

# **Biomimetic Synthesis of Marine Sponge Derived Natural Products**

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B. Sc. (Hons.) Chem

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Doctor of Philosophy



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*In memory of my grandmother, Gan Lian See*

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## Abstract

There is a longstanding interest in the total synthesis of meroterpenoid natural products. These secondary metabolites of marine sponge origin not only display interesting biological activity, but also possess an intriguing molecular architecture, and thus have emerged as appealing targets for total synthesis. Herein this thesis, we report the synthesis of several marine natural products starting from (+)-sclareolide, a cheap and commercially available chiral pool starting material. A brief account on the recent applications of (+)-sclareolide in the field of total synthesis is first described in chapter one.

An improved total synthesis of (+)-liphagal is reported in chapter two. The key intermediate can be obtained from (+)-sclareolide in just 10 steps. The construction of the 6,7,5,6-tetracyclic framework was achieved via a pinacol ring expansion methodology, followed by formation of the hemiacetal, and subsequent dehydration to form the benzofuran moiety. Alternatively, this ring expansion can also proceed from the *ortho*-quinone methide generated *in-situ* under acidic conditions. Furthermore, the feasibility of a biomimetic conversion of (+)-siphonodictyal B, a co-isolated natural product, to (+)-liphagal was also investigated using a simplified model system. While the results from the model study proved to be encouraging, the formation of a stable *ortho*-quinone methide was observed while attempting this one-pot epoxidation-ring expansion approach.

The preparation of (+)-aureol from (+)-sclareolide is described in chapter three. Key transformations include a series of bioinspired stereospecific [1,2]-hydride and methyl shifts to form the aureane skeleton, and a late stage biomimetic cycloetherification reaction under acidic conditions to afford the desired natural product. In addition, simple modification of the cycloetherification reaction produced a novel tetracyclic molecule with an unprecedented seven-membered cycloether ring.

Finally, recent progress towards frondosin A is described in chapter four. While a convergent strategy approach utilising the key intermediate in chapter three failed to deliver the target molecule, a structural isomer of the natural product could be obtained from a novel ring expansion cascade. This sequence involved a dehydration, ring expansion, di-TBS deprotection, and cycloether formation in a one-pot operation. Preliminary attempts to convert this structural isomer to frondosin A or its quinone derivative are reported.

## Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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.....

Kevin Kuan

.....

Date

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## List of Abbreviations

|                  |  |
|------------------|--|
| $[\alpha]_D$     | specific rotation at wavelength of sodium D line |
| Å                | angstrom(s)                                      |
| aq.              | aqueous  |
| Asp              | aspartic acid                                    |
| atm              | atmosphere                                       |
| Bn               | benzyl   |
| Boc              | <i>tert</i> -butyloxycarbonyl                    |
| br               | broad  |
| Bu               | butyl  |
| <i>n</i> -Bu     | butyl  |
| <i>t</i> -Bu     | <i>tert</i> -butyl                               |
| c                | concentration for specific rotation measurements |
| CAN              | ceric ammonium nitrate                           |
| $^{13}\text{C}$  | carbon-13 isotope                                |
| cat.             | catalytic  |
| °C               | degrees Celsius                                  |
| $\text{cm}^{-1}$ | wavenumber(s)                                    |
| conc.            | concentrated                                     |
| CSA              | camphorsulfonic acid                             |
| 1,2-DCE          | 1,2-dichloroethane                               |
| 1,2-DCB          | 1,2-dichlorobenzene                              |
| DDQ              | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone        |

|                  |  |
|------------------|--|
| (-)-DET          | D-(-)-diethyl tartrate                     |
| DIBAL-H          | diisobutylaluminium hydride                |
| DMAP             | 4-dimethylaminopyridine                    |
| DMDO             | dimethyldioxirane                          |
| DMF              | <i>N,N</i> -dimethylformamide              |
| EI               | electron impact                            |
| <i>epi</i>       | epimer                                     |
| equiv            | equivalent                                 |
| ESI              | electrospray ionization                    |
| Et               | ethyl                                      |
| g                | gram(s)                                    |
| gCOSY            | gradient-selected Correlation Spectroscopy |
| h                | hour(s)                                    |
| <sup>1</sup> H   | proton                                     |
| HFIP             | hexafluoroisopropanol                      |
| HMBC             | Heteronuclear Multiple Bond Correlation    |
| HPLC             | high performance liquid chromatography     |
| HRMS             | high resolution mass spectrometry          |
| HSQC             | Heteronuclear Single Quantum Coherence     |
| <i>hν</i>        | light                                      |
| Hz               | hertz                                      |
| IBX              | 2-iodoxybenzoic acid                       |
| IC <sub>50</sub> | half maximum inhibitory concentration      |
| IR               | infrared (spectroscopy)                    |

|                |   |
|----------------|---|
| $J$            | coupling constant                           |
| KHMDS          | potassium hexamethyldisilazide              |
| MeOH           | methanol                                    |
| $\lambda$      | wavelength                                  |
| L              | litre                                       |
| Lys            | lysine                                      |
| m              | multiplet or milli                          |
| <i>m</i> -CPBA | <i>meta</i> -chloroperoxybenzoic acid       |
| <i>m/z</i>     | mass to charge ratio                        |
| $\mu$          | micro                                       |
| Me             | methyl                                      |
| MHz            | megahertz                                   |
| min            | minute(s)                                   |
| mol            | mole(s)                                     |
| mp             | melting point                               |
| Ms             | methanesulfonyl (mesyl)                     |
| MS             | molecular sieves                            |
| NBS            | <i>N</i> -bromosuccinimide                  |
| nm             | nanometer(s)                                |
| NMO            | <i>N</i> -methylmorpholine <i>N</i> -oxide  |
| NMR            | nuclear magnetic resonance                  |
| NOE            | nuclear Overhauser effect                   |
| NOESY          | nuclear Overhauser enhancement spectroscopy |
| PDC            | pyridinium dichromate                       |

|                |  |
|----------------|--|
| PhH            | benzene  |
| PhMe           | toluene  |
| PPTS           | pyridinium <i>para</i> -toluenesulfonate           |
| <i>p</i> -TsOH | <i>para</i> -toluenesulfonic acid                  |
| ppm            | parts per million                                  |
| Pr             | propyl   |
| <i>i</i> -Pr   | isopropyl  |
| pyr            | pyridine   |
| q              | quartet  |
| RCM            | Ring closing metathesis                            |
| R <sub>f</sub> | retention factor                                   |
| ROESY          | Rotating Frame Overhauser Enhancement Spectroscopy |
| rt             | room temperature                                   |
| s              | singlet or seconds                                 |
| t              | triplet  |
| TBAF           | tetrabutylammonium fluoride                        |
| TBAI           | tetrabutylammonium iodide                          |
| TBS            | <i>tert</i> -butyldimethylsilyl                    |
| Tf             | trifluoromethanesulfonyl                           |
| TFA            | trifluoroacetic acid                               |
| TFE            | 2,2,2-trifluoroethanol                             |
| THF            | tetrahydrofuran                                    |
| THP            | tetrahydropyran                                    |
| TIPS           | triisopropylsilyl                                  |

|       |   |
|-------|---|
| TLC   | thin layer chromatography                       |
| TMEDA | <i>N, N, N', N'</i> -tetramethylethylenediamine |
| TMS   | trimethylsilyl                                  |
| Tr    | triphenylmethyl (trityl)                        |
| Ts    | <i>p</i> -toluenesulfonyl (tosyl)               |
| Tyr   | tyrosine  |
| UV    | ultraviolet                                     |
| W     | watt  |

# CHAPTER ONE

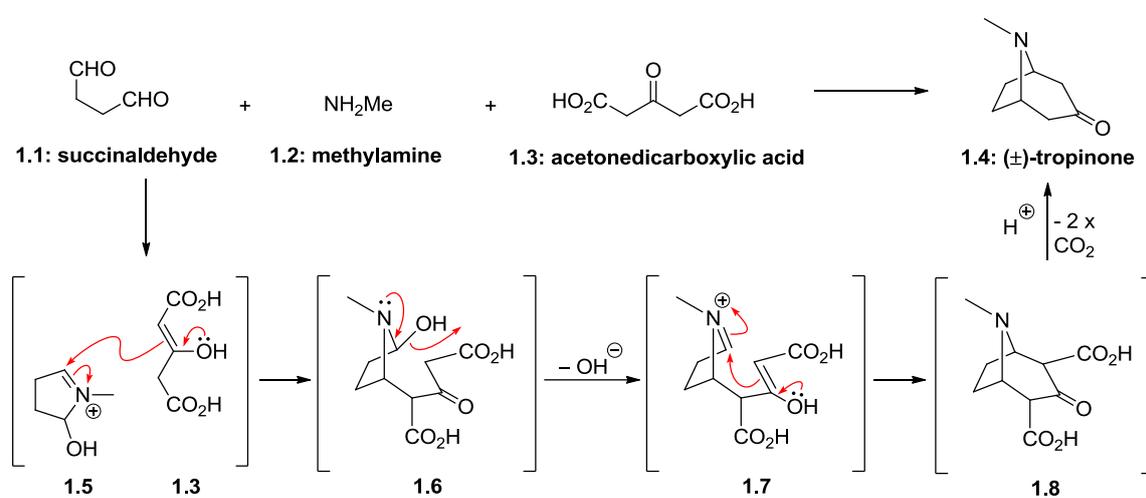
## (+)-Sclareolide in Natural Product Synthesis

### 1.1 Natural Products and Biomimetic Chemistry

The structural complexity and unique architecture of natural products often intrigue organic chemists, while their roles in biological pathways, as well as their medicinal properties are of interest in various fields of science, including, but not limited to, biology, biochemistry, pharmacology and medicine. Indeed, over 40% of drugs available today can be traced back to a natural product source.<sup>1</sup> It is undeniable that natural products play a pivotal role in the development of new therapeutic drugs.<sup>2-5</sup> An intriguing array of biologically active secondary metabolites have been isolated from marine sponges.<sup>6-8</sup> However, these natural products are often isolated in minute quantities from rare or inaccessible sources, resulting in a supply problem which can only be solved by chemical synthesis.

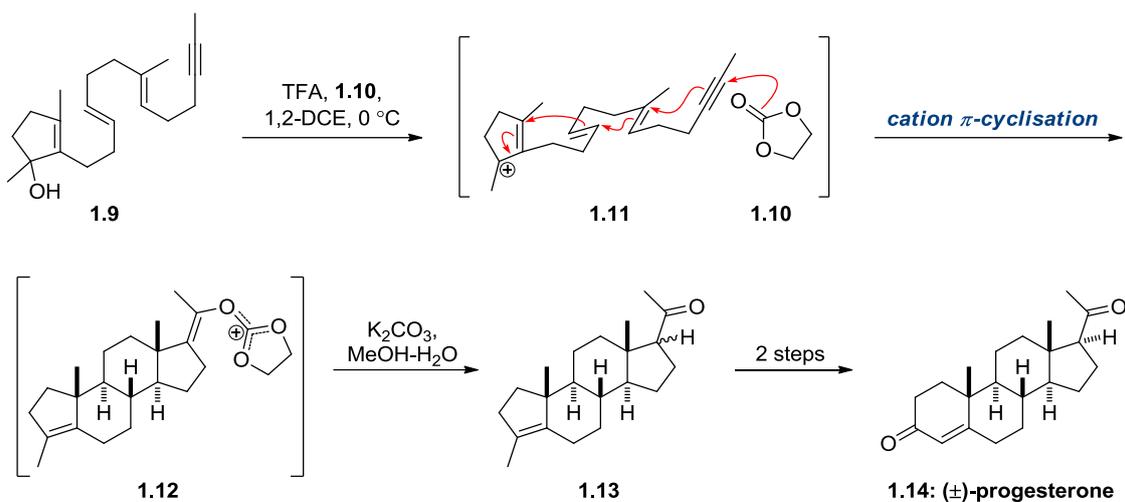
Biomimetic chemistry is a term first coined Breslow in 1972.<sup>9</sup> The definition was elegantly summarised by Heathcock,<sup>10</sup> stating that “*The basic assumption of this approach is that nature is the quintessential process development chemist. We think that the molecular frameworks of most natural products arise by intrinsically favourable chemical pathways – favourable enough that the skeleton could have arisen by a nonenzymic reaction in the primitive organism. If a molecule produced in this purely chemical manner was beneficial to the organism, enzymes would eventually have evolved to facilitate the production of this useful material.*” The idea of biomimetic chemistry, however, is not foreign to organic chemists. This

concept was first demonstrated by Sir Robert Robinson in 1917 in his remarkable one-pot synthesis of ( $\pm$ )-tropinone (**1.4**) from three simple reactants (Scheme 1.1).<sup>11</sup> Succinaldehyde (**1.1**) and methylamine (**1.2**) were first condensed to form the hydroxy heterocycle **1.5**, which in turn reacted with acetonedicarboxylic acid (**1.3**) via a series of intramolecular Mannich reactions. Subsequent double decarboxylation of intermediate **1.8** then provided the racemic natural product.



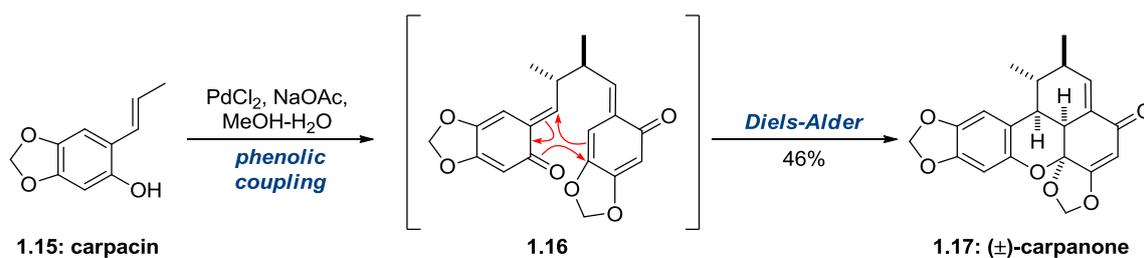
Scheme 1.1

Another landmark in the field of biomimetic chemistry was demonstrated by William S. Johnson in 1971 with his synthesis of progesterone (Scheme 1.2).<sup>12</sup> The unstable trienynol **1.9** was first subjected to TFA to form the tertiary carbocation **1.11**, which was cyclised and trapped by **1.10** to give intermediate **1.12**. Base hydrolysis gave rise to ketone **1.13**, which was later converted into ( $\pm$ )-progesterone (**1.14**) in two steps. Although Johnson's approach produces progesterone as a racemic mixture, the polyene cyclisation route served as a benchmark in steroid chemistry, and variations of this approach have led to the syntheses of other natural products.<sup>13-15</sup>



Scheme 1.2

Chapman's synthesis of ( $\pm$ )-carpanone (**1.17**), also published in 1971 represents yet another elegant example of biomimetic chemistry. Inspired by Barton's work on the synthesis of usnic acid,<sup>16</sup> Chapman realised that ( $\pm$ )-carpanone (**1.17**) could be derived from the oxidative dimerization of carpacin (**1.15**) (Scheme 1.3). Furthermore, the isolation of two other racemic minor stereoisomers suggested that ( $\pm$ )-carpanone (**1.17**) could be derived from a non-enzymatic process in nature.<sup>17</sup> To that end, the Pd catalysed phenolic coupling of carpacin (**1.15**) led to the formation of *ortho*-quinone methide intermediate **1.16**, which readily undergoes an intramolecular hetero Diels-Alder reaction to give ( $\pm$ )-carpanone (**1.17**) with a yield of 46% in a one-pot operation. There is no doubt that biomimetic chemistry allows for rapid access to complex molecular frameworks from relatively simple starting materials. Nonetheless, careful execution of the bio-inspired reaction(s) along with a well thought out synthetic route remain the key factors required for a successful biomimetic strategy.



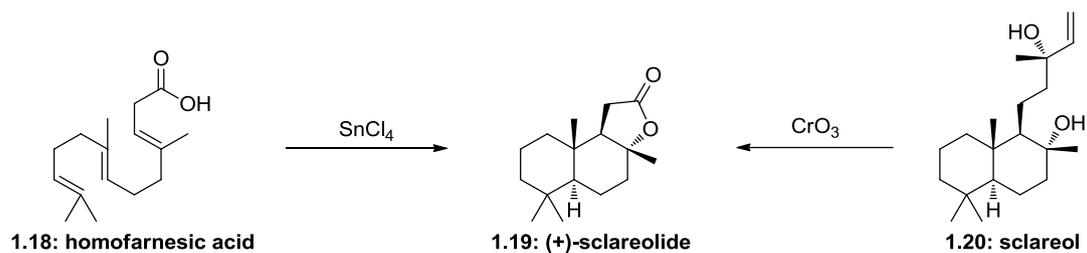
Scheme 1.3

## 1.2 (+)-Sclareolide in Total Synthesis

Total synthesis of complex natural products from a chiral pool relies on the use of a cheap and enantiomerically pure natural product as the starting material. Ideally, the desired starting material would require a minimal amount of functional group interconversion or protecting group(s) to be converted into the desired advanced intermediate, with the retention of the required chiral centres. (+)-Sclareolide (**1.19**), a labdane sesquiterpene, has served as an important chiral pool starting material, often employed in the synthesis of terpene based natural products.

Commercially obtained from the plant species *Salvia sclarea*, sclareolide has also been found in *Salvia yosgadensis* and several tobacco leaves.<sup>18, 19</sup> Whilst (+)-sclareolide (**1.19**) can be formed from the biomimetic cyclisation of homofarnesic acid (**1.18**),<sup>20</sup> commercial (+)-sclareolide (**1.19**) is obtained from the chromic acid oxidation of sclareol (**1.20**), a major constituent of clary sage (Scheme 1.4).<sup>21</sup> In the fragrance industry, (+)-sclareolide serves as a precursor to Ambrox®, a highly valuable synthetic substitute for ambergris.<sup>22</sup> As a result, biotransformations of **1.19** and other labdane sesquiterpenes have been investigated in hopes of finding novel, structurally similar molecules that are not readily accessible by synthetic methods.<sup>23-27</sup> On the other hand, several new synthetic strategies have also been developed to further enhance the synthetic utility of (+)-sclareolide (**1.19**).<sup>28-33</sup> A 2011 review by Frija, Frade

and Afonso described the use of (+)-sclareolide (**1.19**) as a chiral pool starting material for the total synthesis of several natural products (Figure 1.1).<sup>34</sup> However, this section will instead focus on the recent applications of (+)-sclareolide (**1.19**) and other total syntheses that were not covered in the review.



Scheme 1.4

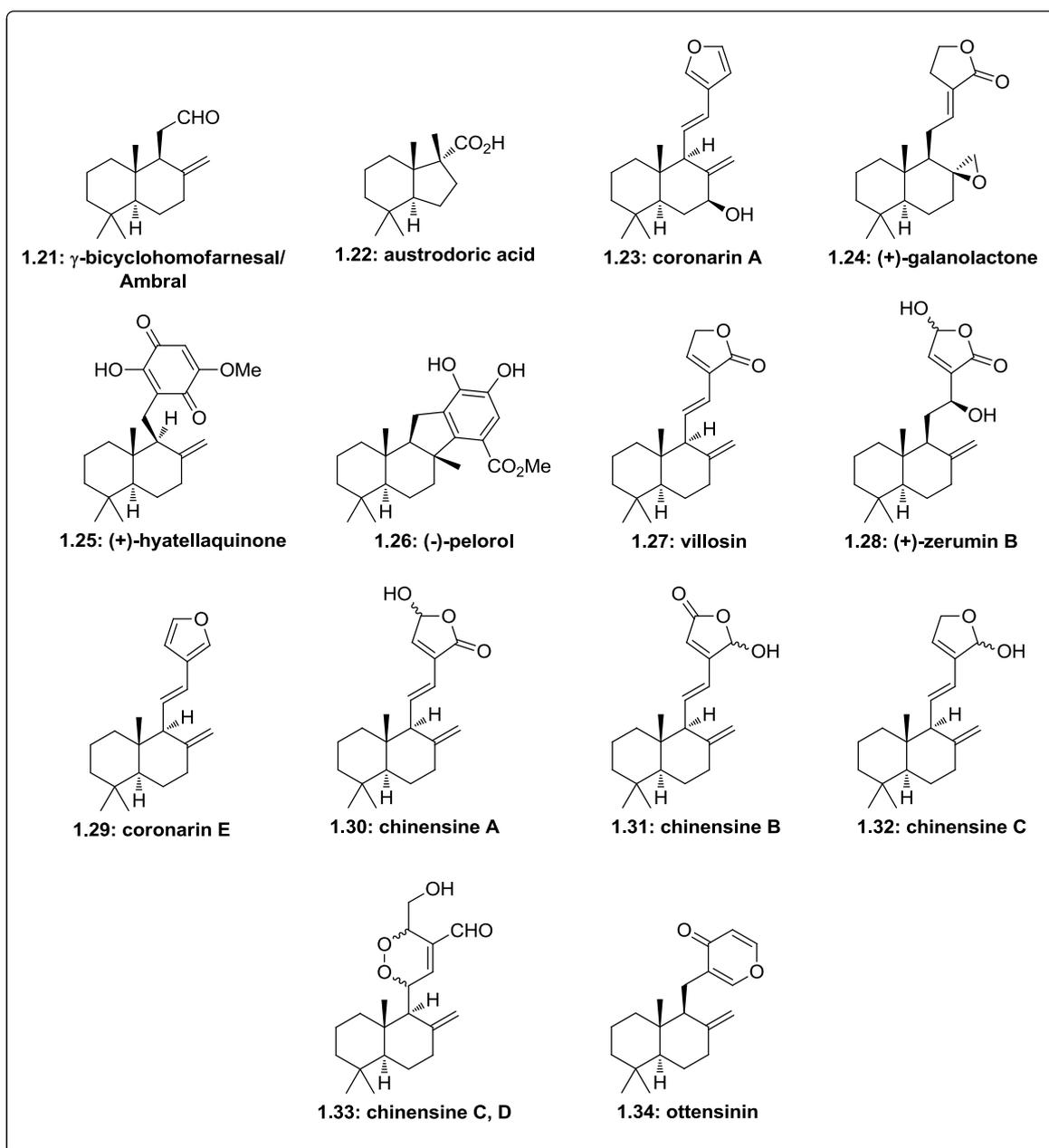
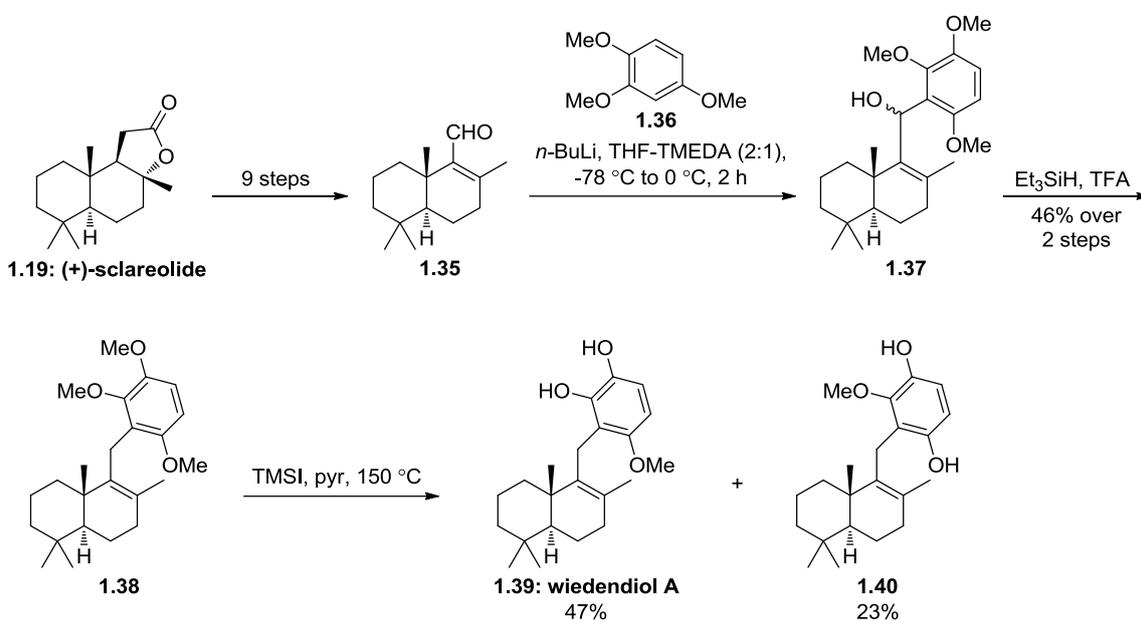


Figure 1.1

One of the earliest examples involving the use of (+)-sclareolide (**1.19**) in total synthesis was Chackalamannil's synthesis of wiedendiol A in 1995 (Scheme 1.5).<sup>35</sup> (+)-Sclareolide (**1.19**) was first converted into aldehyde **1.35** over nine steps. A shorter approach to **1.35** was also examined by the authors. However, the latter route suffered from poor overall yield of the

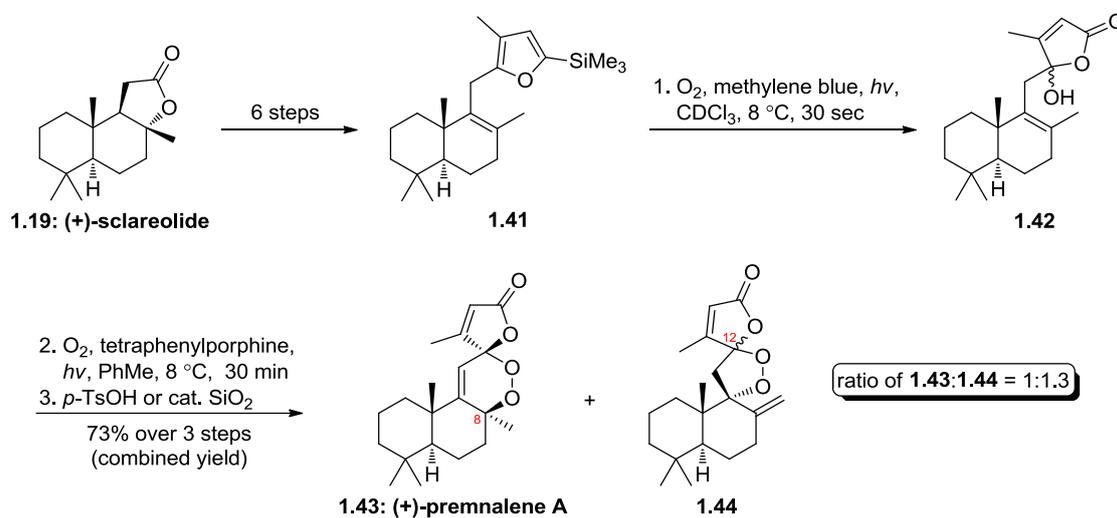
aldehyde compared to the first method. Nevertheless, the importance of aldehyde **1.35** would later be portrayed in the synthesis of several other marine meroterpenoids.<sup>36-38</sup> *Ortho*-lithiation of trimethoxybenzene (**1.36**) followed by addition of aldehyde **1.35** yielded alcohol **1.37** as a mixture of diastereoisomers. Deoxygenation with triethylsilane in the presence of TFA at  $-78$  °C gave the dimethoxywiedendiol A precursor **1.38** in 46% yield over two steps from **1.35**. Double demethylation with excess trimethylsilyl iodide in pyridine at  $150$  °C afforded wiedendiol A (**1.39**) in 47% yield, along with the *p*-hydroquinone isomer **1.40** in 23% yield.



Scheme 1.5

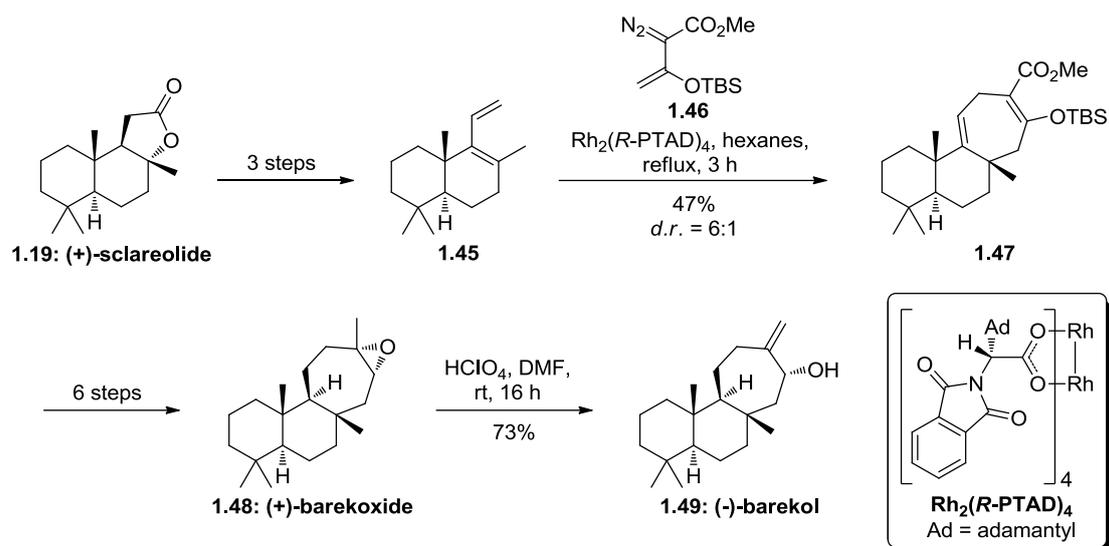
In the synthesis of (+)-premnalene A (**1.43**) (Scheme 1.6), the construction of the key furan intermediate **1.41** was achieved in just six steps from (+)-sclareolide (**1.19**).<sup>39</sup> The final step involved a one-pot biomimetic cascade sequence which is comprised of a [4+2] cycloaddition between  $^1\text{O}_2$  and the furan moiety,<sup>40</sup> followed by an  $^1\text{O}_2$  ene reaction,<sup>41</sup> and

finally ketalization to afford a mixture of [5,5] and [6,5]-spirocyclic compounds. (+)-Premnalene A (**1.43**) was then separated from its C-8 epimer via recrystallization.



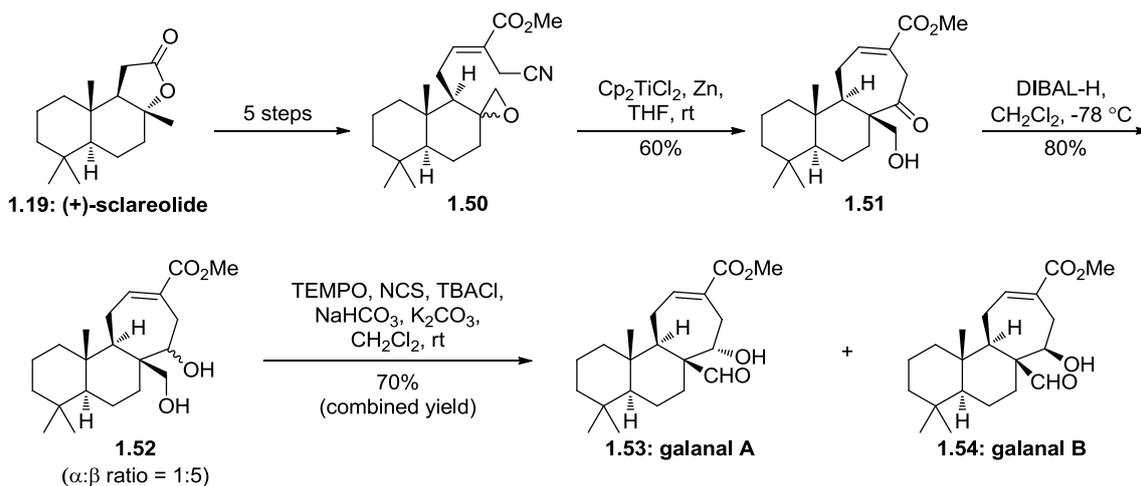
Scheme 1.6

The collaborative efforts of Sarpong's and Davies's research groups resulted in the synthesis of (+)-barekoxide (**1.48**) and (-)-barekol (**1.49**) via a remarkable Rh mediated formal [4+3] cycloaddition between diene **1.45** and vinyl diazoacetate **1.46**, as illustrated in Scheme 1.7.<sup>42</sup> The newly generated the 6,6,7-tricyclic ester **1.47** was converted into (+)-barekoxide (**1.48**) in six steps. Conversion of (+)-barekoxide (**1.48**) to (-)-barekol (**1.49**) was achieved using a previously reported acid catalysed isomerisation reaction.<sup>43</sup>



Scheme 1.7

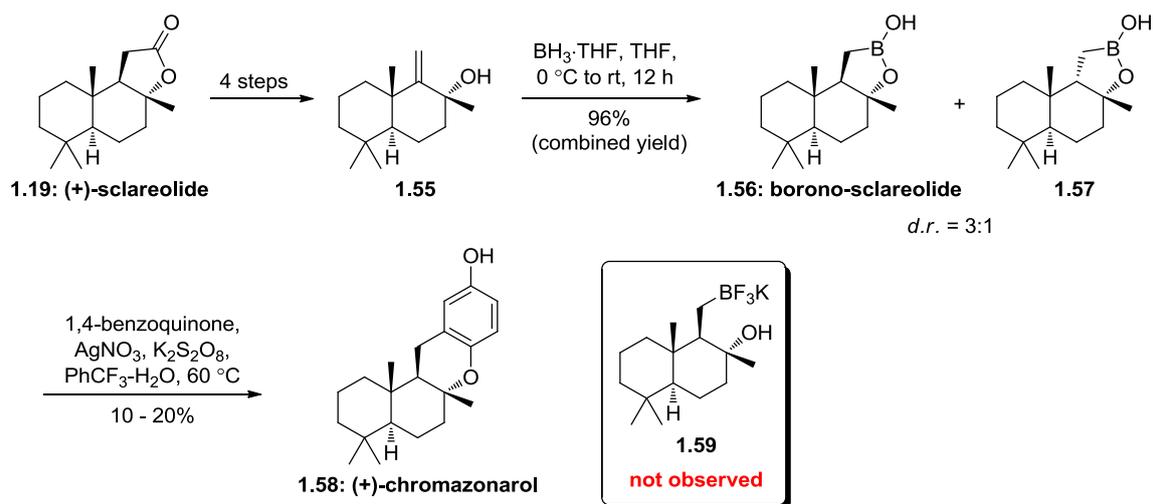
Recently, a short eight step synthesis to both galanal A (**1.53**) and galanal B (**1.54**) were reported by Chein and co-workers.<sup>44</sup> As shown in Scheme 1.8, (+)-sclareolide (**1.19**) was converted into epoxide **1.50** in five steps. An intramolecular radical reaction then ensued using  $\text{Cp}_2\text{TiCl}_2$  in the presence of Zn metal. Homolytic bond cleavage of the most substituted C-O on the epoxide would be induced by the Ti(III) species, generated *in situ*. The newly formed, stable tertiary radical intermediate would then react with an iminyl radical (generated from addition of the titanoxyl radical to the nitrile group) to produce ketone **1.51** upon workup. Subsequent reduction with DIBAL-H afforded diol **1.52**, which underwent selective oxidation to give both galanal A (**1.53**) and galanal B (**1.54**) in a 1:5 ratio.



Scheme 1.8

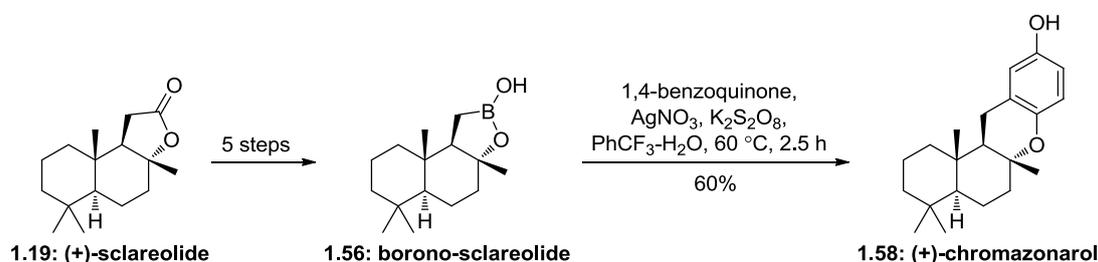
### 1.3 Divergent Synthesis of Sesquiterpene Natural Products from Borono-Sclareolide

A significant progress in quinone/hydroquinone sesquiterpene synthesis using (+)-sclareolide (**1.19**) as the key starting material was published by Baran's group in 2012.<sup>45</sup> Initially, the authors envisioned that these natural products could be derived from a direct coupling between a suitable sesquiterpene backbone and a non-terpenoid moiety, such as 1,4-benzoquinone. After several unsuccessful attempts at coupling various sesquiterpene backbones (with carboxylic, iodide or trifluoroborate functional groups), Baran and co-workers discovered that borono-sclareolide (**1.56**), formed by reacting alkene **1.55** with  $\text{BH}_3 \cdot \text{THF}$  would be a useful synthetic intermediate for this transformation (Scheme 1.9). Alkene **1.55** itself could be synthesised from (+)-sclareolide (**1.19**) in just four simple steps on a multi-gram scale.



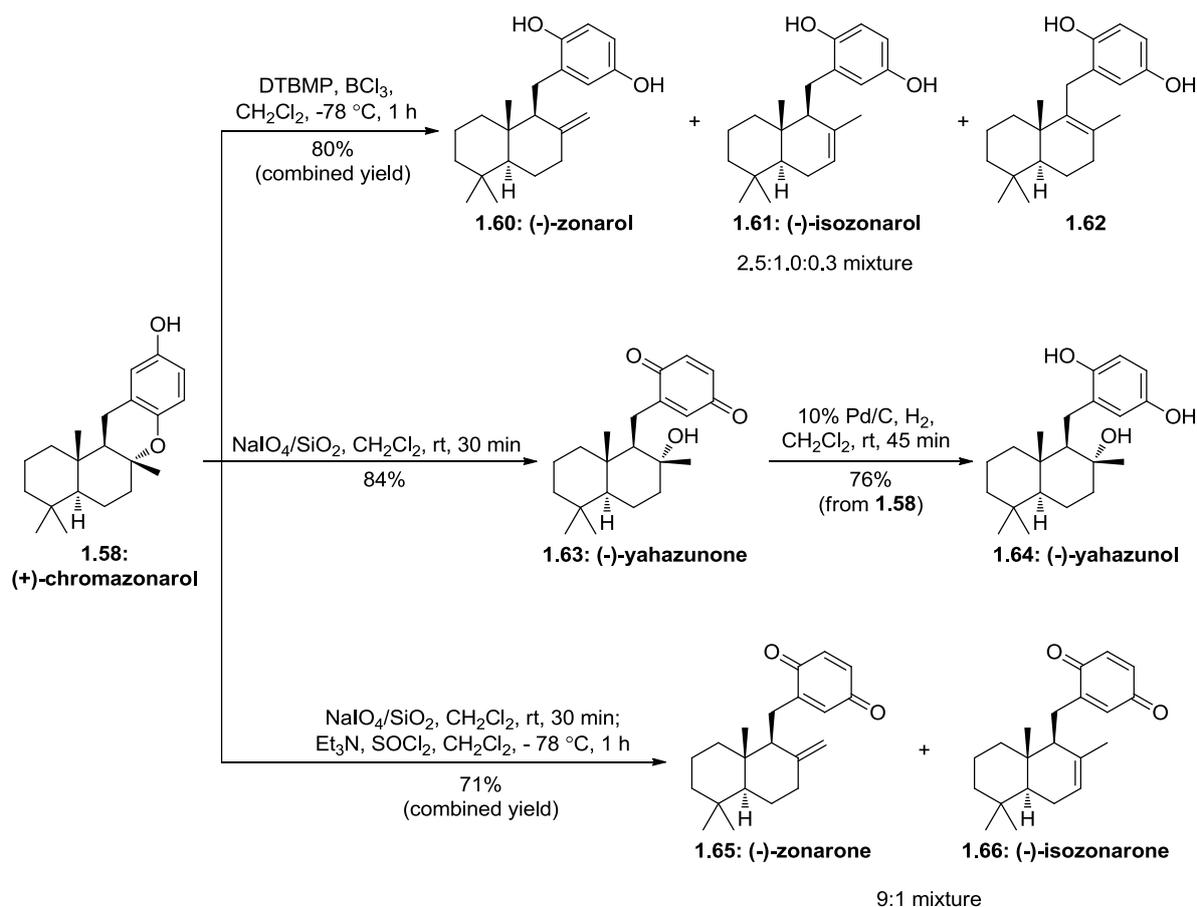
Scheme 1.9

Attempts to convert borono-sclareolide (**1.56**) to the more stable trifluoroborate **1.59** in the presence of  $\text{AgNO}_3$ ,  $\text{K}_2\text{S}_2\text{O}_8$ , and a slight excess of 1,4-benzoquinone, the reaction proved to be unsuccessful. Instead, a small amount of the natural product (+)-chromazonarol (**1.58**) was isolated from the reaction. This serendipitous discovery led to a highly efficient and scalable route towards (+)-chromazonarol (**1.58**) upon optimisation of the reaction conditions (Scheme 1.10). In addition, **1.56** would later serve as precursor for the synthesis of other marine meroterpenoids.



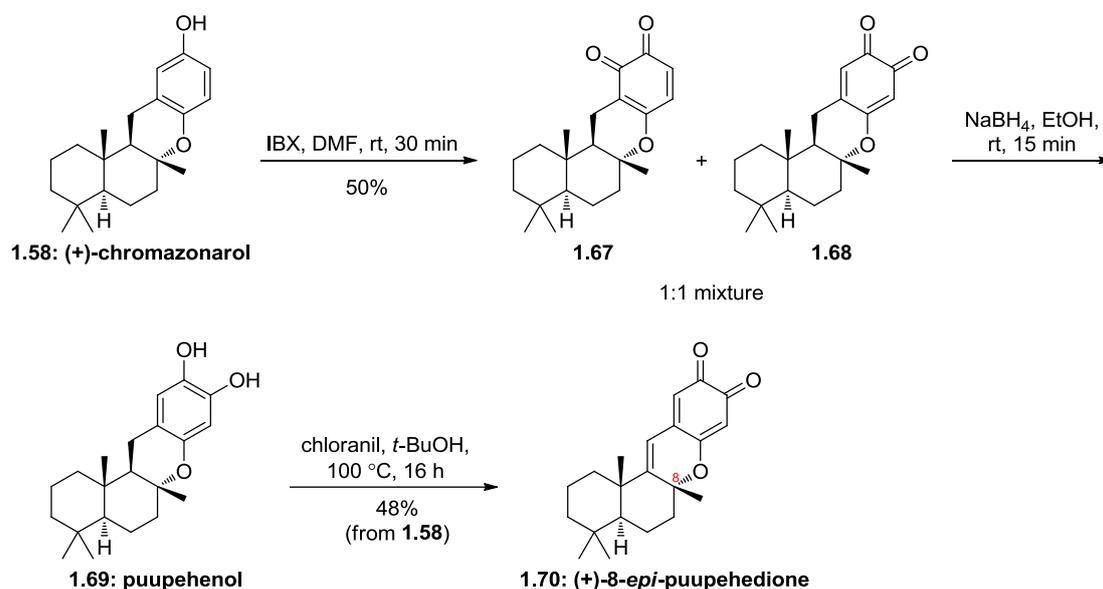
Scheme 1.10

For instance, by treating **1.58** with  $\text{BCl}_3$  in the presence of 2,6-di-tert-butyl-4-methylpiperidine (DTBMP) at  $-78\text{ }^\circ\text{C}$ , a mixture of (–)-zonarol (**1.60**), (–)-isozonarol (**1.61**) and hydroquinone **1.62** was obtained in a 2.5:1.0:0.3 ratio (Scheme 1.11, top). Additionally, **1.58** could undergo an oxidative cleavage reaction in the presence of  $\text{NaIO}_4$  embedded in silica gel to give (–)-yahazunone (**1.63**), as depicted in Scheme 1.11 (mid). Furthermore, hydrogenation of **1.63** would lead to the formation of (–)-yahazunol (**1.64**). Transformations of **1.58** are not only limited to stepwise reactions; oxidative cleavage and dehydration reaction of **1.58** can be conducted in a single-pot operation to give a 9:1 mixture of (–)-zonarone (**1.65**) and (–)-isozonarone (**1.66**) with a combined yield of 71% (Scheme 1.11, bottom).



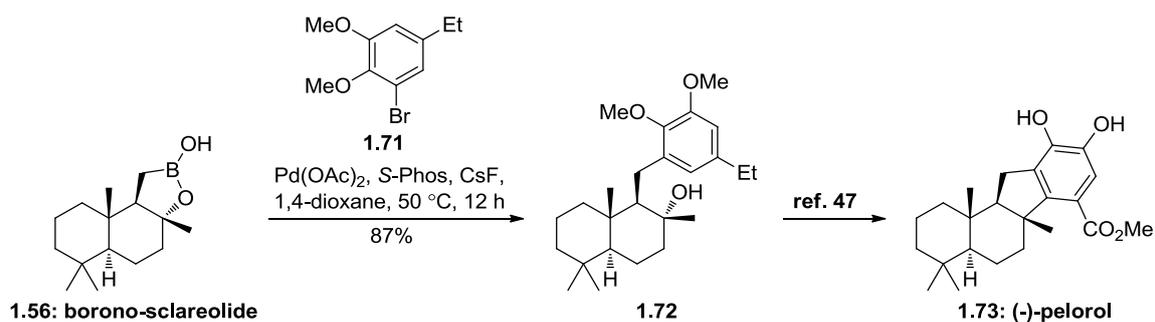
Scheme 1.11

Treatment of **1.58** with IBX in DMF yielded a 1:1 mixture of *o*-quinone products **1.67** and **1.68**, which were separable by flash column chromatography (Scheme 1.12). **1.68** could be reduced with NaBH<sub>4</sub> in EtOH to give puupehenol (**1.69**), and subsequently oxidised again to give (+)-8-*epi*-puupehedione (**1.70**).



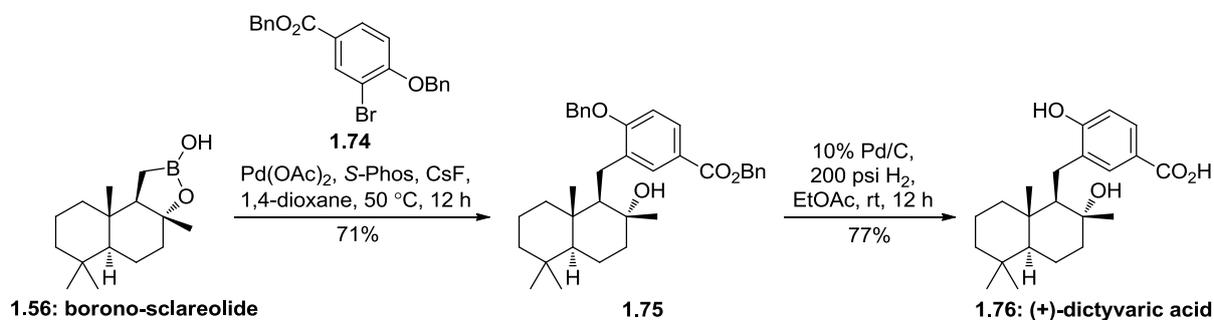
Scheme 1.12

Borono-sclareolide (**1.56**) could also undergo a Suzuki coupling with an aryl bromide. Therefore, according to Buchwald's modified procedure,<sup>46</sup> aryl bromide **1.71** was coupled to Borono-sclareolide (**1.56**) in the presence of Pd(OAc)<sub>2</sub> and *S*-Phos as a chiral ligand under basic conditions to yield tertiary alcohol **1.72** (Scheme 1.13). Since **1.72** had been previously converted into (–)-pelorol (**1.73**) by Anderson,<sup>47</sup> this approach constitutes a formal synthesis of the natural product.



Scheme 1.13

The first synthesis of (+)-dictyvaric acid (**1.76**) was also conducted in a similar manner (Scheme 1.14). Coupling of aryl bromide **1.74** to **1.56** would give tertiary alcohol **1.75**, followed by global deprotection of **1.75** under hydrogenation conditions at 200 psi to afford natural product in just seven steps, starting from (+)-sclareolide (**1.19**).



Scheme 1.14

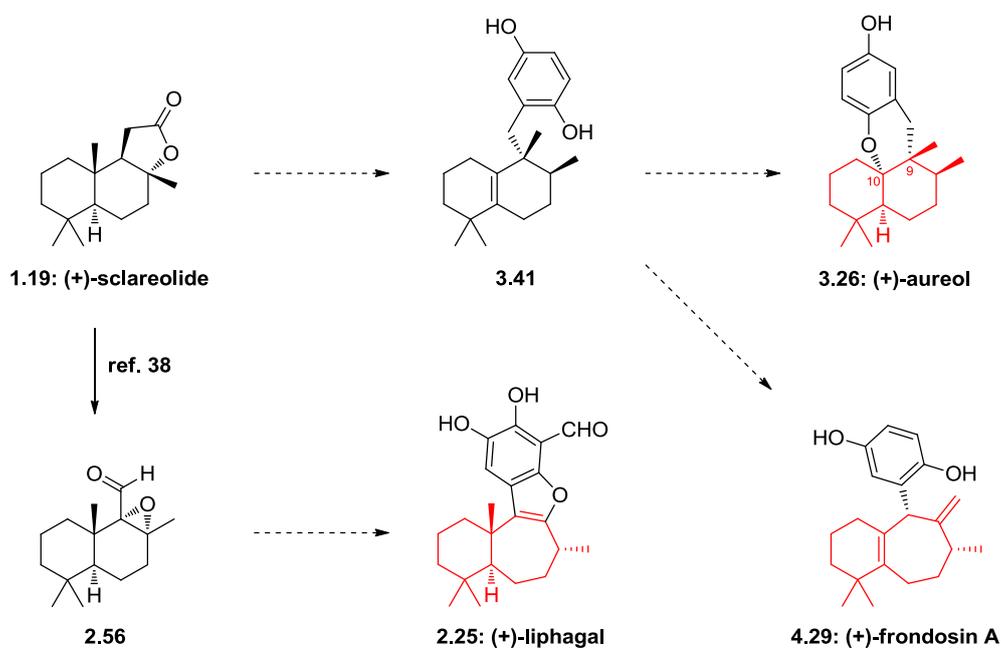
Baran's divergent approach towards these marine natural products, via borono-sclareolide (**1.56**), resulted in an improved synthesis of nine meroterpenoids, a formal synthesis

of (-)-pelorol (**1.73**) and the first total synthesis of (+)-dictyvaric acid (**1.76**). More recently, this method was extended towards the synthesis of (+)-hongoquercin A.<sup>48</sup>

## 1.4 Research Outlook

As previously described in section 1.2, a vast array of natural products have been assembled using the (+)-sclareolide (**1.19**). The sesquiterpene backbone is preserved almost exclusively, and manipulations of the molecule were mainly performed on the lactone ring. Our aim was to exploit the synthetic utility of **1.19** by converting it into other meroterpenoid natural products. Targets of interests include:

1. (+)-Liphagal, a unique 6,7-benzofuran fused natural product,
2. (+)-Aureol, a constitutional isomer of (+)-chromazonarol (**1.58**), with the cycloether connected at the C-10 carbon and the methyl group shifted to the C-9 carbon, and
3. (-)-Frondosin A, a unique meroterpenoid with an unusual bicyclo[5.4.0]undecane ring system attached to a hydroquinone moiety.



Scheme 1.23

## 1.5 References

1. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311-335.
2. Butler, M. S.; Buss, A. D. *Biochem. Pharmacol.* **2006**, *71*, 919-929.
3. Dias, D. A.; Urban, S.; Roessner, U. *Metabolites* **2012**, *2*, 303-336.
4. Rishton, G. M. *Am. J. Cardiol.* **2008**, *101*, S43-S49.
5. Cragg, G. M.; Newman, D. J. *Biochim. Biophys. Acta, Gen. Subj.* **2013**, *1830*, 3670-3695.
6. Laport, M. S.; Santos, O. C. S.; Muricy, G. *Curr. Pharm. Biotechnol.* **2009**, *10*, 86-105.
7. Newman, D.; Cragg, G. *Mar. Drugs* **2014**, *12*, 255-278.
8. Shan, W.-G.; Ying, Y.-M.; Ma, L.-F.; Zhan, Z.-J., Chapter 6 - Drimane-Related Merosquiterpenoids, a Promising Library of Metabolites for Drug Development. In *Studies in Natural Products Chemistry*, Atta ur, R., Ed. Elsevier 2015; Vol. Volume 45, pp 147-215.
9. Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553-80.
10. Heathcock, C. H. *Proc. Natl. Acad. Sci. U. S. A.* **1996**, *93*, 14323-14327.
11. Robinson, R. *J. Chem. Soc., Trans.* **1917**, *111*, 762-8.
12. Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332-4334.
13. Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51-98.
14. Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777-4779.
15. Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730-4756.
16. Barton, D. H. R.; Deflorin, A. M.; Edwards, O. E. *J. Chem. Soc.* **1956**, 530-534.
17. Brophy, G. C.; Mohandas, J.; Slaytor, M.; Sternhell, S.; Watson, T. R.; Wilson, L. A. *Tetrahedron Lett.* **1969**, *10*, 5159-5162.

18. Topcu, G.; Ulubelen, A.; Tam, T. C.-M.; Che, C.-T. *J. Nat. Prod.* **1996**, *59*, 113-116.
19. Radulović, N.; Stojanović, G.; Palić, R.; Alagić, S. *J. Essent. Oil Res.* **2006**, *18*, 562-565.
20. Upar, K. B.; Mishra, S. J.; Nalawade, S. P.; Singh, S. A.; Khandare, R. P.; Bhat, S. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1637-1640.
21. Kirk-Othmer, *Chemical Technology of Cosmetics*. John Wiley & Sons 2012.
22. Serra, S.; Fuganti, C.; Brenna, E. *Trends Biotechnol.* **2005**, *23*, 193-198.
23. Aranda, G.; El Kortbi, M. S.; Lallemand, J. Y.; Neuman, A.; Hammoumi, A.; Facon, I.; Azerad, R. *Tetrahedron* **1991**, *47*, 8339-50.
24. Hanson, J. R.; Truneh, A. *Phytochemistry* **1996**, *42*, 1021-1023.
25. Atta ur, R.; Farooq, A.; Choudhary, M. I. *J. Nat. Prod.* **1997**, *60*, 1038-1040.
26. Ata, A.; Conci, L. J.; Betteridge, J.; Orhan, I.; Sener, B. *Chem. Pharm. Bull.* **2007**, *55*, 118-123.
27. Cano, A.; Ramirez-Apan, M. T.; Delgado, G. *J. Braz. Chem. Soc.* **2011**, *22*, 1177-1182.
28. Helmlinger, D.; Frater, G. *Tetrahedron Lett.* **1992**, *33*, 6119-22.
29. George, J. H.; McArdle, M.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron* **2010**, *66*, 6321-6330.
30. Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847-12849.
31. Riofski, M. V.; John, J. P.; Zheng, M. M.; Kirshner, J.; Colby, D. A. *J. Org. Chem.* **2011**, *76*, 3676-3683.
32. Zhou, M.; Hintermair, U.; Hashiguchi, B. G.; Parent, A. R.; Hashmi, S. M.; Elimelech, M.; Periana, R. A.; Brudvig, G. W.; Crabtree, R. H. *Organometallics* **2013**, *32*, 957-965.
33. Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389-14392.

34. Frija, L. M. T.; Frade, R. F. M.; Afonso, C. A. M. *Chem. Rev.* **2011**, *111*, 4418-4452.
35. Chackalamannil, S.; Wang, Y.; Xia, Y.; Czarniecki, M. *Tetrahedron Lett.* **1995**, *36*, 5315-5318.
36. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron* **1998**, *54*, 5635-5650.
37. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortes, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181-15208.
38. George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394-2397.
39. Margaros, I.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2007**, *9*, 5585-5588.
40. Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057-2068.
41. Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595-1615.
42. Lian, Y.; Miller, L. C.; Born, S.; Sarpong, R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 12422-12425.
43. Justicia, J.; Oller-López, J. L.; Campaña, A. G.; Oltra, J. E.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911-14921.
44. Kumar, C. N. S. S. P.; Chein, R.-J. *Org. Lett.* **2014**, *16*, 2990-2992.
45. Dixon, D. D.; Lockner, J. W.; Zhou, Q.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 8432-8435.
46. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871-1876.
47. Yang, L.; Williams, D. E.; Mui, A.; Ong, C.; Krystal, G.; van Soest, R.; Andersen, R. *J. Org. Lett.* **2005**, *7*, 1073-1076.
48. Rosen, B. R.; Simke, L. R.; Thuy-Boun, P. S.; Dixon, D. D.; Yu, J.-Q.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7317-7320.

## CHAPTER TWO

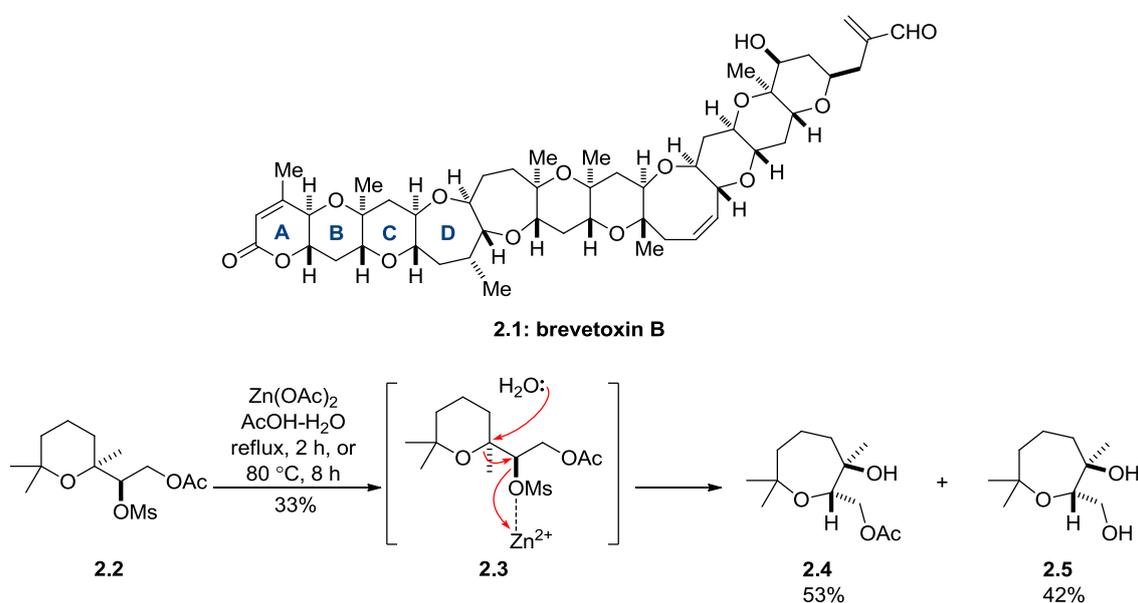
### Synthetic Studies on (+)-Liphagal

#### 2.1 Formation of Seven-Membered Rings in Total Synthesis by Ring Expansion

Organic chemists are often intrigued by the structural diversity of natural products. While nature has evolved over time to develop enzymes and metabolic pathways that are responsible for the rapid construction of complex cyclic scaffolds, synthesis of these carbon frameworks remains a challenge in the laboratory. Therefore, new synthetic methodologies are constantly being developed to enable access to these novel structures. For example, seven-membered ring systems are a common occurrence in nature and can be found in a plethora of natural products. However, commercially available cycloheptanoid starting materials are uncommon and therefore have found limited applications in total synthesis. Over the years, several strategies have been utilised for the construction of this structural motif. Seven-membered ring systems, derived from either fragmentation of smaller fused ring systems, heteroatom insertion reactions, radical cyclisations, [4+3] or [5+2]-cycloaddition reactions, ring expansions, and more recently, ring-closing metathesis (RCM), have received significant interest among the synthetic community.<sup>1-9</sup>

Synthetic studies towards the formation of the seven-membered ring systems in polycyclic natural products represent one such example. For instance, Nakata and co-workers investigated the formation of the D ring found in the polycyclic marine natural product

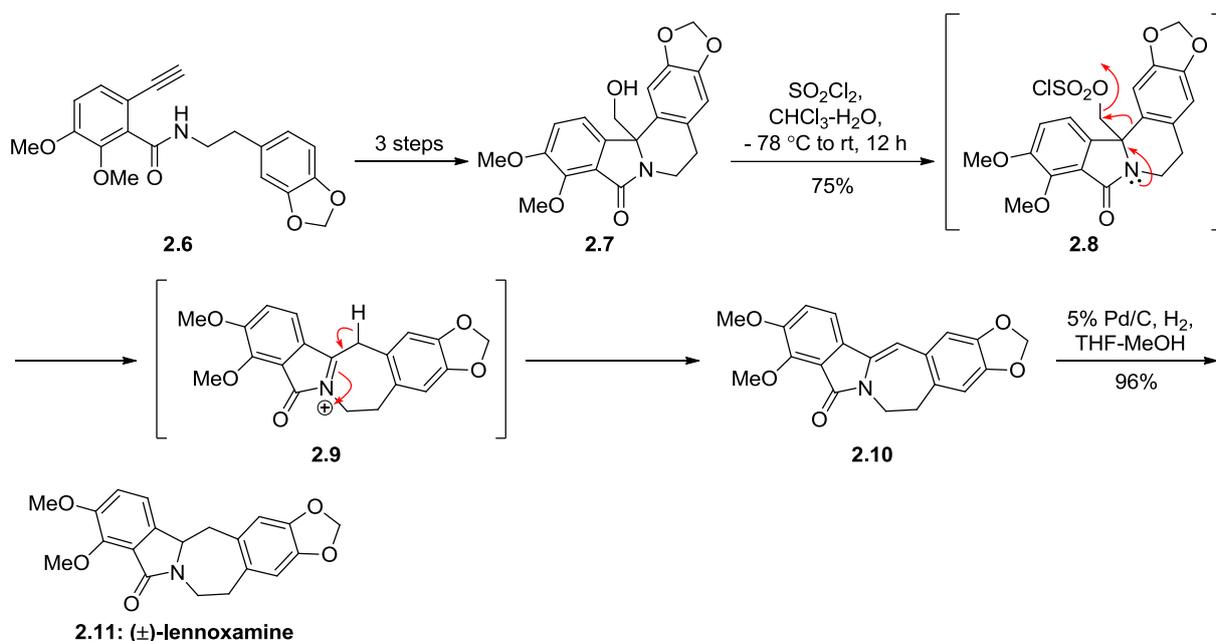
brevetoxin B (**2.1**) using a simplified model system (Scheme 2.1).<sup>10</sup> In the course of their study, the authors reported that the tetrahydropyran **2.2** underwent a ring expansion reaction in the presence of  $\text{Zn}(\text{OAc})_2$  under acidic conditions, forming cycloether **2.4** in 53% yield along with the hydrolysed diol **2.5** in 42% yield. Ring expansion was thought to have taken place in a stepwise manner via intermediate **2.3**, with the OMs group chelating to  $\text{Zn}^{2+}$ . This ring expansion strategy has also been applied to the synthesis of other polycyclic natural products containing seven-membered ring systems.<sup>11</sup>



Scheme 2.1

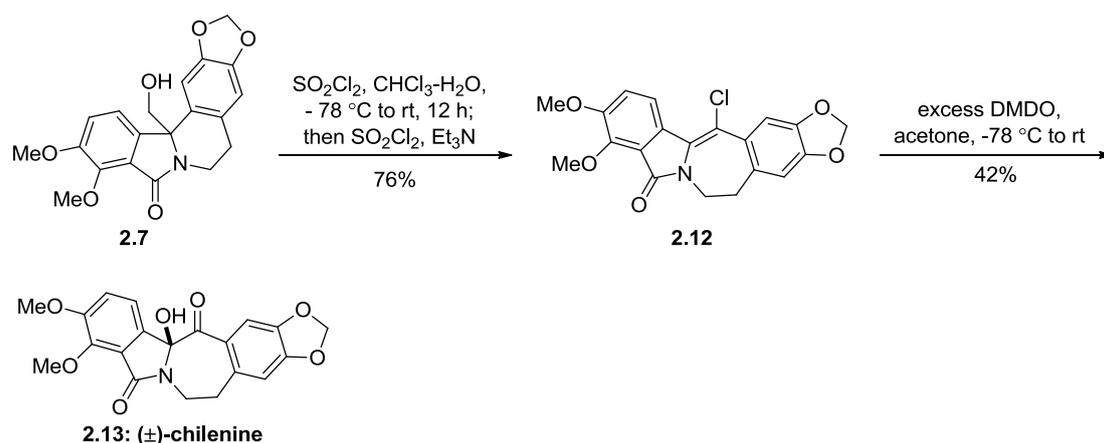
In 1999, Nagasaka's group reported the use of a novel ring expansion strategy as a general method of accessing isoindole-containing alkaloids ( $\pm$ )-lennoxamine (**2.11**) and ( $\pm$ )-chilenine (**2.13**).<sup>12</sup> This unified approach first involved the synthesis of key intermediate isoindole **2.7** from benzamide **2.6** over three steps (Scheme 2.2). Chlorosulfonylation of the hydroxy group with  $\text{SO}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  then afforded intermediate **2.8**. Upon warming to room

temperature, ring expansion of **2.8** produced the stable acyliminium cation intermediate **2.9**, which was followed by loss of a proton to yield **2.10**. Pd-catalysed hydrogenation of **2.10** would then deliver lennoxamine (**2.11**) as a racemic mixture.



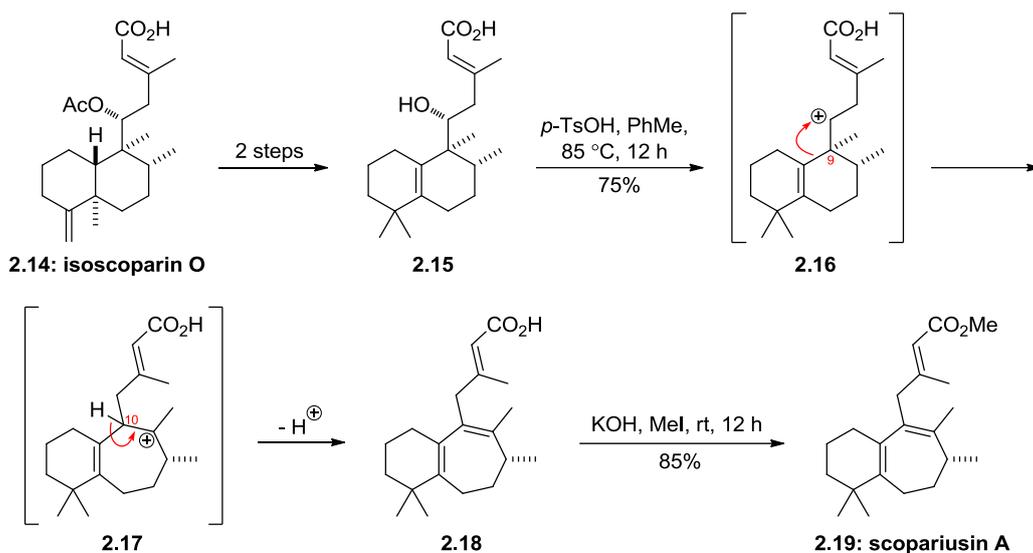
Scheme 2.2

On the other hand, *in-situ* chlorination of **2.10** by further addition of  $\text{SO}_2\text{Cl}_2$  at room temperature gave chloroisindole **2.12**, which was later oxidised with excess DMDO to produce ( $\pm$ )-chilenine (**2.13**) (Scheme 2.3).



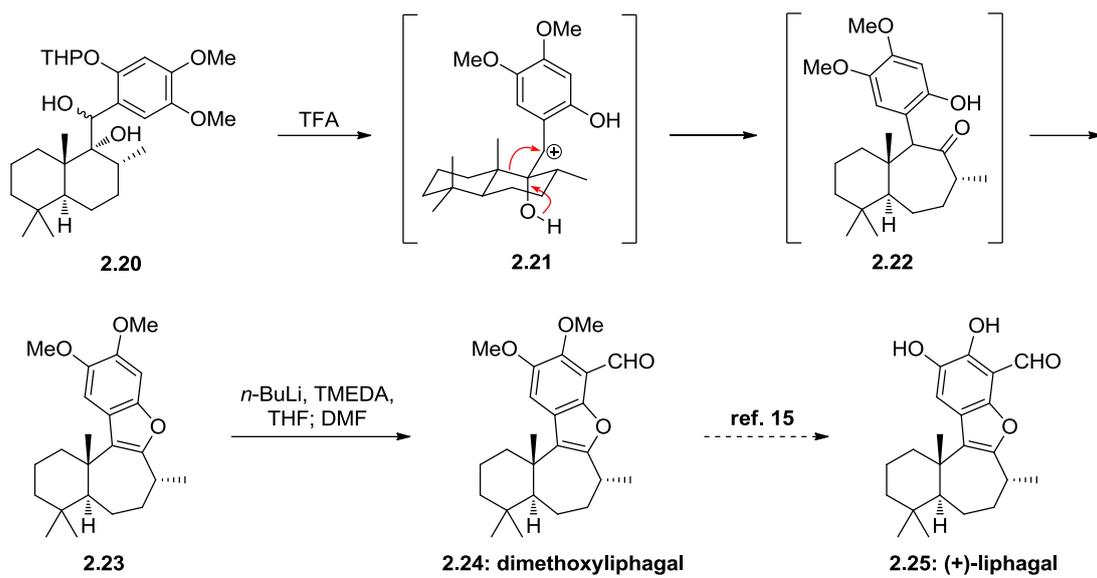
Scheme 2.3

Another example of seven-membered ring formation by way of alkyl shifts can be found Sun's biomimetic semisynthesis of scopariusin A (**2.19**) starting from isoscoparin O (**2.14**).<sup>13</sup> The clerodane skeleton of **2.14** was first converted into alcohol **2.15** with an internal C=C bond (Scheme 2.4). Treatment of **2.15** with *p*-TsOH then formed the secondary carbocation intermediate **2.16**, which underwent ring expansion to produce the more stable tertiary carbocation intermediate **2.17**. Proton loss from the C-10 carbon afforded diene **2.18**, which was followed by an esterification reaction to yield the target molecule, scopariusin A (**2.19**).



Scheme 2.4

In 2010, George and co-workers reported a bio-inspired, enantiospecific synthesis of the marine meroterpenoid (+)-liphagal (**2.25**). The liphagane skeleton was formed through the pinacol rearrangement reaction of diol **2.20**, as shown in Scheme 2.5.<sup>14</sup> Benzylic carbocation **2.21** was generated *in situ* upon treatment of **2.20** with TFA. This was proceeded by a pinacol rearrangement to afford ketone **2.22**, followed by dehydration to form the benzofuran ring of **2.23**. *Ortho*-lithiation of benzofuran **2.23** and subsequent quenching of the resultant aryllithium species with DMF gave dimethoxyliphagal (**2.24**). Demethylation of the advanced intermediate **2.24** has been previously demonstrated by Andersen using BI<sub>3</sub> to produce the target molecule, (+)-liphagal (**2.25**).<sup>15</sup> As such, George's synthetic endeavour represents a formal synthesis of the natural product.



Scheme 2.5

## 2.2 Liphagal, an Isoform Selective Inhibitor of Phosphatidylinositol 3-Kinase (PI3K)

### 2.2.1 Isolation and Biological Activity

(+)-Liphagal (**2.25**) is a meroterpenoid natural product isolated by Andersen and co-workers in 2006 as part of an ongoing effort to identify novel isoform selective inhibitors of PI3K $\alpha$  (Figure 2.1).<sup>15</sup> Collected from the MeOH extracts of the Dominican marine sponge *Aka coralliphaga*, (+)-liphagal (**2.25**) displayed potent inhibitory activity against PI3K $\alpha$  with an IC<sub>50</sub> of 100 nM. (+)-Liphagal (**2.25**) was found to be less potent towards PI3K $\gamma$ , showing a 10-fold decrease in IC<sub>50</sub> activity. Furthermore, *in vitro* studies indicated that (+)-liphagal (**2.25**) exhibited cytotoxic activity towards human colon and breast cancer cells. To date, (+)-liphagal (**2.25**) represents the first natural product to display isoform selective inhibition towards PI3K enzymes. Intriguingly, the NMR data of (+)-liphagal (**2.25**) was similar to that of siphonodictyal B (**2.26**), a natural product previously isolated from *Aka coralliphaga* specimens found in Belize (Figure 2.1).<sup>16, 17</sup> While the structural features suggested that both natural products may be related, a comprehensive analysis of the 2D NMR data later revealed that (+)-liphagal (**2.25**) possessed a unique 6,7- ring system fused to a benzofuran moiety. We have recently published the first total synthesis and structure reassignment of siphonodictyal B.<sup>18</sup> Upon thorough comparison of our spectroscopic data with the isolated natural product, we deduced that the C-10 and C-8 methyl groups in siphonodictyal B (**2.26**) exist in the *trans* configuration, and not *cis*, as previously assigned by Faulkner.<sup>16, 17, 19</sup>

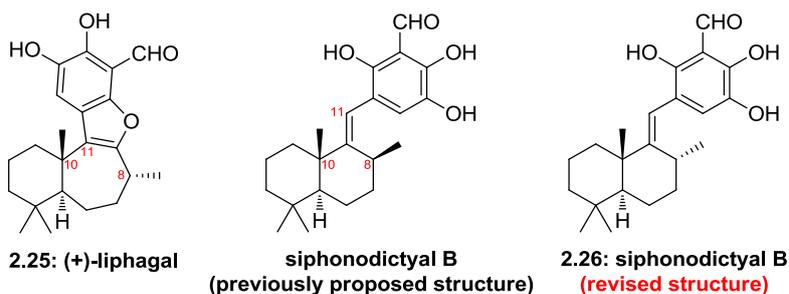


Figure 2.1: *Aka coralliphaga* marine sponge, the chemical structure of liphagal (**2.25**), proposed chemical and revised structures of siphonodictyal B (**2.26**).

### 2.2.2 Computational Studies on Liphagal

Two docking studies were conducted on (+)-liphagal (**2.25**). Wright and co-workers first docked the structure of wortmannin (**2.27**) to the PI3K $\gamma$  active site in order to assess the orientation of the amino acid residues with respect to **2.27**.<sup>20</sup> As **2.27** is the most active inhibitor of PI3K $\gamma$ , it was assumed that this docking model could be transposed to (+)-liphagal (**2.25**). Indeed, Wright and co-workers were able to establish several important interactions between liphagal (**2.25**) and the enzyme active site (Figure 2.2).

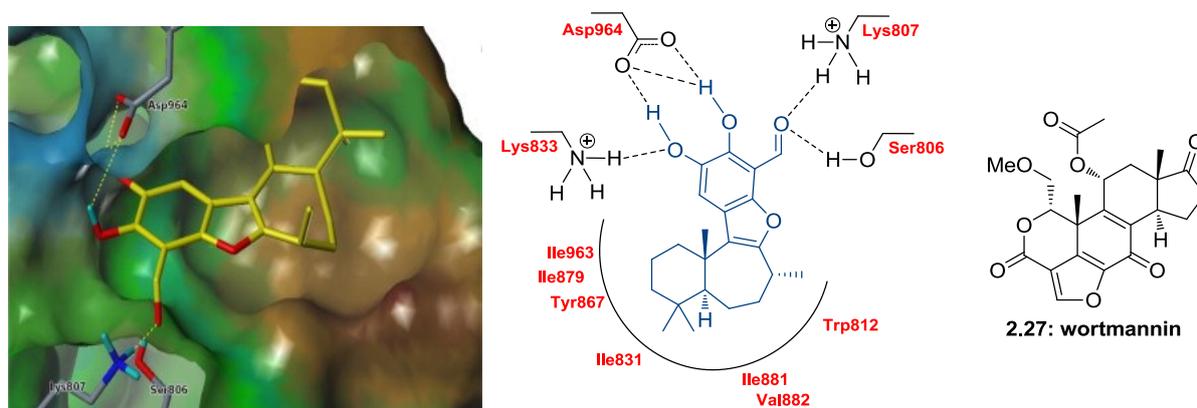


Figure 2.2: Left – Docked model of (+)-liphagal (**2.25**) to PI3K $\gamma$ ; Right – interaction map between (+)-liphagal (**2.25**) with PI3K $\gamma$ .

(+)-Liphagal (**2.25**) was docked against PI3K $\alpha$  H1047R mutant using molecular dynamics simulation by Zhong and co-workers (Figure 2.3).<sup>21</sup> The H1047R mutant was chosen for this study as it was the most prevalent mutation found in PI3K $\alpha$ . Approximately 80% of various known cancer cells displayed this specific mutation, which results in a two-fold increase in enzymatic activity.<sup>22</sup> Ligand interactions between (+)-liphagal (**2.25**) and PI3K $\alpha$  H1047R indicated hydrogen bonding with Tyr836, Lys802 and Asp933 residues (Figure 2.3, right). Similar hydrogen bonding interactions were also reported in the PI3K $\alpha$  H1047R mutant co-crystallised with wortmannin (**2.27**).<sup>23</sup> More importantly, no such interactions were observed between liphagal and PI3K $\gamma$ , which was consistent with the *in vitro* assay results reported by Andersen.<sup>15</sup> Structure activity relationship (SAR) studies conducted by Andersen and co-workers further strengthens the computational result, as monomethyl or dimethyl derivatives of liphagal showed a decrease in PI3K $\alpha$  inhibition.<sup>24</sup> The removal of the aldehyde or phenol functionality also produced a loss in inhibitory activity. From these results, it is clear that the highly substituted aromatic ring is required for PI3K $\alpha$  inhibitory activity.

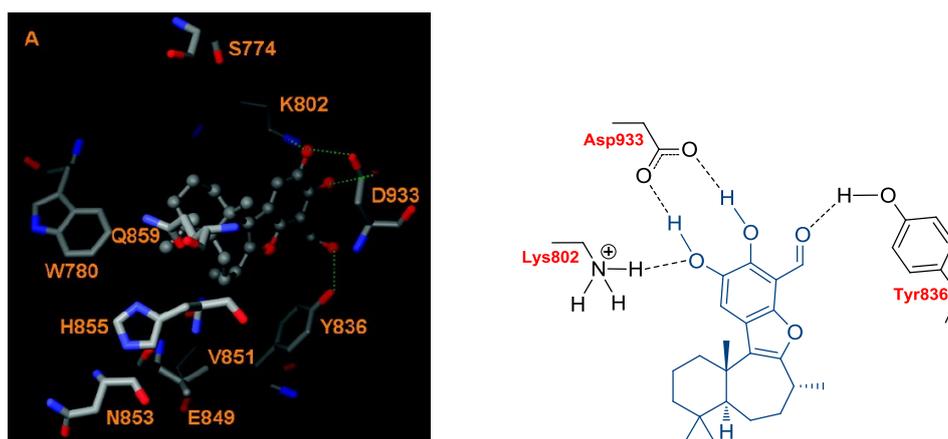
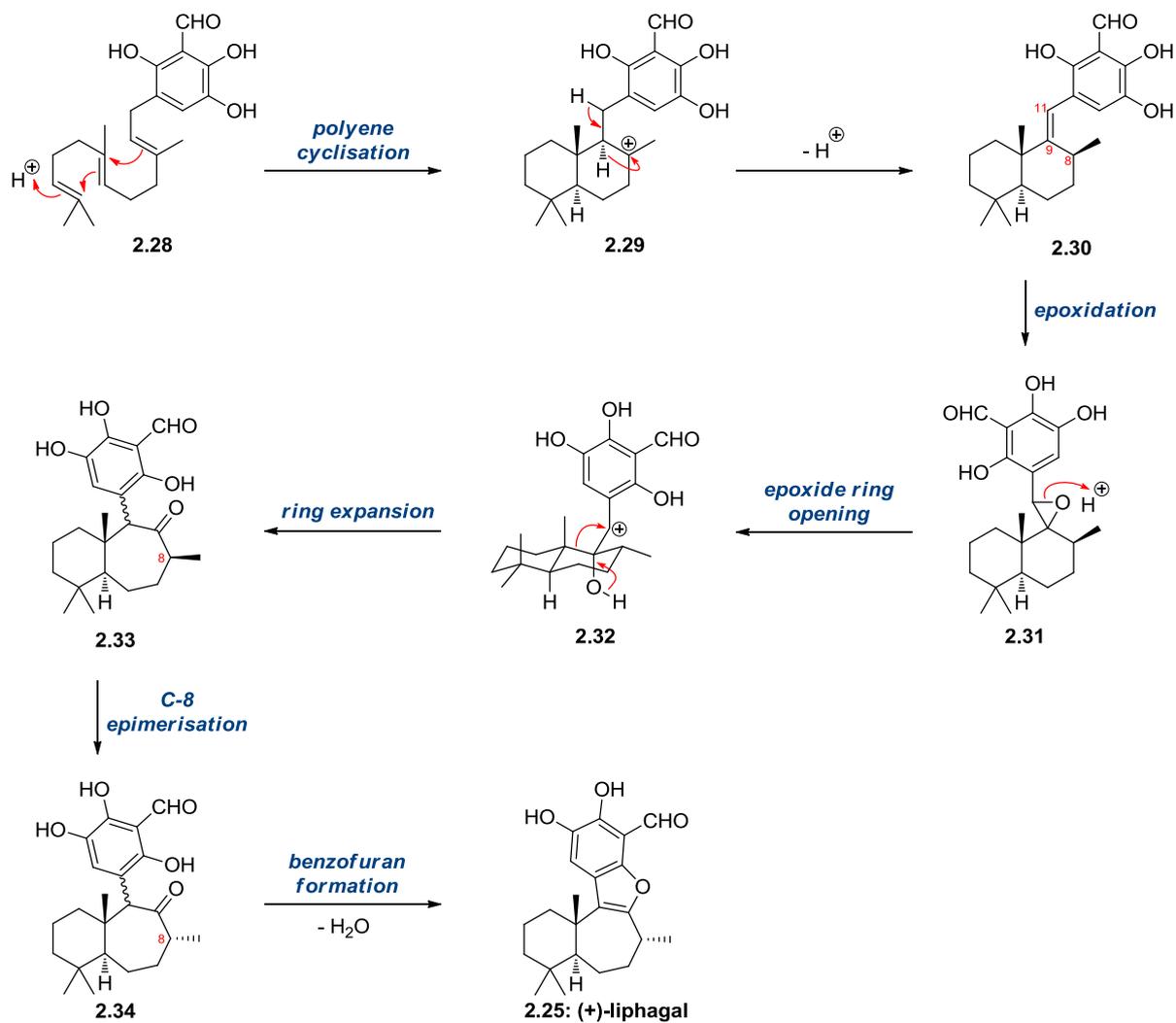


Figure 2.3: Left – Docked model of (+)-liphagal (**2.25**) to PI3K $\alpha$ ; Right – interaction map between (+)-liphagal (**2.25**) with PI3K $\alpha$ .

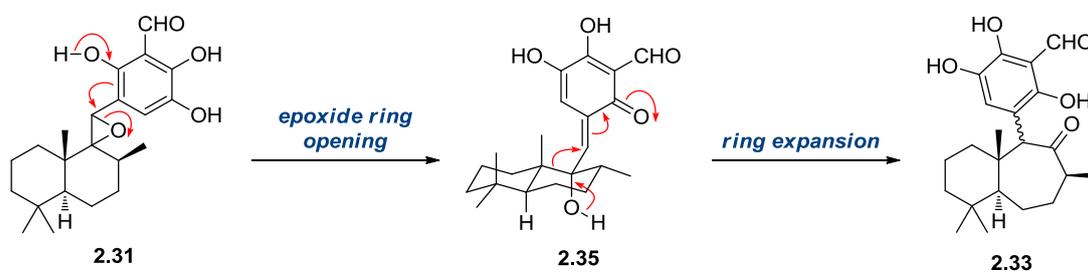
### 2.3 Biosynthesis of Liphagal

Although the biosynthesis of (+)-liphagal (**2.25**) has not been studied in detail, Andersen proposed two plausible biogenetic pathways for the formation of (+)-liphagal (**2.25**) in nature.<sup>15</sup> The first, pathway A (Scheme 2.6), involves the polyene cyclisation of the farnesyl side chain of trihydroxybenzaldehyde **2.28** to generate the tertiary carbocation intermediate **2.29**. A hydride shift, accompanied by deprotonation of **2.29** would then form trihydroxybenzaldehyde **2.30**, a C-8 epimer of siphonodictyal B (**2.26**). Epoxidation of **2.30** would afford a stable benzylic carbocation intermediate **2.32**, which is followed by a ring expansion of **2.32** to furnish cycloheptanone **2.33**. Finally, an epimerisation at the C-8 carbon would produce **2.34**, followed by benzofuran formation would then produce (+)-liphagal (**2.25**). In addition, George and co-workers reasoned that the ring expansion reaction of **2.31** in pathway A could also occur through *ortho*-quinone methide intermediate **2.35**, analogous to that of an  $\alpha$ -hydroxy aldehyde rearrangement or pinacol rearrangement (Scheme 2.7). George's seminal work on the formal synthesis of (+)-liphagal (**2.25**) suggests that the biosynthesis of the natural product via pathway A is more likely to occur in nature, since 6,6-ring formations are generally favoured in polyene cyclisation pathways.<sup>14</sup>

**Pathway A**



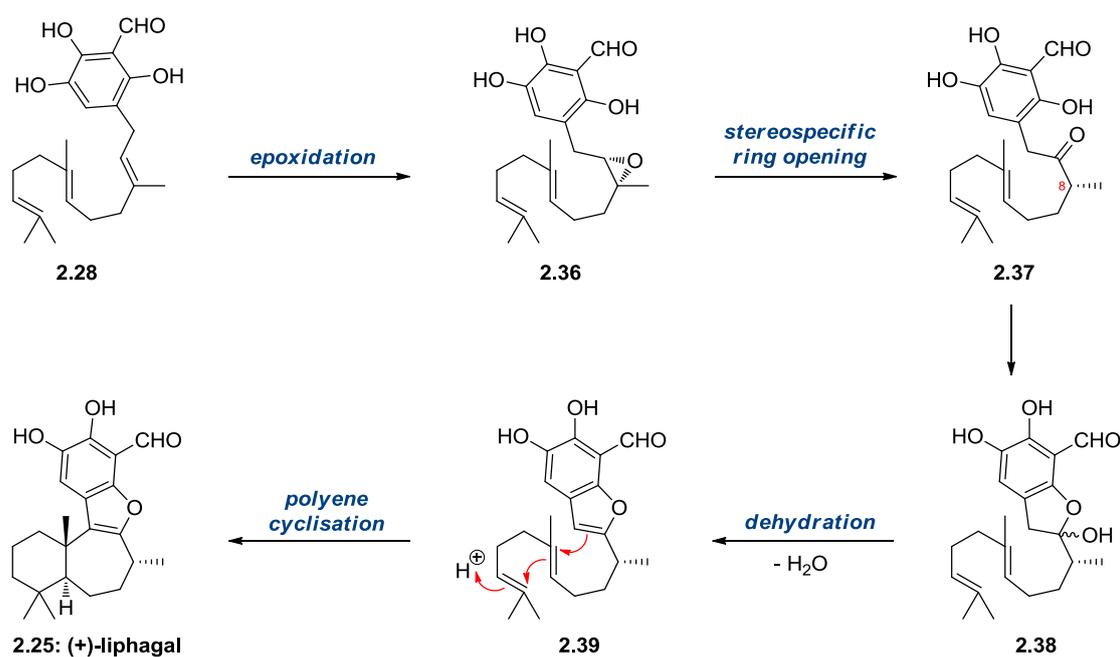
Scheme 2.6



Scheme 2.7

On the contrary, Andersen argued that initial pre-organisation of the benzofuran moiety is believed to assist in the polyene cyclisation step to generate the bicyclic 6,7- ring system, as proposed in pathway B (Scheme 2.8). This proposal first requires an epoxidation reaction to take place on the C=C bond closest to the aromatic ring of **2.28** to generate epoxide **2.36**. Presumably, a stereospecific ring opening and subsequent oxidation of the alcohol then produces ketone **2.37**. Hemiketal **2.38** can be spontaneously derived from ketone **2.37** and subsequent dehydration of **2.38** would provide the benzofuran ring of **2.39**. Ultimately, the natural product could then be realised by the polyene cyclisation of benzofuran **2.39**.

**Pathway B**

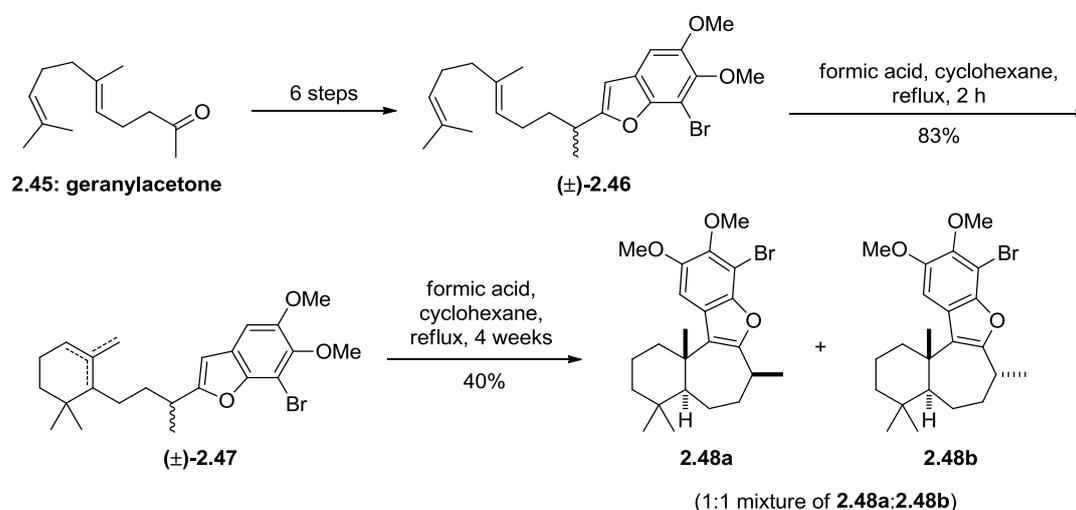


Scheme 2.8

## 2.4 Previous Synthetic Work

### 2.4.1 Andersen's Cationic Polyene Cyclisation Approach to (±)-Liphagal

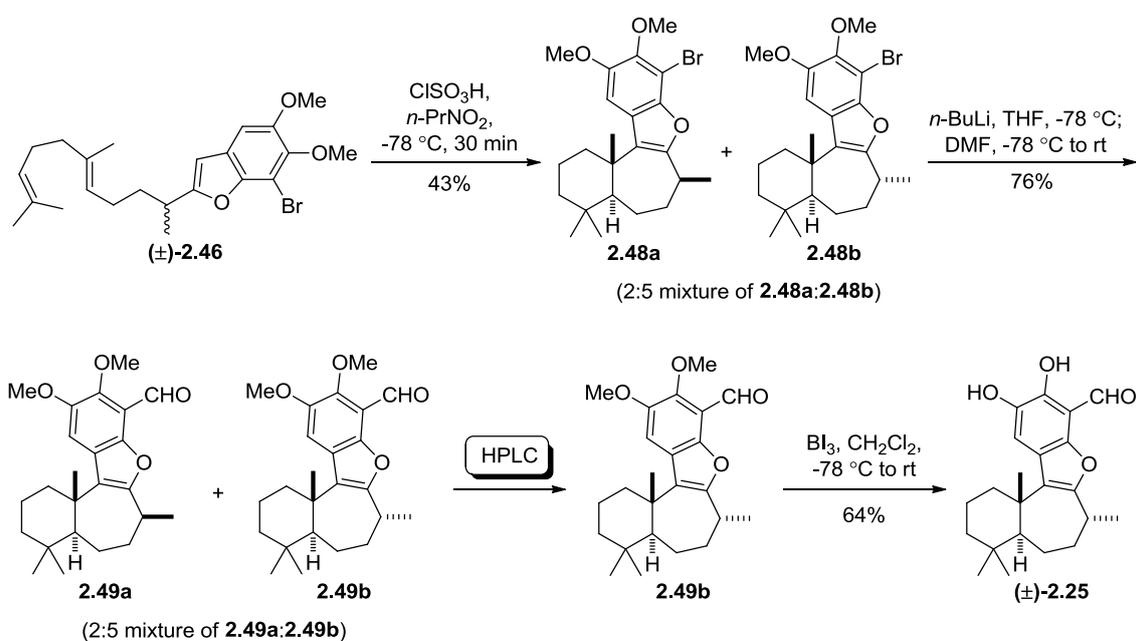
In conjunction with the proposed biosynthetic pathways, Andersen and co-workers also reported the synthesis of (±)-**2.25** in their original isolation paper.<sup>15</sup> Following their proposed pathway B, the total synthesis began with the conversion of geranylacetone (**2.45**) to benzofuran (±)-**2.46** over six steps (Scheme 2.9). The key cyclisation step was carried out by refluxing benzofuran (±)-**2.46** in a biphasic solution of formic acid and cyclohexanone. Partial cyclisation was observed after two hours to give a complex mixture of *endo*- and *exo*-cyclic alkene products. Prolonged heating of mixture (±)-**2.47** over a period of four weeks gave the desired tetracycles **2.48a** and **2.48b** in a modest yield of 40% as a 1:1 mixture of diastereomers.



Scheme 2.9

Alternatively, the generation of tetracycles **2.48a** and **2.48b** could be accelerated with the use of chlorosulfonic acid in nitropropane at  $-78\text{ }^{\circ}\text{C}$  (Scheme 2.10). While no distinct improvement in the yield of the cyclisation was observed, the diastereomeric ratio improved

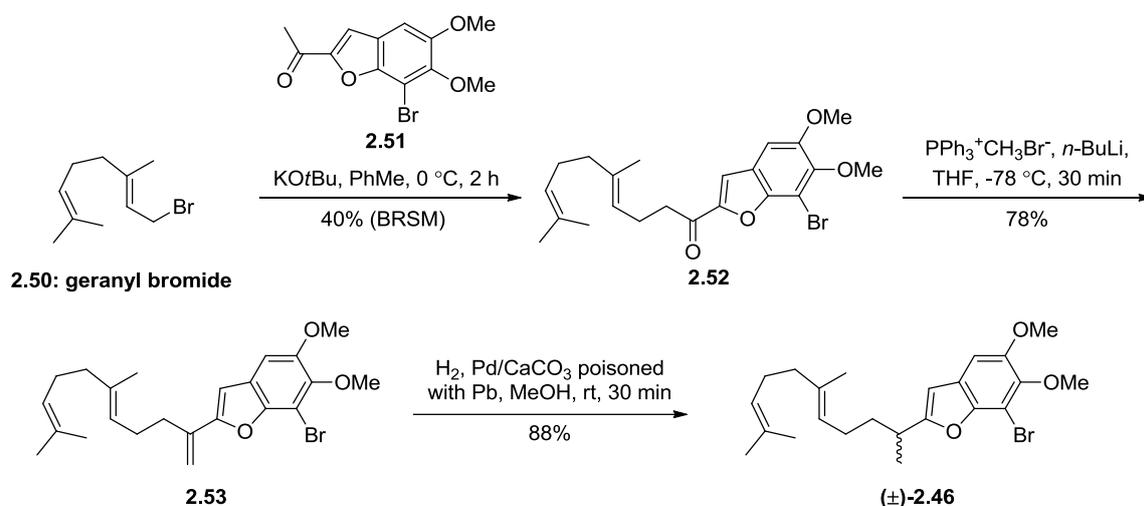
slightly to afford a 2:5 mixture of **2.48a** and **2.48b** in favour of the *trans* configuration. The aldehyde functionality was introduced via a lithium-halogen exchange reaction between mixtures of **2.48a** and **2.48b** with *n*-BuLi, followed by quenching of the aryllithium species with DMF to produce a mixture of **2.49a** and **2.49b**. The desired diastereoisomer was isolated by HPLC, and **2.49b** was demethylated with BI<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C to afford the racemic natural product in 64% yield. Andersen's route yielded the natural product in nine linear steps with an overall yield of 8%, and centred on the initial formation of the benzofuran ring, as proposed in pathway B.



#### 2.4.2 Mehta's Formal Synthesis of (±)-Liphagal

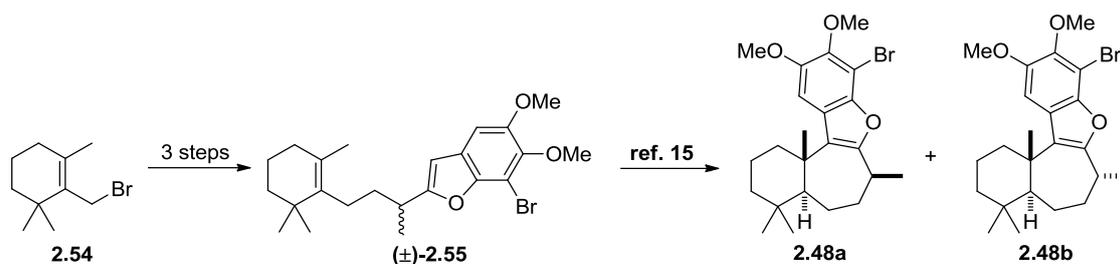
Mehta and co-workers also pursued the synthesis of liphagal following Andersen's proposed biosynthetic pathway B.<sup>25</sup> As shown in Scheme 2.11, enolisation of ketone **2.51**,

prepared in 3 steps from commercially available 2,4,5-trimethoxybenzaldehyde, with KOtBu and subsequent reaction with geranyl bromide (**2.50**) afforded ketone **2.52**. Wittig olefination of the ketone moiety then produced **2.53**, and the methylene group was selectively hydrogenated in the presence of Pd poisoned with CaCO<sub>3</sub> and Pb to give benzofuran (±)-**2.46**, Andersen's non-cyclised benzofuran intermediate.



Scheme 2.11

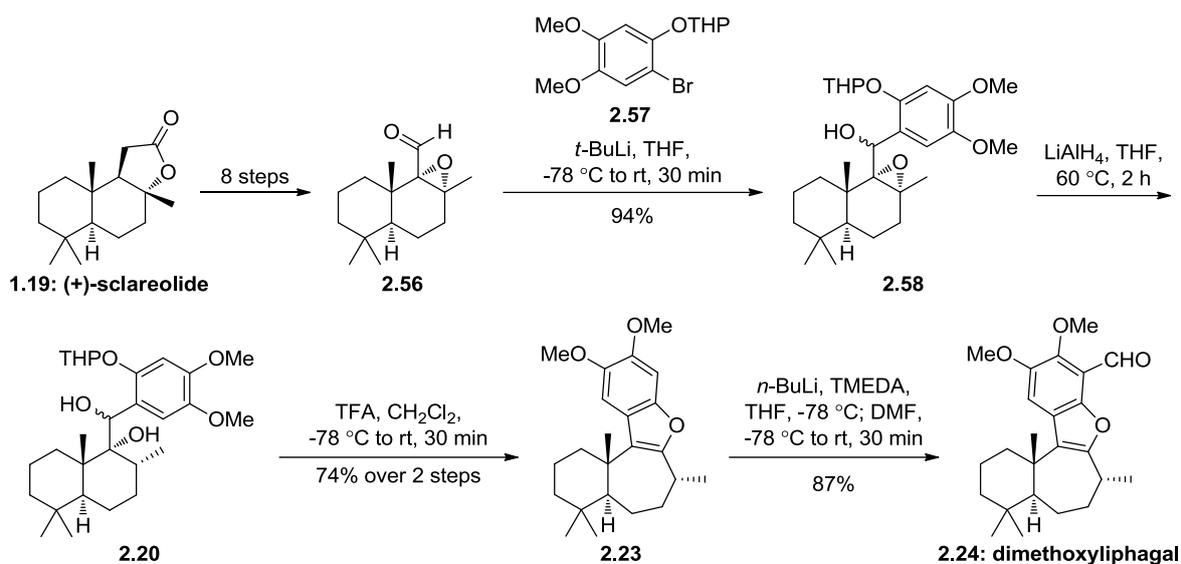
Alternatively, Mehta's group also showed that benzofuran (±)-**2.55**, an intermediate in the synthesis of **2.48a/b**, could be generated from cyclogeranyl bromide **2.54** in just three short steps (Scheme 2.12). As (±)-**2.46** and mixtures of **2.48a/b** have previously been synthesised by Andersen's group, Mehta's concise approach towards the tetracyclic core of liphagal constitutes a formal synthesis of the natural product.



Scheme 2.12

### 2.4.3 George's Enantiospecific Formal Synthesis of (+)-Liphagal

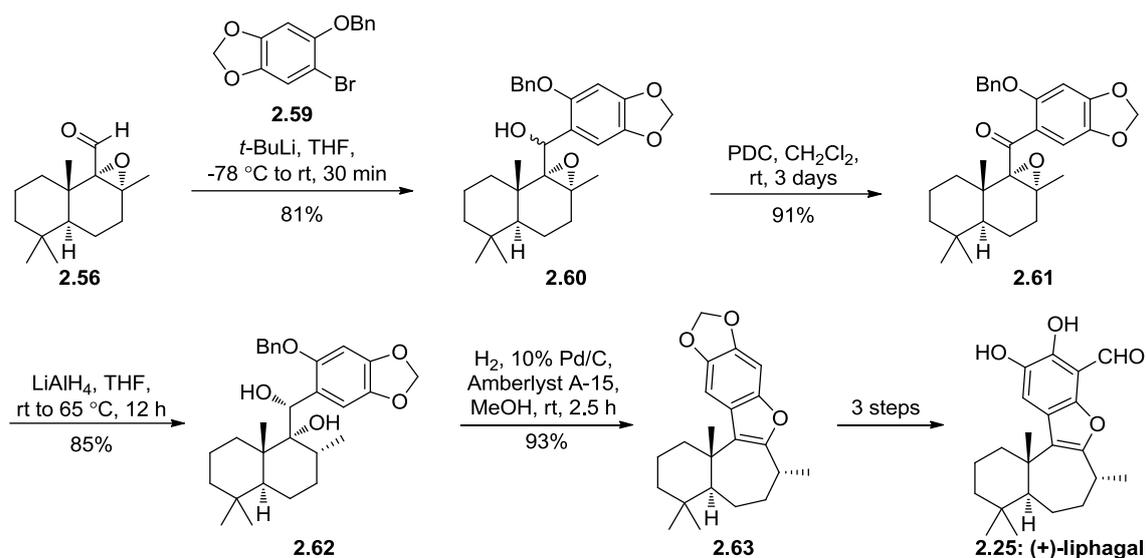
George and co-workers were the first to demonstrate an enantioselective, formal synthesis of (+)-liphagal (**2.25**) in 2010 which adheres to the proposed biosynthetic pathway A.<sup>14</sup> The synthesis began with the conversion of (+)-sclareolide (**1.19**) into aldehyde **2.56** over eight steps (Scheme 2.13). Aryl bromide **2.57** was reacted with *t*-BuLi, and the aryllithium species was reacted with aldehyde **2.56** to then form benzylic alcohol **2.58**. Stereospecific ring opening of the epoxide ring was achieved by treating alcohol **2.58** with LiAlH<sub>4</sub> and heating the resultant solution to 60 °C. Diol **2.20** was then treated with TFA to initiate a pinacol ring expansion, followed by *in situ* dehydration to afford tetracyclic benzofuran **2.23**. Finally, an *ortho*-lithiation protocol with *n*-BuLi, TMEDA and DMF then furnished dimethoxyliphagal (**2.24**). George's formal synthesis of (+)-liphagal (**2.25**), which mimics the proposed biosynthetic pathway A, was achieved in 13 steps with an overall yield of 9% starting from (+)-sclareolide (**1.19**).



Scheme 2.13

#### 2.4.4 Alvarez-Manzaneda's Total Synthesis of (+)-Liphagal

Shortly after George's publication, an enantioselective total synthesis of the meroterpenoid natural product was accomplished by Alvarez-Manzaneda's group. Construction of benzylic alcohol **2.60** was almost identical to George's approach, varying only by the use of different protecting groups on aryl bromide **2.59** (Scheme 2.14).<sup>26</sup> Benzylic alcohol **2.60** was first oxidised to ketone **2.61** with PDC in CH<sub>2</sub>Cl<sub>2</sub> over three days; subsequent treatment with LiAlH<sub>4</sub> under refluxing conditions over 12 hours provided the key diol **2.62**. The authors discovered that hydrogenation of the benzyl group in the presence of a cationic resin, such as Amberlyst A-15, provided the ring expanded benzofuran **2.63** in a single operation. Finally, benzofuran **2.63** could be converted into (+)-liphagal (**2.25**) over three steps.

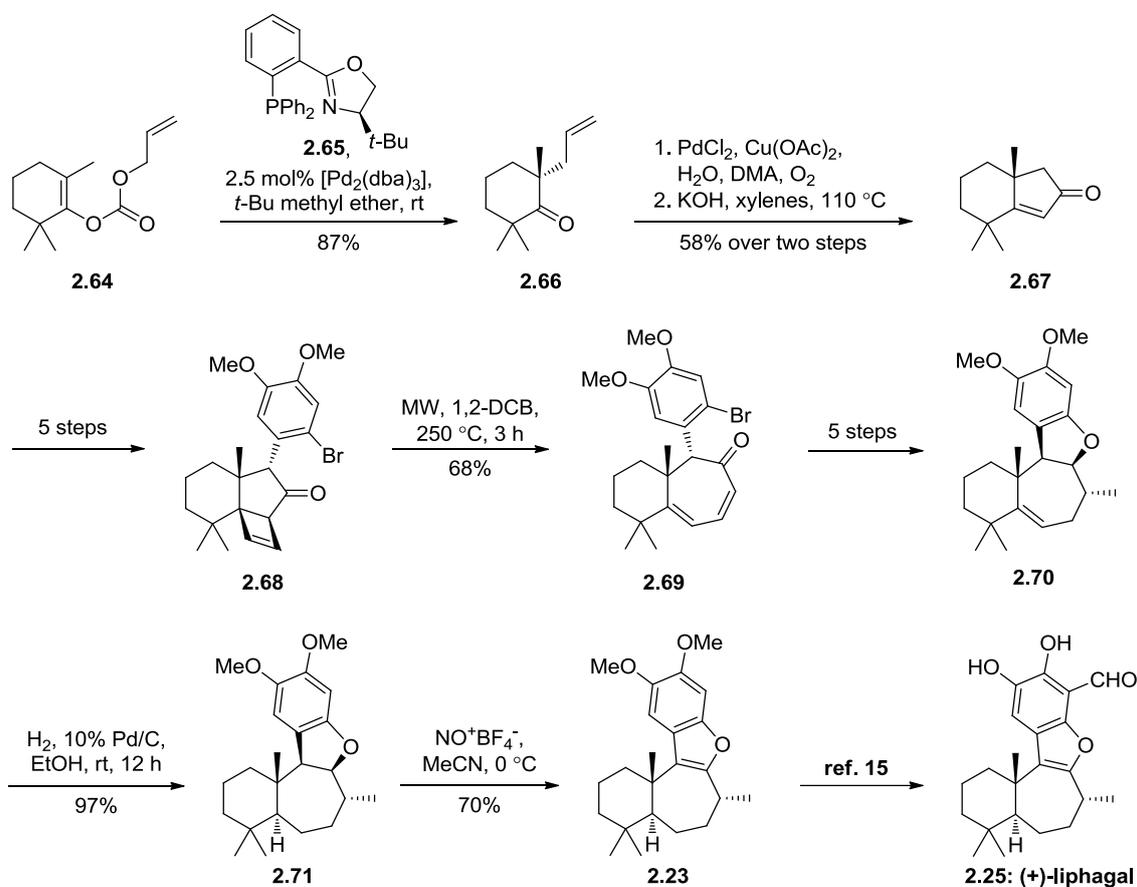


Scheme 2.14

#### 2.4.5 Stoltz's Catalytic Enantioselective Approach to (+)-Liphagal

So far, the syntheses of (+)-liphagal (**2.25**) have been biosynthetically inspired, mimicking either pathway A<sup>14, 26</sup> or pathway B.<sup>15, 25</sup> In 2011, the Stoltz group showed that the total synthesis of (+)-liphagal (**2.25**) could be achieved using a non-biomimetic approach.<sup>27</sup> Enol carbonate **2.64** first underwent a Pd-catalysed enantioselective alkylation in the presence of the *t*-Bu-PHOX ligand (**2.65**) to afford ketone **2.66**, as illustrated in Scheme 2.15. Ketone **2.66** was converted into enone **2.67** over two steps according to previously reported conditions.<sup>28</sup> Elaboration of **2.67** to cyclobutene **2.68** was achieved over the next five steps. This was followed by fragmentation of the cyclobutene ring of **2.68** via microwave irradiation in 1,2-DCB at 250 °C for three hours to produce the cycloheptanone ring of **2.69**. A further five steps was required for the functionalisation and subsequent conversion of cycloheptanone **2.69** to dihydrobenzofuran **2.70**. Stereoselective hydrogenation of the trisubstituted olefin group of **2.70** furnished dihydrobenzofuran **2.71**. Initial oxidation of **2.71** to its corresponding benzofuran with DDQ proved to be a difficult task, as it often led to over-oxidation of the starting material. Fortunately, oxidation could be accomplished via hydride abstraction with

the use of nitronium tetrafluoroborate ( $\text{NO}^+\text{BF}_4^-$ ) to yield benzofuran **2.23**.<sup>29</sup> Lastly, the formylation and demethylation steps were carried out according to known literature procedures<sup>15</sup> to generate (+)-liphagal (**2.25**). To date, Stoltz's catalytic enantioselective approach represents the longest route to the natural product, generating (+)-liphagal (**2.25**) in 19 steps with an overall yield of 6%.

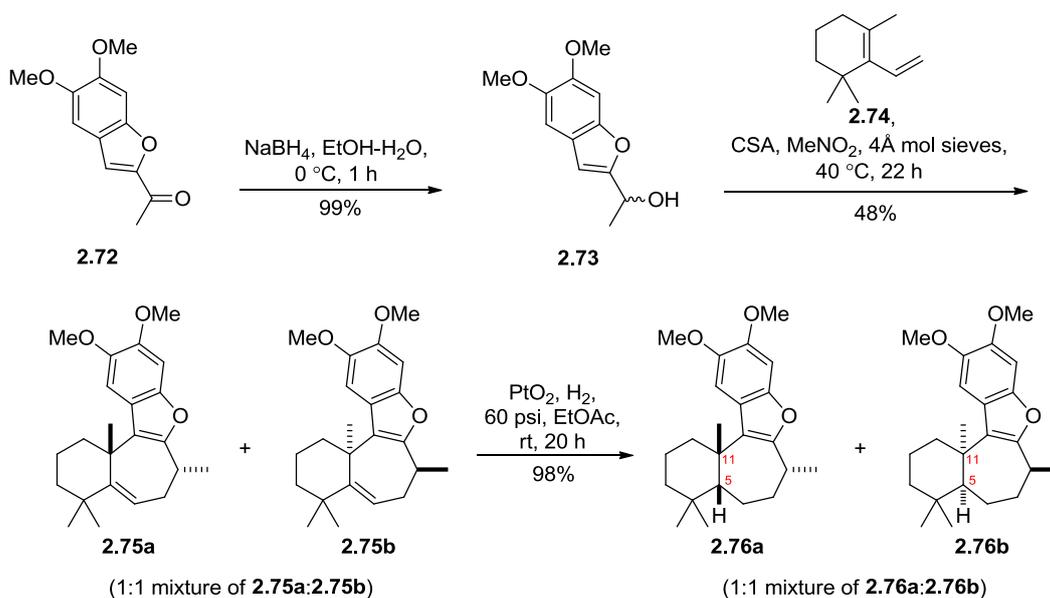


Scheme 2.15

#### 2.4.6 Li's and Winne's [4+3]-Cycloaddition Approach to ( $\pm$ )-5-*epi*-Liphagal

Another interesting approach towards the tetracyclic core of (+)-liphagal (**2.25**) has been demonstrated independently by two research groups.<sup>30, 31</sup> Li and co-workers were the first

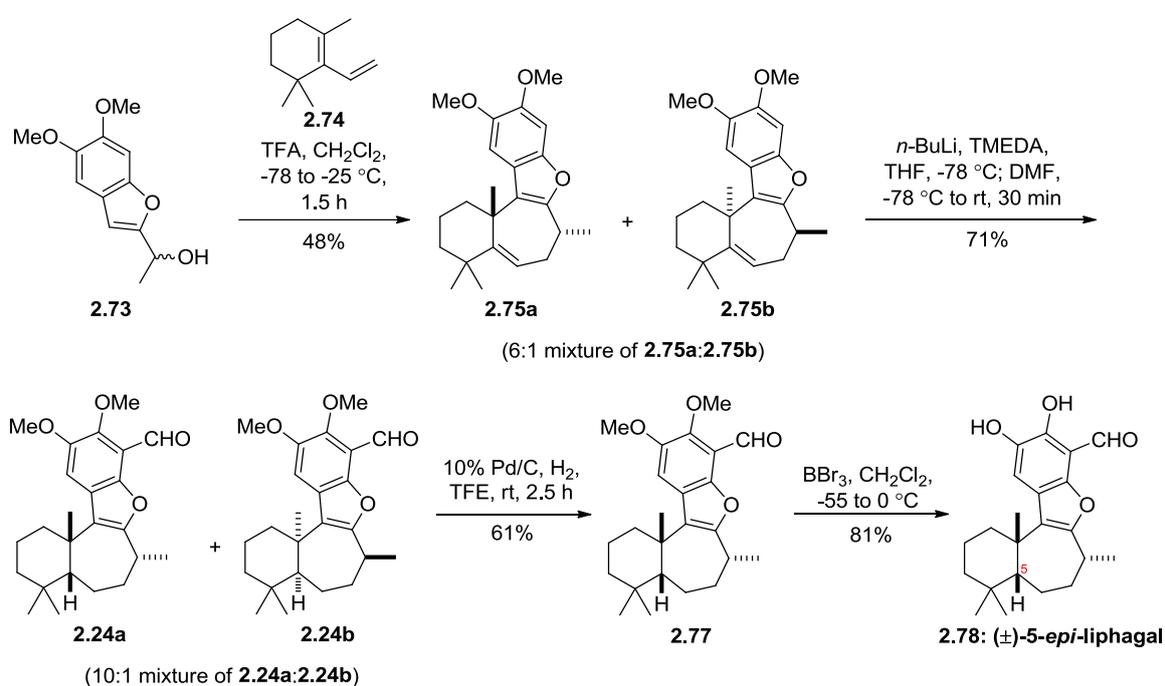
to suggest that the seven membered ring could be generated via a [4+3]-cycloaddition reaction between a diene and a cationic allyl precursor.<sup>30</sup> With this strategy in mind, acetylbenzofuran **2.72** was effectively reduced to yield alcohol **2.73**, the 3- $\pi$  precursor (Scheme 2.16). Exposure of alcohol **2.73** to known diene **2.74** in the presence of CSA and nitromethane, along with gentle heating over 22 hours gave a 1:1 mixture of benzofurans **2.75a/b**. As expected, hydrogenation with PtO<sub>2</sub> proceeded via of the convex face of **2.75a/b** to yield benzofurans **2.76a/b**, bearing a *cis* relationship between the C-5 hydrogen and the C-11 methyl along the 6,7- ring junction. While the framework of liphagal was achieved in just three steps from acetylbenzofuran **2.72**, functionalisation of the aromatic ring and removal of the protecting groups was not carried out by the authors.



Scheme 2.16

Winne's group took this a step further by completing the total synthesis of ( $\pm$ )-5-*epi*-liphagal (**2.80**), two years after Li's group published their findings (Scheme 2.17).<sup>31</sup> In addition,

diastereomeric ratios of the [4+3]-cycloaddition were improved (6:1 in favour of the desired diastereoisomer) with the use of TFA and lower reaction temperatures ( $-78\text{ }^{\circ}\text{C}$  to  $-25\text{ }^{\circ}\text{C}$ ). Formylation of **2.75a/b** was carried out according to George's *ortho*-lithiation protocol to afford a 10:1 mixture of **2.24a** and **2.24b**.<sup>14</sup> Surprisingly, hydrogenation of mixture **2.24a/b** in TFE at room temperature afforded **2.77** as a single diastereomer. Subsequently, demethylation of **2.77** with  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  between  $-55\text{ }^{\circ}\text{C}$  to  $0\text{ }^{\circ}\text{C}$  to produced ( $\pm$ )-5-*epi*-liphagal (**2.78**).

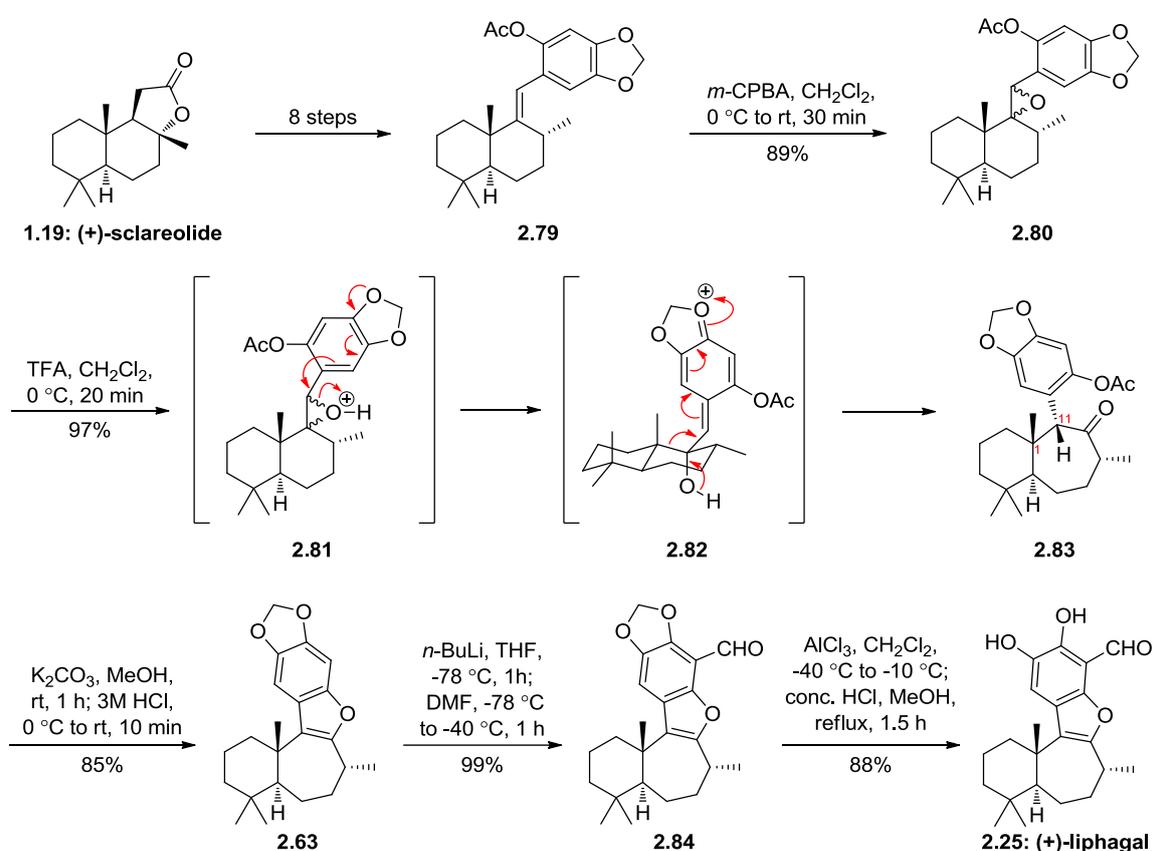


Scheme 2.17

#### 2.4.7 Katoh's Approach to (+)-Liphagal

Recently, Katoh and co-workers published their synthesis of (+)-liphagal (**2.25**).<sup>32</sup> Firstly, (+)-sclareolide (**1.19**) was efficiently converted into olefin **2.79** in just eight steps (Scheme 2.18). Epoxidation of the double bond with *m*-CPBA led to the formation of epoxide **2.80**. Next, the addition of TFA to **2.80** in  $\text{CH}_2\text{Cl}_2$  at  $0\text{ }^{\circ}\text{C}$  generated cycloheptanone **2.83** almost

quantitatively. This process presumably proceeded through the oxonium ion intermediate **2.82**, which in turn was formed via the ring opening of oxonium epoxide species **2.81**. Basic hydrolysis of the acetate group, followed by *in situ* treatment of the crude mixture with 3M HCl afforded benzofuran **2.63**. Formylation of **2.63** furnished the aldehyde functionality in **2.84**, and finally, methylenedioxy deprotection was achieved using Goodman's conditions<sup>33</sup> to produce the corresponding natural product.



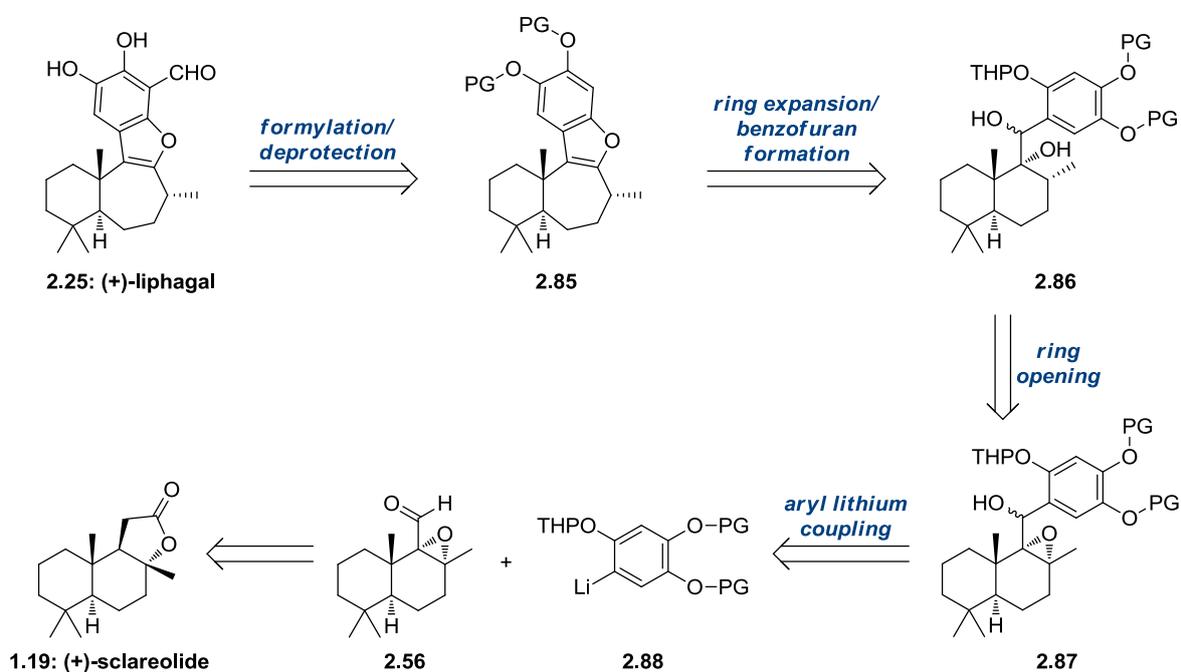
Scheme 2.18

Though the biosynthesis of marine metabolites from the marine sponge *Aka coralliphaga* have been scantily studied since their isolation, the unique structure as well as biological activity of liphagal has made it a valuable target for total synthesis. A testament to

this is the number of synthetic approaches towards the target molecule in literature; five biomimetic syntheses, one catalytic enantioselective synthesis, and two synthetic approaches involving a [4+3]-cycloaddition. Furthermore, several authors have also reported their synthetic strategies toward key liphagal intermediates,<sup>34, 35</sup> while Andersen's group have disclosed the synthesis and biological evaluation of liphagal related analogues.<sup>24</sup> However, despite this previous work, we believed that further improvements to the liphagal synthesis could be made, in addition to further biosynthetic insights.

## 2.5 Retrosynthetic Analysis of (+)-Liphagal

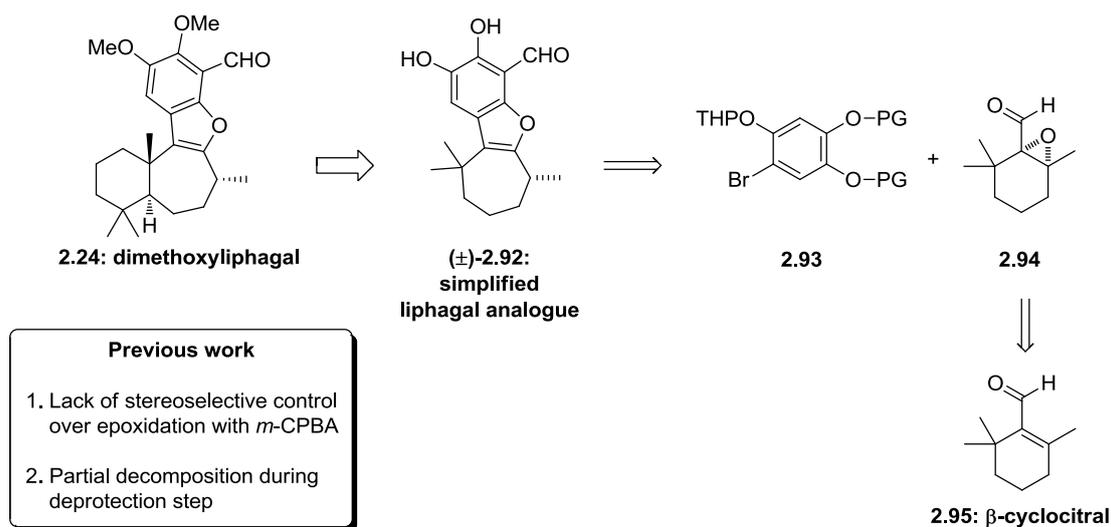
The retrosynthetic analysis of (+)-liphagal (**2.25**) is outlined in Scheme 2.19. It is our belief that (+)-liphagal (**2.25**) could be generated from an *ortho*-formylation reaction followed by deprotection of benzofuran **2.85**. As documented by George and co-workers, benzofuran **2.85** could be formed from the 1,2-diol **2.86** via a pinacol-type ring expansion reaction, previously outlined in Scheme 2.5. Alternatively, this ring expansion could also proceed from the *ortho*-quinone methide, as previously discussed (Scheme 2.7). The diol **2.86** could be generated from the ring opening of the epoxide on benzylic alcohol **2.87**. We envisaged that the benzylic alcohol **2.87**, in turn, could be derived from the coupling of aryllithium **2.88** and epoxyaldehyde **2.56**. Ultimately, epoxyaldehyde **2.56** could be synthesised from (+)-sclareolide (**1.19**), a cheap, commercially available chiral building block.



Scheme 2.19

In the original synthesis of liphagal by the George group, epoxidation with *m*-CPBA produced a mixture of epoxyalcohols in a 3:1 mixture, favouring the desired  $\alpha$ -epoxide.<sup>14</sup> However, the lack of stereoselective control calls for the separation of the undesired  $\beta$ -epoxide from the desired  $\alpha$ -epoxide, which limits the overall efficiency of this method. Furthermore, complete removal of the *meta*-chlorobenzoic acid proved to be a difficult task even after chromatographic purification. As an improvement, we envisioned that the desired epoxyalcohol possessing the required stereochemistry could be obtained with greater selectivity by Sharpless asymmetric epoxidation.<sup>36</sup>

Additionally, the reproducibility of the demethylation yields were also questionable, as the reactions were previously conducted on such small quantities (Andersen's and Stoltz's group both conducted the demethylation step on 5 mg and 1.7 mg of **2.24** respectively). In our hands, the use of a strong Lewis acid such as BI<sub>3</sub> or BBr<sub>3</sub> led to either partial or complete decomposition of the starting material. Winne and co-workers had also reported similar observations in their synthesis of ( $\pm$ )-5-*epi*-liphagal (**2.78**). Our aim was therefore to employ the use of a different protecting group which would allow for selective deprotection under mild conditions. For this purpose, the synthesis of a simplified analogue will be undertaken to investigate the feasibility of the new protecting group strategy (Scheme 2.20). This model system, which contains the tricyclic 7,5,6- framework, could be easily derived from  $\beta$ -cyclocitral (**2.95**).



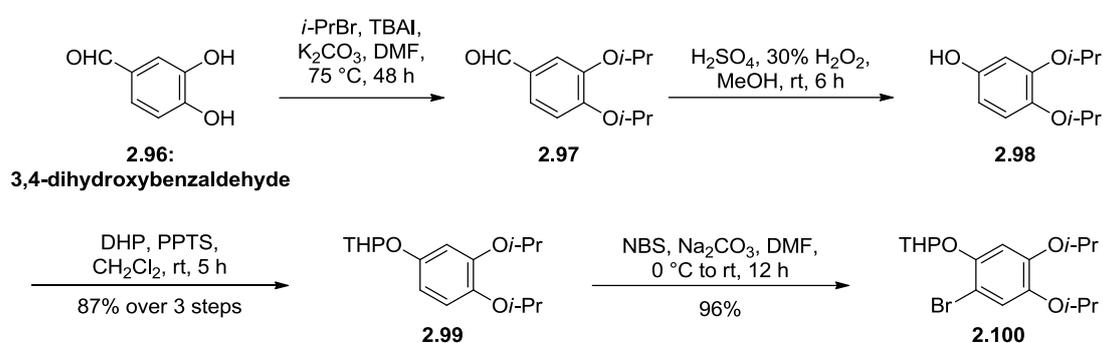
Scheme 2.20

## 2.6 Second Generation Total Synthesis of Liphagal

### 2.6.1 Preparation of Aryl Bromide 2.100

Based on previous observations, the choice of protecting groups was identified to be crucial towards the synthesis of liphagal. A quick survey of the literature had shown that aryllithium coupling of benzyl protected aromatics are often low yielding, mainly attributed the steric bulk of the benzyl groups.<sup>37, 38</sup> *t*-Butyldimethylsilyl (TBS) and methylenedioxy groups, on the other hand, are prone to cleavage under acidic conditions and thus might not survive the ring expansion step when treated with TFA. The isopropyl group however, was considered ideal due to its tolerance to TFA and ease of removal using a milder Lewis acid during late stage manipulations.<sup>39</sup> Our initial objective was to prepare the aryl bromide **2.100** with the desired isopropyl protecting groups, then couple it to epoxyaldehyde **2.56**. As such, 3,4-dihydroxybenzaldehyde (**2.96**) was first converted into phenol **2.98** according to methodology previously established by Yang and co-workers (Scheme 2.21).<sup>40</sup> Isopropyl protection of the phenolic hydroxy groups followed by acid catalysed Dakin oxidation

conditions furnished the desired 3,4-diisopropoxyphenol **2.98**, which was THP protected and purified to give THP-ether **2.99** in 87% yield over three steps. Treatment of THP-ether **2.99** with NBS overnight resulted in the formation of the desired aryl bromide **2.100** in 96% yield. Banwell and co-workers had reported that the aryl bromide was obtained as a pure compound after aqueous workup.<sup>41</sup> In our hands, trace impurities were present even after repeating the aforementioned workup procedure. To prevent the trace impurities from affecting the next reaction, the crude aryl bromide was purified via flash column chromatography over silica gel.

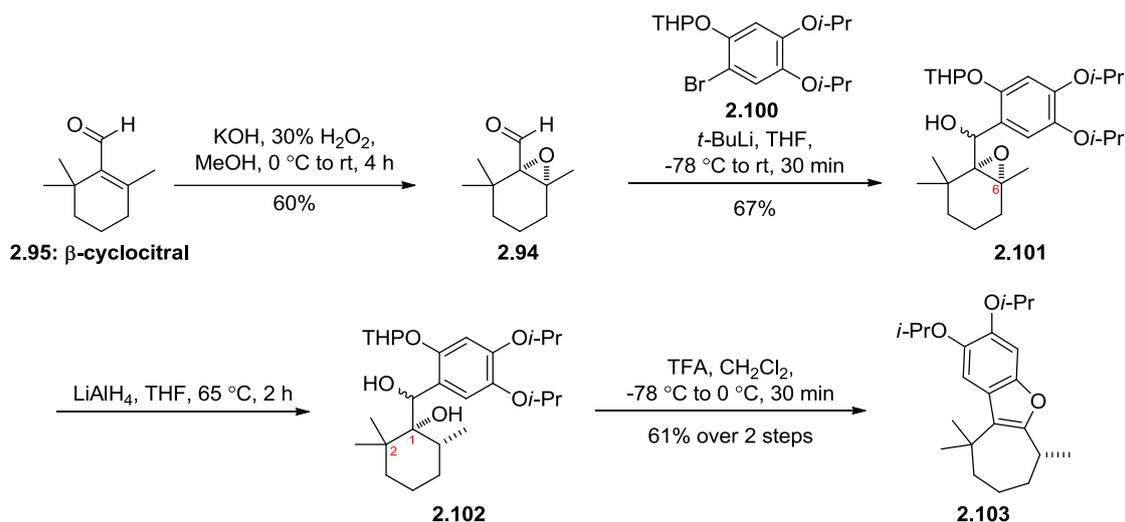


Scheme 2.21

## 2.6.2 Construction of the 7-5-6 Tricyclic Core

With the desired aryl bromide in hand, our attention was directed towards the synthesis of epoxyaldehyde **2.94**. Direct epoxidation of the cyclic  $\alpha,\beta$ -unsaturated natural product  $\beta$ -cyclocitral (**2.95**) with *m*-CPBA failed to give the corresponding epoxyaldehyde. Instead, multiple spots were observed on the TLC of the reaction mixture, with only trace amounts of the starting material present. We suspected that *m*-CPBA could have oxidised the aldehyde, which resulted in the formation of unstable side products. Indeed, side products were observed by List and co-workers when they attempted to epoxidise  $\beta$ -cyclocitral (**2.95**) using an

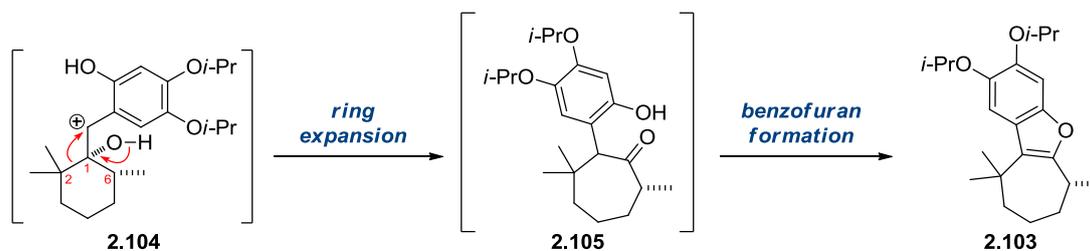
asymmetric aminocatalyst.<sup>42</sup> Nevertheless, successful epoxidation was achieved by careful addition of hydrogen peroxide to a solution of KOH and  $\beta$ -cyclocitral (**2.95**) in methanol at 0 °C (Scheme 2.22).<sup>43</sup> As there was no change between the  $R_f$  values of the starting material and the epoxyaldehyde on TLC, the reaction was monitored by <sup>1</sup>H NMR. Complete consumption of the starting material was observed with the disappearance of the aldehyde signal at 10.13 ppm, and the formation of a new signal at 9.74 ppm, which corresponded to the aldehyde proton of the epoxyaldehyde **2.94**. Isolation and purification of the target material proved to be an arduous task, as the epoxyaldehyde **2.94** is extremely volatile and prone to decomposition.



Scheme 2.22

Aryl bromide **2.100** underwent a lithium-halogen exchange reaction with *t*-BuLi at -78 °C to form the corresponding aryl lithium species, which was then coupled to the freshly prepared epoxyaldehyde **2.94** to give the desired benzylic alcohol **2.101** in 67% yield. Full NMR characterisation of the alcohol was not possible due to the mixture of diastereoisomers formed. However, formation of the desired product was confirmed by HRMS analysis.

Benzylic alcohol **2.101** was treated with excess LiAlH<sub>4</sub> and heated to 60 °C for two hours to ring open the epoxide at the less hindered C-6 position. Upon cooling to 0 °C, the mixture was carefully quenched with aqueous 1M HCl solution to remove any remaining LiAlH<sub>4</sub>. The lithium salt was filtered through Celite and the crude product was used immediately without further purification. Analogous to alcohol **2.101**, the formation of diol **2.102** was confirmed by HRMS analysis. Subsequently, the diol was subjected to the biomimetic ring expansion conditions previously documented by George *et. al.*<sup>14</sup> Thus, treatment of diol **2.102** with five equivalents of TFA at –78 °C followed by quenching of the reaction mixture at 0 °C after 30 minutes gave the ring expanded benzofuran **2.103** in 61% yield over two steps. Only the more electron-rich C-1 – C-2 bond was found to migrate in preference to the C-1 – C-6 bond in the ring expansion step (Scheme 2.23). Similar to the mechanism previously described in Scheme 2.5, the ring expansion could proceed via benzylic cation intermediate **2.104** to afford cycloheptanone **2.105**, followed by *in-situ* formation of benzofuran **2.103**.

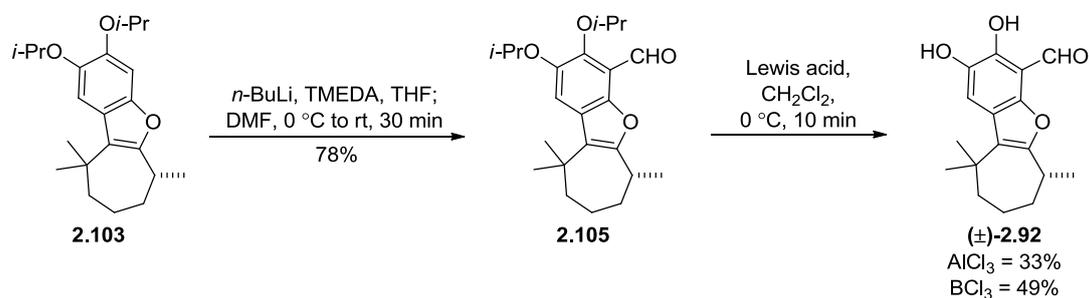


Scheme 2.23

### 2.6.3 Synthesis of Simplified Liphagal Analogue (±)-2.92

Having obtained the desired benzofuran **2.103**, our efforts turned towards the formylation of the aromatic ring and deprotection of the isopropyl groups to complete the racemic synthesis of the simplified liphagal analogue. Functionalisation of the aromatic ring

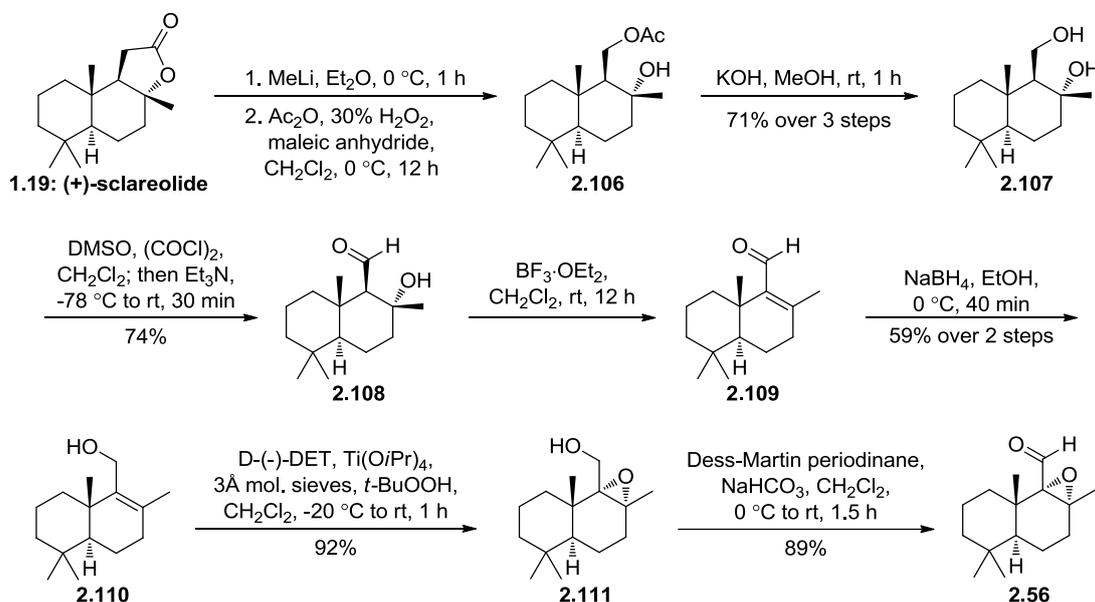
was achieved following *ortho*-formylation conditions as previously reported to give aldehyde **2.105** in 78% yield (Scheme 2.24).<sup>14</sup> Deprotection following Banwell's protocol (AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt) led to partial decomposition of the starting material, indicated by a streak on the TLC.<sup>39</sup> Nonetheless, a small amount of desired product was obtained upon work-up and subsequent flash column chromatography, which led to the isolation of **2.92** in 33% yield. In contrast, cleavage of the isopropyl group was completed almost immediately after the addition of BCl<sub>3</sub> to the benzofuran at 0 °C. To our delight, decomposition products were not observed and the crude product was purified easily to give the liphagal analogue **2.92** as a yellow oil. Thus, deprotection of benzofuran **2.105** with BCl<sub>3</sub> furnished the desired benzofuran backbone with a slightly improved yield of 49%. At this stage, we were convinced that the total synthesis of liphagal can be achieved with the use of the more labile isopropyl protecting group.



Scheme 2.24

## 2.6.4 Preparation of Epoxyaldehyde 2.56

The revised route to liphagal began with the construction of the desired allylic alcohol **2.110** from (+)-sclareolide (**1.19**) as outlined in George's formal synthesis.<sup>14</sup> (+)-Sclareolide (**1.19**) was first converted into diol **2.107** with a known three-step protocol which involved a MeLi mediated ring opening of the lactone functionality of **1.19**, followed by a Bayer-Villiger reaction and acetate hydrolysis of alcohol **2.106** to afford diol **2.107** (Scheme 2.25).<sup>44</sup> Subsequent Swern oxidation and dehydration with  $\text{BF}_3 \cdot \text{OEt}_2$  produced  $\alpha,\beta$ -unsaturated aldehyde **2.109**. Finally, reduction of the aldehyde functionality with  $\text{NaBH}_4$  generated the allylic alcohol **2.110** with an overall yield of 31% over six steps starting from (+)-sclareolide (**1.19**).



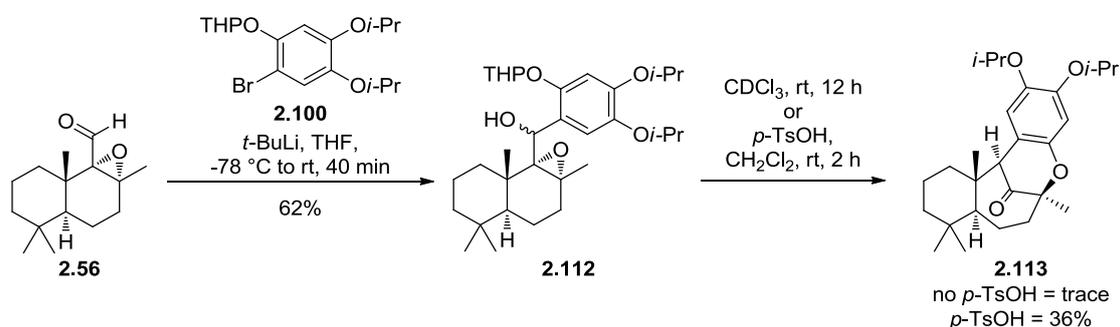
Scheme 2.25

As aforementioned, Sharpless asymmetric epoxidation was tested on the allylic alcohol **2.110**. The use of D-(-)-diethyl tartrate as the chiral ligand alongside Ti(O*i*Pr)<sub>4</sub> as the metal

catalyst and *t*-BuOOH as the oxidising agent should form the desired epoxyalcohol **2.111**. To our delight, following a related procedure reported by de Lera *et. al.*, the epoxidation of **2.111** proceeded in excellent yield of 92% with >99% *de* of the desired product, as observed by <sup>1</sup>H NMR.<sup>36</sup> Oxidation of epoxyalcohol **2.111** with Dess-Martin periodinane then afforded the target epoxyaldehyde **2.56**.

### 2.6.5 Formation of an Unusual 6,7,6,6- Tetracyclic Ring System

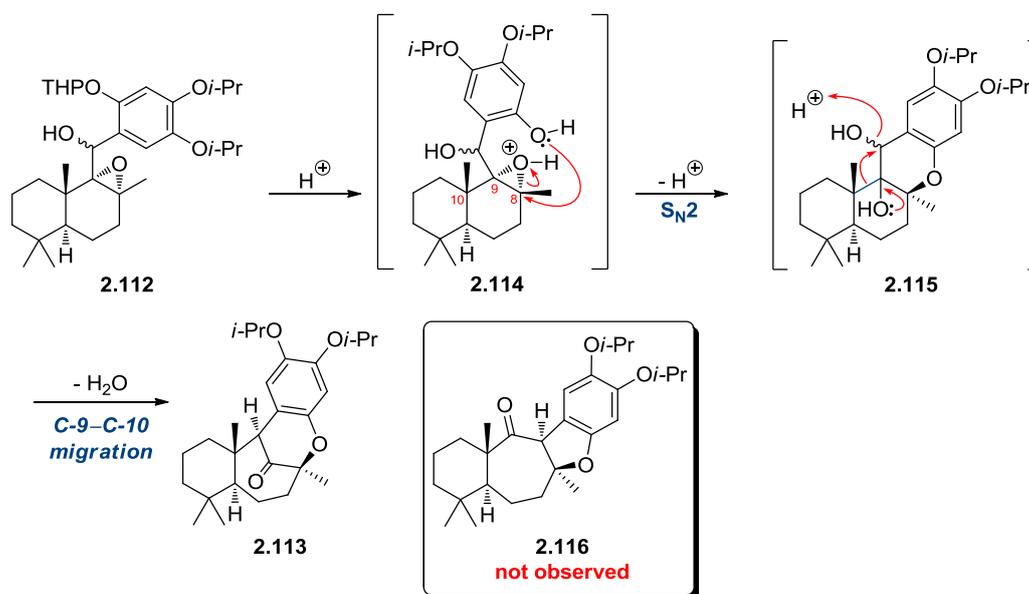
With the key intermediates in hand, aryl bromide **2.100** was coupled to epoxyaldehyde **2.56** under the previously mentioned metal-halogen exchange reaction conditions to give benzylic alcohol **2.112** in good yield (Scheme 2.26).



Scheme 2.26

During the course of <sup>1</sup>H and <sup>13</sup>C NMR acquisition, we noticed that the clear sample solution containing **2.112** in CDCl<sub>3</sub> had gradually turned yellow over time. TLC analysis of the solution showed trace amount of a new compound that was significantly less polar than **2.112**. The unknown substance was separated via flash column chromatography, and preliminary analysis of the 2D NMR spectra revealed an unusual ring expanded product had formed.

Suspecting that the mildly acidic nature of the deuterated solvent could have contributed to the formation of cycloheptanone **2.113**, the treatment of alcohol **2.112** under acidic conditions should produce a similar result. To our delight, cycloheptanone **2.113** was obtained in 36% yield when alcohol **2.112** was reacted with two equivalents of *p*-TsOH in CH<sub>2</sub>Cl<sub>2</sub> over two hours. A quick literature survey indicated that this type ring expansion was also previously observed by Shinonaga's group while they attempted the TBS deprotection of a structurally related meroterpenoid.<sup>38</sup> Formation of **2.113** could be derived from the ring opening of an oxonium intermediate such as **2.114**, under acidic conditions, accompanied by a S<sub>N</sub>2 inversion at the C-8 stereocenter (Scheme 2.28). Pinacol ring expansion of the tetracyclic diol **2.115** would then give the bridged ketone **2.113**.



Scheme 2.27

The HRMS of this compound showed a mass of 429.2990 [M + H]<sup>+</sup> and was in agreement with a chemical formula of C<sub>27</sub>H<sub>40</sub>O<sub>4</sub>. The COSY, ROESY and HMBC correlations

of **2.113** is shown in Figure 2.4. The absence of the C-8–C-9 bond migration product, cycloheptanone **2.116**, implied that the ring expansion is highly stereospecific, as migration occurs only from the more electron rich C-9–C-10 bond. Due to the unstable nature of the molecule, benzylic alcohol **2.112** was taken through to the next step immediately after purification.

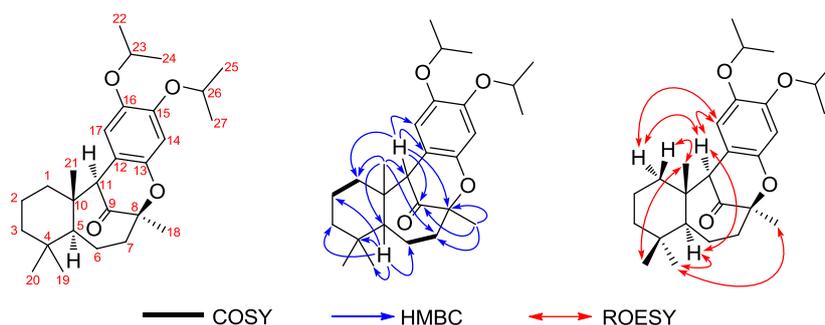
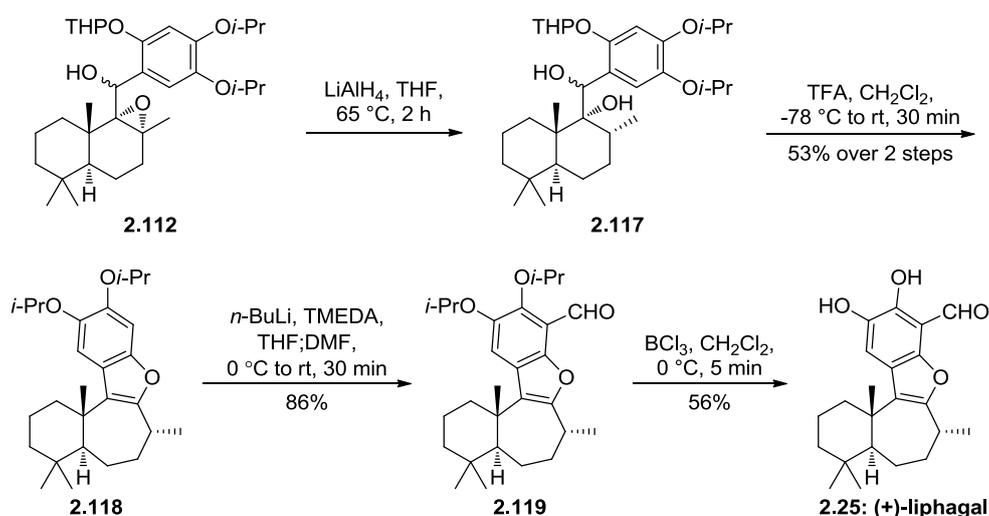


Figure 2.4: Left – carbon numbering of **2.113**; centre – selected HMBC (H → C) correlations; right – key ROESY correlations.

### 2.6.6 Key Pinacol-Type Ring Expansion Reaction and Synthesis of Liphagal

Ring opening of freshly prepared epoxide **2.112** with excess  $\text{LiAlH}_4$  gave diol **2.117**, which was also used in the next step without further purification (Scheme 2.28). Again, the biomimetic ring expansion of diol **2.117** with TFA afforded benzofuran **2.118** in good yield over two steps. Only two tasks remained with the carbon framework now completed, namely, *ortho*-formylation of the aromatic ring and the removal of the isopropyl protecting groups. Installation of the aldehyde functional group on benzofuran **2.118** yielded liphagal precursor **2.119** in excellent yield of 86%. Finally, the isopropyl protecting groups were removed with five equivalents of  $\text{BCl}_3$  in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  to produce (+)-liphagal (**2.25**). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of synthetic (+)-liphagal (**2.25**) were identical to the isolated (+)-liphagal (**2.25**)

previously reported. The optical rotation of the natural product matched the synthetic sample of (+)-liphagal (**2.25**) previously reported by Stoltz and co-workers (Stoltz's synthetic (+)-liphagal:  $[\alpha]^{25}_D +25.99^\circ$  ( $c$  0.072,  $\text{CHCl}_3$ ); this work:  $[\alpha]^{25}_D +22.60^\circ$  ( $c$  0.5,  $\text{CHCl}_3$ )).<sup>27</sup> This revised route allows access to enantiopure (+)-liphagal (**2.25**) in 4% overall yield in just 13 steps from (+)-sclareolide (**1.19**).



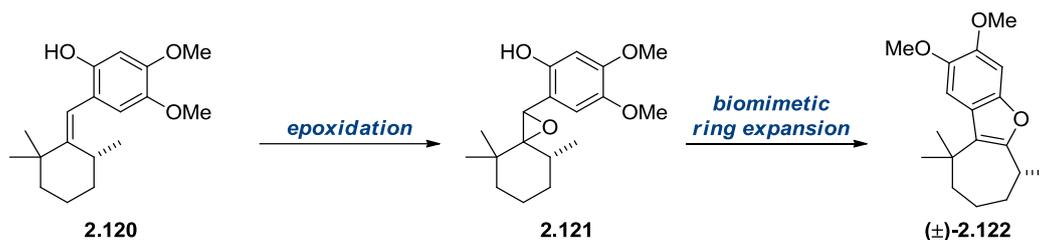
Scheme 2.28

## 2.7 One-Pot Epoxidation-Ring Expansion Approach

### 2.7.1 Model Study and the Formation of a Stable *ortho*-Quinone Methide

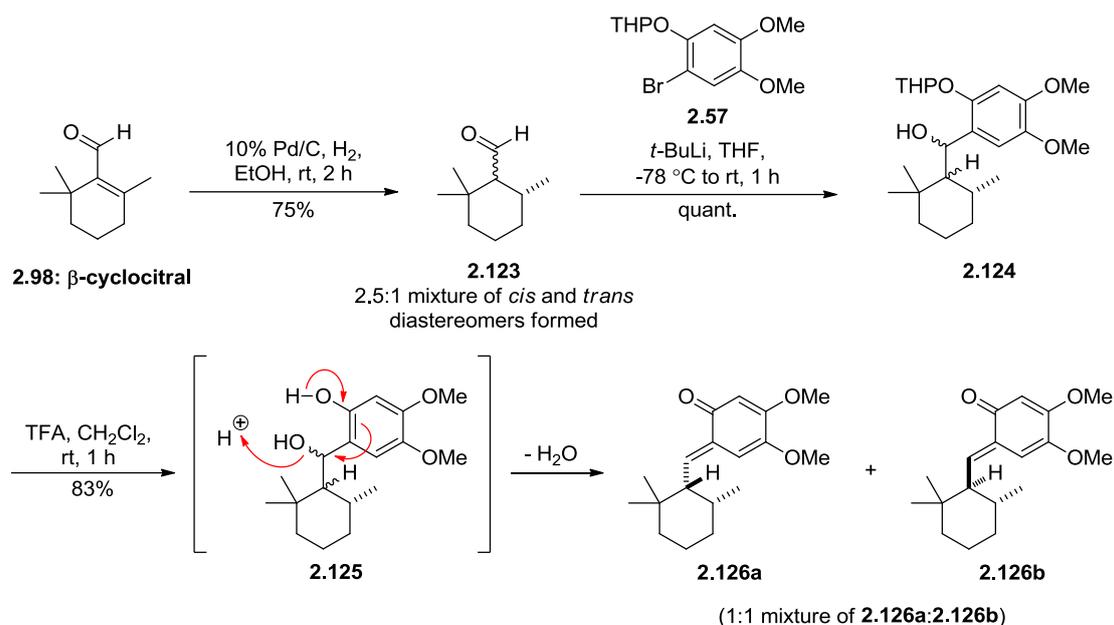
Diversity in nature is often generated from the manipulation of pre-existing molecules with predisposed functionalities. Therefore, there is potential for these molecules to act as precursors to other natural products. On the basis of this hypothesis, a “true” biomimetic process would be the direct conversion of siphonodictyal B (**2.26**) to (+)-liphagal (**2.25**) via a putative epoxide intermediate, as previously depicted in Scheme 2.6. Previous success with the synthesis of simplified liphagal analogue **2.92** suggests that a simplified system could be used

to probe this biomimetic transformation (Scheme 2.29). Additionally, while this study was undertaken, Katoh's group published a synthetic approach towards the liphagal framework via olefin **2.79**, which was essentially a protected derivative of siphonodictyal B (**2.26**).<sup>32</sup> Evidence from Katoh's work further strengthens our biomimetic hypothesis.



Scheme 2.29

Construction of the model siphonodictyal B analogue **2.122** first began with the hydrogenation of the  $\alpha,\beta$ -unsaturated natural product,  $\beta$ -cyclocitral (**2.95**). Catalytic hydrogenation of  $\beta$ -cyclocitral in EtOH at room temperature gave a mixture of *cis* and *trans* aldehydes **2.123** in 2.5:1 ratio, which were inseparable by column chromatography (Scheme 2.30). <sup>1</sup>H and <sup>13</sup>C NMR signals of both the *cis* and *trans* products in the NMR spectra matched those reported in literature.<sup>45, 46</sup> While this result was undesirable, the lack of relative stereochemistry should not affect the outcome of the key reaction that was to be examined.



Scheme 2.30

The aryllithium, generated from known aryl bromide **2.57** and *t*-BuLi in THF at  $-78^\circ\text{C}$ , was coupled with the aldehyde mixture **2.123** to produce benzylic alcohol **2.124** in quantitative yield. A variety of conditions for the dehydration of **2.124** were first screened (MsCl, pyr or Et<sub>3</sub>N; SOCl<sub>2</sub>, pyr; and SO<sub>3</sub>·pyr). However, these conditions failed to give the desired alkene. In contrast, treatment of benzylic alcohol **2.124** with stoichiometric excess of acid<sup>37, 47</sup> gave a 1:1 mixture of *ortho*-quinone methides **2.126a** and **2.126b**. Presumably, *ortho*-quinone methides **2.126a** and **2.126b** are formed by facile cleavage of the THP group followed by loss of a water molecule (Scheme 2.30). Varying the acid used only resulted in a slight change of the reaction yield, while the diastereomeric ratio of the *cis* and *trans* products were unaffected (Table 2.1).

Table 2.1: Acidic conditions for the formation of *ortho*-quinone methide **2.130**.

| Entry | Conditions   | Yield (%) | Ratio of <i>cis</i> and <i>trans</i> |
|-------|--|-----------|--------------------------------------|
| 1     | <i>p</i> -TsOH, CH <sub>2</sub> Cl <sub>2</sub> , rt, 10 min | 71        | 1:1                                  |
| 2     | PPTS, CH <sub>2</sub> Cl <sub>2</sub> , rt, 1 h              | 81        | 1:1                                  |
| 3     | TFA, CH <sub>2</sub> Cl <sub>2</sub> , rt, 1 h               | 93        | 1:1                                  |

Isolation of the *ortho*-quinone methides **2.126a/b** are highly unusual, as *ortho*-quinone methides are known to be very reactive intermediates in organic synthesis.<sup>48-51</sup> Evidence for the formation of an *ortho*-quinone methide could be identified by the distinct carbonyl characteristics on the UV-Vis, IR and <sup>13</sup>C NMR spectra. The UV-Vis spectrum of **2.126a/b** in methanol gave an absorption value of 0.30 at 405 nm, which could be attributed to the  $\pi \rightarrow \pi^*$  transition state of the carbonyl group (Figure 2.5). This is not unusual, as conjugation of the carbonyl group with double bonds shifts the transition states to longer wavelengths. The IR spectrum of **2.126a/b** also showed a carbonyl absorption peak at 1649 cm<sup>-1</sup>, and finally, two carbonyl peaks at 184.3 and 184.1 ppm for the two diastereomers were observed in the <sup>13</sup>C NMR spectrum.

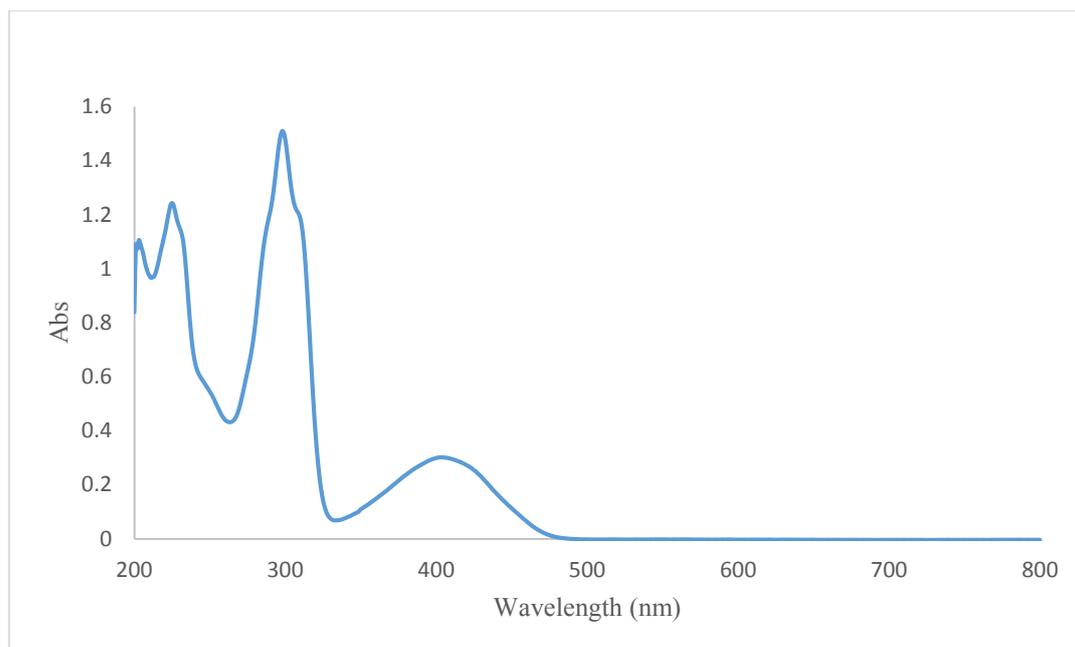
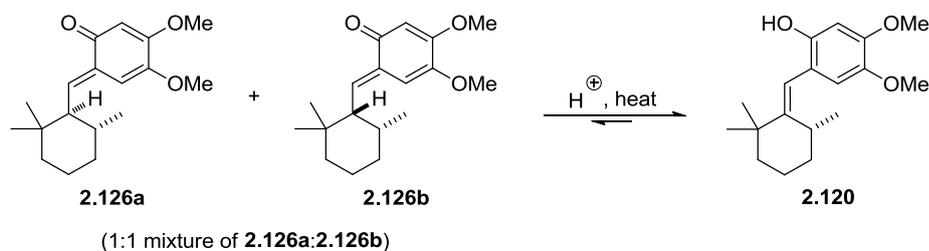


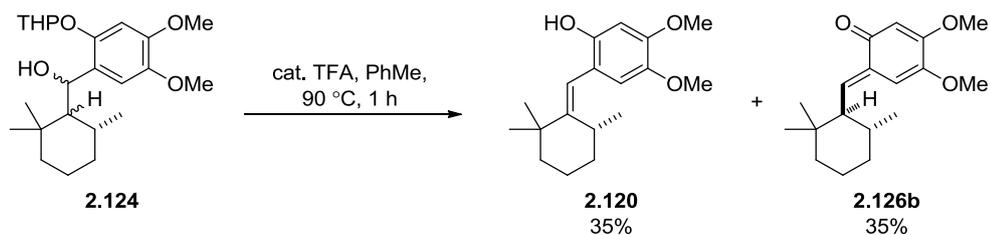
Figure 2.5: UV-Vis spectrum of **2.126a/b** in methanol

Interestingly, *ortho*-quinone methides **2.126a/b** were stable at room temperature, and did not decompose even when exposed to heat (up to 100 °C). Furthermore, efforts to tautomerise **2.126a/b** to its phenol isomer **2.120** failed to take place under various acidic and basic conditions at room temperature (Scheme 2.31). On the other hand, the combined effect of heating **2.126a/b** with catalytic amount of TFA in toluene provided some encouraging results. After 30 min at 90 °C, trace amounts of phenol **2.120** could be observed on the TLC plate. Regrettably, prolonged heating led to the decomposition of both **2.126a/b** and **2.120**.



Scheme 2.31

Inspired by the preliminary results, we reinvestigated the dehydration of **2.126a/b** under the aforementioned conditions. A mixture of phenol **2.120** and *ortho*-quinone methide **2.126b** was obtained in modest yield when alcohol **2.124** was treated with 0.1 equivalents of TFA in PhMe at 90 °C for one hour (Scheme 2.32).



Scheme 2.32

Interestingly, only the *ortho*-quinone methide **2.126b** was isolated under these conditions, as elucidated by 2D NMR spectroscopy. The key NOESY correlations are shown in Figure 2.6. The configuration of the *ortho*-quinone methide was also established to be in the *trans* configuration relative to the cyclohexane ring. To further prove that the *ortho*-quinone methide was isolated, *trans* **2.126b** was reduced with NaBH<sub>4</sub> to provide phenol **2.127** in 45% yield (Scheme 2.33).

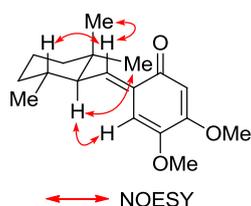
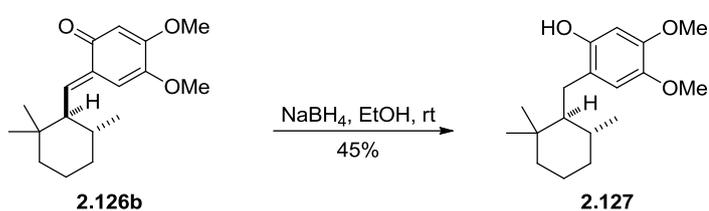


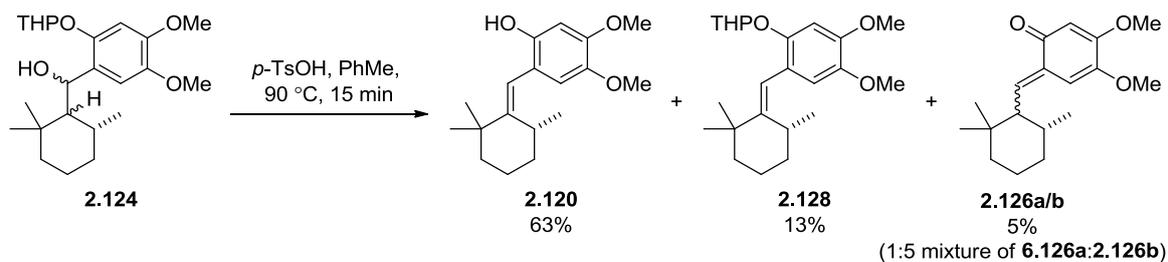
Figure 2.6: Key NOESY correlations of *ortho*-quinone methide **2.126b** (*trans* diastereomer).

These results inferred that initial exposure to TFA produced a mixture of *cis* and *trans* diastereomers of **2.126a/b**. However, only the *cis* diastereomer of **2.126a** was tautomerised to phenol **2.120** over a prolonged period of time. It is worth noting that phenol **2.120** does not revert back to *ortho*-quinone methides **2.126a/b** when heated in the presence of acid. From these results, we speculate that *ortho*-quinone methides **2.126a/b** are the kinetic product, while phenol **2.120** is the thermodynamic product of the dehydration reaction.



Scheme 2.33

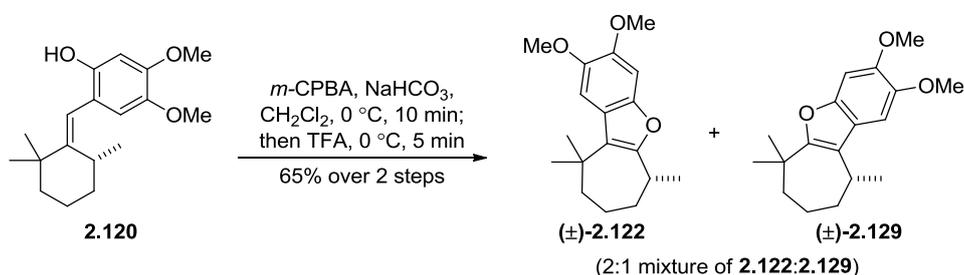
Gratifyingly, phenol **2.120** could be obtained from alcohol **2.124** in a decent yield of 63% if catalytic *p*-TsOH was used in place of TFA (Scheme 2.34). The reaction proceeded to completion in just 15 minutes, as opposed to the one hour reaction time with TFA. Moreover, the major side product isolated was the THP protected alkene **2.128**, while *ortho*-quinone methides **2.126a/b** were the minor side product. This time however, a 1:5 mixture of *cis* and *trans* diastereomers of the *ortho*-quinone methide were isolated after purification. The shortened reaction time could have prevented the complete tautomerisation of the *cis* **2.126a** to phenol **2.120**. The presence of alkene **2.128** also suggests a competing reaction pathway; the dehydration of alcohol **2.124** would take place first to form **2.128**, followed by subsequent THP cleavage to reveal the alcohol group of phenol **2.120**. Having established the optimum dehydration conditions, the key biomimetic cascade reaction could now be investigated.



Scheme 2.34

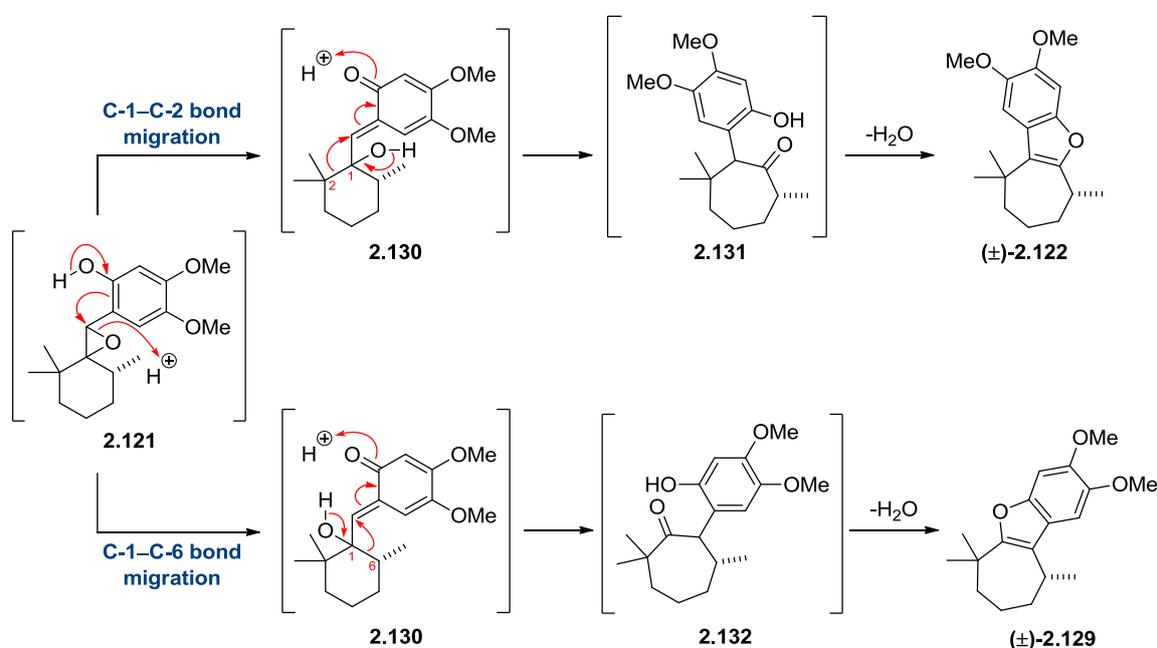
## 2.7.2 Biomimetic Ring Expansion Cascade

The ring expansion cascade of phenol **2.120** was initially carried out according to Katoh's protocol.<sup>32</sup> In our hands, the use of excess *m*-CPBA reagent (2.5 equivalents) led to the decomposition of the starting material. A small amount of the desired intermediate, epoxide **2.121** (30% yield) could be isolated if the amount of *m*-CPBA added was reduced to 1.05 equivalents (Scheme 2.29). Extensive screening of the reaction conditions revealed that phenol **2.120** could be converted into a 2:1 mixture of liphagal analogues **2.122** and **2.129** (65% combined yield) upon treatment with *m*-CPBA (buffered with NaHCO<sub>3</sub>) in CH<sub>2</sub>Cl<sub>2</sub> followed by subsequent addition of TFA at 0 °C (Scheme 2.35).



Scheme 2.35

A plausible mechanism for the formation of benzofurans **2.122** and **2.129** is presented in Scheme 2.36. After the initial epoxidation step, *in-situ* ring opening of epoxide **2.121** was initiated under acidic conditions to give *ortho*-quinone methide **2.130**. This reactive intermediate could then undergo a ring expansion by migration of the C-1–C-2 bond to afford cycloheptanone **2.131**, followed by dehydration to afford benzofuran **2.122**. Alternatively, migration of the C-1–C-6 bond would form cycloheptanone **2.132**, which in turn could undergo dehydration to afford **2.129** (Scheme 2.36, bottom pathway).



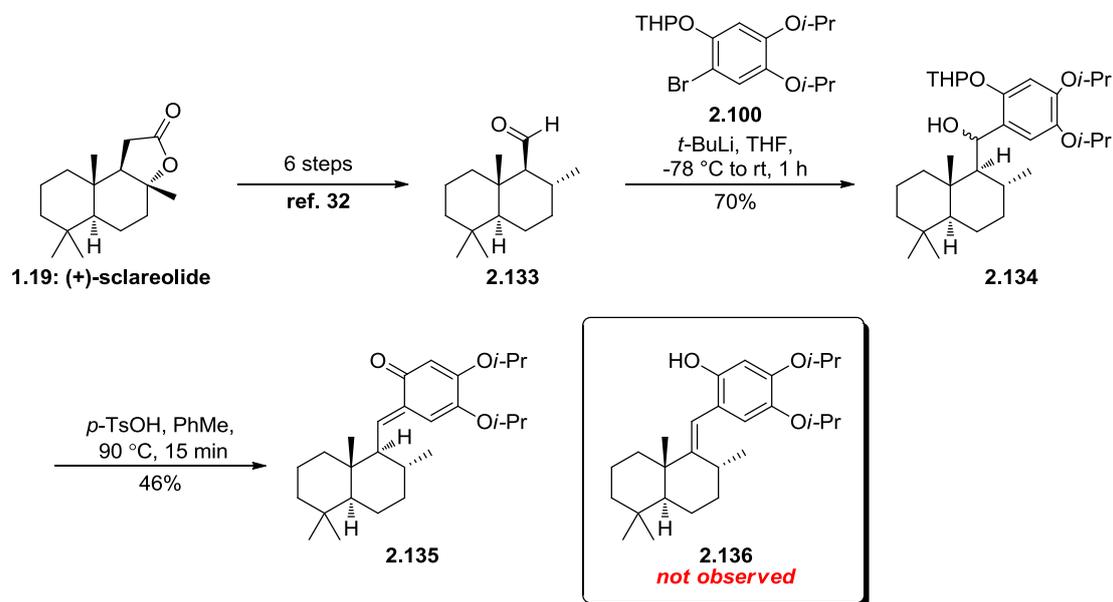
Scheme 2.36

Attempts to increase the ratio of the desired benzofuran **2.122** by altering the temperature at which TFA was added were unsuccessful, with the same ratio of products formed each time. Nevertheless, the success of this transformation under mild conditions using simple reagents suggest that the direct conversion of siphonodictyal B (**2.26**) to (+)-liphagal (**2.25**) is possible. Thus, preliminary studies on the synthesis of siphonodictyal B was pursued.

## 2.8 Biomimetic Conversion of Siphonodictyal B into Liphagal

### 2.8.1 Preliminary Studies on the Synthesis of Siphonodictyal B

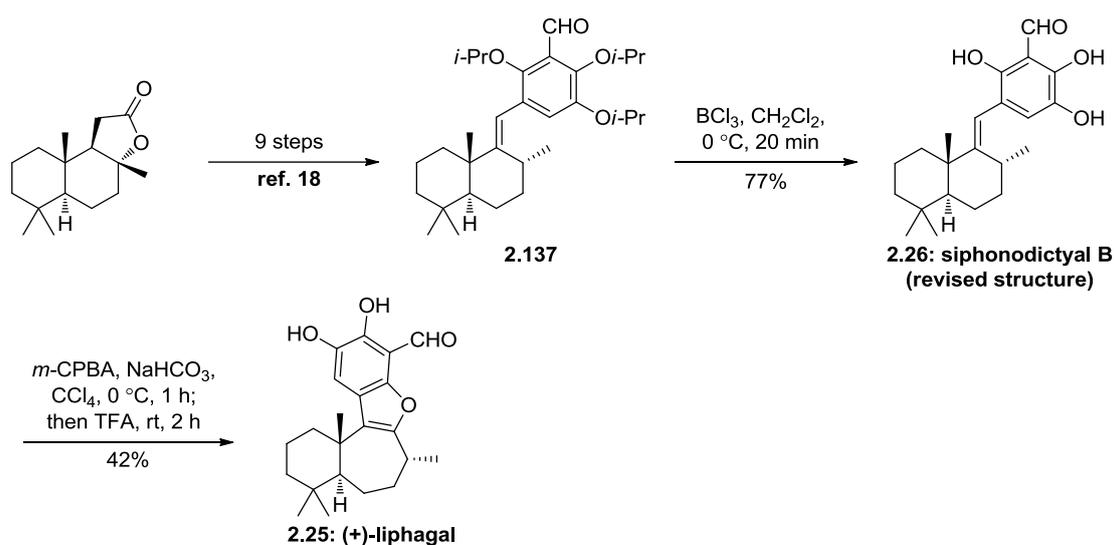
Aldehyde **2.133**, synthesised according to Katoh's procedure<sup>32</sup>, was reacted with the aryllithium species generated *in situ* by treatment of aryl bromide **2.100** with *t*-BuLi to give benzylic alcohol **2.134** in 70% yield as a complex mixture of diastereomers. With the key intermediate in hand, benzylic alcohol **2.134** was subjected to acid catalysed dehydration conditions as previously established. However, dehydration of benzylic alcohol **2.134** with catalytic *p*-TsOH led to the exclusive formation of *ortho*-quinone methide **2.135**, presumably attributed to the facile cleavage of the phenolic THP group. The absence of the desired phenol **2.136** implied that the conditions required for a successful dehydration reaction is substrate dependant, and would require further optimisation.



Scheme 2.38

## 2.8.2 Revised Synthesis of Siphonodictyal B

At the time of writing, this project was inherited by another student in our laboratory. We found that by simple substitution of the THP protecting group to the isopropyl group, the desired product from the dehydration reaction could be obtained from the benzylic precursor (Scheme 2.39).<sup>18</sup> Our revised strategy allowed access to siphonodictyal B precursor **2.137** in just nine steps from (+)-sclareolide (**1.19**). Removal of the isopropyl ether protecting groups was accomplished using  $\text{BCl}_3$  to give siphonodictyal B (**2.26**) in 77% yield. Furthermore, the biomimetic conversion of siphonodictyal B (**2.26**) into (+)-liphagal (**2.25**) was obtained in 42% yield using an optimised epoxidation/ ring expansion cascade protocol described earlier.



Scheme 2.39

## 2.9 Conclusion

In summary, the total synthesis of (+)-liphagal (**2.25**) was completed in 13 steps with 4% overall yield starting from the commercially available enantiopure natural product (+)-sclareolide (**1.19**). This 2<sup>nd</sup> generation approach was based on a revised version of George's formal synthesis, which featured the use of isopropyl protecting groups instead of methyl groups on the aromatic phenols. Furthermore, Sharpless asymmetric epoxidation of allylic alcohol **2.110** formed only the desired enantiomer of epoxyaldehyde **2.56**, which possess the required stereochemistry for the synthesis of the natural product. Preliminary studies based on a simplified model system showed that phenol **2.120** can be converted into benzofurans **2.122** and **2.129**, featuring a one-pot epoxidation-ring expansion-benzofuran formation cascade. This was in agreement with Andersen's proposed biosynthetic pathway A, which implied that the conversion of siphonodictyal B to liphagal could be a biomimetic process. However, dehydration of benzylic alcohol **2.134** bearing the carbon framework of siphonodictyal B was marred by the exclusive formation of the *ortho*-quinone methide **2.135**. On the other hand, subtle revision of the protecting groups (THP to *i*-Pr) on the aromatic ring led to the first total synthesis of siphonodictyal B (**2.26**) (along with the structural revision of the natural product) and ultimately, its biomimetic conversion to (+)-liphagal (**2.25**).

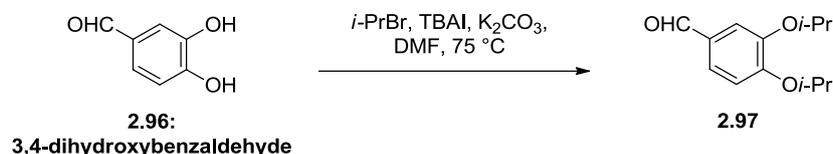
## 2.10 Experimental Section

### 2.10.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using Merck aluminium sheets silica gel 60 F<sub>255</sub>. Visualisation was aided by viewing under a UV lamp and staining with CAM stain followed by heating. All R<sub>f</sub> values were rounded to the nearest 0.05. Flash chromatography was performed using Davisil (40-63 micron) grade silica gel. Melting points were recorded on a SRS Digimelt MPA 161 melting apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer Spectrum BX FT-IR system spectrometer as the neat compounds. Optical rotations were obtained on a P0A1 AR21 polarimeter. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using a Varian Inova-6000 spectrometer (<sup>1</sup>H at 600 MHz, <sup>13</sup>C at 150 MHz) or a Varian Inova 500 MHz spectrometer (<sup>1</sup>H at 500 MHz, <sup>13</sup>C at 125 MHz). The NMR solvent used was CDCl<sub>3</sub> unless otherwise specified. <sup>1</sup>H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and <sup>13</sup>C NMR are reported in ppm relative to chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quint) quintet, (sext) sextet, (hept) heptet, and (m) multiplet. All *J* values were rounded to the nearest 0.5 Hz. EI low resolution mass spectra were recorded on a Shimadzu GCMS-QP 5050A mass spectrometer.

## 2.10.2 Preparative Procedures and Spectroscopic Data

### 3,4-Diisopropoxybenzaldehyde 2.97



Potassium carbonate (6.00 g, 43.4 mmol), 2-bromopropane (4.10 mL, 43.4 mmol) and TBAI (0.54 g, 1.49 mmol) were added sequentially to a solution of 3,4-dihydroxybenzaldehyde (2.00 g, 14.5 mmol) in DMF (30 mL). The reaction mixture was stirred at 75 °C for 48 hours, and then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined and concentrated *in vacuo*. The residue was dissolved in Et<sub>2</sub>O (100 mL), washed with water (50 mL) and brine (50 mL), then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield crude 3,4-diisopropoxybenzaldehyde **2.97** (2.97 g) as a brown oil, which was used in the next step without further purification. The spectroscopic data for this compound matched that previously reported.<sup>41</sup>

#### Partial data for 3,4-diisopropoxybenzaldehyde 2.97:

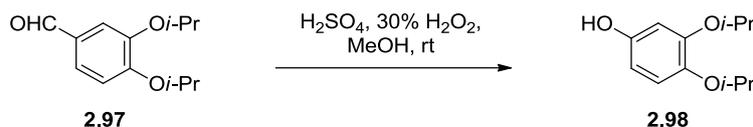
**R<sub>f</sub>** = 0.70 (petrol/EtOAc, 2:1)

**IR (neat):** 2978, 2934, 1687, 1594, 1579, 1500, 1433, 1261 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 9.83 (s, 1H), 7.45 – 7.43 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 4.64 (hept, *J* = 6.0 Hz, 1H), 4.53 (hept, *J* = 6.0 Hz, 1H), 1.39 (d, *J* = 6.0 Hz, 6H), 1.36 (d, *J* = 6.0 Hz, 6H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 190.9, 155.0, 149.0, 130.1, 126.4, 116.2, 114.9, 72.5, 71.8, 22.1, 22.0.

### 3,4-Diisopropoxyphenol **2.98**



Conc. H<sub>2</sub>SO<sub>4</sub> (0.60 mL, 10.7 mmol) was added dropwise to a solution of 3,4-diisopropoxybenzaldehyde **2.97** (2.97 g, 13.4 mmol) in MeOH (55 mL) at room temperature. 30% H<sub>2</sub>O<sub>2</sub> (10.6 mL, 103 mmol) was then added in one portion and the reaction mixture was stirred at room temperature for 6 hours. Upon completion, the resulting mixture was quenched with saturated aqueous NaHCO<sub>3</sub> solution (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield crude 3,4-diisopropoxyphenol **2.98** (3.04 g) as a brown gum, which was used in the next step without further purification. The spectroscopic data for this compound matched that previously reported.<sup>41</sup>

#### Partial data for 3,4-diisopropoxyphenol **2.98**:

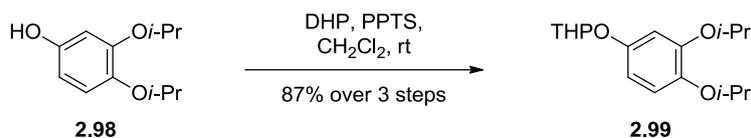
**R<sub>f</sub>** = 0.35 (petrol/EtOAc, 4:1)

**IR (neat)**: 3367, 2977, 2933, 1602, 1504, 1454, 1373, 1290, 1210 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)**: δ 6.79 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 3.0 Hz, 1H), 6.31 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.59 (d, *J* = 4.5 Hz, 1H), 4.46 (hept, *J* = 6.0 Hz, 1H), 4.28 (hept, *J* = 6.0 Hz, 1H), 1.33 (d, *J* = 6.0 Hz, 6H), 1.28 (d, *J* = 6.0 Hz, 6H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)**: δ 151.1, 150.7, 142.6, 121.2, 107.0, 105.0, 73.7, 71.5, 22.3, 22.2.

## 2-(3,4-Diisopropoxyphenoxy)tetrahydro-2H-pyran **2.99**



To a solution of 3,4-diisopropoxyphenol **2.98** (3.04 g, 13.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (9.5 mL) was added DHP (3.70 mL, 40.0 mmol) followed by PPTS (0.34 g, 1.33 mmol) at room temperature. The resulting mixture was allowed to stir for 5 hours, then diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield a dark red oil, which was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 5:1) to give pure **2.99** as a colourless oil (3.41 g, 87% over 3 steps). The spectroscopic data for this compound matched that previously reported.<sup>41</sup>

### Partial data for 2-(3,4-diisopropoxyphenoxy)tetrahydro-2H-pyran **2.99**:

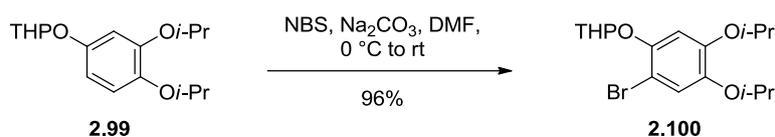
R<sub>f</sub> = 0.70 (petrol/EtOAc, 4:1)

IR (neat): 2941, 2872, 1719, 1597, 1508, 1452, 1356 cm<sup>-1</sup>.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 6.83 (d, *J* = 9.0 Hz, 1H), 6.66 (d, *J* = 3.0 Hz, 1H), 6.57 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.29 (t, *J* = 3.0 Hz, 1H), 4.48 (hept, *J* = 6.0 Hz, 1H), 4.31 (hept, *J* = 6.0 Hz, 1H), 3.97 – 3.92 (m, 1H), 3.62 – 3.58 (m, 1H), 2.03 – 1.95 (m, 1H), 1.88 – 1.79 (m, 2H), 1.70 – 1.58 (m, 3H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.33 (overlapped d, *J* = 6.0 Hz, 3H), 1.29 (s, 3H), 1.28 (s, 3H).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>): δ 152.6, 150.3, 143.6, 120.5, 108.4, 107.0, 97.2, 73.4, 71.6, 62.2, 30.5, 25.3, 22.34, 22.34, 22.21, 22.20, 19.01.

## Aryl bromide 2.100



Compound **2.99** (0.82 g, 2.80 mmol) and Na<sub>2</sub>CO<sub>3</sub> (2.08g, 19.61 mmol) were dissolved in DMF (9 mL) and the resultant solution was cooled to 0 °C. NBS (0.70 g, 3.92 mmol) was added portion wise over 5 min at 0 °C. The reaction mixture was stirred at room temperature over 12 h, then diluted with EtOAc (20 mL) and water (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 4:1) to give pure aryl bromide **2.100** as a light brown solid (1.00 g, 96%). The spectroscopic data for this compound matched that previously reported.<sup>41</sup>

### Data for **2.100**:

**R<sub>f</sub>** = 0.65 (petrol/EtOAc, 4:1)

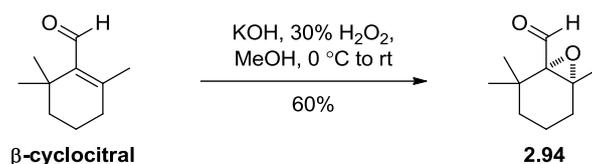
**IR (neat)**: 2975, 2939, 2873, 1726, 1578, 1489, 1383, 1258, 1195, 1107 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: δ 7.08 (s, 1H), 6.81 (s, 1H), 5.34 (t, *J* = 3.0 Hz, 1H), 4.45 (hept, *J* = 6.0 Hz, 1H), 4.33 (hept, *J* = 6.0 Hz, 1H), 3.96 (dt, *J* = 11.0, 3.0 Hz, 1H), 3.63 – 3.59 (m, 1H), 2.12 – 2.03 (m, 1H), 1.97 – 1.94 (m, 1H), 1.89 – 1.83 (m, 1H), 1.74 – 1.61 (m, 3H), 1.32 – 1.29 (overlapped d, 12H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: δ 149.3, 148.6, 144.4, 123.3, 108.1, 103.6, 97.9, 73.5, 72.3, 61.9, 30.3, 25.3, 22.2, 22.1, 22.1, 18.5.

**HRMS (ESI)**: calculated for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>Br 287.0288 [M–THP]<sup>-</sup>, found 287.0283.

## Epoxyaldehyde **2.94**



To a solution of  $\beta$ -cyclocitral (1.00 g, 6.57 mmol) in MeOH (7 mL) was added KOH (0.65 g, 13.1 mmol) in one portion at 0 °C. 30% H<sub>2</sub>O<sub>2</sub> (1.15 mL, 11.7 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 4 hours. The resulting mixture was quenched with water (20 mL) and extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/Et<sub>2</sub>O, 10:1) to give **2.94** as a colourless oil (0.66 g, 60%). The spectroscopic data for this compound matched that previously reported.<sup>36</sup>

### Partial data for **2.94**:

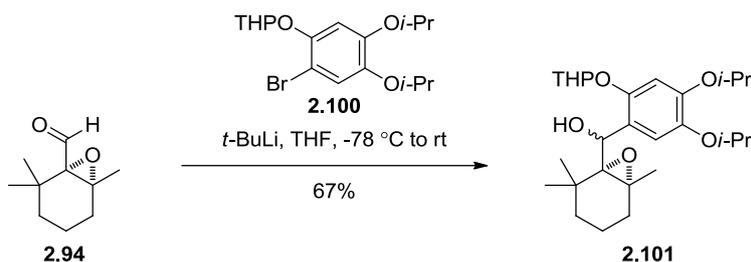
**R<sub>f</sub>** = 0.70 (petrol/EtOAc, 4:1)

**IR (neat)**: 2934, 2872, 1724, 1673, 1613, 1460, 1380, 1365 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  9.74 (s, 1H), 1.95 – 1.87 (m, 1H), 1.79 – 1.74 (m, 1H), 1.50 – 1.41 (m, 4H), 1.32 (s, 3H), 1.28 (s, 3H), 1.06 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**:  $\delta$  201.7, 73.1, 65.2, 35.3, 32.6, 29.4, 26.1, 24.4, 21.4, 16.7.

## Benzylic alcohol **2.101**



To a solution of **2.100** (3.78 g, 10.1 mmol) in anhydrous Et<sub>2</sub>O (30 mL) was added *t*-BuLi (1.7 M in pentane, 4.95 mL, 8.43 mmol) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 30 min. A solution of epoxy aldehyde **2.94** (0.57 g, 3.37 mmol) in anhydrous Et<sub>2</sub>O (30 mL) was then added dropwise over 10 min at -78 °C. The reaction mixture was stirred at -78 °C for a further 30 min, then allowed to warm to room temperature. The mixture was quenched with saturated aqueous NH<sub>4</sub>Cl solution (30 mL) and extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 20:1 → 5:1) to give **2.101** as a yellow gum (1.06 g, 67%). <sup>1</sup>H NMR showed a complex mixture of four diastereoisomers, therefore **2.101** was not fully characterised.

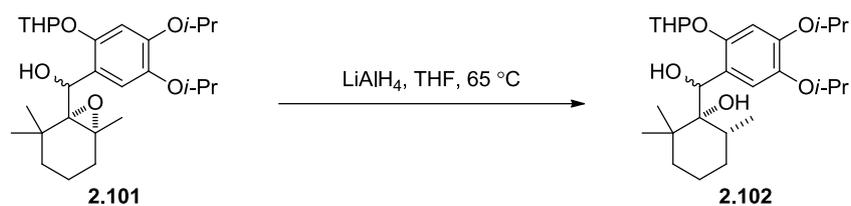
### Partial data for **2.101**:

**R<sub>f</sub>** = 0.50 (petrol/EtOAc, 4:1)

**IR (neat)**: 3484, 2972, 2935, 2872, 1609, 1583, 1501, 1381, 1305, 1192 cm<sup>-1</sup>.

**HRMS (ESI)**: calculated for C<sub>27</sub>H<sub>43</sub>O<sub>6</sub> 463.3060 [M+H]<sup>+</sup>, found 463.3059.

## Diol 2.102



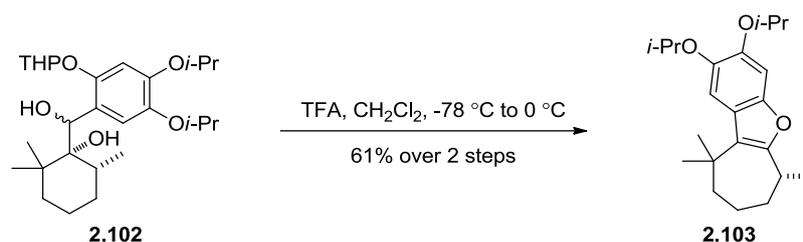
To a solution of benzylic alcohol **2.101** (0.99 g, 2.14 mmol) in anhydrous THF (21 mL) was added  $\text{LiAlH}_4$  (2.0M in THF, 5.40 mL, 10.80 mmol) dropwise at  $0\text{ }^\circ\text{C}$ . The reaction mixture was heated to  $65\text{ }^\circ\text{C}$  for 2 hours, then cooled to room temperature. The mixture was diluted with EtOAc (10 mL) and carefully quenched with 1 M HCl solution (5 mL) at  $0\text{ }^\circ\text{C}$ . The precipitate was filtered through Celite and washed thoroughly with EtOAc ( $2 \times 20\text{ mL}$ ). The organic fractions were combined and concentrated *in vacuo* to give crude diol **2.102** (0.75 g) as a yellow gum, which was used in the next step without further purification.

### Partial data for **2.102**:

$R_f = 0.45$  (petrol/EtOAc, 4:1)

**HRMS (ESI)**: calculated for  $\text{C}_{22}\text{H}_{35}\text{O}_5$  379.2490  $[\text{M}-\text{THP}]^-$ , found 379.2487.

## Benzofuran 2.103



To a solution of crude diol **2.102** (0.75 g, 2.14 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (55 mL) was added TFA (0.80 mL, 10.72 mmol) dropwise at -78 °C. The reaction mixture was allowed to gradually warm up to room temperature over 30 min. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> solution (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give benzofuran **2.103** as a colourless gum (450 mg, 61% over two steps).

### Data for **2.103**:

**R<sub>f</sub>** = 0.80 (petrol/EtOAc, 4:1)

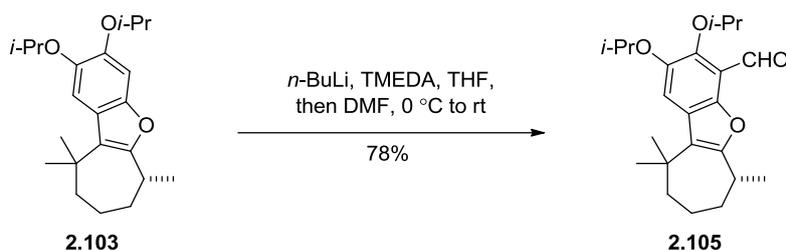
**IR (neat)**: 2972, 2927, 2859, 1623, 1474, 1381, 1304, 1183, 1111 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: δ 7.25 (s, 1H), 6.95 (s, 1H), 4.47 (hept, *J* = 6.0 Hz, 1H), 4.35 (hept, *J* = 6.0 Hz, 1H), 3.21 – 3.15 (m, 1H), 1.91 – 1.62 (m, 6H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 6H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 6H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: δ 156.3, 149.5, 147.0, 144.4, 122.3, 121.6, 113.1, 100.2, 74.0, 72.1, 43.3, 34.7, 34.5, 32.9, 29.7, 29.6, 29.0, 22.3, 22.19, 22.18, 21.8, 19.5.

**HRMS (ESI)**: calculated for C<sub>22</sub>H<sub>33</sub>O<sub>3</sub> 345.2430 [M+H]<sup>+</sup>, found 345.2421.

## Aldehyde **2.105**



Benzofuran **2.103** (63 mg, 0.18 mmol) was dissolved in anhydrous THF (3.5 mL) and the resultant solution was cooled to 0 °C. TMEDA (0.05 mL, 0.36 mmol) and *n*-BuLi (2.5 M in hexanes, 1.45 mL, 0.36 mmol) were added dropwise, and the resultant mixture was stirred at 0 °C for 30 min. DMF (1.40 mL, 1.81 mmol) was then added dropwise, and the reaction mixture was allowed to warm to room temperature over 20 min. The mixture was quenched with saturated aqueous NH<sub>4</sub>Cl solution (10 mL) and extracted with Et<sub>2</sub>O (2 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give aldehyde **2.105** as a yellow oil (53 mg, 78%).

### Data for **2.105**:

**R<sub>f</sub>** = 0.70 (petrol/EtOAc, 4:1)

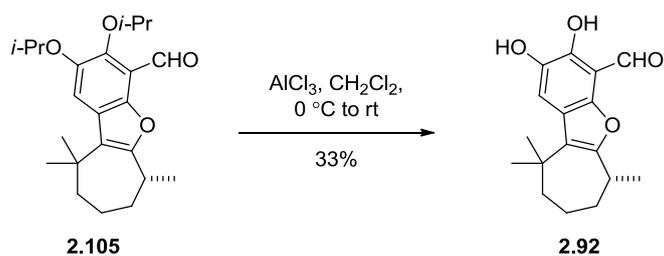
**IR (neat):** 2972, 2932, 2863, 2872, 1688, 1607, 1587, 1445, 1307 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 10.56 (s, 1H), 7.50 (s, 1H), 4.69 (hept, *J* = 6.0 Hz, 1H), 4.51 (hept, *J* = 6.0 Hz, 1H), 3.32 – 3.25 (m, 1H), 1.94 – 1.84 (m, 3H), 1.81 – 1.62 (m, 3H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.42 (overlapped s, 3H), 1.41 (s, 3H), 1.36 (d, *J* = 6.1 Hz, 6H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.33 (d, *J* = 6.5 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 189.3, 158.9, 149.2, 146.7, 146.0, 125.7, 121.0, 117.5, 116.4, 76.6, 73.1, 43.3, 34.3 (2 overlapped peaks), 33.0, 29.7, 29.2, 22.30, 22.25, 22.18, 22.17, 21.6, 19.5.

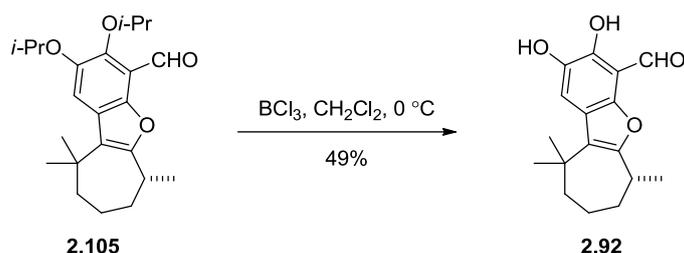
**HRMS (ESI):** calculated for C<sub>23</sub>H<sub>33</sub>O<sub>4</sub> 373.2379 [M+H]<sup>+</sup>, found 373.2388.

## Simplified liphagal analogue **2.92**



To a solution of aldehyde **2.105** (20 mg, 0.05 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1 mL) was added  $\text{AlCl}_3$  (21 mg, 0.16 mmol) at  $0\text{ }^\circ\text{C}$ . The reaction mixture was stirred at  $0\text{ }^\circ\text{C}$  for 5 min, then warmed to room temperature for a further 50 min. The reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (10 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (petrol/EtOAc, 4:1) to give **2.92** as a yellow oil (5 mg, 33%).

## Simplified liphagal analogue **2.92**



To a solution of aldehyde **2.105** (21 mg, 0.06 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (2 mL) was added  $\text{BCl}_3$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 0.30 mL, 0.30 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, then quenched with water (10 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (petrol/EtOAc, 10:1) to give **2.92** as a yellow solid (8 mg, 49%).

### Data for **2.92**:

$R_f$  = 0.55 (petrol/EtOAc, 4:1)

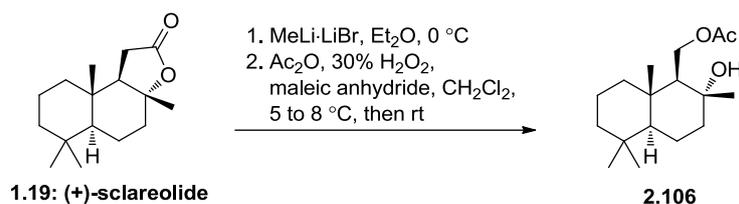
**IR (neat):** 3560, 3426, 2960, 2927, 2859, 1653, 1453, 1336, 1311, 1190  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  11.24 (s, 1H), 10.45 (s, 1H), 7.54 (s, 1H), 5.35 (s, 1H), 3.26 – 3.19 (m, 1H), 1.94 – 1.62 (m, 6H), 1.41 (s, 3H), 1.39 (s, 3H), 1.38 (d,  $J$  = 7.1 Hz, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  192.4, 156.7, 147.8, 145.4, 139.8, 121.9, 121.1, 114.8, 106.4, 43.3, 34.6, 34.3, 32.9, 29.6, 29.0, 21.7, 19.4.

**HRMS (ESI):** calculated for  $\text{C}_{17}\text{H}_{19}\text{O}_4$  287.1289  $[\text{M}-\text{H}]^-$ , found 287.1284.

## Acetate 2.106



To a solution of (+)-sclareolide (**1.19**) (10.0 g, 40.0 mmol) in anhydrous Et<sub>2</sub>O (150 mL) was added MeLi·LiBr (1.5 M in Et<sub>2</sub>O, 50.0 mL, 75.0 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The mixture was quenched with 10% H<sub>2</sub>SO<sub>4</sub> aqueous solution (50 mL) and warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (2 × 100 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> solution (100 mL), water (100 mL) and brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield ketone **I** (11.4 g) as a white oil, which was used in the next step without further purification.

### Partial data for ketone **I**:

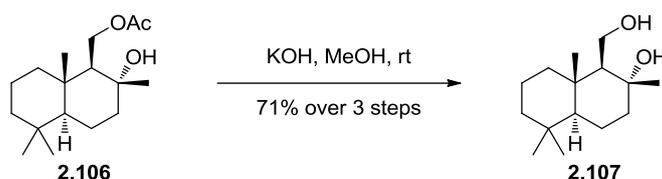
R<sub>f</sub> = 0.20 (petrol/EtOAc, 2:1)

To a solution of Ac<sub>2</sub>O (50.0 mL, 530 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (70 mL) was added 30% H<sub>2</sub>O<sub>2</sub> (46.0 mL, 457 mmol) at 5 °C. The resulting mixture was stirred at 5 °C for 1 hour. Maleic anhydride (30.0 g, 306 mmol) was then added in 10.0 g portions over 20 min at 8 °C. The mixture was stirred at 8 °C for 1 hour before warming to room temperature and stirring for another 1 hour. Ketone **5KK16** (10.6 g, 39.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was then added dropwise over 20 min at room temperature. The reaction mixture was stirred at room temperature for a further 12 hours. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (60 mL). The organic layer was separated and washed with saturated aqueous NaHCO<sub>3</sub> solution (100 mL), water (100 mL) and brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield crude acetate **510a** (13.9 g) as a white oil, which was used in the next step without further purification.

### Partial data for **510a**:

R<sub>f</sub> = 0.30 (petrol/EtOAc, 2:1)

## Diol 2.107



A 10% solution of KOH (11.2 g, 200 mmol) in MeOH (200 mL) was added to a flask containing crude acetate **2.106** (11.3 g, 39.9 mmol). The reaction was stirred at room temperature for 1 hour, then diluted with saturated  $\text{NH}_4\text{Cl}$  solution (150 mL) and  $\text{Et}_2\text{O}$  (150 mL). The organic layer was separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  ( $2 \times 50$  mL). The combined organic extracts were washed with brine (100 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude diol was purified by flash column chromatography on  $\text{SiO}_2$  (gradient elution, petrol/ $\text{EtOAc}$ , 4:1  $\rightarrow$  2:1) to give diol **2.107** as a white solid (6.82 g, 71% over 3 steps). The spectroscopic data for this compound matched that previously reported.<sup>44</sup>

### Partial data for 2.107:

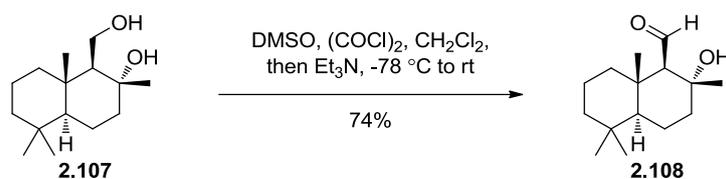
$R_f = 0.10$  (petrol/ $\text{EtOAc}$ , 4:1)

**IR (neat):** 3312, 2921, 1455, 1383, 1051, 1021, 910  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  3.91 (d,  $J = 7.0$  Hz, 2H), 3.58 (br s, 1H), 3.21 (br s, 1H), 1.88 (dt,  $J = 12.0, 3.0$  Hz, 1H), 1.75 – 1.37 (m, 6H), 1.34 (s, 3H), 1.31 – 1.06 (m, 4H), 0.97 (dd,  $J = 12.2, 2.0$  Hz, 1H), 0.88 (s, 3H), 0.79 (s, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  75.1, 61.1, 60.6, 55.9, 44.5, 41.7, 40.0, 37.5, 33.5, 33.3, 24.3, 21.6, 20.2, 18.6, 16.0.

## Aldehyde **2.108**



To a solution of DMSO (12.1 mL, 170 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (140 mL) was added (COCl)<sub>2</sub> (7.27 mL, 85.2 mmol) dropwise at -78 °C. The mixture was stirred at -78 °C for 10 min. Diol **2.107** (6.82 g, 28.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (140 mL) was then added dropwise over 10 min at -78 °C. The reaction mixture was stirred for a further 10 min at -78 °C. Et<sub>3</sub>N (39.4 mL, 284 mmol) was then added at -78 °C. The reaction mixture was then slowly warmed to room temperature over 10 min. The mixture was quenched with water (150 mL). The organic layer was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 150 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 4:1) to give aldehyde **2.108** as a white solid (4.98 g, 74%).

### Partial data for **2.108**:

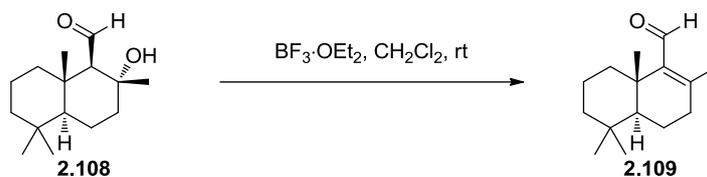
R<sub>f</sub> = 0.35 (petrol/EtOAc, 4:1)

IR (neat): 3438, 2925, 1713, 1463, 1388, 1113, 1084, 1069, 939, 787 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 10.03 (d, *J* = 1.0 Hz, 1H), 3.14 (br s, 1H), 2.08 (s, 1H), 1.98 – 1.96 (m, 1H), 1.82 (dt, *J* = 13.0, 3.0 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.54 – 1.43 (m, 3H), 1.38 (s, 3H), 1.37 – 1.28 (m, 1H), 1.22 (td, *J* = 13.0, 4.0 Hz, 2H), 1.12 (s, 3H), 0.97 (dd, *J* = 12.0, 2.0 Hz, 1H), 0.90 (s, 3H), 0.84 (s, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 208.2, 72.8, 71.3, 55.2, 42.7, 41.6, 39.8, 37.3, 33.3, 33.2, 25.3, 21.4, 19.9, 18.2, 17.6.

### $\alpha,\beta$ -Unsaturated aldehyde **2.109**

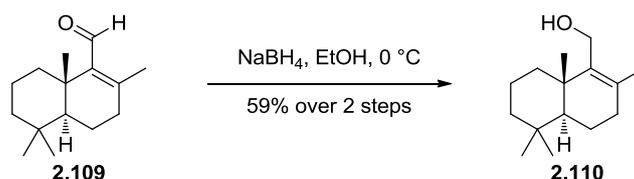


To a solution of aldehyde **2.108** (3.32 g, 13.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (87 mL) was added  $\text{BF}_3 \cdot \text{OEt}_2$  (3.45 mL, 27.9 mmol) dropwise at room temperature. The resulting mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL) and quenched with water (100 mL). The layers were separated and the organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to yield crude  $\alpha,\beta$ -unsaturated aldehyde **2.109** (3.22 g) as a brown oil, which was used in the next step without further purification. The spectroscopic data for this compound matched that previously reported.<sup>52</sup>

#### Partial data for **2.109**:

$R_f$  = 0.50 (petrol/EtOAc, 4:1)

## Allylic alcohol **2.110**



To a solution of allylic aldehyde **2.109** (3.07 g, 13.9 mmol) in EtOH (70 mL) was added NaBH<sub>4</sub> (1.05 g, 27.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 40 min. The reaction mixture was quenched with 10% H<sub>2</sub>SO<sub>4</sub> aqueous solution (50 mL) and extracted with Et<sub>2</sub>O (2 × 50 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> solution (50 mL), water (50 mL) and brine (50 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 20:1 → 4:1) to give allylic alcohol **2.110** as a white solid (1.83 g, 59% over 2 steps). The spectroscopic data for this compound matched that previously reported.<sup>52</sup>

### Partial data for **2.110**:

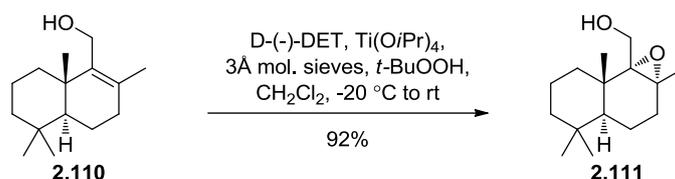
**R<sub>f</sub>** = 0.40 (petrol/EtOAc, 4:1)

**IR (neat)**: 3360, 2896, 1374, 998, 982 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)**: δ 4.20 (d, *J* = 11.5 Hz, 1H), 4.05 (d, *J* = 11.5 Hz, 1H), 2.12 – 2.01 (m, 2H), 1.90 – 1.88 (m, 1H), 1.72 (s, 3H), 1.69 – 1.66 (m, 1H), 1.63 (dt, *J* = 13.5, 3.5 Hz, 1H), 1.54 – 1.49 (m, 1H), 1.46 – 1.39 (m, 2H), 1.26 (td, *J* = 13.0, 4.0 Hz, 1H), 1.18 (dd, *J* = 13.5, 4.0 Hz, 1H), 1.14 (dd, *J* = 13.0, 2.0 Hz, 1H), 0.97 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)**: δ 141.0, 132.4, 58.3, 51.7, 41.7, 38.1, 36.8, 33.7, 33.26, 33.25, 21.6, 20.7, 19.3, 19.0, 18.9.

## Epoxyalcohol 2.111



To a solution of D-(-)-DET (1.66 mL, 9.72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) containing 3Å molecular sieves was added Ti(OiPr)<sub>4</sub> (2.88 mL, 9.72 mmol) at -20 °C. The mixture was stirred at -20 °C for 10 min, followed by the addition of *t*-BuOOH (5.5 M in decane, 7.10 mL, 38.9 mmol). The resulting mixture was stirred for 30 min at -20 °C. Alcohol **2.110** (4.32 g, 19.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added dropwise over 10 min, and the reaction mixture was stirred at -20 °C for a further 1 hour. The reaction mixture was diluted with Et<sub>2</sub>O (100 mL), quenched with 30% NaOH aqueous solution (1.50 mL) and brine (1.50 mL), and was allowed to warm to room temperature. Anhydrous MgSO<sub>4</sub> was added, and the reaction mixture was filtered through a pad of Celite, which was washed with Et<sub>2</sub>O (100 mL) and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give epoxy alcohol **2.111** as a white solid (4.26 g, 92%). The spectroscopic data for this compound matched that previously reported.<sup>52</sup>

### Partial data for 2.111:

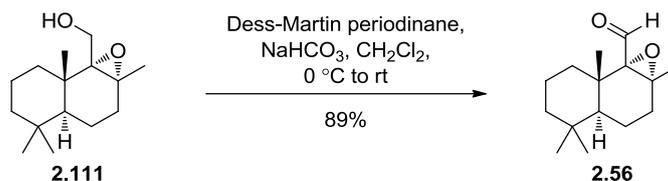
R<sub>f</sub> = 0.45 (petrol/EtOAc, 2:1)

IR (neat): 3405, 2922, 1456, 1364, 1025 cm<sup>-1</sup>.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 3.88 (dd, *J* = 11.0, 6.0 Hz, 1H), 3.55 (dd, *J* = 11.0, 2.5 Hz, 1H), 1.99 – 1.93 (m, 2H), 1.85 – 1.78 (m, 2H), 1.60 – 1.49 (m, 2H), 1.43 – 1.33 (m, 4H), 1.30 (s, 3H), 1.28 – 1.23 (m, 1H), 1.17 (td, *J* = 13.0, 4.5 Hz, 1H), 0.97 (s, 3H), 0.85 (s, 3H), 0.81 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 71.2, 64.5, 56.9, 43.2, 41.4, 37.1, 33.9, 33.5, 32.9, 29.4, 21.5, 21.4, 18.3, 17.1, 16.2.

## Epoxyaldehyde 2.56



To a solution of **2.111** (280 mg, 1.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was added NaHCO<sub>3</sub> (150 mg, 1.74 mmol) and Dess-Martin periodinane (0.74 g, 1.74 mmol) in one portion at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with water (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give epoxyaldehyde **2.56** as a white solid (240 mg, 89%).

### Partial data for 2.56:

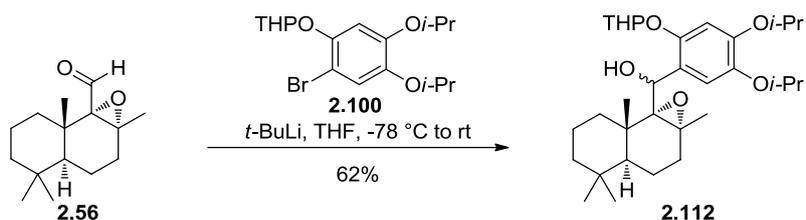
**R<sub>f</sub>** = 0.55 (petrol/EtOAc, 4:1)

**IR (neat):** 2948, 1723, 1458, 1381 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 9.70 (s, 1H), 2.04 – 1.97 (m, 1H), 1.86 (ddd, *J* = 16.0, 9.0, 1.0 Hz, 1H), 1.66 – 1.64 (m, 1H), 1.60 – 1.54 (m, 2H), 1.52 (dd, *J* = 13.0, 3.0 Hz, 1H), 1.49 – 1.42 (m, 4H), 1.37 (s, 3H), 1.25 (s, 3H), 1.21 – 1.18 (m, 1H), 0.84 (s, 6H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 201.7, 75.3, 64.4, 42.0, 41.3, 36.6, 35.3, 33.4, 32.9, 28.6, 21.4, 21.3, 18.2, 17.2, 16.8.

## Benzylic alcohol **2.112**



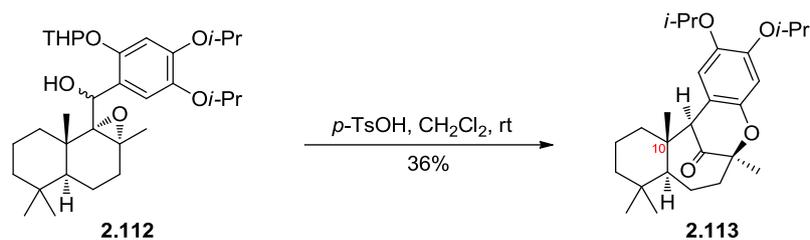
To a solution of **2.100** (1.11 g, 2.98 mmol) in anhydrous THF (12 mL) was added *t*-BuLi (1.7 M in pentane, 1.70 mL, 2.89 mmol) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 30 min. A solution of aldehyde **2.56** (340 mg, 1.42 mmol) in anhydrous THF (12 mL) was then added dropwise over 10 min at -78 °C. The reaction mixture was stirred at -78 °C for a further 30 min, then allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl solution (20 mL) and extracted with Et<sub>2</sub>O (2 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give benzylic alcohol **2.112** as a white foam (464 mg, 62%). <sup>1</sup>H NMR showed a complex mixture of four diastereoisomers, therefore **2.112** was not fully characterised.

### Partial data for **2.112**:

**R<sub>f</sub>** = 0.40 (petrol/EtOAc, 4:1)

**HRMS (ESI)**: calculated for C<sub>32</sub>H<sub>50</sub>O<sub>6</sub>Na 553.3505 [M+Na]<sup>+</sup>, found 553.3493.

## Cycloheptanone **2.113**



To a solution of alcohol **2.112** (83 mg, 0.16 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (3 mL) was added  $p$ -TsOH (60 mg, 0.31 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours, then quenched with water (5 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (gradient elution, petrol/EtOAc, 10:1  $\rightarrow$  4:1) to give cycloheptanone **2.113** as a colourless oil (24 mg, 36%).

### Data for **2.113**:

$R_f$  = 0.80 (petrol/EtOAc, 4:1)

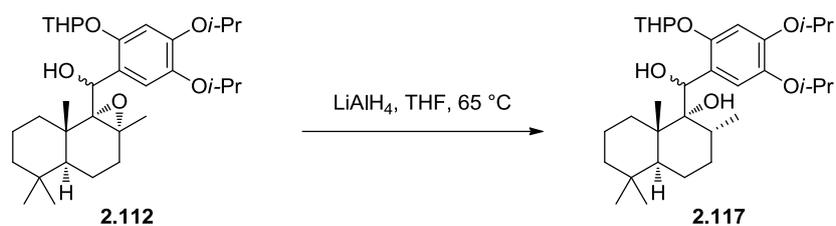
**IR (neat):** 2973, 2929, 2869, 1716, 1613, 1496, 1111  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.50 (s, 1H), 6.48 (s, 1H), 4.49 – 4.42 (m, 1H), 4.33 – 4.26 (m, 1H), 3.20 (s, 1H), 1.96 (dt,  $J$  = 13.5, 3.5 Hz, 1H), 1.82 – 1.80 (m, 1H), 1.73 – 1.70 (m, 1H), 1.61 – 1.44 (m, 5H), 1.41 – 1.37 (overlapped m, 1H), 1.38 (s, 3H), 1.34 (d,  $J$  = 6.0 Hz, 3H), 1.33 (d,  $J$  = 6.0 Hz, 3H), 1.28 (d,  $J$  = 6.0 Hz, 3H), 1.27 (d,  $J$  = 6.0 Hz, 3H), 1.24 – 1.19 (m, 1H), 1.06 (d,  $J$  = 9.0 Hz, 1H), 0.90 (s, 3H), 0.82 (s, 3H), 0.71 (s, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  210.6, 150.3, 148.9, 143.8, 121.8, 116.8, 106.0, 85.4, 73.6, 71.5, 65.8, 51.9, 46.7, 41.5, 40.5, 35.6, 33.6, 24.3, 22.3, 22.24, 22.16, 22.12, 22.10, 21.4, 19.5, 19.1. The C-10 quaternary carbon was not observed.

**HRMS (ESI):** calculated for  $\text{C}_{27}\text{H}_{41}\text{O}_4$  429.3005  $[\text{M}+\text{H}]^+$ , found 429.2990.

## Diol 2.117



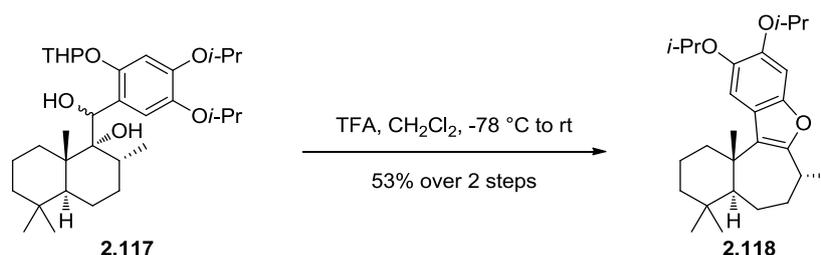
To a solution of benzylic alcohol **2.112** (464 mg, 0.87 mmol) in anhydrous THF (9 mL) was added  $\text{LiAlH}_4$  (2.0 M in THF, 2.20 mL, 4.40 mmol) dropwise at  $0\text{ }^\circ\text{C}$ . The reaction mixture was heated to  $65\text{ }^\circ\text{C}$  for 2 hours, then cooled to room temperature. The mixture was diluted with EtOAc (10 mL) and carefully quenched with 1M HCl solution (3 mL) at  $0\text{ }^\circ\text{C}$ . The precipitate was filtered through Celite and washed thoroughly with EtOAc ( $2 \times 20\text{ mL}$ ). The organic fractions were combined and concentrated *in vacuo* to give **2.117** (390 mg) as a white foam, which was used in the next step without further purification.

### Partial data for **2.117**:

$R_f = 0.40$  (petrol/EtOAc, 4:1)

**HRMS (ESI)**: calculated for  $\text{C}_{32}\text{H}_{51}\text{O}_6$  531.3691  $[\text{M}-\text{H}]^-$ , found 531.3679.

## Benzofuran 2.118



To a solution of crude diol **2.117** (390 mg, 0.73 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added TFA (0.28 mL, 3.66 mmol) at -78 °C. The reaction mixture was allowed to gradually warm up to room temperature over 30 min. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give benzofuran **2.118** as a colourless gum (160 mg, 53% over two steps).

### Data for **2.118**:

R<sub>f</sub> = 0.80 (petrol/EtOAc, 4:1)

[α]<sub>D</sub><sup>25</sup> = +10.3 (*c* 0.89, CHCl<sub>3</sub>)

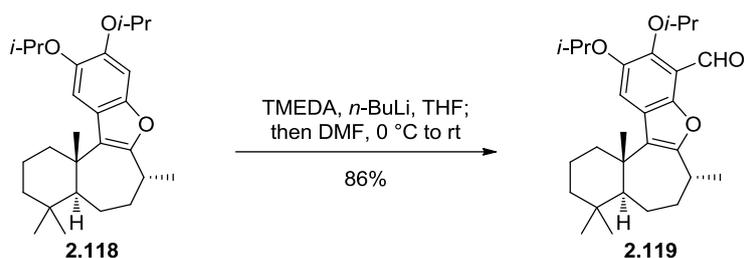
IR (neat): 2972, 2930, 2869, 1717, 1621, 1474, 1380, 1309, 1111 cm<sup>-1</sup>.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.25 (s, 1H), 6.92 (s, 1H), 4.47 (hept, *J* = 6.0 Hz, 1H), 4.34 (hept, *J* = 6.0 Hz, 1H), 3.17 (sext, *J* = 7.0 Hz, 1H), 2.60 – 2.58 (m, 1H), 2.19 – 2.12 (m, 1H), 1.87 – 1.81 (m, 1H), 1.75 – 1.66 (m, 1H), 1.64 – 1.44 (m, 7H), 1.41 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 3H), 1.35 (d, *J* = 6.4 Hz, 6H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.31 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 3H), 0.94 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 156.0, 149.6, 147.1, 144.0, 125.2, 121.5, 114.5, 99.8, 74.1, 71.9, 53.7, 42.1, 40.2, 39.5, 35.2, 34.8, 33.6, 33.3, 24.2, 22.3, 22.3, 22.2, 22.1, 22.0, 21.8, 20.2, 18.9.

HRMS (ESI): calculated for C<sub>27</sub>H<sub>41</sub>O<sub>3</sub> 413.3056 [M+H]<sup>+</sup>, found 413.3048.

## Aldehyde 2.119



Benzofuran **2.118** (140 mg, 0.34 mmol) was dissolved in anhydrous THF (5 mL) and the resultant solution was cooled to 0 °C. TMEDA (0.08 mL, 0.53 mmol) and *n*-BuLi (2.5 M in hexanes, 0.22 mL, 0.53 mmol) were added dropwise, and the resultant mixture was stirred at 0 °C for 30 min. DMF (0.21 mL, 2.65 mmol) was then added dropwise, and the reaction mixture was allowed to warm to room temperature over 20 min. The mixture was quenched with saturated aqueous NH<sub>4</sub>Cl solution (10 mL) and extracted with Et<sub>2</sub>O (2 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give aldehyde **2.119** as a white oil (130 mg, 86%).

### Data for 2.119:

**R<sub>f</sub>** = 0.70 (petrol/EtOAc, 4:1)

**[α]<sub>D</sub><sup>25</sup>** = +2.5 (*c* 1.56, CHCl<sub>3</sub>)

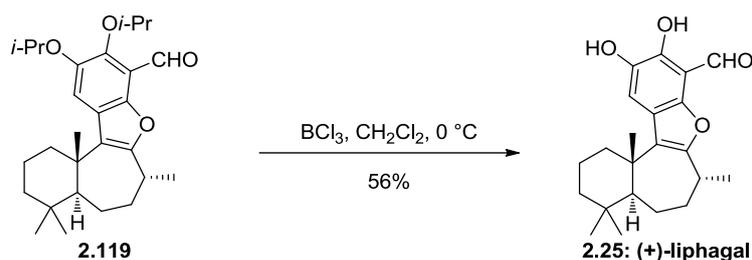
**IR (neat):** 2971, 2929, 2868, 1690, 1605, 1445, 1381, 1320, 1298, 1236, 1101 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 10.56 (s, 1H), 7.50 (s, 1H), 4.70 (hept, *J* = 6.0 Hz, 1H), 4.50 (hept, *J* = 6.0 Hz, 1H), 3.31 (sext, *J* = 7.0 Hz, 1H), 2.53 – 2.51 (m, 1H), 2.21 – 2.16 (m, 1H), 1.88 – 1.83 (m, 1H), 1.77 – 1.68 (m, 1H), 1.63 – 1.50 (m, 7H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 3H), 1.36 – 1.32 (overlapped d, 12H), 0.99 (s, 3H), 0.95 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 189.4, 158.5, 149.3, 147.0, 145.6, 125.0, 124.5, 119.0, 116.1, 76.5, 73.2, 53.5, 41.9, 40.3, 39.5, 34.8, 34.8, 33.5, 33.3, 24.0, 22.29, 22.26, 22.21, 22.15, 22.10, 22.0, 20.3, 18.9.

**HRMS (ESI):** calculated for C<sub>28</sub>H<sub>41</sub>O<sub>4</sub> 441.3005 [M+H]<sup>+</sup>, found 441.3020.

## (+)-Liphagal 2.25



To a solution of aldehyde **2.119** (84 mg, 0.19 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (2 mL) was added  $\text{BCl}_3$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 0.95 mL, 0.95 mmol) dropwise at  $0\text{ }^\circ\text{C}$ . A dark red solution was formed. The reaction mixture was stirred at  $0\text{ }^\circ\text{C}$  for 5 min, then quenched with water (10 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (petrol/EtOAc, 10:1) to give (+)-liphagal (**2.25**) as a yellow solid (38 mg, 56%).

### Data for (+)-liphagal:

$R_f = 0.45$  (petrol/EtOAc, 4:1)

$[\alpha]_D^{25} = +22.6$  ( $c$  0.50,  $\text{CHCl}_3$ ), lit. value  $[\alpha]_D^{25} = +25.99$  ( $c$  0.072,  $\text{CHCl}_3$ )<sup>27</sup>

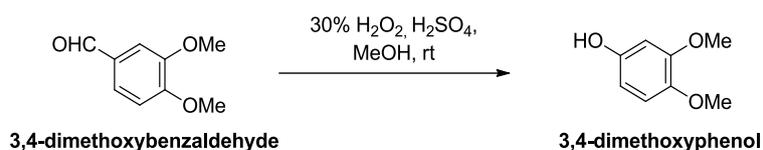
**IR (neat):** 3417, 2930, 2868, 1654, 1455, 1389, 1328, 1301  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  11.24 (s, 1H), 10.44 (s, 1H), 7.55 (s, 1H), 5.32 (s, 1H), 3.21 (sext,  $J = 7.0\text{ Hz}$ , 1H), 2.55 – 2.53 (m, 1H), 2.20 – 2.15 (m, 1H), 1.91 – 1.83 (m, 1H), 1.76 – 1.65 (m, 1H), 1.64 – 1.45 (m, 6H), 1.43 (d,  $J = 7.0\text{ Hz}$ , 3H), 1.35 (s, 3H), 1.25 (ddd,  $J = 13.0, 13.0, 3.0\text{ Hz}$ , 1H), 0.98 (s, 3H), 0.95 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  192.6, 156.7, 148.2, 145.5, 139.6, 125.7, 120.5, 116.2, 106.5, 53.9, 42.1, 40.5, 39.7, 35.4, 35.0, 33.9, 33.5, 24.4, 22.2, 21.9, 20.4, 19.0.

**HRMS (ESI):** calculated for  $\text{C}_{22}\text{H}_{29}\text{O}_4$  357.2066  $[\text{M}+\text{H}]^+$ , found 357.2060.

### 3,4-Dimethoxyphenol



Conc.  $\text{H}_2\text{SO}_4$  (1.28 mL, 24.1 mmol) was added dropwise to a solution of 3,4-dimethoxybenzaldehyde (5.00 g, 30.1 mmol) in MeOH (120 mL) at room temperature. 30%  $\text{H}_2\text{O}_2$  (23.9 mL, 232 mmol) was then added in one portion and the reaction mixture was stirred at room temperature for 6 hours. Upon completion, the resulting mixture was quenched with saturated aqueous  $\text{NaHCO}_3$  solution (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 50$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to yield crude 3,4-dimethoxyphenol (4.64 g) as a brown gum, which was used in the next step without further purification. The spectroscopic data for this compound matched that previously reported.<sup>53</sup>

#### Partial data for 3,4-dimethoxyphenol:

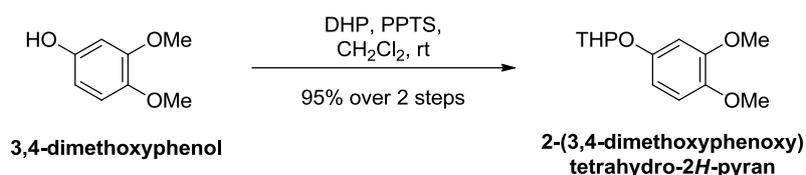
$R_f = 0.35$  (petrol/EtOAc, 2:1)

**IR (neat):** 3420, 2838, 1508, 1477, 1193, 1127, 949, 804  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.73 (d,  $J = 9.0$  Hz, 1H), 6.47 (d,  $J = 3.0$  Hz, 1H), 6.34 (dd,  $J = 9.0, 3.0$  Hz, 1H), 4.74 (br s, 1H), 3.84 (s, 3H), 3.82 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  150.04, 149.95, 143.3, 112.4, 105.8, 100.6, 56.6, 55.8.

## 2-(3,4-Dimethoxyphenoxy)tetrahydro-2H-pyran



To a solution of 3,4-dimethoxyphenol (4.64 g, 30.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (22 mL) was added DHP (8.25 mL, 90.3 mmol) followed by PPTS (0.76 g, 3.01 mmol) at room temperature. The resulting mixture was allowed to stir for 2 hours, then diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to yield a dark red oil. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (petrol/EtOAc, 10:1) to give pure 2-(3,4-dimethoxyphenoxy)tetrahydro-2H-pyran as a colourless oil (6.84 g, 95% over 2 steps). The spectroscopic data for this compound matched that previously reported.<sup>53</sup>

### Partial data for 2-(3,4-dimethoxyphenoxy)tetrahydro-2H-pyran:

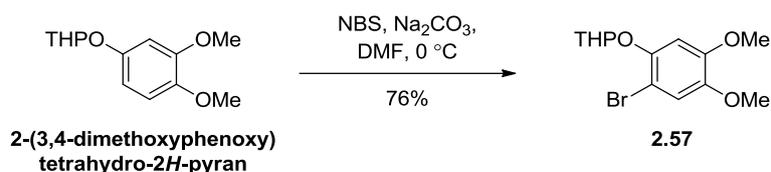
$R_f = 0.50$  (petrol/EtOAc, 2:1)

**IR (neat):** 2941, 2878, 1509, 1196, 1104, 1022, 991, 790  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.78 (d,  $J = 9.0$  Hz, 1H), 6.66 (d,  $J = 3.0$  Hz, 1H), 6.61 (dd,  $J = 9.0, 3.0$  Hz, 1H), 5.32 (t,  $J = 4.0$  Hz, 1H), 3.97 – 3.93 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.62 – 3.59 (m, 1H), 2.03 – 1.96 (m, 1H), 1.87 – 1.82 (m, 2H), 1.71 – 1.59 (m, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.6, 149.6, 144.1, 111.8, 107.1, 102.3, 97.3, 62.1, 56.4, 55.9, 30.5, 25.3, 18.9.

## Aryl bromide 2.57



2-(3,4-dimethoxyphenoxy)tetrahydro-2H-pyran (4.66 g, 19.6 mmol) and  $\text{Na}_2\text{CO}_3$  (14.5 g, 136.8 mmol) were dissolved in DMF (65 mL) and the resultant solution was cooled to 0 °C. NBS (4.87 g, 27.4 mmol) was added portion wise over 5 min at 0 °C. The reaction mixture was stirred at room temperature over 12 hours, then diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2  $\times$  30 mL). The combined organic extracts were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on basic  $\text{SiO}_2$  (petrol/EtOAc in 5%  $\text{Et}_3\text{N}$ , 4:1). The combined organic fractions were concentrated *in vacuo* and redissolved in  $\text{Et}_2\text{O}$  (30 mL). The organic layer was washed with water (50 mL), brine (50 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give pure aryl bromide **2.57** as a white solid (4.69 g, 76%). The spectroscopic data for this compound matched that previously reported.<sup>53</sup>

### Partial data for 2.57:

$R_f$  = 0.30 (petrol/EtOAc, 6:1)

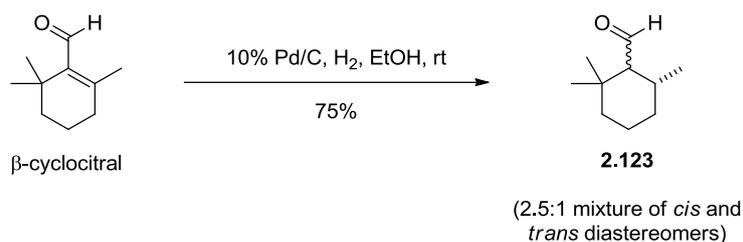
M.p. = 70 – 74 °C

IR (neat): 2943, 1505, 1441, 1214, 1200, 1020, 985, 802  $\text{cm}^{-1}$ .

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.01 (s, 1H), 6.81 (s, 1H), 5.36 (t,  $J$  = 3.0 Hz, 1H), 3.98 (dt,  $J$  = 11.0, 3.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.62 (dt,  $J$  = 7.0, 3.0 Hz, 1H), 2.13 – 2.03 (m, 1H), 2.00 – 1.94 (m, 1H), 1.92 – 1.84 (m, 1H), 1.75 – 1.61 (m, 4H).

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.9, 147.7, 144.7, 115.7, 103.1, 102.9, 98.2, 62.0, 56.5, 56.1, 30.3, 25.3, 18.5.

## Aldehyde 2.123



To a solution of  $\beta$ -cyclocitral (1.00 g, 6.57 mmol) in EtOH (25 mL) was added 10% Pd/C (0.10 g, 0.94 mmol). The reaction mixture was sparged with H<sub>2</sub> for 2 hours. The reaction mixture was filtered through a pad of Celite, which was washed thoroughly with EtOH (50 mL). The organic extract was concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give aldehyde **2.123** as a colourless oil (0.76 g, 75%). The spectroscopic data for these compounds matched that previously reported.<sup>45</sup>

### Partial data for 2.123:

R<sub>f</sub> = 0.80 (petrol/EtOAc, 4:1)

IR (neat): 2955, 2928, 2867, 1718, 1458, 1388, 1370 cm<sup>-1</sup>.

### Data for *cis* product (major):

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.95 (d, *J* = 6.0 Hz, 1H), 1.93 (t, *J* = 5.0 Hz, 1H), 1.75 – 1.71 overlapped (m, 2H), 1.66 – 1.62 (overlapped m, 3H), 1.44 – 1.35 (overlapped m, 2H), 1.02 (s, 3H), 0.92 (s, 3H), 0.91 (d, *J* = 7.0 Hz, 3H).

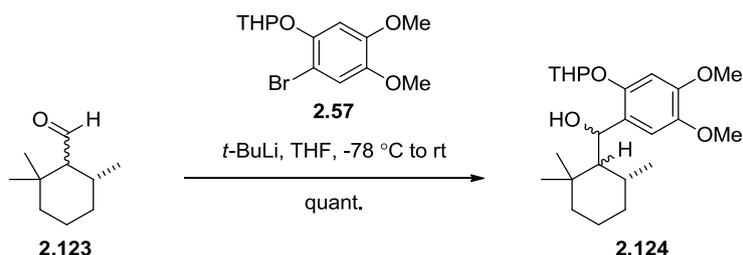
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  208.0, 62.5, 35.6, 33.1, 30.7, 30.2, 29.8, 27.3, 22.1, 20.1.

### Data for *trans* product (minor):

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.64 (d, *J* = 5.0 Hz, 1H), 2.02 – 1.96 (overlapped m, 1H), 1.80 – 1.74 (overlapped m, 2H), 1.63 – 1.60 (overlapped m, 1H), 1.58 – 1.49 (overlapped m, 2H), 1.24 – 1.13 (overlapped m, 2H), 1.03 (s, 3H), 0.98 (s, 3H), 0.82 (d, *J* = 6.5 Hz, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  207.4, 66.2, 41.5, 34.3, 33.8, 31.0, 27.7, 21.7, 21.0, 20.8.

## Benzylic alcohol **2.124**



To a solution of **2.57** (1.24 g, 3.89 mmol) in anhydrous THF (10 mL) was added *t*-BuLi (1.7 M in pentane, 1.90 mL, 3.24 mmol) dropwise at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min. A solution of aldehyde **2.123** (200 mg, 1.30 mmol) in anhydrous THF (10 mL) was then added dropwise over 10 min at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 30 min, then allowed to warm to room temperature. The mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (10 mL) and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (petrol/ $\text{EtOAc}$ , 5:1) to give **2.124** as a yellow gum (0.46 g, quantitative).  $^1\text{H}$  NMR showed a complex mixture of four diastereoisomers, therefore **2.124** was not fully characterised.

### Partial data for **2.124**:

$R_f = 0.20$  (petrol/ $\text{EtOAc}$ , 4:1)

**IR (neat):** 3518, 2941, 2867, 1610, 1509, 1463, 1386  $\text{cm}^{-1}$ .

### Data for phenol **2.127**:

$R_f = 0.30$  (petrol/ $\text{EtOAc}$ , 4:1)

**IR (neat):** 3449, 2928, 2867, 1614, 1509, 1464, 1451, 1412, 1204  $\text{cm}^{-1}$ .

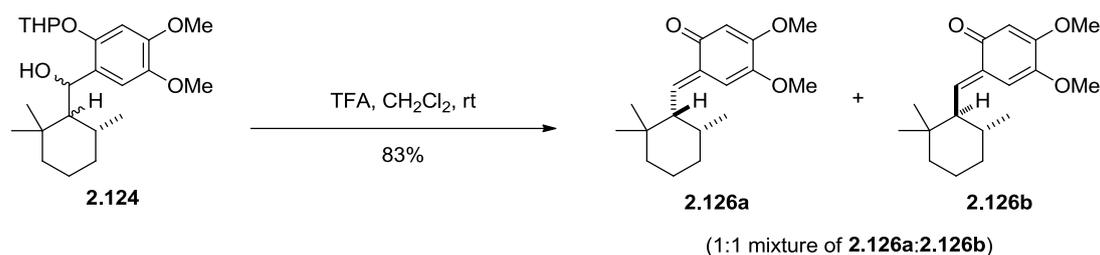
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.07 (s, 1H), 7.04 (s, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 5.32 (d,  $J = 5.97\text{ Hz}$ , 2H), 5.27 (t,  $J = 3.68\text{ Hz}$ , 1H), 5.25 (dd,  $J = 4.75, 2.23\text{ Hz}$ , 1H), 3.98 – 3.93 (m, 2H), 3.89 – 3.86 (m, 2H), 3.85 (s, 6H), 3.84 (s, 6H), 3.68 – 3.59 (m, 2H), 2.88 (br s, 1H), 2.51 (br s, 1H), 2.01 – 1.85 (m, 8H), 1.69 – 1.63 (m, 8H), 1.52 – 1.47 (m, 4H), 1.41 – 1.39 (m, 2H),

1.33 – 1.24 (m, 4H), 1.11 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.86 (d,  $J = 6.48$  Hz, 3H), 0.76 (d,  $J = 6.48$  Hz, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  148.3, 148.0, 147.99, 147.8, 143.5, 143.1, 127.4, 126.5, 111.7, 111.6, 101.4, 100.3, 99.5, 98.5, 68.9, 68.3, 63.4, 62.9, 56.5, 56.4, 55.99, 55.98, 55.4, 55.3, 43.1, 43.0, 37.4, 37.37, 34.9, 34.85, 31.8, 31.7, 31.0, 30.7, 28.8, 28.7, 25.1, 25.06, 23.3, 22.9, 22.5, 22.2, 22.1, 22.0, 19.9, 19.88.

**HRMS (ESI):** calculated for  $\text{C}_{18}\text{H}_{27}\text{O}_4$  307.1915  $[\text{M}-\text{THP}]^-$ , found 307.1914.

### **Ortho-quinone methides 2.126a/b**



To a solution **2.124** (95.0 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added TFA (0.10 mL, 1.21 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/EtOAc, 4:1) to give *ortho*-quinone methides **2.126a/b** as a yellow oil (58.5 mg, 83%).

#### **Data for 2.126a/b:**

**R<sub>f</sub>** = 0.10 (petrol/EtOAc, 4:1)

**IR (neat):** 2925, 2866, 1649, 1617, 1567, 1457, 1414, 1239 cm<sup>-1</sup>.

**HRMS (ESI):** calculated for C<sub>18</sub>H<sub>26</sub>O<sub>3</sub> 291.1960 [M+H]<sup>+</sup>, found 291.1952.

#### **Data for *cis* product 2.126a:**

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 7.35 (d, *J* = 13.0 Hz, 1H), 6.10 (s, 1H), 5.78 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.37 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.66 – 1.56 (m, 3H), 1.45 – 1.42 (m, 1H), 1.34 – 1.31 (m, 1H), 1.24 – 1.22 (m, 1H), 1.11 (s, 3H), 0.75 (s, 3H), 0.73 (d, *J* = 7.0 Hz, 3H).

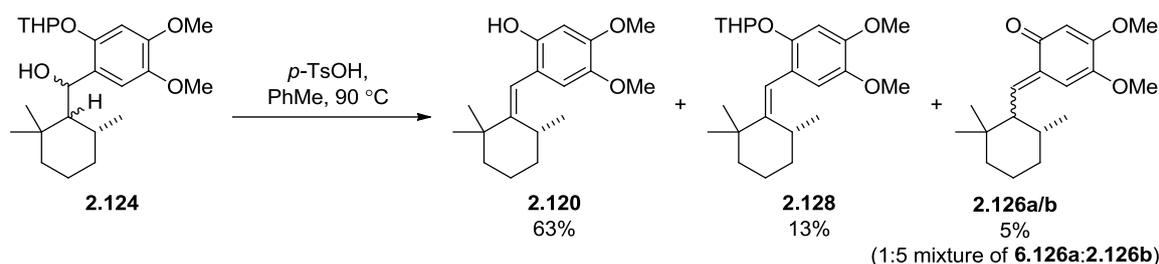
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 184.1, 164.6, 147.9, 147.6, 133.6, 104.3, 100.4, 56.3, 55.6, 49.8, 34.9, 34.0, 31.9, 31.0, 29.3, 27.4, 22.21, 20.9.

**Data for *trans* product 2.126b:**

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.04 (d, *J* = 11.8 Hz, 1H), 6.08 (s, 1H), 5.78 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 1.94 (dd, *J* = 11.3, 10.9 Hz, 1H), 1.79 (dd, *J* = 13.5, 3.0 Hz, 1H), 1.73 – 1.64 (m, 1H), 1.58 – 1.46 (m, 3H), 1.30 – 1.22 (m, 1H), 0.99 – 0.96 (overlapped m, 1H), 0.97 (s, 3H), 0.79 (s, 3H), 0.72 (d, *J* = 6.5 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 184.3, 164.7, 150.1, 147.6, 133.2, 104.2, 100.8, 56.3, 55.6, 53.9, 41.5, 35.6, 35.1, 32.4, 31.8, 21.8, 21.7, 20.7.

## Phenol **2.120**



To a solution **2.124** (230 mg, 0.59 mmol) in PhMe (10 mL) was added  $p$ -TsOH (12 mg, 0.06 mmol) at room temperature. The reaction mixture was heated to 90 °C for 15 min. The reaction mixture was cooled to room temperature, then quenched with saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 4:1 → 2:1) to give phenol **2.120** as a yellow gum (110 mg, 63%).

### Data for phenol **2.120**:

R<sub>f</sub> = 0.30 (petrol/EtOAc, 4:1)

IR (neat): 3449, 2928, 2867, 1614, 1509, 1464, 1451, 1412, 1204 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.53 (s, 1H), 6.52 (s, 1H), 6.10 (s, 1H), 4.76 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.79 – 2.74 (m, 1H), 1.82 (dt,  $J$  = 7.0, 3.0 Hz, 1H), 1.59 – 1.45 (m, 4H), 1.38 (dt,  $J$  = 13.0, 3.0 Hz, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 1.11 (d,  $J$  = 7.5 Hz, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 160.0, 148.8, 146.6, 142.6, 115.5, 114.7, 112.8, 99.4, 56.6, 55.9, 41.9, 37.0, 33.4, 31.7, 31.4, 29.7, 21.6, 17.8.

HRMS (ESI): calculated for C<sub>18</sub>H<sub>26</sub>O<sub>3</sub> 291.1960 [M+H]<sup>+</sup>, found 291.1963.

**Partial data for 2.128:**

**R<sub>f</sub>** = 0.45 (petrol/EtOAc, 4:1)

**IR (neat):** 2935, 2868, 1609, 1508, 1452 cm<sup>-1</sup>.

**HRMS (ESI):** calculated for C<sub>23</sub>H<sub>35</sub>O<sub>4</sub> 375.2535 [M+H]<sup>+</sup>, found 375.2530.

**Data for 2.126b:**

**R<sub>f</sub>** = 0.15 (petrol/EtOAc, 4:1)

**IR (neat):** 2925, 2866, 1649, 1617, 1565, 1456, 1413, 1366 cm<sup>-1</sup>.

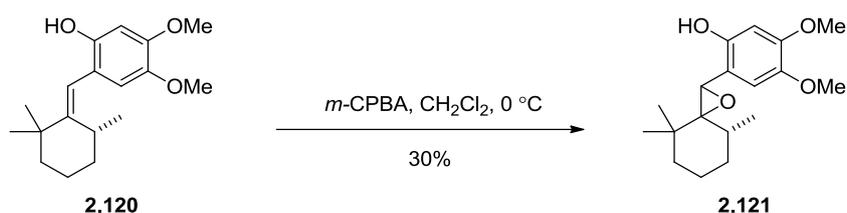
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 7.04 (d, *J* = 11.8 Hz, 1H), 6.08 (s, 1H), 5.78 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 1.94 (dd, *J* = 11.3, 10.9 Hz, 1H), 1.79 (dd, *J* = 13.5, 3.0 Hz, 1H), 1.73 – 1.64 (m, 1H), 1.58 – 1.46 (m, 3H), 1.30 – 1.22 (m, 1H), 0.99 – 0.96 (overlapped m, 1H), 0.97 (s, 3H), 0.79 (s, 3H), 0.72 (d, *J* = 6.5 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 184.3, 164.7, 150.1, 147.6, 133.2, 104.2, 100.8, 56.3, 55.6, 53.9, 41.5, 35.6, 35.1, 32.4, 31.8, 21.8, 21.7, 20.7.

**HRMS (ESI):** calculated for C<sub>18</sub>H<sub>27</sub>O<sub>3</sub> 291.1960 [M+H]<sup>+</sup>, found 291.1967.



## Epoxide **2.121**



To a solution of **2.120** (16 mg, 0.06 mmol) in  $CH_2Cl_2$  (0.5 mL) was added *m*-CPBA ( $\leq 77\%$ , 14 mg, 0.06 mmol) in one portion at  $0\text{ }^\circ C$ . The reaction mixture was stirred at  $0\text{ }^\circ C$  for 1 hour. The resulting mixture was quenched with saturated aqueous  $NaHCO_3$  solution (10 mL) and extracted with  $CH_2Cl_2$  ( $3 \times 10$  mL). The combined organic extracts were dried over  $MgSO_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $SiO_2$  (petrol/ $Et_2O$ , 4:1) to give **2.121** as a colourless oil (5 mg, 30%).

### Data for **2.121**:

$R_f = 0.30$  (petrol/ $EtOAc$ , 4:1)

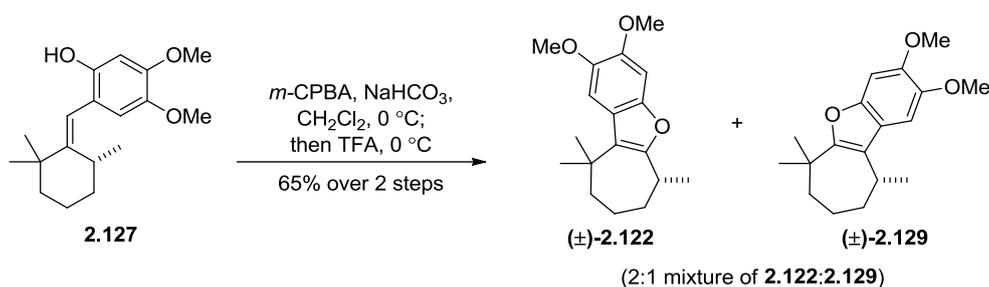
**IR (neat):** 3449, 3229, 2959, 2928, 2866, 1741, 1705, 1684, 1618, 1508, 1451, 1250  $cm^{-1}$ .

**$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  9.43 (br s, 1H), 6.56 (s, 1H), 6.40 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.71 (d,  $J = 11.0$  Hz, 1H), 2.30 – 2.24 (m, 1H), 1.98 – 1.93 (m, 1H), 1.83 – 1.77 (m, 3H), 1.26 – 1.22 (overlapped m, 2H), 1.23 (s, 3H), 1.10 (s, 3H), 0.70 (d,  $J = 7.0$  Hz, 3H).

**$^{13}C$  NMR (125 MHz,  $CDCl_3$ ):**  $\delta$  150.3, 149.4, 142.2, 116.2, 115.4, 103.4, 60.2, 56.9, 55.8, 48.3, 39.5, 39.3, 36.2, 26.3, 23.08, 23.07, 20.9.

**HRMS (ESI):** calculated for  $C_{18}H_{26}O_4$  307.1909  $[M+H]^+$ , found 307.1907.

## Benzofurans 2.122/2.129



To a solution of **2.127** (48 mg, 0.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) was added NaHCO<sub>3</sub> (21 mg, 0.25 mmol) and *m*-CPBA ( $\leq 77\%$ , 37 mg, 0.17 mmol) in one portion at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. TFA (0.06 mL, 0.83 mmol) was added dropwise to the reaction and the resulting mixture was stirred at 0 °C for a further 5 min. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (petrol/Et<sub>2</sub>O, 10:1) to give a 2:1 mixture of **2.122** and **2.129** as a colourless oil (31 mg, 65% over 2 steps).

### Data for **2.122/2.129**:

**R<sub>f</sub>** = 0.55 (petrol/EtOAc, 4:1)

**IR (neat)**: 2960, 2935, 1783, 1608, 1593, 1519, 1486, 1465 cm<sup>-1</sup>.

**HRMS (ESI)**: calculated for C<sub>18</sub>H<sub>25</sub>O<sub>3</sub> 289.1804 [M+H]<sup>+</sup>, found 289.1801.

### Data for major product **2.122**:

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  7.16 (s, 1H), 6.96 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.23 – 3.16 (m, 1H), 2.01 – 1.84 (m, 3H), 1.82 – 1.70 (m, 2H), 1.67 – 1.61 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H).

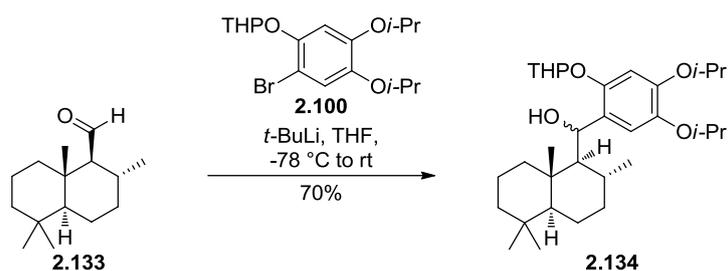
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**:  $\delta$  156.1, 148.3, 146.8, 145.2, 121.7, 121.1, 104.2, 95.1, 56.8, 56.2, 43.2, 34.7, 34.5, 32.9, 29.7, 29.0, 21.8, 19.4.

**Data for minor product 2.129:**

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 6.98 (s, 1H), 6.86 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.23 – 3.16 (m, 1H), 2.01 – 1.84 (m, 3H), 1.82 – 1.70 (m, 2H), 1.67 – 1.61 (m, 1H), 1.41 (s, 3H), 1.27 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 158.8, 147.5, 147.1, 145.9, 122.0, 118.1, 100.8, 95.2, 56.7, 56.3, 42.8, 37.2, 34.9, 28.8, 28.6, 28.2, 20.5, 19.9.

## Benzylic alcohol **2.134**



To a solution of **2.100** (0.60 g, 1.62 mmol) in anhydrous THF (4.5 mL) was added *t*-BuLi (1.7 M in pentane, 0.80 mL, 1.35 mmol) dropwise at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min. A solution of aldehyde **2.133** (120 mg, 0.54 mmol) in anhydrous THF (4.5 mL) was then added dropwise over 10 min at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 30 min, then allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (20 mL) and extracted with  $\text{Et}_2\text{O}$  ( $2 \times 10$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (petrol/ $\text{EtOAc}$ , 10:1) to give benzylic alcohol **2.134** as a colourless oil (195 mg, 70%).  $^1\text{H}$  NMR showed a complex mixture of four diastereoisomers and was not fully characterised.

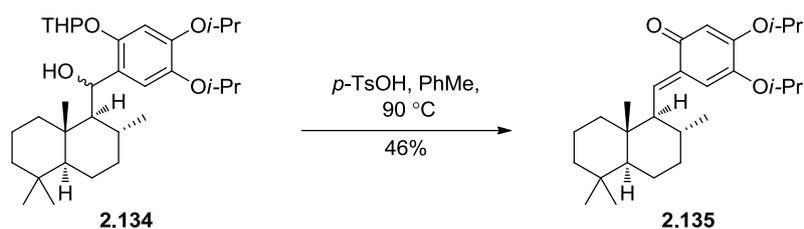
### Partial data for **2.134**:

**R<sub>f</sub>** = 0.65 (petrol/ $\text{EtOAc}$ , 4:1)

**IR (neat)**: 3472, 2971, 2931, 2868, 2843, 1500, 1382, 1189, 1178, 1111  $\text{cm}^{-1}$ .

**HRMS (ESI)**: calculated for  $\text{C}_{32}\text{H}_{52}\text{O}_5$  431.3167 [ $\text{M}-\text{THP}$ ] $^-$ , found 431.3164.

### Ortho-quinone methide **2.135**



To a solution **2.134** (123 mg, 0.24 mmol) in PhMe (4 mL) was added *p*-TsOH (5 mg, 23.7  $\mu\text{mol}$ ) at room temperature. The reaction mixture was heated to 90  $^\circ\text{C}$  for 15 min. The reaction mixture was cooled to room temperature, then quenched with saturated aqueous  $\text{NaHCO}_3$  solution (10 mL) and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (gradient elution, petrol/ $\text{EtOAc}$ , 5:1  $\rightarrow$  3:1) to give *ortho*-quinone methide **2.135** as a yellow film (45.5 mg, 46%).

#### Data for **2.135**:

$R_f$  = 0.35 (petrol/ $\text{EtOAc}$ , 4:1)

**IR (neat)**: 2925, 2853, 1650, 1619, 1561, 1455, 1425, 1372, 1229  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**:  $\delta$  7.06 (d,  $J$  = 11.0 Hz, 1H), 6.18 (s, 1H), 5.71 (s, 1H), 4.48 (hept,  $J$  = 6.0 Hz, 1H), 4.35 (hept,  $J$  = 6.0 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.83 (t,  $J$  = 11.0 Hz, 1H), 1.79 – 1.73 (m, 1H), 1.65 – 1.62 (m, 1H), 1.52 – 1.49 (m, 1H), 1.43 – 1.30 (overlapped m, 4H), 1.37 (d,  $J$  = 6.0 Hz, 6H), 1.34 (d,  $J$  = 6.0 Hz, 6H), 1.18 – 1.12 (m, 1H), 1.09 – 1.00 (overlapped m, 1H), 1.03 (s, 3H), 0.93 (dd,  $J$  = 12.5, 2.2 Hz, 1H), 0.88 – 0.83 (overlapped m, 1H), 0.88 (s, 3H), 0.85 (s, 3H), 0.66 (d,  $J$  = 6.0 Hz, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**:  $\delta$  184.3, 164.4, 149.4, 146.0, 133.6, 106.8, 104.8, 71.58, 71.57, 58.1, 54.9, 42.2, 41.3, 39.3, 36.2, 33.6, 33.5, 31.8, 22.0, 21.7, 21.7, 21.7, 21.6, 21.47, 21.45, 18.7, 15.2.

**HRMS (ESI)**: calculated for  $\text{C}_{27}\text{H}_{43}\text{O}_3$  415.3212  $[\text{M}+\text{H}]^+$ , found 415.3129.

## 2.11 References

1. Fujiwara, H.; Kurogi, T.; Okaya, S.; Okano, K.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 13062-13065.
2. Nagamine, T.; Inomata, K.; Endo, Y.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 123-131.
3. Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317-4353.
4. White, J. D.; Hrcnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871-7884.
5. Paquette, L. A.; Wang, H.-L. *Tetrahedron Lett.* **1995**, *36*, 6005-6008.
6. Petasis, N. A.; Patane, M. A. *Tetrahedron Lett.* **1990**, *31*, 6799-6802.
7. Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485-492.
8. Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1963**, *85*, 362-363.
9. Blatt, A. H. *Chem. Rev.* **1933**, *12*, 215-260.
10. Nakata, T.; Nomura, S.; Matsukura, H. *Tetrahedron Lett.* **1996**, *37*, 213-16.
11. Nakata, T.; Nomura, S.; Matsukura, H. *Chem. Pharm. Bull.* **1996**, *44*, 627-9.
12. Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169-2172.
13. Zhou, M.; Geng, H.-C.; Zhang, H.-B.; Dong, K.; Wang, W.-G.; Du, X.; Li, X.-N.; He, F.; Qin, H.-B.; Li, Y.; Pu, J.-X.; Sun, H.-D. *Org. Lett.* **2013**, *15*, 314-317.
14. George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394-2397.
15. Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321-324.
16. Sullivan, B.; Djura, P.; McIntyre, D. E.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 979-82.
17. Sullivan, B. W.; Faulkner, D. J.; Matsumoto, G. K.; He, C. H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568-73.
18. Markwell-Heys, A. W.; Kuan, K. K. W.; George, J. H. *Org. Lett.* **2015**, *17*, 4228-4231.

19. Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Koeck, M. *J. Nat. Prod.* **2007**, *70*, 504-509.
20. Zhang, Y.; Oblak, E. Z.; Bolstad, E. S. D.; Anderson, A. C.; Jasinski, J. P.; Butcher, R. J.; Wright, D. L. *Tetrahedron Lett.* **2010**, *51*, 6120-6122.
21. Sabbah, D. A.; Vennerstrom, J. L.; Zhong, H. *J. Chem. Inf. Model.* **2010**, *50*, 1887-1898.
22. Carson, J. D.; Van Aller, G.; Lehr, R.; Sinnamon, R. H.; Kirkpatrick, R. B.; Auger, K. R.; Dhanak, D.; Copeland, R. A.; Gontarek, R. R.; Tummino, P. J.; Luo, L. *Biochem. J.* **2008**, *409*, 519-524.
23. Mandelker, D.; Gabelli, S. B.; Schmidt-Kittler, O.; Zhu, J.; Cheong, I.; Huang, C.-H.; Kinzler, K. W.; Vogelstein, B.; Amzel, L. M. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 16996-17001.
24. Pereira, A. R.; Strangman, W. K.; Marion, F.; Feldberg, L.; Roll, D.; Mallon, R.; Hollander, I.; Andersen, R. J. *J. Med. Chem.* **2010**, *53*, 8523-8533.
25. Mehta, G.; Likhite, N. S.; Ananda Kumar, C. S. *Tetrahedron Lett.* **2009**, *50*, 5260-5262.
26. Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Cano, M. J.; Haidour, A.; Alvarez-Manzaneda, R. *Org. Lett.* **2010**, *12*, 4450-4453.
27. Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814-6818, S6814/1-S6814/64.
28. McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738-7739.
29. Olah, G. A.; Salem, G.; Staral, J. S.; Ho, T.-L. *J. Org. Chem.* **1978**, *43*, 173-175.
30. Zhang, J.; Li, L.; Wang, Y.; Wang, W.; Xue, J.; Li, Y. *Org. Lett.* **2012**, *14*, 4528-4530.
31. Laplace, D. R.; Verbraeken, B.; Van Hecke, K.; Winne, J. M. *Chem. - Eur. J.* **2014**, *20*, 253-262.

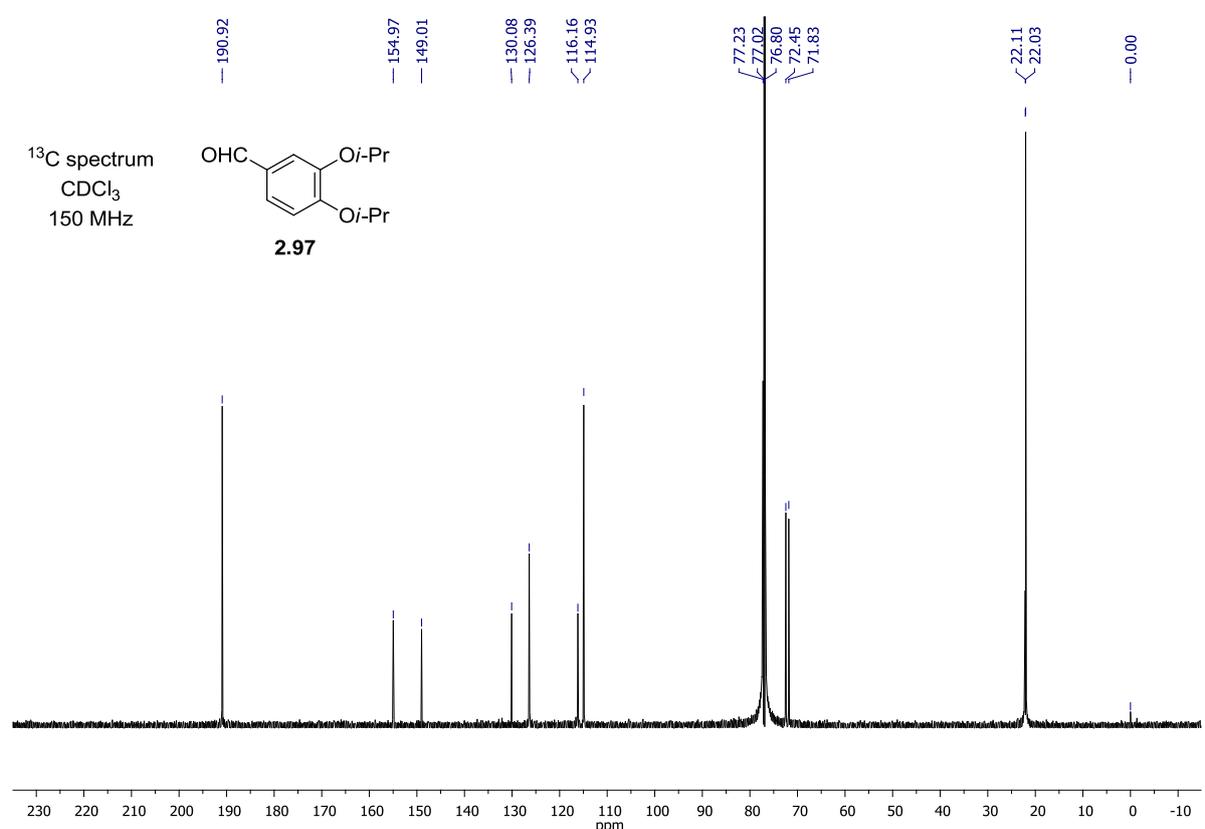
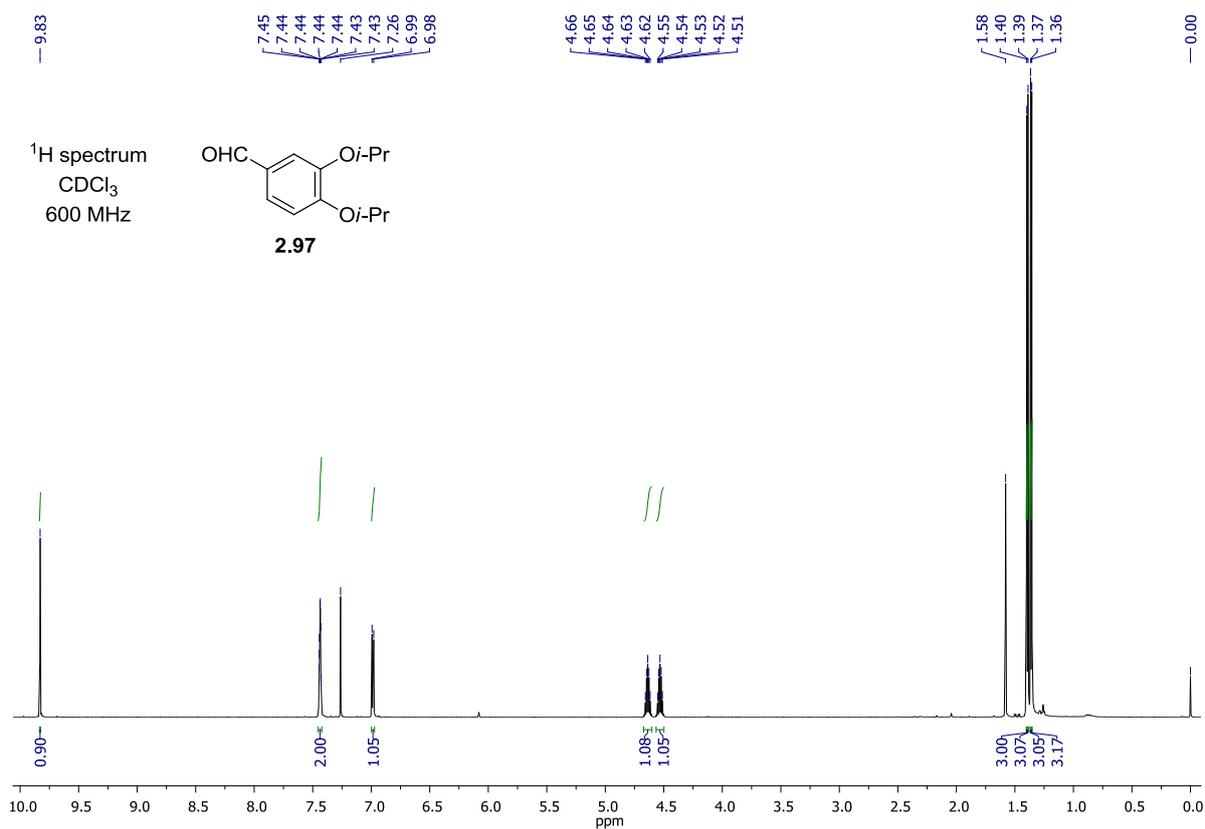
32. Kamishima, T.; Kikuchi, T.; Narita, K.; Katoh, T. *Eur. J. Org. Chem.* **2014**, *2014*, 3443-3450.
33. Reitz, A.; Avery, M. A.; Verlander, M. S.; Goodman, M. *J. Org. Chem.* **1981**, *46*, 4859-4863.
34. Deore, V.; Lohar, M. K.; Mundada, R.; Roychowdhury, A.; Vishwakarma, R.; Kumar, S. *Synth. Commun.* **2011**, *41*, 177-183.
35. Jiang, H.; Tian, L. F.; Li, Z. T.; Liu, Q.; Li, C. C.; Yao, X. S.; Yang, Z. *Sci. China: Chem.* **2012**, *55*, 36-42.
36. Vaz, B.; Domínguez, M.; Alvarez, R.; de Lera, A. R. *Chem. - Eur. J.* **2007**, *13*, 1273-1290.
37. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **1997**, *38*, 8101-8104.
38. Takao, K.-i.; Sasaki, T.; Kozaki, T.; Yanagisawa, Y.; Tadano, K.-i.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291-4294.
39. Banwell, M. G.; Flynn, B. L.; Stewart, S. G. *J. Org. Chem.* **1998**, *63*, 9139-9144.
40. Yang, L.-Y.; Chang, C.-F.; Huang, Y.-C.; Lee, Y.-J.; Hu, C.-C.; Tseng, T.-H. *Synthesis* **2009**, 1175-1179.
41. Hasse, K.; Willis, A. C.; Banwell, M. G. *Eur. J. Org. Chem.* **2011**, 88-99.
42. Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *Chem. - Eur. J.* **2013**, *135*, 6677-6693.
43. Li, W.-D. Z.; Gao, Z.-H. *Org. Lett.* **2005**, *7*, 2917-2920.
44. Vadapalli, S.; Kane, C. T. *Org. Prep. Proced. Int.* **2008**, *40*, 201-204.
45. Simmons, D. P.; Reichlin, D.; Skuy, D. *Helv. Chim. Acta* **1988**, *71*, 1000-1004.
46. Chapuis, C.; Brauchli, R. *Helv. Chim. Acta* **1993**, *76*, 2070-2088.
47. Bernet, A.; Seifert, K. *Helv. Chim. Acta* **2006**, *89*, 784-796.

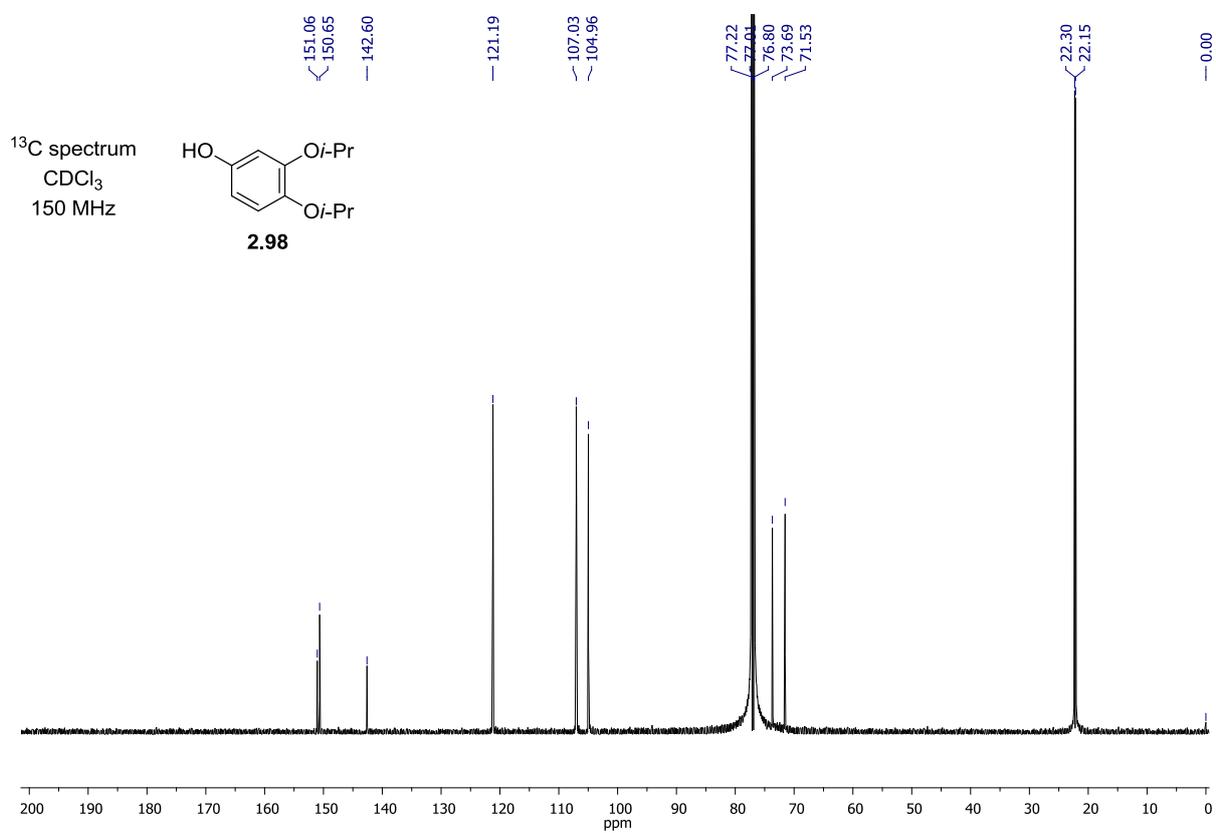
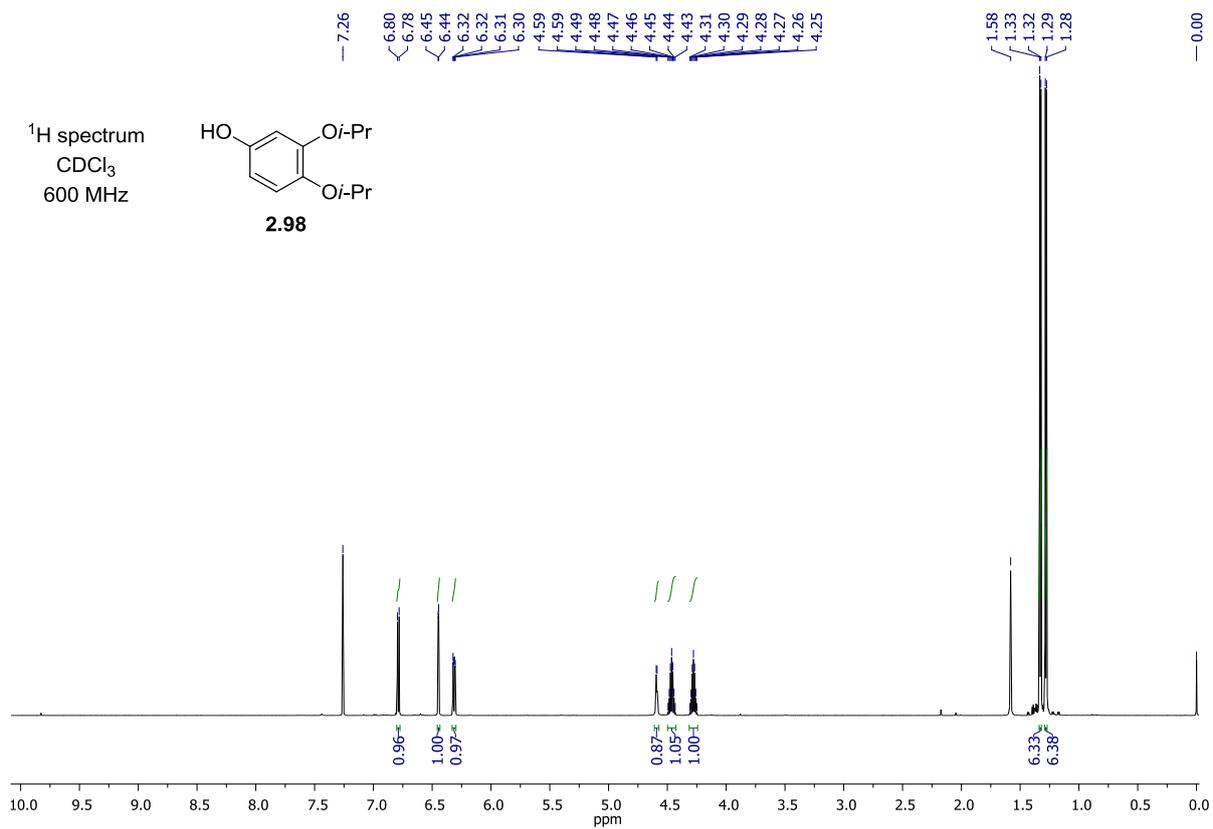
48. Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367-5405.
49. Willis, N. J.; Bray, C. D. *Chem. - Eur. J.* **2012**, *18*, 9160-9173.
50. Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655-3664.
51. Singh, M. S.; Nagaraju, A.; Anand, N.; Chowdhury, S. *RSC Adv.* **2014**, *4*, 55924-55959.
52. Kulciński, V.; Ungur, N.; Gavagnin, M.; Carbone, M.; Cimino, G. *Eur. J. Org. Chem.* **2005**, *2005*, 1816-1822.
53. Hasse, K.; Willis, A. C.; Banwell, M. G. *Aust. J. Chem.* **2009**, *62*, 683-691.

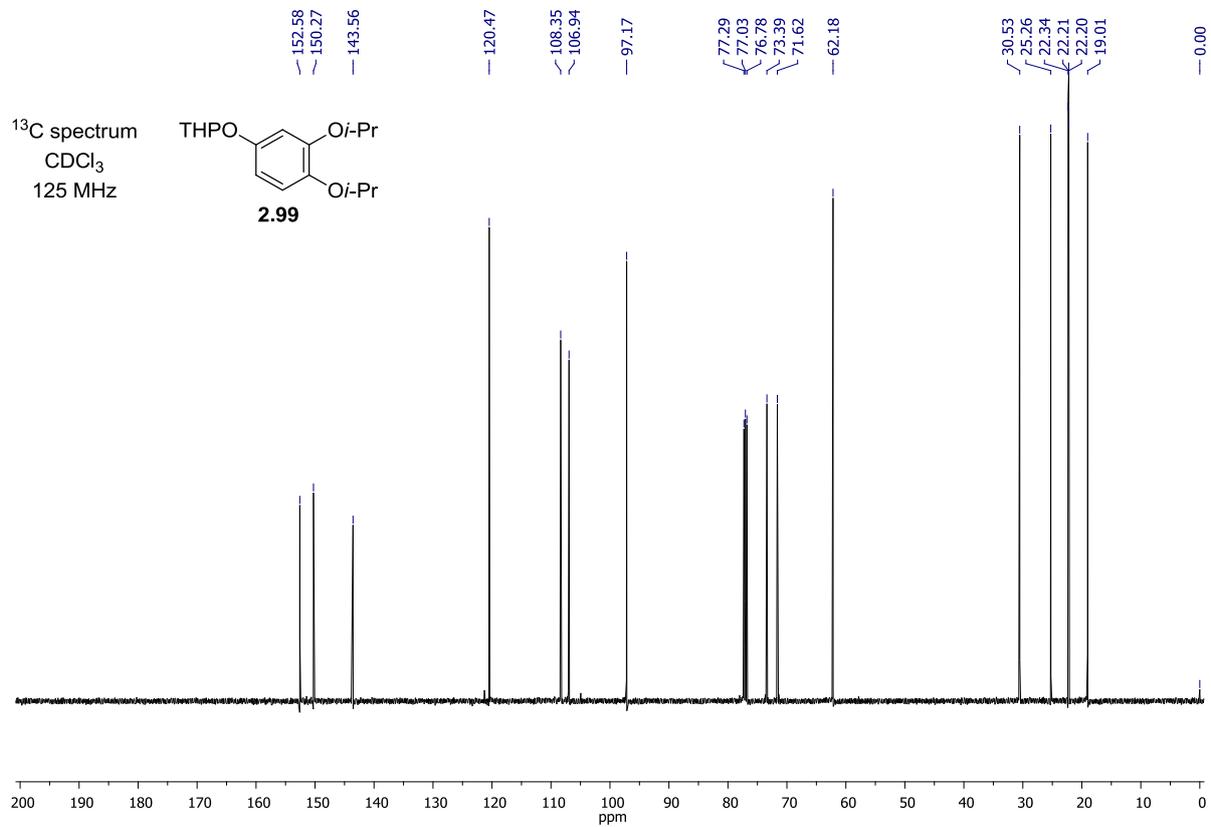
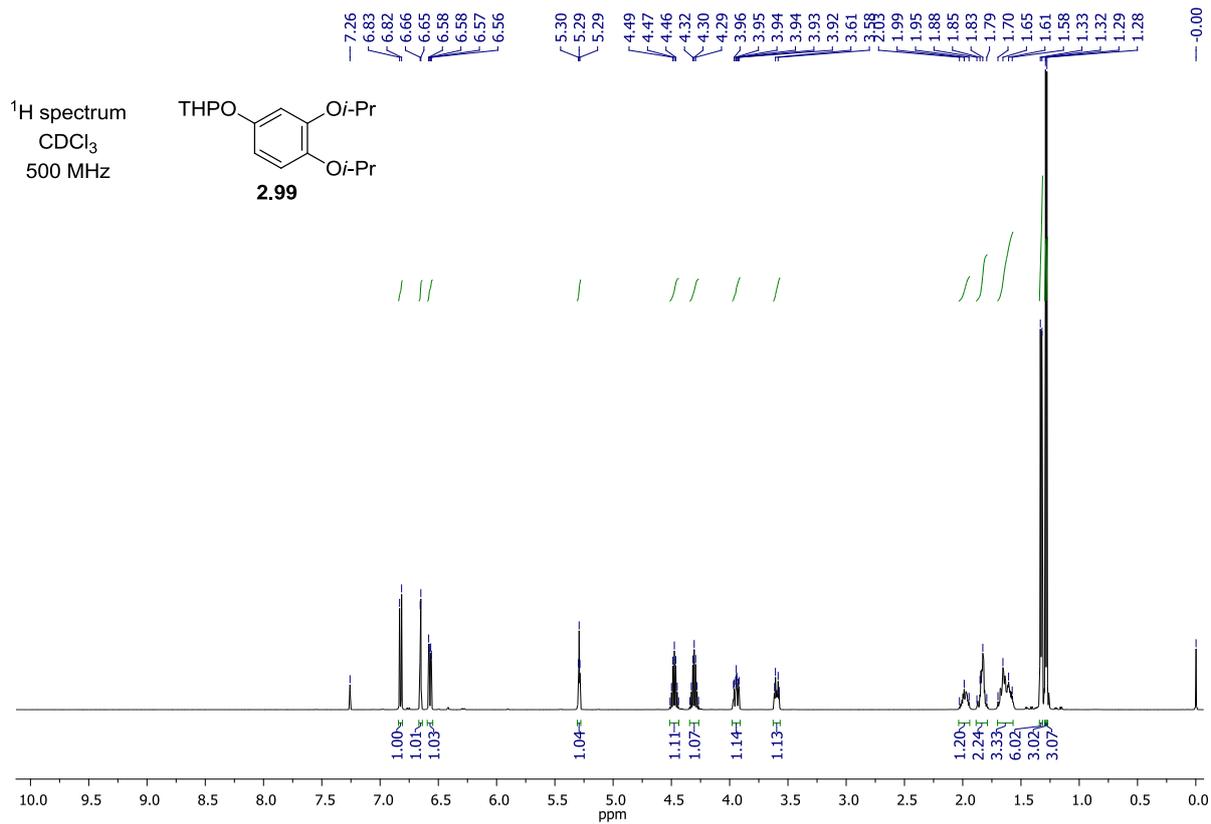
## **Appendix One**

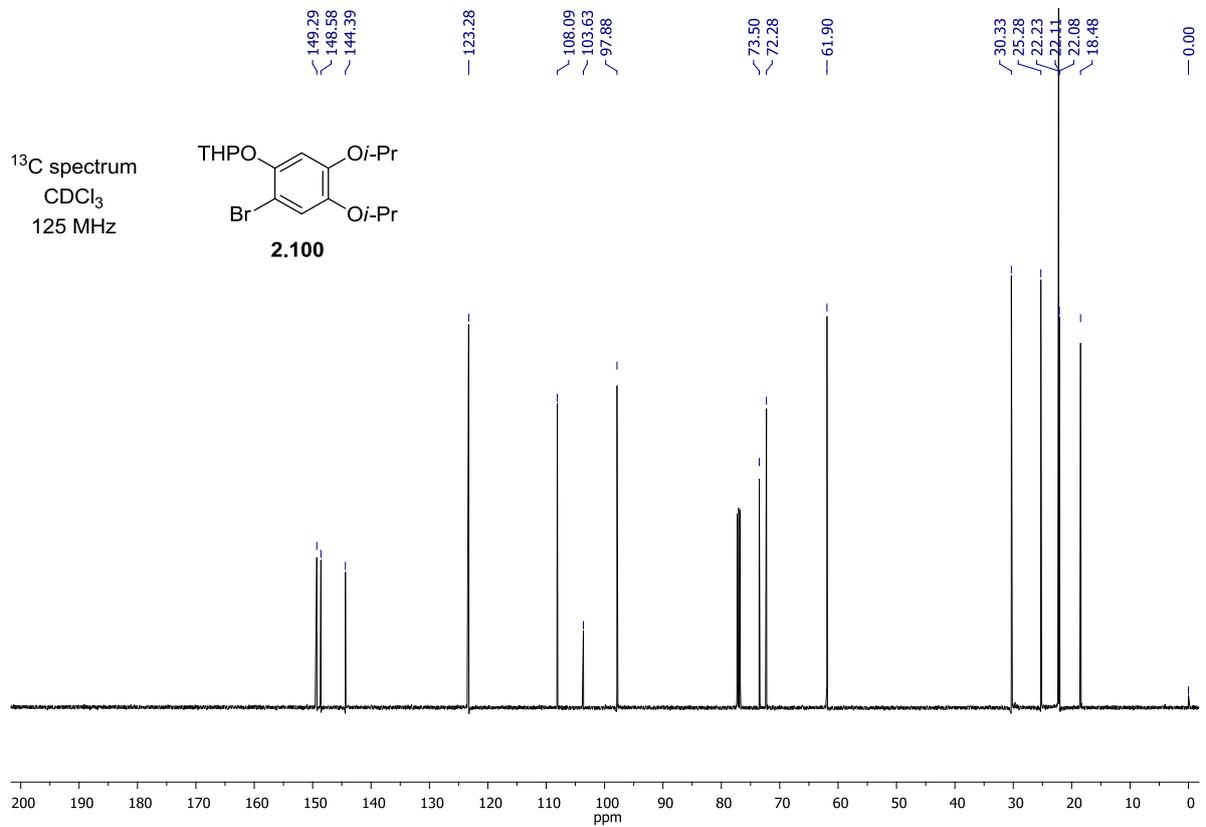
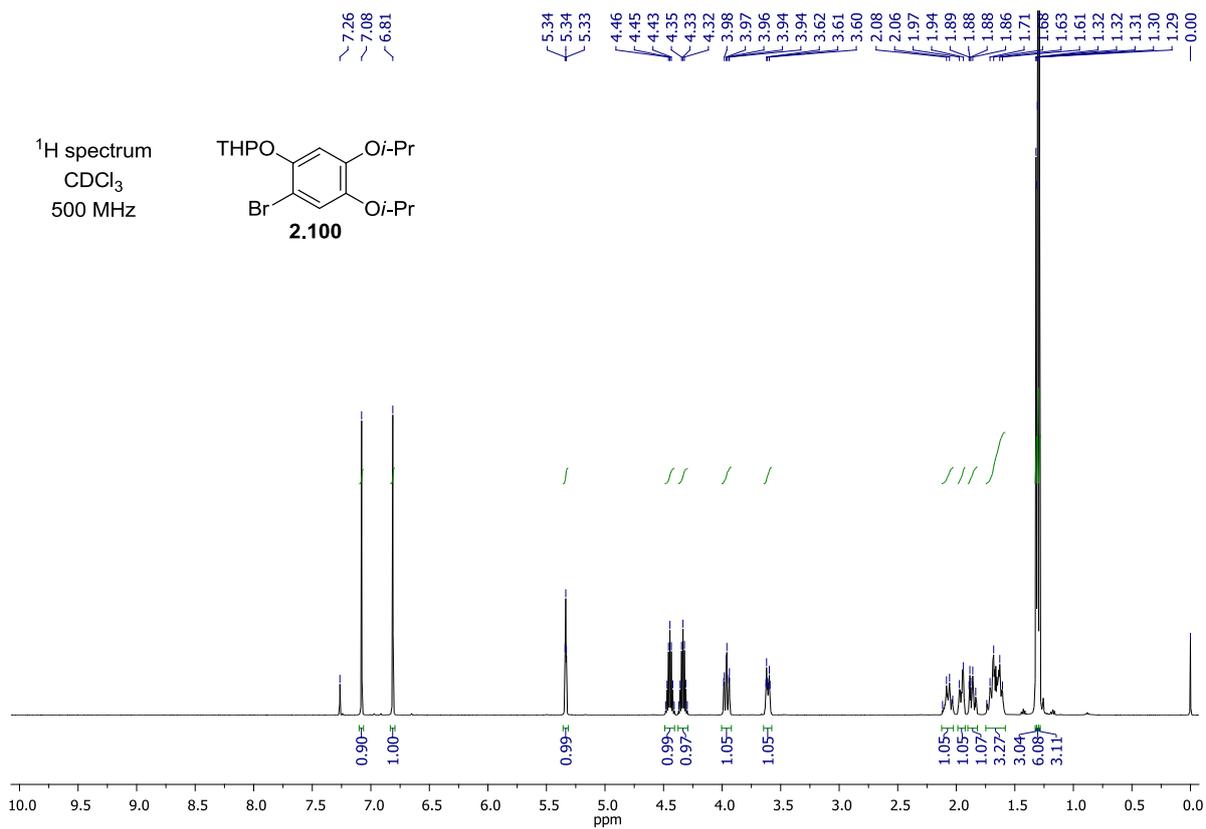
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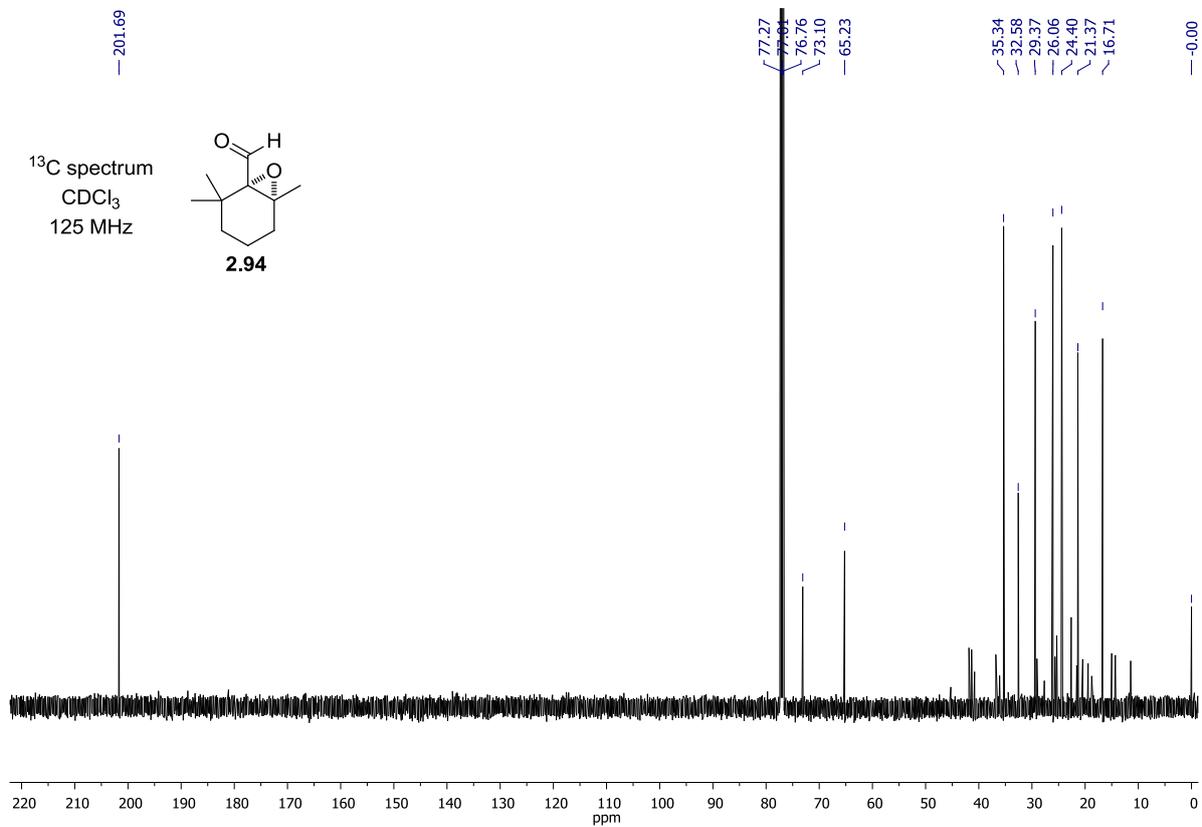
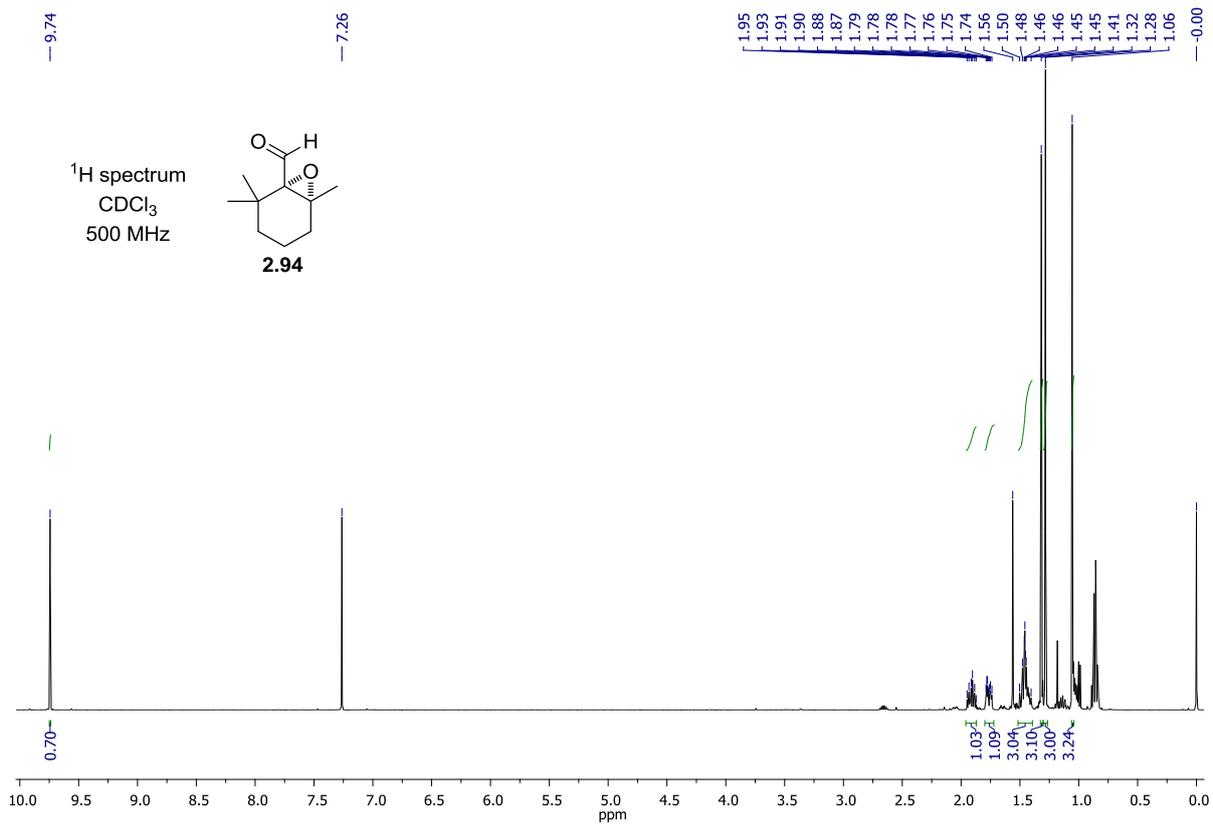
**Synthetic Studies on (+)-Liphagal**

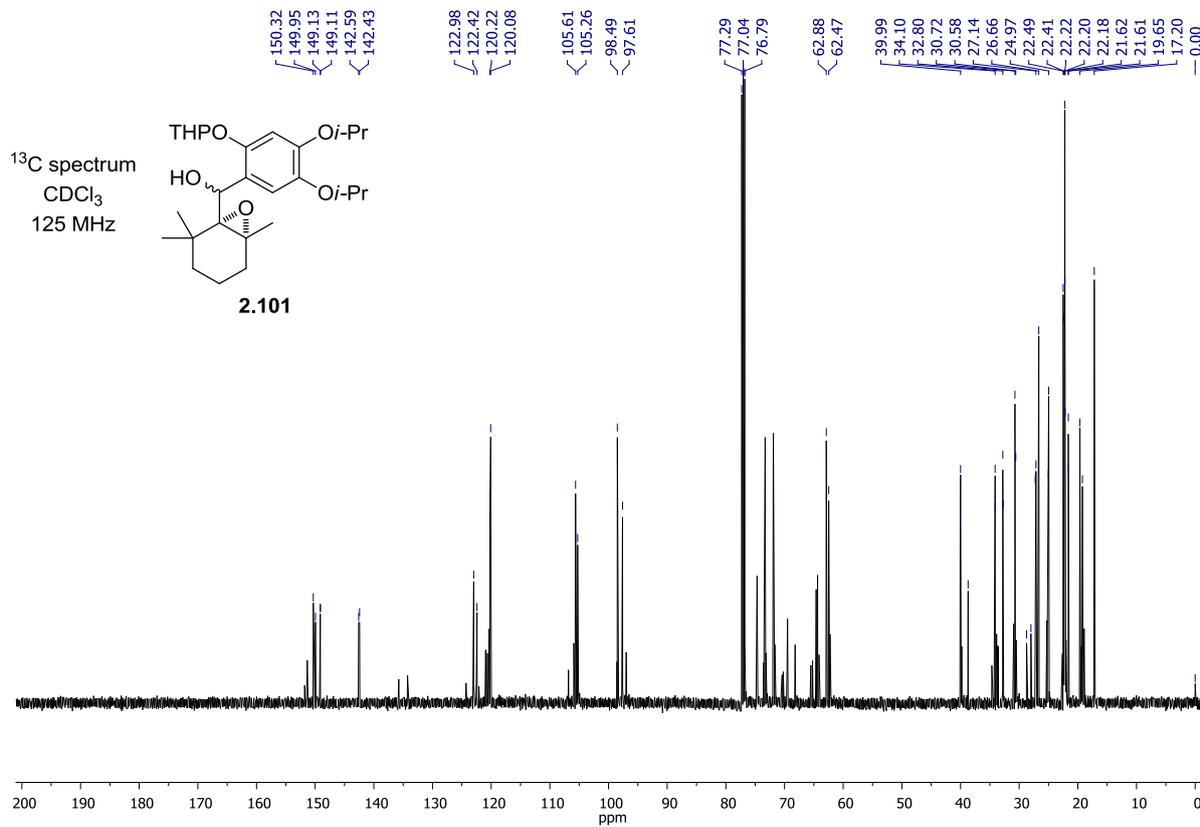
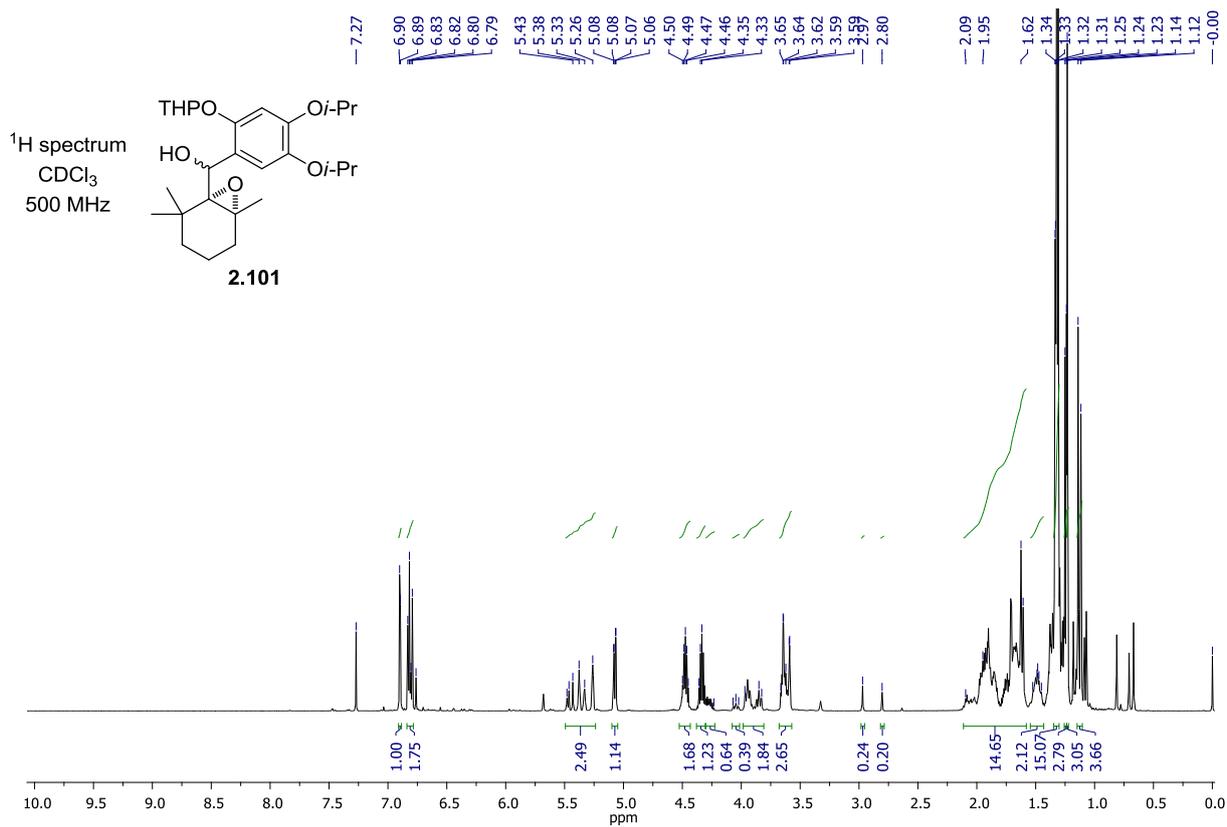




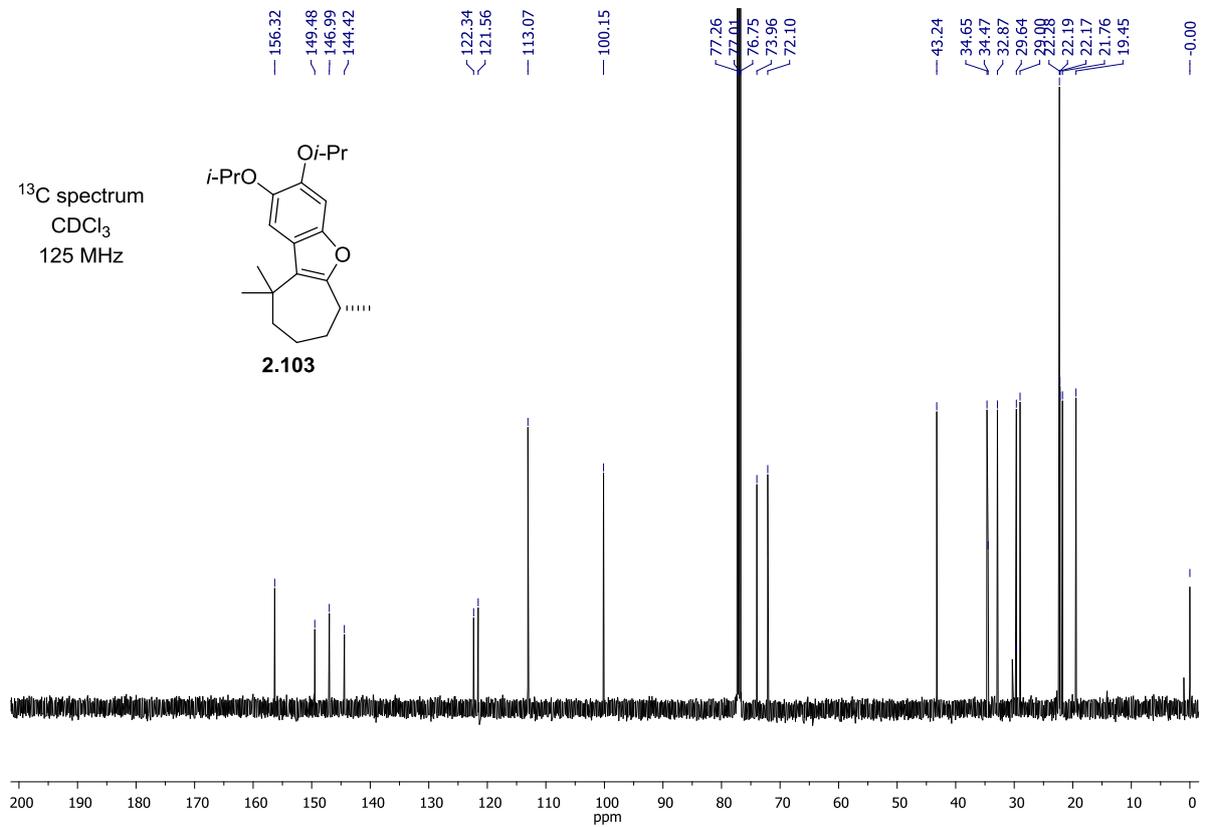
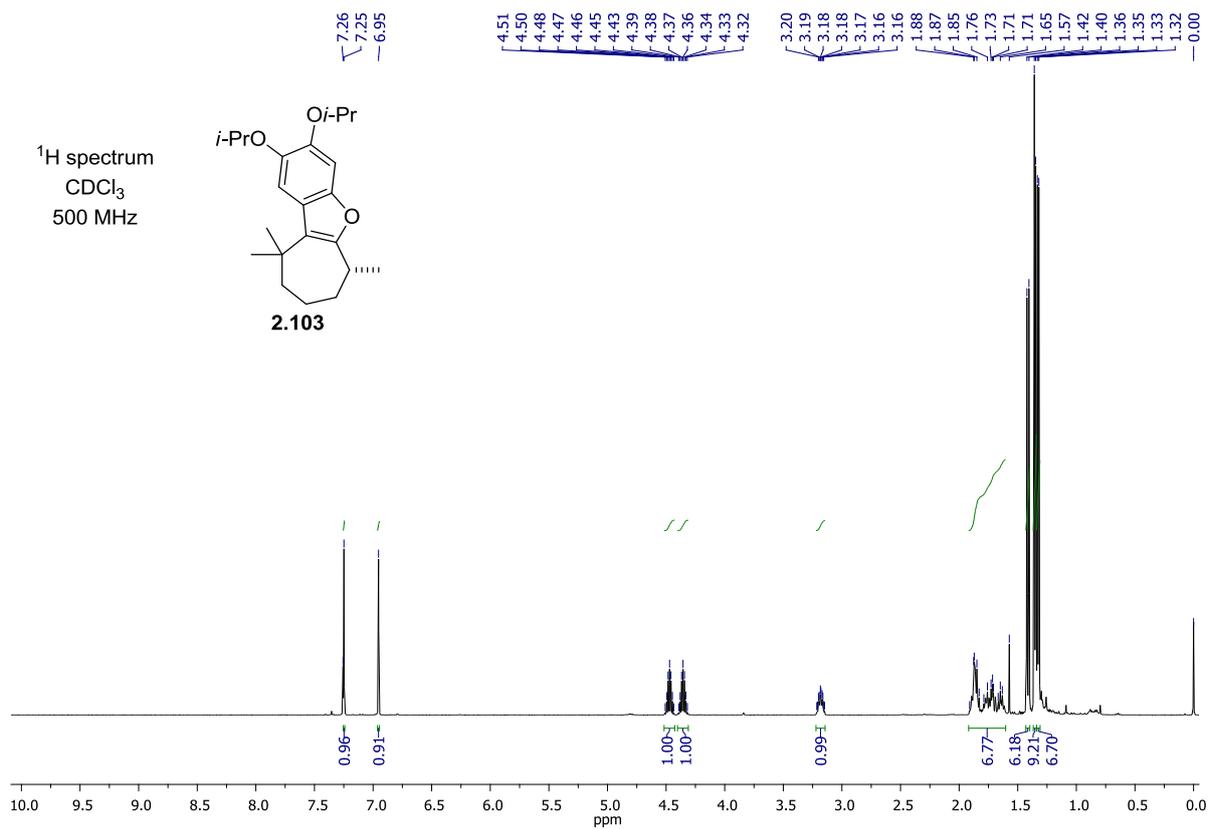


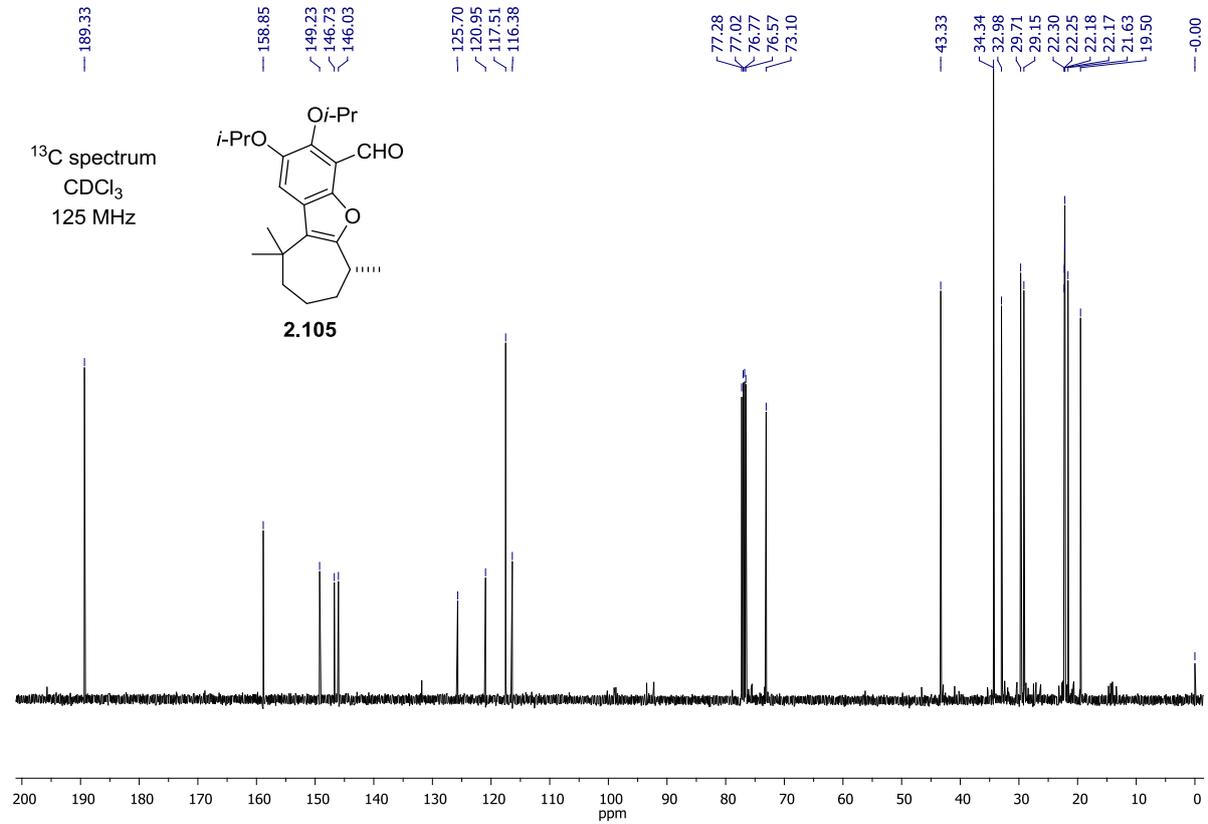
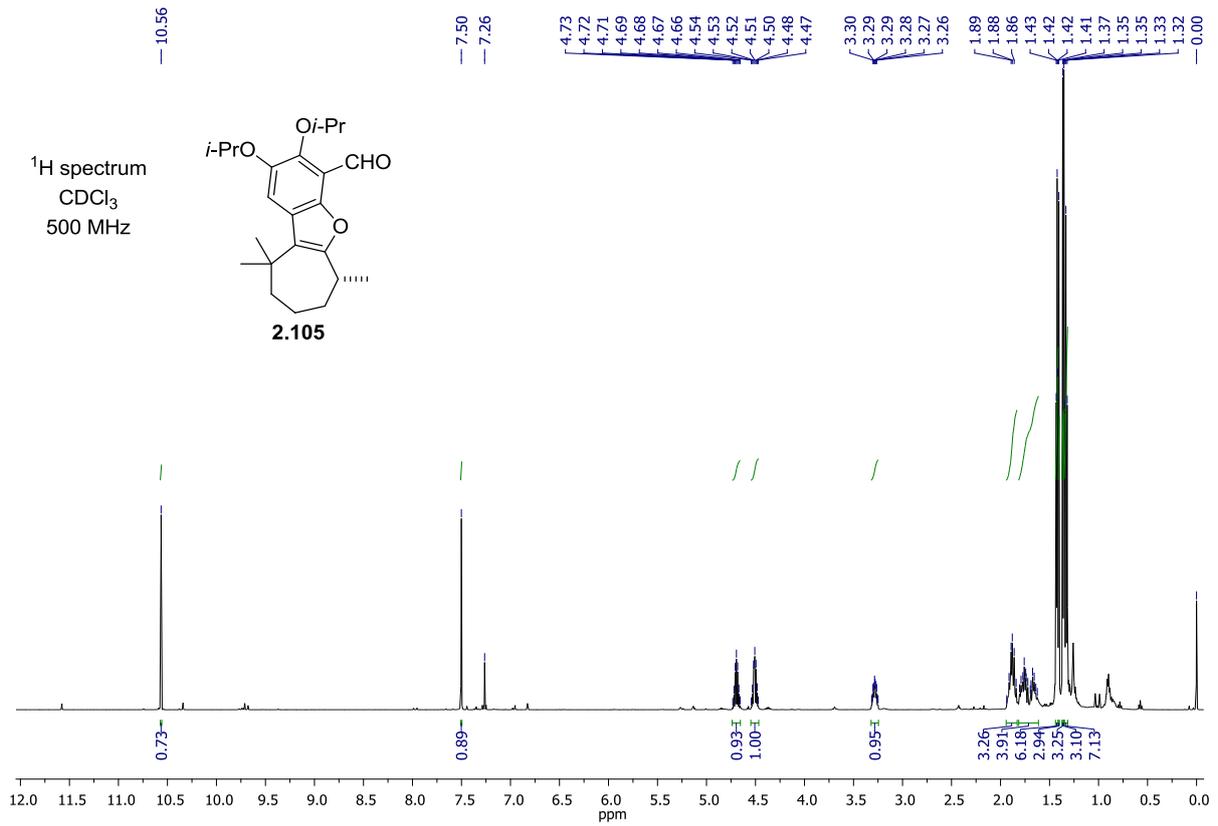


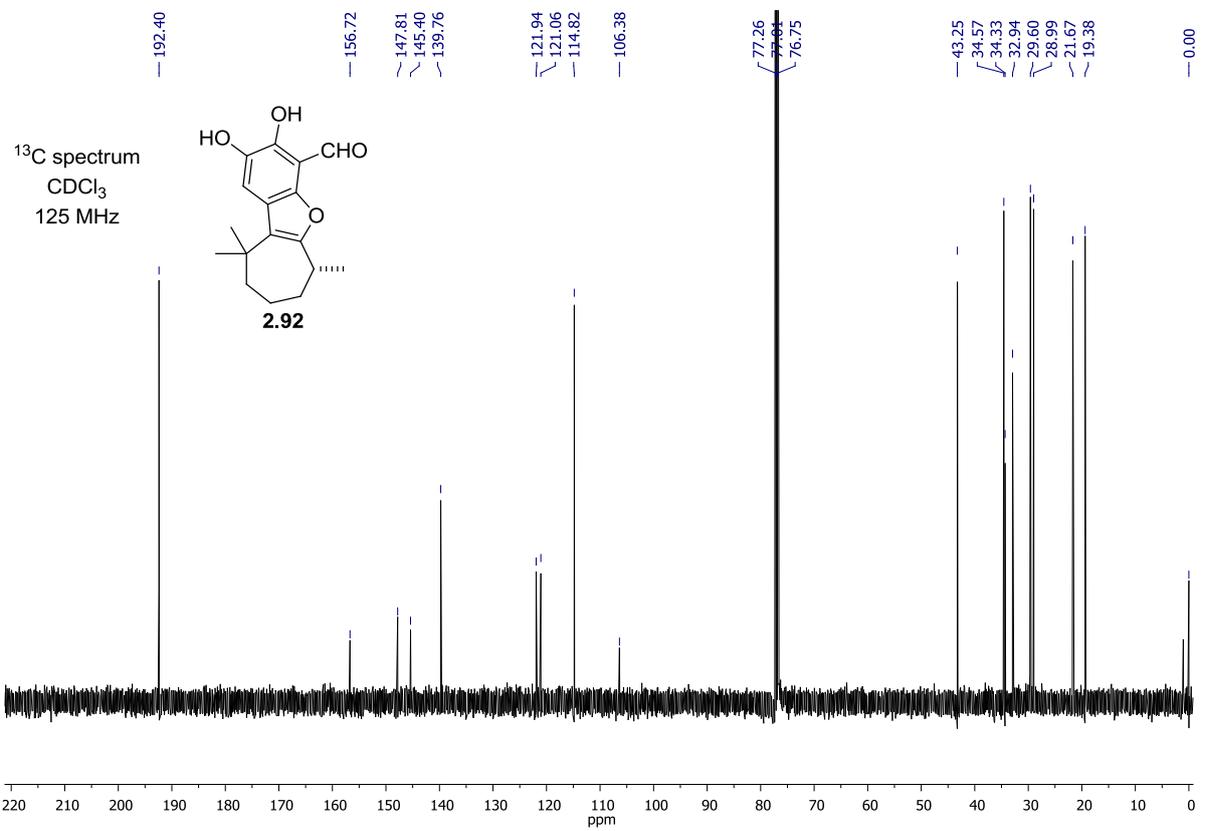
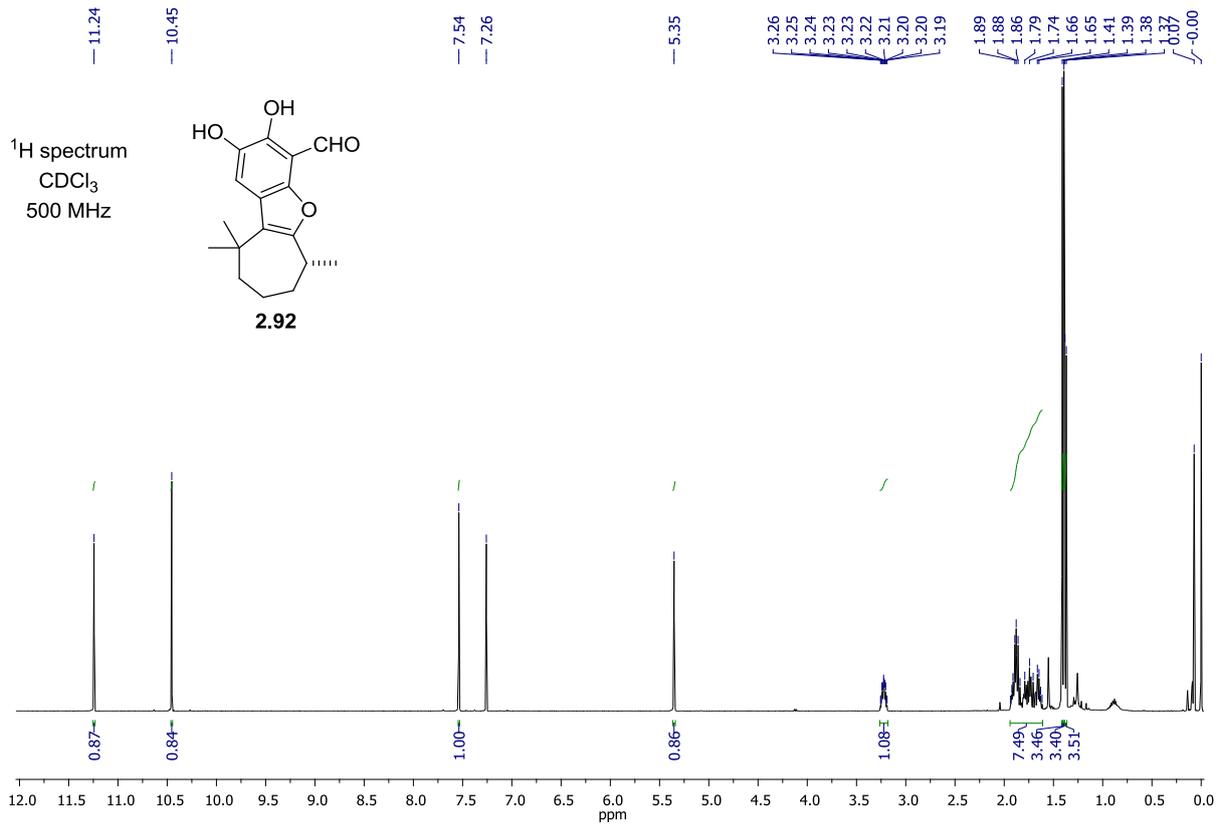




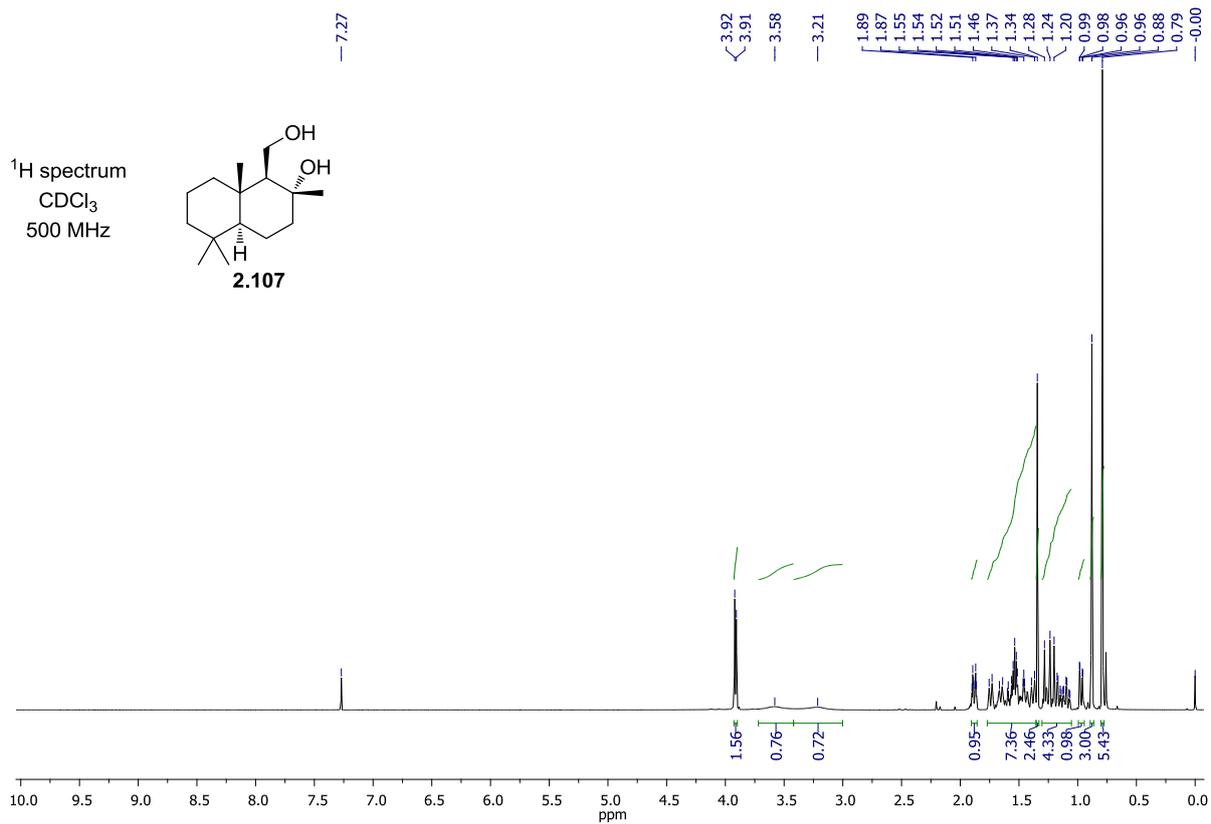
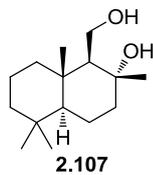
This compound readily decomposes during NMR acquisition.



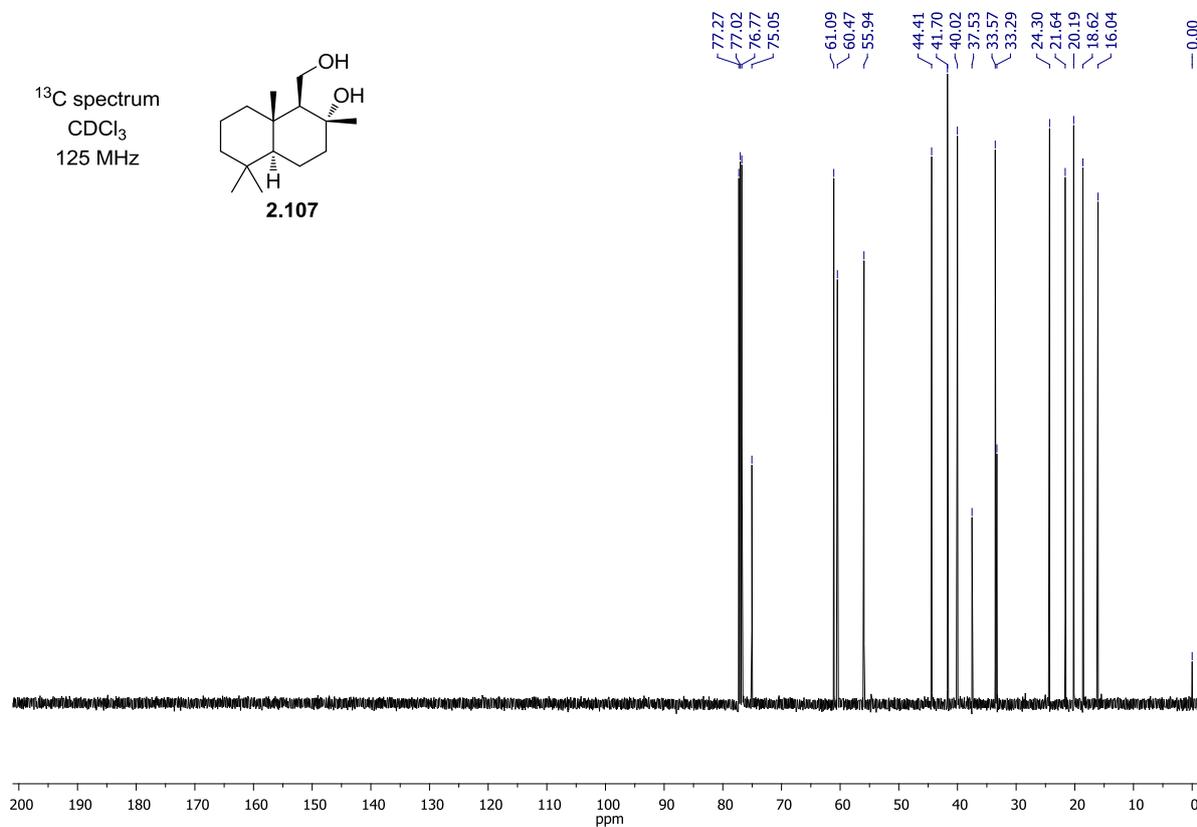
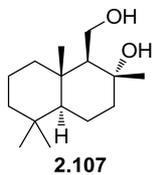


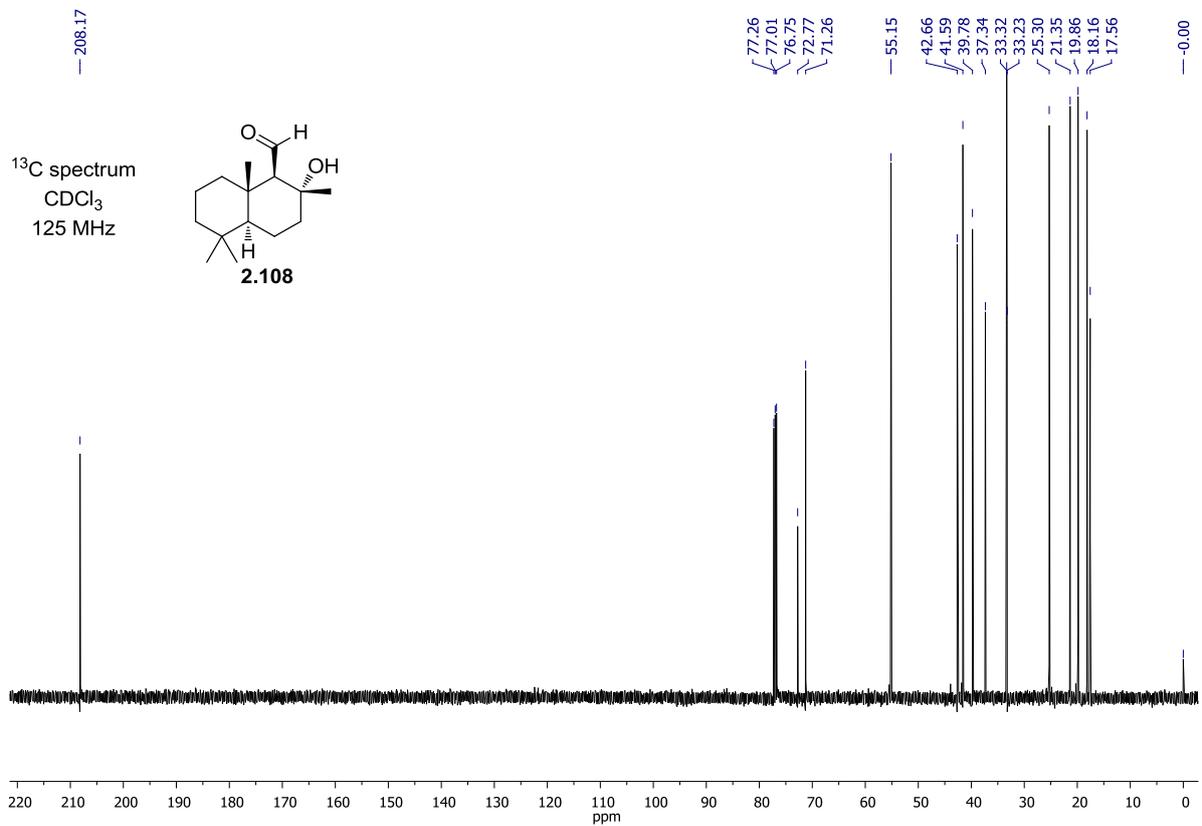
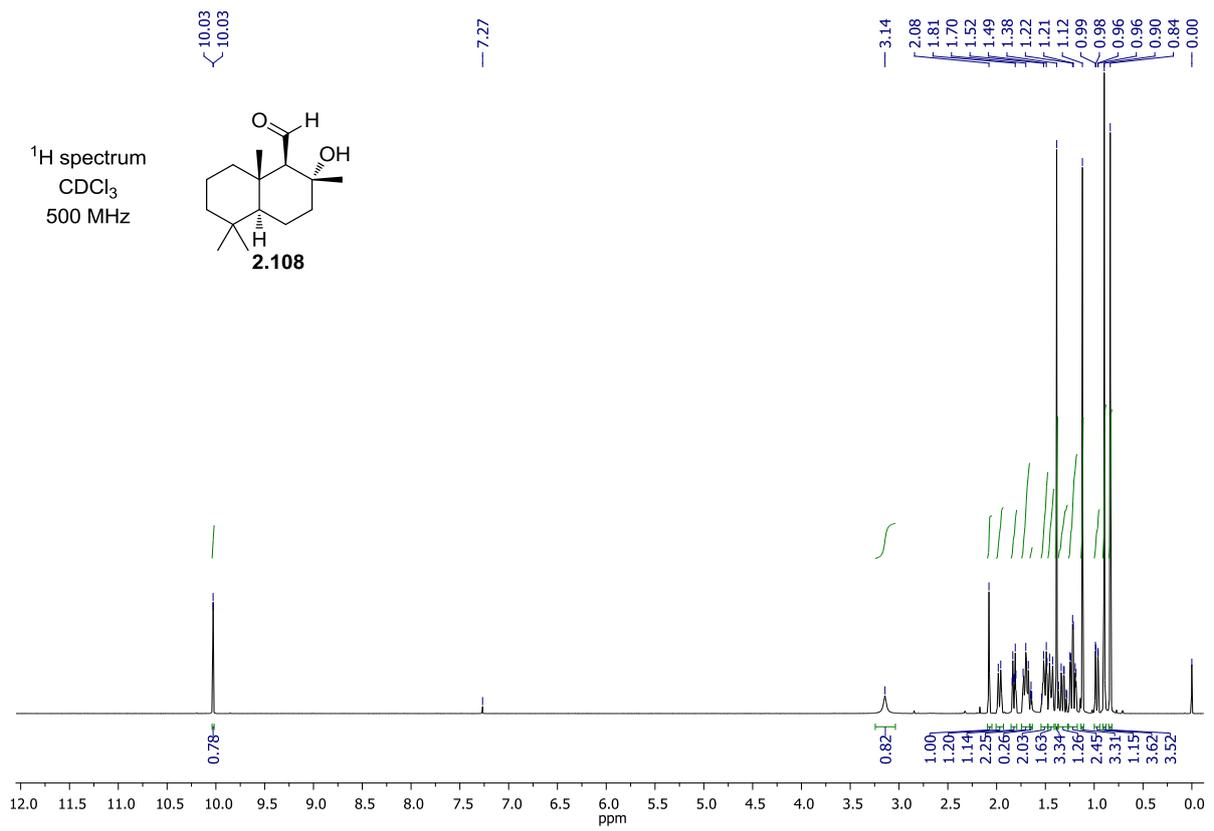


<sup>1</sup>H spectrum  
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500 MHz

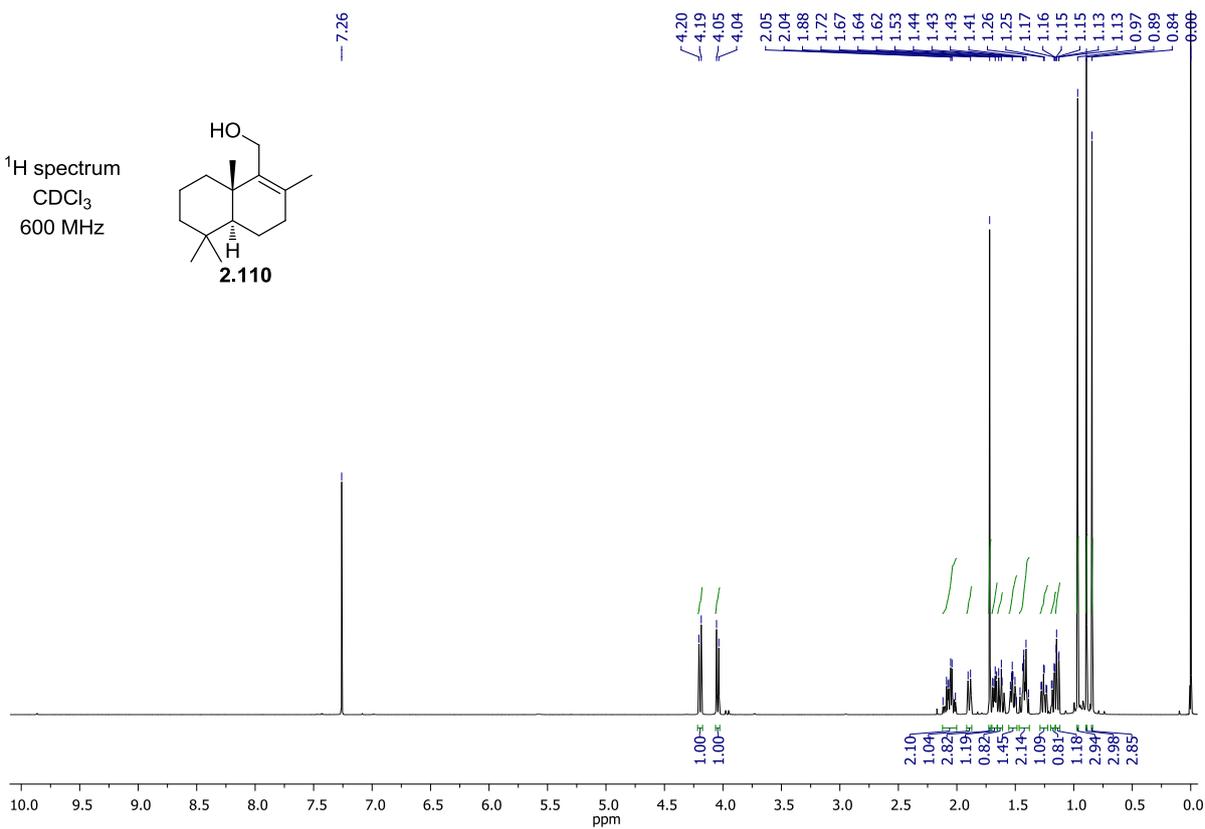
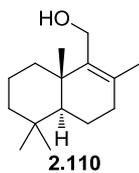


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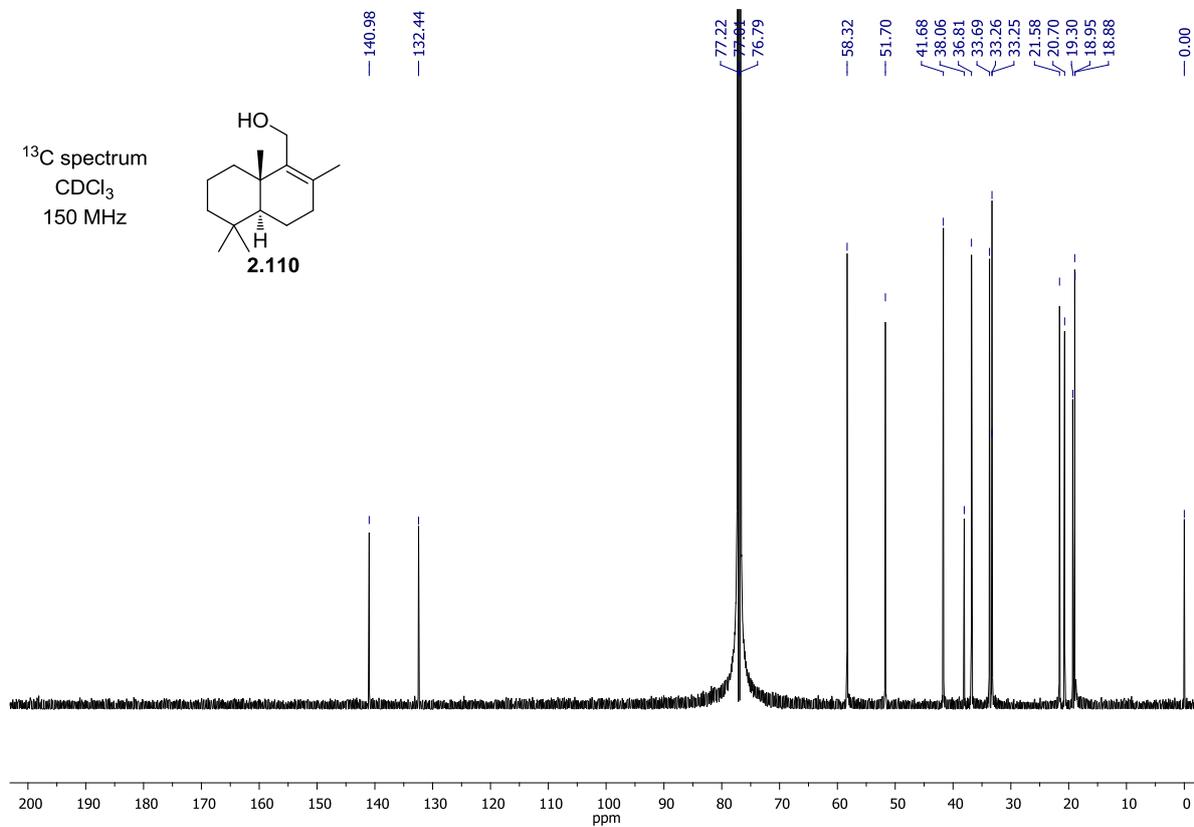
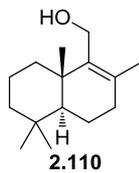




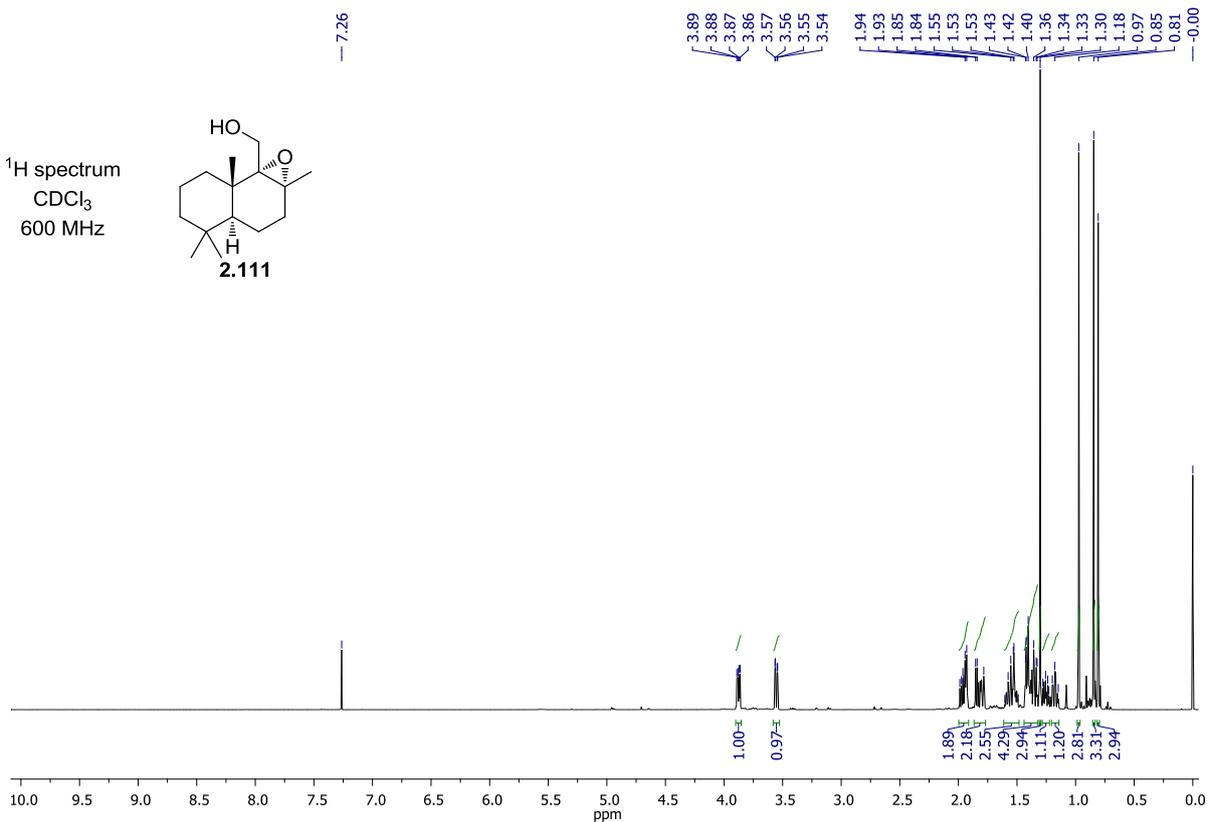
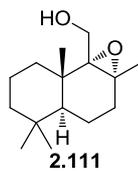
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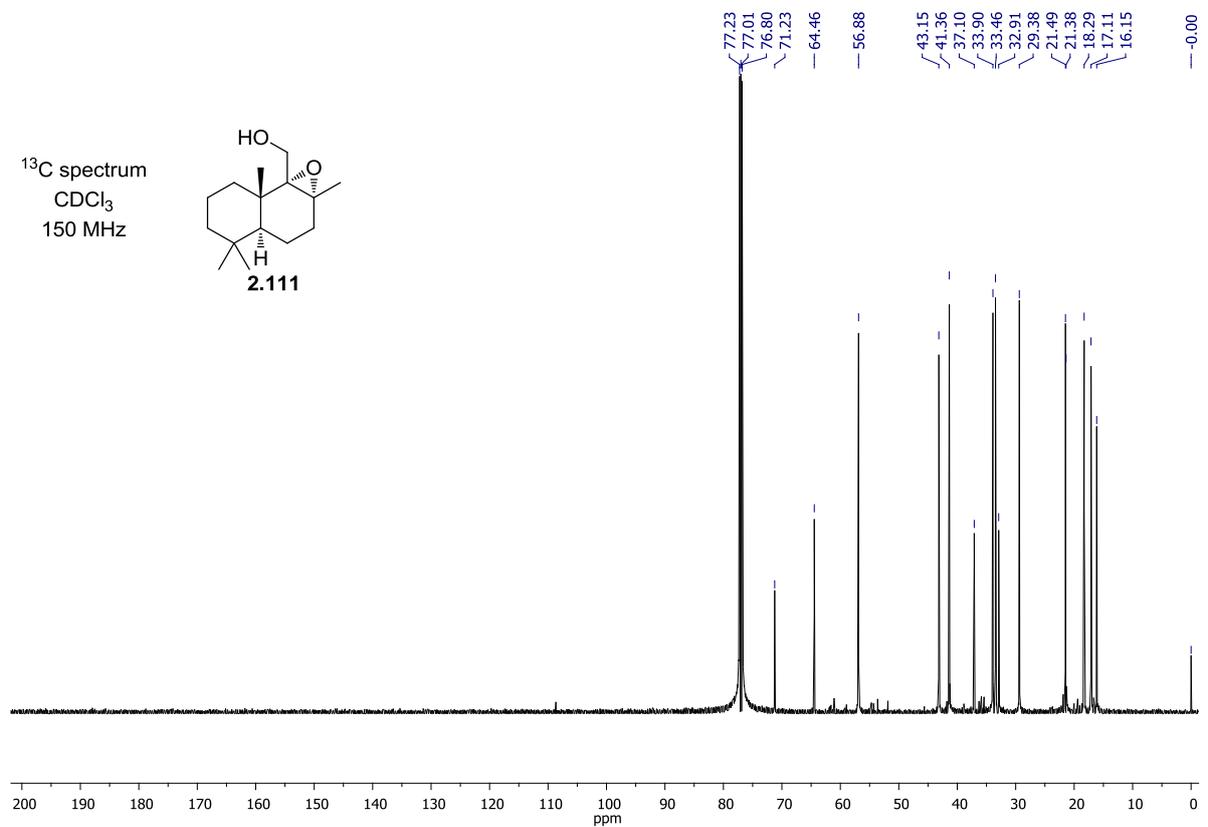
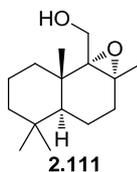
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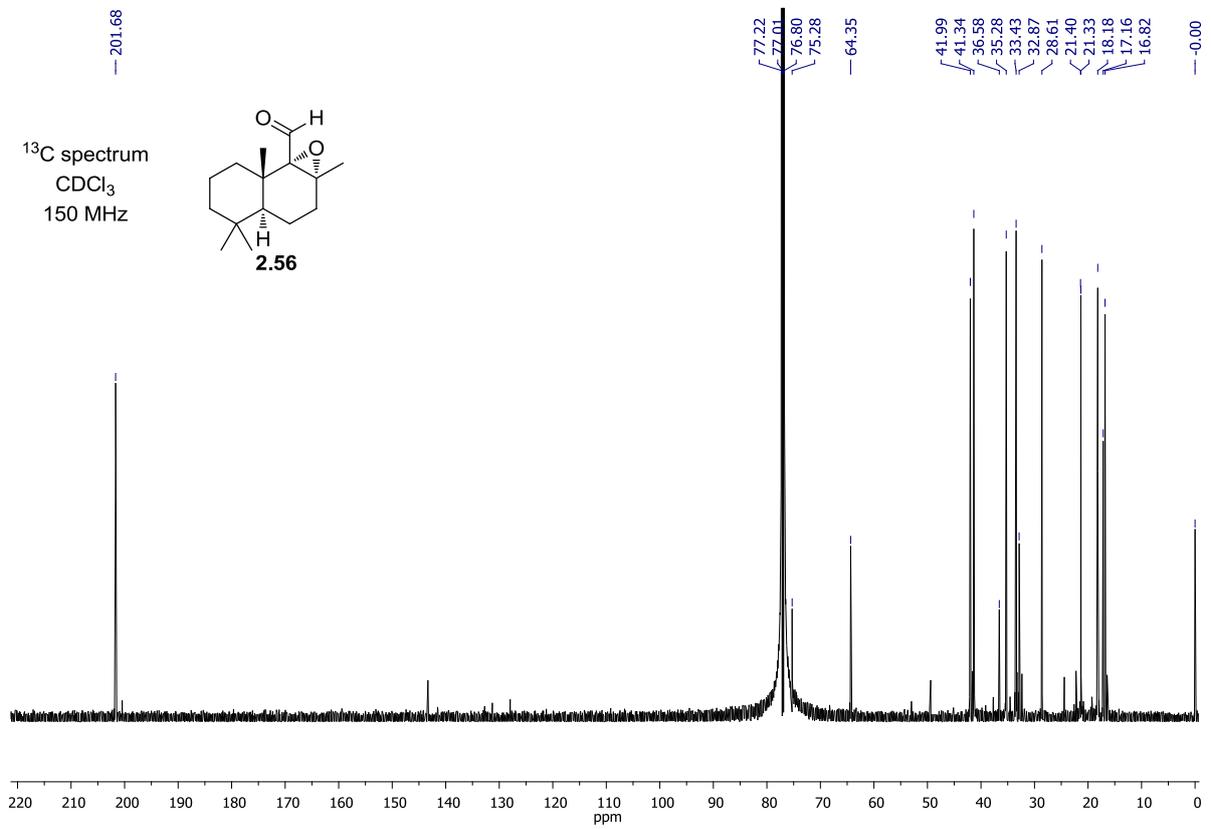
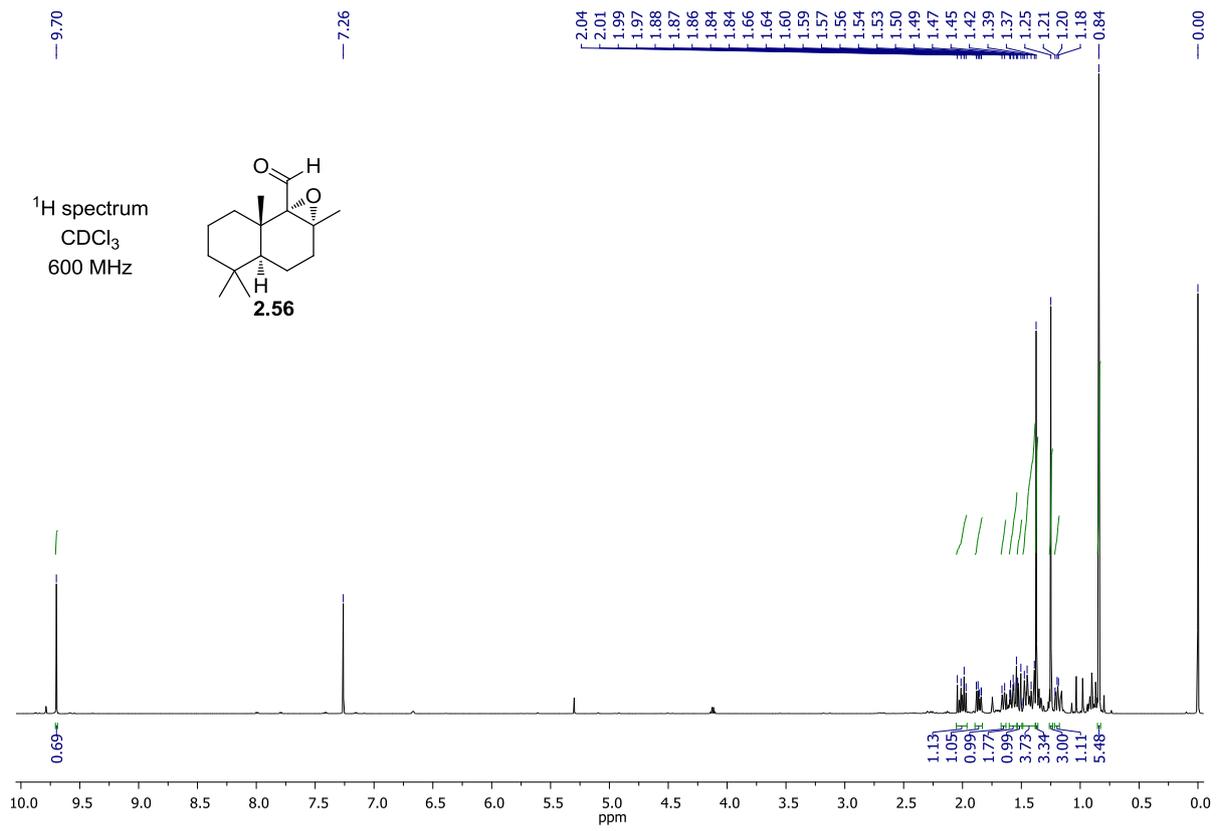


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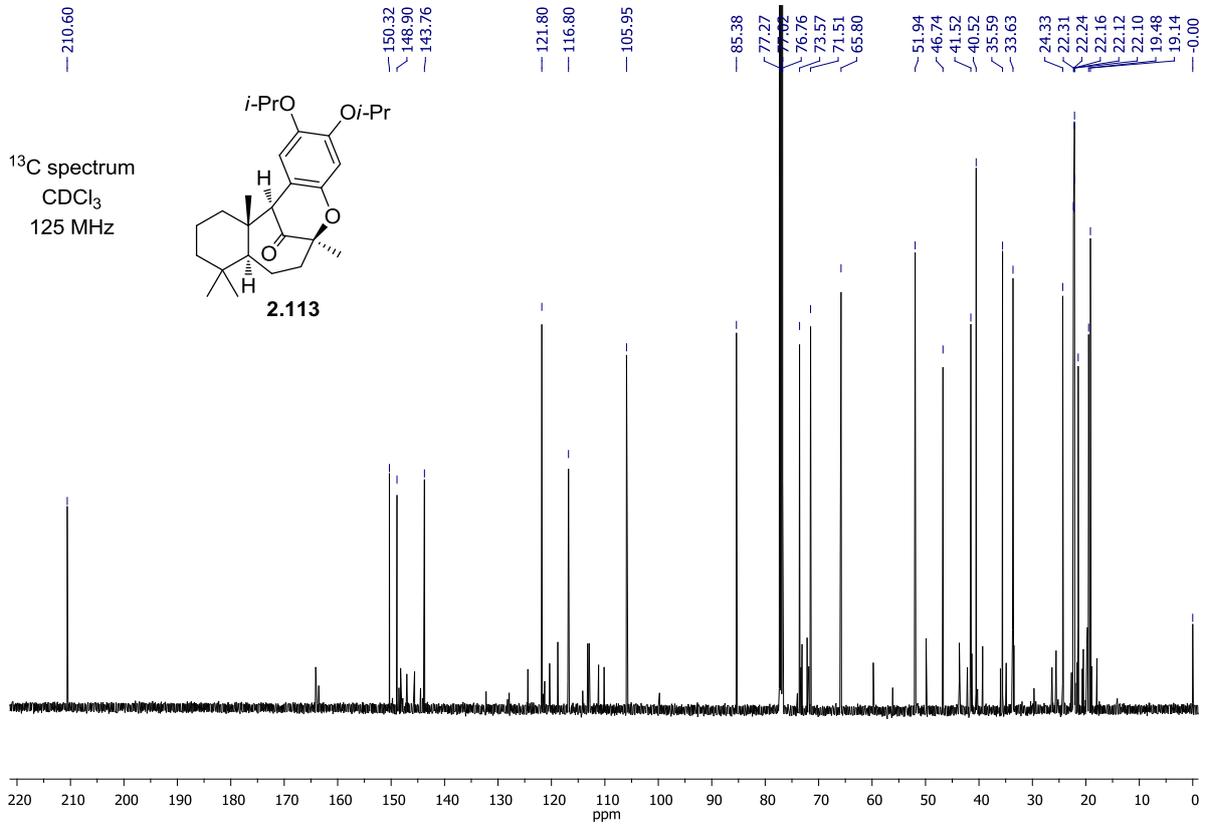
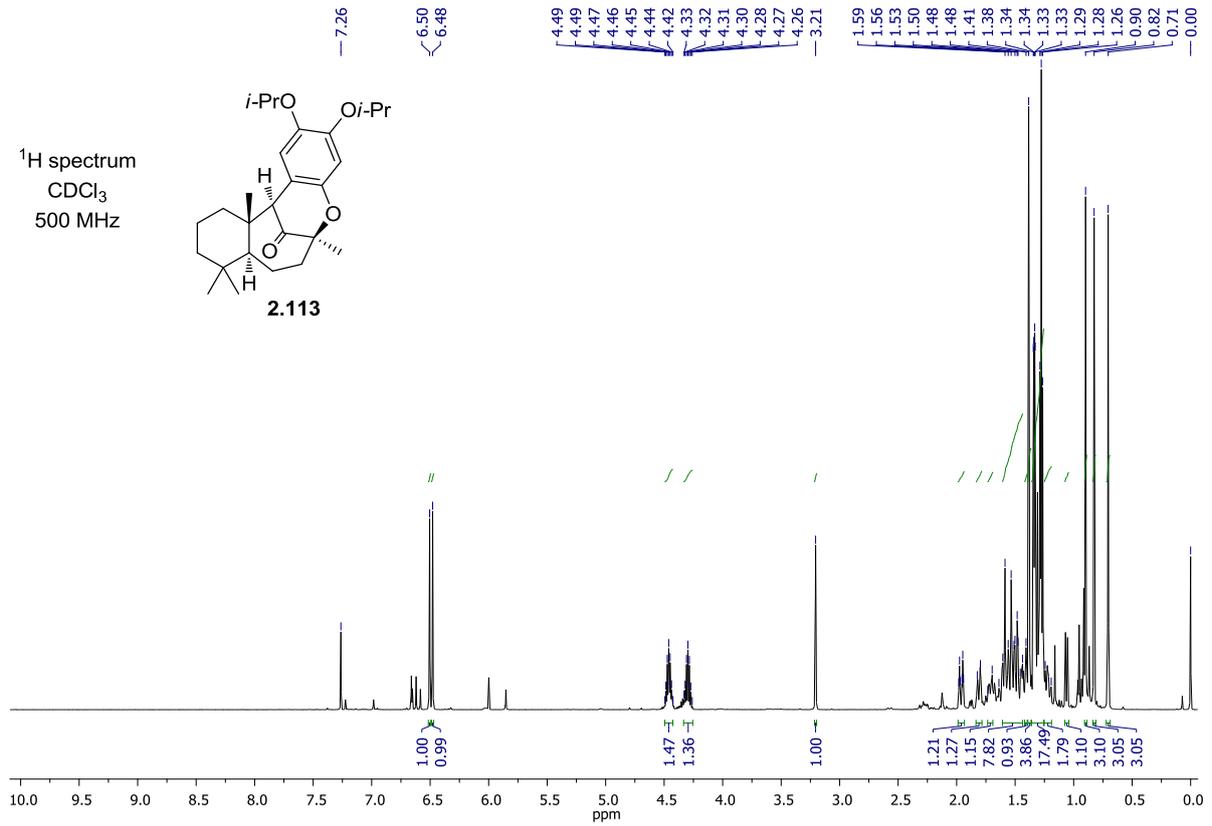
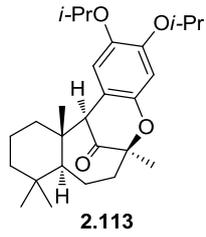


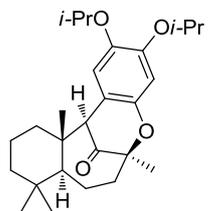
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150 MHz



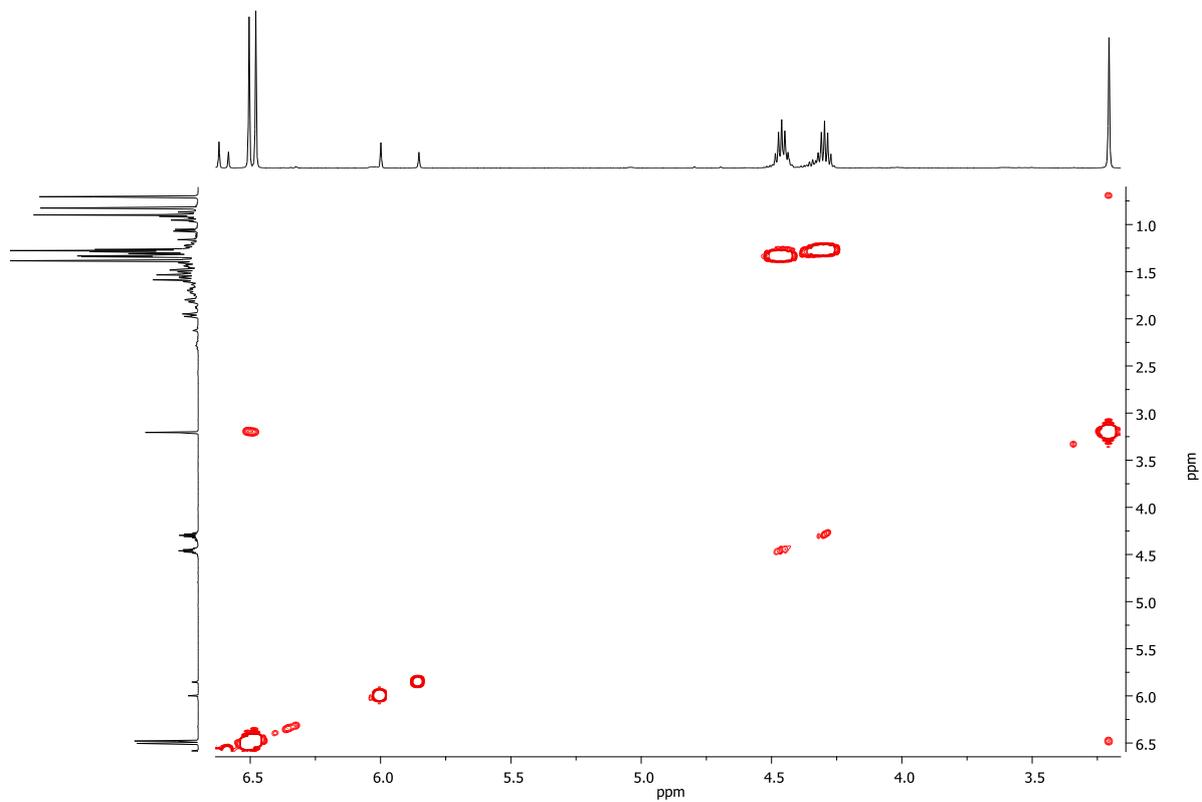
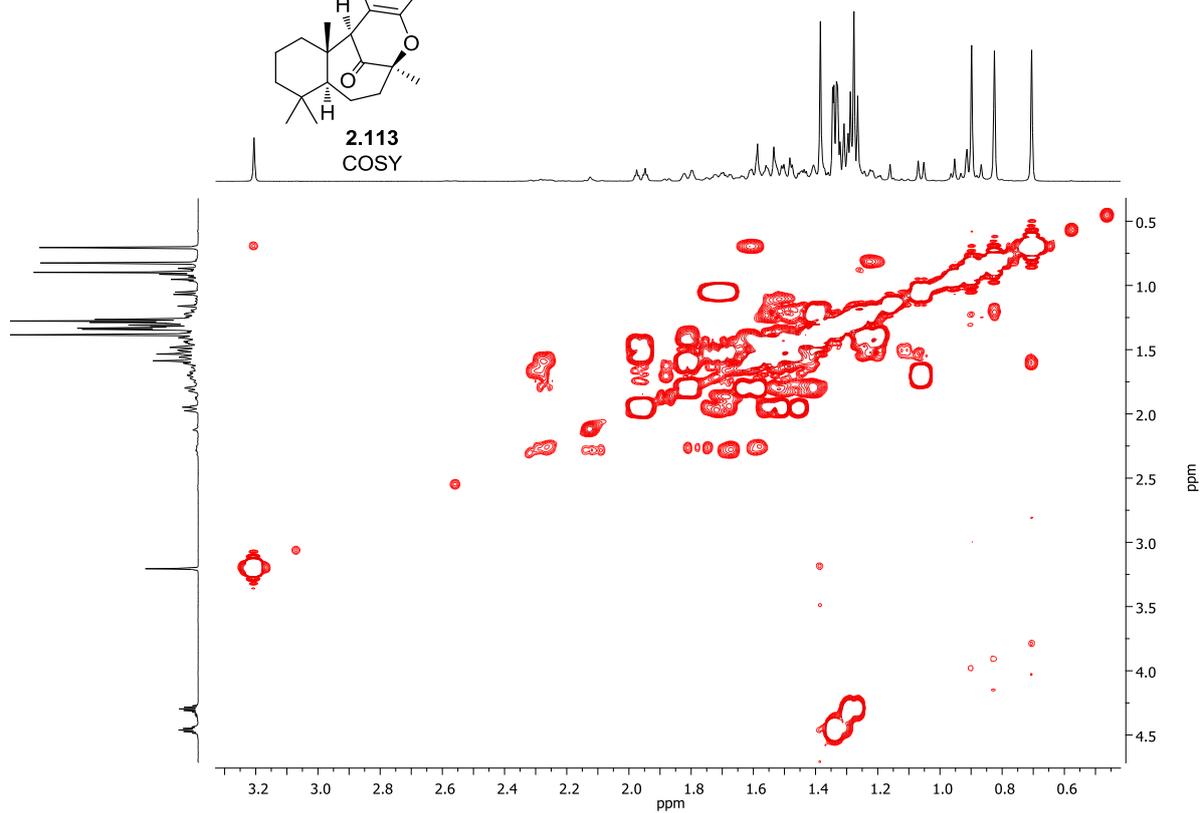


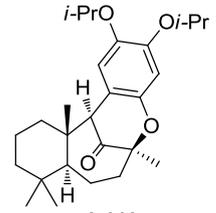
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500 MHz



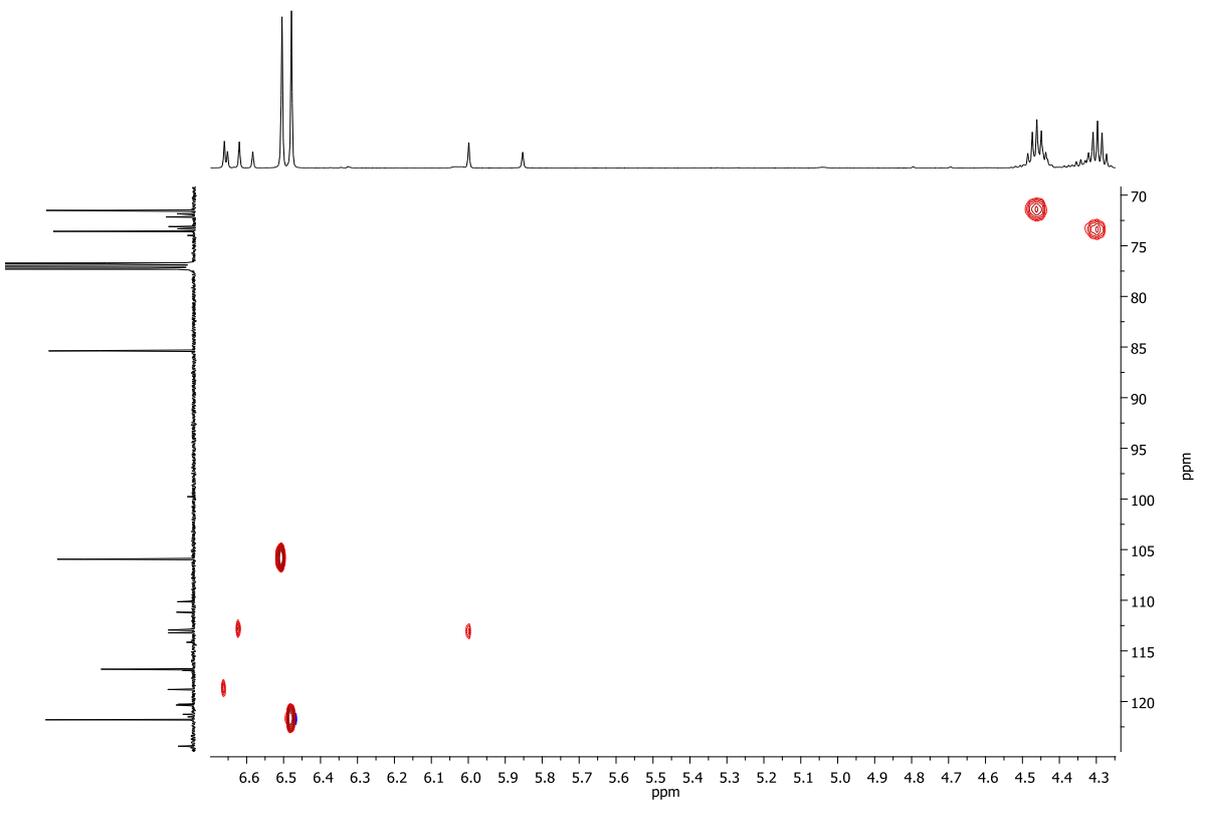
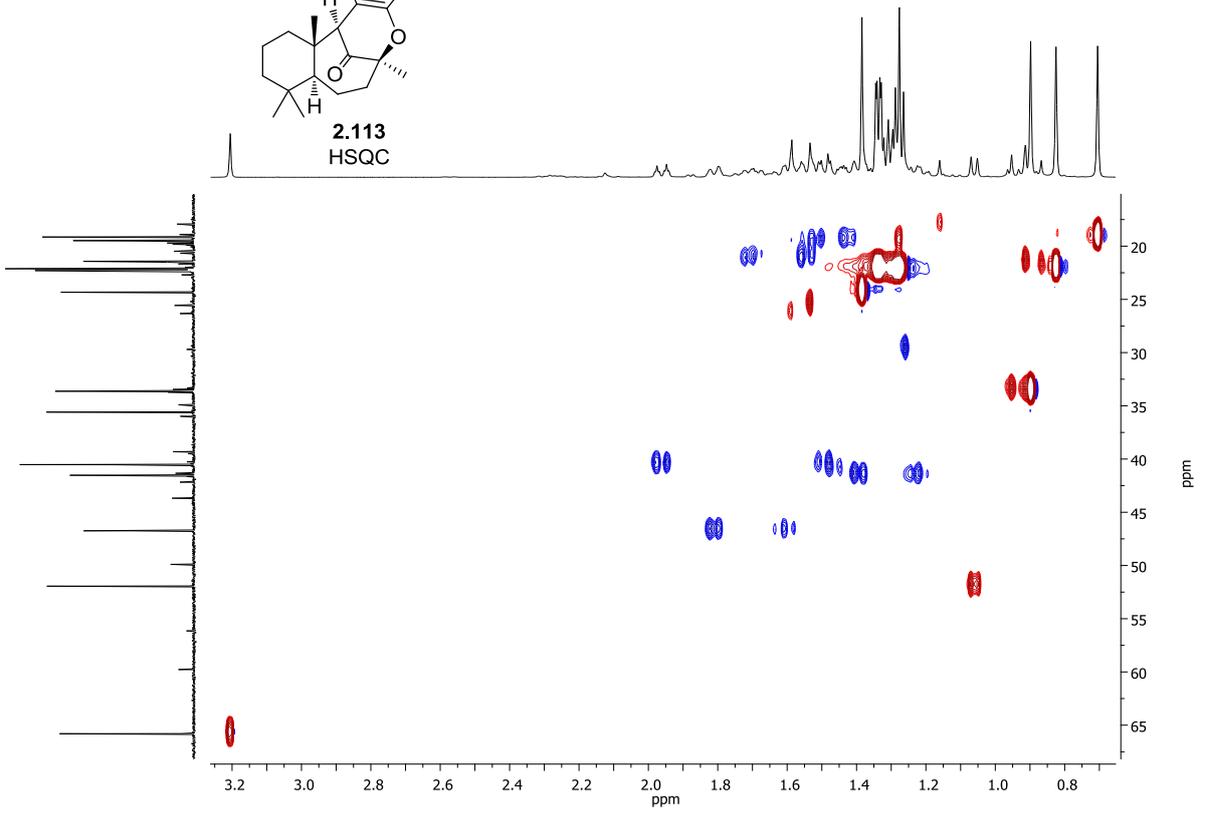


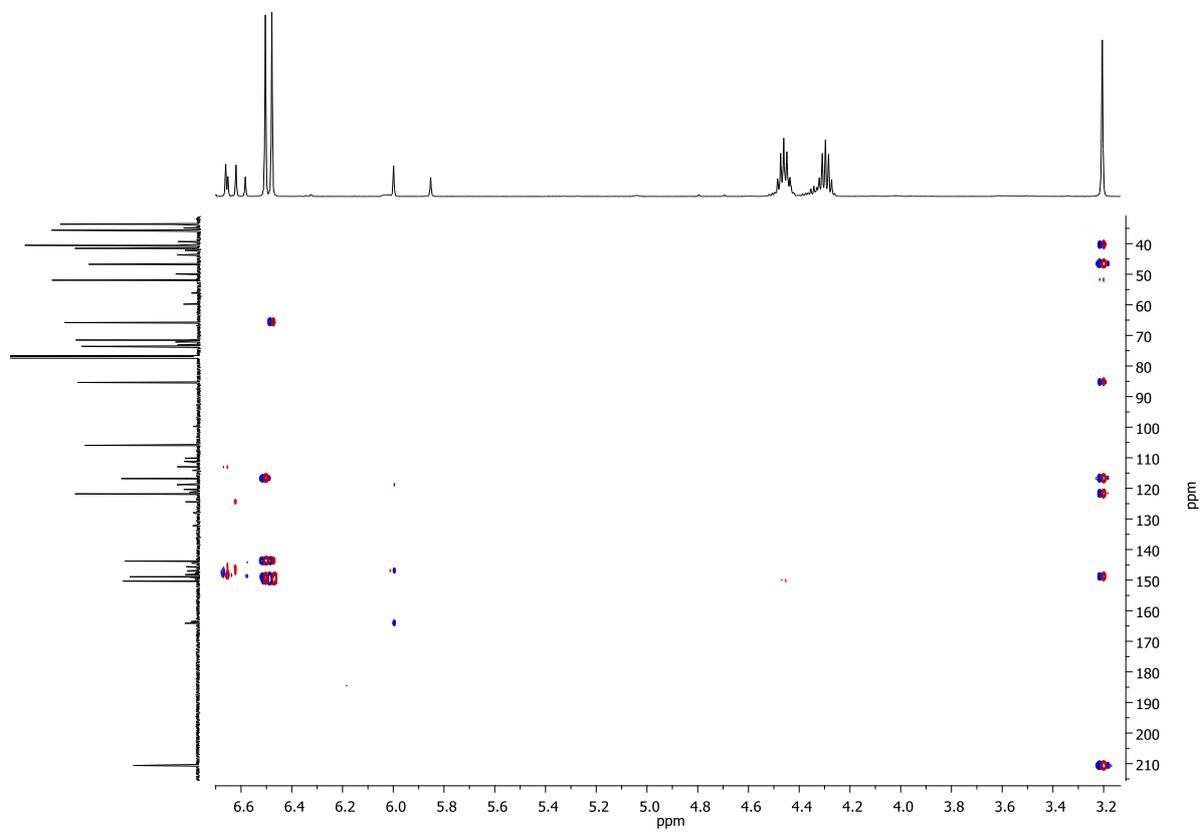
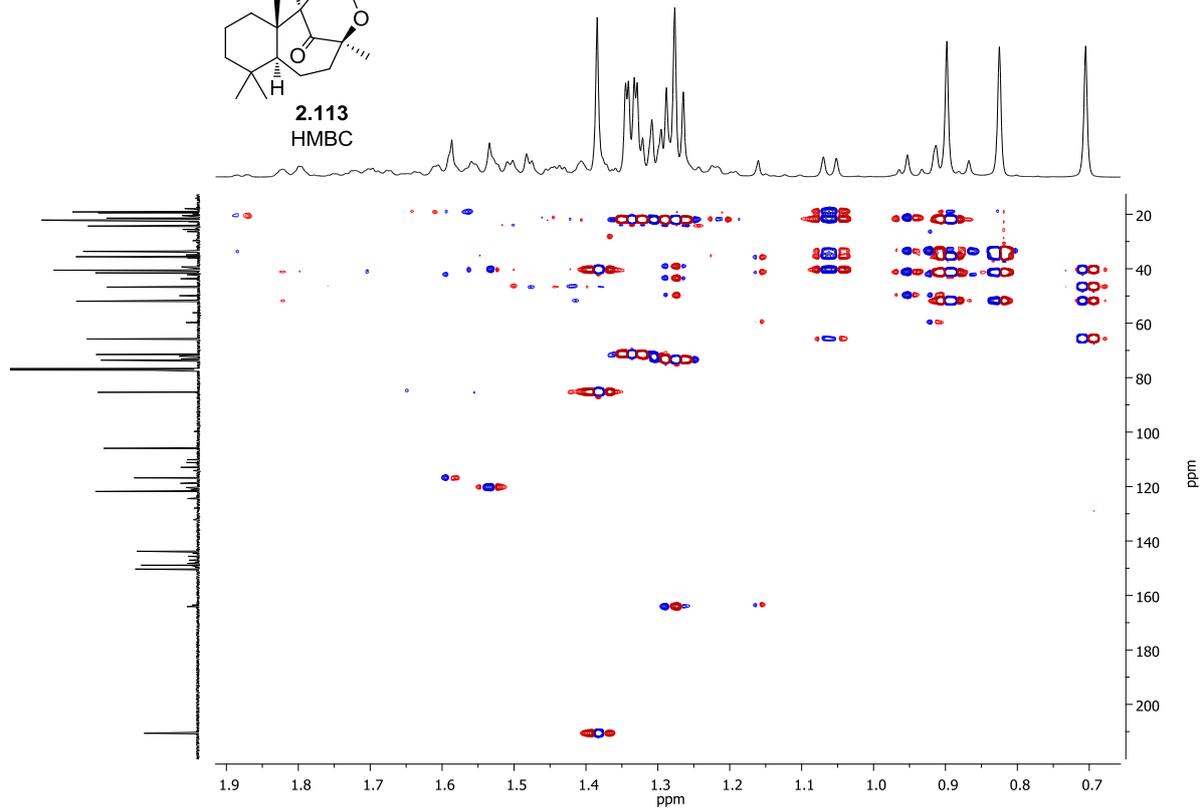
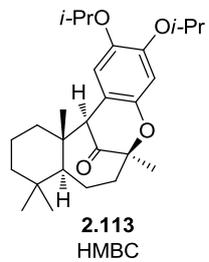
2.113  
COSY

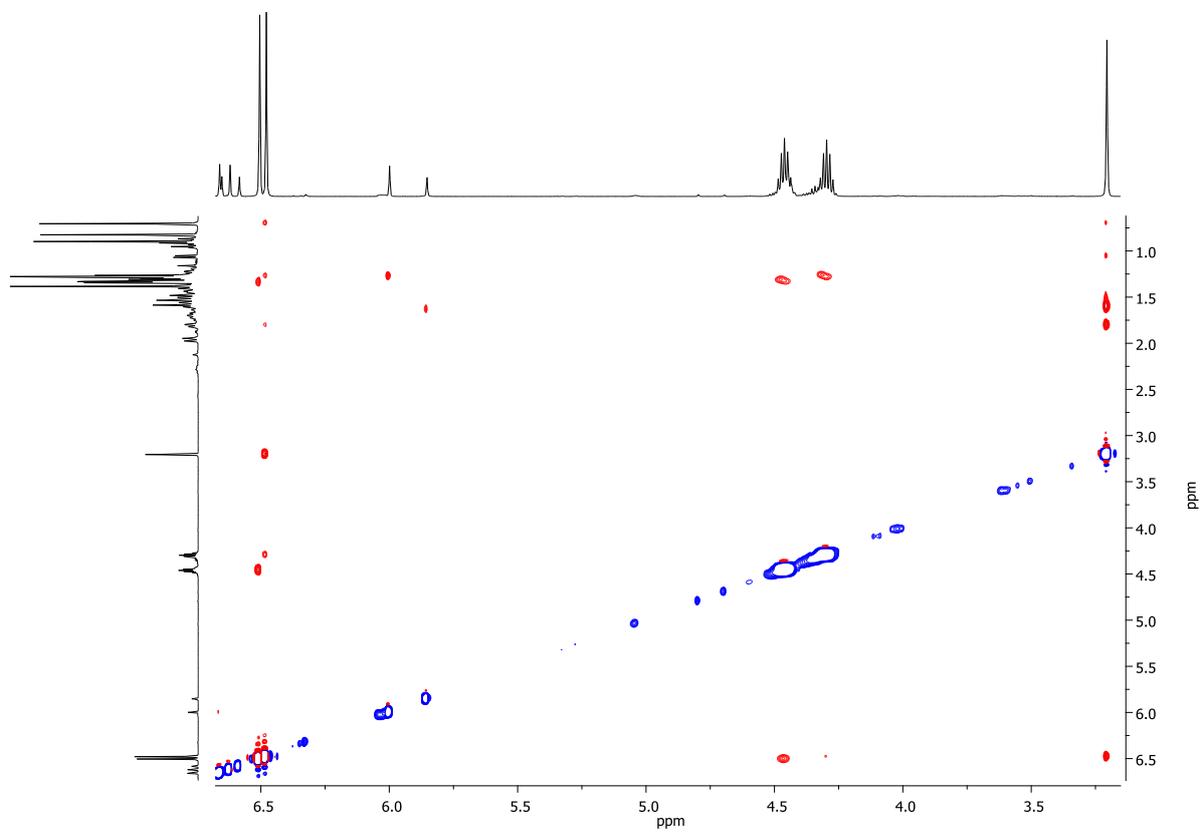
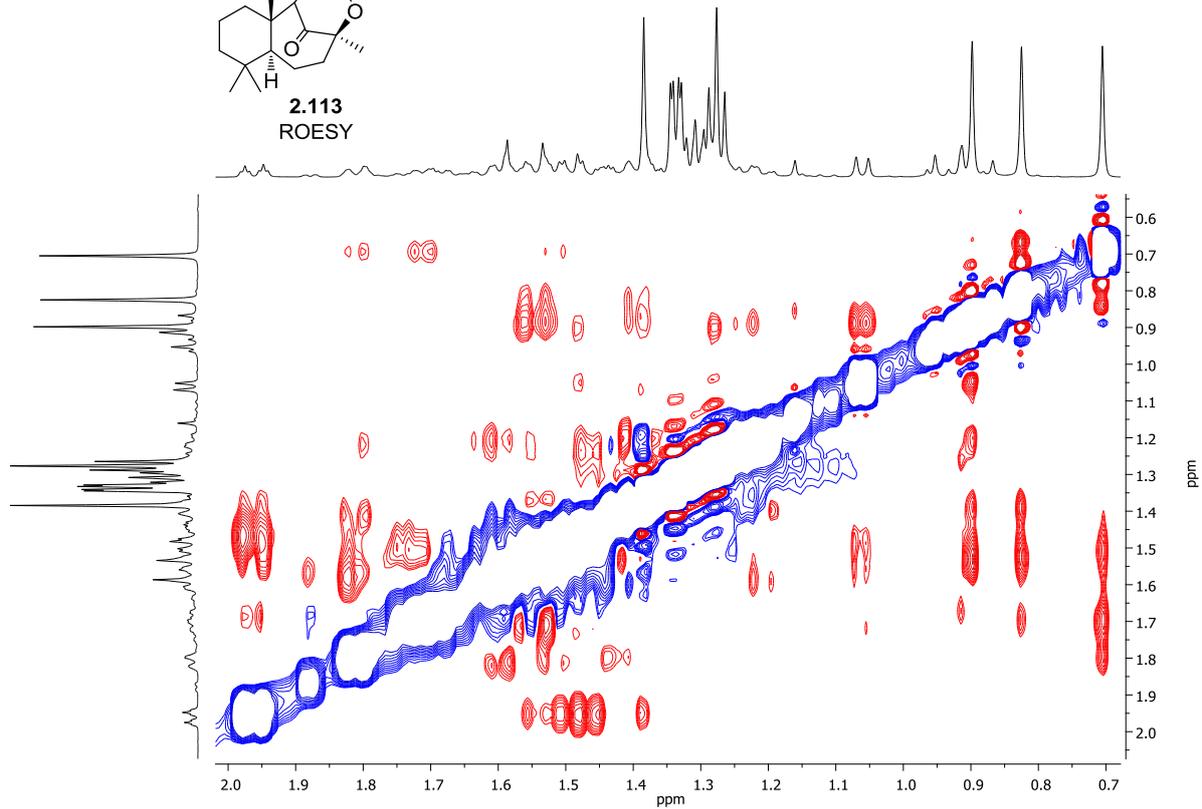
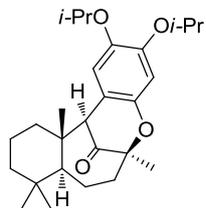


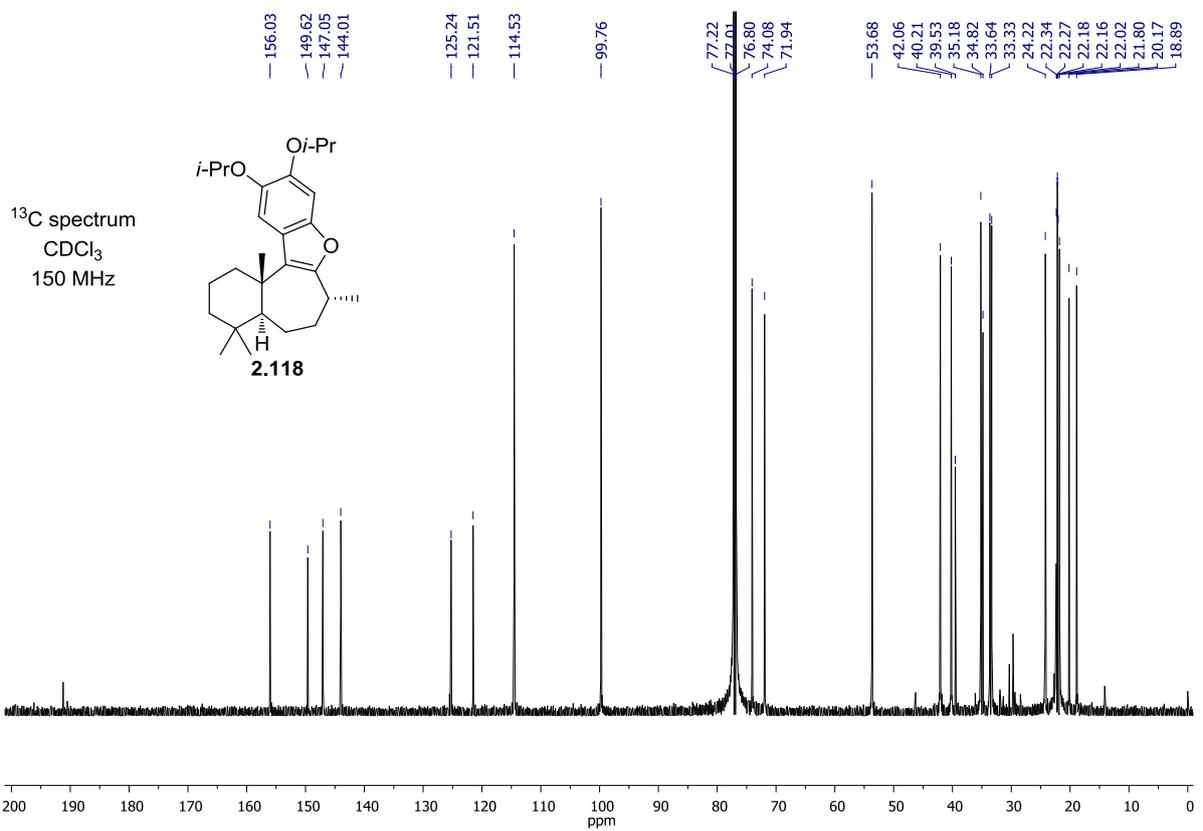
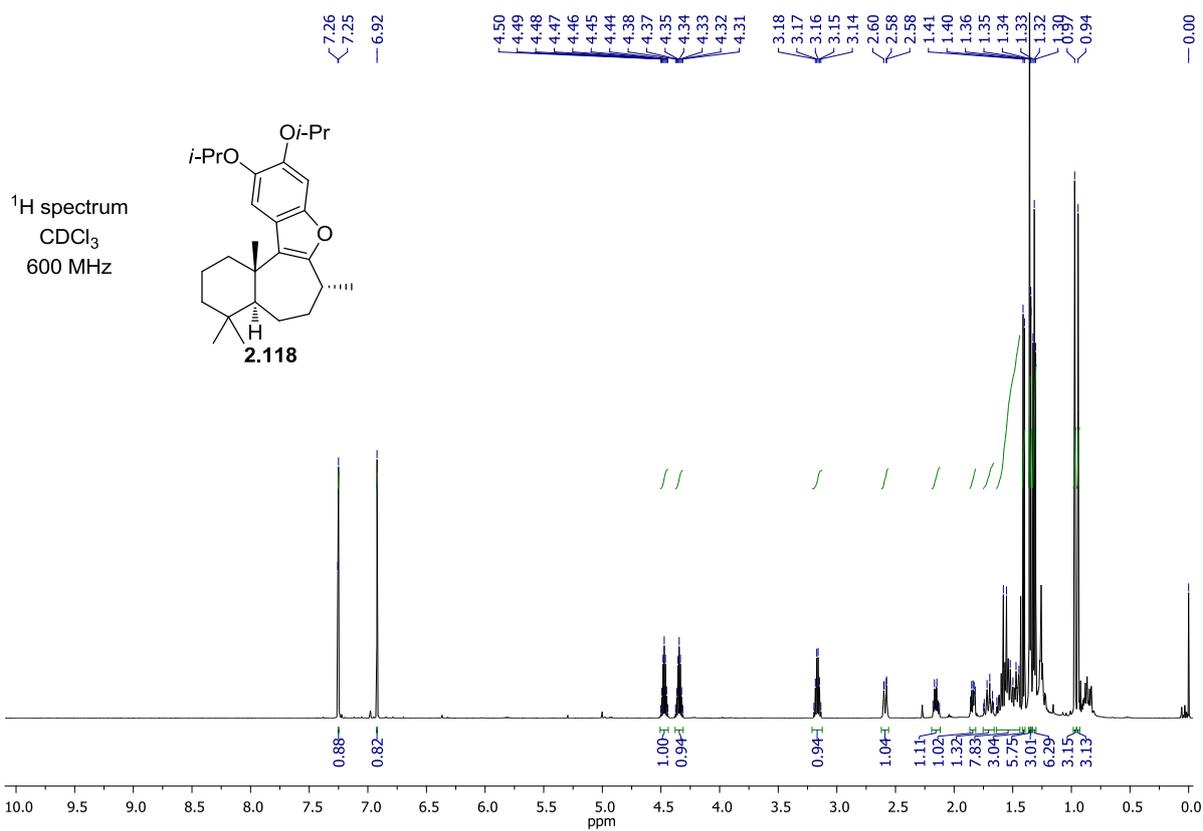


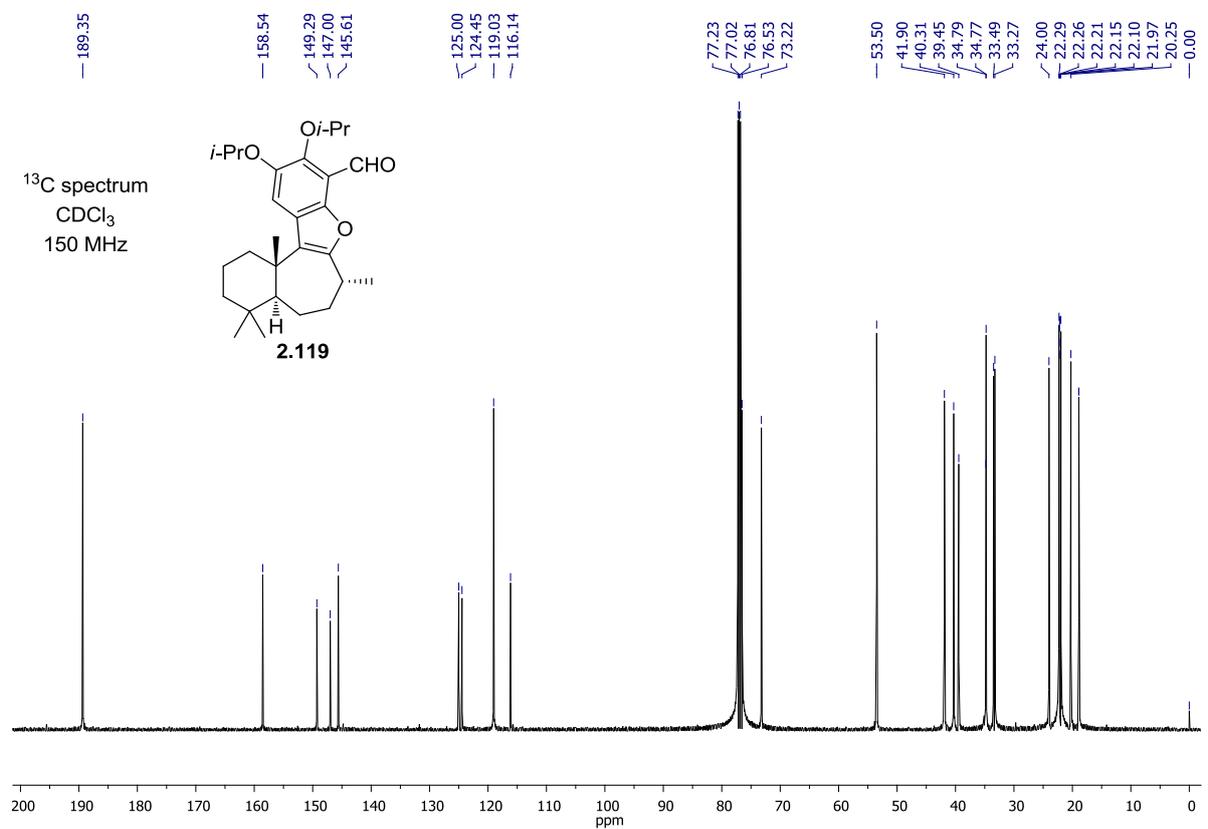
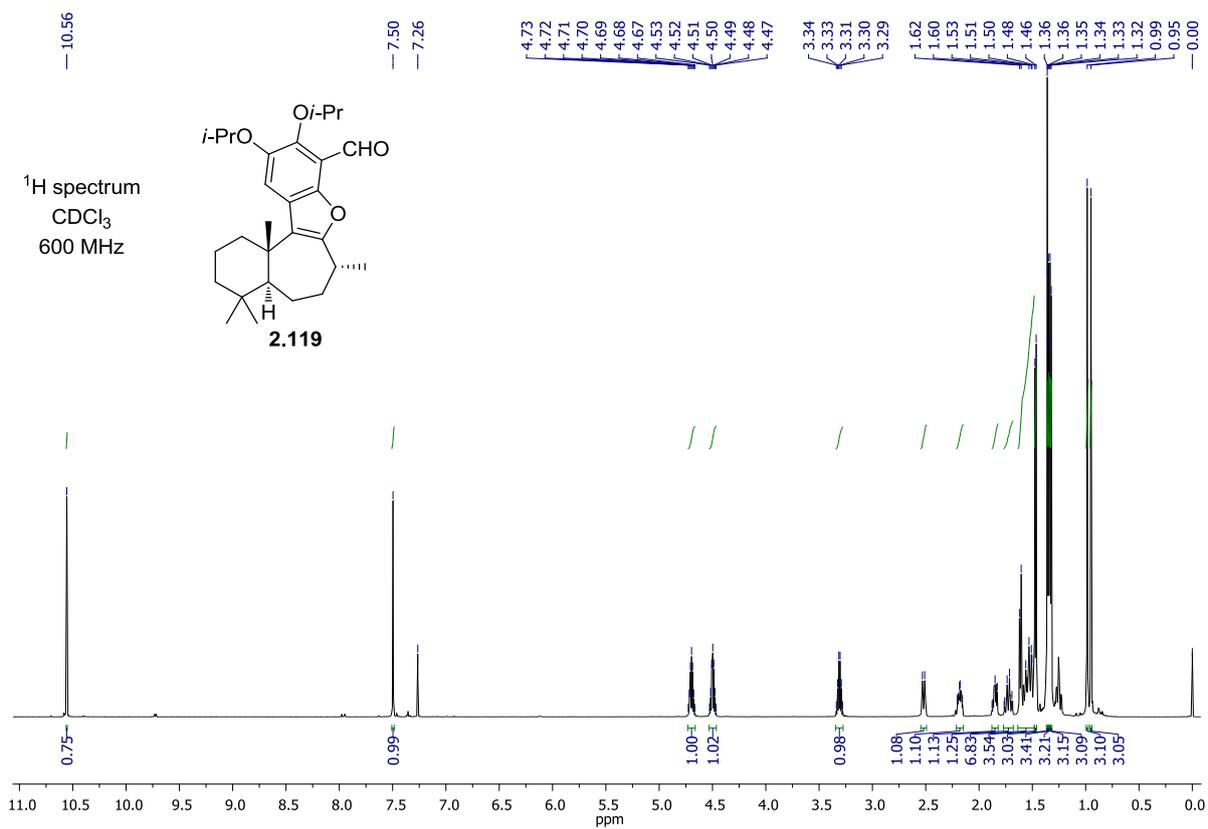
2.113  
HSQC

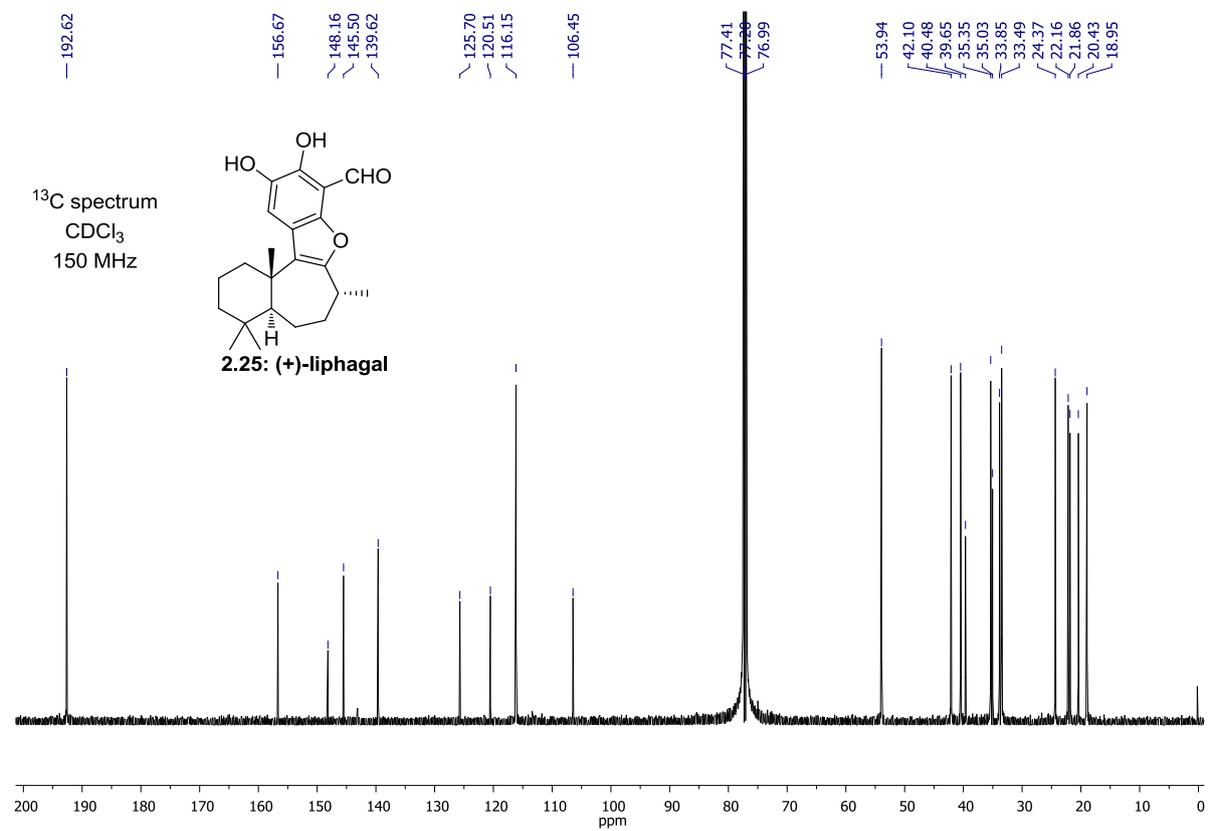
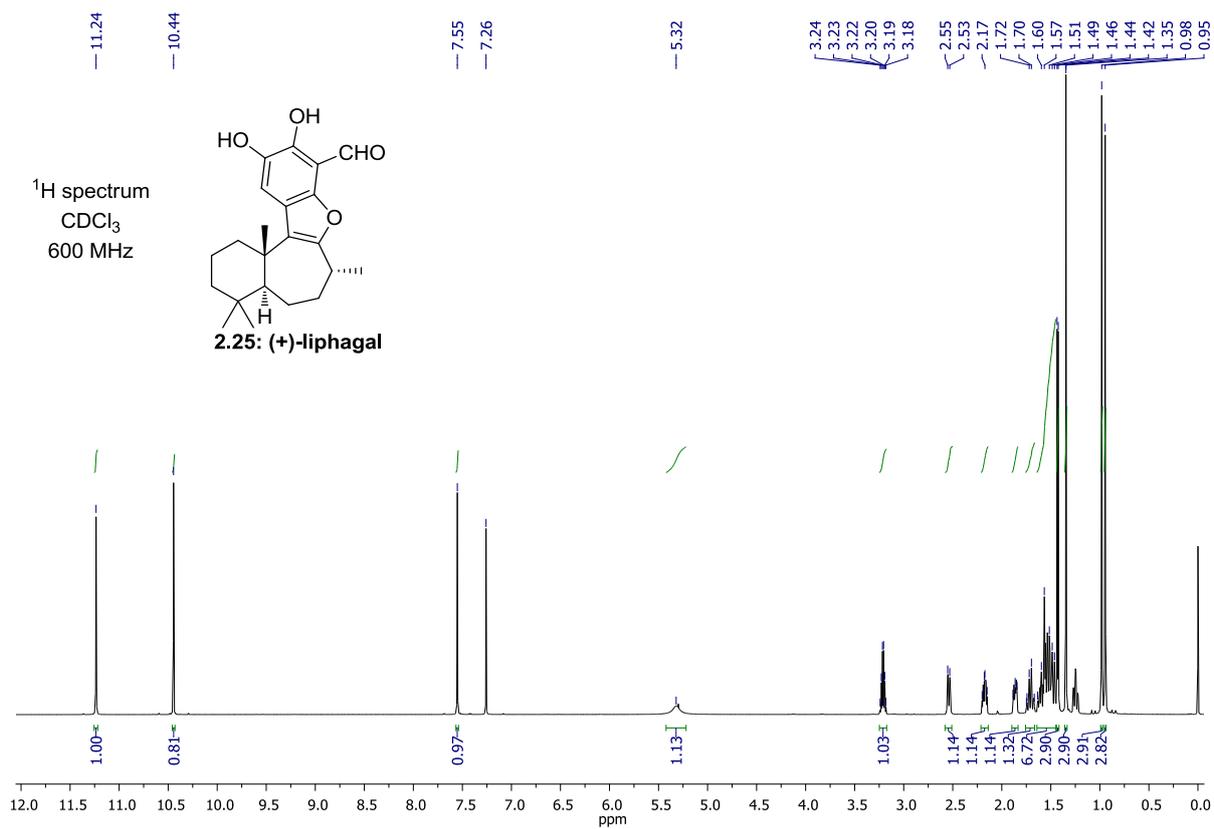


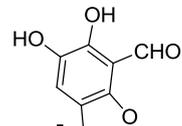




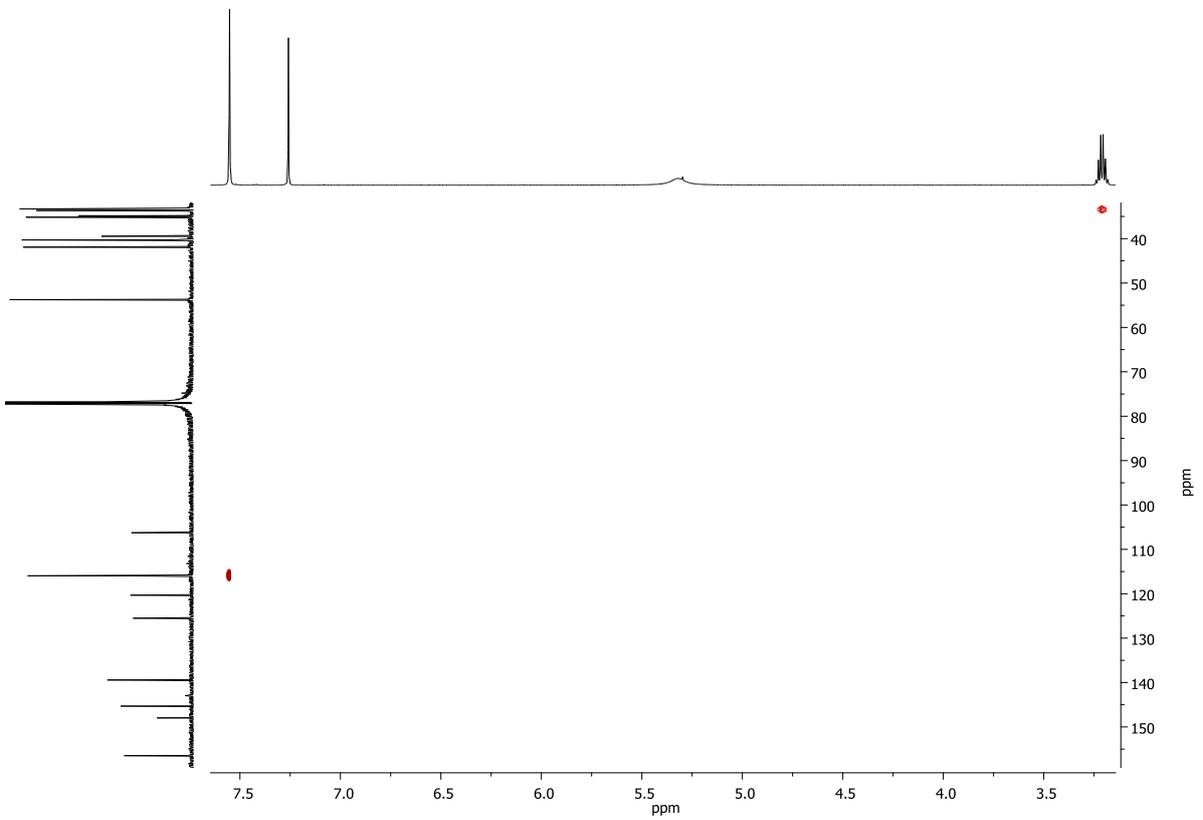
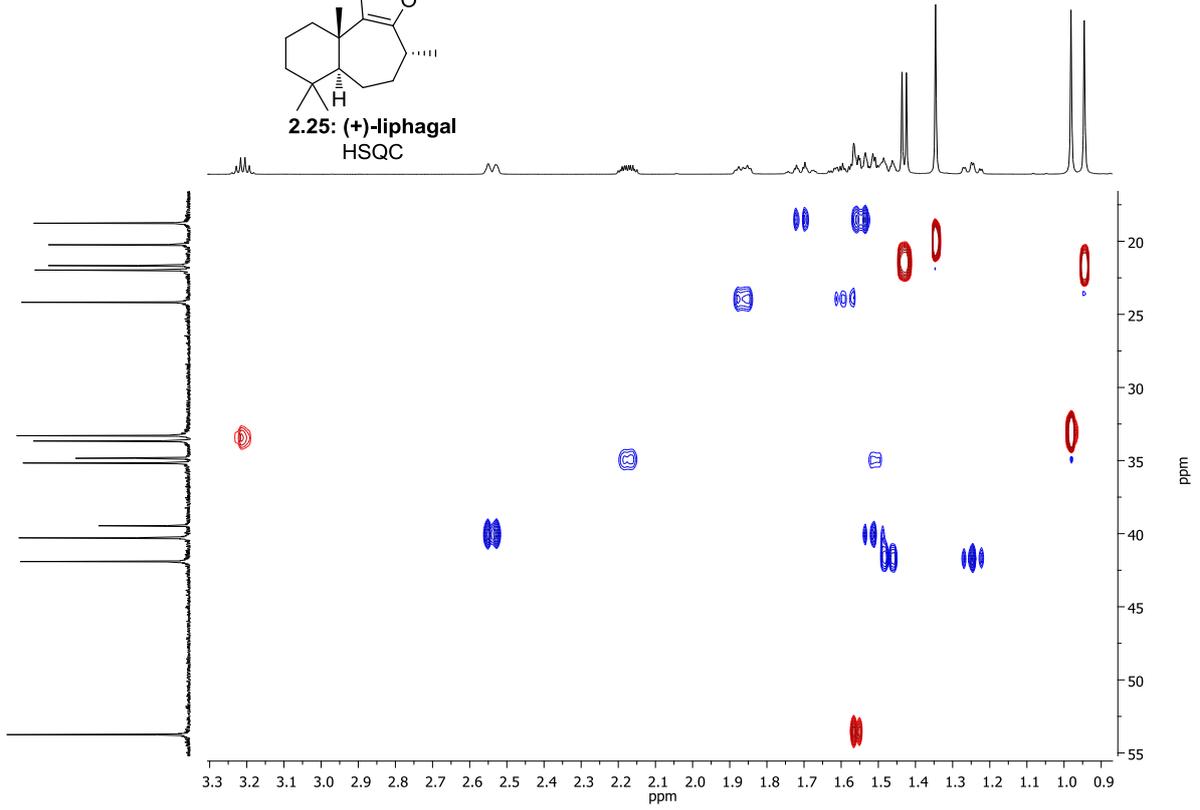


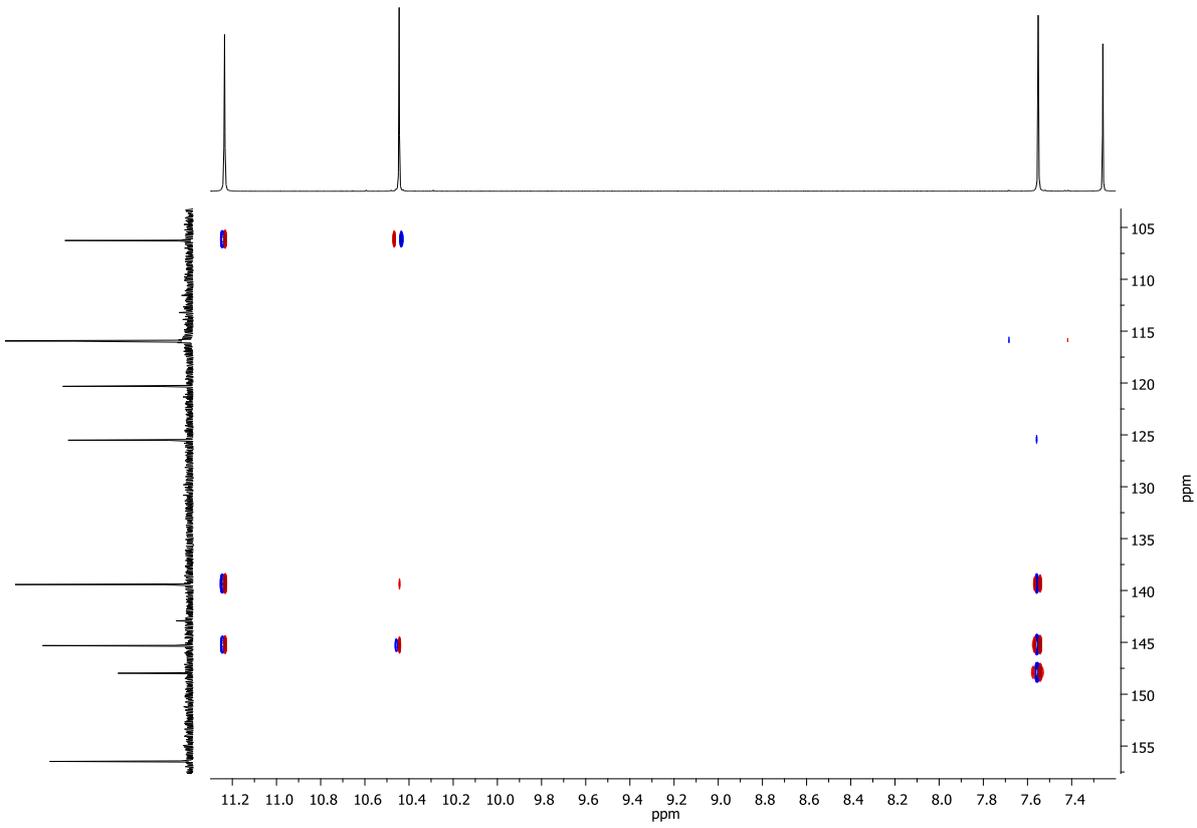
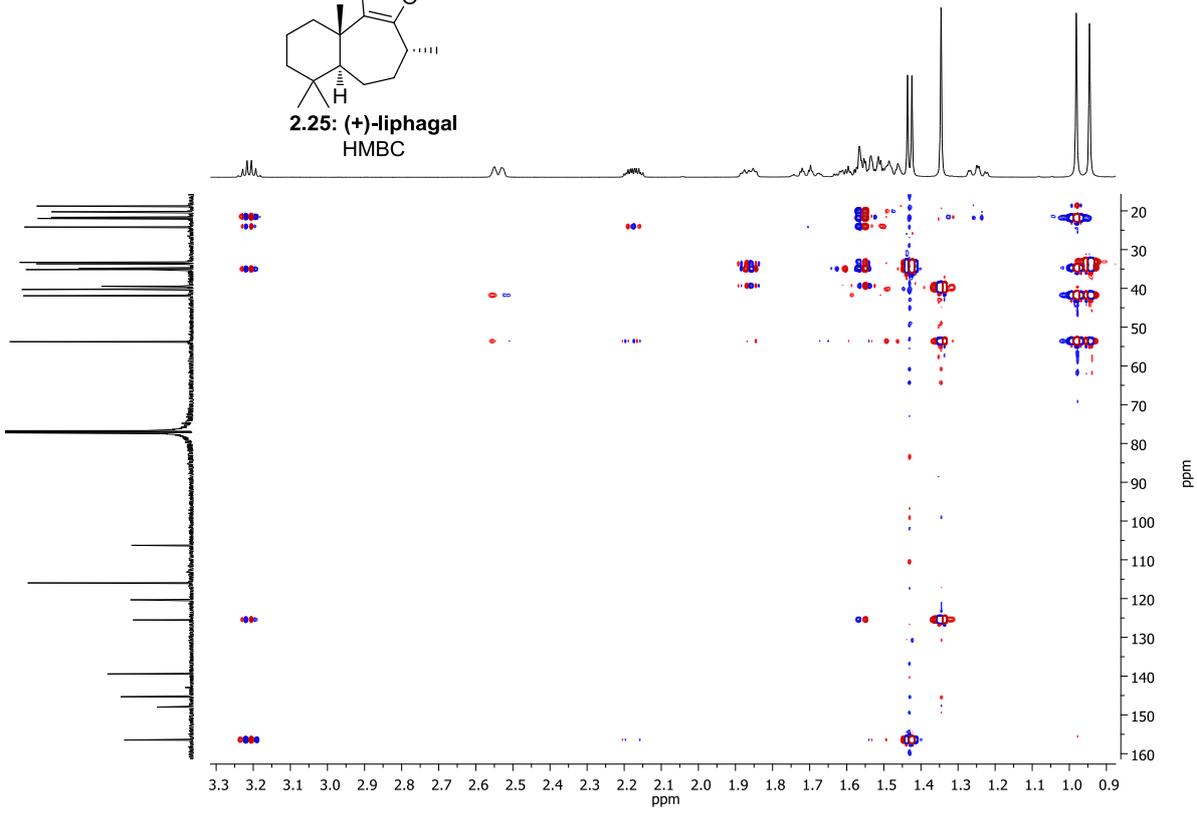
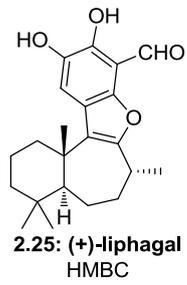


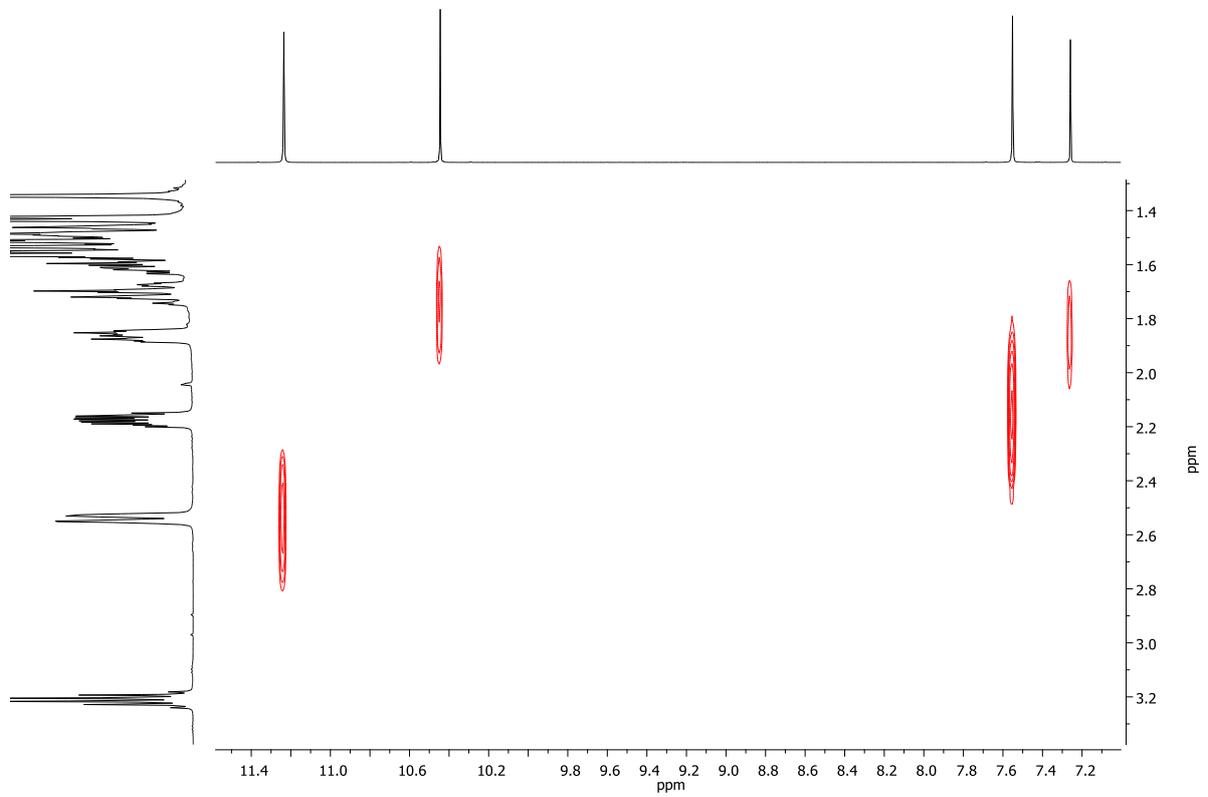
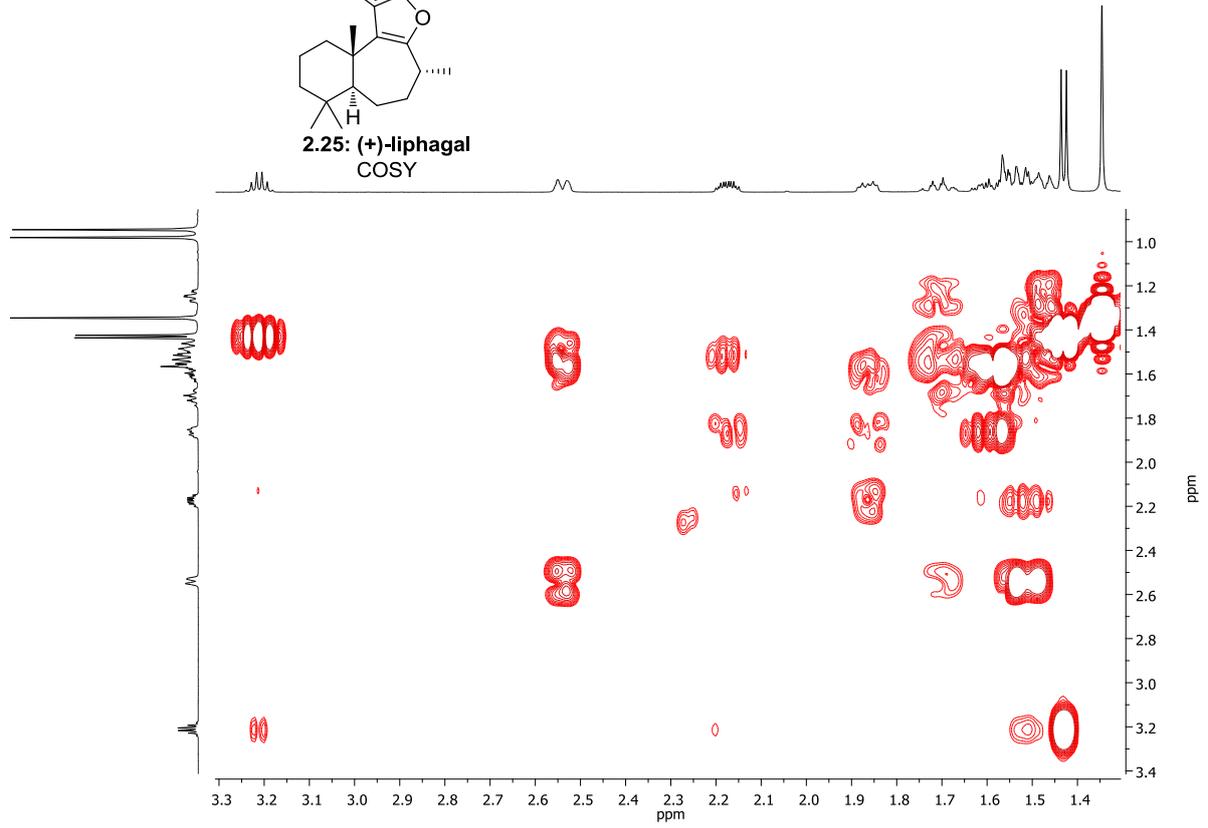
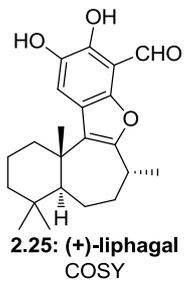


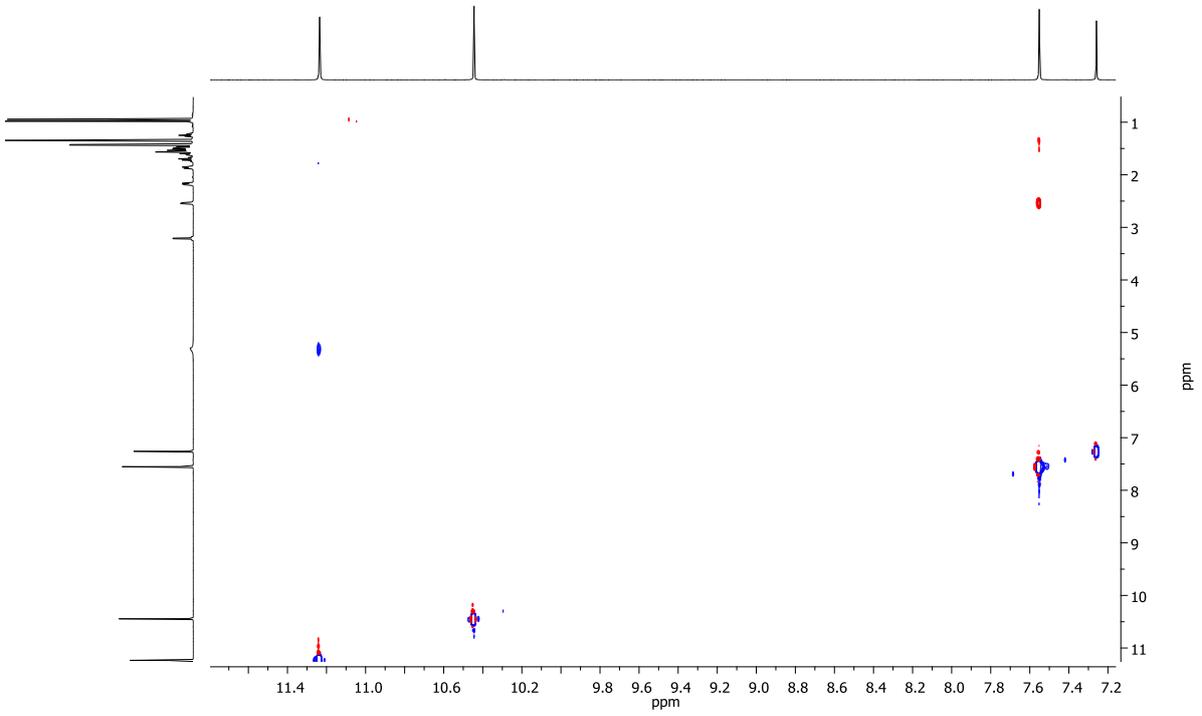
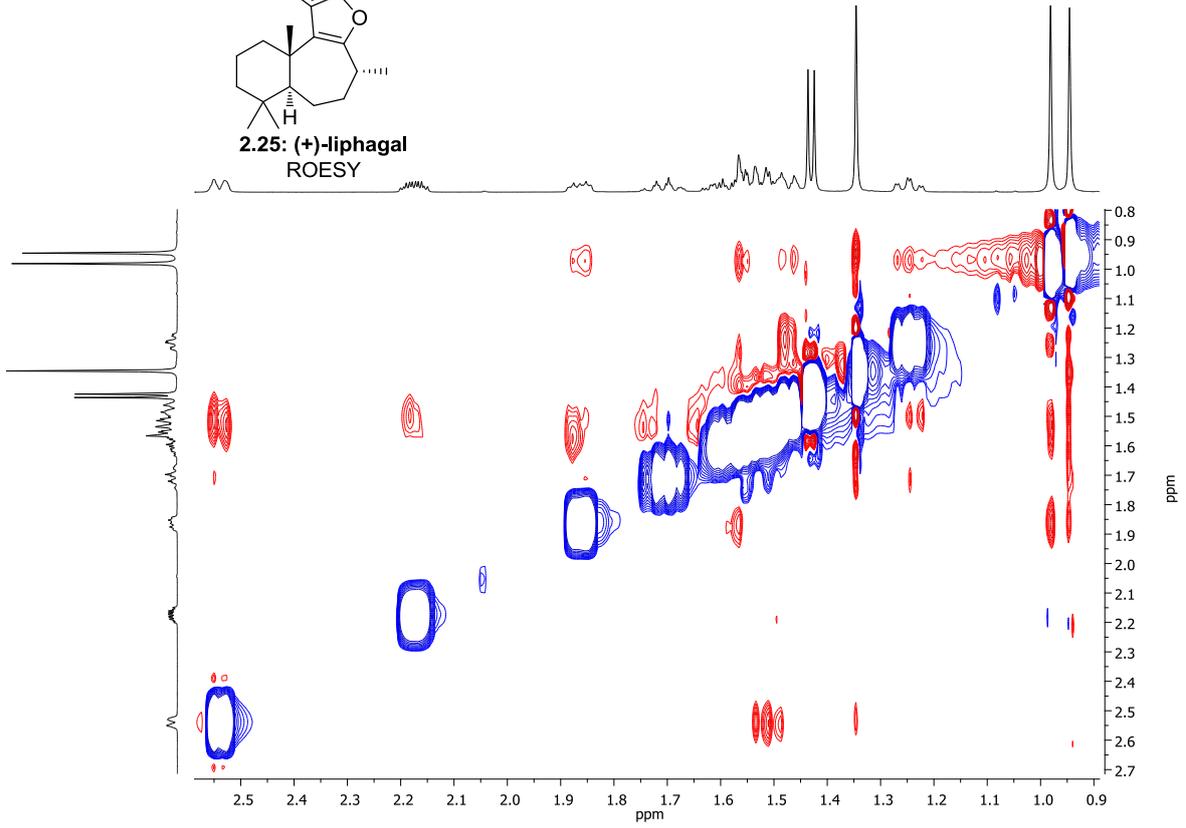
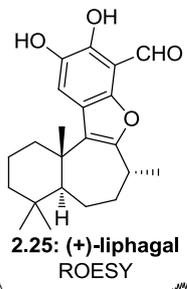


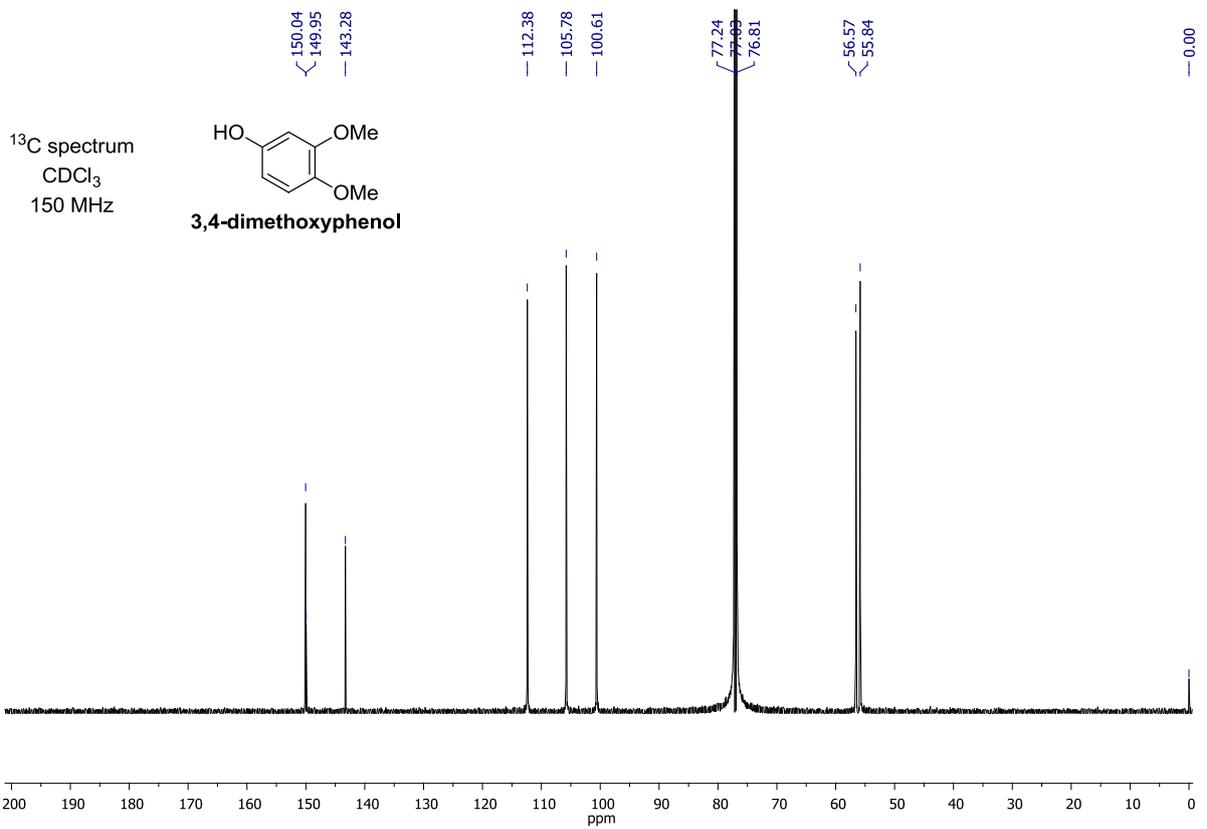
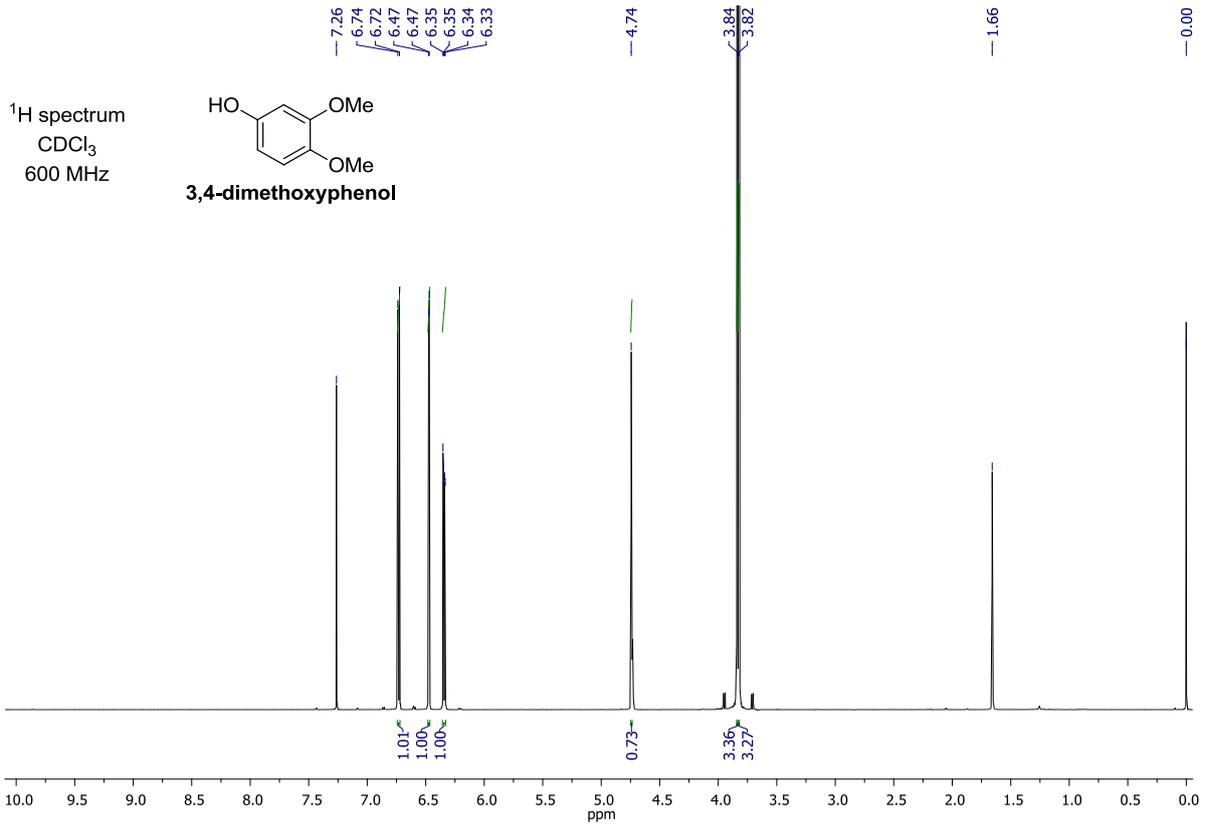
2.25: (+)-liphagal  
HSQC

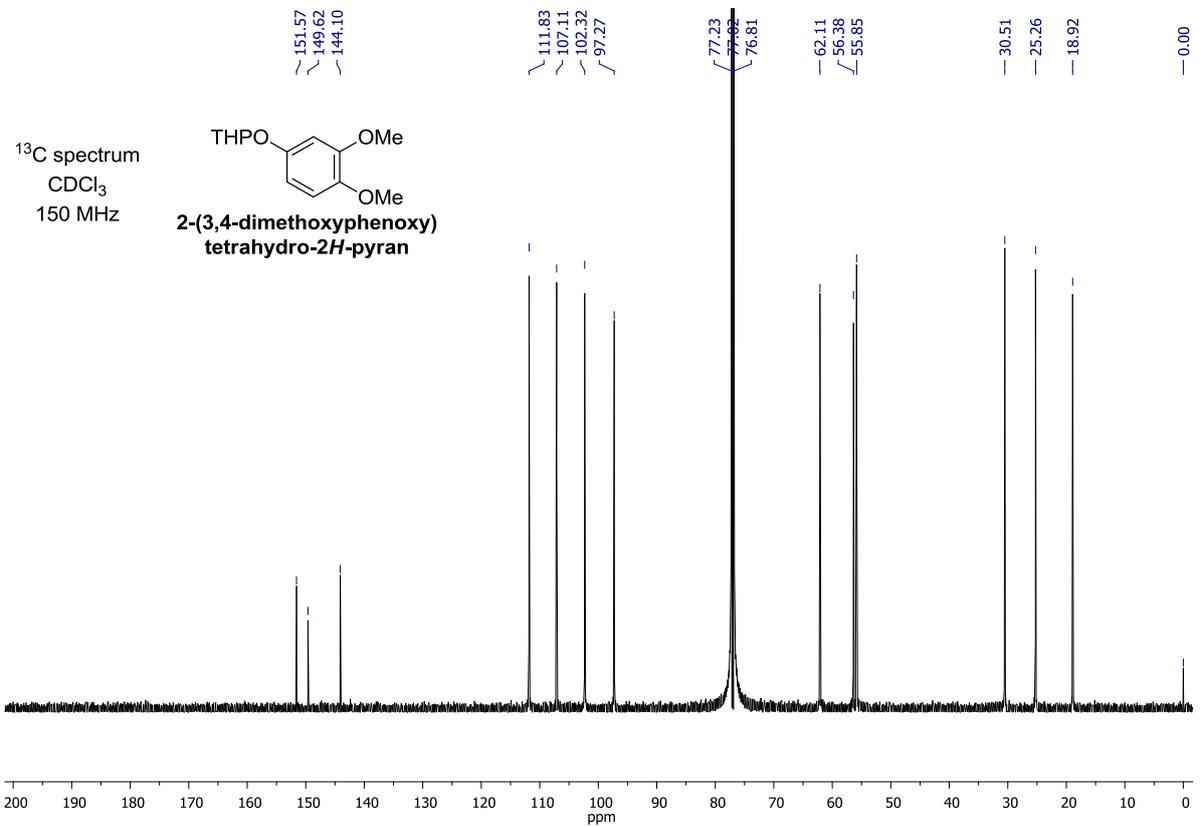
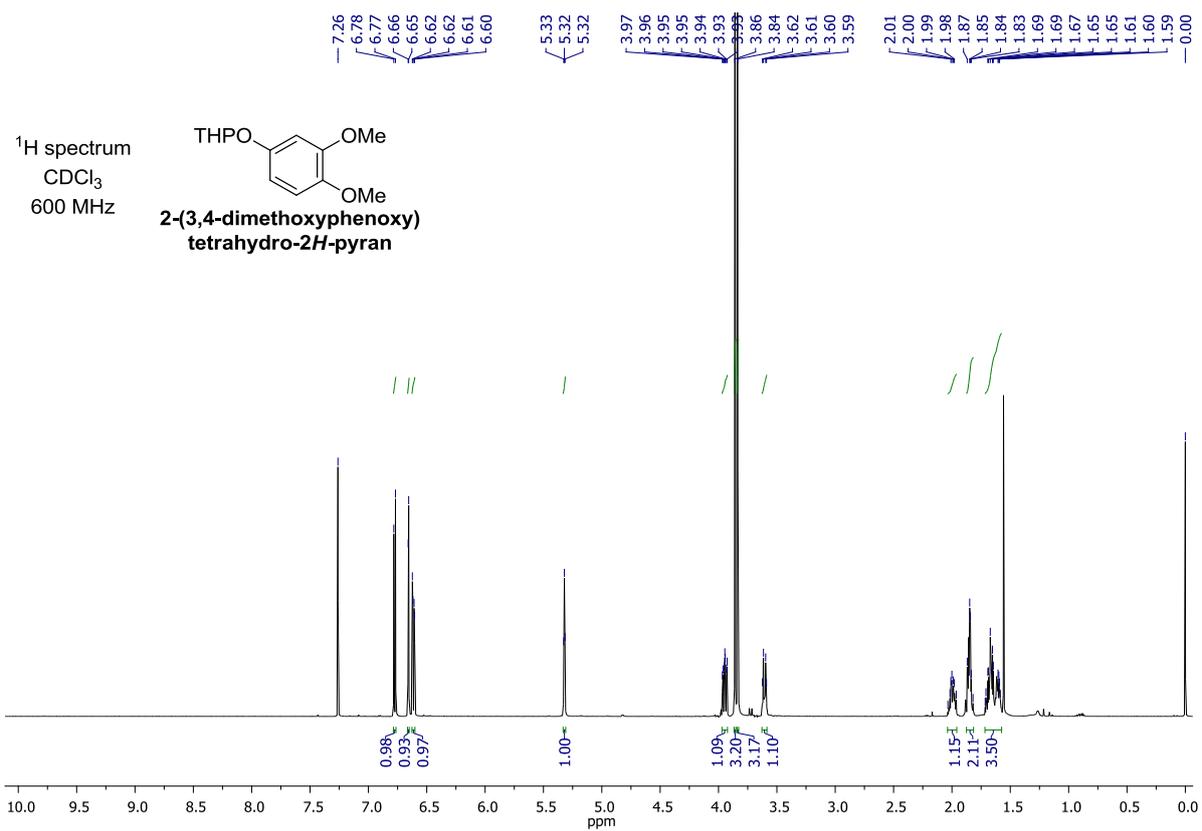


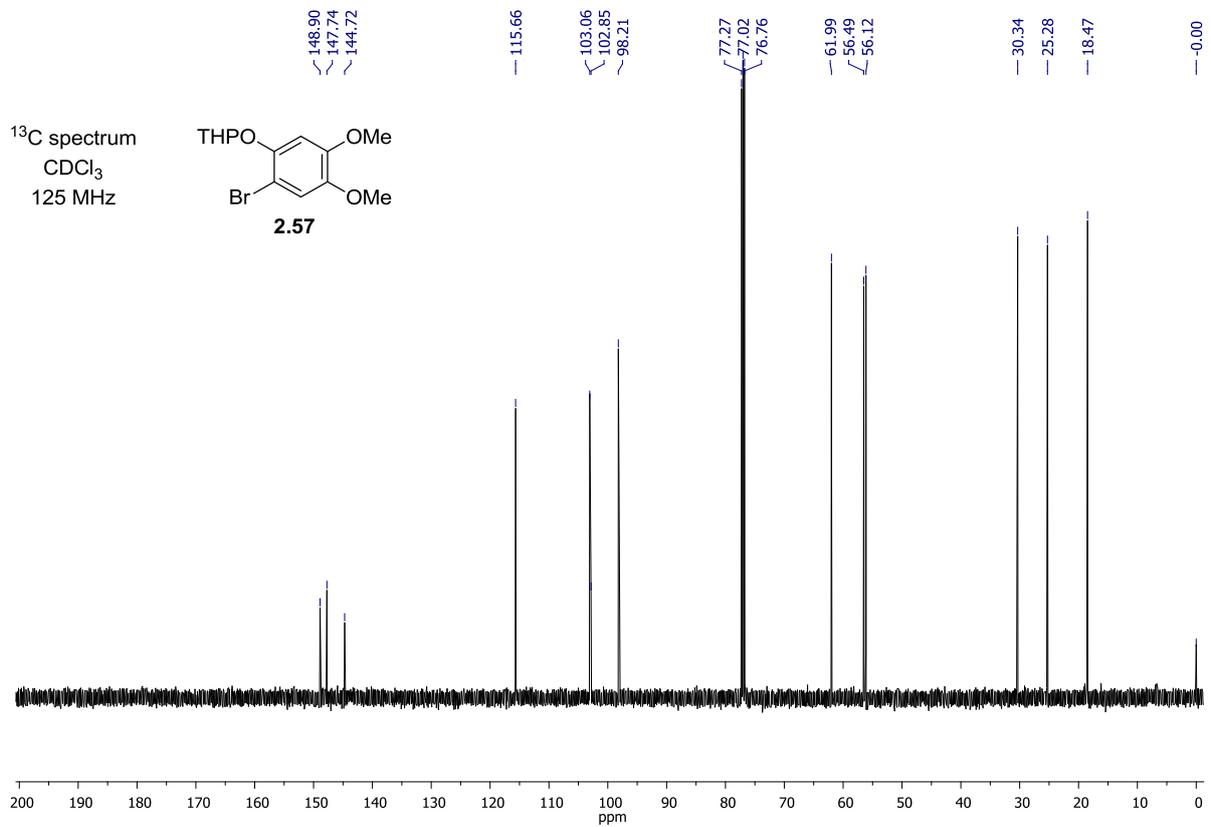
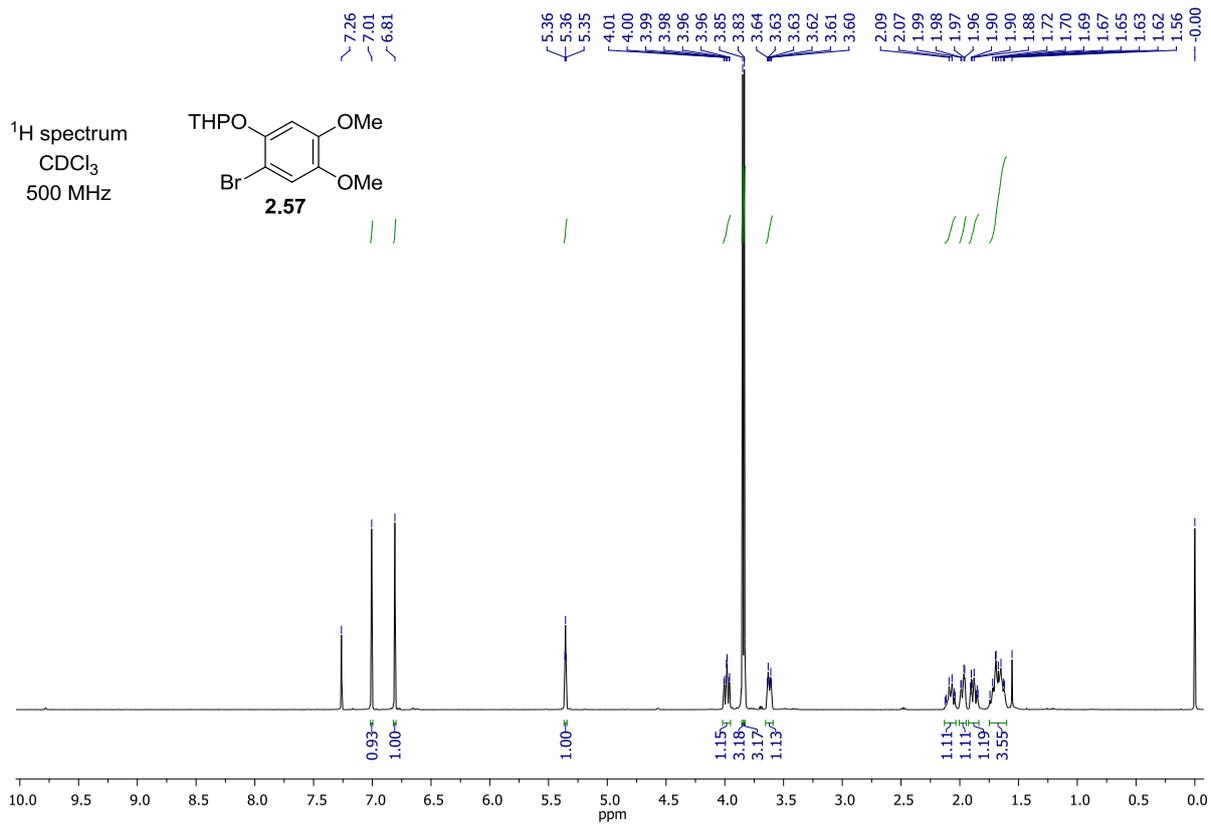


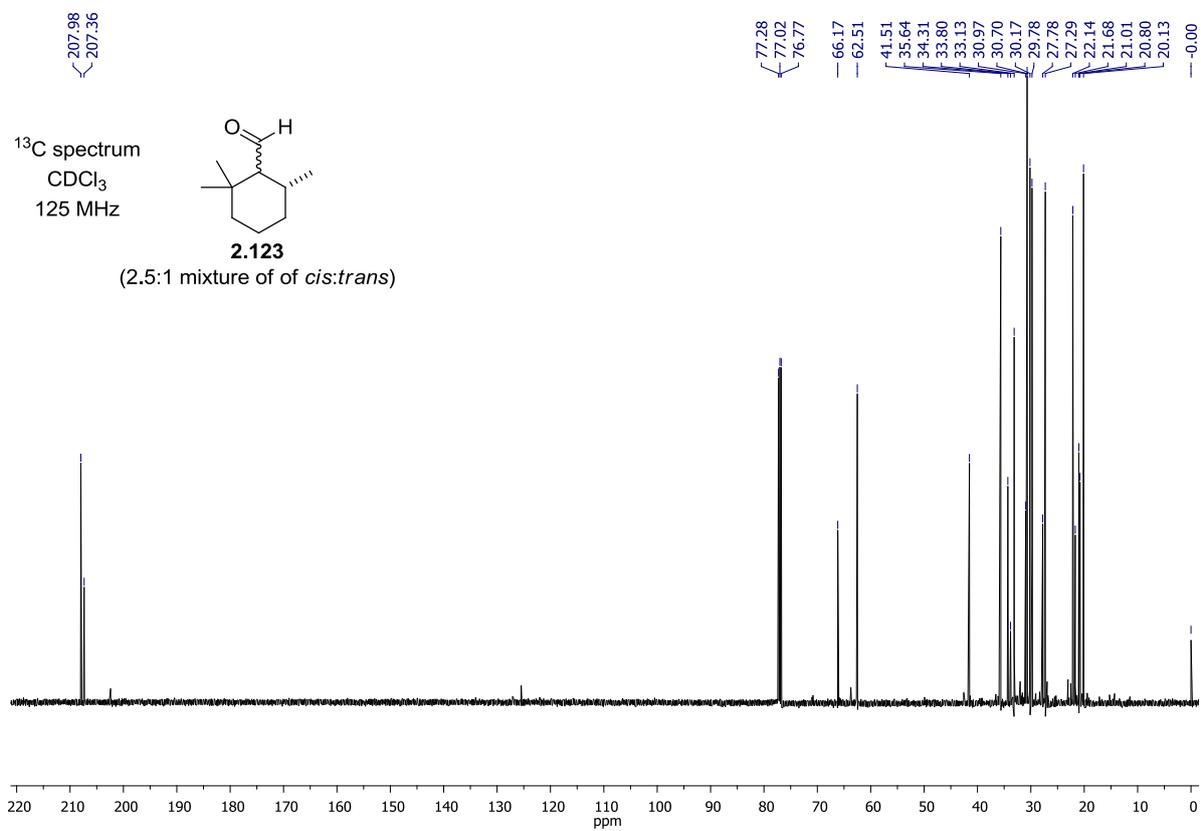
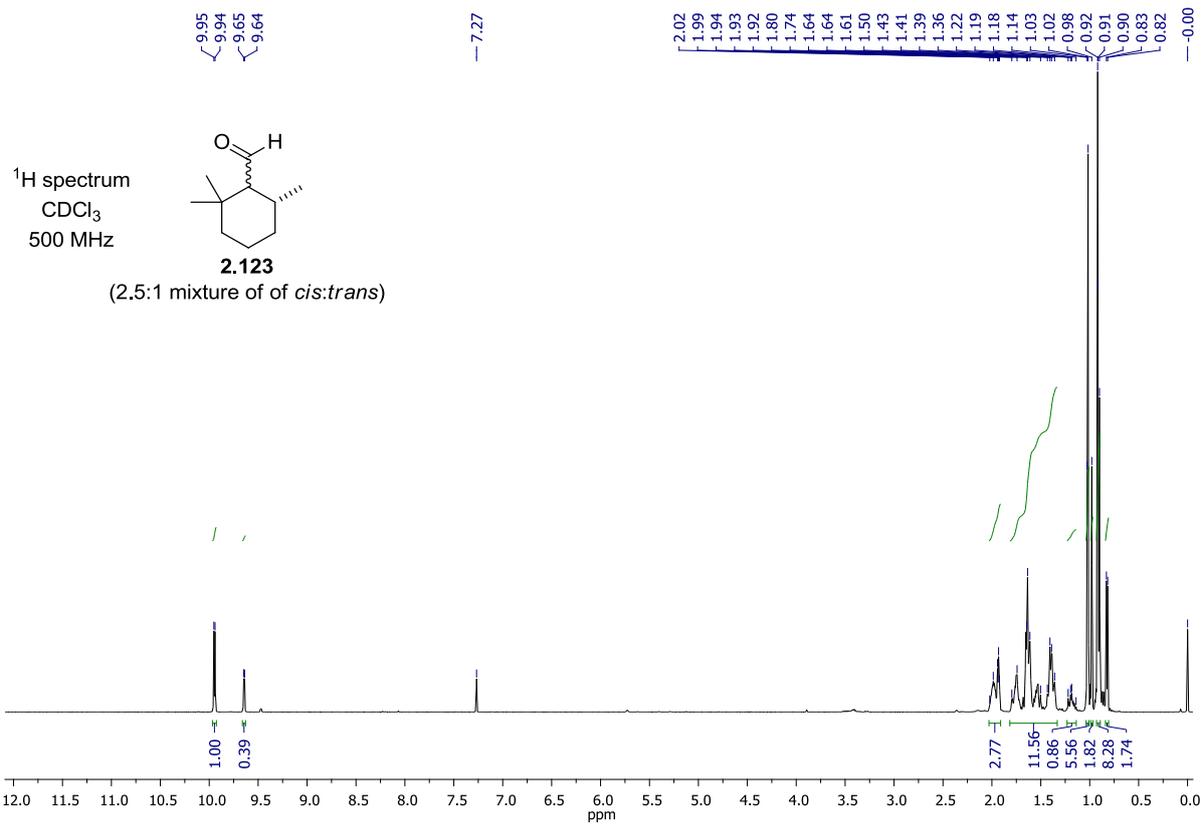


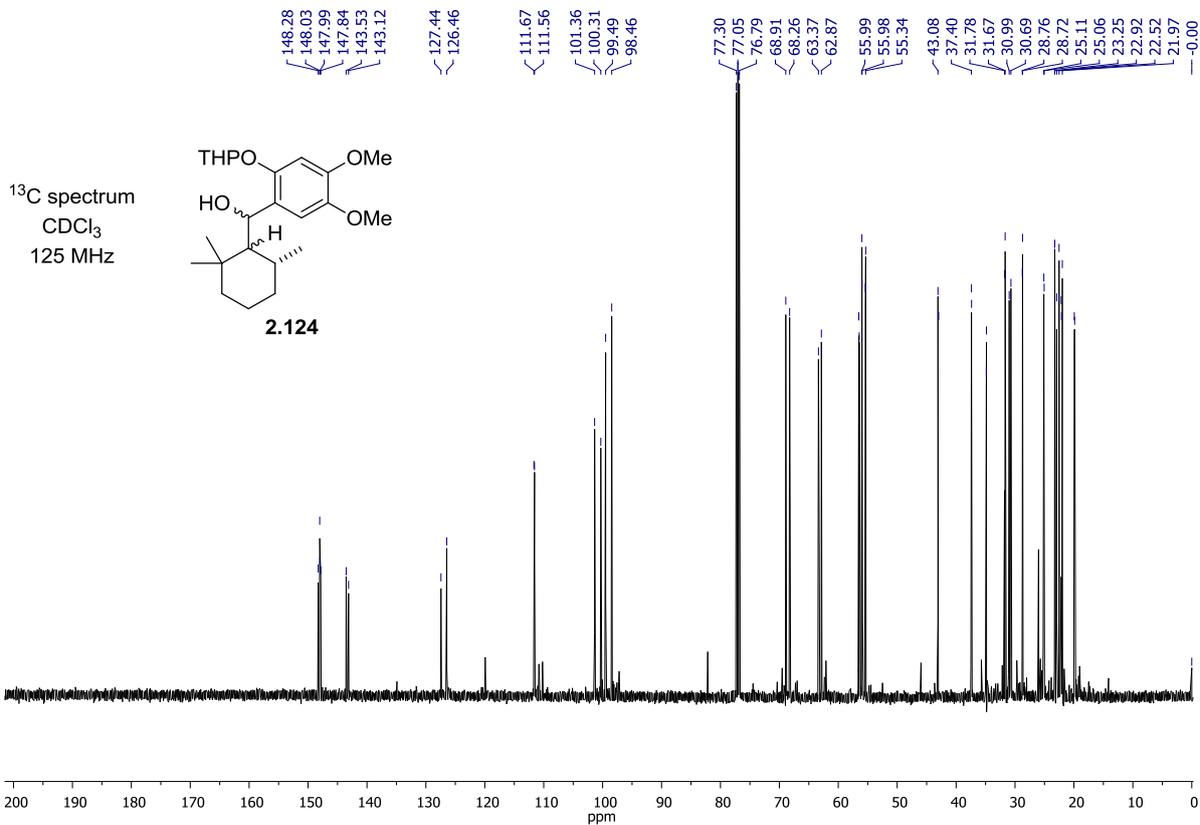
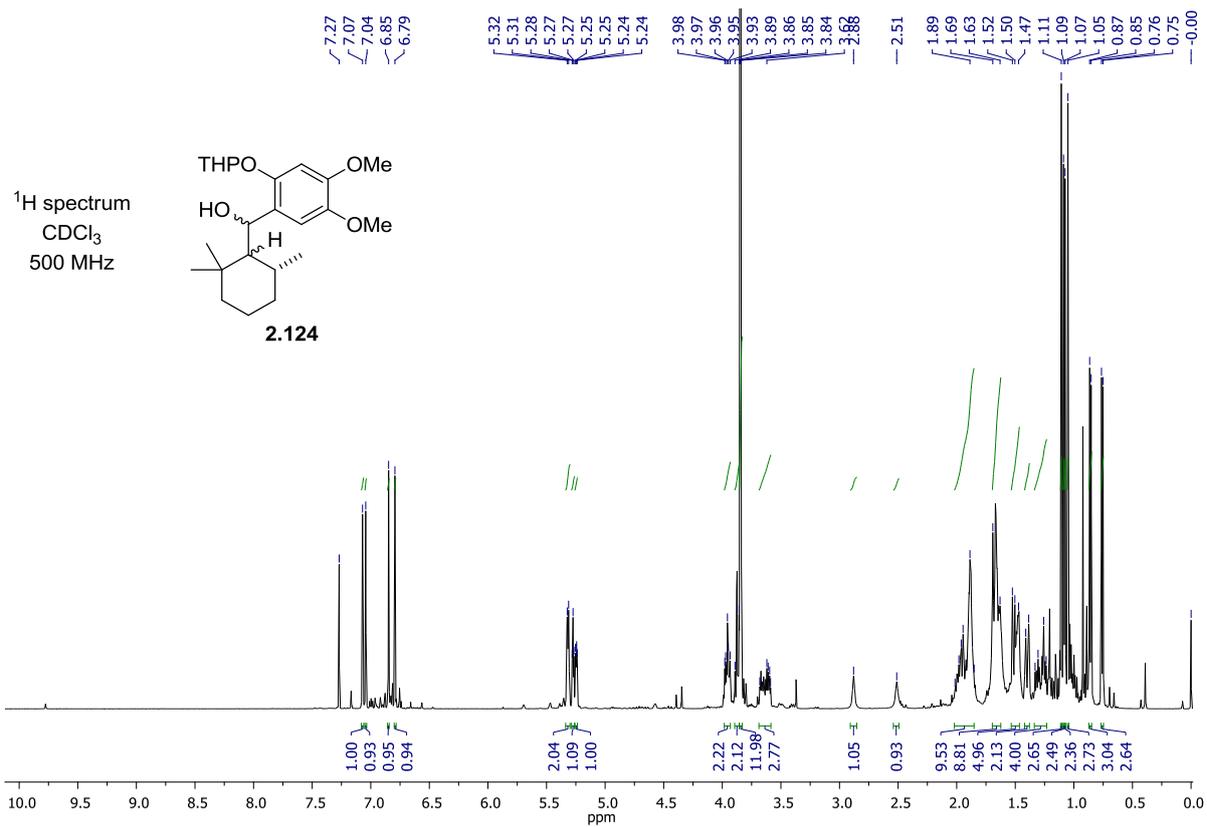




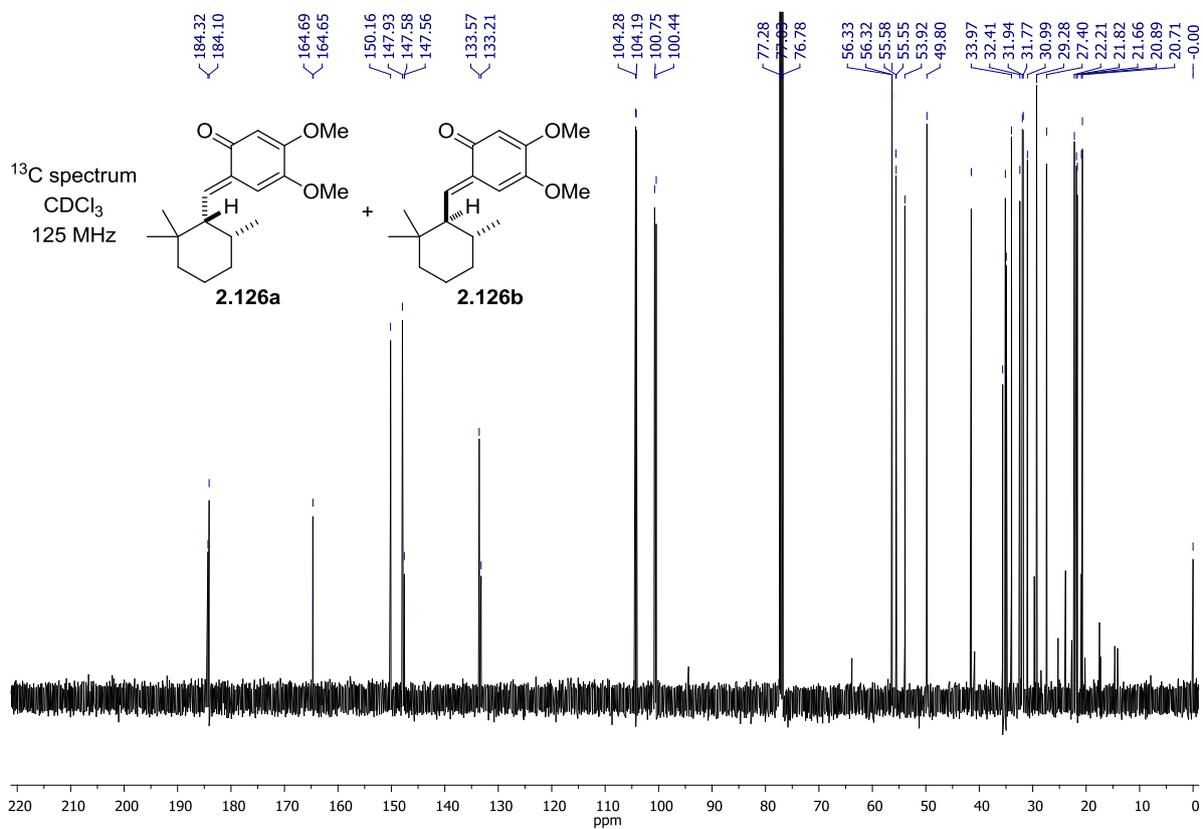
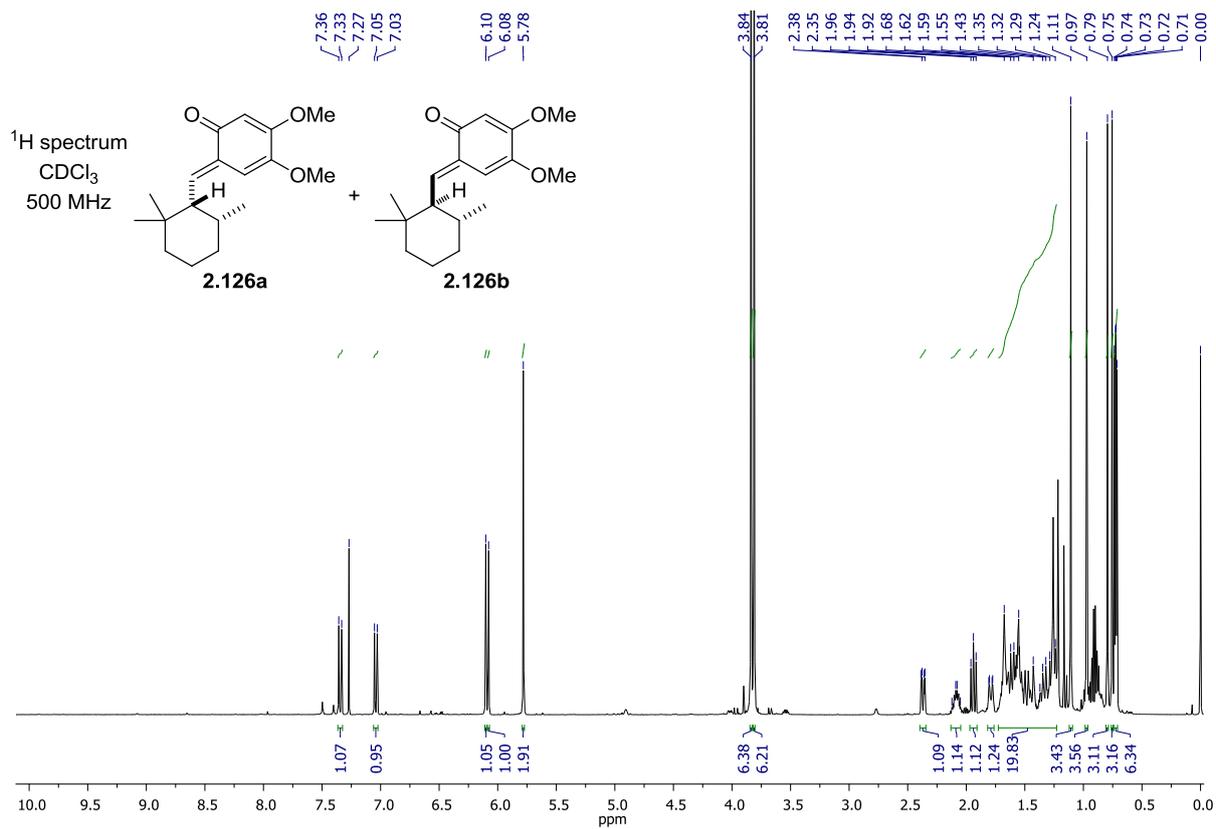




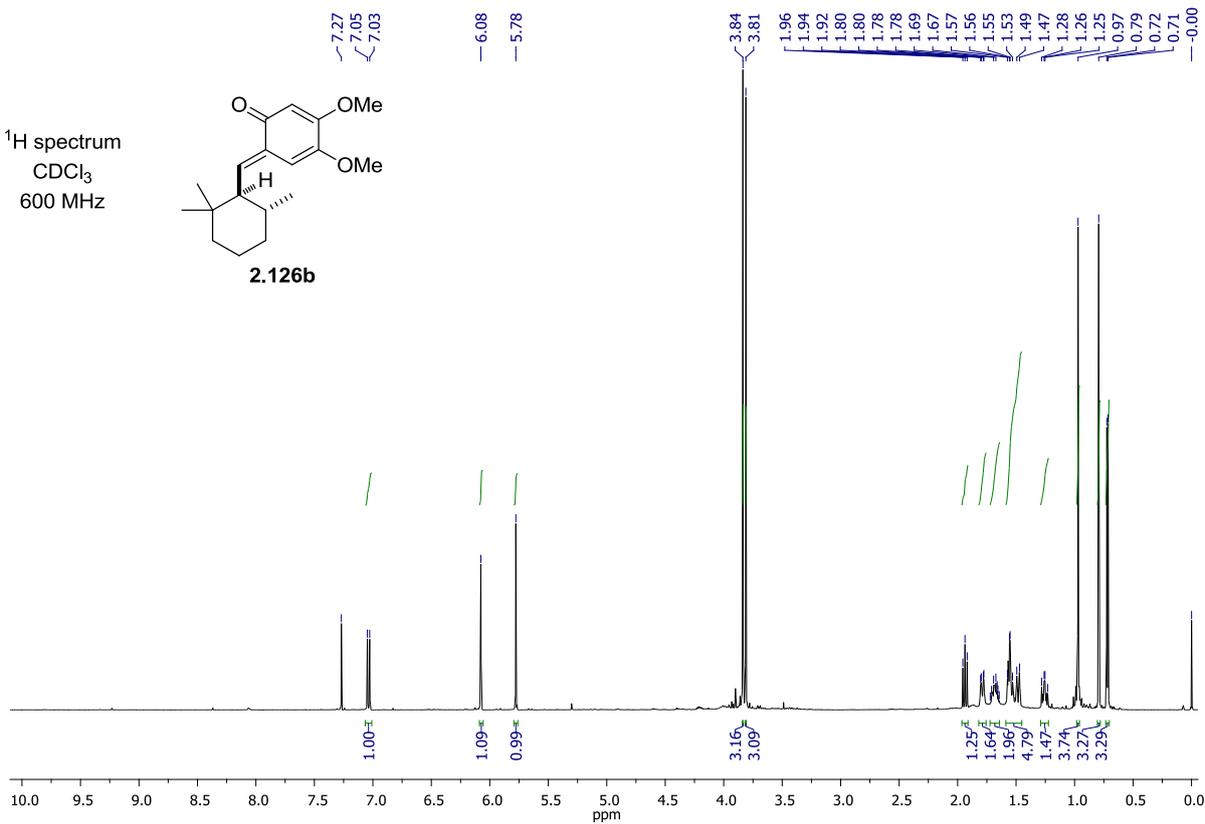
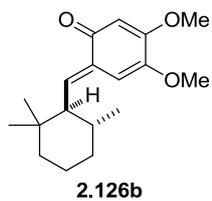




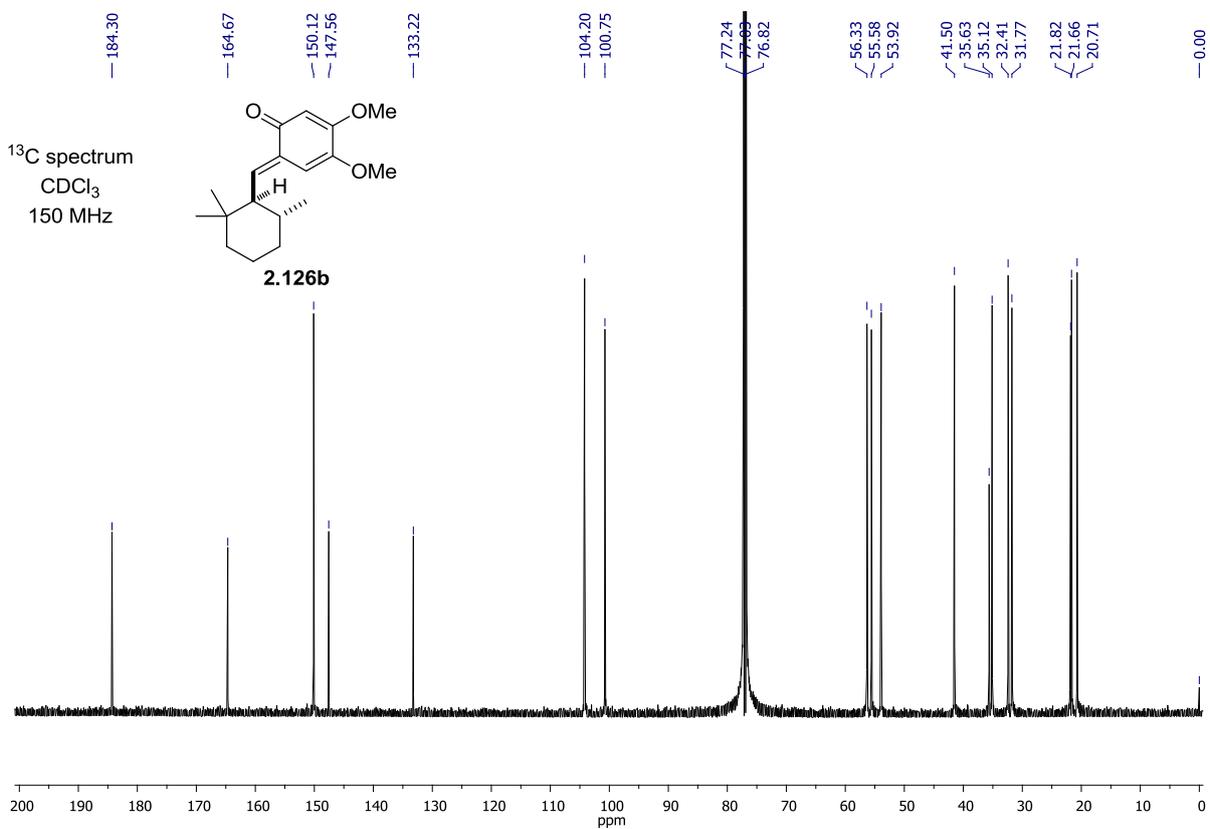
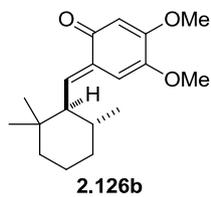
This compound readily decomposes during NMR acquisition.

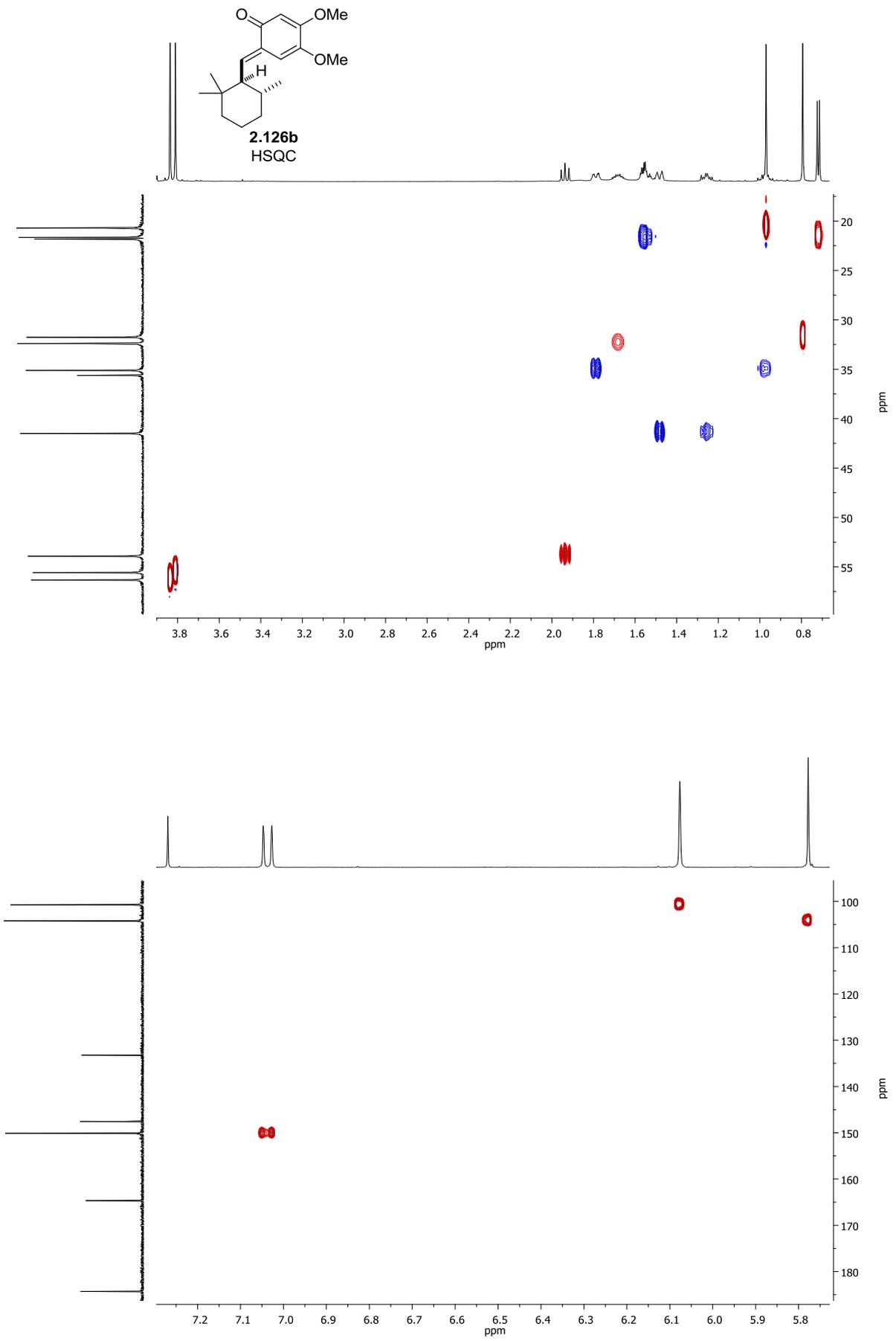


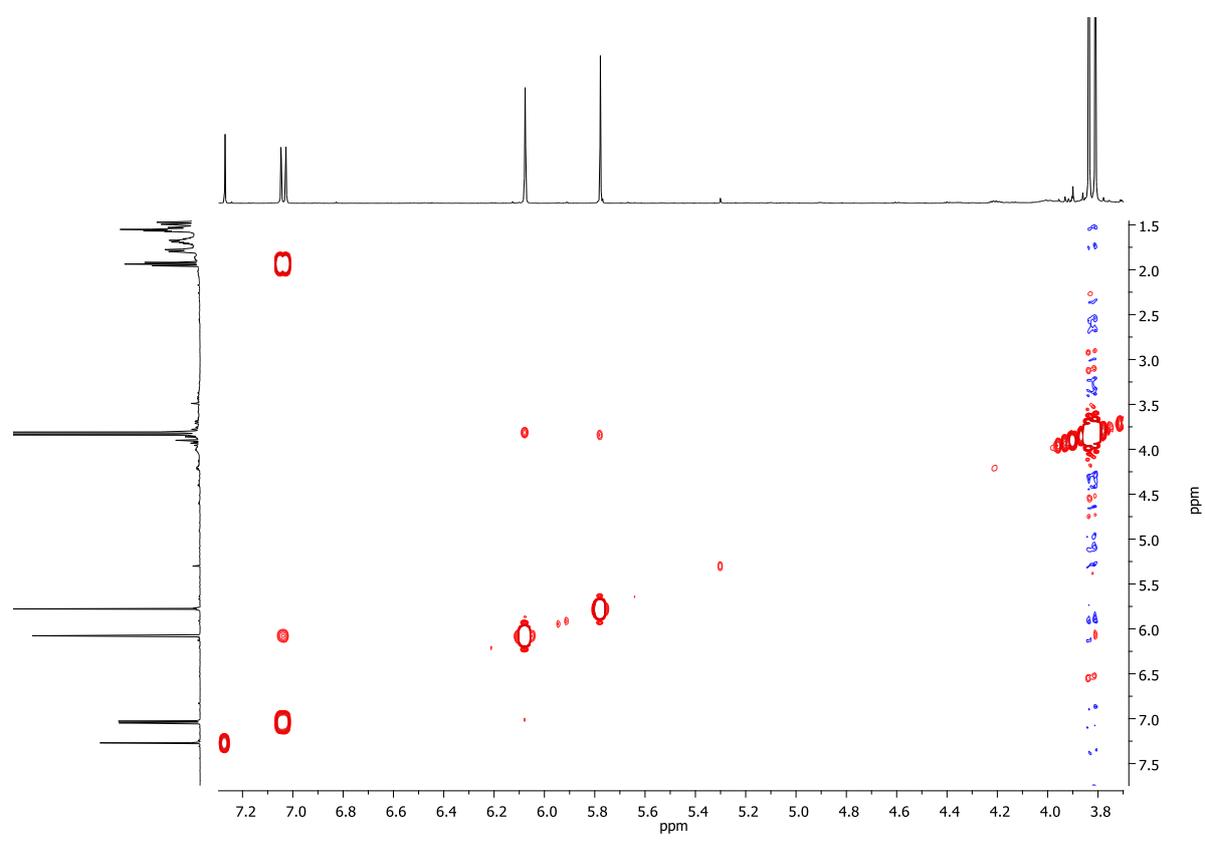
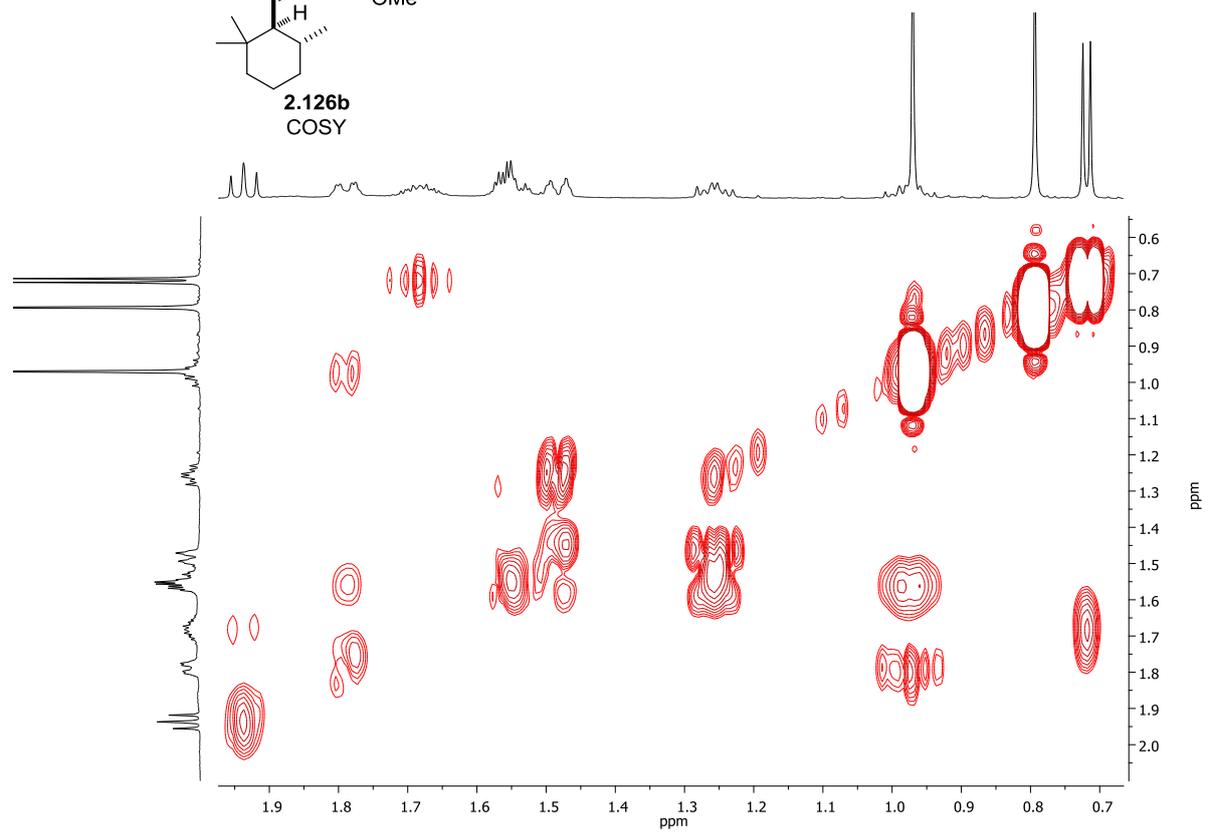
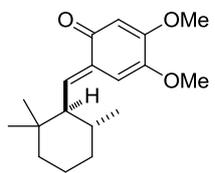
<sup>1</sup>H spectrum  
CDCl<sub>3</sub>  
600 MHz

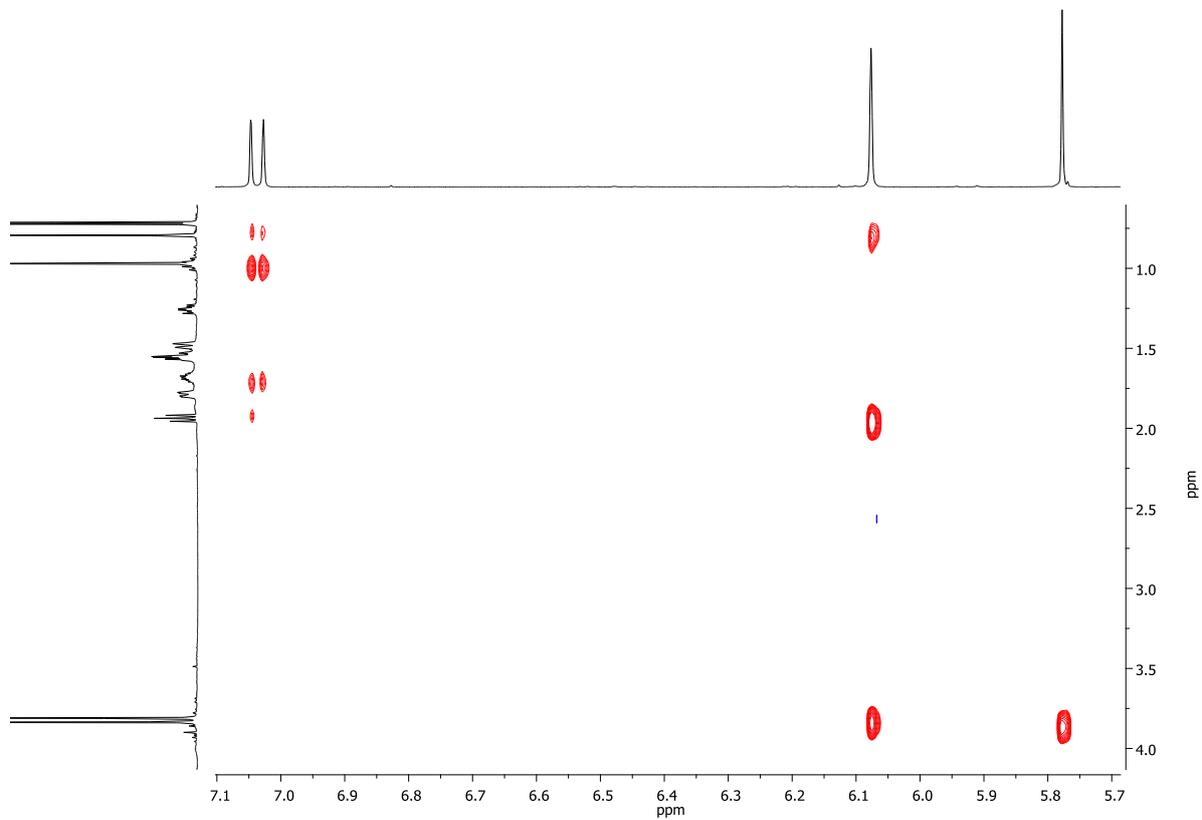
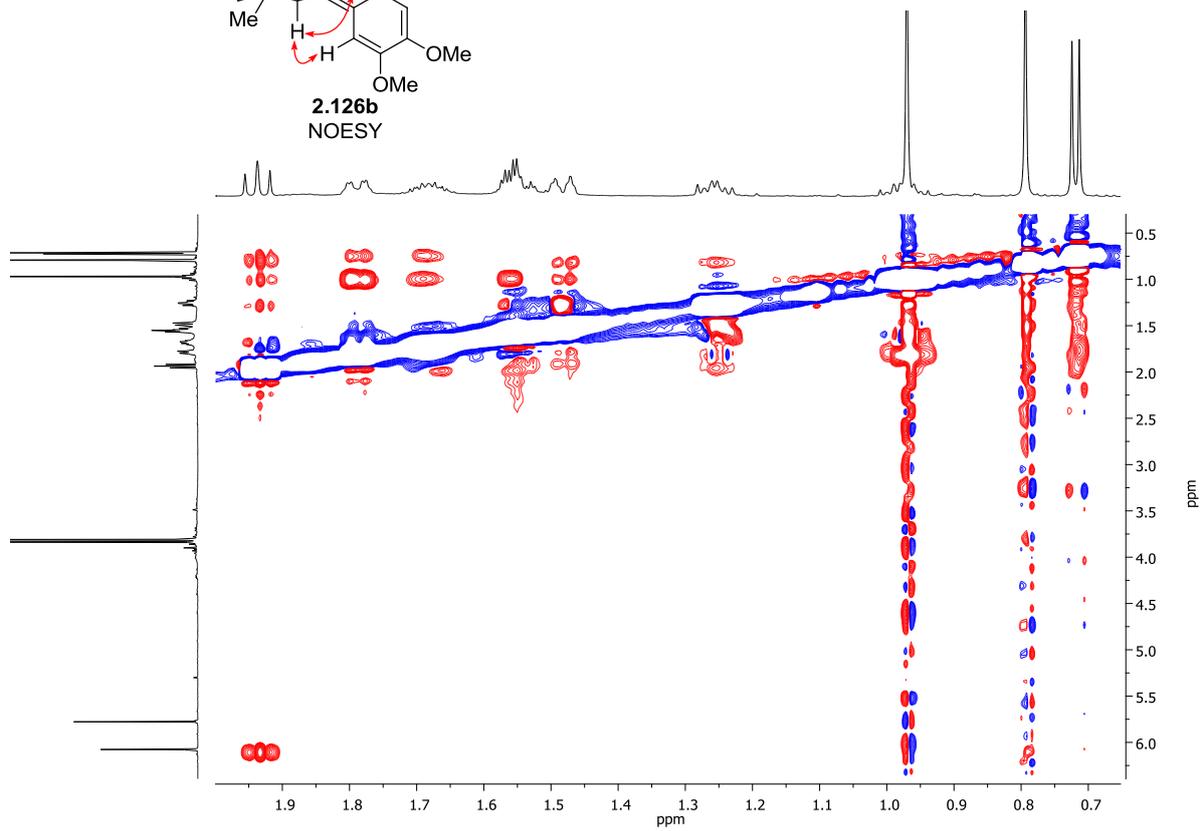
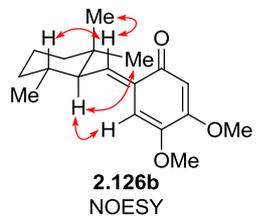


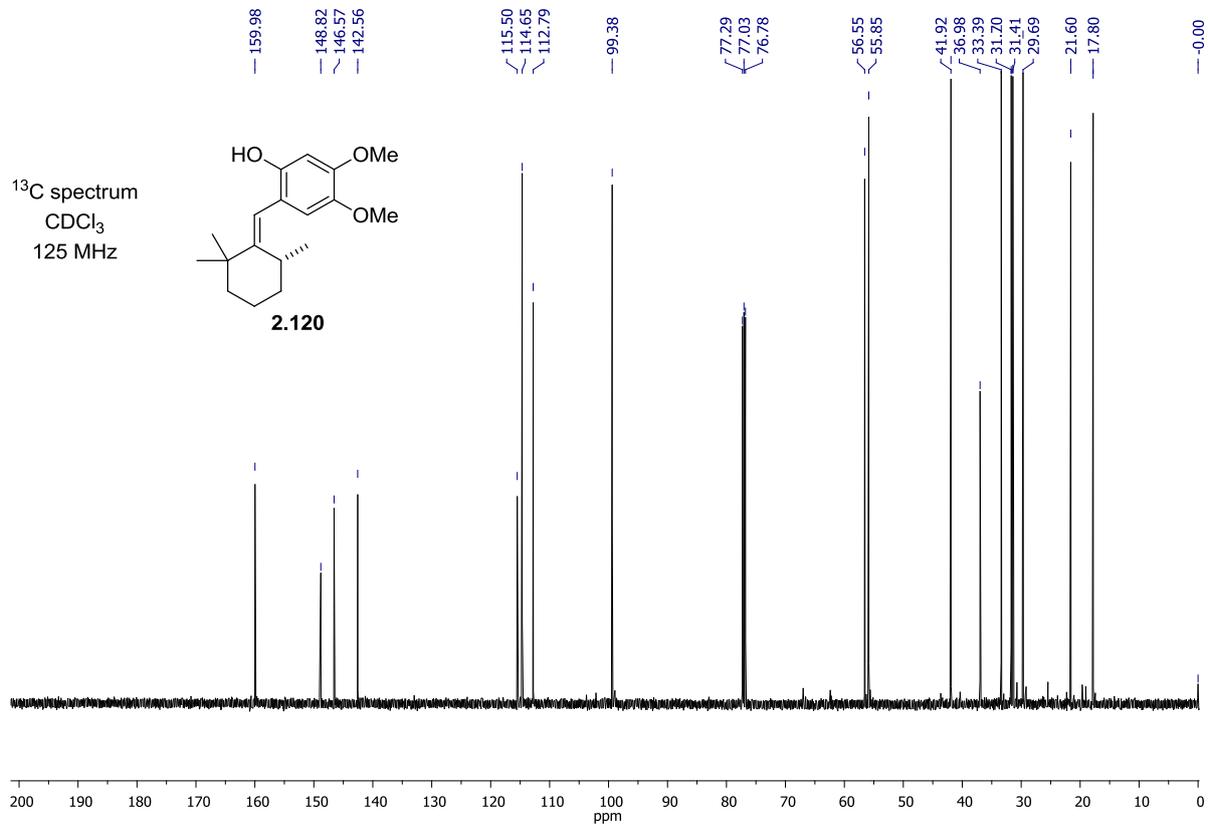
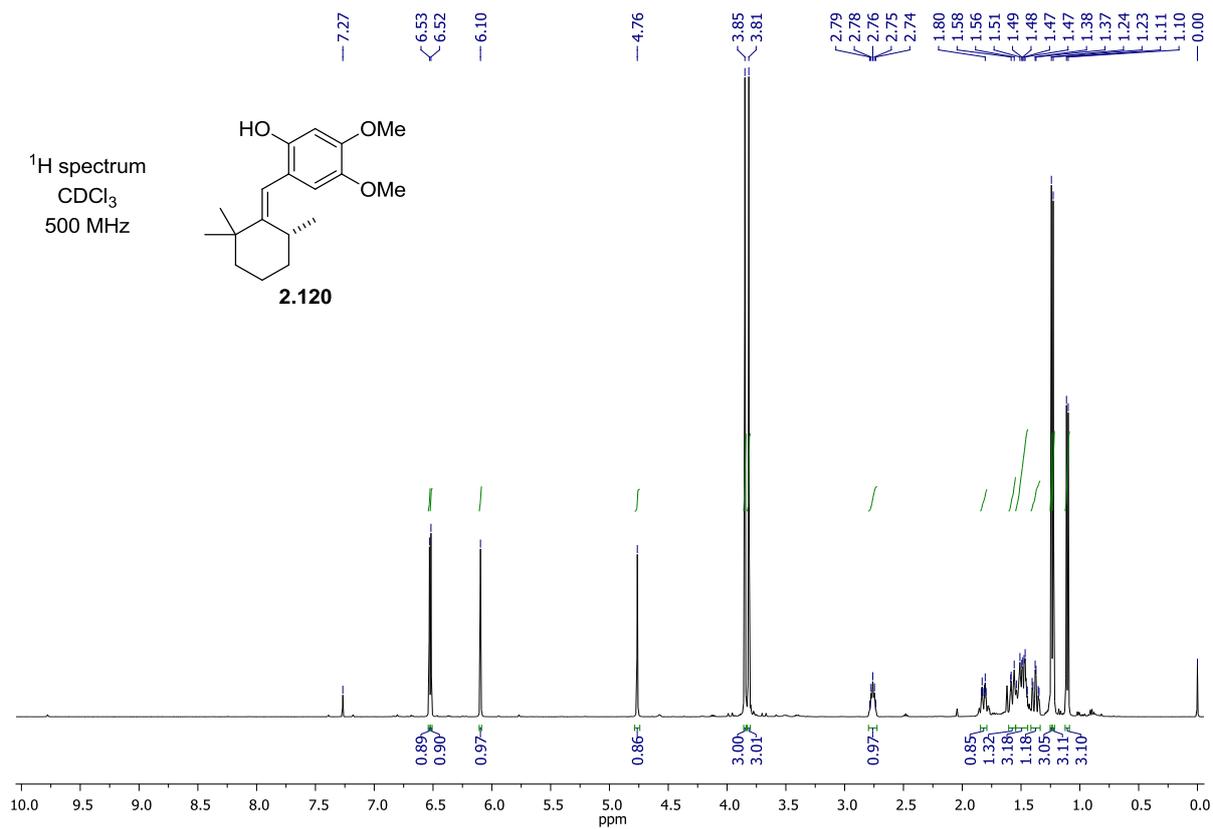
<sup>13</sup>C spectrum  
CDCl<sub>3</sub>  
150 MHz

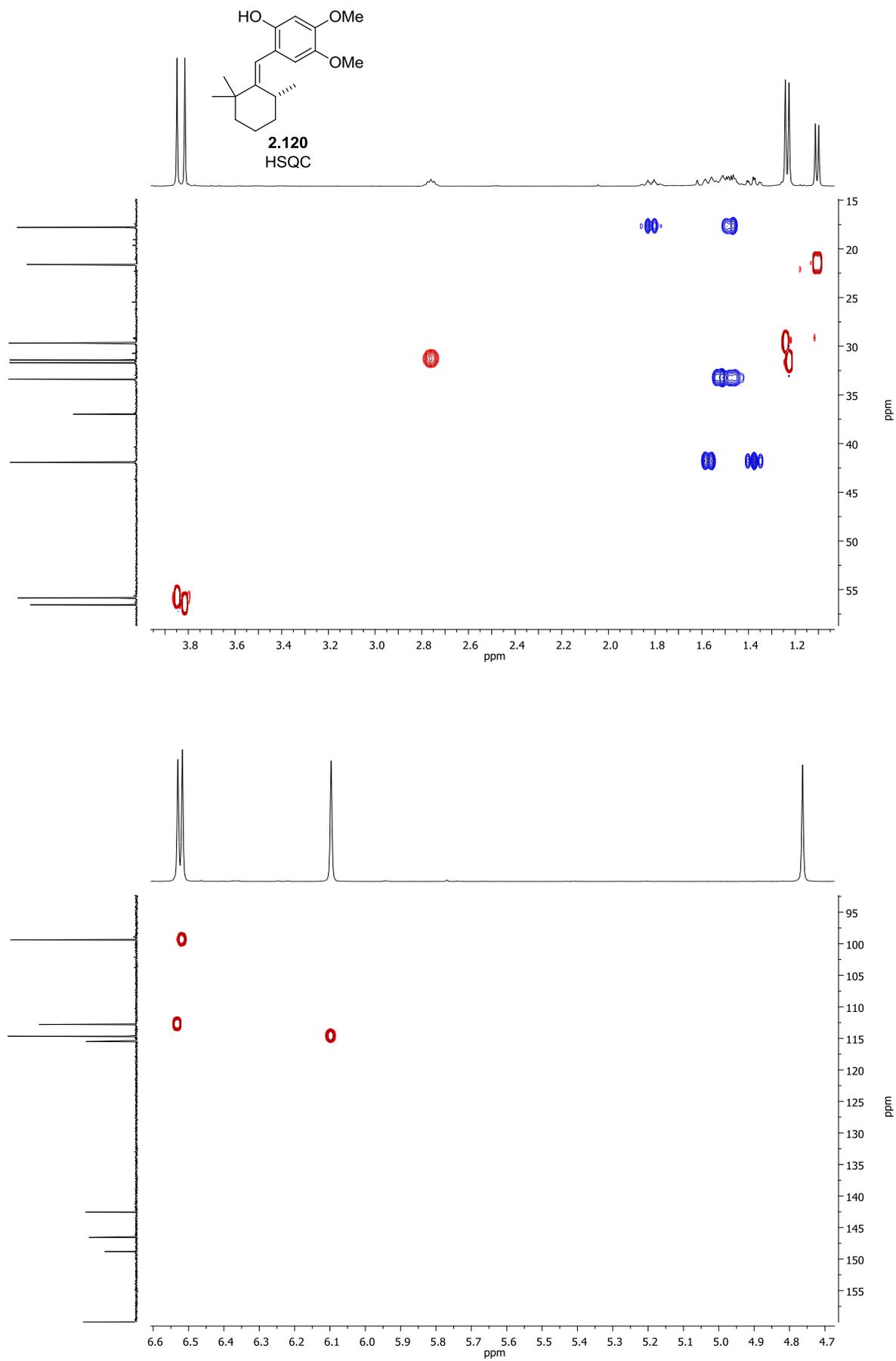


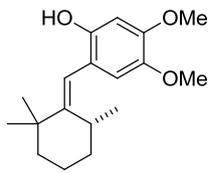




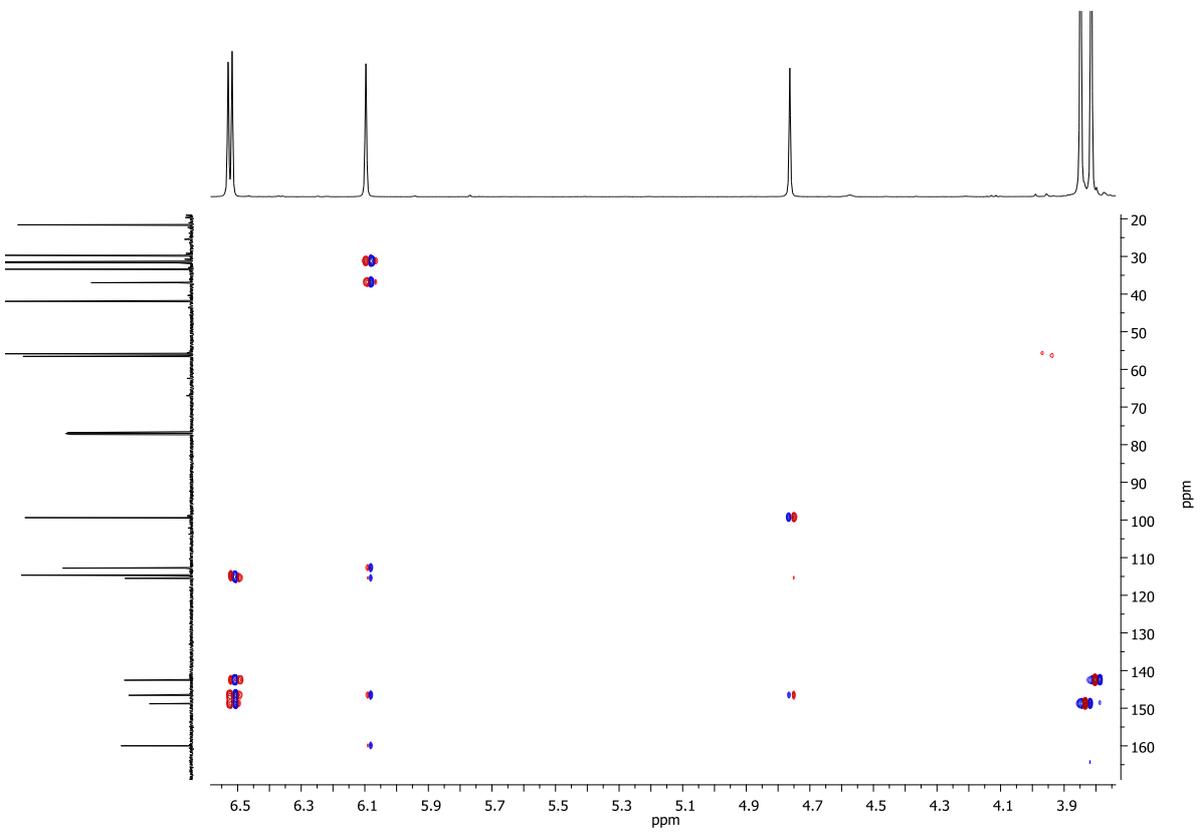
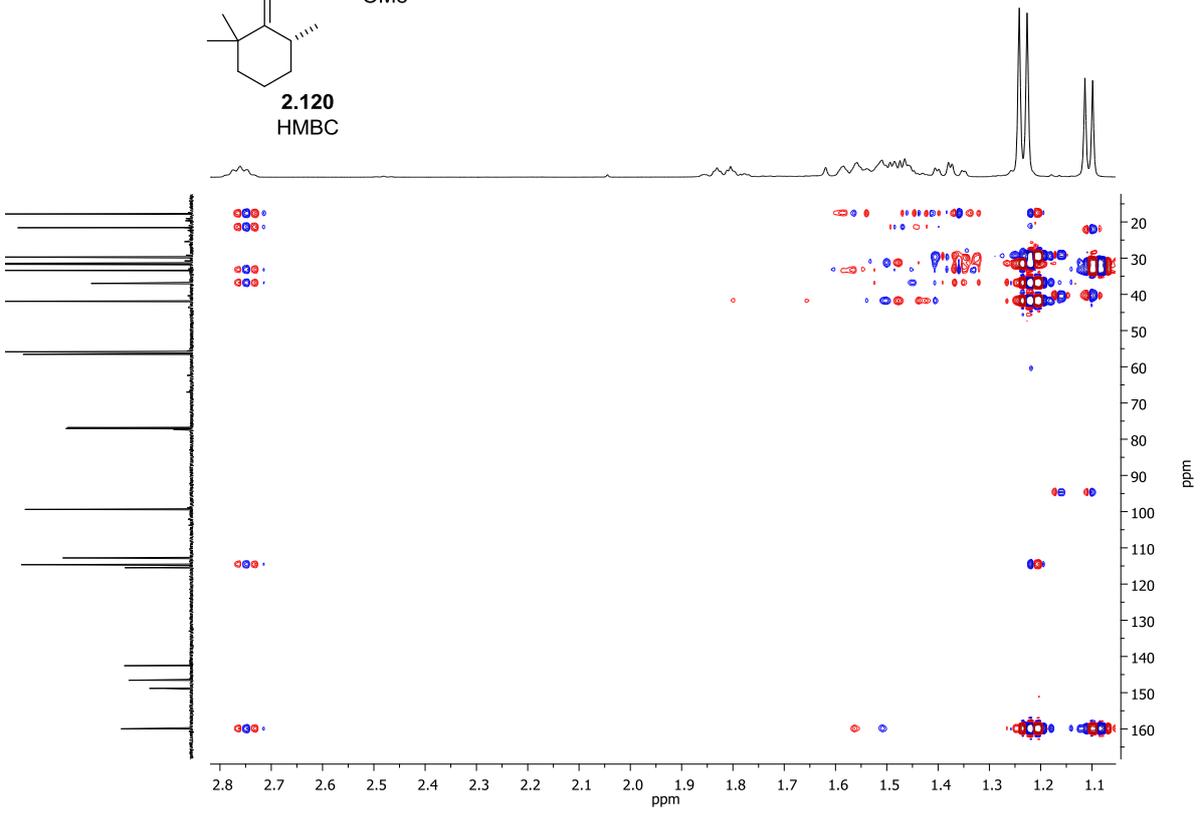


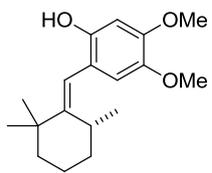




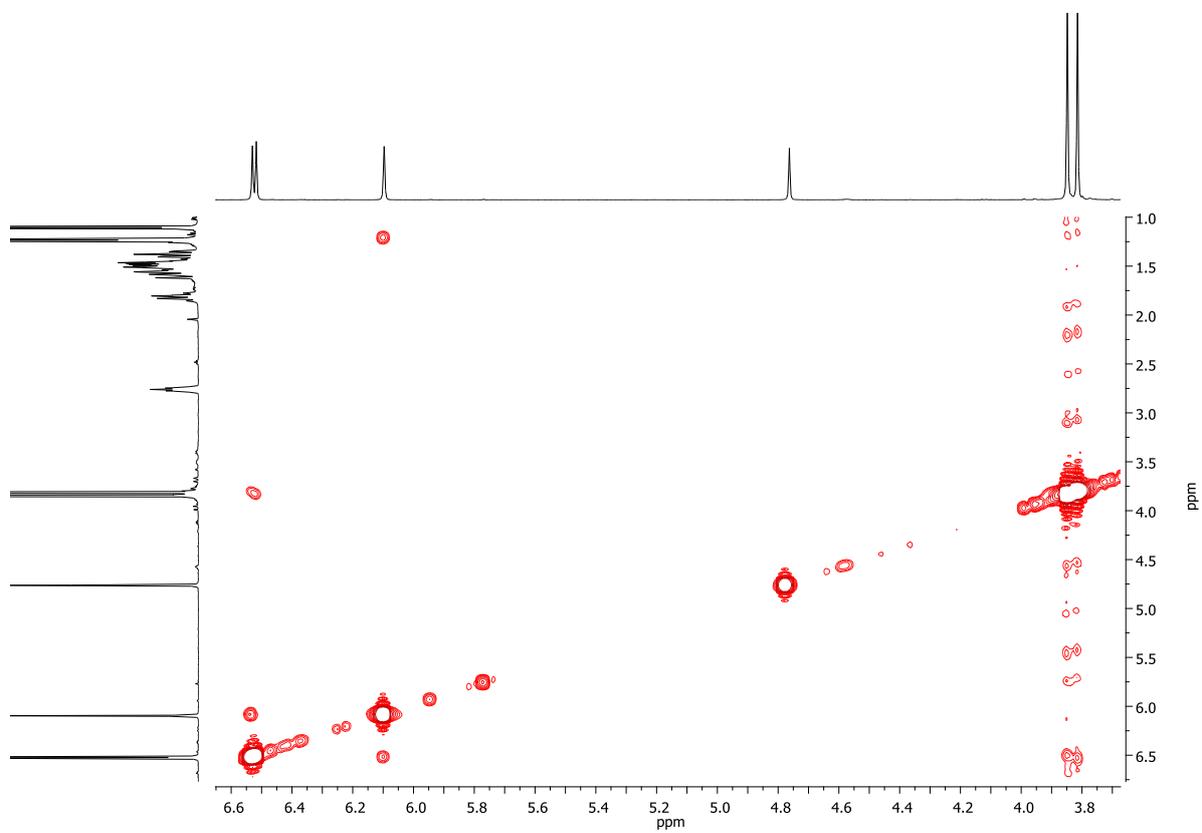
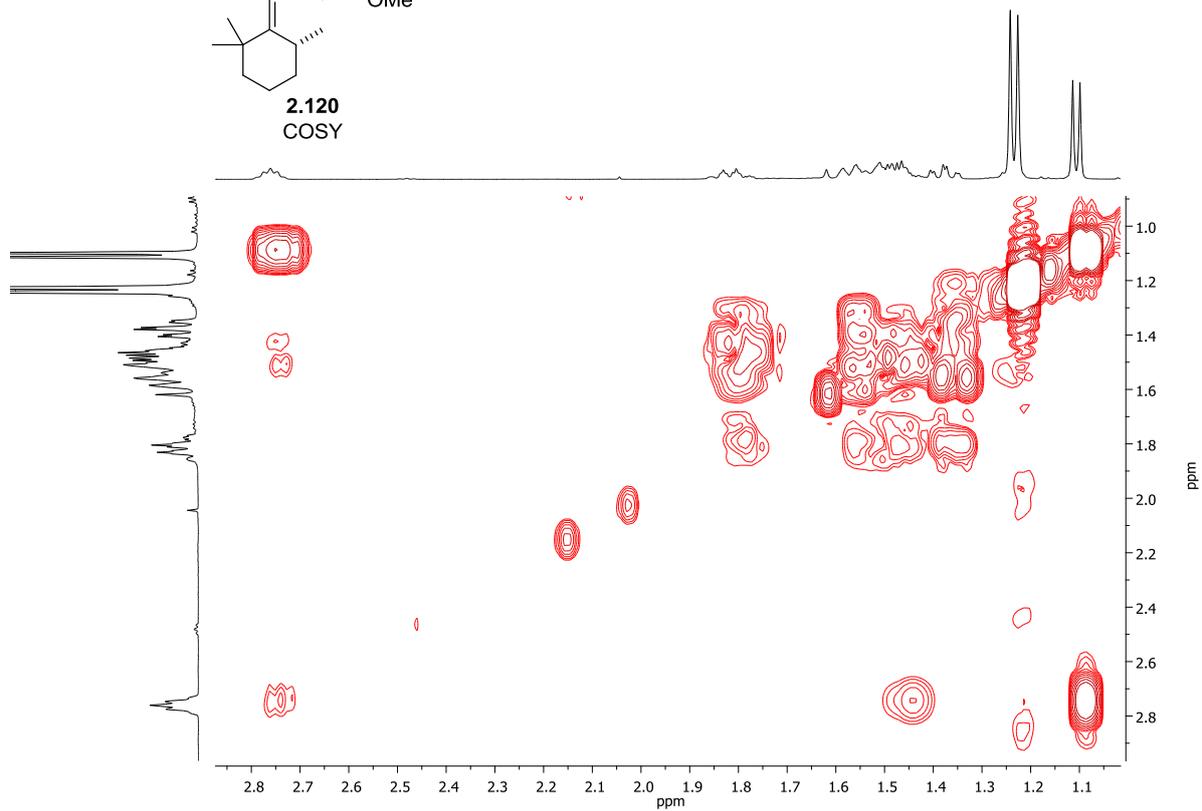


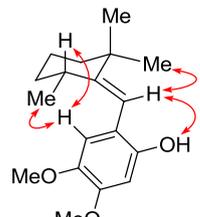
**2.120**  
HMBC



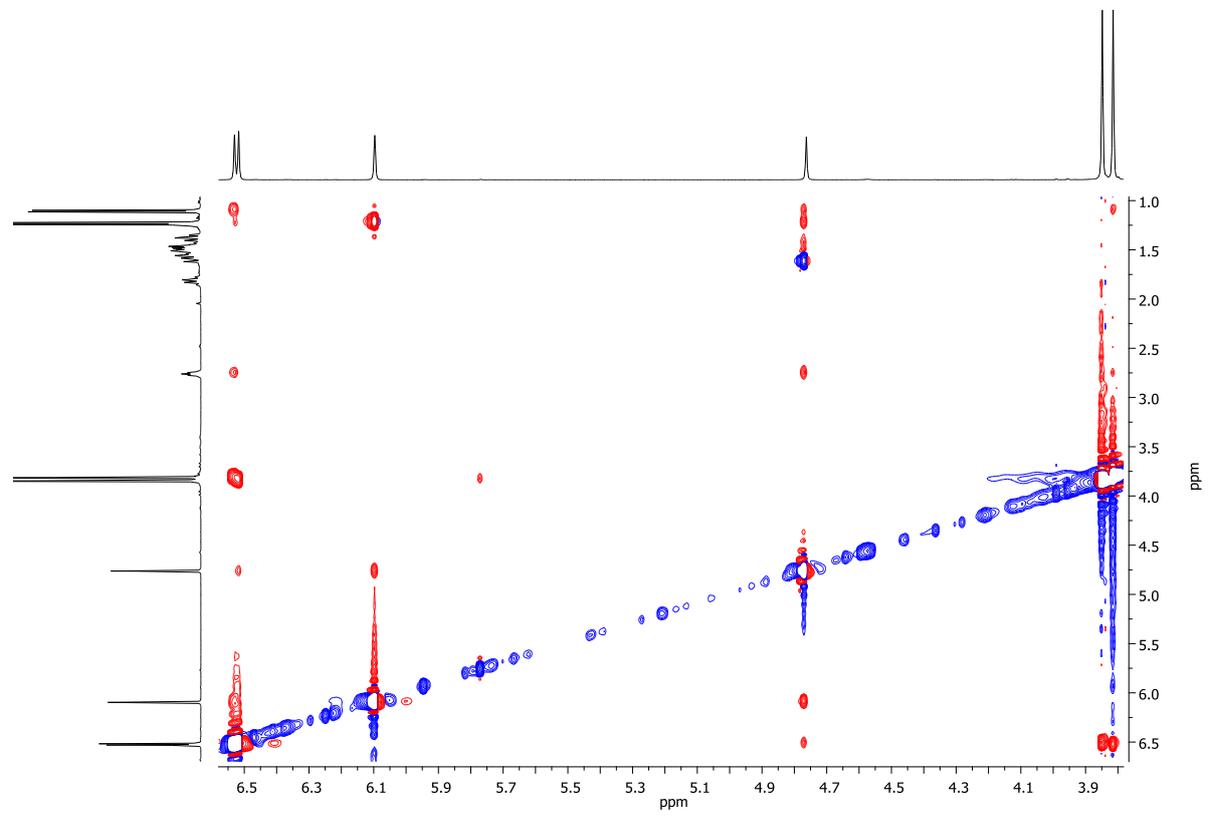
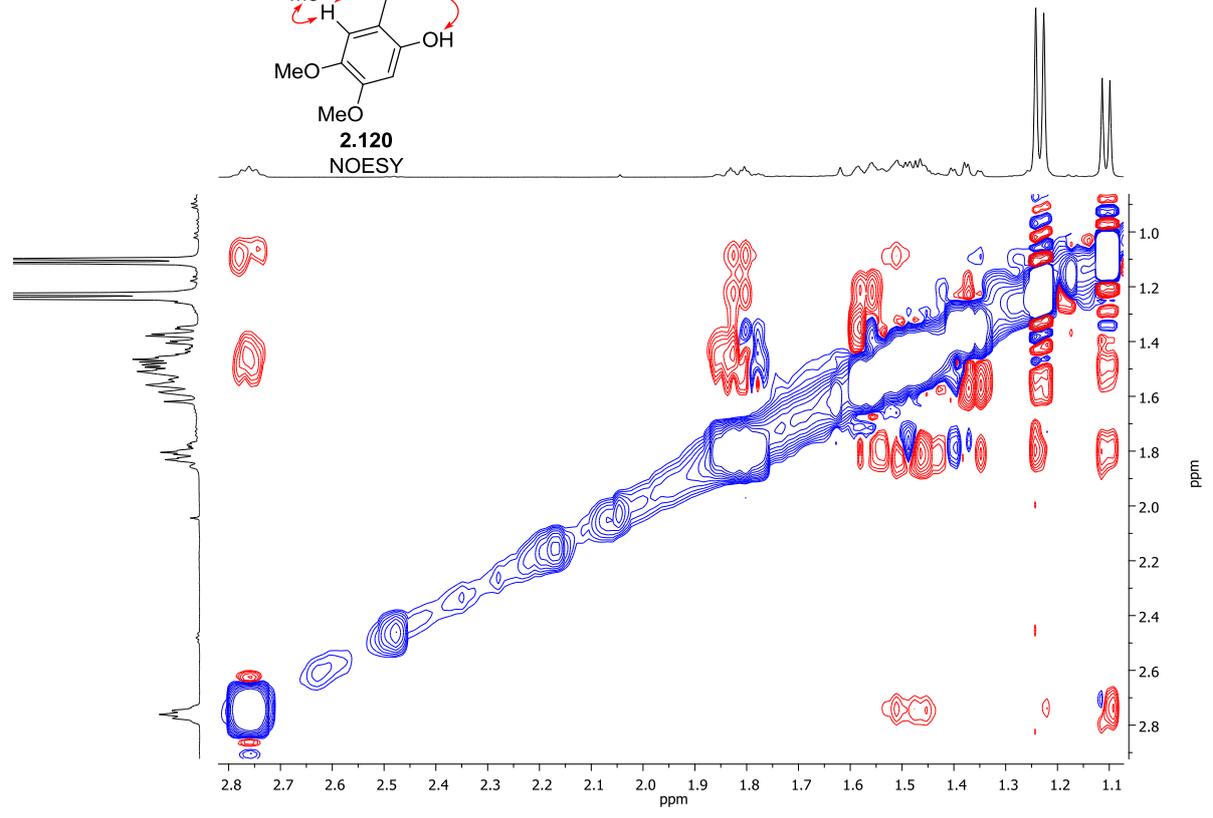


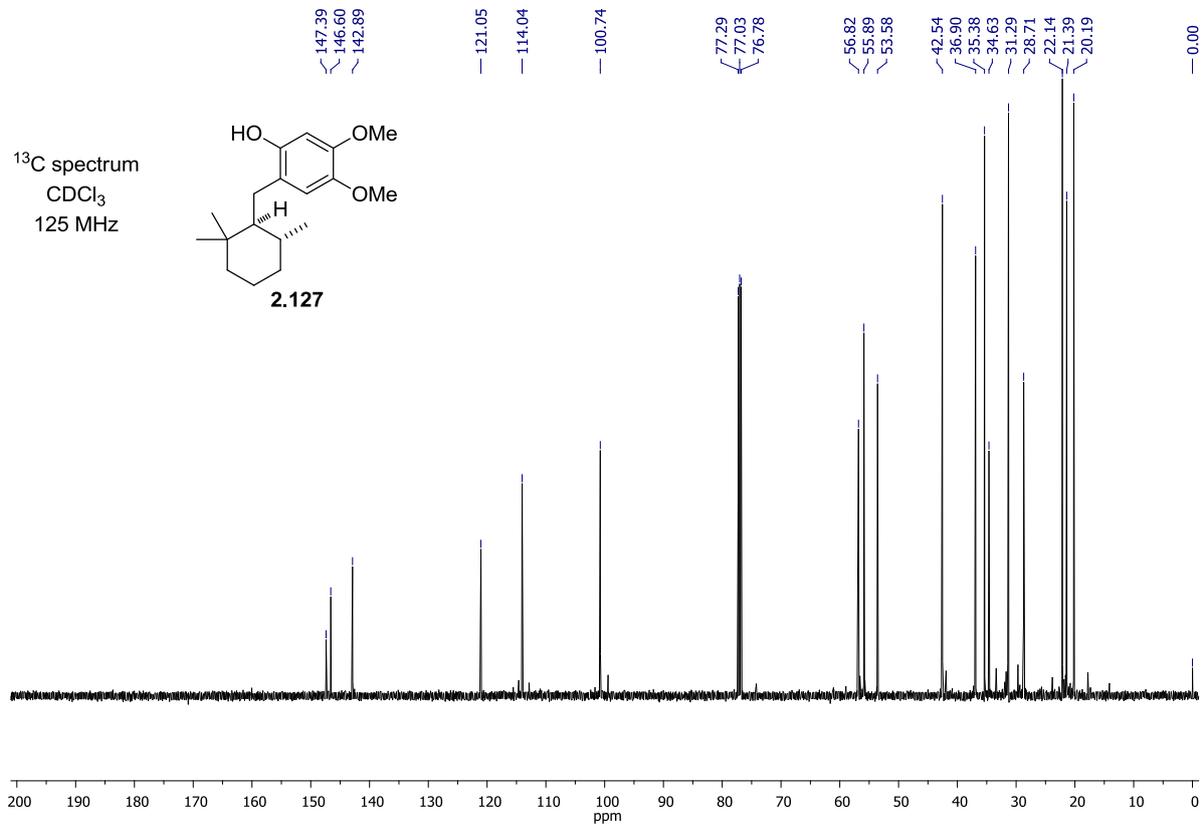
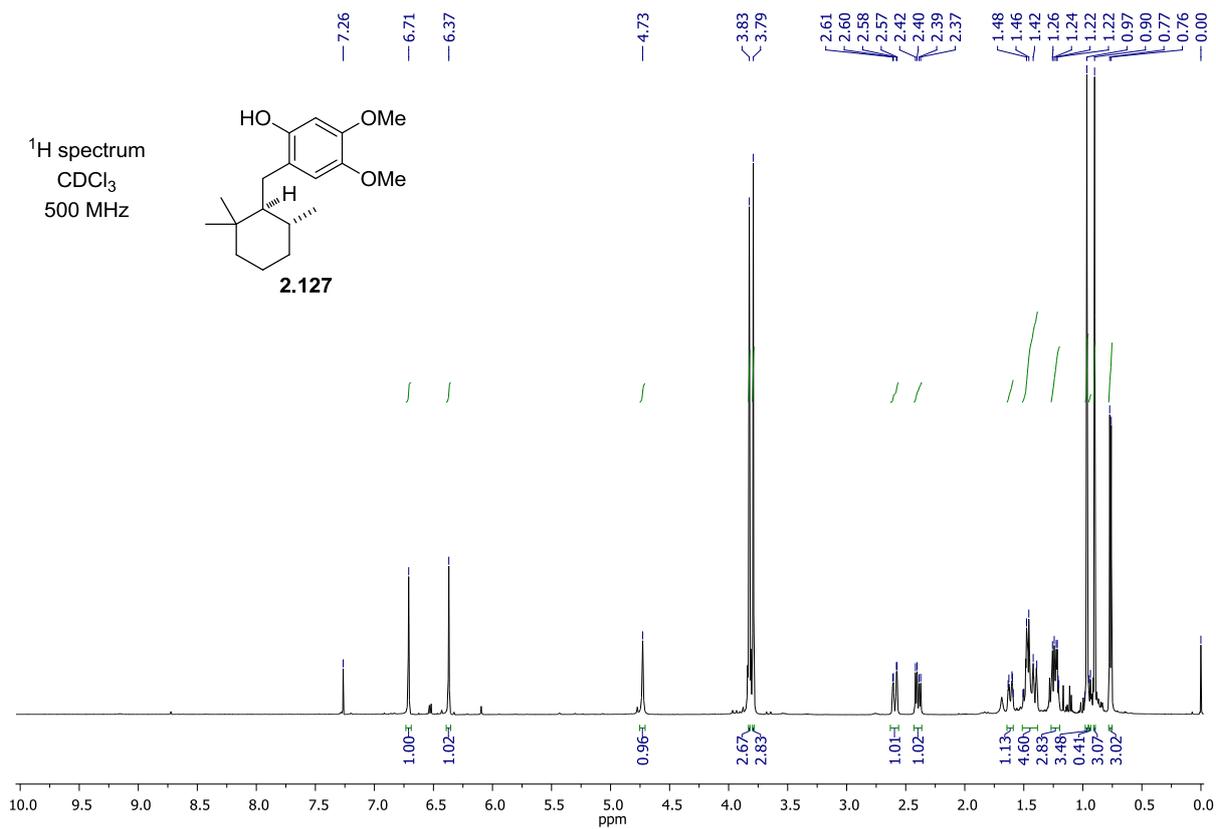
**2.120**  
COSY

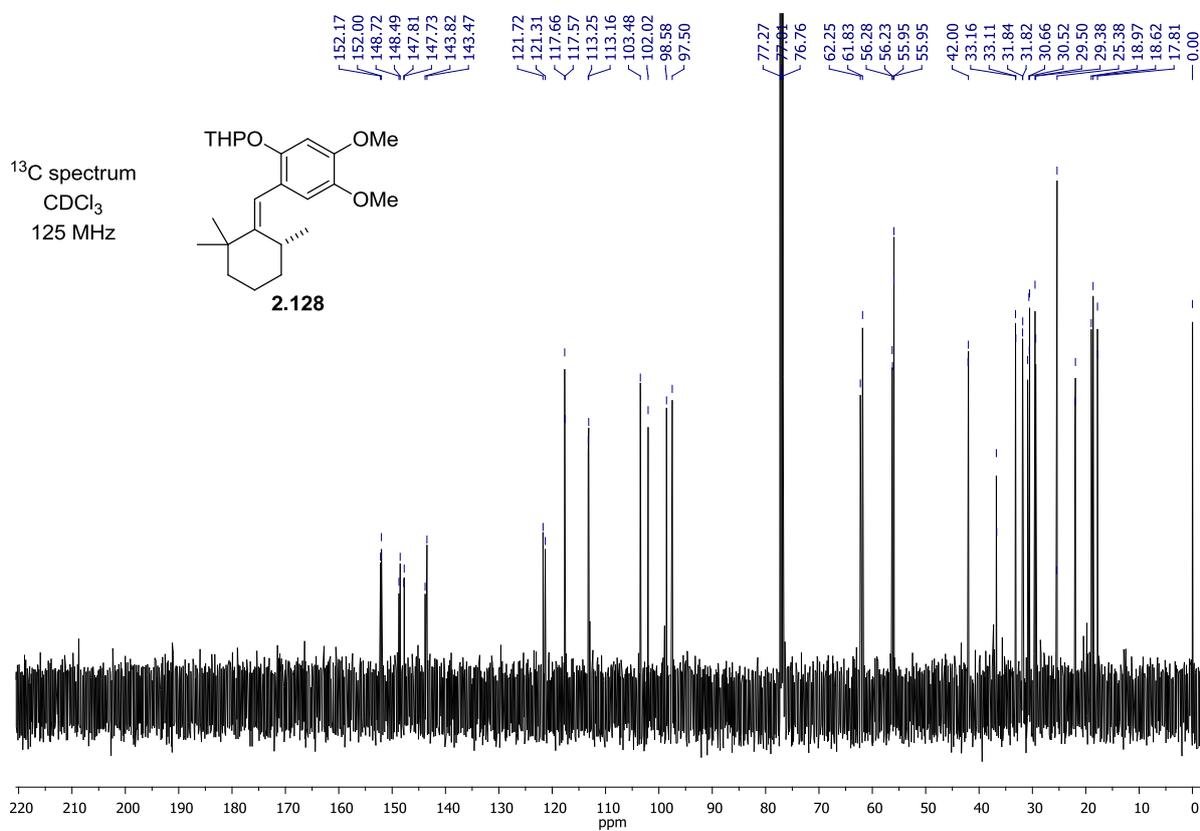
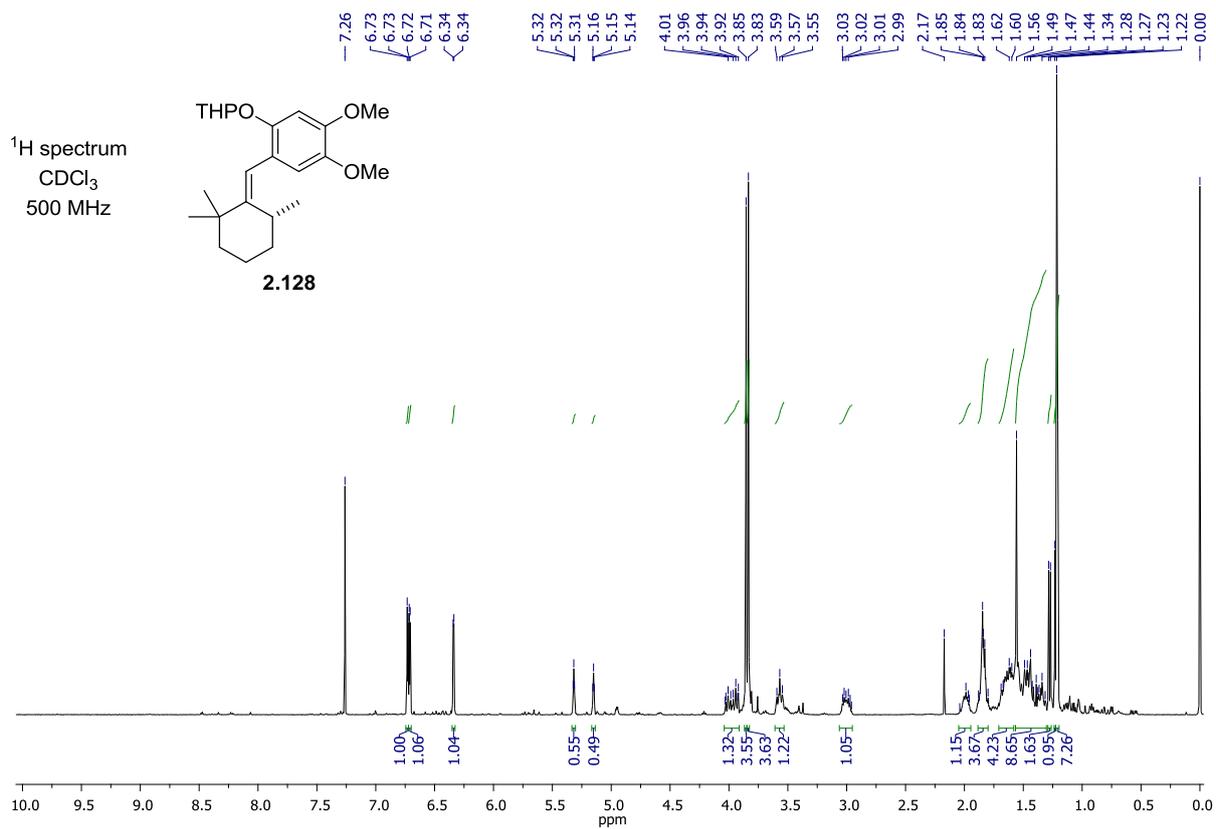


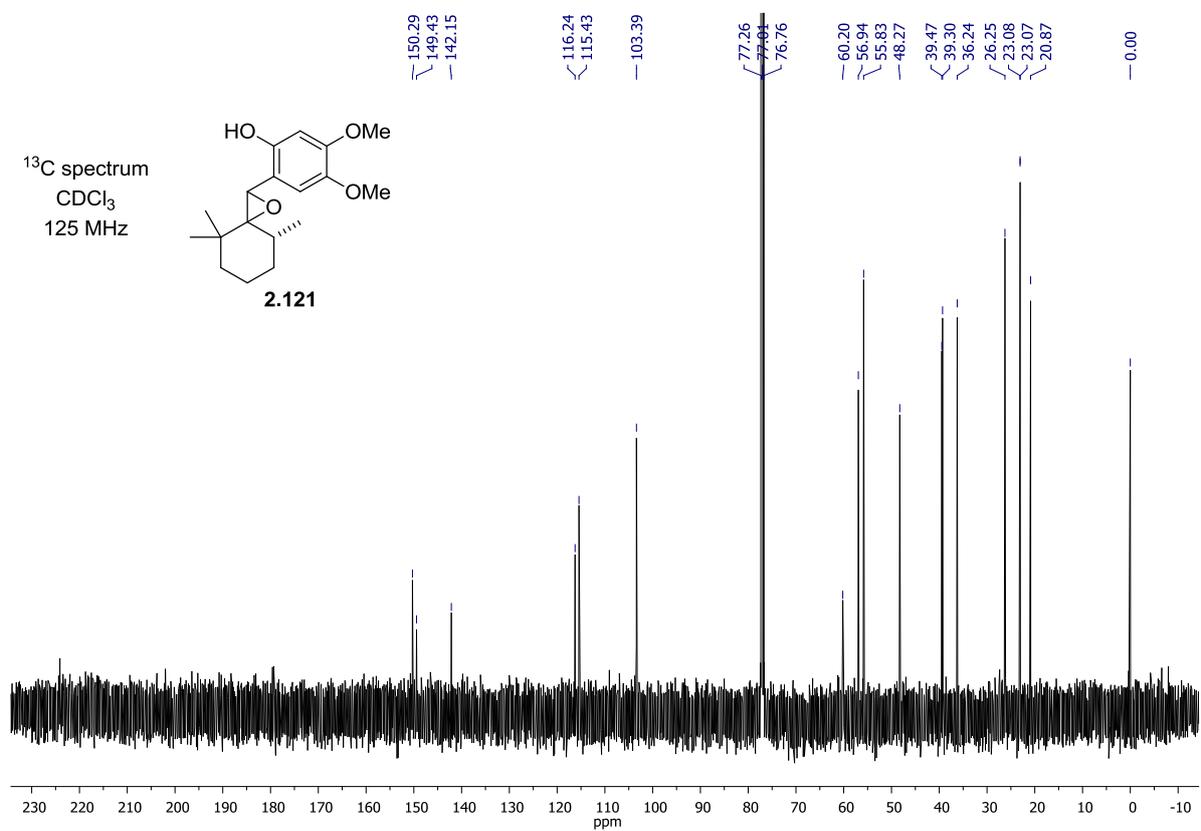
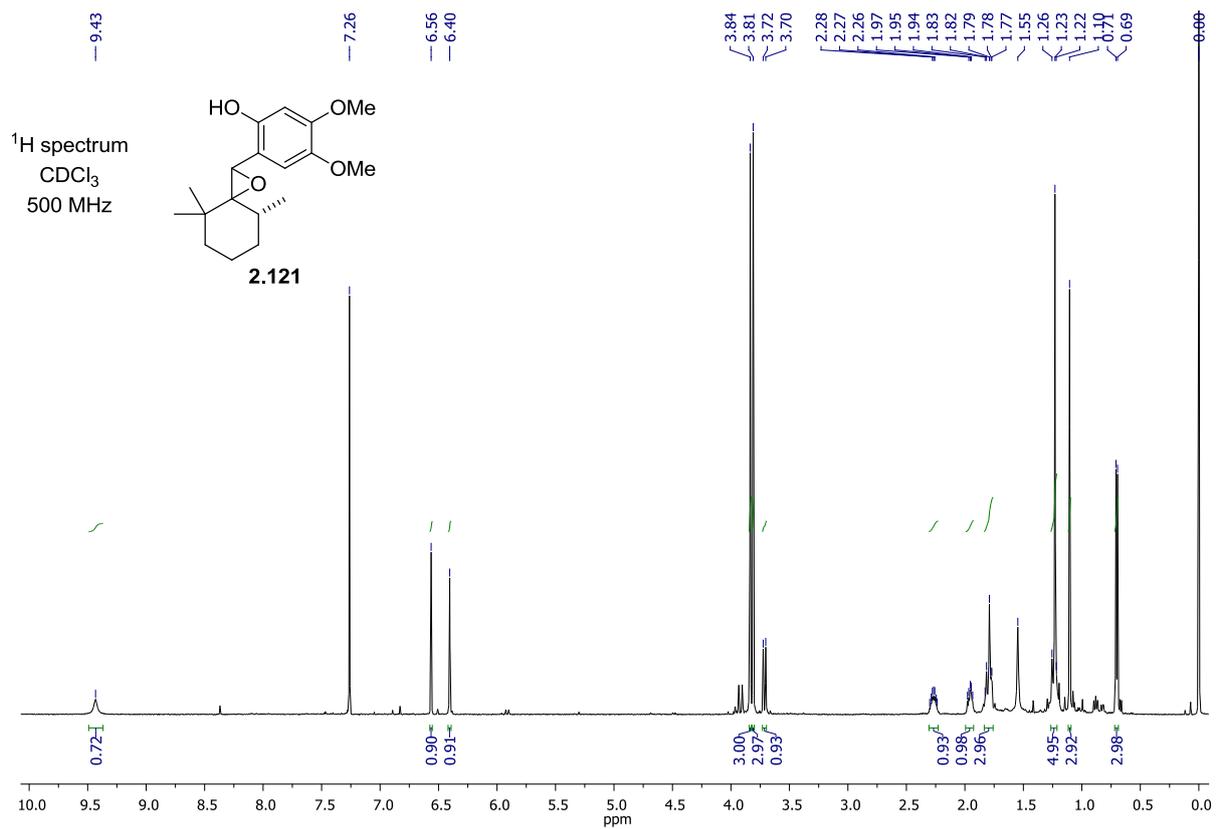


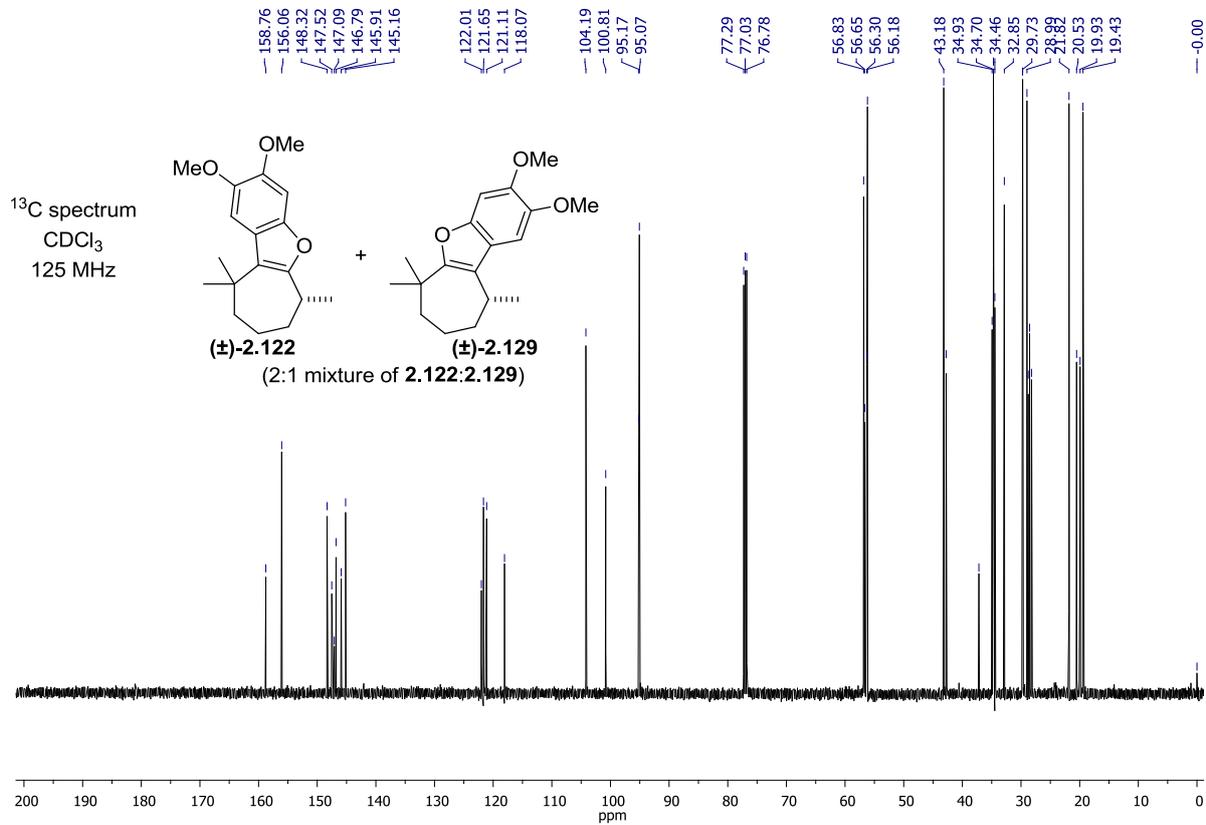
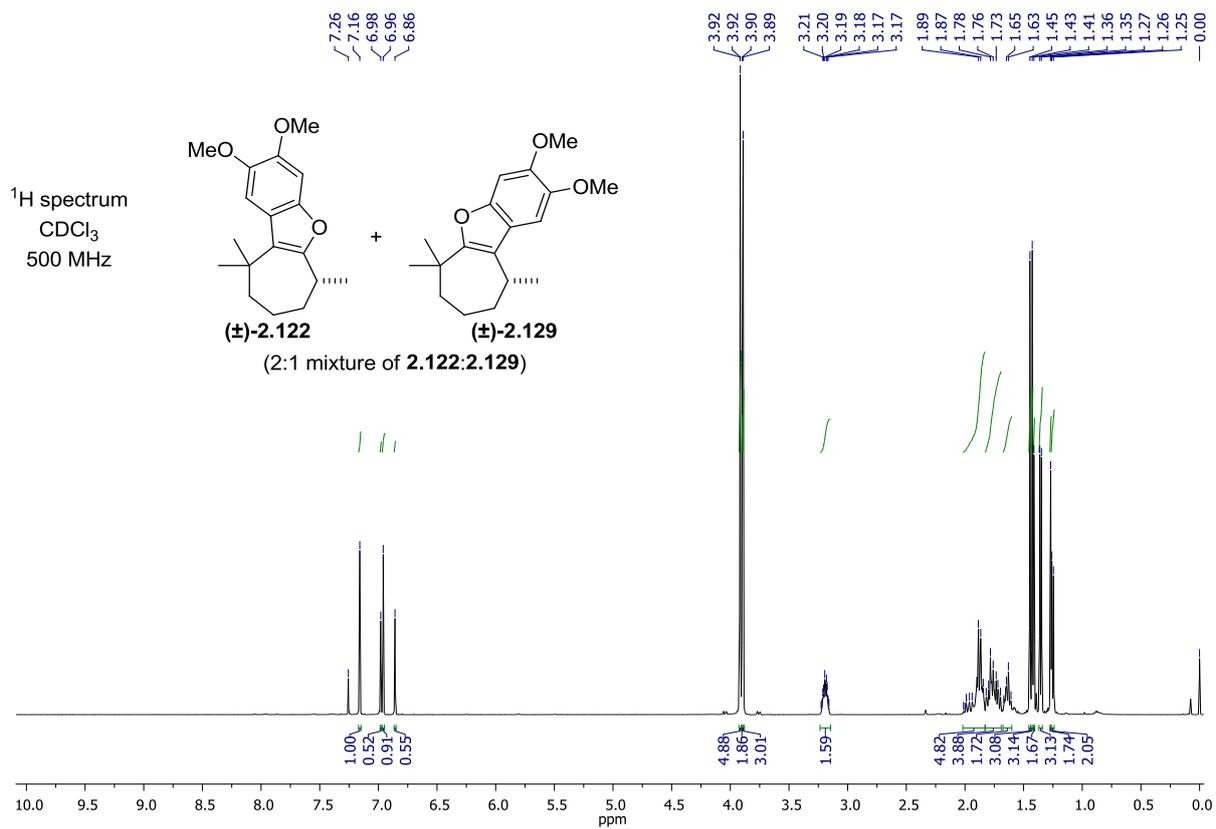
2.120  
NOESY

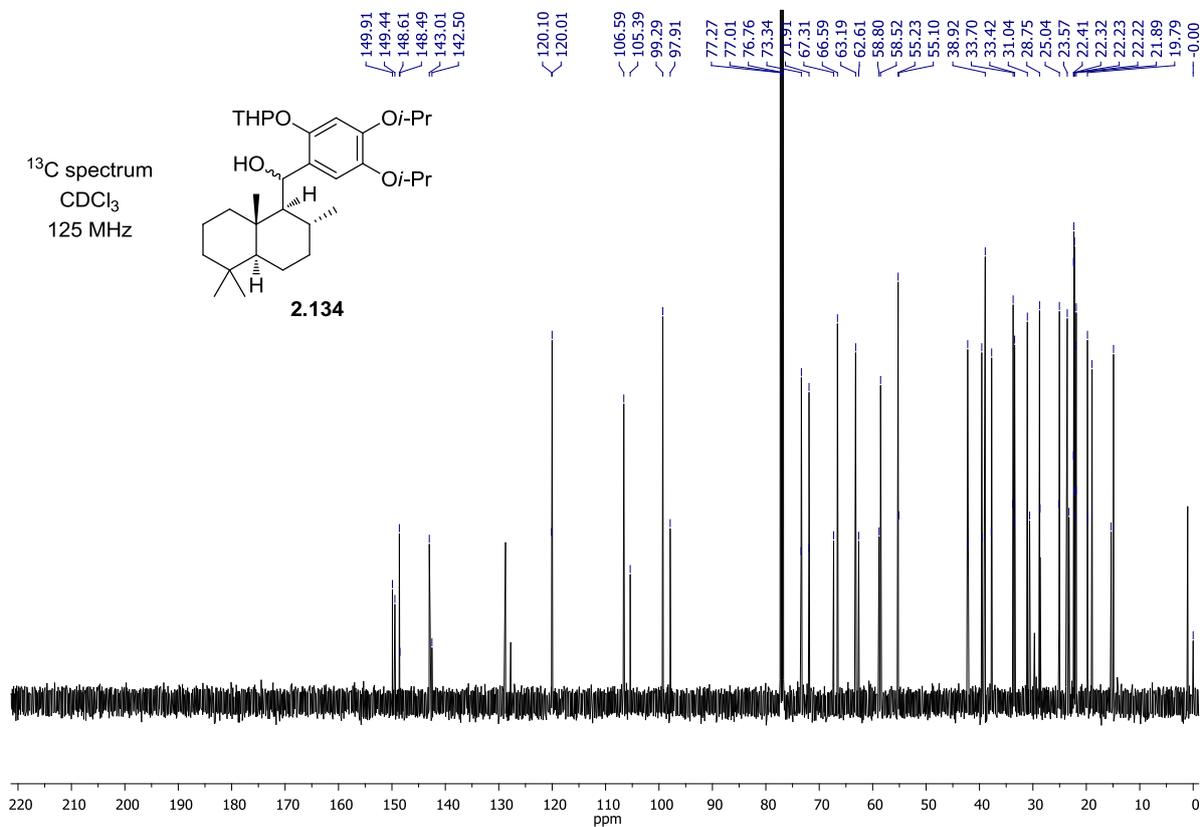
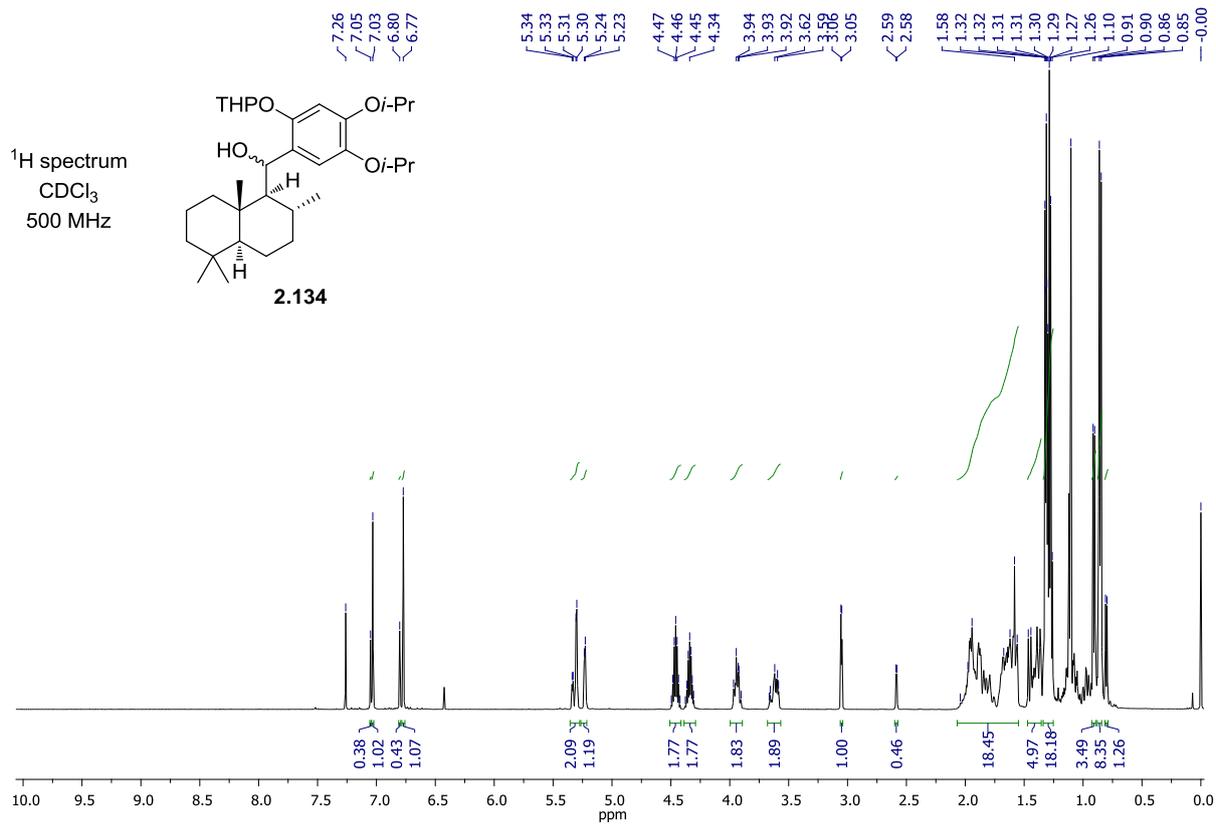


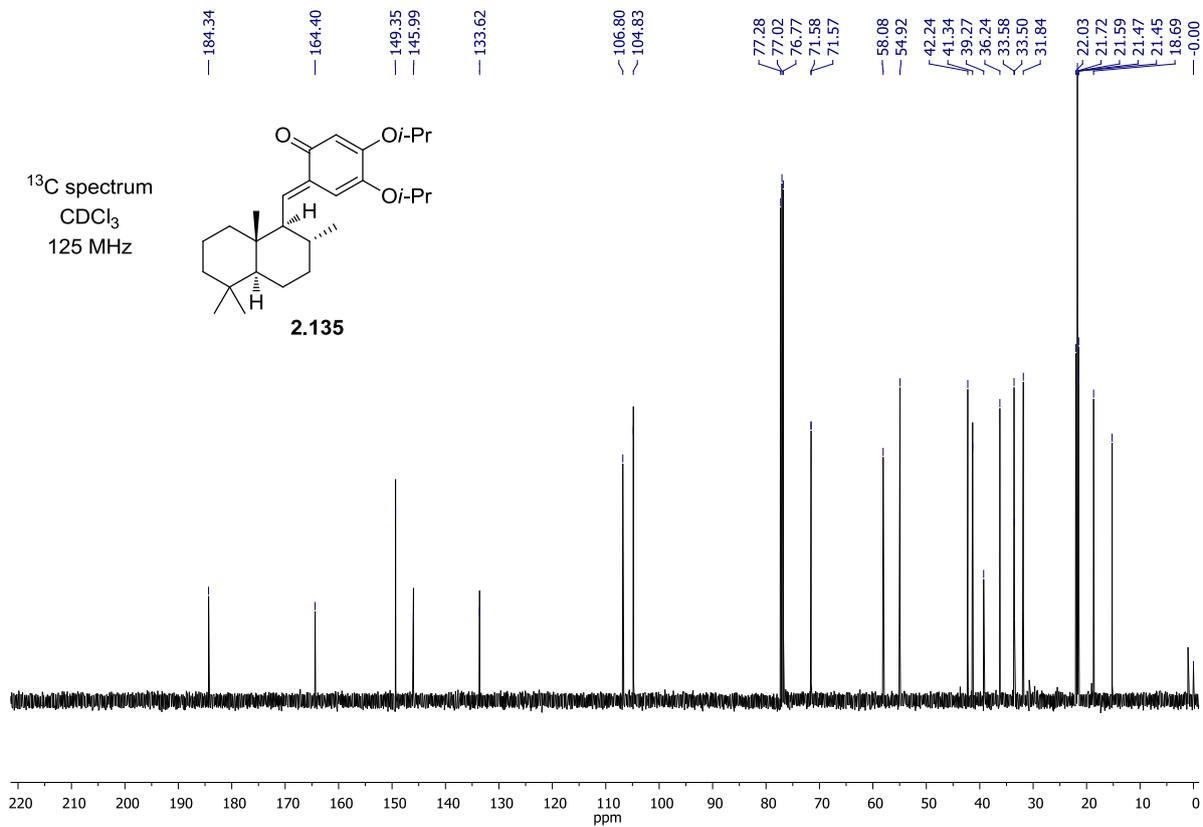
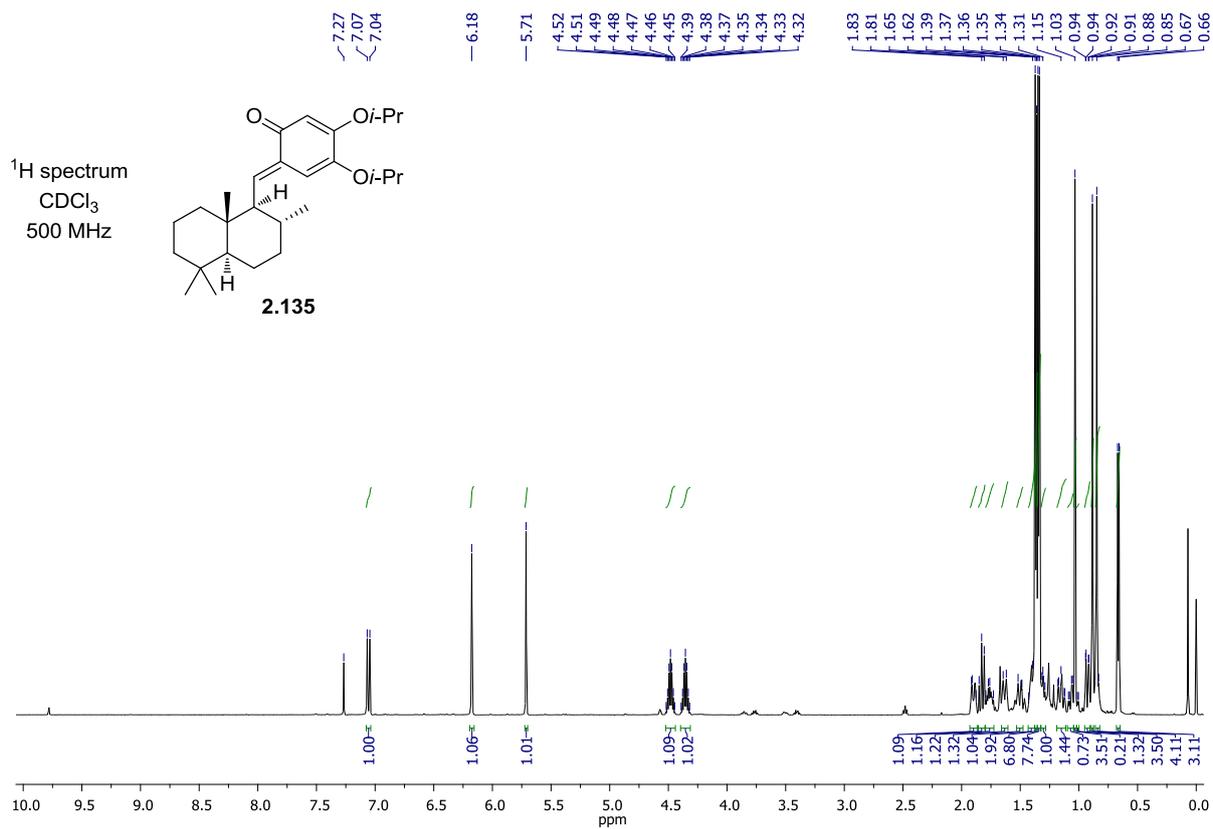


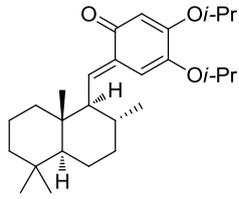




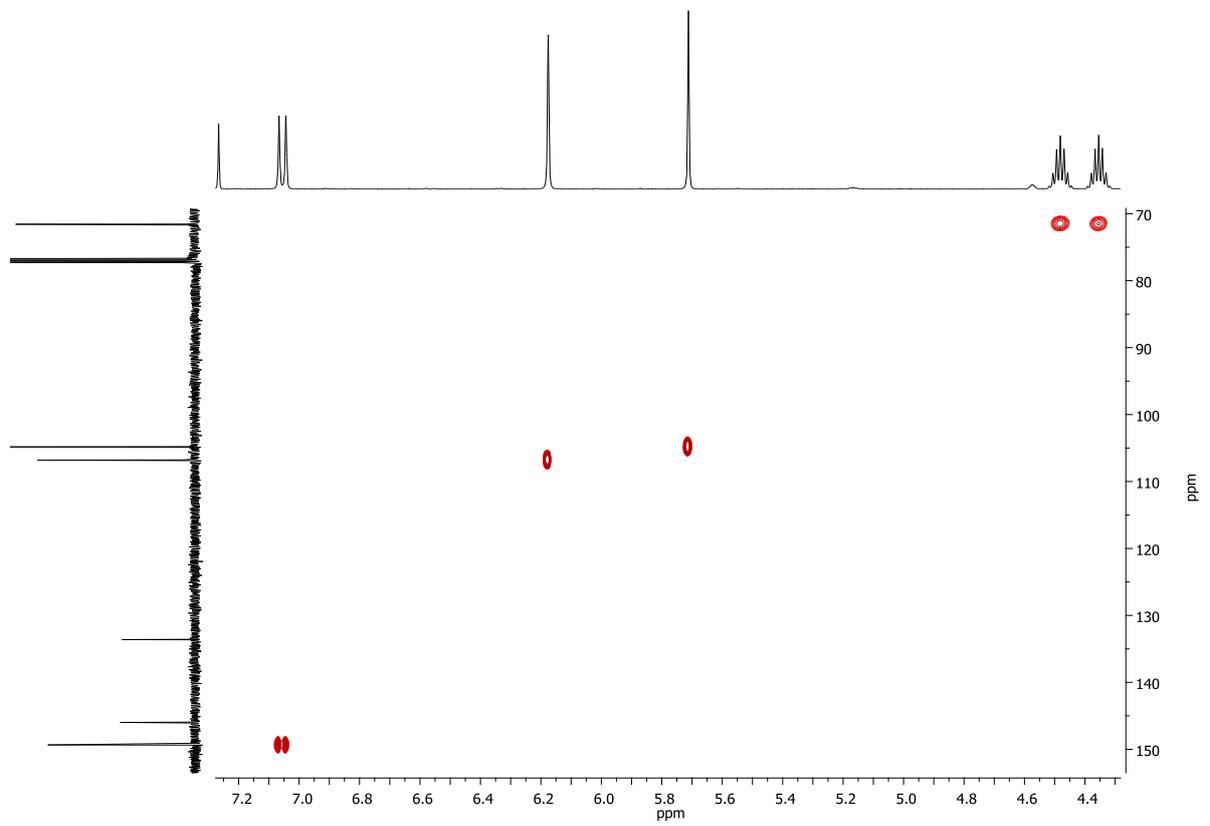
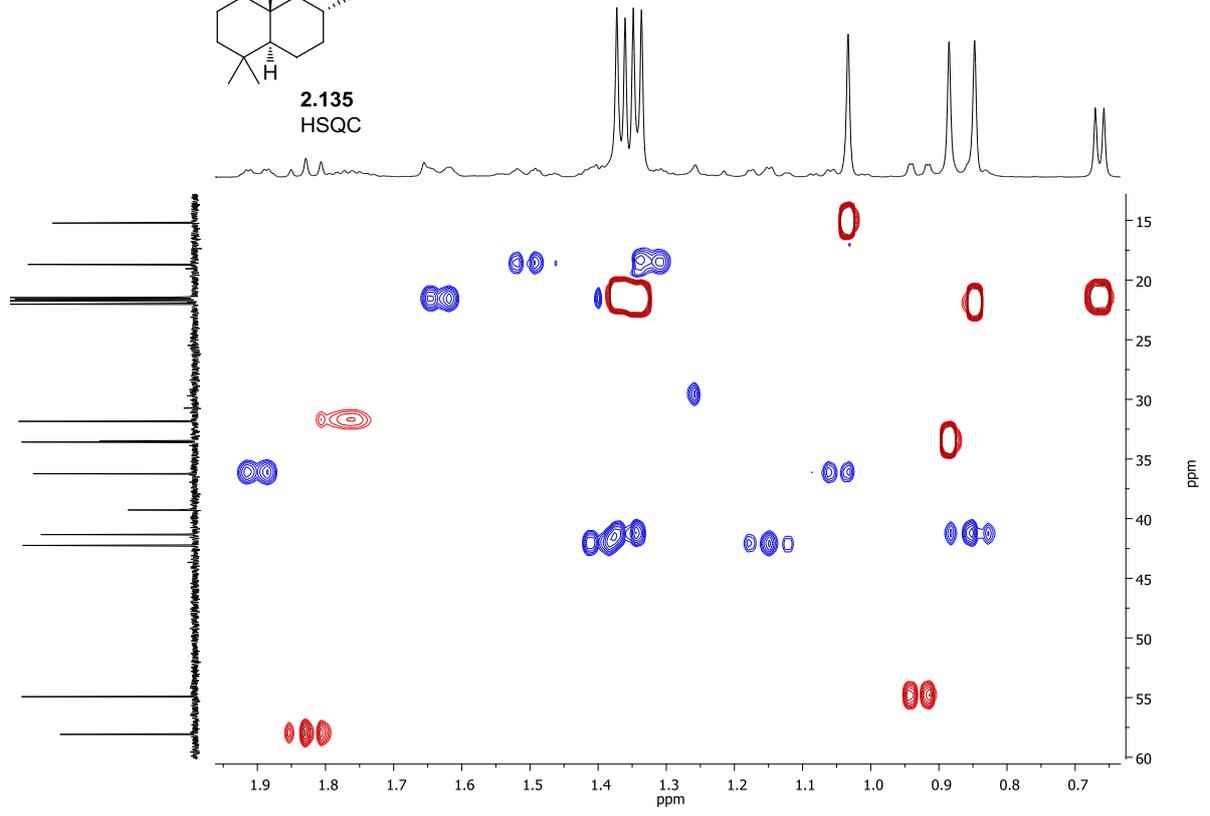


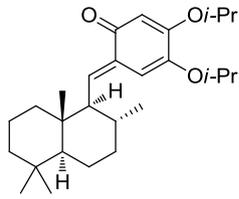




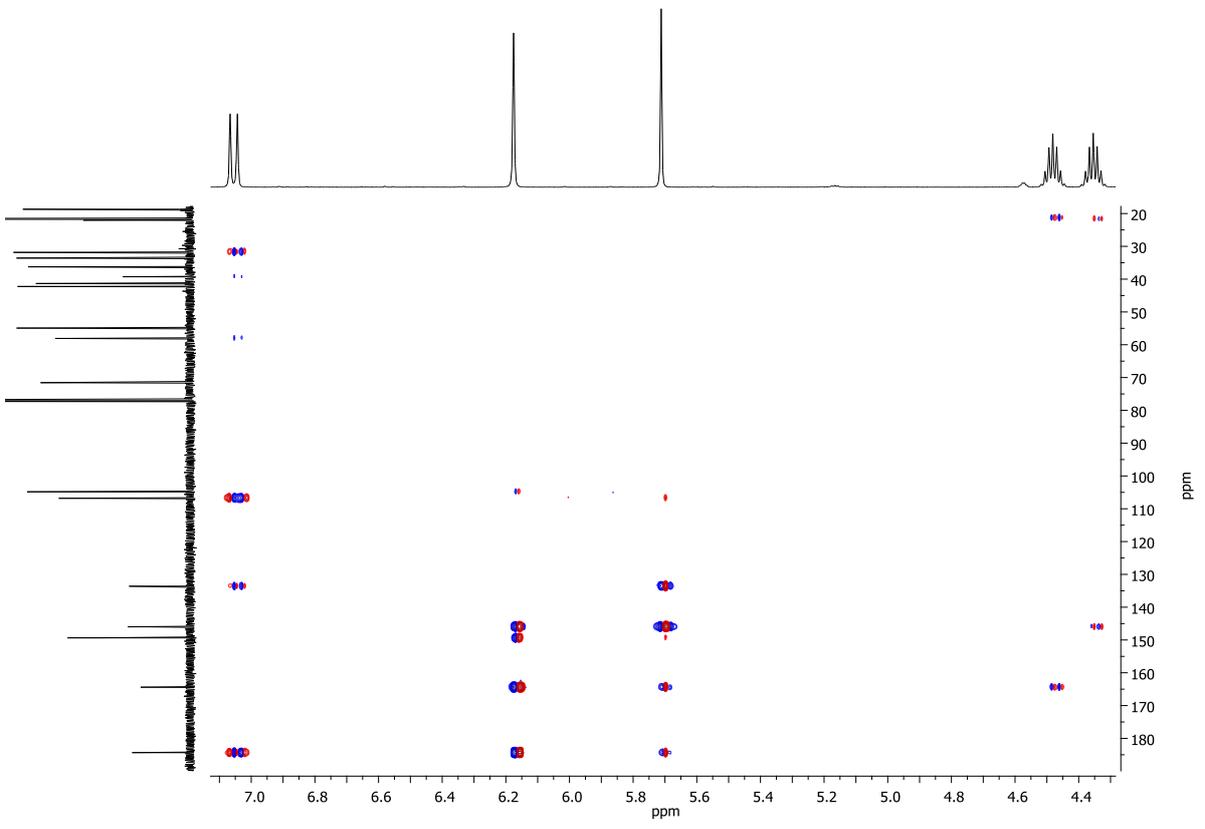
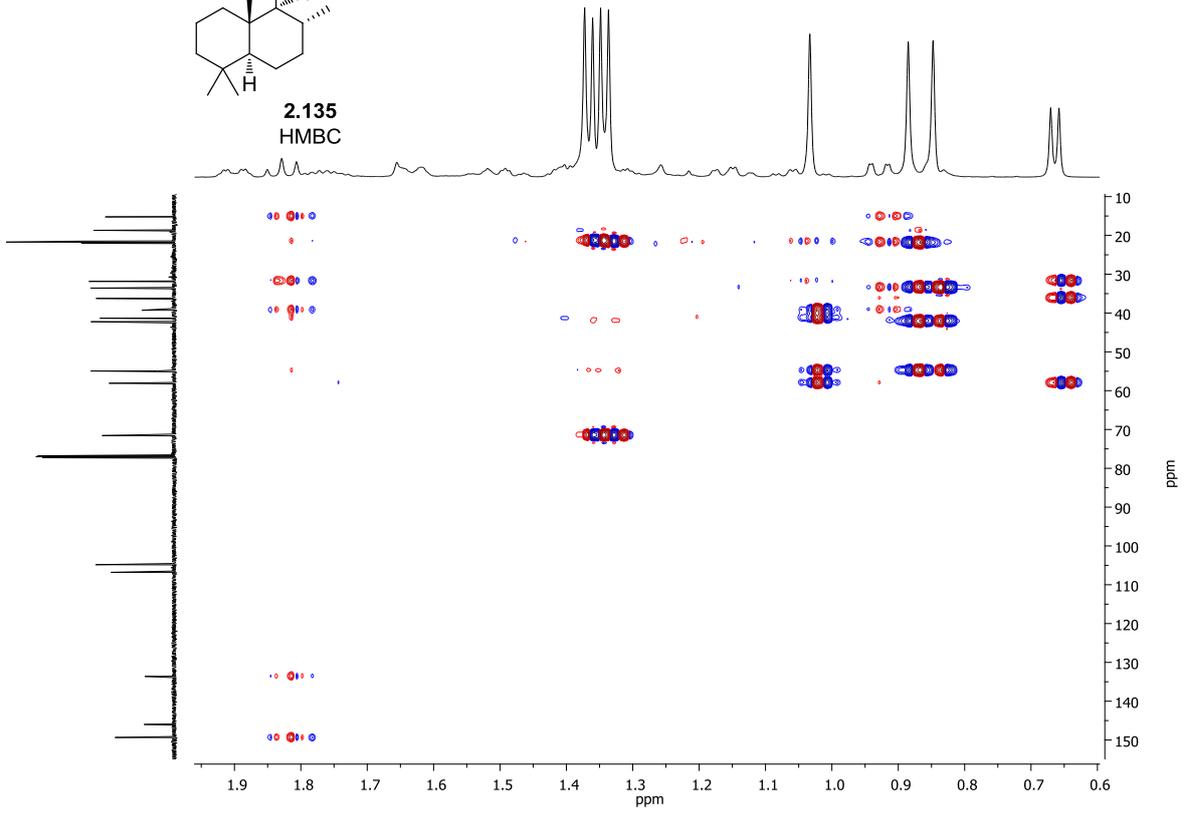


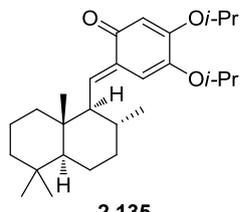
2.135  
HSQC



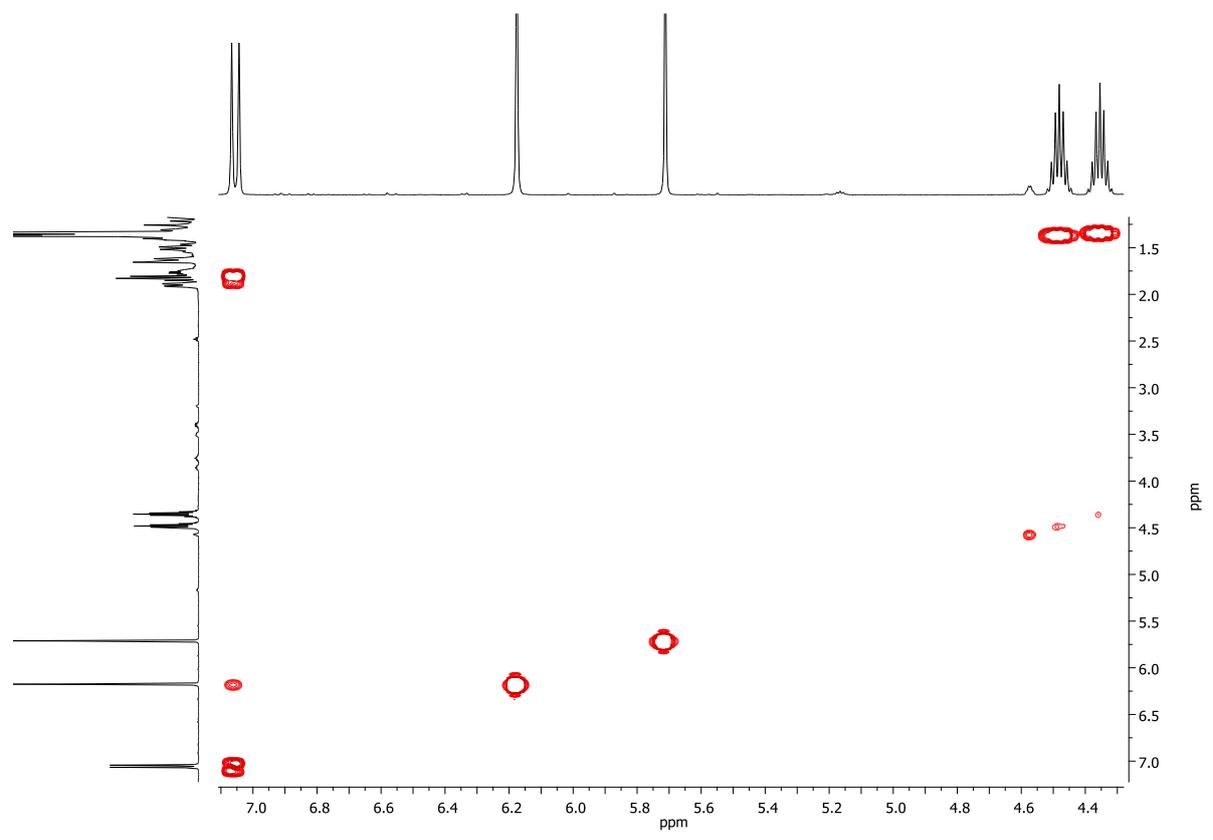
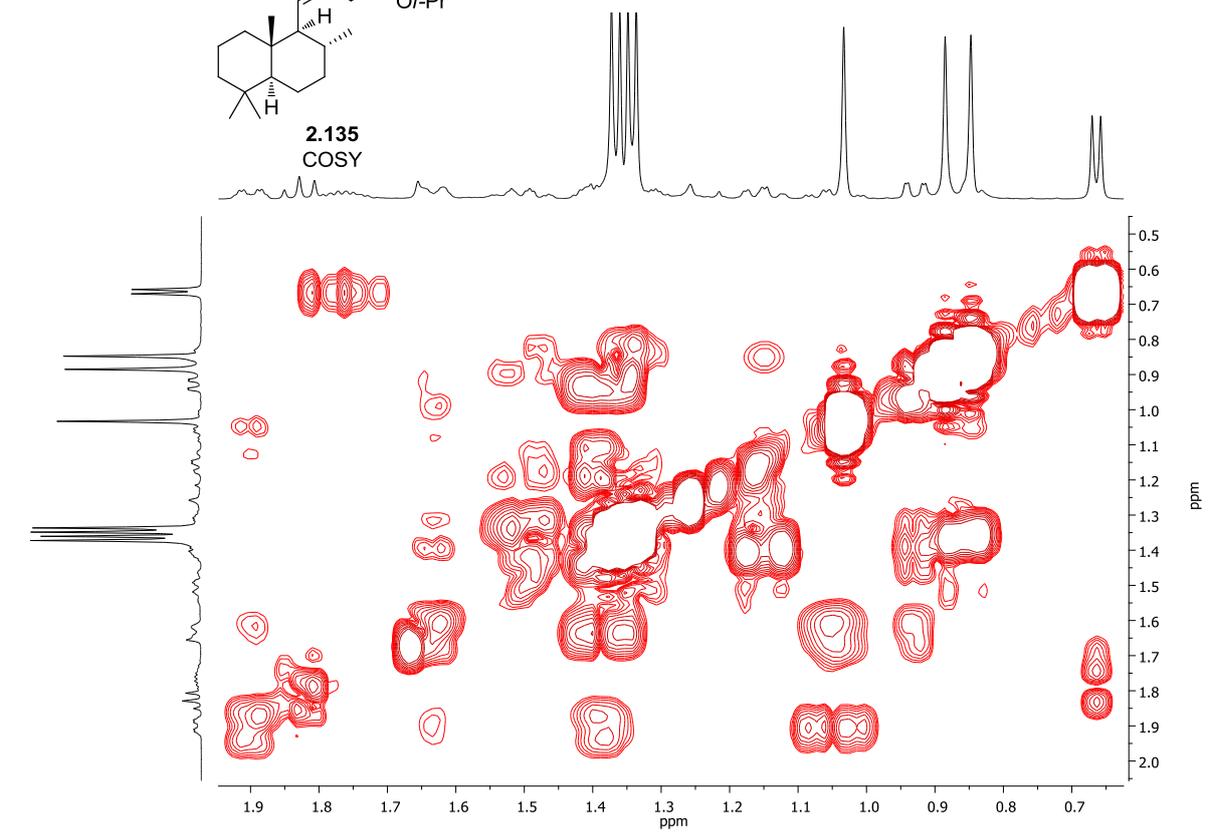


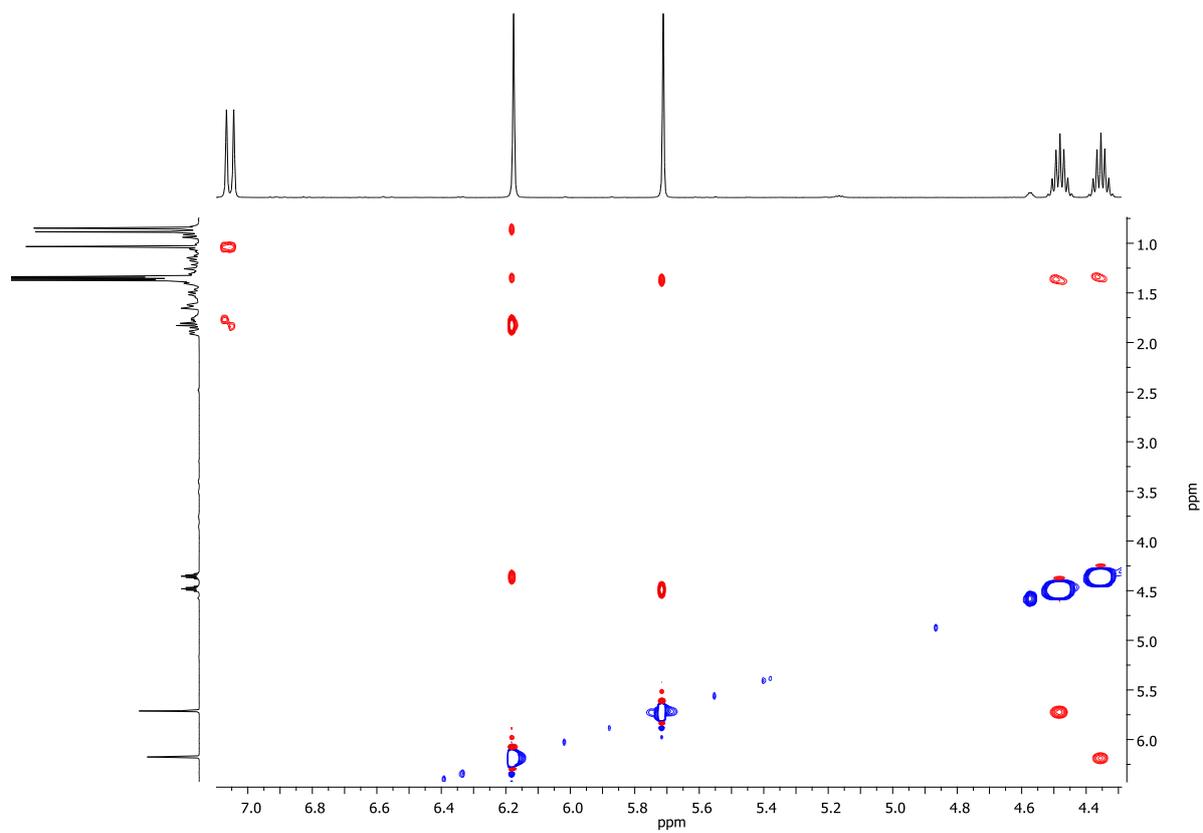
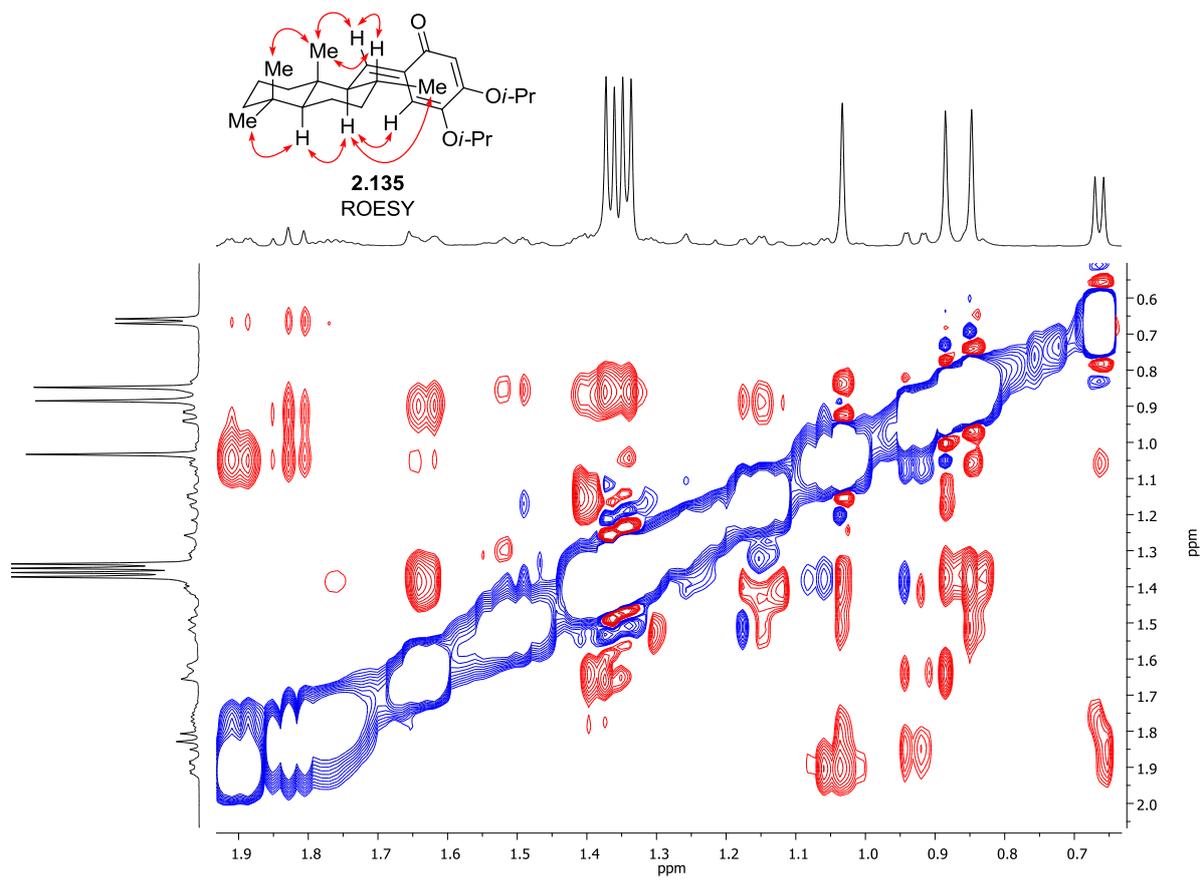
2.135  
HMBC





2.135  
COSY





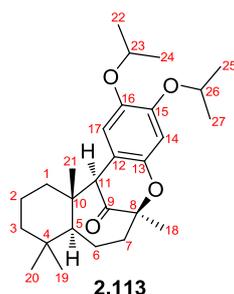


Table 2.2: <sup>1</sup>H NMR assignment of cycloheptanone **2.113**.

| Assignment                          | 500 MHz, CDCl <sub>3</sub>        |
|-------------------------------------|-----------------------------------|
| <b>H-14</b>                         | 6.50 (s, 1H)                      |
| <b>H-17</b>                         | 6.48 (s, 1H)                      |
| <b>H-23*</b>                        | 4.49 – 4.42 (m, 1H)               |
| <b>H-26*</b>                        | 4.33 – 4.26 (m, 1H)               |
| <b>H-11</b>                         | 3.20 (s, 1H)                      |
| <b>H-7a</b>                         | 1.96 (dt, $J = 13.5, 3.5$ Hz, 1H) |
| <b>H-1a</b>                         | 1.82 – 1.80 (m, 1H)               |
| <b>H-6a</b>                         | 1.73 – 1.70 (m, 1H)               |
| <b>H-1b, H-2a, H-2b, H-6b, H-7b</b> | 1.61 – 1.41 (m, 5H)               |
| <b>H-3a</b>                         | 1.41 – 1.37 (overlapped m, 1H)    |
| <b>H-18</b>                         | 1.38 (s, 3H)                      |
| <b>Me-22*</b>                       | 1.34 (d, $J = 6.0$ Hz, 3H)        |
| <b>Me-24*</b>                       | 1.33 (d, $J = 6.0$ Hz, 3H)        |
| <b>Me-25*</b>                       | 1.28 (d, $J = 6.0$ Hz, 3H)        |
| <b>Me-27*</b>                       | 1.27 (d, $J = 6.0$ Hz, 3H)        |
| <b>H-3b</b>                         | 1.24 – 1.19 (m, 1H)               |
| <b>H-5</b>                          | 1.06 (d, $J = 9.0$ Hz, 1H)        |
| <b>Me-20</b>                        | 0.90 (s, 3H)                      |
| <b>Me-19</b>                        | 0.82 (s, 3H)                      |
| <b>Me-21</b>                        | 0.71 (s, 3H)                      |

\* Me-22/ Me-24 and Me-25/Me-27 signals may be interchanged.

Table 2.3:  $^{13}\text{C}$  NMR assignment of cycloheptanone **2.113**.

| Assignment | 125 MHz, $\text{CDCl}_3$ |
|------------|--------------------------|
| C-1        | 46.7                     |
| C-2        | 19.5                     |
| C-3        | 41.5                     |
| C-4        | 35.6                     |
| C-5        | 52.0                     |
| C-6        | 21.4                     |
| C-7        | 40.5                     |
| C-8        | 85.4                     |
| C-9        | 210.6                    |
| C-10       | Not observed             |
| C-11       | 65.8                     |
| C-12       | 148.9                    |
| C-13       | 150.3                    |
| C-14       | 106.0                    |
| C-15       | 143.8                    |
| C-16       | 116.8                    |
| C-17       | 121.8                    |
| C-18       | 24.3                     |
| C-19       | 22.12                    |
| C-20       | 33.6                     |
| C-21       | 19.1                     |
| C-22*      | 22.10                    |
| C-23       | 71.5                     |
| C-24*      | 22.16                    |
| C-25*      | 22.24                    |
| C-26       | 73.6                     |
| C-27*      | 22.3                     |

\* C-22/ C-24 and C-25/C-27 signals may be interchanged.



Table 2.4: Comparison of the  $^1\text{H}$  NMR spectra of synthetic liphagal prepared by Andersen, Stoltz and this work.

| Assignment                                   | Andersen,<br>400 MHz, $\text{CDCl}_3$ | Stoltz,<br>600 MHz, $\text{CDCl}_3$        | George,<br>600 MHz, $\text{CDCl}_3$   |
|--|---------------------------------------|--|---------------------------------------|
| <b>15-OH</b>                                 | 11.24 (s)                             | 11.24 (s)                                  | 11.24 (s)                             |
| <b>H-18</b>                                  | 10.45 (s)                             | 10.45 (s)                                  | 10.44 (s)                             |
| <b>H-17</b>                                  | 7.55 (s)                              | 7.55 (s)                                   | 7.55 (s)                              |
| <b>16-OH</b>                                 | 5.32 (br s)                           | 5.30 (s)                                   | 5.32 (s)                              |
| <b>H-8</b>                                   | 3.20 (m)                              | 3.22 (sextet, $J = 7.0$ )                  | 3.21 (sextet, $J = 7.0$ )             |
| <b>H-1a</b>                                  | 2.54 (m)                              | 2.54 (m)                                   | 2.54 (m)                              |
| <b>H-7a</b>                                  | 2.17 (m)                              | 2.18 (dddd, $J = 13.1$ ,<br>6.4, 6.4, 3.5) | 2.18 (m)                              |
| <b>H-6a</b>                                  | 1.86 (m)                              | 1.87 (m)                                   | 1.87 (m)                              |
| <b>H-2a</b>                                  | –                                     | 1.71 (m)                                   | 1.71 (m)                              |
| <b>H-1b, H-2b, H-3a,<br/>H-5, H-6b, H-7b</b> | 1.8 – 1.5 (m)                         | 1.65 – 1.45 (m)                            | 1.64 – 1.45 (m)                       |
| <b>Me-21</b>                                 | 1.43 (d, $J = 7.0$ )                  | 1.43 (d, $J = 7.0$ )                       | 1.43 (d, $J = 7.0$ )                  |
| <b>Me-22</b>                                 | 1.34 (s)                              | 1.35 (s)                                   | 1.35 (s)                              |
| <b>H-3b</b>                                  | 1.25 (m)                              | 1.25 (ddd, $J = 13.3$ ,<br>13.3, 3.1)      | 1.25 (ddd, $J = 13.0$ ,<br>13.0, 3.0) |
| <b>Me-19</b>                                 | 0.98 (s)                              | 0.98 (s)                                   | 0.98 (s)                              |
| <b>Me-20</b>                                 | 0.95 (s)                              | 0.95 (s)                                   | 0.95 (s)                              |

Note that the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of natural liphagal were only recorded in  $\text{DMSO-d}_6$ . However, Andersen and co-workers correlated the NMR spectra of their synthetic material (recorded in  $\text{CDCl}_3$  and  $\text{DMSO-d}_6$ ) with that of natural liphagal.

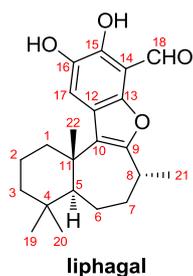


Table 2.5: Comparison of the  $^{13}\text{C}$  NMR spectra of synthetic liphagal prepared by Andersen, Stoltz and this work.

| Assignment | Andersen,<br>100 MHz, $\text{CDCl}_3$ | Stoltz,<br>150 MHz, $\text{CDCl}_3$ | George,<br>150 MHz, $\text{CDCl}_3$ |
|------------|---------------------------------------|-------------------------------------|-------------------------------------|
| C-1        | 40.4                                  | 40.5                                | 40.5                                |
| C-2        | 18.9                                  | 19.0                                | 19.0                                |
| C-3        | 42.1                                  | 42.1                                | 42.1                                |
| C-4        | 35.0                                  | 35.1                                | 35.0                                |
| C-5        | 53.9                                  | 54.0                                | 53.9                                |
| C-6        | 24.3                                  | 24.4                                | 24.4                                |
| C-7        | 35.3                                  | 35.4                                | 35.4                                |
| C-8        | 33.8                                  | 33.9                                | 33.9                                |
| C-9        | 156.7                                 | 156.7                               | 156.7                               |
| C-10       | 125.7                                 | 125.7                               | 125.7                               |
| C-11       | 39.6                                  | 39.7                                | 39.7                                |
| C-12       | 120.5                                 | 120.5                               | 120.5                               |
| C-13*      | 148.1                                 | 148.2                               | 148.2                               |
| C-14       | 139.6                                 | 139.6                               | 139.6                               |
| C-15*      | 145.5                                 | 145.5                               | 145.5                               |
| C-16       | 106.4                                 | 106.5                               | 106.5                               |
| C-17       | 116.1                                 | 116.2                               | 116.2                               |
| C-18       | 192.6                                 | 192.7                               | 192.6                               |
| C-19*      | 33.5                                  | 33.5                                | 33.5                                |
| C-20*      | 22.1                                  | 22.2                                | 22.2                                |
| C-21       | 21.8                                  | 21.9                                | 21.9                                |
| C-22       | 20.4                                  | 20.5                                | 20.4                                |

\* C-13/C-15 and C-19/C-20 signals may be interchanged.

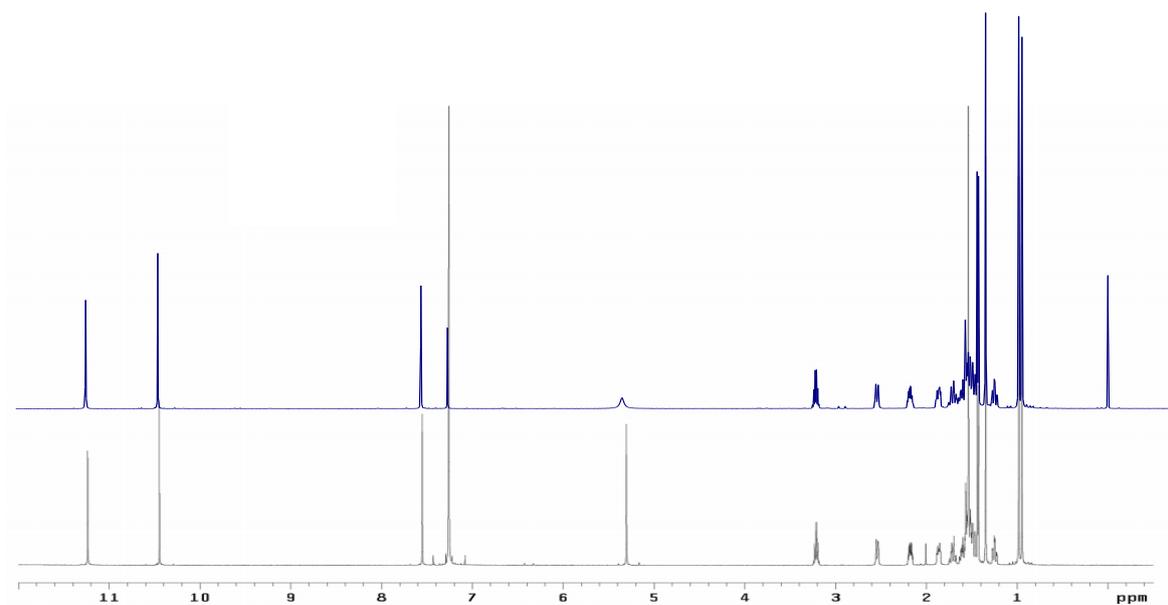


Figure 2.7:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (+)-liphagal (**2.25**); top – synthetic sample from this work; bottom – synthetic sample from Stoltz.

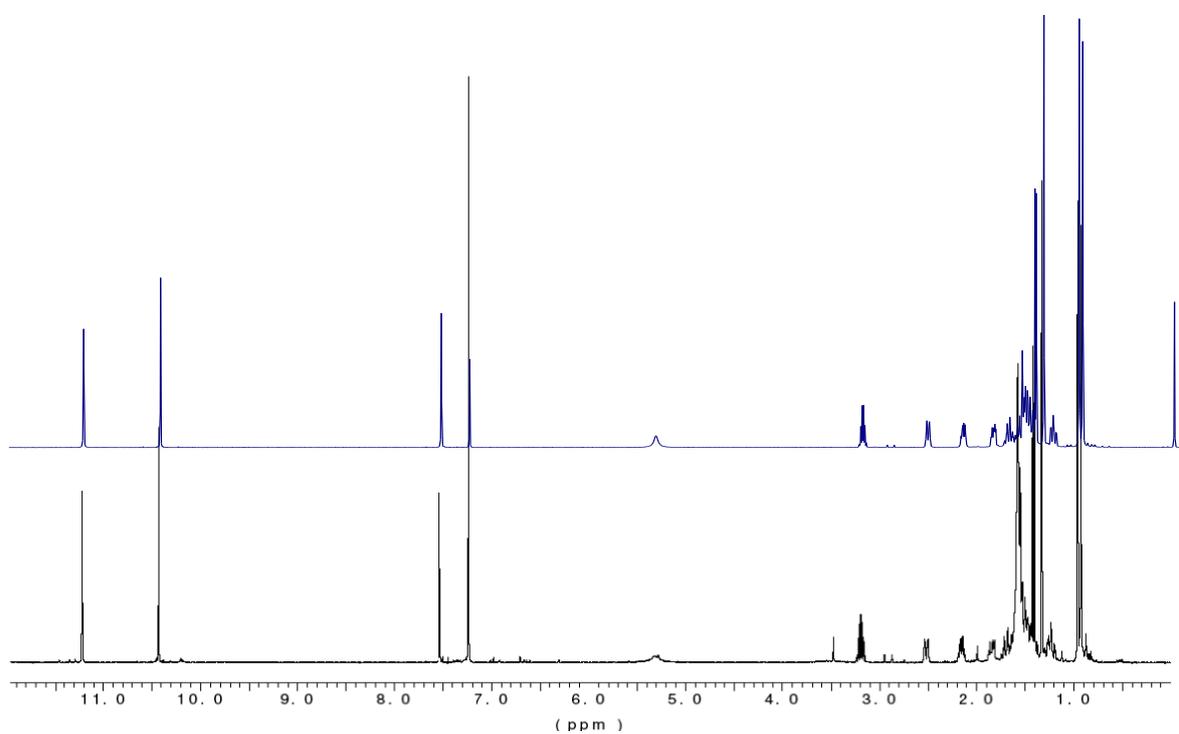


Figure 2.8:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (+)-liphagal (**2.25**); top – synthetic sample from this work; bottom – synthetic sample from Andersen.

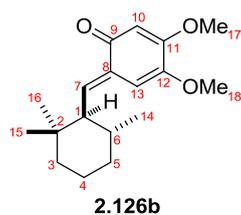


Table 2.8: <sup>1</sup>H NMR assignment of *trans ortho*-quinone methide **2.126b**.

| Assignment        | 600 MHz, CDCl <sub>3</sub>         |
|-------------------|------------------------------------|
| <b>H-7</b>        | 7.04 (d, $J = 11.8$ Hz, 1H)        |
| <b>H-13</b>       | 6.08 (s, 1H)                       |
| <b>H-10</b>       | 5.78 (s, 1H)                       |
| <b>OMe-17</b>     | 3.84 (s, 3H)                       |
| <b>OMe-18</b>     | 3.81 (s, 3H)                       |
| <b>H-1</b>        | 1.94 (dd, $J = 11.3, 10.9$ Hz, 1H) |
| <b>H-3a</b>       | 1.79 (dd, $J = 13.5, 3.0$ Hz, 1H)  |
| <b>H-6</b>        | 1.71 – 1.66 (m, 1H)                |
| <b>H-5a, H-5b</b> | 1.57 – 1.52 (m, 2H)                |
| <b>H-4a</b>       | 1.49 – 1.47 (m, 1H)                |
| <b>H-4b</b>       | 1.28 – 1.23 (m, 1H)                |
| <b>H-3b</b>       | 0.99 – 0.96 (overlapped m, 1H)     |
| <b>Me-15</b>      | 0.97 (s, 3H)                       |
| <b>Me-16</b>      | 0.72 (s, 3H)                       |
| <b>Me-14</b>      | 0.72 (d, $J = 6.5$ Hz, 3H)         |

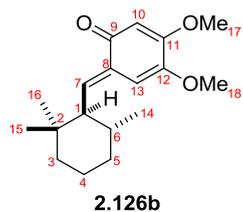


Table 2.9:  $^{13}\text{C}$  NMR assignment of *trans ortho*-quinone methide **2.126b**.

| Assignment    | 150 MHz, $\text{CDCl}_3$ |
|---------------|--------------------------|
| <b>C-1</b>    | 53.9                     |
| <b>C-2</b>    | 35.6                     |
| <b>C-3</b>    | 35.1                     |
| <b>C-4</b>    | 21.8                     |
| <b>C-5</b>    | 41.5                     |
| <b>C-6</b>    | 32.4                     |
| <b>C-7</b>    | 150.1                    |
| <b>C-8</b>    | 133.2                    |
| <b>C-9</b>    | 184.3                    |
| <b>C-10</b>   | 104.2                    |
| <b>C-11</b>   | 164.7                    |
| <b>C-12</b>   | 147.6                    |
| <b>C-13</b>   | 100.8                    |
| <b>C-14</b>   | 21.7                     |
| <b>C-15</b>   | 20.7                     |
| <b>C-16</b>   | 31.8                     |
| <b>OMe-17</b> | 56.3                     |
| <b>OMe-18</b> | 55.8                     |

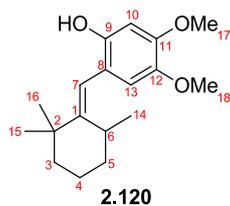


Table 2.10:  $^1\text{H}$  NMR assignment of phenol **2.120**.

| Assignment                    | 500 MHz, $\text{CDCl}_3$          |
|-------------------------------|-----------------------------------|
| <b>H-10</b>                   | 6.53 (s, 1H)                      |
| <b>H-13</b>                   | 6.52 (s, 1H)                      |
| <b>H-7</b>                    | 6.10 (s, 1H)                      |
| <b>6-OH</b>                   | 4.76 (s, 1H)                      |
| <b>OMe-18</b>                 | 3.85 (s, 3H)                      |
| <b>OMe-17</b>                 | 3.81 (s, 3H)                      |
| <b>H-6</b>                    | 2.79 – 2.74 (m, 1H)               |
| <b>H-4a</b>                   | 1.82 (dt, $J = 7.0, 3.0$ Hz, 1H)  |
| <b>H-3a, H-4b, H-5a, H-5b</b> | 1.59 – 1.45 (m, 4H)               |
| <b>H-3b</b>                   | 1.38 (dt, $J = 13.0, 3.0$ Hz, 1H) |
| <b>Me-15*</b>                 | 1.24 (s, 3H)                      |
| <b>Me-16*</b>                 | 1.23 (s, 3H)                      |
| <b>Me-14</b>                  | 1.11 (d, $J = 7.5$ Hz, 3H)        |

\* Me-15/Me-16 signals may be interchanged.

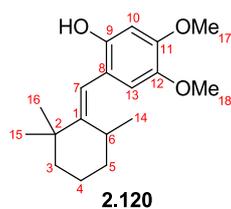


Table 2.11:  $^{13}\text{C}$  NMR assignment of phenol **2.120**.

| Assignment    | 125 MHz, $\text{CDCl}_3$ |
|---------------|--------------------------|
| <b>C-1</b>    | 115.5                    |
| <b>C-2</b>    | 37.0                     |
| <b>C-3</b>    | 41.9                     |
| <b>C-4</b>    | 17.8                     |
| <b>C-5</b>    | 33.4                     |
| <b>C-6</b>    | 31.4                     |
| <b>C-7</b>    | 114.7                    |
| <b>C-8</b>    | 148.8                    |
| <b>C-9</b>    | 160.0                    |
| <b>C-10</b>   | 112.8                    |
| <b>C-11</b>   | 146.6                    |
| <b>C-12</b>   | 142.6                    |
| <b>C-13</b>   | 99.4                     |
| <b>C-14</b>   | 21.6                     |
| <b>C-15*</b>  | 29.7                     |
| <b>C-16*</b>  | 31.7                     |
| <b>OMe-17</b> | 55.9                     |
| <b>OMe-18</b> | 56.6                     |

\* C-15/C-16 signals may be interchanged.

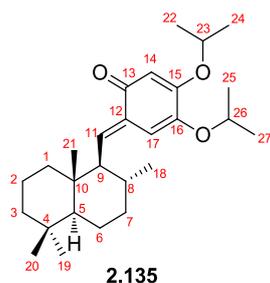


Table 2.12: <sup>1</sup>H NMR assignment of *ortho*-quinone methide **2.135**.

| Assignment                    | 500 MHz, CDCl <sub>3</sub>          |
|-------------------------------|-------------------------------------|
| <b>H-11</b>                   | 7.06 (d, $J = 11.0$ Hz, 1H)         |
| <b>H-17</b>                   | 6.18 (s, 1H)                        |
| <b>H-14</b>                   | 5.71 (s, 1H)                        |
| <b>H-23</b>                   | 4.48 (hept, $J = 6.07$ Hz, 1H)      |
| <b>H-26</b>                   | 4.35 (hept, $J = 6.07$ Hz, 1H)      |
| <b>H-7a</b>                   | 1.92 – 1.82 (m, 1H)                 |
| <b>H-9</b>                    | 1.83 (t, $J = 11.0$ Hz, 1H)         |
| <b>H-8</b>                    | 1.79 – 1.73 (m, 1H)                 |
| <b>H-6a</b>                   | 1.65 – 1.62 (m, 1H)                 |
| <b>H-2a</b>                   | 1.52 – 1.49 (m, 1H)                 |
| <b>H-2b, H-3a, H-6b, H-1a</b> | 1.43 – 1.30 (overlapped m, 4H)      |
| <b>Me-22, Me-24</b>           | 1.37 (d, $J = 6.07$ Hz, 6H)         |
| <b>Me-25, Me-27</b>           | 1.34 (d, $J = 6.07$ Hz, 6H)         |
| <b>H-3b</b>                   | 1.18 – 1.12 (s, 1H)                 |
| <b>H-7b</b>                   | 1.09 – 1.00 (overlapped m, 1H)      |
| <b>Me-21</b>                  | 1.03 (s, 3H)                        |
| <b>H-5</b>                    | 0.93 (dd, $J = 12.48, 2.19$ Hz, 1H) |
| <b>H-1b</b>                   | 0.88 – 0.83 (overlapped m, 1H)      |
| <b>Me-19</b>                  | 0.88 (s, 3H)                        |
| <b>Me-20</b>                  | 0.85 (s, 3H)                        |
| <b>Me-18</b>                  | 0.66 (d, $J = 6.23$ Hz, 3H)         |

Table 2.13:  $^{13}\text{C}$  NMR assignment of *ortho*-quinone methide **2.135**.

| Assignment | 125 MHz, $\text{CDCl}_3$ |
|------------|--------------------------|
| C-1        | 41.3                     |
| C-2        | 18.7                     |
| C-3        | 42.4                     |
| C-4        | 33.5                     |
| C-5        | 54.9                     |
| C-6        | 21.6                     |
| C-7        | 36.2                     |
| C-8        | 31.8                     |
| C-9        | 58.1                     |
| C-10       | 39.3                     |
| C-11       | 149.4                    |
| C-12       | 133.6                    |
| C-13       | 184.3                    |
| C-14       | 104.8                    |
| C-15       | 164.4                    |
| C-16       | 146.0                    |
| C-17       | 106.8                    |
| C-18       | 21.7                     |
| C-19       | 33.6                     |
| C-20       | 22.0                     |
| C-21       | 15.2                     |
| C-22       | 21.7                     |
| C-23*      | 71.58                    |
| C-24       | 21.7                     |
| C-25       | 21.47                    |
| C-26*      | 71.57                    |
| C-27       | 21.45                    |

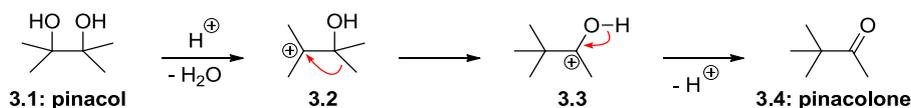
\* C-23/C-26 signals may be interchanged.

## CHAPTER THREE

### The Total Synthesis of (+)-Aureol

#### 3.1 Methyl and Hydride Shifts in Biosynthesis

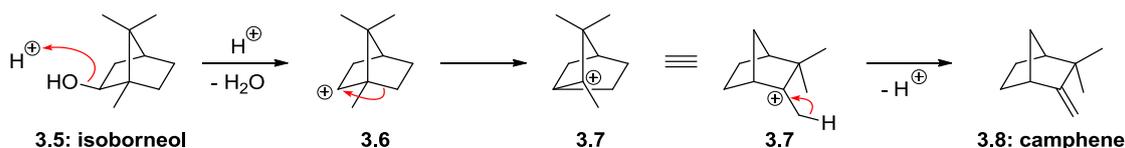
The discovery of carbocation rearrangements can be traced back as far as the mid-1800s, with the formation of pinacolone (**3.4**) from pinacol (**3.1**), first described by Wilhelm R. Fittig (Scheme 3.1).<sup>1</sup> In the presence of acid, elimination of water from the 1,2-diol afforded the tertiary carbocation **3.2**. The intermediate would then undergo a [1,2]-Me shift to generate the oxonium ion **3.3**, followed by the loss of proton to reveal the ketone functionality in pinacolone (**3.4**). This type of rearrangement later became known as the pinacol rearrangement.



Scheme 3.1

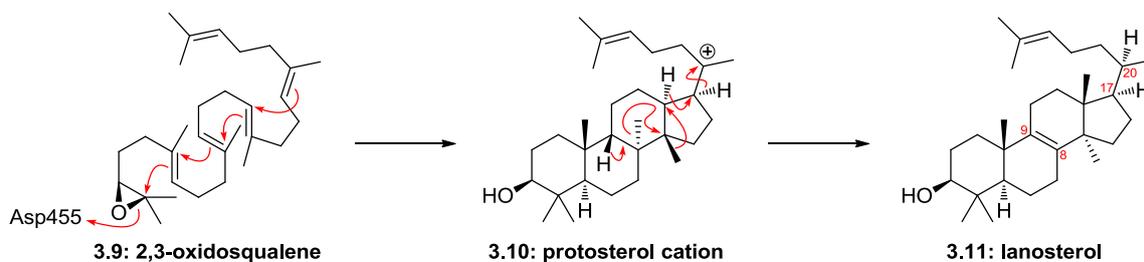
An important contribution in the field came from Wagner and Meerwein with mechanistic studies on the rearrangement of isoborneol (**3.5**) to camphene (**3.8**), a bicyclic monoterpene that could be easily purified at the time. Wagner had proposed that isoborneol (**3.5**), when subjected to an acid-catalysed dehydration reaction, had the propensity to

undergo an alkyl migration to form the more stable tertiary carbocation intermediate **3.7** from the secondary carbocation **3.6** (Scheme 3.2). The geminal alkene is then formed with the loss of a proton to afford camphene (**3.8**). This classic [1,2]-rearrangement reaction is now known as the Wagner-Meerwein rearrangement.



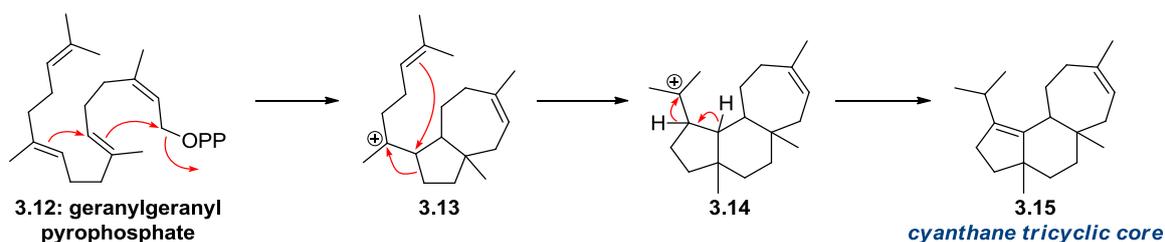
Scheme 3.2

Methyl and hydride shifts have been implicated in the biosynthesis of lanosterol (**3.11**), an important intermediate in the steroidal biosynthetic pathway.<sup>2</sup> It has been shown by researchers at Hoffmann-La Roche that the Asp455 residue of oxidosqualene cyclase is responsible for triggering the polyene cyclisation of 2,3-oxidosqualene (**3.9**).<sup>3</sup> Shown in Scheme 3.3, a skeletal rearrangement of the protosterol cation (**3.10**) involving five consecutive methyl and hydride shifts then proceeds, followed by an elimination reaction to give lanosterol (**3.11**).



Scheme 3.3

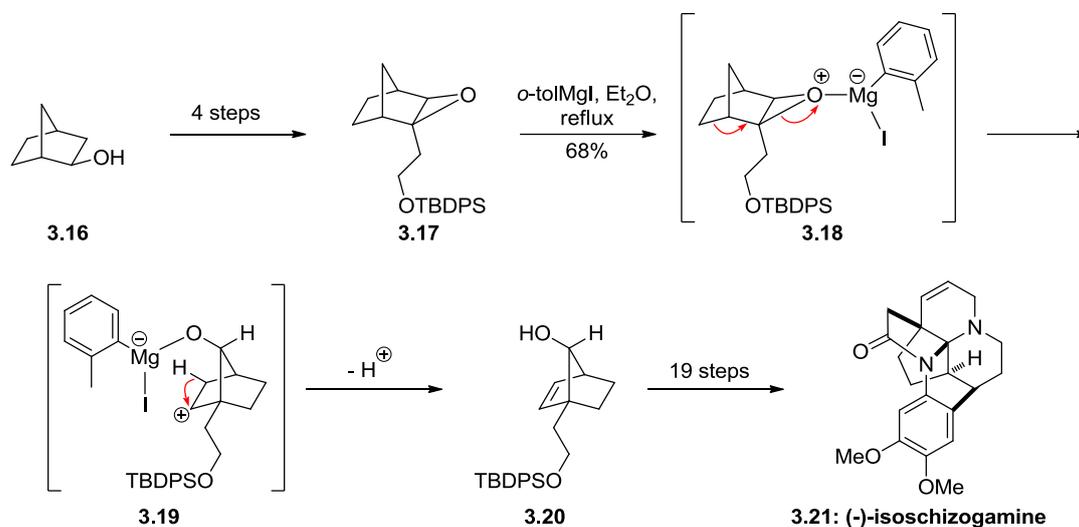
The Wagner-Meerwein rearrangement is also involved in the biosynthesis of cyanthane diterpenoids, first isolated from the bird's nest fungi of the genus *Cyathus*, and later from a variety of fungi, sponges and fruiting plants.<sup>4, 5</sup> Using <sup>13</sup>C radioisotope labelling studies and <sup>13</sup>C NMR analysis, Ayer and co-workers established that the 5-6-7 tricyclic core of cyanthane molecules first involved the cyclisation of geranylgeranyl pyrophosphate (**3.12**), to afford the 5-7 bicyclic carbocation intermediate **3.13**, which then underwent a ring expansion to afford intermediate **3.14**, with the two methyl groups now predisposed in a 1,4-relationship (Scheme 3.4). Subsequent hydride shift onto the isopropyl tertiary carbocation and proton loss then produces the cyanthane tricyclic core **3.15**. Subsequent oxidation of the tricyclic core **3.15** would then give rise to various cyanthane-type natural products.



Scheme 3.4

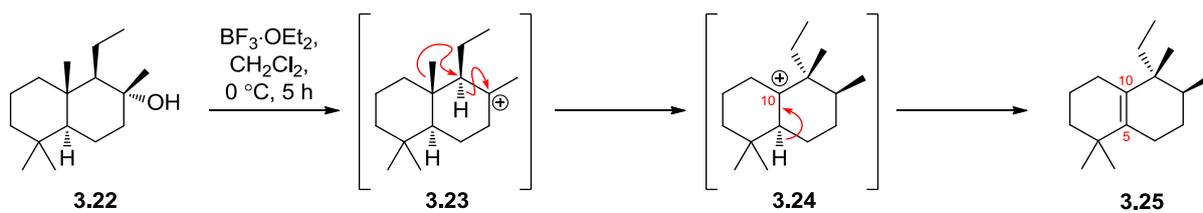
More recently, the Wagner-Meerwein rearrangement has been applied to the synthesis of the indole alkaloid (–)-isoschizogamine (**3.21**) (Scheme 3.5).<sup>6</sup> Miura and co-workers demonstrated that epoxide **3.17**, obtained from norborneol **3.16** in four steps, underwent Wagner-Meerwein rearrangement using a modified procedure previously developed by Kleinfelter.<sup>7</sup> The Grignard reagent, *ortho*-tolylmagnesium iodide, would first react with the epoxide, forming intermediate **3.18**. Wagner-Meerwein rearrangement followed by ring opening of the epoxide later gave the carbocation intermediate **3.19**, which underwent

subsequent proton elimination to form alkene **3.20**. An extensive 19 steps was required to convert alcohol **3.20** to the desired natural product **3.21**.



Scheme 3.5

The occurrence of methyl and hydride shifts in nature serves as an inspiration for a biomimetic [1,2]-hydride and [1,2]-methyl shifts in the laboratory. While investigating biomimetic rearrangements of simplified labdane analogues, George and co-workers discovered that alcohol **3.22** can be converted into alkene **3.25**, with a rearranged drimane skeleton (Scheme 3.6).<sup>8</sup> The authors proposed that carbocation **3.23**, obtained from acid-catalysed dehydration of alcohol **3.22**, can undergo a series of stereospecific [1,2]-methyl and hydride shifts to afford intermediate **3.24** with a carbocation at the C-10 carbon centre. The loss of a proton would then form the  $\Delta^{5,10}$  double bond, giving rise to alkene **3.25**.



Scheme 3.6

We believe that this biomimetic [1,2]-hydride and [1,2]-methyl shifts can be applied towards the synthesis of (+)-aureol (**3.26**), a tetracyclic meroterpenoid. This biomimetic approach would ultimately lead to a more concise, bio-inspired synthesis of the natural product and could serve as a general method of accessing other related sesquiterpenes.

### 3.2 Isolation and Biological Activity

(+)-Aureol (**3.26**) was originally isolated in 1980 by Faulkner from the Caribbean marine sponge *Smenospongia aurea*,<sup>9</sup> and subsequently in 2000 by Fattorusso and co-workers from the marine sponge *Verongula gigantea*.<sup>10</sup> More recently, (+)-aureol was also co-isolated from the South Pacific marine sponge *Hyrtios* sp.<sup>11</sup> The absolute configuration of the natural product was determined by X-ray crystallographic analysis of the corresponding brominated *O*-acetyl derivative of (+)-aureol. It reveals that (+)-aureol contains a compact tetracyclic ring system, with four contiguous stereocenters and a *cis*-relationship between the two cyclohexane rings of the decalin fragment. Since its isolation, several structurally related natural products have also been reported, such as stronglylin A (**3.27**),<sup>12</sup> stachyflin (**3.28**)<sup>13</sup> and cyclosmenospongine (**3.29**)<sup>14</sup> (Figure 3.1). (+)-Aureol (**3.26**) has been shown to exhibit selective cytotoxicity against several human tumour cell lines, such as the non-small cell lung carcinoma A549 (IC<sub>50</sub> = 4.3 μg/mL), colon adenocarcinoma HT-29 (IC<sub>50</sub> = 4.7 μg/mL), Hepa59T/VGH (IC<sub>50</sub> = 5.8 μg/mL), and HeLa cell lines (IC<sub>50</sub> = 7.7 μg/mL).<sup>15, 16</sup> In addition, (+)-aureol also shows anti-influenza A virus activity (IC<sub>50</sub> = 11.6 μM).<sup>17</sup> The intrinsic biological properties and unique structural features of this tetracyclic natural product, as well as its limited availability from natural resources, has prompted the total synthesis of (+)-aureol (**3.26**) by several research groups.<sup>18-21</sup>

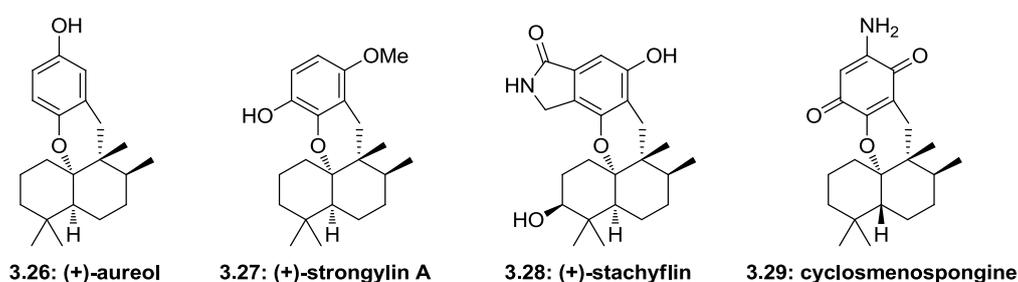
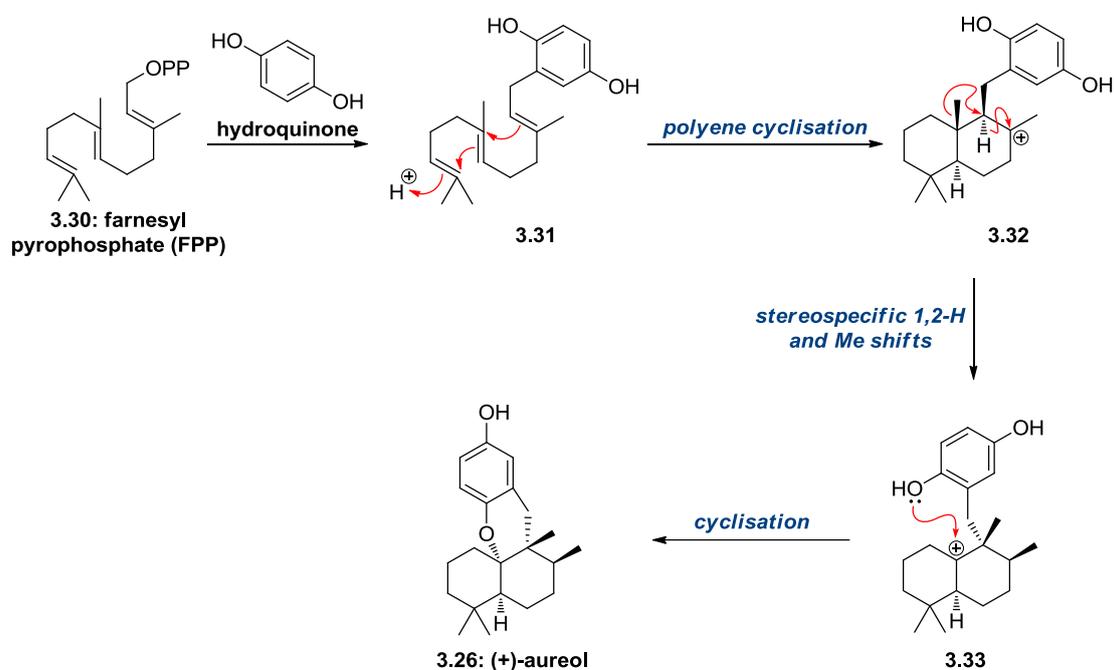


Figure 3.1 Sesquiterpenoid natural products bearing a similar tetracyclic core

### 3.3 Proposed Biosynthesis of (+)-Aureol

While several research groups have alluded to the possible biogenetic link between (+)-aureol and meroterpenoids such as (+)-avarol (**3.34**) and arenarol (**3.37**) (*vide infra*, Section 3.4.1), a direct conclusion could not be drawn as these natural products have not been co-isolated alongside (+)-aureol (**3.26**). Instead, we propose that the biosynthesis of (+)-aureol (**3.26**) first involves the union of farnesyl pyrophosphate (**3.30**) and a hydroquinone molecule to afford the polyene **3.31** (Scheme 3.7). Stereoselective cyclisation of the electron rich polyene **3.31** would generate the tertiary carbocation **3.32** bearing the positive charge at the C-8 carbon atom. This carbocation could then undergo a sequence of stereospecific [1,2]-hydride and methyl shifts to give a second carbocation **3.33**, this time with the charge situated at the C-10 carbon. An intramolecular attack by the adjacent hydroquinone would then give **3.26**.

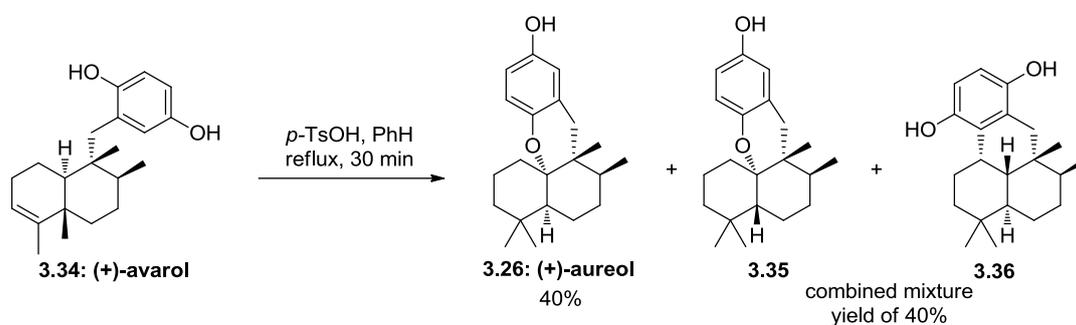


Scheme 3.7

### 3.4 Previous Work

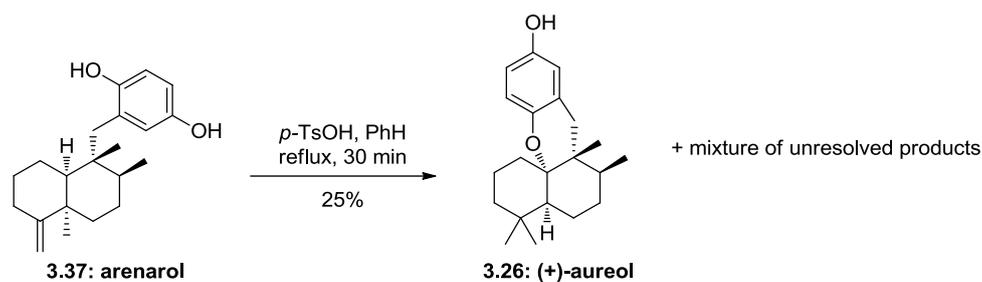
#### 3.4.1 Mechanistic Investigations by Urban and Capon

In an attempt to resolve the absolute stereochemistry of several marine sponge meroterpenoids, Urban and Capon observed that treatment of (+)-avarol (**3.34**) with anhydrous *p*-TsOH in benzene under reflux produced a mixture of (+)-aureol (**3.26**), its *trans*-fused stereoisomer **3.35**, and tetracyclic hydroquinone **3.36** (Scheme 3.8).<sup>22</sup>



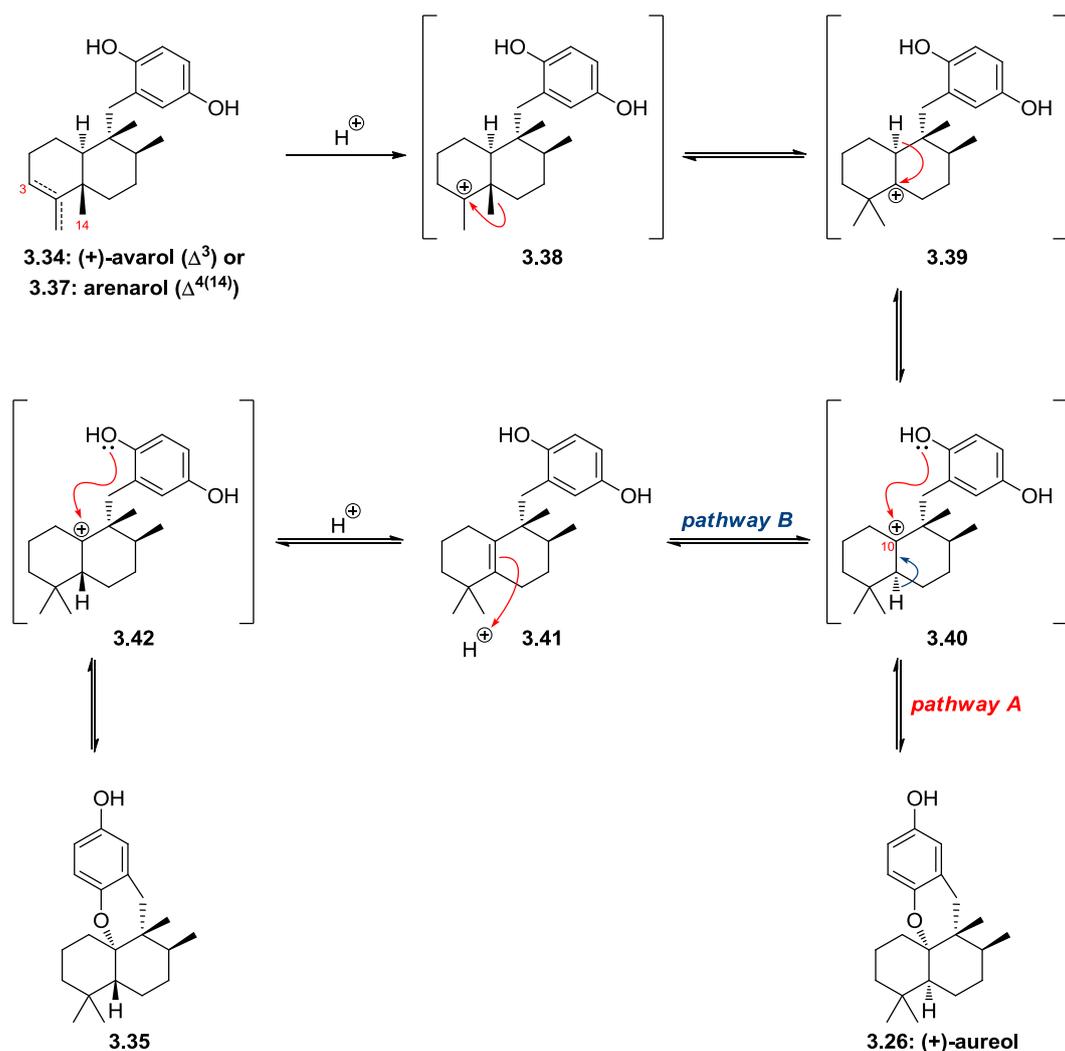
Scheme 3.8

In a similar fashion, (+)-aureol (**3.26**) could also be generated from arenarol (**3.37**), albeit in a slightly lower yield (Scheme 3.9). Furthermore, Urban and Capon found that the authentic sample of arenarol (**3.37**) provided by the original authors had undergone complete conversion to (+)-aureol (**3.26**) after several years of storage. This transformation was presumed to be due to the acidic phenolic group intrinsic to arenarol (**3.37**). It is interesting to note that Schmitz and co-workers observed exclusive formation of stereoisomer **3.35** when arenarol (**3.37**) was first treated with *p*-TsOH at room temperature for 12 hours, prior to the 30 minute reflux.<sup>23</sup>



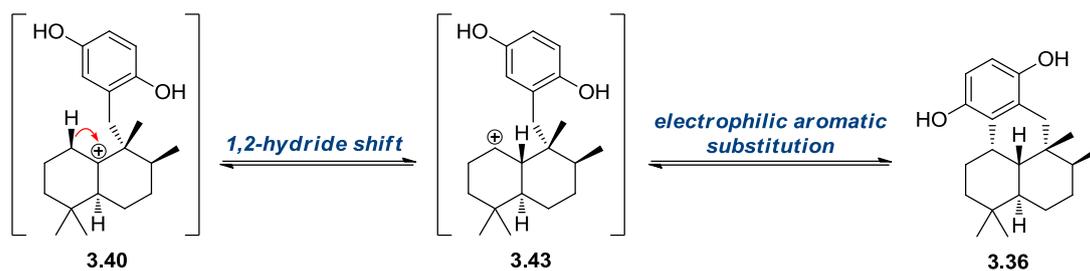
Scheme 3.9

Based on these observations, Urban and Capon proposed that the conversion of (+)-avarol (**3.34**) and arenarol (**3.37**) to (+)-aureol (**3.26**) occurs via an acid catalysed rearrangement mechanism, as outlined in Scheme 3.10. Exposure of either natural product precursors to acid would generate the first carbocation intermediate **3.38**. A methyl shift then generates the second tertiary carbocation intermediate **3.39**, which would then undergo a [1,2]-hydride shift, forming intermediate **3.40** with the tertiary carbocation at the C-10 carbon. **3.40** was presumably the key intermediate in the acid catalysed rearrangement reaction, as intramolecular cycloetherification would lead to the formation of (+)-aureol (**3.26**) (pathway A). Alternatively, stabilisation of **3.40** by proton loss would generate hydroquinone **3.41** with an internal alkene at the  $\Delta^5$  bond (pathway B). The intermediate **3.42**, arising from the protonation of hydroquinone **3.41**, could also be trapped by the phenolic hydroxy group to form the cycloether ring bearing a *trans* configuration with respect to the C-5 proton. This proposed pathway was in agreement with the observed results, as the *trans*-fused isomer **3.35** was also isolated in the acid catalysed rearrangement reaction.



Scheme 3.10

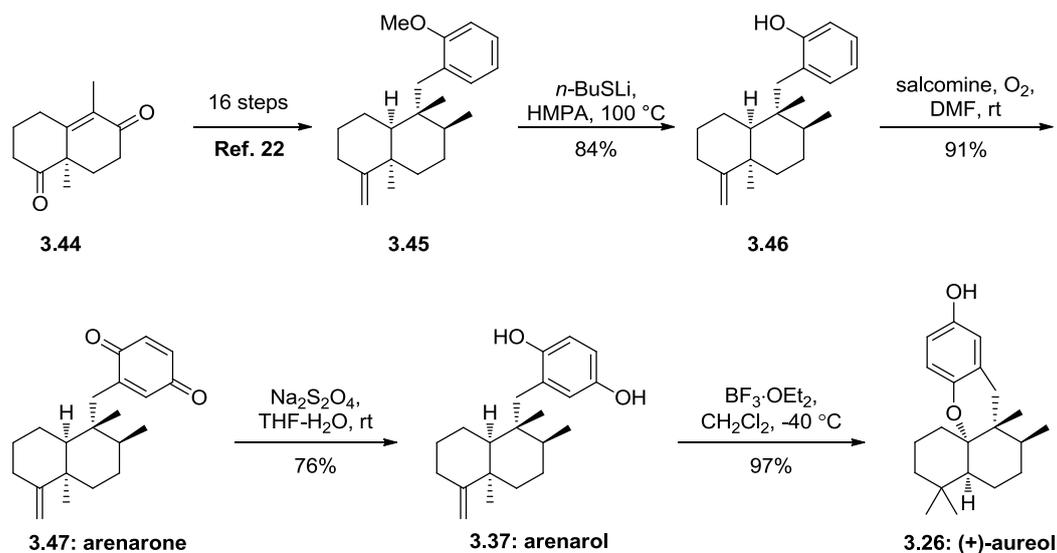
A third pathway, which involves a [1,2]-hydride shift from the C-1 position of intermediate **3.40** would then generate the highly unstable secondary carbocation intermediate **3.43** (Scheme 3.11). However, instead of being trapped by the hydroxy group of the aromatic ring, cyclisation could occur via an electrophilic substitution reaction, thereby giving rise to the tetracyclic hydroquinone **3.36**. Although the total synthesis of (+)-aureol (**3.26**) was not pursued, the results from Urban and Capon's 1994 investigation into the acid catalysed rearrangement reactions of (+)-avarol (**3.34**) and arenarol (**3.37**) hinted at a plausible biogenetic link between these natural products and (+)-aureol (**3.26**).



Scheme 3.11

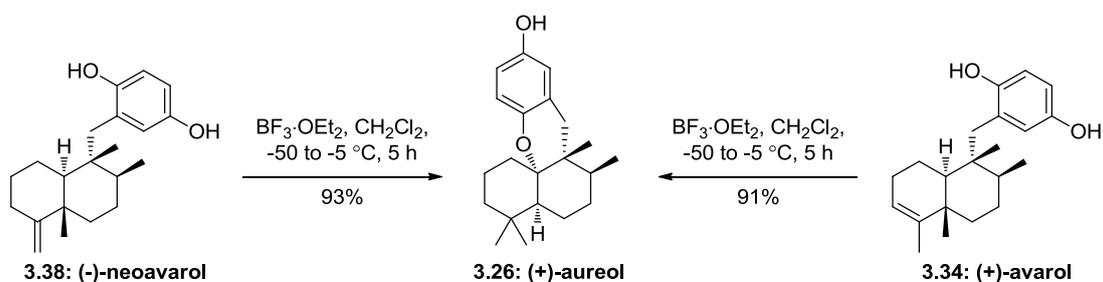
### 3.4.2 Katoh's Lewis Acid Catalysed Rearrangement Approach

Katoh and co-workers first reported the total synthesis of (+)-aureol (**3.26**) in conjunction with their improvised approach towards meroterpenoids arenarone (**3.47**) and arenarol (**3.37**) in 2002.<sup>18, 19</sup> The exocyclic alkene precursor **3.45**, bearing the desired carbon framework, was first prepared from the known (–)-Weiland-Miescher ketone **3.44** in 16 steps (Scheme 3.12).<sup>24</sup> Demethylation of **3.45** was achieved using a stoichiometric excess of *n*-butylthiolate (10 equiv.) in HMPA under reflux conditions to give phenol **3.46** in good yield. Subsequent oxidation of phenol **3.46** in the presence of salcomine under an oxygen atmosphere in DMF led to the formation of the natural product **3.47**. This oxidation reaction represents the key feature of Katoh's revised synthetic route. Reduction of the quinone moiety with sodium dithionite in THF-H<sub>2</sub>O then gave rise to the corresponding hydroquinone natural product, arenarol (**3.37**).



Scheme 3.12

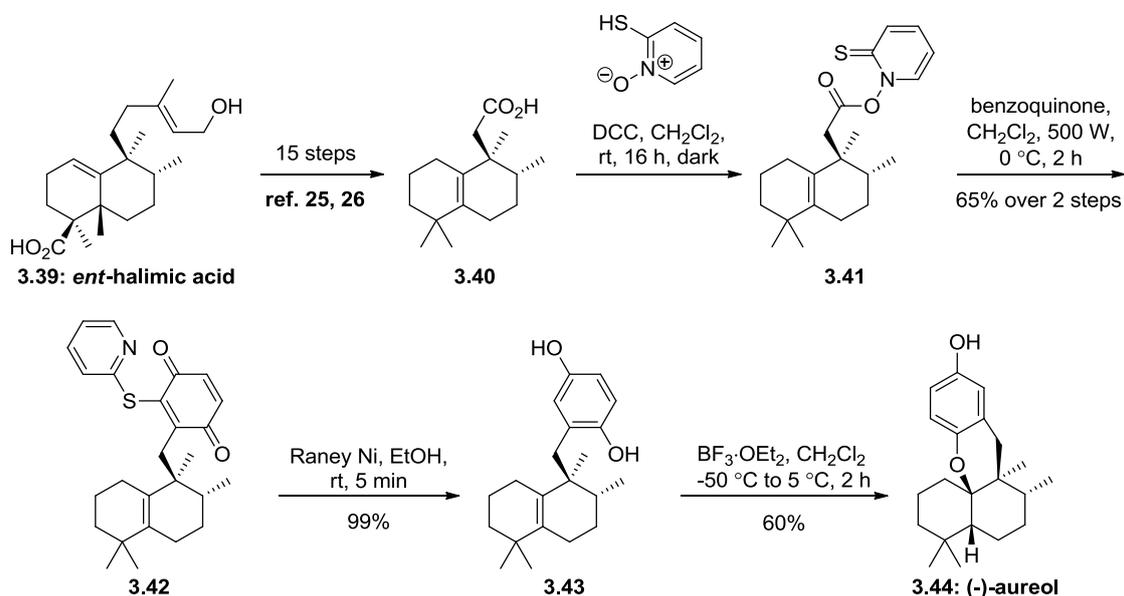
While previous acid catalysed rearrangement reactions of arenarol (**3.37**) proved to be low yielding and lacked the necessary stereocontrol, Katoh and co-workers were delighted to find that treatment of arenarol (**3.37**) with  $\text{BF}_3\cdot\text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$  at  $-40\text{ }^\circ\text{C}$  for three hours led to the exclusive formation of (+)-aureol (**3.26**) in excellent yield. Katoh and co-workers again demonstrated the feasibility of this Lewis acid promoted rearrangement reaction by converting both (–)-neoavarol (**3.38**) and (+)-avarol (**3.34**) to (+)-aureol (**3.26**) under similar conditions (Scheme 3.13).<sup>21</sup>



Scheme 3.13

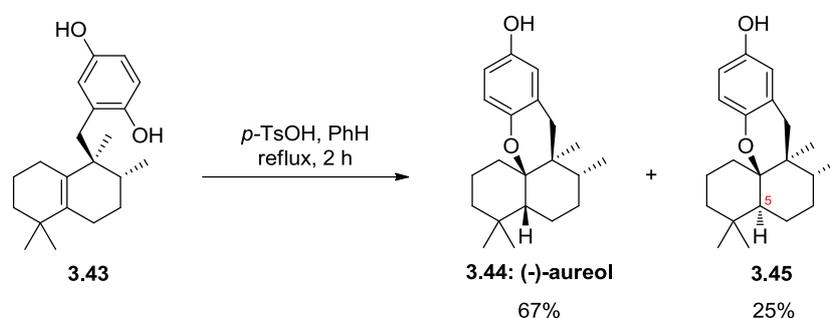
### 3.4.3 Marcos's Synthesis of (-)-Aureol

In 2010, Marcos and co-workers reported a successful synthetic route to (-)-aureol (**3.44**) and several other quinone/hydroquinone sesquiterpene natural products.<sup>25</sup> Their strategy first involved the elaboration of *ent*-halimic acid (**3.39**) to carboxylic acid **3.40** via a series of functional group manipulations (Scheme 3.14).<sup>26, 27</sup> Then, coupling of carboxylic acid **3.40** with 2-mercaptopyridine *N*-oxide at room temperature in the absence of light over 16 hours generated the photo labile ester **3.41**. Barton decarboxylation of **3.41** was triggered with a 500 W lamp in the presence of excess benzoquinone to give quinone **3.42**.<sup>28, 29</sup> Subsequent reduction of **3.42** with Raney Ni in EtOH produced hydroquinone **3.43**. For the final step, hydroquinone **3.43** was treated with  $\text{BF}_3 \cdot \text{OEt}_2$  under similar conditions previously reported<sup>21</sup> to give (-)-aureol (**3.44**) as the exclusive product in reasonable yield.



Scheme 3.14

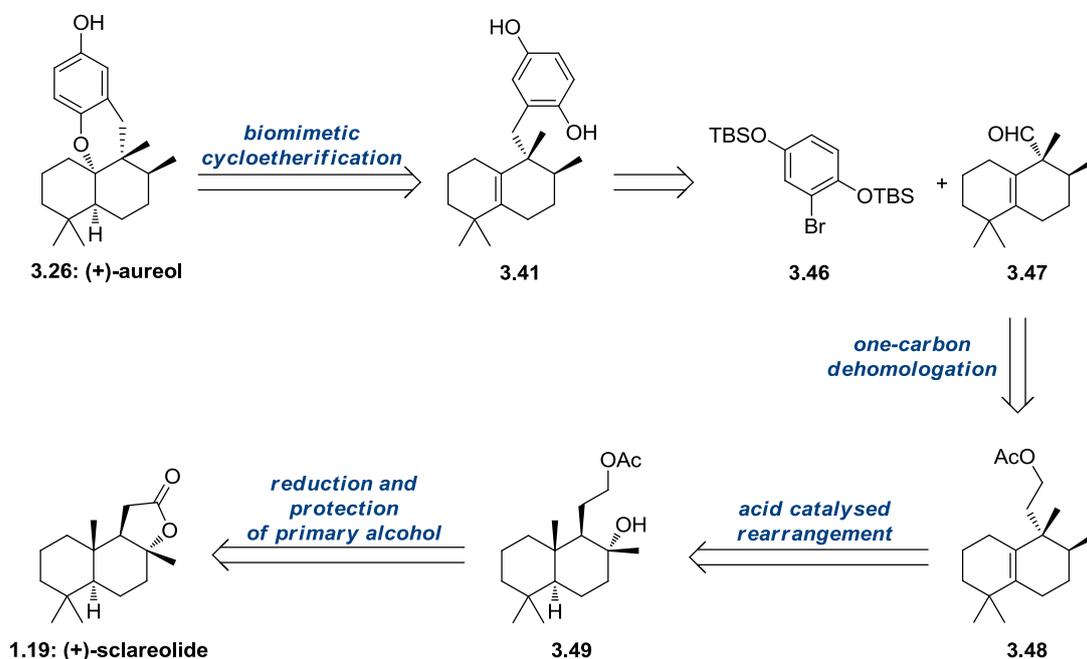
It was worth noting that when hydroquinone **3.43** was refluxed in the presence of *p*-TsOH for two hours, an unstable mixture of **3.44** and its C-5 epimer **3.45** was formed in a 2.7:1 ratio (Scheme 3.15). Acetylation was found to be necessary for stabilisation and separation of the two products. Although Marcos's route features a unique Barton decarboxylation reaction for the installation of the benzoquinone moiety to the aureane backbone, this method was hampered by the lengthy conversion of *ent*-halimic acid **3.39** to the required carboxylic acid **3.40**.



Scheme 3.15

### 3.5 Retrosynthetic Analysis of (+)-Aureol

Our retrosynthetic analysis of (+)-aureol (**3.26**) is shown in Scheme 3.16. We believed that biomimetic cycloetherification of **3.26** could be generated from hydroquinone **3.41** under previously reported conditions. Compound **3.41** could be formed from the addition of an aryllithium species derived from aryl bromide **3.46** to aldehyde **3.47**, followed by deoxygenation of the benzylic alcohol and removal of the protecting groups. The aldehyde **3.47** could be obtained from acetate **3.48** by a one-carbon dehomologation sequence. Acetate **3.48** could presumably be derived from tertiary alcohol **3.49** via a biomimetic sequence of stereospecific [1,2]-hydride and methyl shifts, as previously showcased by George and co-workers.<sup>8</sup> Finally, alcohol **3.49** could be formed by the reduction and monoprotection of (+)-sclareolide (**1.19**), a cheap and commercially available enantiopure starting material.



Scheme 3.16

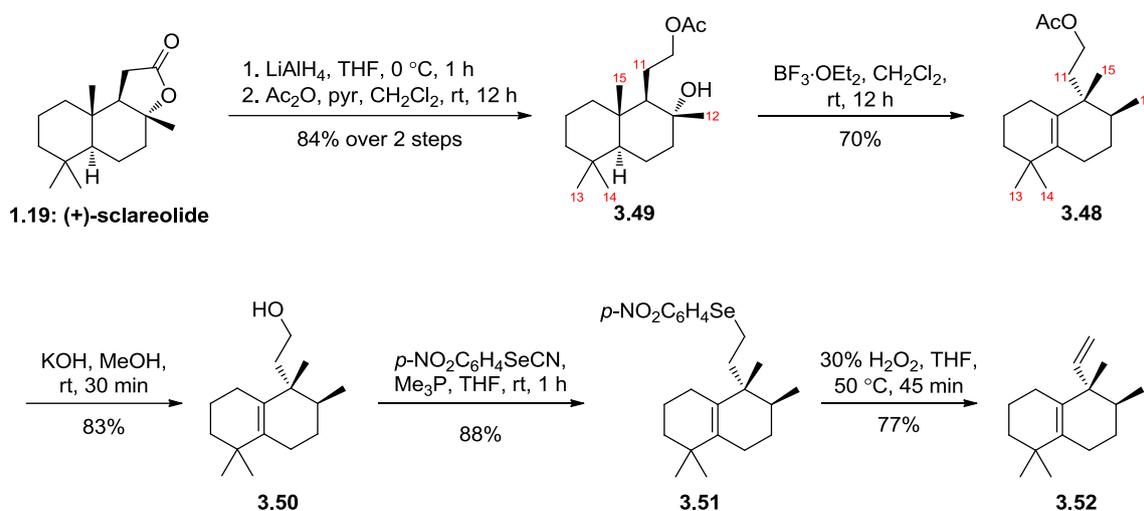
While the cycloetherification reaction occurs immediately after the biomimetic [1,2]-hydride and methyl shift sequence in the proposed biosynthetic pathway for the natural product, it is not possible to replicate this exact scenario in the laboratory. This highlights that nature, the quintessential chemist, has evolved in such a way that it is able to perform such difficult reactions in the simplest and most efficient manner.

## 3.6 Synthesis of (+)-Aureol

### 3.6.1 Preparation of Alkene 3.52

The total synthesis of **3.26** began with the construction of aldehyde **3.47** (Scheme 3.17). (+)-Sclareolide (**1.19**) was ring opened under LiAlH<sub>4</sub> reducing conditions, and the exposed primary alcohol was acetate protected in the presence of Ac<sub>2</sub>O and pyridine to yield the monoprotected tertiary alcohol **3.49** in good yield over two steps. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of alcohol **3.49** were identical to previously reported literature data.<sup>30</sup> The first pivotal step in the overall synthesis was achieved by reacting alcohol **3.49** with BF<sub>3</sub>·OEt<sub>2</sub> at room temperature for 12 hours.<sup>8</sup> Under these conditions, a sequence of stereospecific [1,2]-Me and hydride shifts generated the desired acetate **3.48** as a single stereoisomer in 70% yield. Evidence of this transformation could be observed from the Me and H shifts on the <sup>1</sup>H NMR spectra. The H-5 proton at δ 0.92 ppm is no longer observed in the <sup>1</sup>H NMR spectrum of acetate **3.48**. Furthermore, the H-9 proton is now located on the C-8 carbon atom. The H-12 hydrogen signals now appear as a doublet at δ 0.87 ppm, evidently coupled to the H-8 proton. The internal Δ<sup>5,10</sup> C=C bond was confirmed with two new signals appearing in the <sup>13</sup>C NMR at δ 137.5 and 131.9 ppm and also by X-ray crystallography. Ester hydrolysis of the newly formed acetate **3.48** with KOH in MeOH then furnished alcohol **3.50**. One carbon dehomologation was accomplished using a Grieco-Sharpless elimination<sup>31</sup> protocol followed by oxidative cleavage to generate the desired alkene with an exocyclic olefin functional group. To that end, treatment of alcohol **3.50** with 2-nitrophenyl selenocyanate and *n*-Me<sub>3</sub>P gave aryl selenide **3.51** in 88% yield. Oxidative cleavage was achieved on exposure of **3.51** to 30% H<sub>2</sub>O<sub>2</sub> to give alkene **3.52** in 77% yield. Two dd signals at δ 5.03 and 4.88 ppm have relatively small coupling constants of 1.5 Hz each, a common characteristic of geminal coupling in unsaturated sp<sup>2</sup> carbons. While the Grieco-Sharpless elimination sequence has been extensively utilised in organic synthesis for one carbon dehomologation reactions, this

reaction proved to be uneconomical on a multigram scale. In addition to the inherent toxicity of the organoselenium reagent, stoichiometric excess of 2-nitrophenyl selenocyanate and *n*-Bu<sub>3</sub>P had to be used to drive the reaction to completion. Furthermore, large scale purification of **3.51** proved to be challenging. Thus, an alternative route for the conversion of alcohol **3.50** to alkene **3.52** was sought out.

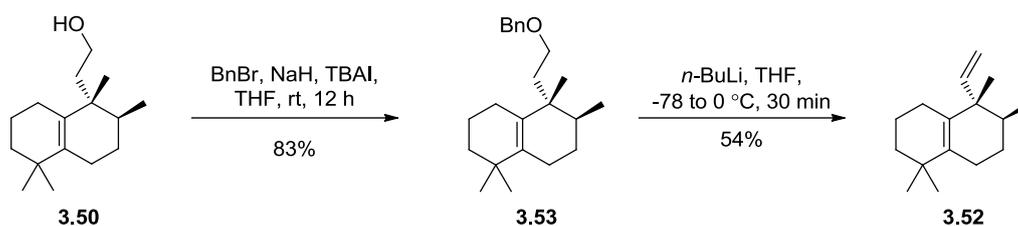


Scheme 3.17

### 3.6.2 [2,3]-Wittig Type Fragmentation of Benzyl Ether **3.53**

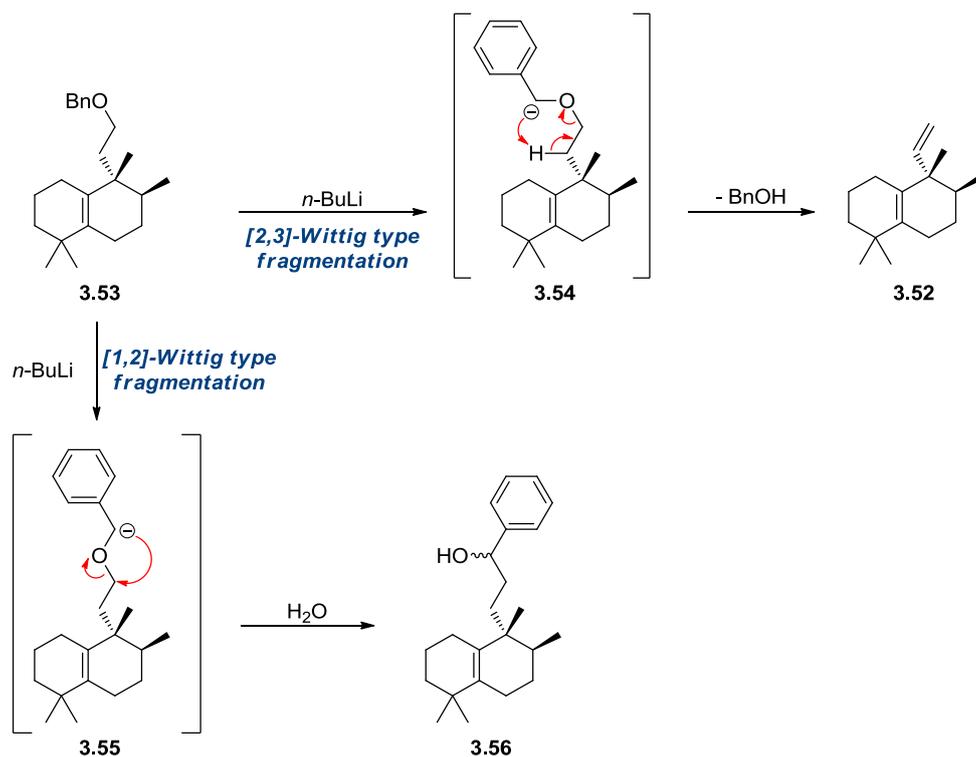
Literature survey quickly revealed that Kodama and co-workers had previously developed a facile conversion of primary alcohols into their corresponding alkenes via [2,3]-Wittig type fragmentation of benzyl ethers.<sup>32</sup> The transformation occurs exclusively for primary benzyl ethers, while a [1,2]-Wittig type fragmentation was found to compete with the [2,3]-Wittig type fragmentation for secondary benzyl ethers, and only [1,2]-Wittig type fragmentation products were observed for tertiary benzyl ethers. In addition, the reaction tolerates a variety of other hydroxy protecting groups (TBS, Tr, THP, MOM, and dimethyl

acetals). The lack of functional groups in alcohol **3.50** prompted us to investigate this approach. Thus, alcohol **3.50** was first benzylated with BnBr, NaH and catalytic TBAI in THF overnight to give the benzyl ether **3.53** in 83% yield (Scheme 3.18). Treatment of benzyl ether with *n*-BuLi at  $-78\text{ }^{\circ}\text{C}$ , followed by subsequent warming to  $0\text{ }^{\circ}\text{C}$  for 30 minutes furnished the desired alkene **3.52** in 54% yield.



Scheme 3.18

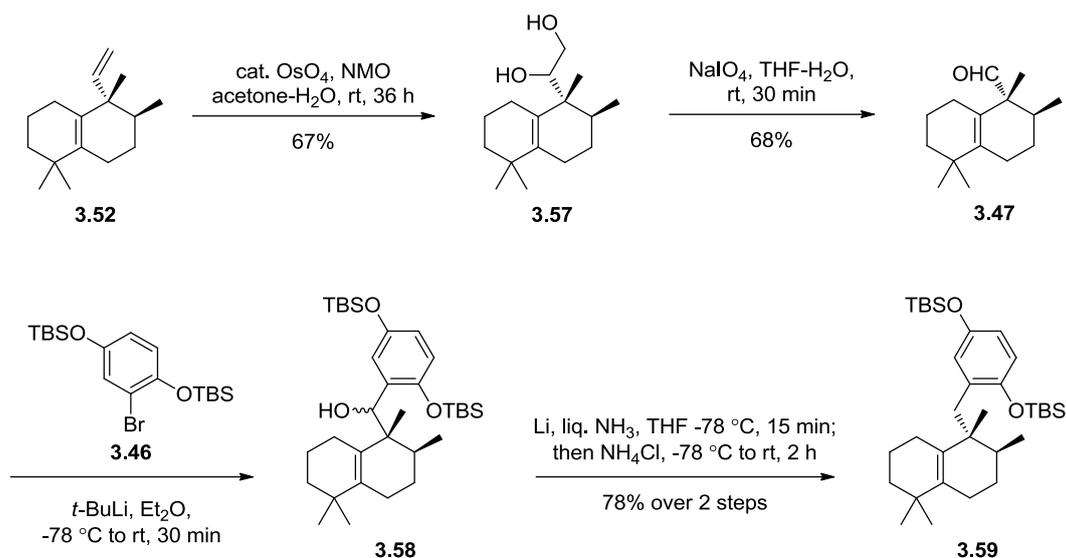
The low yield for this reaction was due to the competing [1,2]-Wittig side reaction, which forms secondary alcohol **3.56** as a mixture of diastereoisomers (Scheme 3.19). Nevertheless, this method was preferred over the Grieco-Sharpless protocol on a multi-gram scale as it avoids the generation of selenium and phosphorus waste products. Furthermore, the desired alkene **3.52** could be easily separated from the undesired benzyl alcohol **3.56** via flash column chromatography on silica gel, using only neat petroleum ether as the elution solvent.



Scheme 3.19

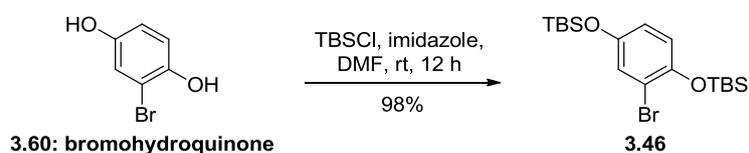
### 3.6.3 Completion of (+)-Aureol and Unusual Rearrangement Side Product

Having established a convenient route to alkene **3.52**, formation of aldehyde **3.47** proceeded via an Upjohn dihydroxylation<sup>33</sup> with  $\text{OsO}_4/\text{NMO}$  to first give diol **3.57** as a mixture of diastereoisomers, which then underwent oxidative cleavage in the presence of  $\text{NaIO}_4$  (Scheme 3.20). Characteristics of this aldehyde functional group was apparent on both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, with the aldehyde proton appearing at  $\delta$  9.17 ppm and the aldehyde carbonyl group at  $\delta$  204.5 ppm.



Scheme 3.20

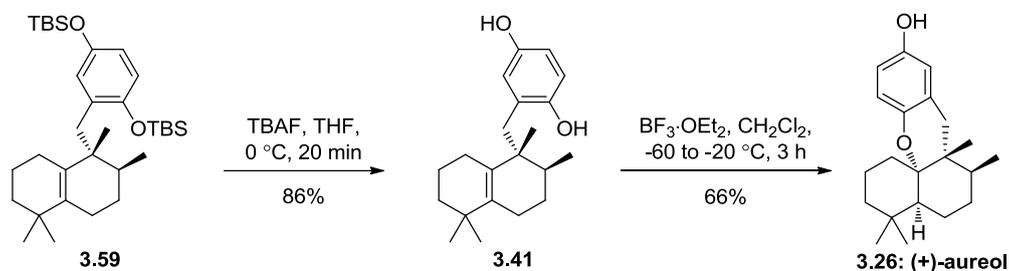
Treatment of aryl bromide **3.46**,<sup>34</sup> formed via di-TBS protection of commercially available bromohydroquinone (Scheme 3.21), with *t*-BuLi at  $-78 \text{ } ^\circ\text{C}$  formed the desired aryllithium species that was then added to aldehyde **3.47** to generate benzylic alcohol **3.58** as a mixture of diastereoisomers. Deoxygenation of **3.58** was achieved under Birch reduction conditions to yield **3.59** in 78% over two steps.



Scheme 3.21

Removal of the TBS protecting groups with TBAF in THF at  $0 \text{ } ^\circ\text{C}$  gave hydroquinone **3.41** in 86% yield (Scheme 3.22). The spectroscopic data for **3.41** was identical with those

originally reported by Faulkner.<sup>9</sup> To our delight, treatment of hydroquinone **3.41** with  $\text{BF}_3 \cdot \text{OEt}_2$  at  $-60\text{ }^\circ\text{C}$  to  $-20\text{ }^\circ\text{C}$  for three hours then gave (+)-aureol (**3.26**) in 66% yield.



Scheme 3.22

Interestingly, if the cycloetherification reaction was quenched at  $0\text{ }^\circ\text{C}$ , trace amounts of a second product was observed (Figure 3.2, middle). When the reaction was quenched at room temperature,  $^1\text{H}$  NMR analysis of the purified material revealed that it did not match the spectroscopic data of **3.26**. Instead, a new broad singlet peak was observed at  $\delta$  3.88 ppm and the benzylic  $\text{CH}_2$  signals were now spread further apart (Figure 3.2, bottom). Additionally, all four methyl peaks appeared to have been shifted further upfield relative to the positions of the methyl peaks of (+)-aureol (**3.26**), as shown in Figure 3.2 (top). 2D NMR analysis identified that the molecule has four CH protons, located at  $\delta$  3.88, 2.04, 1.53 and 1.48 ppm respectively.

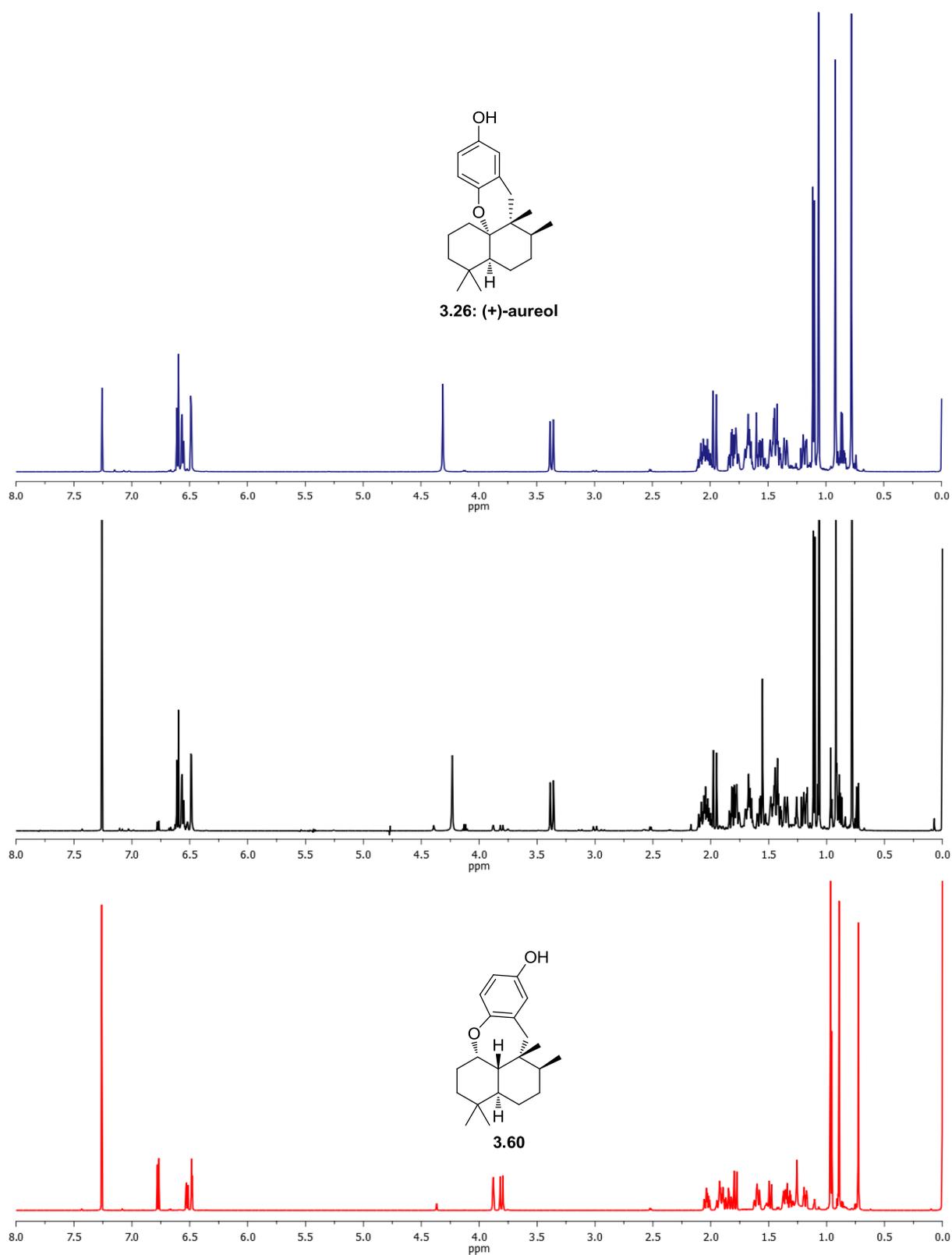


Figure 3.2  $^1\text{H}$  NMR of cycloetherification reaction product; when quenched at  $-20\text{ }^\circ\text{C}$  (top, (+)-aureol (**3.26**)),  $0\text{ }^\circ\text{C}$  (middle), and room temperature (bottom, **3.60**).

ROESY NMR analysis showed a cross peak between the C-11 methyl signal at  $\delta$  0.72 ppm and a CH signal at  $\delta$  3.88 ppm (Figure 3.3, left). Likewise, a cross peak between the CH signal at  $\delta$  2.04 and the C-12 methyl signal at  $\delta$  0.96 ppm was also evident on the 2D NMR spectrum. Fortunately, the unknown compound could be crystallised, and X-ray crystallography revealed that this rearranged compound contains a seven membered cycloether ring system (Figure 3.3, right).

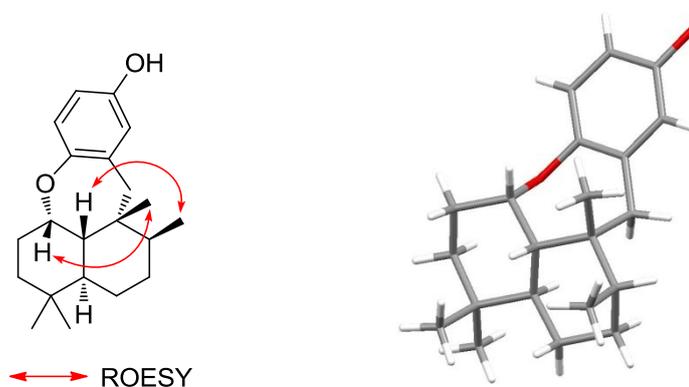
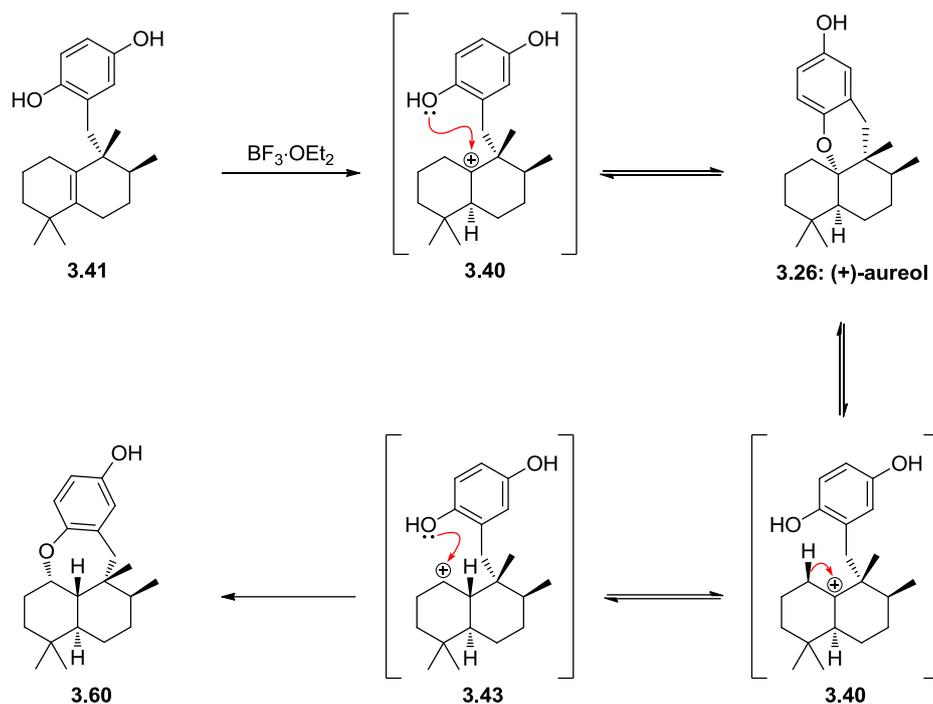


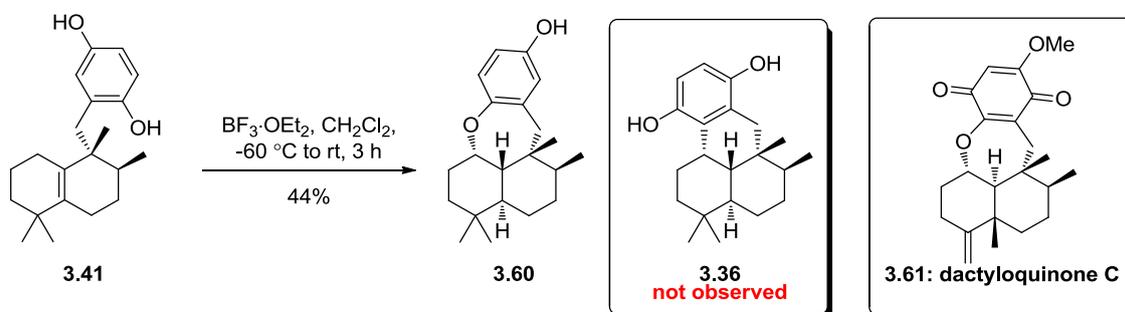
Figure 3.3 Key ROESY correlations (left) and X-ray structure of cyclic ether **3.60** (right).

Based on these observations, we decided to propose a plausible mechanism for the formation of cyclic ether **3.60** (Scheme 3.23). The tertiary carbocation intermediate **3.40** is first formed upon treatment of hydroquinone **3.41** with  $\text{BF}_3 \cdot \text{OEt}_2$ . Formation of the cycloether ring at the C-10 position would then generate (+)-aureol (**3.26**), the kinetic product. This process has been previously shown by Faulkner to be reversible.<sup>9</sup> However, instead of a hydride elimination to reform hydroquinone **3.41**, a [1,2]-hydride shift could occur at elevated temperatures to form the less stable secondary carbocation intermediate **3.43**. The resultant seven membered cycloether ring can be formed via carbocation **3.43**, and would be the thermodynamic product of this reaction.



Scheme 3.23

Indeed, when hydroquinone **3.41** was treated with  $\text{BF}_3 \cdot \text{OEt}_2$  at  $-60^\circ\text{C}$  and quenched at room temperature, cyclic ether **3.60** was formed in 44% yield, as shown in Scheme 3.24. Interestingly, the formation of the electrophilic aromatic substituted tetracyclic hydroquinone **3.36** was not observed in our experiment.



Scheme 3.24

To the best of our knowledge, this represents the first example of a biomimetic cycloetherification reaction whereby a seven membered cycloether ring is formed. A quick literature survey revealed that the meroterpenoid dactyloquinone C (**3.61**) shares a similar 6-6-7-6 tetracyclic core with a quinone moiety instead of the hydroquinone ring (Scheme 2.34, right).<sup>35</sup> It is possible that the formation of dactyloquinone C (**3.61**) occurs via a similar biomimetic cycloetherification pathway in nature.

### 3.7 Conclusion

In summary, a biosynthetically inspired total synthesis of (+)-aureol (**3.26**) was achieved in 12 steps with 6% overall yield starting from (+)-sclareolide (**1.19**). The key transformations of the synthesis include a biomimetic sequence of [1,2]-hydride and methyl shifts, and a late stage biomimetic cycloetherification reaction. Furthermore, we have demonstrated that a seven membered cyclic ether ring system, similar to that of dactyloquinone C (**3.61**) can be easily achieved by simply altering the quenching temperature of the cycloetherification reaction, potentially allowing access to natural products with a similar carbon framework.

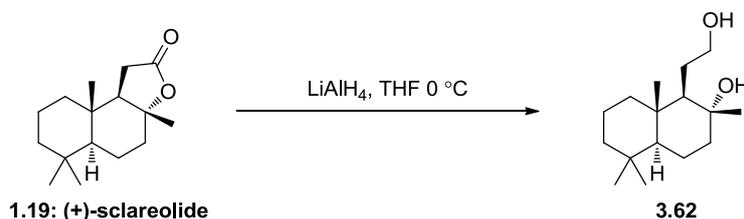
## 3.8 Experimental Section

### 3.8.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using Merck aluminium sheets silica gel 60 F<sub>255</sub>. Visualisation was aided by viewing under a UV lamp and staining with CAM stain followed by heating. All R<sub>f</sub> values were rounded to the nearest 0.05. Flash chromatography was performed using Davisil (40-63 micron) grade silica gel. Melting points were recorded on a SRS Digimelt MPA 161 melting apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer Spectrum BX FT-IR system spectrometer as the neat compounds. Optical rotations were obtained on a P0A1 AR21 polarimeter. X-ray structure was obtained using Mo-target Oxford Diffraction X-Calibur X-ray diffractometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using a Varian Inova-6000 spectrometer (<sup>1</sup>H at 600 MHz, <sup>13</sup>C at 150 MHz). The NMR solvent used was CDCl<sub>3</sub> unless otherwise specified. <sup>1</sup>H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and <sup>13</sup>C NMR are reported in ppm relative to chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quint) quintet, (sext) sextet, (hept) heptet and (m) multiplet. All *J* values were rounded to the nearest 0.5 Hz. EI low resolution mass spectra were recorded on a Shimadzu GCMS-QP 5050A mass spectrometer.

### 3.8.2 Preparative Procedures and Spectroscopic Data

#### Diol 3.62



LiAlH<sub>4</sub> (2.0 M in THF, 20 mL, 40.0 mmol) was added dropwise to a solution of (+)-sclareolide (**1.19**) (10.0 g, 40.0 mmol) in anhydrous THF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction was quenched with EtOAc (10 mL), then diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and 1 M HCl (150 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 100 mL), washed with 1 M HCl (100 mL), water (100 mL) and brine (100 mL), then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield crude diol **3.62** (9.76 g) as a white solid, which was used in the next step without further purification.

#### Data for 3.62:

R<sub>f</sub> = 0.30 (petrol/EtOAc, 1:1)

M.p. = 128 – 130 °C

[α]<sub>D</sub><sup>25</sup> = -16.2° (c 1.11, CHCl<sub>3</sub>)

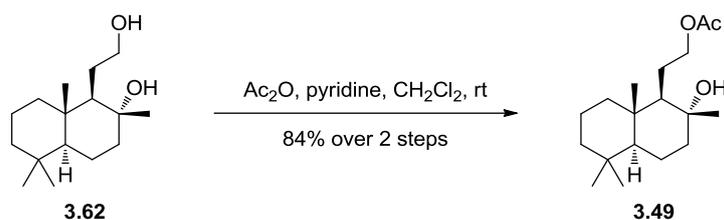
IR (Diamond/ZnSe): 3230, 2918, 1460, 1441, 1389 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.74 (br s, 2H), 3.69 (dt, *J* = 10.0, 4.5 Hz, 1H), 3.39 – 3.33 (m, 1H), 1.83 (dt, *J* = 12.5, 3.0 Hz, 1H), 1.61 – 1.03 (overlapped m, 11H), 1.11 (s, 3H), 0.87 (m, 2H), 0.80 (s, 3H), 0.72 (s, 6H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 72.8, 63.9, 59.3, 56.0, 44.0, 41.9, 39.3, 38.9, 33.4, 33.2, 27.8, 24.5, 21.5, 20.4, 18.4, 15.3.

HRMS (ESI): calculated for C<sub>16</sub>H<sub>30</sub>O<sub>2</sub>Na 277.2138 [M+Na]<sup>+</sup>, found 277.2134.

### Acetate ester **3.49**



To a solution of diol **3.62** (9.58 g, 37.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL) was added Ac<sub>2</sub>O (5.33 mL, 56.4 mmol) followed by pyridine (6.07 mL, 75.3 mmol). The reaction mixture was stirred at room temperature for 12 hours, then quenched with saturated aqueous NH<sub>4</sub>Cl solution (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 100 mL). The combined organic extracts were washed with saturated aqueous NH<sub>4</sub>Cl solution (100 mL), water (100 mL), and brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 5:1 → 1:1) to give acetate ester **3.49** as a colourless oil (9.66 g, 84% over 2 steps).

#### Data for **3.49**:

R<sub>f</sub> = 0.30 (petrol/EtOAc, 5:1)

[α]<sub>D</sub><sup>25</sup> = +1.1° (c 1.76, CHCl<sub>3</sub>)

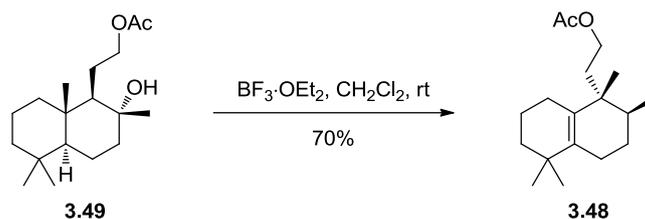
IR (Diamond/ZnSe): 3472, 2925, 2868, 1736, 1721, 1460, 1388, 1366 cm<sup>-1</sup>.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 4.16 – 4.08 (m, 2H), 2.05 (s, 3H), 1.89 (dt, *J* = 12.0, 3.0 Hz, 1H), 1.76 – 1.09 (overlapped m, 12H), 1.16 (s, 3H) 0.92 (d, *J* = 12.0 Hz, 2H), 0.87 (s, 3H), 0.79 (s, 6H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.1, 73.5, 66.6, 58.0, 56.0, 44.4, 41.9, 39.6, 38.7, 33.4, 33.3, 24.5, 23.9, 21.5, 21.1, 20.5, 18.4, 15.3.

HRMS (ESI): calculated for C<sub>18</sub>H<sub>32</sub>O<sub>3</sub>Na 319.2244 [M+Na]<sup>+</sup>, found 319.2224.

### Acetate ester **3.48**



To a solution of acetate ester **3.49** (12.2 g, 41.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (140 mL) was added  $\text{BF}_3 \cdot \text{OEt}_2$  (20.2 mL, 164 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. The mixture was diluted with water (100 mL) and  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic layer was separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 50$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (gradient elution, petrol/EtOAc, 100:0  $\rightarrow$  10:1) to give acetate ester **3.48** as a colourless oil (7.76 g, 70%).

#### Data for **3.48**:

$R_f = 0.70$  (petrol/EtOAc, 5:1)

$[\alpha]_D^{25} = -75.2^\circ$  (c 1.36,  $\text{CHCl}_3$ )

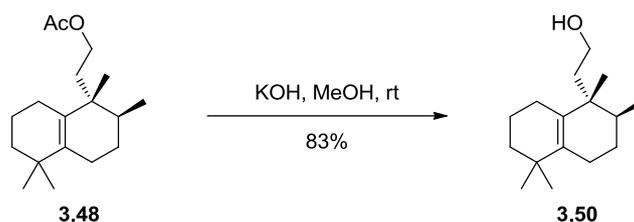
**IR (Diamond/ZnSe):** 2924, 1741, 1458, 1364, 1231  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.06 – 4.01 (m, 1H), 3.87 – 3.83 (m, 1H), 2.06 – 1.27 (overlapped m, 13H), 2.02 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.88 (d,  $J = 7.0$  Hz, 3H), 0.84 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.4, 137.5, 131.9, 62.3, 40.0, 39.9, 34.6, 34.6, 34.5, 29.2, 27.8, 27.3, 26.0, 25.2, 21.3, 21.2, 20.1, 16.3.

**HRMS (ESI):** calculated for  $\text{C}_{18}\text{H}_{30}\text{O}_2\text{Na}$  301.2138  $[\text{M}+\text{Na}]^+$ , found 301.2139.

### Alcohol 3.50



A 10% solution of KOH (21.9 g, 391.2 mmol) in MeOH (220 mL) was added to a flask containing ester **3.48** (7.74 g, 27.8 mmol). The reaction mixture was stirred at room temperature for 30 min, then diluted with saturated aqueous NH<sub>4</sub>Cl solution (150 mL) and Et<sub>2</sub>O (150 mL). The organic layer was separated and the aqueous phase extracted with Et<sub>2</sub>O (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 5:1 → 3:1) to give alcohol **3.50** as a white solid (5.48 g, 83%).

#### Data for 3.50:

**R<sub>f</sub>** = 0.35 (petrol/EtOAc, 5:1)

**M.p.** = 46 – 48 °C

**[α]<sub>D</sub><sup>25</sup>** = -101.6° (c 1.21, CHCl<sub>3</sub>)

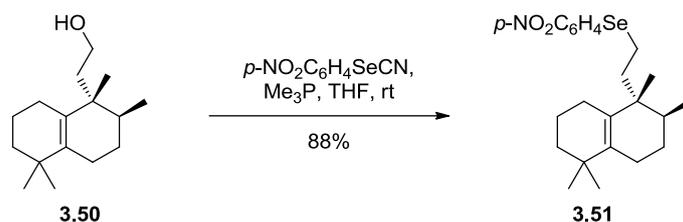
**IR (Diamond/ZnSe):** 3308, 2923, 1458, 1359, 1015 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 3.63 – 3.59 (m, 1H), 3.51 – 3.47 (m, 1H), 2.04 – 1.30 (m, 14H), 0.98 (s, 3H), 0.95 (s, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 137.1, 132.6, 60.1, 39.9, 38.9, 34.6, 34.5, 29.1, 27.7, 27.2, 26.1, 25.1, 21.2, 19.9, 16.3.

**HRMS (EI):** calculated for C<sub>16</sub>H<sub>28</sub>O 236.2140 [M]<sup>+</sup>, found 236.2141.

## Aryl selenide **3.51**



To a solution of alcohol **3.50** (1.30 g, 5.52 mmol) in anhydrous THF (25 mL) was added 2-nitrophenylselenocyanate (1.88 g, 8.29 mmol) and  $\text{Me}_3\text{P}$  (1.0 M in THF, 11.2 mL, 11.2 mmol). The reaction mixture was stirred at room temperature for 1 hour, then quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (50 mL). The mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic extracts were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on  $\text{SiO}_2$  (gradient elution, petrol/ $\text{EtOAc}$ , 100:0  $\rightarrow$  10:1) to give aryl selenide **3.51** as a bright yellow oil (2.29 g, 88%).

### Data for **3.51**:

$R_f = 0.55$  (petrol/ $\text{EtOAc}$ , 10:1)

$[\alpha]_D^{25} = -31.1^\circ$  (c 1.42,  $\text{CHCl}_3$ )

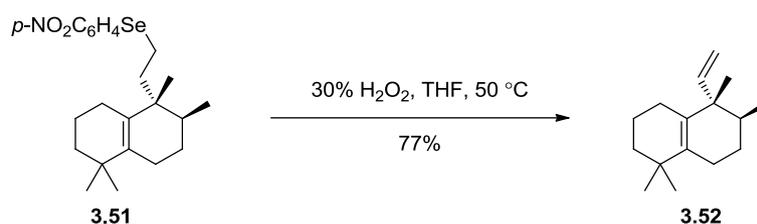
**IR (Diamond/ $\text{ZnSe}$ ):** 2923, 1738, 1590, 1511, 1452, 1330, 728  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.19 (d,  $J = 8.0$  Hz, 1H), 7.44 – 7.41 (m, 2H), 7.24 – 7.19 (m, 1H), 2.80 – 2.73 (m, 1H), 2.52 – 2.45 (m, 1H), 1.95 – 1.93 (m, 3H), 1.73 – 1.25 (m, 10H), 0.91 (s, 6H), 0.81 (d,  $J = 7.0$  Hz, 3H), 0.78 (s, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  145.7, 137.2, 133.3, 132.5, 130.4, 128.1, 125.4, 124.2, 40.9, 38.8, 33.5, 33.2, 32.8, 28.2, 26.6, 26.0, 24.9, 24.0, 20.5, 19.9, 18.8, 15.3.

**HRMS (EI):** calculated for  $\text{C}_{22}\text{H}_{32}\text{NO}_2\text{Se}$  421.1521  $[\text{M}+\text{H}]^+$ , found 421.1510.

## Alkene 3.52



To a solution of aryl selenide **3.51** (2.23 g, 5.31 mmol) in THF (34 mL) was added 30% H<sub>2</sub>O<sub>2</sub> (1.09 mL, 10.6 mmol). The reaction mixture was stirred at room temperature for 15 min, then heated to 50 °C for 45 min. The reaction mixture was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (50 mL) and extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> (neat petrol) to give alkene **3.52** as a colourless oil (0.90 g, 77%).

### Data for 3.52:

R<sub>f</sub> = 0.80 (neat petrol)

[α]<sub>D</sub><sup>25</sup> = +54.1° (c 1.52, CHCl<sub>3</sub>)

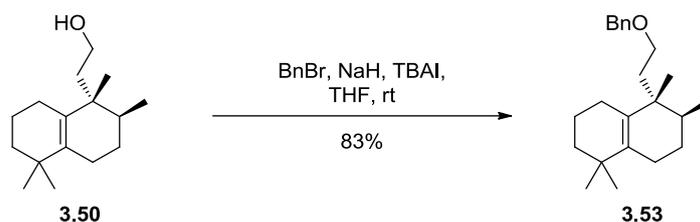
IR (Diamond/ZnSe): 2923, 1631, 1459, 1360 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.55 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.03 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.88 (dd, *J* = 17.5, 1.5 Hz, 1H), 2.08 – 1.92 (m, 2H), 1.84 – 1.78 (m, 2H), 1.65 – 1.27 (m, 7H), 1.00 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.81 (d, *J* = 7.0 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 147.9, 135.5, 131.2, 112.3, 45.0, 39.9, 37.0, 34.3, 28.6, 28.2, 27.5, 26.5, 24.0, 20.0, 17.4, 15.9.

HRMS (EI): calculated for C<sub>16</sub>H<sub>26</sub> 218.2034 [M<sup>+</sup>], found 218.2037.

### Benzyl ether **3.53**



To a solution of alcohol **3.50** (270 mg, 1.14 mmol) in anhydrous THF (3 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.06 g, 1.37 mmol) portion wise and TBAI (4.20 mg, 0.01 mmol). The reaction was stirred at 0 °C for 15 min, followed by the addition of BnBr (0.16 mL, 1.37 mmol). The mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was quenched with MeOH (1 mL), diluted with water (100 mL) and extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 50:1 → 10:1) to give benzyl ether **3.53** as a bright colourless oil (0.31 g, 83%).

#### Data for **3.53**:

R<sub>f</sub> = 0.80 (petrol/EtOAc, 10:1)

[α]<sub>D</sub><sup>25</sup> = -36.8° (c 1.23, CHCl<sub>3</sub>)

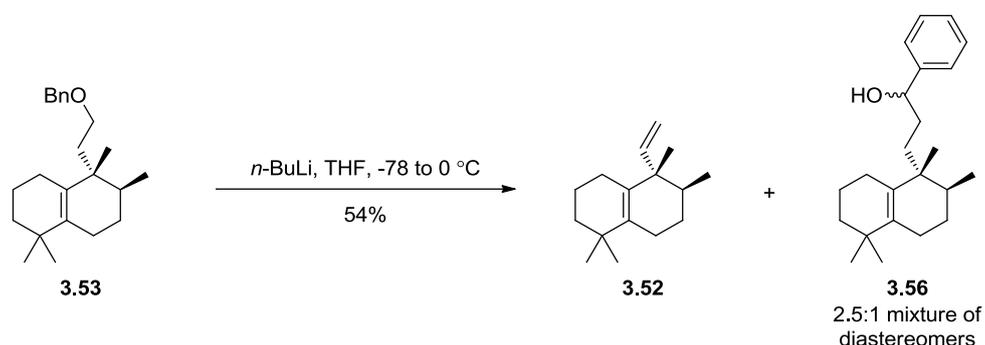
IR (Diamond/ZnSe): 2926, 2871, 1496, 1454, 1310 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.38 – 7.22 (m, 5H), 4.51 – 4.42 (, 2H), 3.46 – 3.37 (, 1H), 3.30 – 3.22 (dt, *J* = 9.0, 5.0 Hz, 1H), 2.05 – 1.67 (m, 6H), 1.61 – 1.32 (m, 7H), 0.96 (s, 3H), 0.91 (s, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.82 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 138.7, 136.8, 132.3, 128.3, 127.6, 127.4, 72.9, 67.4, 39.88, 39.86, 35.6, 34.6, 34.4, 29.1, 27.7, 27.2, 25.9, 25.1, 21.0, 19.9, 16.3.

HRMS (ESI): calculated for C<sub>23</sub>H<sub>35</sub>O 327.2682 [M+H]<sup>+</sup>, found 327.2685.

## Alkene 3.52



To a solution of benzyl ether **3.53** (1.61 g, 4.92 mmol) in anhydrous THF (50 mL) was added  $n\text{-BuLi}$  (2.5 M in hexane, 9.86 mL, 24.7 mmol) dropwise at  $-78$  °C under inert atmosphere. The reaction mixture was stirred at  $-78$  °C for 30 min, then warmed to  $0$  °C and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (20 mL). The reaction mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic extracts were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (neat petrol) to give alkene **3.52** as a colourless oil (0.58 g, 54%).

### Data for 3.52:

$R_f = 0.80$  (neat petrol)

$[\alpha]_D^{25} = +54.1^\circ$  (c 1.52,  $\text{CHCl}_3$ )

**IR (Diamond/ZnSe):** 2923, 1631, 1459, 1360  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.55 (dd,  $J = 17.5, 10.5$  Hz, 1H), 5.03 (dd,  $J = 10.5, 1.5$  Hz, 1H), 4.88 (dd,  $J = 17.5, 1.5$  Hz, 1H), 2.08 – 1.92 (m, 2H), 1.84 – 1.78 (m, 2H), 1.65 – 1.27 (m, 7H), 1.00 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.81 (d,  $J = 7.0$  Hz, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  147.9, 135.5, 131.2, 112.3, 45.0, 39.9, 37.0, 34.3, 28.6, 28.2, 27.5, 26.5, 24.0, 20.0, 17.4, 15.9.

**HRMS (EI):** calculated for  $\text{C}_{16}\text{H}_{26}$  218.2034 [ $\text{M}^+$ ], found 218.2037.

**Data for 3.56:**

$R_f = 0.60$  (petrol/EtOAc, 4:1)

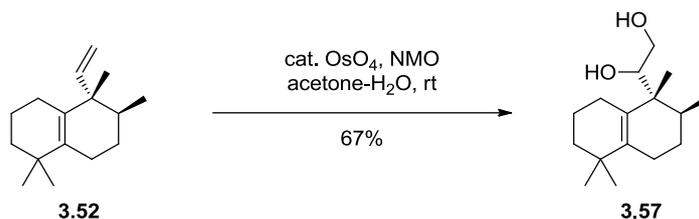
**IR (Diamond/ZnSe):** 3351, 2960, 2923, 2867, 1493, 1454  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.36 – 7.26 (m, 10H), 4.60 – 4.56 (m, 2H), 1.98 – 1.24 (m, 30H), 0.96 (s, 3H), 0.94 (overlapped s, 3H), 0.94 (overlapped s, 3H), 0.93 (s, 3H), 0.82 (d,  $J = 7.0$  Hz, 3H). 0.77 (s 3H), 0.76 (s, 3H), 0.71 (d,  $J = 7.0$  Hz, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  144.9, 144.8, 137.1, 137.0, 132.4, 132.3, 128.44, 128.38, 127.6, 127.5, 126.01, 125.96, 75.6, 75.5, 40.5, 40.4, 39.94, 39.91, 34.4, 34.4, 33.8, 33.7, 33.6, 33.4, 32.0, 31.9, 29.2, 29.2, 27.68, 27.66, 27.23, 27.21, 25.7, 25.5, 25.3, 25.3, 21.2, 21.1, 20.00, 19.95, 16.1, 16.0.

**HRMS (EI):** calculated for  $\text{C}_{23}\text{H}_{33}$  309.2582 [ $\text{M}^+$ ], found 309.2575.

## Diol 3.57



To a solution of alkene **3.52** (302 mg, 1.38 mmol) in acetone-H<sub>2</sub>O (9:1, 10 mL) was added NMO (324 mg, 2.77 mmol) and OsO<sub>4</sub> (18 mg, 0.07 mmol) at room temperature. The reaction mixture was stirred at room temperature for 36 hours. The mixture was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (10 mL), then diluted with Et<sub>2</sub>O (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 5: 1 → 2:1) to give diol **3.57** as a colourless oil (232 mg, 67%).

### Data for **3.57**:

R<sub>f</sub> = 0.35 (petrol/EtOAc, 20:1)

[α]<sub>D</sub><sup>25</sup> = -0.9° (c 1.01, CHCl<sub>3</sub>)

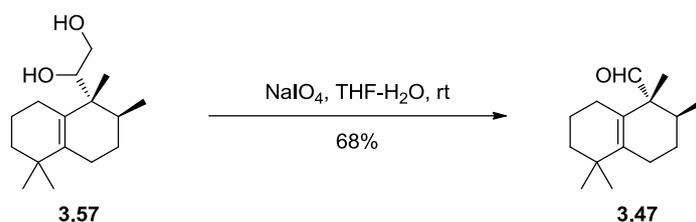
IR (Diamond/ZnSe): 3387, 2924, 1459, 1016, 1059 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.60 (s, 3H), 2.10 – 1.83 (m, 6H), 1.66 – 1.62 (m, 2H), 1.57 – 1.48 (m, 2H), 1.40 – 1.37 (m, 2H), 1.25 – 1.19 (m, 1H), 0.96 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H), 0.77 (d, *J* = 7.0 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 141.2, 128.5, 77.9, 63.9, 44.4, 39.7, 34.9, 32.5, 29.0, 28.5, 26.9, 26.1, 22.0, 19.9, 19.6, 17.5.

HRMS (ESI): calculated for C<sub>16</sub>H<sub>28</sub>O<sub>2</sub>Na 275.1982 [M+Na]<sup>+</sup>, found 275.1980.

## Aldehyde 3.47



To a solution of diol **3.57** (0.67 g, 2.66 mmol) in THF-H<sub>2</sub>O (2:1, 100 mL) was added NaIO<sub>4</sub> (1.37 g, 6.39 mmol). The reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with water (50 mL) and Et<sub>2</sub>O (50 mL). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO<sub>2</sub> (petrol/EtOAc, 10:1) to give aldehyde **3.47** (0.40 g, 68%) as a colourless solid.

### Data for **3.47**:

**R<sub>f</sub>** = 0.80 (petrol/EtOAc, 5:1)

**Mp** = 37 – 39 °C

$[\alpha]_D^{25} = +92.4^\circ$  (c 1.80, CHCl<sub>3</sub>)

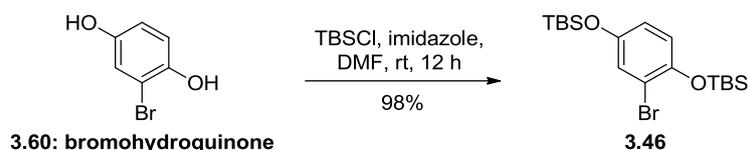
**IR (Diamond/ZnSe):** 2927, 1722, 1458 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 9.17 (s, 1H), 2.04 – 2.00 (m, 2H), 1.90 – 1.85 (m, 1H), 1.82 – 1.75 (m, 1H), 1.61 – 1.27 (m, 7H), 0.95 (s, 3H), 0.93 (s, 6H), 0.69 (d, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 204.5, 138.9, 125.5, 54.5, 38.5, 33.4, 30.8, 27.6, 26.84, 26.75, 25.2, 23.8, 18.6, 15.2, 11.9.

**HRMS (ESI):** calculated for C<sub>15</sub>H<sub>24</sub>O 220.1827 [M<sup>+</sup>], found 220.1835

## Aryl Bromide 3.46



To a solution of bromohydroquinone (5.00 g, 26.45 mmol) in DMF (40 mL) was added TBSCl (11.96 g, 79.36 mmol) and imidazole (10.81 g, 158.72 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. The mixture was diluted with water (50 mL) and Et<sub>2</sub>O (50 mL). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO<sub>2</sub> (gradient elution, petrol/EtOAc, 50:1 → 20:1) to give **3.46** (10.82 g, 98%) as a white solid. The spectroscopic data for this compound matched those previously reported.<sup>34</sup>

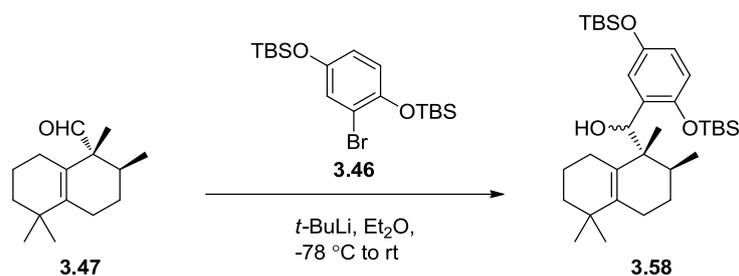
### Partial data for 3.46:

R<sub>f</sub> = 0.80 (petrol/EtOAc, 20:1)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.01 (d, *J* = 3.0 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.64 (dd, *J* = 8.5, 3.0 Hz, 1H), 1.03 (s, 9H), 0.96 (s, 9H), 0.21 (s, 6H), 0.17 (s, 6H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 150.1, 147.2, 124.7, 120.3, 119.6, 115.0, 25.9, 25.8, 18.5, 18.3, -4.1, -4.4.

## Benzylic alcohol 3.58



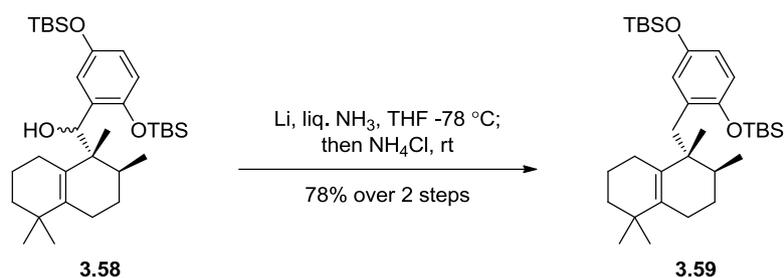
To a solution of **3.46** (0.82 g, 1.95 mmol) in anhydrous  $\text{Et}_2\text{O}$  (6 mL) was added  $t\text{-BuLi}$  (1.7 M in pentene, 1.10 mL, 1.87 mmol) dropwise at  $-78\text{ }^\circ\text{C}$ . The reaction was stirred at  $-78\text{ }^\circ\text{C}$  for 30 min and a solution of aldehyde **3.47** (210 mg, 0.93 mmol) in anhydrous  $\text{Et}_2\text{O}$  (6 mL) was added dropwise. The resultant mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 30 min, then allowed to warm to room temperature. The mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (50 mL) and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on  $\text{SiO}_2$  (gradient elution, petrol/ $\text{EtOAc}$ , 50:1  $\rightarrow$  20:1) to give **3.58** as a mixture of diastereomers with some inseparable impurities. The crude material was then used directly in the next step without further purification.

### Data for **3.58**:

$R_f$  = 0.60 (petrol/ $\text{EtOAc}$ , 20:1)

IR (Diamond/ $\text{ZnSe}$ ): 3508, 2956, 2929, 1253, 911, 837, 778  $\text{cm}^{-1}$ .

### TBS-protected hydroquinone **3.59**



To a stirred mixture of liquid NH<sub>3</sub> (35 mL) and anhydrous THF (18 mL) at -78 °C was added Li (65 mg, 9.29 mmol). The mixture was stirred for 15 min, followed by dropwise addition of **3.58** (0.52 g, crude from the previous step) in THF (10 mL). The reaction stirred at -78 °C for 15 min, then quenched with solid NH<sub>4</sub>Cl (2.00 g) and the NH<sub>3</sub> was allowed to evaporate over 2 hours by warming to room temperature. The resultant mixture was diluted with H<sub>2</sub>O (100 mL) and extracted with Et<sub>2</sub>O (3 × 50 mL). The organic extracts were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/EtOAc, 50:1) to give **3.59** as a colourless oil (390 mg, 78% over two steps).

#### Data for **3.59**:

R<sub>f</sub> = 0.80 (petrol/EtOAc, 50:1)

[α]<sub>D</sub><sup>25</sup> = -3.1° (c 1.89, CHCl<sub>3</sub>)

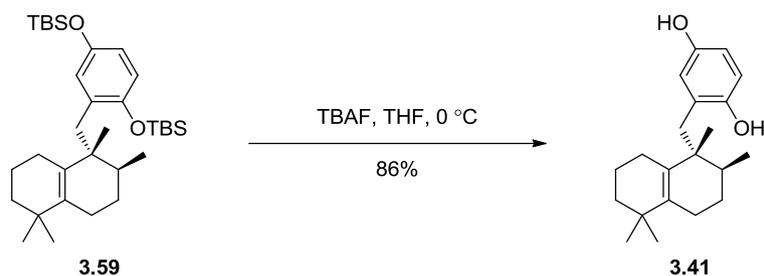
IR (Diamond/ZnSe): 2927, 1489, 1211, 918, 837, 777 cm<sup>-1</sup>.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 6.76 (d, *J* = 3.0 Hz, 1H), 6.60 (d, *J* = 9.0 Hz, 1H), 6.48 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.87 (d, *J* = 15.5 Hz, 1H), 2.55 (d, *J* = 15.5 Hz, 1H), 2.09 – 1.92 (m, 5H), 1.71 – 1.55 (m, 5H), 1.47 – 1.45 (m, 2H), 1.38 – 1.32 (m, 2H), 1.03 (s, 3H), 1.00 (s, 9H), 0.99 (s, 3H), 0.96 (s, 9H), 0.92 (s, 3H), 0.75 (d, *J* = 7.0 Hz, 3H), 0.17 (d, *J* = 10.5 Hz, 6H), 0.14 (s, 6H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 148.9, 148.3, 135.8, 133.0, 131.6, 122.0, 118.6, 116.9, 41.6, 39.8, 35.0, 34.4, 33.5, 28.5, 28.1, 27.1, 26.5, 26.03, 25.95, 25.8, 24.0, 22.4, 20.1, 18.3, 18.1, 16.2, -4.1, -4.2, -4.38, -4.40.

HRMS (ESI): calculated for C<sub>33</sub>H<sub>58</sub>O<sub>2</sub>Si<sub>2</sub>Na 565.3868 [M+Na]<sup>+</sup>, found 565.3862.

### Hydroquinone 3.41



To a solution of **3.59** (190 mg, 0.34 mmol) in anhydrous THF (4 mL) was added TBAF (1 M in THF, 0.80 mL, 0.80 mmol) at 0 °C. The reaction was stirred at 0 °C for 20 min, then quenched with water (30 mL) and extracted with Et<sub>2</sub>O (3 × 20 mL). The organic extracts were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient elution, petrol/EtOAc, 10:1 → 4:1 → 2:1) to give **3.41** as a white solid (93 mg, 86%).

#### Data for 3.41:

**R<sub>f</sub>** = 0.35 (petrol/EtOAc, 4:1)

**Mp** = 134 – 135 °C

$[\alpha]_{\text{D}}^{25} = +40.6^\circ$  (c 0.99, CHCl<sub>3</sub>)

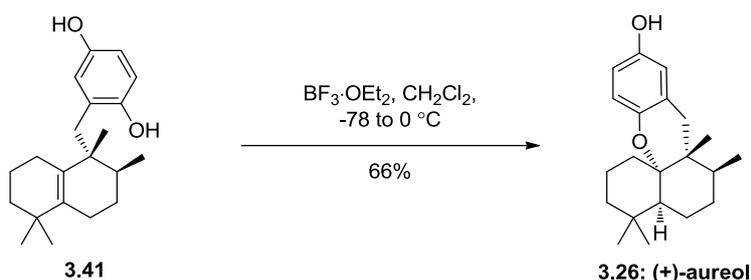
**IR (Diamond/ZnSe):** 3367, 2925, 2870, 1499, 1454, 1196, 908 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 6.67 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 3.0 Hz, 1H), 6.55 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.87 (s, 1H), 4.31 (s, 1H), 2.93 (d, *J* = 14.5 Hz, 1H), 2.50 (d, *J* = 14.5 Hz, 1H), 2.13 – 2.08 (m, 1H), 2.00 – 1.95 (m, 1H), 1.91 – 1.86 (m, 2H), 1.76 – 1.73 (m, 1H), 1.66 – 1.63 (m, 1H), 1.59 – 1.39 (m, 5H), 1.05 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.84 (d, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 148.9, 148.7, 137.8, 132.7, 127.7, 118.4, 116.5, 113.7, 41.7, 40.5, 39.6, 35.7, 34.6, 28.5, 28.1, 27.1, 26.2, 22.4, 22.3, 19.7, 15.8.

**HRMS (EI):** calculated for C<sub>21</sub>H<sub>30</sub>O<sub>2</sub> 315.2319 [M+H]<sup>+</sup>, found 315.2310.

### (+)-Aureol (3.26)



To a solution of hydroquinone **3.41** (79 mg, 0.25 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (25 mL) was added  $\text{BF}_3 \cdot \text{OEt}_2$  (0.14 mL, 1.13 mmol) at  $-60$  °C. The reaction mixture was stirred for 3 hours at  $-60$  °C, then warmed to  $-20$  °C for 1 hour and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (30 mL). The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (petrol/EtOAc, 4:1) to give (+)-aureol (**3.26**) as a white solid (52 mg, 66%).

#### Data for (+)-aureol:

$R_f = 0.50$  (petrol/EtOAc, 4:1)

$\text{Mp} = 143 - 144$  °C [lit., mp  $144 - 145$  °C]

$[\alpha]_D^{25} = +52.3^\circ$  (c 0.84,  $\text{CHCl}_3$ ), lit. value  $[\alpha]_D^{25} = +65^\circ$  (c 2.0,  $\text{CCl}_4$ )<sup>9</sup>

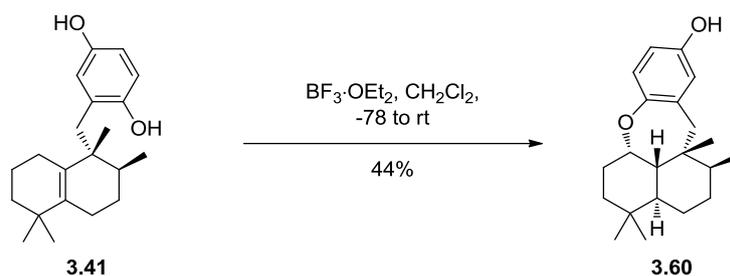
**IR (Diamond/ZnSe):** 3298, 2935, 2870, 1495, 1450, 952  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.60 (d,  $J = 9.0$  Hz, 1H), 6.56 (dd,  $J = 9.0, 3.0$  Hz, 1H), 6.49 (d,  $J = 3.0$  Hz, 1H), 4.23 (br s, 1H), 3.37 (d,  $J = 17.0$  Hz, 1H), 2.11 – 1.99 (m, 2H), 1.96 (d,  $J = 17.0$  Hz, 1H), 1.84 – 1.76 (m, 2H), 1.71 – 1.64 (m, 2H), 1.60 – 1.53 (m, 1H), 1.50 – 1.34 (m, 4H), 1.11 (d,  $J = 7.5$  Hz, 3H), 1.06 (s, 3H), 0.92 (s, 3H), 0.78 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  148.3, 145.8, 122.2, 117.3, 115.1, 114.0, 82.4, 44.0, 39.3, 38.1, 37.4, 33.9, 33.8, 31.9, 29.8, 29.3, 27.9, 22.2, 20.2, 18.4, 17.3.

**HRMS (EI):** calculated for  $\text{C}_{21}\text{H}_{30}\text{O}_2$  315.2319  $[\text{M}+\text{H}]^+$ , found 315.2312.

### Cyclic ether 3.60



To a solution of hydroquinone **3.41** (61 mg, 0.19 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (20 mL) was added  $\text{BF}_3 \cdot \text{OEt}_2$  (0.10 mL, 0.81 mmol) at  $-60$  °C. The reaction mixture was stirred for 3 hours at  $-60$  °C, then warmed to room temperature for 10 min and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (30 mL). The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The organic phases were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (petrol/EtOAc, 4:1) to give **3.60** as a white solid (27 mg, 44%).

#### Data for 3.60:

$R_f = 0.50$  (petrol/EtOAc, 4:1)

$\text{Mp} = 189 - 191$  °C

$[\alpha]_D^{25} = -3.0^\circ$  (c 0.66,  $\text{CHCl}_3$ )

**IR (Diamond/ZnSe):** 3390, 2942, 2909, 2869, 1606, 1501, 1449, 1368  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.77 (d,  $J = 8.5$  Hz, 1H), 6.52 (dd,  $J = 8.5, 3.0$  Hz, 1H), 6.48 (d,  $J = 3.0$  Hz, 1H), 4.37 (s, 1H), 3.88 (br s, 1H), 3.81 (d,  $J = 14.0$  Hz, 1H), 2.03 (dt,  $J = 12.0, 4.0$  Hz, 1H), 1.95 – 1.89 (m, 2H), 1.84 (dt,  $J = 14.0, 4.0$  Hz, 1H), 1.79 (d,  $J = 14.0$  Hz, 1H), 1.63 – 1.57 (m, 2H), 1.53 – 1.51 (m, 1H), 1.49 (d,  $J = 12.0$  Hz, 1H), 1.38 – 1.33 (m, 1H), 1.30 (dd,  $J = 13.0, 4.0$  Hz, 1H), 1.19 (dt,  $J = 10.0, 3.0$  Hz, 1H), 0.97 (s, 3H), 0.95 (overlapped d, 3H), 0.89 (s, 3H), 0.72 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  153.1, 151.0, 136.1, 121.3, 117.6, 113.1, 76.3, 43.2, 42.8, 41.9, 39.1, 35.9, 35.8, 33.3, 30.5, 30.0, 27.8, 24.4, 19.7, 19.6, 15.2.

### 3.9 References

1. Birladeanu, L. *J. Chem. Educ.* **2000**, *77*, 858-863.
2. Huff, M. W.; Telford, D. E. *Trends Pharmacol. Sci.* **2005**, *26*, 335-340.
3. Thoma, R.; Schulz-Gasch, T.; D'Arcy, B.; Benz, J.; Aebi, J.; Dehmlow, H.; Hennig, M.; Stihle, M.; Ruf, A. *Nature* **2004**, *432*, 118-122.
4. Ayer, W. A.; Lee, S. P.; Nakashima, T. T. *Can. J. Chem.* **1979**, *57*, 3338-43.
5. Wright, D. L.; Whitehead, C. R. *Org. Prep. Proced. Int.* **2000**, *32*, 307, 309-330.
6. Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2012**, *134*, 11995-11997.
7. Kleinfelter, D. C.; Gerteisen, T. J. *J. Org. Chem.* **1971**, *36*, 3255-9.
8. George, J. H.; McArdle, M.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron* **2010**, *66*, 6321-6330.
9. Djura, P.; Stierle, D. B.; Sullivan, B.; Faulkner, D. J.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1435-41.
10. Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Magno, S.; Pansini, M. *J. Nat. Prod.* **2000**, *63*, 263-266.
11. Longeon, A.; Copp, B. R.; Quévrain, E.; Roué, M.; Kientz, B.; Cresteil, T.; Petek, S.; Debitus, C.; Bourguet-Kondracki, M.-L. *Mar. Drugs* **2011**, *9*, 879-888.
12. Wright, A. E.; Rueth, S. A.; Cross, S. S. *J. Nat. Prod.* **1991**, *54*, 1108-11.
13. Taishi, T.; Takechi, S.; Mori, S. *Tetrahedron Lett.* **1998**, *39*, 4347-4350.
14. Utkina, N. K.; Denisenko, V. A.; Scholokova, O. V.; Virovaya, M. V.; Prokofeva, N. G. *Tetrahedron Lett.* **2003**, *44*, 101-102.
15. Longley, R. E.; McConnell, O. J.; Essich, E.; Harmody, D. *J. Nat. Prod.* **1993**, *56*, 915-20.

16. Shen, Y.-C.; Liaw, C.-C.; Ho, J.-R.; Khalil, A. T.; Kuo, Y.-H. *Nat. Prod. Res.* **2006**, *20*, 578-585.
17. Wright, A. E.; Cross, S. S.; Burren, N. S.; Koehn, F. Antiviral and antitumor terpene hydroquinones from marine sponge and methods of use. WO9112250A1, 1991.
18. Nakamura, M.; Suzuki, A.; Nakatani, M.; Fuchikami, T.; Inoue, M.; Katoh, T. *Tetrahedron Lett.* **2002**, *43*, 6929-6932.
19. Nakatani, M.; Nakamura, M.; Suzuki, A.; Fuchikami, T.; Inoue, M.; Katoh, T. *ARKIVOC (Gainesville, FL, U. S.)* **2003**, 45-57.
20. Suzuki, A.; Nakatani, M.; Nakamura, M.; Kawaguchi, K.; Inoue, M.; Katoh, T. *Synlett* **2003**, 329-332.
21. Sakurai, J.; Oguchi, T.; Watanabe, K.; Abe, H.; Kanno, S.-i.; Ishikawa, M.; Katoh, T. *Chem. - Eur. J.* **2008**, *14*, 829-837.
22. Urban, S.; Capon, R. J. *Aust. J. Chem.* **1994**, *47*, 1023-9.
23. Lakshmi, V.; Gunasekera, S. P.; Schmitz, F. J.; Ji, X.; Van der Helm, D. *J. Org. Chem.* **1990**, *55*, 4709-11.
24. Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 7769-7772.
25. Marcos, I. S.; Conde, A.; Moro, R. F.; Basabe, P.; Díez, D.; Urones, J. G. *Tetrahedron* **2010**, *66*, 8280-8290.
26. Marcos, I. S.; Hernández, F. A.; Sexmero, M. J.; Díez, D.; Basabe, P.; Pedrero, A. B.; García, N.; Sanz, F.; Urones, J. G. *Tetrahedron Lett.* **2002**, *43*, 1243-1245.
27. Marcos, I. S.; García, N.; Sexmero, M. J.; Hernández, F. A.; Escola, M. A.; Basabe, P.; Díez, D.; Urones, J. G. *Tetrahedron* **2007**, *63*, 2335-2350.
28. Ling, T.; Poupon, E.; Rueden, E. J.; Kim, S. H.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2002**, *124*, 12261-12267.

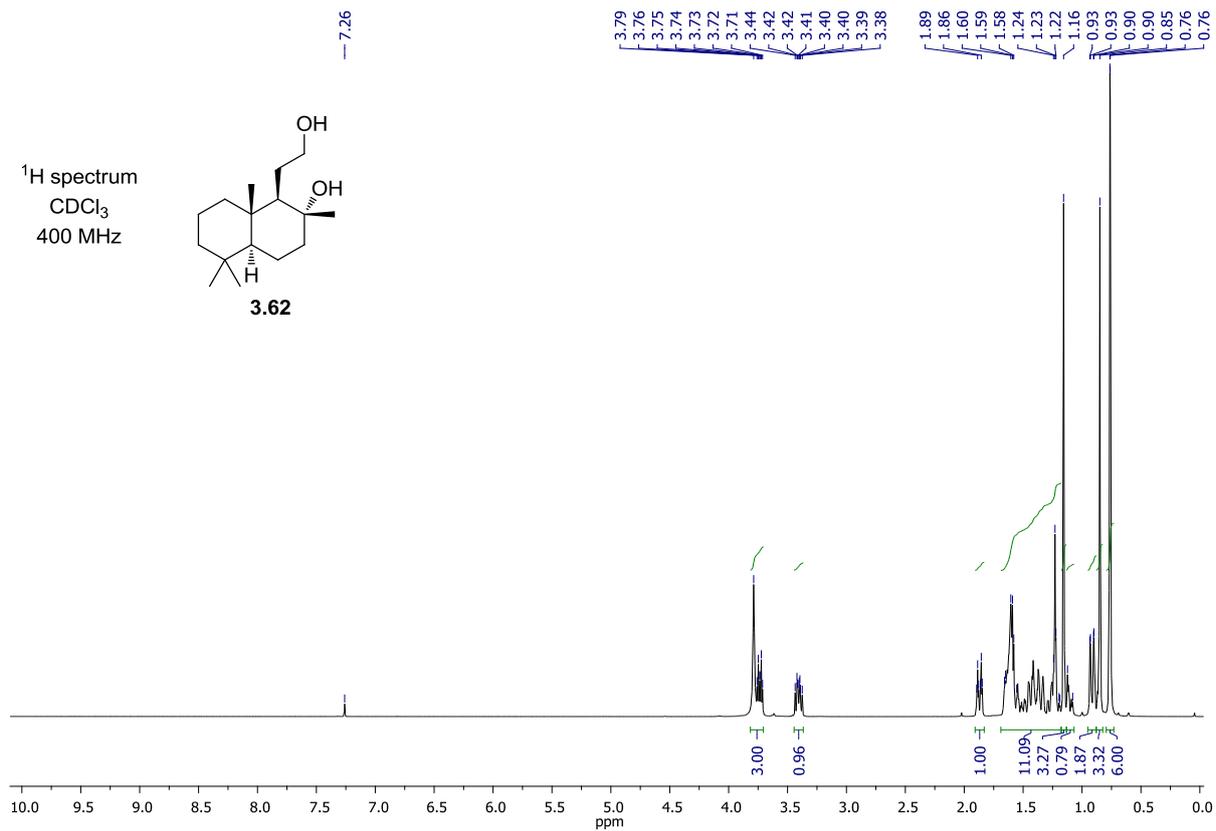
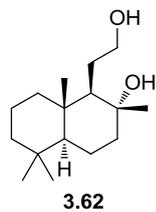
29. Ling, T.; Poupon, E.; Rueden, E. J.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 819-822.
30. Cambie, R.; Moratti, S.; Rutledge, P.; Weston, R.; Woodgate, P. *Aust. J. Chem.* **1990**, *43*, 1151-1162.
31. Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947-9.
32. Matsushita, M.; Nagaoka, Y.; Hioki, H.; Fukuyama, Y.; Kodama, M. *Chem. Lett.* **1996**, 1039-1040.
33. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Letters* **1976**, *17*, 1973-1976.
34. Willis, J. P.; Gogins, K. A. Z.; Miller, L. L. *J. Org. Chem.* **1981**, *46*, 3215-18.
35. Mitome, H.; Nagasawa, T.; Miyaoka, H.; Yamada, Y.; van Soest, R. W. M. *Tetrahedron* **2002**, *58*, 1693-1696.

## **Appendix Two**

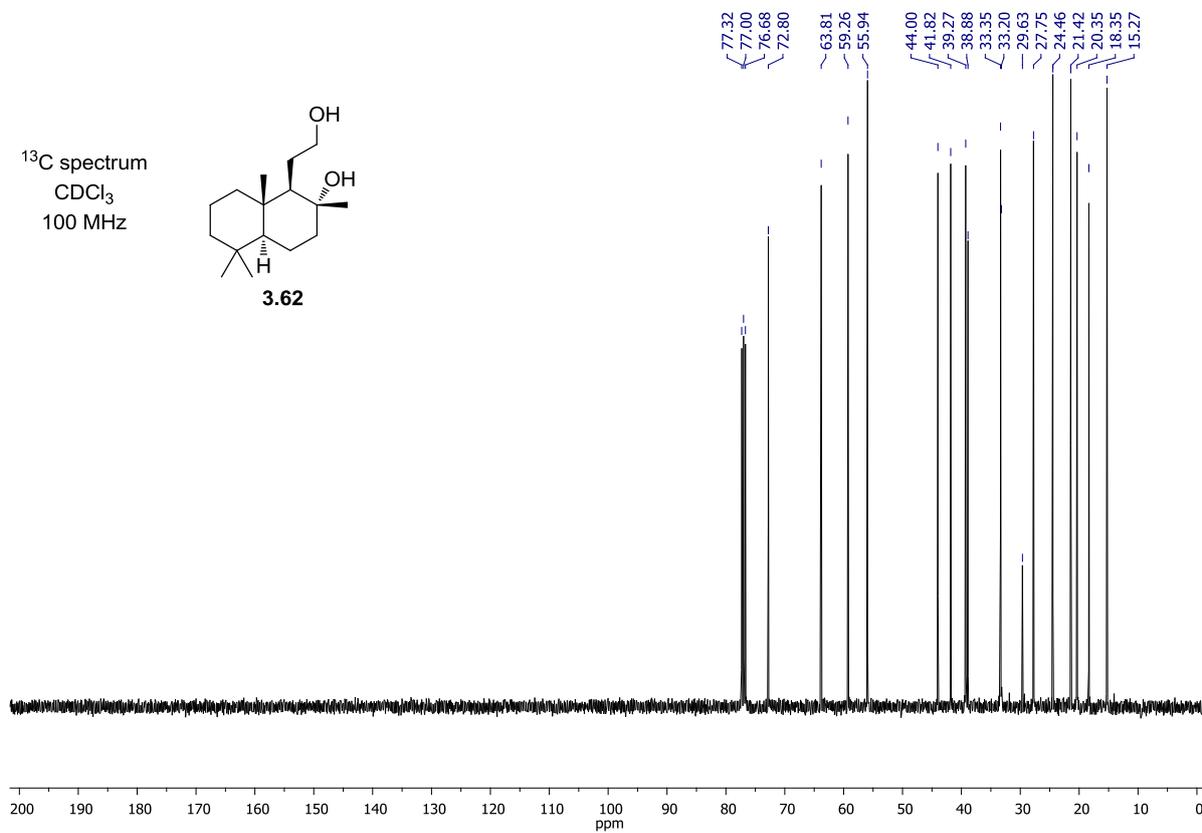
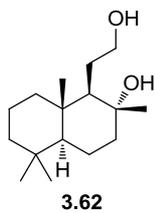
**Spectra Relevant to Chapter Three:**

**The Total Synthesis of (+)-Aureol**

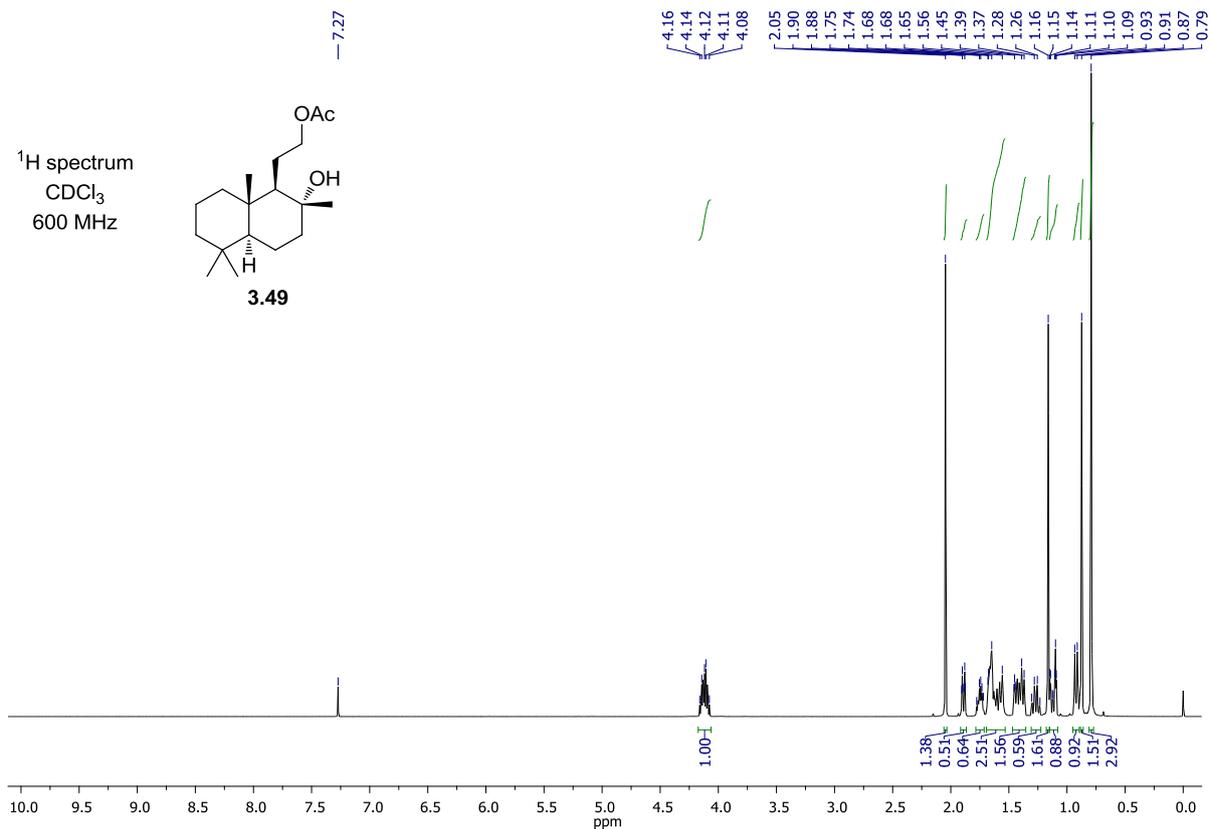
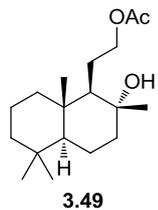
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400 MHz



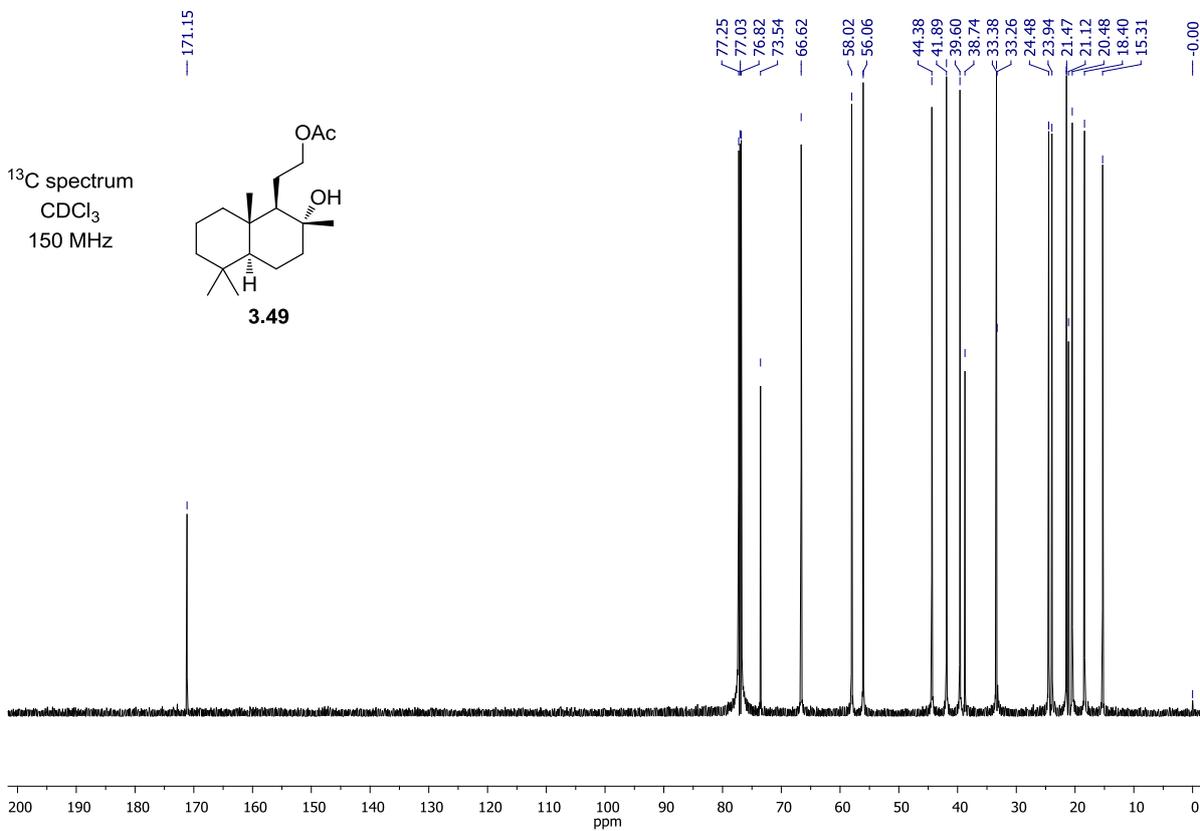
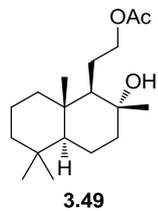
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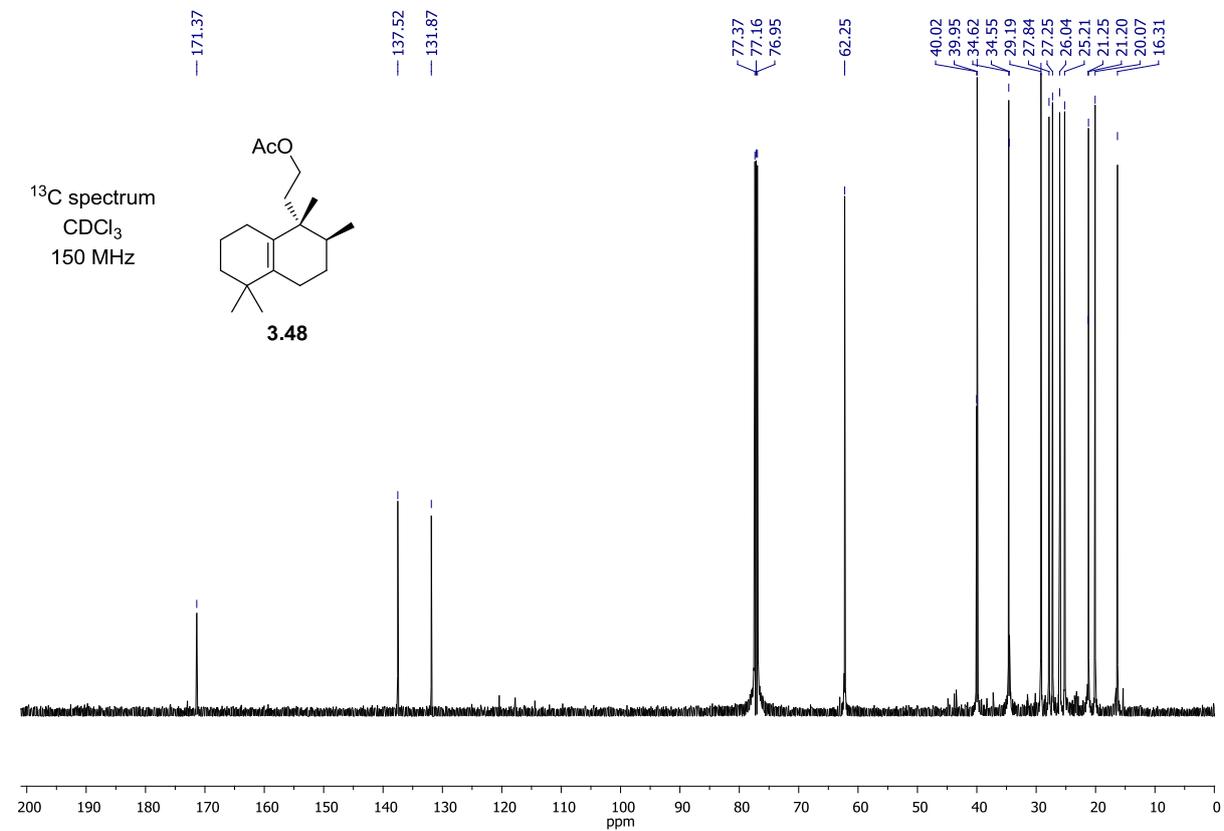
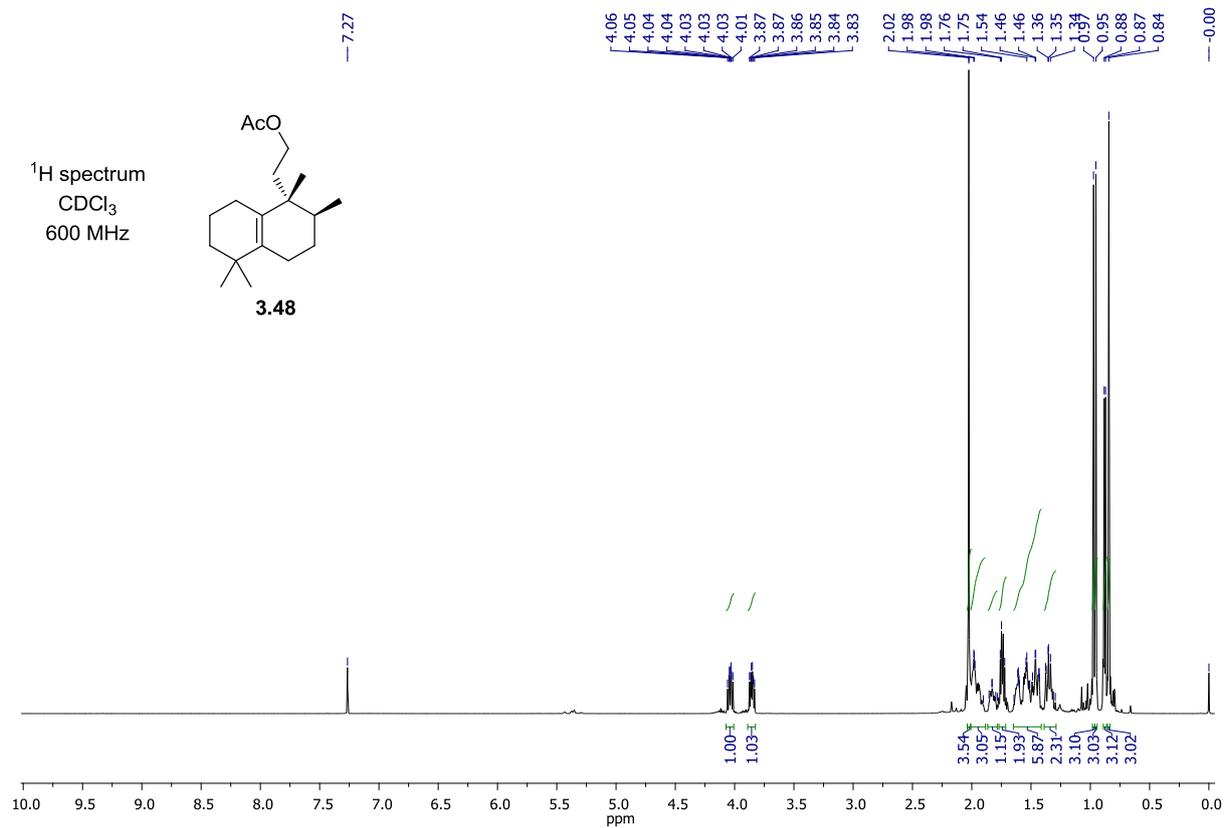


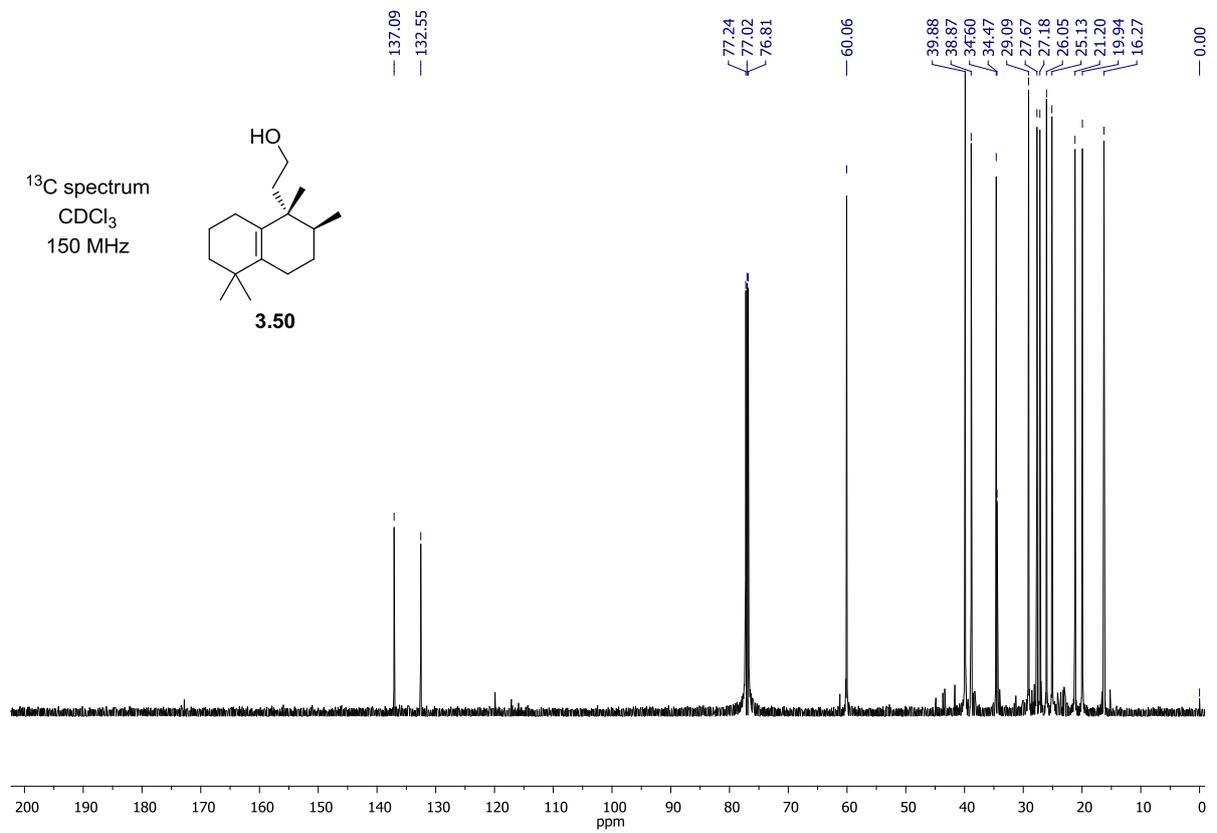
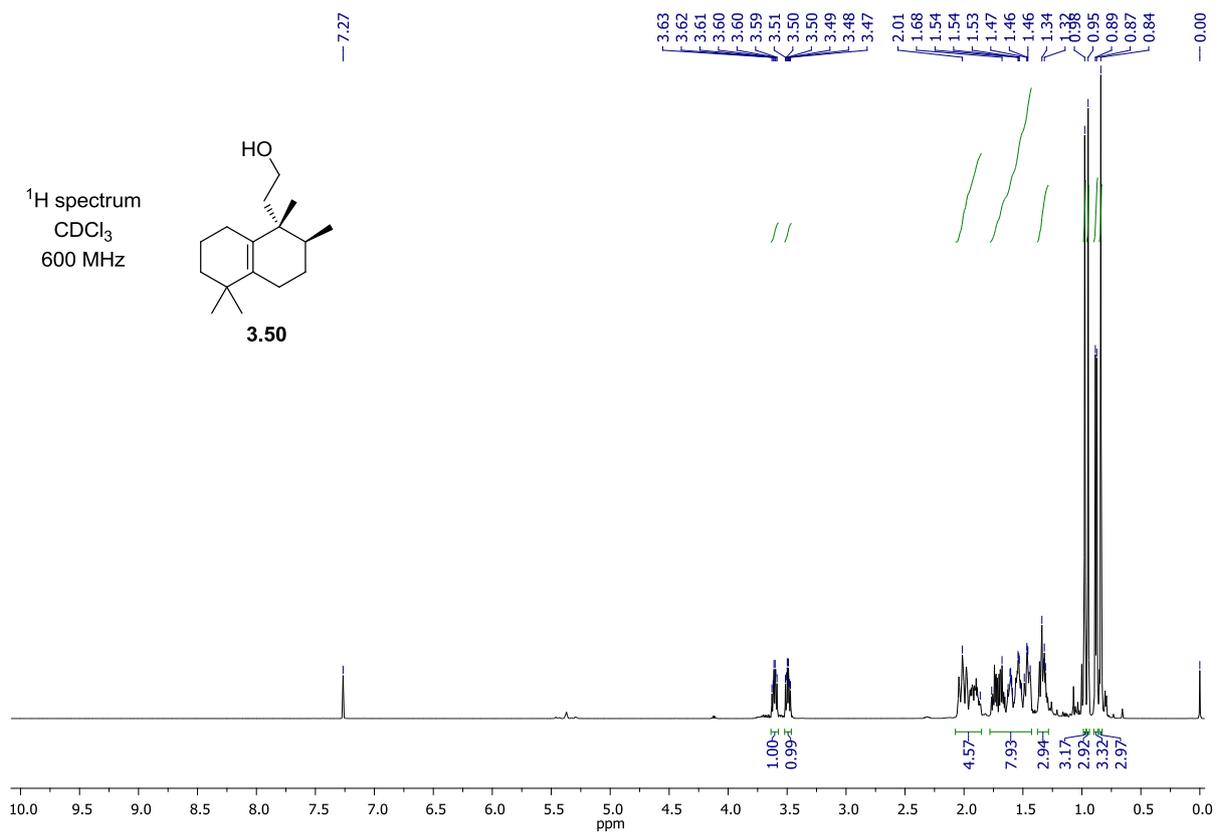
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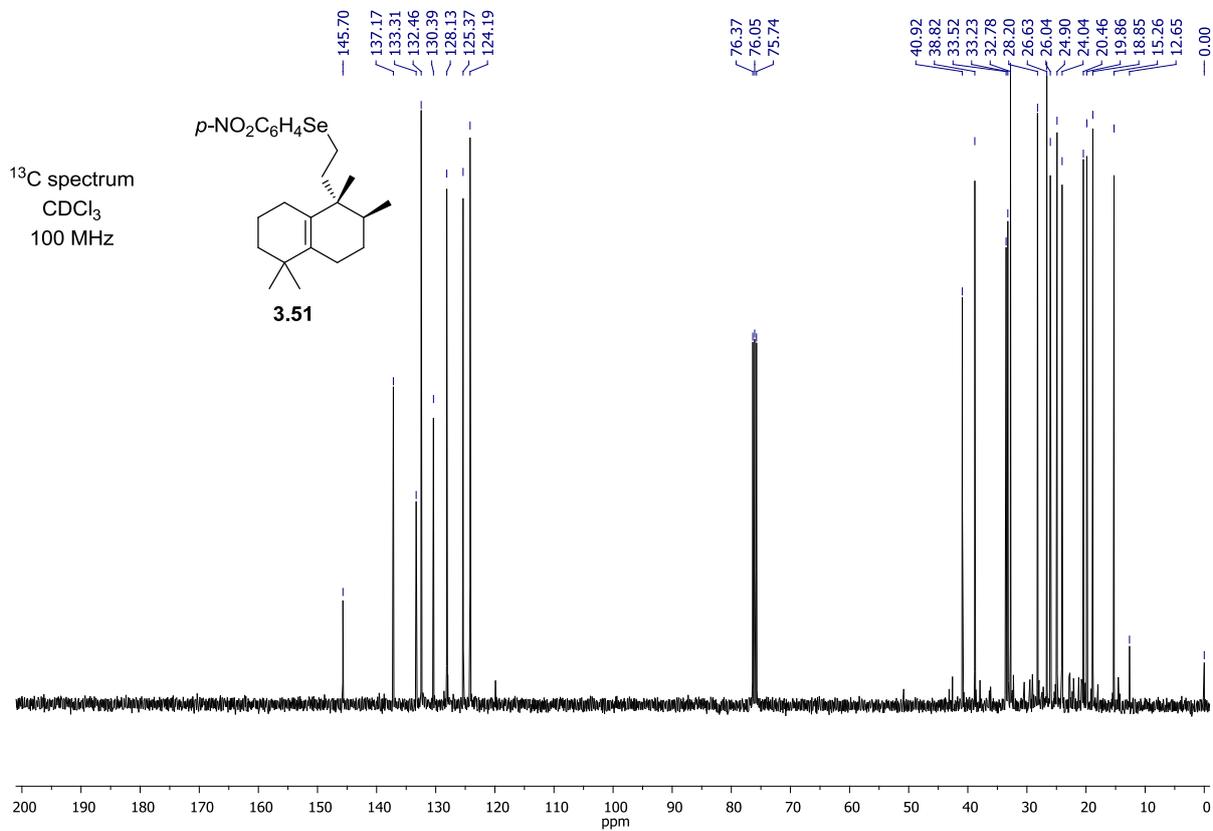
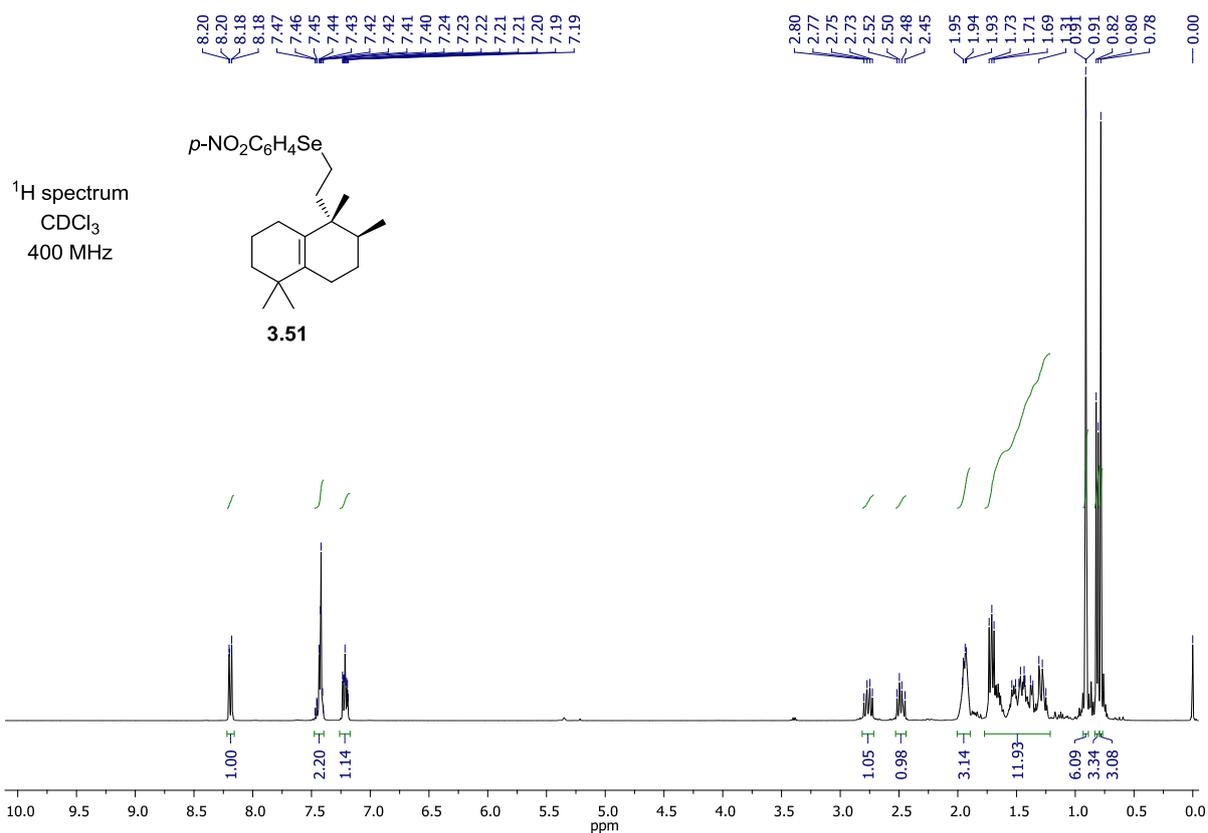


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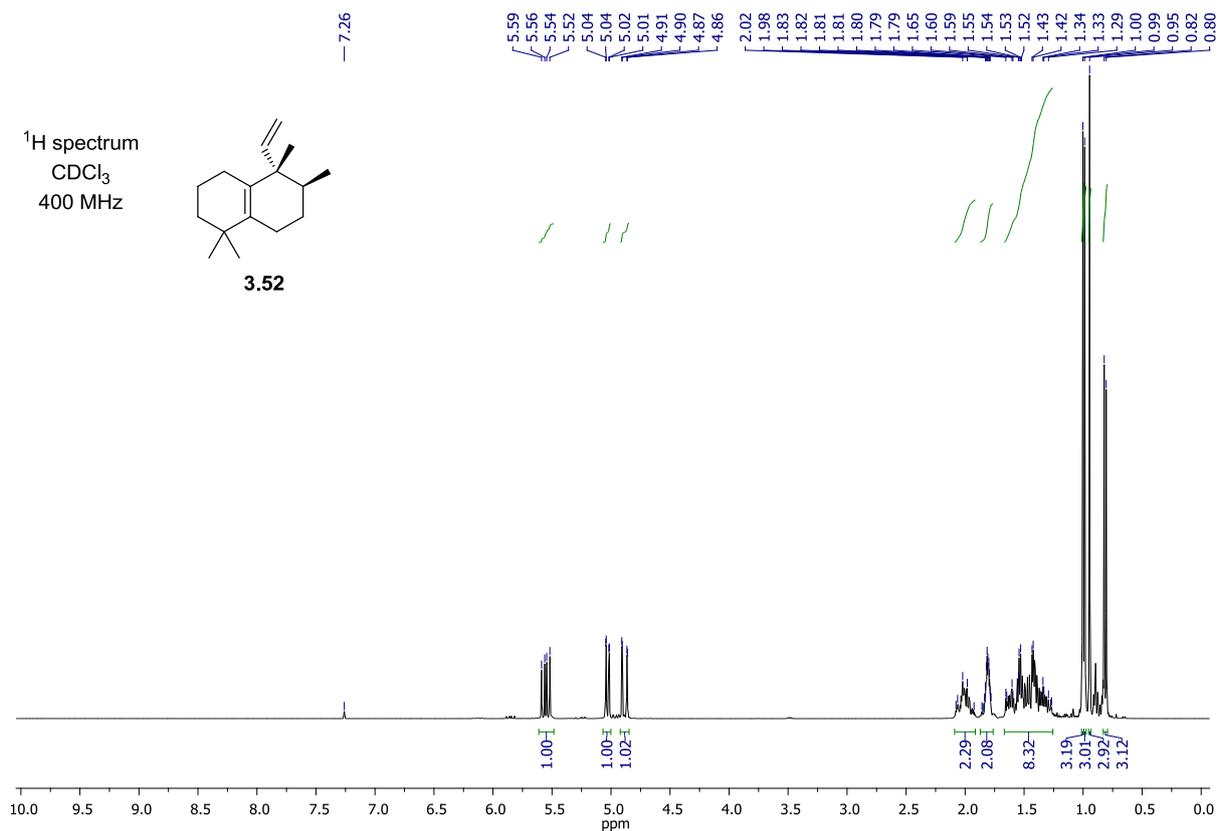
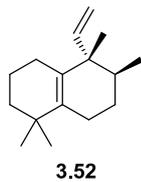




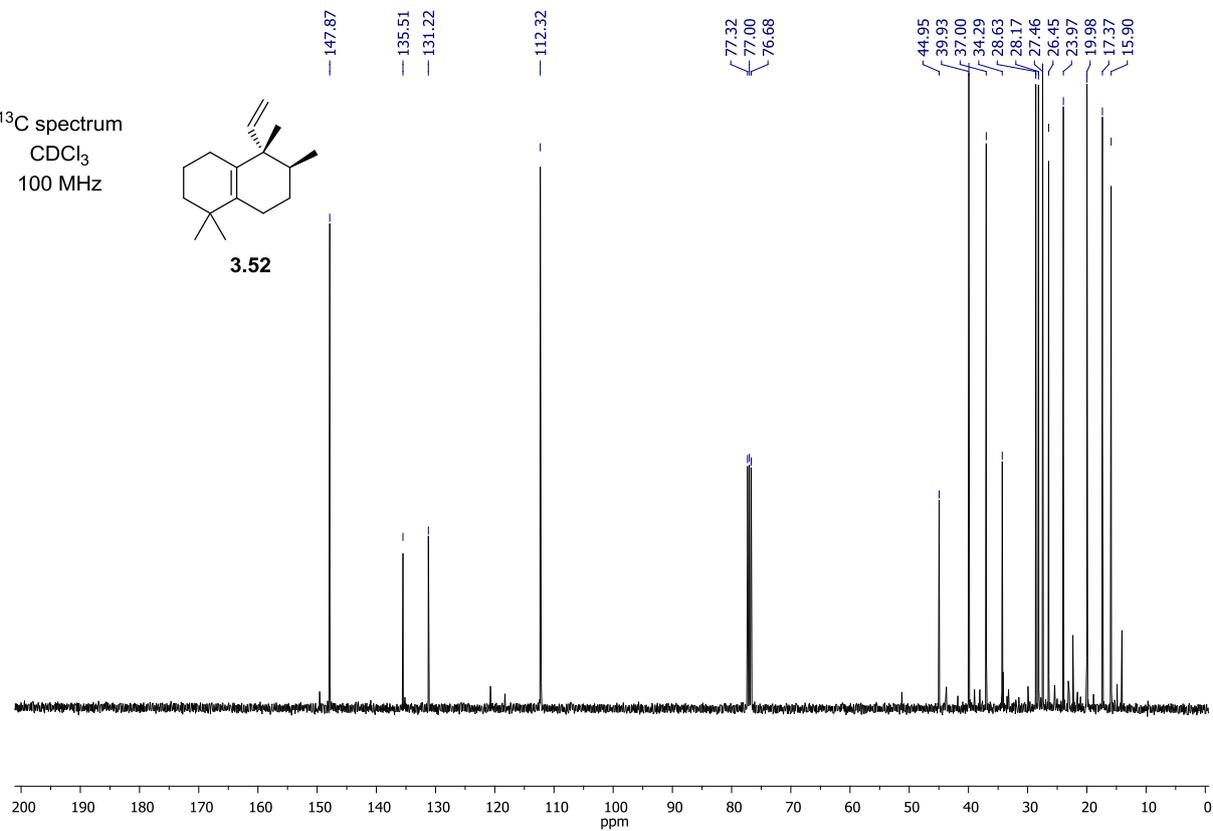
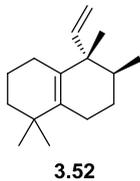


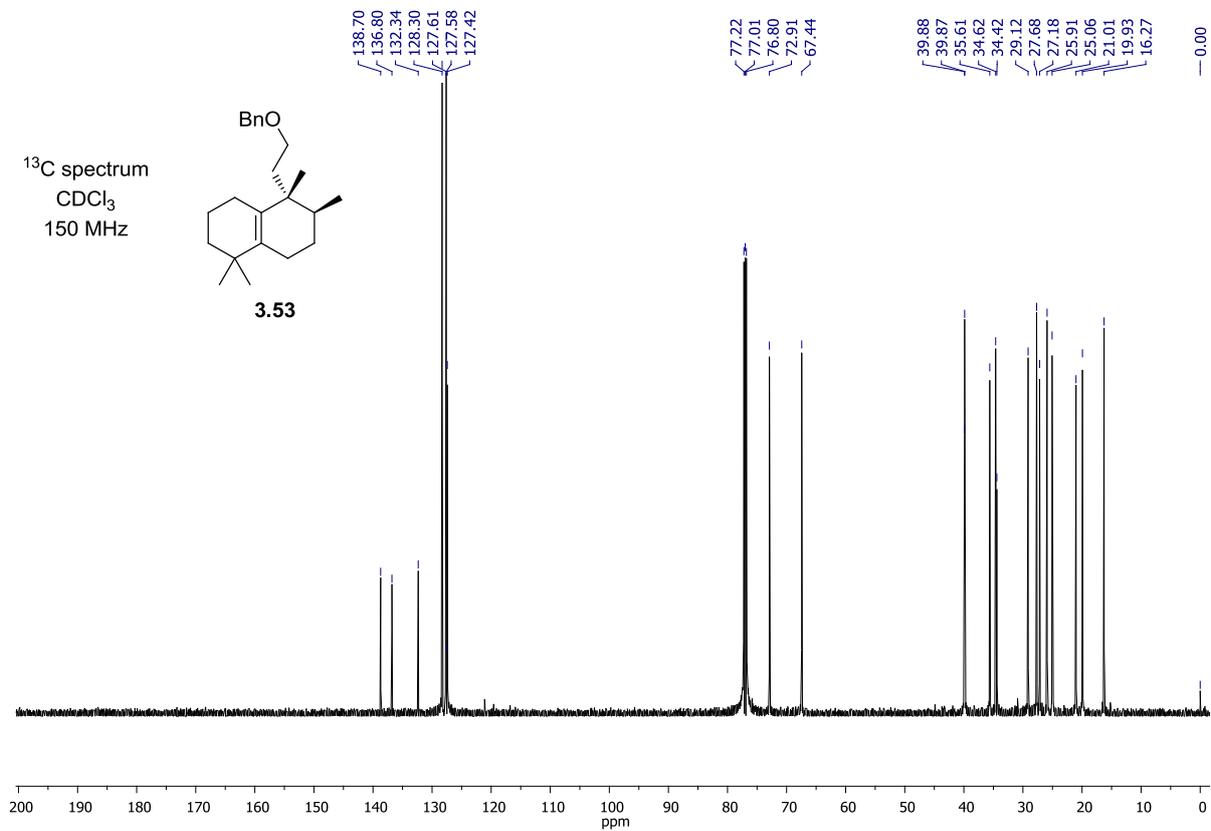
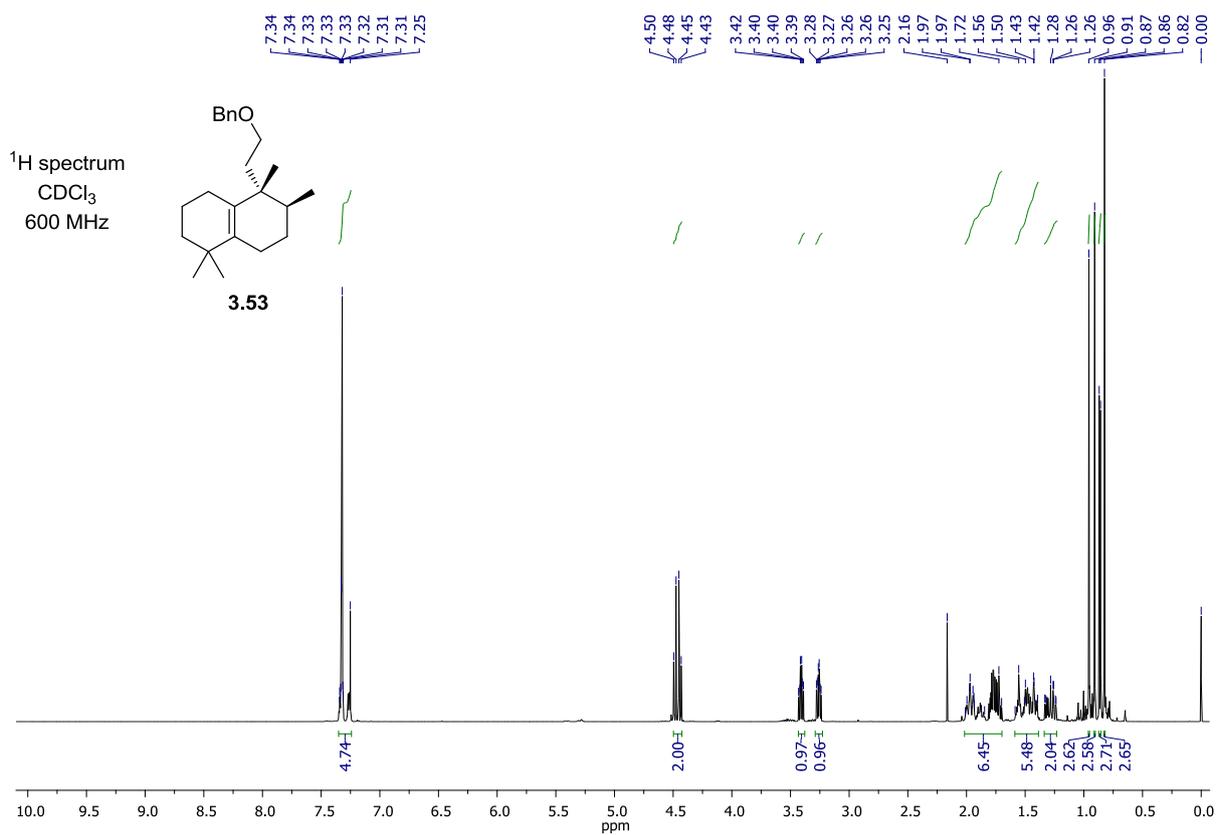


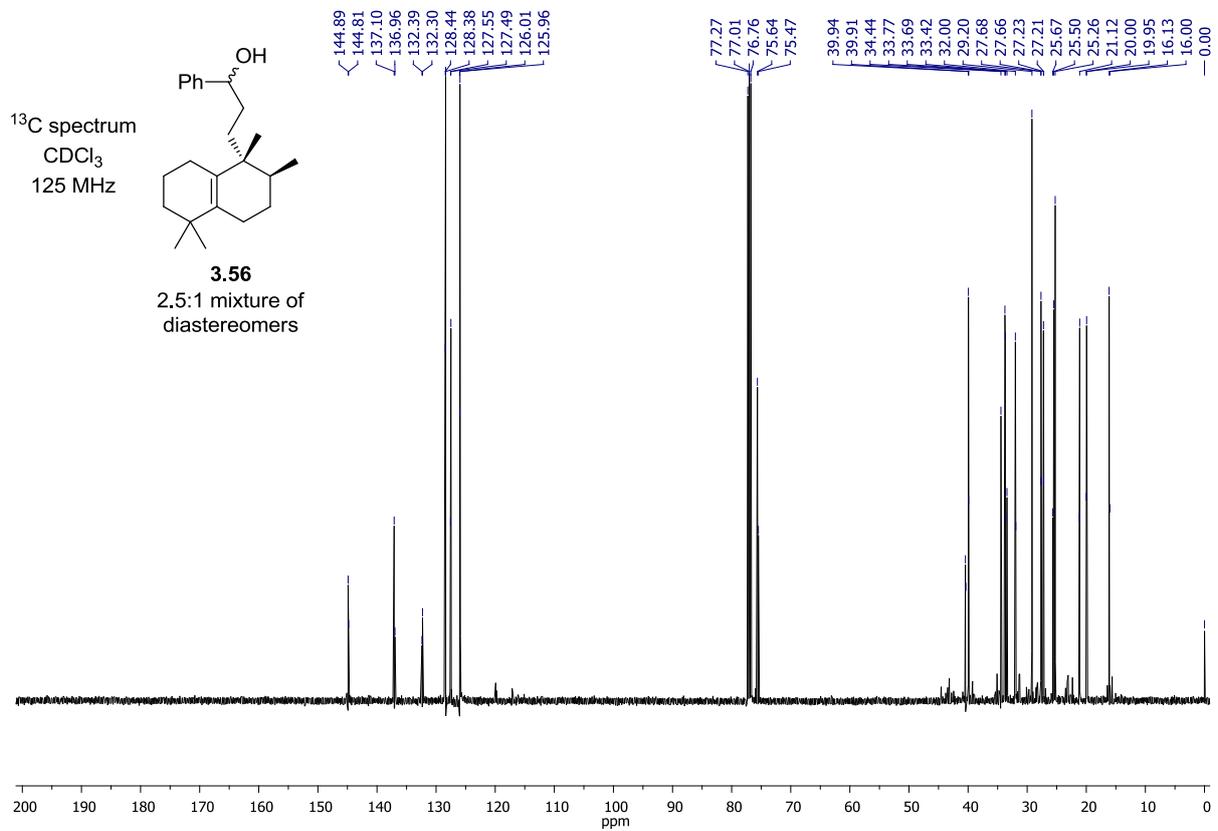
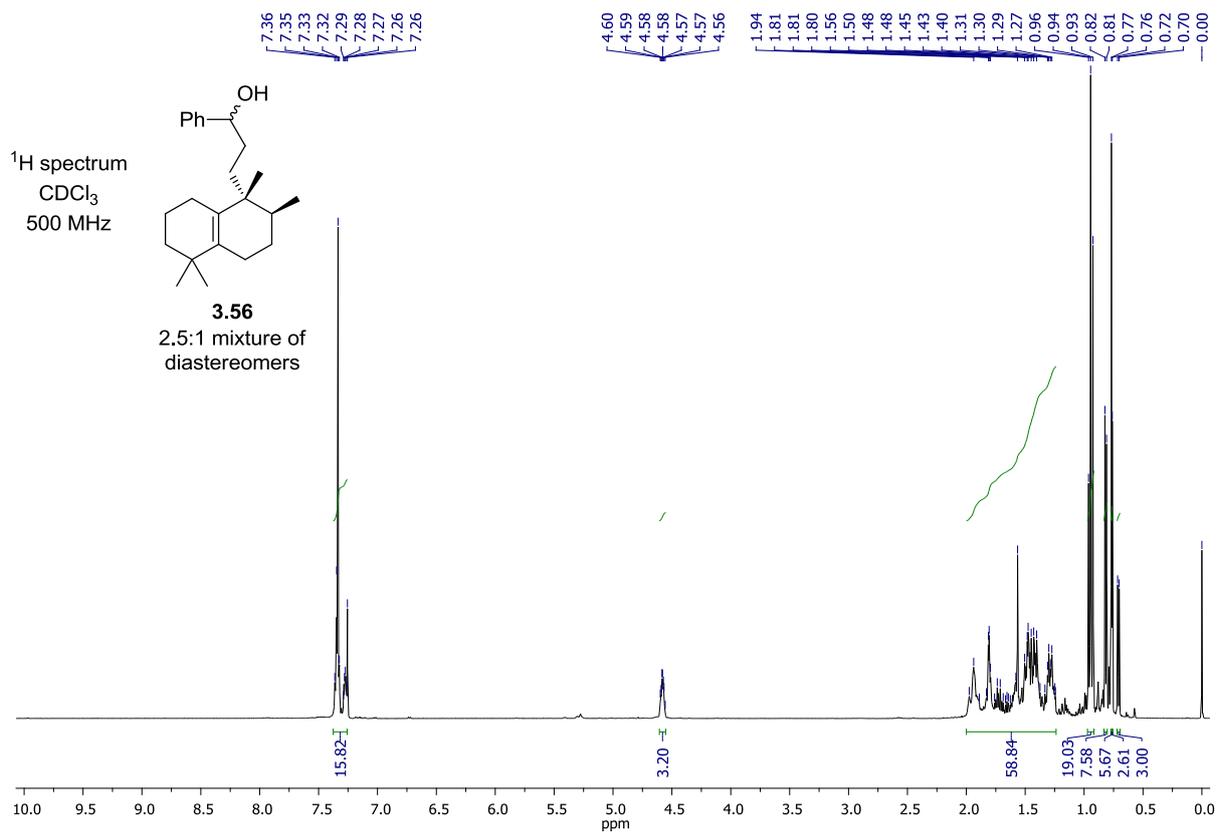
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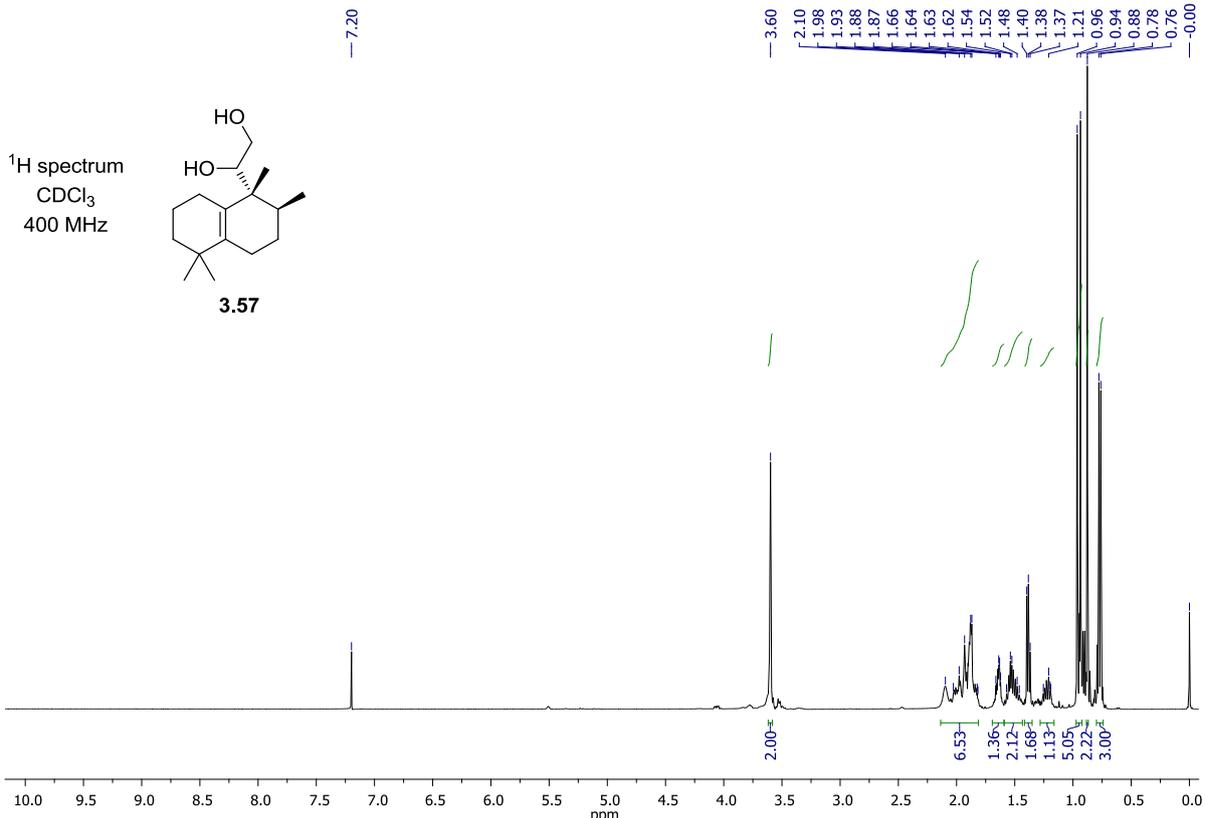
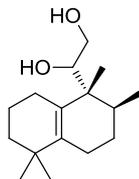
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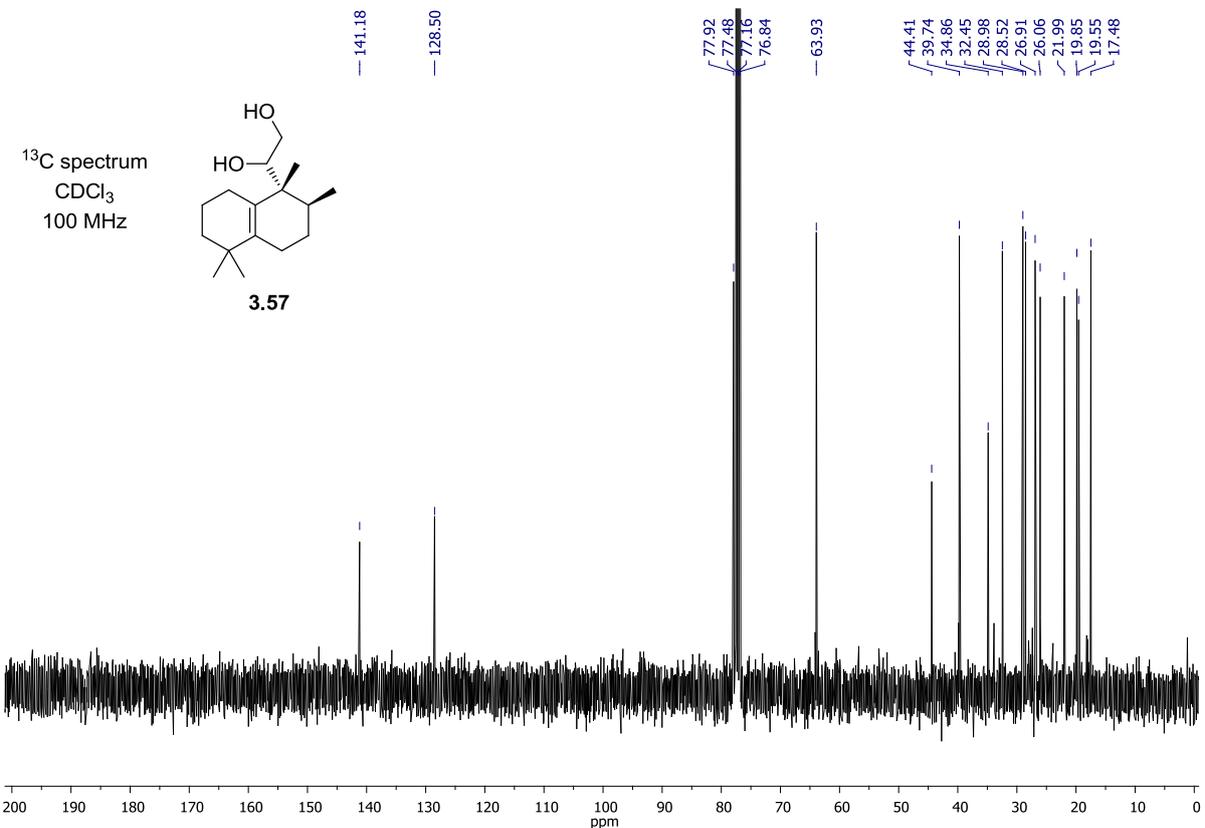
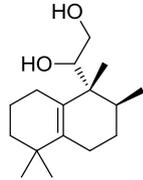


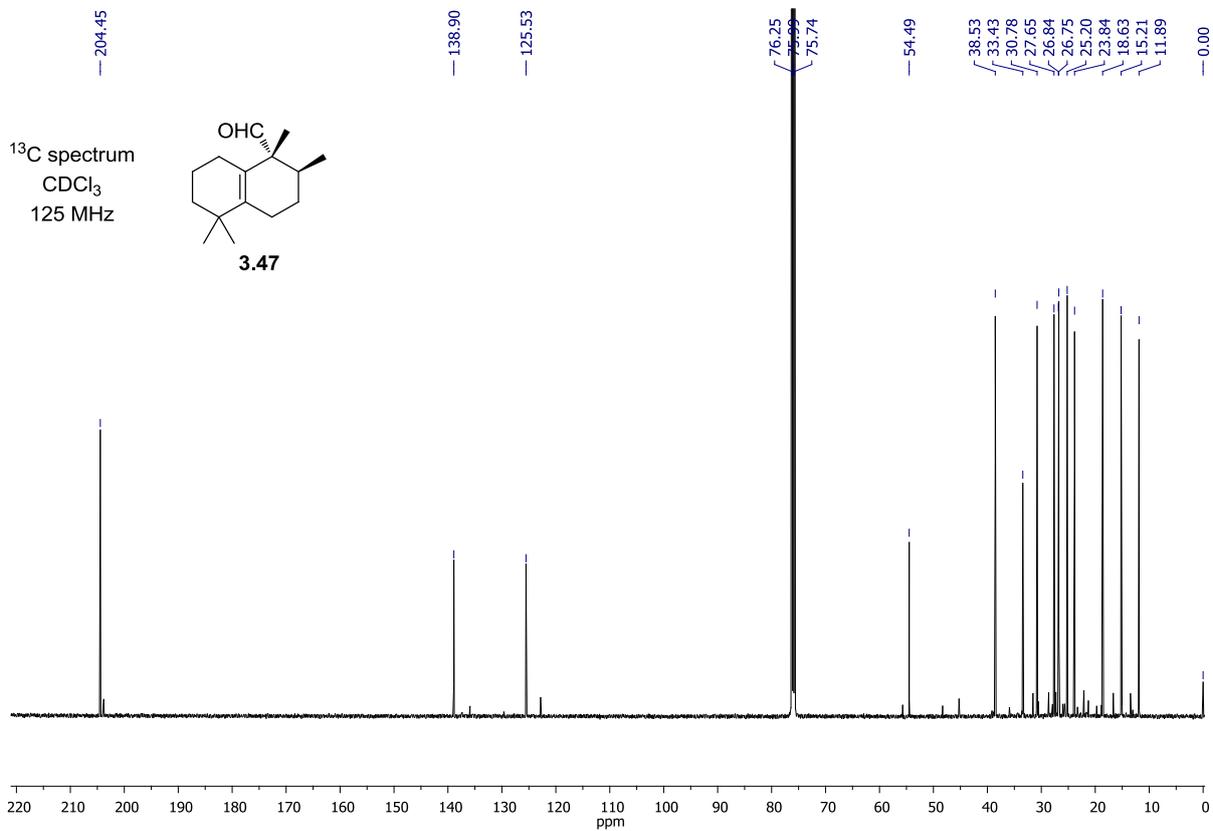
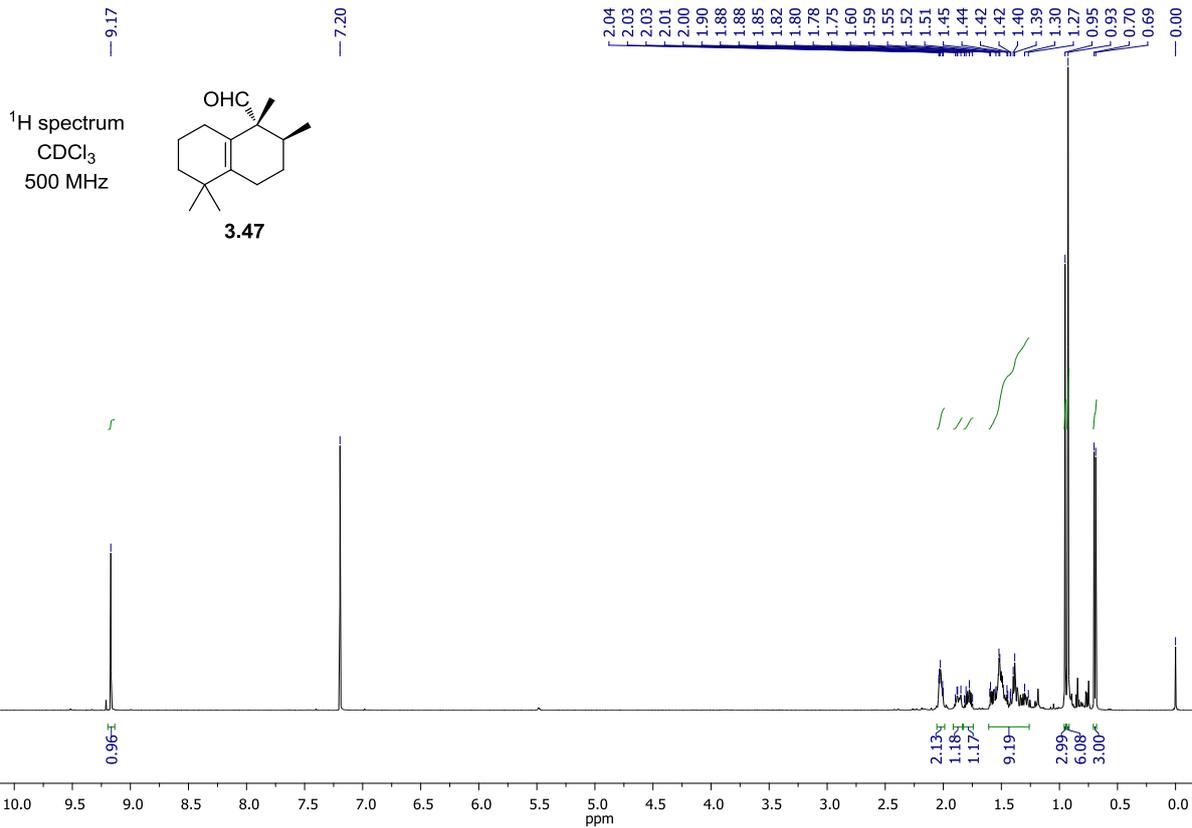


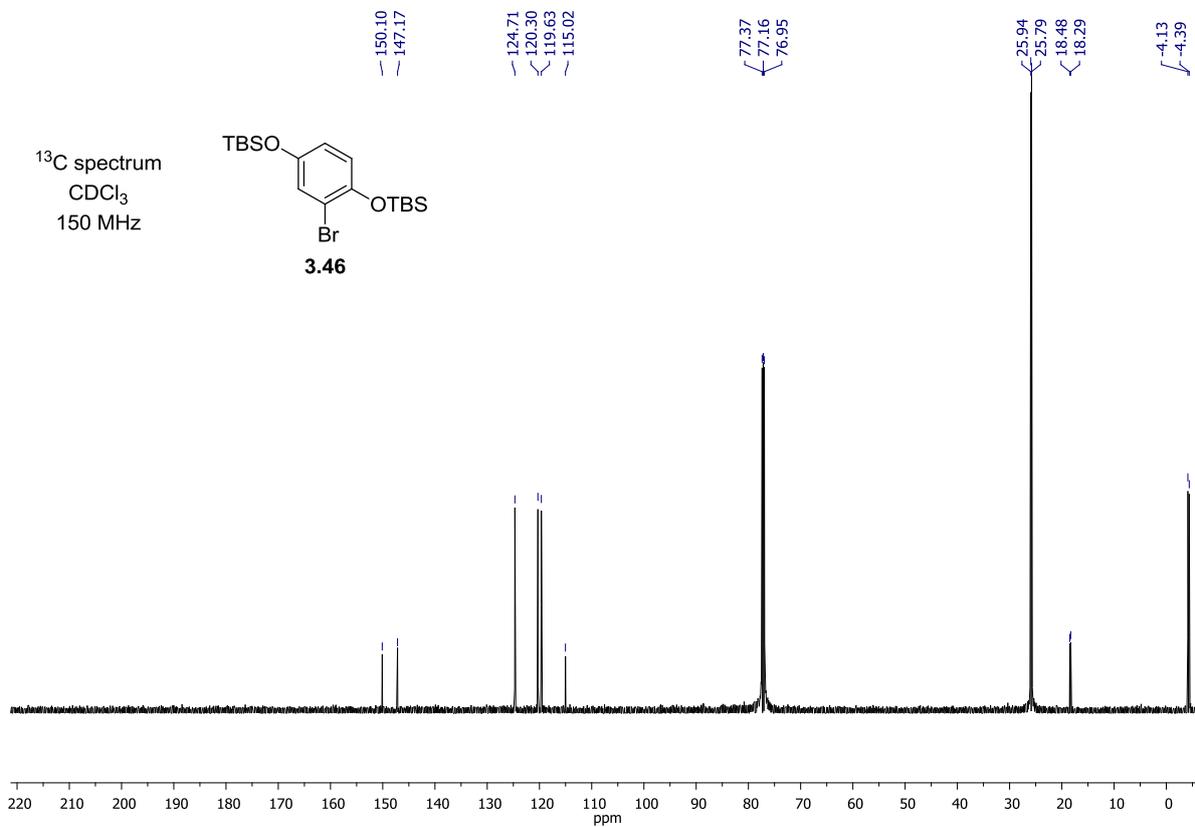
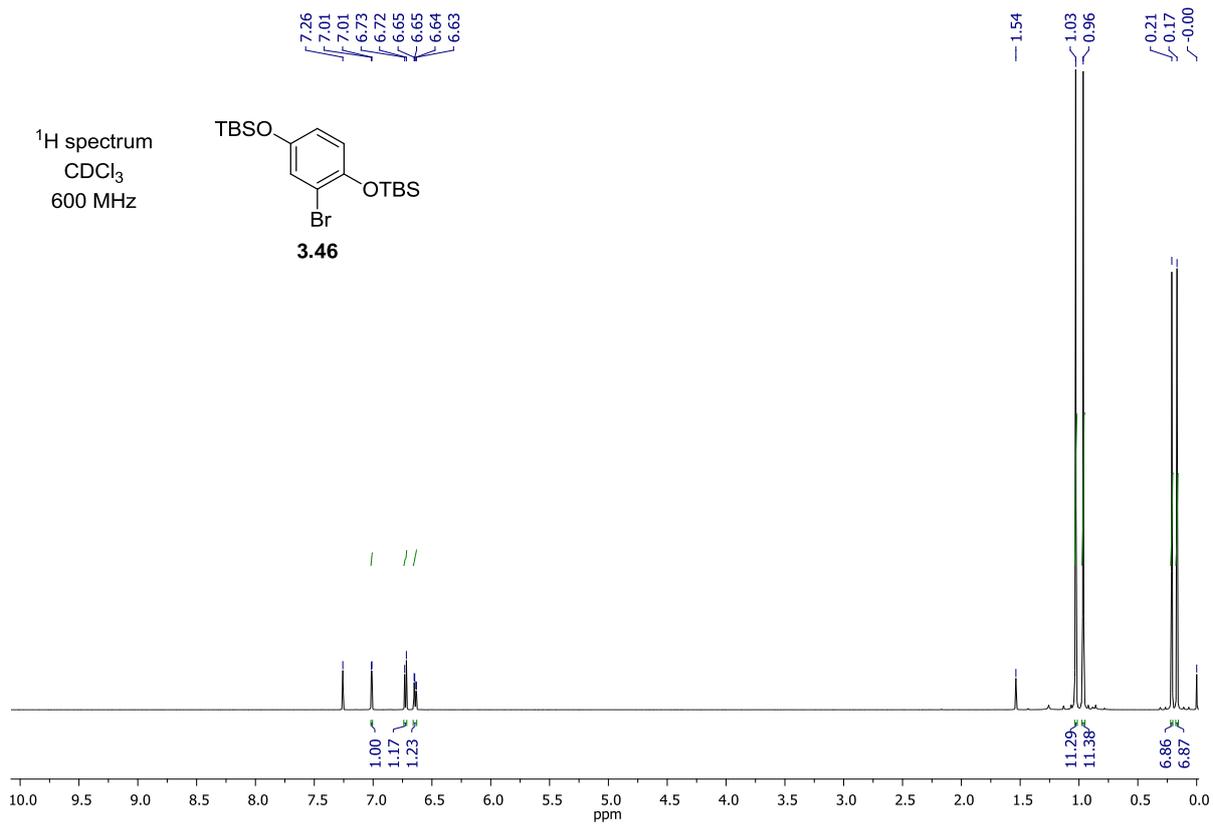
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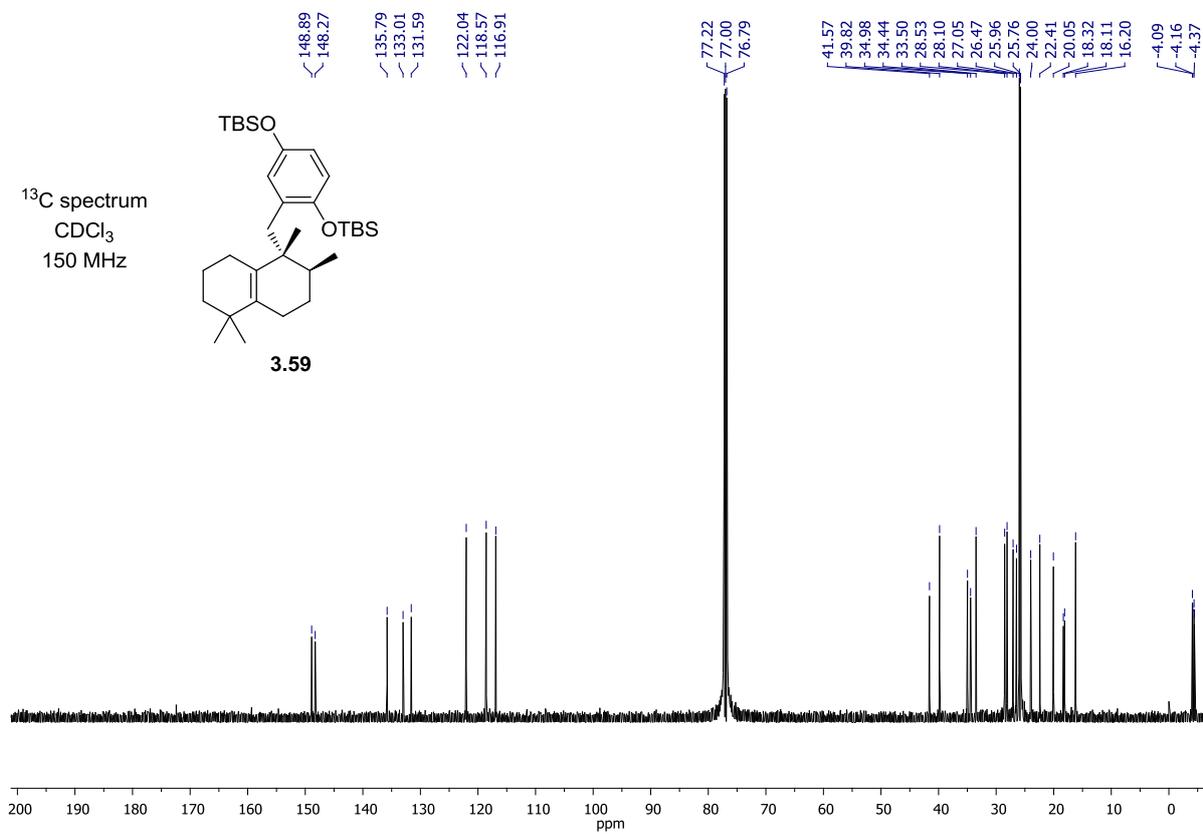
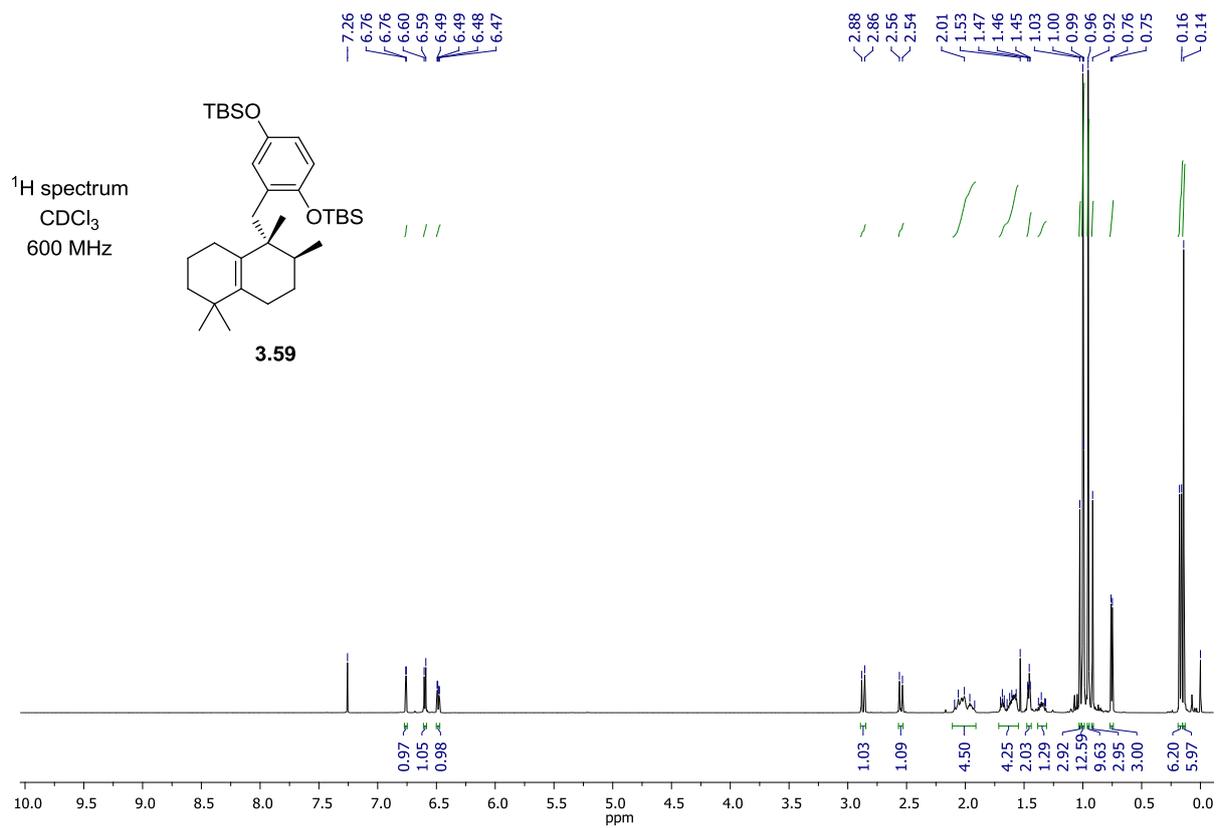


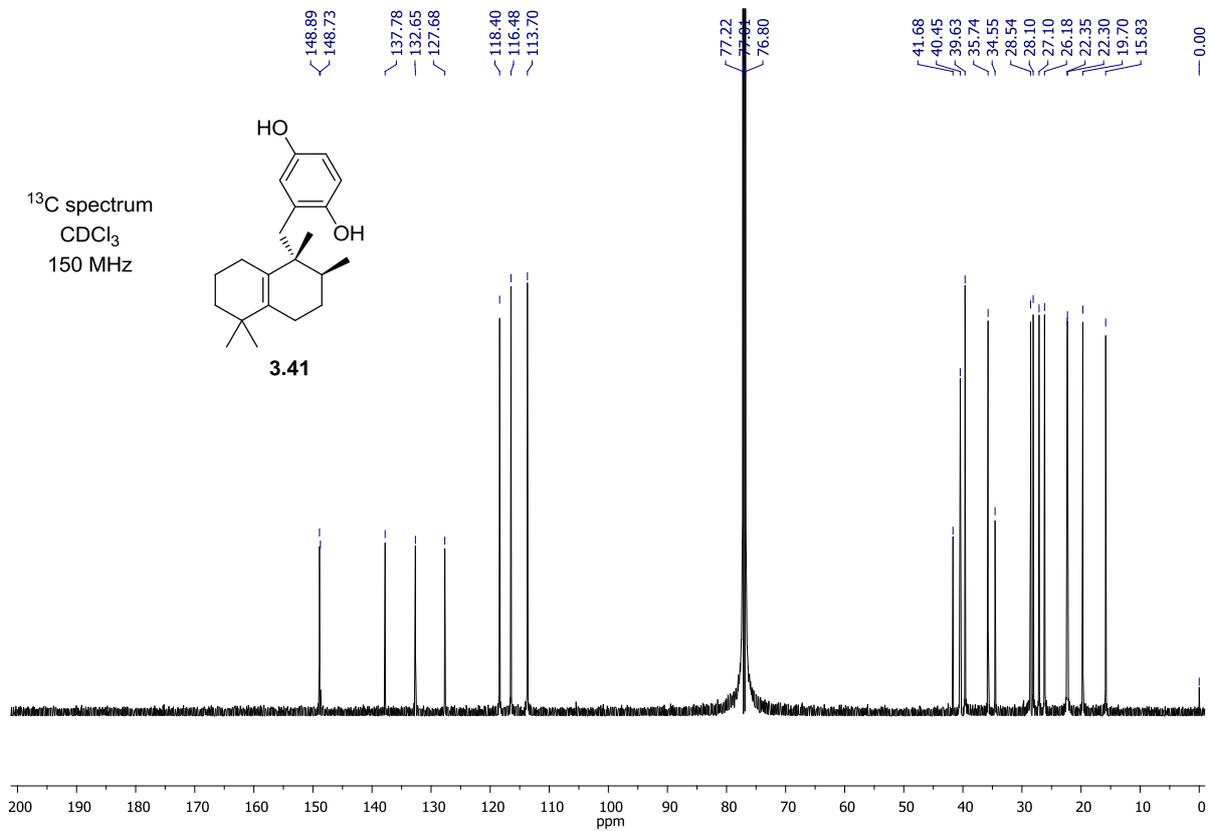
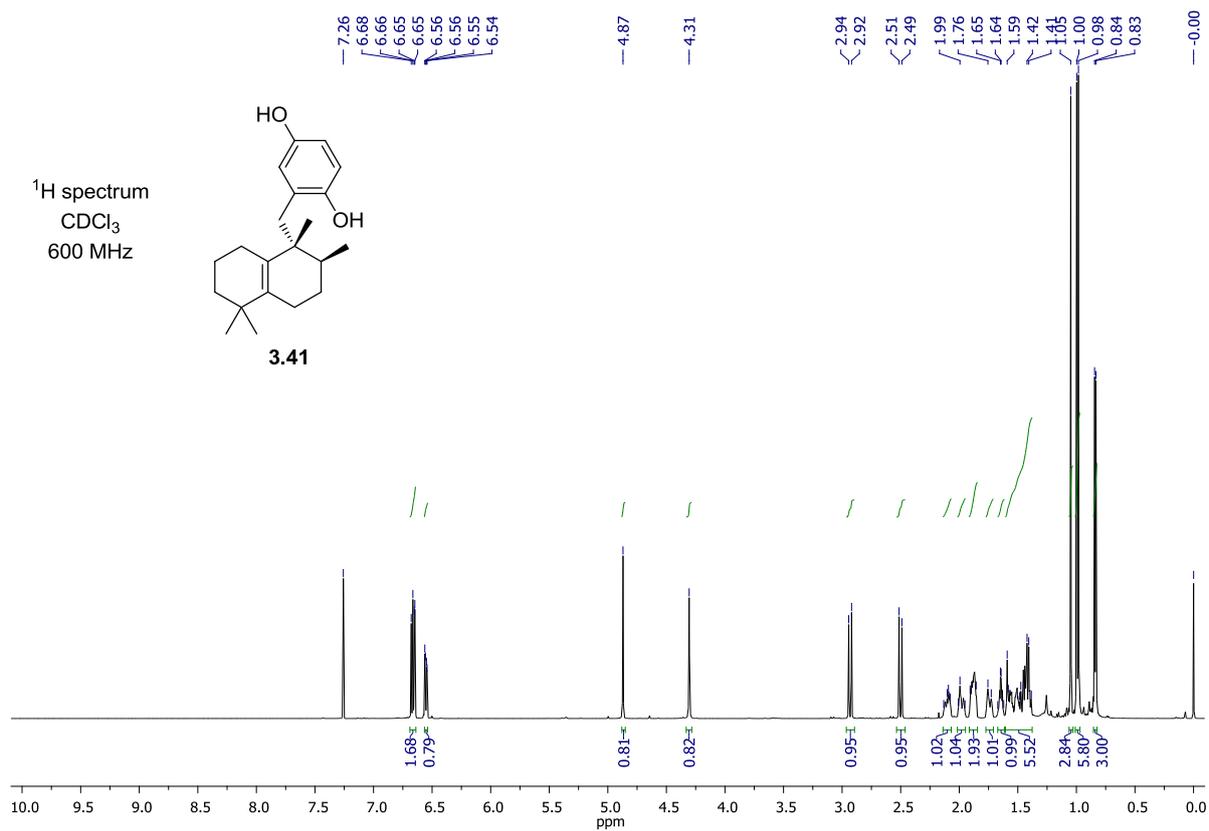
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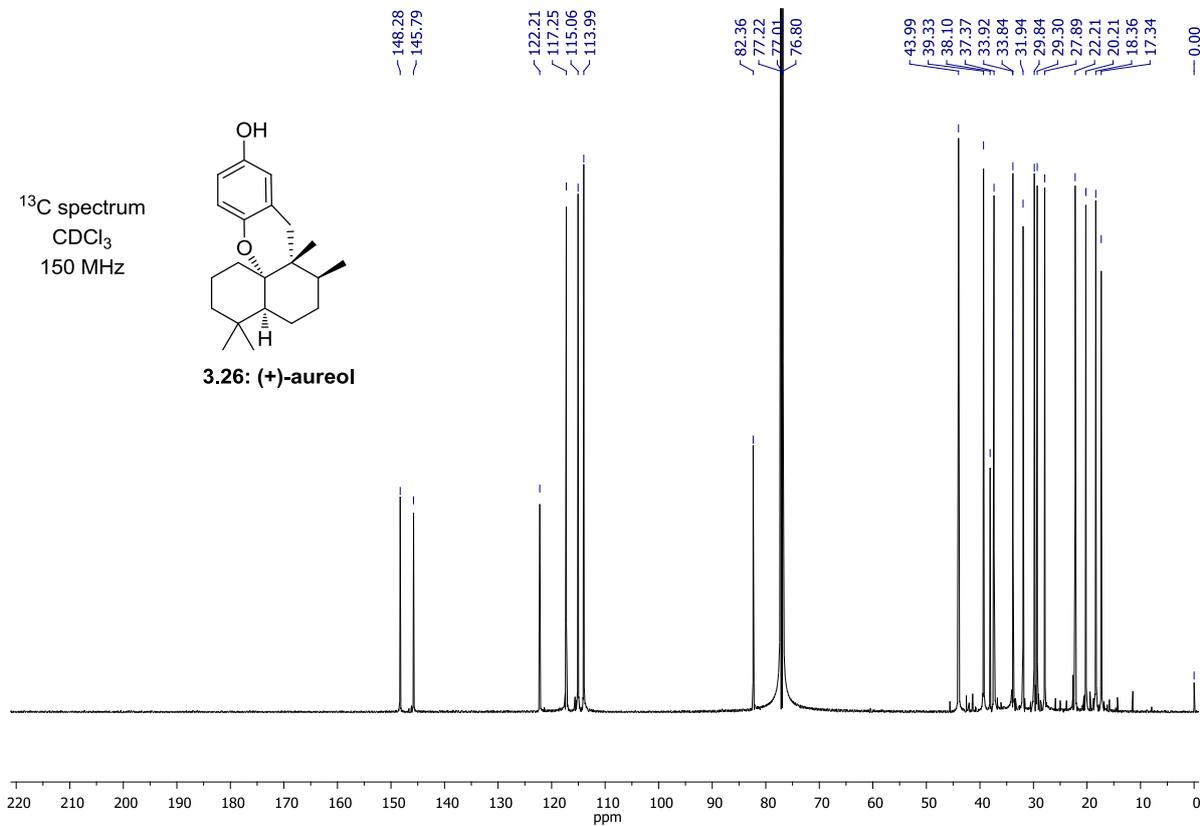
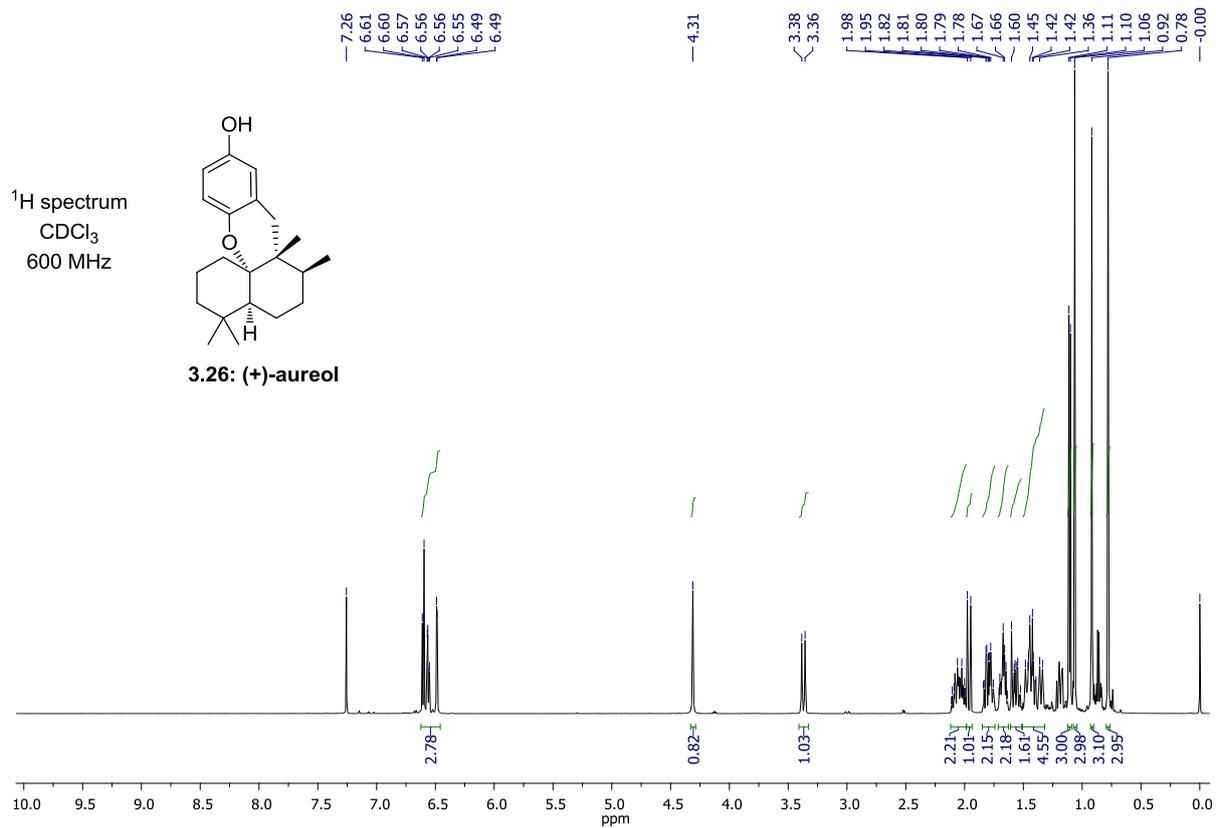


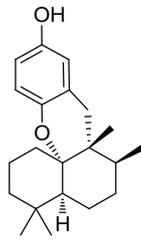




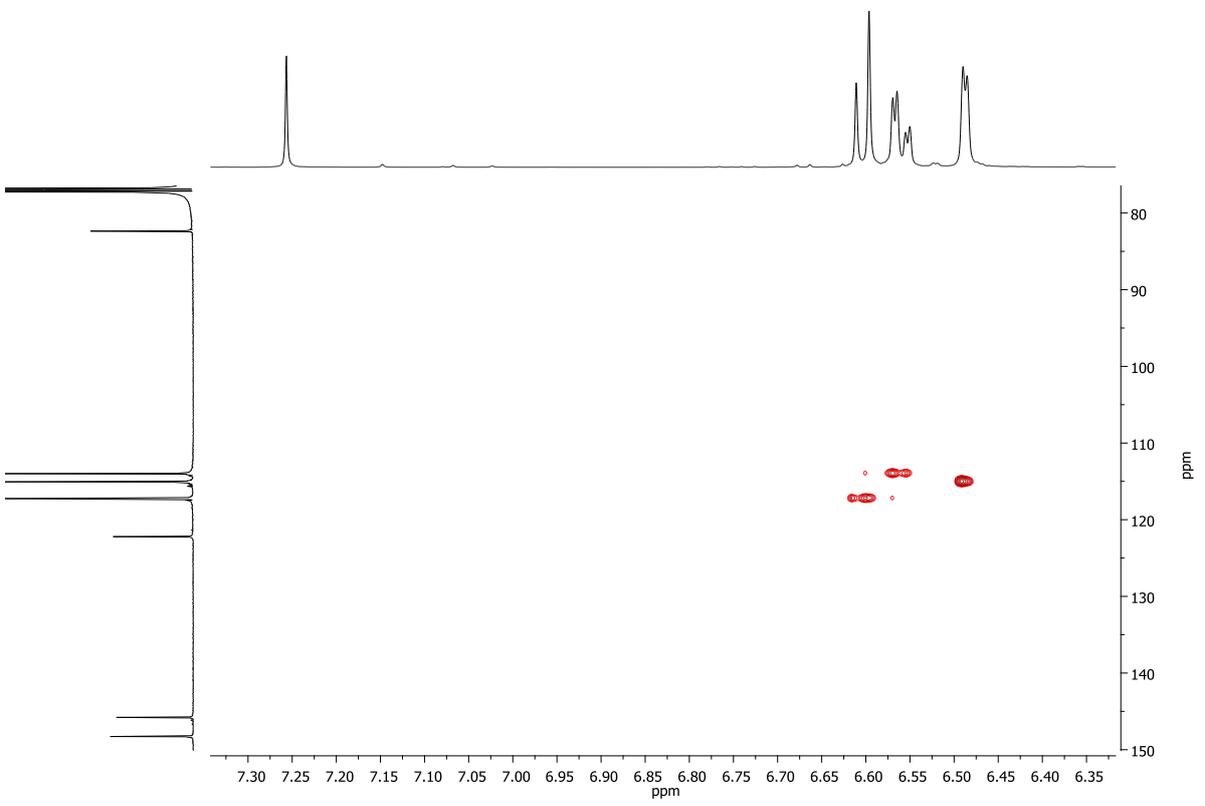
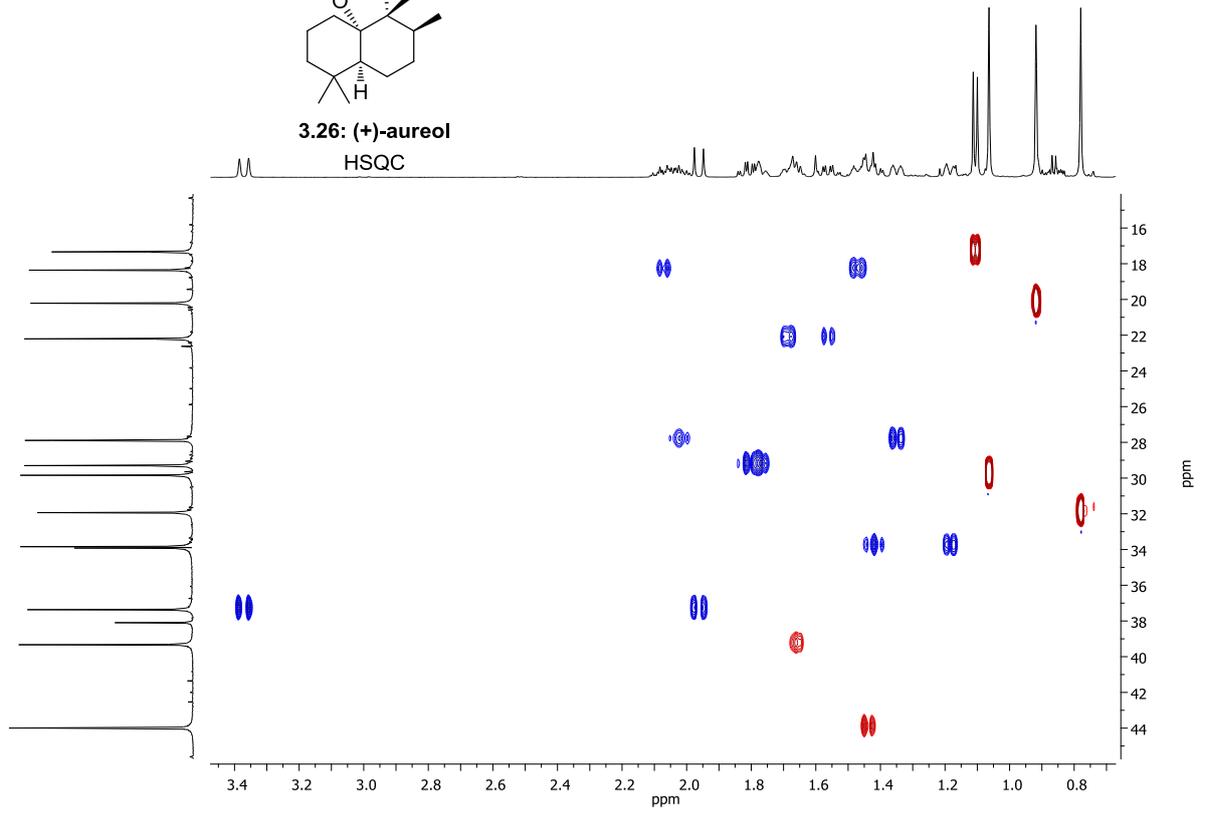


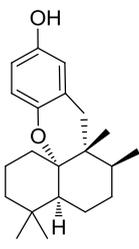




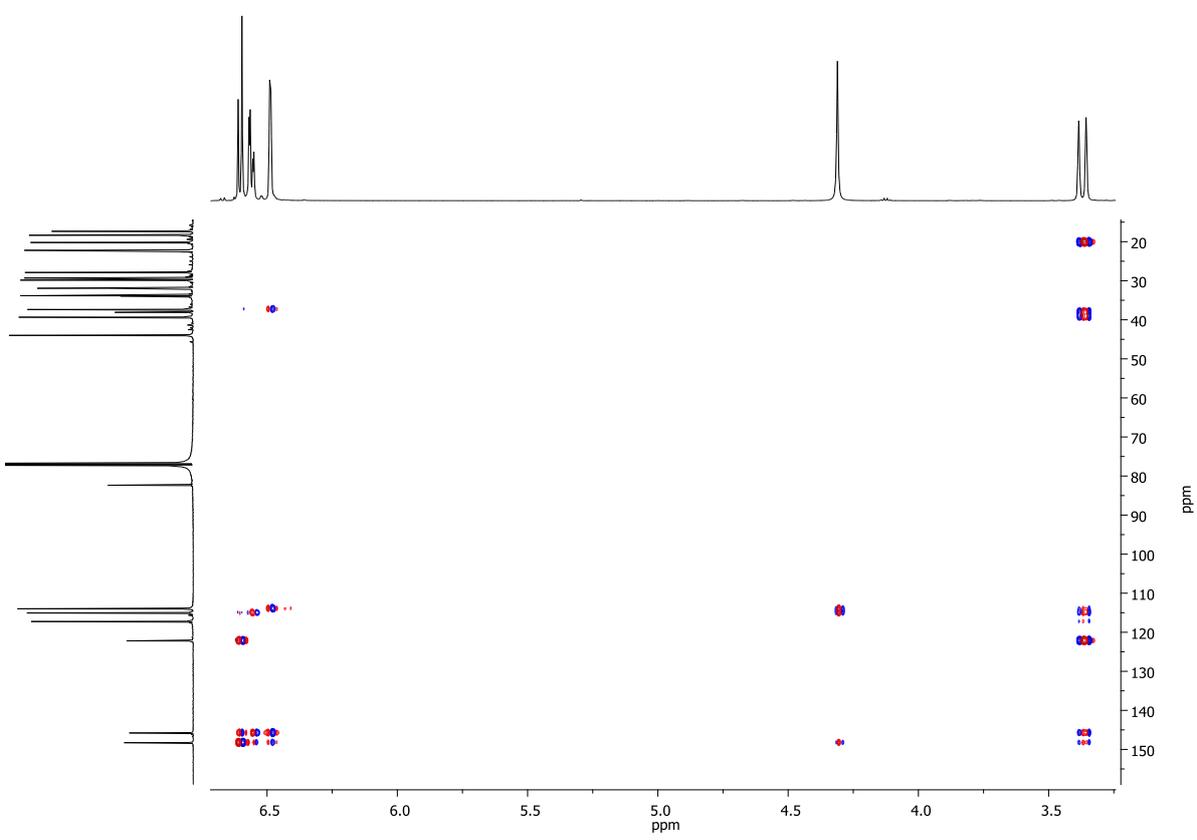
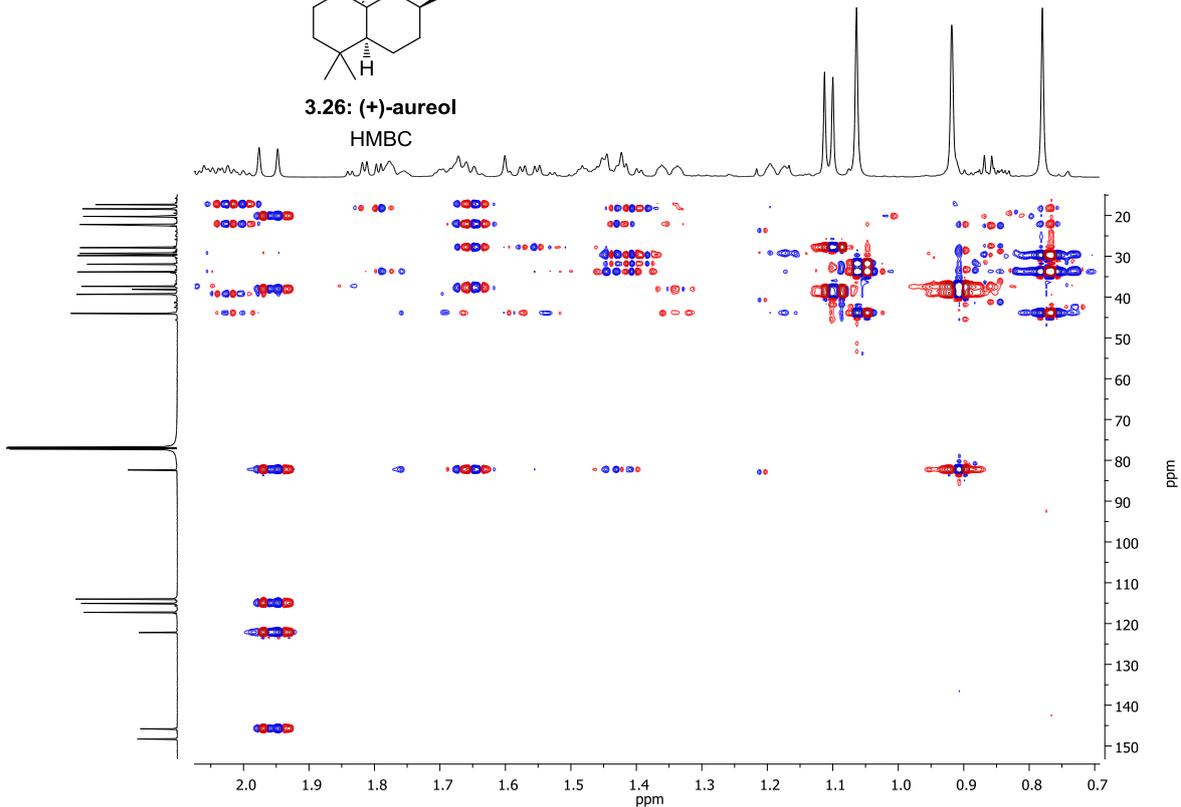


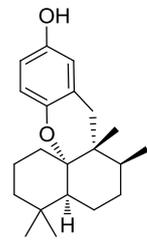
3.26: (+)-aureol  
HSQC



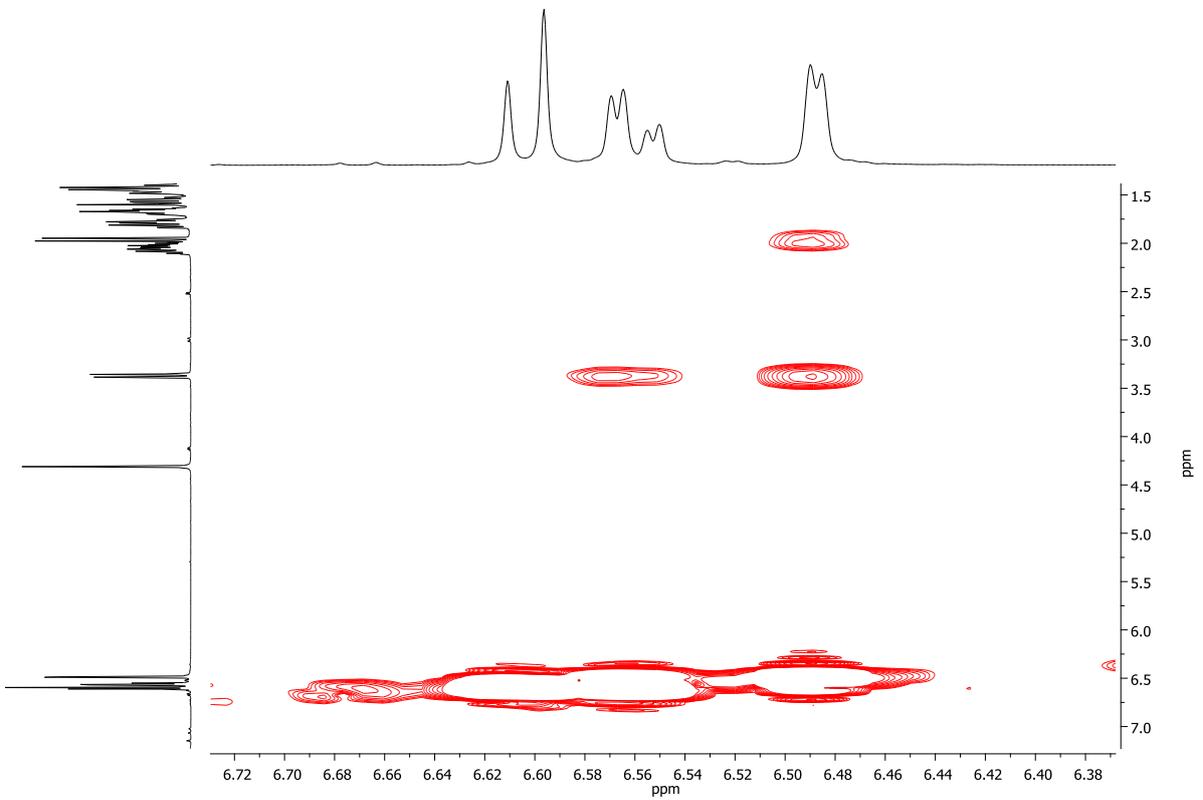
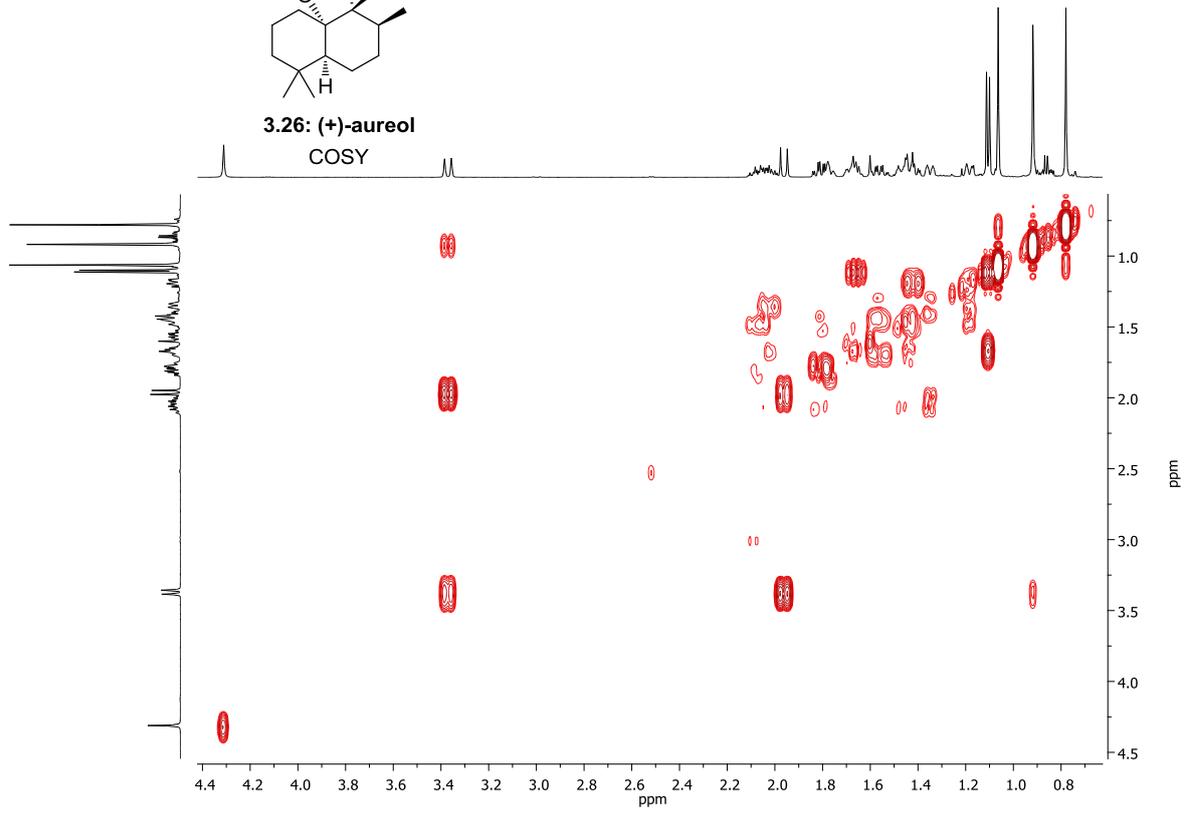


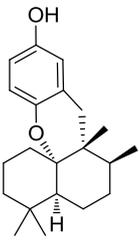
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HMBC



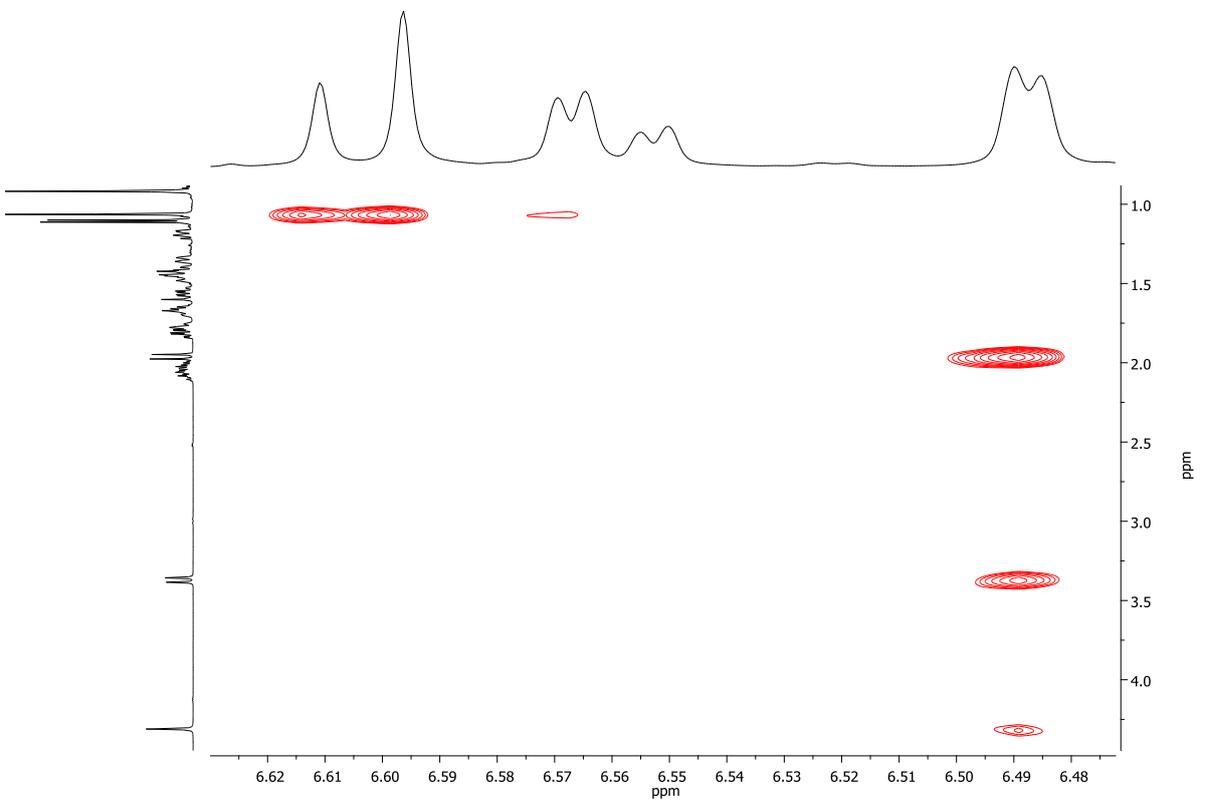
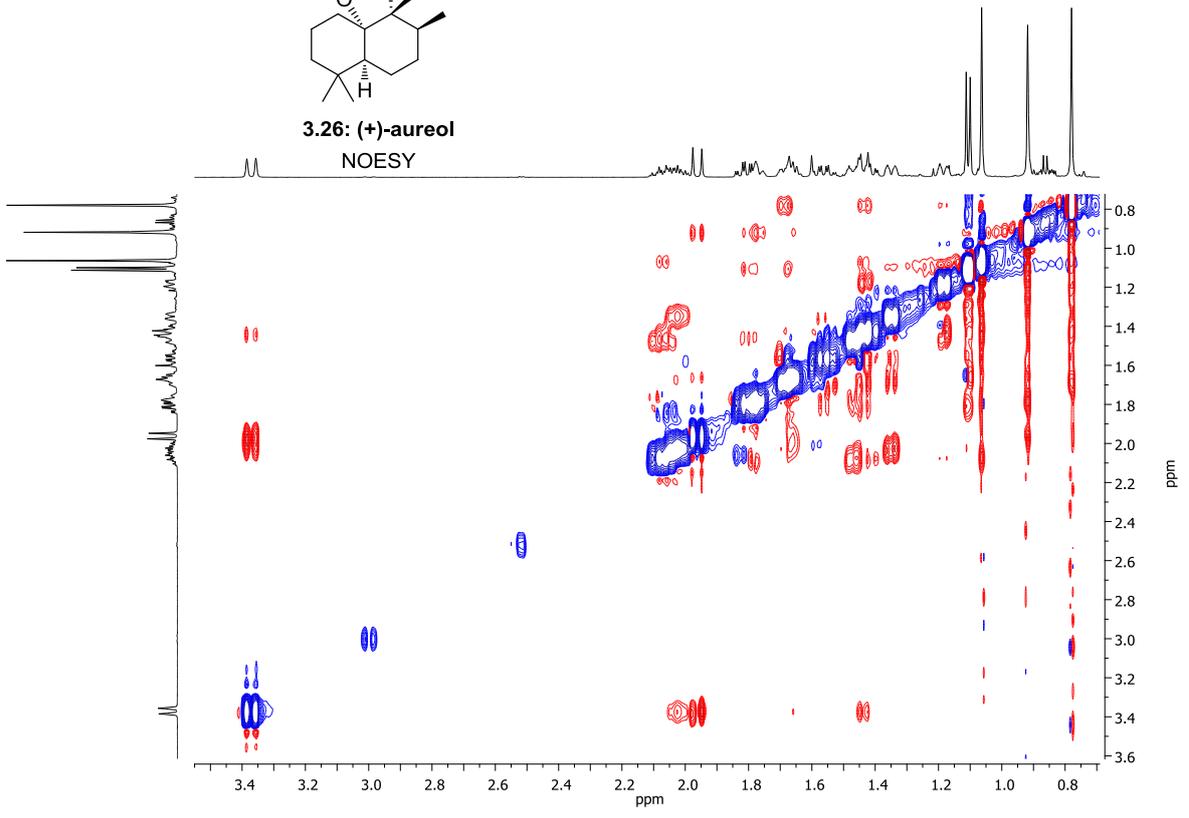


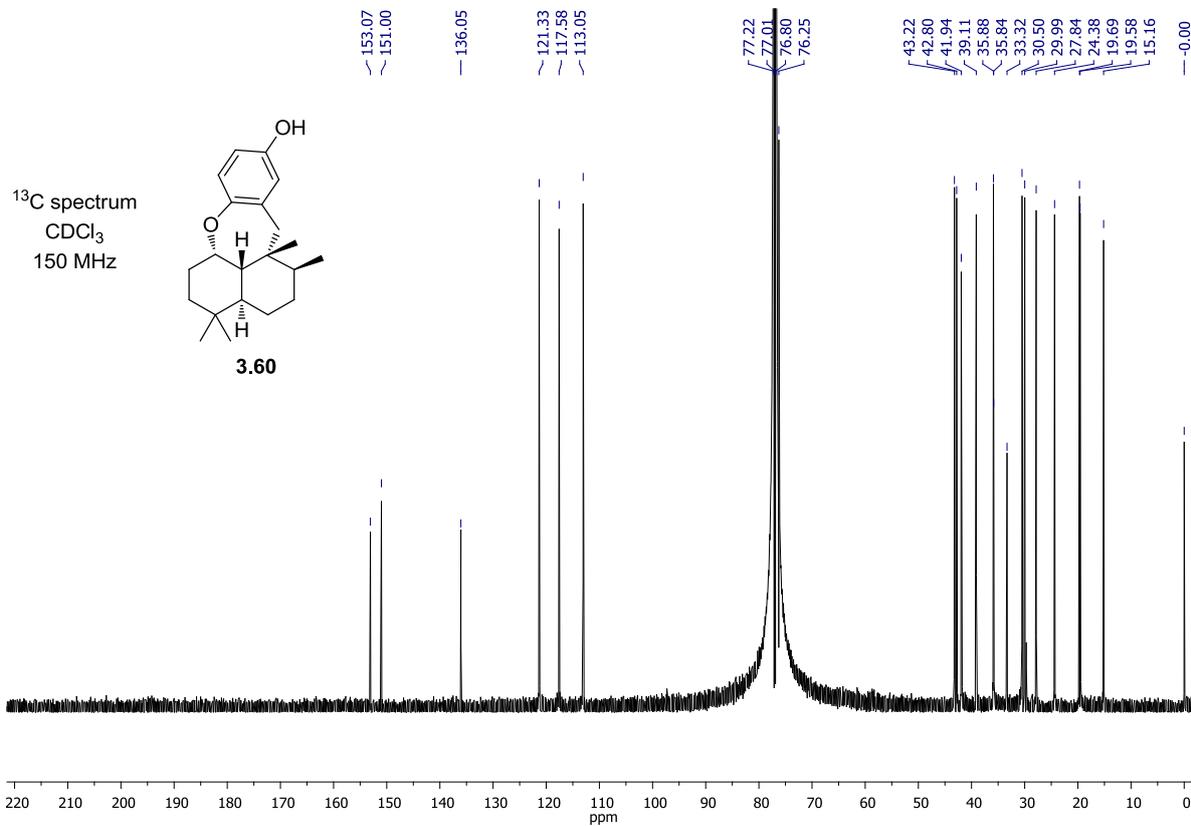
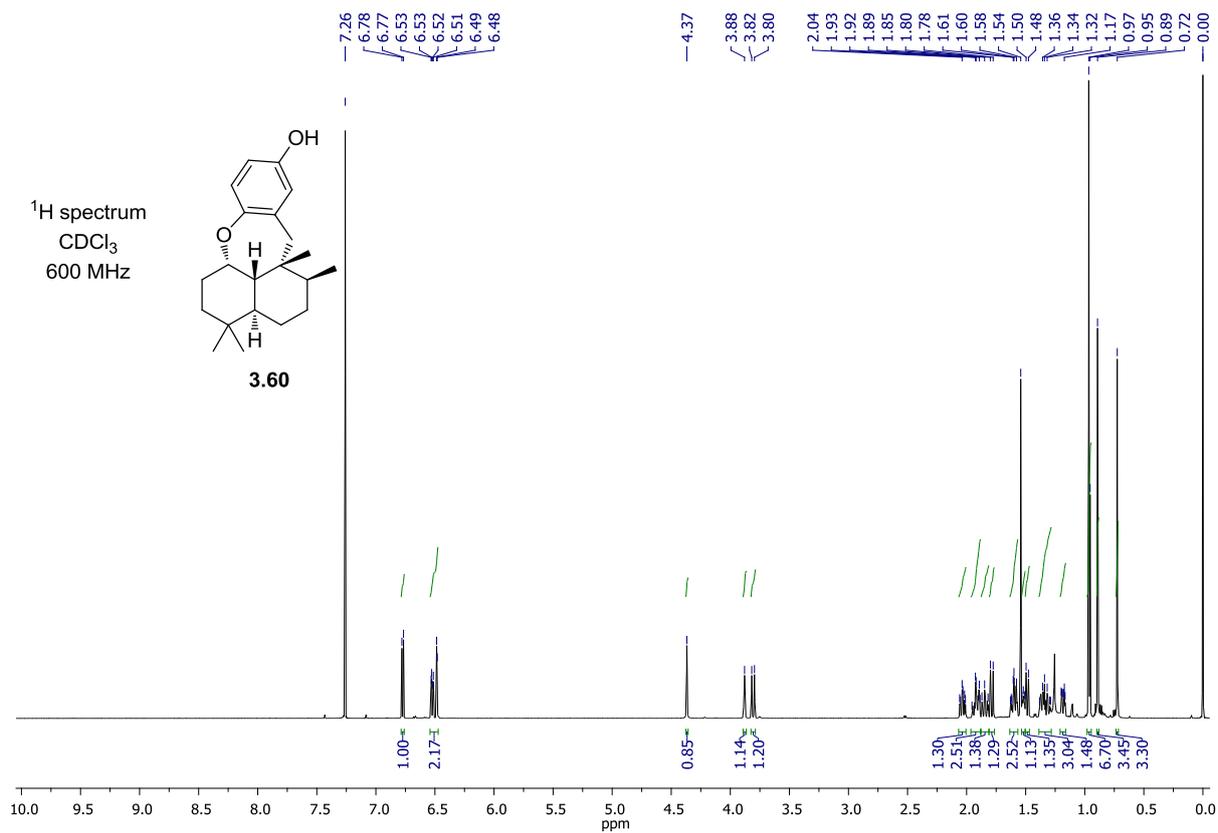
3.26: (+)-aureol  
COSY

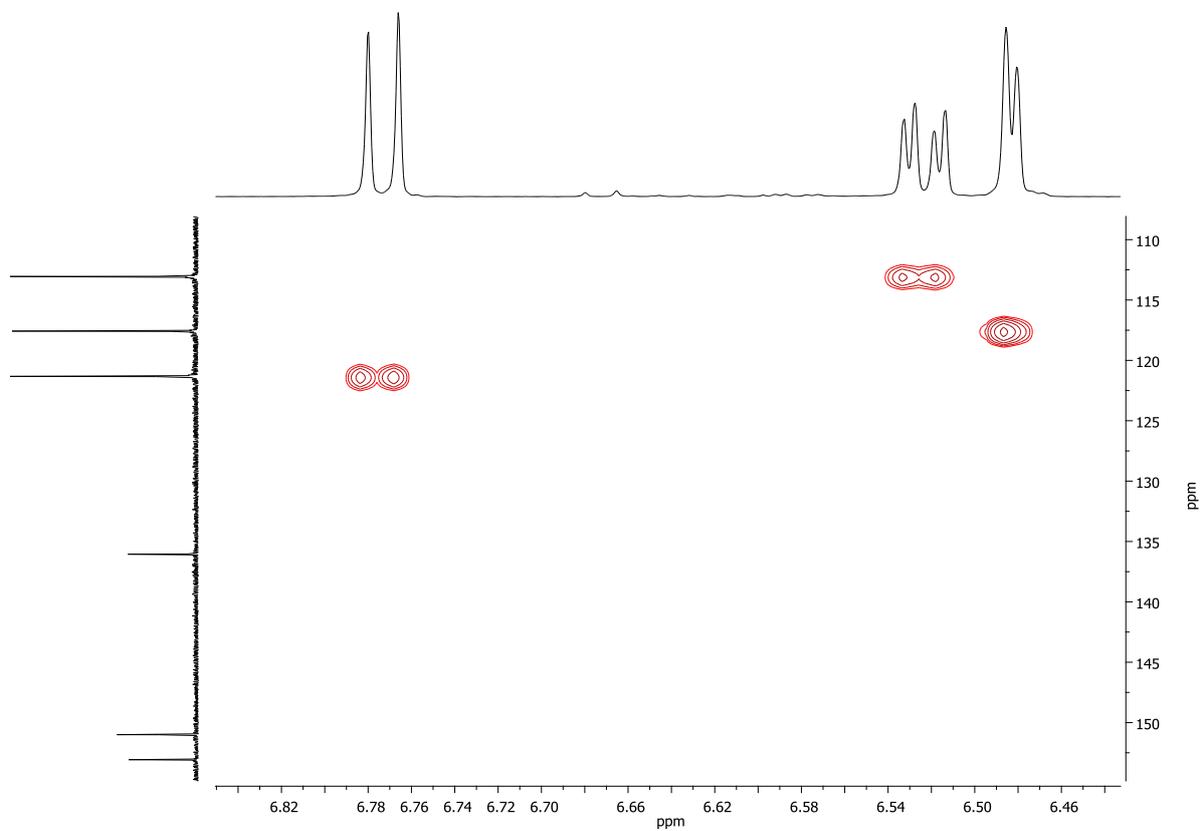
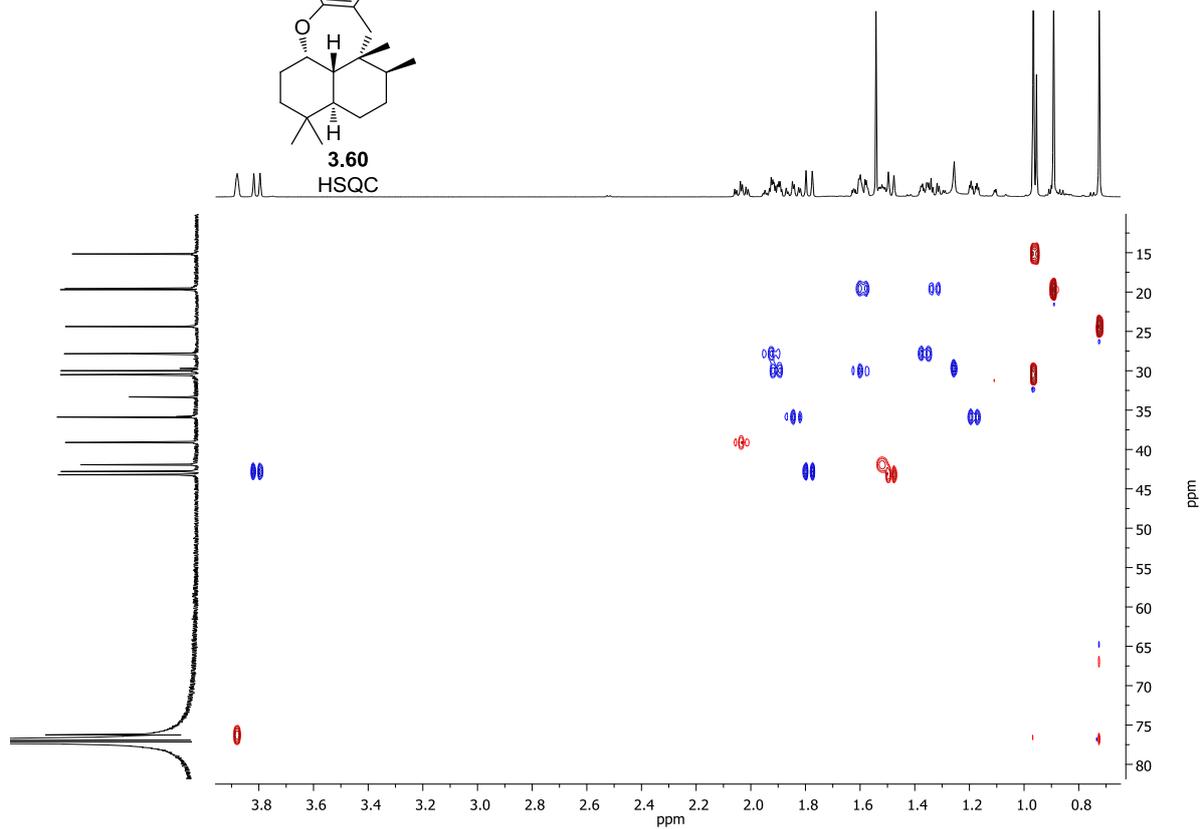
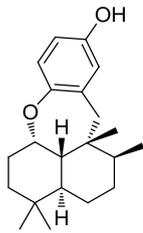


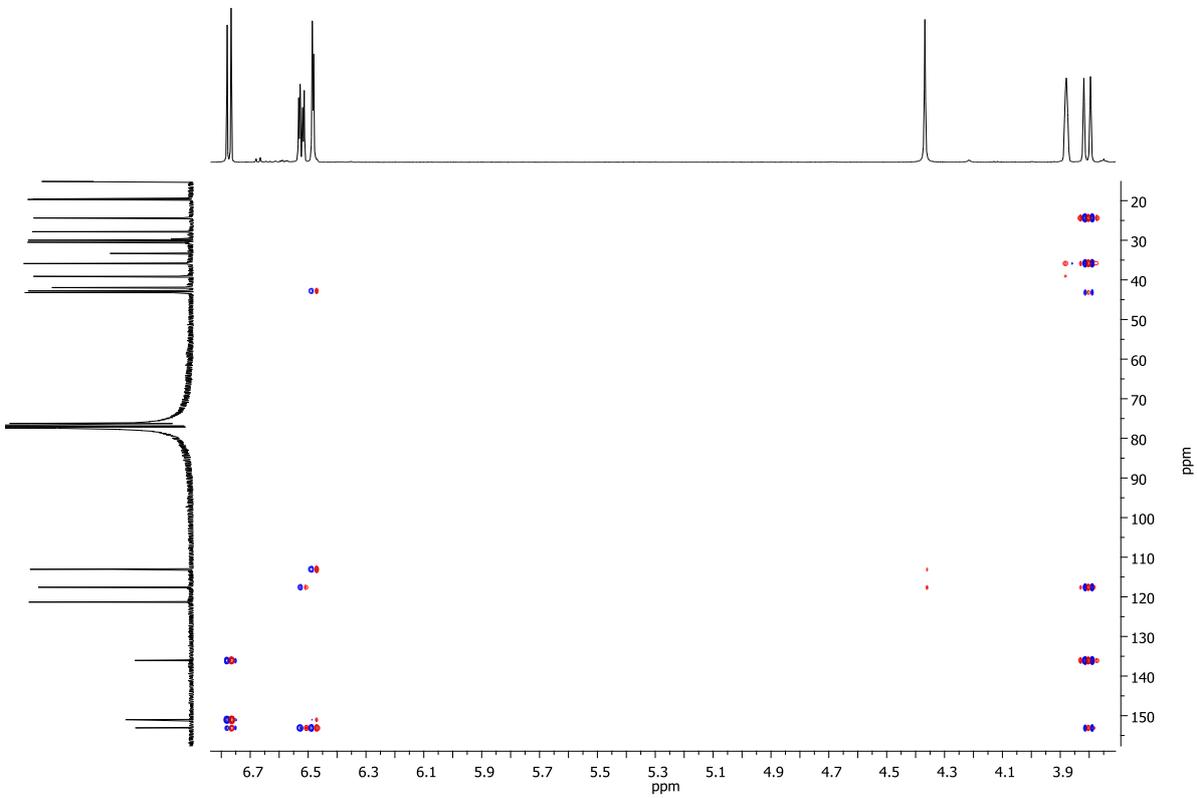
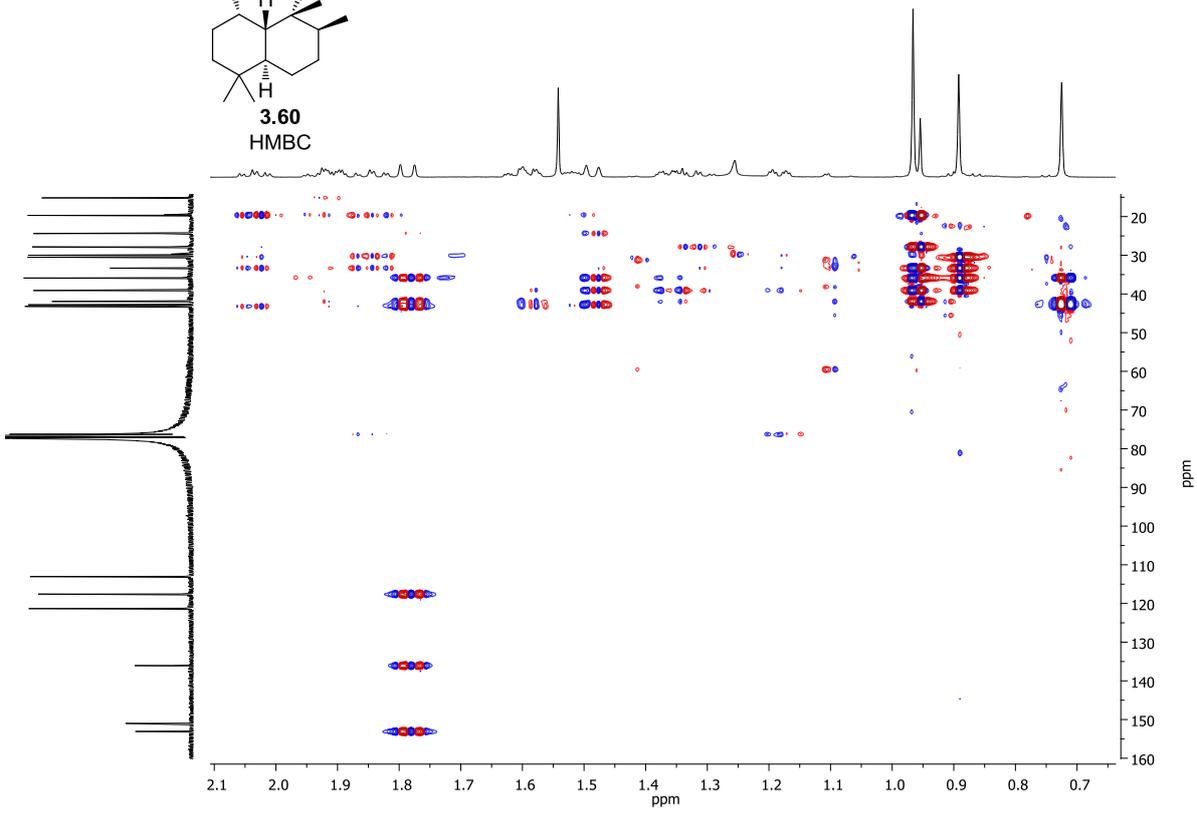
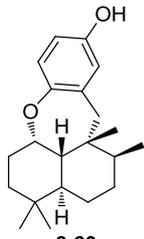


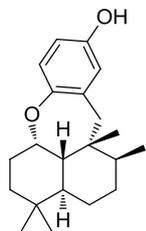
3.26: (+)-aureol  
NOESY



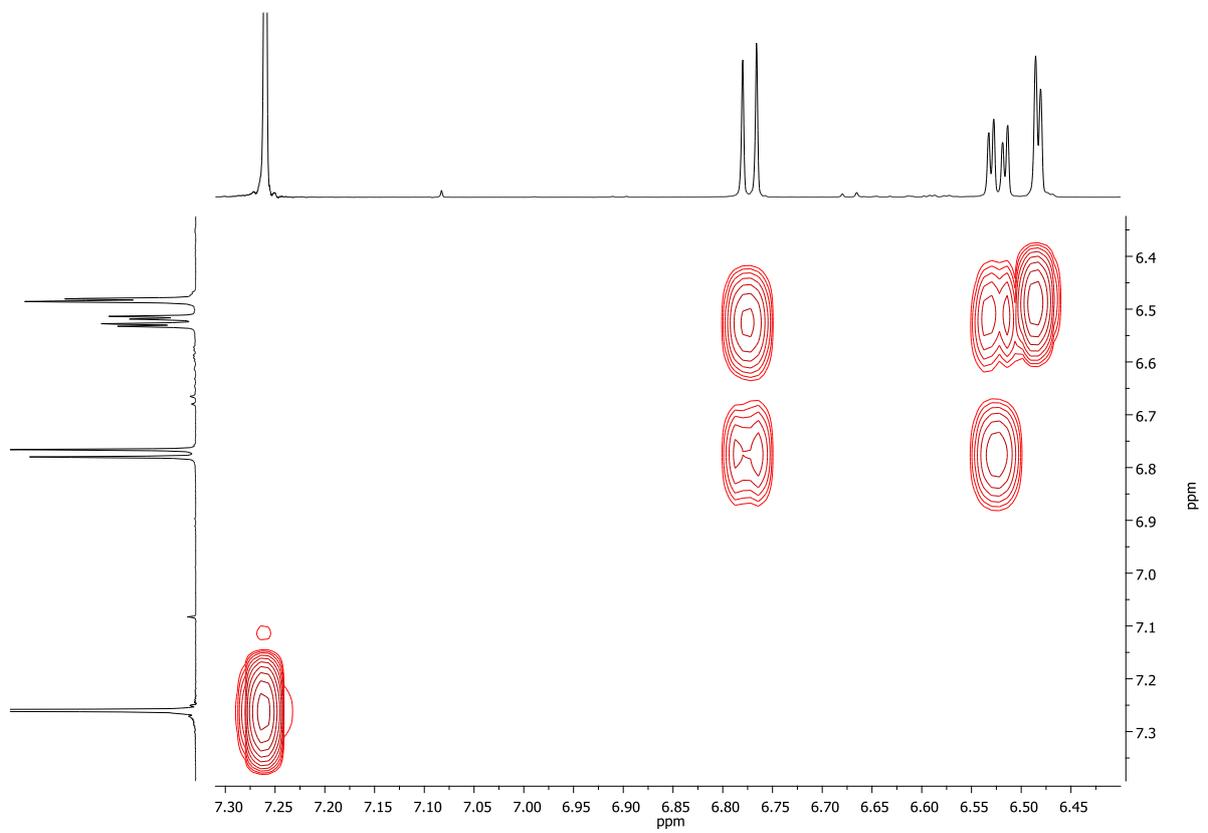
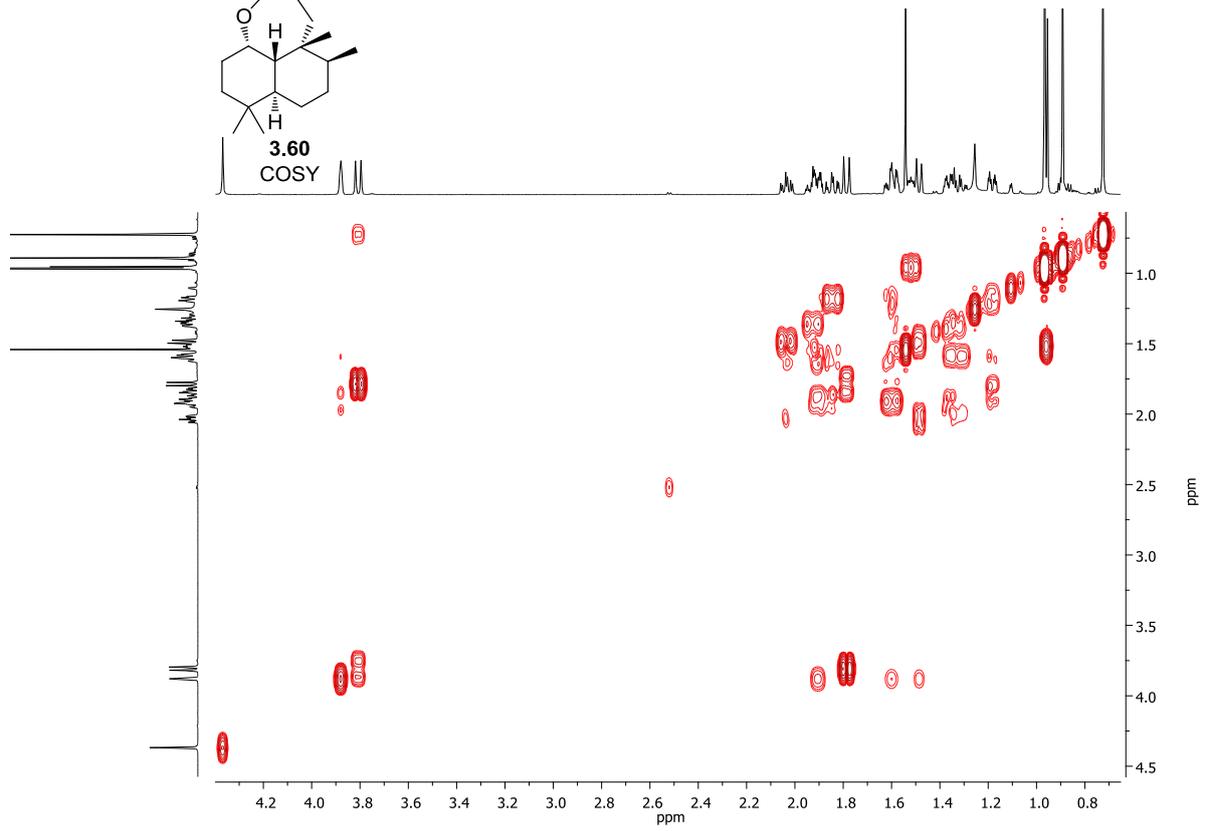


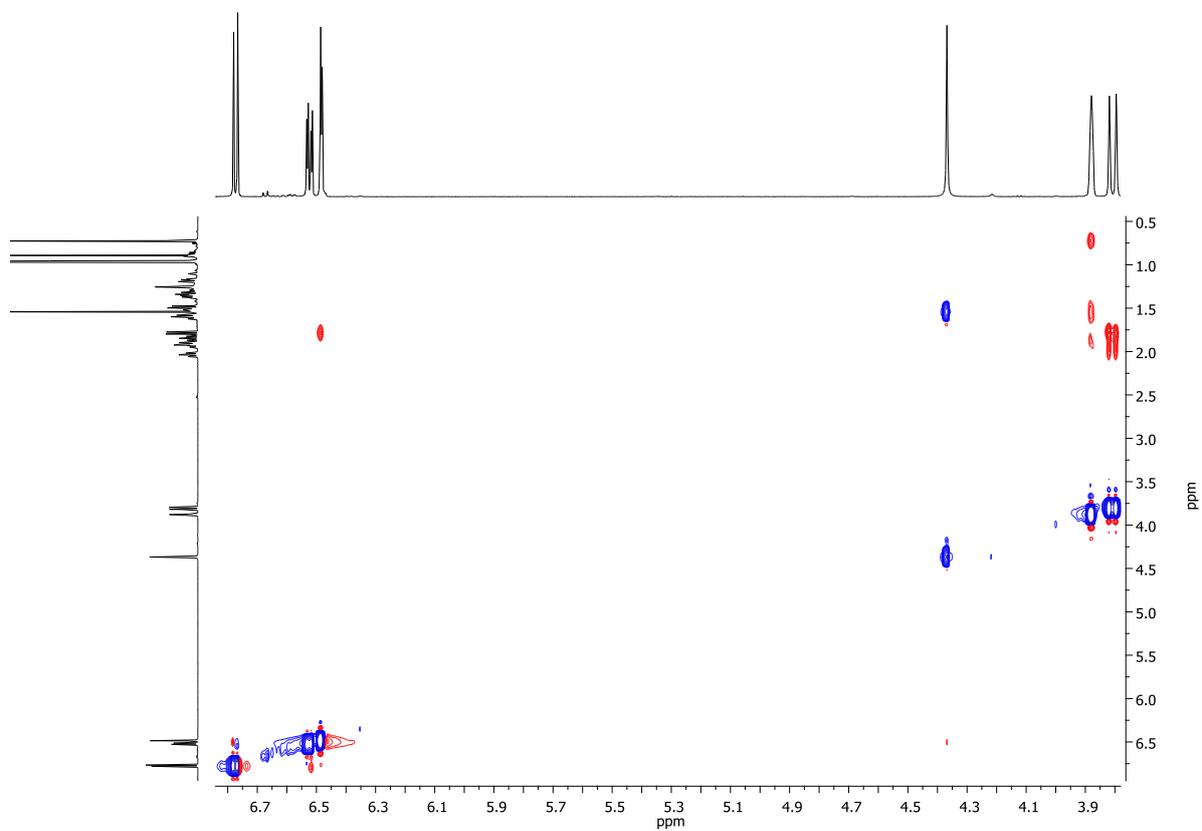
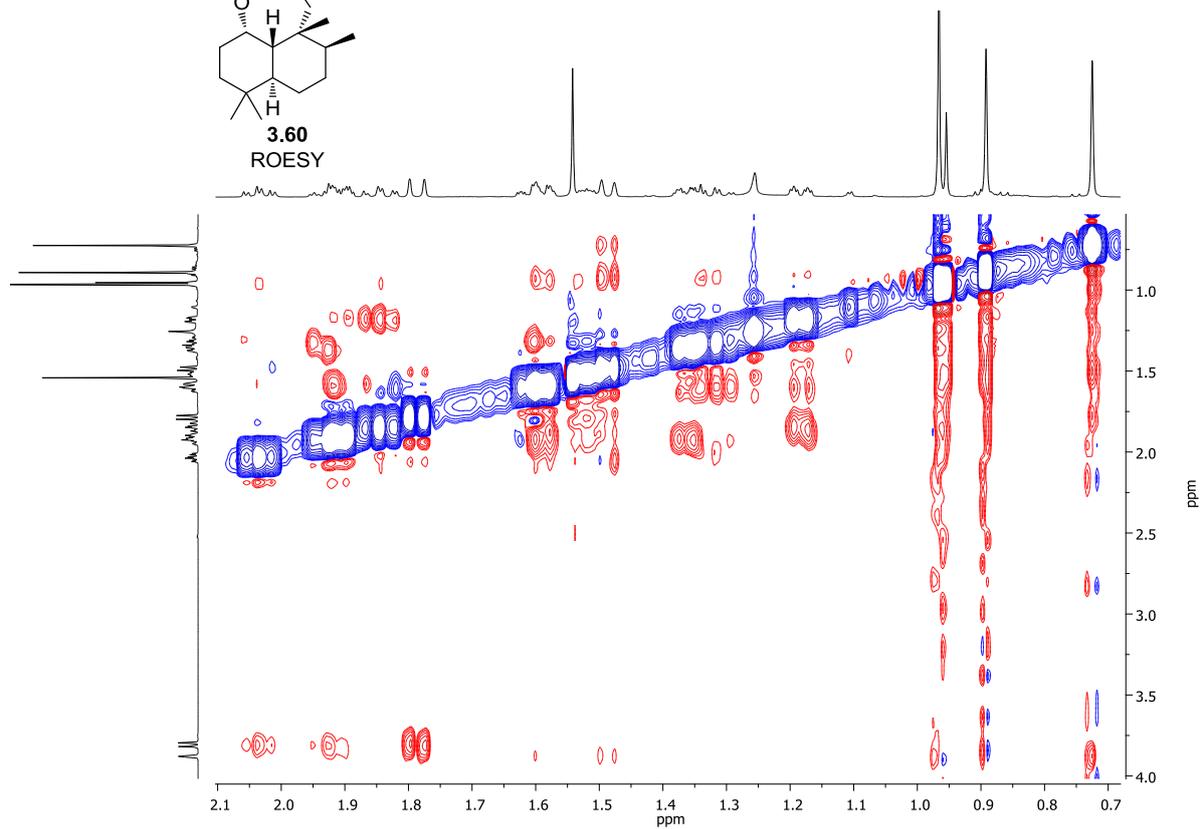
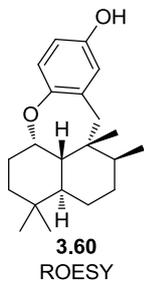






3.60  
COSY





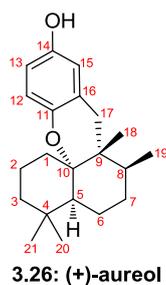


Table 2.1: Comparison of the <sup>1</sup>H NMR spectra of natural and synthetic (+)-aureol.

| Assignment                   | Faulkner,<br>200 MHz, CDCl <sub>3</sub> | George,<br>600 MHz, CDCl <sub>3</sub> |
|------------------------------|---|---------------------------------------|
| <b>H-12</b>                  | 6.62 (m, 2H)                            | 6.60 (d, <i>J</i> = 9.0 Hz, 1H)       |
| <b>H-13</b>                  | -                                       | 6.56 (dd, <i>J</i> = 9.0, 3.0 Hz, 1H) |
| <b>H-15</b>                  | 6.50 (br s, 1H)                         | 6.49 (d, <i>J</i> = 3.0 Hz, 1H)       |
| <b>14-OH</b>                 | -                                       | 4.23 (br s, 1H)                       |
| <b>H-17a</b>                 | 3.38 (d, <i>J</i> = 16.0 Hz, 1H)        | 3.37 (d, <i>J</i> = 17.0 Hz, 1H)      |
| <b>H-1a, H-2a</b>            | -                                       | 2.11 – 1.99 (m, 2H)                   |
| <b>H-17b</b>                 | 1.96 (d, <i>J</i> = 16.0 Hz, 1H)        | 1.96 (d, <i>J</i> = 17.0 Hz, 1H)      |
| <b>H-7a, H-7b</b>            | -                                       | 1.84 – 1.76 (m, 2H)                   |
| <b>H-6a, H-8</b>             | -                                       | 1.71 – 1.64 (m, 2H)                   |
| <b>H-6b</b>                  | -                                       | 1.60 – 1.53 (m, 1H)                   |
| <b>H-1b, H-2b, H-3b, H-5</b> | -                                       | 1.50 – 1.34 (m, 4H)                   |
| <b>Me-19</b>                 | 1.11 (d, <i>J</i> = 7.0 Hz, 3H)         | 1.11 (d, <i>J</i> = 7.5 Hz, 3H)       |
| <b>Me-18</b>                 | 1.06 (s, 3H)                            | 1.06 (s, 3H)                          |
| <b>Me-21*</b>                | 0.92 (s, 3H)                            | 0.92 (s, 3H)                          |
| <b>Me-20*</b>                | 0.78 (s, 3H)                            | 0.78 (s, 3H)                          |

\*Me-20/Me-21 signals may be interchanged.

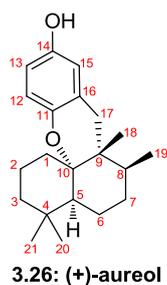


Table 2.2: Comparison of the  $^{13}\text{C}$  NMR spectra of natural and synthetic (+)-aureol.

| Assignment | Faulkner,<br>20 MHz, $\text{CDCl}_3$ | George,<br>150 MHz, $\text{CDCl}_3$ |
|------------|--------------------------------------|-------------------------------------|
| C-1        | 27.9                                 | 27.9                                |
| C-2        | 18.4                                 | 18.4                                |
| C-3        | 33.9                                 | 33.8                                |
| C-4        | 33.9                                 | 33.9                                |
| C-5        | 44.0                                 | 44.0                                |
| C-6        | 22.2                                 | 22.2                                |
| C-7        | 29.3                                 | 29.3                                |
| C-8        | 39.3                                 | 39.3                                |
| C-9        | 38.1                                 | 38.1                                |
| C-10       | 82.4                                 | 82.4                                |
| C-11       | 145.8                                | 145.8                               |
| C-12       | 117.2                                | 117.3                               |
| C-13       | 114.1                                | 114.0                               |
| C-14       | 148.2                                | 148.3                               |
| C-15       | 115.2                                | 115.1                               |
| C-16       | 122.2                                | 122.2                               |
| C-17       | 37.4                                 | 37.4                                |
| C-18       | 29.8                                 | 29.8                                |
| C-19       | 17.3                                 | 17.3                                |
| C-20*      | 31.9                                 | 31.9                                |
| C-21*      | 20.2                                 | 20.2                                |

\*C-20/C-21 signals may be interchanged.

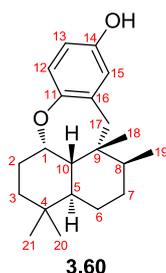


Table 2.3: Comparison of the  $^1\text{H}$  NMR spectra of **3.60**.

| Assignment        | George,<br>600 MHz, $\text{CDCl}_3$ |
|-------------------|-------------------------------------|
| <b>H-12</b>       | 6.77 (d, $J = 8.4$ Hz, 1H)          |
| <b>H-13</b>       | 6.52 (dd, $J = 8.4, 3.0$ Hz, 1H)    |
| <b>H-15</b>       | 6.48 (d, $J = 3.0$ Hz, 1H)          |
| <b>14-OH</b>      | 4.37 (br s, 1H)                     |
| <b>H-1</b>        | 3.88 (br s, 1H)                     |
| <b>H-17a</b>      | 3.81 (d, $J = 13.8$ Hz, 1H)         |
| <b>H-5</b>        | 2.03 (dt, $J = 12.5, 4.5$ Hz, 1H)   |
| <b>H-3a, H-7a</b> | 1.95 – 1.89 (m, 2H)                 |
| <b>H-2a</b>       | 1.84 (dt, $J = 8.4, 3.0$ Hz, 1H)    |
| <b>H-17b</b>      | 1.79 (d, $J = 13.8$ Hz, 1H)         |
| <b>H-3b, H-6a</b> | 1.63 – 1.57 (m, 2H)                 |
| <b>H-8</b>        | 1.53 – 1.51 (m, 1H)                 |
| <b>H-10</b>       | 1.49 (d, $J = 12.0$ Hz, 1H)         |
| <b>H-6b, H-7b</b> | 1.38 – 1.29 (m, 2H)                 |
| <b>H-2b</b>       | 1.18 (dt, $J = 8.4, 3.0$ Hz, 1H)    |
| <b>Me-19</b>      | 0.96 (d, $J = 7.0$ Hz, 3H)          |
| <b>Me-18</b>      | 0.73 (s, 3H)                        |
| <b>Me-21*</b>     | 0.97 (s, 3H)                        |
| <b>Me-20*</b>     | 0.89 (s, 3H)                        |

\*Me-20/Me-21 signals may be interchanged.

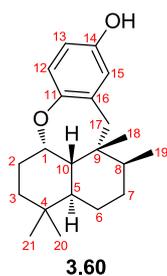


Table 2.4: Comparison of the  $^{13}\text{C}$  NMR spectra of **3.60**.

| Assignment | George,<br>150 MHz, $\text{CDCl}_3$ |
|------------|-------------------------------------|
| C-1        | 76.3                                |
| C-2        | 35.9                                |
| C-3        | 30.0                                |
| C-4        | 33.3                                |
| C-5        | 39.1                                |
| C-6        | 19.6                                |
| C-7        | 27.8                                |
| C-8        | 41.9                                |
| C-9        | 35.8                                |
| C-10       | 43.2                                |
| C-11       | 151.0                               |
| C-12       | 121.3                               |
| C-13       | 113.1                               |
| C-14       | 153.1                               |
| C-15       | 117.6                               |
| C-16       | 136.1                               |
| C-17       | 42.8                                |
| C-18       | 24.4                                |
| C-19       | 15.2                                |
| C-20*      | 30.5                                |
| C-21*      | 19.7                                |

\*C-20/C-21 signals may be interchanged.

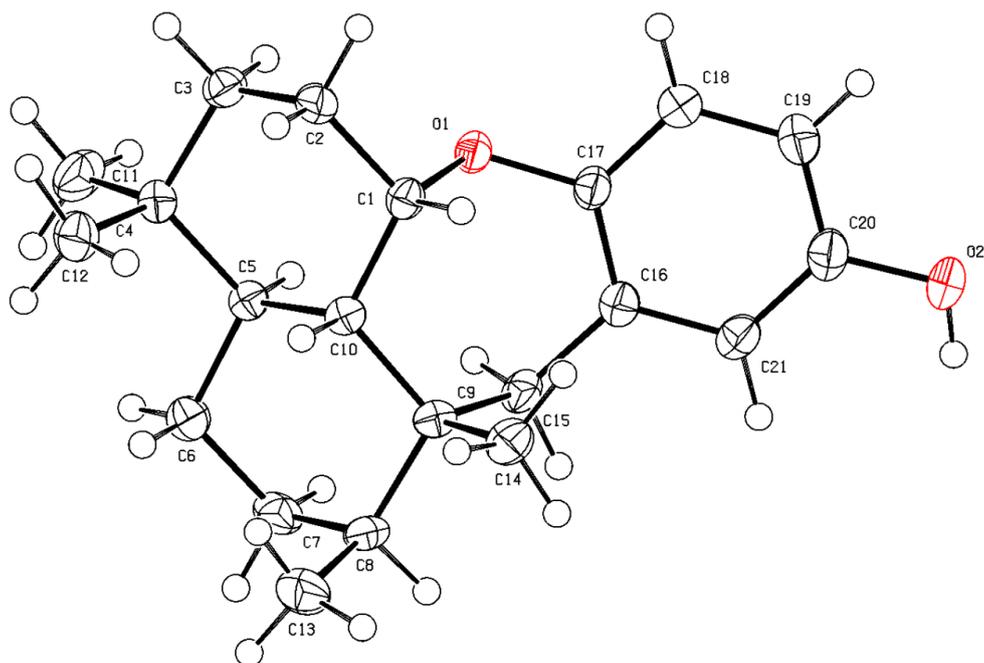


Figure 3.4: Crystal structure of **3.60**.

| <b>Compound</b>   | <b>3.60</b>   |
|---|---|
| Empirical formula   | C <sub>21</sub> H <sub>30</sub> O <sub>2</sub>        |
| Formula weight  | 314.45  |
| Crystal system  | Orthorhombic  |
| Space group   | <i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> |
| <i>a</i> (Å)  | 9.8774(4)   |
| <i>b</i> (Å)  | 11.7193(5)  |
| <i>c</i> (Å)  | 15.3374(6)  |
| $\alpha$ (°)  | 90  |
| $\beta$ (°)   | 90  |
| $\gamma$ (°)  | 90  |
| Volume (Å <sup>3</sup> )                                    | 1775.40(13)   |
| <i>Z</i>  | 4   |
| Density (calc.) (Mg/m <sup>3</sup> )                        | 1.176   |
| Absorption coefficient (mm <sup>-1</sup> )                  | 0.073   |
| <i>F</i> (000)  | 688   |
| Crystal size (mm <sup>3</sup> )                             | 0.39 × 0.25 × 0.18                                    |
| $\theta$ range for data collection (°)                      | 2.66 to 27.00   |
| Reflections collected                                       | 11033   |
| Observed reflections [ <i>R</i> (int)]                      | 3791 [0.0517]   |
| Completeness (%)  | 98.9 %  |
| Goodness-of-fit on <i>F</i> <sup>2</sup>                    | 1.072   |
| <i>R</i> <sub>1</sub> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )] | 0.0522  |
| <i>wR</i> <sub>2</sub> (all data)                           | 0.1075  |
| Largest diff. peak and hole (e.Å <sup>-3</sup> )            | 0.171 and -0.206                                      |

## CHAPTER FOUR

### Progress Towards the Biomimetic Synthesis of (–)-Fronodosin A

#### 4.1 *Ortho*-Quinone Methides in Natural Product Synthesis

*Ortho*-quinone methides were once thought to be highly unstable, short-lived intermediates and were therefore underutilised in organic synthesis. Over the last two decades however, these transient intermediates have been emerging as useful tools in complex molecule synthesis. The careful manipulation of *ortho*-quinone methides have allowed organic chemists to access a wide variety of structurally complex natural products, which have been highlighted in several reviews.<sup>1-4</sup> These intermediates have also been applied in other areas such as catalysis, asymmetric synthesis, and more recently, bioorthogonal ligation.<sup>5-11</sup> Recent advances in the development of metal stabilised *ortho*-quinone methide complexes have also been recently reviewed.<sup>12</sup>

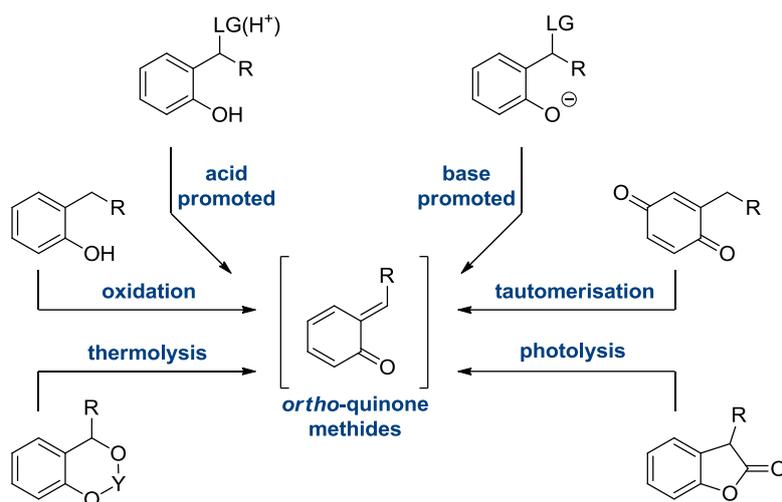
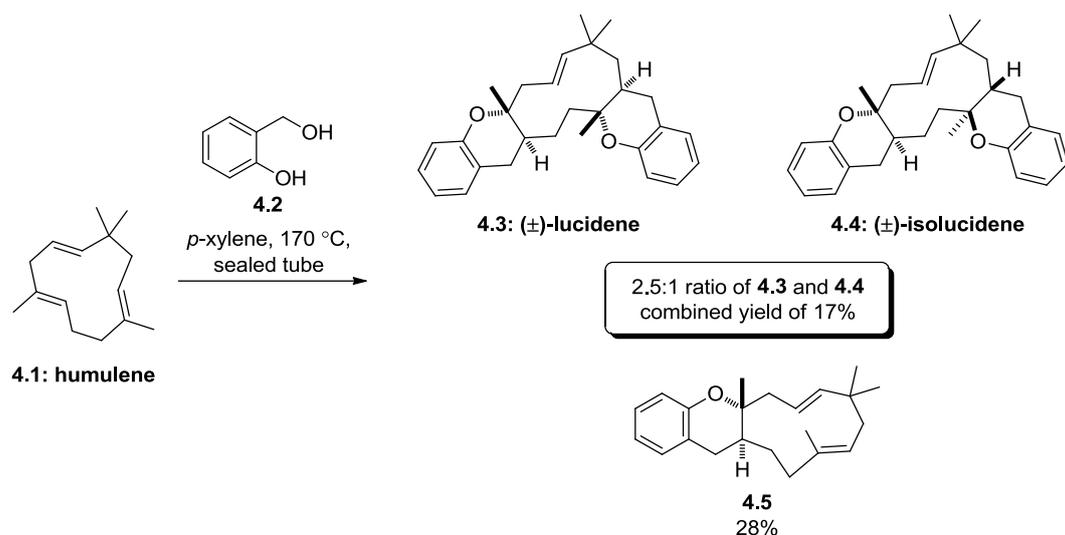


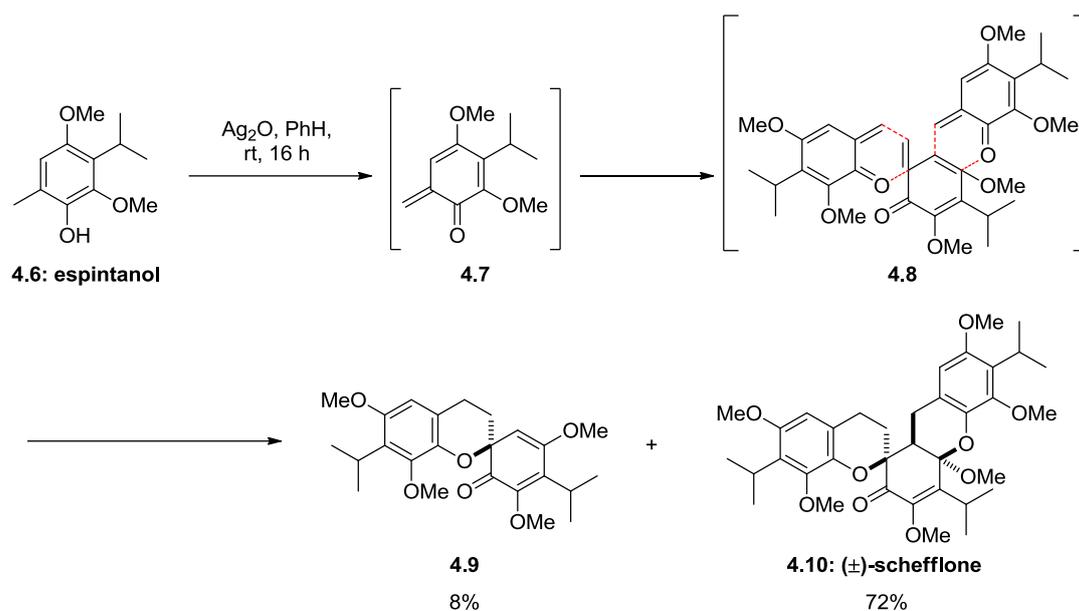
Figure 4.1: Methods of generating *ortho*-quinone methides.

*Ortho*-quinone methides can be generated under a variety of conditions, as shown in Figure 4.1.<sup>1-3</sup> Due to their electron-deficient nature, *ortho*-quinone methides have a propensity to readily undergo [4+2] cycloadditions, oxa  $6\pi$ -electrocyclisations, or Michael addition reactions with electron rich dienophiles. For example, in 1999, Baldwin and co-workers reported the biomimetic synthesis of ( $\pm$ )-lucidene (**4.3**) by reacting humulene (**4.1**) with an *in situ* generated *ortho*-benzoquinone methide (generated from phenol **4.2**) under thermal conditions (Scheme 4.1).<sup>13</sup> Baldwin hypothesised that the *ortho*-quinone methide would preferentially undergo two hetero Diels-Alder reactions with the trisubstituted double bonds as the disubstituted double bonds are more sterically hindered. As predicted, ( $\pm$ )-lucidene (**4.3**) and ( $\pm$ )-isolucidene (**4.4**) were isolated in a combined yield of 17% along with 28% of the mono-adduct **4.5**.



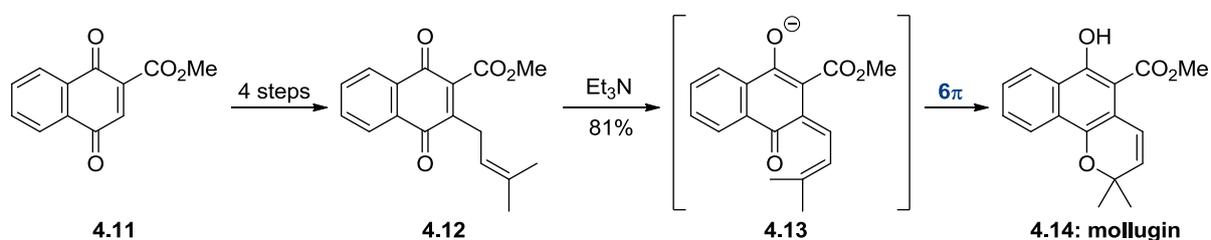
Scheme 4.1

Natural products that are a result of *ortho*-quinone methide trimerisation reactions have also appeared in nature. For example, schefflone (**4.10**) is a pentacyclic natural product that is derived from the oxidation of three espintanol (**4.6**) molecules (Scheme 4.2).<sup>14</sup> By careful consideration of the molecular architecture, Lei and co-workers demonstrated that *ortho*-quinone methide **4.7**, formed by treatment of espintanol (**4.6**) with Ag<sub>2</sub>O in benzene for 16 hours at room temperature readily afforded the natural product in 72% yield. A trace quantity of the spirocyclic dimer **4.9** was also co-isolated in the same reaction, suggesting that the apparent hetero Diels-Alder reaction occurs in a stepwise process.



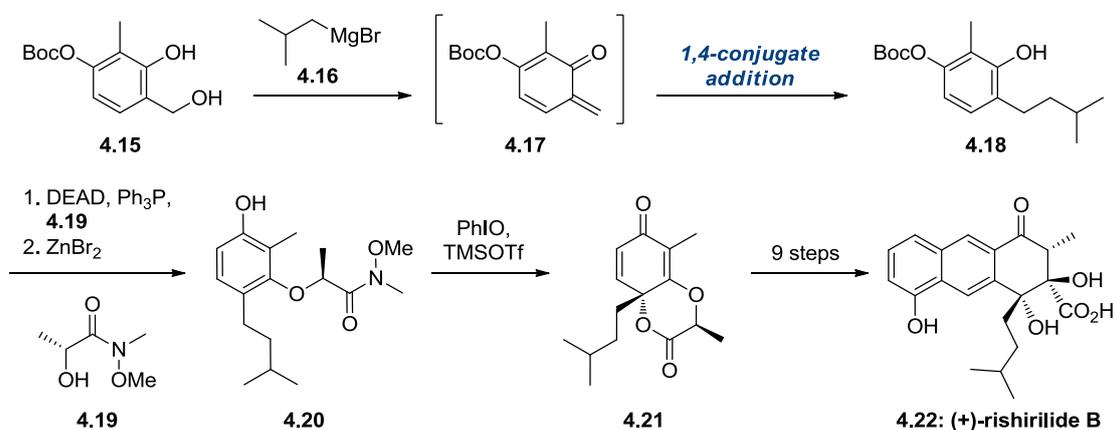
Scheme 4.2

An intramolecular reaction involving *ortho*-quinone methides can be found in Trauner's synthesis of mollugin (**4.14**).<sup>15</sup> Illustrated in Scheme 4.3, quinone **4.12**, derived from quinone **4.11** over four steps, was readily tautomerised with Et<sub>3</sub>N to the transient *ortho*-quinone methide **4.13**, which then undergoes an oxa 6 $\pi$ -electrocyclisation reaction to afford the target natural product. This concept was later extended to the synthesis of microphyllaquinone in the same publication.



Scheme 4.3

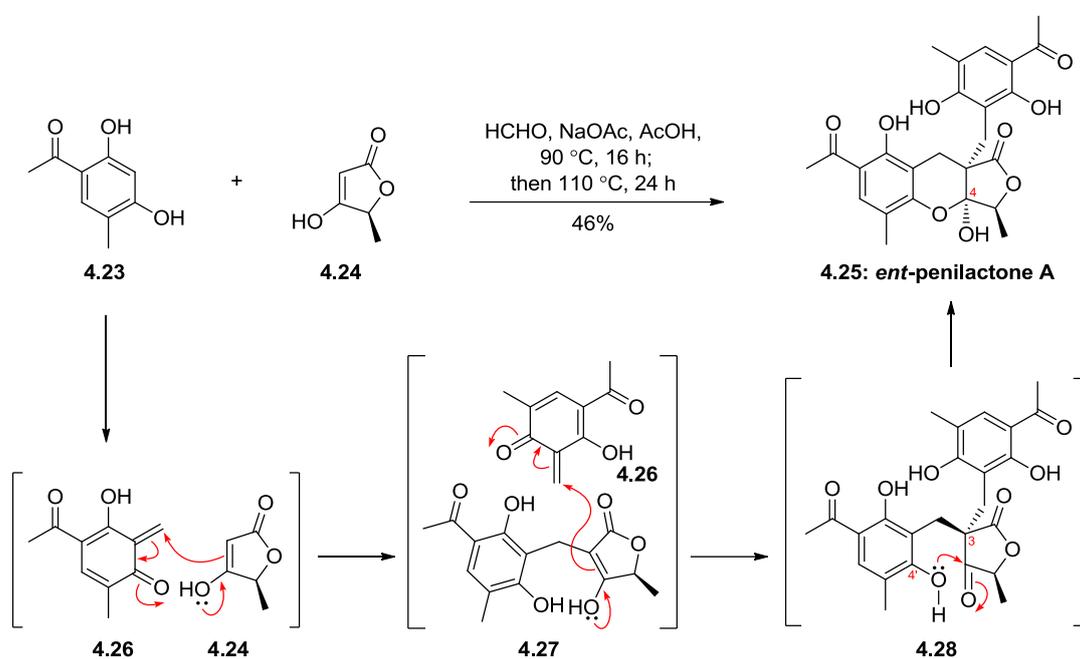
In 2004, Pettus and co-workers discovered that *ortho*-quinone methides can be generated from Boc-protected phenols with organometallic reagents such as Grignard reagents via a novel reaction cascade.<sup>16</sup> Furthermore, if an excess of the Grignard reagent was used, the *ortho*-quinone methide generated *in situ* would readily undergo a 1,4-conjugate addition to produce *ortho*-alkyl substituted phenols. This newfound methodology was applied to the synthesis of (+)-rishirilide B (**4.22**) (Scheme 4.4).<sup>17</sup> Phenol **15** was reacted with excess **4.16** to first generate the desired *ortho*-quinone methide **4.17**, which underwent 1,4-conjugate addition with the remaining Grignard reagent to afford phenol **4.18**. Mitsunobu reaction, followed by Boc deprotection gave phenol **4.20**, which underwent diastereoselective oxidative dearomatization to afford lactone **4.21**. The desired natural product was later obtained from lactone **4.21** over 8 steps.



Scheme 4.4

More recently, our group also demonstrated that *ortho*-quinone methides can undergo a series of Michael addition reactions with tetronic acids to generate polyketide natural products.<sup>18</sup> In this one pot, five component cascade reaction, *ortho*-quinone methide **4.26** was

first generated from resorcinol derivative **4.23** by reaction with formaldehyde under thermal acidic conditions (Scheme 4.5). The first Michael addition between tetronic acid **4.24** and *ortho*-quinone methide **4.26** would form **4.27**, which can undergo a second Michael addition with another molecule of *ortho*-quinone methide **4.26** to afford ketone **4.28** with a quaternary carbon centre at C-3. Stereoselective nucleophilic attack of the C-4' hydroxy group at the C-4 carbonyl group then formed *ent*-penilactone A (**4.25**).



Scheme 4.5

## 4.2 Isolation and Biological Activity of the Frondosins

Frondosins A – E (Figure 4.2) represent a family of meroterpenoid natural products bearing an unusual bicyclo[5.4.0]undecane ring system which is attached to either a hydroquinone or quinone moiety.<sup>19</sup> The frondosins were first isolated by Patil and co-workers from the Micronesian marine sponge *Dysidea frondosa* in 1997, while enantiomeric variants of frondosins A and D from the Micronesian sponge *Euryspongia sp.* were reported by Hallock and co-workers in the following year (Table 4.1).<sup>20</sup> However, the reported optical rotations of (–)-frondosin A and (–)-frondosin D are suspiciously large in magnitude.

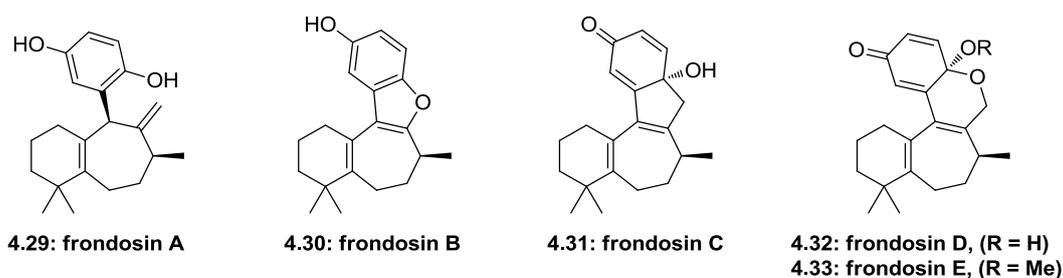


Figure 4.2 The frondosins, meroterpenoid natural products isolated from *Dysidea Frondosa*

Biological test results revealed that frondosins inhibit the binding of interleukin-8 (IL-8), a neutrophil-activating peptide which is produced by several cell types in response to inflammatory stimuli. IL-8 has been implicated in a wide range of acute and chronic inflammatory disorders, such as psoriasis and rheumatoid arthritis. In particular, frondosin A was the most potent of the frondosin family, showing promising activity against both IL-8 receptors  $\alpha$  and  $\beta$ , as well as protein kinase C (PKC) (Table 4.1).<sup>21-23</sup> Furthermore, frondosin A also inhibits the proliferation of lymphocytic cell lines.<sup>24</sup> However, dimethyl and diacetate derivatives of frondosin A displayed weak or no biological activity, suggesting that the

hydroquinone moiety is required for biological activity. In addition, Hallock and co-workers also reported that frondosins A and D showed moderate anti-HIV properties.<sup>20</sup>

Table 4.1: Biological activity and optical rotation values of frondosins A – E.

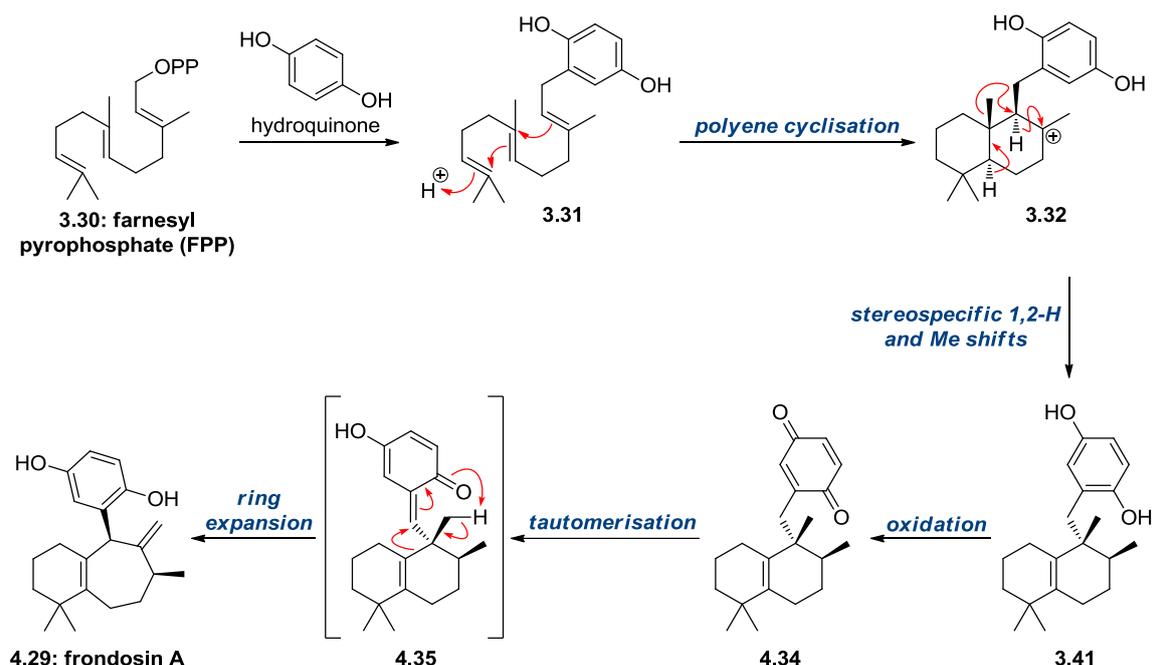
| Compound    | IC <sub>50</sub> (μM) |         |       | [α] <sub>D</sub>        |                        |
|-------------|-----------------------|---------|-------|-------------------------|------------------------|
|             | IL-8 Rα               | IL-8 Rβ | PKC-α | <i>Dysidea frondosa</i> | <i>Euryspongia sp.</i> |
| FronDOSin A | 3.4                   | 3.2     | 1.8   | +31.5°                  | -210°                  |
| FronDOSin B | 9.6                   | 10.8    | 4.8   | +18.6°                  | -                      |
| FronDOSin C | 84.0                  | 23.6    | 20.9  | +9.4°                   | -                      |
| FronDOSin D | 98.0                  | 10.8    | 26.0  | +19.6°                  | -211°                  |
| FronDOSin E | 64.0                  | 37.1    | 30.6  | +26.1°                  | -                      |

### 4.3 Proposed Biosynthesis of the Frondosins

#### 4.3.1 Biosynthesis of FronDOSin A

Analogous to the proposed biosynthesis of (+)-aureol (**3.26**), described in the previous chapter, we speculated that the biosynthesis of frondosin A is derived from similar biogenetic precursors. The formation of the hydroquinone **3.41** would be identical to the pathway outlined in Scheme 3.7. From this point onwards, the biosynthetic pathway diverges from that of (+)-aureol (**3.26**). In the case of (+)-aureol, the rearrangement of carbocation **3.32** via sequential [1,2]-hydride and methyl shifts would produce a second carbocation intermediate. The positive charge at the C-10 carbon is then trapped by the hydroquinone moiety to form the cycloether ring of (+)-aureol (refer to Scheme 3.7). In contrast, oxidation of the hydroquinone moiety of **3.41** would produce benzoquinone **4.34**, which could potentially be converted into its *ortho*-quinone methide tautomer **4.35** under relatively mild conditions

(Scheme 4.6). We anticipate that *ortho*-quinone methide **4.35** is then primed to undergo a novel ring expansion reaction to generate the bicyclo[5.4.0]undecane framework, perhaps with intramolecular proton transfer to control the formation of the exocyclic methylene group. Finally, rearomatisation of the hydroquinone ring would give frondosin A (**4.29**).

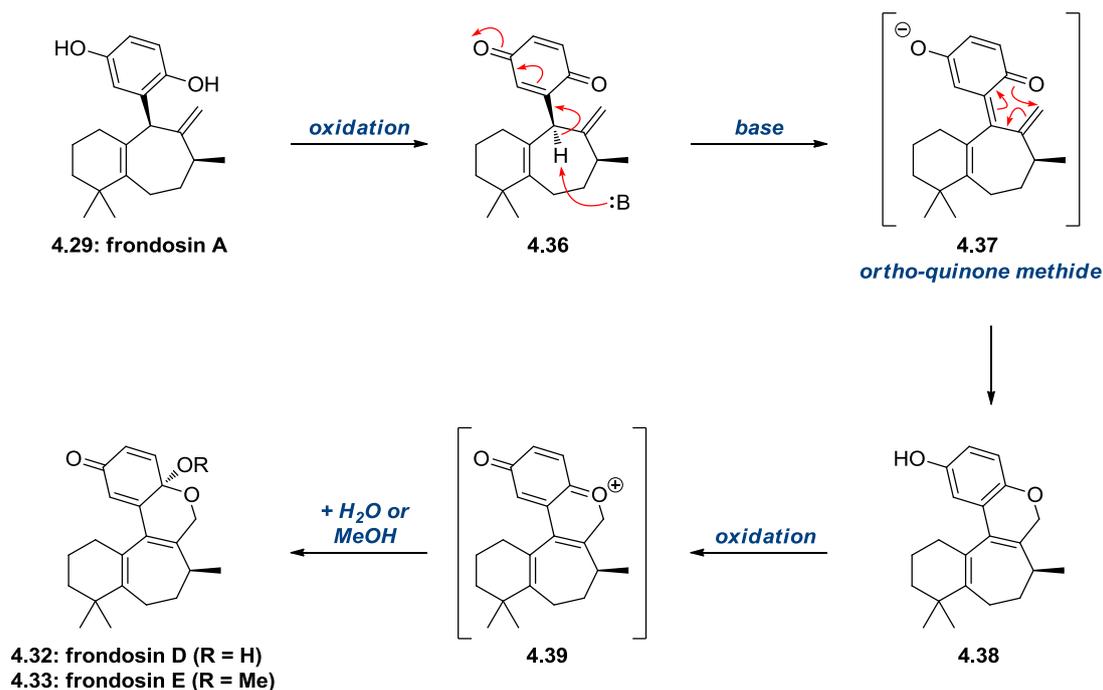


Scheme 4.6

### 4.3.2 Biosynthesis of Frondosins B, D and E

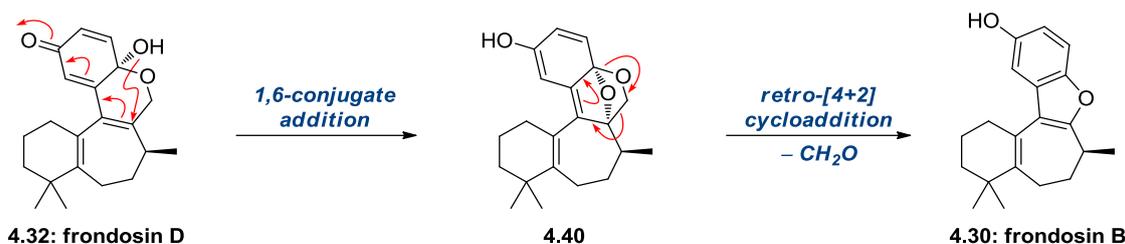
It is our belief that frondosin A could be the main precursor to frondosins B – E. Interestingly, a similar proposal had been presented earlier by Pettus and co-workers, who highlighted that the formation of frondosins B – E were presumably a result of subsequent oxidative dearomatisation cascade reactions.<sup>25</sup> For instance, further oxidation of frondosin A would afford benzoquinone **4.36** (Scheme 4.7). Formation of *ortho*-quinone methide **4.37** from benzoquinone **4.36** under basic conditions, followed by an intramolecular  $6\pi$

electrocyclisation would then generate the tetracycle **4.38**. Oxidative dearomatisation of **4.38** would proceed to afford the quinone cation **4.39**, which, in the presence of water, would produce frondosin D (**4.32**). Alternatively, oxidation of **4.38** in the presence of MeOH would give frondosin E (**4.33**).



Scheme 4.7

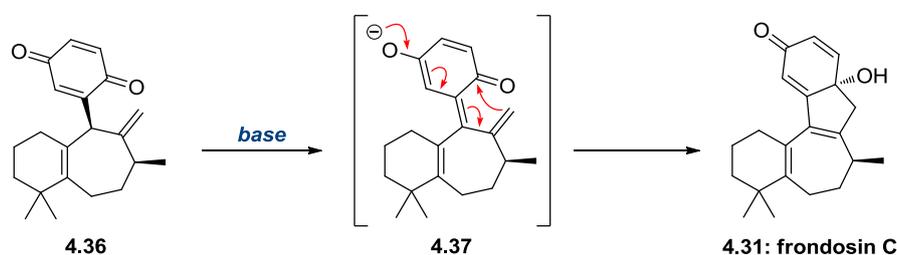
Frondosin D (**4.33**) could potentially undergo a one-carbon dehomologation to give frondosin B (**4.30**). As illustrated in Scheme 4.8, an intramolecular 1,6-conjugate addition of frondosin D (**4.32**) would give **4.40**, followed by a retro [4+2] cycloaddition with the elimination of formaldehyde to then form the desired natural product.



Scheme 4.8

### 4.3.3 Biosynthesis of Frondosin C

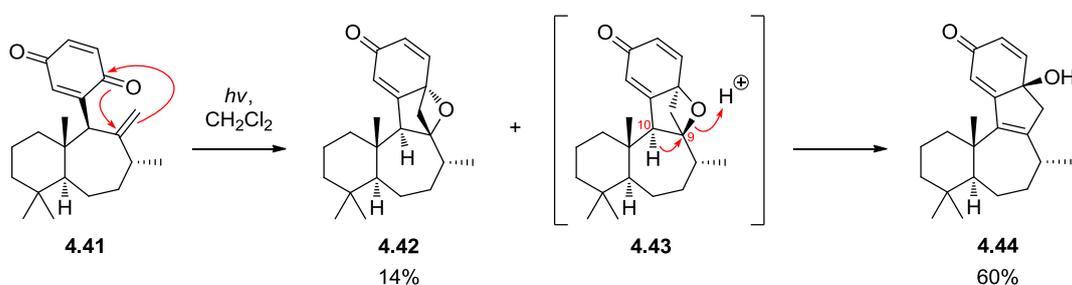
Initially, a vinylogous aldol reaction of the *ortho*-quinone methide **4.37** was thought to contribute to the formation of frondosin C in nature (Scheme 4.9). This hypothesis had also been previously outlined by Pettus.<sup>25</sup> However, recent findings within our group have suggested an alternative biosynthetic pathway for the formation of frondosin C (**4.31**).



Scheme 4.9

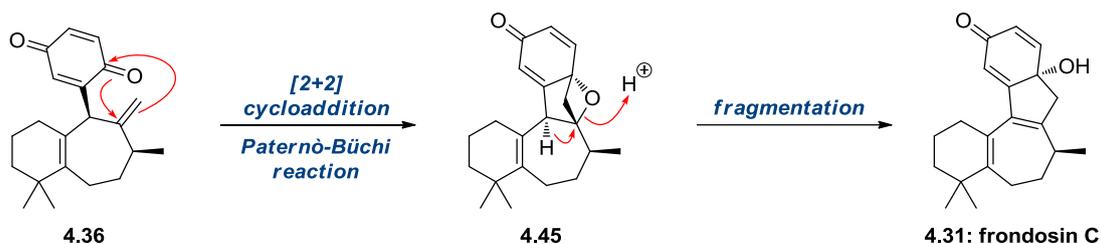
A model 6,7-bicyclic framework, **4.41**, that mimics the quinone scaffold of **4.36** was used to probe the proposed biosynthetic transformations. We discovered that quinone **4.41** would readily undergo a photochemical [2+2] cycloaddition (Paternò-Büchi reaction) between the exocyclic alkene and the adjacent quinone carbonyl group followed by facile fragmentation to form **4.43**, which possessed the same 6,7,5,6- ring system as frondosin C

(4.31) (Scheme 4.10).<sup>26</sup> A small amount of bicyclic oxetane **4.42** was also isolated from the reaction, which lends further support to the photochemical transformation. Mechanistically, we believe that the photochemical [2+2] cycloaddition initially gives a mixture of diastereomeric oxetanes **4.42** and **4.43** with unusual 6-oxabicyclo[2.2.1]hexane ring systems. While the bicyclic oxetane **4.42** is stable under the reaction conditions (and at elevated temperatures), oxetane intermediate **4.43** could readily undergo fragmentation to give **4.44** due to existing the antiperiplanar relationship between the C-10 proton and the C-O bond of the C-9 carbon.



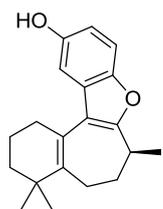
Scheme 4.10

In light of these findings, we speculate that a similar process is responsible for the formation of frondosin C (**4.31**). Namely, the [2+2] cycloaddition of quinone **4.36** would give oxetane **4.45**, which then undergoes subsequent fragmentation to give the natural product (Scheme 4.11).



Scheme 4.11

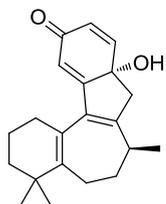
The close biosynthetic relationship between the frondosins makes the total synthesis of frondosin A very attractive, as we could potentially convert it into frondosins B – E using predisposed biomimetic reactions. Since the first isolation of these bicyclo[5.4.0]undecane meroterpenoids in 1997, numerous research groups have attempted the total synthesis of these natural products. Frondosin B (**4.30**) has been the most popular target amongst the frondosin family, culminating in a total of 13 publications related to the synthesis of the natural product to date (five enantioselective<sup>24, 27-32</sup>, six racemic<sup>33-38</sup>, and two formal approaches<sup>39, 40</sup>). Meanwhile, Ovaska and co-workers<sup>41</sup> are the first to report a racemic synthesis of frondosin C (**4.31**), whereas the total synthesis of frondosins D and E are yet to be reported (Flynn and Masters were the only group to establish a Pd-catalysed approach towards the polycyclic scaffold of frondosin D (**4.32**)).<sup>42</sup>



**4.30: frondosin B**

**Enantioselective total synthesis**

|             |      |                     |
|-------------|------|---------------------|
| Danishefsky | 2001 | 17 steps, 1% yield  |
| Trauner     | 2002 | 20 steps, 7% yield  |
| Ovaska      | 2009 | 10 steps, 13% yield |
| MacMillan   | 2010 | 3 steps, 50% yield  |
| Wright      | 2014 | 15 steps, 26% yield |



**4.31: frondosin C**

**Racemic total synthesis**

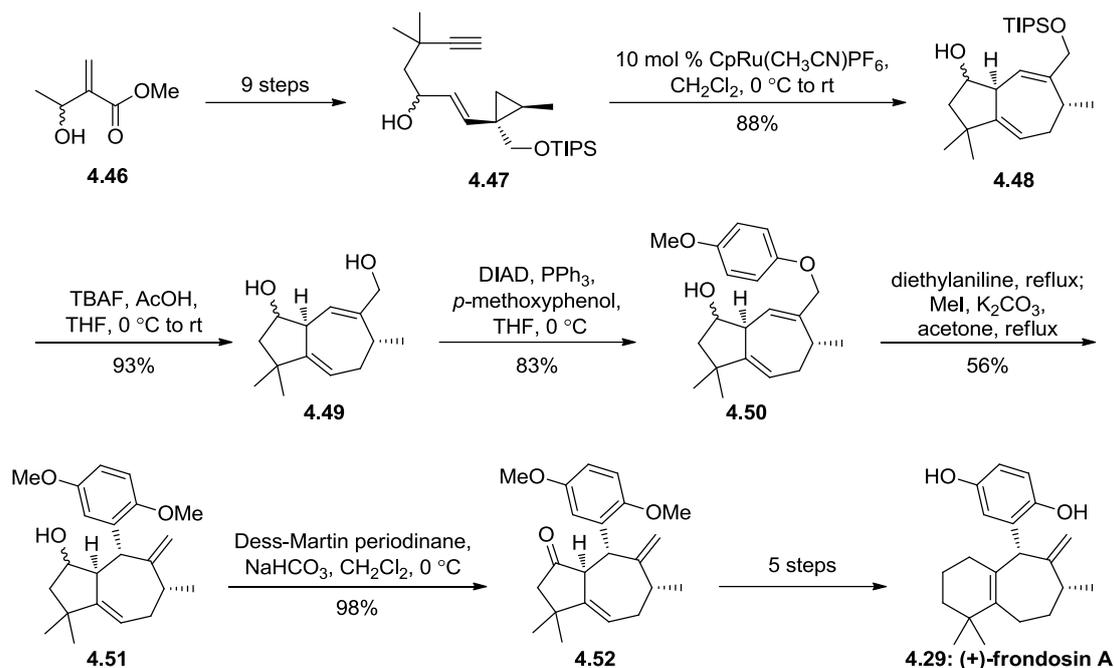
|        |      |                     |
|--------|------|---------------------|
| Ovaska | 2007 | 12 steps, 12% yield |
|--------|------|---------------------|

Figure 4.3 Previously reported syntheses of frondosins B and C

## 4.4 Previous Work on the Synthesis of Frondosin A

### 4.4.1 Enantioselective Total Synthesis of (+)-Frondosin A by Trost

The first total synthesis of (+)-frondosin A (**4.29**) was reported by Trost in 2007.<sup>43</sup> Trost's enantioselective approach takes advantage of a Ru-catalysed [5+2] cycloaddition reaction to assemble the key precursor **4.47**. To achieve this, methyl ester **4.46** was first converted into alkyne **4.47** in nine steps (Scheme 4.12). After extensive screening, alkyne **4.47** was subjected to catalytic amounts of CpRu(CH<sub>3</sub>CN)PF<sub>6</sub> in CH<sub>2</sub>Cl<sub>2</sub> to afford the cycloaddition product **4.48** in good yield. The primary alcohol functionality was revealed using TBAF buffered with acetic acid to give **4.49**, which was then reacted with *p*-methoxyphenol under Mitsunobu conditions to afford compound **4.50**. Thermal Claisen rearrangement in diethylaniline, followed by methylation of the newly exposed phenol functionality gave **4.51**. With the right side of the molecule now constructed, efforts were directed towards the construction of the bicyclo[5.4.0] core. Dess-Martin oxidation of **4.51** afforded ketone **4.52**. Ring expansion, deoxygenation and demethylation of ketone **4.52** was achieved over five steps to produce (+)-frondosin A (**4.29**). Trost's expeditious strategy (a total of 21 steps with an overall yield of 7%) highlights the first application of the Ru-catalysed [5+2] cycloaddition in natural product synthesis.

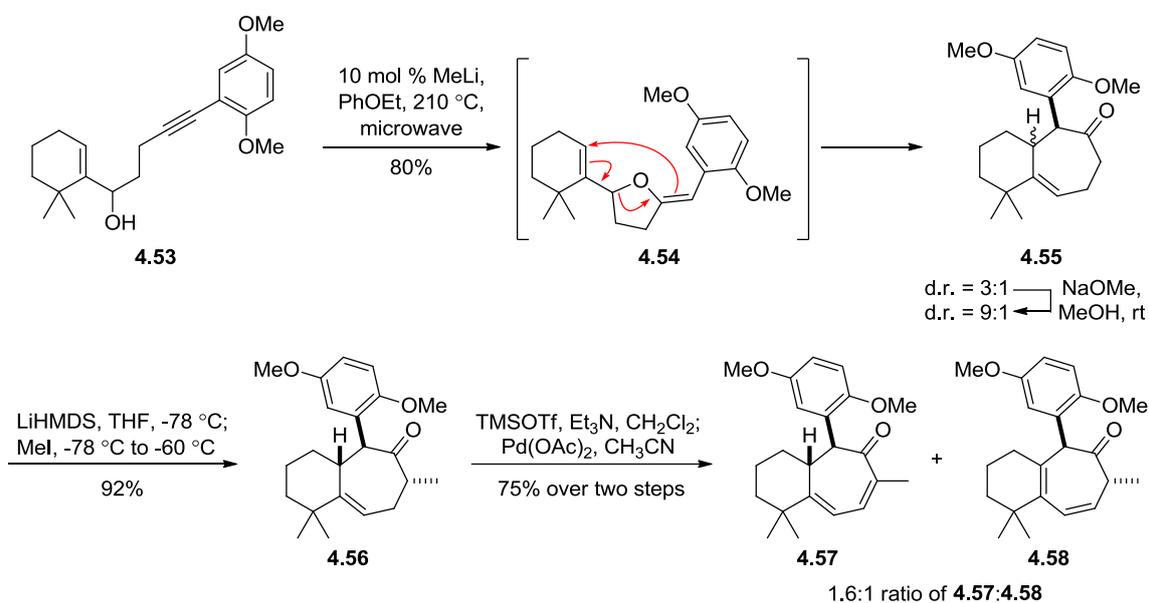


Scheme 4.12

#### 4.4.2 Ovaska's Approach

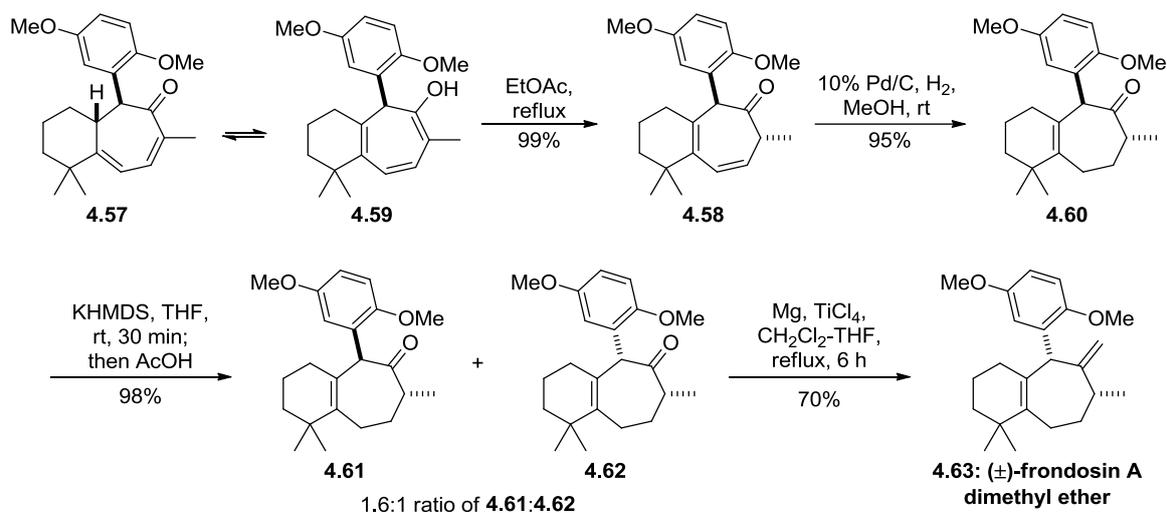
The second total synthesis of frondosin A was reported by Ovaska a year after Trost's publication.<sup>44</sup> Building upon the group's successful synthesis of ( $\pm$ )-frondosin B,<sup>34</sup> the bicyclo[5.4.0]undecane core was constructed using a microwave-assisted tandem 5-*exo* cyclisation-Claisen rearrangement. Alkyne **4.53** was subjected to base catalysed intramolecular oxyanionic cyclisation in the presence of MeLi to produce tetrahydrofuran **4.54**, which later underwent an *in situ* Claisen rearrangement to generate cycloheptanone **4.55** (Scheme 4.13) as a 3:1 mixture of diastereomers. The diastereomeric ratio was further increased to 9:1 in favour of the desired diastereomer when cycloheptanone **4.55** was treated with NaOMe in MeOH. Installation of the C-8 methyl group then proceeded efficiently to give **4.56**. It is worthy to note that cycloheptanone **4.56** had previously been converted into ( $\pm$ )-frondosin B by Ovaska, as discussed *vide supra* (Figure 4.3). Unfortunately, isomerisation of the C-5–C-6 bond proved to be more challenging than initially anticipated.

The tetrasubstituted  $\Delta^5$  bond was introduced indirectly via Saegusa oxidation over two steps to give a 1.6:1 mixture of **4.57** and **4.58**.<sup>45</sup>



Scheme 4.13

Cycloheptanone **4.57** could be converted into the less conjugated, desired isomer **4.58** by simply refluxing the mixture in EtOAc (Scheme 4.14). This process presumably occurs via the fully conjugated enol tautomer of **4.57**, enol **4.59**. Interestingly, ketone **4.58**, bearing a *trans* relationship between the aryl and methyl substituents on the cycloheptanone ring, was the sole product of this “deconjugative” process. Catalytic hydrogenation of the trisubstituted double bond proceeded smoothly to give ketone **4.60**. Treatment of **4.60** with KHMDS followed by protonation with AcOH gave a mixture of **4.61** and **4.62** in a 1.6:1 ratio, which could be separated readily. Finally, completion of the formal synthesis was accomplished by olefination of the desired ketone **4.62** with Mg and TiCl<sub>4</sub> to produce (±)-frondosin A dimethyl ether (**4.63**), an advanced intermediate previously reported by Trost.<sup>43</sup>

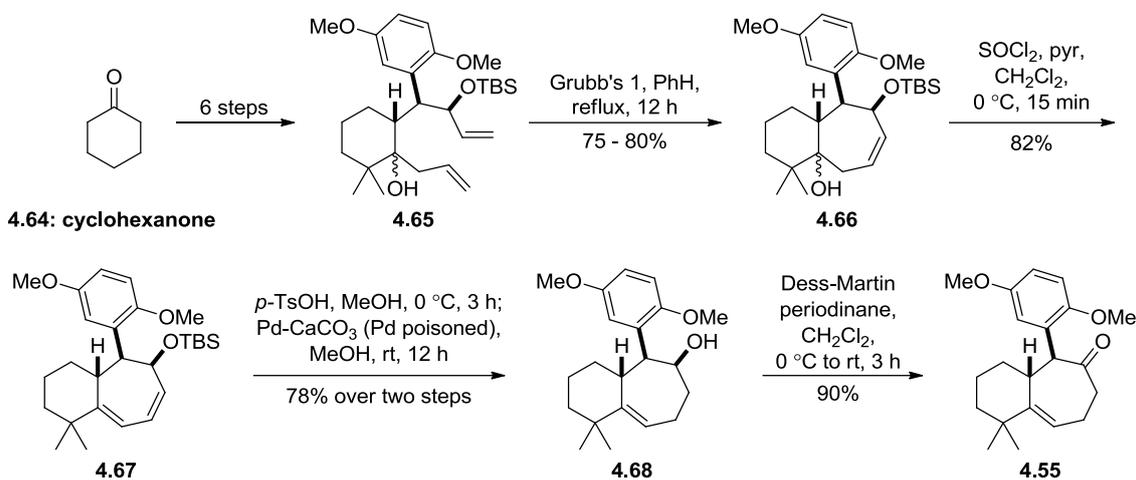


Scheme 4.14

#### 4.4.3 Mehta's Ring Closing Metathesis Approach

The formal synthesis of ( $\pm$ )-frondosin A presented by Mehta and Likhite involved the use of a ring closing metathesis (RCM) reaction to generate the seven membered ring of the bicyclo[5.4.0]undecane core. The RCM precursor **4.65** was generated from cyclohexanone (**4.64**) in six short steps (Scheme 4.15). Ring closing metathesis was achieved with the use of Grubb's first generation catalyst to afford the bicyclic alcohol **4.66**, which was subsequently dehydrated upon exposure to thionyl chloride and pyridine to produce diene **4.67**. TBS deprotection revealed the hydroxy functionality of **4.67**, and selective hydrogenation of the least substituted double bond was obtained using Lindlar's catalyst poisoned with Pb to give alcohol **4.68**. Dess-Martin oxidation of alcohol **4.68** lead to the formation of cycloheptanone **4.55**, which had been previously described by Ovaska, and thus constitutes the formal synthesis of ( $\pm$ )-frondosin A (**4.29**). Analogous to Ovaska's strategy, subsequent synthetic

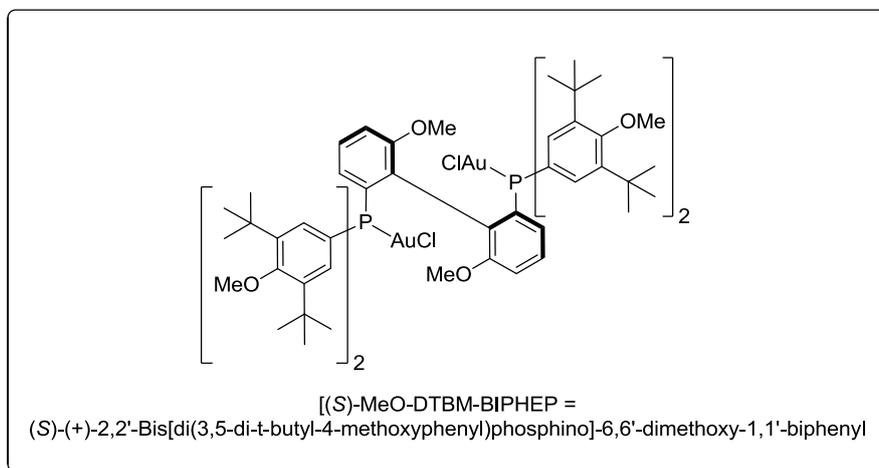
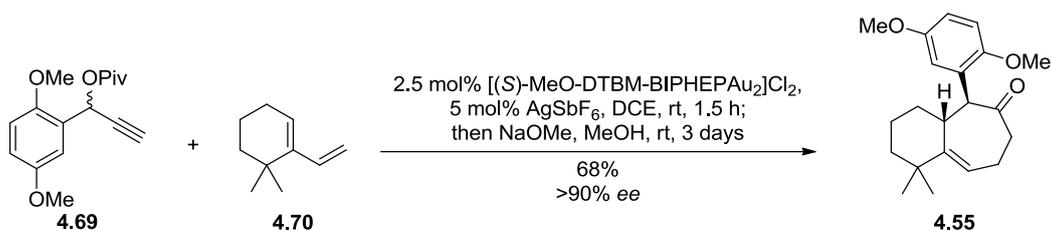
manipulations of cycloheptanone **4.55** would additionally give rise to ( $\pm$ )-frondosin B (**4.30**).<sup>34, 38</sup>



Scheme 4.15

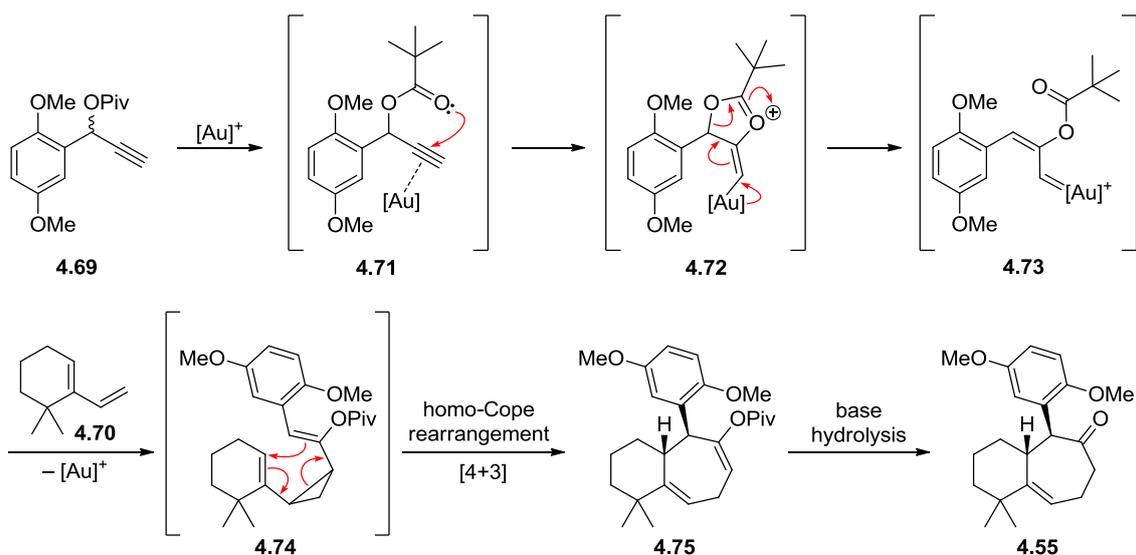
#### 4.4.4 Nevado's Gold Catalysed Ring Expansion Approach

In 2011, Christina Nevado's group demonstrated that the 6-7 ring system of the frondosins can be obtained via a gold catalysed cascade reaction.<sup>39,46</sup> After extensive screening, Nevado and co-workers discovered that treatment of alkyne **4.69** and cyclohexene **4.70** with 2.5 mol% of (*S*)-MeO-DTBM-BIPHEP-gold(I) complex, followed by base hydrolysis, afforded cycloheptanone **4.55** with excellent diastereoselectivity (Scheme 4.16).



Scheme 4.16

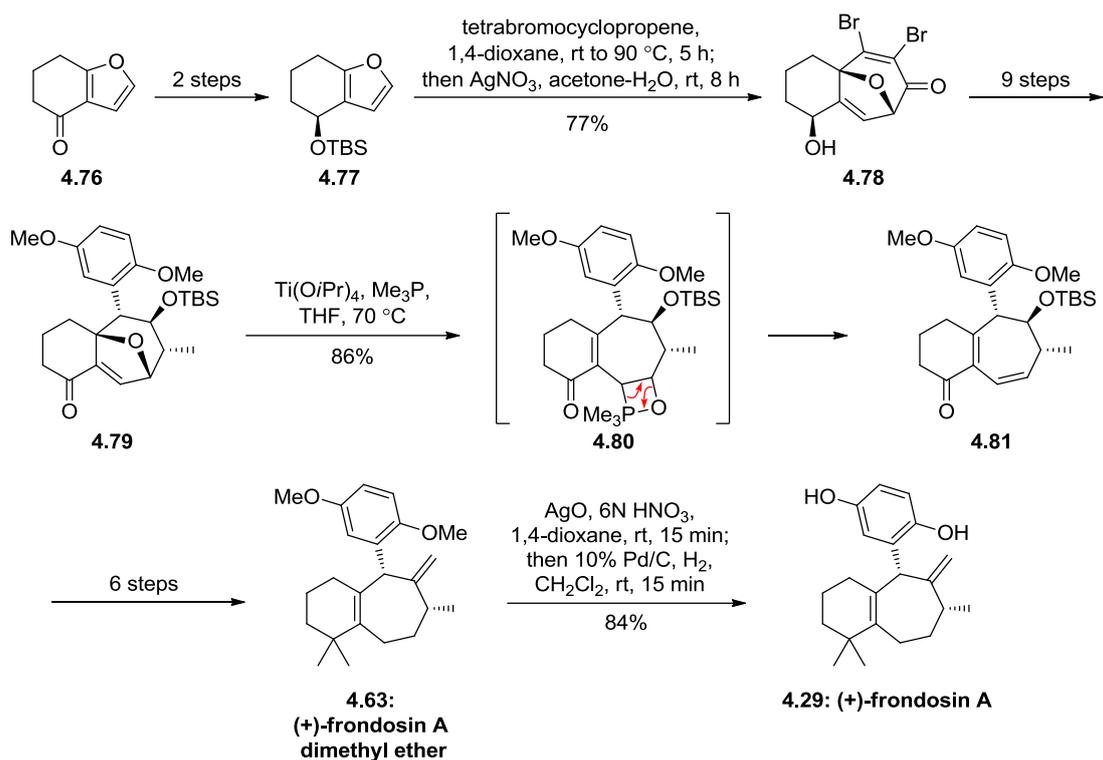
The authors proposed that the mechanism first involves a gold catalyzed 1,2-acetyloxy migration of the propargyl ester of **4.69** to afford the gold carbene intermediate **4.73** (Scheme 4.17). An *in situ* olefin cyclopropanation reaction then proceeds in the presence of cyclohexene **4.70** to generate the cyclopropane intermediate **4.74**, which is then primed to undergo a homo-Cope rearrangement to form the seven membered ring of **4.75**. Finally, removal of the pivaloyl protecting group followed by subsequent equilibration of the reaction mixture in NaOMe-MeOH yielded the thermodynamically favoured cycloheptanone **4.55**. This diastereoselective, three-step cascade provides a short and concise route to Ovaska's intermediate.



Scheme 4.17

#### 4.4.5 Wright's Cyclopropene Cycloaddition Approach to (+)-Fronodosin A

The most recent total synthesis of (+)-fronodosin A (**4.29**) was reported by Wright and co-workers in early 2014.<sup>24</sup> The key oxa-bridged intermediate **4.78** was efficiently synthesised via a [4+3] cycloaddition of tetrabromocyclopropene with furan **4.77**, which in turn was obtained from commercially available furan **4.76** according to a two-step asymmetric reduction/ TBS protection protocol reported by Noyori (Scheme 4.18).<sup>47</sup> Subsequent functionalisation of **4.78** produced ketone **4.79** over nine elaborate steps. Ring opening of the ether bridge was achieved when **4.79** was treated with  $Me_3P$  in the presence of  $Ti(OiPr)_4$  to produce the cross conjugated dienone **4.81**, presumably via the reduction of phosphine intermediate **4.80** *in situ*. Dienone **4.81** was further elaborated to (+)-fronodosin A dimethyl ether (**4.63**) over six steps. Finally, oxidation to the corresponding benzoquinone with  $AgO$  in the presence of  $HNO_3$ , followed by catalytic hydrogenation, provided (+)-fronodosin A (**4.29**) in good yield over two steps.

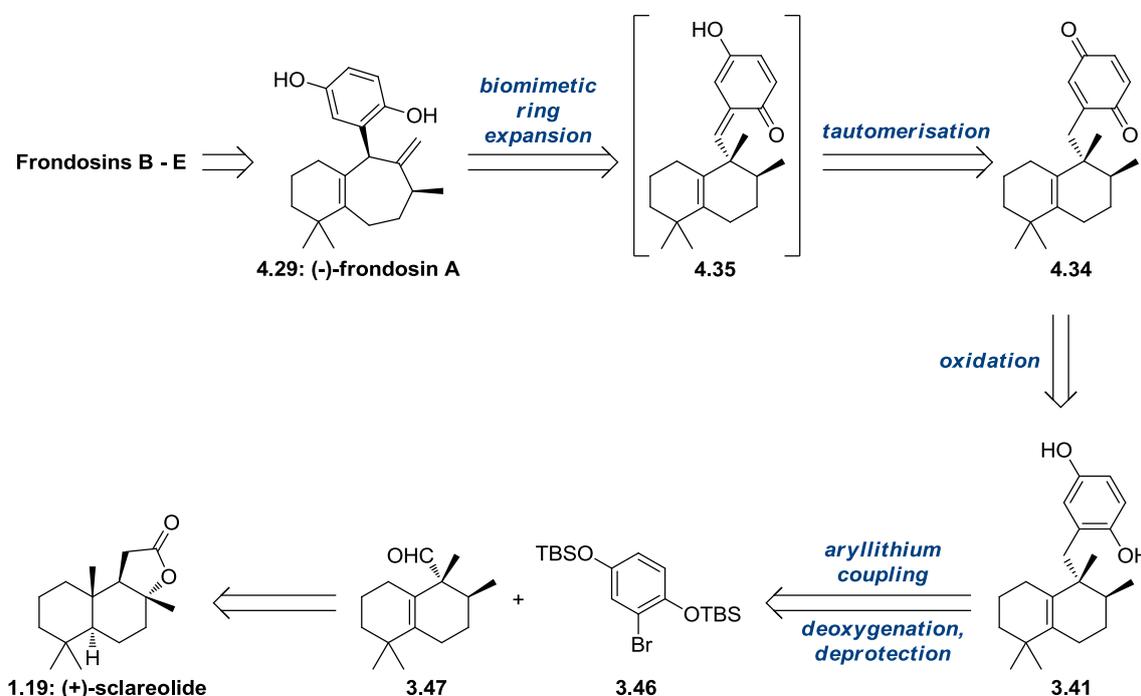


Scheme 4.18

In summary, there have been five literature reports on the total or formal synthesis of frondosin A over the period of 2007 to 2014 – enantioselective approaches were disclosed by both Trost (2007) and Wright (2014), while two formal racemic syntheses were reported by Ovaska and Mehta concurrently in 2008. Furthermore, a formal enantioselective synthesis of frondosin A was achieved with the use of a gold catalyst in 2011 by Nevada's group. However, to the best of our knowledge, a biomimetic approach towards the frondosin family of natural products has yet to be reported. Building on our previous success with the total synthesis of (+)-aureol, we believe that a biomimetic synthesis of frondosin A, and thus, a unified approach towards the other members of the frondosin family of natural products is plausible. In addition, we anticipate the discovery of a novel biomimetic ring expansion reaction that would involve a transient *ortho*-quinone methide intermediate, as proposed in the previous section (see Section 4.3, Schemes 4.6, 4.7, 4.8 and 4.11).

## 4.5 Retrosynthetic Analysis of Frondosin A

A key challenge of this project is developing an efficient biomimetic route to access sufficient quantities of frondosin A (**4.29**). A successful synthesis of frondosin A could allow access to other members of the frondosin family using pre-disposed biomimetic reactions, as outlined earlier. We propose that the 6,7-ring system of the natural product could be derived from a biomimetic ring expansion involving *ortho*-quinone methide **4.35** as the key intermediate (Scheme 4.19). *Ortho*-quinone methide **4.35** itself could be generated from the tautomerisation of quinone **4.34**. Quinone **4.34** could easily be derived from the oxidation of hydroquinone **3.41**. Hydroquinone **3.41** could be formed from the addition of an aryllithium species derived from aryl bromide **3.46** to aldehyde **3.47**, followed by deoxygenation of the benzylic alcohol and removal of the protecting groups. Aldehyde **3.47**, in turn, could be elaborated from (+)-sclareolide (**1.19**) through a series of functional group manipulations analogous to that previously reported in the synthesis of (+)-aureol (**3.26**).

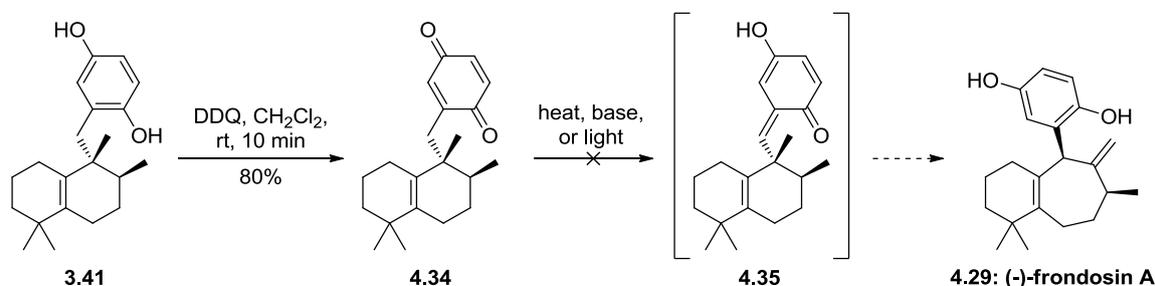


Scheme 4.19

## 4.6 Results and Discussion

### 4.6.1 Attempted Biomimetic Ring Expansion of Quinone 4.34

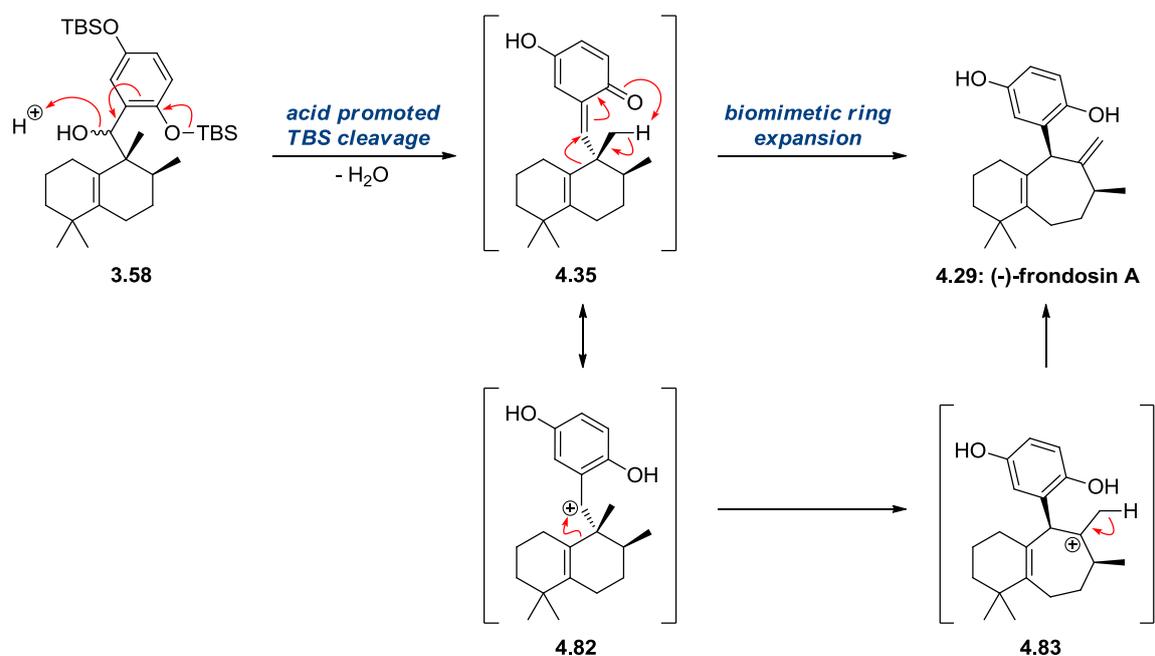
Our previous synthetic endeavour with (+)-aureol has allowed us to quickly investigate the aforementioned biomimetic route. Hydroquinone **3.41** was synthesised according to Scheme 3.20, then oxidised with DDQ in CH<sub>2</sub>Cl<sub>2</sub> at room temperature to afford quinone **4.34** as a bright yellow oil (Scheme 4.20). Quinone **4.34** had a tendency to decompose very quickly and therefore had to be used immediately after purification. With the precursor at hand, we turned our attention towards the formation of (-)-frondosin A. Unfortunately, attempts to tautomerise quinone **4.34** with base (pyridine), heat (up to 90 °C) or exposure to sunlight only led to the decomposition of the starting material. As the stability of the starting material itself was questionable, we decided to investigate the possibility of generating the desired *ortho*-quinone methide from benzylic alcohol **3.58** instead.



Scheme 4.20

We envisaged that *ortho*-quinone methide **4.35** could be generated from a facile dehydration of the benzylic alcohol prompted by spontaneous cleavage of the adjacent TBS protecting group under mild acidic conditions (Scheme 4.21). The proposed biomimetic ring expansion could occur under these conditions to give (-)-frondosin A (**4.29**). Alternatively,

the reaction could also proceed via a highly stabilised benzylic carbocation intermediate **4.82** to generate the tertiary carbocation intermediate **4.83**, followed by elimination of a proton to deliver the desired target molecule.



Scheme 4.21

#### 4.6.2 Formation of Cycloether **4.84**, a Structural Isomer of (-)-Frondosin A

Benzylic alcohol **3.58** was initially treated with one equivalent of *p*-TsOH in CH<sub>2</sub>Cl<sub>2</sub> at room temperature and the reaction was monitored by TLC (Table 4.2). While no reaction was observed after 15 minutes, decomposition of the starting material occurred when the reaction mixture was left over a period of 12 hours. A more encouraging result was obtained when the reaction was conducted in PhMe under reflux conditions (Table 4.2, entry 3). Interestingly, upon purification and characterisation, the NMR data obtained did not match the corresponding natural product. Careful analysis of the NMR data revealed that a structural

isomer of (-)-frondosin A, cycloether **4.84** was produced from the acid mediated ring expansion reaction.

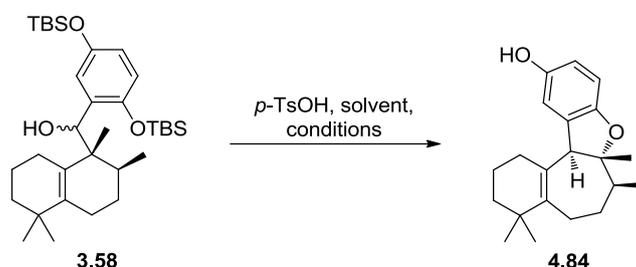
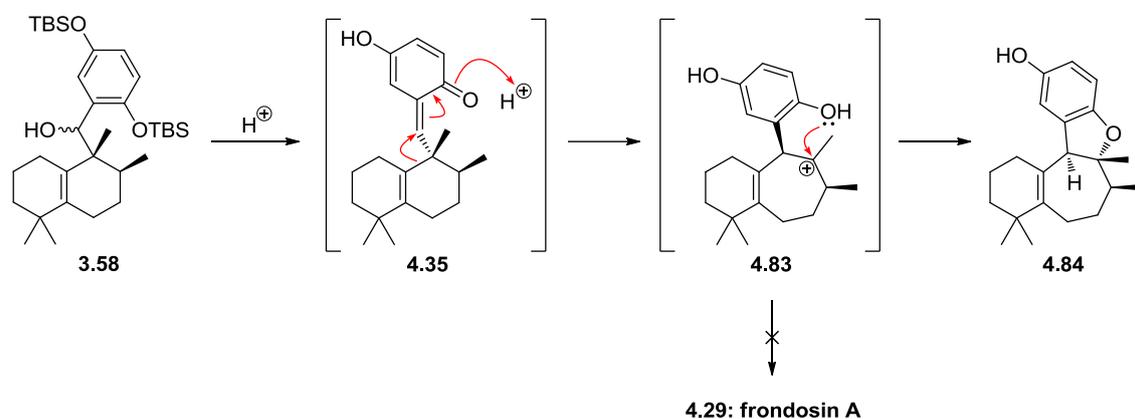


Table 4.2: Conditions for acid mediated ring expansion of **3.58** to give **4.84**.

| Entry | Solvent/ conditions                                      | Yield (%)     |
|-------|--|---------------|
| 1     | CH <sub>2</sub> Cl <sub>2</sub> , rt, 15 min             | No reaction   |
| 2     | CH <sub>2</sub> Cl <sub>2</sub> , rt, 12 h               | Decomposition |
| 3     | PhMe, reflux, 12 h                                       | 50            |
| 4     | CH <sub>3</sub> CN, reflux, 1.5 h                        | 69            |
| 5     | CH <sub>3</sub> CN:H <sub>2</sub> O (2:1), reflux, 1.5 h | 78            |
| 6     | MeOH, reflux, 2 h  | 81            |

We reasoned that upon exposure to acid, di-TBS deprotection, and dehydration of the benzylic alcohol, followed by formation of *ortho*-quinone methide **4.35**, would facilitate the ring expansion to afford a stable tertiary carbocation intermediate **4.83** (Scheme 4.22). However, instead of forming the exocyclic alkene by way of an E1 elimination mechanism, an intramolecular trapping of the carbocation by the hydroxyl group of the aromatic ring resulted in the formation of a five membered cycloether ring. Alternatively, this reaction could be considered to proceed via the ring expansion of a highly stabilised benzylic carbocation species. Furthermore, the yield of this cascade sequence could be further improved if the reaction was carried out in either CH<sub>3</sub>CN or MeOH (Table 4.2, entries 4 – 6).

This proved to be a promising result, as cycloether **4.84** possesses similar structural features to its natural product counterpart.



Scheme 4.22

The IR spectrum showed the presence of an OH group at  $3364\text{ cm}^{-1}$ , while HRMS analysis gave a molecular ion peak of 313.2162, corresponding to a chemical formula of  $\text{C}_{21}\text{H}_{29}\text{O}_2$   $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR analysis showed an aromatic ABX spin system between  $\delta$  6.69 – 6.54 ppm, a hydroxyl signal at  $\delta$  4.43 ppm, a CH signal at  $\delta$  4.28 ppm, five pairs of  $\text{CH}_2$  multiplets and a CH hydrogen between  $\delta$  2.39 – 1.44 ppm, a methyl doublet at  $\delta$  1.04 ( $J = 6.7$  Hz), and a nine proton singlet stacked closely at  $\delta$  1.02 ppm representing three methyl groups. The  $^{13}\text{C}$  NMR indicated the presence of eight  $\text{sp}^2$  carbons, five of which were quaternary carbons. In addition, a new quaternary carbon signal was also observed at  $\delta$  92.2 ppm, which indicated that it could be connected to an electronegative atom. COSY correlations were observed between the H-1, H-2 and H-3 protons, H-6, H-7 and H-8 protons, as well as H-8 with H-19 protons (Figure 4.4). Analogous to the natural product, the H-10 proton showed HMBC correlations with C-12, C-13 and C-17 of the aromatic ring, the C-5 and C-11 quaternary olefin carbons, and C-1 carbon of the six membered ring. Furthermore,

HMBC correlations with the seven membered ring could also be observed; correlations were also established with the C-9 quaternary carbon, the C-18 methyl group, and the C-8 carbon. The Me-19 protons showed HMBC correlations with C-7, C-8 and C-9 (not shown in Figure 4.4). Finally, the geminal Me-20 protons indicated correlations with C-21, C-3, C-4, C-5 and the C-6 methylene carbon (similar HMBC correlations were also observed for Me-21). The 2D ROESY NMR showed correlations between the H-13 aromatic proton and the H-1 methylene proton, and correlation between the H-9 and H-8 protons indicated that they were situated on the same face of the ring, pointing behind the molecule. It is important to note that the aromatic group exhibits a *cis* relationship with the Me-19 methyl group, similar to that found in frondosin A.

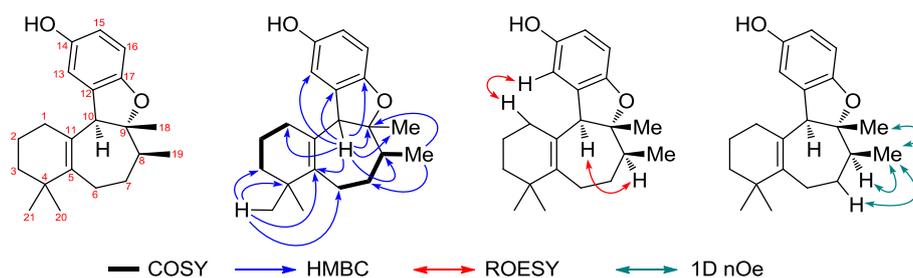


Figure 4.4: 1D nOe and 2D NMR correlations observed for **4.84**.

To establish the relative stereochemistry of the C18 methyl group, cycloether **4.84** was fully characterised in  $C_6D_6$ , which resolved the three methyl peaks previously stacked together at  $\delta$  1.02 ppm. The Me-19 doublet signal was now situated at  $\delta$  1.11 ppm, while the Me-18 methyl singlet was observed at  $\delta$  1.02 ppm, now clearly separated from the two geminal methyl peaks (at  $\delta$  0.96 and 0.90 ppm respectively). Correlations between Me-18 with Me-19, while unresolved in the 2D ROESY NMR spectrum, could be observed in the 1D nOe NMR spectrum (Figure 4.5). The 1D nOe NMR experiment, whereby the Me-19

doublet signal was selectively pulsed and inverted in order to establish nOe between Me-19 with nearby protons also showed correlations with H-7 and H-8 protons.

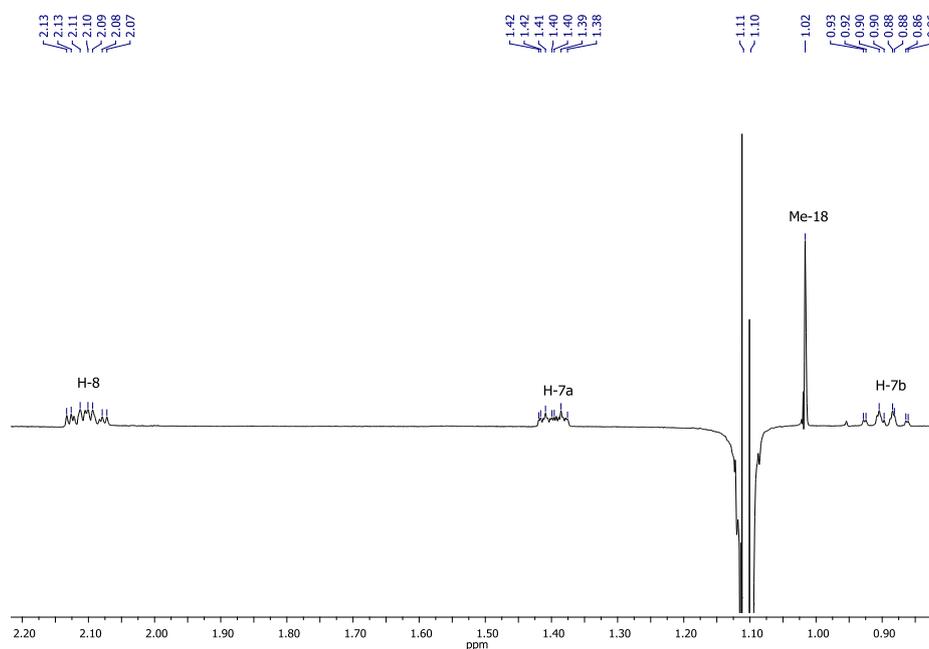
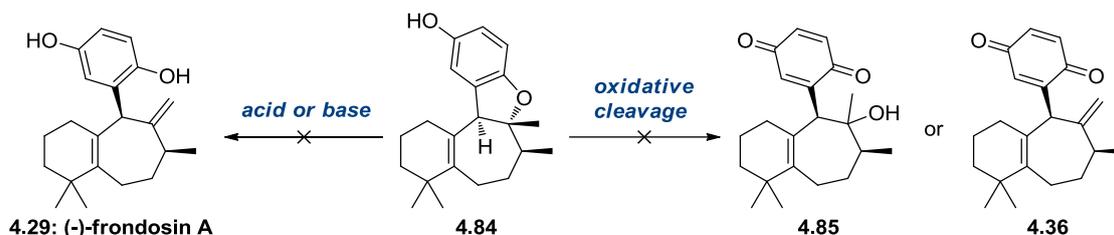


Figure 4.5: 1D nOe NMR of cycloether **4.84** in  $C_6D_6$  irradiated at  $\delta$  1.11 ppm (Me-19).

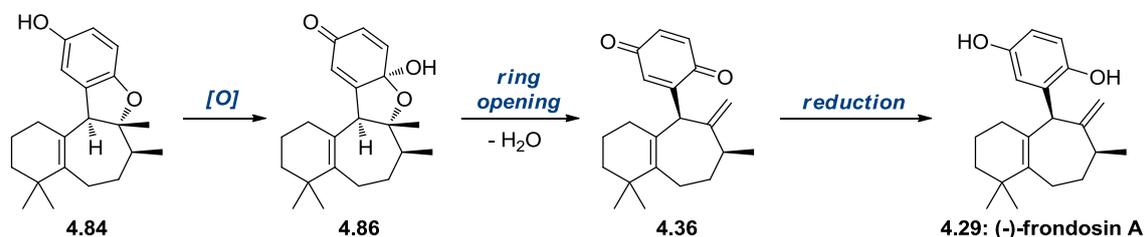
The ring opening of cycloethers has been documented on several polycyclic ring systems, and we decided to investigate the option of directly converting cycloether **4.84** to frondosin A (**4.29**) under acidic or basic conditions.<sup>48-50</sup> Alternatively, oxidative cleavage of the C-O bond could give either quinone **4.85** or **4.36**, which can then be converted into phenol **4.38**, the common intermediate proposed for the synthesis of frondosins B, D and E.<sup>51-56</sup> However, in our hands, the direct conversion of cycloether **4.84** to either (–)-frondosin A or quinone **4.36** according to previously reported conditions ( $BCl_3$ ,  $FeCl_3$ ,  $NaIO_4$ , or  $Ac_2O$ -pyr) failed to deliver the desired results (Scheme 4.23).



Scheme 4.23

### 4.6.3 Attempted Ring Opening of Hemiacetal 4.86

The synthesis of cycloether **4.84** prompted us to re-evaluate our synthetic strategy. As shown in Scheme 4.24, cycloether **4.84** could be oxidised to give hemiacetal **4.86**, which could potentially undergo a dehydration reaction to generate quinone **4.36**. Reduction of quinone **4.36** would then yield the desired natural product.



Scheme 4.24

Initial attempts to oxidise cycloether **4.84** using AgO/HNO<sub>3</sub>, DDQ or CAN failed to produce the desired hemiacetal and resulted in decomposition of the starting material (Table 4.3, entries 1 – 3).<sup>24, 51</sup> The use of a hypervalent iodine reagent for oxidative dearomatisation of phenolic systems has been well documented<sup>52, 57, 58</sup> and under these conditions, the treatment of cycloether **4.84** with (diacetoxyiodo)benzene in degassed CH<sub>3</sub>CN:H<sub>2</sub>O at 0 °C for 15 minutes afforded hemiacetal **4.86** in excellent yield (Table 4.3, entry 4).

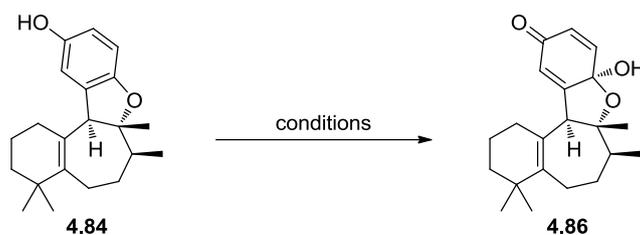
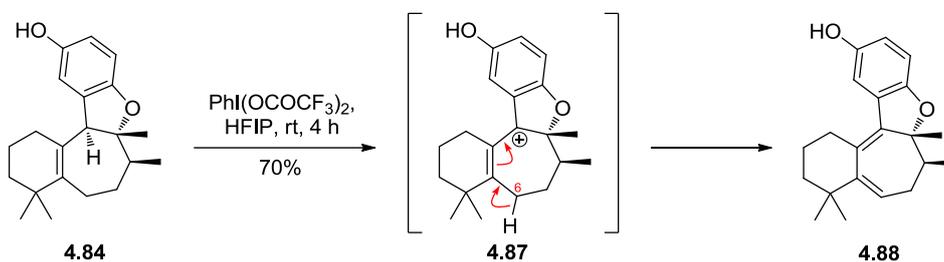


Table 4.3: Conditions for oxidation of **4.84**.

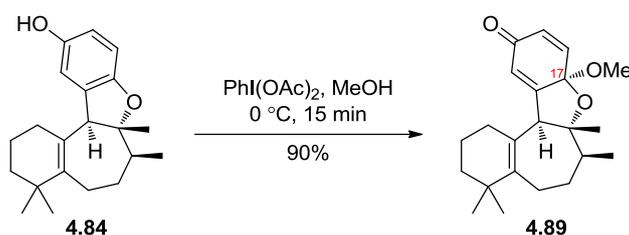
| Entry | Solvent/ conditions  | Yield (%)     |
|-------|--|---------------|
| 1     | DDQ, CH <sub>2</sub> Cl <sub>2</sub> , rt, 15 min                                | Decomposition |
| 2     | CAN, CH <sub>3</sub> CN:H <sub>2</sub> O (10:1), 0 °C, 15 min                    | Decomposition |
| 3     | AgO, 6 N HNO <sub>3</sub> , 1,4-dioxane, rt, 15 min                              | Decomposition |
| 4     | PhI(OAc) <sub>2</sub> , CH <sub>3</sub> CN:H <sub>2</sub> O (10:1), 0 °C, 15 min | 87            |

Interestingly, a highly UV active product was formed when the oxidative dearomatisation of cycloether **4.84** was carried out with (trifluoroacetoxyiodo)benzene in HFIP at temperatures above 0 °C.<sup>52</sup> As illustrated in Scheme 4.25, oxidation could also take place at the benzylic position at room temperature, generating carbocation intermediate **4.87**. The loss of a H-6 proton would then deliver the conjugated cycloether **4.88**.



Scheme 4.25

The relative stereochemistry of the three contiguous stereocentres was established according to the same methodology described previously for cycloether **4.84**. In order to elucidate the relative stereochemistry of the C-17 quaternary carbon, oxidative dearomatisation of cycloether **4.84** was conducted in MeOH to produce the methoxy derivative **4.89** in good yield (Scheme 4.26).



Scheme 4.26

The 1D nOe NMR spectrum of hemiacetal **4.89** in  $\text{C}_6\text{D}_6$  displayed correlations between OMe-22 and the H-8, H-10 and H16 protons (Figure 4.6). As the methoxy group exhibits free rotation along the C-O bond, an nOe interaction could also be observed with Me-19. Based on the 1D nOe NMR results, we concluded that the OH group in hemiacetal **4.86** would also have similar relative stereochemistry as shown above.

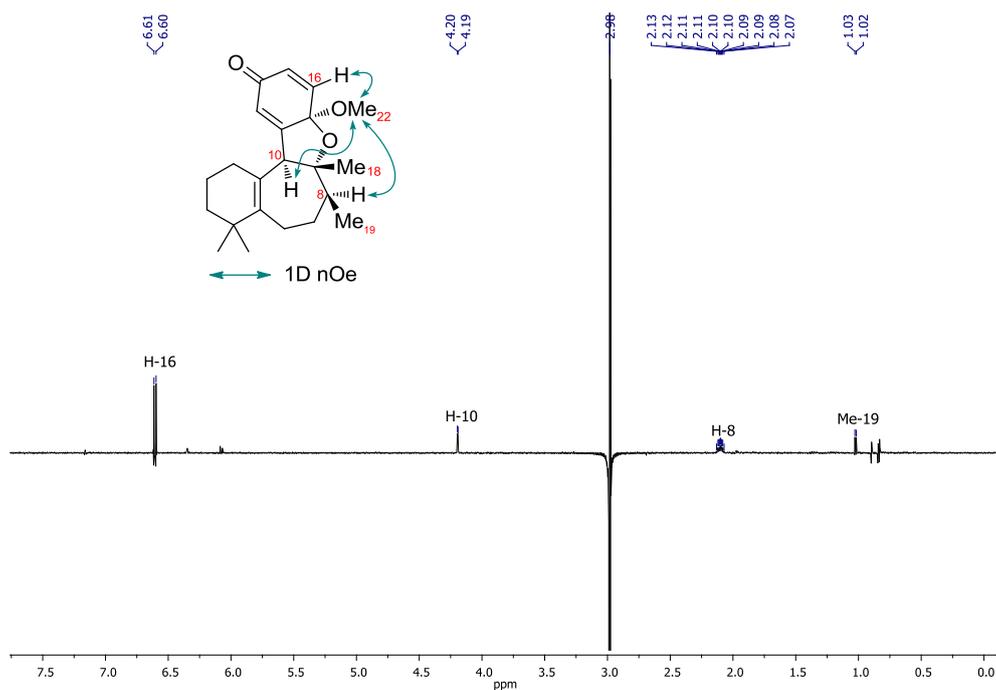
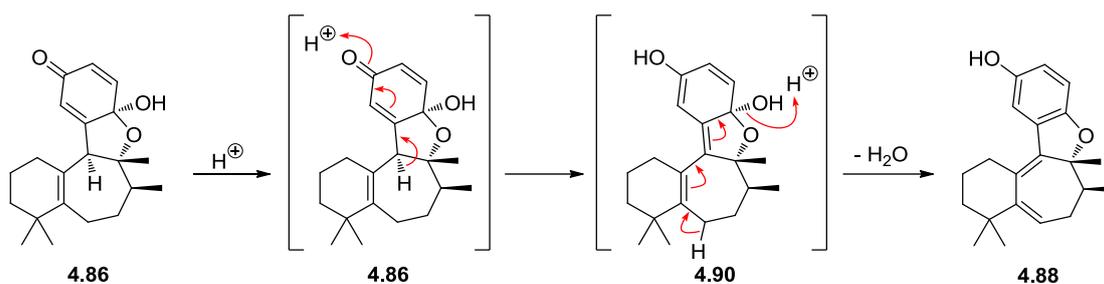


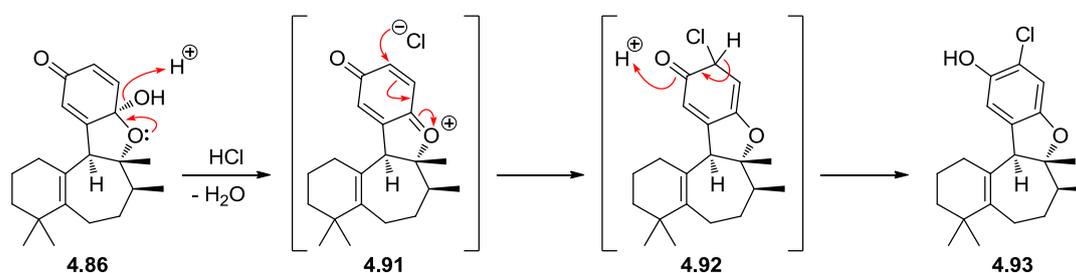
Figure 4.6: 1D NOESY NMR of hemiacetal **4.89** in  $C_6D_6$  irradiated at  $\delta$  2.98 ppm (OMe-22).

Nevertheless, having established the relative configuration of the molecule, we then conducted a series of dehydration experiments on hemiacetal **4.86**. Treatment of hemiacetal **4.86** under various other acidic conditions (CSA, *p*-TsOH or PPTS) often resulted in decomposition of the starting material alongside formation of a complex mixture of products. The main product isolated under these conditions, however, was the highly conjugated cycloether **4.88**. We propose that the formation of this highly conjugated product proceeds via the highly conjugated enol intermediate **4.90**, generated under acidic conditions (Scheme 4.27). Rearomatisation of enol **4.90** followed by the loss of water would later give rise to **4.88**.



Scheme 4.27

On the other hand, in the presence of 5% aqueous HCl, chlorine substitution could occur on the highly reactive quinone ring of hemiacetal **4.86**, followed by reformation of the phenolic ring system to generate *ortho*-chlorophenol **4.93**. We believe this reaction first follows an E1 mechanism pathway to give the oxonium intermediate **4.91** (Scheme 4.28). Chlorine substitution then forms **4.92**, followed by rearomatisation to give *ortho*-chlorophenol **4.93**. Furthermore, trace amounts of *ortho*-chlorophenol **4.93** were also isolated under basic dehydration conditions (SOCl<sub>2</sub>, pyr), whereas reactions of hemiacetal **4.86** with other known dehydrating agents such as Martin sulfurane and Burgess reagent only led to the decomposition of the natural product. Photochemical reactions in a range of solvents according to literature precedent also failed to provide the desired target molecule.<sup>59, 60</sup>



Scheme 4.28

## 4.7 Conclusion

A biosynthetically inspired synthesis of frondosin A (and therefore, the rest of the frondosin family of natural products) from (+)-sclareolide using our previously described route was proposed (refer to section 4.3). This approach, however, while feasible on paper, proved to be a challenging task; the instability of quinone towards various tautomerisation conditions only resulted in decomposition of the starting material, and while the 6-7 ring system can be formed via a novel ring expansion pathway from benzylic alcohol **3.58**, attempted ring opening of cycloether **4.84** or hemiacetal **4.86** to the corresponding hydroquinone/ quinone target molecules was unsuccessful under a variety of conditions. In addition, the inherent reactivity of the internal double bond was unexpected and often led to the formation of the undesired conjugated cycloether **4.88**.

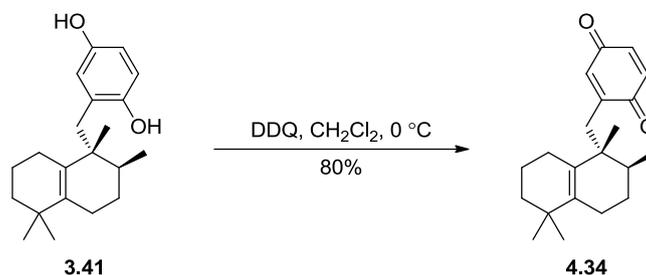
## 4.8 Experimental Section

### 4.8.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using Merck aluminium sheets silica gel 60 F<sub>255</sub>. Visualisation was aided by viewing under a UV lamp and staining with CAM stain followed by heating. All R<sub>f</sub> values were rounded to the nearest 0.05. Flash chromatography was performed using Davisil (40-63 micron) grade silica gel. Melting points were recorded on a SRS Digimelt MPA 161 melting apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer Spectrum BX FT-IR system spectrometer as the neat compounds. Optical rotations were obtained on a P0A1 AR21 polarimeter. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using a Varian Inova-6000 spectrometer (<sup>1</sup>H at 600 MHz, <sup>13</sup>C at 150 MHz). The NMR solvent used was CDCl<sub>3</sub> unless otherwise specified. <sup>1</sup>H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and <sup>13</sup>C NMR are reported in ppm relative to chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quint) quintet, (sext) sextet, (hept) heptet and (m) multiplet. All *J* values were rounded to the nearest 0.5 Hz. EI low resolution mass spectra were recorded on a Shimadzu GCMS-QP 5050A mass spectrometer.

## 4.8.2 Preparative Procedures and Spectroscopic Data

### Quinone 4.34



To a solution of **3.41** (50 mg, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added DDQ (36 mg, 0.16 mmol) at 0 °C. The reaction mixture was stirred for 10 mins at 0 °C, then quenched with saturated NaHCO<sub>3</sub> solution (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc, 10:1) to give **4.34** as a yellow oil (40 mg, 80%).

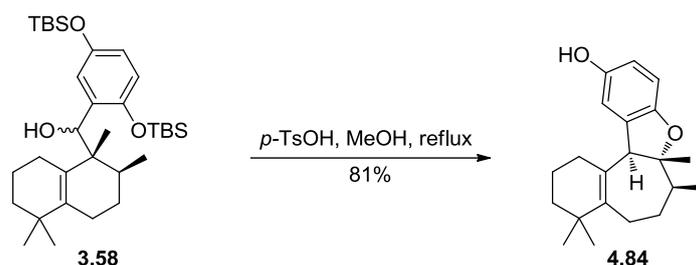
#### Partial Data for 4.34:

R<sub>f</sub> = 0.80 (petrol/EtOAc, 4:1)

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 6.75 – 6.73 (m, 1H), 6.69 – 6.67 (m, 2H), 2.77 (d, *J* = 16.5 Hz, 1H), 2.39 (dd, *J* = 16.5, 1.4 Hz, 1H), 2.07 – 2.04 (m, 2H), 1.98 – 1.94 (m, 1H), 1.86 – 1.81 (m, 1H), 1.60 – 1.57 (m, 4H), 1.48 – 1.44 (m, 1H), 1.41 – 1.35 (m, 2H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 187.7, 187.6, 147.2, 138.1, 136.9, 136.0, 133.9, 131.2, 41.8, 39.7, 34.6, 34.1, 33.4, 28.5, 27.9, 26.9, 26.4, 24.1, 22.2, 19.8, 16.4.

## Cycloether 4.84



To a solution of **3.58** (1.55 g, 2.78 mmol) in MeOH (140 mL) was added  $p$ -TsOH (0.63 g, 3.33 mmol) at room temperature. The reaction mixture was refluxed for 2 h and then allowed to cool to room temperature. The reaction mixture was quenched with saturated NaHCO<sub>3</sub> solution (30 mL) and extracted with Et<sub>2</sub>O (2 × 30 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (gradient elution, petroleum ether/EtOAc, 10:1 → 4:1) to give **4.84** as a white foam (0.70 g, 81%).

### Data for **4.84**:

$R_f$  = 0.50 (petrol/EtOAc, 4:1)

$[\alpha]_D^{25} = -107.5^\circ$  (c 1.09, CHCl<sub>3</sub>)

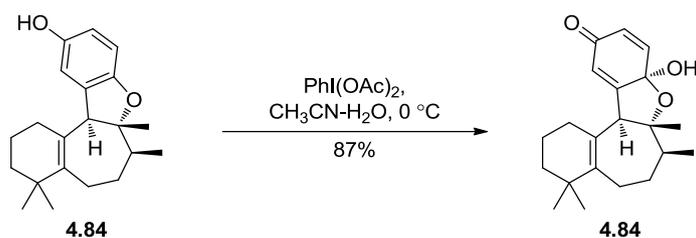
**IR (neat):** 3364, 2956, 2922, 2850, 1605, 1485, 1457, 1375, 1340, 1266, 1205 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  6.69 (s, 1H), 6.60 (d,  $J$  = 8.4 Hz, 1H), 6.55 (dd,  $J$  = 8.4, 2.5 Hz, 1H), 4.43 (s, 1H), 4.28 (s, 1H), 2.40 – 2.17 (m, 4H), 1.93 – 1.90 (m, 1H), 1.73 – 1.68 (m, 1H), 1.65 – 1.60 (m, 1H), 1.54 – 1.44 (m, 3H), 1.07 – 1.05 (overlapped m, 1H), 1.04 (d,  $J$  = 6.7 Hz, 3H), 1.02 (s, 3H), 1.02 (s, 6H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  153.2, 148.9, 142.6, 130.6, 129.0, 114.1, 113.6, 109.6, 92.2, 55.6, 46.1, 39.6, 35.6, 32.4, 30.1, 28.3, 27.4, 27.0, 19.8, 17.3, 13.3.

**HRMS (ESI):** calculated for C<sub>21</sub>H<sub>29</sub>O<sub>2</sub> 313.2186 [M+H]<sup>+</sup>, found 313.2162.

## Hemiacetal 4.86



To a solution of **4.84** (100 mg, 0.33 mmol) in degassed  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  (2:1, 6 mL) was added  $\text{PhI}(\text{OAc})_2$  (160 mg, 0.49 mmol) at  $0\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 15 min at  $0\text{ }^\circ\text{C}$ . The resulting mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc, 4:1) to give **4.86** as a yellow oil (94 mg, 87%).

### Data for 4.86:

$R_f = 0.30$  (petrol/EtOAc, 4:1)

$[\alpha]_D^{25} = +2.2^\circ$  (c 0.86,  $\text{CHCl}_3$ )

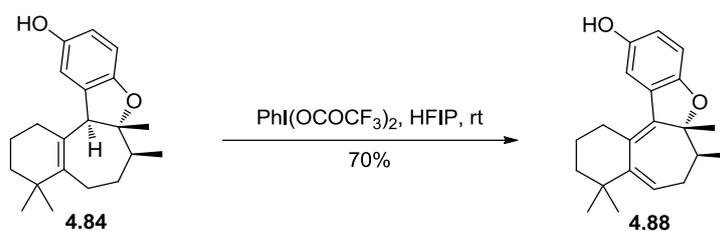
**IR (neat):** 3358, 2957, 2925, 2851, 1677, 1650, 1615, 1458  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.95 (d,  $J = 10.0$  Hz, 1H), 6.26 (dd,  $J = 3.0, 1.5$  Hz, 1H), 6.07 (dd,  $J = 10.0, 1.5$  Hz, 1H), 4.39 (d,  $J = 3.0$  Hz, 1H), 2.99 (s, 1H), 2.32 – 2.25 (m, 3H), 2.18 – 2.12 (m, 2H), 1.74 – 1.64 (m, 2H), 1.56 – 1.51 (m, 1H), 1.47 – 1.40 (m, 2H), 1.01 – 0.99 (overlapped m, 1H), 1.00 (s, 6H), 0.98 (d,  $J = 7.0$  Hz, 3H), 0.93 (s, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  186.5, 161.7, 144.7, 143.2, 127.3, 126.9, 121.7, 93.8, 89.3, 51.8, 48.9, 39.3, 35.8, 33.3, 30.4, 28.5, 27.4, 26.8, 19.9, 17.1, 16.5.

**HRMS (ESI):** calculated for  $\text{C}_{21}\text{H}_{27}\text{O}_3$  327.1960  $[\text{M}-\text{H}]^-$ , found 327.1960.

## Cycloether 4.88



To a solution of **4.84** (26 mg, 0.08 mmol) in degassed HFIP (1.5 mL) was added  $\text{PhI}(\text{OCOCF}_3)_2$  (36 mg, 0.08 mmol) at room temperature. The reaction mixture was stirred for 4 hours at room temperature. The resulting mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc, 4:1) to give **4.88** as a yellow oil (18 mg, 70%).

### Partial Data for **4.88**:

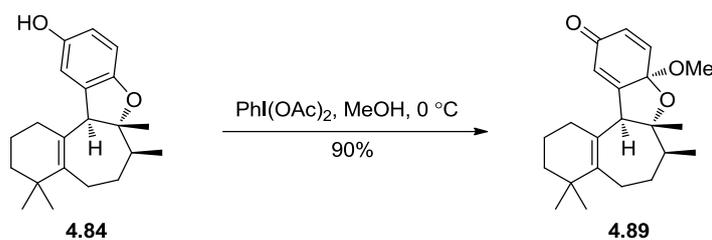
$R_f$  = 0.50 (petrol/EtOAc, 4:1)

**IR (neat):** 3368, 2960, 2929, 1593, 1482, 1460, 1375, 1367, 1223  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.16 (d,  $J$  = 2.5 Hz, 1H), 6.68 (d,  $J$  = 8.4, 2.5 Hz, 1H), 6.65 (d,  $J$  = 8.4 Hz, 1H), 5.87 (dd,  $J$  = 8.2, 6.2 Hz, 1H), 4.36 (s, 3H), 3.07 (dt,  $J$  = 15.0, 4.8 Hz, 1H), 2.74 (pd,  $J$  = 7.3, 1.7 Hz, 1H), 2.30 – 2.19 (m, 2H), 1.81 – 1.73 (m, 2H), 1.70 – 1.65 (m, 1H), 1.52 – 1.46 (m, 2H), 1.27 (s, 3H), 1.16 (s, 3H), 1.10 (d,  $J$  = 7.3 Hz, 3H), 1.08 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  155.2, 149.7, 148.8, 141.8, 130.5, 126.9, 122.2, 115.9, 111.9, 109.9, 92.8, 55.1, 40.4, 36.3, 32.3, 30.2, 29.4, 29.2, 21.1, 21.0, 15.6.

## Hemiacetal 4.89



To a solution of **4.84** (44 mg, 0.14 mmol) in degassed MeOH (3 mL) was added  $\text{PhI}(\text{OAc})_2$  (68 mg, 0.21 mmol) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. The resulting mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc, 10:1) to give **4.89** as a yellow oil (44 mg, 90%).

### Partial Data for 4.89:

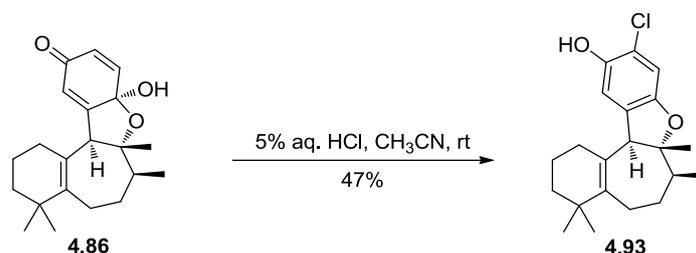
$R_f$  = 0.60 (petrol/EtOAc, 4:1)

**IR (neat):** 2956, 2926, 2850, 1679, 1653, 1618, 1458  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.92 (d,  $J$  = 10.0 Hz, 1H), 6.32 (s, 1H), 6.19 (d,  $J$  = 10.0 Hz, 1H), 4.22 (d,  $J$  = 2.0 Hz, 1H), 3.21 (s, 3H), 2.31 – 2.25 (m, 3H), 2.16 – 2.09 (m, 2H), 1.74 – 1.63 (m, 2H), 1.56 – 1.51 (m, 1H), 1.48 – 1.40 (m, 2H), 1.01 (overlapped d,  $J$  = 7.0 Hz, 3H), 1.01 – 0.99 (overlapped m, 1H), 1.00 (s, 6H), 0.95 (s, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  186.2, 160.4, 144.4, 140.8, 128.9, 127.4, 122.9, 97.1, 89.5, 51.8, 50.0, 48.4, 39.3, 35.8, 33.2, 30.4, 28.5, 27.4, 26.8, 19.9, 17.0, 16.7.

### Ortho-Chlorophenol 4.93



To a solution of **4.86** (18 mg, 0.06 mmol) in CH<sub>3</sub>CN (5 mL) was added 5% aq. HCl (500  $\mu$ L, 0.06 mmol) at room temperature. The reaction mixture was stirred for 15 min at room temperature. The resulting mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc, 4:1) to give **4.93** as a clear oil (9 mg, 47%).

#### Partial Data for 4.93:

**R<sub>f</sub>** = 0.80 (petrol/EtOAc, 4:1)

**IR (neat):** 3556, 3428, 2956, 2923, 2851, 1615, 1596, 1468, cm<sup>-1</sup>.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  6.84 (s, 1H), 6.70 (s, 1H), 5.08 (s, 1H), 4.25 (s, 1H), 2.37 – 2.16 (m, 4H), 1.91 – 1.87 (m, 1H), 1.74 – 1.69 (m, 1H), 1.66 – 1.62 (m, 1H), 1.55 – 1.47 (m, 3H), 1.09 – 1.03 (overlapped m, 1H), 1.03 (d,  $J$  = 6.7 Hz, 3H), 1.01 (s, 6H), 1.009 (overlapped s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  153.1, 144.7, 142.9, 130.1, 128.6, 117.5, 114.1, 109.5, 93.0, 55.3, 46.1, 39.5, 35.6, 32.3, 30.0, 28.2, 27.4, 26.9, 19.8, 17.2, 13.3.

**HRMS (ESI):** calculated for C<sub>21</sub>H<sub>27</sub>ClKO<sub>2</sub> 385.1337 [M+K]<sup>+</sup>, found 385.1333.

## 4.9 References

1. Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367-5405.
2. Willis, N. J.; Bray, C. D. *Chem. - Eur. J.* **2012**, *18*, 9160-9173.
3. Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655-3664.
4. Singh, M. S.; Nagaraju, A.; Anand, N.; Chowdhury, S. *RSC Adv.* **2014**, *4*, 55924-55959.
5. Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210-9215.
6. Li, Q.; Dong, T.; Liu, X.; Zhang, X.; Yang, X.; Lei, X. *Curr. Org. Chem.* **2014**, *18*, 86-92.
7. Sugimoto, H.; Nakamura, S.; Ohwada, T. *Adv. Synth. Catal.* **2007**, *349*, 669-679.
8. Marsini, M. A.; Huang, Y.; Lindsey, C. C.; Wu, K.-L.; Pettus, T. R. R. *Org. Lett.* **2008**, *10*, 1477-1480.
9. Kumar, A.; Kumar, M.; Gupta, M. K. *Green Chem.* **2012**, *14*, 2677-2681.
10. Hovey, M. T.; Check, C. T.; Sipher, A. F.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 9603-9607.
11. Li, Q.; Dong, T.; Liu, X.; Lei, X. *J. Am. Chem. Soc.* **2013**, *135*, 4996-4999.
12. Amouri, H.; Le Bras, J. *Acc. Chem. Res.* **2002**, *35*, 501-510.
13. Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Williams, A. J.; Watkin, D. J. *Org. Lett.* **1999**, *1*, 1937-1939.
14. Liao, D.; Li, H.; Lei, X. *Org. Lett.* **2012**, *14*, 18-21.
15. Lumb, J.-P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865-5868.
16. Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2004**, *69*, 9196-9203.
17. Mejorado, L. H.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2006**, *128*, 15625-15631.
18. Spence, J. T. J.; George, J. H. *Org. Lett.* **2013**, *15*, 3891-3893.
19. Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047-5060.
20. Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153-160.

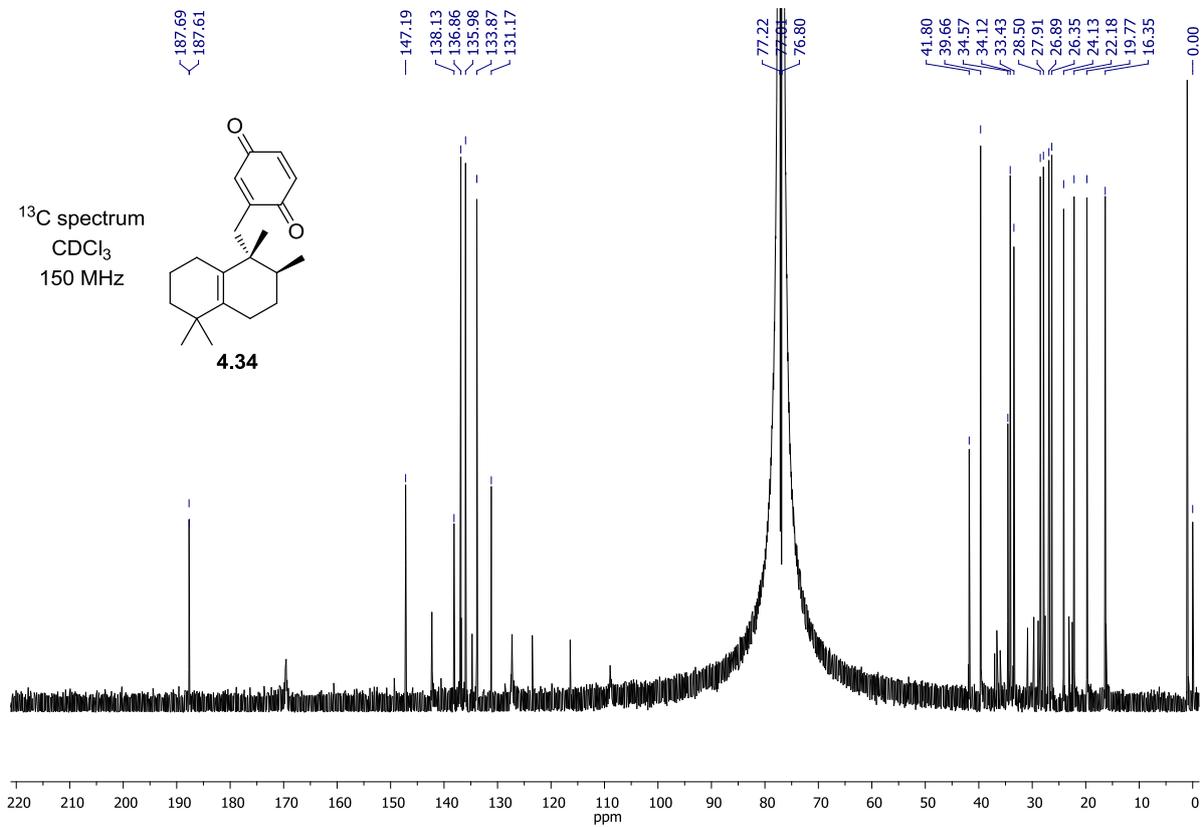
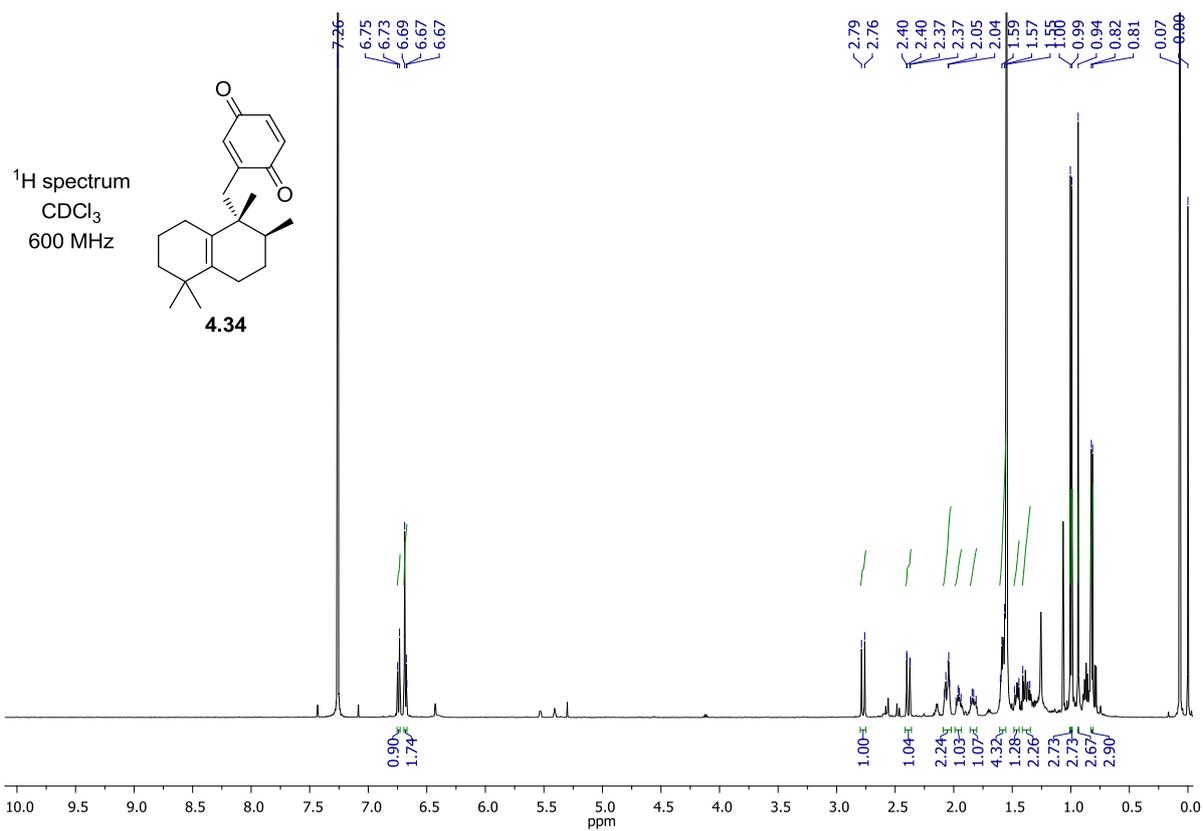
21. Hoch, R. C.; Schraufstatter, I. U.; Cochrane, C. G. *J. Lab. Clin. Med.* **1996**, *128*, 134-145.
22. Zhu, Y. M.; Webster, S. J.; Flower, D.; Woll, P. J. *Br. J. Cancer* **2004**, *91*, 1970-1976.
23. Brat, D. J.; Bellail, A. C.; Van Meir, E. G. *Neuro-Oncology* **2005**, *7*, 122-133.
24. Oblak, E. Z.; VanHeyst, M. D.; Li, J.; Wiemer, A. J.; Wright, D. L. *J. Am. Chem. Soc.* **2014**, *136*, 4309-4315.
25. Jackson, S. K.; Wu, K.-L.; Pettus, T. R. R., Sequential Reactions Initiated by Oxidative Dearomatization. Biomimicry or Artifact? In *Biomimetic Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA 2011; pp 723-749.
26. Pepper, H. P.; Kuan, K. K. W.; George, J. H. *Org. Lett.* **2012**, *14*, 1524-1527.
27. Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761-764.
28. Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878-1889.
29. Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569-1572.
30. Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675-9686.
31. Ovaska, T. V.; Sullivan, J. A.; Ovaska, S. I.; Winegrad, J. B.; Fair, J. D. *Org. Lett.* **2009**, *11*, 2715-2718.
32. Reiter, M.; Torssell, S.; Lee, S.; MacMillan, D. W. C. *Chem. Sci.* **2010**, *1*, 37-42.
33. Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457-460.
34. Li, X.; Ovaska, T. V. *Org. Lett.* **2007**, *9*, 3837-3840.
35. Masters, K.-S.; Flynn, B. L. *Org. Biomol. Chem.* **2010**, *8*, 1290-1292.
36. Zhang, J.; Li, L.; Wang, Y.; Wang, W.; Xue, J.; Li, Y. *Org. Lett.* **2012**, *14*, 4528-4530.
37. Laplace, D. R.; Verbraeken, B.; Van Hecke, K.; Winne, J. M. *Chem. - Eur. J.* **2014**, *20*, 253-262.
38. Mehta, G.; Likhite, N. S. *Tetrahedron Lett.* **2008**, *49*, 7113-7116.
39. Garayalde, D.; Krueger, K.; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 911-915.
40. Olson, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573-576.
41. Li, X.; Kyne, R. E.; Ovaska, T. V. *Tetrahedron* **2007**, *63*, 1899-1906.
42. Masters, K.-S.; Flynn, B. L. *J. Org. Chem.* **2008**, *73*, 8081-8084.

43. Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781-11790.
44. Li, X.; Keon, A. E.; Sullivan, J. A.; Ovaska, T. V. *Org. Lett.* **2008**, *10*, 3287-3290.
45. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011-1013.
46. Garayalde, D.; Nevado, C. *Beilstein J. Org. Chem.* **2011**, *7*, 767-780, No. 87.
47. Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681-2683.
48. Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303-14314.
49. Dixon, D. D.; Lockner, J. W.; Zhou, Q.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 8432-8435.
50. Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878-882.
51. Kozuka, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2922-7.
52. Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797-10815.
53. Kozuka, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2415-23.
54. Okamoto, K.; Watanabe, M.; Kawada, M.; Goto, G.; Ashida, Y.; Oda, K.; Yajima, A.; Imada, I.; Morimoto, H. *Chem. Pharm. Bull.* **1982**, *30*, 2797-819.
55. Schaedel, U.; Habicher, W. D. *Synthesis* **1998**, 293-296.
56. Novak, L.; Kovacs, P.; Kolonits, P.; Orovecz, O.; Fekete, J.; Szantay, C. *Synthesis* **2000**, 809-812.
57. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299-5358.
58. Silva, L. F., Jr.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722-1754.
59. Hewgill, F. R.; Raston, C. L.; Skelton, B. W.; Webb, R. J.; White, A. H. *Aust. J. Chem.* **1983**, *36*, 1603-14.
60. Takeya, T.; Kondo, H.; Otsuka, T.; Tomita, K.; Okamoto, I.; Tamura, O. *Org. Lett.* **2007**, *9*, 2807-2810.

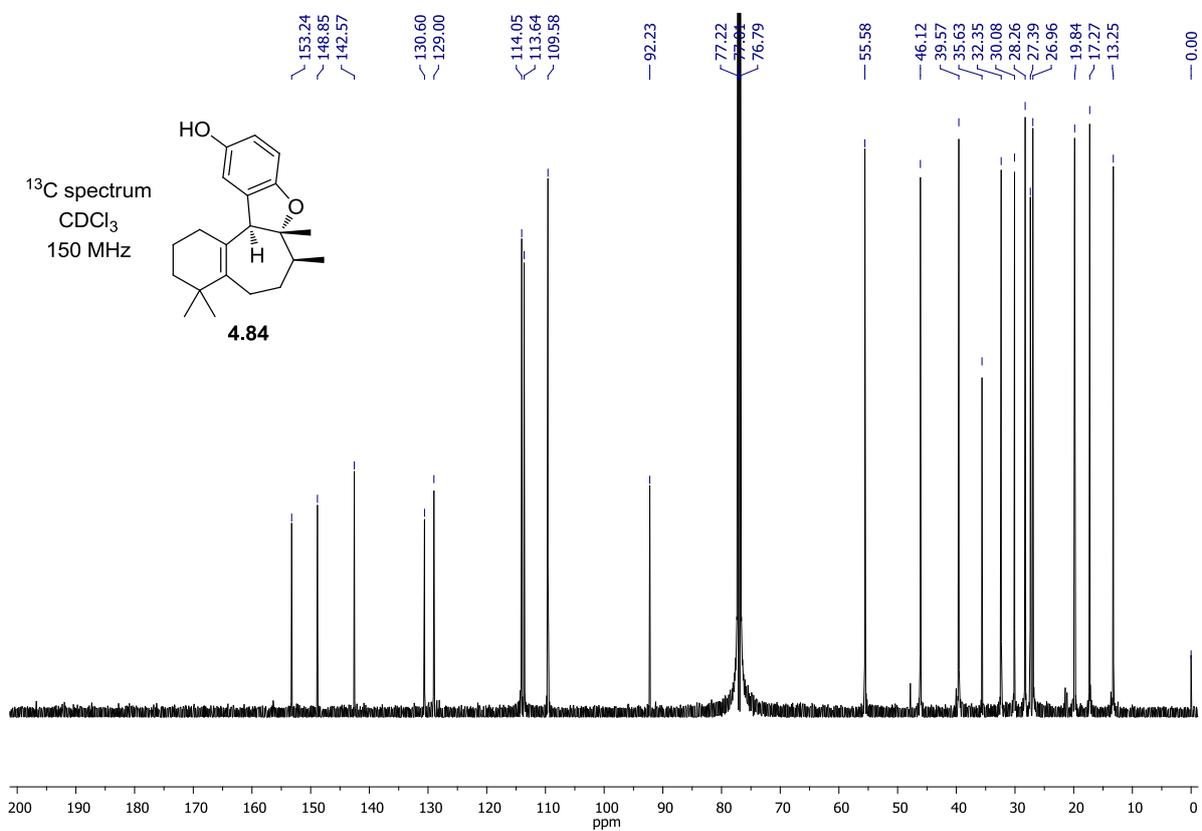
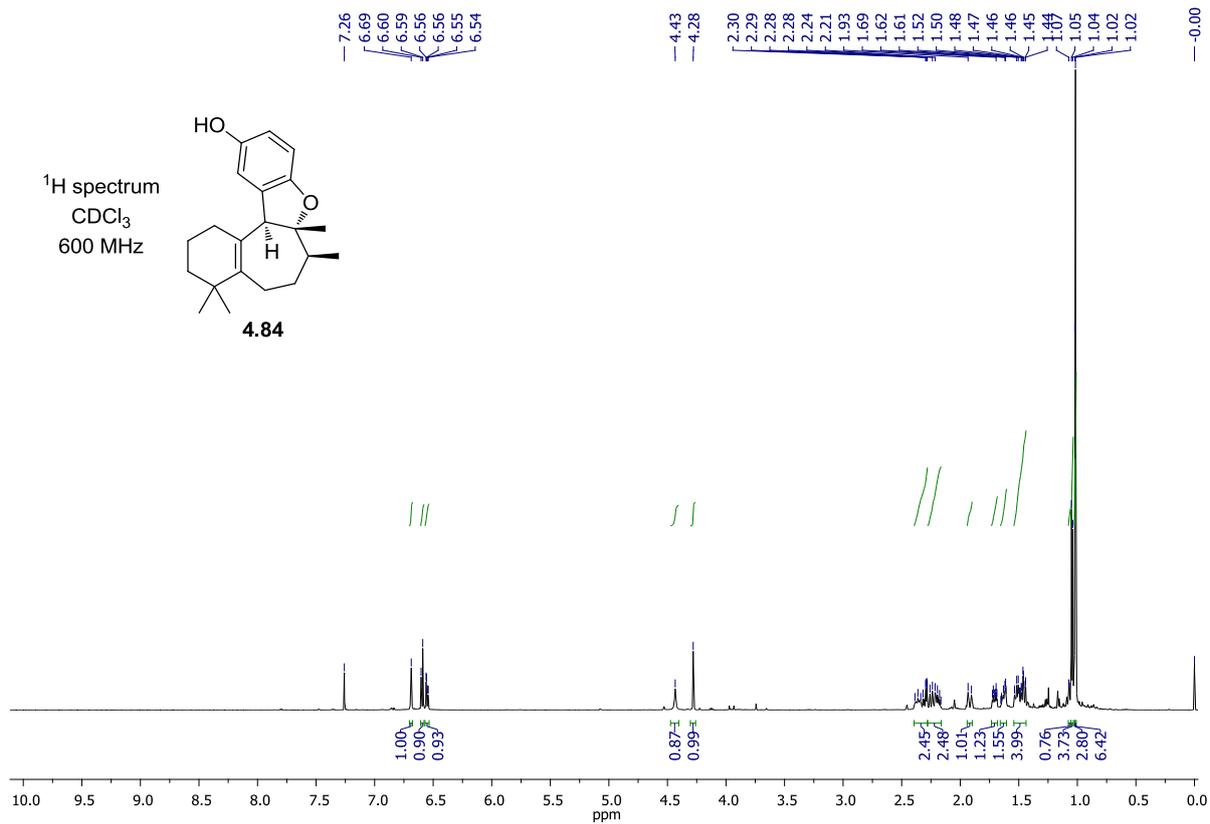
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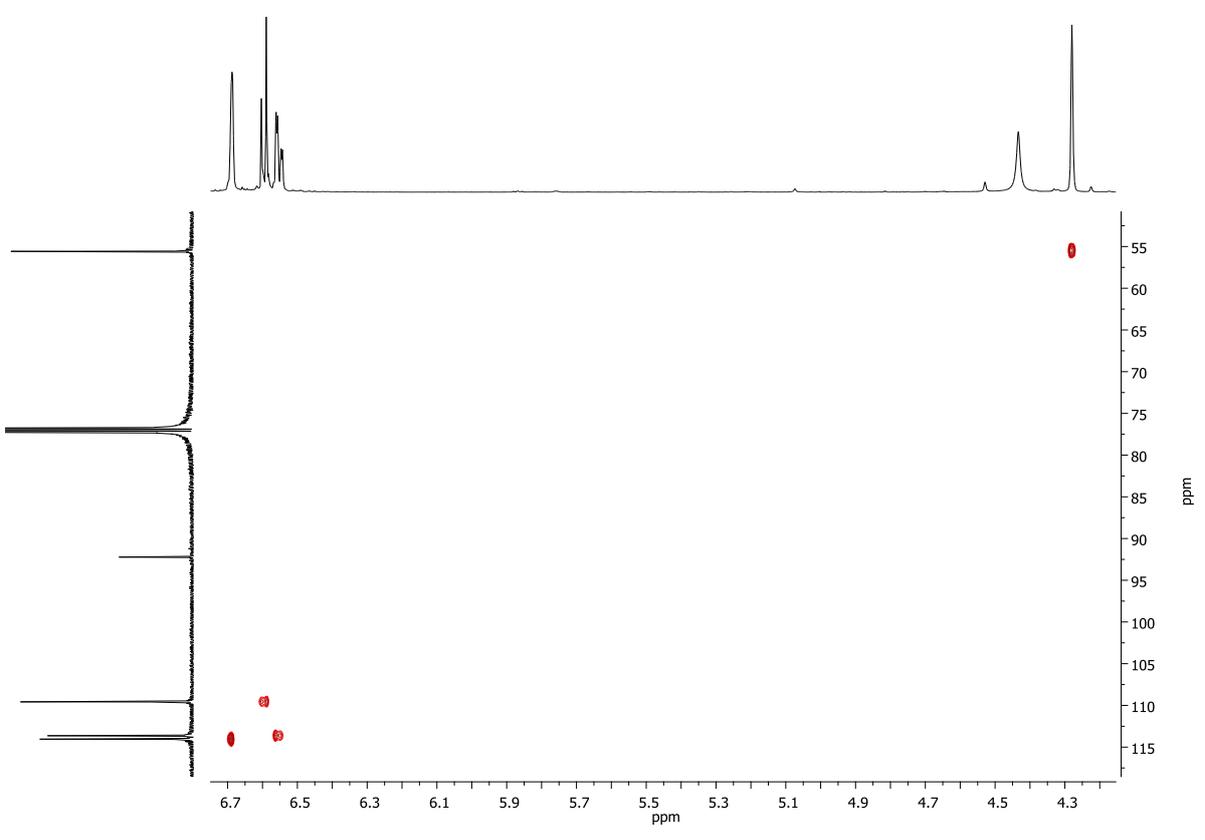
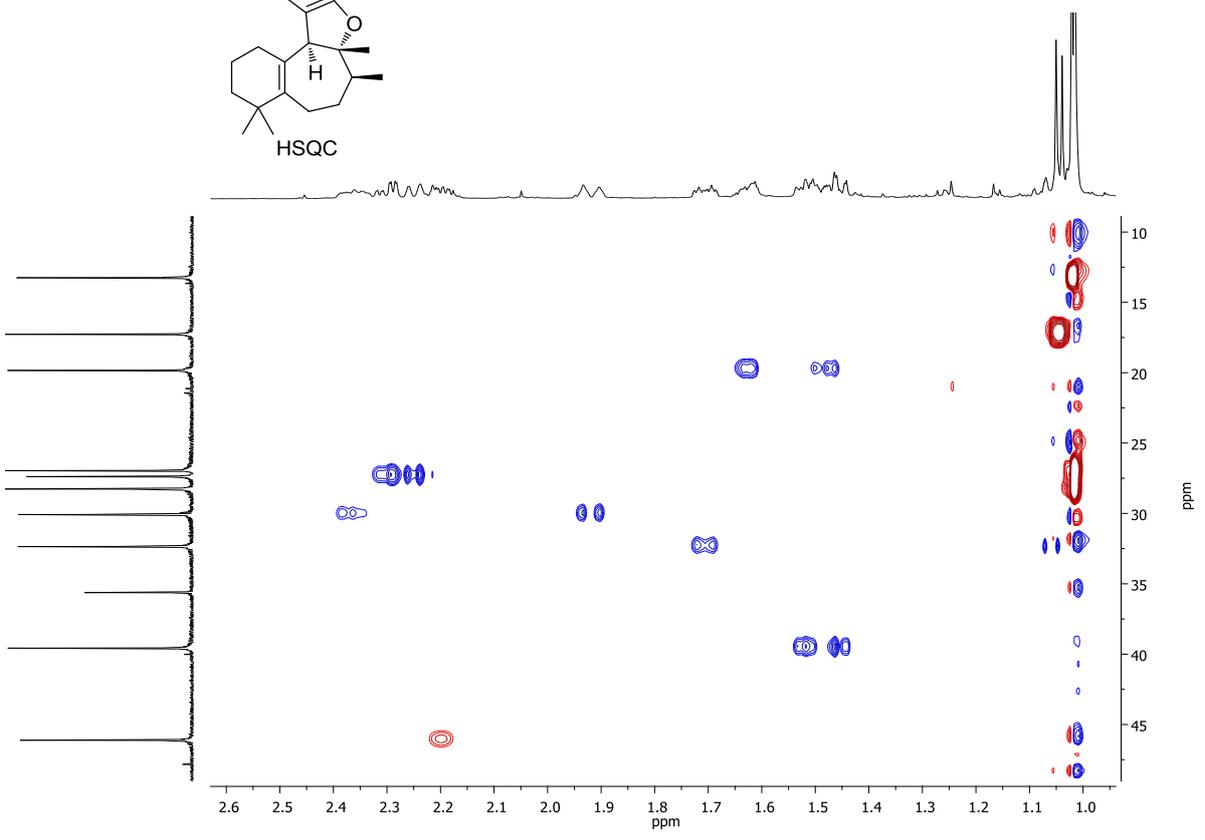
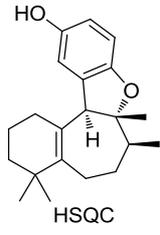
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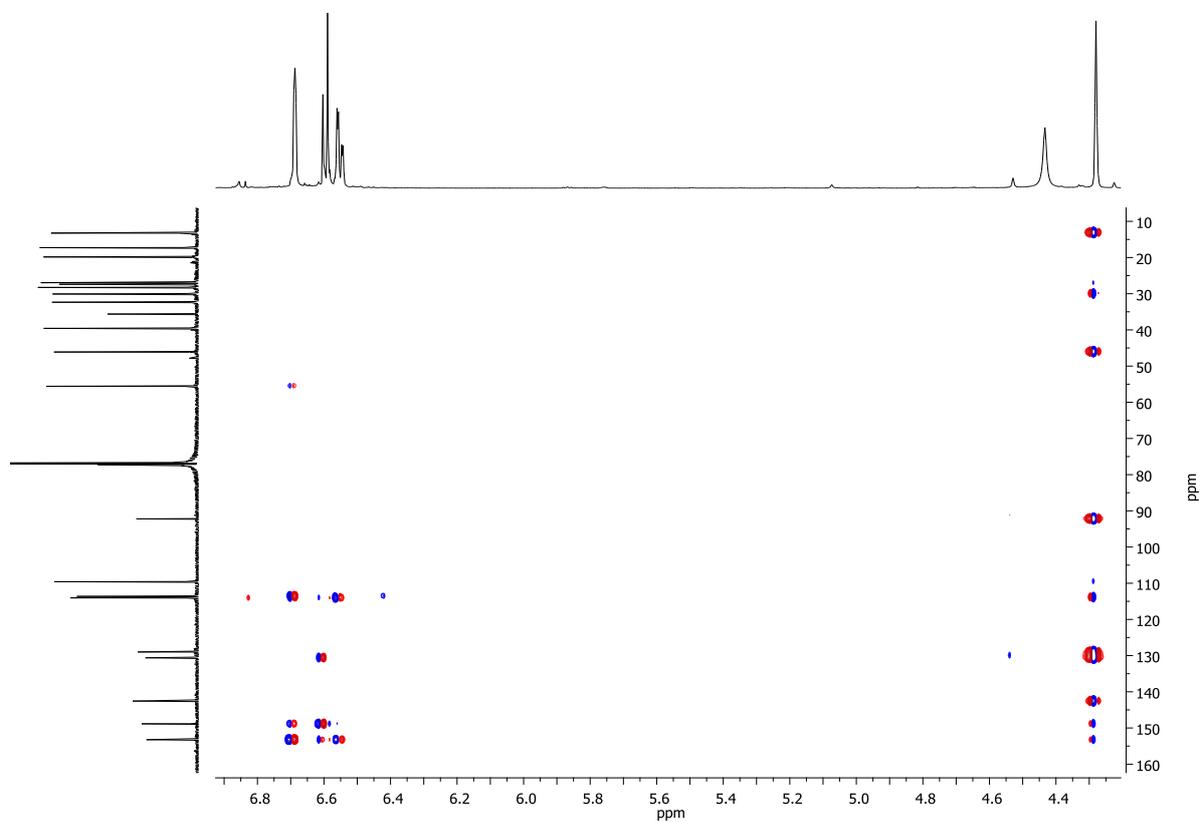
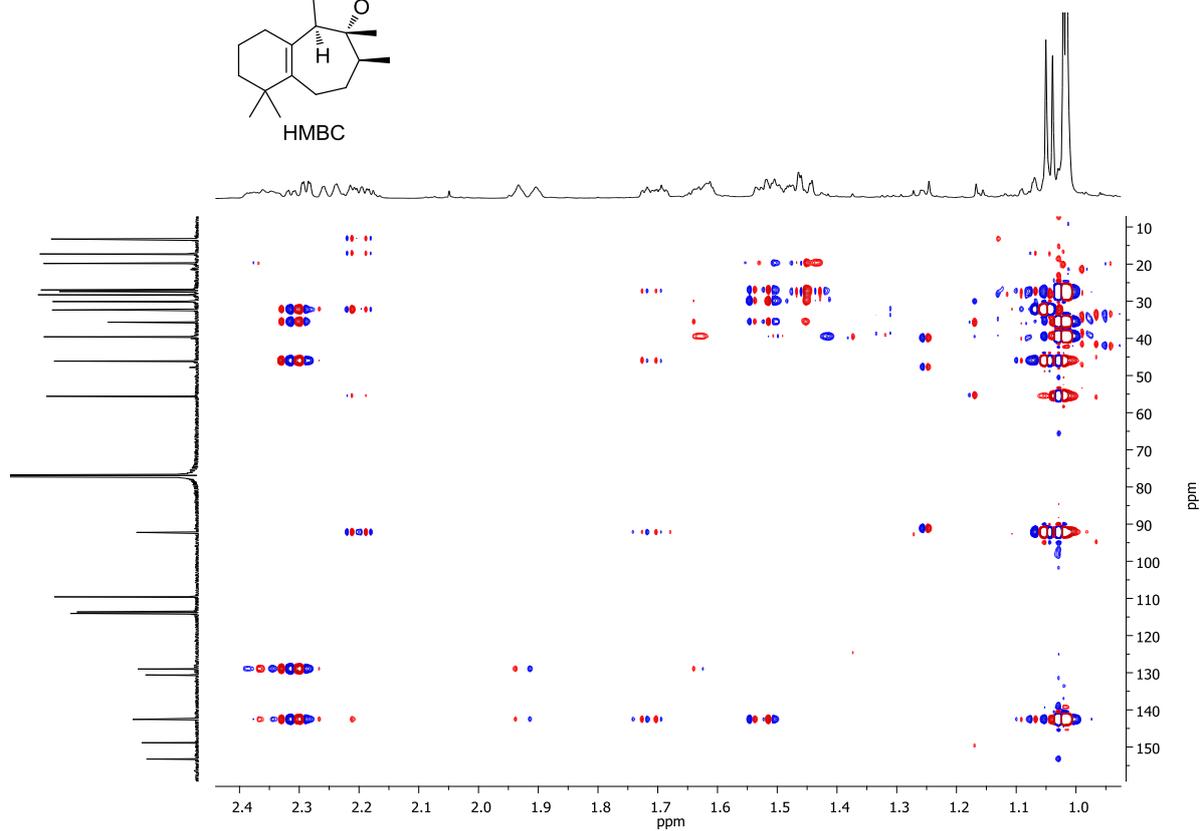
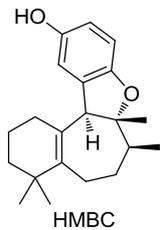
#### **Progress Towards the Biomimetic Synthesis of (-)-Fronodosin A**

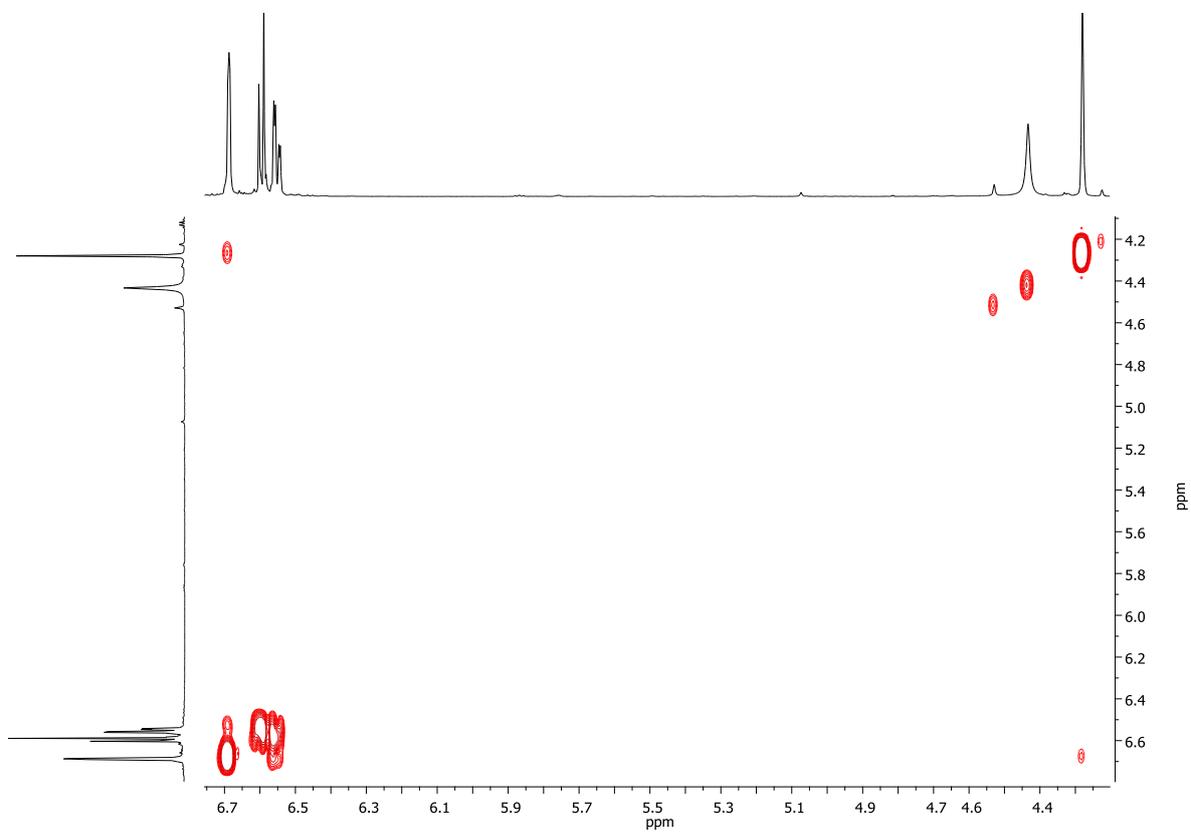
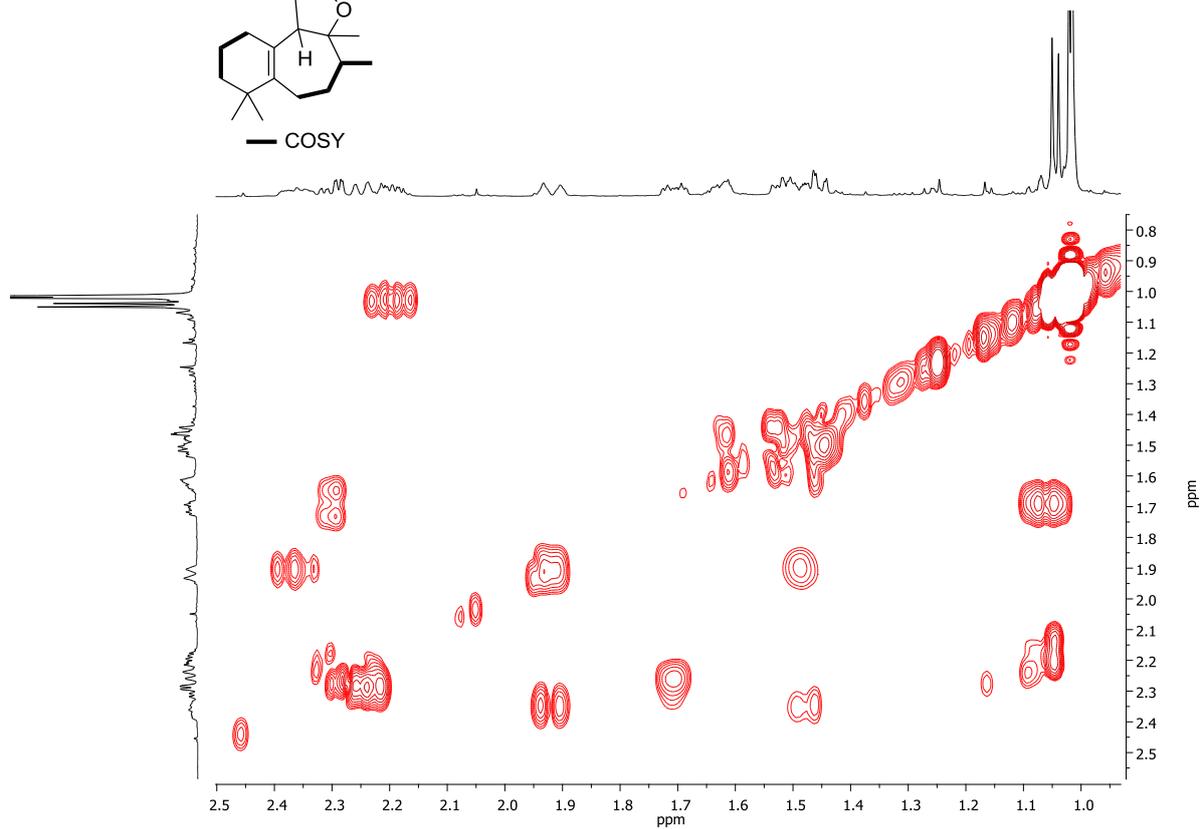
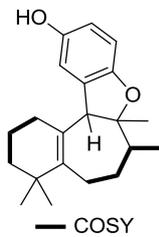


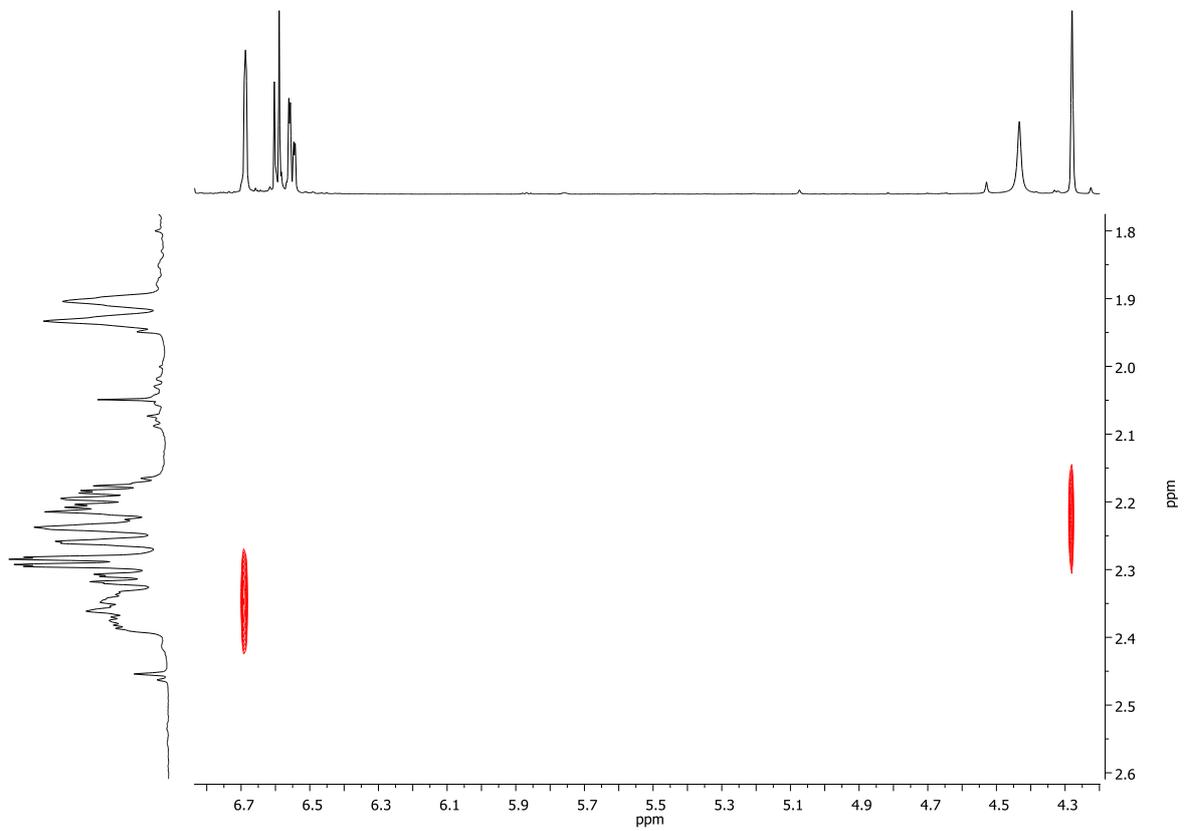
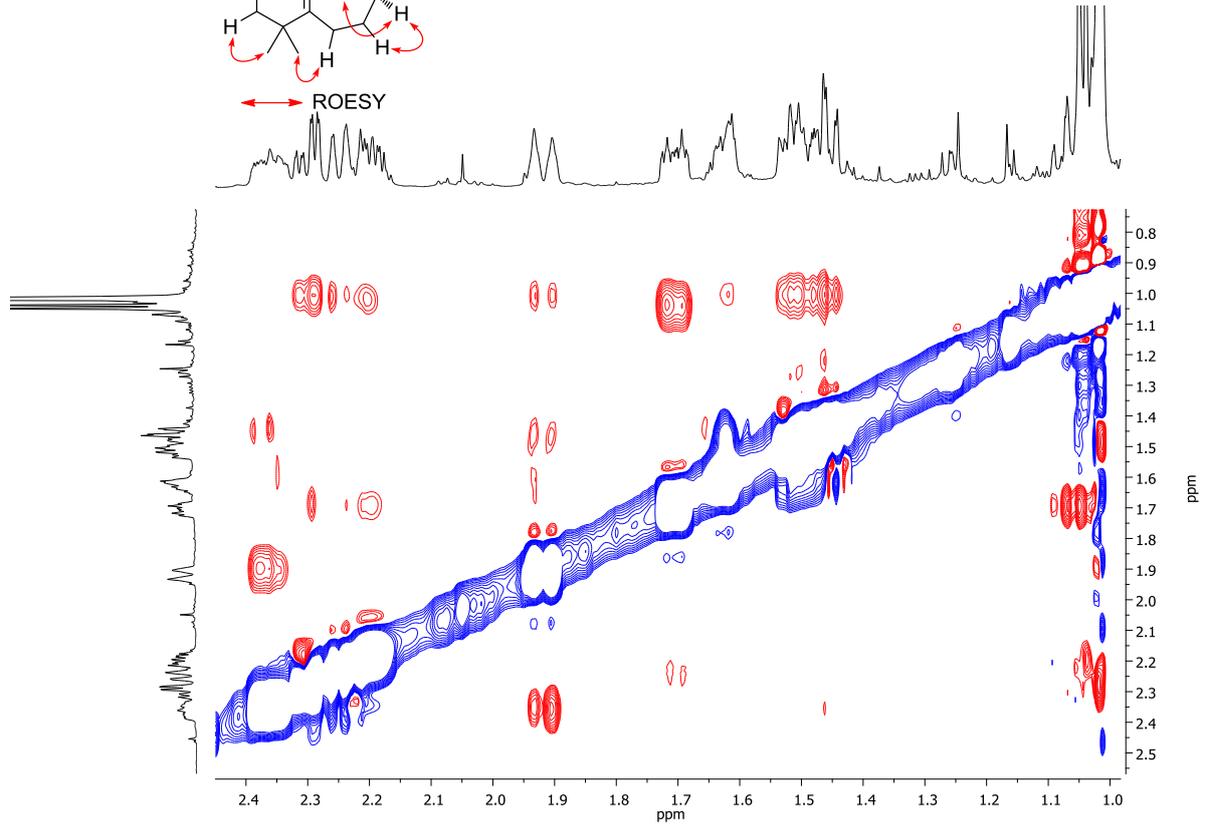
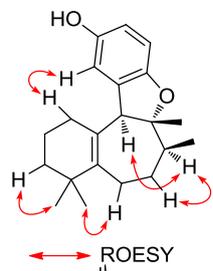
Pure <sup>1</sup>H and <sup>13</sup>C NMR could not be obtained as the **4.34** decomposes readily.

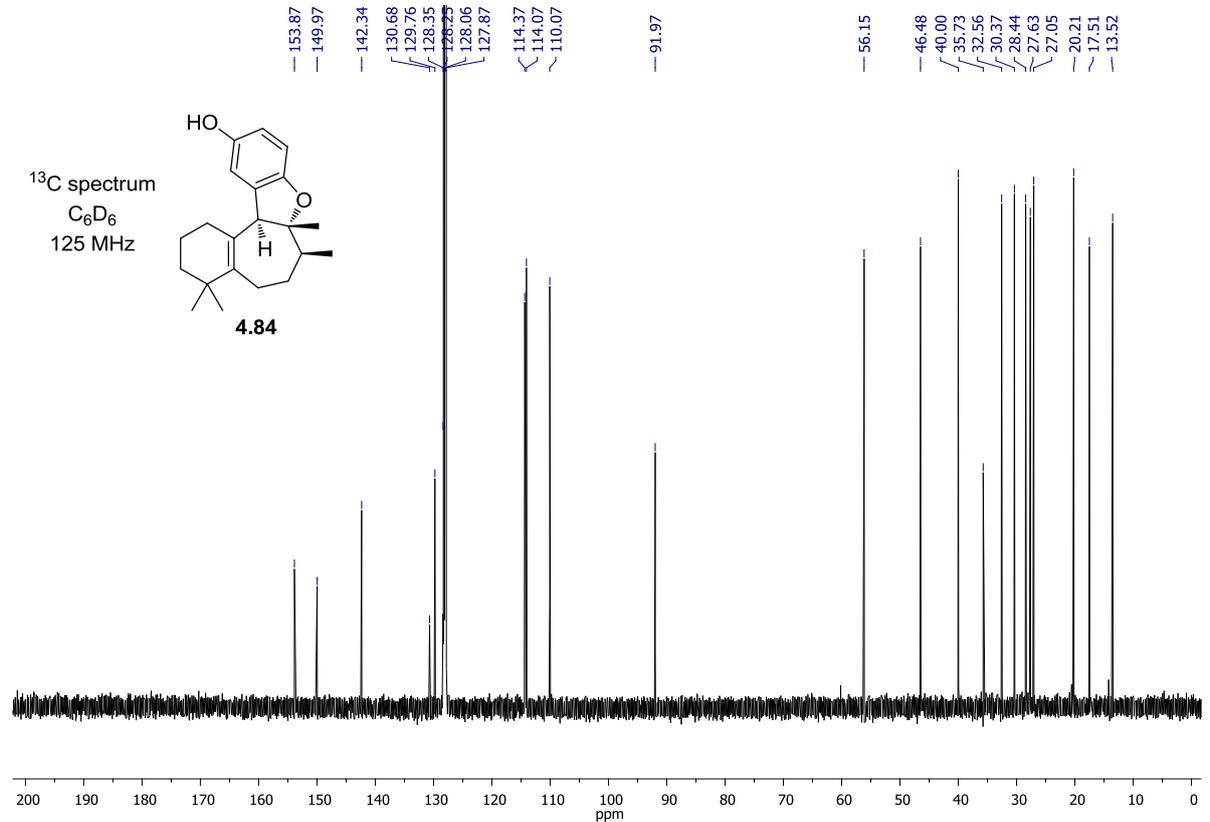
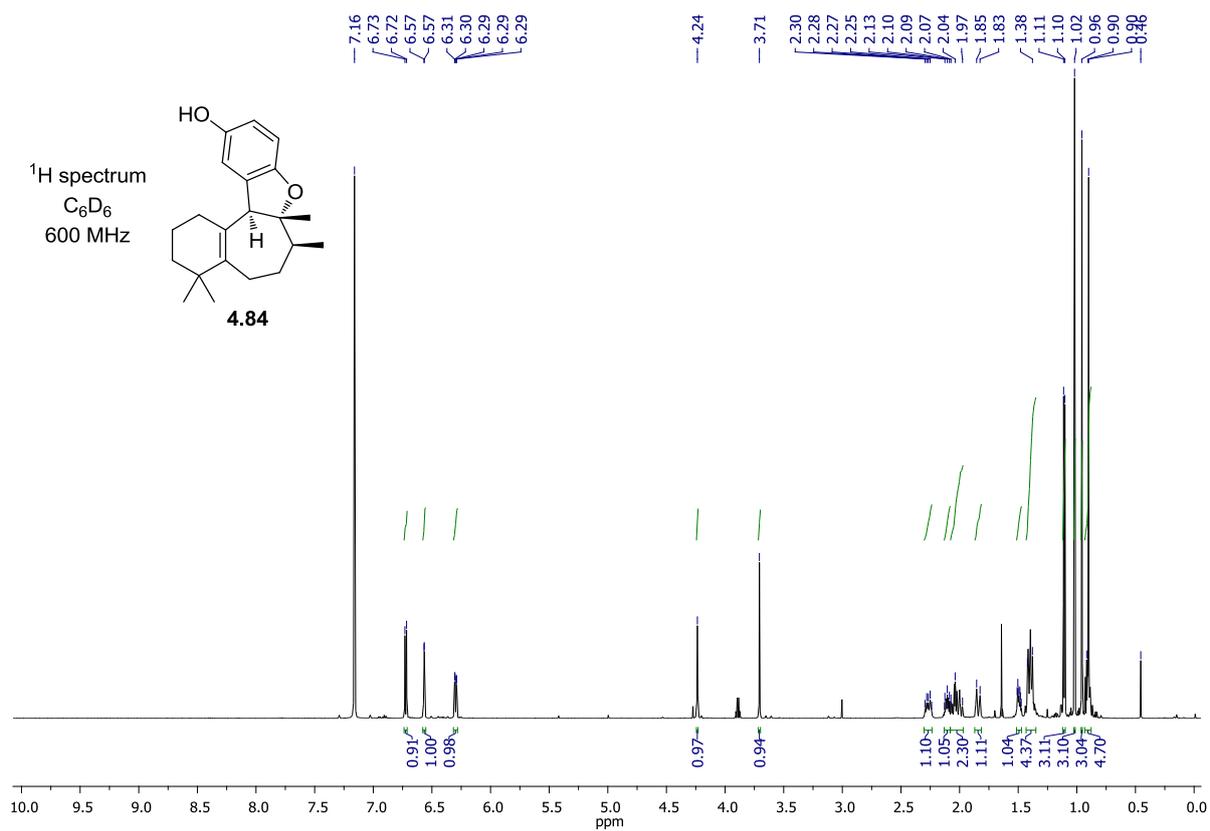


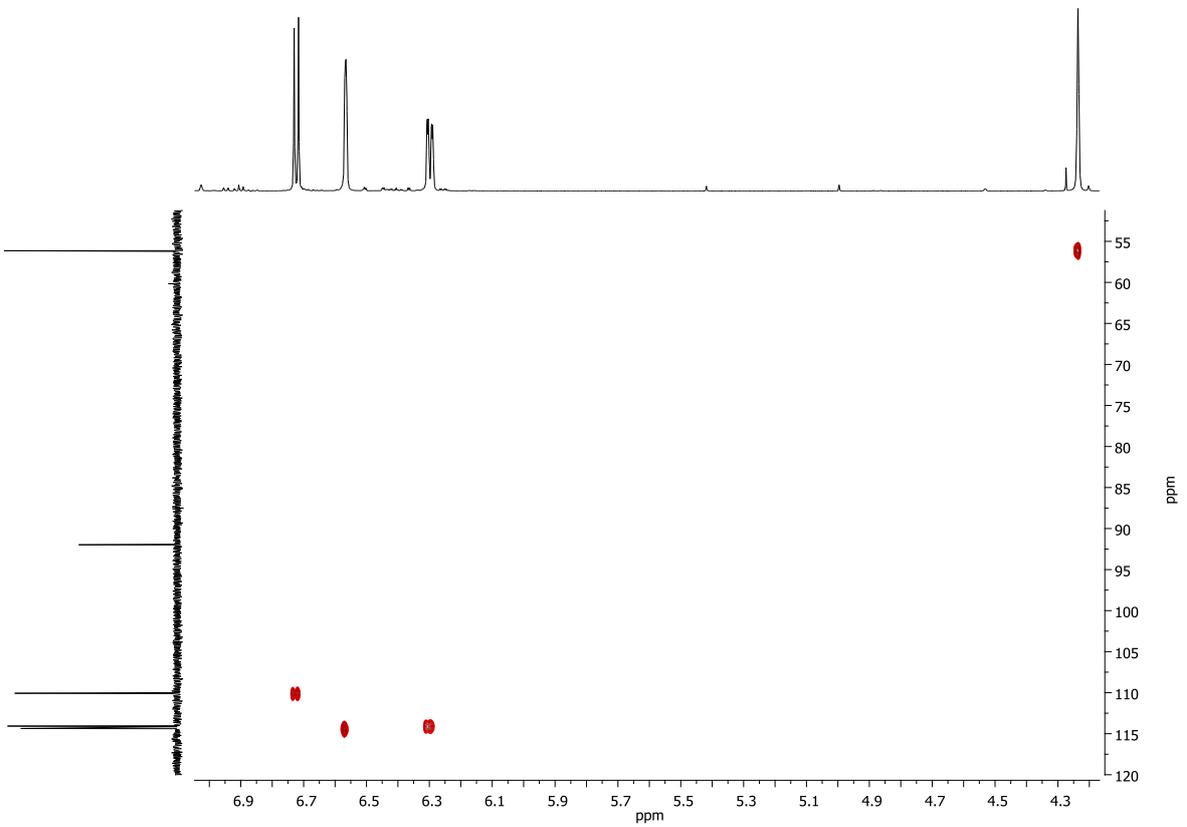
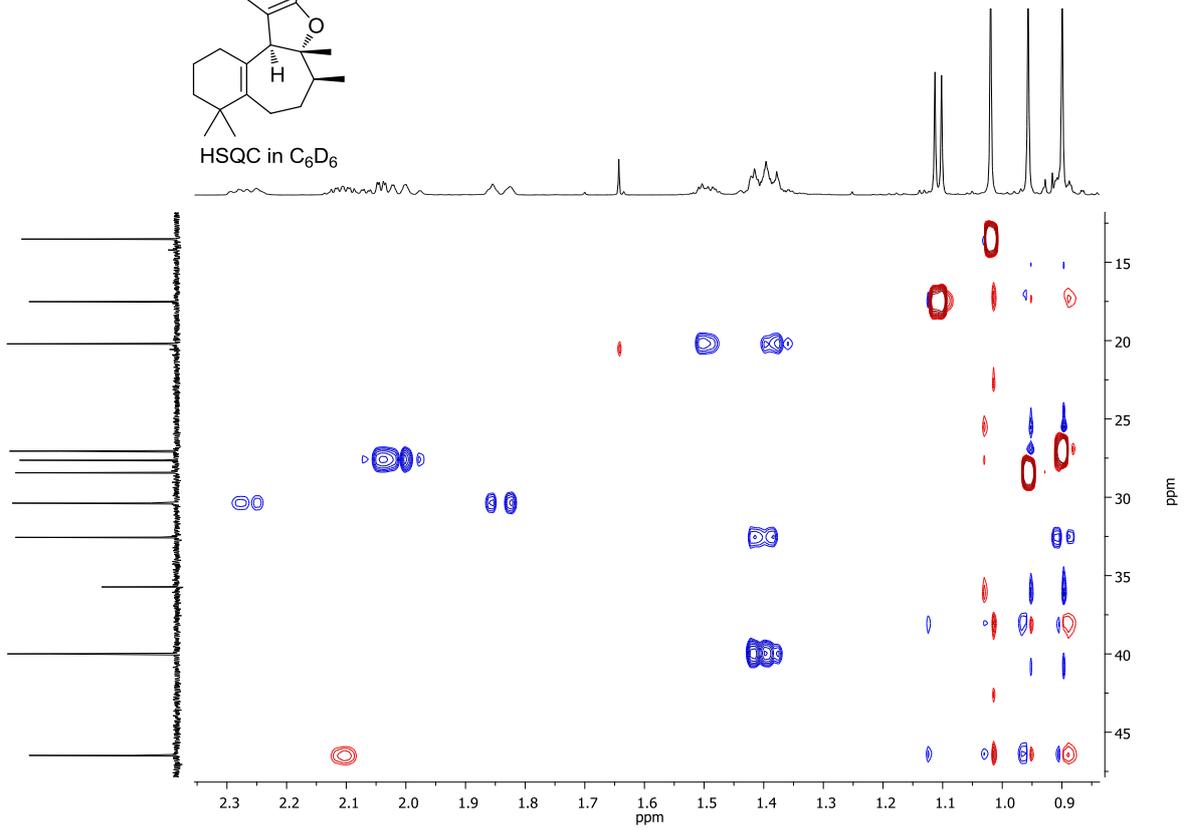
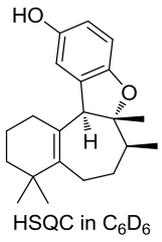


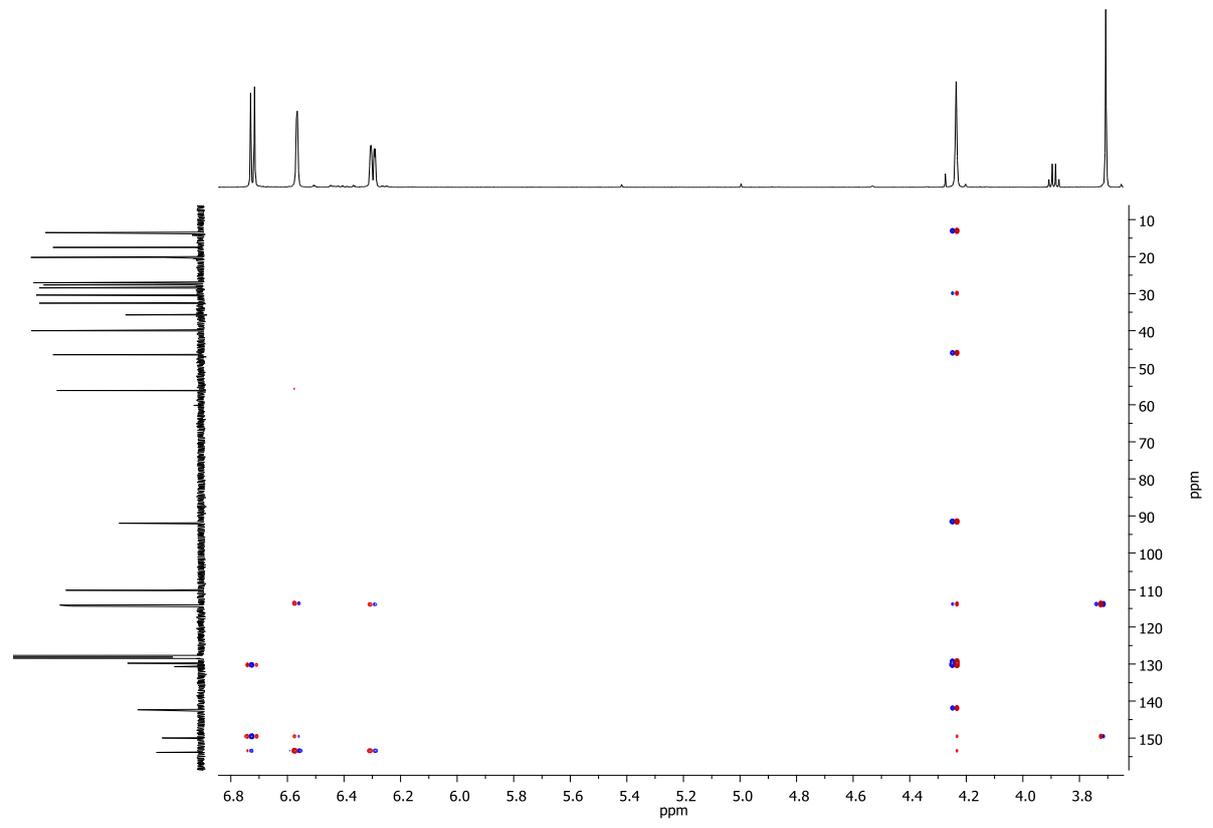
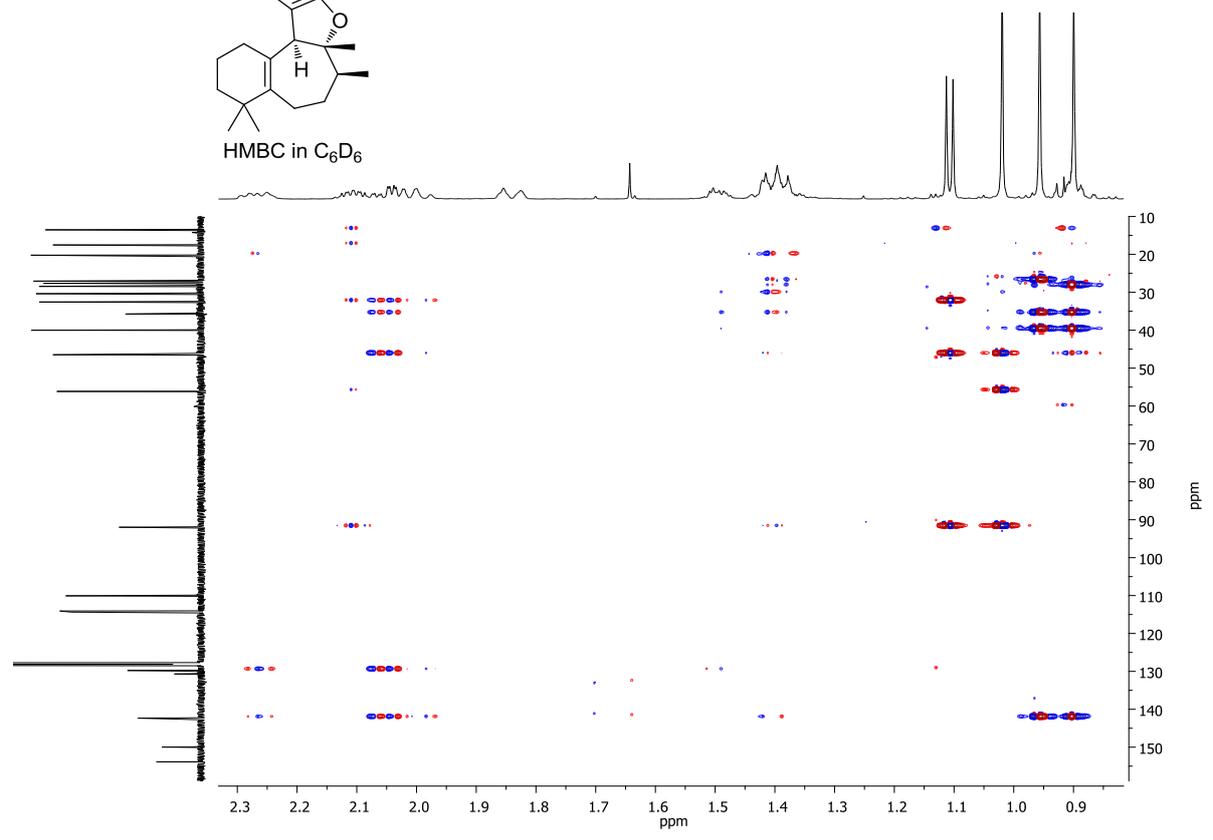
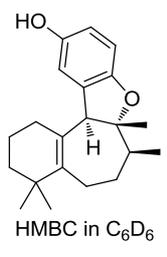


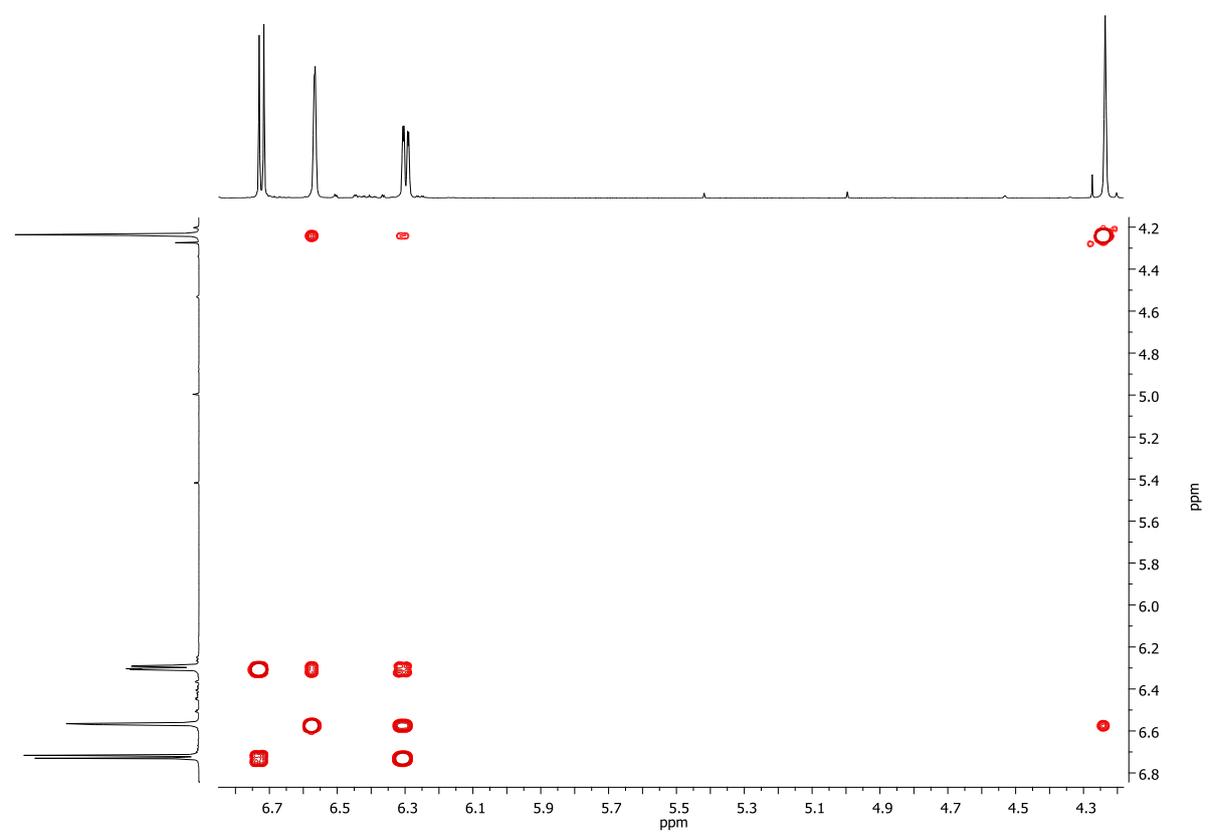
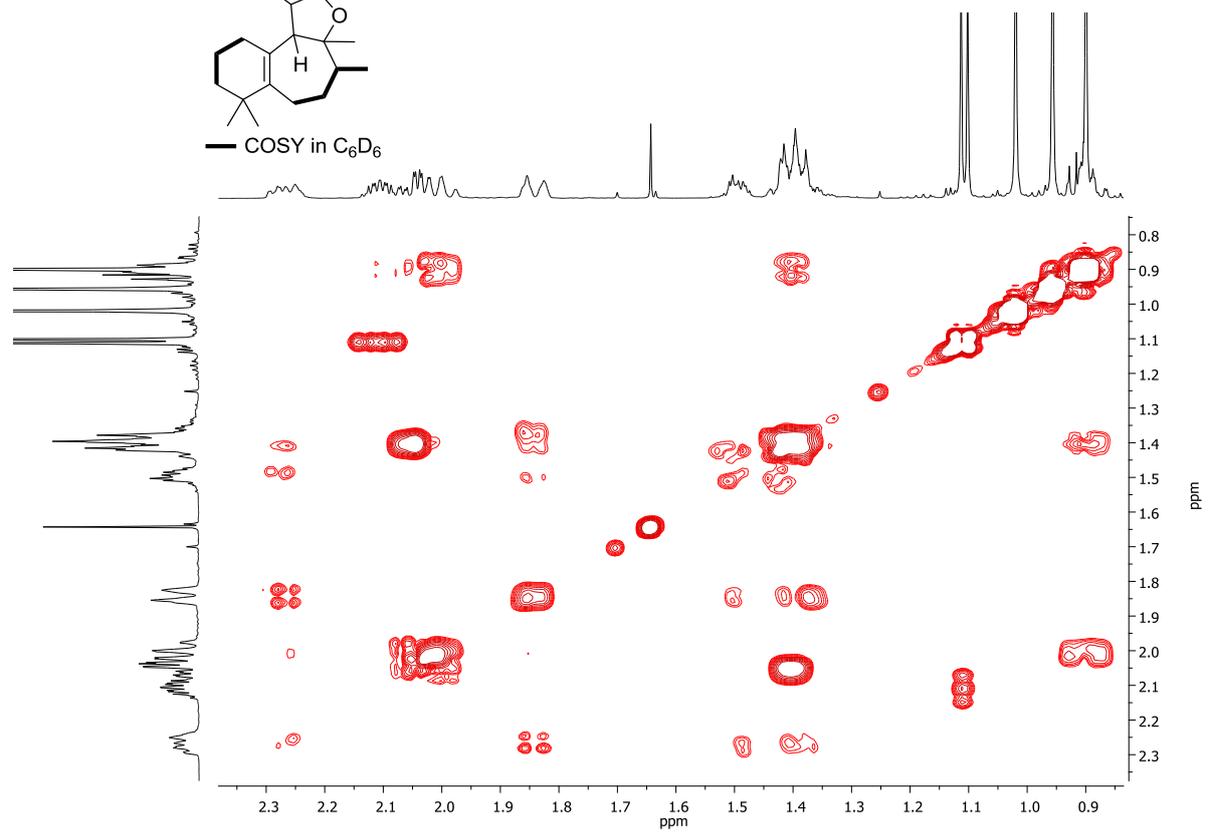
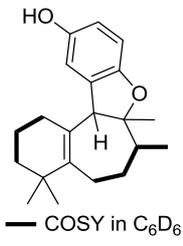


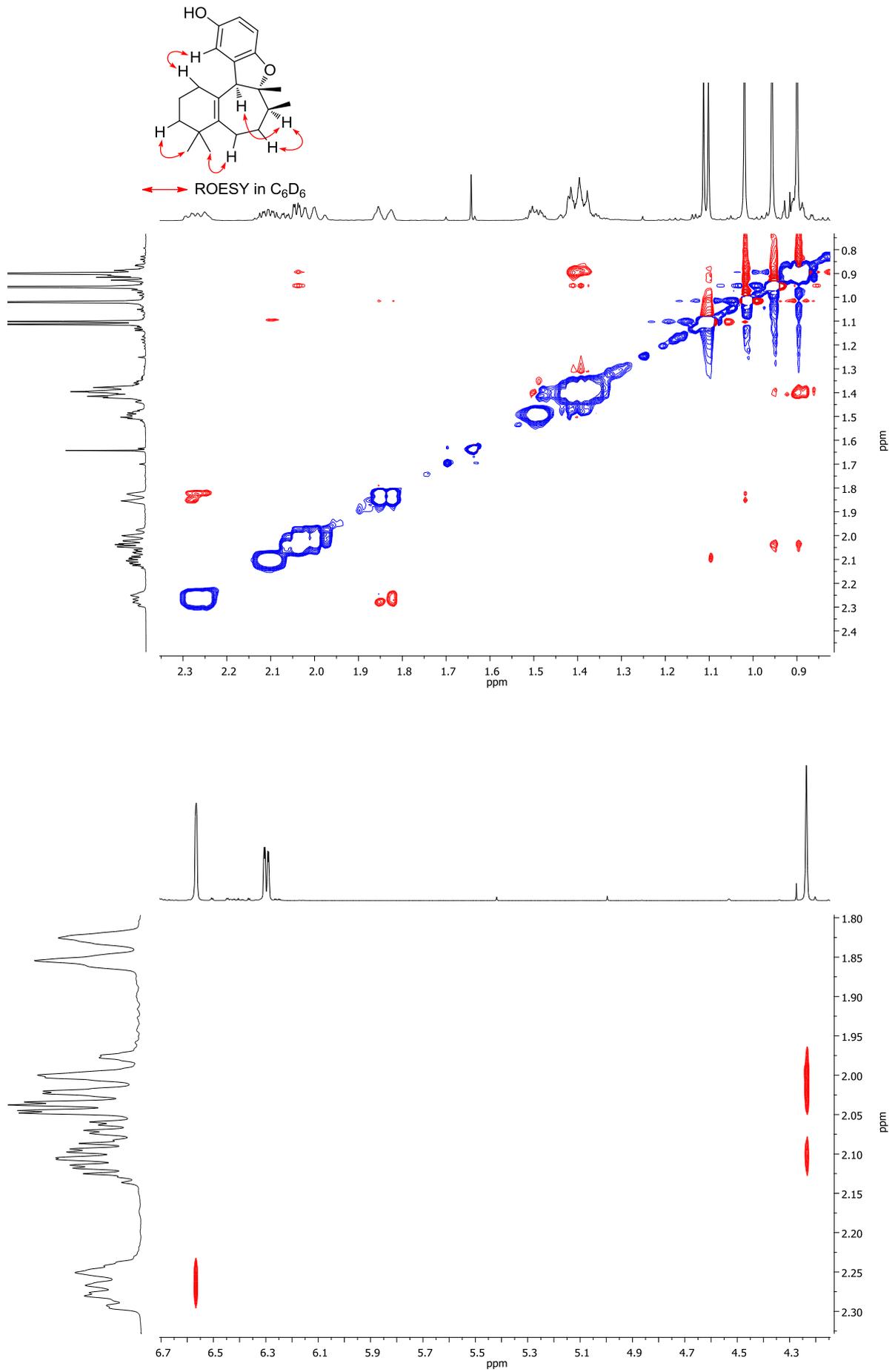




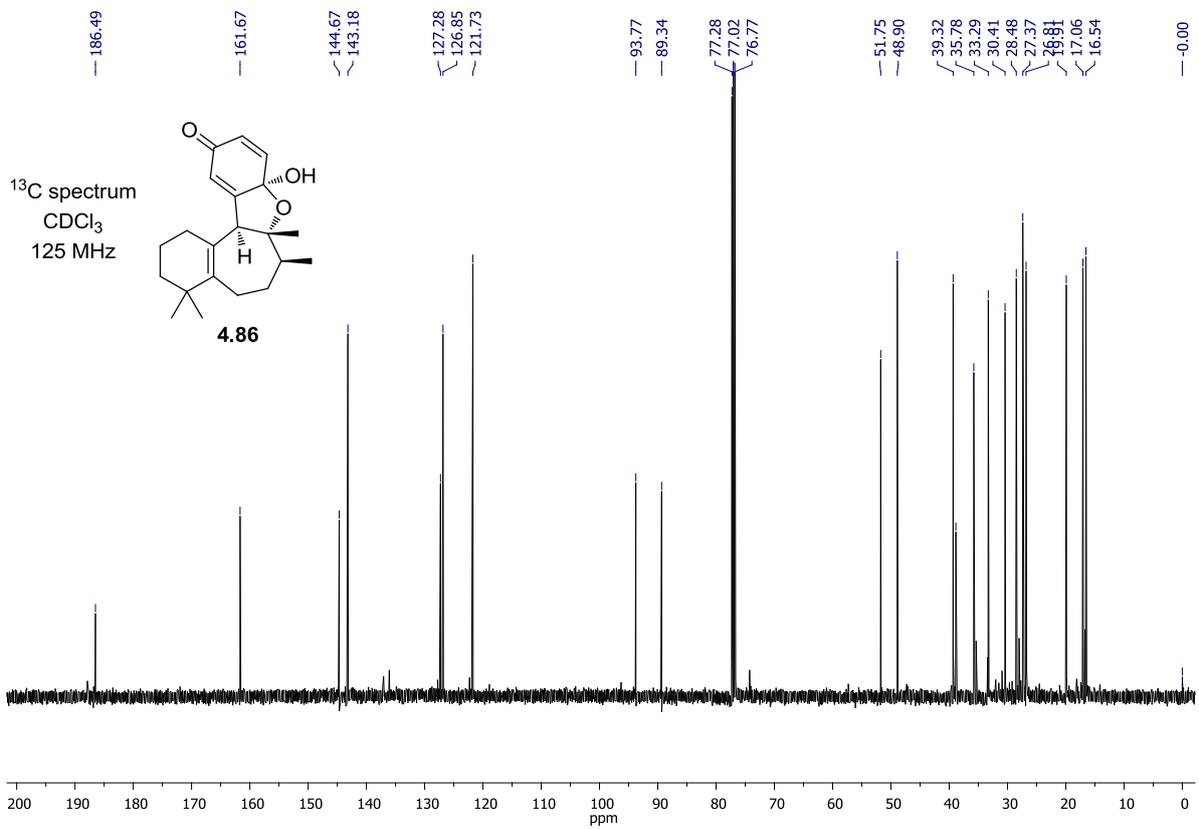
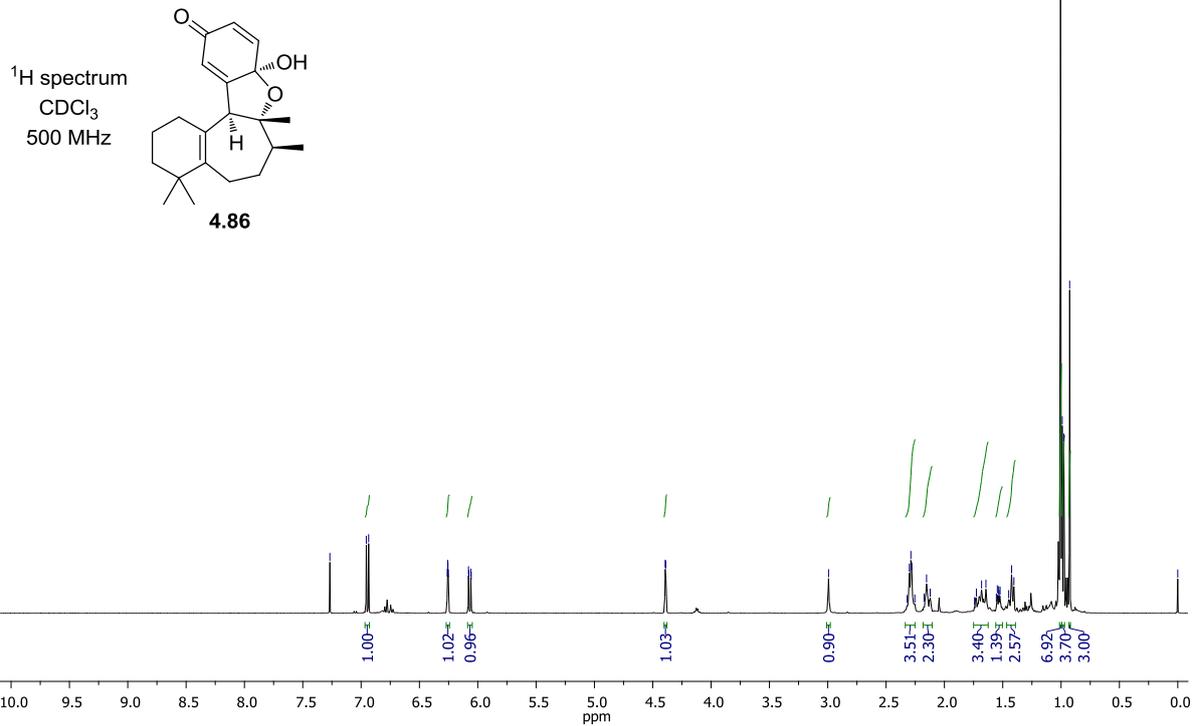


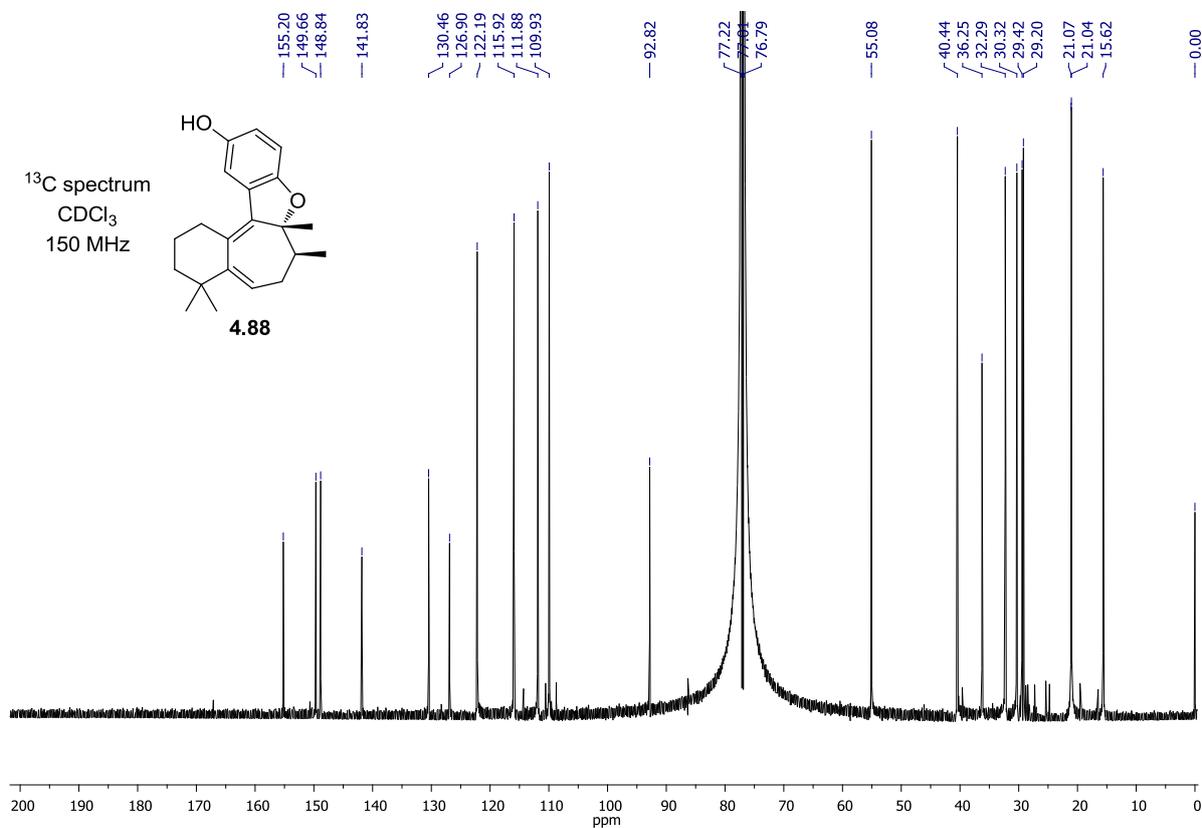
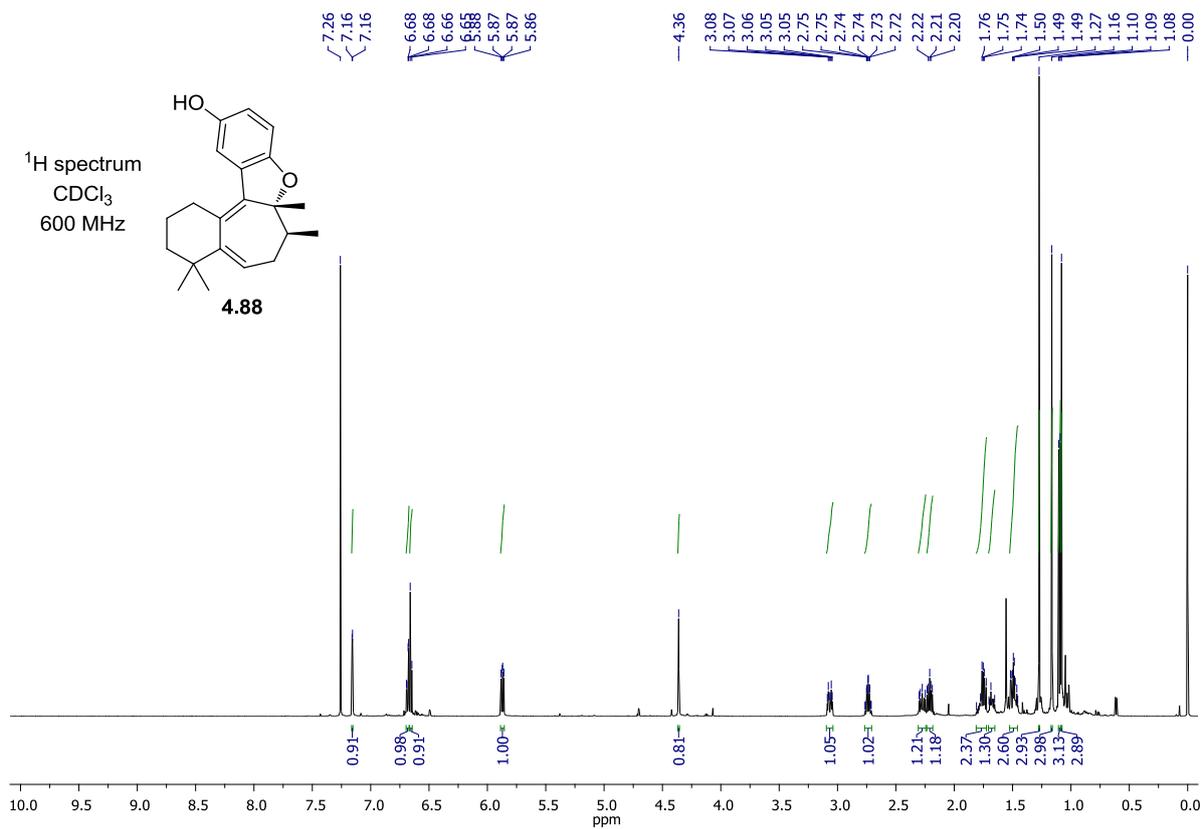


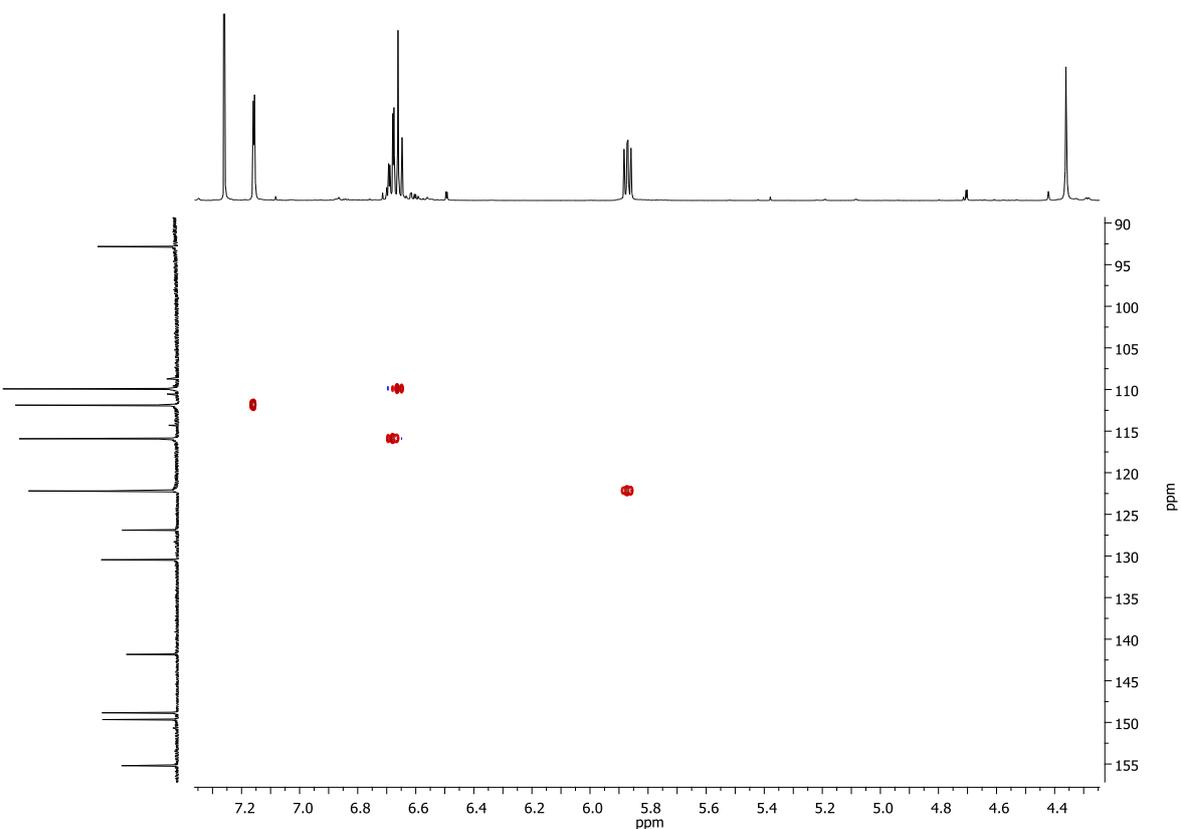
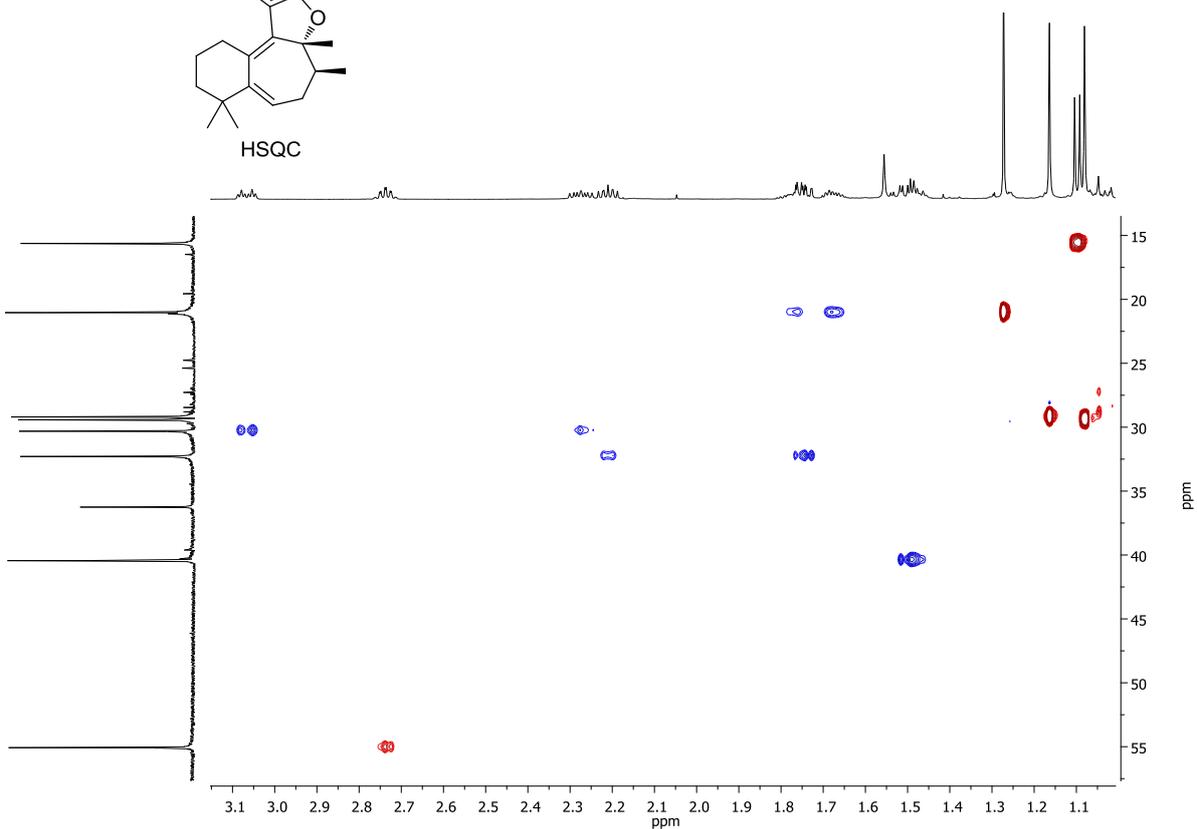
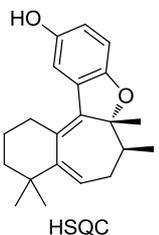


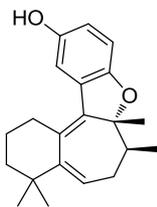




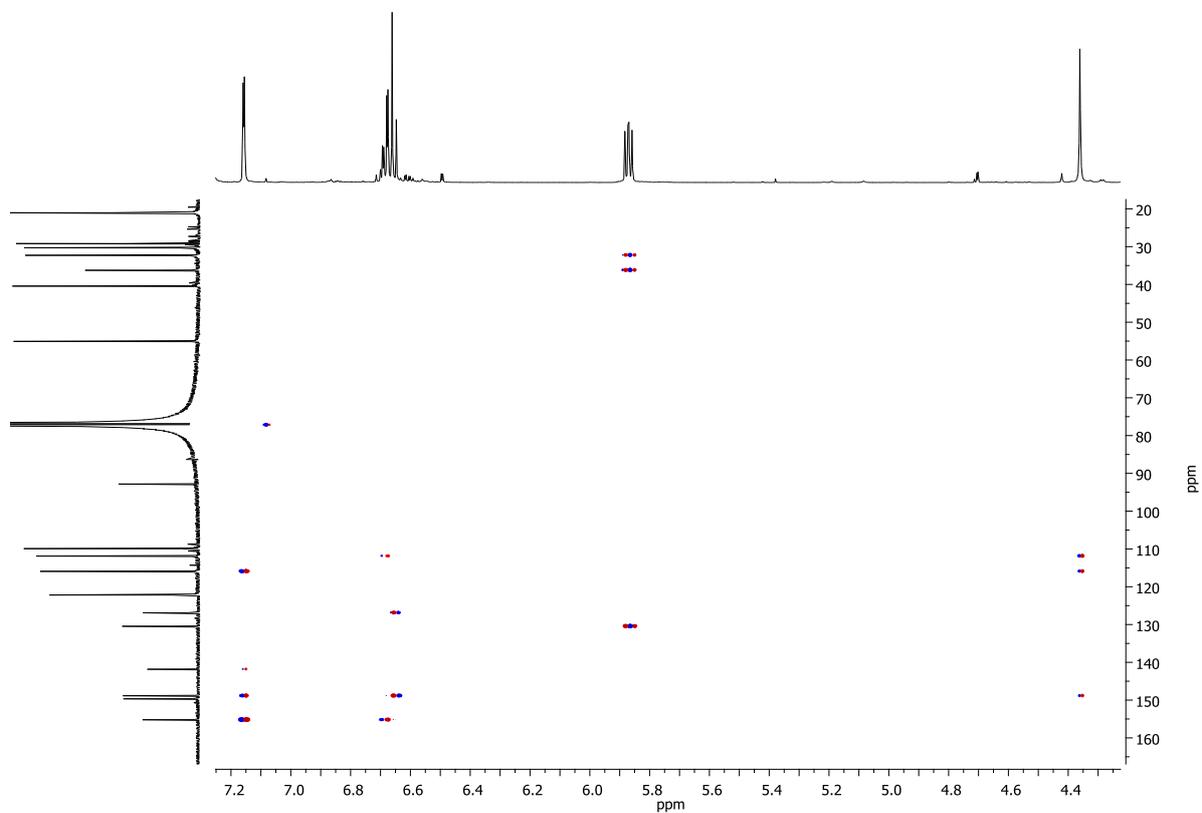
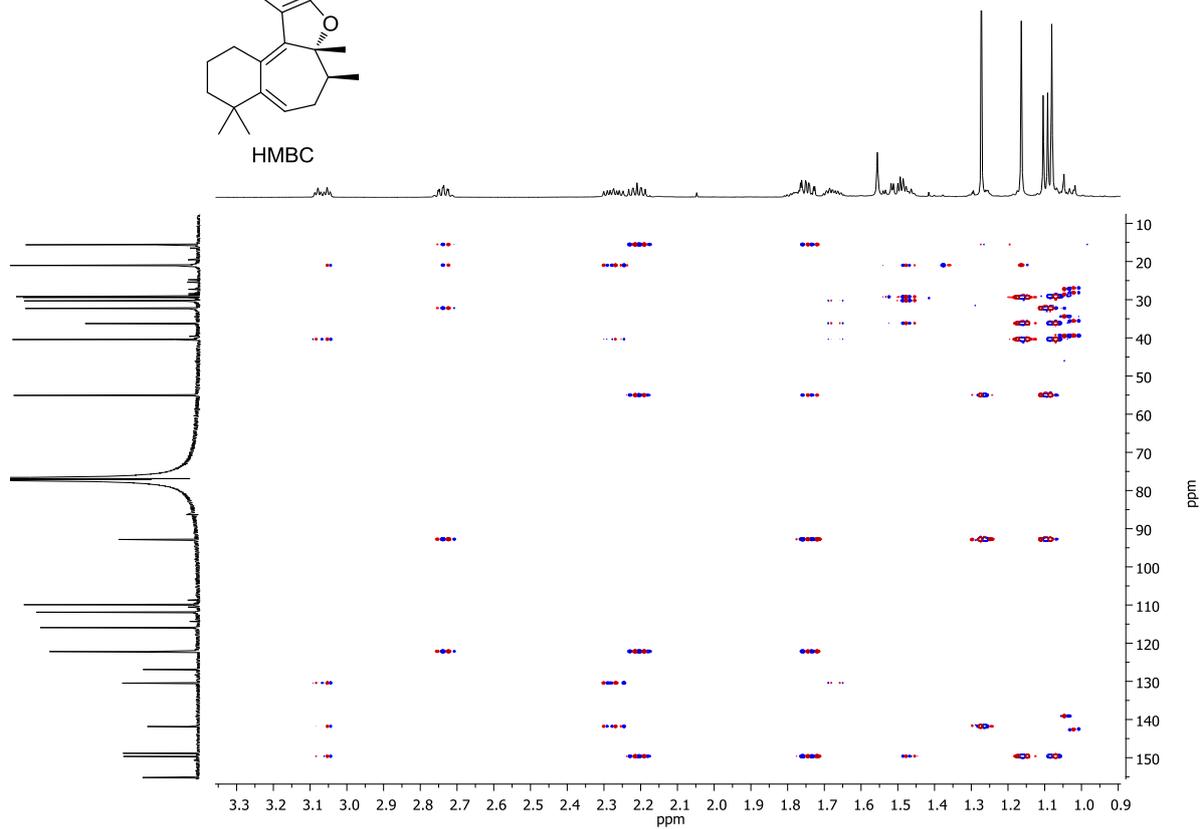


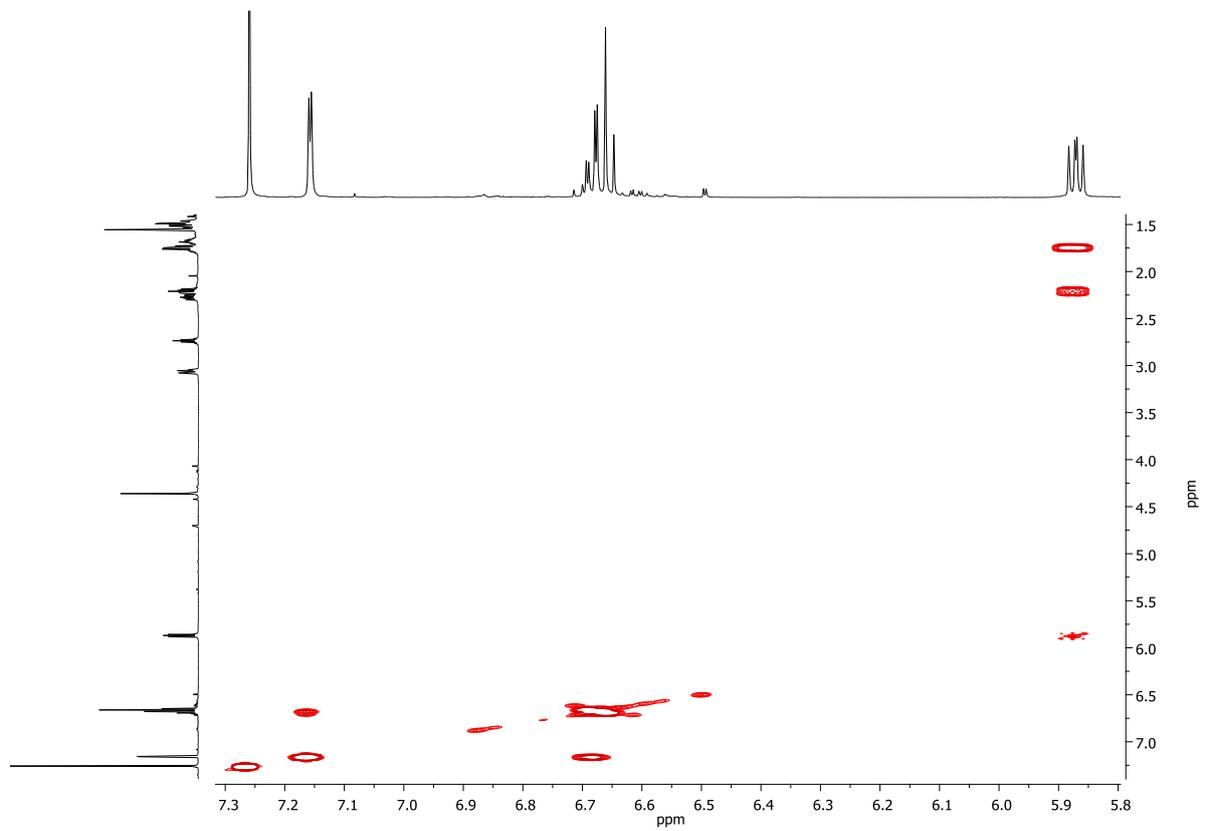
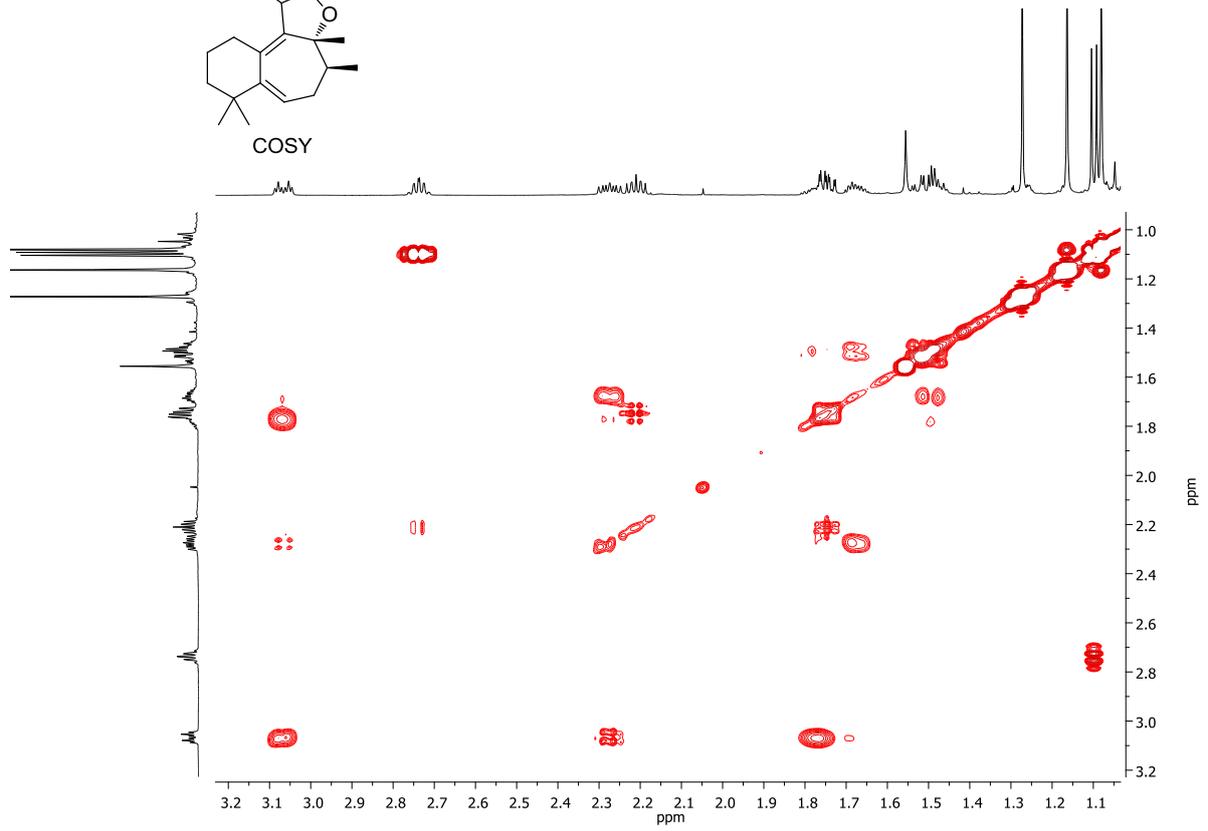
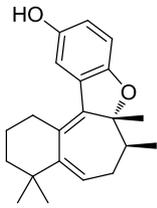


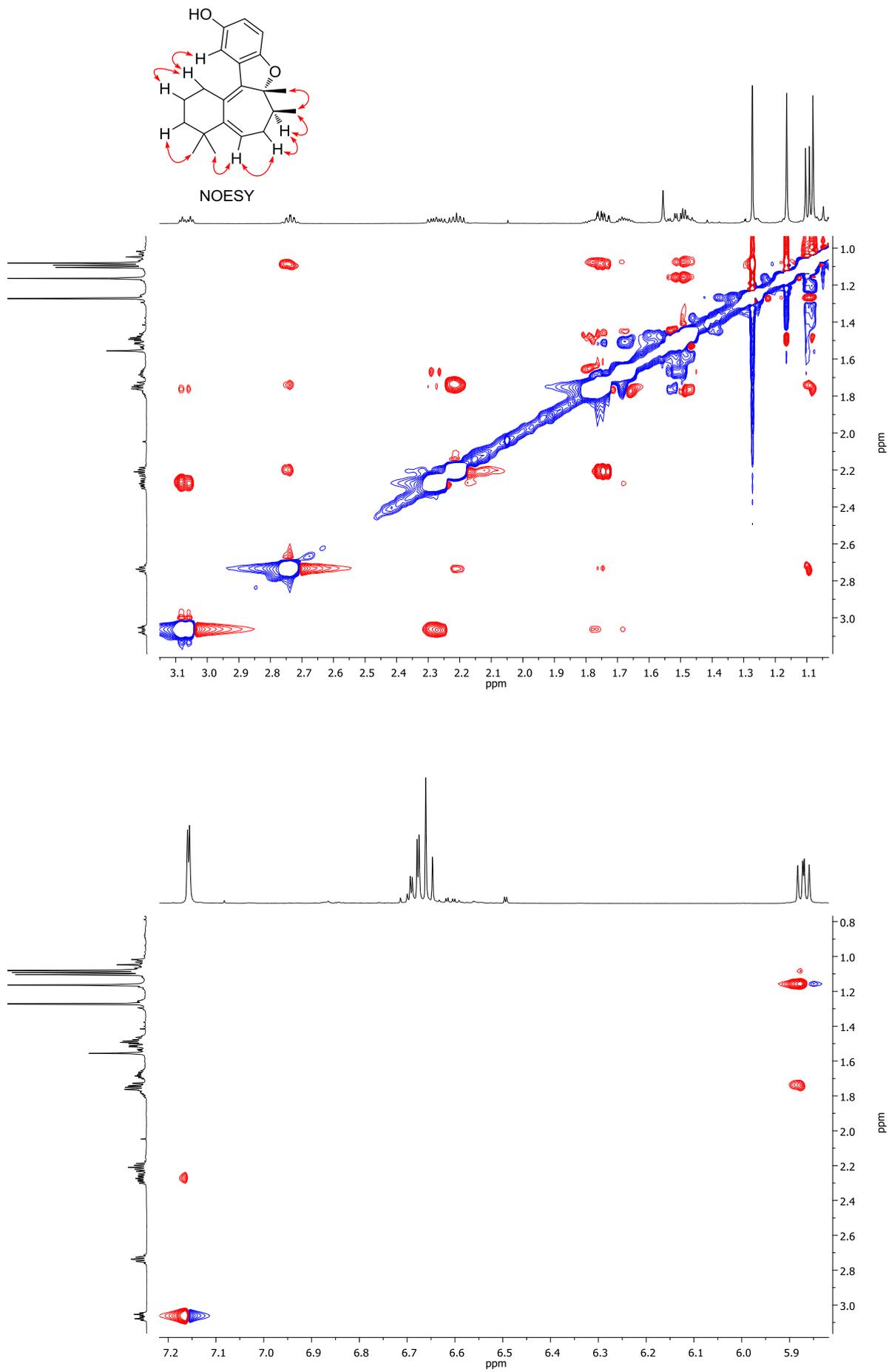


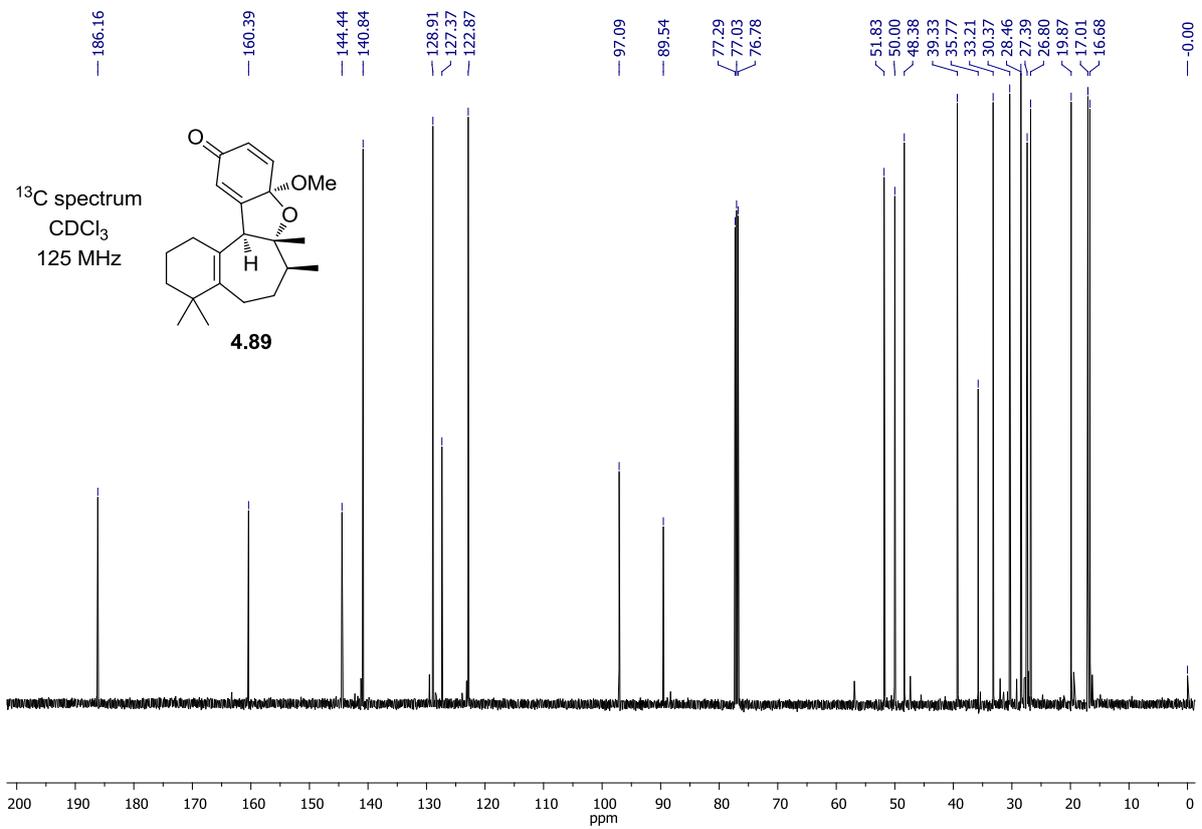
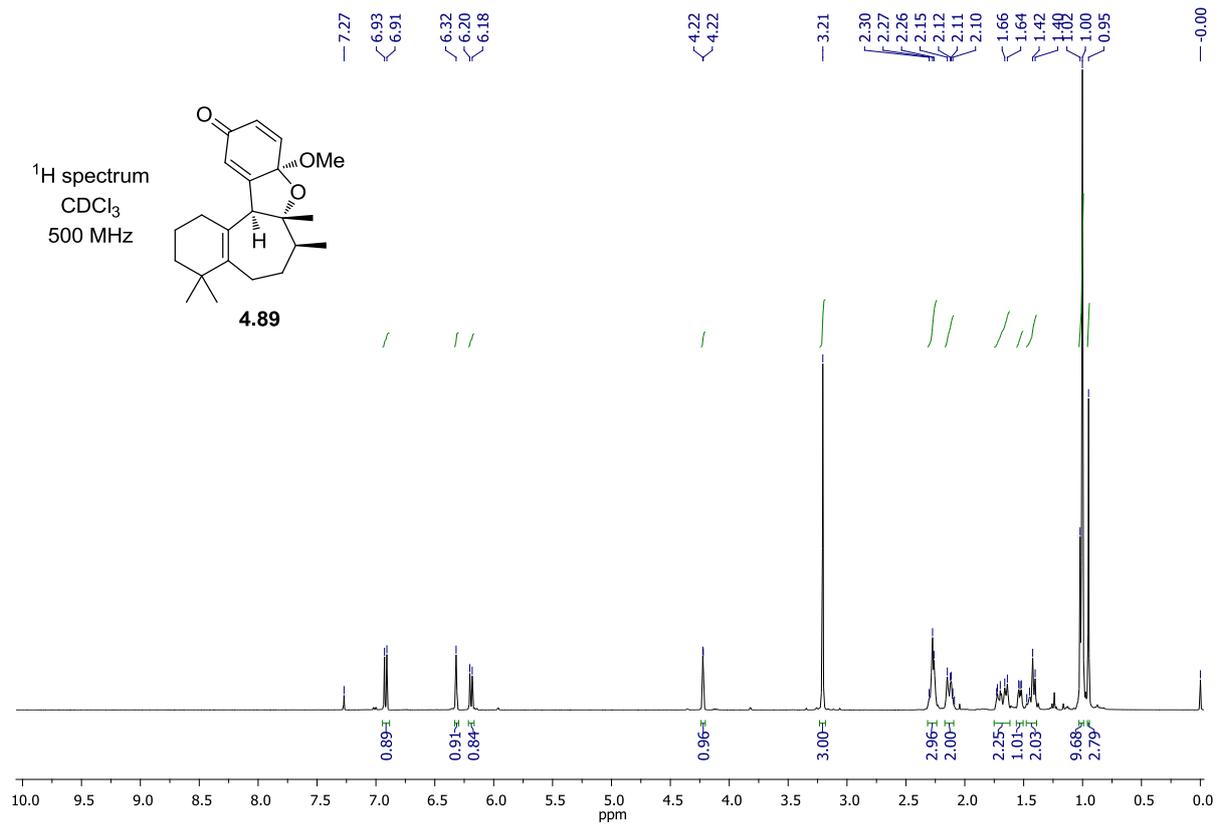


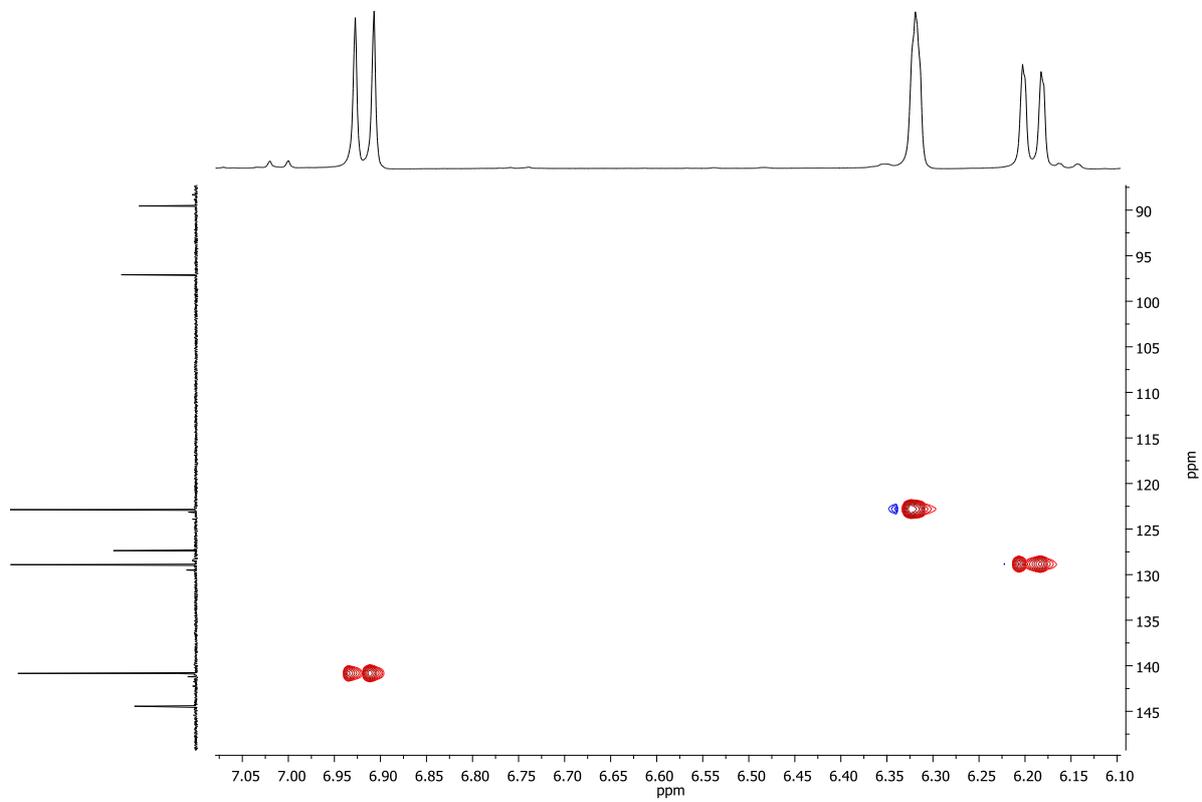
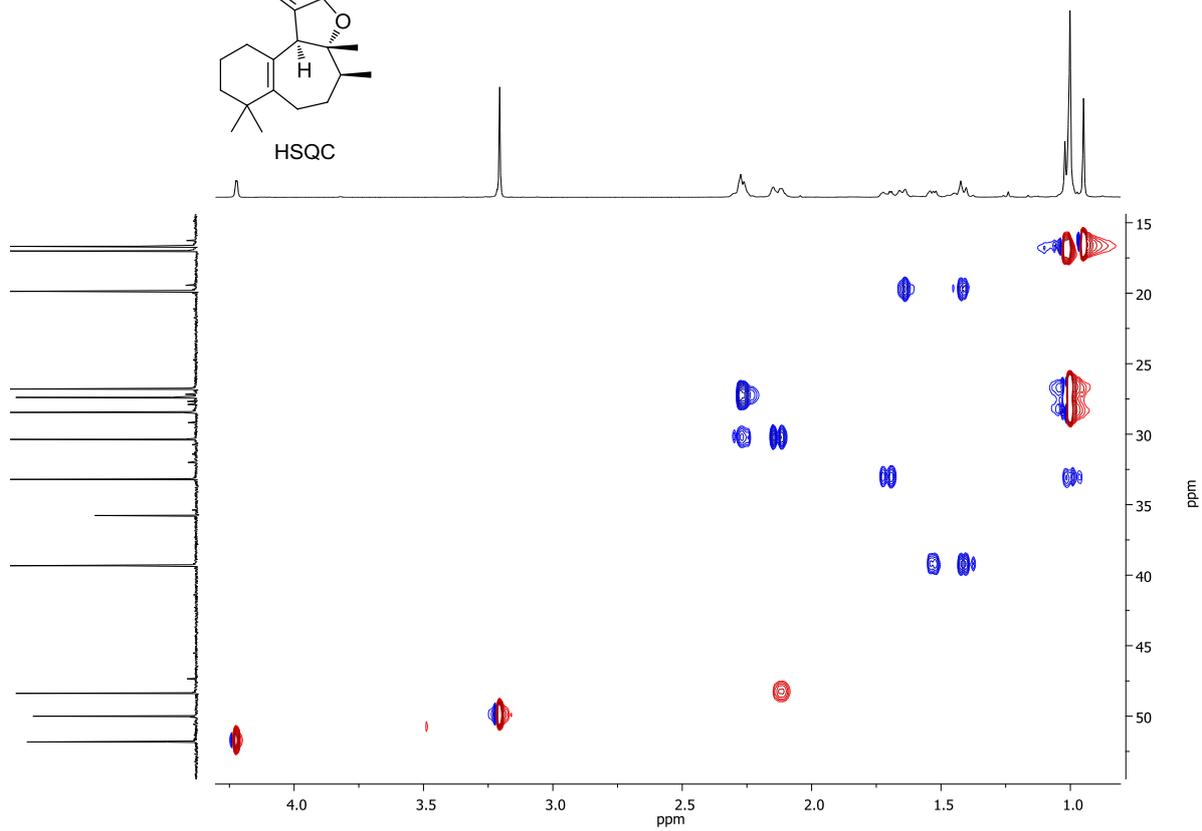
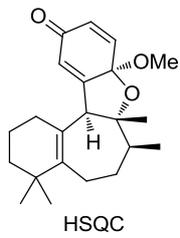
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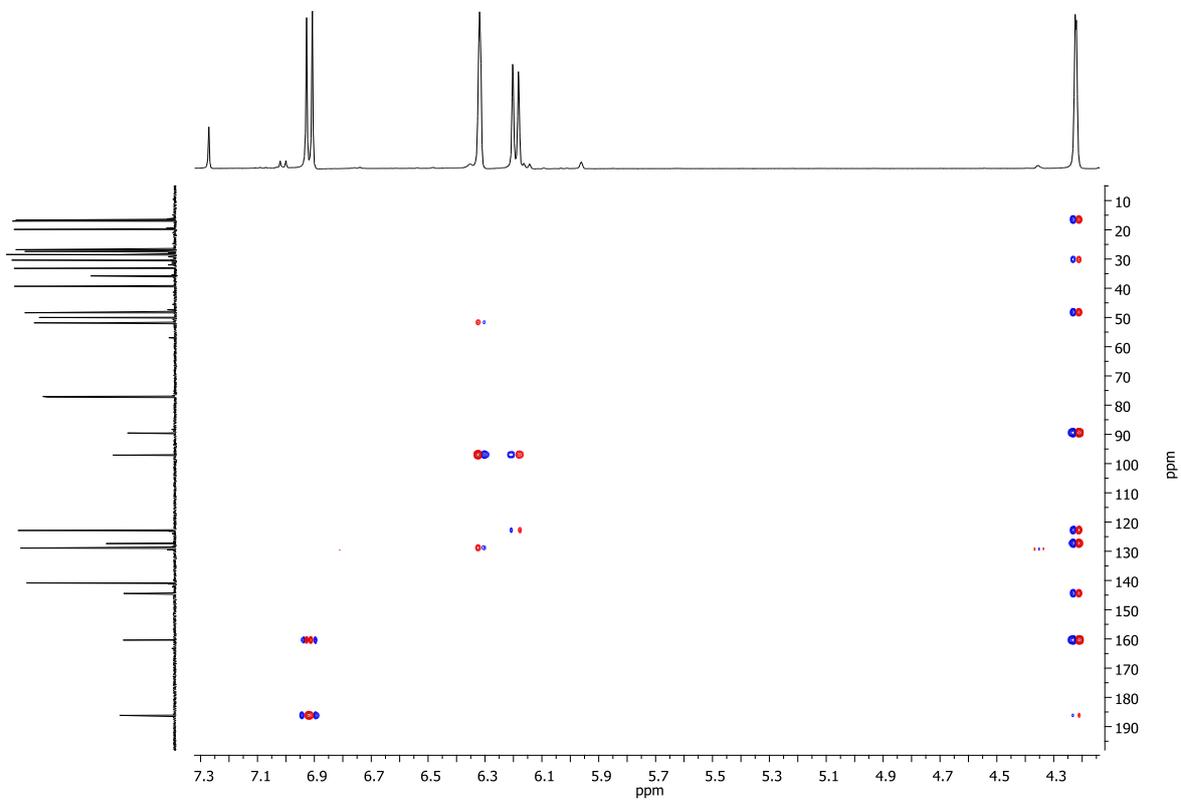
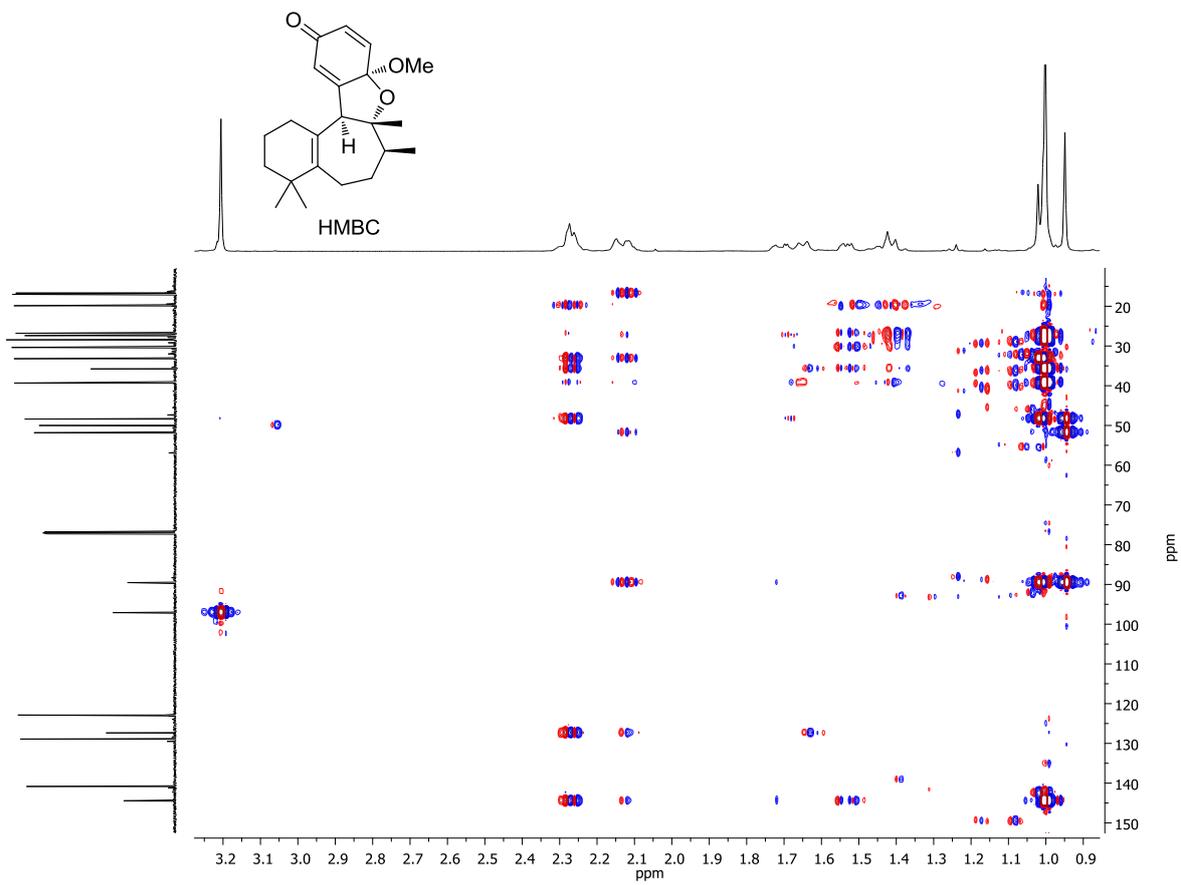


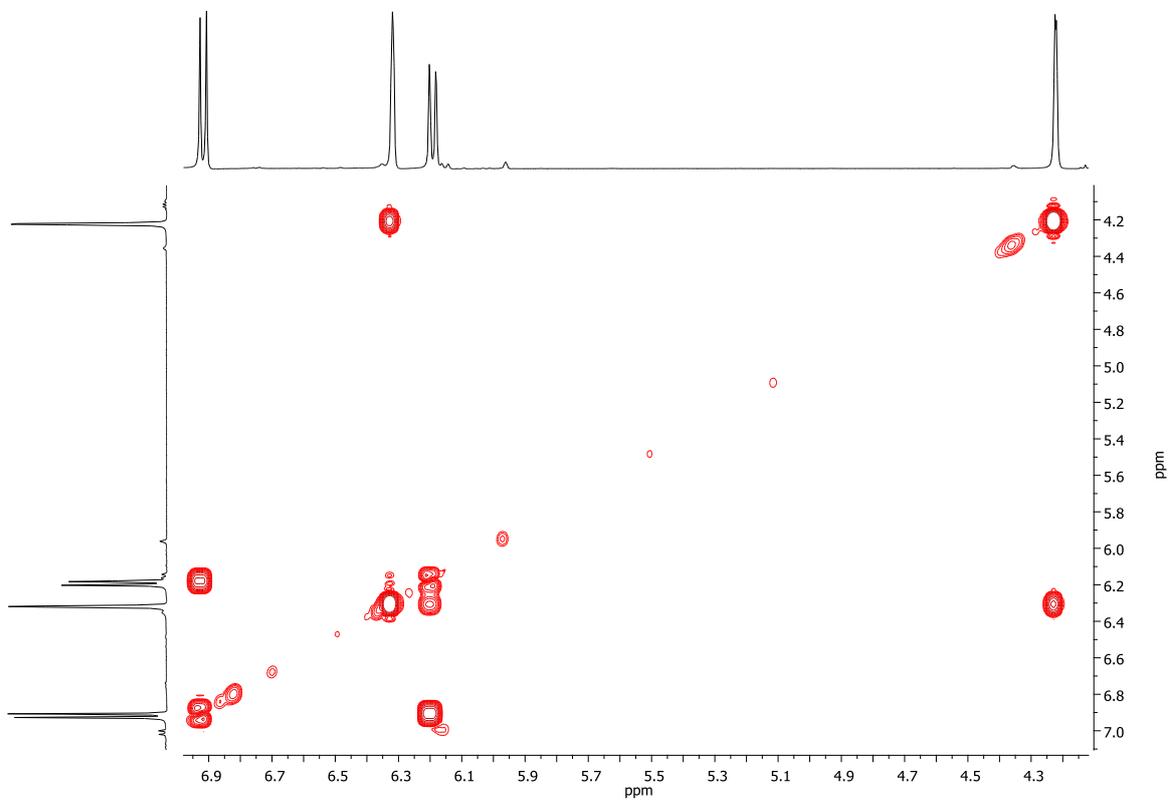
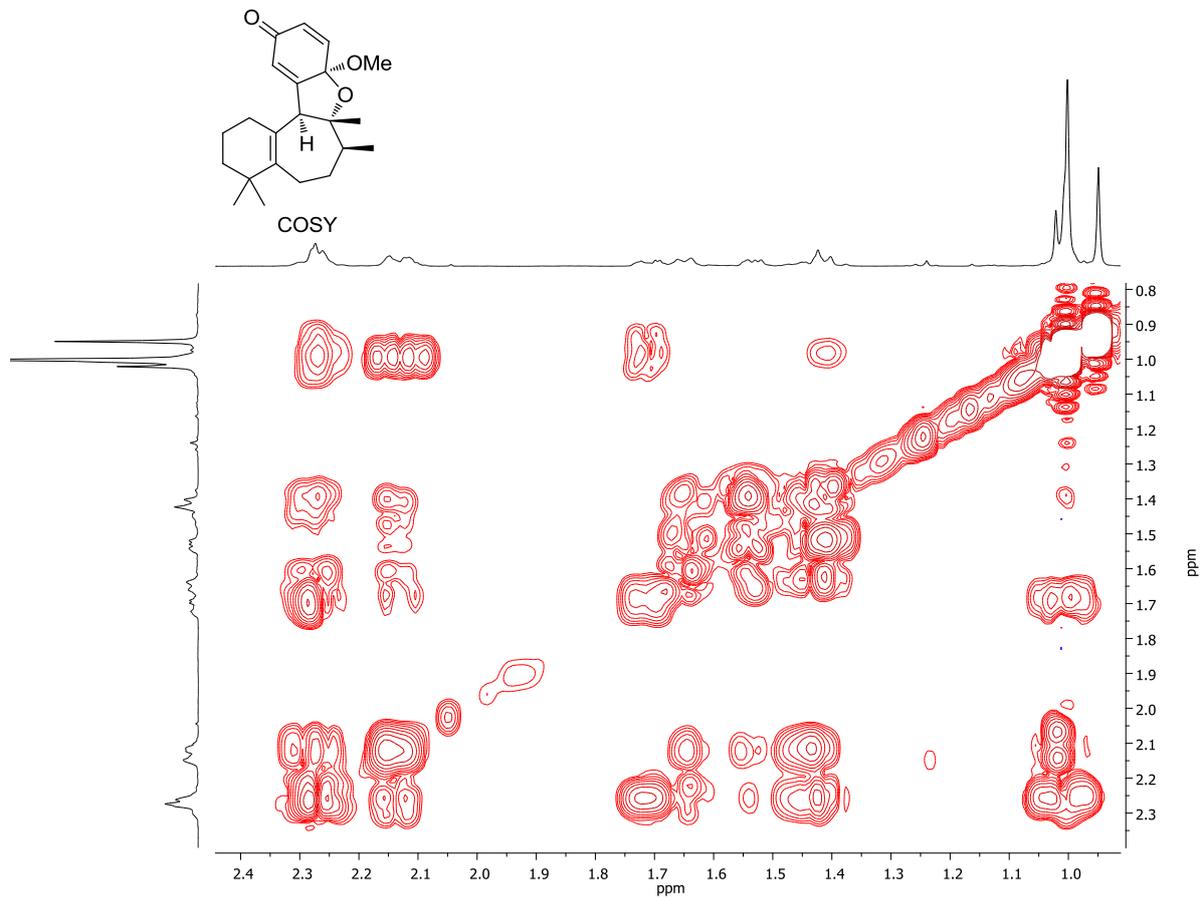


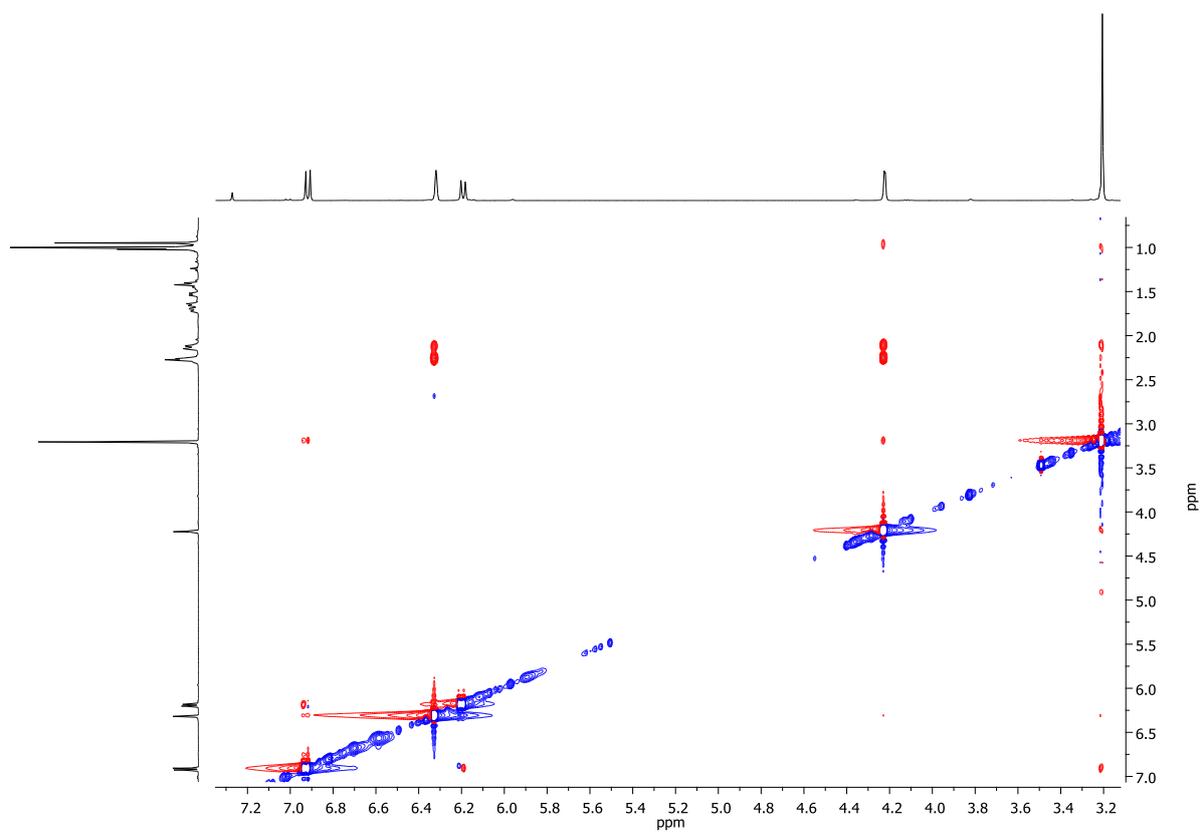
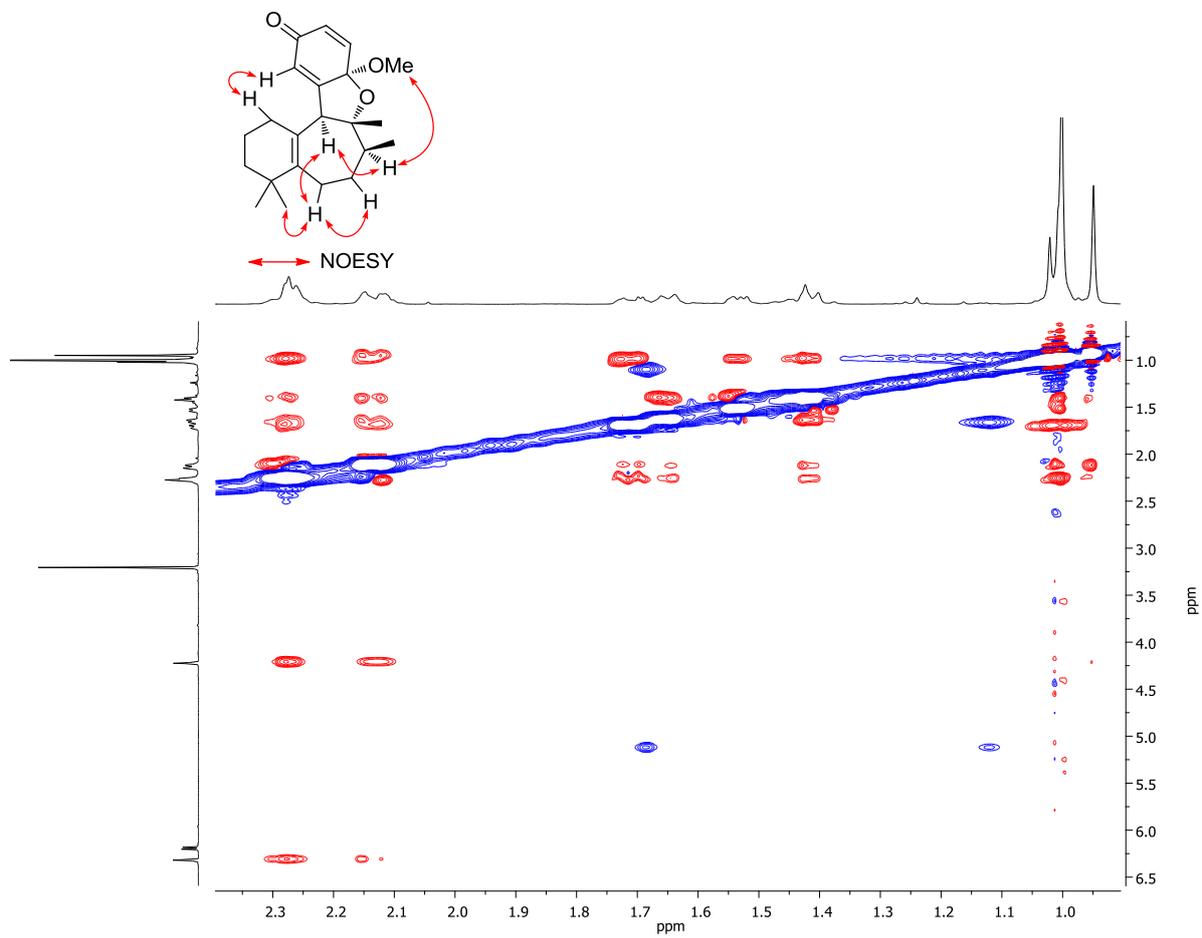


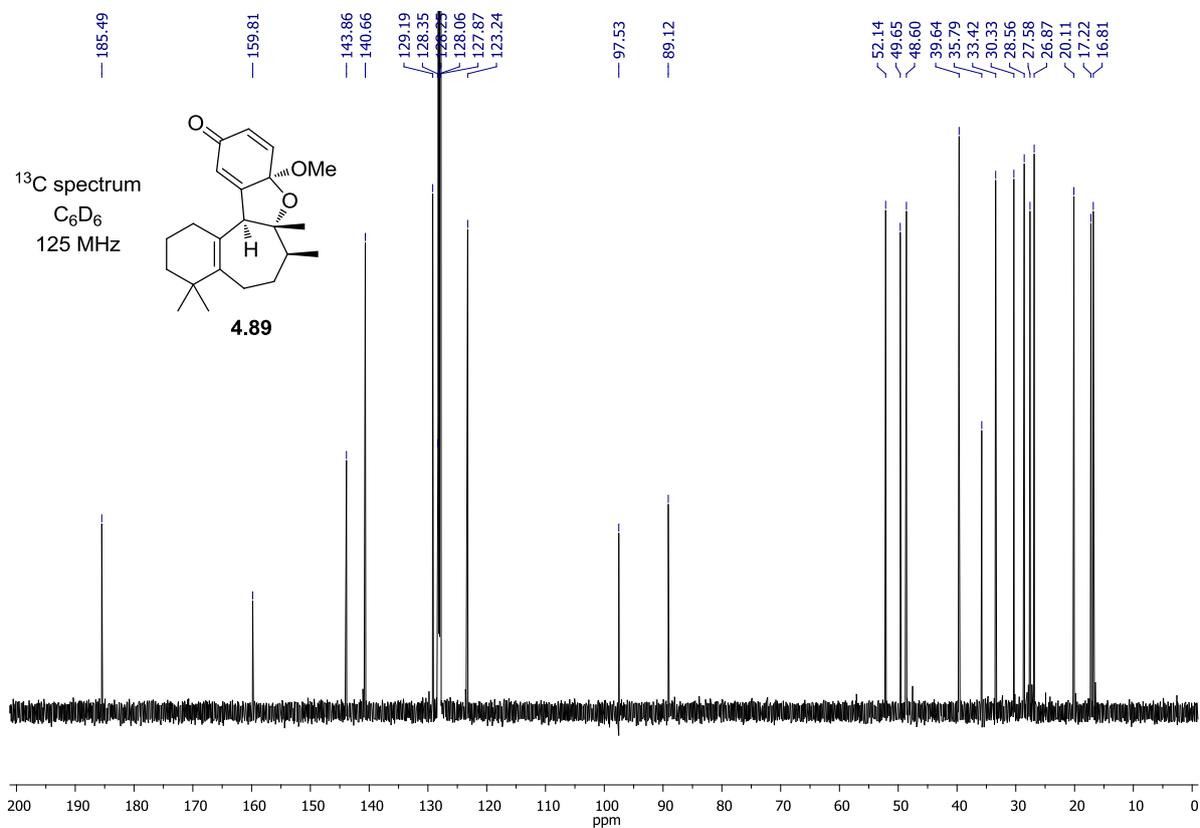
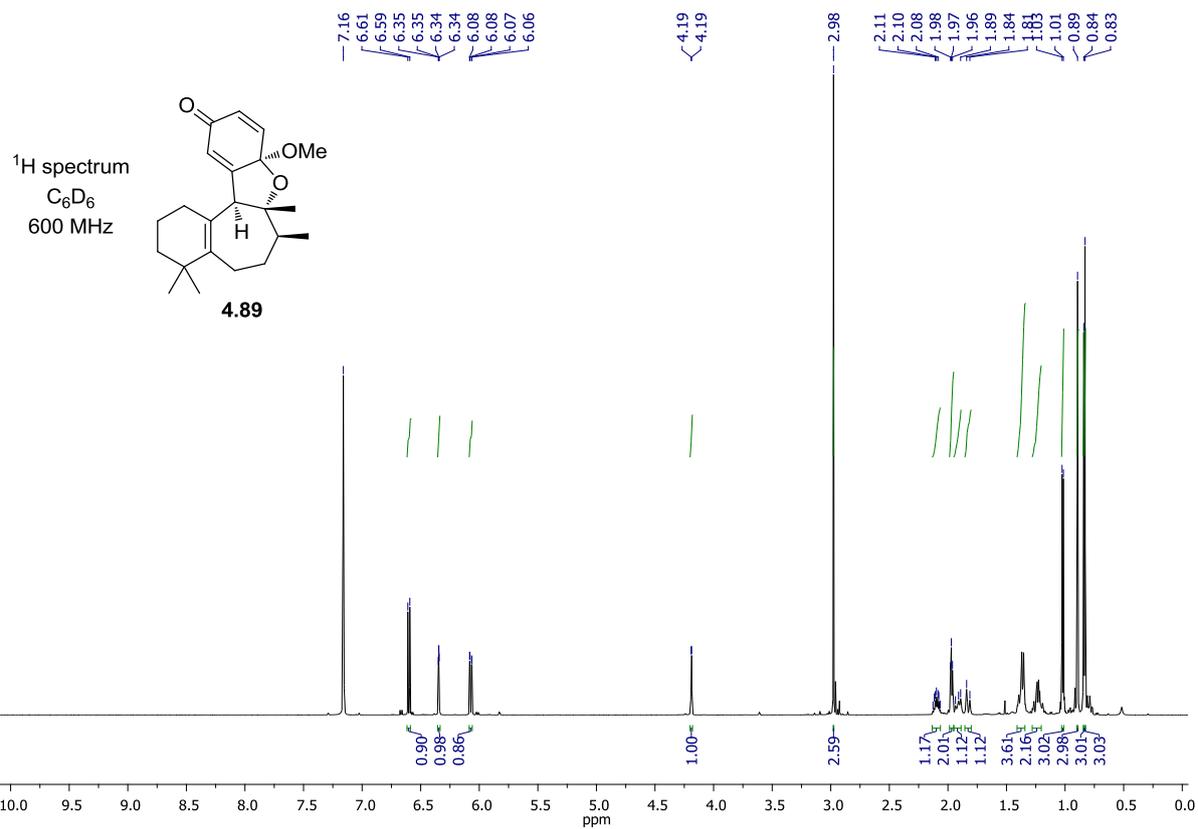


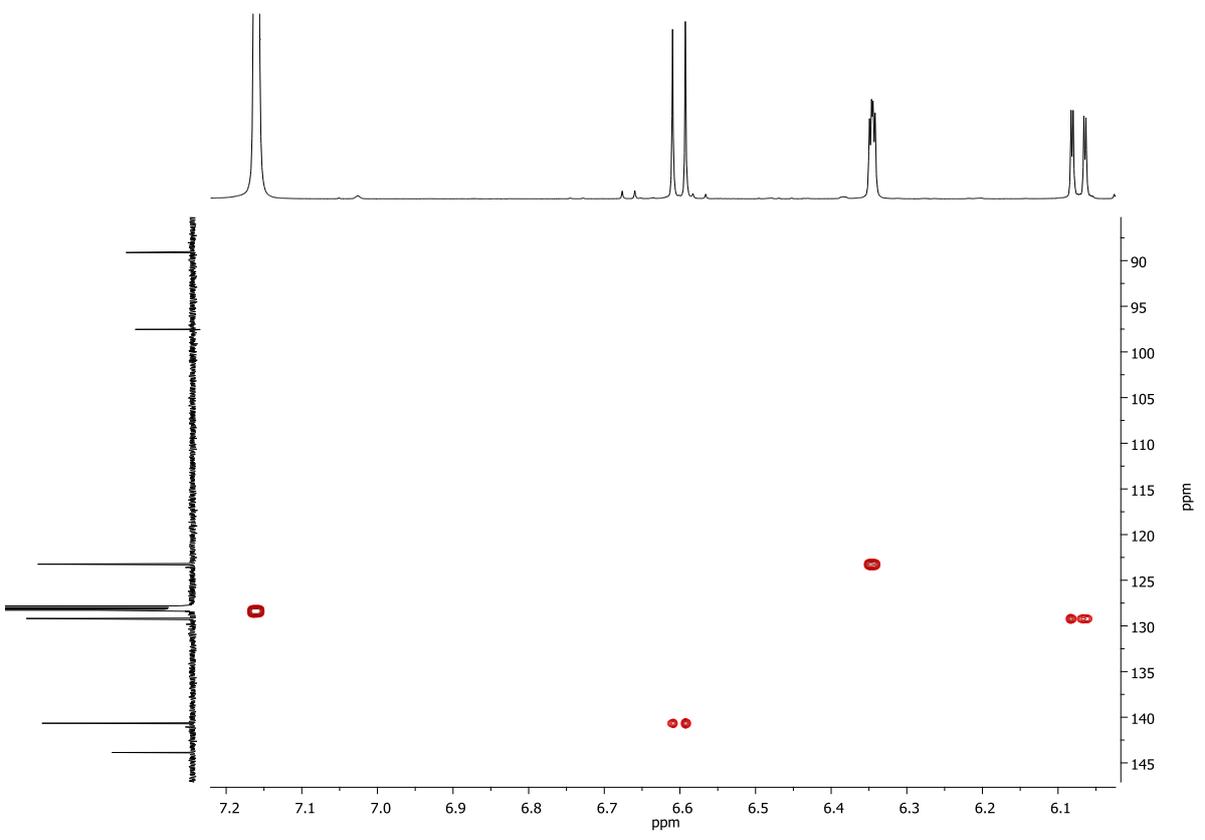
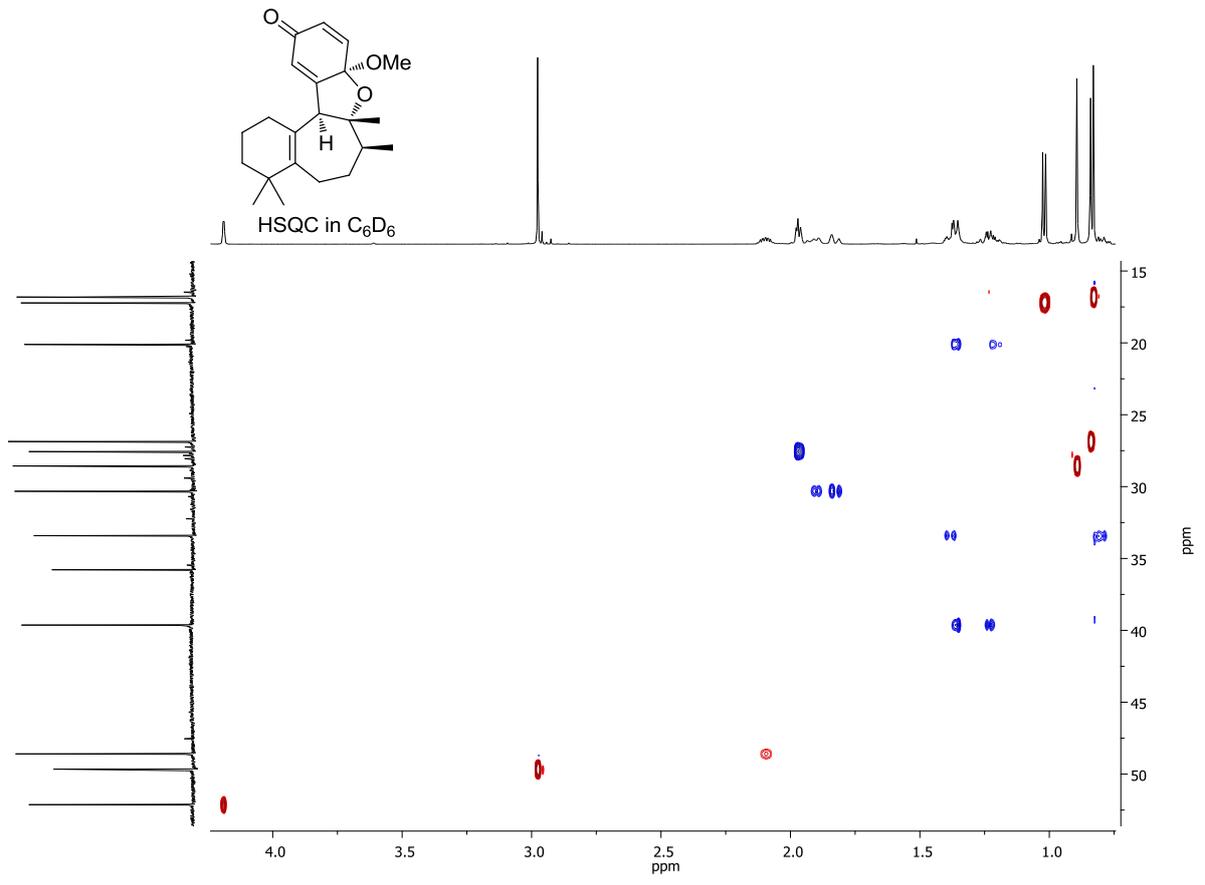


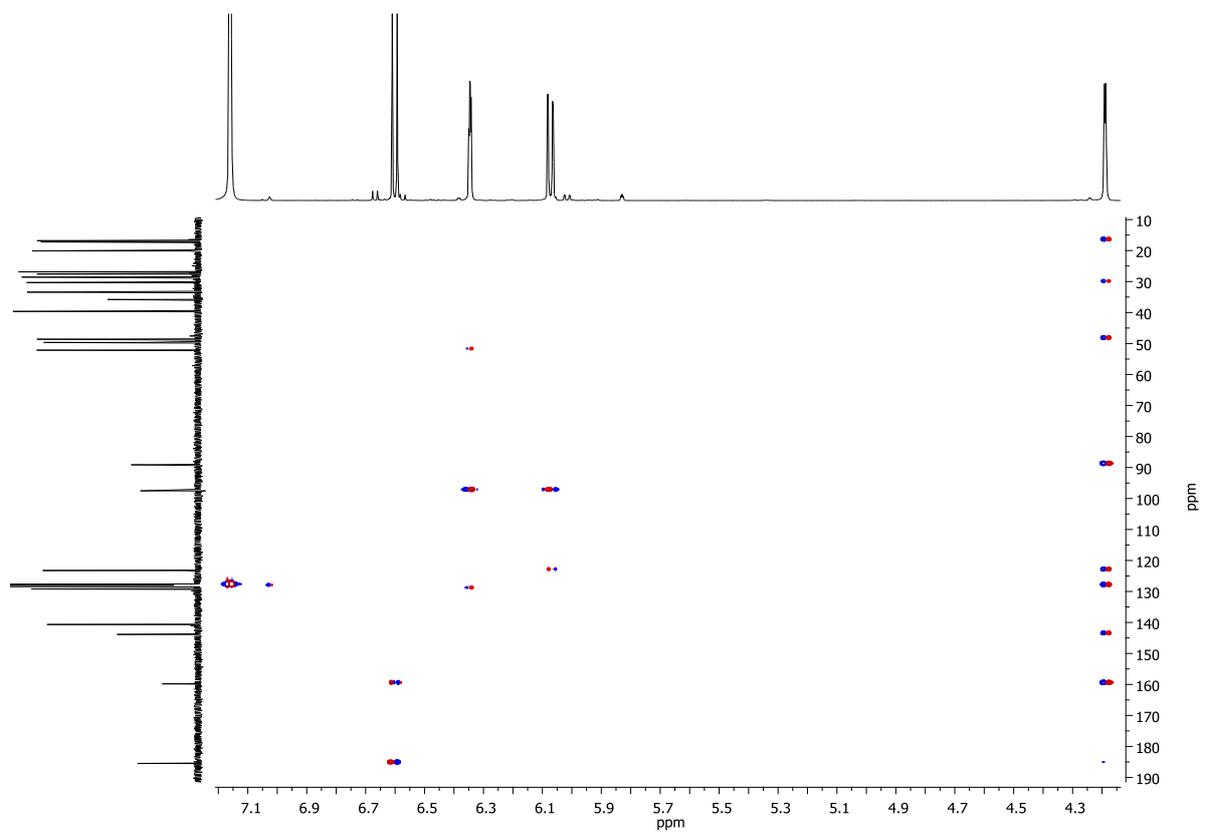
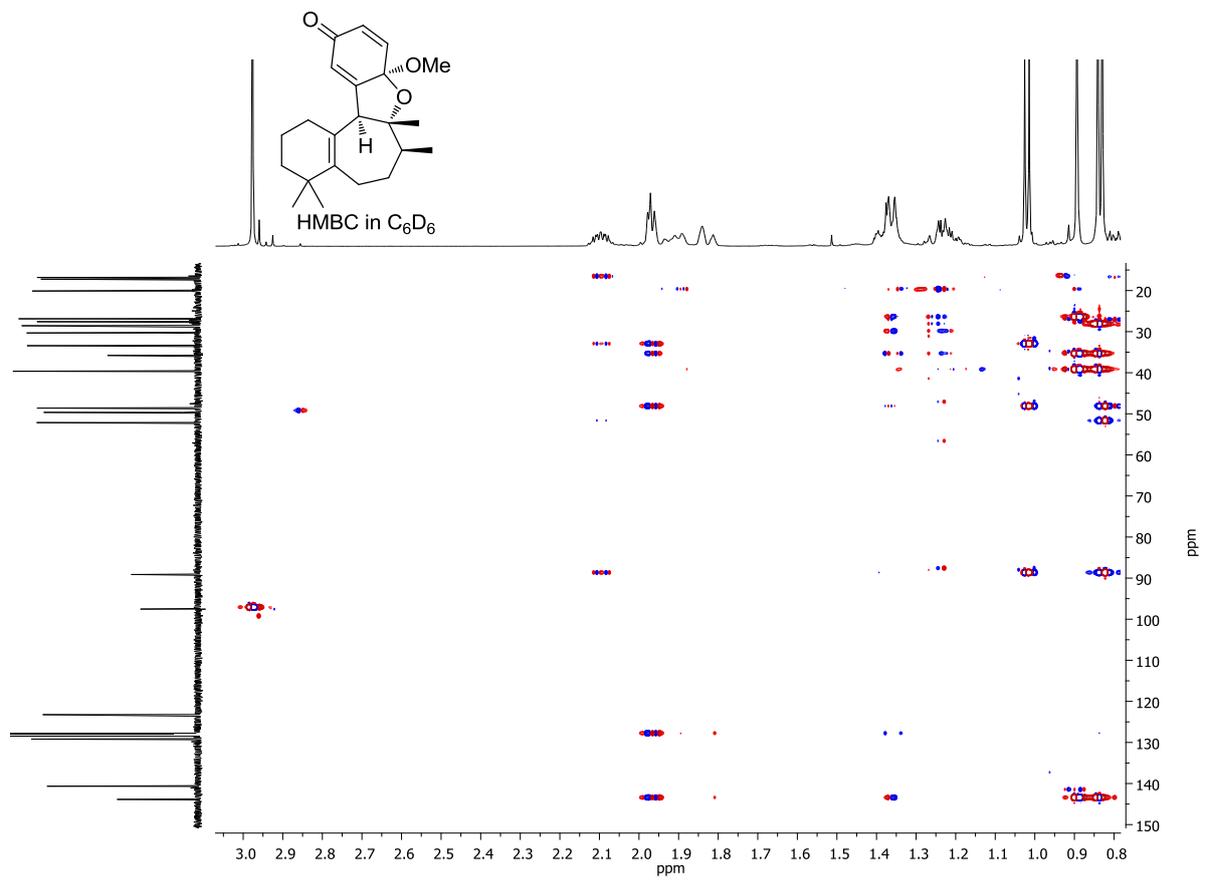


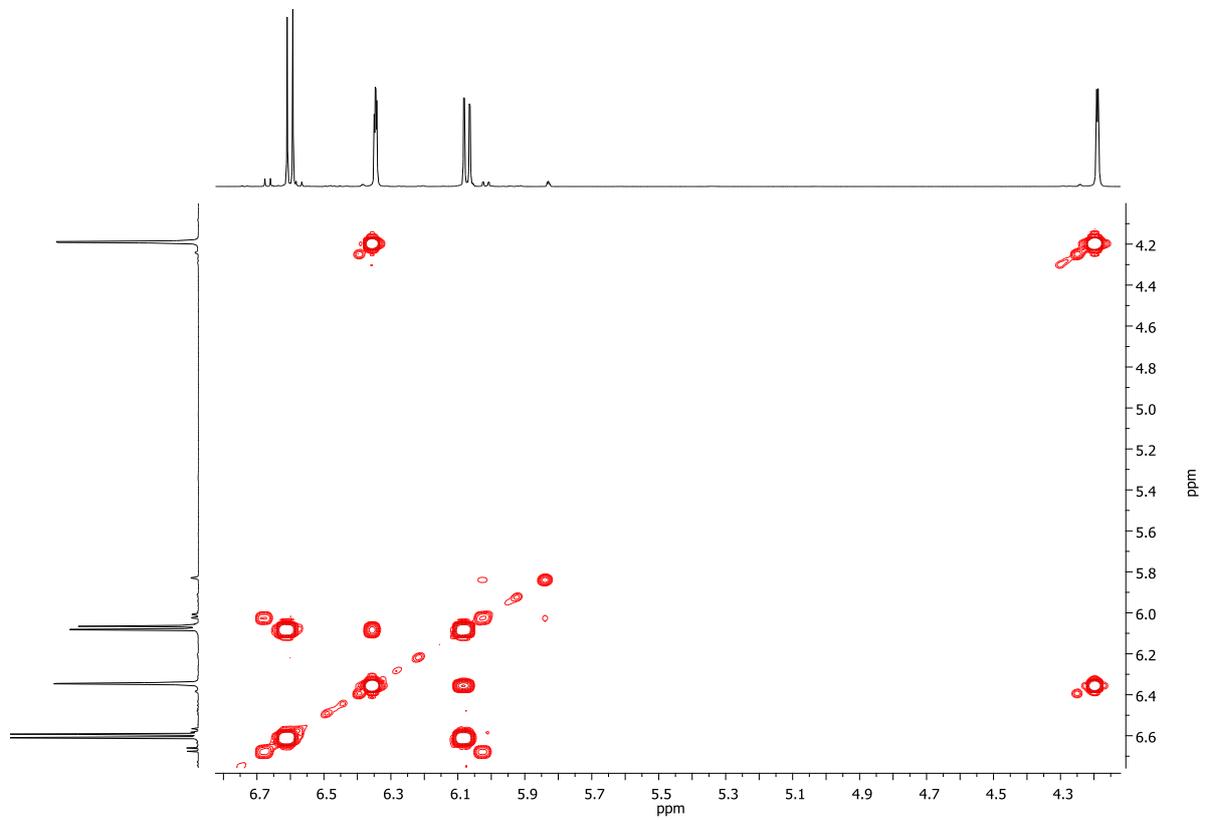
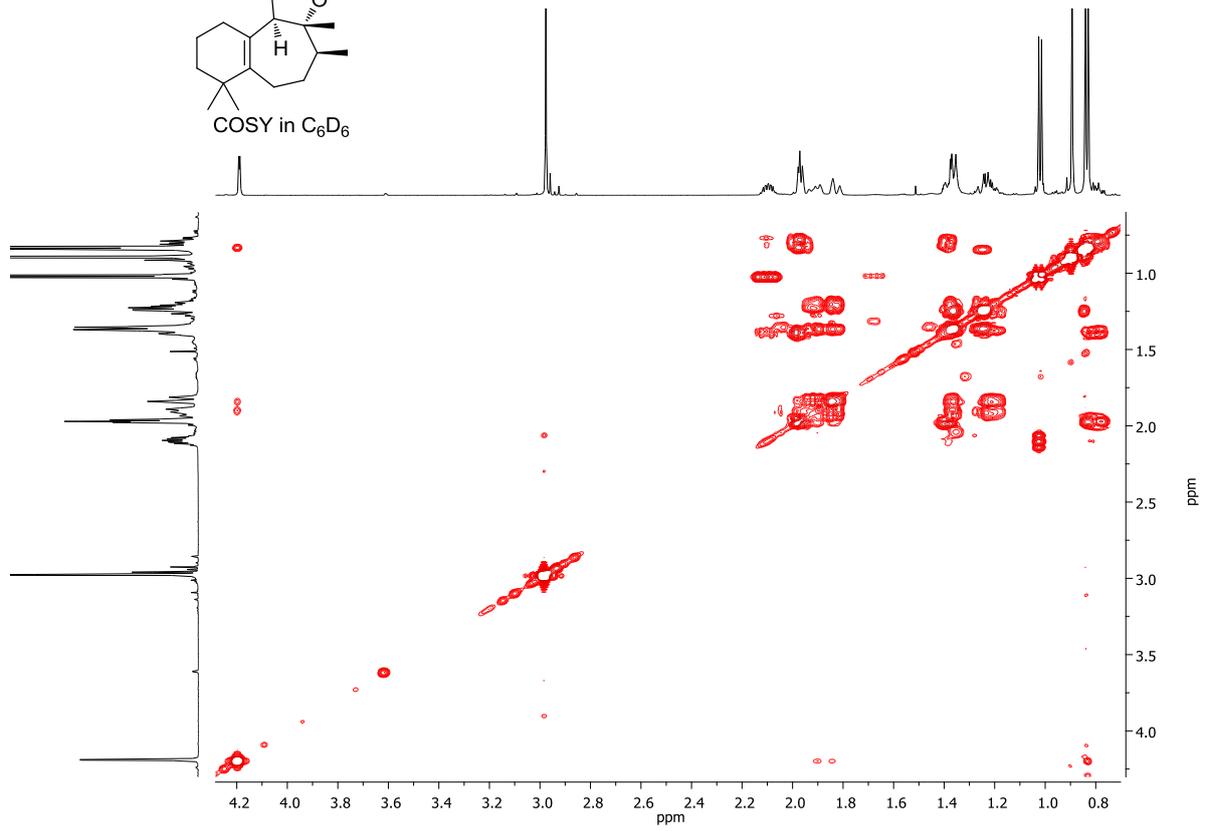
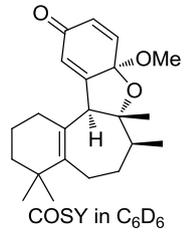


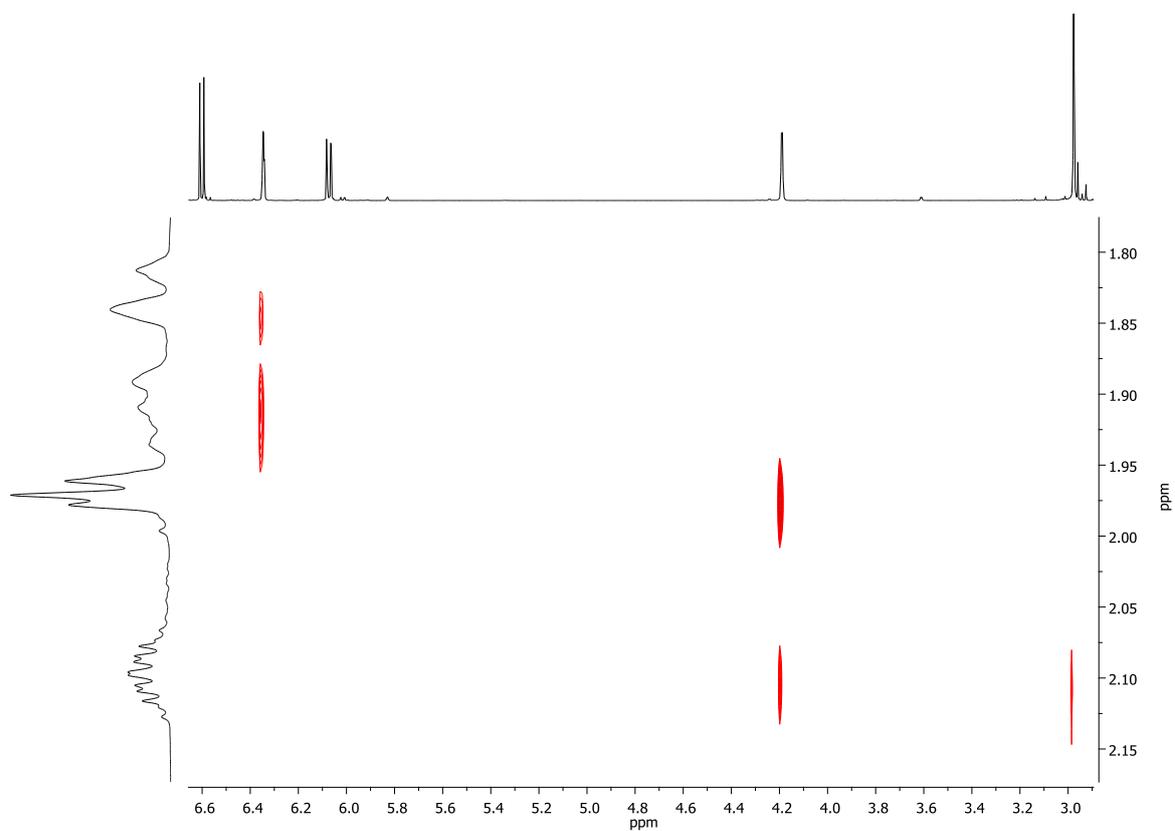
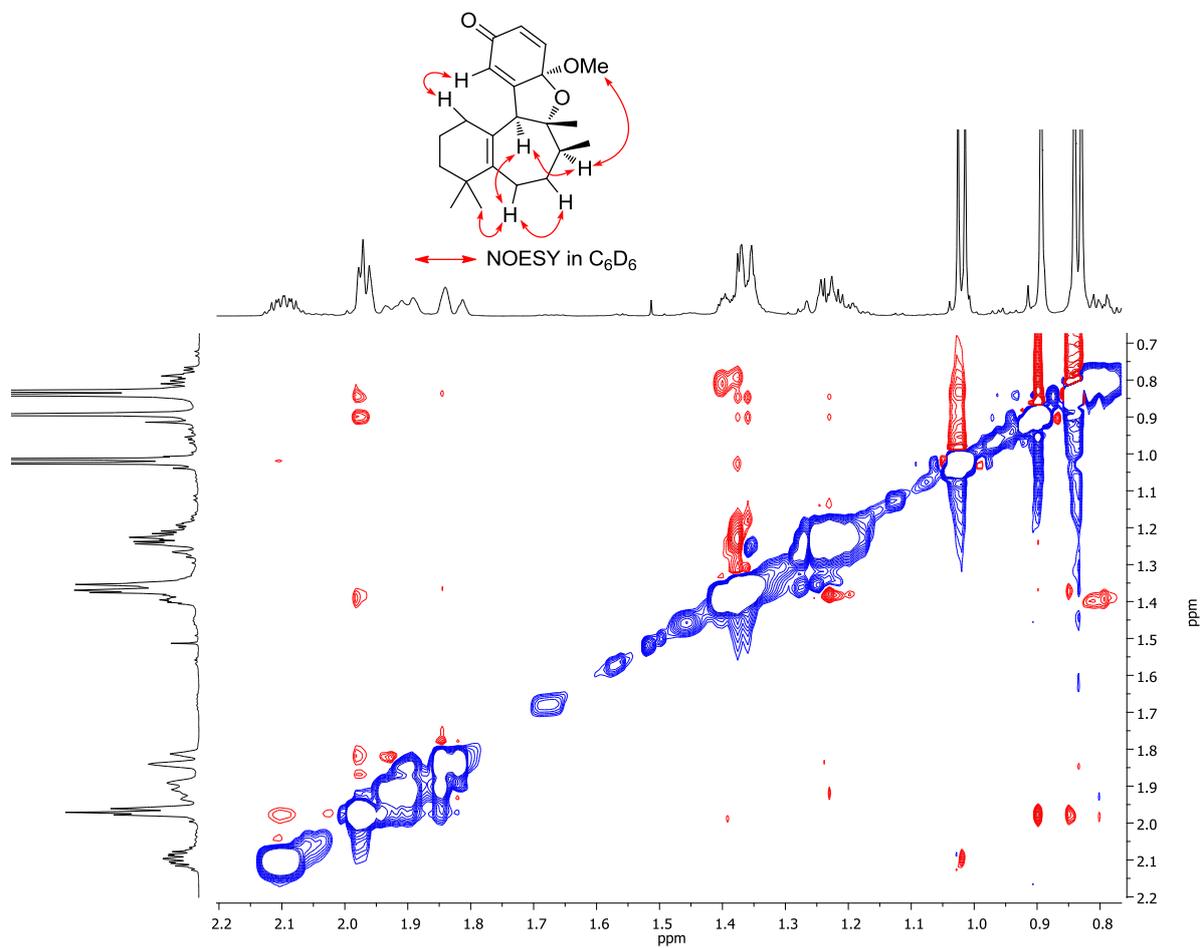


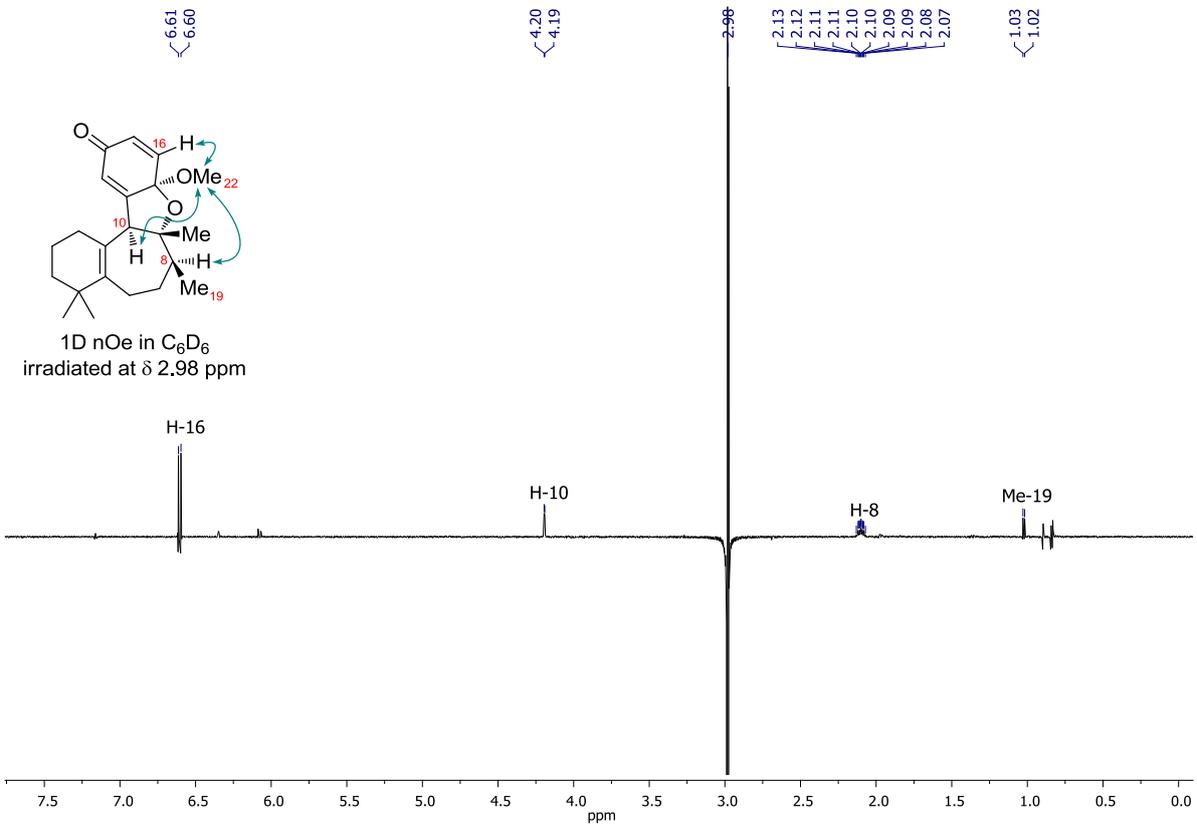
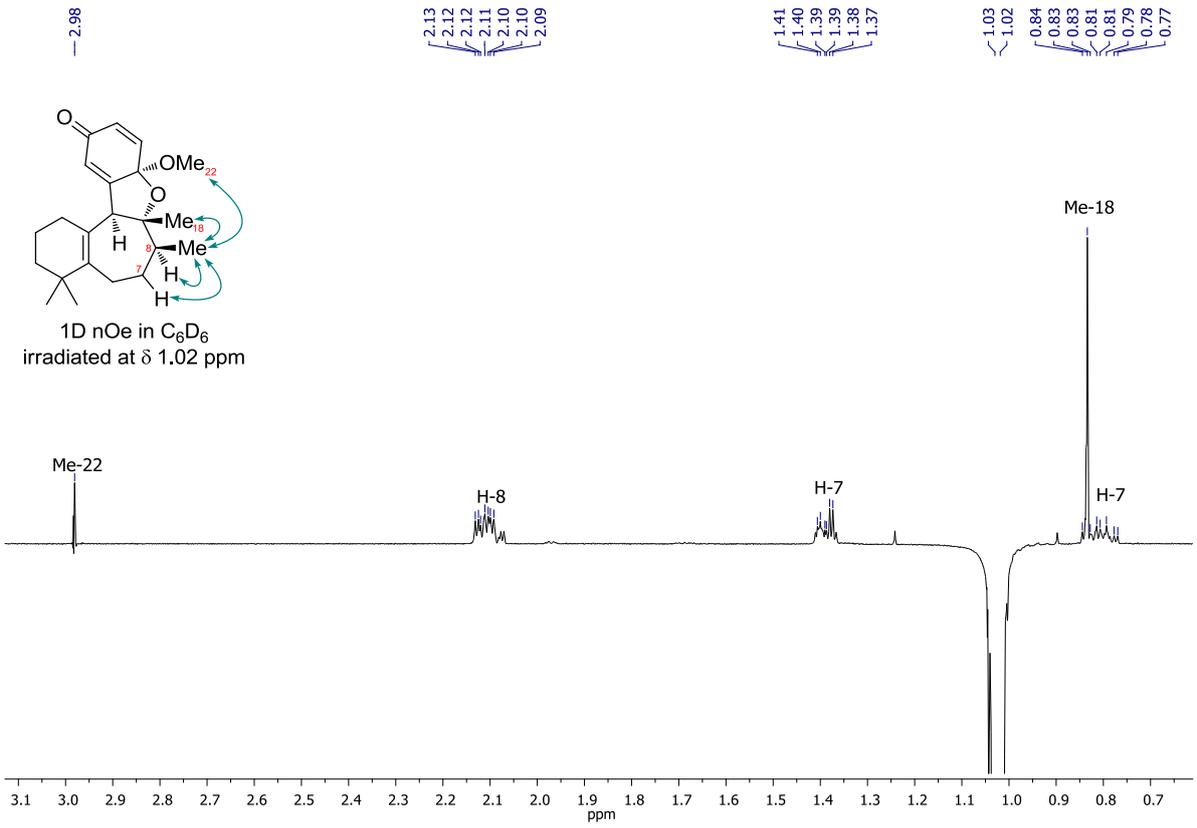


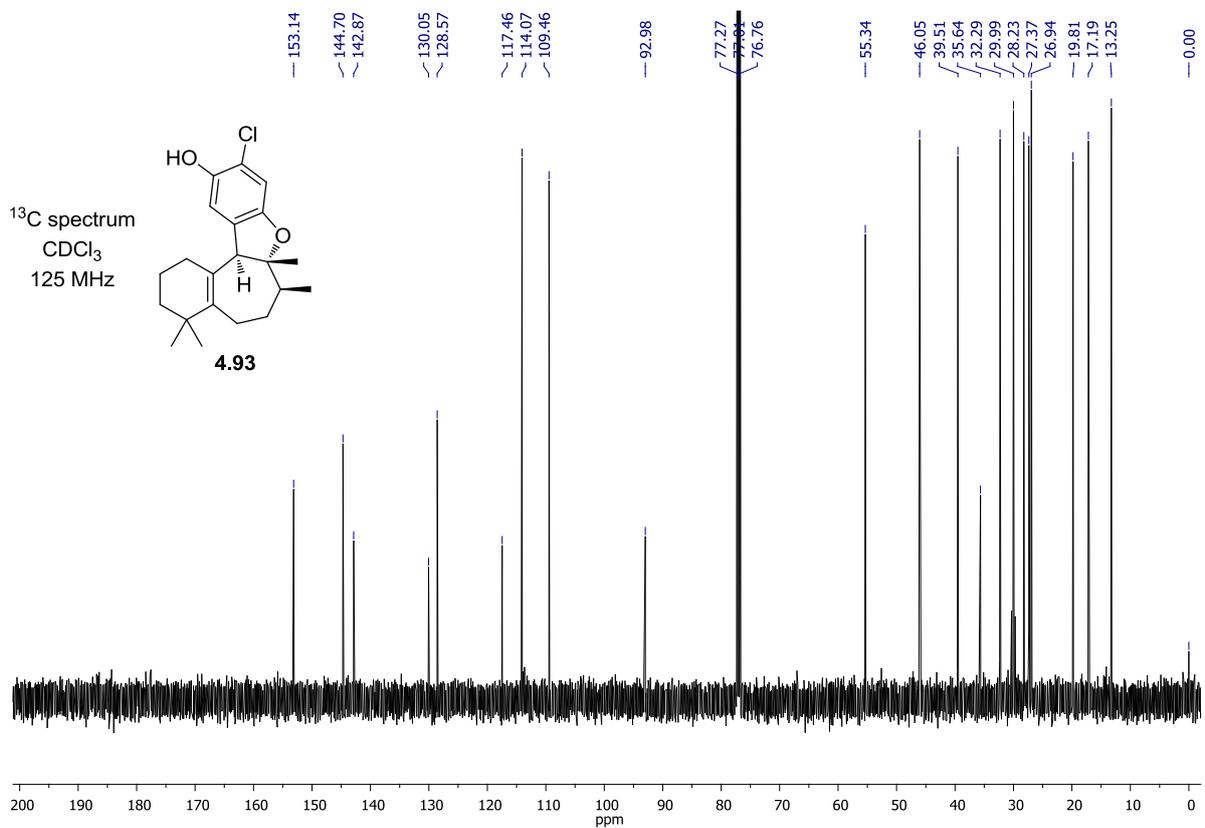
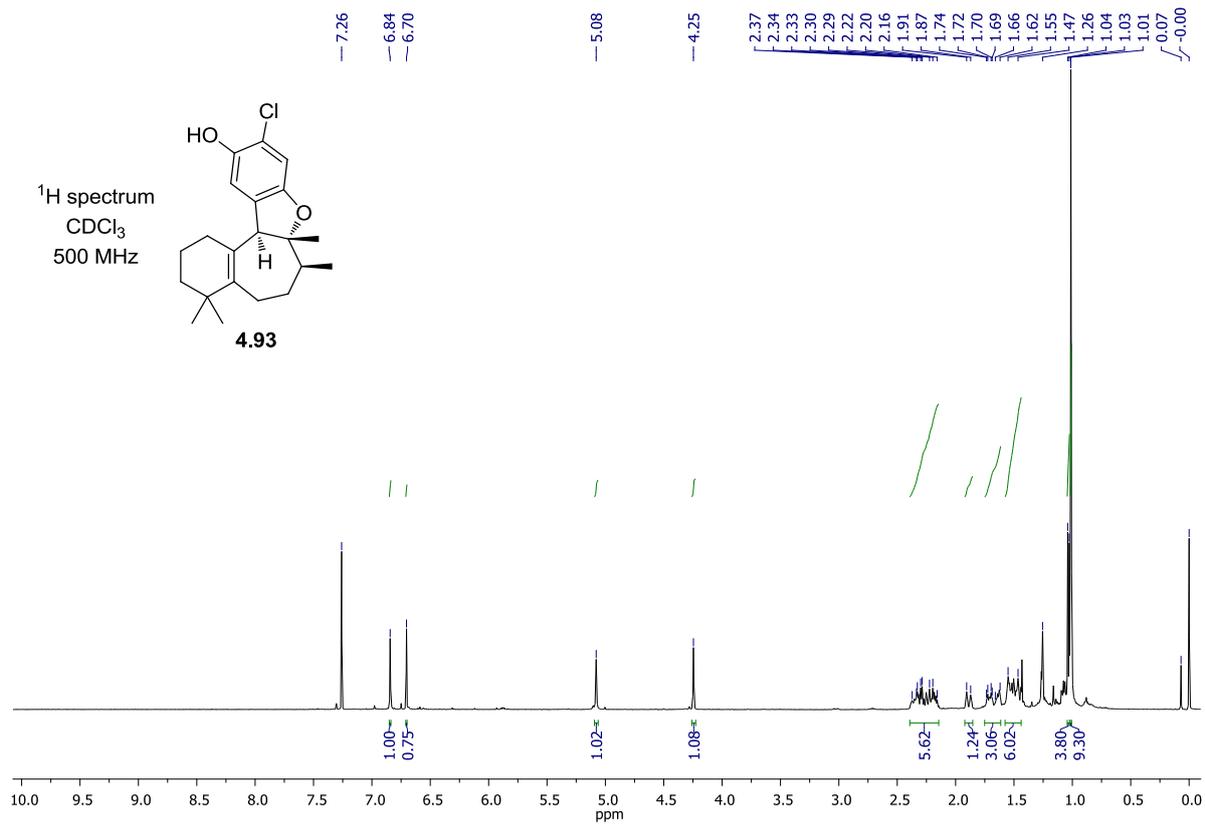












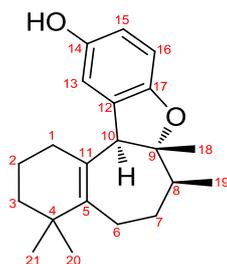


Table 4.4:  $^1\text{H}$  NMR assignment of cycloether **4.84**.

| Assignment              | 600 MHz, $\text{CDCl}_3$         | Assignment                    | 600 MHz, $\text{C}_6\text{D}_6$         |
|-------------------------|----------------------------------|-------------------------------|---|
| <b>H-16</b>             | 6.60 (d, $J = 8.4$ Hz, 1H)       | <b>H-16</b>                   | 6.73 (d, $J = 8.4$ Hz, 1H)              |
| <b>H-13</b>             | 6.69 (s, 1H)                     | <b>H-13</b>                   | 6.57 – 6.56 (m, 1H)                     |
| <b>H-15</b>             | 6.55 (dd, $J = 8.4, 2.5$ Hz, 1H) | <b>H-15</b>                   | 6.31 – 6.29 (dd, $J = 8.4, 1.8$ Hz, 1H) |
| <b>H-10</b>             | 4.28 (s, 1H)                     | <b>H-10</b>                   | 4.24 (s, 1H)                            |
| <b>14-OH</b>            | 4.43 (s, 1H)                     | <b>14-OH</b>                  | 3.71 (s, 1H)                            |
| <b>H-1a</b>             | 2.39 – 2.33 (m, 1H)              | <b>H-1a</b>                   | 2.30 – 2.24 (m, 1H)                     |
| <b>H-6a, H-6b</b>       | 2.32 – 2.24 (m, 2H)              | <b>H-8</b>                    | 2.13 – 2.08 (m, 1H)                     |
| <b>H-8</b>              | 2.21 – 2.17 (m, 1H)              | <b>H-3a, H-3b</b>             | 2.07 – 1.97 (m, 2H)                     |
| <b>H-1b</b>             | 1.93 – 1.90 (m, 1H)              | <b>H-1b</b>                   | 1.85 – 1.83 (m, 1H)                     |
| <b>H-7a</b>             | 1.73 – 1.68 (m, 1H)              | <b>H-2a</b>                   | 1.51 – 1.47 (m, 1H)                     |
| <b>H-2a</b>             | 1.65 – 1.60 (m, 1H)              | <b>H-2b, H-6a, H-6b, H-7a</b> | 1.43 – 1.37 (m, 4H)                     |
| <b>H-3a, H-3b, H-2b</b> | 1.54 – 1.42 (m, 3H)              | <b>Me-19</b>                  | 1.11 (d, $J = 6.7$ Hz, 3H)              |
| <b>Me-19</b>            | 1.04 (d, $J = 6.7$ Hz, 3H)       | <b>Me-18</b>                  | 1.02 (s, 3H)                            |
| <b>Me-18</b>            | 1.02 (s, 3H)                     | <b>Me-20</b>                  | 0.96 (s, 3H)                            |
| <b>Me-20</b>            | 1.016 (s, 3H)                    | <b>Me-21</b>                  | 0.90 (s, 3H)                            |
| <b>Me-21</b>            | 1.016 (s, 3H)                    | <b>H-7b</b>                   | 0.93 – 0.86 (overlapped m, 1H)          |
| <b>H-7b</b>             | 1.07 – 1.05 (overlapped m, 1H)   |                               |   |

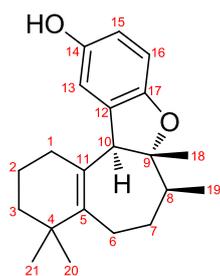


Table 4.5:  $^{13}\text{C}$  NMR assignment of cycloether **4.84**.

| Assignment | 150 MHz, $\text{CDCl}_3$ | 125 MHz, $\text{C}_6\text{D}_6$ |
|------------|--------------------------|---------------------------------|
| C-1        | 30.1                     | 30.4                            |
| C-2        | 19.8                     | 20.2                            |
| C-3        | 27.4                     | 27.6                            |
| C-4        | 35.6                     | 35.7                            |
| C-5        | 142.6                    | 142.3                           |
| C-6        | 39.6                     | 40.0                            |
| C-7        | 32.4                     | 32.6                            |
| C-8        | 46.1                     | 46.5                            |
| C-9        | 92.2                     | 92.0                            |
| C-10       | 55.6                     | 56.1                            |
| C-11       | 129.0                    | 129.8                           |
| C-12       | 130.6                    | 130.7                           |
| C-13       | 114.1                    | 114.4                           |
| C-14       | 153.2                    | 153.9                           |
| C-15       | 113.6                    | 114.1                           |
| C-16       | 109.6                    | 110.1                           |
| C-17       | 148.9                    | 150.0                           |
| C-18       | 13.3                     | 13.5                            |
| C-19       | 17.3                     | 17.5                            |
| C-20*      | 28.3                     | 28.4                            |
| C-21*      | 27.0                     | 27.1                            |

\* C-20/C-21 signals may be interchanged.

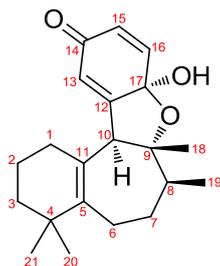


Table 4.6:  $^1\text{H}$  NMR assignment of cycloether **4.86**.

| Assignment              | 500 MHz, $\text{CDCl}_3$          |
|-------------------------|-----------------------------------|
| <b>H-16</b>             | 6.95 (d, $J = 10.0$ Hz, 1H)       |
| <b>H-13</b>             | 6.26 (dd, $J = 3.0, 1.5$ Hz, 1H)  |
| <b>H-15</b>             | 6.07 (dd, $J = 10.0, 1.5$ Hz, 1H) |
| <b>H-10</b>             | 4.39 (d, $J = 3.0$ Hz, 1H)        |
| <b>22-OH</b>            | 2.99 (br s, 1H)                   |
| <b>H-1a, H-3a, H-3b</b> | 2.32 – 2.25 (m, 3H)               |
| <b>H-1b, H-8</b>        | 2.18 – 2.12 (m, 2H)               |
| <b>H-2a, H-7a</b>       | 1.74 – 1.64 (m, 2H)               |
| <b>H-6a</b>             | 1.56 – 1.51 (m, 1H)               |
| <b>H-2b, H-6b</b>       | 1.47 – 1.40 (m, 2H)               |
| <b>H-7b</b>             | 1.01 – 0.99 (overlapped m, 1H)    |
| <b>Me-20, Me-21</b>     | 1.00 (s, 6H)                      |
| <b>Me-19</b>            | 0.98 (d, $J = 7.0$ Hz, 3H)        |
| <b>Me-18</b>            | 0.93 (s, 3H)                      |

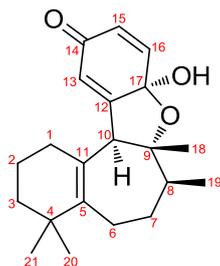


Table 4.7:  $^{13}\text{C}$  NMR assignment of cycloether **4.86**.

| Assignment | 125 MHz, $\text{CDCl}_3$ |
|------------|--------------------------|
| C-1        | 30.4                     |
| C-2        | 19.9                     |
| C-3        | 27.4                     |
| C-4        | 35.8                     |
| C-5        | 144.7                    |
| C-6        | 39.3                     |
| C-7        | 33.3                     |
| C-8        | 48.9                     |
| C-9        | 89.3                     |
| C-10       | 51.8                     |
| C-11       | 127.3                    |
| C-12       | 161.7                    |
| C-13       | 121.7                    |
| C-14       | 186.5                    |
| C-15       | 126.9                    |
| C-16       | 143.2                    |
| C-17       | 93.8                     |
| C-18       | 16.5                     |
| C-19       | 17.1                     |
| C-20*      | 28.5                     |
| C-21*      | 26.8                     |

\* C-20/C-21 signals may be interchanged.

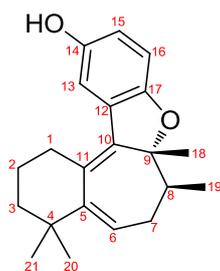


Table 4.8:  $^1\text{H}$  assignment of cycloether **4.88**.

| Assignment        | 600 MHz, $\text{CDCl}_3$          |
|-------------------|-----------------------------------|
| <b>H-13</b>       | 7.16 (d, $J = 2.5$ Hz, 1H)        |
| <b>H-15</b>       | 6.68 (d, $J = 8.4, 2.5$ Hz, 1H)   |
| <b>H-16</b>       | 6.65 (d, $J = 8.4$ Hz, 1H)        |
| <b>H-6</b>        | 5.87 (dd, $J = 8.2, 6.2$ Hz, 1H)  |
| <b>14-OH</b>      | 4.36 (s, 1H)                      |
| <b>H-1a</b>       | 3.07 (dt, $J = 15.0, 4.8$ Hz, 1H) |
| <b>H-8</b>        | 2.74 (dp, $J = 7.3, 1.7$ Hz, 1H)  |
| <b>H-1b</b>       | 2.30 – 2.25 (m, 1H)               |
| <b>H-7a</b>       | 2.23 – 2.19 (m, 1H)               |
| <b>H-2a, H-7b</b> | 1.79 – 1.73 (m, 2H)               |
| <b>H-2b</b>       | 1.70 – 1.65 (m, 1H)               |
| <b>H-3a, H-3b</b> | 1.52 – 1.46 (m, 2H)               |
| <b>Me-18</b>      | 1.27 (s, 3H)                      |
| <b>Me-20*</b>     | 1.16 (s, 3H)                      |
| <b>Me-19</b>      | 1.10 (d, $J = 7.3$ Hz, 3H)        |
| <b>Me-21*</b>     | 1.08 (s, 3H)                      |

\* Me-20/Me-21 signals may be interchanged.

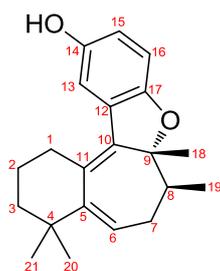


Table 4.9:  $^{13}\text{C}$  NMR assignment of cycloether **4.86**.

| Assignment | 150 MHz, $\text{CDCl}_3$ |
|------------|--------------------------|
| C-1        | 30.3                     |
| C-2        | 21.4                     |
| C-3        | 40.4                     |
| C-4        | 36.3                     |
| C-5        | 149.7                    |
| C-6        | 122.2                    |
| C-7        | 32.3                     |
| C-8        | 55.1                     |
| C-9        | 92.8                     |
| C-10       | 141.8                    |
| C-11       | 130.5                    |
| C-12       | 126.9                    |
| C-13       | 111.9                    |
| C-14       | 155.2                    |
| C-15       | 115.9                    |
| C-16       | 109.9                    |
| C-17       | 148.8                    |
| C-18       | 21.1                     |
| C-19       | 15.6                     |
| C-20*      | 29.2                     |
| C-21*      | 29.4                     |

\* C-20/C-21 signals may be interchanged.

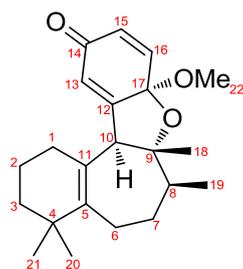


Table 4.10:  $^1\text{H}$  NMR assignment of hemiacetal **4.89**.

| Assignment              | 600 MHz, $\text{CDCl}_3$              | Assignment              | 600 MHz, $\text{C}_6\text{D}_6$   |
|-------------------------|---------------------------------------|-------------------------|-----------------------------------|
| <b>H-16</b>             | 6.92 (d, $J = 10.1$ Hz, 1H)           | <b>H-16</b>             | 6.60 (d, $J = 10.2$ Hz, 1H)       |
| <b>H-13</b>             | 6.33 – 6.31 (br m, 1H)                | <b>H-13</b>             | 6.35 (dd, $J = 2.7, 1.7$ Hz, 1H)  |
| <b>H-15</b>             | 6.19 (d, $J = 10.1$ Hz, 1H)           | <b>H-15</b>             | 6.07 (dd, $J = 10.2, 1.7$ Hz, 1H) |
| <b>H-10</b>             | 4.22 (d, $J = 2.3$ Hz, 1H)            | <b>H-10</b>             | 4.19 (d, $J = 2.7$ Hz, 1H)        |
| <b>OMe-22</b>           | 3.21 (s, 3H)                          | <b>OMe-22</b>           | 2.98 (s, 3H)                      |
| <b>H-1a, H-3a, H-3b</b> | 2.30 – 2.26 (m, 3H)                   | <b>H-8</b>              | 2.13 – 2.07 (m, 1H)               |
| <b>H-1b, H-8</b>        | 2.15 – 2.09 (m, 2H)                   | <b>H-3a, H-3b</b>       | 1.98 – 1.96 (m, 2H)               |
| <b>H-2a, H-7a</b>       | 1.73 – 1.64 (m, 2H)                   | <b>H-1a, H-1b</b>       | 1.91 – 1.81 (m, 2H)               |
| <b>H-6a</b>             | 1.54 – 1.52 (m, 1H)                   | <b>H-2a, H-6a, H-7a</b> | 1.41 – 1.34 (m, 3H)               |
| <b>H-2b, H-6b</b>       | 1.47 – 1.40 (m, 2H)                   | <b>H-2b, H-6b</b>       | 1.25 – 1.18 (m, 2H)               |
| <b>Me-19</b>            | 1.01 (overlapped d, $J = 6.7$ Hz, 3H) | <b>Me-19</b>            | 1.02 (d, $J = 6.7$ Hz, 3H)        |
| <b>Me-20</b>            | 1.00 (overlapped s, 3H)               | <b>Me-20</b>            | 0.89 (s, 3H)                      |
| <b>Me-21</b>            | 1.00 (overlapped s, 3H)               | <b>Me-21</b>            | 0.84 (s, 3H)                      |
| <b>Me-18</b>            | 0.95 (s, 3H)                          | <b>Me-18</b>            | 0.83 (s, 3H)                      |
| <b>H-7b</b>             | 1.03 – 0.95 (overlapped m, 1H)        | <b>H-7b</b>             | 0.83 – 0.77 (overlapped m, 1H)    |

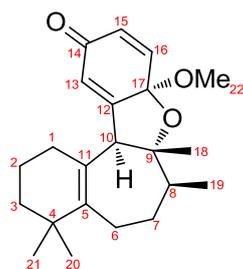


Table 4.11:  $^{13}\text{C}$  NMR assignment of hemiacetal **4.89**.

| Assignment | 150 MHz, $\text{CDCl}_3$ | 125 MHz, $\text{C}_6\text{D}_6$ |
|------------|--------------------------|---------------------------------|
| C-1        | 30.4                     | 30.3                            |
| C-2        | 19.9                     | 20.1                            |
| C-3        | 27.4                     | 27.6                            |
| C-4        | 35.8                     | 35.8                            |
| C-5        | 144.4                    | 143.8                           |
| C-6        | 39.3                     | 39.6                            |
| C-7        | 33.2                     | 33.4                            |
| C-8        | 48.4                     | 48.6                            |
| C-9        | 89.5                     | 89.1                            |
| C-10       | 51.8                     | 52.1                            |
| C-11       | 127.4                    | 128.4                           |
| C-12       | 160.4                    | 159.8                           |
| C-13       | 122.9                    | 123.2                           |
| C-14       | 186.2                    | 185.5                           |
| C-15       | 128.9                    | 129.2                           |
| C-16       | 140.8                    | 140.7                           |
| C-17       | 97.1                     | 97.5                            |
| C-18       | 16.7                     | 16.8                            |
| C-19       | 17.0                     | 17.2                            |
| C-20*      | 28.5                     | 28.6                            |
| C-21*      | 26.8                     | 26.9                            |
| C-22       | 50.0                     | 49.7                            |

\* C-20/C-21 signals may be interchanged.