

**Department of Chemistry**

**Chemistry of Clerodane Diterpenes Isolated from  
*Dodonaea* Species in Western Australia**

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This thesis is presented for the Degree of  
**Doctor of Philosophy**  
of  
**Curtin University**

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## **Declaration**

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any other university.

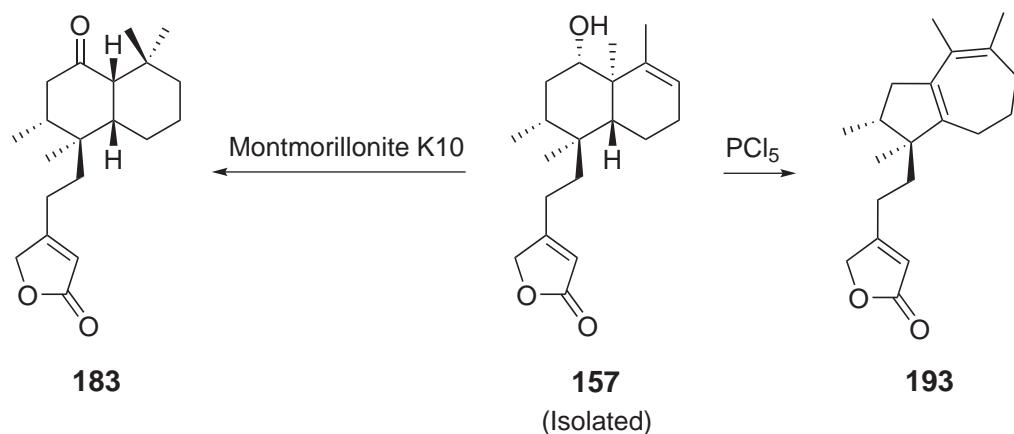
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## Abstract

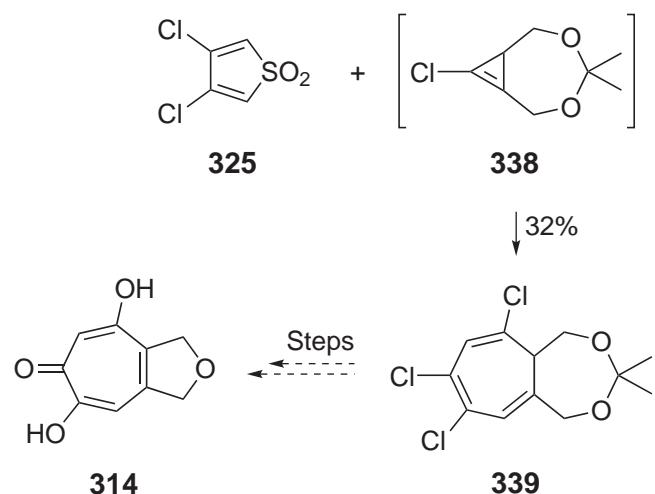
The genus *Dodonaea* is commonly found in Australia and is a good source of clerodane diterpenes. *D. viscosa* ssp. *angustissima* and *D. ceratocarpa* are two species growing in Western Australia that are yet to be thoroughly investigated. The compounds in the leaf resins of the two *Dodonaea* species grown in Balingup, WA were studied using a rapid extraction technique with diethyl ether. This solvent was effective in only isolating clerodanes within the leaf resin. Isolation and structural elucidation of the compounds found within the resins was accomplished. Three clerodane diterpenes were isolated from each plant, some were unreported compounds.

The leaf resin of *D. ceratocarpa* contained a new clerodane **157** which was isolated in an appreciable quantity (0.5% w/w plant). The chemistry of the major compound was made the focus of this work. All three rings were selectively functionalised to introduce complexity to the molecule. A variety of reactions were studied which provided a suite of new clerodanes. Oxidations, reductions, epoxidations and dihydroxylations were achieved. For example, acid-catalysed eliminations of the alcohol functional group caused different rearrangements of the clerodane structure **157** upon treatment with different acid sources. These rearrangements provided two new compounds, **183** and **193**.



Cordytopolone **314** is a natural product that was first isolated from the fungus *Cordyceps* in Thailand. Cordytopolone **314** was tested for its antimalarial properties and gave moderate inhibition against a *P. falciparum* strain *in vivo* ( $IC_{50} = 2.12 \mu\text{g/mL}$ ). A total synthesis of this unique molecule is yet to be achieved. A synthesis of **314** was planned using a thiophene-1,1-dioxide **325** and a cyclopropene **338** to form the cycloheptatriene

**339.** The reaction of **325** and **338** formed the key cycloheptatriene adduct **339** in 32% yield.



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## List of abbreviations

Ac	Acetyl
AD	Asymmetric dihydroxylation
ATR	Attenuated total reflectance
AIBN	Azobisisobutyronitrile
Bn	Benzyl
br	Broad
c	Concentration in g/mL
cat.	Catalytic/catalyst
CDCl <sub>3</sub>	Deuterated chloroform
COSY	Correlated spectroscopy
<i>m</i> -CPBA	<i>m</i> -Chloroperoxybenzoic acid
CSA	Camphorsulfonic acid
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dt	Doublet of triplets
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
DMAP	4-( <i>N,N</i> -Dimethylamino)pyridine
DMDO	Dimethyldioxirane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
EC <sub>50</sub>	Half maximal effective concentration
eq.	Equivalent(s)
EI	Electron ionisation
h	Hour(s)
HMBC	Heteronuclear multiple bond correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence

IBX	2-Iodoxybenzoic acid
IC <sub>50</sub>	Half maximal inhibitory concentration
IR	Infrared
<i>J</i>	Coupling constant
LDA	Lithium <i>N,N</i> -diisopropylamide
[M] <sup>+</sup>	Molecular ion
[M + H] <sup>+</sup>	Protonated molecular ion
<i>m/z</i>	Mass to charge ratio
m.p.	Melting point
MPO	4-Methoxypyridine <i>N</i> -oxide
NBS	<i>N</i> -Bromosuccinimide
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
NOE(SY)	Nuclear Overhauser effect (spectroscopy)
o/n	Overnight
PCC	Pyridinium chlorochromate
Ph	Phenyl
ppm	Parts per million
Py	Pyridine
q	Quartet
RT	Room temperature
s	Singlet
ssp.	Subspecies
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAHS	Tetrabutylammonium hydrogensulfate
TBS	<i>tert</i> -Butyldimethylsilyl
td	Triplet of doublets
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl

TLC	Thin layer chromatography
TMS	Trimethylsilyl
tt	Triplet of triplets
$\delta$	Chemical shift
$\nu$	Frequency
$\lambda$	Wavelength
$[\alpha]_D^T$	Specific rotation

# Chapter 1

## Clerodane Diterpenes

### 1.1. *Dodonaeas* as sources of diterpenes

Diterpenes are ubiquitous, structurally diverse compounds that are commonly found in plants.<sup>1,2</sup> The term "diterpene" can include diterpenoids, and this more broader meaning will be used throughout this thesis. They are formed in the chloroplasts via the mevalonate or deoxysylulose phosphate pathways.<sup>3</sup> Diterpenes are associated with plant resins and are usually isolated in a polyoxygenated form containing hydroxyl or keto groups.<sup>2</sup> Plants of the *Dodonaea* genus are good sources of diterpenes, particularly clerodane diterpenes.<sup>4</sup> *Dodonaea* is a genus of plant in the soapberry family Sapindaceae that is named after Dutch herbologist and physician Rembert Dodoens.<sup>5</sup> There are over 68 species that have been discovered, and most of these originate and grow in Australia.<sup>6</sup> All species in the *Dodonaea* genus are woody perennials that grow between 1-4 m in height.<sup>6</sup> Many have resinous exudates on their leaves, particularly Australian natives.<sup>4</sup> The most abundant species is *D. viscosa*, which has been well-studied by botanists and chemists. *D. viscosa* has been shown to be an excellent source of clerodane diterpenes.<sup>7</sup>

### 1.2. Clerodane diterpene biosynthesis

The general structure of a clerodane skeleton **1** is shown (Figure 1.1). Clerodanes **1** are structurally similar to labdane diterpenes **2** as they are derived from them, though they differ by the location of the methyl substituents. Labdananes **2** contain a geminal

dimethyl attached to C4, a methyl attached to C8 and one located on the decalin ring junction attached to C10. Conversely, clerodanes contain methyl substituents attached to C4, C5, C8 and C9. These methyl groups are formally assigned as C18, C19, C17 and C20. Clerodanes are named after the model compound clerodin **3**, a diterpene isolated from *Clerodendron infortunatum* by Banerjee.<sup>8</sup> The stereochemistry of clerodin was determined by X-ray crystallography.<sup>9,10</sup>

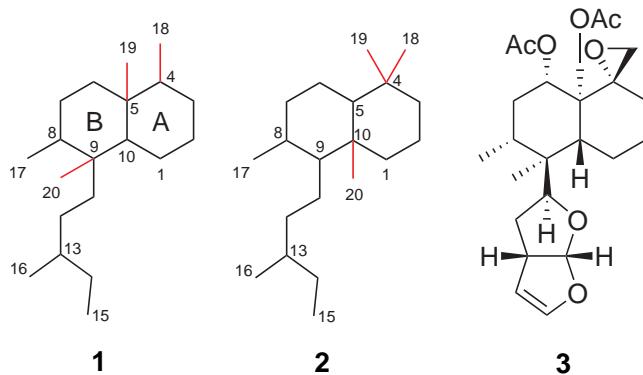


Figure 1.1: Structures of a general clerodane **1**, labdane **2** and clerodin **3**.

Many clerodanes in the literature refer to substituents having an  $\alpha$ - or  $\beta$ -orientation. The  $\alpha$ -face of a clerodane refers to the bottom face of the molecule positioned below the page, whilst the  $\beta$ -face refers to the top face of the molecule positioned above the page (Figure 1.2). An example is compound **4**, which has the H10 methine in a  $\beta$ -orientation, while the H19 methyl group has an  $\alpha$ -orientation. As all of the structures in this thesis are drawn in the same orientation, this terminology will be used.

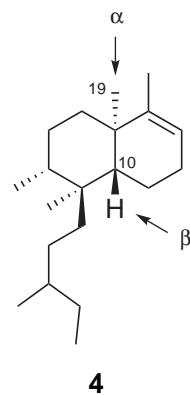


Figure 1.2: Definition of the  $\alpha$  and  $\beta$  bond orientations.

Approximately three-quarters of the clerodane diterpenes that have been identified have a *trans* relationship at the decalin ring junction.<sup>11</sup> This conformation is the most stable

and exhibits the least ring strain. The clerodane backbone has four stereocenters at the C5, C8, C9 and C10 positions. Tokoroyama has described the classification of clerodanes (Figure 1.3).<sup>11</sup> *Neo*-clerodanes have an  $\alpha$ -C20 methyl and  $\beta$ -C11, as well as a  $\beta$ -methine hydrogen at C10. *Ent-neo*-clerodanes have the opposite stereochemistry at these three positions. Four *neo*-clerodanes and another four *ent-neo*-clerodanes could exist. In addition to the *ent/ent-neo* classification applied to clerodanes, they can also be referred to as TC, TT, CC and CT types. The "C" and "T" stand for "*cis*" and "*trans*". The first letter defines the *cis/trans* relationship between H10 and the C19 methyl group (ring fusion positions). The second letter refers to the *cis/trans* relationship between the C17 and C20 methyl groups attached to the C8 and C9 positions, respectively. All eight types of clerodane have been isolated and/or synthesised.

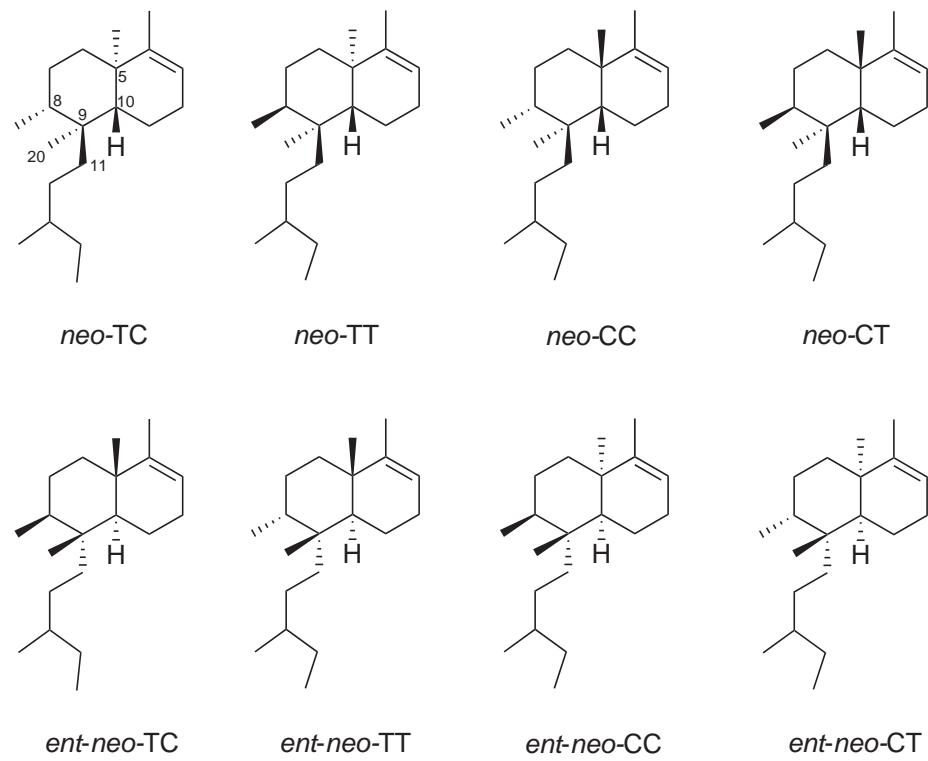
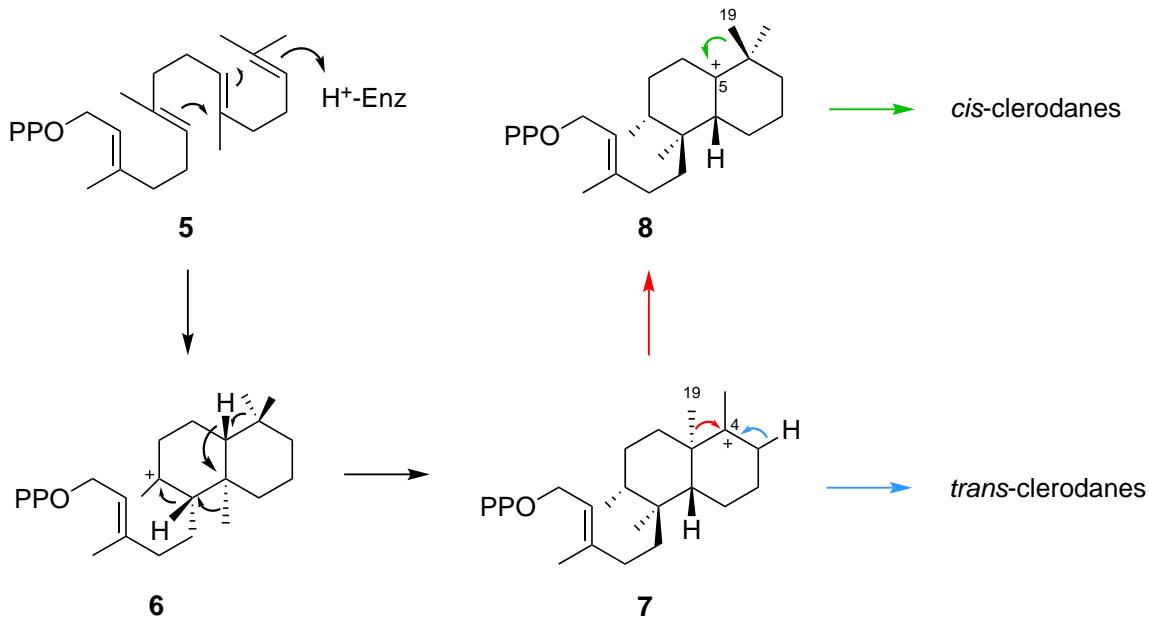


Figure 1.3: Stereochemical variety of clerodanes.

Clerodanes are derived from geranylgeranyl pyrophosphate (GGPP) **5**. Cyclisation of **5** gives a cyclised intermediate known as the labdadienyl cation **6**. Migration of two methyl groups in the carbocation **6** occurs to give the clerodane cation **7**. The carbocation **7** can lead to two different products. Elimination of H<sup>+</sup> (blue pathway) affords *trans*-clerodanes. Alternatively, a 1,2-methyl shift from C5 to C4 (red pathway) could give a clerodane cation **8**. A second 1,2-methyl shift from C4 to C5 within **8** (green pathway) could then provide a *cis*-clerodane (Scheme 1.1).<sup>11,12</sup>



Scheme 1.1: Biosynthesis of clerodanes via GGPP, adapted from Tokoroyama.<sup>11</sup>

### 1.3. Biological activity of clerodanes

The biological activities of the majority of clerodanes have not been reported, however, those that have been tested have shown interesting properties.<sup>13</sup> Clerodanes are widely recognized as insect antifeedants.<sup>14,15</sup> Additionally, some display anticholesterol, antibacterial, antitumoral, antiinflammatory and hallucinogenic properties.<sup>16</sup>

#### 1.3.1. Insect antifeedants

Insect antifeedants are chemicals that effectively deter insects from eating plants rather than directly killing them.<sup>17</sup> Numerous plants, particularly ones growing in Australia, have gradually evolved to increase their chemical defence mechanisms to the harsh environments they grow in as well as from predation from pests such as insects. Many

antifeedant compounds are bitter, which also renders them unpalatable to livestock and other herbivores.<sup>18</sup>

Ajugarin I **9** is a clerodane known widely for its insect antifeedant activity (Figure 1.4). It was first isolated from *Ajuga remota* in 1976,<sup>19</sup> and the total synthesis of **9** was first achieved seven years later by Ley *et al.*<sup>20</sup> Ajugarin I **9** is a powerful antifeedant against African armyworms (*Spodoptera exempta*), as well as Egyptian cotton leaf worms (*Spodoptera littoralis*).<sup>19</sup> Ley and colleagues completed a structure-activity study of **9** by synthesising analogues and modified natural products.<sup>21</sup> The essential structural requirements that made these compounds better antifeedants were the C4 epoxide and the two acetates attached to the C6 and C19 positions (red).<sup>18,21</sup> Other members of the ajugarin family demonstrate insect antifeedant activity, for example, ajugarin IV **10** which was also isolated from *Ajuga remota* (Figure 1.4).<sup>22</sup> Ajugarin IV **10** also exhibited moderate antifeedant activity against the silkworm *Bombyx mori*.<sup>22</sup>

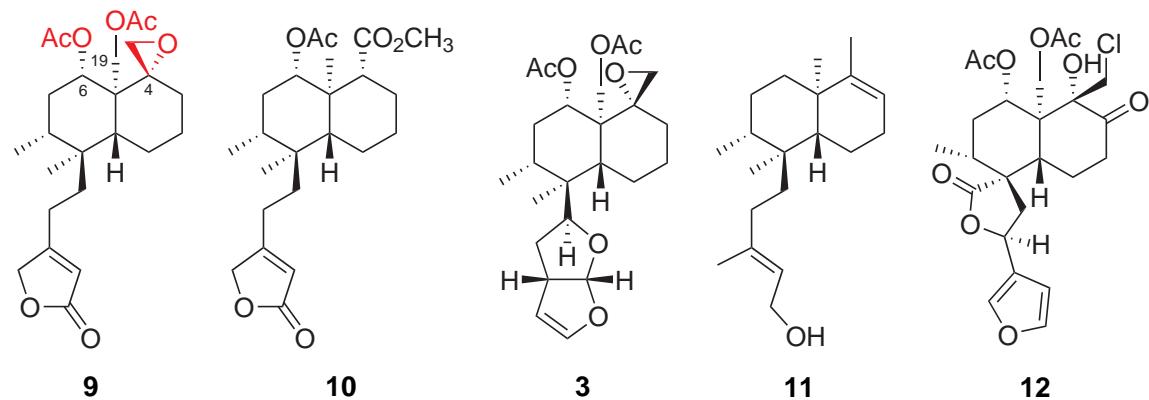


Figure 1.4: Structures of selected clerodane insect antifeedants.

Clerodin **3** is another clerodane which showed excellent insect antifeedant activity against *S. exempta*, *S. littoralis* and *S. frugiperda* (Figure 1.1).<sup>23</sup> Kolavenol **11** has also shown antifeedant activity and has been isolated from plants such as *Plazia daphnoides*,<sup>24</sup> *Solidago altissima*<sup>25</sup> and *Melampodium divaricatum*.<sup>26</sup> Howard and colleagues found that it prevented leaf cutter ants (*Atta cephalotes*) from feeding.<sup>27</sup> Tafricanin B **12** is also an effective insect antifeedant, which Hanson and co-workers determined was as active as clerodin **3** against migratory locusts (*Locusta migratoria*).<sup>28,29</sup>

### 1.3.2. HMG-CoA reductase inhibitors

Sashidhara and co-workers have shown that clerodanes **13** and **14** isolated from an active extract of *Polyalthia longifolia* var. *pendula* have comparable lipid-lowering properties to lovastatin **15** (Figure 1.5).<sup>30</sup> Lovastatin (Mevacor®) is a drug that inhibits HMG-CoA reductase, the enzyme responsible for producing isoprenoids such as cholesterol in the human body.<sup>31</sup> To prevent high serum cholesterol levels (hypercholesterolemia), the HMG-CoA reductase enzyme must be inhibited. Compound **15** was first discovered in 1978 by Alberts and colleagues at Merck Research Laboratories in a fermentation broth of *Aspergillus terreus*.<sup>32</sup> In 1987, **15** was released as the first HMG-CoA reductase inhibitor made available to the general public.<sup>33</sup>

The research presented by Sashidhara *et al.* was based on the lipid-lowering activity of high fat diet (HFD) hamsters in an *in vivo* model (Figure 1.6).<sup>30</sup> When the HFD hamsters were given a 25 mg/kg body weight dose of the hydroxylactone clerodane **13**, a 45% decrease in triglyceride was observed, though lovastatin **15** only afforded a 29% decrease. Compound **13** gave a 41% decrease of total cholesterol (TC), whereas **15** only reduced TC by 9%. Additionally, the HDL/TC ratio obtained with **13** was increased at 48%, whereas **15** only increased this ratio by 12%. At 100 µM, **13** had a maximum inhibition of 78% and an IC<sub>50</sub> of 30.2 µM, whilst **15** had an IC<sub>50</sub> of 20.1 µM.

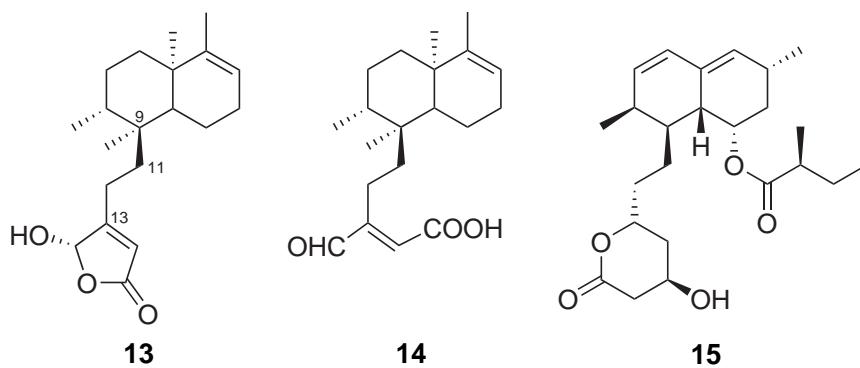


Figure 1.5: Structures of some lipid-lowering clerodanes and lovastatin.

Compound **14** is a ring-opened derivative of the hydroxylactone **13**. Interestingly, **14** was not as good as **13** overall. Compound **14** reduced triglyceride levels by 25%, which was slightly less than what **15** achieved. The ring-opened derivative **14** was better than lovastatin **15** in lowering TC with a 36% decrease. Lastly, **14** gave a HDL/TC ratio of +24%, which was not as good as **13** but better than lovastatin **15**.

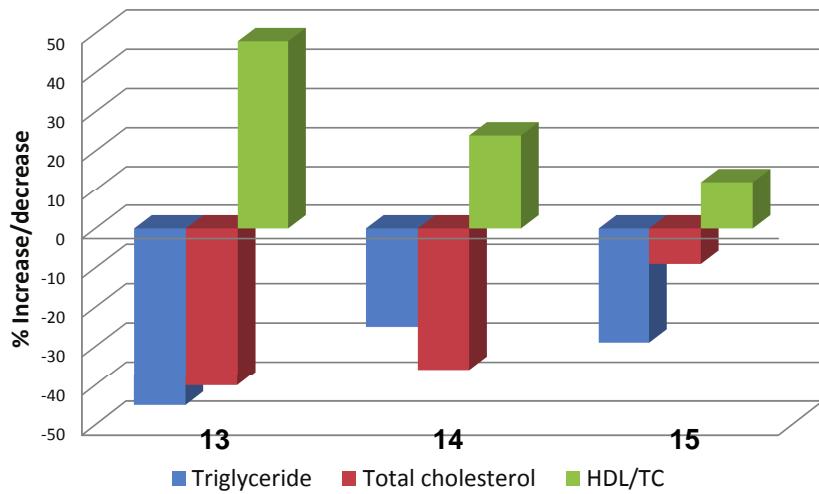
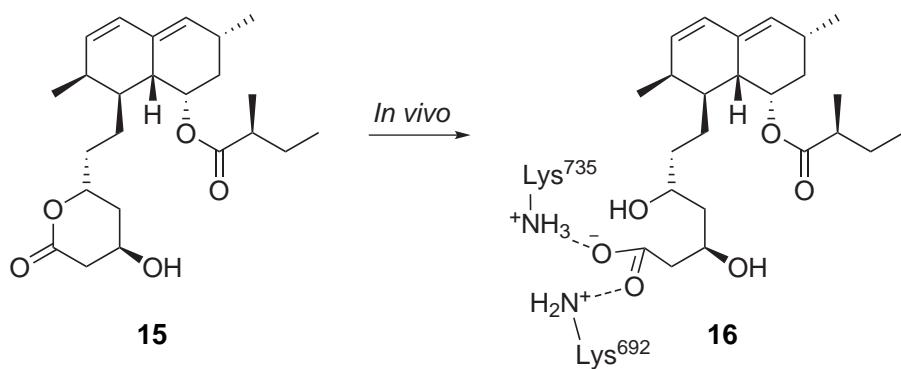


Figure 1.6: Lipid-lowering profile at 25 mg/kg body weight dose in HFD hamsters.<sup>30</sup>

Lovastatin **15** has some structural similarities to clerodanes, as they both contain a decalin core. Additionally, many clerodanes contain a  $\gamma$ -butyrolactone, whilst **15** has a  $\delta$ -valerolactone unit at the equivalent position. According to Jones, **15** is a prodrug because the lactone causes the drug to be in a less active/inactive form.<sup>33</sup> Once ingested, specific enzymes in the liver hydrolyse **15** to the  $\beta$ -hydroxyacid **16**, which is the active form of the drug (Scheme 1.2). The  $\beta$ -hydroxyacid portion of compound **16** mimics HMG-CoA.<sup>34</sup> Key interactions exist between the carboxylate within **16** and the lys692 and lys735 residues of HMG-CoA reductase.<sup>35</sup> This mode of action could explain why compound **14** has activity.

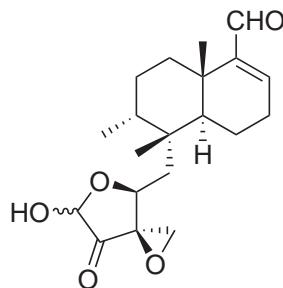


Scheme 1.2: Hydrolysis of lovastatin **15** by enzymes in the liver to form the  $\beta$ -hydroxyacid **16**.

### 1.3.3. Antibacterials

Many clerodanes have demonstrated good antibacterial activity. An example is clerocidin **17**, which was isolated from a number of strains of *Oidiodendron truncatum* (Table 1.1).<sup>36–38</sup> Compound **17** was tested for potential antibacterial activity via the standard agar dilution and broth dilution assays, and the zones of inhibition against an array of bacteria were noted. Clerocidin **17** demonstrated excellent activity against both Gram-negative and Gram-positive bacteria with minimum inhibitory concentrations (MICs) in the microgram range, though some were effective below 1 µg/mL (Table 1.1).<sup>36</sup> This compound was later determined to inhibit bacterial DNA gyrase, which is the target of many effective antibiotics.<sup>39</sup>

Table 1.1: *In vitro* antibacterial activities of some bacteria treated with clerocidin **17**.

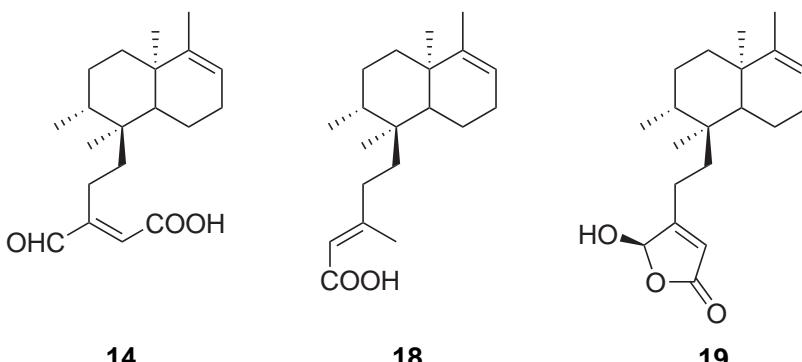


**17**

Bacteria	MIC (µg/mL)
<i>Staphylococcus aureus</i>	0.1
<i>Streptococcus pyogenes</i>	0.1
<i>Bacillus subtilis</i>	0.1
<i>Mycobacterium phlei</i>	1
<i>Escherichia coli</i>	3

Many more clerodanes were found to exhibit good antibacterial activity. Three clerodanes **14**, **18** and **19** were isolated from *Polyalthia longifolia* var. *pendulla* and were tested against a range of Gram-negative and Gram-positive bacteria (Table 1.2).<sup>40</sup> When compared to the known antibacterial kanamycin **20**, all three clerodanes gave good inhibition, particularly **14**. The aldehyde-carboxylic acid clerodane **14** gave the best zone of inhibition data against five out of seven of the Gram-positive bacteria tested (12.00–20.66 mm in a 30 µg/disk).

Table 1.2: *In vitro* antibacterial zones of inhibition of some bacteria treated with three clerodanes.<sup>40</sup>



Bacteria	Zone of inhibition diameters (mm)			
	14*	18*	19*	20†
<i>Streptococcus β-haemolyticus</i>	22.33	10.33	18.33	19.33
<i>Bacillus cereus</i>	14.00	11.33	14.66	14.00
<i>Shigella dysenteriae</i>	16.66	10.33	14.66	15.33
<i>Salmonella typhi A</i>	19.33	11.00	14.33	19.00
<i>Salmonella typhi B-62</i>	21.33	10.00	18.66	18.00

\* 100 µg/disk dose, † 30 µg kanamycin 20/disk dose.

### 1.3.4. Antitumorals

Dysidiolide **21** is a sesterterpene with a clerodane skeleton that was isolated in 1996 from a Caribbean marine sponge *Dysidea etheria* de Laubenfels (Figure 1.7).<sup>41</sup> Compound **21** is an antitumoral agent, as it exhibited good activity against P388 murine leukemia cancer cells ( $IC_{50}$  1.5 µM) and A-549 human lung carcinoma cells ( $IC_{50}$  4.7 µM) by inhibiting the cdc25A protein phosphatase enzyme.<sup>42</sup>

Compound **22** is a clerodane that contains a γ-hydroxybutenolide (Figure 1.7). It was isolated from *Polyalthia longifolia* var. *pendula* and its cytotoxicity was tested against MDA-MB-231 (human breast adenocarcinoma), HepG2 and Hep3B (hepatocellular carcinoma) cancer cell lines.<sup>43</sup> Compound **22** gave  $IC_{50}$  values of 2.88-4.50 µg/mL, which were good when compared to other clerodane compounds that were tested in the study. Although these preliminary results were promising, the  $IC_{50}$  values were not as significant as those obtained from the reference compound doxorubicin (chemotherapeutic).

Columbin **23** was isolated from the roots of *Calumbae radix* (Figure 1.7).<sup>44</sup> This compound was found to moderately inhibit rat colonic carcinoma cells in an

azoxymethane (AOM)-induced rat colon tumorigenesis study.<sup>45</sup> Rats that had AOM-induced colon tumorigenesis (control) had an 85% incidence of neoplasms in the entire intestine, whilst rats with AOM given a 100 ppm dose of **23** were found to have a 40% incidence of neoplasms.

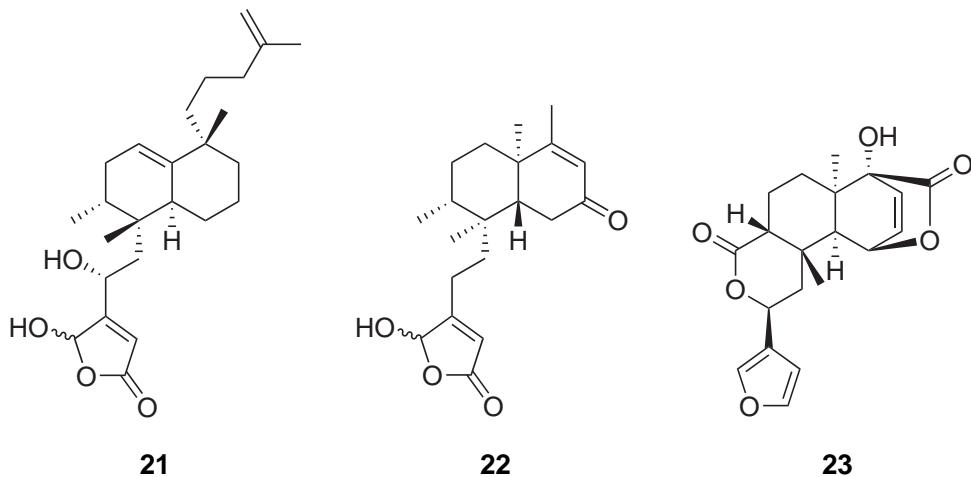


Figure 1.7: Structures of some antitumoral clerodanes.

### 1.3.5. Antiinflammatories

*Trans*-clerodanes have been isolated from *Dodonaea polyandra* Merr. & L.M.Perry grown in Queensland, Australia (Figure 1.8).<sup>46,47</sup> The plant has been used by indigenous Australians in Queensland as an antiinflammatory to treat toothaches.<sup>48</sup> In 2011, the active constituents of *D. polyandra* were determined to be four clerodanes containing a benzoate ester **24**, **25**, **26** and **27**. One of these compounds, later termed polyandric acid A **24**, was the most potent out of the four isolated. When tested in a tetradecanoylphorbol acetate (TPA)-induced mouse ear edema model, polyandric acid A **24** exhibited a maximum inhibition of  $70.2\% \pm 10.0\%$  at a dose of  $0.91 \mu\text{mol}$  *in vivo*. This was comparable to a control antiinflammatory drug betamethasone dipropionate (90% inhibition at  $0.90 \mu\text{mol}$ ).<sup>46</sup>

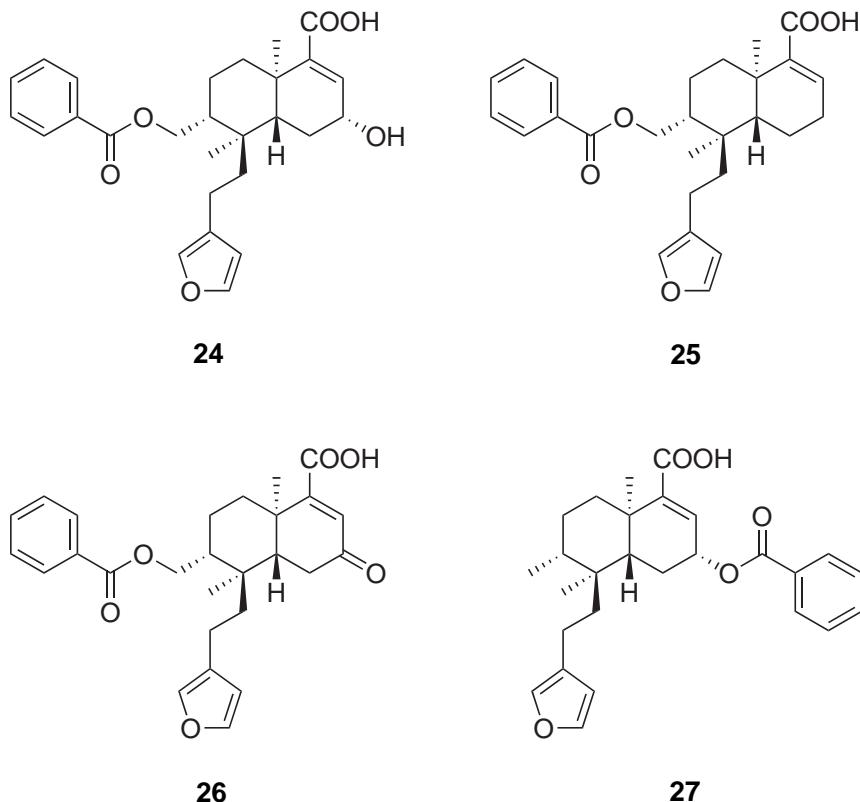


Figure 1.8: Structures of four polyandric acids isolated from *Dodonaea polyandra*.<sup>46</sup>

Hautriwaic acid **28** is a clerodane isolated from *Dodonaea viscosa* found to have antiinflammatory activity (Figure 1.9). Compound **28** was tested in a TPA-induced mouse ear edema model like that described above and demonstrated a  $87.1 \pm 6.4\%$  inhibition of edema at a dose of 1.0 mg/ear.<sup>49</sup> This result was equivalent to the value obtained when indomethacin, a known antiinflammatory, was used for comparative purposes ( $86.0 \pm 6.4\%$  at 1.0 mg/ear).

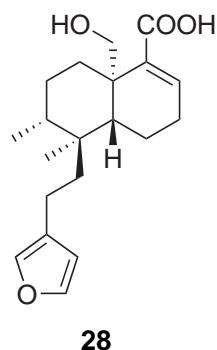


Figure 1.9: Structure of hautriwaic acid **28**.

### 1.3.6. Hallucinogens

Salvinorin A **29** is a hallucinogenic *trans*-clerodane isolated from the psychoactive sage *Salvia divinorum*.<sup>50</sup> The leaves have been used for medical and ritual purposes by the indigenous Mazatecs of Mexico.<sup>51</sup> Due to the psychedelic potency of the plant and the isolated compound **29**, both were banned in Australia in 2003.<sup>52</sup> The increased recreational use of the plant and isolated substance has led to more countries restricting their availability.<sup>53</sup> Salvinorin A **29** is a selective  $\kappa$ -opioid receptor antagonist.<sup>54</sup> When vaporised and inhaled, it has shown activity at a dose as low as 200  $\mu\text{g}$ .<sup>55</sup> Interestingly, unlike many other compounds acting on the  $\kappa$ -opioid receptor, **29** is distinct as it is not an alkaloid.

Since the isolation of **29**, other clerodanes with similar properties have been isolated and synthesised. Salvinicins A and B **30** and **31** were also isolated from *S. divinorum*.<sup>56</sup> Salvinicin A **30** has partial  $\kappa$ -opioid receptor agonist activity, with an EC<sub>50</sub> of  $4.1 \pm 0.6 \mu\text{M}$ . On the contrary, salvinicin B **31** was determined to be the first clerodane to demonstrate  $\mu$ -opioid antagonist activity, having a inhibition constant ( $K_i$ )  $> 1.9 \mu\text{M}$ .

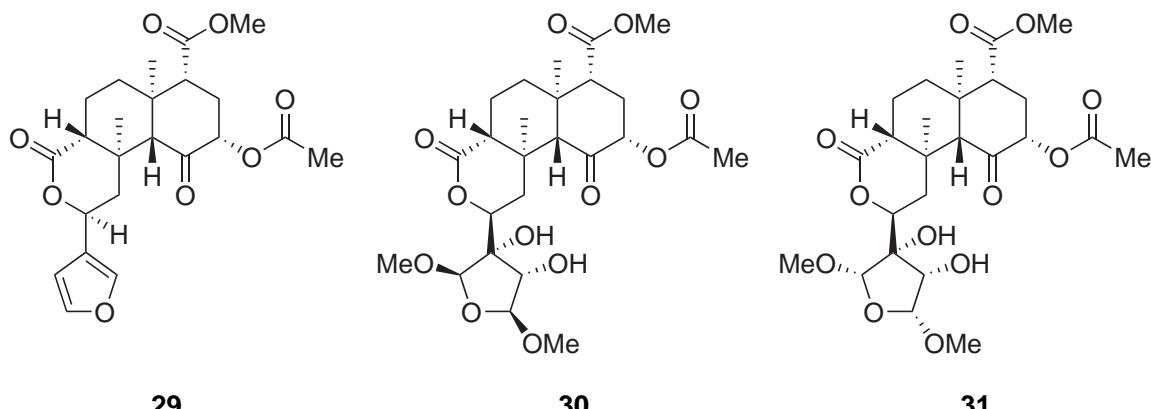


Figure 1.10: Structures of some hallucinogenic clerodanes.

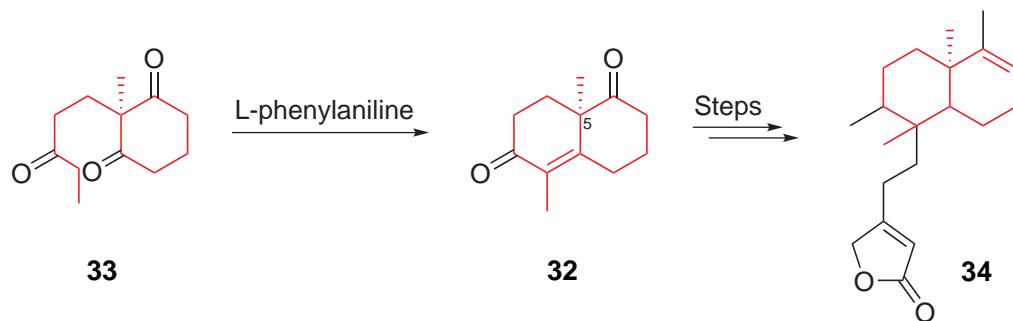
## 1.4. Total synthesis of clerodanes

The biological activity associated with clerodanes have made them attractive targets to synthetic chemists. The structural complexity of these compounds is also a factor that inspires synthetic chemists to pursue clerodanes in total synthesis. The total synthesis of clerodanes is challenging, and this is partly because of the prominence of epoxides, lactones and furan groups which can be sensitive under either acidic or basic conditions.

The most challenging aspect is obtaining the correct stereochemistry around the decalin ring. There are two general methods of synthesising clerodanes: the first starts with either a Wieland-Miescher ketone or a cyclohexanone derivative, the second uses an intermolecular Diels-Alder reaction to form the decalin ring.

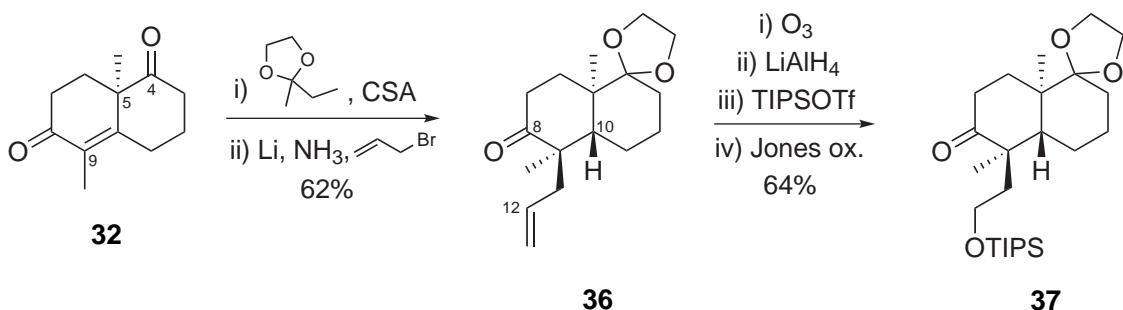
#### 1.4.1. Syntheses starting from a Wieland-Miescher ketone

The Wieland-Miescher ketone **32** is a good starting material as it contains the decalin ring and a methyl group at the correct ring junction position (C5) required for clerodanes. The enantiopure Wieland-Miescher ketone **32** can be prepared by treating the triketone compound **33** with L-phenylalaniline (Scheme 1.3).<sup>57–59</sup> Compound **32** provides the backbone of a clerodane **34**, as highlighted.



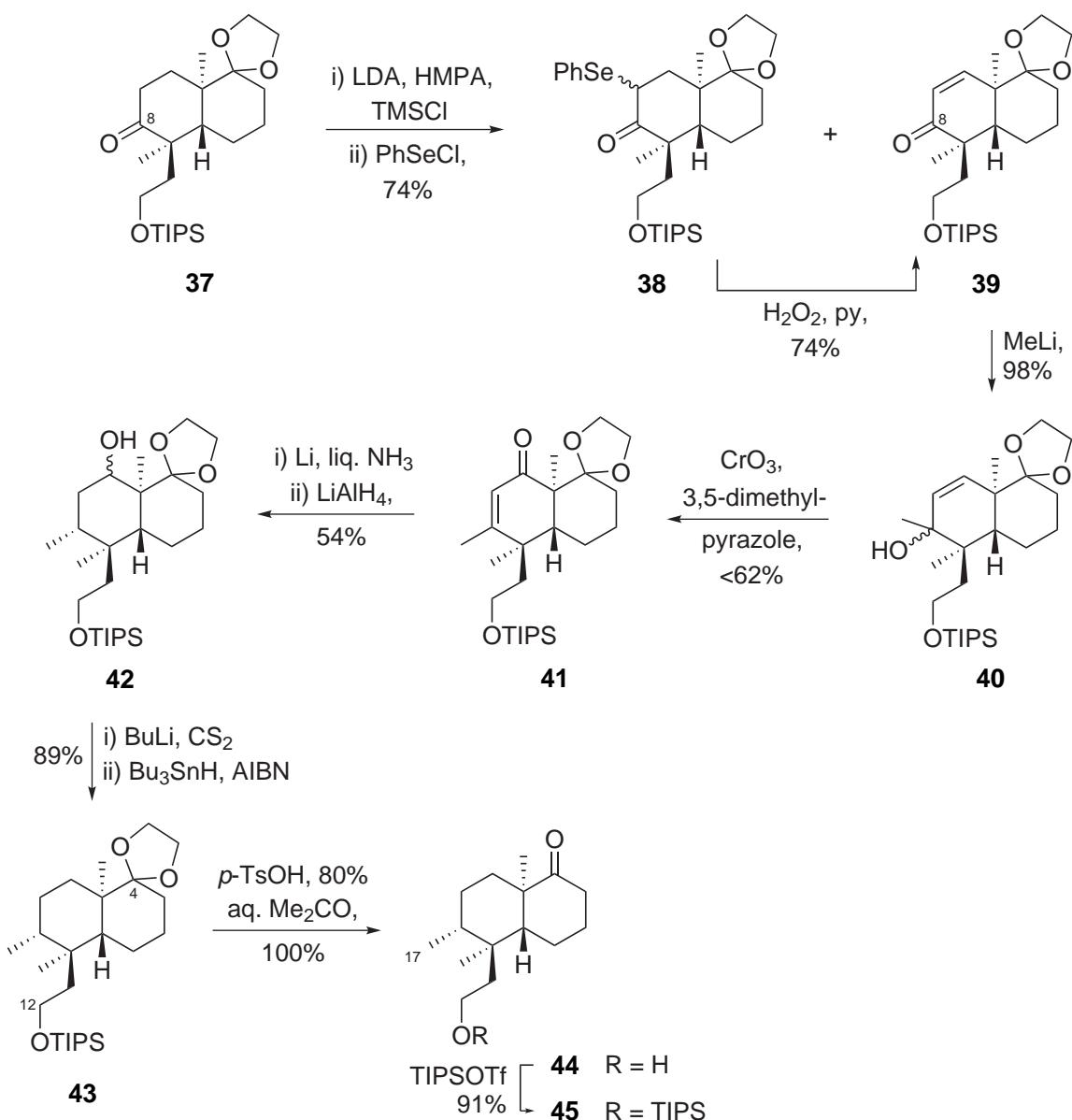
Scheme 1.3: Clerodane synthesis starting with a Wieland-Miescher ketone.

A Wieland-Miescher ketone precursor was used by Hagiwara *et al.* in the total synthesis of an antibacterial clerodane **35** (Scheme 1.4).<sup>58,60</sup> After protection of the C4 ketone within **32**, the key step was the reductive allylation of the enone. The stereochemistry of the product **36** was mostly governed by the  $\alpha$ -methyl group at C5, because the *trans*-decalin bridge product is more favoured than the *cis* counterpart. Compound **36** now had the correct stereochemistry at the C5, C9 and C10 positions. Ozonolysis of the alkene followed by several functional group transformations gave **37**.



Scheme 1.4: First part of Hagiwara's total synthesis of a clerodane via a Wieland-Miescher ketone **32**.<sup>60</sup>

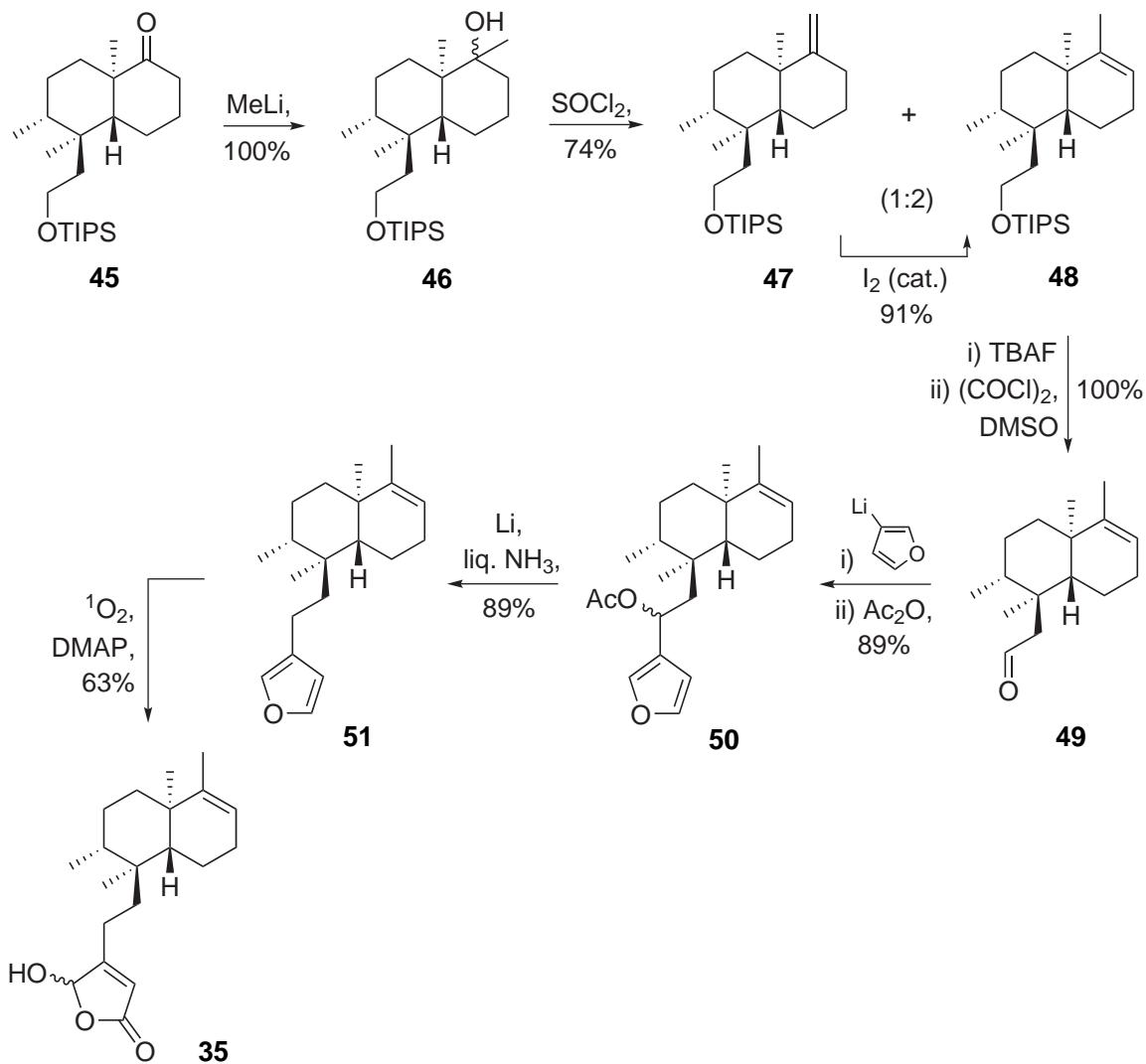
Introduction of the last methyl group at C8 with the correct stereochemistry was achieved from the ketone **37** in six steps. Compound **37** was treated with LDA and TMSCl to form the silyl enol ether, which was converted to the selenide **38** with phenylselenyl chloride. Oxidative elimination of **38** with hydrogen peroxide gave the enone **39**. Addition of methylolithium to the enone afforded the allylic alcohol **40**. This subsequently underwent an oxidative rearrangement upon treatment with chromium trioxide and 3,5-dimethylpyrazole to yield a new enone **41**. To obtain the correct stereocenter at C8, the alkene was reduced with lithium metal in liquid ammonia. The least hindered face was hydrogenated to yield the  $\alpha$ -methyl decalone with good selectivity over the  $\beta$ -product (9:1). Now that the four asymmetric centers of the clerodane skeleton were established, the  $\alpha$ -methyl decalone was reduced with lithium aluminium hydride to produce the alcohol **42** as a mixture of epimers. Following a Barton-McCombie deoxygenation protocol,<sup>61</sup> the alcohol was then converted to the xanthate and removed to give the deoxygenated product **43**. Deprotection of the acetal at C4 with *p*-TsOH yielded the ketone **44** which also removed the TIPS protecting group at C12. The alcohol was reprotected upon treatment of **44** with TIPSOTf to yield **45**.



Scheme 1.5: Second part of Hagiwara's total synthesis of a clerodane via a Wieland-Miescher ketone.<sup>60</sup>

Treatment of **45** with methylolithium afforded a diastereometric mixture of the alcohols **46** (4:1). Dehydration of the newly formed alcohol with thionyl chloride formed a mixture of alkenes: the exocyclic alkene **47** and the cyclic alkene **48** in a 1:2 ratio, respectively. The mixture of alkenes **47** and **48** was treated with catalytic iodine in xylene to exclusively provide **48**. Deprotection of the TIPS ether followed by Swern oxidation of the alcohol gave the aldehyde **49**. The addition of 3-furyllithium to **49** gave an epimeric mixture of the furan alcohol, which was then acetylated to yield **50**. To form the basic clerodane skeleton, reductive elimination of the acetate with lithium and liquid ammonia afforded

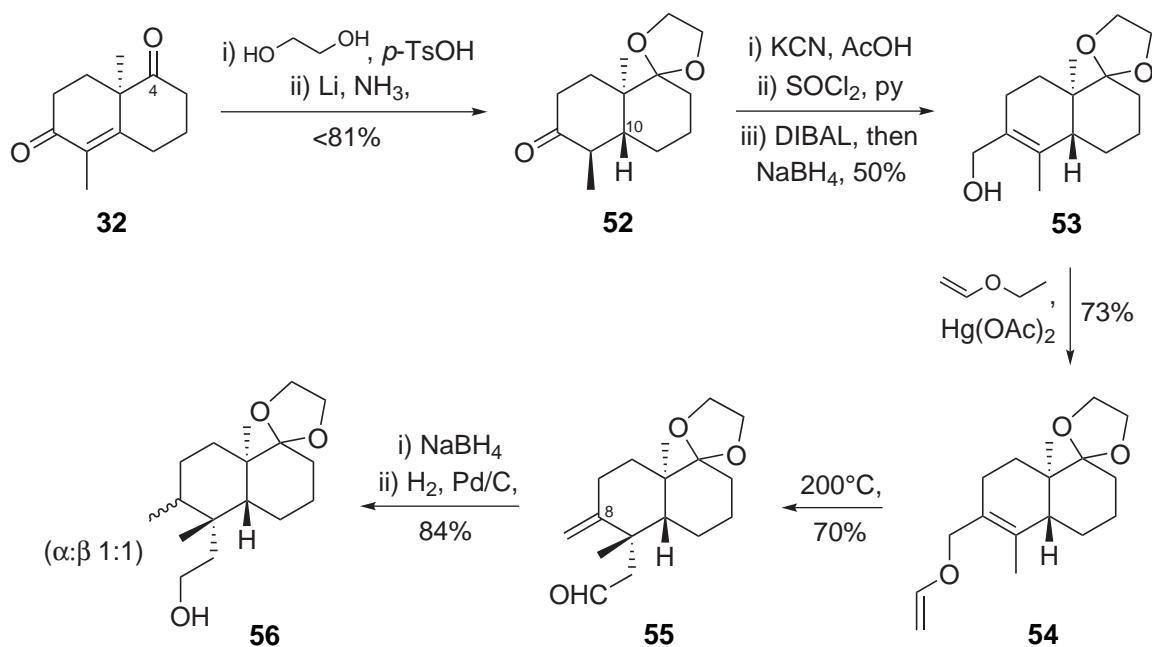
**51.** The target compound **35** in Hagiwara's total synthesis was formed by photochemical oxidation of the furan **51** with oxygen, a photosensitiser (Rose Bengal) and a light source. These reaction conditions produce singlet oxygen which added to the furan in a [4+2] cycloaddition reaction to give an ozonide. The ozonide was cleaved with DMAP to yield the hydroxylactone **35** as a mixture of diastereoisomers.



Scheme 1.6: Final stages of Hagiwara's total synthesis of the antibacterial clerodane **35**.<sup>60</sup>

Like the previous synthesis, Xiang and co-workers started with a Wieland-Miescher ketone **32** in the total synthesis of the antibacterial clerocidin **17** (Scheme 1.7).<sup>60,62</sup> The C4 ketone in **32** was protected and the enone was reduced under Birch conditions to provide **52** with a *trans*-ring junction.<sup>63</sup> Following the Kakisawa method, potassium cyanide was added to **52** to form the cyanohydrin, which was then dehydrated with thionyl chloride to give the  $\alpha,\beta$ -unsaturated nitrile.<sup>63</sup> The  $\alpha,\beta$ -unsaturated nitrile was converted to

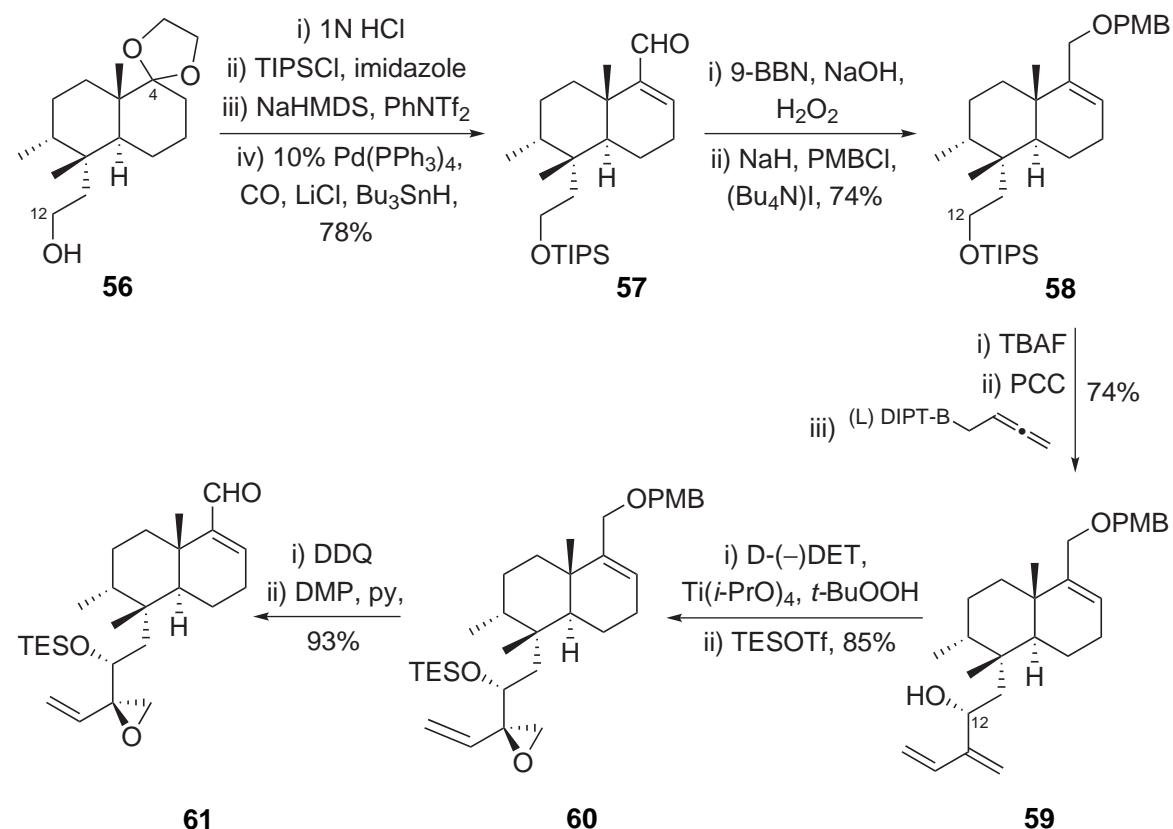
an allyl alcohol **53** by a two-step reduction. Treatment of **53** with ethyl vinyl ether and mercury acetate yielded the vinyl ether **54**. This was then heated in decalin at 200°C to enable a Claisen rearrangement. The aldehyde **55** was formed with high stereoselectivity (85%) based upon the integration ratio from the <sup>1</sup>H NMR spectrum of the crude product (70% isolated yield). Reduction of the aldehyde **55** with sodium borohydride gave the alcohol. The exocyclic alkene at C8 within this product was then hydrogenated with H<sub>2</sub> and Pd/C to afford a 1:1 mixture of the  $\alpha$ -methyl compound **56** and the  $\beta$ -methyl compound.



Scheme 1.7: Synthesis of the clerodane precursor for Xiang's total synthesis of clerocidin **17**.<sup>62,63</sup>

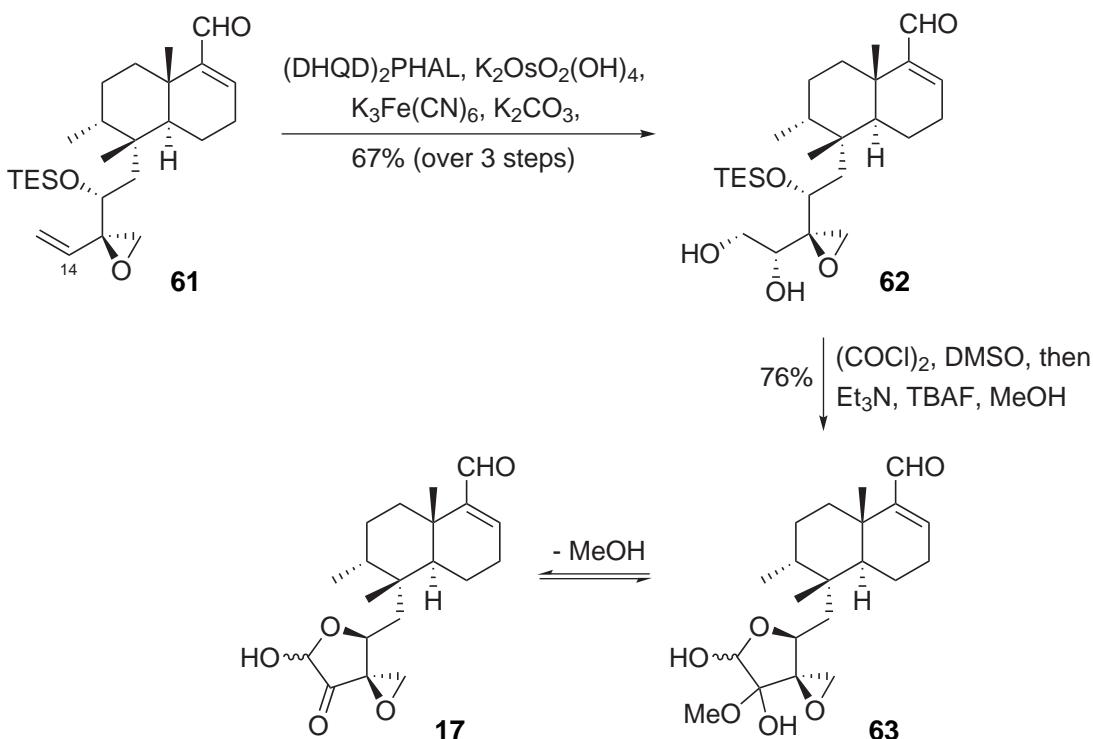
Upon obtaining **56**, the acetal at C4 was deprotected with hydrochloric acid and the C12 alcohol was protected with TIPS. The enol triflate was formed upon addition of sodium bis(trimethylsilyl)amide (NaHMDS) and *N*-phenyl-bis(trifluoromethanesulfonamide) (PhNTf<sub>2</sub>). The enol triflate was converted to the  $\alpha,\beta$ -unsaturated aldehyde **57** with carbon monoxide, tributyltin hydride and tetrakis(triphenylphosphine)palladium(0), inspired by the work of Stille.<sup>64</sup> Reduction of the aldehyde in **57** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by protection of the alcohol provided the *p*-methoxybenzyl (PMB) ether **58**. Deprotection of the silyl ether with TBAF and oxidation with PCC gave the C12 aldehyde. The next step towards the synthesis of clerocidin **17** used Brown's asymmetric homoallenylboration protocol to give compound **59**.<sup>65</sup> This was a key step in

the synthesis as it enabled construction of the third ring attached to C12 with the correct stereochemistry. This outcome was dictated by the chiral substituent on the boronate ester. Sharpless asymmetric epoxidation of **59** with D-(–)-diethyl tartrate (D-(–)-DET) yielded the secondary alcohol, which was then protected with the TES group to provide **60**. This compound was treated with DDQ followed by Dess-Martin periodinane to afford the deprotected  $\alpha,\beta$ -unsaturated aldehyde **61**.



Scheme 1.8: Part of Xiang's total synthesis of clerocidin **17**.<sup>62</sup>

The last few steps towards the total synthesis of clerocidin involved a Sharpless asymmetric dihydroxylation of the terminal alkene at C14 **61** to give the diol **62**. Swern oxidation of the diol **62**, removal of the TES group and subsequent addition of methanol afforded the methanol adduct of clerocidin **63**. Since this product existed in an equilibrium with clerocidin **17**, conversion of **63** to the target compound **17** was achieved upon removal of the solvent. The overall yield of **17** from **56** was 0.19%.



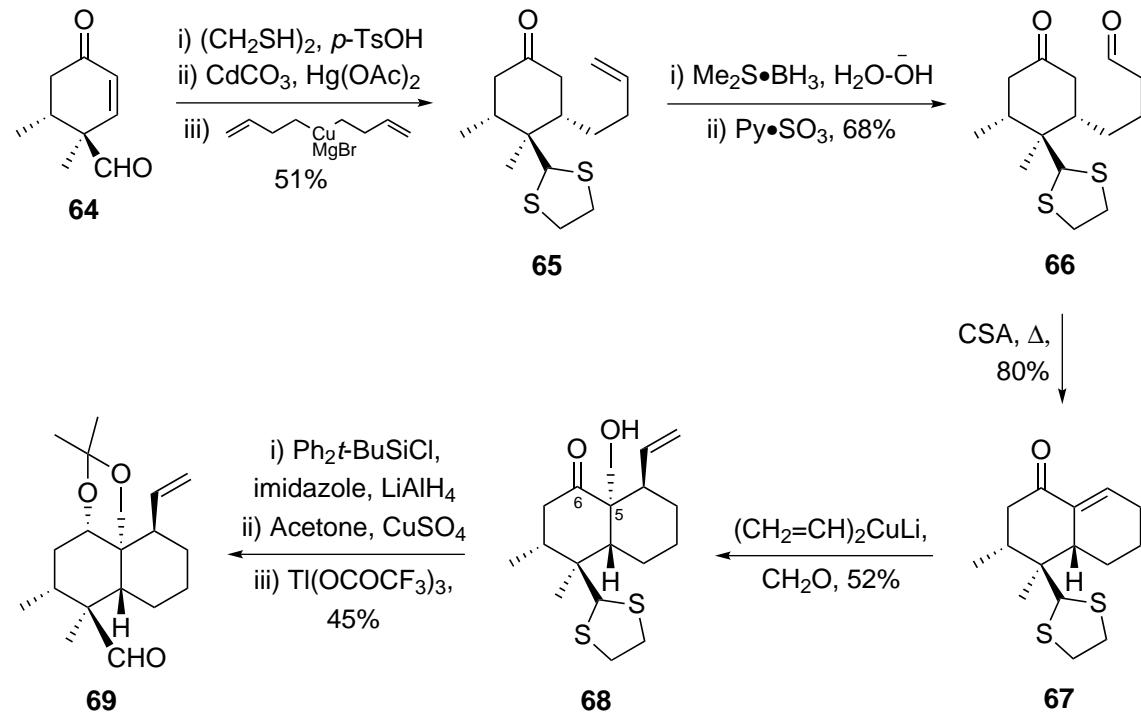
Scheme 1.9: Completion of Xiang's total synthesis of clerocidin **17**.<sup>62</sup>

#### 1.4.2. Syntheses starting from cyclohexanone derivatives

Cyclohexanones are another viable option in the total synthesis of clerodanes. Ley *et al.* used the cyclohexenone **64** in the total synthesis of ajugarin I **9** (Scheme 1.10).<sup>20</sup> Compound **64** was prepared by reacting (*E*)-2-methylbut-2-enal with 3-trimethylsilyloxybutadiene (Danishefsky's diene) in a Diels-Alder reaction. The aldehyde of **64** was then protected by a 1,3-dithiolane. This occurred via diprotection of the two carbonyl groups followed by deprotection of the more labile dithiolane of the ketone with  $CdCO_3$  and  $Hg(OAc)_2$ . Addition of 2 equivalents of (dibutetyl)coppermagnesium bromide afforded a 3-buten-1-yl intermediate **65** in the  $\alpha$ -orientation by a conjugate addition. Introduction of the dithiolane was important, as it directed cuprate addition to the top face of the molecule. Ley stated that the first equivalent of cuprate was necessary to coordinate with the diothiolane on the top face, whilst the second equivalent was required to complete the conjugate addition on the enone.<sup>66</sup> The stereochemistry of the product was important because this would lead to a *trans*-clerodane at a later stage.

Hydration of **65** was proceeded by oxidation of the primary alcohol to yield the aldehyde **66**. Intramolecular aldol condensation of **66** catalysed with CSA generated the decalin

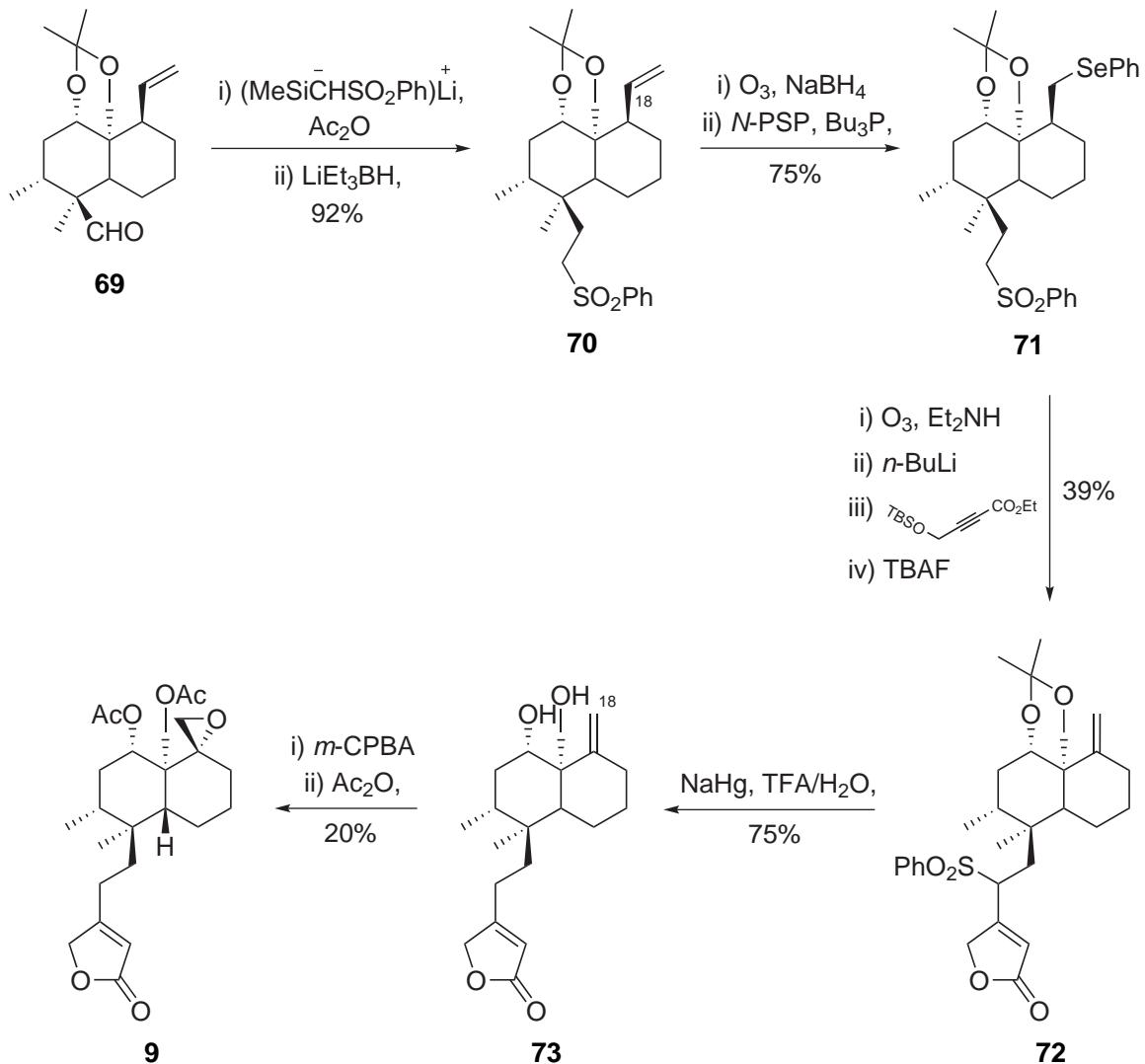
backbone **67**. From **64**, it took six steps to obtain the decalin skeleton **67**. Conjugate addition of vinyl cuprate to the enone **67** followed by addition of formaldehyde gave compound **68**. This compound now had the correct stereochemistry at C5. The next steps transformed compound **68** to compound **69**. The ketone **68** was reduced upon treatment with lithium aluminium hydride to afford the diol. The newly formed alcohol group at C6 had an  $\alpha$ -orientation. The diol was then protected to form the acetonide and the dithiolane group was removed to afford **69**.



Scheme 1.10: First half of Ley's total synthesis of ajugarin I **9** via a cyclohexane precursor.<sup>20</sup>

In order to establish the butenolide in the clerodane, a phenyl sulfone was introduced. Once the phenyl sulfone **70** was prepared, the C18 alkene was converted into the selenide **71** in two steps. Compound **71** was then subjected to ozone and diethylamine to give the exocyclic alkene. The anion of **71** was formed upon treatment with *n*-butyllithium, then addition of the butenolide synthon, TBSOCH<sub>2</sub>C≡CCO<sub>2</sub>Et, followed by TBAF-initiated removal of the TBS group and cyclisation afforded the butenolide **72**. Treatment of **72** with a sodium-mercury amalgam resulted in the desulfonated product, and deprotection of the acetonide with TFA gave the diol **73**. The last two steps involved epoxidation of the C18 alkene with *m*-CPBA, which gave the  $\beta$ -C18 epoxide. This compound was

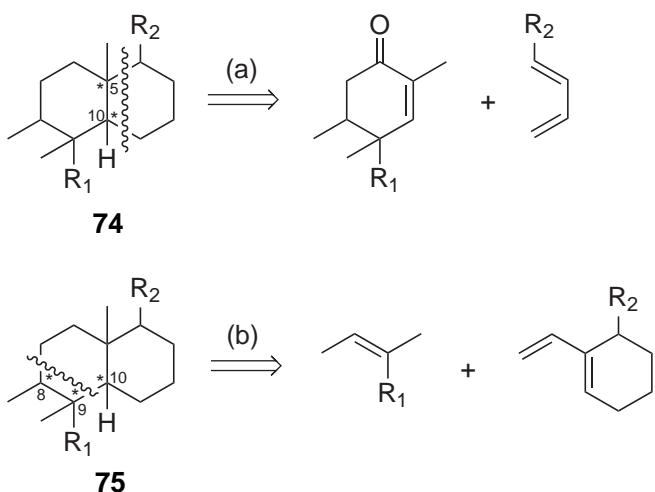
subsequently treated with acetic anhydride to afford the diacetylated final product ajugarin **I 9**. The overall yield over 20 steps was 0.08%.



Scheme 1.11: Second half of Ley's total synthesis of ajugarin **I 9** via a cyclohexane precursor.<sup>20</sup>

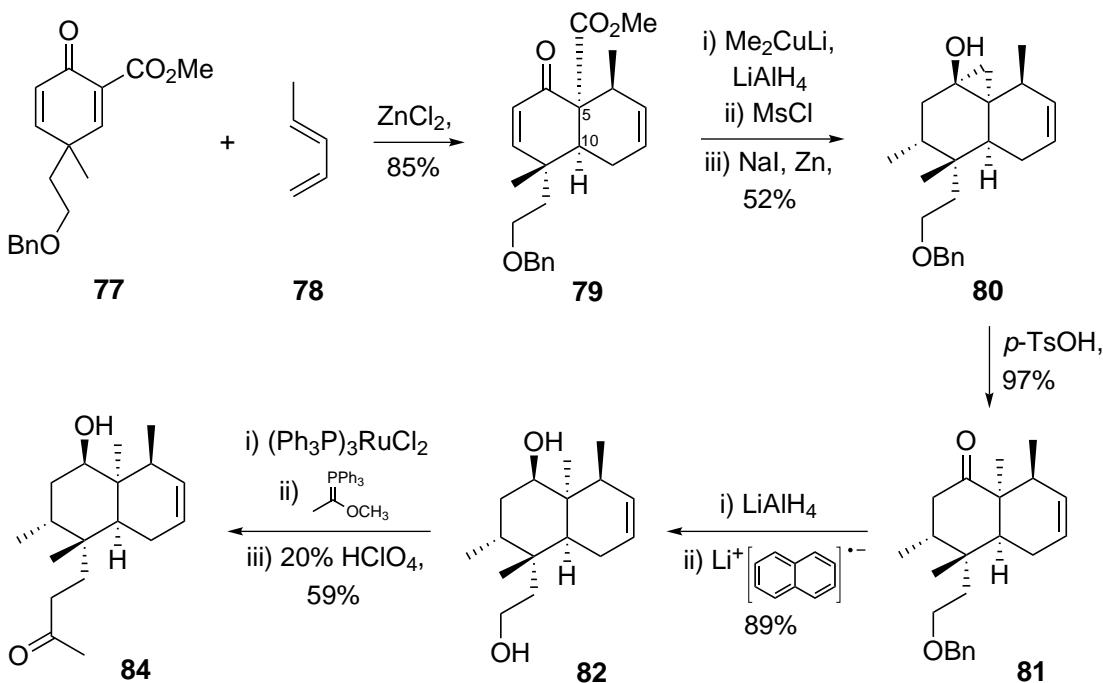
#### 1.4.3. Syntheses using intermolecular Diels-Alder reactions

An alternate method to synthesise a clerodane was to use a Diels-Alder reaction to form the decalin ring. The Diels-Alder route could be employed two ways. Pathway (a) would incorporate the C5 and C10 stereocenters to form **74**, and pathway (b) would create the C8, C9 and C10 stereocenters to provide **75** (Scheme 1.12).



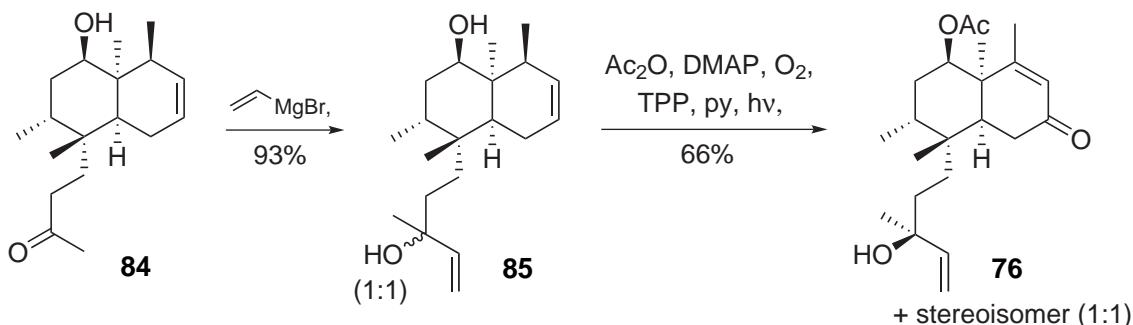
Scheme 1.12: Intermolecular Diels-Alder retrosyntheses of clerodanes.

Liu *et al.* established the C5 and C10 stereocenters first in the total synthesis of 6-acetoxy-2-oxokolavenool **76** (Scheme 1.13 & Scheme 1.14).<sup>67,68</sup> This was achieved by reacting **77** and *trans*-piperylene **78** promoted by a Lewis acid ( $ZnCl_2$ ) to give the Diels-Alder adduct **79** in 85% yield. The reaction was regioselective and stereoselective to only provide the *ortho*-, *endo*- adduct.  $\pi$ -Facial selectivity was favoured from the least hindered methyl face of the dienophile **77**.<sup>67</sup> Conjugate addition of lithium dimethylcuprate to **79** followed by reduction of the methyl ester with lithium aluminium hydride gave the keto alcohol. The alcohol functional group was mesylated, and this compound was then treated with sodium iodide and zinc metal to yield the cyclopropane **80**. Cleavage of the cyclopropane ring with *p*-TsOH afforded **81**. The ketone **81** was then reduced with lithium aluminium hydride to afford the alcohol as a single stereoisomer. This was the expected product because hydride addition was likely to occur from the convex face.<sup>68</sup> Reductive debenzylation with lithium naphthalenide gave the diol **82**. Selective oxidation of the primary alcohol in compound **83** with dichlorotris(triphenylphosphine)ruthenium(II) yielded the aldehyde, which was treated with a Wittig reagent to form an enol ether. Hydrolysis of this compound with 20% perchloric acid gave the methyl ketone **84**.



Scheme 1.13: First part of Liu's total synthesis of a clerodane via a Diels-Alder reaction.<sup>67,68</sup>

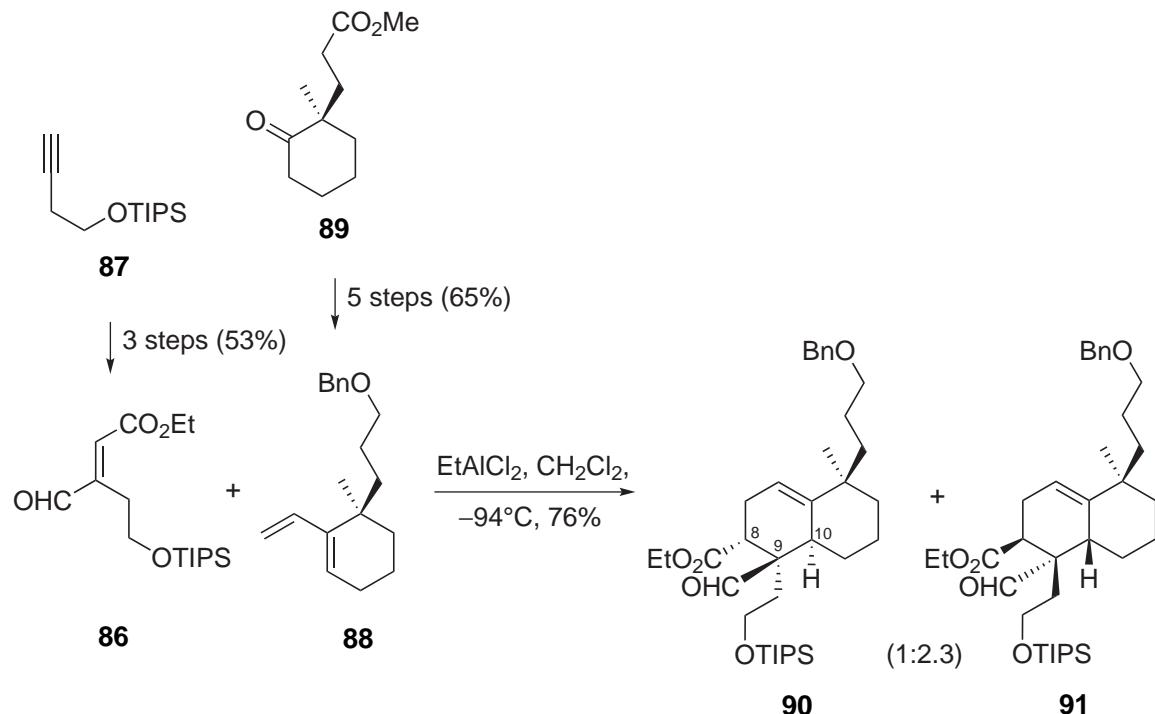
The last two steps in Liu's total synthesis of 6-acetoxy-2-oxokolavenool **76** involved the Grignard addition of vinylmagnesium bromide to **84** to form the allylic alcohol **85** as a mixture of stereoisomers. Photooxygenation of this mixture with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) and oxygen gave the final compound **76** with an overall reaction yield of 0.01% from **77**.



Scheme 1.14: Final two steps of Liu's total synthesis of a clerodane via a Diels-Alder reaction.<sup>68</sup>

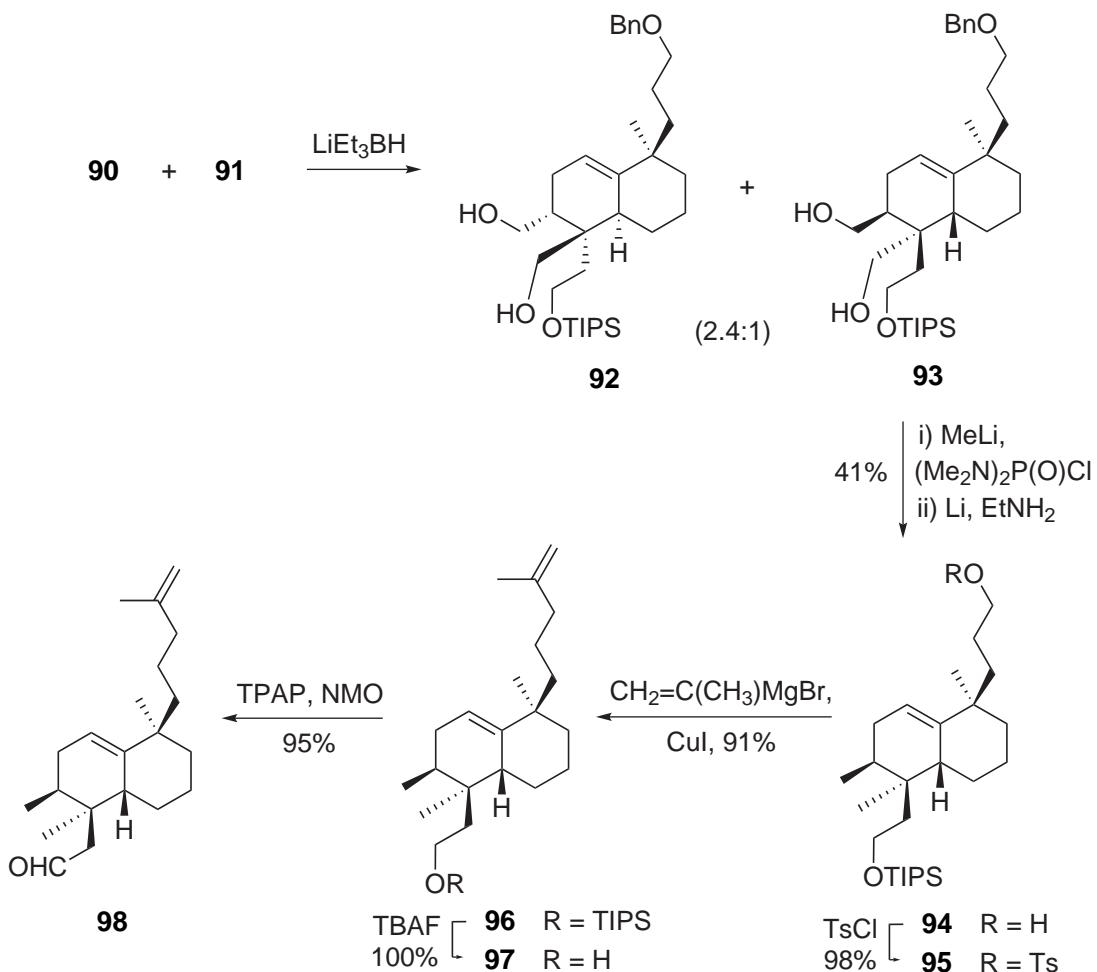
Boukouvalas *et al.* have used the Diels-Alder reaction to establish the C8, C9 and C10 stereocenters in the total synthesis of ( $\pm$ )-dysidiolide **21** (Scheme 1.15).<sup>69</sup> A dienophile **86** was prepared in three steps from **87** and reacted with a diene **88** that was prepared in

five steps from a readily accessible precursor **89**. This afforded a 1:2.3 mixture of *endo* Diels-Alder adducts **90** and **91**, respectively.



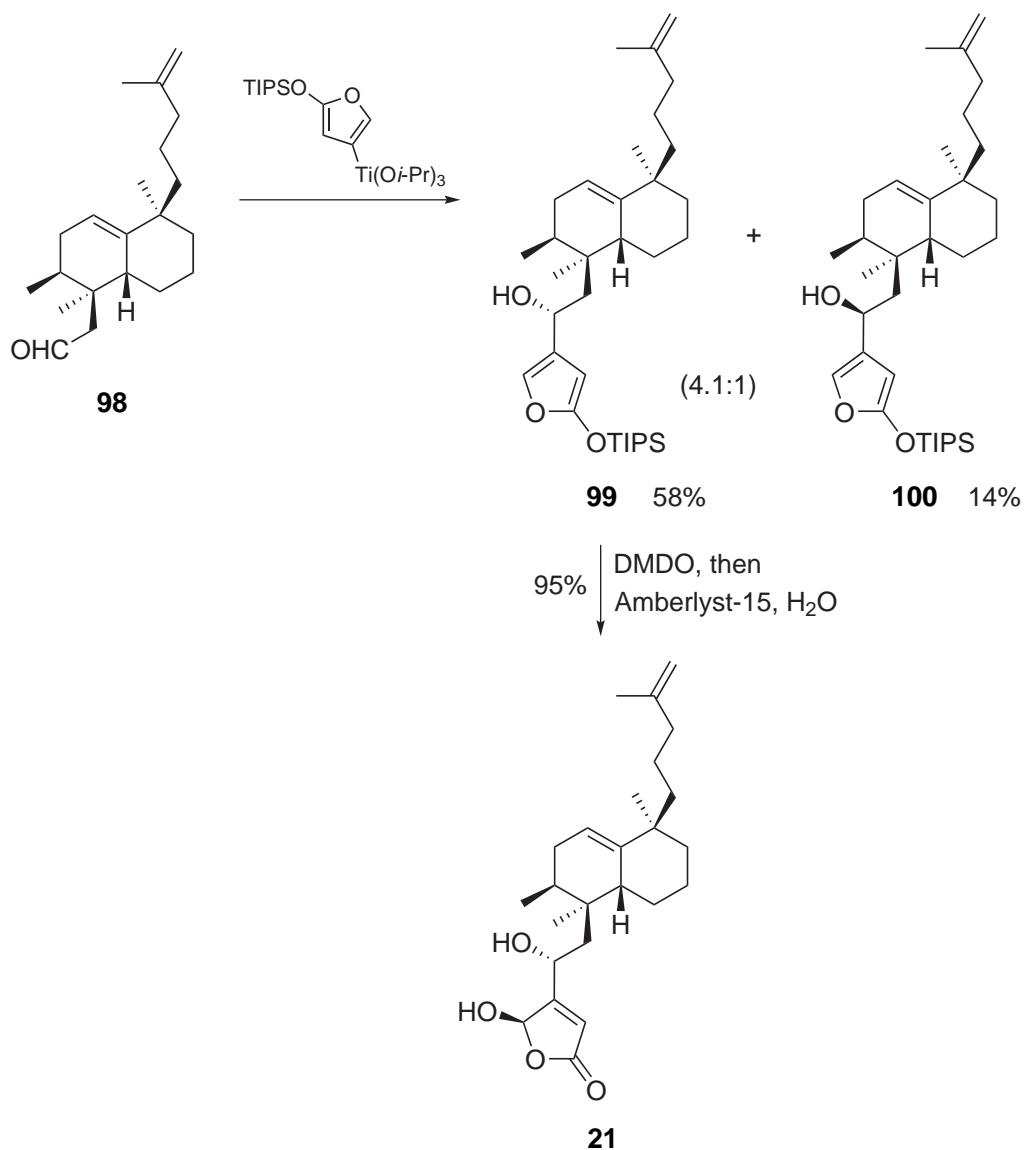
Scheme 1.15: Diels-Alder reaction implemented in the total synthesis of  $(\pm)$ -dysidiolide **21**.<sup>69</sup>

The Diels-Alder adducts **90** and **91** were then reduced with lithium triethylborohydride to form the diols **92** and **93** which were easy to separate.<sup>69</sup> Compound **93** was deoxygenated and deprotected through an adapted Ireland phosphoramidate method,<sup>70</sup> then subjected to a Benkeser reduction to yield the alcohol **94**. The alcohol **94** was then tosylated to give **95**. Treatment of **95** with 1-methylethenylmagnesium bromide furnished compound **96**. This was followed by desilylation to afford the alcohol **97**, and oxidation of the alcohol with tetrapropylammonium perruthenate (TPAP) gave the aldehyde **98**.



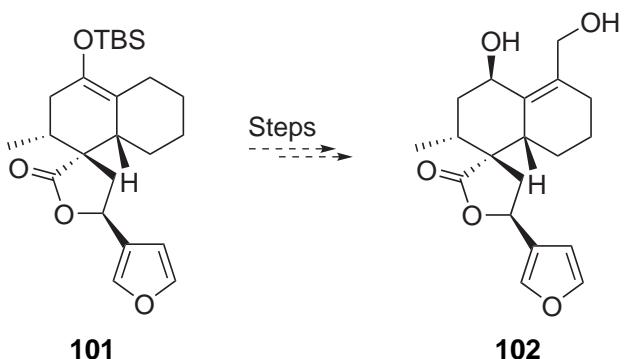
Scheme 1.16: Core of Boukouvalas' method to synthesise ( $\pm$ )-dysidiolide **21**.<sup>69</sup>

The furan ring was then introduced upon addition of a (TIPS-furanyl)titanium reagent to **98** to form a mixture of alcohols **99** (58%) and **100** (14%). The major product **99** was separated and the furan group was oxidised with DMDO to afford the hydroxylactone of (+)-dysidiolide **21**. This oxidation protocol of converting a furan to a  $\gamma$ -hydroxybutenolide was also published by Boukouvalas' group shortly before the total synthesis of **21** was released.<sup>71</sup>



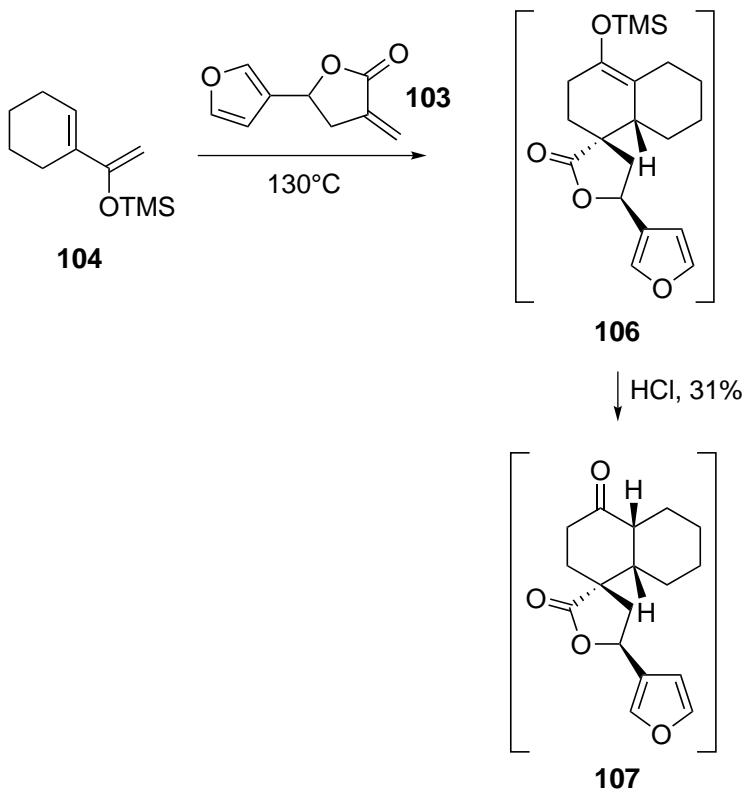
Scheme 1.17: The last two steps of Boukouvalas' synthesis of ( $\pm$ )-dysidiolide **21**.<sup>69</sup>

Williams and Ley have designed a direct Diels-Alder approach to synthesise spiro- $\gamma$ -lactone clerodanes from advanced intermediates rather than applying Diels-Alder chemistry at the early stages of the synthesis.<sup>72</sup> Following on from this strategy first proposed by Jung,<sup>73</sup> the work aimed to produce a similar target **101** that could be further functionalised to provide furanospiro- $\gamma$ -lactone clerodanes such as montanin B **102** that have previously been isolated (Scheme 1.18).



Scheme 1.18: Diels-Alder adduct targeted as a potential precursor to Montanin B.<sup>72</sup>

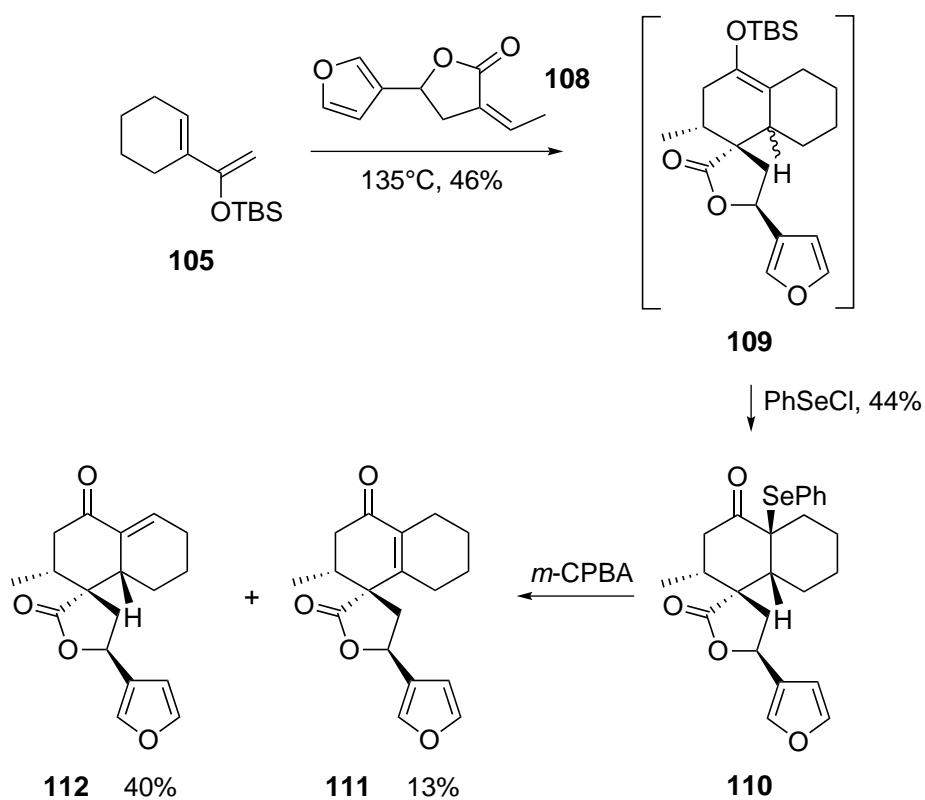
The model dienophile **103** along with the TMSO-diene **104** and its TBSO-analogue **105** were used in this study. The reaction between **103** and **104** could not be coerced with Lewis acids. The reaction was only successful when it was heated to 130°C in a presilylated glass pressure vessel to give **106**, which was worked up with hydrochloric acid to afford the *cis*-decalin adduct **107** as the only product in 31% yield (Scheme 1.19).



Scheme 1.19: Diels-Alder reaction achieved by Williams *et al.*<sup>72</sup>

The dienophile *cis*-furanospiro- $\gamma$ -lactone **108** was synthesised as it contained an extra methyl group required in Montanin B **102**. Compound **108** was combined with **105**

and treated with a range of Lewis acids, though no product was formed. Heating the precursors in a presilylated glass pressure vessel at 135°C gave **109** as a mixture of three diastereomers (Scheme 1.20). The loss of stereocontrol in this reaction was due to the methyl group in the dienophile **108**. Desilylation of **109** with acid did not give the desired product, so another approach had to be used. Treatment of **109** with phenylselenyl chloride produced **110**, which upon elimination with *m*-CPBA gave a mixture of enones **111** (40%) and **112** (13%). Overall, this research furthered work that had been previously attempted and gave good results. This could serve as an excellent methodology to synthesise spiro- $\gamma$ -lactone clerodanes.

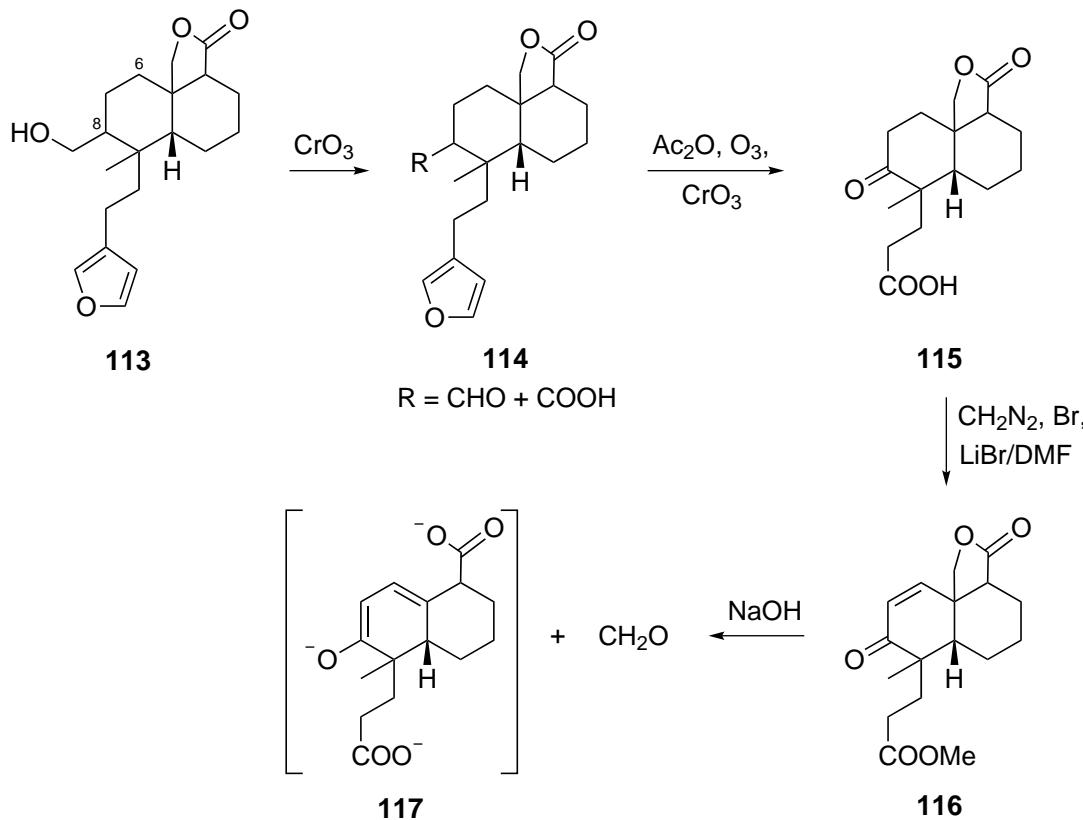


Scheme 1.20: A Diels-Alder reaction with different precursors.<sup>72</sup>

## 1.5. Chemistry of isolated clerodanes

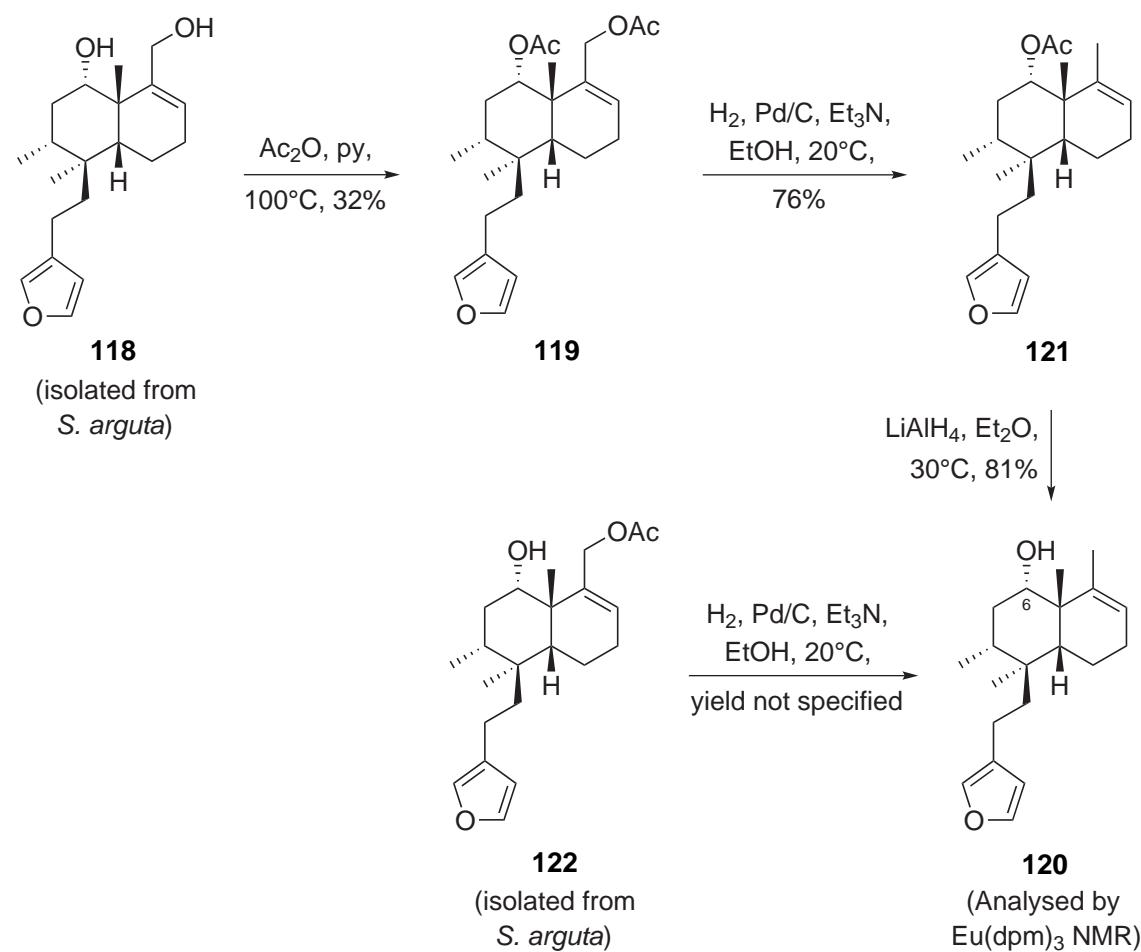
The chemistry of clerodanes isolated from natural sources has been investigated either for structural determination or used as starting materials in synthesis. When structural elucidation of isolated clerodanes by NMR techniques alone was not possible before the mid-1970s, they were subjected to degradation studies to simplify the structure. Derivatisation reactions were also utilized to convert isolated compounds to known

clerodanes. The reactivity of all two or three rings has been shown in many examples in the literature. Payne and Jefferies isolated some clerodanes from *Dodonaea attenuata* var. *linearis* and needed to establish the correct structures.<sup>74</sup> The location of the hydroxymethyl substituent on ring B of an advanced intermediate **113** was uncertain. The C6 and C8 positions were the two likely places on the ring where the hydroxymethyl could be attached to. To determine the correct structure, **113** was oxidised with chromium trioxide to oxidise the alcohol to the aldehyde and carboxylic acid **114**. Further oxidation of **114** with acetic anhydride, ozone and chromium trioxide afforded the ketone **115**. The next reaction was considered an important step in determining the correct structure of **113**. The ketone **115** was treated with diazomethane, bromine and then lithium bromide to form the dehydrogenated product **116**. A base-catalysed retro-Aldol reaction of **116** with sodium hydroxide afforded formaldehyde and presumably the carboxylate salt **117** (Scheme 1.21).<sup>74</sup> Formaldehyde was detected by a chromotropic test described by Bricker and Johnson.<sup>75</sup> As no formaldehyde was observed when the methyl ester of **116** was reacted under the same conditions, the location of the hydroxymethyl group was confirmed to be at C8.



Scheme 1.21: Degradation studies of a clerodane.<sup>74</sup>

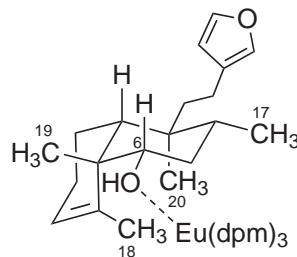
McCrindle and colleagues isolated six new furyl clerodanes from the roots of *Solidago arguta* Ait.<sup>76</sup> To confirm the structure of these new compounds, the researchers conducted a series of chemical transformations to compare the spectral data of the compounds and assign the stereocenters correctly. One of the six new isolated compounds was **118**. Compound **118** was acetylated to form the diacetate **119** (Scheme 1.22). The relative configuration of the four methyl groups was determined by transforming **119** to **120**. The diacetate **119** was hydrogenated to remove the allylic acetate group and afford **121**. The acetate **121** was then treated with lithium aluminium hydride to afford the alcohol **120**. Compound **120** could also be formed from a hydroxy-acetate compound **122** also isolated from the plant.



Scheme 1.22: Hydrogenation and reduction reactions performed by McCrindle.<sup>76</sup>

Compound **120** was important because the alcohol functional group could be complexed with  $\text{Eu}(\text{dpm})_3$  in an NMR shift experiment. Coordination of a hydroxyl group with  $\text{Eu}(\text{dpm})_3$  induces shifting of the methyl resonances in the  $^1\text{H}$  NMR spectrum. The

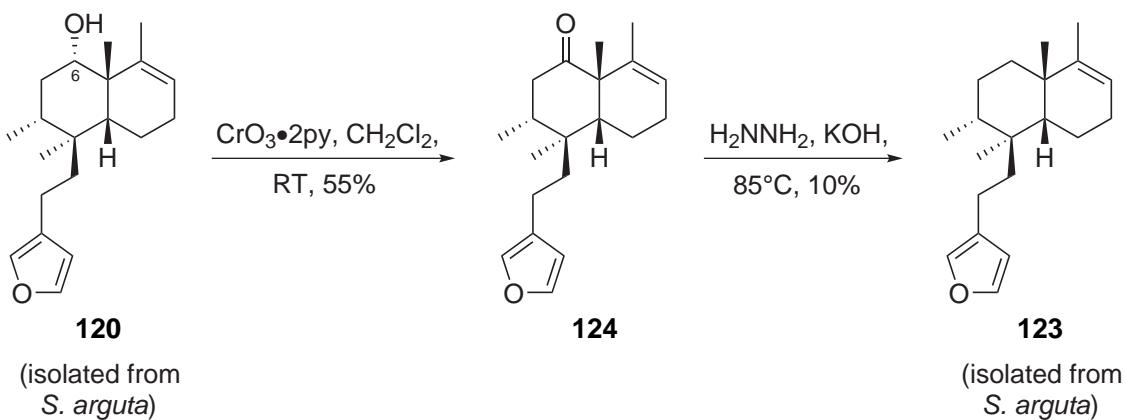
strongest chemical shifts are due to close interactions with the  $6\alpha$ -hydroxyl group coordinated to Eu(dpm)<sub>3</sub>. A normalised ratio of 10:9.6:1.7:4.2 ppm was obtained, and this ratio was compared to some terpenoid ratios published by Buckley and colleagues.<sup>77</sup> After careful examination of the Eu-induced shifted signals, the obtained ratio was assigned to the C18, C19, C17 and C20 methyl groups, respectively. The C18 methyl exhibited the biggest change in chemical shift (to 10.0 ppm) as it was relatively close to the hydroxyl and hydrogen bonding was likely to occur between these two positions. As the  $6\alpha$ -hydroxyl was in the equatorial position, it would also be close to the C19 methyl that must have an axial conformation to enable such a big shift (9.6 ppm) to occur. The  $6\alpha$ -hydroxyl was also close to the C20 methyl which must have an axial orientation, and despite the two positions being separated by four carbons, it does have a significant chemical shift change of 4.2 ppm. The C17 methyl had the smallest chemical shift change, and this was because it exists in the equatorial conformation and points away from B ring and its substituents.



**120**

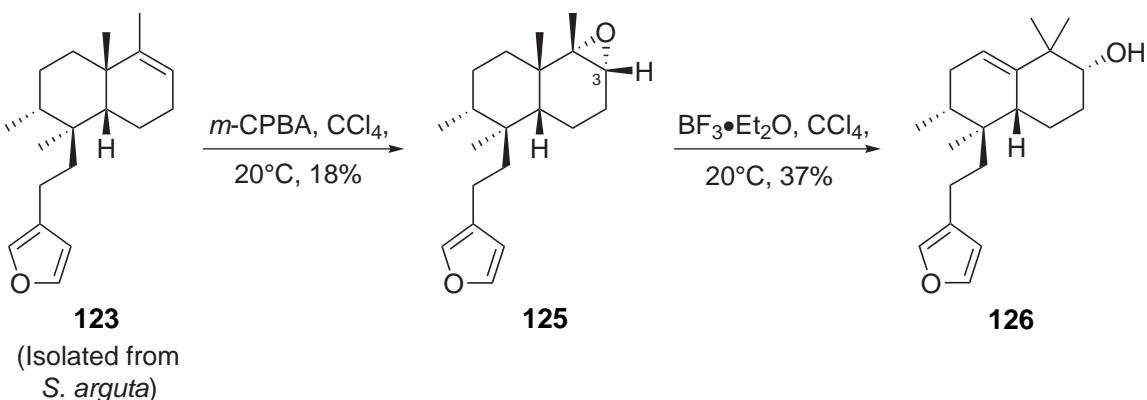
Figure 1.11: Location of the C6 Eu-coordinated alcohol with respect to the methyl substituents, adapted from McCrindle.<sup>76</sup>

Another method to confirm the stereochemistry of the clerodane backbone in **120** was to eliminate the hydroxyl group at C6 to form the known compound **123**. The alcohol was oxidised with Collins reagent to afford the ketone **124** in acceptable yield (Scheme 1.23). A Wolff-Kishner reduction of the ketone **124** gave the deoxygenated product **123**. This compound had identical spectral properties to the clerodane isolated from *Solidago arguta* Ait.



Scheme 1.23: Oxidation and Wolff-Kishner reactions demonstrated by McCrindle.<sup>76</sup>

McCrindle also derivatised other clerodanes to identify their structure. When **123** was treated with *m*-CPBA to form the epoxide **125**, the configuration of the H3 proton was unknown. The orientation of the epoxide could not be confidently assigned as a result of this. The authors overcame this predicament by performing an acid-catalysed rearrangement of **125** with boron trifluoride diethyl etherate to yield the alcohol **126**. The alcohol was determined to have an  $\alpha$ -orientation, which corroborates that the epoxide **125** must also exist in an  $\alpha$ -orientation.

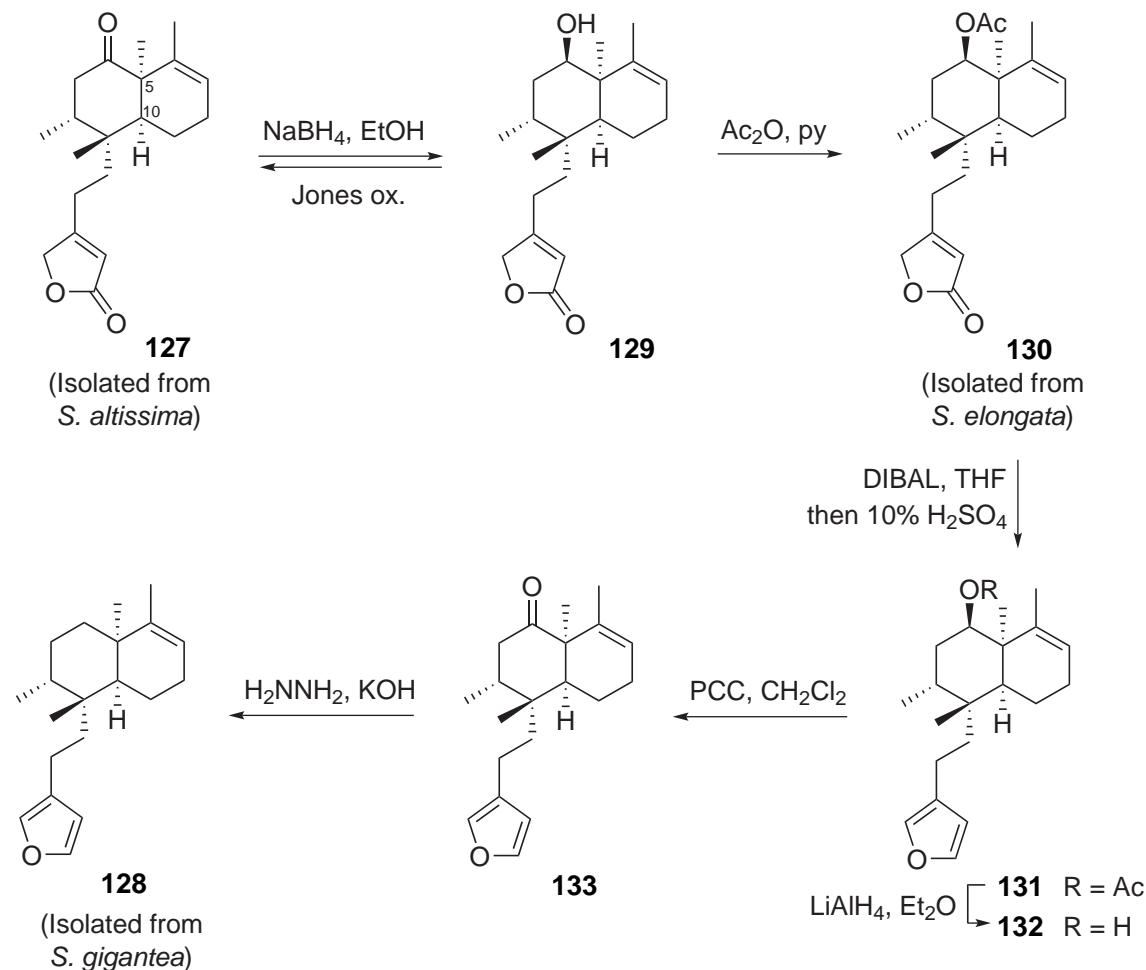


Scheme 1.24: Epoxidation and nucleophilic substitution reactions achieved by McCrindle.<sup>76</sup>

Yamamura and Niwa isolated some clerodanes from the plant *Solidago altissima* L.,<sup>78</sup> and these clerodanes had been previously isolated by Okazaki.<sup>79</sup> Okazaki noted that some of these clerodanes were identical to those that were isolated from *Solidago elongata* Nutt. by Anthonsen and McCrindle.<sup>80</sup> The clerodanes were thought to be *trans*-clerodanes at C5 and C10, however, Yamamura discovered that these compounds exist in a *cis*-

configuration. Reexamination of seven clerodanes has confirmed this, and this was achieved by conducting a series of derivatisation reactions on the isolated compounds.

The isolated clerodane **127** was transformed over a series of steps to **128** to compare the spectral data previously obtained of **128** and therefore determine the stereochemistry. The ketone **127** was reduced to the alcohol **129**, whose structure was confirmed upon oxidation of **129** to **127** with Jones reagent. Compound **129** was acetylated to form the known acetate **130**.<sup>80</sup> The acetate **130** was reduced with DIBAL to transform the butenolide to the furan **131**. The transformation was confirmed upon the loss of the butenolide frequencies at  $\nu = 1790$  and  $1640\text{ cm}^{-1}$  in addition to the loss of the butenolide peaks in the  $^1\text{H}$  NMR spectrum. Reduction of the acetate **131** with lithium aluminium hydride gave the alcohol **132**. Oxidation of **132** with PCC afforded the ketone **133** in almost quantitative yield. The final step was to reduce the ketone in **133** to form the known clerodane **128**.<sup>81</sup> This was achieved by a Wolff-Kishner reduction.



Scheme 1.25: Reactions accomplished by Yamamura to confirm clerodane structures.<sup>78</sup>

Once **128** was synthesised, its NMR spectra was compared to that of **134** previously published by Okazaki<sup>79</sup> as well as McCrindle.<sup>82,83</sup> Differences were noted in the <sup>1</sup>H NMR spectra, particularly with regard to the C17 and 20 methyl groups. The compound prepared by Yamamura **128** has a C17 methyl at 0.90 (d) and a C20 methyl at 1.09 ppm (s). The compound investigated by Okazaki and McCrindle **134** had peaks for C17 and C20 at 0.86 (d) and 0.74 ppm (s), respectively. Yamamura explained that the significant difference observed for the C17 and C20 protons of **128** strongly indicated that they exist in different environments. As equatorial protons on a cyclohexane ring tend to have a downfield shift/magnetic field in <sup>1</sup>H NMR spectroscopy due to anisotropic effects,<sup>84</sup> it was suggested that C20 existed in the equatorial conformation whilst C17 existed in the axial conformation (Figure 1.12). Conversely, **135** has an axial C20 and equatorial C17 conformation.

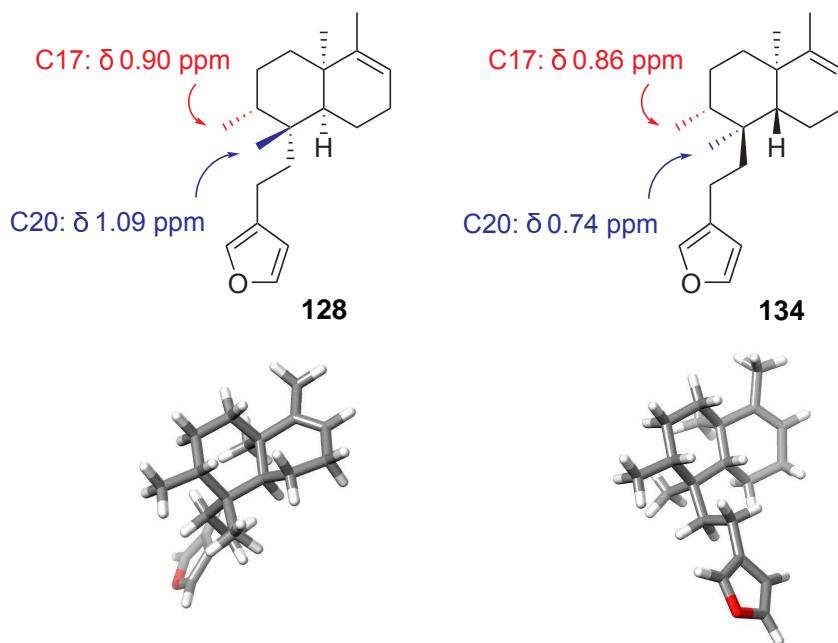
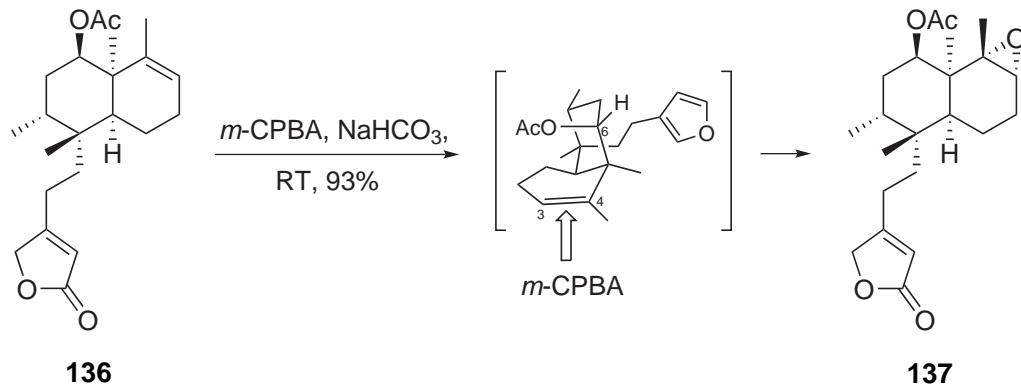


Figure 1.12: Comparison of the C17 and 20 methyl group shifts.

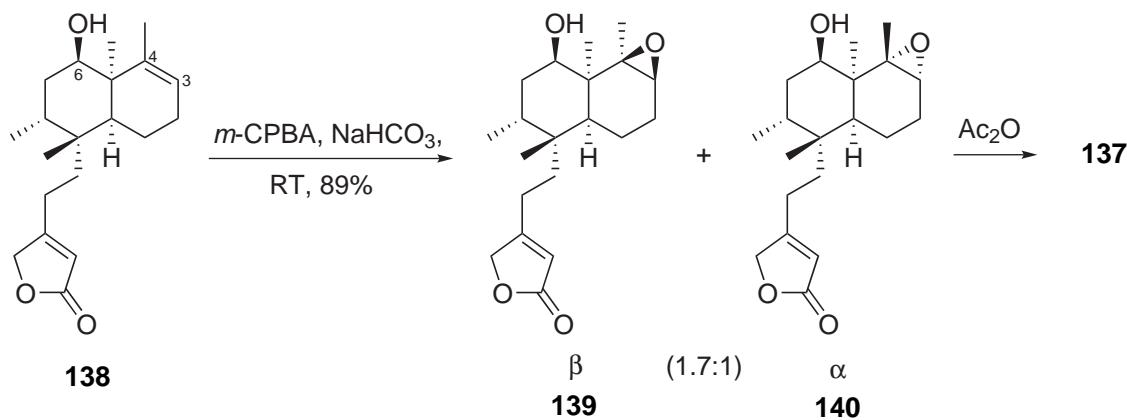
In 1986, Nishino reported some *cis*-clerodanes isolated from *Solidago altissima* L.<sup>85</sup> Like Yamamura, the researchers reported the correct absolute configurations of some clerodanes previously published. Nishino paid particular attention to the epoxidation of these clerodanes. The acetate **136** was treated with *m*-CPBA at room temperature which selectively provided the  $\alpha$ -epoxide **137** in excellent yield (Scheme 1.26). Examination of the 3D orientation of **136** rationalises why only the  $\alpha$ -epoxide was obtained. The acetate group at C6 appears to be blocking the top face of the C3-C4 alkene, making the approach

and addition of *m*-CPBA unlikely. Epoxidation occurred at the less-sterically hindered face to give **137**.



Scheme 1.26: Epoxidation of the acetate compound **136** to form the  $\alpha$ -epoxide **137**.<sup>85</sup>

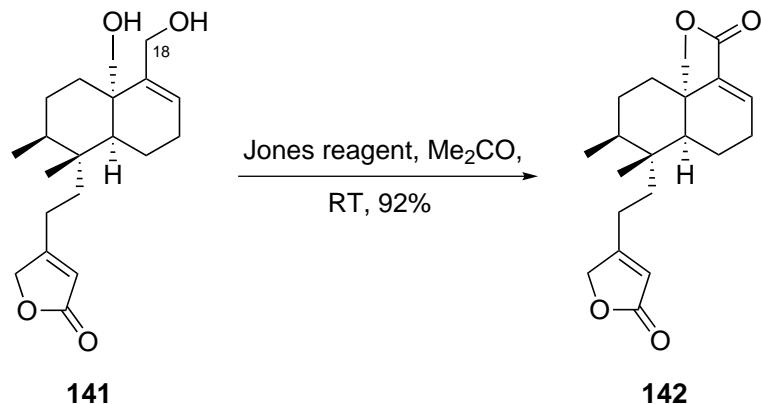
Conversely, the same reaction was applied to the alcohol compound **138**, yet this did not give full selectivity for one epoxide (Scheme 1.27). The  $\beta$ -epoxide **139** was formed with greater preference over the  $\alpha$ -epoxide **140** (1.7:1). Unlike the acetate **136** used in the previous example, the alcohol at C6 was less bulky and therefore *m*-CPBA was able to add to the C3-C4 alkene via the top face and the bottom face of the **138**. Structural confirmation of **140** was proven upon acetylation to yield **137** which was previously synthesised in Scheme 1.26.



Scheme 1.27: Epoxidation of the alcohol compound **138** to form mixed epoxides.<sup>85</sup>

In 1987, Gao and Mabry isolated ten new clerodane diterpenes from *Gutierrezia texana*.<sup>86</sup> To aid in the structural elucidation of these compounds, a diol compound that was isolated **141** was oxidised to form a diolide **142**, which was another compound the authors had isolated. This reaction was achieved with Jones reagent and gave excellent yield of **142**.

(Scheme 1.28).  $^1\text{H}$  NMR spectroscopy of the synthesised diolide and isolated diolide gave identical spectra, confirming they were the same compound.



Scheme 1.28: Oxidation of a C18 alcohol to form a cyclic ester, reported by Gao and Mabry.<sup>86</sup>

## 1.6. *Dodonaeas* growing in Australia and overseas

*Dodonaeas* are widespread in Australia, as 61 of the 68+ species that are available in Australia are natives.<sup>6</sup> *Dodonaeas* grow in coastal and inland regions of Australia. Other regions around the world that grow *Dodonaeas* include Africa (Madagascar, South Africa),<sup>87,88</sup> South America (Mexico, Uruguay)<sup>89</sup> and Asia (Papua New Guinea, Pakistan, India).<sup>6,90,91</sup> *Dodonaeas* are versatile plants that can grow in a range of different habitats in Australia such as near creeks, rainforests and rocky areas.<sup>6</sup> *Dodonaeas* growing in Australia have adapted to the harsh arid/semi-arid climate as they are evergreen and mostly drought tolerant.

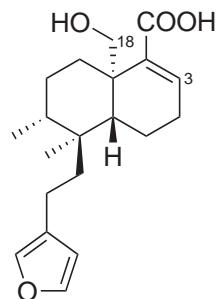
### 1.6.1. Ethnopharmacology of some *Dodonaeas*

The high prevalence of *Dodonaeas* available in Australia has made these plants known to indigenous communities. Some *Dodonaeas* have been used by indigenous communities medicinally to treat a range of different ailments. For example, *D. viscosa* is a species that has been used by native Australian Aborigines as an analgesic.<sup>4</sup> Specifically, the leaves are chewed to alleviate tooth and gum aches, as well as relieve pain associated with stingray wounds.<sup>92</sup> Madagascans use the leaves to ease the symptoms of sore throats and fever, whilst South Africans use the plant to treat a range of stomach disorders. The leaf is also said to relieve rheumatism symptoms and skin infections.<sup>93</sup> Mexicans have

used *D. viscosa* to alleviate inflammation, rheumatism and general pain.<sup>94</sup> There have been no reported complaints of *D. viscosa* causing adverse effects upon traditional use.<sup>95</sup> *D. viscosa* ssp. *angustissima* is another Australian species that Aborigines in central Australia relied heavily upon to treat an array of ailments. For example, an infusion of the leaves can be applied to the body and forehead to treat fever.<sup>4</sup> *D. viscosa* ssp. *angustifolia* has been used to treat oral infections as it prevents biofilms of *Streptococcus mutans*.<sup>96</sup> Leaves of *D. lanceolata* have been used as a local analgesic by Aborigines in WA and are commonly applied to snake bite wounds.<sup>97</sup> A decoction of the leaves has also proven effective against toothaches.<sup>92</sup> The medicinal effects of *Dodonaeas* implemented for traditional use has led to thorough chemical analysis of some samples to determine the active constituents.

#### 1.6.2. Clerodanes isolated from *Dodonaeas*

The first clerodane isolated from a *Dodonaea* species was hautriwaic acid **28**, found in the resin of *D. viscosa* (Figure 1.13 & Section 1.3.5).<sup>25</sup> Compound **28** was initially thought to be a monohydroxycarboxylic acid, with the official structure not determined. Analysis of the IR spectrum of **28** showed that the compound had an  $\alpha,\beta$ -disubstituted acrylic acid with absorptions at 1660 and 2700  $\text{cm}^{-1}$ .<sup>98</sup> A vinylic signal was found in the  $^1\text{H}$  NMR spectrum at 6.60 ppm, assigned as H3. A primary alcohol was evident too, as an IR absorption at 3140  $\text{cm}^{-1}$  was apparent. The C18 methylene attached to the primary alcohol was assigned by  $^1\text{H}$  NMR as a pair of doublets at 3.75 and 4.61 ppm which each had an integration of one hydrogen.<sup>98</sup> Payne and Jefferies also described obtaining hautriwaic acid **28**, though only the melting point (183–184°C) and optical rotation ( $[\alpha]_D -105$ ) were provided.<sup>99</sup>



**28**

Figure 1.13: Structure of hautriwaic acid, the first clerodane isolated from a *Dodonaea*.<sup>25</sup>

Hautriwaic acid **28** is a biologically active compound, exhibiting good antiinflammatory and insect antifeedant activity.<sup>49,100</sup> Derivatives of **28** have been synthesised to test the structure-activity relationships. Since the isolation and characterisation of **28**, other clerodanes have been isolated from different species in the *Dodonaea* genus. Plants in the *Dodonaea* genus are known as a good source of clerodane diterpenes (albeit in low isolated yields), particularly the resin coating the leaves. Previous work has described the isolation of a clerodane diterpene **143** from the dried, ground aerial parts of *D. viscosa* grown in Saudi Arabia (Figure 1.14).<sup>101</sup> This lactone compound constituted 4.3% of the crude plant extract and 0.17% of the total plant material.<sup>101</sup> A study of *D. viscosa* grown in Mexico found three novel clerodanes (**144**, **145** and **146**) from the leaves.<sup>102</sup> These compounds were isolated in respective yields of 0.050%, 0.033% and 0.007% based on the total mass of plant used. Another research group examined *D. viscosa* grown in Mexico which led to the isolation of a novel clerodane diol **147** with alcohol substituents at C3 and C8.<sup>94</sup> The aerial parts of another sample of *D. viscosa* from India gave a clerodane termed dodonic acid **148** that made up 0.56% of the crude plant extract and 0.06% of the total plant used.<sup>103</sup> This compound has a carboxylic acid at C4 and a  $\beta$ -alcohol at C6.

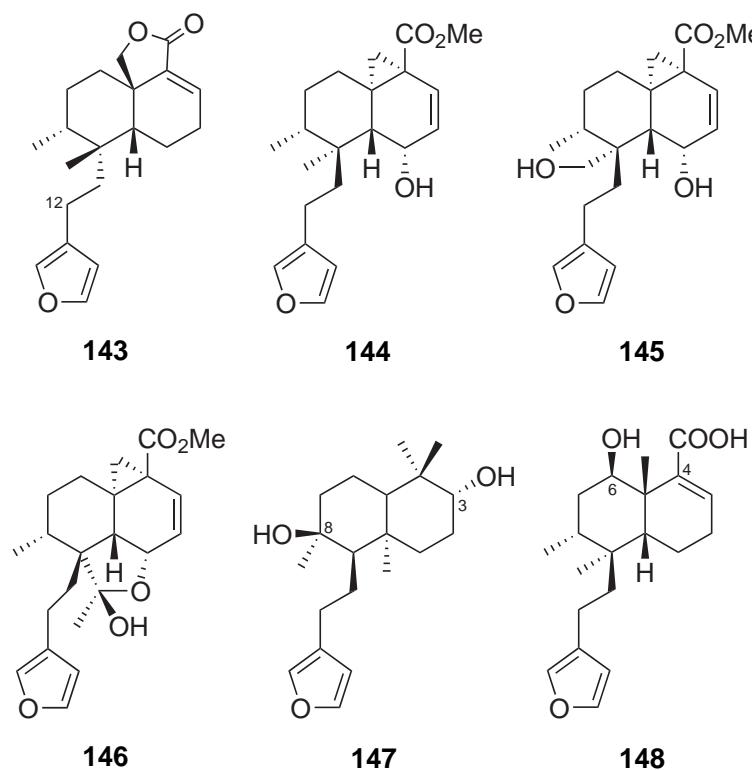


Figure 1.14: Structures of some clerodanes isolated from various *D. viscosa* samples.

What all these compounds have in common is the 3-furyl group attached to C12 of the clerodane. *D. viscosa* is commonly known to natural product chemists and phytochemists as being a good source of clerodanes containing a furan. Although the clerodanes were all isolated from the same species of *D. viscosa* grown in different locations, the structures are all different and have a good spread of functional groups. This is due to geographical variations such as climate (temperature, humidity), soil quality, fertilisation and water availability.<sup>104,105</sup>

## 1.7. Project aims

Clerodanes can be obtained through two different methods, through a total synthesis or through isolation from a natural source. As highlighted in the discussed examples, the total synthesis of clerodanes requires upwards of 14 reaction steps. Moreover, the overall yield of the target clerodane is very low, often below 0.1%. Isolation of novel clerodanes is still a strong possibility from plants. Plants in the *Dodonaea* genus have been a rich source of clerodanes and the chemistry of many species is yet to be investigated.

*D. viscosa* ssp. *angustissima*, commonly known as the slender hopbush, is a subspecies widespread in Australia (Figure 1.15). It was initially referred to as *D. attenuata*.<sup>6</sup> This plant is distributed throughout Western Australia, South Australia, New South Wales and Victoria. This subspecies typically thrives in semi-arid and arid regions.<sup>6</sup> Its leaves are simple, sessile and linear, though some display a wider appearance and are narrowly oblong.<sup>106</sup> This shrub is able to grow to a height of 4 m and produces brown to pink-red flowers during summer.<sup>4,106</sup> *D. viscosa* ssp. *angustissima* from Murchison River, WA has been studied previously under the name of *D. attenuata* var *linearis*<sup>74,99,107,108</sup>. Although this species has been examined, variations could occur depending on growth ecology.<sup>109,110</sup> *D. viscosa* ssp. *angustissima* from south-western WA has not been analysed.



Figure 1.15: *D. viscosa* ssp. *angustissima* shrubs growing in Western Australia.

The natural products of *D. ceratocarpa* have yet to be investigated, with only limited botanical studies reported.<sup>106</sup> *D. ceratocarpa*, commonly known as horny hopbush, is found at coastal regions of south-western WA (Figure 1.16). It has a high growth distribution between Perth and Israelite Bay in WA. Its leaves are simple, sessile and oblanceolate, 1.1-7.0 cm long and 0.2-1.3 cm wide (Figure 2.6). This drought tolerant shrub grows to 2.5 m high and gives pale brown to purple-brown flowers in August-December.<sup>106</sup>



Figure 1.16: *D. ceratocarpa* shrubs located in Western Australia.

This project will examine the compounds from *D. viscosa* ssp. *angustissima* and *D. ceratocarpa* by extracting and analysing the compounds contained within the leaf resin. Upon identification of the compounds, this project will focus on the chemistry of the major constituents. The inherent chemistry of the major compound will be explored by transforming it into different and more complex analogs.

Upon investigation of the reactivity, the synthesis of a potentially useful bioactive compound is planned. Natural products isolated from plants are a source of useful precursors for the pharmaceutical industry.<sup>111</sup> Many compounds that are derived from plants have been utilized as drugs.<sup>112</sup> Although drugs such as pseudoephedrine and taxol have been isolated from plant sources, today they are manufactured in a large scale by pharmaceutical companies. Harvesting plants to derive these drugs can be expensive and lengthy, but in some cases (such as morphine) this is recognised as the only option as the total synthesis of the drugs may be inefficient.<sup>113,114</sup> Many compounds containing a  $\gamma$ -hydroxybutenolide have demonstrated good biological activities. For example, dysidiolide **21** (discussed in Section 1.3.4, Figure 1.7) contains a  $\gamma$ -hydroxybutenolide and has shown promise as an antitumoral agent, along with compound **22**.<sup>41,43</sup> As many clerodanes contain a butenolide within their structure, the second aim of this project was to introduce a hydroxyl group at the C16 ( $\gamma$ ) position. This may confer interesting biological activity that could be tested following synthesis and confirmation of structure.

# Chapter 2

## Identification of Starting Materials Isolated from *Dodonaeas*

The aerial parts of two *Dodonaea* species were analysed: *D. viscosa* ssp. *angustissima* and *D. ceratocarpa*. Extraction of the compounds found within the leaf resin was planned to determine what compounds were present. The aim of this study was to find a clerodane which could be isolated in an appreciable quantity for further synthetic investigation.

### 2.1. Isolation of compounds from *Dodonaea viscosa* ssp. *angustissima*

*D. viscosa* ssp. *angustissima* was collected from Wright's Bridge on the Balingup Nannup Road, WA (Figure 2.1). The leaves were dried for at least two days in air to remove excess moisture prior to storage. In the laboratory, the leaves were steeped in diethyl ether for 20-30 minutes. The extract was filtered and concentration *in vacuo*. A yellow solid was obtained in a yield of 4.2% from the total plant used. The <sup>1</sup>H NMR spectrum of the crude material indicated that at least two compounds contained a 3-substituted furan as peaks were found at 7.35, 7.20 and 6.25 ppm (Figure 2.3). Resonances located between 3.70-4.20 ppm suggested that there were methylenes next to alcohol or ester functional groups. As most of the substituents in the crude leaf resin were polar, chromatography was challenging, nonetheless three clerodane diterpenes were identified.



Figure 2.1: *D. viscosa* ssp. *angustissima* leaves

The first compound **28** contained a furan as peaks were seen at 6.24, 7.17 and 7.34 ppm in the  $^1\text{H}$  NMR spectrum. A pair of doublets were found at 3.72 and 4.18 ppm which each had an integration of one hydrogen. The multiplicity and downfield position of these signals was indicative of a methylene attached to an alcohol. A resonance at 6.75 ppm was attributed to a vinylic hydrogen of an  $\alpha,\beta$ -unsaturated carboxylic acid. All of these key signals were identical to hautriwaic acid **28** (Figure 2.2) which was also isolated from this species grown in Murchison River, WA.<sup>99</sup>

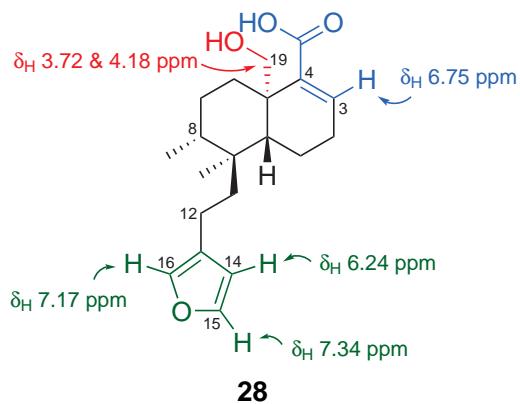


Figure 2.2: Structure assigned to **28** isolated from the leaf resin of *D. viscosa* ssp. *angustissima*.

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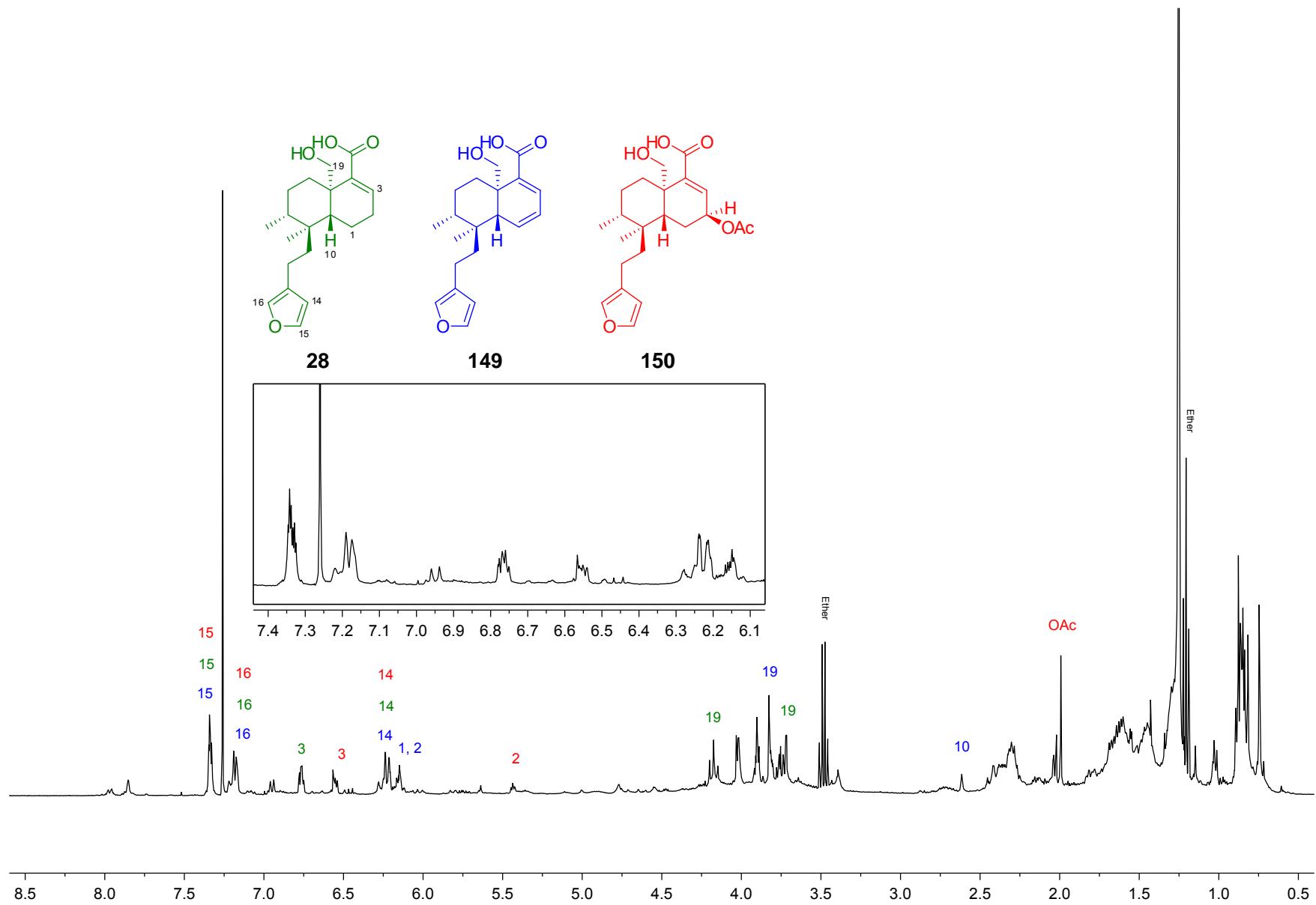


Figure 2.3: Crude  $^1\text{H}$  NMR spectrum of *D. viscosa* ssp. *angustissima* leaf resin (ppm).

The second compound **149** also had a furan within its structure as signals were detected at 6.21, 7.17 and 7.33 ppm in the  $^1\text{H}$  NMR spectrum. A singlet integrating for two hydrogens was found at 3.83 ppm, which was indicative of a methylene connected to a primary alcohol. As observed with **28**, a signal was located at 6.78 ppm which was ascribed to a vinylic hydrogen next to a carboxylic acid. A broad resonance at 6.14 ppm with an integration of two hydrogens suggested a pair of alkene hydrogens within a conjugated diene. The stereochemistry of compound **149** was presumed to be the same as that of hautriwaic acid **28** also isolated from the same plant. Based upon these significant signals in the  $^1\text{H}$  NMR spectrum, a structure for **149** was proposed and confirmed (Figure 2.4). This compound was previously isolated by Payne and Jefferies,<sup>74</sup> though the  $^1\text{H}$  NMR data better matched the values provided by Giordano and colleagues.<sup>115</sup>

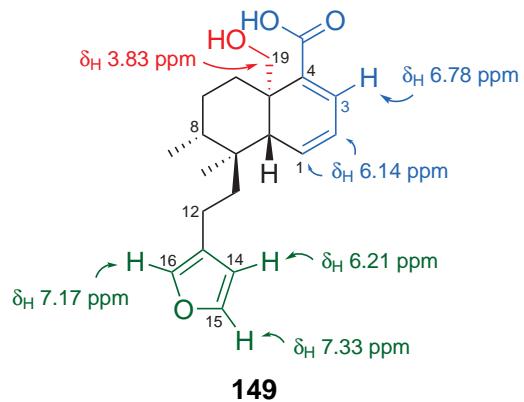


Figure 2.4: Structure given to **149** isolated from the leaf resin of *D. viscosa* ssp. *angustissima*.

The final compound **150** also contained a furan ring as the  $^1\text{H}$  NMR spectrum showed three signals in the characteristic regions. A sharp singlet was found at 1.99 ppm. The chemical shift and integration of this resonance was typical of methyl hydrogens within an acetate functional group. Additionally, a triplet located at 5.44 ppm was likely to be attributed to the methine hydrogen geminal to the acetate group. The NMR signals for this compound were alike to those of the known diacetate clerodane **151** (Figure 2.5).<sup>116</sup>

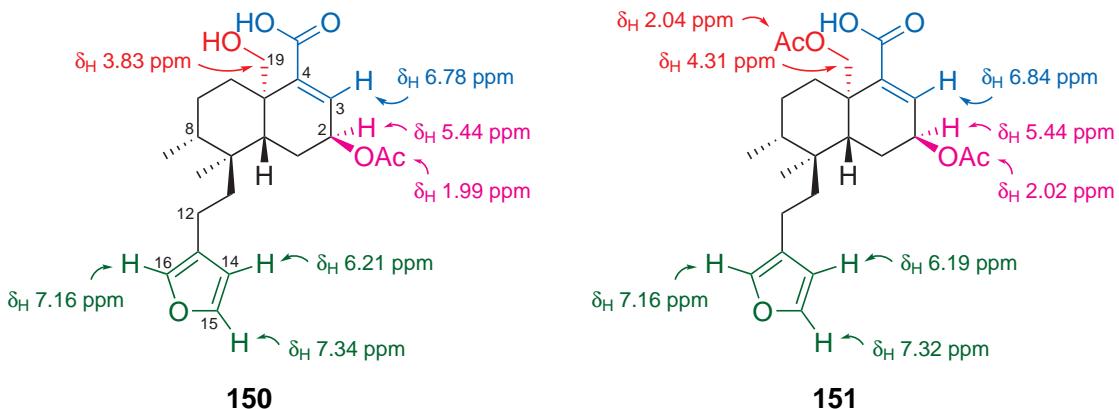
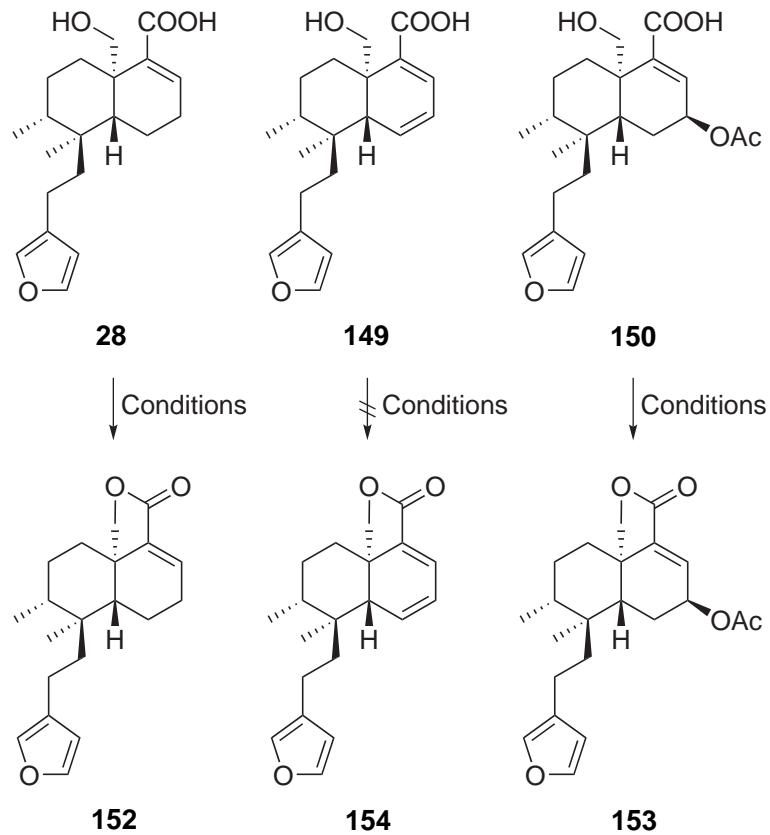


Figure 2.5: Final structure given to **150** isolated from the leaf resin of *D. viscosa* ssp. *angustissima* and its comparison to the known compound **151**.<sup>116</sup>

An alternative and more selective extraction method needed to be implemented to make separation of the compounds easier. Since these compounds contained carboxylic acid groups, the leaves were soaked in an aqueous base solution to deprotonate the acidic components. This method could selectively extract any acidic compounds and water soluble compounds. Thus, *D. viscosa* ssp. *angustissima* leaves were soaked in 5% aqueous sodium carbonate solution overnight and filtered. The filtrate was acidified to pH 1-2 and the solution was extracted with dichloromethane to remove the neutralised acids. Flash chromatography afforded three polar compounds. <sup>1</sup>H NMR spectroscopy confirmed that these were the same three clerodanes determined previously. Although this method gave the three aforementioned clerodane carboxylic acids more cleanly, separation of the individual compounds was still challenging. Compound **149** only differed from **28** in that it had an extra alkene within its structure, which caused co-elution of these two similar compounds. Interestingly, previous studies on the same plant (referred to as *D. attenuata* A. Cunn.) only discussed the isolation and chemistry of hautriwaic acid **28** which was described as the major acidic constituent.<sup>74,99</sup> The isolation or chemistry of compounds **149** and **150** was not mentioned. The three clerodanes isolated from *D. viscosa* ssp. *angustissima* in this study were not further explored during this project.

After this project concluded, a simpler method to separate these compounds was discovered using a selective lactonisation procedure (Scheme 2.1).<sup>117</sup> The optimised procedure treated a mixture of compounds **28**, **149** and **150** with 5 mol % CSA in DCE at reflux for 48 hours to form the lactones **152** and **153**. The diene clerodane **149** was

not lactonised to form **154** with this method, and could now be isolated using acid-base chemistry.



Scheme 2.1: Lactonisation of a mixture of compounds **28**, **149** and **150**.<sup>117</sup> Conditions: 5 mol % CSA, DCE, 84°C, 48 h.

## 2.2. Isolation of compounds from *Dodonaea ceratocarpa*

*D. ceratocarpa* shrubs were grown from seedlings and collected near Balingup, WA from private land owners (Figure 2.6). Upon collection, the leaves were dried over two days in air to remove excess moisture. The leaves were steeped in methanol for 20-30 minutes at room temperature. Methanol is the extraction solvent of choice with fresh plant material.<sup>118</sup> Exhaustive extraction of the plant is typically performed with boiling methanol to remove as much of the chemical substituents possible, however, in this case it was not required. After filtration, the green filtrate was evaporated to leave a yellow-green foamy solid and a residue. The <sup>1</sup>H NMR spectrum of the crude resin showed an extremely complex mixture of compounds.



Figure 2.6: Dried *D. ceratocarpa* leaves.

To prevent the extraction of polar compounds such as chlorophyll and other complex plant macromolecules, a less polar solvent was used. The leaves were steeped in diethyl ether for 20-30 minutes at room temperature and then filtered. The filtrate was evaporated under reduced pressure to afford the resin as a yellow solid. The  $^1\text{H}$  NMR spectrum of the resin was complex, though it was less complicated than the spectrum obtained via the methanol extraction method. The individual components of the leaf resin were isolated by flash chromatography. Three compounds were isolated from the resin mixture: **155** (3.5% w/w resin), **156** (0.9% w/w resin) and **157** (28% w/w resin).

Clerodane **155** was the least polar of the three clerodanes and was identified using spectroscopic techniques. In the  $^1\text{H}$  NMR spectrum, three resonances at 7.34 (1H, t,  $J$  = 1.7 Hz), 7.19 (1H, m,  $J$  = 1.7, 0.9 Hz) and 6.25 ppm (1H, dd,  $J$  = 1.7, 0.9 Hz) suggested that a 3-substituted furan was present within compound **155**. The coupling constants between these peaks were characteristic for furans.<sup>119</sup> The COSY NMR spectrum showed a correlation between 7.34 and 7.19 ppm, as well as 6.25 and 7.34 ppm. The presence of the furan within the structure was confirmed by peaks at 125.7, 111.1, 142.9 and 138.5 ppm in the  $^{13}\text{C}$  NMR spectrum. Typically, many clerodanes contain a furan ring, particularly ones attached to the C12 position (Figure 2.7).<sup>99,120–122</sup>

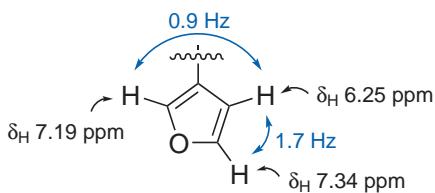


Figure 2.7: Structure of the furan fragment determined via NMR spectroscopy.

A signal at 5.24 ppm (1H, br s) was evident and could be ascribed to a vinylic hydrogen. Four methyl groups were observed at 1.85 (m), 1.03 (s), 0.85 (d) and 0.73 ppm (s). The deshielded methyl signal at 1.85 ppm was presumably allylic. The vinylic hydrogen at 5.24 ppm exhibited a correlation with the methyl hydrogens at 1.85 ppm, which was indicative of the methyl group being attached to the alkene. Alkene carbons were observed at 122.4 (CH) and 143.9 ppm (quaternary C). A resonance at 3.57 ppm (1H, dd,  $J = 11.2, 4.9$  Hz) was detected which was expected to be a methine attached to the same carbon as an electronegative atom, such as a hydroxyl group. A peak at 75.8 ppm was determined as a CH carbon via a DEPT analysis. The IR spectrum of **155** showed an absorbance at  $3620\text{ cm}^{-1}$  which affirmed the alcohol functional group. Additionally, the doublet at 0.85 ppm was indicative of a methyl substituent adjacent to a methine hydrogen. This information suggested the presence of three additional fragments within compound **155** (Figure 2.8).

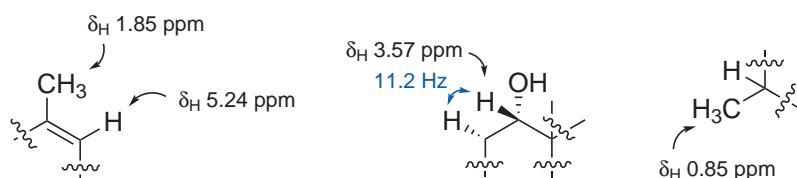


Figure 2.8: Other fragments determined via NMR spectroscopy.

A tentative structure was assigned based upon the assignments of some fragments (Figure 2.9). The structure of compound **155** was a clerodane with an alcohol at C6 and a furan attached to the C12 carbon (Figure 2.9). The C6 alcohol was assigned to an  $\alpha$ -orientation, making H6 a  $\beta$ -hydrogen. Typically in *trans*-clerodane systems,  $\beta$ -hydrogens attached to an  $\alpha$ -alcohol have a chemical shift of 3.30-3.60 ppm.

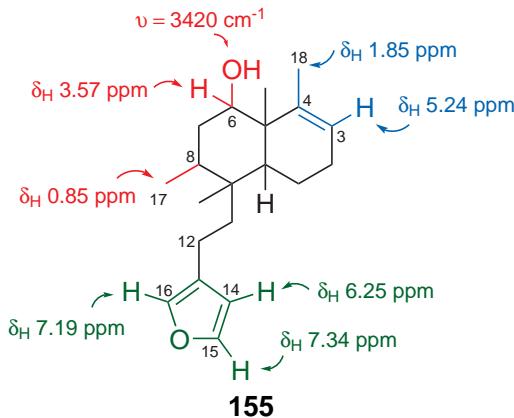
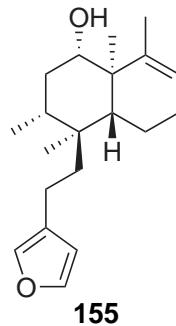


Figure 2.9: Tentative structure of the furan clerodane **155** isolated from *D. ceratocarpa*.

Confirmation of the structure, particularly the stereochemistry, was achieved upon comparison with other similar clerodanes (Table 2.1). A compound isolated from *Croton sonderianus* by Silveira and McChesney shared  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals that were identical to compound **155** obtained from the leaf resin of *D. ceratocarpa* (Table 2.1).<sup>123</sup> Spectral data from both sources only differed in spectrometer resolution. This evidence suggested that compound **155** was the same known compound (Table 2.1).

Table 2.1: NMR comparison of compound **155** (ppm).



Position	<i>D. ceratocarpa</i> <b>155</b> <sup>†</sup>		<i>C. sonderianus</i> <sup>123*</sup>	
	$^1\text{H}$	$^{13}\text{C}$	$^1\text{H}$	$^{13}\text{C}$
3	5.24, br s	122.4	5.30, br s	122.0
6	3.57, dd	75.8	3.60, dd	75.5
14	6.25, dd	111.1	6.30, m	110.9
15	7.34, t	138.5	7.40, m	138.3
16	7.19, m	142.9	7.28, br s	142.8
17	0.85, d	15.8	0.85, d	15.6
18	1.85, m	22.5	1.87, br s	22.3 <sup>‡</sup>
19	1.03, s	15.1	1.05, s	15.0 <sup>‡</sup>
20	0.73, s	17.9	0.75, s	17.7

<sup>†</sup> $^1\text{H}$  400 MHz,  $^{13}\text{C}$  200 MHz. <sup>\*</sup> $^1\text{H}$  200 MHz or 90 MHz,  $^{13}\text{C}$  50 MHz or 15 MHz

<sup>‡</sup> The C18 and C19 shifts were incorrectly labelled, so the values have been amended in the table<sup>123</sup>

Compound **156** has a molecular ion  $[M - H]^+$  of 333.2058 that was consistent with a molecular formula of  $C_{20}H_{30}O_4$ . The IR spectrum showed a broad hydroxyl absorbance at  $3354\text{ cm}^{-1}$ , indicating the presence of an alcohol group. The  $^1\text{H}$  NMR spectrum showed a pair of doublets at 4.03 and 4.28 ppm assigned as a methylene attached to an oxygen, most likely an allylic primary alcohol. These signals have an AB splitting pattern with identical coupling constants of 12.0 Hz. A correlation was detected between 4.03 and 4.28 ppm in the COSY spectrum. Three remaining methyl peaks were found at 1.10, 0.85 and 0.78 ppm. It was expected that **156** was a *trans*-clerodane like **155**, so H10 and the methyl group attached to C5 were likely to have a  $\beta$ -orientation and  $\alpha$ -orientation, respectively. C17, C19 and C20 were ascribed to the resonances at 0.85, 1.10 and 0.78 ppm, respectively. A signal located at 5.59 ppm was detected which was assigned to H3. It was likely that this signal corresponded to a vinylic hydrogen, which was more downfield than expected. This could be caused by the electron withdrawing nature of the allylic alcohol nearby. Peaks attributed to a  $\beta$ -substituted butenolide were apparent at 5.83 and 4.73 ppm, as similar peaks have been seen in some published clerodanes.<sup>85,86</sup> IR spectroscopy provided further evidence of the butenolide with frequencies of  $\nu = 1779$ , 1738 and  $1636\text{ cm}^{-1}$ . A peak at 3.66 ppm was found by  $^1\text{H}$  NMR spectroscopy. This signal was likely to be a methine hydrogen adjacent to an alcohol. A similar shift ( $\beta$ -H6) was observed previously upon analysis of the furan compound **155**. Based upon these findings, a tentative structure was put forward (Figure 2.10).

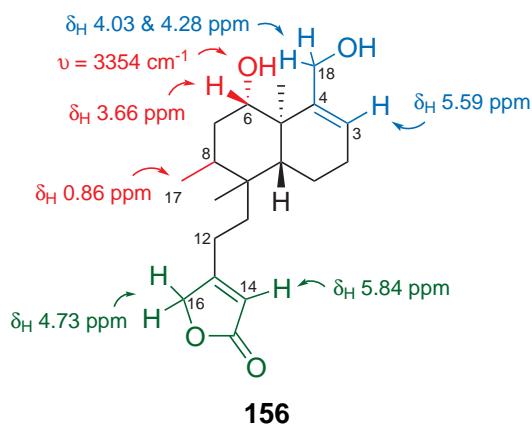


Figure 2.10: Tentative structure of the allyl alcohol clerodane **156** isolated from the leaf resin of *D. ceratocarpa*.

The stereochemistry of compound **156** at the five asymmetric centers as well as the C18 methylene were compared to two compounds **158** isolated from *Gutierrezia texana* and **159** isolated from *Amphiachyris dracunculoides* which had a *cis*-decalin ring junction.<sup>17,18</sup> The two compounds differed only by the orientation of the C6 hydroxyl group. An inaccuracy was found in the paper containing compound **159** (Table 2.2).<sup>124</sup> The H18, C18, H19 and C19 shifts were incorrectly assigned to each other. The labels have been swapped to the correct positions in Table 2.2. Interestingly, the <sup>1</sup>H and <sup>13</sup>C NMR data obtained for compounds **158** and **159** were remarkably alike. The H6 shifts for both compounds were reported as a doublet of doublets at 3.42 ppm, which confirmed that one compound had been incorrectly assigned. It is likely that compound **159**, isolated from *A. dracunculoides*,<sup>124</sup> was incorrectly assigned as an  $\alpha$ -H6 instead of a  $\beta$ -H6 similar to compound **158**.<sup>86</sup> To support this, NMR data of *cis*-clerodanes containing a C6 alcohol were used to for comparative purposes. Compound **160** is a *cis*-clerodane with a  $\beta$ -alcohol at C6. The  $\alpha$ -H6 resonance for this compound was reported at 3.64 ppm, which was as expected.<sup>78</sup> When juxtaposed with **160**, the H6 methine in compound **159** has a low chemical shift for it to truly be assigned to an  $\alpha$ -conformation. Based upon this information, the reported compounds **158** and **159** were identical, and **158** was the correct structure.

Table 2.2: Comparative NMR analysis of **156** to the diastereomeric clerodanes published in literature (ppm).<sup>86,124</sup>

**156**

**158**

**159**

**160**

Incorrect  
stereochemistry

$\delta_H$  3.64 ppm

Position	<i>D. ceratocarpa</i> <b>156</b>		Compound <b>158</b> <sup>86</sup>		Compound <b>159</b> <sup>124</sup>	
	<sup>1</sup> H	<sup>13</sup> C	<sup>1</sup> H	<sup>13</sup> C	<sup>1</sup> H	<sup>13</sup> C
3	5.59, dd	128.4	5.59, t	129.4	5.59, dd	129.5
4	-	146.2	-	141.4		141.5
6	3.66, dd	75.1	3.42, dd	79.7	3.42, dd	79.9
10	1.29, d	45.5	-	45.5	1.30, br d	45.8
13	-	170.6	-	171.1	-	171.2
14	5.83, m	115.4	5.82, br s	115.0	5.83, m	115.2
15	-	174.0	-	174.2	-	174.3
16	4.73, d	73.2	4.72, br s	73.0	4.74, d	73.3
17	0.85, d	15.8	0.79, d	15.5	0.80, d	15.7
18	4.28, d	66.9	4.28, d	67.6	4.30, d <sup>†</sup>	
18'	4.03, d		4.10, d		4.09, d <sup>†</sup>	67.8 <sup>†</sup>
19	1.10, s	16.4	1.31, s	31.0	1.31, s <sup>†</sup>	31.3 <sup>†</sup>
20	0.78, s	18.0	0.81, s	17.6	0.82, s	17.9

<sup>†</sup>Harraz *et al.* incorrectly labelled the <sup>1</sup>H and <sup>13</sup>C NMR data for the C18 and C19 positions. The chemical shifts have been switched in the table above to correct this.<sup>124</sup>

The <sup>1</sup>H NMR data of **156** obtained in this work was different to **158** used for comparative purposes. The two obvious differences between the clerodane isolated from *D. ceratocarpa* and the literature compound were the C6 and C19 positions. The structure of compound **156** is assigned in Figure 2.11. This compound **156** has not been reported to date. Furthermore, it was likely that **156** would have the same stereochemistry of the three methyl groups attached to the asymmetric carbons identified with the furan compound **155** discussed earlier in Section 2.3.1.

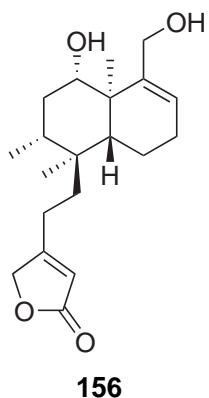


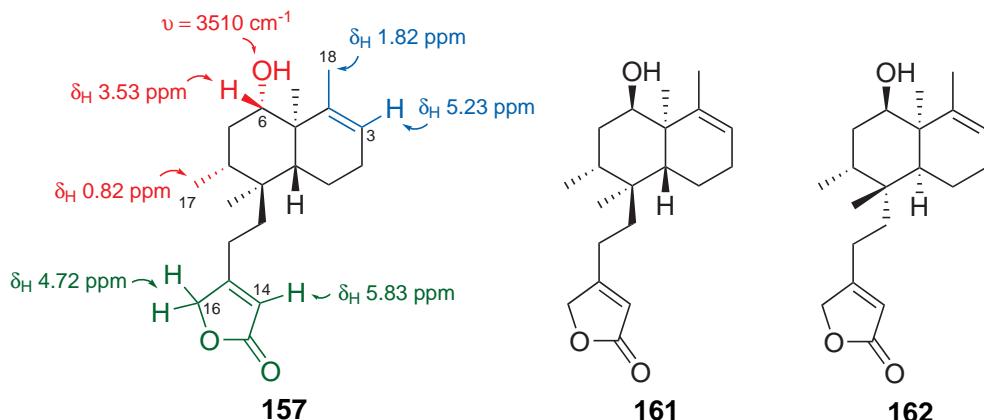
Figure 2.11: Final structure assigned to the allylic alcohol clerodane **156** isolated from *D. ceratocarpa* leaf resin.

Compound **157**, a pale yellow powder, was the most abundant in the diethyl ether extract, accounting for 3.5% w/w of the plant leaves. **157** had a molecular formula of  $C_{20}H_{30}O_3$  by HRMS. The IR spectrum confirmed the presence of a hydroxyl group at ( $3510\text{ cm}^{-1}$ ). Three other frequencies were observed at  $\nu = 1786, 1743$  and  $1635\text{ cm}^{-1}$ . These three signals were suggestive of a  $\beta$ -substituted butenolide. The carbonyl stretching frequency at  $\nu = 1786\text{ cm}^{-1}$  was higher than non-lactone carbonyls due to the ring strain. The  $^1\text{H}$  NMR spectrum of compound **157** was obtained (Figure 2.12). The spectrum showed two signals at 5.83 (1H, m) and 4.72 ppm (2H, d), which had a strong correlation in the COSY spectrum. These two resonances are typical values of C14 and C16 protons for a clerodane with a butenolide. A vinylic signal on the clerodane skeleton at 5.23 ppm (1H, br s) was evident. A doublet of doublets was observed at 3.53 ppm (1H) and was assigned the  $\alpha$ -C6 methine adjacent to a C6 hydroxyl group. The highest chemical shift for a methyl substituent was located at 1.82 ppm (s). This signal was assigned as the C18 methyl and was downfield relative to the other methyl signals due to its attachment to the C4 alkene. Another methyl resonance was observed at 0.82 ppm as a doublet which was assigned as the C17 methyl group. This methyl group had a correlation to another methyl substituent at 0.76 ppm (s) in the COSY spectrum that could only be assigned as C20. The remaining methyl group at 1.02 ppm (s) was assigned as C19.

The NMR data of compound **157** was compared to some reported stereoisomers **161** and **162** (Table 2.3).<sup>79,80,125</sup> A tentative structure for compound **157** was assigned. When compared to the two literature structures, it appeared that the compound isolated from

the leaf resin of *D. ceratocarpa* was different. The first difference noted was the C6 position. Both compounds **161** and **162** had reported  $\alpha$ -H6 resonances, with the signal for **161** located at 3.76 ppm. This did not match that observed for compound **157** which could be found at 3.53 ppm. Based on these findings, it is likely that compound **157** exhibited a  $\alpha$ -C6 OH substitution. The orientation of the C6 alcohol would affect the C19 methyl nearby, which was confirmed. The C19 of compound **157** was upfield at 1.02 ppm, whereas the chemical shifts for the same positions of compounds **161** and **162** were observed at 1.18 and 1.15 ppm, respectively. It was highly probable that the stereochemistry of compound **157** at the five stereocenters would be the same as that of the two aforementioned clerodanes **155** and **156**. A literature search was conducted of all the stereoisomers possible of compound **157**. The NMR data obtained was inconsistent with that acquired from the clerodane isolated from *D. ceratocarpa*. Since this was a new compound, the structure of compound **157** was confirmed with X-ray crystallography.

Table 2.3: NMR chemical shifts obtained for the tentative structure of **157** and its stereoisomers (ppm).<sup>79,80,125</sup>



Position	<i>D. ceratocarpa</i> <b>157</b>	Compound <b>161</b> <sup>79†*</sup>	Compound <b>162</b> <sup>125</sup>
	<sup>1</sup> H	<sup>1</sup> H	<sup>1</sup> H
3	5.23, br s	5.90, br s	
6	3.53, dd	3.76, br s	
14	5.83, m	5.90, br s	
16	4.72, d	4.81, d ‡	
17	0.82, d	0.90, d	0.88
18	1.82, s	1.77, s	1.70
19	1.02, s	1.18, s	1.15
20	0.76, s	1.04, s	1.03

\* Although Anthonsen was the first researcher to isolate this compound, NMR data in the table is from Okazaki in  $\text{CDCl}_3$ .<sup>79,80</sup> Anthonsen stated fewer shifts which were run in  $\text{CCl}_4$

† This value was incorrectly assigned to H13, so this was corrected in the table.<sup>79</sup>

56

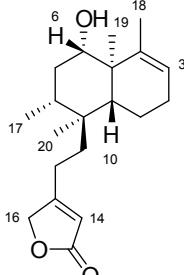
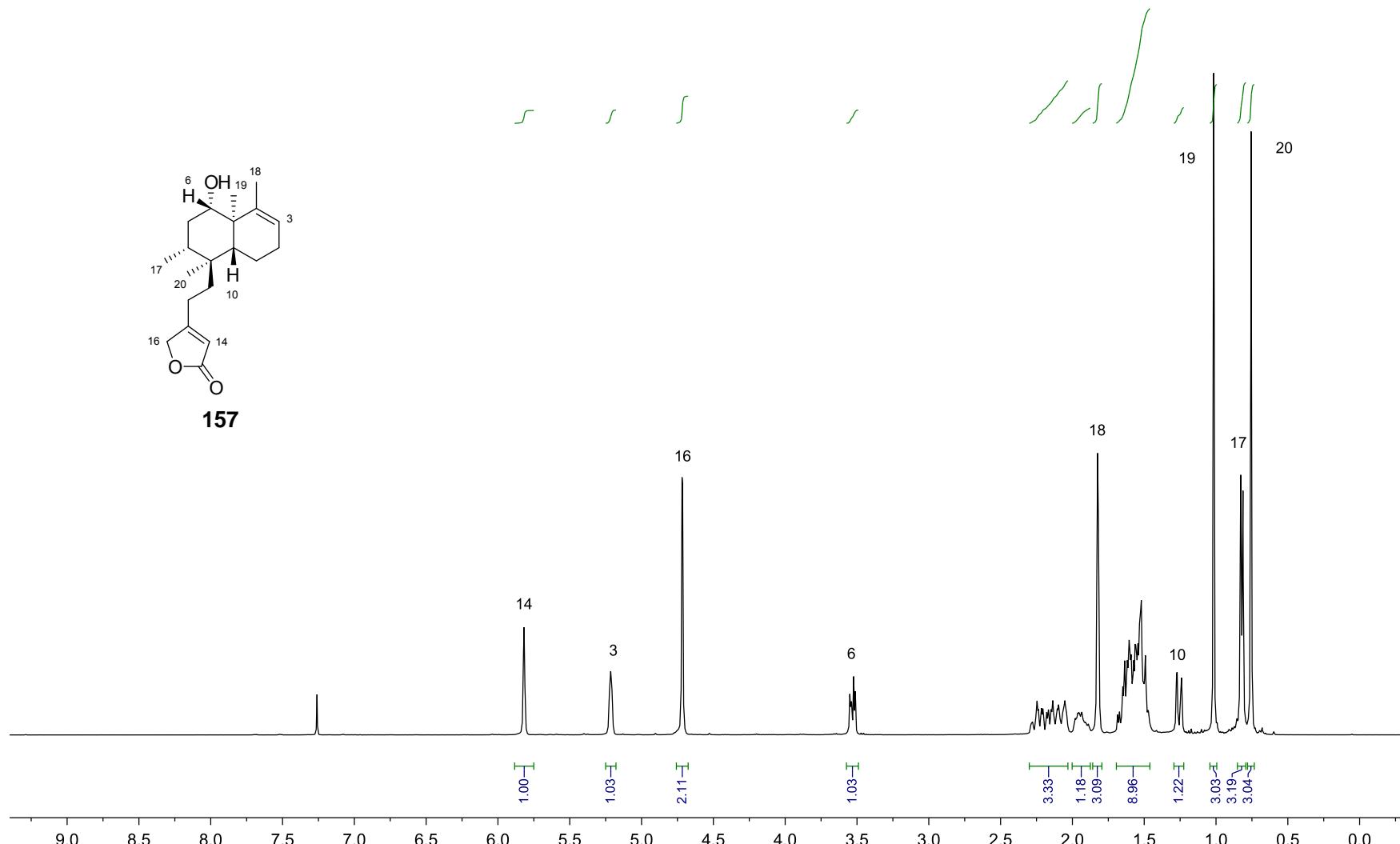
**157**

Figure 2.12:  $^1\text{H}$  NMR spectrum of the major compound **157** isolated from *D. ceratocarpa* (ppm).

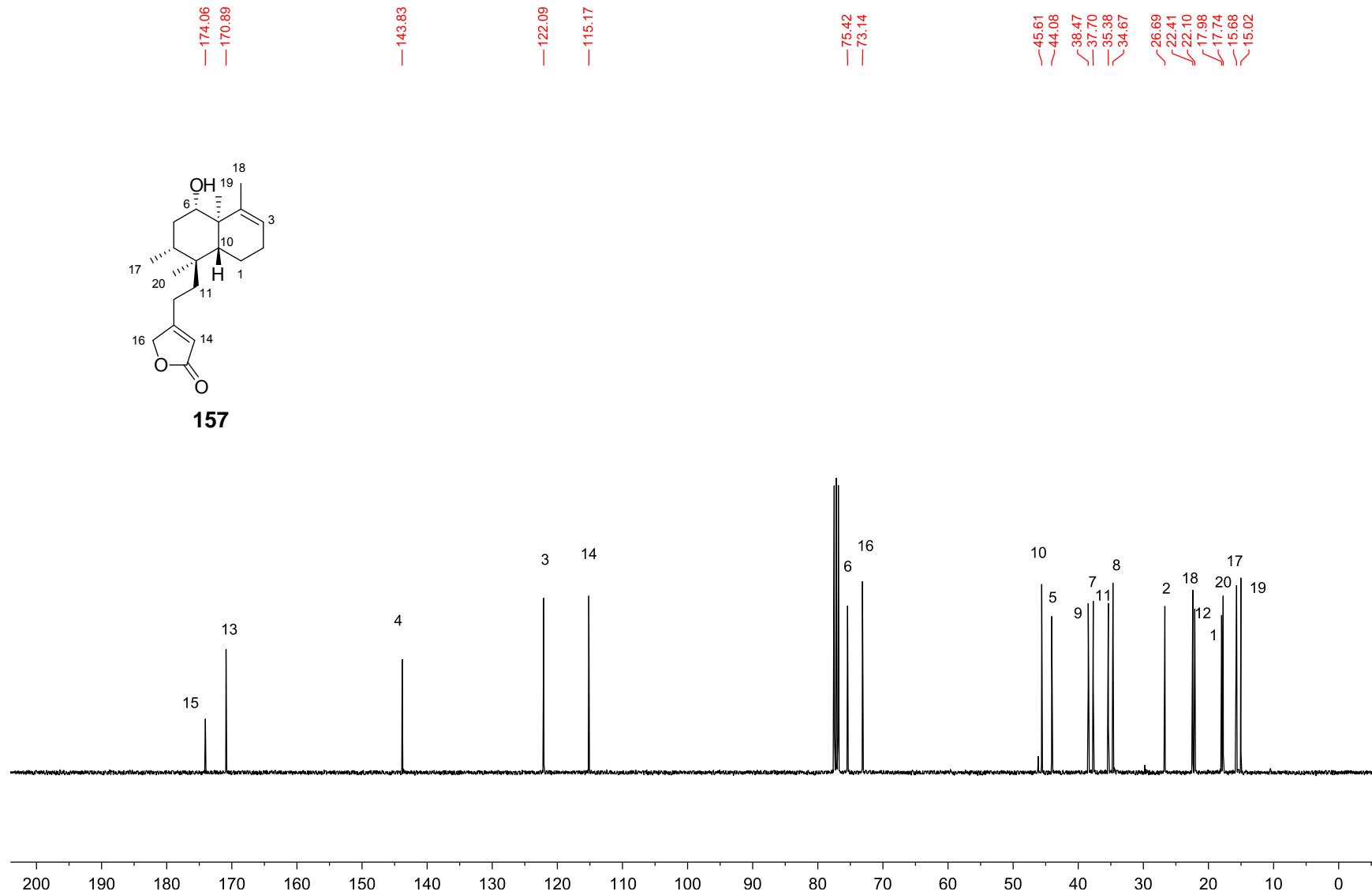


Figure 2.13:  $^{13}\text{C}$  NMR spectrum of the major isolated compound **157** (ppm).

Crystals suitable for X-ray analysis were obtained upon diffusion of vapours from a solution of **157** in diethyl ether and petrol. Structural determination was performed by Associate Professor Brian Skelton at University of Western Australia (Figure 2.14). The absolute configuration was determined only at a moderate level of confidence. X-ray crystallography confirmed that rings A and B had a chair conformation, with an axial orientation of H10 and C19 (*trans*-decalin bridge). The stereochemistries of the C17, C18, C19 and C20 methyl groups were confirmed to what was proposed for all the clerodanes isolated from *D. ceratocarpa*. C17 and C19 adopted an axial conformation and C20 had an equatorial conformation. C18 was confirmed as being attached to an alkene at C4, as it existed in a planar orientation on ring A. The hydroxyl group at C6 was equatorial, pointing back to the bottom face of the molecule. The equatorial hydroxyl group at C6 had a hydrogen bond with the butenolide C15 oxygen atom ( $H(6)\dots O(15) = 2.07 \text{ \AA}$ ). The orientation of the two C19 and C20 methyl groups forced ring B away from a perfect chair conformation. This configuration confirmed that **157** was an unreported compound.

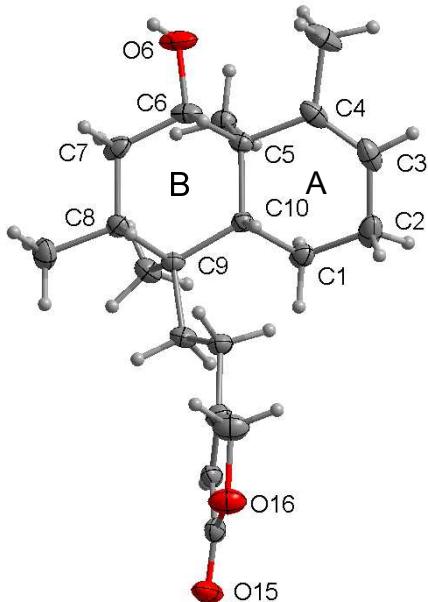
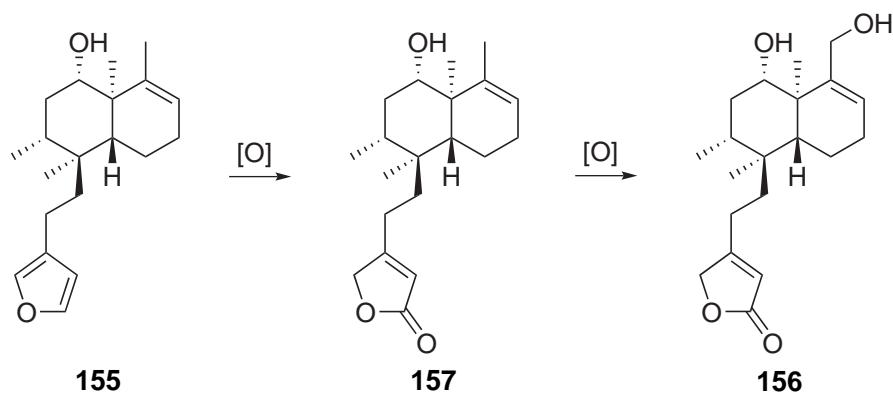


Figure 2.14: X-ray structure of **157**.

The structures of the three isolated clerodanes **155**, **157** and **156** are similar. Their presence could be concomitant with their biosynthesis (Scheme 2.2). The furan **155** could be oxidised to form the butenolide **157**. Compound **157** could then undergo an allylic oxidation to form the allyl alcohol **156**.



Scheme 2.2: Proposed biosynthesis of the three isolated clerodanes.

### 2.2.1. Potential chemistry of the major clerodane **157**

Since the clerodane **157** was the most abundant compound in the resin and could be isolated in gram quantities, its chemistry was investigated. All three rings have functional groups that are capable of reacting with an array of reagents and reaction conditions to form a new suite of analogues. Each ring could be selectively functionalised to demonstrate the structural manipulations possible, and to introduce extra complexity into the molecule (Figure 2.15).

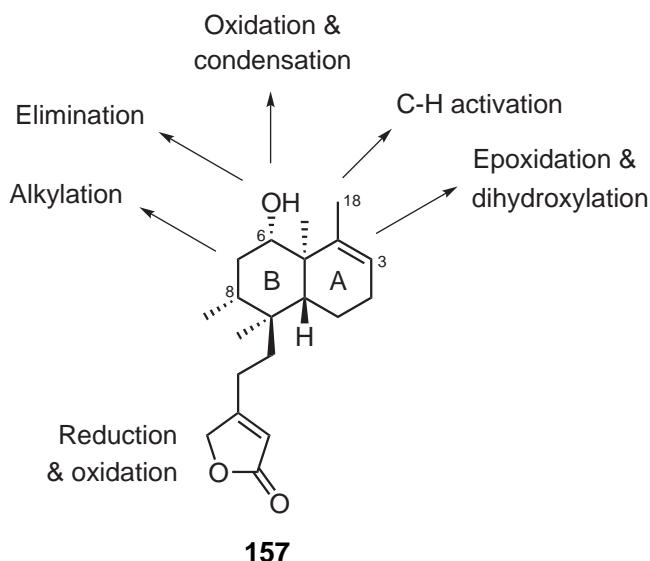


Figure 2.15: Possible derivatisation sites of **157**.

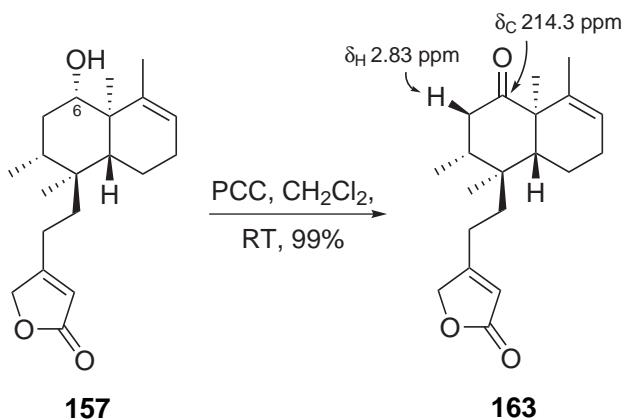
Ring A has an alkene at C3-C4. This position could undergo epoxidation and dihydroxylation reactions. Additionally, the C18 position could be functionalised to form the acetate via a C-H activation reaction directed by a C6 oxime. Ring B has more

reaction potential than ring A, mostly due to the versatility introduced by the C6 alcohol. The C6 alcohol could be oxidised to form a ketone. This position could also undergo condensation reactions to form oximes and hydrazones. Elimination of the alcohol is also a possibility to form the C6-C7 alkene. If the alcohol is oxidised to a ketone, alkylation at the  $\alpha$ -position (C7) may be feasible. Additionally, olefination of the C7-C8 position could occur to give the  $\alpha,\beta$ -unsaturated ketone. The butenolide could also be reduced to a furan or oxidised to give a  $\gamma$ -hydroxybutenolide.

# Chapter 3

## Reactions and Rearrangements of the Alcohol Clerodane **157**

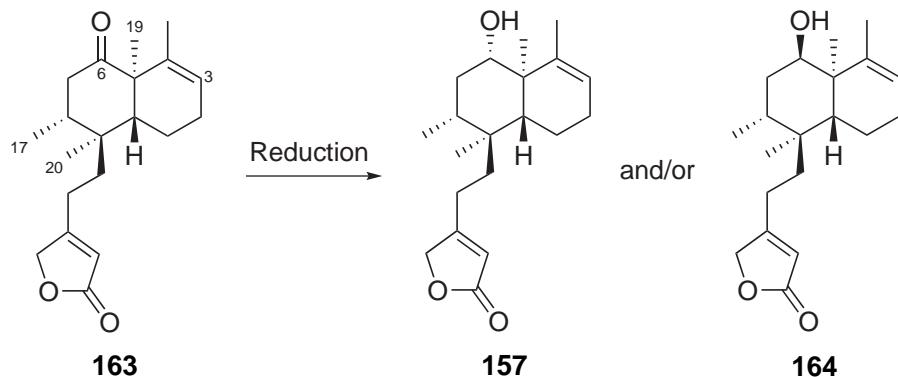
During the initial isolation of the alcohol clerodane **157**, the compound appeared to decompose during normal laboratory manipulations. The C6 alcohol **157** was identified as a potential site for degradation through an acid-catalysed elimination reaction. To overcome this problem, the alcohol was oxidised to the ketone **163**. Oxidation of **157** with 1.5 equivalents of PCC in dichloromethane for 8 hours afforded the ketone **163** in 99% yield (Scheme 3.1). Purification of the crude reaction mixture was unnecessary. It is important to note that if the reaction was left stirring for more than 8 hours, a reduction in product yield would occur. The newly formed ketone was identified by a new absorbance at  $1702\text{ cm}^{-1}$  in the IR spectrum. Additionally, the  $^1\text{H}$  NMR spectrum did not have the distinctive resonance of the H6 methine hydrogen of the alcohol **157** at 3.53 ppm. A new doublet of doublets at 2.83 ppm appeared which was attributed to a new  $\beta$ -H7 signal orientated in the same plane of the carbonyl within compound **163**. A new ketone carbonyl peak was observed at 214.3 ppm in the  $^{13}\text{C}$  NMR spectrum, whilst the C-OH peak at 75.4 ppm corresponding to the starting material was absent. The butenolide portion of the molecule remained intact. As the ketone **163** was stable, it was used as a starting material for most of this work.



Scheme 3.1: Synthesis of the ketone **163**.

### 3.1. Reduction of the ketone

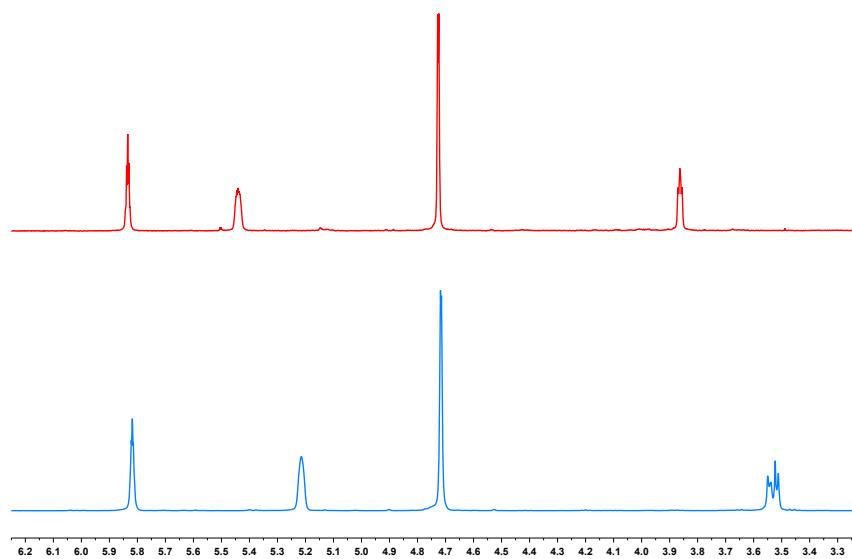
Reduction of the ketone **163** was investigated to examine the reversibility of the oxidation reaction described in Scheme 3.1. Reduction of **163** could give two possible products, the  $\alpha$ -alcohol **157** (which was isolated from the plant) or the epimer  $\beta$ -alcohol **164** (Scheme 3.2). These products are formed by addition of hydride to the carbonyl on opposite faces. The most hindered side of the molecule **163** is the bottom, as the C17, C19 and C20 methyl groups are all orientated in this direction. Thus, the anticipated product was initially the  $\alpha$ -alcohol **157**.



Scheme 3.2: Products that could form in the reduction of **163**.

To avoid reduction of the butenolide, sodium borohydride was used as a chemoselective reducing agent. Reduction of the ketone **163** with 1 equivalent of sodium borohydride in methanol at  $-84^{\circ}\text{C}$  gave a single product which was not the expected product **157**. The  $^1\text{H}$  NMR spectrum of this new product (red) was similar but slightly different to the spectrum of the alcohol **157** (blue) (Table 3.1).

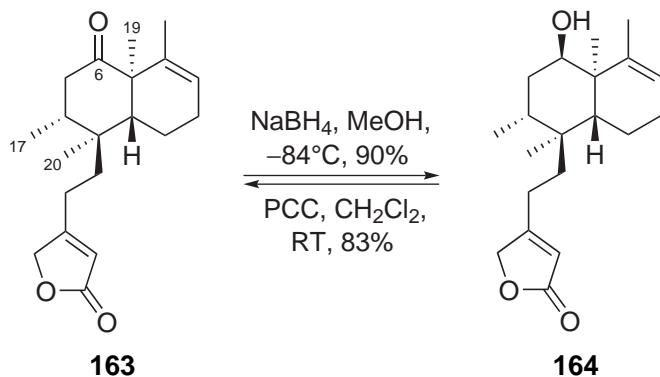
Table 3.1: NMR comparison of the reduction product (red) and the  $\alpha$ -alcohol **157** (blue) (ppm).



Compound	Position	$^1\text{H}$	$^{13}\text{C}$
New compound	3	5.44, m	125.3
	6	3.86, t	71.3
<b>157</b>	3	5.23, br s	122.1
	6	3.53, dd	75.4

The key differences between **157** and this new, unknown compound are discerned in the NMR spectra. What appeared to be the H6 methine signal for this new compound was a triplet at 3.86 ppm, whereas the signal observed for **157** was a doublet of doublets located at 3.53 ppm. In addition, the H3 vinylic resonance for the new compound was a multiplet at 5.44 ppm, whilst the same signal for **157** was a broad singlet which had a upfield shift at 5.23 ppm. The C6 peak observed for the new compound was positioned at 71.3 ppm, whilst it was located at 75.4 ppm for **157**. A variation was also noticed in the OH stretch region of the IR spectra of the new compound ( $3478\text{ cm}^{-1}$ ) compared to **157** ( $3510\text{ cm}^{-1}$ ).

It was proposed that the epimer of **157**, the  $\beta$ -alcohol **164**, was formed. To confirm whether this was the case, oxidation of the new compound should provide the ketone **163**. Treatment of **164** with 1.5 equivalents of PCC in dichloromethane gave the ketone **163** in 83% yield, therefore the new compound could only be the  $\beta$ -alcohol **164**. (Scheme 3.3).



Scheme 3.3: Reversibility of the  $\text{NaBH}_4$  reduction of **163** to form the  $\beta$ -alcohol **164**.

The outcome of the reduction of the ketone **163** seemed counterintuitive. It was thought that the methyl groups at the C17, C19 and C20 positions would hinder the bottom face of the molecule from nucleophilic addition. Examination of the 3D molecular model of **163** shows how the C6 ketone carbonyl points towards the top face of the molecule so that the ring maintains the energetically favourable chair conformation (Figure 3.1). Taking into account the Bürgi-Dunitz trajectory of addition of a nucleophile to ketones ( $105 \pm 5^\circ$ ), the only possible outcome in this reduction process was the  $\beta$ -alcohol **164**.

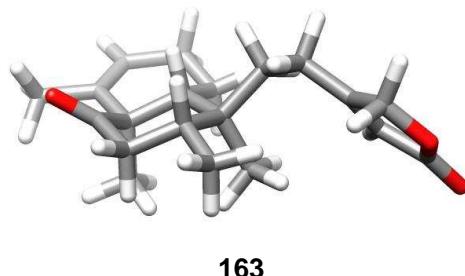
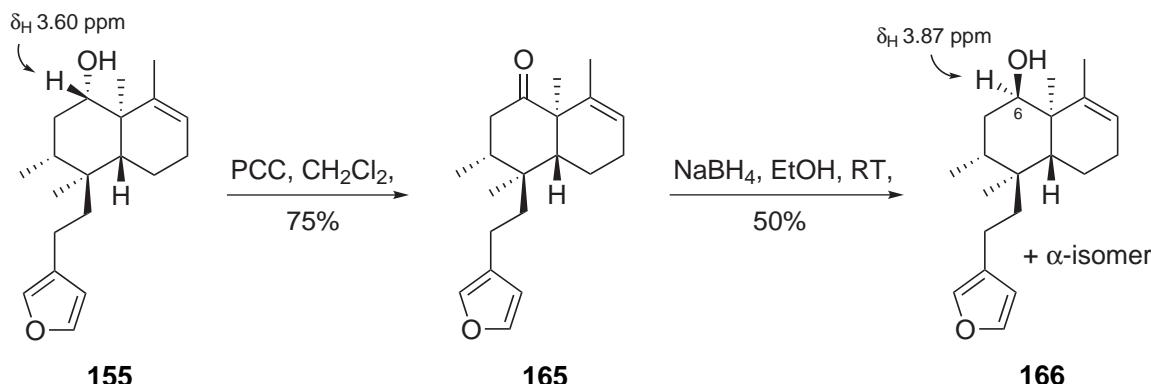


Figure 3.1: 3D molecular model of the ketone **163**.

A similar stereoselective reduction has been reported by Silveira and McChesney.<sup>123</sup> A clerodane alcohol **155** isolated from *Croton sonderianus* and also the leaf resin of *D. ceratocarpa* exhibited the same stereochemistry as **157**. The isolated  $\alpha$ -alcohol **155** was oxidised with PCC to give the ketone **165** in good yield. The ketone **165** was then subjected to sodium borohydride reduction in ethanol at room temperature to afford the axial,  $\beta$ -alcohol **166** in acceptable yield (Scheme 3.4). Some  $\alpha$ -alcohol was also recovered as a minor product, however the ratio or mass obtained was not reported. The IR spectra of **155** and **166** were similar except for the subtle change in the hydroxyl group

stretching frequencies. The  $^1\text{H}$  NMR spectrum of **166** displayed a triplet at 3.87 ppm which corresponded to the new H6 methine in the major product. This chemical shift was more deshielded compared to the same proton observed for the epimer **155** (3.60 ppm, dd), which supported the equatorial conformation of H6. The researchers explained the formation of the  $\beta$ -alcohol **166** based on steric approach control.<sup>123</sup>



Scheme 3.4: Oxidation of a C6 alcohol and reduction achieved by Silveira.<sup>123</sup>

### 3.1.1. Luche reduction of the ketone

As the reduction of **163** did not give the intended  $\alpha$ -alcohol **157** as the product, other reduction conditions were tested. Luche reductions are known to modify the selectivity of hydride addition to a carbonyl. Krief and Surleraux reported a change in stereoselectivity in the reduction of diones when sodium borohydride was used alone versus when  $\text{CeCl}_3$  and sodium borohydride were used (Table 3.2).<sup>126</sup> Interestingly, the reduction of **167** with  $\text{CeCl}_3$  and sodium borohydride at  $-78^\circ\text{C}$  afforded an 85% yield of **168** and **169** in a 96:4

Table 3.2: Contrasting stereoselectivities of the Luche and non-Luche  $\text{NaBH}_4$  reductions.<sup>126</sup>

Entry	Conditions	Yield	Ratio*	
			<b>168</b>	<b>169</b>
1	$\text{NaBH}_4$ , $\text{CeCl}_3$ , $\text{MeOH}$ , $-78^\circ\text{C}$ , <0.5 hr	85%	96	4
2	$\text{NaBH}_4$ , $\text{MeOH}$ , $-78^\circ\text{C}$ , 3 h	87%	7	93

\*Ratios obtained by  $^1\text{H}$  NMR spectroscopy

ratio, respectively.  $\text{CeCl}_3$  enabled the reduction to occur from the most hindered *exo* face to favour the *exo*-alcohol **168**. Conversely, when the same reaction was performed in the absence of  $\text{CeCl}_3$ , a 87% mixture of **168** and **169** were obtained in a 7:93 ratio, respectively.

As reduction of the ketone **163** with sodium borohydride selectively provided **164** as the only product, a Luche reduction of **163** was explored to see if addition of  $\text{CeCl}_3$  would afford the epimer alcohol **157**. Initially, treatment of **163** with 1 equivalent of sodium borohydride and  $\text{CeCl}_3$  heptahydrate in methanol at  $-84^\circ\text{C}$  afforded the two epimers in 98% yield (Table 3.3, entry 6). The alcohols **157** and **164** were formed in a 49:51 ratio. To further probe the selectivity, the reaction was repeated with five additional lanthanide chloride Lewis acids. These were  $\text{LaCl}_3$ ,  $\text{SmCl}_3$ ,  $\text{EuCl}_3$ ,  $\text{TbCl}_3$  and  $\text{YbCl}_3$  hydrates. These reactions also afforded mixtures of **157** and **164** with excellent overall yields ranging from 98-100% (Table 3.3). All reactions formed the  $\alpha$ -alcohol **157** in relative percentages of 14-54%. Thus, the addition of lanthanide chlorides improved but did not fully reverse the stereoselectivity of the reduction for **157**. A trend was observed with relation to the lanthanide chloride used and the ratio of products that were obtained.

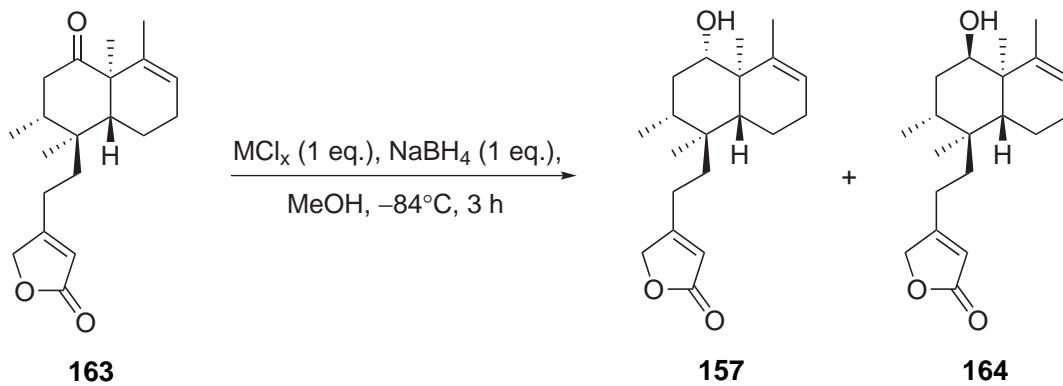
Table 3.3: Luche reductions with **163** and a variety of  $\text{LnCl}_3$  additives.

Entry	$\text{LnCl}_3 \bullet x\text{H}_2\text{O}$	Yield	Ratio*	
			<b>157</b> ( $\alpha$ )	<b>164</b> ( $\beta$ )
1	None	90%	0	100
2	$\text{YbCl}_3$	100%	14	86
3	$\text{TbCl}_3$	99%	22	78
4	$\text{EuCl}_3$	100%	26	74
5	$\text{SmCl}_3$	100%	32	68
6	$\text{CeCl}_3$	98%	49	51
7	$\text{LaCl}_3$	98%	54	46

\*Ratios obtained by  $^1\text{H}$  NMR spectroscopy

The stronger Lewis acids formed more of the  $\beta$ -alcohol **164**. As  $\text{YbCl}_3$  had the highest Lewis acidity of all the lanthanide chlorides used, it gave the lowest ratio of **157:164** of 14:86.  $\text{LaCl}_3$  gave the highest ratio of **157:164** of 54:46. This is the first systematic study that has shown the effect of lanthanides in reduction selectivities. To test this trend, other Lewis acids were trialled that were not lanthanides, including  $\text{ZnCl}_2$  and  $\text{SnCl}_4$  (Table 3.4). As they are stronger Lewis acids than their lanthanide chloride equivalents, it was expected that the  $\beta$ -alcohol **164** would be favoured. This was confirmed for both cases, as the ratio of **164:157** was 100:0. Therefore, it appeared that stronger Lewis acids favoured the selectivity of **164** as the reduction product.

Table 3.4:  $\text{NaBH}_4$  reductions of **163** with  $\text{ZnCl}_2$ ,  $\text{SnCl}_4$  and  $\text{CuCl}$ .

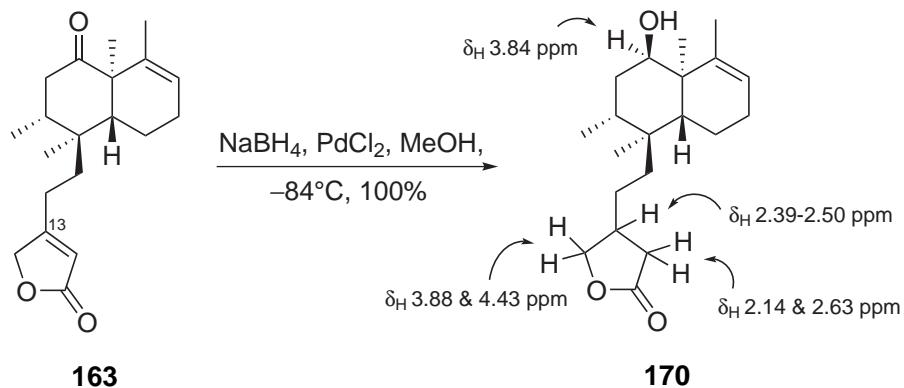


Entry	$\text{MCl}_x$	Yield	Ratio*	
			<b>157 (<math>\alpha</math>)</b>	<b>164 (<math>\beta</math>)</b>
1	$\text{ZnCl}_2$	100%	0	100
2	$\text{SnCl}_4$	100%	0	100
3	$\text{CuCl}$	100%	0	100

\*Ratios obtained by  $^1\text{H}$  NMR spectroscopy

Due to the results obtained thus far, it was expected that the  $\alpha$ -alcohol **157** would be the favourable product when using softer Lewis acid chlorides.  $\text{CuCl}$  and  $\text{PdCl}_2$  were two additives that were used to test this theory. Use of 1 equivalent of  $\text{CuCl}$  and sodium borohydride did not follow the expected trend, as it demonstrated 100% selectivity of the  $\beta$ -alcohol **164** under the general reaction conditions (Table 3.4, entry 3). Sodium borohydride- $\text{PdCl}_2$  reductions have been previously published by Satoh *et al.* to reduce ketones to alcohols.<sup>127</sup> The conditions stated in this literature example use 2 equivalents of  $\text{PdCl}_2$  and 10 equivalents of sodium borohydride for 1 equivalent of ketone. Surprisingly, treatment of **163** with 1 equivalent of  $\text{PdCl}_2$  and sodium borohydride gave a different result to that obtained with  $\text{CuCl}$ . Upon introduction of  $\text{PdCl}_2$  to the colourless reaction

mixture, the solution colour changed to red-brown and eventually became black. This observation was indicative of Pd(II) reducing to Pd(0).<sup>128,129</sup> The <sup>1</sup>H NMR spectrum of the crude product appeared to have signals relating to a different compound that were not the epimer alcohols **157** and **164**. No butenolide signals were evident. A new methine peak at 2.39-2.50 ppm (1H, m) was present, along with new signals at 4.43 (1H, ddd), 3.88 (1H, dd), 2.63 (1H, ddd) and 2.14 ppm (1H, ddd). The <sup>13</sup>C NMR spectrum did not display a ketone carbonyl peak, which was suggestive of this group being reduced to an alcohol. A resonance was found at 3.84 ppm (1H, m) assigned to H6 adjacent to an alcohol. As this peak had a value above 3.60 ppm, it was ascribed as an  $\alpha$ -H6 proton. The IR spectrum confirmed the alcohol functional group with an absorbance of 3496 cm<sup>-1</sup>. The compound was identified as a hydrogenated butenolide **170** (Scheme 3.5). A conjugate reduction had occurred, with palladium facilitating the reduction by coordinating to the C13 to C14 alkene. This type of reaction would typically require H<sub>2</sub> and Pd/C, or H<sub>2</sub> and Raney nickel, either under high or atmospheric pressure.<sup>130–132</sup> There are limited examples in the literature that use a sodium borohydride-PdCl<sub>2</sub> system. Satoh *et al.* used sodium borohydride-PdCl<sub>2</sub> to reduce aryl chlorides, aryl ketones and benzylic alcohols to the corresponding hydrocarbons.<sup>127</sup> This study was also successful at reducing hindered steroidal ketones to alcohols, though none of these cases reduced alkenes simultaneously. Suzuki and colleagues have shown that sodium borohydride and PdCl<sub>2</sub> in polyethylene glycol and dichloromethane could effectively hydrogenate alkynes to *cis*-alkenes similar to Lindlar catalyst.<sup>133</sup> This research was performed on alkynes that did not contain a ketone or  $\alpha,\beta$ -unsaturated carbonyl functional group.

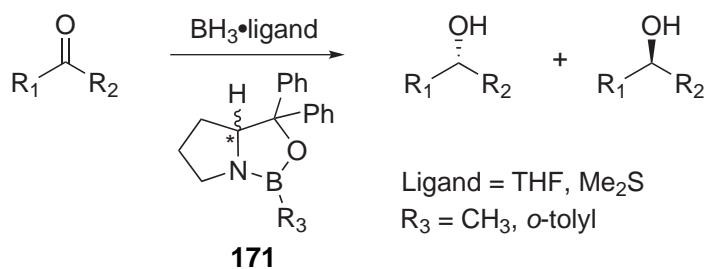


Scheme 3.5: Compound obtained from the reduction of **163** with NaBH<sub>4</sub> and PdCl<sub>2</sub>.

After reviewing these results, the addition of a softer Lewis acid chloride did not favour the formation of **157** upon reduction with sodium borohydride. Reduction of the ketone gave the  $\beta$ -alcohol **164** as the inherently preferred product in all cases. The reaction of the ketone **163** with sodium borohydride-PdCl<sub>2</sub> reduced the C6 ketone to the  $\beta$ -alcohol and caused a 1,4-reduction of the butenolide to form **170**.

### 3.1.2. CBS reduction of the ketone

As the stereoselectivity for the  $\alpha$ -alcohol **157** in the hydride reduction reactions was poor, other stereoselective reduction procedures were pursued. CBS (Corey-Bakshi-Shibata) reduction facilitates the enantioselective reduction of ketones to chiral alcohols using a chiral oxazaborolidine catalyst **171** (CBS catalyst) and a borane-hydride source.<sup>134</sup> Depending on the ketone substrate and CBS catalyst, the stereoselectivity of the reaction can be manipulated to favour one chiral alcohol product over the other enantiomer. The CBS reduction has proven to be a powerful and efficient methodology to synthetic organic chemists, and is widespread in the total synthesis field.<sup>135</sup> There are many different variations of CBS catalysts available that have been tested, yet the (*R*) and (*S*)-2-methyl-oxazaborolidine catalysts are commonly used with borane-THF or borane-dimethyl sulfide stoichiometric reducing agent complexes.<sup>135</sup>

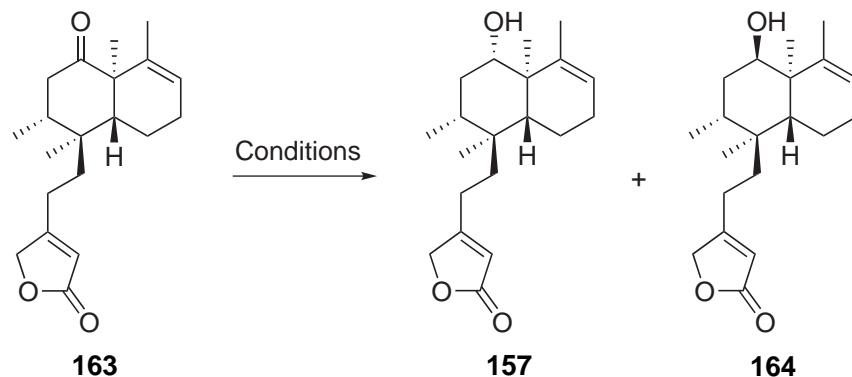


Scheme 3.6: General CBS reduction reaction using a chiral CBS catalyst **171**.

A summary of the reactions used to reduce **163** with CBS catalysts is shown in Table 3.5. Reduction of **163** with 10 mol % of (*R*)-(+) -2-methyl-CBS-oxazaborolidine was used first with the borane-tetrahydrofuran complex at -84 to 10°C, however, only starting material was obtained (Table 3.5, entry 1). Substitution of the borane-tetrahydrofuran complex with the borane-dimethyl sulfide complex at -42 to 10°C gave 18% yield of the  $\beta$ -alcohol **164** and  $\alpha$ -alcohol **157** in an equal ratio (Table 3.5, entry 2). Repeating this reaction at 0 to 10°C significantly improved the conversion of starting material to product at 94%, although the  $\beta$ -alcohol **164** was favoured (77%) over the  $\alpha$ -alcohol **157** (23%).

(Table 3.5, entry 3). After these results, the CBS catalyst was changed to *(S)*-(-)-CBS in an attempt to favour the formation of the  $\alpha$ -alcohol **157**. Repeating the previous reaction conditions except for using 1 equivalent of borane-dimethyl sulfide complex gave a 19% yield mixture of the  $\beta$ -alcohol **164** (71%) and the  $\alpha$ -alcohol **157** (29%) (Table 3.5, entry 4). In view of these results, the  $\beta$ -alcohol **164** was still the favoured product.

Table 3.5: CBS reductions with **163**.



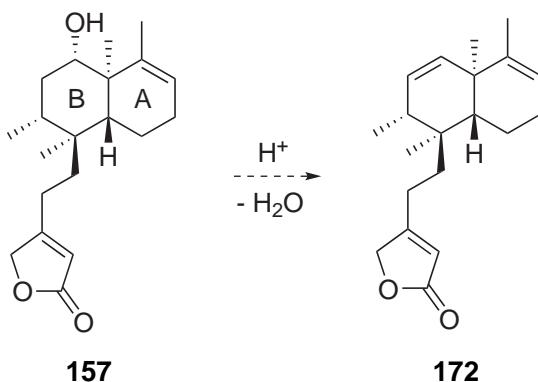
Entry	Conditions	Conversion	Ratio*	
			<b>157</b> ( $\alpha$ )	<b>164</b> ( $\beta$ )
1	<i>(R)</i> -(+)-2-methyl-CBS (10 mol %), BH <sub>3</sub> •THF (0.6 eq.), dry THF, -84 to 10°C, o/n	0%	-	-
2	<i>(R)</i> -(+)-2-methyl-CBS (10 mol %), BH <sub>3</sub> •Me <sub>2</sub> S (0.6 eq.), dry THF, -42 to 10°C, o/n	18%	50	50
3	<i>(R)</i> -(+)-2-methyl-CBS (10 mol %), BH <sub>3</sub> •Me <sub>2</sub> S (0.6 eq.), dry THF, 0 to 10°C, o/n	94%	23	77
4	<i>(S)</i> -(-)-2-methyl-CBS (10 mol %), BH <sub>3</sub> •Me <sub>2</sub> S (1 eq.), dry THF, 0 to 10°C, o/n	19%	29	71

\*Ratios obtained by <sup>1</sup>H NMR spectroscopy

The Luche and CBS reductions could not overcome this inherent selectivity in the reduction of **163**. This work is one of the few studies which has examined the effect of a range of Lewis acid additives to the reduction of ketones. It is also the first assessment of CBS reductions on a clerodane ketone. As mentioned previously, Krief and Surleaux had only compared sodium borohydride reductions to Luche reductions with CeCl<sub>3</sub>.<sup>126</sup> Sodium borohydride reductions with lanthanide chlorides favoured the  $\alpha$ -alcohol **164** if the lanthanide chloride was a weak Lewis acid. As LaCl<sub>3</sub> is the weakest Lewis acid in the lanthanide chloride series, ratios of **157**:**164** higher than 54:46 were unattainable.

### 3.2. Cationic rearrangements of the alcohol clerodane 157

Initially, it was thought that the alcohol **157** isolated from *D. ceratocarpa* was acid-sensitive which led to a dehydration reaction to form the alkene **172** (Scheme 3.7). The alkene **172** was considered an interesting compound to synthesise as it would enable further reactions on ring B. The synthesis of **172** was pursued. Initially, treatment of **157** with acid was thought to allow this transformation to occur.



Scheme 3.7: Conversion of **157** to the alkene **172**.

#### 3.2.1. Treatment of the alcohol with *p*-TsOH

The formation of the alkene **172** was investigated by the addition of catalytic *p*-TsOH to the alcohol **157** in CDCl<sub>3</sub>. The reaction was monitored by <sup>1</sup>H NMR spectroscopy at room temperature over a month. After 24 hours, a different transformation had taken place since the alkene **172** had not formed (Figure 3.2). The integration of the H3 resonance assigned to the starting material at 5.23 ppm proportionally decreased as the reaction was monitored. This suggested that the C3 alkene was transforming into an alkane. New signals were detected alongside starting material at 5.42 (1H, d, *J* = 1.7 Hz) and 5.14 ppm (1H, br d, *J* = 1.2 Hz) which are typical for alkenes. As these two peaks did not have a vicinal coupling constant, it was probable that they were associated with two different trisubstituted alkenes. Another set of new signals appeared at 3.43 (d, *J* = 15.0 Hz) and 3.10 ppm (d, *J* = 15.0 Hz). These were more intriguing signals as they had an AB pattern and were unrelated to the signals at 5.42 and 5.14 ppm.

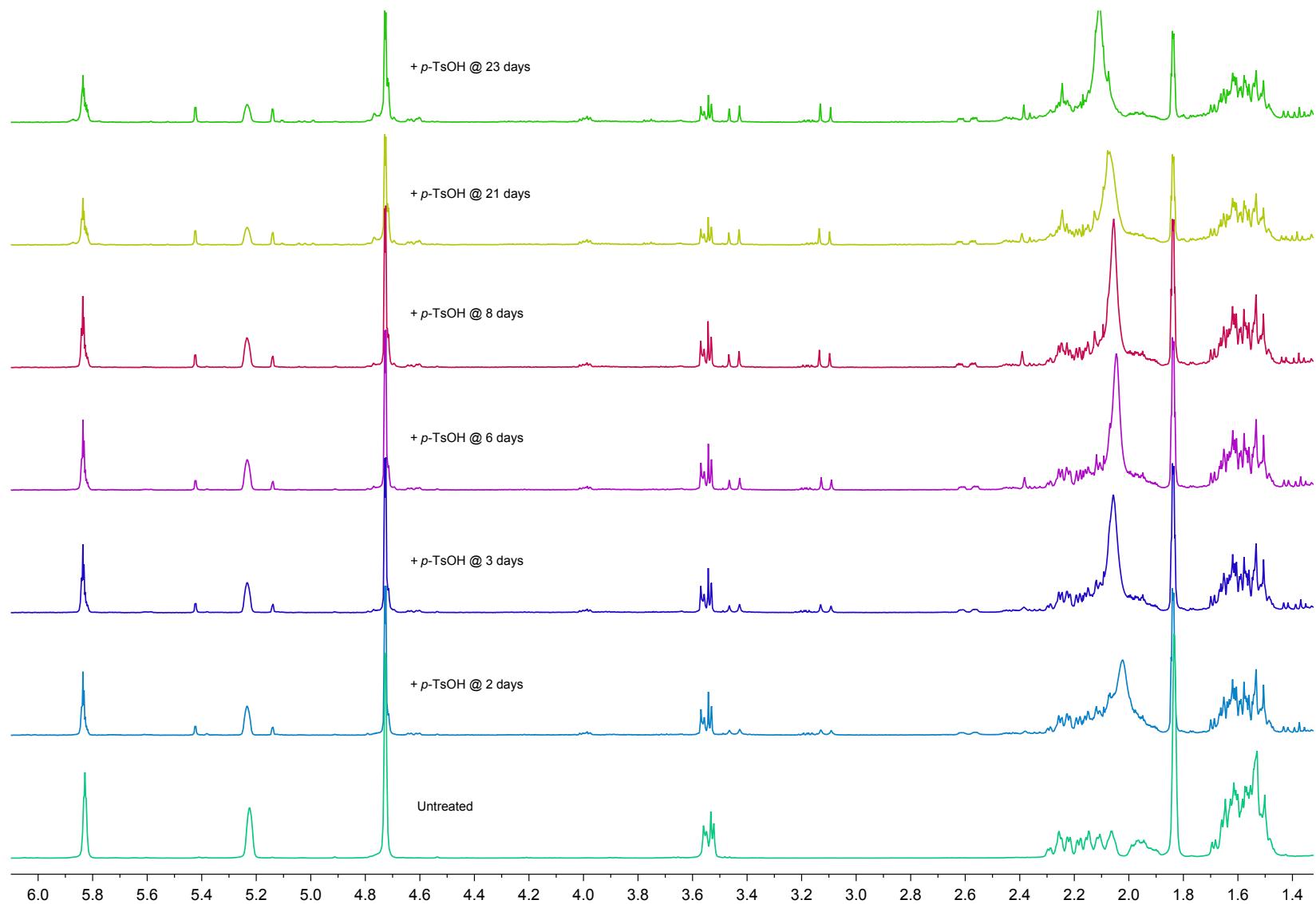
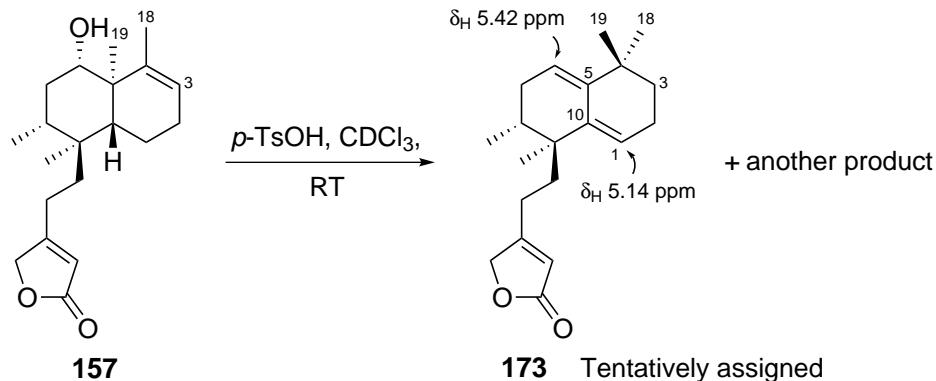


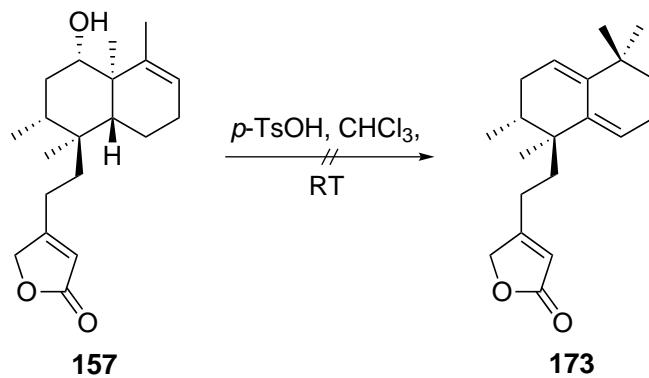
Figure 3.2: Overlaid <sup>1</sup>H NMR spectra of the alcohol **157** treated with *p*-TsOH in  $\text{CDCl}_3$  over time (ppm).

Compound **173** was tentatively assigned to the resonances at 5.42 and 5.14 ppm (Scheme 3.8). It would appear that an acid-catalysed rearrangement of the starting material occurred. Compound **173** contains two trisubstituted alkenes at C10-C1 and C5-C6, and has no C3 alkene. Compound **173** also has a labdane-like structure on ring A, where C18 and C19 are geminally-attached to the C4 quaternary position.



Scheme 3.8: Proposed structure of **173** formed during the *p*-TsOH reaction.

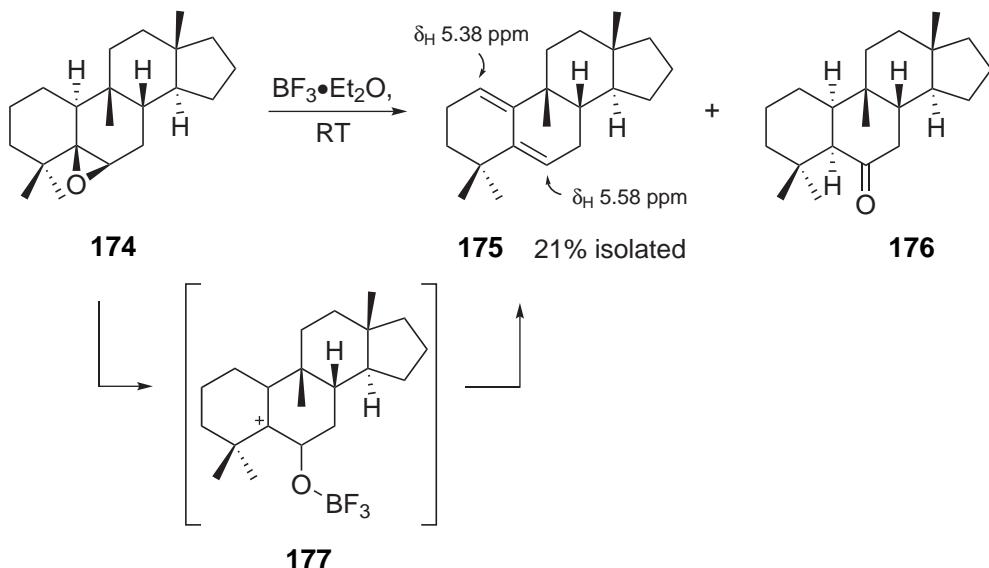
As the aforementioned reaction was performed on a small scale and gave a mixture of compounds, the tentatively assigned product **173** could not be isolated for further analysis. The reaction was repeated on a larger scale with 1 equivalent of **157** and 0.5 equivalents of *p*-TsOH in chloroform, however, no reaction was observed after 9 days (Scheme 3.9). The rearrangement reaction observed in the NMR tube in  $\text{CDCl}_3$  could be attributed to trace DCl formed upon decomposition of  $\text{CDCl}_3$  and not due to *p*-TsOH. Nevertheless, the NMR experiment shows rearrangements are possible under mild conditions.



Scheme 3.9: Unsuccessful scale-up of the cationic rearrangement reaction of **157**.

This cationic rearrangement is similar to that published by Bull and co-workers on a steroid.<sup>136</sup> An epoxide compound **174** was treated with boron trifluoride diethyl etherate

for 15 minutes at room temperature to afford the diene **175** and the ketone **176**. It was likely that the diene **175** was formed upon rearrangement of the cationic borate intermediate **177**. The two key signals attributed to compound **175** were at 5.38 and 5.58 ppm which corresponded to the two alkene hydrogens. These values are akin to the signals assigned to compound **173**.



Scheme 3.10: Literature acid-mediated synthesis of a diene **175**.<sup>136</sup>

A simplified labdane diene **178** similar to **173** was isolated by Baldwin *et al.* (Figure 3.3).<sup>137</sup> The  $^1\text{H}$  NMR spectrum of **178** revealed two alkene resonances at 5.39-5.42 (1H, m) and 5.44-5.48 ppm (1H, m). These chemical shifts are alike to those representative of compounds **173** and **175**, which provided further evidence that the structure assigned to **173** is possible.

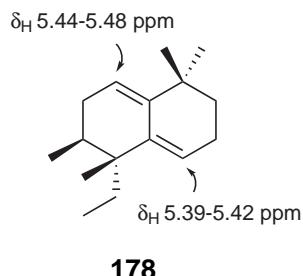
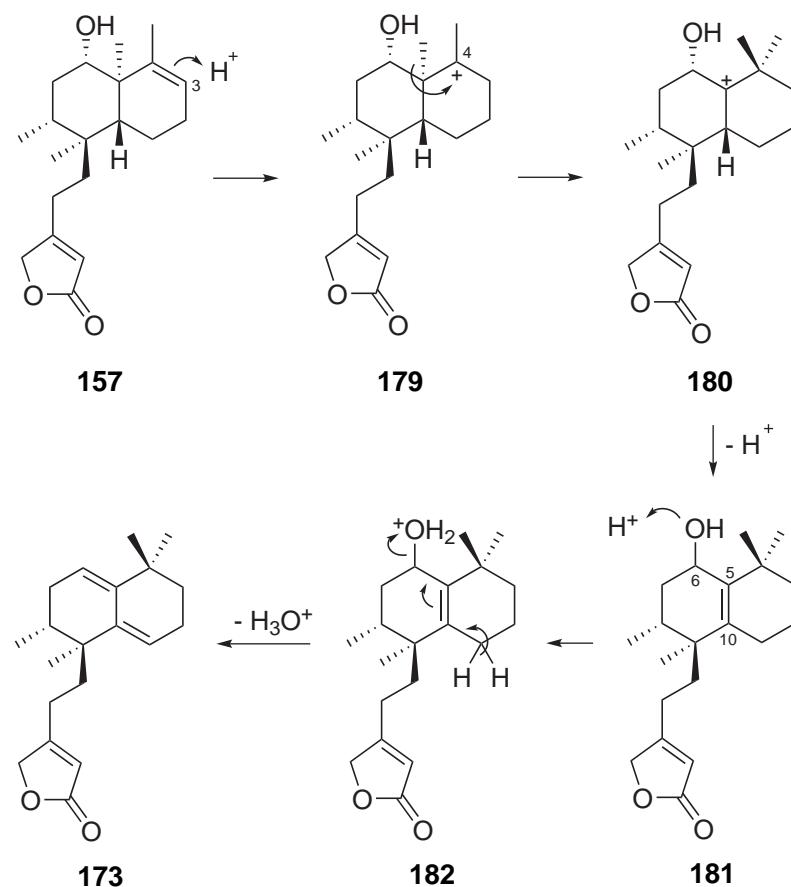


Figure 3.3: Structure of **178**.<sup>137</sup>

A mechanism was proposed for the formation of the tentative structure **173** (Scheme 3.11). Addition of  $\text{H}^+$  to the C3 alkene in **157** could give the tertiary carbocation

at C4 **179**. A 1,2-methyl shift from C5 to the C4 position could follow to provide the geminal dimethyl compound **180**. Elimination of H<sup>+</sup> could then give the alkene at the decalin ring junction (C5-C10) **181**. Protonation of the C6 alcohol could then form **182**, and elimination of water and H<sup>+</sup> would produce the diene **173**. The driving force for the second elimination reaction in the proposed mechanism was the formation of the conjugated diene product **173**.

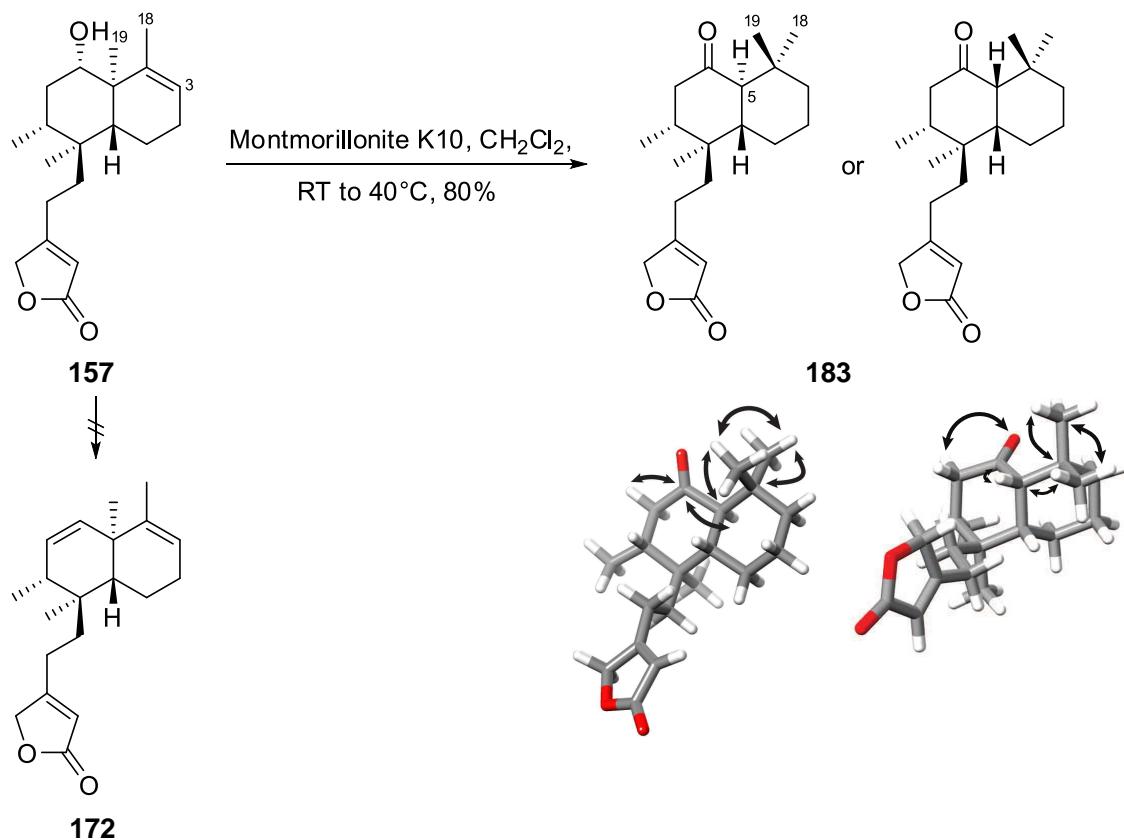


Scheme 3.11: Proposed mechanism of the *p*-TsOH reaction to form **173**.

### 3.2.2. Treatment of the alcohol with montmorillonite K10

The last reaction of the alcohol **157** with *p*-TsOH in CDCl<sub>3</sub> caused an interesting rearrangement that was unanticipated. Another acid source was used to determine if the alkene **172** or a rearrangement product could be synthesised. Montmorillonite K10 was used as an alternative acid source. Montmorillonite K10 is a naturally occurring clay that is frequently used as a solid supported Lewis acid catalyst.<sup>138</sup> The acidity of montmorillonite K10 is comparable to sulfuric and nitric acid, with pK<sub>a</sub> values below -1.5.<sup>139</sup> The acidity of the clay increases upon removal of the water absorbed from the

atmosphere, which is achieved by heating the clay at 120°C for a few hours.<sup>138</sup> Kantam and colleagues performed montmorillonite K10 catalysed dehydrations of secondary and tertiary alcohols to olefins, with yields between 75-91%.<sup>140</sup> A mixture of the alcohol **157** and dried montmorillonite K10 (120°C overnight) in anhydrous dichloromethane was stirred at room temperature for one day, and then heated to reflux for a week (Scheme 3.12). The alcohol **157** was consumed but the expected elimination product **172** was not formed.

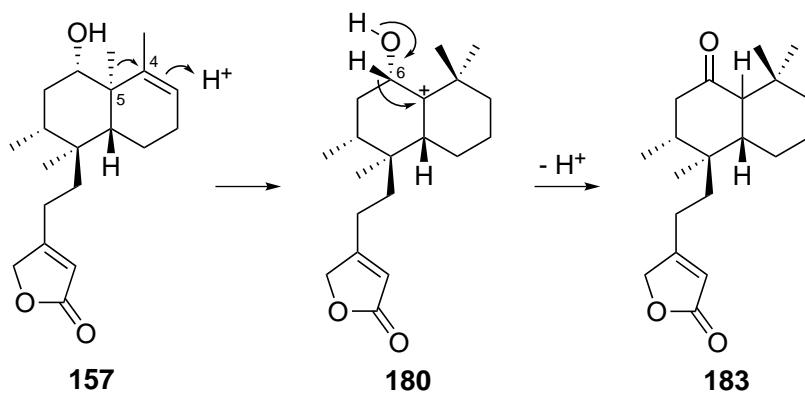


Scheme 3.12: Formation of **183** and the key HMBC correlations detected.

The  $^1\text{H}$  NMR spectrum obtained of the crude mixture showed a single product and the alkene at C3 had disappeared as a H3 shift was absent. Additionally, the H6 methine attributed to the starting material was not observed, which suggested the absence of the C6 alcohol. This was confirmed by IR spectroscopy as the OH stretch at 3510  $\text{cm}^{-1}$  was absent. Unexpectedly, a ketone stretching frequency was detected at 1705  $\text{cm}^{-1}$ . The presence of a ketone functional group was confirmed in the  $^{13}\text{C}$  NMR spectrum (210.0 ppm). The  $^1\text{H}$  NMR spectrum showed another change which was the upfield shift of the H18 methyl protons. H18 in the starting material **157** was located at

1.82 ppm, however it shifted to 1.12 ppm suggesting the methyl group was no longer allylic. The C4 peak in the product  $^{13}\text{C}$  NMR spectrum also changed from that observed in the starting material, as it was now located at 33.7 ppm. The HMBC spectrum showed a strong correlation between H18 and H19 at 31.0 and 20.3 ppm, respectively (Scheme 3.12). Additionally, correlations between H18 and C4 along with H19 and C4 strongly indicated that H18 and H19 were geminal methyl groups. The ketone was confirmed at the C6 position upon finding a strong correlation between 210.0 and 2.00 ppm (d, H5), as well as 210.0 and 2.32 ppm (dd,  $\beta$ -H7). Based on this evidence, the ketone compound **183** was formed in this reaction. The stereochemistry of the H5 methine could not be confidently assigned at this stage. Interestingly, when the reaction was repeated with montmorillonite K10 and dichloromethane that was not dry the rearrangement product **183** did not form. Analysis of the  $^1\text{H}$  NMR spectrum of the crude material revealed a quantitative recovery of the starting material.

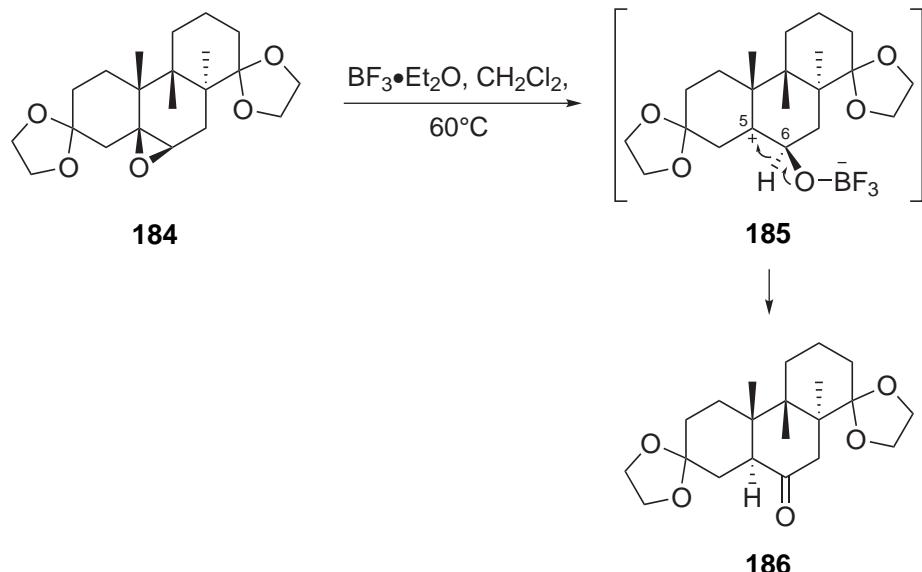
A proposed mechanism for this transformation initially followed the same pathway as shown in Scheme 3.11. An acid-promoted 1,2-methyl shift between C5 and C4 gave the carbocation **180** (Scheme 3.13). A 1,2-hydride shift of the H6 methine to C5 could then eventuate followed by the loss of a proton to afford the ketone compound **183**.



Scheme 3.13: Proposed mechanism for the formation of **183** in the montmorillonite K10 reaction.

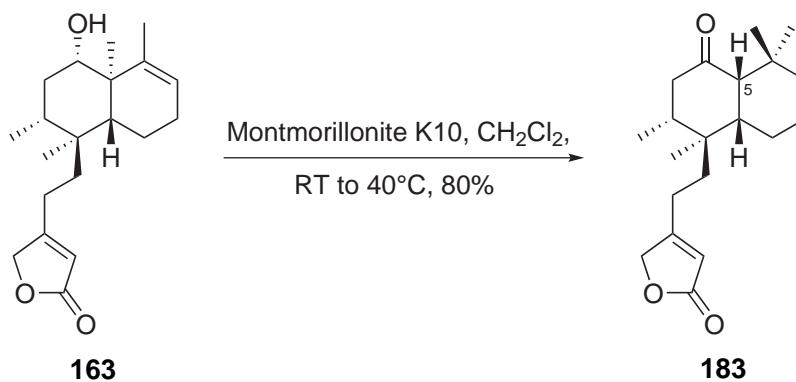
A similar rearrangement was observed upon treatment of the  $\beta$ -epoxide **184** with boron trifluoride (Scheme 3.14).<sup>70</sup> A stereocontrolled migration of H6 to the tertiary carbocation within the reaction intermediate **185** afforded the *trans*-ketone **186**. The researchers who performed this work mentioned that the stereochemistry of the H6 methine was important

in determining the stereochemistry of the product. Specifically, the stereochemistry of H6 remained the same after its migration to the C5 position.



Scheme 3.14: Boron trifluoride catalysed rearrangement of **184** to **186**.<sup>70</sup>

Based upon the information provided by the aforementioned literature reaction, the clerodane **183** obtained from the montmorillonite K10-catalysed rearrangement was proposed to have a  $\beta$ -H5 methine (Scheme 3.15). The stereochemistry of the hydrogens at C5 and C10 inferred that **183** is a *cis*-clerodane. This is the first *cis*-clerodane synthesised in this project.

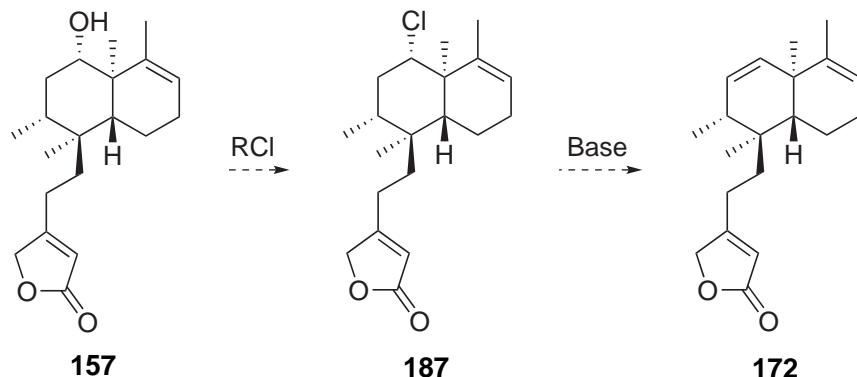


Scheme 3.15: Final structure assigned to **183**.

### 3.2.3. Treatment of the alcohols with $\text{PCl}_5$

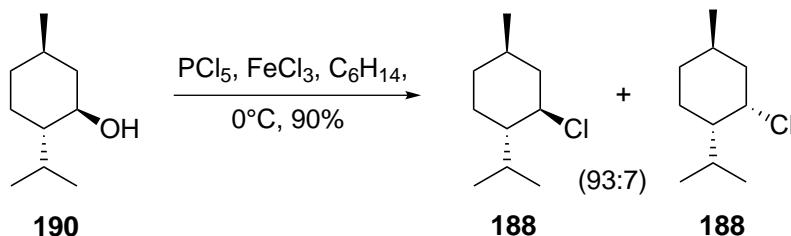
An alternative route to synthesise the alkene **172** was to substitute the hydroxyl functional group **157** to the chloride **187**, and then treatment of this intermediate with base could

enable elimination of hydrochloric acid via an E2 mechanism to afford the desired product (Scheme 3.16).



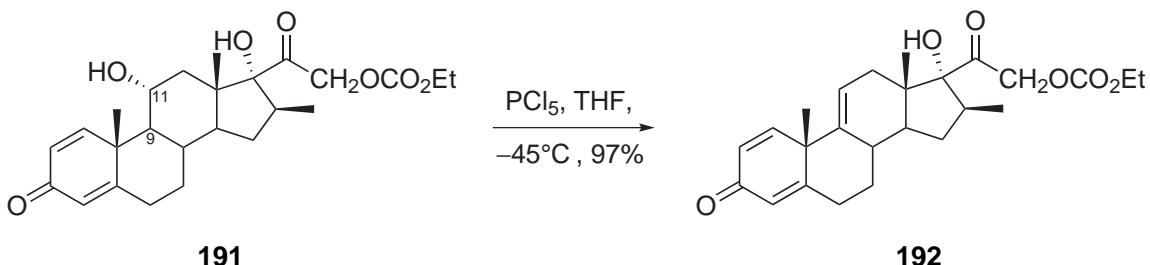
Scheme 3.16: Proposed method to obtain the dehydration alkene derivative **172**.

$\text{PCl}_5$  is a good chlorinating agent that converts alcohols to chlorides with retention of stereochemistry.<sup>141,142</sup> An example has been demonstrated on (*-*)-menthol, where 1.4 equivalents of  $\text{PCl}_5$  and a catalytic quantity of  $\text{FeCl}_3$  was added to the precursor to afford a 93:7 mixture of (*-*)-menthyl chloride **188** and the inverted chloride **189** (Scheme 3.17).<sup>143</sup>



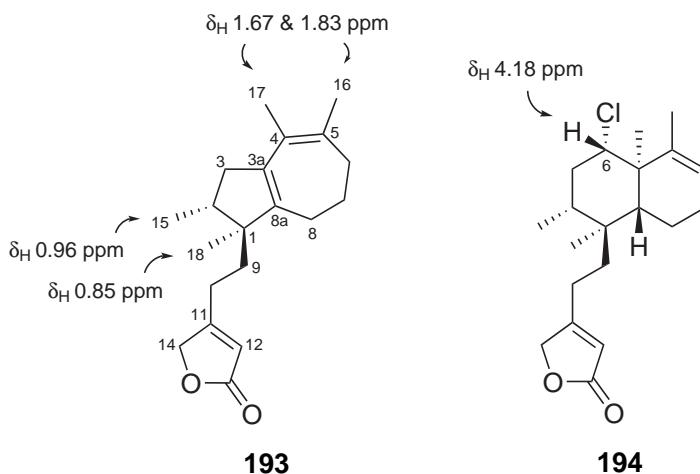
Scheme 3.17: Chlorination of (*-*)-menthol with  $\text{PCl}_5$ .<sup>143</sup>

A secondary alcohol in a corticosteroid **191** was treated with  $\text{PCl}_5$  to form the  $\Delta^9$ ,<sup>11</sup> dehydrated product **192** (Scheme 3.18).<sup>144</sup> The  $\text{POCl}_4$  group was positioned in an anti-coplanar orientation to H9, allowing fast elimination of  $\text{POCl}_3$  via a chloride anion.



Scheme 3.18: Chlorination of a corticosteroid with  $\text{PCl}_5$ .<sup>144</sup>

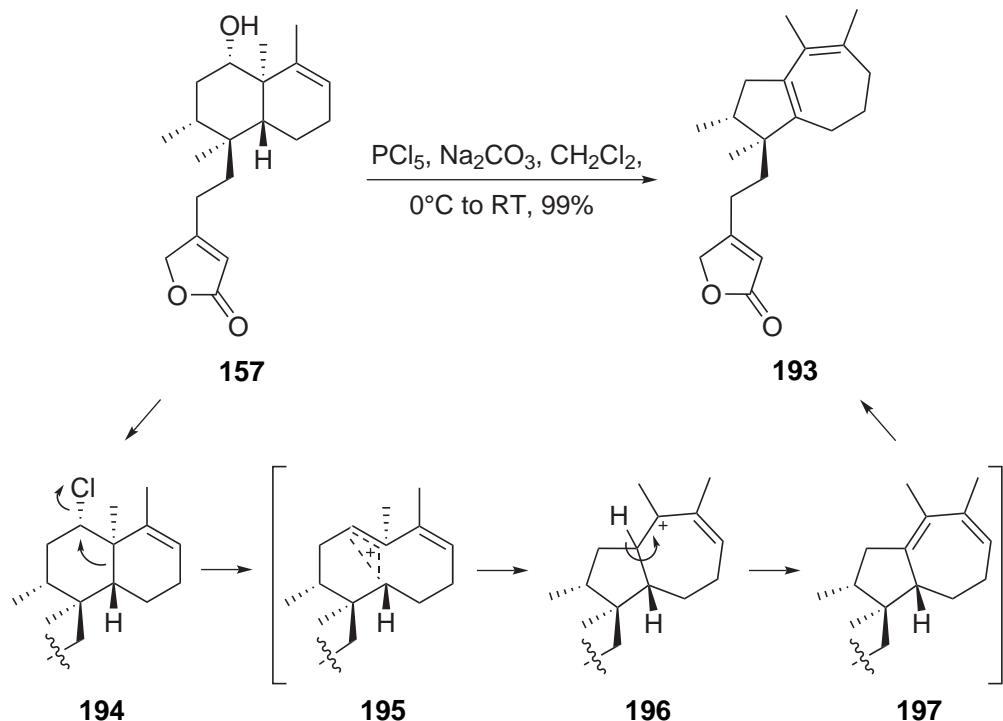
A similar methodology was implemented with the alcohol **157**, however, since  $\text{PCl}_5$  is acidic, a buffered system was used. This was to keep the pH of the reaction near neutral and to avoid acid-mediated rearrangement of **157** as seen earlier in this Chapter. Treatment of **157** with 1.3 equivalents of  $\text{PCl}_5$  with 1 equivalent of sodium carbonate in anhydrous dichloromethane at  $0^\circ\text{C}$  gave a new compound **193** (Scheme 3.19). The NMR spectra did not resemble a clerodane system. The  $^1\text{H}$  NMR spectrum showed two peaks at 5.84 (1H, m) and 4.73 ppm (2H, d) assigned to the butenolide. There were no peaks located between 2.60-4.60 ppm. IR analysis confirmed the absence of a hydroxyl or ketone group. A change in the four methyl group resonances was noted, as these peaks were now located at 1.83, 1.67, 0.96 (H15) and 0.85 ppm (H18). The  $^{13}\text{C}$  and DEPT NMR spectra showed four new quaternary alkene signals at 144.7, 138.9, 134.8 and 127.5 ppm ascribed to the C3a, C4, C5 and C8a positions. The butenolide remained intact. In added evidence, the chloride **194** was observed in some cases in the crude  $^1\text{H}$  NMR spectrum, but it rapidly converted to the rearranged product **193** upon standing (Scheme 3.19). The characteristic methine hydrogen at C6 for the chloride **194** was observed as a doublet of doublets at 4.18 ppm ( $J = 10.3, 5.6 \text{ Hz}$ ). A methine hydrogen attached to the same carbon as a chlorine is typically located between 4.00-4.30 ppm.<sup>145-147</sup>



Scheme 3.19: Structures of **193** and **194**.

A mechanism was proposed for the formation of this new compound (Scheme 3.20). After formation of the chloride **194** with retention of stereochemistry, the carbocation intermediate **195** could have formed. A 1,3-carbon shift may have occurred to give an azulениum carbocation intermediate **196**. Elimination of the bridgehead methine could

then form the neutral azulene diene **197**. This intermediate could then subsequently undergo a 1,5-hydride shift, or isomerism, to provide the more stable diene product **193**.



Scheme 3.20: Reaction of the alcohol **157** with  $\text{PCl}_5$ .

Identical reaction conditions were applied to the  $\beta$ -alcohol **164** to test whether the stereochemistry of the alcohol functional group affected the outcome of the reaction. Treatment of **164** with 1.3 equivalents of  $\text{PCl}_5$  and 1 equivalent of sodium carbonate *did not* afford the same products obtained when using **157**. A 1:1 inseparable mixture of two new non-polar compounds was obtained. The  $^1\text{H}$  NMR spectrum of the crude material showed no peaks attributed to the starting material or the chloride substituted compound **194**. Two new alkene hydrogens were detected at 5.15 and 5.51 ppm. Butenolide signals were found at 4.74 (4H, m) and 5.85 (2H, m), and the integrations of these signals provided further evidence of the formation of two compounds. Eight new methyl signals were also found at 0.56 (3H, s), 0.65 (3H, s), 0.83 (3H, d), 0.86 (3H, d), 1.82 (6H, br s), 1.97 (3H, dd) and 1.99 ppm (3H, m). Four of these methyl groups were allylic methyl groups with different chemical shifts to those observed with compound **193** in the previous reaction (Scheme 3.20). Compounds that had allylic methyl groups were searched to aid in structure elucidation of one of the two new compounds. The  $^1\text{H}$  NMR resonances

of compound **198** synthesised by Ito and co-workers were examined (Figure 3.4). The chemical shifts of the three allylic methyl groups were located at 1.73, 1.88 and 1.94 ppm. The vinylic hydrogen was observed as a broad singlet at 5.53 ppm.

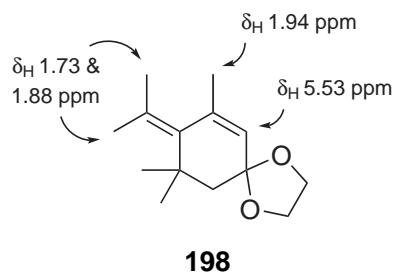
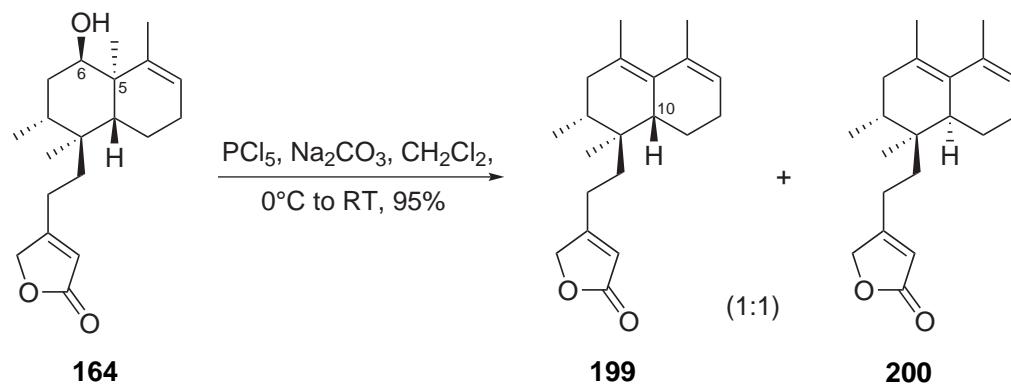


Figure 3.4: Structure of **198** and its key  $^1\text{H}$  NMR resonances.<sup>148</sup>

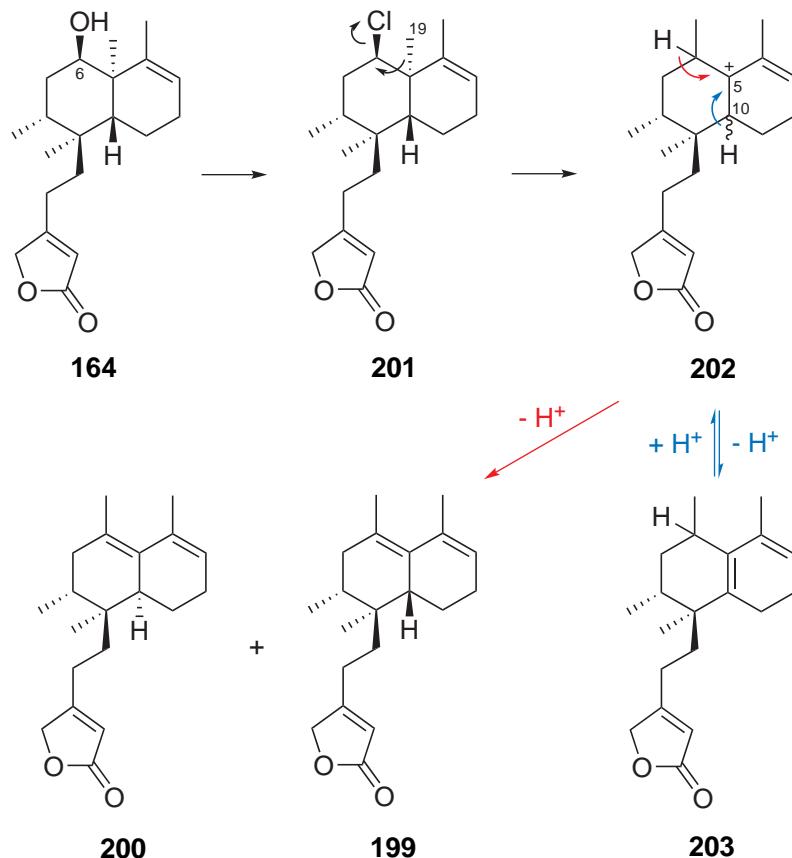
The peaks observed for **198** were similar to some of the peaks found in the  $^1\text{H}$  NMR spectrum of the crude product obtained in Scheme 3.20. One of the structures was tentatively assigned as a clerodane with an eliminated C6 alcohol **199**, whilst the other was proposed to be the H10 isomer **200** (Scheme 3.21).



Scheme 3.21: Reaction of **164** with  $\text{PCl}_5$  to form the proposed products.

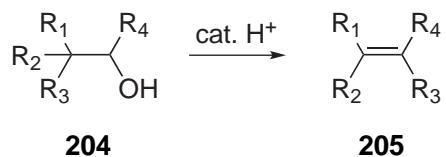
A possible mechanism for the formation of **199** and **200** is shown in Scheme 3.22. The alcohol clerodane **157** was converted to the chloride **201** with retention of stereochemistry. A 1,2-carbon shift of the C19 methyl group to C6 followed by elimination of chloride would give the stable tertiary carbocation at C5 **202**. Two competing pathways were now possible to enable the formation of **199** and **200**. The first pathway (blue) was an elimination of the H10 methine to provide the C5-C10 alkene **203**. This reaction was reversible, because addition of  $H^+$  to **203** would re-form **202** with H10 in either the  $\alpha$ - or  $\beta$ -orientation. The red pathway shows elimination of the H6 methine to provide the dienes

**199** and **200**. For **200** to have formed, the reaction mechanism had to have first followed the blue pathway.



Scheme 3.22: Proposed mechanism for the formation of **199** and **200**.

These two  $\text{PCl}_5$  mediated reactions appeared to be Wagner-Meerwein rearrangements. The Wagner-Meerwein rearrangement involves the acid-catalysed elimination of a hydroxide **204** or a good leaving group, followed by a 1,2-sigmatropic shift to form a rearranged product **205** (Scheme 3.23).<sup>149</sup> Elimination of the leaving group to form the carbocation does not occur, rather bond formation and breakage occurs simultaneously.<sup>150</sup> This type of rearrangement is common in terpenoid systems, particularly branched bicyclic terpenes.<sup>151</sup> The stereochemistry of the hydroxyl/leaving group determines the outcome of the reaction, as discovered in the above two cases.



Scheme 3.23: General reaction scheme of the Wagner-Meerwein rearrangement.

3D structures of the two proposed chloride intermediates formed in both  $\text{PCl}_5$  reactions are shown in Figure 3.5. When the  $\alpha$ -alcohol **157** was used as the starting material, the  $\alpha$ -chloride **194** was believed to have been formed as a reaction intermediate. In concerted rearrangements such as the Wagner-Meerwein type, the alignment of the leaving group and the migrating group has to be antiperiplanar.<sup>152</sup> In the case of **194**, the chloride is perfectly antiperiplanar with the ring junction methine. This enables migration of the ring junction bond and elimination of chloride to provide **196**, which is an intermediate of the final product **193**. Conversely, when the  $\beta$ -alcohol **164** was used as the starting material, it was proposed that the  $\beta$ -chloride **201** was formed as an intermediate. The C19 methyl group and the chloride at C6 has a perfect antiperiplanar orientation. For compounds **199** and **200** to have formed, a 1,2-shift of the C19 methyl at C5 to the C6 position had to have occurred simultaneously as the elimination of the chloride to form **202** as an intermediate.

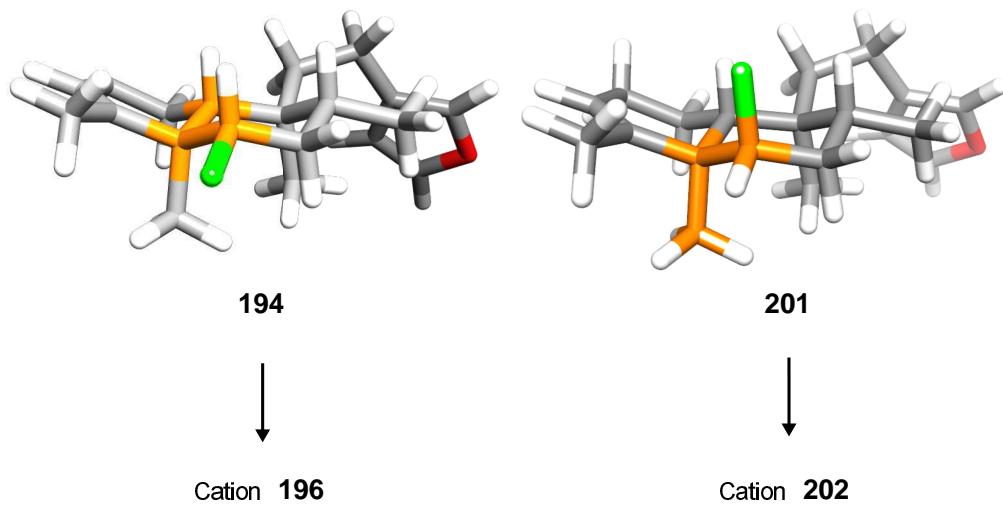
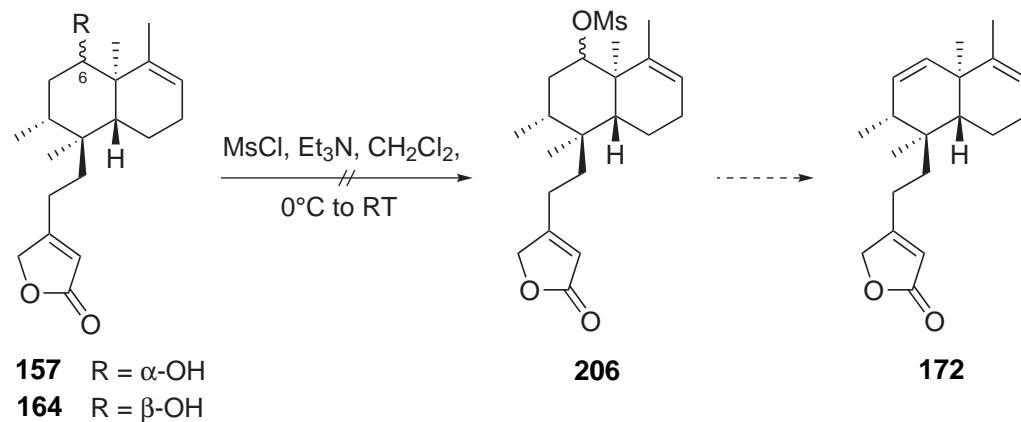


Figure 3.5: 3D structures of the chloride intermediates **194** and **201**.

### 3.3. Esterification of the alcohol

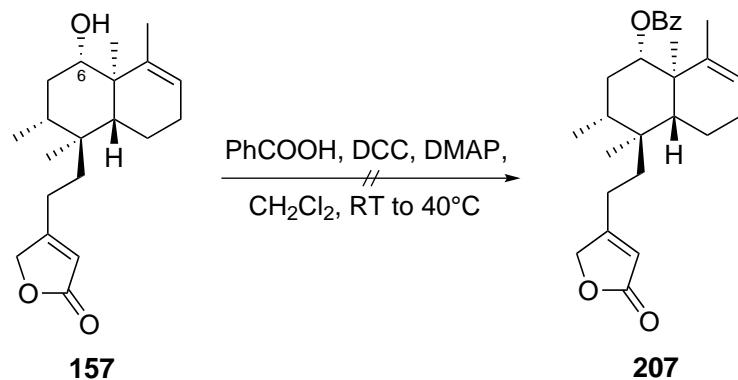
Mesylation of the  $\alpha$ -alcohol **157** was investigated as a method of forming the alkene **172**. Upon forming the mesylate **206** with mesyl chloride, elimination of the mesylate could provide the alkene **172**.<sup>153–155</sup> The conditions that Tufariello and colleagues implemented to convert cyclohexanol to the cyclohexane mesylate were emulated.<sup>156</sup> Addition of 1.1 equivalents of mesyl chloride and 4 equivalents of triethylamine to the  $\alpha$ -alcohol **157** at 0°C did not give the intended product **172** as starting material was recovered (Scheme 3.24). The reaction was attempted with the  $\beta$ -alcohol **164** and this was also

unsuccessful, as the  $^1\text{H}$  NMR spectrum only showed the starting material. It was expected that the axial orientation of the  $\beta$ -alcohol **164** would be less hindered and more reactive than **157** in this reaction, however, this was not observed. These reactions indicated that the alcohol was hindered.



Scheme 3.24: Attempted mesylation of the C6 alcohols.

To test the steric hindrance around the alcohol **157**, a Steglich esterification was investigated. Using conditions adapted from a literature procedure, 1.1 equivalents of benzoic acid, 1.5 equivalents of *N,N'*-dicyclohexylcarbodiimide (DCC) and catalytic DMAP were added to the alcohol **157** in dichloromethane (Scheme 3.25).<sup>157</sup> This did not provide the benzoate product **207**, as the  $^1\text{H}$  NMR spectrum showed the recovery of the starting materials. This result further implied that the alcohol at C6 was not readily accessible due to the hindrance about this position.



Scheme 3.25: Attempted Steglich esterification of **157** to form the benzoate ester.

### 3.4. Conclusions

Oxidation of the  $\alpha$ -alcohol **157** was achieved with PCC in high yield. Reduction of the ketone **163** with sodium borohydride gave the epimer  $\beta$ -alcohol **164** as the only product. Luche and CBS reductions also favoured the formation of the  $\beta$ -alcohol, as all hydride sources preferred nucleophilic addition to the ketone via the bottom face. All attempts to dehydrate the alcohol within compound **157** did not give the alkene **172**, however, three different acidic reaction conditions caused three different cationic rearrangements of **157**. The reaction of **157** with *p*-TsOH gave a compound tentatively assigned as the conjugated diene **173**. The reaction of **157** with montmorillonite K10 gave a labdane-like compound **183** with a ketone at C6. Compound **183** is believed to have a *cis*-decalin ring junction. Lastly, the reaction of **157** with  $\text{PCl}_5$  caused the decalin ring to rearrange to an azulenic framework **193**. Upon treatment of the epimer alcohol **164** with  $\text{PCl}_5$ , two different products were obtained, with the structures tentatively assigned as **199** and **200**. These reactions proved that the stereochemistry of the alcohol precursor was important to the reaction outcome. The three aforementioned cationic rearrangements of **157** outcompeted the elimination reaction to form **172**. All attempts to esterify the C6 alcohol in compound **157** were unsuccessful, which was indicative of this position being obstructed by the four methyl groups.

# Chapter 4

## Reactions of the Ketone on Ring B of Clerodane 163

### 4.1. Enolate chemistry of 163

Chemistry around the C6 ketone within **163** was the next focus of attention. Enolate chemistry was initially investigated, however, compound **163** has two carbonyl groups at C6 and C15. There are two competing sites where deprotonation to form an enolate could occur, therefore enolates of the ketone or the butenolide are possible. As a guide to the relative acidities of the  $\alpha$ -hydrogens of these two groups, the  $pK_a$  values of cyclohexanone **208** and butenolide **209** are shown (Figure 4.1). The  $pK_a$  of the butenolide is substantially lower ( $pK_a \sim 18$ ) due to the formation of an aromatic furan ring **210**, compared to the ketone enolate **211** ( $pK_a \sim 26$ ).<sup>158,159</sup>

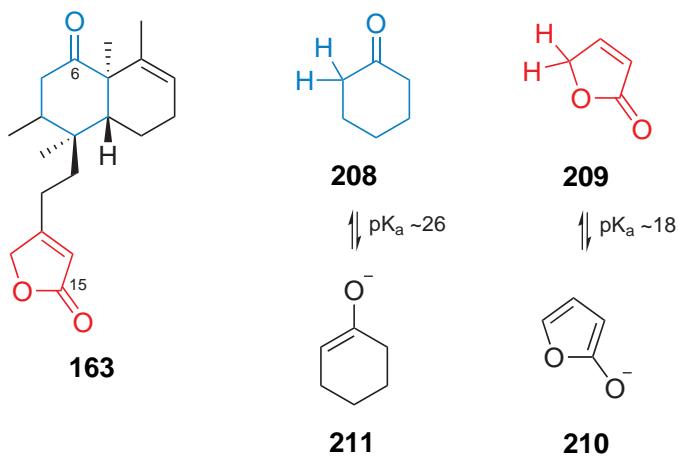
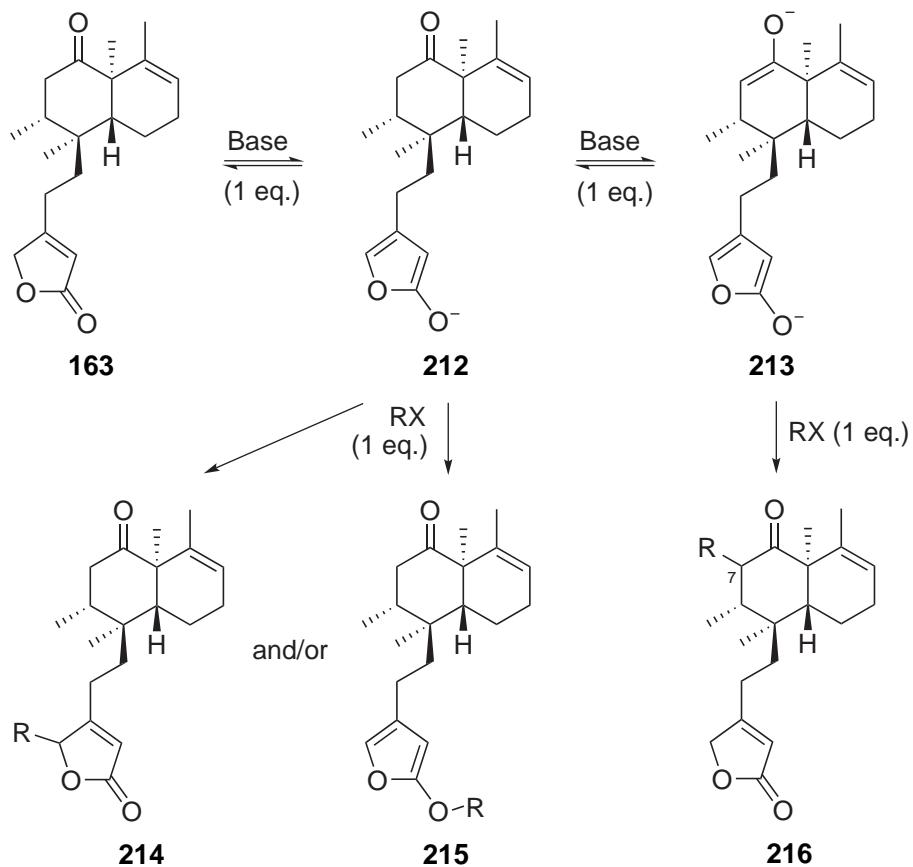


Figure 4.1: Competing deprotonation sites of **163** and  $\text{pK}_a$  values of a carbonyl and butenolide.

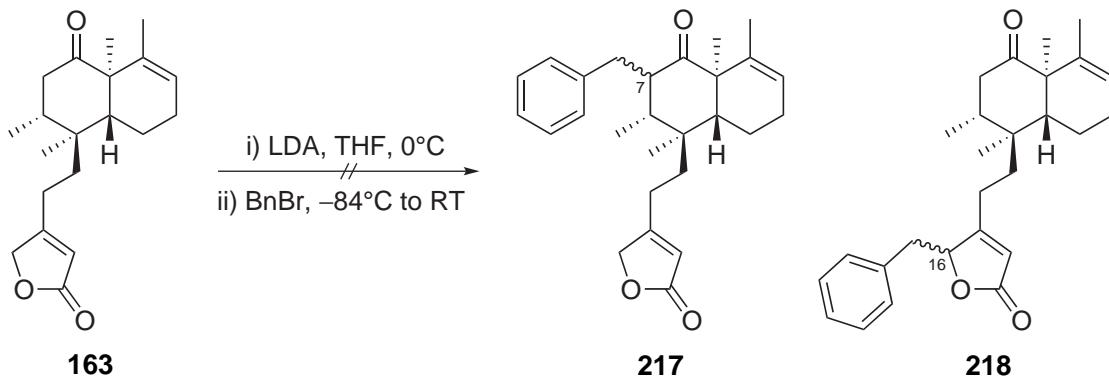
Based on the above acidities of **208** and **209**, clerodane **163** should follow the scheme presented below when treated with a strong base (Scheme 4.1). Addition of base to **163** could form two different enolates: the furanyl enolate **212** or the di-enolate **213**.



Scheme 4.1: Possible pathways available upon treatment of the ketone **163** with a base.

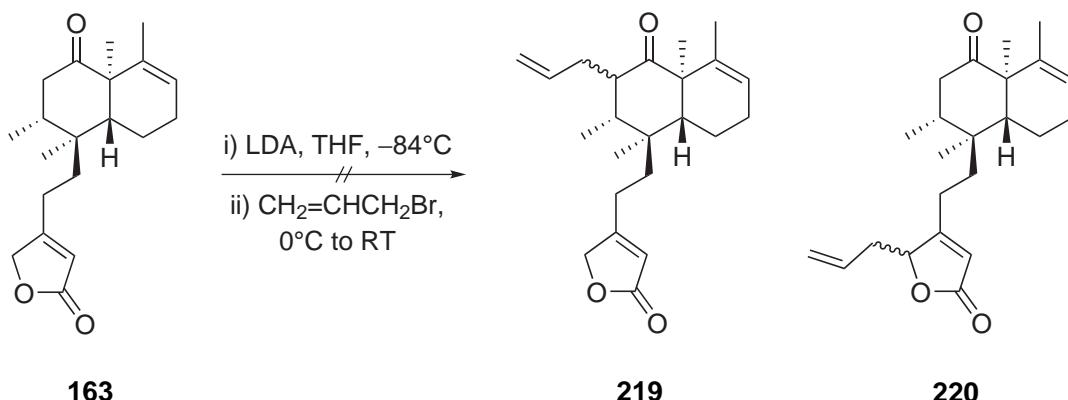
Addition of a strong base first would first form the furanyl enolate **212**, however, addition of more base could also form the di-enolate **213**. If the furanyl enolate **212** was formed, addition of 1 equivalent of an alkyl halide (RX) to this intermediate could form the alkylated  $\alpha,\beta$ -unsaturated butenolide **214** or the *O*-alkylated furan **215**. Conversely, if the di-enolate **213** was formed, addition of 1 equivalent of RX could afford the C7 alkylation product **216**.

Alkylation of the potential enolates with benzyl bromide and allyl bromide was examined. To a solution of the clerodane **163** in tetrahydrofuran at 0°C, 1.3 equivalents of LDA was introduced. The reaction was stirred at 0°C for 1 hour, then cooled to -84°C prior to addition of 1.1 equivalents of benzyl bromide. Neither **217** nor **218** were formed as the  $^1\text{H}$  NMR spectrum of the crude mixture showed the recovery of starting materials. This result could indicate that the electrophile was insufficiently reactive towards the enolates **212** and/or **213**.



Scheme 4.2: Attempted nucleophilic substitution reaction of **163** and BnBr.

Allyl bromide was used instead of benzyl bromide, as it may be a more reactive electrophile in this reaction. Clerodane **163** was stirred with 2.5 equivalents of LDA in tetrahydrofuran at -84 to 0°C for 30 minutes prior to addition of 1.1 equivalents of allyl bromide at 0°C to room temperature (Scheme 4.3). The  $^1\text{H}$  NMR spectrum confirmed the recovery of the starting material.



Scheme 4.3: Attempted nucleophilic substitution reaction of **163** and allyl bromide.

To rationalise why the enolate of the C6 ketone was not formed even when treated with 2.5 equivalents of LDA, 3D models of the starting material **163** and the enolate of the C6 carbonyl **221** were examined (Figure 4.2). Ring B in the ketone **163** is quite rigid and hindered by the three methyl groups on the ring. Enolate formation is affected by the steric effects of the ketone and the base. LDA is a sterically congested base and can only deprotonate hydrogens within **163** that are accessible. If the enolate **221** was to form, it would exist in the half chair conformation. This is because the C6 alkene of the enolate **221** would be flat, and this would increase strain on the molecule by forcing the C19 and C20 methyl groups closer together.

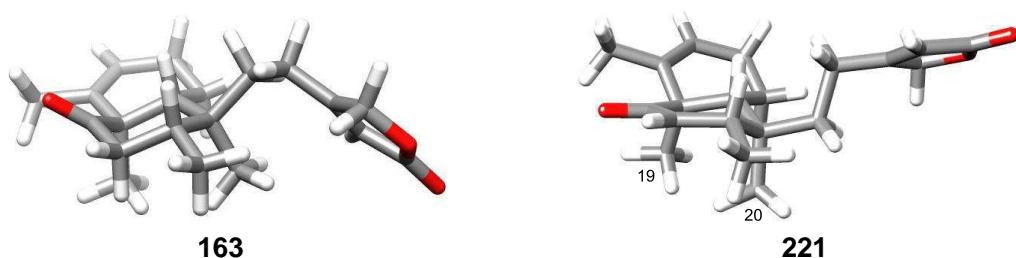
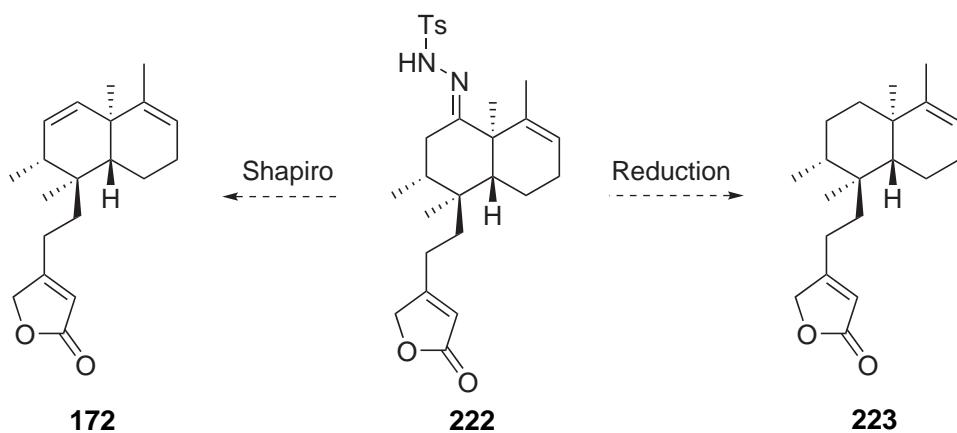


Figure 4.2: Molecular models of **163** and **221** showing the chair and unfavourable half-chair conformations of ring B.

## 4.2. Hydrazones and oximes of the ketone

A tosyl hydrazone **222** could be formed by the condensation of the ketone **163** and tosyl hydrazide. The tosyl hydrazone **222** could be a useful starting material for a number of reactions such as the Shapiro reaction to form the alkene **172** or a reduction reaction to form **223** (Scheme 4.4).<sup>160–165</sup>

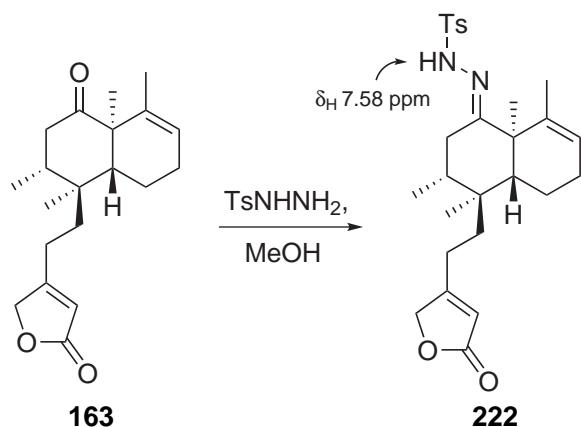


Scheme 4.4: Examples of some reactions possible with a tosyl hydrazone **222**.

Using conditions adapted from Cuevas-Yañez *et al.*, the ketone **163**, 1.4 equivalents of tosyl hydrazide and catalytic 1 M hydrochloric acid were stirred in methanol at room temperature to 40°C (Table 4.1, entry 1).<sup>166</sup> This gave the tosyl hydrazone **222** with a 54% conversion. The <sup>1</sup>H NMR spectrum had new signals at 7.27 (2H, d, *J* = 8.3 Hz), 7.82 (2H, d, *J* = 8.3 Hz) and 2.40 ppm (3H, s) attributed to the tosyl group. A broad NH stretch was detected at 7.58 ppm. This initial reaction was optimised by changing the pH of the reaction. Compound **163** was treated with 1.5 equivalents of tosyl hydrazide and catalytic 10 M hydrochloric acid at 50°C similar to a literature procedure (Table 4.1, entry 2).<sup>167</sup> This gave a 47% conversion to the hydrazone **222**. Upon isolation, the yield of **222** was 46%. Heating **163** with glacial acetic acid in methanol resulted in no reaction, as starting material was recovered (Table 4.1, entry 3).<sup>168,169</sup> Rather than using an acid catalyst, the reaction was performed as described in the previous example but without acid (Table 4.1, entry 4).<sup>170,171</sup> This gave the best result, as a 91% conversion was observed. Purification of **222** reduced the yield to 54% upon isolation. The poor yields of the isolated compounds was a consequence of the tosyl hydrazone hydrolysing. When **222** was allowed to stand in CDCl<sub>3</sub> (neutralised with potassium carbonate) over 12 hours, the <sup>1</sup>H NMR spectrum showed a 1:1.1 mixture of the tosyl hydrazone **222** and the ketone **163**.

Studies by Hayashida and Rawal have shown that a tosyl hydrazone could be reduced with sodium cyanoborohydride and ZnCl<sub>2</sub> in excellent yield.<sup>172</sup> Reduction of the tosyl hydrazone **222** with this method could afford clerodane **223**, which was previously isolated by Okazaki and co-workers.<sup>79</sup> A one-pot procedure was used to circumvent the hydrolysis of the tosyl hydrazone **222** that would occur upon work-up and isolation.

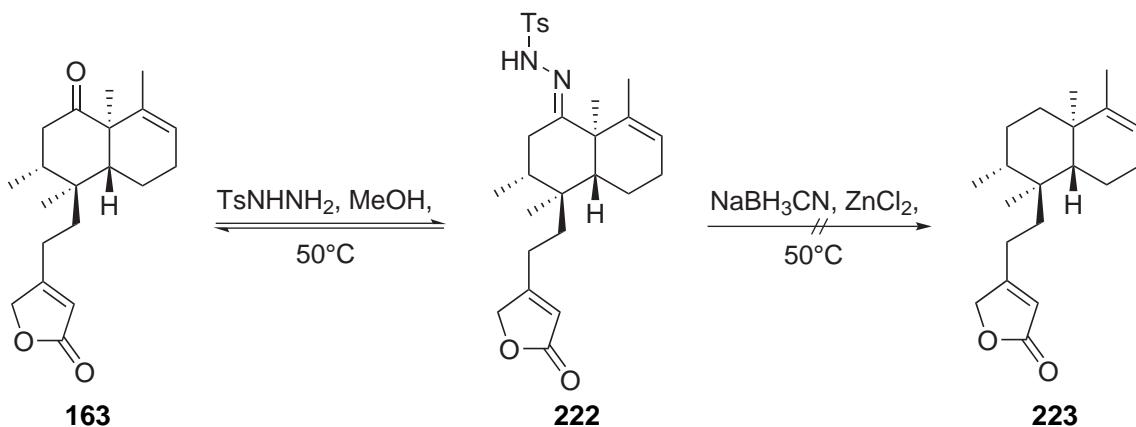
Table 4.1: Conditions used to synthesise the tosyl hydrazone **222**.



Entry	Conditions	Conversion to <b>222</b> * (isolated)
1	TsNHNH <sub>2</sub> (1.1 eq.), 1 M HCl (cat.), RT to 40°C, 3 days	54% (N/A)
2	TsNHNH <sub>2</sub> (1.5 eq.), 10 M HCl (cat.), 50°C, 3 days	47% (46%)
3	TsNHNH <sub>2</sub> (1.5 eq.), 17 M AcOH (cat.), 50°C to 60°C, 6 days	0% (0%)
4	TsNHNH <sub>2</sub> (1.5 eq.), 50°C to 60°C, 2 days	91% (54%)

\*Conversions obtained by <sup>1</sup>H NMR spectroscopy

The ketone **163** was subjected to 1.5 equivalents of tosyl hydrazide in methanol at 50°C (Scheme 4.5). When most of the starting material was consumed (according to TLC), 2 equivalents of sodium cyanoborohydride and 1 equivalent of ZnCl<sub>2</sub> were added and heating continued at 50°C. After another 4 days, the reaction was stopped and the <sup>1</sup>H NMR spectrum of the crude product showed a complex mixture of products.



Scheme 4.5: Attempted synthesis of the eliminated tosyl hydrazone compound **223**.

Like tosyl hydrazones, oximes **224** are versatile functional groups in organic chemistry. They can be hydrolysed to ketones or aldehydes,<sup>173</sup> reduced to amines,<sup>174,175</sup> and form *gem*-dinitro compounds in a Ponzio reaction<sup>176</sup> (Figure 4.3). Oximes can also be converted to amide derivatives via a Beckmann rearrangement.<sup>177</sup>

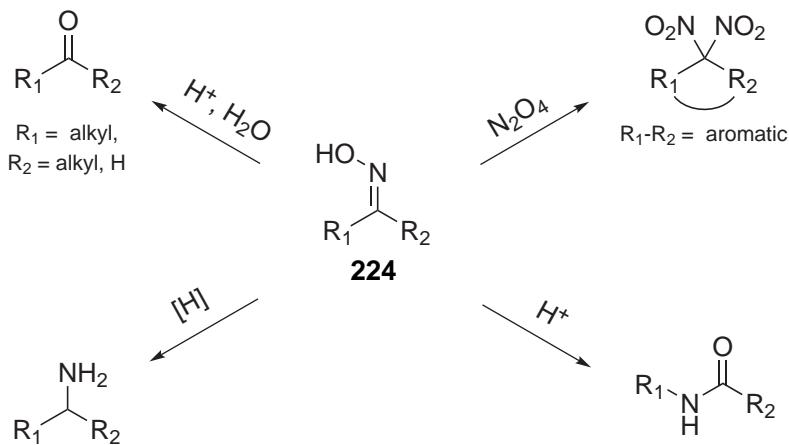
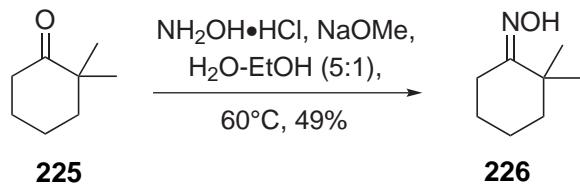


Figure 4.3: Some generalised reactions of oximes.

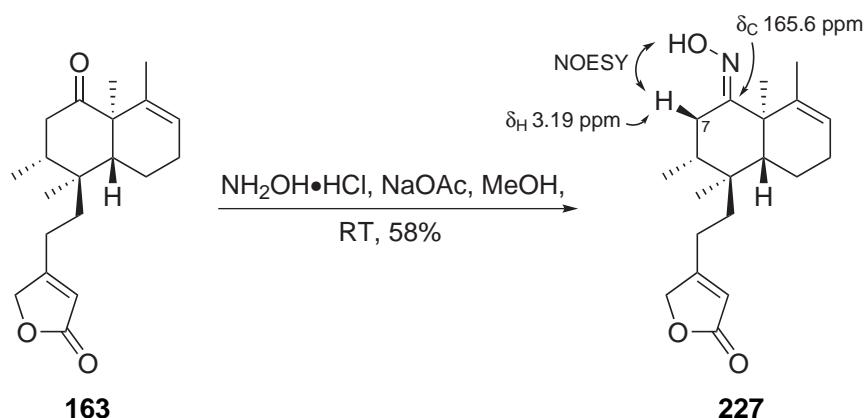
One of the most common methods of synthesising an oxime from a ketone is to treat a ketone precursor with hydroxylamine hydrochloride.<sup>178</sup> White and co-workers achieved this by heating 2,2-dimethylcyclohexanone **225**, 1.5 equivalents of hydroxylamine hydrochloride and 1 equivalent of sodium acetate in a 5:1 mixture of water-ethanol at 60°C to provide (*E*)-2,2-dimethylcyclohexanone oxime **226** (Scheme 4.6).<sup>179</sup> The stereochemistry of the product was not communicated.



Scheme 4.6: Synthesis of 2,2-dimethylcyclohexanone oxime **226**.<sup>179</sup>

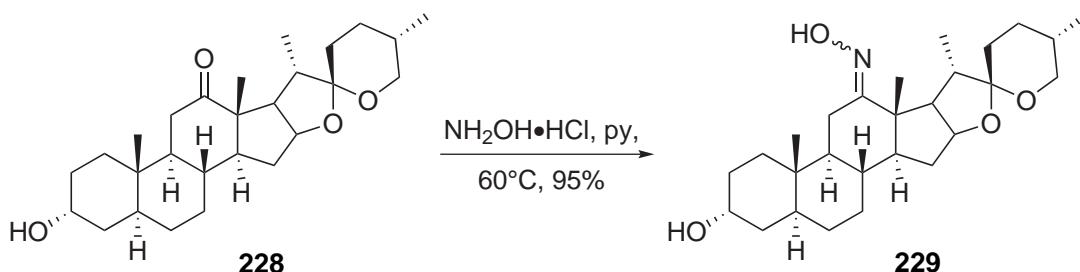
Using an adapted version of the above procedure, the ketone **163** was treated with 1.2 equivalents of hydroxylamine hydrochloride and 1.2 equivalents of sodium acetate in methanol at room temperature (Scheme 4.7). The oxime **227** was isolated in 58% yield without need for purification. One of the most significant differences in the  $^1\text{H}$  NMR spectrum was the shift of the  $\beta$ -H7 signal from 2.83 ppm in the starting material to 3.19 ppm in the oxime **227**. A broad OH signal also appeared between 6.80-7.20 ppm.

This signal was variable in the  $^1\text{H}$  NMR spectra. The  $^{13}\text{C}$  NMR spectrum showed a C=N peak at 165.6 ppm which confirmed the formation of the product **227**. An NOE interaction was evident between the oxime hydrogen and  $\beta$ -H7, which confirmed that the oxime had an (*E*)-orientation.



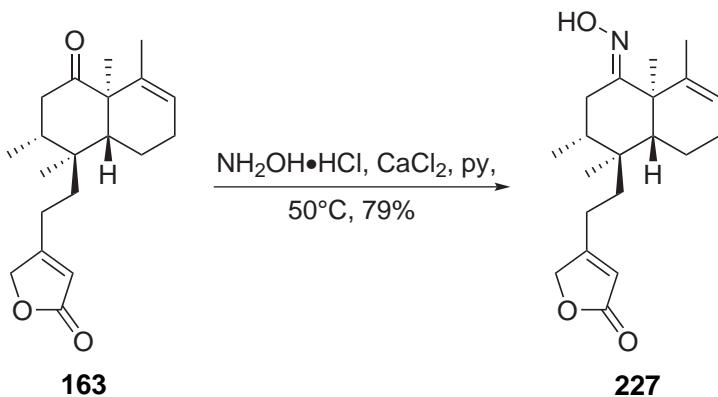
Scheme 4.7: Reaction conditions used to synthesise the oxime **227**.

To optimise this reaction, inspiration was taken from Kasal *et al.*<sup>180</sup> A steroidal ketone derivative **228** was heated with excess hydroxylamine hydrochloride (8.3 equivalents) in pyridine at  $60^\circ\text{C}$  and the oxime **229** was obtained in excellent yield (Scheme 4.8).<sup>180</sup>



Scheme 4.8: Synthesis of a steroidal oxime **229**.<sup>180</sup>

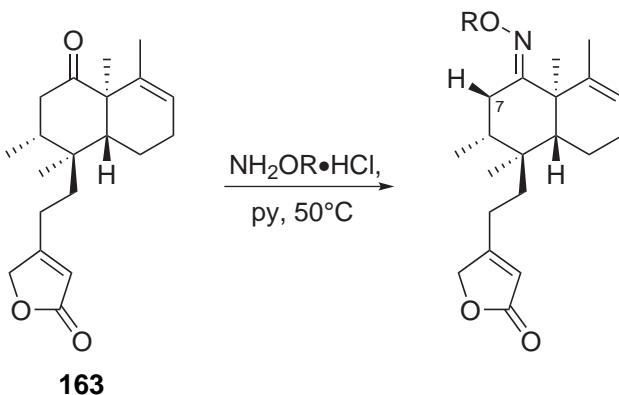
Thus, the ketone **163** was treated with 1.5 equivalents of hydroxylamine hydrochloride in pyridine at  $50^\circ\text{C}$  which provided the oxime **227** in 79% yield (Scheme 4.9). Calcium chloride was used as a desiccant for pyridine and to absorb the water formed during the reaction. The  $^1\text{H}$  NMR spectrum of the product **227** was identical to what was obtained when using hydroxylamine hydrochloride and sodium acetate in methanol (Scheme 4.7).



Scheme 4.9: Optimised reaction conditions to synthesise the oxime **227**.

Alkylated oximes were also synthesised using the optimised conditions. Treatment of the ketone **163** with 1.5 equivalents of methoxyamine hydrochloride and pyridine at 50°C afforded the *O*-methyl oxime **230** in 89% yield (Table 4.2, entry 2). The major changes include the appearance of a  $\text{OCH}_3$  singlet at 3.81 ppm and a doublet of doublets at 3.09 ppm ascribed to  $\beta$ -H7. The  $^{13}\text{C}$  NMR spectrum showed a new signal at 164.1 ppm which was consistent with an oxime. The  $\text{OCH}_3$  resonance was found at 61.2 ppm. NOESY NMR established that the *O*-methyl oxime functional group was in the (*E*)-orientation. A NOE interaction was detected between the *O*-methyl hydrogens and a H7 proton. An *O*-benzyl oxime **231** was also synthesised in 76% yield by using 1.5 equivalents of *O*-benzylhydroxylamine hydrochloride in pyridine at 50°C (Table 4.2,

Table 4.2: General synthesis of the clerodane oximes.



Entry	R	Product	Yield
1*	H	<b>227</b>	79%
2	Me	<b>230</b>	89%
3	Bn	<b>231</b>	76%

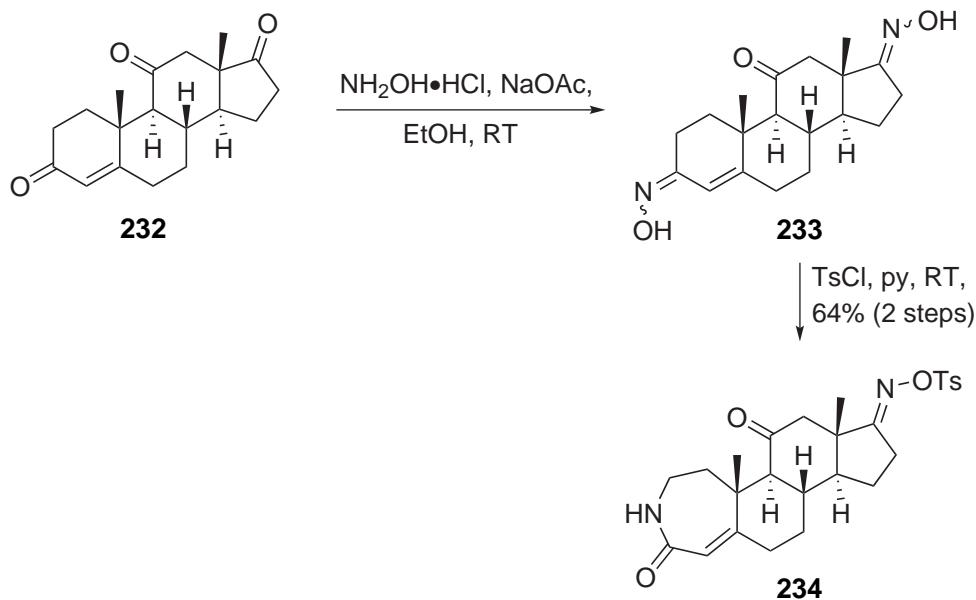
\* $\text{CaCl}_2$  was used as a desiccant in the reaction

entry 3). The characteristic  $\beta$ -H7 peak at 3.18 ppm (1H, dd) was detected in the  $^1\text{H}$  NMR spectrum. Additionally, the  $\text{CH}_2\text{Ph}$  hydrogens had an AB pattern and could be seen at 5.05 (1H, d,  $J = 12.2$  Hz) and 5.11 ppm (1H, d,  $J = 12.2$  Hz). The C=N resonance was found at 164.8 ppm in the  $^{13}\text{C}$  NMR spectrum. The *O*-benzyl oxime also had an (*E*)-orientation according to a NOE experiment, which was expected as the (*Z*)-isomer is the more strained product.

### 4.3. Reactions of the oximes

#### 4.3.1. Beckmann rearrangement

Oximes are precursors for a Beckmann rearrangement. Beckmann rearrangements have been applied in many natural product syntheses.<sup>181,182</sup> For example, adrenosterone **232** was converted to the oxime **233** and then treated with 2 equivalents of tosyl chloride to form the lactam **234** in 64% yield (Scheme 4.10).<sup>183</sup>



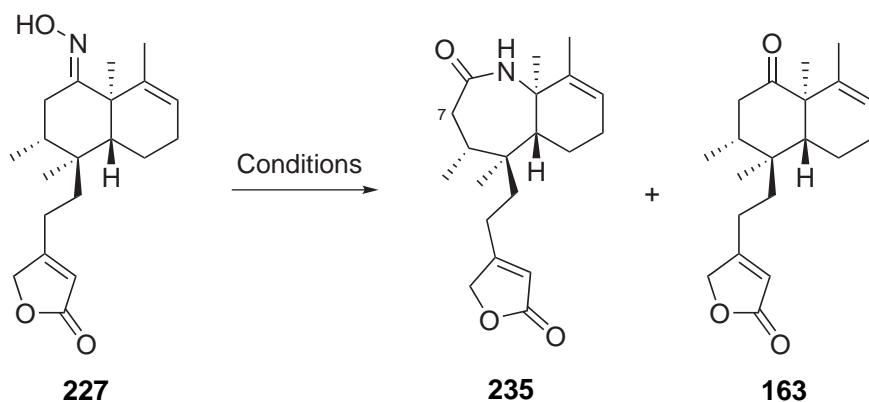
Scheme 4.10: Beckmann rearrangement of adrenosterone oxime **233**.

A Beckmann rearrangement was investigated with the oxime clerodane **227**. To date, no research has been published on Beckmann rearrangements of clerodanes. Using conditions adapted from Burrows and Eastman,<sup>184</sup> the oxime **227** was treated with 1.2 equivalents of tosyl chloride in pyridine at  $0^\circ\text{C}$  to room temperature (Table 4.3, entry 1). The lactam **235** was not produced, as analysis of the  $^1\text{H}$  NMR spectrum concluded

that 79% of what was recovered was unreacted starting material, and the remaining 21% was the ketone **163**. Trace amounts of pyridinium tosylate could have catalysed the hydrolysis of the oxime **227** to the ketone **163**. The reaction was attempted again with catalytic DMAP as reported in literature,<sup>185</sup> and anhydrous calcium chloride was added to prevent hydrolysis (Table 4.3, entry 2). Disappointingly, the hydrolysis product **163** was again observed, but at a higher percentage (44%) to the starting material **227** (56%). Gaware *et al.*<sup>186</sup> and Stevenson<sup>187</sup> have demonstrated that some steroids can be treated with  $\text{PCl}_5$  in dry dichloromethane or chloroform at room temperature to afford the Beckmann rearrangement product. The ketone **163** was subjected to 2.5 equivalents of  $\text{PCl}_5$  in dry dichloromethane under anhydrous conditions (Table 4.3, entry 3). Upon work-up, a  $^1\text{H}$  NMR spectrum was obtained which revealed a complex mixture of products. Unfortunately, none of the products in the crude spectrum could be attributed to the lactam **235**. Microwave-assisted Beckmann rearrangements were another method of creating amides from oximes. Using conditions similar to a literature example,<sup>188</sup> the oxime **227** was treated with 3 equivalents of  $\text{BiCl}_3$  in pyridine and reacted in a microwave at 140°C and at 1 bar pressure for 20 minutes (Table 4.3, entry 4). The crude  $^1\text{H}$  NMR spectrum showed decomposition of the starting material, presumably due to the high temperature.

De Luca and colleagues have shown that Beckmann rearrangements can be achieved with cyanuric chloride **236** in DMF at room temperature.<sup>189</sup> These conditions are quite mild compared to other established media that require strong acids and high reaction temperatures. The reaction mechanism involves a cyanuric chloride-DMF complex, which is similar to a Vilsmeier-Haack intermediate. Treatment of the oxime **227** with 1 equivalent of cyanuric chloride in DMF at room temperature afforded the ketone **163** and starting material **227** (33:67) (Table 4.3, entry 5). A small amount (<13%) of a compound that could be attributed to the lactam **235** was observed. The  $^1\text{H}$  NMR spectrum of the crude product showed a new multiplet at 2.48 ppm and a doublet of doublets at 2.41 ppm. These two signals could be attributed to the two H7 hydrogens. A broad singlet at 5.66 ppm was also discerned which could be the amide hydrogen (NH) of **235**. The  $^1\text{H}$  NMR spectra of some seven-membered ring lactams were studied to compare the chemical shifts and confirm whether **235** had formed (Figure 4.4). The triterpene **237** gave characteristic lactam resonances at 2.46 and 5.69 ppm, which represented the carbonyl  $\alpha$ -hydrogens and amide hydrogen, respectively.<sup>190</sup> The reaction was repeated

Table 4.3: Attempted synthesis of the Beckmann rearrangement product **235**.



Entry	Conditions	Recovery <sup>†</sup>	Product ratio*		
			<b>235</b>	<b>163</b>	<b>227</b>
1	TsCl (1.2 eq.), 0 to 15°C, 2 days	93%	0	21	79
2	TsCl (1.2 eq.), DMAP (cat.), CaCl <sub>2</sub> , 0 to 15°C, 4 days	100%	0	44	56
3	PCl <sub>5</sub> (2.5 eq.), CH <sub>2</sub> Cl <sub>2</sub> , RT, o/n	73%	0	0	0
4	BiCl <sub>3</sub> (3 eq.), py, μ-wave, 140°C, 1 bar, 20 min	100%	0	0	0
5	Cyanuric chloride•DMF (1 eq.), o/n	93%	13	29	58
6	Cyanuric chloride•DMF (1.5 eq.), o/n	69%	0	100	0

<sup>†</sup>Recoveries based on starting material mass. \*Ratios obtained by <sup>1</sup>H NMR spectroscopy

with 1.5 equivalents of cyanuric chloride in DMF at room temperature (Table 4.3, entry 6). Hydrolysis of the starting material **227** had occurred under these conditions to yield the ketone **163** as the only material recovered.

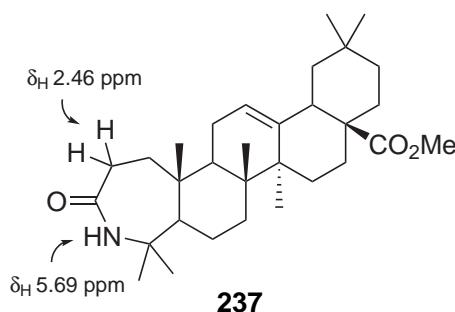


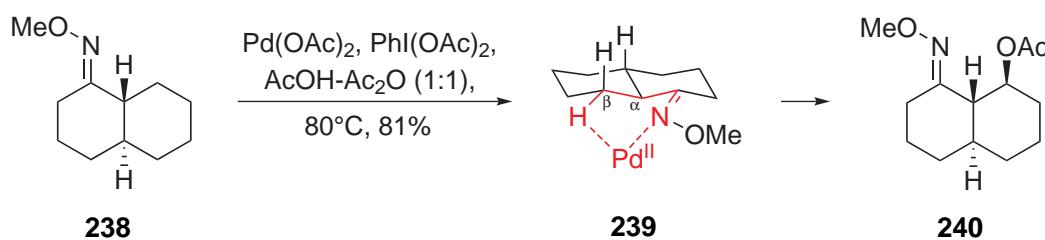
Figure 4.4: <sup>1</sup>H NMR chemical shifts of a lactam.<sup>190</sup>

Disappointingly, most of the procedures that were utilised to convert the oxime **227** to the lactam **235** were unsuccessful. One attempt with cyanuric chloride and DMF may have formed a small quantity of the lactam **235**. As observed with the tosyl hydrazone **222**, the oxime **227** was very susceptible to hydrolysis to form the ketone **163**. Hydrolysis

of the tosyl hydrazone **222** could have competed with the Beckmann rearrangement to synthesise **235**. Hydrolysis was a major factor during these reactions and could have occurred quicker than the rearrangement.

#### 4.3.2. Oxime-directed C-H activation

C-H activation is a method of functionalising unreactive C-H bonds that has fascinated synthetic organic chemists for the past decade.<sup>191,192</sup> This methodology enables direct chemical transformations at positions in the molecule remote to a functional group. Sanford has published work on  $sp^3$  C-H activation reactions directed by oximes.<sup>193</sup> Palladium(II)-catalysed oxygenation of an array of *O*-methyl oxime substrates with PhI(OAc)<sub>2</sub> was achieved with high chemo- and regioselectivity. This reaction was successfully performed on a *trans*-decalone derivative **238** which provided inspiration to apply a C-H activation reaction on a clerodane (Scheme 4.11). The key step involved the formation of the Pd(II) intermediate **239**. Pd(II) coordinates to the oxime nitrogen atom to enable a C-H insertion at the  $\beta$ -position and form the palladacycle **239** (highlighted in red). Oxidative cleavage of the C-Pd bond then occurs with PhI(OAc)<sub>2</sub> to give the final acetoxy product **240**.



Scheme 4.11: Oxime-directed Pd(II)-catalysed  $\text{sp}^3$  C-H activation reaction achieved by Sanford and co-workers.<sup>193</sup>

The conditions reported by Sanford were applied to the *O*-methyl oxime clerodane **230** (Table 4.4). The oxime **230** was treated with 5 mol % Pd(OAc)<sub>2</sub> and 1.5 equivalents of PhI(OAc)<sub>2</sub> in 1:1 acetic acid-acetic anhydride and this was stirred at 80°C overnight. The <sup>1</sup>H NMR spectrum of the crude product did not show the formation of the acetoxy product **241**, but a mixture of products were observed (Table 4.4, entry 1). The starting material was absent, which hinted that it was all converted to products or that decomposition had occurred. Increasing the amount of Pd(OAc)<sub>2</sub> to 8 mol % and raising the temperature to 100°C also gave a complex mixture of products (Table 4.4, entries 2 & 3). Another

attempt with **163**, 10 mol %  $\text{Pd}(\text{OAc})_2$ , 1.5 equivalents of  $\text{PhI}(\text{OAc})_2$  and heating to 100°C in acetic acid-acetic anhydride also provided the same outcome as the previous attempts (Table 4.4, entry 4).

Table 4.4: C-H activation reaction conditions implemented.

**230**

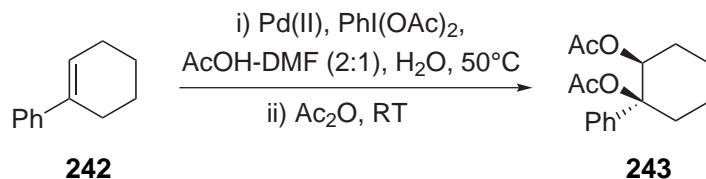
$\xrightarrow[\text{AcOH-Ac}_2\text{O (1:1)}]{\text{Pd}(\text{OAc})_2, \text{PhI}(\text{OAc})_2 //}$

**241**

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Entry	Conditions	Result
1	$\text{Pd}(\text{OAc})_2$ (0.05 eq.), $\text{PhI}(\text{OAc})_2$ (1.5 eq.), 80°C, o/n	Complex mixture
2	$\text{Pd}(\text{OAc})_2$ (0.08 eq.), $\text{PhI}(\text{OAc})_2$ (1.5 eq.), 100°C, 3 h	Complex mixture
3	$\text{Pd}(\text{OAc})_2$ (0.08 eq.), $\text{PhI}(\text{OAc})_2$ (1.5 eq.), 100°C, o/n	Complex mixture
4	$\text{Pd}(\text{OAc})_2$ (0.10 eq.), $\text{PhI}(\text{OAc})_2$ (1.5 eq.), 100°C, o/n	Complex mixture

Intriguingly, the H3 signal attributed to the starting material was absent in every  $^1\text{H}$  NMR spectrum of the crude product.  $\text{PhI}(\text{OAc})_2$  is capable of oxidising alkenes in the presence of acid to give a vicinal diacetate. Kim and Park managed to convert 1-phenyl-1-cyclohexene **242** to the diacetate compound **243** with 1.7 mol % of palladium magnetic particles, 1.2 equivalents of  $\text{PhI}(\text{OAc})_2$  and 1.5 equivalents of water in a 2:1 mixture of acetic acid and DMF, followed by addition of acetic anhydride (Scheme 4.12).<sup>194</sup> This reaction seemed plausible on the clerodane *O*-methyl oxime precursor **230**.

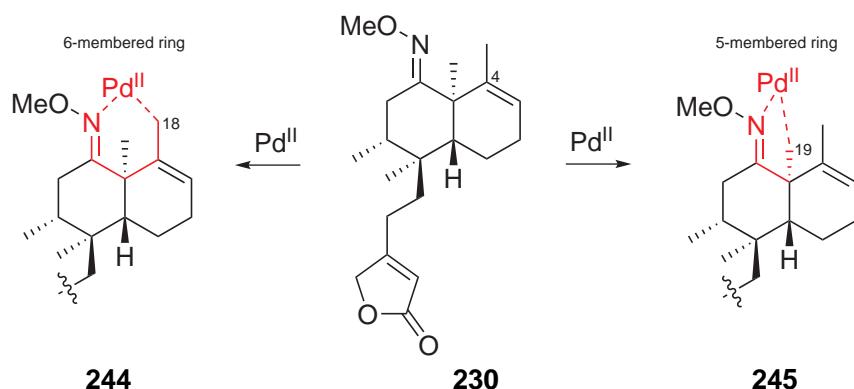


Scheme 4.12: Oxidation of an alkene with  $\text{PhI}(\text{OAc})_2$ .<sup>194</sup>

There are other factors that may have prevented the formation of the acetoxy product **241** in the reaction. Unlike the C-H activation reaction achieved by Sanford and co-workers

on **238** (Scheme 4.11), the oxime clerodane **227** has multiple functional groups which interfered with the reaction. Another issue was the generation of the palladacycle. To form the palladacycle, the oxime directing group must be co-planar to the C-H where coordination of Pd will occur. An example of this is the aforementioned reaction using *trans*-decalone *O*-methyl oxime as the substrate **238** (Scheme 4.11). This reaction used a conformational lock strategy.<sup>195</sup> The equatorial C-H bond at the  $\beta$ -position is locked in the same plane as the *O*-methyl oxime allowing the formation of the six-membered palladacycle **239** and hence the stereoselective formation of **240**.

The *O*-methyl oxime clerodane **230** has  $\beta$ -hydrogens for coordination to Pd(II) at the C18 (**244**) and C19 (**245**) methyl groups (Scheme 4.13). Coordination of Pd(II) with the C19 hydrogens **245** was unlikely as these hydrogens were not co-planar with the oxime directing group. Sterics could have also been an issue. As the starting material **230** contains a C19 methyl substituent, this could have impeded on the formation of the six-membered palladacycle. None of the examples provided by Desai involving ring systems had an  $\alpha$ -methyl to the directing group on the ring to give a  $\beta$ -acetate product on the ring.<sup>195</sup> Additionally, Pd(II) is a moderately-sized cation with an ionic radius of 64 pm (0.64 Å) when in a square planar coordination.<sup>196</sup> All of these factors could have contributed to the product **241** not being formed.

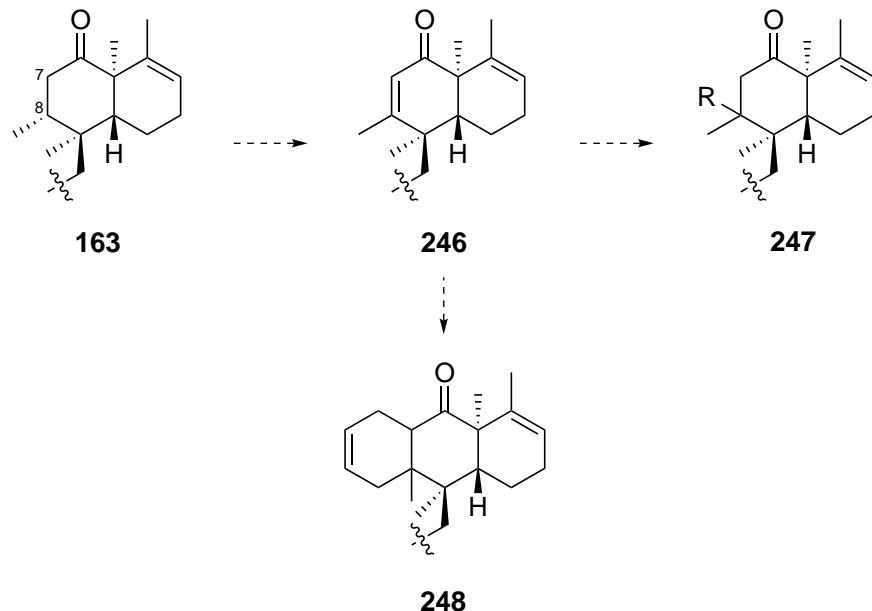


Scheme 4.13: Possible palladacycles that could form within the oxime **230**.

#### 4.4. Synthesis of the $\alpha,\beta$ -unsaturated ketone

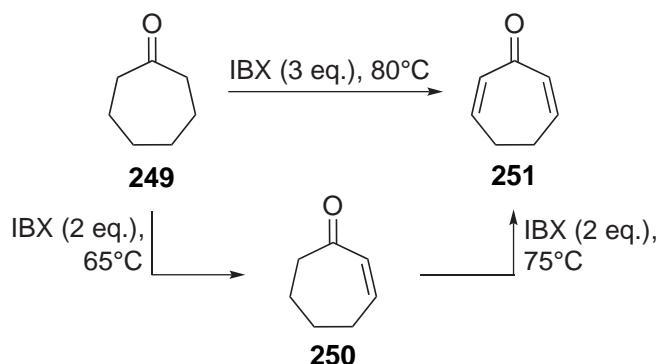
Dehydrogenation at the C7 to C8 positions was investigated to synthesise the  $\alpha,\beta$ -unsaturated system **246**. The enone **246** would be a valuable compound as it could enable a variety of new reactions to occur. For example, the C8 position could be substituted by

a conjugate addition reaction to form **247**. Additionally, enones **246** react as dienophiles in the Diels-Alder reaction to give **248**.



Scheme 4.14: Possible reactions of a clerodane enone **246**.

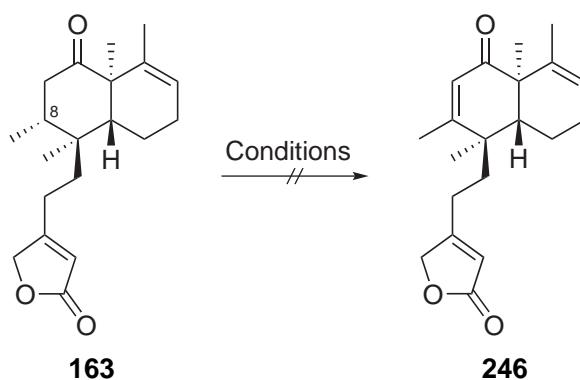
The most convenient method to dehydrogenate ketones to enones uses 2-iodoxybenzoic acid (IBX). Nicolaou and co-workers discovered the IBX-mediated oxidation of alcohols and ketones to enones in 2001.<sup>197</sup> Proof of concept studies were conducted on cycloheptanone **249**, and by manipulating the equivalents of IBX and temperature, both 2-cyclohepten-1-one **250** and cycloheptadienone **251** were selectively obtained (Scheme 4.15).<sup>197</sup> Since this discovery, IBX has been extensively used to form enones.<sup>198–201</sup>



Scheme 4.15: Proof of concept studies conducted on cycloheptanone **249**, adapted from Nicolaou *et al.*<sup>197</sup>

Clerodane **163** was stirred with 1.2 equivalents of IBX in DMSO at room temperature to 40°C, however, only starting material was recovered (Table 4.5, entry 1). Increasing the amount of IBX to 2 equivalents and heating at 65°C afforded a trace amount of **246** (<10%), however starting material was also retrieved (>90%) (Table 4.5, entry 2). Another attempt used 6 equivalents of IBX at the elevated temperature of 80°C to force the reaction to proceed, but only starting material was recovered (Table 4.5, entry 3).

Table 4.5: IBX reaction conditions attempted to synthesise the enone **246**.



Entry	Conditions	Yield of <b>246</b>
1	IBX (1.2 eq.), RT to 40°C, 2 days	0
2	IBX (2 eq.), 65°C, 5 days	Trace (<10%)
3	IBX (6 eq.), 80°C, 2 days	0

A follow up paper published by Nicolaou later in 2002 reported the reaction of IBX complexing to a ligand in a 1:1 ratio, particularly with DMSO **252** and *N*-oxides **253** (Figure 4.5).<sup>202</sup> Compound **252** is useful for the dehydrogenation of aldehydes and ketones, as well as benzylic oxidation. *N*-oxides **253** have an advantage over **252** in that they can dehydrogenate aldehydes and ketones under milder conditions at room temperature.<sup>202</sup> Comparison studies were performed to determine the extent of which IBX *N*-oxide complexes **253** improved the success of dehydrogenation reactions. Cyclooctanone was treated with a range of IBX-ligands in a provided example. The rate of conversion and percentage yield of the dehydrogenated products was significantly greater when using an IBX *N*-oxide complex **253** (IBX-MPO > IBX-NMO > IBX-trimethylamine-*N*-oxide) compared to using IBX-DMSO **252**.

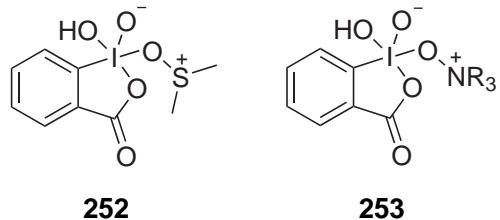
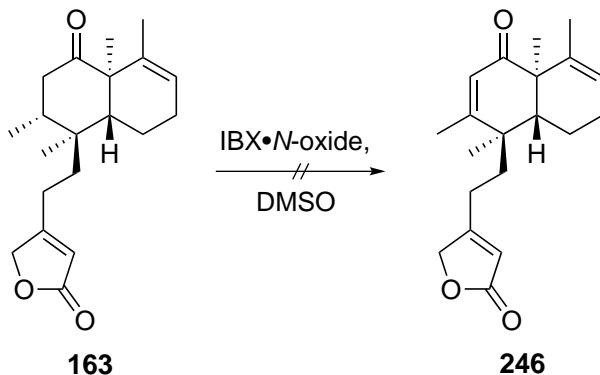


Figure 4.5: IBX complexed to DMSO and *N*-oxide ligands, created by Nicolaou *et al.*<sup>202</sup>

Initially, 1.5 equivalents of IBX and trimethylamine-*N*-oxide hydrate were added to **163** at room temperature, but only starting material was recovered (Table 4.6, entry 1).<sup>202</sup> Increasing the amount of reagents to 6 equivalents and heating the reaction from room temperature to 60°C also provided the same outcome (Table 4.6, entry 2). Rather than using trimethylamine-*N*-oxide hydrate as the ligand coordinating to IBX, 4-methoxypyridine *N*-oxide (MPO) was used. Out of all the *N*-oxides Nicolaou and co-workers tested, MPO gave the best results. All of the tested reaction conditions shown in Table 4.6 with IBX and MPO only recovered the starting material.

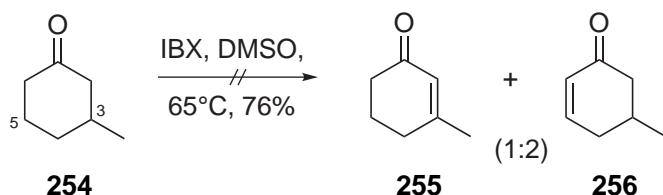
Table 4.6: IBX•*N*-oxide reaction conditions attempted to synthesise the enone **246**.



Entry	Conditions	Yield of <b>246</b>
1	IBX, Me <sub>3</sub> NO•H <sub>2</sub> O (1.5 eq.), RT, o/n	0
2	IBX, Me <sub>3</sub> NO•H <sub>2</sub> O (6 eq.), RT to 60°C, 2 days	0
3	IBX, MPO•xH <sub>2</sub> O (2.4 eq.), RT, 2 days	0
4	IBX, MPO•xH <sub>2</sub> O (5 eq.), DMSO, RT to 60°C, 7 days	0

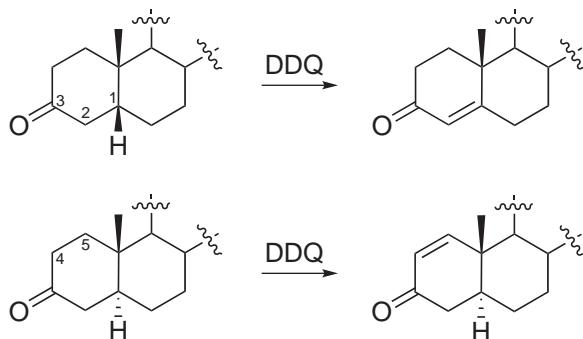
The dehydrogenation reaction using IBX requires the formation of the enol to give the enone **246**. If the ketone **163** cannot form the enol, the dehydrogenation reaction cannot occur. Earlier in this Chapter, attempts to synthesise the enolate of compound **163** were unsuccessful. The difficulties encountered earlier in this Chapter can explain why the dehydrogenation reactions did not provide the enone **246** in satisfactory yields. Nicolaou

and colleagues studied dehydrogenation reactions of some hindered cyclohexanones. Treatment of 3-methylcyclohexanone **254** with 2 equivalents of IBX at 65°C in DMSO afforded a mixture of **255** and **256** (33:67).<sup>197</sup> In this example the starting material 3-methylcyclohexanone **254** was more hindered at the C3 position than the C5 position because of the methyl group attached. This caused the enone **255** to be formed as the minor product, whilst **256** was the major product because the enone was less-hindered.



Scheme 4.16: Dehydrogenation of **254** with IBX.<sup>197</sup>

As IBX appeared to be unreactive towards compound **163**, the more traditional dehydrogenation reagent DDQ was tested. DDQ has been used extensively in steroid reactions to produce enones.<sup>203–205</sup> 3-Ketosteroids can be dehydrogenated with DDQ or chloranil to insert a D<sup>1,2</sup> or D<sup>4,5</sup>-double bond into the structure (Scheme 4.17).<sup>206</sup>

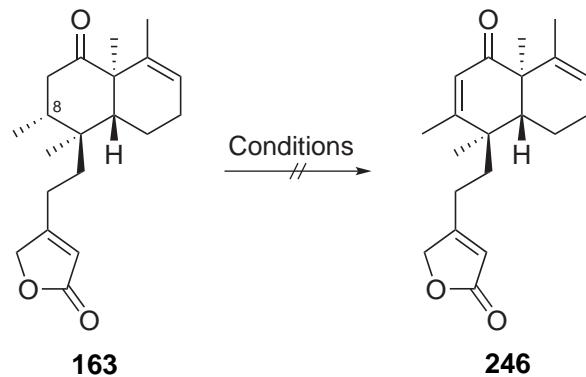


Scheme 4.17: Dehydrogenation of 3-ketosteroids with DDQ.

When the ketone **163** was stirred with 1.5 equivalents of DDQ and catalytic *p*-TsOH in dioxane using conditions similar to those used by Bonet *et al.*, no new products were observed by TLC (Table 4.7, entry 1).<sup>207</sup> Heating the reaction to reflux for 2 days did not produce any product since the starting material was recovered. Rather than using an acid-catalysed medium, a base-promoted reaction was attempted. Following adapted conditions published by Shia *et al.*, the precursor **163** was subjected to 1.5 equivalents of DDQ and potassium carbonate in dichloromethane (Table 4.7, entry 2).<sup>208</sup> The reaction

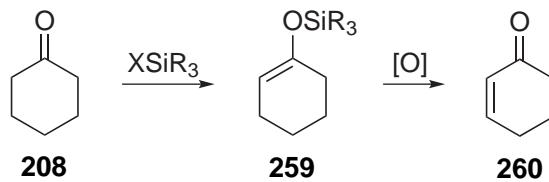
was stopped after 2 days and the  $^1\text{H}$  NMR spectrum obtained of the crude product did not show the formation of product **246**. The lack of reactivity observed with **163** in all of the aforementioned reactions was indicative of steric hindrance about the C8 position. This hindrance prevented the formation of the enol/enolate as encountered when the IBX dehydrogenation reactions were attempted.

Table 4.7: DDQ based reaction conditions to synthesise the enone.



Entry	Conditions	Yield of <b>246</b>
1	DDQ (1.5 eq.), <i>p</i> -TsOH (cat.), dioxane, RT to 101°C, 2 days	0
2	DDQ (1.5 eq.), K <sub>2</sub> CO <sub>3</sub> (1.5 eq.), CH <sub>2</sub> Cl <sub>2</sub> , RT to 40°C, 2 days	0

As a simple dehydrogenation reagent did not react with **163**, a stepwise synthesis of the enone **246** was then explored. Pre-forming the enol/enolate could overcome the issue experienced with IBX and DDQ. It is possible to treat ketones such as cyclohexanone **208** with R<sub>3</sub>SiCl reagents to synthesise R<sub>3</sub>Si-enol ether intermediates **259** (R = Me<sub>3</sub>, Me<sub>2</sub>*t*-Bu, Et<sub>3</sub>).<sup>209–211</sup> Silyl ethers are simple compounds to synthesise and are enol/enolate equivalents of **163**. Oxidation of these compounds with reagents such as Pd(OAc)<sub>2</sub> or a combination of Eosin Y, O<sub>2</sub> and light could lead to the formation of enones **260**.<sup>212,213</sup>

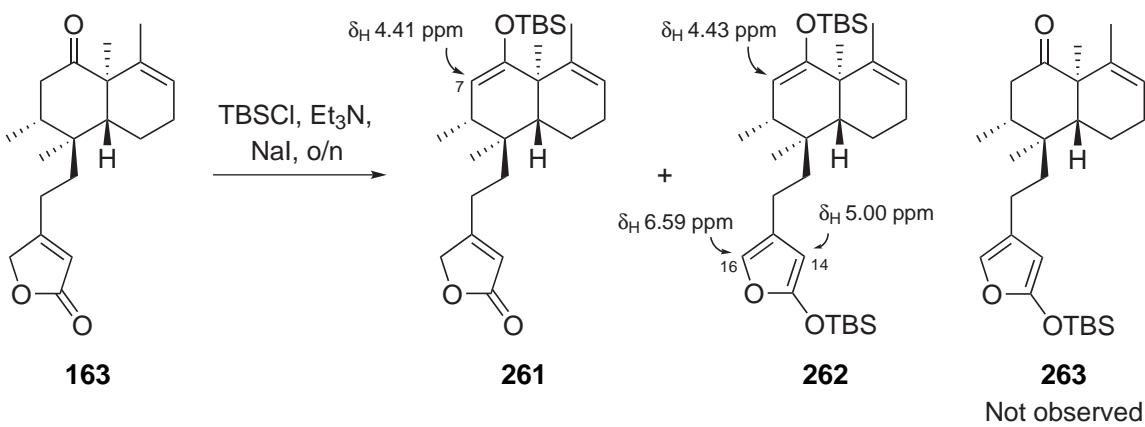


Scheme 4.18: General reaction scheme for the SiR<sub>3</sub> enol ether route to synthesise enones.

Synthesis of a TBS enol ether was attempted as TMS enol ethers are quite labile under both acidic and basic conditions. When the ketone **163** was treated with 2.1 equivalents each of TBSCl, triethylamine and sodium iodide in DMF at 0°C to room temperature (Table 4.8, entry 1),<sup>210</sup> only the starting material was recovered. Switching the solvent from DMF to freshly distilled acetonitrile at room temperature gave a mixture of the mono TBS ether **261** and the di TBS ether **262** in a 40:60 ratio, respectively (Table 4.8, entry 2).<sup>211</sup> It was vital that all reagents were dried vigorously prior to the commencement of the reaction and a vast excess of reagents also had to be used to increase the conversion of the starting material to the product(s). The <sup>1</sup>H NMR spectrum of **261** gave signals typical of a TBS group along with a doublet at 4.41 ppm assigned to H7. These signals signified the formation of the mono TBS enol ether **261**. The di TBS compound **262** had a doublet at 4.43 ppm corresponding to H7, along with doublets at 5.00 and 6.59 ppm ascribed to H14 and H16, respectively. This reaction was capricious as no two attempts gave reproducible results. One attempt gave full conversion of the starting material to the mono TBS ether **261** (Table 4.8, entry 3). Another reaction furnished the di TBS ether **262** as the only product (Table 4.8, entry 4). A further two attempts gave a mixture of the mono TBS ether **261** and recovered starting material (Table 4.8, entries 5 & 6). Both products **261** and **262** were highly prone to hydrolysis if trace acid was present. Purification via radial chromatography often gave significantly lower isolated yields of products, particularly of **262**. The di TBS ether **262** is a very reactive compound, and was unstable at room temperature and when stored at 0°C. Due to its instability, a molecular ion via HRMS and a microanalysis of this compound could not be obtained despite numerous attempts. Compound **263** was not observed during any of the reactions, presumably because it readily hydrolysed during work-up.

Rather than using 20 equivalents of TBSCl, sodium iodide and triethylamine, 10 equivalents each of these reagents was trialled. The first attempt provided a mixture of the mono TBS ether **261** and the di TBS ether **262** in a 17:83 ratio (Table 4.8, entry 7). Repetition of the reaction afforded the di TBS ether **262** as the only product in quantitative yield (Table 4.8, entry 8). Again, as observed in the previous experiments, the reaction provided inconsistent results.

Table 4.8: Unreproducible results obtained from the TBS enol ether syntheses.



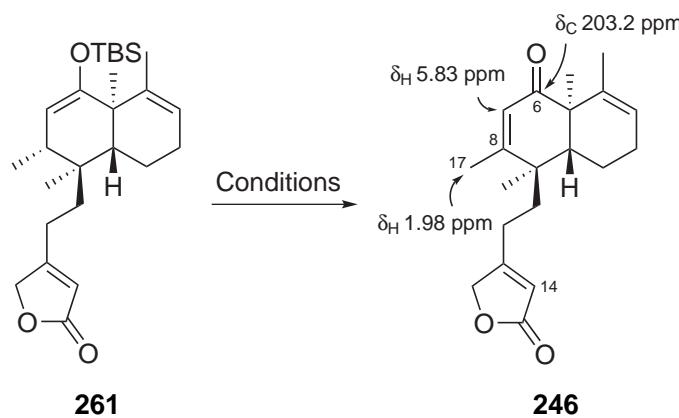
Entry	Conditions	Yield/ recovery <sup>†</sup>	Product ratio*		
			<b>261</b>	<b>262</b>	<b>163</b>
1	TBSCl (2.1 eq.), NaI (2.1 eq.), Et <sub>3</sub> N (2.1 eq.), DMF, 0°C to RT	100%	0	0	100
2	TBSCl (20 eq.), NaI (20 eq.), Et <sub>3</sub> N (20 eq.), dry MeCN, RT	152% <sup>†</sup>	40	60	0
3	(Same as above)	58%	100	0	0
4	(Same as above)	94%	0	100	0
5	(Same as above)	134% <sup>†</sup>	74	0	26
6	(Same as above)	118% <sup>†</sup>	66	0	34
7	TBSCl (10 eq.), NaI (10 eq.), Et <sub>3</sub> N (10 eq.), dry MeCN, RT	148% <sup>†</sup>	17	83	0
8	(Same as above)	100%	0	100	0

<sup>†</sup>Recoveries based on starting material mass. \*Ratios obtained by <sup>1</sup>H NMR spectroscopy

With the silyl ether **261** in hand, Saegusa-Ito oxidation was considered to be a viable method of synthesising the enone. Saegusa-Ito oxidations rely on Pd(OAc)<sub>2</sub> and the optional addition of a stoichiometric or catalytic quantity of benzoquinone as a co-oxidant.<sup>214</sup> Following literature procedures, treatment of **261** with 1 equivalent of Pd(OAc)<sub>2</sub> in anhydrous acetonitrile at 0°C to room temperature did not afford the product (Table 4.9, entry 1).<sup>215</sup> Fleming and Paterson have reported that DDQ and collidine can oxidise a silyl enol ether to an enone derivative.<sup>216</sup> This method has proven particularly useful with cyclohexanone derivatives. According to the researchers, collidine removes the acidic bi-product 2,3-dichloro-5,6-dicyanohydroquinone (DDQH<sub>2</sub>) from the reaction. Addition of 4 equivalents of DDQ and 2 equivalents of *sym*-collidine to the enol ether **261** in acetonitrile did not afford any product (Table 4.9, entry 2). An attempt with 2 equivalents of DDQ and 1 equivalent of *sym*-collidine in freshly dried acetonitrile gave the enone **246** in an isolated yield of 47% (Table 4.9, entry 3). The <sup>1</sup>H NMR spectrum

of **246** in  $\text{CDCl}_3$  gave a new signal at 5.83 ppm (1H, m) assigned to the H7 methine, though this resonance appeared to overlap the H14 signal also at 5.83 ppm. Two distinct vinylic signals attributed to H7 (5.74 ppm) and H14 (5.90 ppm) were observed in the  $^1\text{H}$  NMR spectrum run in  $d_6$ -acetone, which confirmed the enone **246**. The peak attributed to the C17 methyl hydrogens in the product had a downfield shift to 1.98 ppm (3H, d) due to the deshielding nature of the newly-formed C8 alkene. The C6 enone carbonyl shifted upfield to 203.2 ppm compared to the starting material. The C7 CH resonance was found at 128.0 ppm, whilst the quaternary C8 carbon was observed at 159.0 ppm. Changing the solvent from anhydrous acetonitrile to anhydrous dichloromethane and using 4 equivalents of DDQ and 2 equivalents of *sym*-collidine increased the yield of **246** slightly to 53% (Table 4.9, entry 4).

Table 4.9: Oxidative conditions used to synthesise the enone **246** from **261**.



Entry	Conditions	Yield of <b>246</b>
1	$\text{Pd}(\text{OAc})_2$ (1 eq.), $\text{MeCN}$ , $0^\circ\text{C}$ to RT, o/n	0
2	DDQ (4 eq.), <i>sym</i> -collidine (2 eq.), $\text{MeCN}$ , RT, o/n	0
3	DDQ (2 eq.), <i>sym</i> -collidine (1 eq.), dry $\text{MeCN}$ , RT, o/n	47
4	DDQ (4 eq.), <i>sym</i> -collidine (2 eq.), dry $\text{CH}_2\text{Cl}_2$ , RT, o/n	53

Additionally, the di TBS ether **262** was oxidised to the enone **246**. Addition of 4 equivalents of DDQ and 2 equivalents of *sym*-collidine in dry dichloromethane at room temperature afforded **246** in 45% yield (Table 4.10, entry 1). Repetition of the same conditions in anhydrous acetonitrile gave **246** in 47% (Table 4.10, entry 2). The reaction of the di TBS ether **262** to the enone **246** was generally quicker than when the mono TBS ether **261** was the starting material. The TBS furan within **262** was not oxidised during the reaction, rather it hydrolyses back to the butenolide.

Table 4.10: Oxidative conditions used to synthesise the enone **246** from **262**.

Entry	Conditions	Yield of <b>246</b>
1	DDQ (4 eq.), <i>sym</i> -collidine (2 eq.), dry CH <sub>2</sub> Cl <sub>2</sub> , o/n	45
2	DDQ (4 eq.), <i>sym</i> -collidine (2 eq.), dry MeCN, 5 h	47

To improve the yield of the enone **246** synthesised and avoid the work-up of the TBS enol ethers **261** and **262** which easily hydrolysed, a one-pot procedure was attempted (Scheme 4.19). The ketone **163**, 15 equivalents of TBSCl, 15 equivalents of sodium iodide and 15 equivalents of triethylamine were combined at 0°C in anhydrous acetonitrile and stirred at room temperature for 2 days. When TLC analysis showed the formation of the silylation products, 2 equivalents of DDQ and 1 equivalent of *sym*-collidine were added to the reaction and the solution continued to stir overnight prior to work-up. The <sup>1</sup>H NMR spectrum of the crude product showed that the starting material **163** and mono TBS ether **261** (67:33) were the two recovered compounds.



Scheme 4.19: Attempted one-pot synthesis of the enone **246**.

Having finally formed the enone **246**, further reactions of this compound were not attempted due to the limited amounts of the ketone **163** available. *D. ceratocarpa*

was harvested once a year, which restricted the amount of material available for each transformation.

#### 4.5. Biological testing of some clerodanes

Three clerodanes **157**, **163** and **227** were sent to Dr Sumalee Kamchonwongpaisan at BIOTEC in Thailand for biological testing against human African trypanosomiasis (HAT) and malaria. Testing against HAT was done with the subspecies *Trypanosoma brucei rhodesiense*, which causes fast onset acute trypanosomiasis amongst the human population. The three tested clerodanes only differ by their functionalisation at C6. The results provided have high IC<sub>50</sub> values which were above average (Table 4.11). The alcohol **157** provided the best results (IC<sub>50</sub> 21.97 ± 0.71 µM), followed by the ketone **163** (IC<sub>50</sub> 24.05 ± 0.85 µM). The oxime **227** had the least activity (IC<sub>50</sub> 69.53 ± 1.00 µM), with an approximately 3-fold decrease in activity against *T. brucei rhodesiense* compared to **157** and **163**. The cytotoxicity of the clerodanes was also tested against vero cells. All three clerodanes were found to be non-toxic.

Table 4.11: HAT and cytotoxicity results for clerodanes **157**, **163** and **227**.

**157**
**163**
**227**

	<i>T. brucei rhodesiense</i>	Cytotoxicity (vero)
	IC <sub>50</sub> (µM)	IC <sub>50</sub> (µM)
<b>157</b>	21.97 ± 0.71	>100
<b>163</b>	24.05 ± 0.85	>100
<b>227</b>	69.53 ± 1.00	>50

Clerodanes **157**, **163** and **227** were also tested for their antimalarial activities against two types of *Plasmodium falciparum*: *TM4/8.2* and *K1CB1*. The *TM4/8.2* type is the sensitive strain, whilst the *K1CB1* type is the multidrug resistant strain. To understand the significance of the IC<sub>50</sub> values obtained of the clerodanes, three commercial antimalarial

drugs were also tested for comparative purposes. These were cycloguanil **264**, WR99210 **265** and pyrimethamine **266**, with WR99210 **265** being the most potent.

The clerodanes tested against *P. falciparum* (*TM4/8.2*) gave modest activities (Table 4.12). The most active of the three clerodanes was the alcohol **157**, closely followed by the oxime **227** and the ketone **163**. The results obtained from testing the three clerodanes against the multidrug resistant strain *P. falciparum* (*K1CB1*) showed little improvement. Again, the alcohol **157** had the best inhibition, followed by the ketone **163** and the oxime **227**. The IC<sub>50</sub> values for **157**, **163** and **227** were close to the IC<sub>50</sub> of pyrimethamine **266**.

Table 4.12: Antimalarial results for clerodanes **157**, **163** and **227**.

The figure displays six chemical structures. At the top are three clerodane diterpenes: **157** (alcohol), **163** (ketone), and **227** (oxime). Below them are three reference compounds: **264** (cycloguanil), **265** (WR99210), and **266** (pyrimethamine).

	<i>P. falciparum</i> ( <i>TM4/8.2</i> )	<i>P. falciparum</i> ( <i>K1CB1</i> )
	IC <sub>50</sub> (µM)	IC <sub>50</sub> (µM)
<b>157</b>	35.49 ± 4.45	33.59 ± 3.75
<b>163</b>	59.90 ± 5.82	51.06 ± 5.94
<b>227</b>	36.39 ± 5.73	>50
Cycloguanil <b>264</b>	0.053 ± 0.015	4.93 ± 1.49
WR99210 <b>265</b>	0.0034 ± 0.0000	0.0046 ± 0.0010
Pyrimethamine <b>266</b>	0.100 ± 0.042	25.1 ± 6.9

## 4.6. Conclusions

One of the main themes discussed in this Chapter was the inherent difficulty in preparing the enol/enolate of compound **163**. Alkylation of **163** were not possible adjacent to the

C6 ketone or at the butenolide. This was due to the steric bulk attributed to ring B which reduced the accessibility of **163** to an electrophile. Condensation reactions were achieved with the ketone **163**. Three oximes were synthesised from **163** by using 1.5 equivalents of a NH<sub>2</sub>OR-HCl complex in pyridine. Synthesis of a tosyl hydrazone **222** was successful, however it was prone to hydrolysis. A Beckmann rearrangement of the oxime **227** was attempted under an array of different reaction conditions, though the lactam **235** could not be synthesised. C-H activation reactions were attempted with the *O*-methyl oxime substrate **230** by following conditions published by Sanford and co-workers,<sup>193</sup> though none afforded the acetoxy product **241**. It was suggested that the precursor was too hindered, therefore the formation of a palladacycle was unlikely. Additionally, one of the reagents used in the reaction, PhI(OAc)<sub>2</sub>, appeared to have caused diacetylation of the C3-C4 alkene. Synthesis of the  $\alpha,\beta$ -unsaturated ketone **246** was unattainable via a one-step route with reagents such as IBX and DDQ. The generation of the enol/enolate intermediate required for the formation of the product was identified as the cause of the unreactivity of the starting material **163**. A two-step procedure to synthesise the enone **246** was achieved upon synthesis of the mono TBS ether **261** and the di TBS ether **262**. Compound **262** was very reactive, as the furan ring readily hydrolysed upon work-up and isolation. The hydrolysis of this compound outcompeted any further reactions that could have occurred on the furan. The TBS ethers **261** and **262** were converted to the enone **246** with DDQ and *sym*-collidine in good yields.

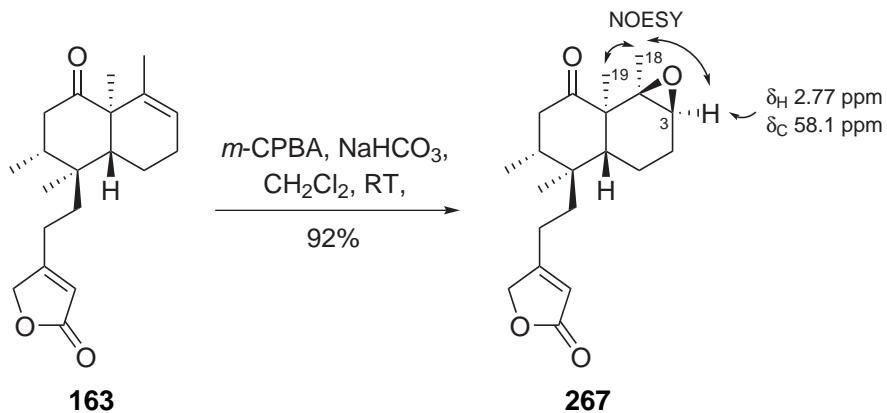
# Chapter 5

## Reactions of the Alkene on Ring A of Clerodane **163**

Functionalisations on ring A are based on the oxidation of the C3 alkene. Epoxidation and dihydroxylation of the C3 alkene of compound **163** was attempted to investigate the inherent stereoselectivity of these reactions.

### 5.1. Epoxidation

Epoxidation of the ketone compound **163** was investigated with *m*-CPBA using conditions similar to Manabe and Nishino.<sup>85</sup> Reaction of **163** with 1.5 equivalents of *m*-CPBA and 2 equivalents of sodium bicarbonate gave the epoxide **267** as the only stereoisomer in 92% yield (Scheme 5.1). This result was inconsistent to that observed by Manabe and Nishino who obtained a mixture of epoxides.<sup>85</sup> The conversion of the starting material to the epoxide was supported by <sup>1</sup>H NMR spectroscopy, as the vinylic hydrogen signal characteristic of the starting material was absent. A characteristic doublet resonance for an epoxide methine was observed at 2.77 ppm (*J* = 4.9 Hz) attributed to H3. The C3 position was located at 58.1 ppm in the <sup>13</sup>C NMR spectrum and the DEPT spectrum confirmed this signal as a CH. The stereochemistry of the epoxide and the C18 methyl group was determined by a NOESY experiment. The two key correlations were between H3 and H18, as well as between H18 and H19, indicating that these hydrogens are all on the same face.



Scheme 5.1: Epoxidation of the ketone **163**.

A clerodane **268** with an epoxide at C3-C4 synthesised by Rodríguez-Hahn and co-workers had a comparable H3 methine chemical shift to **267** (Figure 5.1).<sup>217</sup> The <sup>1</sup>H NMR spectrum of the epoxide **268** showed a doublet at 2.92 ppm (*J* = 5.0 Hz). The coupling constant was close to that found for **267** (*J* = 4.9 Hz).

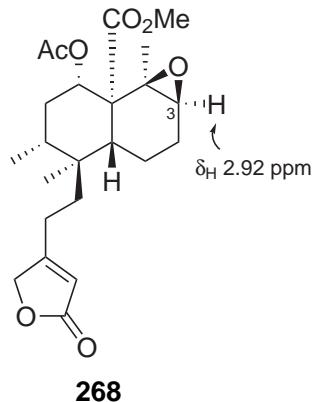


Figure 5.1: Structure of **268** and the key <sup>1</sup>H NMR epoxide resonance.

## 5.2. Sharpless asymmetric dihydroxylation

The Sharpless asymmetric dihydroxylation is a reliable method of forming chiral 1,2-diols from alkenes.<sup>218</sup> Sharpless' AD-mixes are convenient, preprepared reagent mixes that can be bought commercially. They contain potassium osmate as the source of osmium tetroxide, potassium ferricyanide as the re-oxidant, potassium carbonate as the base, and one of two chiral phthalazine ligands.<sup>219</sup> AD-mix $\alpha$  contains a dihydroquinine-phthalazine ligand ((DHQ)<sub>2</sub>PHAL), and AD-mix $\beta$  contains a dihydroquinidine-phthalazine ligand

$((DHQD)_2PHAL)$ . The stereochemical outcome of the diol product is dependent on what AD-mix is used. Usually AD-mix $\alpha$  gives the  $\alpha$ -diol, whilst AD-mix $\beta$  gives the  $\beta$ -diol.

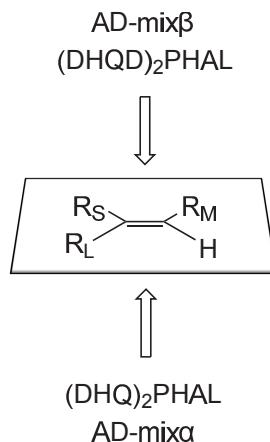
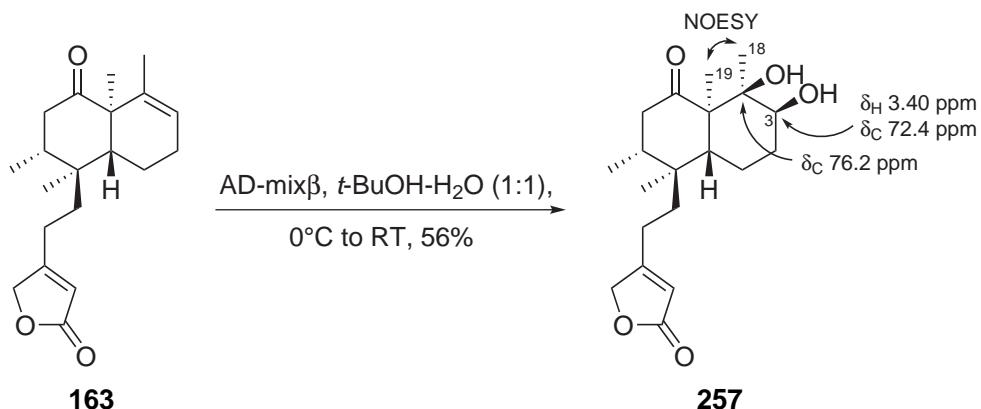


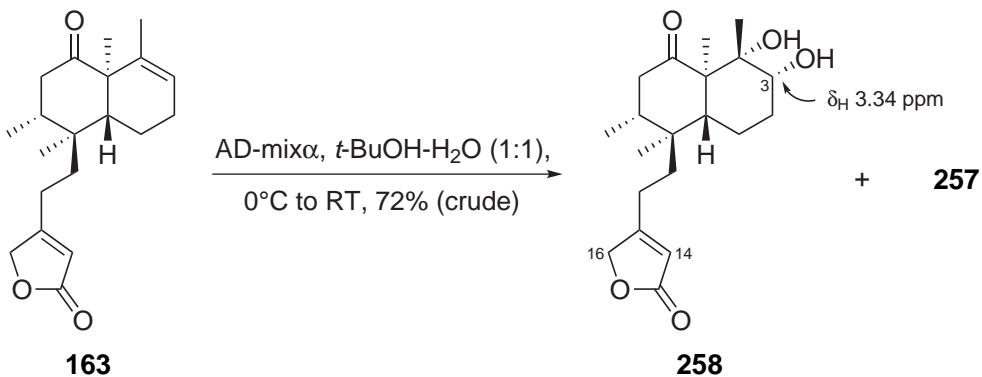
Figure 5.2: Facial selectivity of Sharpless' AD mixes with alkenes, adapted from Sharpless *et al.*<sup>219</sup> R group subscripts: S = small, M = medium and L = large.

Dihydroxylation of **163** using both of Sharpless' commercial AD-mixes gave different results. There are two possible stereoisomeric products that could be formed: the *re*- and the *si*-product. Following the general conditions given by Sharpless,<sup>219</sup> the ketone **163** was treated with AD-mix $\beta$  in a 1:1 mixture of *tert*-butanol and water at 0°C. This gave a 56% conversion to the *re*-diol **257** along with unreacted starting material (Scheme 5.2). The  $^1H$  NMR spectrum of the product had an upfield methyl singlet ascribed to C18 at 1.46 ppm. The C19 resonance of the starting material was replaced with a singlet further upfield at 1.28 ppm. The most significant signal noted in the  $^1H$  NMR spectrum was the H3 resonance, which relocated from 5.37 ppm to a doublet of doublets at 3.40 ppm. This hydrogen had an  $\alpha$ -orientation, as it must exist in the same plane as C18. A correlation between C18 and C19 was found in the NOESY spectrum, and since C19 already exists in the  $\alpha$ -orientation, this inferred that C18 must also have an  $\alpha$ -orientation. IR analysis of the product confirmed the diol as an OH stretch was evident at  $\nu = 3446\text{ cm}^{-1}$ .



Scheme 5.2: Sharpless' dihydroxylation of **163** with AD-mix $\beta$ .

Conversely, when the reaction was repeated with AD-mix $\alpha$  under identical conditions, a 1:1 mixture of the *re*- (**257**) and *si*- (**258**) diols was obtained as an inseparable mixture in 72% yield (Scheme 5.3). The key signal in the  $^1\text{H}$  NMR spectrum attributed to **258** was the broad singlet at 3.34 ppm assigned to H3 which had a  $\beta$ -orientation. The *si*-diol **258** also gave a multiplet at 5.82 ppm assigned to H14 and another multiplet at 4.71 ppm ascribed to H16. These signals proved that the C14 alkene within the butenolide portion had not reacted. The four methyl groups attributed to **258** could be distinguished from the mixture. H17, H18, H19 and H20 were found at 0.95, 1.43, 0.92 and 1.02 ppm.

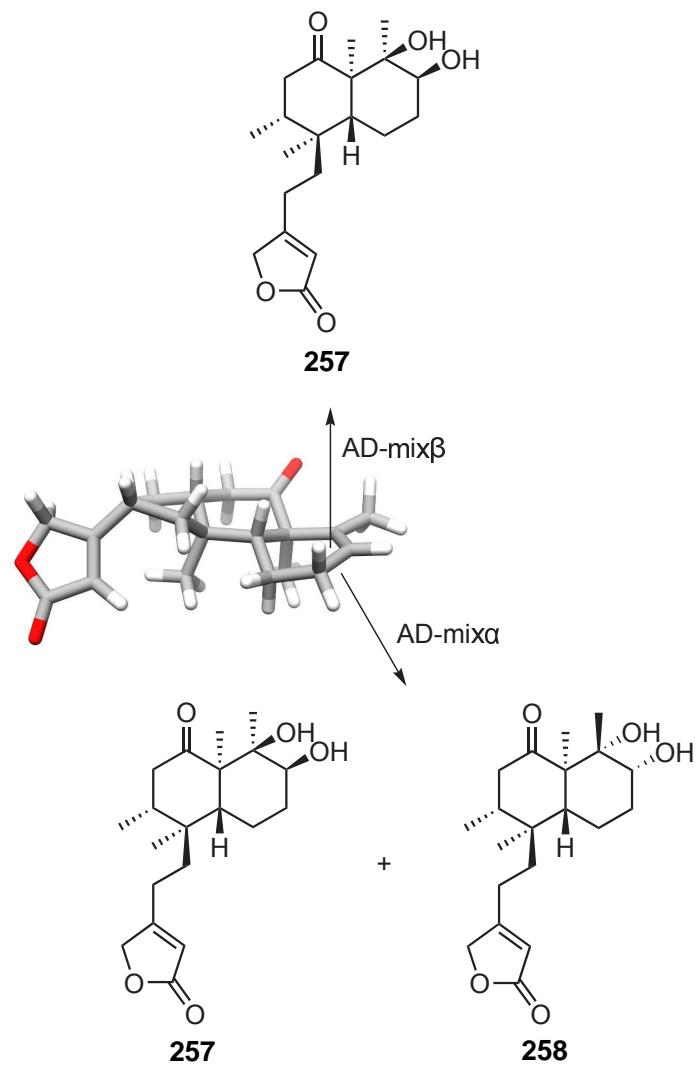


Scheme 5.3: Sharpless' dihydroxylation of **163** with AD-mix $\alpha$ .

### 5.3. Conclusions

To summarise, the epoxidation and dihydroxylation reactions were highly selective oxidations of the C3 alkene. Epoxidation of **163** afforded an epoxide **267** as a single stereoisomer. Sharpless dihydroxylation of **163** with two AD-mixes gave different results.

Both reactions formed the *re*-diol **257** as the more favourable product. The *re*-diol **257** exhibits the least hindrance and interaction with other portions of the clerodane such as the C19 methyl group. With regard to selectivity, this outcome did corroborate well with the results obtained from the epoxidation reaction. The bottom face of the molecule **163** is more hindered than the top, resulting in addition products that favour top face *re*-addition. This is the first Sharpless dihydroxylation study that has been undertaken on clerodanes.

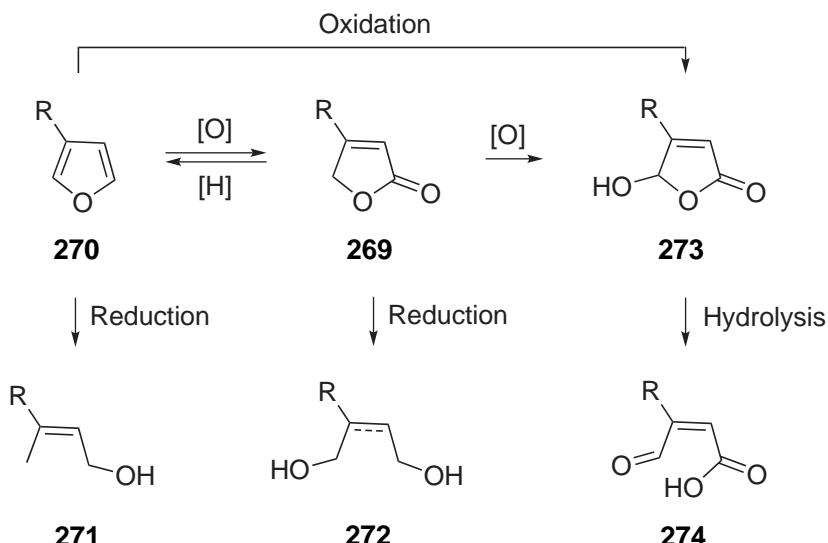


Scheme 5.4: Overview of the asymmetric diols formed with Sharpless' AD mixes and **163**.

# Chapter 6

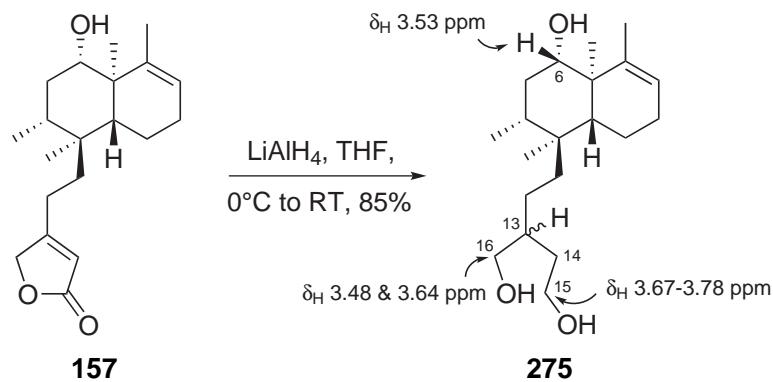
## Reactions on Ring C of Clerodanes 157 & 163

All of the substructures in Scheme 6.1 are found in clerodanes isolated from natural sources, and these have also been synthesised. Most of the clerodanes in this project contain a butenolide which can be transformed into these derivatives. Butenolides **269** can be converted to furans **270** upon reduction with DIBAL.<sup>220,221</sup> Further reduction of a furan could provide an allylic alcohol derivative **271**.<sup>222</sup> Reduction of a butenolide with lithium aluminium hydride could synthesise a ring-opened diol **272**, the alkene could remain intact or get reduced.<sup>223,224</sup>  $\gamma$ -Hydroxybutenolides **273** are commonly synthesised from a furan **270** via singlet oxygen.<sup>221,225,226</sup> Additionally, butenolide derivatives **269** can be oxidised to form **273**.<sup>227</sup>  $\gamma$ -Hydroxybutenolides are "masked" aldehyde-carboxylic acids **274** in their ring-opened form.<sup>228</sup>



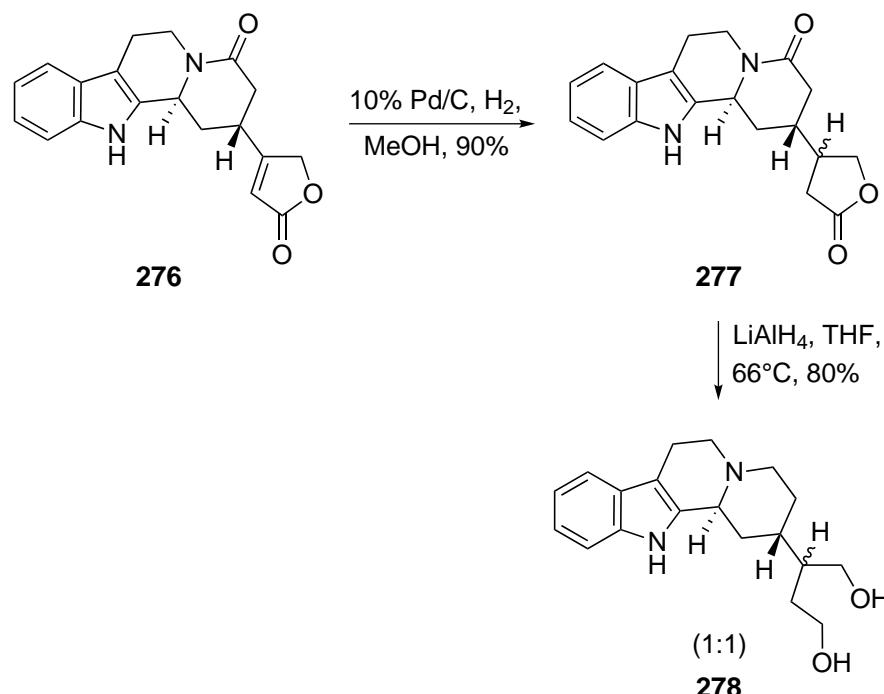
Scheme 6.1: Reactions of the butenolide **269**.

Reduction of the butenolide within **157** was attempted with lithium aluminium hydride. Reduction of compound **157** was feasible with 3 equivalents of lithium aluminium hydride in tetrahydrofuran at 0°C to room temperature to give the triol **275** as a mixture of diastereomeric diols (Scheme 6.2). The C13-C14 alkene was also reduced in this reaction. A doublet of doublets was found at 3.53 ppm in the <sup>1</sup>H NMR spectrum attributed to H6. Peaks at 3.48 (1H, m) and 3.64 ppm (1H, dt) were evident, and these resonances are attributed to the H16 methylene attached to an alcohol. A multiplet at 3.67-3.78 ppm was assigned to the H15 methylene attached to the other alcohol. The <sup>13</sup>C NMR spectrum revealed a new downfield methylene signal at 61.3 ppm assigned to the primary alcohol carbon at C15. The primary alcohol at C16 gave two resonances at 66.52 and 66.56 ppm. The <sup>13</sup>C NMR spectrum also contained more duplicate signals, which confirmed the formation of the diastereoisomers.



Scheme 6.2: Reduction of the butenolide to the triol.

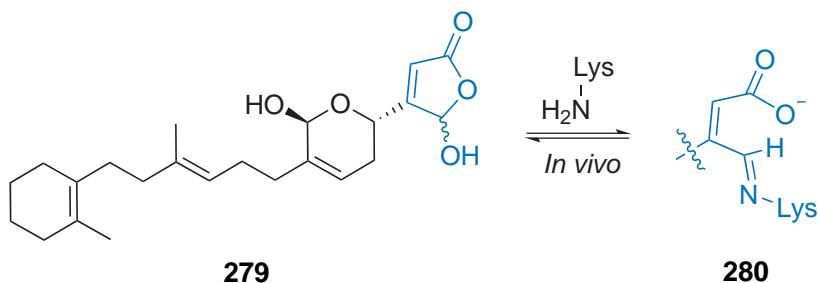
This reaction is similar to the transformation achieved by Pancrazi and co-workers on an indole alkaloid.<sup>229</sup> The butenolide **276** was reduced using a two-step process. The first step treated **276** with 10% Pd/C and H<sub>2</sub> in methanol to reduce the double bond and give **277**. The second step subjected **277** to lithium aluminium hydride which afforded the diastereomeric diols **278** (1:1).<sup>229</sup> Compared to this literature example, the reduction of the butenolide **157** to the triol **275** shown in Scheme 6.2 shows that this type of transformation can be undertaken in a single step.



Scheme 6.3: Two-step reduction of a butenolide to a diol.<sup>229</sup>

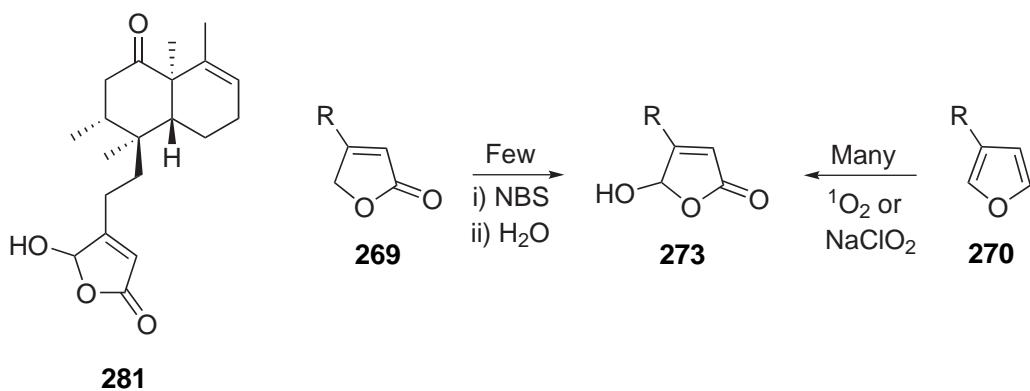
## 6.1. Synthesis of a hydroxylactone

Natural products that contain a  $\gamma$ -hydroxybutenolide moiety **273** often have interesting biological activities.<sup>225,230</sup> A prominent example is manoalide **279**, a sesquiterpene that was first isolated in 1980 by De Silva and Scheuer from the marine sponge *Luffariella variabilis* (Polejaeff) (Scheme 6.4).<sup>231</sup> Manoalide **279** is known for its potent antiinflammatory activity *in vivo*, as it inactivates the phospholipase A<sub>2</sub> enzyme (PLA<sub>2</sub>) from bee, scorpion and cobra venom.<sup>232</sup> PLA<sub>2</sub> is responsible for the release of lysophospholipids and arachidonic acid which cause inflammation.<sup>233</sup> The active portion of manoalide **279** is the  $\gamma$ -hydroxybutenolide site, as it has been reported that interactions occur between this moiety and lysine residues **280** at the lipid-PLA<sub>2</sub> interface.<sup>234,235</sup>



Scheme 6.4: Structure of manoalide **279** and its interaction with lysine.

The  $\gamma$ -hydroxybutenolide clerodane **281** was considered as a potential target, because this compound could exhibit an enhanced biological activity (Scheme 6.5). As the clerodane **157** isolated from *D. ceratocarpa* contains a butenolide, conversion of **157** to **281** was pursued. The disadvantage of synthesising a hydroxylactone **273** from a butenolide **269** is that there are few procedures and examples that allow this, whilst there are many examples that have been achieved on furan derivatives **270** (Scheme 6.5). Literature procedures have transformed a furan to a hydroxylactone with singlet oxygen<sup>60,225,236,237</sup> and sodium chlorite.<sup>238–240</sup> A butenolide could be reduced to a furan prior to treatment with singlet oxygen or sodium chlorite. Another method of transforming a butenolide to a hydroxylactone also requires two steps. Bromination of a butenolide with NBS could form the bromide compound, and then hydrolysis of this may then yield a hydroxylactone **273**.<sup>241,242</sup>

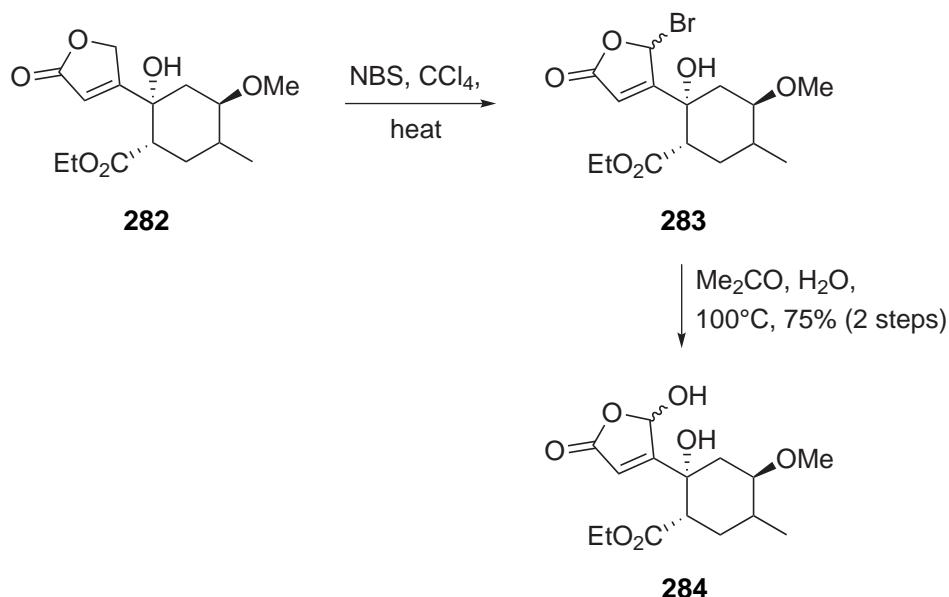


Scheme 6.5: Structure of the clerodane target **281** and access to a hydroxylactone **273**.

#### 6.1.1. Radical allylic bromination

The allylic bromination pathway is the most common method of synthesising a hydroxylactone from a lactone. This reaction was first demonstrated by Sauer and Koten

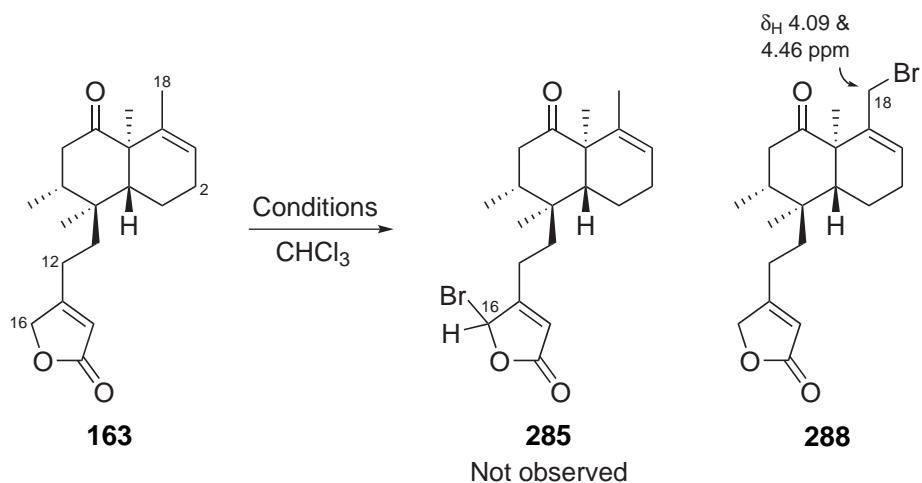
in 1962, where phthalide was treated with NBS in carbon tetrachloride at reflux with a light source (100W) to form 3-bromophthalide.<sup>243</sup> Another example is given by Thomas *et al.*, where a butenolide **282** was treated with NBS in carbon tetrachloride with heat to afford the bromide **283** (Scheme 6.6).<sup>244</sup> Hydrolysis of compound **283** provided the hydroxylactone **284** in 75% yield over two steps.



Scheme 6.6: Synthesis of a hydroxylactone **284** via a bromide intermediate **283**.<sup>244</sup>

Allylic bromination of the clerodane **163** was explored to form the brominated butenolide **285**, however, compound **163** has four allylic positions at C2, C12, C16 and C18 where the reaction could occur. When the clerodane **163**, 1 equivalent of NBS and a catalytic quantity of lauroyl peroxide were heated at reflux in chloroform, the crude reaction mixture had a complex <sup>1</sup>H NMR spectrum (Table 6.1, entry 1). The spectrum had signals with a distinctive AB pattern at 4.09 (1H, d, *J* = 12.4 Hz) and 4.46 ppm (1H, dt, *J* = 12.4, 1.3 Hz). These signals were indicative of a methylene bromide, and were similar to resonances observed for compound **286** synthesised by Barrero and co-workers (Figure 6.1).<sup>245</sup> The methylene hydrogens of **286** were found at 4.03 (d, *J* = 11.6 Hz) and 4.17 ppm (d, *J* = 11.6 Hz). A compound **287** synthesised by Koike and Tokoroyama also had similar signals to compound **286** attributed to a methylene bromide.<sup>246</sup> These signals also had an AB pattern and were found at 4.06 and 4.22 ppm (d, *J* = 10.0 Hz). Thus, the signals found in the <sup>1</sup>H NMR spectrum of the crude reaction mixture at 4.09 and 4.46 ppm were assigned to the H18 protons of the methylene bromide compound **288**.

Table 6.1: Attempted allylic bromination conditions used on the ketone precursor **163**.



Entry	Conditions	Mass	Ratio*	
		recovery <sup>†</sup>	288	163
1	NBS (1 eq.), lauroyl peroxide (cat.), 65°C, 2 h	124%	100	0
2	Recrystallised NBS (1.05 eq.), lauroyl peroxide (cat.), RT, 1.5 h	113%	36	64
3	Recrystallised NBS (1 eq.), lauroyl peroxide (cat.), 65°C, 500W lamp, 1 h	120%	73	27
4	Recrystallised NBS (1 eq.), lauroyl peroxide (cat.), 65°C, 2 h	123%	58	42
5	Recrystallised NBS (2 eq.), 65°C, 500W lamp, 4 days	125%	100	0
6	Recrystallised NBS (1 eq.), 0-10°C, 500W lamp, 0.5 h	110%	0	100

<sup>†</sup>Mass recoveries based on starting material mass. \*Ratios of **288:163** only were obtained by <sup>1</sup>H NMR spectroscopy

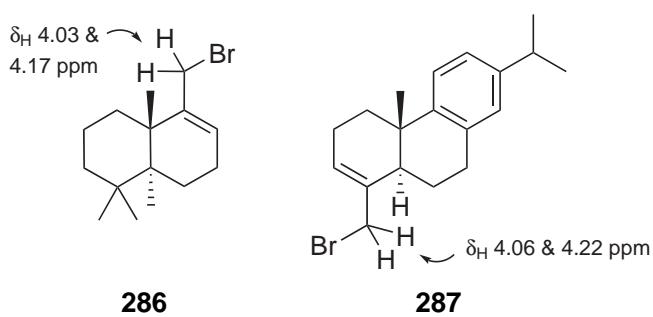


Figure 6.1: Methylenic  $^1\text{H}$  NMR chemical shifts attributed to **286** and **287**.<sup>245,246</sup>

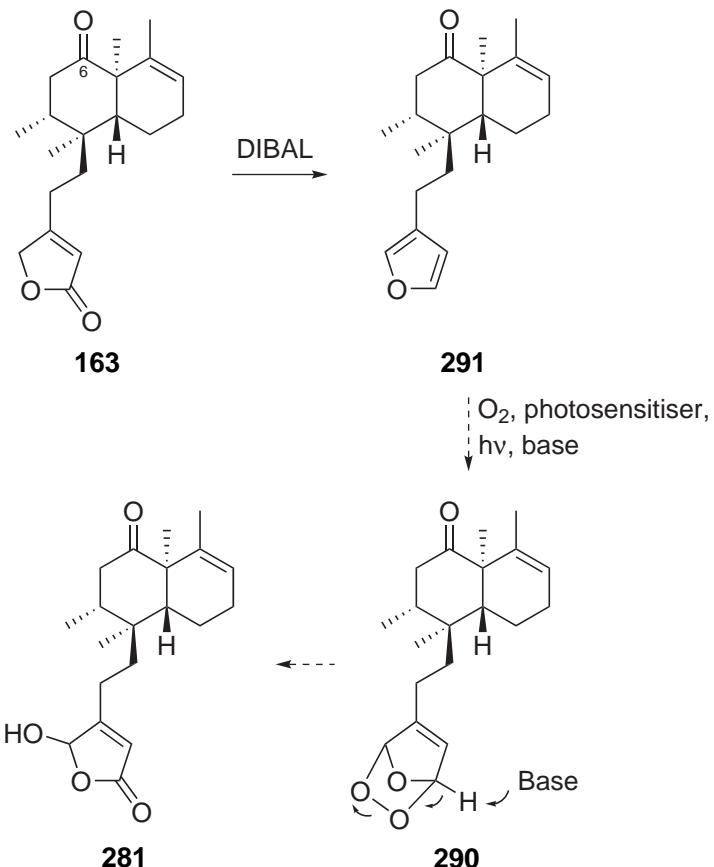
A small doublet at 6.23 ppm was also discerned, which was not the H16 methine of the brominated butenolide **285**. The chemical shift was too low to be H16 of the brominated butenolide **285**, since this resonance is typically located between 6.70-7.00 ppm.<sup>241,242,247</sup>

The methylene bromide **288** and other bromination products were present that could not be confidently identified. Attempts to isolate individual compounds was challenging, as co-elution of the bromination products occurred. The reaction was repeated with 1 equivalent of recrystallised NBS and catalytic lauroyl peroxide at room temperature (Table 6.1, entry 2). The methylene bromide **288** and unreacted starting material were obtained (36:64), yet there were other impurity peaks present. More peaks were detected between 5.20-6.40 ppm in the <sup>1</sup>H NMR spectrum, so selectivity was decreased. Another attempt with 1 equivalent of recrystallised NBS heated to 65°C via a 500W heat lamp also provided a mixture of products (Table 6.1, entry 3). The methylene bromide **288** and unreacted starting material were in the crude product in a ratio of 73:27. The conditions used in entry 1 of Table 6.1 were repeated, however with recrystallised NBS (Table 6.1, entry 4). When compared to the results obtained in entry 1, this attempt did not consume all of the starting material. This reaction did not reduce the number of reaction products formed or provide the brominated butenolide **285**. Rather than using 1 equivalent of NBS, the ketone **163** was treated with 2 equivalents of NBS and heated to 65°C with a 500W heat lamp for a longer reaction time of 4 days (Table 6.1, entry 5). The <sup>1</sup>H NMR spectrum of the reaction mixture was not as complex as the previous spectra obtained. The spectrum contained the methylene bromide **288**. The starting material was completely consumed, and trace amounts of other brominated products were also produced. After reviewing the results obtained thus far, the methylene bromide **288** was consistently the most favoured bromination product. To minimise the formation of side-products and possibly allow the formation of **285**, clerodane **163** was subjected to 1 equivalent of recrystallised NBS without catalytic lauroyl peroxide at 0-10°C. This did not give any products as starting material was recovered. As the intended product **285** was not formed in all the attempted reactions, this route to obtain the hydroxylactone **281** was discontinued for another.

#### *6.1.2. DIBAL reduction of the butenolide to the furan*

As photooxidation of furans is the most common method to prepare hydroxylactones, the conversion of compound **163** to the furan **289** was investigated. Reduction of butenolides to furans have been reported.<sup>60,225,236,237</sup> DIBAL has been shown to reduce butenolides to furans in clerodane systems.<sup>248,249</sup> A [4+2] cycloaddition of a furan derivative with singlet oxygen may afford an ozonide **290**, which could get cleaved by addition of a non-nucleophilic base to yield the hydroxylactone **281** (Scheme 6.7). Bisabe and colleagues

have reported this photooxidation on a clerodane similar to **163** without the carbonyl group at the C6 position.<sup>225</sup>



Scheme 6.7: Proposed reduction of the butenolide to the furan **291** and addition of singlet oxygen to form the hydroxylactone **281**.

Depending on the amount of DIBAL used, **163** could be reduced to form three compounds. These are the furan **289**, the alcohol **164** and the ring-opened butenolide **292**. Compound **163** was treated with 2 equivalents of DIBAL at  $-84^{\circ}\text{C}$  and warmed to room temperature (Table 6.2, entry 1). This afforded a trace amount of the furan **289**, the  $\beta$ -alcohol **164** and unreacted starting material (6:47:47). In an attempt to reduce the formation of the  $\beta$ -alcohol **164**, the reaction was repeated except it was kept at  $-84^{\circ}\text{C}$  (Table 6.2, entry 2). This provided the furan **289**, along with less  $\beta$ -alcohol **164** than before and more unreacted starting material (13:28:59). Treating the ketone **163** with 4 equivalents of DIBAL at  $-84^{\circ}\text{C}$  gave the furan **289**, the  $\beta$ -alcohol **164** and unreacted starting material (10:31:56) (Table 6.2, entry 3). Interestingly, a trace amount of a different compound was observed in the  $^1\text{H}$  NMR spectrum. This new compound gave signals at 3.83 (1H, m), 4.16 (2H, s), 4.19 (2H, d), 5.43 (1H, br s) and 5.61 ppm (1H, t).

These signals were assigned to compound **292**. This compound had a  $\beta$ -alcohol at C6 and had a reduced butenolide with the C13-C14 alkene still intact. Repetition of the reaction with 4 equivalents of DIBAL but starting the reaction at  $-84^{\circ}\text{C}$  and warming it up to  $-41^{\circ}\text{C}$  gave different ratios of the products (Table 6.2, entry 4). The furan **289**,  $\beta$ -alcohol **164**, ring-opened butenolide **292** and starting material **163** were recovered in a 19:54:7:20 ratio. The major difference with this attempt was that more of the starting material was converted to the  $\beta$ -alcohol **164**. The final conditions implemented on the ketone precursor **163** involved addition of 6 equivalents of DIBAL at  $-84$  to  $-41^{\circ}\text{C}$  (Table 6.2, entry 5). It appeared that the excess quantity of DIBAL had increased the conversion of starting material to the furan **289** and the reduced butenolide **292**, whilst a small amount of the starting material remained and none of the  $\beta$ -alcohol **164** was formed.

Table 6.2: Reduction conditions used to transform **157** to the furan **289**.

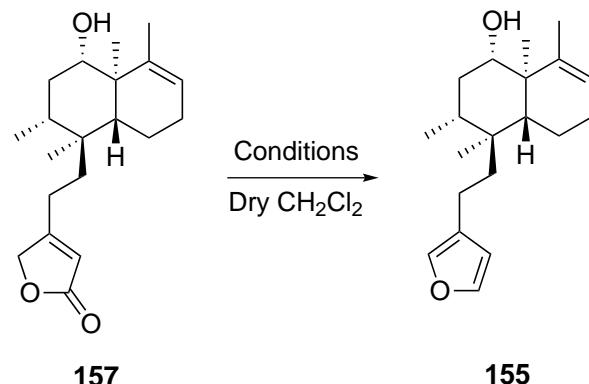
Entry	Conditions	Mass recovery <sup>†</sup>	289	164	292	163
1	DIBAL (2 eq.), $-84^{\circ}\text{C}$ to RT, o/n	60%	6	47	0	47
2	DIBAL (2 eq.), $-84^{\circ}\text{C}$ , 3 h	72%	13	28	0	59
3	DIBAL (4 eq.), $-84^{\circ}\text{C}$ , 3 h	80%	10	31	3	56
4	DIBAL (4 eq.), $-84$ to $-41^{\circ}\text{C}$ , 5 h	105%	19	54	7	20
5	DIBAL (6 eq.), $-84$ to $-41^{\circ}\text{C}$ , 5 h	85%	30	0	61	9

<sup>†</sup>Recoveries based on starting material mass. \*Ratios of **289**:**164**:**292**:**163** only were obtained by  $^1\text{H}$  NMR spectroscopy

A way to eliminate the competing reduction of the C6 ketone within **163** to form the alcohol **164** was to use the  $\alpha$ -alcohol **157** isolated from *D. ceratocarpa*. When 2.1 equivalents of DIBAL was added to **157** in dry dichloromethane at  $-84$  to  $-20^{\circ}\text{C}$ , a quantitative recovery of starting material was obtained (Table 6.3, entry 1). Another attempt subjected **157** to 3 equivalents of DIBAL in dry dichloromethane at  $-84$  to  $-20^{\circ}\text{C}$  (Table 6.3, entry 2). This provided a trace amount of product, though the majority of what

was recovered was unreacted starting material. Although the DIBAL reduction reactions attempted thus far did provide the furans **289** and **155**, the yields were not high enough to carry forward for the singlet oxidation reaction.

Table 6.3: Reduction conditions used to transform **157** to the furan **155**.

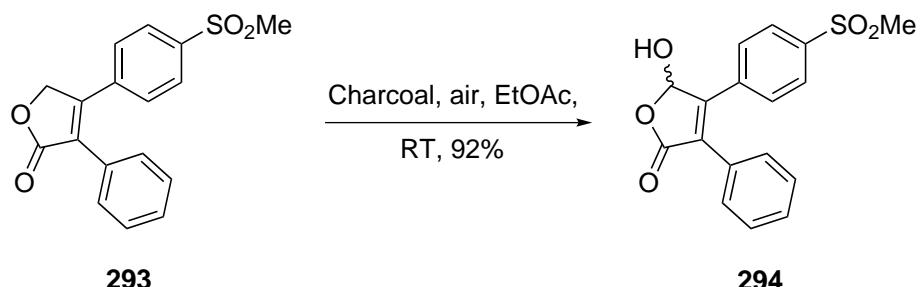


Entry	Conditions	Mass recovery <sup>†</sup>	Ratio*	
			<b>155</b>	<b>157</b>
1	DIBAL (2.1 eq.), -84 to -20°C, 3 h	100%	0	100
2	DIBAL (3 eq.), -84 to -20°C, 3 h	100%	6	94

<sup>†</sup>Recoveries based on starting material mass. \*Ratios of **155**:**157** were obtained by <sup>1</sup>H NMR spectroscopy

### 6.1.3. Charcoal-mediated oxidation with oxygen

Nicoll-Griffith and co-workers discovered that the non-steroidal antiinflammatory drug rofecoxib (Vioxx™) **293** gets metabolised in a rats liver with oxygen and hepatic enzymes to form the hydroxylactone 5-hydroxyrofecoxib **294**.<sup>227</sup> The HPLC chromatogram and mass spectral data of the biosynthetic metabolite **294** needed to be compared to a synthetic version of this compound in order to confirm the structure. To do this, **293** was stirred with charcoal in ethyl acetate and air at room temperature to give the product 5-hydroxyrofecoxib **294** in 92% yield (Scheme 6.8).<sup>227</sup> The authors of this research did not specify the role of charcoal in this reaction.



Scheme 6.8: Air oxidation of rofecoxib **293** by Nicoll-Griffith *et al.*<sup>227</sup>

Although **293** is a more activated system than the clerodane **163**, the same reaction conditions were used. Compound **163** was dissolved in ethyl acetate and stirred with charcoal in air at room temperature (Table 6.4, entry 1). Disappointingly, starting material was all that was recovered after 1 week. Since air contains 21% oxygen, oxygen gas was used to force the reaction to proceed. Compound **163** was again dissolved in ethyl acetate and stirred in charcoal at room temperature under oxygen (Table 6.4, entry 2). After 2 weeks, the reaction was stopped and the  $^1\text{H}$  NMR spectrum was obtained (Figure 6.3). The spectrum showed that only two products were present, the starting material (86%) and a new compound (14%).

Table 6.4: Synthesis of the hydroxylactone **281** with  $\text{O}_2$  and charcoal.

Entry	Conditions	Time stopped	Conversion to <b>281</b> *
1	Charcoal, air, EtOAc, RT	14 days	0%
2	Charcoal, $\text{O}_2$ , EtOAc, RT	14 days	14%

\*Conversions obtained by  $^1\text{H}$  NMR spectroscopy

This new compound was identified as the hydroxylactone **281**. The product was evident by the formation of a new singlet peak at 6.00 ppm attributed to H16. Typically, the methine resonance of a hydroxylactone is a singlet observed between 5.95-6.10 ppm.<sup>225,248</sup> Examples of similar compounds to **281** are the hydroxylactones **295** and **296**.<sup>225,248</sup> The H16 chemical shift for **295** was found at 5.99 ppm, whilst that for **296** was 6.04 ppm.

130

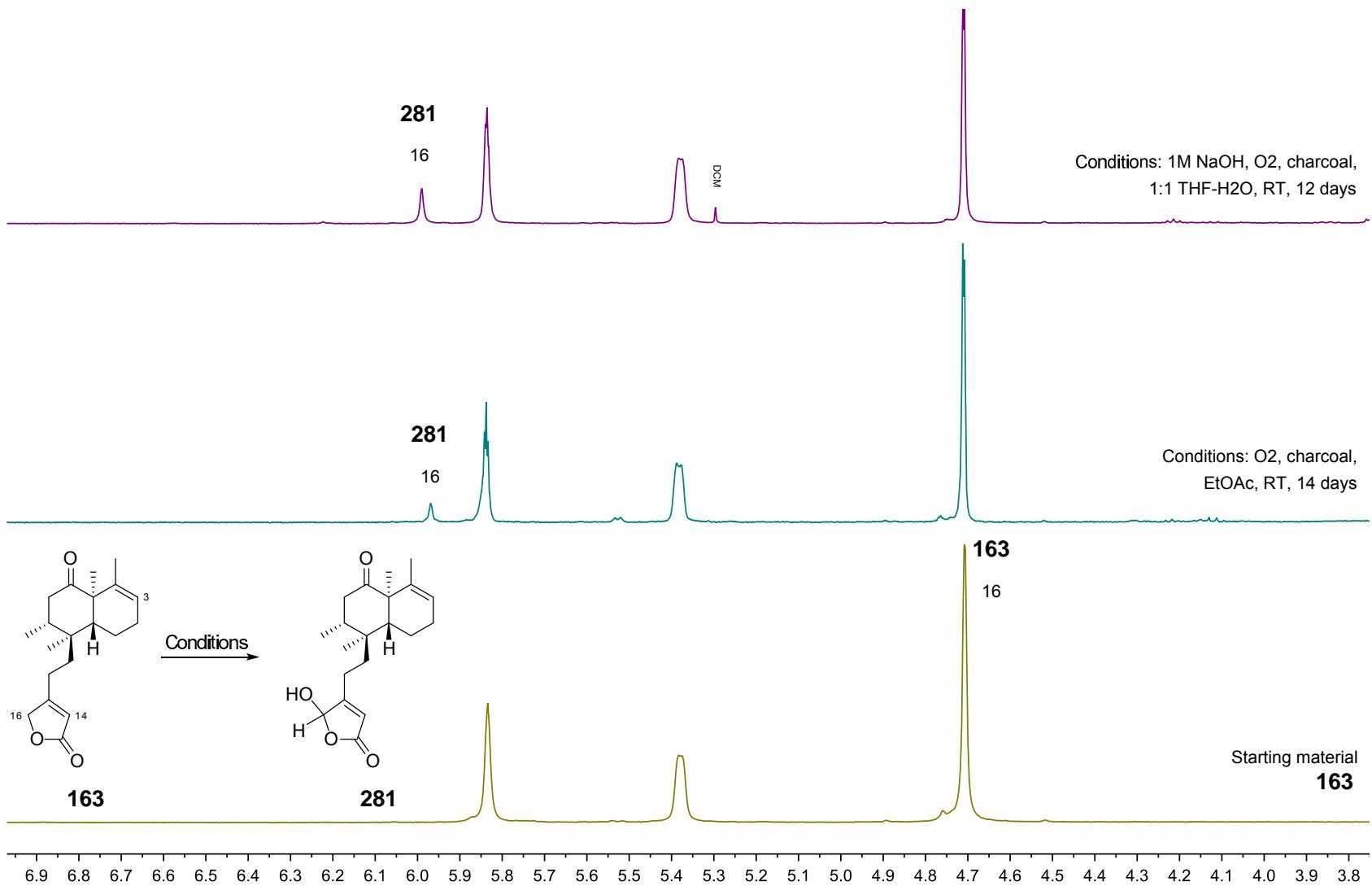


Figure 6.2: Zoomed  $^1\text{H}$  NMR overlay of the crude reaction mixtures in the synthesis of the hydroxylactone (ppm).

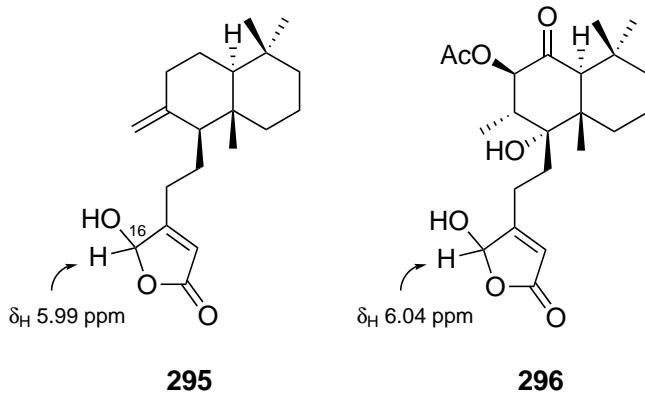
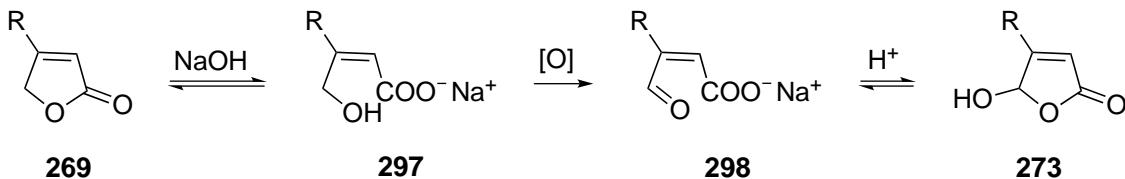


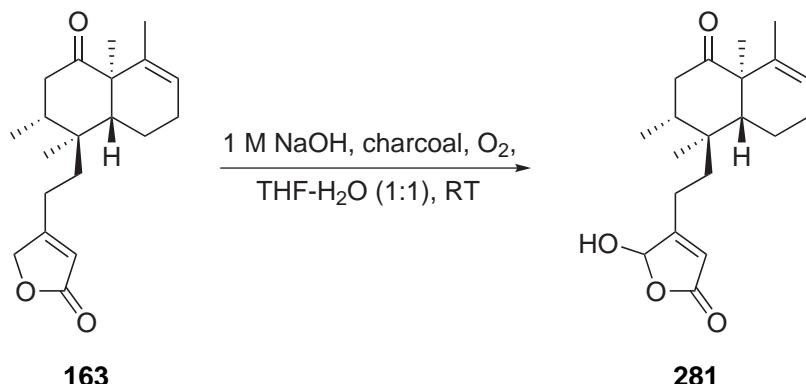
Figure 6.3:  $^1\text{H}$  NMR chemical shifts of some literature compounds which contain a hydroxylactone.<sup>225,248</sup>

As the conditions appeared to be quite mild, further optimisation needed to occur to increase the percentage conversion of the precursor **163** to the hydroxylactone **281**. It was proposed that addition of a base such as sodium hydroxide to the reaction would enable the butenolide ring **269** to open and form an alcohol-carboxylate derivative **297**. Oxidation of the alcohol portion of **297** could then proceed to give the aldehyde **298**. Hydrolysis of this could then cyclise the ring to give a hydroxylactone **273** (Scheme 6.9).



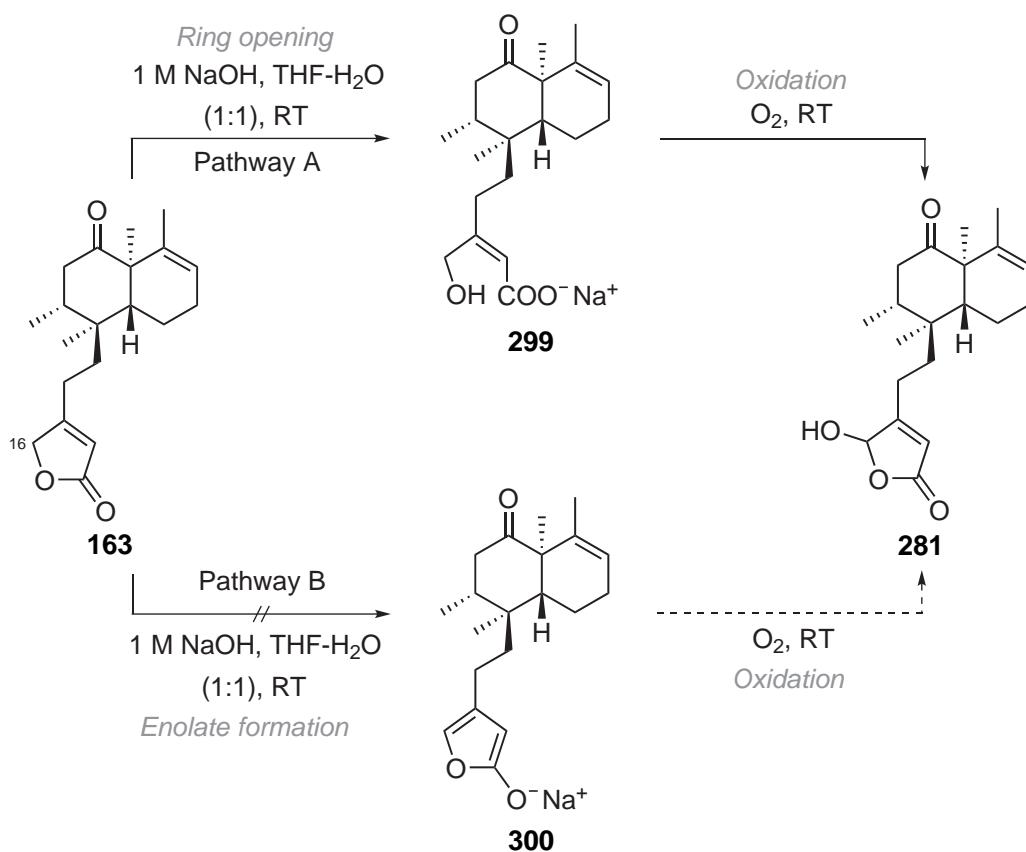
Scheme 6.9: Proposed synthesis of a hydroxylactone derivative **273**.

To test this method, the butenolide **163** was stirred with 1 equivalent of aqueous sodium hydroxide (1 M) and charcoal in a 1:1 solution of tetrahydrofuran and water under oxygen (Scheme 6.10). After 12 days, the reaction was stopped and a  $^1\text{H}$  NMR spectrum was obtained (Figure 6.3). The spectrum revealed that the product **281** had formed with a 30% conversion, whilst the remaining 70% accounted for starting material. This result was an improvement to the previous conditions (Table 6.4, entry 2), though the conversion of starting material **163** to product **281** was still low.



Scheme 6.10: Synthesis of the hydroxylactone **281** with NaOH, O<sub>2</sub> and charcoal.

To investigate the mechanism of this reaction further, it was proposed that the butenolide **163** could be treated with the reagents in a sequential manner to see what intermediates would form. The possible mechanism shown in Scheme 6.11 could follow two pathways.



Scheme 6.11: Proposed mechanistic pathways possible via addition of OH<sup>-</sup> to 163.

The first (Pathway A) involves a ring-opening reaction to form a carboxylate salt **299**. Oxidation of this salt could then form the aldehyde-carboxylate, which would equilibrate

with its ring-closed form **281**. The second (Pathway B) involves the base removing a H16 proton from the precursor **163** to form an enolate of the butenolide (furanyl species) **300**.

To determine the most probable pathway, the butenolide **163** was treated with 2 equivalents of 1 M sodium hydroxide and stirred in a 1:1 tetrahydrofuran-water solution. The salt **299** was isolated as a yellow solid in 99% yield (Table 6.5). The IR spectrum showed that the butenolide peaks were no longer apparent. These peaks were replaced with typical carboxylate stretching frequencies at 1560 and 1401 cm<sup>-1</sup>. Additionally, O-H stretching and bending frequencies were observed at 3378 and 1432 cm<sup>-1</sup>, respectively. Compound **299** was noticeably more polar than the starting material **163**. The formation of the carboxylate **299** suggested that the Pathway A mechanism in Scheme 6.11 occurs during this reaction.

Table 6.5: Synthesis of the salt derivative **299** and its IR data.

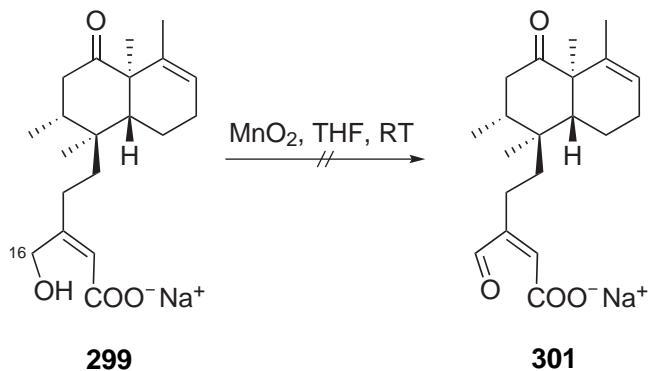
**163**

1 M NaOH, THF-H<sub>2</sub>O (1:1),  
RT, 99%

**299**

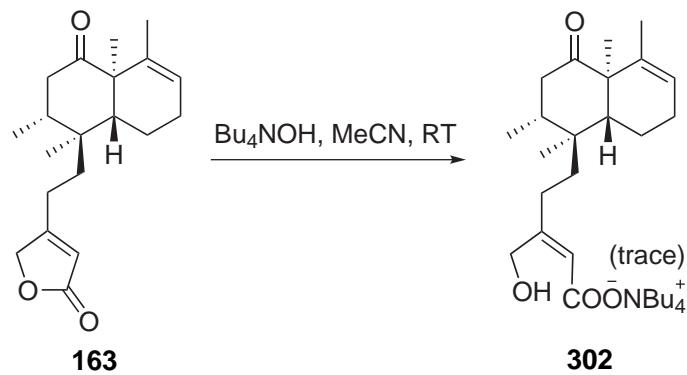
Functional group	Assignment	Frequency (cm <sup>-1</sup> )
Alcohol	O-H stretch	3378
Alcohol	O-H bend	1432
Ketone	C=O stretch	1705
COO <sup>-</sup> Na <sup>+</sup>	COO <sup>-</sup> asym stretch	1560
COO <sup>-</sup> Na <sup>+</sup>	COO <sup>-</sup> sym stretch	1401

With the salt **299** in hand, oxidation of the C16 alcohol to the aldehyde **301** was required prior to cyclisation. The salt **299** was treated with 10 equivalents of activated manganese dioxide in tetrahydrofuran and stirred at room temperature, but no reaction was observed after 1 week (Scheme 6.12). As the salt **299** was insoluble in many solvents, this may have impeded the progress of the reaction.



Scheme 6.12: Oxidation of the salt **299**.

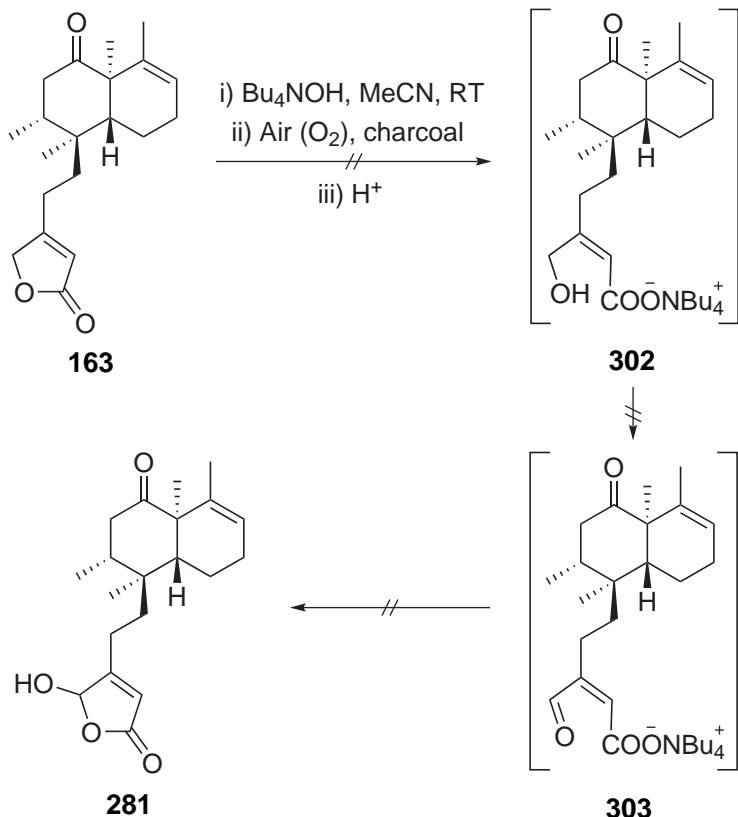
Rather than using sodium hydroxide as the base in a tetrahydrofuran-water solvent mixture to form the insoluble salt **299**, tetrabutylammonium hydroxide could be used to form an organic-soluble carboxylate salt **302**.<sup>250</sup> The butenolide **163** was treated with 2 equivalents of tetrabutylammonium hydroxide in acetonitrile at room temperature (Scheme 6.13). A colour change was observed upon addition of tetrabutylammonium hydroxide to the substrate, as the solution transitioned from colourless to yellow-orange. After 2 days, the reaction was stopped and the <sup>1</sup>H NMR spectrum of the crude mixture revealed that a trace amount of the salt **302** was present along with starting materials.



Scheme 6.13: Synthesis of the tetrabutylammonium salt **302**.

A one-pot, three-step synthesis of the hydroxylactone **281** was attempted. The substrate **163** was treated with 2 equivalents of tetrabutylammonium hydroxide in acetonitrile for 1 day (Scheme 6.14). The solvent was then concentrated, charcoal was added and air was bubbled into the reaction mixture to oxidise the alcohol **302** to the aldehyde **303**. After 7 days, hydrochloric acid was then introduced until the system was pH 1-2 to so that **303** could cyclise to form the hydroxylactone **281**. Analysis of the <sup>1</sup>H NMR spectrum of the

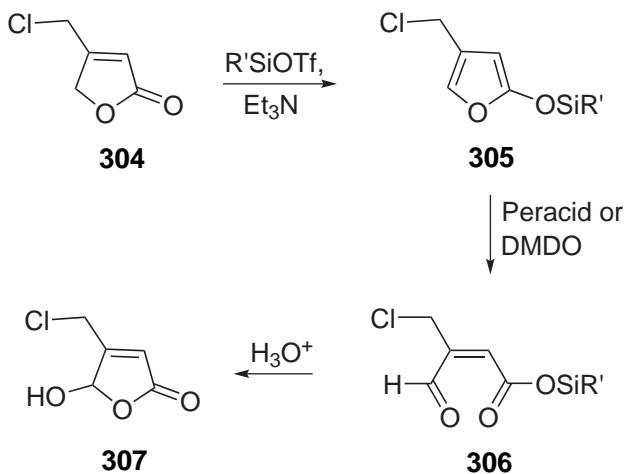
crude product did not show signals of any of the two reaction salt intermediates nor the product.



Scheme 6.14: Attempted synthesis of the hydroxylactone **281** via a tetrabutylammonium salt.

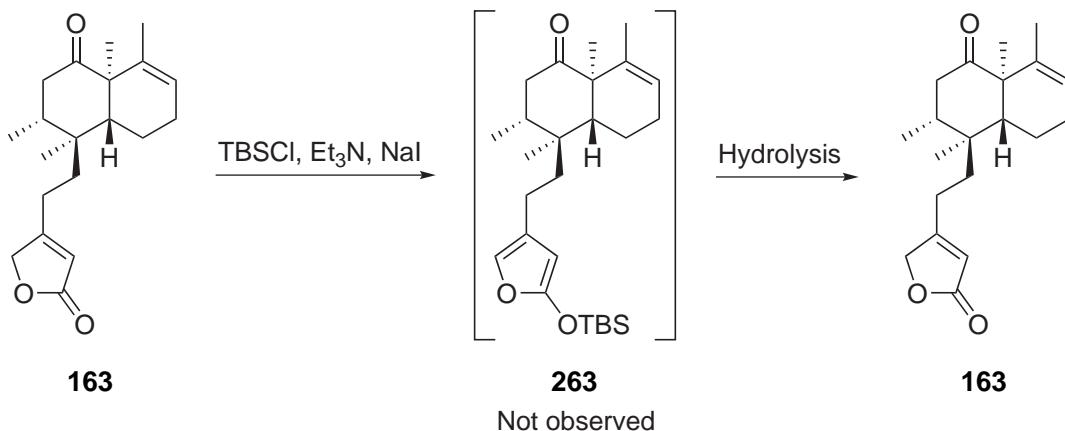
#### 6.1.4. Oxidation of 2-trialkylsilyloxyfurans

Boukouvalas and Lachance reported a method to synthesise hydroxylactones by converting a butenolide **304** to a 2-trialkylsilyloxyfuran **305**, which could then undergo rapid oxidative cleavage upon addition of a peracid or DMDO to form a trialkylsilyl (*Z*)-4-oxo-2-alkenoate **306**.<sup>71</sup> Hydrolysis of **306** afforded the hydroxylactone compound **273** (Scheme 6.15). The trialkylsilyl R' group introduced to form **305** could be TBS or TIPS, though TIPS gives higher yields of products due to its increased stability.<sup>71</sup> The approach used by Boukouvalas and Lachance of using 2-trialkylsilyloxyfurans was inspired by the ability of these compounds to readily undergo oxidative cleavage when treated with DMDO, which was first demonstrated with furans by McKervey *et al.*<sup>251</sup> Hydrolysis of an trialkylsilyl (*Z*)-4-oxo-2-alkenoate **306** was achieved with excess Amberlyst-15 in water to yield the hydroxylactone **307**.<sup>71</sup>



Scheme 6.15: An example of preparing hydroxylactones established by Boukouvalas and Lachance.<sup>71</sup>

Work presented in Chapter 3 has revealed that the mono TBS ether of the ketone **261** and the di TBS ether **262** were the products that were obtained upon treatment of **163** with TBSCl, sodium iodide and triethylamine. The mono TBS ether of the butenolide **263** was not observed during these reactions, however, it may have formed and hydrolysed during work-up due to its reactive nature (Scheme 6.16). The di TBS ether **262** was aimed along with the TIPS equivalent, since this compound may be more stable and less likely to hydrolyse due to the bulkiness introduced by this group.



Scheme 6.16: Possible formation of the furanyl TBS enol ether **263** and hydrolysis.

The ketone **163** was treated with 1.3 equivalents of TBSOTf and 1.4 equivalents of triethylamine in dry dichloromethane at 0°C to room temperature overnight (Table 6.6, entry 1). These conditions only recovered the starting material. The reaction was attempted with 5 equivalents of TBSOTf and 5 equivalents of triethylamine in dry

dichloromethane at 0°C to room temperature (Table 6.6, entry 2). This also did not form any product, as the starting material was obtained. Another attempt treated **163** with 5 equivalents of TBSOTf and 7.4 equivalents of triethylamine at 0°C (Table 6.6, entry 3). This was an improvement to the previous two conditions, as the mono TBS ether **261** and starting material were obtained in a 56:44 ratio, respectively. The starting material that was recovered could be unreacted material or could have been product **261** that hydrolysed during the work-up stage. As experienced in Chapter 3, TBS enol ethers are sensitive to water and acid, particularly the di TBS enol ether **262**. In consideration of this, the reaction was repeated again with 5 equivalents of TBSOTf and 10 equivalents of triethylamine. This gave 100% conversion of the precursor **163** to the mono TBS ether **261** and the di TBS ether **262** in a 81:19 ratio, respectively (Table 6.6, entry 4). Another

Table 6.6: Reaction conditions attempted to form the furanyl TBS enol ether.

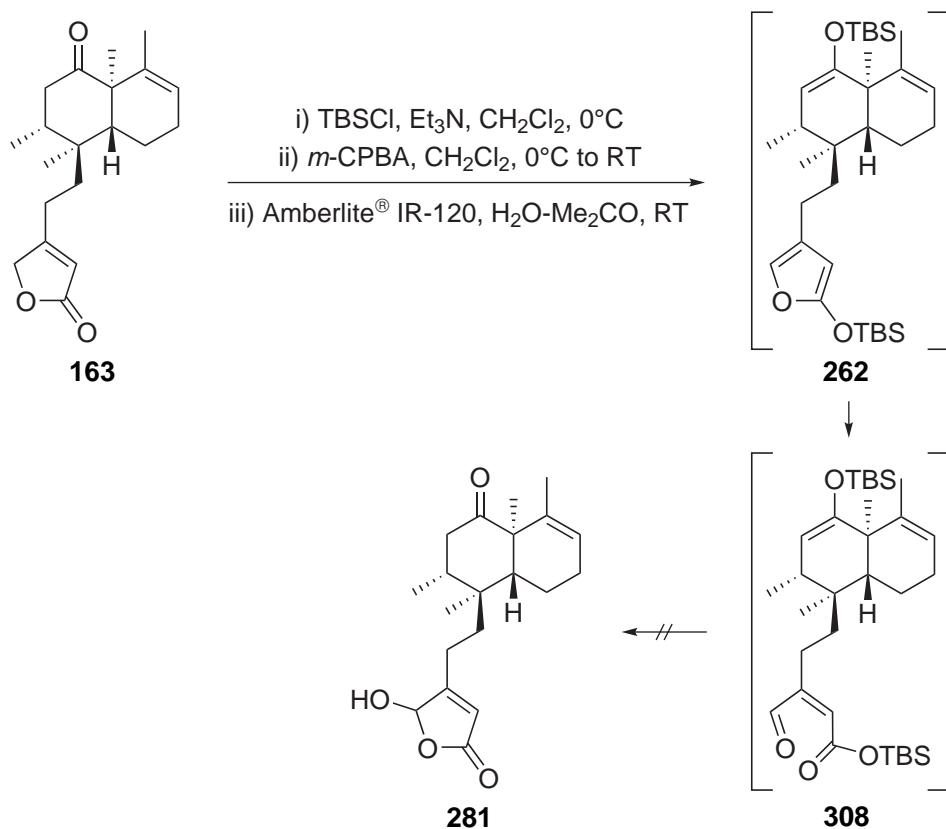
Entry	Conditions	Yield/ recovery <sup>†</sup>	Ratio*		
			<b>262</b>	<b>261</b>	<b>163</b>
1	TBSOTf (1.3 eq.), Et <sub>3</sub> N (1.4 eq.), dry CH <sub>2</sub> Cl <sub>2</sub> , 0°C, o/n	100%	0	0	100
2	TBSOTf (5 eq.), Et <sub>3</sub> N (5 eq.), dry CH <sub>2</sub> Cl <sub>2</sub> , 0°C, o/n	100%	0	0	100
3	TBSOTf (5 eq.), Et <sub>3</sub> N (7.4 eq.), dry CH <sub>2</sub> Cl <sub>2</sub> , 0°C, o/n	127% <sup>†</sup>	0	56	44
4	TBSOTf (5 eq.), Et <sub>3</sub> N (10 eq.), dry CH <sub>2</sub> Cl <sub>2</sub> , 0°C, o/n	113% <sup>†</sup>	19	81	0
5	TBSOTf (5 eq.), Et <sub>3</sub> N (10 eq.), dry CH <sub>2</sub> Cl <sub>2</sub> , 0°C, 0.5 h	86%	100	0	0

<sup>†</sup>Recoveries based on starting material mass. \*Ratios obtained by <sup>1</sup>H NMR spectroscopy

reaction was performed with the same equivalents of reagents except a shorter reaction time of 30 minutes was implemented (Table 6.6, entry 5). This was successful, as the

di TBS ether **262** was the only product formed in 86% yield. Attempts to isolate the product **262** were futile due to rapid hydrolysis, as experienced in Chapter 3.

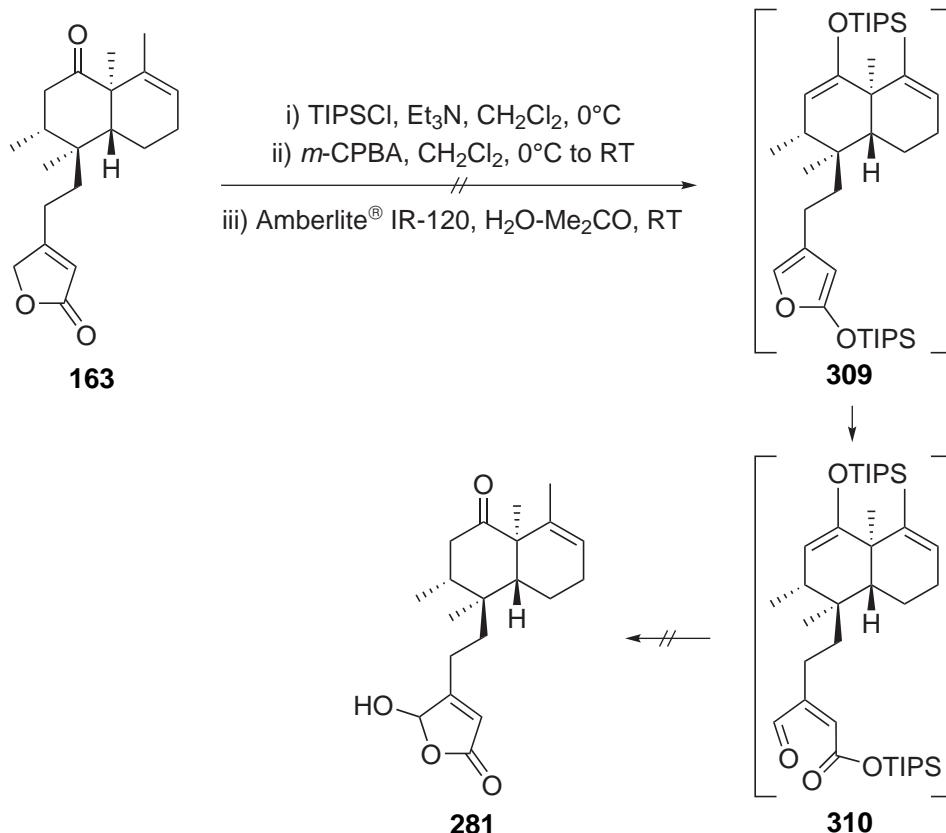
Since the isolation of **262** caused decomposition of this compound, a one-pot procedure to form the hydroxylactone **281** was implemented. The precursor **163** was subjected to 3 equivalents of TBSOTf and 6 equivalents of triethylamine in dry dichloromethane at 0°C. The reaction was monitored by TLC and after 2 hours, the starting material appeared to be consumed. The reaction was then cooled down to 0°C before addition of 3 equivalents of *m*-CPBA (water-removed). A <sup>1</sup>H NMR spectrum of the reaction in progress revealed that the lactone signals characteristic of the starting material had disappeared. The reaction mixture was neutralised with Amberlite® IR-120 and stirred in water and acetone at room temperature. The <sup>1</sup>H NMR spectrum showed that no product **281** had formed, but the starting material **163** and the mono TBS ether **261** were recovered (25:75).



Scheme 6.17: One-pot synthesis of the hydroxylactone **281** via the TBS enol ether **262**.

TIPSOTf was also used as a silylating reagent in a similar one-pot reaction (Scheme 6.18). The precursor **163** was stirred with 4 equivalents of TIPSOTf and 8 equivalents of triethylamine in dry dichloromethane at 0°C for 1 hour. Upon consumption of the starting

material to the di TIPS ether **309**, 2 equivalents of *m*-CPBA (water-removed) was added at 0°C to convert **309** to the oxidised, ring opened furan **310**, and this was stirred for a further 24 hours. The solvent was removed prior to addition of Amberlite® IR-120 and 1:1 acetone-water. After stirring the mixture at room temperature overnight, the reaction was stopped. Again, the <sup>1</sup>H NMR spectrum of the crude reaction mixture showed no peaks representative of the desired product **281**, as only the starting material **163** was recovered.



Scheme 6.18: Attempted one-pot synthesis of the hydroxylactone **281** via a TIPS enol ether **309**.

## 6.2. Conclusions

Synthesis of the hydroxylactone **281** was attempted under an array of different reaction conditions. Allylic bromination of **163** afforded a mixture of brominated products, though the brominated butenolide **285** was not formed. In all cases, the methylene bromide **288** was inherently favoured. Reduction of the butenolide within **163** to the furan **289** gave mixtures of reduction products. The furan **289** was formed in all reaction attempts, however, the selectivity was not optimal because the C6 ketone was also a

site where reduction had occurred. Reduction of compound **157** to the respective furan **155** with DIBAL removed the selectivity issue, as no other reduction products were observed. The furan **155** was synthesised, albeit in a trace yield since conversion of the starting material to the product was low. As the furan products could not be isolated, oxidation via singlet oxygen could not proceed to give the hydroxylactone **281**. A one-pot oxidation of the ketone **163** with charcoal in air was followed according to a literature procedure, though this did not give the hydroxylactone **281**.<sup>227</sup> Repeating the reaction in oxygen with addition of a base provided the hydroxylactone **281** with a 14% conversion. Some optimisation of these reaction conditions improved the conversion yield to 30% upon treatment of **163** with 1 M sodium hydroxide and charcoal under oxygen. Conversion of the ketone precursor **163** to the TBS or TIPS-silyloxyfuran and oxidation to the hydroxylactone **281** was attempted using a literature method.<sup>71</sup> This Chapter has examined a number of approaches to convert the butenolide **163** to a hydroxylactone **281**. The simplest method appeared to be the most promising, using oxygen gas, however a viable route to **281** has yet to be found.

# Chapter 7

## Approaches to the Total Synthesis of Cordytritolone

### 7.1. Malaria

Malaria is a mosquito-borne disease that is transmitted by the infectious parasitic protozoa of the *Plasmodium* genus.<sup>252</sup> Four species of *Plasmodium* cause infection; *P. falciparum* (most common), *P. malariae*, *P. ovale* and *P. vivax*.<sup>253</sup> Malaria can cause death and the worst symptoms are caused by *P. falciparum*.<sup>252</sup> In 2012, a World Health Organisation (WHO) report determined that malaria was estimated to have caused 627,000 deaths worldwide.<sup>254</sup> Control of malaria is difficult in developing regions of the world where most cases originate.<sup>255</sup> This has been attributed to the intervention costs, low health expenditures and favourable climate.<sup>256</sup> The most vulnerable groups are children and pregnant women.<sup>257</sup> Some children have not developed an immunity towards the infection during infancy, while pregnant women have a reduced immunity during their pregnancy. Between 2000 and 2012, the WHO observed a decrease in worldwide malaria mortality rates (Figure 7.1). These encouraging outcomes have been attributed to an increase in funds to prevent and treat the disease, along with administration of more effective antimalarial drugs.<sup>258</sup>

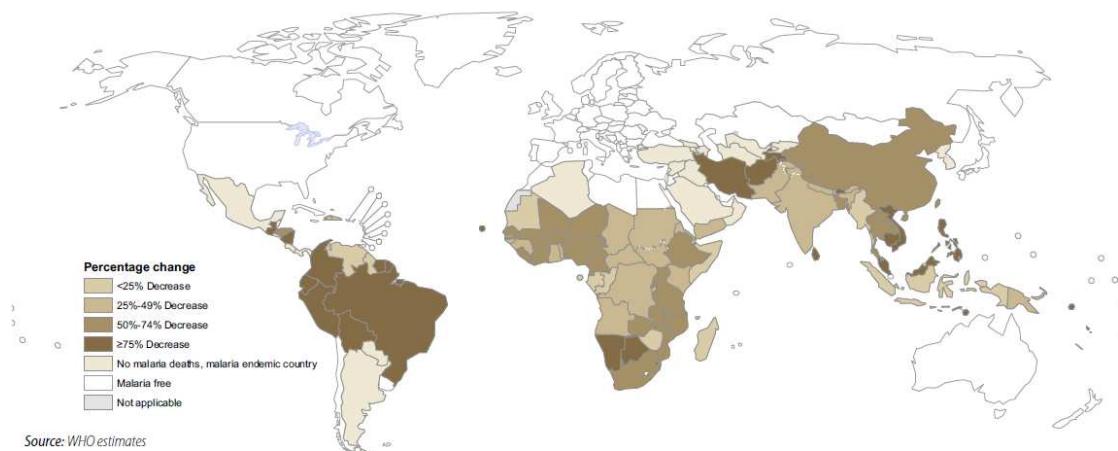


Figure 7.1: Map showing the percentage change in malaria mortality rates between 2000-2012, taken from WHO Report 2013.<sup>254</sup>

Quinine **311** is a natural alkaloid isolated in 1817 and was the first effective drug used to treat malaria (Figure 7.2).<sup>255</sup> Quinine has been the inspiration for improved antimalarial drugs that are currently being used as medications.<sup>259</sup> Many antimalarial drugs exist, however due to parasite resistance, they are becoming less effective.<sup>260</sup> Chloroquine **312** is a 4-aminoquinoline class drug first synthesised by Andersag in a Bayer research laboratory.<sup>261</sup> Chloroquine **312** was one of the most widely-used antimalarial medications for decades,<sup>262,263</sup> however, its effects are deteriorating due to parasite resistance.<sup>264,265</sup> Although quinine and chloroquine have different structures, their mode of action is similar. These antimalarial drugs have three distinct features: an aromatic nitrogen (red), a hydrogen donor atom (blue), and an aliphatic nitrogen (green) (Figure 7.2). These functional groups bind to specific enzymes such as orotidine 5'-monophosphate decarboxylase to prevent the malaria parasite from replicating.<sup>266</sup> Some of the outcomes of these therapeutic agents include cell lysis of the parasite membrane, inhibition of heme degradation and blood schizontocidal activity.<sup>267</sup>

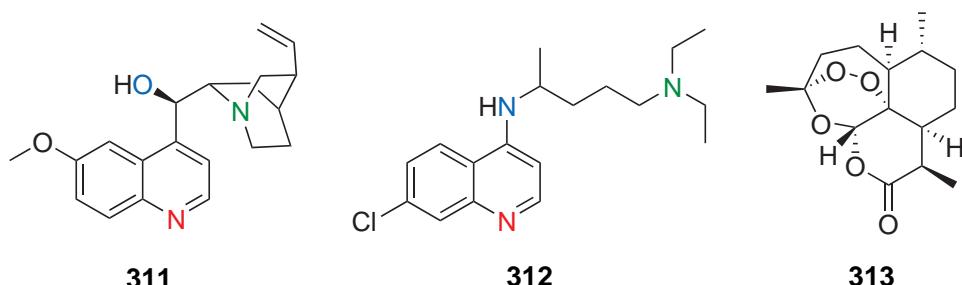
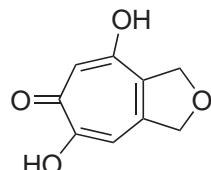


Figure 7.2: Structures of prominent antimalarial drugs.

Artemisinin **313** and artemisinin-based combination therapies (ACTs) are currently the leading treatments of choice for malaria (Figure 7.2).<sup>268,269</sup> According to the WHO, ACTs are first-line treatments because they prevent recrudescence of the *Plasmodium* parasite.<sup>268</sup> Artemisinin **313** was isolated from *Artemisia annua* by Chinese researchers and the structure was confirmed in 1972.<sup>270,271</sup> The structure of **313** differs from the aforementioned medications as it does not contain any nitrogen atoms. Artemisinin **313** is a sesquiterpene polycyclic compound that contains an endoperoxide.<sup>272</sup> These unique characteristic features enable **313** to have a different mode of action towards the malaria parasite to kill the *Plasmodium* gametocytes responsible for the transmission of malaria.<sup>268,273</sup>

## 7.2. Cordytopolone

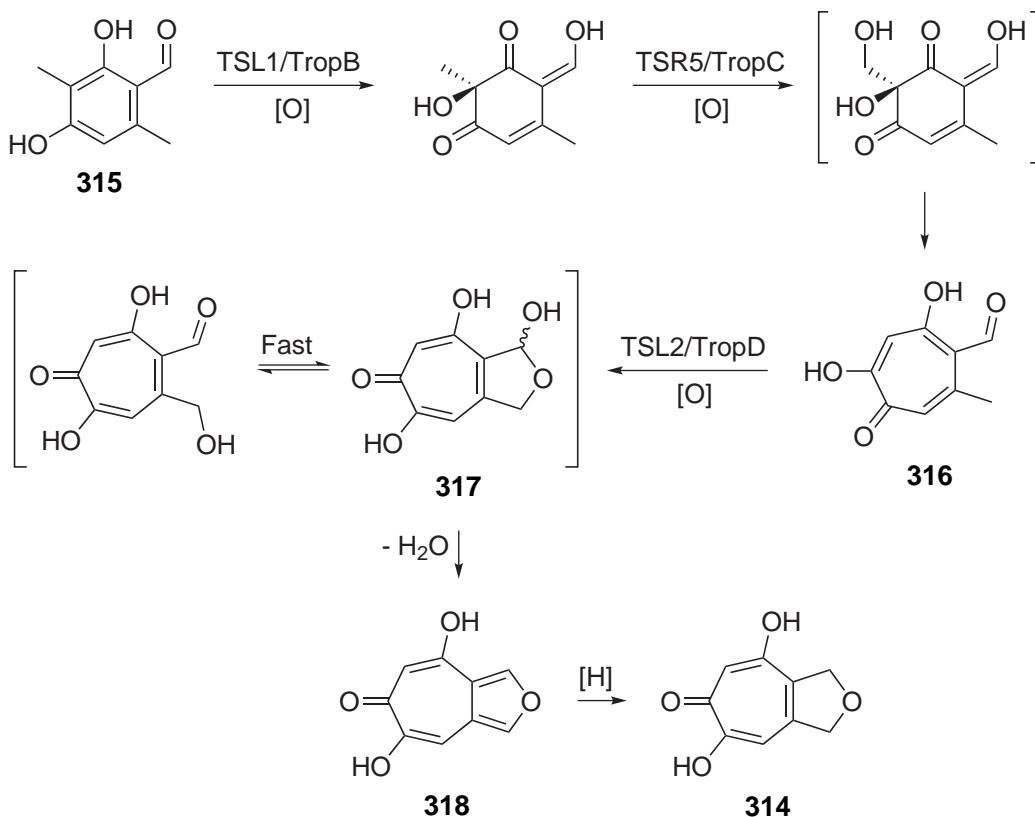
Cordytopolone **314** is a tropolone that was first isolated from the insect pathogenic fungus *Cordyceps* sp. BCC 1681 in Thailand (Figure 7.3).<sup>274</sup> Cordytopolone **314** has been found to exhibit moderate antimalarial properties. When tested *in vitro* against a K1 strain of *P. falciparum*, it had an IC<sub>50</sub> of 2.12 µg/mL.<sup>274</sup> Despite showing promise as a lead compound, the total synthesis of this compound is yet to be completed.



**314**

Figure 7.3: Structure of cordytopolone **314**.

A proposed biosynthesis of cordytopolone **314** has been published by Cox and co-workers (Scheme 7.1).<sup>275</sup> Starting from 3-methylorcinaldehyde **315**, successive oxidation enables ring expansion to the tropolone intermediate **316**. Oxidation of the methyl group affords the hemiacetal **317**, and dehydration provides the furan compound **318**. Reduction of the furan portion of **318** can then produce cordytopolone **314**.



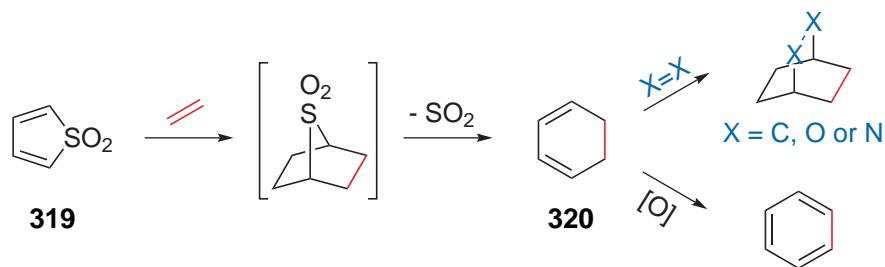
Scheme 7.1: Proposed biosynthesis of cordytopolone **314**.<sup>275</sup>

The synthesis of cordytopolone **314** and its derivatives could be used to map its structure-activity relationships. Unlike some of the aforementioned antimalarial drugs, this molecule is simple and structurally unique. It has a seven-membered tropolone ring fused to a five-membered tetrahydrofuran ring. Like artemisinin, cordytopolone does not contain an aromatic nitrogen heterocycle within its structure. The unique structure of cordytopolone could exhibit a different mode of action to antimalarial medications currently prescribed.

### 7.2.1. Thiophene-1,1-dioxides

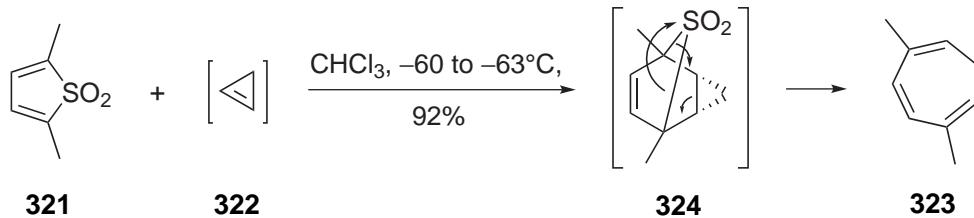
Thiophene-1,1-dioxide **319** is a molecule yet to be utilised in the total synthesis of a natural product. Thiophene-1,1-dioxides are a neglected class of compounds that can be useful building blocks in organic synthesis.<sup>276,277</sup> They are non-aromatic and can participate in a range of reactions including cycloaddition reactions and Michael additions. When thiophene-1,1-dioxide **319** behaves as a diene in a Diels-Alder reaction, the initial adduct spontaneously loses sulfur dioxide to regenerate a diene **320**.

(Scheme 7.2). This diene can then undergo another Diels-Alder reaction or get oxidised to form aromatic derivatives.



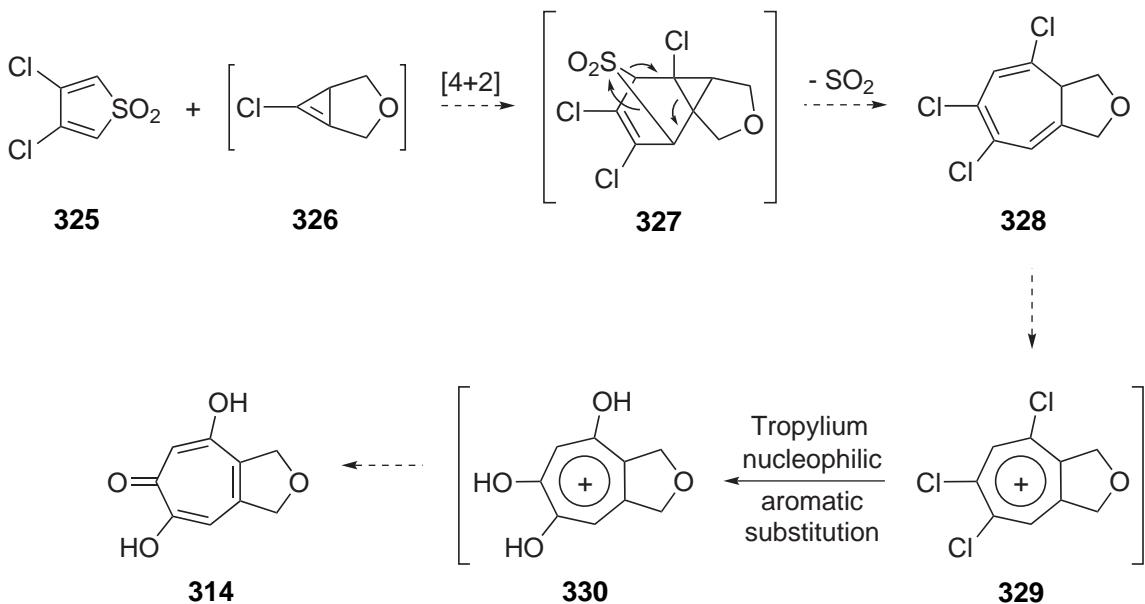
Scheme 7.2: Sequential Diels-Alder reactions with thiophene-1,1-dioxide **319**.

A potentially useful reaction for the synthesis of cordytopolone is shown in Scheme 7.3.<sup>278</sup> When a thiophene-1,1-dioxide adds to a cyclopropene, a cycloheptatriene is produced. For example, a mixture of 2,5-dimethylthiophene-1,1-dioxide **321** reacts with cyclopropene **322** at -60°C to give 3,6-dimethylcycloheptatriene **323** in excellent yield. The initial adduct **324** loses sulfur dioxide by a cheletropic elimination and ring opens to form the cycloheptatriene ring.



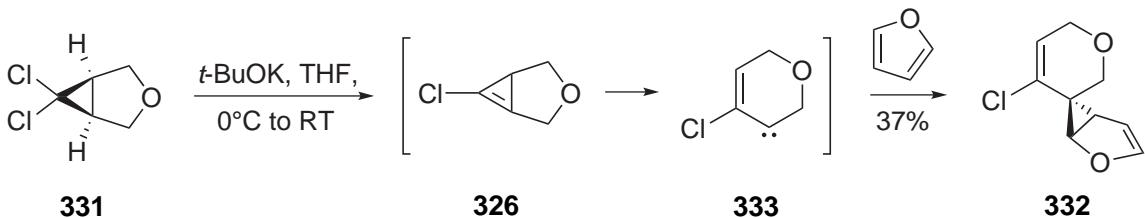
Scheme 7.3: Reaction of a thiophene-1,1-dioxide and cyclopropene.<sup>278</sup>

The synthesis of cordytopolone **314** was designed using the above reaction. There are two key features within the proposed synthesis (Scheme 7.4). The first is a cycloaddition/ring-opening reaction (Scheme 7.3), and the second is a nucleophilic aromatic substitution of a tropyl cation. 3,4-Dichlorothiophene-1,1-dioxide **325** could react with the cyclopropene **326** to form the adduct **327**. Elimination of sulfur dioxide from **327** and ring opening would provide the cycloheptatriene compound **328**. Formation of the trichlorotropyl cation intermediate **329** followed by a nucleophilic aromatic substitution would give the trihydroxytropyl cation compound **330** prior to cordytopolone **314**.



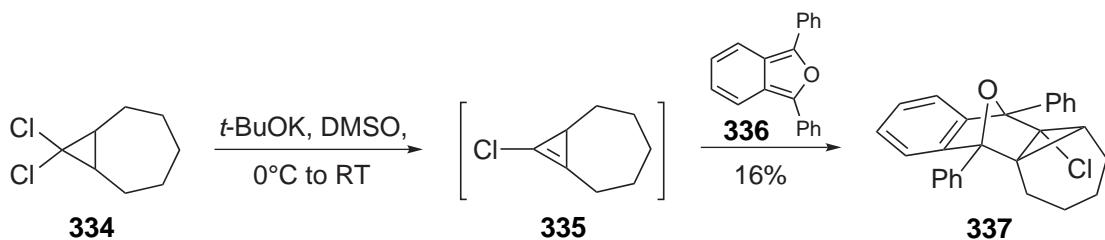
Scheme 7.4: Proposed synthesis of cordytopolone **314**.

Halton and Lovett have shown that the dienophile **326** is very strained and unstable.<sup>279</sup> When compound **331** was treated with potassium *tert*-butoxide in the presence of furan, the tricyclic product **332** was isolated in 37% yield (Scheme 7.5). The proposed mechanism for this reaction is the formation of the cyclopropene **326**, which rapidly rearranges to a more stable carbene **333**. The carbene **333** then gets intercepted by furan to form the tricyclic adduct **332**.



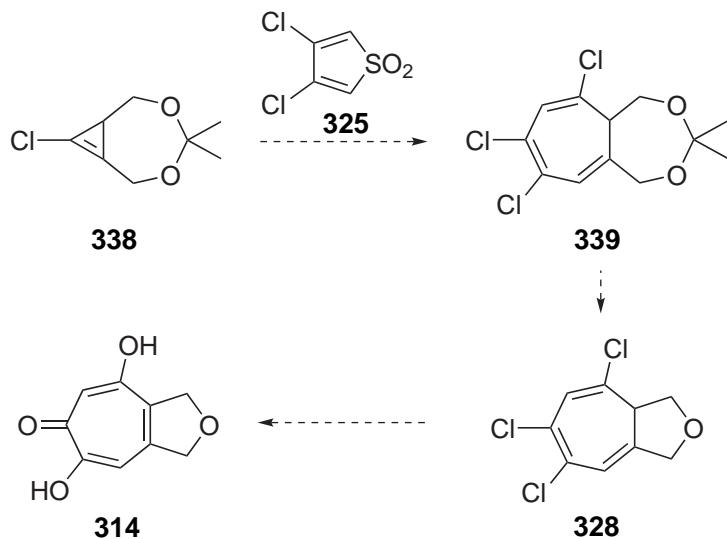
Scheme 7.5: Reaction of **331** with potassium *tert*-butoxide.<sup>279</sup>

A less strained cyclopropene would avoid the rearrangement seen in Scheme 7.5. Halton and co-workers have also demonstrated that less-strained 1,3-bridged cyclopropenes can form Diels-Alder adducts.<sup>280</sup> Treatment of 9,9-dichlorobicyclo[6.1.0]nonane **334** with potassium *tert*-butoxide afforded the respective cyclopropene **335**, which was trapped with 1,3-diphenylisobenzofuran **336** to form the adduct **337** (Scheme 7.6).



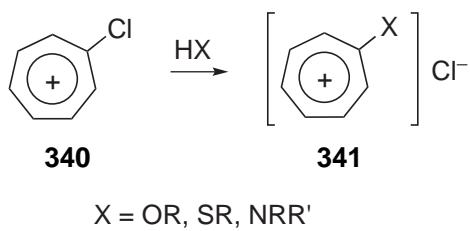
Scheme 7.6: Synthesis and trapping of a cyclopropene **335**.<sup>280</sup>

A dioxepin-fused cyclopropene **338** could be used to synthesise cordytopolone **314**, as it has roughly the same structure as **335** (Scheme 7.7). The dioxepin could be transformed into the tetrahydrofuran **328** later in the synthesis. Deprotection of **339** could form the diol, and cyclisation of the diol could provide **328**. Formation of the tropylium salt followed by nucleophilic aromatic substitution could then provide cordytopolone **314**.



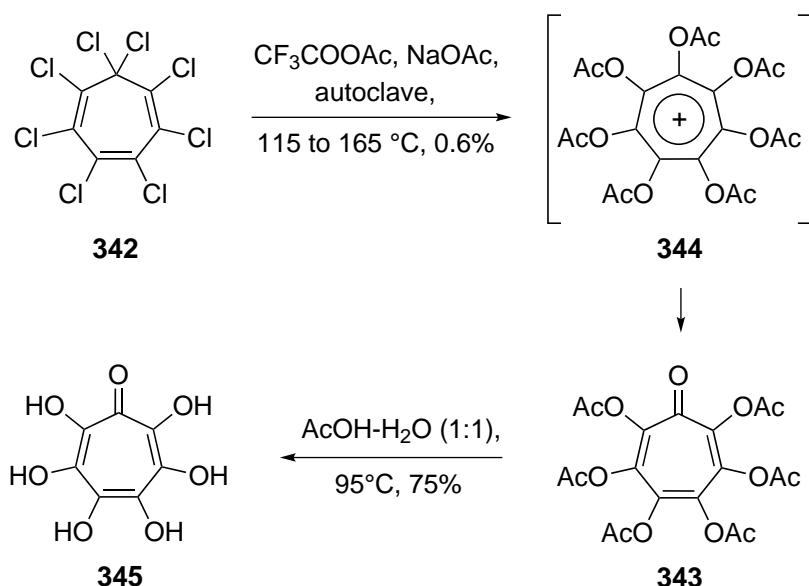
Scheme 7.7: Proposed synthesis of cordytopolone **314** with a dioxepin-fused cyclopropene **338**.

The second key step in the synthesis of cordytopolone **314** was the conversion of the tropylium salt **329** to a tropolone. Tropylium halides **340** can be converted to alkoxy-, alkylthio- and dialkyl(diaryl)amino-tropylium salts **341** (Scheme 7.8).<sup>281–283</sup> The mechanism is effectively a nucleophilic aromatic substitution on the tropylium salt. By using a similar methodology, the chlorides within compound **328** could be substituted for hydroxyl groups to form the required tropolone unit of the final product **314** (Scheme 7.4).



Scheme 7.8: Examples of nucleophilic aromatic substitution of tropylium chloride precursors **340**.<sup>281–283</sup>

In a reaction that is reminiscent of the proposed reaction, Takeshita *et al.* reacted octachlorocycloheptatriene **342** with acetyl trifluoroacetate and sodium acetate to form hexaacetyltropone **343** via the tropylium intermediate **344** (Scheme 7.9).<sup>284</sup> Acid hydrolysis of the acetate functional groups afforded 2,3,4,5,6,7-hexahydroxycycloheptatriene-1-one **345** in good yield.

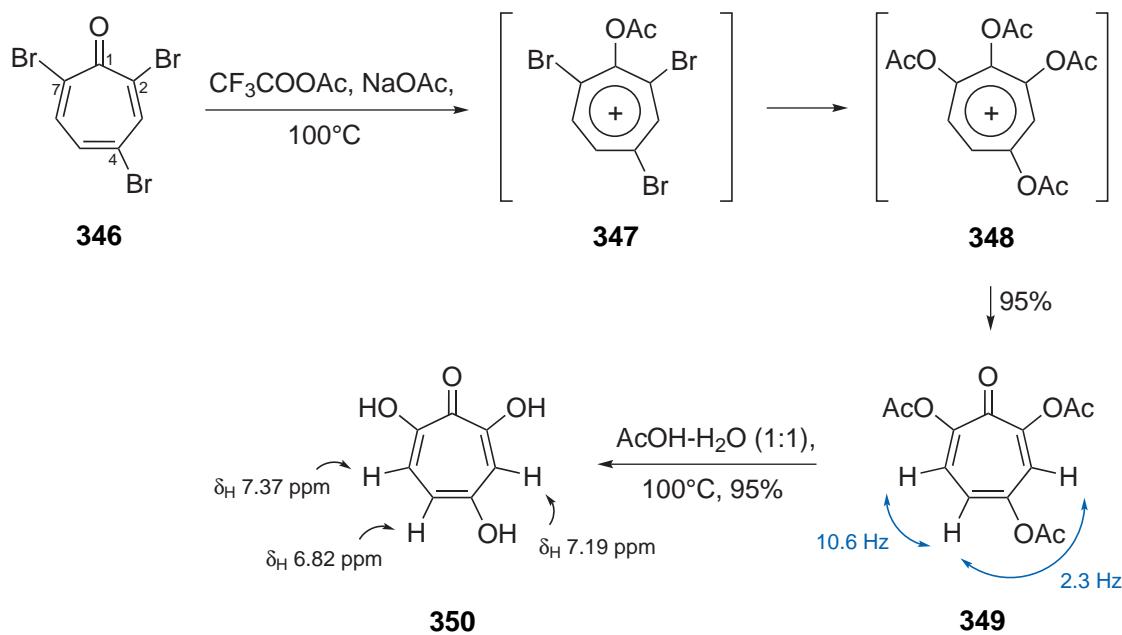


Scheme 7.9: Conversion of a polychlorinated cycloheptatriene **342** to a tropolone compound **345**.<sup>284</sup>

### 7.3. Test studies to generate a tropylium species and a tropolone

Test studies were conducted to determine the feasibility of the nucleophilic aromatic substitution reaction on the tropylium cation required in the final stage of the synthesis of cordyrtropolone **314**. The yield of compound **343** shown in Scheme 7.9 was low, though this was attributed to the inability of **344** to adopt a planar tropylium cation caused by the steric demand of the acetyl substituents.

The conditions used by Takeshita *et al.* were applied to 2,4,7-tribromotropone **346**.<sup>284</sup> This compound closely resembled **328** in the total synthesis of cordytopolone **314** than octachlorocycloheptatriene **342**. Using the conditions reported by von E. Doering, cycloheptanone was treated with 4 equivalents of bromine and acetic acid to yield 2,4,7-tribromotropone **346**.<sup>285</sup> The crude product was immediately used in the next step as attempts to purify the mixture led to decomposition. The general conditions used by Takeshita were implemented in the next step.<sup>284</sup> 2,4,7-Tribromotropone **346** was combined with acetyl trifluoroacetate to form the tropylum cation **347** (Scheme 7.10). The sodium acetate that was present converted **347** to the tetraacetoxytropylum salt **348**. Addition of water to the mixture followed by neutralisation afforded triacetoxytropone **349** in excellent yield (95%). The high yield of product **349** obtained in this reaction is a stark contrast to the yield of **343** in Scheme 7.9. The <sup>1</sup>H NMR spectrum of **349** had three singlets at 2.31, 2.34 and 2.35 ppm which were assigned to the three acetate groups. A doublet of doublets was observed at 6.86 ppm assigned to H5 that had coupling constants of 10.6 and 2.3 Hz. A doublet at 7.14 ppm ascribed to H3 was found to have a coupling constant of 2.3 Hz. The last signal allotted to H6 was a doublet located at 7.24 ppm with a coupling constant of 10.6 Hz. All peaks in the <sup>1</sup>H NMR spectrum matched those provided in the literature of **349** synthesised from a different starting material.<sup>284</sup>



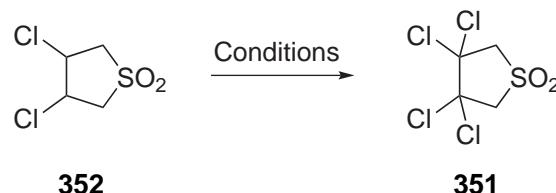
Scheme 7.10: Test reactions achieved to convert tribromotropone **346** to a tropolone **350**.

Acid hydrolysis of the acetate groups at 100°C successfully converted **349** to the trihydroxytropone **350** in 95% yield, which was comparable to the literature yield of 97%.<sup>284</sup> As the tropolone **350** was successfully synthesised from a halogenated cycloheptatriene **346**, attention was redirected to the synthesis of 3,4-dichlorothiophene-1,1-dioxide **325**.

#### 7.4. Synthesis of 3,4-dichlorothiophene-1,1-dioxide

3,4-Dichlorothiophene-1,1-dioxide **325** is prepared from 3,3,4,4-tetrachlorosulfolane **351**. The tetrachloride precursor **351** is made industrially for the agrochemical industry.<sup>286</sup> It was first synthesised by Bluestone *et al.* by performing a radical chlorination of 3,4-dichlorosulfolane **352** in carbon tetrachloride (Table 7.1, entry 1).<sup>287</sup> Numerous variants of this reaction have been published in the patent literature, however most procedures use carbon tetrachloride as a solvent. One method used chlorine and peroxybenzoic acid in carbon tetrachloride to synthesise **351** (Table 7.1, entry 2).<sup>288</sup> As there are environmental concerns involving usage of carbon tetrachloride, it has been restricted in many countries, including Australia.<sup>289</sup> Chlorination of 3,4-dichlorosulfolane **352** can be achieved with other solvents. Fluorinated organic solvents could be used to replace carbon tetrachloride. For example, **352** could be treated with chlorine gas in trifluoromethylbenzene to provide **351** in 71% yield (Table 7.1, entry 3).<sup>290</sup> Repetition of the same reaction with 1,3-bis(trifluoromethyl)benzene instead of trifluoromethylbenzene also produced **351**, but in 77% yield (Table 7.1, entry 4). Straub

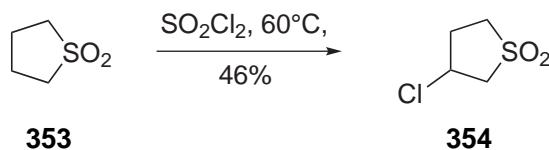
Table 7.1: Conversion of 3,4-dichlorosulfolane **352** to 3,3,4,4-tetrachlorosulfolane **351**.



Entry	Conditions	Yield of <b>351</b>
1	Cl <sub>2</sub> , CCl <sub>4</sub> , hν, heat <sup>287</sup>	71%
2	Cl <sub>2</sub> , PhCO <sub>3</sub> H, CCl <sub>4</sub> , hν, 75°C <sup>288</sup>	67%
3	Cl <sub>2</sub> , trifluoromethylbenzene, hν, 80°C <sup>290</sup>	71%
4	Cl <sub>2</sub> , 1,3-bis(trifluoromethyl)benzene, hν, 80°C <sup>290</sup>	77%
5	Cl <sub>2</sub> , POCl <sub>3</sub> , hν, 65-70°C <sup>291</sup>	72%

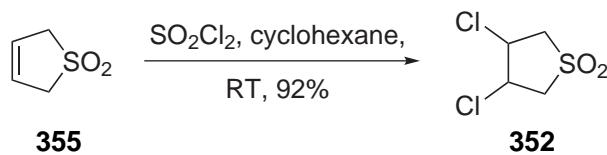
and Ressell reported a procedure where **352** was subjected to chlorine in phosphoryl trichloride under UV light to afford **351** with a yield of 72% (Table 7.1, entry 5). All of the aforementioned patent procedures of forming 3,3,4,4-tetrachlorosulfolane **351** have one thing in common, the inclusion of chlorine gas under UV light.

Sulfuryl chloride is a useful alternative to chlorine gas.<sup>292</sup> It is a versatile chlorinating agent that has been neglected in the chemical community.<sup>293</sup> When compared to chlorine gas, sulfuryl chloride is a liquid which is easier to handle in the laboratory.<sup>294</sup> Chlorination could occur via a radical or cationic mechanism depending on the reaction conditions. An example of an ionic chlorination is the transformation of sulfolane **353** to 3-chlorosulfolane **354** with 10 equivalents of sulfuryl chloride at 60°C (Scheme 7.11).<sup>295</sup>



Scheme 7.11: Chlorination of sulfolane **353** with sulfuryl chloride to form **354**.<sup>295</sup>

Sulfuryl chloride could be used to synthesise 3,3,4,4-tetrachlorosulfolane **351** by acting as the chlorinating agent and solvent, thereby eradicating the need for chlorine gas and carbon tetrachloride. Treatment of 3-sulfolene **355** with 1.1 equivalents of sulfuryl chloride in cyclohexane afforded 3,4-dichlorosulfolane **352** through a literature procedure (Scheme 7.12).<sup>296</sup> The reaction was performed in cyclohexane to keep the reaction temperature constant, because the addition of **355** to sulfuryl chloride is an exothermic reaction.

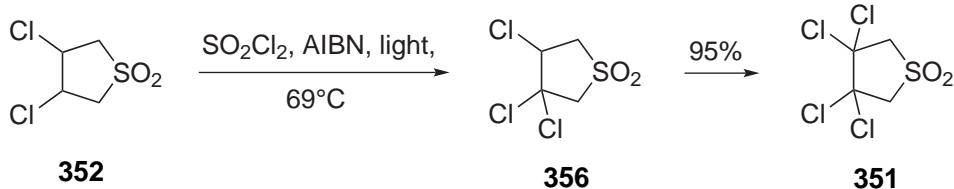


Scheme 7.12: Conversion of 3-sulfolene **355** to 3,4-dichlorosulfolane **352**.<sup>296</sup>

3,4-Dichlorosulfolane **352** was dissolved in sulfuryl chloride with catalytic quantities of AIBN under light to afford 3,3,4-trichlorosulfolane **356** (Table 7.2, entry 1). The light source produced enough heat to cause the solution to reflux. Prolonged chlorination of

the reaction mixture (which was monitored by  $^1\text{H}$  NMR spectroscopy) provided 3,3,4,4-tetrachlorosulfolane **351** in excellent yield (95%). AIBN was added to the experiment every day over 19 days to enable the reaction to progress. The reaction was repeated but without AIBN to determine chlorination efficacy without the radical initiator (Table 7.2, entry 2).  $^1\text{H}$  NMR spectra were obtained every day over a 30 day period, which revealed that chlorination of **352** was much slower than the previous example with AIBN. Both the trichloride **356** and the tetrachloride **351** were formed, though conversion of **356** to **351** was sluggish. The reaction was stopped after 30 days and the  $^1\text{H}$  NMR spectrum of the crude product showed that **356** and **351** were present in a 55:45 ratio.

Table 7.2: Chlorination of 3,4-dichlorosulfolane **352**.

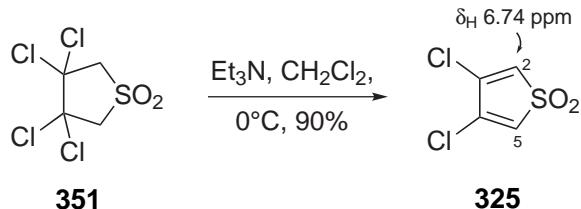


Entry	Conditions	Yield/ recovery <sup>†</sup>	Ratio*	
			<b>356</b>	<b>351</b>
1	SO <sub>2</sub> Cl <sub>2</sub> , AIBN, light, 69°C, 19 days	95%	0	100
2	SO <sub>2</sub> Cl <sub>2</sub> , light, 69°C, 30 days	109% <sup>†</sup>	55	45

<sup>†</sup>Recovery based on starting material mass. \*Ratios obtained by <sup>1</sup>H NMR spectroscopy

3,3,4,4-Tetrachlorosulfolane **351** can be converted to 3,4-dichlorothiophene-1,1-dioxide **325** via elimination of hydrochloric acid with a base. This reaction has been achieved by Bluestone and co-workers, who subjected **351** to a 29% ammonia solution in methanol at 30–35°C to give **325** in 82% yield.<sup>287</sup> Triethylamine was used instead of ammonia. Addition of 2 equivalents of triethylamine to a solution of **351** in dichloromethane at 0°C gave 3,4-dichlorothiophene-1,1-dioxide **325** in excellent yield (Scheme 7.13). The only

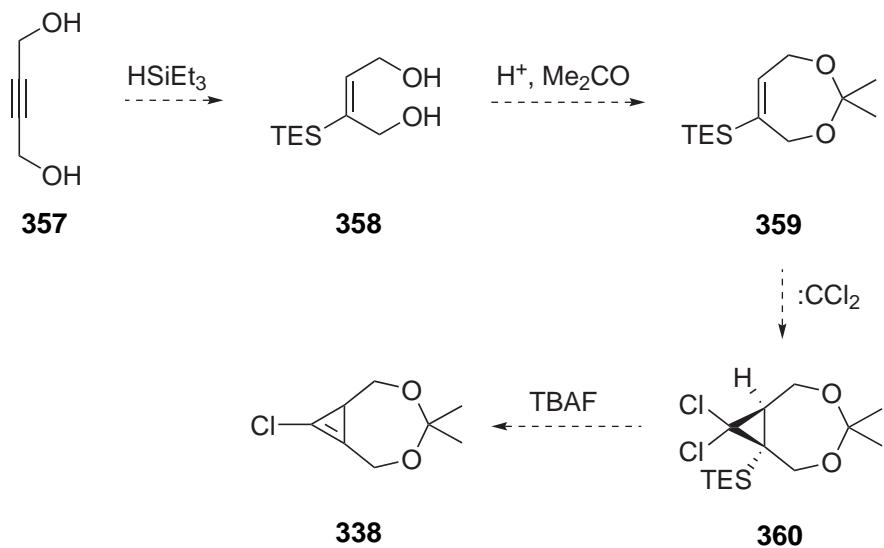
signal in the  $^1\text{H}$  NMR spectrum of **325** was the singlet at 6.74 ppm which corresponded to the H2 and H5 positions.



Scheme 7.13: New method of transforming 3,3,4,4-tetrachlorothiophene-1,1-dioxide **351** to 3,4-dichlorothiophene-1,1-dioxide **325**.

## 7.5. Initial cordytritolone synthesis

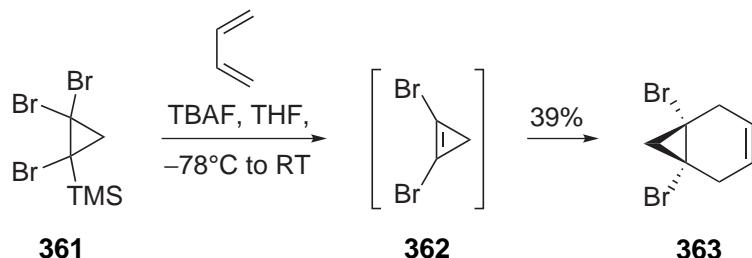
A key aspect of the synthesis of cordytropolone **314** is the preparation of the cyclopropene **338**, which could be made from 2-butyne-1,4-diol **357**. Hydrosilylation of **357** could afford the vinyl silane **358** (Scheme 7.14). Conversion of **358** to the acetal **359** will protect the diol. Formation of the cyclopropene could then occur via a two-step procedure. Addition of dichlorocarbene to **359** could form the adduct **360**. Treatment of **360** with TBAF may give the cyclopropene **338** via a fluoride induced elimination of TESCl.



Scheme 7.14: Planned synthesis of the cyclopropene **338**.

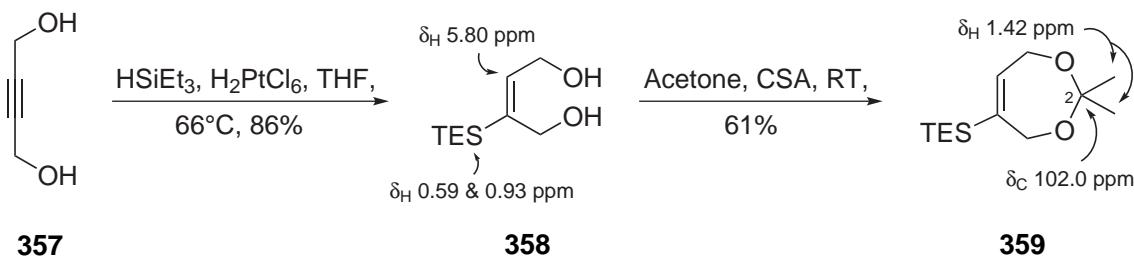
This method of generating the cyclopropene is one of the mildest methods reported. Inspired by the work of Billups,<sup>297</sup> Sim and Wege have shown how a halo(trimethylsilyl)cyclopropane precursor **361** could be converted to the cyclopropene

**362** *in situ* with TBAF (Scheme 7.15).<sup>298</sup> The cyclopropene was trapped with 1,3-butadiene to yield the cyclopropane **363** in 39% yield.



Scheme 7.15: Synthesis and reaction of **362**.<sup>298</sup>

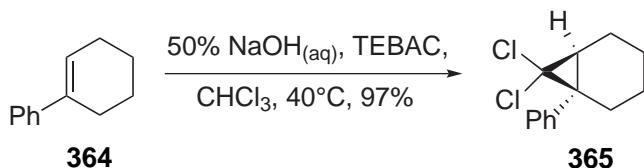
Hydrosilylation of 2-butyne-1,4-diol **357** with triethylsilane and catalytic chloroplatinic acid gave the product **358** in 86% yield (Scheme 7.16).<sup>299</sup> The yield of **358** was higher than the reported yield of 59%. The <sup>1</sup>H NMR spectrum of **358** showed a triplet at 0.59 ppm and a quartet at 0.93 ppm ascribed to the ethyl substituents of the TES group. A multiplet was found at 5.80 ppm and was assigned to the vinylic proton. Acid catalysed protection of the diol was achieved by treating **358** with catalytic CSA and calcium chloride as a desiccant in acetone to furnish the dioxepin **359** in 61% yield. A new signal was detected at 1.42 ppm attributed to the two methyl groups (6H, s). A new quaternary carbon, assigned as C2, was also observed in the <sup>13</sup>C NMR spectrum at 102.0 ppm.



Scheme 7.16: Synthesis of the dioxepin **359**.

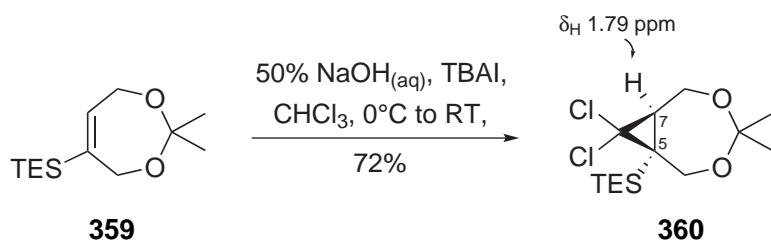
The next step in the synthesis was to add dichlorocarbene to the alkene of **359** to form the dichlorocarbene adduct **360**. There are many ways to generate dichlorocarbene, with most procedures using chloroform and a strong base.<sup>300</sup> A biphasic system using concentrated aqueous sodium hydroxide and chloroform with a phase transfer catalyst is the most common method.<sup>301</sup> Phase transfer catalysts are commonly used if the base is water soluble, as they facilitate the transfer of RO<sup>-</sup> from the aqueous phase to the organic phase. For example, Grupe and von Wangelin used a 50% aqueous solution of sodium

hydroxide in chloroform with triethylbenzylammonium chloride (TEBAC) as the phase transfer catalyst to convert **364** to a dichlorocyclopropane adduct **365** in excellent yield (Scheme 7.17).<sup>302</sup>



Scheme 7.17: Literature synthesis of **365**.<sup>302</sup>

Treatment of **359** with a 50% aqueous solution of sodium hydroxide and tetrabutylammonium iodide (TBAI) in chloroform at 0°C to room temperature afforded the dichlorocarbene adduct **360** in 72% yield (Scheme 7.18). Maintaining the reaction mixture at 0°C was important as the reaction was exothermic and warmer temperatures resulted in more side-products. Attempts to purify the crude product were unsuccessful as decomposition of the product would occur upon either distillation or chromatography. The <sup>1</sup>H NMR spectrum showed the vinylic hydrogen characteristic of the starting material **359** had disappeared. A multiplet was observed at 1.79 ppm which was assigned to the bridgehead methine at H7. A <sup>13</sup>C NMR spectrum of a pure sample was not obtained as decomposition occurred overnight to give a complex mixture of products. It would appear that the bulky structure of **360** caused it to be inherently unstable. The crude product (*ca.* 52% purity) was used in the next step.

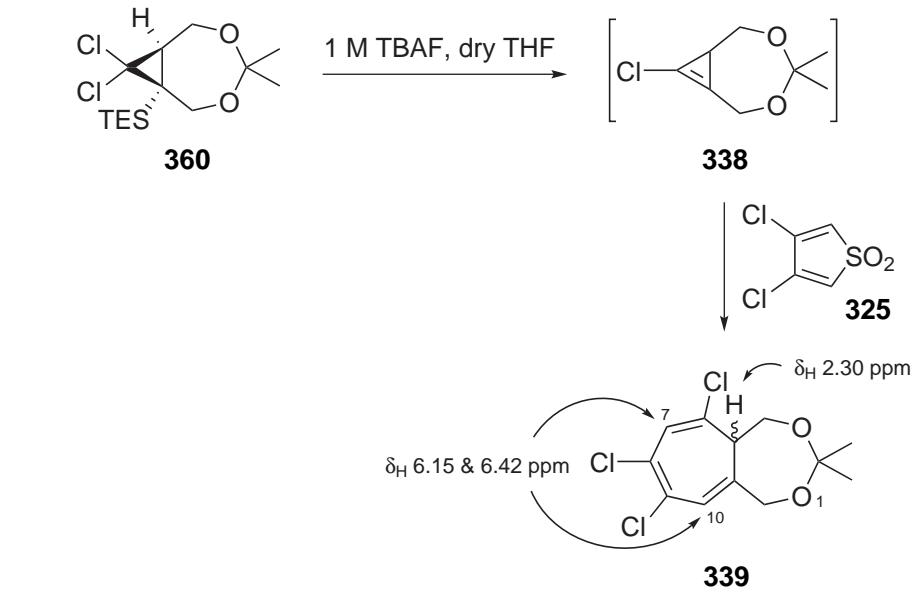


Scheme 7.18: Formation of the dichlorocarbene adduct **360**.

The next step in the synthesis was to convert **360** to the cyclopropene **338**. It was unlikely that the cyclopropene **338** could be isolated, because the analogous compound **335** synthesised by Halton and co-workers was reported to be unstable.<sup>280</sup> The cyclopropane **360** could be treated with TBAF, then 3,4-dichlorothiophene-1,1-dioxide **325** to form the adduct **339** (Table 7.3). Compound **360** was subjected to 1 equivalent of TBAF in dry

tetrahydrofuran at  $-84^{\circ}\text{C}$  prior to addition of 1 equivalent of **325** after 30 minutes. The reaction was allowed to warm to room temperature overnight before work-up after 24 hours (Table 7.3, entry 1). The  $^1\text{H}$  NMR spectrum showed a mixture of compounds was present, most of which was starting material **360**. The product **339** had not formed. To improve the conversion of starting material to the product, **360** was combined with 4 equivalents of TBAF at  $-84^{\circ}\text{C}$  and the reaction was stirred for 10 minutes prior to addition of 2 equivalents of **325** (Table 7.3, entry 2). The reaction was warmed to room temperature overnight and stopped the next day. The  $^1\text{H}$  NMR spectrum of the crude material showed that a trace amount of the product (9%) had formed. Two distinctive new peaks that represented H7 and H10 in **339** were found at 6.15 and 6.42 ppm. The allylic methine at the ring junction was assigned to the signal at 2.30 ppm. These three key resonances each had an integration of one hydrogen. Repetition of the same reaction conditions except addition of 6.6 equivalents of TBAF did not give an improved

Table 7.3: Reaction conditions employed to synthesise the Diels-Alder adduct from **360**.

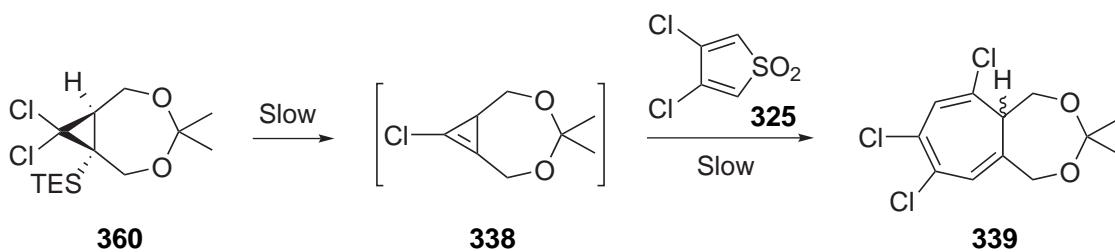


Entry	Conditions	Conversion to <b>339</b> *
1	<b>360</b> (1 eq., 0.12 M), 1 M TBAF (1 eq.), <b>325</b> (1 eq.), $-84^{\circ}\text{C}$ to RT, o/n	0%
2	<b>360</b> (1 eq., 0.05 M), 1 M TBAF (4 eq.), <b>325</b> (2 eq.), $-84^{\circ}\text{C}$ to RT, o/n	9%
3	<b>360</b> (1 eq., 0.10 M), 1 M TBAF (6.6 eq.), <b>325</b> (1.1 eq.), $-84^{\circ}\text{C}$ to RT, o/n	0%
4	<b>360</b> (1 eq., 0.03 M), 1 M TBAF (3.7 eq.), <b>325</b> (1.1 eq.), $-84^{\circ}\text{C}$ , 2 h	10%

\*Conversions are respective of **360** and were obtained by  $^1\text{H}$  NMR spectroscopy

result (Table 7.3, entry 3). Using a smaller amount of TBAF than the previous attempt was investigated to see if conversion of starting material to the cyclopropene **338** improved. Addition of 3.7 equivalents of TBAF and 1.1 equivalents of **325** to the substrate **360** provided the product **339** with a 10% conversion from the starting material **360** (Table 7.3, entry 4).

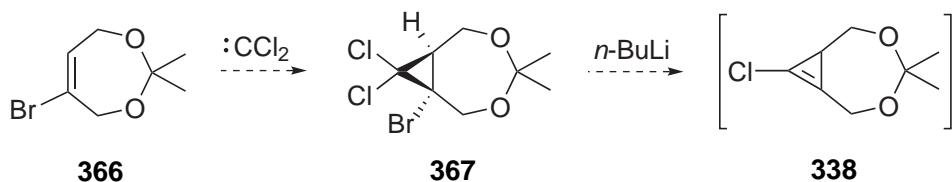
From these results, the reaction shown in Scheme 7.19 does occur, but to a small extent. The yields obtained were acceptable considering the number of transformations that have to occur to convert the cyclopropane **360** to the cycloheptatriene product **339**. There are three likely issues with this reaction. The cyclopropane **360** was not purified prior to the reaction and it was prone to decomposition. This could have played a role in the low yields of the reaction product **339**. The second issue was that **360** contained a TES group, and all of the literature examples of this reaction have a smaller, more labile TMS group.<sup>298,303</sup> The size of the TES group may have inhibited the elimination to form the cyclopropene **338**. Despite the addition of 6.6 equivalents of TBAF to the starting material **360**, there was still a small amount of **360** present. This was indicative of the reaction being slow. The last reason that could have affected the reaction progress was that degradation of the cyclopropene **338** could have occurred faster than the cycloaddition reaction, resulting in a maximum product **339** yield of 10%.



Scheme 7.19: Slow formation of **339**.

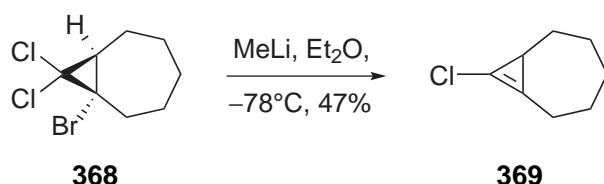
## 7.6. Revised cordytopolone synthesis

An alternative approach to prepare the cyclopropene **338** was to start with the vinyl bromide **366** (Scheme 7.20). Addition of dichlorocarbene to **366** could form the adduct **367**. Treatment of **367** with *n*-butyllithium could enable a lithium-halogen exchange followed by an elimination to provide the cyclopropene compound **338**.



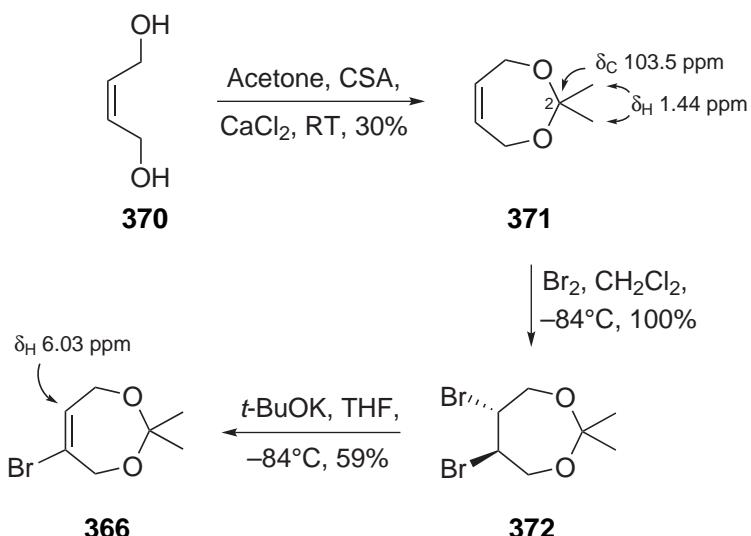
Scheme 7.20: New method to obtain the dioxepin cyclopropene **338**.

This method was similar to that used by Lee and colleagues, who treated compound **368** with methylolithium in diethyl ether at  $-78^{\circ}\text{C}$  to afford the cyclopropene **369** in 47% isolated yield (Scheme 7.21).<sup>304</sup>



Scheme 7.21: Synthesis of cyclopropene **369** using MeLi.<sup>304</sup>

The cyclopropene **338** was synthesised from *cis*-2-butene-1,4-diol **370**. Reaction of *cis*-2-butene-1,4-diol **370** with catalytic CSA, calcium chloride as the desiccant and acetone (solvent) furnished the acetal **371** in 30% yield (Scheme 7.22). The yield of the reaction was low but could be performed on a large scale ( $>50$  g). Bromination of **371** with 1 equivalent of bromine in dichloromethane at  $-84^{\circ}\text{C}$  afforded the *trans*-vicinal dibromide **372** in 100% yield.<sup>305</sup> Treatment of the dibromide **372** with 1.5 equivalents of potassium *tert*-butoxide in dry tetrahydrofuran at  $-84^{\circ}\text{C}$  gave the vinyl bromide **366** in 59% yield. The  $^1\text{H}$  NMR spectrum of **366** showed a vinylic proton at 6.03 ppm (1H, tt), as well as two separate methylene peaks at 4.37 (2H, td) and 4.15 ppm (2H, dt).

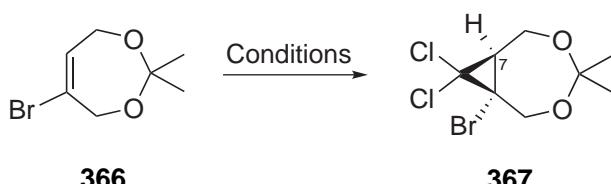


Scheme 7.22: Synthesis of the vinyl bromide **366**.

Addition of dichlorocarbene to the alkene of **366** was investigated to form the dichlorocarbene adduct **367**. The previous synthesis treated **359** with a 50% aqueous solution of sodium hydroxide and tetrabutylammonium iodide in chloroform (Scheme 7.18). This could not be applied to the precursor **366** as it was found to be sensitive to base. Rather than using chloroform and sodium hydroxide to form dichlorocarbene, other milder methods to generate dichlorocarbene were studied.

Dichlorocarbenes can be generated under basic conditions with bases other than sodium hydroxide. Doering and Hoffmann have shown that dichlorocarbene could be synthesised from potassium *tert*-butoxide in chloroform at low temperature.<sup>300</sup> When the vinyl bromide **366** was treated with 1 equivalent of potassium *tert*-butoxide in chloroform and anhydrous tetrahydrofuran at  $-84^\circ\text{C}$ , only starting material was recovered (Table 7.4, entry 1). Ethyl trichloroacetate has been used as an alternative source of dichlorocarbene.<sup>306</sup> Most of these procedures require a base such as sodium methoxide in a non-polar solvent such as petrol or pentane.<sup>307</sup> Addition of 2.1 equivalents of ethyl trichloroacetate and 2 equivalents of sodium methoxide to the precursor **366** in methanol at  $-5^\circ\text{C}$  did not yield any product (Table 7.4, entry 2). Repetition of the reaction with petrol instead of methanol provided the same result (Table 7.4, entry 3). Treatment of **366** with 10.1 equivalents of ethyl trichloroacetate and 10 equivalents of sodium methoxide under the same conditions also resulted in no reaction (Table 7.4, entry 4).

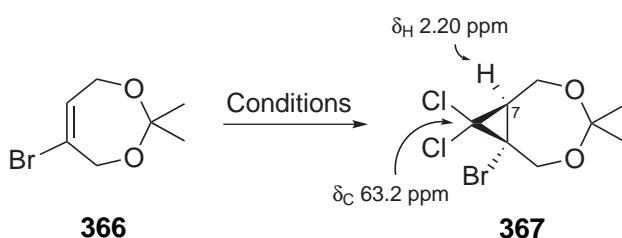
Table 7.4: Reaction conditions attempted to synthesise the dichlorocarbene adduct **367**.



Entry	Conditions	Yield of <b>367</b>
1	<i>t</i> -BuOK (1 eq.), CHCl <sub>3</sub> , dry THF, -84°C to 0°C, o/n	0%
2	Cl <sub>3</sub> CCO <sub>2</sub> Et (2.1 eq.), NaOMe (2 eq.), MeOH, -5°C to RT, o/n	0%
3	Cl <sub>3</sub> CCO <sub>2</sub> Et (2.1 eq.), NaOMe (2 eq.), petrol, -5°C to RT, o/n	0%
4	Cl <sub>3</sub> CCO <sub>2</sub> Et (10.1 eq.), NaOMe (10 eq.), petrol, -5°C to RT, o/n	0%

Phenyl(trichloromethyl)mercury was investigated instead of ethyl trichloroacetate. Thermal decomposition of phenyl(trichloromethyl)mercury provides dichlorocarbene under neutral conditions.<sup>308</sup> Compound **366** was combined with 1.3 equivalents of phenyl(trichloromethyl)mercury in toluene at 100°C for 2 days (Table 7.5, entry 1). This afforded the product **367** in an isolated yield of 10%. The key product signal attributed to **367** was a doublet of doublets found at 2.20 ppm in the <sup>1</sup>H NMR spectrum which was ascribed to the bridgehead hydrogen (H7). A *gem*-CCl<sub>2</sub> peak was observed at 63.2 ppm in the <sup>13</sup>C NMR spectrum which is characteristic of a dichlorocyclopropene (60-70 ppm).<sup>309,310</sup> To improve the yield of product formed, another reagent had to be considered. Thermal decomposition of sodium trichloroacetate is known to generate dichlorocarbene, carbon dioxide and sodium chloride under neutral conditions.<sup>311,312</sup> Treatment of the vinyl bromide **366** with 2 or 20 equivalents of sodium trichloroacetate in

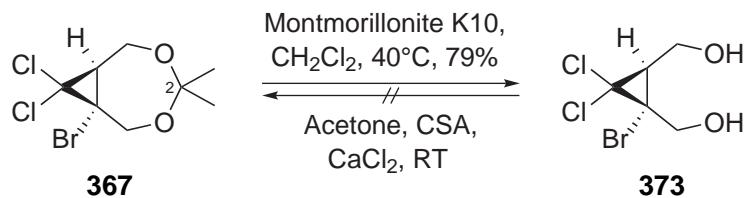
Table 7.5: Neutral conditions used to synthesise the dichlorocarbene adduct **367**.



Entry	Conditions	Yield of <b>367</b>
1	PhHgCCl <sub>3</sub> (1.3 eq.), PhMe, 100°C, 2 days	10%
2	Cl <sub>3</sub> CCO <sub>2</sub> Na (2 eq.), glyme, 85°C, 3 days	3%
3	Cl <sub>3</sub> CCO <sub>2</sub> Na (20 eq.), glyme, 85°C, o/n	0%
4	Cl <sub>3</sub> CCO <sub>2</sub> Na (20 eq.), TBAHS (0.06 eq.), CHCl <sub>3</sub> , 61°C, 8 h	35%
5	Cl <sub>3</sub> CCO <sub>2</sub> Na (13 eq.), TBAHS (0.12 eq.), CHCl <sub>3</sub> , 61°C, 2 days	77%

glyme at reflux only afforded a trace amount (3%) of product **367** at best (Table 7.5, entries 2 & 3). The reaction was repeated with chloroform as the solvent at reflux with catalytic (6 mol %) tetrabutylammonium hydrogen sulfate for 8 hours (Table 7.5, entry 4).<sup>313</sup> This gave the product **367** in 35% yield. The best yields were obtained when the vinyl bromide **366** was subjected to 13 equivalents of sodium trichloroacetate with 12 mol % tetrabutylammonium hydrogen sulfate in chloroform at reflux for 2 days to provide the product **367** in 77% yield (Table 7.5, entry 5).

Unfortunately the acetal within the adduct **367** readily hydrolysed on silica gel (with and without treatment with triethylamine) and alumina (neutral, basic, and acidic). It was also prone to hydrolysis when stored at cold temperatures. To check how easily **367** hydrolysed to form the diol **373**, it was stirred with montmorillonite K10 in dichloromethane under reflux for 1 day (Scheme 7.23). The hydrolysed product **373** was provided in 79% yield. Conversion of the diol **373** back to the acetal **367** was then attempted. Treatment of **373** with catalytic CSA and calcium chloride in acetone at room temperature did not afford the acetal **367** under all conditions attempted. It is likely that the diol **373** is too far apart to enable the formation of the cyclic acetal.

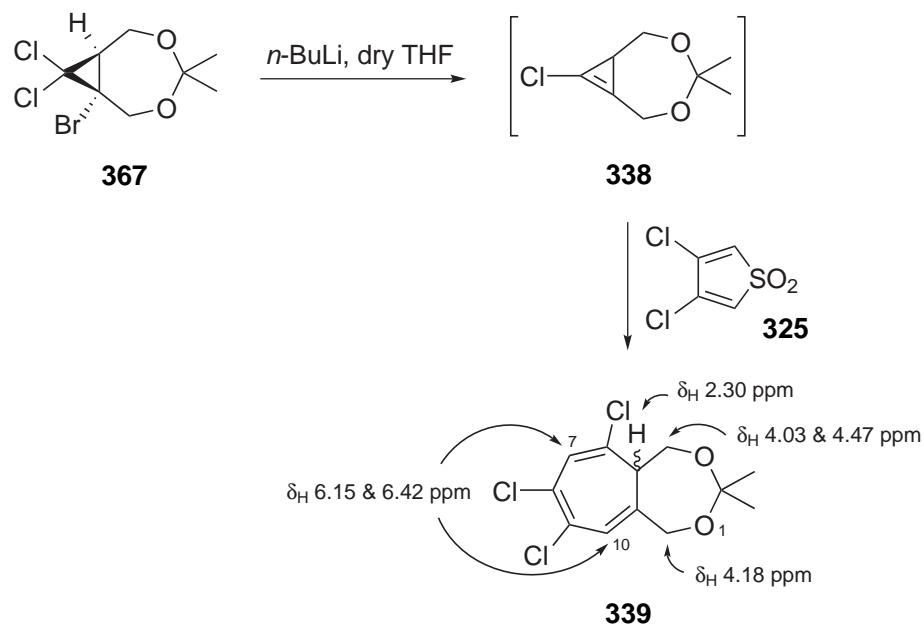


Scheme 7.23: Hydrolysis of **367**.

The next step was one of the two important reactions towards the synthesis of cordytopolone **314**, which was the conversion of the cyclopropane **367** to the cycloheptatriene **339**. To form the cycloheptatriene **339**, the dichlorocarbene adduct **367** was treated with *n*-butyllithium in dry tetrahydrofuran under an assortment of conditions (Table 7.6). The dichlorocarbene adduct **367** was subjected to 1 equivalent of *n*-butyllithium in dry tetrahydrofuran at -84°C for 10 minutes before 3,4-dichlorothiophene-1,1-dioxide **325** was introduced (Table 7.6, entry 1). The reaction was allowed to warm to room temperature for 2 hours before work-up. Gratifyingly, the <sup>1</sup>H NMR spectrum of the crude product showed that the product **339** had formed. The corresponding spectrum enabled the structure of the product **339** to be assigned

with greater confidence than what the previous spectra provided. The cycloheptatriene resonances at 6.15 and 6.42 ppm were apparent, as well as the allylic methine at 2.30 ppm. Two methyl signals were observed at 1.42 and 1.44 ppm. A doublet was found at 4.18 ppm which integrated for two hydrogens. Two other doublets which had an AB pattern were discerned at 4.03 and 4.47 ppm ( $J = 15.0$  Hz), each integrating for one hydrogen. The three doublets were assigned to the methylene hydrogens of the dioxepin. Purification of the crude reaction product was attempted by radial chromatography. The mass recovery was low, as the product was isolated in 32% yield. Decomposition products were observed in the  $^1\text{H}$  NMR spectra of nearly all of the chromatography fractions. The reaction conditions were repeated on numerous occasions but the yield of **339** obtained in Table 7.6, entry 1 could not be reproduced, therefore optimisation was required.

Table 7.6: Reaction conditions employed to synthesise the Diels-Alder adduct from **367**.

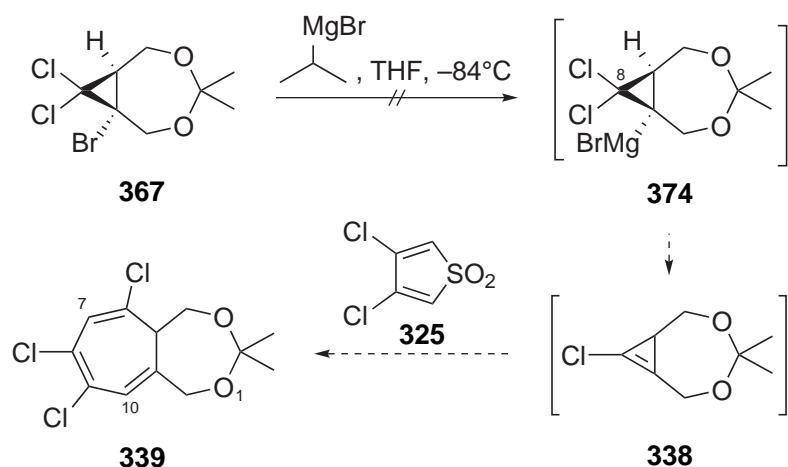


Entry	Conditions	Conversion to <b>339</b> *
1	<b>367</b> (1 eq., 0.32 M), 1.6 M <i>n</i> -BuLi (1 eq.), <b>325</b> (1 eq.), -84°C to RT, 2 h	32% <sup>†</sup>
2	<b>367</b> (1 eq., 1 M), 1.4 M <i>n</i> -BuLi (1 eq.), <b>325</b> (1 eq.), -84°C, 2.5 h	9%
3	<b>367</b> (1 eq., 0.50 M), 1.4 M <i>n</i> -BuLi (1 eq.), <b>325</b> (1 eq.), -84°C, 4 h	13%
4	<b>367</b> (1 eq., 0.25 M), 1.6 M <i>n</i> -BuLi (1 eq.), <b>325</b> (1 eq.), -84°C to RT, 3 days	53%
5	<b>367</b> (1 eq., 0.50 M), 1.4 M <i>n</i> -BuLi (1.2 eq.), <b>325</b> (1 eq.), -84°C to RT, o/n	7%

\*Conversions are respective of **360** and were obtained by  $^1\text{H}$  NMR spectroscopy. <sup>†</sup>Isolated yield

The dichlorocarbene adduct **367** was treated with 1 equivalent of *n*-butyllithium in dry tetrahydrofuran at  $-84^{\circ}\text{C}$  for 10 minutes before 3,4-dichlorothiophene-1,1-dioxide **325** was added (Table 7.6, entry 2). After 2.5 hours at  $-84^{\circ}\text{C}$ , a 9% conversion of the product **339** was formed. The reaction was repeated, however, it was left to stir for 4 hours before work-up (Table 7.6, entry 3). The  $^1\text{H}$  NMR spectrum of the crude product showed a slight improvement in the conversion to **339** (13%). Stirring the reaction under the same conditions for 3 days gave a 53% conversion to **339** (Table 7.6, entry 4). The corresponding  $^1\text{H}$  NMR spectrum of the crude mixture also contained decomposition products along with unreacted 3,4-dichlorothiophene-1,1-dioxide **325**. Purification of the crude reaction product was attempted with radial chromatography. The mass recovery was very low and **339** could not be isolated in a pure state. Treatment of **367** with 1.2 equivalents of *n*-butyllithium in anhydrous tetrahydrofuran at  $-84^{\circ}\text{C}$  followed by addition of 1 equivalent of **325** gave 7% conversion to **339** after 1 day (Table 7.6, entry 5). After examination of the results provided in Table 7.6, the addition of more than 1 equivalent of *n*-butyllithium reduced the yield of product. *n*-Butyllithium may have been too basic for the reaction, and could have caused degradation of the starting materials.

As a Grignard reagent is less basic than *n*-butyllithium, isopropylmagnesium bromide was used instead of *n*-butyllithium. Magnesium-halogen exchange of **367** would give the intermediate **374**, which upon elimination of  $\text{MgBrCl}$  could give the cyclopropene **338**. Compound **367** was treated with 1.1 equivalents of isopropylmagnesium bromide in anhydrous tetrahydrofuran at  $-84^{\circ}\text{C}$  to room temperature before addition of **325** (Scheme 7.24). The reaction was stirred for 2 days at room temperature, but only starting

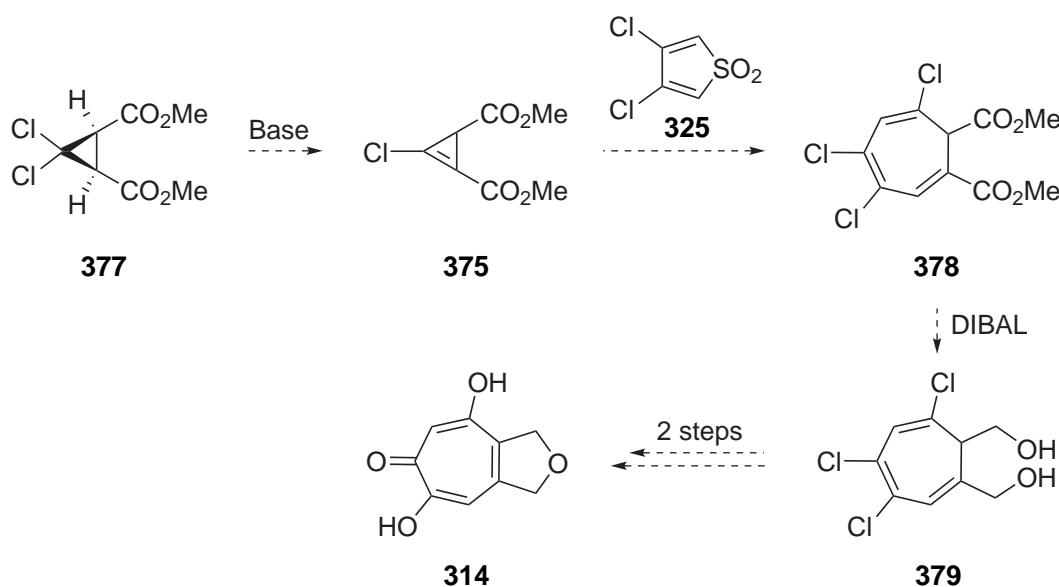


Scheme 7.24: Attempted synthesis of **339** via the Grignard intermediate **374**.

materials were recovered upon work-up. This suggested that the magnesium-bromide exchange did not occur.

## 7.7. Further revised synthesis of cordytopolone

A revised strategy to form cordytopolone **314** was to use a simpler cyclopropene such as **375**. The cyclopropene **375** could be formed in two steps from dimethyl maleate **376**. Addition of dichlorocarbene to dimethyl maleate **376** could form the adduct **377** (Scheme 7.25). Treatment of **377** with a base was expected to provide the cyclopropene intermediate **375**. Compound **375** could then react with 3,4-dichlorothiophene-1,1-dioxide **325** in a Diels-Alder reaction to yield the trichlorocycloheptatriene compound **378**. Reduction of the esters within the Diels-Alder adduct **378** is possible to afford the diol **379**. Cyclisation of the diol to the tetrahydrofuran motif followed by tropylidium nucleophilic aromatic substitution could then lead to cordytopolone **314**.

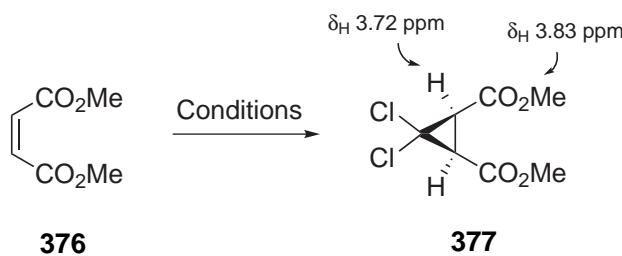


Scheme 7.25: Implementation of dimethylmaleate precursors to synthesise **314**.

Sodium trichloroacetate was used as the source of dichlorocarbene, since it was the most effective reagent used thus far. The alkene in dimethylmaleate **376** is electron poor, so addition of dichlorocarbene would be more difficult than the other aforementioned examples. Additionally, a Michael addition could compete with dichlorocarbene addition to the alkene since dimethylmaleate **376** is a good Michael acceptor, and the dichlorocarbene source sodium trichloroacetate is potentially a Michael donor.<sup>314</sup>

Nonetheless, a mixture of dimethylmaleate **376**, 25 equivalents of sodium trichloroacetate and catalytic (4 mol %) tetrabutylammonium hydrogensulfate in chloroform was heated at reflux for 3 days to form the dichlorocarbene adduct **377** (Table 7.7, entry 1). The <sup>1</sup>H NMR spectrum of the crude product revealed that the starting materials were recovered. Repeating the reaction with glyme at reflux instead of chloroform was also unsuccessful, since starting materials were again recovered (Table 7.7, entry 2). A literature procedure was used which required 1.5 equivalents of sodium trichloroacetate at 140°C without solvent.<sup>315</sup> This harsher method mostly provided the product **377** with a 78% conversion, as indicated by the two singlets at 3.72 and 3.83 ppm in the <sup>1</sup>H NMR spectrum (Table 7.7, entry 3). Unreacted starting material was also present in the crude mixture (22%). Purification of this compound was challenging, as distillation and chromatography would decompose the product. Crude material was used in the next reaction step.

Table 7.7: Synthesis of the dichlorocarbene adduct **377**.



Entry	Conditions	Conversion to <b>377</b>
1	$\text{Cl}_3\text{CCO}_2\text{Na}$ (25 eq.), TBAHS (0.04 eq.), $\text{CHCl}_3$ , 61°C, 3 days	0%
2	$\text{Cl}_3\text{CCO}_2\text{Na}$ (25 eq.), TBAHS (0.04 eq.), glyme, 85°C, 3 days	0%
3	$\text{Cl}_3\text{CCO}_2\text{Na}$ (1.5 eq.), 140°C, 4 h <sup>315</sup>	78%

The next reaction was the formation of the cyclopropene intermediate **375**. The two  $\alpha$ -hydrogens of the esters within **377** were acidic, which made them susceptible to removal using a base. A mixture of the dichlorocarbene adduct **377** and 1 equivalent of 3,4-dichlorothiophene-1,1-dioxide **325** was treated with 1.5 equivalents of potassium hydroxide and 1 equivalent of calcium oxide in toluene, and the reaction was heated to 80°C (Table 7.8, entry 1).<sup>316</sup> <sup>1</sup>H NMR analysis of the reaction mixture in progress did not show any new methine hydrogens which were expected of the cyclopropene intermediate **375** or peaks representative of the expected cycloheptatriene **378**. Rather than using potassium hydroxide, a 1:1 mixture of triethylamine in acetonitrile was implemented

(Table 7.8, entry 2).<sup>317</sup> Regrettably, these conditions only led to decomposition of the starting material. Other less nucleophilic bases were tested to encourage the reaction to proceed. The precursor **377** was subjected to a 1:1 mixture of Hünigs base in acetonitrile (Table 7.8, entry 3). This also led to decomposition of the starting material. The precursor **377** was also treated with 1 equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 80°C (Table 7.8, entry 4).<sup>318,319</sup> This afforded a complex mixture of compounds, none of which were the product. Repetition of the reaction at an elevated temperature (100°C) offered no improvement (Table 7.8, entry 5).

Table 7.8: Attempted conversion of **377** to the cyclopropene **375**.

**377**

Conditions // →

**375**

Conditions // →

**378**

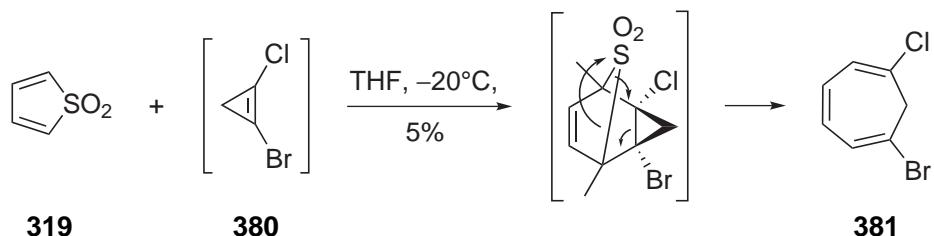
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Entry	Conditions	Yield of <b>375</b>
1	KOH (1.5 eq.), CaO (1 eq.), <b>325</b> (1 eq.), PhMe, 80°C, 4 h	0%
2	Et <sub>3</sub> N-MeCN (1:1) (43 eq.), <b>325</b> (1 eq.), RT to 60°C, 2 days	0%
3	Hünigs base-MeCN (1:1) (40 eq.), <b>325</b> (1 eq.), RT to 80°C, 4 days	0%
4	DBU (1 eq.), <b>325</b> (1 eq.), PhMe, 80°C, 5 days	0%
5	DBU (1 eq.), <b>325</b> (1 eq.), PhMe, 100°C, 2 days	0%

## 7.8. Conclusions

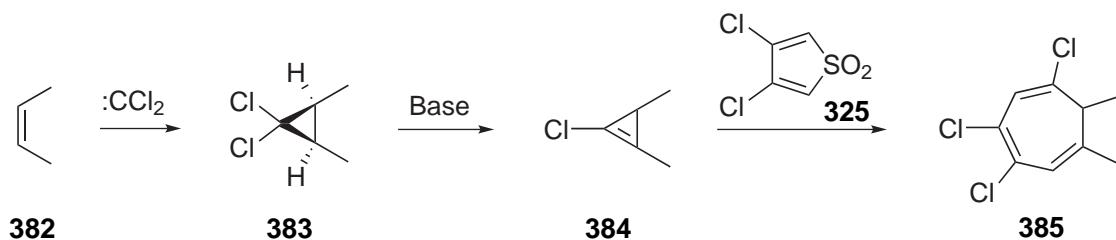
Although the synthesis of cordytopolone **314** was not completed, this work has shown that the two key steps which are the Diels-Alder cycloaddition and tropylidium nucleophilic aromatic substitution can proceed, albeit with isolated yields below 35%. Future work for this project should mostly be focused on the Diels-Alder cycloaddition step and generation of an appropriate cyclopropene. The inherent reactivity of thiophene-1,1-dioxides **319** towards cyclopropenes is not completely understood. The cycloaddition reaction reported by van Tilborg *et al.* used 2,5-dimethylthiophene-1,1-dioxide **321** and cyclopropene **322** to synthesise 3,6-dimethylcycloheptatriene **323** in 92% yield (Scheme 7.3).<sup>278</sup> Conversely, Müller and Schaller combined 1.25 equivalents of thiophene-1,1-dioxide **319** and 1 equivalent of 1-bromo-2-chlorocyclopropene **380**

at  $-20^{\circ}\text{C}$  to produce the cycloheptatriene **381** in 5% yield (Scheme 7.26).<sup>320</sup> The low yield of **381** could be due to the halogen substituents on the cyclopropene **380** hindering the cycloaddition, since the reaction achieved by van Tilborg and co-workers used an unsubstituted cyclopropene **322** and got a high yield of product **323**. Compared to the two aforementioned examples, the cycloheptatriene **339** was synthesised in yields in between those obtained for **323** and **381**. The reactivity of 3,4-dichlorothiophene-1,1-dioxide **325** towards cyclopropenes needs to be further explored.



Scheme 7.26: Synthesis of **381**.<sup>320</sup>

An alternate synthesis could start with *cis*-2-butene **382** to test the viability of **325** and **338** in the Diels-Alder reaction. Addition of dichlorocarbene to **382** could form the dichlorocarbene adduct **383**. This compound could then be treated with a base to form the cyclopropene **384**, which may react with 3,4-dichlorothiophene-1,1-dioxide **325** to form 1,2-dimethyl-4,5,7-trichlorocycloheptatriene **385**. This simplified reaction would determine whether the cyclopropene **384** or 3,4-dichlorothiophene-1,1-dioxide **325** was the cause of the low yields in the major reaction. If the cycloaddition/elimination reaction is successful, this would infer that the cyclopropenes **338** and **375** used throughout this Chapter were detrimental to the success of the reaction.



Scheme 7.27: Future work in this project.

# Chapter 8

## General Conclusions

### 8.1. *Dodonaeas*

The aim of the project was to find a viable source of clerodanes from a *Dodonaea* species growing in WA and investigate their chemistry. Two *Dodonaea* species were examined, and these were *D. viscosa* ssp. *angustissima* and *D. ceratocarpa* from south-western WA. Using a rapid extraction technique, the leaf resin of *D. viscosa* ssp. *angustissima* gave three compounds (Figure 8.1). Compounds **28** and **149** have previously been isolated,<sup>74,99</sup> whilst **150** has been identified recently in this work and continued investigations.<sup>117</sup> *D. ceratocarpa* also provided three compounds: the furan clerodane **155** was a known compound,<sup>123</sup> whilst the allylic alcohol **156** and  $\alpha$ -alcohol **157** were new compounds (Figure 8.1). The alcohol **157** was the major substituent in the leaf resin, accounting for 0.5% w/w of the total mass of the plant used. Since **157** was available in a good quantity, it was used as a starting material. The inherent reactivity of all three rings within **157** was investigated using a variety of reagents.

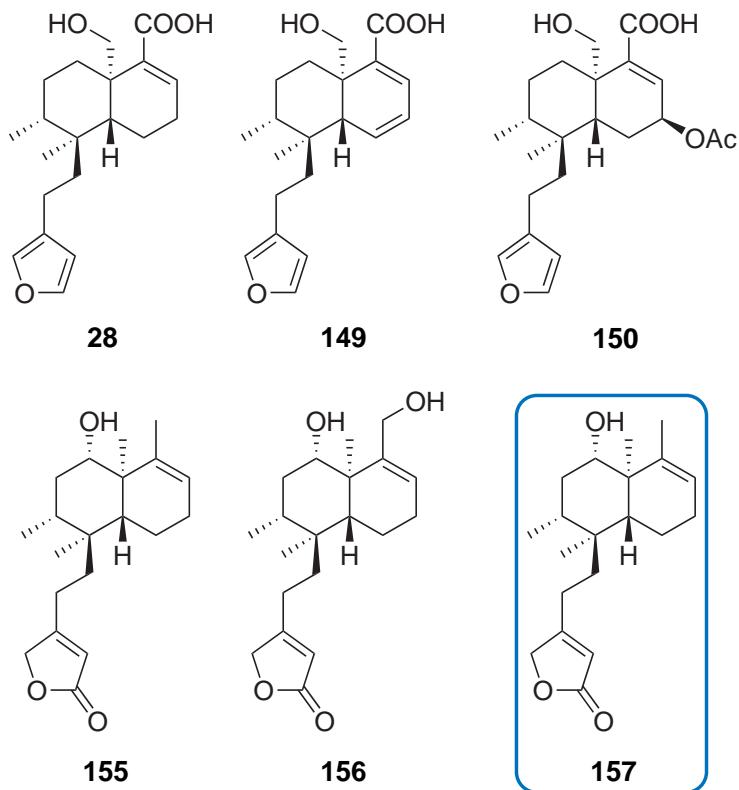
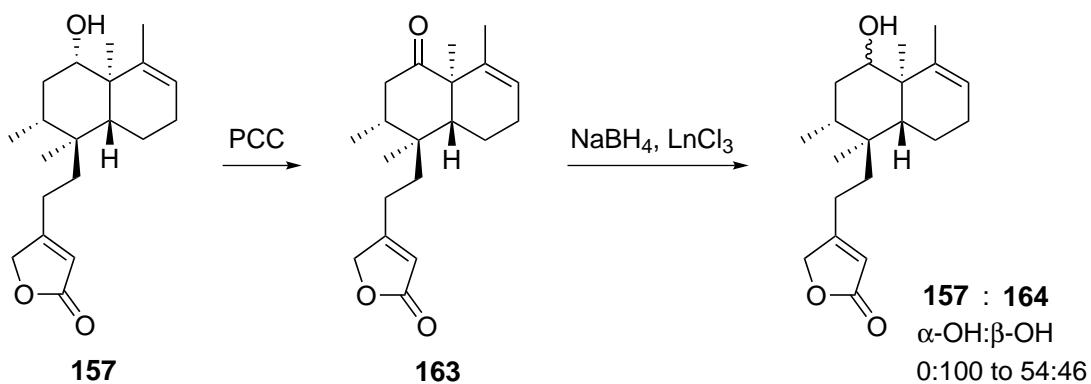


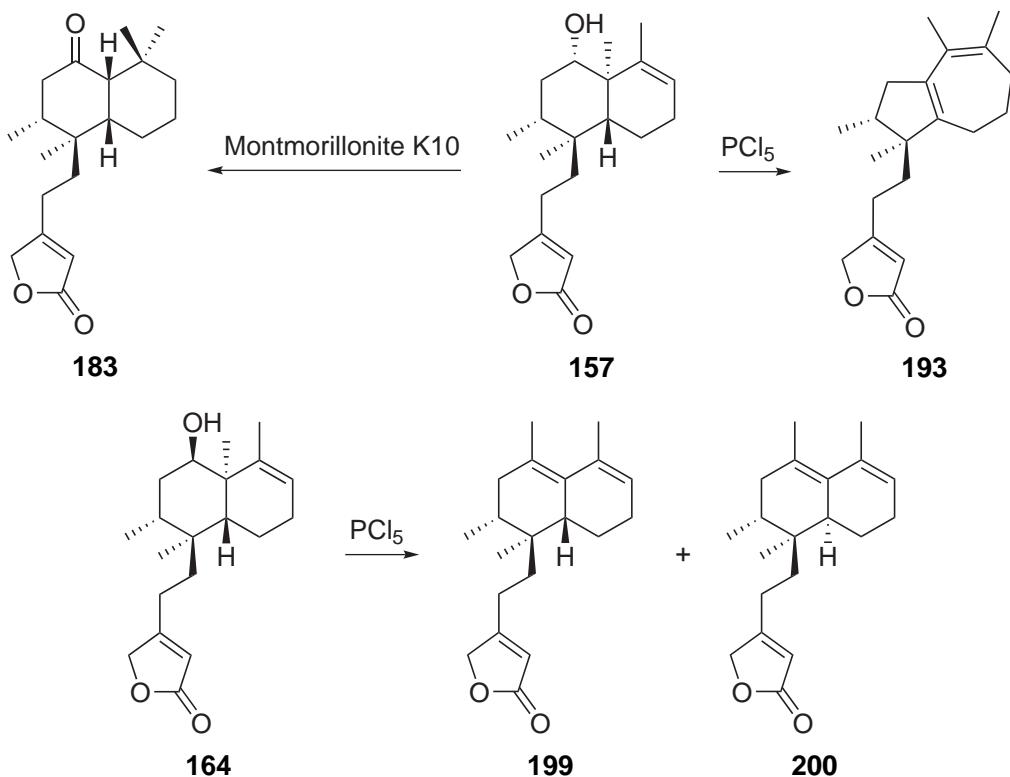
Figure 8.1: Clerodanes isolated from *D. viscosa* ssp. *angustissima* and *D. ceratocarpa*.

Oxidation of the alcohol **157** to the ketone **163** was achieved with PCC (Scheme 8.1). Reduction of **163** with sodium borohydride did not give **157**, but it did selectively produce the epimer **164**. Further reductions with sodium borohydride and lanthanide chlorides were explored, which provided interesting results. The lanthanide chloride additives reduced the selectivity of **164**, as both **157** and **164** were formed in all cases. A trend was observed from the inclusion of the lanthanide chlorides to the sodium borohydride reductions. The lanthanide chlorides that were stronger Lewis acids gave a higher product ratio of **164**, whilst the weaker Lewis acids favoured the formation of **157**.



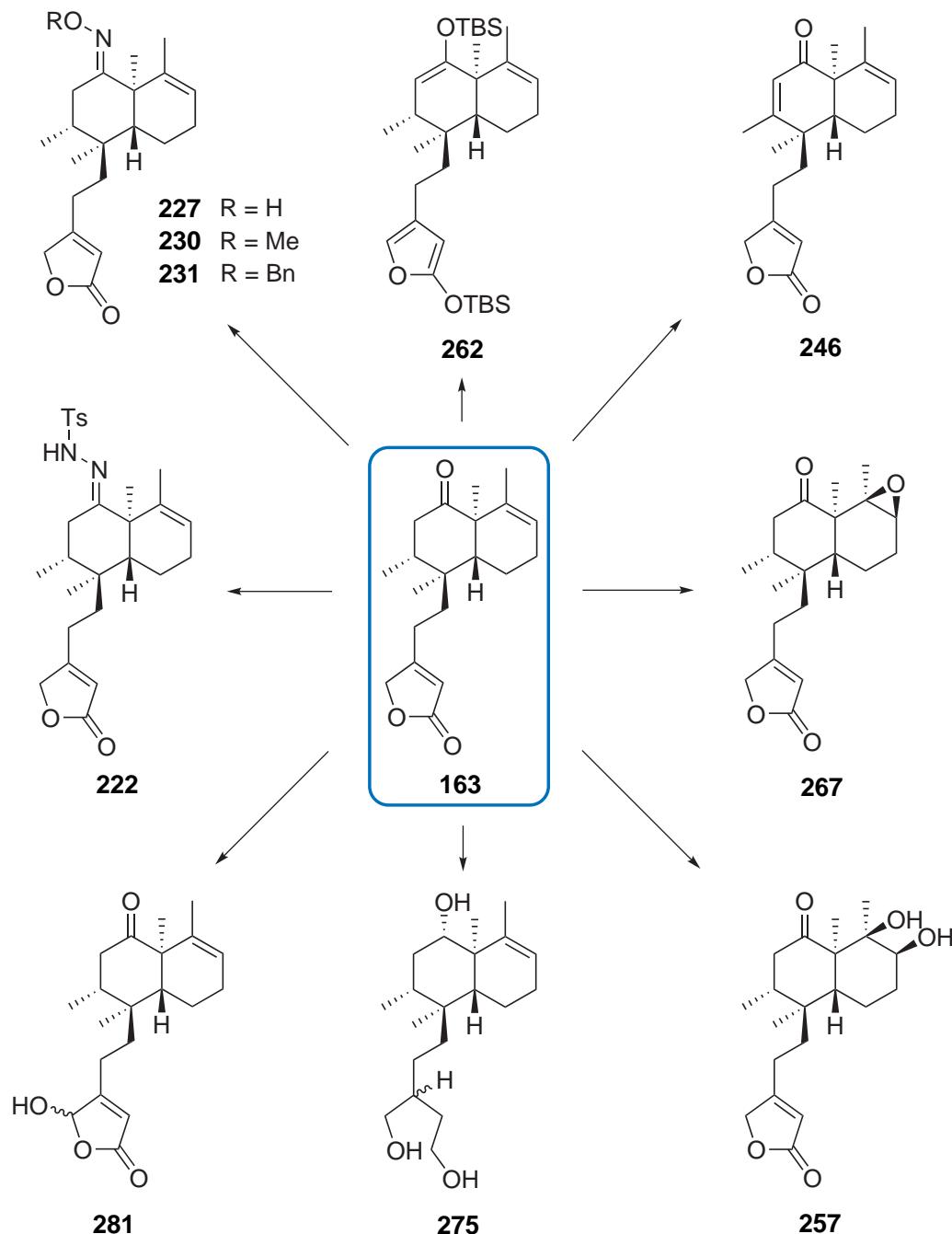
Scheme 8.1: Oxidation of **157** and reduction of **163**.

Rearrangements of the alcohol **157** and its epimer **164** were explored (Scheme 8.2). Treatment of **157** with different acid sources caused divergent reaction outcomes. Addition of dry montmorillonite K10 to **157** in anhydrous dichloromethane gave the labdane-like ketone **183**. Treatment of **157** with PCl<sub>5</sub> and sodium carbonate caused another rearrangement to occur to afford the azulenic compound **193**. Interestingly, when the epimer alcohol **164** was treated under the same reaction conditions, compound **193** was not formed, rather a 1:1 mixture of two compounds proposed to be **199** and **200** were isolated. Such rearrangements have not been observed with clerodanes up until this work.



Scheme 8.2: Rearrangements of alcohols **157** and **164**.

A suite of other new compounds were synthesised upon functionalisation of the ketone **163**. Condensation reactions of the ketone carbonyl within compound **163** were achieved to form new imines. A tosyl hydrazone **222** was synthesised, along with three oximes (**227**, *O*-methyl **230** and *O*-benzyl **231**). All of the oximes had an (*E*)-orientation as these were the least strained isomers. The  $\alpha,\beta$ -unsaturated ketone (enone) **246** was synthesised in a two-step procedure via a TBS enol ether intermediate **262**. The alkene on ring A of **163** was oxidised to form an epoxide **267** as a single stereoisomer. Oxidation of the same



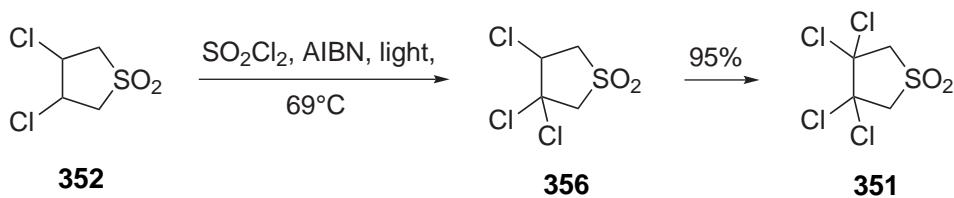
Scheme 8.3: Some transformations achieved using **163** as the substrate.

alkene with AD-mix $\beta$  provided a diol **257** as a single stereoisomer, while addition of AD-mix $\alpha$  to **163** gave a 1:1 mixture of the diols. Reduction of the butenolide was achieved to form the triol **275** as a mixture of diastereoisomers. Oxidation of the butenolide of **163** with charcoal and oxygen formed the hydroxylactone **281** with a 30% conversion. This was a good result, considering that a number of approaches attempted to synthesise **281** were unsuccessful.

This work has shown that compounds **157** and **163** are useful starting materials that were transformed into novel compounds. The availability of these compounds has enabled new reactions that have not been previously studied on clerodanes systems. Many reactions gave the expected products with a high degree of stereoselectivity, however, some unusual rearrangement reactions were observed that gave unexpected products.

## 8.2. Cordytopolone

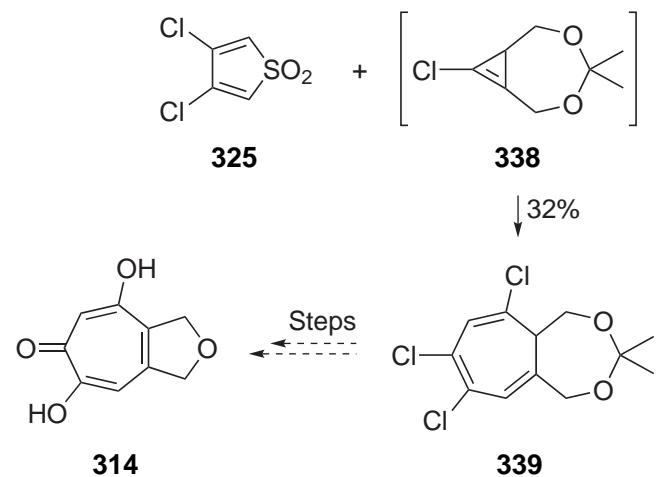
The work presented in Chapter 7 has discussed the progress achieved towards the synthesis of cordytopolone **314**. One highlight was the synthesis of 3,3,4,4-tetrachlorosulfolane **351** without chlorine gas in carbon tetrachloride (Scheme 8.4). Sulfuryl chloride was used as the reagent and solvent to chlorinate 3,4-dichlorosulfolane **352** to 3,3,4-trichlorosulfolane **356** and then **351** in high yield.



Scheme 8.4: Synthesis of 3,3,4,4-tetrachlorosulfolane **351** with sulfuryl chloride.

Important reactions in the synthesis of cordytopolone **314** have been achieved. New dioxepin derivatives were synthesised in the process. The key cycloheptatriene **339** has been synthesised using 3,4-dichlorothiophene-1,1-dioxide **325** and a cyclopropene **338** (Scheme 8.5). Completion of the synthesis of **314** will be the first reported application of a thiophene-1,1-dioxide in a total synthesis. Compound **339** was isolated in a yield of 32%, so optimisation is necessary before the next step in the synthesis is resumed.

Once the Diels-Alder reaction stage is improved to give a much higher yield of **339**, the remaining steps towards the final product **314** are possible.



Scheme 8.5: The achieved preliminary synthesis of the cycloheptatriene **339** towards **314**.

# Chapter 9

## Experimental

All reactions involving moisture or air-sensitive reagents were performed under a positive pressure of nitrogen. Glassware was dried in an oven set at 120°C for at least 30 minutes. Materials were obtained from commercial sources and used without further purification unless otherwise stated. NMR experiments were performed on a Bruker UltraShield Avance III 400 spectrometer ( $^1\text{H}$ , 400.1 MHz;  $^{13}\text{C}$ , 100.6 MHz). Chemical shifts ( $\delta$ ) are expressed in ppm with reference to the solvent resonances of  $\text{CDCl}_3$  ( $^1\text{H}$ , 7.26 ppm;  $^{13}\text{C}$ , 77.16 ppm) and  $(\text{CD}_3)_2\text{CO}$  ( $^1\text{H}$ , 2.05 ppm;  $^{13}\text{C}$ , 29.84 ppm). Infrared spectra were recorded on a Perkin Elmer Fourier Transform-IR spectrometer 100 equipped with a ZnSe-diamond crystal ATR accessory; spectra were acquired between 4000-650  $\text{cm}^{-1}$ . Optical rotations ( $\alpha$ ) were obtained from a Rudolph Research Analytical Autopol I polarimeter. Melting points were determined on a Crown Scientific Barnstead Electrothermal 9100 apparatus. Column/flash chromatography was achieved using SiliaFlash® P60 silica gel (230-400 mesh, SiliaCycle, Canada) with the solvents stated. Radial chromatography was performed on a Harrison Research Chromatotron, model 7924T using chromatotron plates (1 mm and 2 mm) made with Merck silica gel 60 PF<sub>254</sub> containing gypsum. Low resolution and high resolution EI mass spectrometry was recorded on the Shimadzu QP5050A and Waters Xevo QToF instruments respectively, at the School of Chemistry, University of Wollongong, NSW. Electrospray ionisation (ESI) HRMS was also performed on some samples with a Thermo Fisher Scientific LTQ Orbitrap XL at Curtin University. TLC was completed on Merck aluminium backed silica gel 60 F254 sheets and visualised by using short-wave UV light ( $\lambda = 254$  nm)

for aromatics, potassium permanganate and ammonium molybdate solutions. Solvents (tetrahydrofuran, dichloromethane and acetonitrile) were dried using methods described in Armarego and Chai.<sup>321</sup> Petrol refers to the fraction of alkanes that boils between 40-60°C.

## 9.1. *Dodonaea viscosa* ssp. *angustissima*

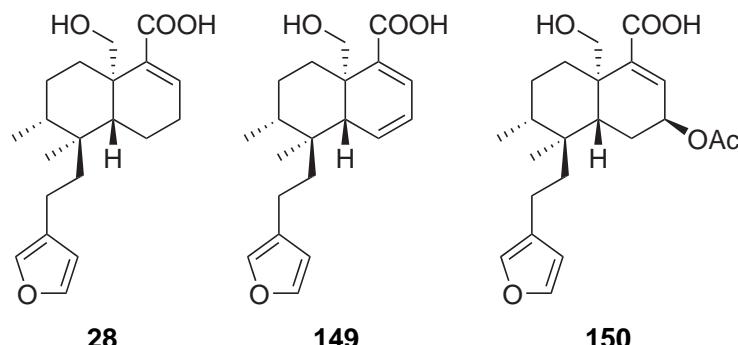
*D. viscosa* ssp. *angustissima* was collected from Wrights Bridge near Blackwood River in Balingup, WA in January 2013. The leaves were sent to Curtin University the following day and left out over the weekend to dry so that any excess moisture was removed. Once the leaves were dry, they were stored in a dark room and used accordingly.

### *Method A - diethyl ether extraction (bulk resin)*

Leaves of *D. viscosa* ssp. *angustissima* (120.00 g) were soaked in diethyl ether (1 L) for 30 minutes. The solution was filtered and the solvent was removed *in vacuo* to afford a yellow solid (4.98 g, 4.2% w/w). The solid was subjected to flash chromatography using silica gel treated with 1% triethylamine. Elution with 30% ethyl acetate in petrol to 50% methanol in ethyl acetate gave compounds **28**, **149** and **150**.

### *Method B - sodium carbonate extraction (acidic components in the resin)*

*D. viscosa* ssp. *angustissima* leaves (197.03 g) were soaked in 5% aqueous sodium carbonate (2 L) overnight. The solution was filtered, and the filtrate was acidified to pH 1-2 with concentrated hydrochloric acid solution (10 M). The solution was extracted with dichloromethane (4 x 500 mL) and dried ( $\text{MgSO}_4$ ). Concentration under reduced pressure afforded a yellow solid (3.00 g, 1.5% w/w). Flash chromatography of the solid using silica gel treated with 1% triethylamine (30% ethyl acetate in petrol to 50% methanol in ethyl acetate) gave compounds **28**, **149** and **150**.



## 9.2. *Dodonaea ceratocarpa*

*D. ceratocarpa* was grown from seedlings on a private property near Balingup, WA. This plant was collected in October 2011, November 2012, November 2013 and October 2014. The leaves were collected and sent the following day to Curtin University. They were left out over the weekend to dry so that any excess moisture was removed. Once the leaves were dry, they were stored at room temperature in a dark room and used accordingly.

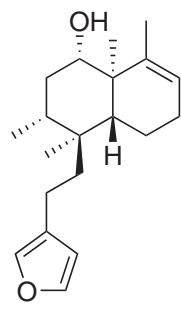
### *Method A - methanol extraction (bulk resin)*

Leaves of *D. ceratocarpa* (20.69 g) were soaked in methanol (100 mL) for 30 minutes. The leaves were filtered and the filtrate was concentrated *in vacuo* to afford a mixture of a green foamy solid and an oily residue (0.83 g, 4.0 % w/w) that consisted of a complex mixture according to the  $^1\text{H}$  NMR spectra.

### *Method B - diethyl ether extraction*

Leaves of *D. ceratocarpa* (200.00 g) were steeped in diethyl ether (1.5 L) for 30 minutes. The extract was filtered and evaporated under reduced pressure to give a yellow-green foamy solid (7.45 g, 3.7% w/w, 3.0-4.3% w/w common). A portion of the resin (3.51 g) was then subjected to flash chromatography on silica gel treated with 1% triethylamine. Elution with 30% ethyl acetate in petrol to 20% methanol in ethyl acetate gave compounds **155** (0.12 g, 3.5% w/w resin), **157** (0.98 g, 28% w/w resin) and **156** (0.03 g, 0.9% w/w resin). This method was used throughout this work to isolate the clerodanes.

### *Furan 155*

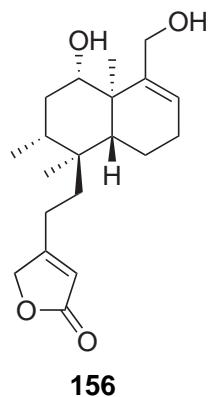


**155**

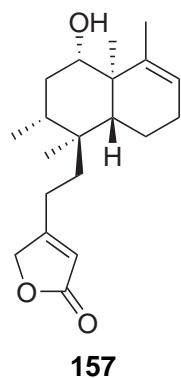
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.34 (1H, t,  $J = 1.7$  Hz), 7.19 (1H, m,  $J = 1.7, 0.9$  Hz), 6.25 (1H, dd,  $J = 1.7, 0.9$  Hz), 5.24 (1H, br s), 3.57 (1H, dd,  $J = 11.1, 4.9$  Hz), 2.32-2.14 (2H, m,

*J* = 11.1, 4.9, 2.4 Hz), 2.07-1.99 (2H, m), 1.85 (3H, m, *J* = 2.4, 1.7 Hz), 1.73-1.66 (2H, m), 1.66-1.59 (4H, m), 1.59-1.54 (6H, m), 1.53 (1H, m), 1.50 (1H, m), 1.39 (1H, d, *J* = 2.4 Hz), 1.36 (1H, d, *J* = 2.4 Hz), 1.03 (3H, s), 0.85 (3H, d, *J* = 6.7 Hz), 0.73 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  143.9 (C), 142.9 (CH), 138.5 (CH), 125.7 (C), 122.4 (CH), 111.1 (CH), 75.8 (CH), 45.7 (CH), 44.2 (C), 38.7 (C), 38.6 (CH<sub>2</sub>), 38.0 (CH<sub>2</sub>), 34.7 (CH), 26.8 (CH<sub>2</sub>), 22.5 (CH<sub>3</sub>), 18.1 (CH<sub>2</sub>), 18.0 (CH<sub>2</sub>), 17.9 (CH<sub>3</sub>), 15.8 (CH<sub>3</sub>), 15.1 (CH<sub>3</sub>). Spectral data for this compound matched that provided in literature.<sup>123</sup>

*Allyl alcohol 156*

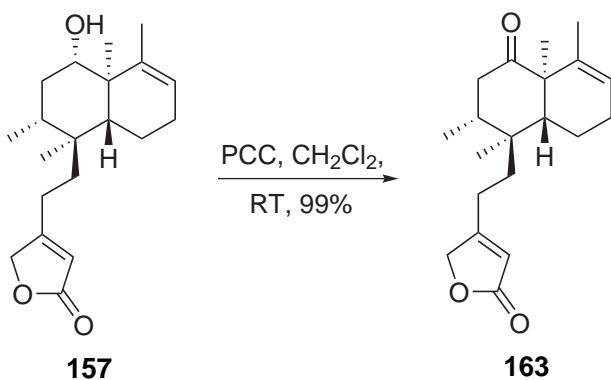


$[\alpha]_D^{25} -42$  (*c* 0.07,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.83 (1H, m, *J* = 1.6 Hz), 5.59 (1H, dd, *J* = 4.5, 2.5 Hz), 4.73 (2H, d, *J* = 1.6 Hz), 4.28 (1H, d, *J* = 12.0 Hz), 4.03 (1H, d, *J* = 12.0 Hz), 3.66 (1H, m), 2.56 (2H, br s), 2.30-2.11 (3H, m), 2.10-1.96 (1H, m), 1.70-1.50 (7H, m), 1.41 (1H, t, *J* = 7.3 Hz), 1.29 (1H, dd, *J* = 12.0, 1.9 Hz), 1.10 (3H, s), 0.85 (3H, d, *J* = 5.8 Hz), 0.78 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  170.8 (C), 146.1 (C), 128.3 (CH), 115.3 (CH), 75.1 (CH), 73.2 (CH<sub>2</sub>), 66.8 (CH<sub>2</sub>), 60.5 (C), 45.6 (CH), 44.3 (C), 38.5 (C), 36.3 (CH<sub>2</sub>), 35.5 (CH<sub>2</sub>), 34.9 (CH), 26.7 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 18.1 (CH<sub>3</sub>), 17.9 (CH<sub>2</sub>), 16.4 (CH<sub>3</sub>), 15.7 (CH<sub>3</sub>). IR (film,  $\text{cm}^{-1}$ ): 3354, 2927, 2874, 1779, 1738, 1636, 1449, 1172, 1016. HRMS (EI) *m/z*  $\text{C}_{20}\text{H}_{30}\text{O}_4$  [M – H]<sup>+</sup> requires 333.2066, found 333.2058.



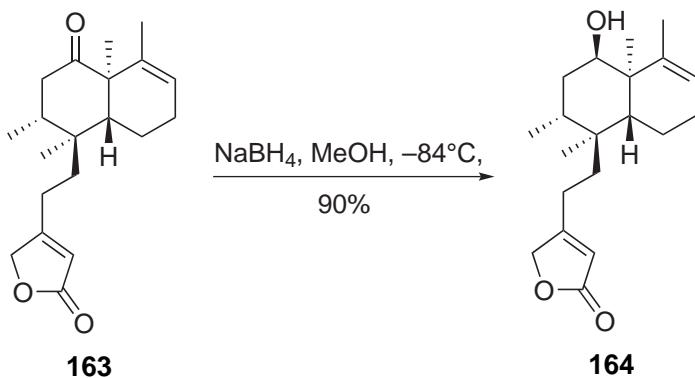
m.p. 144-146°C.  $[\alpha]_D^{25} -40$  (*c* 0.001, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.83 (1H, m, *J* = 1.7 Hz), 5.23 (1H, br s), 4.72 (2H, d, *J* = 1.7 Hz), 3.53 (1H, dd, *J* = 11.1, 4.0 Hz), 2.30-2.03 (3H, m), 1.82 (3H, s), 1.69-1.46 (9H, m), 1.26 (1H, dd, *J* = 12.2, 2.1 Hz), 1.02 (3H, s), 0.82 (3H, d, *J* = 5.9 Hz), 0.76 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  174.1 (C), 170.9 (C), 143.8 (C), 122.1 (CH), 115.2 (CH), 75.4 (CH), 73.1 (CH<sub>2</sub>), 45.6 (CH), 44.1 (C), 38.5 (C), 37.7 (CH<sub>2</sub>), 35.4 (CH<sub>2</sub>), 34.7 (CH), 26.7 (CH<sub>2</sub>), 22.4 (CH<sub>3</sub>), 22.1 (CH<sub>2</sub>), 18.0 (CH<sub>2</sub>), 17.7 (CH<sub>3</sub>), 15.7 (CH<sub>3</sub>), 15.0 (CH<sub>3</sub>). m.p. 144-146°C. IR (film, cm<sup>-1</sup>): 3510, 2947, 1786, 1743, 1635, 1440. HRMS (EI) *m/z* C<sub>20</sub>H<sub>30</sub>O<sub>3</sub> [M]<sup>+</sup> requires 319.2273, found 319.2276.

*Oxidation of 157*



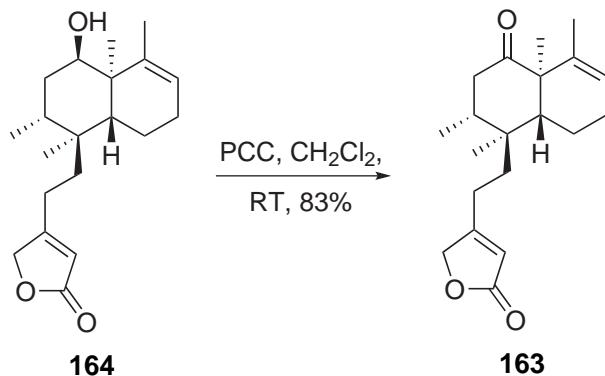
PCC (270 mg, 1.23 mmol, 1.5 eq.) was added to a solution of the alcohol **157** (260 mg, 0.82 mmol, 1 eq.) in dichloromethane (10 mL) and the mixture was stirred at room temperature under a nitrogen atmosphere. After 8 hours, the reaction was diluted with dichloromethane (50 mL) and filtered through a plug of Florisil. The filtrate was washed with 1 M sodium hydroxide (2 x 50 mL) and water (4 x 50 mL). After drying over MgSO<sub>4</sub>, the solution was concentrated under reduced pressure to give **163** as a pale yellow oil which crystallised to a solid (261 mg, 99%), m.p. 118-120°C.  $[\alpha]_D^{25} -147$  (*c* 0.001, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.83 (1H, m, *J* = 1.7 Hz), 5.37 (1H, m), 4.71 (2H, d, *J* = 1.7 Hz), 2.83 (1H, dd, *J* = 13.1, 12.3 Hz), 2.22-2.16 (1H, m), 2.13 (1H, dd, *J* = 12.3, 4.8 Hz), 2.06 (2H, dd, *J* = 12.3, 4.0 Hz), 2.02-1.92 (2H, m), 1.81 (3H, dt, *J* = 2.5, 1.3 Hz), 1.72 (1H, ddd, *J* = 14.4, 12.3, 4.8 Hz), 1.63 (3H, t, *J* = 4.0 Hz), 1.60-1.56 (1H, m), 1.42 (3H, s), 1.02 (3H, s), 0.94 (3H, d, *J* = 6.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  214.3 (C), 174.0 (C), 170.2 (C), 139.5 (C), 123.8 (CH), 115.6 (CH), 73.2 (CH<sub>2</sub>), 55.4 (C), 50.8 (CH), 43.7 (CH<sub>2</sub>), 41.5 (CH), 39.4 (C), 35.8 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 20.2 (CH<sub>3</sub>), 19.9 (CH<sub>3</sub>), 18.64 (CH<sub>3</sub>), 18.59 (CH<sub>2</sub>), 16.4 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2951, 1786, 1755, 1702, 1638, 1436. HRMS (EI) *m/z* C<sub>20</sub>H<sub>28</sub>O [M + H]<sup>+</sup> requires 317.2117, found 317.2112.

*Reduction of 163*



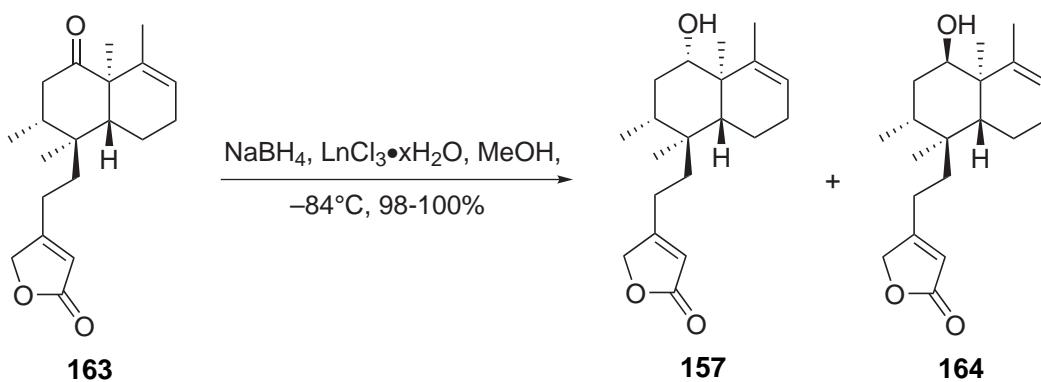
A stirred solution of the ketone **163** (40 mg, 0.126 mmol, 1 eq.) in methanol (0.50 mL) was cooled to  $-84^\circ\text{C}$  under nitrogen. Sodium borohydride (5 mg, 0.126 mmol, 1 eq.) was added and the mixture continued stirring at  $-84^\circ\text{C}$  for 3 hours. The reaction mixture was concentrated and the residue was dissolved with dichloromethane (20 mL). The organic phase was washed with water (4 x 20 mL), dried ( $\text{CaCl}_2$ ) and concentrated under reduced pressure to afford a clear residue. Radial chromatography (1% triethylamine treated silica, 15% ethyl acetate in petrol to 50% ethyl acetate) gave **164** as a colourless oil (36 mg, 90%).  $[\alpha]_D^{25} -114$  (*c* 0.006,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.83 (1H, s), 5.44 (1H, m, *J* = 2.8, 1.2 Hz), 4.73 (2H, d, *J* = 1.2 Hz), 3.86 (1H, t, *J* = 2.8 Hz), 2.36 (1H, ddd, *J* = 16.3, 12.3, 3.8 Hz), 2.23 (1H, ddd, *J* = 16.3, 12.3, 4.6 Hz), 2.07-2.01 (2H, m), 1.84-1.80 (1H, m), 1.77-1.65 (2H, m), 1.73-1.70 (3H, m), 1.60-1.48 (6H, m), 1.04 (3H, s), 0.81 (3H, d, *J* = 6.9 Hz), 0.78 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  174.2 (C), 171.2 (C), 140.6 (C), 125.3 (CH), 115.2 (CH), 73.7 ( $\text{CH}_2$ ), 71.3 (CH), 43.8 (C), 39.1 (CH), 38.6 (C), 35.6 ( $\text{CH}_2$ ), 33.7 ( $\text{CH}_2$ ), 28.9 (CH), 27.0 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_2$ ), 20.5 ( $\text{CH}_3$ ), 18.2 ( $\text{CH}_3$ ), 18.0 ( $\text{CH}_2$ ), 17.6 ( $\text{CH}_3$ ), 15.7 ( $\text{CH}_3$ ). IR (film,  $\text{cm}^{-1}$ ): 3478, 2954, 2929, 1779, 1745, 1636, 1448, 1386, 1171, 1024. HRMS (EI) *m/z*  $\text{C}_{20}\text{H}_{30}\text{O}_3$  [M + H]<sup>+</sup> requires 319.2273, found 319.2274.

*Oxidation of the  $\beta$ -alcohol **164***



The  $\beta$ -alcohol **164** (29 mg, 0.091 mmol, 1 eq.) was dissolved in dichloromethane (5 mL) under nitrogen. PCC (30 mg, 0.136 mmol, 1.5 eq.) was added to the mixture, and stirring was continued overnight at room temperature. The solution was diluted with dichloromethane (20 mL) and filtered through a plug of Florisil. The filtrate was washed with 1 M sodium hydroxide (2 x 20 mL), then water (2 x 20 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to afford the ketone **163** as a white solid (24 mg, 83%). All spectral data were identical to **163** synthesised from the  $\alpha$ -alcohol **157** previously described above.

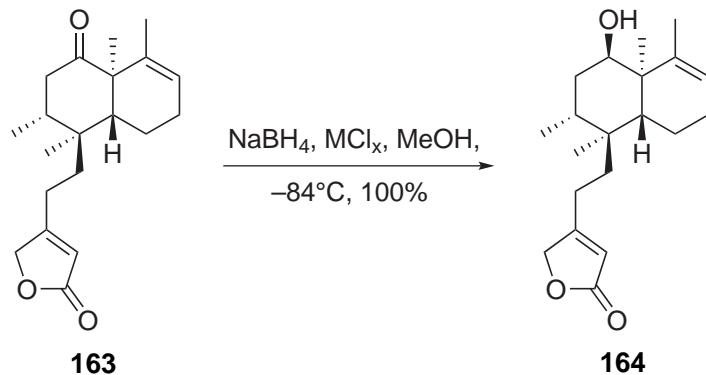
*Reduction of **163** under Luche conditions - general method*



The  $\text{LnCl}_3 \bullet x\text{H}_2\text{O}$  ( $\text{Ln} = \text{La/Ce/Sm/Eu/Tb/Yb}$ , 0.063 mmol, 1 eq.) was dissolved in methanol (0.50 mL) and cooled to  $-84^\circ\text{C}$ . With stirring, the ketone **163** (20 mg, 0.063 mmol, 1 eq.) was added. After a few minutes of stirring, sodium borohydride (2.4 mg, 0.063 mmol, 1 eq.) was added to the reaction in one portion and the reaction

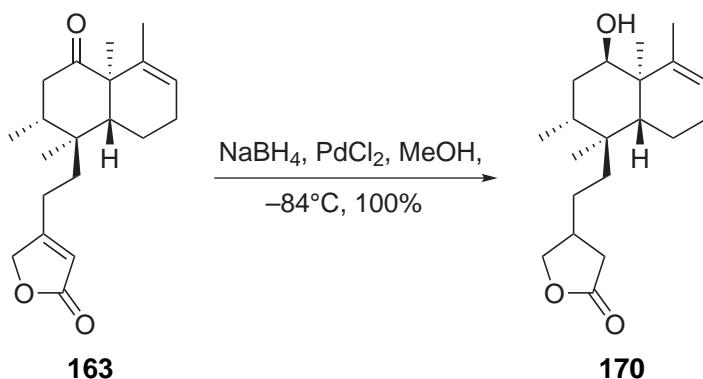
continued stirring at  $-84^{\circ}\text{C}$  for 3 hours. The reaction mixture was concentrated and the residue was dissolved with dichloromethane (20 mL). The organic phase was washed with water (4 x 20 mL), dried ( $\text{CaCl}_2$ ) and concentrated under reduced pressure to afford a colourless residue containing a mixture of compounds **157** and **164** (98-100%).

*Reduction of **163** with  $\text{MCl}_x$  - general method*



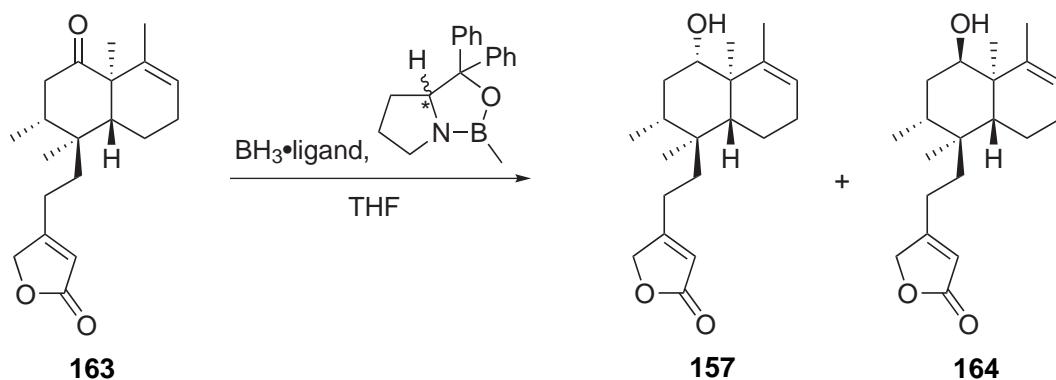
The chosen  $\text{MCl}_x$  ( $\text{M} = \text{Zn}^{2+}/\text{Sn}^{4+}/\text{Cu}^+$ , 0.063 mmol, 1 eq.) was dissolved in methanol (0.50 mL) and cooled to  $-84^{\circ}\text{C}$ . With stirring, the ketone **163** (20 mg, 0.063 mmol, 1 eq.) was added. Once the solution had stirred for a few minutes, sodium borohydride (2.4 mg, 0.063 mmol, 1 eq.) was added to the reaction in one portion. Stirring was continued at  $-84^{\circ}\text{C}$  for 3 hours before the solvent was removed *in vacuo*. Dichloromethane (20 mL) was added to dissolve the residue and this was washed with water (4 x 20 mL), dried ( $\text{CaCl}_2$ ) and concentrated under reduced pressure gave **164** as a colourless oil (20 mg, 100%). The characterisation data for **164** matched that provided previously.

*Conjugate reduction of **163** to form **170***



A stirred solution of PdCl<sub>2</sub> (11 mg, 0.063 mmol, 1 eq.) in methanol (0.50 mL) was cooled to -84°C under nitrogen. The ketone **163** (20 mg, 0.063 mg, 1 eq.) was added to the reaction mixture, followed by sodium borohydride (2.4 mg, 0.063 mmol, 1 eq.) a few minutes later. The resulting solution was stirred at -84°C for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (20 mL). The solution was washed with water (5 x 20 mL), dried (CaCl<sub>2</sub>) and concentrated under reduced pressure to provide **170** as a colourless oil (25 mg, 100%) without the need for further purification.  $[\alpha]_D^{24} -52$  (*c* 0.004, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.43 (1H, m), 4.43 (1H, ddd, *J* = 9.0, 7.5, 1.6 Hz), 3.88 (1H, dd, *J* = 9.0, 7.5 Hz), 3.84 (1H, m), 2.63 (1H, ddd, *J* = 17.2, 8.4, 1.6 Hz), 2.50-2.39 (1H, m), 2.14 (1H, ddd, *J* = 17.2, 8.4, 1.6 Hz), 2.06-1.99 (3H, m), 1.79-1.66 (2H, m), 1.72-1.70 (3H, dt, *J* = 2.2, 1.6 Hz), 1.54-1.38 (5H, m), 1.30-1.24 (3H, m), 1.02 (3H, s), 0.79 (3H, dd, *J* = 6.9, 1.6 Hz), 0.73 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  177.2 (C), 140.7 (C), 125.4 (CH), 73.6 (CH<sub>2</sub>), 71.4 (CH), 43.7 (C), 39.1 (CH), 38.4 (C), 36.5 (CH), 36.2 (CH<sub>2</sub>), 34.8 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 28.8 (CH), 27.0 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 20.6 (CH<sub>3</sub>), 18.3 (CH<sub>3</sub>), 18.1 (CH<sub>2</sub>), 17.6 (CH<sub>3</sub>), 15.7 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 3496, 2927, 1774, 1454, 1385, 1170, 1017. HRMS (EI) *m/z* C<sub>20</sub>H<sub>32</sub>O<sub>3</sub> [M + Na]<sup>+</sup> requires 343.2256, found 343.2249.

*CBS reduction of the ketone **163** - general methods*



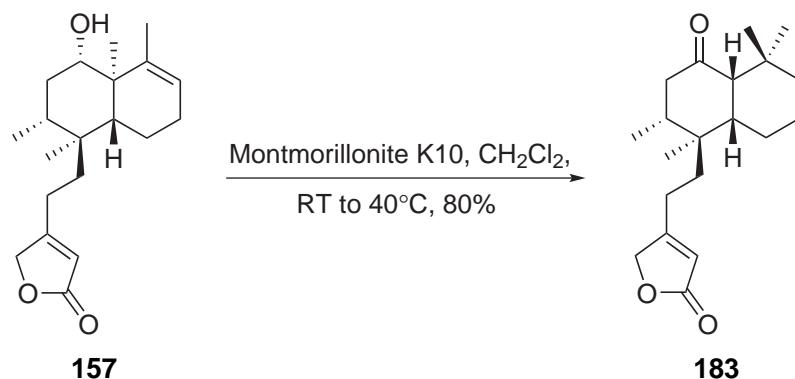
**Method A**

A stirred solution of (*R*)-(+)-2-methyl-CBS (1 mg, 0.003 mmol, 0.1 eq.) in anhydrous tetrahydrofuran (0.60 mL) was cooled to  $-84^{\circ}\text{C}$  under nitrogen. A solution of borane-dimethyl sulfide complex (1 M in tetrahydrofuran, 20  $\mu\text{L}$ , 0.019 mmol, 0.6 eq.) was added and the solution was stirred for a further 5 minutes. The ketone **163** (10 mg, 0.032 mmol, 1 eq.) was then added and the resulting reaction mixture was stirred at  $-84^{\circ}\text{C}$  for 2 hours and allowed to warm to  $10^{\circ}\text{C}$  overnight. The reaction was quenched with methanol (5 mL) and the solution was concentrated under reduced pressure to leave a colourless oil which contained the alcohols **157** and **164** (50:50) with an 18% conversion.

**Method B**

A solution of borane-dimethyl sulfide complex (0.96 M in tetrahydrofuran, 42  $\mu\text{L}$ , 0.032 mmol, 1 eq.) was added to (*S*)-(−)-2-methyl-CBS (1 mg, 0.003 mol, 0.1 eq.) in anhydrous tetrahydrofuran (0.30 mL) at room temperature under nitrogen. After stirring for 20 minutes, the mixture was cooled to  $0^{\circ}\text{C}$  and a solution of the ketone **163** (10 mg, 0.032 mmol, 1 eq.) in anhydrous tetrahydrofuran (0.30 mL) was added dropwise over 10 minutes. The reaction was allowed to warm to  $10^{\circ}\text{C}$  overnight, then quenched with methanol (5 mL). The solution was concentrated *in vacuo* to afford a colourless oil which contained the alcohols **157** and **164** (23:77) with a 94% conversion.

*Preparation of the montmorillonite K10 rearrangement product 183*

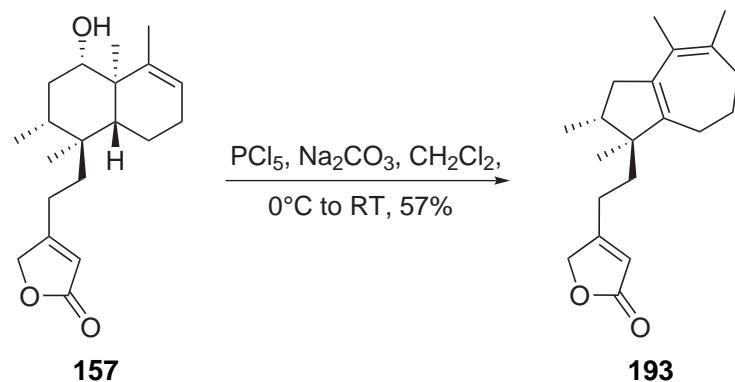


Activated montmorillonite K10<sup>1</sup> (15 mg) was added to a solution of the alcohol **157** (10 mg, 0.031 mmol, 1 eq.) in dry dichloromethane (0.50 mL) under a nitrogen atmosphere. The solution was stirred at room temperature for 1 day, then heated at reflux for 1 week. The reaction mixture was filtered and diluted with dichloromethane (10 mL). The solution was washed with water (1 x 20 mL) and back-extracted with dichloromethane (1 x 5 mL). The organic phases were combined, dried ( $\text{CaCl}_2$ ) and concentrated *in vacuo* to leave a yellow oil. Radial chromatography (20% ethyl acetate in petrol to 40% ethyl acetate) gave the rearrangement product **183** as a pale yellow oil (8 mg, 80%).  $[\alpha]_D^{24} -6.1$  (*c* 0.002,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.86 (1H, m, *J* = 1.7 Hz), 4.75 (2H, d, *J* = 1.7 Hz), 2.32 (1H, dd, *J* = 13.6, 1.0 Hz), 2.27-2.22 (2H, m), 2.13 (1H, dd, *J* = 13.6, 3.8 Hz), 2.04 (1H, s), 2.00 (1H, d, *J* = 11.9 Hz), 1.84 (1H, ddd, *J* = 13.6, 6.5, 3.8 Hz), 1.73-1.69 (1H, m), 1.68 (1H, d, *J* = 1.0 Hz), 1.64 (2H, dd, *J* = 9.8, 6.5 Hz), 1.40 (1H, dt, *J* = 13.6, 3.3 Hz), 1.33-1.28 (2H, m), 1.20 (1H, dd, *J* = 12.6, 4.2 Hz), 1.12 (3H, s), 1.07 (3H, s), 0.97 (3H, s), 0.88 (3H, d, *J* = 6.8 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  210.0 (C), 173.9 (C), 170.2 (C), 115.5 (CH), 73.2 (CH<sub>2</sub>), 57.8 (CH), 47.8 (CH<sub>2</sub>), 43.2 (CH<sub>2</sub>), 43.1 (CH), 38.8 (C), 37.7 (CH), 33.7 (CH<sub>2</sub>), 32.9 (C), 31.0 (CH<sub>3</sub>), 29.9 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 21.5 (CH<sub>2</sub>), 20.3 (CH<sub>3</sub>), 15.9 (CH<sub>3</sub>), 15.1 (CH<sub>3</sub>). IR (film,  $\text{cm}^{-1}$ ): 2926, 2871, 2860, 1779, 1749, 1706, 1639, 1457. HRMS (ESI) *m/z* C<sub>20</sub>H<sub>30</sub>O<sub>3</sub> [M + H]<sup>+</sup> requires 319.2273, found 319.2273.

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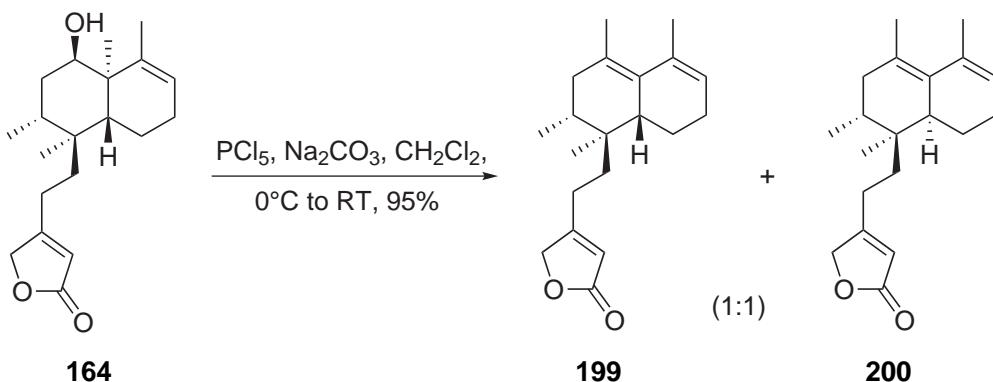
<sup>1</sup>Montmorillonite K10 was activated by drying it in an oven at 120°C overnight.

*Preparation of the PCl<sub>5</sub> rearrangement product 193*



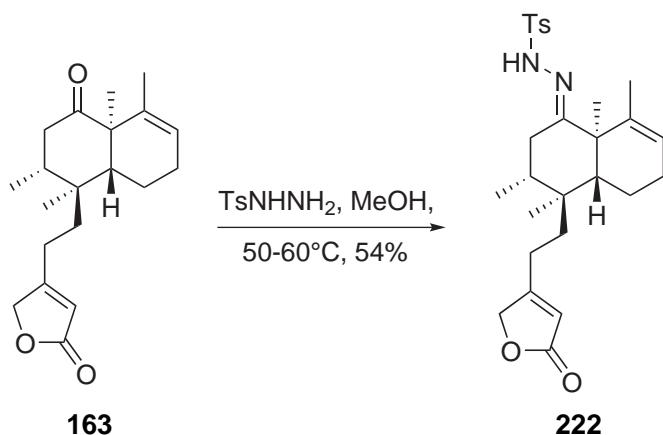
A stirred solution of the alcohol **157** (32 mg, 0.10 mmol, 1 eq.) in freshly dried dichloromethane (1 mL) was cooled to 0°C under nitrogen. Anhydrous sodium carbonate (0.011 g, 0.100 mmol, 1 eq.) was added, followed by phosphorus pentachloride (0.028 g, 0.131 mmol, 1.3 eq.). The reaction was warmed to room temperature overnight, then diluted with dichloromethane (10 mL). The reaction mixture was washed with water (3 x 10 mL), the organic extract was dried (CaCl<sub>2</sub>) then concentrated under reduced pressure to yield a yellow residue. Radial chromatography (100% petrol to 10% ethyl acetate in petrol) afforded **193** as a colourless oil (17 mg, 57%).  $[\alpha]_D^{24} -18$  (*c* 0.002, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.84 (1H, m, *J* = 1.7 Hz), 4.73 (2H, d, *J* = 1.7 Hz), 2.53-2.44 (1H, m), 2.43-2.34 (1H, m), 2.31-2.17 (2H, m), 2.06-1.98 (3H, m), 1.97-1.87 (3H, m), 1.83 (3H, d, *J* = 0.8 Hz), 1.67 (3H, q, *J* = 0.8 Hz), 1.62 (2H, d), 1.04 (1H, dd, *J* = 6.9, 4.7 Hz), 0.96 (3H, d, *J* = 6.9 Hz), 0.85 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  174.3 (C), 171.5 (C), 144.7 (C), 138.9 (C), 134.8 (C), 127.5 (C), 115.1 (CH), 73.3 (CH<sub>2</sub>), 52.0 (C), 40.9 (CH<sub>2</sub>), 37.6 (CH), 35.4 (CH<sub>2</sub>), 34.9 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 24.7 (CH<sub>2</sub>), 20.9 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 16.5 (CH<sub>3</sub>), 15.1 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2956, 2921, 2869, 2852, 1779, 1747, 1638, 1448, 1169, 1128, 1030. HRMS (EI) *m/z* C<sub>20</sub>H<sub>29</sub>O<sub>2</sub> [M + H]<sup>+</sup> requires 301.2168, found 301.2172.

*Preparation of the PCl<sub>5</sub> rearrangement products **199** and **200***



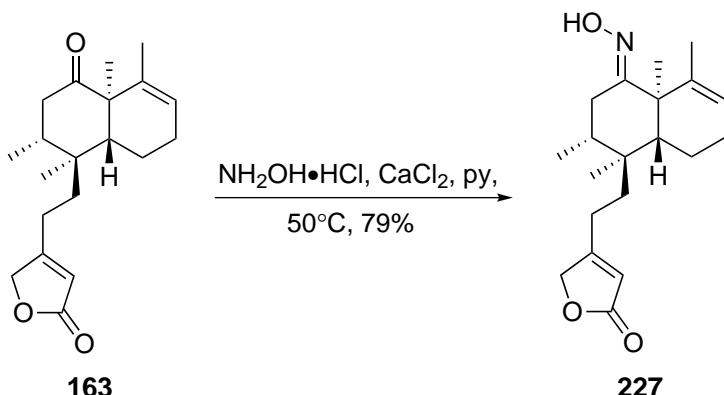
Phosphorus pentachloride (13 mg, 0.061 mmol, 1.3 eq.) and anhydrous sodium carbonate (5 mg, 0.047 mmol, 1 eq.) were added to a stirred solution of the  $\beta$ -alcohol **164** (15 mg, 0.047 mmol, 1 eq.) in dry dichloromethane (1 mL) at  $0^\circ\text{C}$ . The reaction was stirred under nitrogen at  $0^\circ\text{C}$  for 30 minutes and then warmed to room temperature for 3 hours. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water (3 x 20 mL). The organic phase was dried ( $\text{CaCl}_2$ ) and concentrated *in vacuo* to afford a yellow oil. Radial chromatography (1% triethylamine treated silica, 100% petrol) afforded a colourless oil (15 mg, 95%) containing a 1:1 mixture of two compounds tentatively assigned as **199** and **200**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.85 (2H, m,  $J = 1.7$  Hz), 5.51 (1H, s), 5.15 (1H, s), 4.74 (4H, m,  $J = 1.7$  Hz), 2.38-2.29 (4H, m), 2.21-2.09 (4H, m), 1.99 (3H, m), 1.97 (3H, dd,  $J = 2.2, 1.4$  Hz), 1.95-1.89 (3H, m), 1.82 (6H, br s), 1.80-1.69 (6H, m), 1.63 (7H, m), 0.86 (3H, d,  $J = 7.2$  Hz), 0.83 (3H, d,  $J = 6.7$  Hz), 0.65 (3H, s), 0.56 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  174.2 (2 x C), 171.3 (C), 171.2 (C), 134.4 (C), 132.9 (C), 132.4 (C), 131.8 (CH), 131.1 (C), 130.5 (C), 128.5 (C), 127.5 (CH), 115.22 (CH), 115.18 (CH), 73.2 (2 x CH<sub>2</sub>), 43.3 (CH), 42.8 (CH), 41.1 (CH<sub>2</sub>), 39.0 (C), 37.3 (CH), 36.8 (C), 35.1 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 33.2 (CH), 27.3 (CH<sub>2</sub>), 25.6 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 24.4 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 22.5 (CH<sub>3</sub>), 22.4 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 15.7 (CH<sub>3</sub>), 15.14 (CH<sub>3</sub>), 15.13 (CH<sub>3</sub>), 14.7 (CH<sub>3</sub>).

*Preparation of the tosyl hydrazone 222*



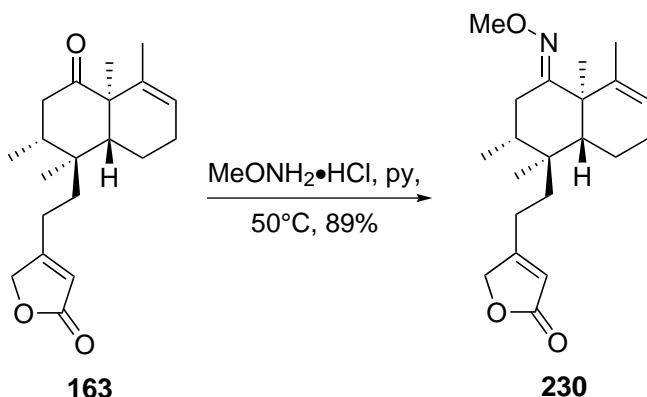
A solution of the ketone **163** (17 mg, 0.05 mmol, 1 eq.) and tosyl hydrazide (15 mg, 0.08 mmol, 1.5 eq.) in methanol (1 mL) was heated to 50-60°C under nitrogen. After 2 days, the solution was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (20 mL). The mixture was washed with 1 M hydrochloric acid (20 mL), followed by water (2 x 20 mL). The organic phase was dried ( $\text{CaCl}_2$ ) and concentrated *in vacuo* to give a colourless oil. Radial chromatography (20% ethyl acetate in petrol to 50% ethyl acetate) afforded **222** as a colourless oil (14 mg, 54%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.82 (2H, d,  $J = 8.1$  Hz), 7.58 (1H, br s), 7.27 (2H, d,  $J = 8.1$  Hz), 5.78 (1H, m,  $J = 1.6$  Hz), 5.32 (1H, d,  $J = 5.3$  Hz), 4.70-4.64 (2H, m), 2.42-2.38 (2H, m), 2.40 (3H, s), 2.05 (2H, t,  $J = 13.4$  Hz), 2.00-1.86 (3H, m), 1.64-1.61 (3H, m), 1.58 (2H, dd,  $J = 12.2, 5.3$  Hz), 1.50-1.40 (3H, m), 1.31 (1H, dd,  $J = 10.7, 2.8$  Hz), 1.23 (3H, s), 0.88 (3H, d,  $J = 6.7$  Hz), 0.86 (3H, s). Further characterisation could not be completed due to hydrolysis back to **163**.

*Preparation of the oxime 227*



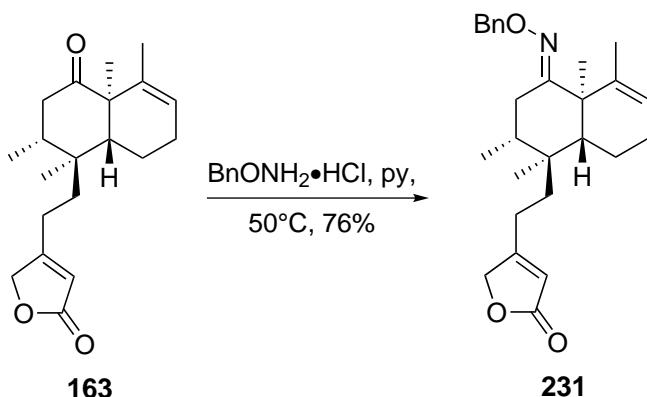
A stirred solution of the oxime **227** (22 mg, 0.07 mmol, 1 eq.),  $\text{CaCl}_2$  (~50 mg) and hydroxylamine hydrochloride (7.2 mg, 0.10 mmol, 1.5 eq.) was dissolved in pyridine (1 mL) and heated to  $50^\circ\text{C}$  for 2 days. The reaction mixture was allowed to cool and diethyl ether (20 mL) was added. The organic phase was washed with 1 M hydrochloric acid (2 x 20 mL), 10% sodium bicarbonate solution (2 x 20 mL), water (2 x 20 mL) and brine (20 mL). The organic phase was dried and concentrated under reduced pressure to afford the oxime **227** as a colourless oil (18 mg, 79%) without the need for further purification.  $[\alpha]_D^{26} -174$  (*c* 0.015,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.10 (1H, s), 5.82 (1H, m, *J* = 1.7 Hz), 5.43 (1H, m), 4.70 (2H, d, *J* = 1.7 Hz), 3.19 (1H, dd, *J* = 12.6, 3.6 Hz), 2.27-2.16 (1H, m), 2.15-2.08 (1H, m), 2.06-1.95 (2H, m), 1.86 (1H, t, *J* = 12.6 Hz), 1.80 (3H, dt, *J* = 2.4, 1.3 Hz), 1.77-1.66 (3H, m), 1.58-1.53 (1H, m), 1.53-1.49 (2H, dd, *J* = 6.6, 3.6 Hz), 1.32 (3H, s), 0.95 (3H, d, *J* = 6.6 Hz), 0.92 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  174.0 (C), 170.5 (C), 165.6 (C), 140.1 (C), 124.0 (CH), 115.3 (CH), 73.1 ( $\text{CH}_2$ ), 52.1 (CH), 48.2 (C), 39.5 (C), 38.9 ( $\text{CH}_3$ ), 35.7 ( $\text{CH}_2$ ), 30.5 (CH), 27.1 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ), 20.0 ( $\text{CH}_3$ ), 18.75 ( $\text{CH}_3$ ), 18.69 ( $\text{CH}_2$ ), 16.2 ( $\text{CH}_3$ ). IR (film,  $\text{cm}^{-1}$ ): 3374, 2957, 2929, 1780, 1744, 1636, 1444, 930, 730. HRMS (ESI) *m/z*  $\text{C}_{20}\text{H}_{29}\text{NO}_3$  [M + H]<sup>+</sup> requires 332.2225, found 332.2221.

*Preparation of the O-methyl oxime 230*



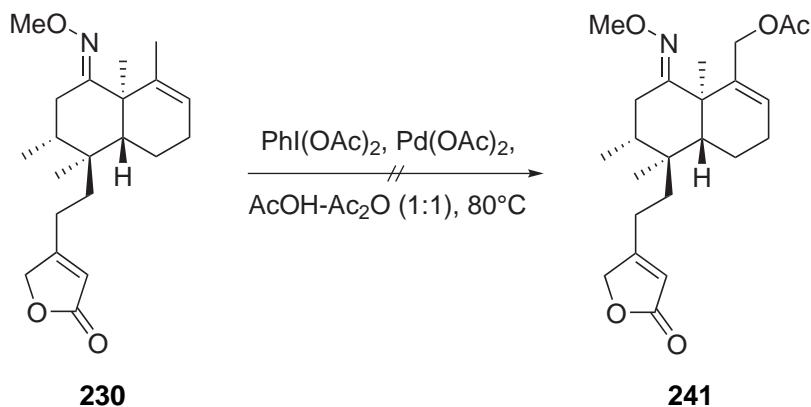
Methoxyamine hydrochloride (22 mg, 0.27 mmol, 1.3 eq.) was added in one portion to a solution of the ketone **163** (65 mg, 0.21 mmol, 1 eq.) in pyridine (2 mL) under nitrogen. The reaction was stirred at 50°C for 20 hours. The reaction mixture was allowed to cool before diethyl ether (100 mL) was added. The solution was washed with 1 M hydrochloric acid (2 x 50 mL), 10% sodium bicarbonate solution (1 x 50 mL) and water (1 x 50 mL). The organic phase was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford **230** as a colourless oil (63 mg, 89%). [α]<sub>D</sub><sup>25</sup> -210 (c 0.001, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.82 (1H, m, *J* = 1.7 Hz), 5.39 (1H, m), 4.70 (2H, d, *J* = 1.7 Hz), 3.81 (3H, s), 3.09 (1H, dd, *J* = 12.9, 3.7 Hz), 2.27-2.11 (2H, m), 2.10-2.01 (2H, m), 1.86 (3H, dt, *J* = 2.3, 1.3 Hz), 1.80 (1H, d, *J* = 12.9 Hz), 1.70-1.64 (2H, m), 1.62 (1H, d, *J* = 5.2 Hz), 1.55 (1H, d, *J* = 4.6 Hz), 1.52-1.46 (4H, m), 1.29 (3H, s), 0.92 (3H, d, *J* = 6.6 Hz), 0.90 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 173.9 (C), 170.7 (C), 163.9 (C), 140.4 (C), 123.5 (CH), 115.0 (CH), 73.1 (CH<sub>2</sub>), 61.2 (CH<sub>3</sub>), 51.4 (CH), 47.7 (C), 39.3 (C), 38.7 (CH), 35.5 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 20.14 (CH<sub>3</sub>), 20.08 (CH<sub>3</sub>), 18.54 (CH<sub>2</sub>), 18.50 (CH<sub>3</sub>), 16.0 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2954, 2936, 1779, 1745, 1637, 1045. HRMS (EI) *m/z* C<sub>21</sub>H<sub>31</sub>NO<sub>3</sub> [M]<sup>+</sup> requires 346.2382, found 346.2387.

*Preparation of the O-benzyl oxime 231*



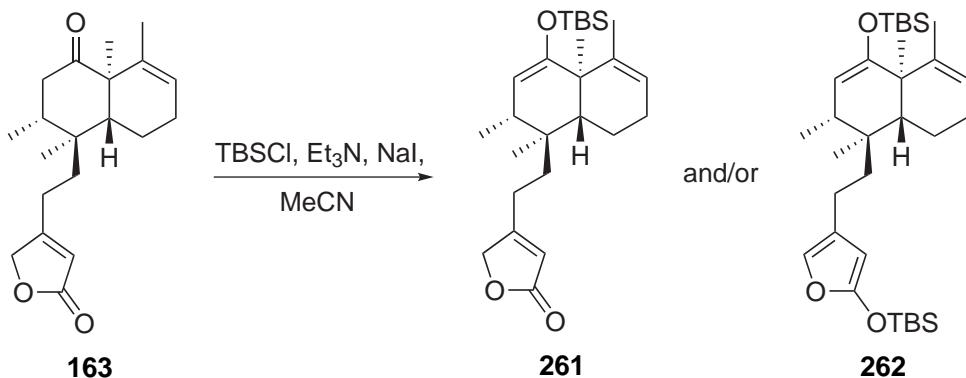
*O*-Benzylhydroxylamine hydrochloride (35 mg, 0.218 mmol, 1.3 eq.) was added to a solution of the ketone **163** (53 mg, 0.167 mmol, 1 eq.) in pyridine (1 mL) under nitrogen. The reaction mixture was stirred at 50°C in an oil bath for 1 day and allowed to cool to room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and washed with 1 M hydrochloric acid (2 x 20 mL), 10% sodium bicarbonate (1 x 20 mL) and water (3 x 20 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to afford a colourless oil. Radial chromatography (1% triethylamine treated silica, 10% ethyl acetate in petrol to 100% ethyl acetate) gave **231** as a colourless oil (54 mg, 76%).  $[\alpha]_D^{25} -144$  (*c* 0.001,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.36-7.27 (5H, m), 5.82 (1H, m, *J* = 1.7 Hz), 5.37 (1H, m), 5.11 (1H, d, *J* = 12.2 Hz), 5.05 (1H, d, *J* = 12.2 Hz), 4.70 (2H, d, *J* = 1.7 Hz), 3.18 (1H, dd, *J* = 12.7, 3.8 Hz), 2.21-2.08 (2H, m), 2.06-2.00 (2H, m), 1.86-1.79 (1H, m), 1.77 (3H, m), 1.71-1.60 (3H, m), 1.53-1.48 (3H, m), 1.27 (3H, s), 0.90 (3H, d, *J* = 6.5 Hz), 0.89 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  174.0 (C), 170.7 (C), 164.8 (C), 140.6 (C), 138.8 (C), 128.35 (CH), 128.31 (CH), 127.6 (CH), 125.6 (CH), 123.4 (CH), 115.2 (CH), 75.4 (CH<sub>2</sub>), 73.2 (CH<sub>2</sub>), 51.6 (CH), 48.0 (C), 39.4 (C), 38.8 (CH), 35.6 (CH<sub>2</sub>), 30.5 (CH), 26.96 (CH<sub>2</sub>), 26.86 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 20.22 (CH<sub>3</sub>), 20.17 (CH<sub>3</sub>), 18.68 (CH<sub>2</sub>), 18.64 (CH<sub>3</sub>), 16.2 (CH<sub>3</sub>). IR (film,  $\text{cm}^{-1}$ ): 3027, 2956, 2926, 2874, 1779, 1748, 1637, 1454, 1168, 1030. HRMS (EI) *m/z* C<sub>27</sub>H<sub>35</sub>NO<sub>3</sub> [M + H]<sup>+</sup> requires 422.2700, found 422.2704.

### *Attempted C-H activation of 230*



The oxime **230** (15 mg, 0.043 mmol, 1 eq.), PhI(OAc)<sub>2</sub> (21 mg, 0.065 mmol, 1.5 eq.) and Pd(OAc)<sub>2</sub> (0.5 mg, 0.002 mmol, 0.05 eq.) were dissolved in a glacial acetic acid-acetic anhydride solution (1:1, 4 mL). The reaction was sealed and heated at 80°C overnight. Ethyl acetate (30 mL) was added and the solution was washed with water (4 x 30 mL). The organic phase was dried and filtered prior to concentration *in vacuo*. An orange residue was recovered which did not contain any of the intended product **241**.

*Preparation of the silyl enol ethers 261 and 262 with TBSCl*



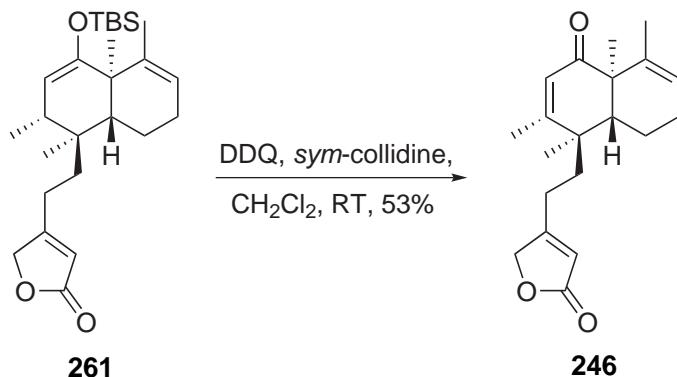
**Compound 261:** The ketone **163** (0.103 g, 0.326 mmol, 1 eq.) was dissolved in freshly dried and distilled acetonitrile (2 mL) and cooled to 0°C under nitrogen. Dry sodium iodide (0.49 g, 3.26 mmol, 10 eq.) was added, followed by dry triethylamine (0.45 mL, 0.33 g, 3.26 mmol, 10 eq.). After 5 minutes of stirring, recrystallised TBSCl (0.49 g, 3.26 mmol, 10 eq.) was added in two portions to the reaction mixture. Stirring was continued and the reaction was warmed to room temperature over 2 days. Petrol

(20 mL) was added to the reaction mixture and the solution was washed with water (~10 x 20 mL), dried ( $\text{CaCl}_2$ ), then concentrated under reduced pressure to afford a yellow/orange oil. Radial chromatography (1% triethylamine treated silica, petrol) afforded the mono TBS ether **261** as a colourless oil (0.090 g, 64%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.83 (1H, m,  $J$  = 1.7 Hz), 5.08 (1H, m), 4.73 (2H, d,  $J$  = 1.7 Hz), 4.41 (1H, d,  $J$  = 1.7 Hz), 2.35 (1H, dd,  $J$  = 7.2, 1.7 Hz), 2.30-2.24 (1H, m), 2.22-2.20 (1H, m), 2.18-2.02 (2H, m), 1.83 (3H, m), 1.76 (1H, s), 1.74-1.65 (1H, m), 1.63 (1H, d,  $J$  = 4.4 Hz), 1.59 (1H, dd,  $J$  = 9.0, 5.1 Hz), 1.55-1.52 (1H, m), 1.15 (3H, s), 0.95 (9H, s), 0.84 (3H, d,  $J$  = 7.2 Hz), 0.74 (3H, s), 0.21 (3H, s), 0.17 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  174.1 (C), 171.0 (C), 153.6 (C), 146.0 (C), 120.4 (CH), 115.2 (CH), 108.1 (CH), 73.2 ( $\text{CH}_2$ ), 46.5 (CH), 44.3 (C), 37.3 (C), 35.4 (CH), 34.8 ( $\text{CH}_2$ ), 26.1 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_3$ ), 22.3 ( $\text{CH}_2$ ), 21.0 ( $\text{CH}_3$ ), 18.5 (C), 17.7 ( $\text{CH}_3$ ), 17.1 ( $\text{CH}_2$ ), 16.1 ( $\text{CH}_3$ ), -3.4 ( $\text{CH}_3$ ), -5.1 ( $\text{CH}_3$ ). IR (film,  $\text{cm}^{-1}$ ): 2957, 2930, 2858, 1780, 1750, 1639, 1253, 1212, 1159, 1071, 1031, 837, 778. HRMS (EI)  $m/z$  [M + H]<sup>+</sup>  $\text{C}_{26}\text{H}_{42}\text{O}_3\text{Si}$  requires 431.2981, found 431.2990.

**Compound 262:** The ketone **163** (0.040 g, 0.126 mmol, 1 eq.) was dissolved in freshly dried and distilled acetonitrile (0.5 mL) under nitrogen. Dry triethylamine (0.176 mL, 0.126 g, 1.26 mmol, 10 eq.) was added, followed by dry sodium iodide (0.49 g, 3.26 mmol, 10 eq.). After 5 minutes of stirring, recrystallised TBSCl (0.191 g, 1.26 mmol, 10 eq.) was added in one portion to the reaction mixture. Stirring was continued at room temperature. After 3 days, the reaction mixture was diluted with petrol (20 mL) and stirred for 5 minutes. The organic phase was washed with water (4 x 20 mL), dried ( $\text{CaCl}_2$ ) then concentrated under reduced pressure to afford a colourless residue. Radial chromatography (1% triethylamine treated silica, petrol) afforded the di TBS ether **262** as a colourless oil (0.029 g, 43%).  $[\alpha]_D^{25} +33$  (*c* 0.01,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.59 (1H, d,  $J$  = 1.2 Hz), 5.09 (1H, m,  $J$  = 3.7, 1.6 Hz), 5.00 (1H, d,  $J$  = 1.2 Hz), 4.43 (1H, d,  $J$  = 1.6 Hz), 2.43 (1H, qd,  $J$  = 7.2, 1.6 Hz), 2.28-2.20 (1H, m), 2.17-2.09 (3H, m), 1.85-1.83 (3H, m), 1.70-1.56 (3H, m), 1.50 (2H, m), 1.15 (3H, s), 0.96 (9H, s), 0.95 (9H, s), 0.84 (3H, d,  $J$  = 7.2 Hz), 0.70 (3H, s), 0.23 (6H, s), 0.21 (3H, s), 0.17 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  156.8 (C), 153.5 (C), 146.0 (C), 127.7 (CH), 127.4 (C), 120.6 (CH), 108.9 (CH), 85.2 (CH), 46.6 (CH), 44.3 (C), 37.47 ( $\text{CH}_2$ ), 37.42 (C), 35.4 (CH), 26.2 ( $\text{CH}_3$ ), 25.6 ( $\text{CH}_3$ ), 25.0 ( $\text{CH}_2$ ), 23.3 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 19.1 ( $\text{CH}_2$ ), 18.6 (C), 18.2 (C),

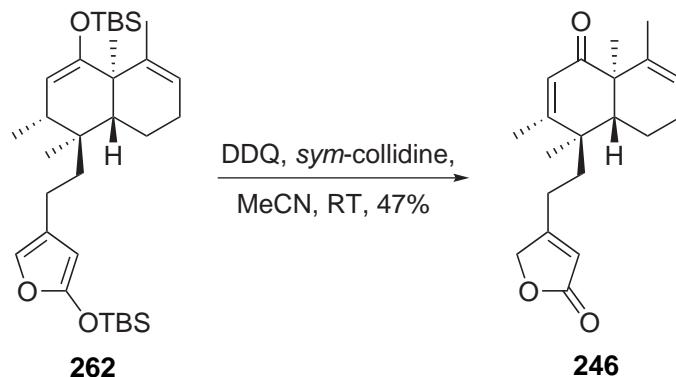
17.9 (CH<sub>3</sub>), 17.0 (CH<sub>2</sub>), 16.1 (CH<sub>3</sub>), -3.4 (CH<sub>3</sub>), -4.6 (CH<sub>3</sub>), -5.1 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2957, 2930, 2858, 1781, 1751, 1624, 1472, 1255, 1211, 1160, 1090, 838, 778. HRMS (ESI): a molecular ion could not be found.

*Preparation of the enone **246** (method 1)*



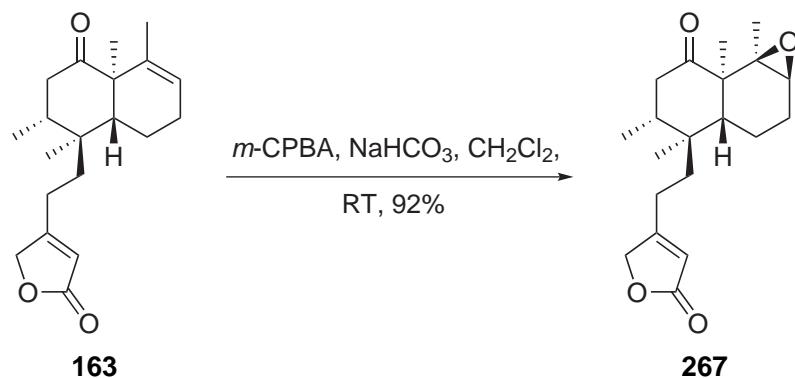
A solution of the mono TBS ether **261** (31 mg, 0.072 mmol, 1 eq.) in freshly dried dichloromethane (3 mL) was stirred at room temperature under nitrogen. DDQ (32 mg, 0.140 mmol, 2 eq.) was added in one portion, followed by dry *sym*-collidine (9.5  $\mu$ L, 0.072 mmol, 1 eq.). After 17 hours, the reaction was diluted with dichloromethane (20 mL). The organic was washed with 5% sodium bicarbonate solution (1 x 20 mL), water (3 x 20 mL) and dried ( $MgSO_4$ ). Concentration under reduced pressure afforded an orange oil. Radial chromatography (1% triethylamine treated silica, petrol to 10% ethyl acetate to 50% ethyl acetate) afforded **246** as a crystalline white solid (12 mg, 53%).  $[\alpha]_D^{25}$  -88 (*c* 0.001, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.83 (2H, m), 5.46 (1H, d, *J* = 5.6 Hz), 4.68 (2H, d, *J* = 1.7 Hz), 2.23 (1H, m, *J* = 4.4, 1.1 Hz), 2.15-2.06 (1H, m), 1.98 (3H, dd, *J* = 2.4, 1.4 Hz), 1.95 (3H, d, *J* = 1.4 Hz), 1.90 (1H, dd, *J* = 13.4, 4.4 Hz), 1.85 (3H, d, *J* = 1.4 Hz), 1.74-1.69 (1H, m), 1.68-1.59 (3H, m), 1.33 (3H, s), 1.21 (3H, s). <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>CO)  $\delta$  5.90 (1H, m, *J* = 1.7 Hz), 5.74 (1H, d, *J* = 1.2 Hz), 5.44-5.37 (1H, m), 4.83 (2H, d, *J* = 1.7 Hz), 2.46-2.37 (1H, m), 2.03-1.98 (4H, m), 1.95 (3H, m), 1.91 (3H, d, *J* = 1.2 Hz), 1.90-1.80 (2H, m), 1.76 (1H, s), 1.65-1.57 (1H, m), 1.31 (3H, s), 1.23 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  203.2 (C), 173.8 (C), 169.7 (C), 159.0 (C), 138.3 (C), 128.0 (CH), 124.6 (CH), 115.4 (CH), 73.1 (CH<sub>2</sub>), 49.9 (C), 43.5 (CH), 42.4 (C), 35.5 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 23.7 (CH<sub>2</sub>), 21.2 (CH<sub>3</sub>), 20.9 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 19.5 (CH<sub>2</sub>), 19.0 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2950, 1779, 1744, 1671, 1636, 1440, 1174, 1029. HRMS (EI) *m/z* [M + H]<sup>+</sup> C<sub>20</sub>H<sub>26</sub>O<sub>3</sub> requires 315.2019, found 315.1966.

*Preparation of the enone **246** (method 2)*



The di TBS ether **262** (30 mg, 0.055 mmol, 1 eq.) was dissolved in dry acetonitrile (3 mL) along with DDQ (50 mg, 0.220 mmol, 4 eq.) and dry *sym*-collidine (14.5  $\mu$ L, 0.0110 mmol, 2 eq.). The reaction was stirred under a nitrogen atmosphere at room temperature for 5 hours. Water (100 mL) was added and the solution was extracted with dichloromethane (4 x 40 mL). The organic phase was washed with sodium bicarbonate solution (1 x 50 mL) and dried ( $\text{MgSO}_4$ ). The solution was concentration *in vacuo* to afford an orange solid. Radial chromatography (1% triethylamine treated silica, petrol to 20% ethyl acetate to 100% ethyl acetate) afforded **246** as a crystalline white solid (8 mg, 47%). Spectral data of **246** matched that provided above.

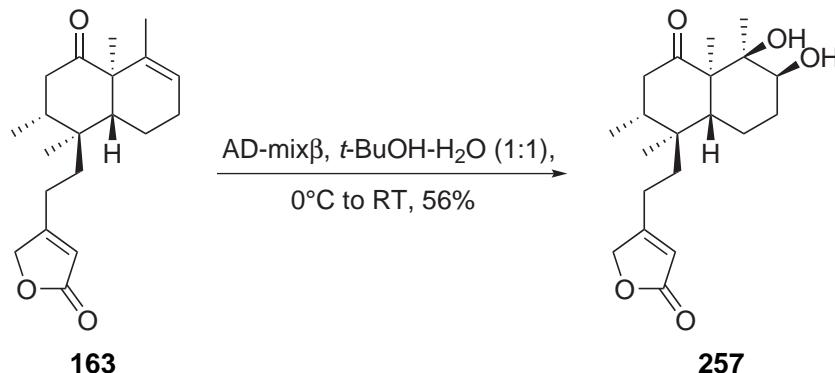
*Epoxidation of **163***



*m*-CPBA (20 mg, 0.116 mmol, 1.5 eq.) and sodium bicarbonate (13 mg, 0.155 mmol, 2 eq.) were added to a solution of the ketone **163** (24 mg, 0.076 mmol, 1 eq.) in dichloromethane (2 mL) under nitrogen. The reaction was stirred at room temperature for

1.5 hours. 20% Sodium thiosulfate solution (20 mL) was added to the reaction mixture and stirred for a further 5 minutes. The organic phase was washed with water (2 x 50 mL) and dried over MgSO<sub>4</sub>. Concentration under reduced pressure provided the epoxide **267** as a colourless oil (23 mg, 92%).  $[\alpha]_D^{25} -44$  (*c* 0.005, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.82 (1H, m, *J* = 1.7 Hz), 4.72 (2H, d, *J* = 1.7 Hz), 2.77 (1H, d, *J* = 4.9 Hz), 2.68 (1H, t, *J* = 12.9 Hz), 2.26-2.13 (2H, m), 2.10 (1H, dd, *J* = 12.9, 3.8 Hz), 2.05-1.88 (3H, m), 1.88-1.78 (1H, m), 1.68-1.59 (2H, m), 1.54-1.47 (2H, m), 1.44 (3H, s), 1.39 (3H, s), 0.98 (3H, s), 0.91 (3H, d, *J* = 6.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  211.9 (C), 173.9 (C), 170.1 (CH), 115.4 (CH), 73.2 (CH<sub>2</sub>), 62.7 (C), 58.1 (CH), 52.4 (C), 43.4 (CH<sub>2</sub>), 41.6 (CH), 39.4 (CH), 38.8 (C), 35.9 (CH<sub>2</sub>), 23.2 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 20.1 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>), 17.2 (CH<sub>3</sub>), 16.8 (CH<sub>2</sub>), 16.2 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2960, 1778, 1744, 1708, 1637, 1449, 1380, 1285, 1171, 1131, 1026, 887, 859. HRMS (EI) *m/z* [M + H]<sup>+</sup> C<sub>20</sub>H<sub>28</sub>O<sub>4</sub> requires 333.2066, found 333.2081.

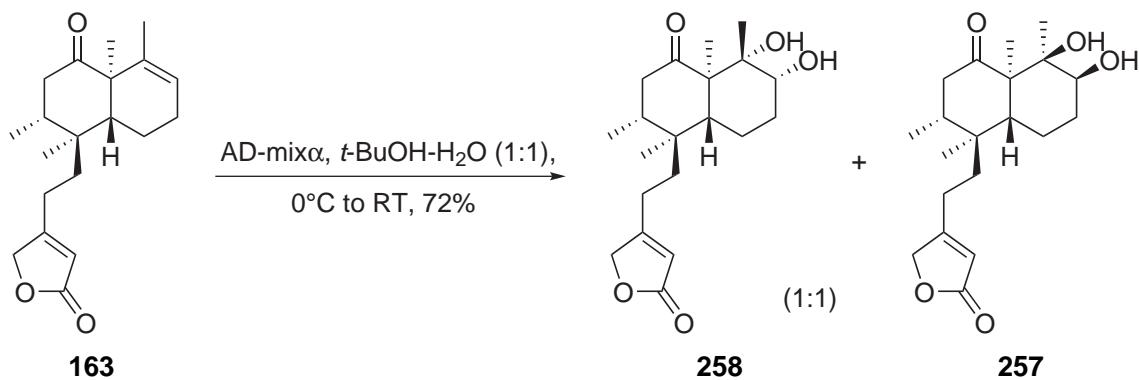
#### *Preparation of the diol **257***



AD-mix $\beta$  (88 mg) was dissolved in 1:1 *tert*-butanol-water and the phases were mixed for 15 minutes under nitrogen. The mixture was cooled to 0°C and the ketone **163** (20 mg, 0.063 mmol, 1 eq.) was introduced in one portion. After 2 days, the reaction was quenched with sodium sulfite (15 mg) at 0°C for 30 minutes. Ethyl acetate (50 mL) was added and the mixture was washed with water (3 x 50 mL), followed by back-extraction of the combined aqueous phases with ethyl acetate (20 mL). The organic phases were combined, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a colourless oil. Radial chromatography (1% triethylamine treated silica, 20% ethyl acetate in petrol to 100% ethyl acetate) furnished the  $\beta$ -diol **257** as a colourless oil (12 mg, 56%).  $[\alpha]_D^{25} -33$

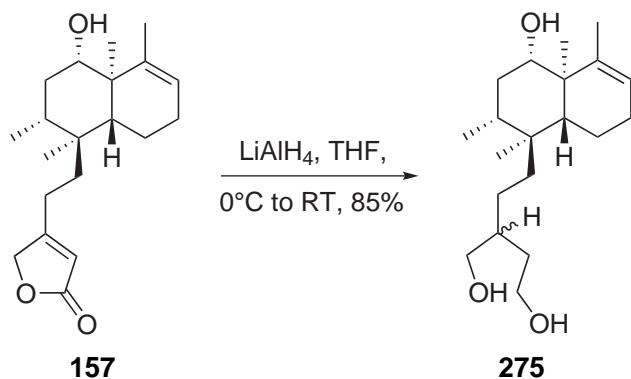
(*c* 0.004,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.85 (1H, m,  $J = 1.7$  Hz), 4.73 (2H, d,  $J = 1.7$  Hz), 3.40 (1H, dd,  $J = 10.8, 4.9$  Hz), 3.34 (1H, s), 2.78 (1H, dd,  $J = 13.5, 12.3$  Hz), 2.20 (2H, dd,  $J = 9.7, 4.9$  Hz), 2.03 (1H, dd,  $J = 12.3, 3.3$  Hz), 1.96-1.88 (2H, m), 1.74 (1H, dd,  $J = 12.3, 5.5$  Hz), 1.70 (1H, dd,  $J = 11.6, 6.1$  Hz), 1.62-1.55 (3H, m), 1.53-1.49 (2H, m), 1.46 (3H, s), 1.28 (3H, s), 1.01 (3H, s), 0.93 (3H, d,  $J = 6.8$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  216.6 (C), 173.8 (C), 169.9 (C), 115.6 (CH), 76.2 (C), 73.2 (CH<sub>2</sub>), 72.4 (CH), 56.9 (C), 44.6 (CH), 43.8 (CH<sub>2</sub>), 40.4 (CH), 39.2 (C), 35.7 (CH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 19.9 (CH<sub>2</sub>), 18.4 (CH<sub>3</sub>), 16.2 (CH<sub>3</sub>), 16.0 (CH<sub>3</sub>). IR (film,  $\text{cm}^{-1}$ ): 3446, 2926, 2855, 1779, 1745, 1698, 1637, 1450, 1379, 1131, 1029. HRMS (EI)  $m/z$  [M + H]<sup>+</sup> requires C<sub>20</sub>H<sub>31</sub>O<sub>5</sub> 351.2171, found 351.2180.

*Preparation of the diol mixture 258 and 257*



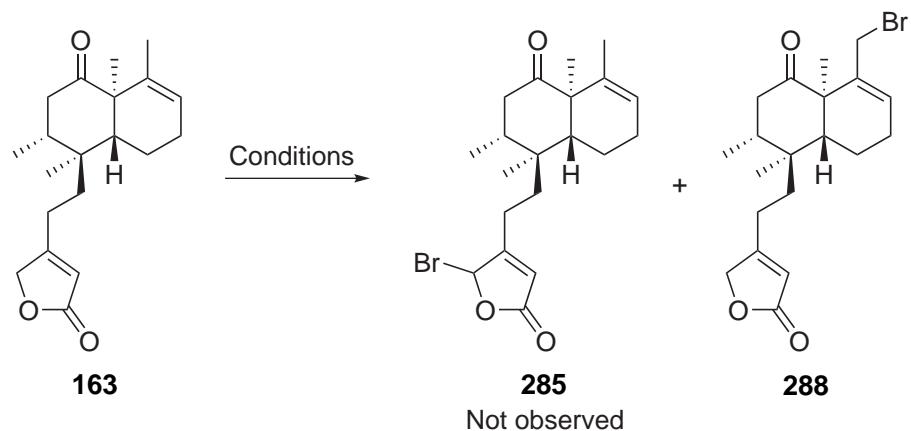
AD-mix $\alpha$  (140 mg) was dissolved in 1:1 *tert*-butanol-water and the phases were mixed for 15 minutes under nitrogen. The mixture was cooled to 0°C and the ketone **163** (23 mg, 0.073 mmol, 1 eq.) was added in one portion. After 4 days at room temperature, the reaction was quenched with sodium sulfite (19 mg) at 0°C for 30 minutes. Ethyl acetate (50 mL) was added and the mixture was washed with water (3 x 50 mL), followed by back-extraction of the combined aqueous phases with ethyl acetate (20 mL). The organic phases were combined, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give a pale yellow oil containing the  $\alpha$ -diol **258** and the  $\beta$ -diol **257** in a 1:1 ratio (18 mg, 72%) as an inseparable mixture.

*Synthesis of the triol 275*



A stirred solution of the alcohol **157** (29 mg, 0.091 mmol, 1 eq.) in dry tetrahydrofuran (2 mL) was cooled to 0°C under nitrogen. Lithium aluminium hydride (10 mg, 0.273 mmol, 3 eq.) was added and the reaction temperature was allowed to warm up to room temperature for a day. Aqueous sodium hydroxide (3 M, 5 mL) was added to the mixture and stirred for 10 minutes. The aqueous phase was removed and the organic phase was washed with water (2 x 20 mL), then dried over MgSO<sub>4</sub>. Concentration *in vacuo* afforded a colourless oil attributed to **275** (25 mg, 85%) as a mixture of diastereoisomers. [α]<sub>D</sub><sup>25</sup> -10 (*c* 0.0012, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.22 (1H, s), 3.78-3.67 (2H, m), 3.64 (1H, dt, *J* = 11.5, 3.0 Hz), 3.53 (1H, dd, *J* = 11.1, 4.7 Hz), 3.48 (1H, m, *J* = 3.0 Hz), 2.04-1.93 (4H, m), 1.87-1.84 (1H, m), 1.83 (3H, m), 1.74-1.65 (1H, m), 1.56 (5H, m), 1.50-1.45 (1H, m), 1.43 (1H, s), 1.40-1.32 (1H, m), 1.31-1.24 (2H, m), 1.23-1.04 (2H, m), 1.00 (3H, s), 0.80 (3H, dd, *J* = 6.6, 1.3 Hz), 0.69 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 143.93 (C), 143.87 (C), 122.43 (CH), 122.36 (CH), 75.8 (CH), 66.56 (CH<sub>2</sub>), 66.52 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 45.52 (CH), 45.49 (CH), 44.1 (C), 40.10 (CH), 40.08 (CH), 38.4 (C), 38.0 (CH<sub>2</sub>), 35.94 (CH<sub>2</sub>), 35.85 (CH<sub>2</sub>), 35.77 (CH<sub>2</sub>), 35.73 (CH<sub>2</sub>), 34.55 (CH), 34.51 (CH), 26.8 (CH<sub>2</sub>), 24.46 (CH<sub>2</sub>), 24.40 (CH<sub>2</sub>), 22.5 (CH<sub>3</sub>), 18.07 (CH<sub>3</sub>), 18.02 (CH<sub>2</sub>), 18.00 (CH<sub>2</sub>), 15.8 (CH<sub>3</sub>), 15.1 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 3344, 2922, 2873, 1446, 1383, 1080, 998.

*Attempted radical bromination of **163***



**Method A**

NBS (8 mg, 0.050 mmol, 1 eq.) and a catalytic quantity of lauroyl peroxide (1 granule) was added to a solution of compound **163** (15 mg, 0.047 mmol, 1 eq.) in ethanol-removed chloroform (1 mL) under nitrogen. The reaction was heated at 65°C for 2 hours and allowed to cool. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water (3 x 20 mL). The organic extract was dried ( $\text{CaCl}_2$ ) and concentrated *in vacuo* to afford a colourless oil. The crude product contained **288** along with other unidentifiable products.

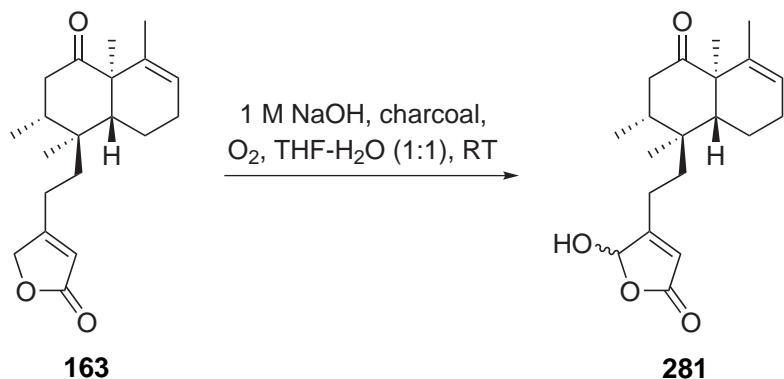
**Method B**

Recrystallised NBS<sup>2</sup> (12 mg, 0.063 mmol, 1 eq.) and a catalytic quantity of lauroyl peroxide (1 granule) was added to a stirred solution of compound **163** (20 mg, 0.063 mmol, 1 eq.) dissolved in ethanol-removed chloroform (1.5 mL) under nitrogen. The reaction mixture was placed under a 500W tungsten-halogen lamp which provided enough heat to reflux the mixture. The reaction was stopped after 1 hour, cooled and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and the solution was washed with water (5 x 50 mL). The organic phase was dried ( $\text{CaCl}_2$ ) and concentrated under reduced pressure to provide a pale yellow oil. The crude product contained a 73:27 mixture of **285:163** along with other unidentifiable products.

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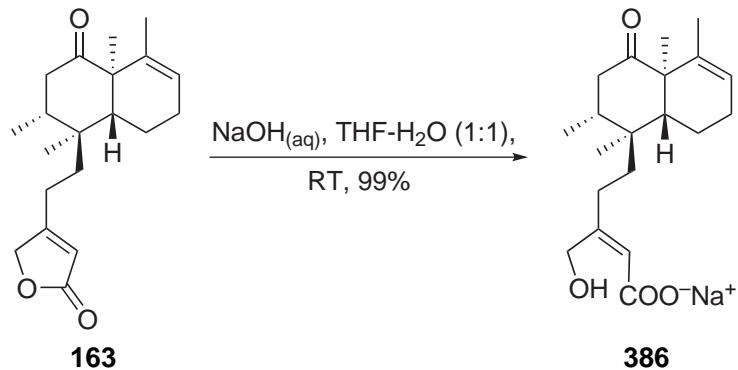
<sup>2</sup>NBS was recrystallised from water.

*Attempted oxidation of **163***



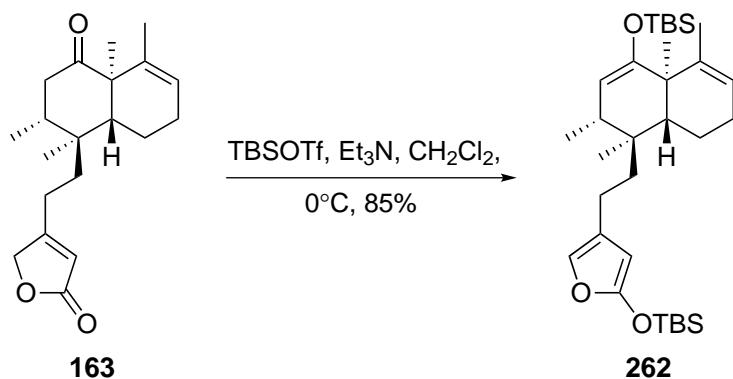
A stirred mixture of compound **163** (63 mg, 0.200 mmol, 1 eq.), aqueous sodium hydroxide solution (0.1 M, 2.1 mL, 0.200 mmol, 1 eq.) and charcoal (~50 mg) in tetrahydrofuran (1 mL) and water (1 mL) was stirred at room temperature under oxygen gas for 12 days. The solution was filtered through alumina and then concentrated under reduced pressure to afford a white foamy solid (34 mg) which contained only the product **281** and the starting material in a 30:70 ratio.

*Synthesis of the sodium carboxylate salt **386***



To a solution of compound **163** (50 mg, 0.159 mmol, 1 eq.) in tetrahydrofuran (0.8 mL) and water (0.8 mL), aqueous sodium hydroxide (0.1 M, 1.67 mL, 0.159 mmol, 1 eq.) was added dropwise. The reaction mixture was stirred at room temperature under nitrogen for 22 hours before the solvent was removed under reduced pressure. The sample was dried under high vacuum to afford the salt **386** as a fine, yellow powder (61 mg, 99%). IR (film,  $\text{cm}^{-1}$ ): 3378, 1705, 1560, 1432, 1401.

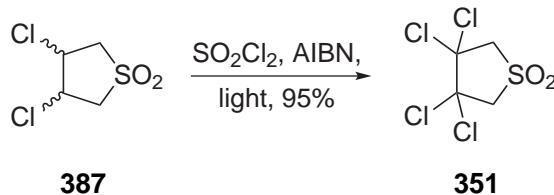
*Synthesis of the di TBS enol ether **262** with TBSOTf*



A solution of the ketone **163** (25 mg, 0.079 mmol, 1 eq.) and triethylamine (110 µL, 80 mg, 0.790 mmol, 10 eq.) in anhydrous dichloromethane (0.50 mL) was cooled to 0°C under nitrogen. TBSOTf (91 µL, 104 mg, 0.395 mmol, 5 eq.) was added and the reaction continued to stir at 0°C for 30 minutes. The mixture was diluted with dichloromethane (20 mL) and washed with water (4 x 20 mL). The organic phase was dried (CaCl<sub>2</sub>) and concentrated *in vacuo*. A pale yellow solid was obtained, which was subjected to radial chromatography (100% petrol to 20% ethyl acetate) to afford the di TBS ether **262** as a colourless oil (37 mg, 86%). The characterisation data for **262** matched that provided previously.

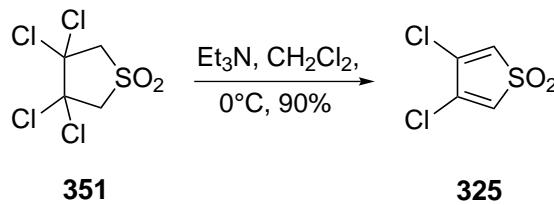
### 9.3. Cordytopolone

*Synthesis of 3,3,4,4,-tetrachlorotetrahydrothiophene-1,1-dioxide 351*



A stirred solution of 3,4-dichlorosulfolane **387** and catalytic AIBN in sulfonyl chloride (60 mL) was irradiated with three 100W tungsten-halogen lamps. The reaction was heated at reflux by the heat provided by the lamps. AIBN was added to the flask every day until TLC and  $^1\text{H}$  NMR showed a maximum product conversion. Once cooled, the solution was diluted in dichloromethane (200 mL) and water (700 mL). The resulting solution was stirred for 1 hour, then filtered through celite. The aqueous phase was removed and the organic phase was washed with water (5 x 400 mL). The organic extract was dried ( $\text{CaCl}_2$ ) and concentrated under reduced pressure to provide the tetrachloride **351** as a yellow solid (6.47 g, 95%), m.p. 175-177°C (lit.<sup>322</sup> 174-176°C).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.25 (4H, s). Characterisation data matched that in literature.<sup>322</sup>

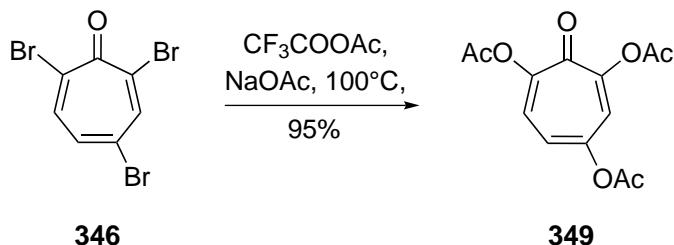
*Synthesis of 3,4,-dichlorothiophene-1,1-dioxide 325*



A stirred solution of the tetrachloride **351** (10.72 g, 41.56 mmol, 1 eq.) in dichloromethane (100 mL) was cooled to 0°C. Triethylamine (11.58 mL, 8.41 g, 83.1 mmol, 2 eq.) was added dropwise to the reaction mixture and the resulting solution was stirred for 1.5 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with 1 M hydrochloric acid (50 mL), water (50 mL), then brine (50 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to afford 3,4-dichlorothiophene-1,1-dioxide **325** as a light yellow solid (6.95 g, 90%), m.p. 111-113°C

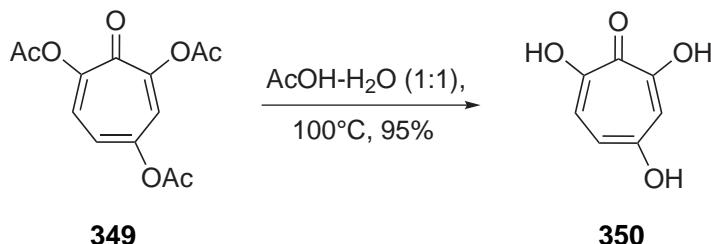
(lit.<sup>287</sup> 112–113°C).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.74 (2H, s). Literature spectral data for **325** matched that provided in literature.<sup>323</sup>

*Synthesis of 2,4,7-triacetyl tropone **349***



A stirred solution of 2,4,7-tribromotropone **346** (22 mg, 0.064 mmol, 1 eq.), an aliquot of an acetyl trifluoroacetate solution (2.7 mL)<sup>284</sup> and sodium acetate (33 mg, 0.402 mmol, 6.3 eq.) was heated in a sealed tube at  $100^\circ\text{C}$  for 3 days. The reaction was allowed to cool to room temperature and diluted with dichloromethane (50 mL). The reaction mixture was washed with water (2 x 50 mL), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to afford the triacetate **349** as a colourless oil (14 mg, 95%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.24 (1H, d,  $J$  = 10.6 Hz), 7.14 (1H, d,  $J$  = 2.2 Hz), 6.86 (1H, dd,  $J$  = 10.6, 2.4 Hz), 2.35 (3H, s), 2.34 (3H, s), 2.31 (3H, s). Characterisation data for **349** matched that provided in literature.<sup>284</sup>

*Synthesis of 2,4,7-trihydroxytropone **350***



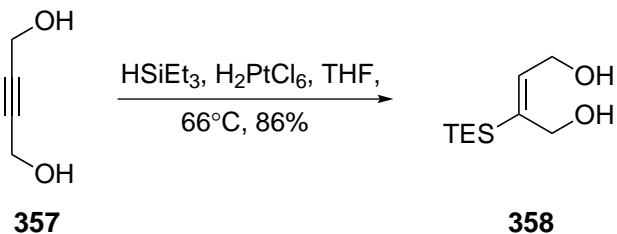
This synthesis of **358** was adapted from the procedure published by Takeshita *et al.*<sup>284</sup>

2,4,7-Triacetyl tropone **349** (18 mg, 0.078 mmol, 1 eq.) was dissolved in a glacial acetic acid-water solution (1:1, 20 mL) and heated at reflux for 1.5 days. The acetic acid and water was removed by downward distillation and the pot residue was dried under high vacuum to leave the product **350** as a brown solid (8 mg, 95%).  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ):

$\delta$  7.37 (1H, d,  $J$  = 11.3 Hz), 7.19 (1H, d,  $J$  = 2.7 Hz), 6.82 (1H, dd,  $J$  = 11.3, 2.7 Hz).

Characterisation data for this compound matched that provided in literature.<sup>284</sup>

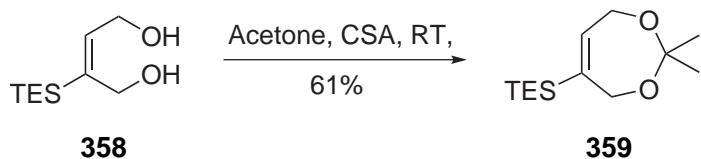
*Synthesis of the vinyl silane diol 358*



This synthesis of **358** was adapted from procedures by Poli *et al.* and Gvardtsiteli *et al.*<sup>299,324</sup>

2-Butyne-1,4-diol **357** (1.77 g, 21.58 mmol, 1 eq.) was dissolved in anhydrous tetrahydrofuran (20 mL) under nitrogen. A solution of chloroplatinic acid hexahydrate in tetrahydrofuran (0.1 M, 125  $\mu$ L, 0.06 eq.) and triethylsilane (3.5 mL, 21.9 mmol, 1.1 eq.) were added to the reaction mixture, and the resulting mixture was heated at reflux for 3 days. The solution was concentrated under reduced pressure to leave a brown oil. Flash chromatography (30% ethyl acetate in petrol to 50% ethyl acetate) provided the hydrosilation product **358** as a colourless oil (3.73 g, 86%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.08 (1H, tt,  $J$  = 6.0, 1.1 Hz), 4.28 (2H, d,  $J$  = 6.0 Hz), 4.25 (2H, m), 2.53 (2H, s), 0.93 (9H, t,  $J$  = 7.7 Hz), 0.63 (6H, q,  $J$  = 7.7 Hz). Characterisation data for this compound matched that provided in literature.<sup>299</sup>

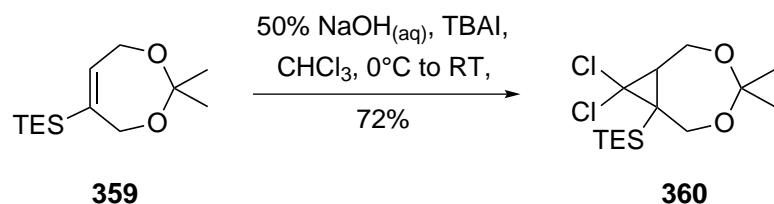
*Synthesis of the silyl dioxepin 359*



A mixture of the diol **358** (50 mg, 0.247 mmol, 1 eq.), catalytic CSA (~5 mg) and anhydrous  $\text{CaCl}_2$  (60 mg) was dissolved in acetone (5 mL) at room temperature. The reaction mixture was stirred under nitrogen at room temperature overnight. Anhydrous

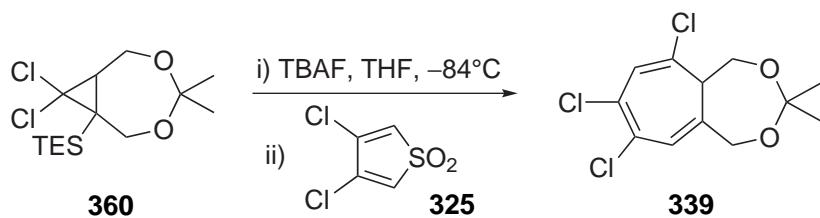
potassium carbonate (2 mg) was added to the reaction mixture and stirring was continued for a further 15 minutes before filtration. The solution was concentrated and the residue was dissolved in petrol (50 mL). The organic extract was washed with water (2 x 20 mL) and dried ( $\text{MgSO}_4$ ). Concentration of the solution *in vacuo* afforded the acetal **359** as a colourless oil (37 mg, 61%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.80 (1H, m), 4.31 (4H, s), 1.42 (6H, s), 0.93 (9H, t,  $J$  = 7.9 Hz), 0.59 (6H, q,  $J$  = 7.9 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  139.9 (C), 138.3 (CH), 102.0 (C), 63.9 ( $\text{CH}_2$ ), 63.3 ( $\text{CH}_2$ ), 24.2 ( $\text{CH}_3$ ), 7.6 ( $\text{CH}_3$ ), 3.0 ( $\text{CH}_2$ ). IR (film,  $\text{cm}^{-1}$ ): 2953, 2910, 2876, 1371, 1217, 1076.

#### *Synthesis of the dichlorocarbene adduct **360***



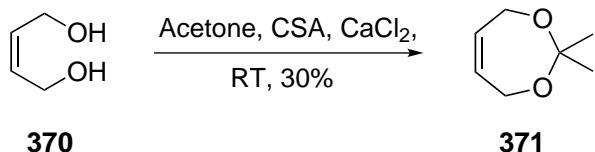
A stirred solution of the acetal **359** (2.24 g, 9.14 mmol, 1 eq.) and TBAI (1.50 g) in chloroform (200 mL) was cooled to 0°C. 50% Aqueous sodium hydroxide (25 M, 150 mL, excess) was added slowly over 15 minutes. After two days, the reaction was stopped and chloroform was added (100 mL). The mixture was washed with water (3 x 100 mL) and dried ( $\text{MgSO}_4$ ). The solution was concentrated under reduced pressure to afford **360** as an unstable brown oil (2.15 g, 72% crude).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.22 (1H, t,  $J$  = 5.9 Hz), 4.16 (1H, dd,  $J$  = 4.7, 2.0 Hz), 4.06 (1H, t,  $J$  = 13.4 Hz), 1.79 (1H, m), 1.33 (3H, s), 1.26 (3H, s), 1.03 (6H, t,  $J$  = 7.9 Hz), 0.52 (9H, q,  $J$  = 7.9 Hz). Further characterisation could not be completed due to decomposition.

*Attempted synthesis of the cycloheptatriene **339***



A stirred solution of the cyclopropane **360** (50 mg, 0.188 mmol, 1 eq.) in dry tetrahydrofuran (5 mL) was cooled to  $-84^{\circ}\text{C}$  under nitrogen. TBAF in tetrahydrofuran (1 M, 0.56 mL, 0.564 mmol, 3.7 eq.) was added dropwise to the solution. After 30 minutes, 3,4-dichlorothiophene-1,1-dioxide **325** (32 mg, 0.370 mmol, 1.1 eq.) was added to the reaction mixture in one portion. The resulting solution continued to stir at  $-84^{\circ}\text{C}$  for 2 hours and was then diluted in diethyl ether (20 mL). The mixture was washed with water (2 x 20 mL), dried ( $\text{CaCl}_2$ ) and concentrated under reduced pressure to afford a yellow oil which contained the product **339** (10%) according to the  $^1\text{H}$  NMR spectrum. The spectral data for **339** is shown on page 210.

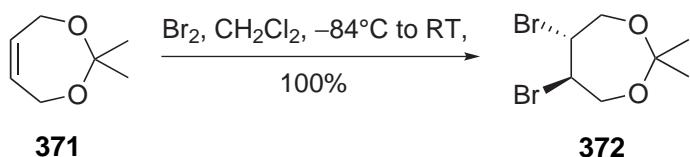
*Synthesis of 4,7-dihydro-2,2-dimethyl-1,3-dioxepin **371***



This synthesis of **371** was adapted from a procedure by Harada *et al.*<sup>325</sup> utilising CSA as the acid catalyst rather than the cited *p*-TsOH.

A mixture of 2-butene-1,4-diol **370** (23 mL, 24.7 g, 0.28 mol, 1 eq.), catalytic CSA (0.3 g) and anhydrous  $\text{CaCl}_2$  (6 g) was dissolved in acetone (250 mL) under nitrogen. The reaction mixture was stirred at room temperature for 3 days. Anhydrous potassium carbonate (0.18 g) was added to the reaction mixture and this was stirred for 30 minutes. The mixture was filtered and the filtrate was concentrated under reduced pressure to leave **371** as a pale yellow oil (10.48 g, 30%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  5.57 (2H, t,  $J = 1.7$  Hz), 4.16 (4H, d,  $J = 1.7$  Hz), 1.35 (6H, s). Characterisation data for this compound matched that provided in literature.<sup>326</sup>

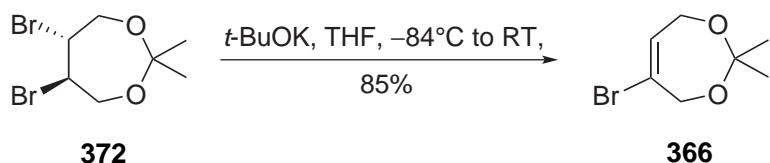
*Synthesis of the brominated dioxepin 372*



The synthesis of **372** was adapted from the method used by Malanga *et al.*<sup>305</sup>

Bromine (3.10 mL, 9.50 g, 0.060 mmol, 1 eq.) was added dropwise over 30 minutes to a cooled solution of the dioxepin **371** (7.69 g, 0.060 mol, 1 eq.) in dichloromethane (50 mL) at  $-84^{\circ}\text{C}$ . The reaction was allowed to warm to room temperature over 22 hours and the solution was concentrated under reduced pressure to afford a pale orange/pink viscous oil. After drying the oil at high vacuum, an orange/pink crystalline solid of **372** formed (17.24 g, 100%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.16-4.05 (4H, m), 3.81-3.76 (2H, m), 1.37 (6H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  102.2 (C), 63.1 ( $\text{CH}_2$ ), 55.0 (C-Br), 24.7 ( $\text{CH}_3$ ). IR (film,  $\text{cm}^{-1}$ ): 2992, 2943, 2872, 1447, 1377, 1258, 1213, 1192, 1151, 1075, 1025, 848. HRMS (ESI): a molecular ion could not be found.

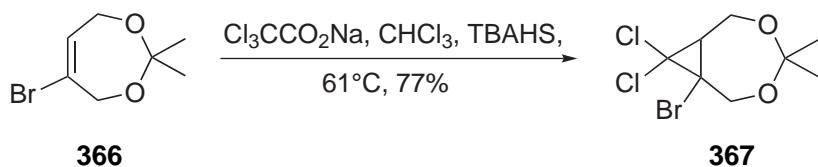
*Synthesis of the vinyl bromide 366*



Potassium *tert*-butoxide (8.01 g, 0.071 mol, 1.5 eq.) was added to a solution of the dibromide **372** (13.71 g, 0.048 mol, 1 eq.) in dry tetrahydrofuran (50 mL) at  $-84^{\circ}\text{C}$ . After the addition was complete, the reaction was allowed to warm to room temperature over 65 hours. The solution was diluted with petrol (20 mL) and washed with water (20 mL). The aqueous phase was back-extracted with petrol (2 x 20 mL). The organic phases were combined and washed with more water (3 x 20 mL), dried ( $\text{CaCl}_2$ ) and concentrated under reduced pressure to give a brown viscous oil. High vacuum distillation gave the product **366** as a colourless oil as the first fraction (8.39 g, 85%), b.p. 100-104°C (0.27 mm Hg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.03 (1H, tt,  $J = 4.1, 1.6$  Hz), 4.37 (2H, td,  $J = 2.2, 1.6$  Hz), 4.15 (2H, dt,  $J = 4.1, 2.2$  Hz), 1.43 (6H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  130.8 (CH),

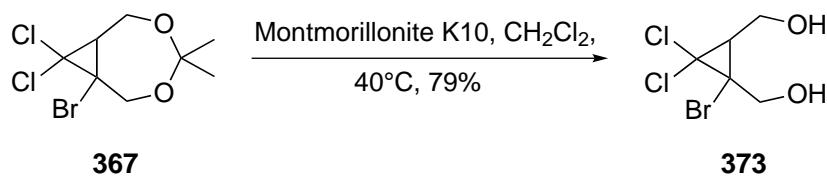
122.4 (C-Br), 102.6 (C), 67.6 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 23.9 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2991, 2944, 2910, 2860, 1656, 1447, 1373, 1278, 1215, 1157, 1078, 1011, 983, 864. HRMS (ESI): a molecular ion could not be found.

*Synthesis of the dichlorocarbene adduct 367*



A mixture of the vinyl bromide **366** (2.57 g, 12.5 mmol, 1 eq.), sodium trichloroacetate (31.00 g, 167.0 mmol, 13 eq.) and tetrabutylammonium hydrogen sulfate (~0.50 g) was dissolved in chloroform (50 mL) at room temperature. The reaction was heated at reflux for 2 days, then cooled to room temperature. The solution was diluted with chloroform (50 mL), filtered through celite and washed with water (10 x 50 mL). The organic phase was dried (CaCl<sub>2</sub>) and concentrated under reduced pressure to leave the cyclopropane **367** as a brown viscous oil (2.76 g, 77%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.48 (1H, d, *J* = 14.0 Hz), 4.38 (1H, d, *J* = 14.0 Hz), 4.23 (1H, dd, *J* = 13.5, 7.9 Hz), 3.94 (1H, dd, *J* = 13.5, 5.1 Hz), 2.20 (1H, dd, *J* = 7.9, 5.1 Hz), 1.41 (3H, s), 1.29 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 103.9 (C), 66.8 (CH<sub>2</sub>), 63.2 (C-Cl), 57.6 (CH<sub>2</sub>), 46.5 (C-Br), 42.8 (CH), 25.2 (CH<sub>3</sub>), 23.6 (CH<sub>3</sub>). IR (film, cm<sup>-1</sup>): 2991, 2948, 1376, 1213, 1155, 1097, 1080, 1048. HRMS (ESI): a molecular ion could not be found.

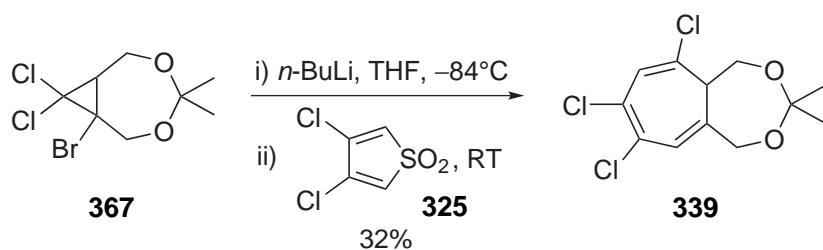
*Synthesis of the diol 373*



Montmorillonite K10 (5 g) was added to a stirred solution of the dichlorocarbene adduct **367** (0.70 g, 2.41 mmol, 1 eq.) in dichloromethane (30 mL). The mixture was stirred at reflux for 1 day and then cooled to room temperature. The reaction mixture was diluted with dichloromethane (200 mL) and filtered through celite. Ethyl acetate-methanol (1:1,

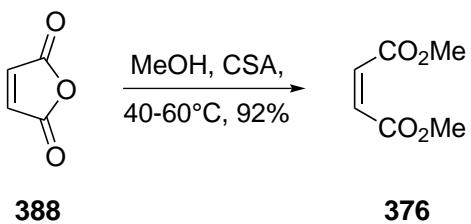
~50 mL) was used to wash the celite. The filtrate was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to afford a yellow crude oil. Radial chromatography (50% ethyl acetate in petrol to 100% ethyl acetate) afforded **373** as a colourless oil (34 mg, 79%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.19 (1H, dd,  $J$  = 13.4, 1.0 Hz), 4.12-4.05 (2H, m), 3.77 (1H, dd,  $J$  = 12.4, 9.0 Hz), 2.31 (1H, ddd,  $J$  = 9.0, 6.9, 1.0 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  65.8 ( $\text{CH}_2$ ), 65.1 (C-Cl), 59.5 ( $\text{CH}_2$ ), 48.7 (C-Br), 43.6 (CH). IR (film,  $\text{cm}^{-1}$ ): 3342, 2924, 2854, 1460, 1040.

*Synthesis of the cycloheptatriene* 339



A solution of the dichlorocarbene adduct **367** (0.186 mg, 0.640 mmol, 1 eq.) in dry tetrahydrofuran (2 mL) was cooled to -84°C under a nitrogen atmosphere. *n*-Butyllithium (1.6 M, 0.40 mL, 0.640 mmol, 1 eq.) was added dropwise to the reaction solution. After 10 minutes, **325** (0.118 mg, 0.640 mmol, 1 eq.) was added in one portion and the reaction mixture was allowed to stir and warm to room temperature for 2 hours. The solution was diluted with dichloromethane (50 mL) and washed with water (2 x 50 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to afford a yellow oil. Radial chromatography (1% triethylamine treated silica, 100% petrol to 20% ethyl acetate) provided the cycloheptatriene product **339** as a yellow oil (60 mg, 32%).

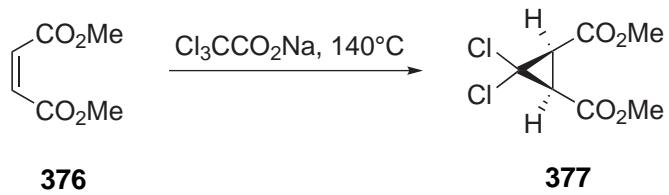
Synthesis of (Z)-dimethyl maleate 376



This procedure was adapted from that published by Makowka and Block.<sup>327</sup>

A mixture of maleic anhydride **388** (7.00 g, 0.071 mol, 1 eq.) and CSA (~50 mg) was dissolved in methanol (35 mL) under nitrogen. The reaction was heated to 40°C for the first hour, then the temperature was increased to 60°C for a further 3 days. Anhydrous potassium carbonate was added until the solution was neutral, then the solution was filtered. The filtrate was concentrated *in vacuo* to afford (*Z*)-dimethyl maleate **376** as a pale yellow oil (9.43 g, 92%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.25 (2H, s), 3.78 (6H, s). Spectral data matched that provided in literature.<sup>327</sup>

*Synthesis of the dichlorocarbene adduct 377*



This procedure was adapted from that published by Yamashita and co-workers.<sup>315</sup>

Dimethyl maleate **376** (0.268 g, 1.860 mmol, 1 eq.) and sodium trichloroacetate (0.517 g, 2.789 mmol, 1.5 eq.) were combined and heated to 140°C under nitrogen. The reaction was stopped after 4 hours and allowed to cool. Diethyl ether (50 mL) was added and the resulting solution was washed with water (3 x 50 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give a light orange solid (0.12 g, 28%) containing the product **377** and unreacted starting material **376** in a 78:22 ratio.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.83 (6H, s), 3.72 (2H, s). Characterisation data for this compound matched that provided in literature.<sup>315</sup>

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## **Appendix A**

### **Crystallography Data**

#### A.0.1. Crystallographic data for the alcohol 157

X-ray crystallography of **157** was performed by Associate Professor Brian Skelton at University of Western Australia. The final assigned structure is presented in Figure A.1 and the crystal data is summarised in Tables 1 and 2. Crystallographic data for the structures were collected at 100(2) K on an Oxford Diffraction Gemini diffractometer fitted with Cu K $\alpha$  radiation. Following multi-scan absorption corrections and solution by direct methods, the structure was refined against F2 with full-matrix least-squares using the program SHELXL-97.<sup>328</sup> The ellipsoids have been drawn at the 50% probability level. The methylfuranone ring was modelled as being disordered over two sets of sites with occupancies refined 0.765(6) and its complement. Geometries of the minor component were restrained to reasonable values. All H-atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on those of the parent atoms. Anisotropic displacement parameters were employed for the non-hydrogen atoms. The absolute configuration was determined only at a moderate level of confidence. (Flack(x) = 0.07(26)). There is a hydrogen bond between the hydroxyl hydrogen atom and the furanone oxygen atom of the molecule related by the crystallographic 21 screw axis parallel to the c-axis.

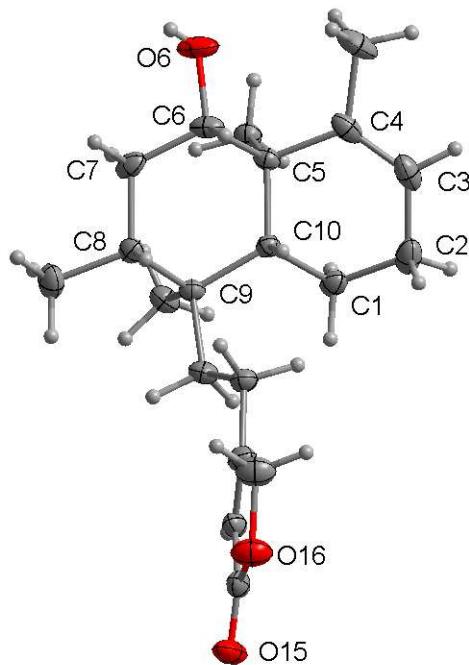


Figure A.1: X-ray structure of **157**.

Table 1. Crystal data and structure refinement for **157**.

Sample code	vm4-036
Empirical formula	C <sub>20</sub> H <sub>30</sub> O <sub>3</sub>
Formula weight	318.44
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell dimensions	$a = 8.29110(10)$ Å $b = 9.87000(10)$ Å $c = 21.3423(3)$ Å
Volume	1746.51(4) Å <sup>3</sup>
Z	4
Density (calculated)	1.211 Mg/m <sup>3</sup>
$\mu$	0.625 mm <sup>-1</sup>
Crystal size	0.25 x 0.23 x 0.20 mm <sup>3</sup>
$\vartheta$ range for data collection	4.14 to 67.14°
Index ranges	-9<=h<=9, -11<=k<=11, -24<=l<=25
Reflections collected	14493
Independent reflections	3108 [ $R(\text{int}) = 0.0206$ ]
Completeness to $\vartheta = 67.14^\circ$	99.8%
Absorption correction	Semi-empirical from equivalents
Max./min. transmission	1.00/0.89
Refinement method	Full-matrix least-squares on $F^2$
Data / restraints / parameters	3108 / 45 / 241
Goodness-of-fit on $F^2$	1.039
Final R indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0381$ , $wR_2 = 0.0980$
R indices (all data)	$R_1 = 0.0382$ , $wR_2 = 0.0981$
Absolute structure parameter	0.07(26)
Largest diff. peak and hole	0.306 and -0.251 e.Å <sup>-3</sup>

Table 2. Hydrogen bonds for **157** [ $\text{\AA}$  and  $^\circ$ ].

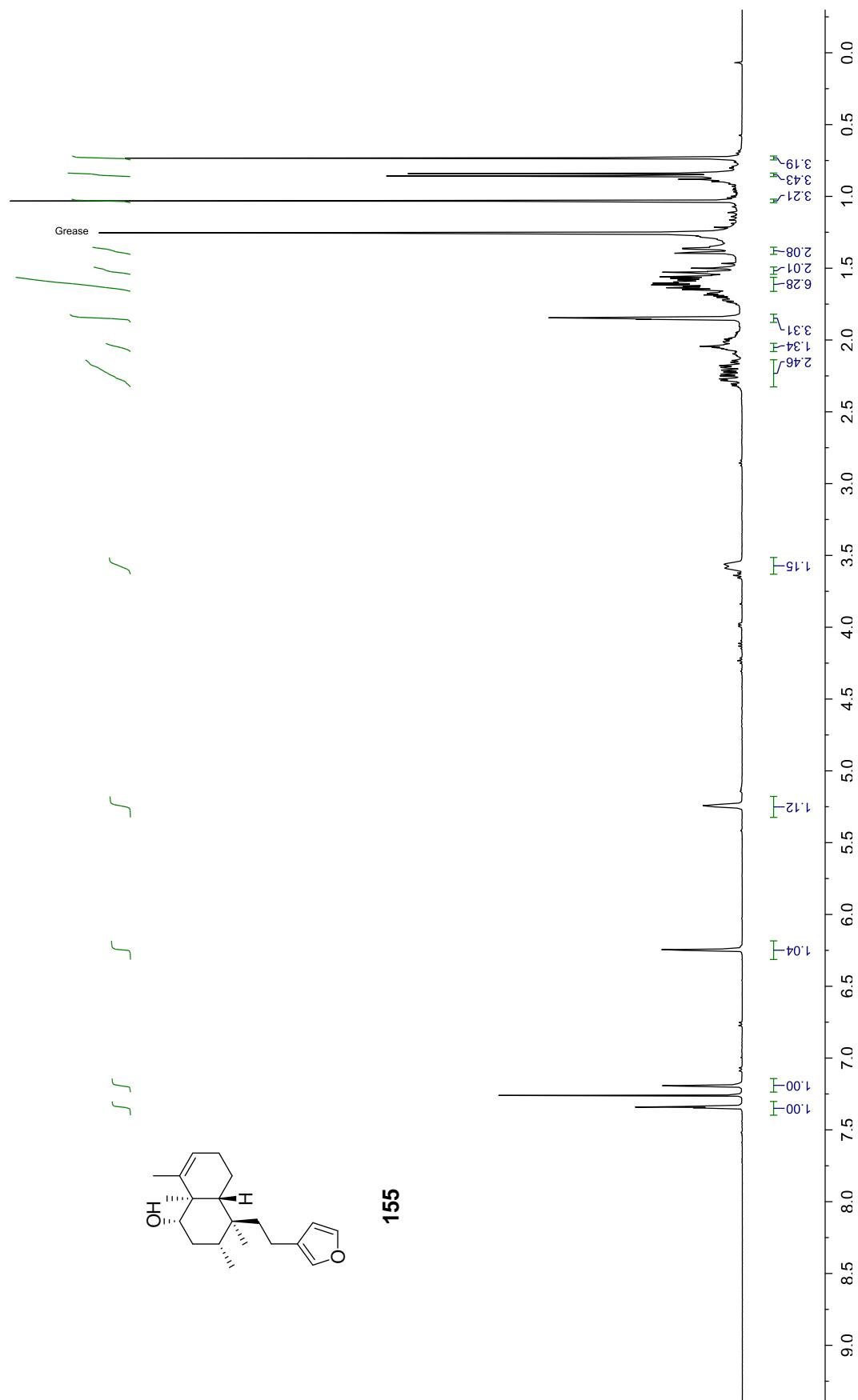
D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle$ (DHA)
O(6)-H(6A)...O(15) <sup>1</sup>	0.84	2.06	2.875(15)	163.4
O(6)-H(6A)...O(15') <sup>1</sup>	0.84	2.08	2.88(5)	159.7

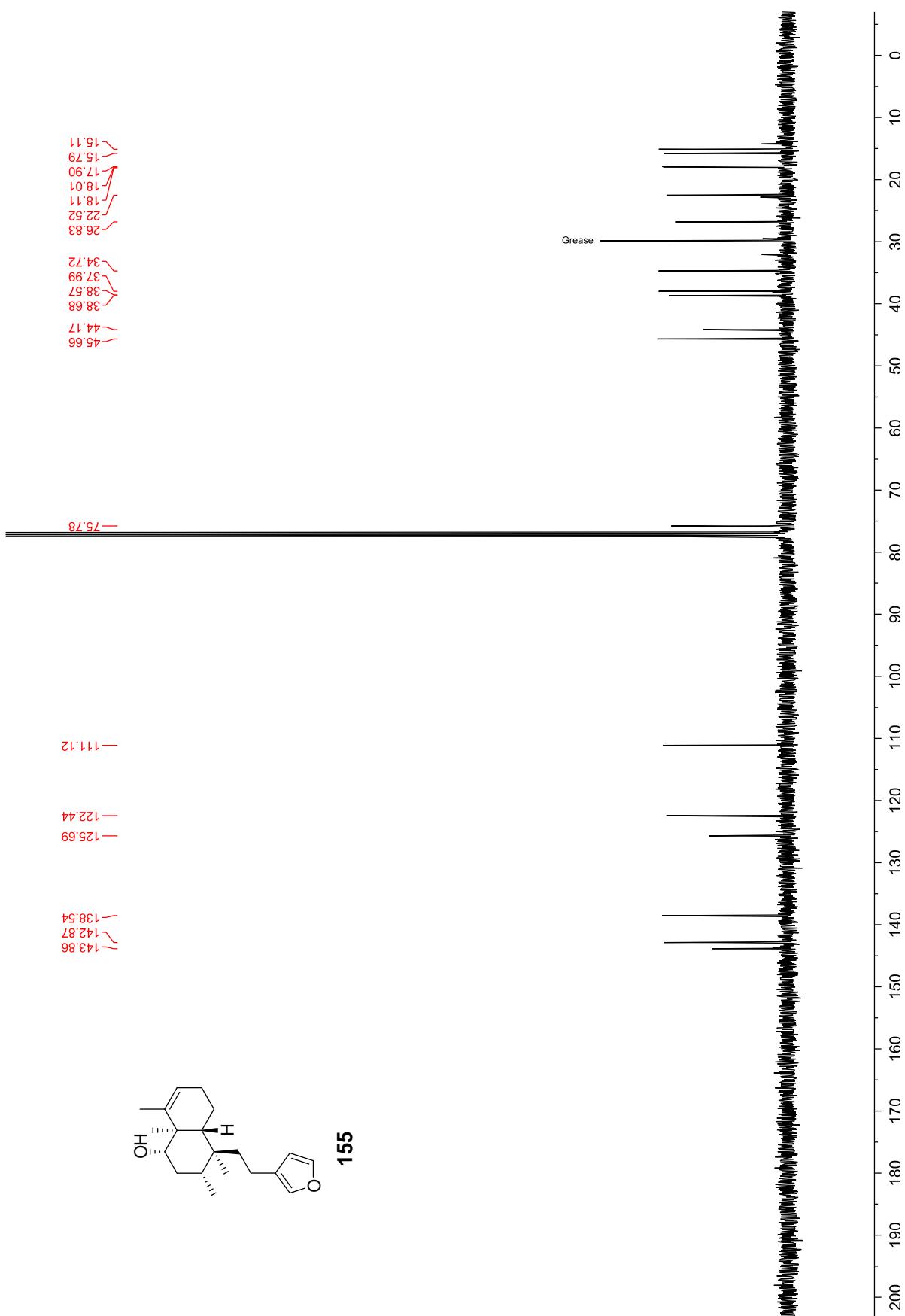
Symmetry transformations used to generate equivalent atoms: <sup>1</sup>1/2-x,1-y,z+1/2

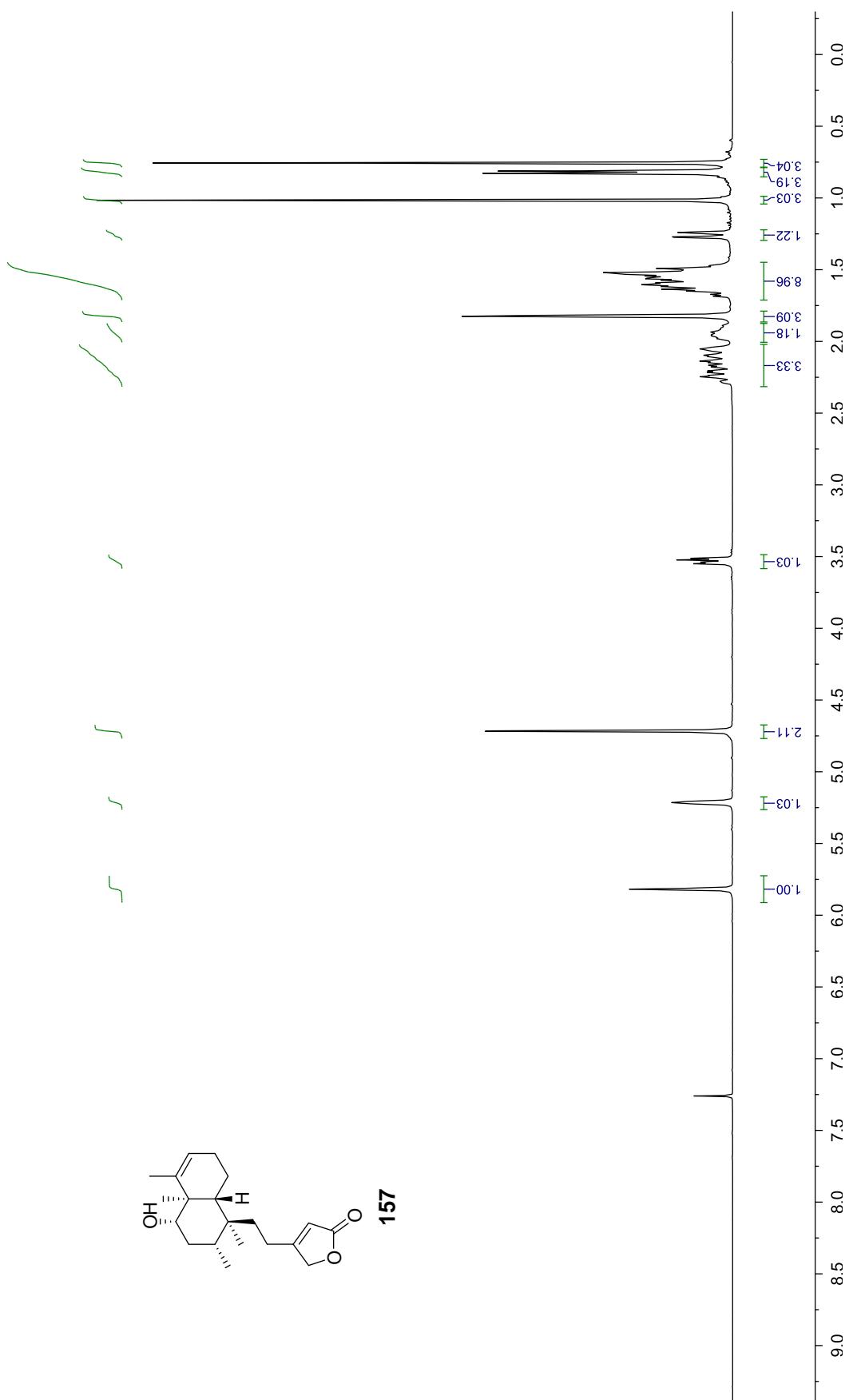
## **Appendix B**

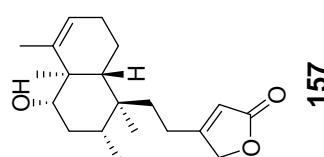
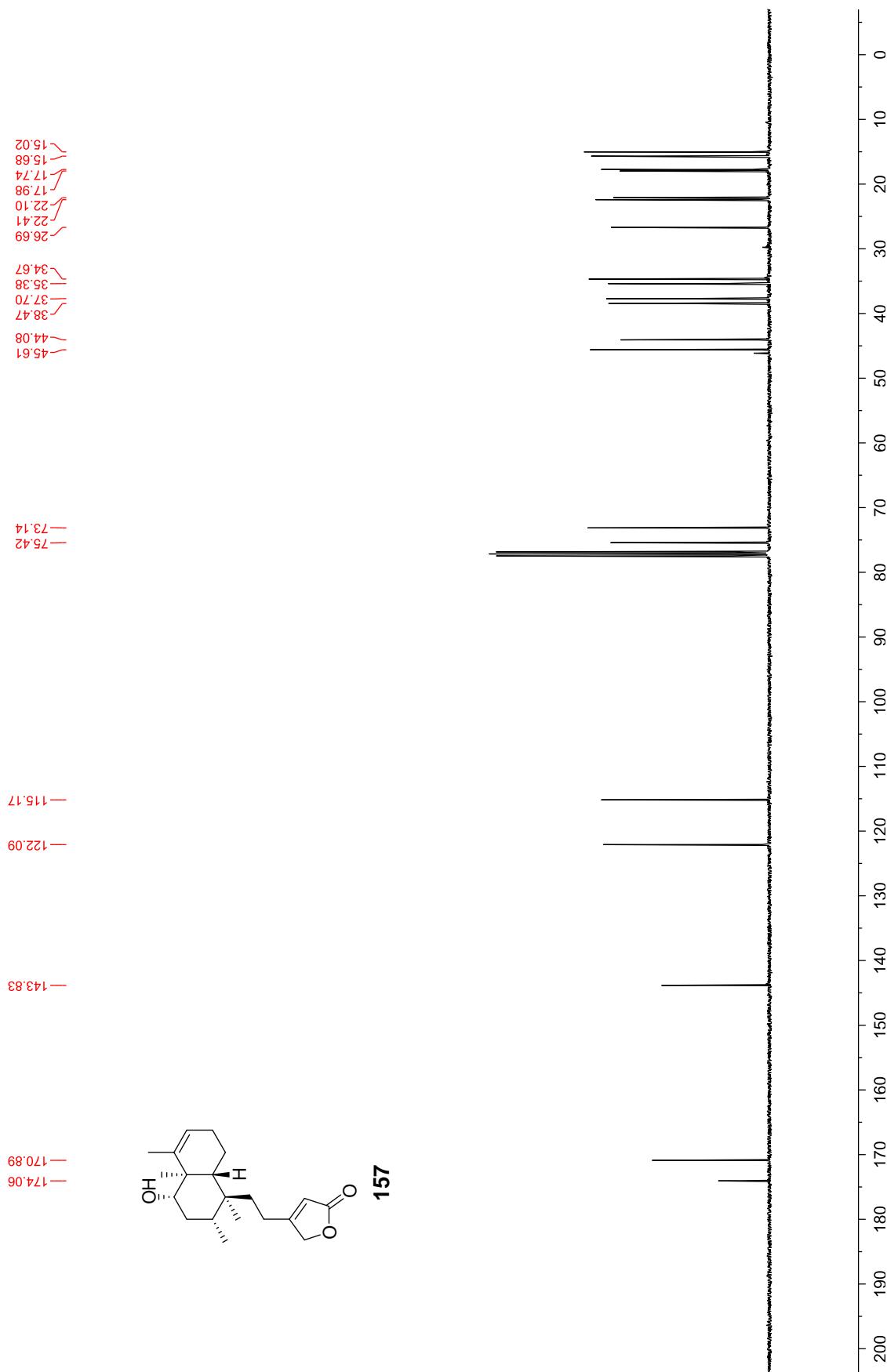
### **NMR Spectra**

**B.1. *Dodonaeas***

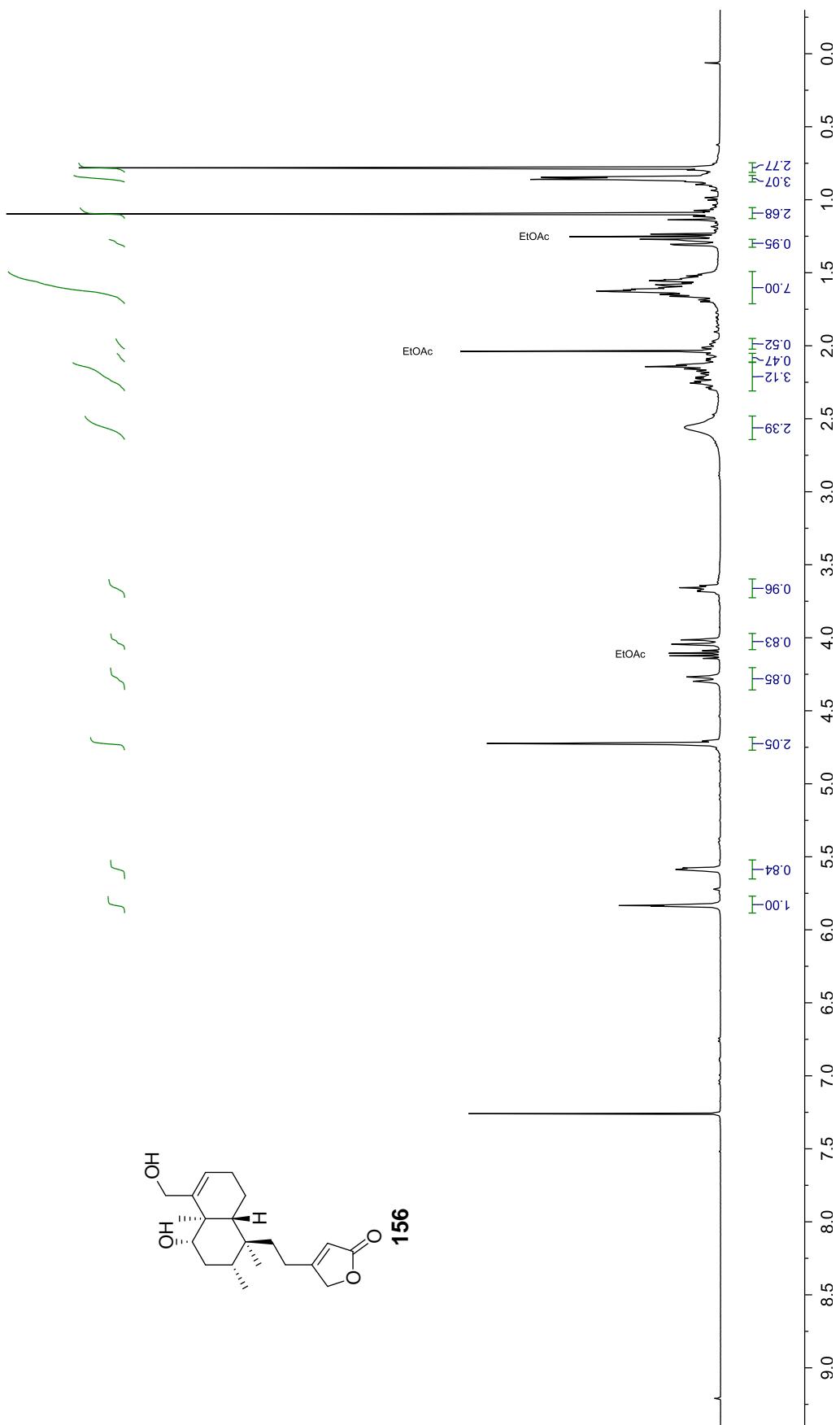


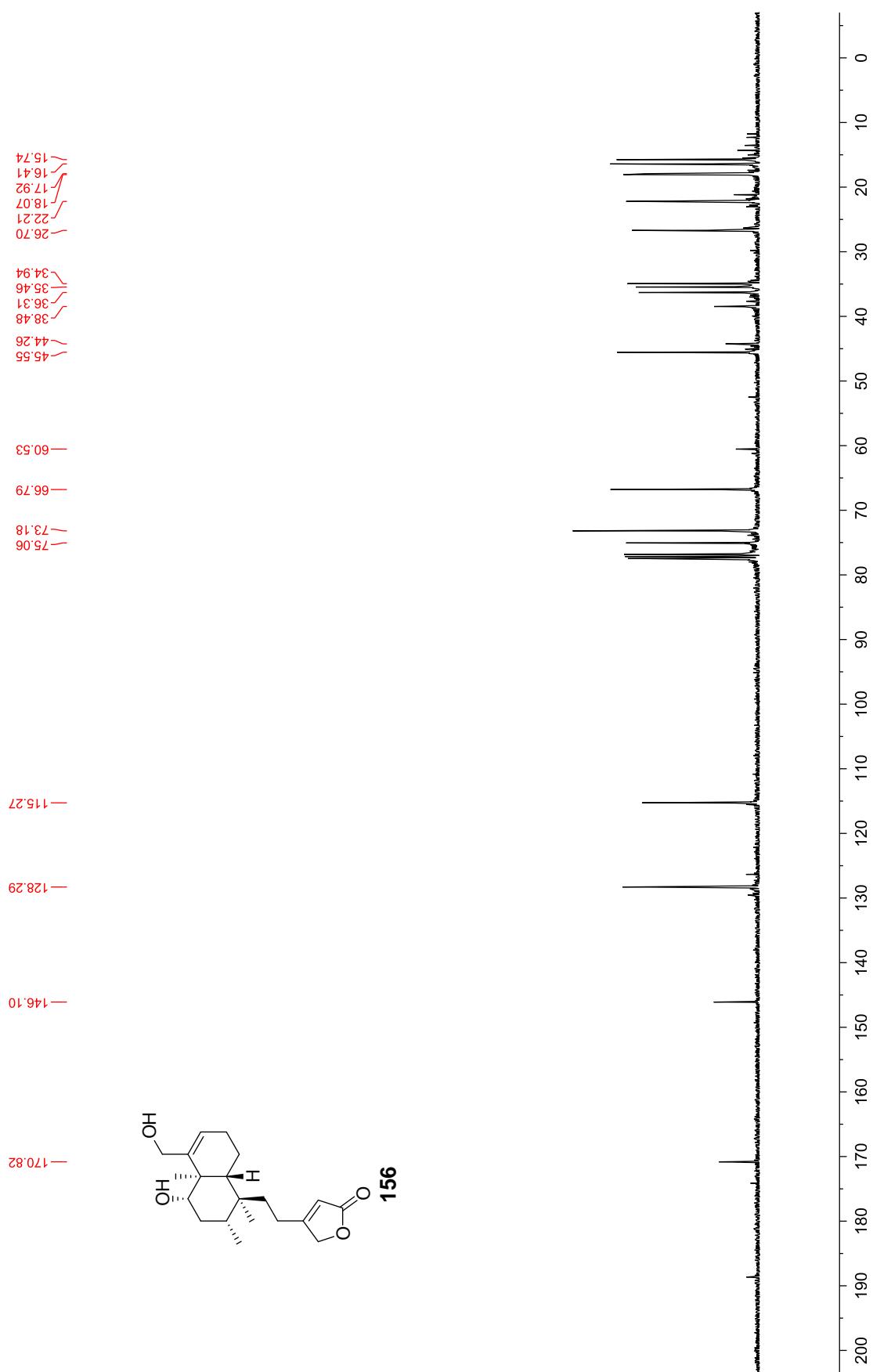


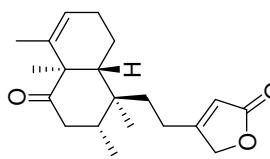
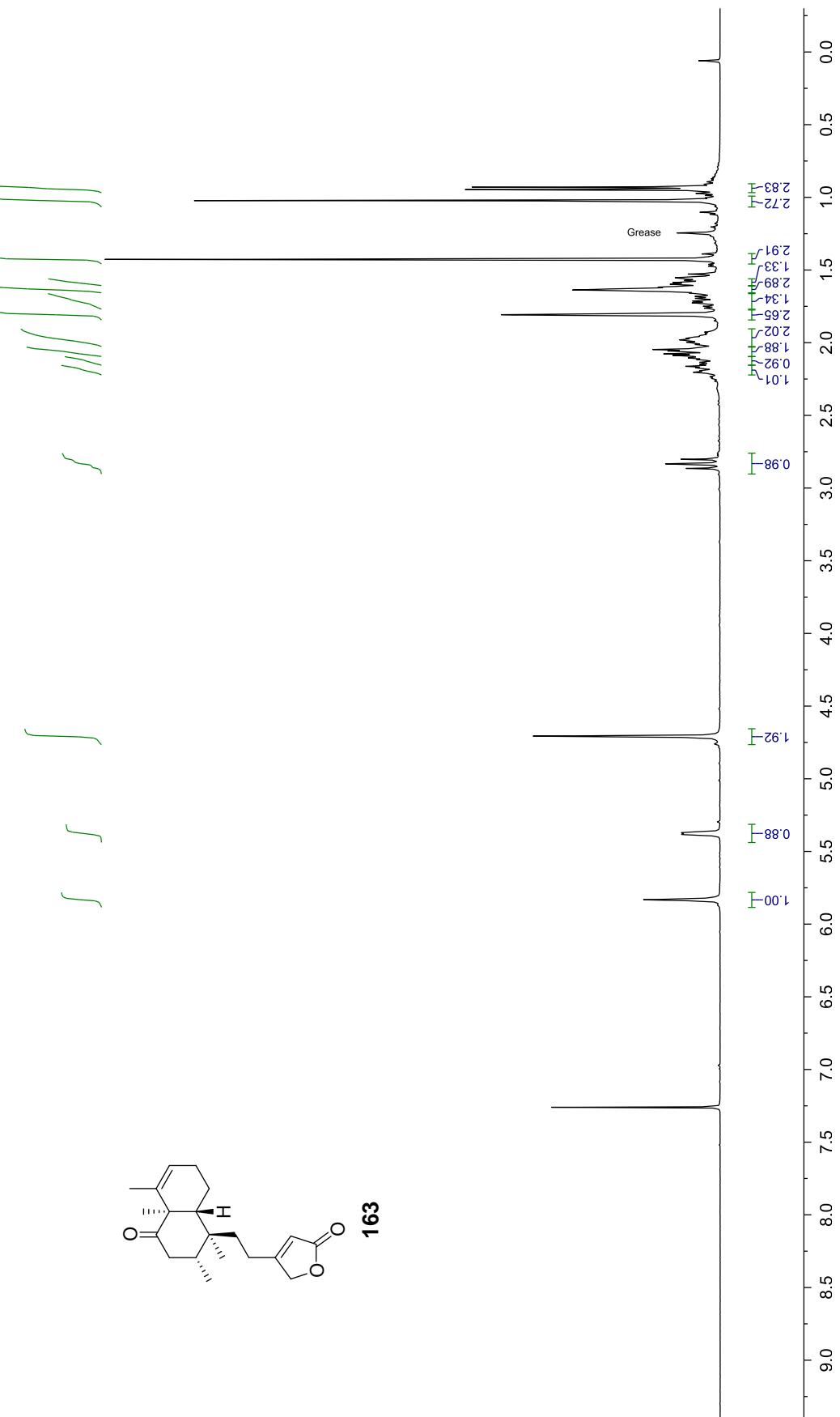




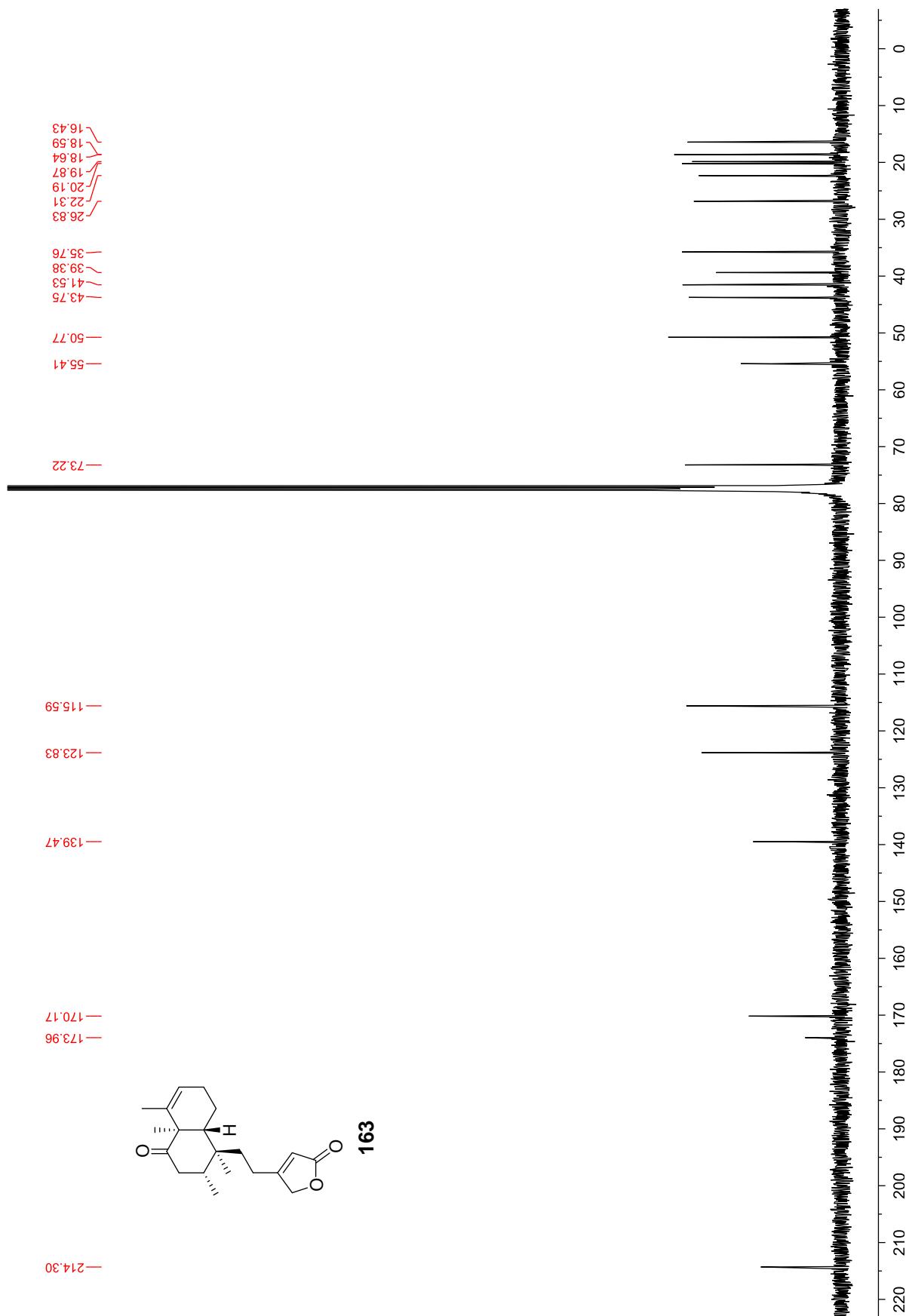
157

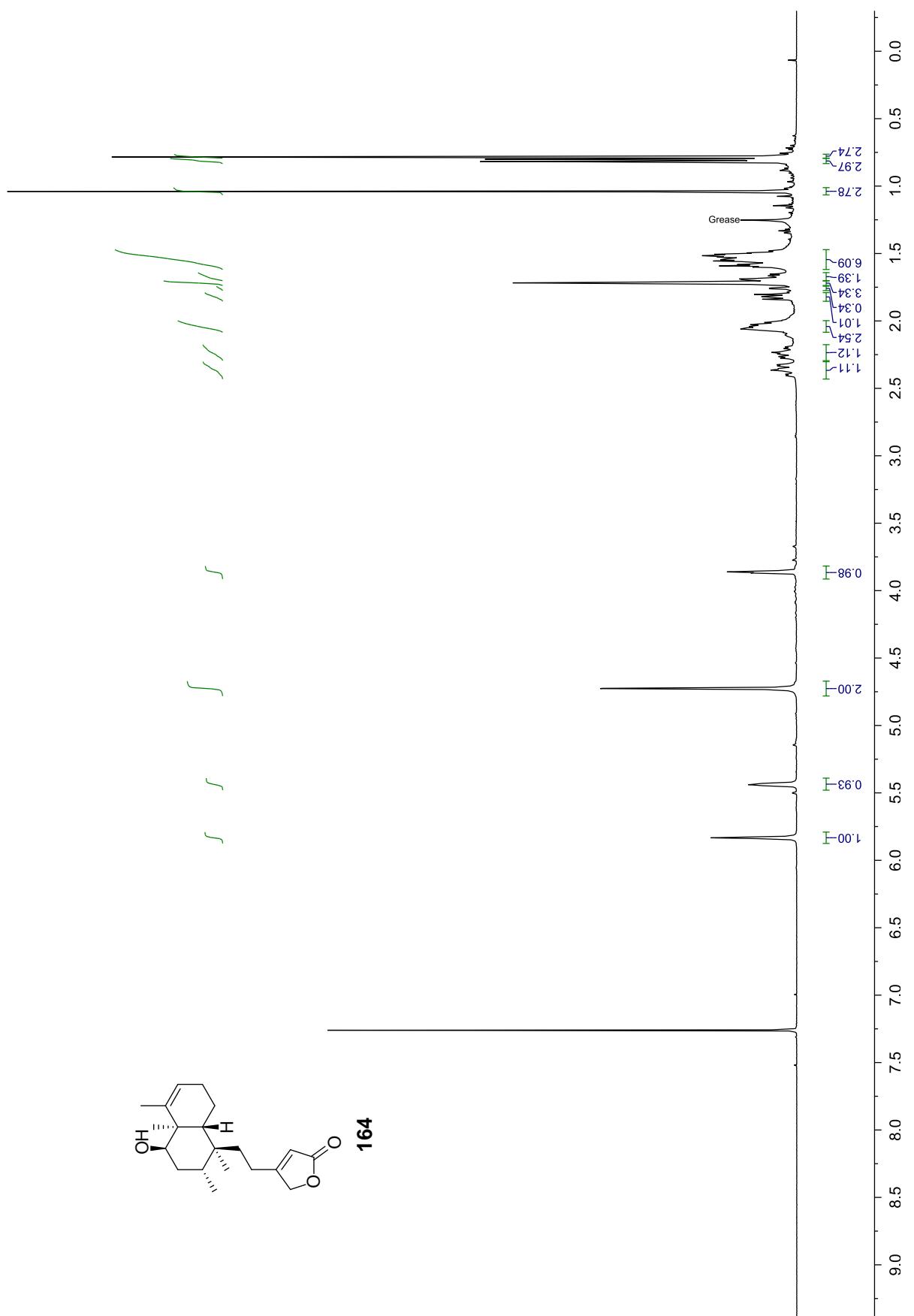


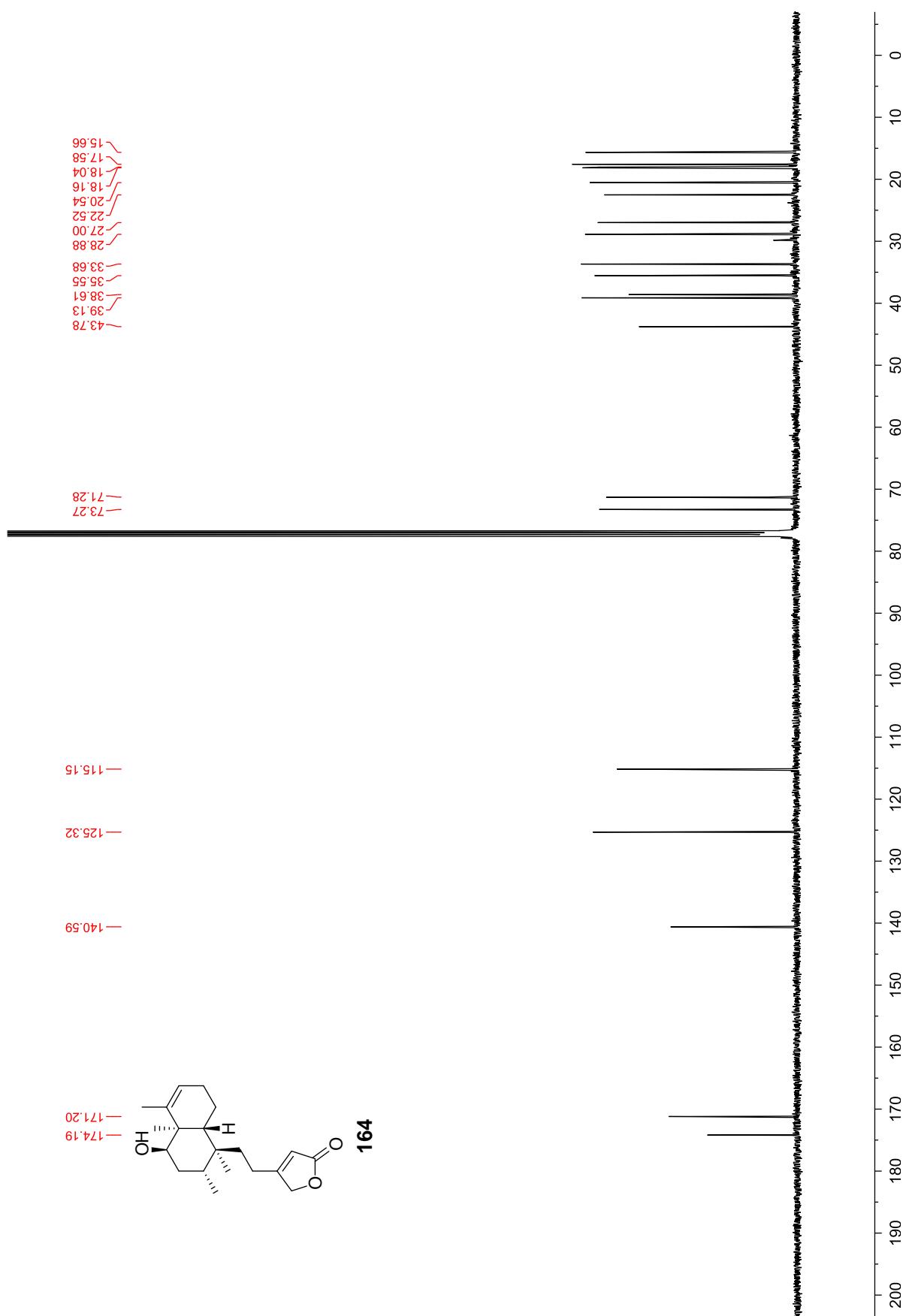


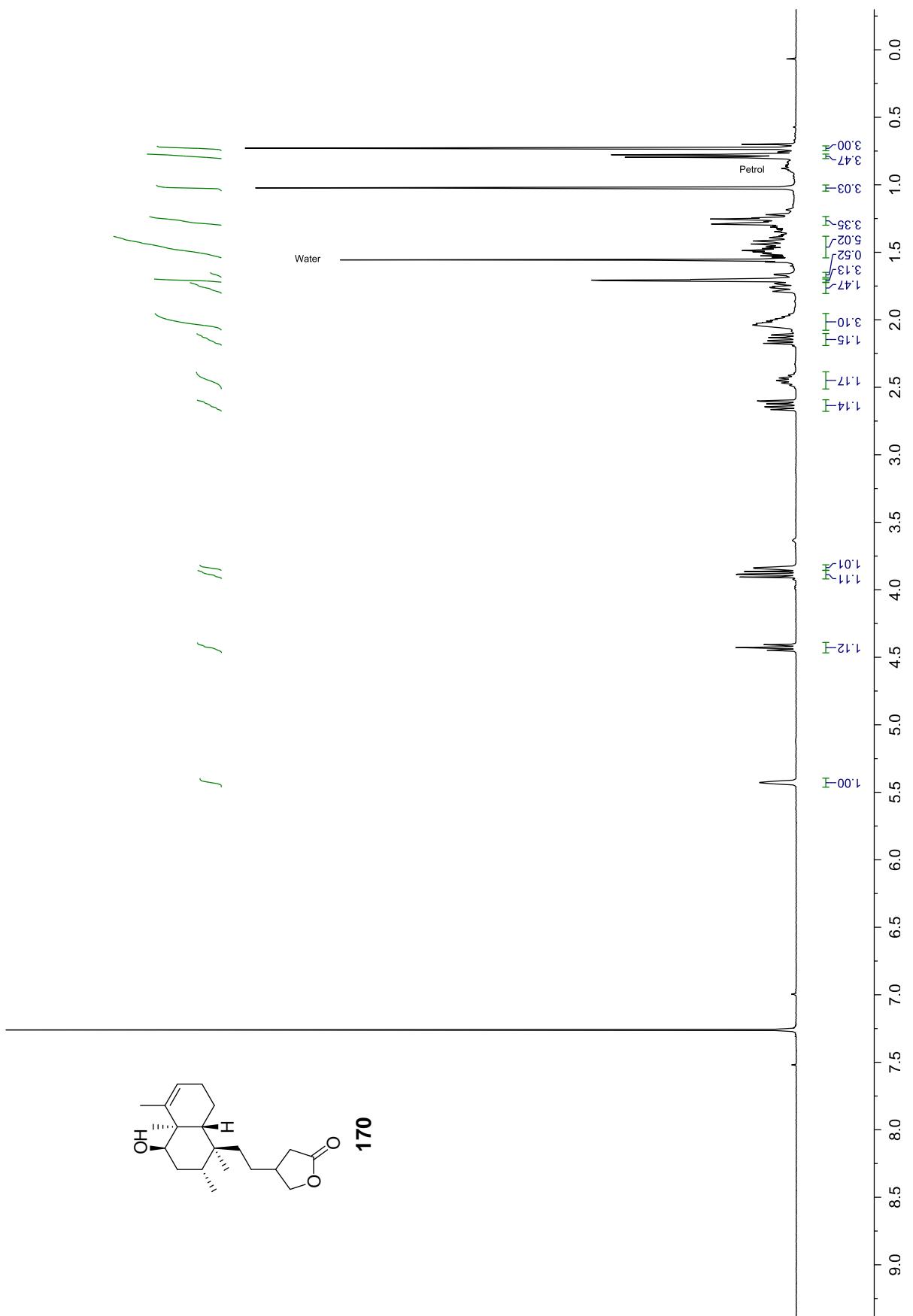


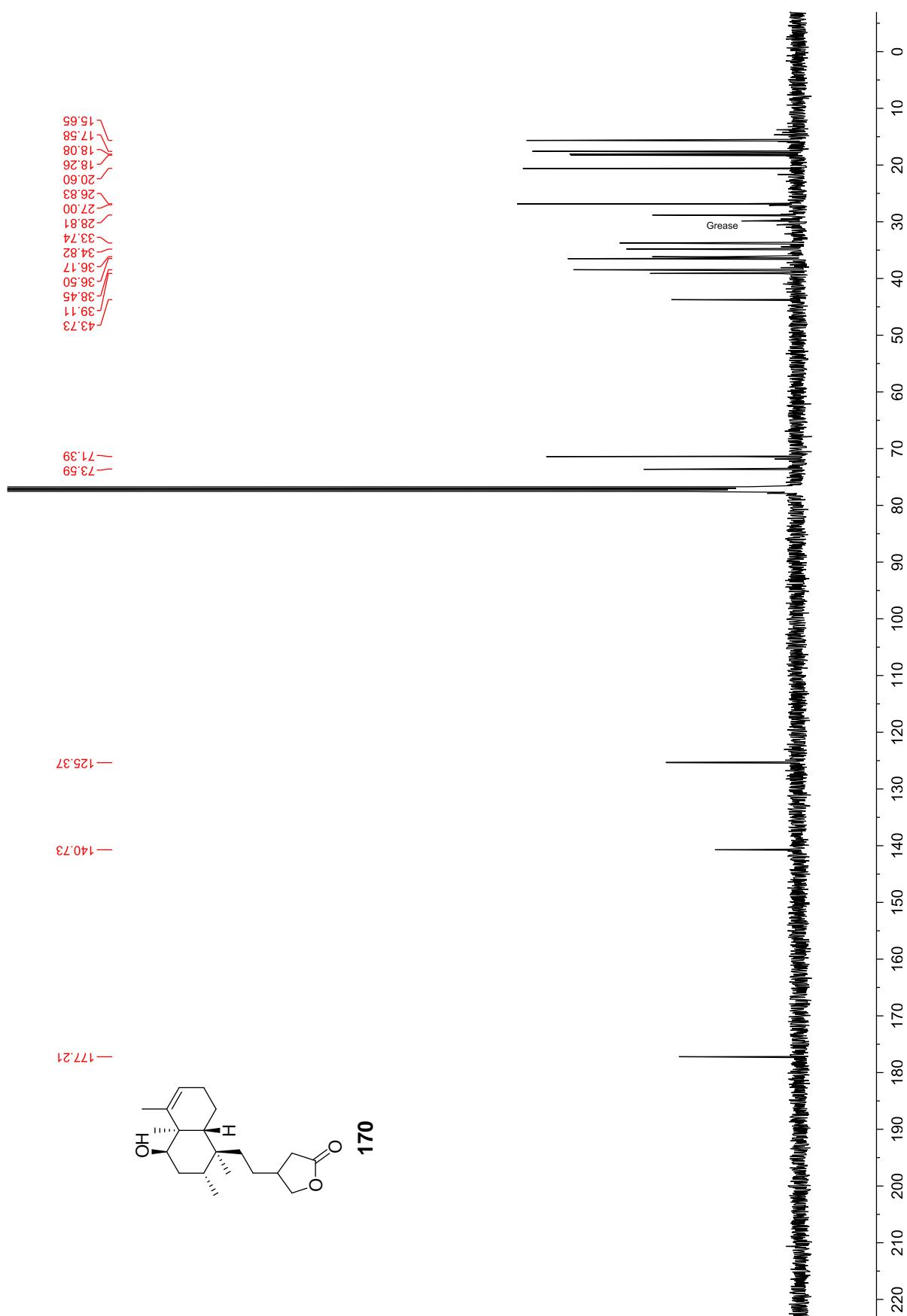
163

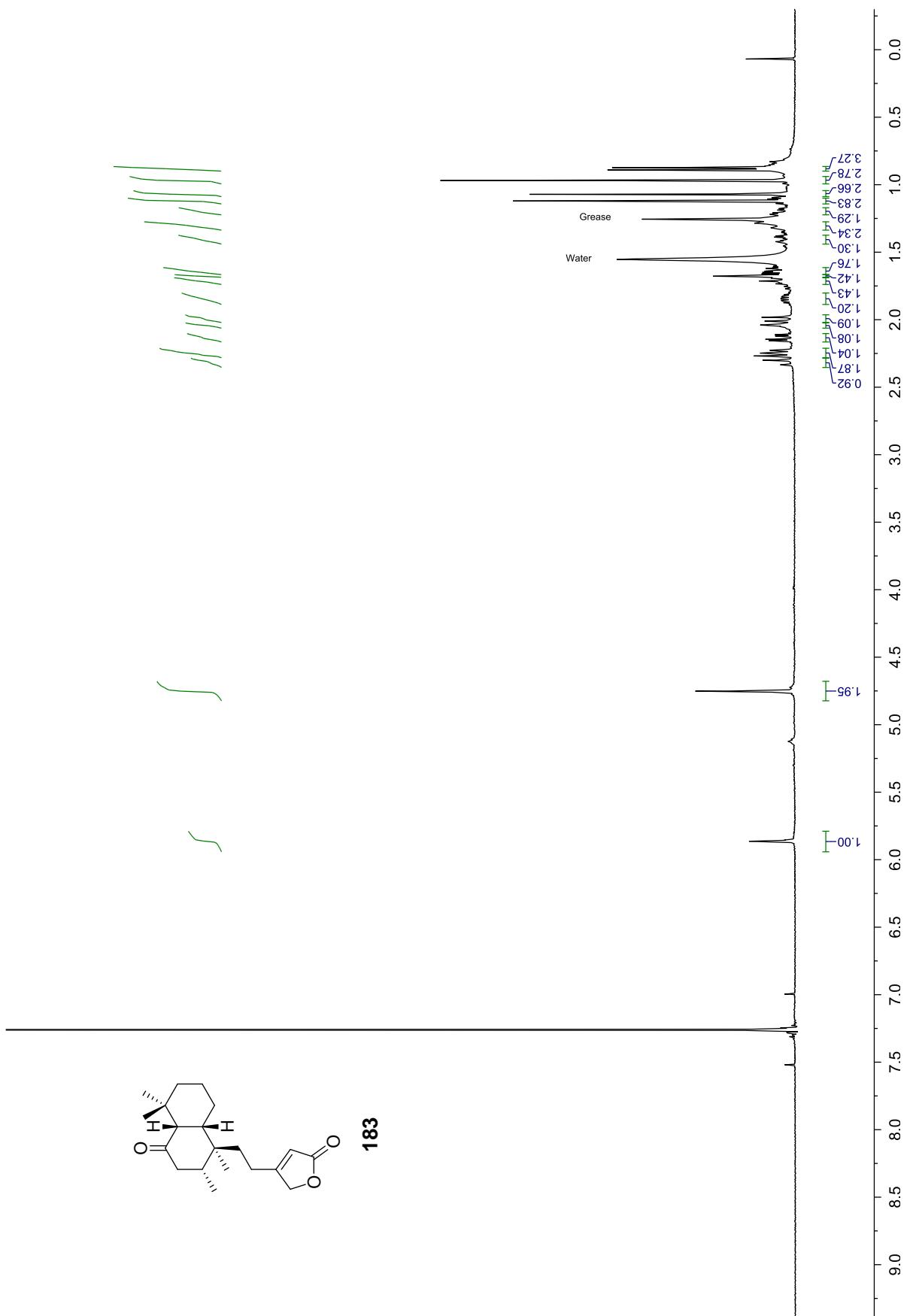


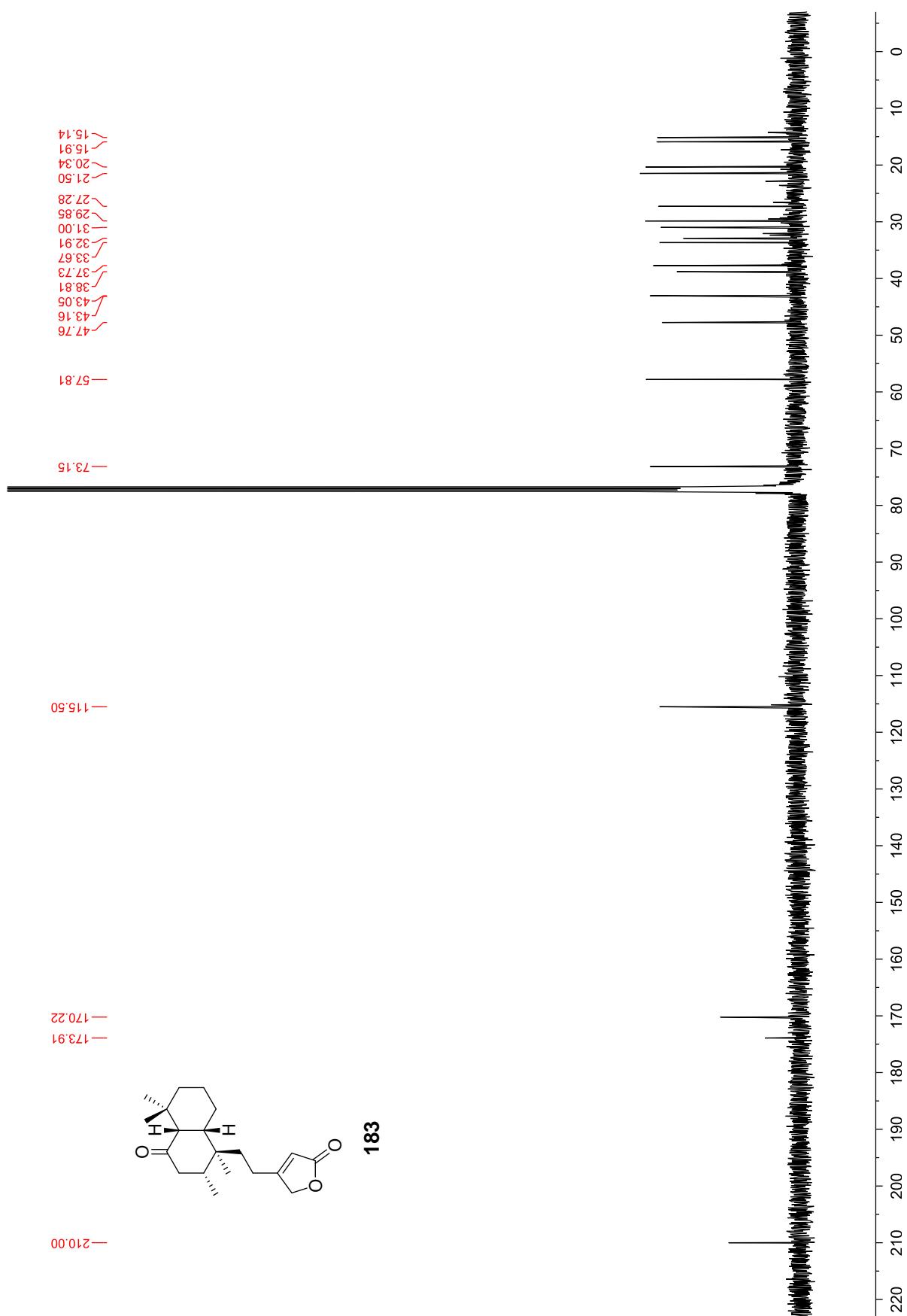


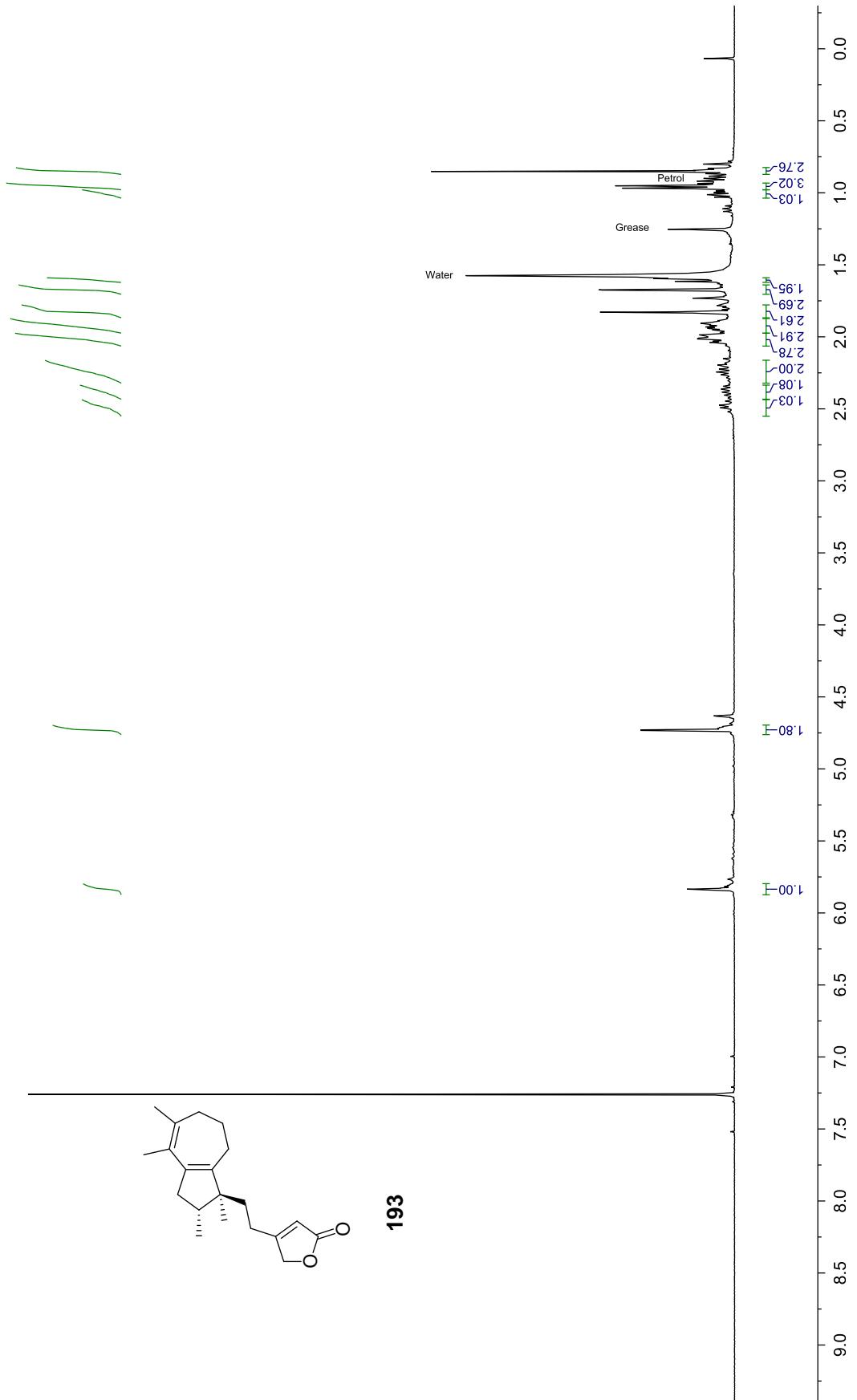


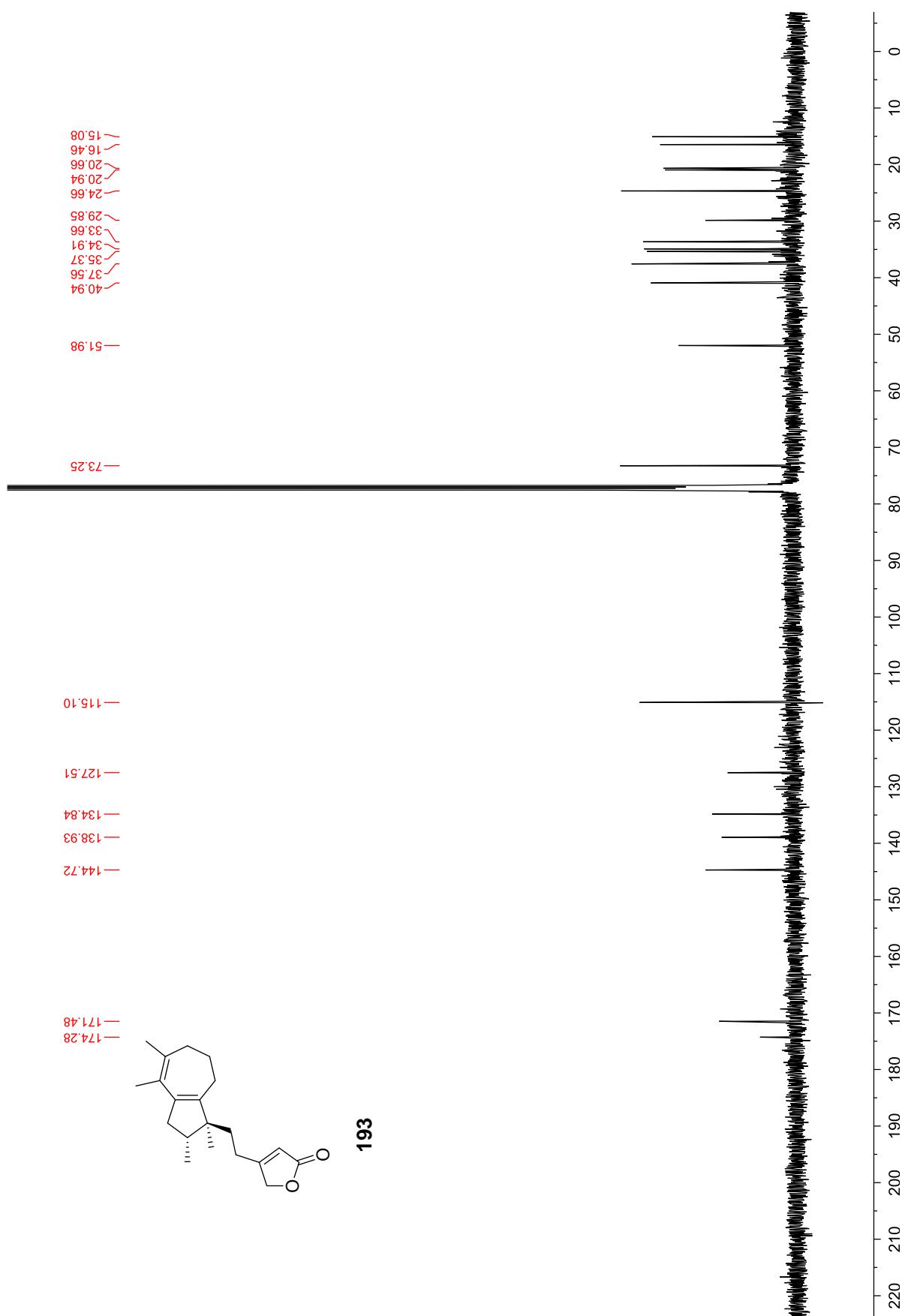




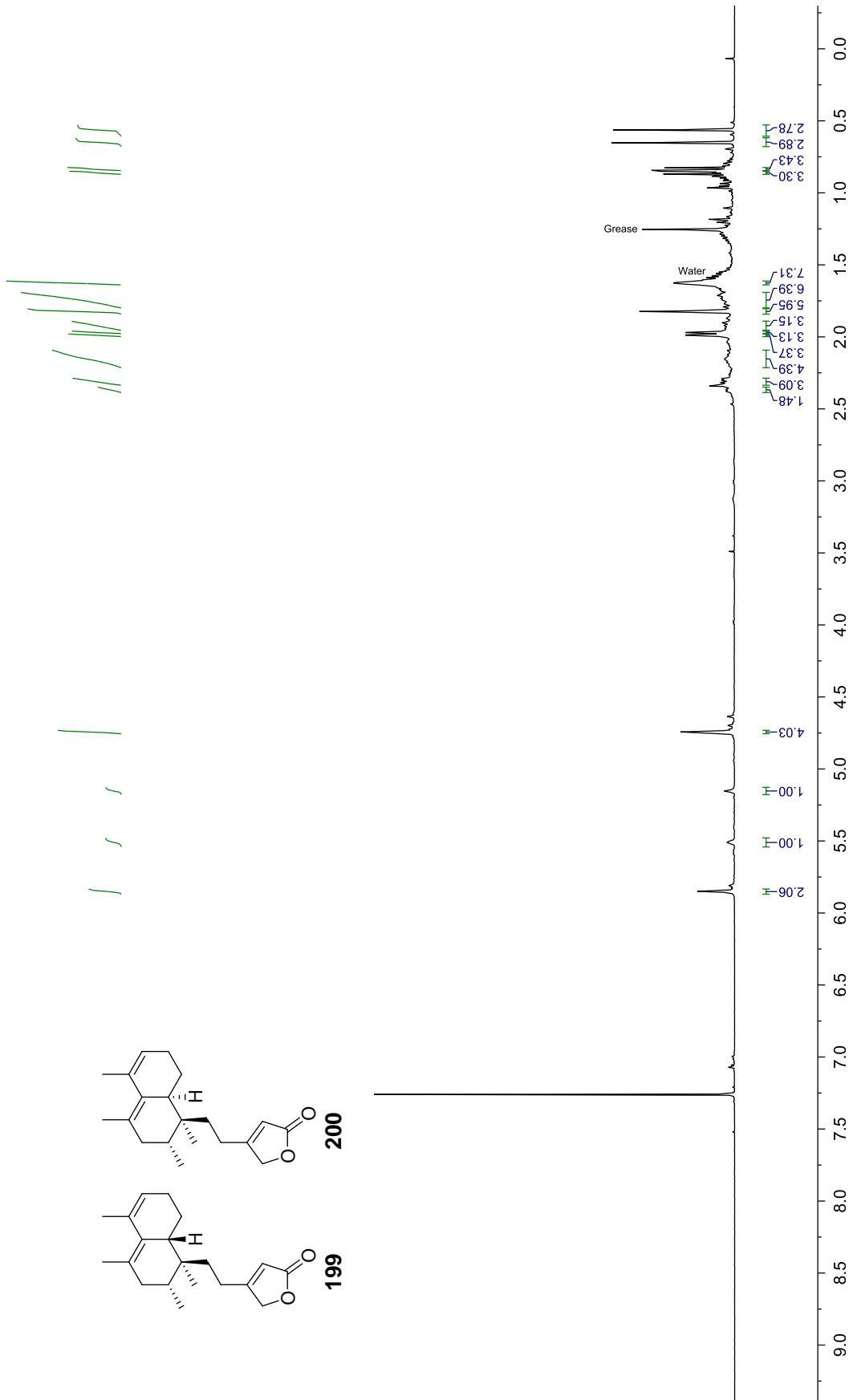


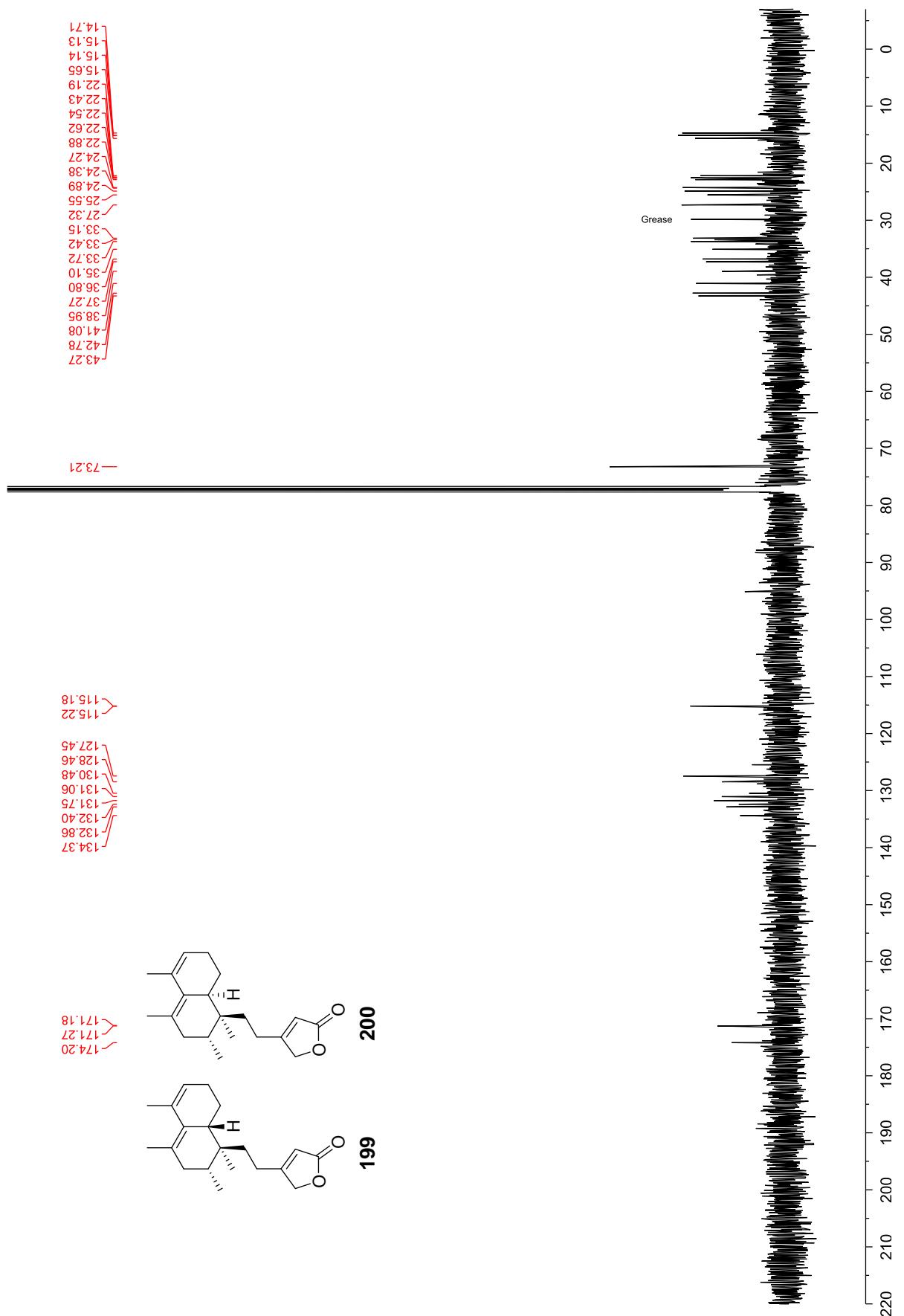


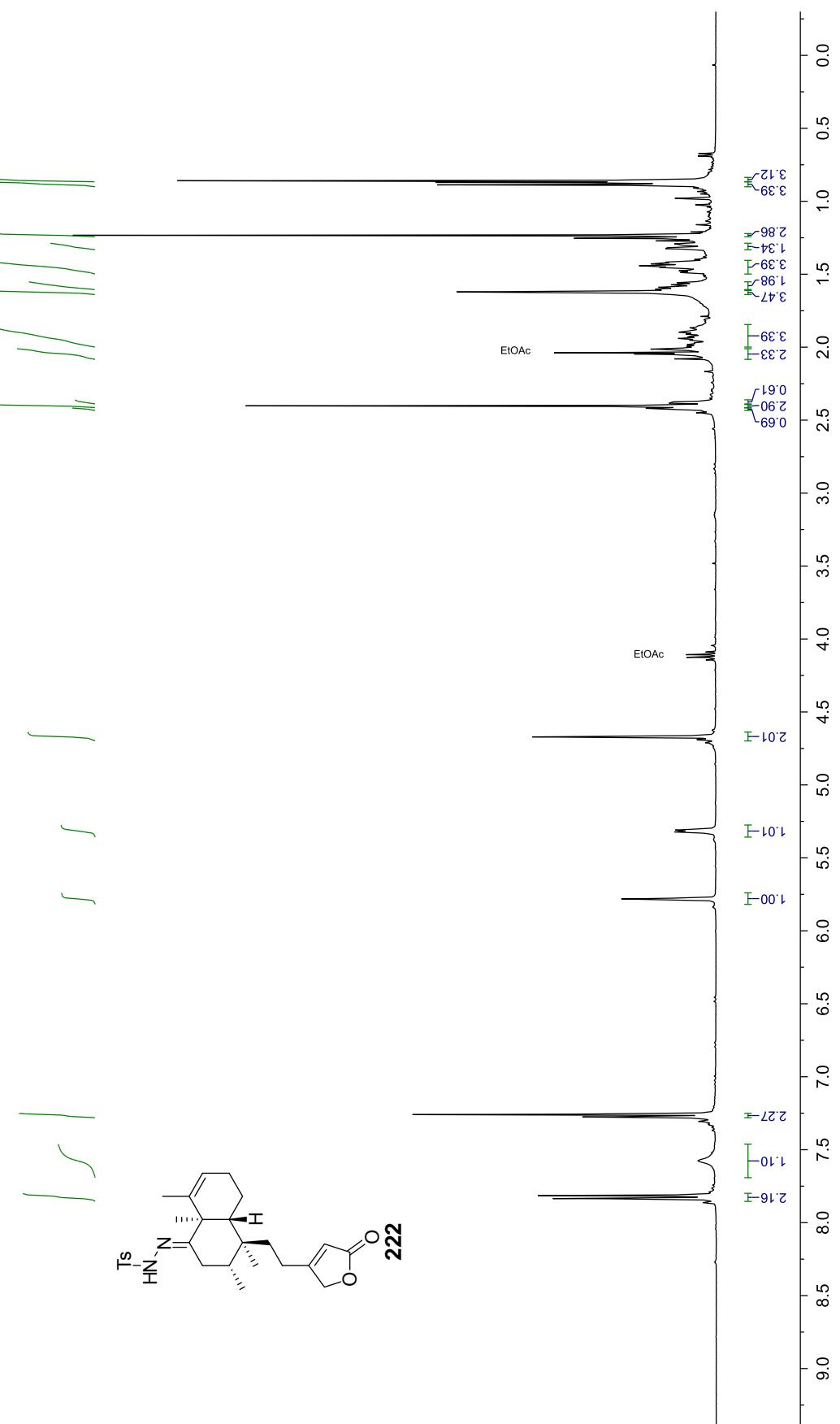


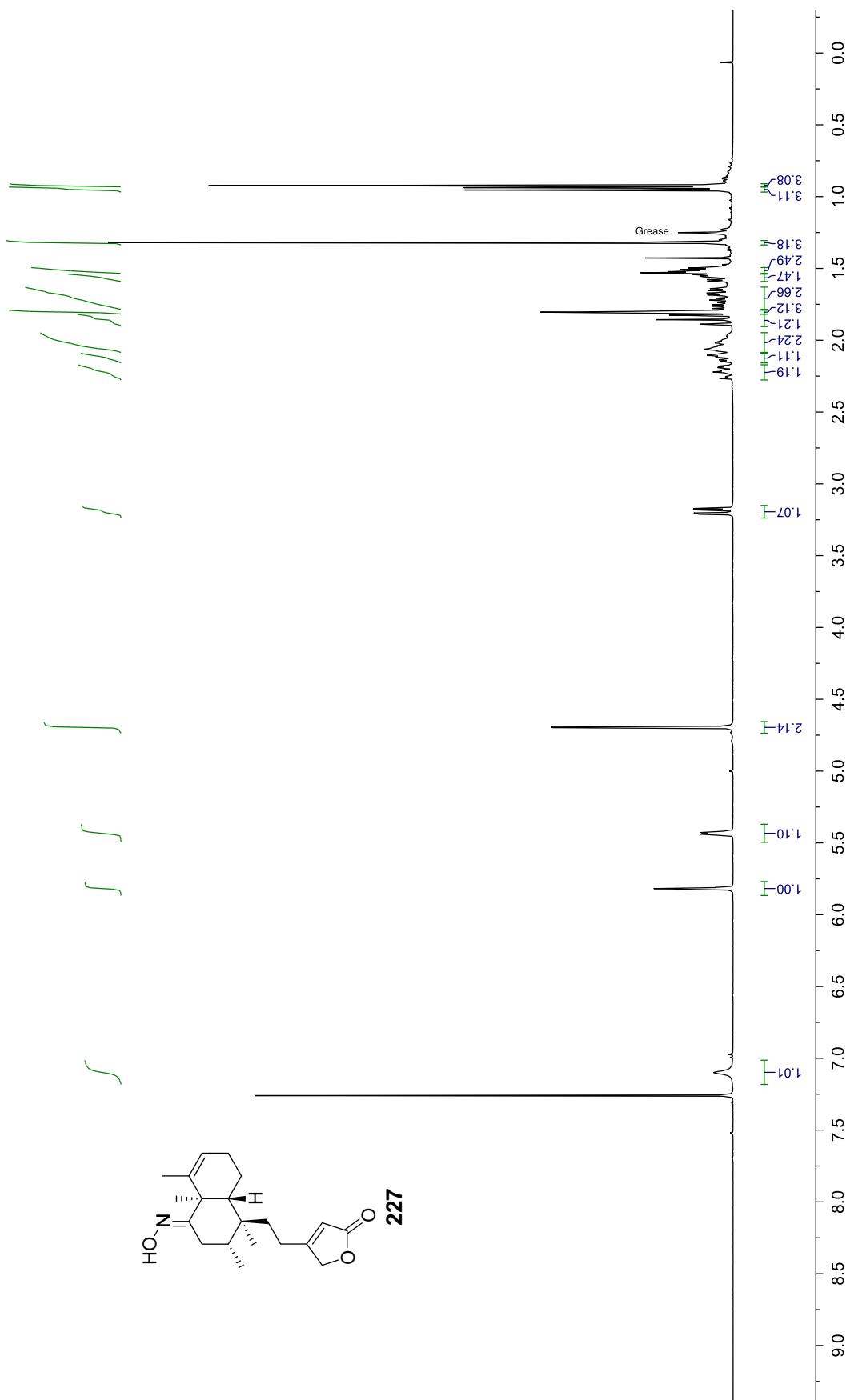


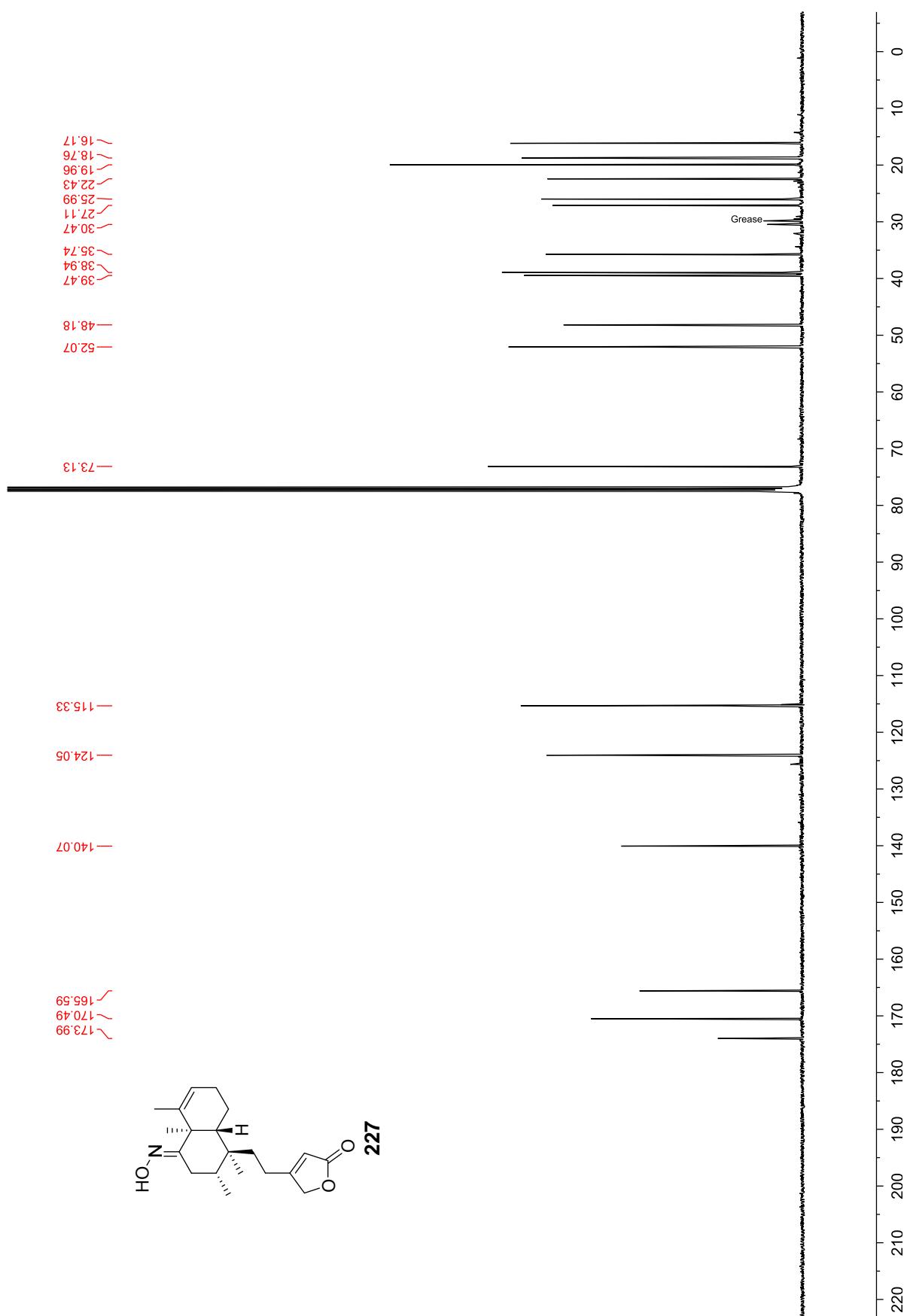
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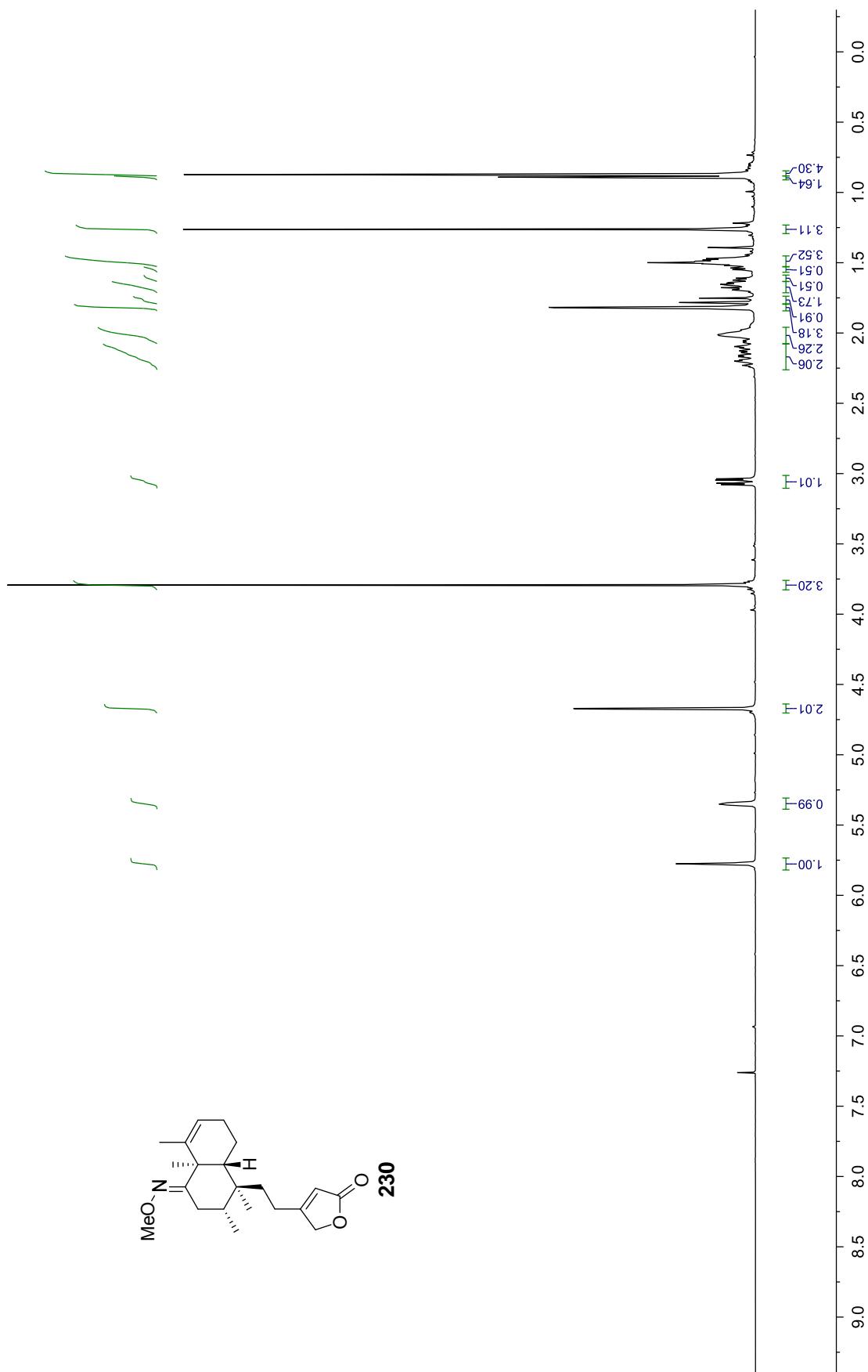


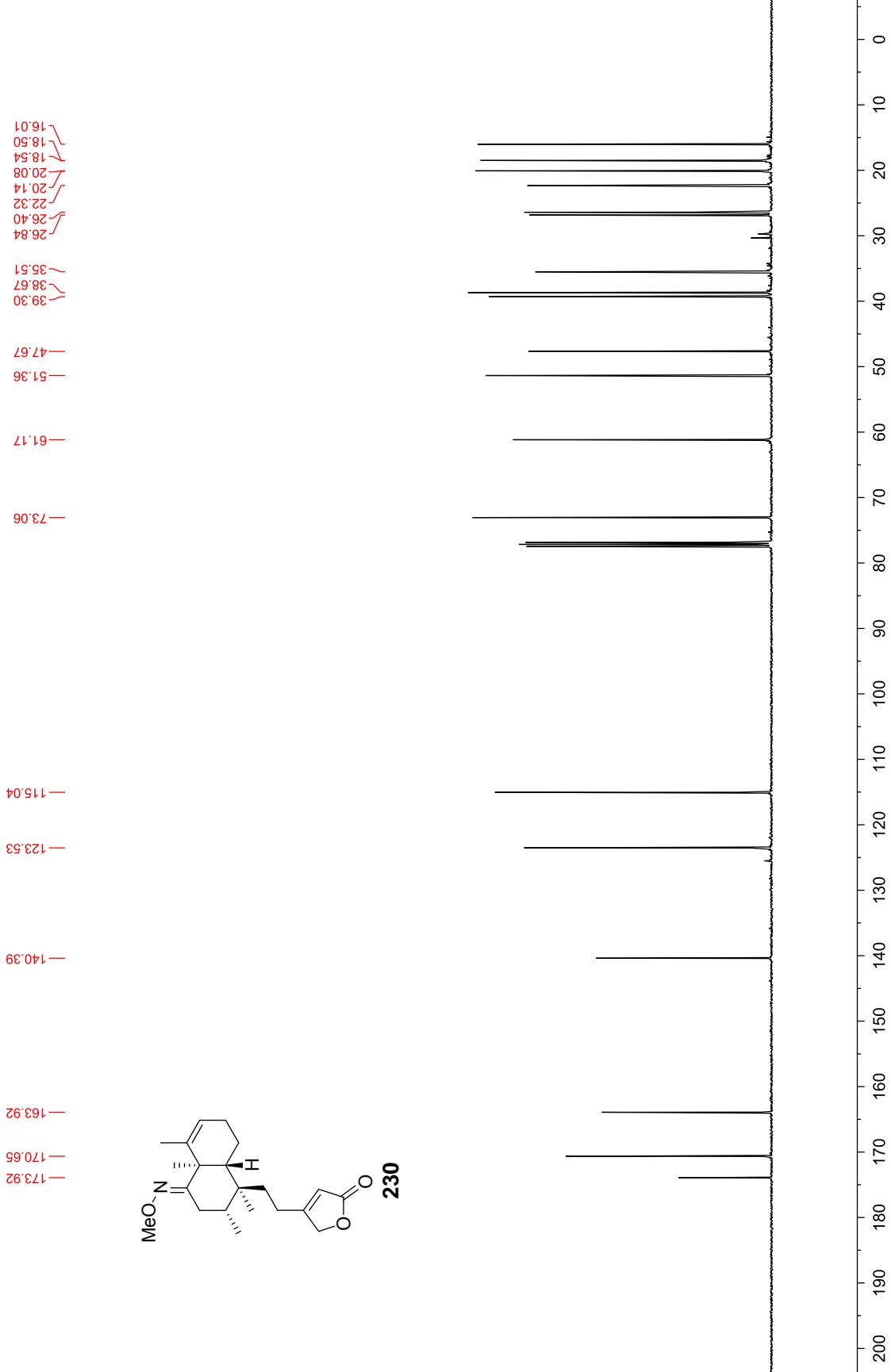


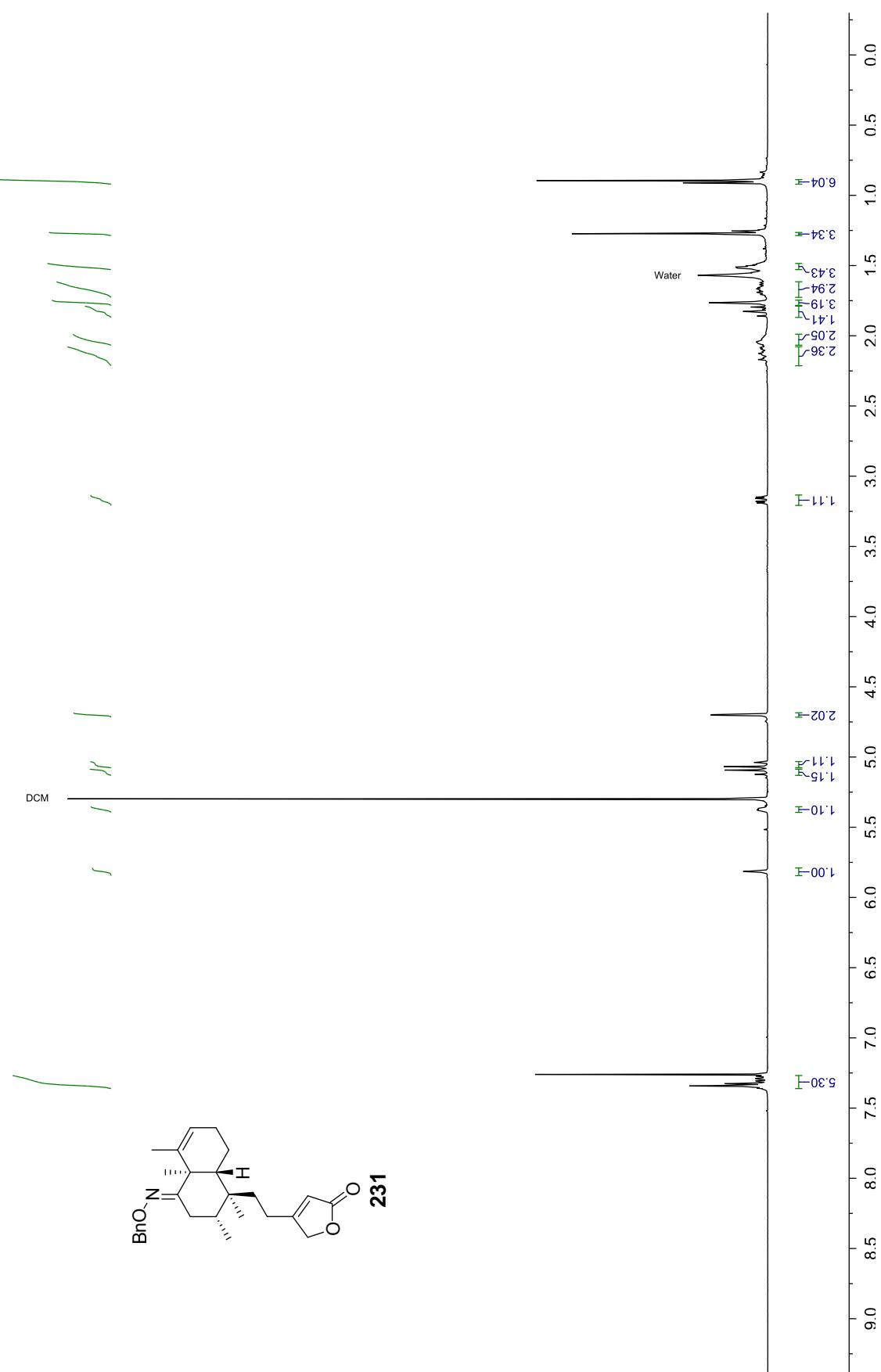


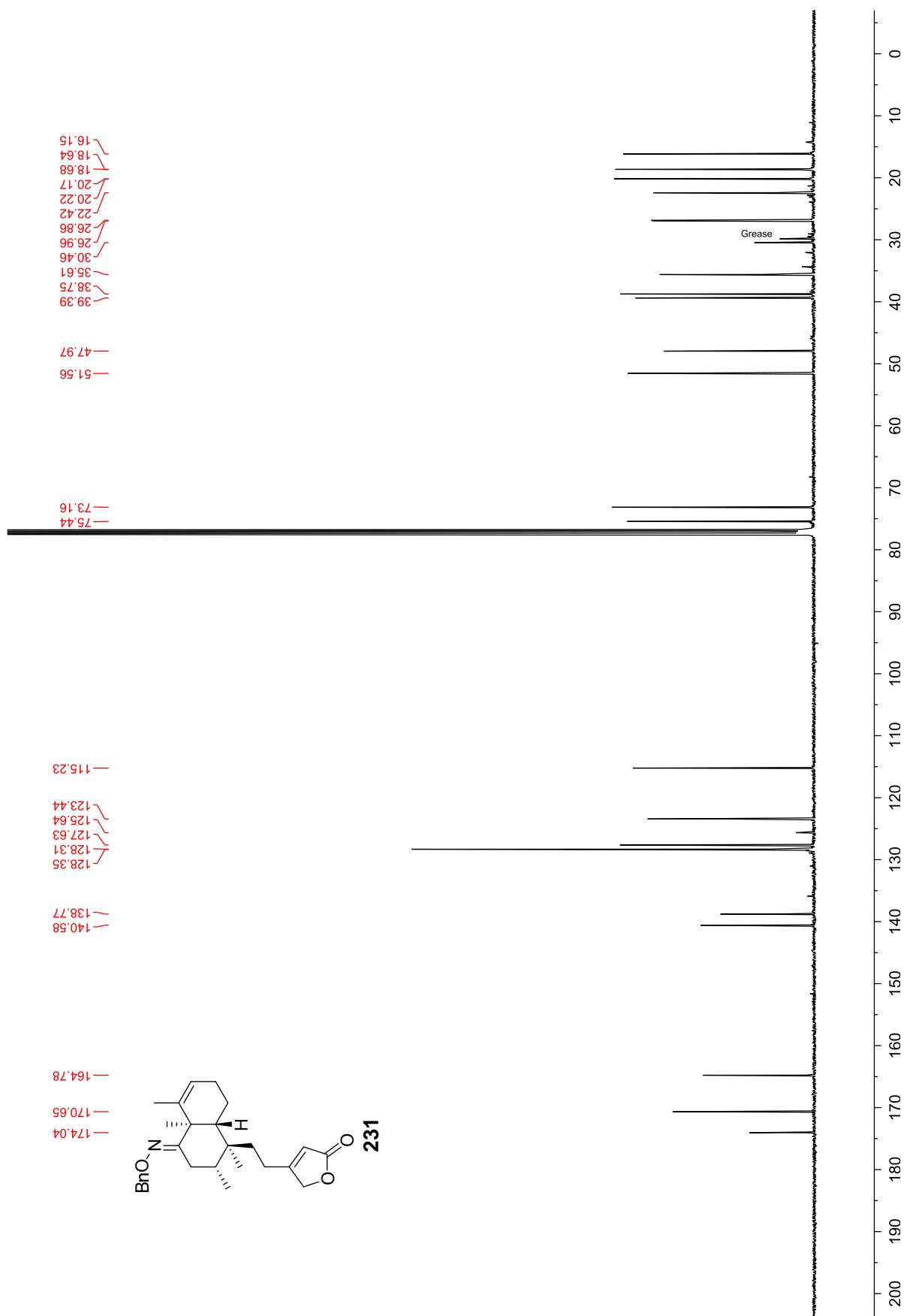


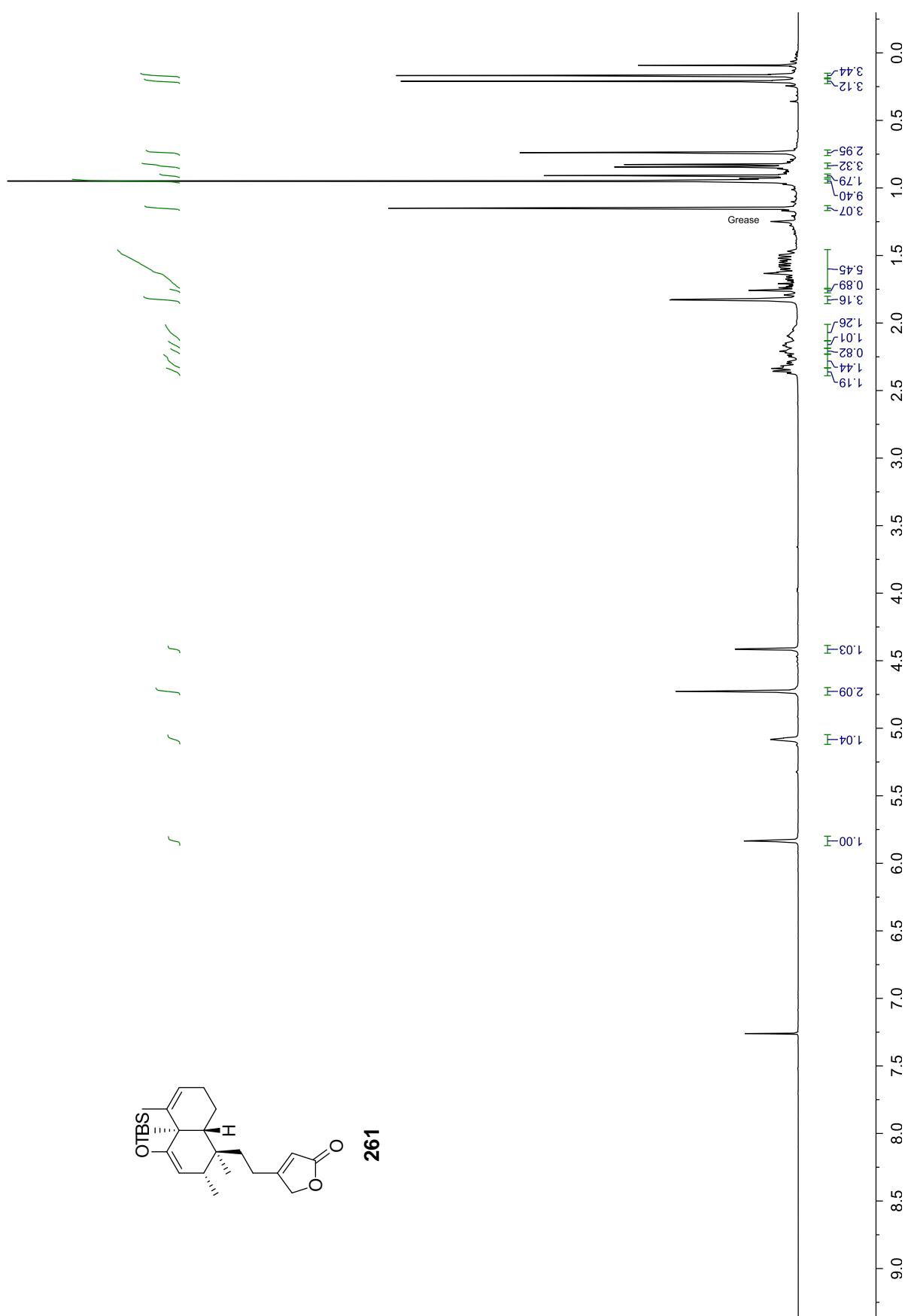


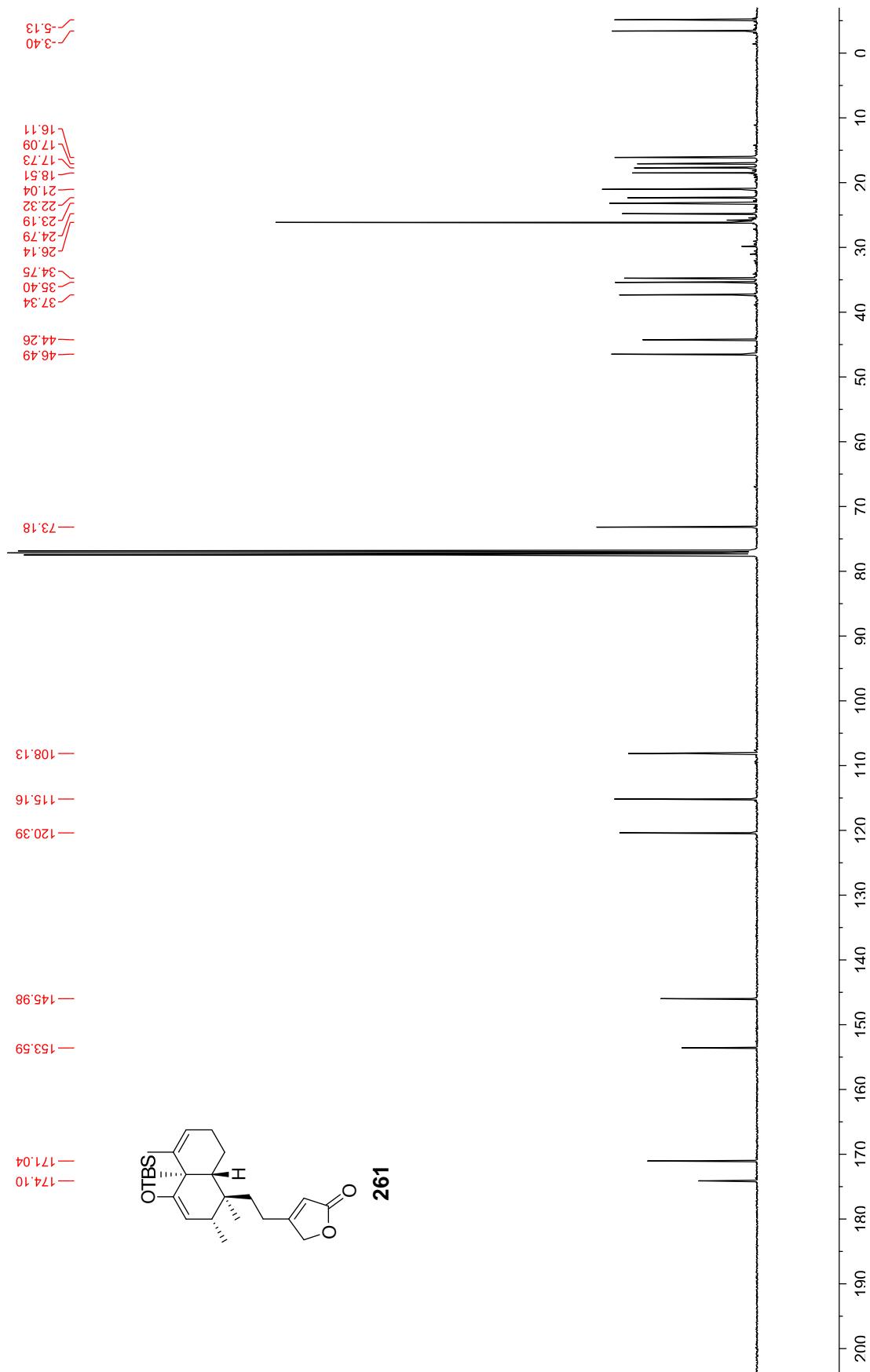


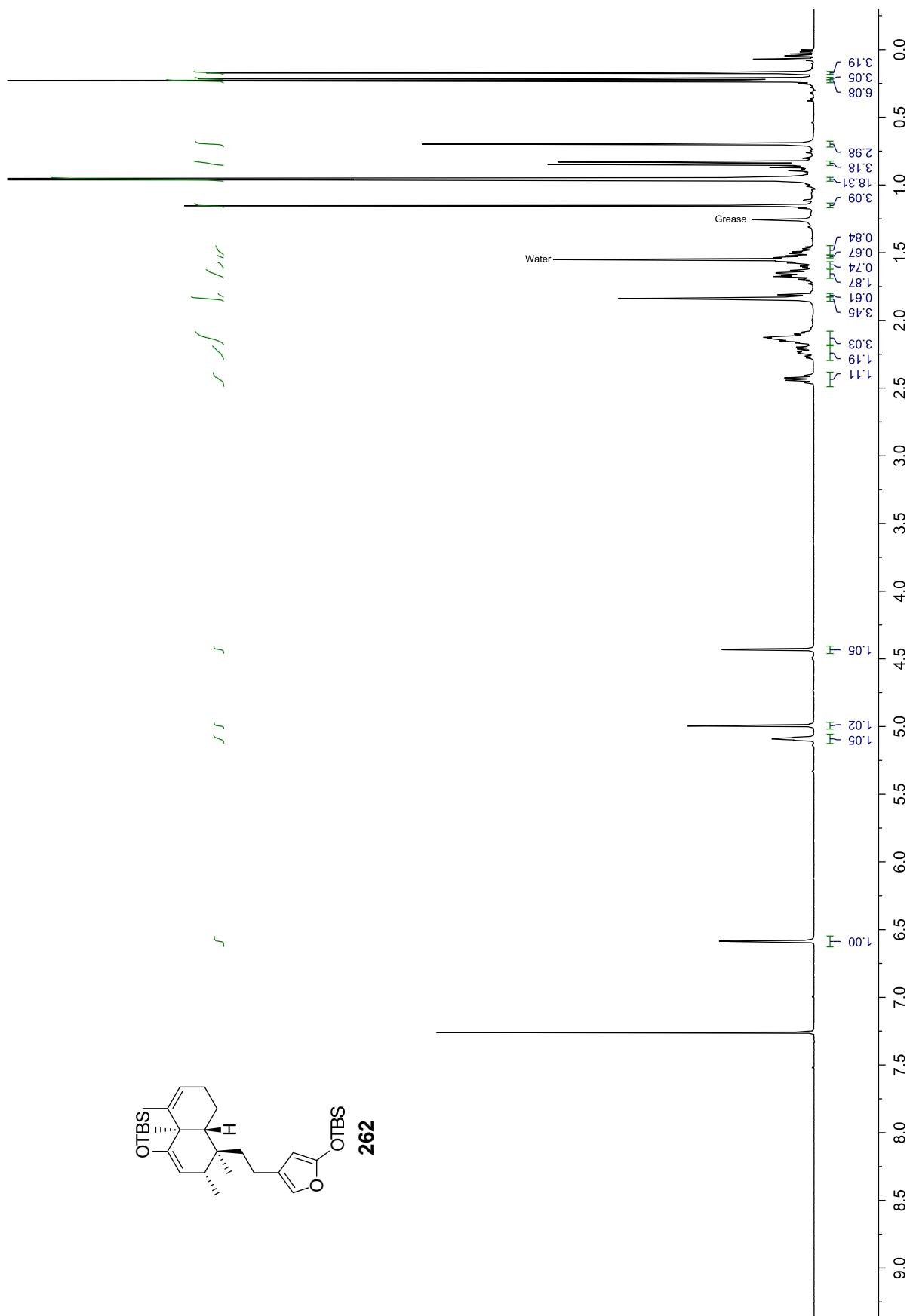


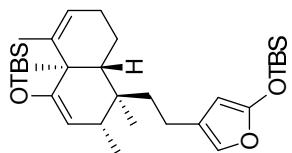
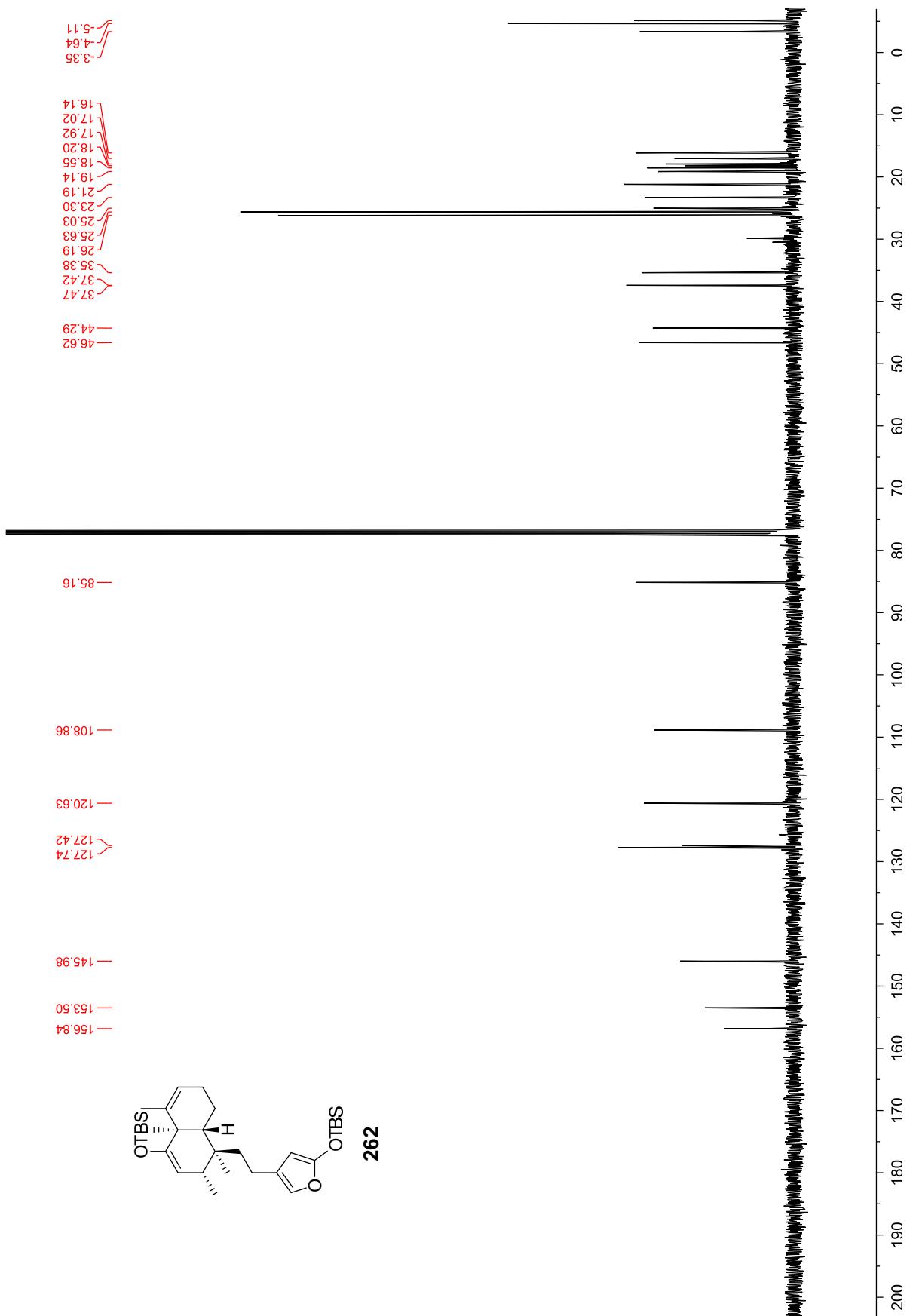




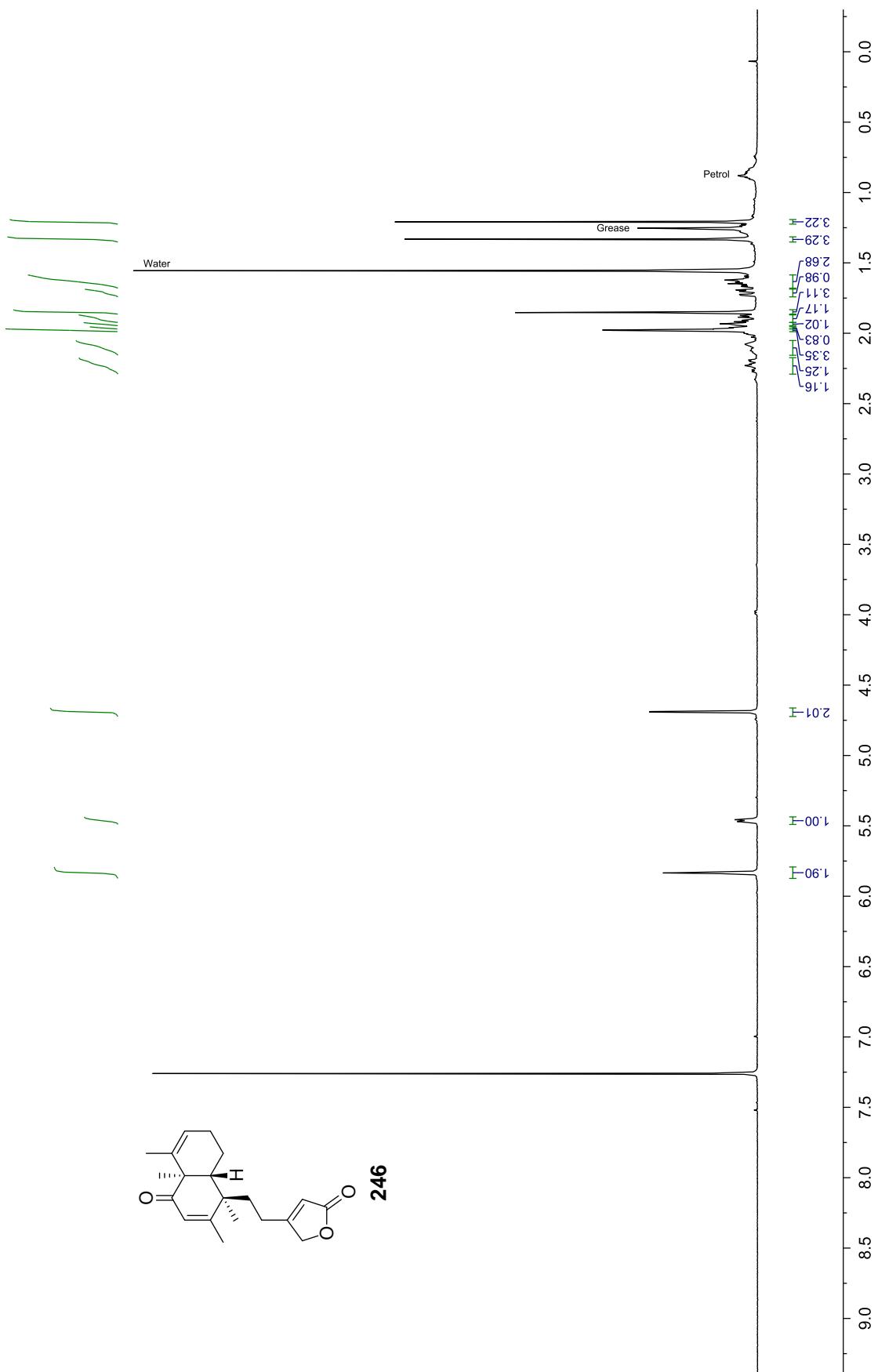


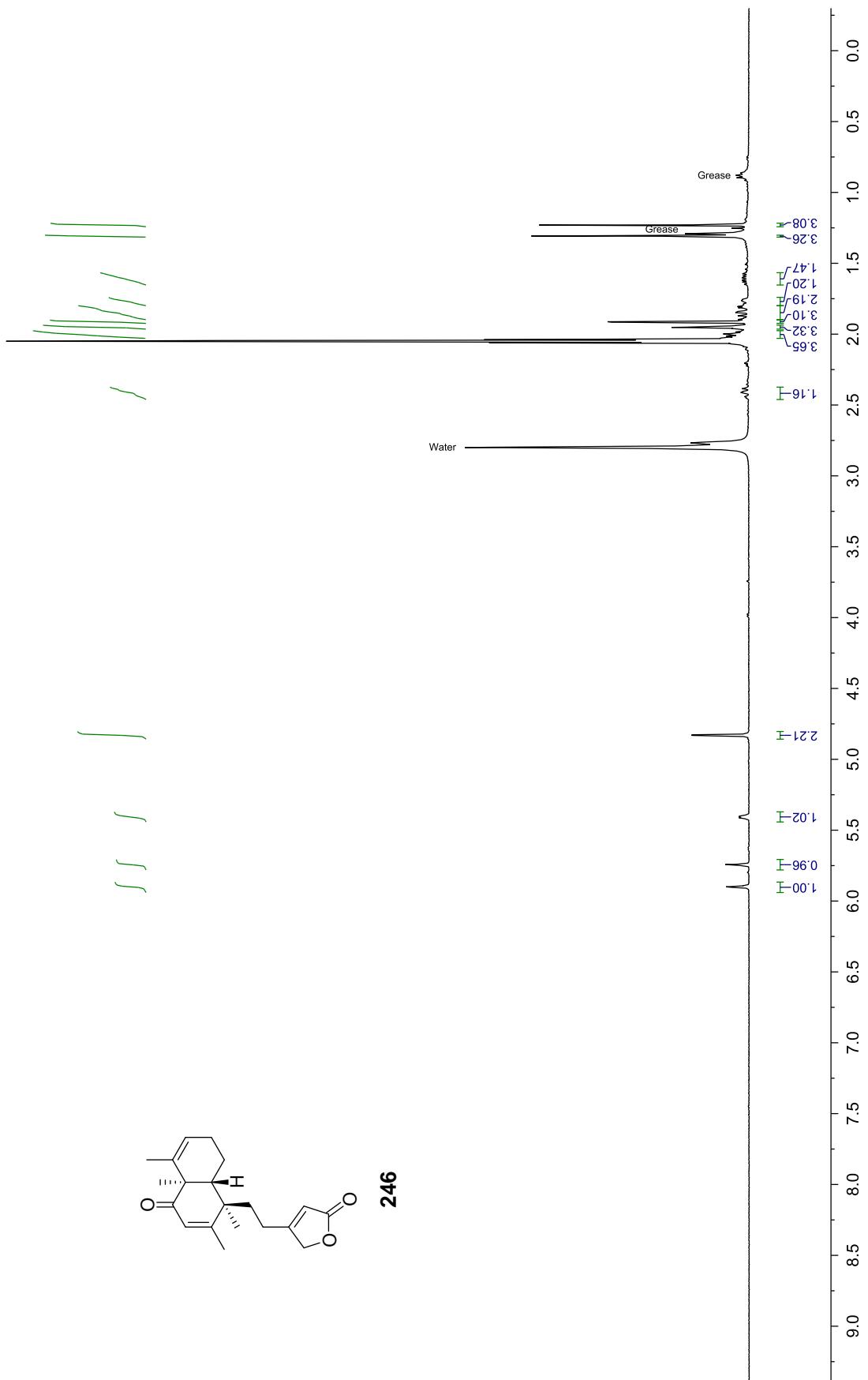


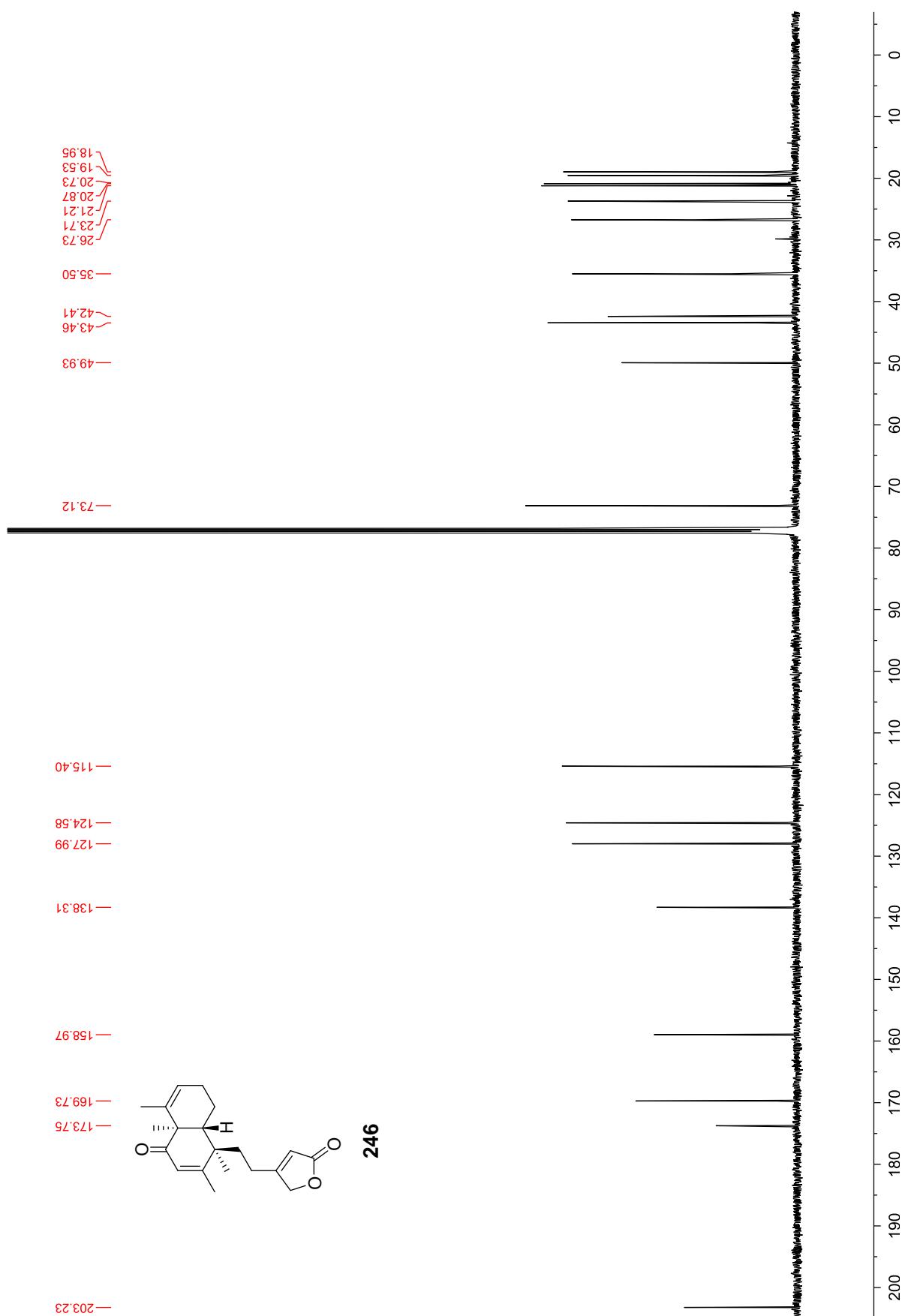




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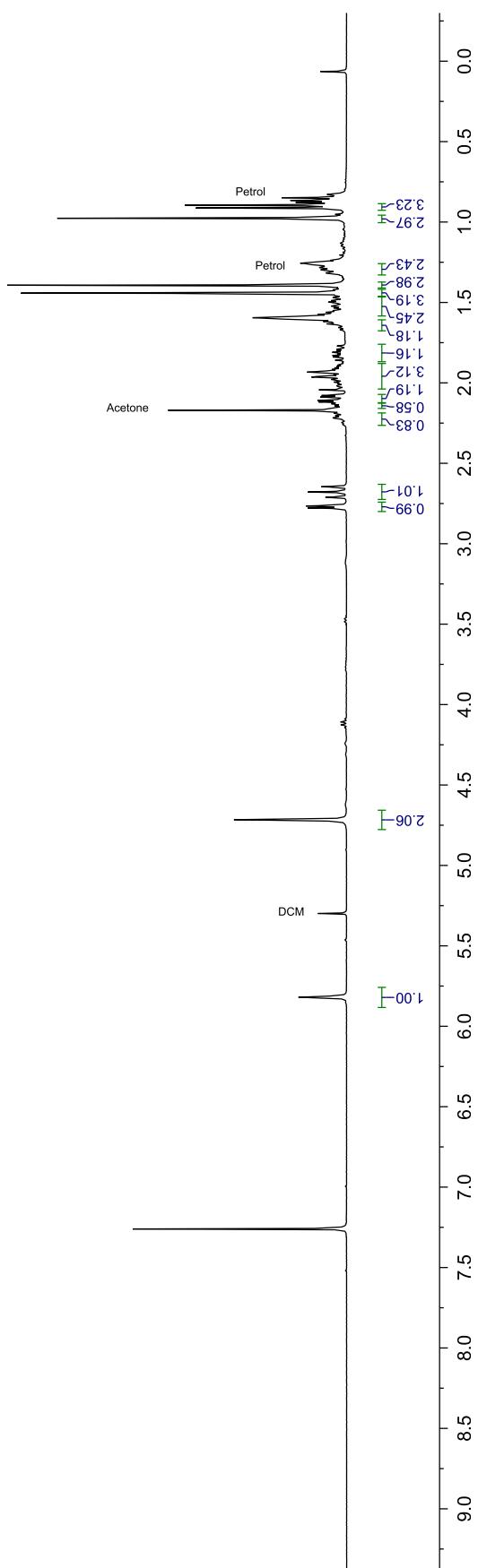


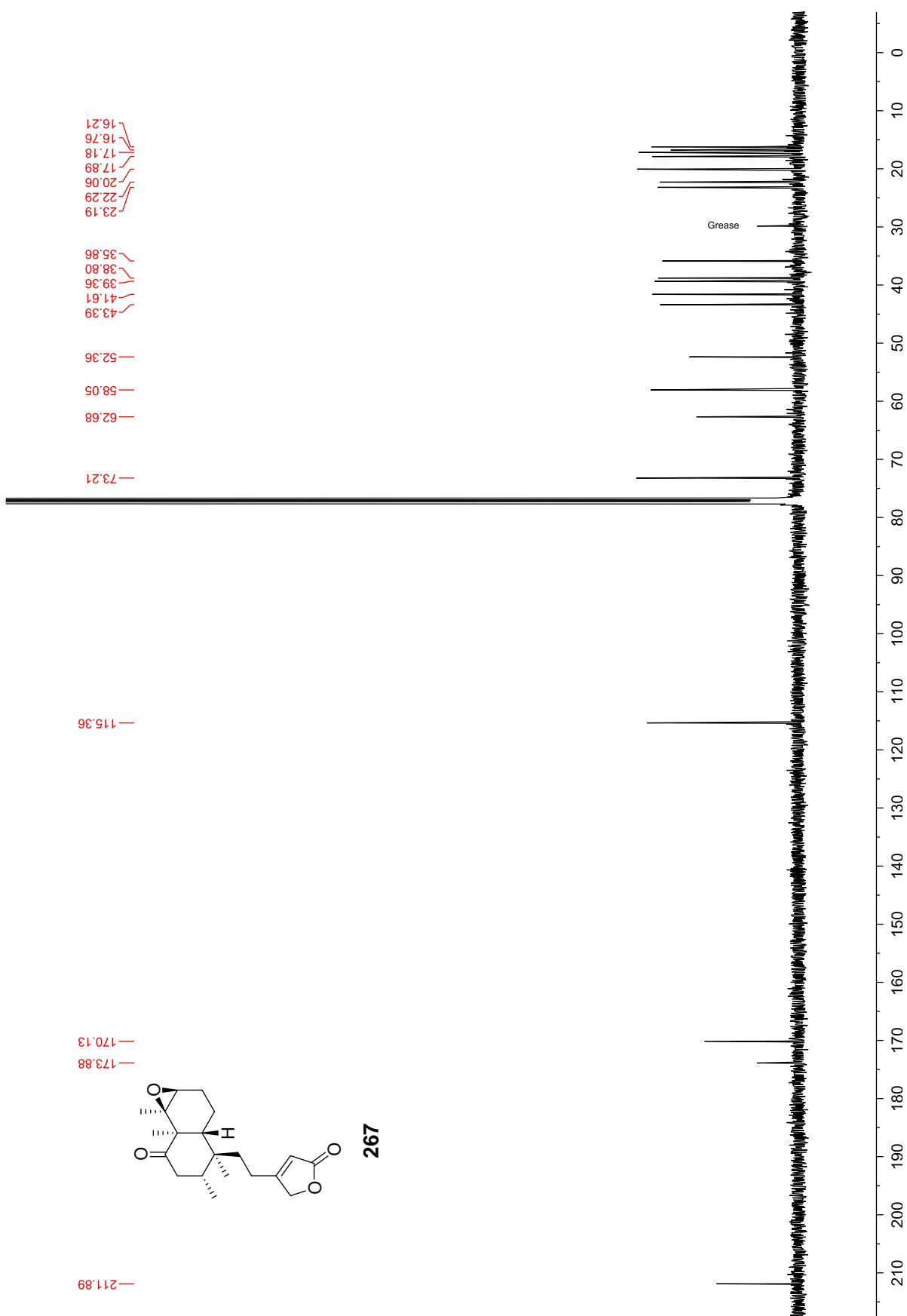




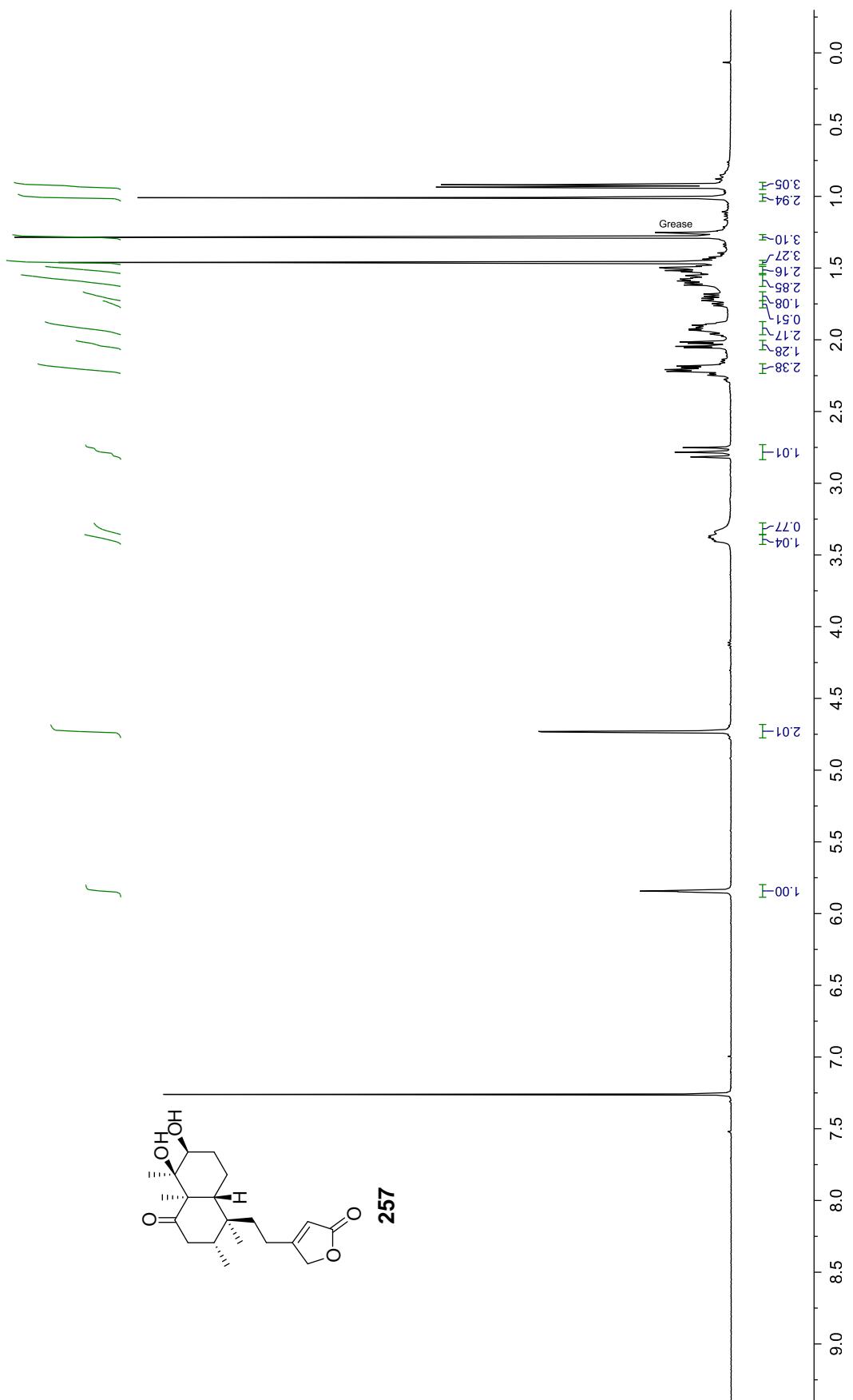


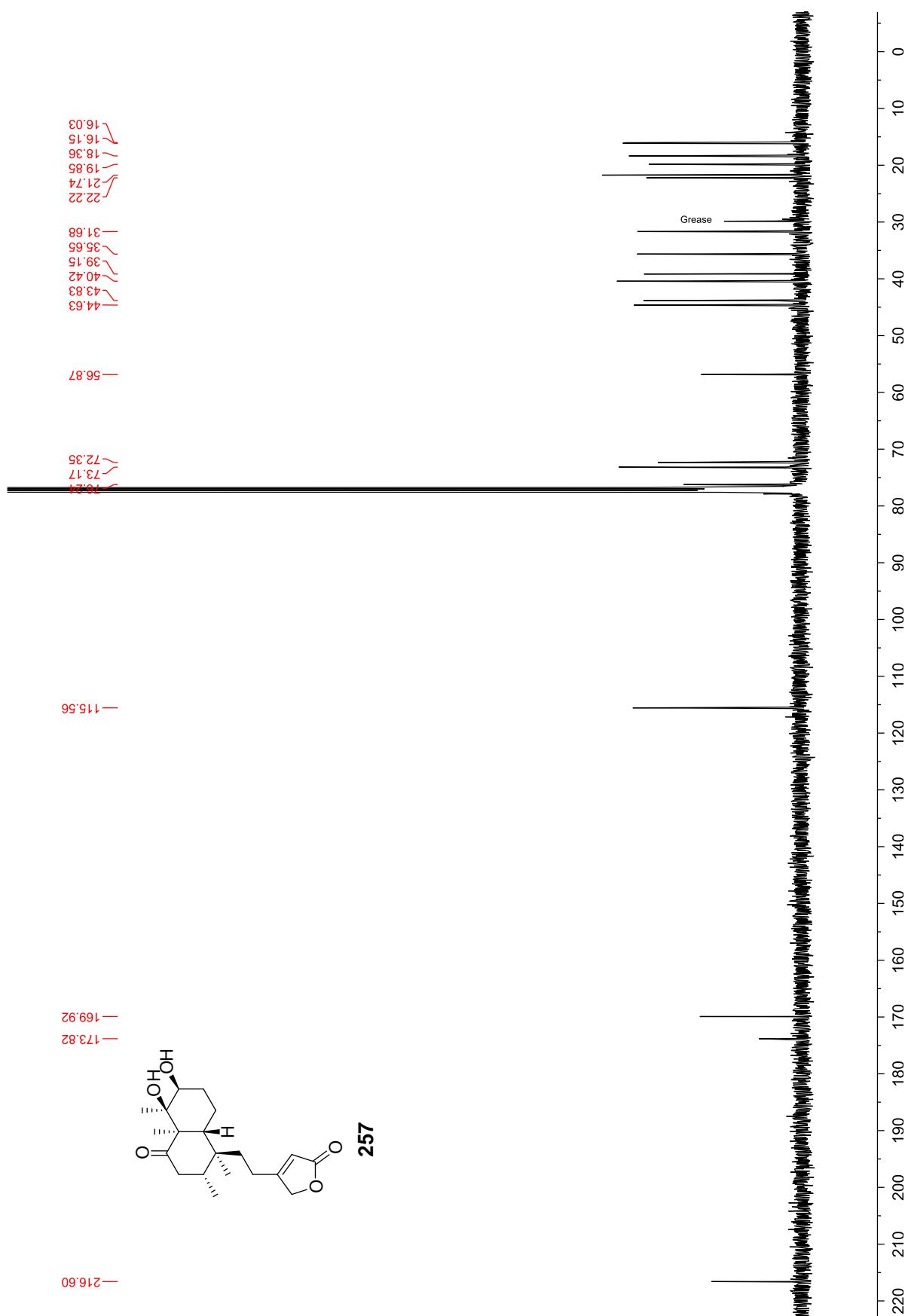
**267**

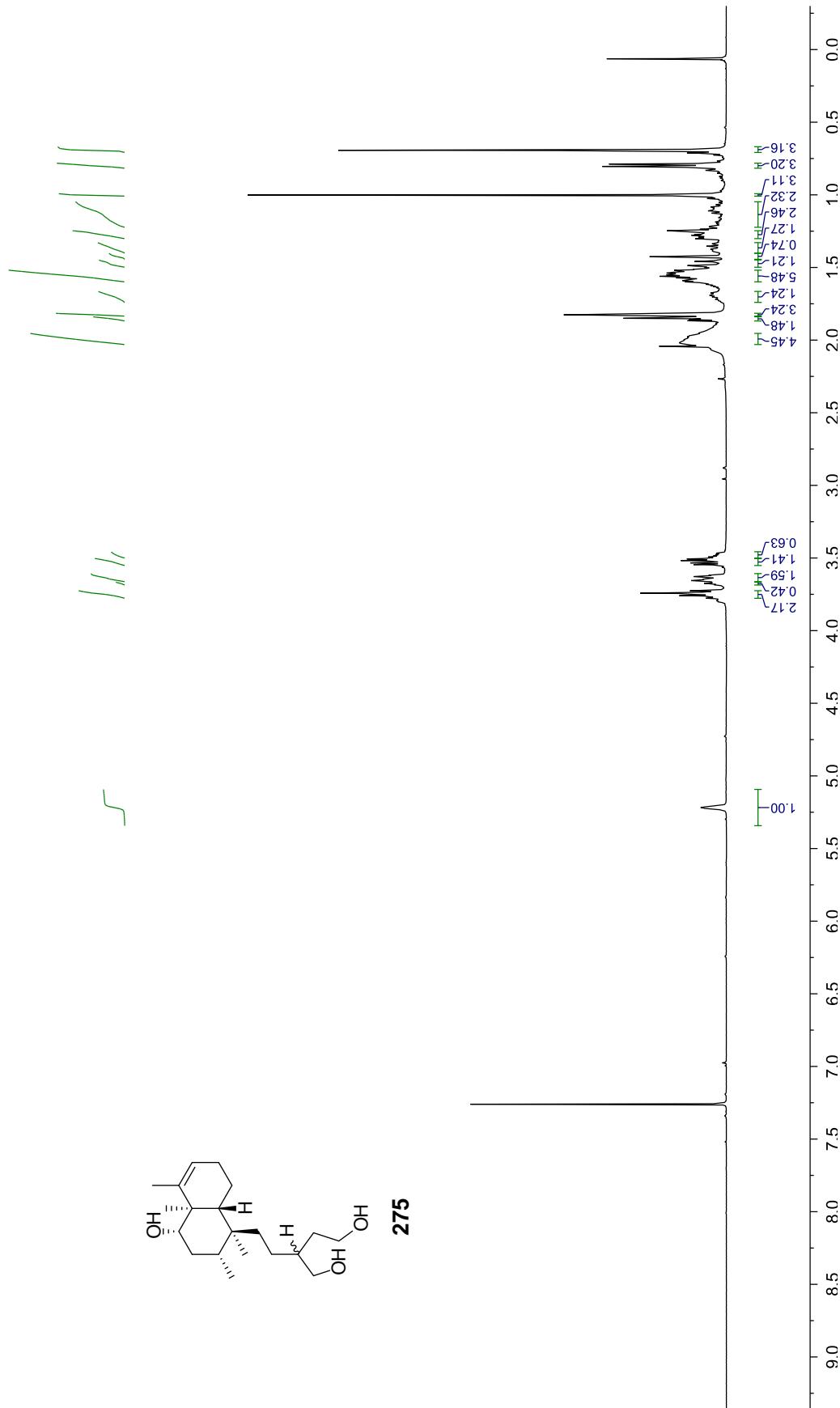


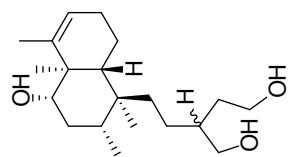
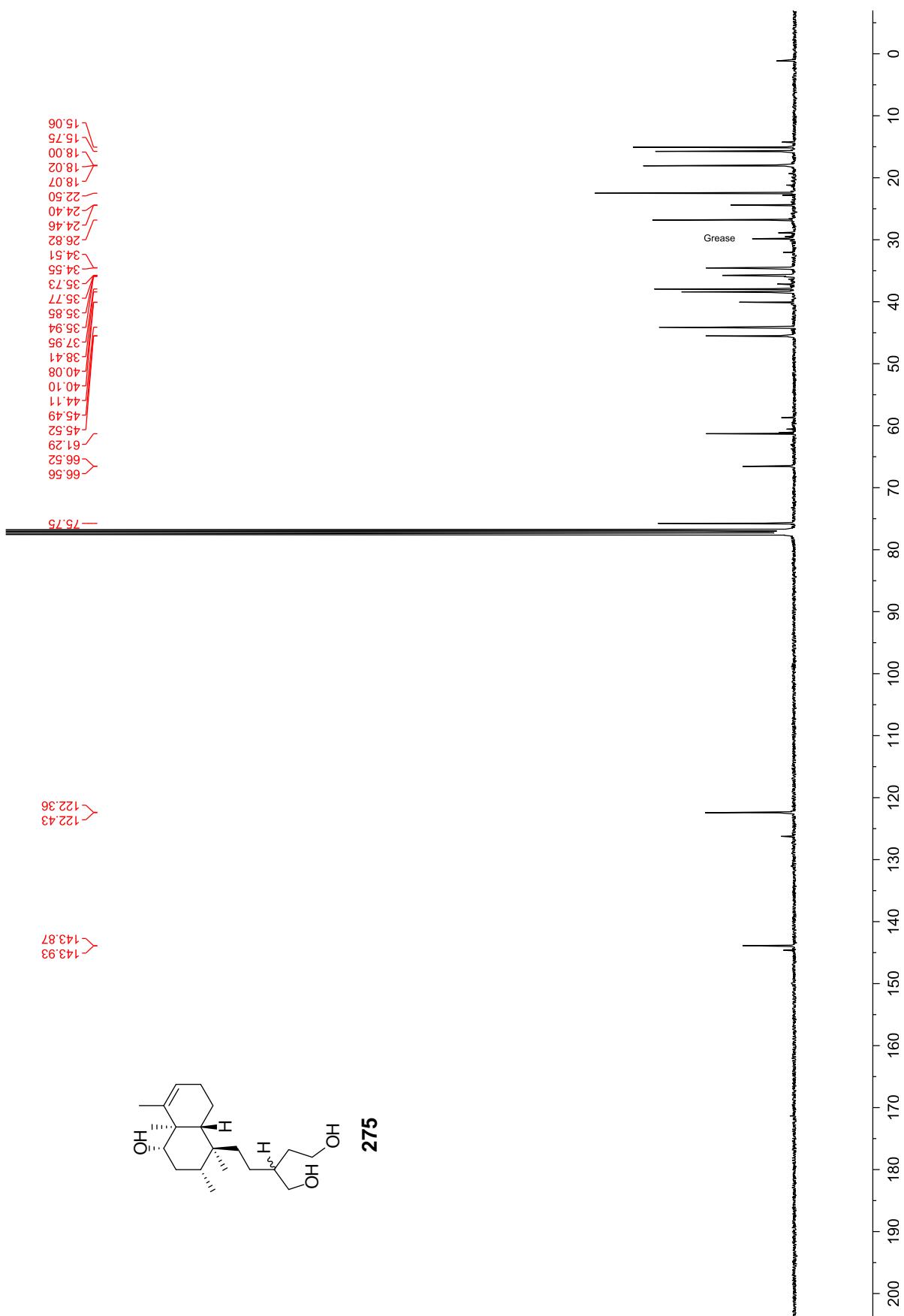


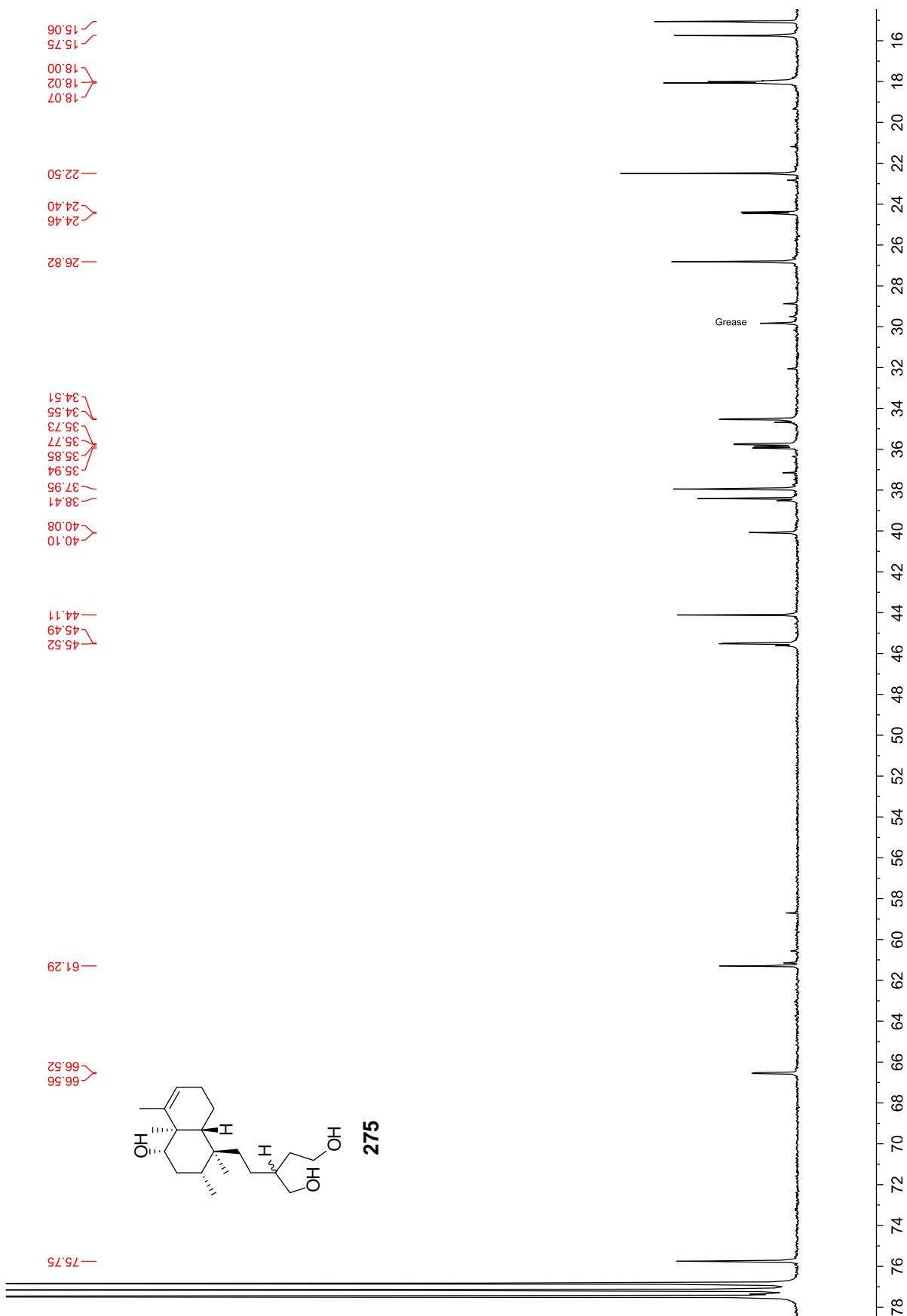
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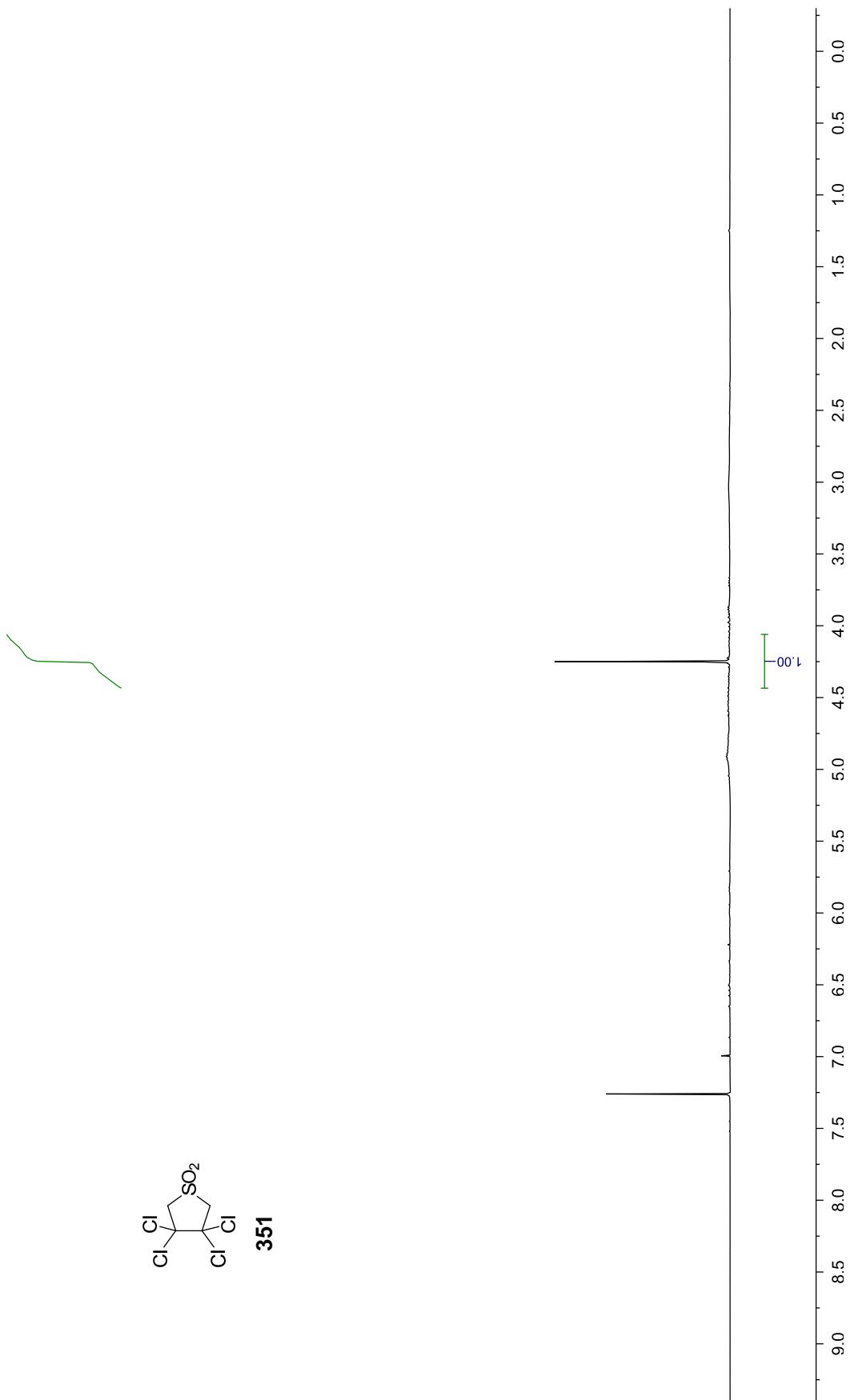




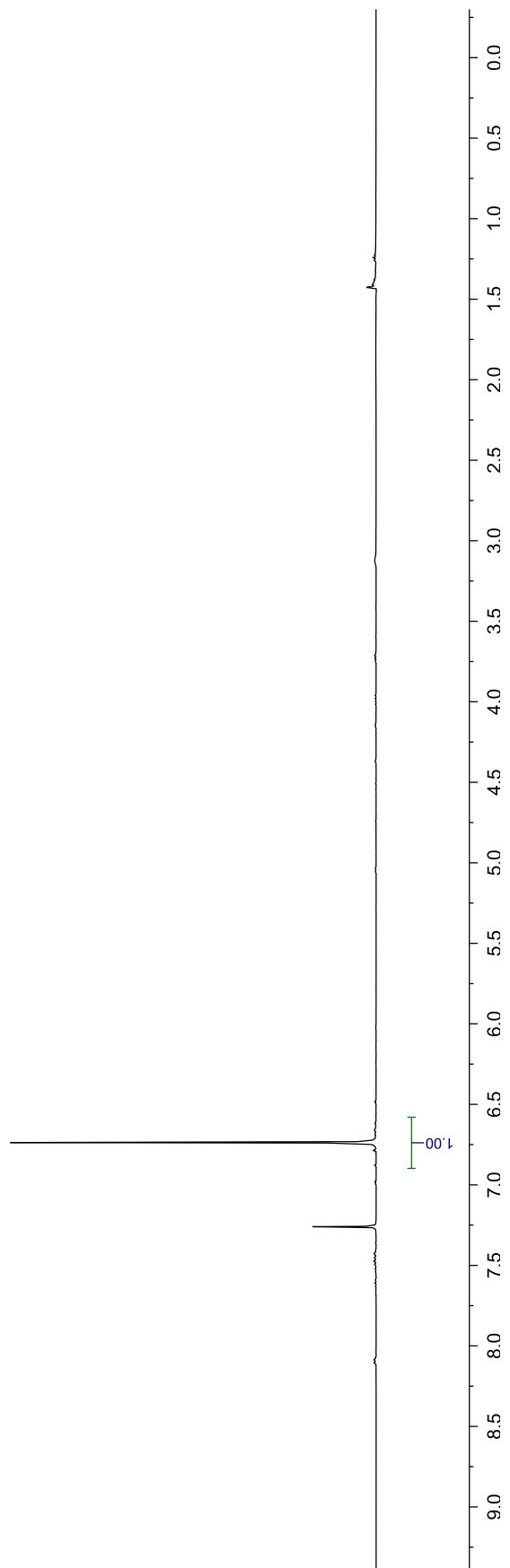
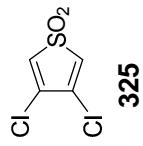


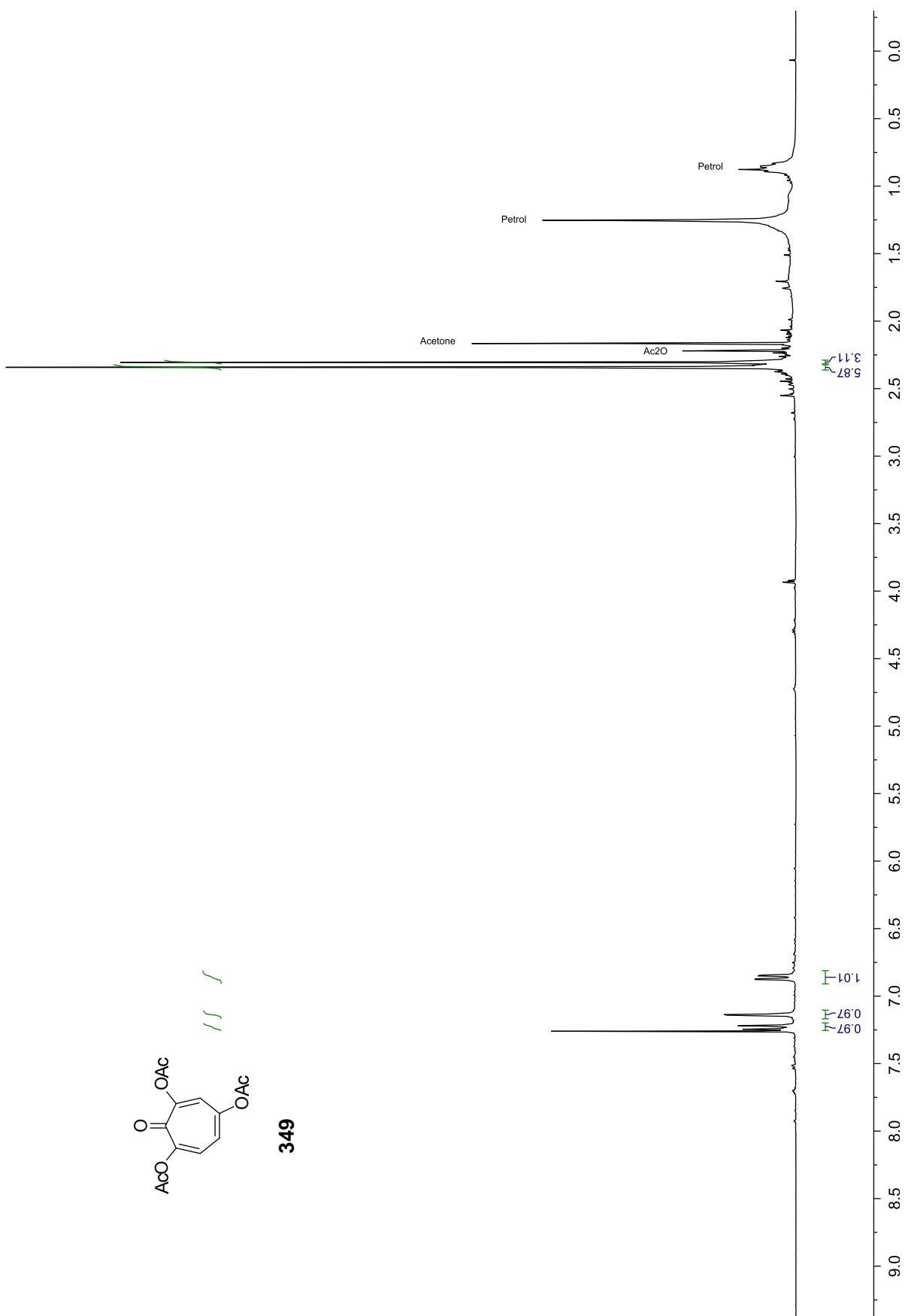
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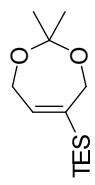
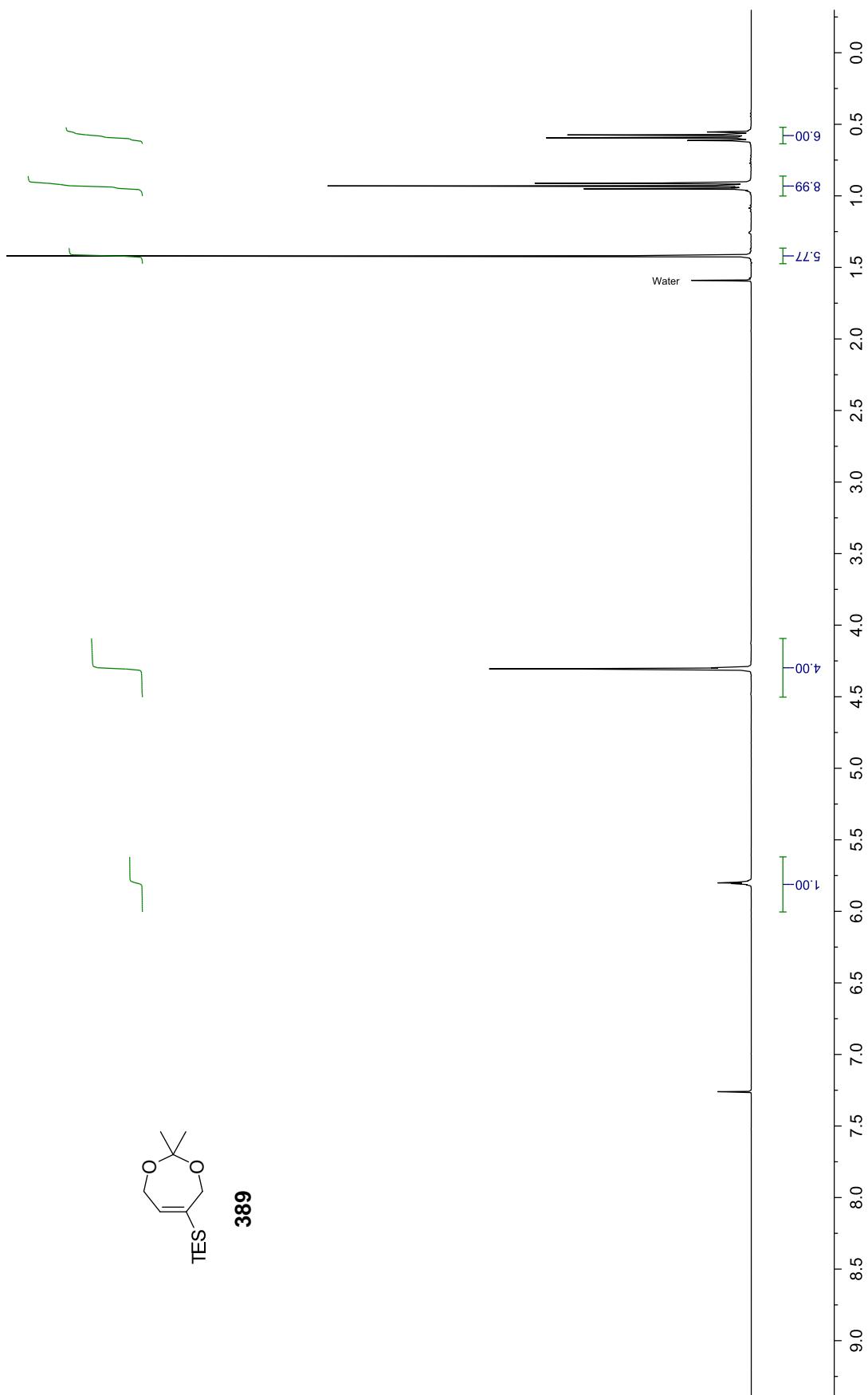
## B.2. Cordytrapolone



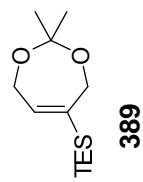
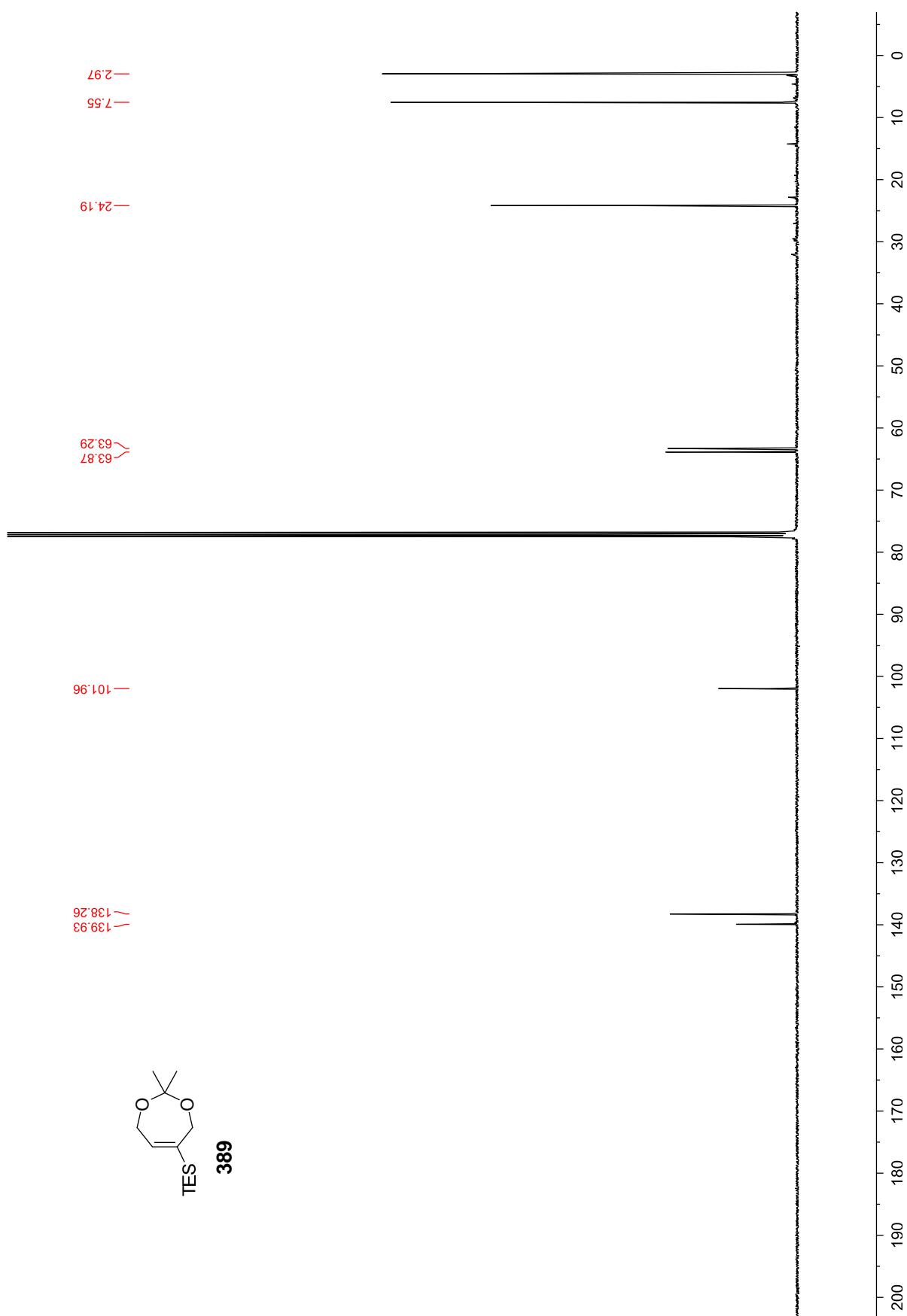
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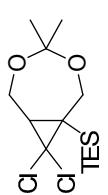
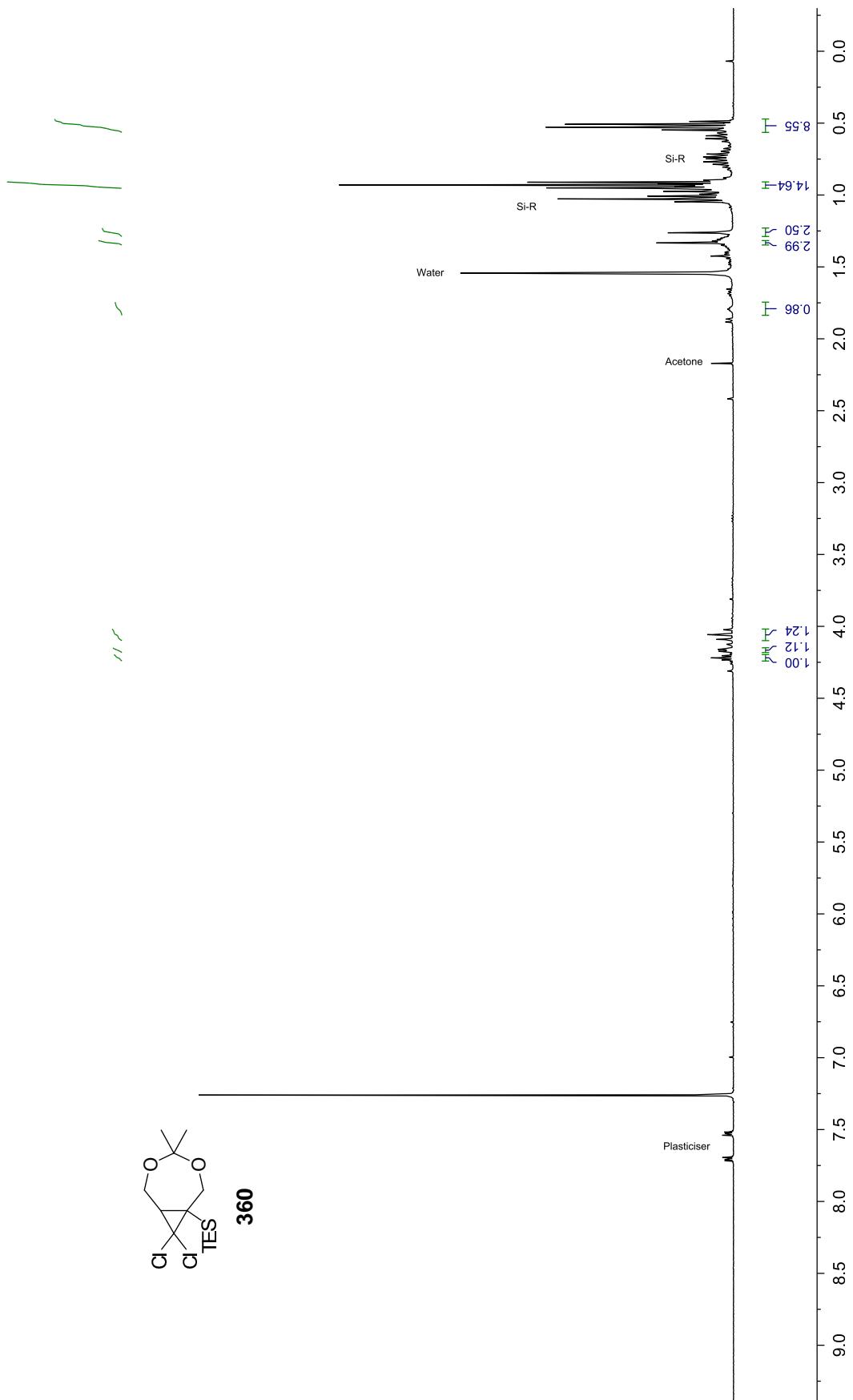




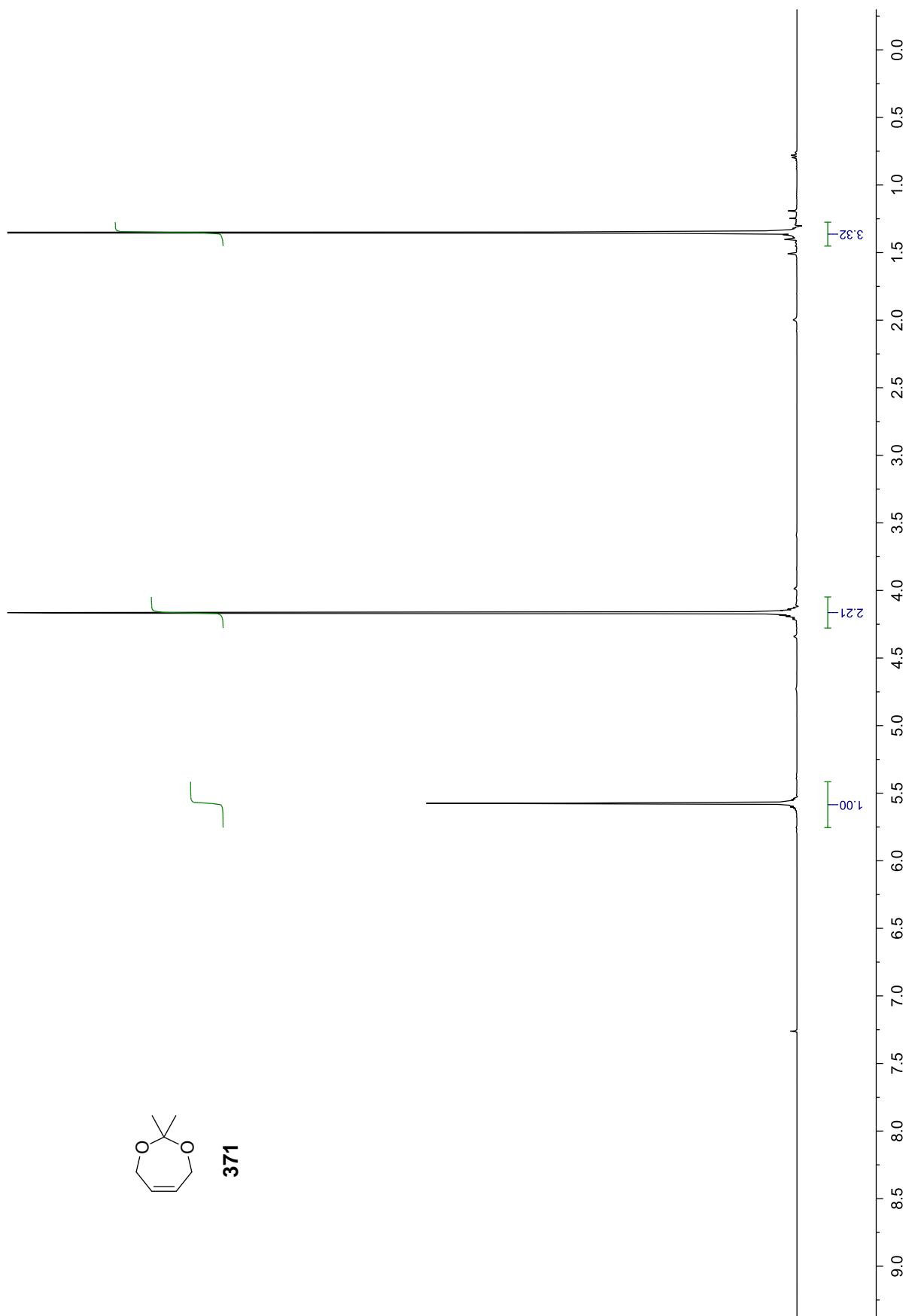


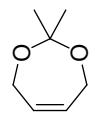
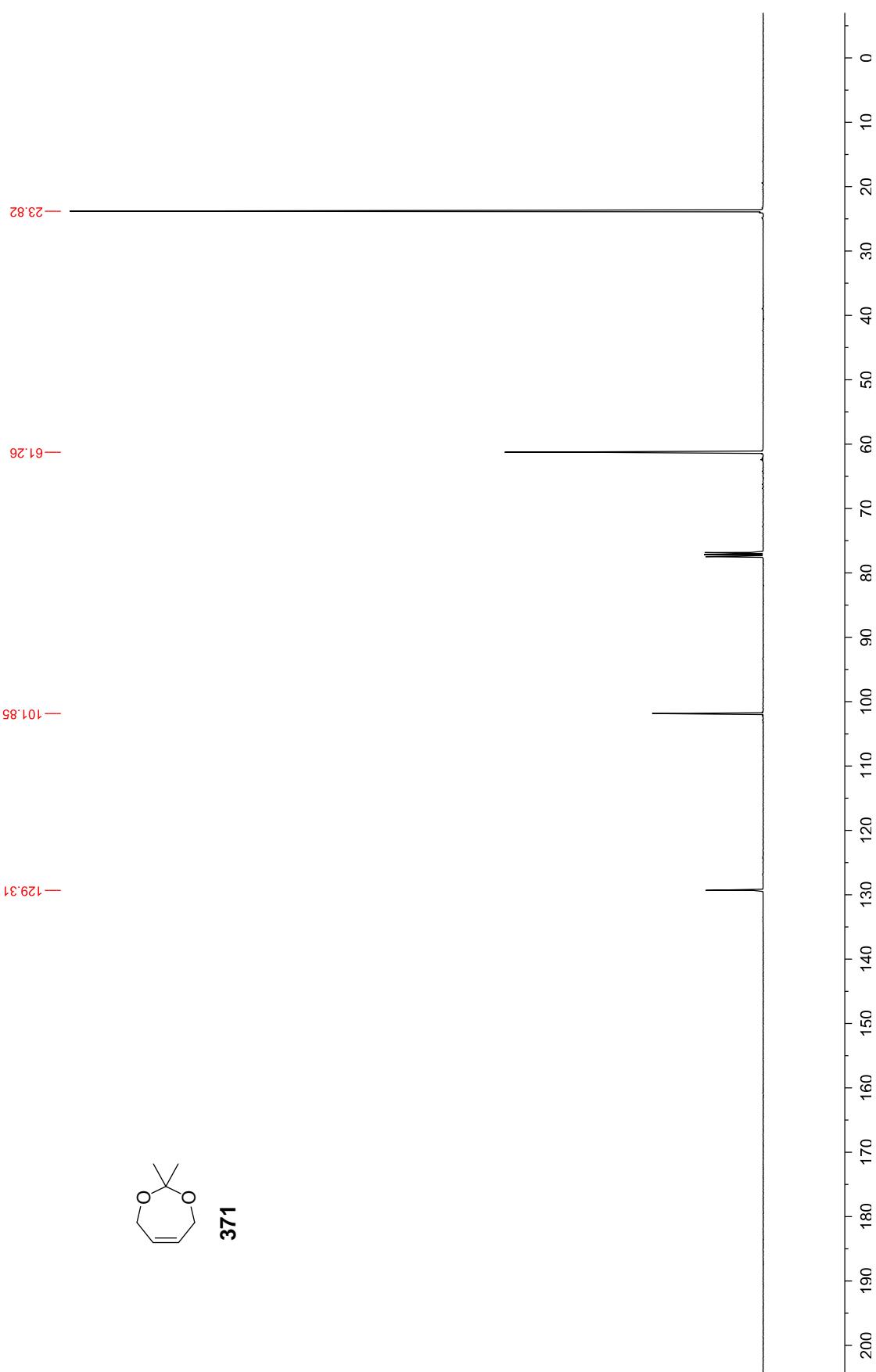
389



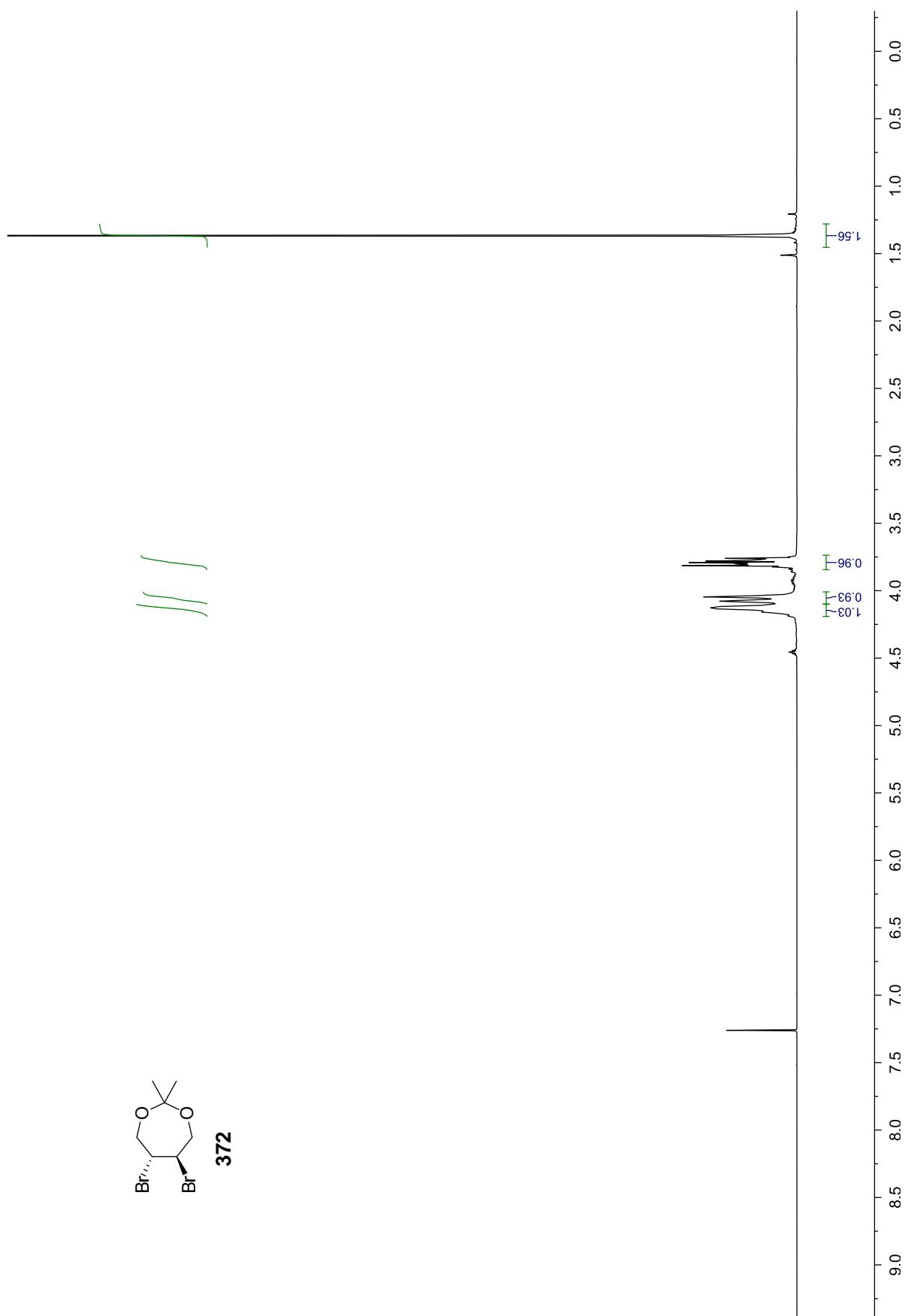


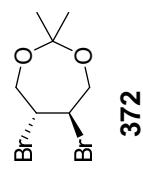
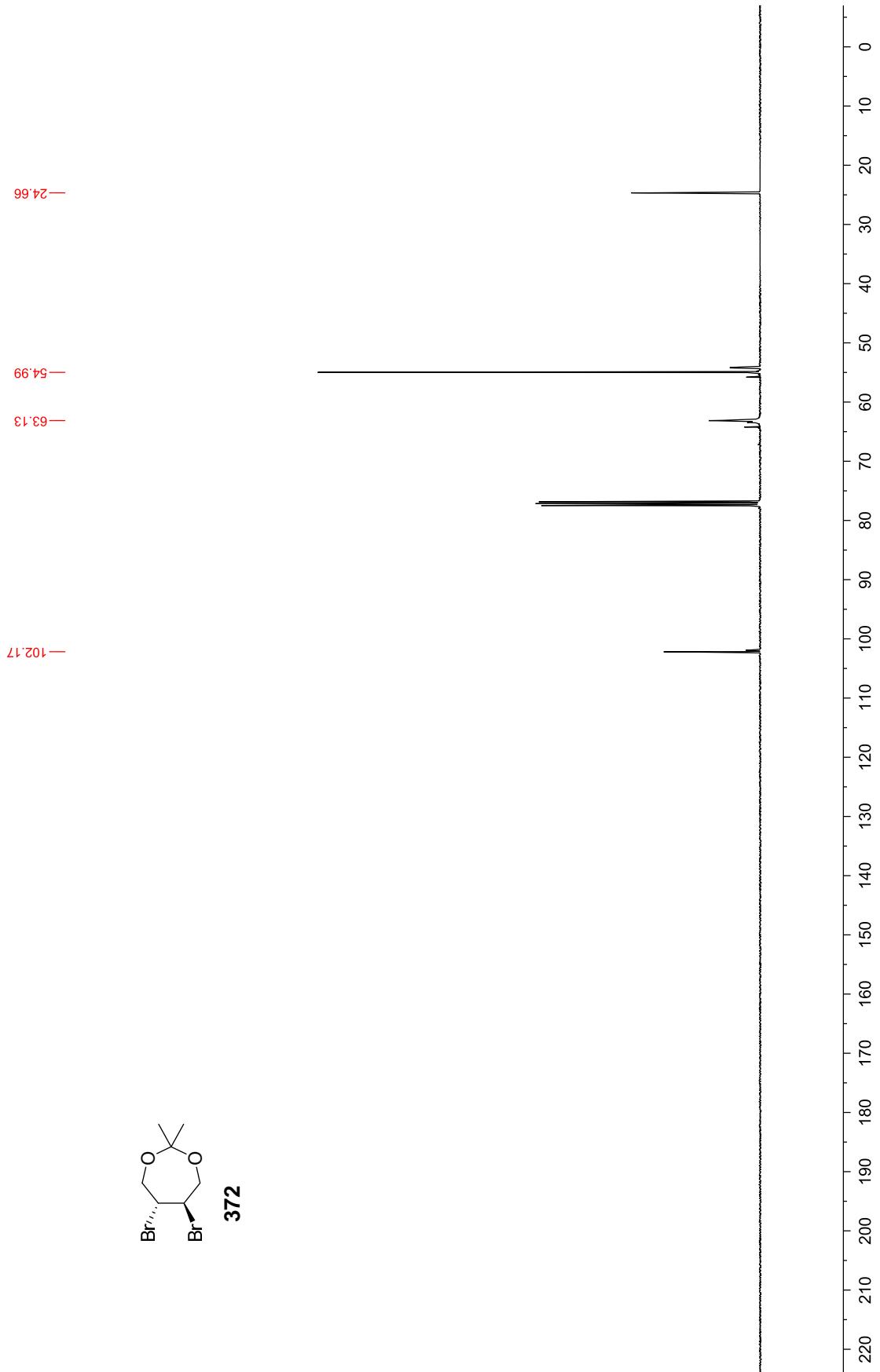
**360**

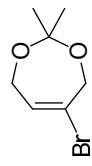
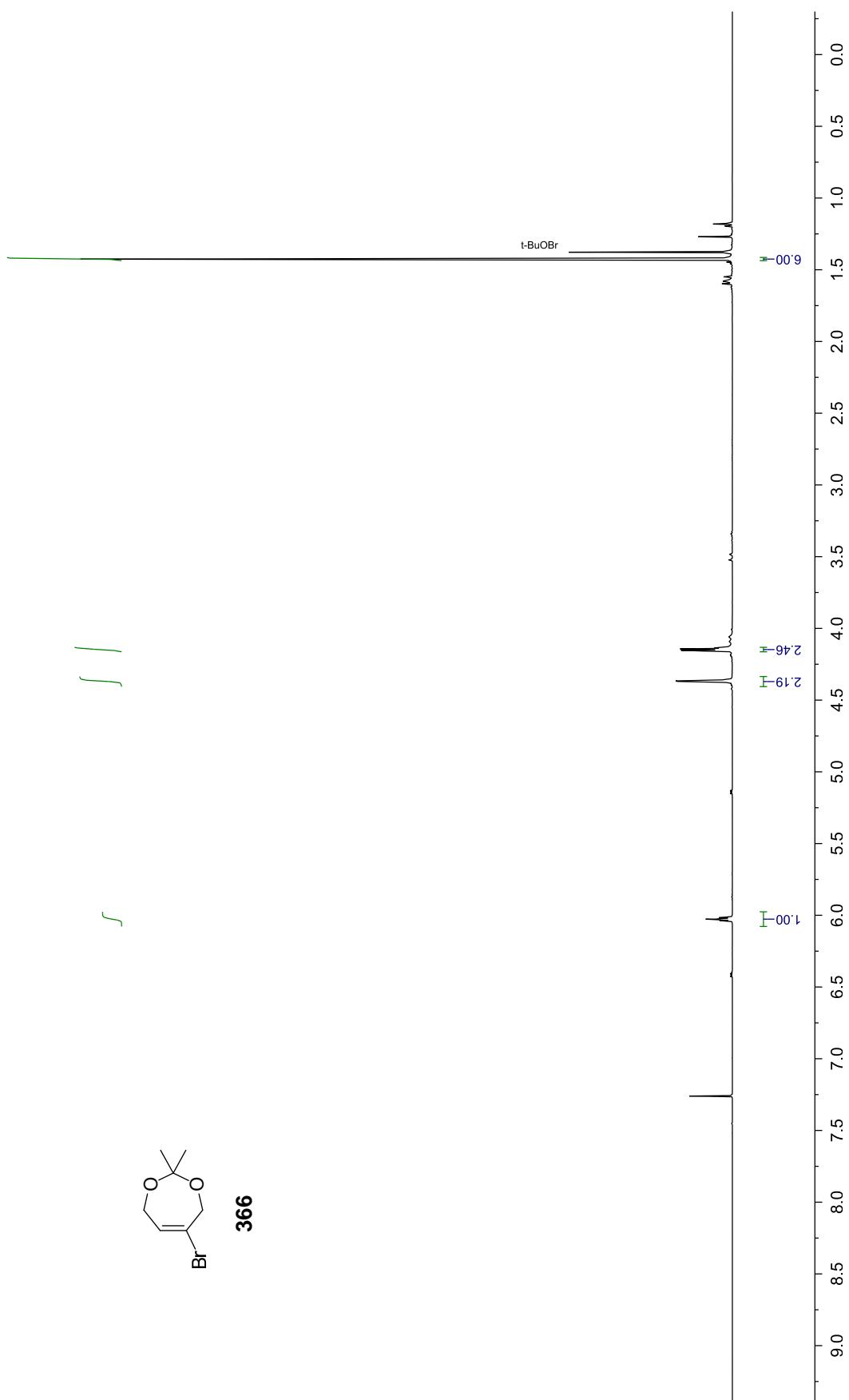




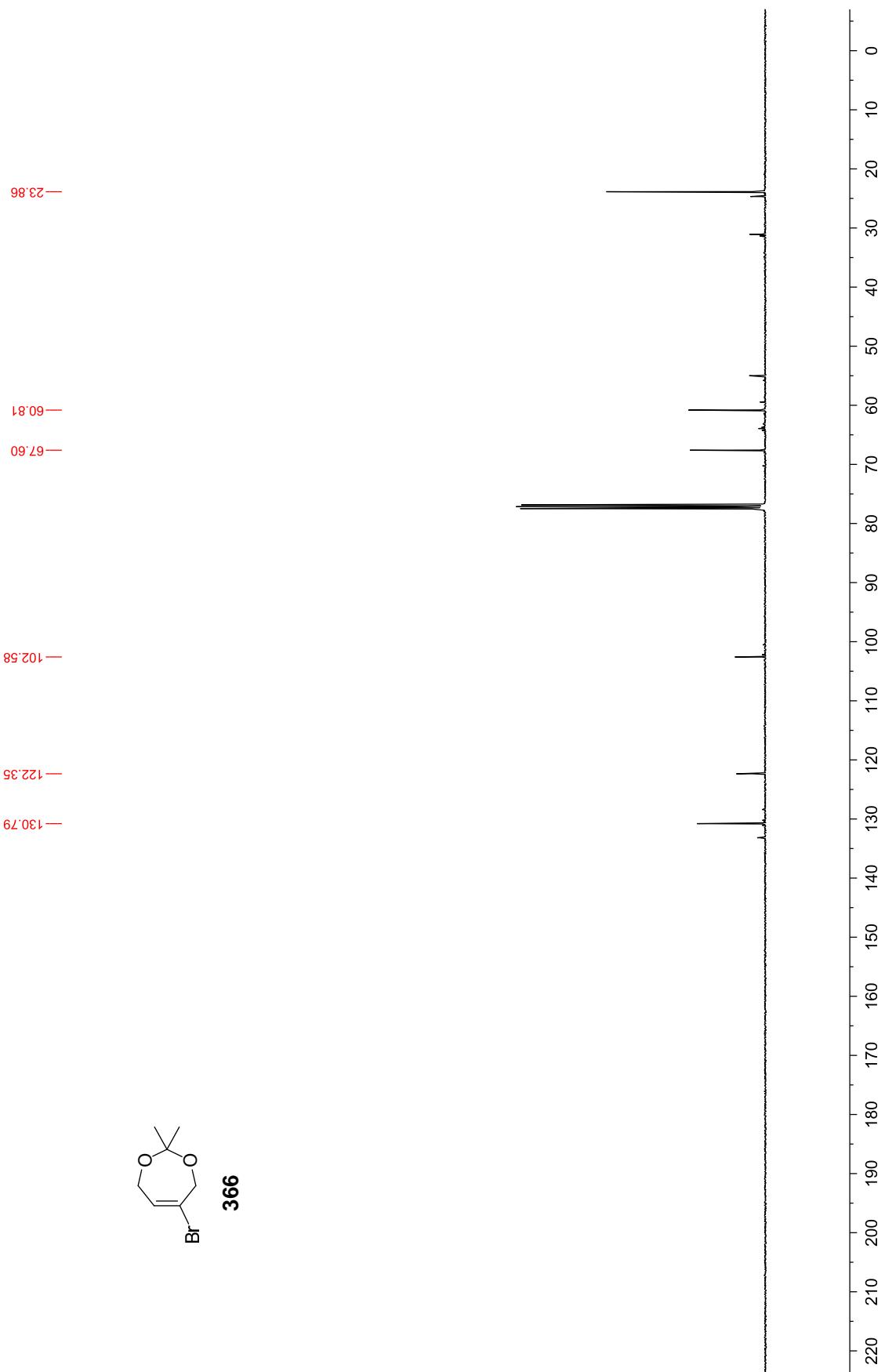
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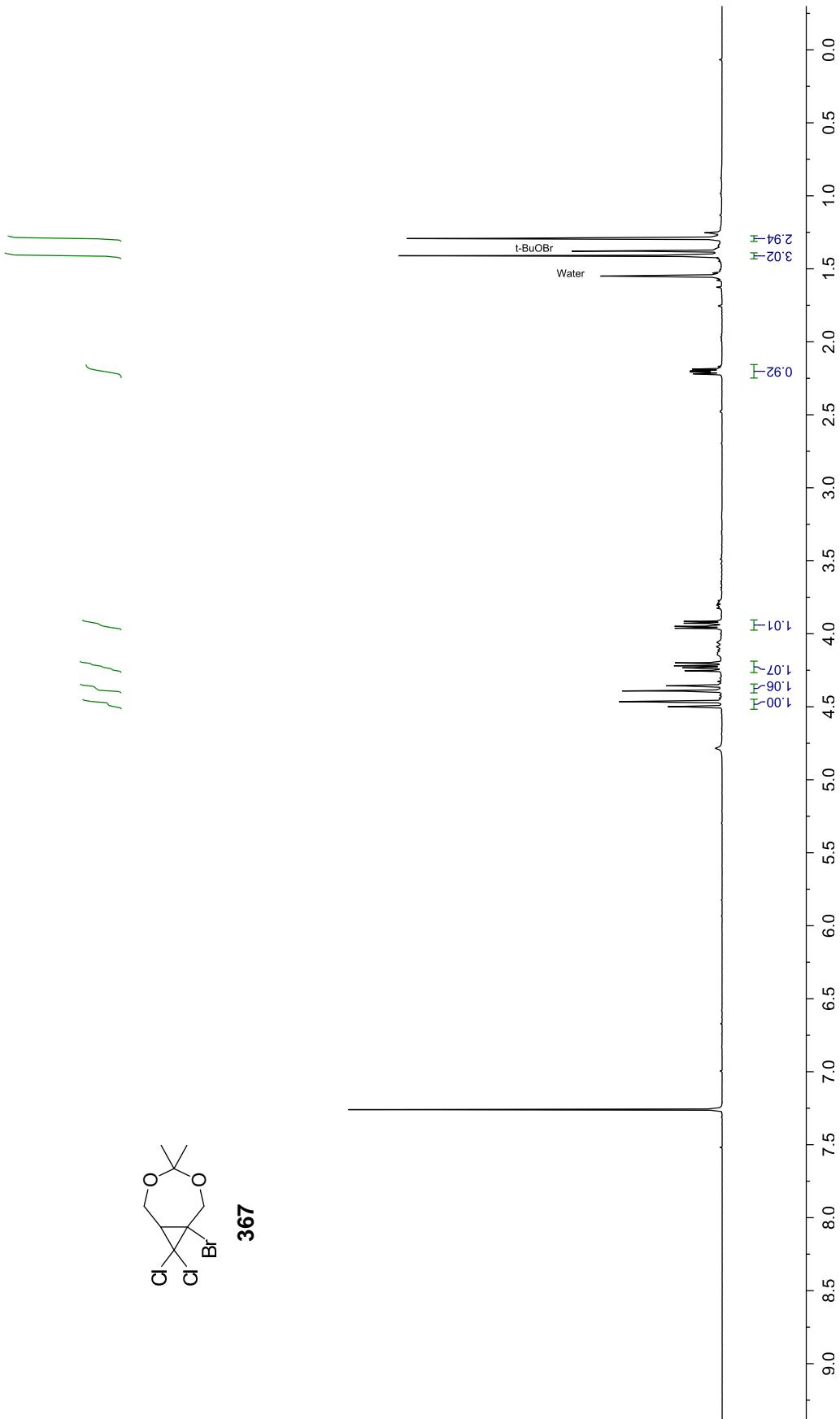


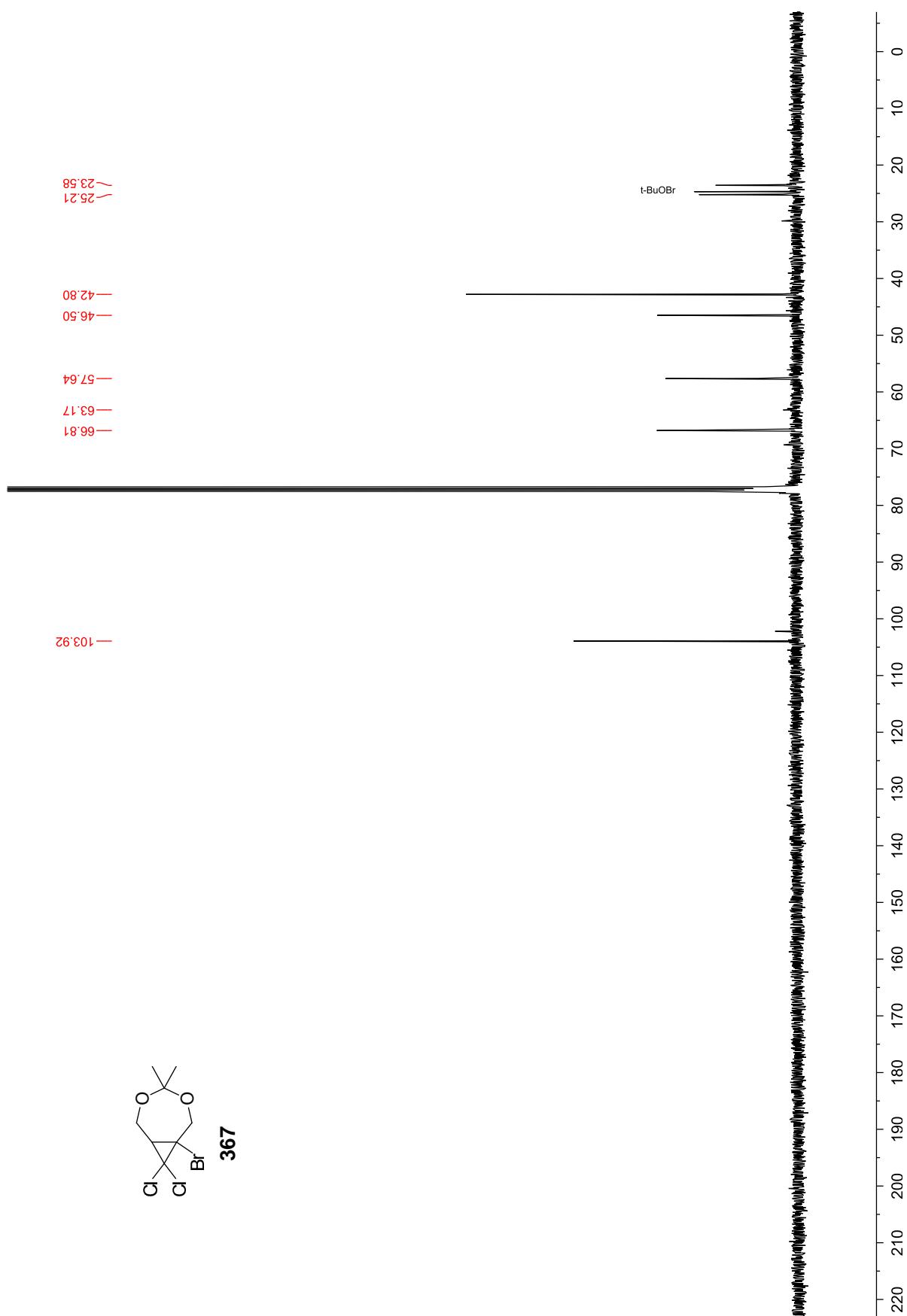


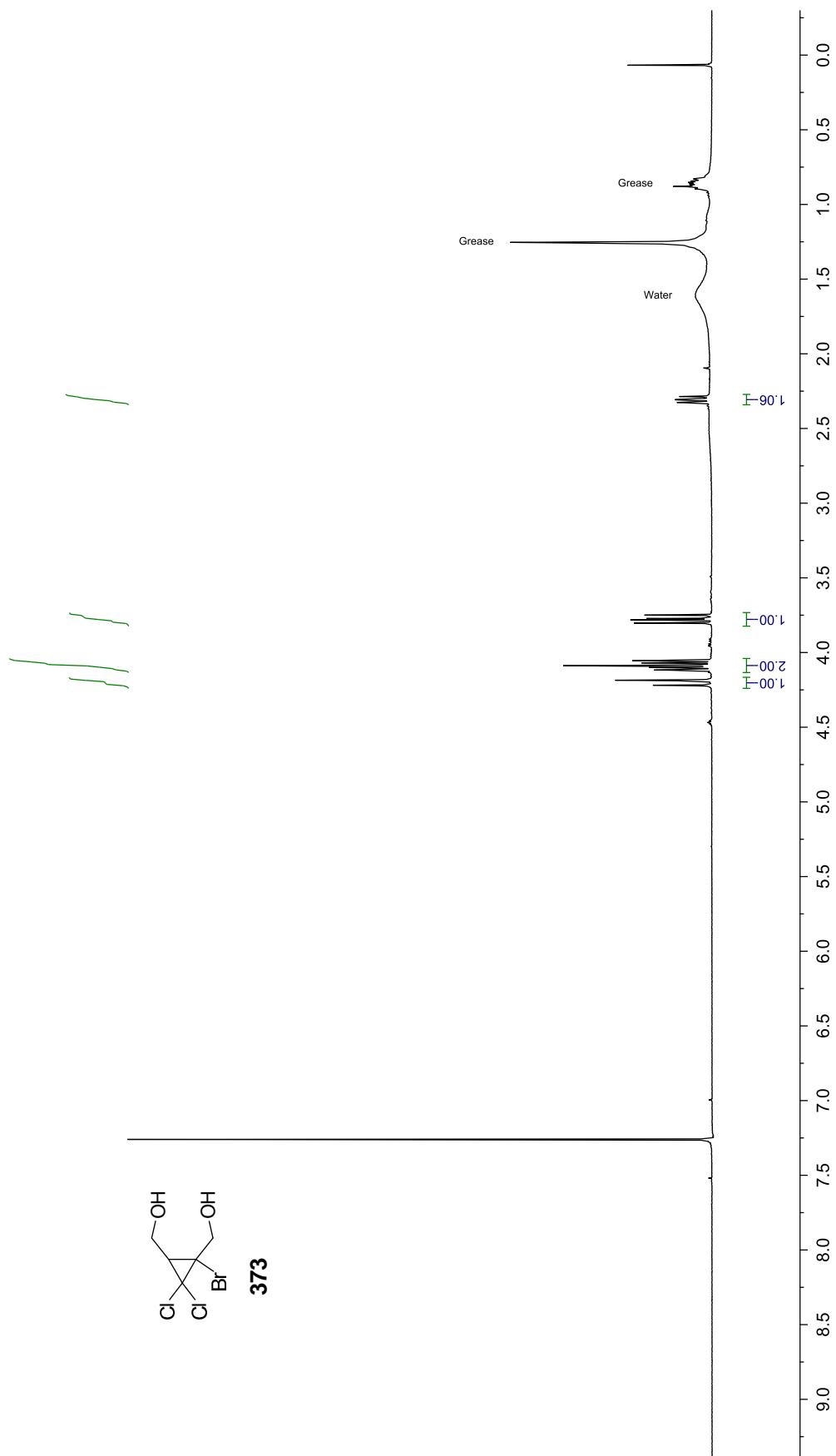


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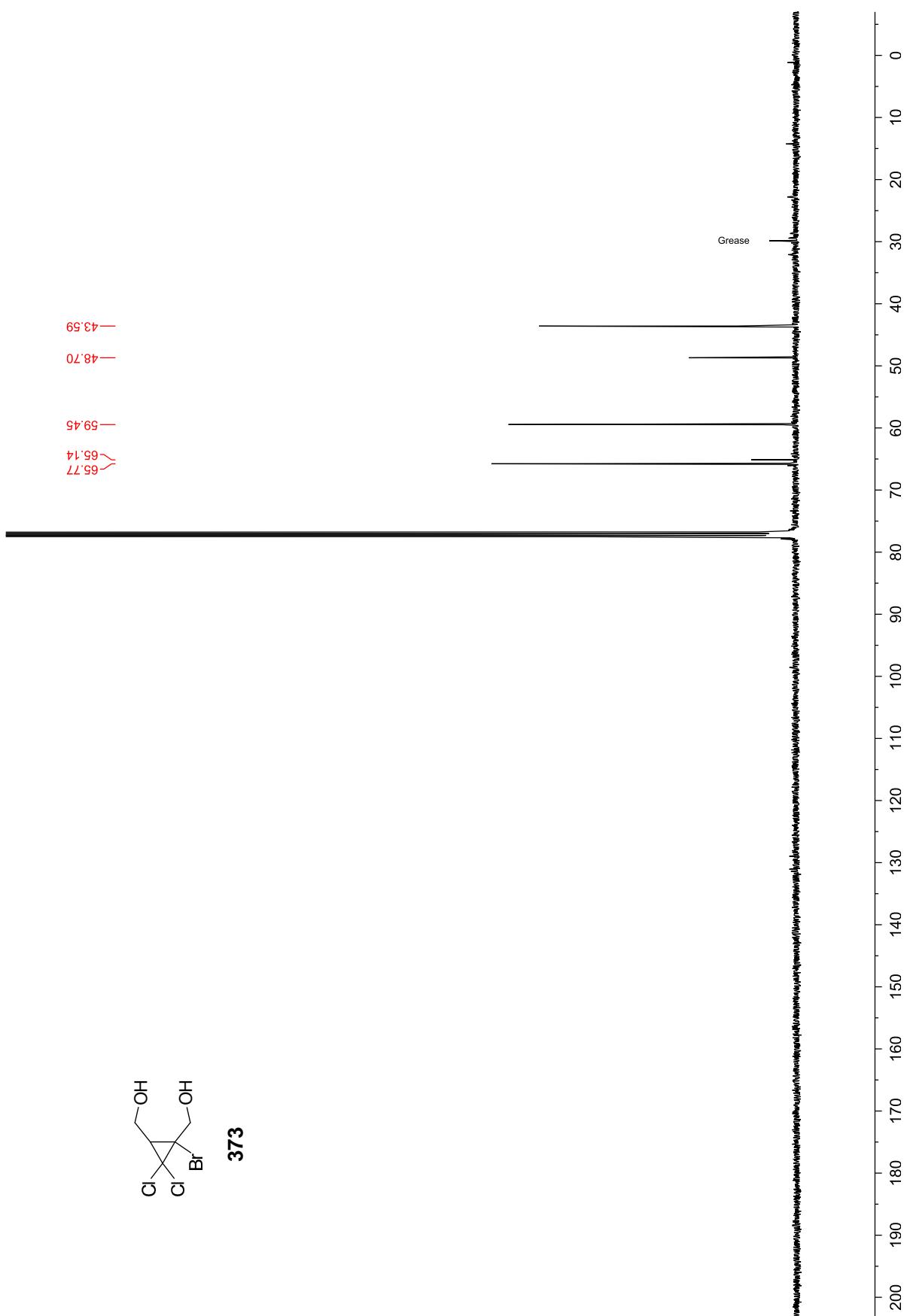


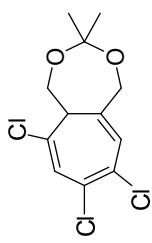






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