data matched those reported in the literature: M. L. Richmond, C. M. Sprout, C. T. Seto, *J. Org. Chem.* **2005**, *70*, 8835–8840.

R_f = 0.37 (EtOAc/pentane 1/3); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.36 (br s, 1H), 4.70 (m, 1H), 3.60–3.41 (m, 2H), 3.35 (dq, J = 14.3, 7.0 Hz, 1H), 3.23 (dq, J = 14.1, 7.1 Hz, 1H), 2.54 (t, J = 7.1, 2H), 2.10 (s, 3H), 1.97–1.78 (m, 2H), 1.43 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H).

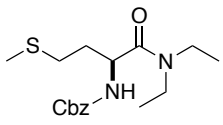
tert-butyl (_S_)-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)(methyl)carbamate (2.53)



The reaction was performed according to the general procedure using BOP. The corresponding carboxylic acid was obtained from methylation of BocMetOH following the literature procedure: S. J. deSolms, S. L. Graham, (Bristol-Myers Squibb Company), US 5439918, **1995**. Purification by column chromatography (EtOAc/pentane 1/2) yielded the title compound **2.53** (80 mg, 86%) as yellow oil.

R_f = 0.68 (EtOAc/pentane 1/1); **^{1}H-NMR** (400 MHz, $CDCl_3$, two rotamer 1/1) δ 5.06 (dd, J = 8.0, 6.6 Hz, 1H), 4.95 (dd, J = 7.8, 6.4 Hz, 1H), 3.49–3.12 (m, 8H), 2.66 (s, 3H), 2.66 (s, 3H), 2.52–2.28 (m, 4H), 2.10–2.0 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 1.89–1.76 (m, 2H), 1.43 (s, 9H), 1.39 (s, 9H), 1.13–1.01 (m, 12H).

benzyl (*S*)-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (2.54)

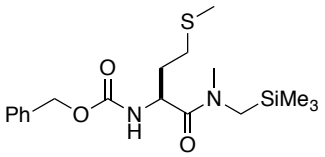


The reaction was performed according to the general procedure using BOP. Purification by column chromatography (EtOAc/pentane 1/2) yielded the title compound **2.54** (580 mg, 99%) as a colourless oil.

R_f = 0.35 (EtOAc/pentane 1/2); $[\alpha]_D$ = -4.8° (*c* = 0.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 5.61 (br d, *J* = 8.5 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 5.00 (d, *J* = 12.3 Hz, 1H), 4.70 (td, *J* = 8.4, 4.5 Hz, 1H), 3.52–3.33 (m, 2H), 3.28 (dq, *J* = 14.4, 7.1 Hz, 1H), 3.15 (dq, *J* = 14.0, 7.1 Hz, 1H), 2.54–2.40 (m, 2H), 2.03 (s, 3H), 1.92–1.73 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.8, 156.2, 136.5, 128.6, 128.3, 128.2, 67.0, 50.0, 42.0, 40.6, 33.7, 30.3, 15.8, 14.7, 13.1; **HRMS ESI** calcd. for $[C_{17}H_{26}N_2NaO_3S]^+$ $[M+Na]^+$: 361.1556; found: 361.1553; **IR** ν = 3233, 3053, 2984, 2930, 1711, 1630, 1541, 1356, 1285, 1255, 1142, 1073, 1041, 975, 790, 734, 690 cm^{-1}.

rac-**2.54**: **M.p.** = 69.7°C (only racemate is crystalline);

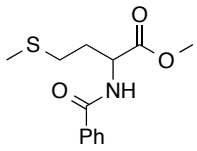
benzyl (*S*)-(1-(methyl((trimethylsilyl)methyl)amino)-4-(methylthio)-1-oxobutan-2-yl)-carbamate (2.76)



The reaction was performed according to the general procedure using BOP. Purification by column chromatography (*t*BME/*c*Hex 1/1) yielded the title compound **2.76** (193 mg, 75%) as colourless oil.

R_f = 0.29 (*t*BME/*c*Hex 1/1); $[\alpha]_D$ = +2.0° (*c* = 0.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$, major rotamer) δ 7.38–7.27 (m, 5H), 5.65 (d, *J* = 8.5 Hz, 1H), 5.10 (s, 2H), 4.84 (td, *J* = 8.3, 4.6 Hz, 1H), 3.11 (s, 3H), 3.07 (d, *J* = 14.9 Hz, 1H), 2.81 (d, *J* = 14.9 Hz, 1H), 2.62–2.48 (m, 2H), 2.10 (s, 3H), 2.00–1.90 (m, 1H), 1.88–1.77 (m, 1H), 0.07 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$, major rotamer) δ 171.4, 157.6, 137.9, 130.0, 129.6, 129.4, 68.3, 51.2, 42.2, 39.2, 34.6, 31.6, 17.2, 0.0; **HRMS ESI** calcd. for $[C_{19}H_{30}N_2O_3SSi]^+$ $[M+H]^+$: 383.1818; found: 383.1817; **IR** ν = 3273, 2953, 1714, 1627, 1497, 1455, 1419, 1247, 1043, 844, 738, 696 cm^{-1}.

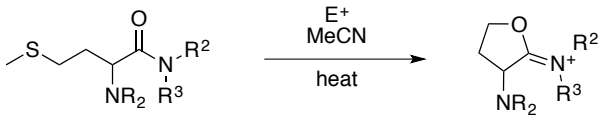
methyl benzoylmethioninate (2.37)



To a solution of carboxylate **2.21** (69 mg, 0.27 mmol) in MeOH (1 mL) at 0°C, thionyl chloride (30 µL, 0.41 mmol) was added slowly and the clear solution was alowed to warm to RT. After stirring for 30 minutes the reaction mixture was evaporated under reduced pressure yielding the ester **2.37** (40 mg, 55%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86–7.79 (m, 2H), 7.57–7.49 (m, 1H), 7.49–7.41 (m, 2H), 6.93 (d, J = 7.7 Hz, 1H), 4.94 (td, J = 7.2, 5.1 Hz, 1H), 3.80 (s, 3H), 2.59 (tt, J = 9.8, 5.2 Hz, 2H), 2.30 (dtd, J = 14.7, 7.4, 5.1 Hz, 1H), 2.19–2.07 (m, 1H).

Methionine to Iminium Lactone Reaction



General procedure for the iminium lactone formation using ethyl iodoacetate

To a solution of the methionine derivative (1.0 eq), in MeCN (c = 0.1 mol/L) at RT, ethyl iodoacetate (1.1 eq) was added. The colourless solution was heated to 50°C for 1 d and the reaction solvent was evaporated under reduced pressure. The respective purification is specified for each product.

General procedure for the iminium lactone formation using Me_3OBF_4 at 80°C

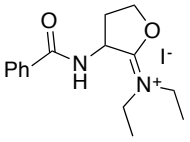
To a solution of the methionine derivative (1.0 eq), in MeCN (c = 0.1– 0.28 mol/L) at RT, Me_3OBF_4 (1.1 eq) was added. The colourless solution was heated to 80°C for 18 h and the reaction solvent was evaporated under reduced pressure. The respective purification is specified for each product.

General procedure for the iminium lactone formation using Me_3OBF_4 at 130°C in the microwave

To a solution of the methionine derivative (1.0 eq), in MeCN (c = 0.15 mol/L) at RT, Me_3OBF_4 (1.1 eq) was added. The colourless solution was heated to 130°C for 0.5 h in a µw

oven and the reaction solvent was evaporated under reduced pressure. The respective purification is specified for each product.

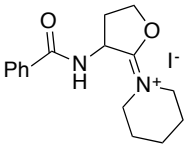
_N_-(3-benzamidodihydrofuran-2(3_H_)-ylidene)-_N_-ethylethanaminium iodide (2.31)



The reaction was performed according to the general procedure using ethyl iodoacetate. The crude product was purified by a quick column chromatography (MeCN) yielding the title compound **2.31** (22 mg, 29%) as colourless oil.

^{1}H-NMR (400 MHz, CD_3CN) δ 9.08 (br d, J = 6.9 Hz, 1H), 7.96–7.87 (m, 2H), 7.50–7.40 (m, 1H), 7.40–7.31 (m, 2H), 5.37 (ddd, J = 11.3, 7.4, 4.5 Hz, 1H), 5.02 (ap td, J = 8.7, 7.7 Hz, 1H), 4.76 (ap td, J = 9.0, 5.1 Hz, 1H), 3.70 (dq, J = 14.3, 7.2 Hz, 1H), 3.57–3.40 (m, 3H), 2.78–2.62 (m, 1H), 2.30 (ap ddt, J = 13.4, 9.0, 4.8 Hz, 1H), 1.12 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); **ESI-MS** m/z = 261.2 $[M\text{-}I]^+$.

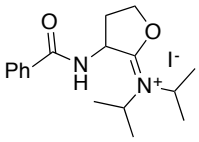
1-(3-benzamidodihydrofuran-2(3_H_)-ylidene)piperidin-1-ium iodide (2.32)



The reaction was performed according to the general procedure using ethyl iodoacetate. The crude product was purified by successive trituration of the residue with MeCN, _t_BME and MeCN yielding the title compound **2.32** (18 mg, 29%) as a brown oil purity.

^{1}H-NMR (400 MHz, CD_3CN) δ 8.89 (br d, J = 4.4 Hz, 1H), 8.05–7.93 (m, 2H), 7.65–7.54 (m, 1H), 7.53–7.40 (m, 2H), 5.39 (ddd, J = 10.9, 7.2, 4.4 Hz, 1H), 5.11 (p q, J = 8.5 Hz, 1H), 4.87 (p td, J = 8.9, 5.0 Hz, 1H), 3.95–3.80 (m, 2H), 3.72–3.55 (m, 2H), 2.92–2.75 (m, 1H), 2.49–2.36 (m, 1H), 1.83–1.57 (m, 4H), 1.53–1.38 (m, 2H); **^{13}C-NMR** (63 MHz, CD_3CN) δ 177.1, 167.9, 133.5, 133.0, 129.7 (2C), 128.7 (2C), 78.9, 52.4, 51.5, 50.3, 31.2, 30.9, 25.8, 23.3; **ESI-MS** m/z = 273.2 $[M\text{-}I]^+$.

_N_-(3-benzamidodihydrofuran-2(3_H_)-ylidene)-_N_-isopropylpropan-2-aminium iodide (2.35)



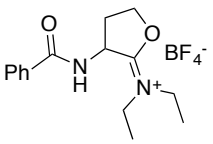
The reaction was performed according to the general procedure using ethyl iodoacetate. The crude product was purified by a quick column chromatography (MeCN) giving title compound **2.35** (46 mg, 63%) as a colourless resin which eventually crystallized.

Or

The reaction was performed according to the general procedure using Me_3OBF_4 at 130°C in the μw oven. Then NaI was added to the reaction mixture and it was stirred for 15 minutes. The colourless mixture was filtered over silica, and the resulting yellow filtrate was evaporated under reduced pressure leaving a yellow solid. The residue triturated with CH_2Cl_2 (4x) to leave a beige solid. The decanted layer was evaporated under reduced pressure and triturated with EtOAc (3x). The combined residues were dried under vacuum to leave the desired iminolactone **2.35** (33 mg, 51%) as beige solid.

^{1}H-NMR (400 MHz, CD_3CN) δ 9.15 (br d, J = 6.6 Hz, 1H), 8.08–7.99 (m, 2H), 7.64–7.55 (m, 1H), 7.54–7.45 (m, 2H), 5.47 (ddd, J = 10.9, 7.1, 3.9 Hz, 1H), 5.17 (ap q, J = 8.6 Hz, 1H), 4.94 (ap td, J = 9.2, 4.5 Hz, 1H), 4.65 (hept, J = 6.6 Hz, 1H), 3.96 (hept, J = 6.8 Hz, 1H), 2.89–2.74 (m, 1H), 2.42–2.30 (m, 1H), 1.42 (d, J = 6.8 Hz, 3H), 1.41 (d, J = 6.8 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); **^{13}C-NMR** (101 MHz, CD_3CN) δ 177.4, 166.8, 132.2, 131.7, 128.4, 127.3, 78.1, 55.4, 52.7, 51.0, 29.1, 18.5, 18.27, 18.25, 17.49; **HRMS ESI** calcd. for $[C_{17}H_{25}N_2O_2]^+$ $[M\text{-}I]^+$: 289.1911; found: 289.1914; **IR** ν = 3450, 3217, 2978, 2361, 2336, 1659, 1523, 1485, 1284, 1047, 905, 719 cm^{-1}; **X-ray**: in the appendix.

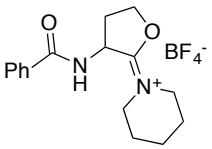
_N_-(3-benzamidodihydrofuran-2(3_H_)-ylidene)-_N_-ethylethanaminium tetrafluoroborate (2.55)



The reaction was performed according to the general procedure using Me_3OBF_4 at 130°C in the μw oven. The crude product was purified by two quick column chromatographies (MeCN and MeCN/_t_BME 1/2) yielding title compound **2.55** (105 mg, 47%) as colourless oil.

^{1}H-NMR (400 MHz, CD_3CN) δ 8.16 (d, J = 7.2 Hz, 1H), 7.88–7.82 (m, 2H), 7.65–7.58 (m, 1H), 7.56–7.48 (m, 2H), 5.27 (ddd, J = 10.7, 7.2, 4.5 Hz, 1H), 5.10 (td, J = 8.7, 7.5 Hz, 1H), 4.90 (td, J = 9.0, 5.1 Hz, 1H), 3.74–3.56 (dq, J = 19.6, 7.1 Hz, 4H), 2.86 (dddd, J = 13.5, 10.5, 9.1, 7.4 Hz, 1H), 2.41 (ddt, J = 13.5, 8.7, 5.1 Hz, 1H), 1.27 (t, J = 7.3 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, CD_3CN) δ 178.8, 168.2, 133.7, 133.1, 129.9 (2C), 128.4 (2C), 79.1, 53.1, 47.6, 46.6, 31.3, 12.4, 12.0; **^{19}F-NMR** (376 MHz, CD_3CN) δ –151.67; **^{11}B-NMR** (128 MHz, CD_3CN) δ –1.12; **ESI-MS** m/z = 261.2 $[M\text{-}BF_4]^+$.

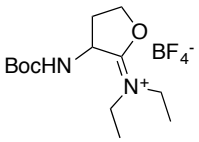
1-(3-benzamidodihydrofuran-2(3*H*)-ylidene)piperidin-1-ium tetrafluoroborate (2.56)



The reaction was performed according to the general procedure using Me_3OBF_4 at 80°C. The crude product was not further purified yielding the title compound **2.56** (59 mg, quant) was isolated as colourless oil.

^{1}H-NMR (400 MHz, CD_3CN) δ 8.15 (d, J = 7.1 Hz, 1H), 7.91–7.81 (m, 2H), 7.66–7.59 (m, 1H), 7.55–7.48 (m, 2H), 5.22 (ddd, J = 10.9, 7.1, 4.3 Hz, 1H), 5.08 (td, J = 8.7, 7.6 Hz, 1H), 4.89 (td, J = 9.0, 5.0 Hz, 1H), 3.97–3.86 (m, 1H), 3.83–3.74 (m, 1H), 3.68–3.56 (m, 2H), 2.90–2.77 (m, 1H), 2.47–2.37 (m, 1H), 1.83–1.59 (m, 5H), 1.50–1.37 (m, 1H); **^{13}C-NMR** (63 MHz, CD_3CN) δ 177.0, 168.3, 133.7, 133.1, 129.9, 128.4, 78.9, 52.8, 51.3, 50.24, 31.2, 26.0, 23.4; **^{19}F-NMR** (376 MHz, CD_3CN) δ –151.33; **ESI-MS** m/z = 273.2 $[M\text{-}BF_4]^+$.

***N*-(3-((*tert*-butoxycarbonyl)amino)dihydrofuran-2(3*H*)-ylidene)-*N*-ethylethanaminium tetrafluoroborate (2.60)**

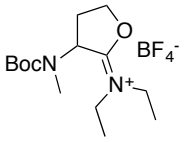


The reaction was performed according to the general procedure using Me_3OBF_4 at 80°C. The crude product was purified by a quick column chromatography (MeCN/*t*BME 4/1) yielding the title compound **2.60** (273 mg, 70%) as colourless oil.

^{1}H-NMR (400 MHz, CD_3CN) δ 6.41 (br d, J = 7.7 Hz, 1H), 5.09–4.95 (m, 2H), 4.82 (ap td, J = 8.9, 5.8 Hz, 1H), 3.83–3.55 (m, 4H), 2.91–2.71 (m, 1H), 2.43–2.25 (m, 1H), 1.46 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, CD_3CN) δ 179.0,

156.0, 82.0, 78.5, 53.6, 47.4, 46.6, 31.1, 28.3 (3C), 12.5, 11.8; **^{19}F-NMR** (376 MHz, CD_3CN) δ –152.23; **^{11}B-NMR** (128 MHz, CD_3CN) δ –1.19; **ESI-MS** m/z = 258.2 $[M\text{-}BF_4]^+$.

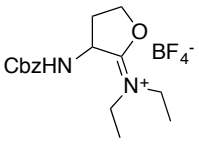
_N_-(3-((_tert_-butoxycarbonyl)(methyl)amino)dihydrofuran-2(3_H_)-ylidene)-_N_-ethylethanaminium tetrafluoroborate (2.61)



The reaction was performed according to the general procedure using Me_3OBF_4 at 80°C. The crude product was purified by a quick column chromatography (MeCN/*t*BME 2/3) yielding the title compound **2.61** (44 mg, 50%) as colourless oil.

^{1}H-NMR (400 MHz, CD_3CN) δ 4.96 (td, J = 8.8, 7.4 Hz, 1H), 4.88–4.75 (m, 2H), 3.70–3.46 (m, 4H), 2.97 (s, 3H), 2.86–2.71 (m, 1H), 2.31 (ddt, J = 13.6, 9.3, 4.8 Hz, 1H), 1.44 (s, 9H), 1.24 (t, J = 7.2, 6H); **ESI-MS** m/z = 271.2 $[M\text{-}BF_4]^+$.

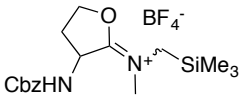
_N_-(3-(((benzyloxy)carbonyl)amino)dihydrofuran-2(3_H_)-ylidene)-_N_-ethylethanaminium tetrafluoroborate (2.62)



The reaction was performed according to the general procedure using Me_3OBF_4 at 130°C in the μw oven. The crude product was purified by trituration and decanting with toluene. In this way the title compound **2.62** was isolated as colourless oil (50 mg, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (br s, 5H), 6.59 (d, J = 7.8 Hz, 1H), 5.06–4.92 (m, 3H), 4.89 (q, J = 8.2 Hz, 1H), 4.77–4.65 (m, 1H), 3.57–3.43 (m, 4H), 2.78–2.62 (m, 1H), 2.30–2.17 (m, 1H), 1.12 (t, J = 7.3 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 177.7, 155.7, 136.3, 128.6, 128.3, 128.2, 77.7, 67.4, 53.0, 46.6, 45.8, 30.1, 11.5, 10.9; **^{19}F-NMR** (376 MHz, $CDCl_3$) δ –152.0; **^{11}B-NMR** (128 MHz, $CDCl_3$) δ –1.14; **ESI-MS** m/z = 291.2 $[M\text{-}BF_4]^+$.

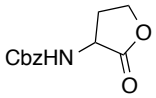
(*E,Z*)-*N*-(3-(((benzyloxy)carbonyl)amino)dihydrofuran-2(3H)-ylidene)-N-methyl-1-(trimethylsilyl)methanaminium tetrafluoroborate (2.77)



The reaction was performed according to the general procedure using Me_3OBF_4 at 90°C in the μw oven. The reaction mixture was evaporated under reduced pressure yielding the title compound **2.77** (25 mg, 84%) as colourless oil.

^{1}H-NMR (400 MHz, CD_3CN, major isomer) δ 7.57–7.42 (m, 5H), 6.79 (br d, J = 7.6 Hz, 1H), 5.25 (d, J = 12.4 Hz, 1H), 5.21 (d, J = 12.3 Hz, 1H), 5.15–5.01 (m, 2H), 4.86 (td, J = 8.8, 5.9 Hz, 1H), 3.49 (d, J = 14.7 Hz, 1H), 3.37 (s, 3H), 3.22 (d, J = 14.7, Hz, 1H), 2.97–2.84 (m, 1H), 2.54–2.43 (m, 1H), 0.24 (s, 9H); **^{13}C-NMR** (101 MHz, CD_3CN, major isomer) δ 176.1, 156.6, 137.3, 129.5, 129.2, 129.0, 128.8, 78.1, 68.2, 53.7, 47.3, 42.0, 31.3, –2.1; **^{19}F-NMR** (376 MHz, CD_3CN) δ –151.7; **HRMS ESI** calcd. for $[C_{17}H_{27}N_2O_3Si]^+$ $[M\text{-}BF_4]^+$: 335.1786; found: 335.1780; **IR** ν = 3372, 2956, 1695, 1523, 1455, 1419, 1252, 1045, 847, 741, 698 cm^{-1}.

benzyl (2-oxotetrahydrofuran-3-yl)carbamate (2.63)

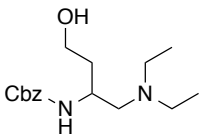


To a solution of imidate **2.62** (58 mg, 0.16 mmol) in MeOH (1 mL) silica gel was added and the suspension was stirred for 2 h at RT. A drop of H_2O was added and the reaction was heated to 50°C and stirred for another 18 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc/pentane 1/1) to yield the lactone **2.63** (17 mg, 47%).

The analytical data matched those reported in the literature: M. S. Lall, C. Karvellas, J. C. Vederas, *Org. Lett.* **1999**, *1*, 803–806.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 5.41 (br s, 1H), 5.13 (s, 2H), 4.42 (q, J = 14.0, 11.5 Hz, 2H), 4.24 (ddd, J = 10.3, 9.6, 6.0 Hz, 1H), 2.85–2.70 (m, 1H), 2.21 (qd, J = 11.7, 9.1 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.9, 156.1, 135.9, 128.6 (2C), 128.3, 128.2 (2C), 67.4, 65.8, 50.5, 30.5; **HRMS ESI** calcd. for $[C_{12}H_{13}NO_4Na]^+$ $[M+Na]^+$: 258.0737; found: 258.0737.

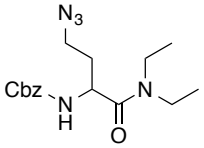
benzyl (1-(diethylamino)-4-hydroxybutan-2-yl)carbamate (2.64)



To a solution of the iminium ether **2.62** (49.2 mg, 0.13 mmol) in MeOH (1 mL) at RT, sodium borohydride (9.8 mg, 0.26 mmol) was added and the colourless solution was stirred for 16 h before it was poured into aq. sat. $NaHCO_3$ (8 mL). The aq. layer was extracted with EtOAc (3x4 mL), and the combined org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was dissolved in a minimum amount of CH_2Cl_2. Then, *t*BME was added and the CH_2Cl_2 was evaporated under reduced pressure to give a white suspension. The suspension was filtered, washed with *t*BME and the filtrate was evaporated under reduced pressure to give the tertiary amine **2.64** (31 mg, 81%) as a colourless oil.

R_f = 0.28 (CH_2Cl_2/MeOH 20/1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.40–7.27(m, 5H), 5.51 (br s, 1H), 5.15–5.0 (m, 1H), 5.09 (q, J = 12.2 Hz, 2H), 3.89–3.75 (m, 1H), 3.72–3.56 (m, J = 4.6 Hz, 2H), 2.65 (dq, J = 14.2, 7.2 Hz, 2H), 2.59–2.47 (m, 3H), 2.46–2.34 (m, 1H), 1.83–1.66 (m, 2H), 1.03 (t, J = 7.2 Hz, 6H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 156.5, 136.5, 128.6 (2C), 128.3, 128.2 (2C), 66.9, 59.6, 58.2, 48.8, 47.1 (2C), 39.1, 11.1 (2C); **HRMS ESI** calcd. for $[C_{16}H_{27}N_2O_3]^+$ $[M+H]^+$: 295.2016; found: 295.2018; **IR** ν = 3314, 2967, 2927, 2849, 1695, 1531, 1455, 1377, 1309, 1244, 1214, 1138, 1055, 1028, 736, 696 cm^{-1}.

benzyl (4-azido-1-(diethylamino)-1-oxobutan-2-yl)carbamate (2.65)

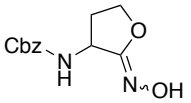


To a solution of iminium ether **2.62** (45.0 mg, 0.12 mmol) in MeCN (0.8 mL) at RT, sodium azide (15.6 mg, 0.24 mmol) was added and the suspension was stirred for 24 h at RT. The resulting milky, thick suspension suspension was diluted with EtOAc (2 mL), filtered over Celite and evaporated under reduced pressure. Purification by column chromatography (*t*BME/*c*Hex 1/1) gave the desired azide **2.65** (14 mg, 35%) as colourless solid.

R_f = 0.28 (*t*BME/*c*Hex 1/1); **M.p.** = 62.2°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 5.70 (d, J = 8.9 Hz, 1H), 5.18–5.02 (m, 2H), 4.73 (td, J = 8.6, 4.0 Hz, 1H), 3.52 (tt, J = 12.7, 6.3 Hz, 1H), 3.47–3.31 (m, 4H), 3.23 (dq, J = 14.0, 7.1 Hz, 1H), 1.97–1.82 (m, 1H), 1.86–1.72 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.5, 156.2, 136.4, 128.7 (2C), 128.3, 128.2 (2C), 67.1, 48.6, 48.0, 42.0, 40.6,

33.6, 14.7, 13.0; **HRMS ESI** calcd. for $[C_{16}H_{24}N_5O_3]^+$ $[M+H]^+$: 334.1874; found: 334.1871; **IR** ν = 3310, 3224, 3062, 3034, 2981, 2360, 2342, 2086, 1777, 1703, 1633, 1542, 1497, 1454, 1441, 1385, 1254, 1170, 1098, 1073, 1024, 980, 946, 908, 848, 823, 779, 743, 694, 669 cm^{-1}.

benzyl (2-(hydroxyimino)tetrahydrofuran-3-yl)carbamate (2.66)



To the reaction mixture of the freshly prepared imium ether **2.62** (55 mg, 0.15 mmol) in MeCN (1 mL) at RT, aq. hydroxylamine (50 wt.%, 45 µL, 0.73 mmol) was added and the mixture was stirred for 24 h. The reaction was quenched with aq. HCl (1M, 5 mL), extracted with EtOAc (3x5 mL) and the org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (*t*BME) gave product **2.66** (8.0 mg, 22%) as a white solid and homoserine lactone **2.63** (6.0 mg, 18%).

R_f = 0.36 (*t*BME); **M.p.** = 141.5 °C; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.44–7.24 (m, 5H), 5.10 (s, 2H), 4.75 (t, *J* = 8.2 Hz, 1H), 4.41 (td, *J* = 8.3, 3.9 Hz, 1H), 4.25 (td, *J* = 8.8, 6.5 Hz, 1H), 2.47 (dddd, *J* = 12.2, 8.0, 6.5, 4.1 Hz, 1H), 2.08 (dtd, *J* = 12.5, 8.6, 8.0 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 158.0, 156.1, 136.2, 128.7 (2C), 128.4, 128.3 (2C), 69.8, 67.4, 50.7, 32.5; **HRMS ESI** calcd. for $[C_{12}H_{15}N_2O_4]^+$ $[M+H]^+$: 251.1026; found: 251.1025; **IR** ν = 3341, 3034, 2911, 1703, 1650, 1540, 1455, 1392, 1361, 1308, 1292, 1254, 1225, 1176, 1080, 1013, 987, 958, 935, 880, 848, 828, 788, 743, 691, 651 cm^{-1}.

benzyl (2-((benzyloxy)imino)tetrahydrofuran-3-yl)carbamate (2.67)

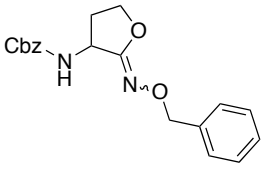
and

benzyl (4-oxo-1,10-diphenyl-2,9-dioxa-3,8-diazadecan-5-yl)carbamate (2.68)

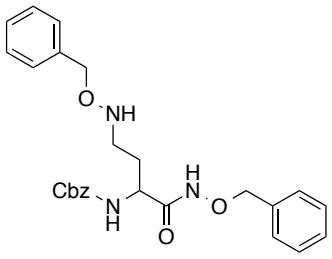
To a solution of iminium ether **2.62** (45.0 mg, 0.12 mmol) in MeCN (0.8 mL) at RT, O-benzylhydroxylamine (30 µl, 0.24 mmol) was added and the suspension was stirred for 48 h at RT. The mixture was quenched with aq. HCl (1M, 3 mL), extracted with EtOAc (3x5 mL) and the org. layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure.

Purification by column chromatography (*t*BME/*c*Hex) gave a inseparable mixture of the products **2.67** (14 mg, 36%, calc. from NMR) and **2.68** (20 mg, 35%, calc. from NMR).

For sake of characterization the two products were separated by recrystallization from hot *c*Hex to give pure **2.67** (12 mg). The filtrate was evaporated and purified further by column chromatography (toluene/EtOAc 3/1) to give product **2.68** (9 mg).

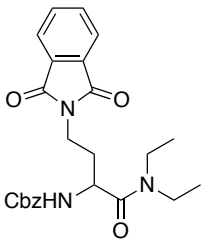


2.67: R_f = 0.23 (*t*BME/cHex 1/1), 0.35 (toluene/EtOAc 3/1); **M.p.** = 105.7 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 10H), 5.25–5.15 (m, 1H), 5.12 (s, 2H), 4.99 (s, 2H), 4.66 (q, J = 7.2, 6.5 Hz, 1H), 4.45 (td, J = 8.6, 2.5 Hz, 1H), 4.23 (td, J = 9.7, 5.8 Hz, 1H), 2.78–2.63 (m, 1H), 2.04 (dtd, J = 12.4, 10.1, 8.4 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 156.6, 156.0, 137.5, 136.2, 128.7 (2C), 128.6 (2C), 128.49 (2C), 128.45, 128.4 (2C), 128.1, 80.1, 69.9, 67.3, 51.0, 32.7; **HRMS ESI** calcd. for $[C_{19}H_{21}N_2O_4]^+$ $[M+H]^+$: 341.1496; found: 341.1493; **IR** ν = 3285, 3031, 2964, 2927, 2361, 2341, 1683, 1537, 1454, 1389, 1357, 1288, 1248, 1225, 1178, 1081, 1043, 983, 917, 883, 834, 781, 753, 741, 694 cm^{-1}.



2.68: R_f = 0.23 (*t*BME/cHex 1/1), 0.22 (toluene/EtOAc 3/1); **^{1}H-NMR** (400 MHz, $CDCl_3$, major rotamer) δ7.77 (s, 1H), 7.41–7.27 (m, 15H), 5.56 (d, J = 8.7 Hz, 1H), 5.14 (d, J = 12.3 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 5.0–4.91 (m, 1H), 4.95 (s, 2H), 4.82 (d, J = 11.1 Hz, 1H), 4.78 (d, J = 11.1 Hz, 1H), 3.72–3.59 (m, 2H), 2.98 (t, J = 6.8 Hz, 1H), 2.17–2.06 (m, 1H), 1.71–1.61 (m, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 156.9, 155.5, 137.3, 136.4, 135.2, 129.4, 128.9, 128.8, 128.7, 128.5, 128.5, 128.4, 128.3, 128.2, 78.9, 76.5, 67.3, 58.7, 46.4, 37.7; **HRMS ESI** calcd. for $[C_{26}H_{30}N_3O_5]^+$ $[M+H]^+$: 464.2180; found: 464.2177; **IR** ν = 3406, 3304, 3062, 3032, 2928, 2877, 2362, 2342, 1704, 1627, 1498, 1454, 1363, 1227, 1144, 1046, 1026, 910, 735, 696 cm^{-1}.

benzyl (1-(diethylamino)-4-(1,3-dioxoisoindolin-2-yl)-1-oxobutan-2-yl)carbamate (2.69)



To a solution of iminium ether **2.62** (45.0 mg, 0.12 mmol) in MeCN (0.8 mL) at RT, potassium phtalimide (44.1 mg, 0.24 mmol) was added. The suspension was stirred for 2 h at RT quickly turning into a orange, thick suspension. The reaction was quenched with water (4 mL), extracted with EtOAc (3x3 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by column chromatography (*t*BME/*c*Hex 1/1) gave the product **2.69** (10 mg, 19%) as a colourless resin.

R_f = 0.15 (*t*BME/*c*Hex 1/1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 5.4, 3.1 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 7.40–7.28 (m, 5H), 5.77 (d, J = 8.7 Hz, 1H), 5.10 (s, 2H), 4.71 (td, J = 8.5, 4.1 Hz, 1H), 3.88–3.73 (m, 2H), 3.50 (dq, J = 14.3, 7.2 Hz, 1H), 3.37 (dp, J = 22.4, 7.6 Hz, 2H), 3.17 (dq, J = 14.0, 7.0 Hz, 1H), 2.20–2.06 (m, 1H), 2.04–1.90 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.2, 168.3, 156.2, 136.5, 134.1, 132.3, 128.6, 128.2, 128.1, 123.4, 67.1, 49.3, 42.0, 40.6, 34.7, 31.9, 14.6, 13.0; **HRMS ESI** calcd. for $[C_{24}H_{28}N_3O_5]^+$ $[M+H]^+$: 438.2024; found: 438.2031; **IR** ν = 3286, 2973, 2934, 2360, 2341, 1772, 1706, 1633, 1525, 1498, 1446, 1396, 1372, 1242, 1217, 1117, 1047, 966, 869, 718, 697 cm^{-1}.

5 Appendices

5.1 List of Abbreviations, Acronyms and Symbols

Ac	acetyl
AcOH	acetic acid
AIBN	azaisobutyronitrile
Ala	alanine
ap	appearing
aq.	aqueous
BDA	butane-1,2-diacetal
Bn	benzyl
brsm	based on recovered starting material
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
Boc	*tert*-butyloxycarbonyl
br	broad
BSP	1-(Phenylsulfinyl)piperidine
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
c	concentration (g/100 mL)
calc.	calculated
CAM	ceric ammonium molybdate
cat.	catalytic

Cbz	carboxybenzyl
CDI	*clostridium difficile* infection
*c*Hex	cyclohexane
conc.	concentrated
δ	chemical shift
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethlaminosulfur trifluoride
d.r.	diastereomeric ratio
DBU	1,8-diazabicyclo[5,6]undec-7-ene
DCC	*N,N'*-diclohexylcarbodiimide
DCE	1,2-dichloroethane
DEAD	Diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethylsulfide
DNA	desoxyribonucleic acid
DTMBP	2,5-di-*tert*-butyl-4-methylpyridine
e.g.	*exempli gratia*
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimid
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl

Et_3N	triethylamine
Et_2O	diethylether
EtOAc	ethylacetate
EtOH	ethanol
equiv	equivalent
FDA	U.S. food and drug administration
g	gram(s)
Gly	glycine
h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
hv	high vacuum
Hz	hertz (s^{-1})
imid.	imidazole
Ipc	isopinocampheyl
*i*Pr	isopropyl
IR	infra red
J	coupling constant
L	liter(s)
LDA	lithium diisopropylamide
M	molarity (mol/L)
m	multiplett
*m*CPBA	*meta*-chloroperoxybenzoic acid
MDR	multi drug resistant

Me	methyl
MeCN	acetonitrile
MEG	methylene ethylene glycol
MeOH	methanol
Met	methionine
MIC	minimal inhibitory concentration
min	minute(s)
MOM	methoxymethylene
M.p.	melting point
MRSA	methicillin resistant *Streptococcus aureus*
m.s.	molecular sieves
MTB	*mycobacterium tuberculosis*
μw	microwave
m/z	mass per charge
NaHMDS	sodium hexamethyl disilazane
n.d.	not determined
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
NP	normal phase
org.	organic
Ph	phenyl

Phe	phenylalanine
PKS	polyketide synthase
PMP	*para*-methoxyphenyl
PMB	*para*-methoxybenzoyl
PPh_3	triphenylphosphine
ppm	parts per million
PTFAI	*N*-phenyltrifluoroacetimidate
q	quartet
quant.	quantitative
RCM	ring closing metathesis
RT	room temperature
R_f	retention factor
RP	reverse phase
R_t	retention time
RNA	ribonucleic acid
RNAP	RNA polymerase
s	singlet
SAR	structure activity relationship
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
soln.	solution
t	triplet
TBAF	tetrabutylammonium fluoride
*t*BME	*tert*-butylmethylether

TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Trt	trityl
Ts	tosyl
TTBP	2,4,6-tri-*tert*-butylpyridine
tol.	toluene
t_r	retention time
UHPLC	ultra high performance liquid chromatography
UV	ultra violet
ν	wavenumber

5.2 Crystal Structures

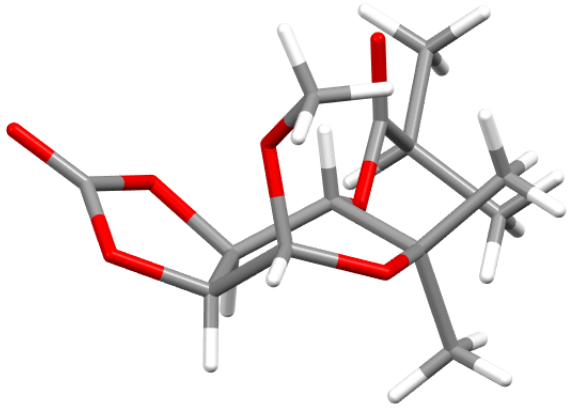


Table 5.1 Crystal data for β-**1.102**

Formula	$C_{13}H_{20}O_7$
Formula weight	288.30 g · Mol^{-1}
Z, calculated density	2, 1.375 Mg · m^{-3}
F(000)	308
Description and size of crystal	colourless needle, 0.020 · 0.030 · 0.190 mm^3
Absorption coefficient	0.950 mm^{-1}
Min/max transmission	0.97 / 0.98
Temperature	123K
Radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	monoclinic, P 2_1
a	7.6012(6) Å
b	6.2321(4) Å
c	14.7178(10) Å
α	90°
β	92.593(5)°
γ	90°
V	696.49(5) $Å^3$
Min/max Θ	5.827° / 68.854°
Number of collected reflections	5345
Number of independent refections	2359 (merging r = 0.033)
Number of observed reflections	2130 (I>2.0σ(I))
Number of refined parameters	182
r	0.0334
rW	0.0427
Goodness of fit	1.1118

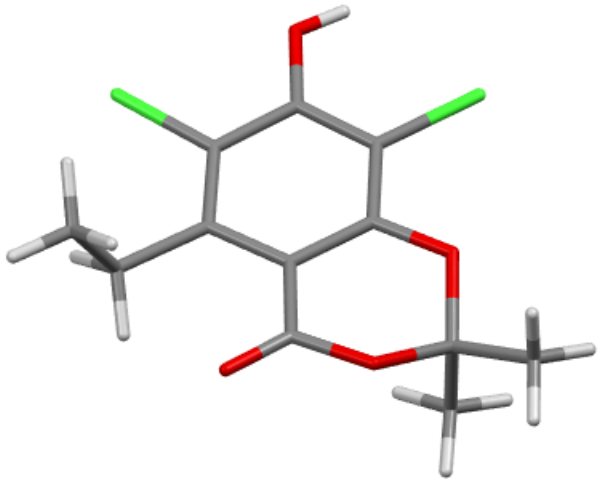


Table 5.2 Crystal data for **1.134**

Formula	$C_{12}H_{12}Cl_2O_4$
Formula weight	291.12 g · Mol^{-1}
Z, calculated density	2, 1.574 Mg · m^{-3}
F(000)	300
Description and size of crystal	colourless prism, 0.13 · 0.20 · 0.25 mm^3
Absorption coefficient	0.531 mm^{-1}
Min/max transmission	0.822 / 0.936
Temperature	160(1)K
Radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	???, ???
a	7.6060(2) Å
b	8.7708(2) Å
c	9.6095(2) Å
α	100.2589(12)°
β	100.4269(14)°
γ	96.0635(13)°
V	614.06(3) $Å^3$
Min/max Θ	2.384° / 30.039°
Number of collected reflections	17761
Number of independent refections	3594 (merging r = 0.0403)
Number of observed reflections	3593 (I > 2σ(I))
Number of refined parameters	170
r	0.0314
rW	0.0820
Goodness of fit	1.045

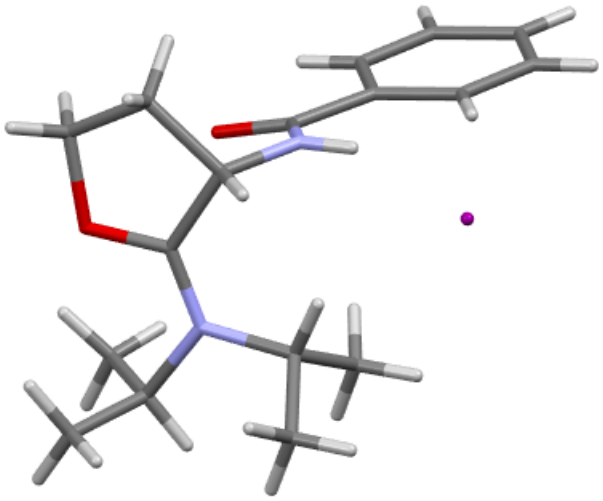


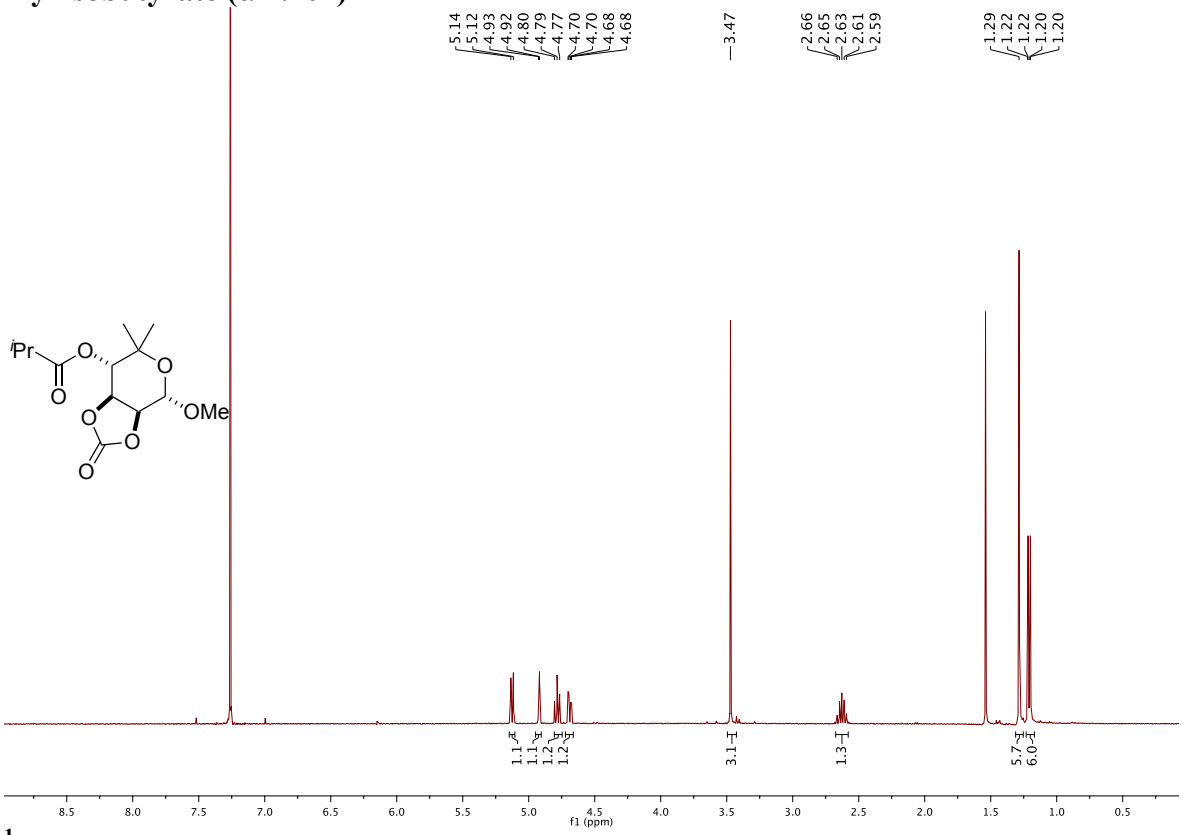
Table 5.3 Crystal data for **2.35**

Formula	$C_{17}H_{25}I_1N_2O_2$
Formula weight	416.30 g · Mol^{-1}
Z, calculated density	4, 1.519 Mg · m^{-3}
F(000)	840
Description and size of crystal	colourless plate, 0.030 · 0.110 · 0.190 mm^3
Absorption coefficient	1.768 mm^{-1}
Min/max transmission	0.82 / 0.95
Temperature	123K
Radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P $2_1/c$
a	11.7141(3) Å
b	14.6710(5) Å
c	11.1342(4) Å
α	90°
β	107.929(2)°
γ	90°
V	1820.57(10) $Å^3$
Min/max Θ	1.827° / 32.578°
Number of collected reflections	22730
Number of independent refections	6575 (merging r = 0.056)
Number of observed reflections	4261 (I>2.0σ(I))
Number of refined parameters	199
r	0.0368
rW	0.0403
Goodness of fit	1.0047

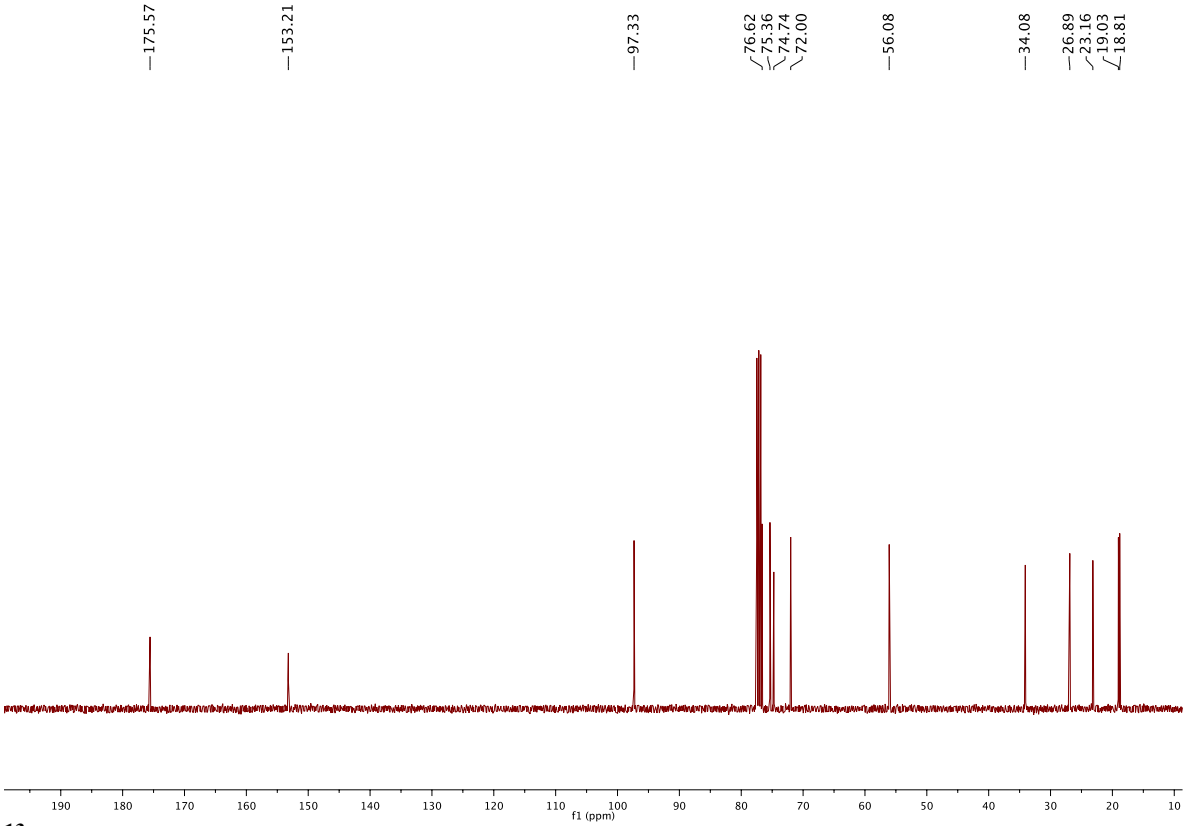
5.3 NMR Spectra

5.3.1 Total Synthesis of Fidaxomicin

(3a*S*,4*S*,7*S*,7a*S*)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (α-1.102)

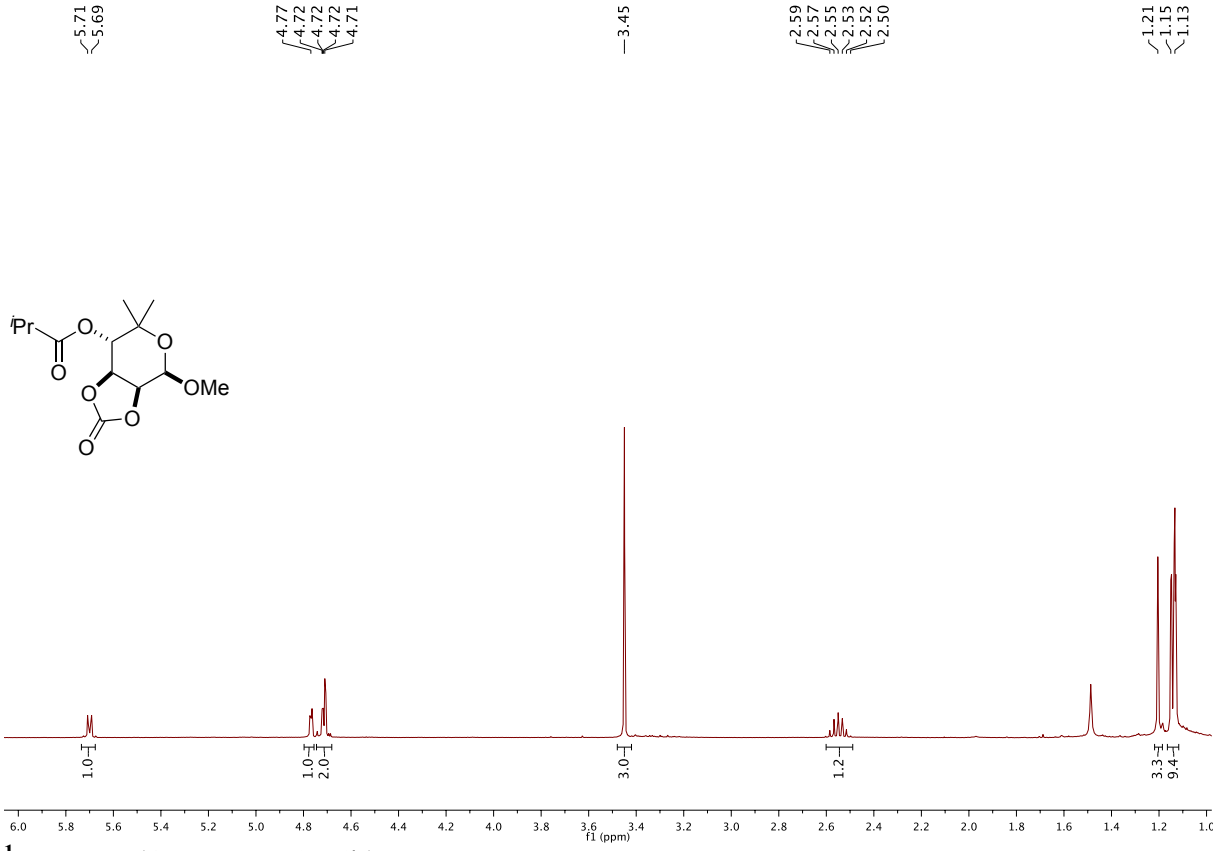


^{1}H-NMR (400 MHz, $CDCl_3$)

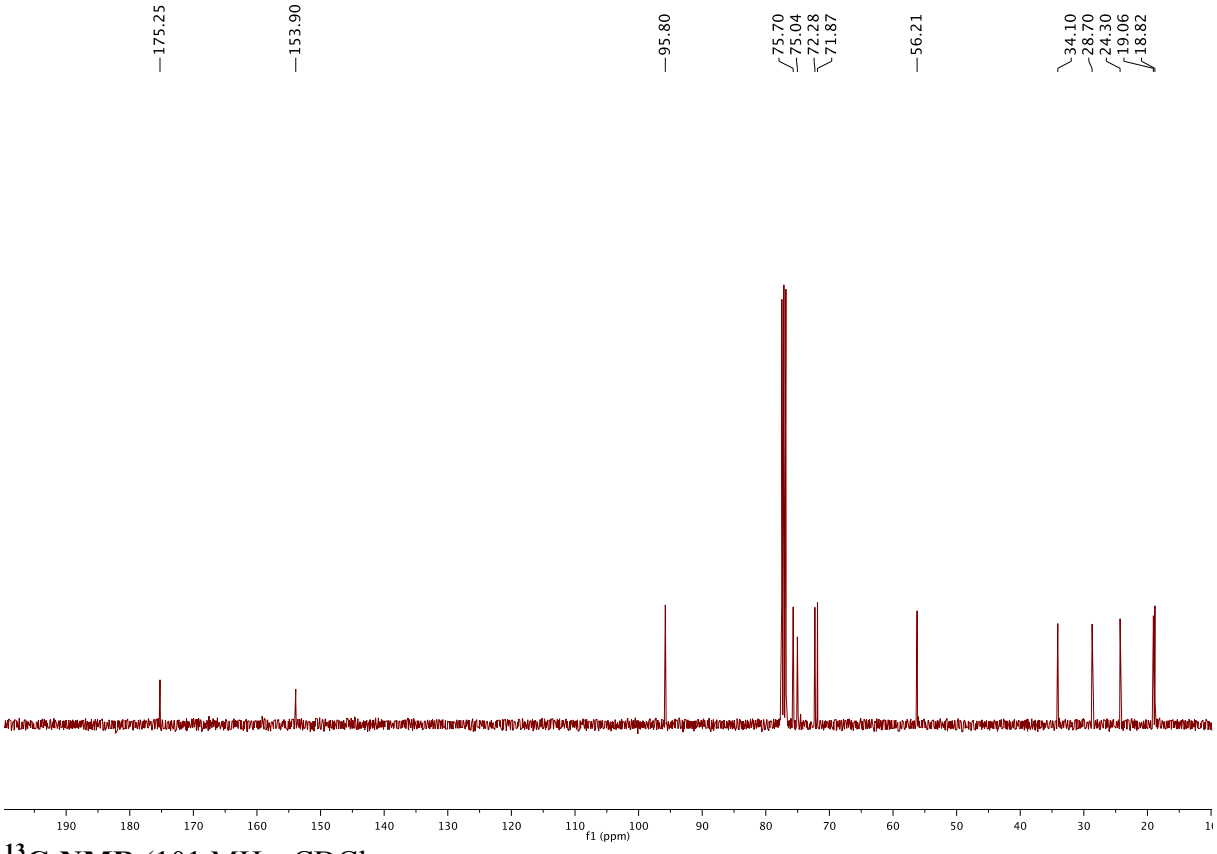


^{13}C-NMR (101 MHz, $CDCl_3$)

(3a*S*,4*S*,7*S*,7a*S*)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (β-1.102)

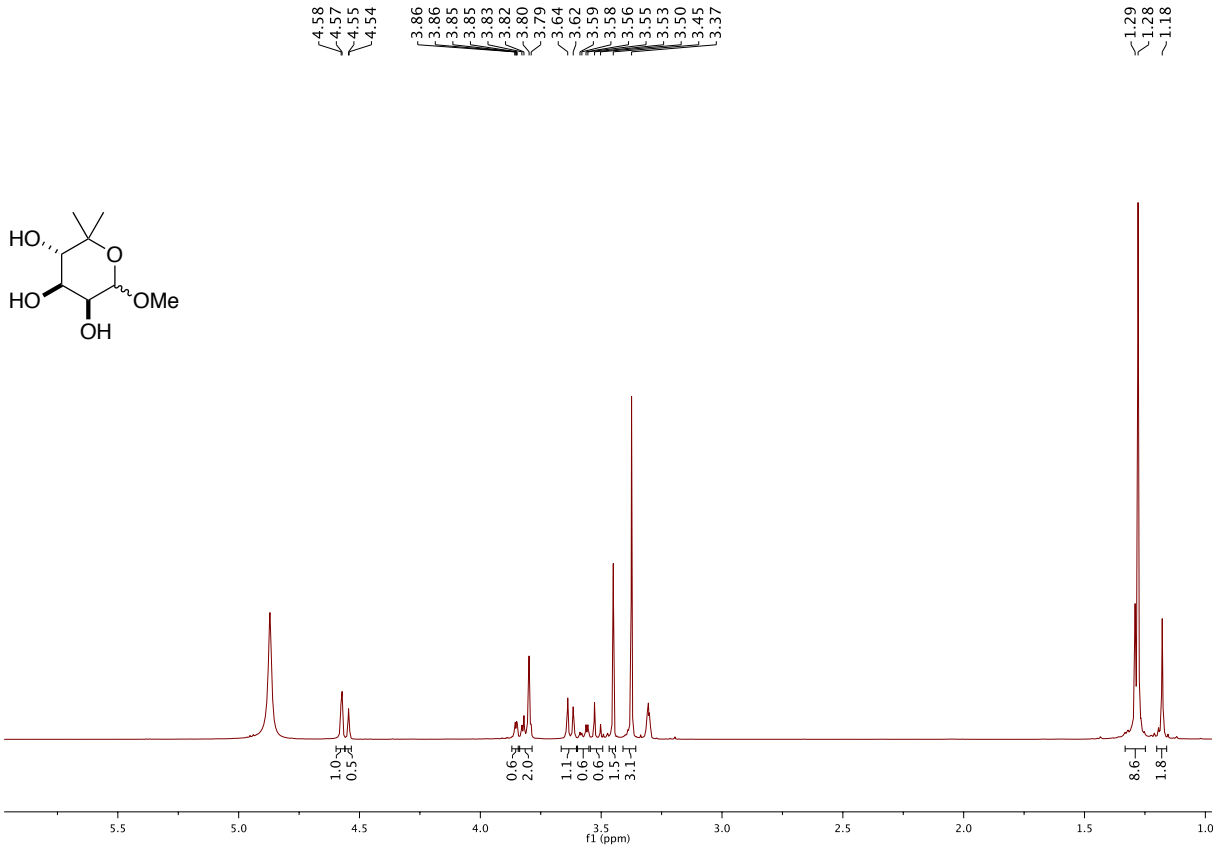


^{1}H-NMR (400 MHz, $CDCl_3$)

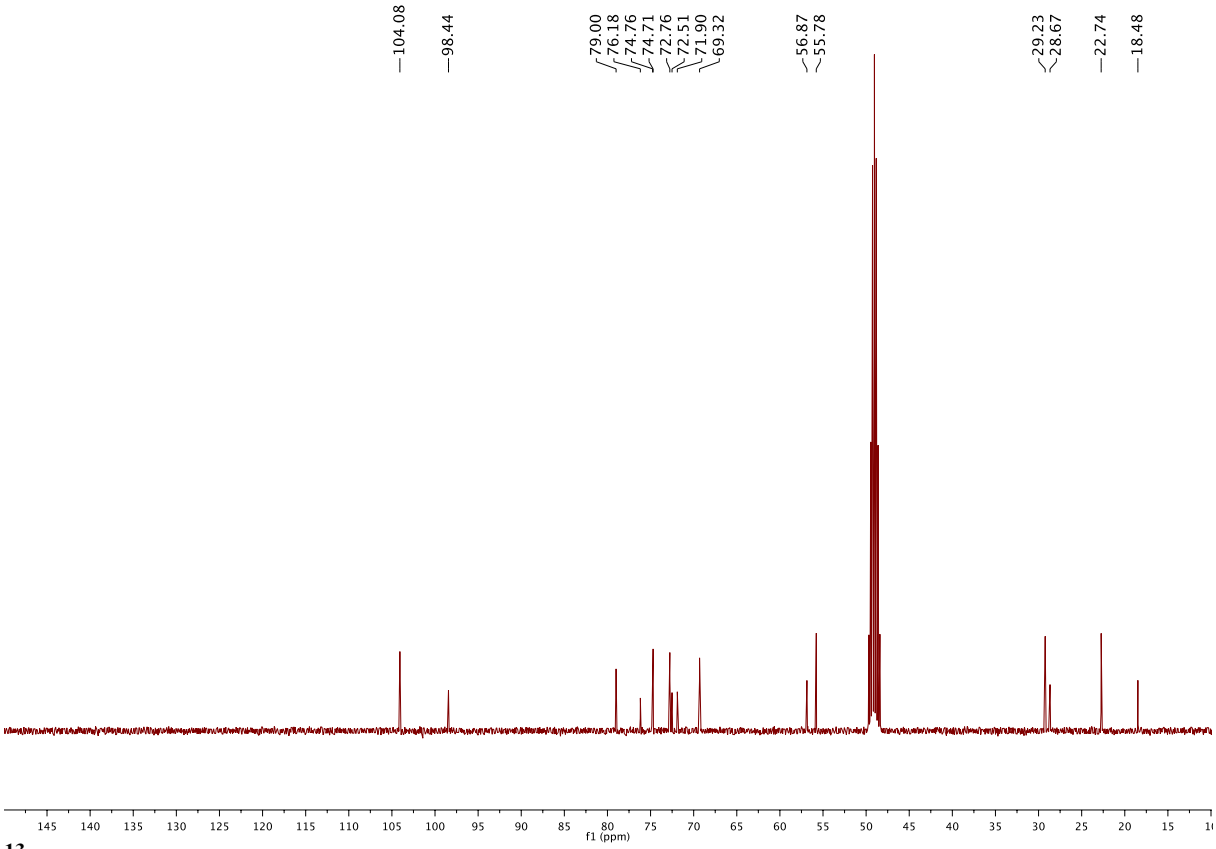


^{13}C-NMR (101 MHz, $CDCl_3$

(3*S*,4*S*,5*S*)-6-methoxy-2,2-dimethyltetrahydro-2*H*-pyran-3,4,5-triol (1.103)

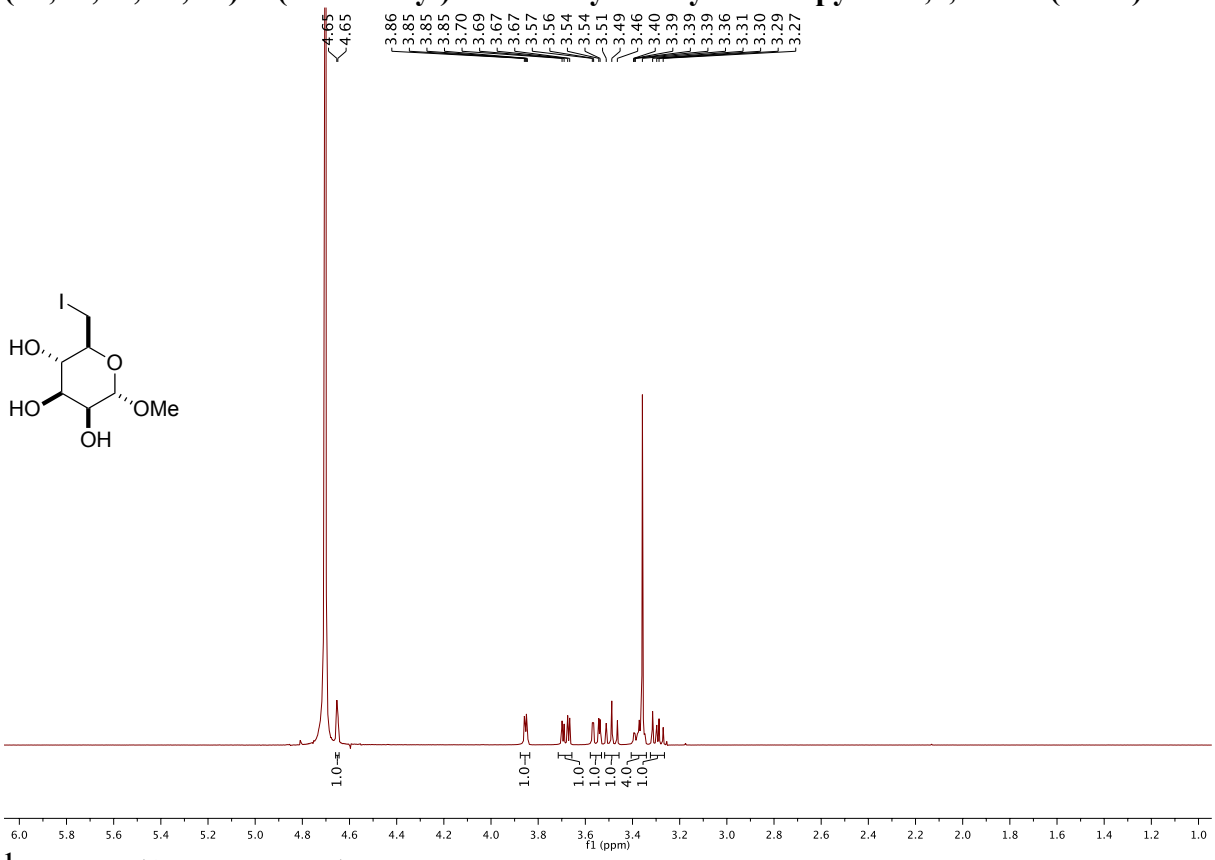


^{1}H-NMR (400 MHz, CD_3OD, α:β 2:1)



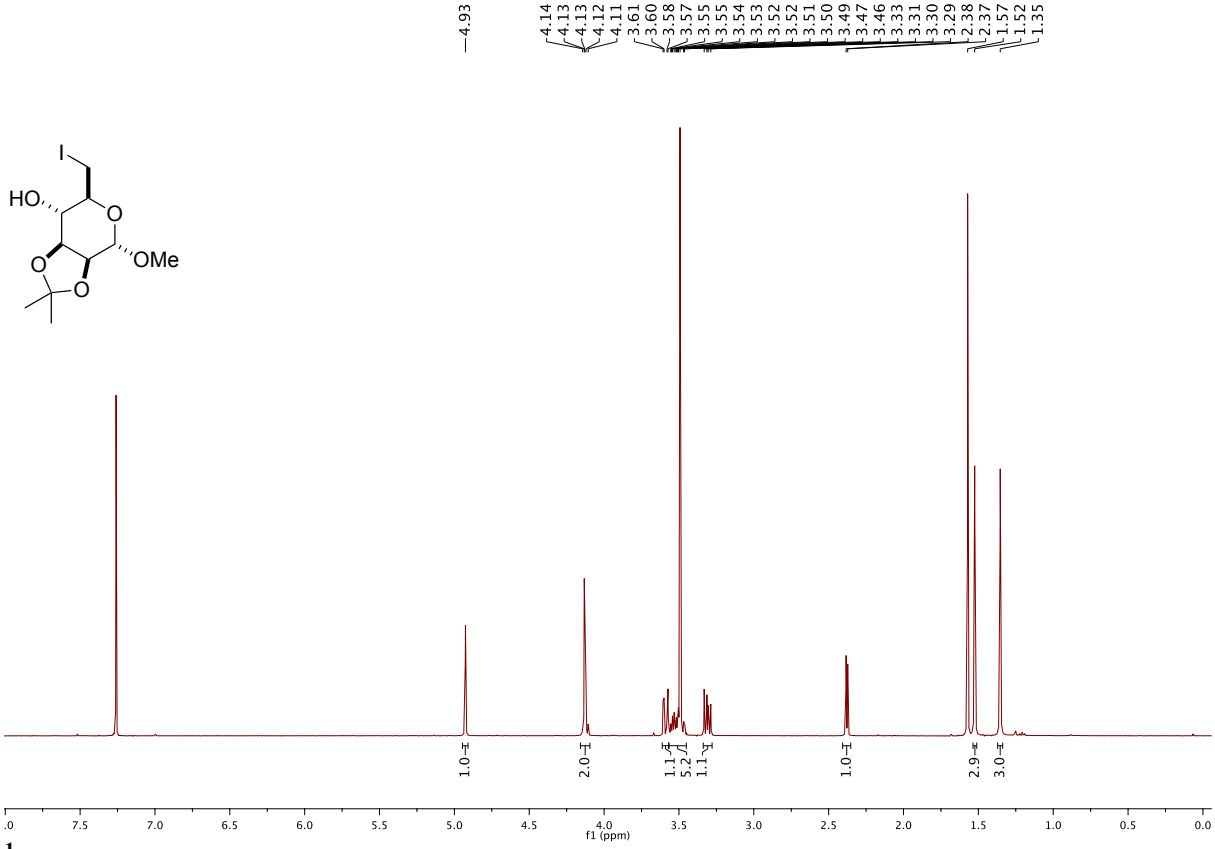
^{13}C-NMR (101 MHz, CD_3OD, α:β 2:1)

(2*S*,3*S*,4*S*, 5*S*, 6*S*)-2-(iodomethyl)-6-methoxytetrahydro-2H-pyran-3,4,5-triol (1.105)

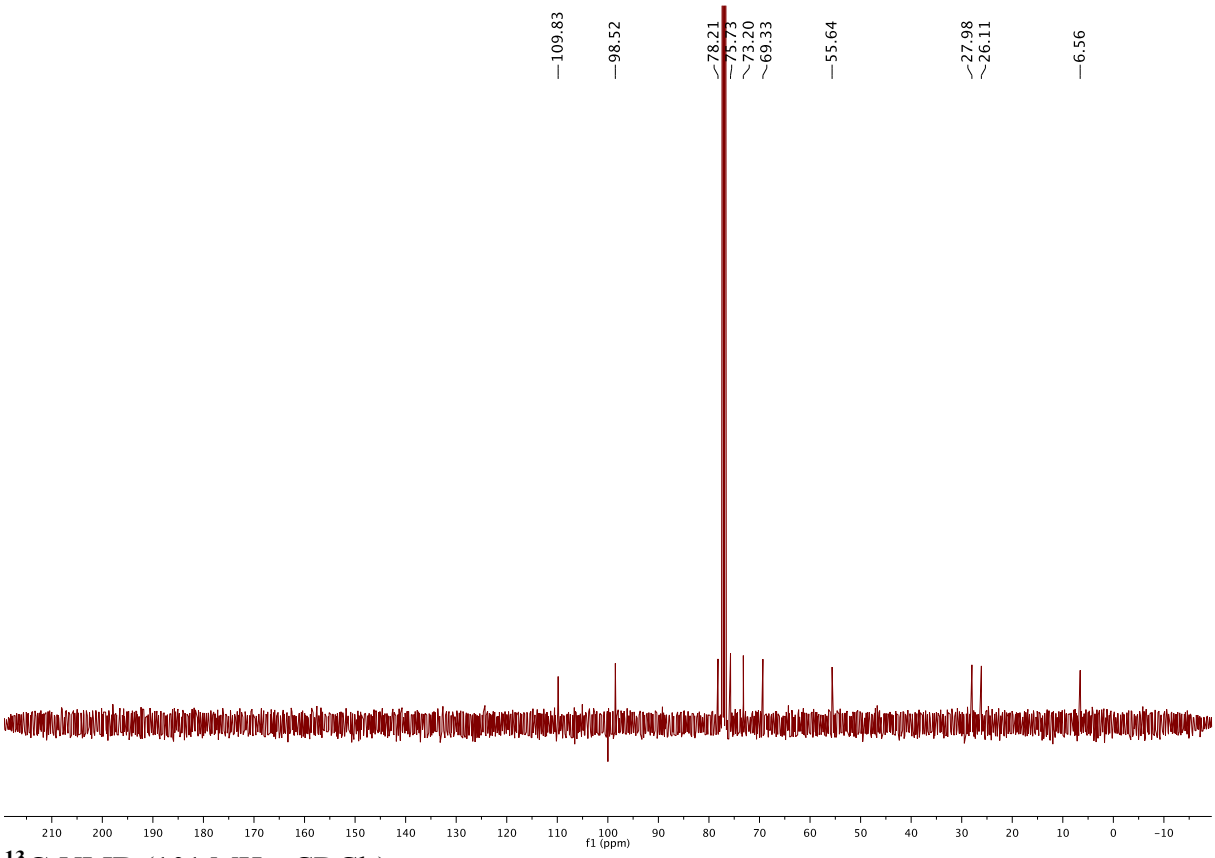


^{1}H-NMR (400 MHz, D_2O)

(3a*S*,4*S*,6*S*,73a*S*,7a*S*)-6-(iodomethyl)-4-methoxy-2,2-dimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-ol (1.106)

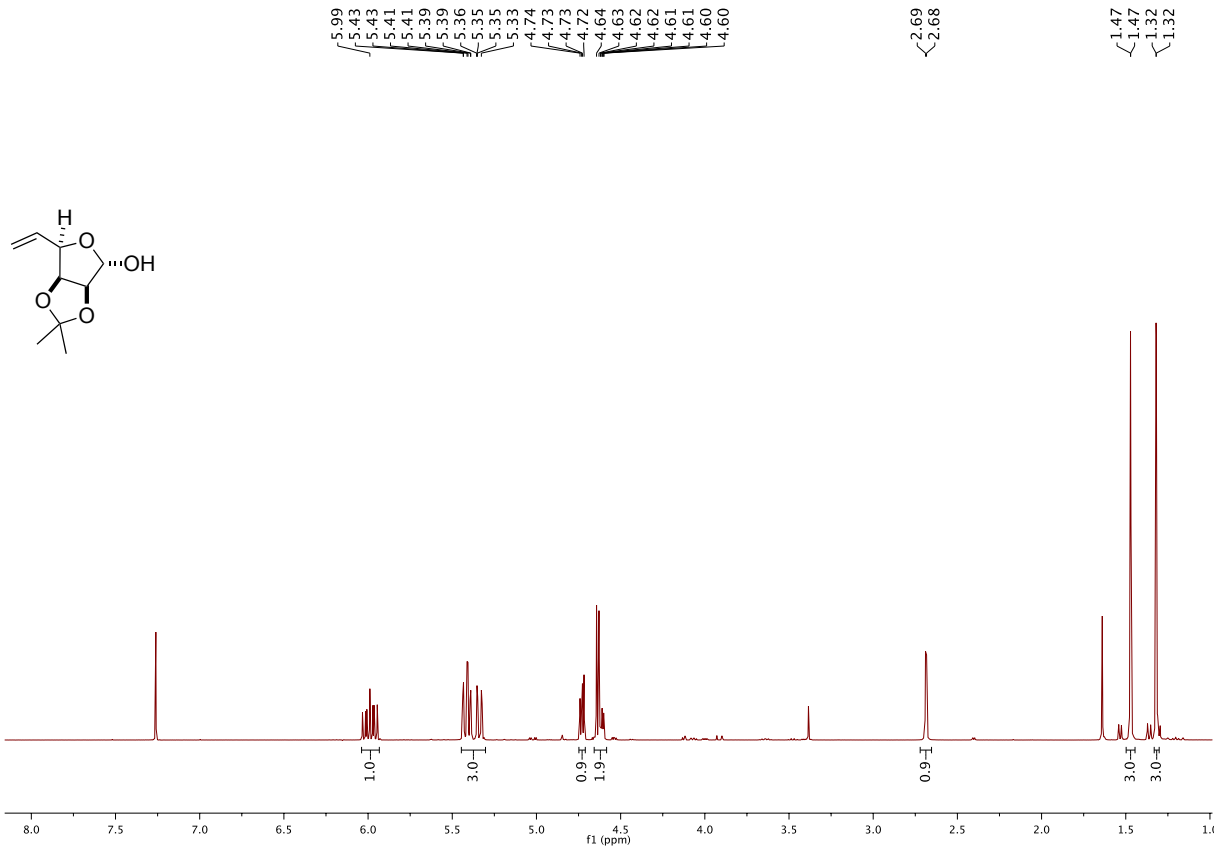


^{1}H-NMR (400 MHz, $CDCl_3$)

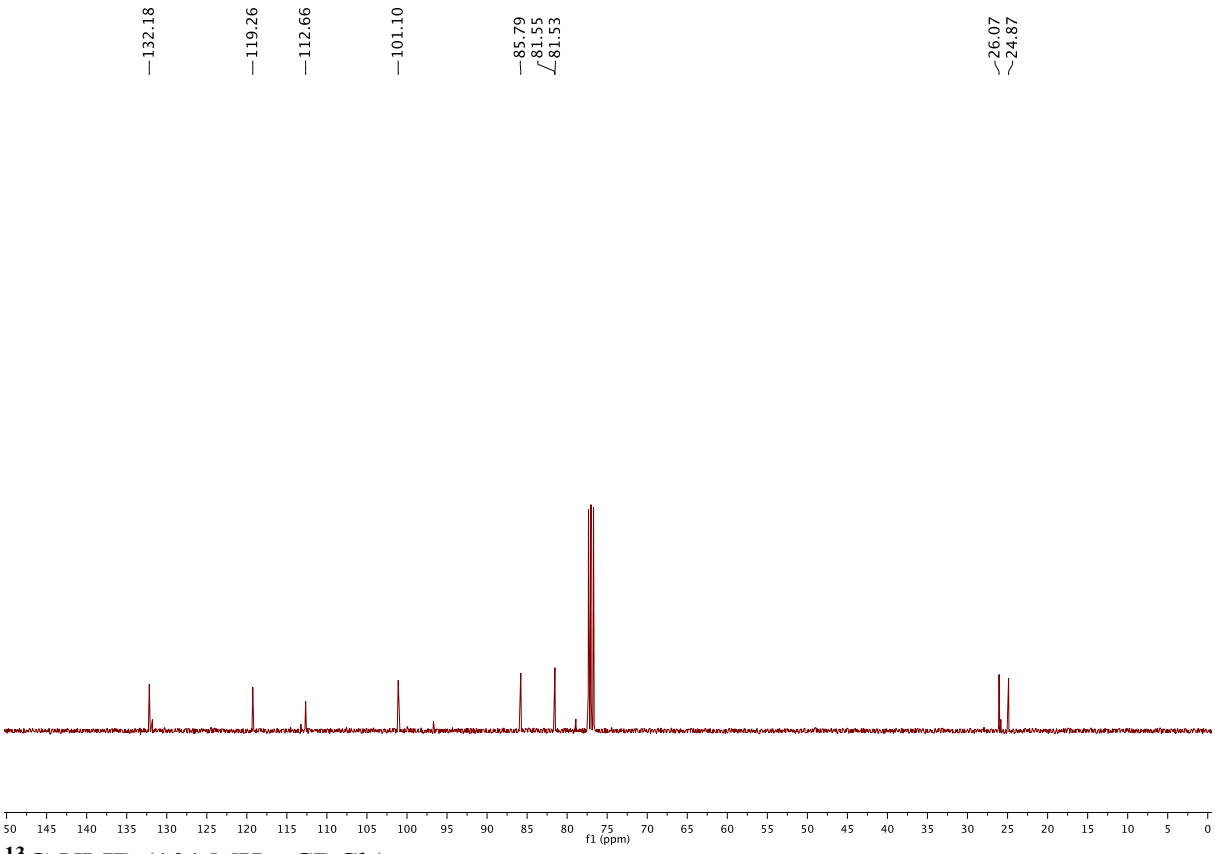


^{13}C-NMR (101 MHz, $CDCl_3$)

(3a*S*, 4*S*, 6*R*,6a*S*)-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (1.107)

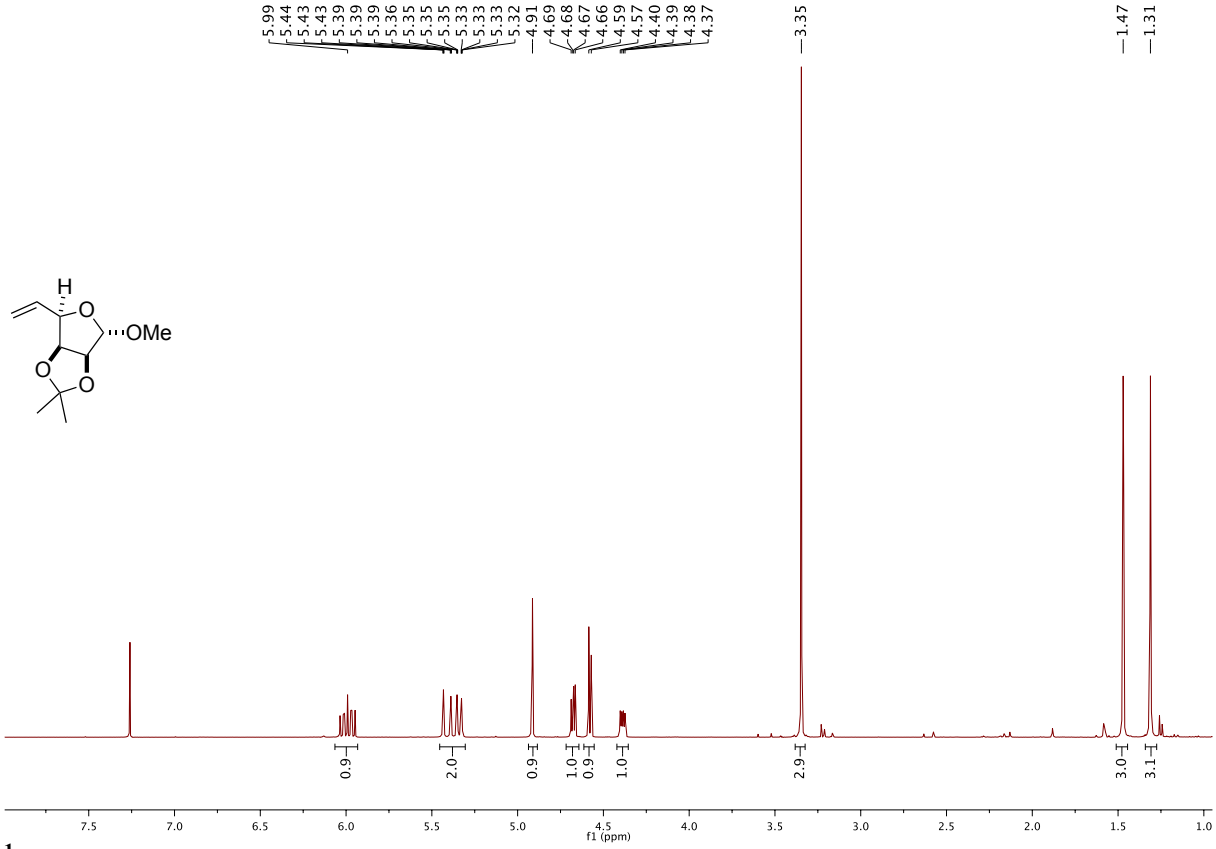


^{1}H-NMR (400 MHz, $CDCl_3$)

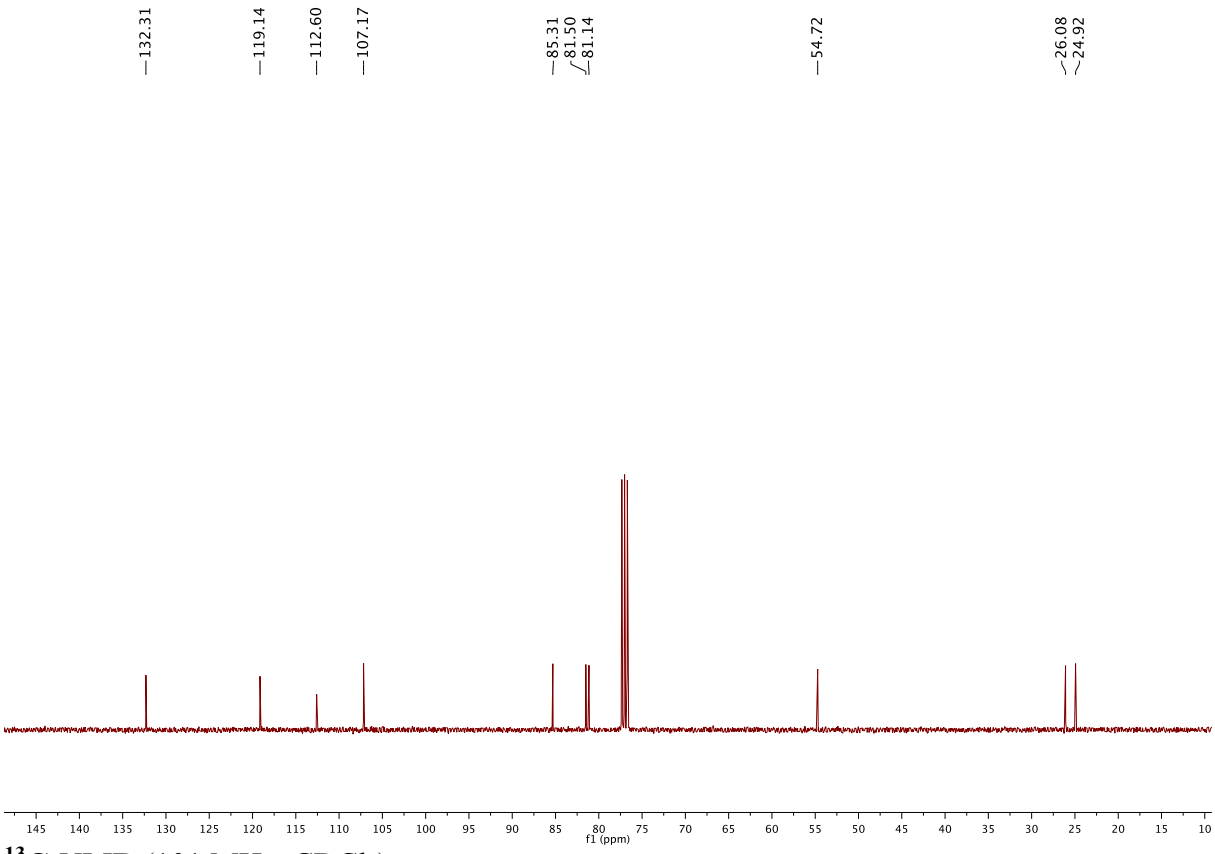


^{13}C-NMR (101 MHz, $CDCl_3$)

(3a*S*,4*S*,6*R*,6a*S*)-4-methoxy-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxole (1.108)

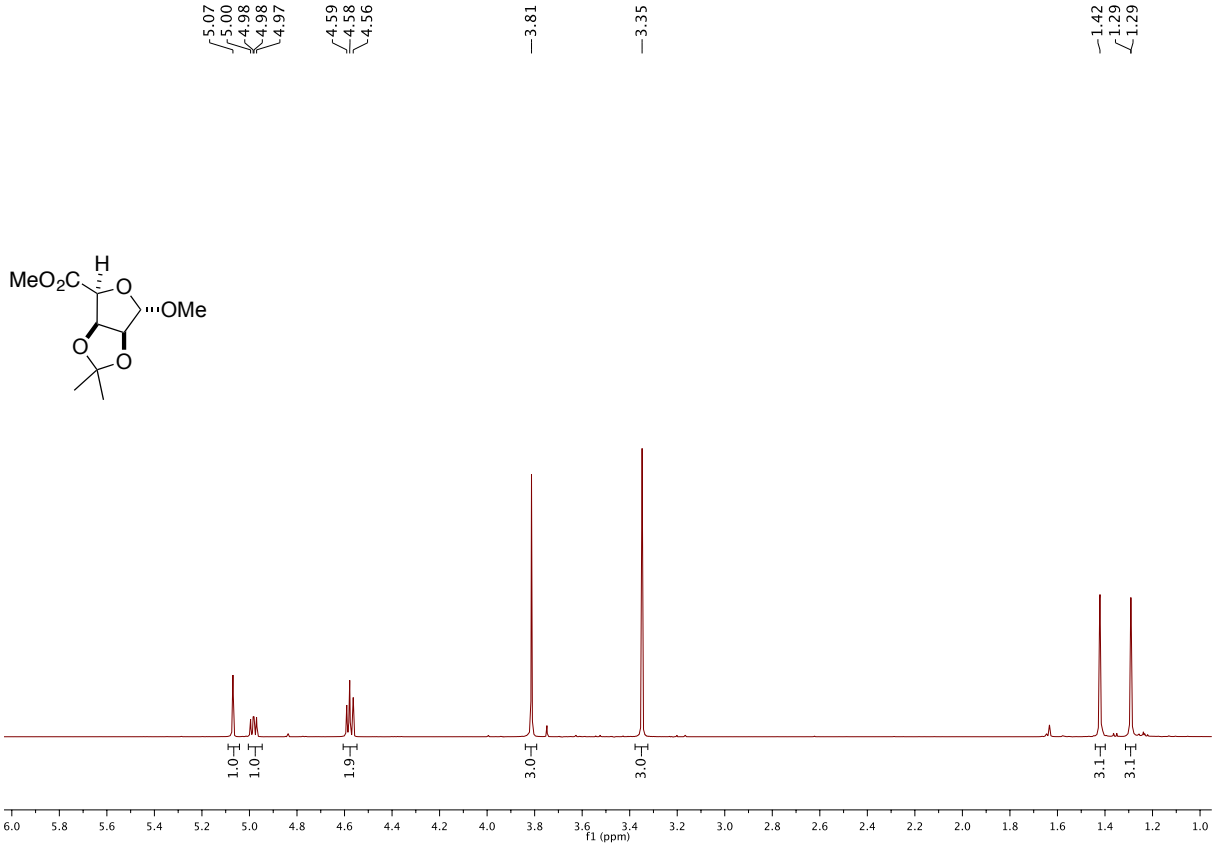


^{1}H-NMR (400 MHz, $CDCl_3$)

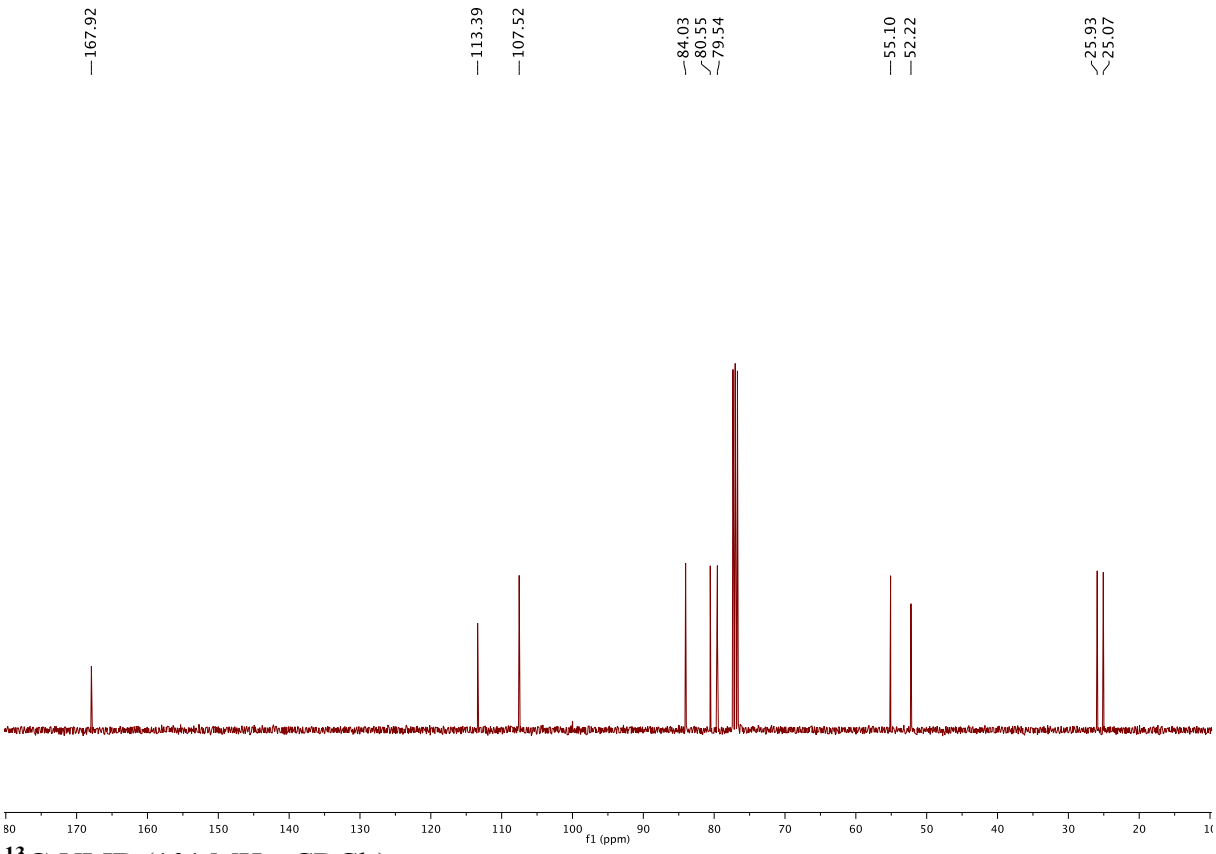


^{13}C-NMR (101 MHz, $CDCl_3$)

methyl (3a*R*,4*S*, 6*S*, 6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (1.109)

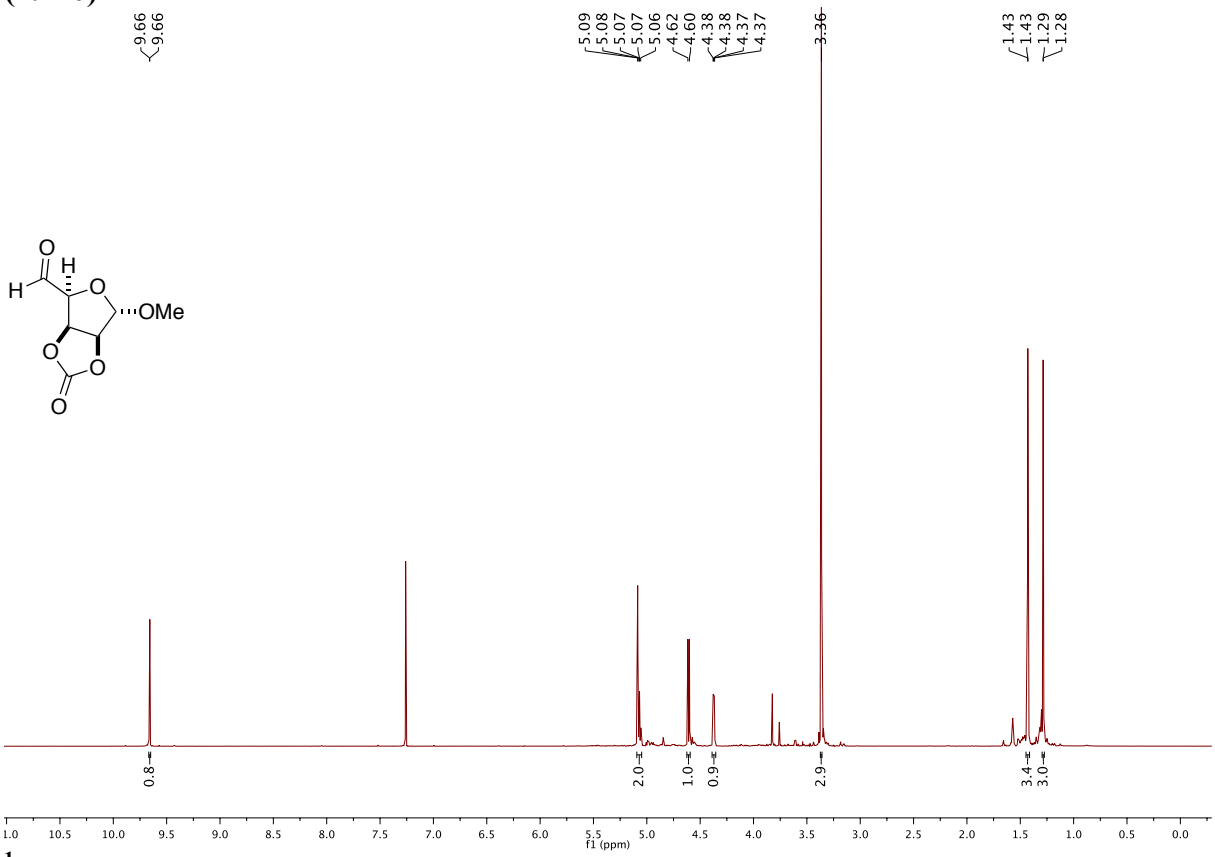


^{1}H-NMR (400 MHz, $CDCl_3$)

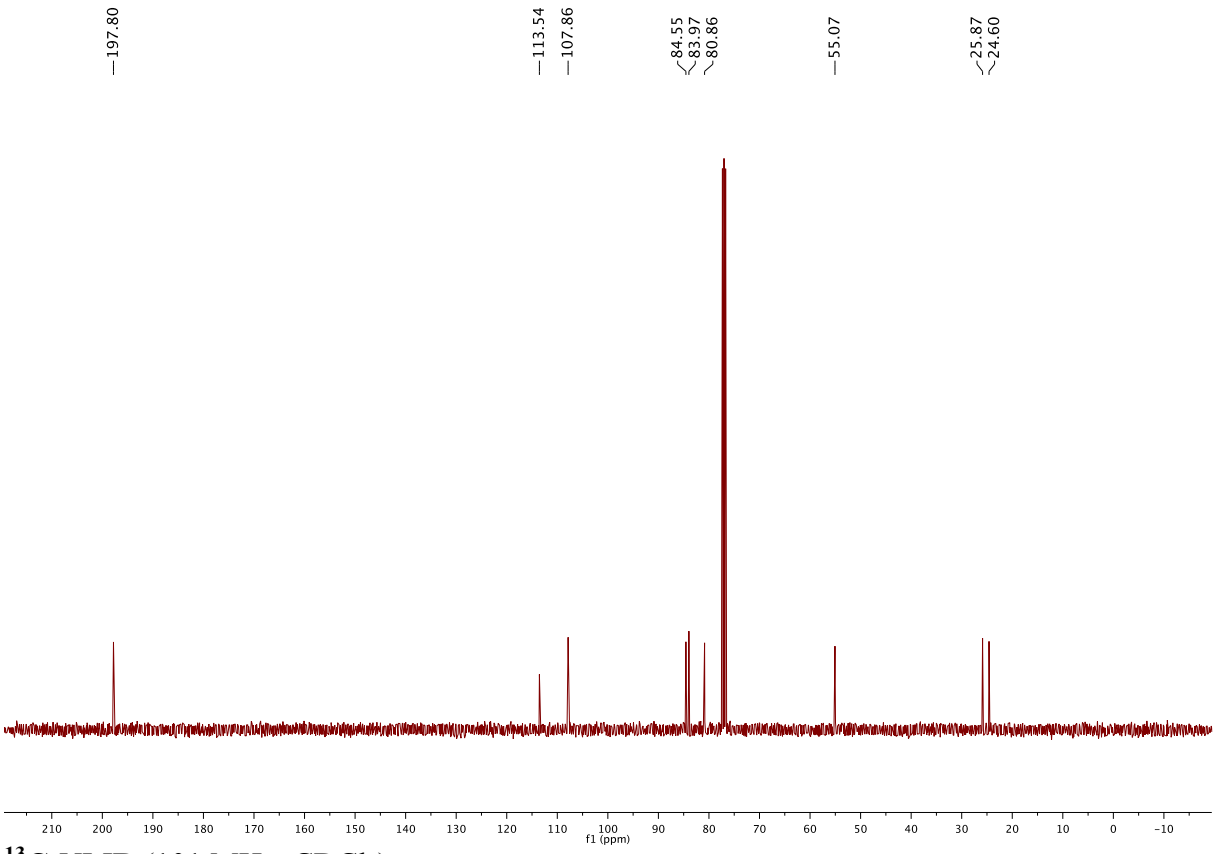


^{13}C-NMR (101 MHz, $CDCl_3$)

(3a*S*,4*S*,6*S*,6a*S*)-6-methoxy-2-oxotetrahydrofuro[3,4-d][1,3]dioxole-4-carbaldehyde (1.110)

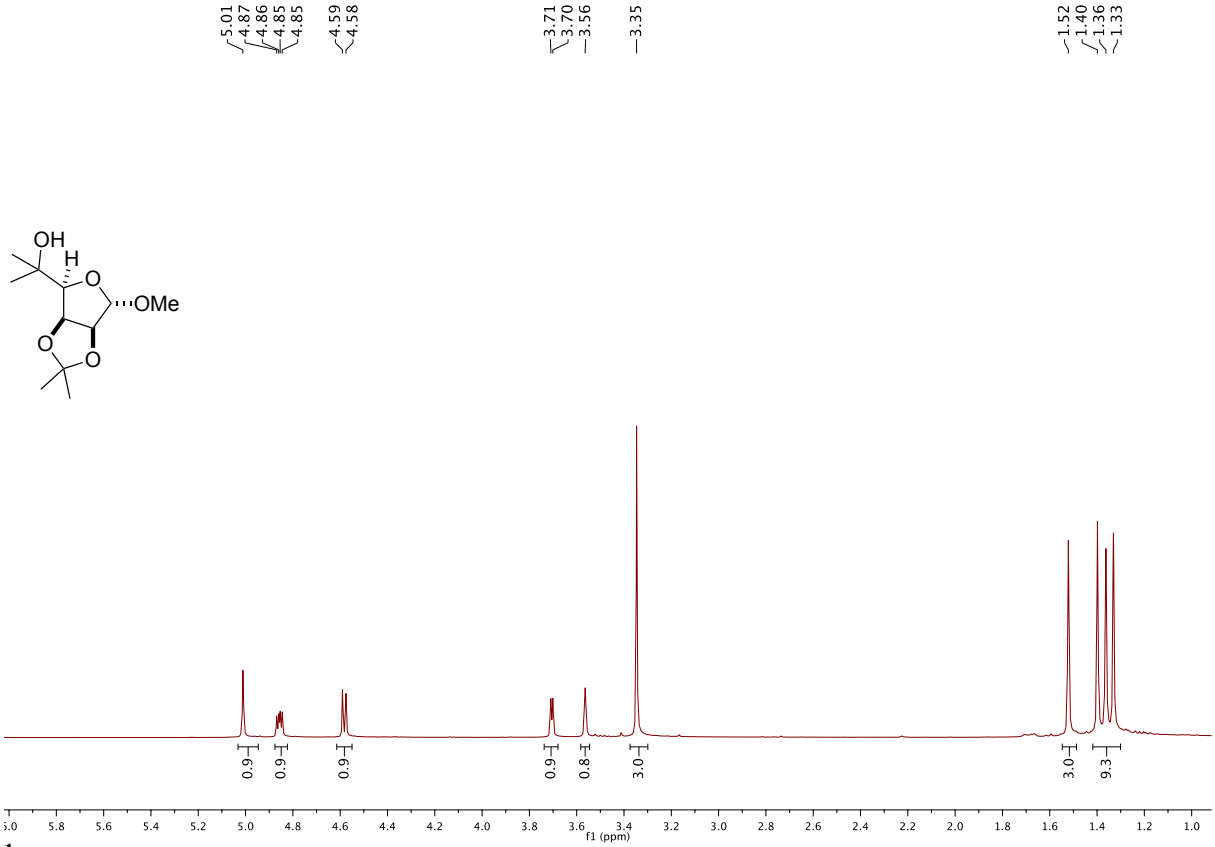


^{1}H-NMR (400 MHz, $CDCl_3$)

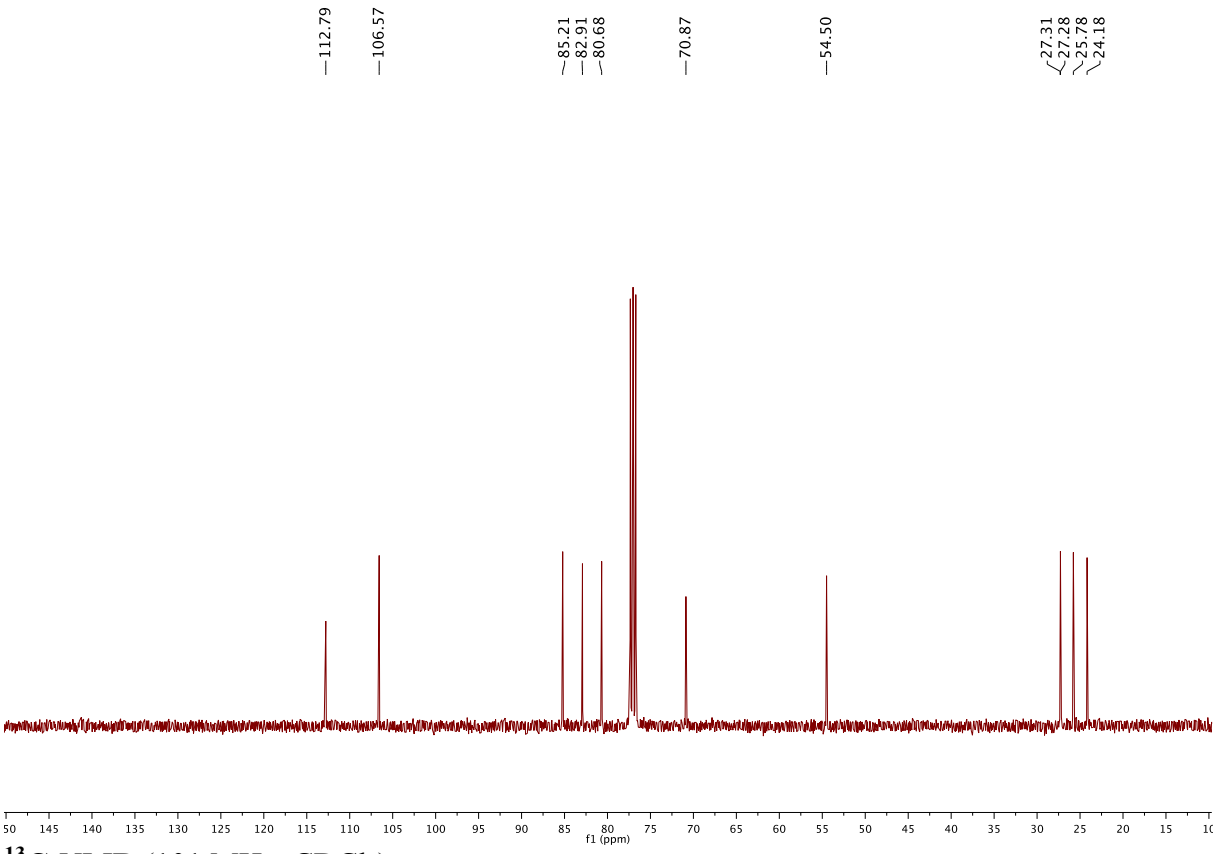


^{13}C-NMR (101 MHz, $CDCl_3$)

2-((3a*S*,4*S*,6*S*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-propan-2-ol (1.112)

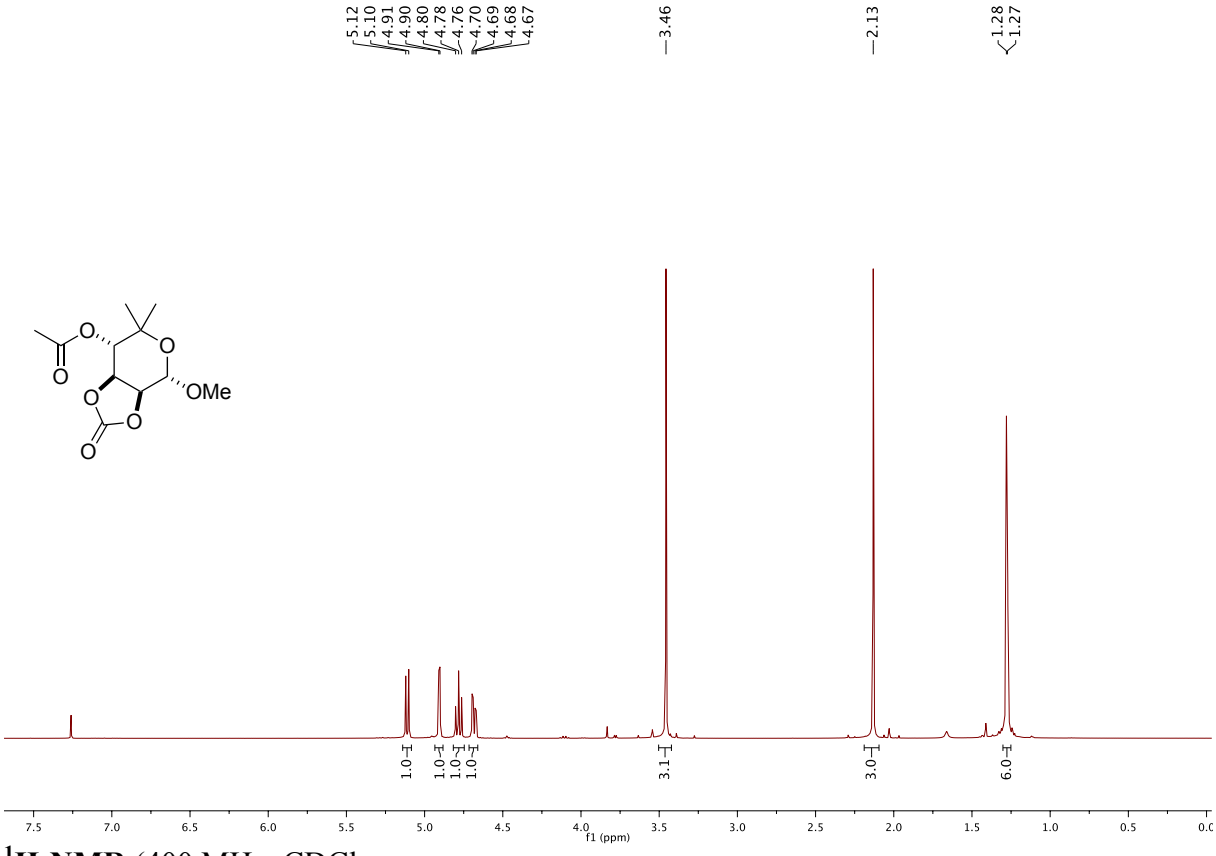


^{1}H-NMR (400 MHz, $CDCl_3$)

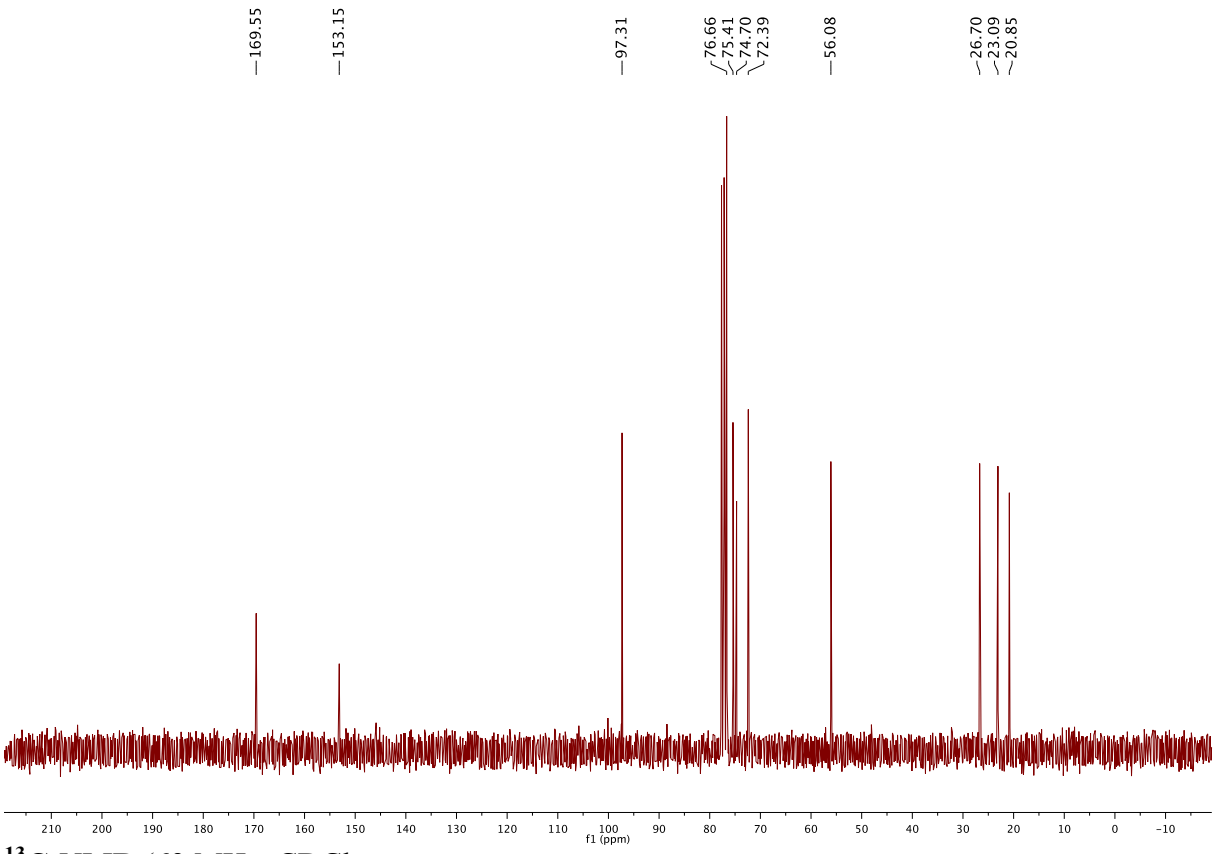


^{13}C-NMR (101 MHz, $CDCl_3$)

(3a*S*,7*S*,7a*S*)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl acetate (α-1.116)

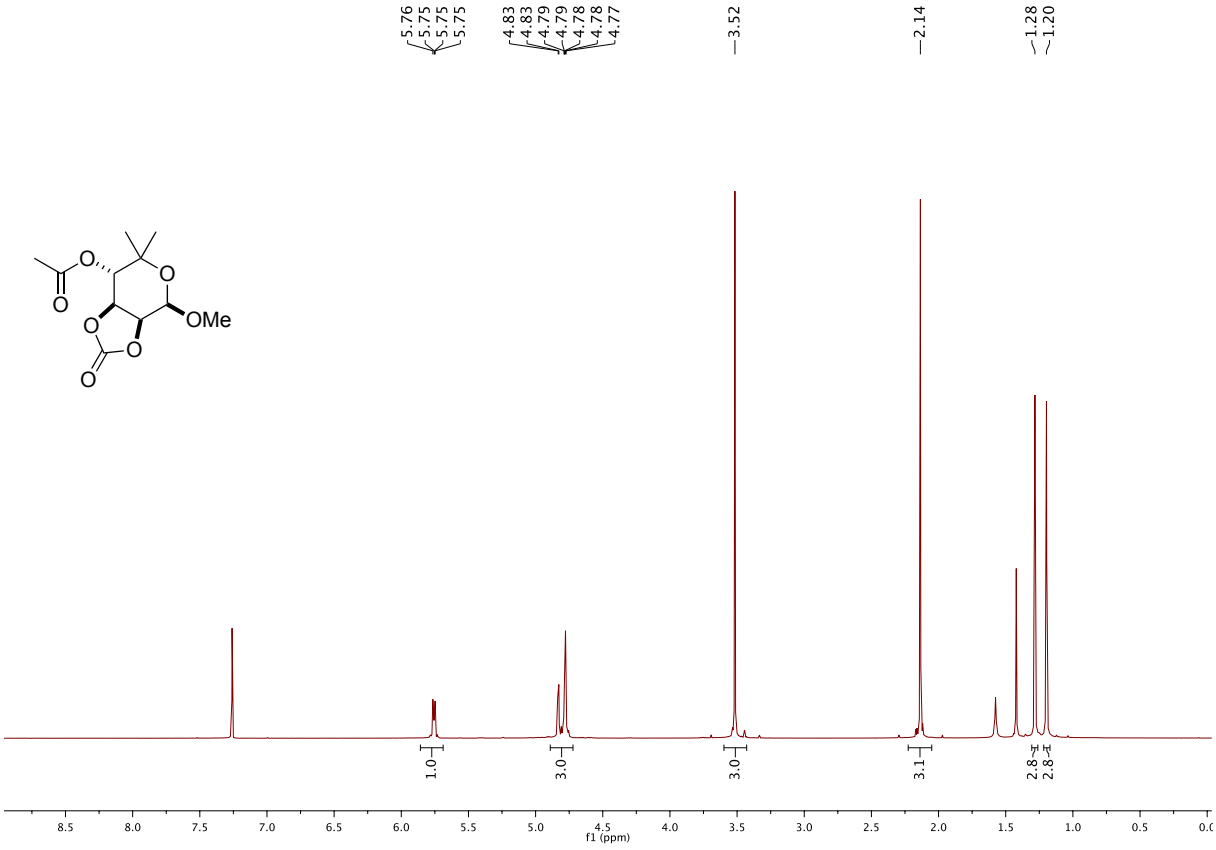


^{1}H-NMR (400 MHz, $CDCl_3$

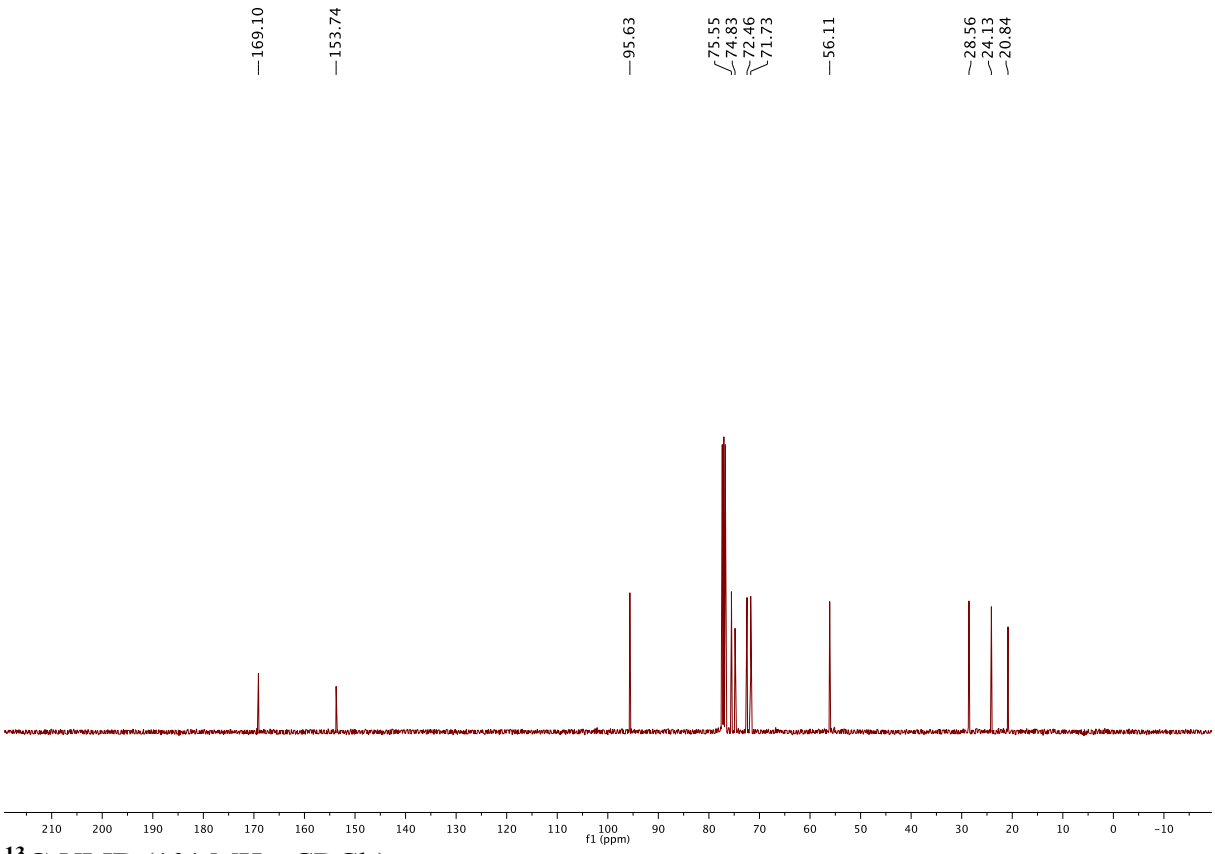


^{13}C-NMR (63 MHz, $CDCl_3$

(3a*S*,7*S*,7a*S*)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl acetate (β-1.116)

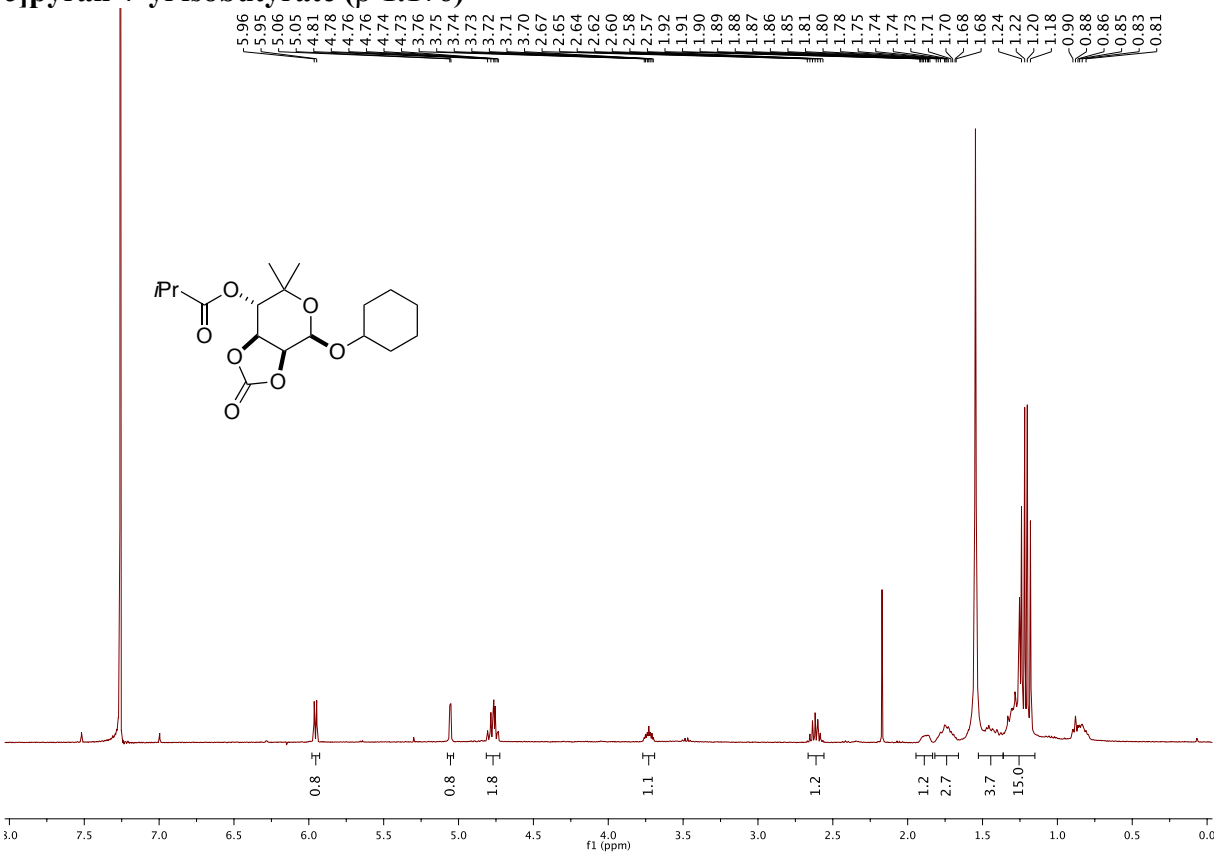


^{1}H-NMR (400 MHz, $CDCl_3$)



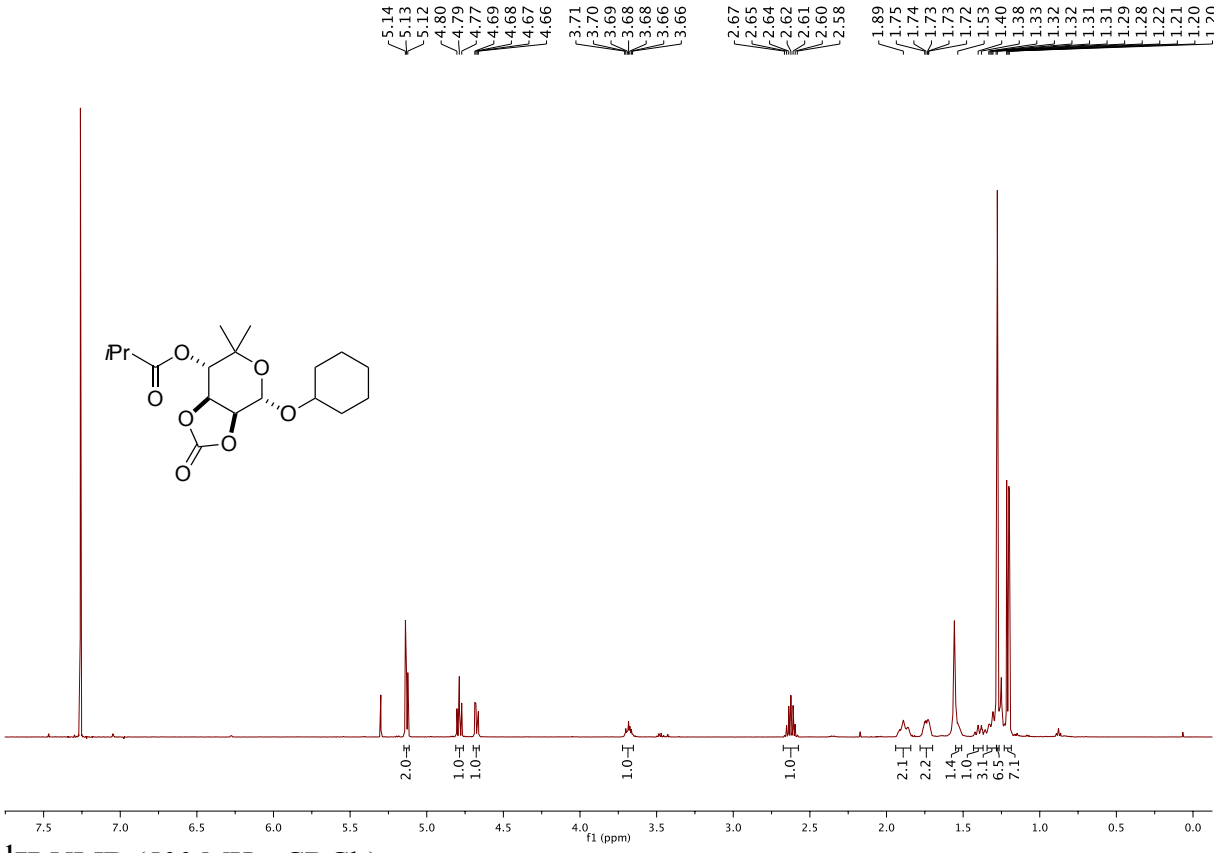
^{13}C-NMR (101 MHz, $CDCl_3$)

(3a*S*,4*R*,7*S*,7a*S*)-4-(cyclohexyloxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (β-1.176)

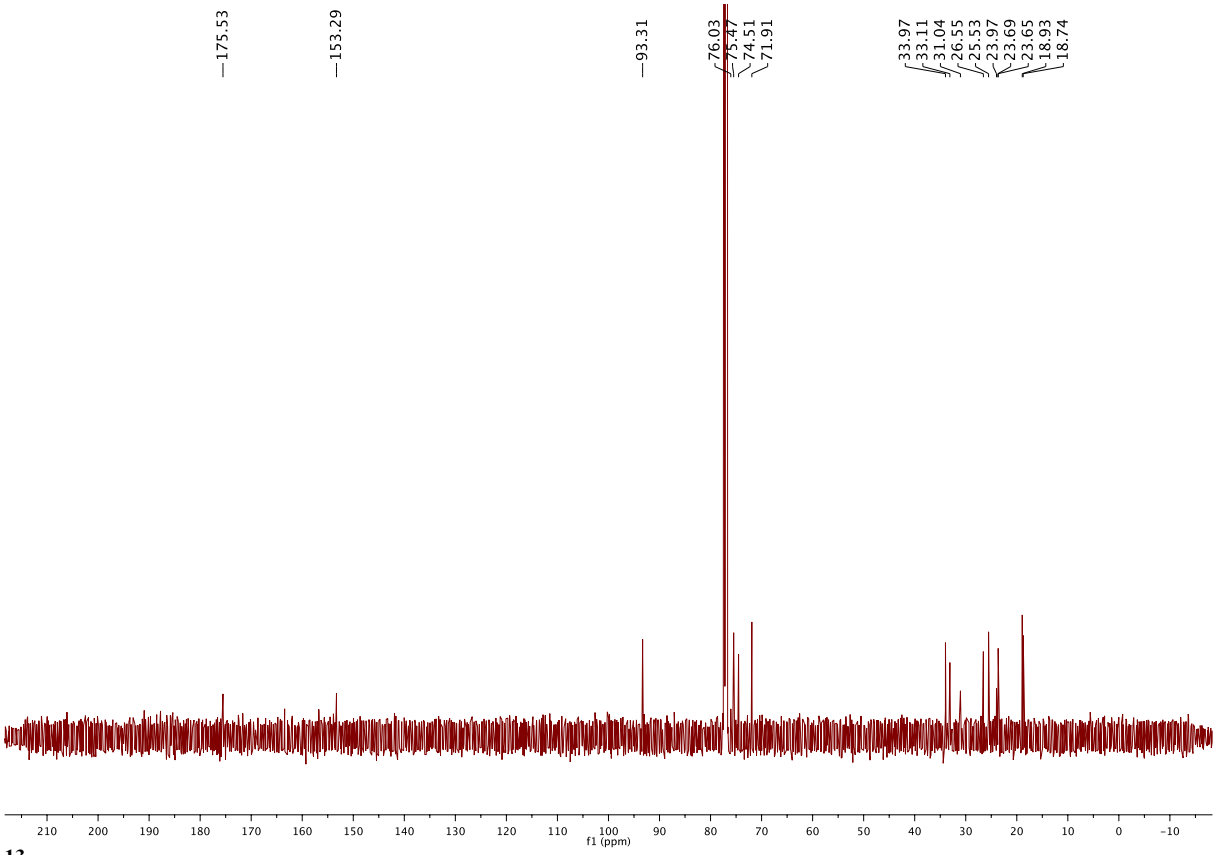


^{1}H-NMR (400 MHz, $CDCl_3$)

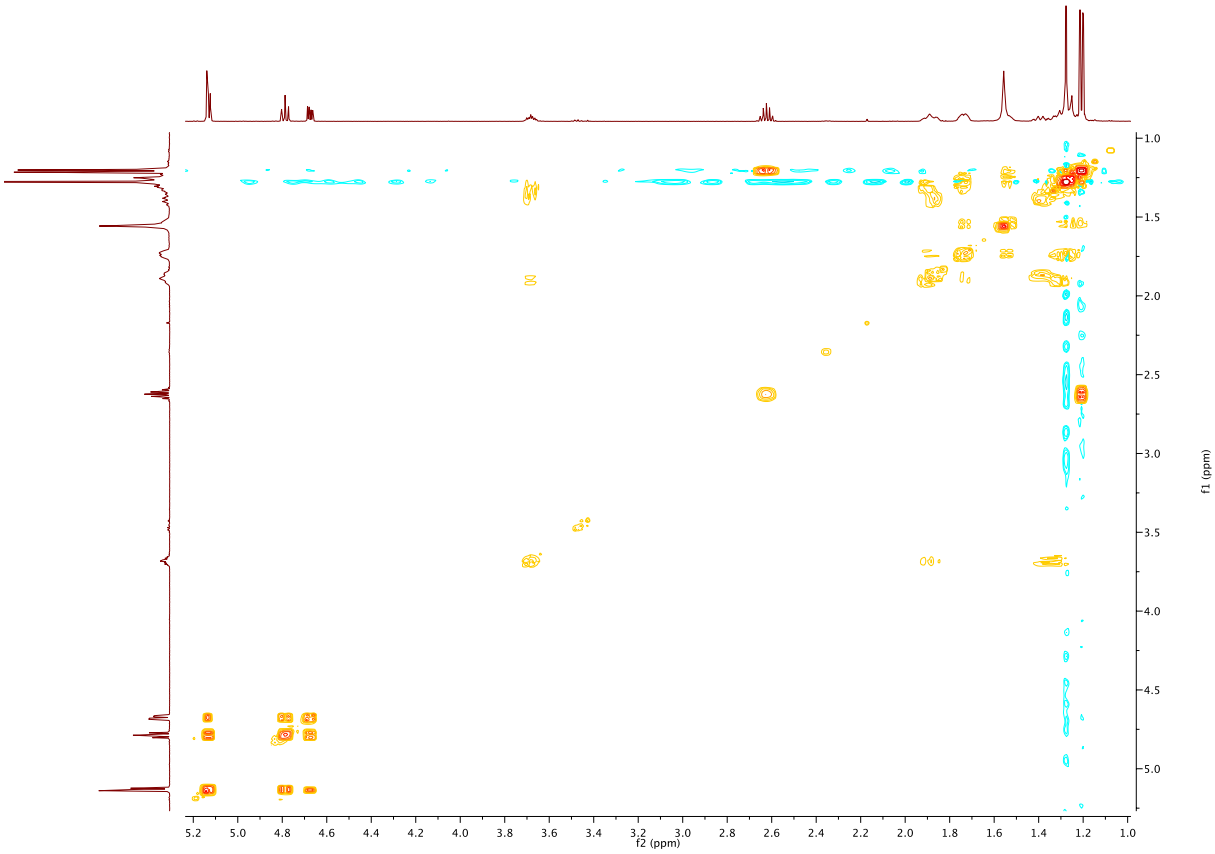
(3a*S*,4*S*,7*S*,7a*S*)-4-(cyclohexyloxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (α-1.176)



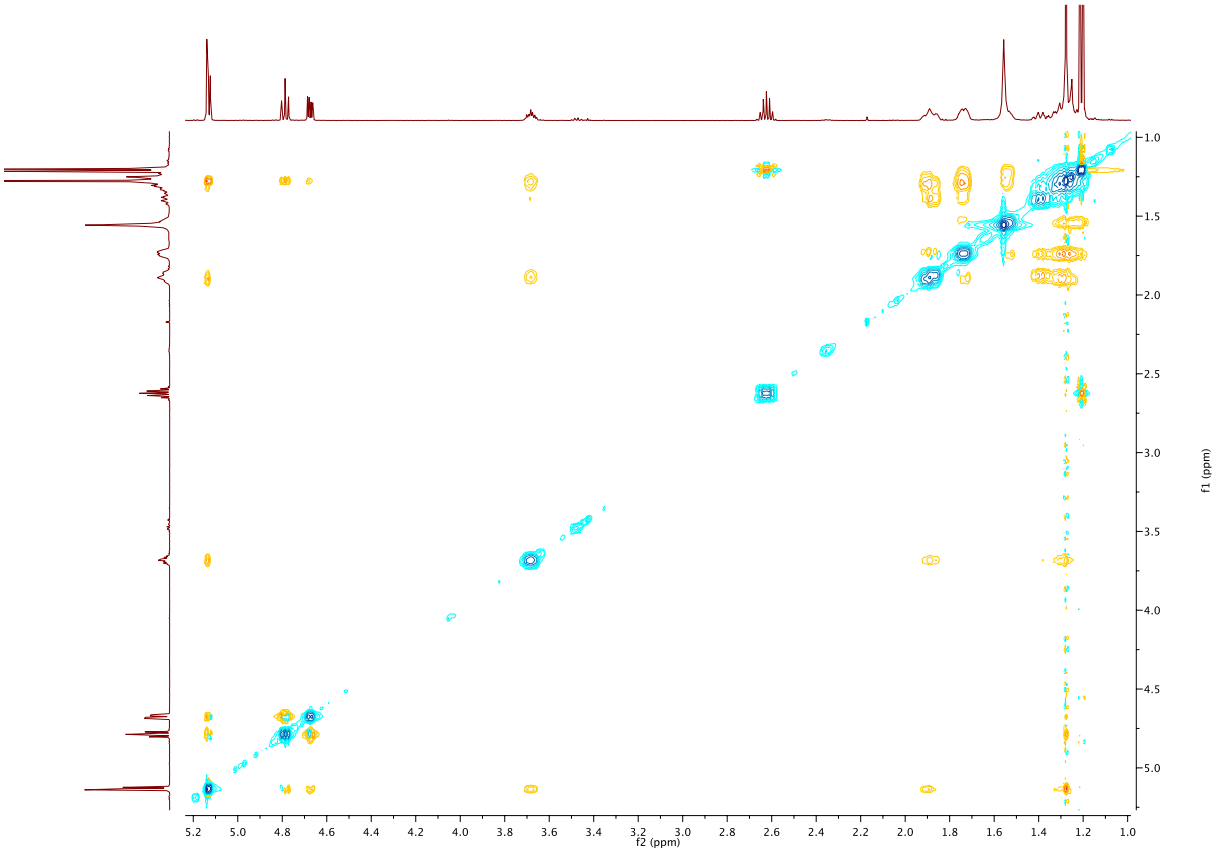
^{1}H-NMR (500 MHz, $CDCl_3$)



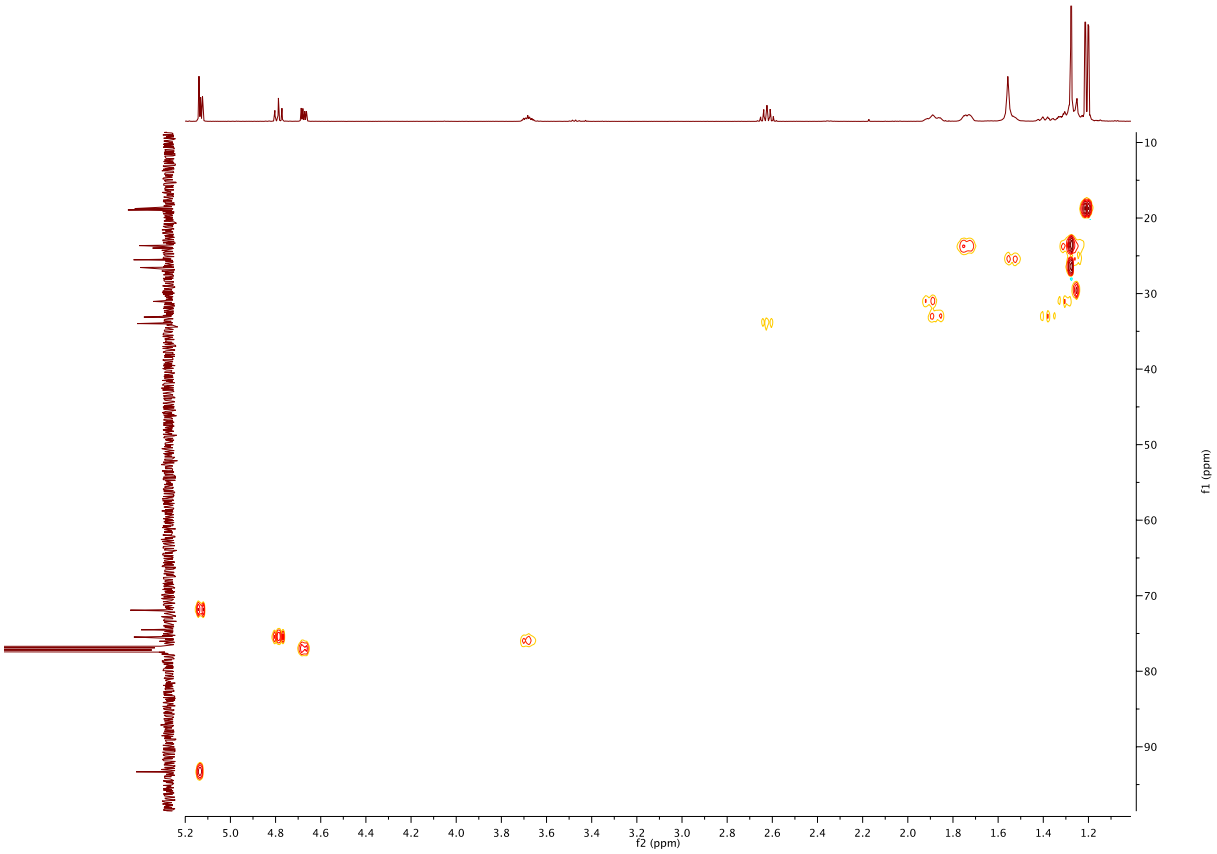
^{13}C-NMR (126 MHz, $CDCl_3$



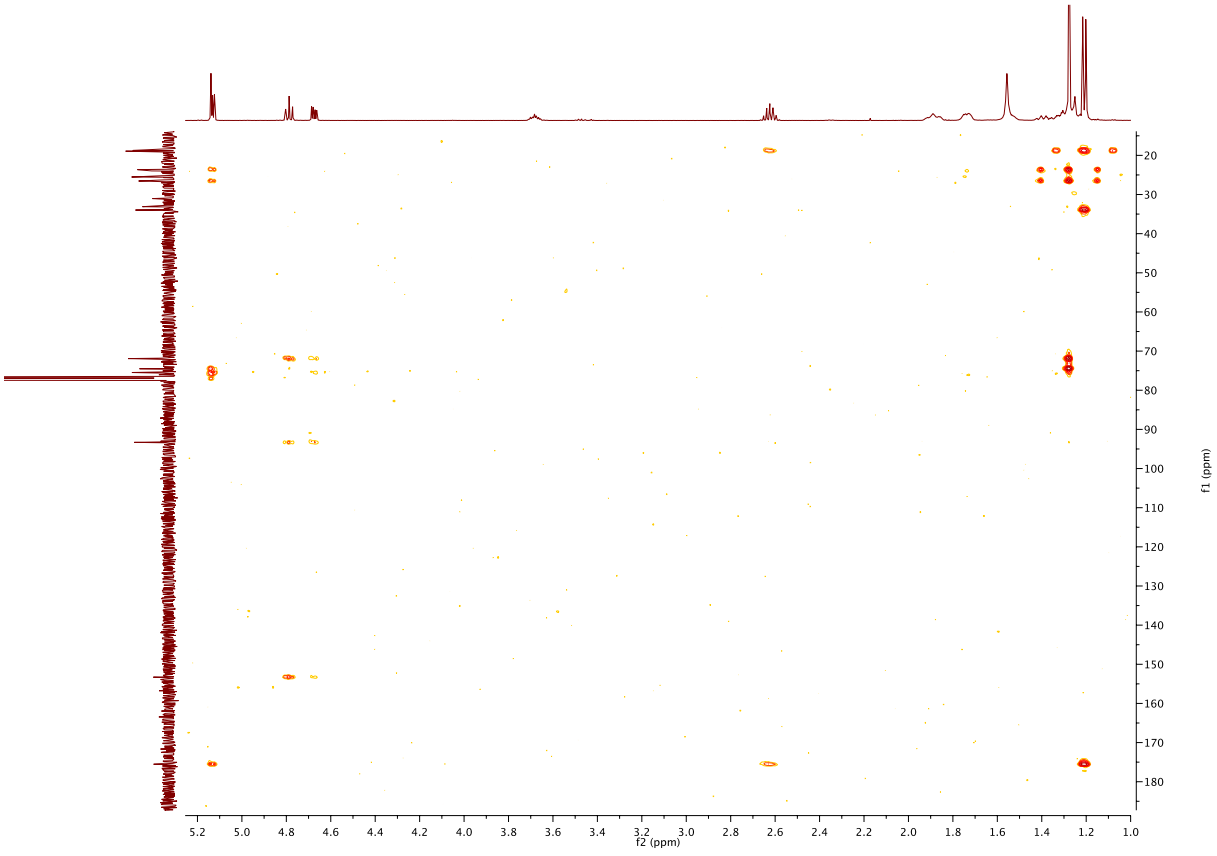
COSY (500 MHz, $CDCl_3$)



NOESY (500 MHz, $CDCl_3$)

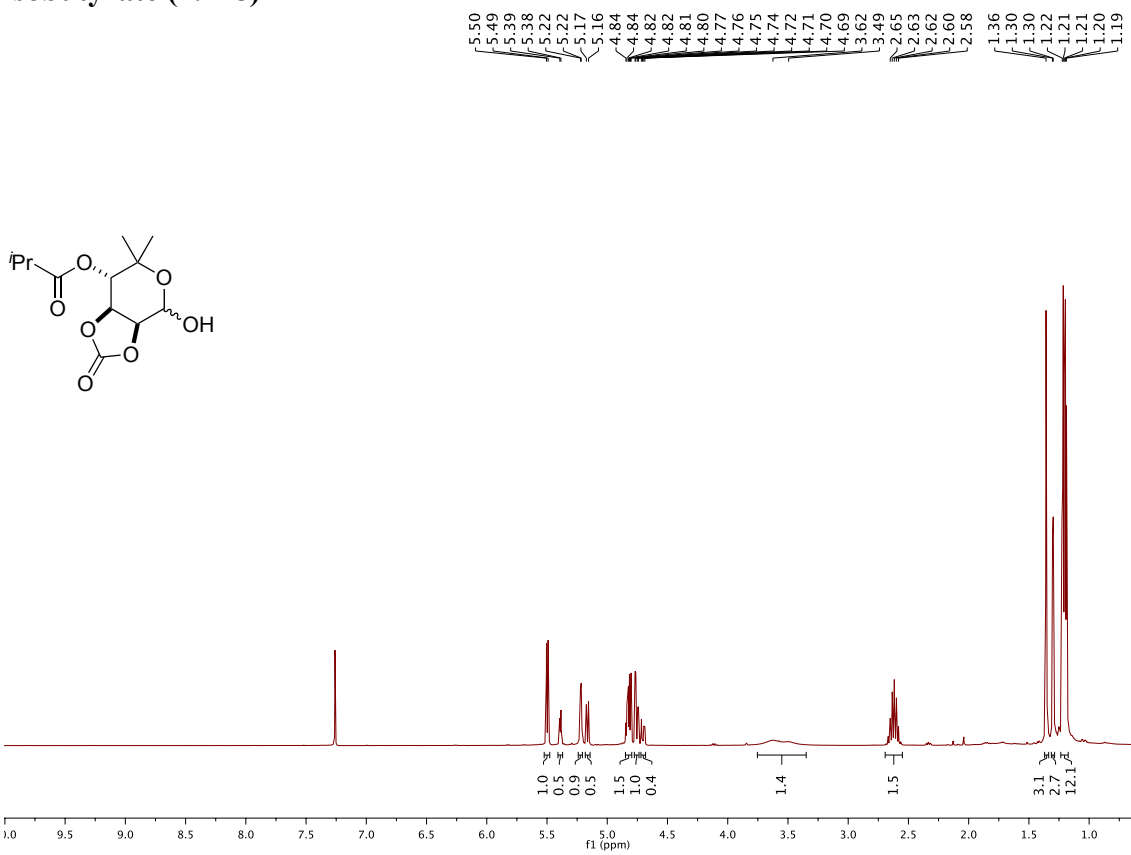


HSQC (500 MHz, $CDCl_3$)

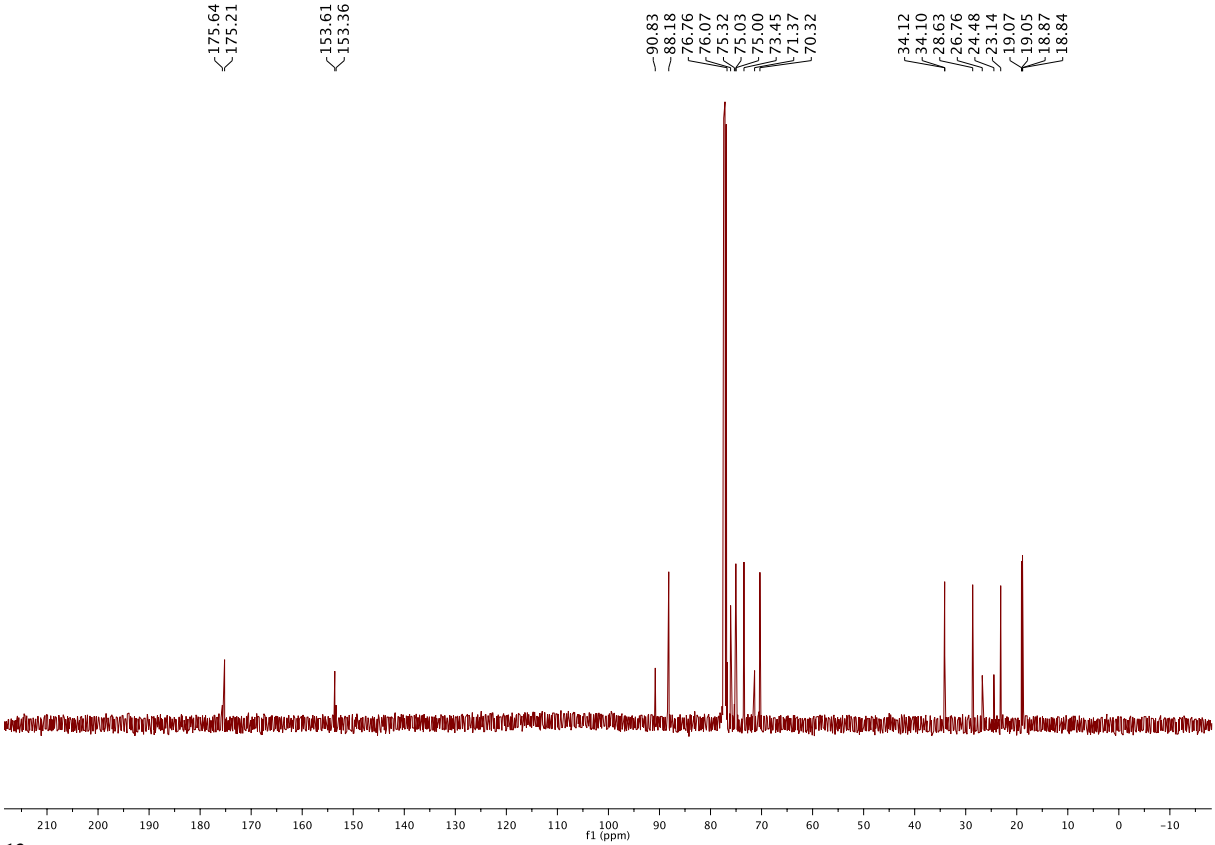


HMBC (500 MHz, $CDCl_3$)

(3a*S*,7*S*,7a*S*)-4-hydroxy-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl isobutyrate (1.178)

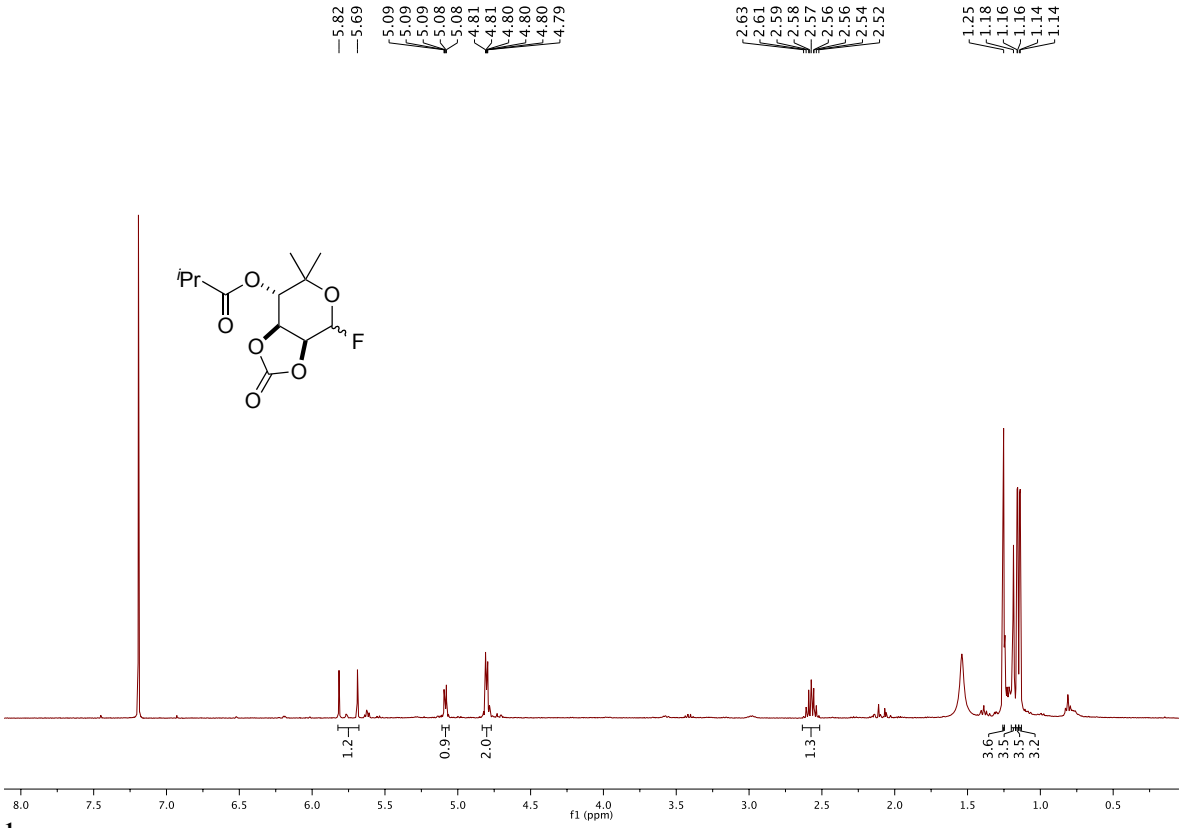


^{1}H-NMR (400 MHz, $CDCl_3$, major/minor anomer 2/1)



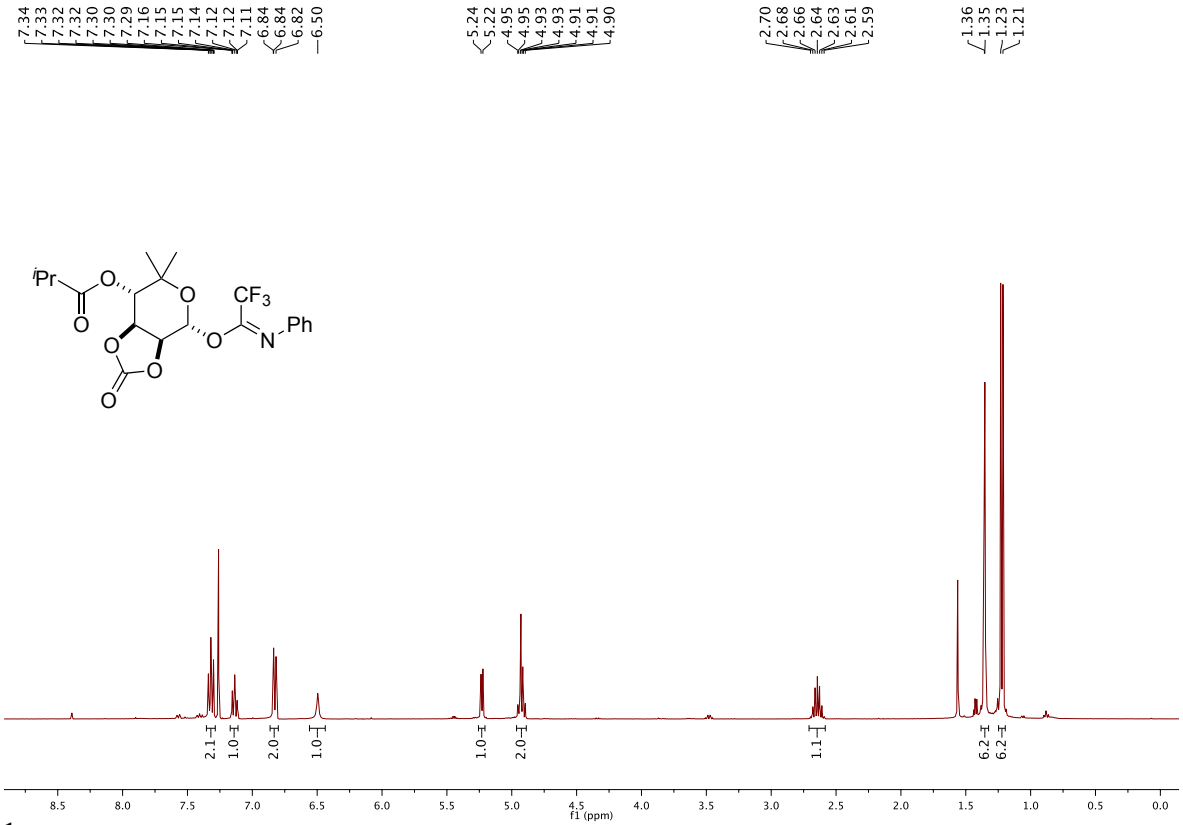
^{13}C-NMR (126 MHz, $CDCl_3$)

(3a*S*,7*S*,7a*S*)-4-fluoro-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (1.179)



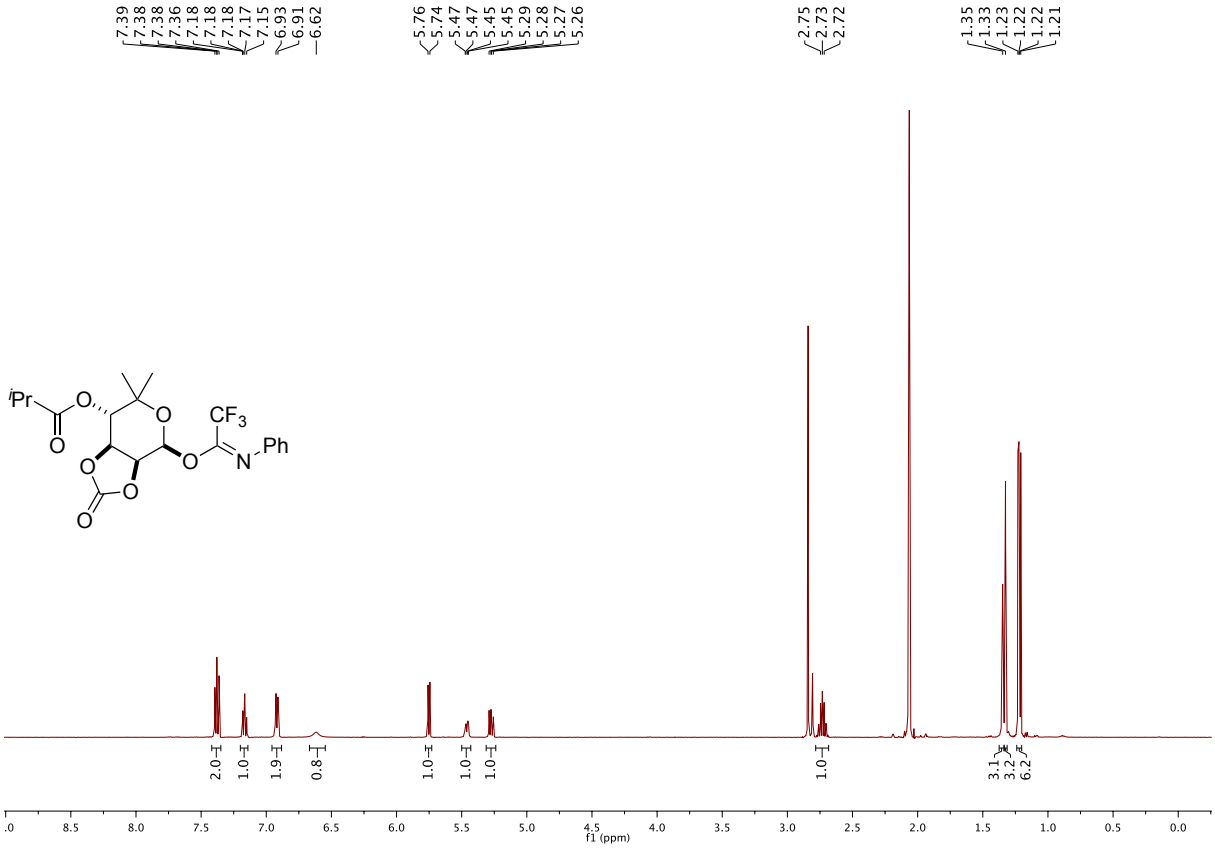
^{1}H-NMR (400 MHz, $CDCl_3$)

(3a*S*,4*S*,7*S*,7a*S*)-6,6-dimethyl-2-oxo-4-((*E*)-2,2,2-trifluoro-1-(phenylimino)ethoxy)-tetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (α-1.181)

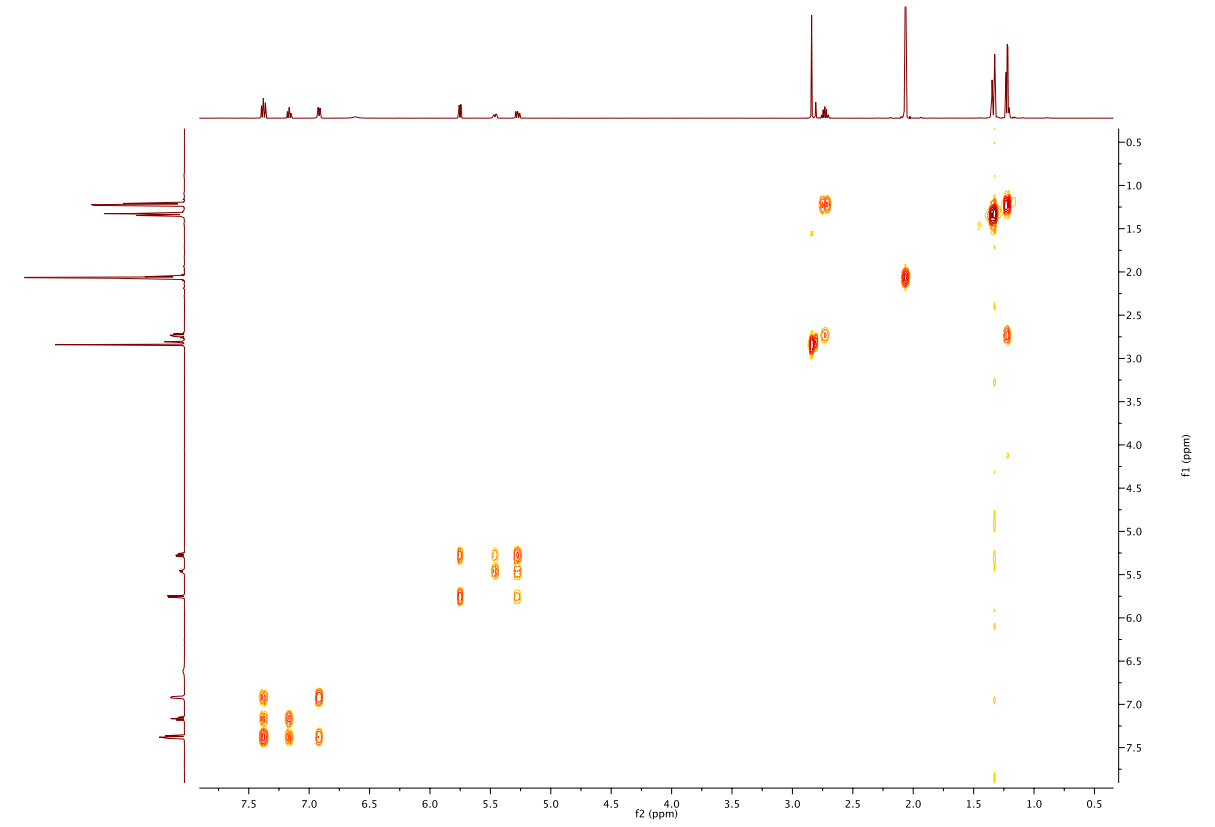


^{1}H-NMR (400 MHz, $CDCl_3$)

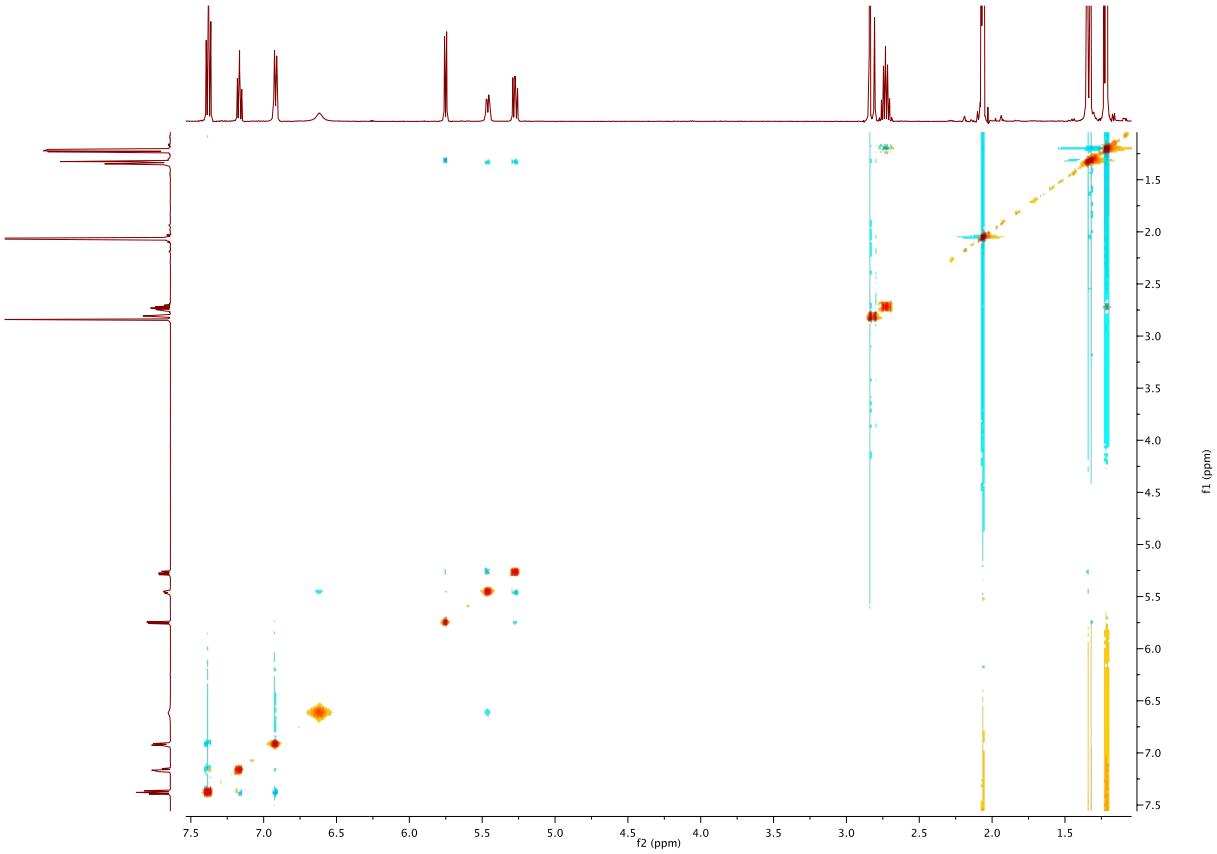
(3a*S*,4*R*,7*S*,7a*S*)-6,6-dimethyl-2-oxo-4-((*E*)-2,2,2-trifluoro-1-(phenylimino)ethoxy)-tetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (β-1.181)



^{1}H-NMR (400 MHz, Acetone-d_6)

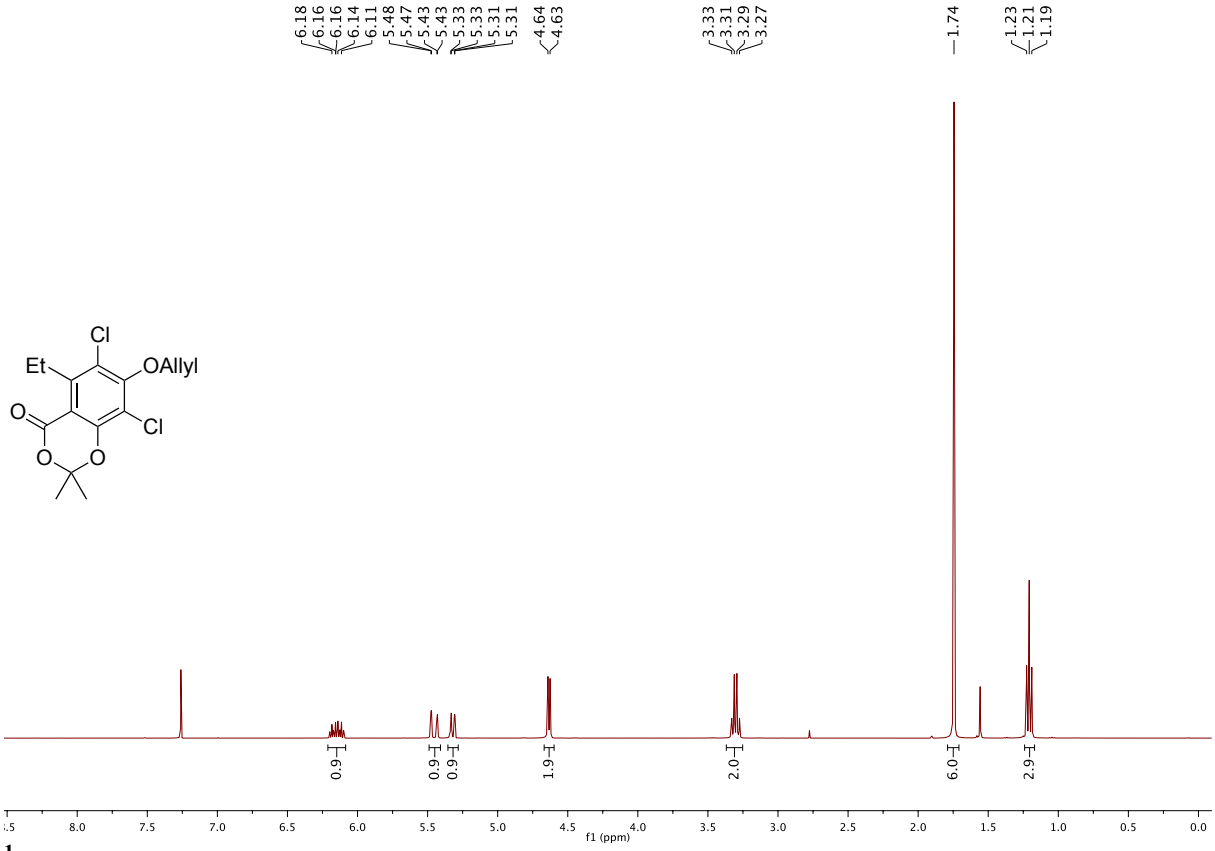


COSY (400 MHz, Acetone-d_6)

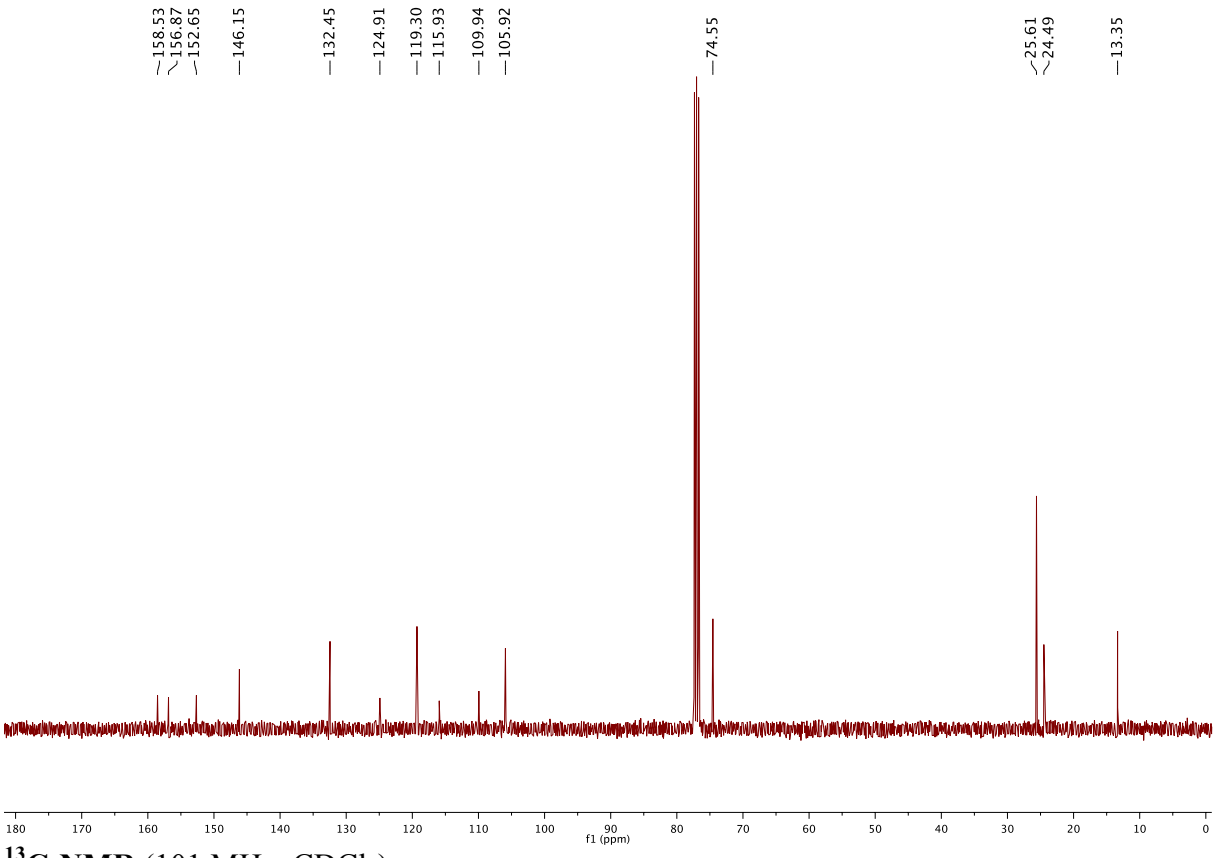


NOESY (400 MHz, Acetone-d_6)

7-(allyloxy)-6,8-dichloro-5-ethyl-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (1.128)

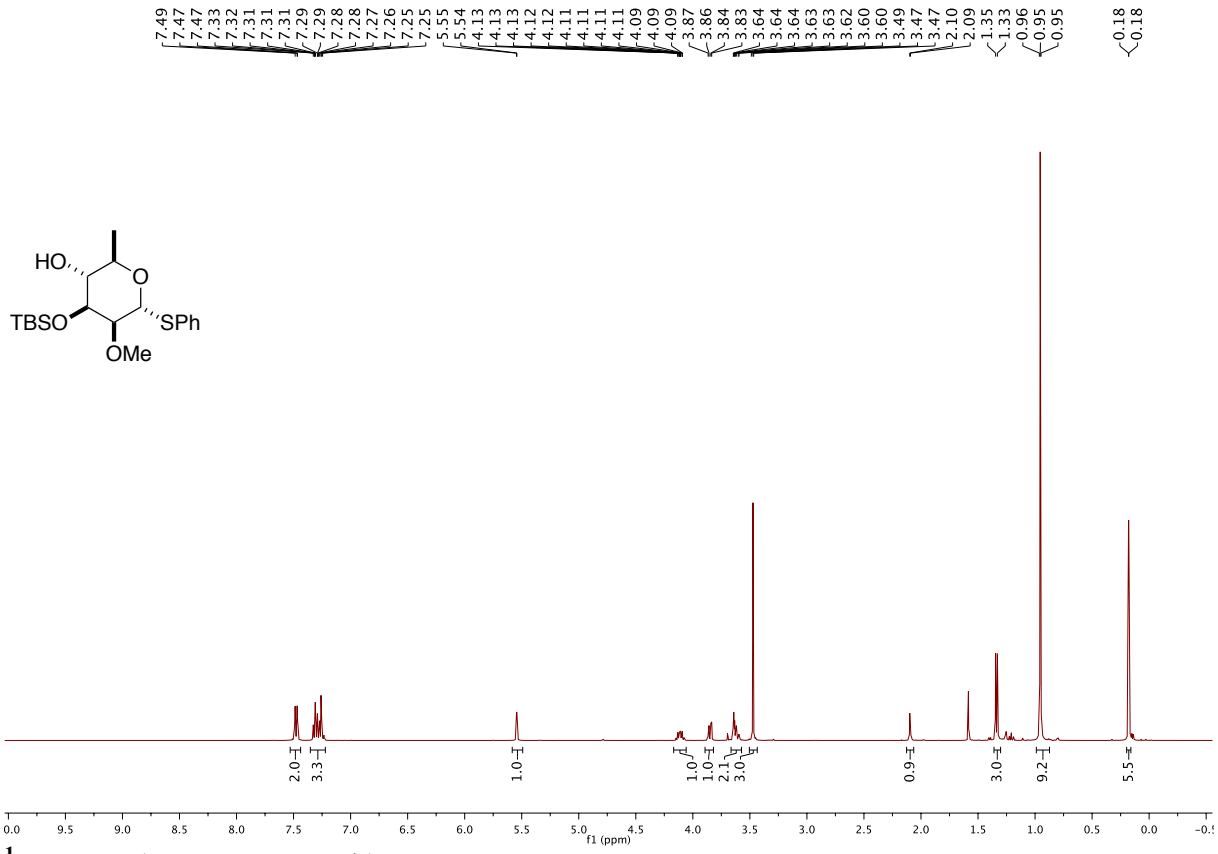


^{1}H-NMR (400 MHz, $CDCl_3$)

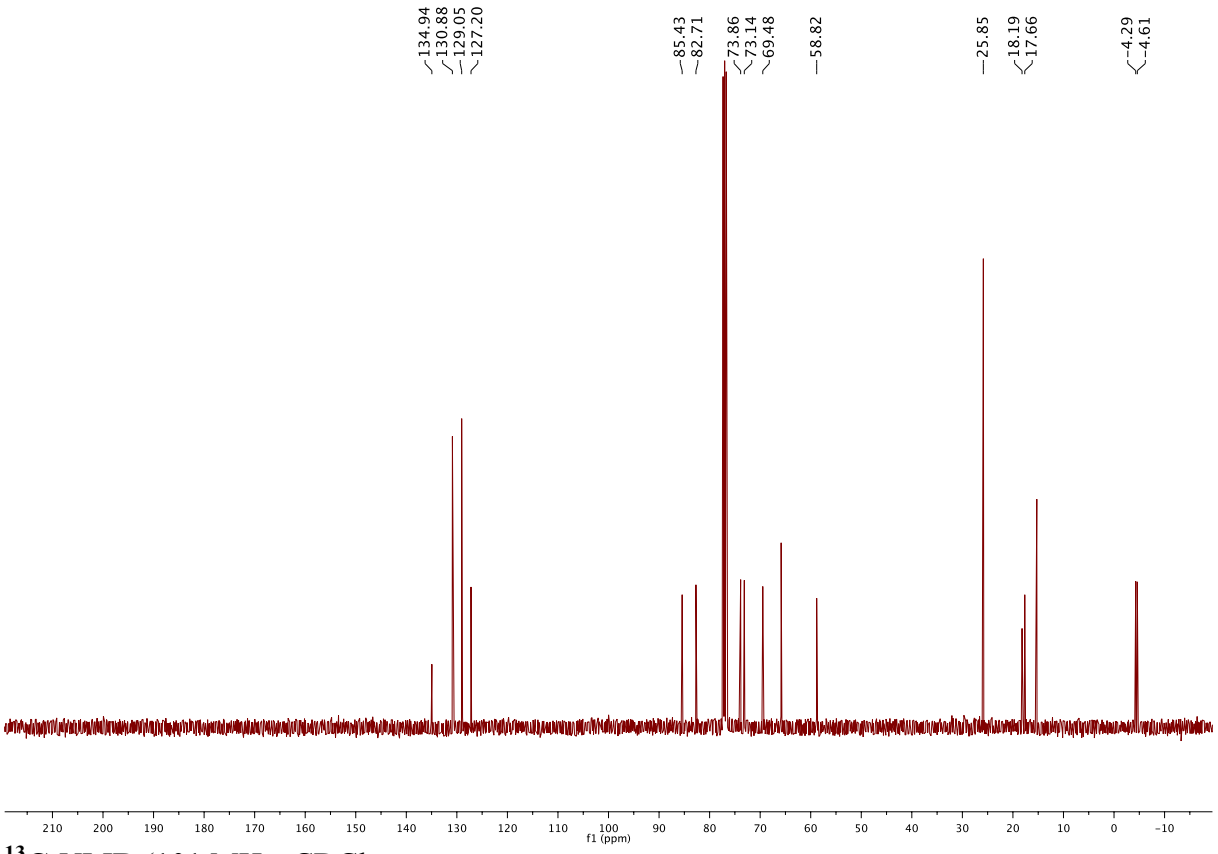


^{13}C-NMR (101 MHz, $CDCl_3$)

2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-ol (1.129)

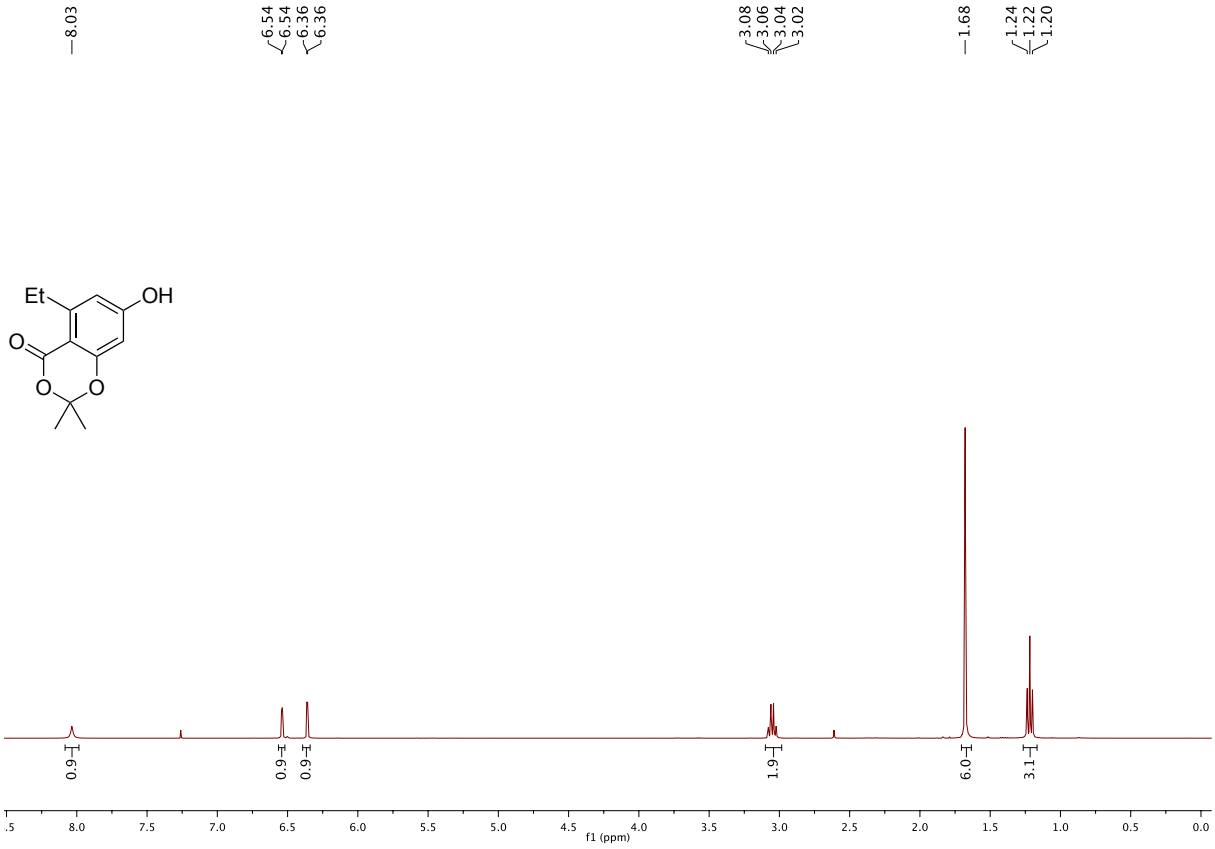


^{1}H-NMR (400 MHz, $CDCl_3$)

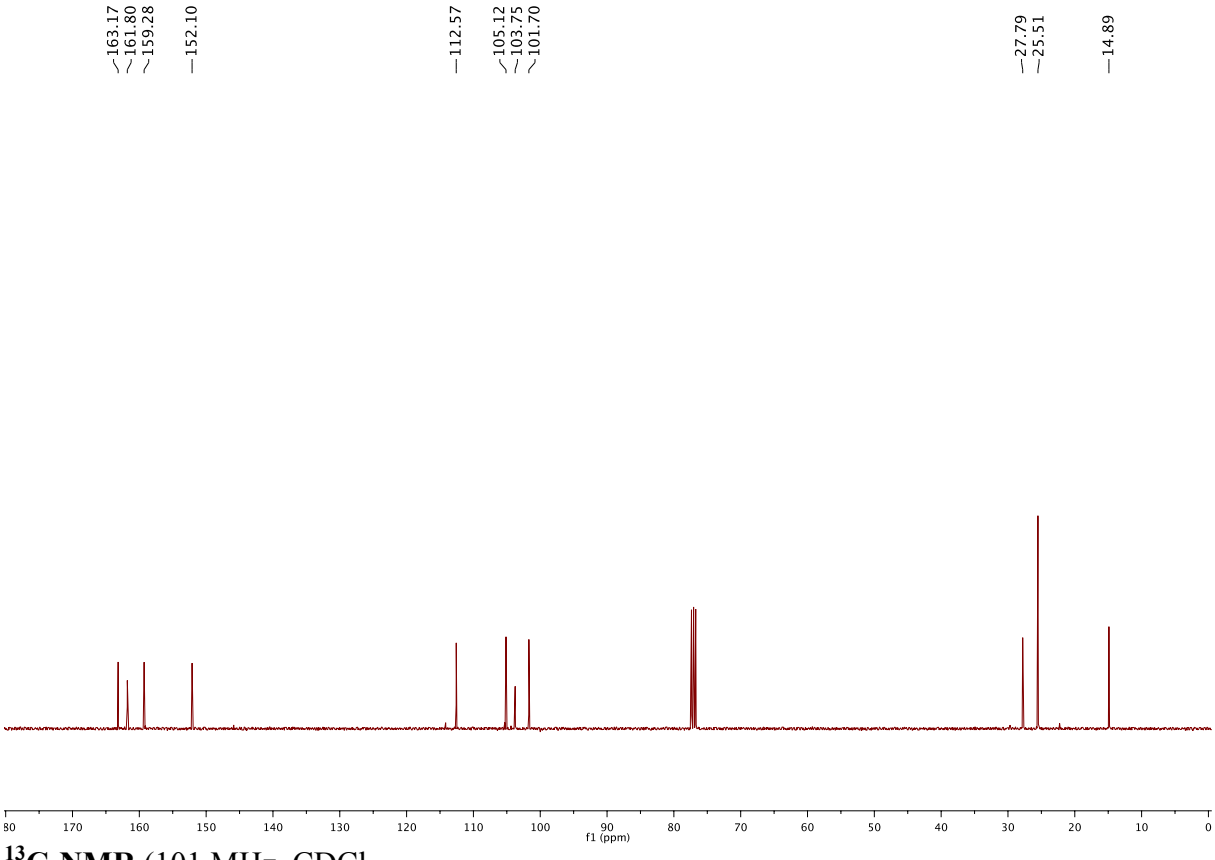


^{13}C-NMR (101 MHz, $CDCl_3$

5-ethyl-7-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (1.133)

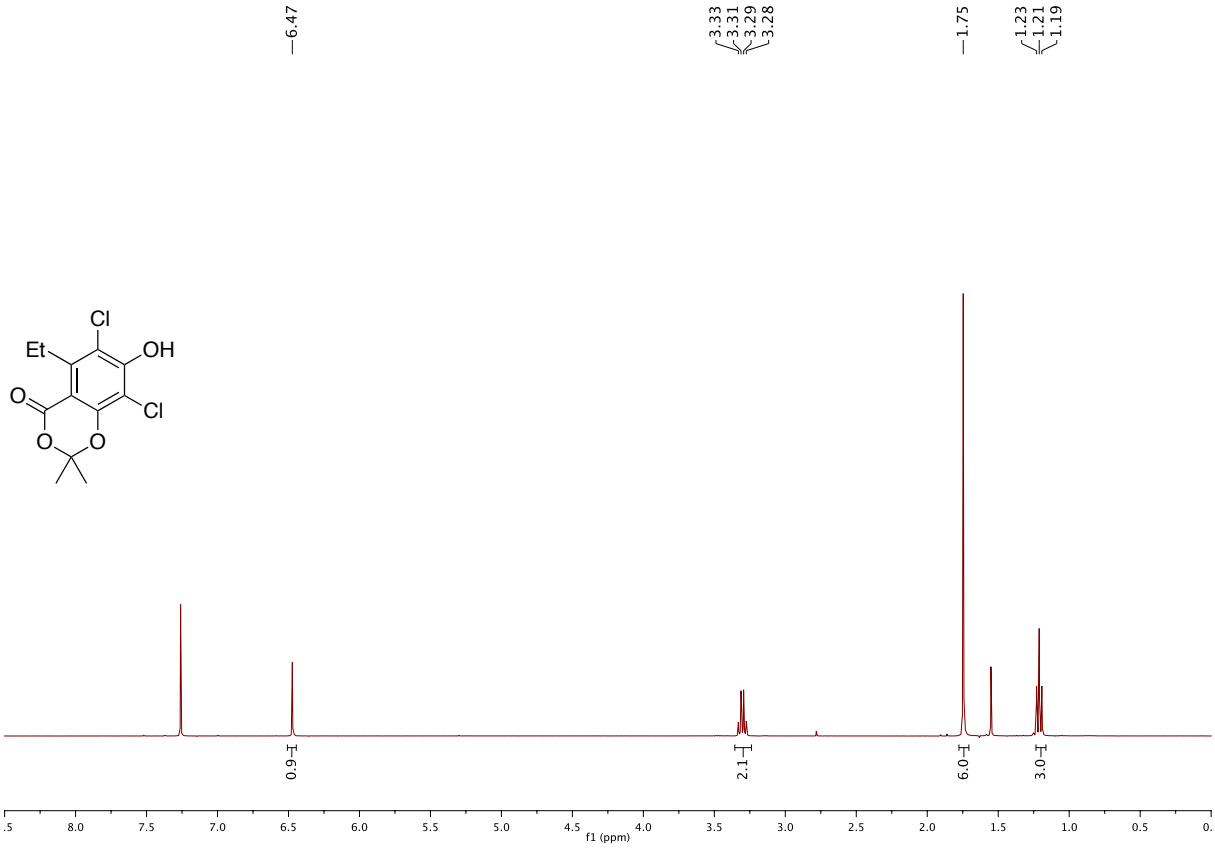


^{1}H-NMR (400 MHz, $CDCl_3$)

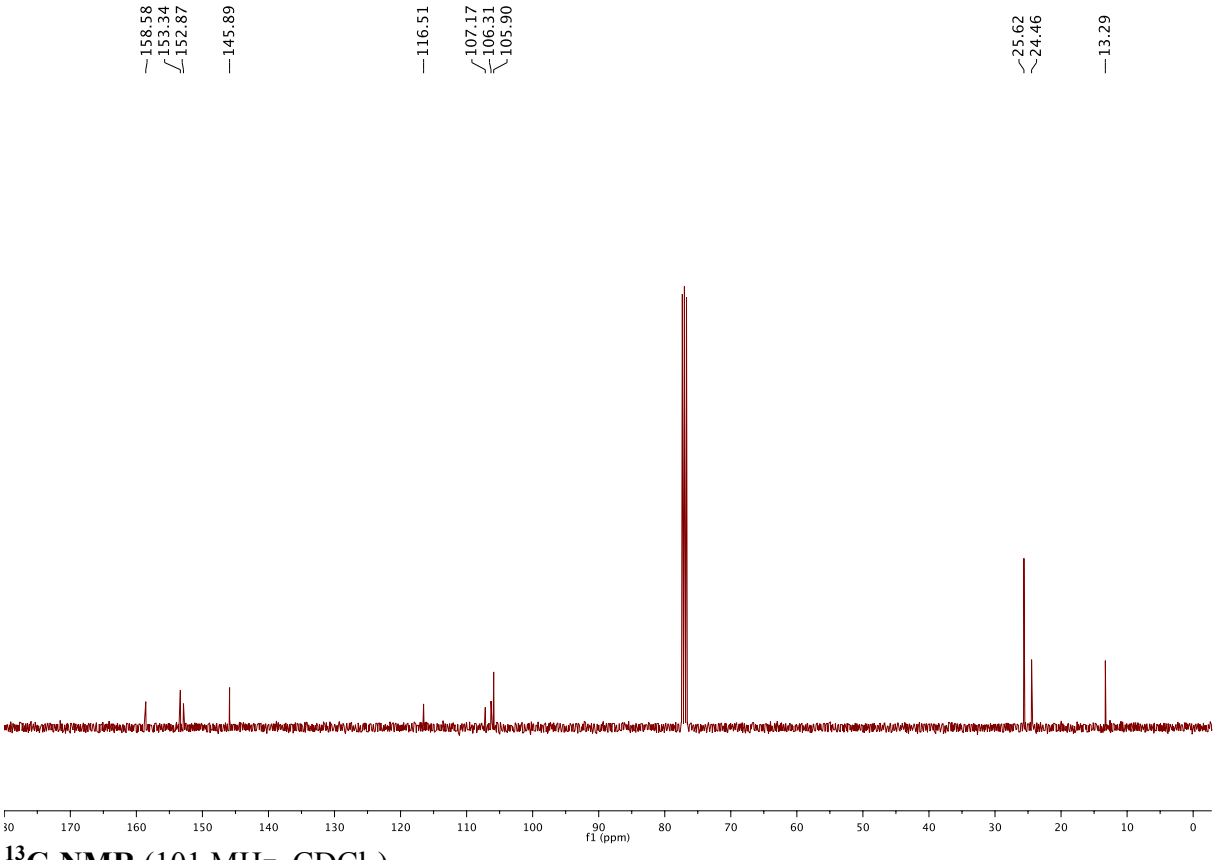


^{13}C-NMR (101 MHz, $CDCl_3$

6,8-dichloro-5-ethyl-7-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (1.134)

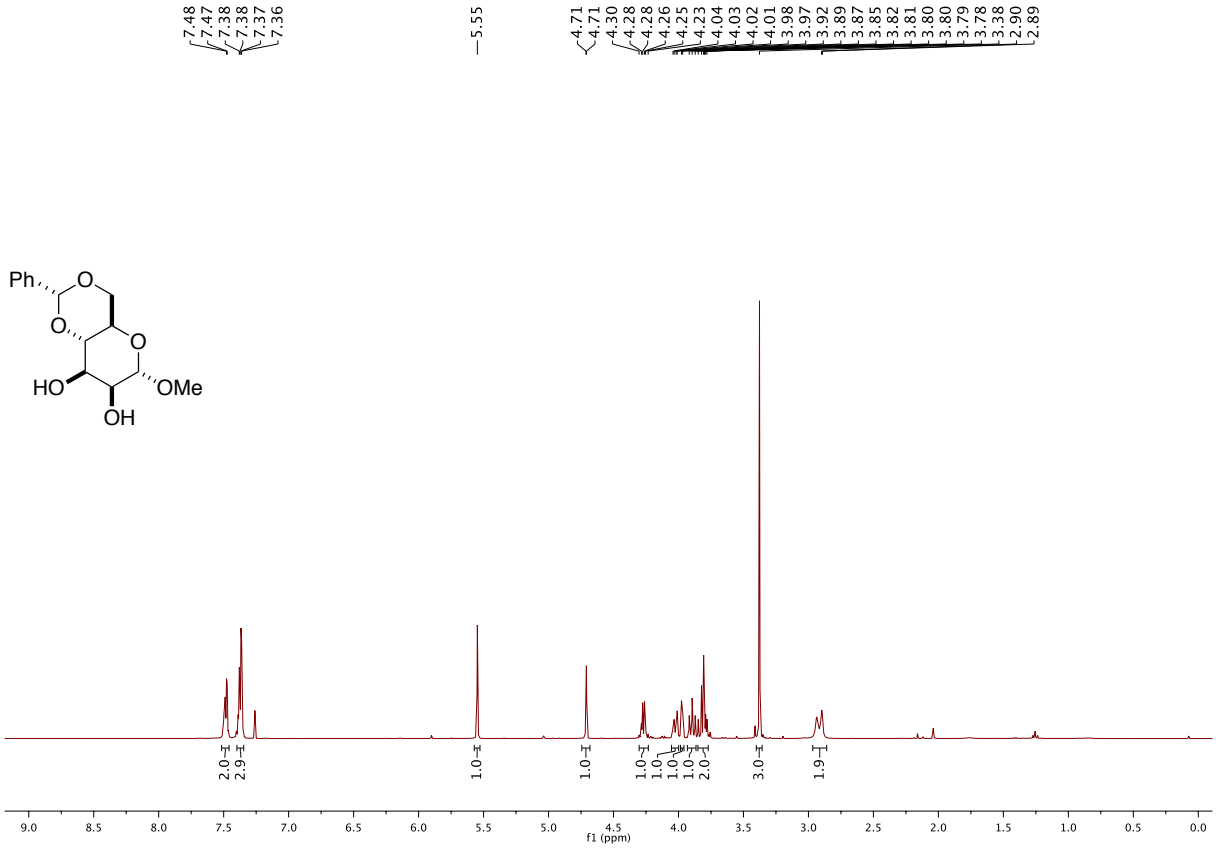


^{1}H-NMR (400 MHz, $CDCl_3$)

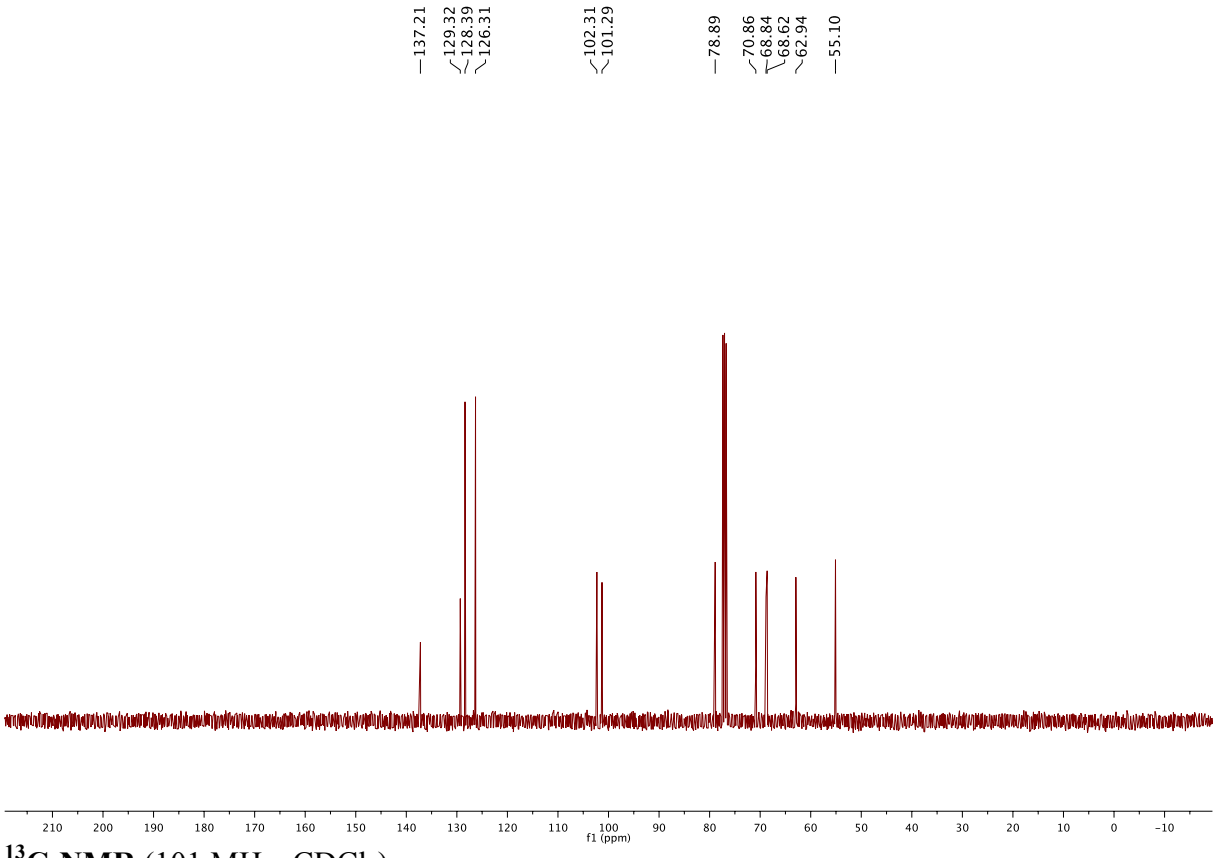


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,4a*R*,6*S*,7*S*,8*R*,8a*S*)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (1.135)

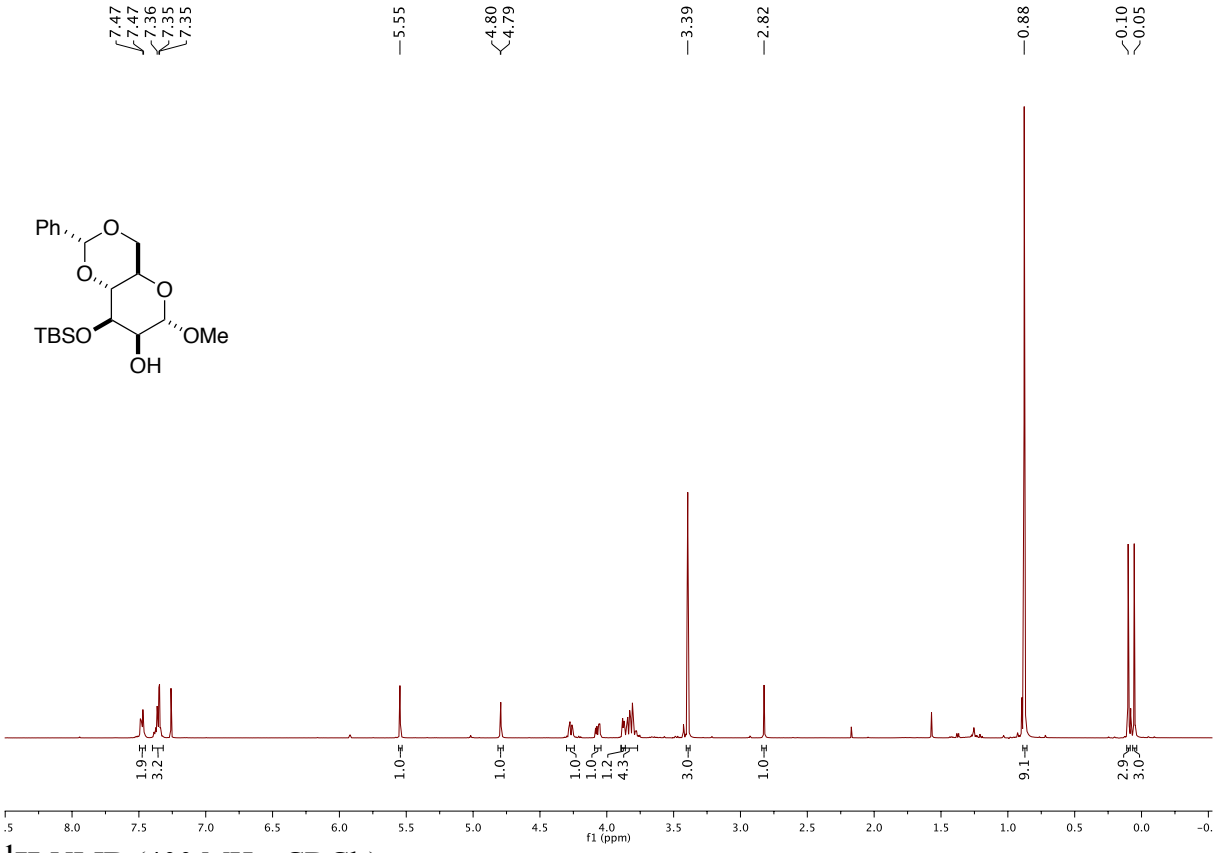


^{1}H-NMR (400 MHz, $CDCl_3$)

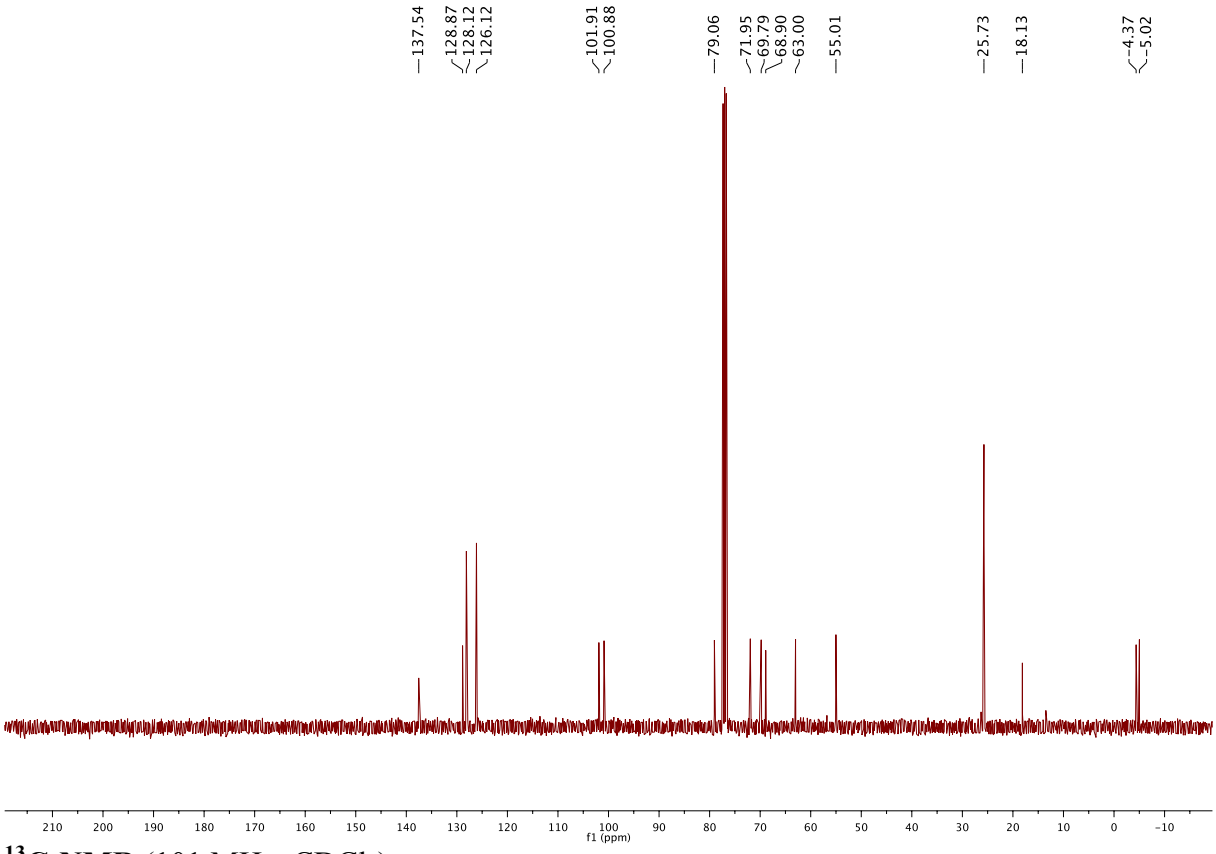


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,4a*R*,6*S*,7*S*,8*R*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (1.135b)

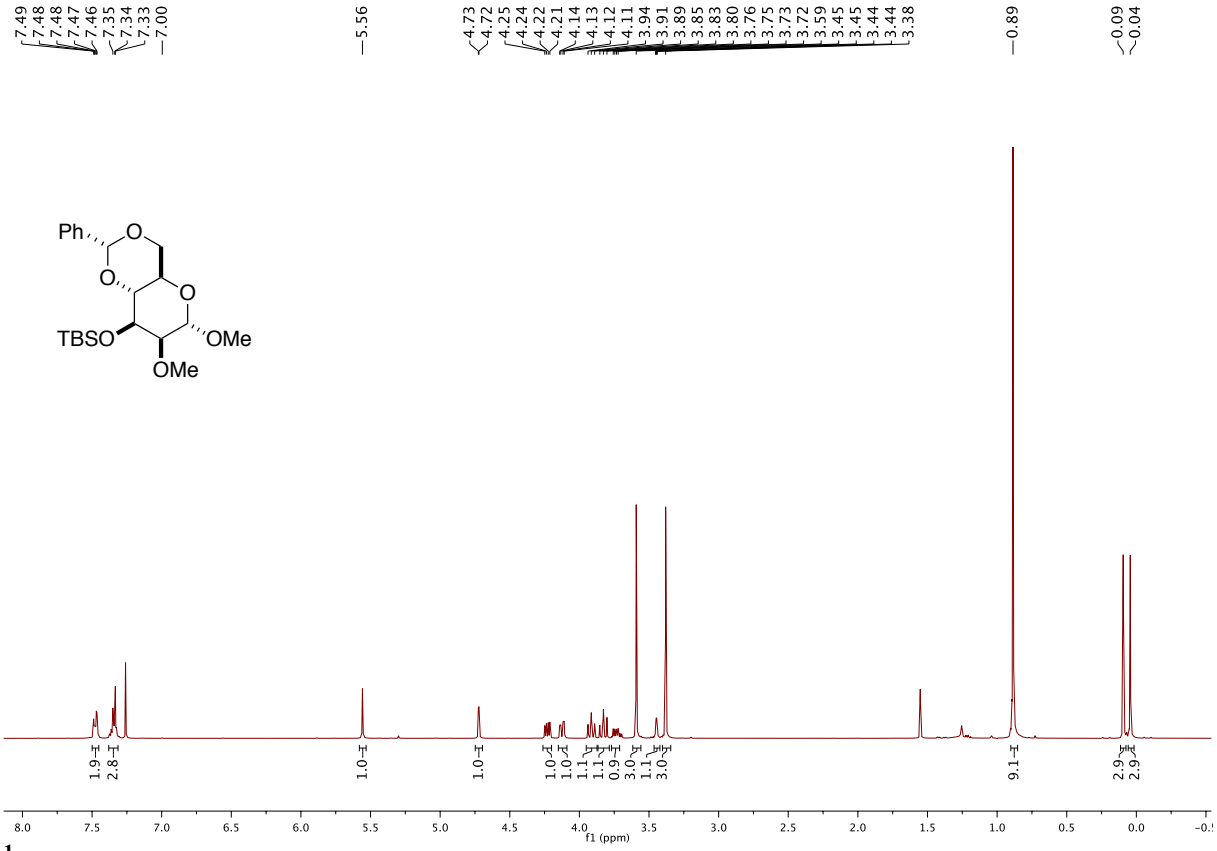


^{1}H-NMR (400 MHz, $CDCl_3$)

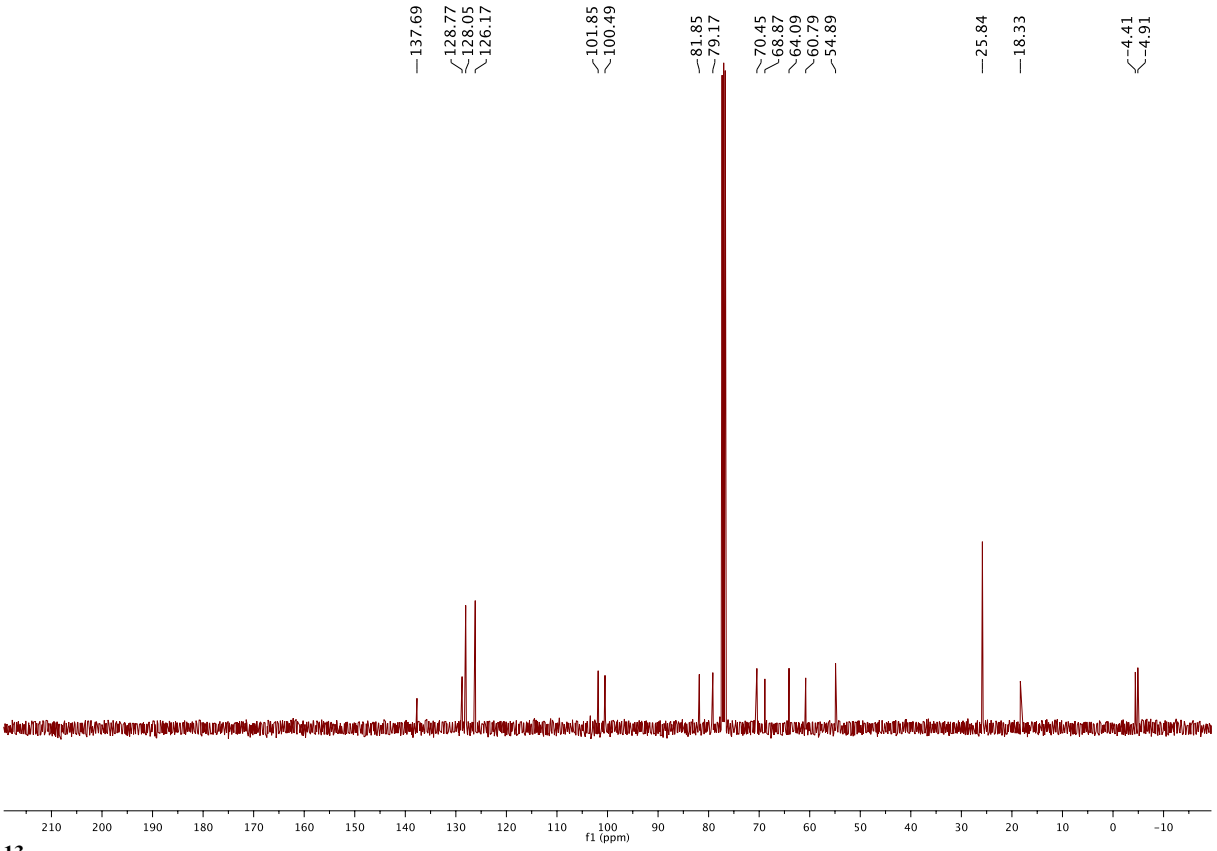


^{13}C-NMR (101 MHz, $CDCl_3$)

tert-butyl(((2*R*,4a*R*,6*S*,7*S*,8*S*,8a*R*)-6,7-dimethoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)oxy)dimethylsilane (1.136)

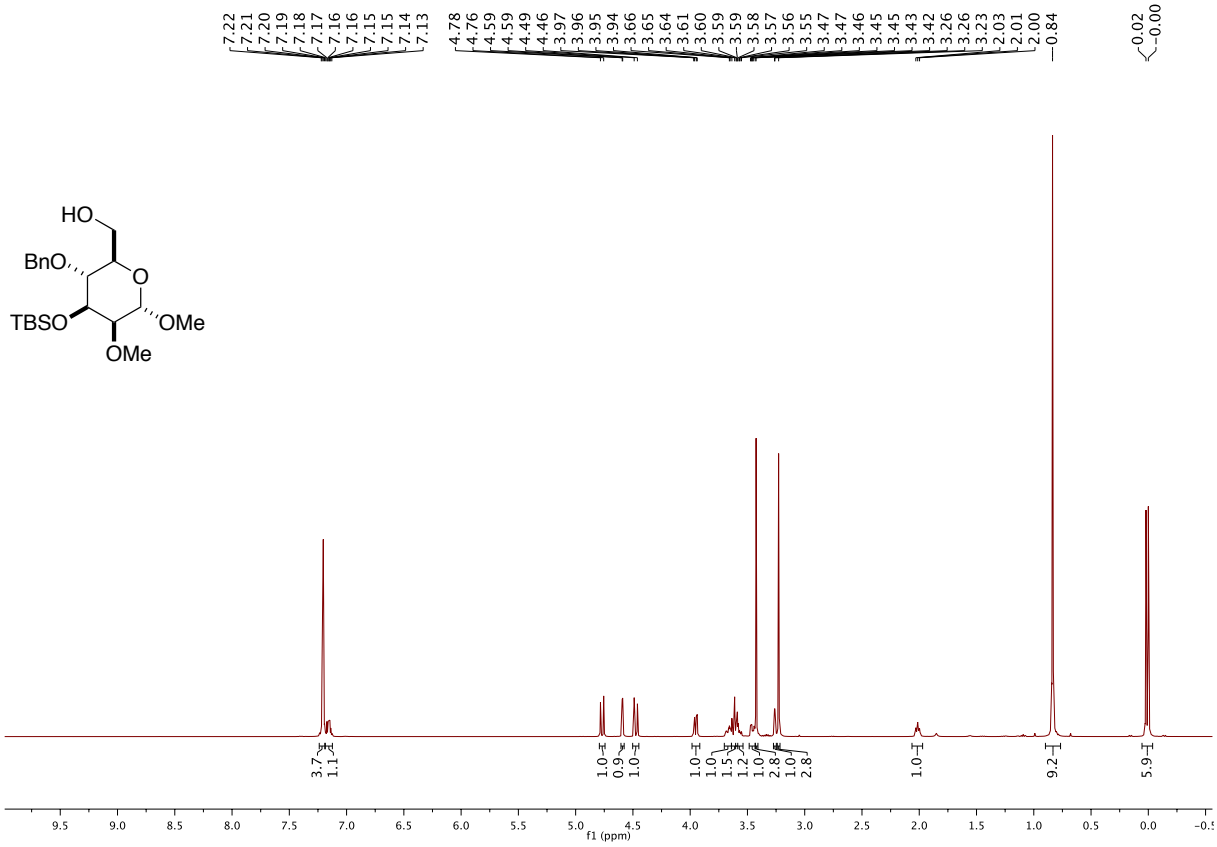


^{1}H-NMR (400 MHz, $CDCl_3$)

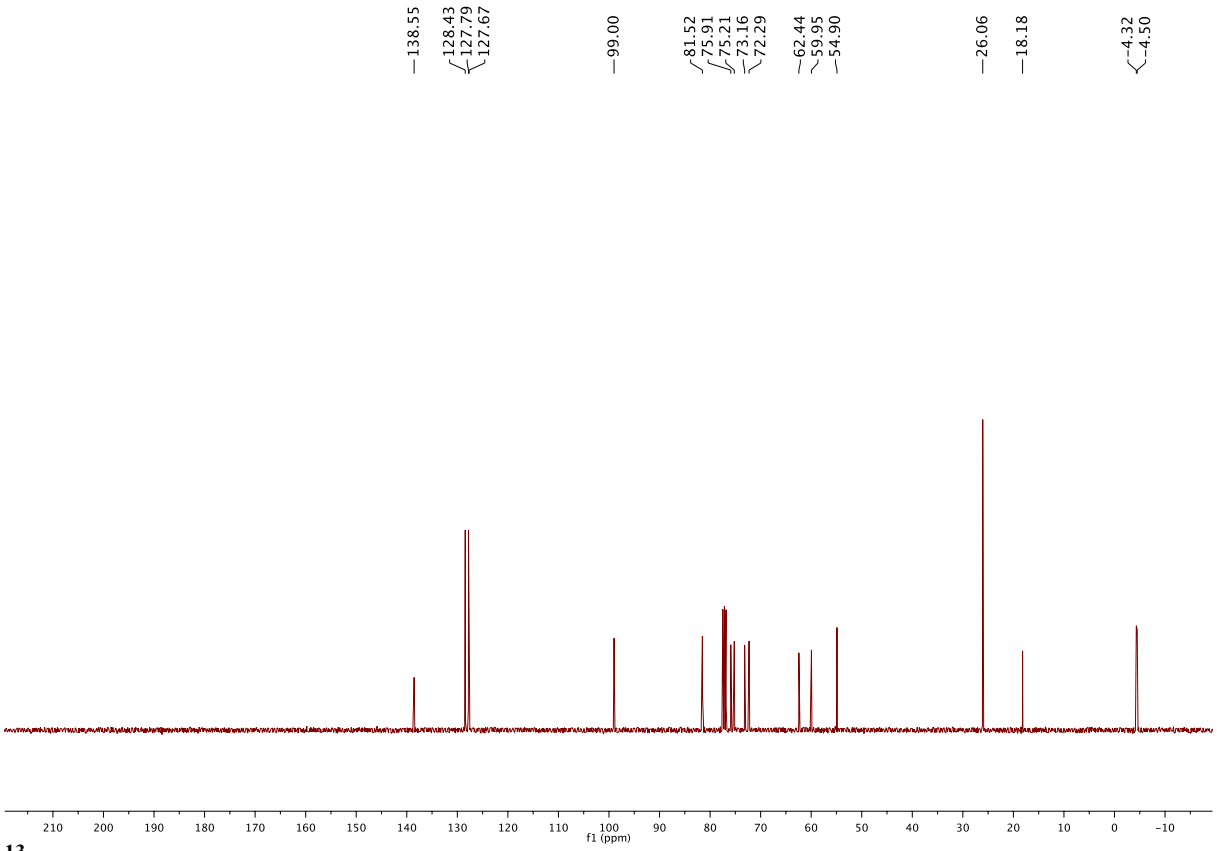


^{13}C-NMR (101 MHz, $CDCl_3$)

((2*R*,3*R*,4*S*,5*S*,6*S*)-3-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-5,6-dimethoxytetrahydro-2*H*-pyran-2-yl)methanol (1.137)

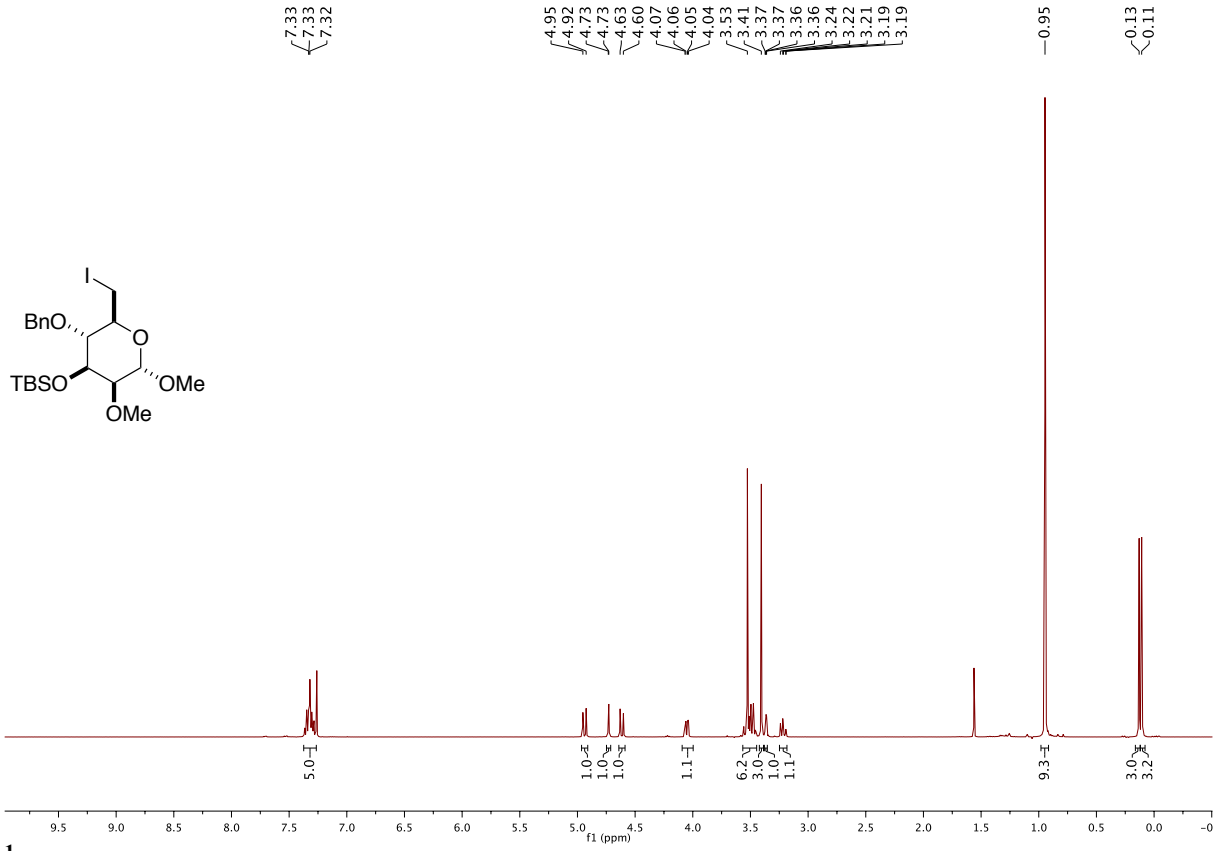


^{1}H-NMR (400 MHz, $CDCl_3$)

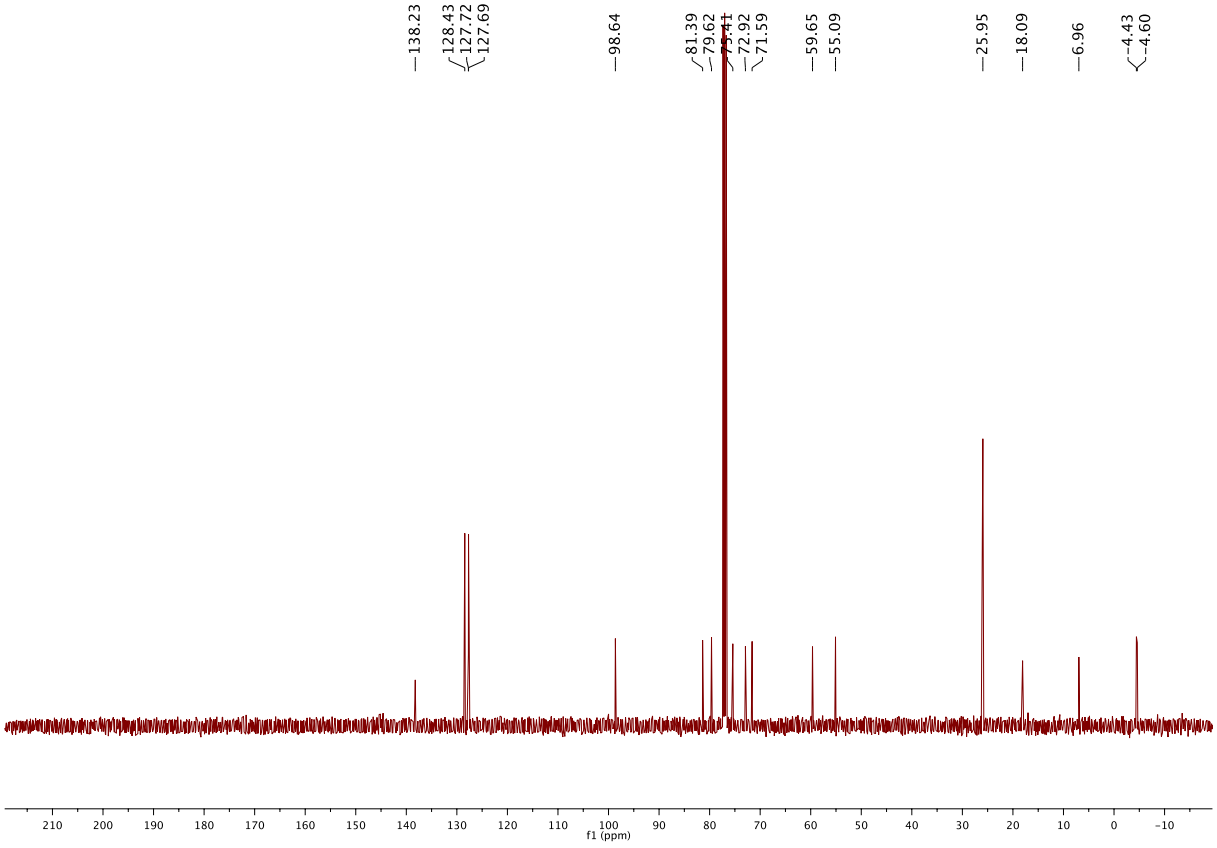


^{13}C-NMR (101 MHz, $CDCl_3$)

(((2*S*,3*R*,4*S*,5*S*,6*S*)-3-(benzyloxy)-2-(iodomethyl)-5,6-dimethoxytetrahydro-2*H*-pyran-4-yl)oxy)(tert-butyl)dimethylsilane (1.137b)

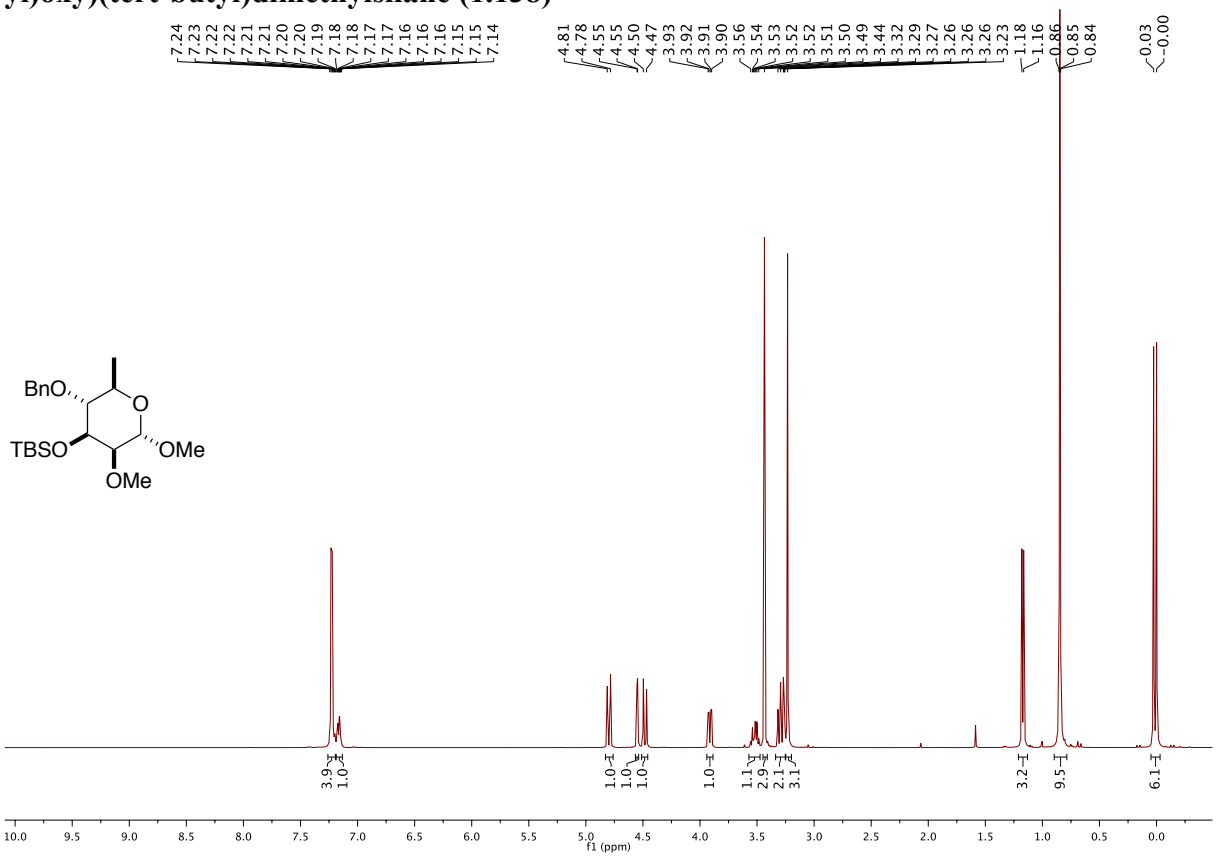


^{1}H-NMR (400 MHz, $CDCl_3$)

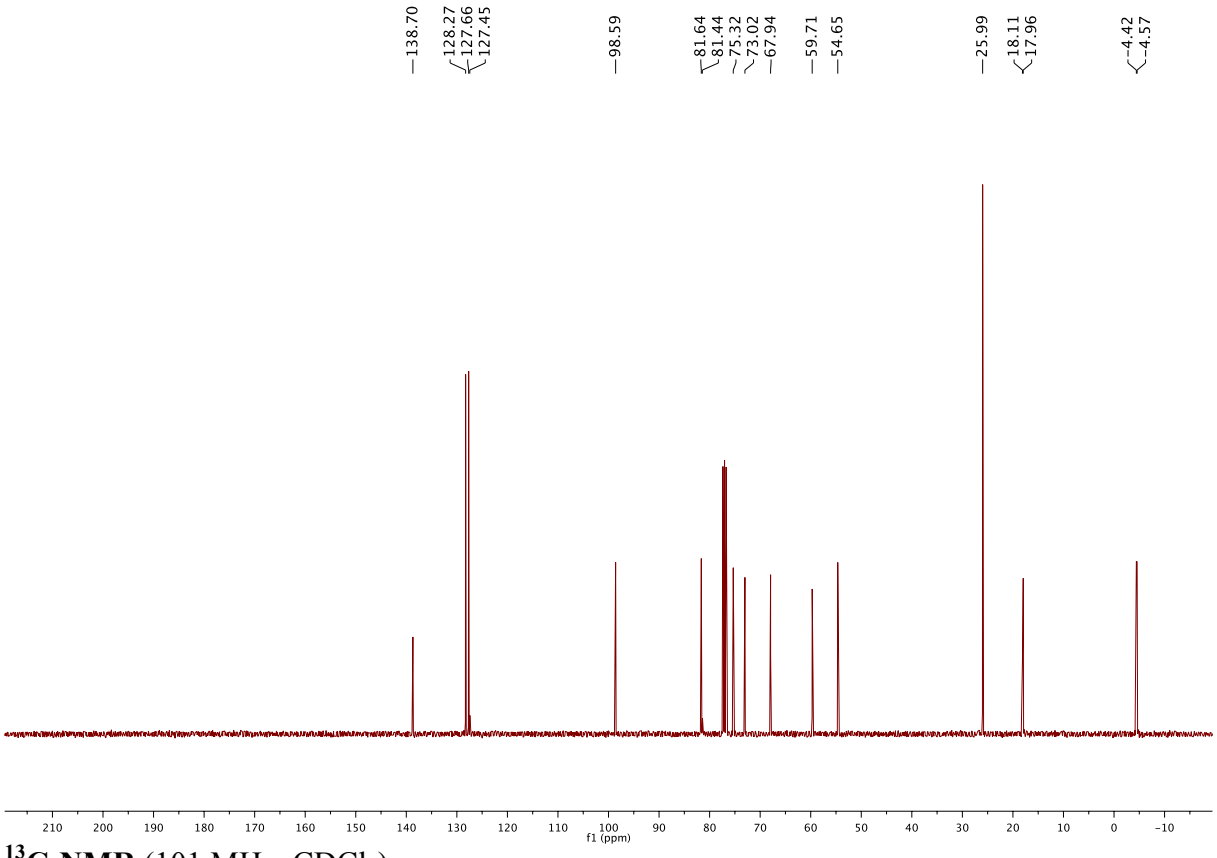


^{13}C-NMR (101 MHz, $CDCl_3$)

(((2*R*,3*R*,4*S*,5*S*,6*S*)-3-(benzyloxy)-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-4-yl)oxy)(tert-butyl)dimethylsilane (1.138)

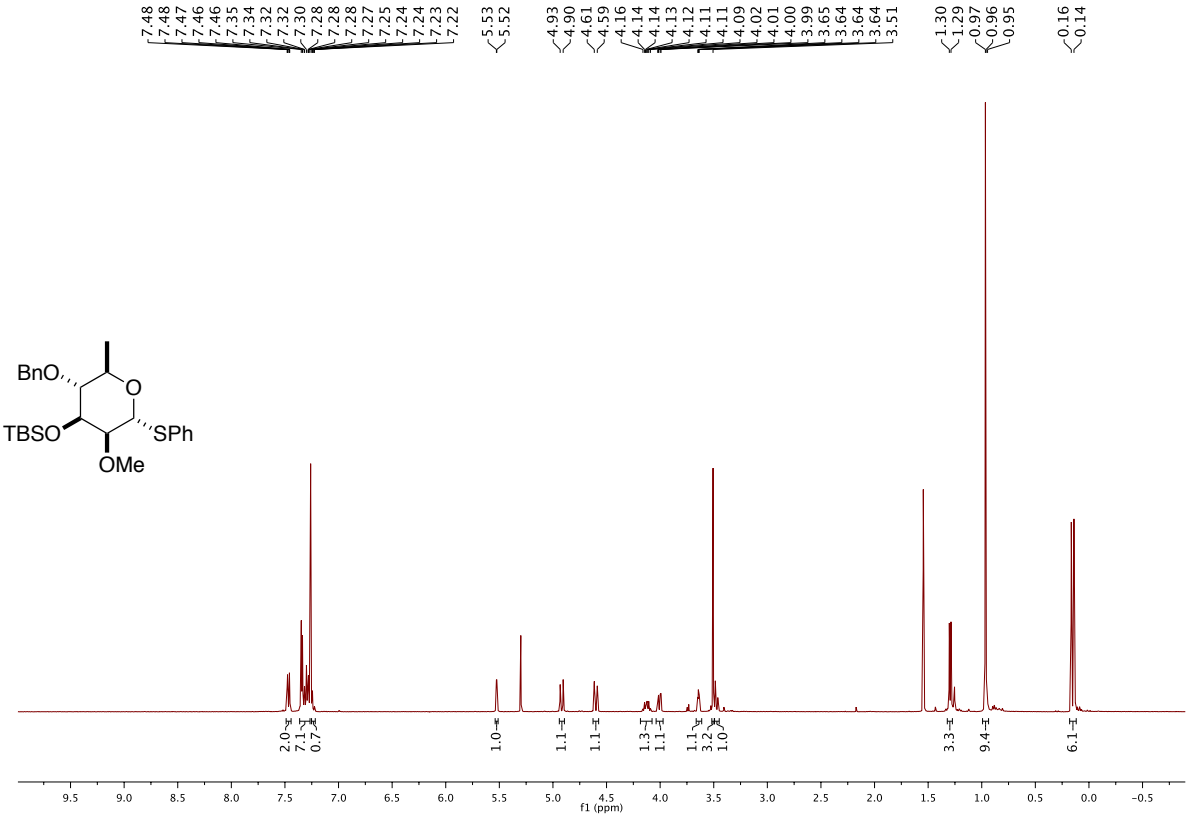


^{1}H-NMR (400 MHz, $CDCl_3$)

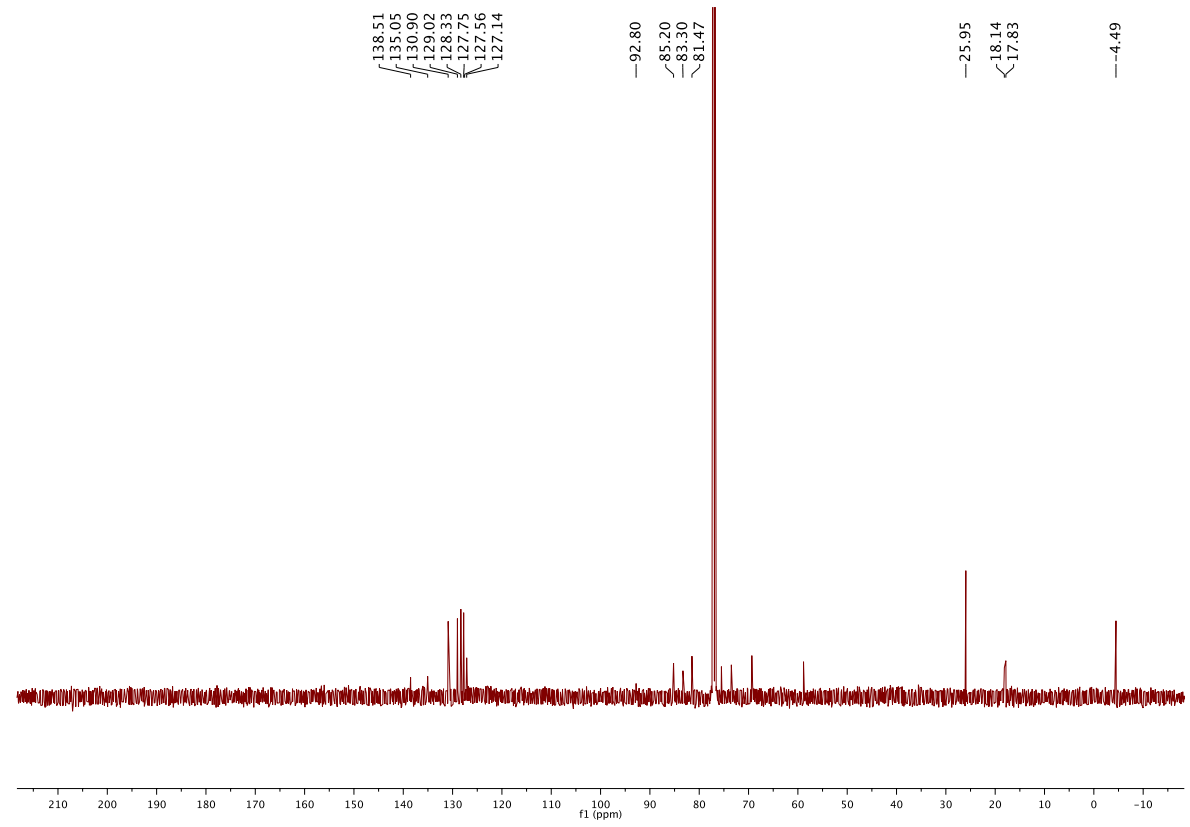


^{13}C-NMR (101 MHz, $CDCl_3$)

(((2*R*,3*R*,4*S*,5*S*,6*R*)-3-(benzyloxy)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-4-yl)oxy)(*tert*-butyl)dimethylsilane (1.139)

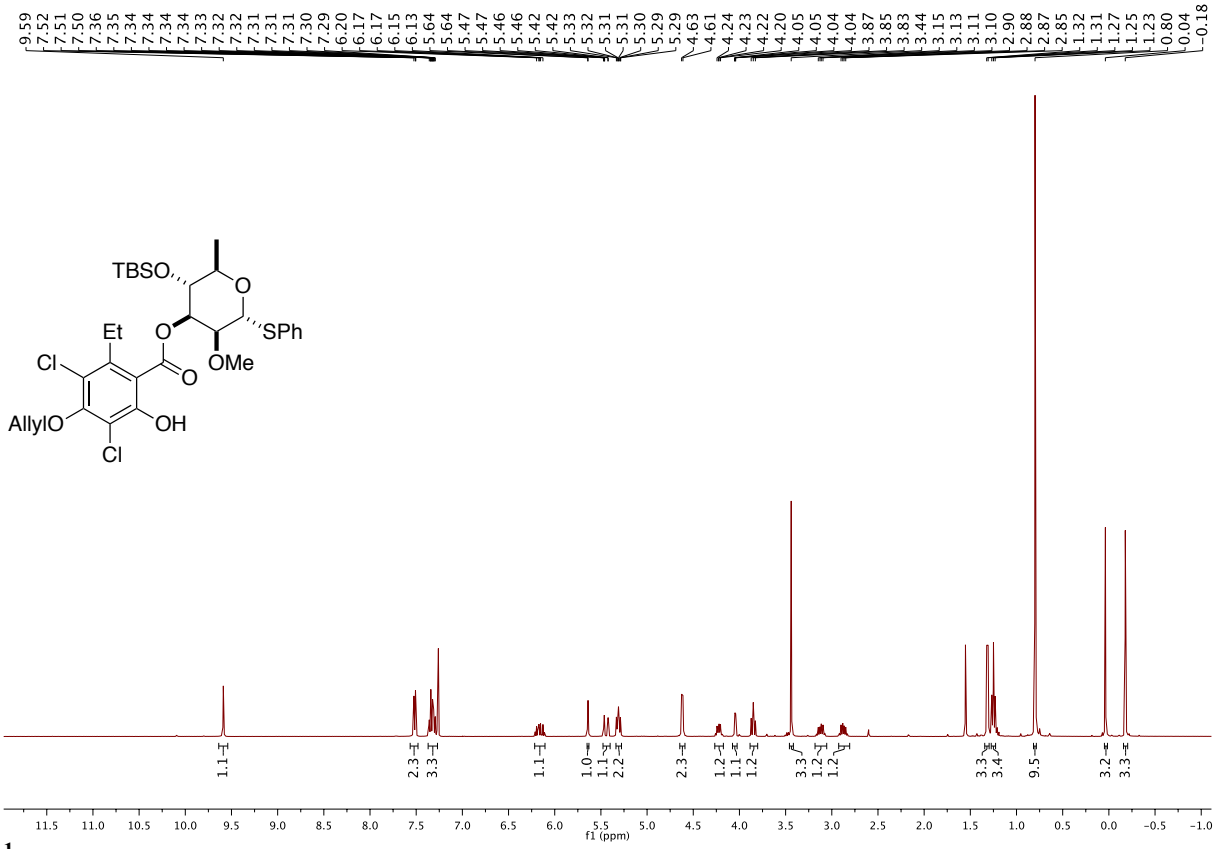


^{1}H-NMR (400 MHz, $CDCl_3$)

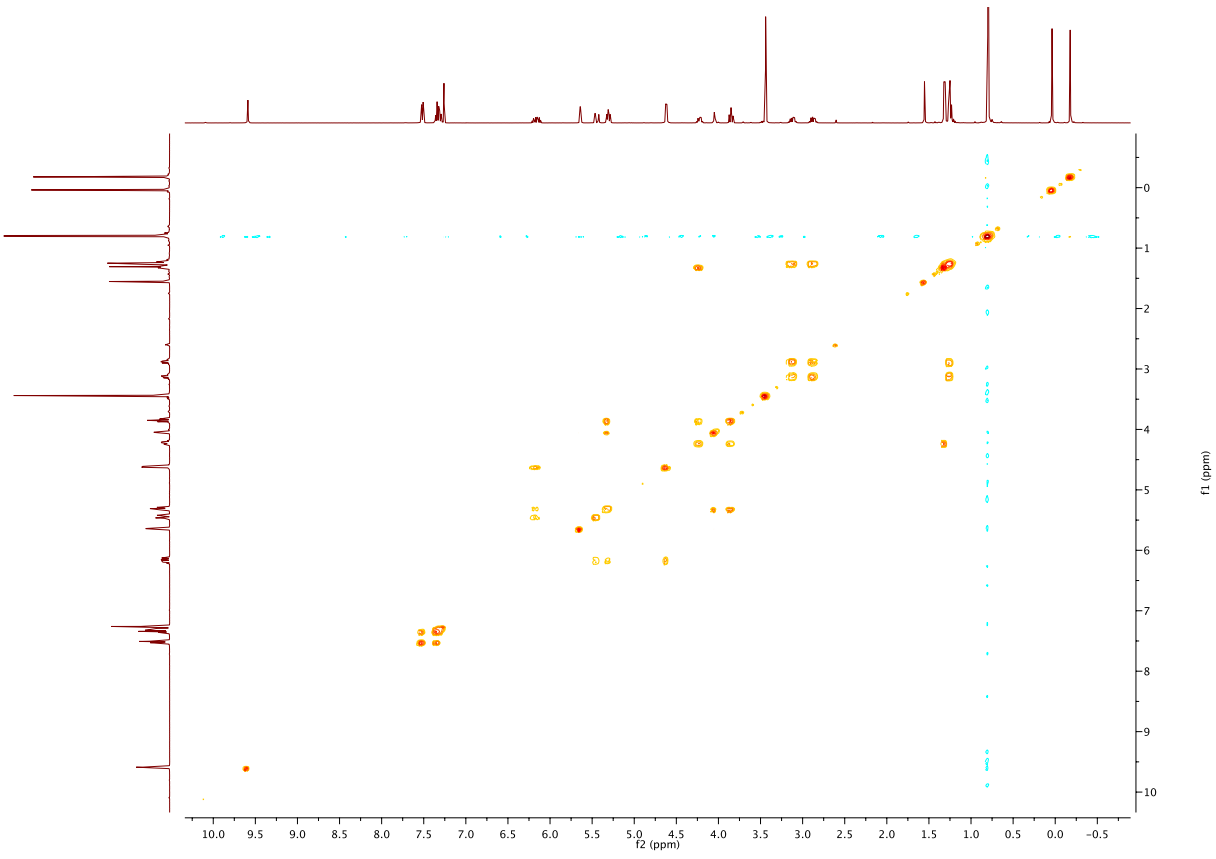


^{13}C-NMR (101 MHz, $CDCl_3$)

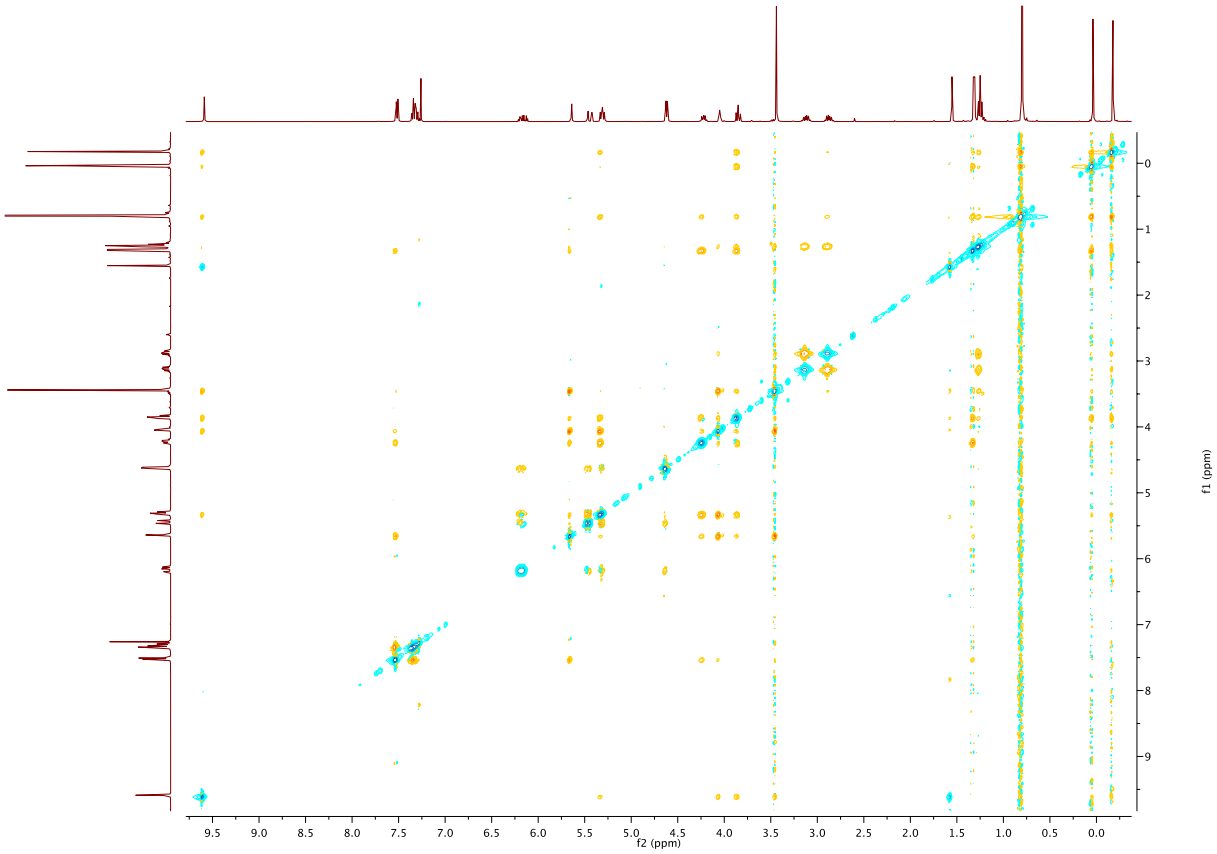
(2*R*,3*R*,4*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)-tetrahydro-2*H*-pyran-4-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.140)



^{1}H-NMR (400 MHz, $CDCl_3$)

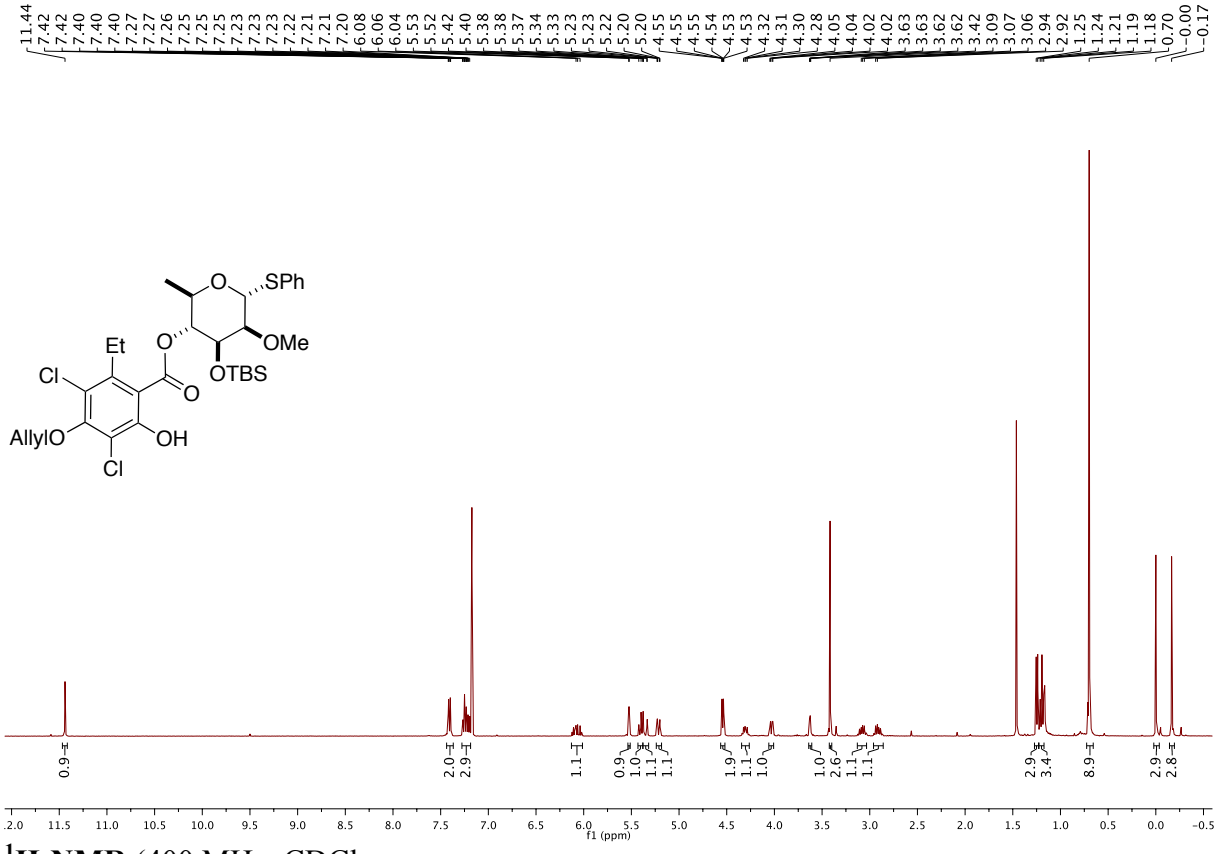


COSY (500 MHz, $CDCl_3$)



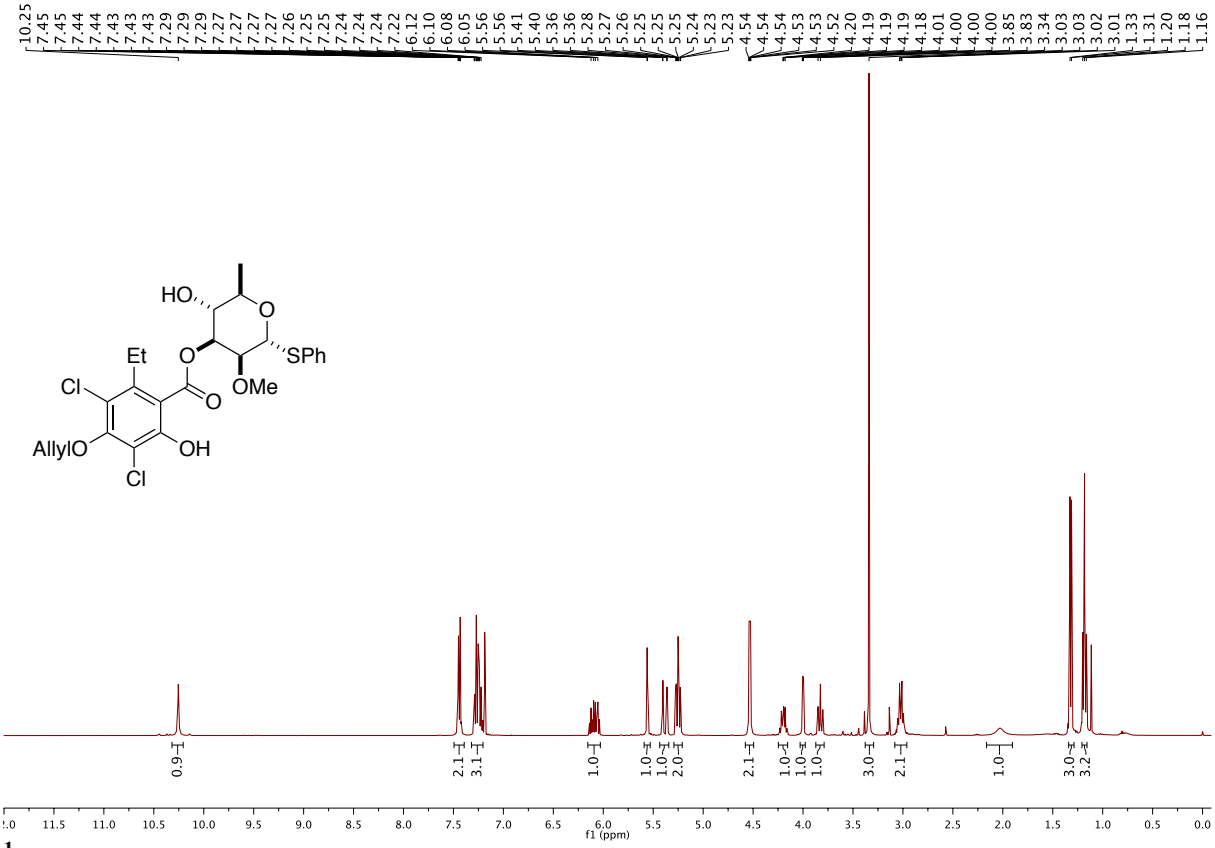
NOESY (500 MHz, $CDCl_3$)

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)-tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.127)

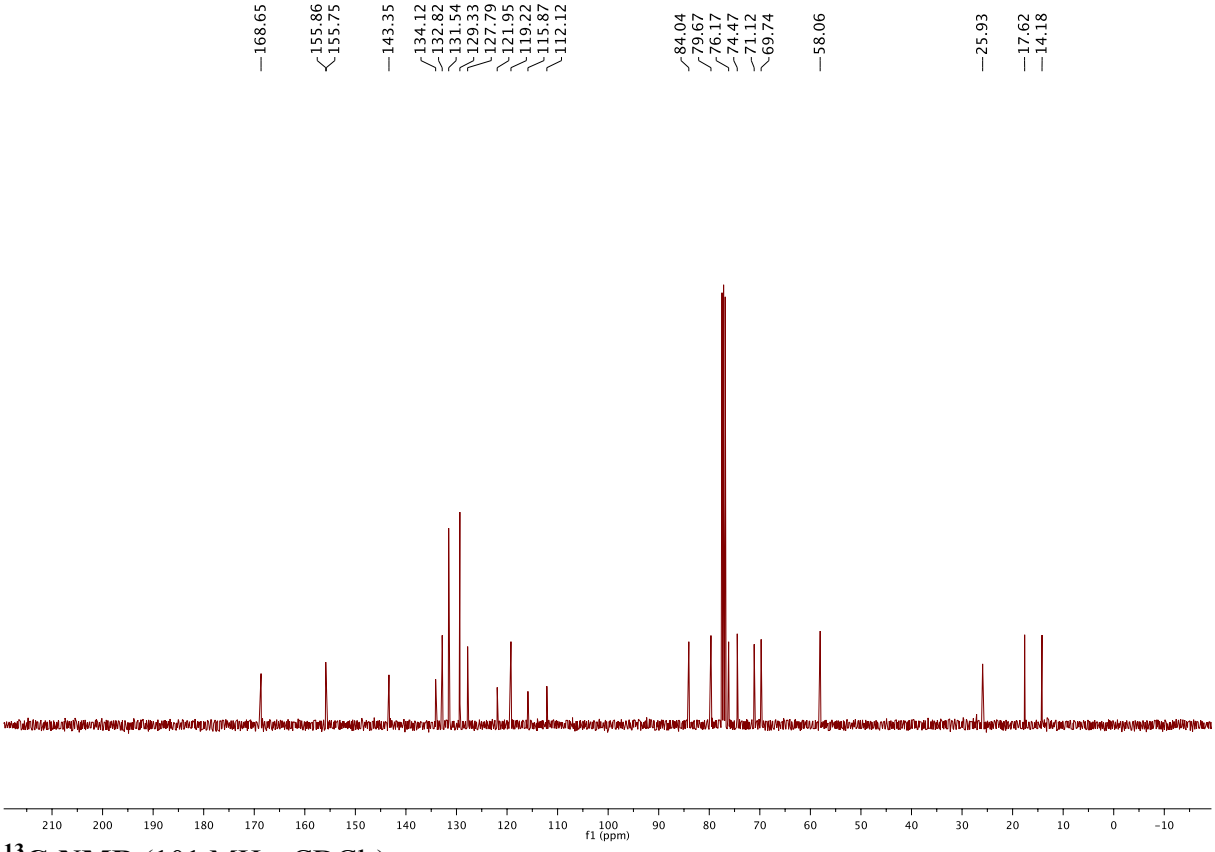


^{1}H-NMR (400 MHz, $CDCl_3$)

(2*R*,3*R*,4*S*,5*S*,6*R*)-3-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-4-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.141)

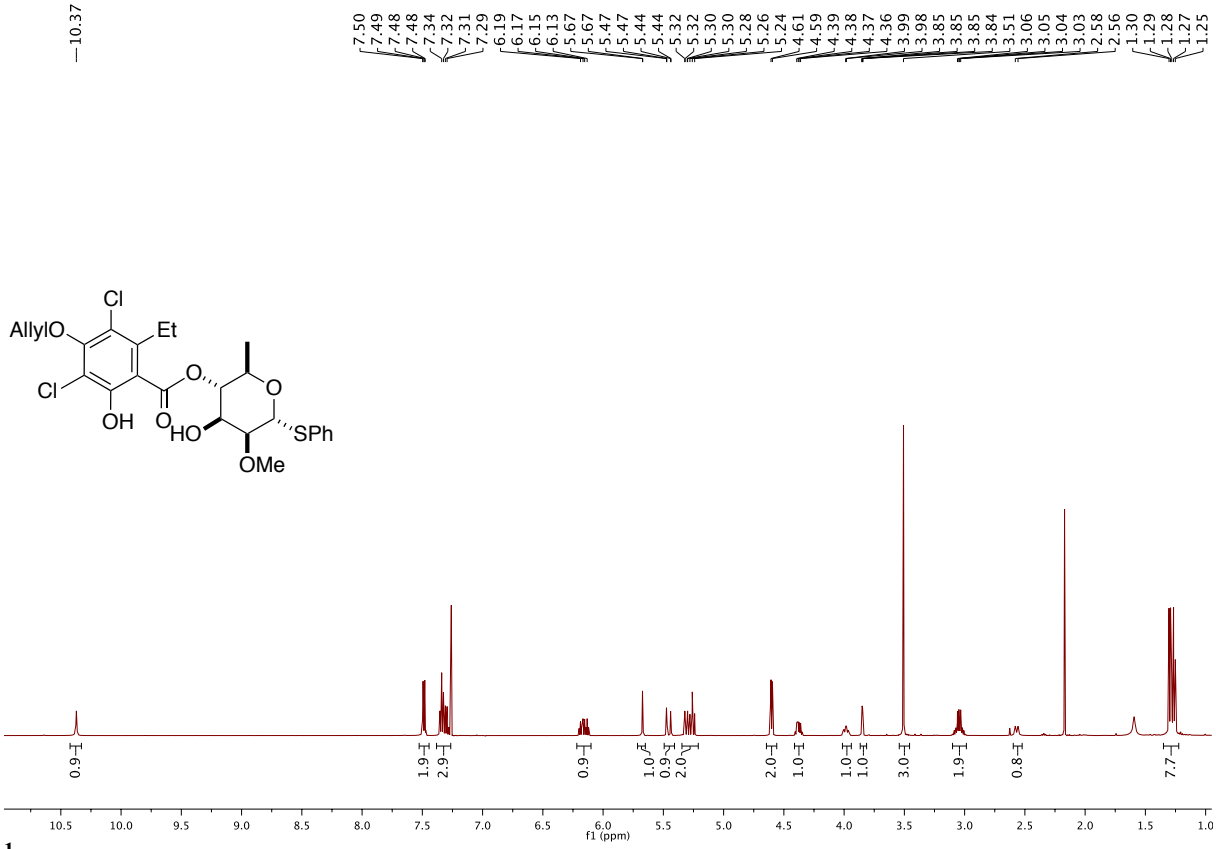


^{1}H-NMR (400 MHz, $CDCl_3$)

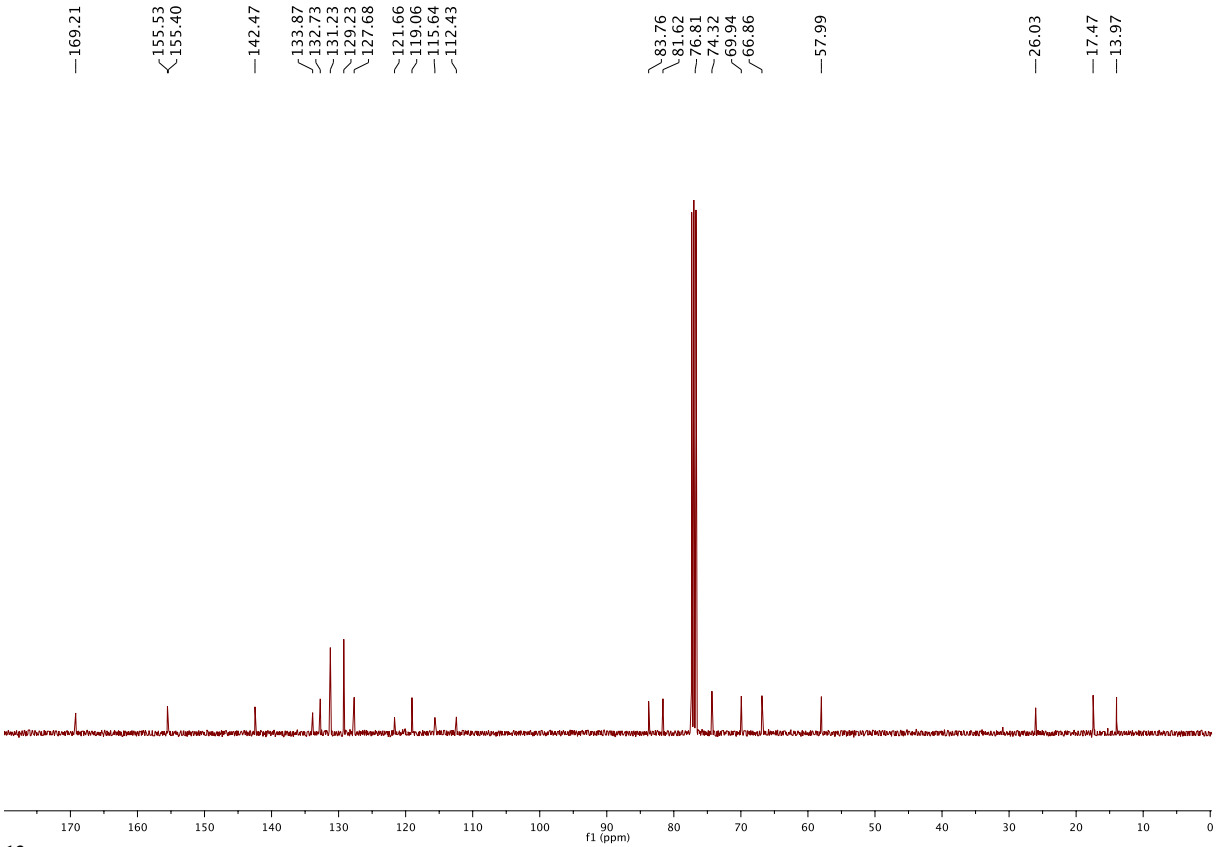


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.142)

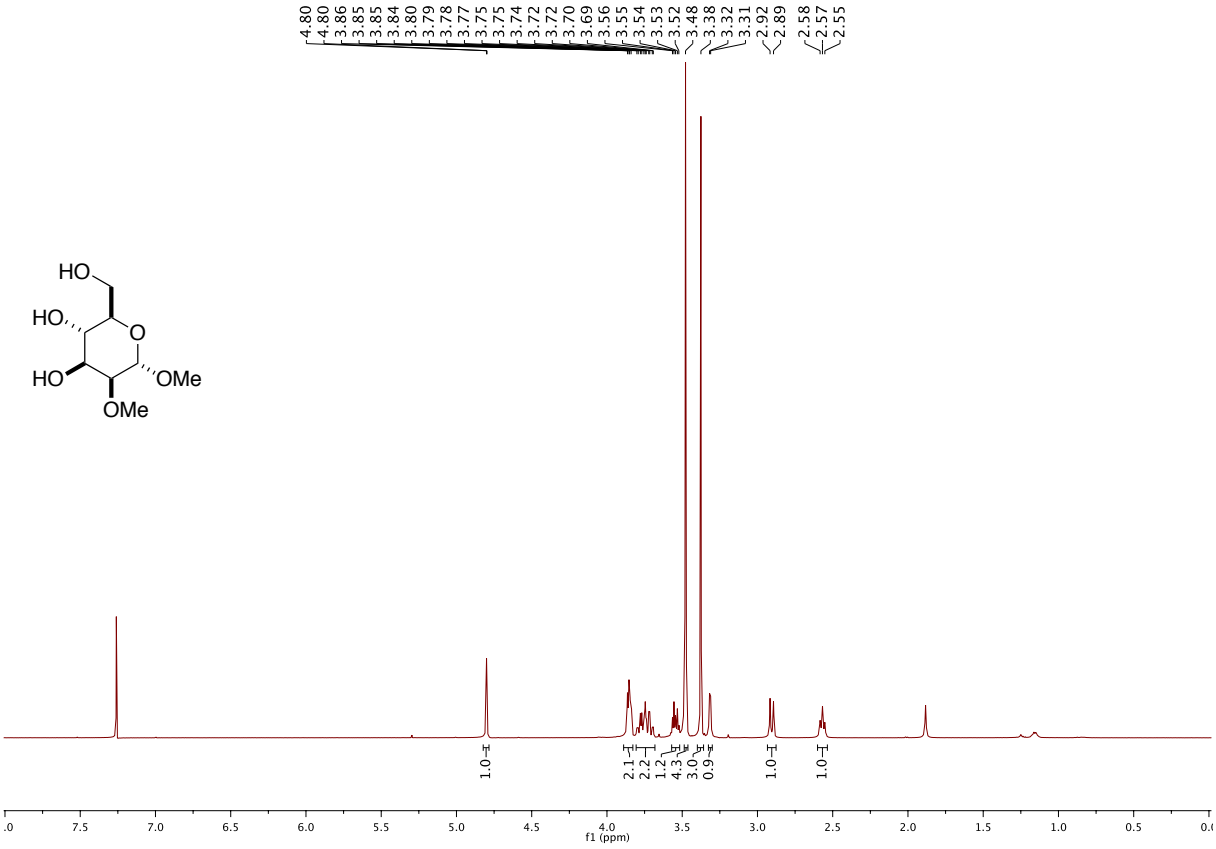


^{1}H-NMR (400 MHz, $CDCl_3$)

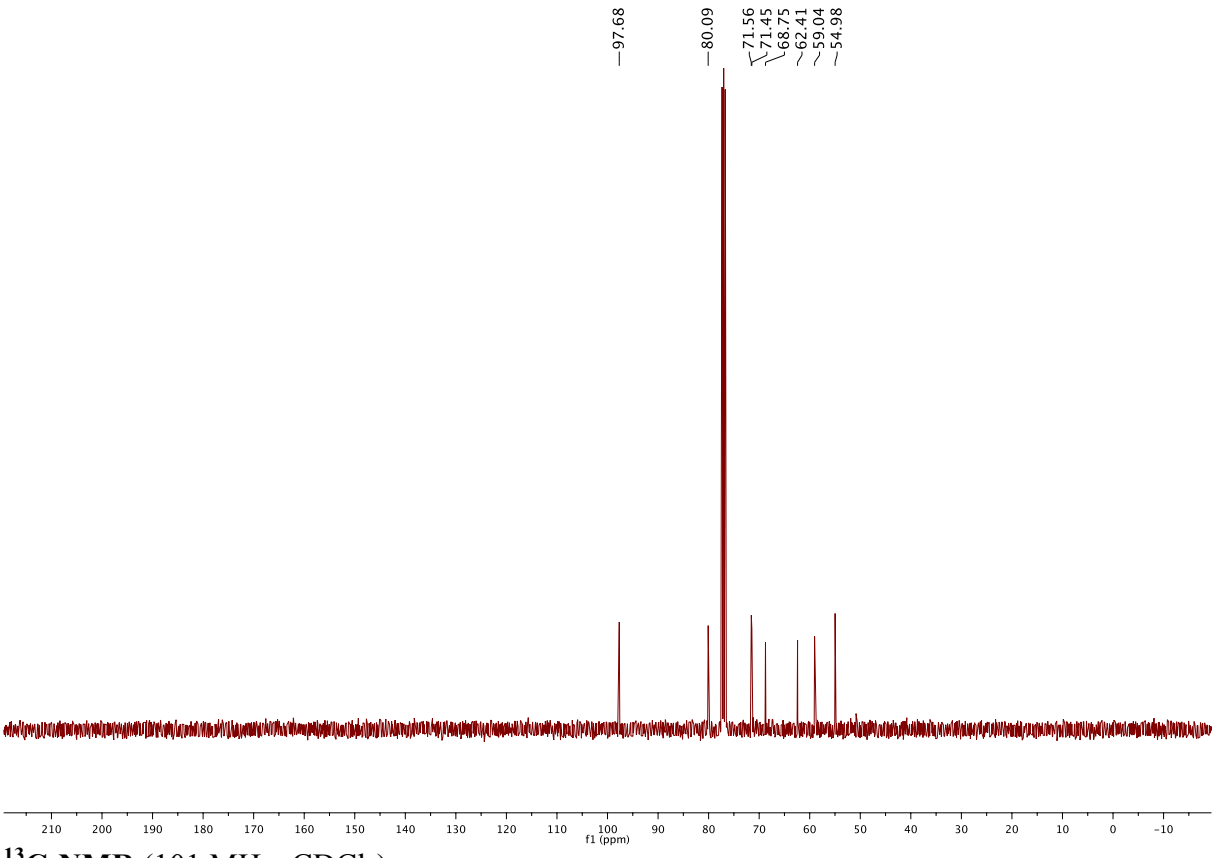


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*S*)-2-(hydroxymethyl)-5,6-dimethoxytetrahydro-2*H*-pyran-3,4-diol (1.143)

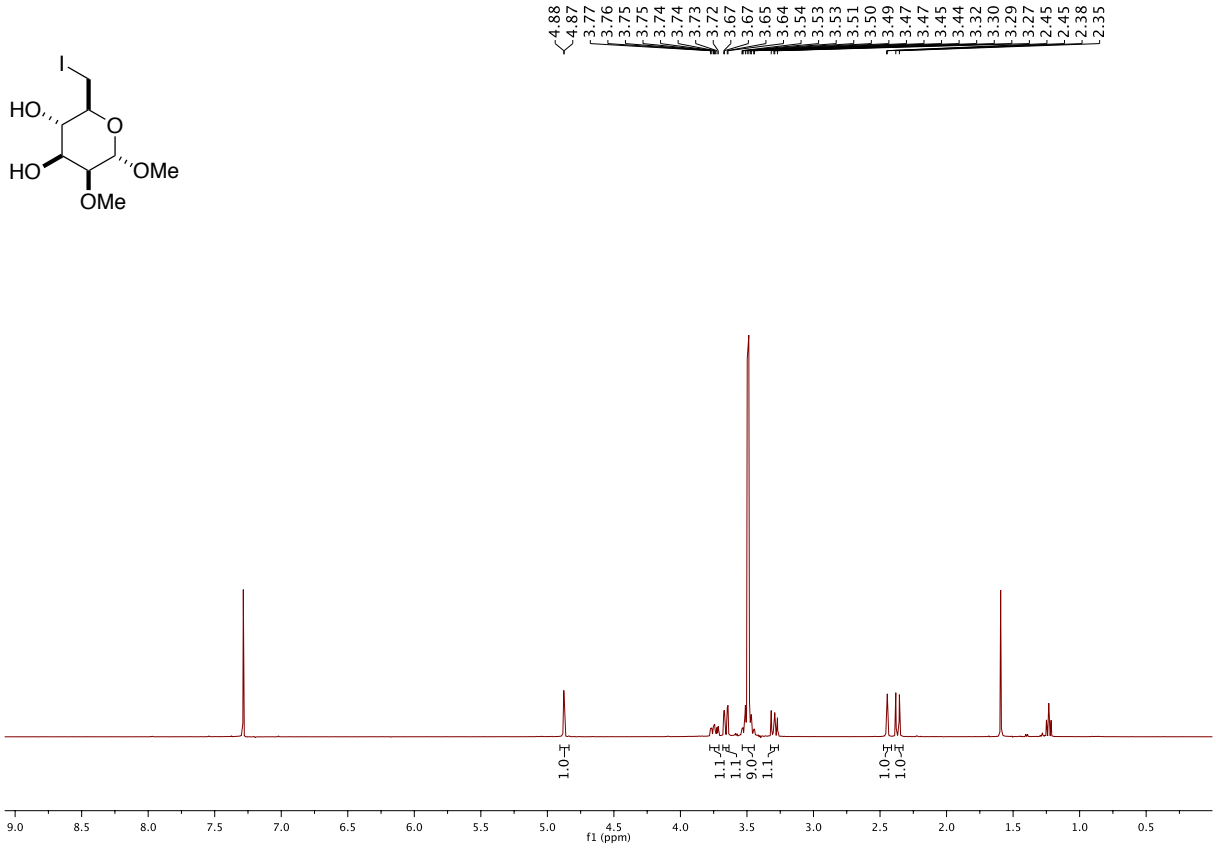


^{1}H-NMR (400 MHz, $CDCl_3$)

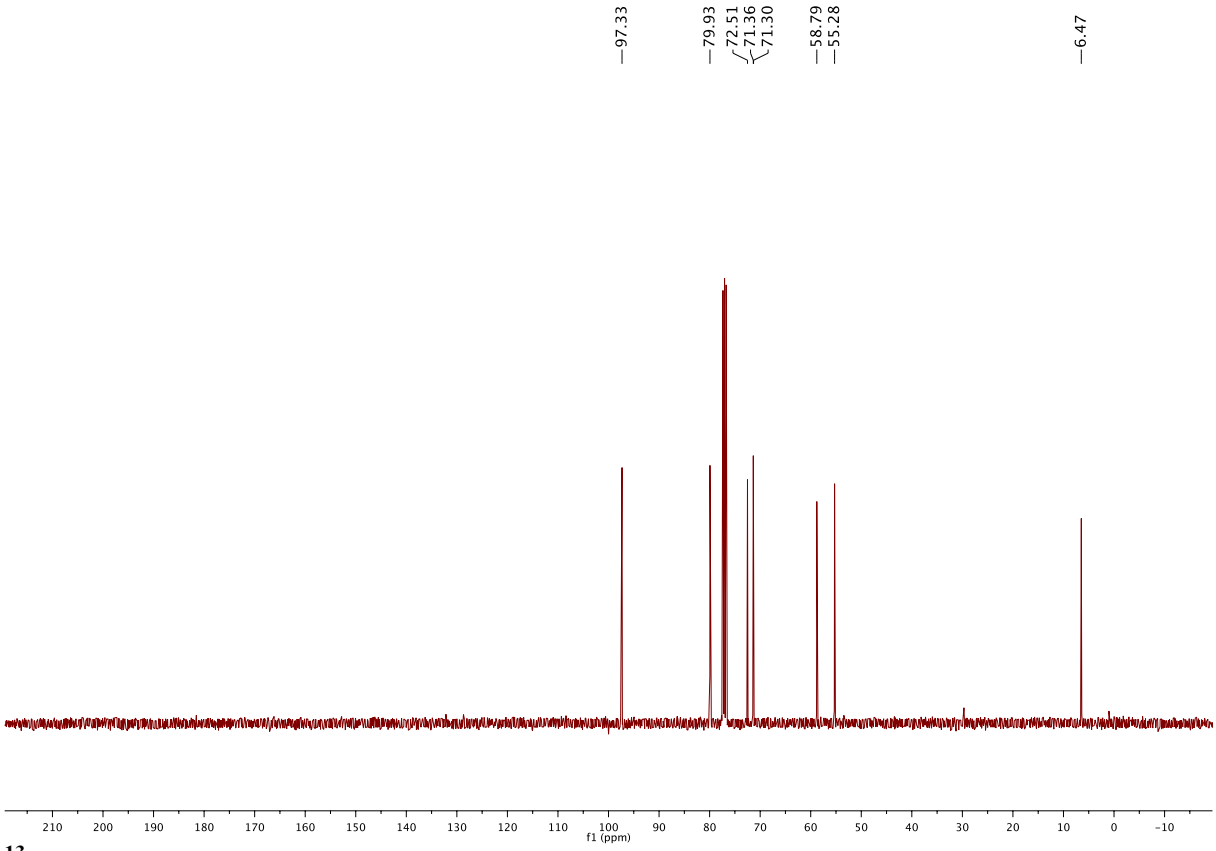


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*S*,3*S*,4*S*,5*S*,6*S*)-2-(iodomethyl)-5,6-dimethoxytetrahydro-2*H*-pyran-3,4-diol (1.143b)

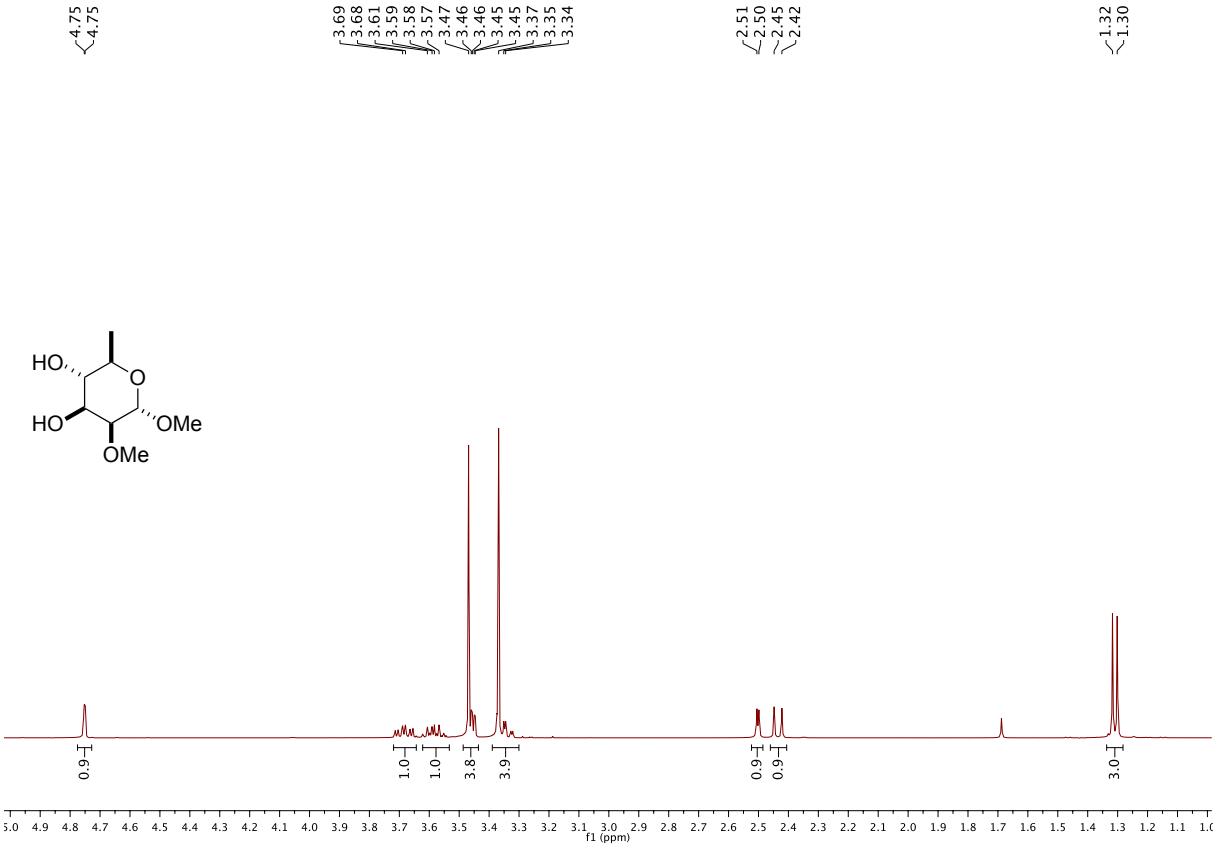


^{1}H-NMR (400 MHz, $CDCl_3$)

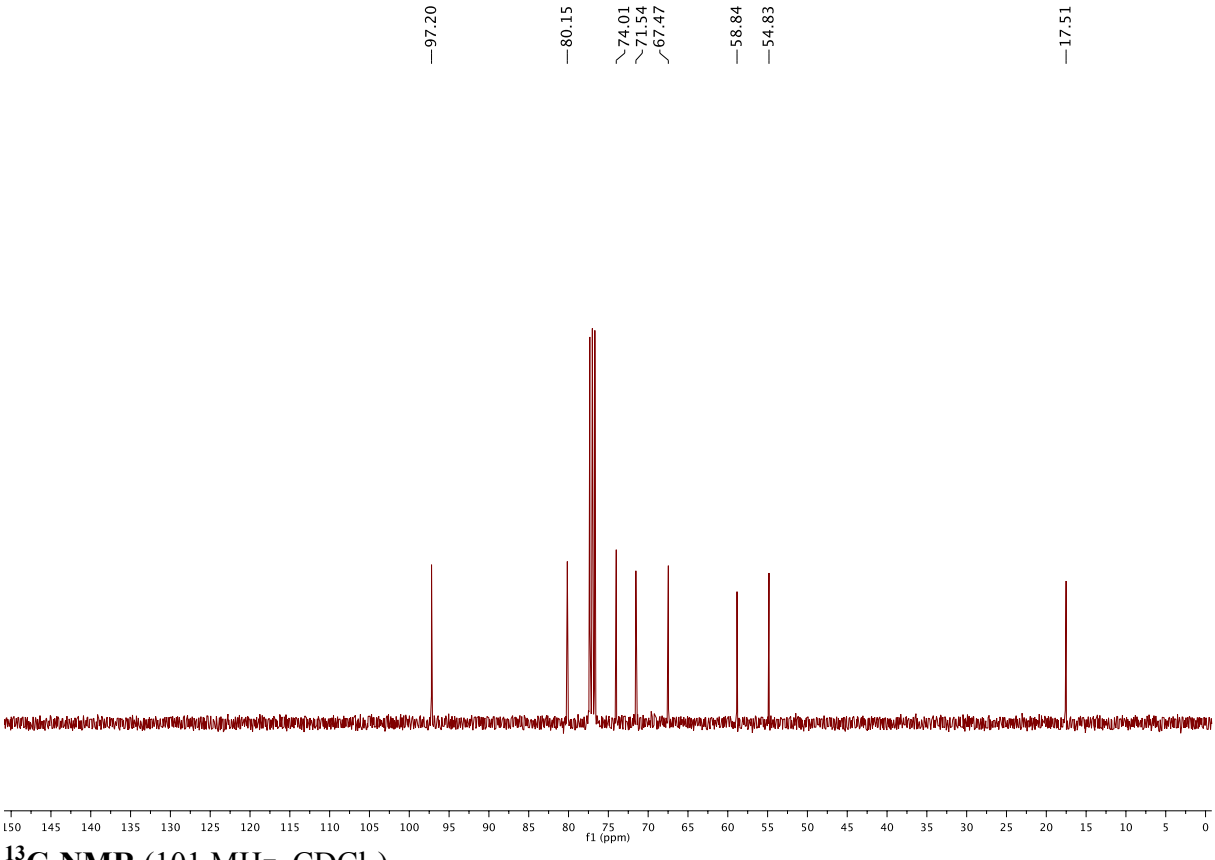


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*S*)-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-3,4-diol (1.144)

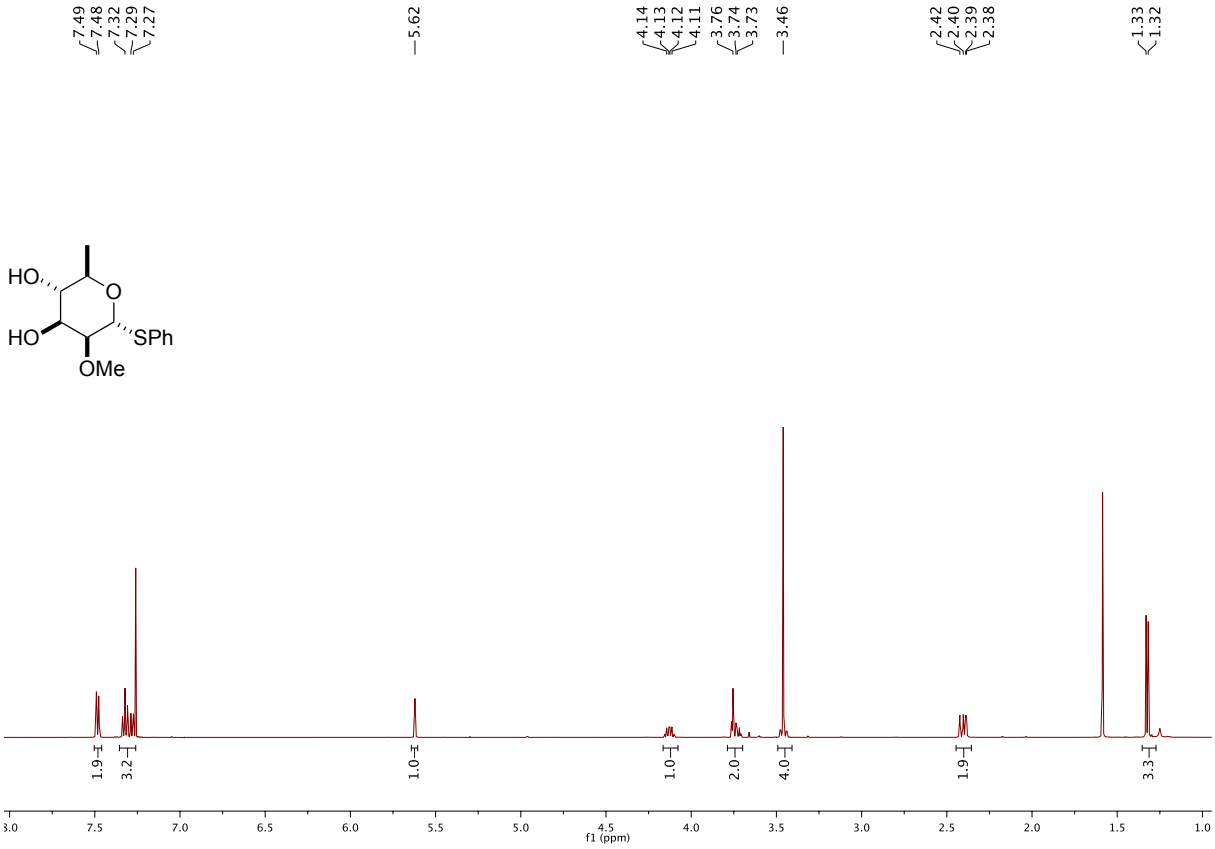


^{1}H-NMR (400 MHz, $CDCl_3$)

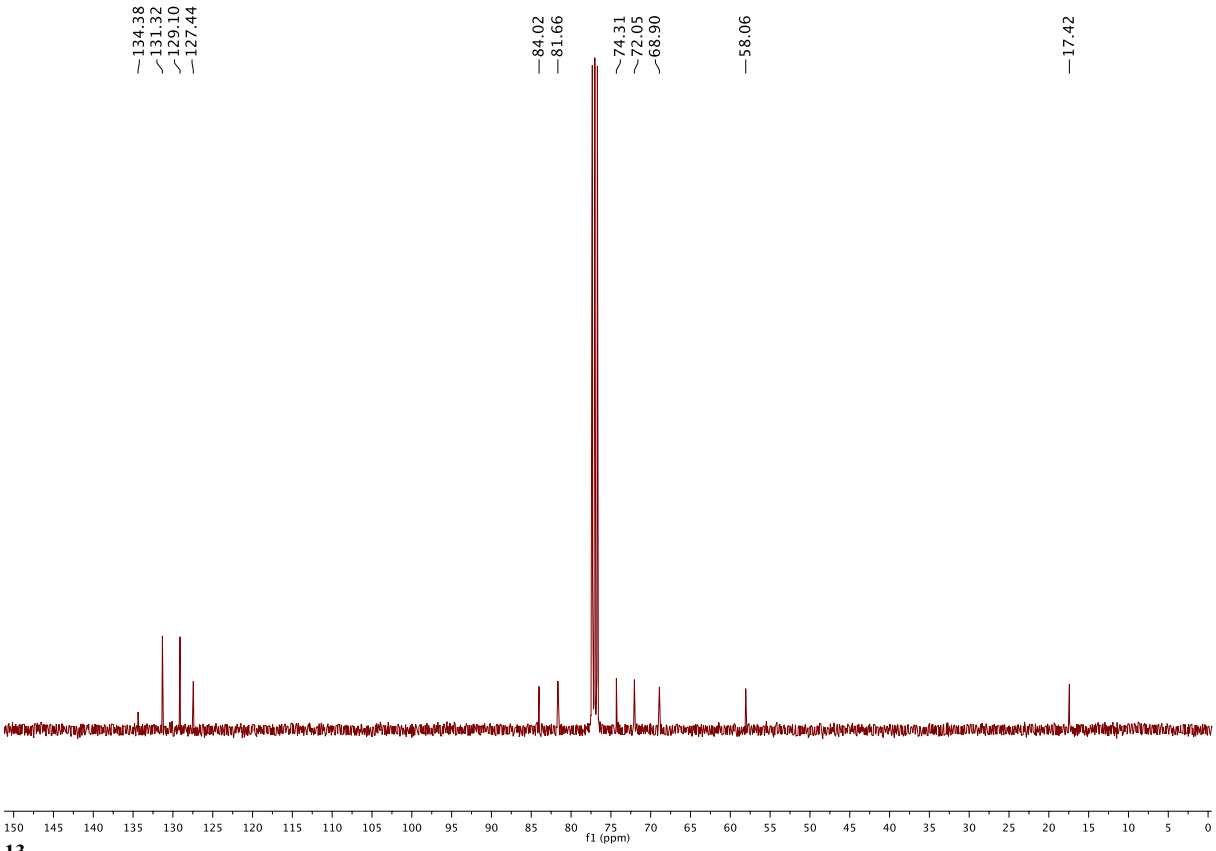


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*R*)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3,4-diol (1.145)

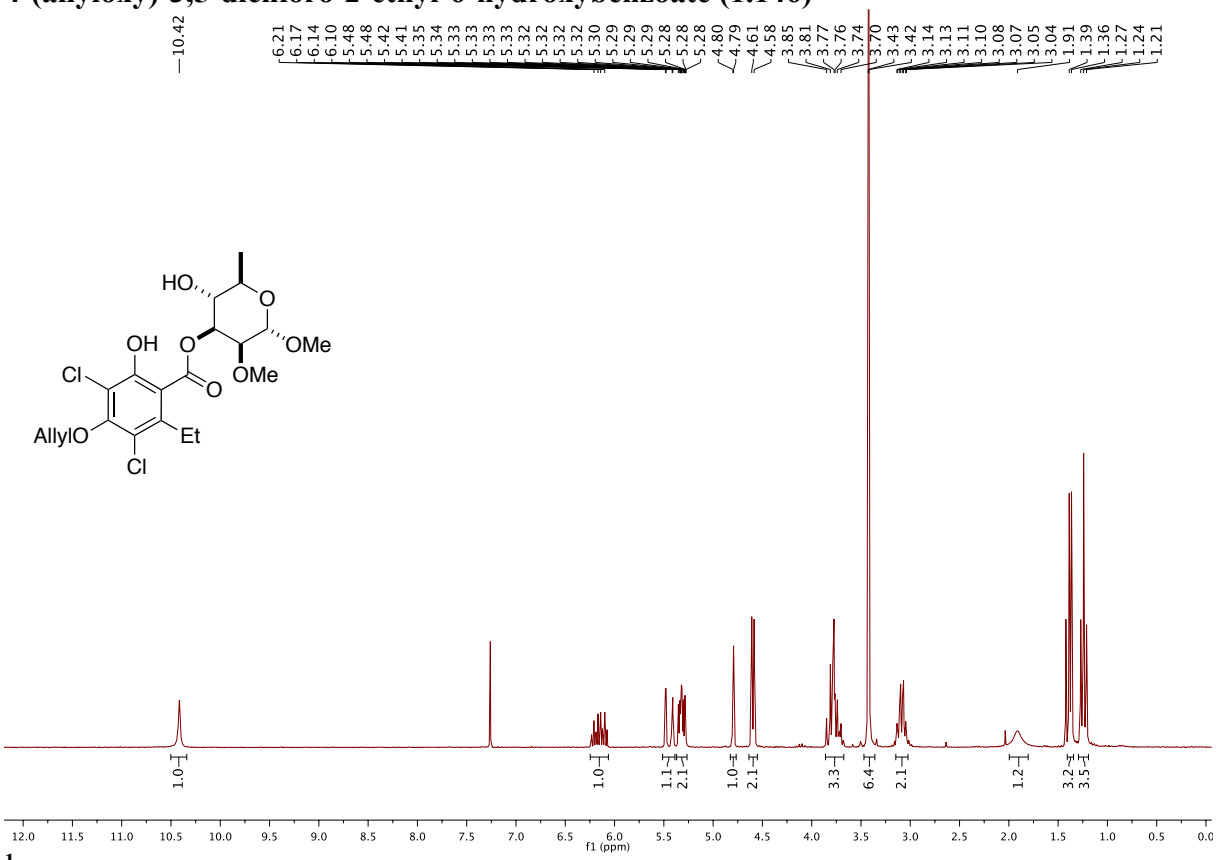


^{1}H-NMR (400 MHz, $CDCl_3$)

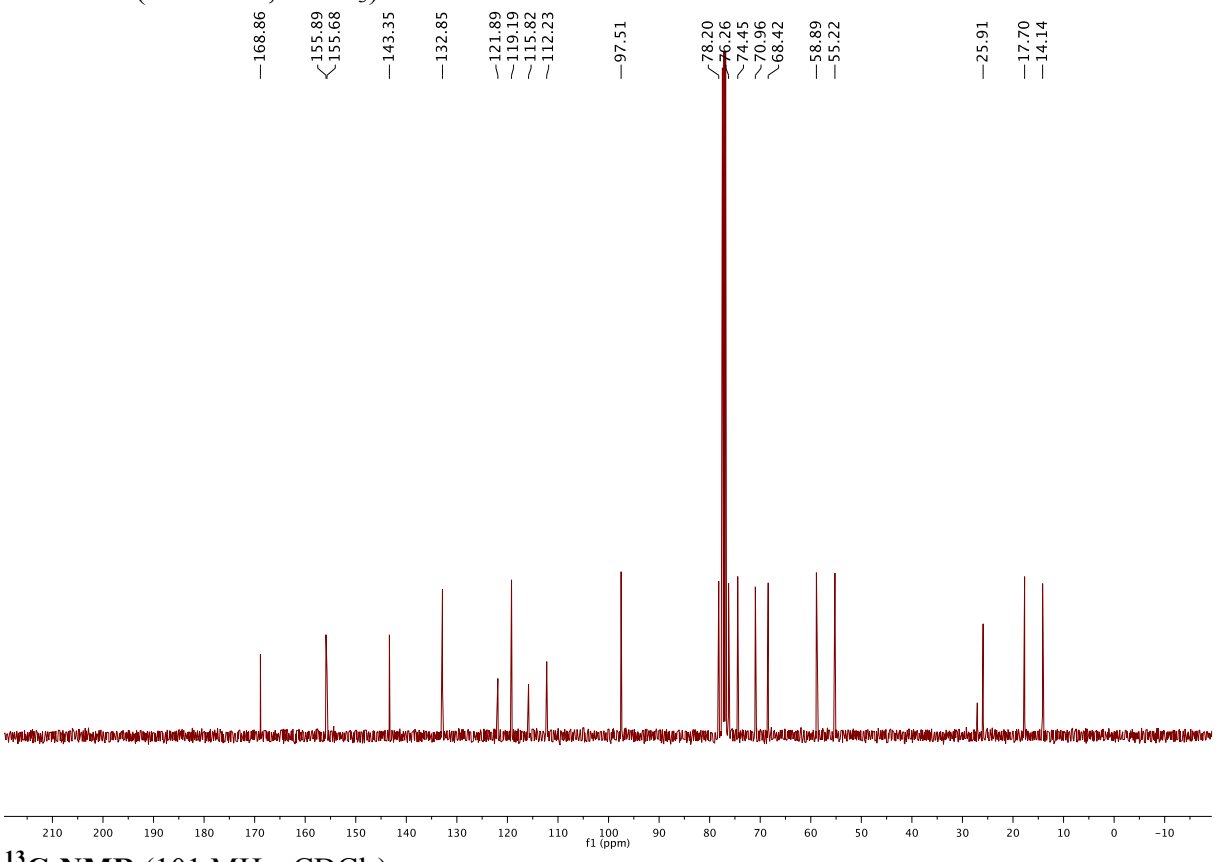


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*R*,4*S*,5*S*,6*S*)-3-hydroxy-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-4-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.146)

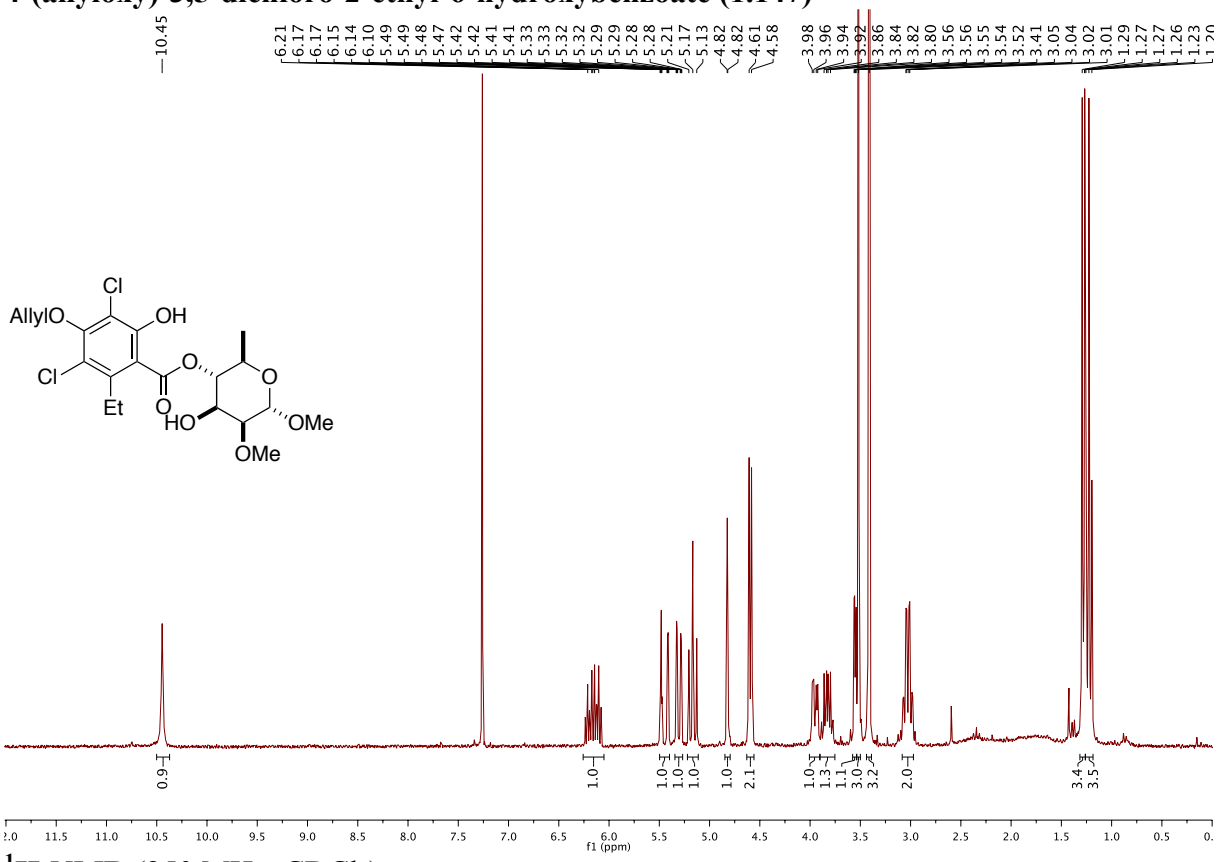


^{1}H-NMR (250 MHz, $CDCl_3$)

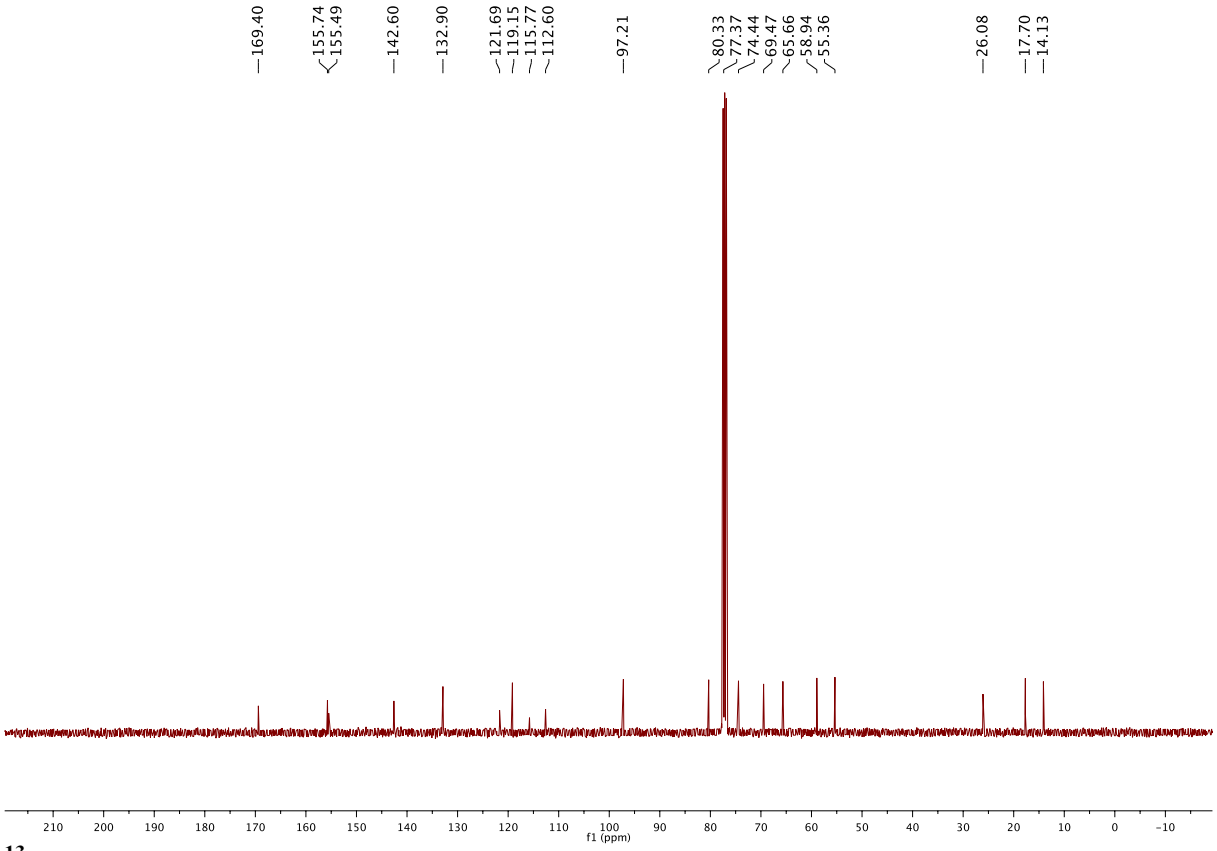


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*S*)-4-hydroxy-5,6-dimethoxy-2-methyltetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.147)

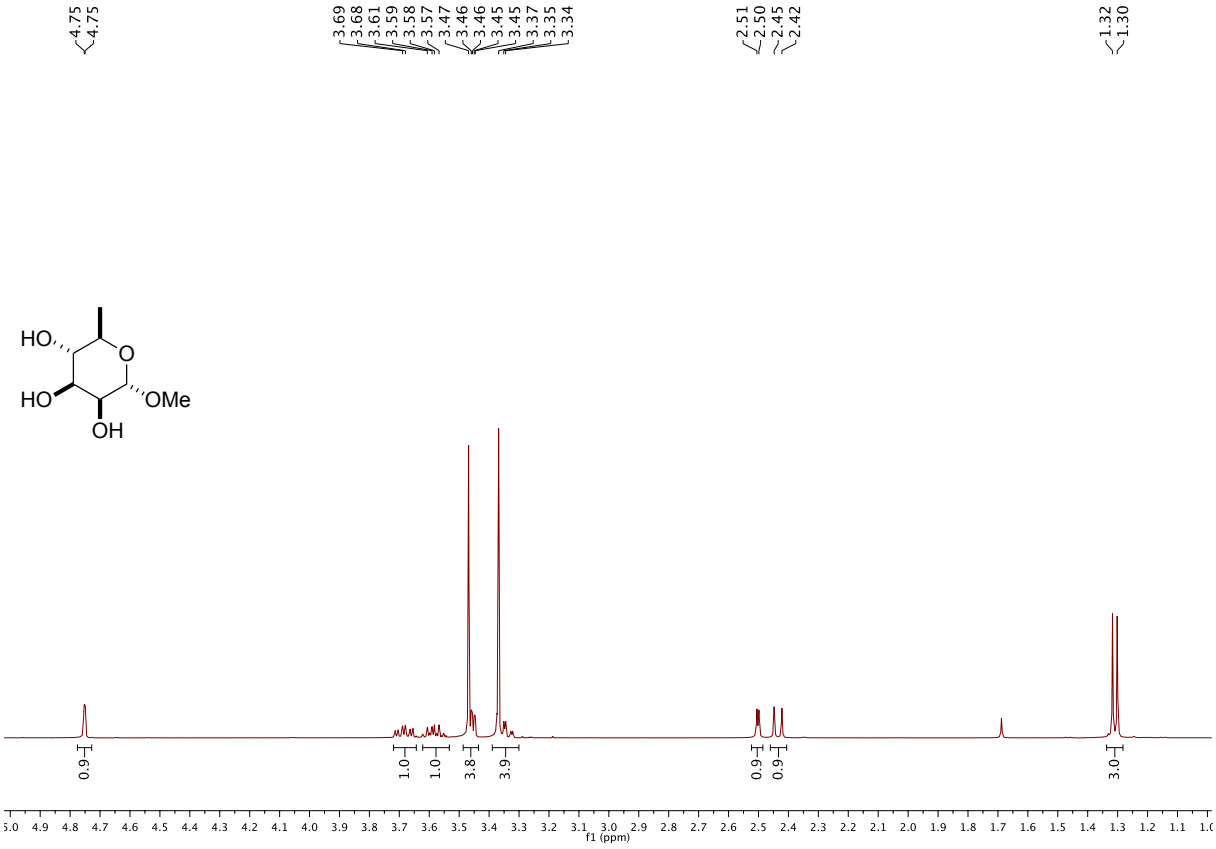


^{1}H-NMR (250 MHz, $CDCl_3$)

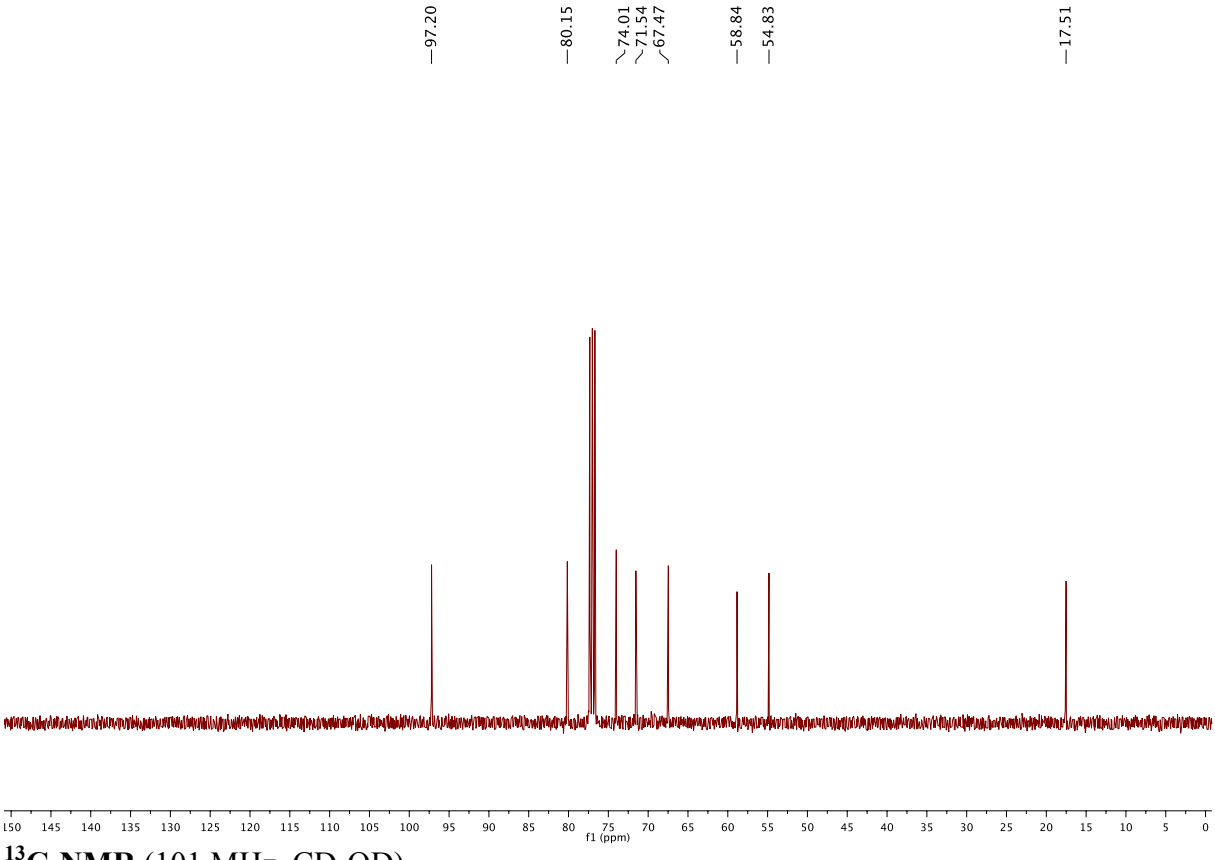


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*S*,3*S*,4*S*,5*S*,6*R*)-2-methoxy-6-methyltetrahydro-2*H*-pyran-3,4,5-triol (1.148)

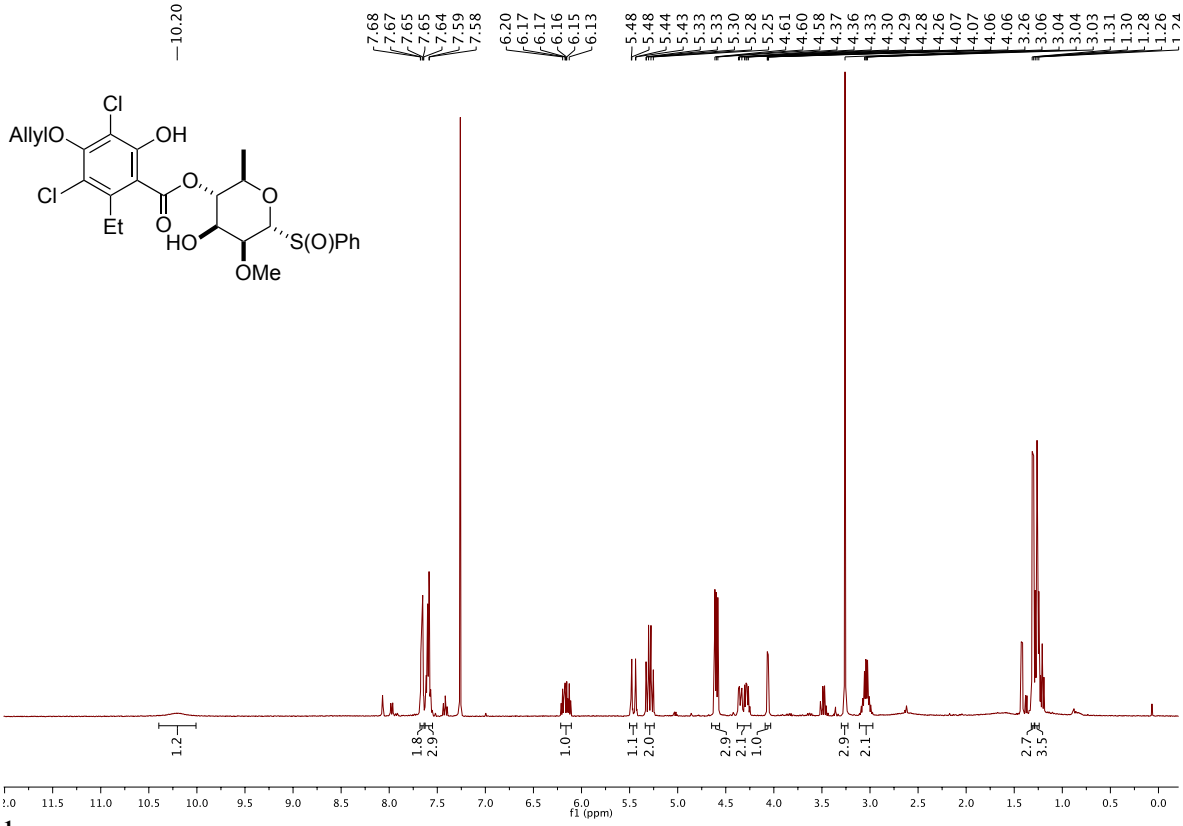


^{1}H-NMR (400 MHz, CD_3OD)



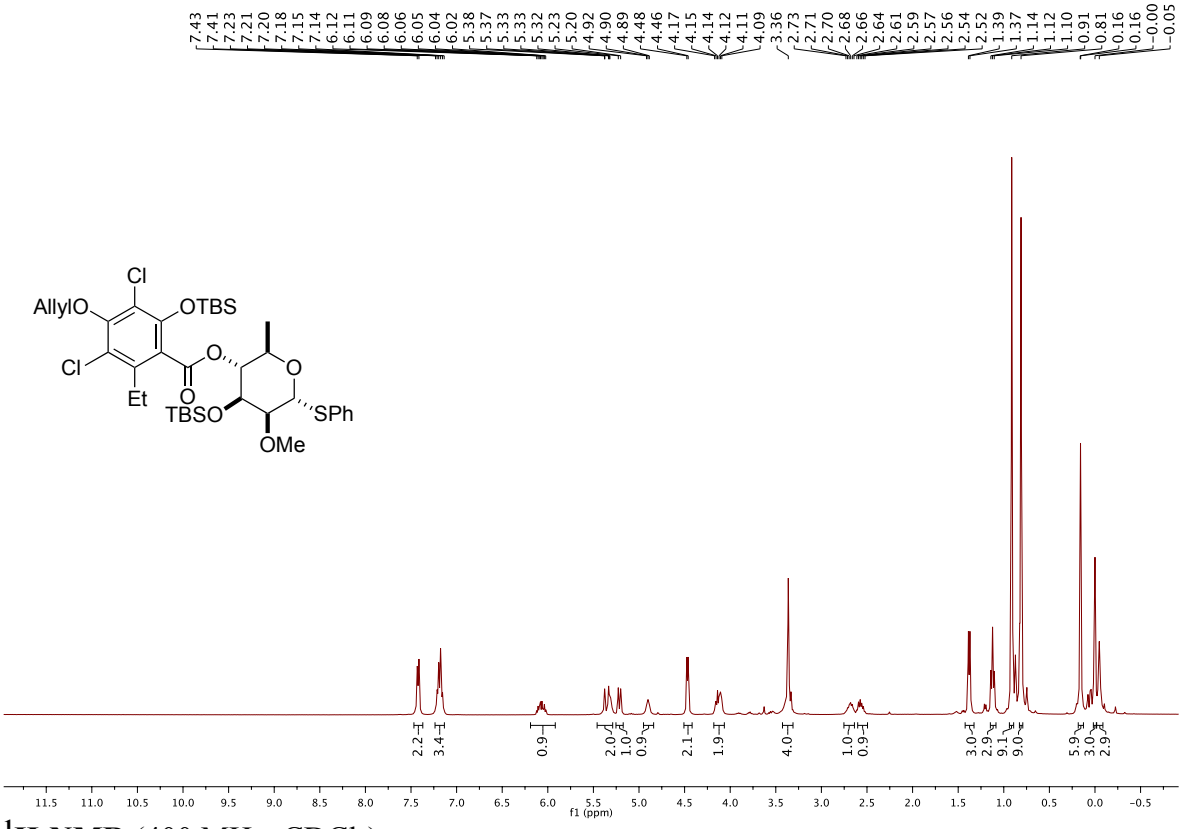
^{13}C-NMR (101 MHz, CD_3OD)

(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-((*S*)-phenylsulfinyl)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (1.156)

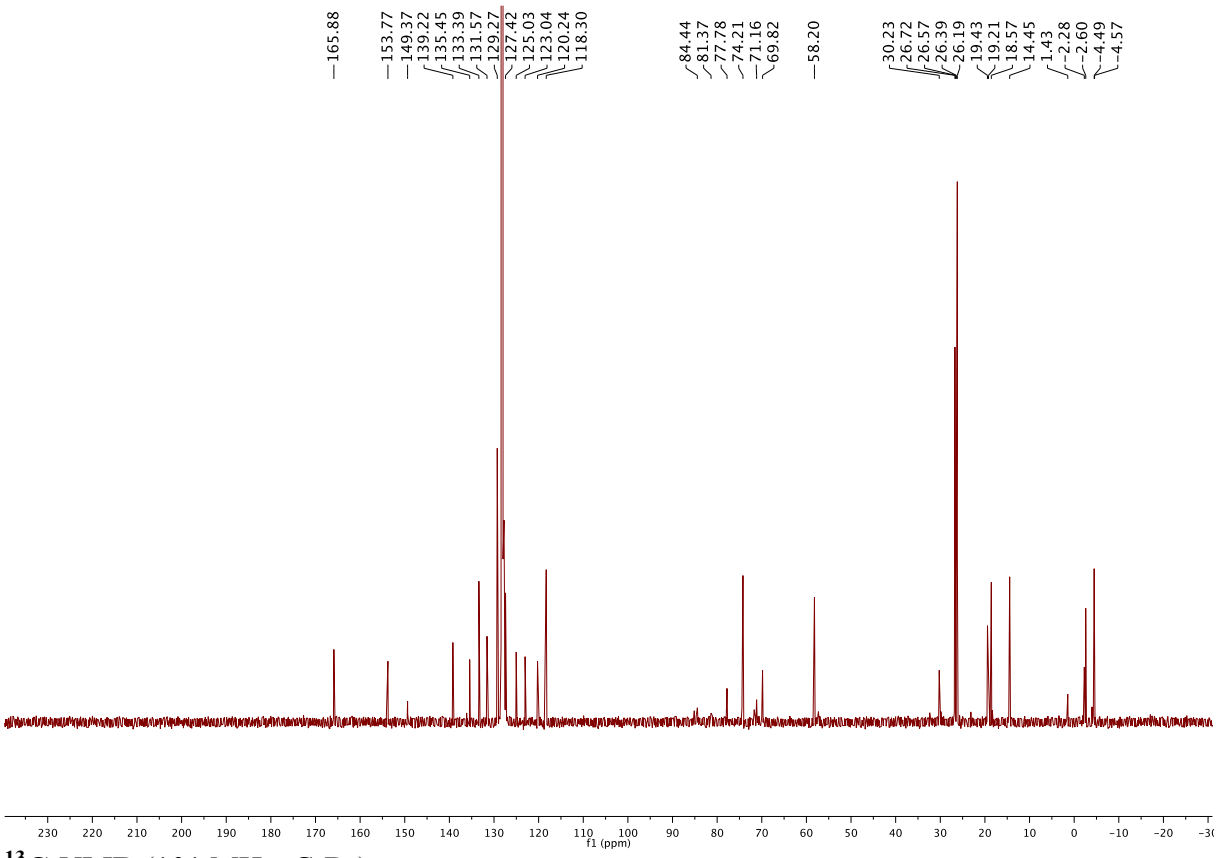


^{1}**H-NMR** (400 MHz, $CDCl_3$)

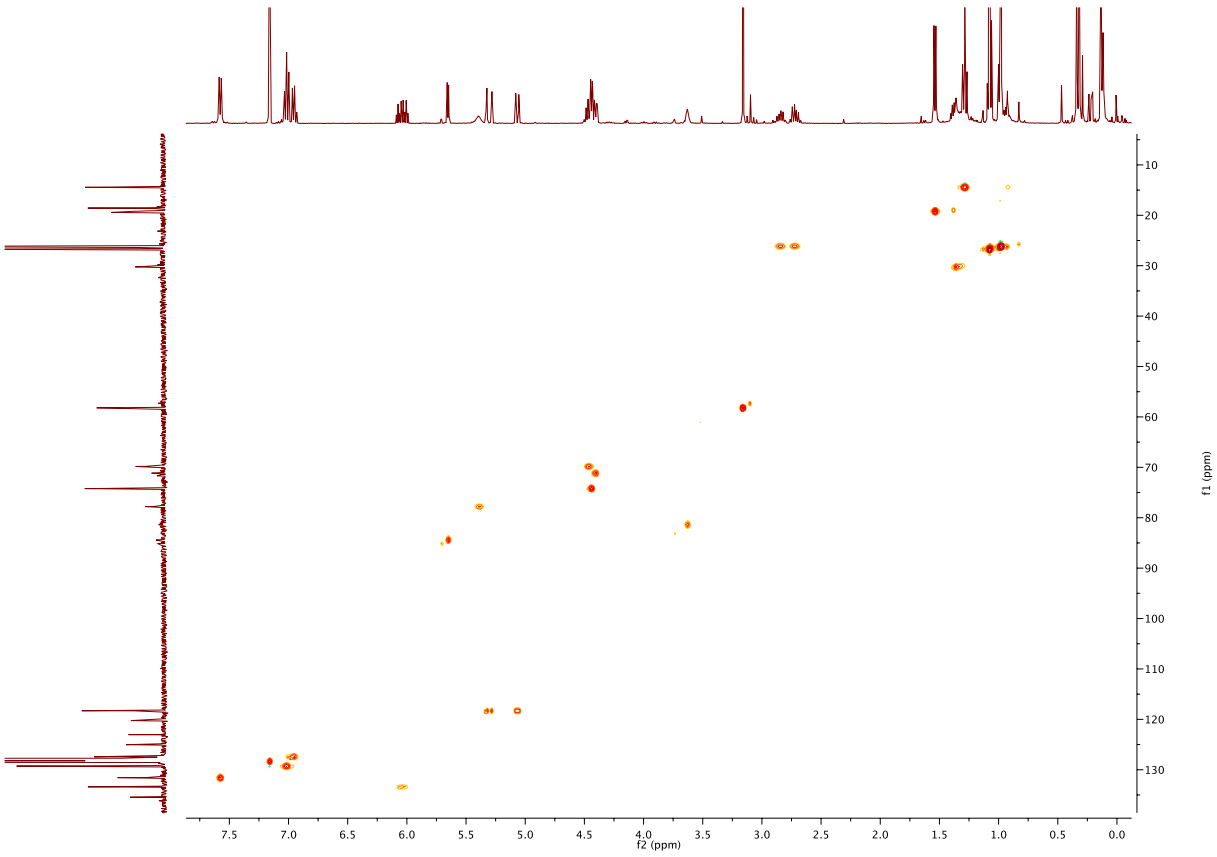
4-((TBS)oxy)-5-methoxy-2-methyl-6-(phenylthio)-tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-2-((tert-butyldimethylsilyl)oxy)-3,5-dichloro-6-ethylbenzoate (1.162)



^{1}**H-NMR** (400 MHz, $CDCl_3$)

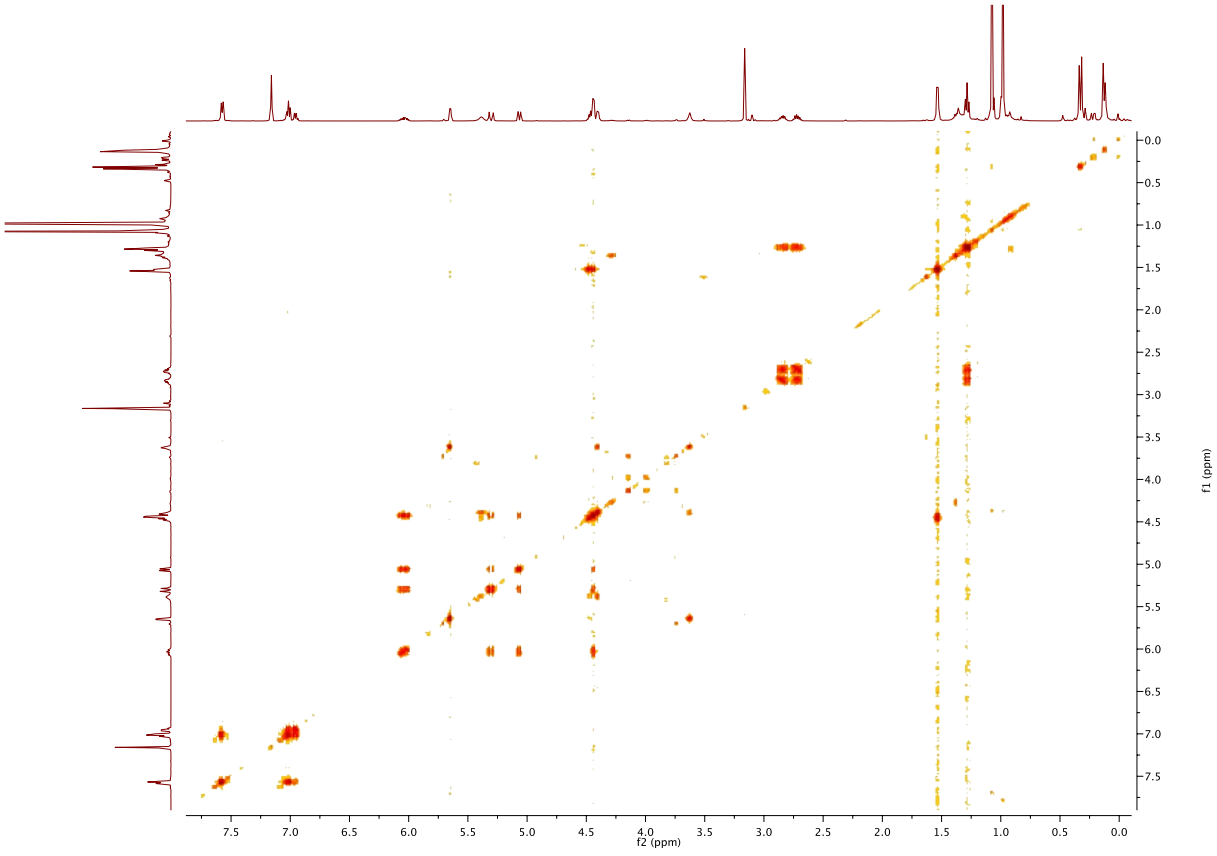


^{13}C-NMR (101 MHz, C_6D_6)



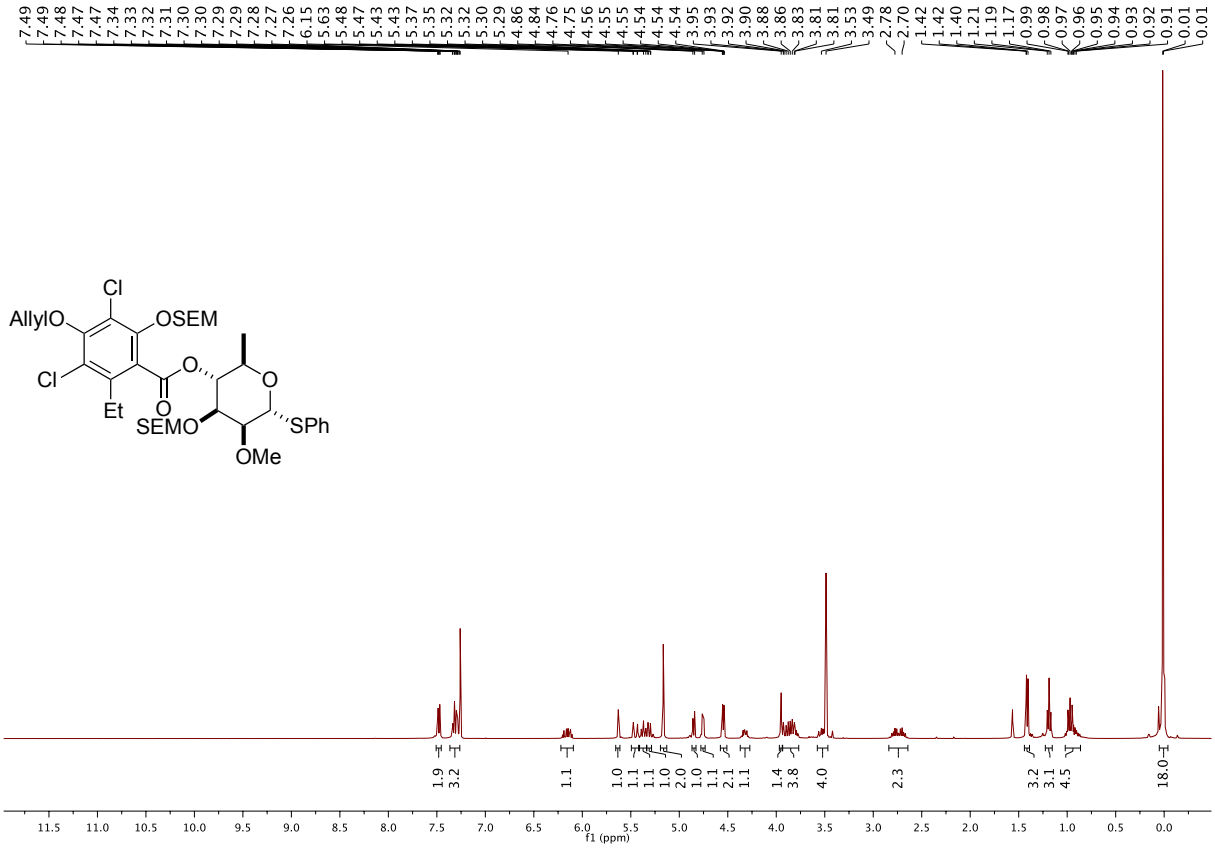
COSY (101 MHz, C_6D_6)

HSQC (101 MHz, C_6D_6)

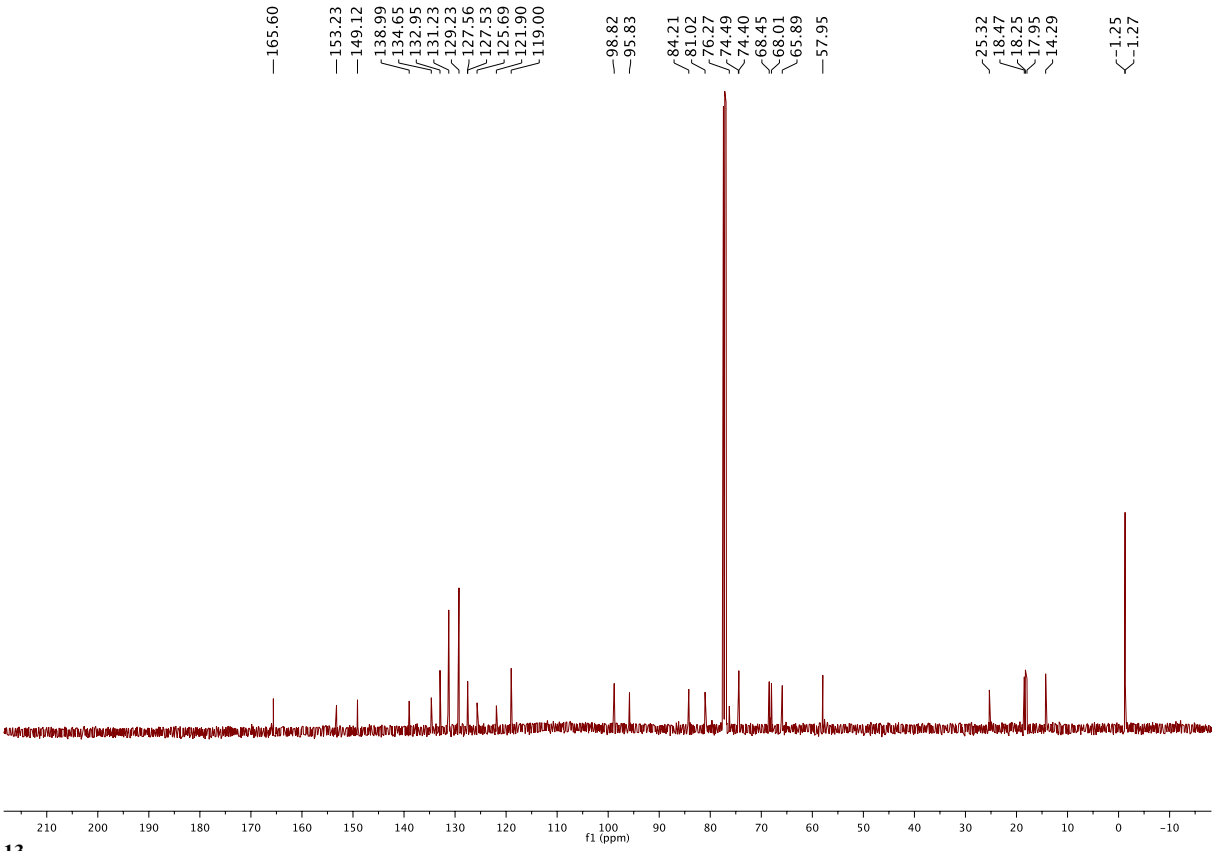


HMBC (101 MHz, C_6D_6)

5-methoxy-2-methyl-6-(phenylthio)-4-((2-(trimethylsilyl)ethoxy)-methoxy)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-(2-SEM)methoxy)benzoate (1.163)

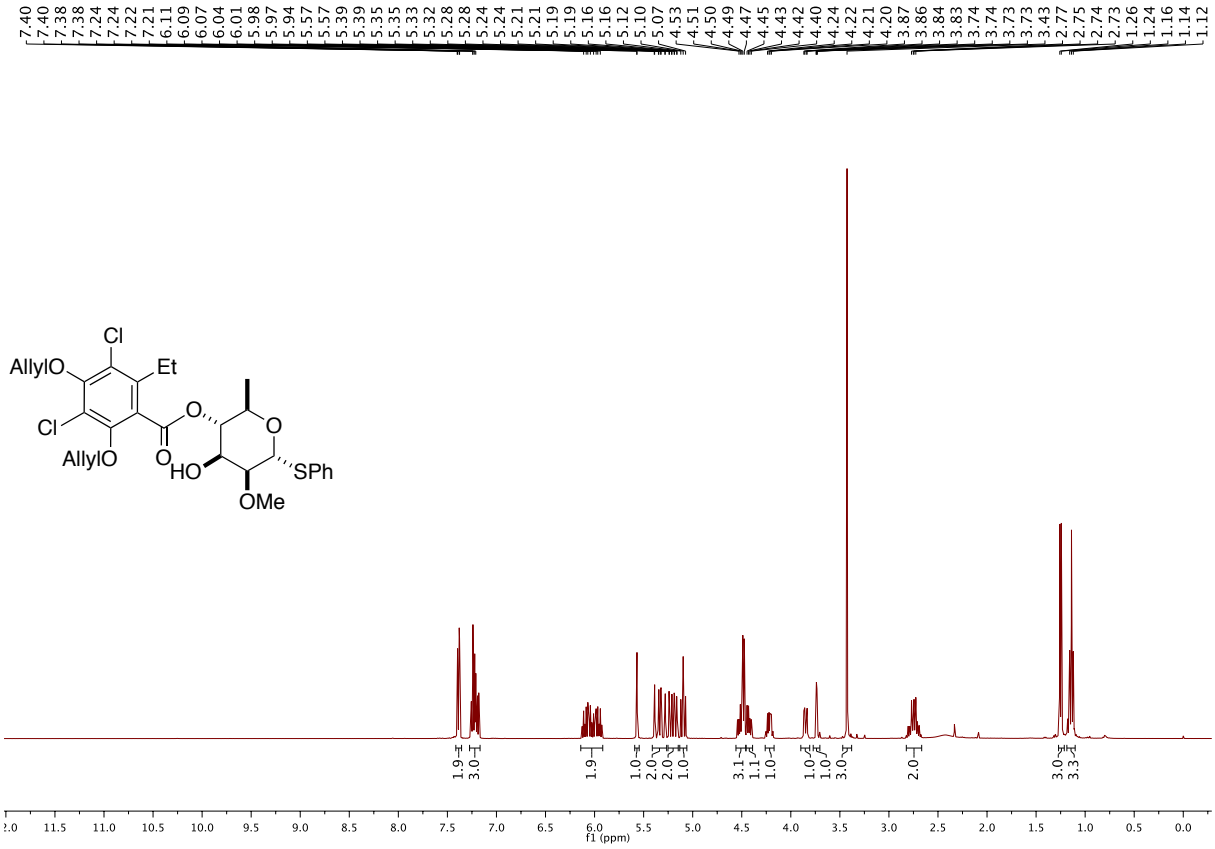


^{1}H-NMR (400 MHz, $CDCl_3$)

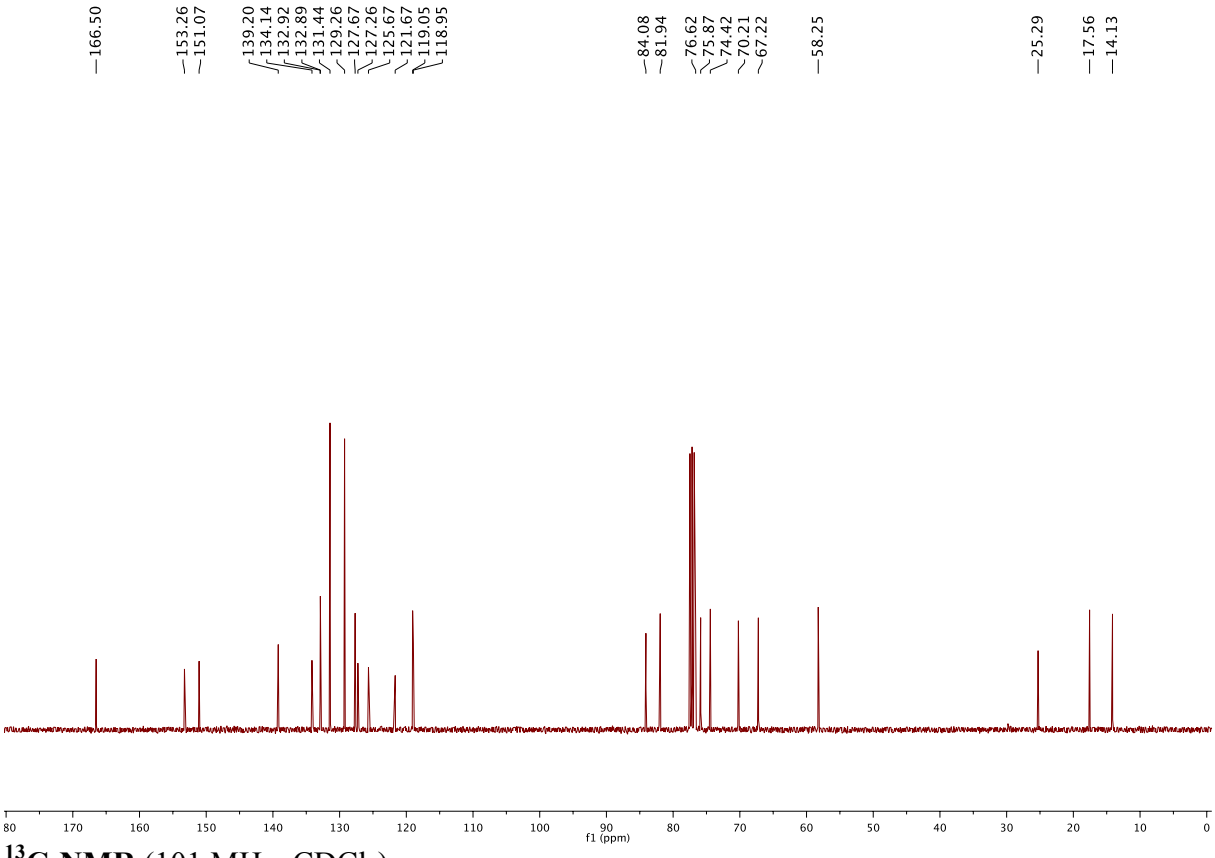


^{13}C-NMR (126 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.164)

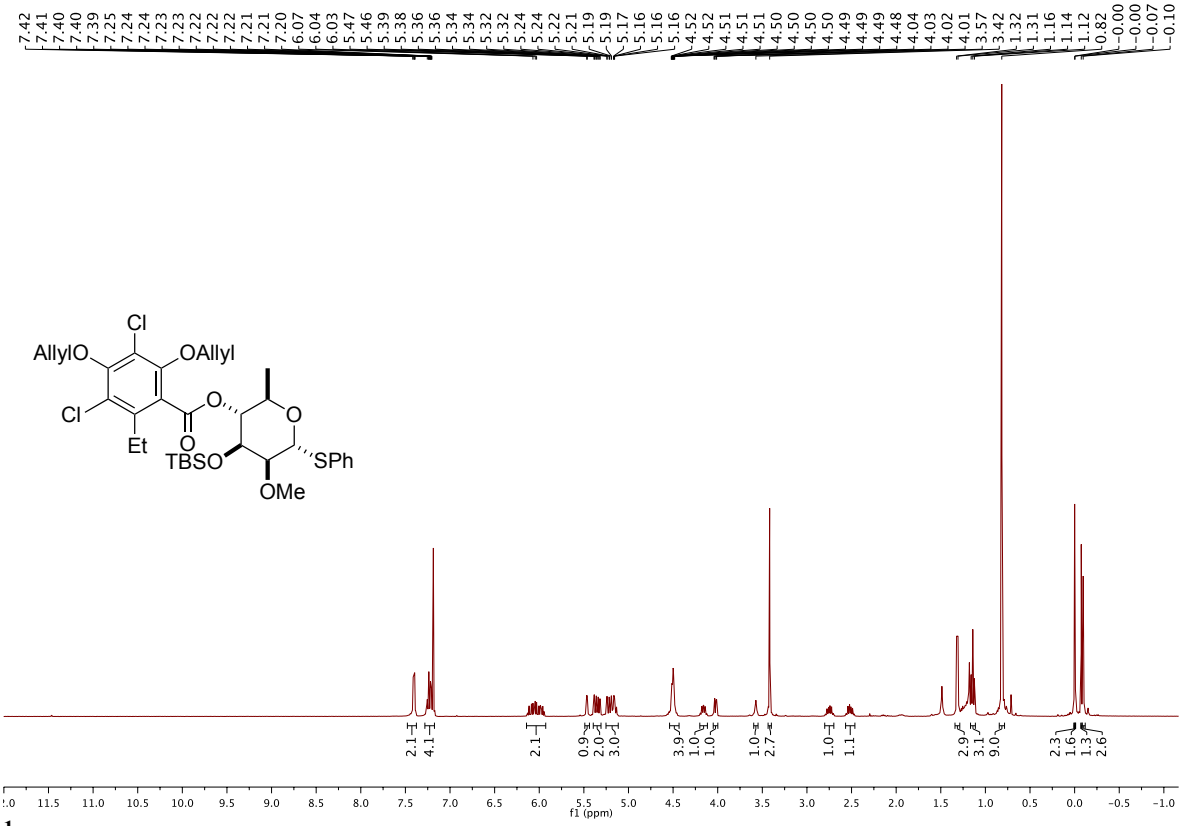


^{1}H-NMR (400 MHz, $CDCl_3$)



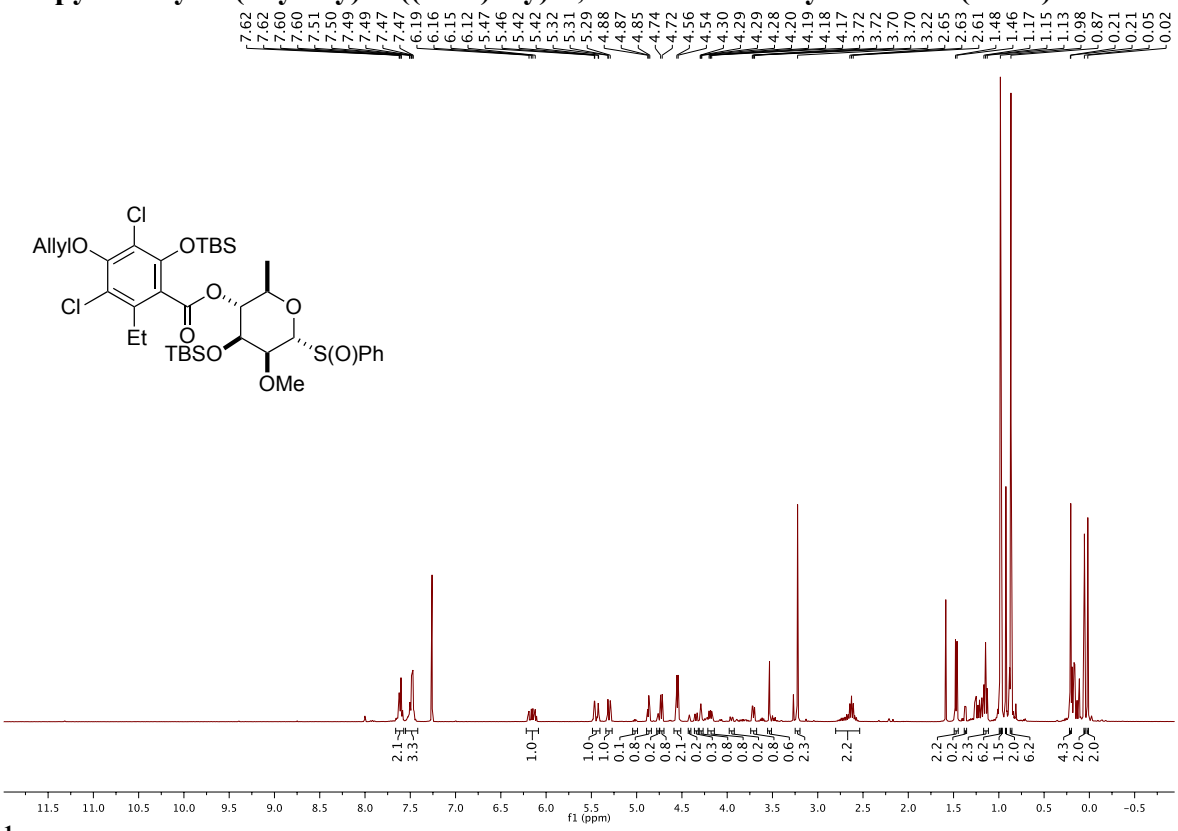
^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)-tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.165)



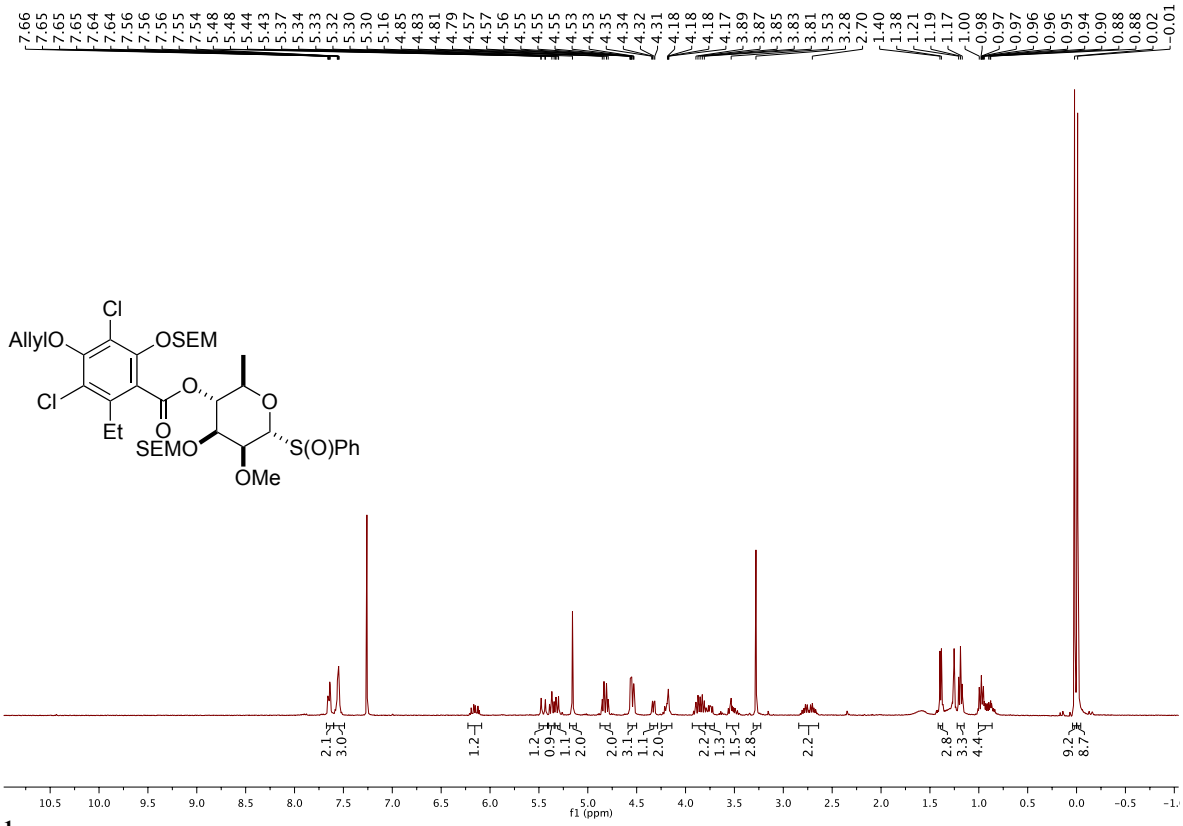
^{1}H-NMR (400 MHz, $CDCl_3$)

4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyl-6-((*S*)-phenylsulfinyl)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-2-((TBS)oxy)-3,5-dichloro-6-ethylbenzoate (1.166)



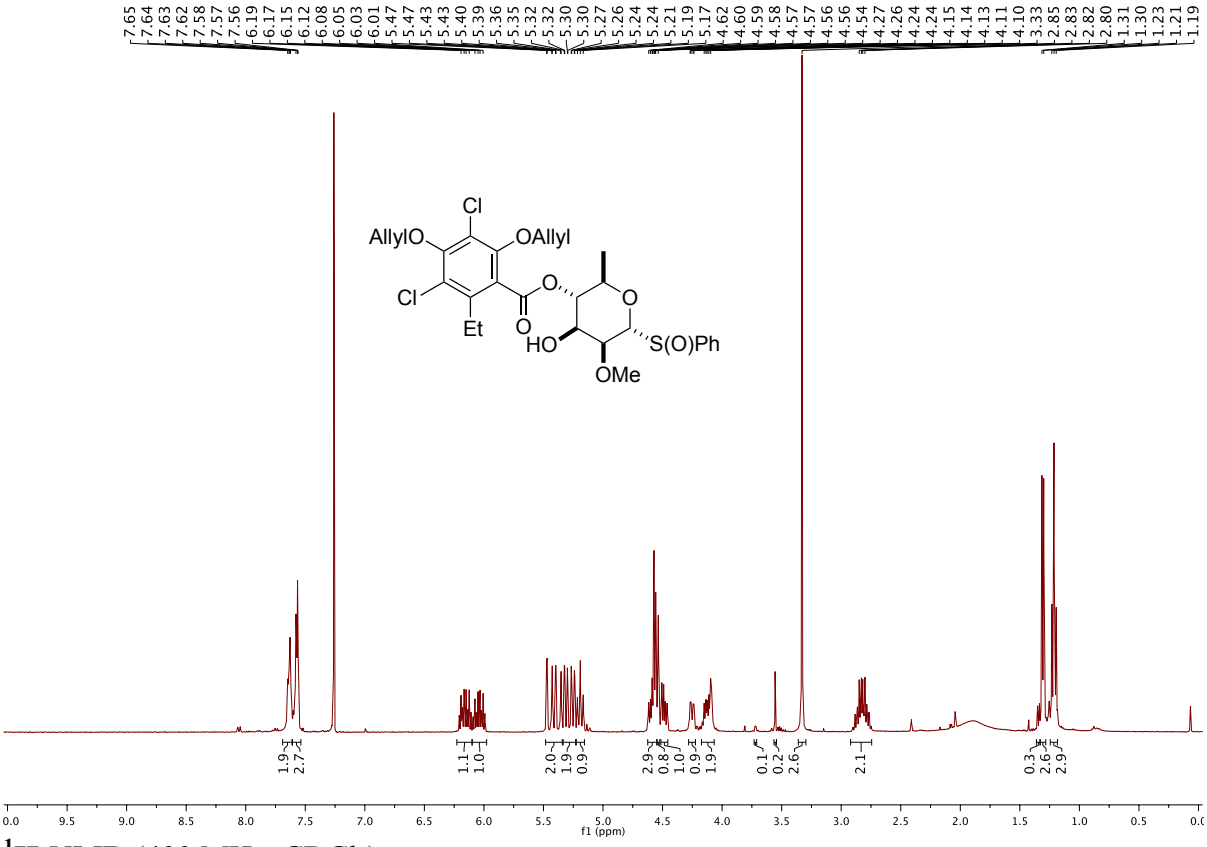
^{1}H-NMR (400 MHz, $CDCl_3$)

5-methoxy-2-methyl-6-((*R*)-phenylsulfinyl)-4-((2-(SEM)methoxy)tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-((2-SEM)methoxy)benzoate (1.167)

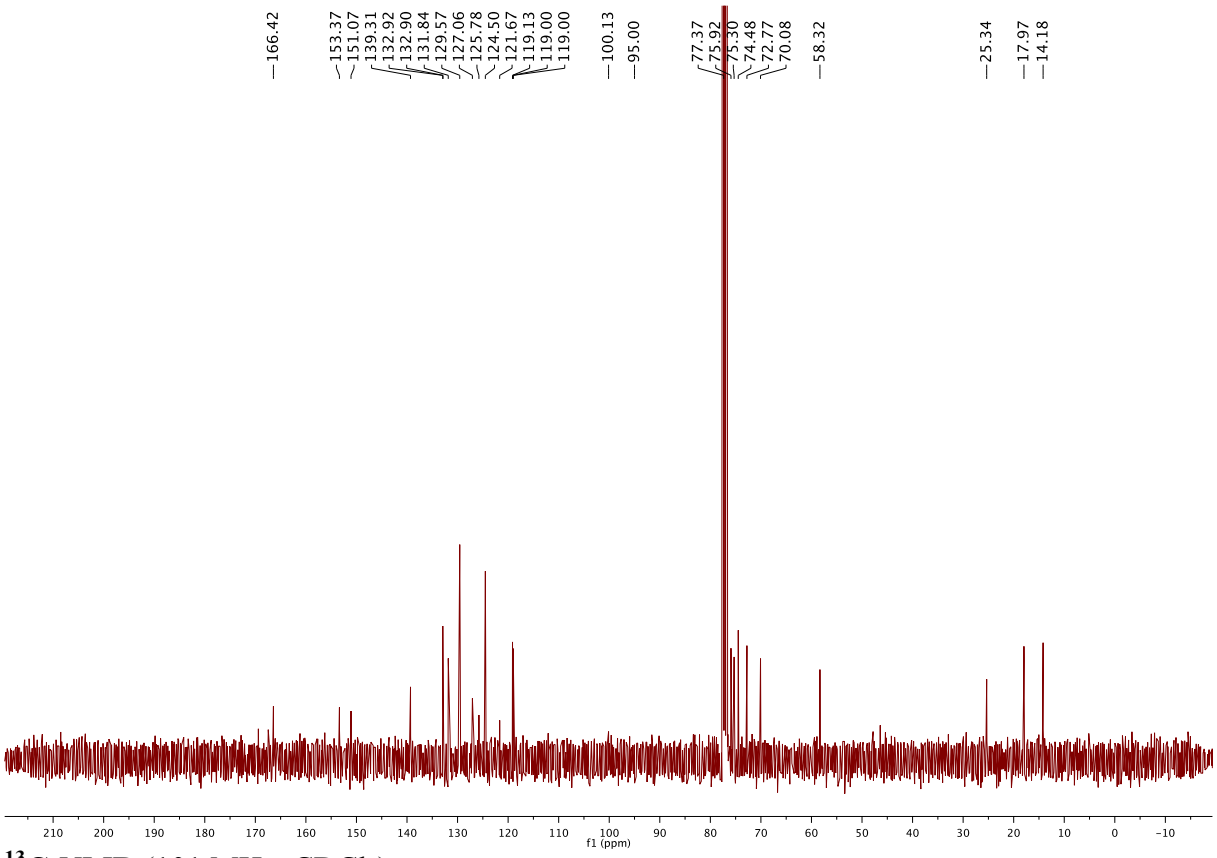


^{1}H-NMR (400 MHz, $CDCl_3$)

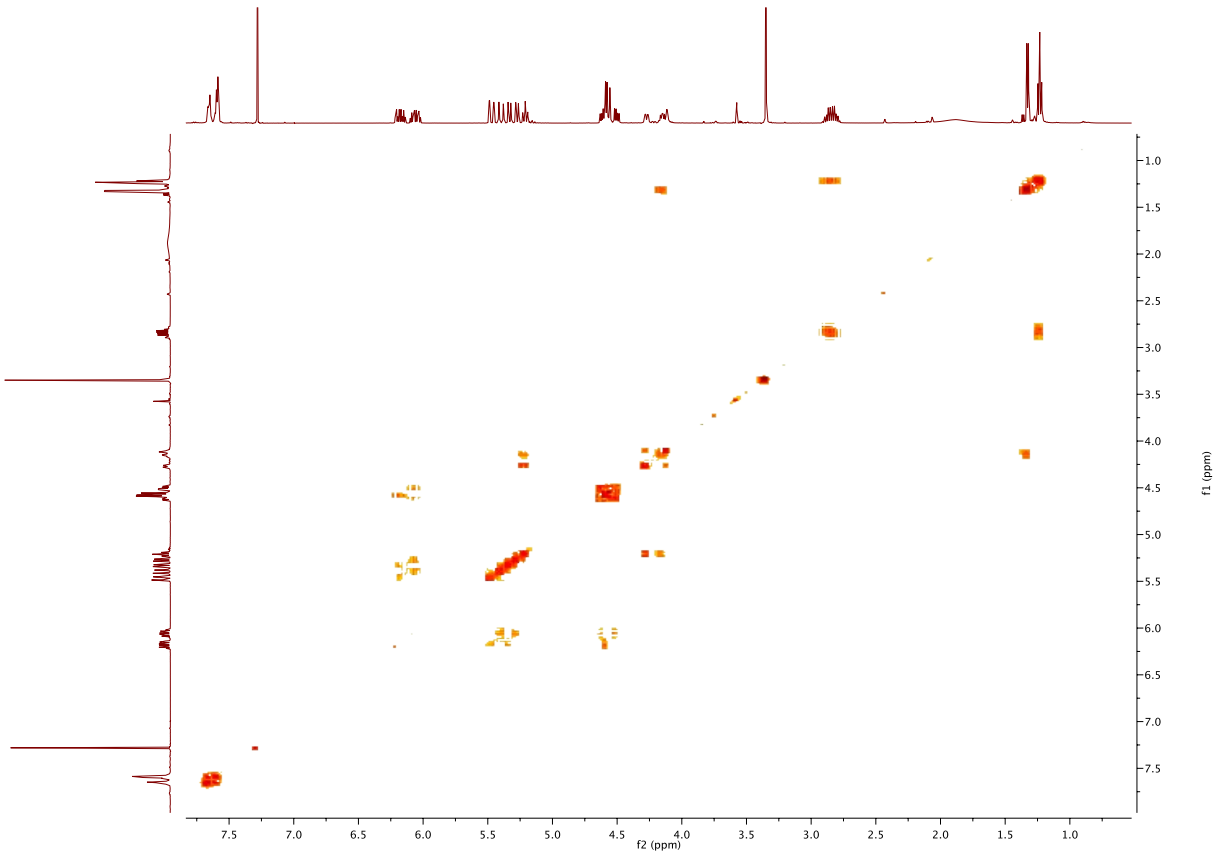
(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-((*S*)-phenylsulfinyl)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.168)



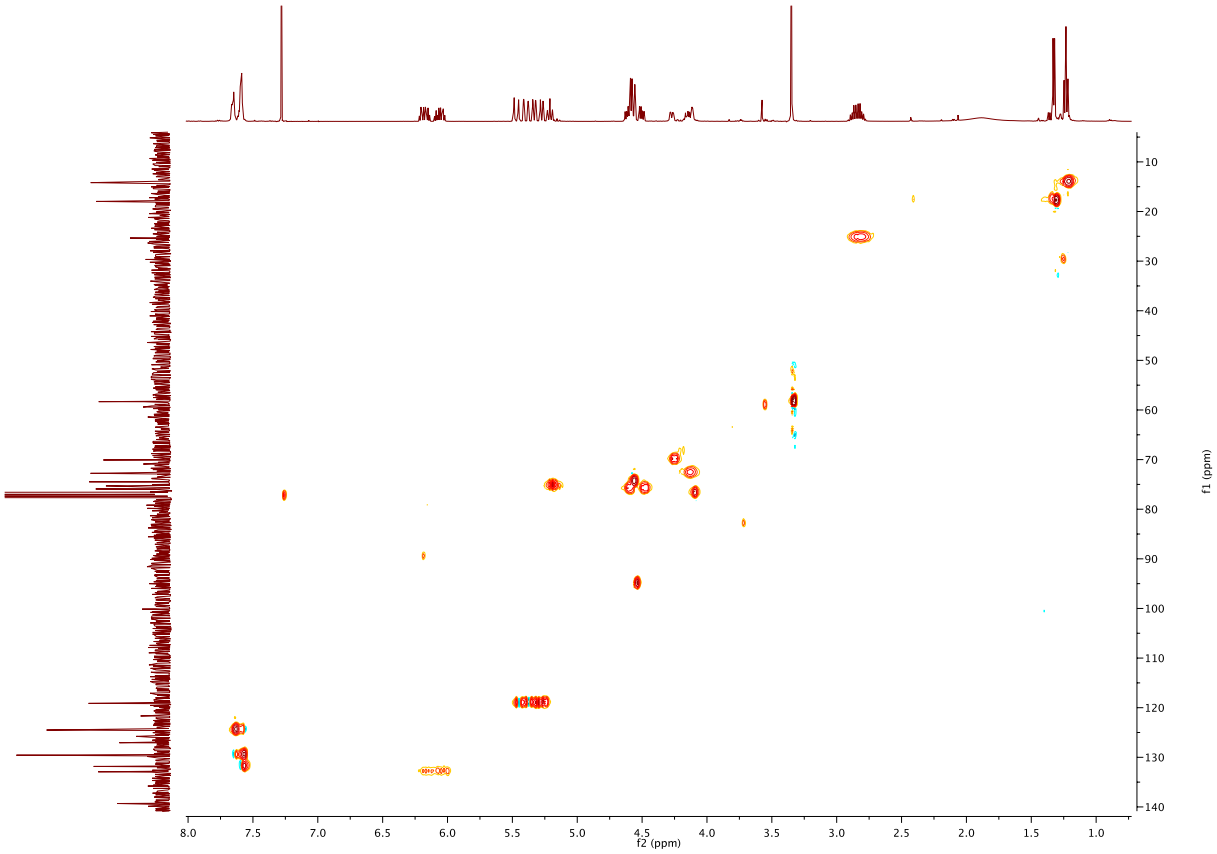
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



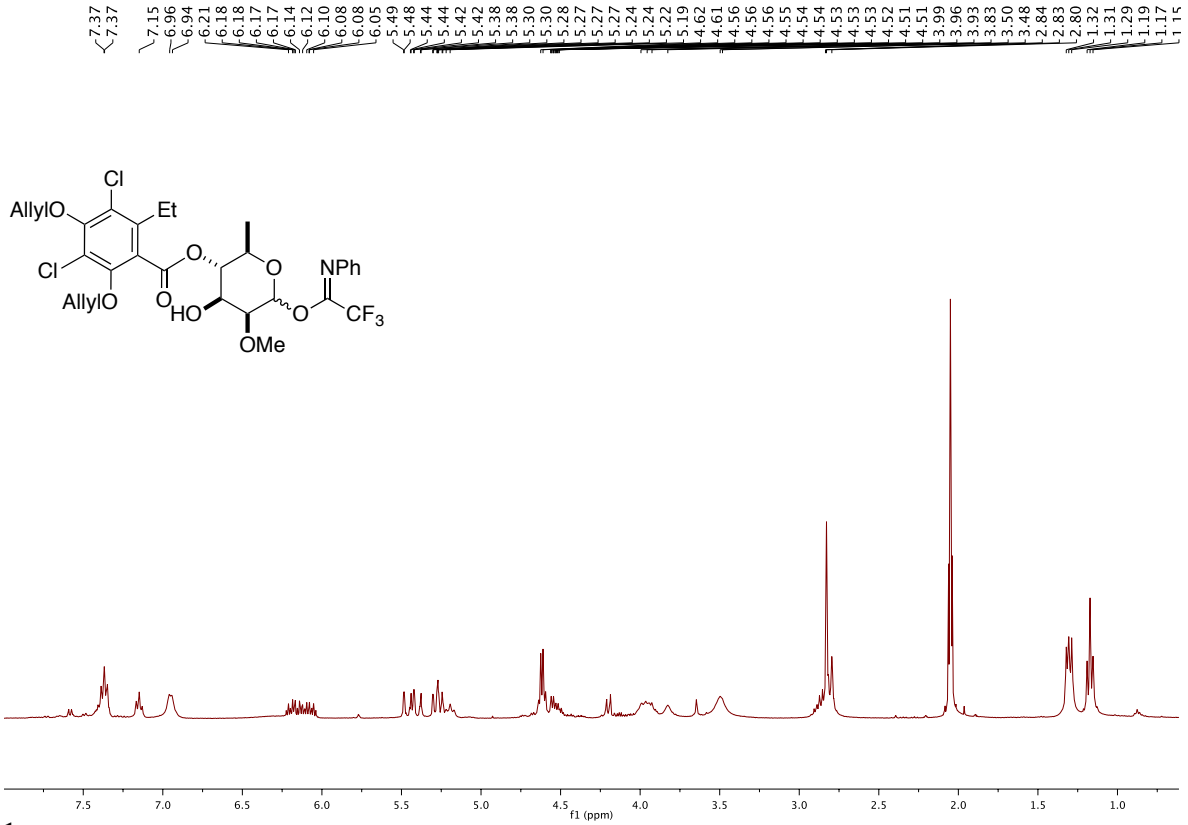
COSY (500 MHz, $CDCl_3$)



HSQC (500 MHz, $CDCl_3$)

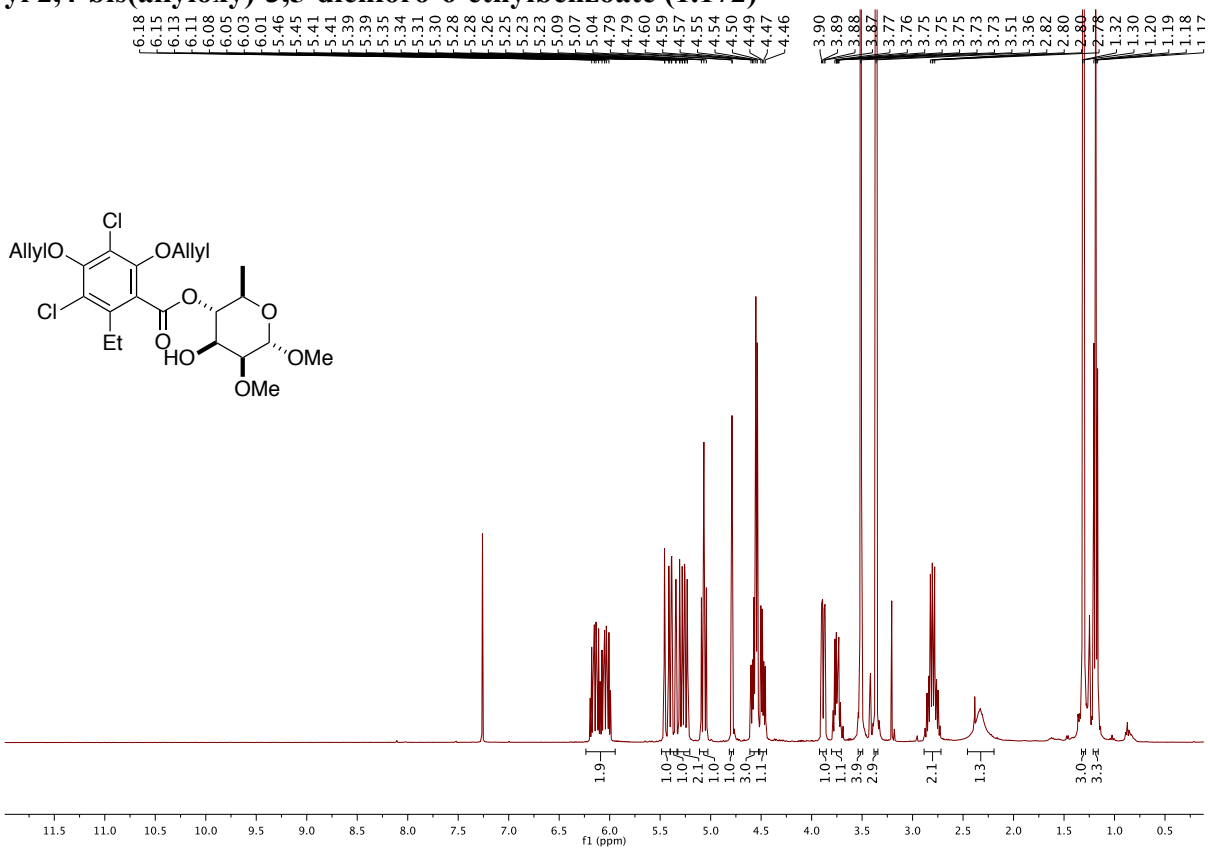
HMBC (500 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-((*E*)-2,2,2-trifluoro-1-(phenylimino)-ethoxy)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.169)

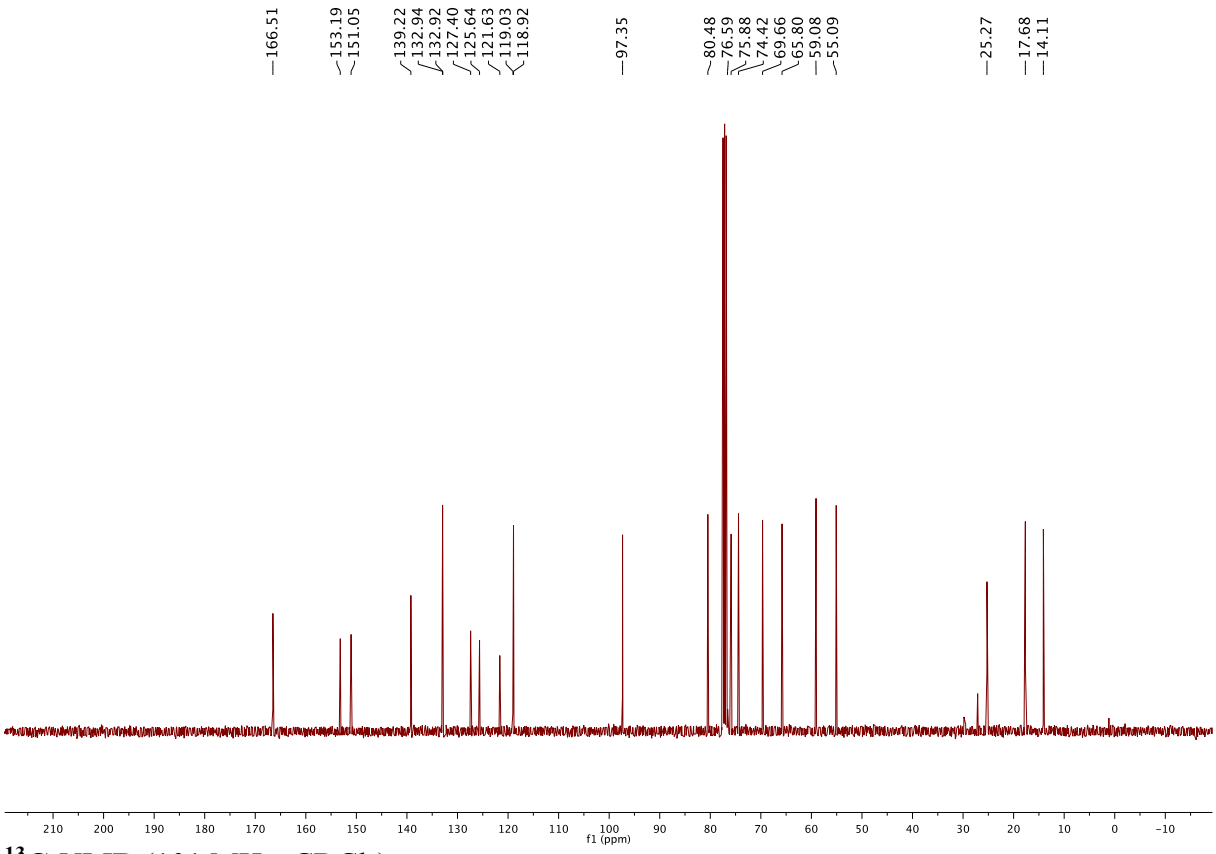


^{1}H-NMR (400 MHz, Acetone-d_6

(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.172)

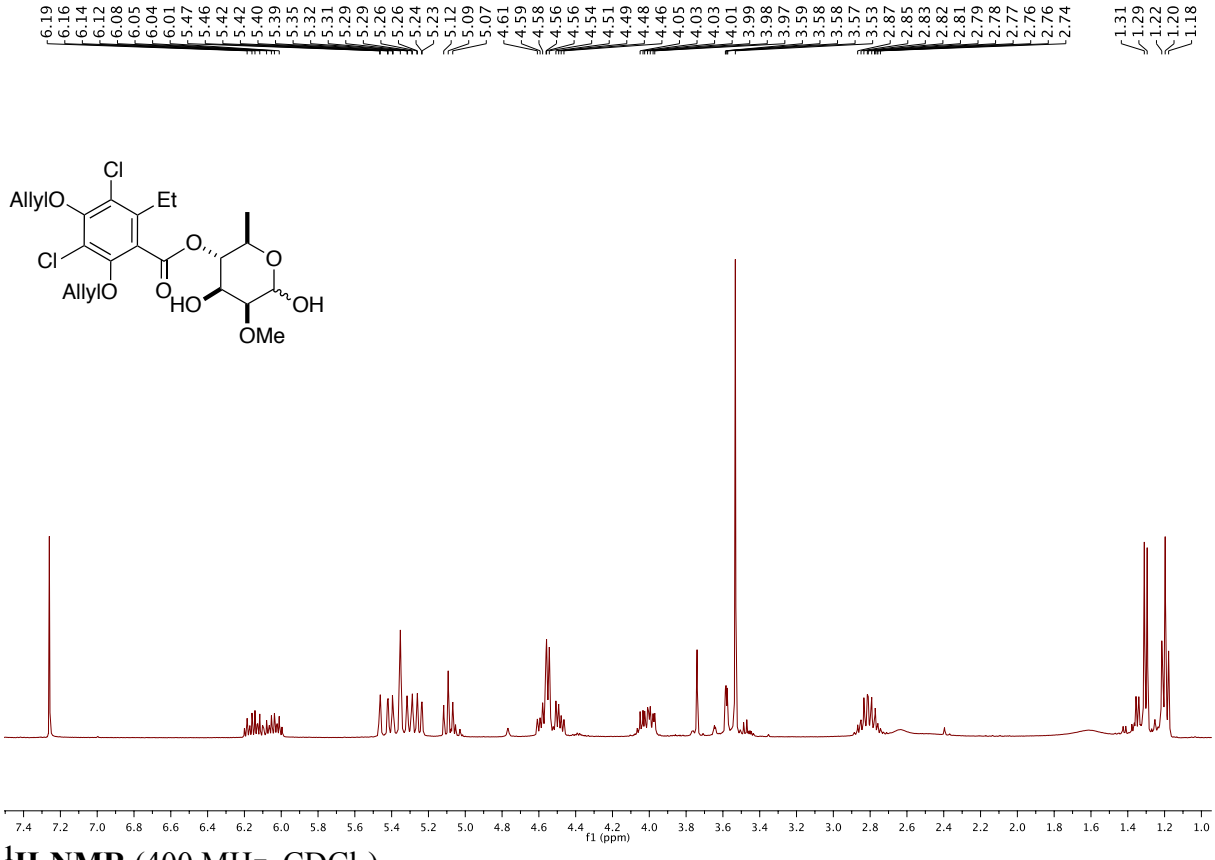


^{1}H-NMR (400 MHz, $CDCl_3$)

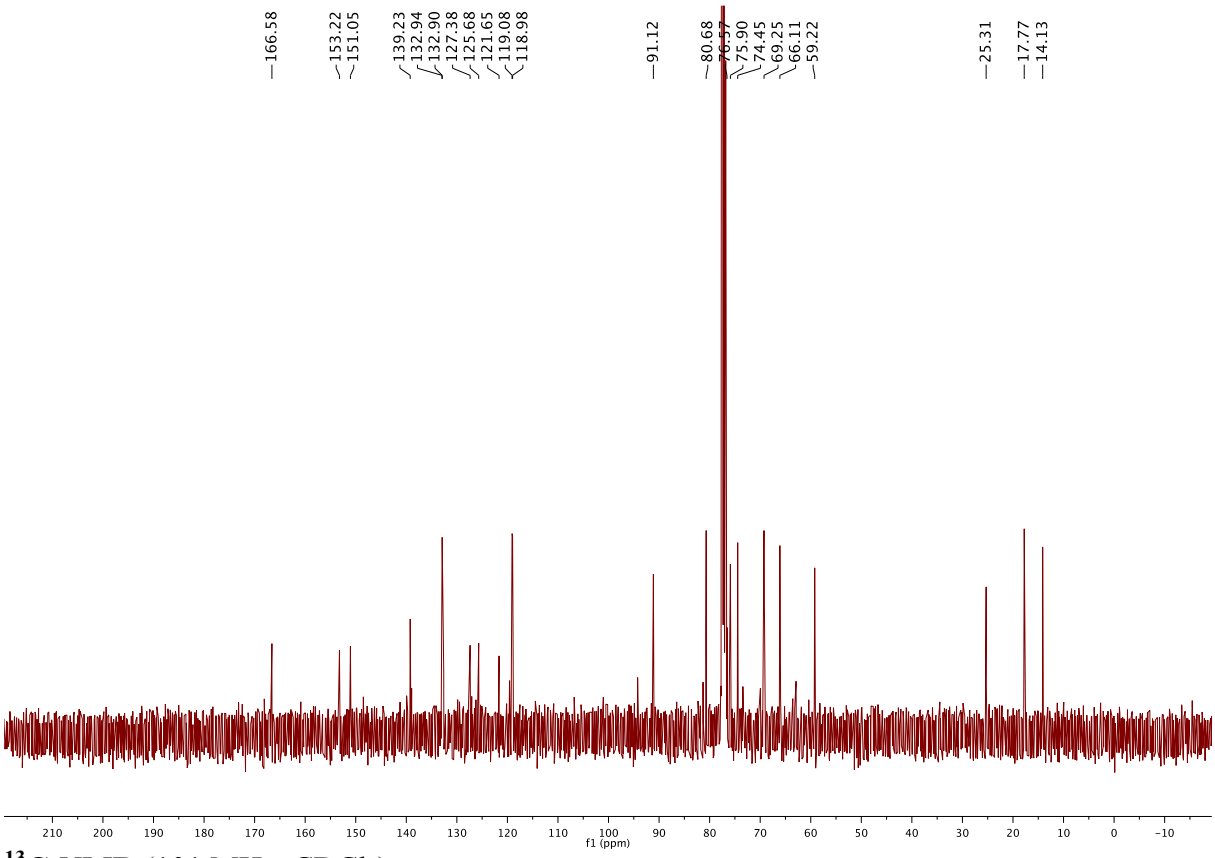


^{13}C-NMR (101 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*)-4,6-dihydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (1.173)

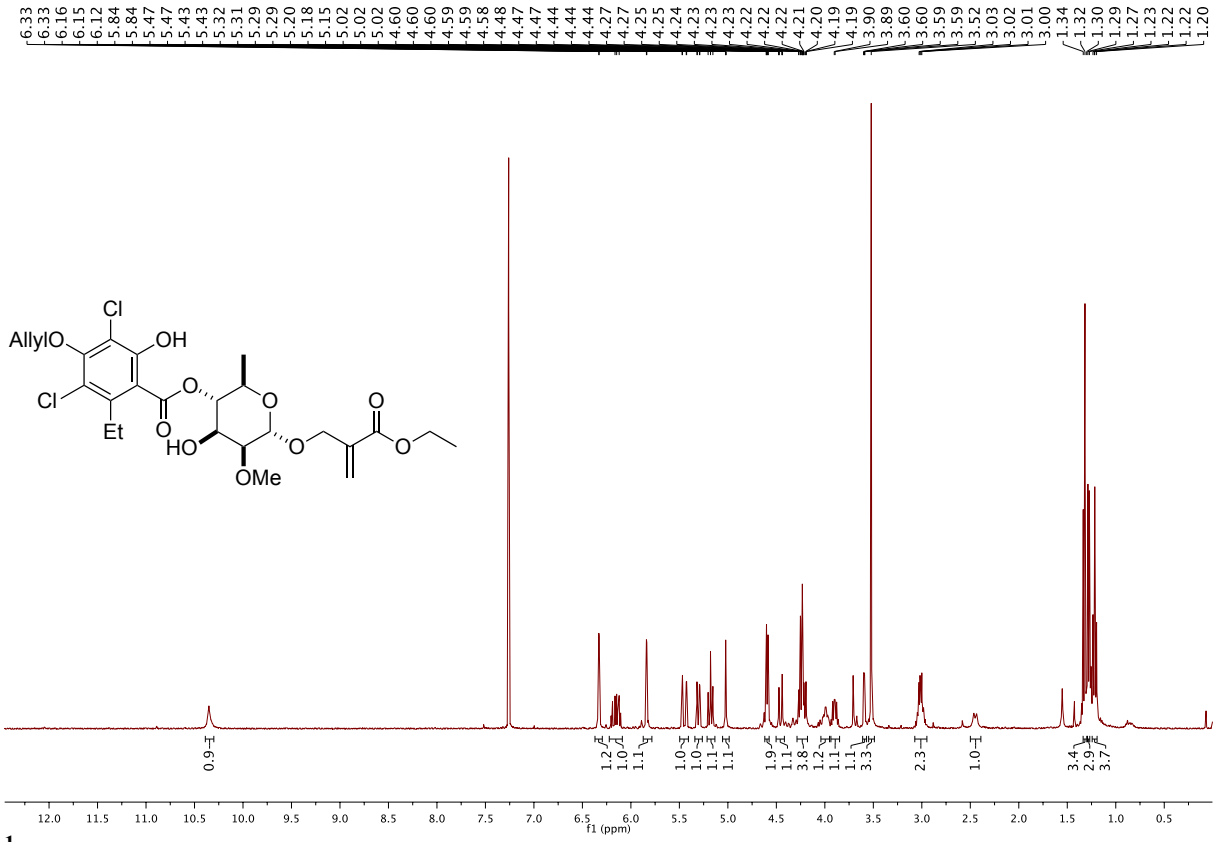


^{1}H-NMR (400 MHz, $CDCl_3$)

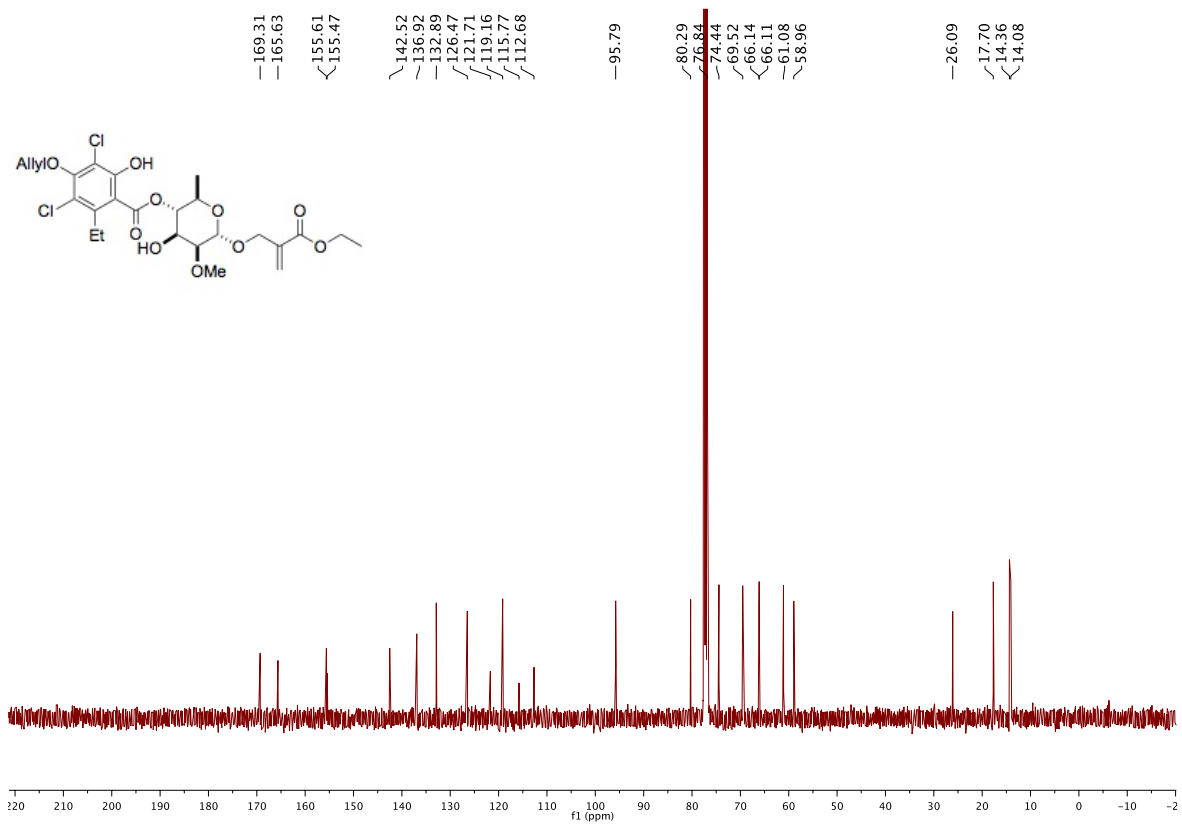


^{13}C-NMR (101 MHz, $CDCl_3$)

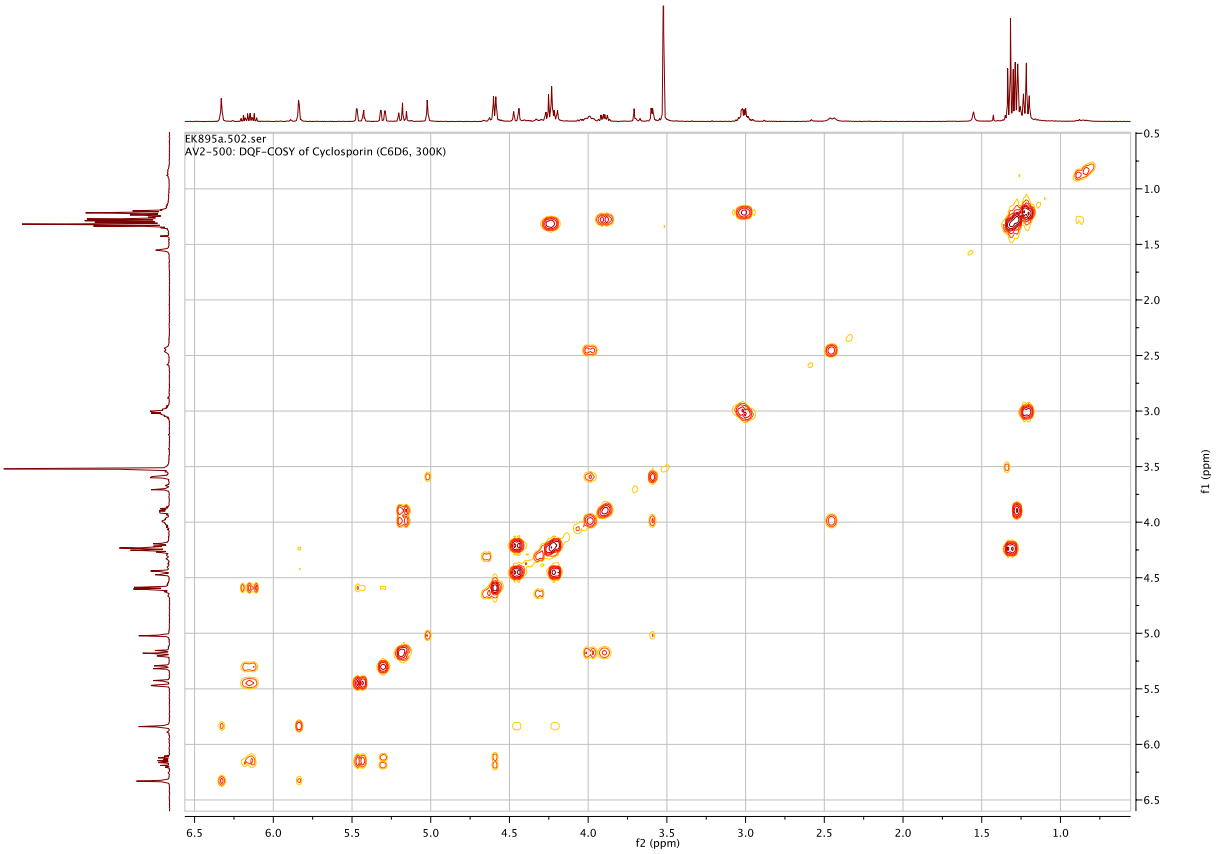
(2*R*,3*S*,4*S*,5*S*,6*S*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (α-1.158)



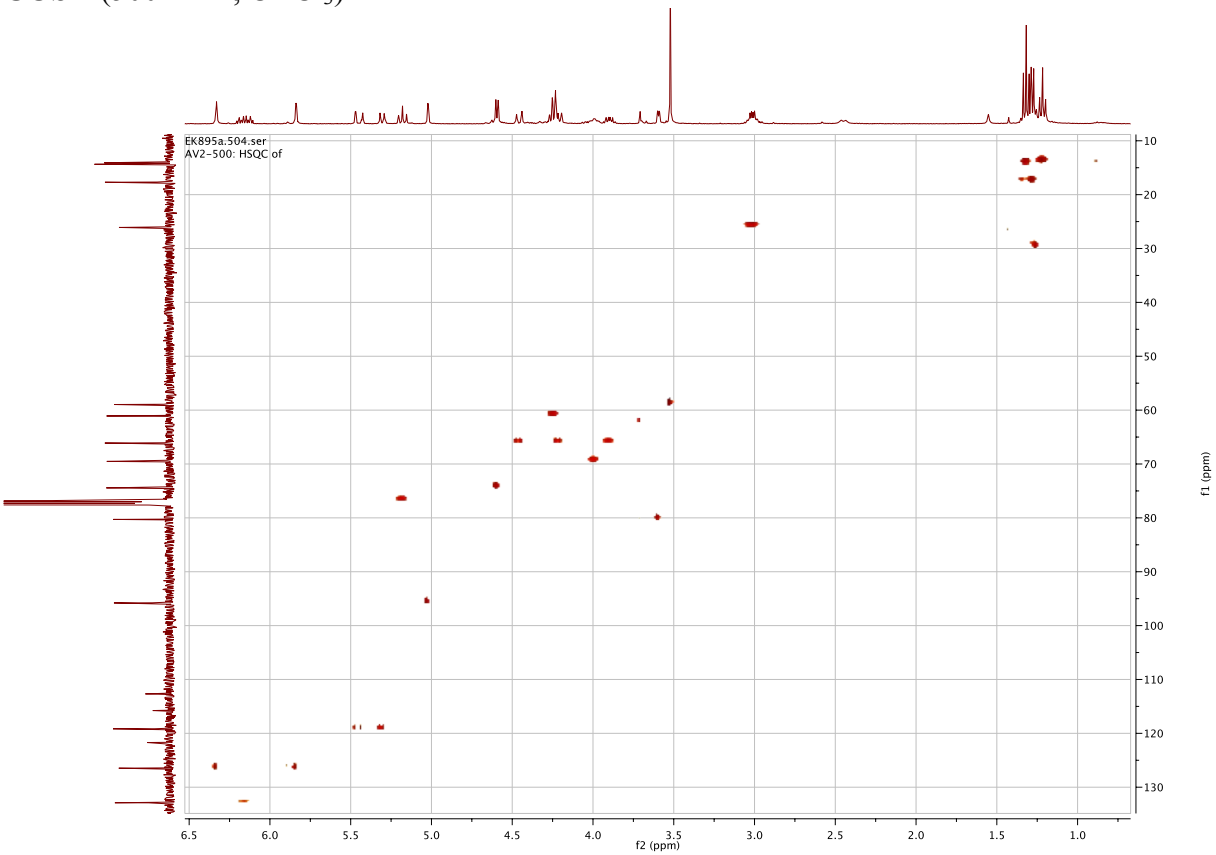
^{1}H-NMR (400 MHz, $CDCl_3$)



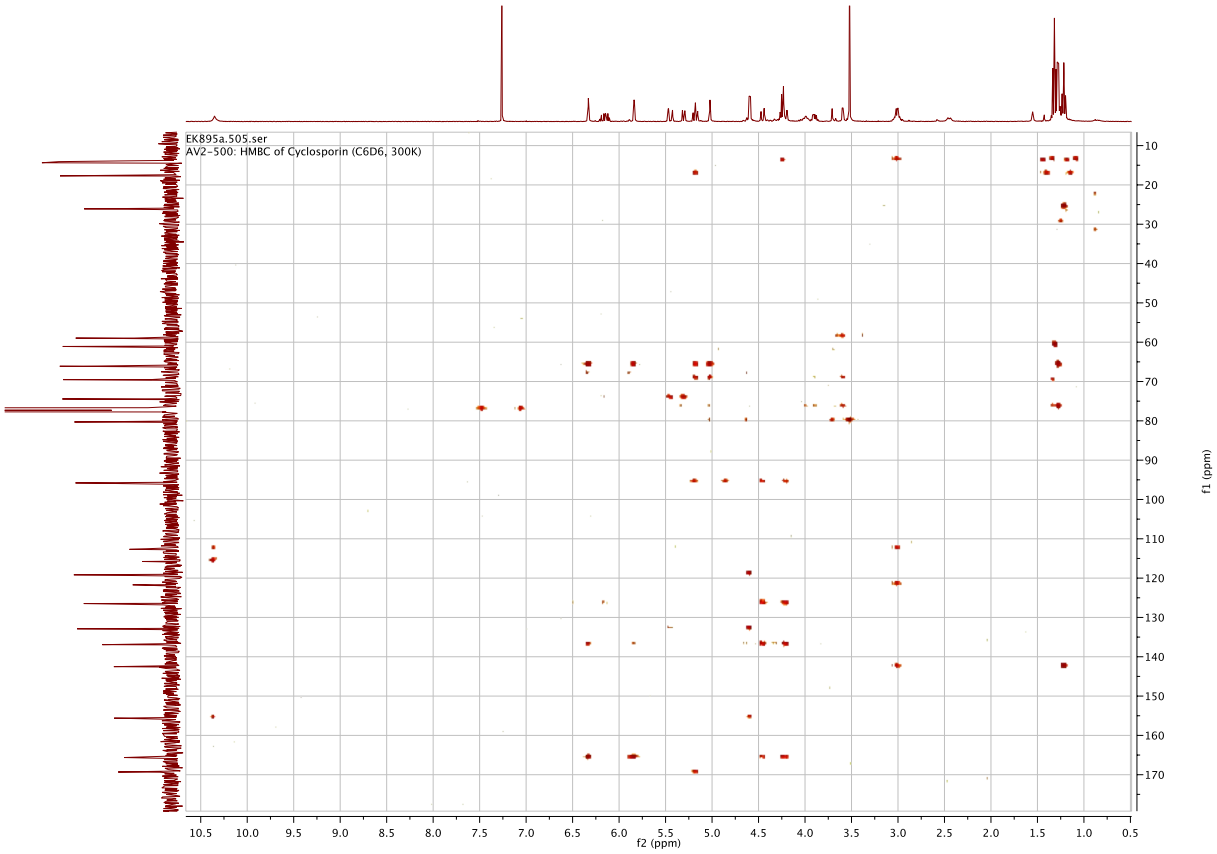
^{13}C-NMR (101 MHz, $CDCl_3$)



COSY (500 MHz, $CDCl_3$)

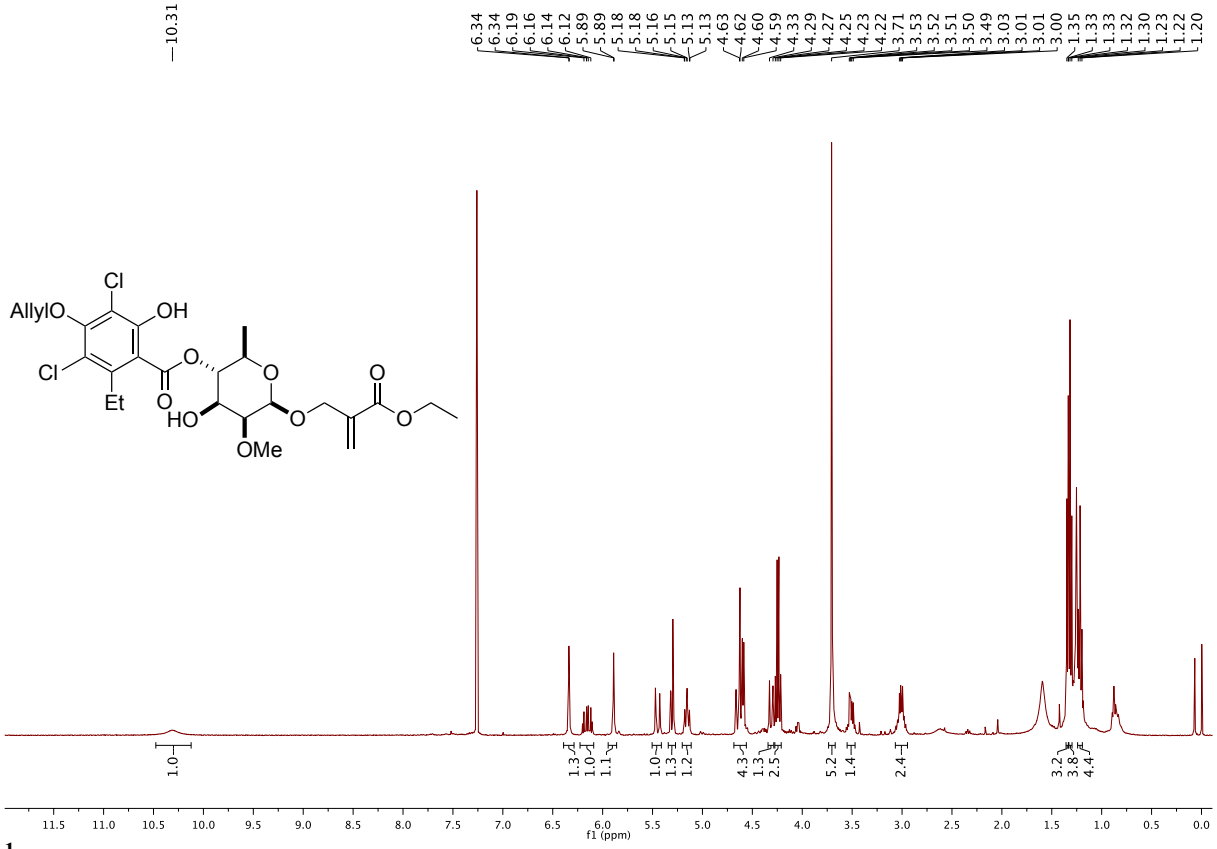


HSQC (500 MHz, $CDCl_3$)

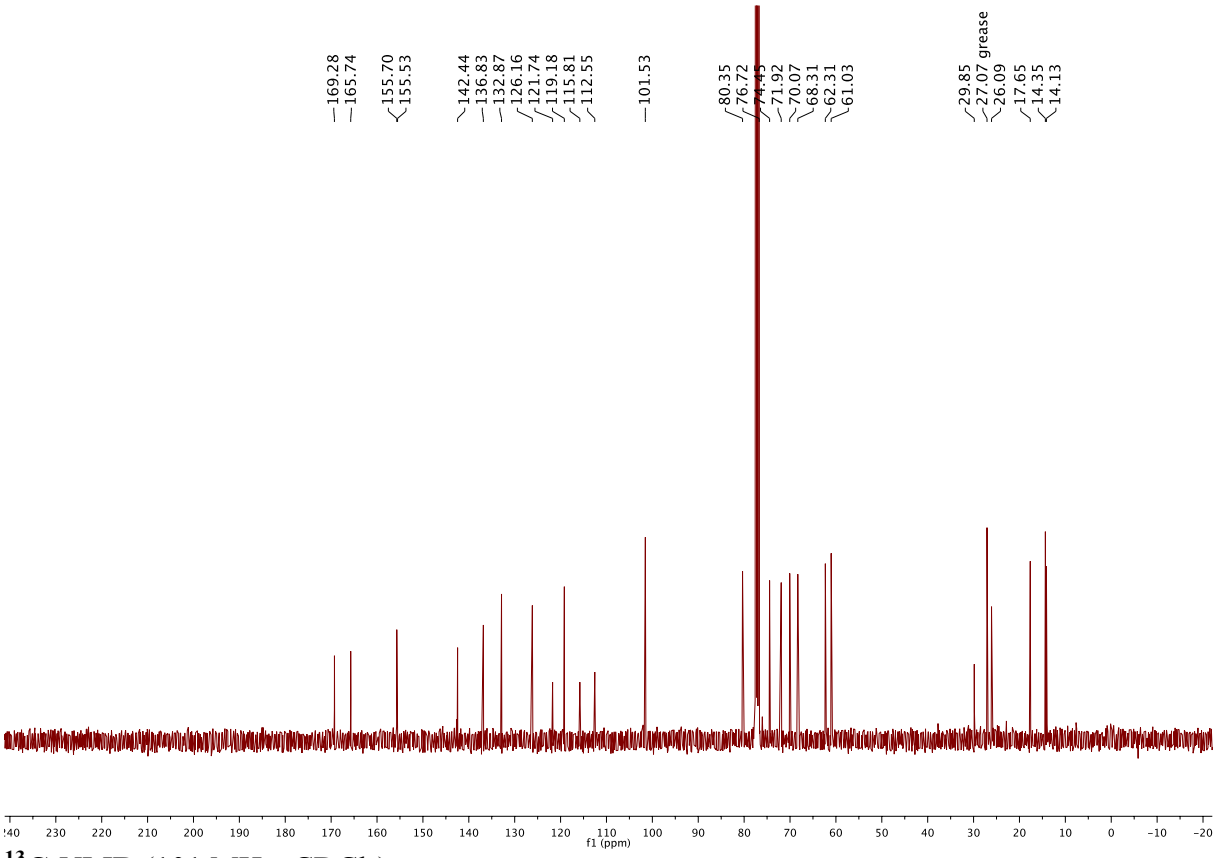


HMBC (500 MHz, $CDCl_3$)

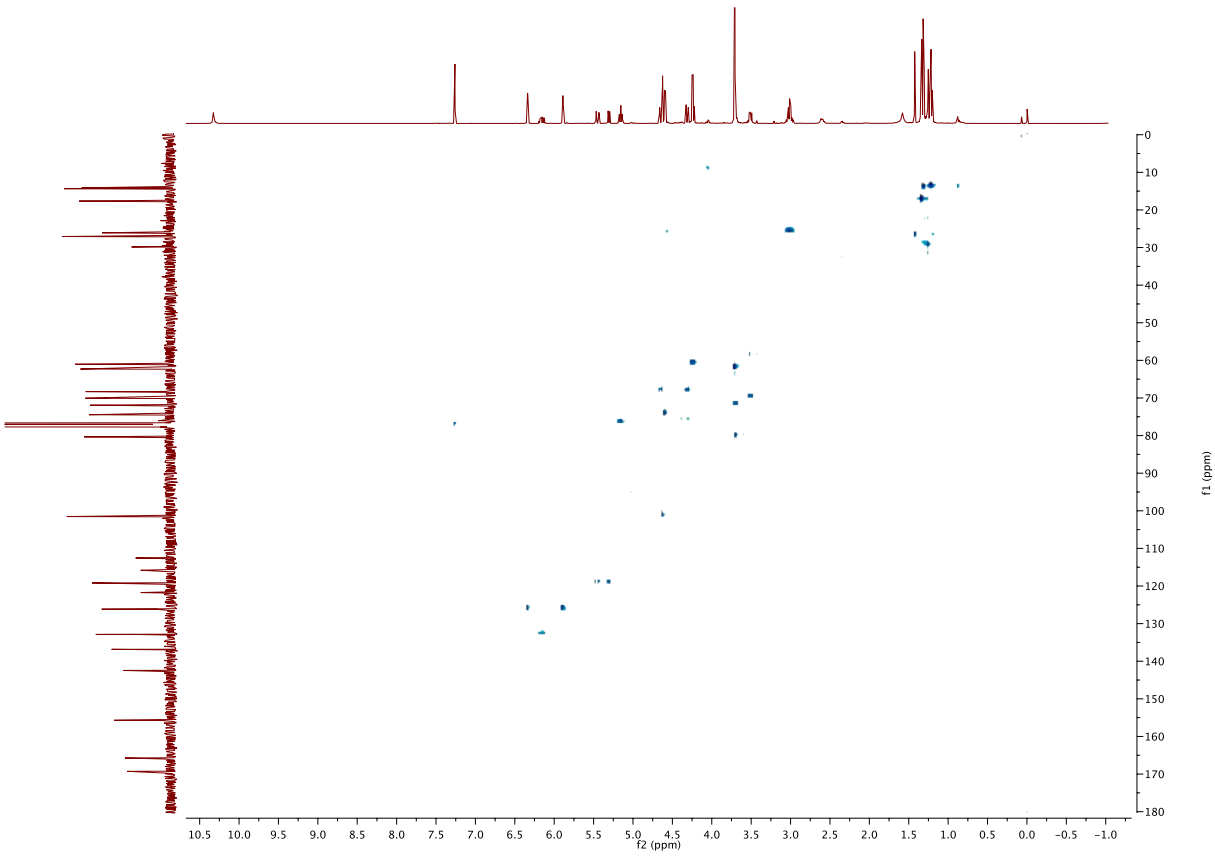
(2*R*,3*S*,4*S*,5*S*,6*R*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyl-tetrahydro-2*H*-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (β-1.158)



^{1}H-NMR (500 MHz, $CDCl_3$)

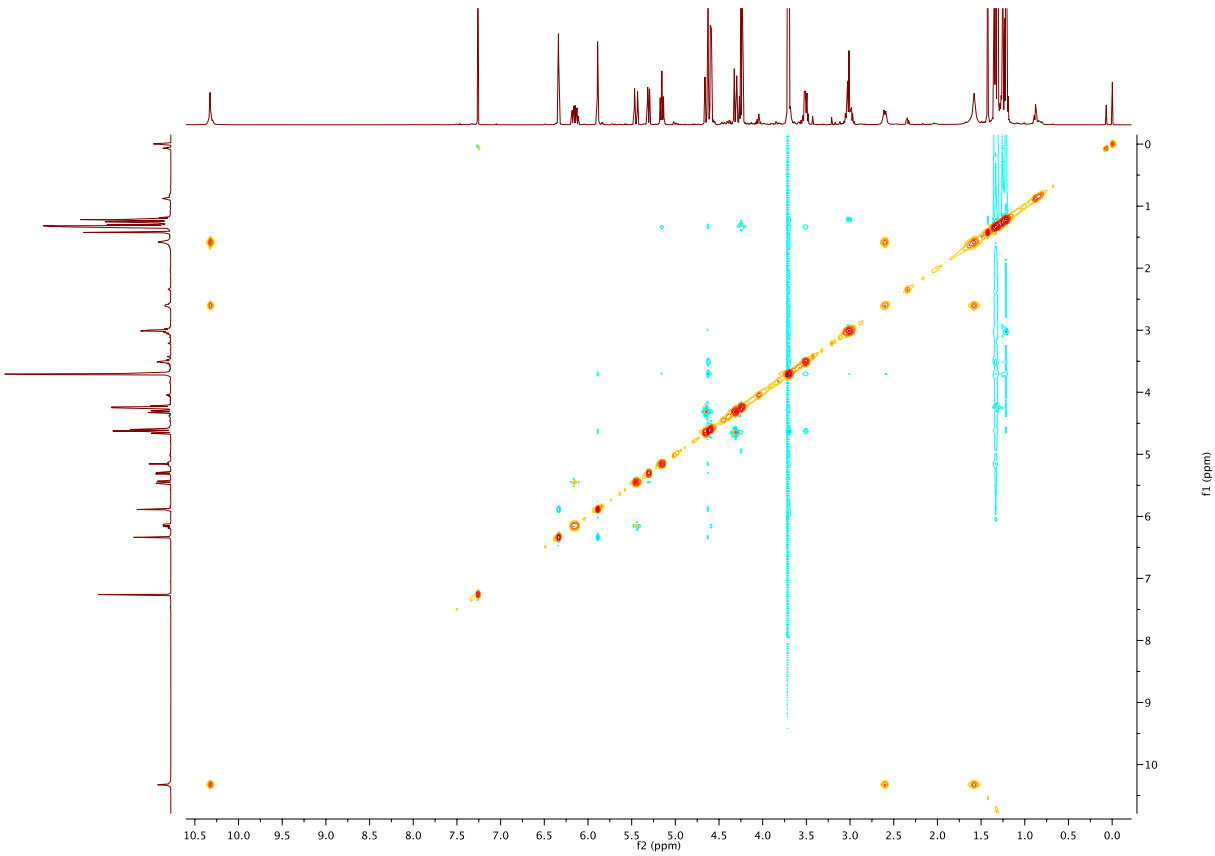


^{13}C-NMR (101 MHz, $CDCl_3$)



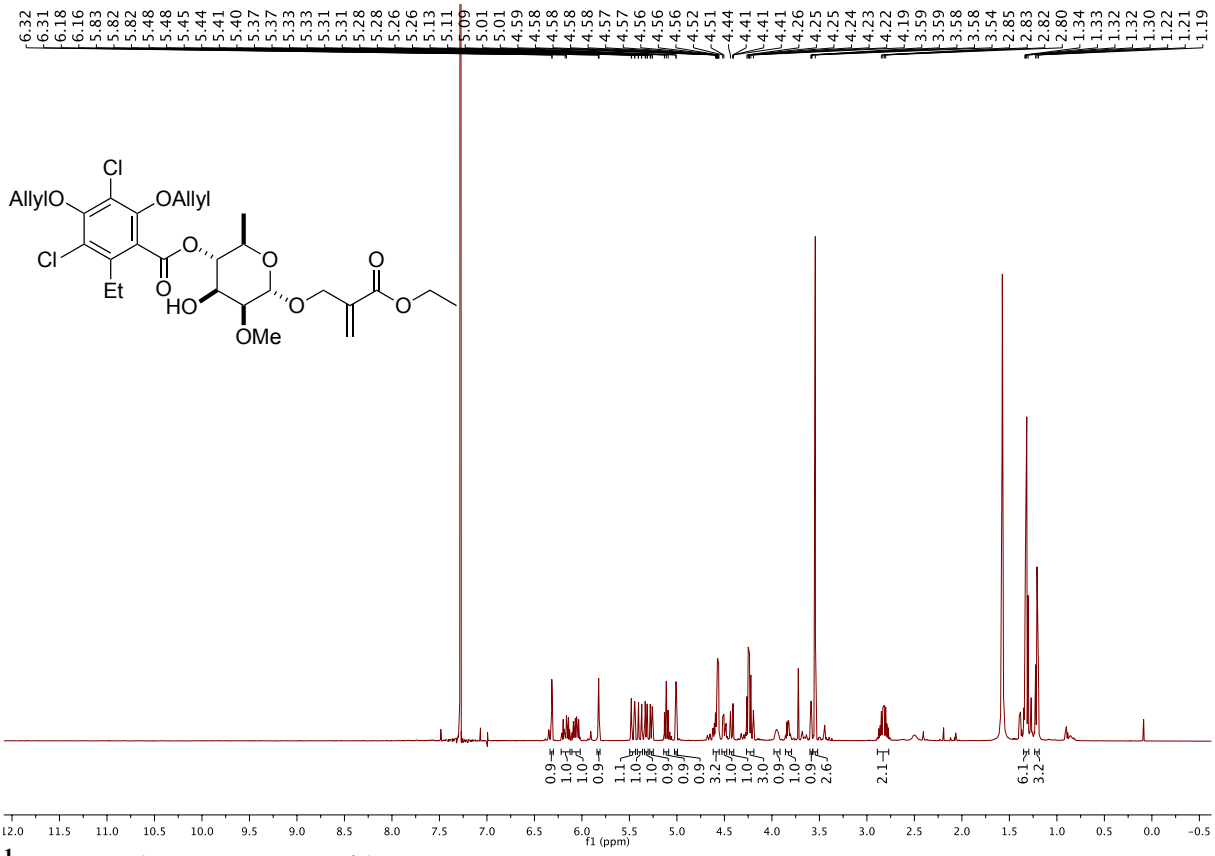
HSQC (500 MHz, $CDCl_3$)

HMBC (500 MHz, $CDCl_3$)

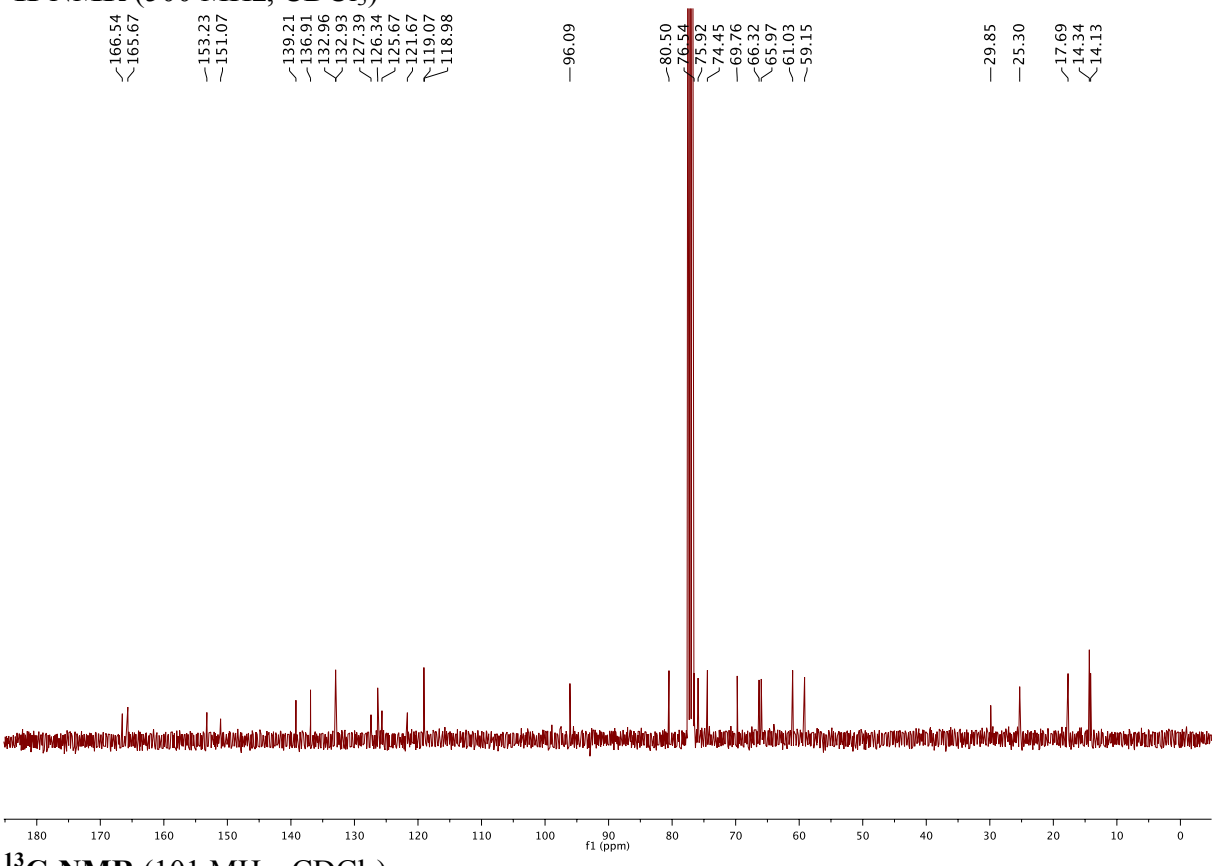


NOESY (500 MHz, $CDCl_3$)

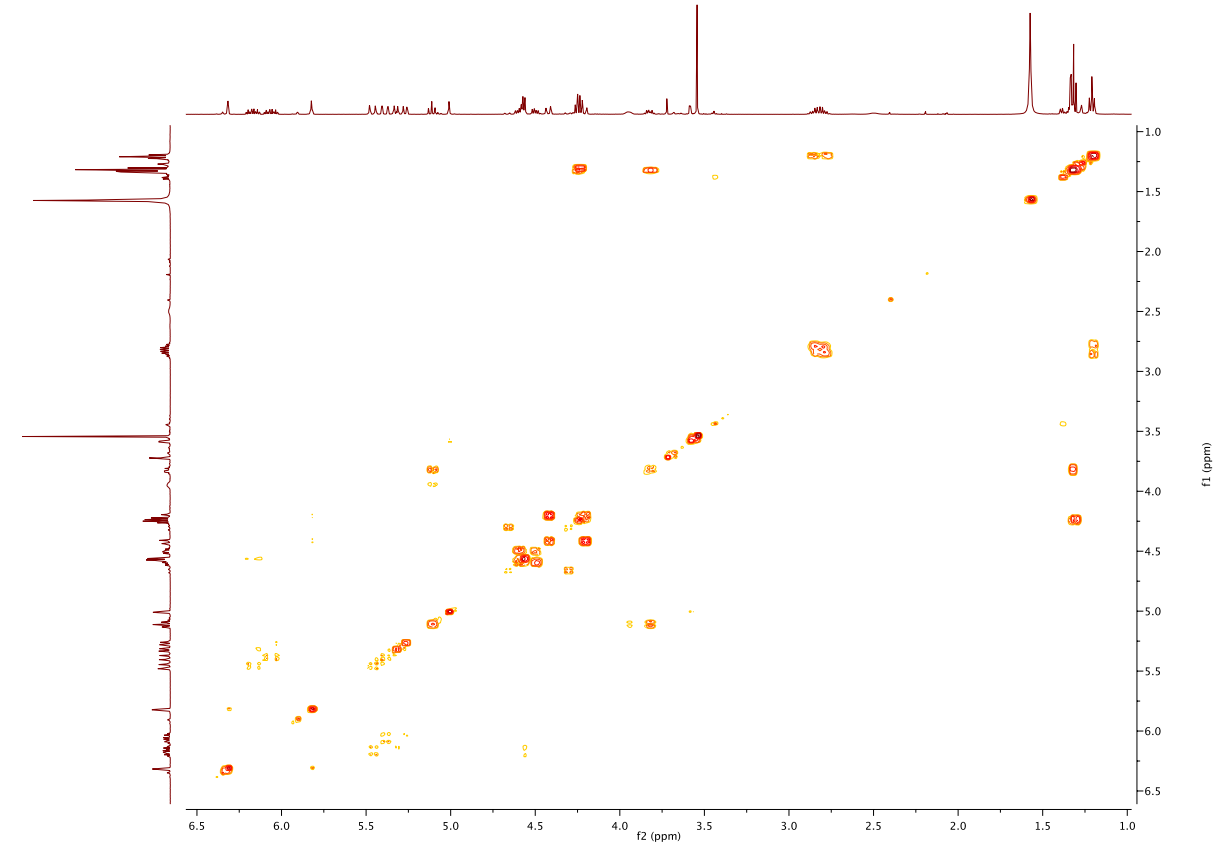
(2*R*,3*S*,4*S*,5*S*,6*S*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (α-1.164b)



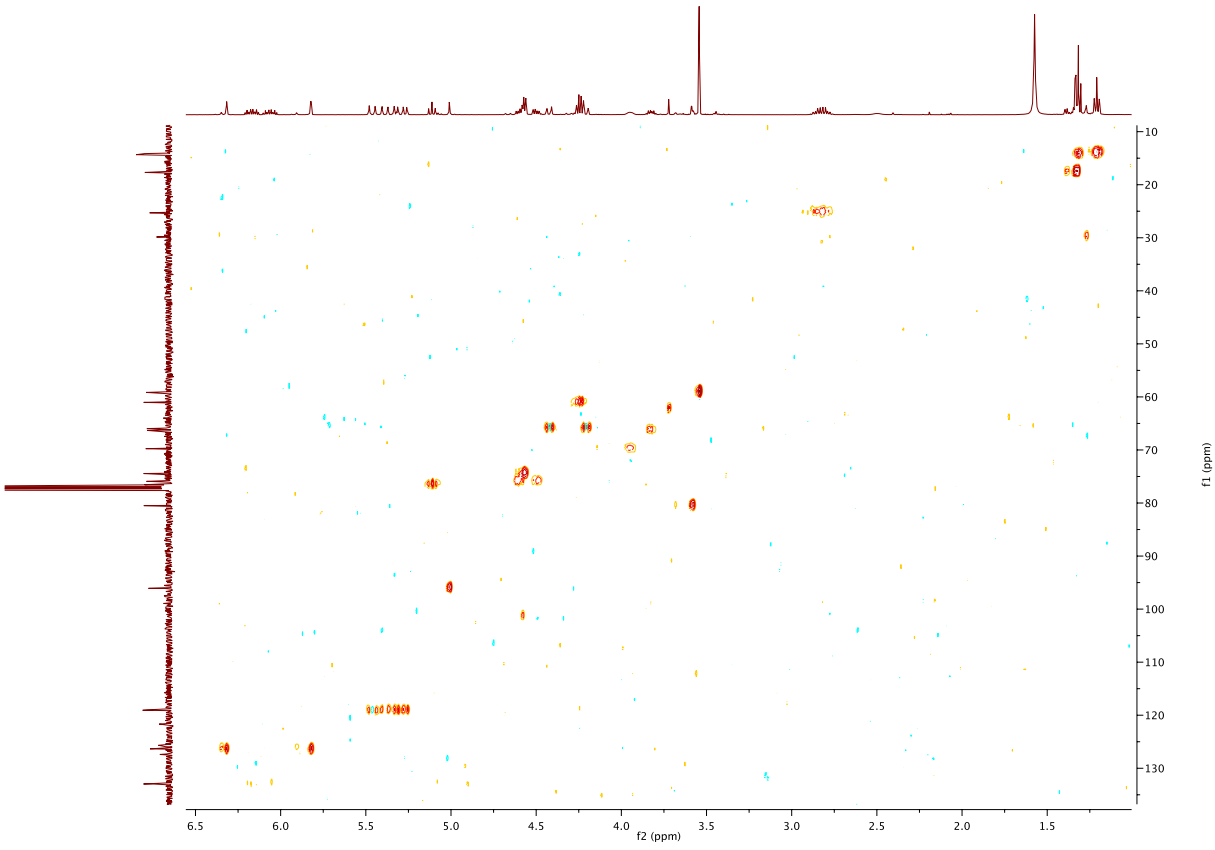
^{1}H-NMR (500 MHz, $CDCl_3$)



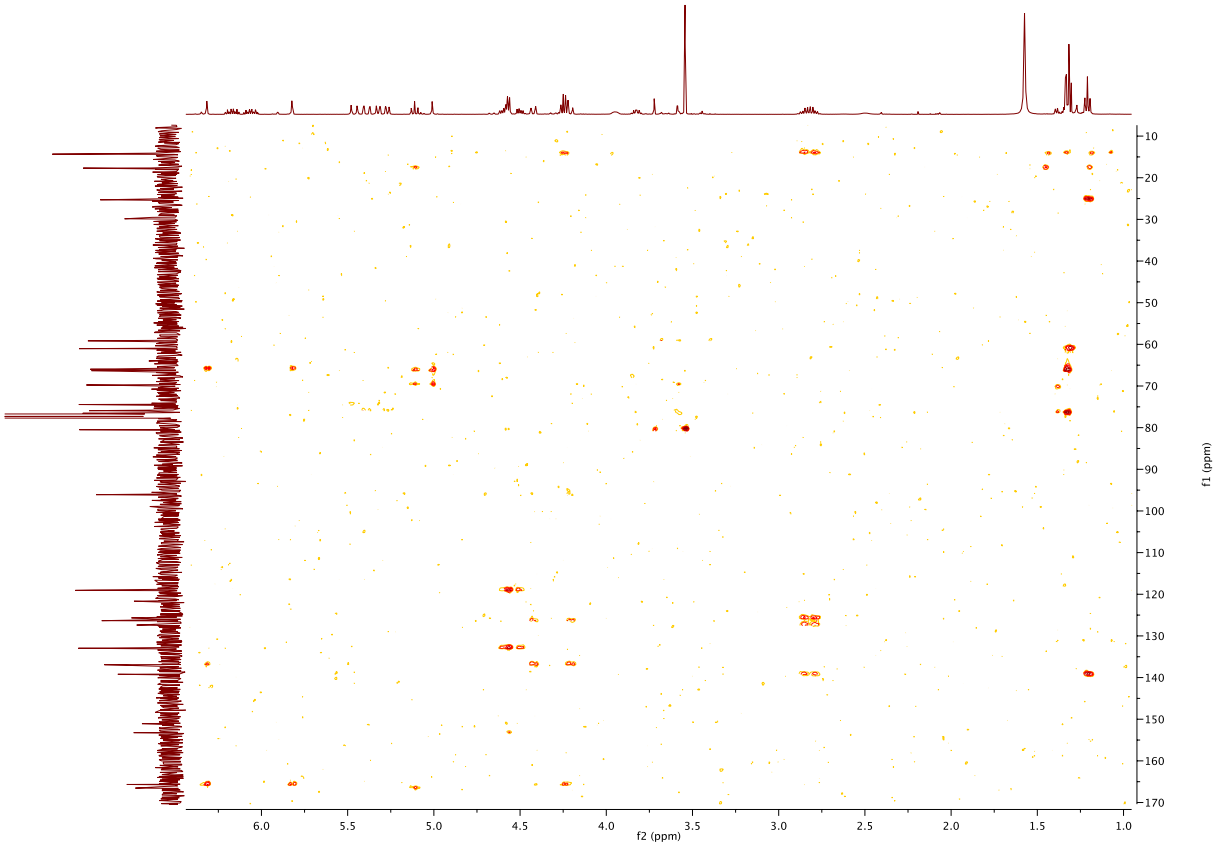
^{13}C-NMR (101 MHz, $CDCl_3$)



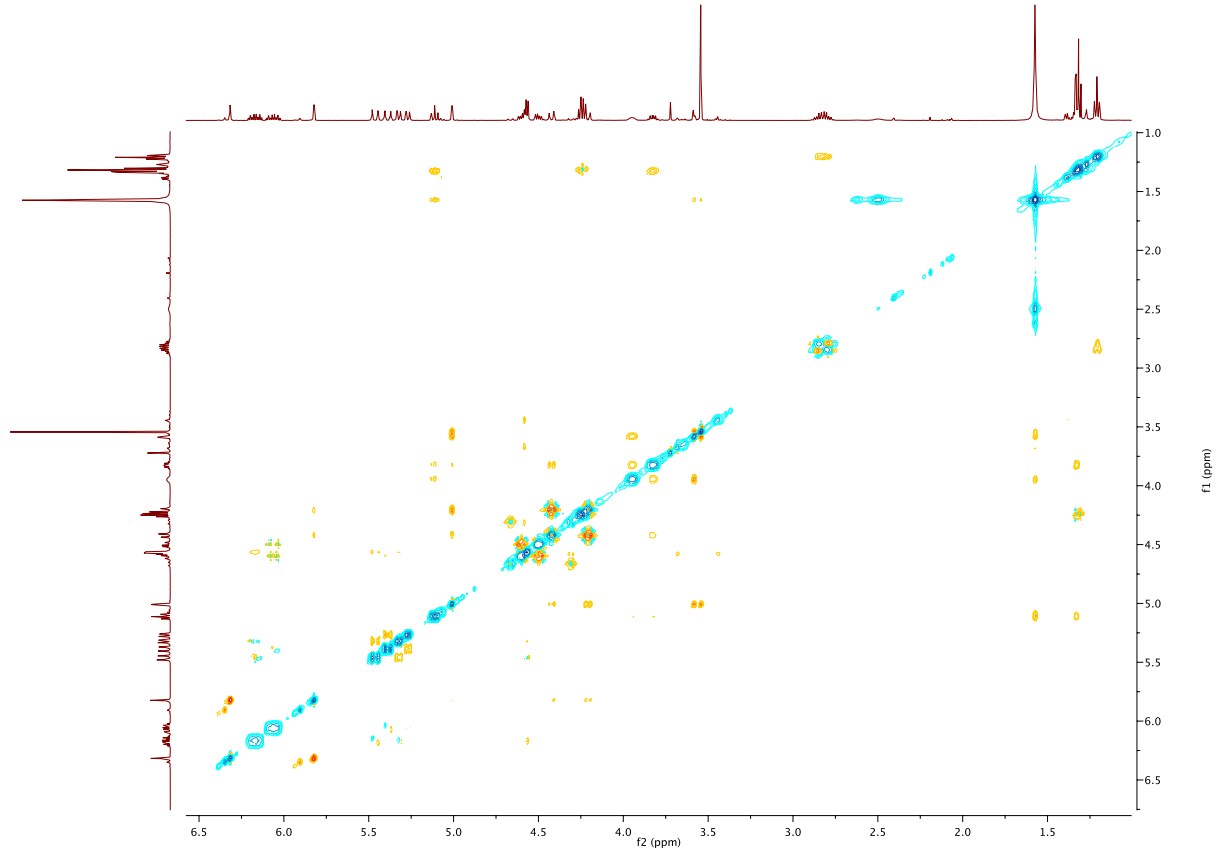
COSY (500 MHz, $CDCl_3$)



HSQC (500 MHz, $CDCl_3$)

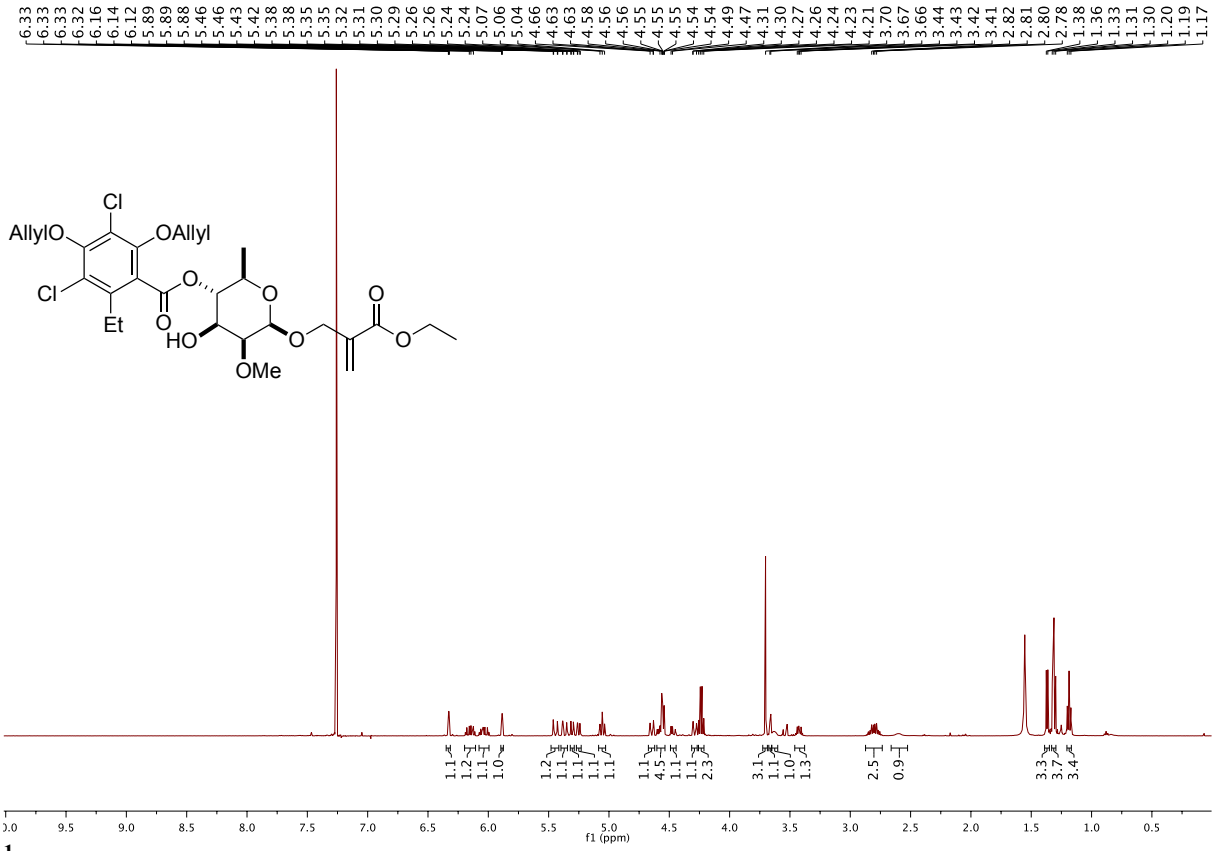


HMBC (500 MHz, $CDCl_3$)

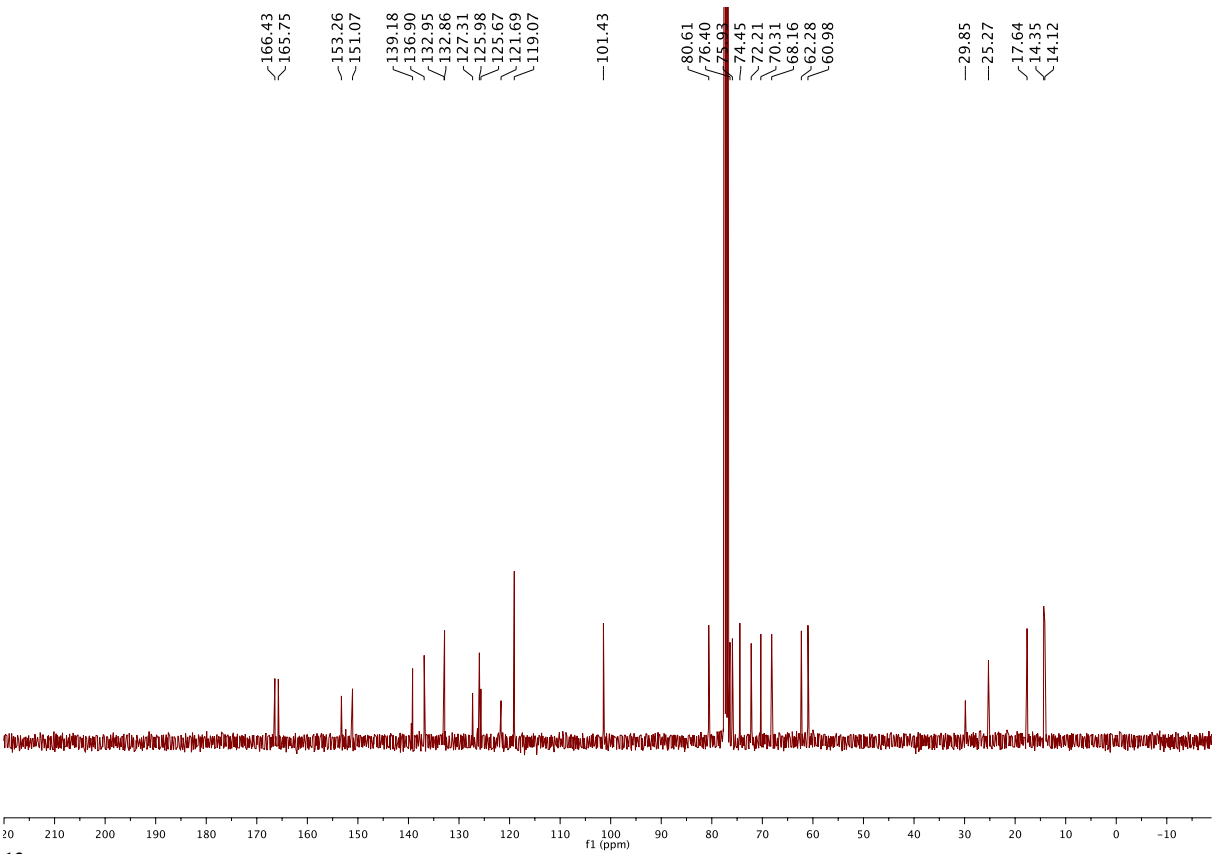


NOESY (500 MHz, $CDCl_3$)

(2*R*,3*S*,4*S*,5*S*,6*R*)-6-((2-(ethoxycarbonyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (β-1.164b)

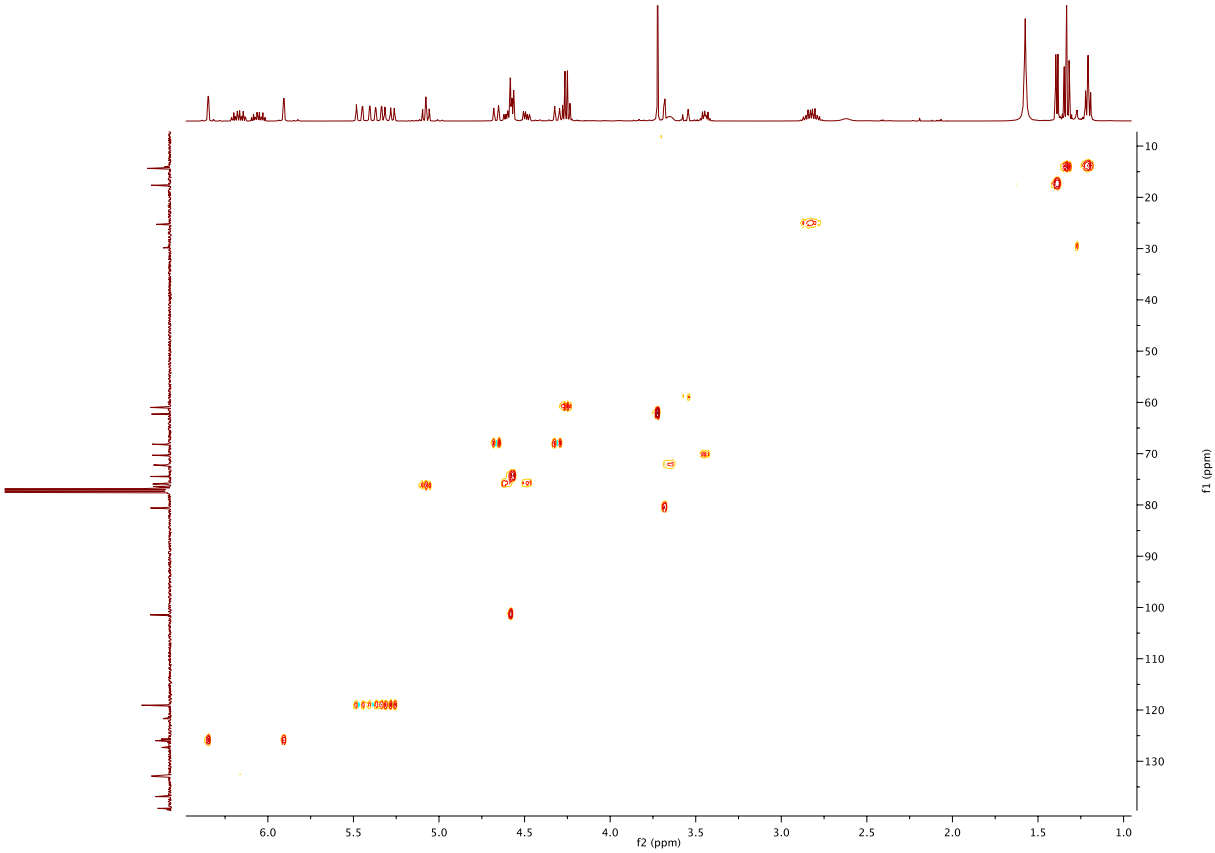


^{1}H-NMR (500 MHz, $CDCl_3$)

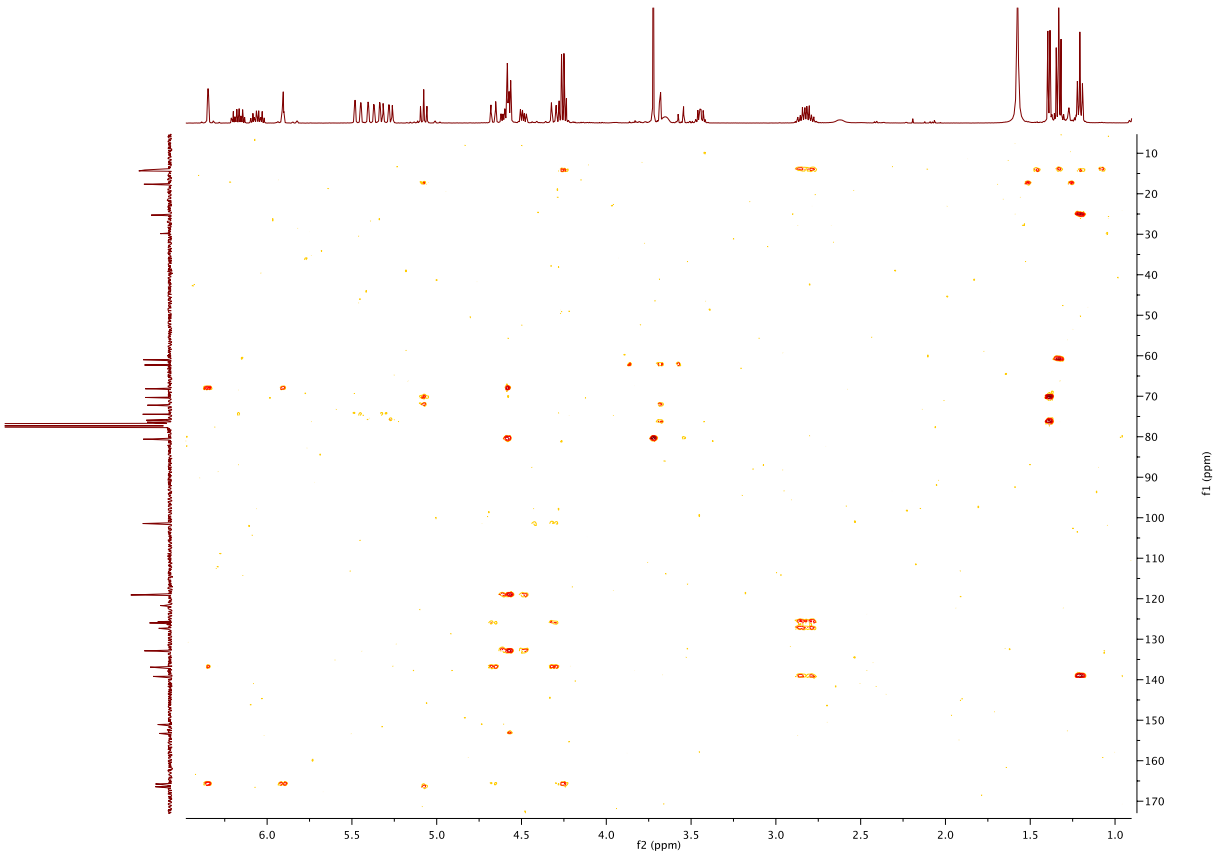


^{13}C-NMR (101 MHz, $CDCl_3$

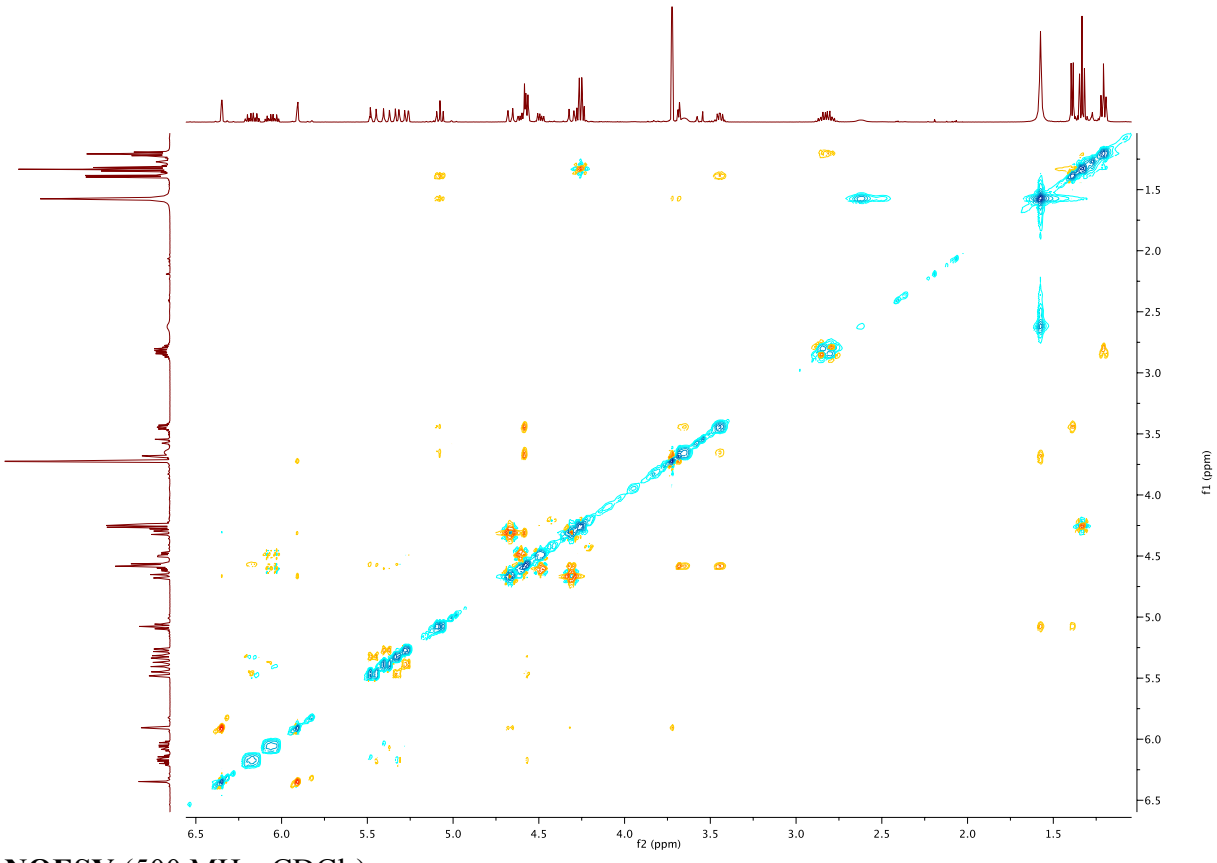
COSY (500 MHz, $CDCl_3$)



HSQC (500 MHz, $CDCl_3$)

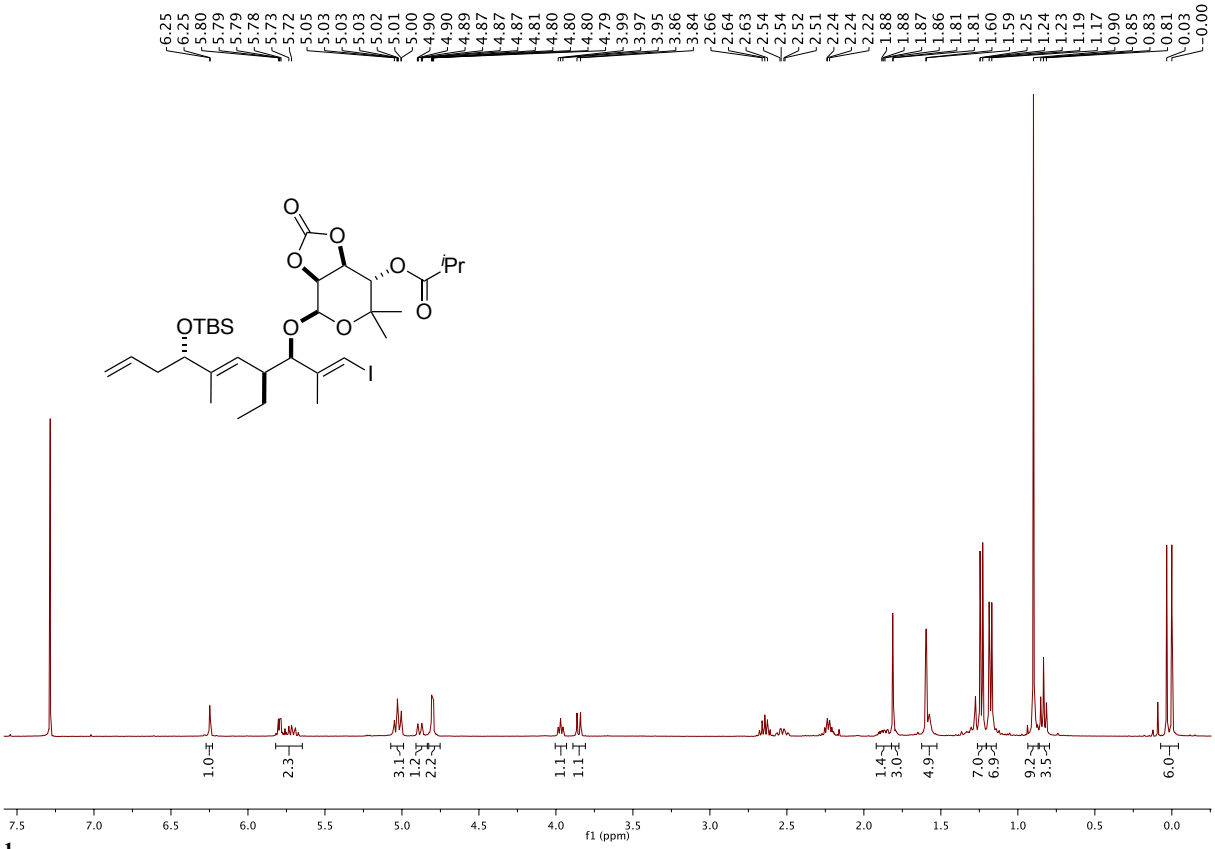


HMBC (500 MHz, $CDCl_3$)

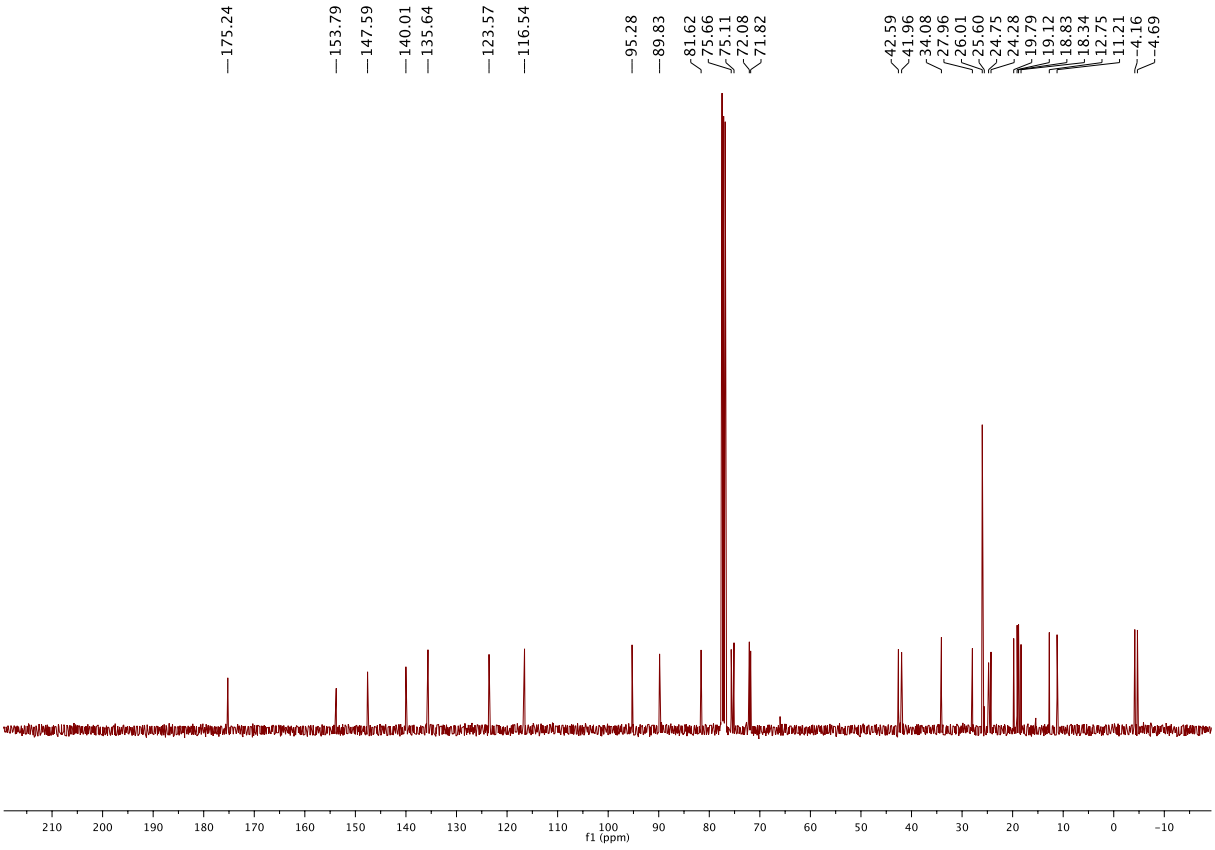


NOESY (500 MHz, $CDCl_3$)

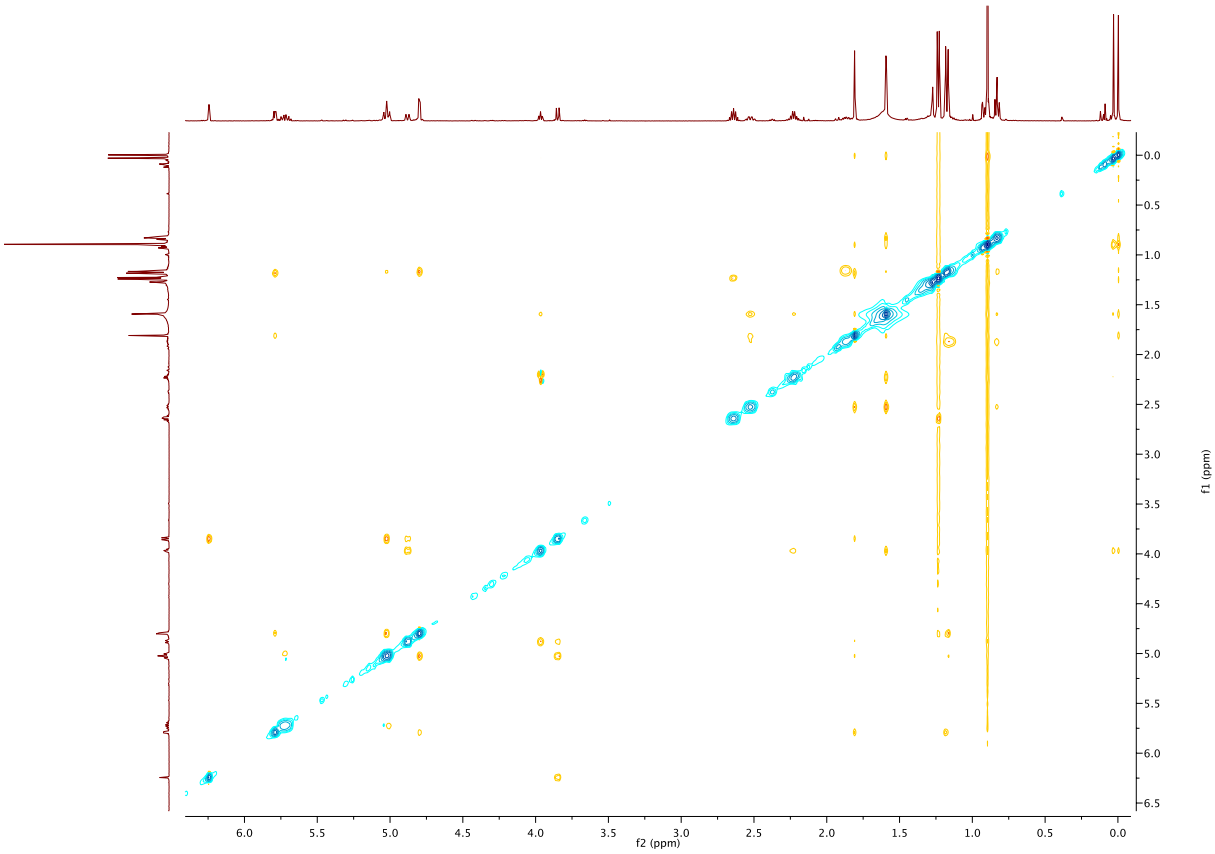
4-(((1*E*,3*R*,4*S*,5*E*,7*S*)-7-((TBS)oxy)-4-ethyl-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (β-1.185)



^{1}H-NMR (400 MHz, $CDCl_3$)

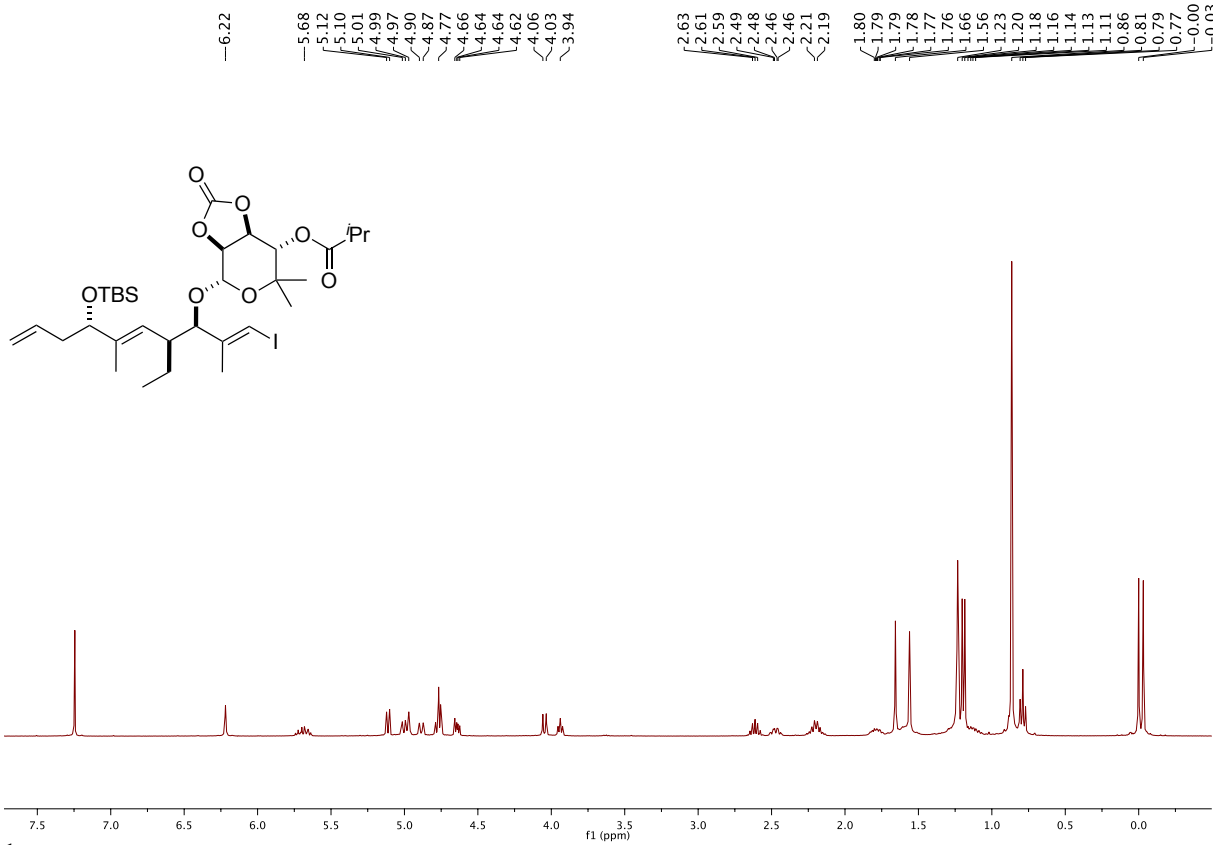


^{13}C-NMR (101 MHz, $CDCl_3$

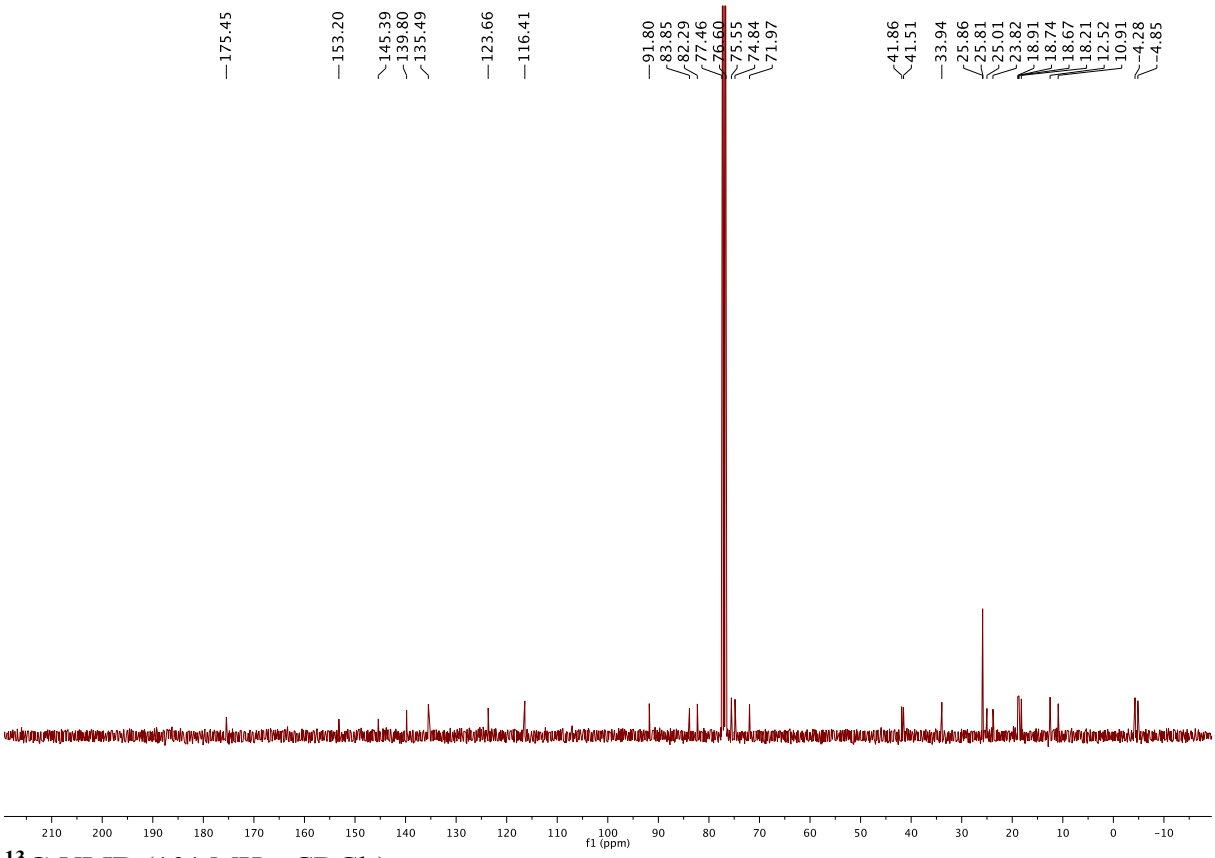


NOESY (500 MHz, $CDCl_3$)

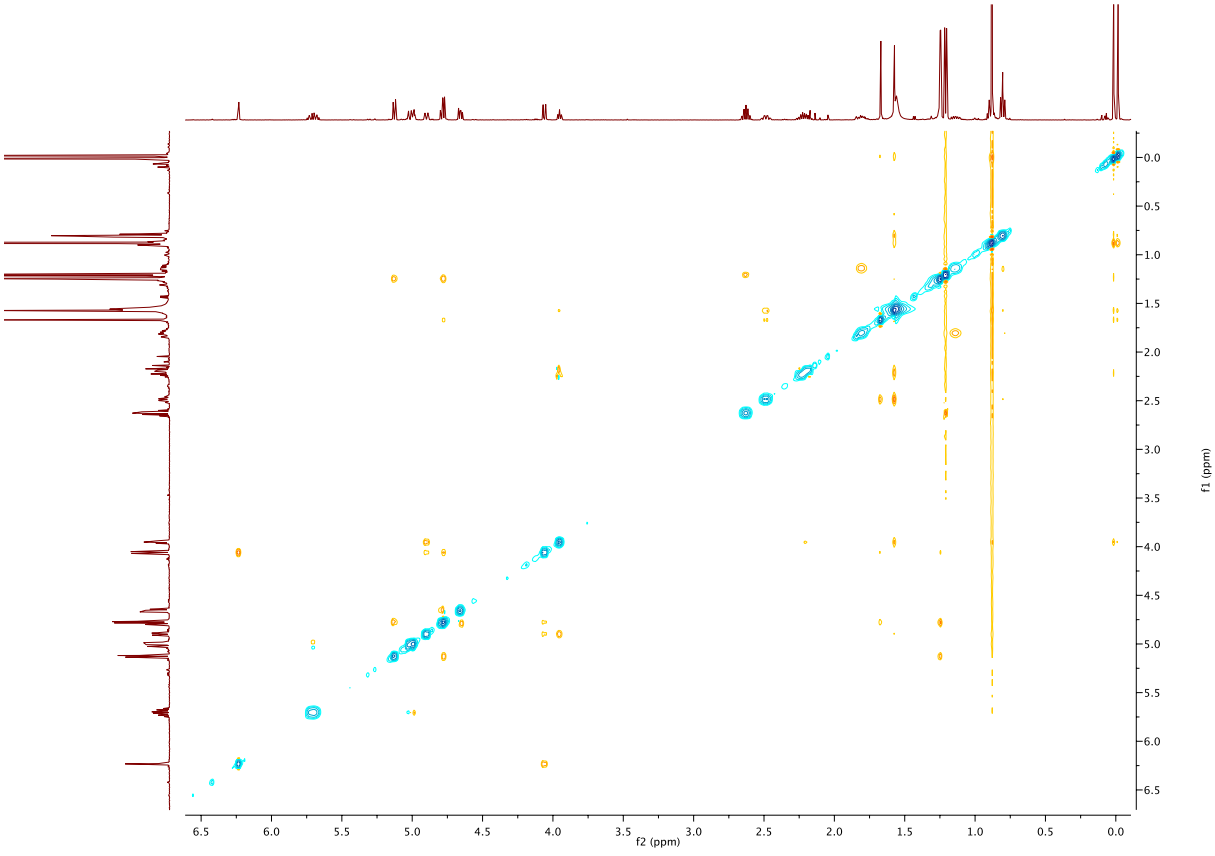
4-(((1*E*,3*R*,4*S*,5*E*,7*S*)-7-((TBS)oxy)-4-ethyl-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (α-1.185)



^{1}H-NMR (400 MHz, $CDCl_3$)

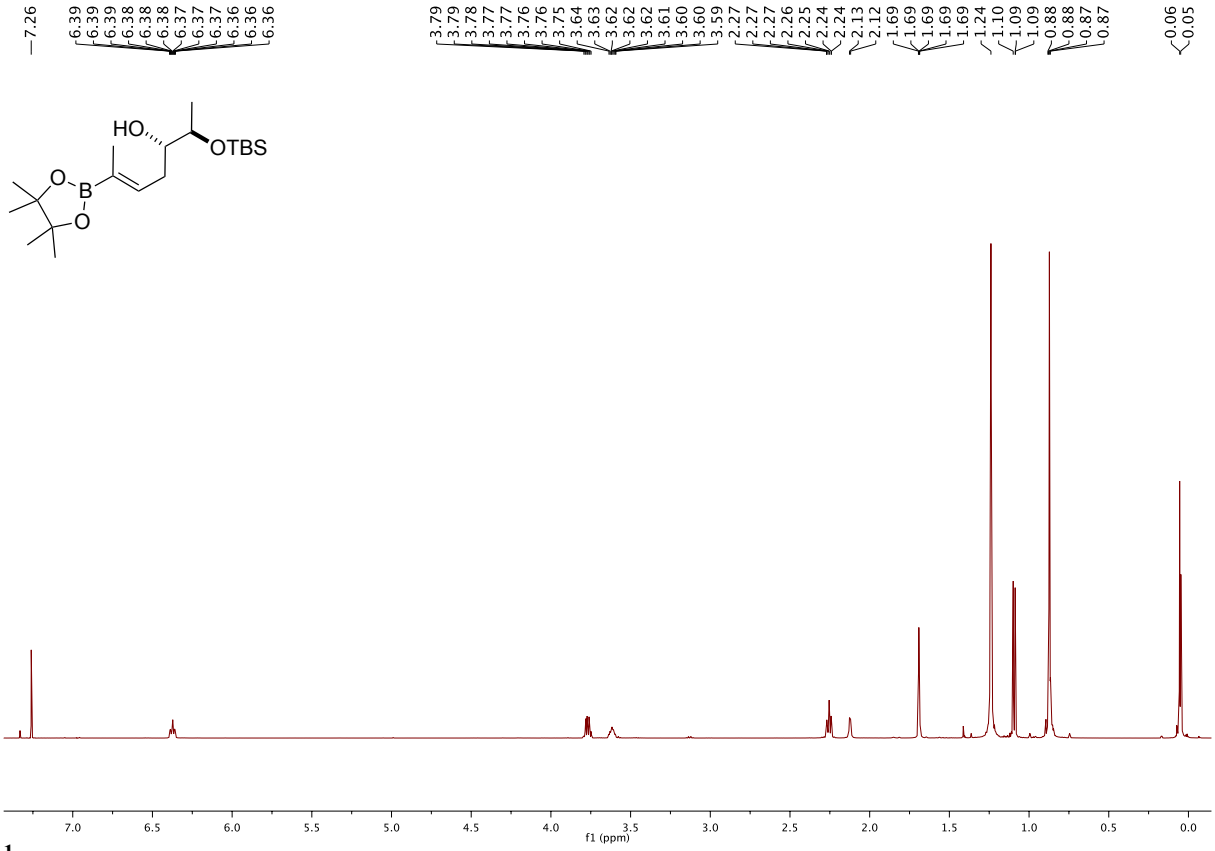


^{13}C-NMR (101 MHz, $CDCl_3$)

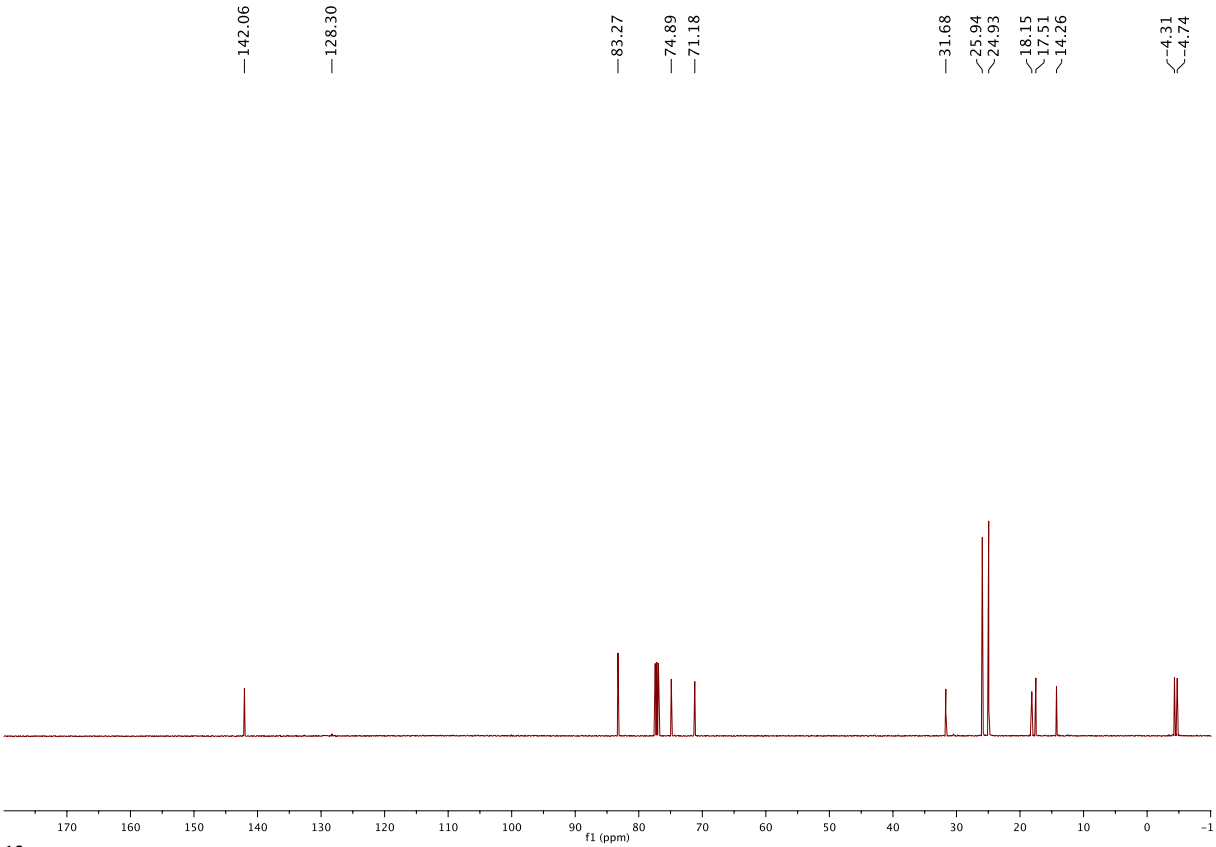


NOESY (500 MHz, $CDCl_3$)

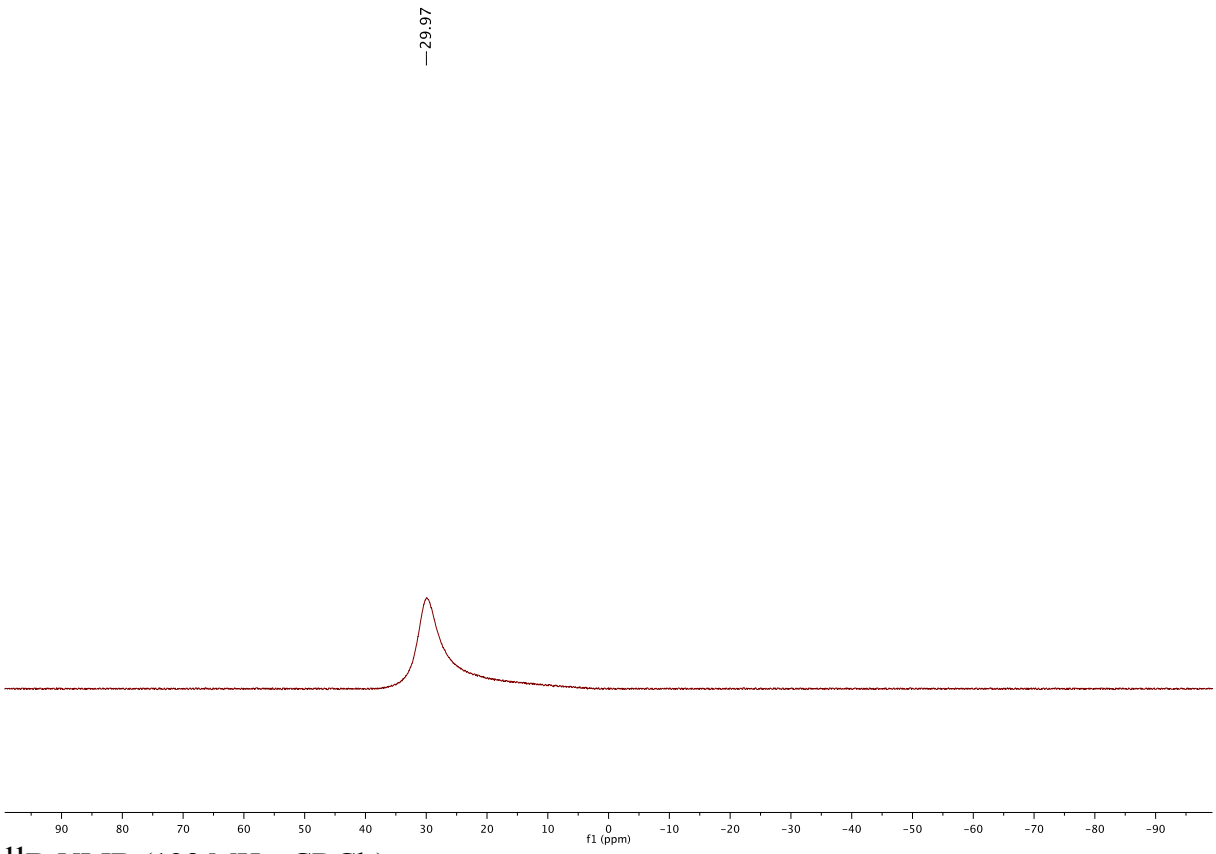
(2*R*,3*S*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-ol (1.41)



^{1}H-NMR (500 MHz, $CDCl_3$)

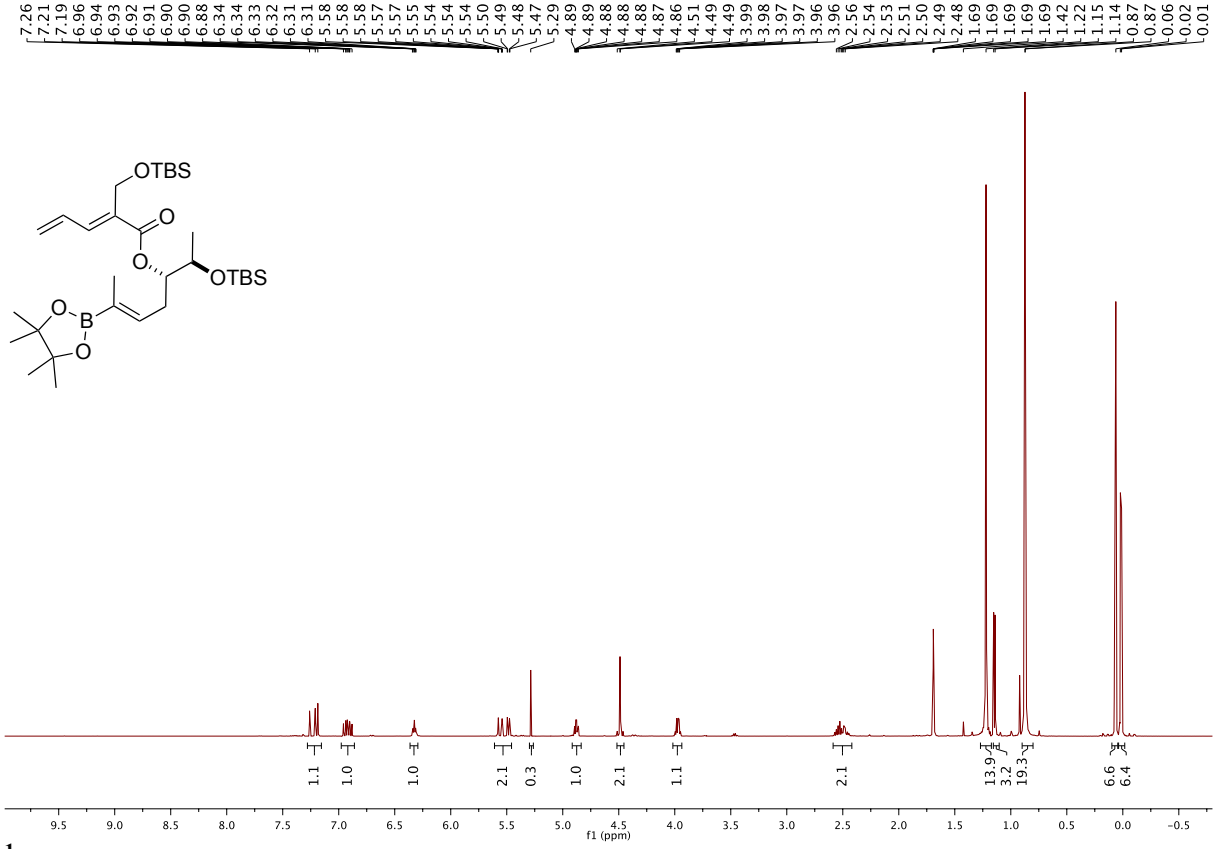


^{13}C-NMR (126 MHz, $CDCl_3$)

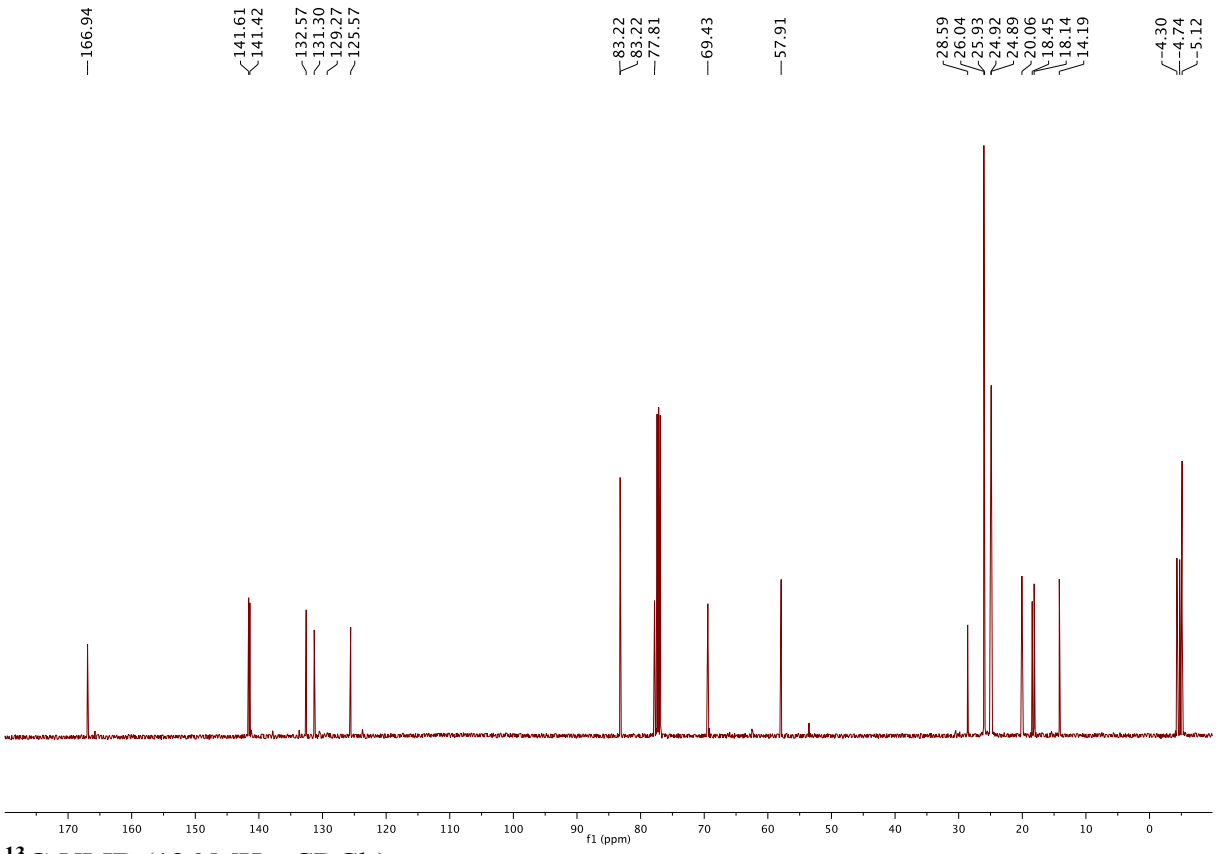


^{11}B-NMR (128 MHz, $CDCl_3$)

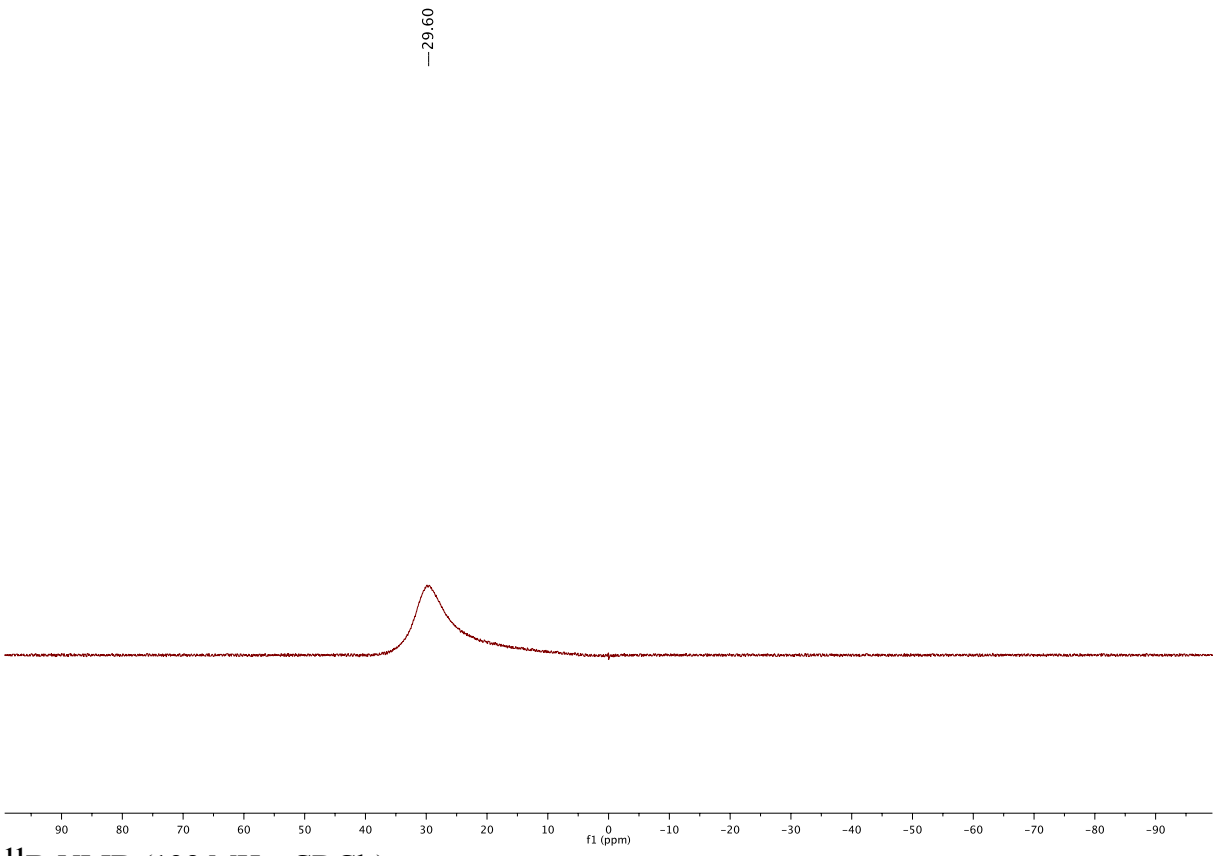
(2*R*,3*S*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-yl (*E*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)penta-2,4-dienoate (1.186)



^{1}H-NMR (500 MHz, $CDCl_3$)

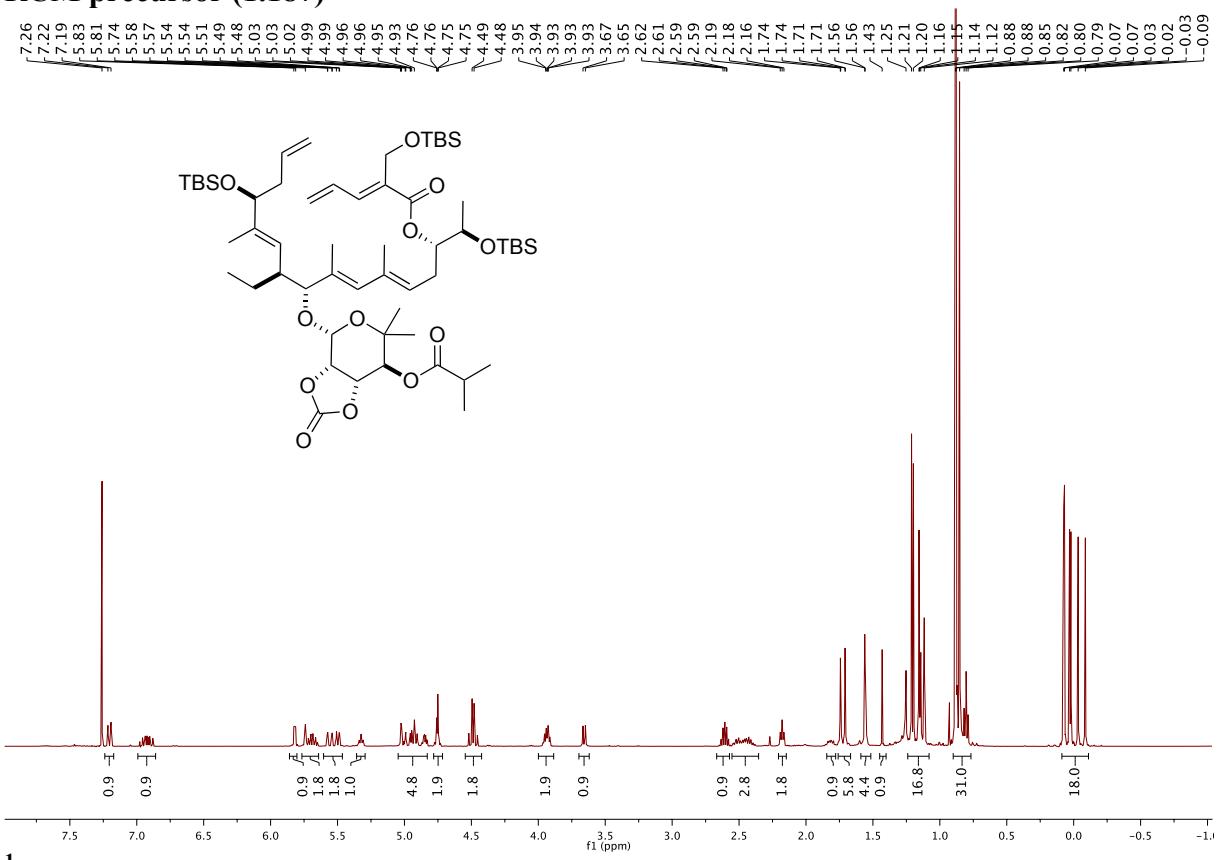


^{13}C-NMR (126 MHz, $CDCl_3$)

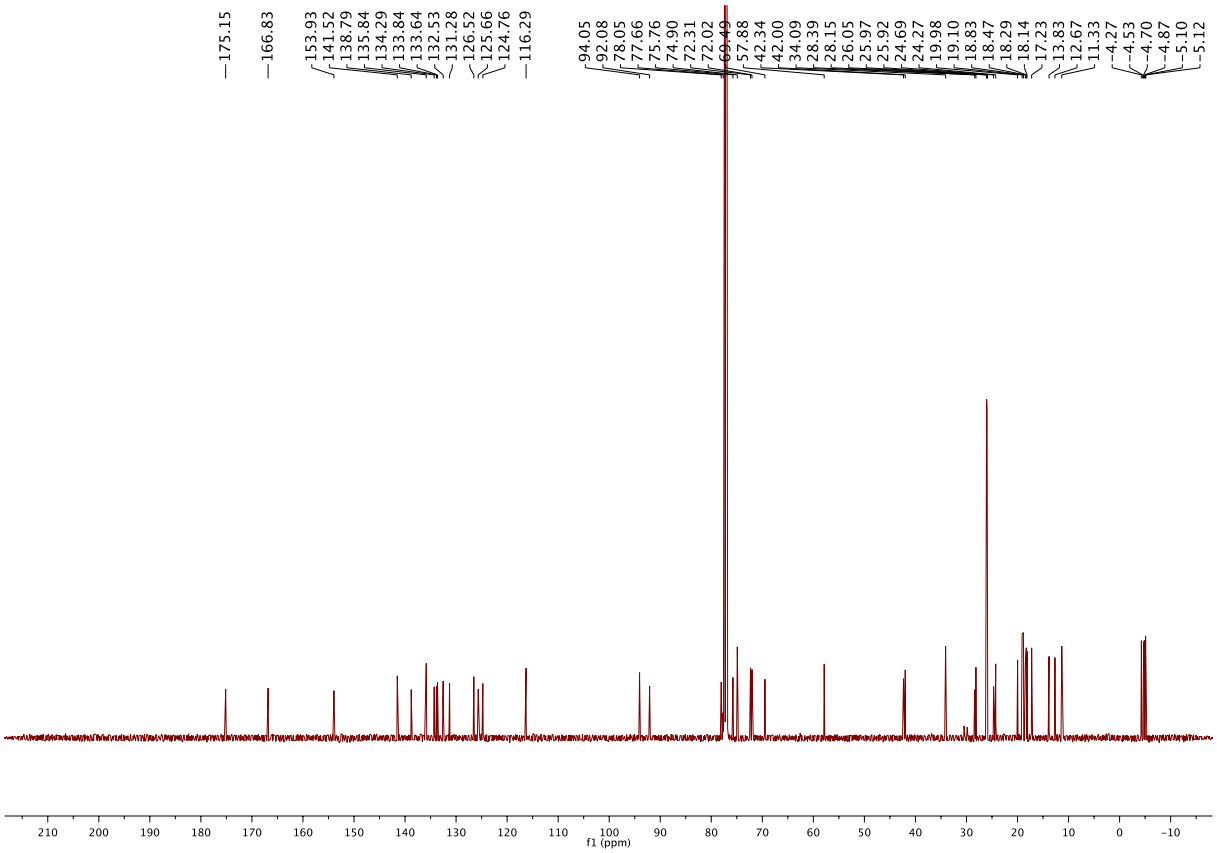


^{11}B-NMR (128 MHz, $CDCl_3$)

RCM precursor (1.187)

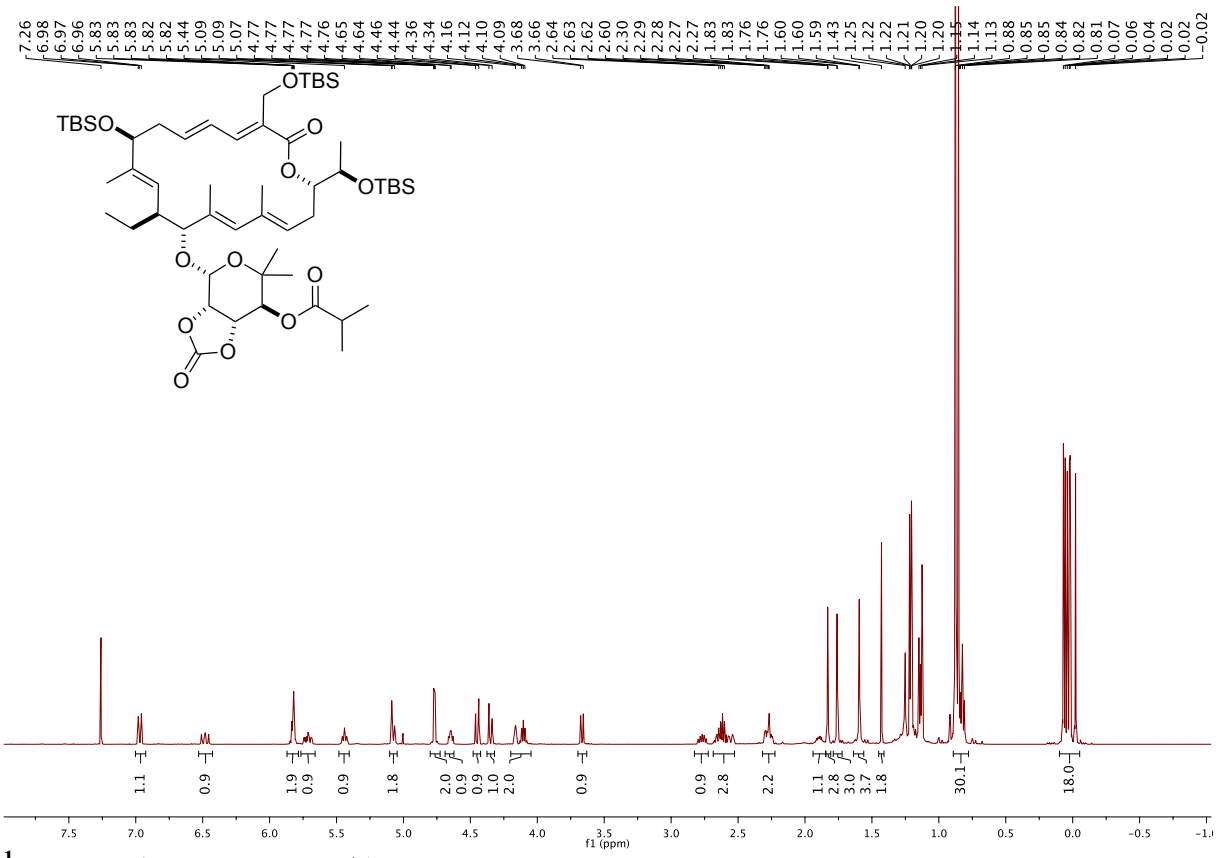


^{1}H-NMR (500 MHz, $CDCl_3$)

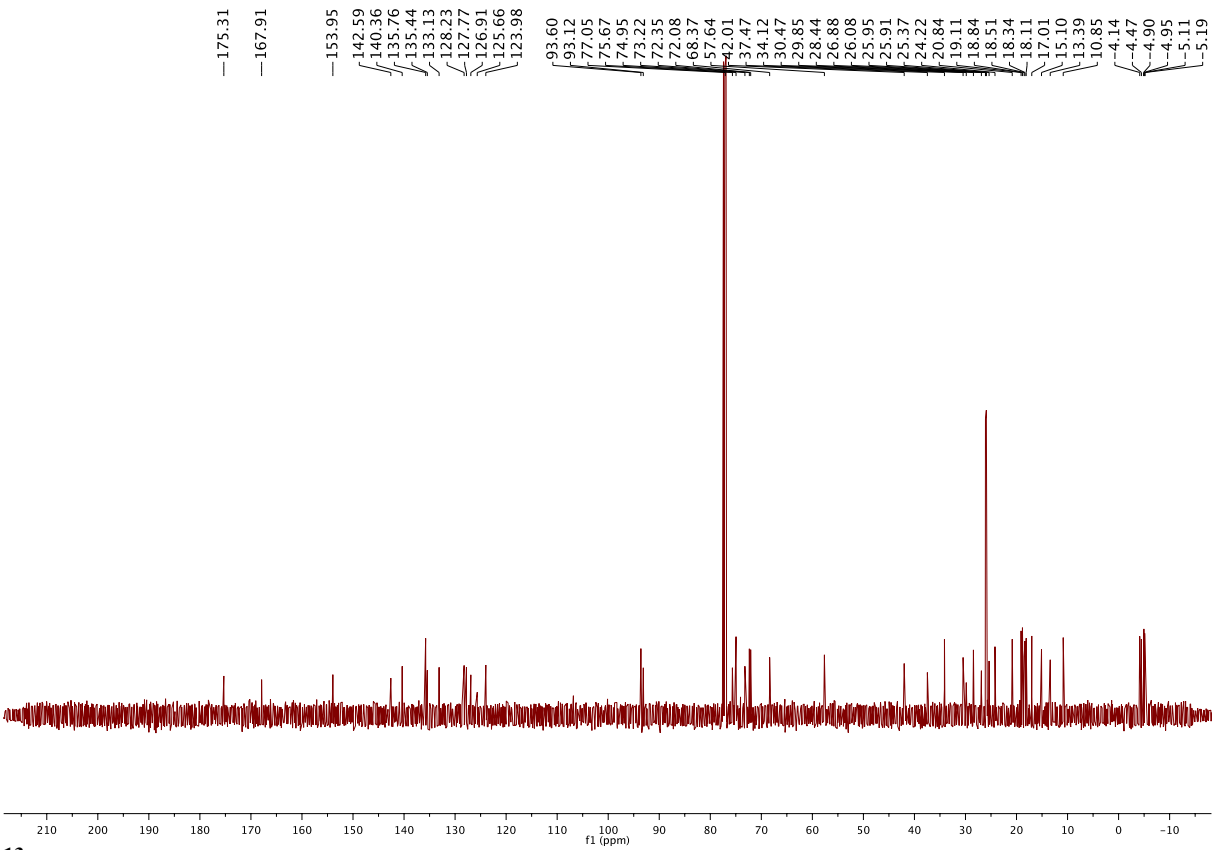


^{13}C-NMR (126 MHz, $CDCl_3$)

E-Macrolide (1.188)

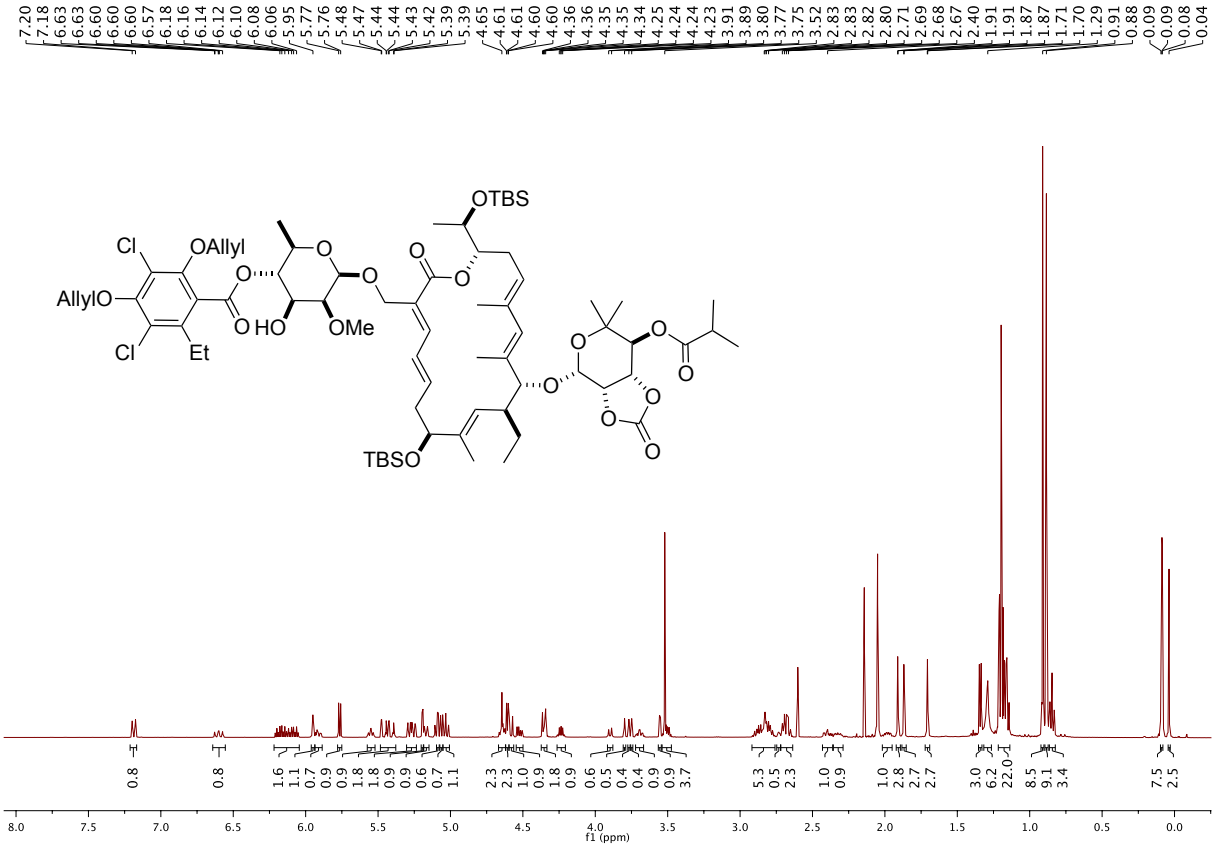


^{1}H-NMR (500 MHz, $CDCl_3$)

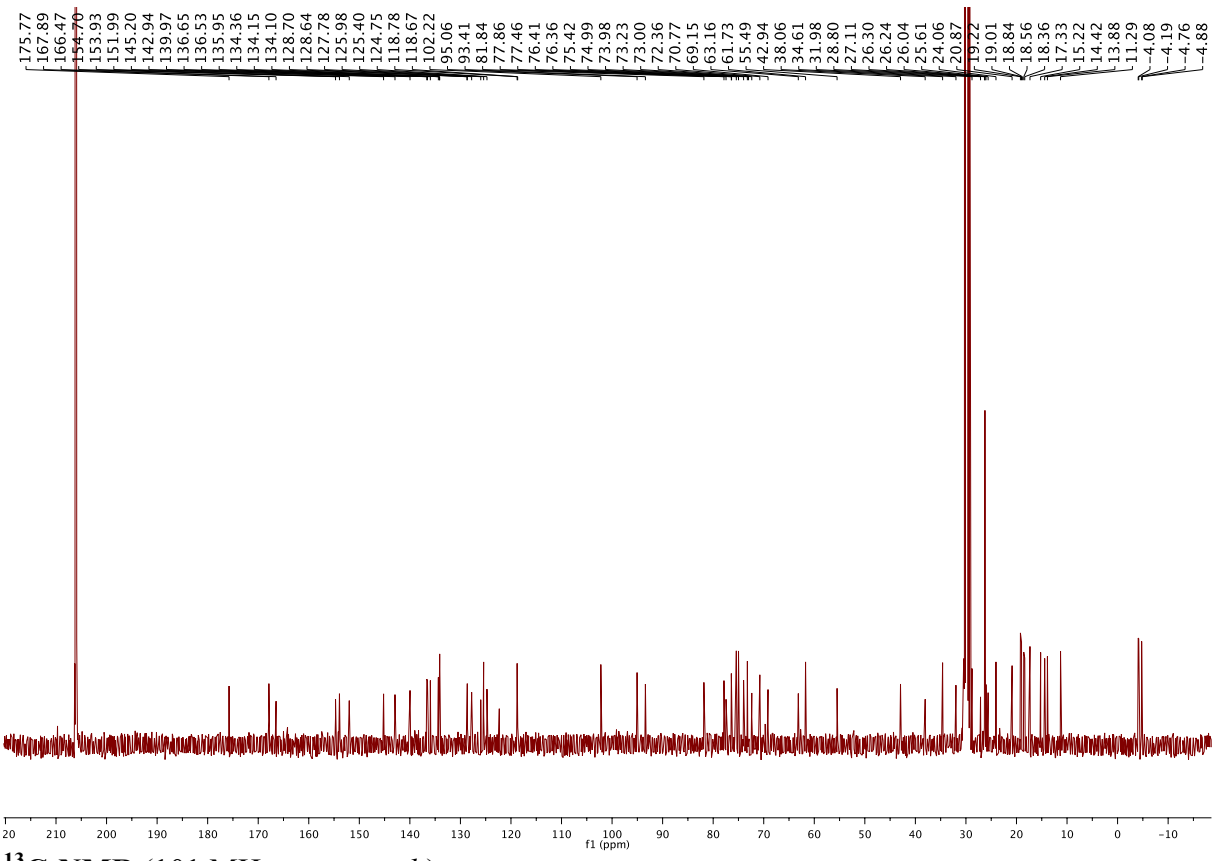


^{13}C-NMR (126 MHz, $CDCl_3$)

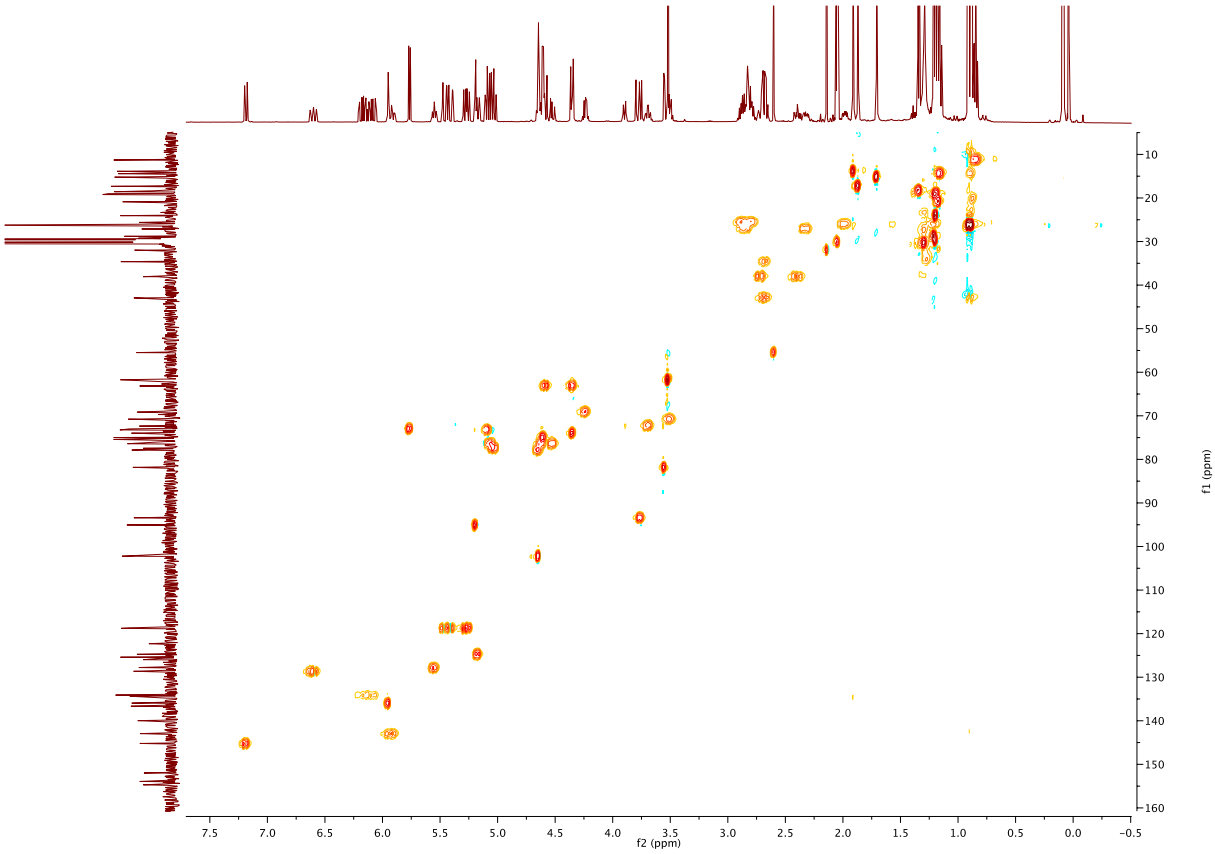
Fully Protected Fidaxomicin (1.189).



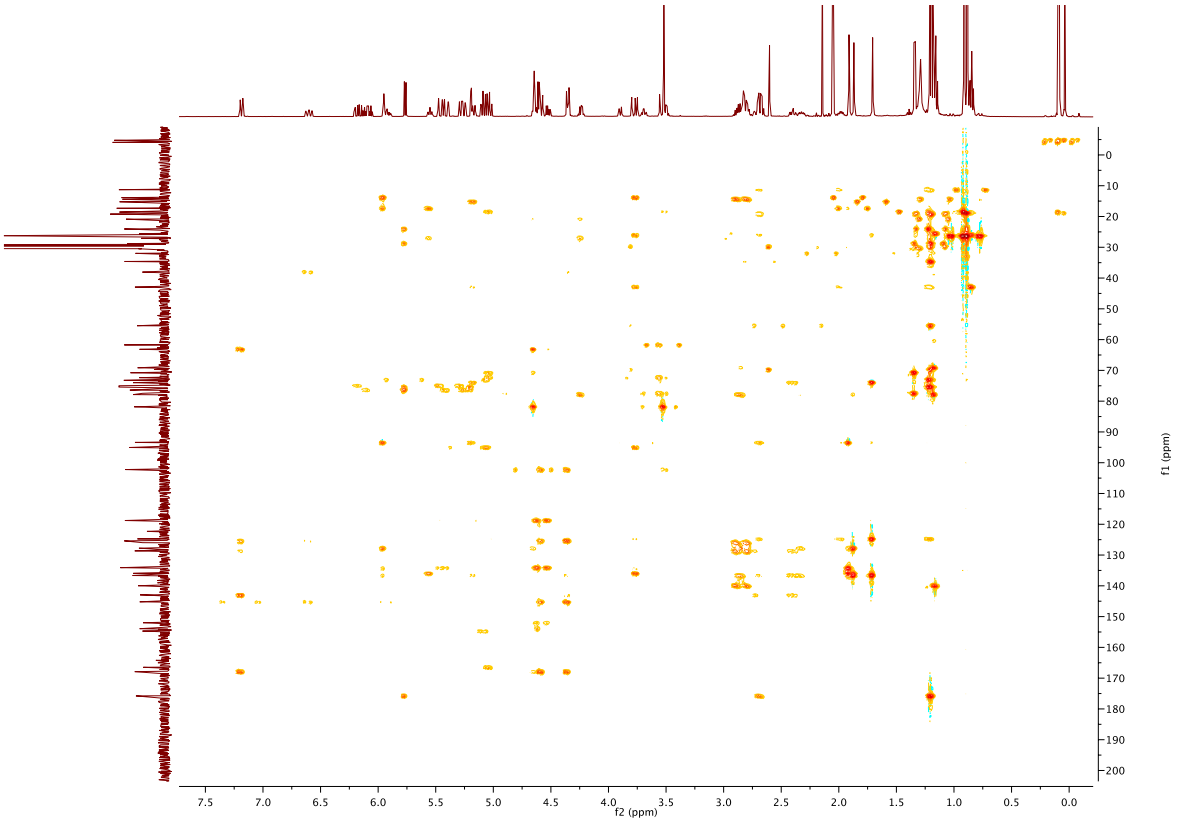
^{1}H-NMR (400 MHz, acetone-d_6)



^{13}C-NMR (101 MHz, acetone-d_6)

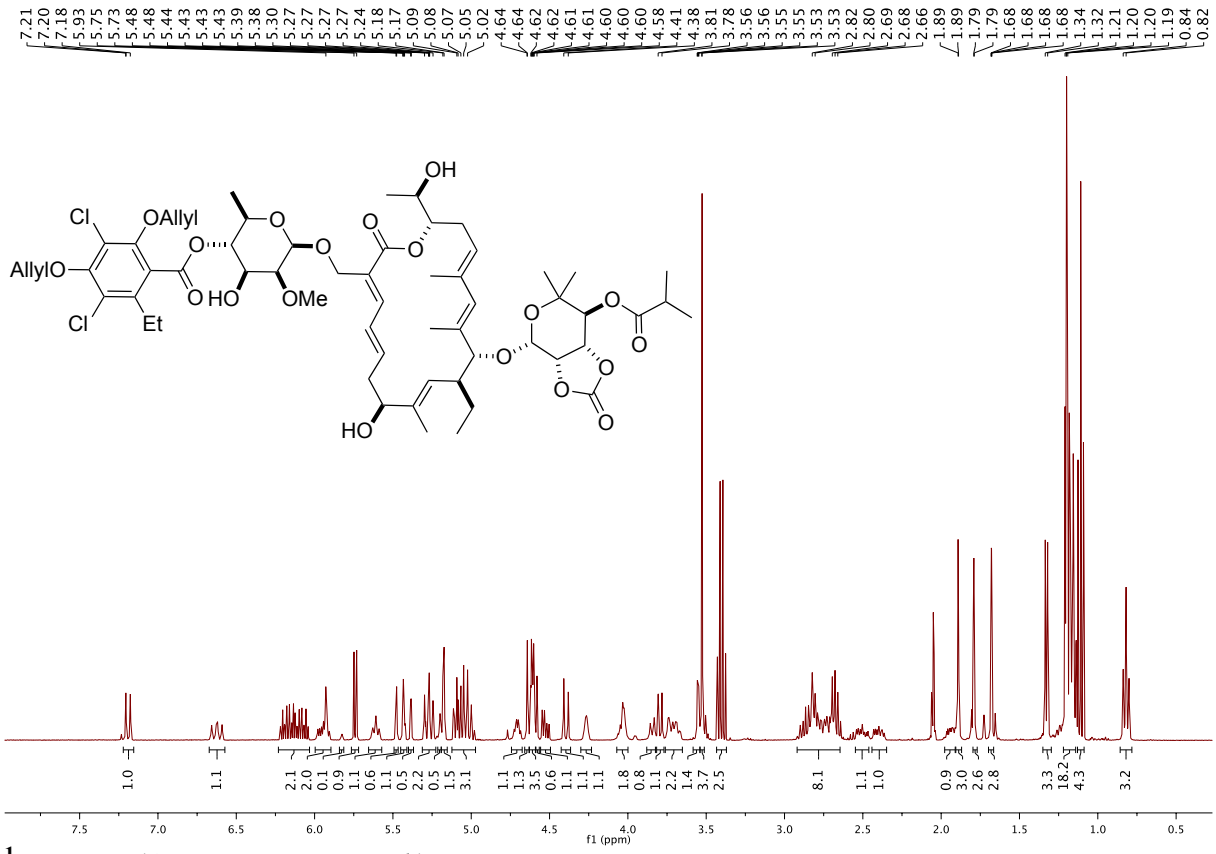


HSQC (500 MHz, acetone-d_6)

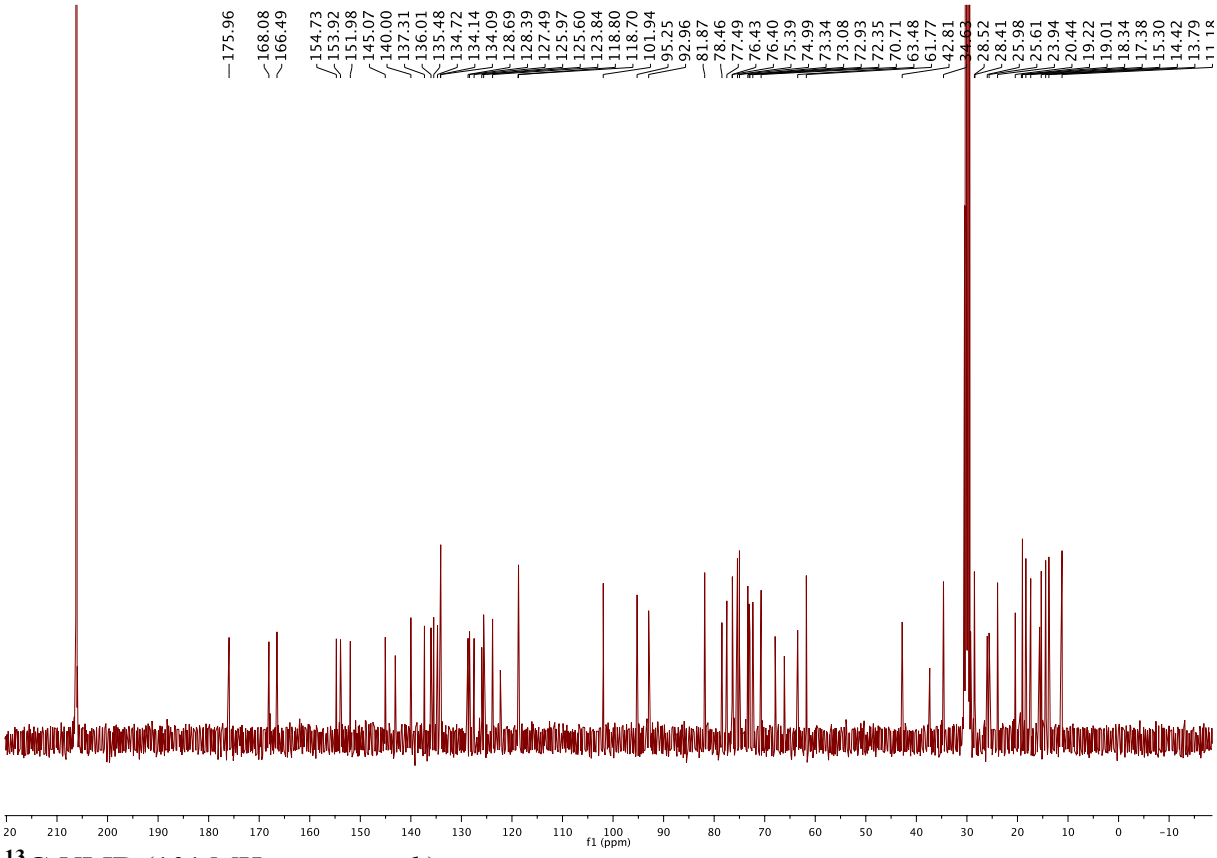


HMBC (500 MHz, acetone-d_6)

Allyl, Carbonate-protected Fidaxomicin (1.190).

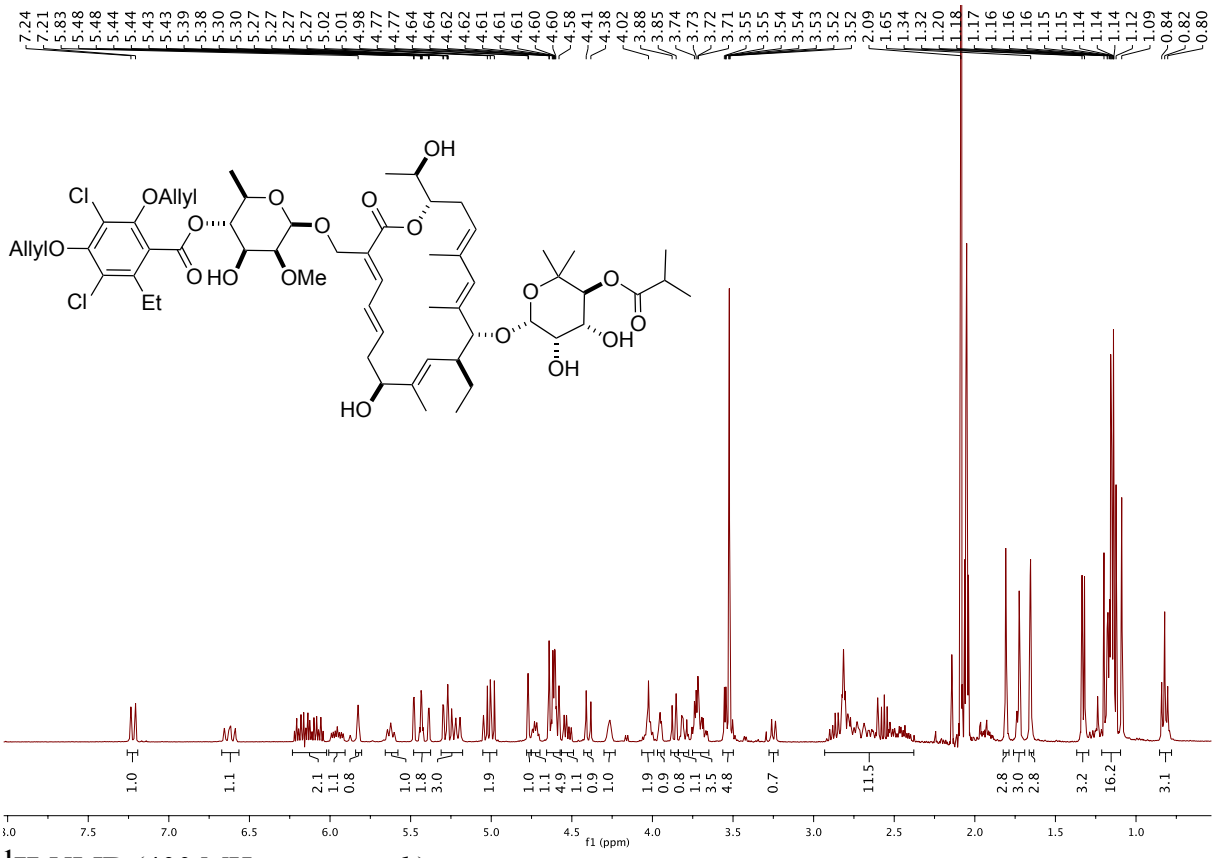


^{1}H-NMR (400 MHz, acetone-d_6)



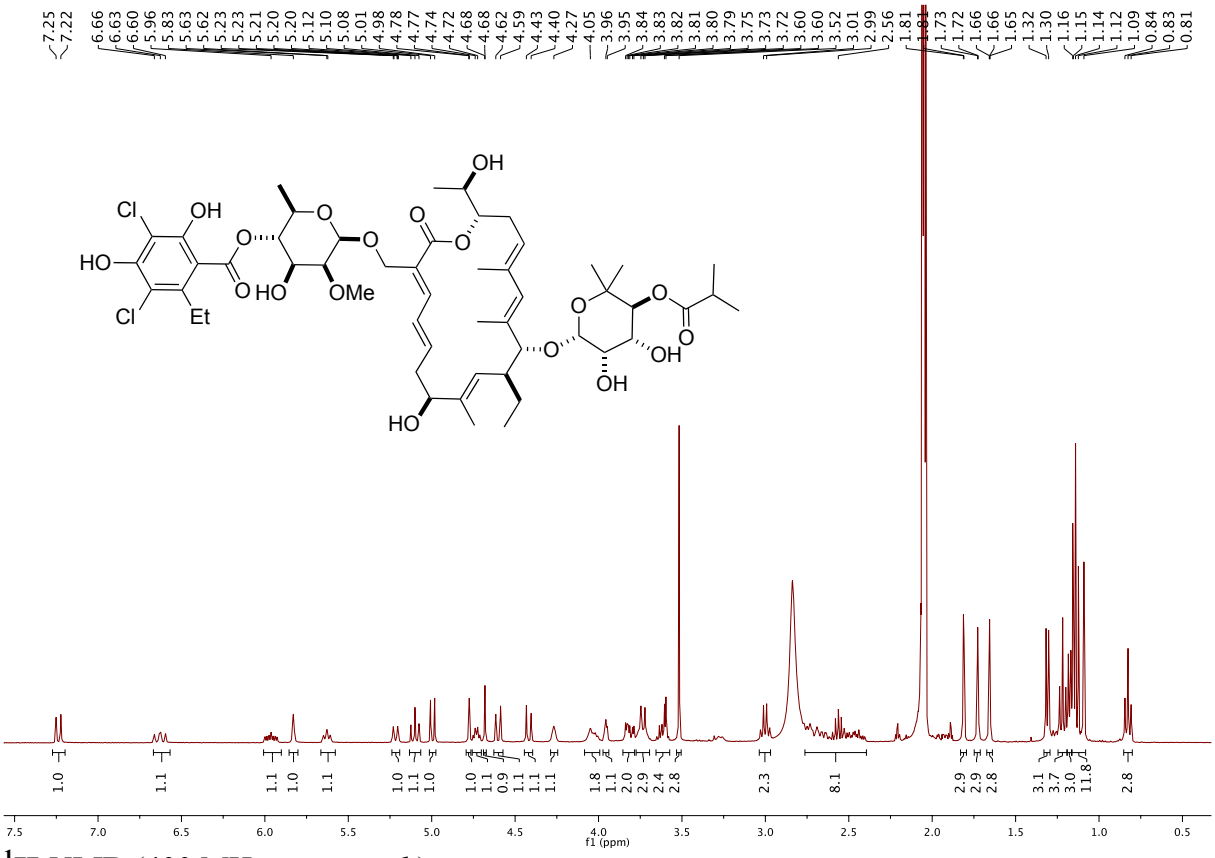
^{13}C-NMR (101 MHz, acetone-d_6)

Allyl-protected Fidaxomicin (1.191)

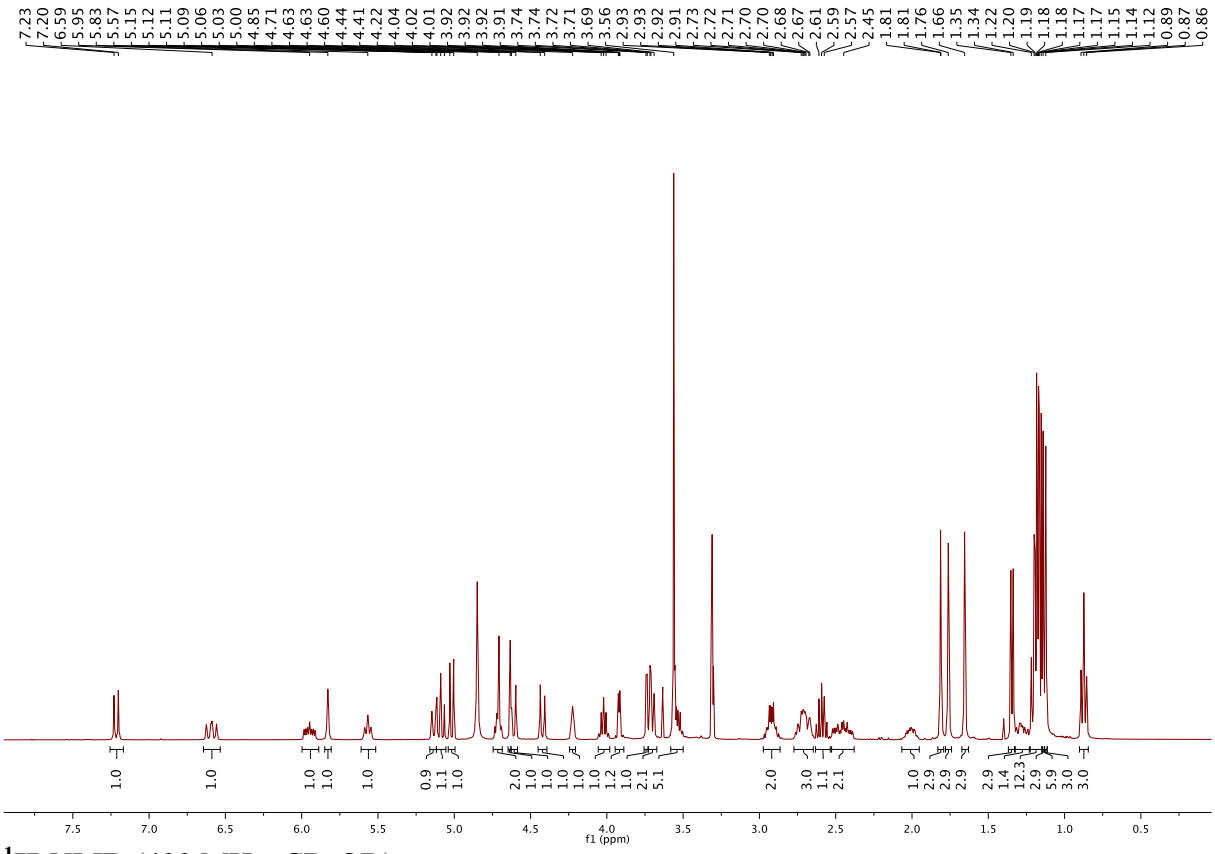


^{1}H-NMR (400 MHz, acetone-d_6)

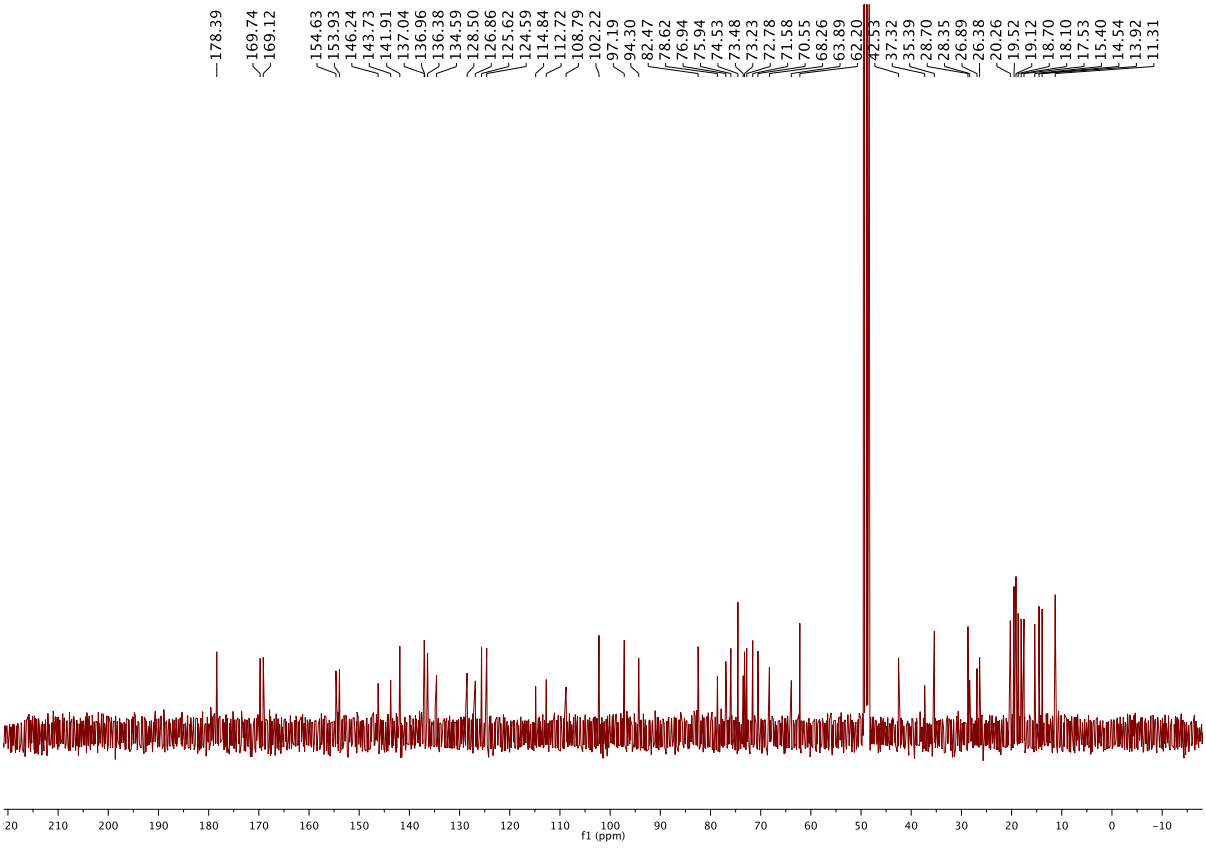
Fidaxomicin (Tiacumicin B, Lipiarmycin A3)



^{1}H-NMR (400 MHz, acetone-d_6)



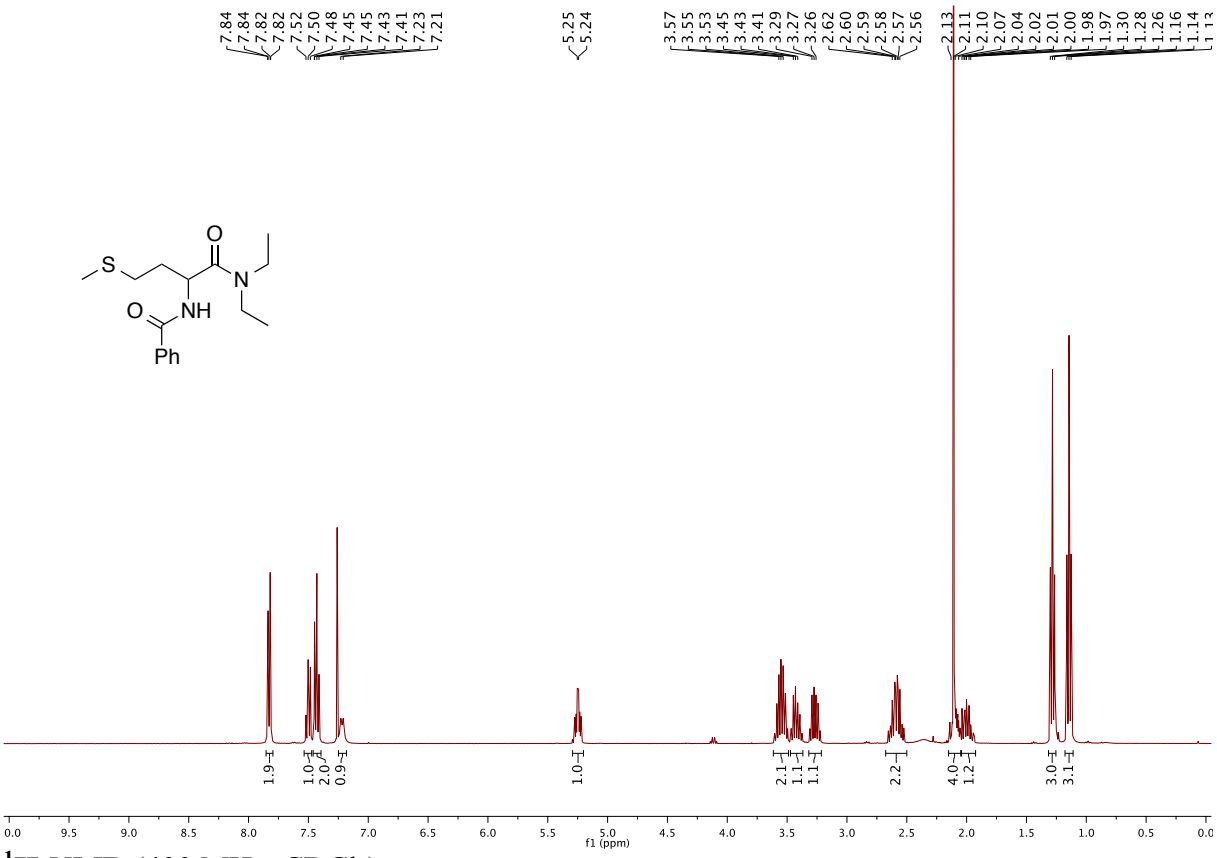
^{1}H-NMR (400 MHz, CD_3OD)



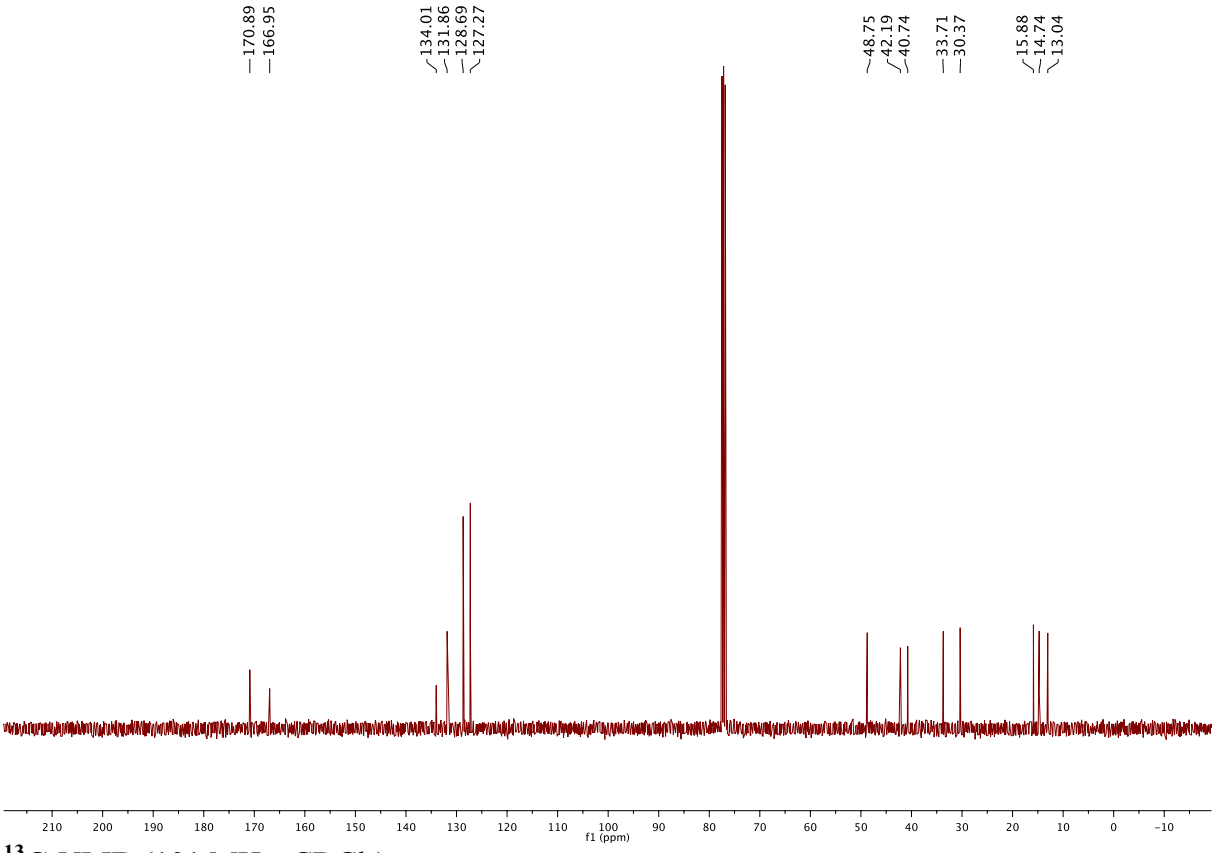
^{13}C-NMR (101 MHz, CD_3OD);

5.3.2 Methionine-Derived Iminium Lactones

***N*-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.23)**

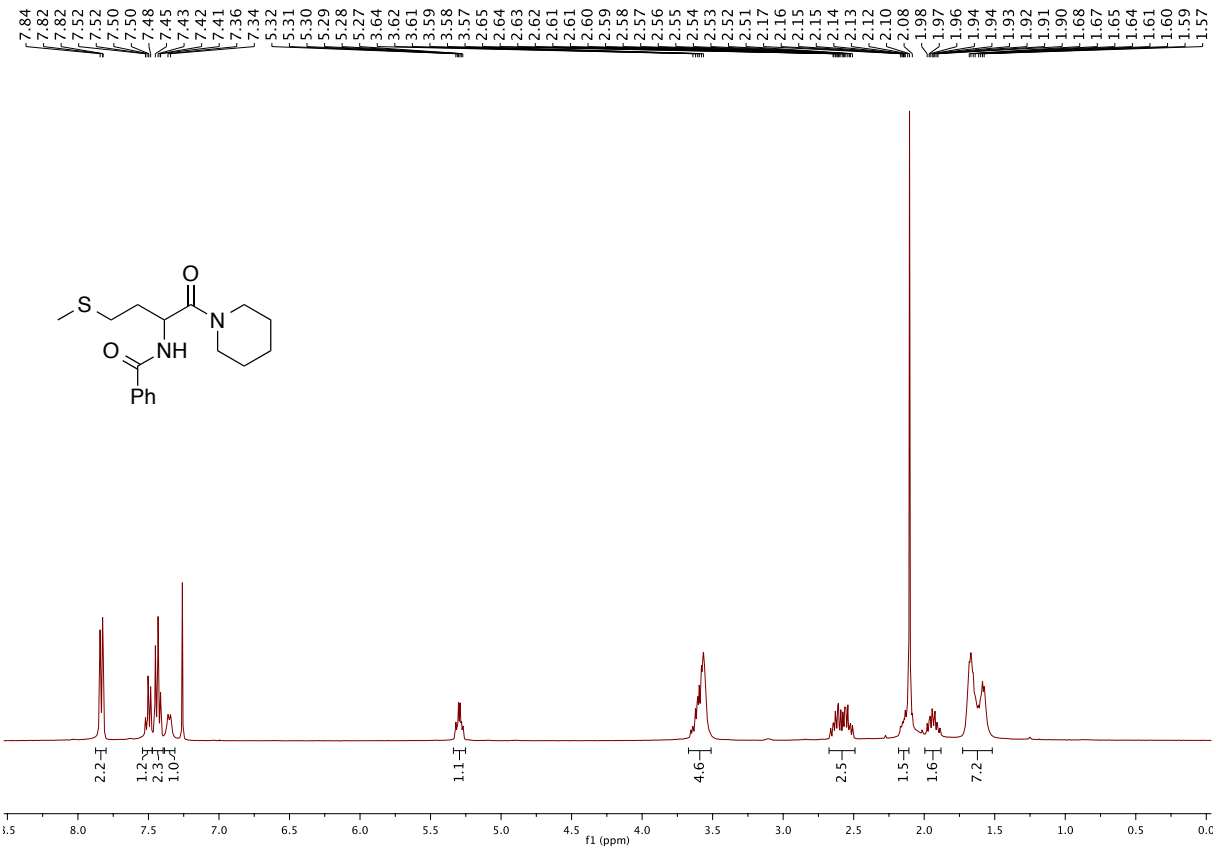


^{1}H-NMR (400 MHz, $CDCl_3$)

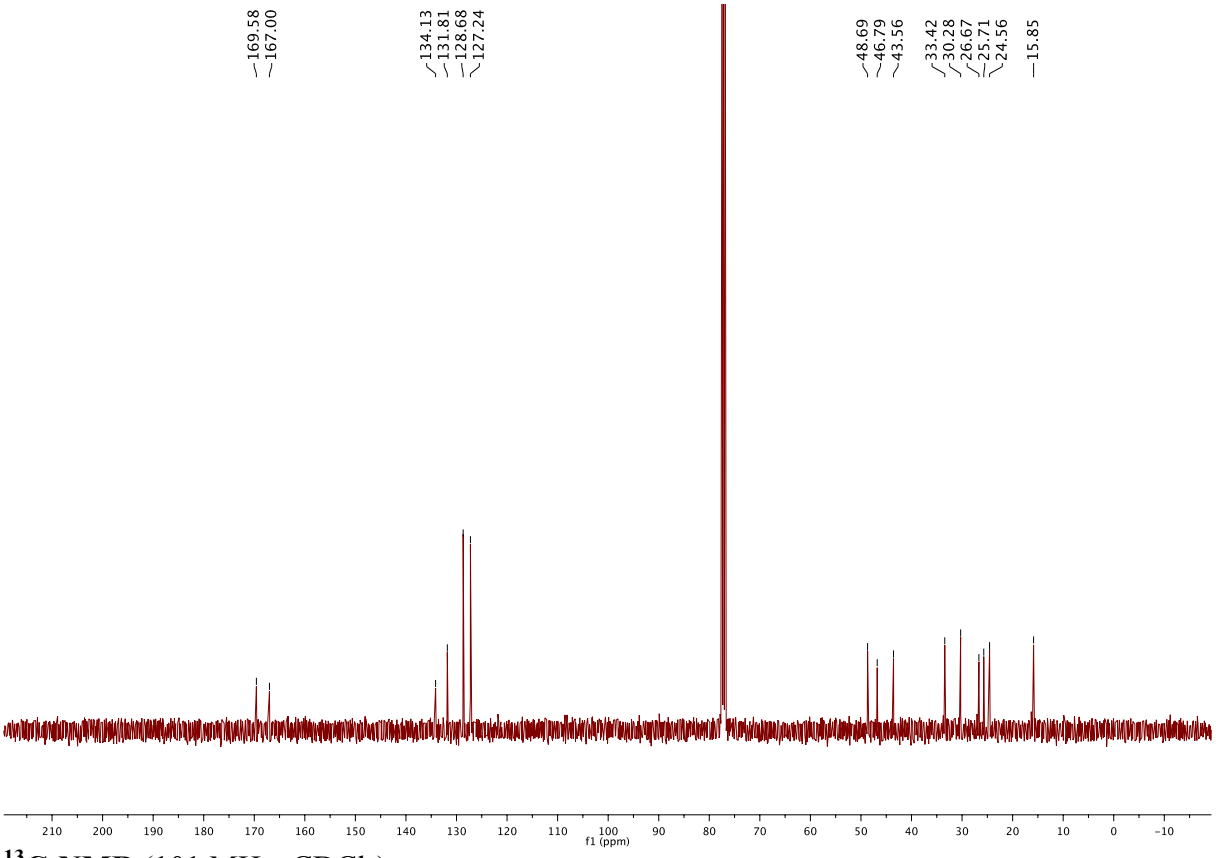


^{13}C-NMR (101 MHz, $CDCl_3$)

N-(4-(methylthio)-1-oxo-1-(piperidin-1-yl)butan-2-yl)benzamide (2.24)

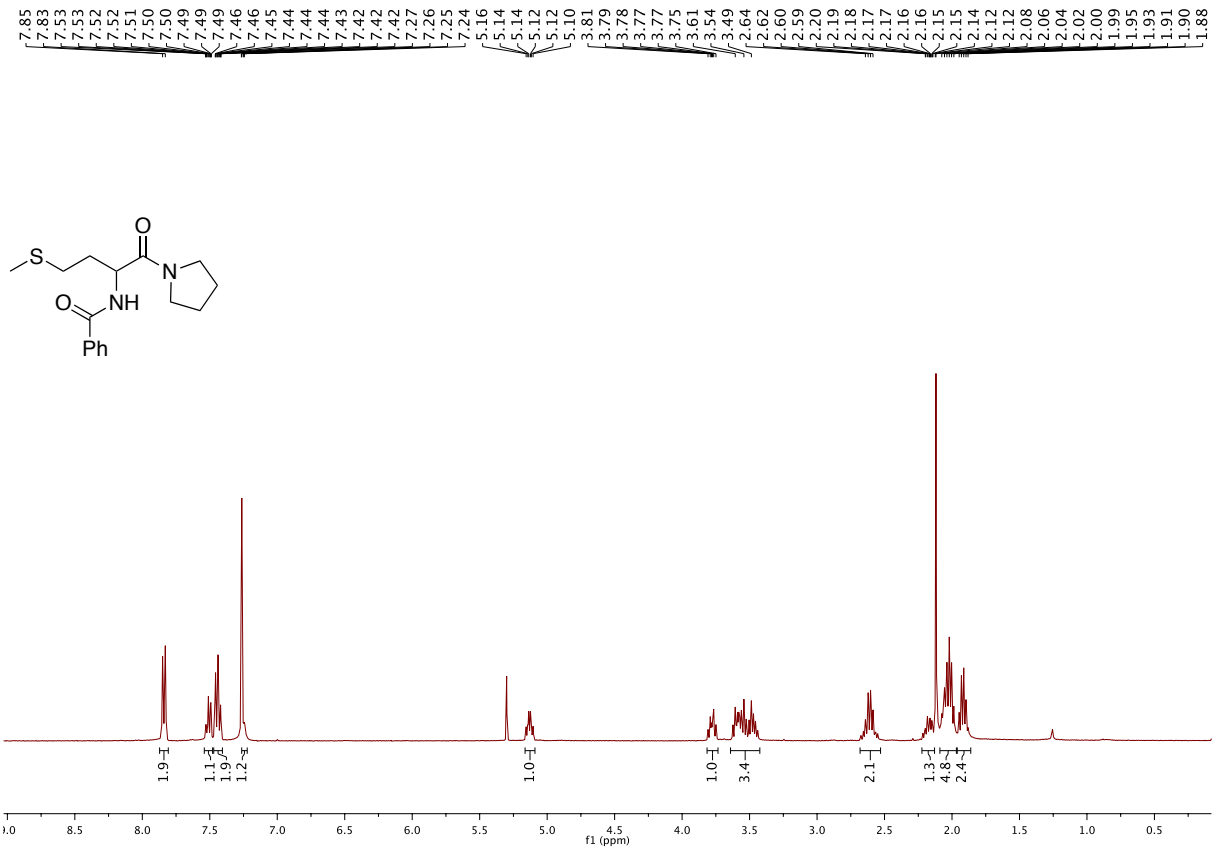


^{1}H-NMR (400 MHz, $CDCl_3$)



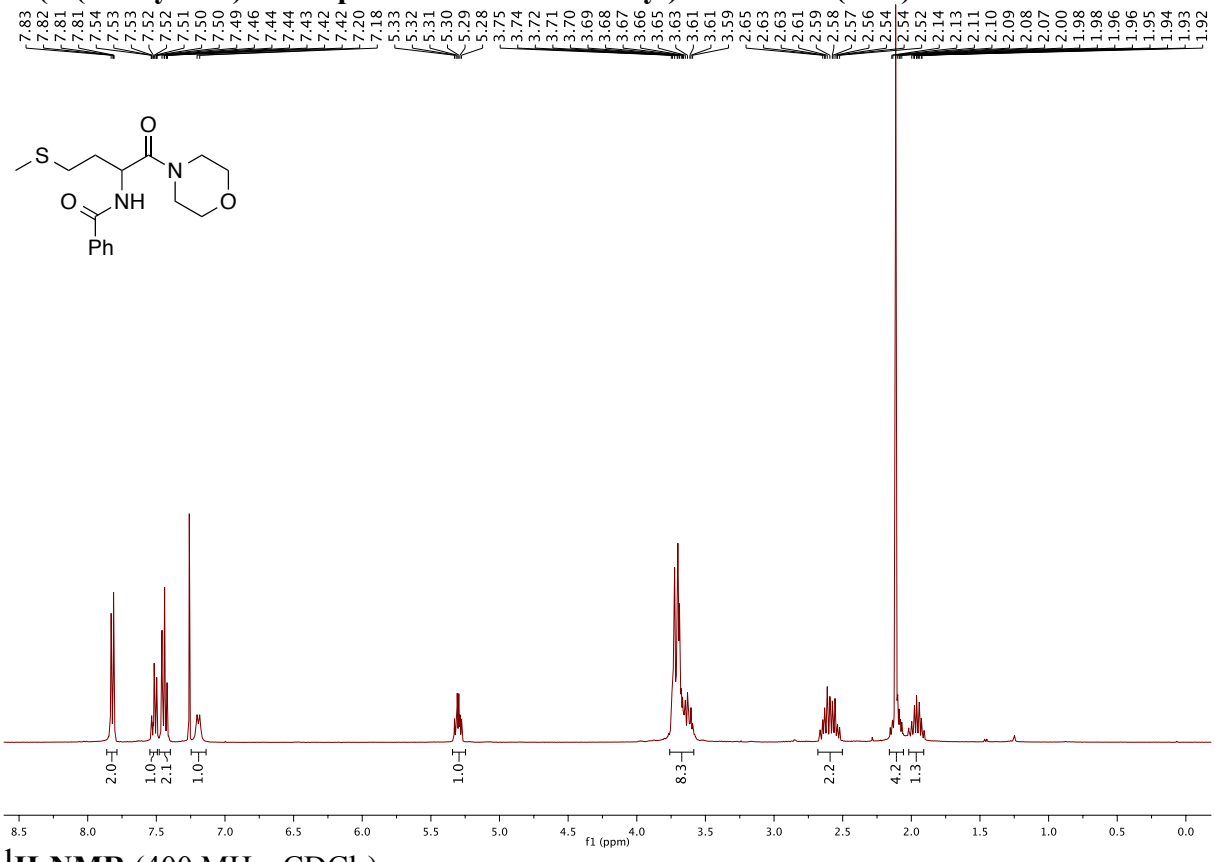
^{13}C-NMR (101 MHz, $CDCl_3$)

_N_-(4-(methylthio)-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)benzamide (2.25)

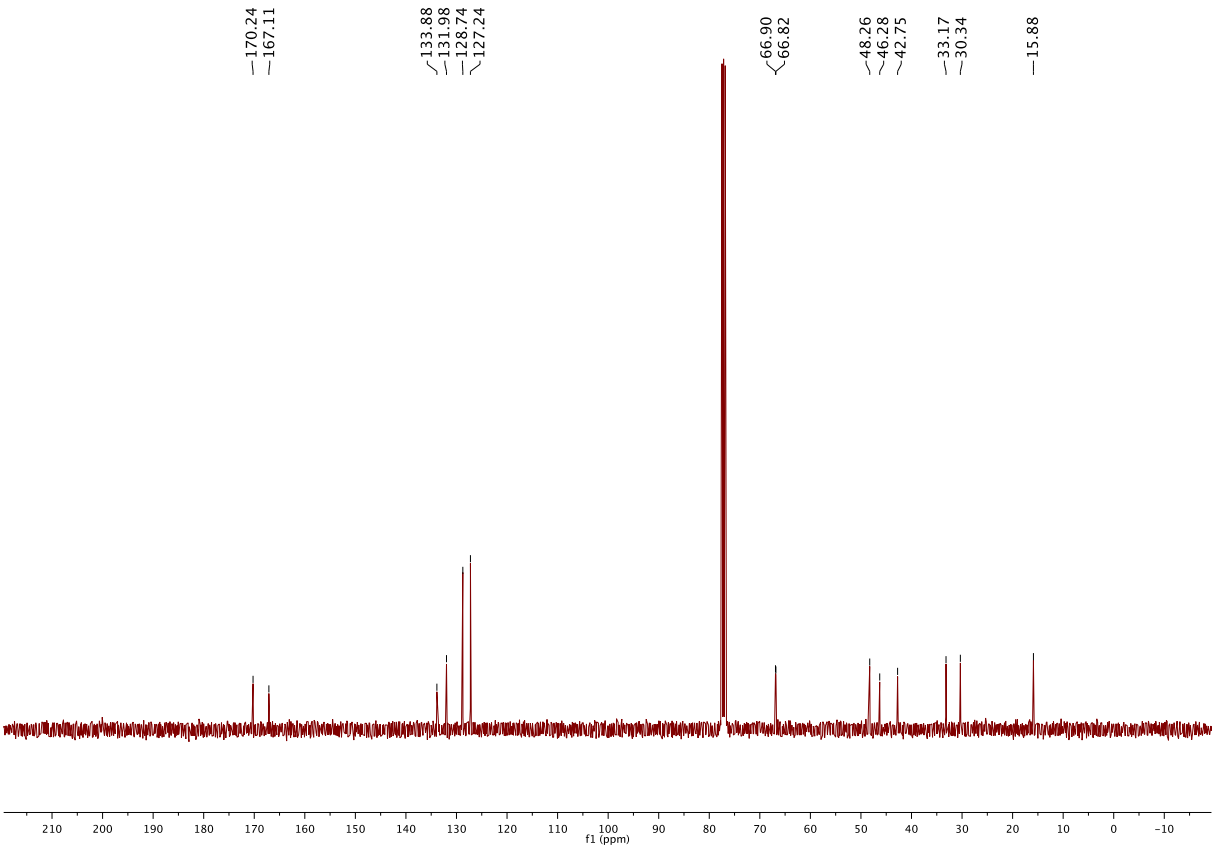


^{1}H-NMR (400 MHz, $CDCl_3$)

_N_-(4-(methylthio)-1-morpholino-1-oxobutan-2-yl)benzamide (2.26)

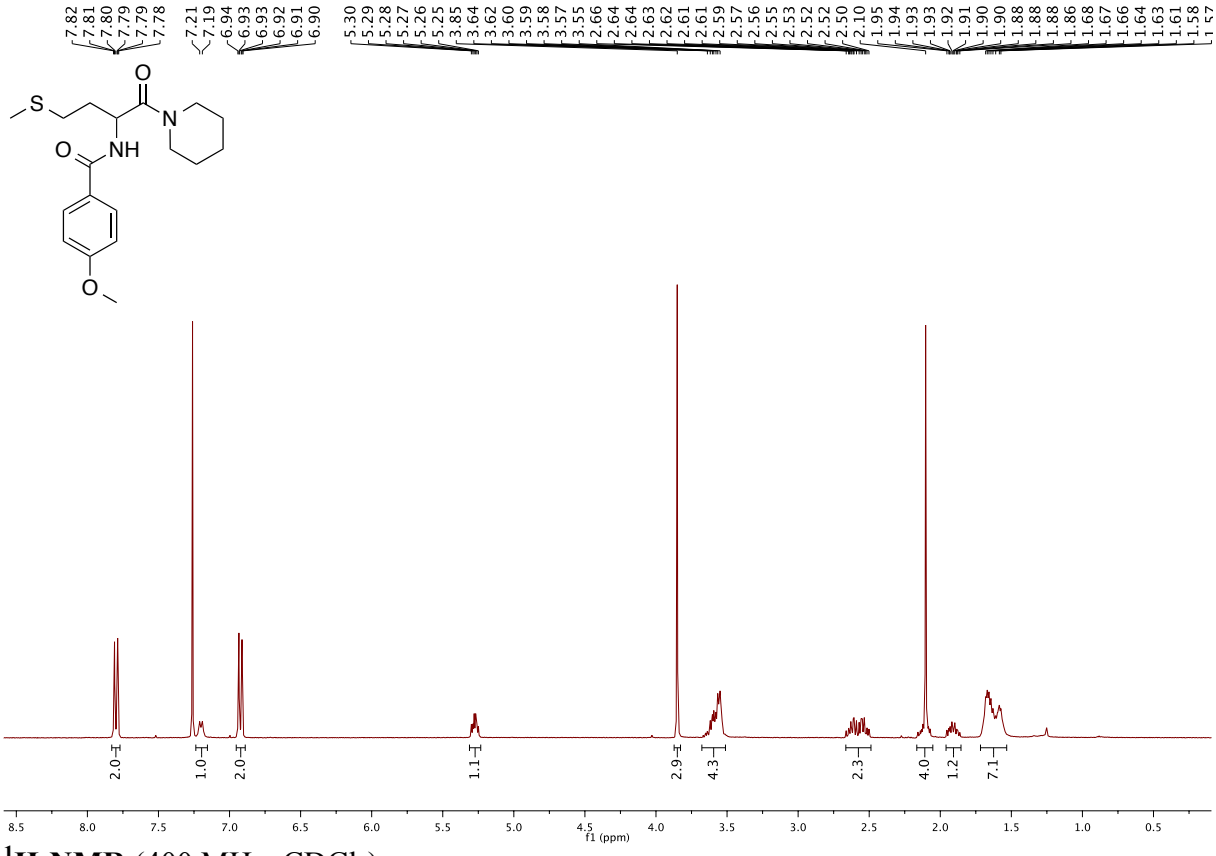


^{1}H-NMR (400 MHz, $CDCl_3$)

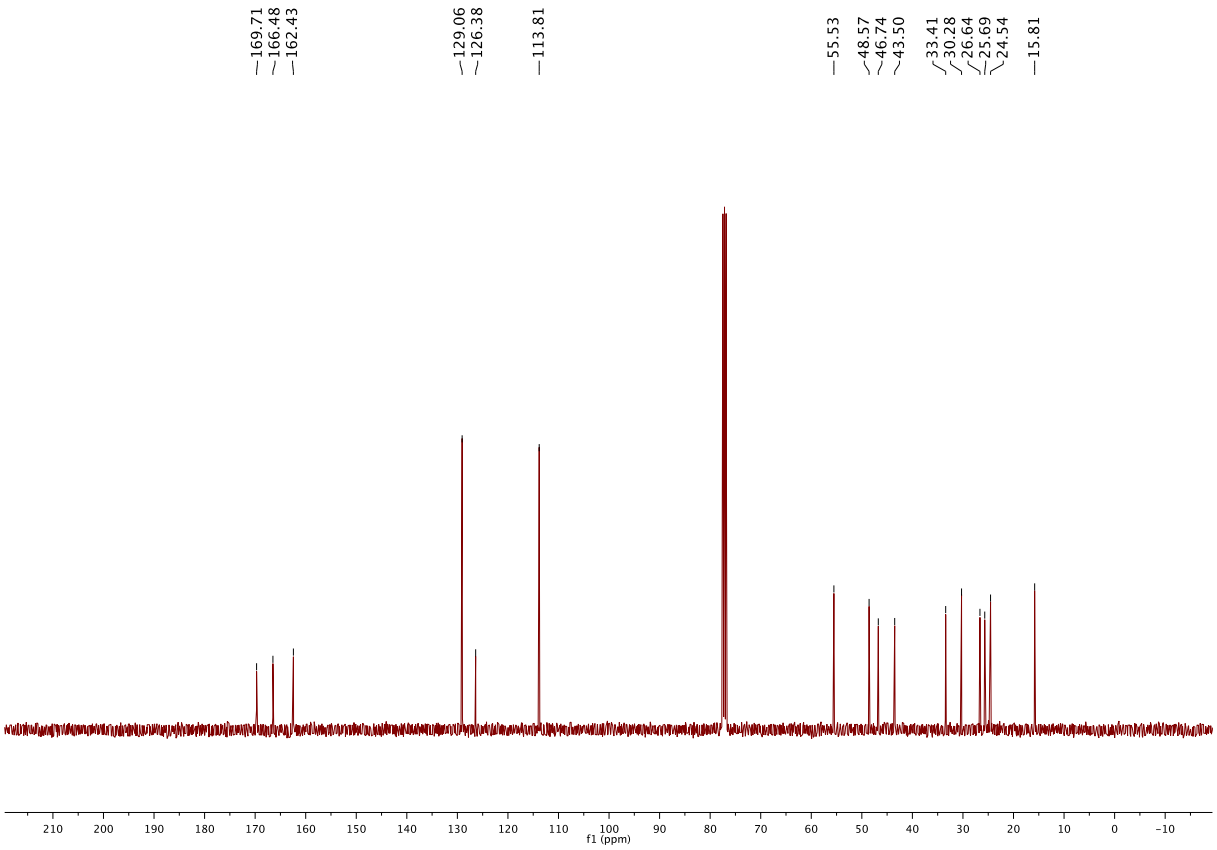


^{13}C-NMR (101 MHz, $CDCl_3$)

4-methoxy-*N*-(4-(methylthio)-1-oxo-1-(piperidin-1-yl)butan-2-yl)benzamide (2.27)

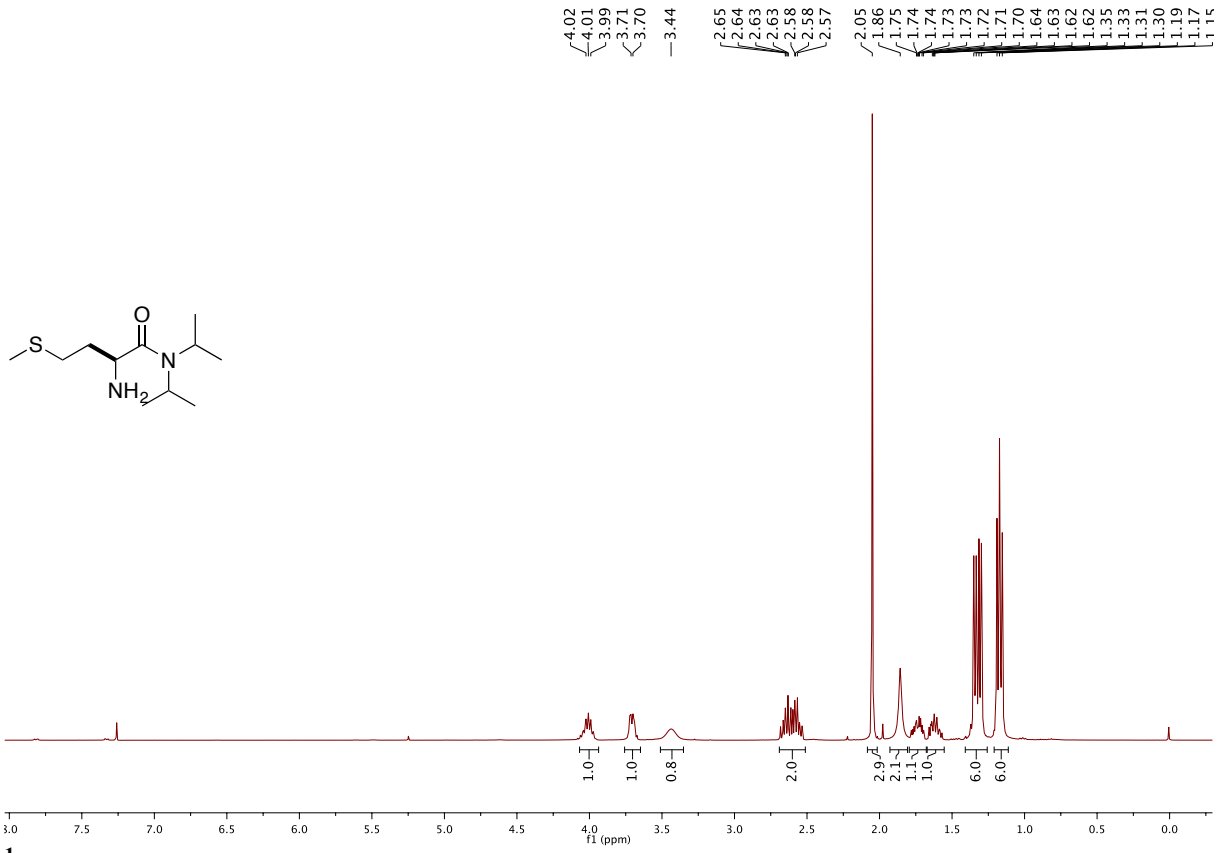


^{1}H-NMR (400 MHz, $CDCl_3$)



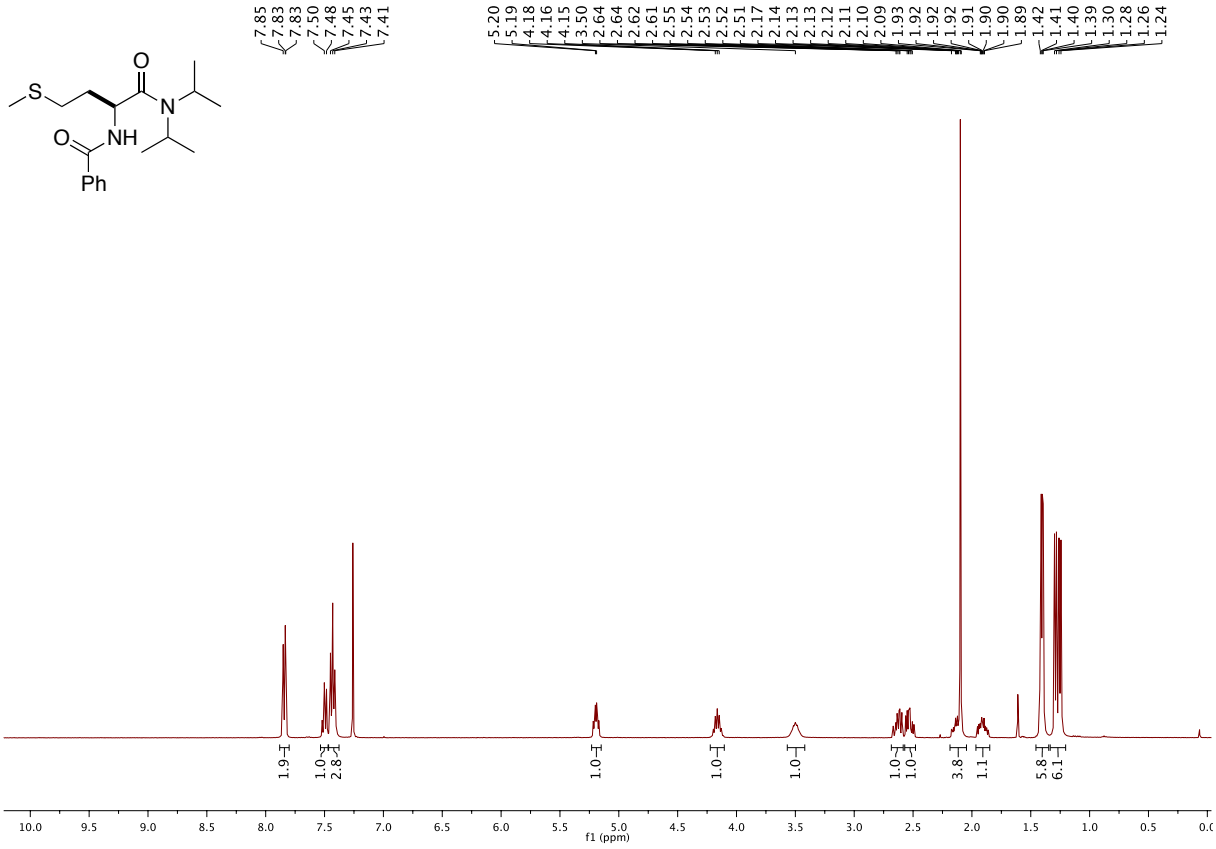
^{13}C-NMR (101 MHz, $CDCl_3$)

(*S*)-2-amino-*N*,*N*-diisopropyl-4-(methylthio)butanamide (2.29)

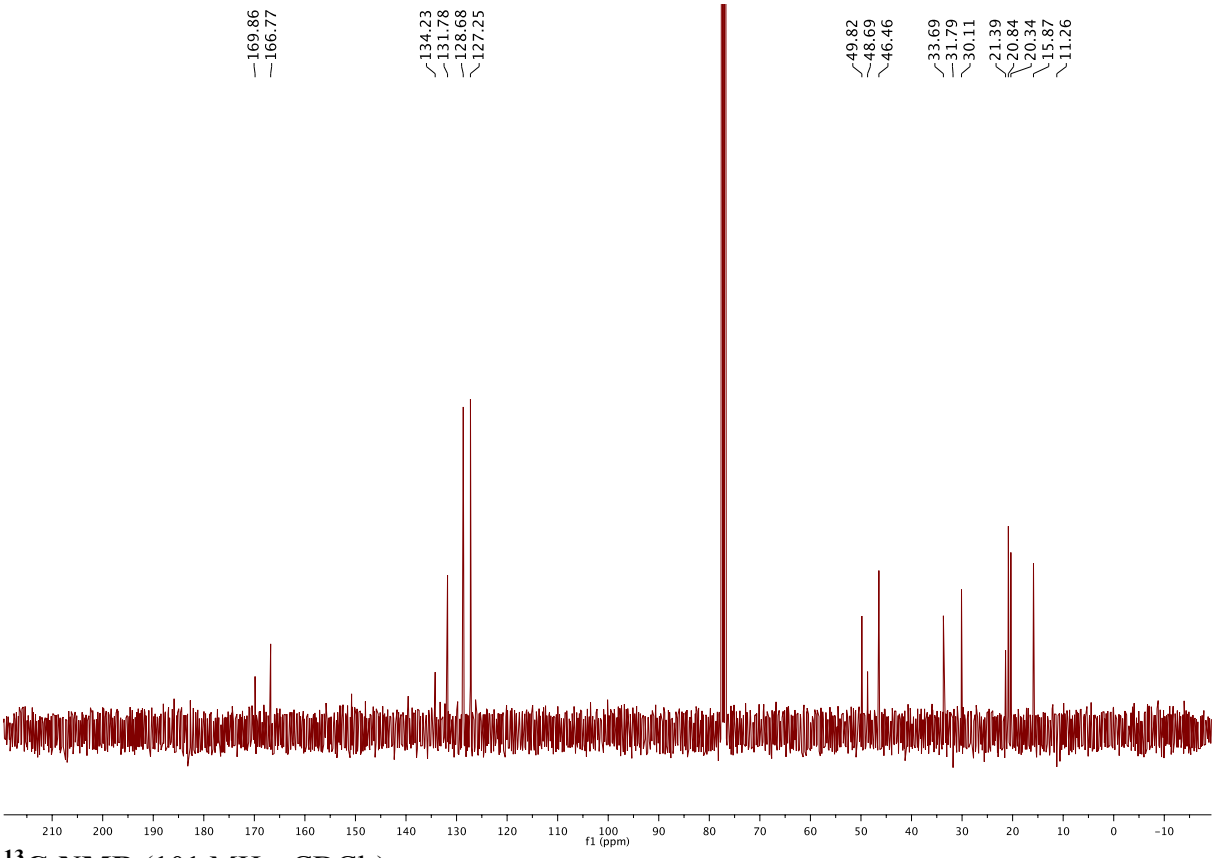


^{1}H-NMR (400 MHz, $CDCl_3$)

(*S*)-*N*-(1-(diisopropylamino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.30)

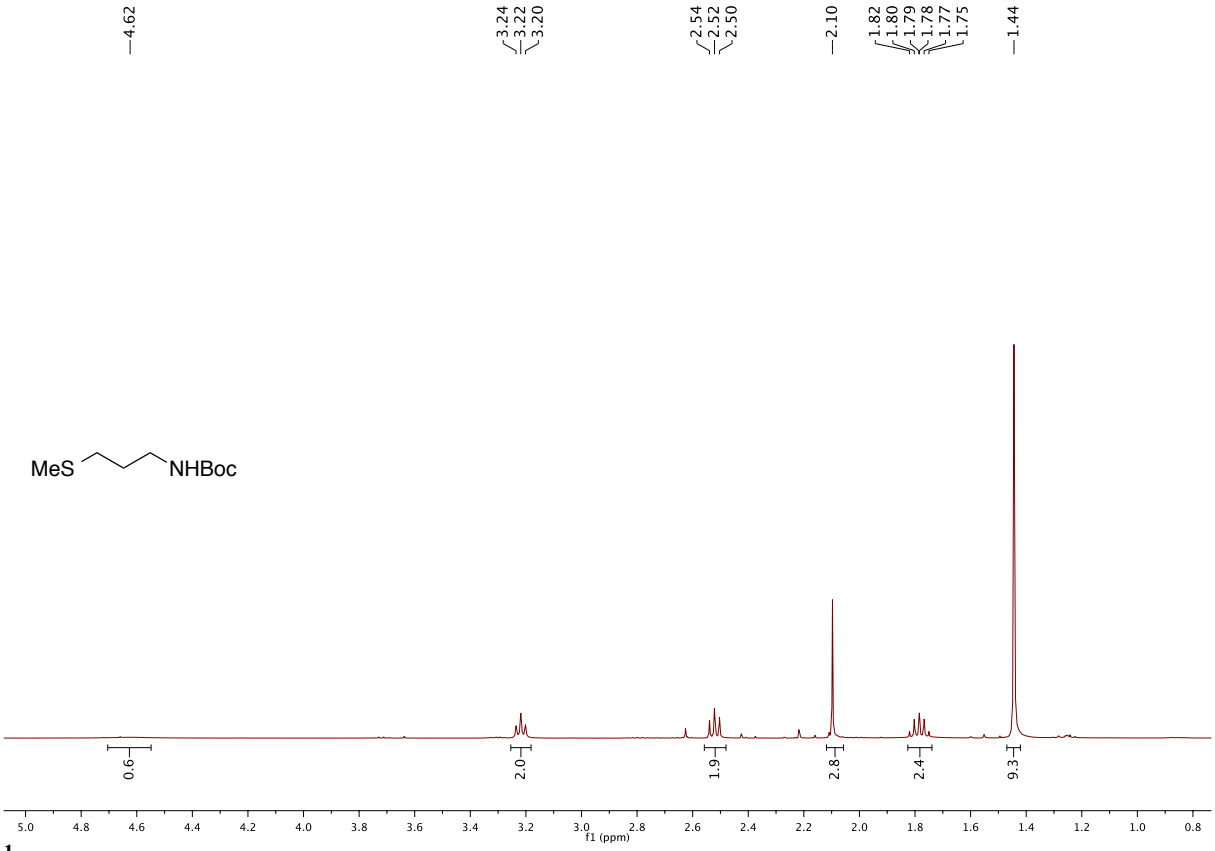


^{1}H-NMR (400 MHz, $CDCl_3$)



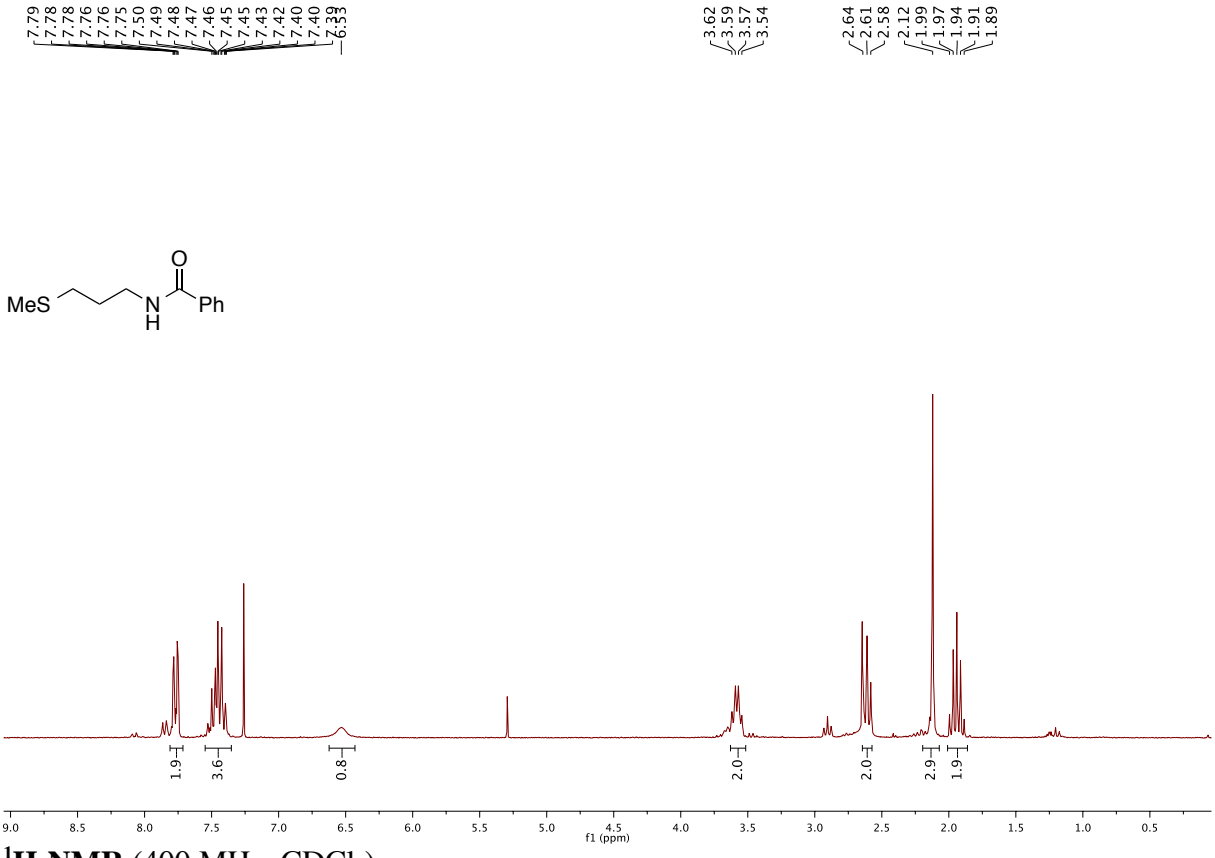
^{13}C-NMR (101 MHz, $CDCl_3$)

tert-butyl (3-(methylthio)propyl)carbamate (2.40)



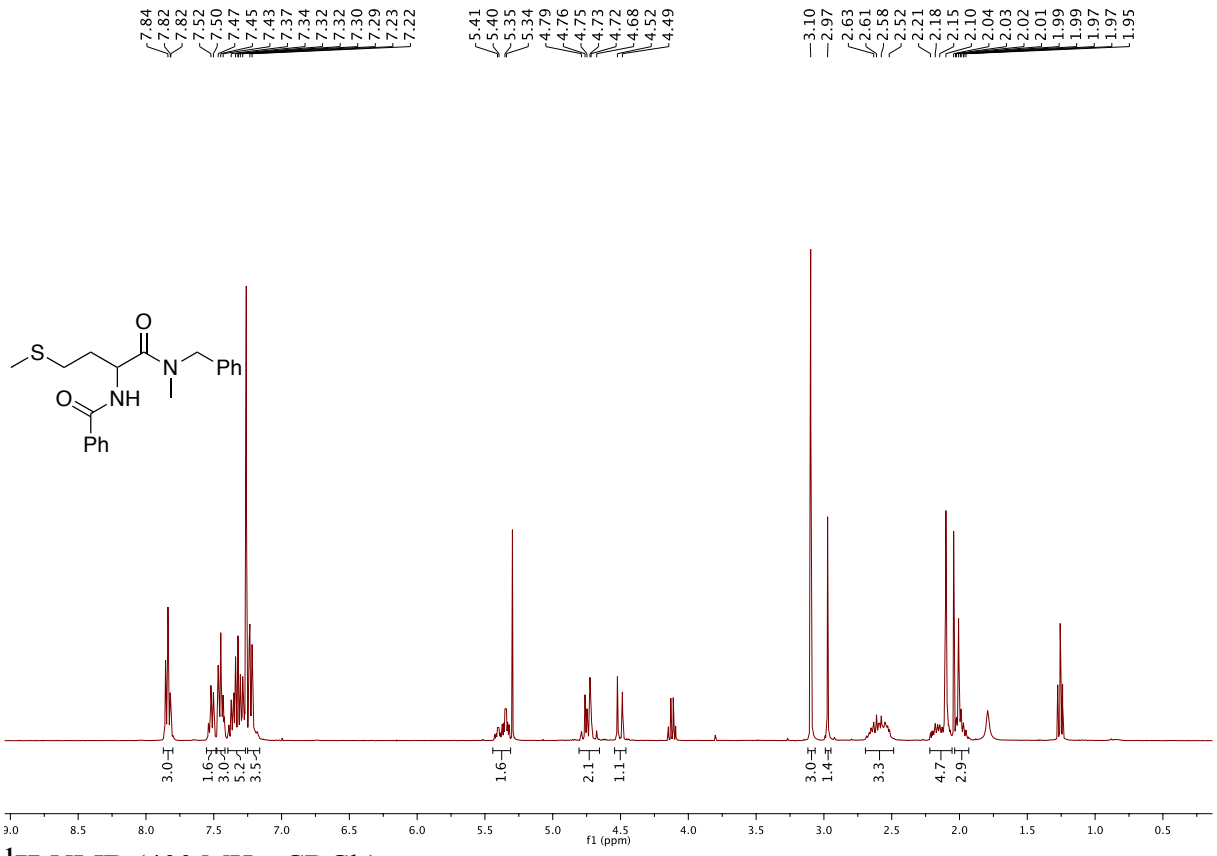
^{1}H-NMR (400 MHz, $CDCl_3$)

***N*-(3-(methylthio)propyl)benzamide (2.42)**



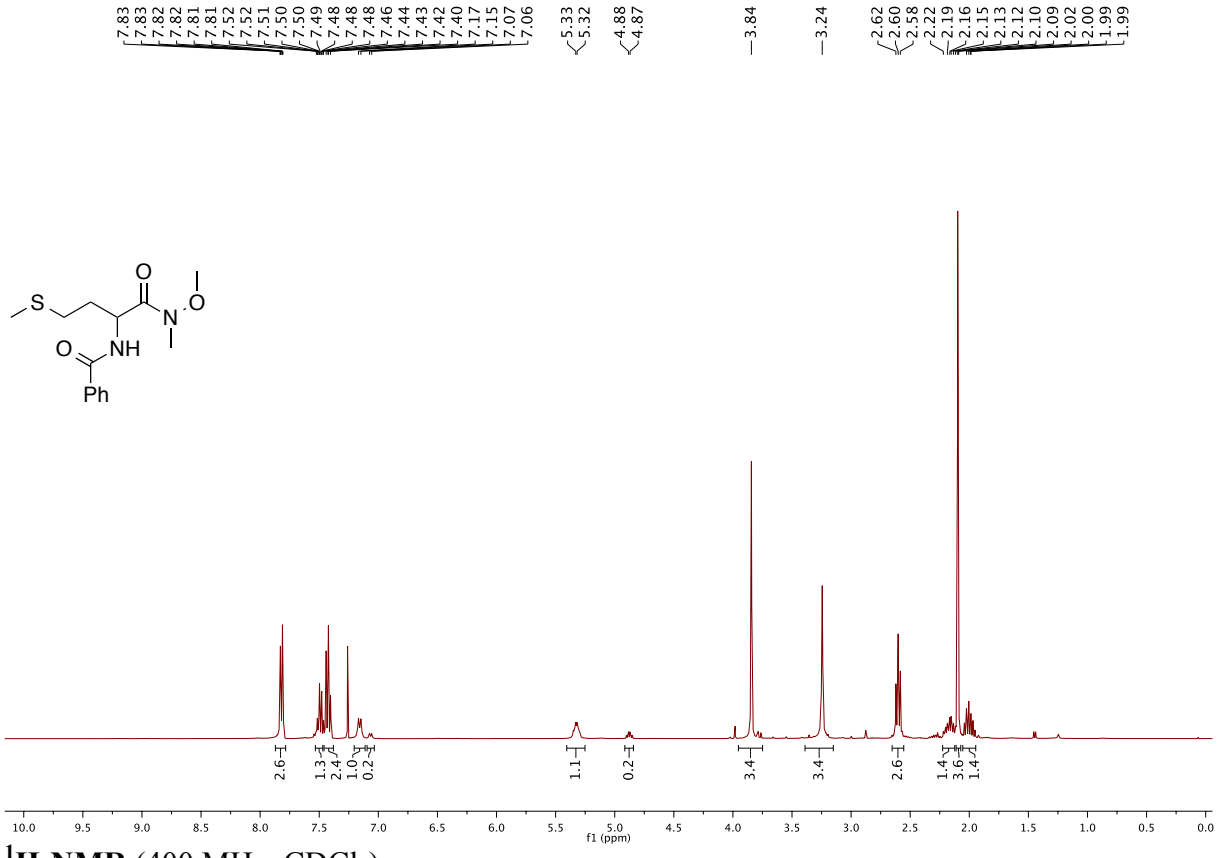
^{1}H-NMR (400 MHz, $CDCl_3$)

_N_-(1-(benzyl(methyl)amino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.49)

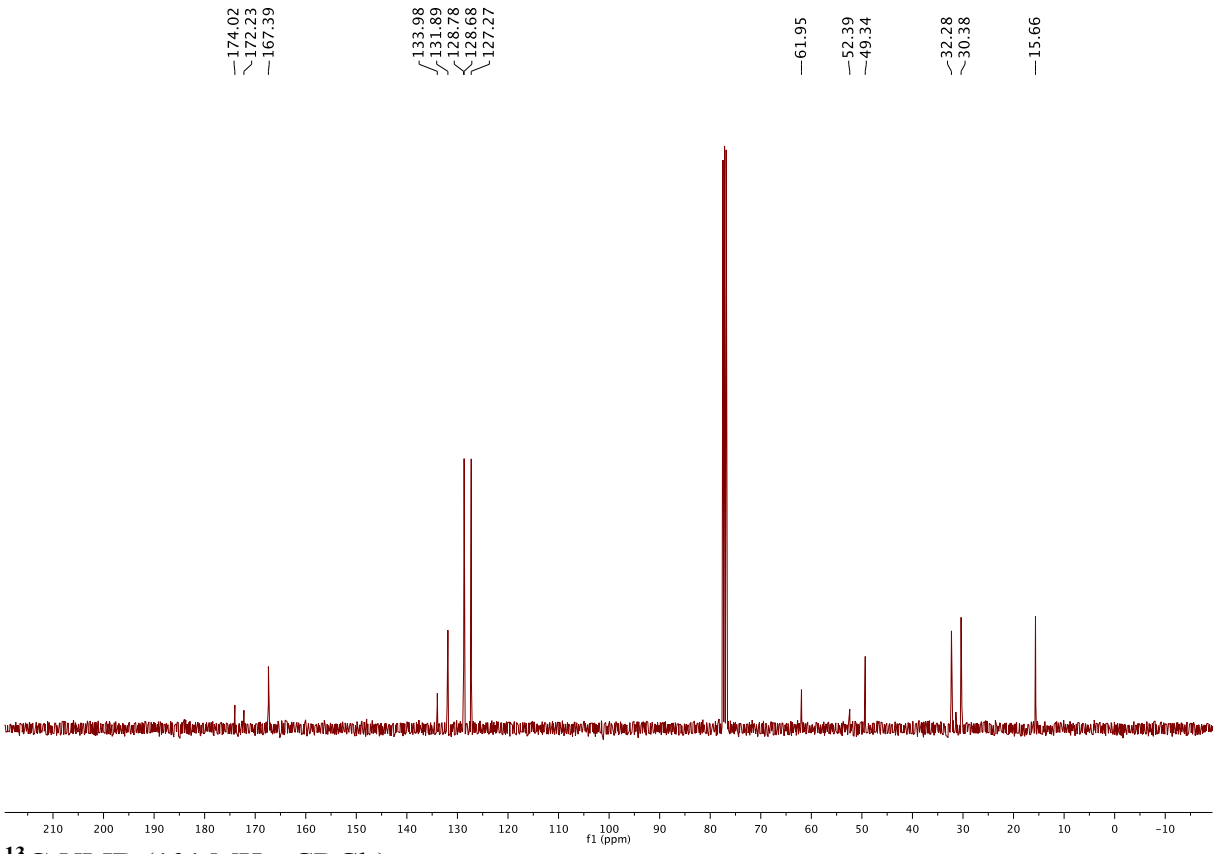


^{1}H-NMR (400 MHz, $CDCl_3$)

_N_-(1-(methoxy(methyl)amino)-4-(methylthio)-1-oxobutan-2-yl)benzamide (2.50)

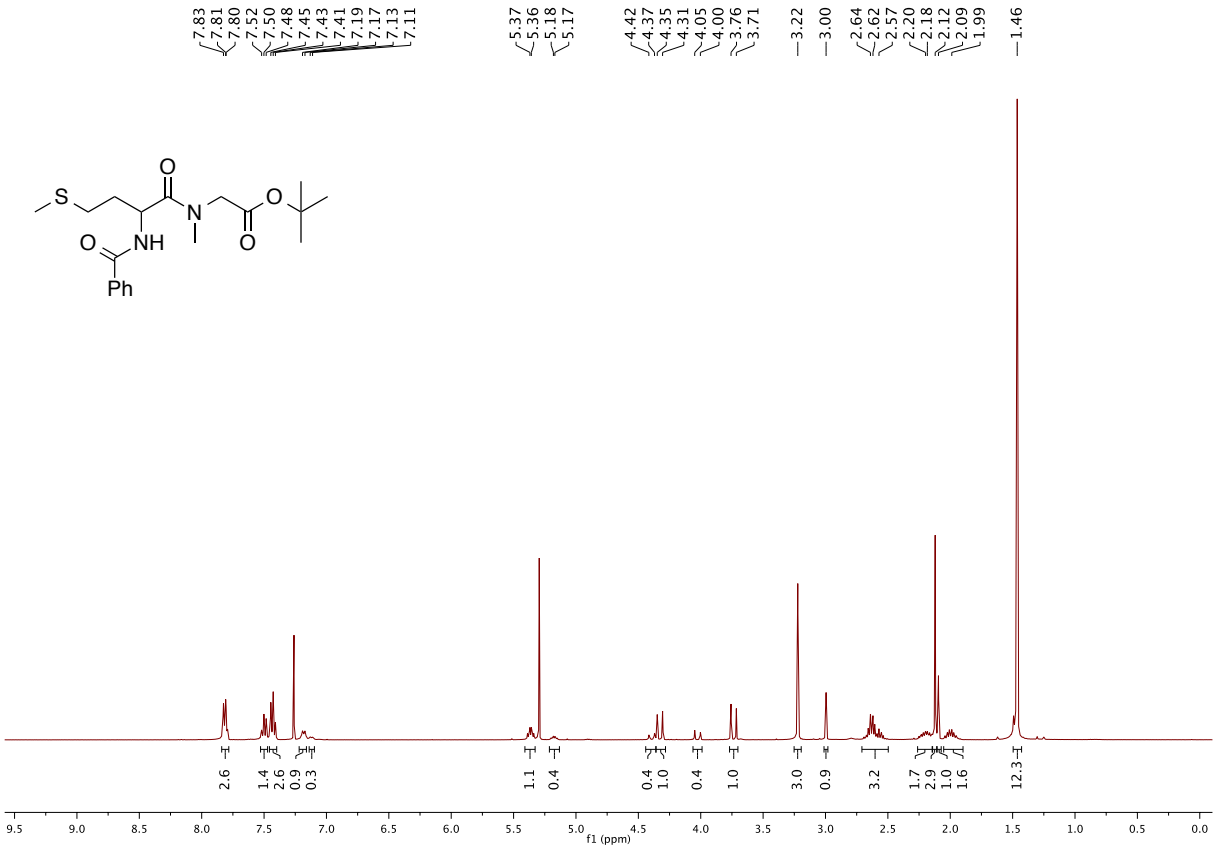


^{1}H-NMR (400 MHz, $CDCl_3$)

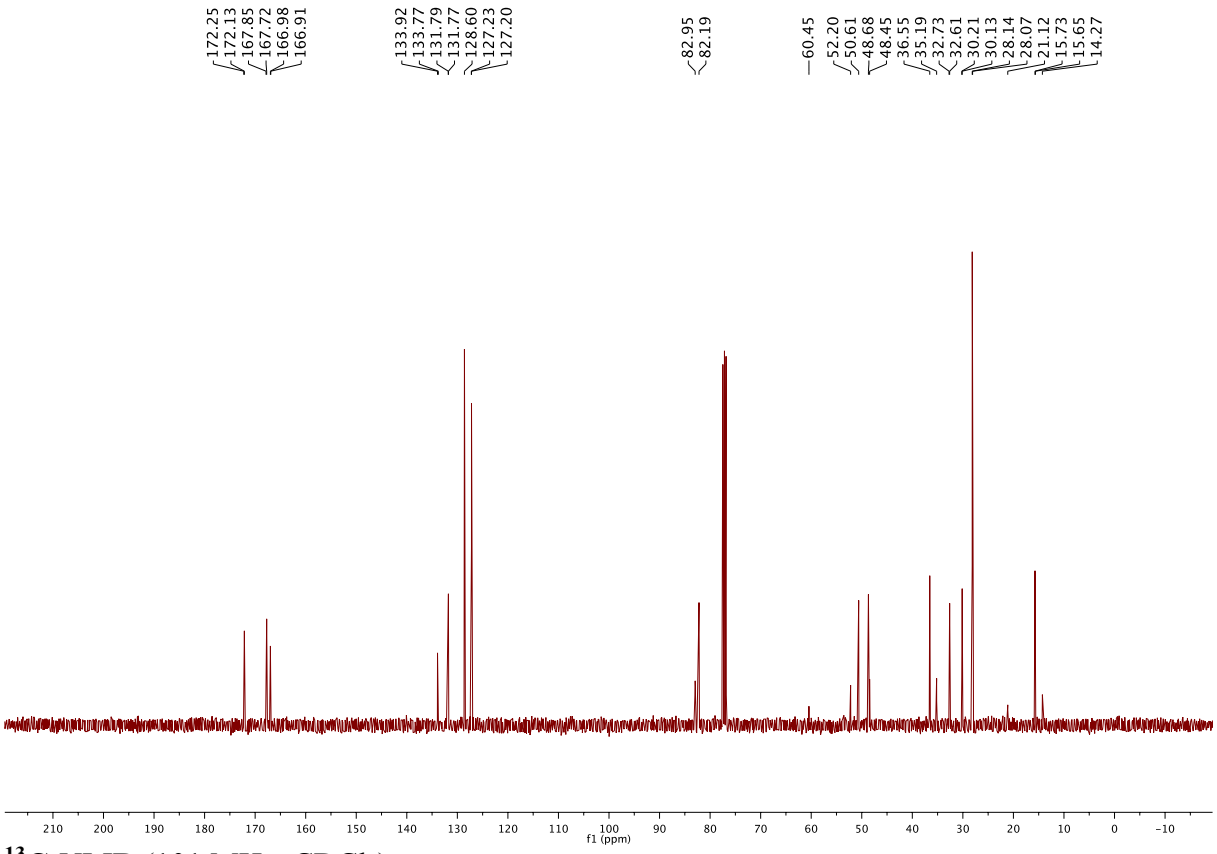


^{13}C-NMR (101 MHz, $CDCl_3$)

***tert*-butyl *N*-(benzoylmethionyl)-*N*-methylglycinate (2.51)**

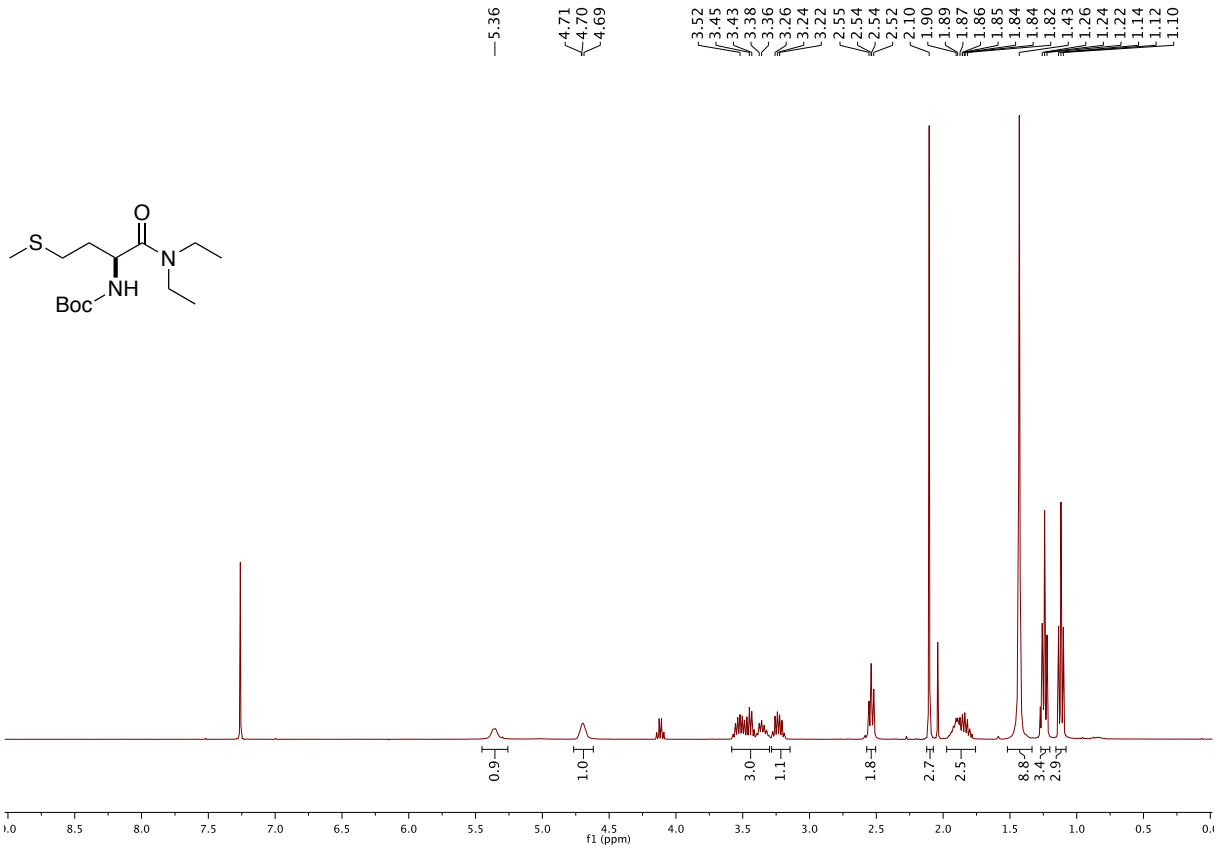


^{1}H-NMR (400 MHz, $CDCl_3$)



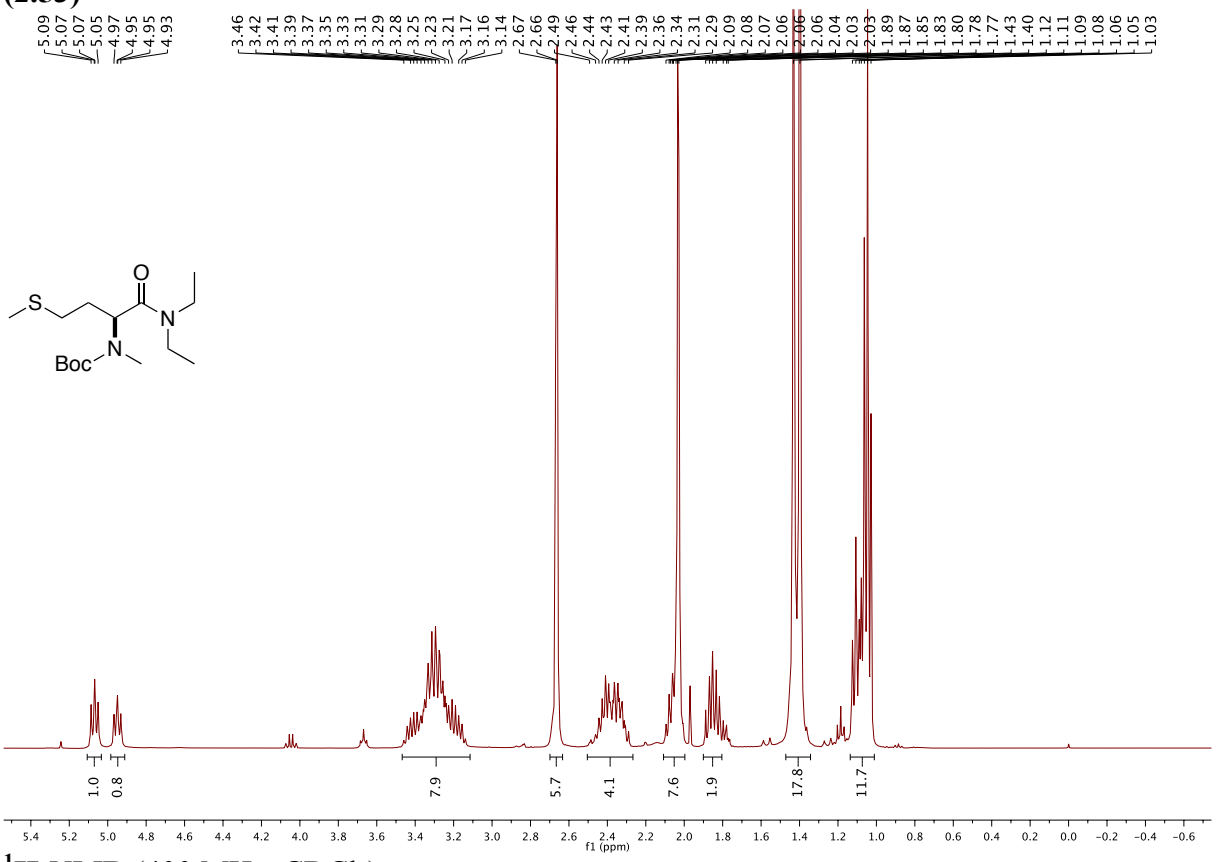
^{13}C-NMR (101 MHz, $CDCl_3$)

***tert*-butyl (*S*)-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (2.52)**



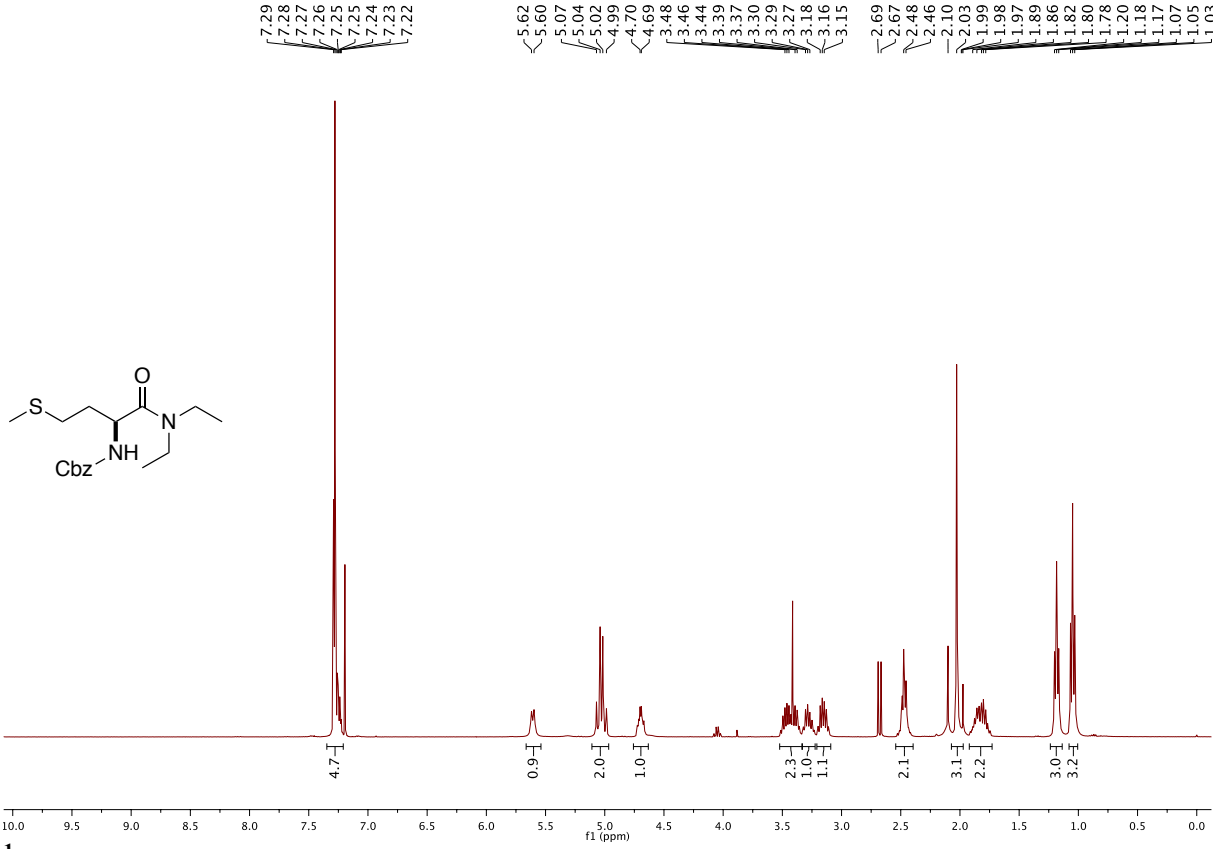
^{1}H-NMR (400 MHz, $CDCl_3$)

***tert*-butyl (*S*)-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)(methyl)carbamate (2.53)**

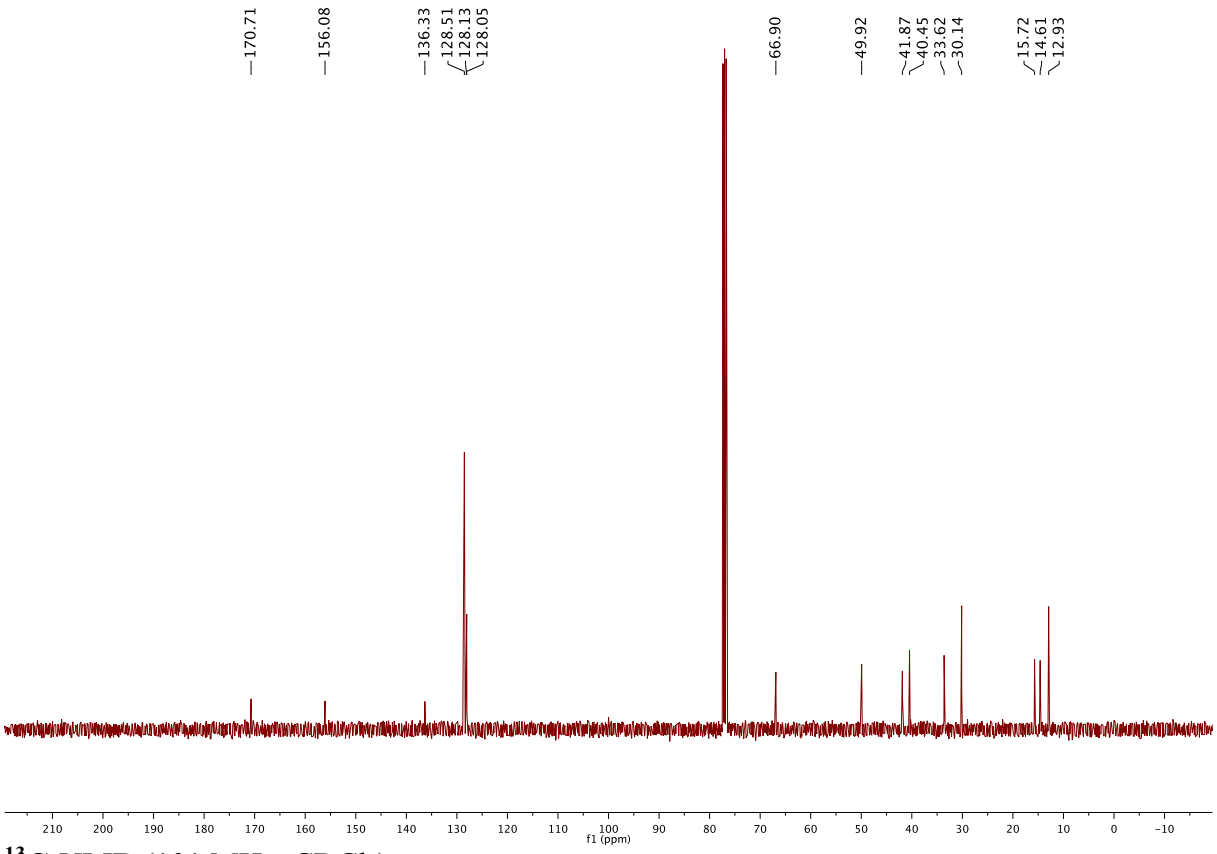


^{1}H-NMR (400 MHz, $CDCl_3$)

benzyl (*S*)-(1-(diethylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (2.54)

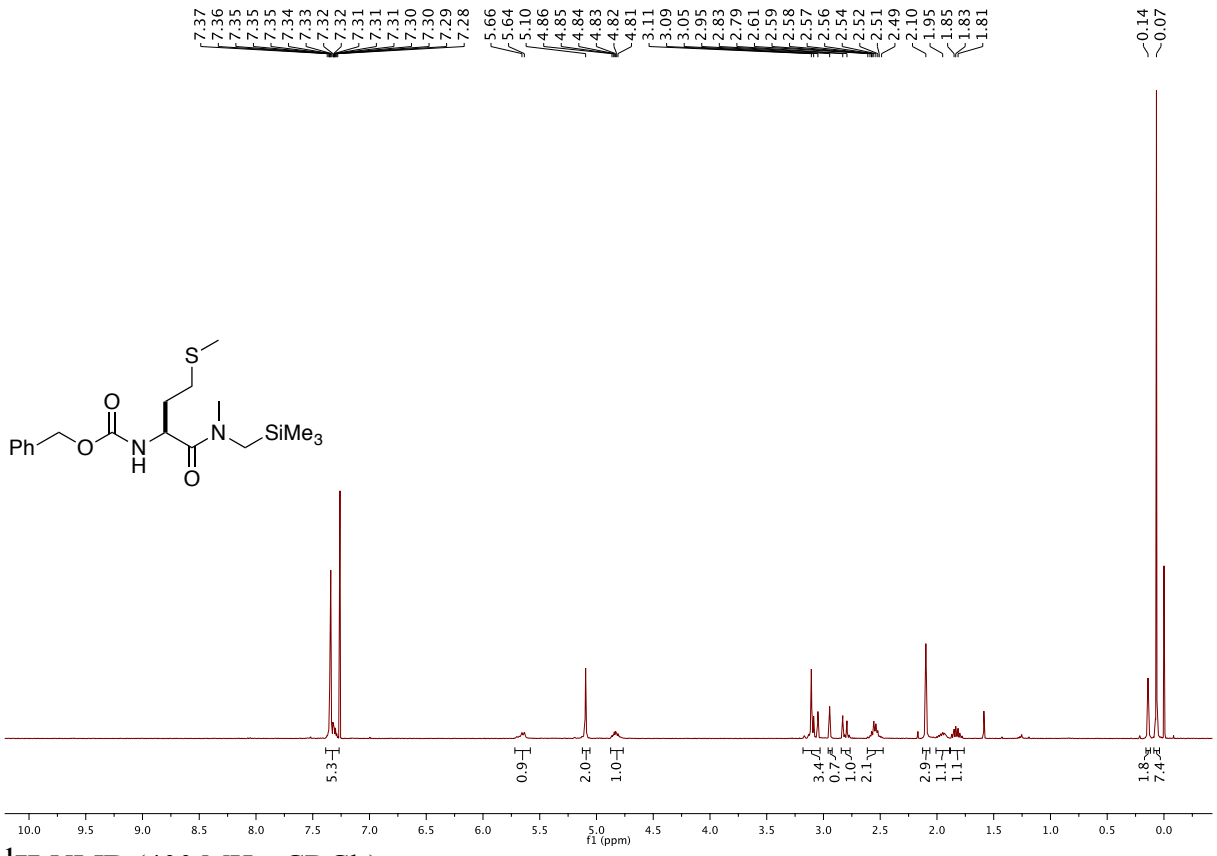


^{1}H-NMR (400 MHz, $CDCl_3$)

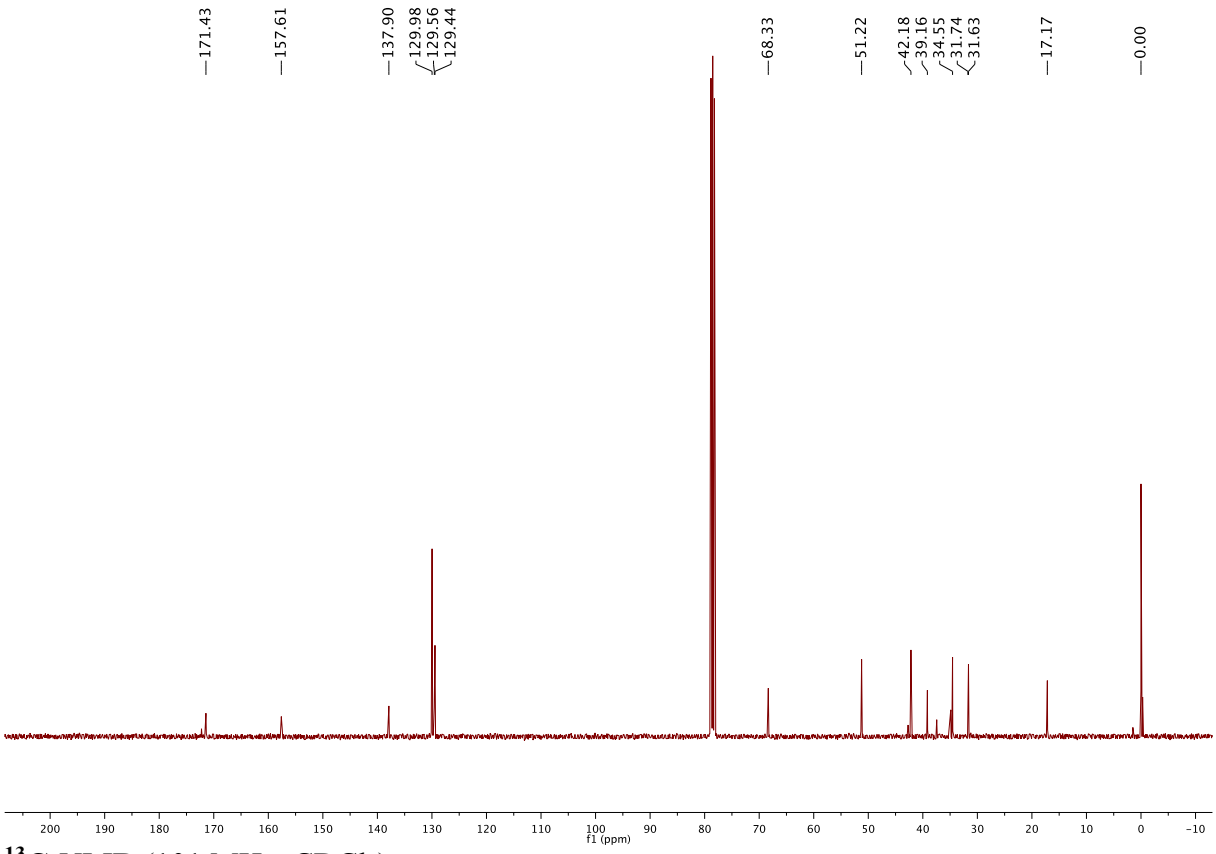


^{13}C-NMR (101 MHz, $CDCl_3$)

benzyl (*S*)-(1-(methyl((trimethylsilyl)methyl)amino)-4-(methylthio)-1-oxobutan-2-yl)-carbamate (2.76)

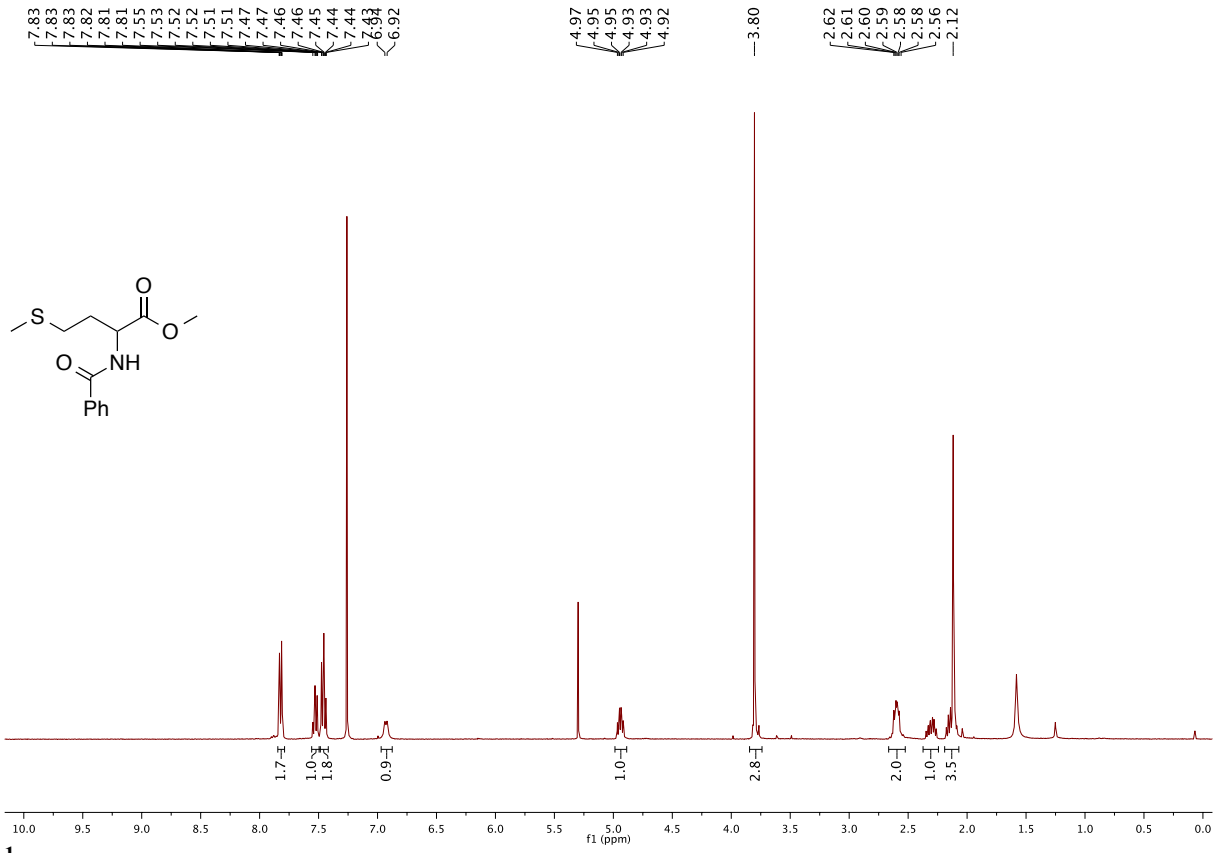


^{1}H-NMR (400 MHz, $CDCl_3$)



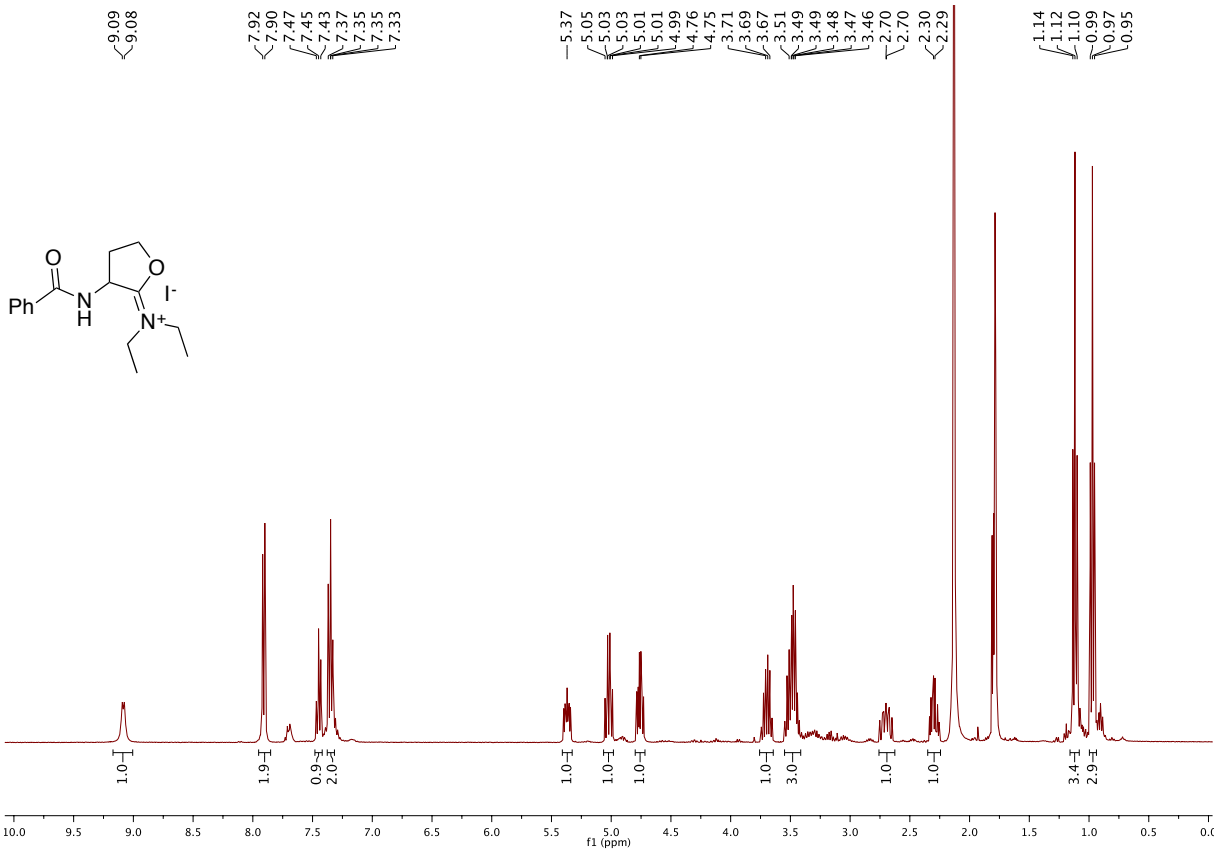
^{13}C-NMR (101 MHz, $CDCl_3$)

methyl benzoylmethioninate (2.37)



^{1}H-NMR (400 MHz, $CDCl_3$)

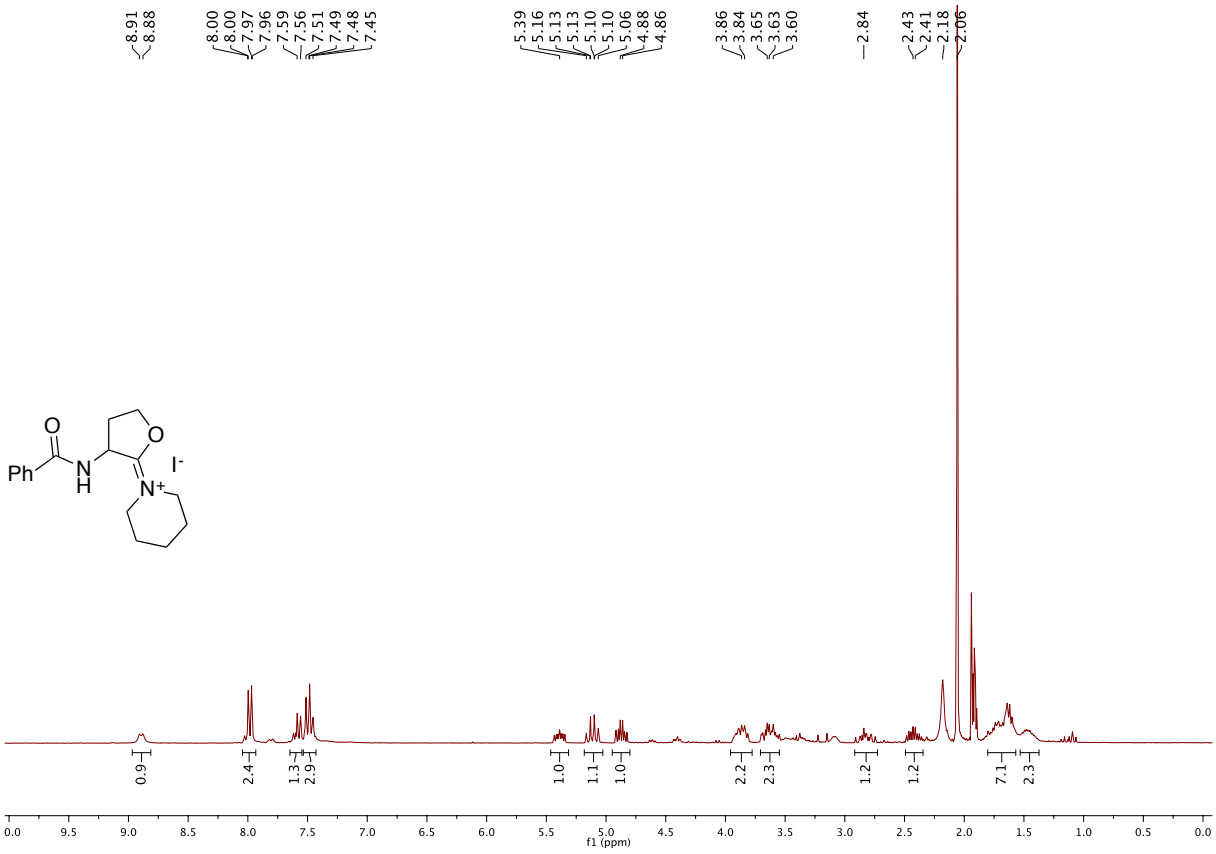
_N_-(3-benzamidodihydrofuran-2(3_H_)-ylidene)-_N_-ethylethanaminium iodide (2.31)



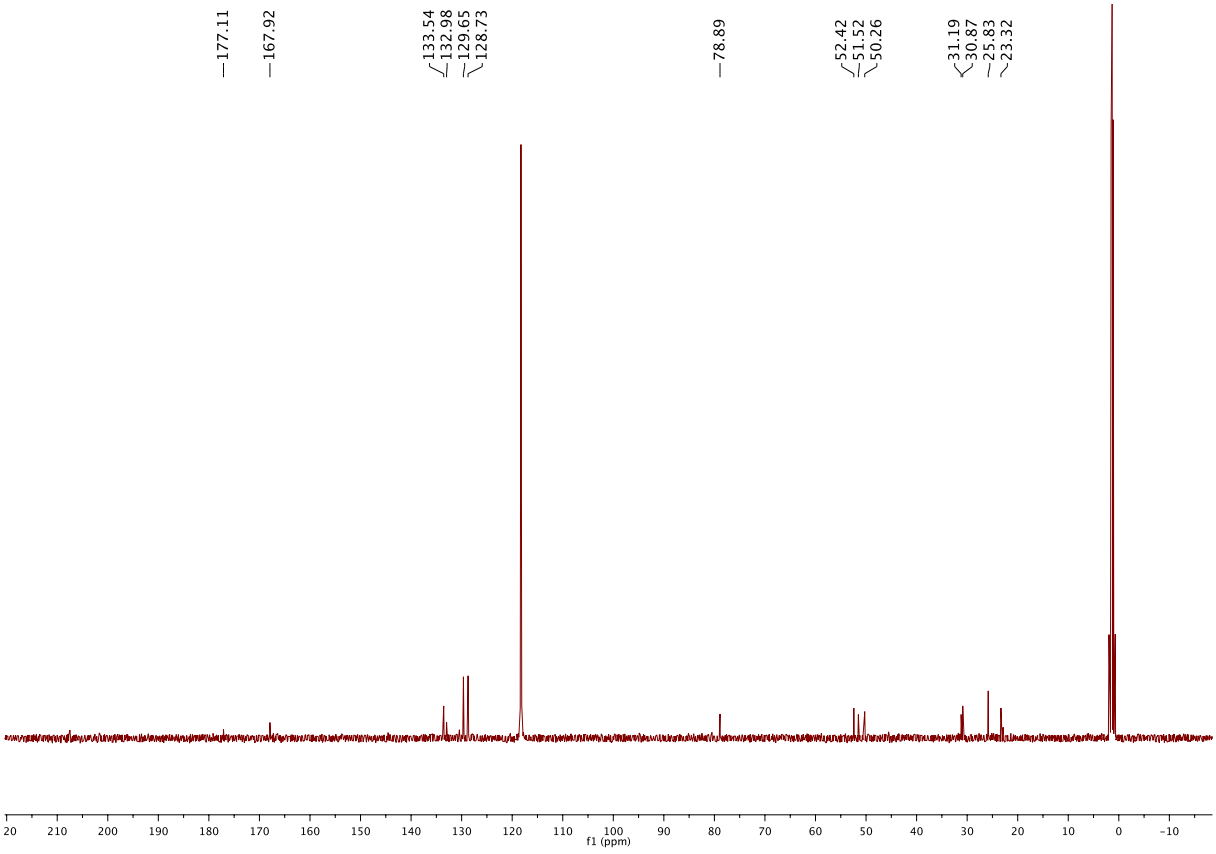
^{1}H-NMR (400 MHz, CD_3CN)

COSY (400 MHz, CD_3CN)

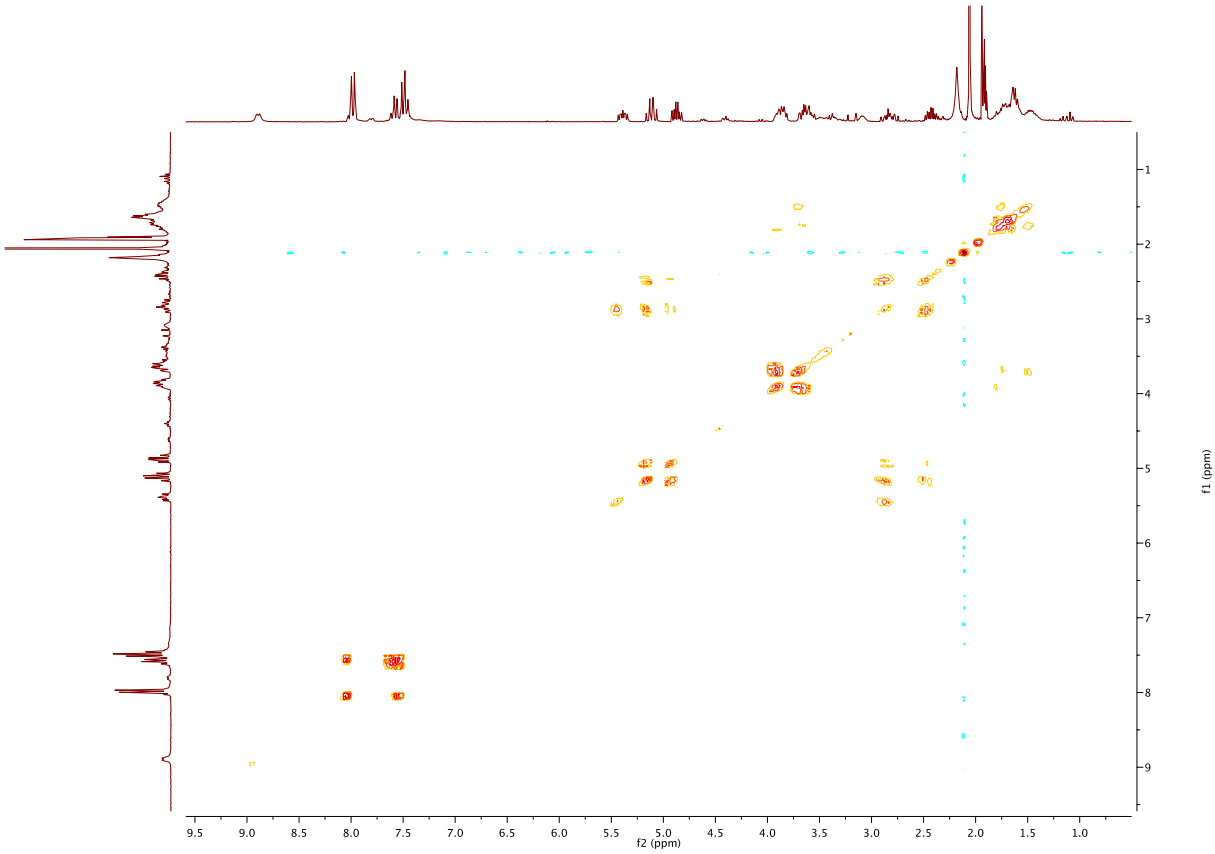
1-(3-benzamidodihydrofuran-2(3*H*)-ylidene)piperidin-1-ium iodide (2.32)



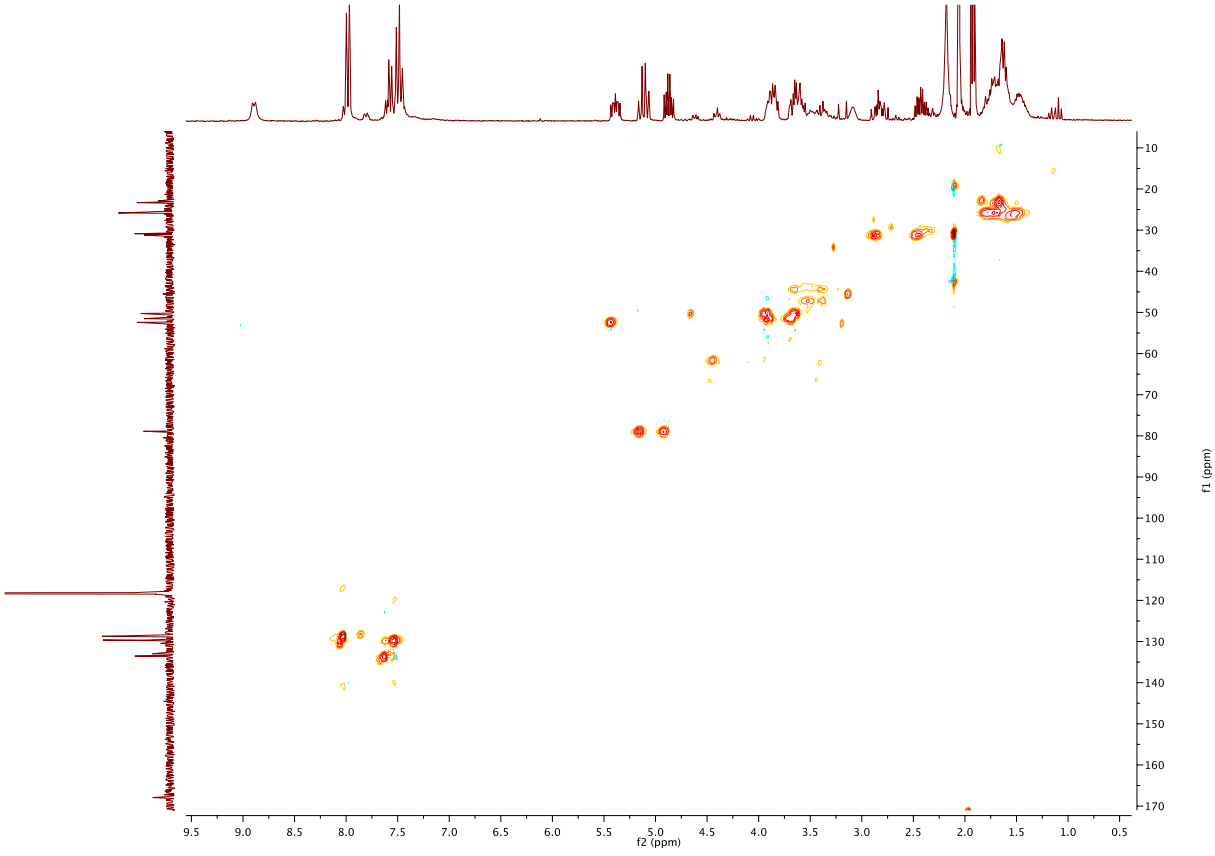
^{1}H-NMR (400 MHz, CD_3CN)



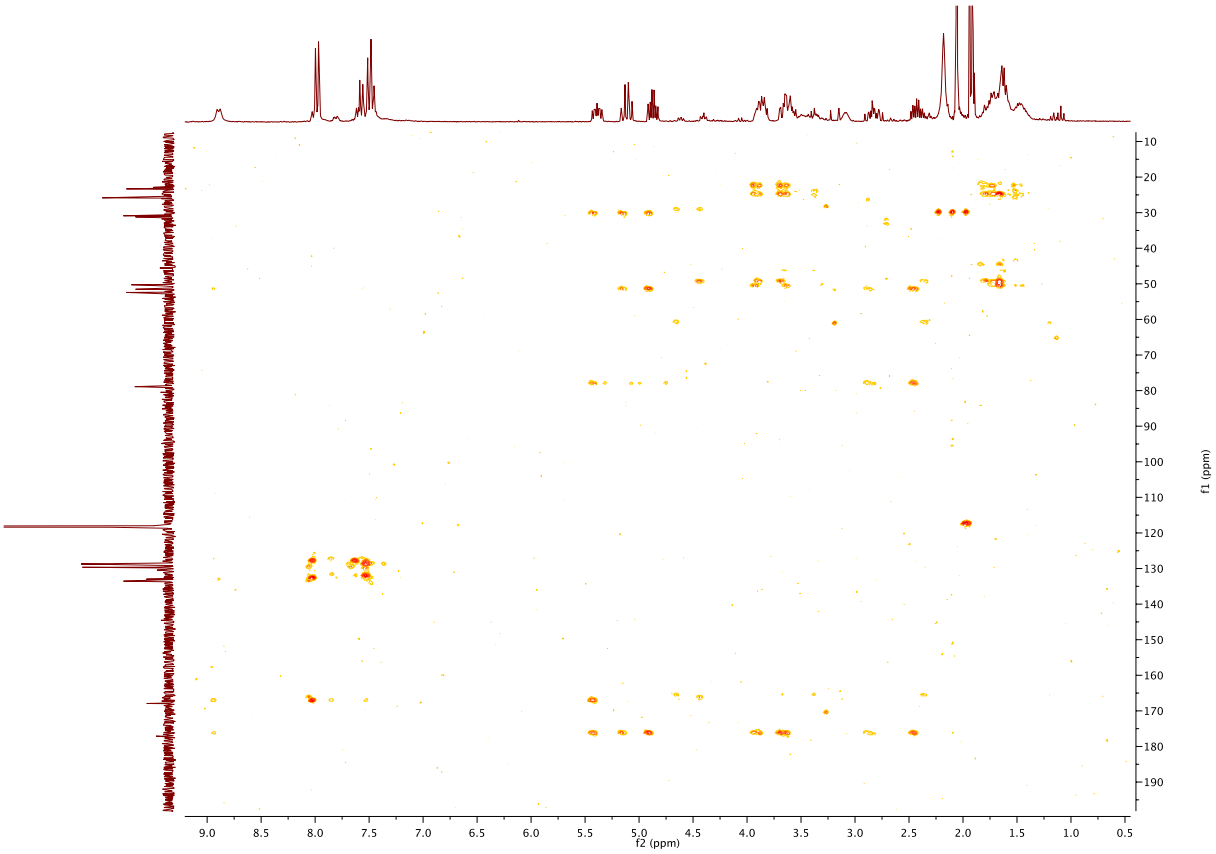
^{13}C-NMR (63 MHz, CD_3CN)



COSY (400 MHz, CD_3CN)

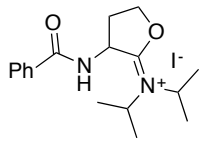


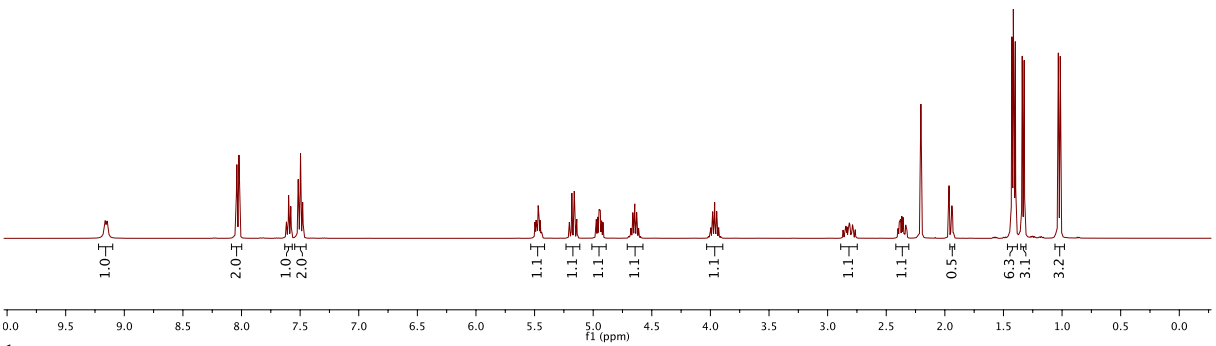
HSQC (400 MHz, CD_3CN)



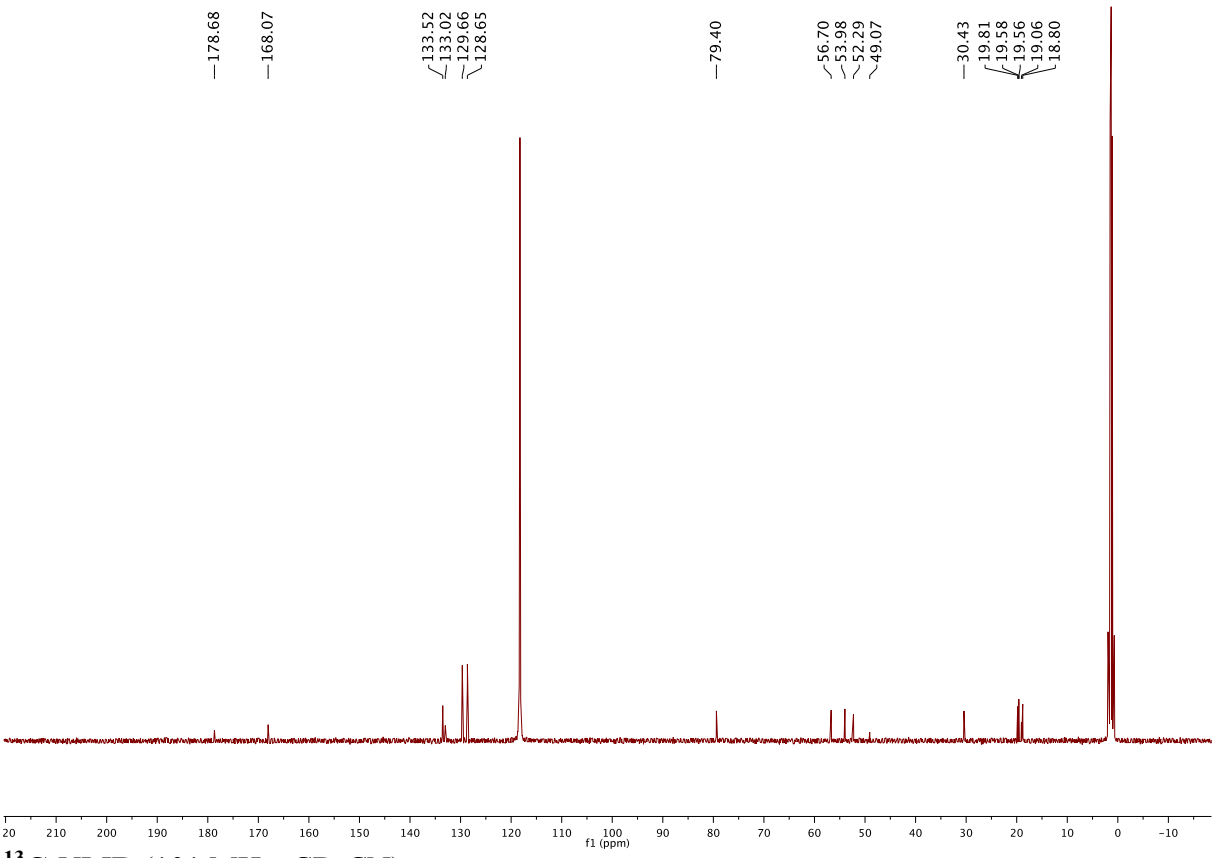
HMBC(400 MHz, CD_3CN)

***N*-(3-benzamidodihydrofuran-2(3*H*)-ylidene)-*N*-isopropylpropan-2-aminium iodide (2.35)**

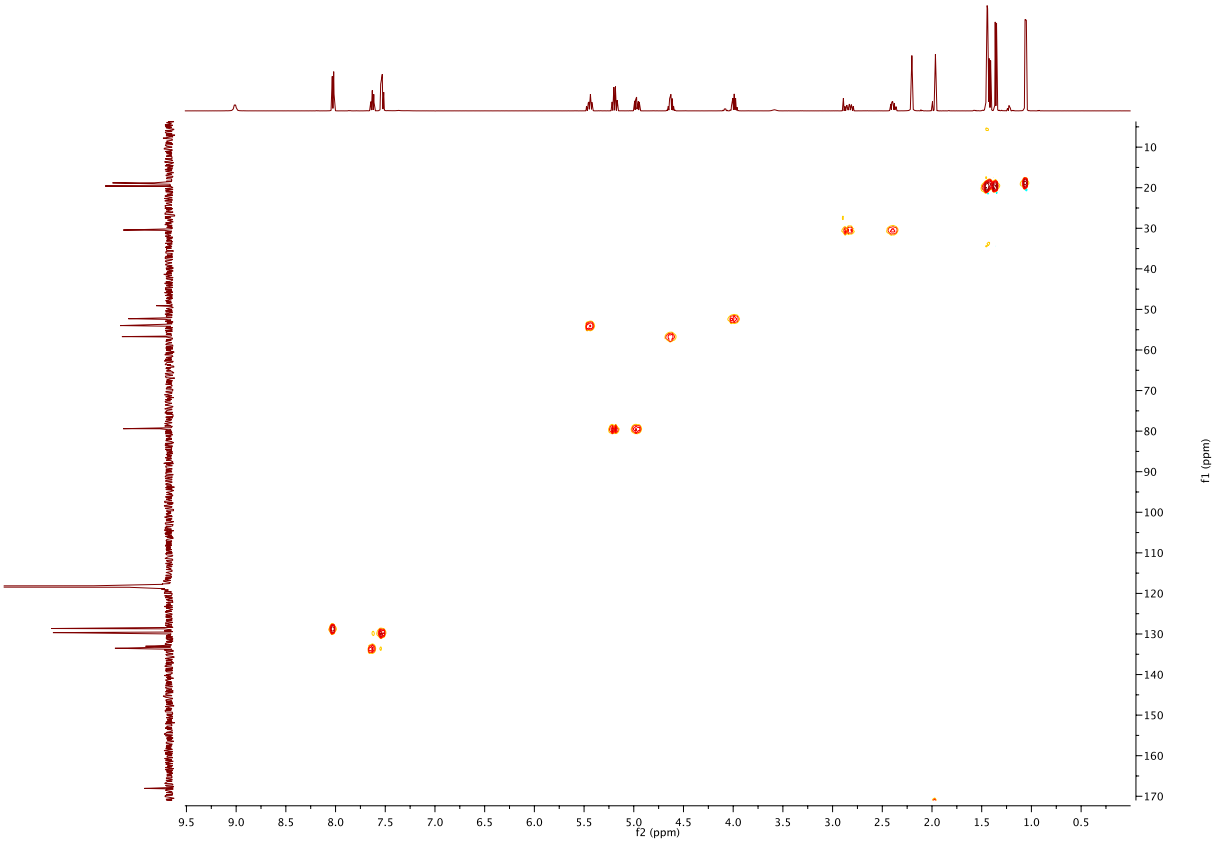




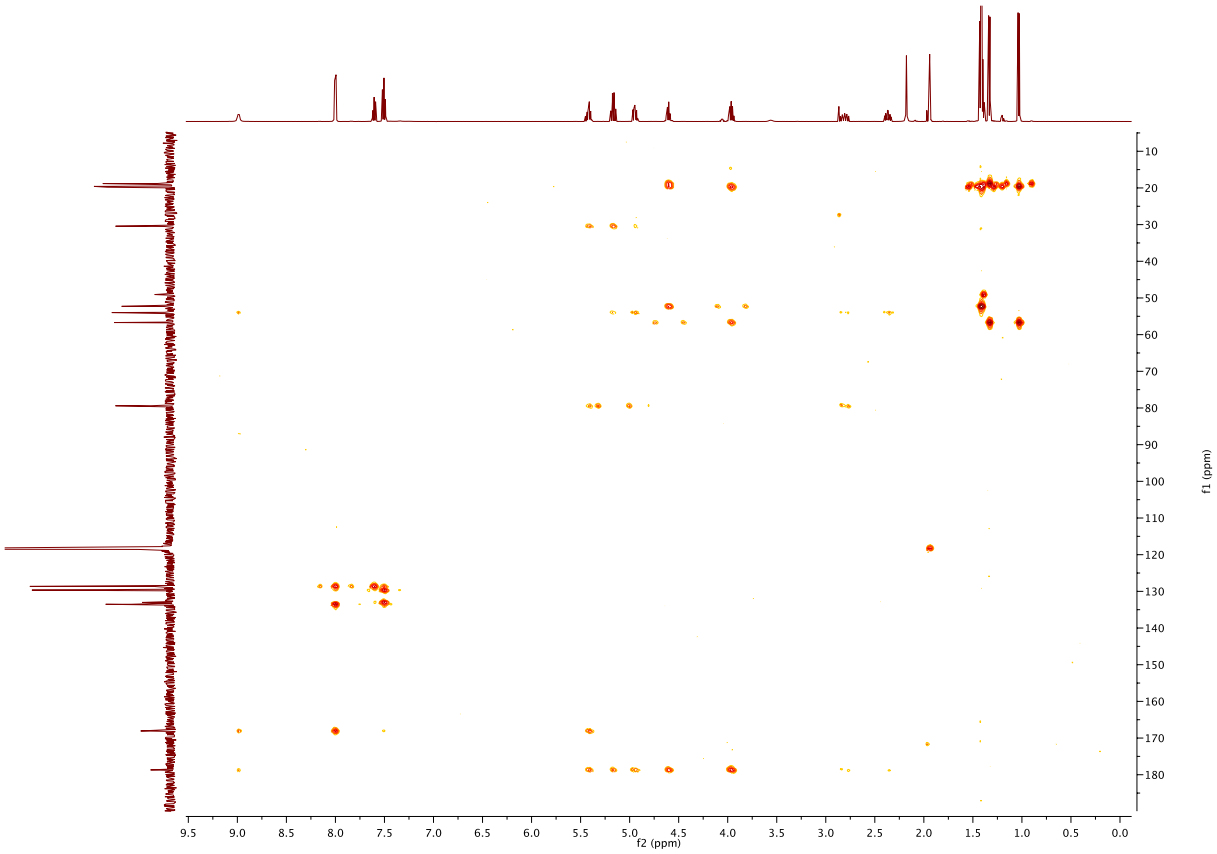
^{1}H-NMR (400 MHz, CD_3CN)



^{13}C-NMR (101 MHz, CD_3CN)

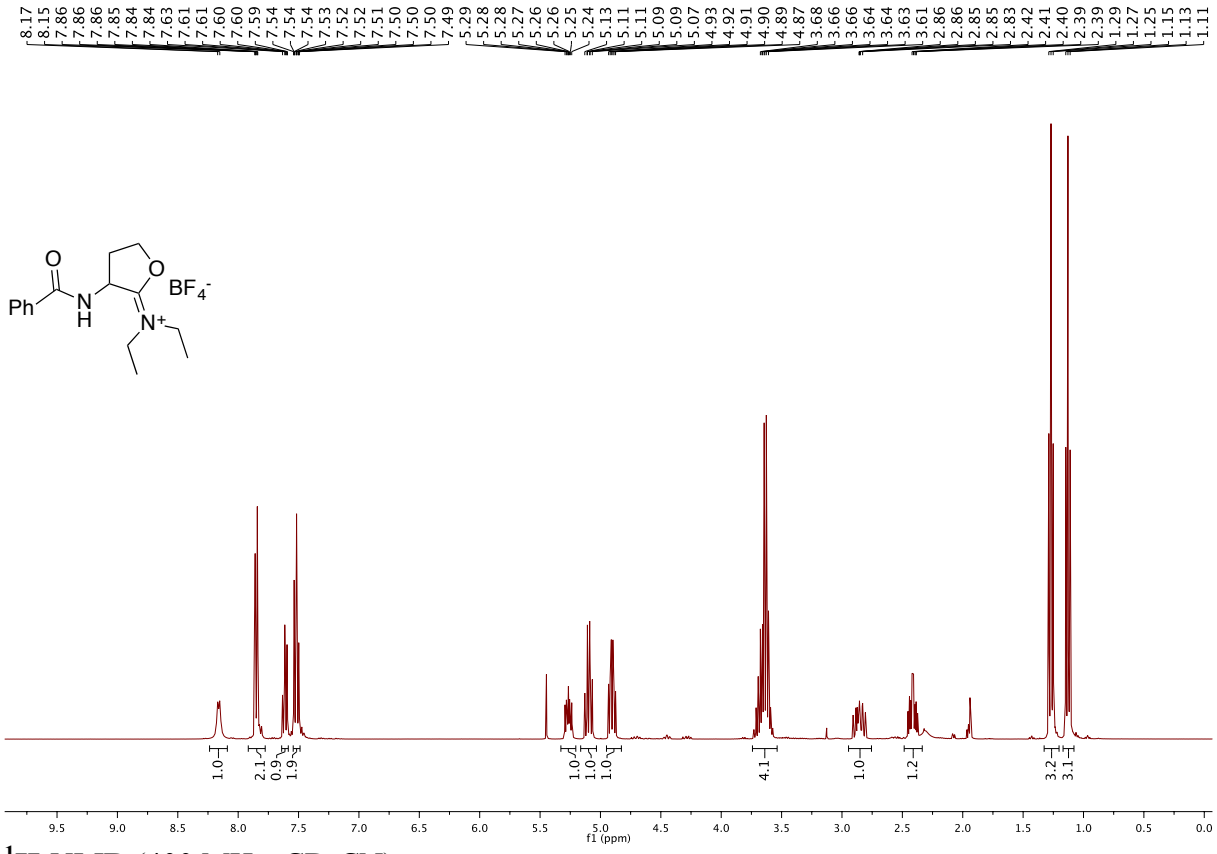


HSQC (500 MHz, CD_3CN)

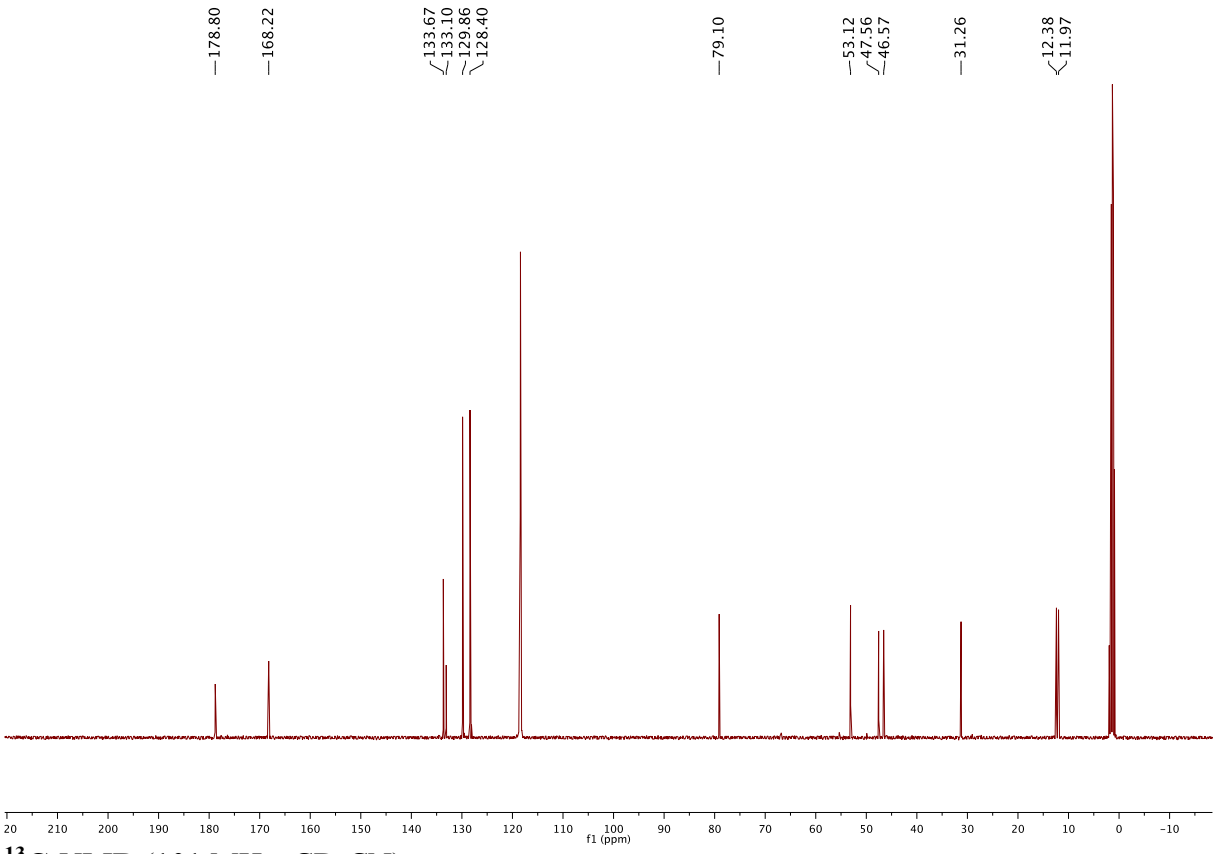


HMBC (500 MHz, CD_3CN)

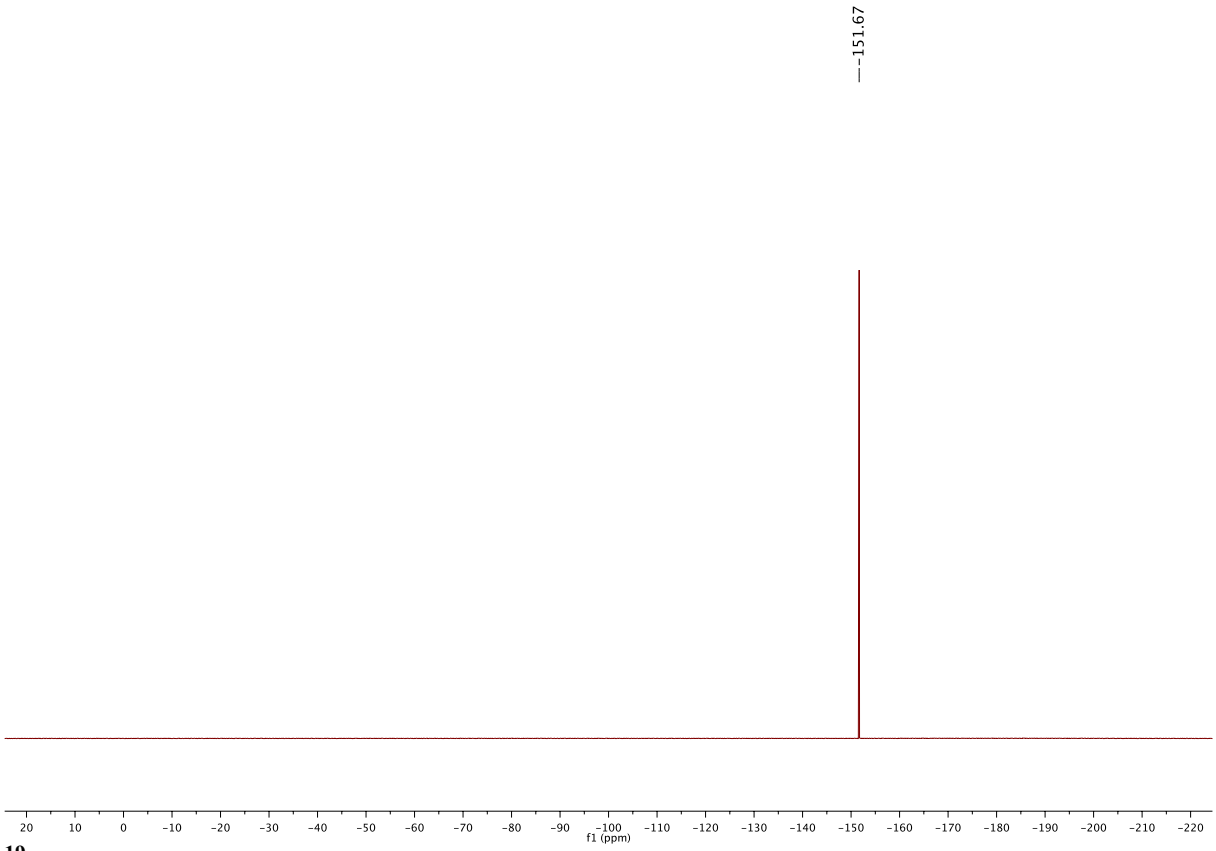
***N*-(3-benzamidodihydrofuran-2(3*H*)-ylidene)-*N*-ethylethanaminium tetrafluoroborate (2.55)**



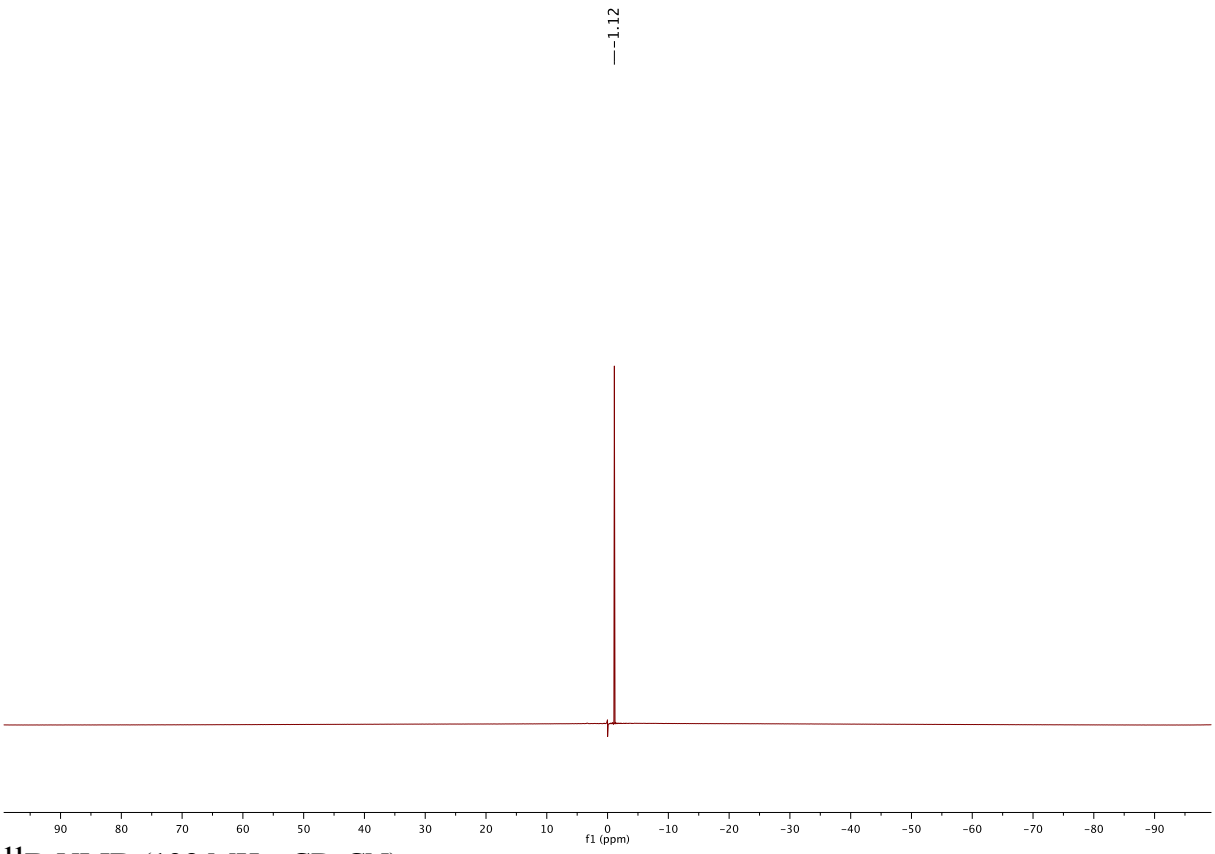
^{1}H-NMR (400 MHz, CD_3CN)



^{13}C-NMR (101 MHz, CD_3CN)

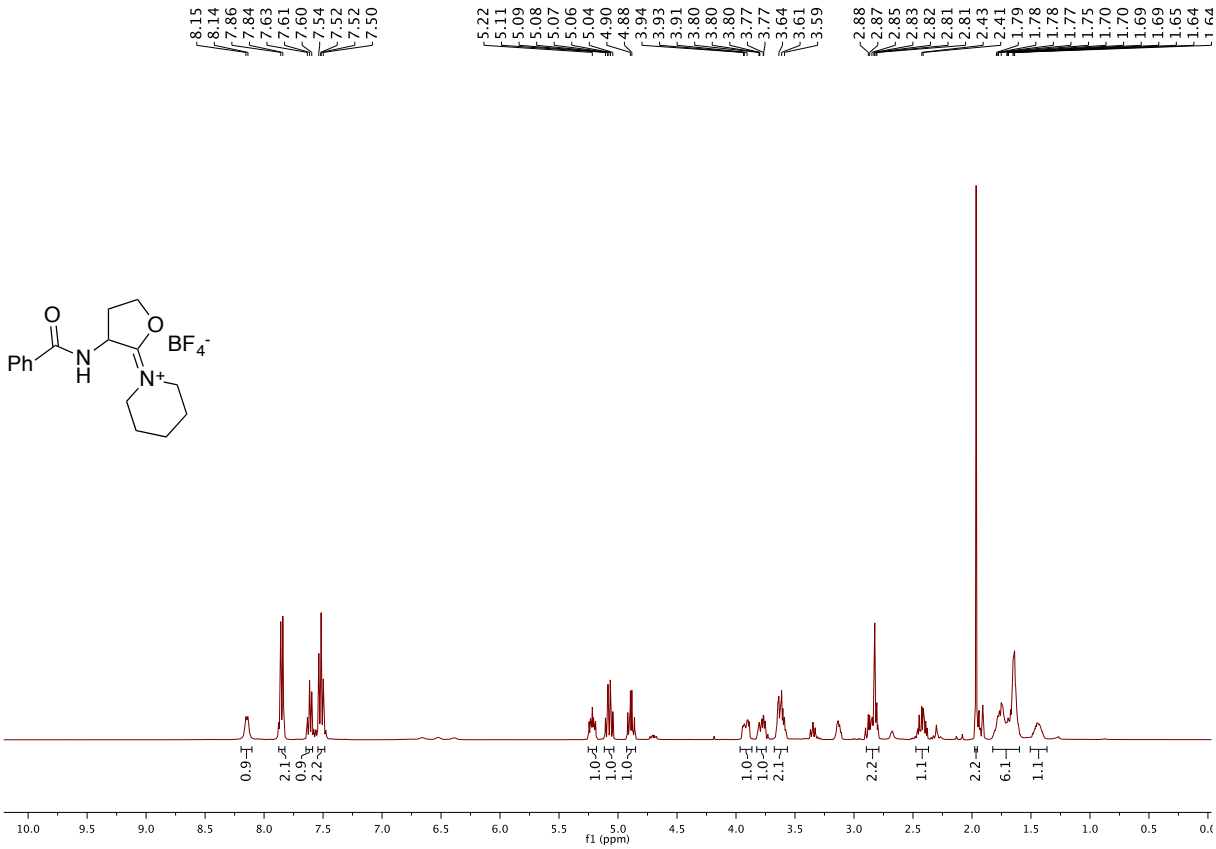


^{19}F-NMR (376 MHz, CD_3CN)

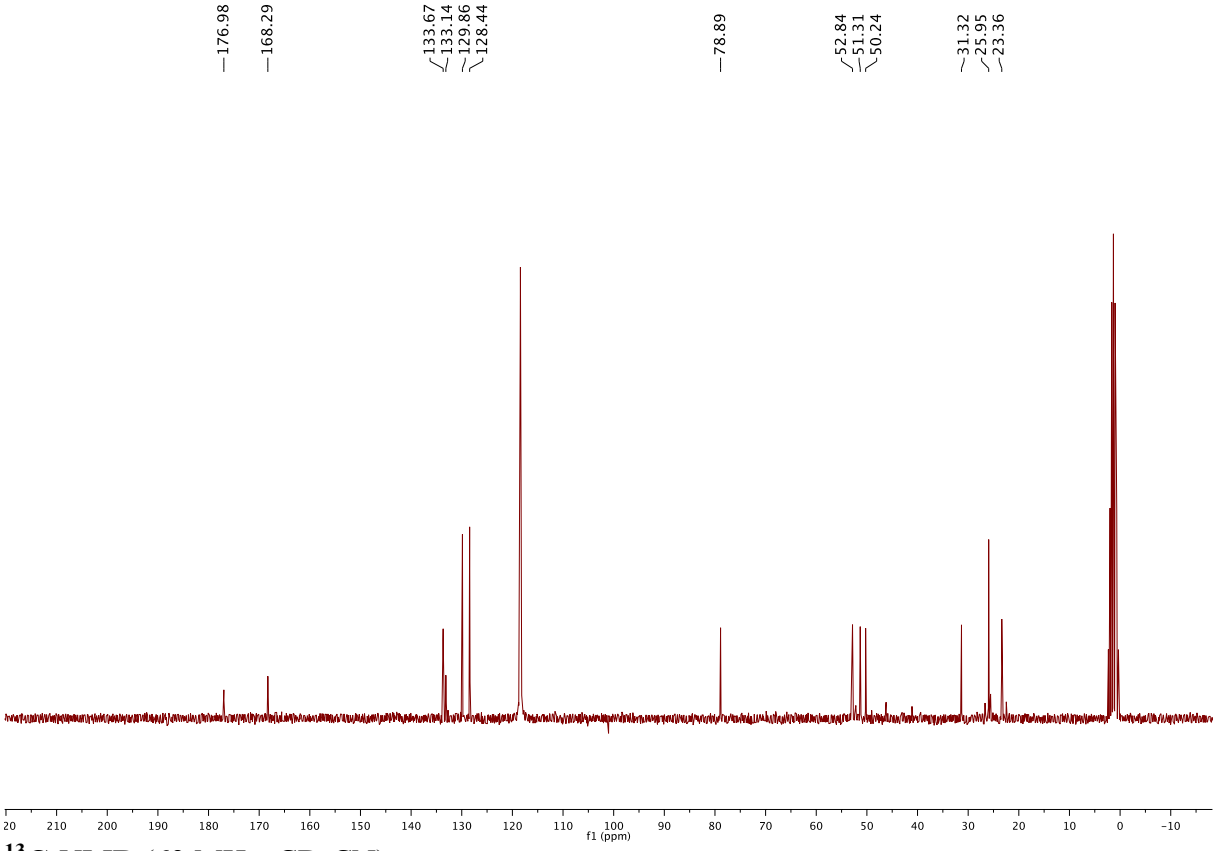


^{11}B-NMR (128 MHz, CD_3CN)

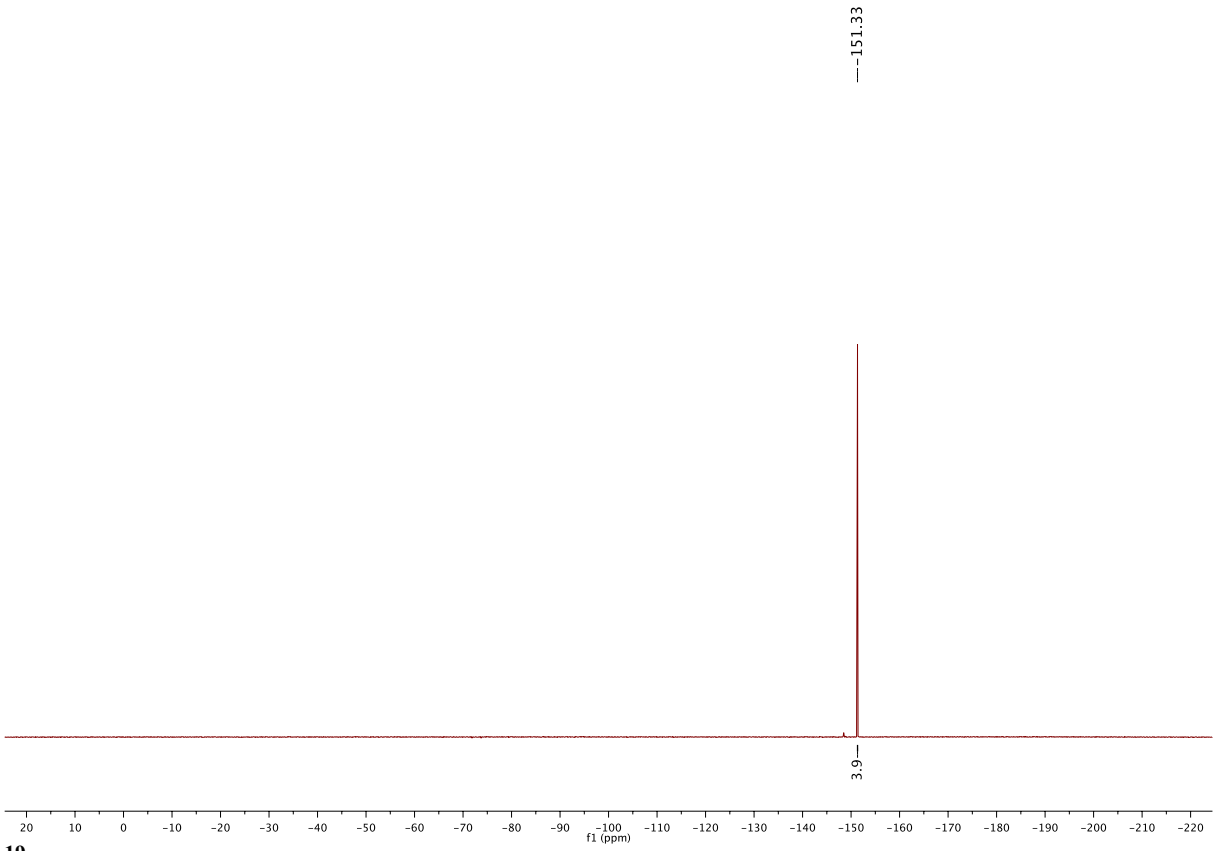
1-(3-benzamidodihydrofuran-2(3*H*)-ylidene)piperidin-1-ium tetrafluoroborate (2.56)



^{1}H-NMR (400 MHz, CD_3CN)

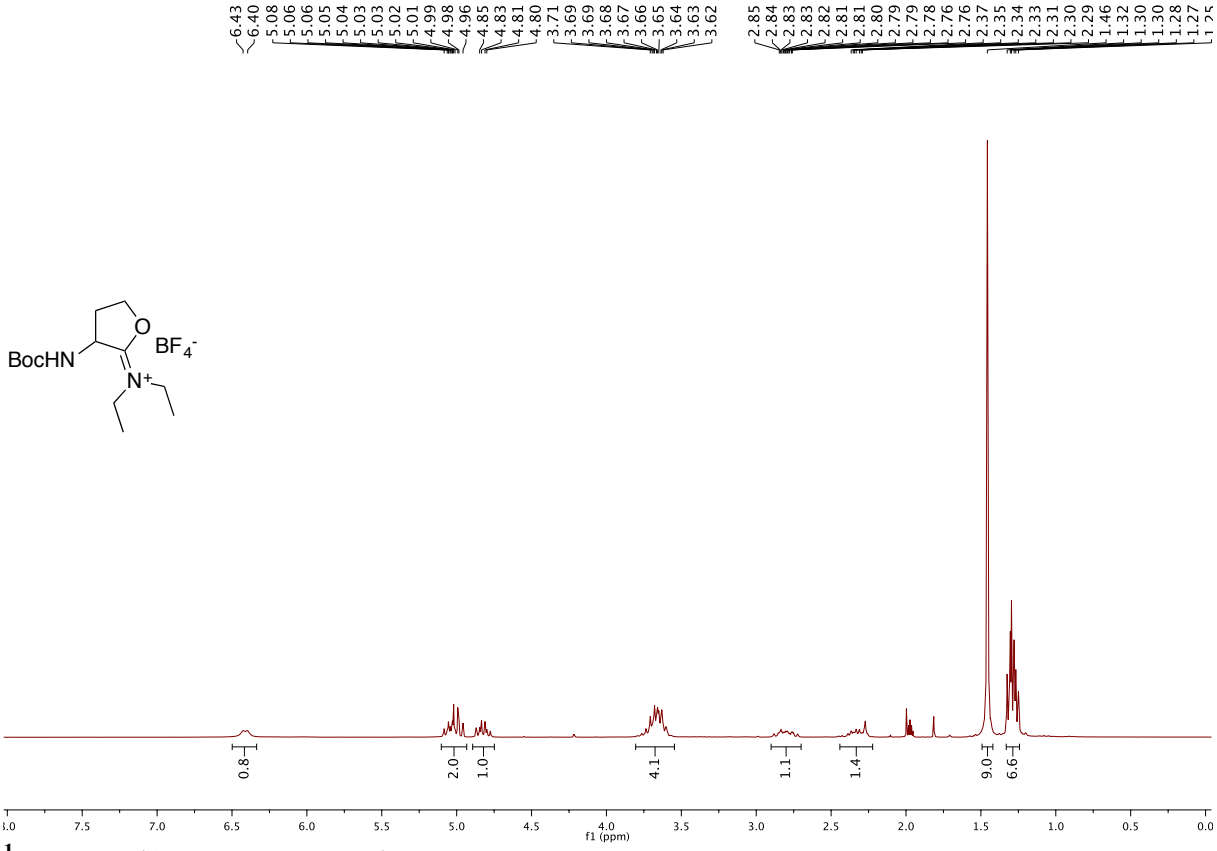


^{13}C-NMR (63 MHz, CD_3CN)

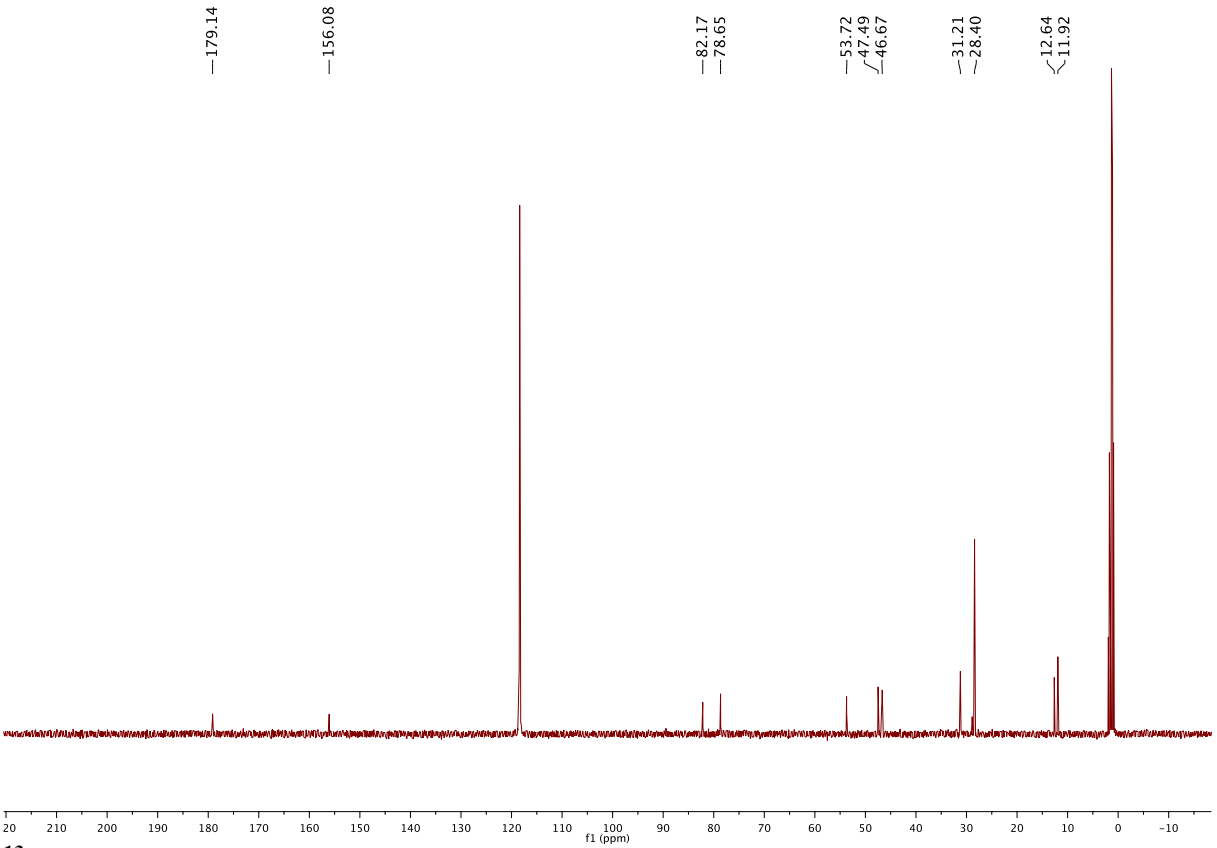


^{19}F-NMR (376 MHz, CD_3CN)

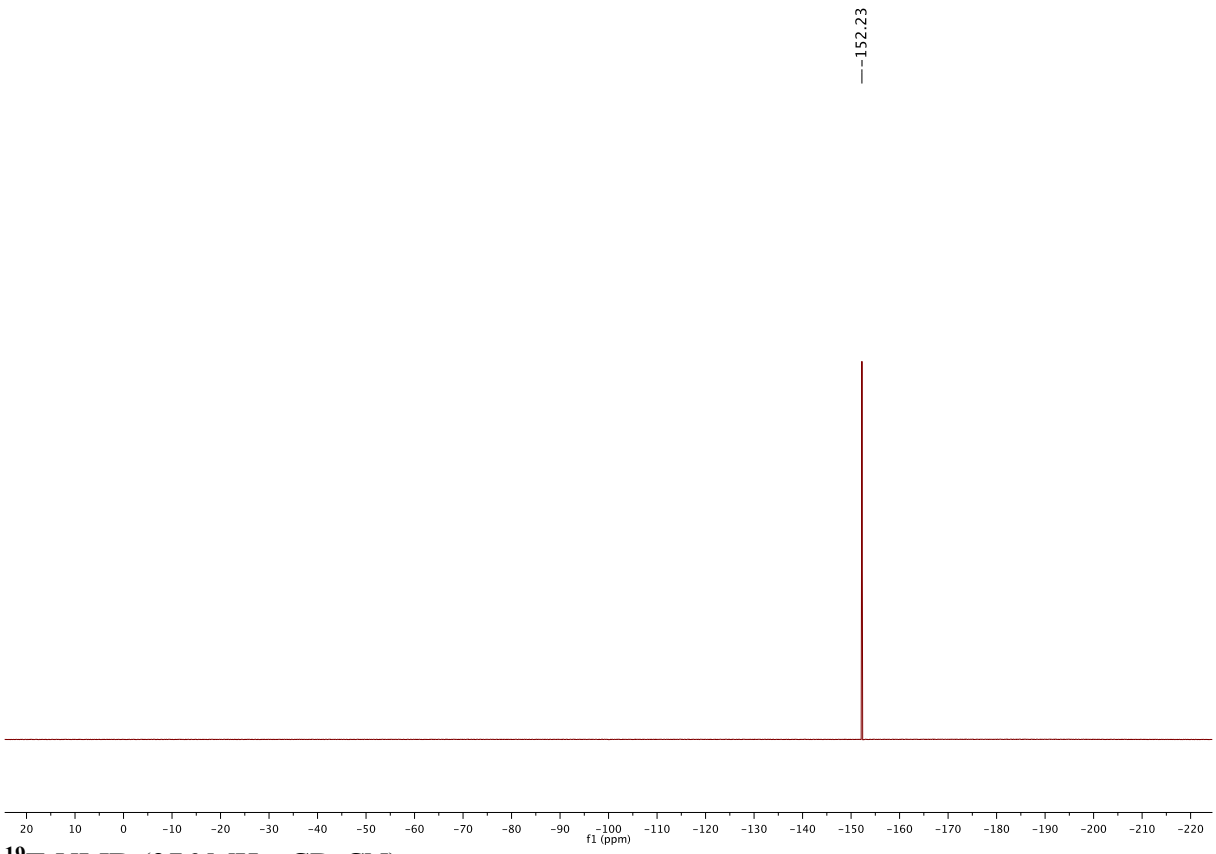
_N_-(3-((_tert_-butoxycarbonyl)amino)dihydrofuran-2(3_H_)-ylidene)-_N_-ethylethanaminium tetrafluoroborate (2.60)



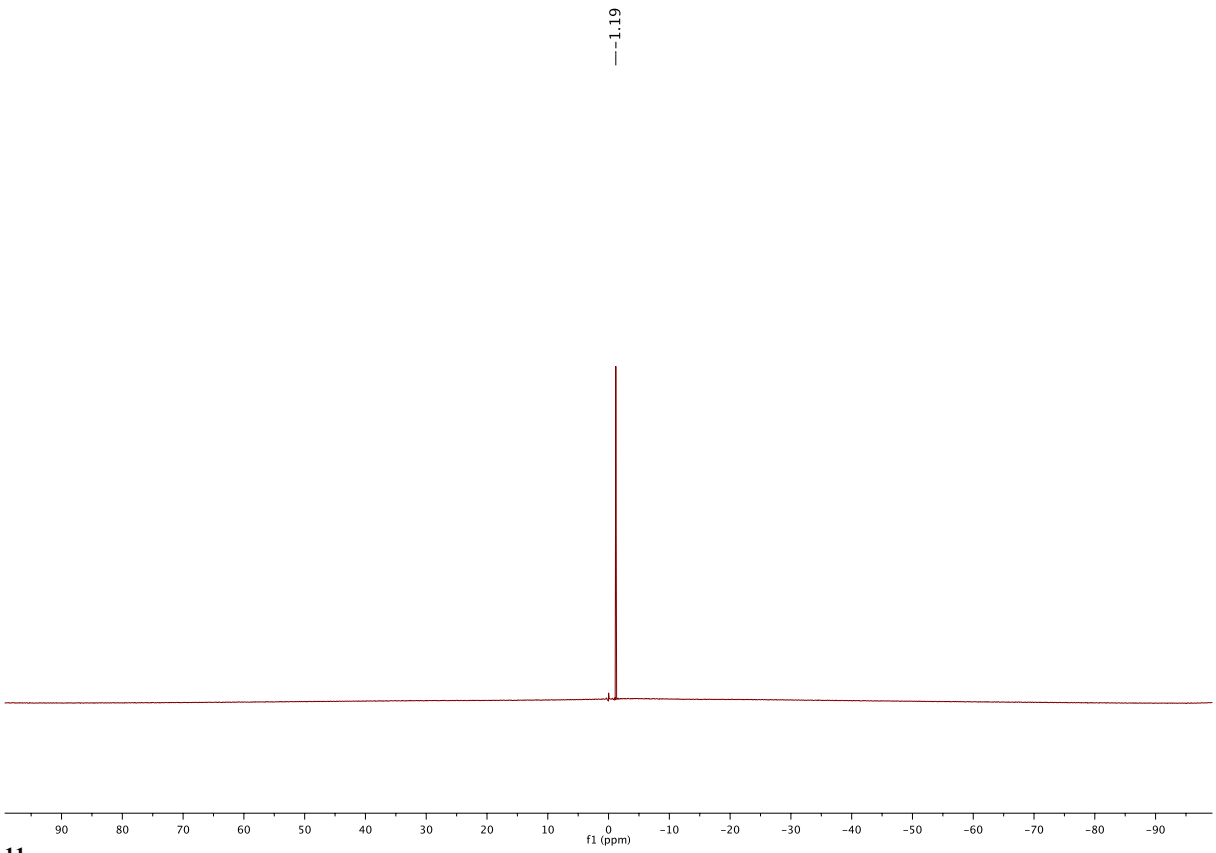
^{1}H-NMR (400 MHz, CD_3CN)



^{13}C-NMR (101 MHz, CD_3CN)

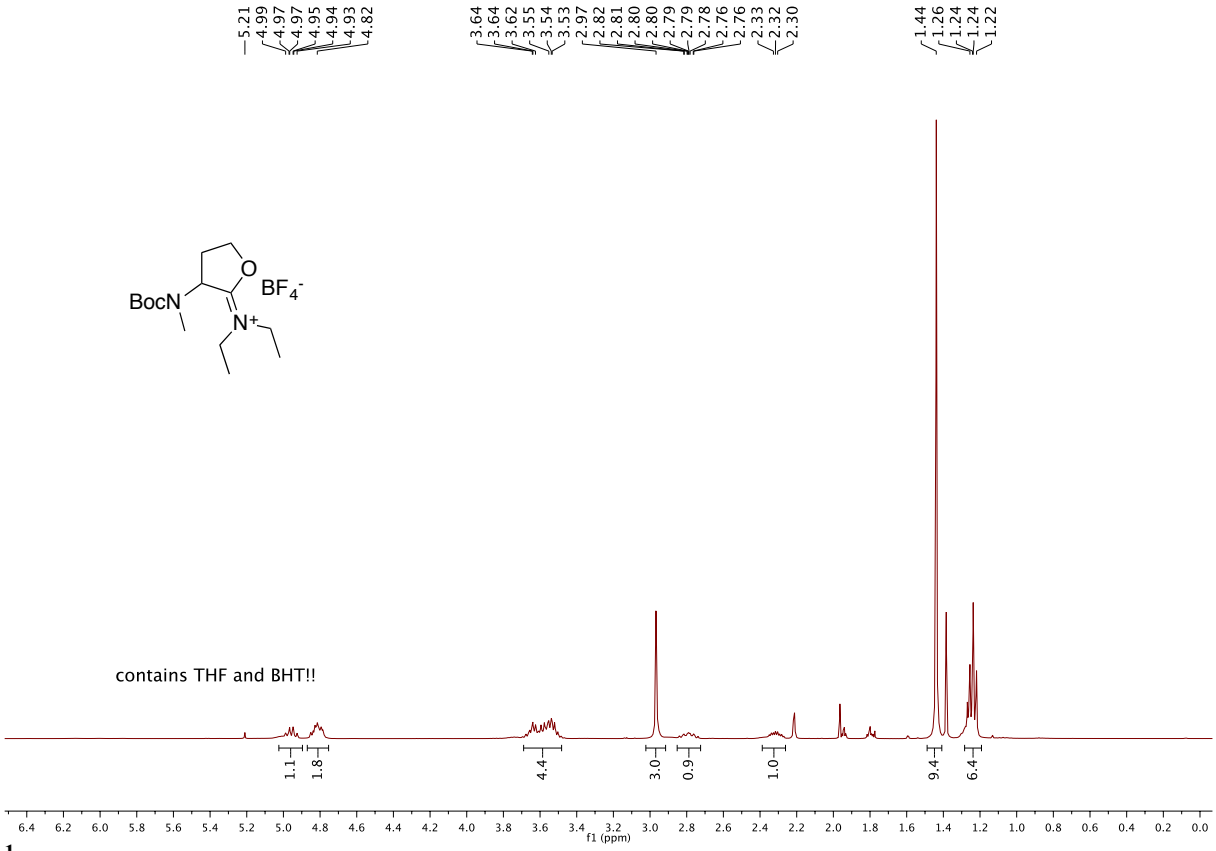


^{19}F-NMR (376 MHz, CD_3CN)



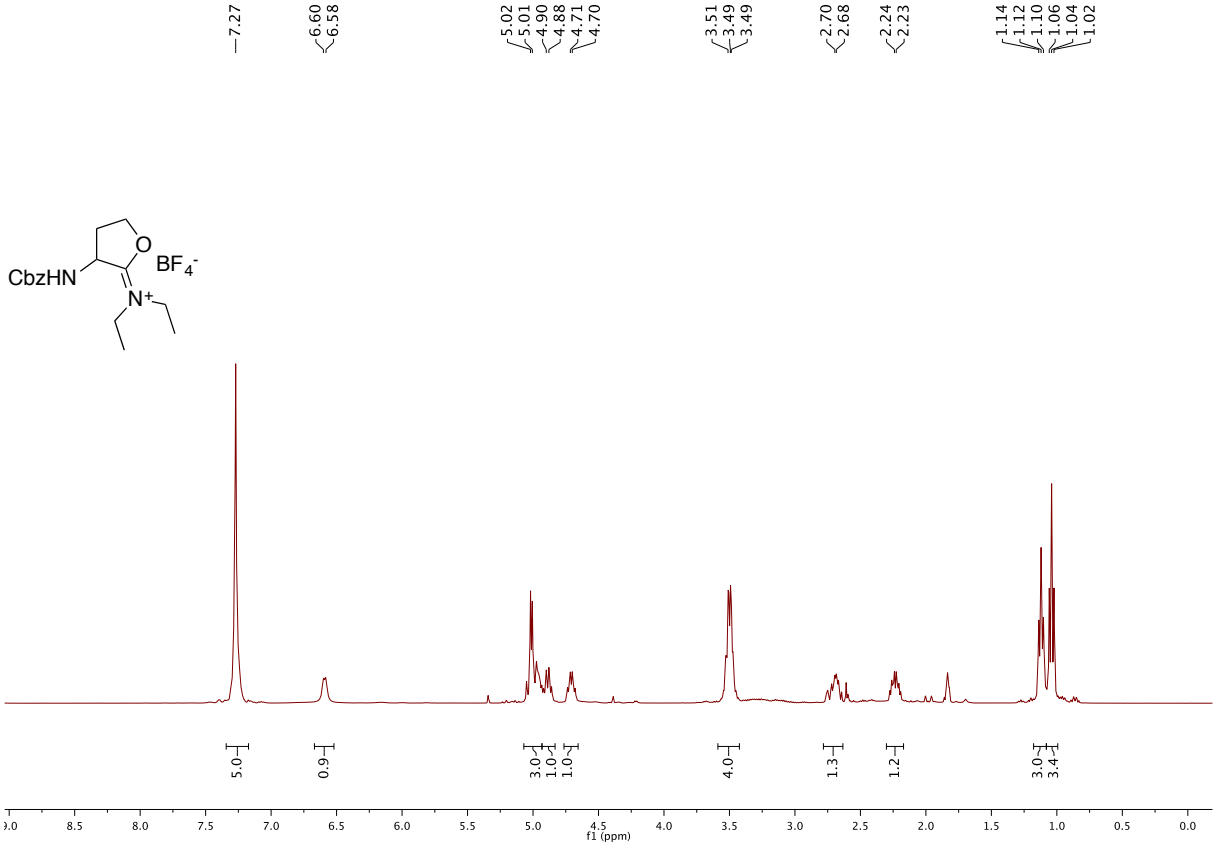
^{11}B-NMR (128 MHz, CD_3CN)

***N*-(3-((*tert*-butoxycarbonyl)(methyl)amino)dihydrofuran-2(3*H*)-ylidene)-*N*-ethylethanaminium tetrafluoroborate (2.61)**

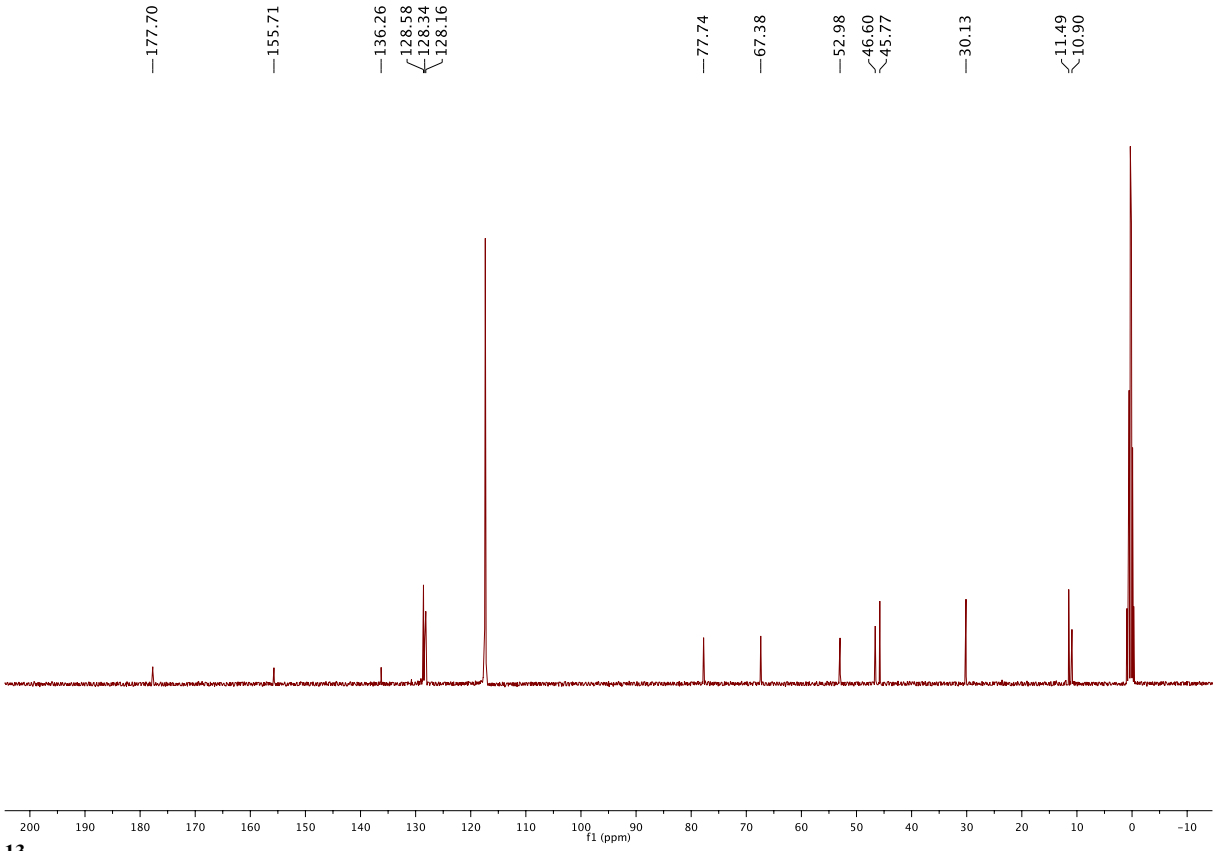


^{1}H-NMR (400 MHz, CD_3CN)

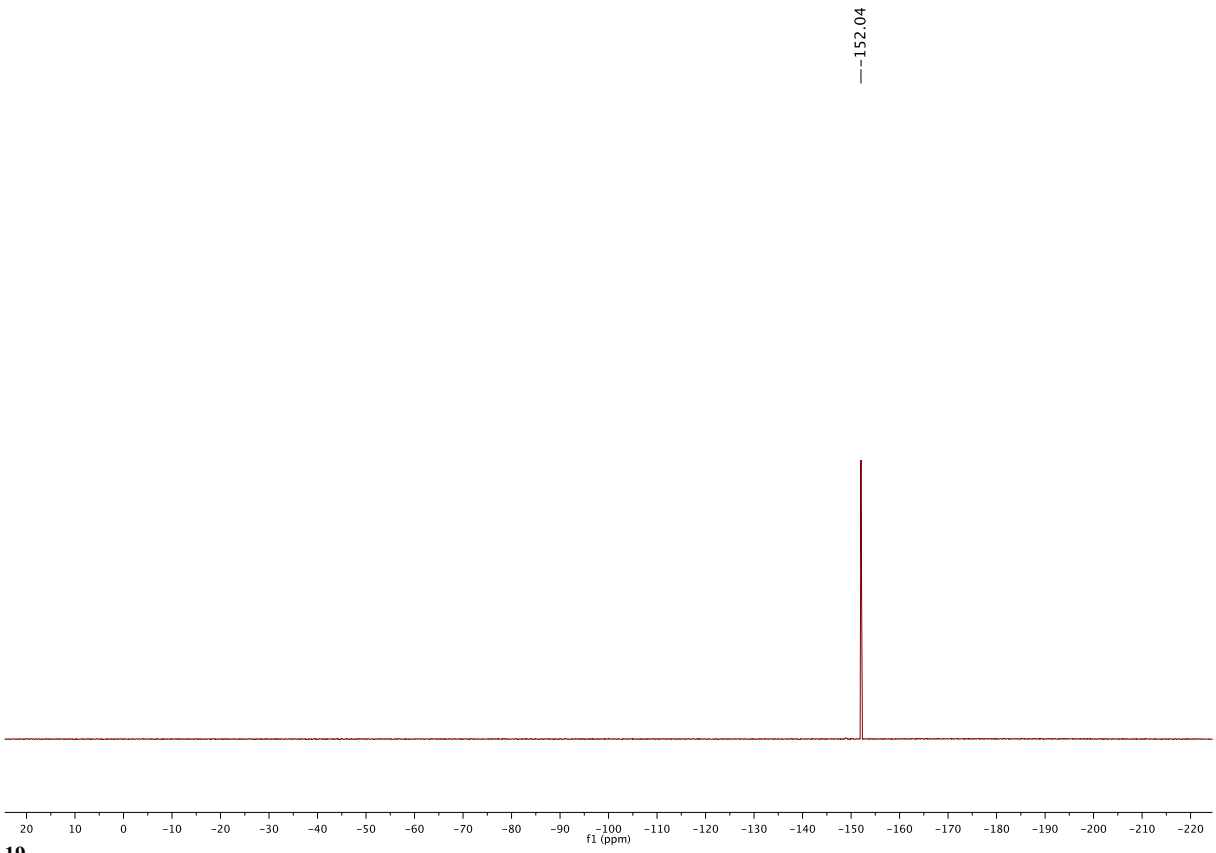
***N*-(3-(((benzyloxy)carbonyl)amino)dihydrofuran-2(3*H*)-ylidene)-*N*-ethylethanaminium tetrafluoroborate (2.62)**



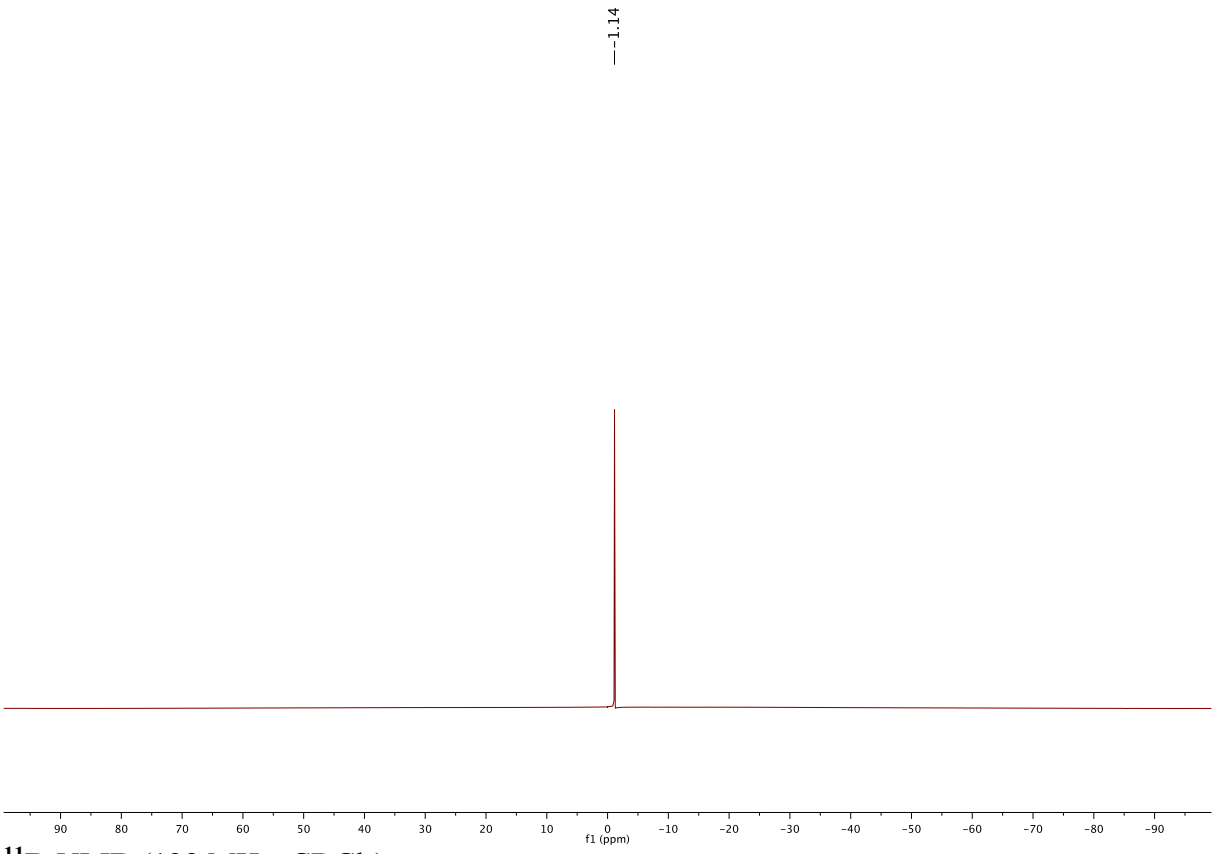
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

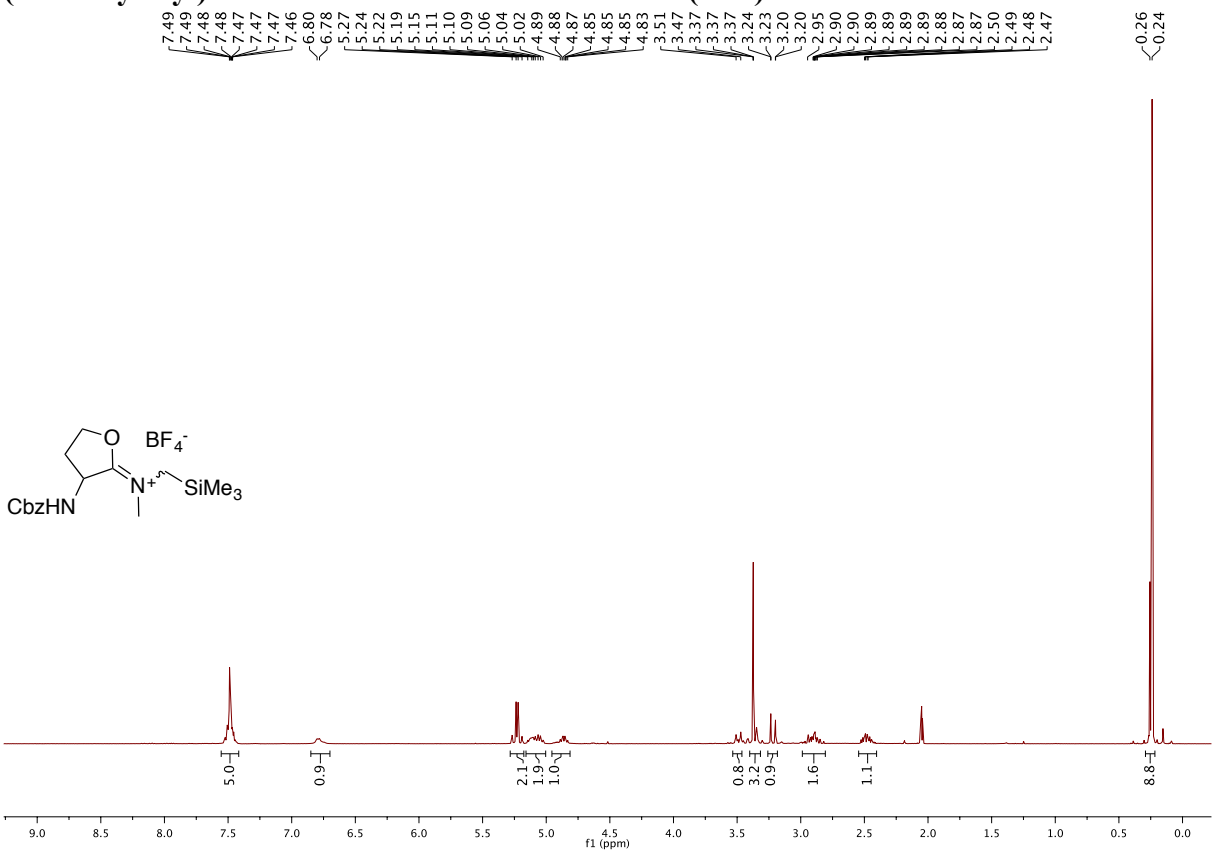


^{19}F-NMR (376 MHz, $CDCl_3$)

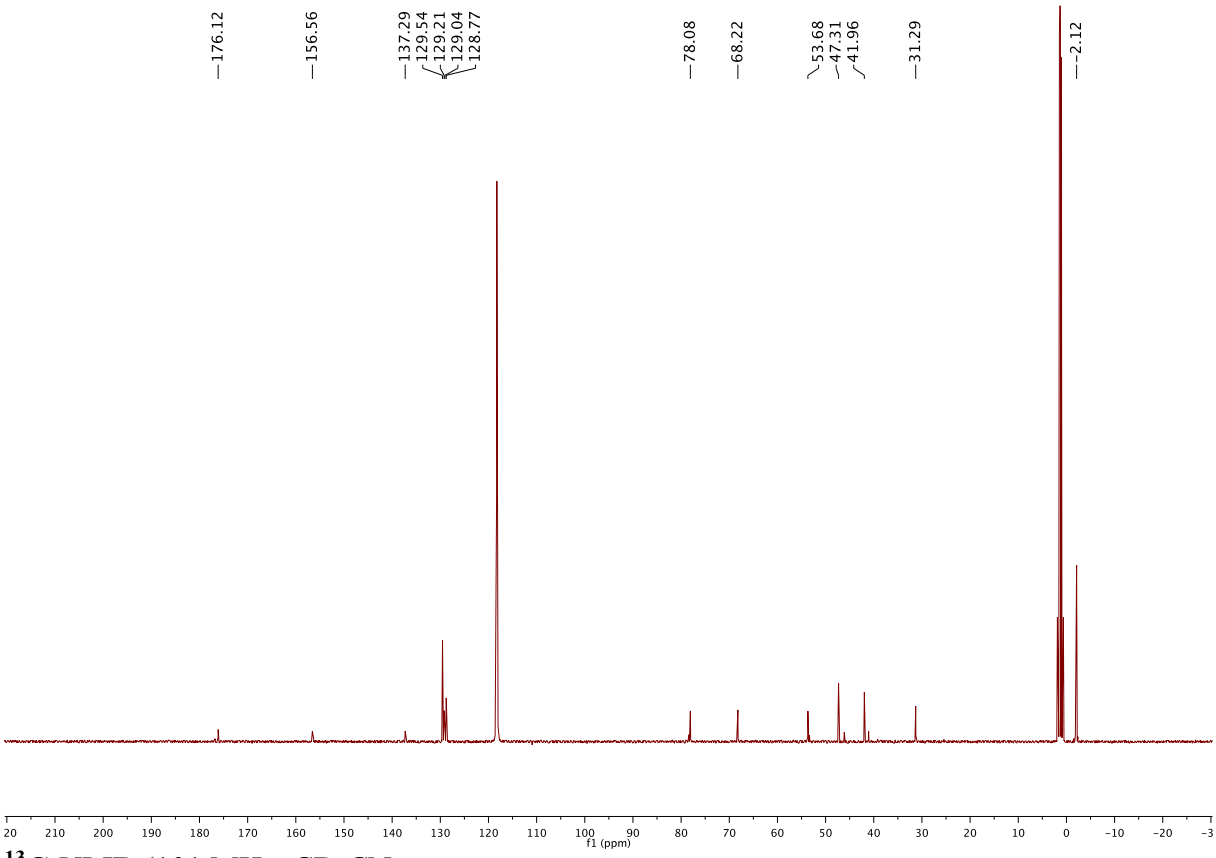


^{11}B-NMR (128 MHz, $CDCl_3$)

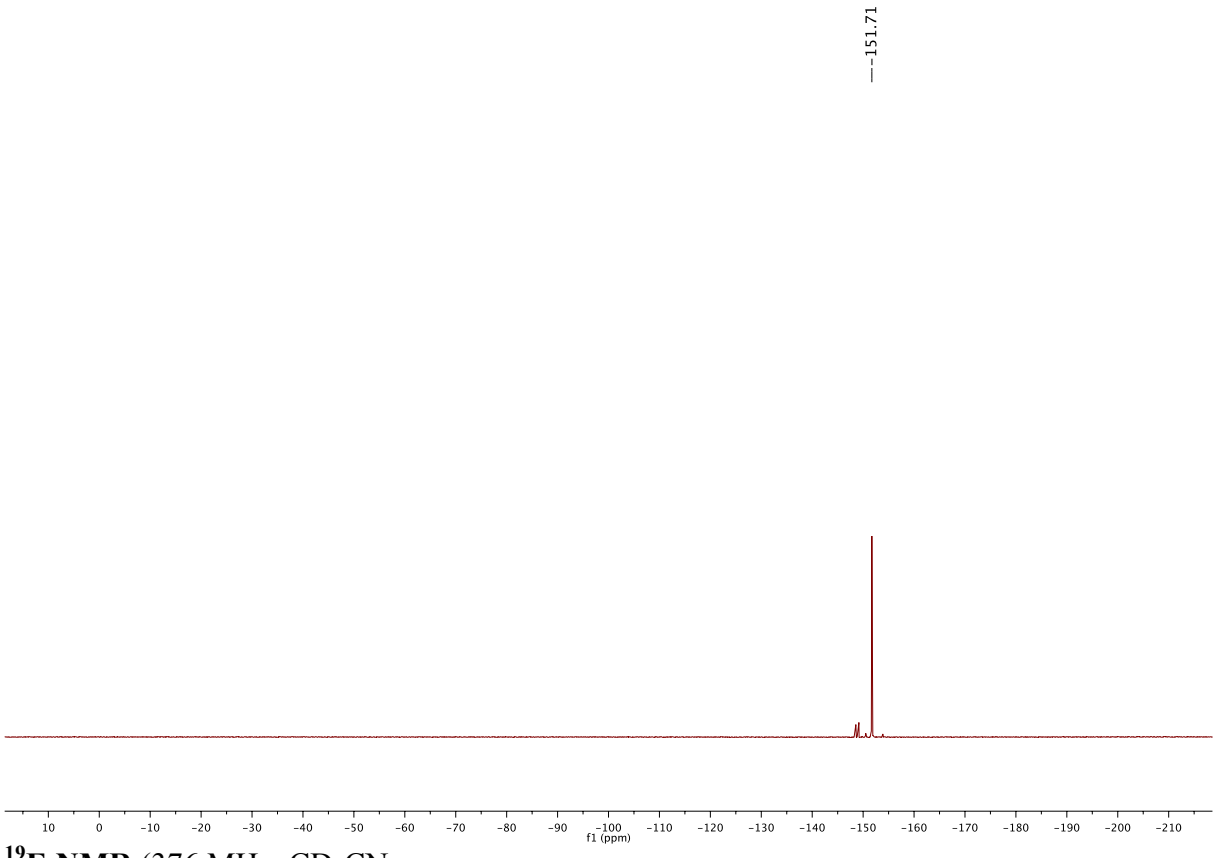
(*E,Z*)-*N*-(3-(((benzyloxy)carbonyl)amino)dihydrofuran-2(3H)-ylidene)-N-methyl-1-(trimethylsilyl)methanaminium tetrafluoroborate (2.77)



^{1}H-NMR (400 MHz, CD_3CN)

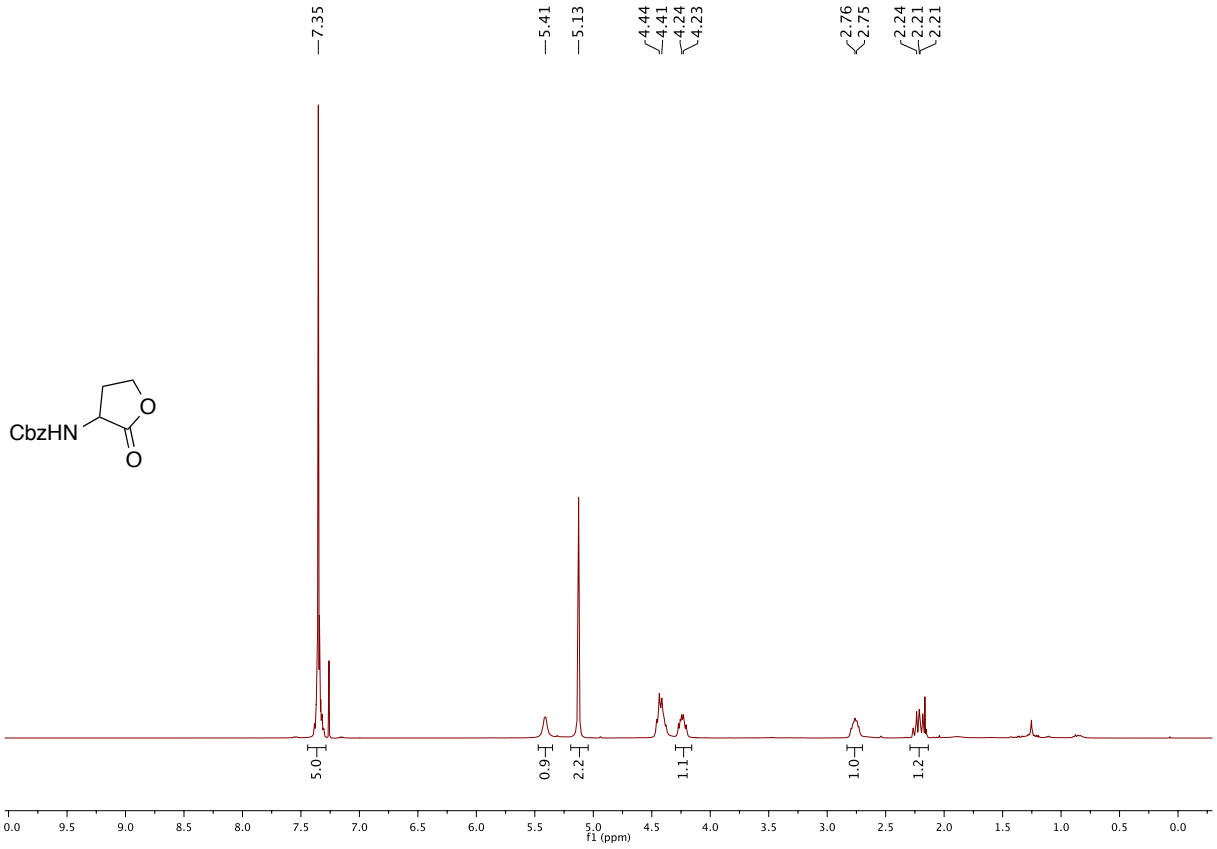


^{13}C-NMR (101 MHz, CD_3CN

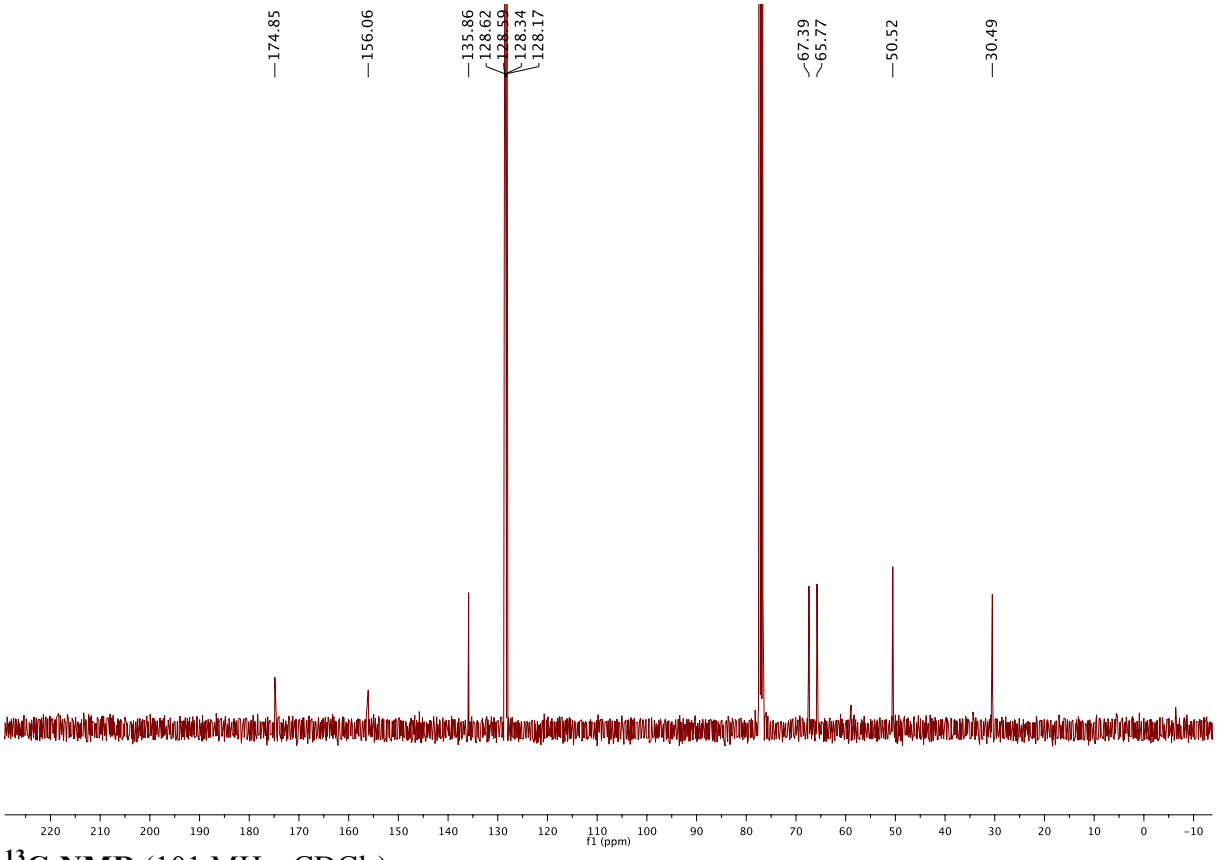


^{19}F-NMR (376 MHz, CD_3CN

benzyl (2-oxotetrahydrofuran-3-yl)carbamate (2.63)

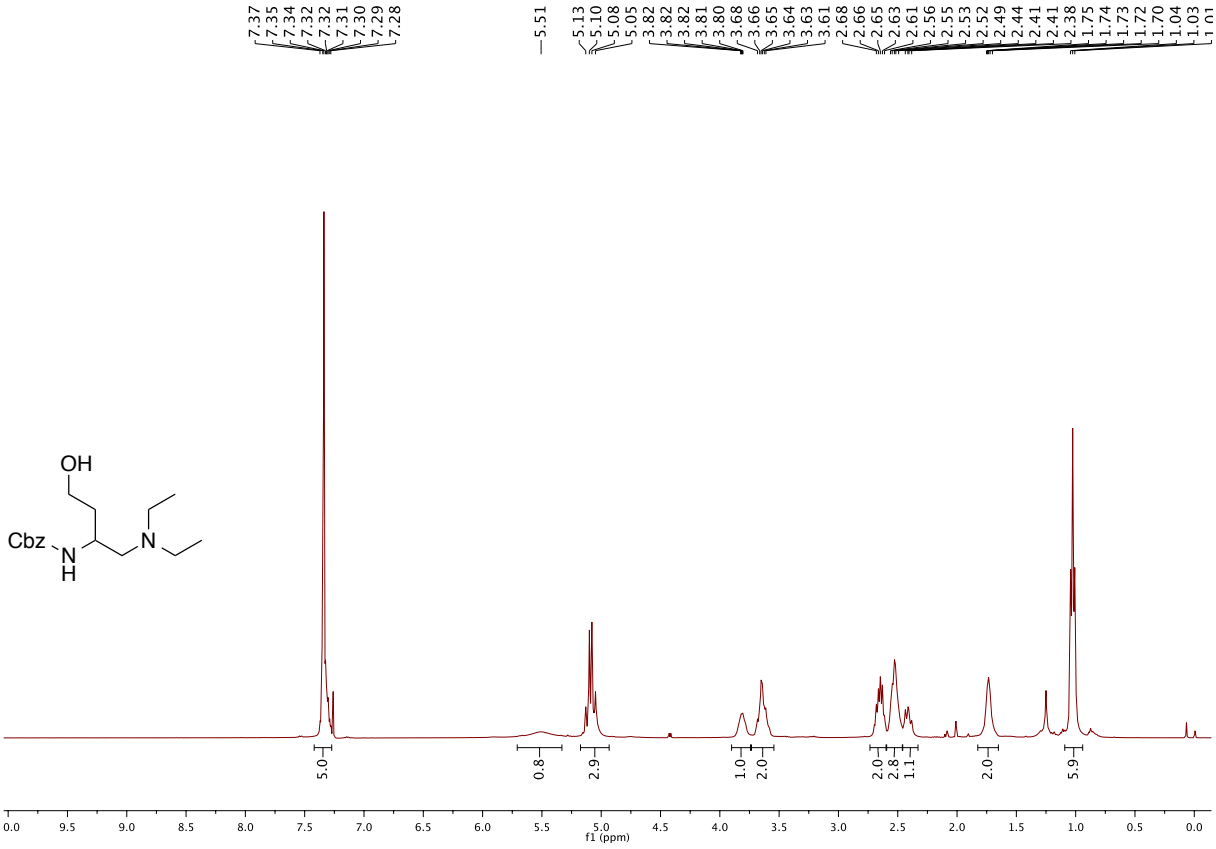


^{1}H-NMR (400 MHz, $CDCl_3$)

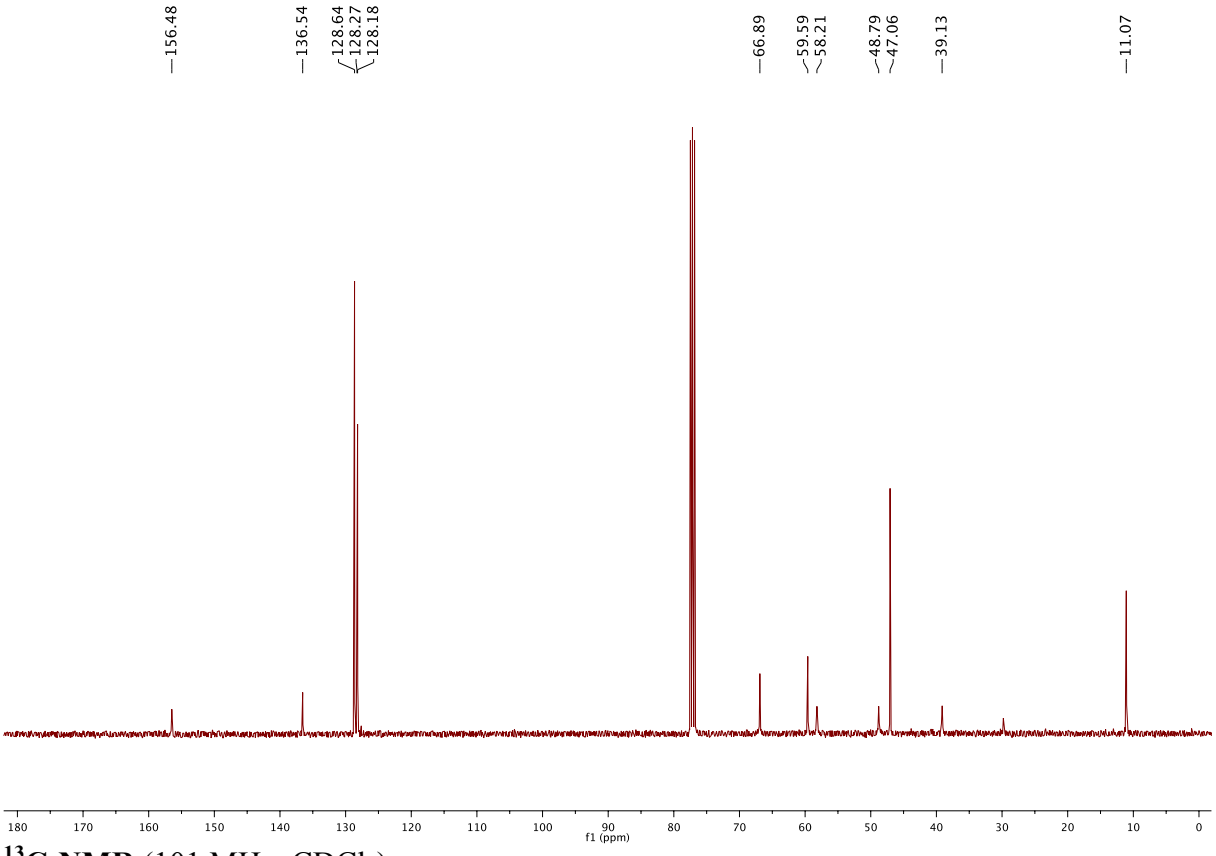


^{13}C-NMR (101 MHz, $CDCl_3$)

benzyl (1-(diethylamino)-4-hydroxybutan-2-yl)carbamate (2.64)

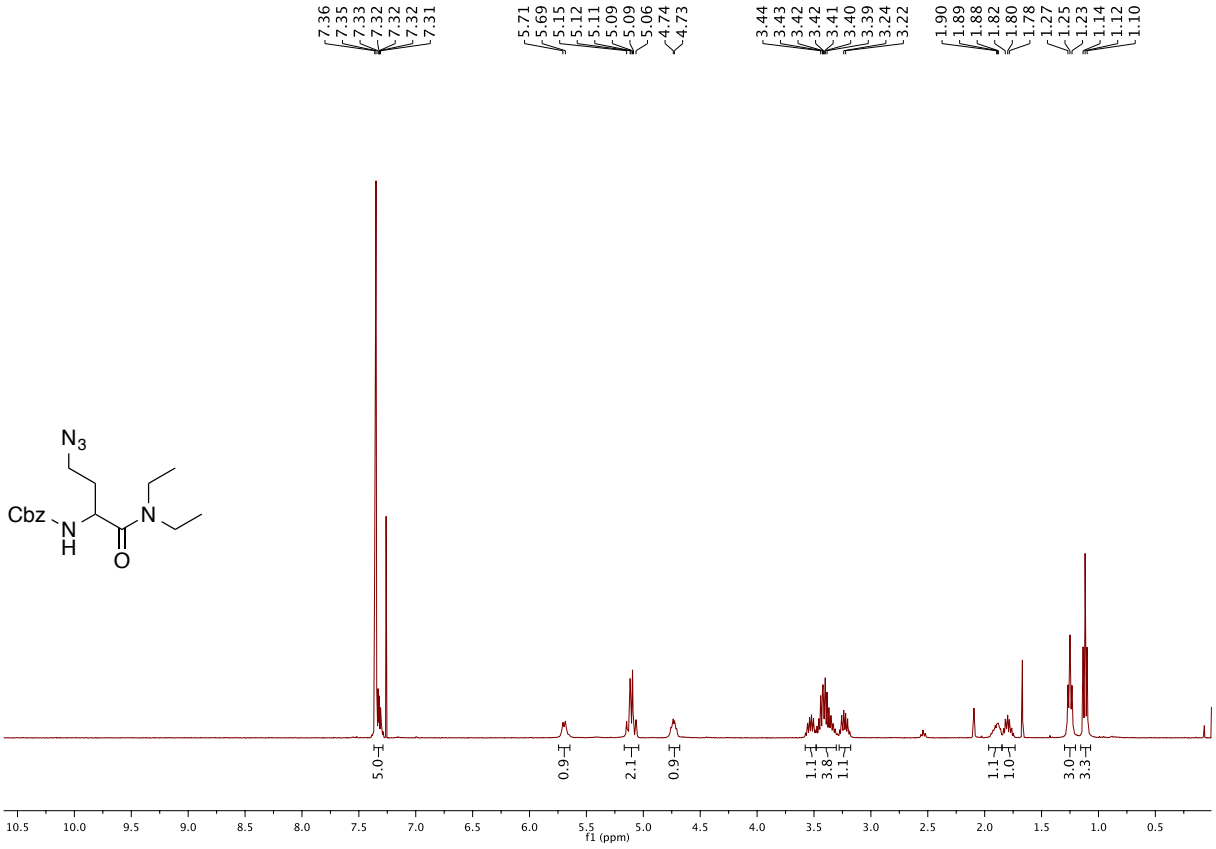


^{1}H-NMR (400 MHz, $CDCl_3$)

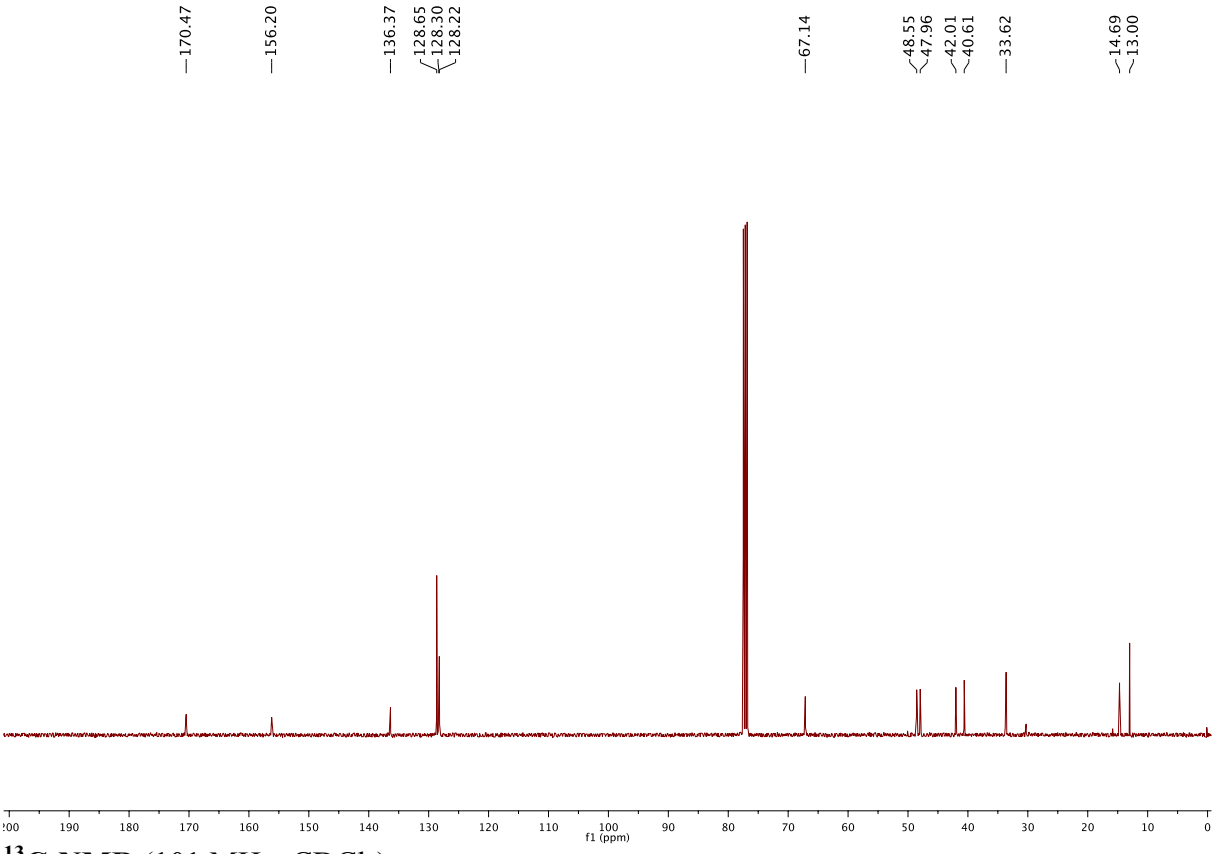


^{13}C-NMR (101 MHz, $CDCl_3$)

benzyl (4-azido-1-(diethylamino)-1-oxobutan-2-yl)carbamate (2.65)

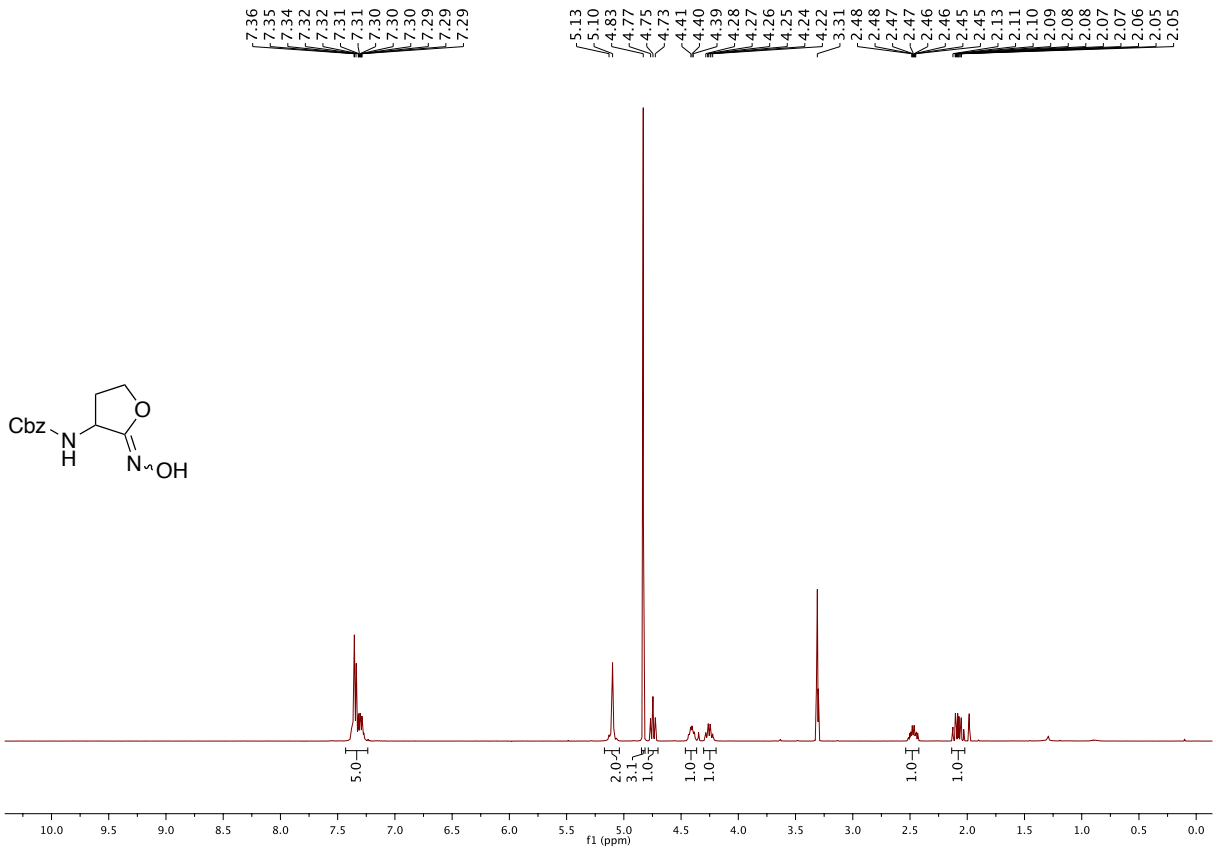


^{1}H-NMR (400 MHz, $CDCl_3$)

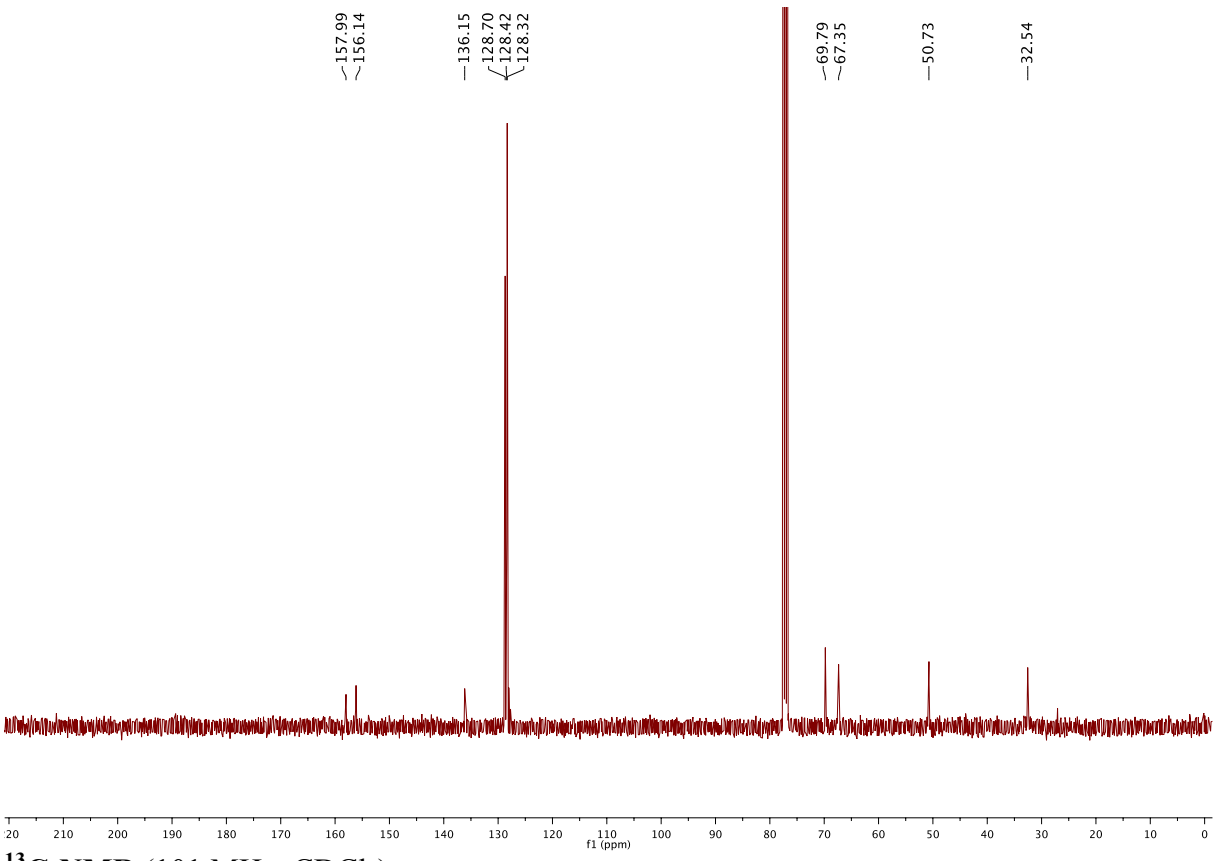


^{13}C-NMR (101 MHz, $CDCl_3$)

benzyl (2-(hydroxyimino)tetrahydrofuran-3-yl)carbamate (2.66)

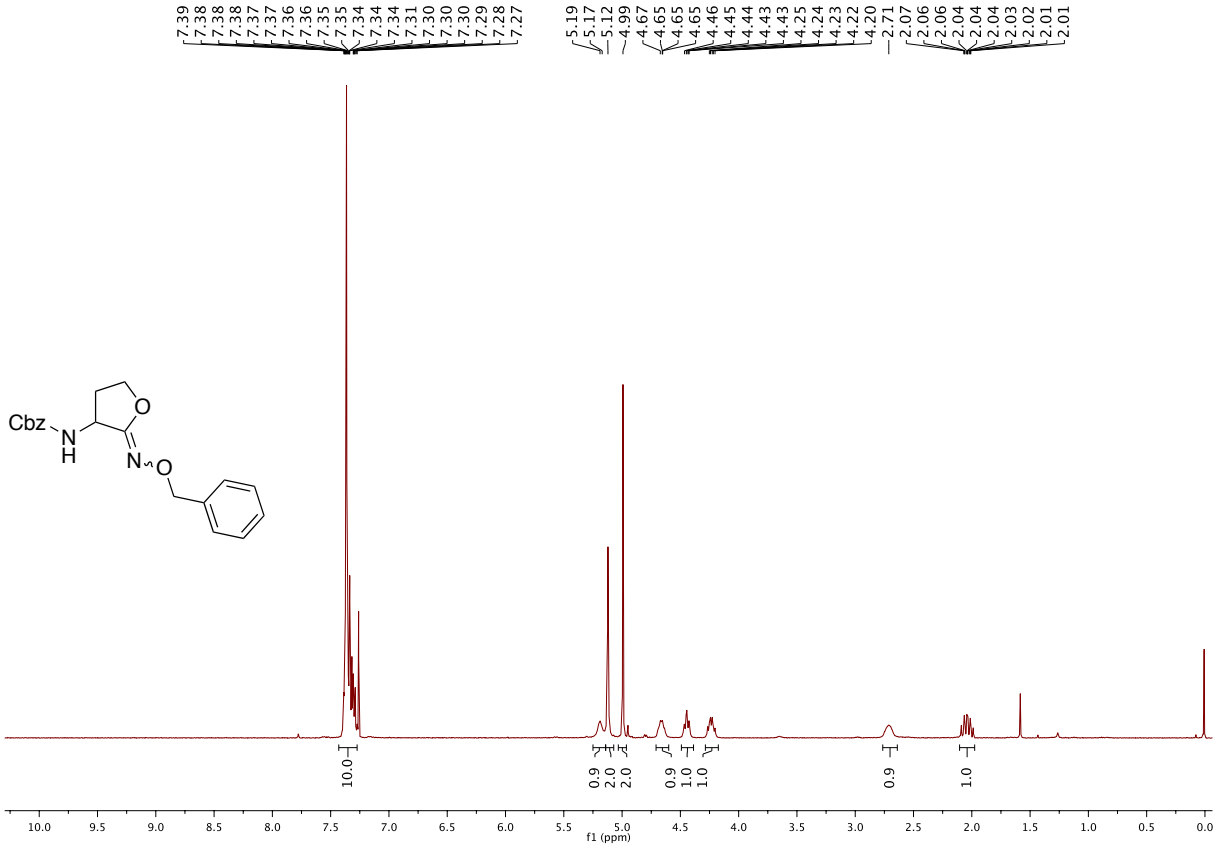


^{1}H-NMR (400 MHz, CD_3OD)

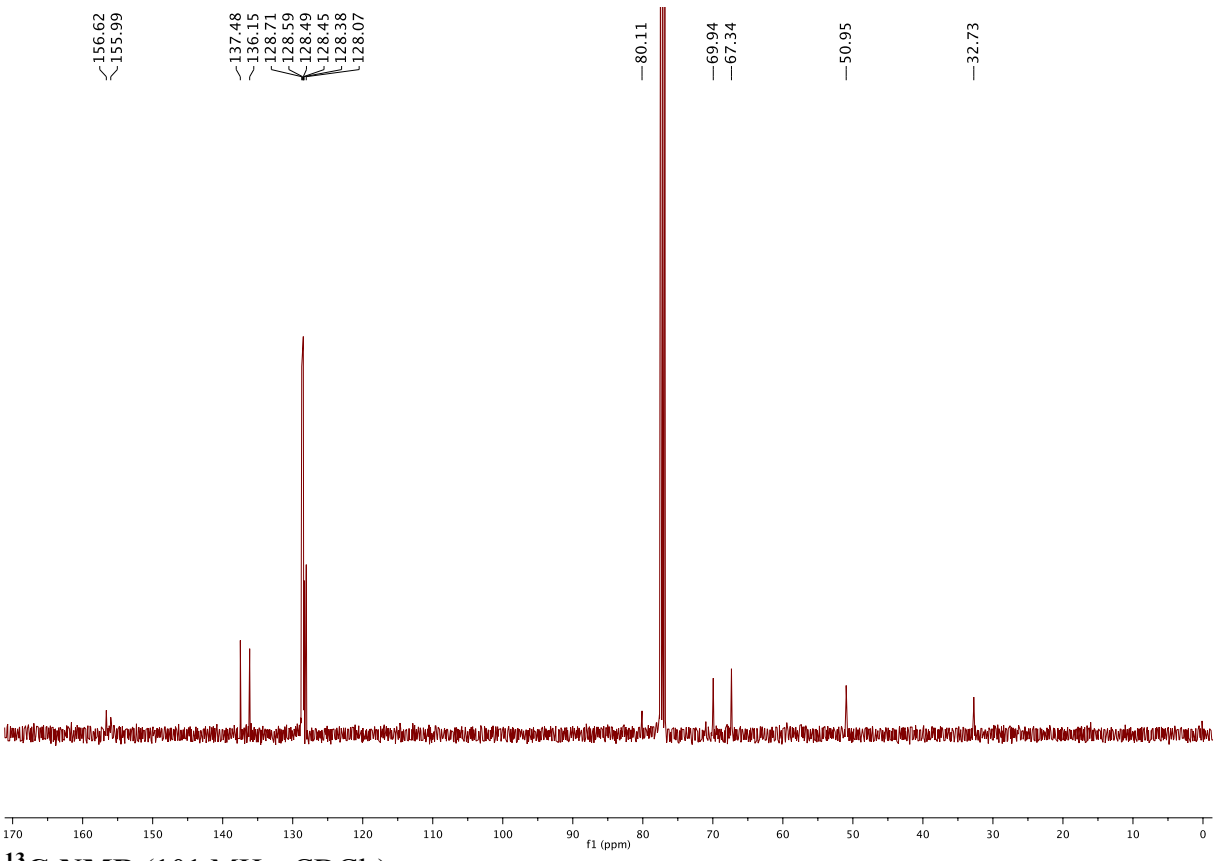


^{13}C-NMR (101 MHz, $CDCl_3$)

benzyl (2-((benzyloxy)imino)tetrahydrofuran-3-yl)carbamate (2.67)

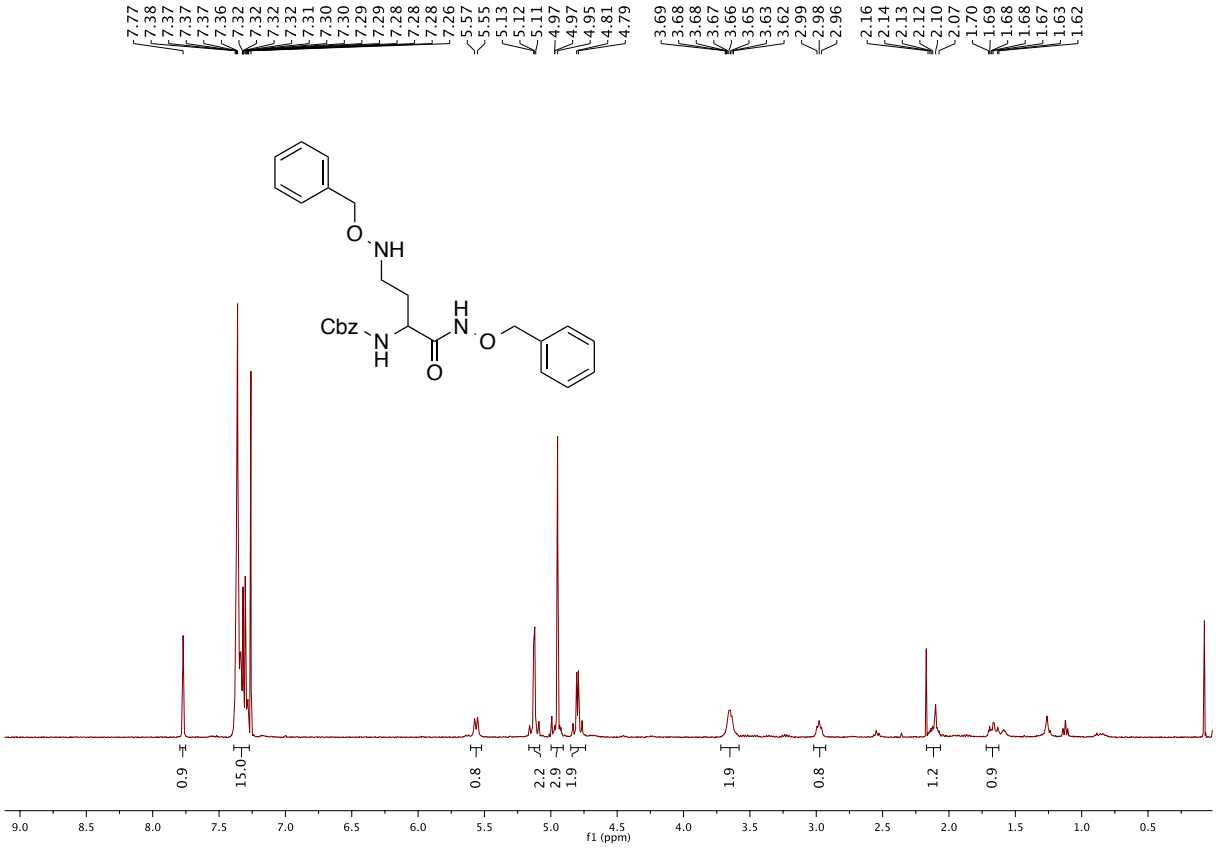


^{1}H-NMR (400 MHz, $CDCl_3$)

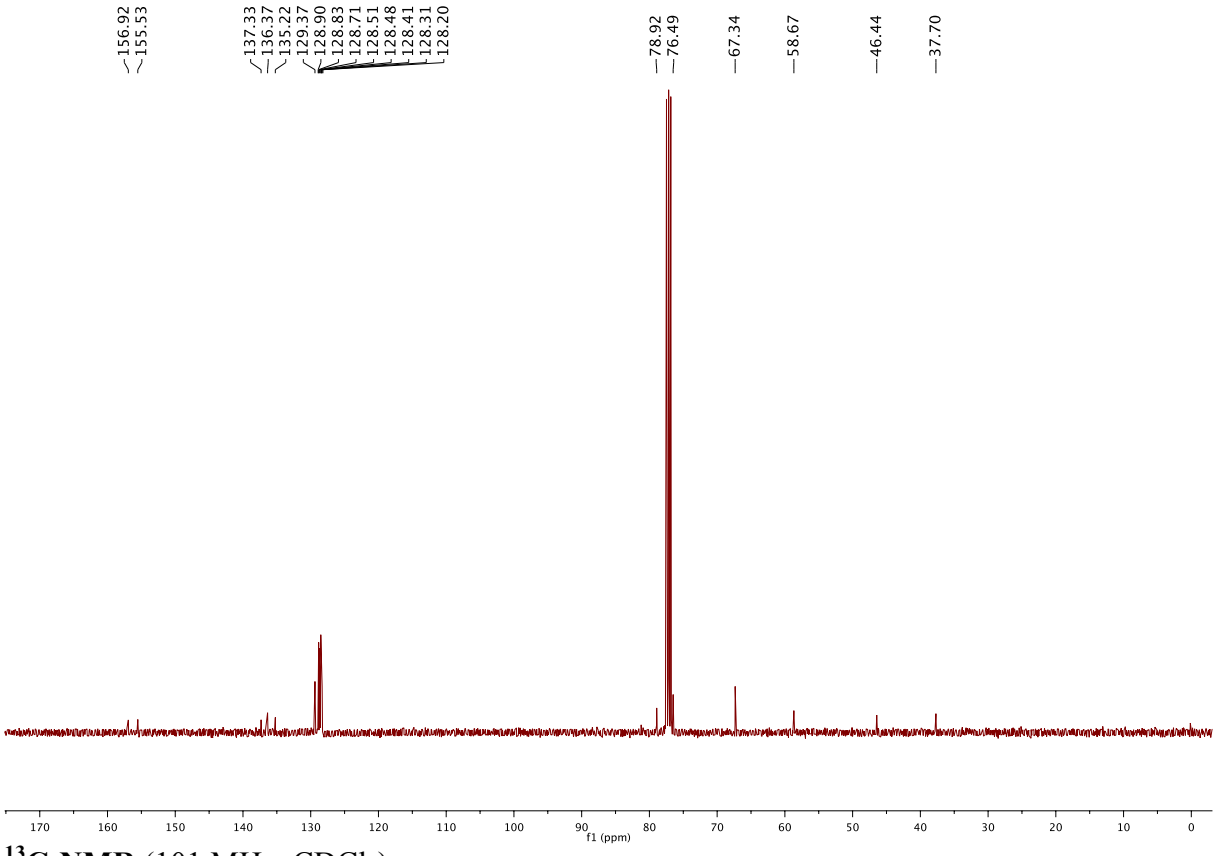


^{13}C-NMR (101 MHz, $CDCl_3$)

benzyl (4-oxo-1,10-diphenyl-2,9-dioxa-3,8-diazadecan-5-yl)carbamate (2.68)

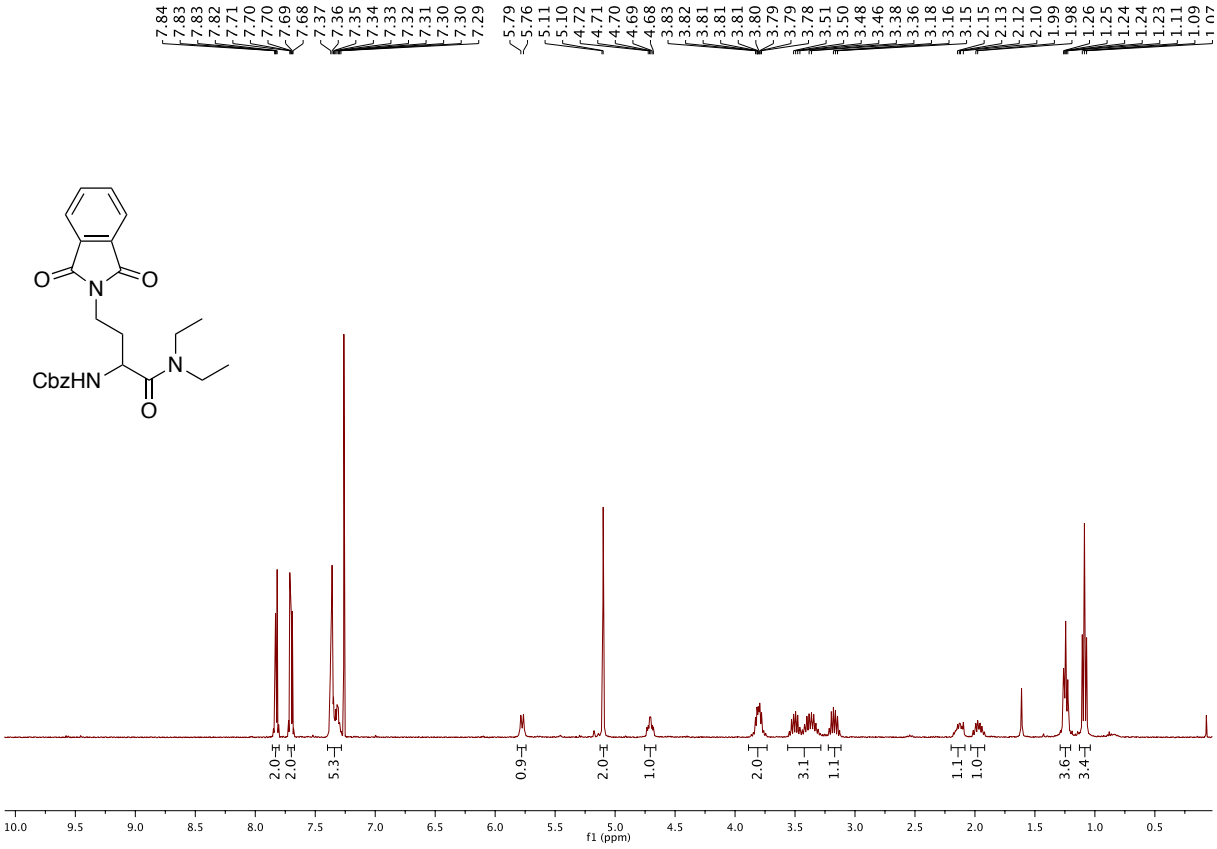


^{1}H-NMR (400 MHz, $CDCl_3$)

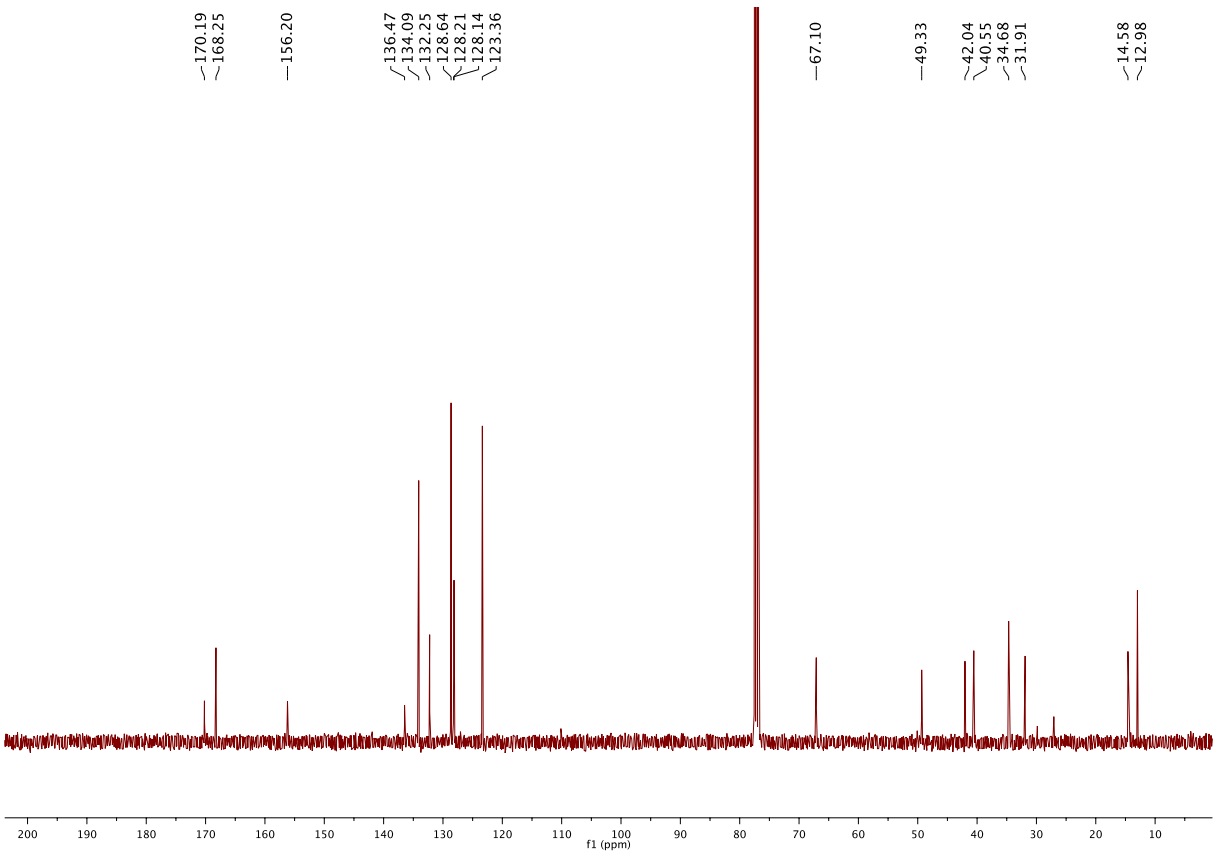


^{13}C-NMR (101 MHz, $CDCl_3$)

benzyl (1-(diethylamino)-4-(1,3-dioxoisoindolin-2-yl)-1-oxobutan-2-yl)carbamate (2.69)



^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

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Desweiteren bin ich meiner Familie, speziell meinen Eltern, unendlich dankbar für die grosse Unterstützung, ohne die all das gar nicht möglich gewesen wäre.

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