Syntheses of Taiwaniaquinoid and Icetexane Natural Products Based on Biogenetic Hypotheses

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auf Antrag von

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Basel, den 23. Juni 2015

Prof. Dr. Jörg Schibler
Dekan

Pour ma famille

"Dans les champs de l’observation le hasard ne favorise que les esprits préparés."

Louis Pasteur (1822-1895)

This PhD-Thesis is based on the following manuscripts:

Syntheses of Taiwaniaquinone F and Taiwaniaquinol A via an Unusual Remote C−H Functionalization, Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett.* **2013**, *15*, 1390−1393.

Divergent Syntheses of Icetexane Natural Products Based on Biogenetic Hypotheses, Thommen, C.; Gademann, K.

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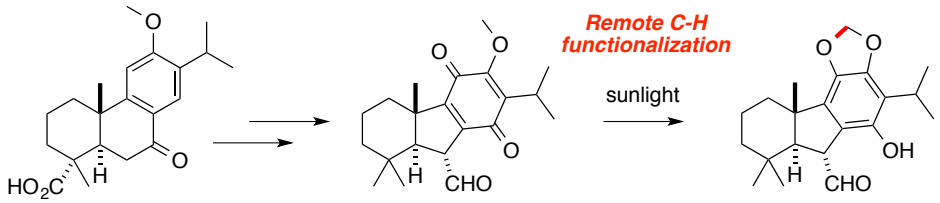
Abstract

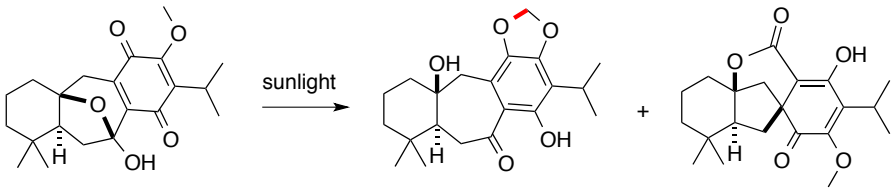
The syntheses of natural products based on biogenetic hypotheses have the potential not only for giving access to short, elegant and efficient synthetic routes, but also to shine light on how nature constructs these breathtaking structures. This work, divided in three experimentally interconnected chapters, will highlight the importance of this approach with the syntheses of taiwaniaquinoid and icetexane natural products.

A protecting-group-free route to (−)-taiwaniaquinone F based on a Wolff-rearrangement ring contraction and subsequent aromatic oxidation of a sugiol derivative was deviced following a proposed biogenetic pathway. In addition, the first synthesis of (+)-taiwaniaquinol A is reported *via* short time exposure of (−)-taiwaniaquinone F to sunlight triggering a remote C−H functionalization. The hypothesis that the biogenesis of several methylenedioxy bridged natural products could proceed *via* similar nonenzymatic mechanisms is presented.



(+)-sugiol methyl ether *(–)-taiwaniaquinone F* *(+)-taiwaniaquinol A*

A divergent synthesis of thirteen members of icetexane natural products based on a proposed biogenetic cationic ring expansion of a reduced carnosic acid derivative is described. Among these members, (+)-salvicanol, (−)-cyclocoulterone, (−)-coulterone, (−)-obtusinone D, (−)-obtusinone E, and (−)-euolutchuol E are synthesized for the first time. Following this approach, an additional support to our methylenedioxy biogenetic hypothesis is reported *via* the photolysis of (+)-komaroviquinone to (−)-cyclocoulterone and (+)-komarovispirone.



(+)-komaroviquinone ***(–)-cyclocoulterone*** ***(+)-komarovispirone***

Preliminary results towards the mechanistic elucidation of the discovered remote C−H activation are outlined. Photolysis of a model substrate shows the formation of the methylenedioxy moiety for the first time on a non-natural quinone. Preliminary evidence that account for the formation of biradical species are given.

List of abbreviations, acronyms and symbols

Ac	acetyl
AcOH	acetic acid
AD-mix	asymmetric dihydroxylation-mix
AIBN	2,2′-azo*bis*(2-methylpropionitrile)
aq.	aqueous
brsm	based on recovered starting material
Boc	*tert*-butyloxycarbonyl
Bu	butyl
°C	degrees centigrade
c	concentration
C#	carbon number #
C+	carbocation
CAN	ceric ammonium nitrate
CAM	ceric ammonium molybdate
cat.	catalytic
cyt.	cytochrome
δ	chemical shift
d	doublet
D	deuterium
dec.	decomposition
d.r.	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DMS	dimethyl sulfide

EI	electron impact ionization
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eq.	equivalent
FTIR	Fourier transform infrared spectroscopy
g	gram(s)
h	hour(s)
HMDS	hexamethyl disilazane
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz (s^{-1})
IBX	2-iodoxybenzoic acid
IC_{50}	50% inhibition concentration
J	coupling constant
L	liter(s)
LDA	lithium diisopropylamide
M	molarity (mol./L^{-1})
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
m_p	melting point
Me	methyl
MeOH	methanol
MOMCl	chloromethyl methyl ether
Ms	mesyl
min	minute(s)
MS	mass spectroscopy
n.d.	not determined
NCS	*N*-chloro-succin-imide
NMO	*N*-methylmorpholine *N*-oxide

NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
OMe	methoxy
Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
quant.	quantitative
rt	room temperature
R_f	retention factor
s	singlet
sat.	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography
Ts	tosyl
UV	ultraviolet
ν	wavenumber

1. Introduction

1.1. Natural products

"... everything that living things do can be understood in terms of the jiggling and wiggling of atoms".[1] This statement of Feynman in 1963, shortly after the discovery of the double-helical structure of DNA, emphasizes how life can be described in terms of the structure and the reactivity of the natural products constituting the living organisms.

Metabolites are small organic compounds that derive from the metabolism, the chemical reactions taking place in living organisms. These organisms need to transform organic compounds from the environment in crucial molecules necessary for their survival, to grow, to develop normally and for reproducing.[2] These reactions are performed by a regulated set of enzymes, which provide the organism with various metabolites (*e.g.* sugars, fatty acids, amino acids, and nucleic acids). Energy precursors of adenosine triphosphate (ATP) and building blocks for the construction of tissues are provided for this purpose. Not all organisms have the same ability to transform and synthesize primary metabolites equally. For instance, plants are very efficient in synthetizing primary metabolites from inorganic nutrients (soil) *via* photosynthesis.[3] Animals rely on food degradation pathways to supply their organism with primary metabolites, whereas the rest is synthesized. However, most of these processes are common for the majority of organisms.

In contrast to these life-essential metabolites, another class, which is not required for the organism survival, is called secondary metabolites. However, these compounds are very important for the prosperity of the organism in its ecological context. The advantage of the produced secondary metabolites is not always known,

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[1] Feynman, R. P.; Leighton, R. B.; Sands, M. *The Feynman Lectures on Physics* Addison Wesley, Reading, **1963**.

[2] Dewick, P. M. "Secondary Metabolism: The Building Blocks and Construction Mechanism." *Medicinal Natural Products a Biosynthetic Approach*. 2nd ed. Chichester, West Sussex, England: Wiley, 2002. 7-8. Print.

[3] Smith, A. "Metabolism." *Plant Biology*, Garland Science: 2009. 167-299. Free download from http://www.garlandscience.com/res/pdf/9780815340256_ch04.pdf

but it can be assumed that their synthesis confers benefit to the producers. Indeed, these metabolites can endorse various roles, such as repellant, attractant, defense chemical, and pigment, rendering the organism more competitive for the natural selection. Interacting with all types of biological targets, such as proteins, nucleotides and membranes of multiple organisms, the immense variety of these organic compounds is consequently a major source of pharmacologically active ingredients. Significantly less distributed in nature than their primary congeners, secondary metabolites are usually referred to as natural products (despite the fact that primary metabolites are natural product as well). As a matter of fact, natural products are only found in specific organisms or family of organisms and are even individually regulated depending on the environmental circumstances. For instance, carnosic acid was found in the leaves of *Rosemarinus officinalis* in highly variable amounts depending on the leave maturation, the season, and the growing origins (wild or cultivated).[4]

Terpenoids belong to one of the largest family of natural products. A linear presursor of terpenoids is geranyl pyrophosphate (GPP, **1.1**, Scheme 1.1), biosynthetically obtained by a transferase mediated condensation of the activated monomers isopentenyl pyrophosphate (IPP, **1.2**) and its isomer dimethylallyl pyrophosphate (DMAPP, **1.3**). These building blocks originate from the primary metabolite acetyl-coenzyme A (AcSCoA, **1.4**).[5] Cyclization of GPP (**1.1**), mediated by a cyclase, leads to limonene (**1.5**), a precursor of monoterpenoids (C_{10}). Two successive condensations of IPP (**1.1**) lead to the synthesis of farnesyl pyrophosphate (FPP, **1.6**) and geranylgeranyl pyrophosphate (GGPP, **1.7**). Cyclization of **1.6** and **1.7** results in sesquiterpenoids (C_{15}) such as germacrene A (**1.8**) and diterpenoids (C_{20}) like abietadiene (**1.9**). Furthermore, coupling of two FPP (**1.6**) and two GGPP (**1.7**) provides the linear squalene (**1.10**) and lycopene (**1.11**), respectively, which, after cyclization, afford trideterpenoids (C_{30}) such as hopene (**1.12**) and tetraterpenoids (C_{40}) such as β−carotene. Additional condensation reactions allow the formation of polymers such as latex.

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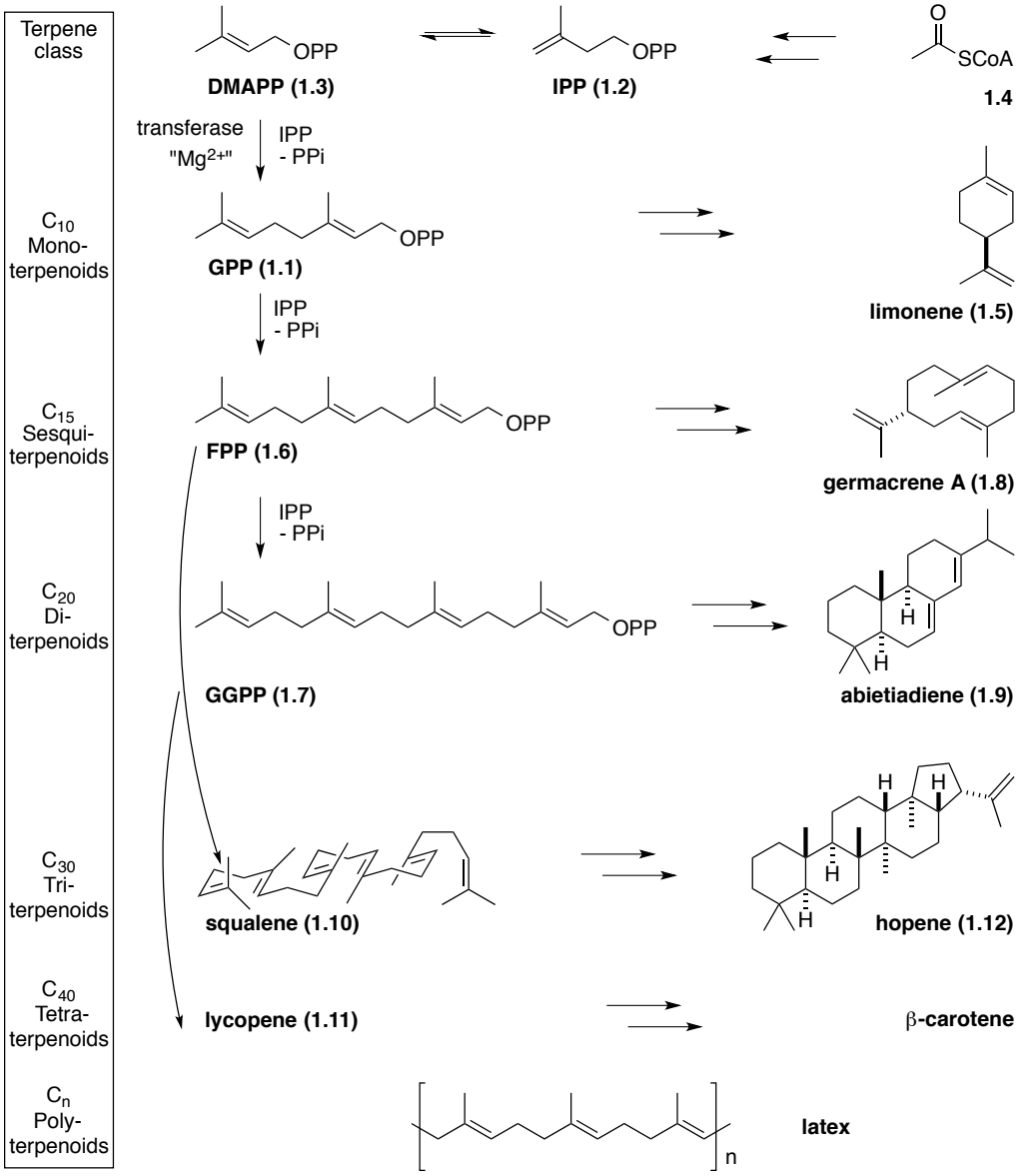
[4] Hidalgo, P. J.; Ubera, J. L.; Tena, M. L.; Valcárcel, M. *J. Agric. Food Chem.* **1998**, *46*, 2624−2627.



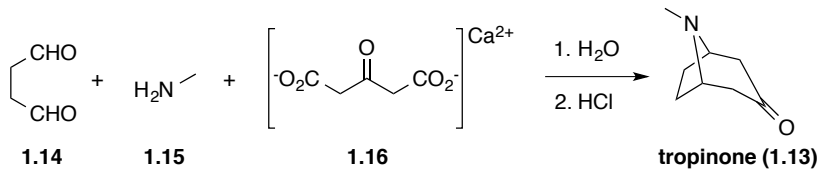
Scheme 1.1: *Biosynthetic overview of terpenoids*[5]

1.2. Syntheses based on biogenetic hypotheses

In admiration of the grandeur of the biosynthesis of various natural products, chemists became interested in mimicking these routes to access the synthesis of several natural products belonging to the same family with elegance and efficiency.[6] In 1917, Robinson invented the concept of biomimetic synthesis with the synthesis of

[5] Review : Ajikumar, P. K.; Tyo, K.; Carlsen, S.; Mucha, O.; Phon, T. H.; Stephanopoulos, G. *Mol. Pharmaceutics* **2008**, *5*, 167−190.
[6] Skyler, D.; Heathcock, C. H. *Org. Lett.* **2001**, *3*, 4323−4324.

tropinone (**1.13**) *via* a one-pot double Mannich reaction of succinaldehyde (**1.14**), methylamine (**1.15**) and calcium acetonedicarboxylate (**1.16**).[7]



Scheme 1.2: *Robinson's synthesis of tropinone (**1.13**).*[7]

The interest in this topic has dramatically increased in the scientific community over the last 15 years. This trend can be illustrated by the rising number of publications containing the concept "biomimetic synthesis" (Figure 1.1).[8]

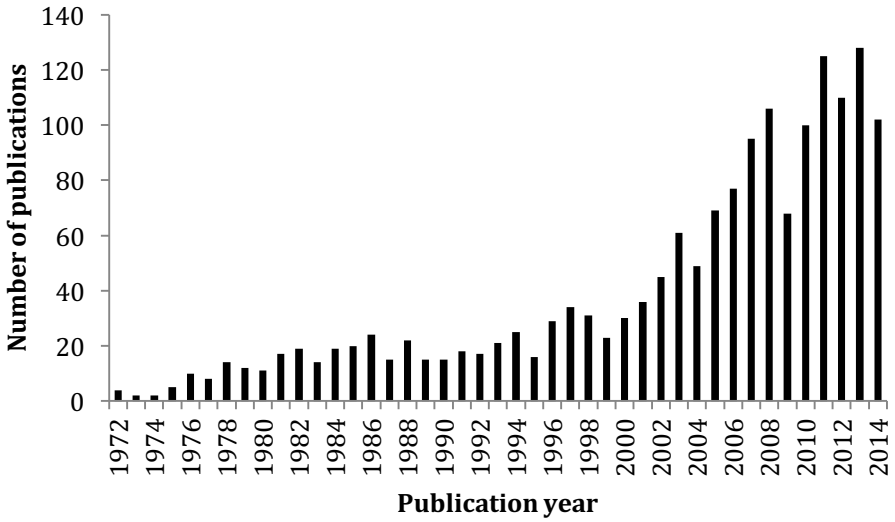


Figure 1.1: *Analysis reference search by Research Topic on SciFinder® (19/05/15) using the entry: "biomimetic synthesis".*

A reaction or a sequence of reactions is qualified as biomimetic when it mimics a proposed biosynthetic pathway.[9] This definition, which is still used nowadays, can be problematic if the corresponding biomimetic reaction is based on a hypothetical biogenetic route. For example, if two successful biomimetic syntheses of

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[7] R. Robinson, *J. Chem. Soc.* **1917**, *111*, 762−768.
[8] "Biomimetic Organic Synthesis: An Introduction." *Biomimetic Organic Synthesis* Ed. Erwan Poupon and Bastien Nay. Vol. 1. Weinheim: Wiley-VCH, 2011. XXIII-XXIV. Print.
[9] Van Tamelen, E. E. *Fortchr. Chem. Org. Naturst.* **1961**, *19*, 242−290.

a natural product from the same organism are based on two distinct biosynthetic hypotheses, at least one of them does not mimic what nature actually does. Both metabolic pathways are indeed possible for the same natural product, however, not in the same organism. For instance, the biosynthesis of IPP (**1.2**) from AcSCoA (**1.4**) can be achieved *via* the so-called mevalonic acid pathway (*e.g.* in animals) and the non-mevalonic acid pathway (*e.g.* in green algea).[10] This problematic was exemplified by a cause célèbre in this field: the biosynthesis of the polyether monensin (**1.17**, Scheme 1.4).[10,11] Initially, Westley and co-workers suggested that a multi-epoxidation of polyalkene **1.18** would generate the tris-epoxide **1.19**, which upon acidic conditions would furnish **1.17** *via* a polyepoxide opening cascade (Scheme 1.3, **A**).[12] Alternatively, Basak and Towne proposed ten years later that a *syn*-oxidative polycyclization of acetal **1.20** mediated by a cytochrome P450 would furnish monensin (**1.17**, Scheme 1.3, **B**).[13] Formation of the hemiacetal-bound oxo metallate **1.21** followed by a [2+2] cycloaddition with the next double bond would generate the metallaoxetane **1.22**. Final reductive elimination along with ring closure would give the tetrahydrofuran **1.23**. Reoxydation of the metal center would regenerate an active metaloxo necessary for the next cyclizations.

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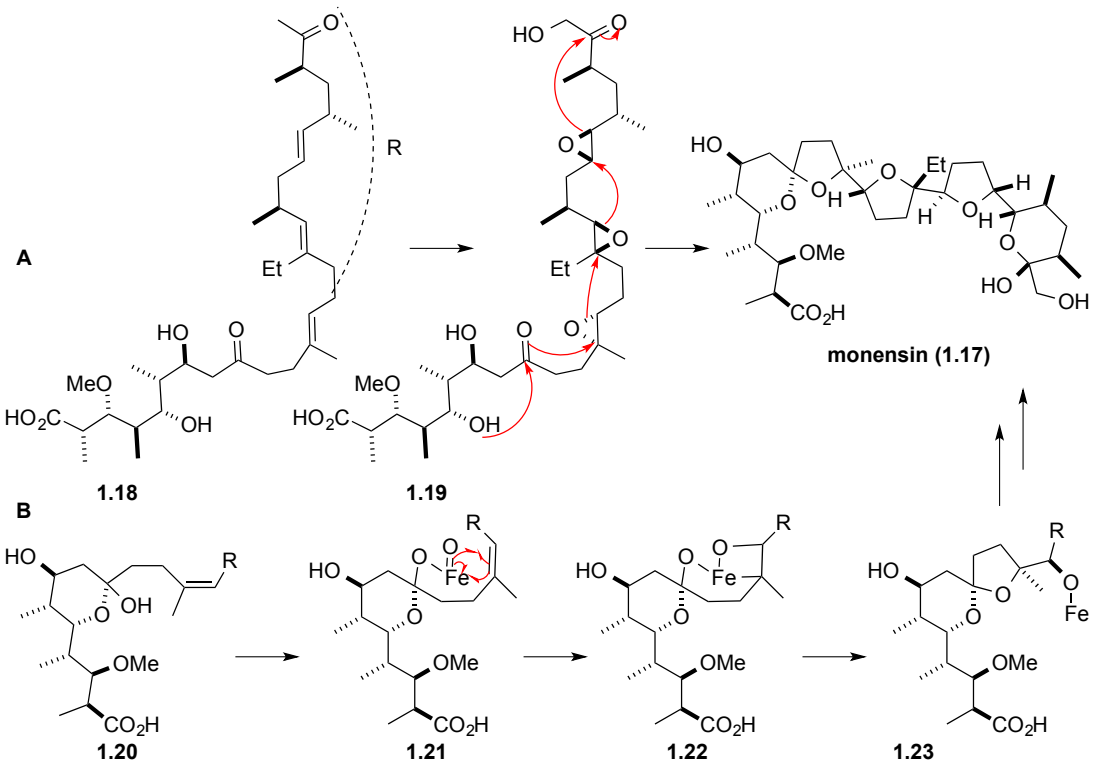
[10] Review: De la Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 160−181.

[11] Koert, U. *Angew. Chem. Int. Ed.* **1995**, *34*, 298−300

[12] Cane, D. A.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.***1983**, *105*, 3594−3600.

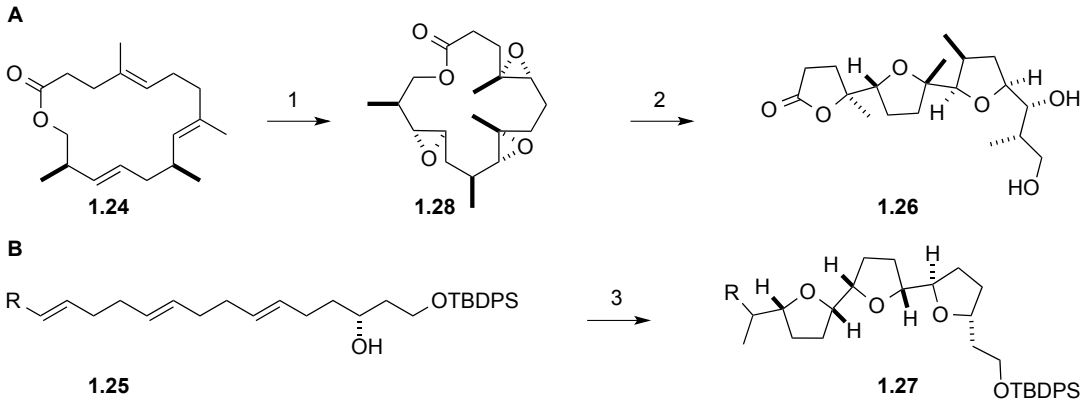
[13] a) Townsend, C. A.; Basak, A. *Tetrahedron* **1991**, *47*, 2591−2602; b) McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc.* **1994**, *116*, 7921−7922.



Scheme 1.3: *Biosynthetic hypotheses of monensin (**1.17**) by A) Westley[12] and B) Basak-Towne.*[13]

Neither of these hypotheses has been directly supported experimentally by the transformation of **1.18** or **1.20** to monensin (**1.17**). However, model substrate **1.24** and **1.25** were successfully converted to the polyether product **1.26** (Scheme 1.4, **A**)[14] and **1.27** (Scheme 1.4, **B**)[15], using in the first case *m*-CPBA followed by an basic/acid treatment of polyepoxy **1.28**, and in the second case Re_2O_7 *via* a one pot tandem oxidative cyclization. Therefore, these "biomimetic" syntheses endorse two distinct biosynthetic hypotheses.

[14] Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105−2106.
[15] Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014−12015.



Scheme 1.4: *Synthetic routes based on the A) Westley*[14] *and B) Basak hypotheses.*[15] 1) *m*-CPBA, $NaHCO_3$; 2) *i.* NaOH; *ii.* AcOH; 3) Re_2O_7, TFAA.

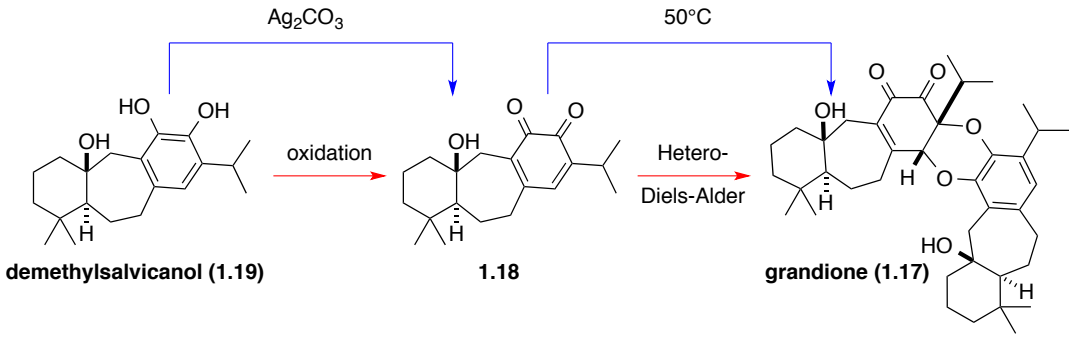
A more suitable description of a synthesis, which aims to support a biosynthetic hypothesis, should be consequently: *a synthesis based on a biogenetic hypothesis*. If such a synthesis is successfully carried out, only the corresponding hypothesis is supported, as other alternative pathways can also be endorsed experimentally.

The terminology *biomimetic* should be employed for a synthesis based on an accepted biosynthetic pathway. Indeed, establishment of biogenetic pathways are for example achieved by first identifying the gene cluster responsible for the synthesis of the natural product by gene knockout experiments and/or homology comparison.[16] Identification of the role of each gene followed by their expression constitutes the next steps. Incubations of the natural product precursors with each isolated enzyme would determine their role if the desired transformations were successfully carried out, thus validating the hypothesis.

The impressive structural diversity of natural products can partly be explained by the intrinsic reactivity of natural product precursors that will undergo self-assembling to create complex structures with a minimal (or non-) enzymatic participation.[10] In fact, if each biosynthetic step towards a natural product would require an enzyme (without taking to account unspecific enzymes), the amount of genes encoding for them would be colossal.[17] Mimicking biosynthetic pathways, relying on the formation of such reactive precursors, would be easier than a fully enzymatic process. It is difficult to compete with the efficiency and selectivity of

[16] Li, H.; Zhang, Q.; Li, S.; Zhu, Y.; Zhang, G.; Zhang, H.; Tian, X.; Zhang, S.; Ju, J.; Zhang, C. *J. Am. Chem. Soc.* **2012**, *134*, 8996−9005.
[17] Review: Gravel, E.; Poupon, E. *Eur. J. Org. Chem.* **2008**, 27−42.

enzymatic reactions, but it should not be concluded that such reactions can not be mimicked.[18] It could be envisaged that sunlight promoted photochemical and multi-component reactions, as well as inter- or intramolecular cycloadditions, are responsible for the synthesis of complex natural products in nature without or with minimal enzyme participation. The photosynthesis of vitamin D in the skin of animals is probably the best example of a sunlight-mediated biosynthesis that does not require any enzyme.[19] Grandione (**1.17**) is an example of a dimeric natural product that was proposed to be biosynthetically produced *via* a Diels-Alder cycloaddition of the orthoquinone **1.18**, which was obtained by oxidation of demethylsalvicanol (**1.19**).[20] This biogenetic hypothesis was supported synthetically by heating **1.18** to furnish grandione (**1.17**). A important example of a multi-component reaction, where such reactive intermediates are produced is the previously described Robinson synthesis.[7]



Scheme 1.5: *Biosynthetic hypothesis and the corresponding synthesis of grandione (**1.17**).*[20] The red arrows represents the proposed biosynthetic steps, the blue ones represents the synthetic ones.

The advantage of syntheses forming reactive intermediates is the ability to identify which step within a biosynthetic pathway is non-enzymatic. Indeed, these steps should be easily mimicked synthetically. In contrary, the steps, which required the use of specific reagent such as chiral Lewis acid (*e.g.* amino acids), could highlight an enzymatic route. Moreover, syntheses based on biogenetic hypothesis have proven to be very efficient in terms of preventing the use of protecting-groups.[21]

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[18] Review: Baunach, M.; Franke, J.; Hertwerck, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 2604−2626.
[19] Holick, M. F. *Am. J. Clin. Nutr.* **2004**, *80*, 1678−1688.
[20] Aoyagi, Y.; Takahashi, Y.; Satake, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Shiina, T.; Kurihara, T. *Tetrahedron Lett.* **2005**, *46*, 7885−7887.
[21] Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem. Eur. J.* **2010**, *16*, 7692−7695.

2. Total synthesis of taiwaniaquinone F and taiwaniaquinol A via an unusual remote C−H activation

2.1. Introduction

2.1.1. Taiwaniaquinoids

Taiwaniaquinoids are natural products with a rearranged diterpenoid structure and were isolated first in 1995 by Cheng and co-workers [22] from *Taiwania cryptomerioides*, an evergreen tree occuring in Taiwan (Figure 2.1).

Figure 2.1: *Picture of Taiwania cryptomerioides by Prof. Dr. Karl Gademann (Brissago Islands, Switzerland).*

Some members of this family were isolated later on from abietane-rich plants such as *Salvia dichroantha*[23] and *Thuja standishii*.[24] Although the biological activity of taiwaniaquinoids was not studied in detail, some of these compounds possess interesting biological properties. Standishinal (**2.1**, Figure 2.2), an aromatase inhibitor (enzymes involved in the synthesis of hormones) acts against breast cancer, as the

[22] Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871−873.
[23] Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sesik, E.; and Yesilada, E. *Phytochemistry* **1999**, *50*, 493−497.
[24] Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419−6422.

growth of these cancerous cells is hormone dependent.[25] Taiwaniaquinone D (**2.2**) and F (**2.3**) showed potent cytotoxicity against epidermoid carcinoma (KB) cancer cell lines. Their unsual 6-5-6 tricyclic core structure in combination with the aldehyde group is believed to be responsible for this activity.[26] As common structural feature, they all possess a 6-5-6 carbon skeleton bearing a highly oxidized C ring. They are divided into two subclasses namely the C_{19} (*e.g.* taiwaniaquinol E (**2.4**) and dichroanone (**2.5**) isolated by Chang[26] and Kawazoe,[23] respectively) and C_{20} (*e.g.* taiwaniaquinone F (**2.3**) and taiwaniaquinone E (**2.6**) isolated by Kuo and co-workers[27] and by Lin *et al.,*[28] respectively) taiwaniaquinoids, describing the numbers of C atoms in their carbon skeleton. Taiwaniaquinones display a quinone C ring in contrast to taiwaniaquinols, which have a phenolic C ring. Moreover, some members of this family are bearing a *cis* fused A/B ring like taiwaniaquinol B (**2.7**)[22] while the majority displays a *trans* fused A/B ring such as taiwaniaquinone G (**2.8**).[26] Interestingly, taiwaniaquinol A (**2.9**) is so far the only taiwaniaquinoid bearing a methylenedioxy bridge[22]. Furthermore, more complex structures, such as taiwaniadduct C (**2.10**), a Diels-Alder cycloaddition adduct of taiwaniaquinone A (**2.11**) and *trans*ozic acid (**2.12**), were isolated from *T. cryptomerioides*.[28]

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[25] Katoh, T.; Akagi, T.; Noguchi, C.; Kajimoto, T.; Node, M.; Tanaka, R.; Nishizawa, M.; Ohtsu, H.; Suzuki, N.; Saito, K. *Bioorg. Med. Chem.* **2007**, *15*, 2736−2748.

[26] Chang, C. I.; Chang, J. Y.; Kuo, C. C.; Pan, W. Y.; Kuo, Y. H. *Planta Med.* **2005**, *71*, 72−76.

[27] Chang, C. I.; Chien, S. C.; Lee, S. M.; Kuo, Y. H. *Chem. Pharm. Bull.* **2003**, *51*, 1420−1422.

[28] Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *42*, 1657−1663.

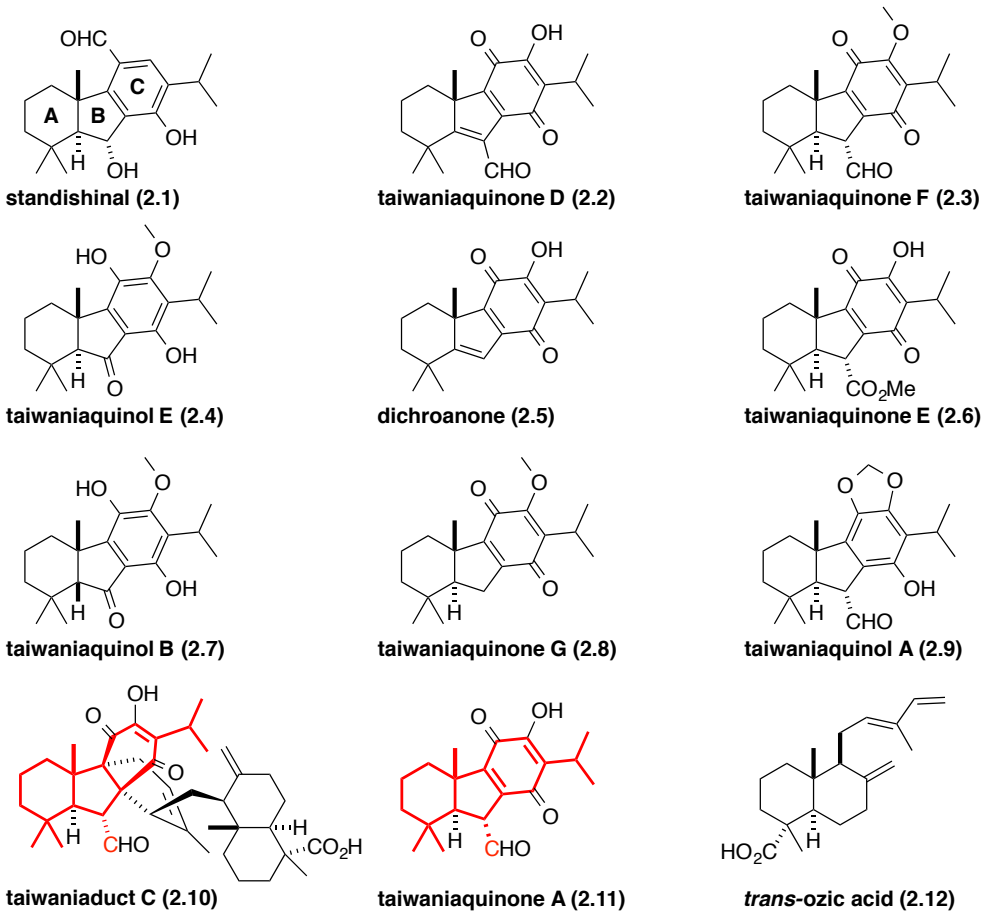


Figure 2.2: *Structure of some representative taiwaniaquinoids (**2.1** to **2.11**) and trans-ozic acid (**2.12**).*

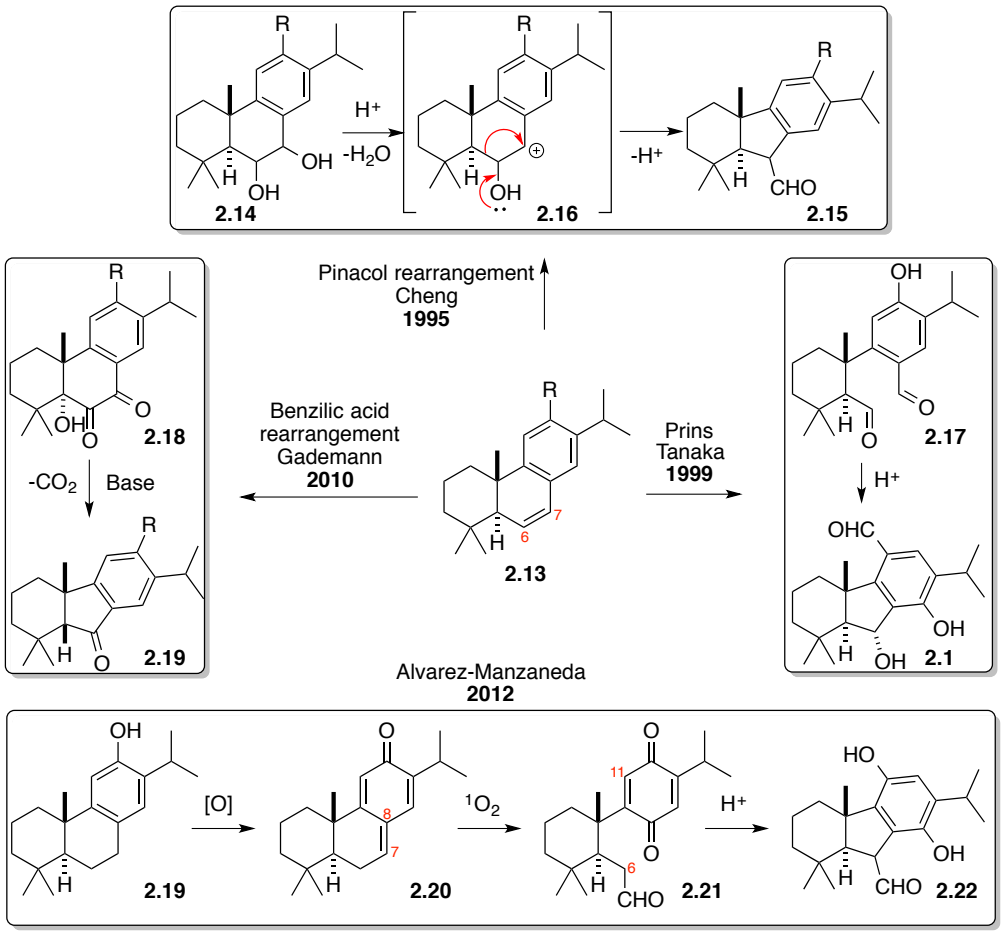
2.1.2. Biogenetic hypotheses of taiwaniaquinoids

As the biogenesis of taiwaniaquinoids has not yet been investigated in detail, general hypotheses for the biosynthetic origin of the unusual 6−5−6 ring system have been proposed by our group[29] and others,[22,24,30] based on the structural features of isolated C_{20} diterpenoids (Scheme 2.1). The first three hypotheses postulate a dehydroabietane derivative (**2.13**) as the biosynthetic precursor. Cheng and co-workers proposed, a Pinacol rearrangement of the diol **2.14** to access the ring-contracted aldehyde **2.15** *via* the formation of the benzylic carbocation **2.16**.[22] However, Alvarez-Manzenada and co-workers[30] recently assessed this hypothesis by treating a diol like **2.14** with different acids. Unfortunately, they only isolated a

[29] (a) Jana, C. K.; Scopelliti, R.; Gademann, K. *Synthesis* **2010**, 2223−2232; (b) Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem. Eur. J.* **2010**, *16*, 7692−7695.

[30] Tapia, R.; Guardia, J. J.; Alvarez, E.; Haidöur, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *J. Org. Chem.* **2012**, 77, 573−584.

dehydrated product. In 1999, Tanaka and co-workers reported the co-isolation of dialdehyde **2.17** and standishinal (**2.1**). They proposed that **2.17**, derived from a C6-C7 oxidative cleavage of **2.13** is biosynthetically converted to standishinal (**2.1**) by a Prins-type reaction.[24] This hypothesis was experimentally supported by converting **2.17** to **2.1**, using BF_3•OEt_2 in CH_2Cl_2.[24] The Gademann group recently proposed that C_{19} taiwaniquinoids could be biosynthetically accessed *via* a benzylic acid rearrangement of a suitably oxidized ferruginol or abietane C_{20} substrate.[29] This hypothesis is the only one that could explain the formation of such nor-diterpenoids. Proposed was that the key step of this reaction is an external base facilitated intramolecular benzilic acid rearrangement of hydroxydiketone **2.18**, followed by a decarboxylation to furnish C_{19} taiwaniaquinoids.

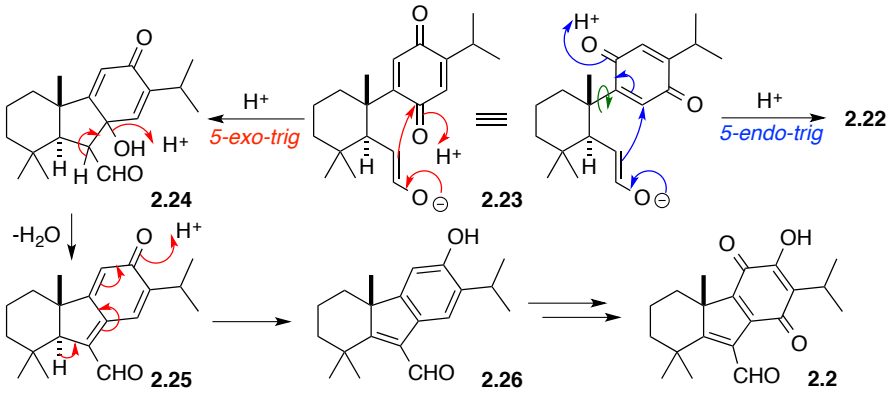


Scheme 2.1: *Biosynthetic hypotheses for taiwaniaquinoids.*

To validate this hypothesis, hydroxydiketone **2.18**, obtained by an over-oxidation of **2.13** using Sharpless dihydroxylation conditions, was treated with LHMDS to form an oxetane intermediate, which gave a ring contracted lactone upon

benzilic acid rearrangement. Decarboxylation of the lactone intermediate gave hexahydrofluorenone **2.19**, which was then utilized for the total synthesis of taiwaniaquinone H and dichroanone (**2.5**). Moreover, access to *cis* fused A/B ring taiwaniaquinoids, such as **2.7**, could be envisaged. Finally, based on the abietanes isolation work of Zhang and co-workers[31], Alvarez-Manzenada *et al.* suggested that an oxidation of ferruginol *via* a hydride transfer to NAD^+ (**2.19**) produces the reactive para-quinone methide **2.20**. Oxidative cleavage of the C7-C8 bond in the presence of singlet oxygen ($^1O_2$), furnished the new *seco*-dipernoid **2.21**. An intramolecular 1,4-addition of the enol aldehyde of **2.21** to the quinone moiety would afford the C6-C11 bond of the newly formed C_{20} taiwaniaquinoid **2.22**.[30]

The last hypothesis by Alvarez-Manzaneda[30] relies on an intramolecular 1,4-addition, which, according to the Baldwin's rules for ring closure, would be a disfavored *5-endo-trig* ring closure.[32] Even though, a disfavored ring closure could still proceed, yet is unlikely, a favored ring closure reaction is possible. Indeed, the same enolate **2.23** can react in an intramolecular 1,2-addition with the quinone moiety *via* a favored 5-exo-trig to furnish the C6−C8 tertiary alcohol **2.24**. Dehydration of **2.24** would give the para-quinone methide **2.25**, which upon tautomerization, would furnish the aromatic alkene **2.26**. Such an advanced intermediate could be used for the synthesis of the related natural product **2.2**. Moreover, the synthesis of the 6-5-6 ring system by Alvarez-Manzenada (section 2.1.3.2) contains a 5-exo-trig ring closure instead of a 5-endo-trig process. This finding supports the exo-pathway rather than the endo one.



Scheme 2.2: *Hypothetical biosynthetic step towards **2.2** and **2.22** utilizing a 5-exo-trig ring closure and a 5-endo-trig,[30] respectively.*

[31] Chen, X.; Ding, J.; Ye, Y.-M.; Zhang, J.-S. *J. Nat. Prod.* **2002**, *65*, 1016−1020.
[32] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

2.1.3. Previous syntheses of taiwaniaquinoids

2.1.3.1. Main Strategies

The rare 6-5-6 ring skeleton of taiwaniaquinoids, coupled with their wide-ranging stereochemical and functional group variety, in combination with promising biological activities and intriguing biogenetic origins, make these compounds challenging targets. Indeed, these compounds attracted considerable interest from both isolation and synthetic chemists alike, and several syntheses of members of this family have been reported.[25,29a,29b,33]

Five mains strategies were used to build the challenging 6-5-6 tricyclic core, whereas the AC−ABC approach was the most extensively studied one.

a) The AC-ABC approach

This predominant strategy for the synthesis of taiwaniaquinoids was accomplished through the coupling of the A ring with the C ring, followed by the construction of the B ring. Trauner and co-workers[33g], which named these compounds "taiwaniaquinoids" for the first time, connected the C ring (**2.27**) with β-cyclocitral (**2.28**) *via* a Li/Br exchange followed by an addition to the aldehyde. The resulting

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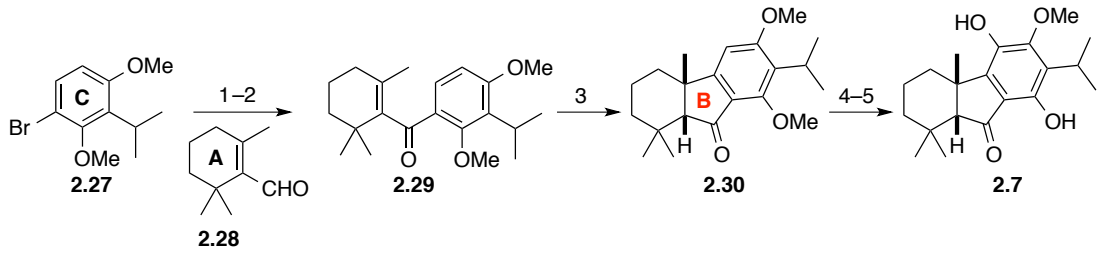
[33] (a) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Org. Lett.* **2003**, *5*, 3931−3933; (b) Fillon, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144−13145; (c) Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896−2898; (d) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. *J. Org. Chem.* **2006**, *71*, 2787−2796; (e) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738−7739; (f) Bhar, S. S.; Ramana, M. M. V. *Tetrahedron Lett.* **2006**, *47*, 7805−7807; (g) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022−11023; (h) Li, S.; Chiu, P.; *Tetrahedron Lett.* **2008**, *49*, 1741−1744; (i) Tang, S.; Xu, Y.; He, J.; He, Y.; Zheng, J.; Pan, X.; She, X. *Org. Lett.* **2008**, *10*, 1855−1858; (j) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidöur, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Charrah, Y.; Es-Samti, H. *Org. Biomol. Chem.* **2009**, *7*, 5146−5155; (k) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidöur, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592−594; (l) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidöur, A.; Alvarez-Manzaneda, R.; Meneses, R.; Es-Samti, H.; Fernàndez, A. *J. Org. Chem.* **2009**, *74*, 3384−3388; (m) Majetich, G.; Shimkus, J. M. *Tetrahedron Lett.* **2009**, *50*, 3311−3113; (n) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. *Chem. Commun.* **2010**, 9244−9246; (o) Liao, X; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088−2091; (p) Yan, X.; Hu, X. *J. Org. Chem.* **2014**, *79*, 5282−5286.

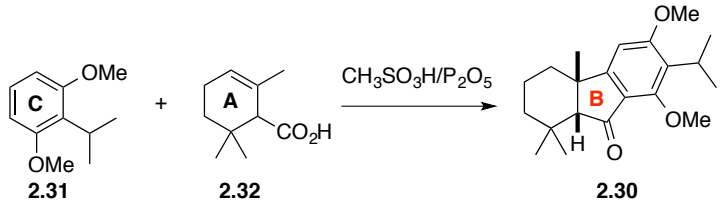
allylic alcohol was oxidized by DMP to enone **2.29** (Scheme 2.3). A Nazarov cyclization of **2.29** to **2.30**, bearing the desired 6-5-6 skeleton, was achieved using TMSOTf. Completion of the synthesis of taiwaniaquinol B (**2.7**) was achieved through a selective C14 demethylation using BCl_3 followed by CAN oxidation to give a 2-methoxy-1,4-quinone. Reduction of the later one through a $Na_2S_2O_4$ aqueous work-up yielded the natural product.



Scheme 2.3: *Trauner's synthesis of taiwaniaquinol B:* [33g] 1) *n*-BuLi, then **2.28**; 2) DMP; 3)TMSOTf; 4) BCl_3; 5) *i.* CAN, *ii.* $Na_2S_2O_4$.

b) The A+C-ABC approach

This strategy is related to the first one as the A and C ring are coupled in the view of forming the B ring. The difference in the synthesis is the single step construction of the taiwaniaquinoid skeleton. The She approach[33i] of the formal synthesis of the same natural product **2.7** includes a domino Friedel-Crafts acylation/alkylation reaction to give the same intermediate **2.30** (Scheme 2.4). This domino reaction was initiated by treating **2.31** and **2.32** with Eaton's reagent (CH_3SO_3H/P_2O_5).

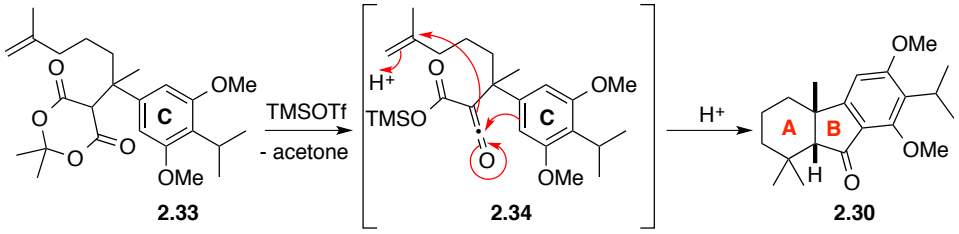


Scheme 2.4: *Formal synthesis of taiwaniaquinol B by She.*[33i]

c) The C-ABC approach

This approach exploited by Fillon and co-workers for the synthesis of **2.7** features the construction of the 6-5-6 cyclic skeleton **2.30** in one step, starting with

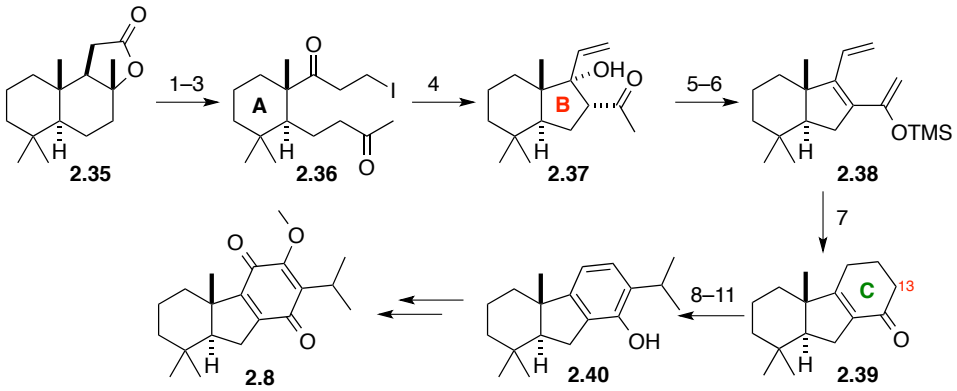
the C ring **2.33** *via* a domino Friedel-Crafts acylation/alkylation protocol (Scheme 2.5) similar to the previously discussed strategy (see Scheme 2.4). Formation of the ketene **2.34** from Meldrum's acid type **2.33** is believed to be a key intermediate for the acylation/alkylation domino reaction, which upon acidic work-up, affords the decarboxylated product **2.30**.



Scheme 2.5: *Fillon's synthesis of taiwaniaquinol B.*[33b]

d) The A-AB-ABC approach

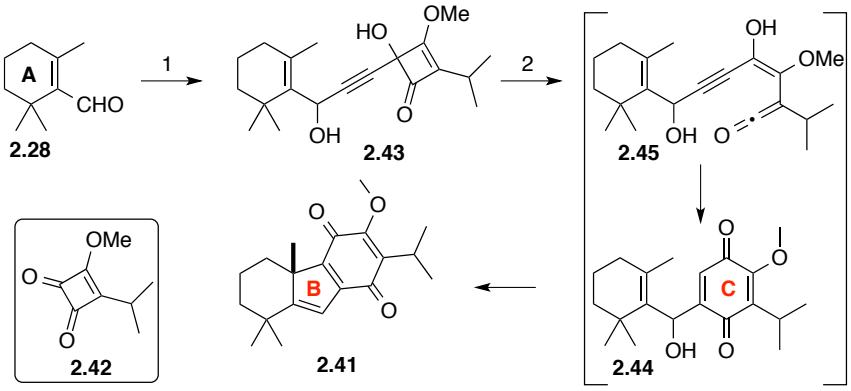
Alvarez-Manzaneda's approach[33k] for the synthesis of taiwaniaquinone G (**2.8**, Scheme 2.6), involves the stepwise synthesis of the B and C ring from the A ring. The synthesis started from the commercially available (+)-sclareolide (**2.35**). The A ring **2.36** was obtained from inexpensive **2.35** through the following steps: (1) reduction of the lactone moiety to a diol; (2) treatment of this diol using Appel conditions simultaneously converting the primary alcohol moiety to a primary alkyl iodide and the tertiary alcohol moiety to the quaternary double bond by dehydration; (3) ozonolysis of the double bond provided the desired substituted A ring **2.36**, ready for cyclization (Scheme 2.6). Indeed, a DBU catalyzed *5-exo-trig* aldol reaction followed by a HI elimination lead to tertiary alcohol **2.37**. A difficult dehydration under harsh acidic conditions followed by the TMSOTf treatment of the acetyl moiety gaving triene **2.38**. A 6π-electrocyclization of this triene allowed the formation of the 6-5-6 tricyclic core (**2.39**). An methyl ester was then introduced at C13 by using $NCCO_2Me$ and LDA. The C ring was aromatized using DDQ. Final alkylation of the ester moiety with MeMgBr was followed by a reduction of the resulting benzylic alcohol furnishing the desired taiwanaiquinoid skeleton phenol **2.40**, which was further transformed to taiwaniaquinone G. This synthesis represents one of the few approaches to access taiwaniaquinoids containing such *trans* fused A/B ring systems.



Scheme 2.6: *Alvarez-Manzaneda's synthesis of taiwaniaquinone G:*[33k] 1) KBH_4; 2) I_2, PPh_3; 3) O_3; 4) DBU; 5) H_2SO_4; 6) TMSOTf; 7) 80 °C; 8) LDA, then $NCCO_2Me$; 9) DDQ; 10) MeMgBr; 11) Et_3SiH, TFA.

e) The A-ABC approach

Finally, the last synthetic strategy employed by Hu and co-workers resemble to the Fillon's C−ABC approach in the sense that two new rings are formed simultaneously from an already established one (Scheme 2.7). The synthesis of taiwaniaquinone H (**2.41**) started with β-cyclocitral (**2.28**), which was treated with ethynylmagnesium bromide, followed by *t*-BuLi. The resulting alkyne lithium reacted with **2.42** to give the diol **2.43** in a one pot reaction. A thermal electrocyclic ring opening/ring-closure cascade of **2.43** was then performed giving the C ring **2.44** probably *via* ketene **2.45**. The mechanism is suggested to proceed through a biradical species.[34] Under thermal conditions only, the formation of the B ring of **2.41** was not observed. However, with addition of $TiCl_4$ to the reaction mixture after the thermal treatment, resulted in the formation of taiwaniaquinone H (**2.41**).[33p]



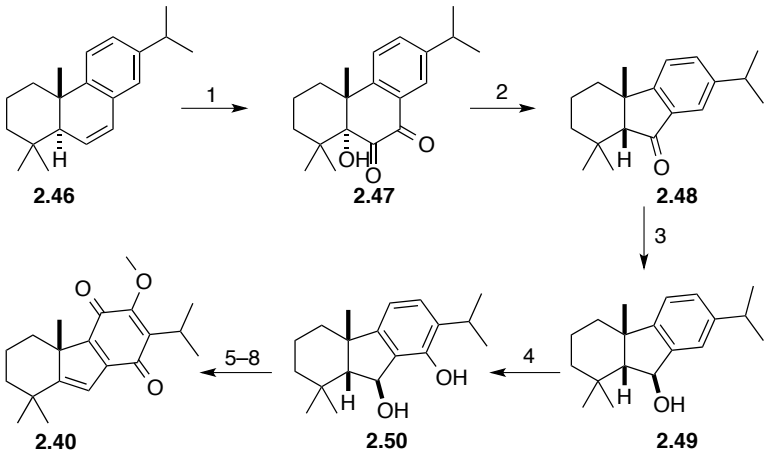
Scheme 2.7: *Hu's synthesis of taiwaniaquinone H:* [33p] 1) *i.* HC_2MgBr, *ii. t*-BuLi, *iii.* **2.42**; 2) 80 °C, then $TiCl_4$.

[34] Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975−989.

2.1.3.2. Syntheses based on biogenetic hypothesis

a) Biomimetic total synthesis of (−)-taiwaniaquinone H

In 2010, the total synthesis of taiwaniaquinone H was reported based on the biogenetic hypothesis connecting C_{20} diterpenoids to C_{19} nor-diterpenoids (see Scheme 2.1).[29] The synthesis started from dehydroabietane (**2.46**), which was obtained from abietic acid *via* known procedures (Scheme 2.8). Treatment of the alkene under standard Sharpless dihydroxylation conditions (AD-mix(β)) furnished the over-oxidized precursor **2.47**, suitable for the subsequent ring contraction (Scheme 2.1). Basic treatment of **2.47** gave the ring-contracted ketone **2.48**. $NaBH_4$ reduction of the ketone **2.48** gave the benzylic alcohol **2.49**, which was used as a directing group to achieve an *ortho*-lithiation of the aromatic ring. The resulting phenyl lithium was reacted with $B(OMe)_3$ followed by H_2O_2 to deliver the phenol **2.50**. This advanced intermediate was further functionalized to give (−)-taiwaniaquinone H (**2.40**).

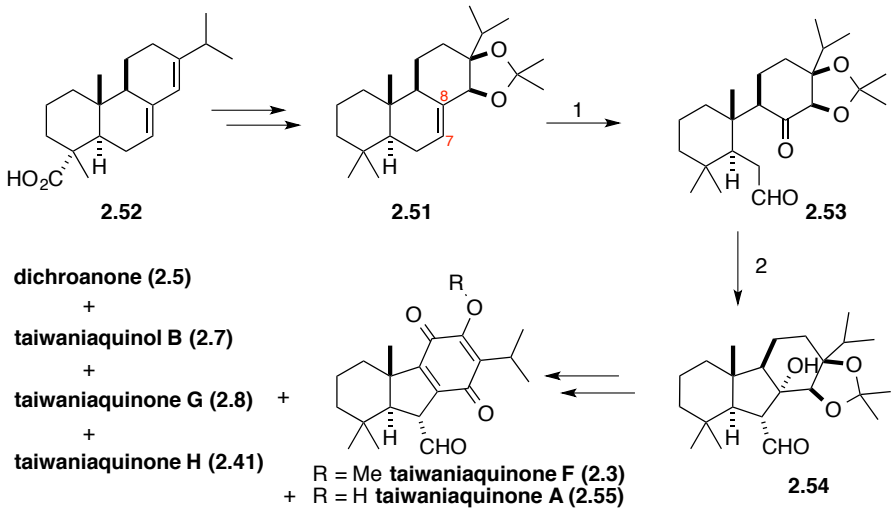


Scheme 2.8: *Gademann's total synthesis of (−)-taiwaniaquinone H:*[29] 1) AD-mix(β); 2) LHMDS; 3) $NaBH_4$; 4) *i.* *n*-BuLi, *ii.* $B(OMe)_3$, *iii.* H_2O_2; 5) HCl; 6) Frémy's salt; 7)Br_2; 8) NaOMe.

b) Biomimetic, divergent total syntheses of taiwaniaquinoids

As already described in section 2.1.2, Alvarez-Manzaneda and co-workers achieved the total synthesis of several members of this natural product class based on a biogenetic hypothesis.[30] The synthesis started with the abietane **2.51**, which was synthesized from carnosic acid (**2.52**). Ozonolysis of the C7−C8 double bond

furnished the ketoaldehyde **2.53**, which underwent a *5-exo-trig* ring closure under basic conditions (DBU) and therewith afforded the taiwaniaquinoids skeleton (**2.54**). Compound **2.54** was used as common intermediate to synthesize natural products **2.5**, **2.7**, **2.8**, **2.40**, **2.55** and taiwaniaquinone F (**2.3**), which will be of specific interest in the next sections.

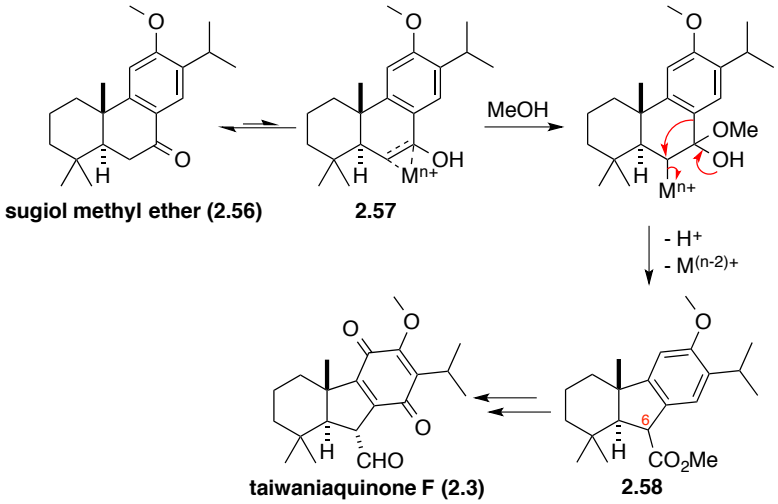


Scheme 2.9: *Alvarez-Manzaneda's biomimietic synthesis of the taiwaniaquinoid skeleton 2.54 and application to the divergent synthesis of several members (**2.3**, **2.5**, **2.7**, **2.8**, **2.41**, and **2.55**):*[30] 1) O_3, then Me_2S; 2) DBU.

2.1.4. Target motivations and synthetic strategies

2.1.4.1. Goal of the study

In continuation of the previous work for the investigation of the biogenesis of taiwaniaquinoids, we became interested to the possible biogenesis of C_{20} taiwaniaquinoids bearing a formyl group at the C6 position. We proposed that the 6-5-6 tricyclic skeleton of C_{20} taiwaniaquinoids could be achieved *via* the ring contraction of a benzylic cyclohexanone, such as sugiol methyl ether (**2.56**, Scheme 2.10). This ring contraction was envisaged to be achieved by an oxidative rearrangement of enol **2.57** in MeOH mediated by a metal such as Tl(III) via intermediate **2.58**. The resulting ring-contracted intermediate **2.59** could be used for the synthesis of a C_{20} taiwaniaquinoids *via* an aromatic oxidation. Due to its intriguing bioactivities and the few numbers of existing synthetic methods targeting the fused *trans* A/B ring system, taiwaniaquinone F (**2.3**) was chosen as the primary target for these synthetic studies.



Scheme 2.10: *Hypothetical biosynthetic ring contractions of abietanes to taiwaniaquinoids.*

2.1.4.2. Retrosynthetic analysis

As mentioned in section 2.1.2, the different biosynthetic hypotheses of C_{19} and C_{20} taiwaniaquinoids, whereby an abietane was suggested as the precursor. Indeed, the abietane origin of taiwaniaquinoids is well accepted in the scientific community.[22,24,29,30] However, the formation of these rearranged abietane skeletons is still under debate, as the biogenesis of these fascinating natural products were not investigated in details. Recognizing the rearranged abietane core of taiwaniaquinoids, we decided to start our synthesis of taiwaniaquinone F (**2.3**, Scheme 2.11) with abietic acid (**2.2**), an inexpensive and abundant abietane acid, which is readily available. This acid is found in high content in the resin of many conifers, such as *Abies grandis* and *Pinus contorta*, and acts as a chemical weapon against insects and pathogens through secretion.[35] Such resins are used for a variety of applications such as food additives and friction-increasing agents (used by musicians, rugby players).[36]

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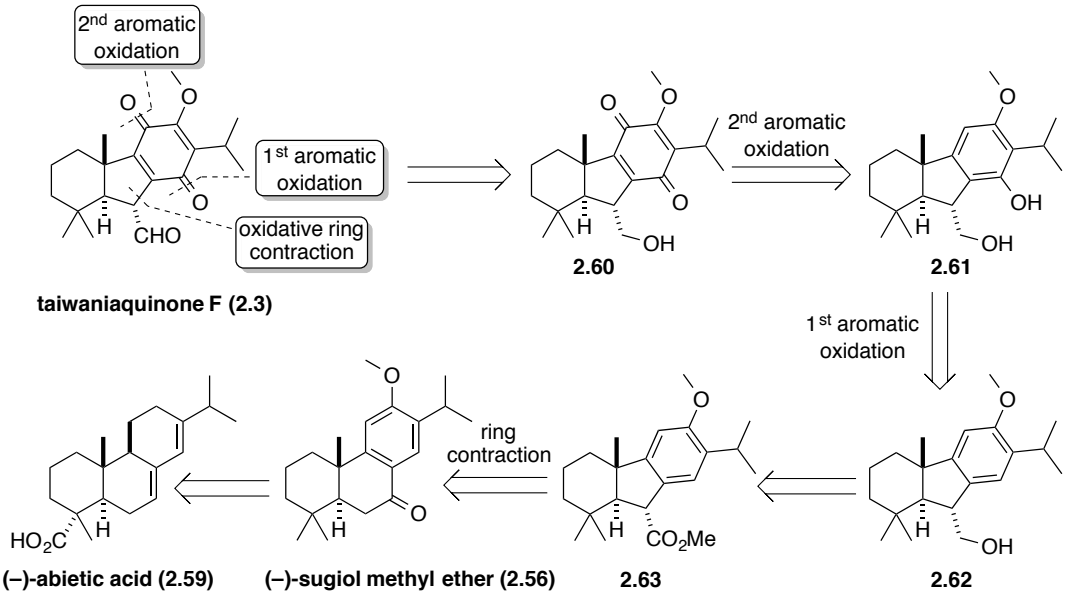
[35] Dewick, P. M. *Nat. Prod. Rep.* **1997**, *14*, 111−144.
[36] Fiebach, K.; Grimm, D. *Ullmann's Encyclopedia of Industrial Chemistry* **2000**, *31*, 477−494.



Scheme 2.11: *Retrosynthetic analysis of taiwaniaquinone F (**2.3**).*

Functional group interconversion of taiwaniaquinone F (**2.3**) would give the primary alcohol **2.60** as a precursor. The quinone moiety formation of **2.60**, described in Scheme 2.11, was envisaged to occur *via* two consecutive aromatic oxidations at the C ring. Oxidation of phenol **2.61**, using, for instance, Fremy's salt or Salcomine under aerobic conditions would provide taiwaniaquinone F (**2.3**). The C14 hydroxyl group in **2.61** could be obtained from **2.62**, using the rather long but usually efficient three step protocol, consisting of a Friedel-Crafts acylation followed by a Bayer-Villiger oxidation and transesterification. Alternatively, a more direct approach would be the directed one pot ortholithiation/boronation/oxidation procedure, developed by Seebach and co-workers,[37] which has been successfully applied in our group for the total synthesis of (−)-taiwaniaquinone H.[29b] The precursor of **2.62** could be the methyl ester derivative **2.63**, which could be obtained *via* a metal mediated oxidative ring contraction[38] of (+)-sugiol methyl ether (**2.56**). This known natural product could be synthesized from the inexpensive and commercially available (−)-abietic acid (**2.59**).

[37] Meyer, N.; Seebach, D. *Angew. Chem.* **1978**, *90*, 553−554.
[38] (a) Singh, O. V.; Muthukrishnan, M. *Synthetic Communications* **2006**, *36*, 943−950; (b) Silva, L. F. *Synlett* **2014**, *25*, 466−476.

2.2. Results and Discussion

2.2.1. Synthesis of (+)-sugiol methyl ether

Sugiol methyl ether (**2.56**) was synthesized from abietic acid (**2.59**), following known synthetic steps (Scheme 2.12) with experimental modifications. [39] Aromatization of abietic acid (**2.59**) with palladium on charcoal afforded aromatic dehydroabietic acid (**2.60**) in excellent yield (95%). Reduction of the ester group to a methyl group was achieved in three consecutive steps: 1) LAH reduction of the carboxylic acid yielded dehydroabietinol (**2.61**, 84%); 2) tosylation using *p*-TsCl with pyridine furnished **2.62** in excellent yield (98%); 3) abietane (**2.63**) was obtained through a reductive removal of the tosyloxy group using NaI and Zn powder in DMF followed by an aqueous HCl workup. This reduction was proceeded in high yield (80%), although a SN_2 reaction at a neopentylic position is known to be difficult. Having abietane (**2.63**) in hands, oxidation of its aromatic C ring was performed in three consecutive steps consisting of: 1) Friedel-Craft acylation of **2.63** yielded the 12-acetyldehydroabietane (**2.64**) in very high yield (90%) using aluminium chloride and acetyl chloride; 2) Bayer-Villiger oxidation of **2.64** with *m*-CPBA affording acetate **2.65** in excellent yield (93%); (3) transesterification with sodium methoxide in MeOH providing the natural phenol ferruginol (**2.66**) in quantitative yield. Finally, methylation of phenol **2.66** using K_2CO_3 and Me_2SO_4 (94%), followed by benzilic oxidation of the resulting ferruginol methyl ether (**2.67**) with CrO_3 in $AcOH/Ac_2O$ (79%), provided our natural precursor sugiol methyl ether (**2.56**) in nine linear steps with very good overall yield (36%) and interconnecting eight natural products.

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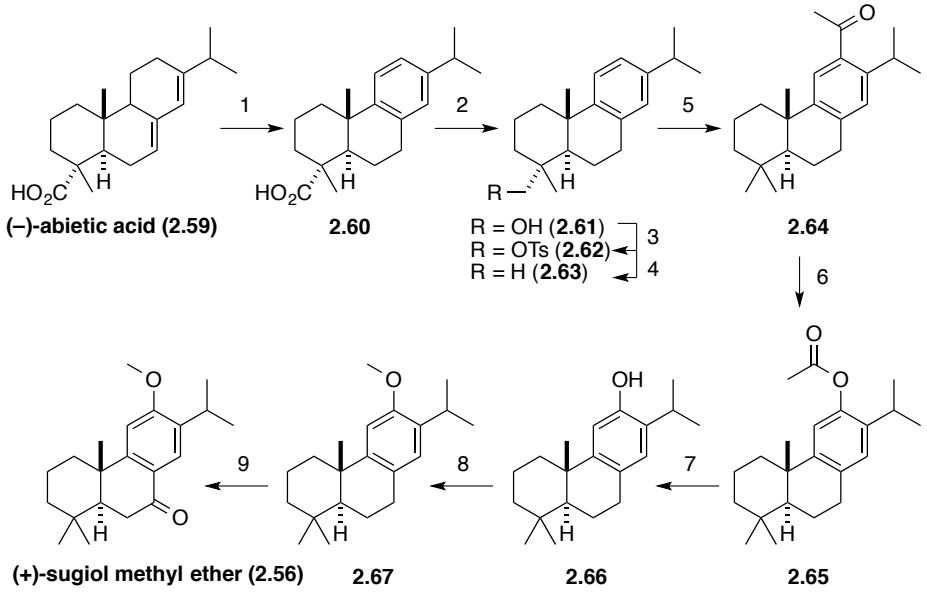
[39] (a) Portmann, C.; Prestinari, C.; Myers, T.; Scharte, J.; Gademann, K. *ChemBioChem* **2009**, *10*, 889−895; (b) González, M. A.; Pérez-Guaita, D.; Correa-Royero, J.; Zapata, B.; Agudelo, L.; Mesa-Arango, A.; Betancur-Galvis, L. *Eur. J. Med. Chem.* **2010**, *45*, 811−816; (c) Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, *17*, 3325−3326; (d) Akita, H.; Oishi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1567−1579; (e) Brandt, C. W.; Neubaeur, L. G. *J. Chem. Soc.* **1939**, 1031−1037; (f) Gan, Y.; Li, A.; Pan, X.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **2000**, *11*, 781−787.

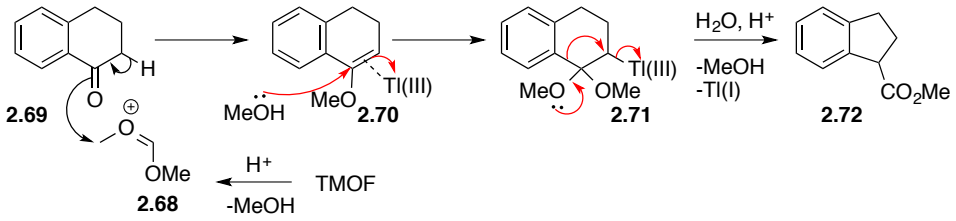


Scheme 2.12: *Synthesis of (+)-sugiol methyl ether (**2.7**) from (−)-abietic acid (**2.1**):* 1) Pd/C, *p*-xylene, 148 °C, 48 h, 95%; 2) LAH, THF, 0 °C-rt, 2.25 h, 84%; 3) *p*-TsCl, pyridine, 0 °C-rt, overnight, 98% 4) NaI, Zn, DMF, 100 °C, 3 days, then 1M HCl, 80%; 5) AcCl, $AlCl_3$, CH_2Cl_2, 0 °C-rt, 2 h, 90%; 6) peracetic acid, CH_2Cl_2, rt, 72 h, 93%; 7) NaOMe, MeOH, rt, 1 h, 99%; 8) K_2CO_3, Me_2SO_4, acetone, 60 °C, overnight, 94%; 9) CrO_3, $AcOH/Ac_2O$, 50 °C, 2 h, 79%.

2.2.2. Ring contraction of sugiol methyl ether

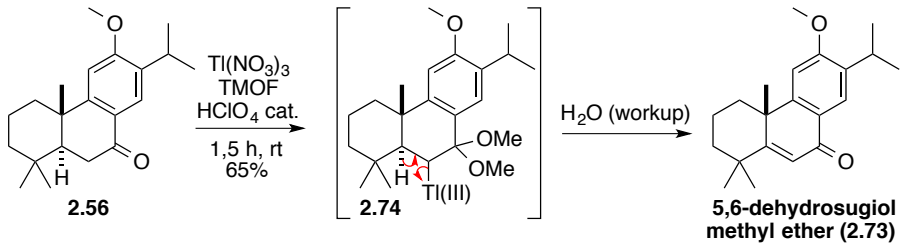
Having our synthetic sugiol methyl ether (**2.56**) in hand, the ring contraction of the B ring to obtain the 6-5-6 ring system was addressed next. The ring contraction of such cyclohexanone rings is usually performed by an oxidative thallium (III) mediated oxidative rearrangement in trimethyl orthoformate under acidic conditions.[40] A general, plausible mechanism for this ring contraction is depicted in Scheme 2.13. Trimethyl orthoformate can generate the oxonium species **2.68** under acidic conditions, which might react as a methylating agent with the ketone **2.69** to form the enol ether **2.70**. Coordination of the Tl(III) species, usually $Tl(NO_3)_3$, to the double bond, followed by a nucleophilic attack affords the C-thallated intermediate **2.71**. A successive migration of the electron rich C−Ar bond to the electron poor C−Tl(III) carbon generates the ring contracted ester **2.72** upon hydrolysis.

[40] Singh, O. V.; Muthukrishnan, M. *Synthetic Communications* **2006**, *36*, 943−950.



Scheme 2.13: *Thallium (III) mediated oxidative ring contraction.*[40]

Therefore, the B ring contraction of **2.56**, using $Tl(NO_3)_3$ in trimethyl orthoformate with a catalytic amount of perchloric acid was studied. Unfortunately, no ring-contracted product could be detected; instead the formation of the known natural product 5,6-dehydrosugiol methyl ether (**2.73**) was obtained in high yield (65%).[41] This could occur through a β-hydride elimination of the thallated substrate **2.74**. (Scheme 2.14).



Scheme 2.14: *Failed ring contraction tentative of sugiol methyl ether.*

As the thallium oxidative ring contraction failed to deliver the desired ring-contracted product, an alternative approach was explored. All carbons of **2.56** must be part of the ring-contracted product in order to access C_{20} taiwaniaquinoids. Such a ring contraction was successfully applied by Mander and co-workers for the total synthesis of gibberellin GA_{73} (**2.75**) *via* a Wolff rearrangement protocol (hv, MeOH) of the diazo-ketone **2.76**.[42] Rearrangement of the resulting carbene **2.77** would form the ketene **2.78**, which would subsequently be attacked by an MeOH to give the ring contracted ester product **2.79**, a precursor of gibberellin GA_{73} (**2.75**, Scheme 2.15).

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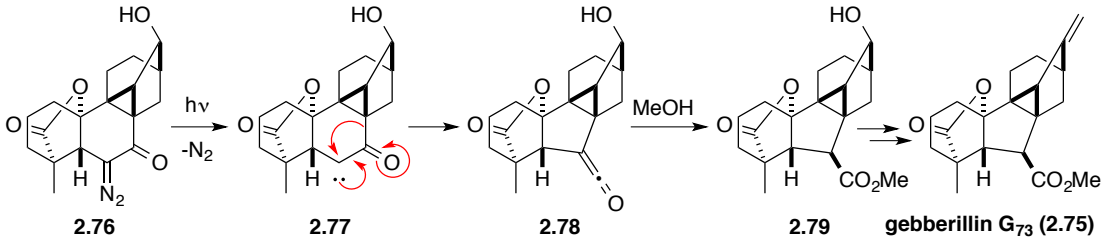
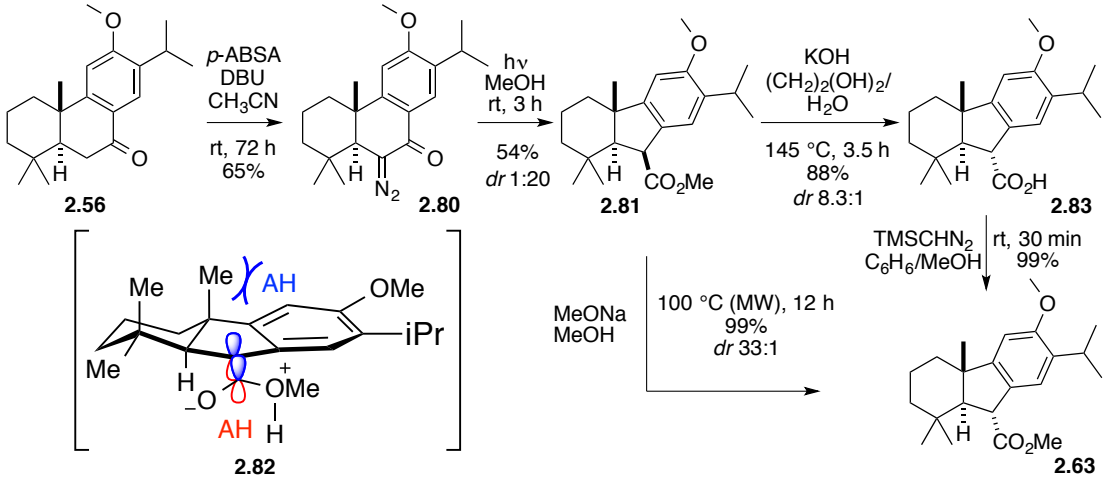
[41] Huo, Y-H. ; Yu, M. T. *Phytochemistry* **1996**, *42*, 779−781.
[42] King, G. R.; Mander, L. N.; Monck, N. J. T.; Morris, J. C.; Zhang, H. *J. Am. Chem. Soc.* **1997**, *119*, 3828−3829.



Scheme 2.15: *Synthesis of gibberillin G_{73} (**2.75**) by Mander.*[42]

Recognizing the analogous 6-6-6 ring system, we decided to investigate the feasibility of such a Wolff rearrangement on our substrate. Therefore, the synthesis of the α-diazoketone **2.80** was addressed next (Scheme 2.16).



Scheme 2.16: *Ring contraction of sugiol methyl ether diazo derivative (**2.80**) to ester **2.28** and C6-epimerization of **2.80** to **2.63**.* AH: Brønsted acid species.

We were pleased to observe a clean conversion of sugiol methyl ether using standard diazo-transfer reaction conditions (*p*-ABSA, DBU), affording the diazo derivative **2.80** in high yield (65%) together with a smaller amount of recovered starting material (30%). The structure of **2.80** was confirmed by X-ray crystallographic analysis (Figure 2.3, **A**).

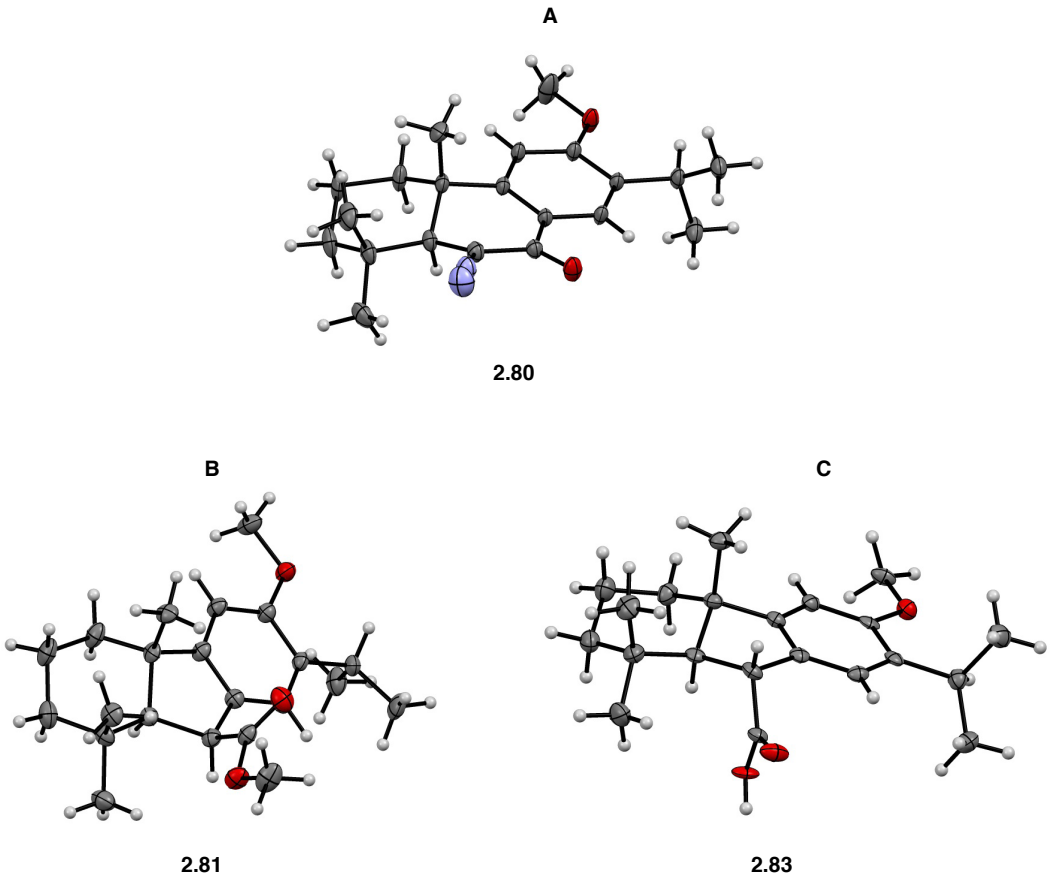


Figure 2.3: *X-ray crystallographic analysis of A) **2.27**, B) **2.28** and C) **2.30**.* Blue = nitrogen, red = oxygen, grey = carbon, white = hydrogen.

With the α-diazoketone **2.80** in hand, different transition metals, such as Rh and Cu, were investigated to generate stabilized carbenes, which could undergo the desired Wolff rearrangement. However, treating **2.80** with $Rh_2(OAc)_4$ or CuI in the presence of MeOH did not lead to conversion or formation of enone **2.73**, respectively. Furthermore, a ring-contracted product could not be detected. In the case of the Rh catalyst, unproductive coordination of the terminal nitrogen or the oxygen of the keto group of **2.80** to the Rh center could cause catalyst deactivation.[43] In the case of the Cu catalyst, we suppose that a fast 1,2-C−H migration takes place instead of the desired 1,2-C−aryl bond migration. Nevertheless, we were delighted to observe a clean and relatively efficient Wolff rearrangement yielding the ring-contracted ester **2.81**, when a dilute solution of the diazoketone **2.80** was irradiated in MeOH using a

[43] (a) Tishinov, K. Phd Thesis: "*New catalytic strategies for DNA and RNA alkylation using rhodium(II) and copper(I) carbenes − a versatile tool for applications in chemical biology*" **2015**, *Chapter 1*, 21−22; (b) Nowland, D. T.; Gregg, T. M.; Davies, H. M, L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, 125, 15902−15911

medium pressure Hg lamp. Remarkably, the reaction was also effective by exposing the dilute solution to direct sunlight (Figure 2.4) giving the same yield (54%) and the same diastereoselectivity (6*R*:6*S*, 1:20, determined by ^{1}H-NMR analysis). However, the stereoselectivity obtained was opposite to the one required for the configuration of the natural product. We postulate that the desired (6*R*)-**2.63** is the thermodynamic more stable product due to the angular C20 methyl group, forcing the bulky ester group into the equatorial position. Therefore, the major product (6*S*)-**2.81** obtained would be the kinetic product. This kinetic selectivity is predicted by the stereoselectivity of ketonization of enols and enolates, developed by Zimmerman in 1955.[44] The protonation of the enolate **2.82** occurs from the less hindered face of the double bond, in this case from the α-face of **2.82** due to the open trajectory for the protonating species (AH approach vs AH approach in **2.82**), therefore yielding the thermodynamically less stable product **2.81**. However, under thermal and acidic or basic conditions, the thermodynamic equilibrium can be reached. Thus, the kinetic product **2.81** was treated with KOH in ethylene glycol under thermal conditions (145 °C) and the (6*S*)-carboxylic acid **2.83** was successfully obtained in good yield (88%) and diastereoselectivity (6*R*:6*S*, 8.3:1, determined by ^{1}H-NMR analysis). The (6*R*)-ester **2.63**, required for the next steps, was quantitatively obtained by methylation of (6*R*)-**2.83** using $TMSCHN_2$. Alternatively, **2.63** was quantitatively obtained in excellent diastereoselectivity (6*R*:6*S*, 33:1, determined by ^{1}H-NMR analysis) by the epimerization of **2.81** using NaOMe in MeOH under microwave irradiation (100 °C, 12 h). The absolute configuration of **2.81** and **2.83** was determined by ^{1}H-NMR analysis and confirmed by X-ray crystallographic analysis (Figure 2.3, **B** and **C** respectively). Therefore, these isomerization reactions confirmed **2.63** to be the thermodynamic product and **2.81** as the kinetic one.

[44] (a) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557; (b) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *50*, 1637−1646

Figure 2.4: *Sunlight experimental set-up of the Wolff rearrangement.*

It is noteworthy to mention that a few weeks after our publication,[45] a divergent synthesis of taiwaniaquinoids including taiwaniaquinone F (**2.3**) was reported by Li and co-workers.[46] In this report, a similar Wolff rearrangement was used for the ring contraction of a diazoketone abietane substrate. This emphasizes the generality of this concept for the synthesis of such natural products.

2.2.3. First and second aromatic oxidation and synthesis of taiwaniaquinone F

With the ring-contracted ester in hand, the aromatic oxidation to access phenol **2.61**, was investigated next. Following the Seebach methodology for the aromatic hydroxylation of benzylic alcohols,[37] the reduction of ester **2.63**, was achieved using LAH in THF, yielding the desired alcohol **2.62** in quantitative yield. Although the Seebach strategy relies on the formation of *ortho*-lithiated benzylic alcohol derivatives, the *ortho*-lithiation of the homobenzylic **2.62** alcohol was nevertheless performed using *n*-BuLi, TMEDA, followed by $B(OMe)_3$ and H_2O_2 in hexane at 75 °C. NMR data analysis of the product, obtained in 55% yield, showed the presence of phenol **2.84**, the C11 regio isomer of the desired **2.61** (Scheme 2.17). These results emphasize the importance of the benzylic nature of the alcohol to achieve a directed

[45] Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett.* **2013**, *15*, 1390−1393.
[46] Deng, J.; Li, R.; Luo, Y.; Li, J.; Zhou, S.; Li, Y.; Hu, J.; Li, A. *Org. Lett.* **2013**, *15*, 2022−2025.

ortho-lithiation. Therefore, the obtained selectivity can be explained by an *ortho*-lithiation assisted by the C12 methoxy subtituent and not by the homobenzylic alcohol. As the obtained isomer was also synthetically useful, we decided to continue our synthesis with **2.84**. However, the harsh conditions employed (*n*-BuLi, 75 °C), necessary to achieve conversion, did not allow us to reproduce these results in synthetically useful amounts. Alternatively, the synthesis of bromo compound **2.85** was carried out in high yield (82%). Subsequently, a one pot lithiation-boronation-oxidation reaction using *n*-BuLi, TMEDA, $B(OMe)_3$ and H_2O_2 was attempted to convert **2.85** to phenol **2.84**. Interestingly, traces of product could already be detected by TLC after the lithiation step, which led us to the assumption that O_2 (dissolved in the solvent) could act as the oxidant in this reaction. To our great satisfaction, a simplified, reproducible and scalable procedure, using a one pot lithiation/oxygenation protocol with *n*-BuLi, TMEDA and oxygen at low temperature (−10 °C), afforded the phenol **2.84** in 58% yield together with a smaller amount of recovered starting material (**2.85**, 30%). This methodology was described for the first time by Parker and co-workers in 1986,[47] and has received only little attention from the scientific community. Oxidation of phenol **2.84** to the corresponding *p*-quinone **2.60** was accomplished in quantitative yield using Co(salen) with oxygen in CH_3CN at rt.[48] It is noteworthy that the reaction and the purification of the product were carried out under exclusion from light to avoid decomposition of this sensitive compound. Final oxidation of **2.3** was achieved by treatment with Dess−Martin periodinane (DMP) in CH_2Cl_2 in the dark, to furnish (−)-taiwaniaquinone F (**2.1)** in quantitative yield. All spectroscopic data of this synthetic compound were in agreement with those reported for the isolated natural product.[6]

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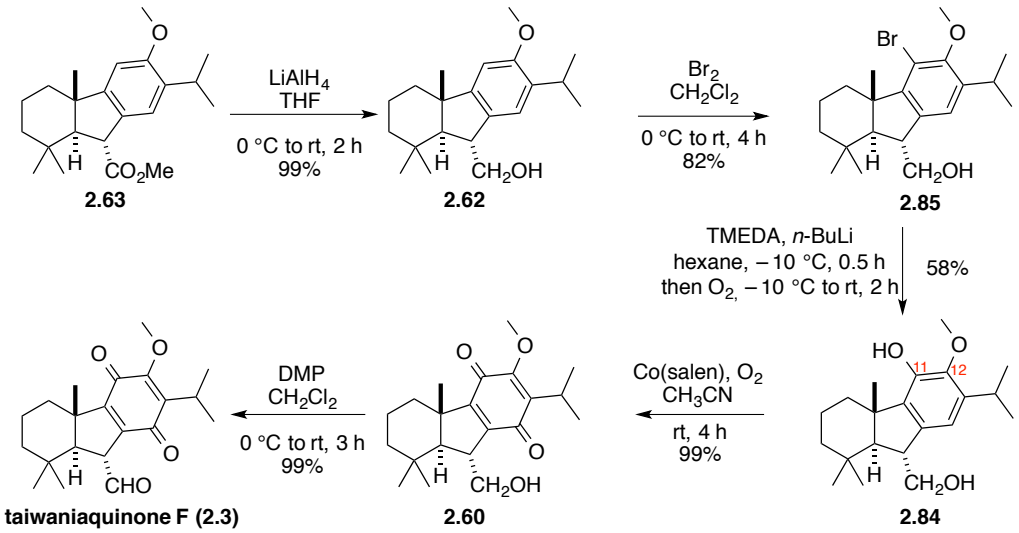
[47] Parker, K. A.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 674−676.
[48] Liu, W.; Liao, X.; Dong, W.; Yan, Z.; Wang, N.; Liu, Z. *Tetrahedron* **2012**, *68*, 2759−2764.



Scheme 2.17: *Completion of the synthesis of taiwaniaquinone F (**2.3**).*

2.2.4. Photolysis of taiwaniaquinone F and first synthesis of taiwaniaquinol A

To avoid decomposition of the natural product (−)-taiwaniaquinone F (**2.3**), it was essential to perform the work-up and purification under strict exclusion from light. To our great surprise, if such precautions were not taken, minor amounts of impurities corresponding to (+)-taiwaniaquinol A (**2.9**) were detected by ^{1}H-NMR analysis (Figure 2.5).

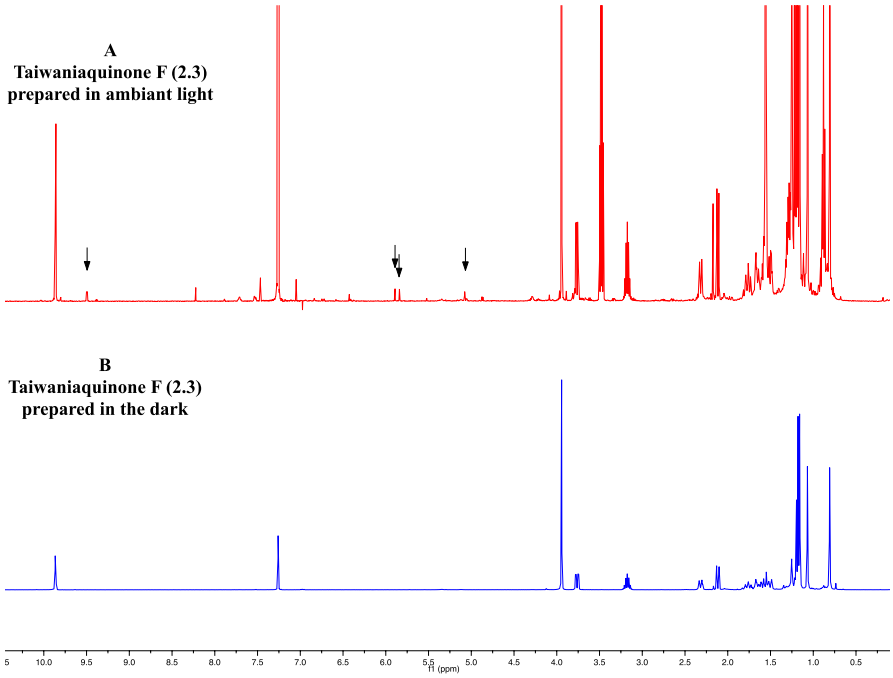
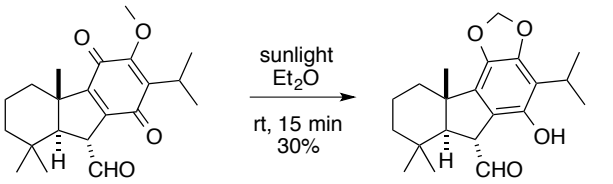


Figure 2.5: *^{1}H-NMR spectrum of taiwaniaquinone F synthesized and purified in the ambient light (**A**) and in the dark (**B**).* The arrows show the ^{1}H-NMR peaks corresponding to taiwaniaquinol A (**2.9**).

Consequently, a diluted solution of (−)-taiwaniaquinone F (**2.3**) in Et_2O was exposed to direct sunlight to produce (+)-taiwaniaquinol A (**2.9**) in 30% yield (Scheme 2.18). All spectroscopic data of synthetic **2.9** were in agreement with the isolated natural product.



taiwaniaquinone F (2.3) **taiwaniaquinol A (2.9)**

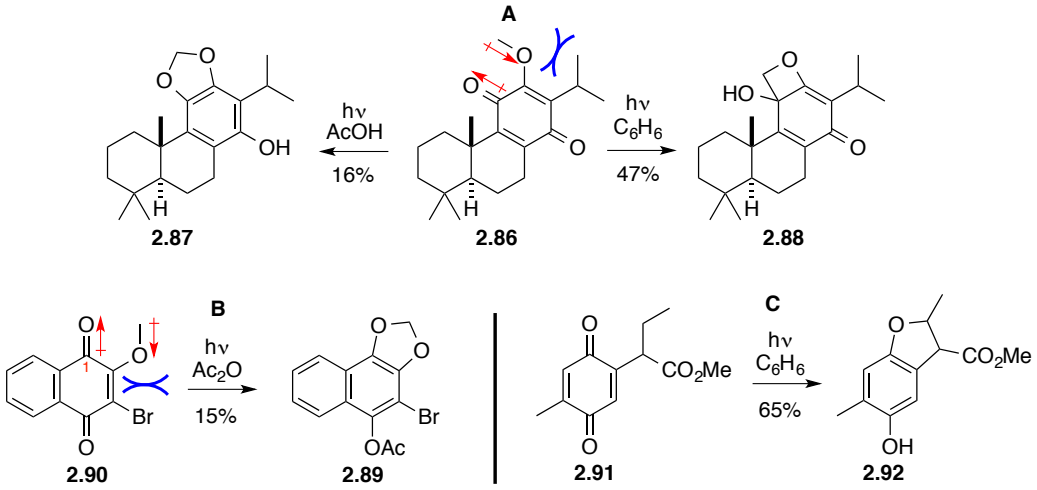
Scheme 2.18: *First synthesis of (−)-taiwaniaquinol A (**2.9**) via the photolysis of taiwaniaquinone F (**2.3**).*

Mechanistic studies to investigate this transformation will be discussed in chapter 4, however, several possible hypotheses have been postulated for related quinone photolysis reactions (Scheme 2.19).[49] Photolysis involving a possible 1,5-hydrogen abstraction reaction (1,5-HAT) of a similar quinone moiety was achieved in 1978 by Edwards *et al*., but has received only little attention afterwards.[50] Indeed, photolysis of royleanone methyl ether (**2.86**) produced the methylenedioxy **2.87**, however, in lower yield (16%). Moreover, irradiation in benzene lead to the Yang photocyclized product **2.88**, most probably *via* a successive 1,5-HAT and radical recombination of the resulting 1,4-diradical. The first step (the γ-hydrogen abstraction) is therefore proposed to take place in the mechanism of the formation of **2.87**. Analogous to the Baldwin's hypothesis for the formation of the methylenedioxy **2.89** from quinone **2.90**,[32] Edwards and co-workers suggested that a dipolar ionic intermediate generated *via* a direct intramolecular electron transfer of a biradical species, was responsible for the methylenedioxy bond formation. The presence of this zwitterionic species was supported by the absence of methylenedioxy product when the photolysis was conducted in an apolar solvent such as benzene. Kozuka and co-workers reported an impressive photolysis of the 2-alkylated-1,4-quinone

[49] (a) Review: Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000−1045. Selected examples: (b) Bruce, J. M. *Q. Rev. Chem. Soc.* **1967**, *21*, 405−428; (c) Bruce, J. M.; Creed, D.; (d) Dawes, K. *J. Chem. Soc. C* **1971**, 2244−2252; (e) Kozuka, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2415−2423; (f) Farid, S. *J. Chem. Soc. D* **1971**, 73−74; (g) Maruyama, K.; Kozuka, T. *Chemistry Letters* **1980**, 341−342.

[50] Edwards, O. E.; Ho, P.-T. *Can. J. Chem.* **1978**, *56*, 733−742.

2.91 bearing an ester group in the alkyl side chain. The obtained high yield of **2.92** was rationalized by the conformation of the alkyl chain, where the γ-hydrogen pointing towards the C1 oxygen atom due to the dipole-dipole repulsion between the ester and the C1=O bond. In a similar manner, Baldwin suggested that the bulky Br group in **2.90** forces the methoxy substituent to point in the direction to the quinonoid carbonyl, therefore facilitating the 1,5-hydrogen transfer. Additionally to the steric argument, the dipole-dipole minimization could also be considered for substrate **2.86**, **2.90** and **2.3**. Indeed, as depicted in Scheme 2.19, the dipole moment of the O−CH_3 bond minimizes the one of the C1=O bond.



Scheme 2.19: *A) Photolysis of royleanone methyl ether by Edwards;*[50] ***B)*** *Synthesis of a methylenedioxy from a methoxy-group by Baldwin;*[32] ***C)*** *Photocylization of quinone **2.39** by Kozuka.*[49e]

The photolysis of **2.3** could generate an alkoxy radical (**2.93**) that would abstract a proton from the OMe group, which is sterically and electronically forced to occupy a favorable position for 1,5−HAT abstraction (Scheme 2.20) to give the methoxy radical **2.94**.[51] With the recent emergence of remote C−H functionalization methods for complex unprotected substrates,[52] this interesting transformation might add novel aspects for strategic disconnections in natural product synthesis. Hydrogen atom transfer from the C14 hydroxyl to the C11 hydroxy radical would generate the 1,5-biradical **2.95**, which upon recombination, would afford taiwaniaquinol A (**2.9**).

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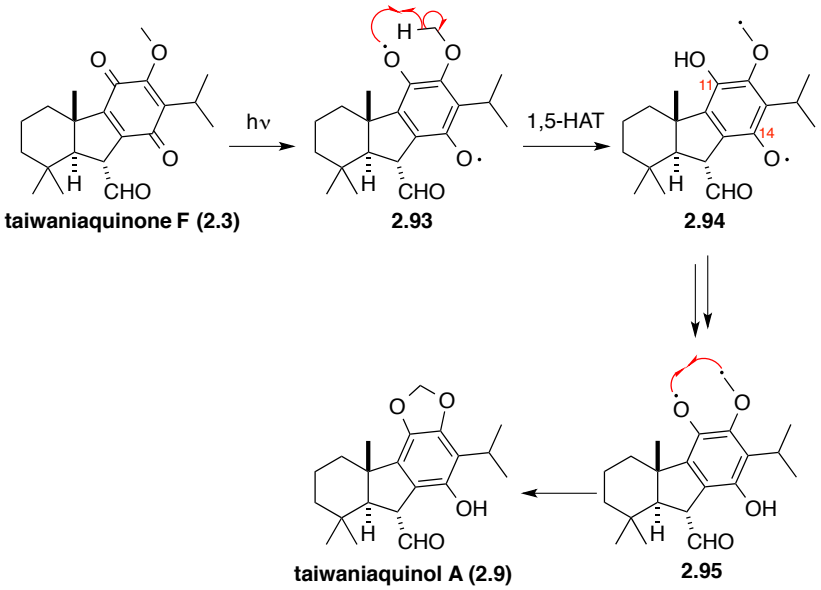
[51] Baldwin, J. E.; Brown, J. E. *J. Chem. Soc. D.* **1969**, 167−168.

[52] (a) Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, *339*, 59−63; Bigi, M. A.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721−9726; (b) Jana, C. K.; Hoecker, J.; Woods, T. M.; Jessen, H. J.; Neuburger, M.; Gademann, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 8407−8411.

The fact that the photolysis was achieved in a non-polar and aprotic solvent (Et_2O) brings support to our fully radical mechanism as the formation of a zwitterionic species requires a polar and protic solvent. In such a case, a switch to ionic pathways appears difficult. However, further experimental studies need be performed to validate this hypothesis.



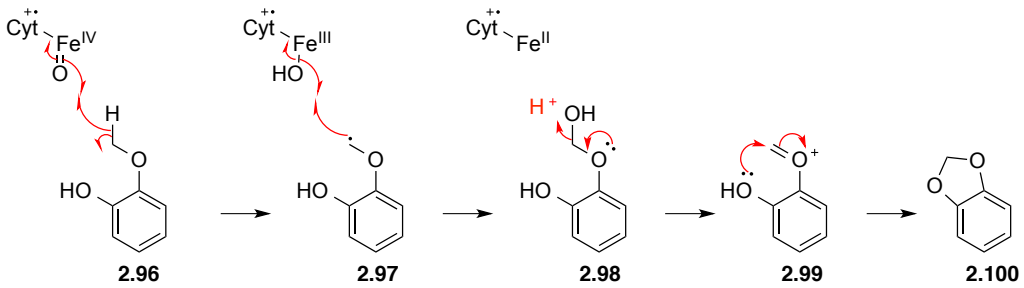
Scheme 2.20: *Mechanistic proposal for the formation of taiwaniaquinol A (**2.9**).*

2.2.5. Biosynthetic proposal for the formation of taiwaniaquinol A

The ease of this remote C−H activation by simply exposing the quinone to sunlight leading to product conversion suggests that this transformation could be part of the biosynthetic pathway at *Taiwania cryptomoides*. Interestingly, taiwaniaquinone F (**2.3**) was isolated from the bark of *T. cryptomerioides*, whereas taiwaniaquinol A (**2.9**) was isolated from the leaves of the same tree,[7] further supporting this biosynthetic hypothesis. It might be possible that the transformation observed in our synthetic studies also occurs in the leaves of *T. cryptomerioides* that are exposed to sunlight.

The previously proposed mechanisms for the biogenesis of methylenedioxy bridged natural products invoked the participation of cytochrome P450 enzymes in an oxidative cyclization of a 1,2-hydroxymethoxy-substituted aromatic ring as depicted

in Scheme 2.21.[53] It is suggested that the cytochrome P450 undergoes a monooxygenation of the methoxy group *via* the usual oxygenation sequence consisting of a C−H abstraction of the methoxy **2.96** followed by a rebound mechanism with the resulting reduced Fe^{III}−OH catalyst and the methoxy-radical **2.97** to produce the hemiacetal **2.98**. Dehydration of **2.98** would produce the oxonium ion **2.99**, which upon nucleophilic attack of the ortho alcohol would furnish the methylenedioxy moiety **2.100**. The absence of any enzymes in our synthetic route suggests that this non-enzymatic pathway could present a viable biogenetic option for other methylenedioxy bridged catechols, in particular the ones having an extra para-hydroxylate carbon. Given the prevalence of these compounds in nature,[54] we propose that other members of this class could be formed by a similar non-enzymatic mechanism.



Scheme 2.21: *Generaly accepted cyt. P450 mechanism for the biosynthesis of methylenedioxy natural products.*[54]

2.2.6. Conclusion and outlook

In summary, a new protecting-group-free route to (−)-taiwaniaquinone F (**2.3**) and the first synthesis of (+)-taiwaniaquinol A (**2.9**) was developed starting from commercially available abietic acid. Salient features of this synthesis include: (1) a Wolff ring contraction of the diazo derivative of (+)-sugiol methyl ether **2.80**; (2) an aromatic oxidations of the ring contracted product **2.81** by molecular oxygen; and (3) an unanticipated formation of a methylenecatechol moiety *via* the photolysis of (−)-taiwaniaquinone F (**2.3**) to (+)-taiwaniaquinol A (**2.9**) *via* a remote C−H

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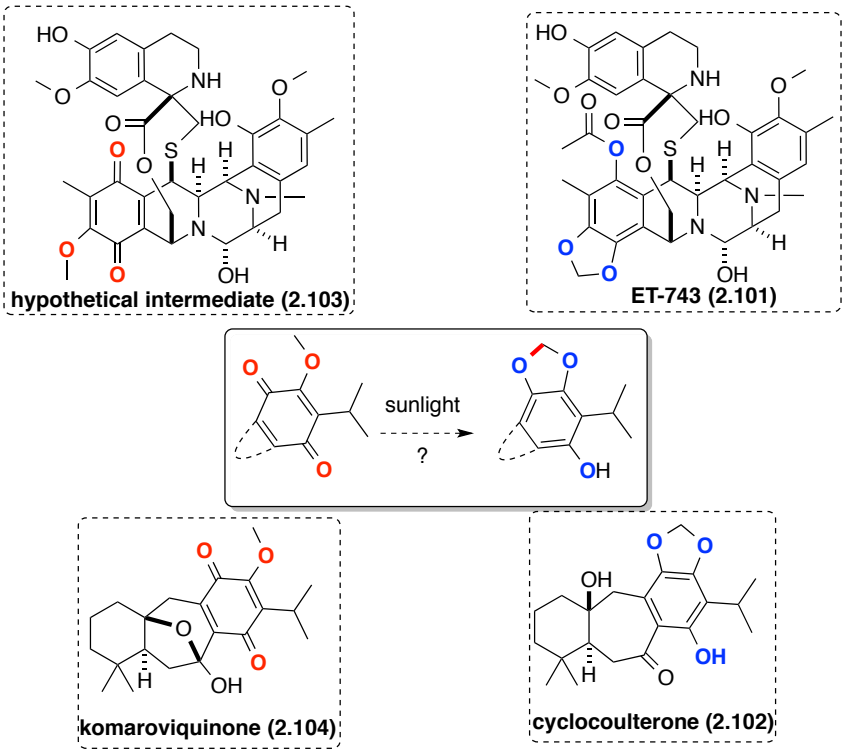
[53] (a) Bauer, W.; Zhenk, M. H. *Phytochemistry* **1991**, *30*, 2953−2961; (b) Ono, E.; Nakai, M.; Fukui, Y.; Tomomori, N.; Fukuchi-Mizutami, M.; Saito, M.; Satake, H.; Tanaka, T.; Katzuka, M.; Umezawa, T.; Tanaka, Y. *PNAS* **2006**, *103*, 10116−10121; Ikezawa, N.; Iwasa, K.; Sato, F. *FEBS Journal* **2007**, *274*, 1019−1035.

[54] Review: Kerr, R. G.; Miranda, N. F. *J. Nat. Prod.* **1995**, *58*, 1618−1621.

functionalization. A hypothesis for the biogenesis of the frequently encountered methylenedioxy motif in natural products was proposed, and bioactive compounds, such as ecteinascidin 743 (ET-743, **2.101**) and cyclocoulterone (**2.102**),[55] could be generated either synthetically or biosynthetically from a quinone precursor (**2.103** and **2.104** respectively) through a very similar mechanism. This hypothesis may provide further insight to the biogenesis of this interesting class of natural products.

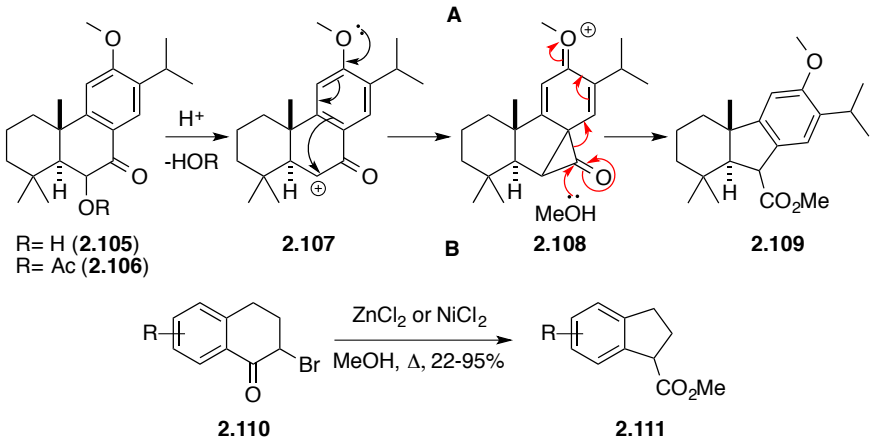


Scheme 2.22: *Possible targets for the remote C−H functionalization.*

Moreover, the potential of the "biomimetic" nature of our synthesis could be further investigated. Indeed, the known hydroxy-derivatives of sugiol methyl ether (**2.56**), **2.105** and **2.106**,[56] could, upon solvolysis, generate the carbocation **2.107** (Scheme 2.23, **A**). This carbocation could be trapped intramolecularly by the electron rich aromatic ring to form the cyclopropanone intermediate **2.108**, resembling an intermediate of a Favorskii reaction.[57] Nucleophilic attack of methanol would open the cyclopropanone moiety of **2.108** to form the ring contracted ester **2.109**. Such

[55] Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128−131.
[56] Li, X.; She, X.; Zhang, J.; Wu, T.; Pan, X. *Tetrahedron* **2003**, *59*, 5737−5741.
[57] Kammath, V. B.; Šolomek, T.; Ngoy, B. P.; Heger, D.; Klán, P.; Rubina, M.; Givens, R. S. *J. Org. Chem.* **2013**, *78*, 1718−1729.

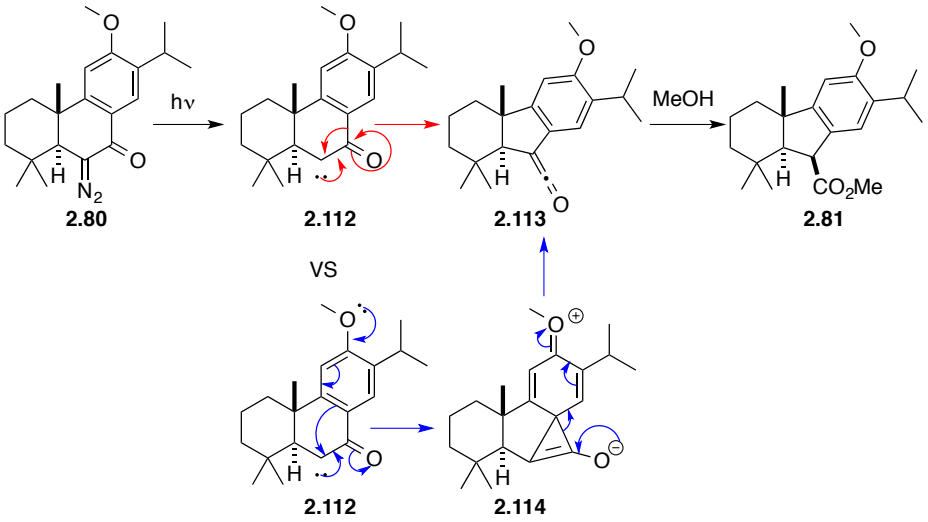
acidic Favorskii-type reactions have already been performed with α-bromo-cycloalkyl-arylketone such as **2.110** using $ZnCl_2$[58] or $NiCl_2$[59] in methanol to yield the desired ring contracted methyl ester **2.111** (Scheme 2.23, **B**). The expected feasibility of this reaction could be experimentally assessed by treating the α-hydroxy-ketone **2.105**, its acetyl derivative **2.106** or a α-halo sugiol methyl ether derivative, with either a Brønsted or a Lewis acid in methanol (or other alcoholic or aqueous solvents).



Scheme 2.23: A) *Hypothetical Favorskii-type ring contraction of sugiol methyl ether derivative **2.105** or **2.106**; **B)** Cationic Favorskii-type ring contraction by Chatterjee*[58] *and Gautam.*[59]

The synthesis of the ring contracted product **2.81**, includes most probably the carbene intermediate **2.112**, which formed the ketene **2.113** *via* an 1,2-aryl shift (red pathway, Scheme 2.24). However, it could be envisaged that such an electrodeficient carbene (**2.112**) could form the cyclopropyl enolate intermediate **2.114** through a nucleophilic attack of the electron rich aryl, which would furnish the same ring-contracted ketene **2.113** (blue pathway, Scheme 2.24). Intermediate **2.114** would therefore resemble the hypothetical Favorskii-type cyclopropanone **2.108**.

[58] Maiti, S. B.; Chaudhuri, S. R. R.; Chatterjee, A. *Synthesis* **1987**, 806−809.
[59] Tandon, V. K.; Awasthi, A. K.; Singh, K. A.; Maurya, H. K.; Gautam, S. K. *Heterocycles* **2010**, *80*, 593−600.

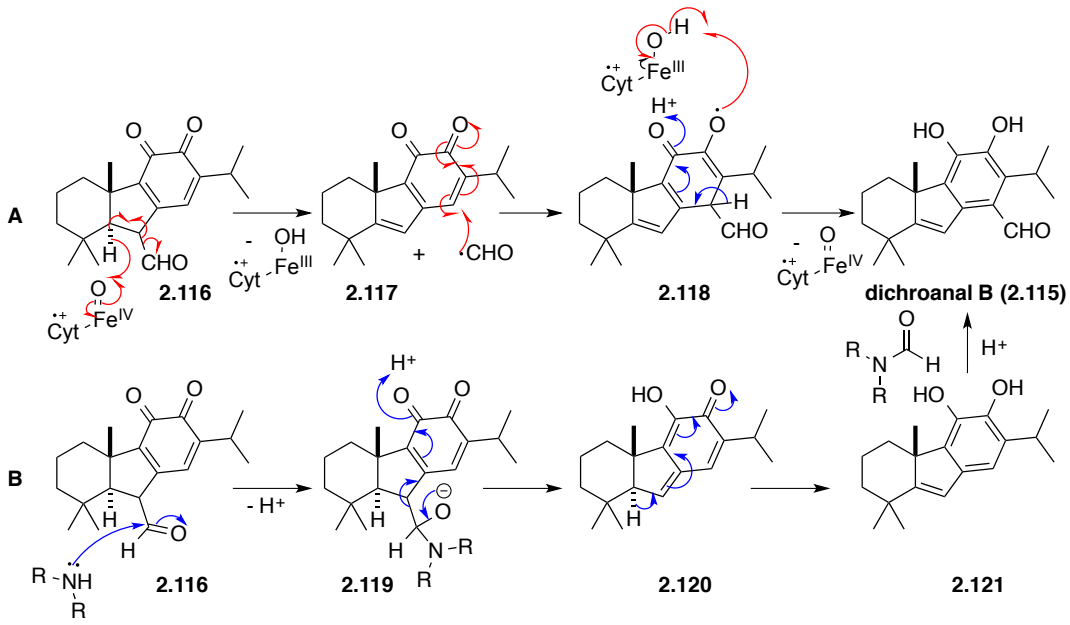


Scheme 2.24: *Wolff rearrangement of **2.80** via a hypothetical cyclopropyl enolate intermediate **2.114**.*

Unfortunately, neither this hypothesis, nor any of the previously described hypotheses accounted for the synthesis of C_{20} taiwaniaquinoids, having a formyl group at an unusual position such as dichroanal B (**2.115**). Therefore, other pathways must exist to generate such species. Indeed, orthoquinone aldehyde **2.116**, which could be generated through the biogenetic hypothesis (Scheme 2.24, **A**) earlier described, would undergo a nucleophilic deformylation to yield the orthoquinone **2.117**. This process could be promoted by a cyt. P450 thereby generating a formyl radical and the reduced cyt.$^{(+\cdot)}$Fe^{III}–OH (Scheme 2.25, **A**).[60] The addition of the formyl radical to **2.117** would generate the alkoxy radical **2.118**, which, upon H atom transfer with cyt.$^{(+\cdot)}$Fe^{III}–OH would yield dichroanal B (**2.115**) after tautomerization and the reoxidized cyt.$^{(+\cdot)}$Fe^{IV}=O. According to this mechanism, this process would be redox neutral. Alternatively, a nucleophilic amine could promote a deformylation of **2.119** upon nucleophilic attack of aldehyde **2.116** (Scheme 2.25, **B**). The resulting orthoquinone methide **2.120** would provide the catechol **2.64** by tautomerization. Electrophilic acylation of **2.121** by the previously formed formamide could lead to dichroanal B (**2.115**). The second hypothesis could be straightforwardly be assessed in the laboratory. Treatment of **2.116** with $NaN(Me)_2$ at high temperature would provide catechol **2.121** and DMF as by-product. A final Friedel-Crafts acylation

[60] Akhtar, M.; Corina, D.; Miller, S.; Shyadehi, A. Z.; Wright, J. N. *Biochemistry* **1994**, *33*, 4410−4418.

using DMF and $POCl_3$ would complete the synthesis of dichroanal B (**2.115**).[61] Node and co-workers previously performed such a formylation of **2.121**, using Rieche formylation conditions,[62] therefore supporting this hypothesis. In Nature, formylations are performed by formyltransferase through a similar mechanism.[63]



Scheme 2.25: *Hypothetical nucleophilic deformylation biosynthesis of dichroanal B (**2.115**) via a A) radical or B) ionic mechanism.*

[61] Ueki, R.; Yamaguchi, K.; Nonaka, H.; Sando, S. *J. Am. Chem. Soc.* **2012**, *134*, 12398−12401.

[62] Node, M.; Ozeki, M.; Planas, L.; Nakano, M.; Takita, H.; Mori, D.; Tamatani, S.; Kajimoto, T. *J. Org. Chem.* **2010**, *75*, 190−196.

[63] (a) Dickerman H. W.; Steers E. Jr.; Redfield B. G.; Weissbach H. *J. Biol. Chem.* **1967**, *242*, 1522−1525; (b) Qiao, Q. A.; Jin, Y.; Yang, C.; Zhang, Z.; Wang, M. *Biophysical Chemistry* **2005**, *118*, 78−83.

3. Divergent Biomimetic Synthesis of Structurally Diverse Icetexane Members

3.1. Introduction

3.1.1. Plant extract as a source of bioactive compounds and their pharmacological and industrial use

The use of plants for medicinal, culinary or aromatic purposes is as old as human history. Indeed, archeological evidence showed that herbalism (the medicinal use of plants or their extracts) was already used by Neanderthals.[64] Herbal medicine is still widely used due to its abundance, accessibility and low cost, especially in developing countries where modern medicine is not accessible to millions of people.[65] Nevertheless, a fast growing market of plant extracts is observed in industrialized countries, which contributes to the development of this traditional discipline. The commercially available extracts typically contain several active principles, which make them usually more effective than the standard mono-therapy in modern medicine thanks to possible synergic effect of the different active principles. However, the dosage of these plants (or their extract) has to carefully evaluated taking in account where and when the plant was harvested due to active principle variation. If not, over dosage can lead to severe side effects or even death. For instance, *Datura stramonium*, known as Jimeson weed, was used as very powerful treatment for asthma, however recreational misuse of this plant can lead to anticholinergic intoxication, which can be fatal. The toxicity is observed in slightly higher dosage than the medicinal usage.[66] Moreover, due to resource limitations of certain plant species, especially the ones that can't be easily cultivated, and the increasing demand for alternative medicine, the use of such medicine should only be seen as complementary medicine to avoid the diminution of natural resources. Apart from

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[64] Solecki, R. C. *Science* **1975**, *190*, 880−881.
[65] WHO Traditional Medicine Strategy: 2014−2023; ISBN: 9789241506090, page 15−19.
[66] Coremans, P.; Lambrecht, G.; Schepens, P.; Vanwelden, J.; Verhaegen, H. *Clinical Toxicology* **1994**, *32*, 589−592.

medicinal utilization of such extracts, industry widely uses natural products in a variety of applications ranging from fragrance to food supplements. Unfortunately, the preparation of such extracts is still done by some "specialists" using old methods that do not guarantee the integrity, the quality and the dosage of such preparations. These old technologies should therefore be replaced or improved by new or modified technologies of extraction, purification and formulations.[67] For example the use of renewable and eco-friendly supercritical CO_2 to replace petroleum based solvents or utilization of sonicators for extraction are important and effective alternatives. Furthermore, modern quality and quantity control measures ensure appropriate and high quality extracts for various consumer applications. The pharmacological industry utilizes such technologies to produce not only plant extracts in different galenical forms from natural sources, but also to isolate pure active compound for a direct use (fidaxomycin, quinine, carnosic acid, …) or intermediates for semi-synthesis of important biological principles (ET-743, Taxol, Vinorelbine, …).[68]

3.1.2. Icetexanes

Icetexanes[69] are a variety of diterpenoids isolated from diverse plant sources especially from the Labiatae family. Icetexone was the first member to be isolated and characterized from *Salvia ballotaeflora*.[70] These compounds exhibit a unique carbon skeleton consisting of a 6-7-6 tricyclic core structure (Figure 3.1) with the systematic name 9(10→20)-*abeo*-abietane. This systematic appellation refers to their hypothetical abietane biosynthetic origin (see details in section 3.1.3). As already seen in chapter 2, taiwaniaquinoids possess, compared to icetexanes, an 6(7→8)-*abeo*-abietane or 5(6→7)-*abeo*-abietane skeleton depending on which biosynthetic hypothesis is postulated for these compounds.

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[67] Bonati, A. *J. Ethnopharmacol.* **1980**, *2*, 167−171.
[68] De Silva, T. *Industrial utilization of medicinal plants in developing countries* Medicinal plants for conservation and health care, Food and Agricultural Organization of the United Nations **1995**.
[69] Simmons, E. M.; Sarpong, R. *Nat. Prod. Rep.* **2009**, *26*, 1195−1217.
[70] Watson, W. H.; Taira, Z.; Dominguez, X. A.; Gonzales, H.; Guiterrez, M.; Aragon, R. *Tetrahedron Lett.* **1976**, *17*, 2501−2502.

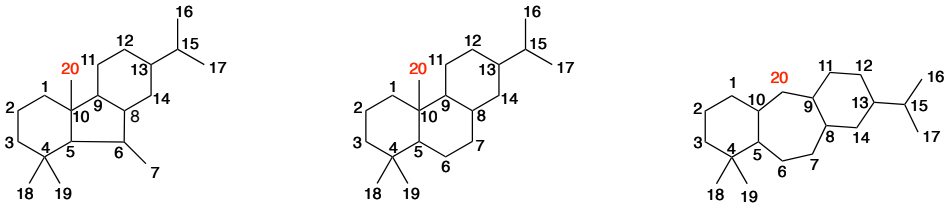


Figure 3.1: *Abietane and the rearranged taiwaniaquinoids and icetexane skeleton.*

According to Sarpong's classification of icetexanes[69], *abeo*-abietanes can be differentiated depending on their oxygenation state at C3, C11, C14 and C19. Figure 3.2 shows three subclasses of these natural products: (1) pisiferins, lacking of oxygenation at C3, C11, C14 and C19, obtained their name from the natural product pisiferin (**3.1**). It was first isolated from *Chamaecyparis pisifera* in 1980 and structurally misassigned[71] before being reassigned four years later after re-isolation from the same plant [72]. Most of pisiferins were exclusively found in the *Chamaecyparis* genus. However, exceptions such as pisiferanol (**3.2**) and euolutchuol E (**3.3**) were isolated from *Salvia lanigera* and *Euonymus lutchuensis*, respectively. All other pisiferins shown in Figure 3.2 bearing a β-C10 oxygenation (**3.2**−**3.4**), in contrast to the parent compound pisiferin (**3.1**), will be discussed in more details in section 3.2.7. (2) The second class was named after barbatusol (**3.5**), bearing an additional oxygenation at C11 compared to pisiferins. It was isolated from *Coleus barbatus* and showed hypotensive activity in rats.[73] Salvicanol (**3.6**), brussonol (**3.7**), przewalskin E (**3.8**) and other barbatusols bearing a β-C10 oxygenation, will be discussed in more details in section 3.2.6. (3) coulterones, which have an additional hydroxyl group at C14, are named after coulterone (**3.9**), which first isolated from *Salvia coulteri* in 1994[74] and eleven years later from *Hyptis platanifolia*.[75] Congeners of coulterone (**3.9**), cyclocoulterone (**3.10**), komaroviquinone (**3.11**) and komarovispirone (**3.12**) were all isolated by Kiuchi and co-workers from *Dracocephalum komarovi.* Both **3.11** and **3.12** have shown trypanocidal activity

[71] Yatagai, M.; Takahashi, T. *Phytochemistry* **1980**, *19*, 1149−1151.
[72] Hasegawa, S.; Hirose, Y.; Yatagai, M.; Takahashi, T. *Chem. Lett.* **1984**, 1837−1838.
[73] Kelecom, A. *Tetrahedron* **1983**, *39*, 3603−3608.
[74] Frontana, B.; Cárdenas, J.; Rodríguez-Hahn, L. *Phytochemistry* **1994**, *36*, 739−741.
[75] Araujo, E. C. C.; Lima, M. A. S.; Nunes, E. P.; Silveira, E. R. *J. Braz. Chem. Soc.*, **2005**, *16*, 1336−1341.

against the parasite responsible for the Chagas disease, whereat komaroviquinone (**3.11**) showed the best results (LD_{50} = 0.4 μM).[76] Although komarovispirone (**3.12**) bears a rearranged icetexane skeleton, **3.12** belongs to coulterone subclasses due to the proposed biosynthetic connection with **3.11**[76b,69]. Nevertheless, **3.12** was assigned to another family name where it is the unique member: the komarovispiranes[77]. Two additional subclasses, the taxamarins and the icetexones carry oxygenations at C3 and C11, and at C11, C14 and C19 respectively.

[76] (a) Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128−131; (b) Uchiyama, N.; Ito, M.; Kiuchi, F.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *Tetrahedron Lett.* **2004**, *45*, 531−533.

[77] Srikrishna, A.; Beeraiah, B. *Indian J. Chem.* **2007**, *46B*, 1999−2003.

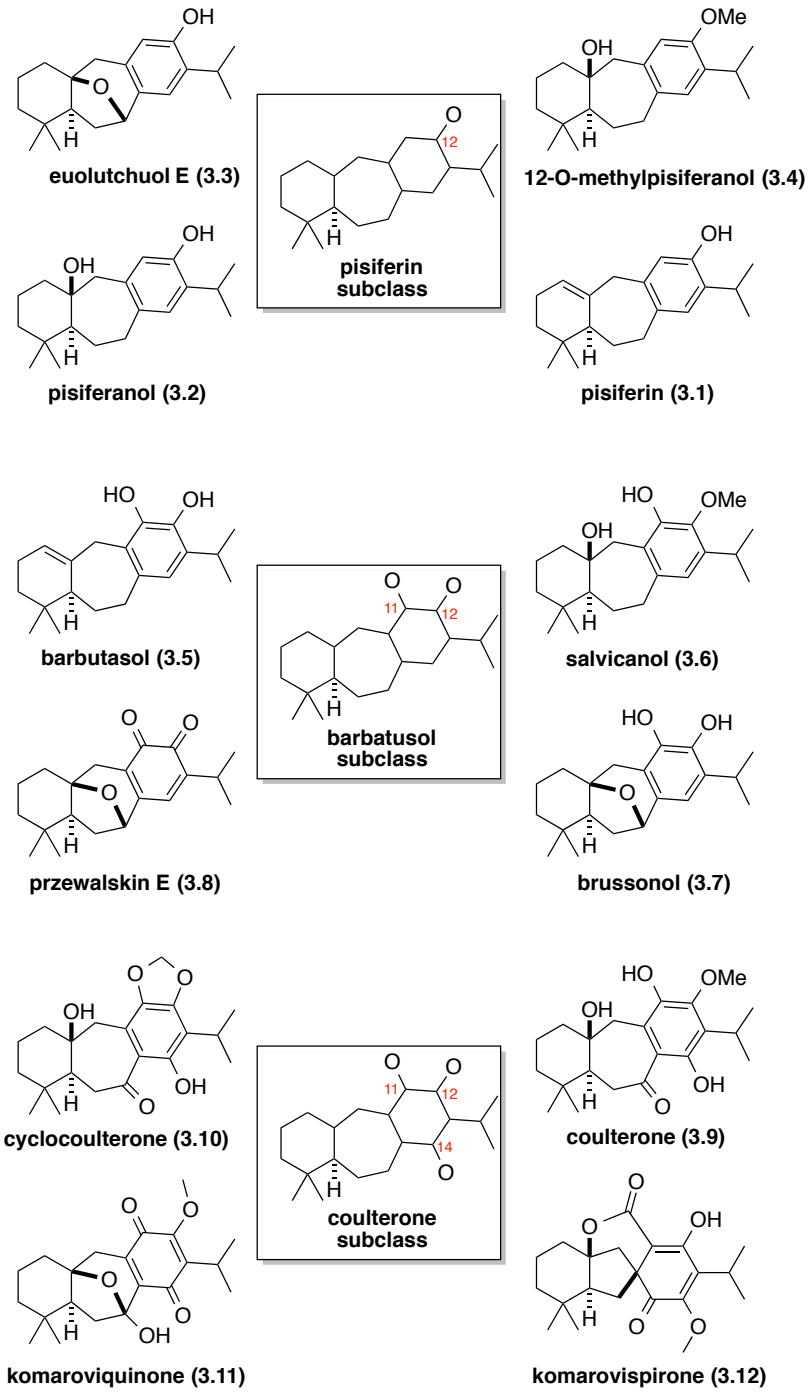
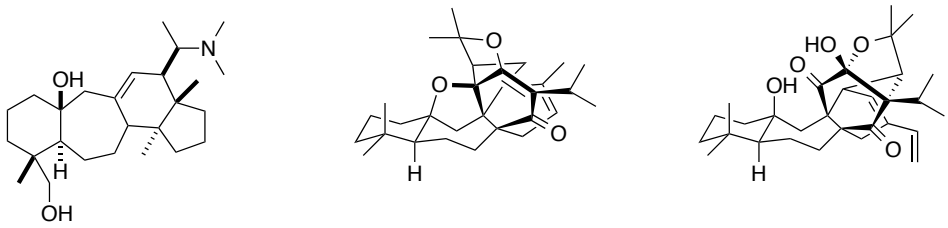


Figure 3.2: *Examples of subclasses of icetexanes according to Sarpong.*[69]

Other natural products were found to have an icetexane framework in their skeleton [78,79,80] (Figure 3.3).

[78] Bénéchie, M.; Khuong-Huu, F. *Tetrahedron* **1976**, *32*, 701−707.
[79] Parvez, A.; Choudhary, M. I.; Akhter, F.; Noorwala, M.; Mohammad, F. V.; Hasan, N. M.; Zamir, T.; Ahmad, V. U. *J. Org. Chem.* **1992**, *57*, 4339−4340.

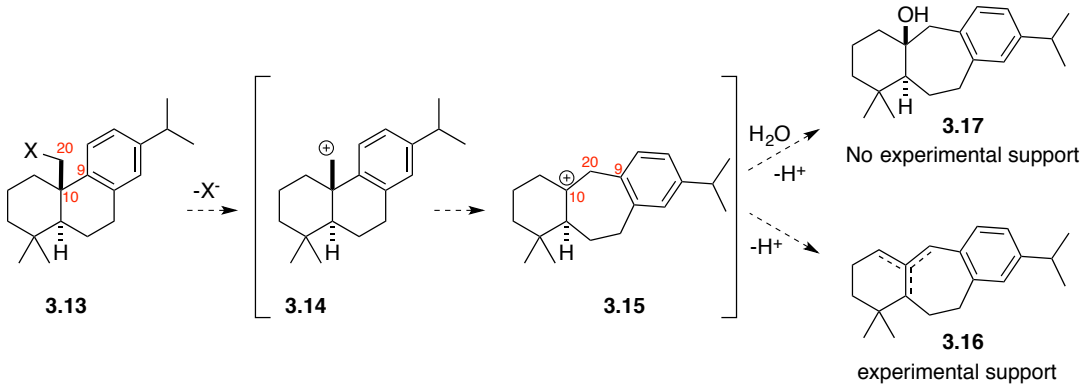


***N*-isobutyryl-buxaline F** **(+)-perovskone** **(+)-salvadione-B**

Figure 3.3: *Structures of natural products having a 6-7-6 membered ring system.*[78,79,80]

3.1.3. Biogenetic hypothesis of icetexanes

As showed in section 3.1.2, the systematic name 9(10→20)-*abeo*-abietane given to icetexanes indicates that the abietane biosynthetic origin of icetexanes is well accepted throughout the scientific community. To the best of our knowledge, Watson and Dominguez[70] were the first research group to propose such a connection between abietanes and icetexanes, but various other research labs[81] have proposed a similar mechanism to associate abietanes to their rearranged congeners (see Scheme 3.1).



Scheme 3.1: *Hypothetical biogenetic abietane ring expansion to icetexanes.*[70,81] X = H or OH.

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[80] (a) Ahmad, V. U.; Zahid, M.; Ali, M. S.; Ali, Z.; Jassbi, A. R.; Abbas, M.; Clardy, J.; Lobkovsky, E.; Tareen, R. B.; Iqbal, M. Z. *J. Org. Chem.* **1999**, *64*, 8465−8467; (b) Majetich, G.; Zou, G.; Shougang, H. *Org. Lett.* **2013**, *15*, 4924−4927.

[81] (a) Sánchez, C.; Cárdenas, J.; Rodríguez-Hahn, L.; Ramamoorthy, T. P. *Phytochemistry* **1989**, *28*, 1681−1684; (b) González, A. G.; Andrés, L. S.; Luis, J. G.; Brito, I.; Rodríguez, M. L. *Phytochemistry* **1991**, 30, 4067−4070; (c) Fraga, B. M.; Díaz, C. E.; Guadaño, A.; González-Coloma, A. *J. Agric. Food Chem.* **2005**, *53*, 5200−5206; (d) Simmons, E. M.; Yen, J. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2705−2707; (e) Ziang, Z.-Y.; Huang, C.-G.; Xiong, H.-B.; Tian, K.; Liu, W.-X.; Hu, Q.-F.; Wang, H.-B.; Yang, G.-Y.; Huang, X.-Z. *Tetrahedron Lett.* **2013**, *54*, 3886−3888.

Hydride abstraction from the angular methyl group (X = H) or solvolysis of the primary alcohol (X = OH) **3.13** generates a primary cation **3.14** that immediately rearranges to the more stable ring expanded tertiary carbocation **3.15**, to form the icetexane core structure. Ring expansions which lead to alkenes **3.16** *via* a deprotonation of carbocation **3.15** were experimentally supported. Indeed, such rearrangement were performed by treating primary hydroxyl abietanes such as **3.13** with either thionyl chloride in dry benzene or *p*-TsCl in dry pyridine to yield alkene icetexanes such as **3.16**.[82] Although, the carbocation (**3.15**) trapping by a water molecule was frequently suggested to access icetexanes bearing a C10 hydroxyl group like **3.17**, no experimental evidence of such a mechanism was given.

Before being reassigned,[72] the structure of pisiferin (**3.1**) was initially described as shown in Scheme 3.2 (**3.18**).[71] Indeed, three bonds are susceptible to take part in the formation of a more stable tertiary carbocation: (1) the C10-C9 bond migration (red pathway in Scheme 3.2) leads to carbocation **3.19** and then to pisiferin (**3.1**) upon deprotonation; (2) and (3) the C10-C1 or C10-C5 bonds migration (blue and green pathway, respectively) would generate carbocations **3.20** or **3.21**, respectively, which are both tertiary and benzylic carbocations and therefore more stable than **3.19** (if the conformational energy difference induced by the newly formed sp^2 C+ is ignored). However, only structures featuring the icetexane skeleton were isolated, showing the prevalence of the C-aryl bond to undergo migration. This could be rationalized by a partial interaction of the empty p-orbital of the primary carbocation **3.22** with the partial negative charge, built up by the π electrons of the electron rich aryl group, therefore directing this p-orbital parallel to the electron rich C10-C9(aryl) σ-bond allowing an optimal orbital overlap for a nucleophilic attack (see box in Scheme 3.2).

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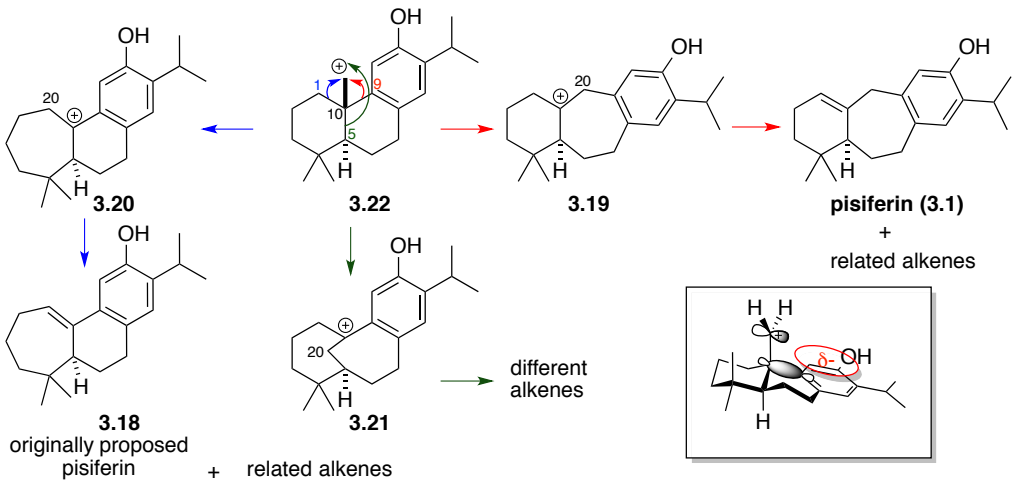
[82] (a) Yatagai, M.; Takahashi, T. *Phytochemistry* **1980**, *19*, 1149−1151; Kelecom, A. *Tetrahedron* **1983**, *39*, 3603−3608; (b) Hasegawa, S.; Hirose, Y.; Yatagai, M.; Takahashi, T. *Chem. Lett.* **1984**, 1837−1838; (c) Kametani, T.; Kondoh, H.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Trans. 1* **1990**, 5−10.



Scheme 3.2: *Possible ring expansion of a ferruginol C20 carbocation toward pisiferin.*[71,72]

3.1.4. Previous syntheses of icetexanes members

The rare fused 6-7-6 ring system skeleton of icetexanes coupled with their wide-range of stereochemical and functional groups, their rich biological activity and intriguing biogenetic origin, make these compounds challenging targets for synthetic chemists. Indeed, the first total synthesis of racemic pisiferin (**3.1**) was accomplished in 1986 by Matsumoto and co-workers using a A + C → ABC strategy.[83] During the last three decades, this predominant strategy for the synthesis of icetexanes was achieved through the coupling of the A ring with the C ring followed by the construction of the B ring. Six different variants of this strategy are shown in Scheme 3.3 to Scheme 3.7, whereat the synthetic precursors will be linked to the corresponding retrosynthetic synthons. One example of an icetexane total synthesis will be given for each strategy. The syntheses of the B ring could be further classified into a top-down or a bottom-up approach whether the coupling of the A and C ring forms the top of the B ring or the bottom of this ring, respectively. The latter perspective will be discussed first.

The first variant (Scheme 3.3) to be employed for the synthesis of icetexanes was disclosed in the Matsumoto[83] synthesis of pisiferin where aldehyde **3.23** and phosphonium salt **3.24**, corresponding to synthons **3.25** and **3.26**, were coupled *via* a Wittig olefination to give the attached A and C ring in which the bottom part of the B

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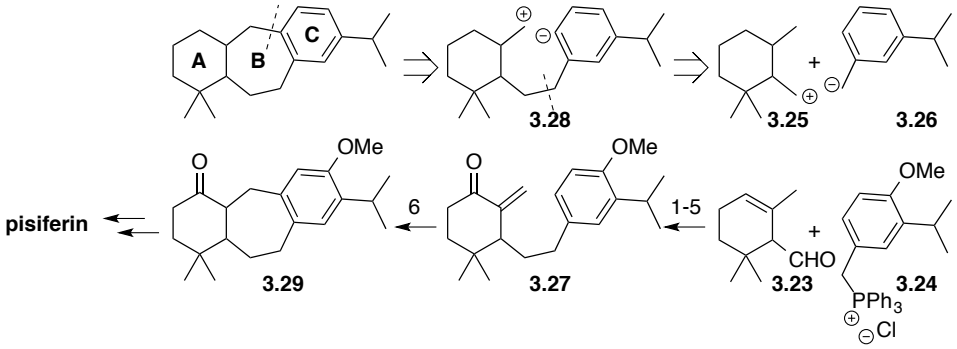
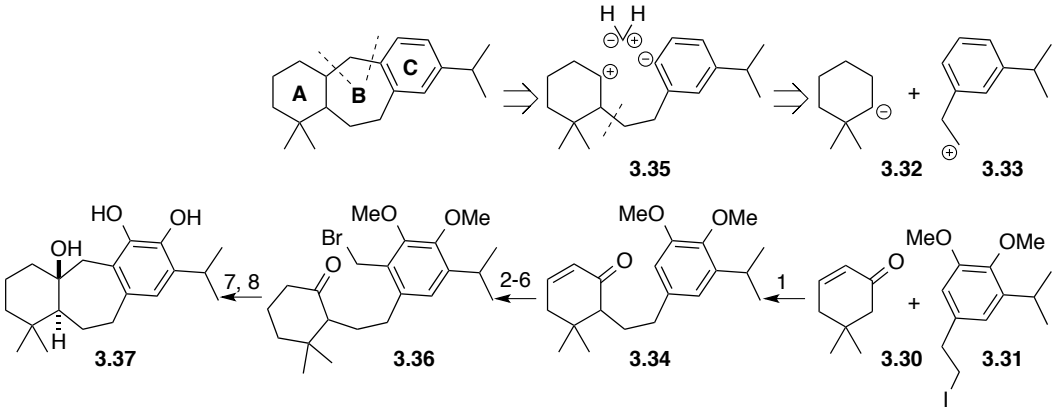
[83] Matsumoto, T.; Imai, S.; Yoshinari, T.; Matsuno, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3103−3108.

ring is formed. A successive double bond reduction, epoxidation, base catalyzed epoxide opening and allylic alcohol oxidation delivered enone **3.27** corresponding to synthon **3.28**. Formation of the B ring of **3.29** was accomplished through an acidic intramolecular cyclization. Final steps include reduction and elimination reactions, which delivered the (±)-pisiferin.



Scheme 3.3: *Total synthesis of pisiferin by Matsumoto through variant A:*[83] 1) *n*-BuLi, then **3.23**; 2) H_2, Pd/C; 3) *m*-CPBA; 4)$LiNEt_2$; 5) PCC; 6) PPA.

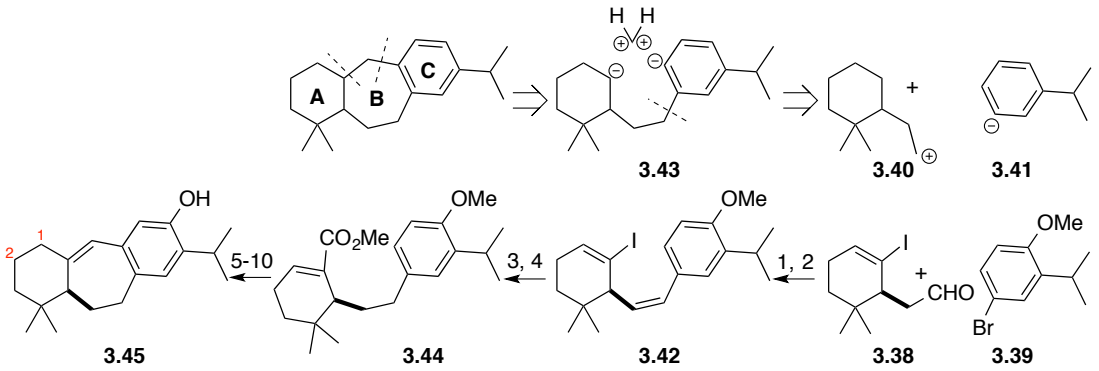
The second variant used by Pan and co-workers, starts with enone **3.30** and alkyl iodide **3.31** (Scheme 3.4) corresponding to synthons **3.32** and **3.33** that were joined *via* a base catalyzed alkylation to furnish the attached A and C rings product **3.34** corresponding to synthon **3.35**.[84] A sequence protocol consisting of a double bond reduction, a keto group protection, a formylation, a bromination of a primary alcohol and a keto deprotection furnished the alkyl bromide **3.36**. The formation of the B ring was accomplished through an intramolecular Barbier reaction. Final dimethyl deprotection delivered the (±)-demethylsalvicanol **3.37**.



Scheme 3.4: *Total synthesis of demethylsalvicanol by Pan through variant B:*[84] 1) LDA then **3.31**; 2) Li, NH_3; 3) BF_3•OEt_2, $(OHCH_2)_2$; 4) *n*-BuLi, then PFA; 5) PBr_3; 6) aq. HCl; 7) Zn; 8) NaH, EtSH.

[84] Wang, X.; Pan, X.; Cui, Y.; Chen, Y. *Tetrahedron* **1996**, *52*, 10659−10666.

The third variant used by Shia and co-workers, starts with aldehyde **3.38** and aryl bromide **3.39**, corresponding to synthons **3.40** and **3.41** (Scheme 3.5), which were coupled through a bromo-lithium exchange of **3.39** followed by an alkylation of **3.38**.[85] A subsequent acidic dehydration furnished the alkene **3.42** corresponding to synthon **3.43**. Double bond hydrogenation followed by an I/Li exchange/acylation sequence, generated ester **3.44**, which displays the complete icetexane structural core. A five steps protocol consisting of a saponification, acidic intramolecular Friedel-Crafts acylation forming the icetexane skeleton, ketone reduction, dehydration, C1-C2 double bond reduction and deprotection, provided the (−)-isopisiferinc (**3.45**).



Scheme 3.5: *Total synthesis of (−)-isopisiferin by Liu and Shia through variant C*:[85] 1) *n*-BuLi, then **3.38**; 2) p-TsOH; 3) *n*-BuLi, then $ClCO_2Me$; 4) H_2, Pd/C; 5) KOH; 6) TFAA, TFA; 7) $NaBH_4$; 8) Et_3N, MsCl; 9) H_2, Pd/C; 10) NaH, EtSH.

The fourth variant used by Jennings and co-workers,[86] a top-down approach, starts with ketone **3.46** and aryl **3.47** (Scheme 3.6) corresponding to synthons **3.48** and **3.49**. Benzylic lithiation of **3.47** followed by addition of **3.46** furnished the tertiary alcohol **3.50** corresponding to the synthon **3.51**. A sequence protocol consisting of an ozonolysis and Marson type cyclization delivered the B ring of the cyclic ether **3.52**, displaying the icetexane skeleton. Final dimethyl deprotection delivered (±)-brussonol (**3.7**).[81d]

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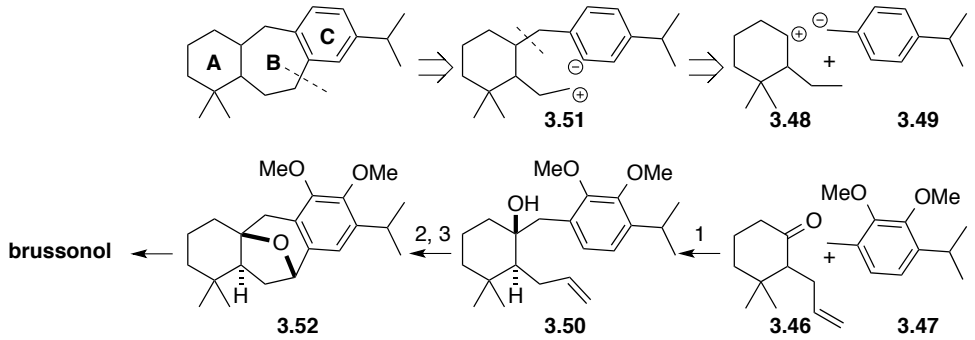
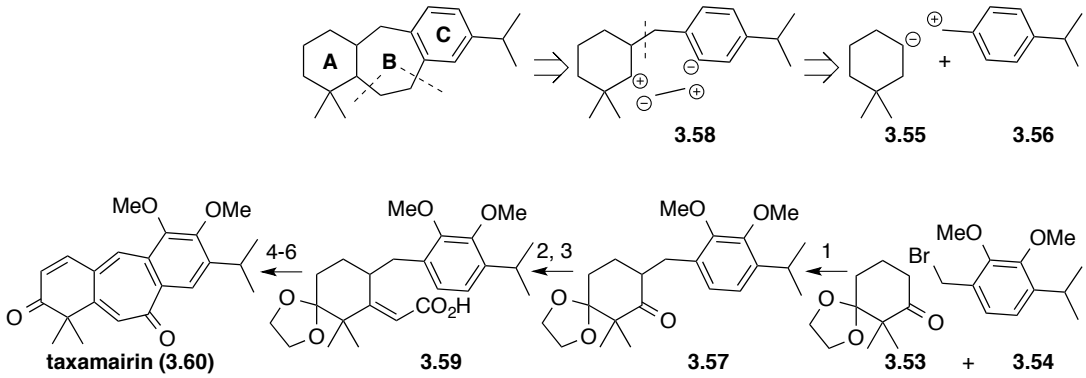
[85] Jan, N.-W.; Liu, H.-J.; Hsieh, M.-T.; Shia, K.-S. *Eur. J. Org. Chem.* **2010**, 4271−4275.

[86] Martinez-Solorio, D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 189−192.



Scheme 3.6: *Formal total synthesis of brussonol dimethyl ether by Jennings through variant D*:[86] 1) *n*-BuLi, then **3.46**; 2) O_3, then PPh_3; 3) BF_3•OEt_2.

The variant described by Pan and co-workers, starts with ketone **3.53** and aryl bromide **3.54**, corresponding to synthons **3.55** and **3.56** (Scheme 3.7), which were combined through a base catalyzed alkylation to furnish **3.57** in line with synthon **3.58**.[87] The ketone **3.57** was treated with vinyl magnesium bromide to form a tertiary alcohol that was directly transformed using chromic(VI) acid to yield the carboxylic acid **3.59**. A sequence protocol consisting of a Friedel-Crafts acylation forming the icetexane skeleton succeeded by a A and B ring DDQ oxidation. Finally a selective reduction of a conjugated isopropene unit furnished the natural product taxamairin B (**3.60**).

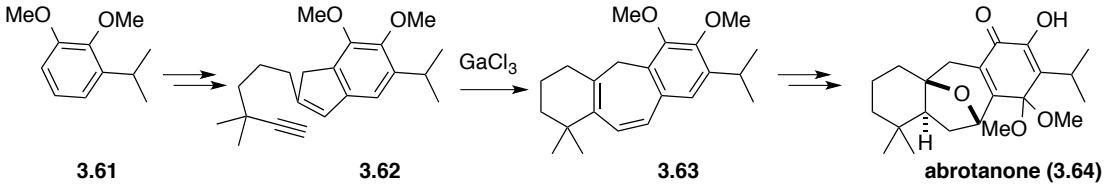


Scheme 3.7: *Total synthesis of taxamairin (**3.60**) by Pan through variant E*:[87] 1) KH, then **3.54**; 2) H_2C=CHMgBr; 3) CrO_3 in aq. H_2SO_4; 4) PPA; 5) DDQ; 6) H_2, Pd/C.

Alternatively to the A + C → ABC approach, Sarpong and co-workers[81d] developed an elegant and efficient C (**3.61**) → ABC strategy towards the synthesis of icetexanes *via* an impressive Lewis acid mediated cycloisomerization of **3.62** to furnish the icetexane skeleton **3.63** that was further functionalized to form several

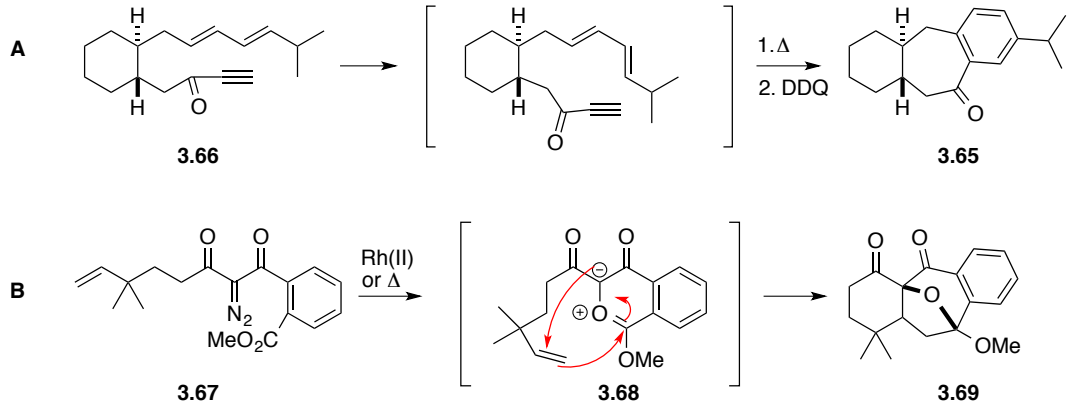
[87] Jan, N.-W.; Liu, H.-J.; Hsieh, M.-T.; Shia, K.-S. *Eur. J. Org. Chem.* **2010**, 4271−4275.

natural products such as the coulterone family member abrotanone (**3.64**, Scheme 3.8).



Scheme 3.8: *Total synthesis of abrotanone (**3.64**) by Sarpong through a C → ABC strategy.*[81d]

Furthermore, strategies towards the icetexane tricyclic core structure were developed without forming the complete icetexane skeletons. In 1998, Whitby and co-workers [88] developed a rapid access to the tricyclic **3.65** through an efficient intramolecular Diels-Alder reaction to form the B and C ring starting from the substituted A ring **3.66** (Scheme 3.9, **A**). The tandem cyclization-cycloaddition of rhodium (II) stabilized carbenes, providing an entry to the synthesis of diverse tetrahydrofurans, was developed by Padwa and co-workers[89] and used towards the synthesis of icetexanes.[90] The diazoketone **3.67** was able to generate the carbonyl ylide **3.68**, which under the effect of either a rhodium(II) catalyst or heating, was able to undergo an impressive [3+2] cycloaddition thereby forming the desired tricyclic core of komaroviquinone (**3.11**) and the required β C10−O ether bond (**3.69**).



Scheme 3.9: *A) Whitby*[88] *and B) Padwa*[89,90] *strategies for the synthesis of 6-7-6 tricyclic core.*

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[88] Tuckett, M. W.; Watkins, W. J.; Whitby, R. J. *Tetrahedron Lett.* **1998**, *39*, 123−126.
[89] Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100−3109.
[90] Padwa, A.; Chughtai, M. J.; Boonsombat, J.; Rashatasakhon, P. *Tetrahedron* **2008**, *64*, 4758−4767.

3.1.5. Target motivations and synthetic strategies

3.1.5.1. Goal of the study

In chapter 2, we reported the photolysis of taiwaniaquinone F (**2.3**) to taiwaniaquinol A (**2.9**) (Scheme 3.10, **A**) through which we proposed a hypothesis where such a methylenedioxy bridge bearing a 1,2,4-hydroxylated aryl moiety could be biosynthetically generated *via* a light promoted remote C−H activation. In biosynthesis, this postulate would then be complementary to the already accepted and established cytochrome P450 mechanism to produce methylenedioxy bridge (like cheilanthifoline), especially in the plant kingdom where the use of light as a source of energy is omnipresent. We also postulated that other natural products such as cyclocoulterone (**3.10**) and ET-743 (**2.101**, Scheme 3.10, **B**) could be formed *via* a similar mechanism. Therefore, the goal of this chapter is to demonstrate that the previously discovered photolysis of taiwaniaquinone F (**2.3**) is not limited to this substrate but in contrary, presents general validity to many other natural products displaying such motifs. In order to support this proposed, we envisaged to synthesize an additional natural product quinone with the general formula **3.70** to perform its photolysis to the methylenedioxy congener **3.71**. Ideally, both natural products would be co-isolated from the same plant and therefore give further confirmation of our hypothesis. As already mentioned above, komaroviquinone (**3.11**) was isolated from *D. komarovi* (the whole plant) besides cyclocoulterone (**3.10**), indicating a possible biogenetic connection between both natural products. Furthermore, having obtained experience in diterpenoids natural products, komaroviquinone (**3.11**) was chosen as the target molecule, which could generate cyclocoulterone (**3.10**) under sunlight irradiation, and through this would validate our hypothesis. Although a previous report of Majetich and co-workers[91] on the photolysis of komaroviquinone (**3.11**) in cyclohexane, which furnished komarovispirone (**3.12**) in high yield, we expected that the use of the conditions developed for the photolysis of taiwaniaquinone F (**2.3**) would change the course of the photolysis of komaroviquinone (**3.11**) in favor of cyclocoulterone (**3.10**).

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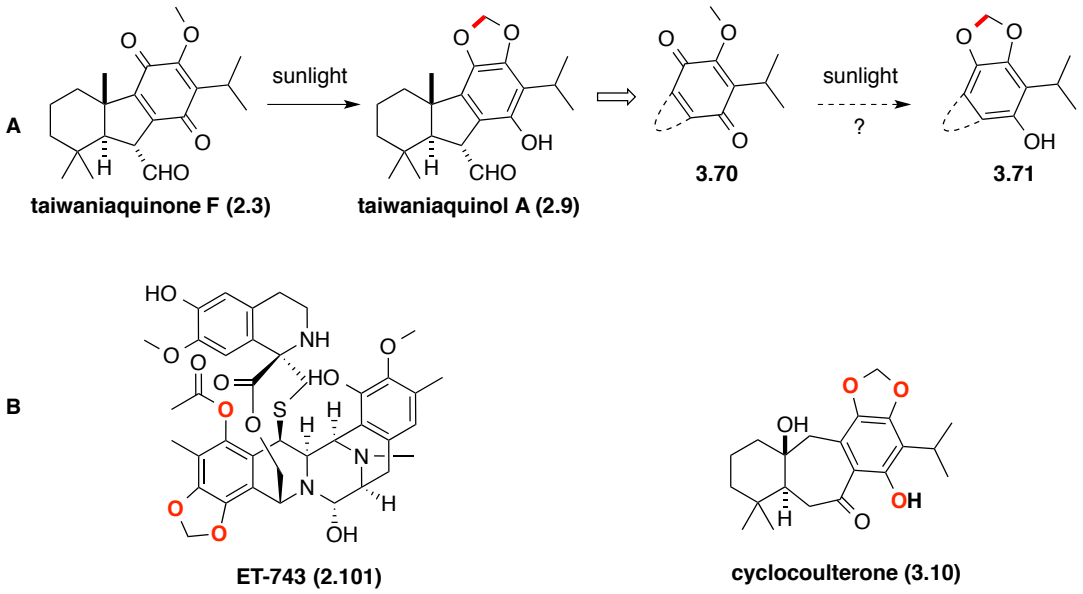
[91] Majetich, G.; Jianhua, Y. *Org. Lett.* **2008**, *10*, 89−91.

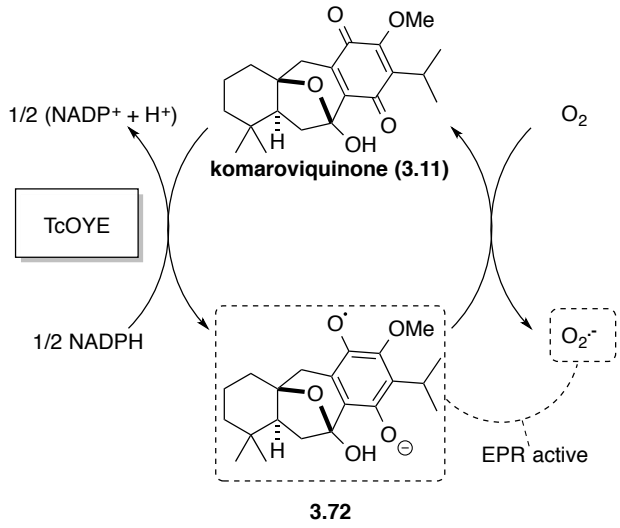


Scheme 3.10: *A) Remote C−H activation of taiwaniaquinone F (**2.3**) to taiwaniaquinol A (**2.9**); B) Possible methylenedioxy candidates biosynthesized via a quinone photolysis precursors.*

As described in section 3.1.2, komaroviquinone (**3.11**) was found as an exceptionally efficient antichagasic agent.[76] Chagas disease is a chronic and potentially mortal disease affecting about 8 million people mainly in Central and South America caused by the parasite *Trypanosoma cruzi*, which has a complex life cycle,[92] therefore rendering treatments difficult. Indeed, the kissing bugs carrying the trypomastigotes, the infectious form of the parasite, bites the victim and defaces close to the wound provoking an infection. After cell penetration, the trypomastigotes transform to amastigotes, which duplicate and transform back to the infectious form. This phenomena causes the cell to burst and liberates the trypomastigotes into the blood stream, therefore causing tissues lesions. The mechanism of action of komaroviquinone (**3.11**) as trypanocidal active ingredient was elucidated by Uchiyama *et al.,*[93] the same group that isolated most of the coulterones including komaroviquinone (**3.11**) and cyclocoulterone (**3.10**). The potency of komaroviquinone (**3.11**) as an antichagasic agent is attributed to a one electron reduction to the semiquinone radical anion **3.72** (under O_2 free conditions and in presence of NADPH) by the reductase TcOYE, presents in all parasite forms (Scheme 3.11). The radical anion could be characterized by Electron Paramagnetic Resonance (EPR)

[92] Rassi Jr, A.; Rassi, A.; Marin-Neto, J. A. *Lancet* **2010**, 375, 1388−1402.
[93] Uchiyama, N.; Kabututu, Z.; Kubata, B. K.; Kiuchi, F.; Ito, M.; Nakajima-Shimada, J.; Aoki, T.; Ohkubo, K.; Fukuzumi, S.; Martin, S. K.; Honda, G.; Urade, Y. *Antimicrob. Agents Chemother.* **2005**, *49*, 5123−5126.

spectroscopy. Once the reaction conditions were switched to aerobic, the quinone could be regenerated by oxidation with oxygen and produce a reactive oxygen species, the superoxide radical anion $O_2^{\bullet -}$. Superoxide radical anion was therefore detected by EPR and is perhaps responsible to the parasite death.



Scheme 3.11: *Redox cycle of komaroviquinone (**3.11**) in presence of TcOYE, NADPH in aerobic conditions.*[93]

The first total synthesis of (±)-komaroviquinone (**3.11**) was achieved by Banerjee and co-workers in 2005 using an approach corresponding to the previously described strategy D (Scheme 3.6) *via* an intramolecular Heck reaction.[94] Two years later, Majetich and co-workersreported a racemic and an enantioselective total synthesis of komaroviquinone this time based on strategy E (Scheme 3.7).[95] Recently, Iwasaki and co-workers, published a short and efficient enantioselective total synthesis of komaroviquinone (**3.11**) *via* strategy D (Scheme 3.6) with an elegant introduction of the C10-OH group through an acidic lactonization.[96]

3.1.5.2. Retrosynthetic Analysis

As discussed in the previous section, the biosynthetic abietane origin of icetexanes was determinant for choosing an abietane as starting material. Ideally this

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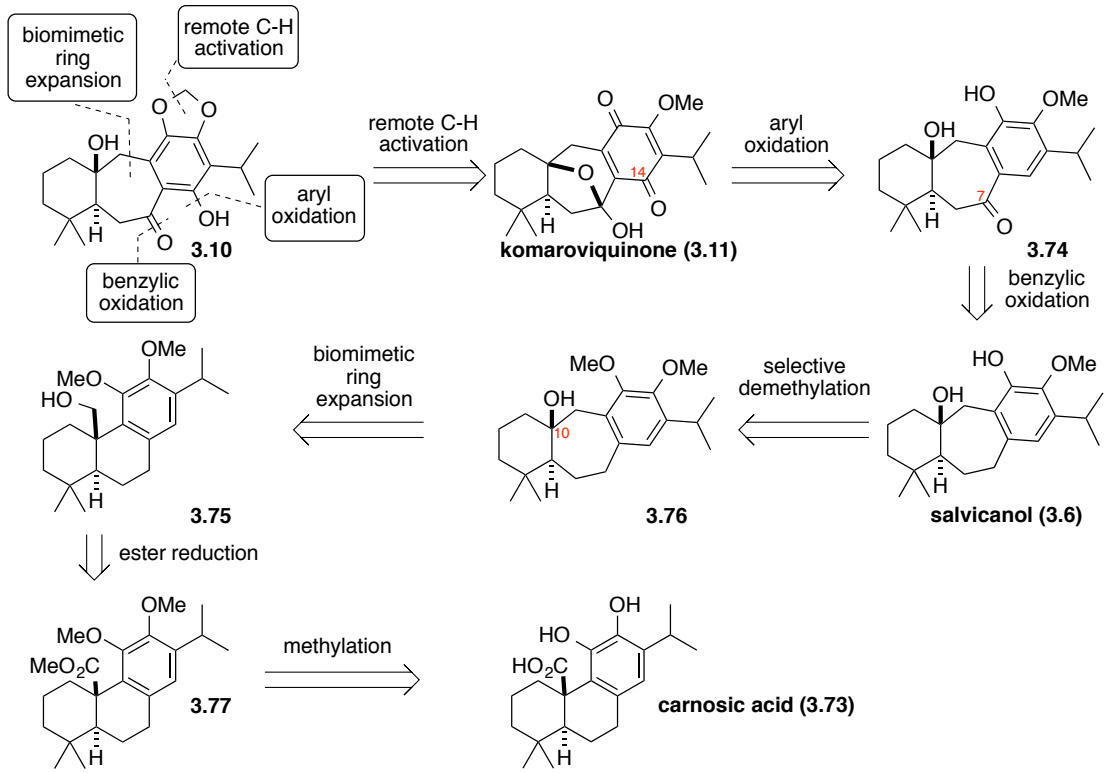
[94] Sengupta, S.; Drew, M. G. B.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2005**, *70*, 7694−7700.

[95] (a) Majetich, G.; Li, Y.; Zou, G. *Heterocycles* **2007**, *73*, 217−225; (b) Majetich, G.; Yu, J.; Li, Y. *Heterocycles* **2007**, *73*, 227−235.

[96] Suto, Y.; Kaneko, K.; Yamagiwa, N.; Iwasaki, G. *Tetrahedron Lett.* **2010**, *51*, 6329−6330.

abietane should be commercially available, or naturally abundant and possess the optimal structural features for a redox and a protecting group economy synthetic route. With these objectives in mind, the commercially available and naturally abundant carnosic acid (**3.73**), which is used as an antioxidant and food preservative,[97] was chosen as the starting material. The chirality of this material offers the advantage that no enantioselective step is necessary.



Scheme 3.12: *Retrosynthetic analysis of cyclocoulterone (**3.10**).*

The methylenedioxy bridge formation, described in Scheme 3.12, was envisioned to occur *via* a remote C−H functionalization of komaroviquinone (**3.11**), as observed in chapter 2 for the synthesis of taiwaniaquinol A (**2.9**). The C14 hydroxyl group was envisaged to be installed *via* an aromatic aerobic oxidation of the phenol **3.74** as already encountered for the synthesis of intermediate **2.84**. A benzylic oxidation of the natural product salvicanol (**3.6**), which could be challenging due to the presence of several benzylic positions was required to introduce the C7 ketone in

[97] Aguilar, F.; Autrup, H.; Barlow, S.; Castle, L; Crebelli, R.; Dekant, W.; Engel, K.-H.; Gontard, N.; Gott, D.; Grilli, S.; Gürtler, R.; Larsen, J. C.; Leclercq, C.; Leblanc, J.-C.; Malcata, F. X.; Mennes, W.; Milana, M. R.; Pratt, I.; Rietjens, Y.; Tobback, P.; Toldrá, F. *The EFSA Journal* **2008**, *721*, 1−29.

3.74.[98] An acid catalyzed ring expansion of dimethoxy abietane (**3.75**) was anticipated to yield the seven membered ring as well as the β-C10 angular hydroxyl group of methylsalvicanol (**3.76**) as depicted in Scheme 3.1. A selective demethylation of **3.76** should afford salvicanol (**3.6**). Finally, methylation and reduction of the carnosic acid (**3.73**) would allow the formation of **3.77** and **3.75**, respectively.

3.2. Results and Discussion

3.2.1. Isolation and derivatization of Carnosic Acid

Carnosic acid[99] (**3.73**) is found in significant amount in *Lamiaceae* (mint family) and particularly in *Rosmarinus officinalis* (common rosemary, Figure 3.4) and *Salvia officinalis* (common sage). The content of **3.73** in the dried leaves is varying in proportion from 1% to 10% (on weight basis), depending on the species, the plant age and the environmental stress.[100] The European Commission approved rosemary extracts with high content of carnosic acid (**3.73**) as food additives (E392) in 2010, although such extracts were already used in food industry for more than 20 years.[101] Four different extraction methods are regulated by the European Commission for the production of rosemary extracts as food additives (acetone, supercritical CO_2, ethanol and hexane followed by ethanol)[102]. The method developed by Albu *et al.*[103] using ethanol as extraction solvent combined with sonication was chosen for its simple operation and extraction efficiency. Ultrasounds enhance significantly the extraction efficiency due to the cavitation bubbles, which are able to break the cell walls of the plant, allowing the solvent to dissolve the internal components, such as carnosic acid (**3.73**). This method has the advantage to be fast and requires lower extraction temperature, which is crucial for carnosic acid (**3.73**) due to its temperature but also oxygen and light sensitivity.[104]

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[98] Majetich, G.; Li, Y.; Zou, G. *Heterocycles* **2007**, *73*, 217−225.
[99] For a review on carnosic acid see: Birtić, S.; *et al.* Carnosic acid. *Phytochemistry* **2015**, http://dx.doi.org/10.1016/j.phytochem.2014.12.026.
[100] Munné-Bosch, S.; Alegre, L. *Planta* **2000**, *210*, 925−931.
[101] http://www.astro-verl.com/de/wurst-abc/216-Carnosolsaeure
[102] Commission Regulation (EU) No 231/2012.
[103] Albu, S.; Joyce, E.; Paniwnyk, L.; Lorimer, J. P.; Mason, T. J. *Ultrason. Sonochem.* **2004**, *11*, 261−265.
[104] Zhang, Y.; Smuts, J. P.; Dodbiba, E.; Rangarajan, R.; Lang, J. C.; Armstrong, D. W. *J. Agric. Food Chem.* **2012**, *60*, 9305−9314.

Figure 3.4: *Common rosemary (Italy).*

The purification and isolation of carnosic acid (**3.73**) from crushed and dried leaves of rosemary (*Rosmarinus officinalis*, origin: Portugal) was achieved by HPLC as reported by Albu *et al.*[103] However, due to the high sensitivity of carnosic acid (**3.73**), long storage of the extracted product was difficult as **3.73** has to be pure, protected from light, under argon at low temperature (-20 °C). The triple methylation of pure carnosic acid (**3.73**) using the modified conditions of Theoduloz *et al.*[105] (NaH, Me_2SO_4, THF, then MeOH) gave only a moderate yield of **3.77** (66%). Evidence in literature of the different constituents of rosemary (Figure 3.5), we changed our strategy in order to obtain higher quantities of **3.77**. Indeed, these natural products (**3.70**, **3.78**-**3.81**), could be converted to **3.77** through one step (methylation, **3.78**-**3.79**) or two steps (methylation and hydrogenation, **3.80**-**3.81**), whereby carnosol[106] **(3.80)** was also found as a major constituent of rosemary extracts. These findings increased the potential to obtain **3.77** in high amounts from rosemary extracts containing all the natural products.

[105] Theoduloz, C.; Pertino, M. W.; Rodríguez, J. A.; Schmeda-Hirschmann, G. *Planta Med.* **2011**, *77*, 882−887.
[106] Doolaege, E. H. A.; Raes, K.; Smet, K.; Andjelkovic, M.; Van Poucke, C.; De Smet, S.; Verhé, R. *J. Agric. Food Chem.* **2007**, *55*, 7283−7287.

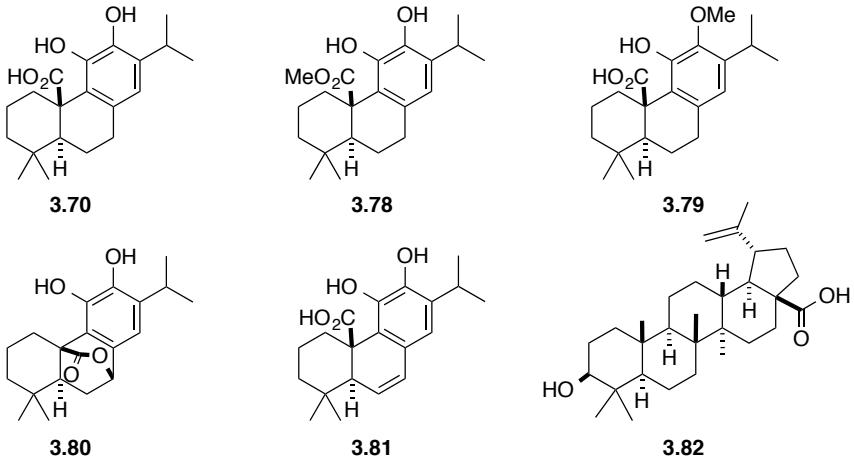
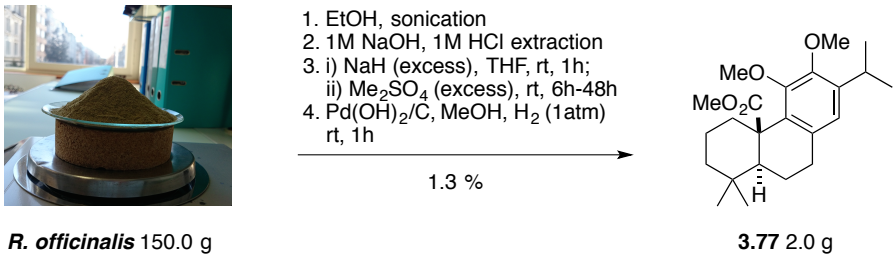


Figure 3.5: *Different phenolic compounds isolated from rosmarinus officinalis.*[106]

In this regard, the dried ethanolic extract of rosemary, which was dissolved in Et_2O (Scheme 3.13) was extracted with NaOH (1 M) in order to form the aqueous soluble sodium salt of phenols **3.70** and **3.78-3.81**. Acidification (1 M aq. HCl) and ethereal extraction of the aqueous phase yielded an phenolic abietane enriched extract, which was subjected to the previously mentioned methylation conditions to yield a mixture of trimethylated carnosic acid (**3.77**), trimethylated **3.81** and dimethylated **3.82**. The mixture was dissolved in MeOH, the undesired dimethylated **3.82** precipitated and filtrated to leave an inseparable mixture of **3.77** and trimethylated **3.81** (1.46:1.00). This mixture was hydrogenated using $Pd(OH)_2$ on charcoal under hydrogen atmosphere for 1 h to yield pure **3.77** (1.3% from dried and crushed rosemary).



R. officinalis 150.0 g

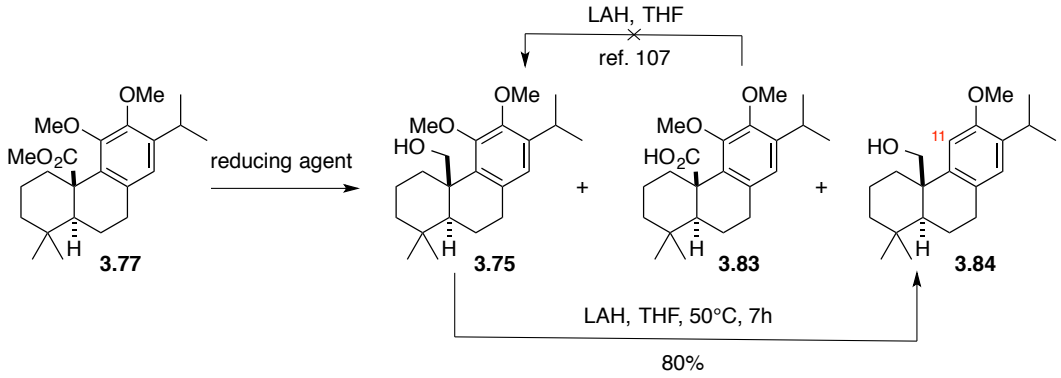
3.77 2.0 g

Scheme 3.13: *Isolation and derivatization of carnosic acid (**3.70**).*

3.2.2. Reduction of a congested angular ester

Reduction of the angular methoxy ester group of **3.77** was necessary to access the primary alcohol **3.75** (Scheme 3.14), set up for a ring expansion towards the

icetexane skeleton (see following section). The known procedure,[107] consisting of treating **3.77** with $LiAlH_4$ (LAH) in refluxing THF in 3 h, furnished the desired primary alcohol **3.75** in moderate yields (40−60%) with side-product **3.83** (20−30%) and unreacted starting material (**3.77**). As reported by Kelecom and co-workers[107], **3.83** could not be converted to **3.75**, even is if higher temperature were employed.



Scheme 3.14: *Reduction of trimethylcarnosic acid (**3.77**).*

The use of alternative reducing agent, such as $LiBH_4$ (with or without Lewis acid),[108] Superhydride,[109] BH_3·DMS,[110] BH_3·THF[111] or SmI_2 (with pyrrolidine and water),[112] lead to no or small conversion to the desired primary alcohol. The inertness of this reduction was attributed to the congested nature of the ester group. Finally, refluxing a solution of **3.77** in Et_2O in presence of excess of LAH for 6 h furnished the desired 3.75 in excellent yield (89%). Astonishingly, if the reaction was performed in THF in a closed vessel, a similar conversion could be observed (TLC analysis) after 12 h at 60 °C, however, NMR, and mass data analysis revealed that the major product of the reaction was actually the Ar-OMe hydrogenolysis product **3.84**, which was formed in high yield (83%).

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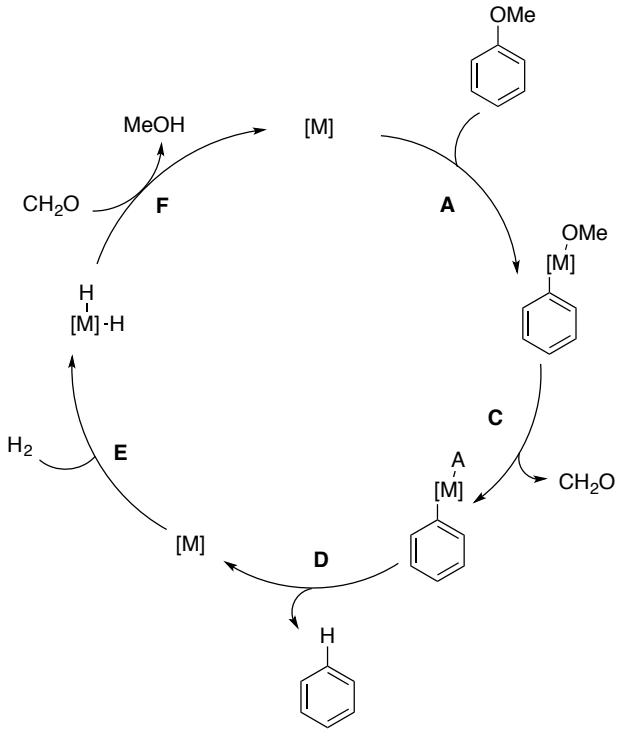
[107] Kelecom, A. *Tetrahedron* **1983**, *39*, 3603−3608.
[108] Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1984**, *49*, 3891−3898.
[109] Brown, H. C.; Kim, S. C.; Krishnamurty, S. *J. Org. Chem.* **1980**, *45*, 1−12.
[110] Truong, A. P.; Tóth, G.; Probst, G. D.; Sealy, J. M.; Bowers, S.; Wone, D. W. G.; Dressen, D.; Hom, R. K.; Konradi, A. W.; Sham, H. L.; Wu, J.; Peterson, B. T.; Ruslim, L.; Bova, M. P.; Kholodenko, D.; Motter, R. N.; Bard, F.; Santiago, P.; Ni, H.; Chian, D.; Soriano, F.; Cole, T.; Brigham, E. F.; Wong, K.; Zmolek, W.; Goldbach, E.; Samant, B.; Chen, L.; Zhang, H.; Nakamura, D. F.; Quinn, K. P.; Yednock, T. A.; Sauer, J.-M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6231−6236.
[111] Brown, H. C.; Stocky, T. P. *J. Am. Chem. Soc.* **1977**, *99*, 8218−8226.
[112] Fazakerley, N. J.; Helm, M. D.; Procter, D. J. *Chem. Eur. J.* **2013**, *19*, 6718−6723.

Hydrogenolysis of Ar-OAlkyl bond can be carried out in a limited number of ways with a prevalence use of Ni[113] and Ir[114] catalysts under relatively harsh (1 atm H_2, 120 °C, 48 h and 1 atm H_2, 200 °C, 20 h, respectively). A possible mechanism is shown in Scheme 3.15. A metal oxidative insertion of an aryl methoxy substrate (A), followed by a β-hydride elimination would generate formaldehyde and an aryl metal-hydride (B). Reductive elimination of this metal hydride would release the hydrogenolyzed aryl and the metal center (C), which under H_2 conditions reduces formaldehyde to methanol (D).[115]



Scheme 3.15: *Possible metal catalysed hydrogenolysis of aryl-OMe.*[115]

A selective reductive aryl methyl ether bond cleavage was achieved very recently with the help of LAH as reducing agent, however, based on iron catalysis.[116] To the best of our knowledge, the only example showing a Aryl-OAlkyl

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[113] Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439−443.
[114] Kusumoto, S.; Nozaki, K. *Nature Communications* **2015**, 6, 1–7. DOI: 10.1038/ncomms7296.
[115] Zaheer, M.; Kempe, R. *ACS Catalysis* **2015**, *5*, 1675−1684.
[116] Ren, Y.; Yan, M.; Wang, J.; Zhang, Z. C.; Yao, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 12674−12678.

hydrogenolitic reactivity with the sole use of LAH was reported by Tweedie[117] *et al.* in 1956. However, only 12% conversion was observed and the major compound of the reaction was the ArylO−Alkyl bond hydrogenolysis product and not the desired Aryl−OAlkyl bond.

In order to rationalize this unexpected result, we performed various experiments to determine the reaction intermediate, the active species responsible for this over-reduction product (Scheme 3.14), and finally the origin of the installed hydrogen atom at C11. The early formation of **3.75**, observed using the Kelecom conditions, strongly supports our theory that the ester reduction happened first, which further emphasized that the second reduction would be achieved *via* a OH deprotonated **3.75**. Indeed, treatment of **3.75** with the best reaction conditions (LAH, THF, 50 °C, 7 h, closed vessel) smoothly furnished methylpisiferol (**3.84**) in high yield (80%). Longer reaction time (48 h) lead to an efficient formation of pisiferol (68%) *via* a hydride promoted demethylation[118] or *via* ArO-CH_3 hydrogenolysis.

As no precedence of such efficient reactions could be found in literature using solely LAH, we aimed to investigate the possibility that this process could be facilitated by a degradation product of LAH (Li_3AlH_6, LiH, Al, H_2)[119] or trace amounts of a metallic residue. With this intention, the hydrogenolysis of **3.75** was undertaken with freshly purified LAH (see SI for experimental details, THF, 70 °C, 15 h, under Ar atmosphere) only as well as in combination of one of the different thermal decomposition products of LAH, and finally in combination of all of them (Table 3.1). The first general observation made, was a slower reaction rate. Indeed, the conversion with commercially available LAH was completed within 7 h at 50 °C. The hydrogenolysis product/starting material ratio (**3.84**/**3.75**) was higher for entry 1, 3, and 5. These results were not sufficient to identify a thermal degradation product as the key component for the reactivity of the hydrogenolysis. Moreover, the generally lower reaction rate indicated that the commercially available reagent contains an additional additive (or in higher amount), necessary for a faster hydrogenolysis.

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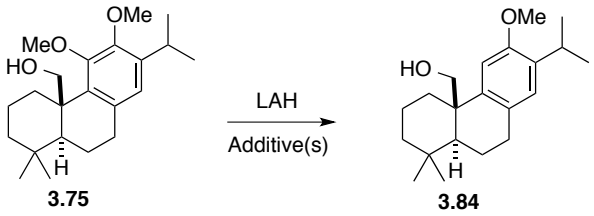
[117] Tweedie, V. L.; Cuscurida, M. *J. Am. Chem. Soc. Chem.* **1956**, *79*, 5463−5466.
[118] Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, *35*, 8727−8730.
[119] Dilts, J. A.; Ashby, E. C. *Inorg. Chem.* **1972**, *11*, 1230−1236.

Table 3.1: *Scope of additives to LAH hydrogenolysis.*



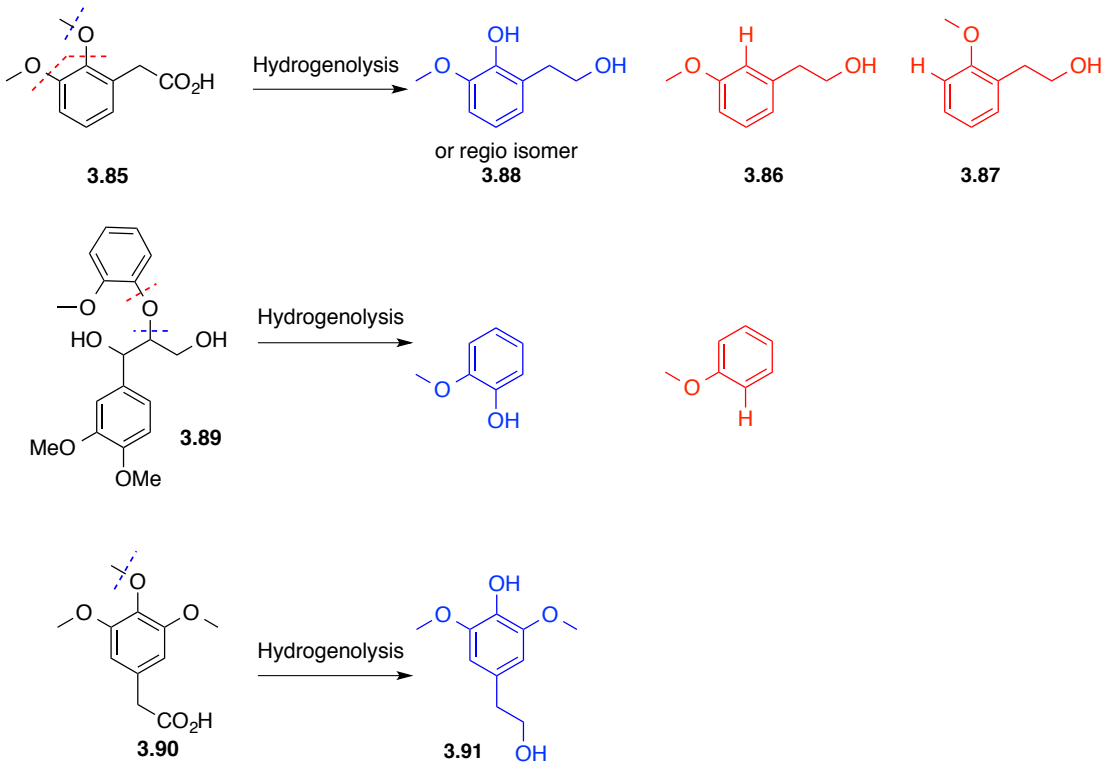
3.75 **3.84**

Entry[a]	$LiAl_3H_6$	LiH	Al	3.84/3.75 [b]
1				1.00/0.49
2	✗			1.00/1.15
3		✗		1.00/0.53
4			✗	1.00/1.27
5	✗	✗	✗	1.00/0.43

[a] Reaction conditions: LAH (6.4 eq.), Li_3AlH_6 (1.7 eq), LiH (4.3 eq), Al (2.3 eq.), 70 °C, 15 h. [b] Ratio determined by ^{1}H-NMR.

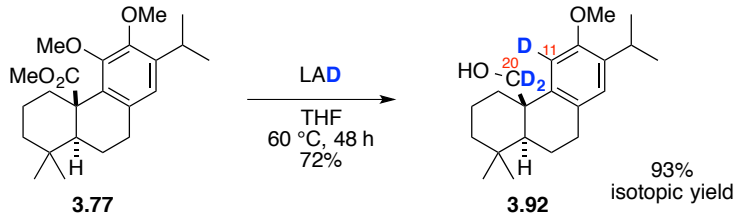
We then explored the role of H_2 (either produced by the reaction of the alcohol substrate or by thermal degradation of LAH) by changing the Ar to a H_2 or a D_2 atmosphere. The reaction still proceeds as usual, however no rate enhancement, neither deuterium incorporation (with D_2) was observed.

Preliminary studies (GC analysis of the reaction mixtures) of the reduction of three model substrates to analyze the substrate scope of this reaction were undertaken. Reduction of compound **3.85**, showed Aryl−OMe hydrogenolysis products (**3.86**, **3.87**). However, ArylO−Me hydrogenolysis product (**3.88**, Scheme 3.16) could also be detected. The same conclusion could be made for the hydrogenolysis of the lignin model compound **3.89**. Reduction of **3.90** showed, only traces of ArylO−Me hydrogenolysis product **3.91**. This emphasizes the importance of the δ-position of the −OH group to the Aryl−OMe as well as the necessary conformation.



Scheme 3.16: *Hydrogenolysis of various model substrate. In red are the Aryl−OMe hydrogenolysis product. In blue are the ArylO−Me hydrogenolysis product.*

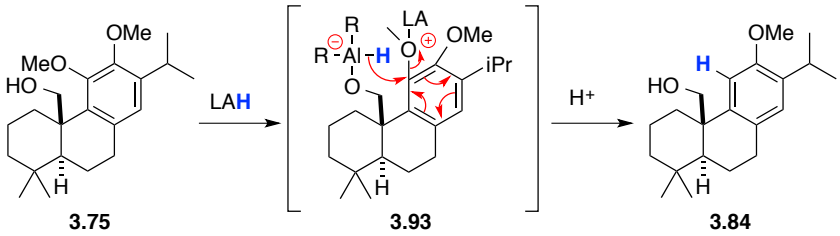
Finally, the LAH origin of the C11 hydrogen atom in **3.84** was confirmed by a LAD reduction of ester **3.77** (THF, 60 °C, 48 h), which delivered the C20 and C14 deuterated product **3.92** in high isolated (72%) and isotopic yield (93%, Scheme 3.17).



Scheme 3.17: *LAD reduction of trimethylcarnosic acid (3.77).*

From these preliminary results and literature precedences, a mechanism could be suggested where the alkoxyhydroxyaluminate **3.93**, formed after LAH treatment of the alcohol **3.75**, undergoes an intramolecular hydride transfer to an eventual Lewis acid coordinated C11-OMe (Scheme 3.18). Indeed, alkoxyhydroaluminates are known

to possess enhanced hydride delivery abilities.[120,121] Furthermore, coordination of the methoxy group to a Lewis acid, such as Li^+, or some metallic residues from commercially available LAH, would decrease the electron density in the aromatic ring and therefore facilitate the hydride transfer.



3.75 **3.93** **3.84**

Scheme 3.18: *Proposed mechanism for the hydrogenolysis of **3.77**.* LA = Lewis acid.

Further mechanistic experiments such as NMR studies are required to support this proposed mechanism. Treatment of alcohol **3.75** with LAH in fully deuterated THF should show the formation of the alkoxyhydroaluminate **3.93** and any coordination of a Lewis acid to the C11-OMe would display a clear methoxy downfield signal. Finally, increasing the measurement temperature could reveal the existence of transition states and/or other intermediates.

3.2.3. Ring expansion based on a biogenetic hypothesis and first synthesis of salvicanol

The B ring expansion of **3.75** based on the previously described hypothesis was addressed next. Thus, we aim to follow the strategy described in section 3.1.3 *via* the formation of carbocation, such as **3.15**, and its selective β-trapping with a water molecule. Although all reported examples showed a ring expansion followed by deprotonation yielding alkenes such as **3.16**, no example of icetexane synthesis showed an introduction of a C10 hydroxyl group throughout the numerous successful ring expansions. The trapping of carbocation such as **3.15** would experimentally validate the reported biosynthetic hypothesis of icetexanes bearing a β-C10 angular hydroxyl group like salvicanol (**3.6**). Previous installations of C10 hydroxyl group on already constructed icetexane skeletons were performed over two steps from an

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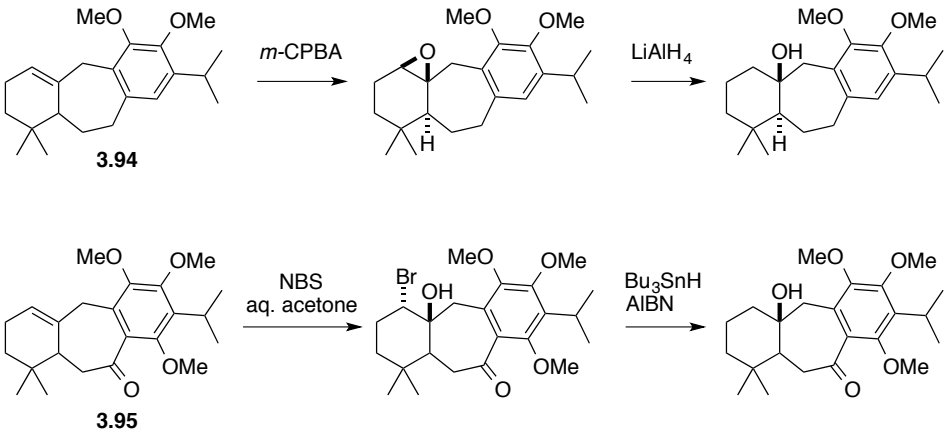
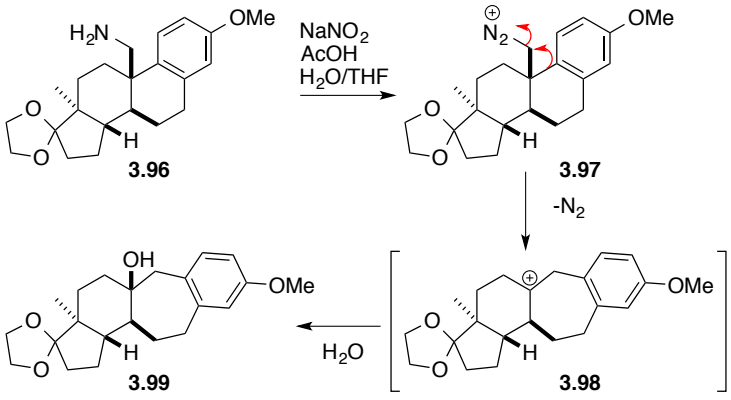
[120] Baudouy, R.; Goré, J. *Tetrahedron Lett.* **1974**, 1593−1596.
[121] Breeden, W. B.; Coop, A.; Husbands, S. M.; Lewis, J. W. *Helv. Chim. Acta* **1999**, *82*, 1978−1980.

alkene **3.94** or **3.95** through an epoxidation followed by a hydride epoxide opening[122] or, *via* an aqueous alkene bromination followed by a radical dehalogenation,[123] respectively (Scheme 3.19).



Scheme 3.19: *Precedent strategies to install C10-OH group.*[122,123]

A different approach by Corey and co-workers demonstrated that such transformations were feasible with a similar 6-6-6 ring system by treating the primary amine **3.96** with $NaNO_2$, which forms the diazonium species **3.97** (Scheme 3.20).[124] Cationic ring expansion of the latter produced the tertiary carbocation **3.98**, which upon water trapping, leads to the formation of the ring-expanded product **3.99** bearing an angular hydroxyl group.



Scheme 3.20: *Corey's ring expansion towards cortistatins.*[124]

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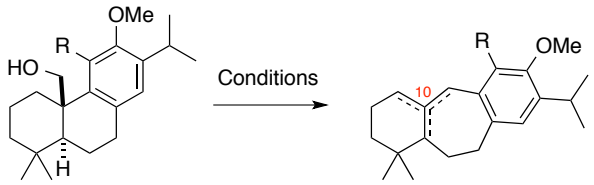
[122] Majetich, G.; Zou, G. *Org. Lett.* **2008**, *10*, 81−83.
[123] Majetich, G.; Yu, J.; Li, Y. *Heterocycles* **2007**, *73*, 227−235.
[124] Kürti, L.; Czakó, B.; Corey, E. J. *Org. Lett.* **2008**, *10*, 5247−5250.

Studies towards the ring expansion of the primary alcohols **3.75** or **3.84** were initiated under acidic conditions (Table 3.2, entry 1−6) in aqueous solution in order to trap the postulated formed carbocation to install the C10 hydroxyl group. However, none of the described conditions were able to provide the C10-OH icetexane. Nevertheless, treatment of **3.75** with either HPF_6 (entry 3) or Amberlite 15 (entry 6) delivered an inseparable mixture of ring expanded icetexane alkenes **3.100**. To the best of our knowledge, this is the first Brønsted acid mediated ring expansion of a non-activated primary alcohol like **3.75** to icetexanes.

Table 3.2: *Ring expansion studies towards icetexane skeleton.*



R = H **3.84**
R = OMe **3.75**

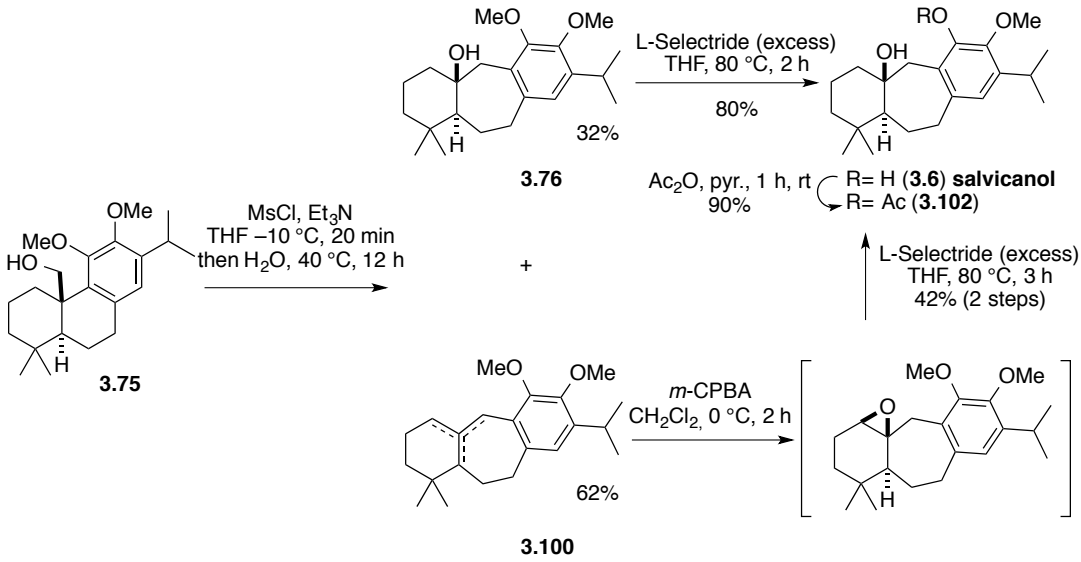
R = H **3.101**
R = OMe **3.100**

Entry	Substrate	Conditions	Observations[a]
1	**3.84**	HCO_2H, 50 °C	formylated SM
2	**3.84** or **3.75**	Conc. H_2SO_4	Complex mixture
3	**3.75**	HPF_6, aq. CH_3CN	**3.100**
4	**3.75**	Wet SiO_2, 50 °C (MW)	No reaction
5	**3.75**	Amberlite IR120	No reaction
6	**3.75**	Amberlite 15	**3.100**
7	**3.75**	MsCl, Et_3N, CH_2Cl_2	**3.100**
8	**3.84**	MsCl, Et_3N, CH_2Cl_2	**3.101**

[a] SM: Starting material

The earlier employed harsh conditions that promoted the ring expansion of **3.75** to **3.100** (entry 3 and 6) did not allow the formation of a C10 hydroxyl product. Indeed, such acidic conditions induce dehydration of tertiary alcohols. To prevent this side reaction, higher pH conditions were necessary. Therefore **3.75** and **3.84** were subjected to mesylation under basic conditions (MsCl, Et_3N, DCM, entries 7 and 8) to form the corresponding mesylate esters. After work-up, during solvent evaporation at 40 °C, the activated mesylate ester of **3.75** underwent a fast ring expansion to the

corresponding alkenes **3.100**. Absorption on silica gel was sufficient in promoting the rearrangement at rt. The mesylate ester of **3.84** was less heat sensitive but underwent a ring-expansion to **3.101** when absorbed on silica gel. Taking advantage of this silica gel mediated ring expansion, we decided then to combine both Kelekom and Corey's strategies to obtain a ring-expanded icetexane with a C10 tertiary alcohol. To this end, the mesylation reaction mixture containing the mesylate ester **3.75** was absorbed on freshly prepared wet silica gel (1.5 mL H_2O for 4.0 g of SiO_2). The ring expanded tertiary alcohol **3.75** was obtained in this manner after five days at rt (Scheme 3.21) in acceptable yield (29%) along with an inseparable mixture of alkenes **3.100** (31%) and unreacted starting material (**3.75**, 7%). This ring expansion is the first experimental study that allows a water mediated trapping of a tertiary carbocation like **3.15**. This constitutes the first experimental confirmation that validates the biosynthetic hypothesis of icetexane bearing a C10 tertiary alcohol, shown earlier (Scheme 3.1). The attack of water of such a carbocation was suggested to be disfavored from the β-face according to Dreiding's model and therefore supporting an enzymatically guided attack.[125] However, our exclusive β-selectivity challenges this hypothesis and thus supports a non-enzymatic mechanism.



Scheme 3.21: *Optimized ring expansion and first synthesis of salvicanol (**3.6**).*

[125] Gonzales, A. G.; Andres, L. S.; Luis, J. G.; Ravelo, A. G. *Phytochemistry* **1991**, *30*, 4067−4070.

An optimized protocol for the ring expansion was developed by changing the reaction solvent to THF, quenching the reaction mixture with water (0.80 mL for 1.0 mL of THF) and heating the monophasic mixture to 40 °C for 12 h, allowing a combined yield increase to 94% for a lower reaction time (Scheme 3.21). A selective hydride mediated demethylation (L-selectrive in THF, 80 °C, 2 h) developed by Majetich *et al*.[126] on alkene **3.94** was successfully applied to the tertiary alcohol **3.76**. Indeed, the less congested C11 methoxy was selectively demethylated with complete regioselectivity in high yield (80%) and shorter reaction time, leading to the first synthesis of salvicanol (**3.6**). All spectroscopic data is in agreement with the natural sample. The significant reaction rate enhancement could be explained by coordination effect attributed to the additional hydroxyl group of **3.76** with the bulky borane reagent as well as a C11-OMe-Li^+ coordination. The alkenes **3.100**, obtained in the course of the ring expansion of **3.75**, could be converted to salvicanol in two consecutive steps consisting of an epoxidation carried out using a known procedure with *m*-CPBA,[122] and a well established one-pot hydride (L-selectride) mediated epoxide opening / demethylation[118] in 42% yield over two steps. Salicanol (**3.6**) could also be acetylated[127] in high yield (90%) to afford salvicanol acetate (**3.102**), which was used for later studies.

3.2.4. Benzylic oxidation of salvicanol and its derivatives

Having salvicanol (**3.6**) and its methyl and acetate derivatives (**3.76** and **3.102**, respectively) in hand, the C7 benzylic oxidation as well as the aromatic oxidation were the missing steps to accomplish the synthesis of komaroviquinone (**3.11**). As described previously, Majetich and co-workers[95a] reported an unsuccessful C7 selective benzylic oxidation of a similar substrate **3.103** using the CrO_3 (Scheme 3.22). They conclude that the tertiary alcohol **3.103** would not allow oxidative conditions. Indeed, the tertiary alcohol was believed to form a free radical, responsible for the C10-C20 oxidative cleavage forming **3.104**.

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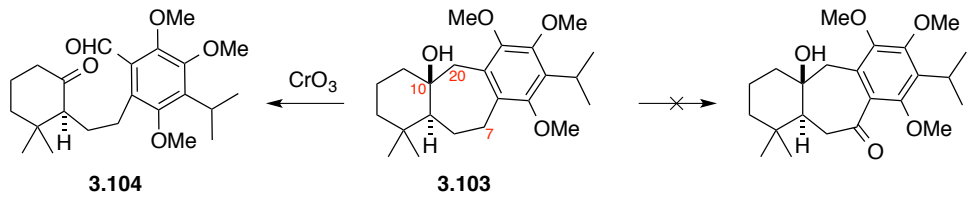
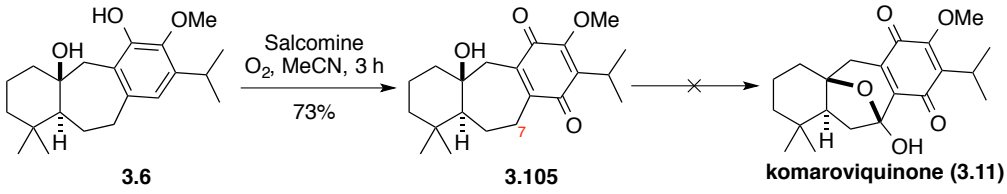
[126] Majetich, G.; Zhang, Y.; Tian, X.; Briton, J. E.; Li, Y.; Phillips, R. *Tetrahedron* **2011**, *67*, 10129−10146.

[127] Fraga, B. M.; González, A. G.; Herrera, J. R.; Luis, J. G.; Ravelo, A. G. *Phytochemistry* **1986**, *25*, 269−271.



Scheme 3.22: *Attempted selective C7 benzylic oxidation of **3.103** by Majetich.*[95a]

Due to the expected challenging benzylic oxidation, the aromatic oxidation of salvicanol (**3.6**) was first performed under aerobic conditions as described in chapter 2 (O_2, salcomine, MeCN) for the synthesis of **2.60** (see chapter 2). We were pleased to see that the same reaction condition furnished quinone **3.105** in 73% yield (Scheme 3.23). Different oxidation strategies were investigated to install a keto-group at the C7 position, which would result in the natural product komaroviquinone (**3.11**) (Table 3.3, entry 4-7). Quinone **3.105** did not react with SeO_2 oxidation in various solvent (dioxane, MeOH, AcOH, entry 4) although this method was known to efficiently oxidize this position in a very similar quinone system.[128] The same findings could be made for the allylic oxidation approach using $Co(acac)_2$ and TBHP (entry5).[129] However, complete conversion of **3.105** was observed after reacting with CrO_3 in AcOH (entry 6), yet the isolated product, which could not be structurally identified, showed to be different from komaroviquinone (**3.11**). A complex mixture was obtained when **3.105** was subjected to Sulikowski conditions (nPr_4NRuO_4, NMO, entry 7).[130]



Scheme 3.23: *Aromatic oxidation of salvicanol (**3.6**).*

As the standard procedures to oxidized **3.105** were unsuccessful to give the desired natural product, we next tried the direct benzylic oxidation of salvicanol (**3.6**), the corresponding methyl ether (**3.76**) and acetate (**3.102**) derivatives (Table 3.3).

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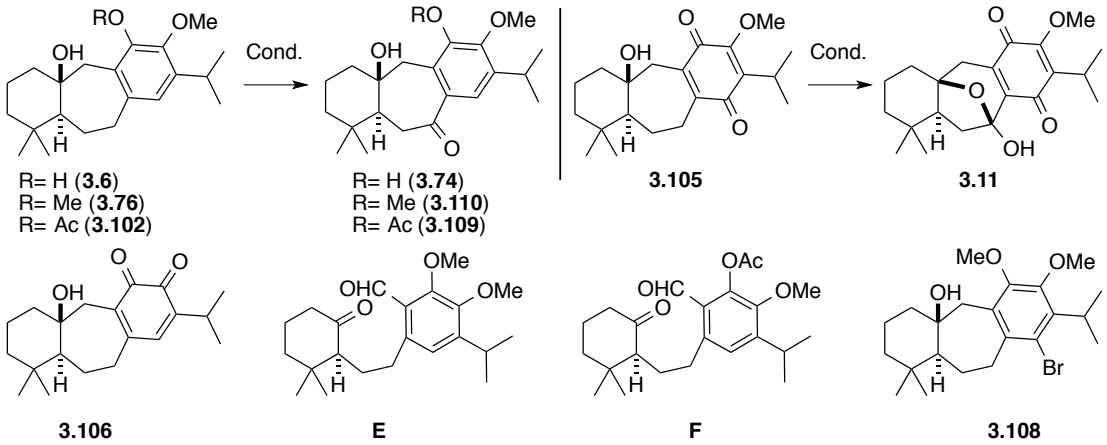
[128] Yokoya, M.; Ito, H.; Saito, N. *Tetrahedron* **2011**, *67*, 9185−9192.
[129] Han, X.; Zhou, Z.; Wan, C.; Xiao, Y.; Qin, Z. *Synthesis* **2013**, *45*, 615−620.
[130] Boyd, V. A.; Reibenspies, J.; Sulikowski, G. A. *Tetrahedron Lett.* **1995**, *36*, 4001−4004.

Selective functionalization of the benzylic positions, especially benzylic oxidation, is a long-established objective in organic synthesis. However, it was difficult to find the appropriate conditions for our substrates, due to the tremendous number of existing methods and the limiting substrate scope. Nevertheless, a long and careful screening was performed to obtain a method, which would provide reasonable yields of a selective benzylic oxidized product.

Table 3.3: *Benzylic oxidation screening.*



Entry	Conditions	Substrate	Observations
1	DDQ, aq. acetone (or AcOH)	**3.6**	**3.106** (96%)
2	$RuCl_3 \bullet xH_2O$, TBHP	**3.6**	**3.105**[a]
3	Bi(0), picolinic acid, TBHP	**3.6**	Complex mixture
4	SeO_2	**3.6**, **3.76** or **3.105**	No conversion
5	TBHP, $Co(acac)_2$	**3.105**	No conversion
6	CrO_3	**3.105**	Unknown compound
7	nPr_4NRuO_4, NMO	**3.105**	Complex mixture
8	KBr, Oxone, DCM/H_2O	**3.76**	**3.108**[a]
9	$NaOCl_2$, NHPI, CH_3CN/H_2O	**3.76**	No conversion
10	NaOCl, TEMPO, $Co(OAc)_2$, DCM	**3.76**	Complex mixture
11	DDQ, aq. acetone (or AcOH)	**3.76** or **3.102**	No conversion
12	DCN, THF/H_2O	**3.76** or **3.102**	No conversion

13	NaN_3, $PhI(OAc)_2$	**3.102**	Low conversion
14	I_2, pyr., TBHP	**3.102**	Low conversion
15	Bu_4NI, TBHP	**3.102**	Low conversion
16	IBX	**3.102**	No conversion
17	TBHP, MW	**3.102**	**3.109**[a]
18	CrO_3	**3.76**	**E**[a]
19	CrO_3	**3.102**	**F**[a]
20	$KMnO_4$, $MgSO_4$, NaOH, *t*-BuOH	**3.76**	No conversion
21	TBHP, $Co(acac)_2$	**3.76**	No conversion
22	$Cr(CO)_6$, TBHP	**3.76**	No conversion
23	$Cr(CO)_6$, TBHP	**3.102**	**3.109**: 10%
24	CrO_3, TBHP	**3.102**	No conversion
25	$Co(OAc)_2$, TBHP	**3.102**	Low conversion
26	$FeCl_3 \bullet 6H_2O$, TBHP	**3.102**	Complex mixture
27	$Bi(OTf)_3$, picolinic acid, TBHP	**3.102**	Low conversion
28	$Rh_2(cap)_4$, TBHP	**3.102**	**3.109**[a]
29	$Ru(Cl)_2(PPh_3)_2$, TBHP	**3.102**	**3.109**: 10%, **3.102**: 40%
30	$ReOCl_3(OPPh_3)(SMe)_2$, TBHP	**3.102**	**3.109**[a]
31	VCp_2Cl_2, TBHP	**3.102**	No conversion
32	Bi(0), picolinic acid, TBHP	**3.102**	**3.109**: 17%, **3.102**: 13%
33	$RuCl_3 \bullet xH_2O$	**3.102**	**3.109**: 31%, **3.102**: 19%
34	$Fe(OTf)_2$, ligands, H_2O_2	**3.102**	**3.109**[a]
35	$CuSO_4 \bullet 5H_2O$, $K_2S_2O_8$	**3.102**	Complex mixture
36	$NaIO_4$, $RuCl_3 \bullet xH_2O$	**3.102**	Complex mixture
37	$KMnO_4/CuSO_4 \bullet 5H_2O$	**3.102**	**3.109**[a]
38	$KMnO_4/CuSO_4 \bullet 5H_2O$	**3.76**	**3.110**[a]

Cond.: Conditions; NHPI: *N*-hydroxyphthalimide; TBHP: *t*-butyl hydroperoxide; DDQ: 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; DCN: 1,4-dicyanonaphtalene; NMO: *N*-methyl morpholine-*N*-oxide; [a] trace amounts

Salvicanol (**3.6**) was the first substrate that was subjected to benzylic oxidation conditions (Table 3.3, entries 1-4). DDQ oxidation (entry 1) in aqueous acetone failed to yield the desired ketone **3.74**. Instead, the orthoquinone **3.106** was obtained in excellent yield (96% crude)[122] perhaps through an aromatic oxidative

demethylation. Compound **3.106**, very recently isolated from *Perovskia atriplicifolia*,[131] has already been synthesized by Takeya[132] and Majetich[122] and our spectral data was in good agreements with both natural and synthetic samples. To the extent of our knowledge, this unexpected oxidation of monomethoxy catechol in presence of DDQ was reported only three times in poor to moderate yield (15-52%) and has received little attention.[133] We believe that the importance of water as co-solvent is the key to this high yielding reaction. Indeed, such a reaction could proceed *via* hydride transfer from the methoxy phenol **3.6** to DDQ, resulting in the formation of the reactive species **3.107** (Scheme 3.24). Nucleophilic attack of water on the oxonium methyl (red pathway) or on the C12 carbonyl atom (green pathway) would give the orthoquinone **3.106**. To determine which pathway is preferred, the reaction should be performed in isotopically labeled water ($^{18}OH_2$). An investigation of the substrate scope could also be of interest. Another aromatic oxidation occurred when salvicanol (**3.6**) was treated with $RuCl_3$ in presence of aqueous TBHP[134] (entry 2) yielding trace amount of **3.105** without detection of the desired product **3.11**. Moreover the use of Bi(0) catalyst in presence of TBHP (entry 3) or utilization of SeO_2 (entry 4) lead to a complex mixture or no reaction conversion respectively.

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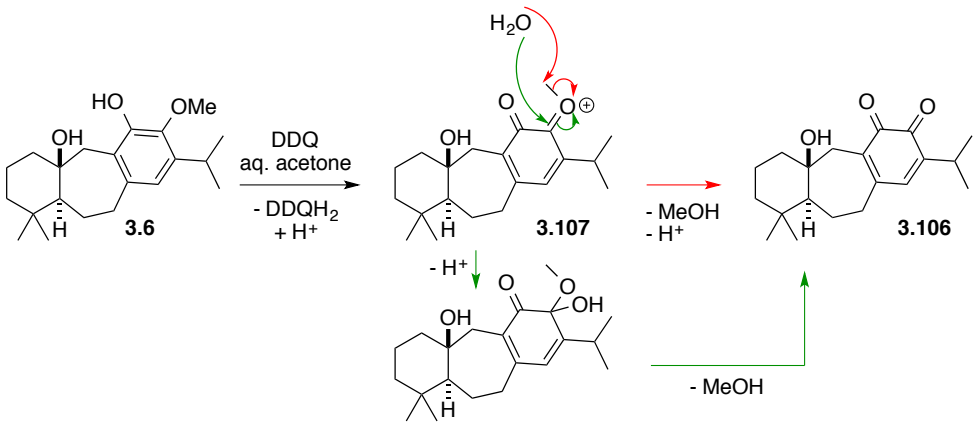
[131] Jiang, Z.-Y.; Yu, Y.-J.; Huang, C.-G.; Huang, X.-Z.; Hu, Q.-F.; Yang, G.-Y.; Wang, H.-B.; Zhang, X.-Y.; Li, G.-P. *Planta Med.* **2015**, *81*, 241−246.

[132] Aoyagi, Y.; Takahashi, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Kurihara, T. *Chem. Pharm. Bull.* **2006**, *54*, 1602−1604.

[133] (a) Boldt, P.; Paul, K.-P. *Chem. Ber.* **1966**, *99*, 2337−2344; (b) Cimino, G.; De Luca, P.; De Stephano, S.; Minale, L. *Tetrahedron* **1975**, *31*, 271−275; (c) Magauer, T.; Martin, H. J.; Mulzer, J. *Chem. Eur. J.* **2010**, *16*, 507−519.

[134] Amaya, T.; Hifumi, M.; Okada, M.; Shimizu, Y.; Moriushi, T.; Segawa, K.; Ando, Y.; Hirao, T. *J. Org. Chem*. **2011**, *76*, 8049−8052.



Scheme 3.24: *Possible mechanism for the DDQ oxidation of salvicanol (**3.6**).*

The benzylic oxidation of the ring expanded alcohol **3.76** and salvicanol acetate (**3.102**) was explored as next. All benzylic oxidation attempts imply the possible formation of benzylic radicals. Among them, the use of halogenated species to generate these radicals (entries 8-10) resulted in either the formation of the side-product **3.108** (entry 8, presumably *via* the bromination with a Br^+ species),[135] no conversion (entry 9),[136] or a complex mixture (entry10).[137] The use of transition metal free conditions (entries 11-16)[138] lead to low or no conversion with the exception of using of TBHP under microwave conditions (180 °C, CH_3CN, entry 17)[139] where the desired benzylic oxidized product **3.109** could be detected by ^{1}H-NMR. Similar C10-C20 oxidative cleavage product, described by Majetich and co-workers (see Scheme 3.22), could be detected ^{1}H-NMR when substrates **3.76** (entry 18) and **3.102** (entry 19) were treated with CrO_3 in acidic medium. Substrate **3.76** remained unreactive when treated with $KMnO_4$ under basic conditions (entry 20).

The successful formation of **3.109** motivated us to investigate additional combinations of transition metal catalysts in TBHP (entries 21-33). Indeed, the

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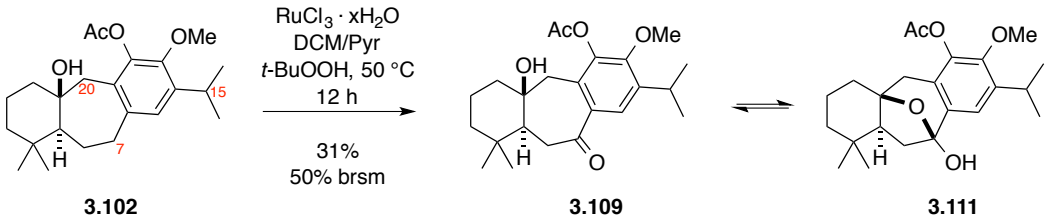
[135] Moriyama, K.; Takemura, M.; Togo, H. *Org. Lett.* **2012**, *14*, 2414−2417.
[136] Silvestre, S. M.; Salvador, J. A. R. *Tetrahedron* **2007**, *63*, 2439−2445.
[137] Jin, C.; Zhang, L.; Su, W. *Synlett.* **2011**, *11*, 1435−1438.
[138] (a) Amemiya, T.; Yasunami, M.; Takase, K. *Chem. Lett.* **1977**, 587−590; (b) Pandey, G.; Pal, S.; Laha, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 5146−5149; (c) PhD thesis of Sasane, Kulbhushan A. *Novel Synthetic Methodologies for Bioactive Molecules* **2013**, Chapter 3, p 96−126; (d) Zhang, J.; Wang, Z.; Wang, Y.; Wan, C.; Zheng, X.; Wang, Z. *Green Chem.* **2009**, *11*, 1973−1978; (e) Majji, G.; Guin, S.; Gogoi, A.; Rout, S. K.; Patel, B. K. *Chem. Comm.* **2013**, *49*, 3031−3033; (f) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.
[139] He, H.; Pei, P.-J.; Lee, A. W. N. *Green Chem.* **2009**, *11*, 1857−1861.

formation of the desired product **3.109** was observed for several transition metals (entries 23, 28-30, 32 and 33)[140]. The optimal conversion was identified while reacting acetate **3.102** with modified conditions of the Hirao protocol ($RuCl_3$•xH_2O, TBHP, entry 33).[140k] The benzylic oxidation product was obtained in moderate yield (31%) along with starting material (19%). NMR analysis of this compound was difficult due to the keto-hemiketal tautomerism equilibrium between the open (**3.109**) and the closed form (**3.111**) (Scheme 3.25), as already observed on a similar hydroxy-ketone by Suto and co-workers.[96]

Conditions using transition metals without TBHP were also investigated (entries 34-38).[141] However, compounds **3.110** (entry 38) or **3.109** (entries 34 and 37), were produced only in trace amounts.



Scheme 3.25: *Optimized benzylic oxidation conditions of **3.102** and product keto-hemiketal tautomerism.*

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[140] (a) Han, X.; Zhou, Z.; Wan, C.; Xiao, Y.; Qin, Z. *Synthesis* **2013**, *45*, 615−620; (b) Pearson, A. J.; Chen, Y.-S.; Hsu, S.-Y.; Ray, T. *Tetrahedron Lett.* 1984, 25, 1235−1238; (c) Modica, E.; Bombieri, G.; Colombo, D.; Marchini, N.; Ronchetti, F.; Scala, A.; Toma, L. *Eur. J. Org. Chem.* **2003**, 2964−2971; (d) Nakanishi, M.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 861−864; (e) Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barret, A. G. M. *Org. Lett.* **2005**, *7*, 4549−4552; (f) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167−5170; (g) Murahashi, S.-I.; Komiya, N.; Oda, Y.; Kuwabara, T.; Naota, T. *J. Org. Chem.* **2000**, *65*, 9186−9193; (h) Peng, H.; Lin, A.; Zhang, Y.; Jiang, H.; Zhou, J.; Cheng, Y.; Zhu, C.; Hu, H. *ACS Catal.* **2012**, *2*, 163−167; (i) Xia, J.-B.; Cormier, K. W.; Chen, C. *Chem. Sci.* **2012**, *3*, 2240−2245; (j) Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barrett, A. G. M. *Org. Lett.* **2005**, *7*, 4549−4552; (k) Amaya, T.; Hifumi, M.; Okada, M.; Shimizu, Y.; Moriushi, T.; Segawa, K.; Ando, Y.; Hirao, T. *J. Org. Chem.* **2011**, *76*, 8049−8052.

[141] (a) Olivo, G.; Arancio, G.; Mandolini, L.; Lanzalunga, O.; Di Stephano, S. Catal. *Sci. Technol*. **2014**, *4*, 2900−2903; (b) Bhatt, M. T.; Perumal, P. T. *Tetrahedron Lett.* **1981**, *22*, 2605−2608; (c) Ghosh, S.; Ghatak, U. R. *Tetrahedron* **1992**, *48*, 7289−7296; (d) Noureldin, N. A.; Zhao, D.; Lee, D. G. *J. Org. Chem.* **1997**, *62*, 8767−8772.

The problems encountered in the benzylic oxidations of salvicanol derivatives could be explained by the three benzylic C-H present at C7, C15 and C20, which are prone to oxidation in substrates **3.6**, **3.76** and **3.102**. The improved results obtained with salvicanol acetate (**3.102**) are due to the electronic effect of the acetate group,[142] which deactivates the *ortho* position (C20) for oxidation and therefore directs the course of the reaction preferably to the *para* position (C7) of the methoxy substituent. The second explanation would associate the ring size fused to the aromatic ring, with the efficiency of the benzylic oxidation. Indeed, a former study by Miller addressing the problematic benzylic oxidation of a seven membered ring system, suggested a greater ring strain to force the orbital occupied by the unpaired electron of the newly formed radical (or the empty p-orbital in case of a newly formed carbocation) in the same plane as the aromatic ring (to maximize the overlap of the p-orbital with the π-system for radical or carbocation stabilization, Figure 3.6).[143]

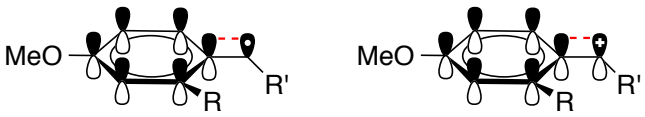

Figure 3.6: *Benzylic radical or carbocation stabilization.*

This interpretation was supported with the construction of a space-filling model of compound **3.112** and **3.113**, whereby the benzylic carbon, in *para* position to the methoxy substituent (C6) was sp^2 hybridized (to mimic the radical or carbocation character, Figure 3.6). A bigger ring strain was observed in a seven membered ring than in a six membered system, when the sp^2 C7 was forced to be in the phenyl plane. Besides what, the chemical shift of the vinyl proton H_a and H_b of compounds **3.114** and **3.115**, both having an exocyclic sp^2 C6 methylidene group, were compared in NMR studies (Figure 3.7). In the case of the six membered ring **3.114**, it was found that the chemical shift of H_a was significantly higher than H_b, indicating the relative planarity of the C6 center, H_a being closer to the deshielding region of the aromatic ring. Regarding the seven membered ring of **3.115**, the chemical shifts of both, H_a and H_b, were identical and lower, resulting from a

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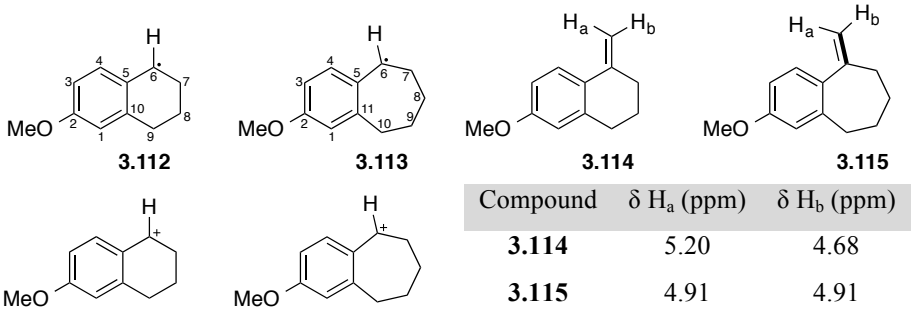
[142] Ramdayal, F. D.; Kiemle, D. J.; Lalonde, R. T. *J. Org. Chem.* **1999**, *64*, 4607−4609.
[143] Miller, R. B.; Gutierrez, C. G. *J. Org. Chem.* **1978**, *43*, 1569−1573.

deviation out of the plane of the sp^2 C6 methylidene group as depicted in Figure 3.7. For stabilization of any radical or carbocation, the sp^2 C6 atom of a seven membered ring system has to be in the plane of the aromatic ring, thus requiring higher torsional strain than for the six membered ring.



Compound	δ H_a (ppm)	δ H_b (ppm)
3.114	5.20	4.68
3.115	4.91	4.91

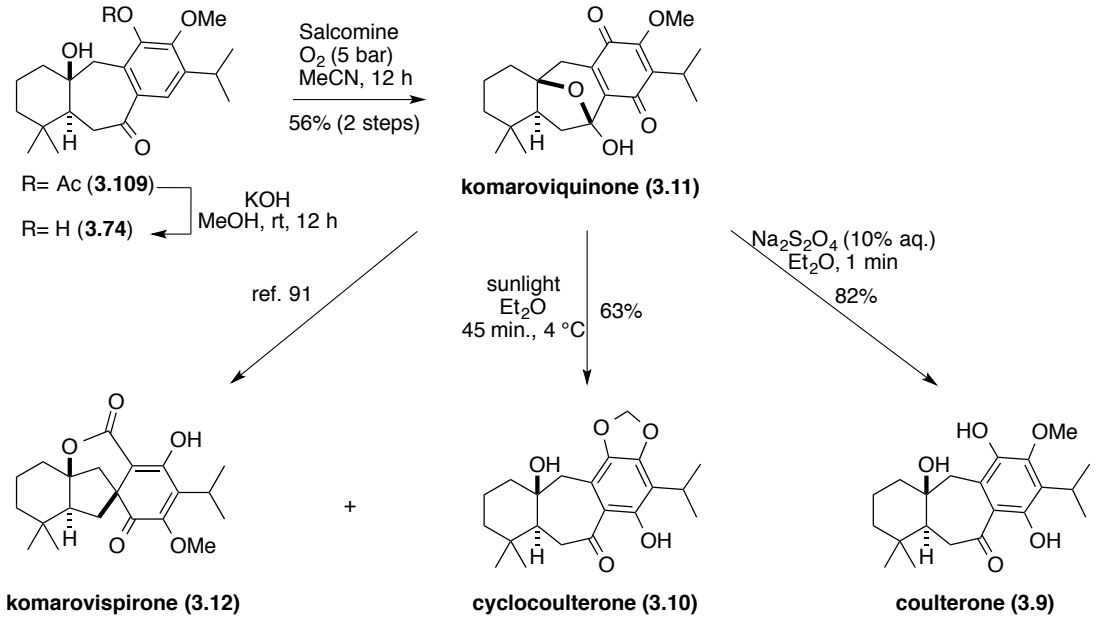
Figure 3.7: *Space-filling model and NMR studies of different ring system C6 benzylic positions reported by Miller.*[143]

3.2.5. Synthesis and photolysis of komaroviquinone

For the completion of the synthesis of komaroviquinone (**3.11**, Scheme 3.26), the benzylic oxidized acetate was first deacetylated using KOH in methanol at rt for 12 h. The crude mixture was subsequently submitted to aromatic oxidation of phenol **3.74** using Salcomine in an O_2 atmosphere with strict exclusion from light to yield the synthetic komaroviquinone (**3.11**) in 56% yield over two steps. However, longer reaction time (12 h) and high oxygen pressure (5 bar) were necessary in this case. These required condition adjustments could be explained by the C7 keto group, which lowers the electron density of the aromatic ring and therefore decreases the reactivity towards an aromatic oxidation. Furthermore, komaroviquinone (**3.11**) was obtained as the sole tautomer, which could be explained by the newly formed H-bond at the C14-keto group, and by the increased electrophilicity of the C7-vinylogous ketone compared to the benzylic ketone in structure **3.109**.

Next, the photolysis of komaroviquinone (**3.11**), applying similar conditions as used for the synthesis of taiwaniaquinol A (**2.9**) (Et_2O, sunlight, rt), was successfully carried out. We were delighted to observe the formation of the first synthetic cyclocoulterone as well as the known komarovispirone (**3.12**) in nearly equimolar ratio with an overall yield of 63%.

Additionally, quinone **3.11** in an ethereal solution was reduced using an aqueous solution $Na_2S_2O_4$ in a separatory funnel at rt for 1 min, which affords the first synthesis of coulterone (**3.9**) in high yield (82%). Finally, we could confirm the relative configuration of coulterone (**3.9**) by its chemical synthesis from the precursor salvicanol (**3.6**). To this point the relative configuration of **3.9** was previously assigned by ^{1}H-NMR chemical shifts comparisons with salvicanol (**3.6**), which absolute configuration was determined by X-ray diffraction.[125]

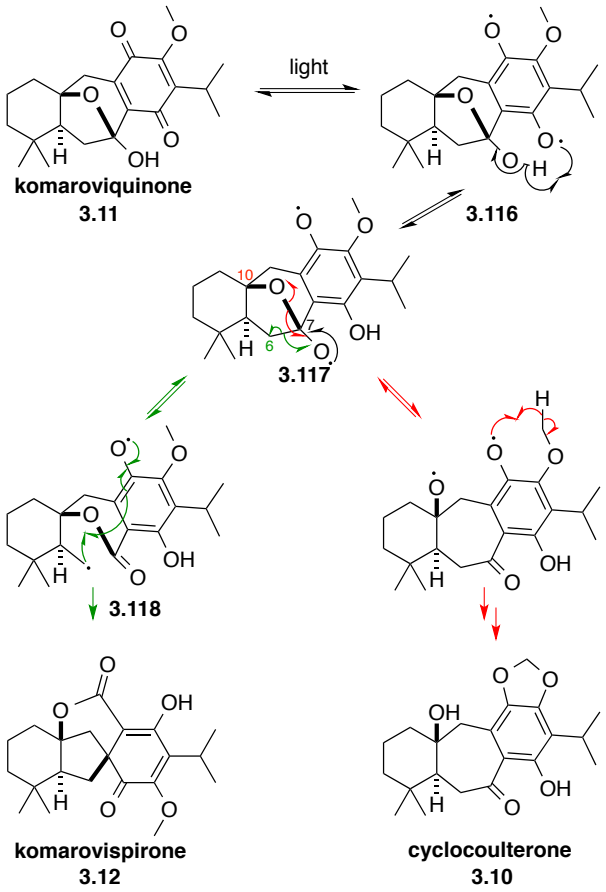


Scheme 3.26: *Synthesis, photolysis and reduction of komaroviquinone, first synthesis of cyclocoulterone (**3.10**) and coulterone (**3.9**).*

As mentioned before, the previous photolysis of komaroviquinone (**3.11**), achieved with a low-pressure mercury lamp by Majetich and co-workers[91] in cyclohexane, lead to the formation of komarovispirone (**3.12**) as the sole product. However, under sunlight irradiation, the authors reported the formation of an additional unknown compound in a $CDCl_3$ solution. This could correspond to cyclocoulterone, but no analytical data was reported to verify this hypothesis.

A possible mechanism, in accordance with the suggested proposal for the formation of komarovispirone (Majetich *et al.*[91]), is depicted in Scheme 3.27 to rationalize the formation of cyclocoulterone (**3.10**) using our established conditions. Light excitation of the n → π* transition of the quinone **3.11** generates the quinol diradical **3.116** that can undergo a 1,5-HAT between the alkoxy radical at C14 and the hydroxyl group at C7 to give **3.117**. At this point, the compound **3.117** can either

fragment at the C6-C7 bond to form the biradical **3.118**, which recombined to komarovispirone (**3.12**), or at the C7-O(C10) ether bond, which after a second 1,5-HAT, recombine to yield cyclocoulterone (**3.10**).

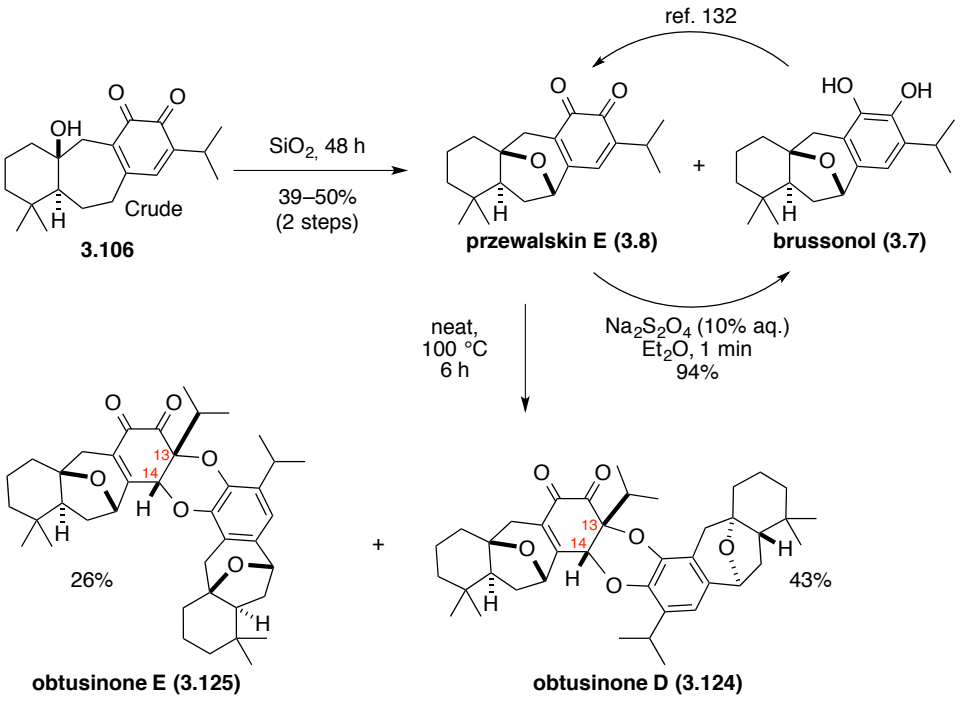


Scheme 3.27: *Suggested mechanism for the co-formation of cyclocoulterone (**3.10**) and komarovispirone (**3.12**) through the photolysis of komaroviquinone (**3.11**).*

3.2.6. Synthesis of barbutasol family members

As the direct benzylic oxidation of salvicanol (**3.6**) with DDQ generated the aromatic oxidized orthoquinone **3.106** in excellent yield (96%), which could not be purified by column chromatography on silica gel due to stability issues, we decided to investigate the outcome of a prolonged exposure of **3.106** on silica gel upon absorption. After 48 h at rt, the purification of the mixture by column chromatography on silica gel afforded two main products, identified as przewalskin E (**3.8**) and brussonol (**3.7**, Scheme 3.28). Interestingly, when the absorbed orthoquinone (**3.106**) was left in an open flask with frequent mixing (every 4 hours), higher yields of

przewalskin E (**3.8**, 50%) were obtained and no formation of brussonol (**3.7**) was observed.

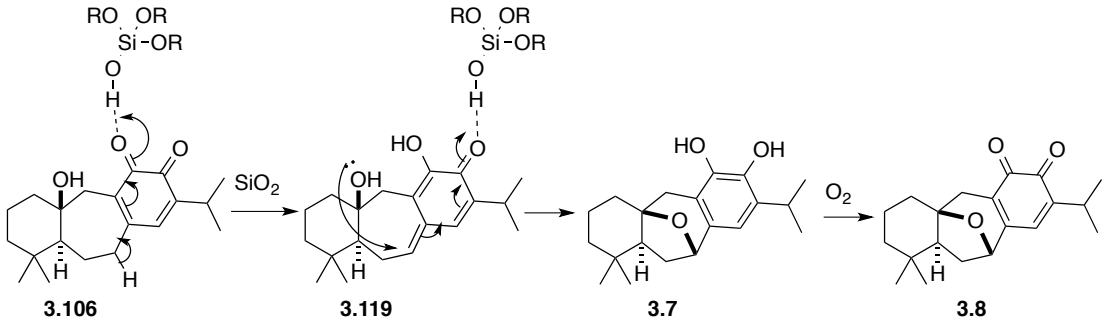


Scheme 3.28: *Synthesis of przewalskin E (**3.8**), brussonol (**3.7**) and first synthesis of obtusinone D (**3.124**) and E (**3.125**).*

The outcome of this reaction could be rationalized by a silica gel acid catalyzed tautomerization, forming the reactive quinone-methide intermediate **3.119** (Scheme 3.29), which upon nucleophilic attack of the angular C10-OH on the electrophilic C7, delivers the natural brussonol (**3.7**). Upon aerobic condition, **3.7** converts into its natural congener przewalskin E (**3.8**). Majetich and co-workers already reported such synthesis of brussonol (**3.7**) from **3.106** through heating a concentrated solution of **3.106** in Et_2O (60 °C, 40 h, 70%).[122] Similarly, Takeya and co-workers[132] described the same transformation by heating **3.106**, absorbed on magnesium silicates (Florisil®) in a microwave oven (150 °C, 5 min, 37%). However, none of these methods were suitable to produce przewalskin E (**3.8**) directly from **3.106**. Interestingly, only very few reports of catechols oxidation to orthoquinone were described on silica gel under aerobic conditions.[144] Futhermore, the crucial role

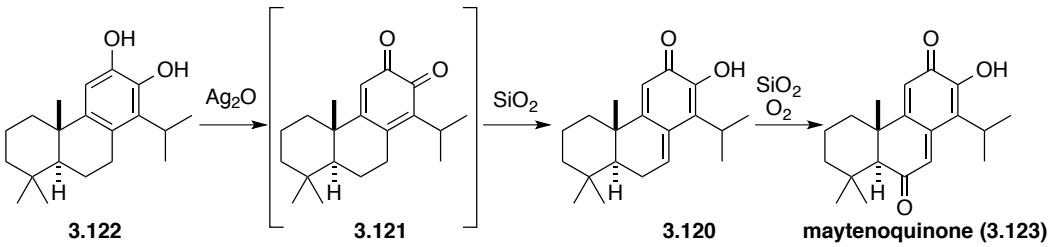
[144] (a) Takuwa, A.; Ryoji, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 623−625; (b) Vol'eva, V. B.; Belostotskaya, I. S.; Bundel', A. Y.; Komissarova, N. L.; Ershov, V. V. *Russ. Chem. Bull.* **1997**, *46*, 385−386; (c) Vol'eva, V. B.; Prokof'ev, A. I.; Karmilov, A.

of silica gel was emphasized, when an acetonitrile or acetone solution of brussonol was stirred under oxygen atmosphere and only trace amounts of przewalskin E (**3.8**) could be observed after several days.



Scheme 3.29: *Mechanistic proposal for the formation brussunol (**3.7**) und przewalskin E (**3.8**).*

Formation of such a reactive quinone methide from orthoquinone **3.119** under comparable reaction conditions, was reported by Burnell and co-workers.[145] In their study, they synthesized paraquinone methide **3.120** from orthoquinone **3.121**, which was obtained from the silver(I) oxide oxidation of catechol **3.122**. Prolongated exposure of **3.120** to silica gel and air, produced the autooxidized maytenoquinone **3.123** (Scheme 3.30).



Scheme 3.30: *Aerobic silica gel tandem tautomerization/oxidation of orthoquinone **3.121** by Burnell.*[145]

The spectral data of brussonol (**3.7**), first isolated from *Salvia brussonetii* and showing insecticidal[81c] and anti-P388 leukemia cell acitivity,[132] were in good agreement with those reported for the natural and synthetic products. The spectral data of przewalskin E (**3.8**), first synthetically prepared from natural

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Y.; Komissarova, N. L.; Belostotskaya, I. S.; Prokof'eva, T. I.; Ershov, V. V. *Russ. Chem. Bull.* **1998**, *47*, 1920−1923; (d) Vol'eva, V. B.; Prokof'eva, T. I.; Belostotskaya, I. S.; Komissarova, N. L.; Ershov, V. V. *Russ. Chem. Bull.* **1997**, *46*, 385−386.

[145] Burnell, R. H.; Jean, M.; Marceau, S. *Can. J. Chem.* **1987**, *66*, 227−230.

demethylsalvicanol,[132] and subsequently isolated from *Salvia przewalskii MAXIM,*[146] corresponds perfectly to the synthetic material, but significantly deviates from the natural sample. Although the ^{13}C-NMR chemical shifts (0.1-0.4 ppm) and the optical activity of the isolated sample reasonably matches with our synthetic substance, the ^{1}H-NMR chemical shifts (0.01-0.08 ppm) and FT-IR absorption bands (the main signal at 1660 cm^{-1} was not reported, and signals at 1722, and 1680 cm^{-1} were found with much lower intensity) significantly diverges from the synthesized samples. Moreover, the natural compound was isolated as a white powder and our synthetic sample as a red amorphous solid, the typical color of orthoquinones. Unfortunately, the authors did not compare their sample with the synthetic compound of Takeya. However, the structure of przewalskin E (**3.8**) could be verified by interconverting it to brussonol (**3.7**) by reduction with aqueous $Na_2S_2O_4$ in excellent yield (94%, Scheme 3.28). The resulting brussonol (**3.7**) was then oxidized back to przewalskin E (**3.8**) following the Takeya protocol (DDQ, dioxane).[132]

Having confirmed the structure of our synthetic **3.8**, the synthesis of the rarely found dimeric icetexanes obtusinones D (**3.124**) and E (**3.125**) was addressed next (Scheme 3.28). The first example of such icetexane dimers is grandione, which was isolated by Riccio *et al.* [147] in 1999 from *Toreya grandis* and synthesized by Takeya and co-workers in 2005 (the structure was reassigned later) *via* a solid state hetero-Diels-Alder dimerization of orthoquinone **3.106**.[148] Obtusinone D (**3.124**) and E (**3.125**), which were recently isolated by Salae and Boonnak,[149] were suggested to biogenetically originate from a similar Diels-Alder dimerization of przewalskin E (**3.8**). Having **3.8** in hand, modified Takeya conditions (neat, 100 °C, 6 h) were applied to achieve the first synthesis of both obtusinone D (**3.124**) and E (**3.125**) (1.7 : 1.0), in high overall yield (69%). The separation of both synthesized natural products proved to be difficult, using either column chromatography or pTLC on silica gel utilizing the eluent reported in the isolation study.[149] We expected that

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[146] Xu, G.; Peng, L.-Y.; Tu, L.; Li, X.-L.; Zhao, Y.; Zhang, P.-T.; Zhao, Q.-S. *Helv. Chim. Acta* **2009**, *92*, 409−413.

[147] Galli, B.; Gasparrini, F.; Lanzotti, V.; Misiti, D.; Riccio, R.; Villani, C.; Guan-Fu, H.; Zhong-Wu, M.; Wan-Fen, Y. *Tetrahedron* **1999**, *55*, 11385−11394.

[148] Aoyagi, Y.; Takahashi, Y.; Satake, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Shiina, T.; Kurihara, T. *Tetrahedron Lett.* **2005**, *46*, 7885−7887.

[149] Salae, A.-W.; Boonnak, N. *Tetrahedron Lett.* **2013**, *54*, 1356−1359.

the π-stacking of both natural products could be responsible for the same retention time. Consequently, we decided to change our eluent system by adding toluene to our solvent mixture, to break the π-stacking between **3.124** and **3.125**. Fortunately, the natural products were then successfully separated by pTLC with the optimized eluent (pentane/toluene/Et_2O, 5/5/1). The spectral data of both synthetic natural products was in perfect agreements with the natural samples. However, an X-ray analysis of a single crystal of obtusinone D (**3.124**, Figure 3.8) could be obtained and the structure shows an opposite C13 and C14 configuration as reported by Salae and Boonnak.[149] Indeed, these authors established the C13 and C14 stereochemical assignement of **3.124** based on a NOESY correlation between H7 and H14 and between H14 and Me16. The close proximity of H7 and H14 revealed by the X-ray crystallographic analysis of **3.124** (Figure 3.8), could explain the NOESY correlation measured by Salae and Boonnak[149] between these two centers. This NOESY correlation was later confirmed by us, therefore further supporting the authenticity of our synthetic obtusinone D.

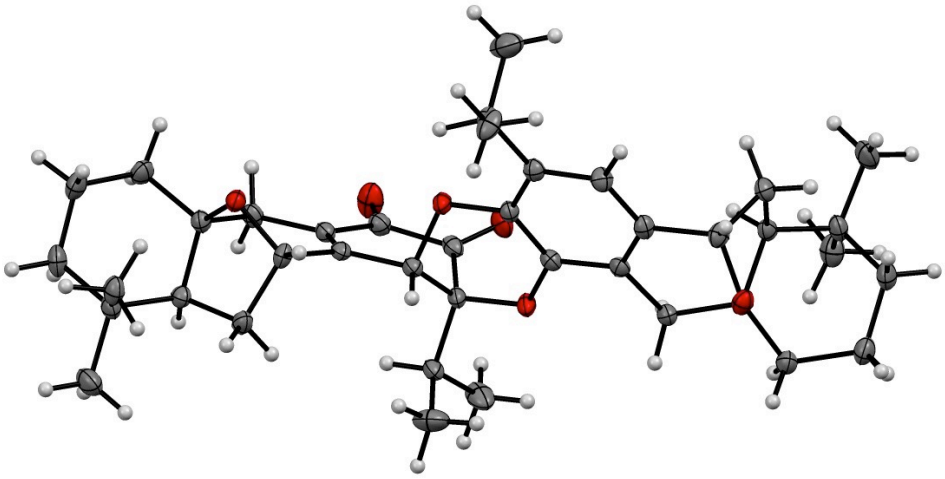


Figure 3.8: *X-ray crystallographic analysis of **3.124**.* Red = oxygen, grey = carbon, white = hydrogen.

The synthetic X-ray crystallographic analysis of **3.124** (Figure 3.8) unambiguously leads to the structural reassignment of the natural product obtusinone D (**3.124),** represented by the revised structure **R3.124** (Figure 3.9, **B**). Consequently, the C13 and C14 configuration of obtusinone E (**3.125**) is suggested to be identical with obtusinone D (**3.124**), shown in the revised structure **R3.125** (Figure 3.9, **B**).

Figure 1. Examples of subclasses of icetexanes according to Sarpong.

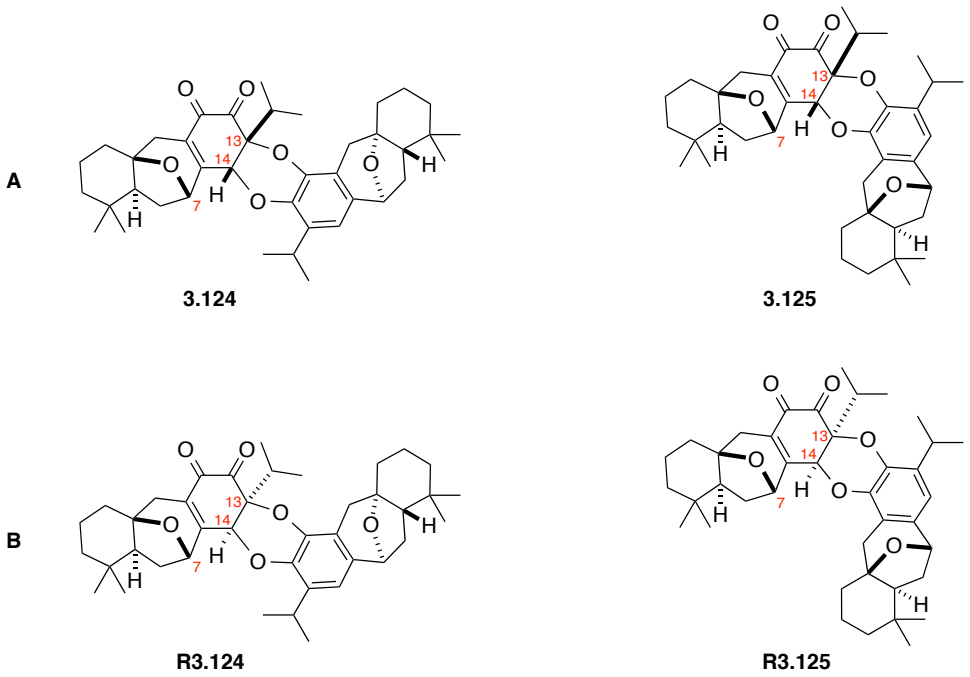


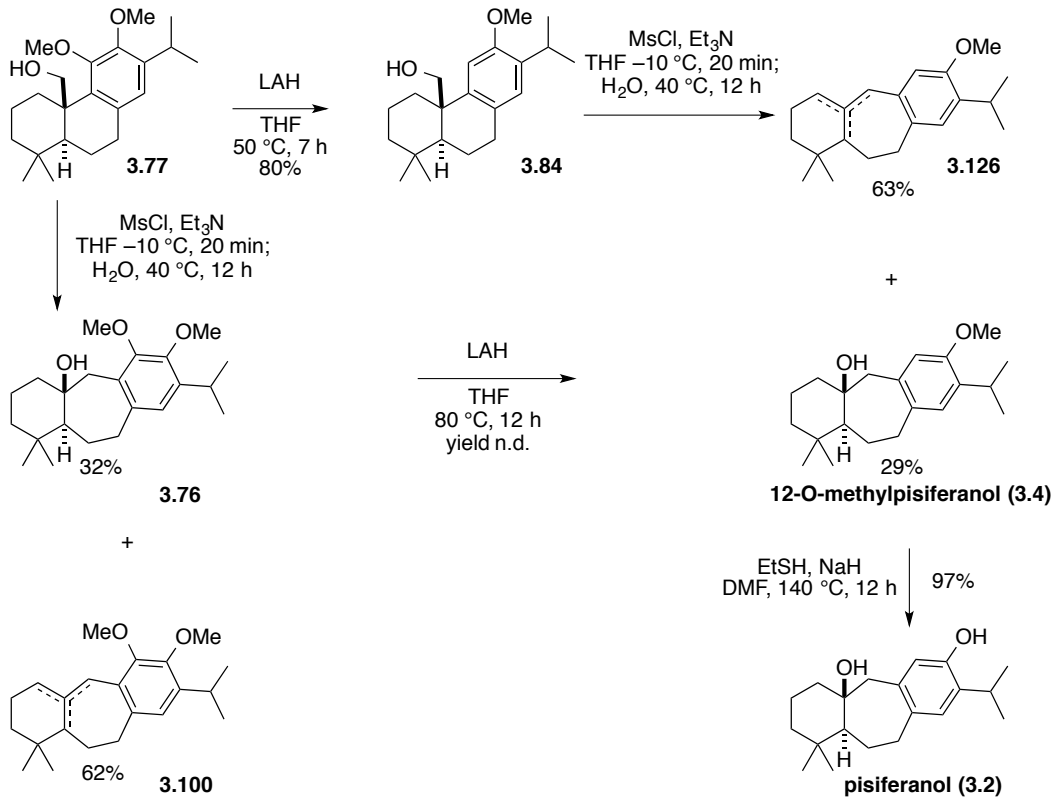
Figure 3.9: ***A)*** *Originally proposed and* ***B)*** *revised structure of obtusinones D and E.*

The different regioselectivity ratio of the isolated natural products (**3.124**:**3.125**, 4:1) compared to the synthetic study (**3.124**:**3.125**, 1.7:1.0) could be explained by the higher temperature needed to achieve the Diels-Alder reaction in high yield and reasonable reaction time. Indeed, the authors justified their ratio by steric arguments. When the reaction was performed at 55 °C, the reaction conversion was only 43% after 18 h (instead of 6 h at 100 °C, see above), therefore, at physiological conditions, the thermal Diels-Alder does not appeared realistic. Consequently, the higher selectivity achieved by nature, could be explained by an acid catalyzed Diels-Alder that would lower the energy the LUMO of the dienophile and therefore increasing the reactivity. The difference in orbital coefficients of the LUMO would also be increased, thus increasing the regioselectivity. To test our hypothesis, przewalskin E (**3.8**) was stirred at rt in DCM in presence of $AlCl_3$. However, this resulted only in a complex mixture. Due to limitation of material we could not further investigate additional acids such as TFA or boronic acids.

3.2.7. Synthesis of pisiferin family members

Since methylpisiferol (**3.84**) was accessible from the hydrogenolysis of hydroxyl compound **3.77** in substantial amounts, we decided to continue our effort with the synthesis of pisiferin family members such as euolutchuol E (**3.3**) using our aqueous ring expansion strategy. Consequently, **3.84** (Scheme 3.31) was subjected to the ring expansion conditions developed earlier (MsCl, Et_3N, THF, −10 °C, 20 min; then H_2O, 40 °C, 12 h). To our delight, these conditions afforded the ring expanded tertiary alcohol methylpisiferanol (**3.4**, 29%), which spectral data being in excellent agreement with the natural sample isolated from the leaves of *Chamaecyparis formosensis*.[150] Additionally, an inseparable mixture of ring expanded alkenes **3.126** was isolated in 62% yield, therefore giving an excellent overall yield (92%) of the ring expansion (Scheme 3.31). Interestingly, the methoxy hydrogenolysis of methylsalvicanol (**3.76**) was also possible, using commercial LAH (detected by ^{1}H-NMR). However, a complete conversion could not be achieved (starting material and product were inseparable), and longer reaction time, lead to decomposition of both starting material and product. This emphasizes once again the importance of the conformational bias of the hydroxyl group to achieve an efficient hydrogenolysis.

[150] Lin, T.-C.; Fang, J.-M.; Cheng, Y. S. *Phytochemistry* **1999**, *51*, 793−791.



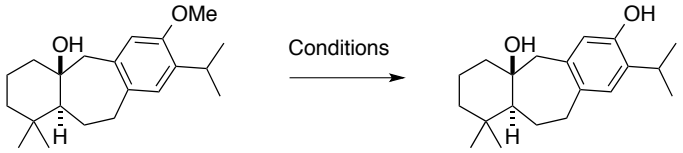
Scheme 3.31: *Synthesis of 12-O-methylpisiferanol, pisiferanol (**3.2**).*

Demethylation of **3.4** using the previously applied conditions (L-Selectride in THF, 80 °C, 3 h, Table 3.4, entry 1) resulted only in a complex mixture without traces of the desired pisiferanol (**3.2**). The use of BBr_3 in DCM or $AlCl_3$ in combination with EtSH (entry 2 and 3), lead to similar results. In contrast, basic conditions using EtSNa in DMF at 140 °C for 12 h (entry 4), lead to a low conversion of starting material and traces of psiferanol (**3.2**). Encouraged by these results, the reaction was repeated with slight modifications utilizing *in situ* prepared EtSNa (from NaH and EtSH in DMF, **entry 5**). In this regard, **3.2** was obtained in excellent yield (97%). Part of the spectral data was in excellent agreement (FTIR, [α]) with the natural sample isolated from *Chamaecyparis pisifera*.[151] Unfortunately, the ^{1}H-NMR and the ^{13}C-NMR chemical shifts showed significant deviation, especially concerning the aromatic signals. Extensive literature research revealed only one set of NMR data of pisiferanol (**3.2**) (here named lanigerol), re-isolate of from *Salvia lanigera.*[152] Also here, our spectral data did not match the reported one, although the spectral data varied from the one of

[151] Hasegawa, S.; Kojima, T.; Hirose, Y. *Phytochemistry* **1985**, *24*, 1545−1551.
[152] El-Lakany, A. M.; Abdel-Kader, M. S.; Sabri, N. N.; Stermitz, F. R. *Planta Med.* **1995**, *61*, 559−560.

Hasegawa. In order to confirm the structure of our synthetic pisiferanol (**3.2**), a full spectroscopic characterization was performed, which confirmed the structure of our synthetic sample.

Table 3.4: *Aromatic demethylation of methylpisiferanol (**3.4**).*



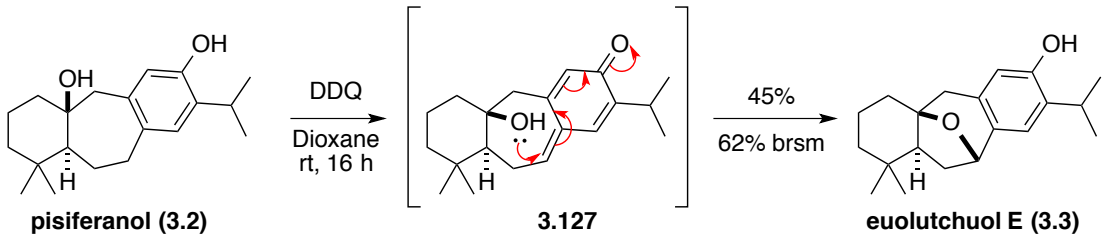
methylpisiferanol (3.4) **pisiferanol (3.2)**

Entry	Conditions	Observation
1	L-Selectride in THF, 80 °C, 3 h	Complex mixture
2	BBr_3, DCM, −78 °C to 0 °C, 20 min.	Complex mixture
3	$AlCl_3$, DCM, EtSH, 0 °C to rt, 20 min.	Complex mixture
4	NaSEt, DMF, 140 °C, 12 h	Low conversion, traces of **3.2**
5	NaH, EtSH, DMF, 140 °C, 12 h	**3.2** (97%)

With pisiferanol (**3.2**) in hand, the synthesis of euolutchuol E (**3.3**), an icetexane isolated from *Euonymus lutchuensis*,[153] was attempted with the objective to form the intermediate orthoquinone methide **3.125** (Scheme 3.32). This reactive species should deliver euolutchuol E (**3.3**) upon nucleophilic attack on C7, *via* an analogous approach used for the synthesis of brussonol (**3.7**). Consequently, pisiferanol (**3.2**) was treated with an excess of DDQ in dioxane at rt for 16 h and an aqueous workup with brine followed by a fast pTLC purification resulted in the first synthesis of the natural product euolutchuol E (**3.3**) in moderate yield (45%) along with recovered unreacted pisiferanol (**3.2**, 17%). It is noteworthy to mention that the typical workup procedure for such reaction conditions, including filtering of the reaction mixture through a pad of silica gel or celite, gave only complex mixtures. Such a decomposition was observed by TLC analysis when the starting material and/or the product was in a simultaneous contact with silica gel (on the TLC) and DDQ (in excess in the reaction mixture). This process could be observed by a color change of the absorbed sample from orange to dark brown within a minute. To improve the yield of the reaction, different oxidants such as Ag_2O, or $K_3Fe(CN)_6$ were

[153] Inaba, Y.; Hasuda, T.; Hitotsuyanagi, Y.; Aoyagi, Y.; Fujikawa, N.; Onozaki, A.; Watanabe, A.; Kinoshita, T.; Takeya, K. *J. Nat. Prod.* **2013**, *76*, 1085−1090.

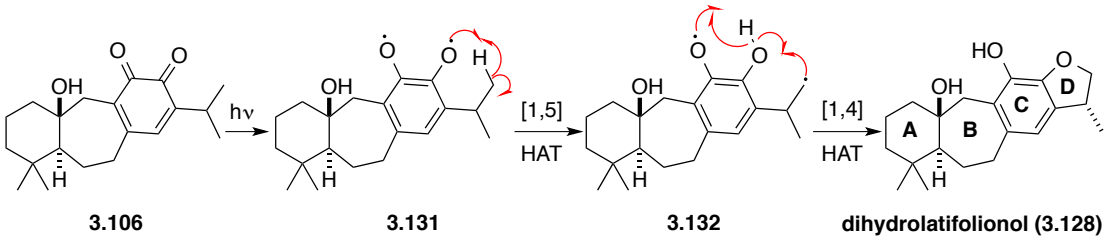
tested in different solvents. However, these experiments resulted only in complex mixtures.



Scheme 3.32: *First synthesis of euolutchuol E (**3.3**).*

3.2.8. Synthetic studies toward the synthesis of dihydrolatifolionol and its congeners

Recently, Babu and co-workers reported the isolation of dihydrolatifolionol (**3.128**, Scheme 3.33) and two related icetexanes (**3.129** and **3.130**, Scheme 3.35) from *Premna latifolia*.[154] These compounds showed cytotoxic activity against HT-29 and Hep-G2 cancer cell lines. As these natural products are structurally related to the previously synthesized orthoquinone **3.106** and przewalskin E (**3.8**), and with our experience in the photolysis of paraquinone **3.11** and taiwaniaquinone F (**2.3**), the synthesis of the D ring of dihydrolatifolionol (**3.128**) might be achieved in similar manner. Indeed, the formation of the biradical species **3.131** *via* a light irradiation of **3.106** would undergo a [1,5]-HAT to form the isopropyl biradical **3.132**, which upon a successive [1,4]-HAT followed by radical recombination should form the D ring of dihydrolatiflionol (**3.128**).



Scheme 3.33: *Hypothetical photolysis of orthoquinone 3.106.*

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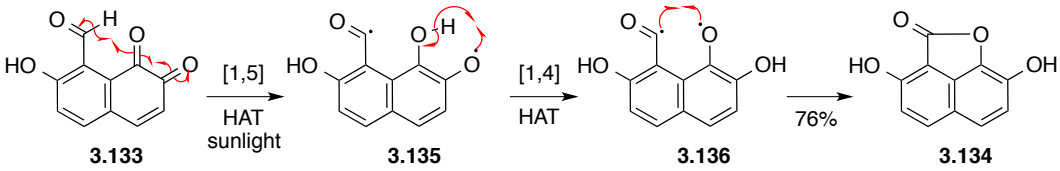
[154] Suresh, G.; Babu, K. S.; Rao, V. R. S.; Rao, M. S. A.; Nayak, V. L.; Ramakrishna, S. *Tetrahedron Letters* **2011**, *52*, 1273−1276.

Previous photolysis of orthoquinones displaying such reactivity was described by Thomson and co-workers.[155] Indeed, sunlight irradiation of quinone **3.133** in an acetonitrile solution yielded lactone **3.134** in high yield (76%). The suggested mechanism in Scheme 3.34 shows a 1,5-HAT of an excited state of quinone **3.133** giving the biradical intermediate **3.135**. A subsequent 1,4-H abstraction would generate the alkoxy radical **3.136**, which upon recombination, furnishes the lactone **3.134**.



Scheme 3.34: *Photolysis of orthoquinone aldehyde **3.133** to lactone **3.134** by Thomson.*[155]

Encouraged by these reported results, the photolysis of the orthoquinone **3.106** was performed with the previously described conditions used for the synthesis of taiwaniaquinol A (**2.9**) and cyclocoulterone (**3.10**, Et_2O, sunlight). A complete discoloration of the iniatially intense orange solution after 30 min. in direct sunlight was observed, along with complete conversion of the starting material. However, analysis of the reaction mixture showed an inseparable complex mixture, whereby NMR analysis did not show any traces of the desired natural product. The same observations were made when the reaction was performed in different solvents such as $CHCl_3$, *t*-BuOH, benzene and aqueous MeOH. Due to these results, the photolysis of przewalskin E (**3.8**), a possible biogenetic precursor of dihydrolatifolionol (**3.128**) was addressed next. Sunlight irradiation of **3.8** would provide the cyclized product **3.137**, which upon exposure to reductive conditions (such as $Pd(OH)_2/C$, H_2, MeOH) would furnish dihydrolatifolionol (**3.128**). Moreover, acid treatment of **3.137** could generate a benzylic carbocation **3.138**, which upon deprotonation would yield the alkene **3.129**. Epoxidation of **3.129** would give the reactive epoxide **3.137** (although the stereoselectivity of this reaction is not clear), which under acidic or basic medium would tautomerize to the desired alcohol **3.130** *via* a Payne-like rearrangement mechanism. Furthermore, reduction of alkene **3.129** would also provide **3.128**.

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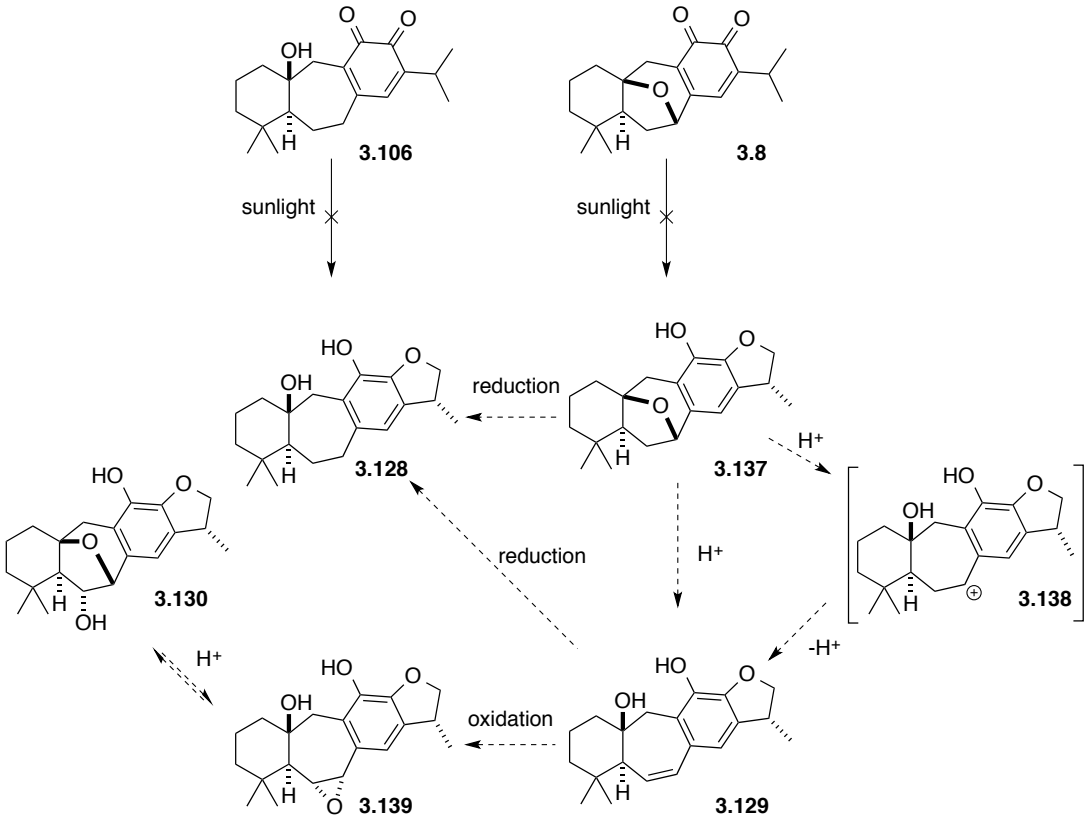
[155] Ferreira, M. A.; King, T. J.; Ali, S.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 249−256.

Consequently, przewalskin E (**3.8**) was exposed to sunlight in an ethereal solution. Unfortunately, the fully converted reaction delivered an unstable product that could not be isolated nor characterized by NMR spectroscopy (thermally and silica gel sensitive). Reduction of the crude mixture using $Pd(OH)_2/C$ in the presence of one atmosphere of H_2 in MeOH did not lead to the formation of the natural product. Instead, a complex mixture was obtained.

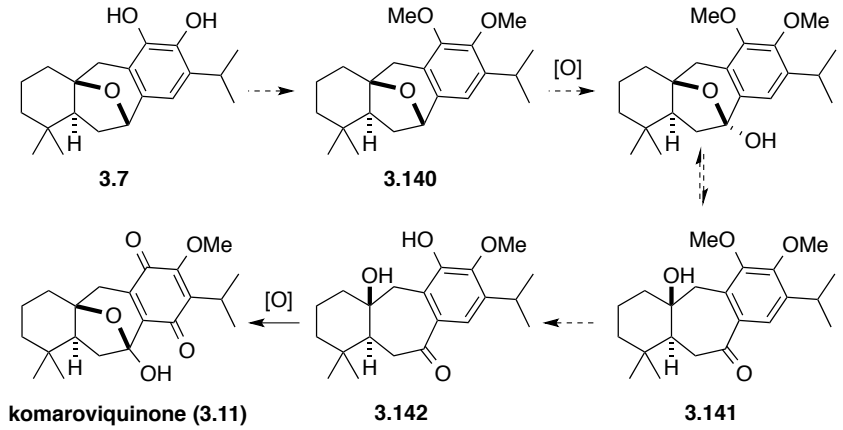


Scheme 3.35: *Photolysis of orthoquinone **3.106** and **3.8** as well as possible biogenetic connection of dihydrolatifolionol and its congeners.*

3.2.9. Conclusion and outlook

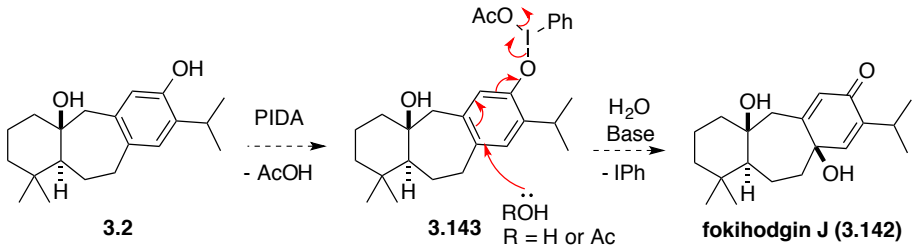
A divergent, elegant and short synthesis of thirteen members of the icetexane natural products was achieved in few steps from the abundant (+)-carnosic acid (**3.73**), isolated from *Rosmarinus officinalis*. Among these members, (+)-salvicanol (**3.6**), (−)-cyclocoulterone (**3.10**), (−)-coulterone (**3.9**), (−)-obtusinone D (**3.122**), (−)-obtusinone E (**3.123**), and (−)-euolutchuol E (**3.3**) were synthesized for the first time. A straightforward, inexpensive and efficient sequence, consisting of methylation and hydrogenation of rosemary ethanol extracts enriched with carnosic acid (**3.73**) was developed to obtain the desired trimethyl carnosic acid **3.77** in high yield. Salient features of the synthesis of salvicanol include a single step ring expansion of the abietane **3.75** to the icetexane **3.76**, bearing an angular hydroxyl group at C10, which constitute the first experimental proof for a tertiary carbocation trapping such as **3.15** by a water molecule, and a selective aromatic demethylation. (+)-Salvicanol (**3.6**) was used as a common intermediate to synthesize: (1) (−)-brussonol (**3.7**) and (−)-przewalskin E (**3.8**) in two steps *via* an aromatic oxidation to form the orthoquinone **3.106**, followed by an aerobic silica gel based tautomerization and oxidation; (2) (−)-obtusinone D (**3.124**) and (−)-obtusinone E (**3.125**) through a hetero-Diels-Alder of (−)-przewalskin E (**3.8**); (3) (+)-komaroviquinone (**3.11**) *via* a selective benzylic oxidation and an aromatic oxidation; (4) (−)-cyclocoulterone (**3.10**) and (+)-komarovispirone (**3.12**) by a sunlight photolysis of (+)-komaroviquinone (**3.11**). This result supports our previous biogenetic hypothesis for the non-enzymatic formation of methylenedioxy catechol natural products; (5) (−)-coulterone (**3.9**) through hydrogenation of (+)-komaroviquinone (**3.11**). Furthermore, pisiferins such as (+)-pisiferanol (**3.2**), (+)-methylpisiferanol (**3.4**) and (−)-euolutchuol E (**3.3**) were synthesized *via* the discovery of an impressive methoxy hydrogenolysis of **3.75** using LAH.

An alternative strategy towards the difficult benzylic oxidation encountered earlier might be provided by the discovery of the silica gel tautomerization of orthoquinone **3.106** to brussonol (**3.7**). Indeed, oxidation reactions at this position might be more favored (Scheme 3.36). Therefore, a benzylic oxidation (DDQ, aq. acetone) of dimethylbrussonol (**3.140**) could deliver the ketone **3.141**, which upon selective demethylation (*t*BuSNa, DMF) would give our already synthesized phenol **3.74**, a direct precursor of komaroviquinone (**3.11**).



Scheme 3.36: *Brussonol (**3.7**) as a substrate candidate for the benzylic oxidation.*

Further targets could be achieved following our synthetic route. Fokihodgin J (**3.142**), isolated from *Fokienia hodginsii* by Zhao and co-workers,[156] could be obtained through an oxidative dearomatization of the natural pisiferanol (**3.2**) using a hypervalent iodine source such as phenyliodine diacetate (PIDA, I^{III}) and a nucleophilic water attack para to the activated intermediate **3.143** (Scheme 3.37).

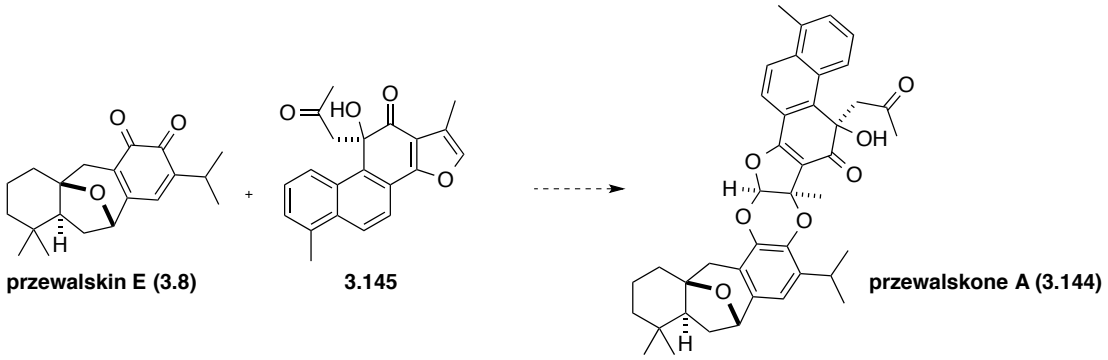


Scheme 3.37: *Oxidative strategy towards the synthesis of fokihodgin J (**3.142**).*

Another accessible target *via* the direct transformation of one of our synthetic natural products could be the przewalskone A (**3.144**), which was isolated from *Salvia przewalskii* in 2012 by the Zhao group.[157] It is noteworthy to mention that the same group isolated przewalskin E (**3.8**) from the same plant.[146] Compound **3.144** could be obtained through a hetero-Diels-Alder cycloaddition of a przewalskin E (**3.8**) diene

[156] Wu, X.-D.; He, J.; Li, X.-Y.; Dong, L.-B.; Gong, X.; Song, L.-D.; Li, Y.; Peng, L.-Y.; Zhao, Q.-S. *J. Nat. Prod.* **2013**, *76*, 1032−1038.
[157] Xu, G.; Yang, X.-W.; Wu, C.-Y.; Li, X.-N.; Su, J.; Deng, X.; Li, Y.; Qin, H.-B.; Yang, L.-X.; Zhao, Q.-S. *Chem. Commun.* **2012**, *48*, 4438−4440.

and a dienophile **3.145** (its enantiomer dehydrodanshenol A[158] was isolated within the same plant, Scheme 3.38). This reaction would be analogous to the one implemented for the synthesis of obtusinones D (**3.124**) and E (**3.125**).



Scheme 3.38: *Hetero-Diels-Alder strategy towards the synthesis of przewalskone A (**3.144**)*

[158] Jiang, H.-L.; Wang, X.-Z.; Xiao, J.; Luo, X.-H.; Yao, X.-J.; Zhao, Y.-Y.; Chen, Y.-J.; Crews, P.; Wu, Q.-X. *Tetrahedron* **2013**, *69*, 6687−6692.

4. Synthetic studies towards the mechanistic elucidation of the remote C−H functionalizytion of taiwaniaquinone F and komaroviquinone

4.1. Introduction

4.1.1. Discovery and beginning of solar chemistry

Sunlight promoted photochemistry arose probably billion years ago on our planet. With photosynthesis arising on the planet, plants utilized sunlight to convert water and CO_2 into solar fuels (*e.g.* sugars) and oxygen. The photolysis of oxygen produced ozone protecting terrestrial life from high energy UV light. These photochemical reactions remained unknown to humans before they started to observe that the appearance of many materials changed upon sunlight exposure.[159]

Three kinds of chemical alterations could be observed by mankind after sunlight exposure of various inorganic and organic compounds: 1) color change; 2) evolution of gas; and 3) the precipitation of less soluble photolyzed products.

In 1886, Klinger observed the formation of a precipitate of an ether solution of benzil (**4.1**).[160] This precipitate was characterized as a 2:1 complex of benzil (**4.1**) and benzoin (**4.2**), respectively. Initially, Klingler could not reproduce these results. Surprisingly, he described his frustration and the time consuming experiments, where the key reaction parameter was unknown. Finally, he recognized that the tubes containing a solution of **4.1** were exposed sunlight, inducing the ketone reduction.

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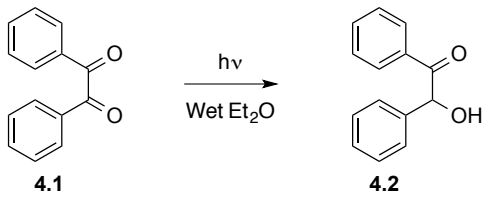
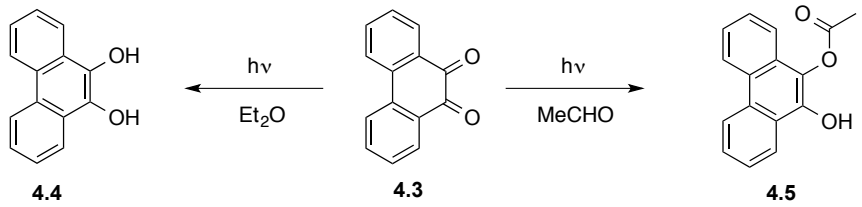
[159] Roth, H. D. *Angew. Chem. Int. Ed.* **1989**, *28*, 1193−1207.
[160] Klinger, H. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1862−1870.



4.1 4.2

Scheme 4.1: *Sunlight mediated reduction of benzil diketone (**4.1**) by Klinger.*[160]

Having recognized the potential of light to induce the reduction of ketones in solution, Klinger performed the reduction of other ketones such as phenanthrenequinone (**4.3**),[160] to obtain the reduced catechol **4.4**. Two years later, he reported the same photolysis, this time in acetaldehyde, and to his own surprise he observed the formation of the acetate **4.5**.[161]



4.4 4.3 4.5

Scheme 4.2: *Sunlight irradiation of **4.3** in Et_2O*[160] *and in MeCHO.*[161]

One of the first photochemical studies and a long-lasting photochemical riddle was the reaction of santonin (**4.6**) with sunlight. Santonin (**4.6**) was first found in two species of the genus *Artemisia* in 1830 by Kahler and Alms.[162] It was traditionally used as a vermifuge,[163] but due to severe side effects, it is no longer used for this purpose. Four years after the first isolation of **4.6**, Trommsdorff observed that crystalline santonin (**4.6**) turned yellow and bursted when exposed to sunlight.[164] This experiment represents the first solid-state photochemical reaction. Using a prism, Trommsdorff reported that only the violet and the blue component of sunlight were able to promote the isomerization to new product (**4.7**) with a different crystal lattice, promoting the rupture of the crystal. Irradiation of **4.6** produced to the biradical **4.8**,

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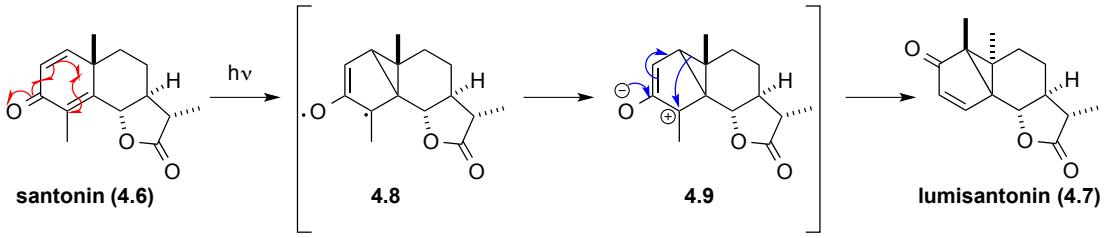
[161] Klinger, H. *Justus Liebigs Ann. Chem.* **1888**, *249*, 137−146.
[162] (a) Kahler *Arch. Pharm.* **1830**, *34*, 318−319; (b) Alms, A. *Arch. Pharm.* **1830**, *34*, 319−320.
[163] Grieve, M. *A Modern Herbal* **1931**.
[164] Trommsdorff, H. *Ann. Chem. Pharm.* **1834**, *11*, 190−208.

which delivered zwitterion **4.9** by a intersystem crossing.[165] A final 1,3- alkyl shift furnished lumisantonin (**4.7**).



Scheme 4.3: *Photolysis of santonin (4.6).*[165]

4.1.2. Target motivations and synthetic strategies

4.1.2.1. Goal of the study

In chapter 2 and 3, two examples of a remote C−H functionalization were described. Initially, the transformation of taiwaniaquinone F (**2.3**) to taiwaniaquinol A (**2.9**) was discovered due to an exposure of **2.3** to ambient light. This unexpected result was later confirmed by direct exposure to sunlight, whereat **2.9** was isolated in 30% yield (Scheme 4.4). The generality of this transformation was further investigated. Therefore, komaroviquinone (**3.11**) was converted to cyclocoulterone (**3.10**) in similar yield (32%). The possibility, that this reaction constitutes a viable biosynthetic alternative to produce such methylenedioxy bridge natural products in nature, encouraged us to investigate the mechanism of this reaction. To accomplish this task, the design of a model substrate that would mimic the reactivity of the above-mentioned natural quinones, was addressed.

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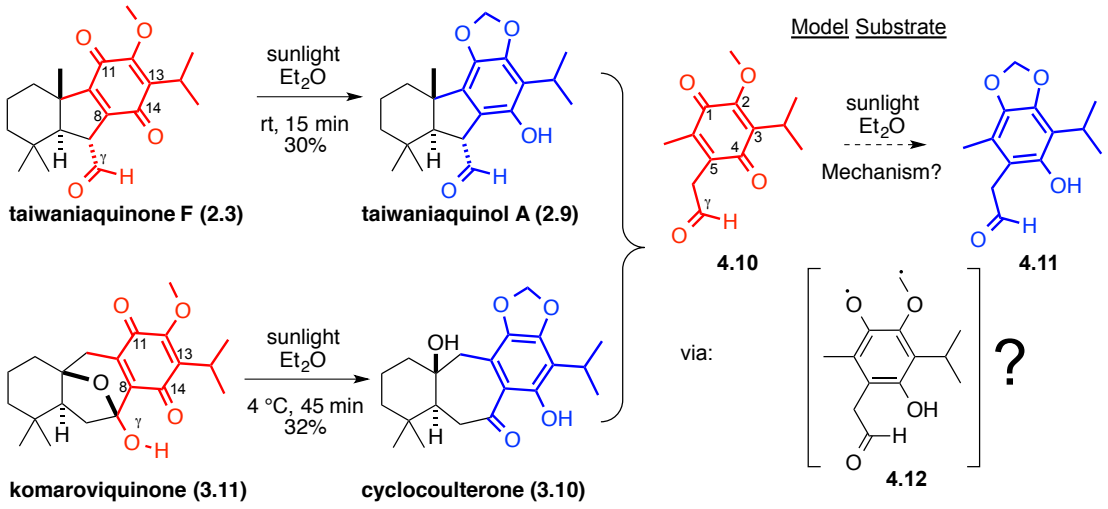
[165] Fisch, M. H.; Richards, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 1547−1553.



Scheme 4.4: *Remote C−H activation of taiwaniaquinone F (**2.3**) and komaroviquinone (**3.11**) and application of the mechanistic studies of a model substrate (**4.10**).*

According to our previous mechanistic proposals (see chapters 2 and 3), the model substrate should possess the common structural features of both natural quinones (**2.3** and **2.9**) that could be relevant for this transformation. The model system should be structurally characterized by a 2-methoxy-1,4-quinone, which is the moiety chemically transformed to a 1,2-methylenedioxy-4-phenol. As seen in chapter 2, an isopropyl group at C3 (or C13 for **2.3** and **2.9**) would force the position the methoxy group towards the C1 keto group (or C11 for the **2.3** and **2.9**) and facilitate the initially proposed 1,5-hydrogen atom transfer (1,5-HAT). Furthermore, the isopropyl group could also be involved in the HAT reaction. The occurrence of a second γ-hydrogen in both **2.3** and **2.9**, could participate in an additional 1,5-HAT reaction. Finally, the model substrate needs to furnish the methylenedioxy quinol upon light irradiation. With these objectives in mind, the target model substrate **4.10**, structurally described by 2-methoxy-3-isopropyl-5-acetyldehyde-1,4-quinone, was chosen to investigate the mechanism of this transformation. In case of successful formation of methylenedioxy **4.11** upon photolysis of **4.10**, it was our goal to substantiate the existence of a biradical species such as **4.12** by radical trapping experiments.

The importance of the γ-hydrogen for a proposed 1,5-HAT, in **2.3** and **3.11**, could be rationalized by the formation of an intramolecular hydrogen-bond (H-bond) in radical intermediates. Grant and co-workers proposed a mechanism to

rationalize the unusual anti-oxidative activity of citrinin.[166] They suggested that the hydrated form of citrinin could react with a radical species to form the C8−O• in **4.13** (Scheme 4.5, **A**). This newly formed radical **4.13** could then be stabilized by a H-bond network, which would facilitate a successive HAT and thereby delocalizing the radical over four additional centers and furnish the C6−O• intermediate **4.14**. The intramolecular nature of the H-bonds is thought to be crucial. Indeed, it is known that intermolecular H-bonds with phenols increase their bond dissociation energy (BDE).[166] This phenomenon is imparted by an unfavored transition state of a HAT reaction, where a covalent ArO-H bond and a H-bond must be broken. In the case of **4.13**, for each broken covalent O-H bond as well as H-bond two new bonds of each type are generated with comparable BDE in a concerted mechanism. An additional radical stabilization effect of H-bonds was observed by Wagner with ketones bearing a γ-hydrogen.[167] As a matter of fact, irradiation of ketone **4.15** (Scheme 4.5, **B**) in H-bond acceptor solvent gave a high selectivity for Norrish type II elimination (acetophenone and propene) and cyclized Yang photoproducts (**4.16**) *via* an 1,5-HAT which formed biradical **4.17** (red pathway, Scheme 4.5, **B**). This selectivity was explained by the H-bond formation between a solvent molecule and the hydroxyl group of the biradical **4.17**, which stabilizes the latter one. This stabilization causes a lower selectivity for a disproportionation (reversion to ketone **4.15** by the inverse 1,5-HAT of **4.17**, blue pathway in Scheme 4.5, **B**). In fact, a disproportionation would break the newly formed H-bond, whereas all other reactions (type II elimination, and Yang cyclizations) would not and are thereby favored. Similarly, if the β-carbon would be replaced by a β-oxygen atom, an intramolecular H-bond would be formed, and therefore prevent reversion to the ketone starting material.[168] Moreover, this intramolecular H-bond would force the biradical into a coiled structure, resulting in the high selectivity for Yang's cyclized products. Norrish type II elimination products require a stretched biradical intermediate where the two half-filled p-orbitals must be aligned with the breaking bond, which is not allowed due to the intramolecular H-bond.

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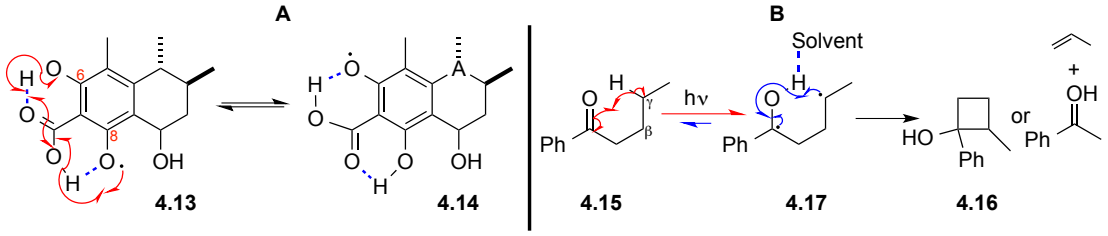
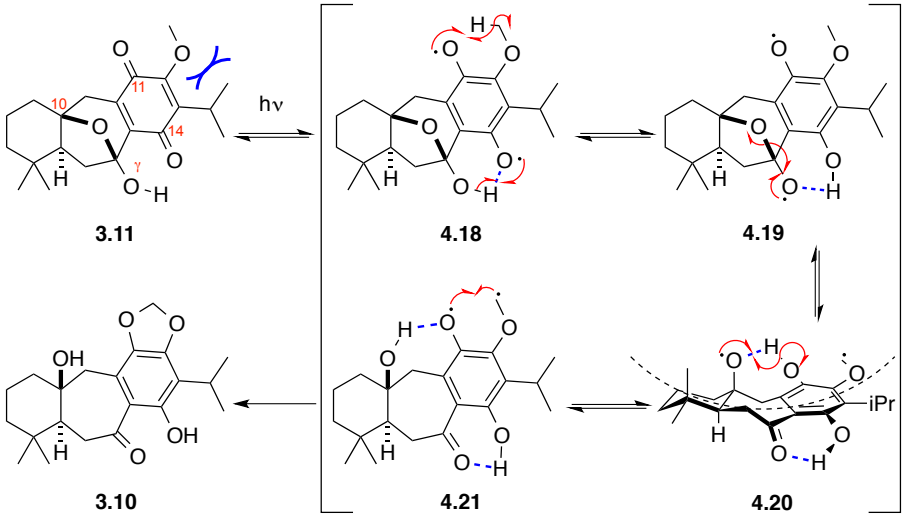
[166] Heider, E. M.; Harper, J. K.; Grant, D. M.; Hoffman, A.; Dugan, F.; Tomer, D. P.; O'Neill, K. L. *Tetrahedron* **2006**, *62*, 1199−1208.
[167] Wagner, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 5898−5901.
[168] Caldwell, R. A.; Majima, T.; Pac, C. *J. Am. Chem. Soc.* **1982**, *104*, 629−630.



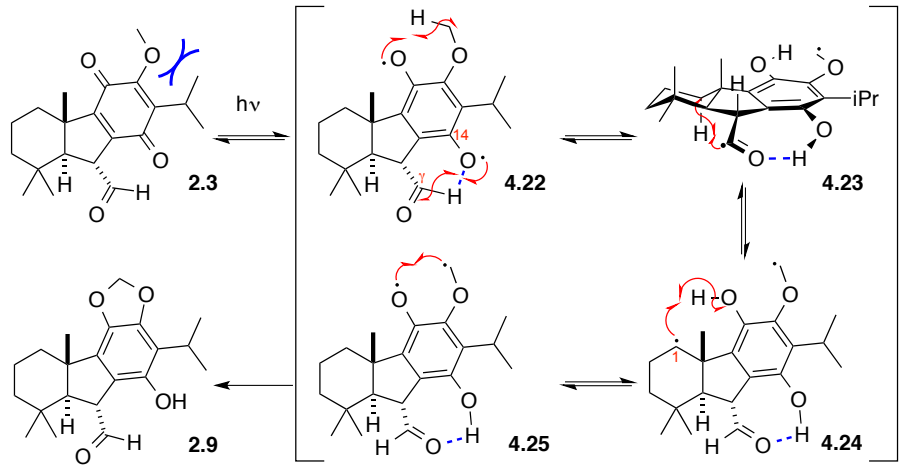
Scheme 4.5: *A) The H-bond network responsible for the facile HAT in hydrated citrinin;*[166] ***B)*** *H-bond stabilization of biradical* ***4.17*** *favors Norrish type II reaction and Yang products.*[167] The dashed blue bonds represent a H-bond.

This biradical stabilization by a H-bond could explain the efficacy of the photolysis of komaroviquinone (**3.11**, Scheme 4.6) and taiwaniaquinone F (**2.3**, Scheme 4.7). As already proposed in chapter 3, the photolysis of **3.11** would generate the biphenoxyl radical **4.18**. An intramolecular H-bond of the C14−O• together with the γ-hydrogen of the hemiacetal group would stabilize the radical. Subsequent 1,5-HAT between these two centers, as well as between the C11−O• and one of the methoxy hydrogen atoms would yield **4.19**. Analogous to the hydrated citrinin radical, two new bonds of each type are generated for each broken covalent and H-bond with comparable BDE in a concerted mechanism. The unpaired electron as well as the hydrogen atom would then be distributed between these two additional centers. Further radical delocalization could be obtained by the homolytic cleavage of the tetrahydrofurane ring of **4.19** to form the tertiary alkoky radical **4.20**. The C10−O• of **4.20** could build a H-bond with the C11−OH group, increasing its stability by a subsequent 1,6-HAT in the concave face of the molecule. Radical recombination of the newly formed C11 phenoxyl radical **4.21** would irreversibly lead to the formation of cyclocoulterone (**3.10**) and therefore driving the whole process towards the natural product.



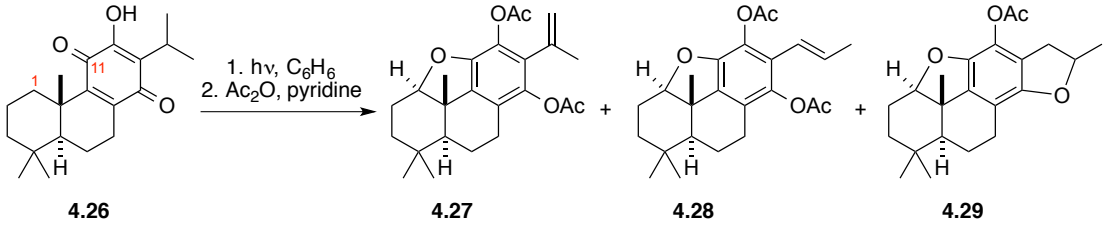
Scheme 4.6: *Proposed effects of H-bonds for HAT reactions during the photolysis of komaroviquinone (**3.11**).*

As described in chapter 2, the photolysis of taiwaniaquinone F (**2.3**) could generate the biphenoxyl radical **4.22**. An intramolecular H-bond of the C14−O• with the γ-hydrogen of the aldehyde group would stabilize the radical. Subsequent 1,5-HAT between these two centers, as well as between the C11−O• and one of the methoxy hydrogen atoms would yield **4.23**. The C11−OH of **4.23** would then form a H-bond with the keto group of the aldehyde, therefore preventing a reverse HAT between these two centers. As a matter of fact, a reversion to **4.22** would result in the breaking of a H-bond, a C6−C7 bond rotation, an 1,5 HAT and the formation of a H-bond. Similar 1,5-HAT were already discussed in chapter 3. An 1,5-HAT from the C1−H to the formyl radical would generate the intermediate **4.24**. A subsequent 1,5-HAT from the C11−OH to the C1• would engender **4.25**, which, upon radical recombination, would yield taiwaniaquinol A (**2.9**).



Scheme 4.7: *Proposed effects of the H-bond for HAT reaction during the taiwaniaquinone F (**2.3**) photolysis.*

The feasibility of this 1,5-HAT was supported by the previous work of Edwards and co-workers[169] with the photolysis of royleanone (**4.26**, Scheme 4.8) in benzene and acetylation of the resulting mixture. Indeed, three of the photoproducts obtained (**4.27** to **4.29**), displayed a C11−O−C1 ether bond, possibly resulting from an initial 1,5-HAT between a C1−H and the C11=O.



Scheme 4.8: *Photolysis of royleanone and subsequent acetylation.*[169]

4.1.2.2. Retrosynthetic analysis

To support or refute our mechanistical hypothesis, the synthesis of the model substrate **4.10** was addressed first. The known compound **4.29**, which was obtained from the inexpensive and commercially available 2,4-dimethoxy benzene (**4.31**) *via* known procedures,[170] was chosen as starting material. The model substrate **4.10** could be obtained *via* an oxidative demethylation of the corresponding 1,2,4-trimethoxy-3-isopropyl-5-acetaldehyde-6-methylphenyl **4.32**. A primary aliphatic alcohol oxidation of the C5-ethanol side chain of **4.33** would afford the hexasubstituted acetaldehyde **4.32**. Several possibilities to introduce the C5-ethanol side chain of **4.33** could be envisaged. The most direct disconnection would be at the C5-C2' bond resulting in the Ar−H **4.34** and ethylene oxide as synthons. An *ortho*-lithiation of **4.34** followed by the addition of ethylene oxide would deliver **4.33**. As an alternative, a Friedel-Crafts ring opening of ethylene oxide could be envisaged. Finally, the C6 methyl group of **4.34** could originate from a reduction of the starting compound **4.30**.

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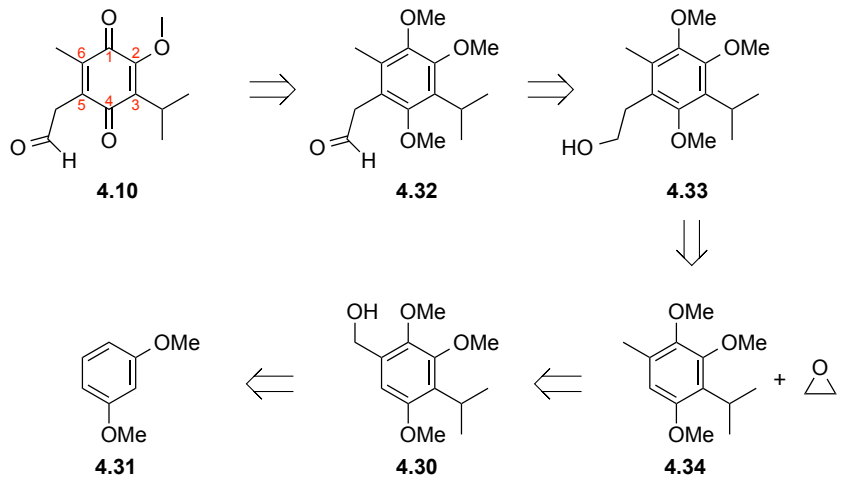
[169] Edwards, O. E.; Ho, P.-T. *Can. J. Chem.* **1978**, *56*, 733−742.
[170] (a) Burnell, R. H.; Caron, S. *Can. J. Chem.* **1992**, *70*, 1446−1454; (b) Maier, M. E.; Bayer, A. *Eur. J. Org. Chem.* **2006**, 4034−4043.

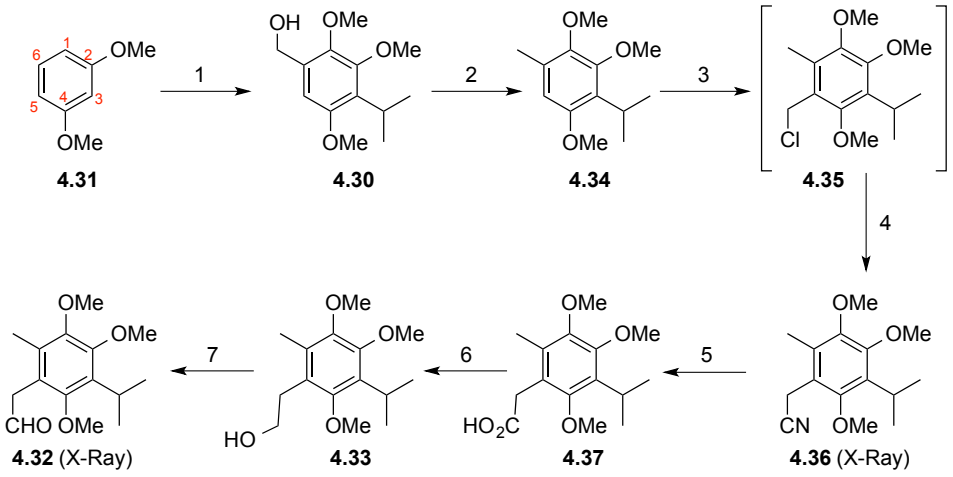


Scheme 4.9: *Retrosynthetic analysis of model substrate **4.10**.*

4.2. Results and discussion

4.2.1. Model substrate synthesis

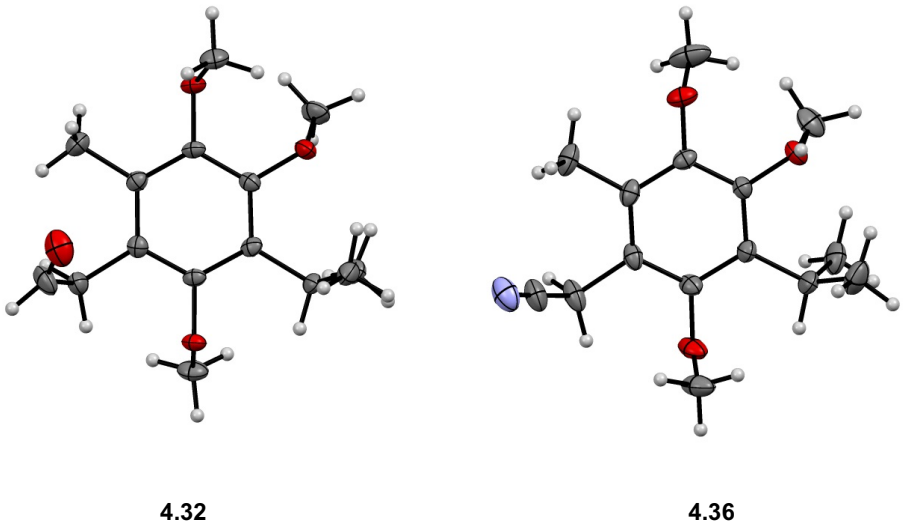
The synthesis of the model substrate started with the known intermediate **4.30**, which was obtained from the commercially available **4.31** in seven steps in 23% overall yield.[170]



Scheme 4.10: *Synthesis of hexasubstituted aromatic ring **4.32**:* 1) Ref. 170, 23% over 7 steps; 2) $Pd(OH)_2/C$, MeOH, H_2 (80 bar), 2 h, 98%; 3) MOMCl, $SnCl_4$, CH_2Cl_2, −10 °C to rt, 3 h; 4) KCN, DMSO, rt, 12 h, 97% (over two steps); 5) NaOH, H_2O, 115 °C, 24 h, 99%; 6) LAH, Et_2O, 0 °C to rt, 3 h, 98%; 7) DMP, CH_2Cl_2, 0 °C to rt, 85%, 2 h.

The benzylic alcohol was hydrogenated in a methanolic solutiuon using $Pd(OH)_2/C$ to yield the reduced compound **4.34** in excellent yield. Although the oxirane strategy,[170b] discussed in the previous section, would allow the synthesis of

4.33 in one step, a less hazardous, more efficient and stepwise alternative approach was pursued. Indeed, ethylene oxide is a dangerous explosive, and similar protocols using it lead to low yield of alcohol.[170b] Chloromethylation of **4.34** using MOMCl and $SnCl_4$ in CH_2Cl_2 yielded the benzylic chloride **4.35**.[171] Due to silica gel stability issues, crude **4.35** was further reacted with KCN in DMSO to furnish the benzylic cyanide **4.36** (the structure was confirmed by single crystal X-ray analysis, Figure 4.1) in nearly quantitative yield over two steps (97%). Alkaline hydrolysis (NaOH, H_2O, 115 °C) of **4.36** gave the carboxylic acid **4.37** in quantitative yield after acidic workup, which was later reduced to the primary alcohol **4.33** in 98% yield using LAH in Et_2O. Finally, DMP oxidation of **2.33** delivered the hexasubstituted aldehyde **4.32** in 85% yield. The structure was confirmed by single crystal X-ray analysis (Figure 4.1).



4.32 **4.36**

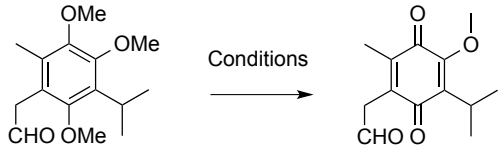
Figure 4.1: *X-ray analysis of the structure of **4.32** and **4.36**.*

Several attempts to perform an oxidative demethylation of the hexasubstituted benzene **4.32** to provide the desired model substrate **4.10** (Table 4.1, entries 1 to 6) failed. The use of silver(II) oxide as a one electron oxidant furnished the model system, however in very poor yield (~5%).[172] Unfortunately, these results could not be reproduced, and the instability of the model substrate **4.10** did not allow further studies. Alternative oxidants were subsequently investigated. However, the use of

[171] Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759−2770.
[172] Snyder, D. C.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *91*, 227−231.

ceric ammonium nitrate (CAN, entry 2)[173] or hypervalent iodine reagents (entries 3 to 6),[174] lead only to complex mixtures or starting material. The 1H-NMR data analysis of the crude mixture of the reaction using silver(II) oxide, showed the formation of unknown side−products with an aldehyde signals. Therefore, a protecting group strategy was not considered.

Table 4.1: *Oxidative demethylation attemps towards the model substrate **4.10**.*



4.32 **4.10**

Entry	Conditions[a]	Observations
1	AgO, HNO_3 (6 M), dioxane, 0 °C to rt	**4.10** (<5%) + complex mixture
2	CAN, MeCN/H_2O, rt	Complex mixture
3	PIDA, H_2O/MeOH, rt to 50 °C	Starting material
4	HITB, MeCN, rt to 90 °C	Complex mixture
5	PIFA in various solvents	Complex mixture
6	ArI, oxone®, CF_3CH_2OH/H_2O, rt	Complex mixture

[a] HITB: [hydroxy(tosyloxy)iodo]benzene, ArI: 4-iodophenoxyacetic acid.

4.2.2. Alternative model substrate design and synthesis

Since the final oxidation of the advanced aldehyde **4.32** failed to furnish the model system **4.10** in reasonable and reproducible yield, the synthesis of the simpler model substrate **4.38** was addressed next (Scheme 4.11). The need of a hexasubstituted model substrate was crucial to avoid biaryl coupling during the oxidative demethylation but also during the photolysis. With this substrate, the influence of the γ-hydrogen could not be investigated, however, the existence of a biradical species could still be explored. The synthesis of **4.38** started with

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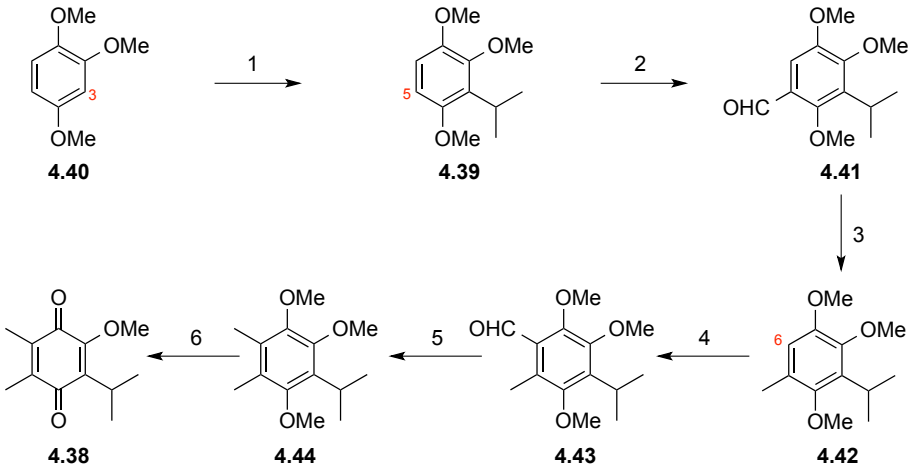
[173] Jacob, P.; Callery, P. S.; Castagnoli, N. Jr. *J. Org. Chem.* **1976**, *41*, 3627−3629.

[174] (a) Tohma, H.; Morioka, H.; Harayama, Y.; Hashizume, M.; Yasuyuki, K. *Tetrahedron Lett*. **2001**, *42*, 6899−6902; (b) Ortín, I.; González, J. F.; Cuesta, E.; Avendaño, C. *Tetrahedron* **2010**, *66*, 646−652; (c) Yakura, T.; Yamaushi, Y.; Tian, Y.; Omoto, M. *Chem. Pharm. Bull.* **2008**, *56*, 1632−1634.

1,2,4-trimethoxy-3-isopropyl-phenyl **4.39**, which was obtained *via* known procedures[175] from the commercially available **4.40** in two steps in 45% overall yield. Rieche formylation of **4.39** yielded the C5-aldehyde **4.41** in an excellent yield of 96%. The previous synthesis of this compound was achieved in lower overall yield (78%) from the same starting material in two steps *via* a C5 bromination followed by a Grignard reagent formation using Mg and addition of DMF.[170a] The aldehyde **4.41** was reduced using $Pd(OH)_2/C$ in methanol under H_2 pressure (80 bar) to the electron rich methylphenyl **4.42** in good yield (77%). The same formylation and reduction sequence furnished the hexasubstituted benzene **4.44**, *via* aldehyde **4.43**, in good overall yield of 84%. Silver(II) oxide oxidation of **4.44** succeeded to provide the model substrate **4.38** in good yield (62%).



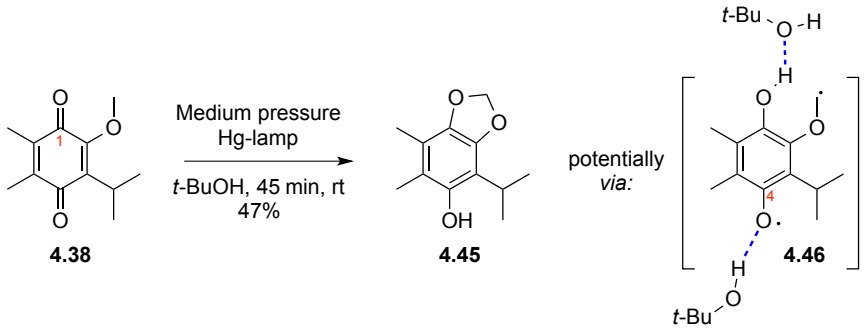
Scheme 4.11: *Synthesis of model substrate **4.38**:* 1) Ref. 175, 45% over 2 steps; 2) $TiCl_4$, CH_2Cl_2, Cl_2CHOMe, −10 °C to rt, 2 h, 96%; 3) $Pd(OH)_2/C$, MeOH, H_2 (80 bar), 24 h, 77%; 4) $TiCl_4$, CH_2Cl_2, Cl_2CHOMe, −10 °C to rt, 12 h, 98%; 5) $Pd(OH)_2/C$, MeOH, H_2 (80 bar), 18 h, 86%; 6) AgO, HNO_3, (6 M), dioxane, rt, 80 min, 62%.

4.2.3. Photolysis

Having the model system in hand, the remote C−H functionalization achieved with taiwaniaquinone F (**2.9**) and komaroviquinone (**3.11**) was explored with compound **4.38**. Applying the conditions developed earlier for the photolysis of **2.9** and **3.11** (direct sunlight, Et_2O, rt) led to a full conversion of the starting material (observed by decoloration of the reaction mixture and confirmed by TLC analysis), however, without formation of the desired methylenedioxy bridge. Different solvents

[175] Majetich, G.; Zhang, Y.; Tian, X.; Britton, J. E.; Li, Y.; Phillips, R. *Tetrahedron* **2011**, *67*, 10129−10146.

(benzene, *t*-BuOH, $CHCl_3$) and light sources (sunlight, medium pressure mercury lamp) were screened. Photolysis of **4.38** in *t*-BuOH was effective to form the desired compound with the methylenedioxy bridge **4.45** in 47% yield using a medium pressure Hg lamp at rt (Scheme 4.12). This feasibility of the reaction in *t*-BuOH rather than in Et_2O could be explained by the ability of *t*-BuOH to forms H-bonds with HO−C• (see Scheme 4.5, **B**). An initial 1,5-HAT between the C1=O and a methoxy hydrogen atom would form the biradical **4.46**, which would be stabilized by H-bonds with *t*-BuOH at C4−O•. Moreover, a second H−bond of an additional *t*-BuOH with the C1−OH would increase the BDE and thus rendering the reversion to the quinone **4.38** unfavorable. Furthermore, when the photolysis was performed in fully deuterated *t*-BuOH (d10) the yield of the reaction dropped down to 15% and the reaction time for the full conversion was doubled. In this case, this kinetic isotopic effect indicates the participation of a *t*-BuOH molecule in the HAT processes.



4.38 **4.45** **4.46**

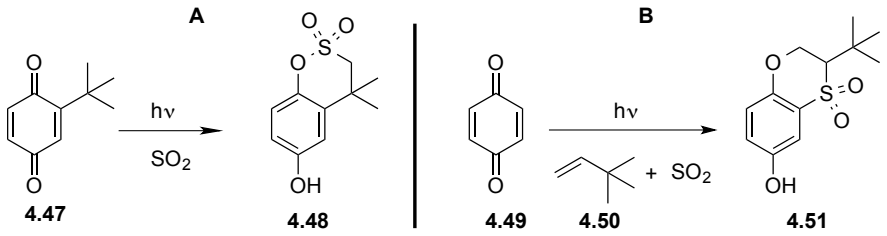
Scheme 4.12: *Successful photolysis of model substrate **4.29**.*

4.2.4. Biradical trapping upon model substrate photolysis

The formation of biradical species upon quinone photolysis was previously postulated and experimentally verified by biradical trapping experiments using paramagnetic reagent such as SO_2,[176] O_2,[177] alkenes and NO.[178] Farid and co-workers demonstrated the biradical nature of quinone photolysis intermediates *via* the photolysis of **4.47** in condensed SO_2, forming the sulfone **4.48** (Scheme 4.13, **A**).[176]

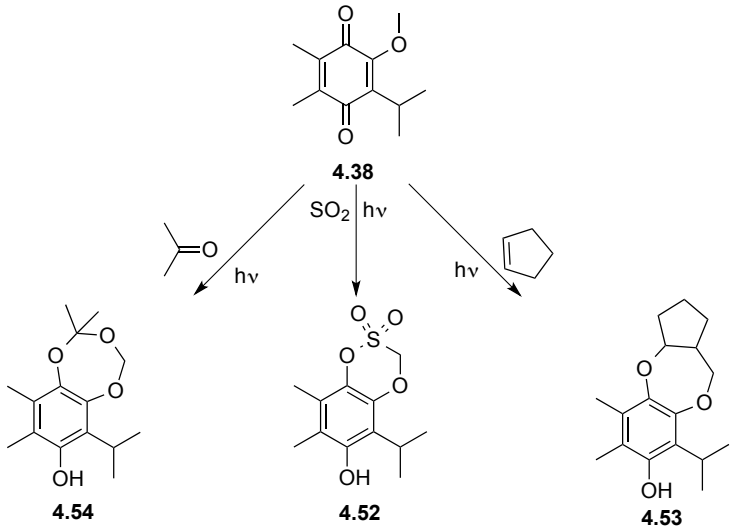
[176] Farid, S. *Chem. Comm.* **1971**, 73−74.
[177] Wilson, R. M.; Wunderly, S. W.; Walsh, T. F.; Musser, A. K.; Outcalt, R.; Geiser, F.; Gee, S. K.; Brabender, W.; Yerino Jr.; L.; Conrad, T. T.; Tharp, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 4429−4446.
[178] Depew, C. M.; Adeleke, B. B.; Rutter, A.; Wan, J. K. S. *Can. J. Chem.* **1985**, *63*, 2281−2284.

Similarly, Wilson and co-workers reported the biradical trapping of a photolyzed benzoquinone **4.49** by the alkene **4.50** and SO_2 simultaneously to give sulfone **4.51** (Scheme 4.13, **B**).[177]



Scheme 4.13: *A) SO_2 biradical trapping experiments by Farid;*[176] ***B)*** *SO_2 and alkene biradical trapping experiments by Wilson.*[177]

Inspired by these results, the trapping of a hypothetical biradical intermediate with SO_2 was explored. Irradiation (medium pressure Hg lamp) of a SO_2 saturated solution of **4.38** in *t*-BuOH was performed. Attempts to purify the reaction mixture were unsuccessful due to decomposition reactions (observed by TLC analysis). However, GC-HRMS data analysis of this mixture showed the formation of a SO_2 adduct such as **4.52** (Scheme 4.14). Analogous results were obtained when a solution of **4.38** was irradiated in acetone or cyclopentene to furnish an acetone adduct such as **4.53** or a cycloaddition adduct such as **4.54**, respectively. Unfortunately, no complete characterization of thes biradical trapped adduct could be obtained due to stability and purification issues.

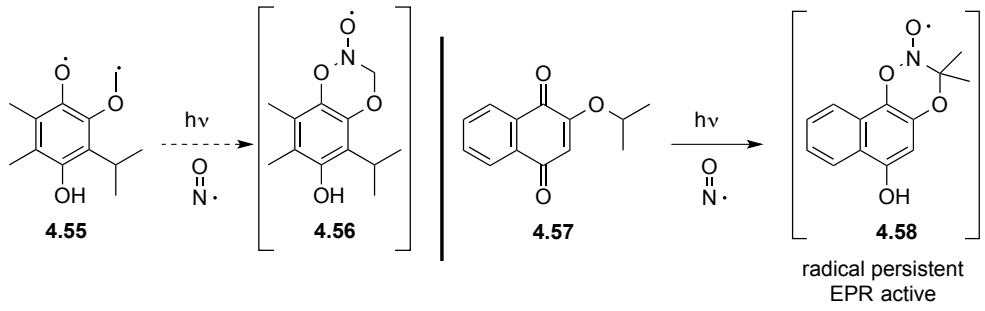


Scheme 4.14: *Preliminary results of biradical trapping.*

4.2.5. Conclusion and future directions

A short, efficient and scalable synthesis of the hexasubsituted benzene **4.32**, precursor of **4.10** was achieved from the known intermediate **4.30** in six steps in excellent overall yield of 78%. The model substrate **4.38** was successfully synthesized from the known isopropyl **4.39** in five steps in a good overall yield of 38%. Furthermore, the photolysis of this model system to the corresponding methylenedioxy bridge was achieved in highier yield than the ones obtained with the natural products **2.9** and **3.11**. Preliminary evidences of the formation of biradical quinoids were obtained by SO_2, acetone and cyclopentene trapping experiments. Furthermore, indication of a bimolecular mechanism, involving a HAT from a *t*-BuOH molecule was suggested for the photolysis of **2.38** in *t*-BuOH.

Strong support for the biradical intermediate **4.55** could be obtained by NO trapping, which would produce the EPR active persistent nitroxide radical. Depew *et al.* demonstrated this concept by the photolysis of 2-isopropyloxy-1,4-naphtoquinone (**4.57**) in a NO saturated benzene solution, which delivered the nitroxide radical **4.58** (Scheme 4.15).[178]



Scheme 4.15: *Envisaged nitrogen monoxide trapping of **4.55** inspired by the formation of **4.58** by Depew.*[178]

A design of another model substrate bearing a γ-hydrogen would allow the investigation of the effect of intramolecular H-bonds on HAT reactions. Furthermore, the conditions developed for the model substrate could be applied on the natural product to assess differences in efficacy.

5. Conclusion

This PhD thesis gave several examples of the potential of mimicking proposed biosynthetic pathways relying on the formation of intermediates with inherent reactivities. The focus on the successful key transformations of several reactive intermediates gave the ability to reproduce what nature might use to access such structurally diverse natural products. Moreover, a careful observation of the interaction of the different intermediates and natural products with light, oxygen and silica gel was central for the discovery of unusual reactions allowing us the formulation of several biosynthetic hypotheses.

The protecting-group free synthesis of (−)-taiwaniaquinone F was achieved in 17 steps from the commercially available (−)-abietic acid *via* a Wolff ring contraction of a (+)-sugiol methyl ether diazo derivative. Furthermore, a sunlight-induced transformation of (−)-taiwaniaquinone F to (+)-taiwaniaquinol A was discovered and a biosynthetic hypothesis for the formation of such methylenedioxy moiety was proposed. Further support for this hypothesis was brought by the successful photolysis of (+)-komaroviquinone to afford the first synthesis of (−)-cyclocoulterone. The synthesis of (+)-komaroviquinone was achieved in eight steps from carnosic acid, isolated from *Rosemarinus officinalis*. The key features of the synthesis include: (1) a ring-expansion of a reactive abietane intermediate based on a biogenetic hypothesis, where the first experimental proof of such ring expanded carbocation trapping with water was given; and (2) a selective benzylic oxidation of salvicanol acetate. Using this strategy, (+)-salvicanol, (−)-coulterone, (−)-obtusinone D, (−)-obtusinone E, and (−)-euolutchuol E were synthesized for the first time along with seven additional known natural products. The stereochemical configuration of (−)-obtusinone D was unambiguously reassigned by X-ray crystallography. Furthermore, these syntheses allowed us to support other biosynthetic pathways.

Finally, the preliminary results indicating the presence of biradicalar intermediates responsible for the formation of the methylenedioxy moiety of (+)-taiwaniaquinol A and (−)-cyclocoulterone using radical trapping reagents were described. This transformation was successfully applied for the first time on a non-natural model substrate, showing the generality of this process.

6. Experimental part

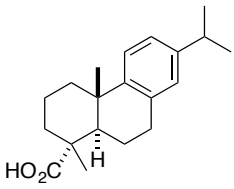
6.1. General method and materials

Unless otherwise stated, chemials were purchased from Sigma-Aldrich, ABCR, Acros or Landcaster and used without any further purification. Solvents used for work-up and chromatography were distilled from technical quality. Solvents used for the chemical transformation were either *puriss.* quality or dried by filtration through activated aluminiumoxide under argon or nitrogen (H_2O content < 10 ppm, *Karl-Fisher* titration) atmosphere. Reactions involving air or moisture sensitive reagents or intermediates, were performed under argon or nitrogen atmosphere in oven dried or flame dried under high vacuum glassware. Microwave-assisted (MW) reactions were conducted with sealed vessels using a Biotage Initiator + instrument. The temperature was measured with an IR sensor. Concentration under reduced pressure was performed by rotatory evaporation at 40 °C (unless otherwise specified). Yields refer to purified, dried and spectroscopically pure compounds. Analytical thin layer chromatography (TLC) was performed on Merk silica gel 60 F254 plates (0.25 mm thickness) precoated with a fluorescent indicator. The developed plates were examined under UV light and by staining with ceric ammonium molybdate and heating. Flash chromatography was performed on silica gel 60 (230−240 mesh) from Fluka or Silicycle using forced-flow elution at 0.3−0.5 bar pressure. All ^{1}H and ^{13}C NMR spectra were recorded by using Bruker Avance 400 MHz (^{1}H) and 101 MHz (^{13}C), Bruker Avance 500 MHz (^{1}H) and 126 MHz (^{13}C) or Bruker Advance 600 MHz (^{1}H) and 151 MHz (^{13}C) spectrometers at room temperature. Chemical shifts (δ values) are reported in ppm, spectra were calibrated related to solvent's residual proton chemical shift ($CHCl_3$, δ = 7.26) and the solvent residual carbon chemical shift ($CDCl_3$, δ = 77.16). Multiplicity is reported as follows: s−singlet, br, s−broad singlet, d−doublet, t−triplet, q−quartet, hept−heptet, m−multiplet or unresolved and coupling constant *J* in Hz. IR spectra were recorded using a *Varian 800 FT-IR ATR Spectrometer, Paragon 1001 FTIR Spectrometer* or a *Bruker Alpha FT-IR Platinum-ATR Spectrometer*. The absorptions are reported in cm^{-1}. Optical rotations $[\alpha]_D$ were measured at the sodium D line using a 1 mL or 2 mL cell with a 1 dm path length on a

Jasco P-2000 digital polarimeter or a *Perkin-Elmer Polarimeter 341* and the concentration *c* is given in g/100 mL. All mass spectra were recorded by the mass spectrometric Service of the University of Basel on a *Bruker maXis 4G mass spectrometer* using electrospray ionization (HRMS-ESI) and by the mass spectrometry laboratory of the institute of organic chemistry of University of Zurich on a *Thermo Fischer DFS spectrometer* (HRMS-EI). X-ray analyses: Data collections for crystal structures were peformed at low temperature (123 K) using Mo *K*a radiation on an Bruker Kappa APEX diffractometer. Integration of the frames and data reduction was carried out using APEX2. The structures were solved by direct methods using SIR92. All non hydrogen atom were refined using anisotropically by full-matrix least squares on *F* using CRYSTALS. Hydrogen atoms were placed in their calculated positions by means of the 'riding' model. Melting points (m.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected.

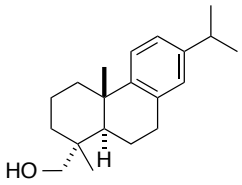
6.2. Total synthesis of taiwaniquinone F and taiwaniaquinol A

Dehydroabietic acid (2.60)*:*



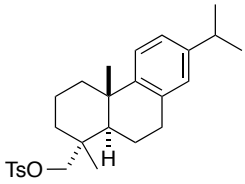
A solution of abietic acid **2.59** (10.0 g, 28.1 mmol) in *p*-xylene was prepared in a dried flask. Pd/C (1.00 g, 10 w%) was added and the resulting mixture was stirred under reflux (148 °C). After 48 h, the reaction was filtered through celite with Et_2O washing (50 mL) and concentrated *in vacuo*. Recrystallization (Et_2O:pentane) gave white needles (8.00 g, 26.0 mmol, 95 %). $\mathbf{R_f}$ = 0.48 (CH_2Cl_2:MeOH 20:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.89 (s, 1H), 2.98−2.87 (m, 2H), 2.82 (hept, *J* = 7.2 Hz, 1H), 2.28−2.34 (m, 1H), 2.24 (dd, *J* = 12.5, 2.1 Hz, 1H), 1.69−1.84 (m, 4H), 1.57−1.49 (m, 3H), 1.28 (s, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.22 (s, 3H), 1.21 (s, 3H). All analytical data are in agreement with literature values: Halbrook, N. J.; Laurence, R. V. J. *J. Org. Chem.* **1966**, *31*, 4246−4647.

Dehydroabietinol (2.61):



A solution of dehydroabietic acid (**2.60**, 10.0 g, 33.3 mmol) in dry THF (40 mL) was added to a suspension of $LiAlH_4$ (6.31g, 166 mmol) in dry THF (40 mL) dropwise at 0 °C over 15 min. The reaction was stirred for 30 min at 0 °C then warmed up to rt and stirred for 2 h. Then an aqueous solution of H_2SO_4 (10%, 200 mL) was added slowly at 0 °C to the reaction mixture followed by Et_2O (100 mL). The organic phase and the aqueous phase were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were successively washed with an aqueous saturated solution of $NaHCO_3$ (200 mL) and brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography column on silica gel (Et_2O:pentane, 8:5) to afford dehydroabietinol (**2.61**) as colourless gum (8.00 g, 27.9 mmol, 84 %). $\mathbf{R_f}$ = 0.67 (CH_2Cl_2: MeOH, 20:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.19 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.90 (s, 1H), 3.48 (d, *J* = 10.7 Hz, 1H), 3.24 (d, *J* = 10.7 Hz, 1H), 2.98−2.76 (m, 3H), 2.30 (d, *J* = 12.7 Hz, 1H), 1.88−1.61 (m, 5H), 1.47−1.36 (m, 4H), 1.28−1.20 (m, 9H), 0.90 (d, *J* = 2.2 Hz, 3H). All analytical data are in agreement with literature values: (a) Woldemichael, G. M.; Wächter, G. Singh, M. P.; Maiese, W. M.; Timmermann, B. N. *J. Nat. Prod.* **2003**, *66*, 242−246; Ulubelen, A.; Topcu, G. *Phytochemistry* **1992**, *31*, 3949−3951.

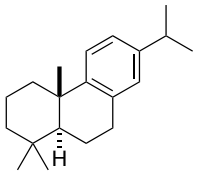
Abietadien-18-yl *p*-toluene sulfonate (2.62):



To a solution of dehydroabietinol (**2.61**, 9.71 g, 33.9 mmol) in pyridine (270 mL) was added *p*-toluenesulfonyl chloride (38.8 g, 203 mmol) at 0 °C. The resulting mixture was stirred 5 h at 0 °C and overnight at rt. Ice water (200mL) was then added and the resulting mixture was extracted with Et_2O (3 x 150 mL). The combined organic phases were washed successively with an aqueous solution of HCl (1 mol/L, 3 x 150 mL), water (3 x 150 mL) and brine (3 x 150 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography column on silica gel (Et_2O:pentane, 1:15) to afford tosylate abietadien-18-yl *p*-toluene sulfonate (**2.62**) as white solid (14.7 g, 33.3 μmol, 98 %). $\mathbf{R_f}$ = 0.32 (Et_2O:pentane,

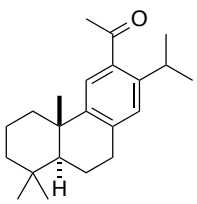
1:15). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.03 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.91 (s, 1H), 3.87 (d, *J* = 9.3 Hz, 1H), 3.64 (d, *J* = 9.3 Hz, 1H), 2.92−2.76 (m, 3H), 2.48 (s, 3H), 2.29 (d, *J* = 12.8 Hz, 1H), 1.84−1.43 (m, 8H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.22 (s, 3H), 0.92 (s, 3H). All analytical data are in agreement with literature values: Tada, M.; Ishimaru, K. *Chem. Pharm. Bull.* **2006**, *54*, 1412−1417.

Dehydroabietane (2.63):



To a solution of abietadien-18-yl *p*-toluene sulfonate (**2.62**, 760 mg, 1.72 mmol) and dried NaI (1.90 g, 12.7 mmol) in dry DMF (40 mL) was added Zn powder (1.13 g, 17.4 mmol) in three portions at 100 °C every 5 h. The resulting mixture was stirred at 100 °C for 3 d. The reaction mixture was then filtered through celite and the cake was successively washed with an aqueous solution of HCl (1 M, 100 mL), pentane (100 mL). The aqueous phase of the filtrate was extracted with pentane (2 x 50 mL). The combined organic phases were washed successively with an aqueous solution of HCl (1 mol/L, 100 mL), an aqueous saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography column on silica gel (pentane) to afford dehydroabietane (**2.63**) as colourless oil (373 mg, 1.38 mmol, 80 %). $\mathbf{R}_f$ = 0.72 (pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.90 (s, 1H), 2.99−2.75 (m, 3H), 2.28 (br d, *J* = 11.6 Hz, 1H), 1.92−1.84 (m, 1H), 1.83−1.56 (m, 3H), 1.52−1.26 (m, 4H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.19 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H). All analytical data are in agreement with literature values: Tada, M.; Ishimaru, K. *Chem. Pharm. Bull.* **2006**, *54*, 1412−1417.

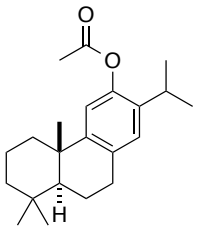
12-Acetyldehydroabietane (2.64):



Freshly distilled AcCl (1.17 mL, 16.3 mmol) was added to a solution of dehydroabietane (**2.63**, 2.00 g, 7.39 mmol) in CH_2Cl_2 (31 mL). The resulting reaction mixture was stirred at 0 °C for 5 min. Then $AlCl_3$ (1.97 g, 14.8 mmol) was added at 0 °C. After 45 min. at 0° C the reaction mixture was stirred to rt for 1 h. The reaction mixture was quenched with

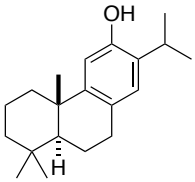
a saturated aqueous solution of $NaHCO_3$ (50 mL) at 0 °C. The mixture was extracted with Et_2O (3 x 20 mL) and the combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane: Et_2O, 30:1) to give 12-acetyldehydroabietane (**2.64**) as pale yellow solid (2.08 g, 10.6 mmol, 90%). $\mathbf{R_f}$ = 0.51 (pentane: Et_2O 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 (s, 1H), 7.04 (s, 1H), 3.47 (hept, *J* = 6.8 Hz, 1H), 2.99−2.79 (m, 2H), 2.54 (s, 3H), 2.32−2.25 (m, 1H), 1.93−1.86 (m, 1H), 1.80−1.59 (m, 3H), 1.52−1.46 (m, 1H), 1.46−1.37 (m, 1H), 1.32 (dd, *J* = 12.4, 2.3 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.18 (s, 3H), 1.18 (s, 1H), 0.95 (s, 3H), 0.93 (s, 3H). All analytical data are in agreement with literature values: Akita, H.; Oishi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1567−1579.

***O*-Acetyl-ferruginol (2.65):**



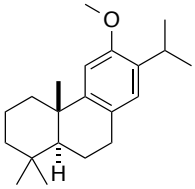
To a solution of 12-acetyldehydroabietane (**2.64**, 6.10 g, 19.5 mmol) in CH_2Cl_2 (24 mL) was added a solution of peracetic acid (35 w%, 40 mL, 209 mmol) in AcOH. The resulting mixture was then stirred at rt over 72 h and water (200 mL) was added. After extraction with Et_2O (100 mL), the aqueous phase was extracted with Et_2O (2 x 100 mL), the combined organic phases were successively washed with a saturated aqueous solution of $NaHCO_3$ (2 x 300 mL) and brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O, 30:1) to give *O*-Acetyl-ferruginol (**2.65**) as pale yellow oil (5.99 g, 18.2 mmol, 93%). $\mathbf{R_f}$ = 0.51 (pentane:Et_2O 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.94 (s, 1H), 6.82 (s, 1H), 2.95−2.76 (m, 3H), 2.30 (s, 3H), 2.19−2.13 (m, 1H), 1.91−1.83 (m, 1H), 1.78−1.64 (m, 2H), 1.61−1.54 (m, 2H), 1.49−1.36 (m, 2H), 1.33 (dd, *J* = 12.4, 2.3 Hz, 1H), 1.18 (m, 9H), 0.93 (d, *J* = 5.3 Hz, 3H), 0.92 (s, 3H). All analytical data are in agreement with literature values: Akita, H.; Oishi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1567−1579.

Ferruginol (2.66):



A solution of NaOMe in MeOH (0.50 mol/L, 7.80 mL, 3.90 mmol) was added dropwise at rt to a solution of *O*-Acetyl-ferruginol (**2.65**, 960 mg, 2.92 mmol) in MeOH (8.1 mL). The resulting reaction mixture was stirred for 1 h at rt. Amberlyst-15 (100 mg) was then added and the resulting mixture was stirred until acidic pH was observed. The reaction mixture was filtered, washed with MeOH (50 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O:pentane, 1:30) to afford ferruginol (**2.66**) as pale yellow oil (828 mg, 2.89 mmol, 99%). $\mathbf{R}_f$ = 0.37 (pentane: Et_2O 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.84 (s, 1H), 6.63 (s, 1H), 4.54 (s, 1H), 3.12 (hept, *J* = 6.8 Hz, 1H), 2.92−2.70 (m, 2H), 2.17 (d, *J* = 12.7 Hz, 1H), 1.89−1.54 (m, 4H), 1.50−1.30 (m, 4H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.17 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H). All analytical data are in agreement with literature values: Tada, M.; Kurabe, J.; Yoshida, T.; Ohkanda, T.; Matsumoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 818−824.

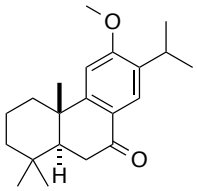
Ferruginol methyl ether (2.67):



K_2CO_3 (811 mg, 5.88 mmol) and Me_2SO_4 (835 µL, 8.82 mmol) were added to a solution of ferruginol (**2.66**, 840 mg, 2.94 mmol) in acetone (16.2 mL). The resulting mixture was stirred overnight at 60 °C. The reaction mixture was filtered and the cake was washed with acetone. The solvents were removed under reduced pressure and the residue was diluted with Et_2O (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (30 mL). The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane: Et_2O 1:100) to give ferruginol methyl ether (**2.67**) as orange oil (820 mg, 2.75 mmol, 94%). $\mathbf{R}_f$ = 0.83 (pentane:Et_2O 50:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.84 (s, 1H), 6.72 (s, 1H), 3.79 (s, 3H), 3.22 (hept, *J* = 7.2 Hz, 1H), 2.91−2.71 (m, 2H), 2.29−2.20 (m, 1H), 1.86 (dd, *J* = 13.1, 7.2 Hz, 1H), 1.79−1.56 (m, 3H), 1.51−1.32 (m, 4H), 1.20 (s, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H),

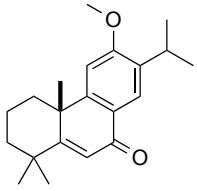
0.94 (s, 3H), 0.92 (s, 3H). All analytical data are in agreement with literature values: Tahara, A.; Ohtsuka, Y. *Chem. Pharm. Bull*. **1972**, *20*, 1637−1647.

Sugiol methyl ether (2.56):



A solution of CrO_3 (273 mg, 2.73 mmol) in AcOH:Ac_2O (1:2, 12.9 mL) was added to a solution of ferruginol methyl ether (**2.67**, 684 mg, 2.28 mmol) in AcOH (7.5 mL). The resulting mixture was stirred at rt for 25 min and was heated to 50 °C for 90 min. The reaction mixture was then immersed into an ice bath and a saturated aqueous solution of $NaHCO_3$ (500 mL) was slowly added until no more effervescence occurred. Then water (500 mL), CH_2Cl_2 (200 mL) and more of saturated aqueous solution of $NaHCO_3$ (500 mL) were added. After separation of the organic phase, the water phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were successively washed with a saturated aqueous solution of $NaHCO_3$ (200 mL), brine (200 mL) and dried over Na_2SO_4. The combined organic phases were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (pentane:Et_2O 1:20) to afford sugiol methyl ether (**2.56**) as white solid (541 mg, 1.80 mmol, 79%). $\mathbf{R_f}$ = 0.30 (pentane:Et_2O 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.89 (s, 1H), 6.75 (s, 1H), 3.89 (s, 3H), 3.24 (hept, *J* = 7.2 Hz, 1H), 2.73−2.54 (m, 2H), 2.30 (d, *J* = 11.9 Hz, 1H), 1.91−1.65 (m, 3H), 1.62−1.50 (m, 2H), 1.32−1.24 (m, 1H), 1.27 (s, 1H), 1.25 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 3H), 0.97 (s, 1H), 0.93 (s, 3H). All analytical data are in agreement with literature values: Kuo, Y. H.; Yu, M.T. *Phytochemistry* **1996**, *42*, 779−781.

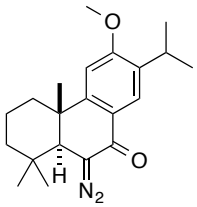
5,6-dehydrosugiol methyl ether (2.73):



A drop of concentrated $HClO_4$ was added to a solution of (**2.56**, 31 mg, 98.6 μmol) in TMOF (1 mL). The resulting mixture was stirred for 15 minutes and $Tl(ONO_2)_3$ (52.6 mg, 0.118 mmol) was added. The reaction mixture was stirred for 1.5 hours. Then 2.5 mL of CH_2Cl_2 was added and the reaction mixture was filtered. Solids were washed with CH_2Cl_2 (10 mL). The filtrate was then successively washed with water (10 mL x 2) and with a saturated aqueous solution of $NaHCO_3$ (10 mL x 1), dried (Na_2SO_4) and

concentrated under reduced pressure. The residue was purified by chromatography column on silica gel (pentane:ether, 10:1) to give 5,6-dehydrosugiol methyl ether as white amorphous solid (**2.73**, 20 mg, 64.0 μmol, 65%). $\mathbf{R}_f$ = 0.10 (pentane:Et_2O, 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 (s, 1H), 6.85 (s, 1H), 6.46 (s, 1H), 6.36 (s, 1H), 3.90 (s, 3H), 3.28 (hept, *J* = 6.8 Hz, 1H), 2.47−2.39 (m, 1H), 2.11−1.96 (m, 1H), 1.79−1.72 (m, 1H), 1.69−1.63 (m, 1H), 1.54 (s, 3H), 1.43 (td, *J* = 13.3, 3.9 Hz, 1H), 1.35 (s, 2H), 1.31 (s, 1H), 1.26 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H). All analytical data are in agreement with literature values: Kuo, Y. H.; Yu, M.T. *Phytochemistry* **1996**, *42*, 779−781.

Diazoketone 2.80:[179]



To a solution of ketone **2.56** (1.33 g, 4.22 mmol) in MeCN (15 mL) and *p*-acetamidobenzenesulfonyl azide (2.43 g, 7.94 mmol) was added DBU (1.54 mL, 10.3 mmol) dropwise at rt. The reaction mixture was stirred for 72 h at rt and the solvents were removed under reduced pressure. The residue was filtered through a pad of celite and through a pad silica gel with Et_2O washing (100 mL). After concentration of the filtrate under reduced pressure, the residue was purified by column chromatography on silica gel (pentane:Et_2O 1:20) to afford diazoketone **2.80** (924 mg, 2.72 mmol, 65%) as a yellow solid together with a smaller amount of starting material (402 mg, 1.28 mmol, 30%): $\mathbf{R}_f$ = 0.21 (pentane:Et_2O 10:1). $\mathbf{m_p}$ = 91.6 °C−92.2 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}} = +6.9$ (*c* 0.30, $CHCl_3$). **IR** (neat) ν = 2928, 2099, 2072, 1732, 1705, 1626, 1592, 1493, 1462, 1276, 1256 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.86 (s, 1H), 6.68 (s, 1H), 3.88 (s, 3H), 3.31−3.19 (m, 1H), 2.81 (s, 1H), 2.29 (d, *J* = 12.2 Hz, 1H), 1.92−1.62 (m, 4H), 1.27 (s, 3H), 1.25 (s, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.17 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 186.1, 161.1, 152.3, 135.5, 125.0, 124.7, 104.1, 55.6, 49.06, 42.7, 39.0, 35.9, 33.4, 33.2, 29.8, 26.7, 24.1, 22.7, 22.5, 21.7, 18.7. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{28}N_2O_2Na^+$ $[M+Na]^+$: 363.2043, found: 363.2044.

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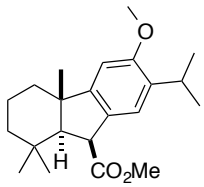
[179] A single crystal suitable for X-ray crystallography was obtained by slow evaporation from Et_2O.

Ester 2.81:[180]



A solution of diazoketone **2.80** (271 mg, 793 µmol) in dry methanol (800 mL) was irradiated with bright sunlight[181] for 3 h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (pentane: Et_2O 1:40) to give ester **2.81** (148 mg, 429 µmol, 54%) as colorless oil with a d.r. of 1 : 20 in favour of the (9*S*)-isomer **2.81** which crystallize at 6 °C as a colourless solid. $\mathbf{R}_f$ = 0.63 (pentane: Et_2O 10:1). $\mathbf{m_p}$ = 61.4 °C−63.9 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}} = -26.9$ (*c* 0.7, $CHCl_3$). **IR** (neat) ν = 2929, 2867, 1737, 1490, 1462, 1282, 1211, 1149 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.05 (s, 1H), 6.62 (s, 1H), 3.94 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.30−3.21 (m, 1H), 2.14 (d, *J* = 8.3 Hz, 1H), 2.08−2.01 (m, 1H), 1.95−1.83 (m, 1H), 1.74−1.61 (m, 1H), 1.53−1.46 (m, 1H), 1.41 (s, 1H), 1.37 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.19−1.15 (m, 6H), 1.01 (s, 3H), 0.98 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.4, 156.9, 154.0, 135.1, 131.6, 122.8, 103.6, 63.1, 55.7, 51.7, 48.7, 46.9, 44.2, 38.3, 34.2, 32.6, 27.0, 24.4, 23.2, 22.8, 21.0, 20.0. **HRMS** (ESI) *m/z*: calcd for $C_{22}H_{32}O_3Na^+$ $[M+Na]^+$: 367.2244, found: 367.2245.

Isomerization of ester 2.81:

To a solution of ester **2.81** (266 mg, 771 µmol) in a solvent mixture of ethylene glycol and water (29 mL, 25:1) was added KOH (1.11 g, 19.8 mmol) and the reaction mixture was stirred at 145 °C in a sealed flask for 3 h. The reaction mixture was then diluted with water and acidified with an aqueous solution of HCl (1mol/L, 100 mL). The reaction mixture was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (2 x 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O 3:1) to afford (9*R*)- carboxylic acid **2.83** as white solid (as well as its diastereoisomer (9*S*)-carboxylic acid **A**, 224.2 mg, 0.678 mmol, 88%) in d.r. of 8.3 : 1 in favour of **2.83** together with **B** as yellow oil (30 mg, 0.080 mmol, 10.4%).

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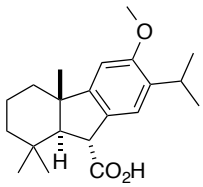
[180] A single crystal suitable for X-ray crystallography was obtained from the pure oil at 6°C.

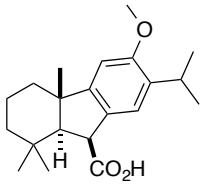
[181] Alternatively, a medium pressure Hg lamp could be employed.

Carboxylic acid 2.83[182]:



$\mathbf{R_f}$ = 0.49 (Et_2O:pentane, 1:1). m.p.: 141.3 °C−141.7 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}} = +40.5$ (*c* 0.25, $CHCl_3$). **IR** (neat) ν = 3480, 3019, 2927, 1707, 1364, 1261, 1215, 1032, 756, 668 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.97 (s, 1H), 6.56 (s, 1H), 3.83 (d, *J* = 11.7 Hz, 1H), 3.81 (s, 3H), 3.30−3.20 (hept, *J* = 7Hz, 1H), 2.25 (d, *J* = 11.5 Hz, 1H), 2.08−2.02 (m, 1H), 1.90−1.76 (m, 1H), 1.71−1.66 (m, 1H), 1.62−1.55 (m, 1H), 1.50 (m, 1H), 1.29 (dd, *J* = 13.3, 4.7 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.11 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 182.3, 156.9, 152.8, 135.3, 131.8, 121.5, 103.0, 64.0, 55.7, 48.1, 46.6, 41.9, 35.6, 34.4, 32.9, 27.0, 23.6, 23.1, 22.9, 21.7, 19.9. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{29}O_3^-$ $[M-H]^-$: 329.2122, found: 329.2123.

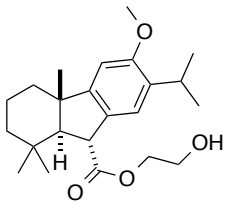
Carboxylic acid A:



$\mathbf{R_f}$ = 0.55 (Et_2O:pentane, 1:1). m.p.: 207.2 °C (dec.). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}} = -42.2$ (*c* 0.6, $CHCl_3$). **IR** (neat) ν = 2928, 2866, 1703, 1462, 1416, 1281, 1222 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.09 (s, 1H), 6.63 (s, 1H), 3.95 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 3.27 (hept, *J* = 6.9 Hz, 1H), 2.18 (d, *J* = 8.3 Hz, 1H), 2.04 (dt, *J* = 12.1, 3.3 Hz, 1H), 1.89 (qt, *J* = 13.6, 4.0 Hz, 1H), 1.69−1.61 (m, 1H), 1.56−1.49 (m, 1H), 1.47−1.38 (m, 1H), 1.37 (s, 3H), 1.27−1.28 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.09 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 181.2, 157.1, 153.0, 135.3, 131.1, 122.9, 103.7, 63.3, 55.7, 48.5, 47.0, 44.4, 38.3, 34.3, 32.5, 27.0, 24.4, 23.3, 22.7, 20.9, 20.0. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{29}O_3^-$ $[M-H]^-$: 329.2122, found: 329.2125.

[182] A single crystal suitable for X-ray crystallography was obtained from crystalization from CH_3CN.

Transester B:



R_f= 0.35 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = +31.9$ (*c* 0.68, $CHCl_3$). **IR** (neat) ν = 3459, 2957, 2929, 1726, 1463, 1287, 1169, 1062, 1030 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.89 (s, 1H), 6.56 (s, 1H), 4.38−4.25 (m, 2H), 3.89−3.82 (m, 3H), 3.81 (s, 3H), 3.25 (hept, *J* = 6.9 Hz, 1H), 2.24 (d, *J* = 11.6 Hz, 1H), 2.05 (dt, *J* = 11.8, 3.4 Hz, 1H), 1.83 (qt, *J* = 13.4, 3.6 Hz, 1H), 1.72−1.65 (m, 1H), 1.62−1.48 (m, 2H), 1.37−1.26 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.11 (s, 3H), 1.07 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.6, 156.7, 152.7, 135.2, 132.4, 121.3, 103.0, 66.5, 63.9, 61.5, 55.7, 48.5, 46.5, 41.9, 35.6, 34.2, 33.0, 26.9, 23.5, 23.1, 22.9, 21.7, 19.9. **HRMS** (ESI) *m/z*: calcd for $C_{23}H_{34}O_4Na^+$ [M+Na]+:397.2349, found: 397.2348.

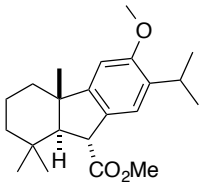
Ester 2.63:

Method 1: from **2.81:**

To a solution of ester **2.81** (139 mg, 404 µmol) in dry MeOH (3.0 mL) was added a solution of MeONa (25w% in MeOH, 185 µL, 805 µmol). The mixture was heated up to 100 °C in a MW reactor for 12 h. The mixture was then diluted with Et_2O (15 mL) and the mixture was filtered through a pad of silica gel with Et_2O washing (50 mL). The combined organic phases were concentrated in reduced pressure and the residue was purified by column chromatography on silica gel (pentane:Et_2O 30:1) to give **2.63** as colourless oil (138 mg, 0.401 mmol, 99%) in a d.r. of 100 : 3 in favour of 9*R*-isomer **2.63**.

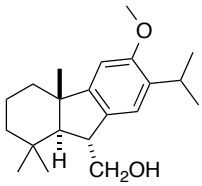
Method 2: from **2.83:**

To a solution of **2.83** (80 mg, 242 µmol) in a mixture solvent of C_6H_6/MeOH (3.5 : 1, 2.2 mL) was added dropwise a solution of $TMSCHN_2$ (2 mol/L in hexanes, 0.25 mL, 500 µmol) in C_6H_6 (500 µL). The reaction was stirred at rt for 30 min. and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O 30:1) to give **2.63** as a colourless oil (85 mg, 241 µmol, 99%).



R_f = 0.63 (pentane:Et_2O 10:1). $[\alpha]_D^{20} = +24.8$ (c 0.5, $CHCl_3$). **IR** (neat) ν = 2953, 2869, 1744, 1788, 1463, 1286, 1151, 630 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.86 (s, 1H), 6.56 (s, 1H), 3.83 (dd, *J* = 11.6, 1.0 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.25 (hept, *J* = 7.0 Hz, 1H), 2.22 (d, *J* = 11.6 Hz, 1H), 2.04 (dt, *J* = 12.4, 3.3 Hz, 1H), 1.82 (m, 1H), 1.71−1.64 (m, 1H), 1.61−1.57 (m, 1H), 1.53−1.47 (m, 1H), 1.28 (dd, *J* = 13.6, 4.7 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.5, 156.7, 152.7, 135.1, 132.4, 121.4, 103.0, 64.0, 55.7, 51.9, 48.4, 46.4, 42.0, 35.6, 34.2, 32.8, 27.0, 23.4, 23.1, 22.9, 21.7, 19.9. **HRMS** (ESI) *m/z*: calcd for $C_{22}H_{32}O_3Na^+$ $[M+Na]^+$: 367.2244, found: 367.2245.

Hydroxy 2.62:

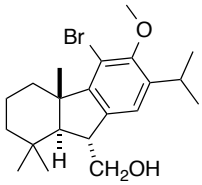


To a suspension of $LiAlH_4$ (49.0 mg, 1.29 mmol) in THF (500 µL) was added a solution of ester **2.63** (87.5 mg, 254 µmol) in THF (800 µL) at 0 °C, the reaction mixture was then stirred 30 min at 0 °C and 2 h at rt. Then an aqueous solution of H_2SO_4 (10%, 50 mL) was added slowly at 0 °C to the reaction mixture followed by Et_2O (20 mL). The organic phase and the aqueous phase were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were successively washed with an aqueous saturated solution of $NaHCO_3$ (40 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue[183] was purified for analysis by chromatography column on silica gel (Et_2O:pentane, 1:3) to afford alcohol **2.62** as white crystalline solid (79.6 mg, 251 µmol, 99%). **R_f** = 0.62 (Et_2O:pentane, 1:1). **m_p** = 99.6 °C−100.6 °C. $[\alpha]_D^{24} = +11.4$ (c 0.5, $CHCl_3$). **IR** (neat) ν = 3361, 2928, 1477, 1462, 1288, 1051 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.12 (s, 1H), 6.59 (s, 1H), 4.38−4.31 (m, 1H), 4.10 (ddd, *J* = 11.8, 8.7, 3.4 Hz, 1H), 3.82 (s, 3H), 3.28 (hept, *J* = 6.9 Hz, 1H), 3.15−3.09 (m, 1H), 2.04 (dt, *J* = 12.0, 3.3 Hz, 1H), 1.89−1.75 (m, 2H), 1.71−1.62 (m, 1H), 1.56−1.46 (m, 2H), 1.29 (td, *J* = 13.2, 4.3 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.14 - 1.17 (m, 1H), 1.14 (s,

[183] The crude residue could be used directly without affecting the outcome of the next reaction.

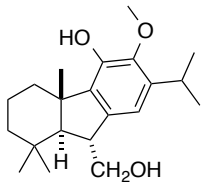
3H), 1.11 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 156.4, 153.8, 134.7, 133.3, 120.4, 103.3, 62.4, 59.1, 55.8, 45.7, 44.7, 42.7, 35.7, 34.2, 34.0, 27.0, 23.7, 23.3, 22.9, 22.4, 20.0. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{32}O_2Na^+$ $[M+Na]^+$: 339.2295, found: 339.2293.

Bromo 2.85:



To a solution of crude alcohol **2.62** (80.4 mg, 254 µmol) in dry CH_2Cl_2 (3.0 mL) was added a solution of Br_2 (26 µL, 508 µmol) in dry CH_2Cl_2 (500 µL) at 0 °C. The solution was then stirred at rt for 4 h. The reaction mixture was then diluted with Et_2O (20 mL) and quenched with a saturated aqueous solution of $NaHSO_3$ (50 mL). After separation of the organic phase, the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (60 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O 7:1) to give bromo **2.85** as a yellow oil (81.7 mg, 206 µmol, 81%). $\mathbf{R_f}$ = 0.42 (Et_2O:pentane, 1:2). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}} = -10.0$ (*c* 0.25, $CHCl_3$). **IR** (neat) ν = 3350, 2928, 2883, 1458, 1397, 1298, 1017 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.11 (s, 1H), 4.39−4.32 (m, 1H), 4.17−4.08 (m, 1H), 3.79 (s, 3H), 3.33 (hept, *J* = 6.9 Hz, 1H), 3.10−3.03 (m, 1H), 2.80−2.71 (m, 1H), 1.88 (d, *J* = 12.0 Hz, 1H), 1.88 (d, *J* = 12.0 Hz, 1H), 1.71−1.62 (m, 2H), 1.50 (m, 1H), 1.33−1.27 (m, 2H), 1.23 (d, *J* = 4.2 Hz, 3H), 1.21 (d, *J* = 4.1 Hz, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 153.1, 150.6, 141.1, 140.5, 119.9, 113.8, 61.9, 61.5, 57.8, 49.2, 45.0, 41.7, 36.3, 33.9, 33.8, 27.5, 24.3, 23.9, 22.8, 20.8, 19.6. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{31}Br_1O_2Na^+$ $[M+Na]^+$: 417.1400, found: 417.1398.

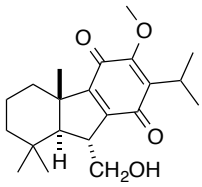
Phenol 2.84:



To a mixture of TMEDA (120 µL, 0.80 mmol) and *n*-BuLi (1.6 M in hexanes, 480 µL, 768 µmol) in hexane (1.5 mL) was added a solution of **2.85** (31.8 mg, 80 µmol) in hexane (300 µL) dropwise at -10 °C under argon. After 20 min at this temperature, a stream of O_2

(1 atm) was bubbled through the solution while the temperature was slowly brought to rt over 2 h. Then a saturated aqueous solution of NH_4Cl (5 mL) was added to the reaction mixture as well as Et_2O (5 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O 7:1) to give phenol **2.84** as yellow oil (15.6 mg, 46.9 µmol, 58%) and alcohol **2.62** (7 mg, 22.1 µmol, 27%). $\mathbf{R_f}$= 0.35 (Et_2O:pentane, 1:2). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}} = -29.4$ (*c* 0.17, $CHCl_3$). **IR** (neat) ν = 3418, 2927, 2869, 1452, 1423, 1310, 1018 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.70 (s, 1H), 5.48 (s, 1H), 4.36−4.29 (m, 1H), 4.15−4.06 (m, 1H), 3.76 (s, 3H), 3.24 (hept, *J* = 6.9 Hz, 1H), 3.11−3.04 (m, 1H), 2.47−2.38 (m, 1H), 1.88−1.82 (m, 1H), 1.83−1.75 (m, 1H), 1.71−1.59 (m, 2H), 1.51−1.44 (m, 1H), 1.34−1.26 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.1, 143.5, 139.3, 139.2, 137.1, 111.5, 62.0, 62.0, 58.5, 46.0, 45.3, 42.4, 36.2, 34.0, 33.9, 26.8, 24.4, 24.0, 22.5, 21.1, 20.0. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{32}O_3Na^+$ $[M+Na]^+$: 355.2244, found: 355.2243.

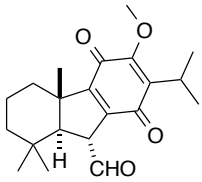
Quinone 2.60:



To a solution of phenol **2.84** (15.6 mg, 47.0 µmol) in MeCN (600 µL) was bubbled a stream of O_2 (1 atm) for 4 h at rt in a flask covered by aluminium foil. The reaction mixture was then diluted with Et_2O and filtered through a pad of silica. The pad was washed with Et_2O (5 mL) and the filtrate was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O, 7:1) to give **2.60** as an intense yellow/orange oil (16.3 mg, 46.9 µmol, 99%). $\mathbf{R_f}$ = 0.37 (Et_2O:pentane, 1:2). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}} = -118.0$ (*c* 0.81, $CHCl_3$). **IR** (neat) ν = 3462, 2927, 1661, 1643, 1588, 1459, 1265, 1020 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.39−4.31 (m, 1H), 4.09 (dd, *J* = 9.9, 2.8 Hz, 1H), 3.95 (s, 3H), 3.60 (ddd, *J* = 11.6, 7.2, 2.6 Hz, 1H), 3.22 (hept, *J* = 7.2 Hz, 1H), 3.11 (ddd, *J* = 11.4, 7.2, 2.4 Hz, 1H), 2.31 (dt, *J* = 12.6, 3.9 Hz, 1H), 1.81−1.66 (m, 1H), 1.65−1.56 (m, 2H), 1.53−1.43 (m, 2H), 1.27−1.23 (m, 1H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.1 Hz, 4H), 1.12 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 189.2, 182.2, 156.1,

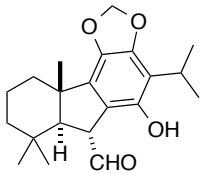
154.8, 148.6, 137.4, 62.7, 61.2, 57.7, 48.1, 47.4, 42.0, 34.9, 34.4, 33.9, 24.8, 22.7, 20.7, 20.6, 20.5, 19.4. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{31}O_4^+$ $[M+H]^+$: 347.2217, found: 347.2213.

Taiwaniaquinone F (2.3):



To a solution of **2.60** (8.8 mg, 25.5 µmol) in CH_2Cl_2 (600 µL) (in a flask covered by aluminium foil) was added DMP (98 mg, 281 µmol) at 0 °C and the reaction mixture was warmed up to rt and stirred over 3 h. The reaction mixture was then diluted with H_2O (2 mL) and Et_2O (2 mL). The aqueous phase was extracted with Et_2O (3 x 1 mL) and the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane: Et_2O, 10:1) to give taiwaniquinone F (**2.3**) as an intense yellow oil (8.6 mg, 0.0250 mmol, 98%). $\mathbf{R_f}$ = 0.53 (Et_2O:pentane, 1:3). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}} = -154$ (*c* 0.86, $CHCl_3$). **IR** (neat) ν = 2922, 2855 1734, 1660, 1583, 1459, 1263 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.86 (d, *J* = 3.9 Hz, 1H), 3.94 (d, *J* = 3.1 Hz, 3H), 3.76 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.18 (hept, *J* = 7.2 Hz, 1H), 2.32 (dt, *J* = 12.8, 3.2 Hz, 1H), 2.12 (d, *J* = 11.5 Hz, 1H), 1.85−1.71 (m, 1H), 1.70−1.47 (m, 3H), 1.25−1.20 (m, 1H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.81 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 200.8, 186.0 181.7, 156.5, 155.3, 146.5, 137.2, 61.7, 61.3, 54.1, 49.3, 41.2, 35.2, 34.5, 33.8, 24.8, 22.0, 20.6, 20.6, 20.2, 19.5. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{28}O_4Na^+$ $[M+Na]^+$: 367.1880, found: 367.1882. All analytical data are in agreement with literature values: Chang, C. I.; Chien, S. C.; Lee, S. M.; Kuo, Y. H. *Chem. Pharm. Bull.* **2003**, *51*, 1420−1422.

Taiwaniaquinol A (2.9):

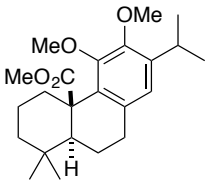


A solution of taiwaniaquinone F (**2.3**) (2 mg, 5.8 µmol) in Et_2O (10 mL) was exposed to daylight for 15 min. The reaction mixture was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O 15:1) to give taiwaniquinol A (**2.9**) as colourless amorphous solid (0.6 mg, 1.74 µmol, 30%). $\mathbf{R_f}$=

0.4 (Et_2O:pentane, 1:2). $[\alpha]_D^{20} = +77.7$ (c 0.040, $CHCl_3$). **IR** (neat) ν = 3373, 2924, 2856, 1716, 1661, 1430, 1259, 1053 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 9.50 (d, *J* = 5.0 Hz, 1H), 5.89 (d, *J* = 1.1 Hz, 1H), 5.84 (d, *J* = 1.0 Hz, 1H), 5.07 (s, 1H), 3.79 (dd, *J* = 11.1, 5.0 Hz, 1H), 3.18 (hept, *J* = 7.2 Hz, 1H), 2.25−2.16 (m, 2H), 2.05−1.99 (m, 1H), 1.83−1.75 (m, 1H), 1.71−1.66 (m, 1H), 1.56 (s, 1H), 1.28 (d, *J* = 7.2 Hz, 6H), 1.12 (s, 3H), 1.08 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 205.2, 147.0, 146.2, 135.3, 132.5, 116.8, 113.3, 101.0, 61.6, 54.6, 46.4, 41.8, 35.8, 34.5, 34.1, 25.3, 22.5, 22.1, 21.3, 21.2, 19.8. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{27}O_4^-$ $[M-H]^-$ 343.1915, found: 343.1917. All analytical data are in agreement with literature values: Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871−873.

6.3. Synthesis of icetexane members

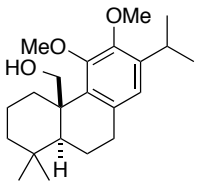
Ester 3.77:



A suspension of 150 g of dried rosemary leaves was sonicated in EtOH (800 mL) at 45 °C for 2 h. The resulting suspension was then filtered through Celite, the cake was washed with EtOH (2 x 200 mL) and the filtrate was concentrated under reduced pressure. The residue was partially dissolved in Et_2O (150 mL), filtrated over celite, the cake was washed with Et_2O (2 x 200 mL) and the combined organic phases were extracted with an aqueous solution of NaOH (1 M, 3 x 150 mL). The combined aqueous phases were acidified with half-concentrated aqueous H_2SO_4 (pH~1) and extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. To a solution of the residue (5.2 g) in dry THF (400 mL) was added portionwise NaH (6.2 g, 60% dispersed in mineral oil). The resulting suspension was stirred for 1 h at rt and Me_2SO_4 (15 mL) was added in one portion. The reaction mixture was stirred overnight at rt. The reaction mixture was then cooled to 0 °C, diluted with Et_2O (400 mL) and MeOH (50 mL) was slowly added until no more H_2 evolution was observed. Finally, distilled water (300 mL) was added and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O:pentane, 1:20) to

afford an inseparable mixture of **3.77**, trimethylated-**3.81** and dimethylated-**3.82** respectively as a yellow oil (2.05 g . A solution of this mixture in MeOH (12 mL) was filtered over a plug of cotton to remove the precipitated dimethylated-**3.82** precipitated (50 mg). To the filtrate was added $Pd(OH)_2/C$ (100 mg) under argon atmosphere and the resulting suspension was flushed with H_2 and vigorously stirred under an atmospheric pressure of H_2 for 1 h at rt. The reaction mixture was then filtered through celite and the cake was washed with MeOH (50 mL). The filtrate was evaporated under reduced pressure and the residue was diluted with Et_2O (50 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure to afford pure **3.77** as a colorless oil (1.97 g, 1.31% from dried mass . $\mathbf{R}_f =$ 0.54 (Et_2O:pentane, 3:10). $[\alpha]_D^{24} = +122$ (*c* 0.20, $CHCl_3$). **IR** (neat) ν = 2958, 2870, 1727, 1447, 1214, 754 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.70 (s, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 3.47−3.41 (m, 1H), 3.24 (hept, *J* = 6.8 Hz, 1H), 2.88−2.82 (m, 2H), 2.32−2.15 (m, 3H), 1.87−1.78 (m, 1H), 1.57−1.50 (m, 3H), 1.33−1.27 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.19−1.15 (m, 1H), 0.99 (s, 3H), 0.79 (s, 3H). All analytical data are in agreement with the litterature values: Kelecom, A. *Tetrahedron* **1983**, *39*, 3603−3608.

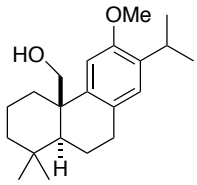
Alkohol 3.75:



To a solution of **3.77** (1.34 g, 3.58 mmol) in dry Et_2O (30 mL) was added dropwise a suspension of LAH (2.2 g, 58.0 mmol) in dry Et_2O (30 mL) under argon at rt and the resulting mixture was refluxed (T = 45 °C) for 6 h. The reaction mixture was then diluted with Et_2O (100 mL) and cooled down to 0 °C and an aqueous H_2SO_4 solution (10%) was added dropwise until no more H_2 evolution was observed (pH~1) with a continuous flow of N_2. Water was then added (50 mL) and the aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure to afford pure **3.75** as a white solid (1.10 g, 3.17 mmol, 89% . $\mathbf{R}_f =$ 0.37 (Et_2O:pentane, 3:10). $\mathbf{m_p} =$ 80.0−81.0 °C. $[\alpha]_D^{25} = +148$ (*c* 0.67, $CHCl_3$). **IR** (neat) ν = 3476, 2957, 2867, 1469, 1401, 1326, 1302, 1049 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.72 (s, 1H), 4.14 (d, *J* = 10.8 Hz, 1H), 3.89 (s, 3H), 3.82 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 3.24

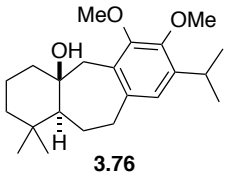
(hept, *J* = 6.9 Hz, 1H), 3.10 (dt, *J* = 13.4, 3.3 Hz, 1H), 2.90−2.82 (m, 2H), 1.82−1.65 (m, 4H), 1.60−1.54 (m, 1H), 1.53−1.47 (m, 1H), 1.44 (dd, *J* = 11.9, 2.7 Hz, 1H), 1.38−1.24 (m, 4H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H). All analytical data are in agreement with the literature values: Kelecom, A. *Tetrahedron* **1983**, *39*, 3603−3608.

Alkohol 3.4:

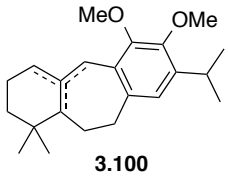


A solution of **3.75** (17.0 mg, 49.1 μmol) in dry THF (1.0 mL) was added dropwise to a suspension of freshly purified $LiAlH_4$ (16.0 mg, 422 μmol) in dry THF (1.0 mL) at rt. The reaction was then warmed up to 50 °C and stirred for 7 h. An aqueous solution of H_2SO_4 (10%, 10 mL) was added slowly at 0 °C to the reaction mixture, followed by addition of Et_2O (10 mL). The organic phase and the aqueous phase were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O:pentane, 1:2) to afford methylpisiferol (**3.4**) as a colourless foam (13.7 mg, 39.5 μmol, 80%). $\mathbf{m_p}$ = 63.7−65.0 °C. $\mathbf{R_f}$ = 0.22 (Et_2O:pentane, 3:10). $[\alpha]_D^{25} = +55.0$ (*c* 0.43, $CHCl_3$). **IR** (neat) ν = 3400, 2923, 2854, 1501, 1462, 1254, 1023, 623 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.92 (s, 1H), 6.75 (s, 1H), 3.96−3.91 (m, 1H), 3.80 (s, 3H), 3.69 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.24 (hept, *J* = 6.8 Hz, 1H), 2.96−2.80 (m, 2H), 2.67−2.60 (m, 1H), 1.92−1.58 (m, 5H), 1.54−1.48 (m, 2H), 1.22 (dd, *J* = 4.6, 2.1 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 6H), 0.85 (d, *J* = 4.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 154.6, 141.5, 135.3, 128.4, 127.3, 108.5, 64.1, 55.8, 50.3, 43.0, 41.9, 33.7, 33.4, 33.1, 28.9, 26.6, 22.9, 22.9, 22.4, 19.1, 18.6. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{33}O_2$ $[M+H]^+$: 317.2475, found: 317.2477.

Biomimetic ring expansion of 3.75:



3.76



3.100

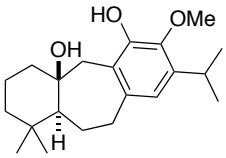
To a solution of **3.75** (1.35 g, 3.90 mmol) in THF (135 mL) was added MsCl (4.0 mL, 51.7 mmol) in one portion at −10 °C, followed by a dropwise addition of Et_3N (7.2 mL, 51.6 mmol). The white milky mixture was stirred at this temperature for 20 min (the mesylation could be followed by TLC) before distilled H_2O (108 mL) was added and the resulting clear solution was stirred at 40 °C for 12 h. The reaction mixture was then diluted with Et_2O (200 mL) and distilled H_2O (200 mL) was added. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4. All volatiles were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using a mixture of pentane:Et_2O (20:1) as eluent to afford a mixture of alkenes mixture **3.100** as a colourless oil (843 mg, 2.43 mmol, 62%) and **3.76** as a white solid (431 mg, 1.24 mmol, 32%).

3.100: $\mathbf{R}_f$ = 0.69 (Et_2O:pentane, 1:10).

3.76: $\mathbf{R}_f$ = 0.28 (Et_2O:pentane, 1:10). $[\alpha]_D^{25} = +17.6$ (c 0.41, $CHCl_3$). $\mathbf{m_p}$ = 80.6−81.6 °C. **IR** (neat) ν = 3475, 2932, 1449, 1412, 1298, 1049, 874 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.74 (s, 1H), 3.81 (s, 6H), 3.27 (hept, J = 6.9 Hz, 1H), 3.23 (d, J = 14.1 Hz, 1H), 2.82−2.74 (m, 1H), 2.71−2.62 (m, 1H), 2.49 (d, J = 14.0 Hz, 1H), 2.02−1.95 (m, 1H), 1.91−1.78 (m, 2H), 1.60−1.50 (m, 1H), 1.48−1.38 (m, 2H), 1.36−1.24 (m, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H), 0.92 (s, 3H), 0.88 (s, 3H). All analytical data are in agreement with the literature values: Majetich, G.; Zou, G. *Org. Lett.* **2008**, *10*, 81−83.

(+)-Salvicanol (3.6):

Method 1: from **3.76**:



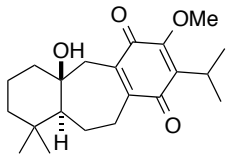
L-Selectride (3.70 mL, 1 M in THF, 3.70 mmol) was added to compound **3.76** (128 mg, 368 μmol) under argon at rt in a sealed tube. The reaction was stirred at 80 °C for 2 h (a longer reaction time lead to the formation of demethylsalvicanol). The reaction mixture was then diluted with Et_2O (10 mL) and cooled down to 0 °C and a saturated aqueous solution of NH_4Cl (10%) was added dropwise until no more H_2 evolution was observed. The aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4. All volatiles were then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O:pentane, 1:5) to afford salvicanol (**3.6**) as a white solid (98 mg, 295 μmol, 80%).

Method 2: from **3.100**:

To a solution of **3.100** (36.4 mg, 111 μmol) in DCM (1 mL) was added *m*-CPBA (83.7 mg, 485 μmol) at 0 °C. The reaction mixture was then stirred for 2 h and quenched with an aqueous solution of NaOH (5%, 10 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with an aqueous solution of NaOH (5%, 3 x 10 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure. To the resulting residue, was added a solution of L-Selectride (1.1 mL, 1 M in THF, 1.1 mmol) under argon in a sealed tube. The reaction mixture was stirred at 80 °C for 3 h (a longer reaction time would lead to the formation of demethylsalvicanol). The reaction mixture was diluted with Et_2O (10 mL) and cooled down to 0 °C. A saturated aqueous solution of NH_4Cl (10%, 10 mL) was added dropwise until no more H_2 evolution was observed. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O:pentane, 1:5) to afford salvicanol (**3.6**) as a white solid (16.5 mg, 48.1 μmol, 42% over two steps).

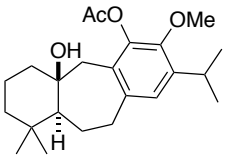
3.6: $\mathbf{R}_f$ = 0.26 (Et_2O:pentane, 2:5). $\mathbf{m_p}$=97−100 °C. $[\alpha]_D^{25} = +39.0$ (*c* 0.19, $CHCl_3$). **IR** (neat) ν = 3486, 2930, 1450, 1422, 1334, 1298, 1079, 972 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.54 (s, 1H), 5.68 (s, 1H), 3.75 (s, 3H), 3.26−3.17 (m, 2H), 2.79−2.62 (m, 3H), 2.51 (d, *J* = 14.2 Hz, 1H), 2.00−1.80 (m, 3H), 1.55 (s, 1H), 1.47−1.38 (m, 3H), 1.34−1.26 (m, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 1.6 Hz, 1H), 0.92 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 148.0, 142.5, 141.6, 139.3, 119.8, 116.90, 71.0, 61.9, 58.3, 42.7, 42.3, 41.2, 36.5, 34.6, 32.4, 26.6, 24.2, 24.1, 23.7, 21.8, 18.9. **HRMS** (ESI) *m/z*: calcd for $C_{21}H_{32}O_3Na_1$ $[M+Na]^+$: 355.2244, found: 355.2244. All analytical data are in agreement with the litterature values: (a) Fraga, B. M.; Gonzalez, A. G.; Herrera, J. R.; Luis, J. G.; Ravelo, A. G. *Phytochemistry* **1986**, *25*, 269−271; (b) Bruno, M.; Savona, G.; Piozzi, F.; de la Torre, M. C.; Rodriguez, B.; Marlier, M. *Phytochemistry* **1991**, *30*, 2339−2343.

Quinone 3.105:



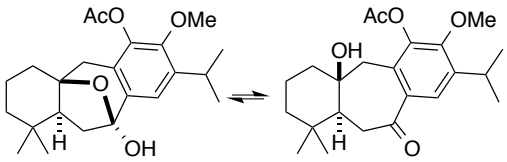
To a solution of **3.6** (16.5 mg, 4.96 μmol) in MeCN (1.0 mL) was added Co(salen) (95%, 17.4 mg, 5.07 μmol) at rt. The resulting mixture was stirred for 3 h under oxygen atmosphere. The reaction mixture was then diluted with Et_2O (3 mL) and filtered through a pad of silica. The pad was washed with Et_2O (2 x 5 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using pentane/Et_2O (20:1) as eluent to yield **3.105** (12.6 mg, 3.64 μmol, 73%) as an orange oil. $\mathbf{R}_f$ = 0.44 (Et_2O:pentane, 2:5). $[\alpha]_D^{25} = +46.6$ (*c* 0.51, $CHCl_3$). **IR** (neat) ν = 3500, 2936, 1647, 1243, 765, 630 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 3.91 (s, 3H), 3.38−3.31 (m, 1H), 3.29−3.21 (m, 1H), 3.14 (d, *J* = 14.2 Hz, 1H), 2.25 (dd, *J* = 14.3, 0.9 Hz, 1H), 2.05−1.97 (m, 1H), 1.90−1.72 (m, 3H), 1.61−1.53 (m, 1H), 1.47−1.38 (m, 2H), 1.34−1.30 (m, 1H), 1.29−1.24 (m, 2H), 1.20 (d, *J* = 7.1 Hz, 6H), 0.91 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 187.1, 184.5, 155.5, 147.2, 140.0, 137.4, 70.8, 61.1, 58.2, 42.7, 42.3, 40.1, 34.5, 32.2, 25.61, 25.0, 21.7, 20.8, 20.8, 20.7, 18.4. **HRMS** (ESI) m/z: calcd for $C_{21}H_{31}O_4$ $[M+H]^+$: 347.2217, found: 347.2218.

Salvicanol acetate (3.112):



To a solution of salvicanol (**3.6**, 10.0 mg, 30.1 μmol) in pyridine (0.5 mL) was added Ac_2O (0.5 mL) at rt. The reaction mixture was stirred for 1 h at rt and subsequently diluted with Et_2O (5 mL) before an aqueous solution of HCl (1 M, 5 mL) was added. The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with aqueous solution of HCl (1 M, 3 x 5 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure to afford pure salvicanol acetate (**3.112**) as a white solid (10.2 mg, 27.2 μmol, 90%). $\mathbf{R}_f$ = 0.61 (Et_2O:pentane, 2:5). $\mathbf{m_p}$ = 98.5−99.9 °C. $[\alpha]_D^{25} = +19.7$ (*c* 0.42, $CHCl_3$). **IR** (neat) ν = 3514, 2945, 1750, 1451, 1374, 1220 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.90 (s, 1H), 3.72 (s, 3H), 3.24 (hept, *J* = 6.9 Hz, 1H), 2.83 (ddd, *J* = 14.4, 7.6, 1.4 Hz, 1H), 2.73−2.59 (m, 3H), 2.37 (s, 3H), 1.97−1.80 (m, 2H), 1.69 (br. s, 1H), 1.62−1.35 (m, 6H), 1.27 (dd, *J* = 8.4, 3.6 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (63 MHz, CDCl3) δ 170.6, 147.1, 143.4, 140.7, 140.6, 127.7, 123.8, 70.7, 61.6, 58.6, 43.5, 42.6, 42.5, 36.6, 34.5, 32.4, 26.7, 24.0, 23.6, 23.6, 21.8, 20.9, 18.8. **HRMS** (ESI) m/z: calcd for $C_{23}H_{34}O_4Na_1$ $[M+Na]^+$: 397.2349, found: 397.2349. All analytical data are in agreement with the literature values: Fraga, B. M.; Gonzalez, A. G.; Herrera, J. R.; Luis, J. G.; Ravelo, A. G. *Phytochemistry* **1986**, *25*, 269−271.

Ketone 3.109:

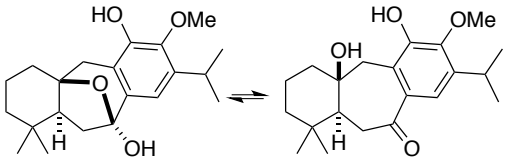


3.109 **3.111**

To a solution of salvicanol acetate (**3.112**) (9.8 mg, 25 μmol) in t-BuOOH (70% aq.) (1 mL) was added a solution of $RuCl_3 \bullet xH_2O$ (167 μg) in pyridine (500 μL), at rt in a sealed tube. The reaction mixture was stirred for 5.5 h at 90 °C. The reaction mixture was diluted with Et_2O (10 mL) and an aqueous solution of HCl (10%, 10 mL) was added. The aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic phases were washed with an aqueous solution of HCl (10%, 3 x 10 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford a mixture of **3.109** and

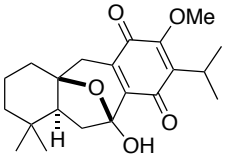
3.111 as an amorphous white solid (3.0 mg, 7.7 µmol, 31%) along with recovered starting material (**3.112**, 1.8 mg, 4.8 µmol, 19%). $\mathbf{R}_f$ = 0.31 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = -15.1 \pm 2.8$ (*c* 0.15, $CHCl_3$). **IR** (neat) ν = 3387, 2934, 1765, 1672, 1200, 781 cm^{-1}. **HRMS** (ESI) m/z: calcd for $C_{23}H_{32}O_5Na_1$ $[M+Na]^+$: 411.2142, found: 411.2141.

Ketone 3.74:



To a solution of **3.109** and **3.111** (5.5 mg, 14.16 µmol) in MeOH (1.0 mL) was added KOH (85%, 34 mg, 515 µmol) at rt. The reaction mixture was allowed to stirr for 12 h at rt. The reaction mixture was then diluted with Et_2O (10 mL) and an aqueous solution of HCl (1 M, 10 mL) was added. The aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic phases were washed with distilled water (3 x 10 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure. The residue (**3.74**, 4.9 mg, 14.14 µmol, 99%) was used without further purification. $\mathbf{R}_f$ = 0.31 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = -10.5$ (*c* 0.24, $CHCl_3$). **IR** (neat) ν = 3381, 2926, 1710, 1670, 1455, 1425, 1314, 1042 cm^{-1}. **HRMS** (ESI) m/z: calcd for $C_{21}H_{31}O_4$ $[M+H]^+$: 347.2217, found: 347.2213.

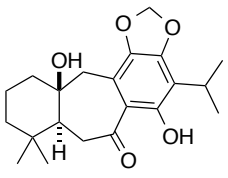
Komaroviquinone (3.11):



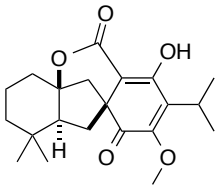
To a solution of crude **3.74** (4.90 mg, 14.1 µmol) in MeCN (6.0 mL) was added Co(salen) (20 mg, 58.4 µmol) at rt. The resulting mixture was stirred 12 h under O_2 pressure (5 bar). The following process was done under exclusion from light. The reaction mixture was diluted with dist. Et_2O (3 mL) and filtered through a pad of silica. The pad was washed with Et_2O (5 mL) and the filtrate was then concentrated under reduced pressure. All volatiles were evaporated under reduced pressure and the residue was purified on column chromatography on silica gel, using pentane:Et_2O (2:1) as eluent to afford pure komaroviquinone (**3.11**, 2.83 mg, 7.85 µmol, 56% over two steps).

R_f = 0.45 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = +40.4$ (*c* 0.14, $CHCl_3$). **IR** (neat) ν = 3405, 2950, 1651, 1603, 1457, 1395, 1243, 1055, 777 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.98 (s, 1H), 3.98 (s, 3H), 3.23 (hept, *J* = 7.1 Hz, 1H), 2.55 (br d, *J* = 19.5 Hz, 1H), 2.29 (dd, *J* = 12.8, 8.6 Hz, 1H), 2.25 (d, *J* = 19.5 Hz, 1H), 2.07−1.98 (m, 2H), 1.94−1.82 (m, 1H), 1.77−1.68 (m, 2H), 1.64−1.56 (m, 3H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.17−1.12 (m, 1H), 0.95 (s, 3H), 0.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.3, 183.7, 156.2, 142.3, 139.1, 137.2, 101.0, 79.5, 61.3, 51.6, 45.9, 39.1, 32.2, 31.3, 30.5, 29.9, 27.2, 24.5, 20.6, 20.5, 15.8. **HRMS** (ESI) m/z: calcd for $C_{21}H_{29}O_5$ [M+H]+:361.2010, found: 361.2010. All analytical data are in agreement with the literature values: Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128−131.

Photolysis of komaroviquinone (3.11):



cyclocoulterone (3.10)



komarovispirone (3.12)

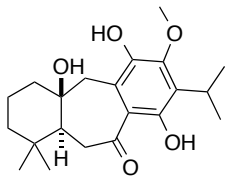
A solution of komaroviquinone (**3.11**, 2.8 mg, 7.8 μmol) in Et_2O (5.0 mL) was exposed to daylight in a glass vial (T = 4 °C) for 45 min. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel, using pentane:Et_2O (3:1) as eluent to yield komarovispirone (**3.12**, 0.85 mg, 2.4 μmol, 31%) as a light yellow oil and cyclocoulterone (**3.10**, 0.90 mg, 2.5 μmol, 32%) as colorless amorphous solid.

Komarovispirone (3.12): **R_f** = 0.65 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = +266$ (*c* 0.040, MeOH). **IR** (neat) ν = 2934, 1651, 1558, 1180, 1100 cm^{-1}. **^{1}H NMR** (600 MHz, C_6D_6) δ = 13.33 (s, 1H), 3.71 (s, 3H), 3.57 (hept, *J* = 7.1 Hz, 1H), 2.05 (d, *J* = 12.0 Hz, 1H), 1.96−1.85 (m, 2H), 1.75 (br d, *J* = 13.7, 1H), 1.48−1.44 (m, 1H), 1.41−1.38 (m, 1H), 1.36 (d, *J* = 6.0 Hz, 5H), 1.35 (d, *J* = 5.8 Hz, 4H), 1.27−1.21 (m, 3H), 1.19 (d, *J* = 12.0 Hz, 1H), 0.89 (dd, *J* = 13.3, 4.3 Hz, 1H), 0.87 (s, 3H), 0.74 (td, *J* = 14.3, 13.8, 4.4 Hz, 1H), 0.52 (s, 3H), 0.39 (s, 6H). **^{13}C NMR** (151 MHz, C_6D_6)

δ = 195.5, 169.6, 160.4, 154.7, 143.6, 107.2, 91.5, 59.9, 55.5, 51.7, 43.6, 40.5, 40.4, 34.4, 33.5, 31.6, 26.1, 20.6, 20.5, 19.9, 18.6. **HRMS** (ESI) m/z: calcd for $C_{21}H_{29}O_5$ $[M+H]^+$: 361.2010, found: 361.2009. All analytical data are in agreement with the literature values: Uchiyama, N.; Ito, M.; Kiuchi, F.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *Tetrahedron Lett.* **2004**, *45*, 531−533.

Cyclocoulterone (3.10): $\mathbf{R}_f$ = 0.38 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = -123$ (*c* 0.040, MeOH). **IR** (neat) ν = 3469, 2930, 1643, 1601, 1436, 1406, 1341, 1174, 1140, 1094, 1060, 970, 933 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 13.42 (s, 1H), 5.94 (d, *J* = 1.2 Hz, 1H), 5.91 (d, *J* = 1.2 Hz, 1H), 3.41 (hept, *J* = 7.2 Hz, 1H), 3.02 (d, *J* = 14.0 Hz), 2.99 (dd, *J* = 18.0, 9.8 Hz, 1H), 2.74 (d, *J* = 14.0 Hz, 1H), 2.62 (d, *J* = 18.0 Hz, 2H), 1.91−1.81 (m, 1H), 1.76−1.68 (m, 1H), 1.59−1.51 (m, 2H), 1.48−1.40 (m, 2H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.21 (ddd, *J* = 7.0, 4.3, 2.7 Hz, 1H), 1.14 (td, *J* = 13.8, 3.0 Hz, 1H), 0.99 (s, 3H), 0.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 208.7, 160.8, 150.8, 139.4, 117.3, 114.9, 112.7, 100.9, 73.8, 49.8, 41.5, 40.7, 40.2, 38.7, 34.1, 32.2, 24.5, 21.6, 20.9, 20.7, 18.8. **HRMS** (ESI) m/z: calcd for $C_{21}H_{29}O_5$ $[M+H]^+$: 361.2010, found: 361.2006. All analytical data are in agreement with the litterature values: Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128−131.

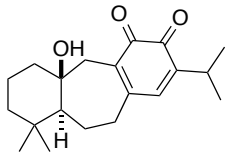
Coulterone (3.9):



To a solution of komaroviquinone (**3.11**, 2.00 mg, 5.55 µmol) in Et_2O (5.0 mL) in a separating funnel was added a solution of $Na_2S_2O_4$ (10% aq., 5.0 mL) and the mixture was shaken until the bright orange solution became slightly yellow. The reaction was followed by TLC. The organic phase was then separated from the aqueous phase, dried over Na_2SO_4 and all volatiles were removed under reduced pressure. The residue was then purified by pTLC using Et_2O:pentane (1:1) as eluent to yield pure coulterone (1.65 mg, 4.55 µmol, 82%). $\mathbf{R}_f$ = 0.28 (pentane:Et_2O, 1:1). $[\alpha]_D^{25} = -209$ (*c* 0.04, MeOH). **IR** (neat) ν = 3405, 2924, 1721, 1612, 1460, 1416, 1259, 801 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.30 (s, 1H), 5.30 (s, 1H), 3.82 (s, 3H), 3.35 (hept, *J* = 6.9 Hz), 3.34 (d, *J* = 14.0 Hz), 3.00 (dd, *J* = 18.4, 10.0 Hz, 2H), 2.66 (d, *J* = 18.4 Hz), 2.65 (d, *J* = 14.0 Hz), 1.88 (dt, *J* = 13.3, 3.7 Hz, 1H), 1.75 (s, 1H), 1.55 (m, 4H), 1.41 (d, *J* = 10.1 Hz), 1.41 (d, *J* = 7.1 Hz, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.14 (td, *J* = 13.5, 3.8 Hz, 1H), 1.00 (s, 3H), 0.85 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 210.8, 157.3, 150.7, 139.7, 127.6, 121.2, 116.9, 73.9, 62.1, 49.1, 40.8, 40.7, 40.6, 38.6, 34.0, 32.3, 26.3, 21.6, 20.8, 20.5, 18.9. **HRMS** (ESI) m/z: calcd for $C_{21}H_{31}O_5$ $[M+H]^+$: 363.2166, found: 363.2166. All analytical data are in agreement with the litterature values: Frontana, B.; Cárdenas, J.; Rodríguez-Hahn, L. *Phytochemistry* **1994**, *36*, 739−741.

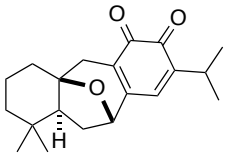
Orthoquinone 3.106:



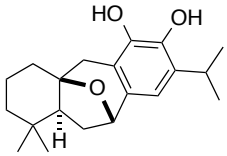
To a solution of salvicanol (**3.6**, 15.0 mg, 45.1 μmol) in aqueous acetone (1.0 mL acetone/dist. water, 9/1) was added DDQ (31 mg, 136.6 μmol). The red reaction mixture was stirred at rt for 10 min and then partitioned between Et_2O (5 mL) and brine (10 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and all volatiles were evaporated under reduced pressure. The residue was passed quickly through a pad of SiO_2 and the cake was washed with Et_2O:pentane (10 mL, 1:1) to yield crude **3.106** (13.7 mg, 43.3 μmol, 96%) as a red amorphous solid. $\mathbf{R}_f$ = 0.50 (Et_2O:pentane, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.59 (s, 1H), 3.05 (d, *J* = 14.7 Hz, 1H), 2.92 (hept, *J* = 6.7 Hz, 1H), 2.63 (dd, *J* = 14.8, 11.5 Hz, 1H), 2.47 (dd, *J* = 14.5, 7.3 Hz, 1H), 2.17 (d, *J* = 14.7 Hz, 1H), 1.91−1.83 (m, 1H), 1.83−1.77 (m, 1H), 1.74−1.68 (m, 1H), 1.60−1.53 (m, 2H), 1.53−1.49 (m, 1H), 1.44−1.39 (m, 1H), 1.42−1.39 (m, 1H), 1.29−1.25 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H), 0.91 (s, 3H). All analytical data are in agreement with the litterature values: Aoyagi, Y.; Takahashi, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Kurihara, T. *Chem. Pharm. Bull.* **2006**, *54*, 1602−1604.

Przewalskin E (3.8) and brussonol (3.7):

Method 1: close system



przewalskin E (3.8)



brussonol (3.7)

A solution of **3.106** (13.7 mg, 43.3 µmol) in Et_2O (1.0 mL) was absorbed on silica gel (1.29 g). The powder mixture was left overnight at rt and purified by column chromatography on silica gel, using pentane:Et_2O (1:1) as eluent to yield przewalskin E (**3.8**, 2.39 mg, 7.60 µmol, 18%) as a red amorphous solid and brusonnol (**3.7**, 2.83 mg, 8.94 µmol, 21%) as a brownish gum.

Method 2: open system

A solution of **3.106** (15 mg, 47.4 µmol) in Et_2O (1.0 mL) was absorbed on silica gel (1.41 g). The powder mixture was left 12 h at rt in an opened round bottom flask with frequent mixing (every 4 h). The powder was then purified by column chromatography on silica gel, using pentane:Et_2O (1:1) as eluent to yield przewalskin E (**3.8**, 7.48 mg, 23.8 µmol, 50%).

Method 3: reduction

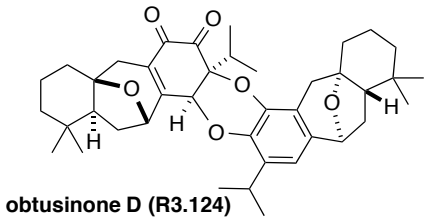
To a solution of przewalskin E (**3.8**, 2.50 mg, 7.95 µmol) in Et_2O (5.0 mL) in a separating funnel was added a solution of $Na_2S_2O_4$ (10% aq., 5.0 mL) and the mixture was shaken until the bright orange solution became slightly yellow. The reaction was followed by TLC. The organic phase was then separated from the aqueous phase, dried over Na_2SO_4 and all volatiles were removed under reduced pressure. The residue was then purified by column chromatographie using Et_2O:pentane (1:1) as eluent to yield pure brussonol (**3.7**, 2.36 mg, 7.47 µmol, 94%).

Przewalskin E (3.8): $\mathbf{R}_f$ = 0.54 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = -85.9$ (*c* 0.097, $CHCl_3$). **IR** (neat) ν = 2949, 1660, 1462, 1396, 1045 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.46 (s, 1H), 4.48 (d, *J* = 6.9 Hz, 1H), 2.95 (hept, *J* = 6.9 Hz, 1H), 2.49 (d, *J* = 18.6 Hz, 1H), 2.18 (d, *J* = 18.8 Hz, 1H), 2.15−2.09 (m, 1H), 2.05 (ddd, *J* = 12.6, 8.4, 1.2 Hz, 1H), 2.00−1.92 (m, 1H), 1.82−1.72 (m, 3H), 1.66−1.57 (m, 1H),

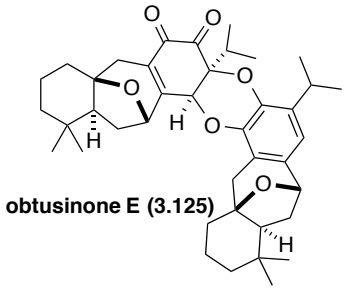
1.52−1.46 (m, 1H), 1.19−1.13 (m, 1H), 1.11 (dd, *J* = 6.9, 2.2 Hz, 6H), 0.97 (s, 3H), 0.85 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 180.7, 179.9, 153.1, 148.1, 132.0, 129.6, 80.5, 75.1, 51.7, 38.3, 38.0, 32.2, 31.8, 30.5, 30.0, 27.4, 26.9, 21.7, 21.7, 16.0. **HRMS** (ESI) m/z: calcd for $C_{20}H_{26}O_3Na_1$ $[M+Na]^+$: 337.1774, found: 337.1776.
All analytical data are in agreement with the litterature values: Aoyagi, Y.; Takahashi, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Kurihara, T. *Chem. Pharm. Bull.* **2006**, *54*, 1602−1604.

Brussonol (3.7): $\mathbf{R}_f$ = 0.29 (Et_2O:pentane, 1:1). $[\alpha]_D^{25} = -54.3$ (*c* 0.14, $CHCl_3$). **IR** (neat) ν = 3365, 2956, 2922, 1458, 1364 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.45 (s, 1H), 4.97 (s, 2H), 4.85 (d, *J* = 6.6 Hz, 1H), 3.11 (hept, *J* = 7.0 Hz, 1H), 2.74 (d, *J* = 16.2 Hz, 1H), 2.39 (d, *J* = 16.2 Hz, 1H), 2.12 (dt, *J* = 11.9, 6.8 Hz, 1H), 2.01 (dt, *J* = 10.5, 3.6 Hz, 1H), 1.89 (ddd, *J* = 12.0, 8.3, 1.0 Hz, 1H), 1.84−1.75 (m, 3H), 1.65−1.59 (m, 1H), 1.54−1.47 (m, 1H), 1.24 (d, *J* = 3.5 Hz, 3H), 1.22 (d, *J* = 3.6 Hz, 3H), 0.96 (s, 3H), 0.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 141.6, 139.5, 134.5, 132.0, 116.6, 112.9, 80.1, 76.3, 51.3, 39.9, 38.9, 32.4, 32.0, 30.9, 30.8, 27.3, 26.8, 22.9, 22.7, 16.3. **HRMS** (ESI) m/z: calcd for $C_{20}H_{27}O_3$ $[M-H]^-$: 315.1966, found: 315.1970. All analytical data are in agreement with the litterature values: Aoyagi, Y.; Takahashi, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Kurihara, T. *Chem. Pharm. Bull.* **2006**, *54*, 1602−1604.

Obtusinone D (R3.124) and obtusinone E (R3.125):



obtusinone D (R3.124)



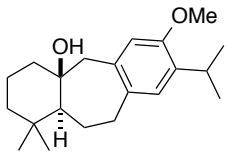
obtusinone E (3.125)

Neat Przewalskin E (**3.8**) (7.01 mg, 22.3 µmol) was heated up in a conical vial at 100 °C for 6 h. The reaction mixture was purified by preparative TLC on silica gel, using pentane:toluene:Et_2O (5:5:1) as eluent. Pure obtusinone D (**R3.124**, 3.02 mg, 4.80 µmol, 43%) as light yellow crystalline solid, obtusinone E (**R3.125**, 1.80 mg, 2.86 µmol, 26%) as a light yellow oil and starting material (**3.8**, 750 µg, 2.38 µmol, 11%) were obtained.

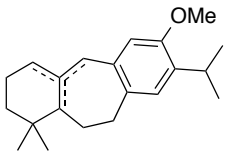
Obtusinone D (R3.124): $\mathbf{R}_f$ = 0.45 (pentane:toluene:Et_2O, 5:5:1). $\mathbf{m_p}$ = 221.0 °C (dec.). $[\alpha]_D^{25} = -292$ (*c* 0.14, $CHCl_3$). **IR** (neat) ν = 2923, 1683, 1449, 1367, 1043, 726 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.45 (s, 1H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.49 (s, 1H), 3.13 (hept, *J* = 6.9 Hz, 1H), 2.76 (d, *J* = 17.1 Hz, 1H), 2.59 (d, *J* = 18.3, 1H), 2.58 (d, *J* = 17.1, 1H), 2.32−1.75 (m, 12H), 1.70−1.47 (m, 5H), 1.23−1.15 (m, 2H), 1.12 (d, *J* = 6.9, 3H), 1.11 (d, *J* = 6.9, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.02 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.99 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 191.9, 185.9, 158.4, 139.8, 138.4, 136.6, 135.7, 134.4, 118.8, 113.3, 86.5, 80.3, 80.2, 76.1, 74.1, 73.0, 51.7, 51.2, 39.6, 38.8, 38.6, 37.9, 32.7, 32.2, 32.1, 31.3, 31.2, 31.1, 30.8, 30.4, 29.7, 27.1, 26.7, 26.6, 23.4, 22.5, 17.1, 16.5, 16.3, 15.9. **HRMS** (ESI) m/z: calcd for $C_{40}H_{52}O_6Na_1$ $[M+Na]^+$: 651.3656, found: 651.3657. All analytical data are in agreement with the litterature values: Sanae, A.-W.; Boonnak, N. *Tetrahedron Lett.* **2013**, *54*, 1356−1359.

Obtusinone E (R3.125): $\mathbf{R}_f$ = 0.27 (pentane:toluene:Et_2O, 5:5:1). $[\alpha]_D^{25} = -283$ (*c* 0.080, $CHCl_3$). **IR** (neat) ν = 2920, 2851, 1741, 1684, 1443, 1044, 726 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.55 (s, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.62 (s, 1H), 3.28 (hept, *J* = 6.7 Hz, 1H), 2.62 (d, *J* = 17.2 Hz, 1H), 2.59 (d, *J* = 18.4 Hz, 1H), 2.34−2.16 (m, 3H), 2.12−1.98 (m, 4H), 1.95−1.73 (m, 5H) 1.68−1.61 (m, 1H), 1.54−1.47 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 191.3, 185.6, 158.2, 139.9, 137.7, 135.9, 134.4, 134.2, 118.9, 115.0, 86.2, 80.4, 80.0, 75.9, 74.0, 72.6, 51.8, 50.9, 40.3, 39.1, 38.6, 37.9, 32.2, 32.0, 31.5, 31.5, 31.1, 30.6, 30.4, 30.1, 29.8, 27.7, 27.3, 27.1, 22.6, 22.3, 17.1, 16.2, 16.1, 15.9. **HRMS** (ESI) m/z: calcd for $C_{40}H_{52}O_6Na_1^+$ [M+Na]+:651.3656, found: 651.3656. All analytical data are in agreement with the litterature values: Sanae, A.-W.; Boonnak, N. *Tetrahedron Lett.* **2013**, *54*, 1356−1359.

Methylpisiferanol (3.4) and 3.124:



methylpisiferanol (3.4)



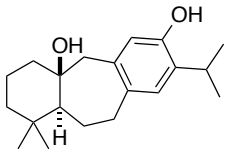
3.126

To a solution of **3.84** (51 mg, 161 µmol) in THF (10 mL) was added MsCl (170 µL, 2.20 mmol) in one portion at −10 °C, followed by a dropwise addition of Et_3N (300 µL, 2.18 mmol). The white milky mixture was stirred at this temperature for 20 min. (the mesylation could be followed by TLC) before distilled H_2O (8 mL) was added and the resulting clear solution was stirred at 40 °C overnight. The reaction mixture was then diluted with Et_2O (200 mL) and distilled H_2O (200 mL) was added. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4. All volatiles were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using a mixture of pentane:Et_2O (20:1) as eluent to afford a mixture of alkenes **3.126** as a colourless oil (30 mg, 102 µmol, 62%) and methylpisiferanol (**3.4**, 15 mg, 47.4 µmol, 29%) as a thick oil.

3.126 : $\mathbf{R}_f$ = 0.85 (Et_2O:pentane, 2:5).

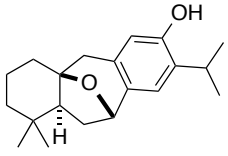
3.4: $\mathbf{R}_f$ = 0.69 (Et_2O:pentane, 2:5). $[\alpha]_D^{25} = +13.0$ (*c* 0.47, MeOH). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.61 (s, 1H), 3.78 (s, 3H), 3.25 (hept, *J* = 7.0 Hz, 1H), 3.01 (d, *J* = 13.9 Hz, 1H), 2.79−2.73 (m, 1H), 2.71−2.63 (m, 1H), 2.54 (d, *J* = 13.9 Hz, 1H), 2.01−1.95 (m, 1H), 1.91−1.74 (m, 2H), 1.54−1.38 (m, 4H), 1.31 (td, *J* = 12.0, 2.9 Hz, 3H), 1.27−1.23 (m, 2H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 1.9 Hz, 1H), 0.92 (s, 3H), 0.88 (s, 3H). **HRMS** (ESI) m/z: calcd for $C_{21}H_{32}O_2Na_1$ $[M+Na]^+$: 339.2293, found: 339.2295. All analytical data are in agreement with the litterature values: Lin, T.-C.; Fang, J.-M.; Cheng, Y. S. *Phytochemistry* **1999**, *51*, 793−791.

Pisiferanol (3.2):



To a solution of EtSH (44.5 µL, 51.7 mg, 832 µmol) in DMF (0.5 mL) was added NaH (60% in mineral oil, 23.6 mg, 354 µmol) and the resulting mixture was stirred at rt for 30 min. To this mixture was added a solution of **3.4** (9.5 mg, 30.0 µmol) in DMF (0.5 mL) at rt. The reaction mixture was stirred for 12 h at 140 °C. The reaction mixture was then diluted with Et_2O (5 mL) and a saturated aqueous solution of NH_4Cl (5 mL) was added. The aqueous phase was extracted with Et_2O (3 x 4 mL). The combined organic phases were dried over Na_2SO_4. All volatiles were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of pentane:Et_2O (5:2) as eluent to afford pisiferanol (**3.2**, 8.82 mg, 29.2 µmol, 97%) as a colorless oil. $\mathbf{R}_f$ = 0.20 (Et_2O:pentane, 5:2). $[\alpha]_D^{25} = +23.2$ (*c* 0.38, MeOH). **IR** (neat) ν = 3549, 3319, 2928, 2869, 1615, 1438, 1265, 733 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.92 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 3.20 (hept, *J* = 7.0 Hz, 1H), 3.05 (d, *J* = 13.9 Hz, 1H), 2.82−2.63 (m, 2H), 2.61 (d, *J* = 14.1 Hz, 1H), 2.07−1.97 (m, 1H), 1.94−1.80 (m, 2H), 1.60−1.51 (m, 1H), 1.45 (dd, *J* = 13.6, 5.0, 2.8 Hz, 2H), 1.35 (dd, *J* = 12.3, 2.5 Hz, 1H), 1.32−1.24 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 151.9, 135.6, 133.4, 133.3, 126.7, 118.9, 71.9, 58.1, 51.1, 42.5, 41.9, 35.5, 34.5, 32.4, 26.7, 24.5, 23.0, 22.7, 21.8, 18.8. **HRMS** (ESI) m/z: calcd for $C_{20}H_{30}O_2Na_1$ $[M+Na]^+$: 325.2138, found: 325.2139.

Euolutchuol E (3.3):

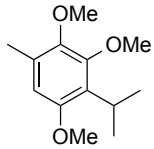


To a solution of **3.2** (1.80 mg, 5.95 µmol) in dioxane (0.6 mL) was added a solution of DDQ (3.00 mg, 13.2 µmol) and the resulting mixture was stirred overnight at rt. The reaction mixture was then diluted with Et_2O and brine. The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. All volatiles were removed under reduced pressure. The residue was purified by pTLC on silica gel, using a mixture of pentane:Et_2O (5:2) as eluent to afford **3.3** as

a white amorphous solid (0.80 mg, 2.66 µmol, 45%) and starting material (0.30 mg, 0.99 µmol, 17%). $\mathbf{R}_f$ = 0.53 (Et_2O:pentane, 3:4). $[\alpha]_D^{25} = -36.5$ (*c* 0.040, MeOH). **IR** (neat) ν = 3321, 2952, 2922, 2853, 1433, 1323, 1234 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 6.81 (s, 1H), 6.45 (s, 1H), 4.87 (d, *J* = 6.6 Hz, 1H), 4.52 (s, 1H), 3.13 (hept, *J* = 6.9 Hz, 1H), 2.87 (d, *J* = 16.4 Hz, 1H), 2.43 (d, *J* = 16.4 Hz, 1H), 2.11 (dt, *J* = 11.7, 6.8 Hz, 2H), 1.96 (td, *J* =7.0, 4.0 Hz, 1H) 1.89 (dd, *J* = 11.5, 8.6 Hz, 1H), 1.83−1.72 (m, 3H), 1.63−1.56 (m, 1H), 1.52−1.47 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.19−1.11 (m, 1H), 0.96 (s, 3H), 0.83 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 151.6, 134.5, 131.7, 131.6, 121.8, 115.6, 80.4, 76.1, 50.7, 43.9, 40.1, 32.0, 32.0, 30.7, 30.5, 27.1, 27.0, 23.0, 22.7, 16.2. **HRMS** (ESI) m/z: calcd for $C_{20}H_{28}O_2Na_1$ $[M+Na]^+$: 323.1982, found: 323.1983. All analytical data are in agreement with the litterature values: Inaba, Y.; Hasuda, T.; Hitotsuyanagi, Y.; Aoyagi, Y.; Fujikawa, N.; Onozaki, A.; Watanabe, A.; Kinoshita, T.; Takeya, K. *J. Nat. Prod.* **2013**, *76*, 1085−1090.

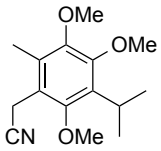
6.4. Synthesis of model systems

Aryl 4.34:



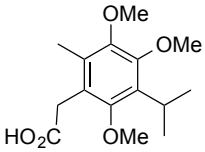
To a solution of benzylic alcohol **4.30** (230 mg, 959 µmol) in MeOH (7.0 mL), was added $Pd(OH)_2$/C (10% on C, 46.1 mg, 32.8 µmol, 3.4 mol%) under an argon atmosphere. The reaction mixture was placed in an autoclave and flushed with H_2 (3 x) and finally stirred for 2 h at rt under a pressure of H_2 (80 bar). The reaction mixture was put back in an atmosphere of argon and filtered through a pad of celite. The cake was washed with MeOH (3 x 5 mL) and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (10 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure to yield **4.34** as a colorless oil (211.4 mg, 942 µmol, 98%), which was used without further purification. $\mathbf{R}_f$ = 0.52 (Et_2O:pentane, 1:10). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.42 (d, *J* = 0.7 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.47 (p, *J* = 7.1 Hz, 1H), 2.24 (d, *J* = 0.7 Hz, 3H), 1.29 (d, *J* = 7.1 Hz, 6H). All analytical data are in agreement with the litterature values: Maier, M. E.; Bayer, A. *Eur. J. Org. Chem.* **2006**, 4034−4043.

Nitrile 4.36:[184]



To a solution of **4.34** (271 mg, 1.21 mmol) in dry CH_2Cl_2 was added MOMCl (184 µL, 2.42 mmol) at −10°C, followed by a slow addition of $SnCl_4$ (142 µL, 1.21 mmol). The reaction mixture was warmed up to rt and stirred for 3 h. The reaction mixture was poured into ice-water (15 mL) and CH_2Cl_2 (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with water (15 mL) and dried over Na_2SO_4. All volatiles were removed under reduced pressure. The residue (329 mg) was dissoled in DMSO (5 mL) and KCN (130 mg, 2.0 mmol) was added at rt and the reaction mixture was stirred 12 h. The reaction mixture was then diluted with Et_2O (15 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over Na_2SO_4. All volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel, using a mixture of pentane:Et_2O (6:1) as eluent to afford **4.36** as a colorless crystalline solid (309 mg, 1.17 mmol, 97% over two steps). $\mathbf{R_f}$ = 0.52 (Et_2O:pentane, 1:2). $\mathbf{m_p}$ = 61.2−62.0 °C. **IR** (neat) ν = 2957, 2360, 1457, 1410, 1342, 1070, 788 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 3.88 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.67 (s, 2H), 3.36 (hept, *J* = 7.1 Hz, 1H), 2.28 (s, 3H), 1.33 (d, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 153.4, 152.2, 148.8, 133.1, 129.6, 118.4, 118.2, 62.6, 60.5, 60.1, 26.27, 22.1, 22.1, 15.5, 12.2. **HRMS** (ESI) m/z: calcd for $C_{15}H_{21}N_1O_3Na_1$ $[M+Na]^+$: 286.1414, found: 286.1416.

Carboxylic acid 4.37:

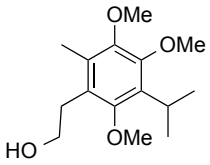


To a suspension of **4.36** (200 mg, 759 µmol) in H_2O (2.0 mL), was added NaOH (63.0 mg, 1.57 mmol) and the resulting suspension was heated up to 115 °C in a sealed tube for 24 h. The resulting solution was diluted with H_2O (5 mL) and Et_2O (5 mL). The aqueous phase was acidified with an aqueous solution of H_2SO_4 (10%, 5 mL) and then extracted with

[184] A single crystal suitable for X-ray crystallography was obtained from crystalization from Et_2O.

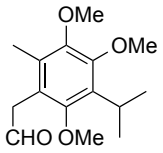
Et_2O (3 x 5 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. All volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel, using a mixture of CH_2Cl_2:MeOH (20:1) as eluent to afford **4.37** as a colorless crystalline solid (214 mg, 758 μmol, 99%). $\mathbf{R}_f$ = 0.10 (Et_2O:pentane, 1:1). $\mathbf{m_p}$ = 103.4−105.5 °C. **IR** (neat) ν = 3672, 2973, 1710, 1454, 1409, 1250, 1070 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.88 (s, 3H), 3.75 (s, 3H), 3.72 (s, 2H), 3.68 (s, 3H), 3.36 (hept, *J* = 7.1 Hz, 1H), 2.17 (s, 3H), 1.33 (d, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 177.1, 152.6, 152.5, 148.6, 132.5, 129.9, 121.6, 62.3, 60.4, 60.0, 32.9, 26.3, 22.2, 22.2, 12.3. **HRMS** (ESI) m/z: calcd for $C_{15}H_{22}O_5Na_1$ $[M+Na]^+$: 305.1359, found: 305.1362.

Compound 4.33:



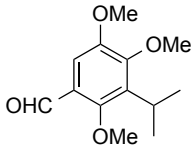
To a solution of LAH (138 mg, 3.64 mmol) in dry Et_2O (2.0 mL) was added dropwise a suspension of **4.37** (206 mg, 730 μmol) in dry Et_2O (2.0 mL) under argon at 0 °C and the resulting mixture was brought to rt and stirred for 3 h. The reaction mixture was then diluted with Et_2O (10 mL), cooled down to 0 °C and an aqueous H_2SO_4 solution (10%, 10 mL) was added dropwise until no more H_2 evolution was observed (pH~1) with a continuous flow of N_2. Water was then added (10 mL) and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. All volatiles were evaporated under reduced pressure to afford pure **4.33** as a white solid (193 mg, 719 μmol, 98% . $\mathbf{R}_f$ = 0.37 (Et_2O:pentane, 1:1). $\mathbf{m_p}$ = 62.0−63.2 °C. **IR** (neat) ν = 3375, 2934, 1454, 1408, 1343, 1121, 633 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.87 (s, 3H), 3.78−3.74 (m, 5H), 3.69 (s, 3H), 3.34 (hept, *J* = 7.1 Hz, 1H), 2.90 (t, *J* = 6.7 Hz, 2H), 2.20 (s, 3H), 1.34 (d, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 152.5, 151.8, 148.8, 132.4, 129.2, 125.7, 63.0, 62.0, 60.4, 59.9, 30.7, 26.3, 22.3, 22.3, 12.1. **HRMS** (ESI) m/z: calcd for $C_{15}H_{24}O_4Na_1$ $[M+Na]^+$: 291.1567, found: 291.1571.

Aldehyde 4.32:[185]



To a solution of **4.33** (105 mg, 391 µmol) in CH_2Cl_2 (4.6 mL) was added DMP (359 mg, 846 µmol) at 0 °C and the reaction mixture was warmed up to rt and stirred over 2 h. The reaction mixture was then diluted with H_2O (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane: Et_2O, 10:1) to give aldehyde **4.32** as a colorless crystalline solid (88.5 mg, 332 µmol, 85%). $\mathbf{R}_f$ = 0.52 (Et_2O:pentane, 1:2). **IR** (neat) ν = 2936, 1724, 1455, 1409, 1342, 1245, 1121, 1077, 1014, 632 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.69 (t, *J* = 2.0 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 3.69 (d, *J* = 2.1 Hz, 2H), 3.60 (s, 3H), 3.37 (hept, *J* = 7.1 Hz, 1H), 2.12 (s, 3H), 1.34 (*d*, J = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.9, 152.8, 152.6, 148.7, 132.7, 129.8, 120.5, 61.8, 60.4, 60.0, 42.9, 26.2, 22.2, 22.2, 12.6. **HRMS** (ESI) m/z: calcd for $C_{15}H_{22}O_4Na_1$ $[M+Na]^+$: 289.1410, found: 289.1412.

Aldehyde 4.41:

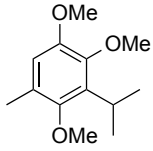


To a solution of **4.39** (500 mg, 2.38 mmol) in dry CH_2Cl_2 (13 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 12 mL, 12 mmol) followed by 1,1-dichlorodimethyl ether (430 µL, 4.75 mmol) at −10 °C. The reaction mixture was stirred for 30 min at -10 °C and 1.5 h at rt. The mixture was slowly poured slowly onto ice-water (20 mL), Et_2O was added (20 mL). The aqueous phase was extracted with Et_2O (2 x 15 mL) and the combined organic phases were washed with water (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure. The residue was purified by column chromatography (silica gel, pentane:Et_2O, 10:1) to afford the aldehyde **4.41** as orange oil (546 mg, 2.29 mmol, 96 %). $\mathbf{R}_f$ = 0.64 (Et_2O:pentane, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.27 (s, 1H), 7.24 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.45 (hept, 1H, *J* =8.0 Hz), 1.35 (d, 6H, *J* = 8.0

[185] A single crystal suitable for X-ray crystallography was obtained from crystalization from Et_2O.

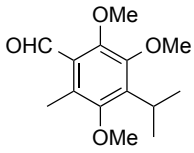
Hz). All analytical data are in agreement with the litterature values: Majetich, G.; Zhang, Y.; Tian, X.; Britton, J. E.; Li, Y.; Philipps, R. *Tetrahedron*, **2011**, *67*, 10129−10146.

Compound 4.42



To a solution a **4.41** (310 mg, 1.30 mmol) in MeOH (9.5 mL), was added $Pd(OH)_2/C$ (10% on C, 62.1 mg, 44.2 μmol, 3.4 mol%) under an argon atmosphere. The reaction mixture was placed in an autoclave and flushed with H_2 (3 x) and finally stirred for 24 h at rt under a pressure of H_2 (80 bar). The reaction mixture was put back in an atmosphere of argon and filtered through a pad of celite. The cake was washed with MeOH (3 x 5 mL) and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (10 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure to yield **4.42** as a colorless oil (224 mg, 1.00 mmol, 77%), which was used without further purification. $\mathbf{R}_f = 0.74$ (Et_2O:pentane, 1:10). **IR** (neat) ν = 2949, 1430, 1337, 1480, 1230, 1116, 1042, 845, 640 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.57 (s, 1H), 3.82 (s, 6H), 3.67 (s, 3H), 3.43 (hept, J = 8.0 Hz, 1H), 2.25 (s, 3H), 1.34 (d, J = 8.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 150.2, 149.4, 146.7, 135.0, 125.8, 112.2 61.2, 60.9, 56.0, 26.1, 22.2, 22.2, 16.6. **HRMS** (ESI) m/z: calcd for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1485, found 225.1485.

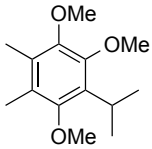
Aldehyde 4.43:



To a solution of **4.42** (224 mg, 1.00 mmol) in dry CH_2Cl_2 (6 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 4.8 mL, 4.8 mmol) followed by 1,1-dichlorodimethyl ether (186 μL, 2.05 mmol) at −10 °C. The reaction mixture was stirred for 30 min at −10 °C and 3.5 h at rt. The mixture was slowly poured slowly onto ice-water (20 mL), Et_2O was added (20 mL). The aqueous phase was extracted with Et_2O (2 x 15 mL) and the combined organic phases were washed with water (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure. The residue was purified by column chromatography (silica gel, pentane:Et_2O, 20:1) to afford the aldehyde **4.43** as yellow oil (248 mg, 985 μmol, 98

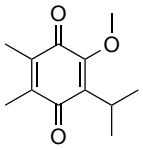
%). $\mathbf{R_f}$ = 0.46 (Et_2O:pentane, 1:5). **IR** (neat) ν = 2949, 1690, 1574, 1457, 1420, 1383, 1339, 1315, 1267, 1124, 1105, 1087, 1035, 1016, 989, 958, 769 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.48 (s, 1H), 3.89 (s, 6H), 3.66 (s, 3H), 3.49 (hept, *J* =7.5 Hz, 1H), 2.46 (s, 3H), 1.35 (d, *J* =7.5 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 192.4, 154.4, 153.2, 150.7, 142.6, 128.7, 127.2, 61.9, 61.5, 60.8, 26.7, 21.9, 21.9, 13.2. **HRMS** (ESI) m/z: calcd for $C_{14}H_{20}O_4Na_1$ $[M+Na]^+$: 275.1254, found 275.1252.

Compound 4.44:



To a solution a **4.43** (500 mg, 1.98 mmol) in MeOH (15 mL), was added $Pd(OH)_2$/C (10% on C, 100 mg, 71.2 μmol, 3.6 mol%) under an argon atmosphere. The reaction mixture was placed in an autoclave and flushed with H_2 (3 x) and finally stirred for 18 h at rt under a pressure of H_2 (80 bar). The reaction mixture was put back in an atmosphere of argon and filtered through a pad of celite. The cake was washed with MeOH (3 x 5 mL) and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (10 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure. The residue was purified by column chromatography (silica gel, pentane:Et_2O, 30:1) to yield **4.44** as a white crystalline solid (224 mg, 1.00 mmol, 77%). $\mathbf{R_f}$ = 0.70 (Et_2O:pentane, 1:3). $\mathbf{m_p}$ = 35.3−35.8 °C. **IR** (neat) ν = 2935, 1457, 1409, 1339, 1258, 1120, 1088, 1057, 1017, 958, 631 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.86 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.42 (hept, *J* =8.0 Hz, 1H), 2.15 (s, 6H), 1.33 (d, *J* =8.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 152.3, 150.6, 148.2, 132.1, 129.1, 125.4, 61.4, 60.6, 60.1, 26.0, 22.4, 22.4, 13.0, 12.4. **HRMS** (ESI) m/z: calcd for $C_{14}H_{22}O_3Na_1$ $[M+Na]^+$: 261.1461, found 261.1459.

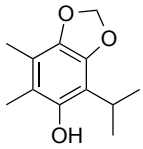
Quinone 4.38:



To a solution of **4.44** (212 mg, 889 μmol) in dioxane (8.9 mL) was added AgO (1.25 g, 10.2 mmol) and the resulting suspension was sonicated for 1 min. An aqueous solution of HNO_3 (6 M, 0.90 mL, 5.3 mmol) was added and the reaction mixture was stirred at rt for 80 min in the dark. An additional amount of HNO_3 (0.90 mL, 5.3 mmol, 6.0 eq.) was added and the reaction mixture was stirred for further 30 min. Et_2O (20 mL) and water (20 mL) were added

to the mixture. The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (silica gel, pentane:Et_2O 30:1) to afford the quinone **4.38** as a intense yellow oil (119 mg, 0.56 mmol, 62 %). $\mathbf{R}_f$ = 0.56 (Et_2O:pentane, 1:10). **IR** (neat) ν = 2932, 1657, 1459, 1377, 1249, 1153, 1050, 650 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.93 (s, 3H), 3.25 (hept, *J* =8.0 Hz, 1H), 2.00 (s, 6H), 1.21 (d, *J* =8.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 188.1, 184.2, 155.8, 141.1, 138.7, 137.7, 61.1, 24.9, 20.7, 20.7, 12.7, 12.0. **HRMS** (ESI) m/z: calcd for $C_{12}H_{17}O_3$ $[M+H]^+$: 209.1174, found 209.1172.

Methylenedioxy bridge 4.45:

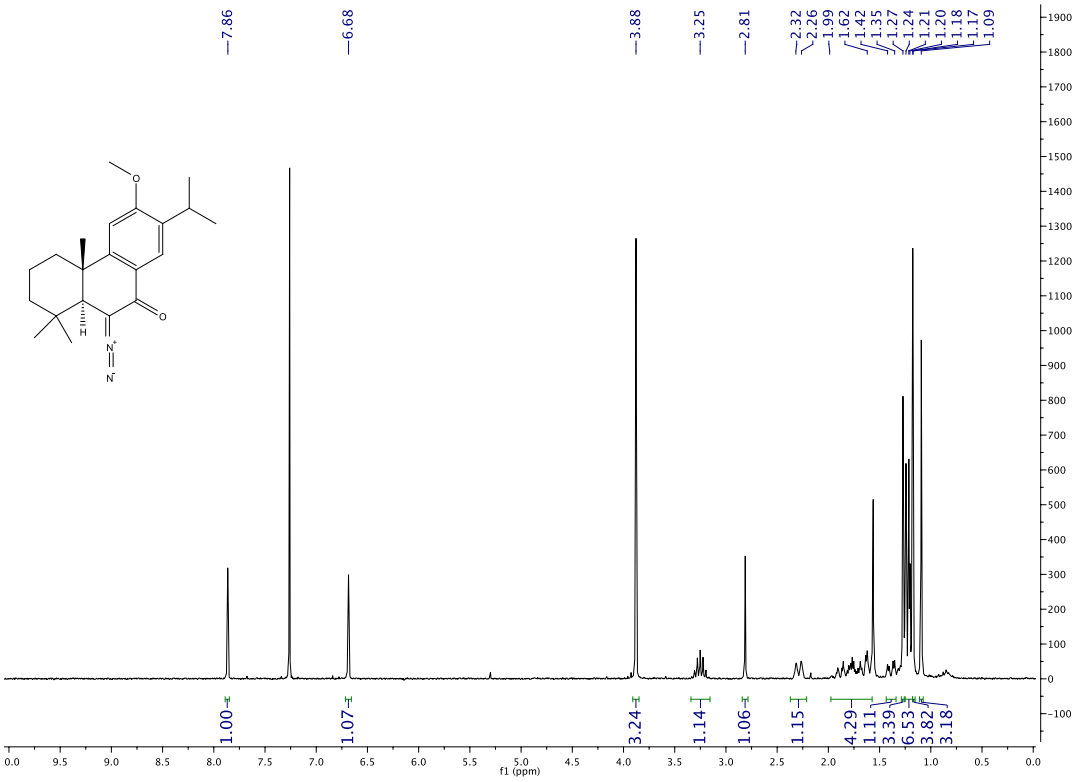


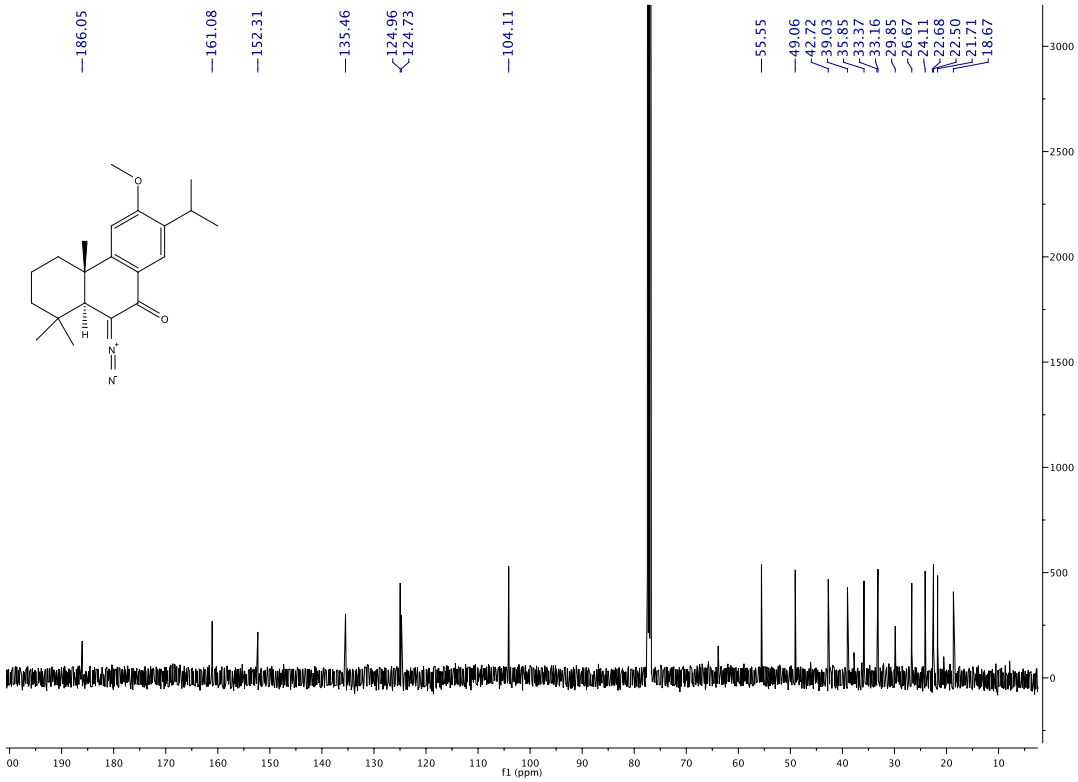
A solution of quinone **4.38** (10.5 mg, 50.4 μmol) in *t*-BuOH (10 mL) was irradiated with a medium pressure mercury lamp at rt for 45 min. The volatiles were removed under reduced pressure and the residue was purified by column chromatography (silica gel, pentane:Et_2O, 10:1) to afford compound **4.45** as a yellow oil (4.94 mg, 23.7 μmol, 47.0 %). $\mathbf{R}_f$ = 0.25 (Et_2O:pentane, 1:10). **IR** (neat) ν = 3487, 2962, 2361, 1428, 1260, 1085, 1028, 959, 880, 798, 660, 614 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.83 (s, 2H), 4.30 (s, 1H), 3.23 (hept, *J* =7.0 Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 1.32 (d, *J* =7.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.6, 143.0, 140.1, 115.7, 115.3, 114.3, 100.0, 25.7, 21.4, 21.4, 12.3, 11.7. **HRMS** (EI) m/z: calcd for $C_{12}H_{16}O_3$ $[M]^+$: 208.10940, found 208.10938.

7. Appendices

7.1. ^{1}H and ^{13}C NMR spectra

7.1.1. Taiwaniaquinoids

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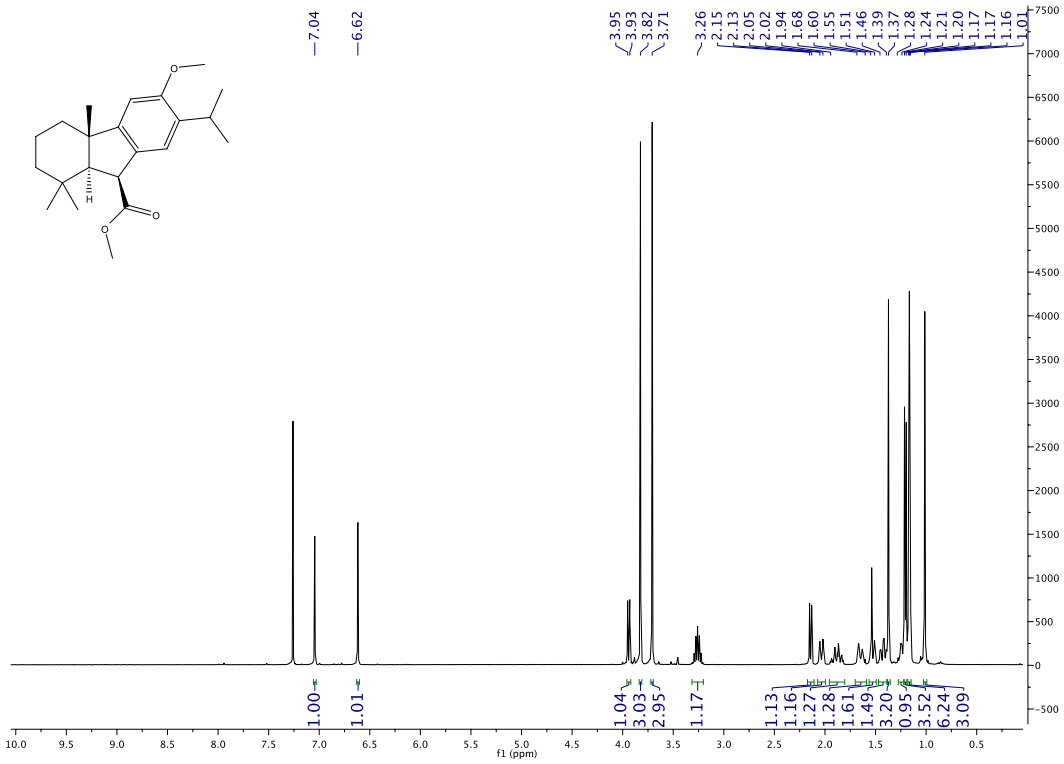
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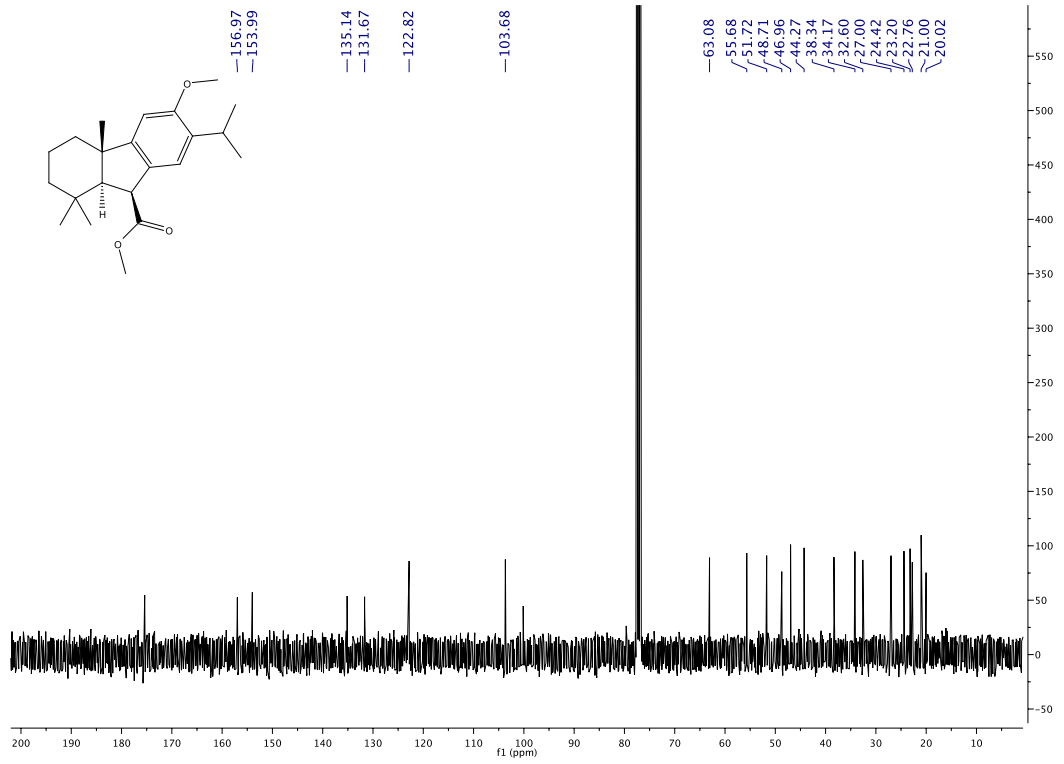
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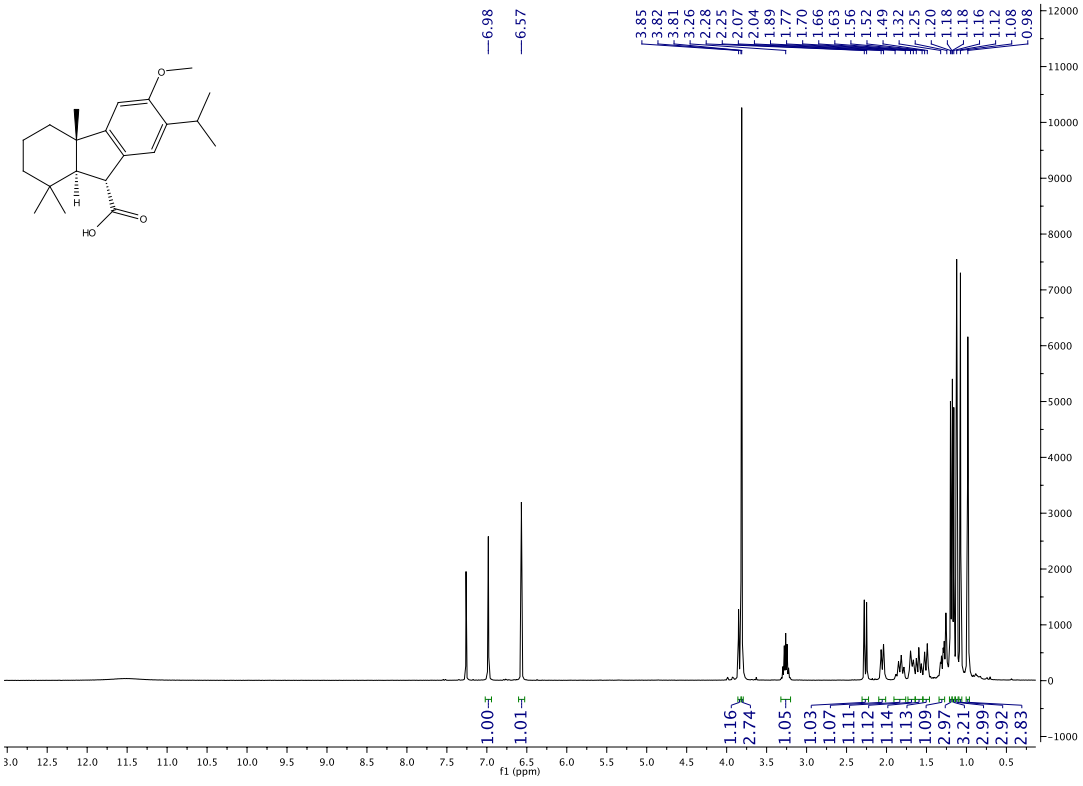
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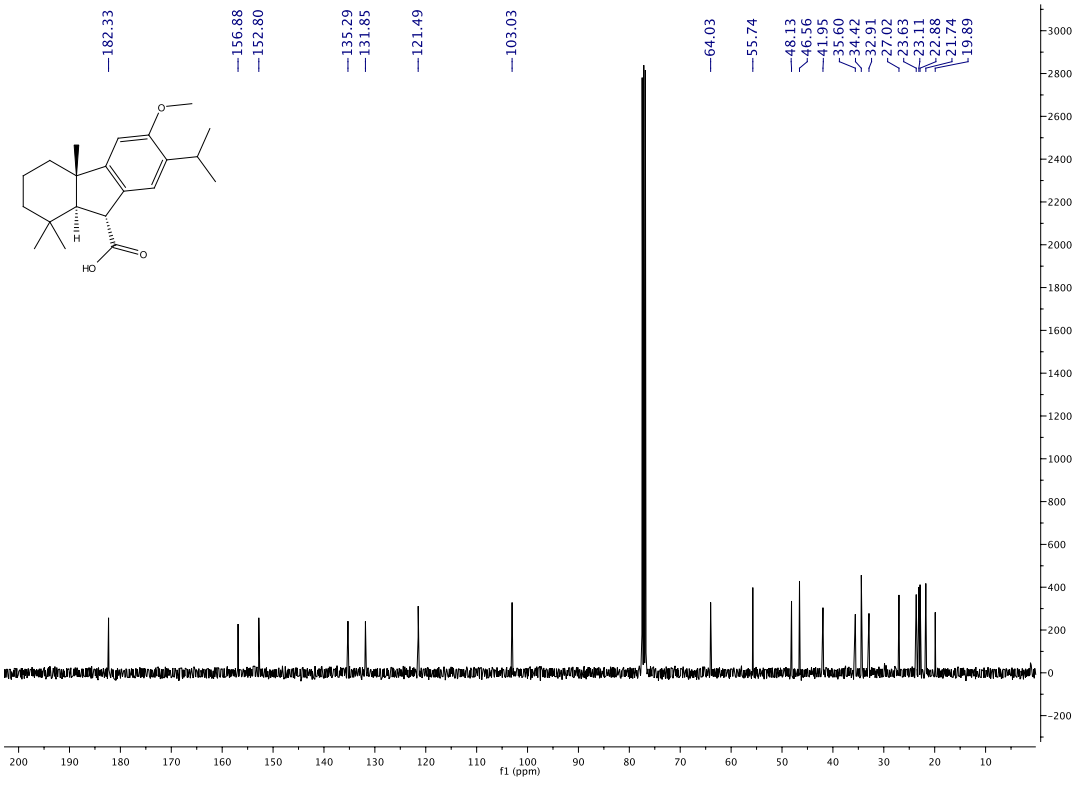
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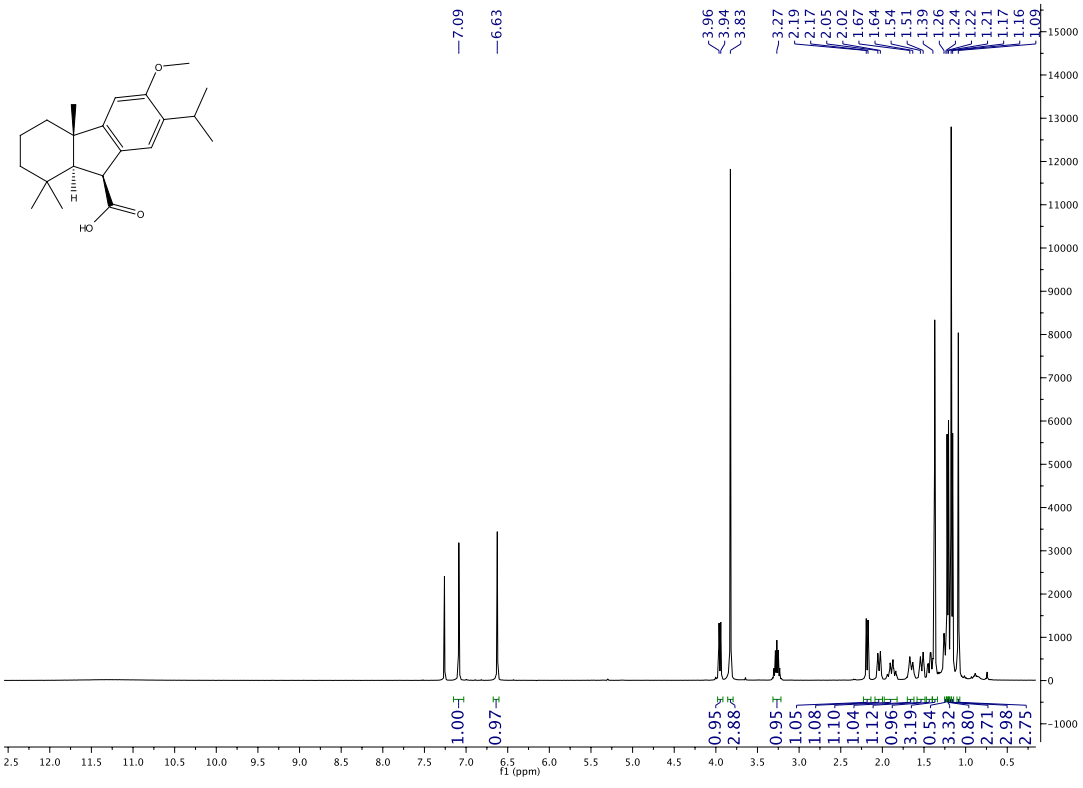
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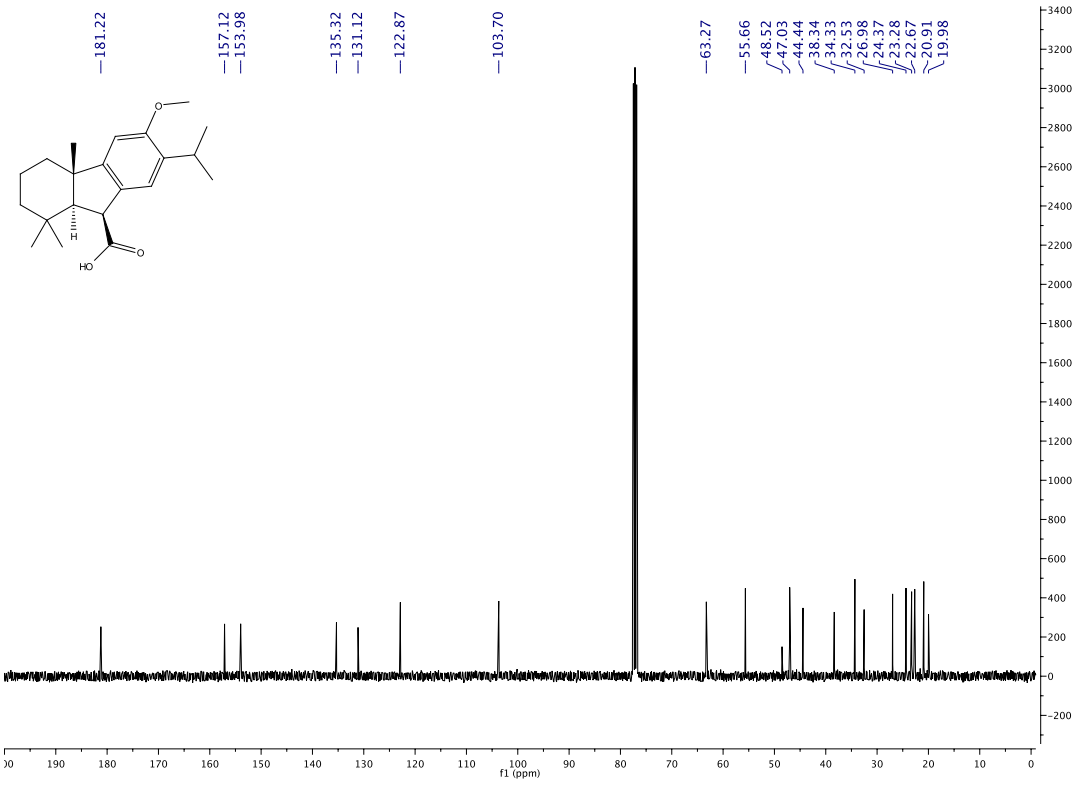
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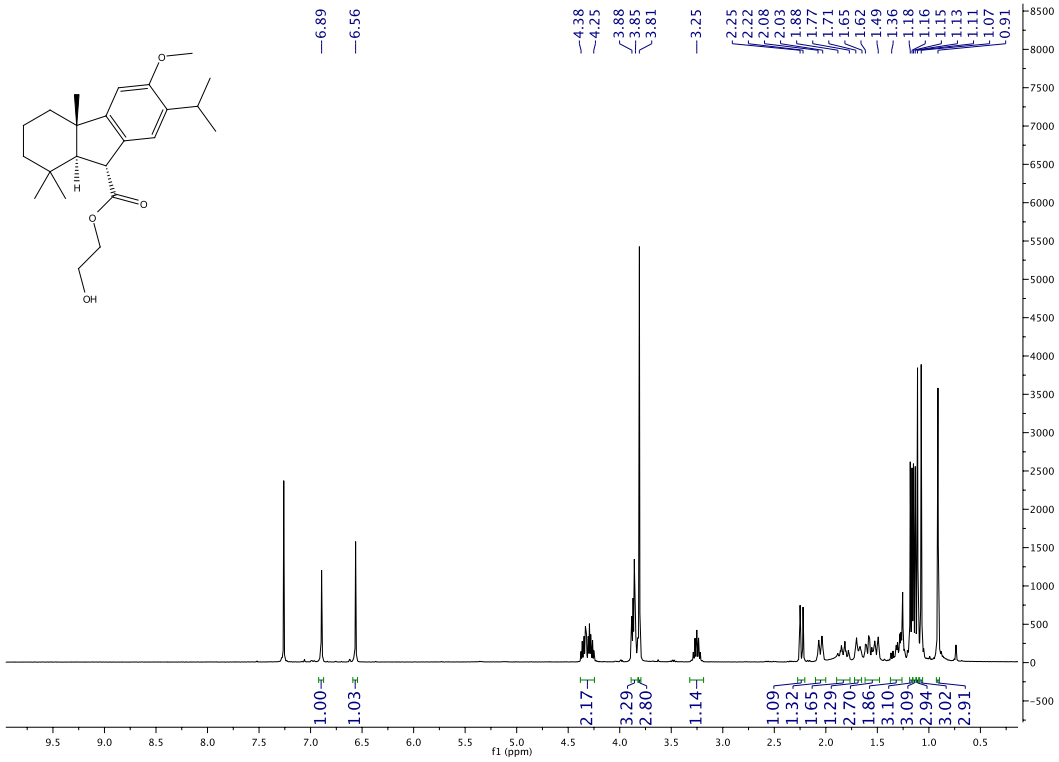
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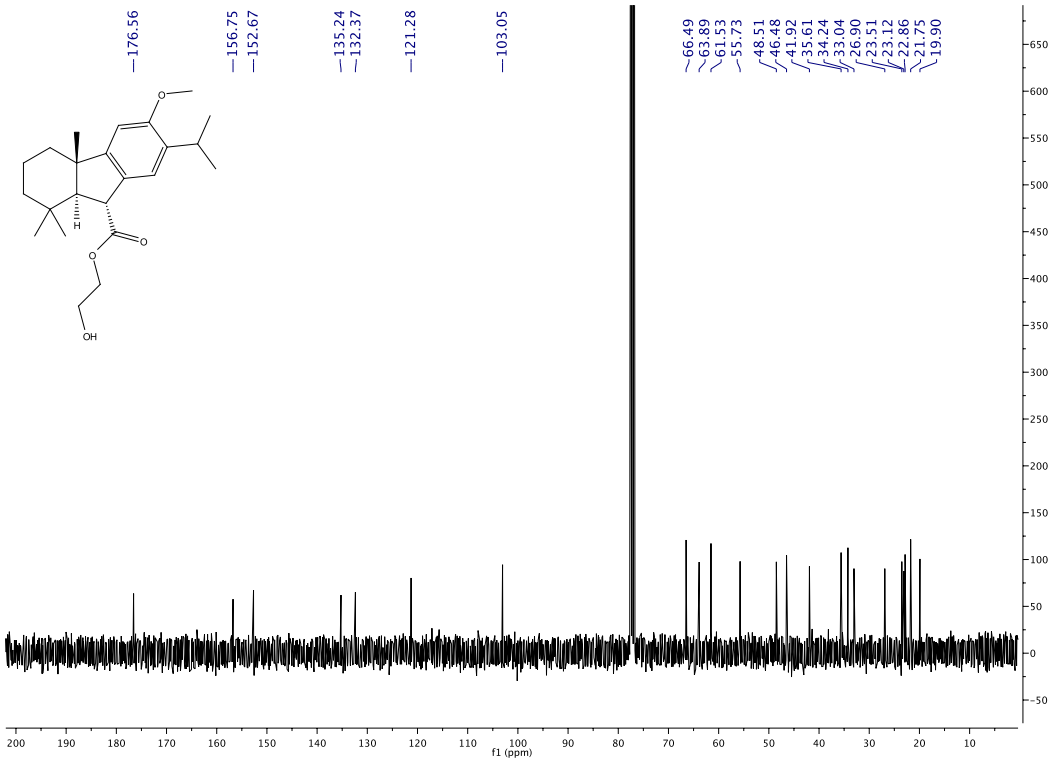
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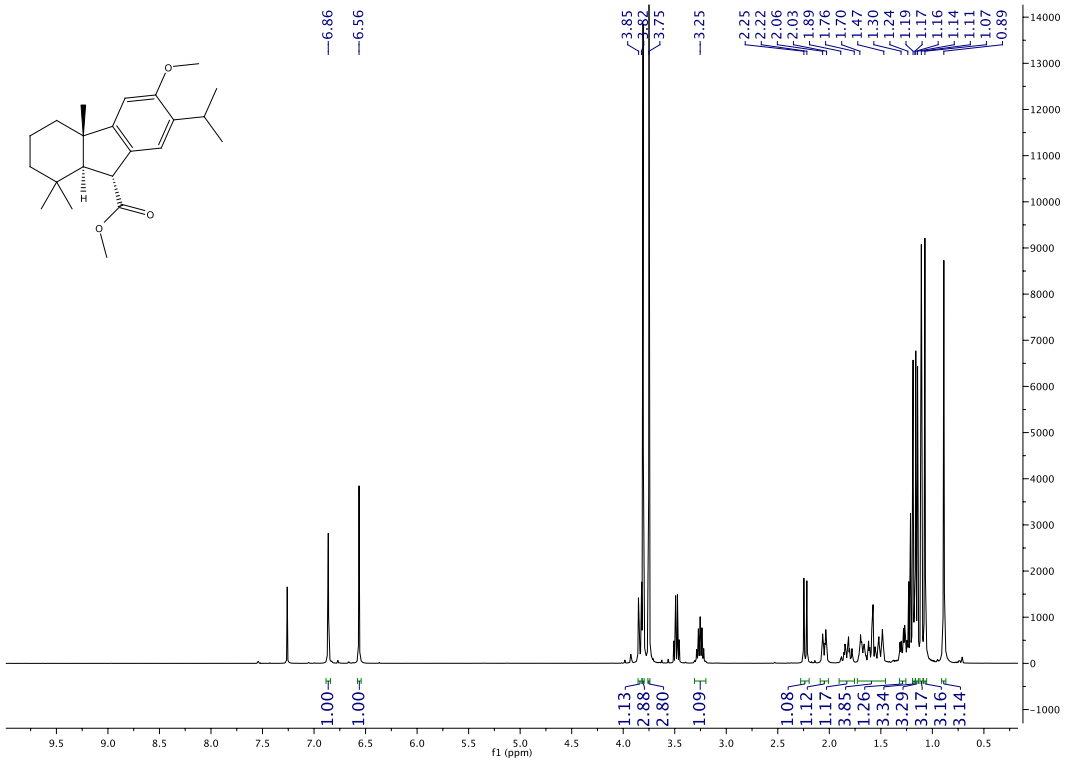
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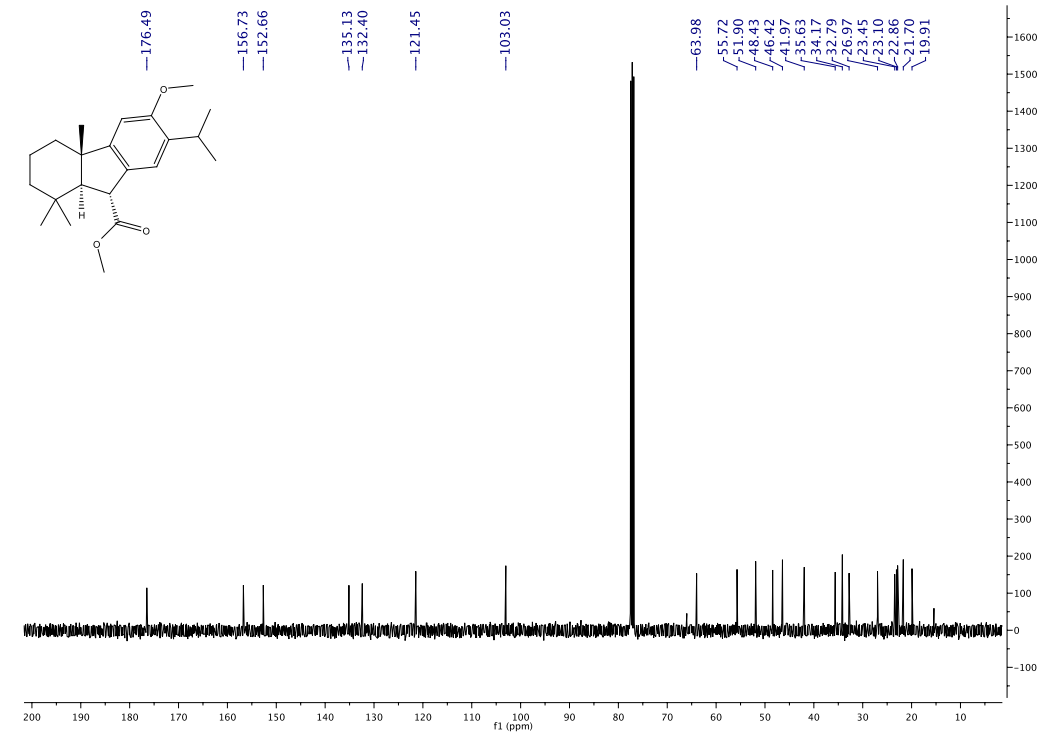
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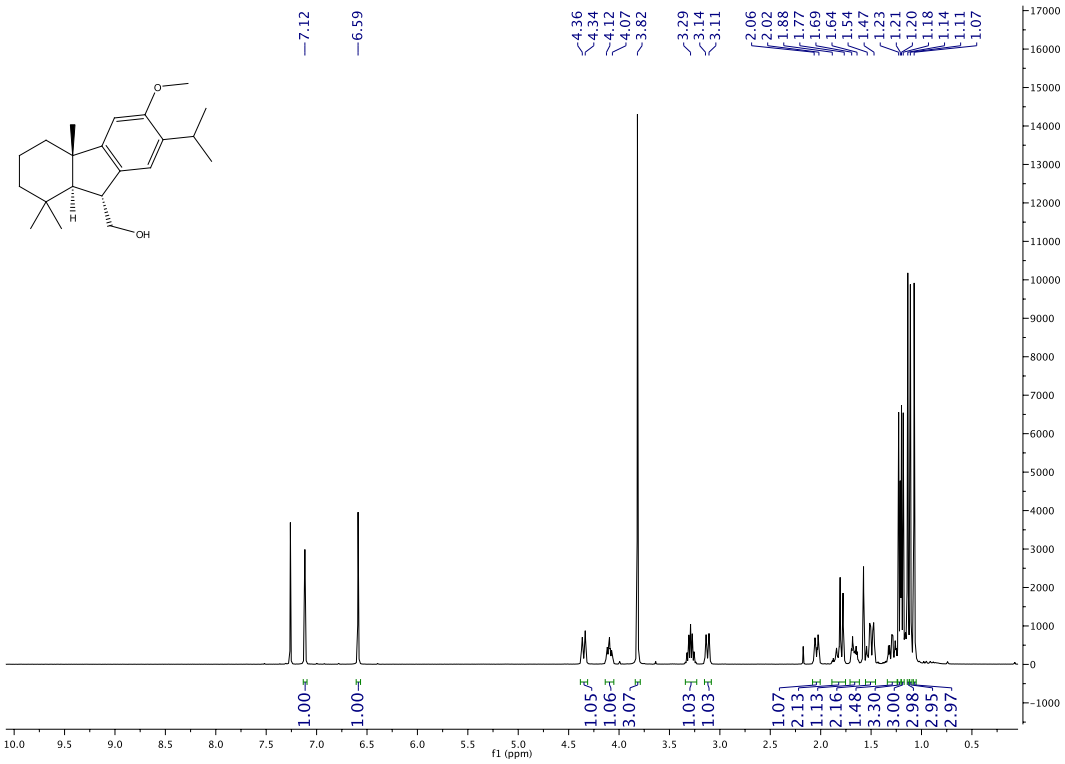
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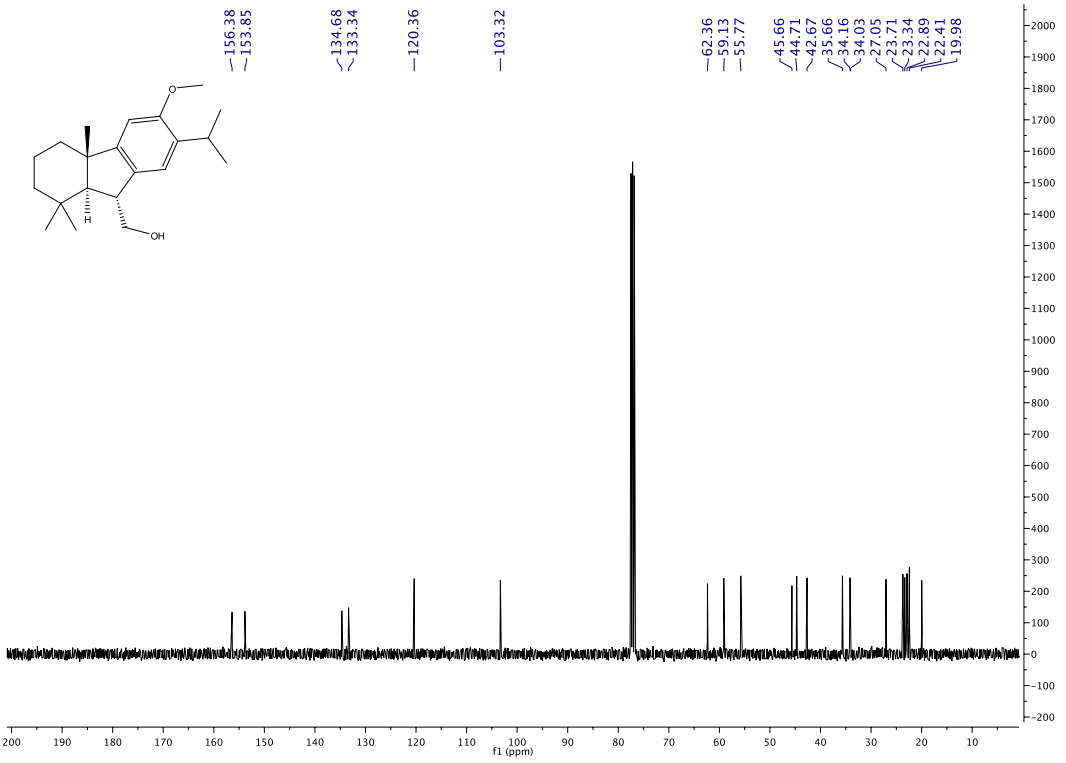
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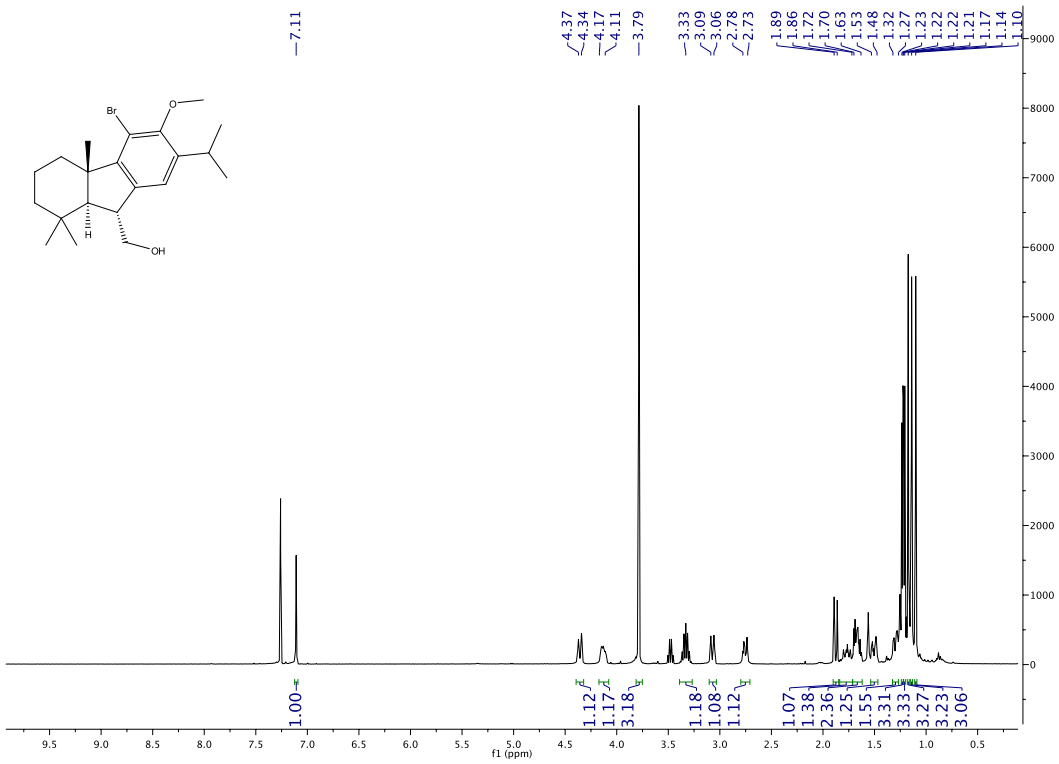
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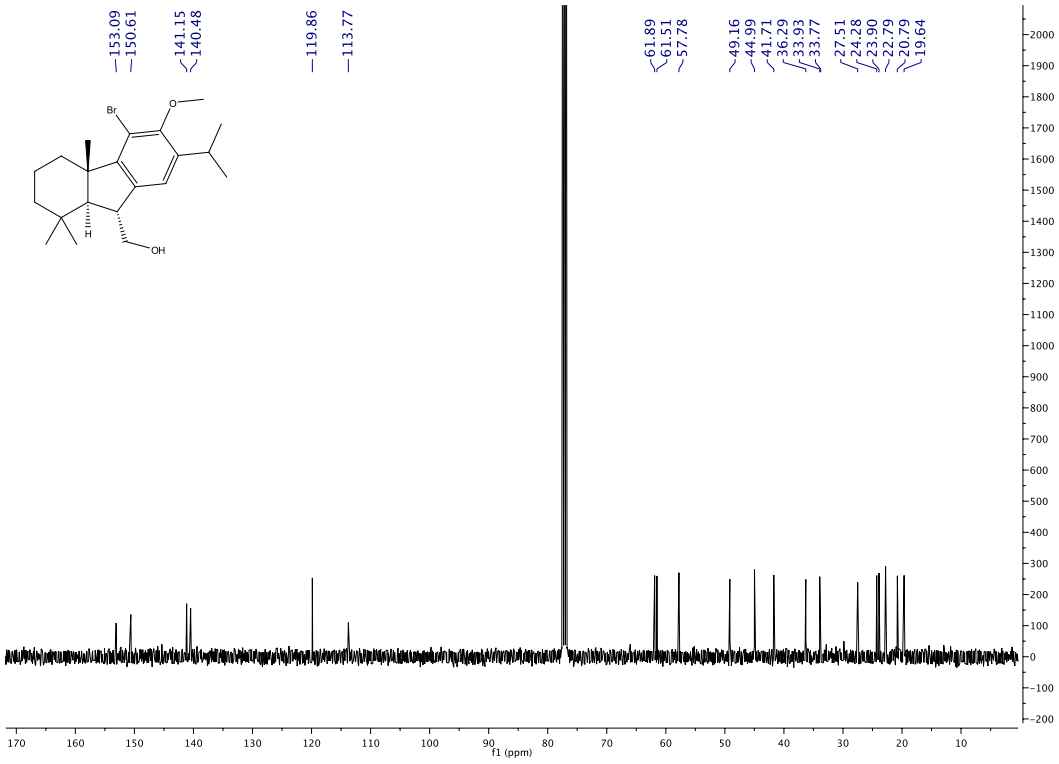
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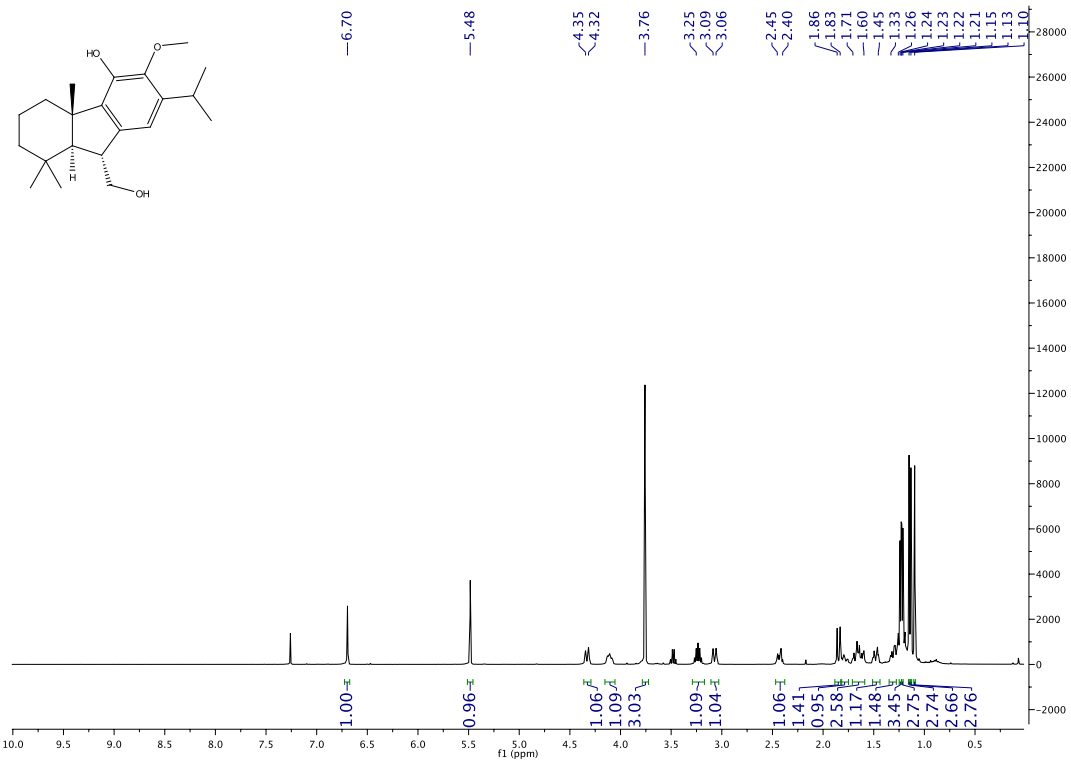
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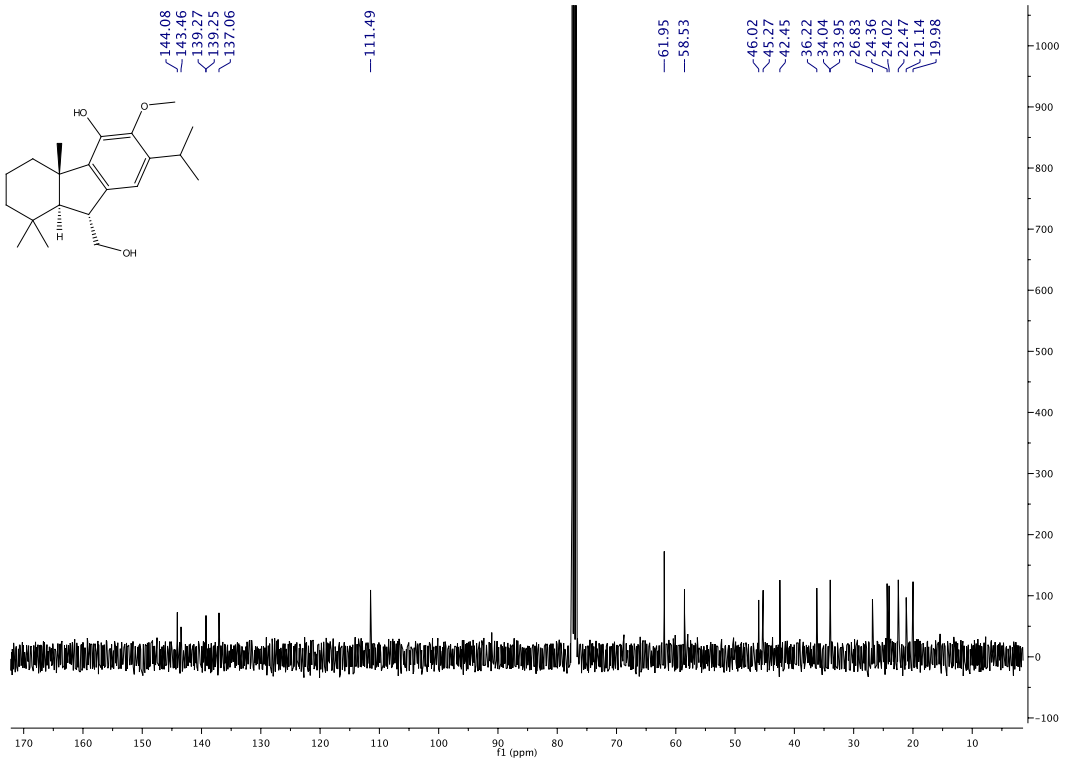
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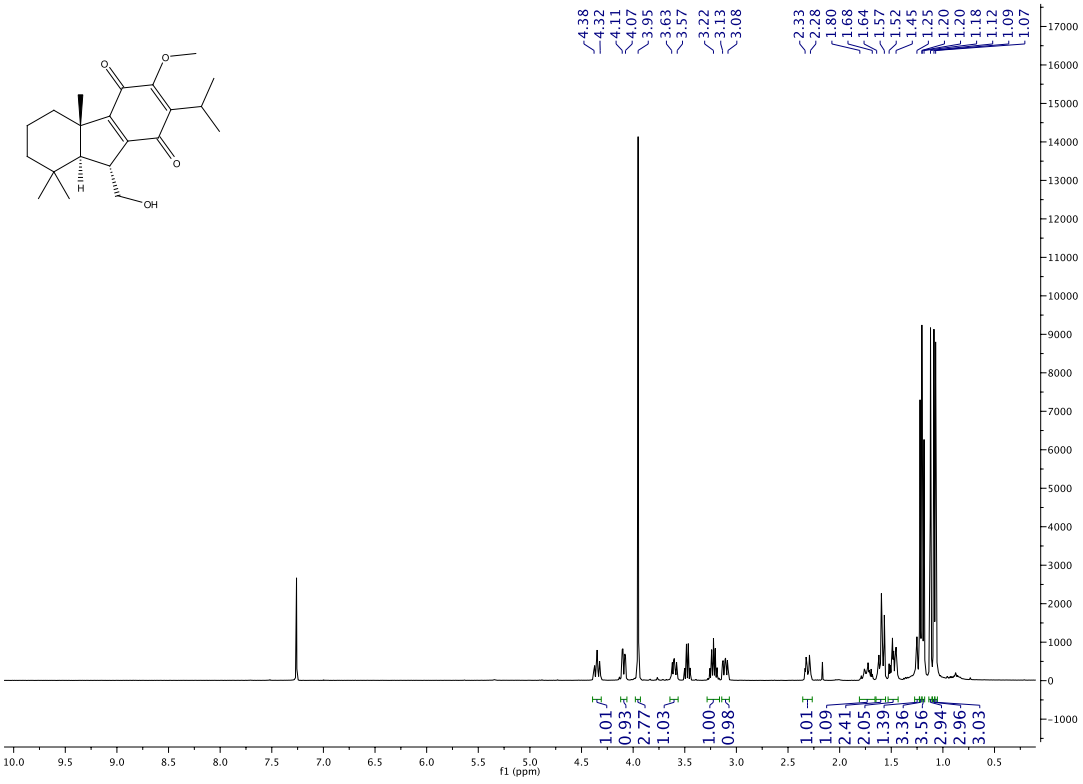
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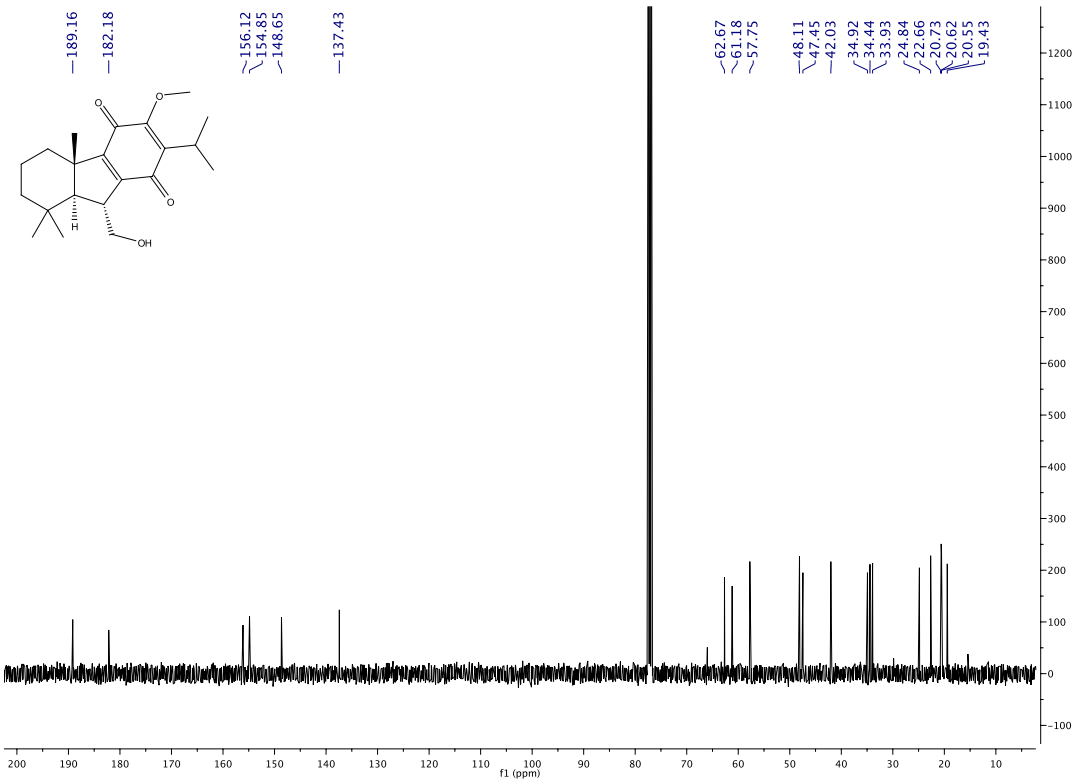
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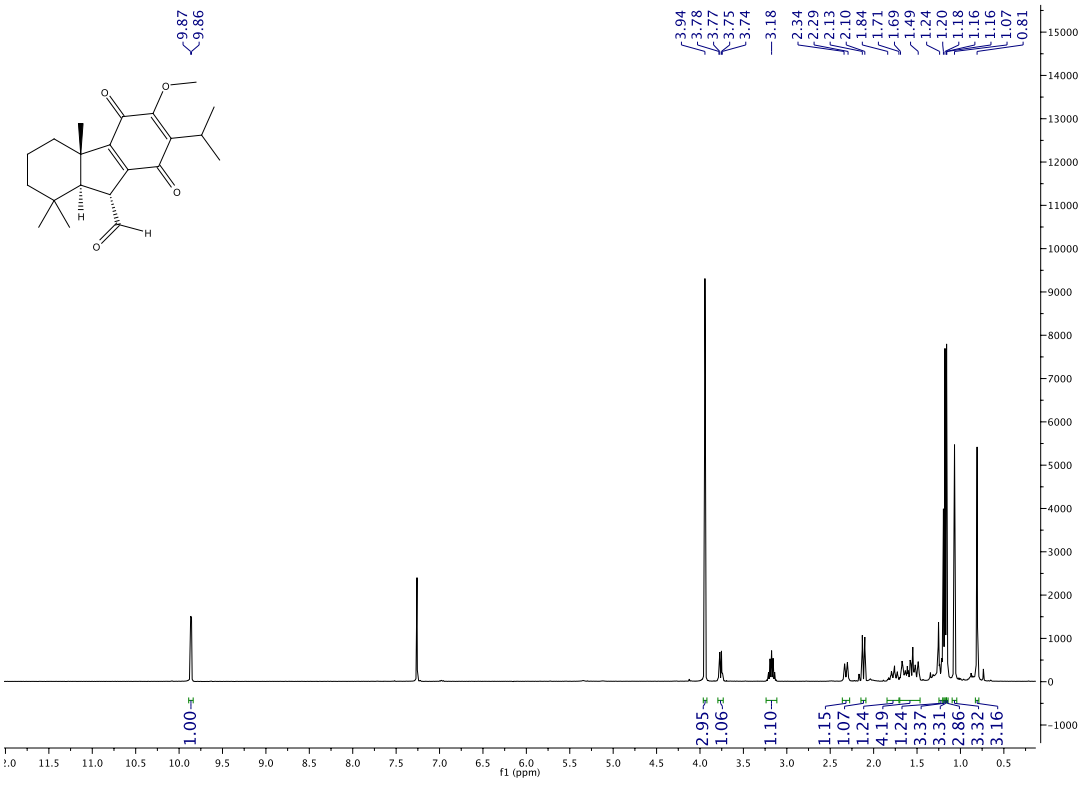
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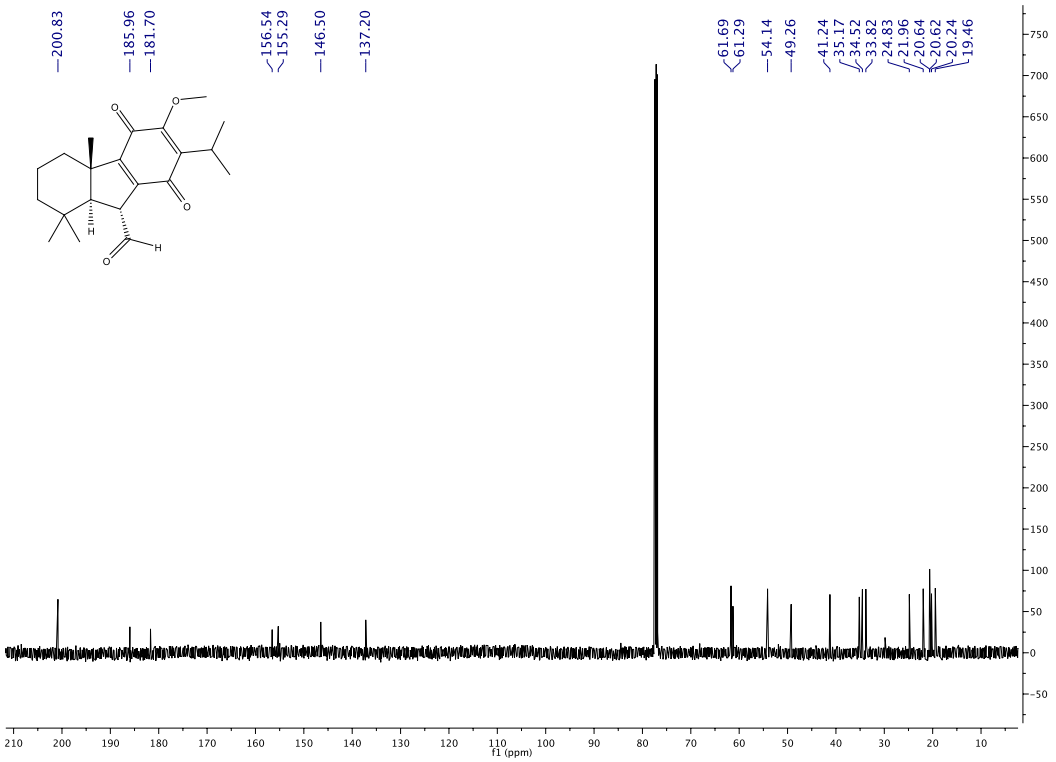
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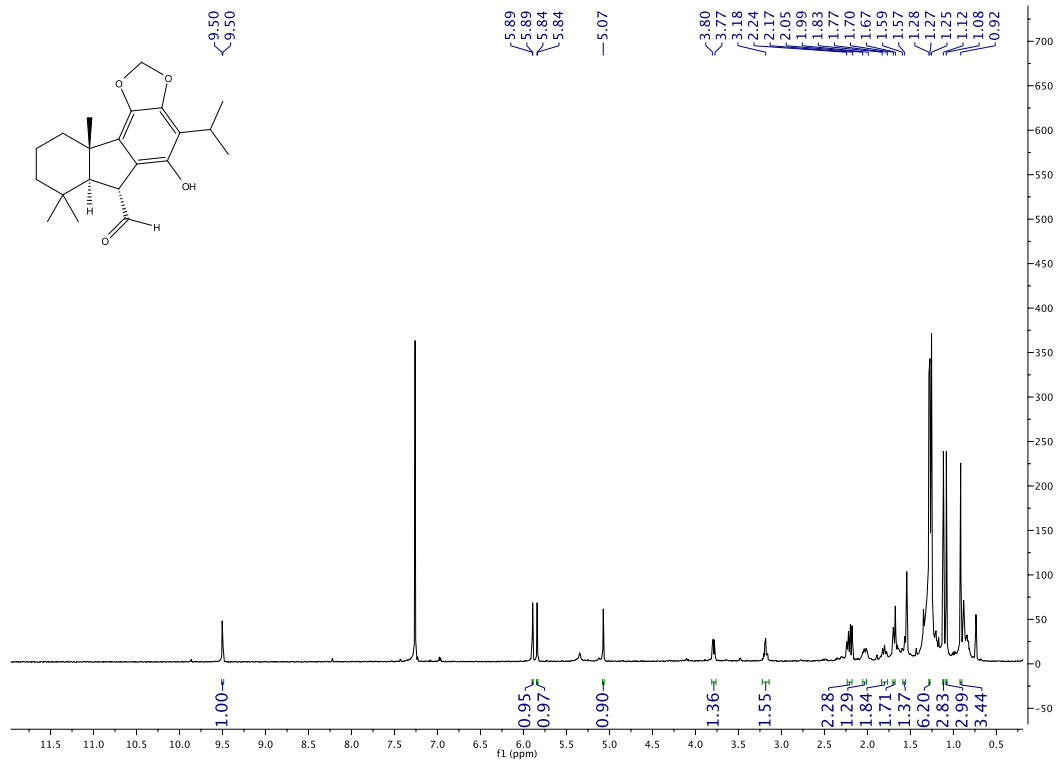
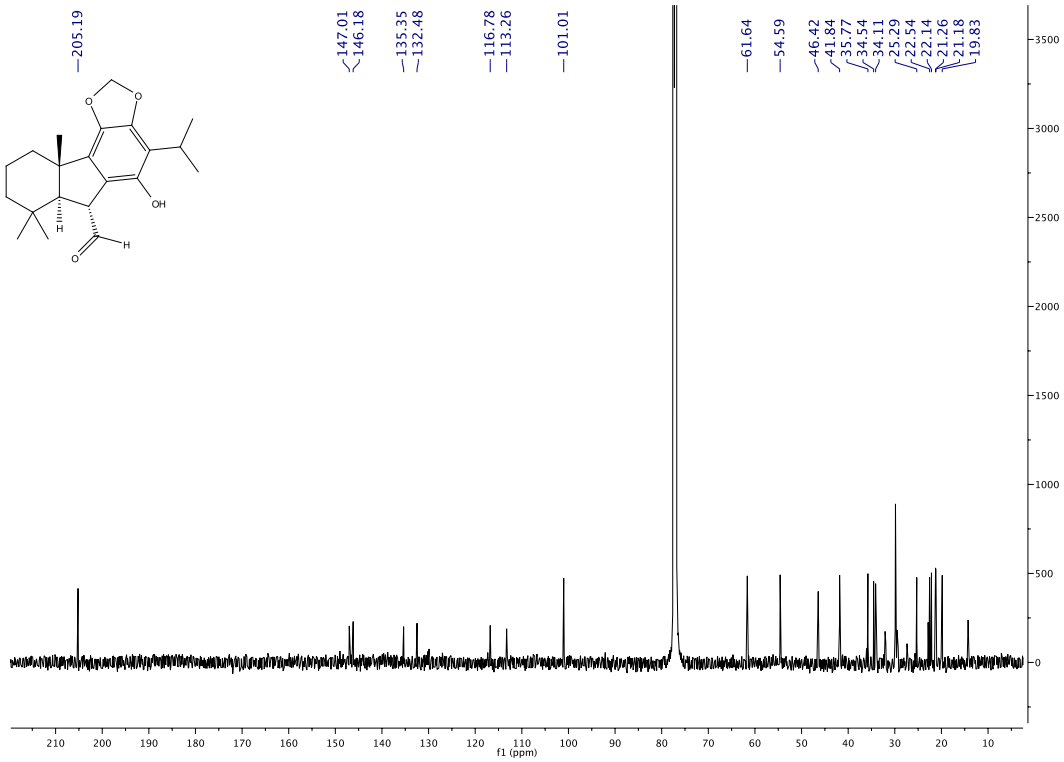
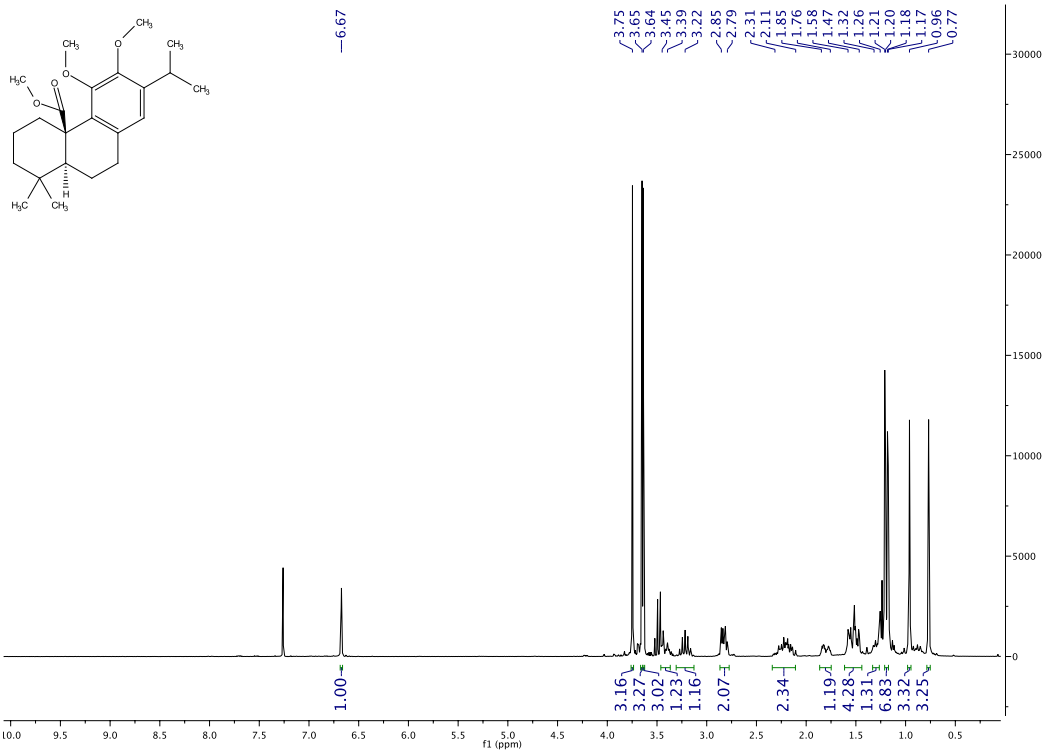
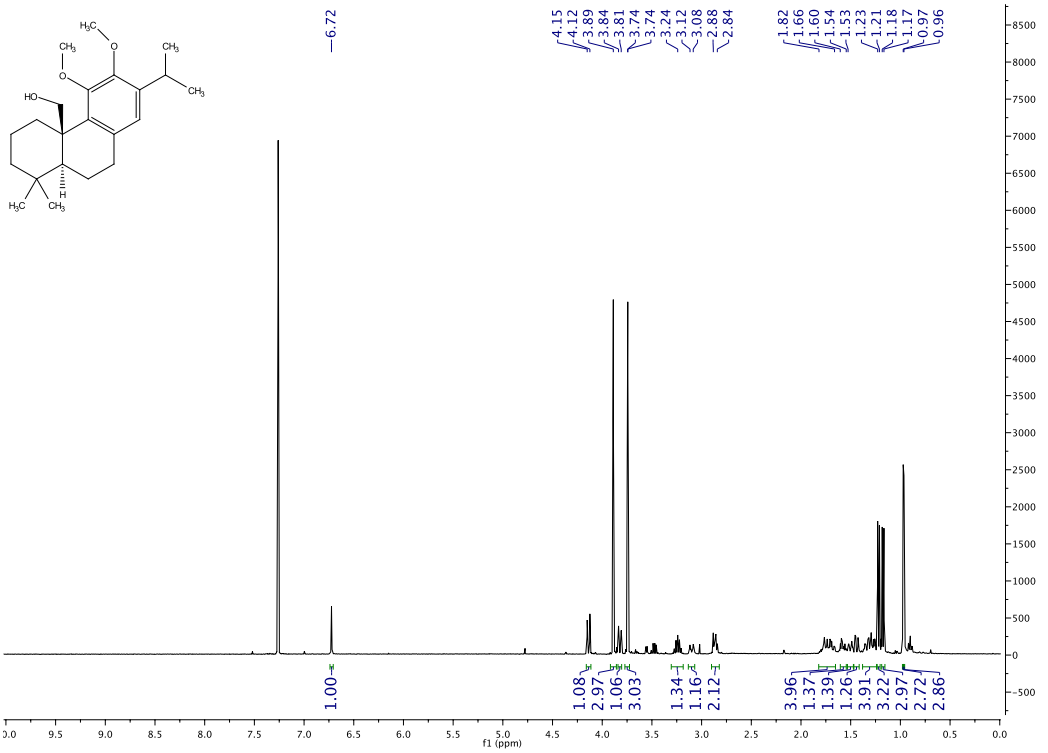
33.82
24.83
21.96
20.64
20.62
20.24
19.46
f1 (ppm)

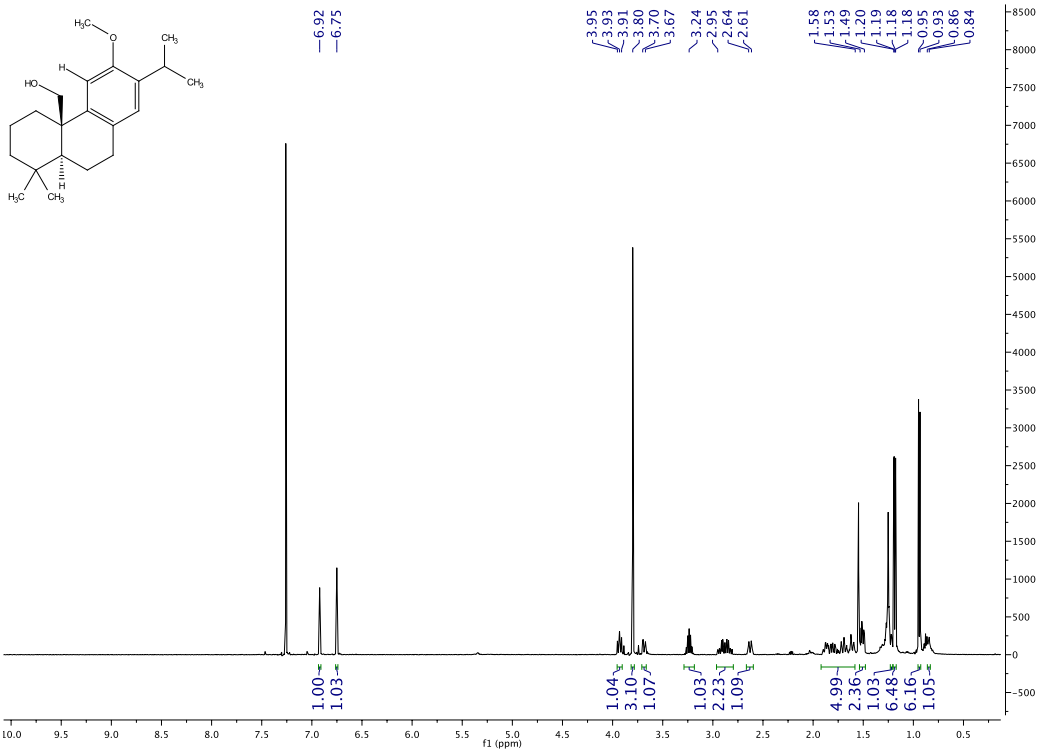

9.50
9.50
5.89
5.89
5.84
5.84
5.07
3.80
3.77
3.18
2.24
2.17
2.05
1.99
1.83
1.77
1.70
1.67
1.59
1.57
1.28
1.27
1.25
1.12
1.08
0.92
OH
H
O
H
1.00
0.95
0.97
0.90
1.36
1.55
2.28
1.29
1.84
1.71
1.37
6.20
2.83
2.99
3.44
f1 (ppm)

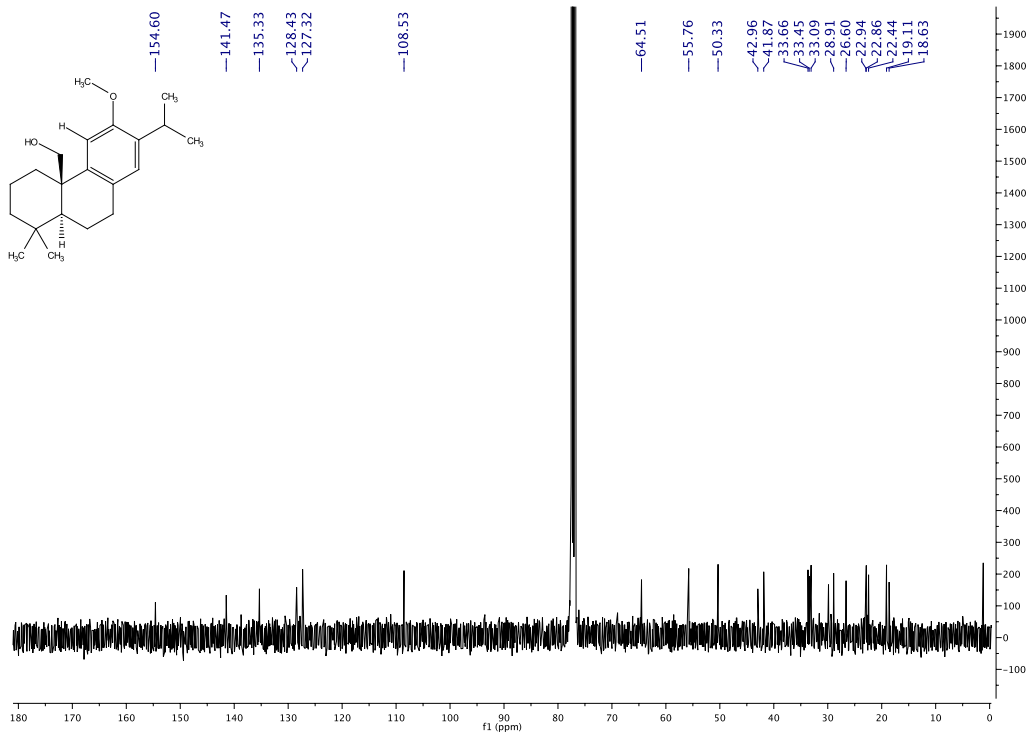

205.19
147.01
146.18
135.35
132.48
116.78
113.26
101.01
61.64
54.59
46.42
41.84
35.77
34.54
34.11
25.29
22.54
22.14
21.26
21.18
19.83
OH
H
O
H
f1 (ppm)

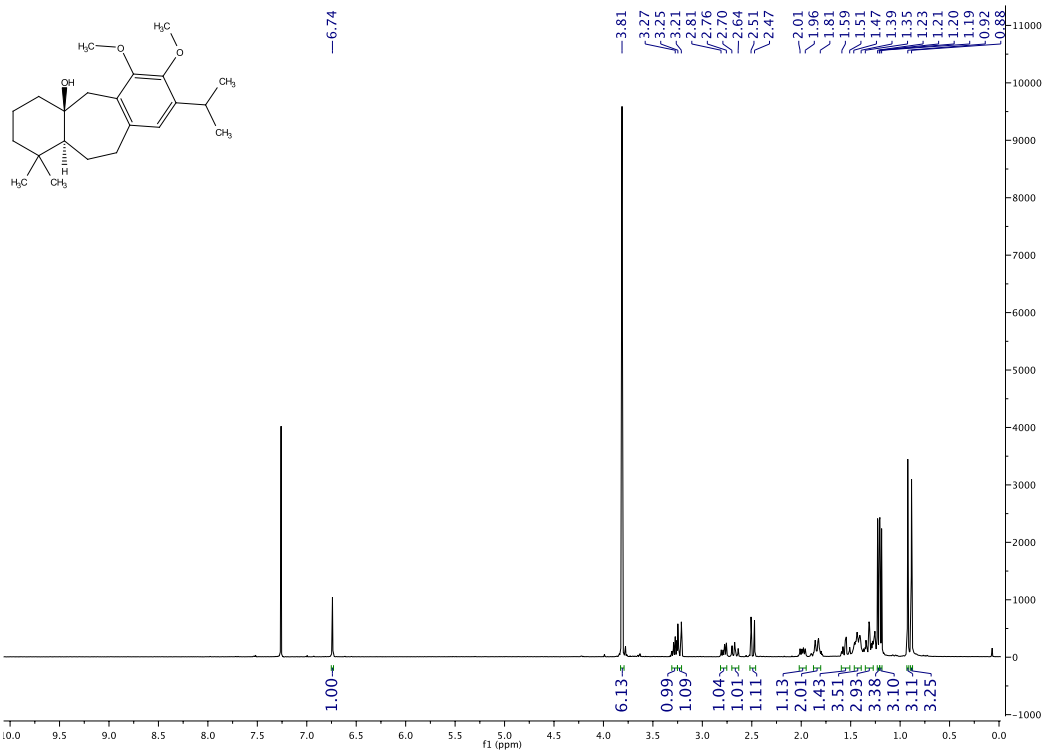
7.1.2. Icetexanes

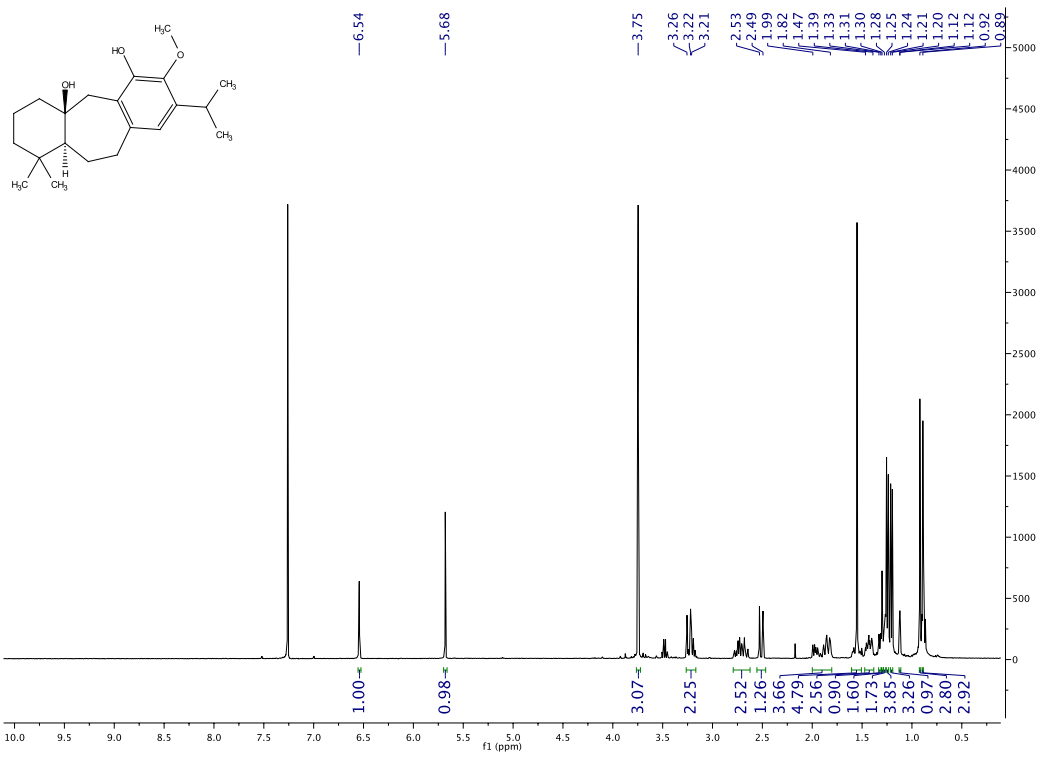


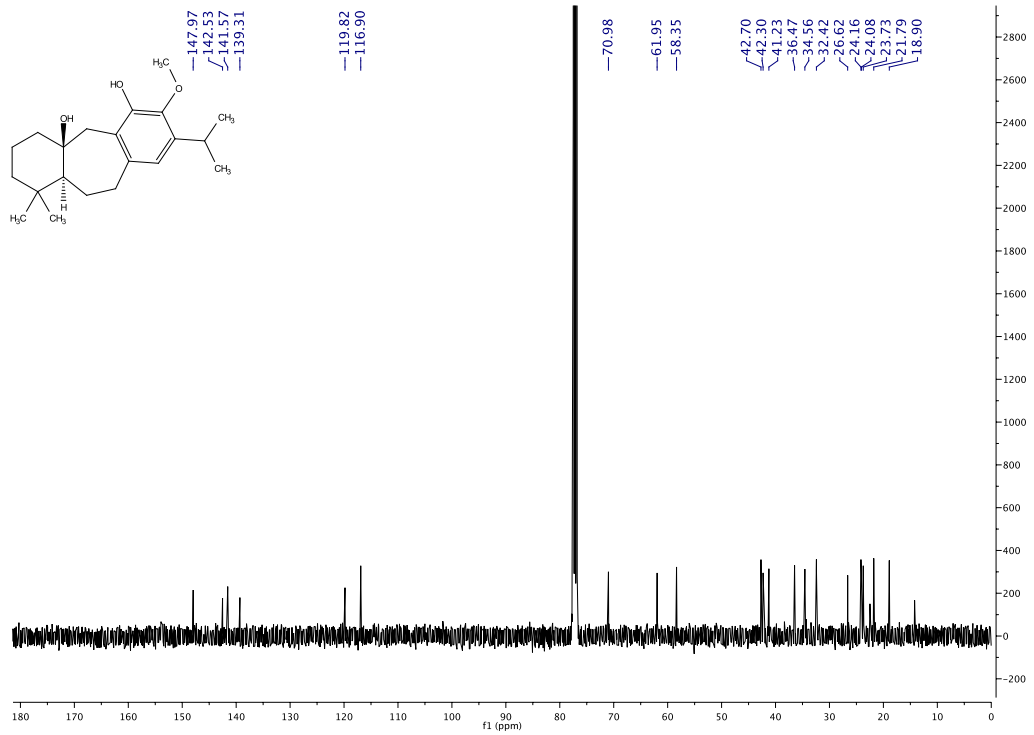



6.92
6.75
3.95
3.93
3.91
3.80
3.70
3.67
3.24
2.95
2.64
2.61
1.58
1.53
1.49
1.20
1.19
1.18
1.18
0.95
0.93
0.86
0.84
1.00
1.03
1.04
3.10
1.07
1.03
2.23
1.09
4.99
2.36
1.03
6.48
6.16
1.05
f1 (ppm)


154.60
141.47
135.33
128.43
127.32
108.53
64.51
55.76
50.33
42.96
41.87
33.66
33.45
33.09
28.91
26.60
22.94
22.86
22.44
19.11
18.63
f1 (ppm)


6.74
3.81
3.27
3.25
3.21
2.81
2.76
2.70
2.64
2.51
2.47
2.01
1.96
1.81
1.59
1.51
1.47
1.39
1.35
1.23
1.21
1.20
1.19
0.92
0.88
1.00
6.13
0.99
1.09
1.04
1.01
1.11
1.13
2.01
1.43
3.51
2.93
3.38
3.10
3.11
3.25
f1 (ppm)


6.54
5.68
3.75
3.26
3.22
3.21
2.53
2.49
1.99
1.82
1.47
1.39
1.33
1.31
1.30
1.28
1.25
1.24
1.21
1.20
1.12
1.12
0.92
0.89
1.00
0.98
3.07
2.25
2.52
1.26
3.66
4.79
2.56
0.90
1.60
1.73
3.85
3.26
0.97
2.80
2.92
f1 (ppm)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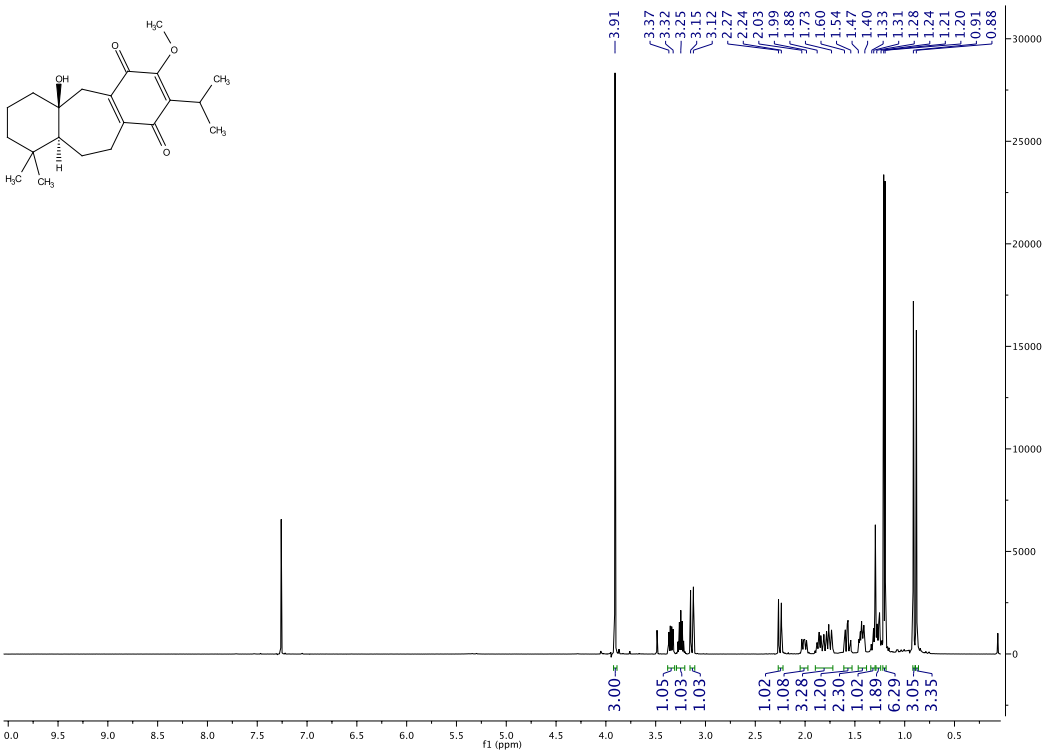
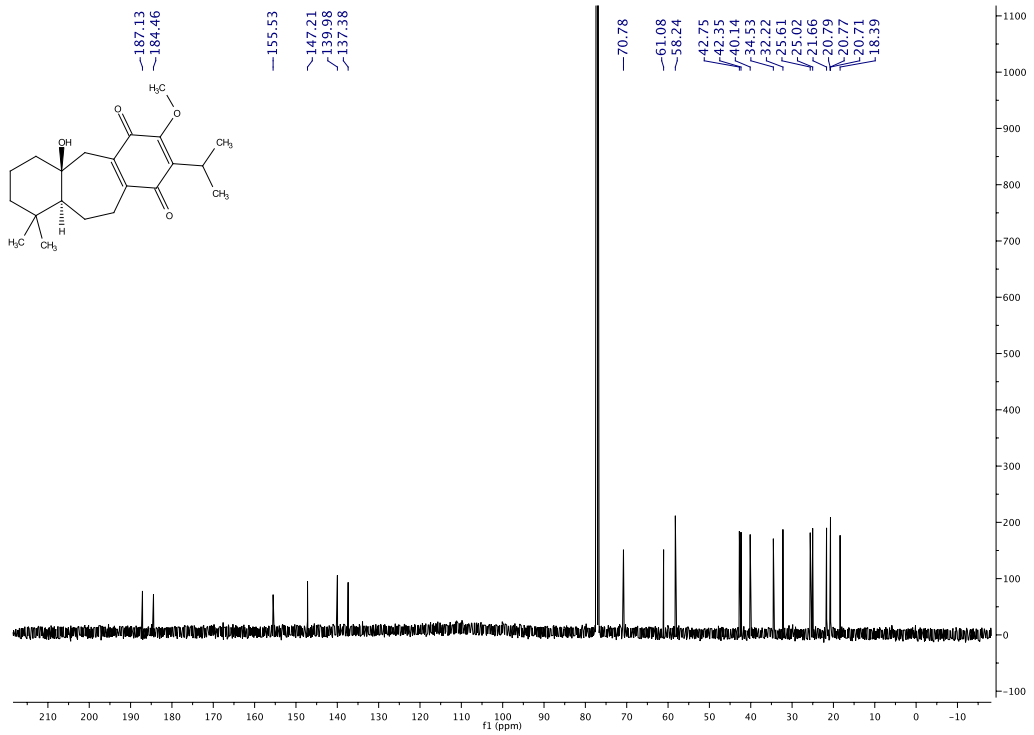
142.53
141.57
139.31
119.82
116.90
70.98
61.95
58.35
42.70
42.30
41.23
36.47
34.56
32.42
26.62
24.16
24.08
23.73
21.79
18.90
f1 (ppm)


3.91
3.37
3.32
3.25
3.15
3.12
2.27
2.24
2.03
1.99
1.88
1.73
1.60
1.54
1.47
1.40
1.33
1.31
1.28
1.24
1.21
1.20
0.91
0.88
3.00
1.05
1.03
1.03
1.02
1.08
3.28
1.20
2.30
1.02
1.89
6.29
3.05
3.35
f1 (ppm)


187.13
184.46
155.53
147.21
139.98
137.38
70.78
61.08
58.24
42.75
42.35
40.14
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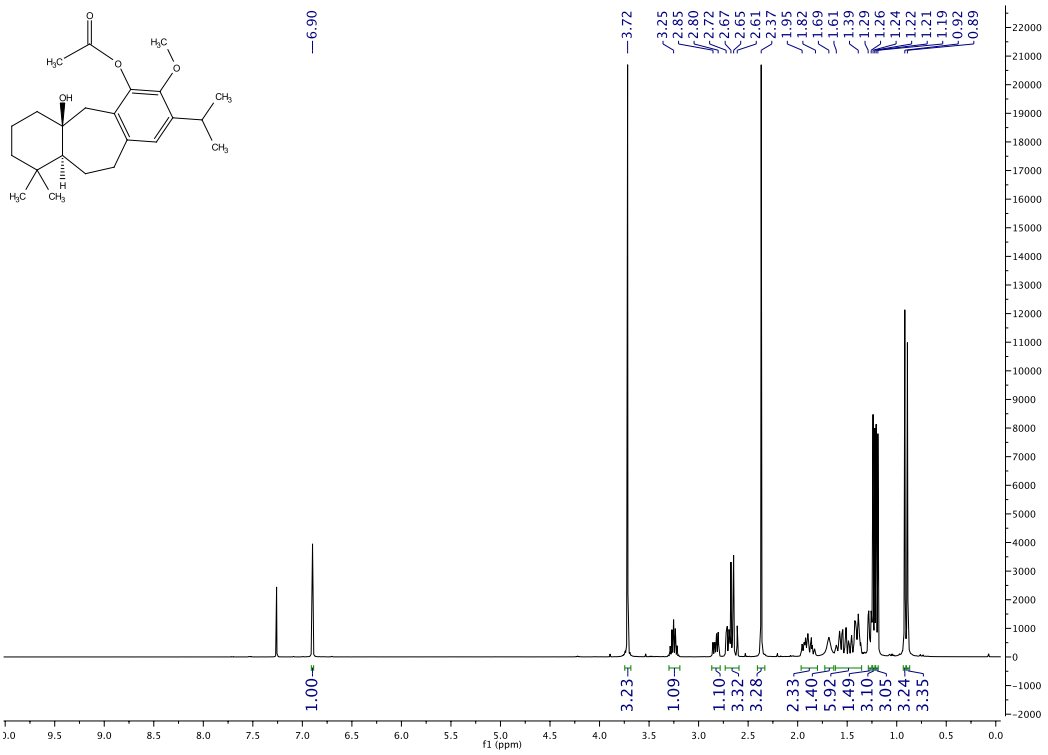
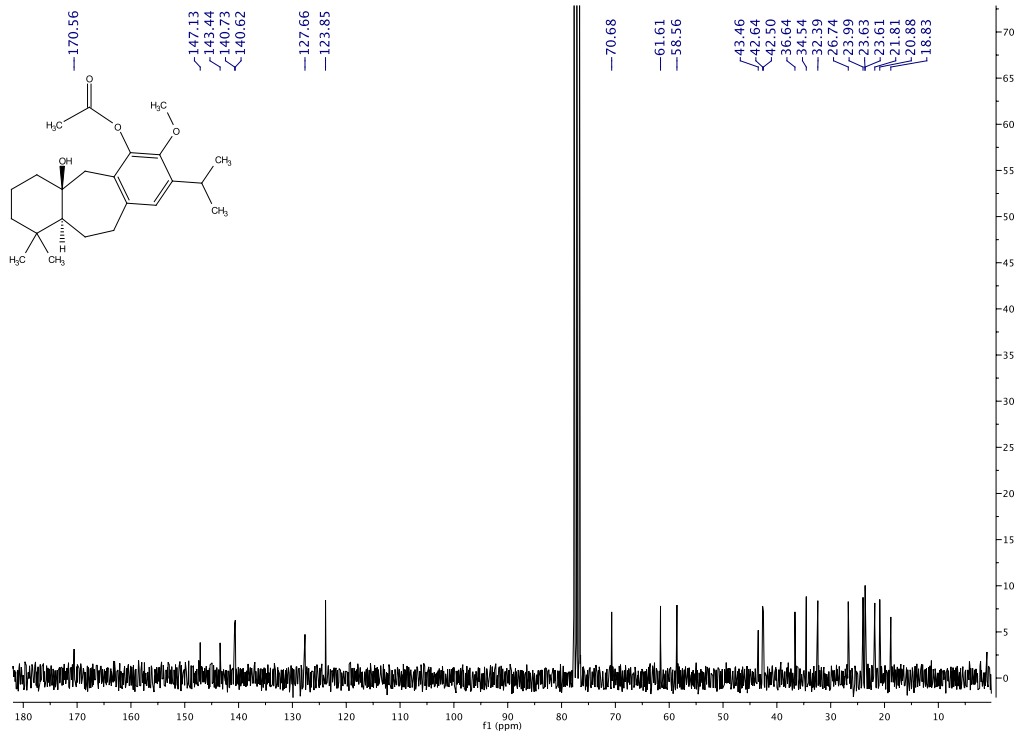
20.79
20.77
20.71
18.39
f1 (ppm)


6.90
3.72
3.25
2.85
2.80
2.72
2.67
2.65
2.61
2.37
1.95
1.82
1.69
1.61
1.39
1.29
1.26
1.24
1.22
1.21
1.19
0.92
0.89
1.00
3.23
1.09
1.10
3.32
3.28
2.33
1.40
5.92
1.49
3.10
3.05
3.24
3.35
f1 (ppm)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147.13
143.44
140.73
140.62
127.66
123.85
70.68
61.61
58.56
43.46
42.64
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32.39
26.74
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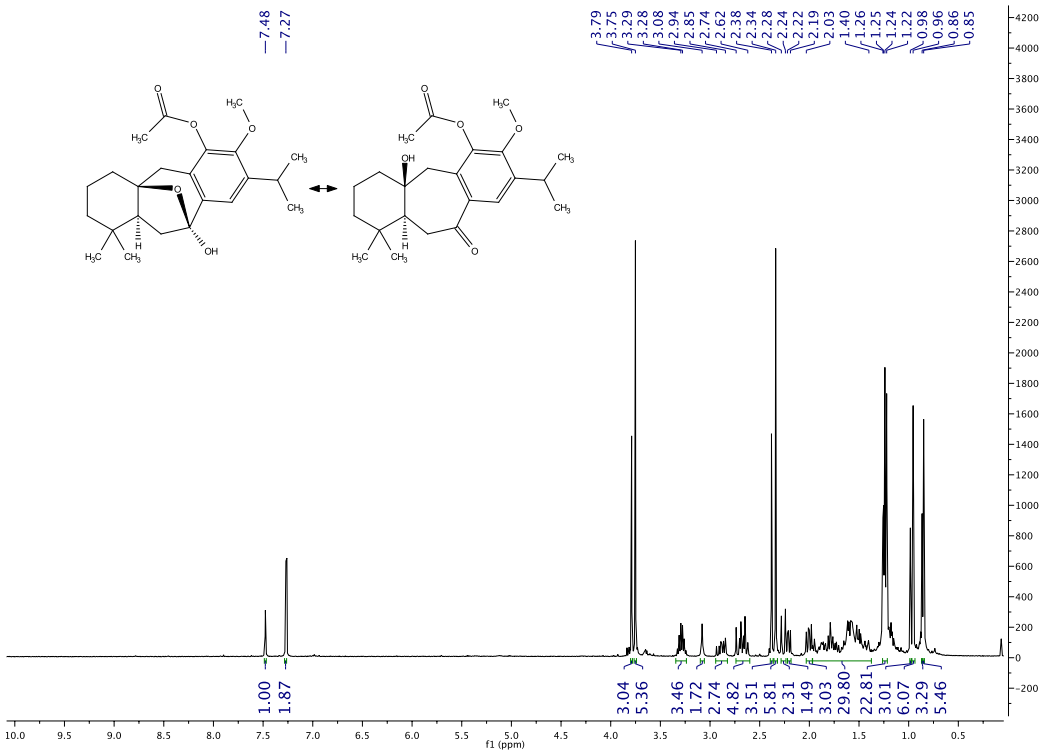
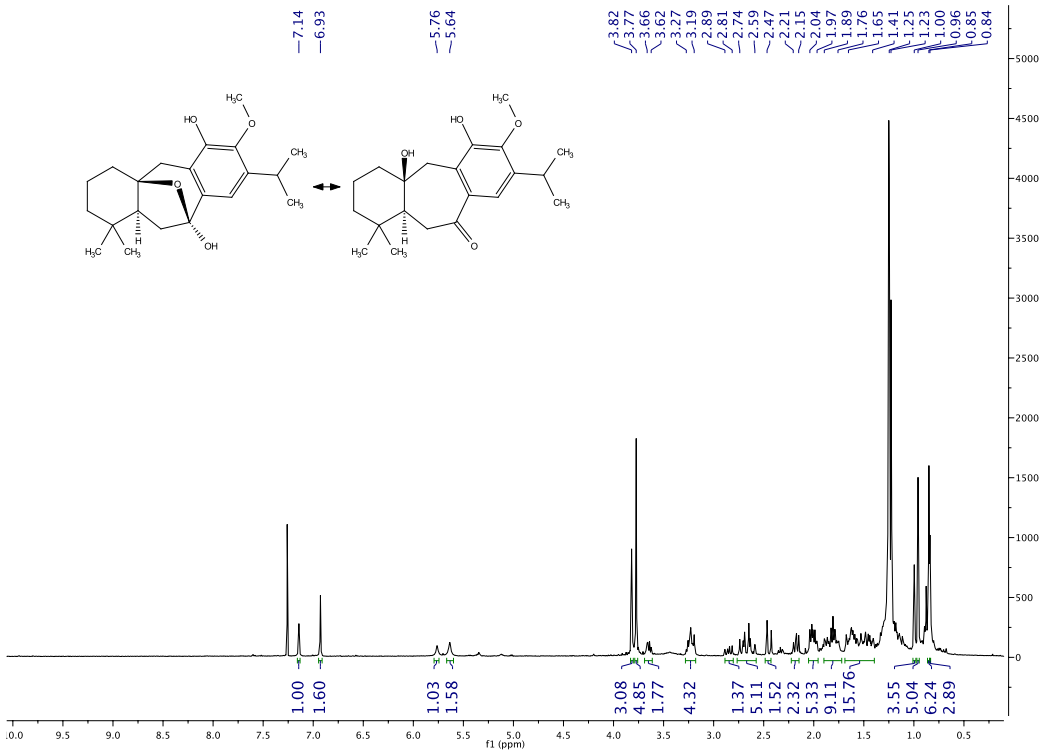
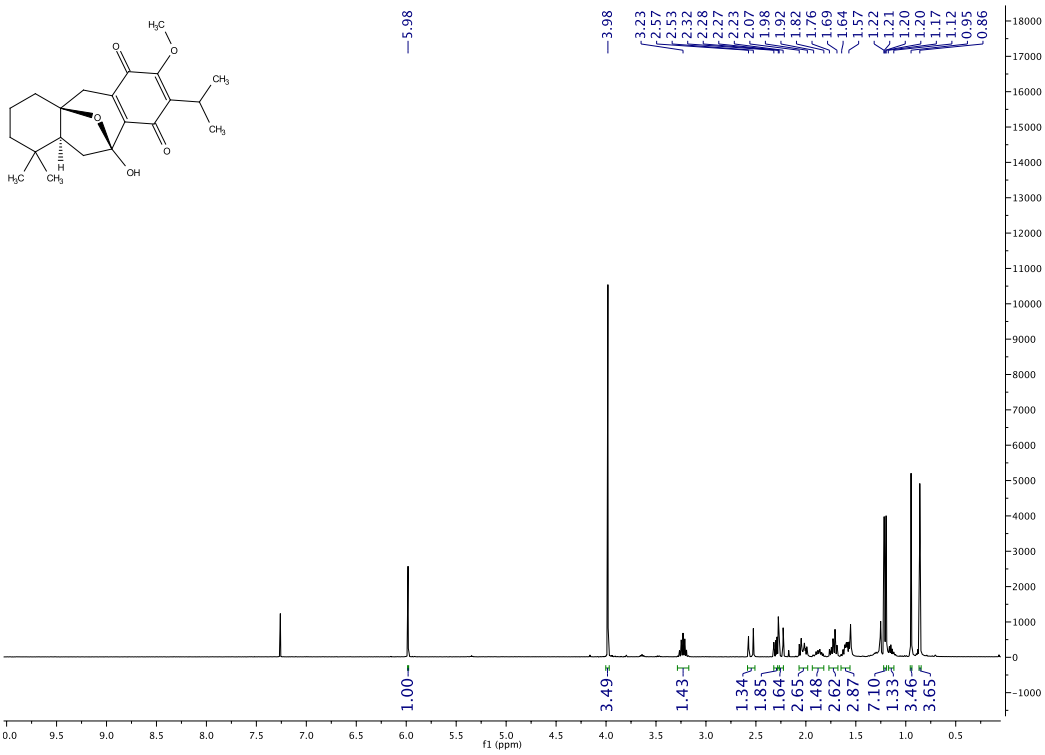
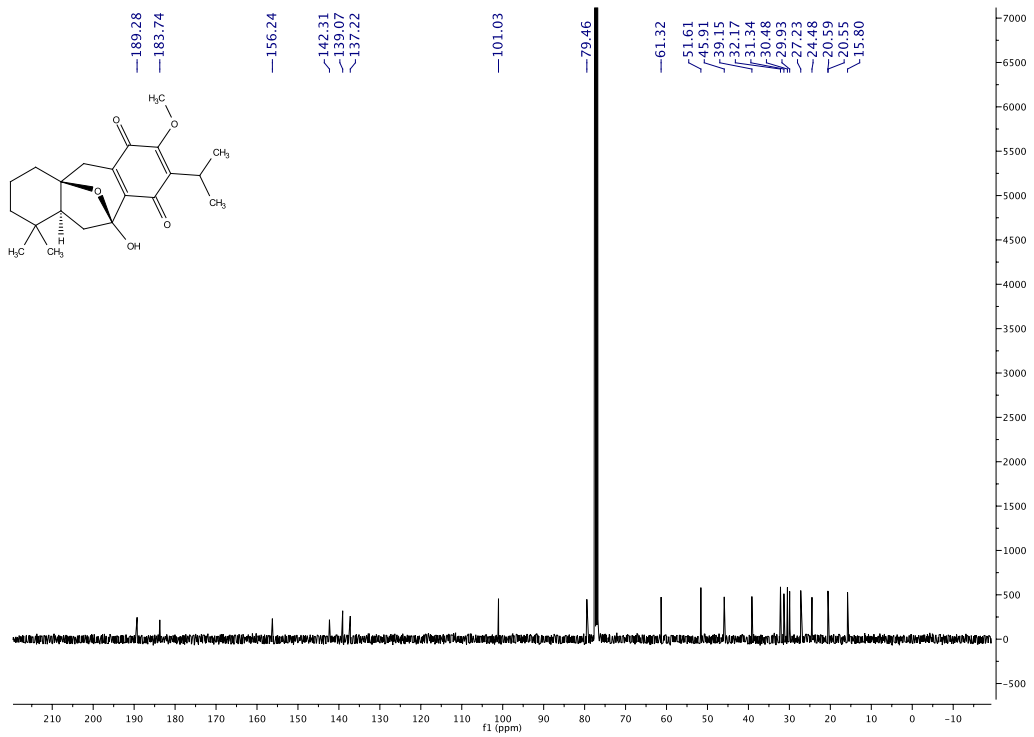
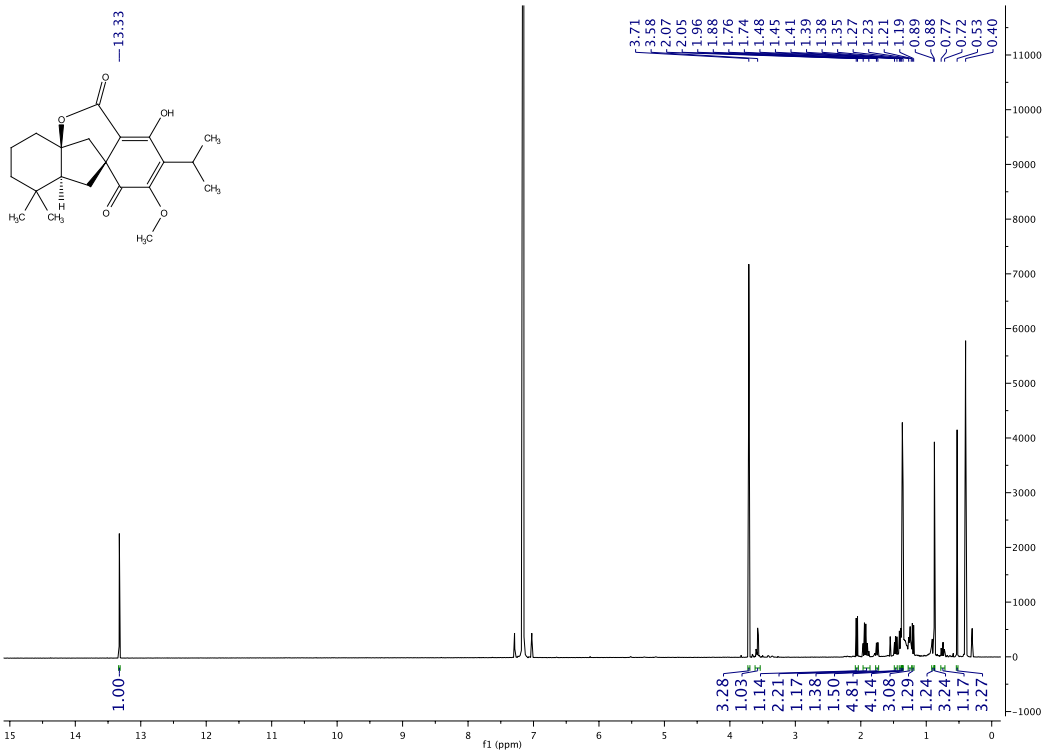
23.63
23.61
21.81
20.88
18.83
f1 (ppm)

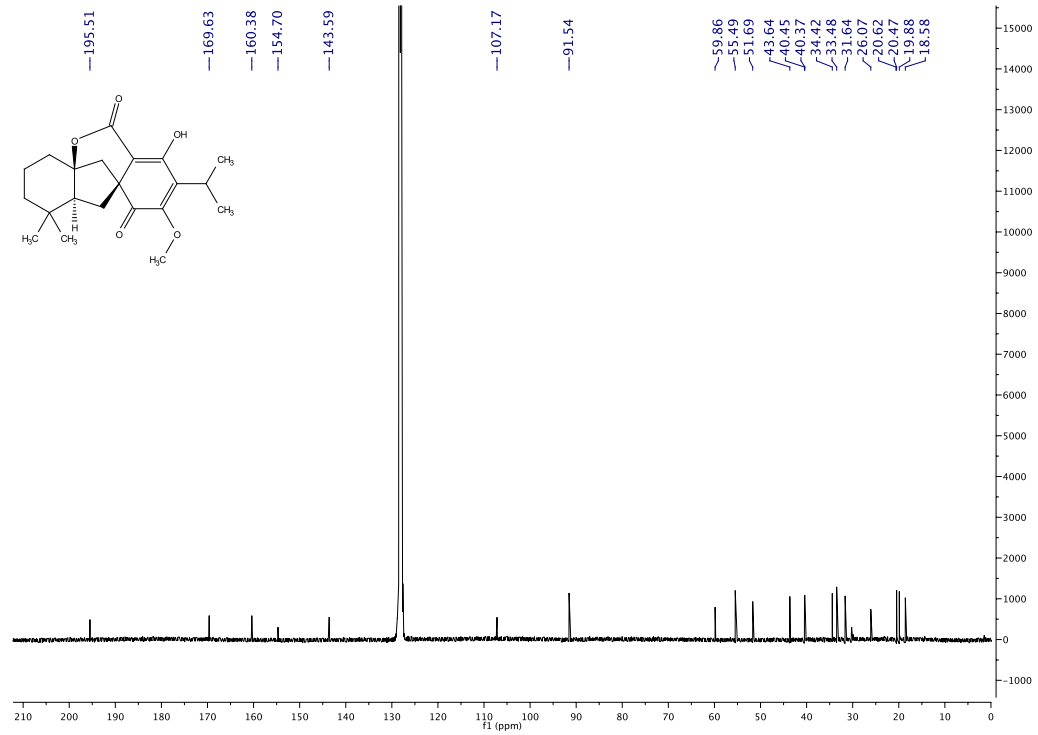

7.48
7.27
3.79
3.75
3.29
3.28
3.08
2.94
2.85
2.74
2.62
2.38
2.34
2.28
2.24
2.22
2.19
2.03
1.40
1.26
1.25
1.24
1.22
0.98
0.96
0.86
0.85
1.00
1.87
3.04
5.36
3.46
1.72
2.74
4.82
3.51
5.81
2.31
1.49
3.03
29.80
22.81
3.01
6.07
3.29
5.46
f1 (ppm)


7.14
6.93
5.76
5.64
3.82
3.77
3.66
3.62
3.27
3.19
2.89
2.81
2.74
2.59
2.47
2.21
2.15
2.04
1.97
1.89
1.76
1.65
1.41
1.25
1.23
1.00
0.96
0.85
0.84
1.00
1.60
1.03
1.58
3.08
4.85
1.77
4.32
1.37
5.11
1.52
2.32
5.33
9.11
15.76
3.55
5.04
6.24
2.89
f1 (ppm)


5.98
3.98
3.23
2.57
2.53
2.32
2.28
2.27
2.23
2.07
1.98
1.92
1.82
1.76
1.69
1.64
1.57
1.22
1.21
1.20
1.17
1.12
0.95
0.86
1.00
3.49
1.43
1.34
1.85
1.64
2.65
1.48
2.62
2.87
7.10
1.33
3.46
3.65
f1 (ppm)


189.28
183.74
156.24
142.31
139.07
137.22
101.03
79.46
61.32
51.61
45.91
39.15
32.17
31.34
30.48
29.93
27.23
24.48
20.59
20.55
15.80
f1 (ppm)


13.33
3.71
3.58
2.07
2.05
1.96
1.88
1.76
1.74
1.48
1.45
1.41
1.39
1.38
1.35
1.27
1.23
1.21
1.19
0.89
0.88
0.77
0.72
0.53
0.40
1.00
3.28
1.03
1.14
2.21
1.17
1.38
1.50
4.81
4.14
3.08
1.29
1.24
3.24
1.17
3.27
f1 (ppm)


195.51
169.63
160.38
154.70
143.59
107.17
91.54
59.86
55.49
51.69
43.64
40.45
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34.42
33.48
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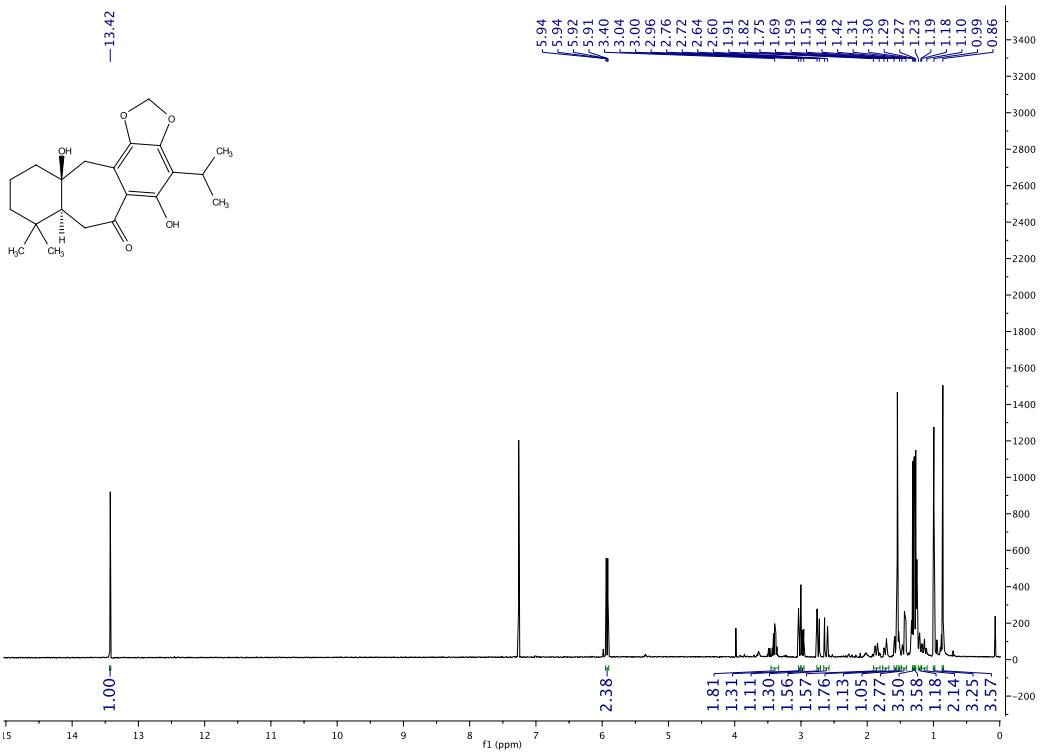
26.07
20.62
20.47
19.88
18.58
f1 (ppm)


13.42
5.94
5.94
5.92
5.91
3.40
3.04
3.00
2.96
2.76
2.72
2.64
2.60
1.91
1.82
1.75
1.69
1.59
1.51
1.48
1.42
1.31
1.30
1.29
1.27
1.23
1.19
1.18
1.10
0.99
0.86
1.00
2.38
1.81
1.31
1.11
1.30
1.56
1.57
1.76
1.13
1.05
2.77
3.50
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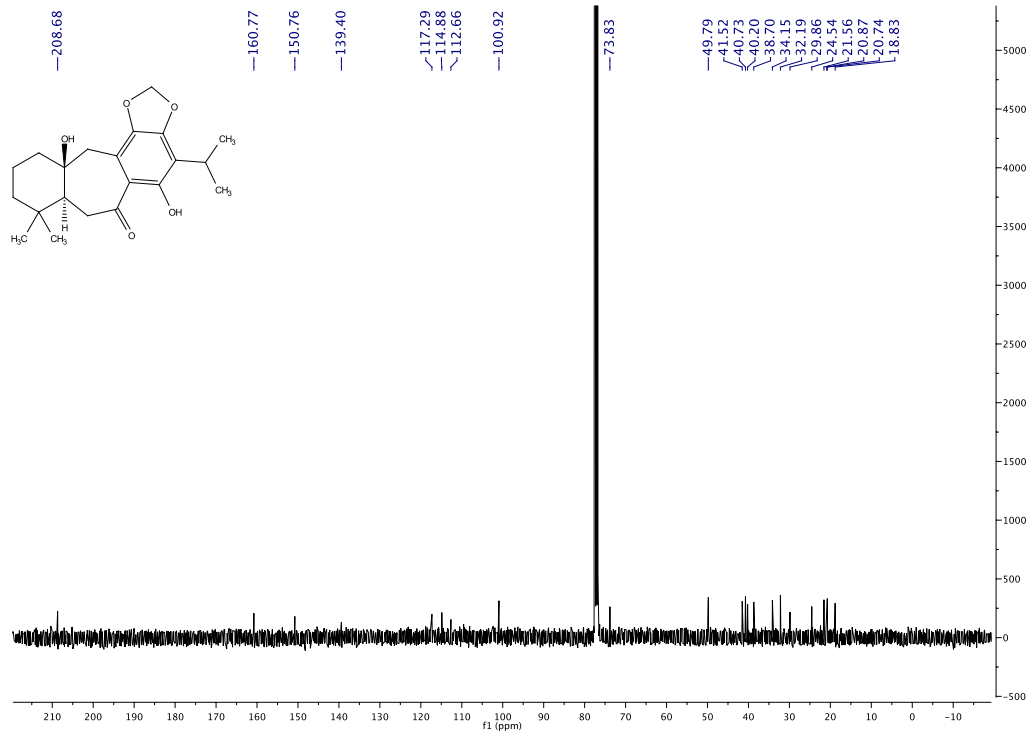
1.18
2.14
3.25
3.57
f1 (ppm)


208.68
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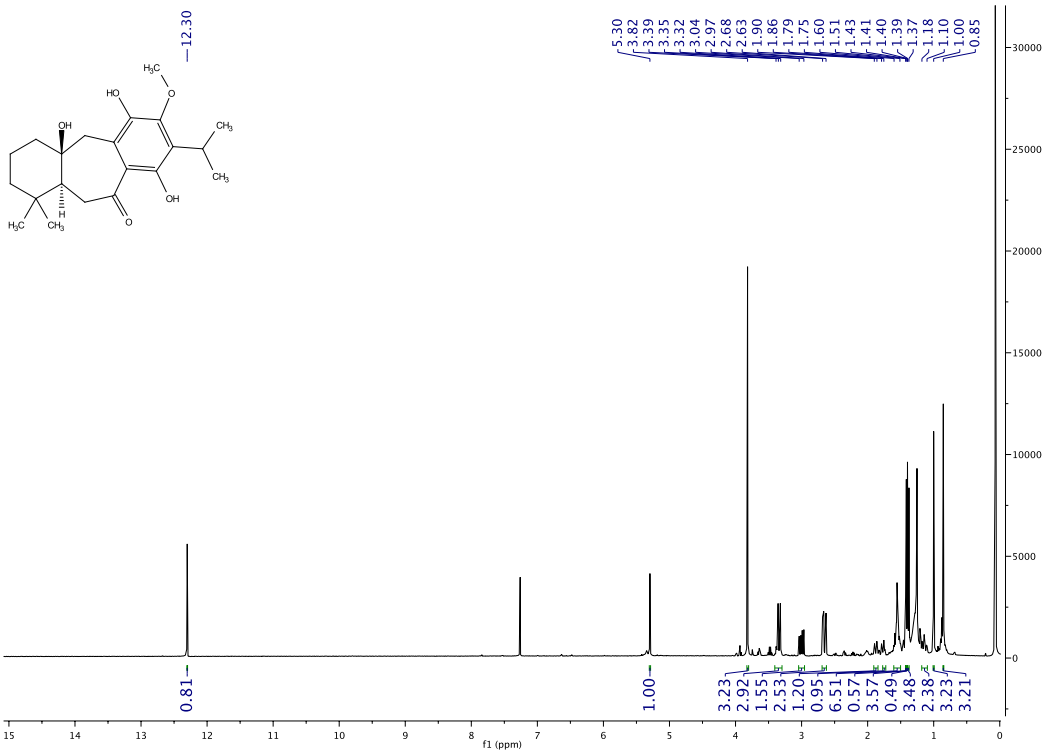
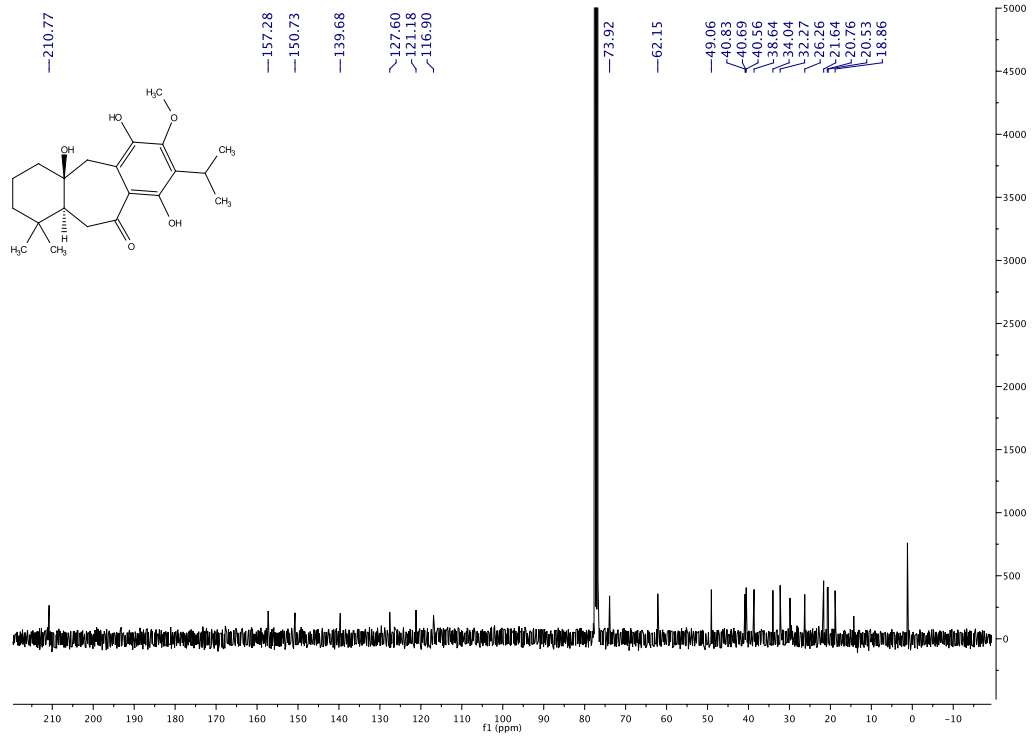
139.40
117.29
114.88
112.66
100.92
73.83
49.79
41.52
40.73
40.20
38.70
34.15
32.19
29.86
24.54
21.56
20.87
20.74
18.83
f1 (ppm)


12.30
5.30
3.82
3.39
3.35
3.32
3.04
2.97
2.68
2.63
1.90
1.86
1.79
1.75
1.60
1.51
1.43
1.41
1.40
1.39
1.37
1.18
1.10
1.00
0.85
0.81
1.00
3.23
2.92
1.55
2.53
1.20
0.95
6.51
0.57
3.57
0.49
3.48
2.38
3.23
3.21
f1 (ppm)


210.77
157.28
150.73
139.68
127.60
121.18
116.90
73.92
62.15
49.06
40.83
40.69
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34.04
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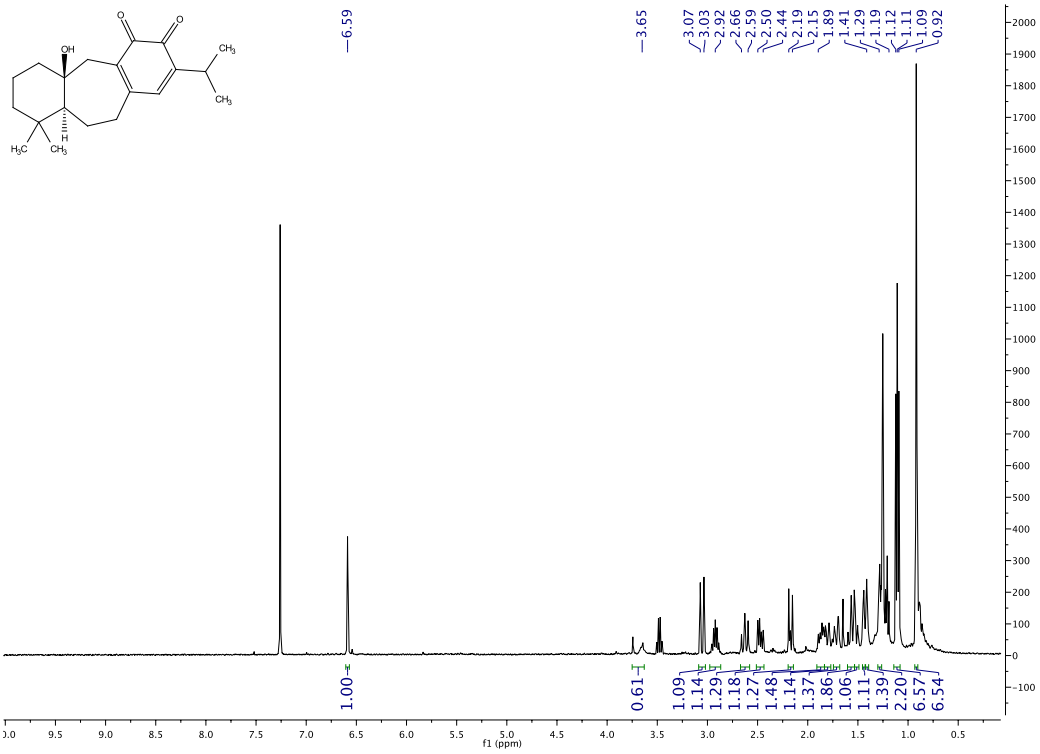
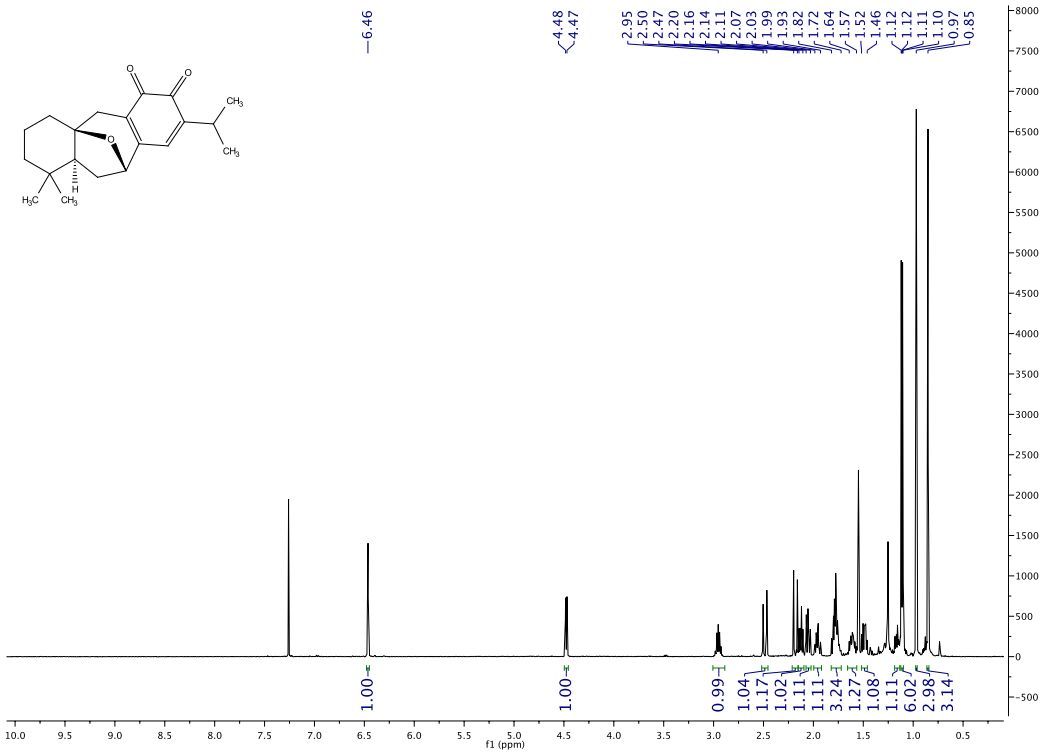
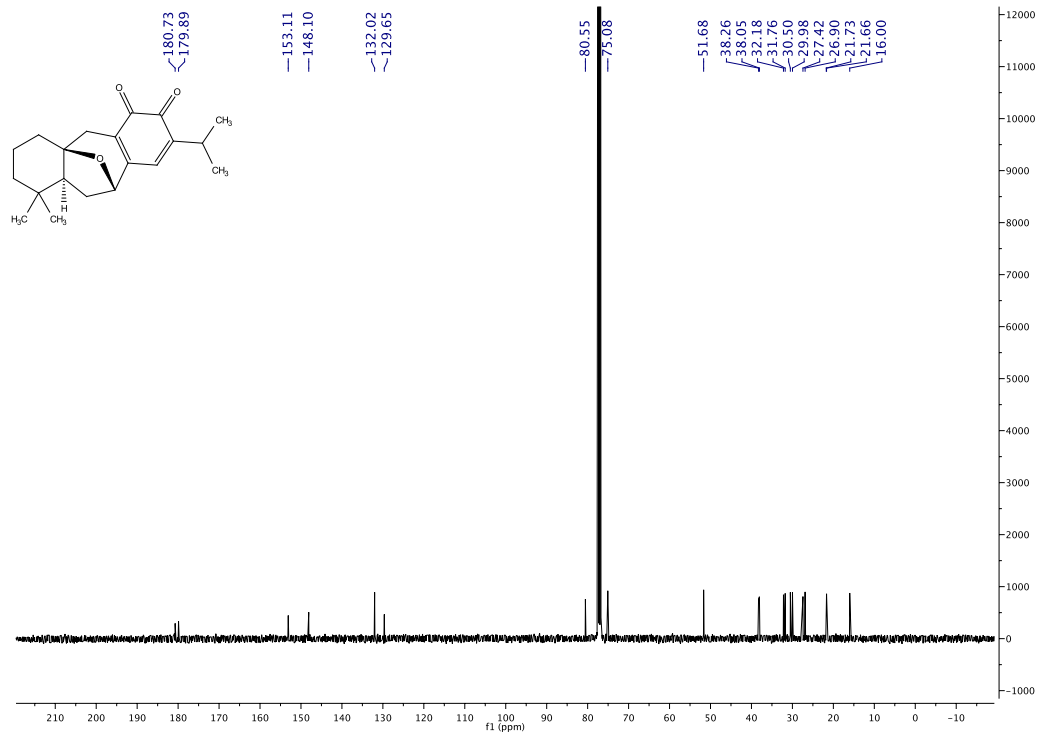
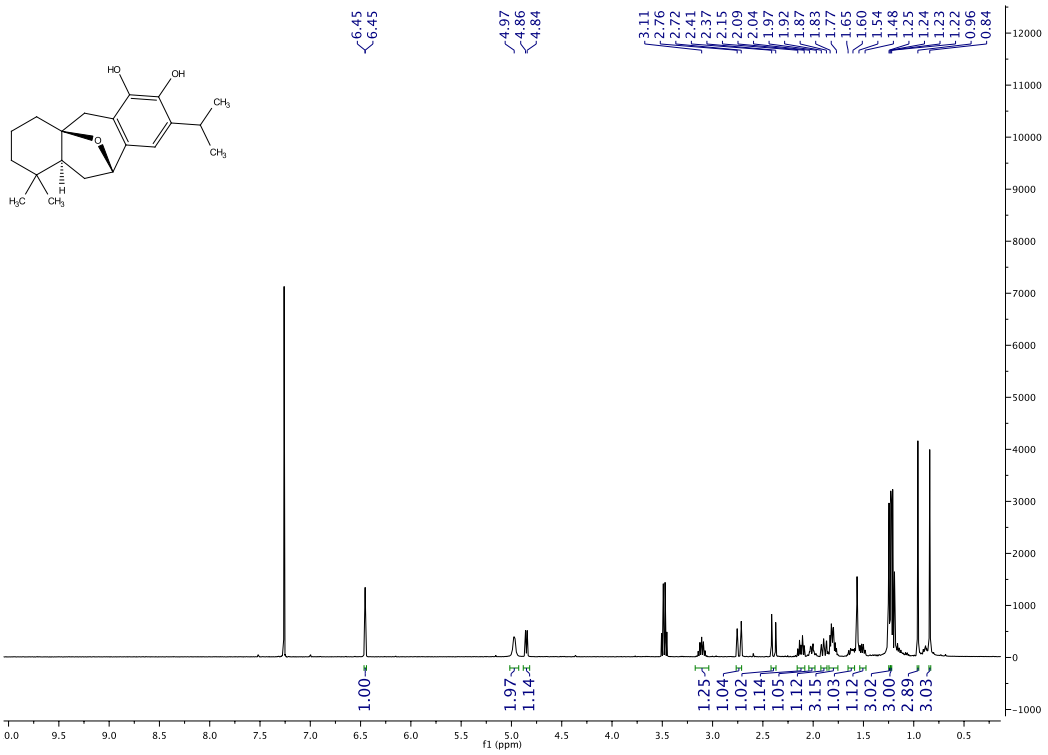
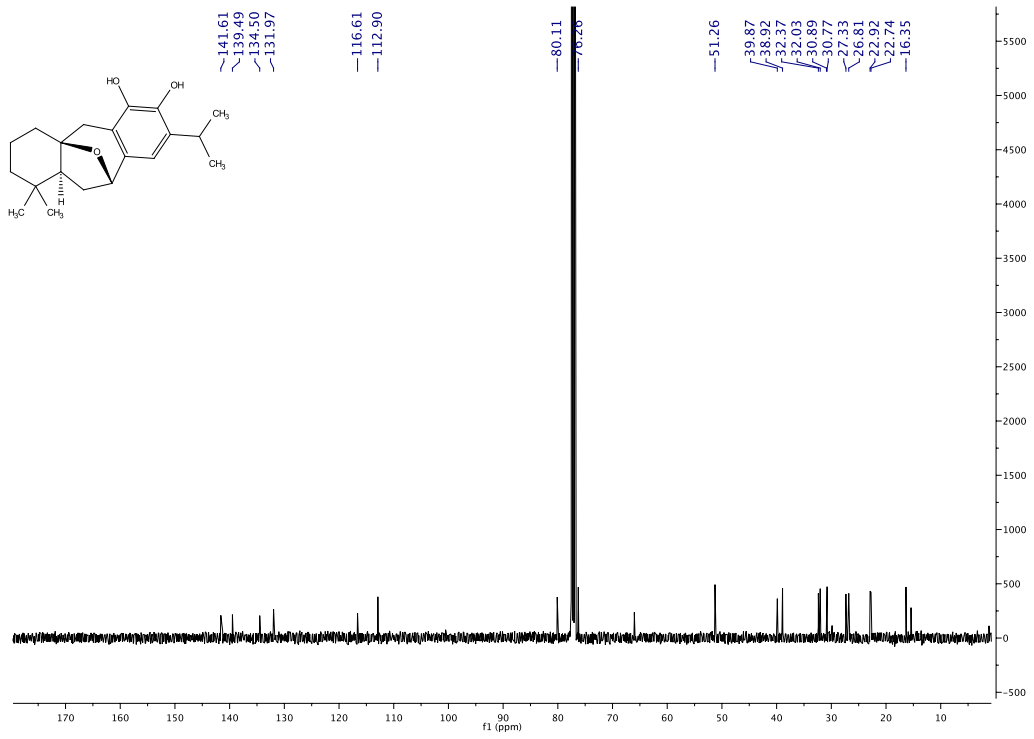
26.26
21.64
20.76
20.53
18.86
f1 (ppm)

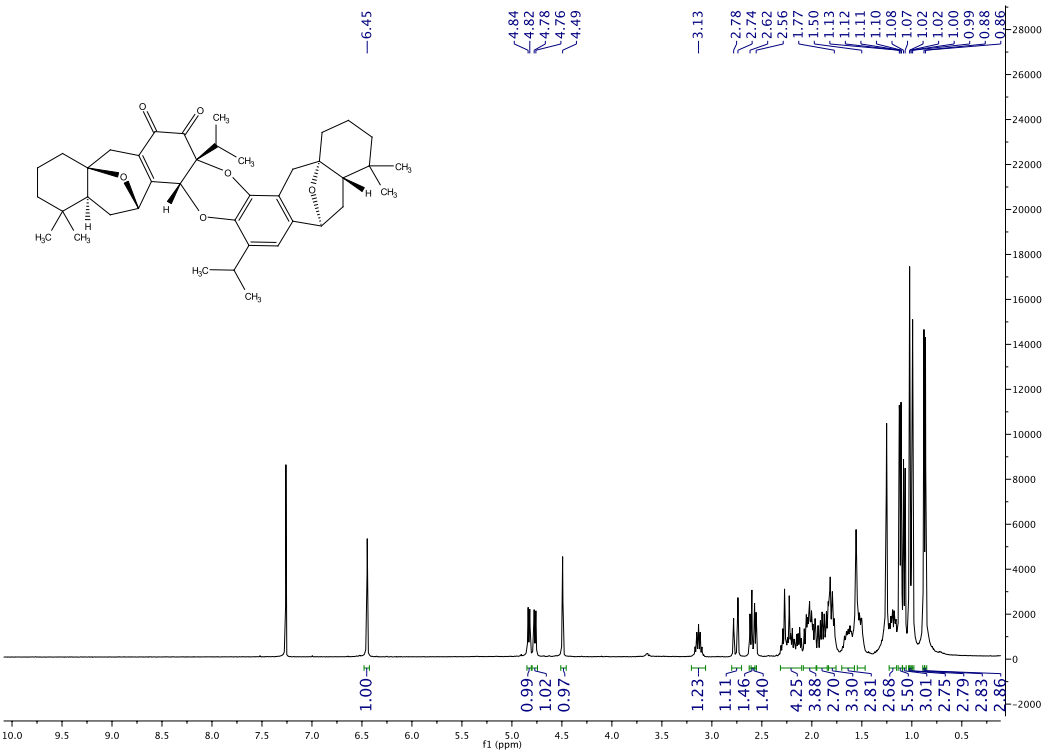

O
O
OH
CH3
CH3
H3C
CH3
H
6.59
3.65
3.07
3.03
2.92
2.66
2.59
2.50
2.44
2.19
2.15
1.89
1.41
1.29
1.19
1.12
1.11
1.09
0.92
1.00
0.61
1.09
1.14
1.29
1.18
1.27
1.48
1.14
1.37
1.86
1.06
1.11
1.39
2.20
6.57
6.54
f1 (ppm)

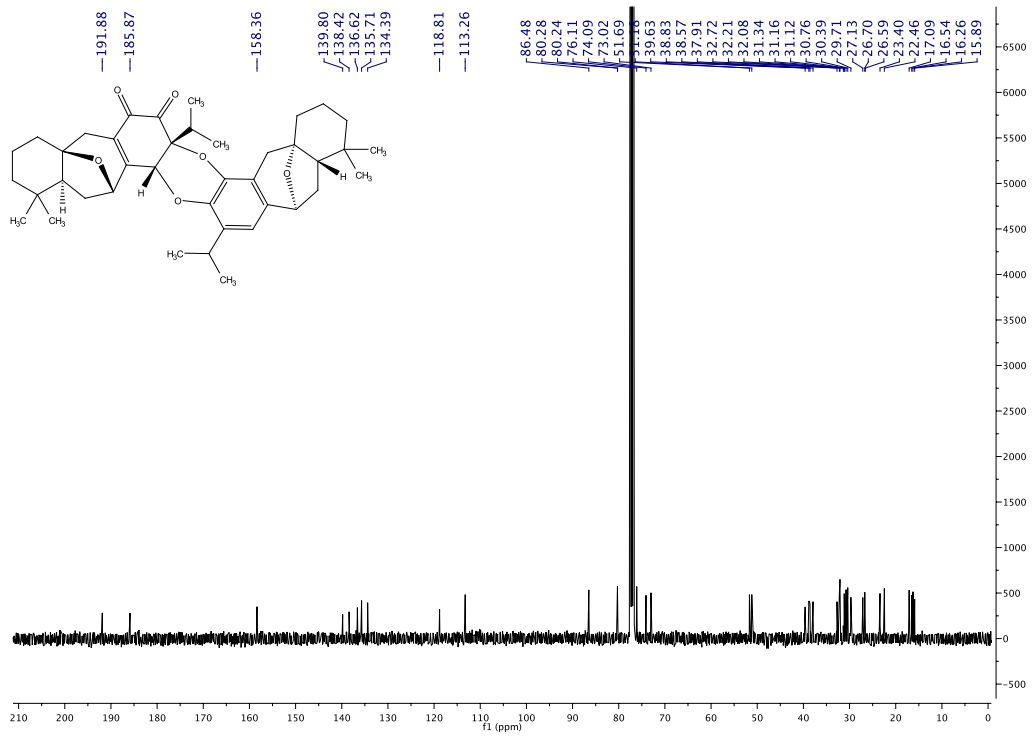

6.46
4.48
4.47
2.95
2.50
2.47
2.20
2.16
2.14
2.11
2.07
2.03
1.99
1.93
1.82
1.72
1.64
1.57
1.52
1.46
1.12
1.12
1.11
1.10
0.97
0.85
1.00
1.00
0.99
1.04
1.17
1.02
1.11
1.11
3.24
1.27
1.08
1.11
6.02
2.98
3.14
f1 (ppm)

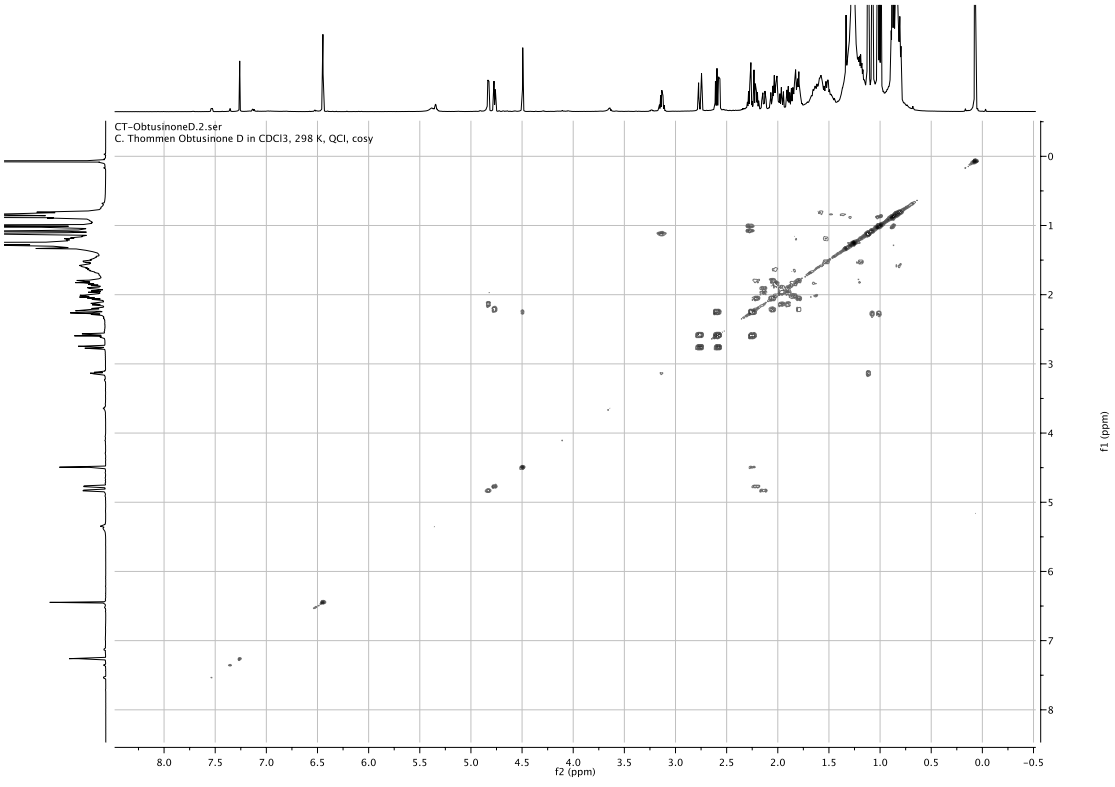

180.73
179.89
153.11
148.10
132.02
129.65
80.55
75.08
51.68
38.26
38.05
32.18
31.76
30.50
29.98
27.42
26.90
21.73
21.66
16.00
f1 (ppm)

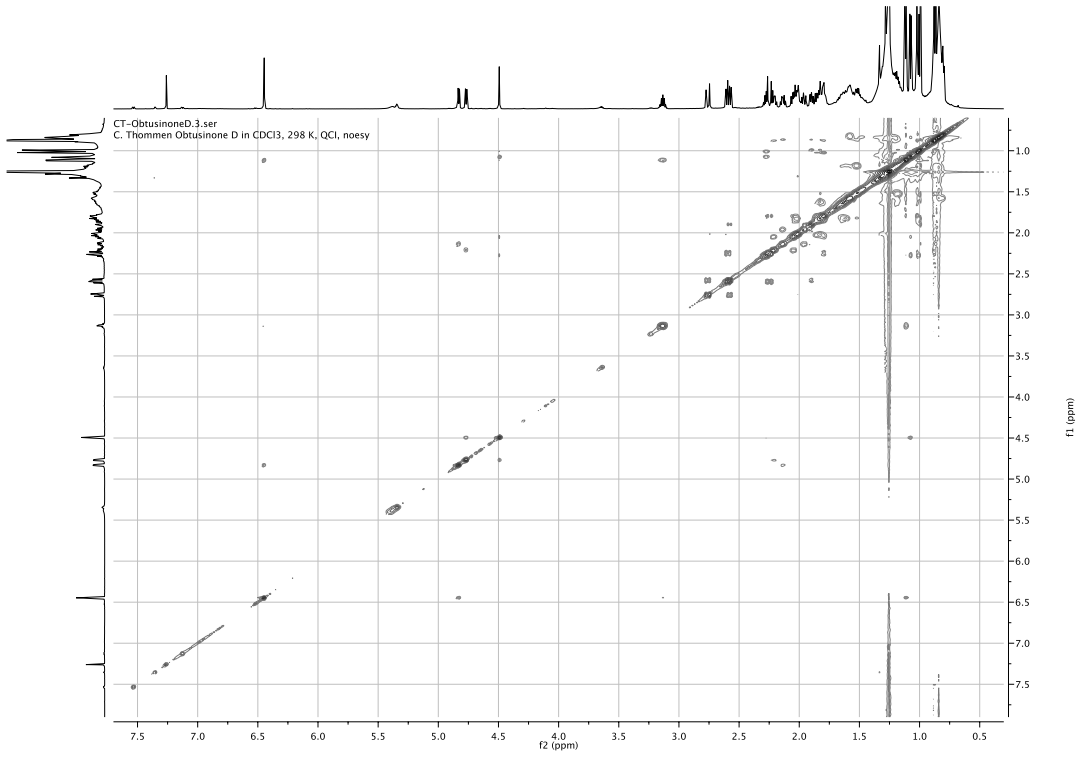

HO
OH
CH3
CH3
O
H
H3C
CH3
6.45
6.45
4.97
4.86
4.84
3.11
2.76
2.72
2.41
2.37
2.15
2.09
2.04
1.97
1.92
1.87
1.83
1.77
1.65
1.60
1.54
1.48
1.25
1.24
1.23
1.22
0.96
0.84
1.00
1.97
1.14
1.25
1.04
1.02
1.14
1.05
1.12
3.15
1.03
1.12
3.02
3.00
2.89
3.03
f1 (ppm)

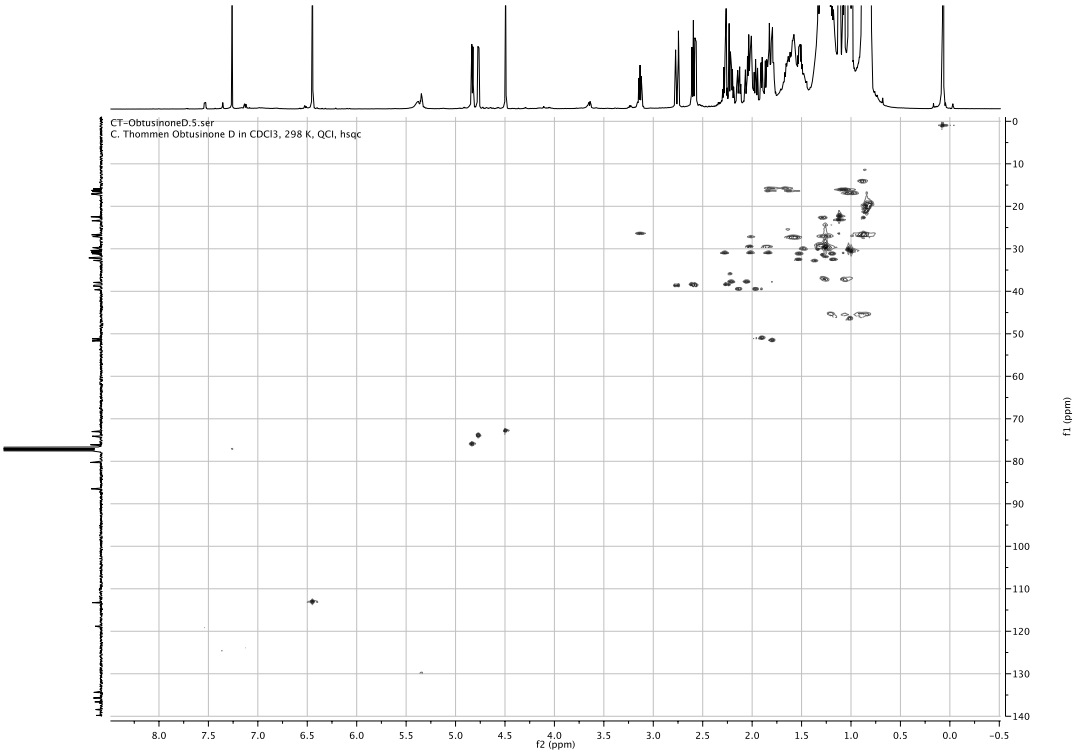

HO
OH
CH3
CH3
O
H
H3C
CH3
141.61
139.49
134.50
131.97
116.61
112.90
80.11
78.26
51.26
39.87
38.92
32.37
32.03
30.89
30.77
27.33
26.81
22.92
22.74
16.35
f1 (ppm)

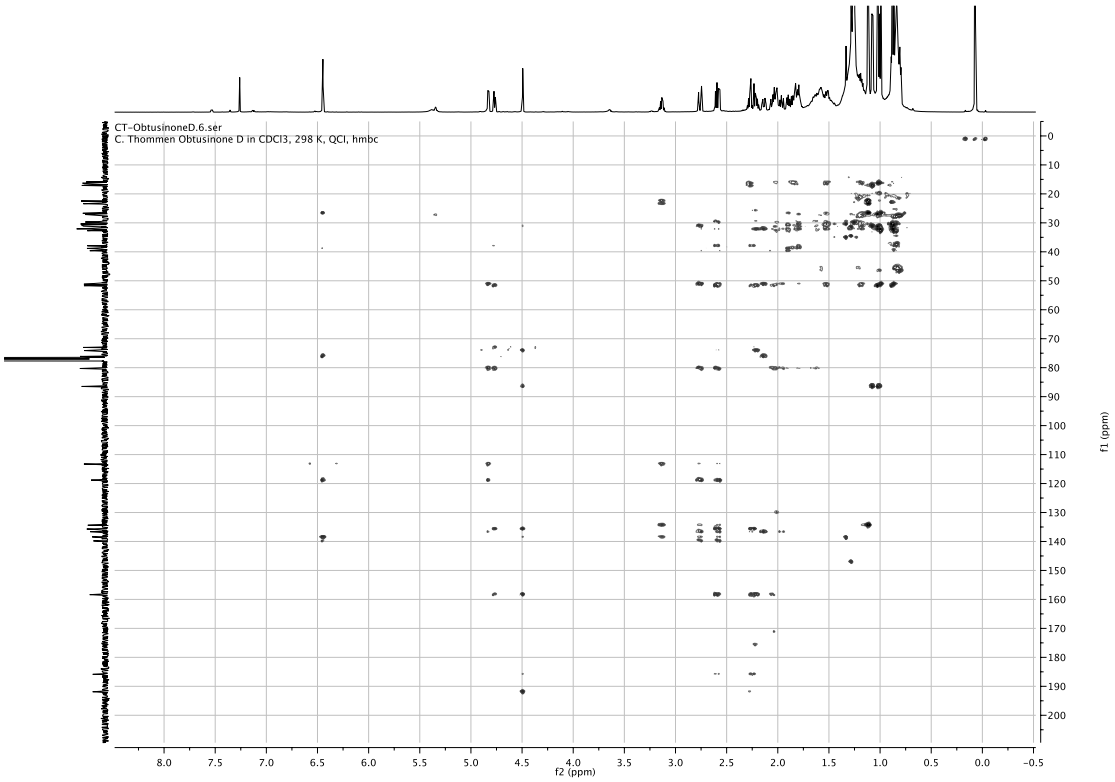

6.45
4.84
4.82
4.78
4.76
4.49
3.13
2.78
2.74
2.62
2.56
1.77
1.50
1.13
1.12
1.11
1.10
1.08
1.07
1.02
1.02
1.00
0.99
0.88
0.86
1.00
0.99
1.02
0.97
1.23
1.11
1.46
1.40
4.25
3.88
2.70
3.30
2.81
2.68
5.50
3.01
2.75
2.79
2.83
2.86
f1 (ppm)

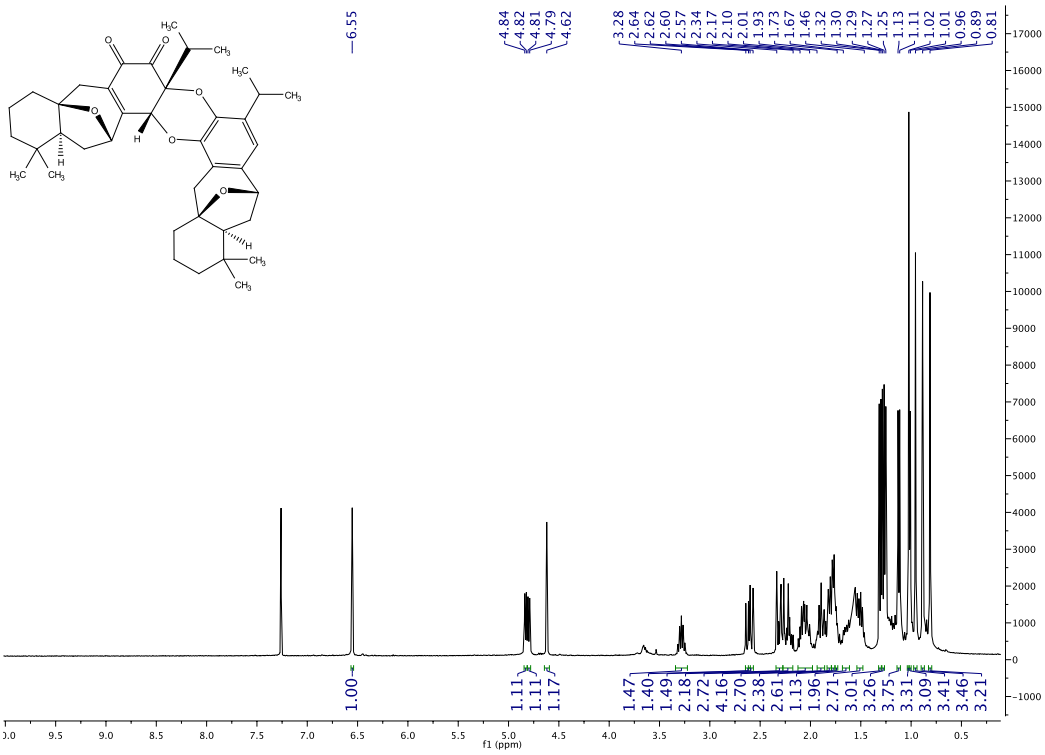

191.88
185.87
158.36
139.80
138.42
136.62
135.71
134.39
118.81
113.26
86.48
80.28
80.24
76.11
74.09
73.02
51.69
51.16
39.63
38.83
38.57
37.91
32.72
32.21
32.08
31.34
31.16
31.12
30.76
30.39
29.71
27.13
26.70
26.59
23.40
22.46
17.09
16.54
16.26
15.89
f1 (ppm)

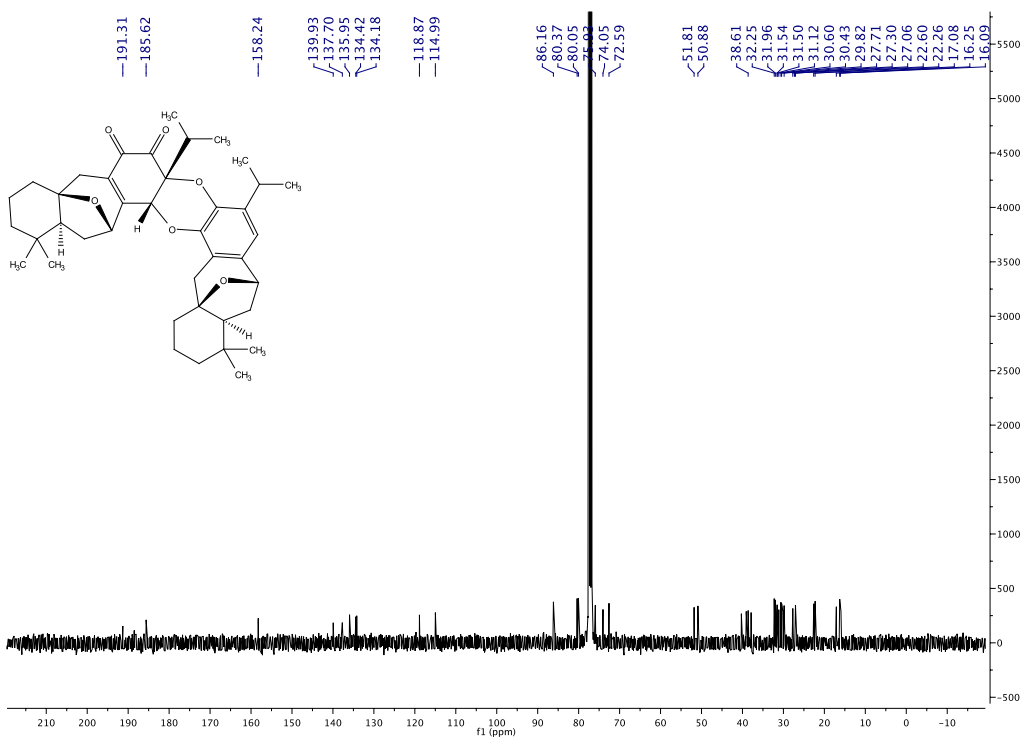

CT-ObtusinoneD.2.ser
C. Thommen Obtusinone D in CDCl3, 298 K, QCI, cosy
f2 (ppm)
f1 (ppm)

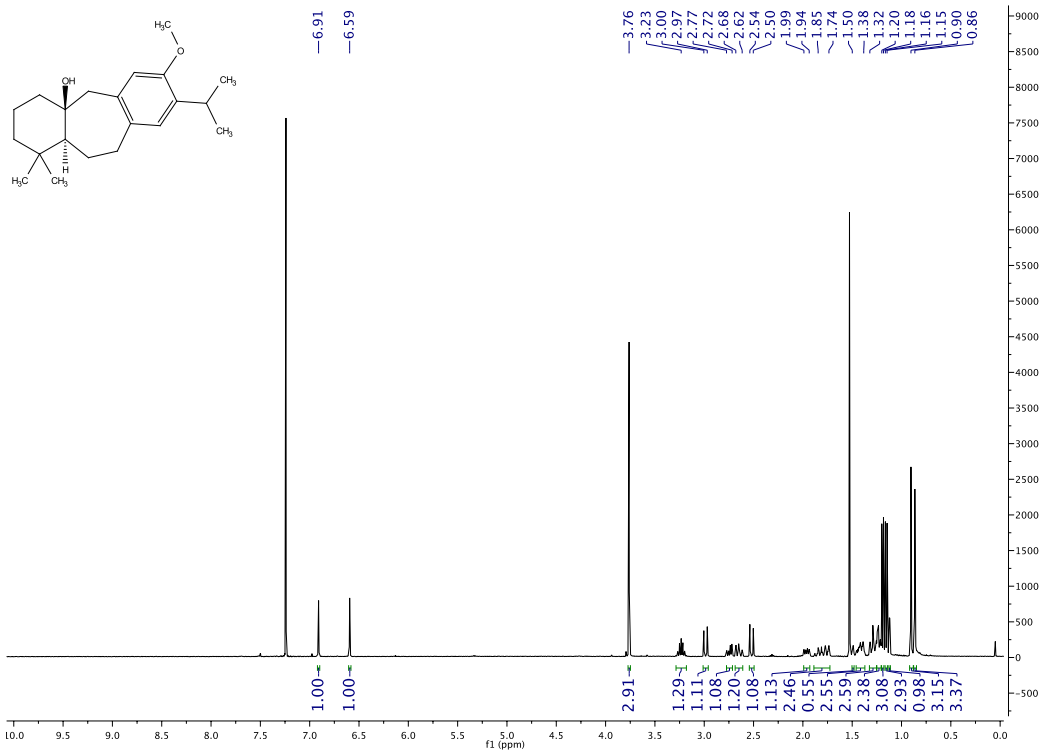

CT-ObtusinoneD.3.ser
C. Thommen Obtusinone D in CDCl3, 298 K, QCI, noesy
f2 (ppm)
f1 (ppm)

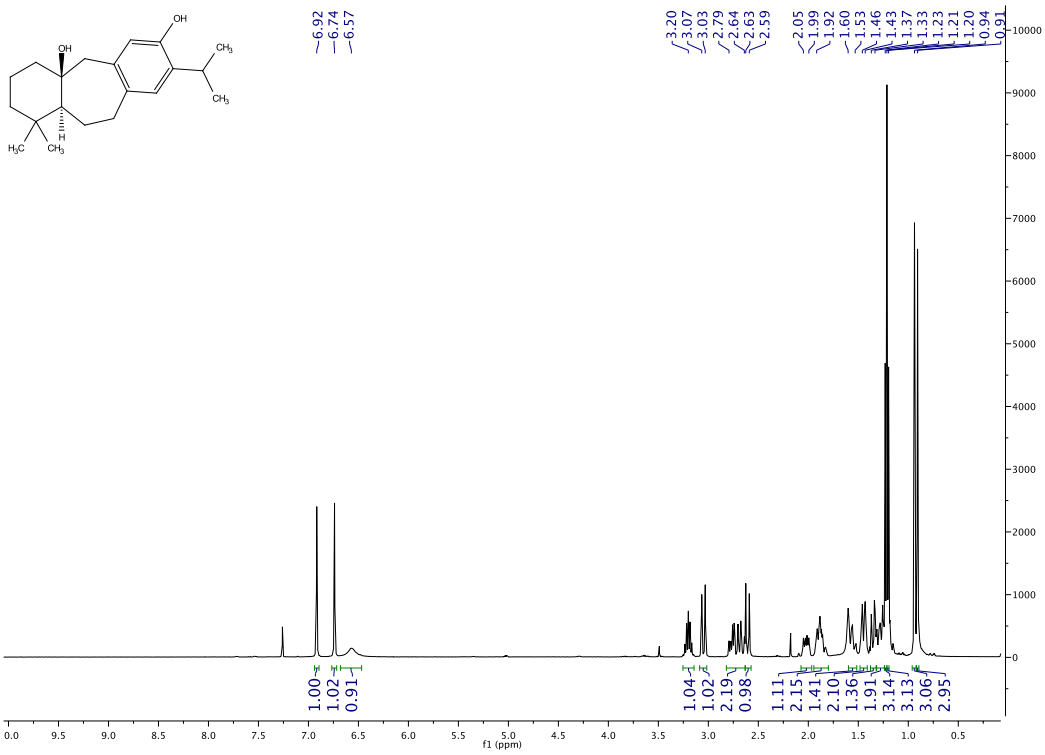

CT-ObtusinoneD.5.ser
C. Thommen Obtusinone D in CDCl3, 298 K, QCI, hsqc
f2 (ppm)
f1 (ppm)

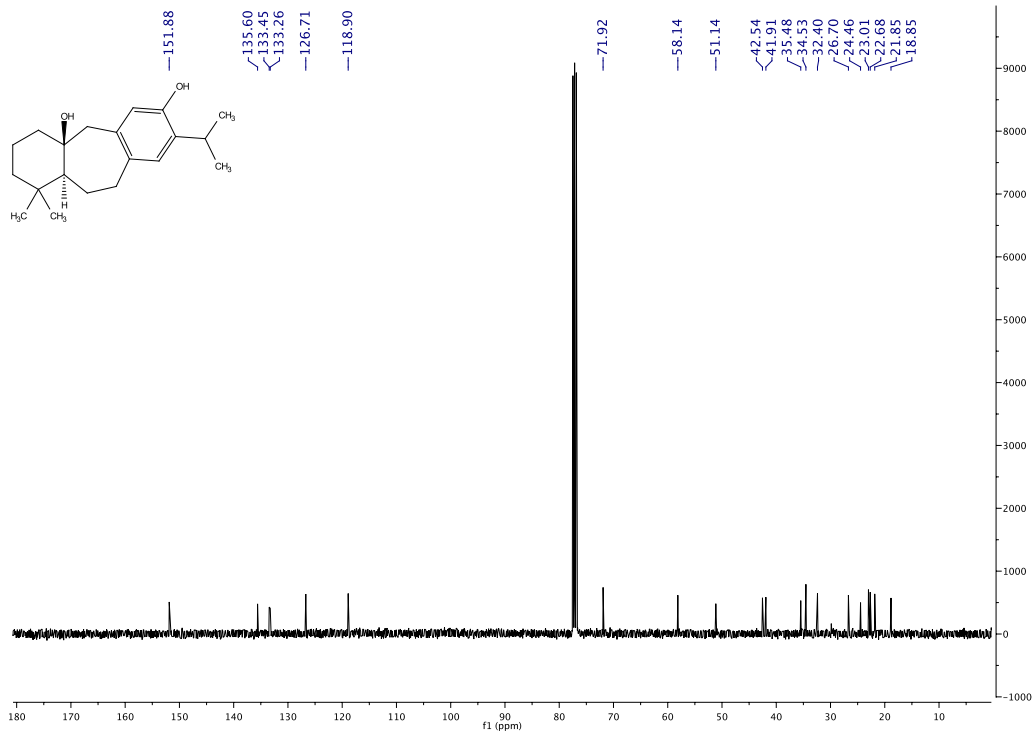

CT-ObtusinoneD.6.ser
C. Thommen Obtusinone D in CDCl3, 298 K, QCI, hmbc
f2 (ppm)
f1 (ppm)

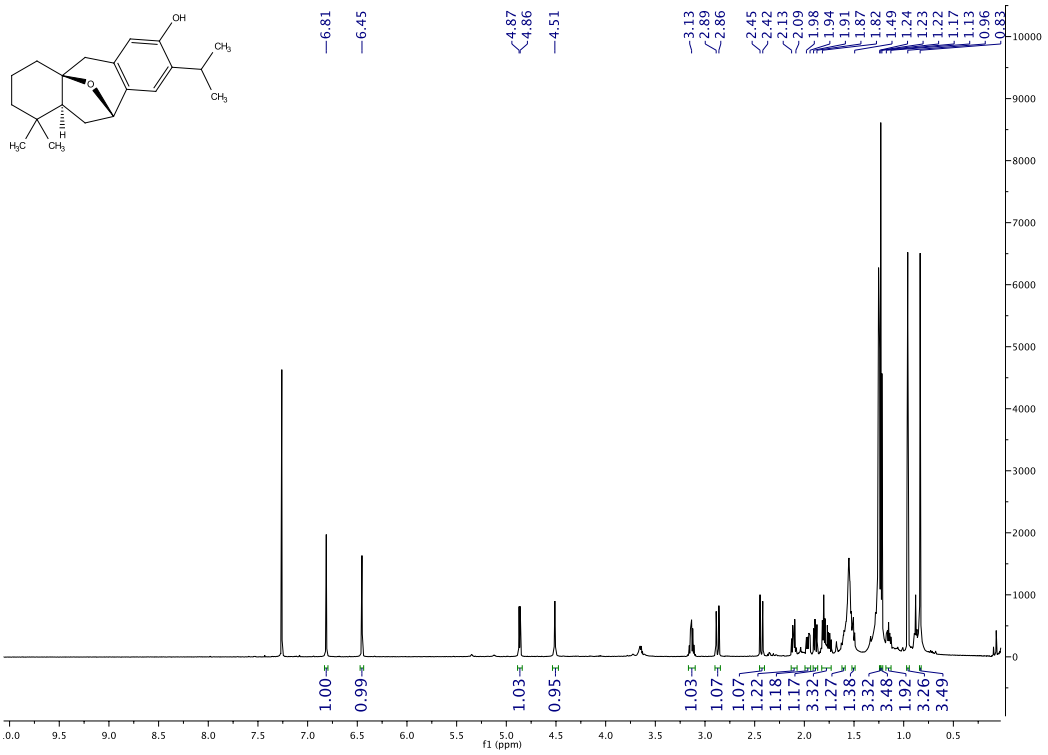

6.55
4.84
4.82
4.81
4.79
4.62
3.28
2.64
2.62
2.60
2.57
2.34
2.17
2.10
2.01
1.93
1.73
1.67
1.46
1.32
1.30
1.29
1.27
1.25
1.13
1.11
1.02
1.01
0.96
0.89
0.81
1.00
1.11
1.11
1.17
1.47
1.40
1.49
2.18
2.72
4.16
2.70
2.38
2.61
1.13
1.96
2.71
3.01
3.26
3.75
3.31
3.09
3.41
3.46
3.21
f1 (ppm)

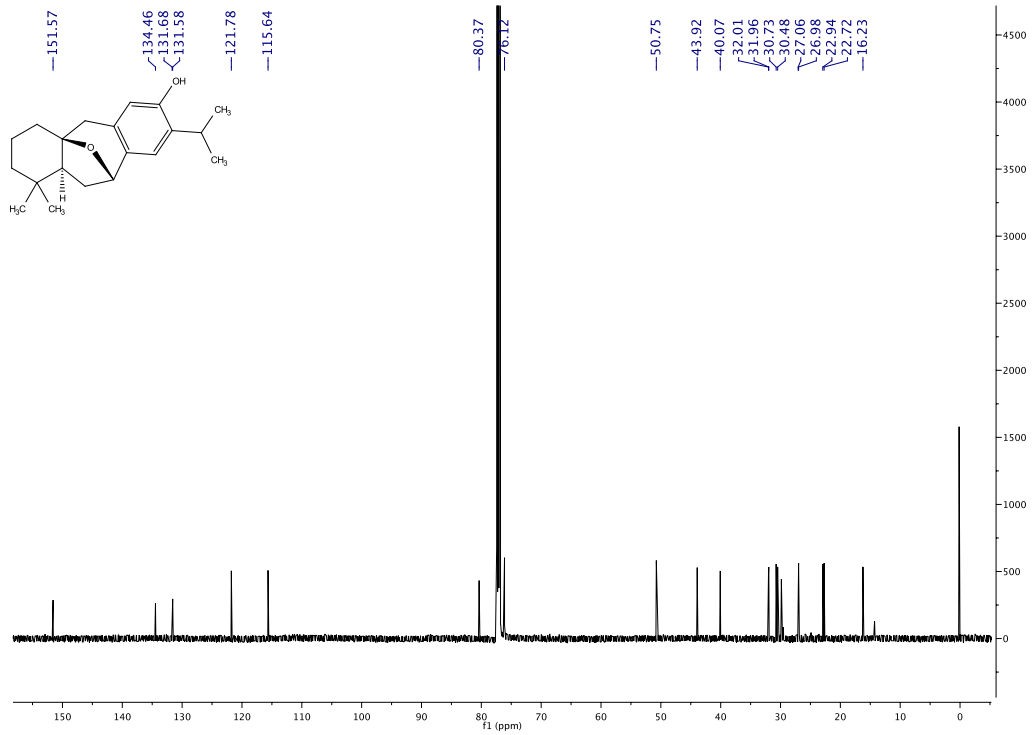

191.31
185.62
158.24
139.93
137.70
135.95
134.42
134.18
118.87
114.99
86.16
80.37
80.05
75.03
74.05
72.59
51.81
50.88
38.61
32.25
31.96
31.54
31.50
31.12
30.60
30.43
29.82
27.71
27.30
27.06
22.60
22.26
17.08
16.25
16.09
f1 (ppm)

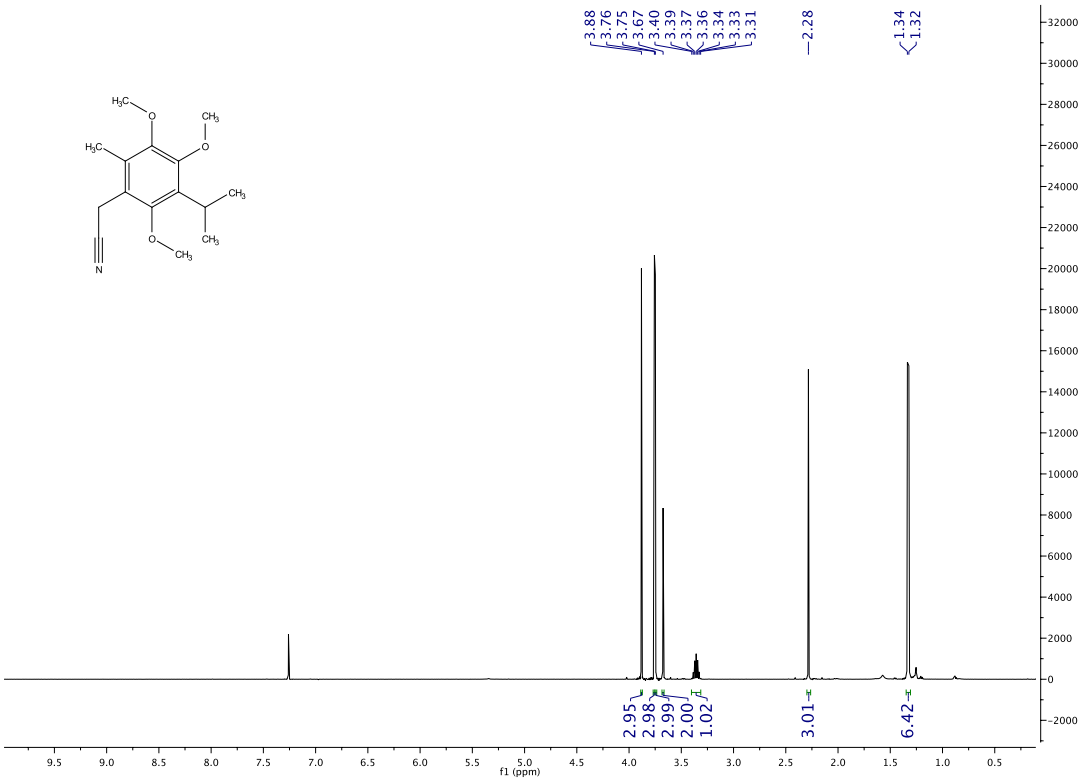

6.91
6.59
3.76
3.23
3.00
2.97
2.77
2.72
2.68
2.62
2.54
2.50
1.99
1.94
1.85
1.74
1.50
1.38
1.32
1.20
1.18
1.16
1.15
0.90
0.86
1.00
1.00
2.91
1.29
1.11
1.08
1.20
1.08
1.13
2.46
0.55
2.55
2.59
2.38
3.08
2.93
0.98
3.15
3.37
f1 (ppm)

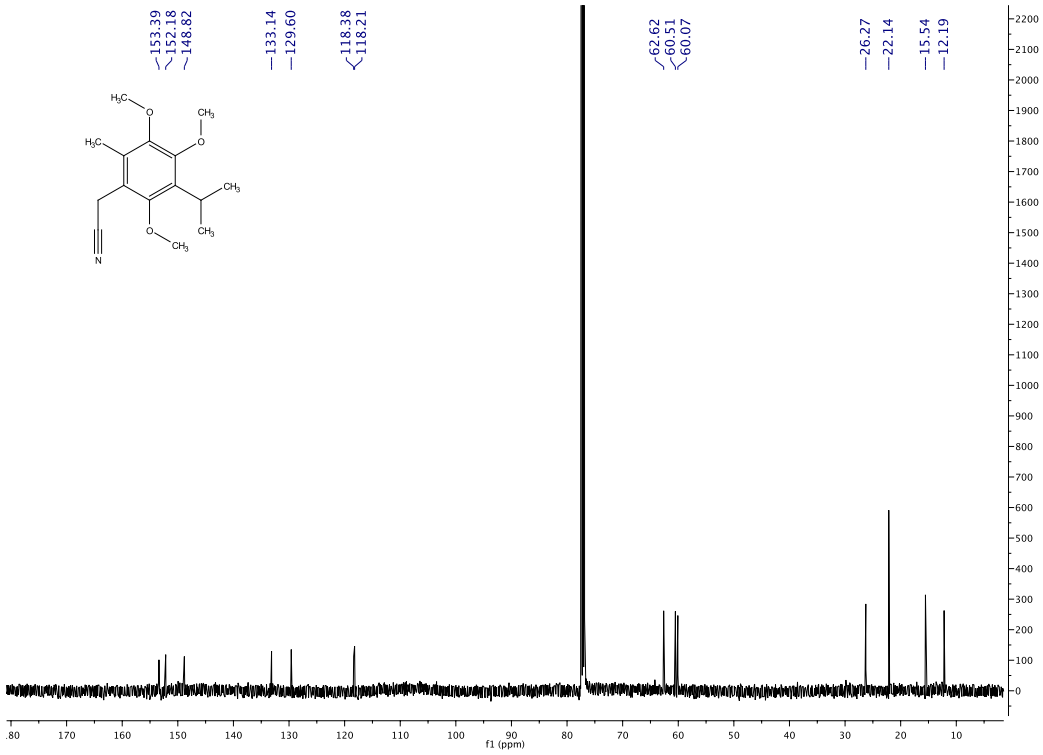

OH
OH
CH3
CH3
H3C
CH3
H
6.92
6.74
6.57
3.20
3.07
3.03
2.79
2.64
2.63
2.59
2.05
1.99
1.92
1.60
1.53
1.46
1.43
1.37
1.33
1.23
1.21
1.20
0.94
0.91
1.00
1.02
0.91
1.04
1.02
2.19
0.98
1.11
2.15
1.41
2.10
1.36
1.91
3.14
3.13
3.06
2.95
f1 (ppm)

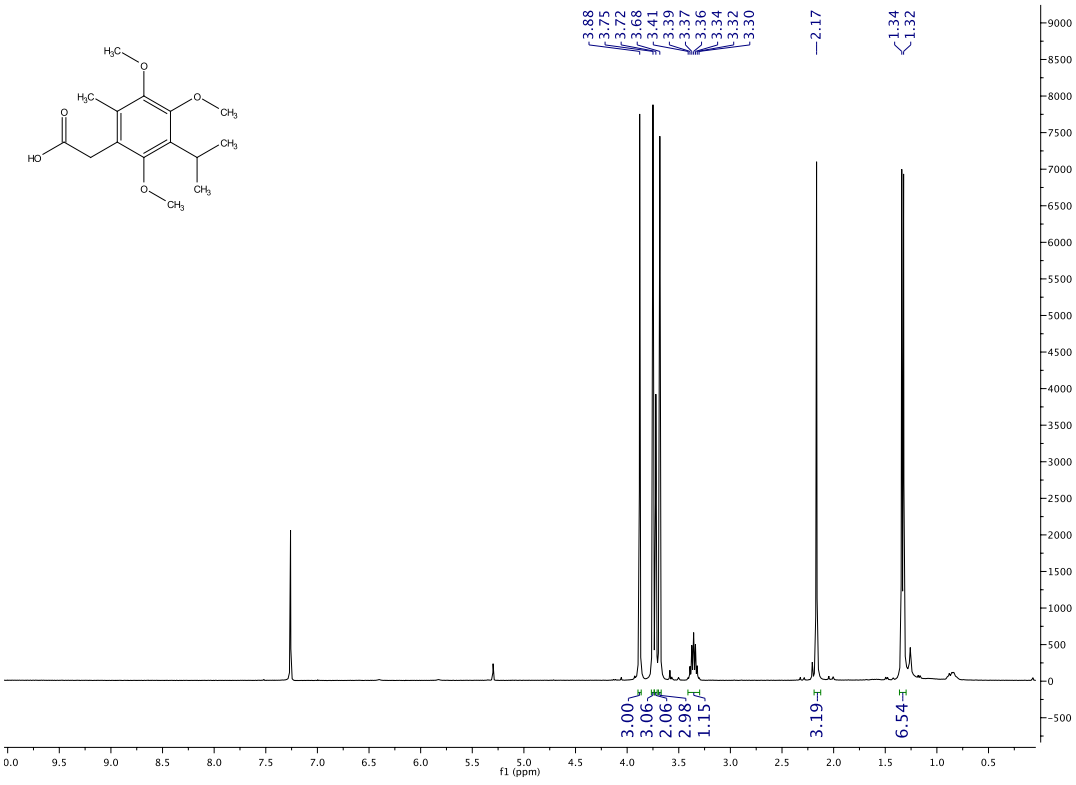

OH
OH
CH3
CH3
H3C
CH3
H
151.88
135.60
133.45
133.26
126.71
118.90
71.92
58.14
51.14
42.54
41.91
35.48
34.53
32.40
26.70
24.46
23.01
22.68
21.85
18.85
f1 (ppm)

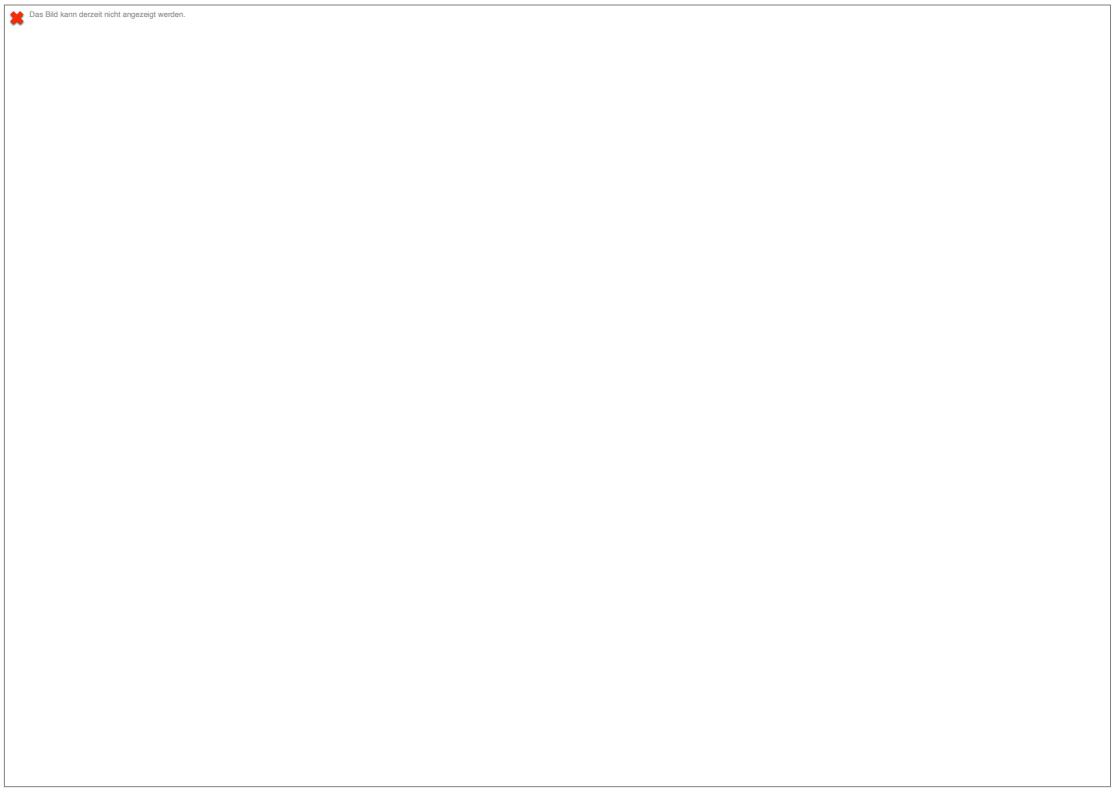

OH
CH3
CH3
O
H
H3C
CH3
6.81
6.45
4.87
4.86
4.51
3.13
2.89
2.86
2.45
2.42
2.13
2.09
1.98
1.94
1.91
1.87
1.82
1.49
1.24
1.23
1.22
1.17
1.13
0.96
0.83
1.00
0.99
1.03
0.95
1.03
1.07
1.07
1.22
1.18
1.17
3.32
1.27
1.38
3.32
3.48
1.92
3.26
3.49
f1 (ppm)

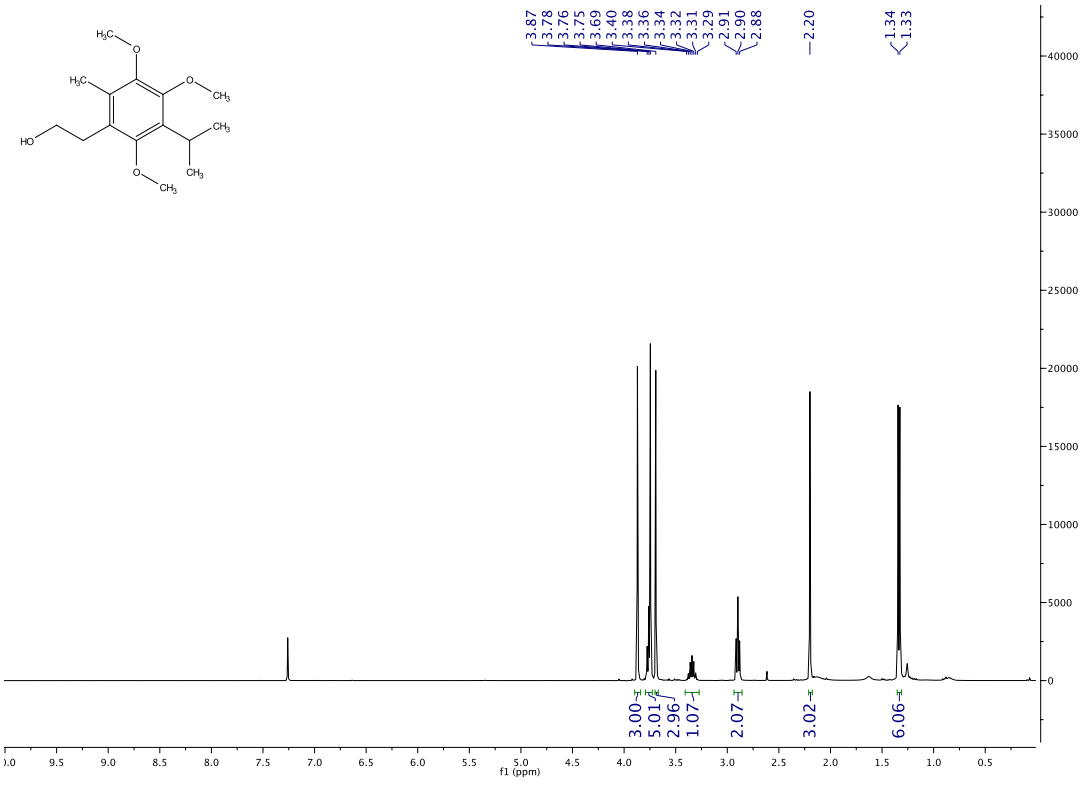

OH
CH3
CH3
O
H
H3C
CH3
151.57
134.46
131.68
131.58
121.78
115.64
80.37
76.12
50.75
43.92
40.07
32.01
31.96
30.73
30.48
27.06
26.98
22.94
22.72
16.23
f1 (ppm)

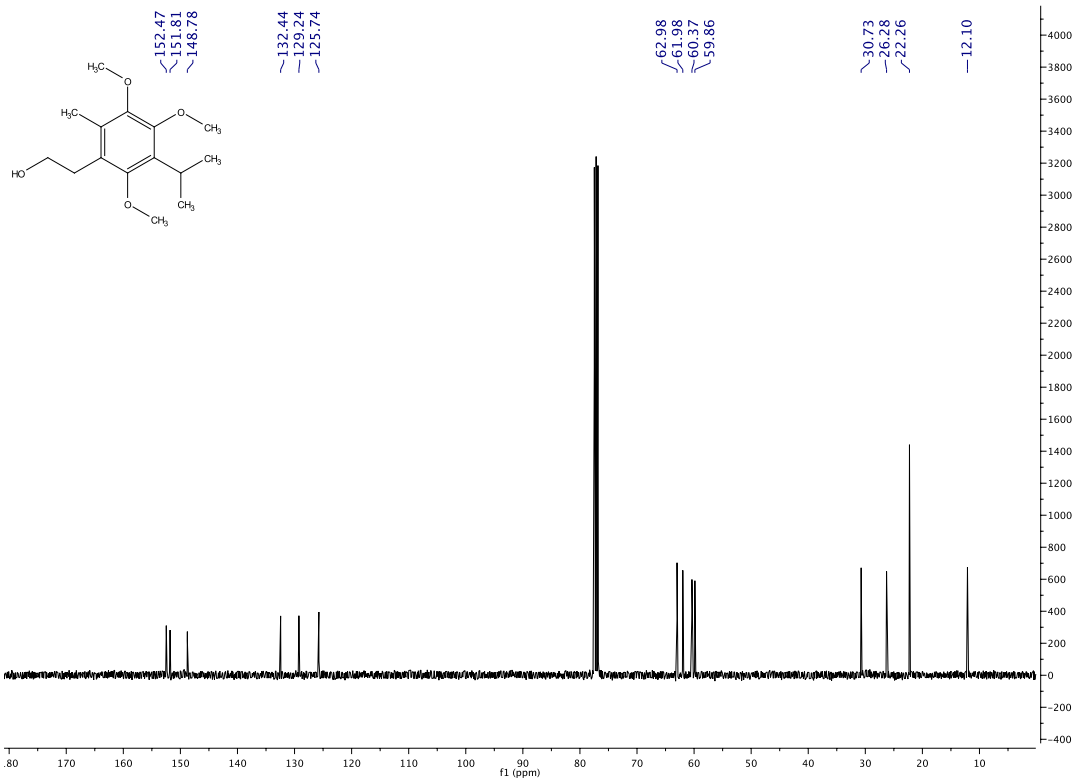

3.88
3.76
3.75
3.67
3.40
3.39
3.37
3.36
3.34
3.33
3.31
2.28
1.34
1.32
2.95
2.98
2.99
2.00
1.02
3.01
6.42
f1 (ppm)

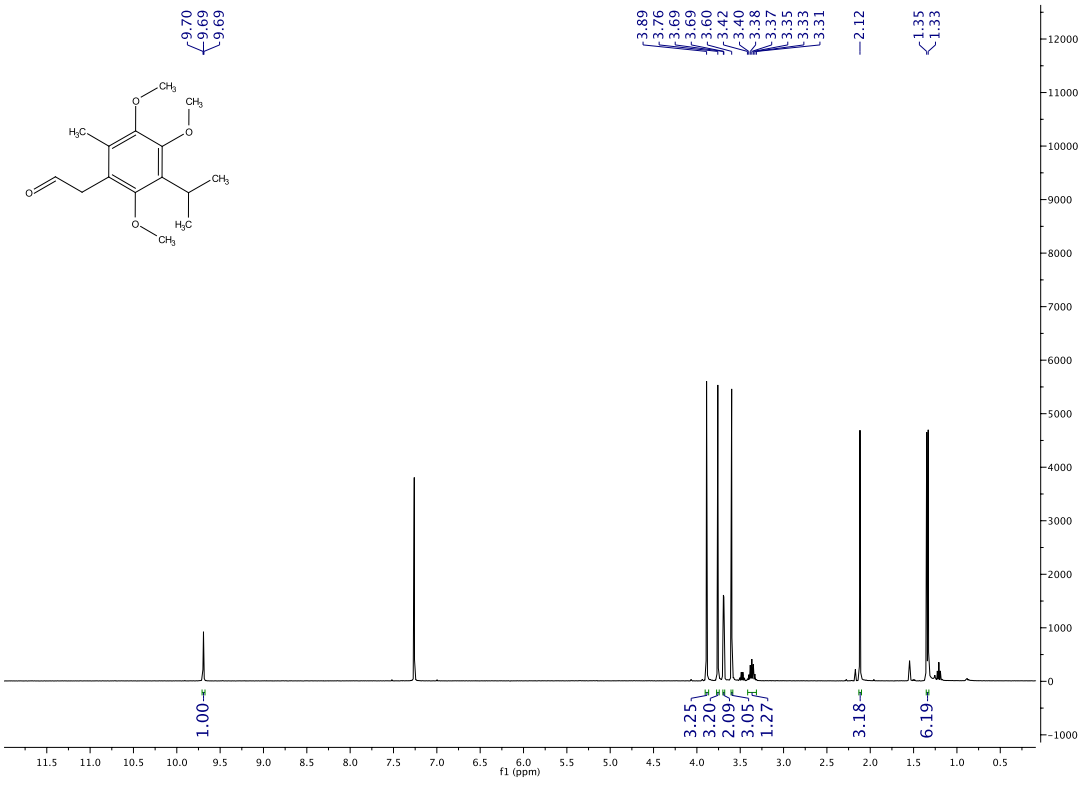

153.39
152.18
148.82
133.14
129.60
118.38
118.21
62.62
60.51
60.07
26.27
22.14
15.54
12.19
f1 (ppm)

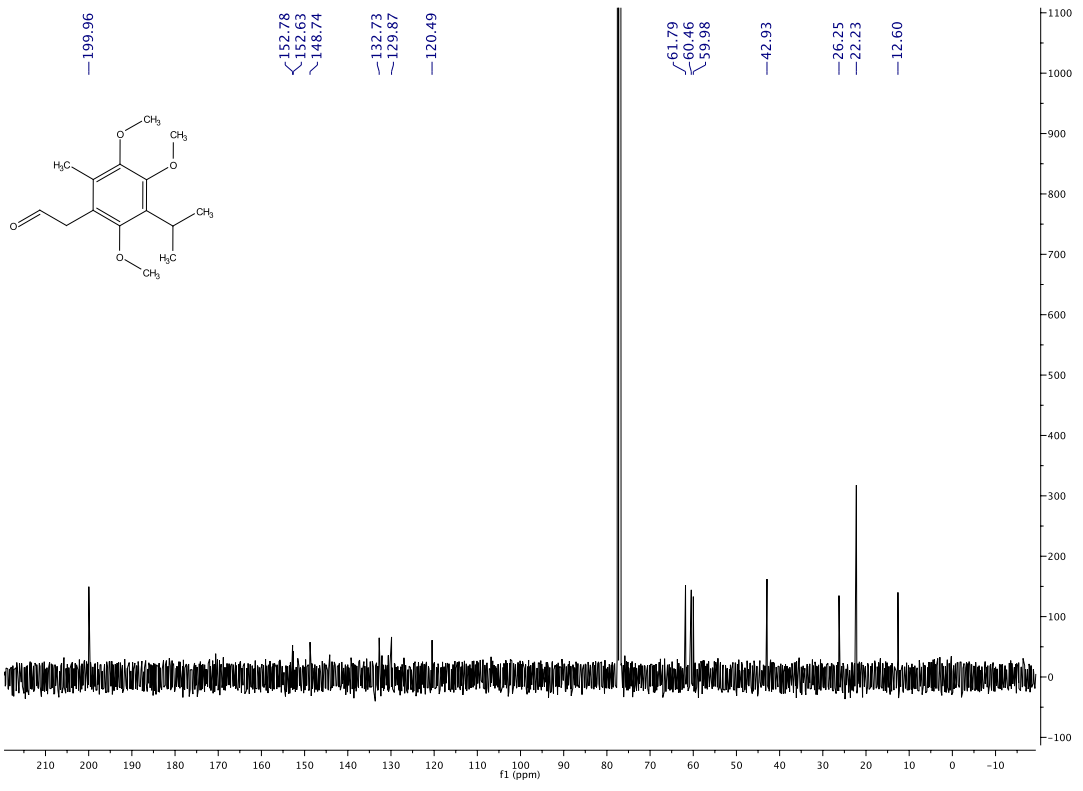

3.88
3.75
3.72
3.68
3.41
3.39
3.37
3.36
3.34
3.32
3.30
2.17
1.34
1.32
3.00
3.06
2.06
2.98
1.15
3.19
6.54
f1 (ppm)

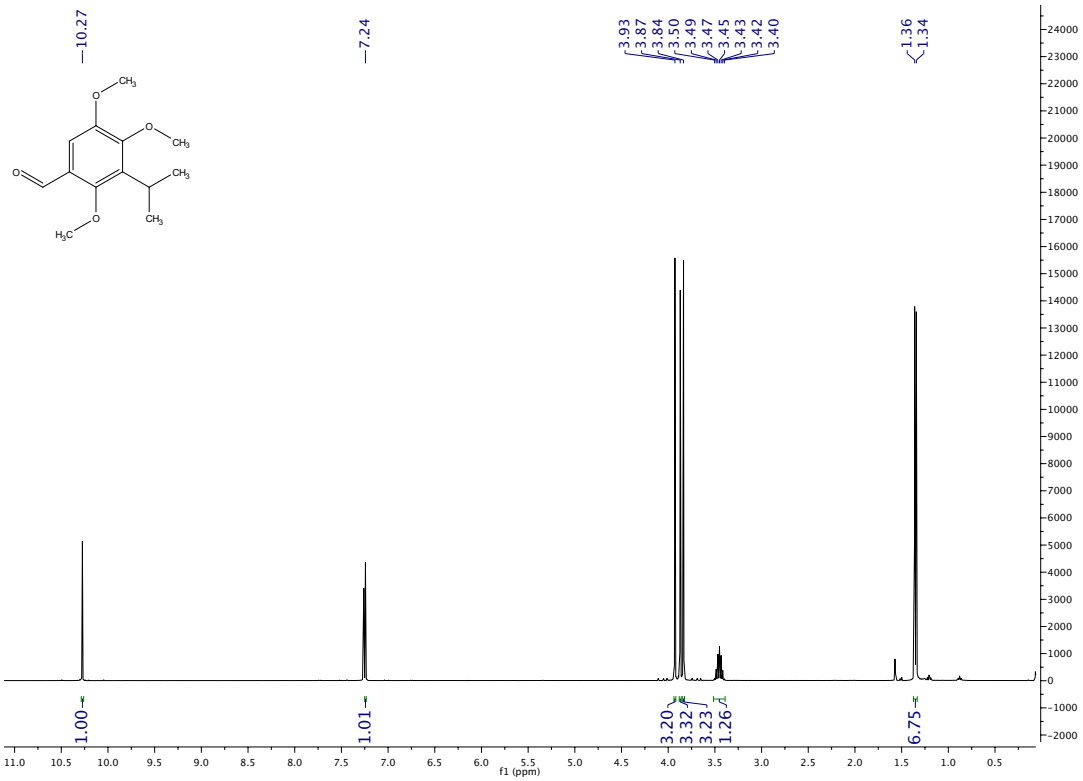

Das Bild kann derzeit nicht angezeigt werden.

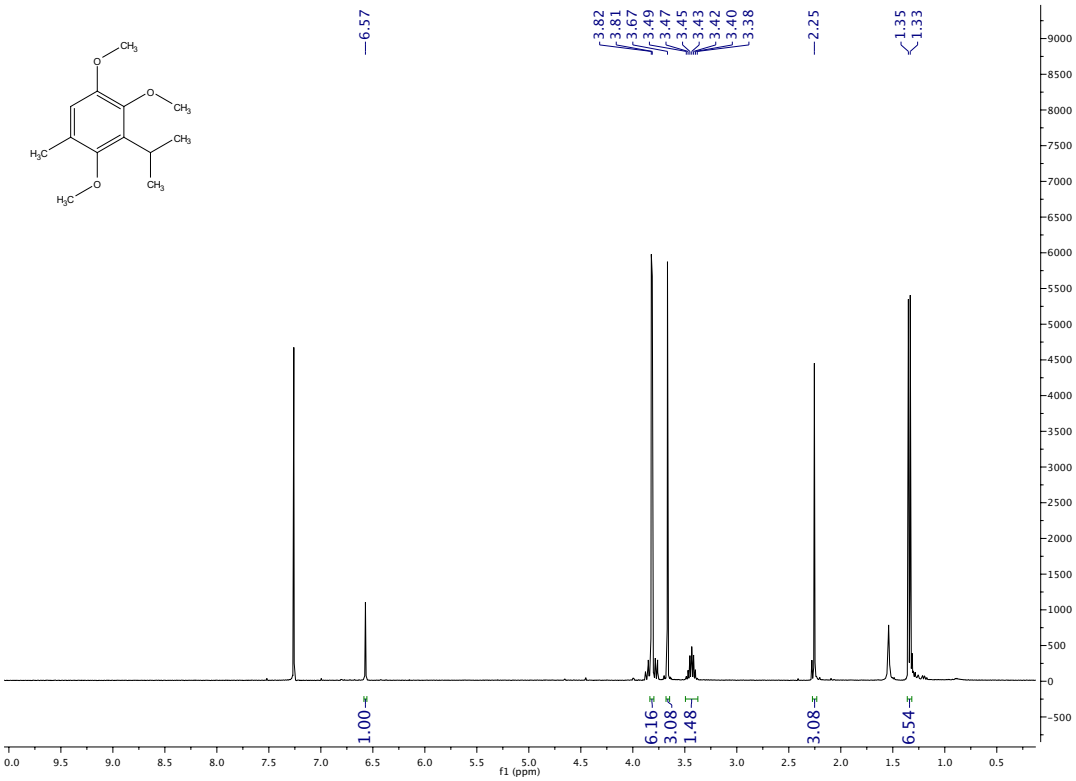

3.87
3.78
3.76
3.75
3.69
3.40
3.38
3.36
3.34
3.32
3.31
3.29
2.91
2.90
2.88
2.20
1.34
1.33
3.00
5.01
2.96
1.07
2.07
3.02
6.06
f1 (ppm)

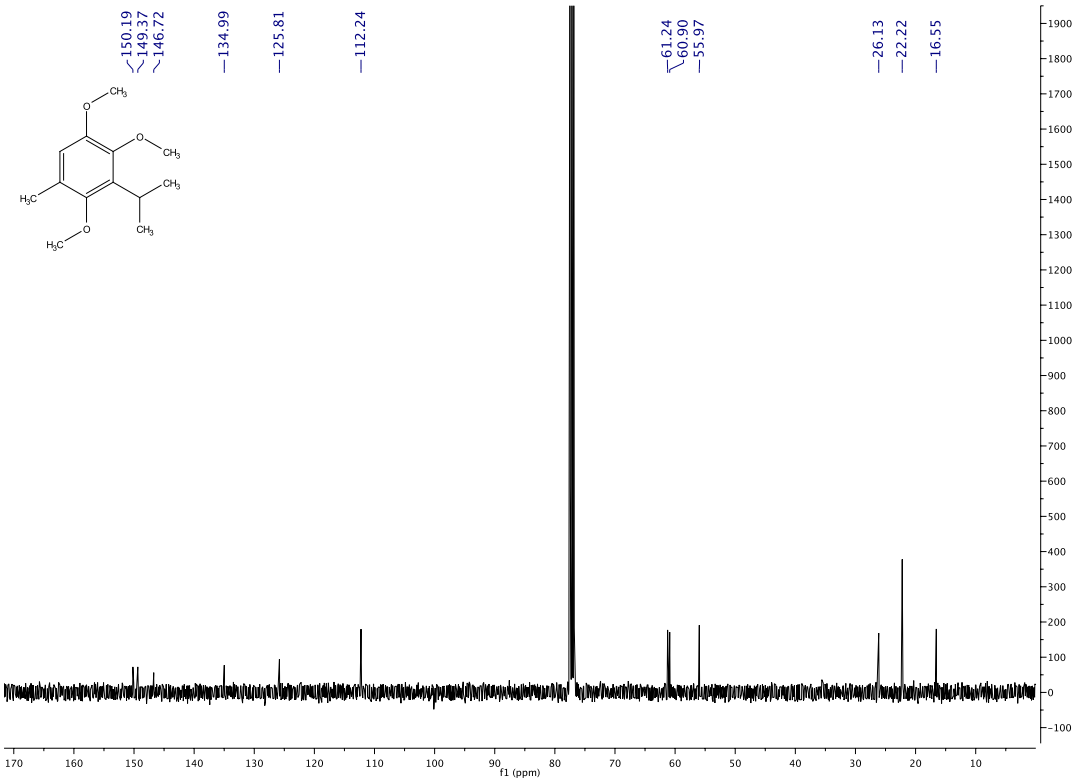

152.47
151.81
148.78
132.44
129.24
125.74
62.98
61.98
60.37
59.86
30.73
26.28
22.26
12.10
f1 (ppm)

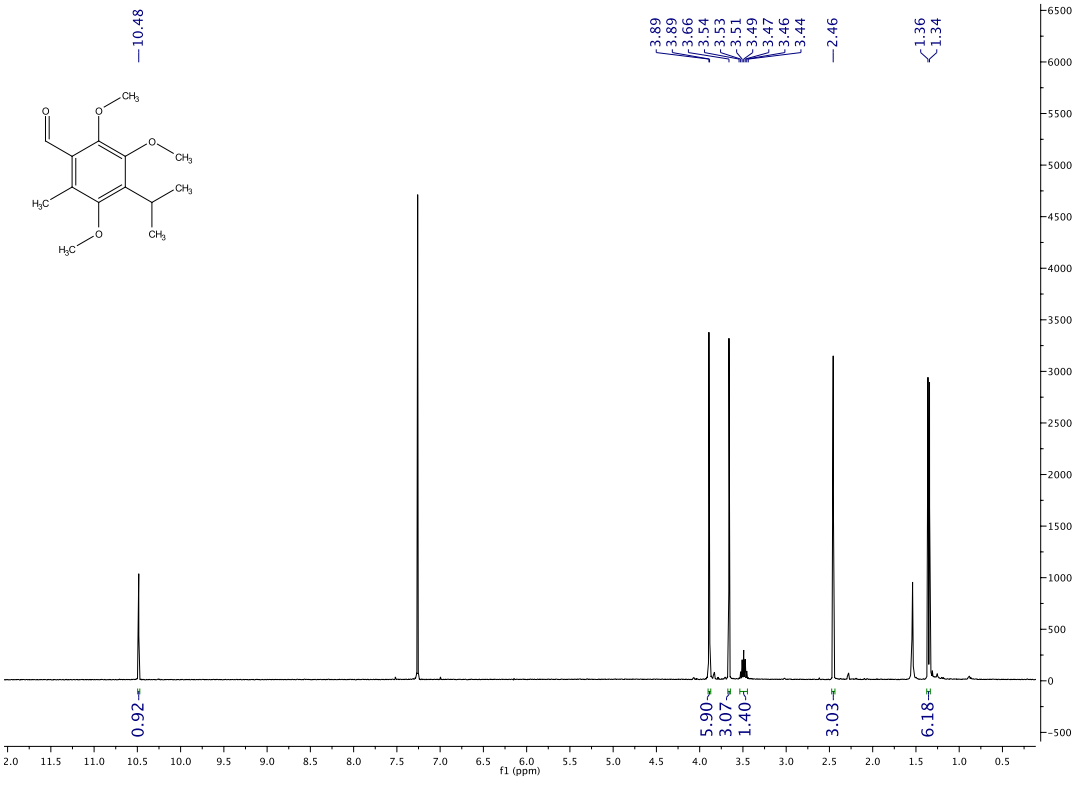

9.70
9.69
9.69
3.89
3.76
3.69
3.69
3.60
3.42
3.40
3.38
3.37
3.35
3.33
3.31
2.12
1.35
1.33
1.00
3.25
3.20
2.09
3.05
1.27
3.18
6.19
f1 (ppm)

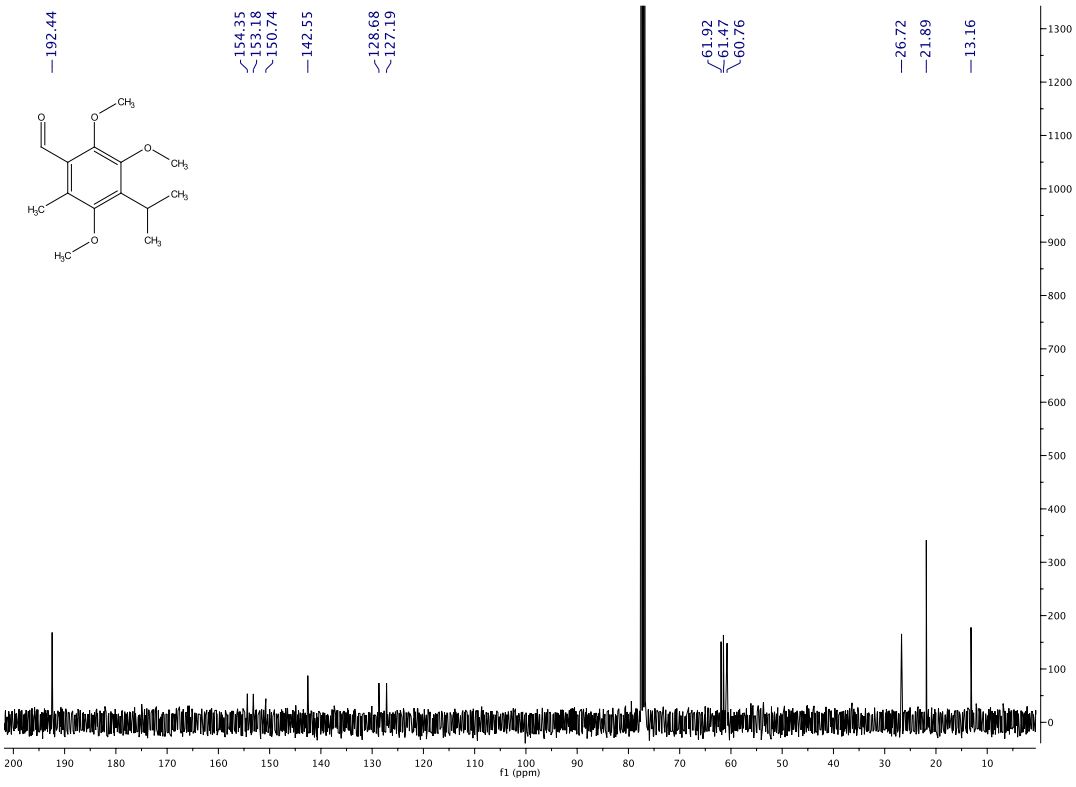

199.96
152.78
152.63
148.74
132.73
129.87
120.49
61.79
60.46
59.98
42.93
26.25
22.23
12.60
f1 (ppm)

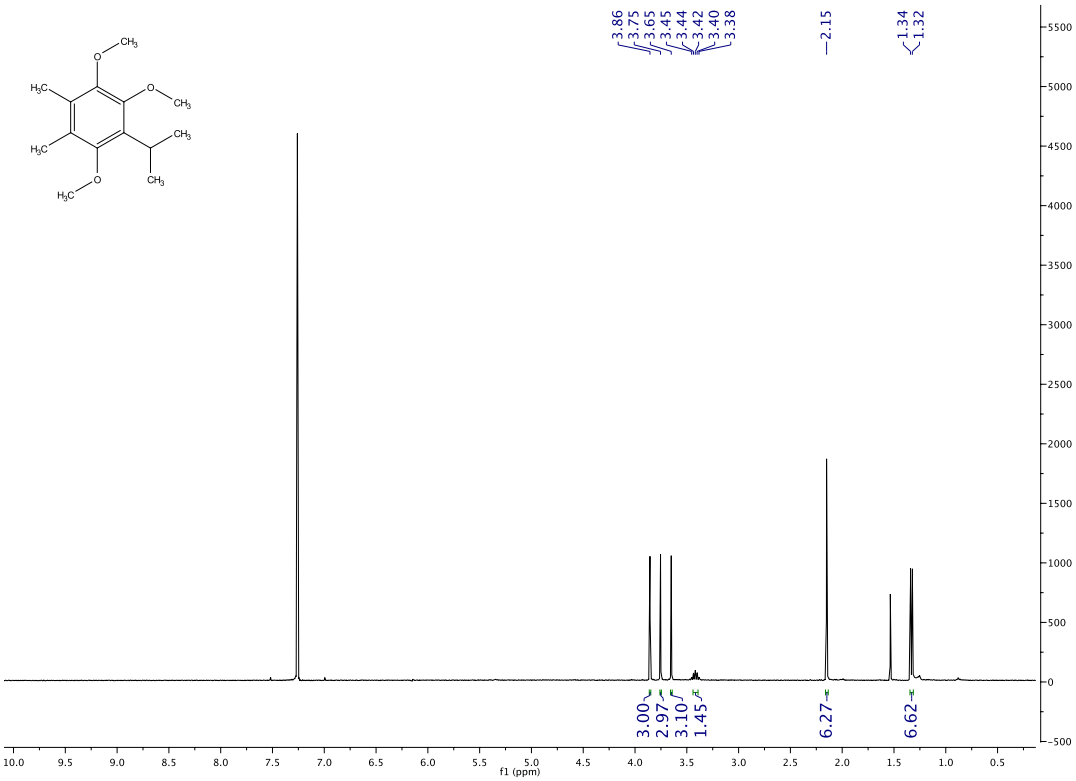

10.27
7.24
3.93
3.87
3.84
3.50
3.49
3.47
3.45
3.43
3.42
3.40
1.36
1.34
1.00
1.01
3.20
3.32
3.23
1.26
6.75
f1 (ppm)

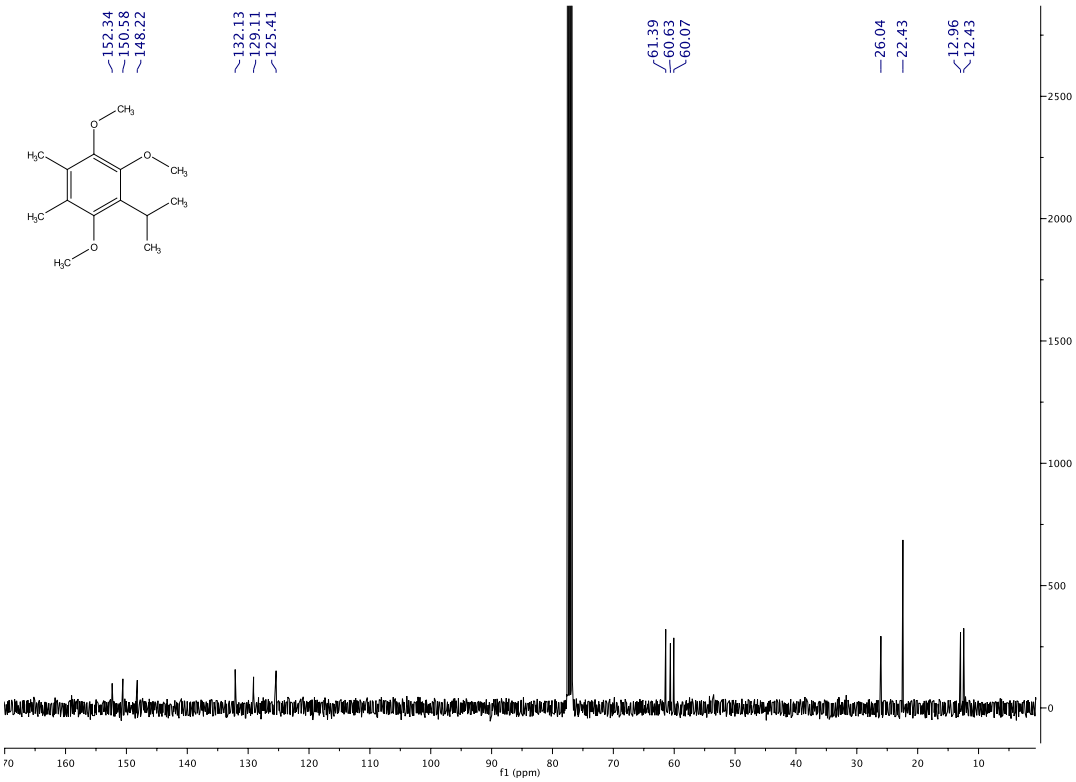

6.57
3.82
3.81
3.67
3.49
3.47
3.45
3.43
3.42
3.40
3.38
2.25
1.35
1.33
1.00
6.16
3.08
1.48
3.08
6.54
f1 (ppm)

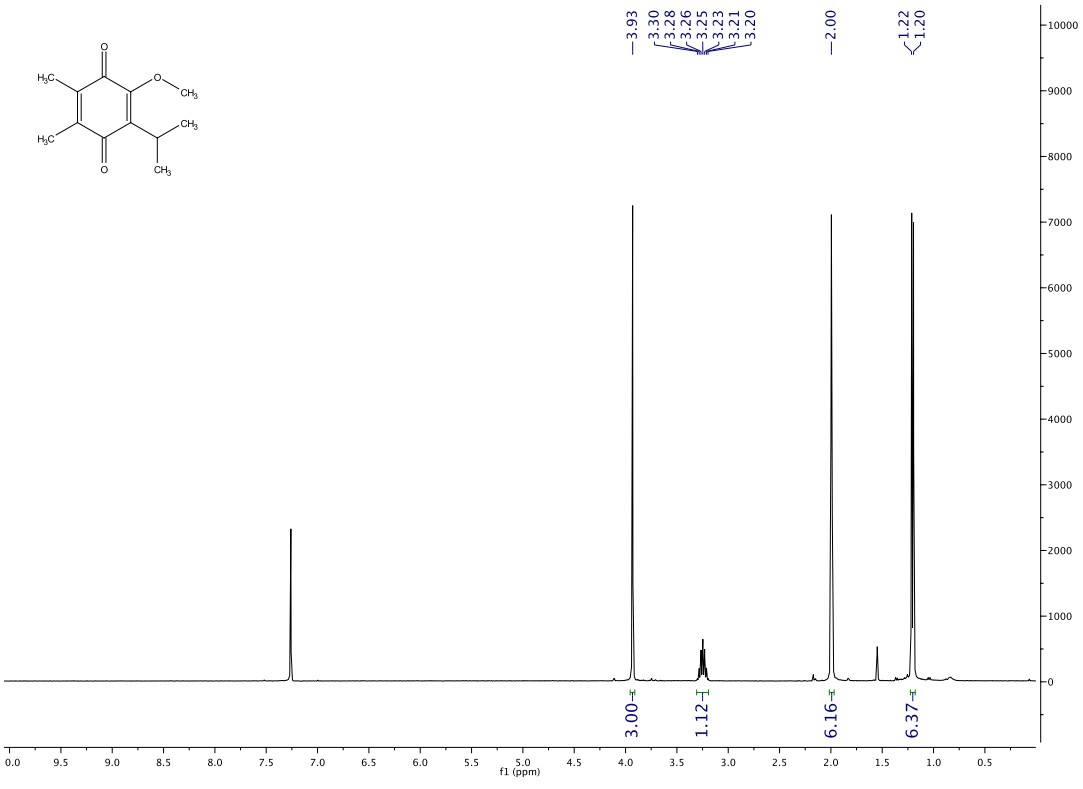

150.19
149.37
146.72
134.99
125.81
112.24
61.24
60.90
55.97
26.13
22.22
16.55
f1 (ppm)

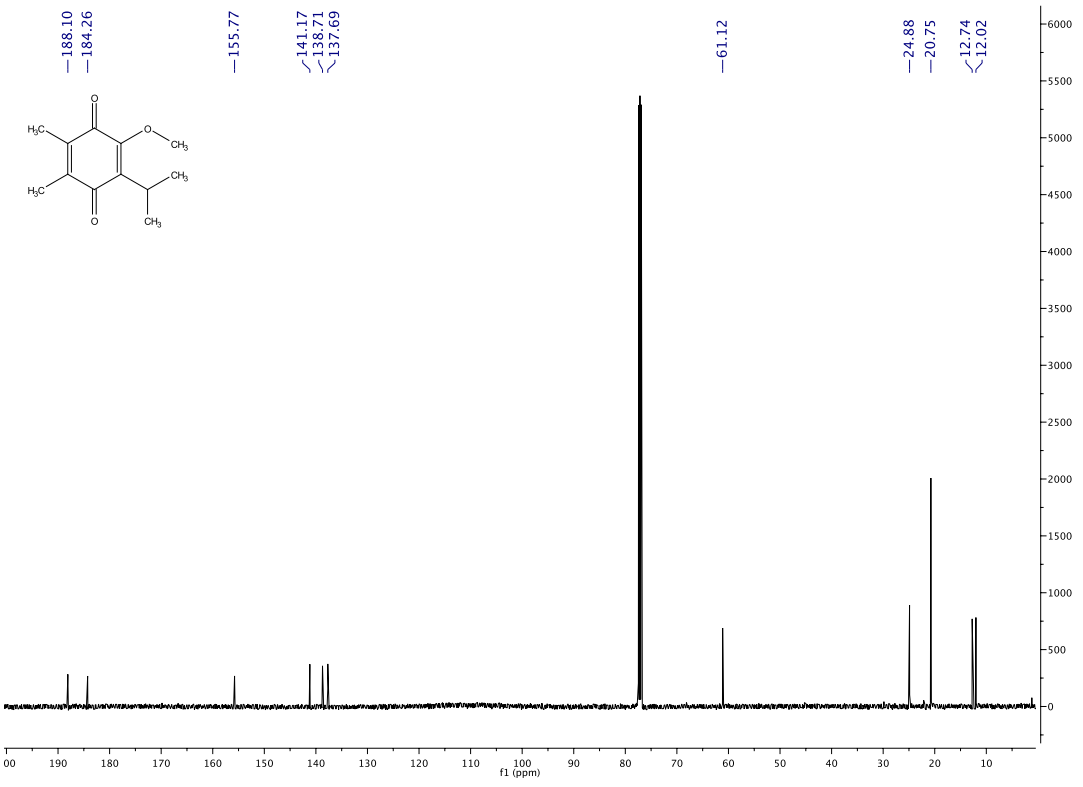

10.48
3.89
3.89
3.66
3.54
3.53
3.51
3.49
3.47
3.46
3.44
2.46
1.36
1.34
0.92
5.90
3.07
1.40
3.03
6.18
f1 (ppm)

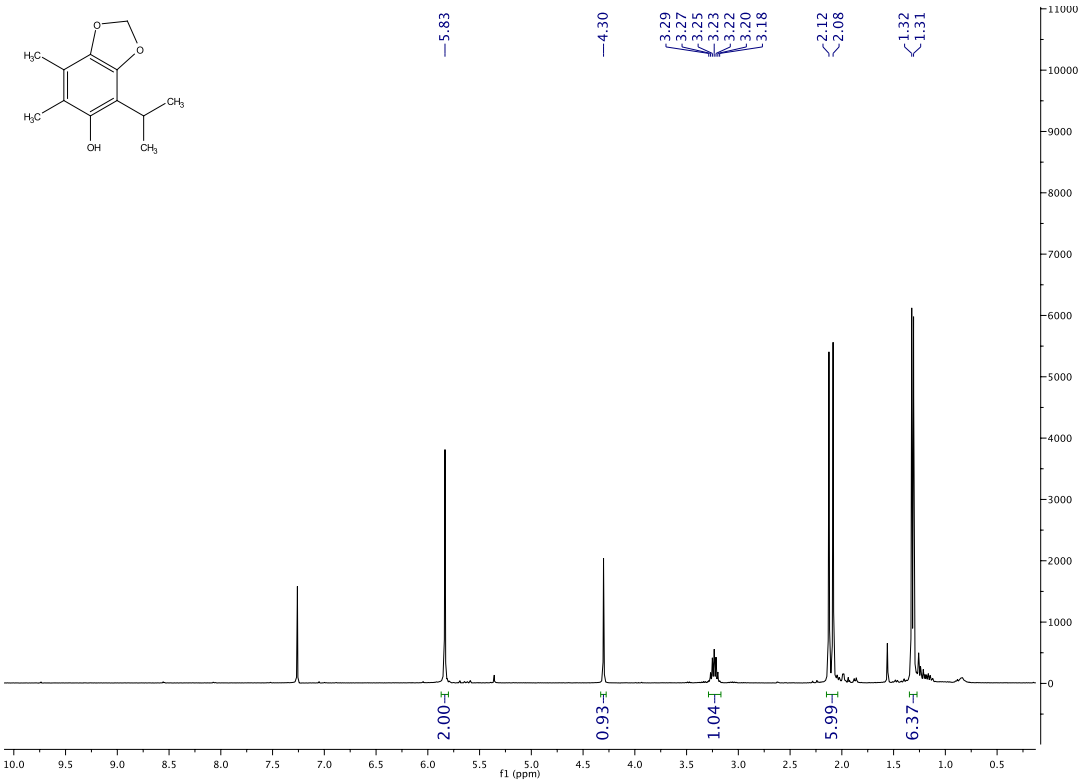

192.44
154.35
153.18
150.74
142.55
128.68
127.19
61.92
61.47
60.76
26.72
21.89
13.16
f1 (ppm)

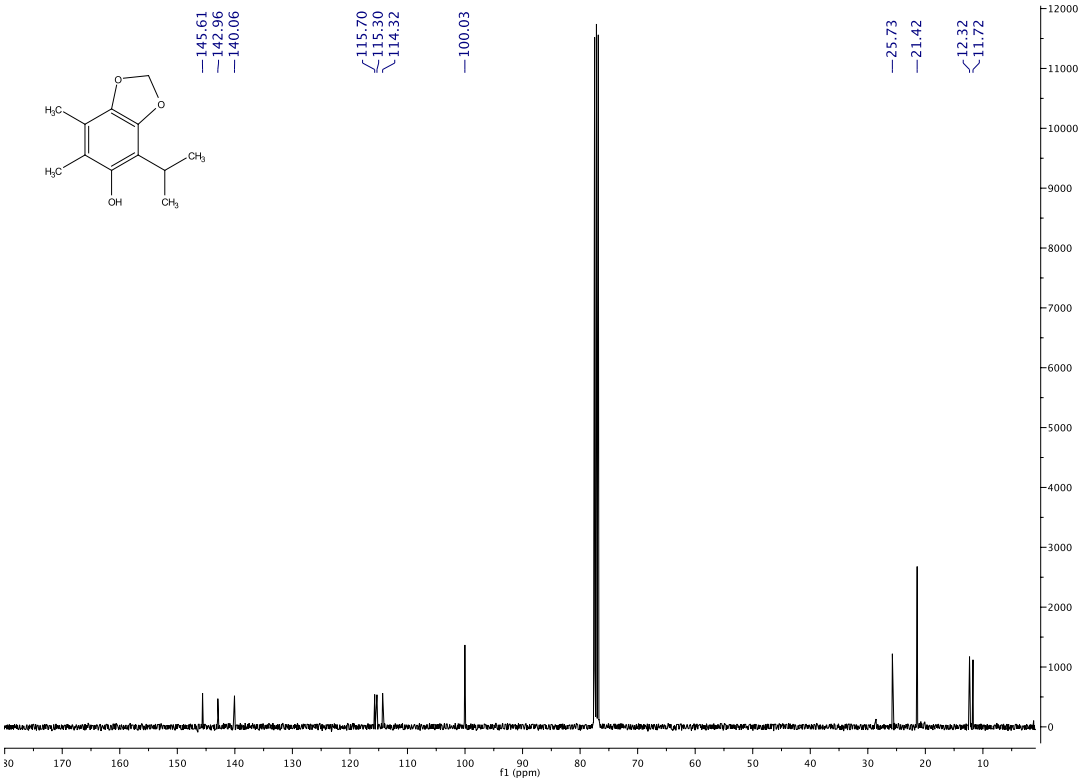

3.86
3.75
3.65
3.45
3.44
3.42
3.40
3.38
2.15
1.34
1.32
3.00
2.97
3.10
1.45
6.27
6.62
f1 (ppm)


152.34
150.58
148.22
132.13
129.11
125.41
61.39
60.63
60.07
26.04
22.43
12.96
12.43
f1 (ppm)

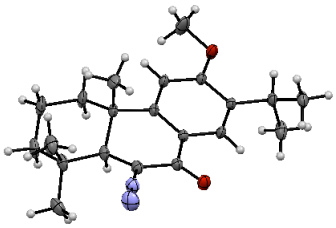

3.93
3.30
3.28
3.26
3.25
3.23
3.21
3.20
2.00
1.22
1.20
3.00
1.12
6.16
6.37
f1 (ppm)

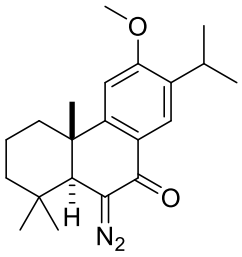

188.10
184.26
155.77
141.17
138.71
137.69
61.12
24.88
20.75
12.74
12.02
f1 (ppm)


5.83
4.30
3.29
3.27
3.25
3.23
3.22
3.20
3.18
2.12
2.08
1.32
1.31
2.00
0.93
1.04
5.99
6.37
f1 (ppm)


145.61
142.96
140.06
115.70
115.30
114.32
100.03
25.73
21.42
12.32
11.72
f1 (ppm)

7.2. Crystal structures

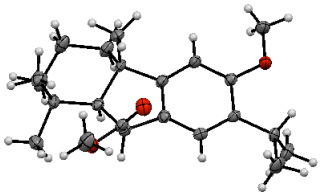


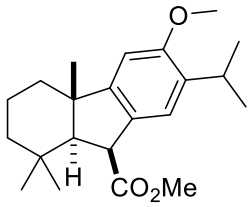


X-ray: Crystal data for **2.80** (CCDC 923474)

Formula	$C_{21}H_{28}N_2O_2$
Formula weight	340.47
Z, calculated density	2, 1.236 Mg · m^{-3}
F(000)	368
Description and size of crystal	colourless plate, 0.020 · 0.210 · 0.290 mm^3
Absorption coefficient	0.079 mm^{-1}
Min/max transmission	0.98 / 1.00
Temperature	123K
Radiation (wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P 2_1
a	8.2832(8)
b	9.5668(10) Å
c	12.0181(13) Å
β	90°
α	106.113(6)°
γ	90°
V	914.67(17) $Å^3$
min/max Θ	2.765° / 36.373°
number of collected reflections	32024
number of independent refections	4635 (merging r = 0.056)

number of observed reflections	3262 (I>2.0σ(I))
number of refined parameters	226
r	0.0488
rW	0.0932
goodness of fit	1.0812

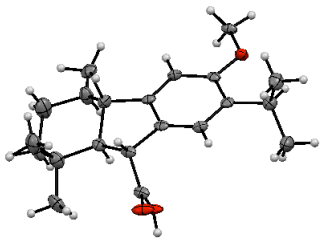


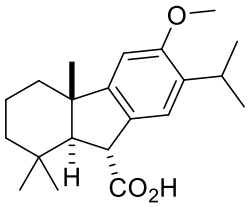


X-ray: Crystal data for **2.81** (CCDC 923475)

Formula	$C_{22}H_{32}O_3$
Formula weight	344.49
Z, calculated density	2, 1.174 Mg · m^{-3}
F(000)	376
Description and size of crystal	colourless plate, 0.030 · 0.170 · 0.220 mm^3
Absorption coefficient	0.076 mm^{-1}
Min/max transmission	0.99 / 1.00
Temperature	123K
Radiation (wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P 1
a	8.6948(3)
b	11.5644(4) Å
c	11.6368(4) Å
β	61.764(2)°
α	79.806(2)°
γ	71.019(2)°
V	974.42(6) $Å^3$

min/max Θ	1.987° / 30.092°
number of collected reflections	16556
number of independent refections	5626 (merging r = 0.069)
number of observed reflections	4610 (I>2.0σ(I))
number of refined parameters	451
r	0.0421
rW	0.0663
goodness of fit	1.1386

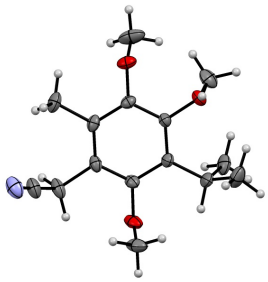


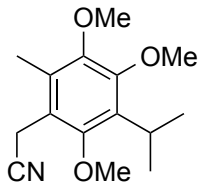


X-ray: Crystal data for **2.83** (CCDC 923476)

Formula	$C_{21}H_{30}O_3$
Formula weight	330.47
Z, calculated density	4, 1.088 Mg · m^{-3}
F(000)	720
Description and size of crystal	colourless plate, 0.030 · 0.110 · 0.250 mm^3
Absorption coefficient	0.071 mm^{-1}
Min/max transmission	0.99 / 1.00
Temperature	123K
Radiation (wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P 2_1
a	6.7983(6)
b	24.649(2) Å

c	12.2575(11) Å
β	90°
α	100.838(6)°
γ	90°
V	2017.3(3) $Å^3$
min/max Θ	1.692° / 30.174°
number of collected reflections	17151
number of independent refections	5955 (merging r = 0.072)
number of observed reflections	4221 (I>2.0σ(I))
number of refined parameters	433
r	0.0699
rW	0.0866
goodness of fit	1.0975

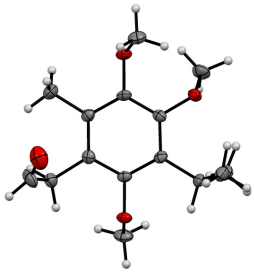


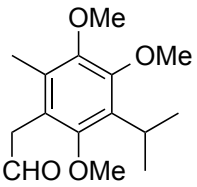


X-ray. Crystal data for **4.36**

Formula	$C_{15}H_{21}N_1O_3$
Formula weight	263.34
Z, calculated density	2, 1.185 Mg · m^{-3}
F(000)	284
Description and size of crystal	colourless plate, 0.020 · 0.090 · 0.190 mm^3
Absorption coefficient	0.082 mm^{-1}
Min/max transmission	0.99 / 1.00
Temperature	123K

Radiation (wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	triclinic, P −1
a	8.8272(8)
b	9.6685(9) Å
c	10.0078(10) Å
β	78.281(6)°
α	67.452(6)°
γ	90°
V	737.85(13) $Å^3$
min/max Θ	2.176° / 28.276°
number of collected reflections	12357
number of independent refections	3643 (merging r = 0.027)
number of observed reflections	2290 (I>2.0σ(I))
number of refined parameters	172
r	0.0409
rW	0.0841
goodness of fit	1.1034

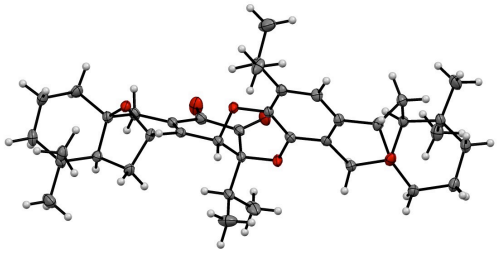


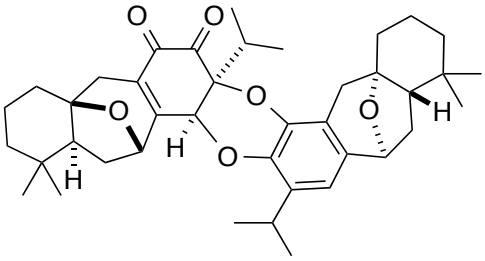


X-ray. Crystal data for **4.32**

Formula	$C_{15}H_{22}O_4$
Formula weight	266.34
Z, calculated density	16, 1.215 Mg · m^{-3}
F(000)	2304

Description and size of crystal	colourless plate, 0.040 · 0.060 · 0.210 mm^3
Absorption coefficient	0.087 mm^{-1}
Min/max transmission	0.99 / 1.00
Temperature	123K
Radiation (wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	orthorhombic, F d d 2
a	17.2182(17)
b	58.441(6) Å
c	5.7859(6) Å
β	90(6)°
α	90°
γ	90°
V	5822.1(10) $Å^3$
min/max Θ	2.466° / 28.323°
number of collected reflections	20964
number of independent refections	1979 (merging r = 0.059)
number of observed reflections	1974 (I>2.0σ(I))
number of refined parameters	191
r	0.0368
rW	0.0970
goodness of fit	0.8900





X-ray. Crystal data for **R3.124**

Formula	$C_{40}H_{52}O_6$
Formula weight	628.85
Z, calculated density	4, 1.219 Mg · m^{-3}
F(000)	1359.987
Description and size of crystal	yellow needle, 0.040 · 0.050 · 0.160 mm^3
Absorption coefficient	0.637 mm^{-1}
Min/max transmission	0.97 / 0.97
Temperature	123K
Radiation (wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	orthorhombic, P 2_1 2_1 2_1
a	11.6660(9) Å
b	12.2902(9) Å
c	23.9003(17) Å
β	90°
α	90°
γ	90°
V	3426.8(2) $Å^3$
min/max Θ	3.699° / 69.119°
number of collected reflections	88204
number of independent refections	6347 (merging r = 0.036)
number of observed reflections	6227 (I>2.0σ(I))
number of refined parameters	438

r	0.0267
rW	0.0294
goodness of fit	1.1150

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Curriculum Vitae

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Conferences	*International Conference on Hydrogen Atom Transfer*, Rome, 2014 (poster)
Award	Best Poster Award (International Conference on Hydrogen Atom Transfer)
Publication	Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett*. **2013**, *15*, 1390.