School of Molecular and Life Sciences

New Routes to Troponoid Natural Products

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Doctor of Philosophy

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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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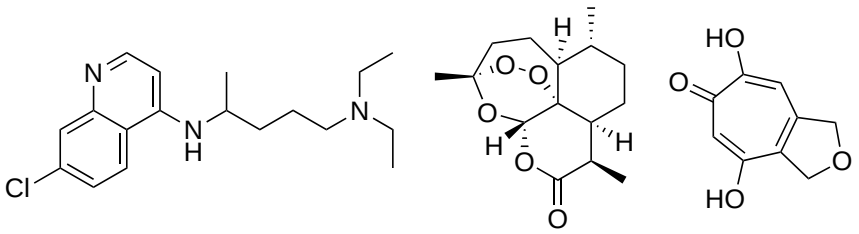
Abstract

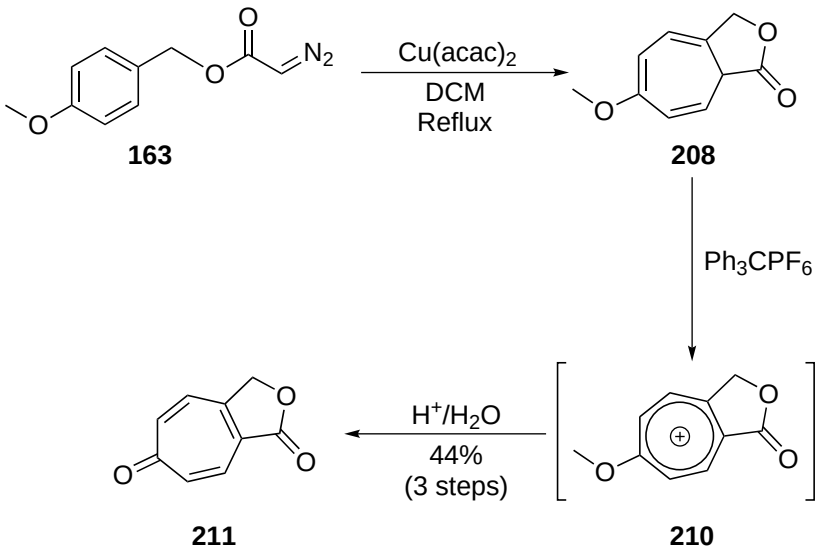
Malaria is an infectious disease found in humans and other animals, it is caused by a single-cell parasite of the *Plasmodium* genus with many different substrains. Of these, *P. falciparum* is the most deadly to humans causing the majority of deaths. Although research into the area of antimalarial compounds is wide spread, few have been developed with new structural features. Cordytropolone **37** is a natural product isolated in 2001 from the insect pathogenic fungus *Cordyceps sp.* BCC 1681 and has been shown to have antimalarial activity against *P. falciparum*. It has a structure unrelated to antimalarial compounds currently used in therapy. It does not contain a peroxide bridge as with artemisinin **25** or quinoline rings as with chloroquine **22**. This unique structure indicates that it could possibly interact with the malaria parasite in a fashion unlike current treatments. In order for cordytropolone to be further developed as a potential treatment, it must first be synthesised in a laboratory environment. This study attempts to develop the first total synthesis of cordytropolone.



22 **25** **37**

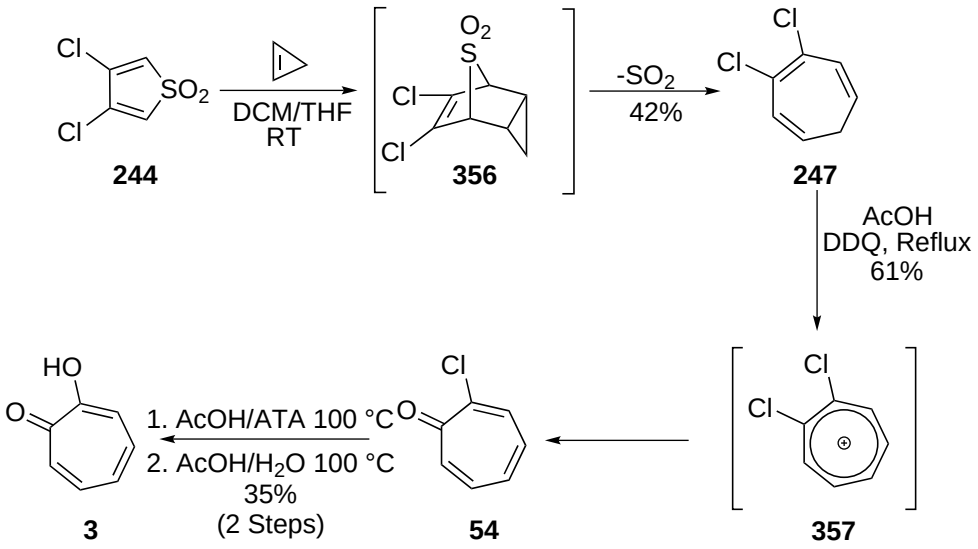
Figure 0.0.1: Cordytropolone **37** has a unique structure compared to the current common malaria treatments

The first method investigated towards the total synthesis of cordytropolone involved an intramolecular Buchner ring expansion. One of the key features of cordytropolone is its bicyclic structure containing a 7 and 5-membered ring. Using diazo compounds such as **163** with a copper catalyst, bicyclic cycloheptatrienes such as **208** were able to be produced. The tropylium ion **210** was then formed via hydride abstraction, followed by nucleophillic aromatic substitution to give tropone **211**. Although the approach worked for tropolone **211** , it was unsuccessful in forming sufficiently substituted tropolones.



Scheme 1: Buchner ring expansion followed by oxidation via hydride abstraction to produce tropone **211**

The other method investigated involved a Diels-Alder reaction between a thiophene-1,1-dioxide and a cyclopropene to produce a cycloheptatriene. In this reaction the diene, 3,4-dichlorothiophene-1,1-dioxide **244** goes through a [4 + 2] cycloaddition with the dienophile cyclopropene. This produces the intermediate **356** which spontaneously eliminates sulfur dioxide to form cycloheptatriene **247**. The tropylium ion **357** was then formed which undergoes nucleophillic aromatic substitution to produce chlorotropone **54**. Chlorotropone **54** was then converted to tropolone **3** by acetolysis followed by hydrolysis. This is the first instance of tropolone synthesis via a Diels-Alder reaction and was expanded to produce several cycloheptatrienes, tropones and tropolones.



Scheme 2: Diels-Alder reaction between a thiophene dioxide and a cyclopropene produces a cycloheptatriene

Acknowledgements

I would like to thank my primary supervisor Dr Alan Payne. Thanks for taking me on as a student and for all your help over the past few years. Also thanks for taking my light hearted jibes as the jokes they were intended to be. Also thanks are deserved by my other two supervisors, Associate Professor Mauro Mocerino and Dr Hendra Gunosewoyo for all their help as well.

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Thank you also to Dr Bruno Bašic for the fun times in the lab and the great conversations and all the advice you offered whilst you were here. You also deserve acknowledgement for convincing me to start a PhD, dubious advice, in hindsight.

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Finally, to Lauren White, your contributions to my time at Curtin University has been immeasurable and so, in lieu of listing everything, I simply wish to thank you for being Lauren White.

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Contents

List of Abbreviations

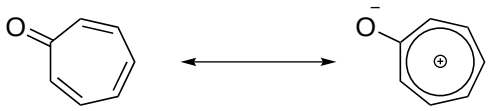
acac	Acetyl acetone
ACHN	1,1´-Azobis(cyclohexanecarbonitrile)
AIBN	Azobisisobutyronitrile
Aq.	Aqueous
Ar	Aryl
ATA	Acetyl Trifluoroacetate
Boc	*tert*-Butyloxycarbonyl
CAN	Ceric ammonium nitrate
cat.	Catalytic/catalyst
$CDCl_3$	Deuterated chloroform
Conc.	Concentrated
COSY	Correlation Spectroscopy
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
eq.	Equivalents
ESI	Electron spray ionisation
FTIR-ATR	Fourier transform infrared - attenuated total reflectance
HRMS	High resolution mass spectrometry
hrs	Hours
hv	Photochemical reaction
IBX	2-Iodoxybenzoic acid
IR	Infrared
m	Multiplet
MP	Melting point
NR	No reaction observed
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
ppm	Parts per million
q	Quartet
RT	Room temperature

s	Singlet
sat.	Saturated
t	Triplet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
δ	Chemical shift in ppm
Δ	Heating

Chapter 1

Tropone and Tropolone

Nonbenzenoid aromatic compounds are compounds which exibit aromatic character, but do not contain a benzene ring. While benzene contains a six membered ring, there are several seven membered ring containing compounds that exibit aromatic character. Tropone (**1**) is one such example. Tropone (**1**) consists of a seven membered ring containing three alkene groups and a carbonyl. The aromatic character of tropone and its derivatives comes from their ability to form the tropylium cation **2**, a seven membered ring system with an aromatic 6π electron system, meeting Huckel's Rule. The tropylium cation allows tropone and derivatives to undergo reactions such as nucleophilic aromatic substitution.[1]



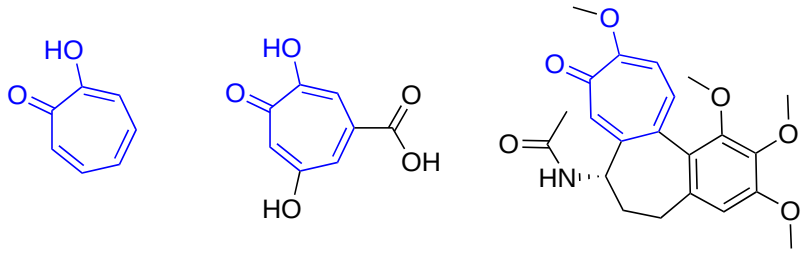
1
Tropone

2
Tropyllium Cation

Figure 1.0.1: The two main resonance contributors of tropone (**1**)

2-Hydroxytropone was first postulated by Dewar in 1945 as a substructure of the mould metabolite stipitatic acid **4**. Dewar named this particular substructure (**3**), tropolone.[2] Later that year, Dewar also postulated that tropolone made up one of the rings of colchicine **5**, a natural product of great interest at the time (Figure 1.0.2),[2] Although Dewar's assertation regarding the structure of colchicine was debated by Cook,[3] Dewar was later proven

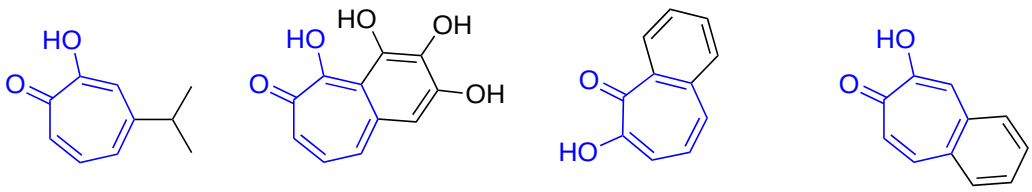
to be correct with the stucture of stipitatic acid confirmed by Corbett *et al.*[4] and the structure of colchicine later confirmed by King *et al.*[5]



3 Tropolone | **4** Stipitatic Acid | **5** Colchicine

Figure 1.0.2: The compounds stipitatic acid **4** and colchicine **5** both contain the tropolone **3** structure

In 1948, Erdtman and Gripenberg isolated several tropolone compounds from the heart wood of *Thuja plicata.*[6] These compounds were named thujaplicins and indentified as an isopropyl tropolone **6**, leading credence to Dewar's claims, although, β-thujaplicin **6** (hinokitiol) was originaly isolated by Nozoe from Taiwanese hinoki in 1936.[7] Later, Haworth *et al.* presented evidence that the compound purpurogallin **7** contained a benztropolone structure.[8] These discoveries, along with Dewar's assertations, stimulated interest into tropolone chemistry. Following this, some of the first tropolone derivatives to be synthesised in the lab were 3,4-benztropolone **8** by Cook *et al.*[9], 4,5-benztropolone **9** by Tarbell *et al.*[10] and purpurogallin **7** by Caunt and Hayworth *et al.*[11] (Figure 1.0.3).

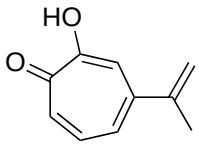


6 ß-Thujaplicin | **7** Purpurogallin | **8** 3,4-benzotropolone | **9** 4,5-benzotropolone

Figure 1.0.3: More compounds were determined to contain the tropolone structure with both **8** and **9** among the first to be synthesised

Tropolone **3** has shown activity as an insecticide, antifungal, metalloprotease inhibitor,[12]

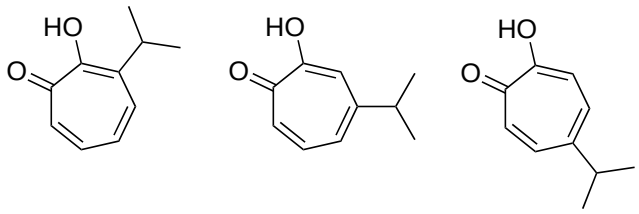
grape polyphenol oxidase inhibitor,[13] and mushroom tyrosinase inhibitor.[14,15] Many substituted tropolones and tropolone containing structures also exhibit biological activity.[16] For example, β-dolabrin **10** (Figure 1.0.4) is another natural product found in western red cedar trees (*Thuja plicata*)[17] and has been shown to display phytogrowth inhibition[18] and antifungal activity.[19]



10
ß-dolabrin

Figure 1.0.4

The thujaplicins (isopropyltropolones) are also found in *Thuja plicata* and are one of the more widely researched tropolone familes (Figure 1.0.5). β-Thujaplicin was one of the first tropolones to be identified.[6,20–22] First synthesised by Nozoe[23] using a Dieckmann condensation followed by decarboxylation of β-isopropylsuberic acid to give isopropylcycloheptanone **14**. The ketone **14** was then oxidised using selenium dioxide to give the isopropylcycloheptadione **15**. The dione **15** was then brominated using NBS followed by elimination of HBr to give β-Thujaplicin **6** (Scheme 1.1).

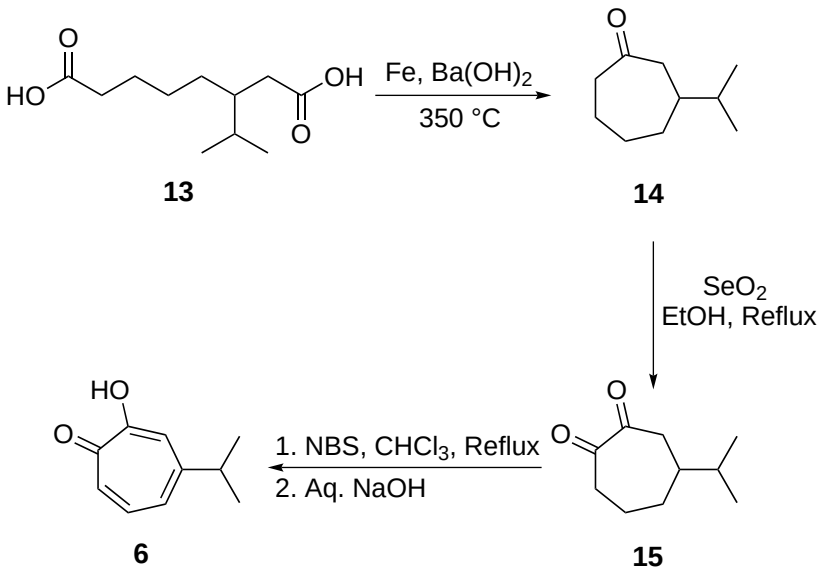


11
α-thujaplicin

6
ß-thujaplicin

12
y-thujaplicin

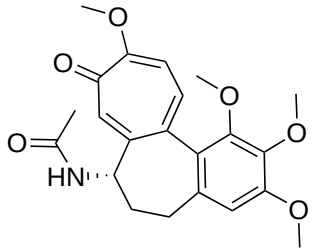
Figure 1.0.5: The thujaplicins



Scheme 1.1: Nozoe's synthesis of β-thujaplcin

β-Thujaplicin has been tested for biological activity against a wide range of targets. It has been shown to have activity as an antifungal[24] and antimicrobial,[25,26] to inhibit skin cancer cells,[27] and melanin synthesis,[28] as well as having an effect on stomach[29] and more recently, colon[30] cancer cells. α-Thujaplicin has been shown to have an effect against similar targets, including leukemia cells.[19] Many other positive effects have also been reported for the thujaplicins.[16,31,32]

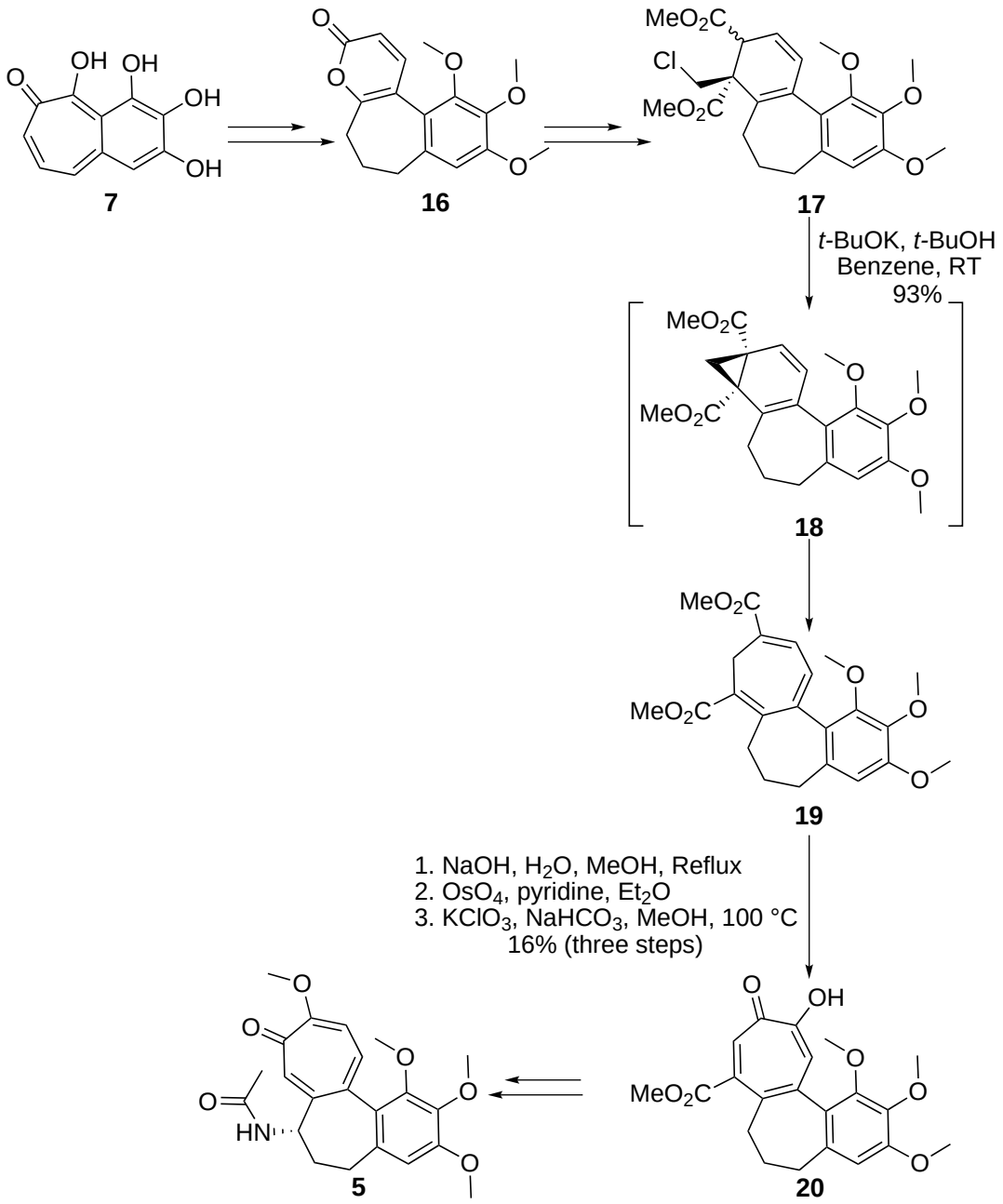
Colchicine **5** (Figure 1.0.6) is another of the more widely researched tropolones. The first isolation of colchicine was in 1820 by Pelletier and Caventou.[33] It is the main alkaloid of the toxic meadow saffron (*Colchicum autumnale* L.).[34] Colchicine has been used as a treatment for gout for more than 2000 years[35,36] with *Colchicum autumnale* referenced in Dioscorides' De Materia Medica.[37]



5
Colchicine

Figure 1.0.6

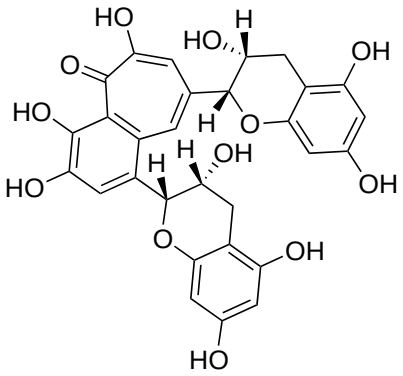
The first total synthesis of colchicine **5** was reported in 1959 by Eschenmoser *et al.*[38] using purpurogallin as the starting material. A similar synthesis was reported just a few months later by van Tamelen *et al.*[39] The initial tropolone ring on the purpurogallin was hydrogenated and used to form the centre 7-membered ring. It was not used to form the basis of tropolone ring of colchicine as one would expect. The 2-pyranone present on the intermediate compound **16** was converted to the diester **17** via a Diels-Alder reaction followed by oxidation. The diester **17** was then converted with base to the norcaradiene intermediate **18**, which underwent an electrocyclic ring expansions to give cycloheptatriene **19**. The cycloheptatriene **19** was then converted into the tropolone via hydrolysis followed by oxidation using OsO_4 and $KClO_3$ to give the tropolone **20**. The tropolone containing compound **20** was eventually converted to colchicine **5** (Scheme 1.2).



Scheme 1.2: Eschenmoser's synthesis of colchicine **5** started with another tropolone, purpurogallin **7**

Colchicine is used primarily in the treatment of gout but is also used in other inflammatory diseases such as familial Mediterranean fever.[40] The effect of colchicine comes from binding to the protein tubulin preventing polymerisation and disrupting various functions of cell transport.[41] In addition to the antiinflammatory effects of colchcine, it has been evaluated as a treatment for post-operative atrial fibrillation, where it was determined to reduce incidence.[42] Behçet's syndrome,[43] Sweet's syndrome,[44] and pericarditis[45] are other diseases where colchicine has been investigated and shown to have an effect. Many other benificial effects of colchicine have also been reported.[46,47]

Another group of tropolone containing compounds are the theaflavins **21** (Figure 1.0.7). Theaflavins are commonly found in black tea. Created during the fermentation stage from the catechins contained in tea they are largely associated with the colour and pigmentation of black tea.[48,49] Theaflavins are potent anti-oxidants,[50–53] an effect which has reported to be benificial against many diseases.[54,55] In addition to the anti-oxidative effect, theaflavins have been investigated as an antimicrobial[56,57] and an HIV-1 inhibitor.[58] They have been shown to reduce cholesterol,[59] and have various positive effects against cancer cells.[60]



21
Theaflavin

Figure 1.0.7

1.1 Malaria and Tropolones

An important world health issue where tropolones may be useful is in the ongoing global fight against malaria. Malaria is an infectious disease found in humans and other animals, it is transmitted by the female Anopheles mosquito.[61] It is caused by single-cell parasite of the *Plasmodium* genus with many different substrains. There are five main strains that infect humans, *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Of these, *P. falciparum* is the most deadly to humans causing the majority of deaths.[61] It was estimated in the year 2017 that 435 000 deaths were caused from the malaria parasite from 298 million cases.[62] Most malaria cases (92%) and deaths (93%) occurred in the sub-Saharan African Region, with Southeast Asia as the area with the second highest prevalence of infection.[63]

Many different drugs and treatments have been used to combat and eradicate malaria throughout recent history. During the 1950's there was a large push by the World Health Organisation, known as the Global Malaria Eradication Campaign (GMEC), to completely eliminate malaria. This involved reduction of mosquito carriers by the use of insecticides, coupled with the widespread use of antimalarial drugs.[64] Chloroquine **22** was one of the drugs involved in this campaign, and was used in mass drug administrations (MDA) during the GMEC.[65] Due to this mass administration and the widespread misuse of chloroquine there is now widespread resistance to this drug in nearly all parts of the world where *P. falciparum* is found.[65] The use of chloroquine became so widespread that in some parts of the tropics chloroquine can be detected in the blood of the majority of the population.[66]

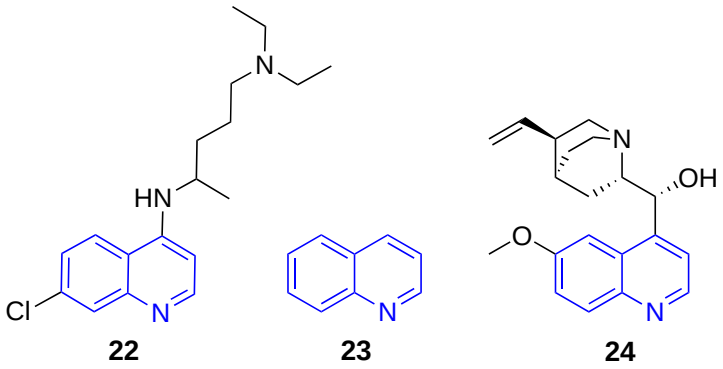


Figure 1.1.1: Chloroquine **22**, quinoline **23** and quinine **24** with the quinoline portion highlighted in blue

Chloroquine **22** belongs to the aminoquinoline group of antimalarial compounds. Compounds in this group all incorporate the structure of quinoline **23** (Figure 1.1.1). Many compounds that incorporate the structure have known antimalarial activity, this includes one of the first known antimalarials, quinine **24**.[67,68] While many aminoquinoline drugs are still in use today, like chloroquine, there is widespread resistance to many of them.[69]

The current recommended drug for treatment of malaria by the World Health Organisation is known as artemisinin **25**.[70] Artemisinin was discovered in China as a direct response to chloroquine resistant *P. falciparum* malaria that was plaguing the North Vietnamese during their conflict with the United States.[71] Artemisinin has a structure which is completely different from previously used antimalarial drugs, it does not contain a quinolone portion. It is instead, a sesquiterpene lactone containing a unique peroxide bridge.[71] It is this peroxide bridge which is believed to give artemisinin its antimalarial activity.[72] Derivatives developed of artemisinin such as artesunate **26** and artemotil **27** all contain this peroxide bridge (Figure 1.1.2).[73]

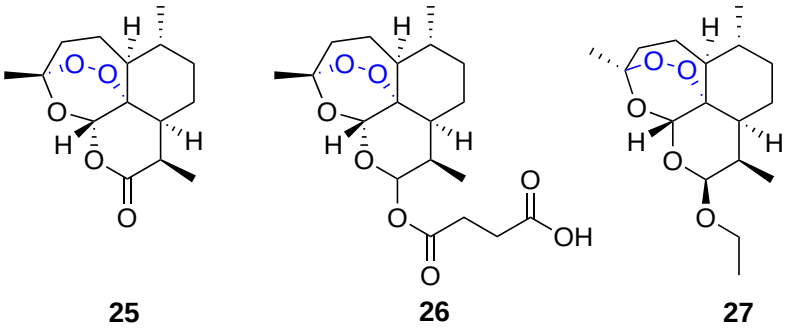


Figure 1.1.2: Artemisinin **25**, artesunate **26** and artemotil **27** with the characteristic peroxide bridge highlighted

Artemisinin **25** is best used in combination with other drugs. The artemisinin based combination therapies (ACT) were developed in order to completely eradicate the parasite from the body to reduce drug resistance.[74] In 2006, the WHO requested that pharmaceutical drug companies completely end the marketing and sale of single drug artemisinin medications to combat the spread of resistance.[75] Despite these efforts to combat resistance, resistant parasites have been discovered in parts of the Greater Mekong subregion in Southeast Asia; Cambodia, the Lao People's Democratic Republic, Thailand and Vietnam.[76,77] Even worse, *P. falciparum* along the Cambodia-Thailand border has become resistant to almost all available antimalarial drugs.[78]

Troponoid compounds having antimalarial activity is significant as they have a structure unrelated to current antimalarial treatments. They do not contain a peroxide bridge as with artemisinin **25** or quinoline rings as with chloroquine **22**. This unique structure indicates that it could possibly interact with the malaria parasite in a fashion unlike current treatments. There would be no resistance by the parasite to this drug. Though there have been previous reports of troponoid compounds having antimalarial activity[79] a structual activity relationship study to probe troponoid antimalarial activity was recently reported by Sennari *et al.*[80]

Sennari *et al.* tested the activity of various tropolone compounds against the chloroquine resistant *P. falciparum* malaria. This included natural products isolated from *Penicillium viticola;*[81] puberulic acid **28**, stipitatic acid **4**, viticolin A **29** and, viticolin B **30**. The results from this study are shown in Figure 1.1.3 and include tropolone **3** itself. There

are some obvious trends in the results, 7-hydroxytropolone **31** has improved activity vs. tropolone **3** and stipitatic acid **4**, indicating a hydroxy group at the seven position improves activity. Pubulic acid **28** was found to have the greatest activity against the malaria parasite. Its structure has three hydroxy groups and an acid group. The results for viticolin A **29** and viticolin B **30** show that masking the hydroxy groups affects the activity.

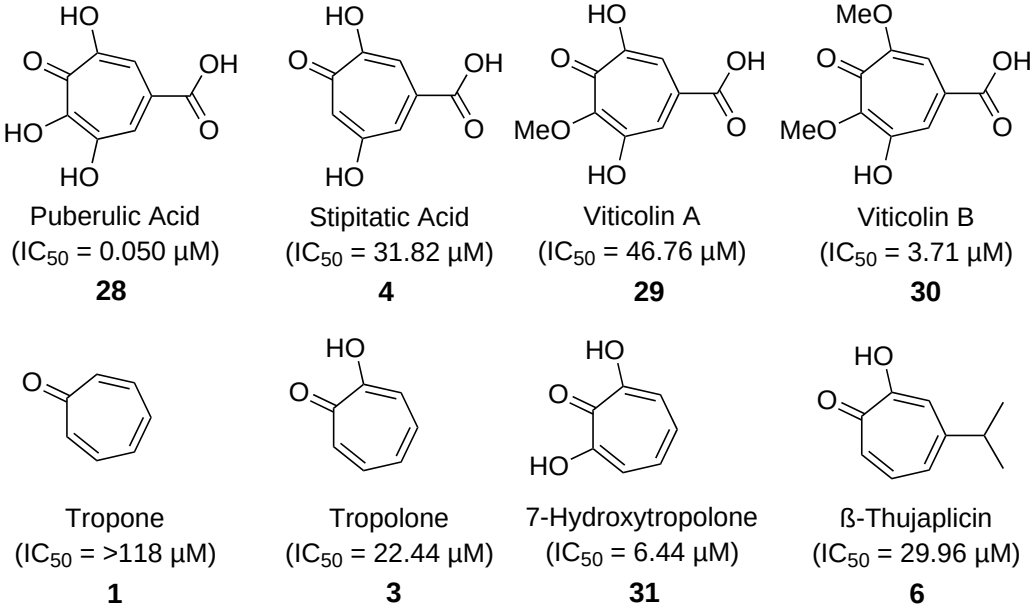


Figure 1.1.3: Tropolone natural products tested against the malaria parasite by Sennari *et al.*[80]

Based on this information Sennari *et al.* synthesised several new 7-hydroxytropolone compounds. The best results are shown in Figure 1.1.4. Compared to puberulic acid **28** none of the newly synthesised compounds were as effective agaisnt the malaria parasite. The presence of an acid, hydroxy methyl, or methoxy methyl group at the 4-position does not appear to affect activity. **34**, **35** and, **36** all have similar activities against the parasite. However these functional groups do affect cytotoxicity, with the acid group providing the least toxicity. Despite this, none of the compounds proved to be more active or less toxic than puberulic acid **28**.

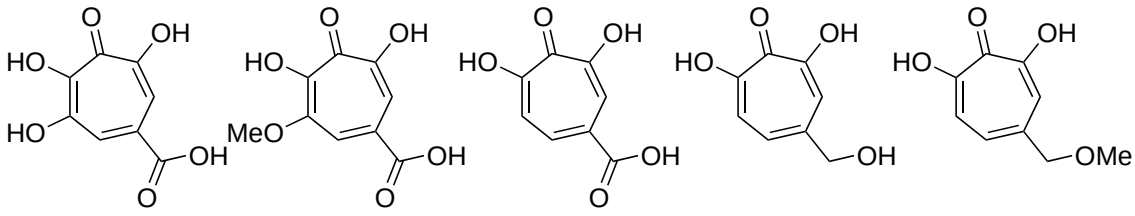


Figure 1.1.4: Tropolones synthesised by Sennari et al compared to puberlic acid

Cordytropolone **37** (Figure 1.1.5) is a natural product isolated in 2001 from the pathogenic fungus *Cordyceps sp.* BCC 1681 and has been shown to have antimalarial activity against *P. falciparum* (IC_{50} = 12.2 µM).[82] Unlike the compounds synthesised by Sennari *et al.* it is a bicyclic troponoid compound with both a 7-membered tropolone ring and a 5-membered tetrahydrofuran ring. It has not been synthesised in the lab to date. Another tropolone with a structure similar to cordytropolone is stipitalide **38**. Isolated from *Penicillium stipitatum* Thom[83] stipitalide has not been tested against malaria, nor been a target for total synthesis. There is an obvious need for a method to produce these bicyclic tropolone strucutres and is the subject of this thesis.

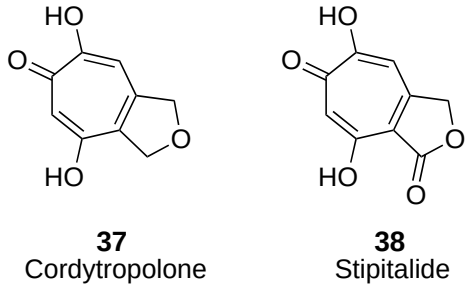
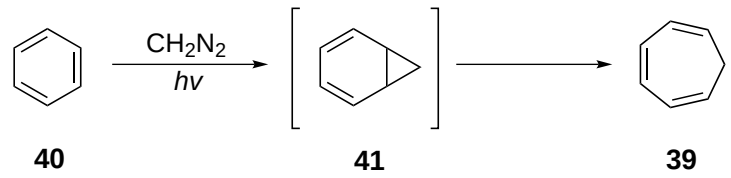


Figure 1.1.5: Cordytropolone **37** and stipitalide **38** are troponoid natural products containing a bicyclic structure

1.2 Synthesis of Cycloheptatrienes, Tropones and Tropolones

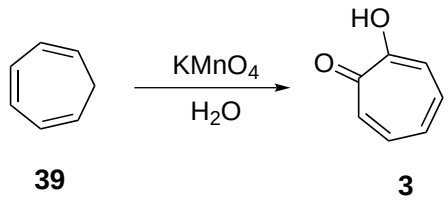
To date, there have been many different methods for the synthesis of seven membered rings.[84] In order to develop a new synthesis of cordytropolone a review of current synthesis

of tropone, tropolone and cycloheptatriene is required. Doering and Knox were one of the first chemists to synthesise tropolone.[85] A solution of diazomethane and benzene **40** was irradiated with light to give cycloheptatriene **39**. Under these irradiation conditions, diazomethane loses a molecule of nitrogen to form a carbene which then reacts in a [1 + 2] cycloaddition to benzene to form the norcaradiene adduct **41**. The norcaradiene adduct **41** then undergoes an electrocyclic ring opening reaction to give cycloheptatriene **39** (Scheme 1.3).

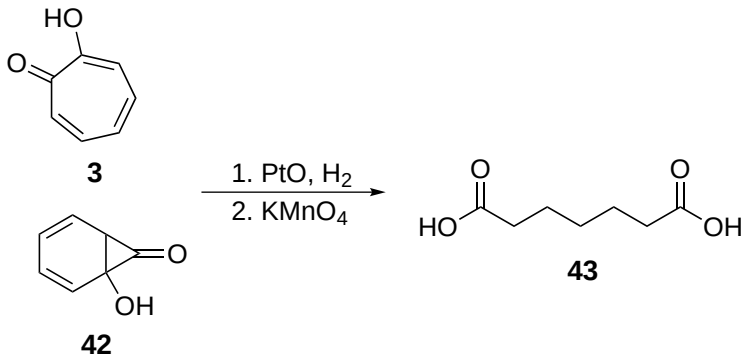


Scheme 1.3: Cycloheptatriene **39** was synthesised from benzene **40** by carbene addition of diazomethane

Cycloheptatriene **39** was then oxidised with 4% aqueous potassium permanganate. After complexation with copper, followed by liberation using hydrogen sulfide, tropolone **3** was isolated as colourless needles (Scheme 1.4). Doering and Knox attempted to confirm the structure of tropolone by hydrogenating with platinum oxide followed by oxidation using permangenate. This gave pimelic acid **43**, an acid containing seven carbons. Doering and Knox concluded that this product was consistant with the hydrogenation and oxidation of tropolone **3** though could not rule out it could also be a product of the same reactions with norcaradiene **42** (Scheme 1.5).

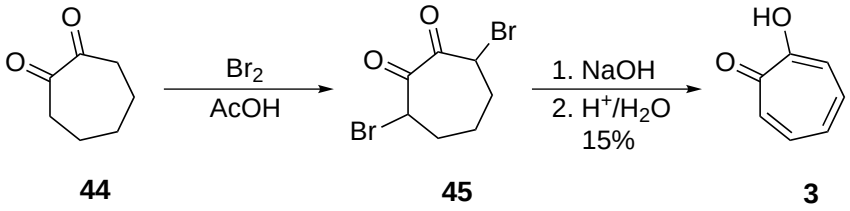


Scheme 1.4: Cycloheptatriene **39** was oxidised to tropolone using permanganate



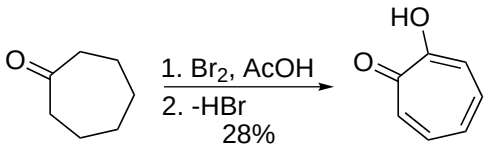
Scheme 1.5: Hydrogenation of tropolone **3** or norcaradiene **42** followed by oxidation gave pimelic acid **43**

Another early synthesis of tropolone was reported by Cook, Gibb, Raphael and Somerville.[86,87] Their synthesis started from cycloheptane-1,2-dione **44** and formed tropolone by a bromination-dehydrobromination approach. Bromine was added to cycloheptane-1,2-dione dissolved in acetic acid. This reaction gave 3,7-dibromocycloheptane-1,2-dione **45** which was purified by distillation. Dehydrobromination of **45** with sodium hydroxide, followed by acidification with aqueous sulfuric acid yielded crude tropolone **3**. The crude was purified by sublimation for a 15% total yield (Scheme 1.6).



Scheme 1.6: Synthesis of tropolone by Cook *et al*.

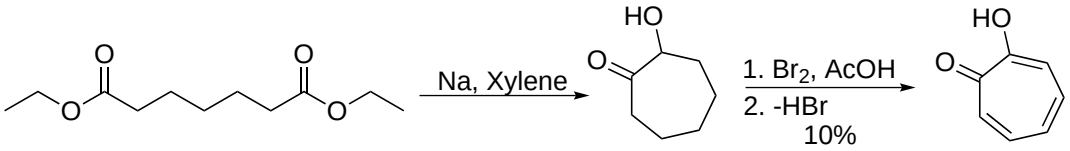
Nozoe *et al*. also synthesised tropolone using the same bromination and dehydrobromination of cycloheptane-1,2-dione **44** as Cook, using *N*-bromosuccinimide instead of bromine **44**.[88] Nozoe *et al.* then went on to report a synthesis of tropolone using cycloheptanone **46** and the bromination/dehydrobromination method.[89] Bromination of **46** gave a mixture of brominated cycloheptanones which after elimination of HBr gave tropolone **3** in 28% yield (Scheme 1.7).



46 **3**

Scheme 1.7: Synthesis of tropolone **3** from **46** by Nozoe *et al.*[89]

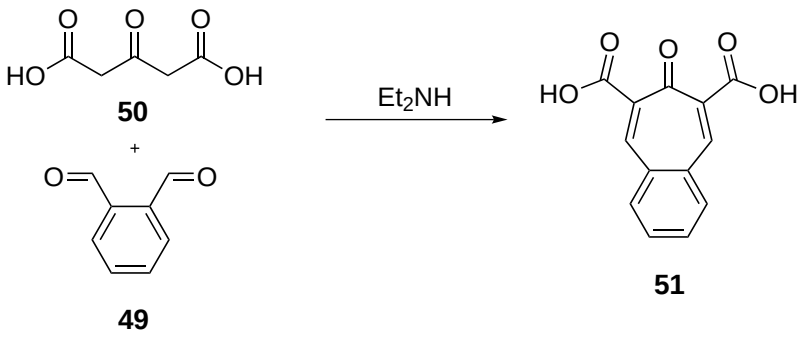
Another synthesis of tropolone **3** reported during the very early 1950s was by Knight and Cram. This synthesis of tropolone does not start with the seven-membered ring already formed. Instead, diethyl pimelate **47** was used.[90] The diester **47** was subjected to an acyloin condensation using sodium to give 1,2-cycloheptanolone **48**. The hydroxyketone **48** was then treated with bromine which, after removal of HBr, gave tropolone **3** in 10% yield (Scheme 1.8).



47 **48** **3**

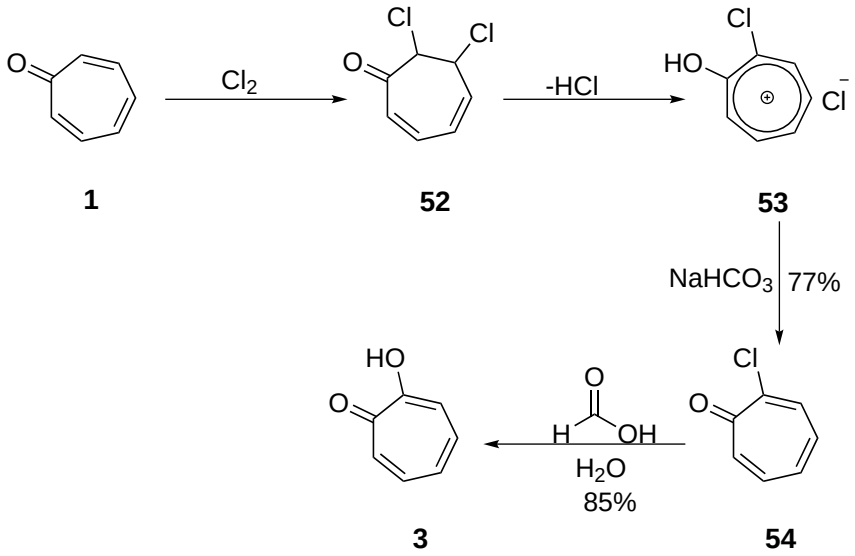
Scheme 1.8: Knight and Cram's synthesis of tropolone using an acyloin condensation[90]

Thiel and Schneider reported a tropolone synthesis using an aldol condensation reaction, though they did not know they had produced a tropone at the time. *o*-Pthalaldehyde **50** was reacted with acetonedicarboxylic acid **49** with three drops of diethylamine to give benzotropone **51**.[91] Thiel *et al.* expanded this reaction to other acetone diesters,[92] the reaction was also used by Tarbell *et al.* in their synthesis of 4,5-benzotropolones[10] and Kakisawa *et al.* in the synthesis of salviolone, a benzotropolone natural product isolated from the fresh root of *Salvia miltirrhiza.*[93–95]



Scheme 1.9: Aldol condensation of **50** and **49**

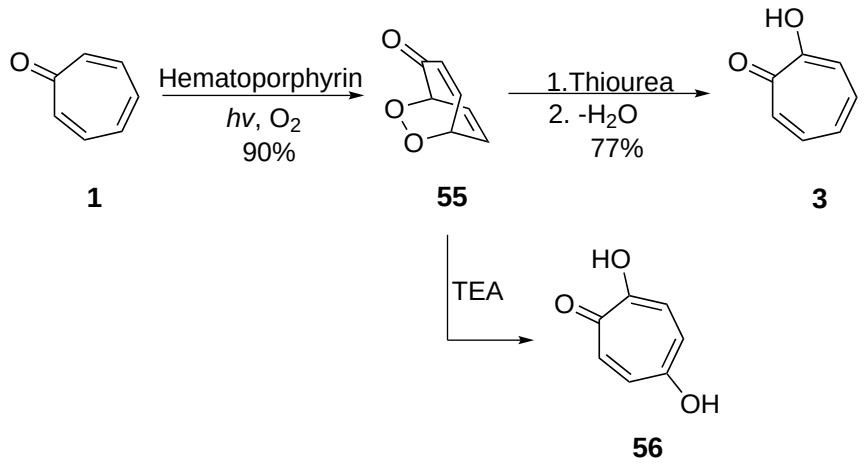
Tropone has been used as a starting material for tropolone in several synthesies. Ter Borg, van Helden and Bickel were able to form tropolone through chlorination of tropone.[96] Tropone was chlorinated using chlorine gas to give tropone dichloride **52** which on standing, underwent HCl elimination to give the 2-chlorotropone hydrochloride salt **53**. After neutralisation with sodium carbonate, 2-chlorotropone **54** was obtained. 2-Chlorotropone **54** was then heated to reflux with 80% aqueous formic acid for two days to give tropolone **3** in 85% yield (Scheme 1.10).



Scheme 1.10: Chlorination of tropone **1** to give tropolone **3**

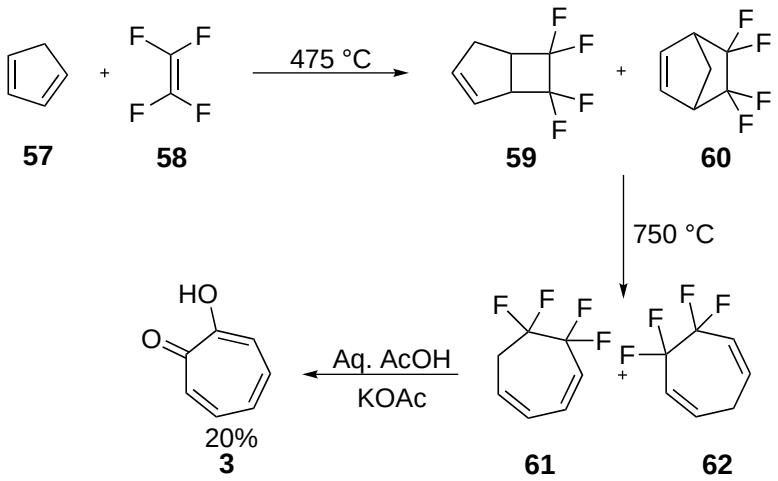
Other syntheses of tropolone from tropone include amination using hydrazine followed by hydrolysis by Nozoe *et al.* and photooxidation followed by reduction by Oda and

Kitahara.[97] Tropone **1** was irradiated in acetone with haematoporphyrin under oxygen with a 300 W lamp. This gave the epidioxide **55** in more than 90% yield. The epidoxide was then reduced using thiourea to give tropolone **3** in 77% yield (Scheme 1.11). Oda also found that when epidioxide **55** was reacted with TEA, the 5-hydroxytropolone **56** was produced in quantitative yield (Scheme 1.11).



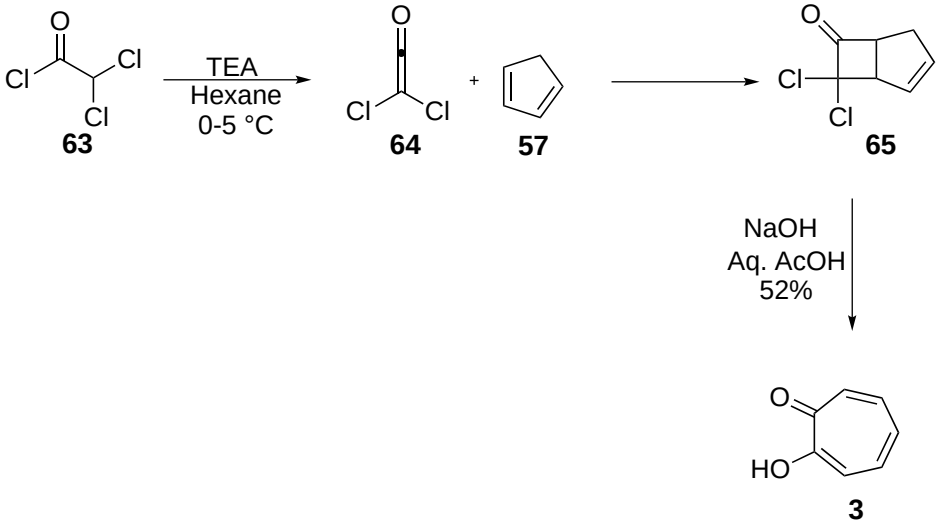
Scheme 1.11: Photooxidation followed by reduction using thiourea gave tropolone **3** from tropone **1**

The more efficient synthesies of tropolone involve a cycloaddition reaction using cyclopentadiene **57** as a starting material. Drysdale *et al.*[98] were one of the first to synthesise tropolone by this method. Tetrafluoroethylene **58** underwent a vapour phase addition to cyclopentadiene **57** at 475 °C to give the cycloaddition adducts **59** and **60**. The cycloaddition adducts **59** and **60** underwent pyrolysis at 750 °C to give a crude mixture containing tetrafluoroheptadienes **61** and **62**. **61** and **62** were then hydrolysed using aqueous acetic acid and potassium acetate to give tropolone **3** in 20% total yield (Scheme 1.12).



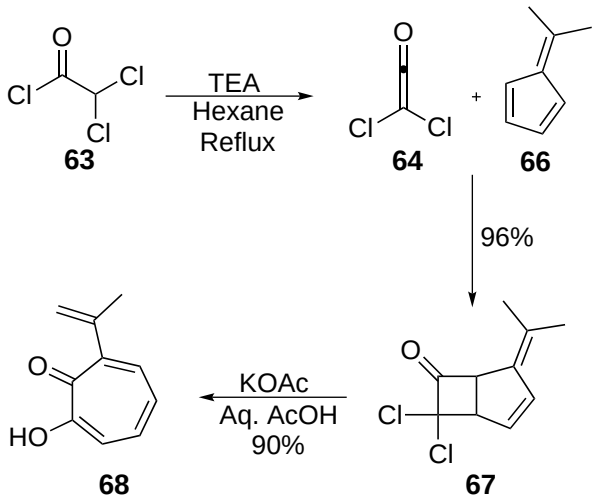
Scheme 1.12: Cycloaddition reaction of cyclopentadiene **57** with **58** gave adducts **59** and **60**. After pyrolysis and hydrolysis, tropolone **3** was obtained in 20% yield

Stevens *et al*. reported a synthesis of tropolone by a similar method. Instead of using tetrafluoroethylene **58**, dichloroacetyl chloride **63** was used.[99,100] In the presence of TEA dichloroacetyl chloride **63** elimates HCl to form dichloroketene **64**.[101] This species is highly reactive towards cycloadditions. The dichloroketene **64** then undergoes a [2 + 2] cycloaddition with cyclopentadiene **57** to give the bicycloheptene **65**. The synthesis of the adduct, bicycloheptene **65** cannot solely be attributed to Stevens. It was also reported by Ghosez *et al.* at a similar time.[102] However, Stevens was the first to hydrolyse **65** using aqueous acetic acid with sodium hydroxide, to obtain tropolone **3** in 52% yield (Scheme 1.13). A patent for this process was later registered to Barlett.[103] This method is the current prefered method for the synthesis of tropolone, the procedure generates a good yield with easily avaliable starting materials.



Scheme 1.13: [2 + 2] Cycloaddition to form cycloadduct **65** which can be hydrolysed to tropolone **3**

The method involving a [2 + 2] cycloadditon with dichloroketene **64** was hence expanded with a wide range olefins to produce subtituted tropolones. Asao *et al*. successfully performed the reaction using 6,6-dimethylfulvene **66** to give several adducts,[104] including the natural products α-dolabrin **68**, β-dolabrin **10**, α-thujaplicin **11** and trace amounts of β-thujaplicin (hinokitiol) **6** (Scheme 1.14, Figure 1.2.1). The reaction has also been performed with other olefins,[105] including indene[106,107] and, isopropylcyclopentadiene[108] to produce thujaplicins.



Scheme 1.14: Synthesis of natural product α-dolabrin **68**

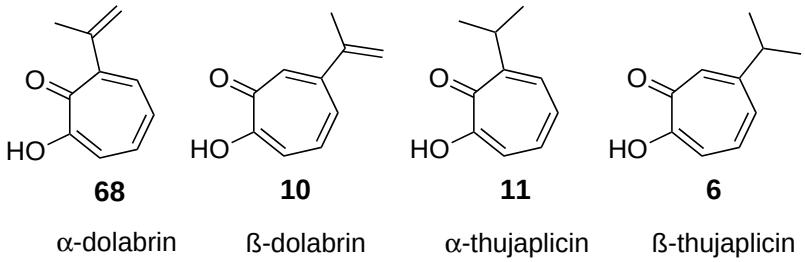
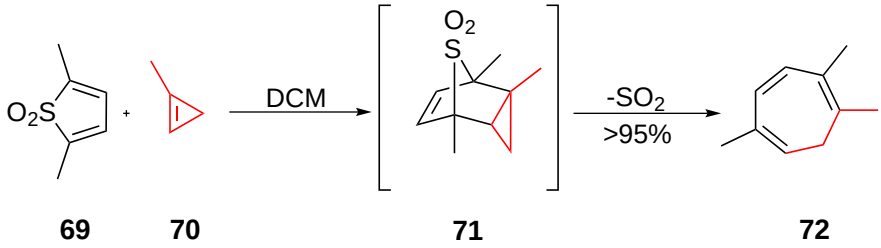


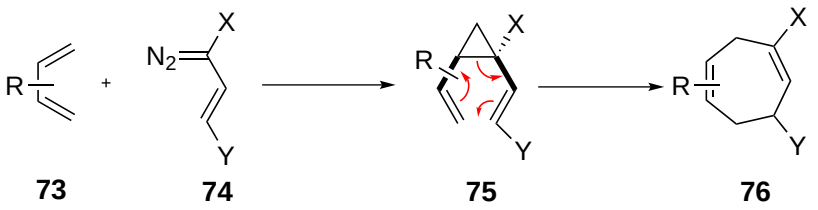
Figure 1.2.1: Natural products produced by Asao et al (1970)[104]

Reinhoudt *et al.* successfully employed substituted thiophene-1,1-dioxides and substituted cyclopropenes to produce a wide range of cycloheptatrienes via a Diels-Alder reaction (Scheme 1.15).[109,110] Dimethylthiophene-1,1-dioxide **69** and 1-methylcyclopropene **70** underwent a Diels-Alder reaction in DCM to produce intermediate **71**. The adduct **71** then spontaneously undergoes a chelotropic elimination of sulfur dixoide and ring expands to produce the trimethylcycloheptatriene **72**. This synthetic sequence produced several different cycloheptatrienes though it was limited in scope by steric hinderence on the starting materials. This approach could be used to synthesise cordytropolone **37**, if an appropriate cyclopropane and thiophene-1,1-dioxide can be formed.



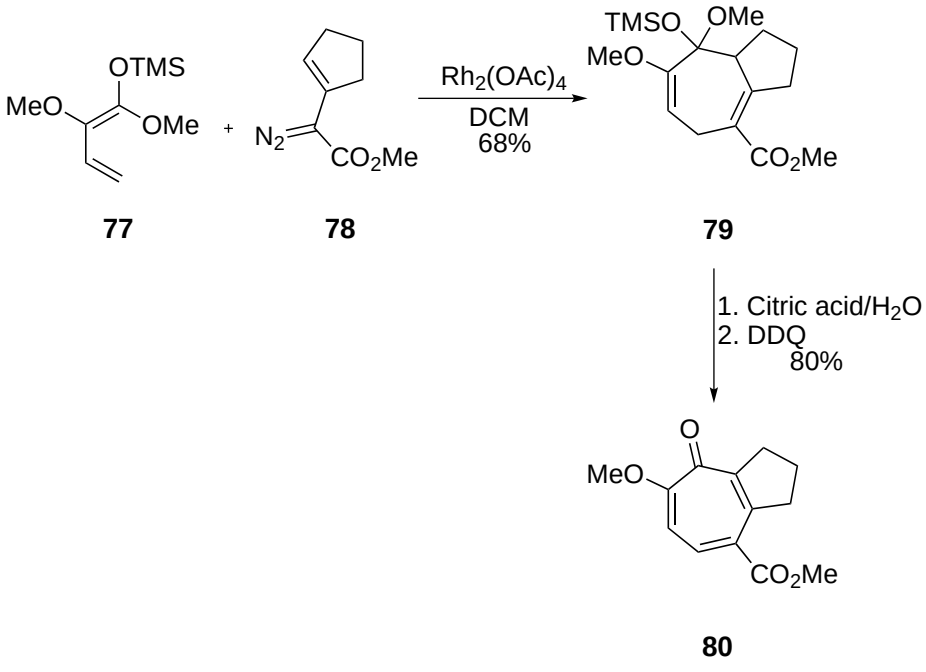
Scheme 1.15: Diels-Alder reaction to produce a substituted cycloheptatriene

Another method for the creation of seven membered rings was developed by Davies in 1993. This method involed cyclopropanation of vinyldiazomethanes followed by a Cope rearrangement to form a cycloheptadiene ring (Scheme 1.16).[111] In this reaction, the diene **73** undergoes a $Rh_2(OAc)_4$ catalysed cyclopropanation with vinyldiazomethane **74** to form **75**. The cyclopropane **75** then undergoes a [3,3]-sigmatropic rearrangement to form the cycloheptadiene **76**. Davies used this method to produce a wide range of different cycloheptadienes.[112]



Scheme 1.16: Davies' cyclopropanation followed by rearrangement to produce a cycloheptadiene

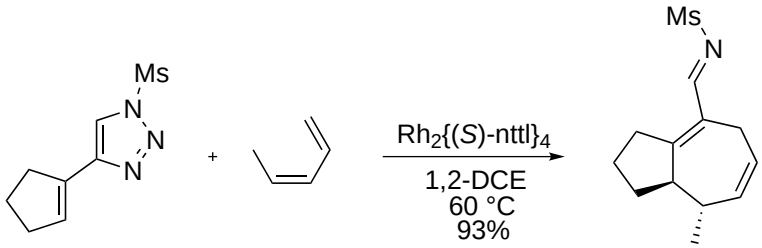
Davies was also able to produce bicylic products which could easily be converted into the corresponding tropolone (Scheme 1.17) using this method. These products bare a marked similarity to cordytropolone **37**. Reaction of vinyldiazomethane **78** with diene **77** produced cycloheptadiene **79** in 68% yield. The cycloheptadiene **79** was converted to tropolone **80** in 80% yield through the use of citric acid and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



Scheme 1.17: Davies' formation of a bicyclic tropone system

More recently, Davies has done some work involving the rhodium catalysed transformation of 1,2,3-triazoles.[113] It was previously found by Fokin *et al.* that 1,2,3-triazoles can act as masked diazo compounds and can be decomposed to produce a metal carbene.[114]

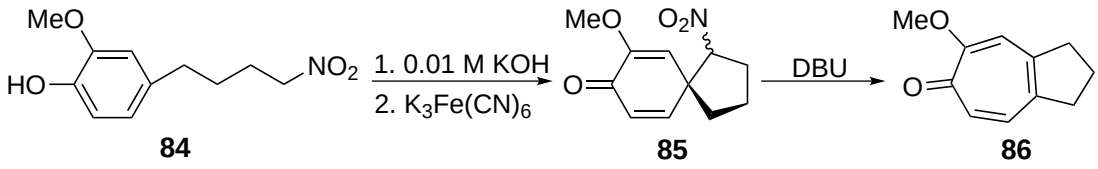
Davies uses this knowledge, in conjunction with the Cope rearrangment, to devise an alternate route to bicyclic cycloheptadiene products (Scheme 1.18). Using tiazole **81** with diene **82** and the use of a rhodium *N*-naphthoyl-(*S*)-*tert*-leucinate catalyst, cycloheptatriene **83** was produced in good yield.



81 **82** **83**

Scheme 1.18: [4+3] Cycloaddition involving a triazole and rhodium catalysis

Another method of synthesising cordytropolone like compounds was reported by Kende in 1986 (Scheme 1.19).[115] Treatment of a phenolic nitroalkane **84** in dilute KOH with $K_3Fe(CN)_6$ produced the nitrodienone **85**. Reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) then induced a rearrangment to produce tropolone **86** in a modest 45-50% overall yield.

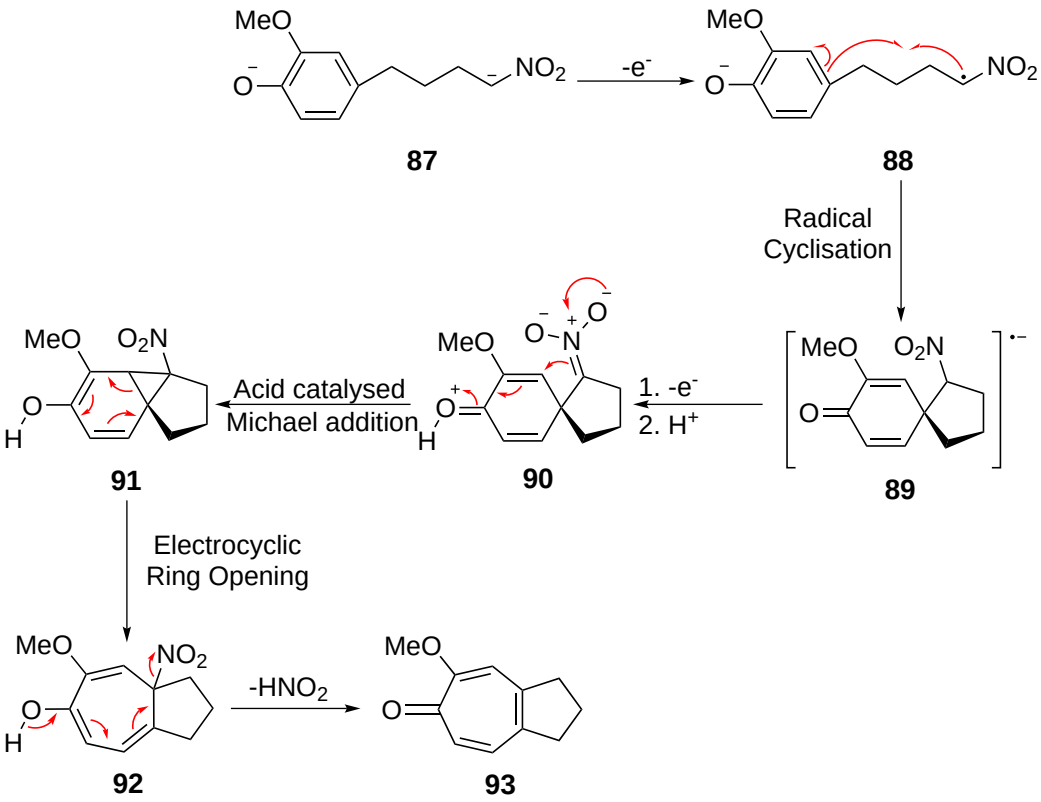


84 **85** **86**

Scheme 1.19: Intramolecular reaction of a phenolic nitro alkane to produce a tropolone

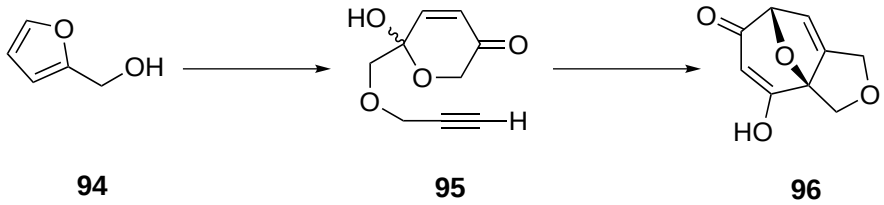
Based on observations reported by Kende regarding the synthesis of these bicyclic compounds a proposed mechanism is illustrated in Scheme 1.20. After deprotonation by the KOH solution the phenolic nitroalkane **87** is oxidised by the $K_3Fe(CN)_6$ forming the radical **88** which then undergoes cyclisation via intermediate **89** to dienone **90**. As Kende reports the rearrangment of **90** occurs rapidly in acidc conditions. It is proposed that it undergoes an acid catalysed Michael addition to produce **91**. Compound **91** undergoes a 6π

electrocyclic ring opening to form the nitrocycloheptatriene **92**, which, upon elimination of the nitro group aromatises to form tropone **93**.[115]



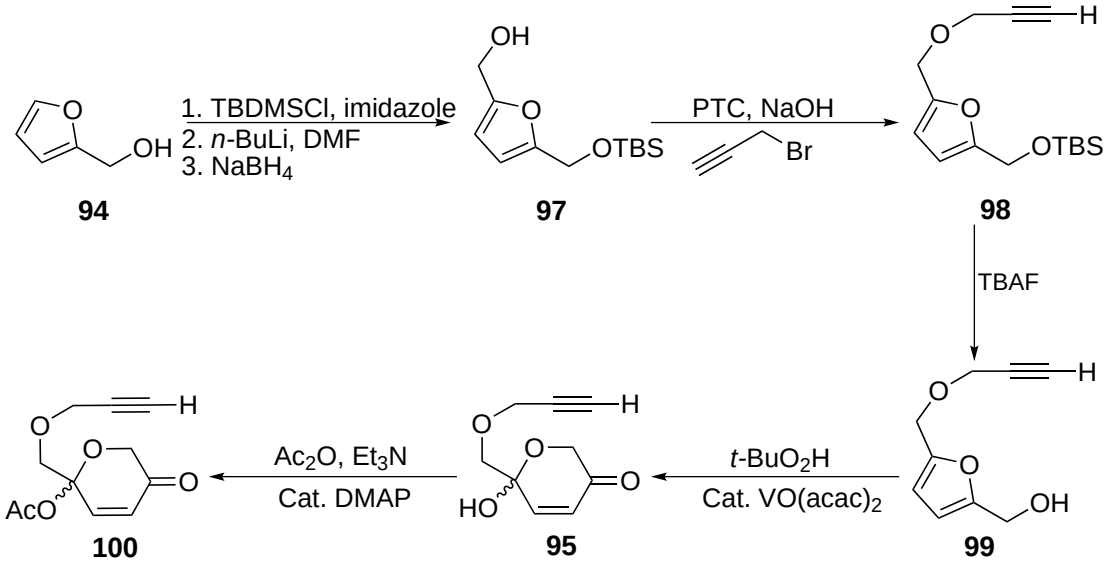
Scheme 1.20: Proposed mechanism for Kende's tropolone synthesis

The only published attempt at the total synthesis of cordytropolone occurred in 2005 by Celanire *et al.* (Scheme 1.21). The key features of this attempted synthesis was the conversion of furfuryl alcohol **94** to **95** by an oxidative rearrangement. This was followed by a [5+2] dipolar cycloaddition to produce the advanced compound **96**.[116]



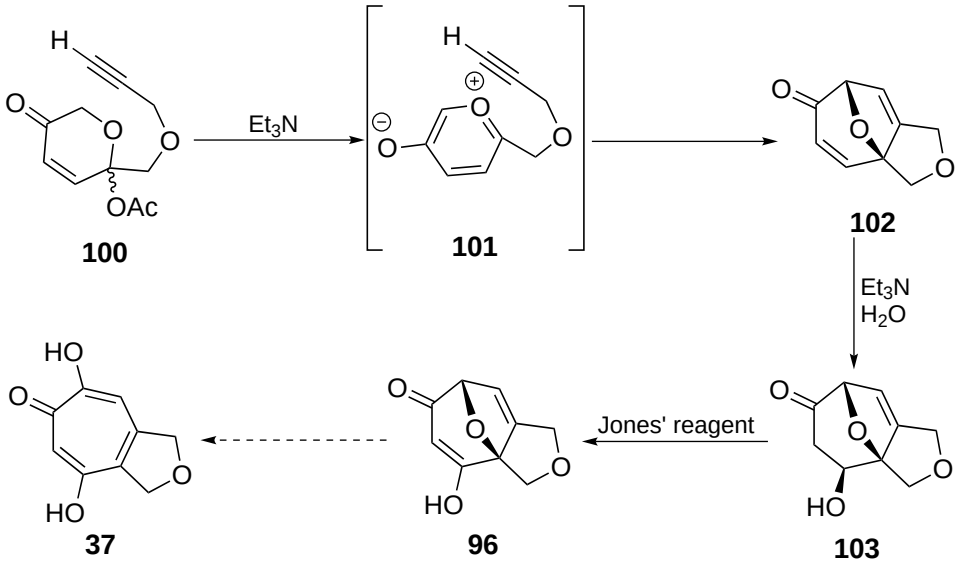
Scheme 1.21: Overview of the attempt at total synthesis of cordytropolone by Celanire *et al.*[116]

The detailed synthesis is described in Scheme 1.22 and Scheme 1.23. The hydroxyl group on the furfuryl alcohol **94** was protected by using *tert*-butyl dimethylsilylether (TBS), followed by a formylation using *n*-BuLi and DMF which was then reduced by sodium borohydride to obtain the alcohol **97**. The available hydroxyl reacted with propargyl bromide to produce the propargylic ether **98**. After removal of the TBS protecting group, the resulting furan **99** was oxidised with *tert*-butylhydroperoxide and vanadyl acetylacetonate to form the hydroxyl-pyranulose **95**. This compound was unstable and required immediate purification. Once **95** had been obtained it was acetylated with acetic anhydride in triethylamine using a catalytic amount of 4-(dimethylamino)pyridine to obtain **100**.



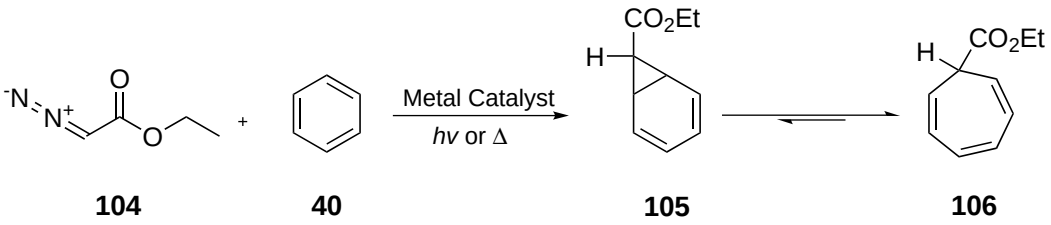
Scheme 1.22: Oxidative rearrangement of furfuryl alcohol **94**

The [5+2] intramolecular dipolar cycloaddition was performed by reacting **100** with triethylamine in toluene at reflux to produce the reactive intermediate, pyrillium salt **101**, which reacts with the pendant alkyne to give the [5+2] cycloadduct **102**. The keto-enol **96** was formed from **102** by a Michael addition of water followed by oxidation of the β-alcohol **103**. There are similarities between **96**, and cordytropolone **37**. The main difference being the oxygen bridge across the seven-membered ring. Initial attempts by Celanire *et al*. to break this bridge and form cordytropolone proved to be "challenging"[116] and no other reports of the completed synthesis have been published.



Scheme 1.23: [5 + 2] dipolar cycloaddition to produce **96**

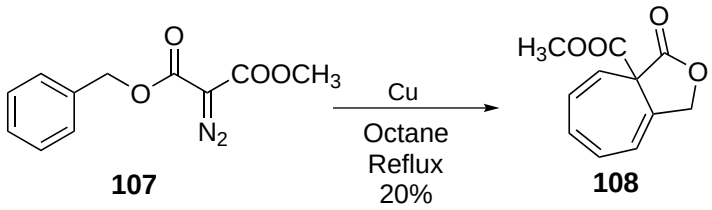
Several of the methods discussed previously already start with compounds with the seven membered ring already formed, formation of the seven membered ring remains one of the more difficult steps.[117] Towards the synthesis of cordytropolone **37** an attractive method of producing seven-membered rings is the reaction known as the Buchner ring expansion (Scheme 1.24). It is a two-step reaction used to form seven-membered rings from benzene rings. The first step involves formation of a metal-carbenoid from a diazoacetate **104**, followed by a cyclopropanation on the aromatic ring **40** to produce bicyclo[4.1.0]heptadiene **105**. Compound **105** is in equilibrium with the cycloheptatriene **106** which is formed by an electrocyclic ring opening. Initially, copper salts were used as catalysts to form the carbene[118–121] but in more recent years rhodium catalysts such as $Rh_2(OAc)_4$ have proven to also be effective.[122] In the case of cordytropolone, a five-membered ring would need to be formed in addition to the seven-membered ring. To facilitate this the Buchner ring expansion would need to be performed intramolecularly.



104 **40** **105** **106**

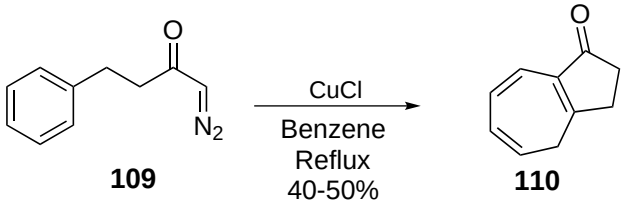
Scheme 1.24: Buchner ring expansion to form a cycloheptatriene

Intramolecular Buchner reactions have been reported since the 1970s. The reaction of diazoketone **107** using a copper catalyst to form the cycloheptatriene derivative **108** by Julia *et al.* in 1970 was one of the first reported instances of this reaction and produced a bicyclic ring system.[123] This reaction used copper as a catalyst in octane at reflux, or benzene at 130 °C and formed the **108** in 20% yield (Scheme 1.25). A similar reaction was reported in 1973 by Scott *et al.* using diazoketone **109** to produce cylcoheptatriene **110** with copper(I) chloride as the catalyst (Scheme 1.26).[124] In the 1980's work by McKervey brought about improvements in the catalysts used. Through the use of a rhodium catalyst instead of a copper based catalyst McKervey was able to significantly improve the yields of the reactions performed by Julia and Scott (Scheme 1.27) .[125,126]



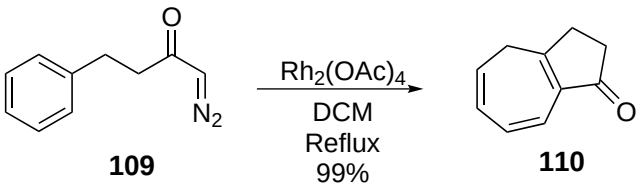
107 **108**

Scheme 1.25: Julia *et al.* intramolecular Buchner ring expansion[123]



109 **110**

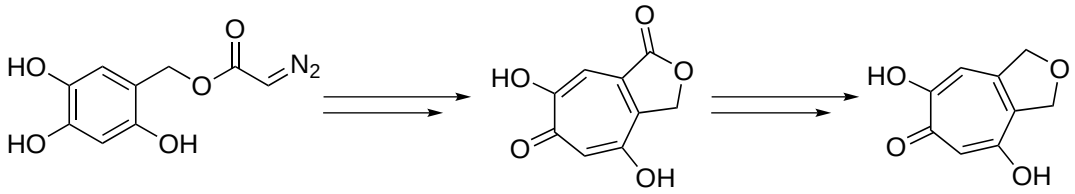
Scheme 1.26: Scott *et al.* intramolecular Buchner ring expansion[124]



109 **110**

Scheme 1.27: Rhodium catalysed Buchner ring expansion

Diazo compounds are inherently unstable, they are known to be explosive and easily undergo liberation of nitrogen gas. The simplest diazo compound, diazomethane is highly toxic and explodes when heated beyond 100 °C. It has also been known to explode when in contact with sharp edges and scratches on glassware.[127] The stability of diazo compounds can be improved by resonance through an adjacent carbonyl, the diazoketone **109** made by Scott *et al.* or the diazodiester **107** by Julia *et al.* are examples. However, synthesis of cordytropolone **37** via carbonyl stabilised diazoester such as **111** would produce lactone **112** that would need to be reduced later, increasing the steps in the synthesis (Scheme 1.28).

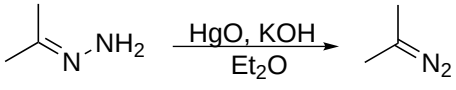


111 **112** **37**

Scheme 1.28: Buchner ring expansion with diazoester **111** would produce lactone **112** which would need to be removed to produce cordytropolone **37**

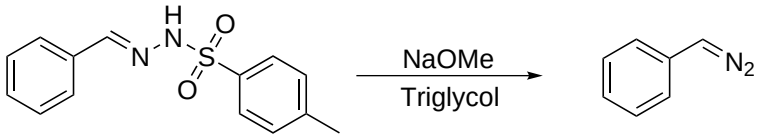
Diazo compounds can also be generated *in situ* from more stable starting materials. Hydrazones can be oxidised to a diazo compound, as in the synthesis of 2-diazopropane **114** by oxidation of hydrazone **113** using HgO (Scheme 1.29).[128] Similarily, tosyl hydrazones can form diazo compounds by deprotonation of the nitrogen using a sufficiently strong base, as in the synthesis of phenyldiazomethane **116** from tosyl hydrazide **115** using sodium methoxide (Scheme 1.30).[129,130] Producing the diazo compound *in situ* this way does not require a stabilising carbonyl group, potentially reducing the steps towards

the total synthesis of cordytropolone.



113 **114**

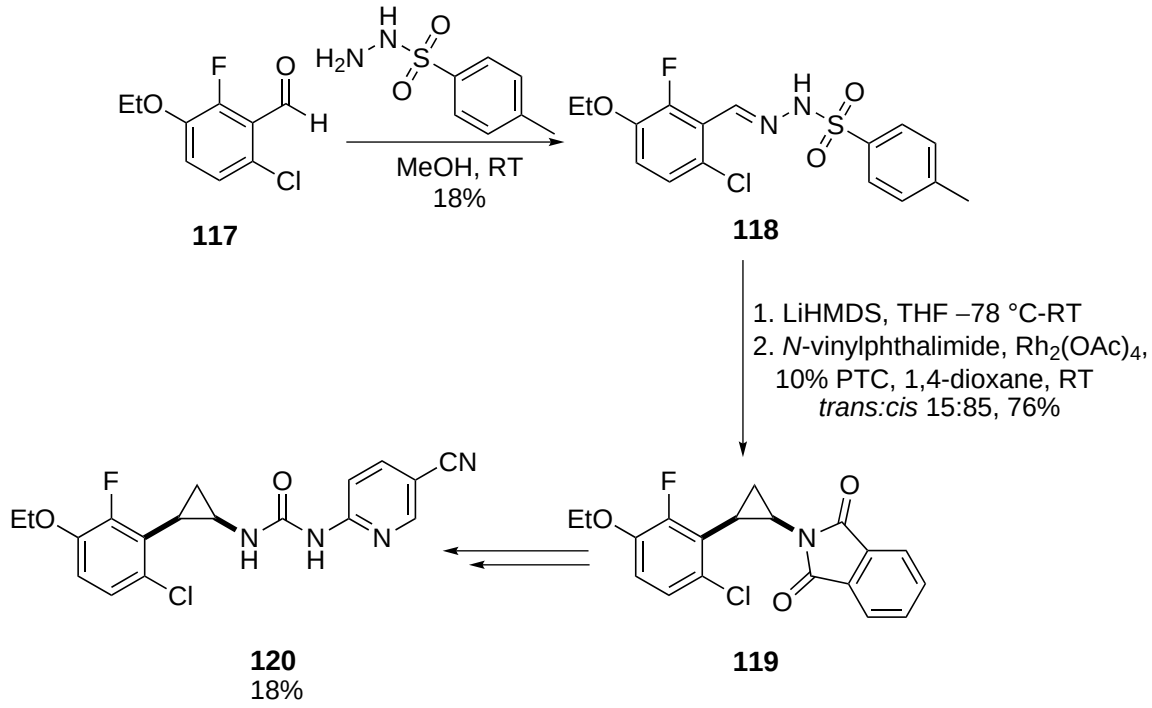
Scheme 1.29: Synthesis of 2-diazopropane via oxidation of hydrazone **113**



115 **116**

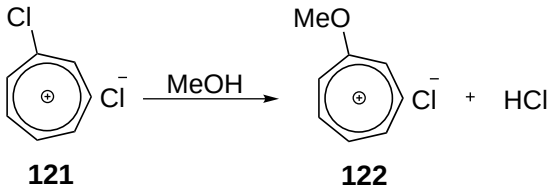
Scheme 1.30: Synthesis of phenyldiazomethane via deprotonation of tosyl hydrazide **115**

Cyclopropanations involving diazo compounds generated *in situ* from a tosyl hydrazone have also been reported. Aggarwal *et al.* used the reaction to produce the potent HIV-1 reverse transcriptase inhibitor **120** (Scheme 1.31).[131] Tosyl hydrazone **118** was produced from aldehyde **117** via a condensation reaction with tosyl hydrazide. Hydrazone **118** was deprotonated with LiHDMS and treated with *N*-vinylpthalimide and $Rh_2(OAc)_4$ in 1,4-dioxane, with a phase transfer catalyst to give cyclopropane **119**. The cyclopropane **119** was then eventually converted to the inhibitor **120** in 18% overall yield. This method was expanded to several produce several other arylcyclopropamines and has also been applied to several other reactions, including asymmetric epoxidation.[121,132]



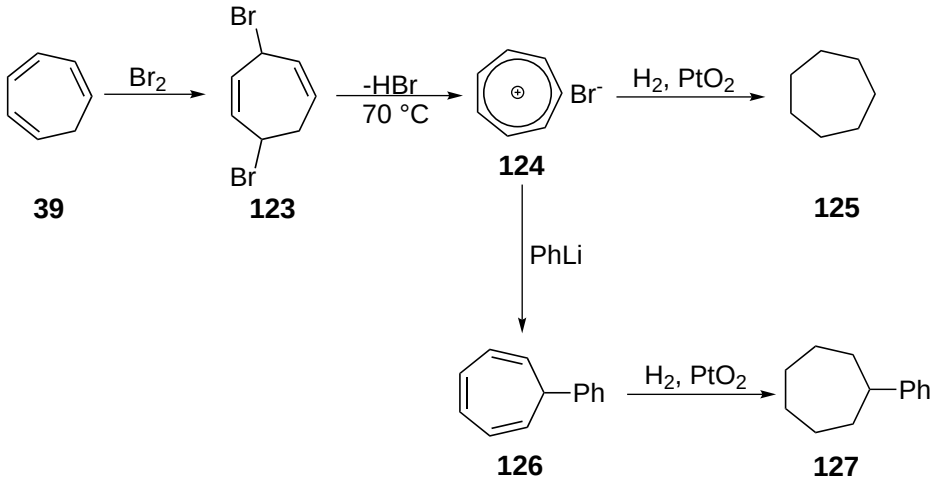
Scheme 1.31: Aggarwal *et al*. synthesis of **120** via Rh catalysed cyclopropanation

While the Buchner ring expansion could be used to form the bicyclic ring system of cordytropolone **37** there is still a need to be able to functionalise the seven membered ring system. One of the unique features of cycloheptatrienes is their ability to form the tropylium ion **122**. The tropylium ion can undergo nucleophillic aromatic substitution reactions. Föhlisch and Haug reported several reactions where a tropylium ion salt was substituted with other nucleophiles such as alcohols.[133] Chlorotropylium chloride **121** was reacted with MeOH to give methoxytropylium chloride **122** (Scheme 1.32). Föhlisch and Haug went on to investigate this reaction further with other nucleophiles including amines and thiols. This feature of cycloheptatrienes is highly advantageous as it can allow late stage functionalisation of the seven membered ring, useful for a probing a compounds potential activity.



Scheme 1.32: Nucleophilic substitution to the tropylium ion

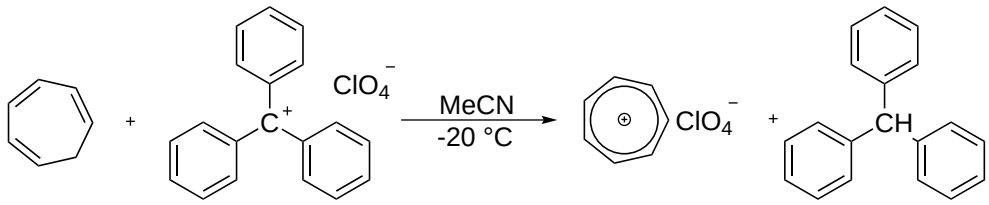
Doering and Knox were one of the first to investigate the tropylium ion.[134] Working with cycloheptatriene **39** they were able to brominate it to form the dibromide **123**. Upon loss of HBr the compound formed a mass of crystals. Doering and Knox believed these crystals to be tropylium bromide **124**. The crystals also reacted with aqueous silver nitrate to give silver bromide, an indication that the crystals were likely a bromine salt. To confirm that the seven membered ring was still intact, the tropylium bromide **124** was hydrogenated to give cycloheptane **125**. Doering and Knox also performed an addition reaction with phenyl lithium to give phenyl cycloheptatriene **126** which had its structure confirmed by hydrogenating to give phenyl cycloheptane **127** (Scheme 1.33). Doering and Knox later went on to investigate other reactions with the tropylium cation, including reaction with ammonia, methoxide ions, hydrogen sulfide and chromic acid.[135]



Scheme 1.33: Doering and Knox[134] were able to perform nucleophilic aromatic substitution on the tropylium cation

Tropylium ion salts are more commonly prepared through hydride abstraction. Dauben

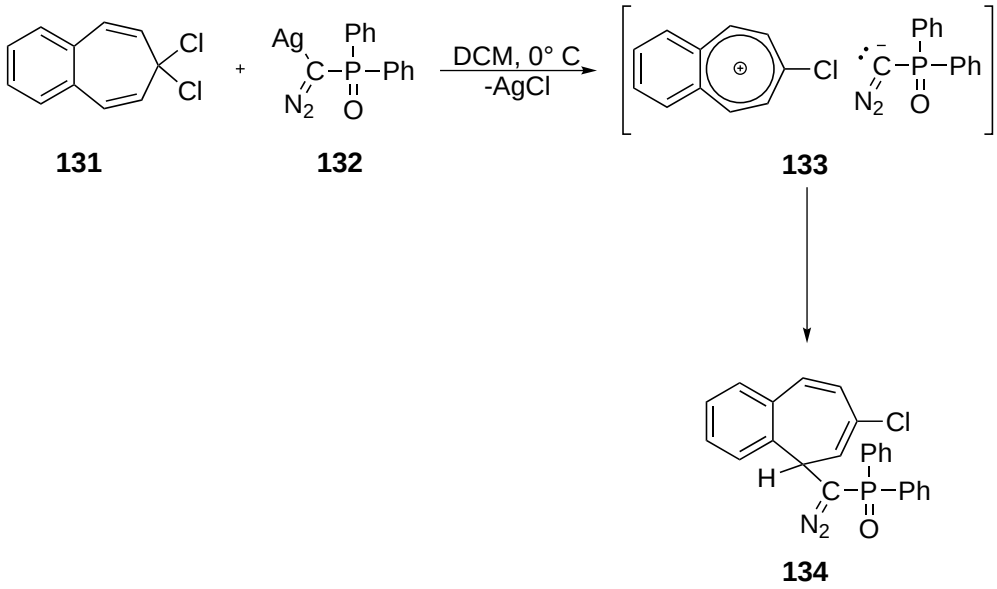
et al. were able to synthesise tropylium salts by reaction of cycloheptatriene **39** with triphenylmethyl cations (Scheme 1.34).[136] Cycloheptatriene **39** was reacted with triphenylmethyl perchlorate **128** in acetonitrile at -20 °C to give tropylium perchlorate **129**. Dauben *et al.* also reported good results with triphenylmethyl tetrafluoroborate and was able to expand the method to substituted cycloheptatrienes including iodide, chloride and, methoxy cycloheptatrienes. Other investigations into the tropylium cation included the formation of several polycyclic ions inluding benzotropylium[137,138] and napthotropylium ions.[1,31]



39 **128** **129** **130**

Scheme 1.34: Dauben *et al.* was able to abstract a hydride from cycloheptatriene **39** to form the perchlorate salt **129**

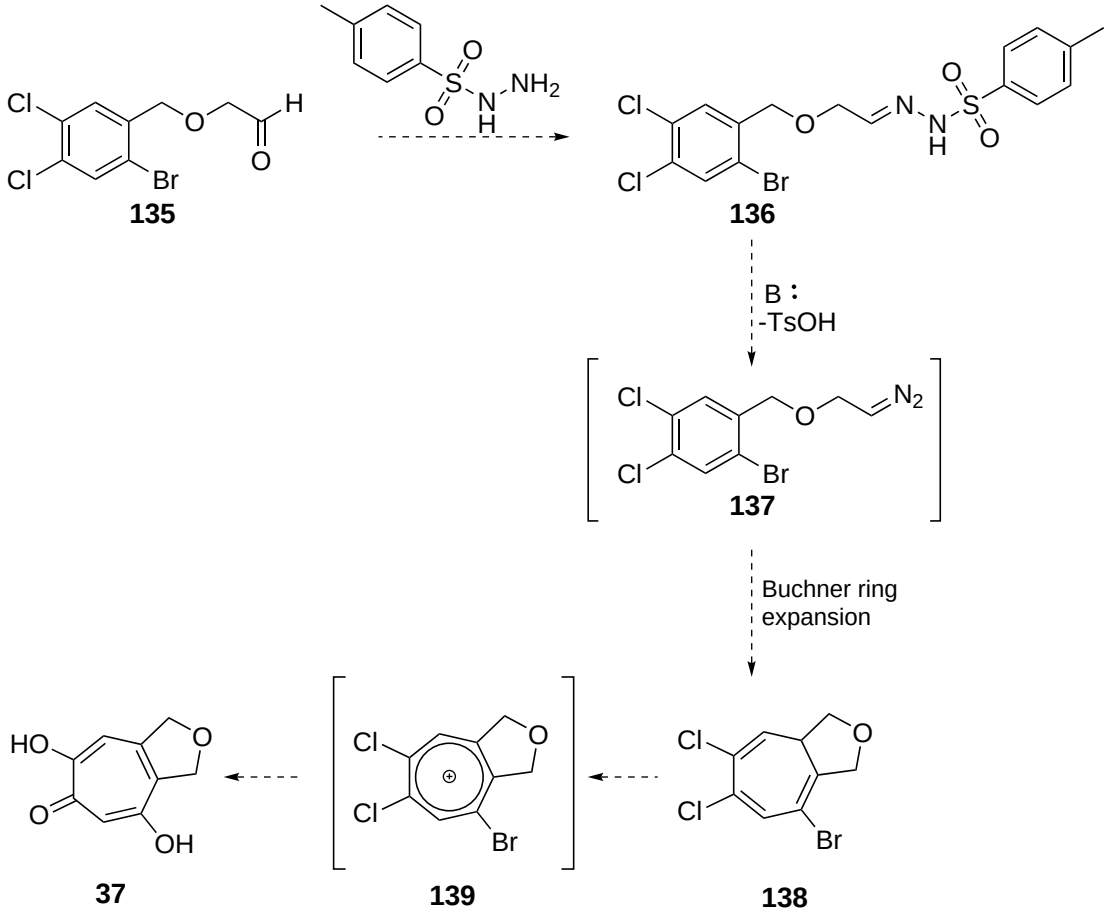
Regitz *et al.* were able to form the tropylium cation from dichlorobenzocycloheptatriene **131** and then substitute it in combination.[139] Reacting dichlorobenzocycloheptatriene **131** with silver diazomethylphosphoryl compound **132** caused silver chloride to eliminate and the tropylium cation **133** to form. The diazomethylphosphoryl compound then adds to the tropylium cation to give benzyocycloheptatriene **134** (Scheme 1.35). Regitz *et al.* went on substitute to the tropylium cation with a variety of reagents.[139,140]



Scheme 1.35: Regitz *et al*. formed the tropylium cation **133** and then substituted it

1.3 Proposed Synthesis of Cordytropolone

Using the chemistry in this review, cordytropolone **37** could be synthesised from a pathway similar to that shown in Scheme 1.36. In this pathway, a compound must be synthesised with appropriate halogen groups substituted around the benzene ring. Having hydroxyl groups present instead, as in the structure of the final target cordytropolone **37**, may give rise to solubility issues as well as potentially causing unwanted side reactions. The halogens can be replaced in the last step of the synthesis. In the proposed synthesis there are two key steps. The first key step involves a Buchner ring expansion using diazo compound **137** generated *in situ* from tosyl hydrazone **136** to form the seven-membered ring **138**. The Buchner ring expansion is an approach rarely used in synthesis. The last step has rarely in total synthesis; the nucleophilic aromatic substitution reaction to the tropylium cation **139** which forms cordytropolone **37** in a reasonably short synthesis.

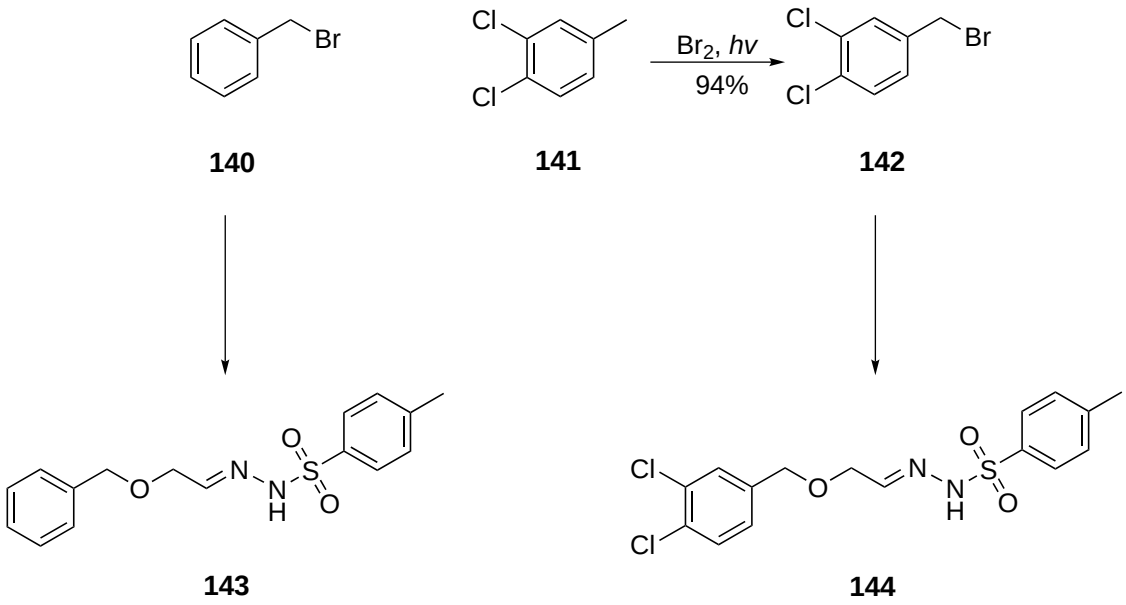


Scheme 1.36: Potential path for the synthesis of cordytropolone **37** using the Buchner ring expansion and nucleophilic aromatic subtitution

Chapter 2

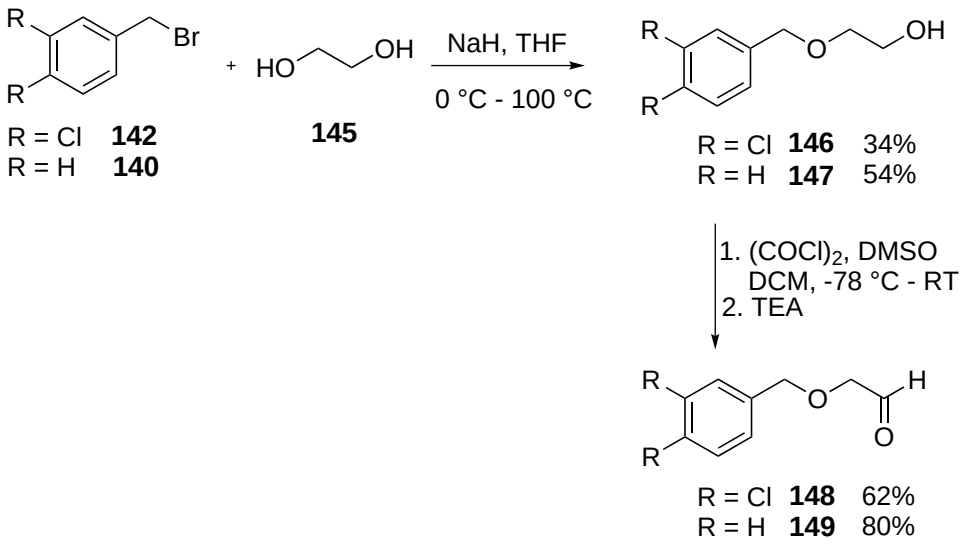
Intramolecular Buchner Ring Expansion via *in situ* Generated Diazo Compounds

The proposed synthesis of cordytropolone as described in Scheme 1.36 requires a tosyl hydrazone to be prepared that would be appropriate for the Buchner ring expansion. Tosyl hydrazones can be produced in a condensation reaction of tosyl hydrazines with aldehydes. To this end, the synthesis of two compounds suitable for a model ring expansion were planned using benzyl bromide **140** and 3,4-dichlorobenzyl bromide **142**. 3,4-Dichlorobenzyl bromide **142** was easily synthesised by a radical bromination of 3,4-dichlorotoluene with Br_2 irradiated by a tungsten lamp (Scheme 2.1).



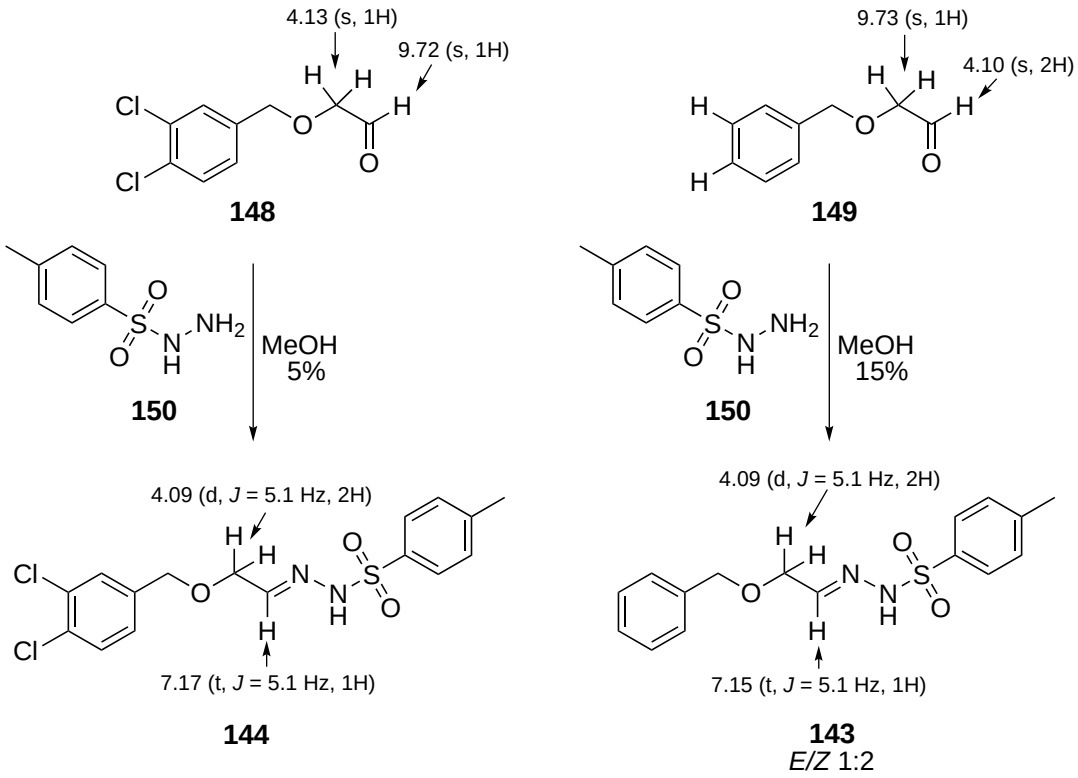
Scheme 2.1: Synthesis of 3,4-dichlorobenzyl bromide **142**

Conversion of the benzyl bromides **140** and **142** to the required aldehydes **148** and **149** was performed in a two step procedure (Scheme 2.2). A solution of ethylene glycol **145** in THF was reacted with sodium hydride to give the monoalkoxide which underwent a substution reaction with the benzyl bromides to produce the benzyloxyethanols **146** and **147** in 34% and 54% yield.[141] Oxidation of the alcohol **146** with PCC only caused decomposition, however by using a Swern oxidation[142] the two aldehydes **148** and **149** were obtained in 62% and 80% yield. (Scheme 2.2). The ^{1}H NMR spectrum of **148** contained three aromatic signals each integrating for 1H. Two signals at 4.55 and 4.12 ppm integrating for 2H which represent the two benzyl hydrogens as well as the two hydrogens alpha to the aldehyde. The aldehyde hydrogen signal appears at 9.70 ppm and integrates for 1H. The ^{1}H NMR spectrum of **149** contained similar signals, a multiplet in the aromatic region for 5H, two signals for 2H at 4.63 and 4.10 ppm. The characteristic aldehyde signal appears at 9.73 ppm, integrating for 1H. Unfortunately, these compounds both decomposed at room temperature. Decomposition of the compounds could be slowed by storage at -19 °C or lower .



Scheme 2.2: Preperation of aldehydes **148** and **149**

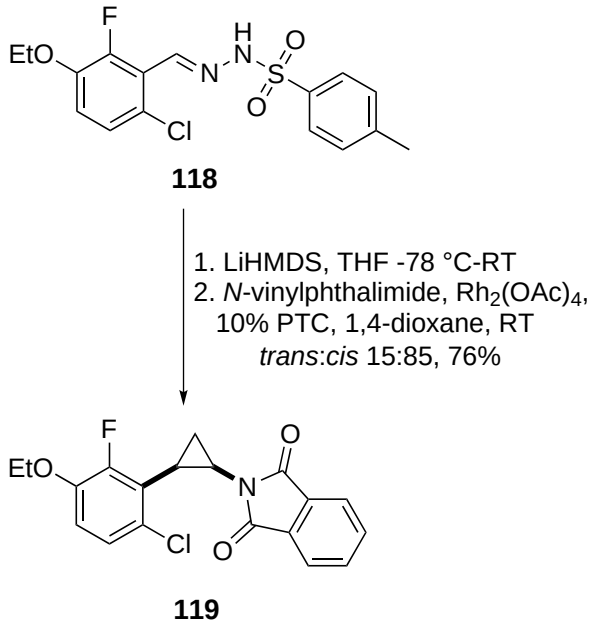
The next step was the condensation reaction with tosylhydrazide (Scheme 2.3). When the aldehyde **148** was reacted with tosylhydrazide in methanol at room temperature, a single unstable product was isolated in 5% yield.[132] The compound was tentatively identified as hydrazone **144**. Hydrazone **143** was obtained in the same way in 15% yield. The isolation and characterisation of these compounds proved to be problematic. The compounds also rapidly decomposed into a complex mixture if not handled correctly.



Scheme 2.3: Condensation reaction with tosyl hyrazide to produce hydrazines **144** and **143**

Nevertheless, the ^{1}H NMR spectrum of the hydrazone **144** was consistant with its structure. There were four signals in the aromatic region from 7.05-7.81 ppm integrating for a total of 7H. A triplet at 7.17 ppm was identified as the hydrazone hydrogen. This triplet, (J = 5.1 Hz) couples with a doublet (J = 5.1 Hz) integrating for 2H at 4.09 ppm (Scheme 2.3). The remaining two signals are a singlet at 4.35 ppm integrating for 2H which is consistant with the benzylic ether hydrogens and, a singlet at 2.43 ppm integrating for 3H consistant with the methyl group on toluene. The structure of the hydrazone **143** was determined in the same way. It too had the tiplet integrating for 1H at 7.15 ppm (J=5.1 Hz) and the doublet integrating for 2H at 4.09 ppm (J = 5.1 Hz) in the ^{1}H NMR spectrum, indicating that the hydrazone had attached to the aldehyde **149**. There were also minor signals that indicated a second hydrazone had formed, this was determined to be the *E* isomer of **143** as the chemical shift of the triplet integrating for 1H had shifted slightly upfield to 6.70 ppm.[143]

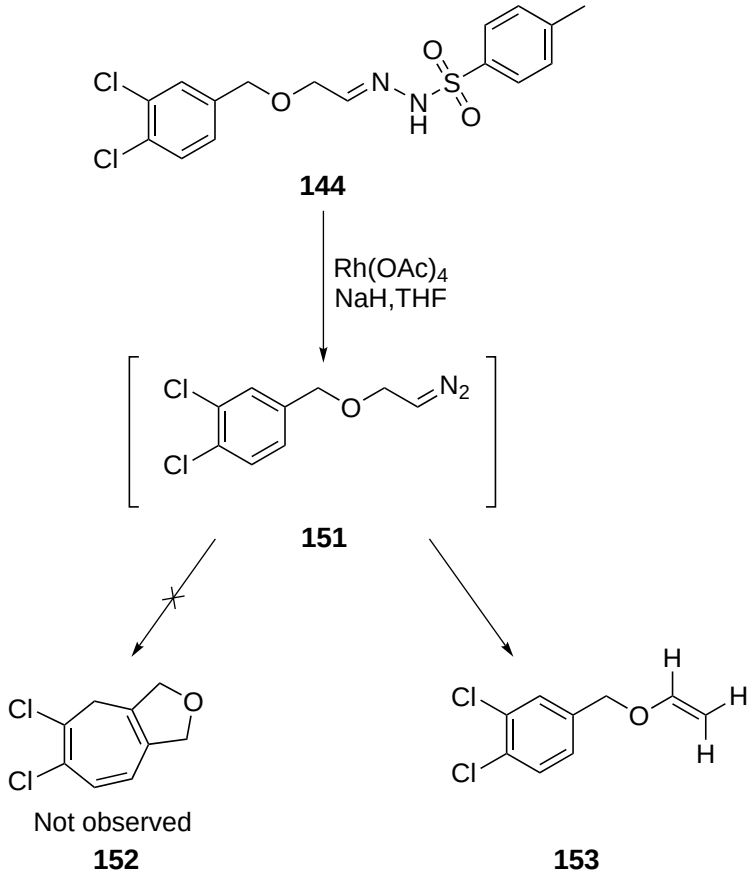
As described in the introduction (Scheme 1.31), Aggarwal *et al.*[131,132] successfully used a rhodium catalysed cyclopropanation with a hydrazone in the synthesis of a potent HIV-1 reverse transcriptase inhibitor. Hydrazone **118** was deprotonated with LiHDMS and treated with *N*-vinylpthalimide and $Rh_2(OAc)_4$ in 1,4-dioxane, with a phase transfer catalyst to give cyclopropane **119** (Scheme 2.4).



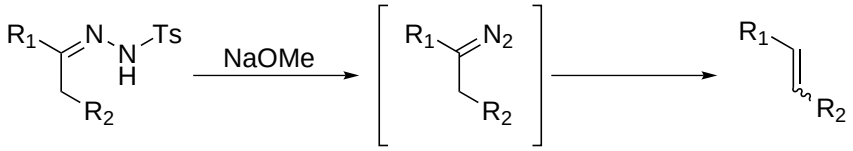
Scheme 2.4: Aggarwal *et al*. synthesis of **119** via Rh catalysed cyclopropanation

The intramolecular ring expansion was attemped on the dichlorohydrazone **144**. A base is needed to deprotonate the hydrazone for it to form the diazo compound *in situ*. Sodium hydride was used as the base with $Rh_2(OAc)_4$ as the catalyst[144] (Scheme 2.5). The hydrazone **144** was dissolved in THF in at 0 °C with sodium hydride and $Rh_2(OAc)_4$, this was then warmed to room temperature before being heated under reflux. The reaction produced a complex mixture but the ^{1}H NMR spectrum showed one very clear signal in the vinyl region (6.00-7.00 ppm) where we would expect signals from a cycloheptatriene ring. A trace amount of the compound was isolated through using a silica plug as it was signifcantly less polar than the rest of the mixture. The ^{1}H NMR spectrum of this product showed the vinyl signal as a doublet of doublets integrating for 1H at 6.54 ppm. The spectrum also had three signals in the aromatic region each integrating for 1H (7.18, 7.43,

7.16 ppm) indicating that the dichlorobenzene ring was still attached. The benzyl hydrogens were also still present, indicated by a singlet at 4.71 ppm for 2H. There were two doublets at 4.12 and 4.28 ppm integrating for 1H each. Unfortunately, the compound was volatile and unstable so further analysis could not be performed. Based on this evidence, the isolated product was thought to be a product from a Bamford-Stevens reaction.[145] In a Bamford-Stevens reaction a tosyl hydrazone decomposes in presence of a strong base to an alkene (Scheme 2.6). If hydrazone **144** had undergone a Bamford-Stevens reaction it would produce enol ether **153** (Scheme 2.5). Although in these reactions sodium methoxide is the traditional base used, sodium hydride has also been reported.[146]



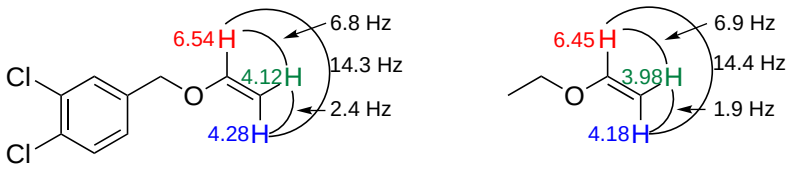
Scheme 2.5: Attempted ring expansion of **144** did not produce **152** but instead produced trace amounts of **153**



154 **155** **156**

Scheme 2.6: In the Bamford-Stevens reaction a hydrazone reacts with a strong base to form an alkene through a diazo intermediate.[130,145]

By comparing the ^{1}H NMR spectrum of the reaction product with the ^{1}H NMR spectrum of ethyl vinyl ether **157** it is highly probable that the unknown compound is the enol ether **153**. Both compounds have the doublet of doublet pattern integrating for 1H in the vinyl region, the isolated product **153** at 6.54 ppm and the ethyl vinyl ether at 6.45 ppm. Both spectra also have two sets of doublet of doublets integrating for 1H each. The isolated product **153** at 4.12 and 4.28 ppm and, the ethyl vinyl ether at 3.95 and 4.18 ppm. From this it would be evident that reaction with sodium hydride was causing the hydrazones to decompose to form the Bamford-Stevens product **153** (Figure 2.0.1, Figure 2.0.2).



153 **157**

Figure 2.0.1: Comparison of the two compounds indicates that **153** is the product being formed

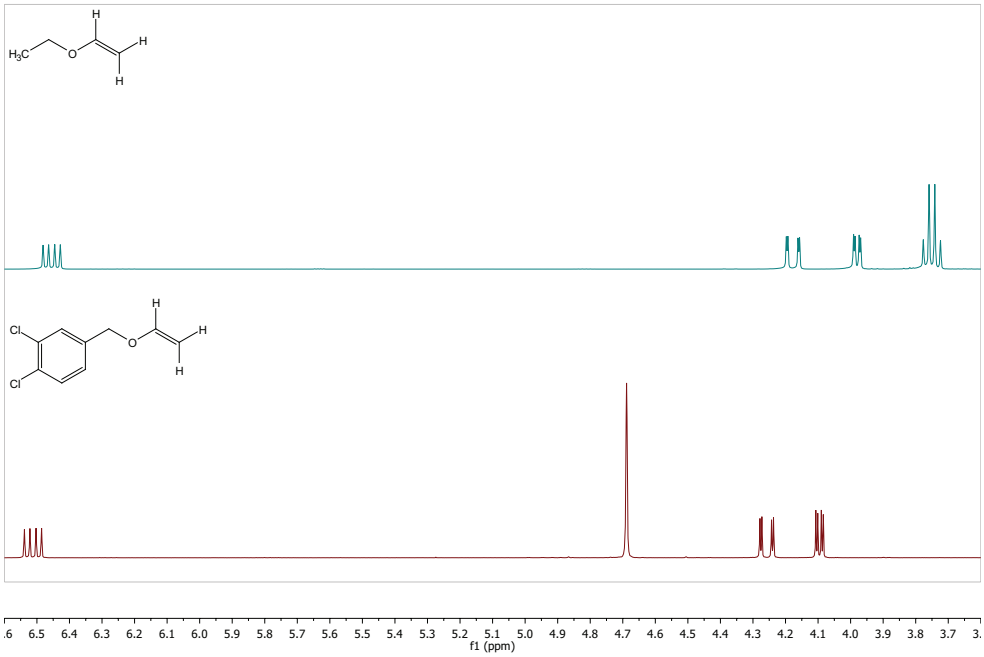
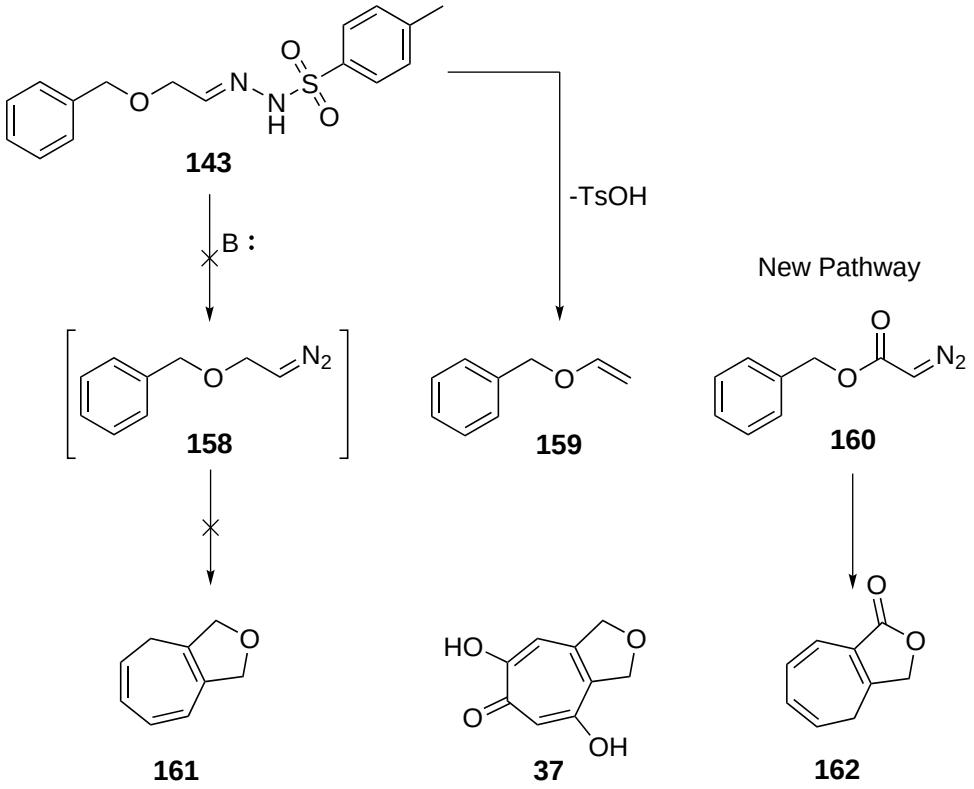


Figure 2.0.2: Comparison of the ^{1}H NMR spectrum of ethyl vinyl ether **157** compound **153**

Due to the difficulty in purification of the hydrazones, the unstable nature of the aldehyde precursor and the formation of the vinyl ether instead of a carbene adduct, further investigation in this synthetic pathway was discontinued. Instead, it was thought that the additon of a stabilising carbonyl group on the molecule as present in diazoester **160** which may be stable enough to isolate. While the stability of the compounds would increase it means there would now be a carbonyl present on the ring expansion product that is not present in cordytropolone **37**, potentially adding unwanted reduction steps to the synthesis (Scheme 2.7).



Scheme 2.7: The addition of the carbonyl group as in the diazoester **160** increases the stability of the diazo intermediate product but requires removal at a later step

Chapter 3

Intramolecular Buchner Ring Expansion via Diazoesters

In light of the competing Bamford-Stevens reaction in the fomration of the previous diazocompounds, diazoesters were investigated as they are isolatable and easier to prepare. Several diazoesters have been prepared from glycine esters using sodium nitrite. Including, but not limited to ethyl diazoacetate **104**,[147] benzyl diazoacetate **160** and, 4-methoxybenzyl diazoacetate **163** and 4-nitrobenzyl diazoacetate **164**[148] (Figure 3.0.1). Cordytropolone **37** could be synthesised from a pathway similar to that shown in Scheme 3.1. An appropriate benzyl glycine **165** could be diazotised to give **166**. The diazoester **166** would then undergo the Buchner ring expansion to give cycloheptatriene **138** which is analagous to the reaction by Scott *et al.*[124] (Scheme 3.2). Unlike the proposed synthesis in Chapter 2, the lactone will need to be dexoygenated, prior to tropylium ion formation and nucleophilc aromatic substitution to give corydtropolone **37**.

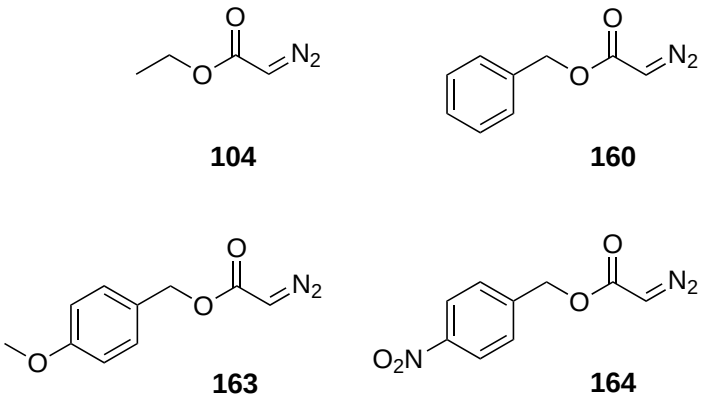
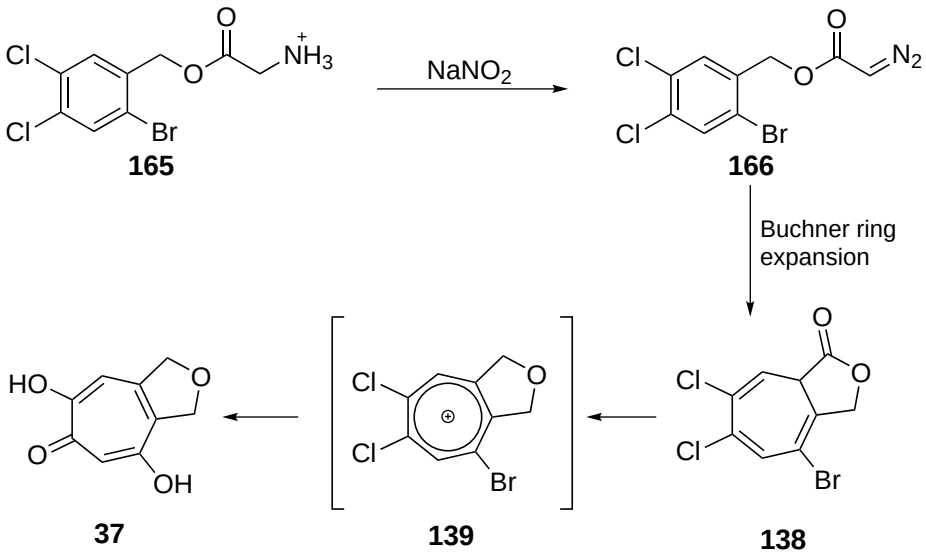
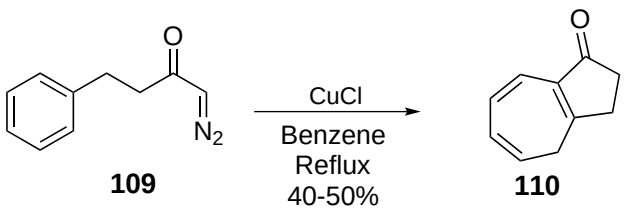


Figure 3.0.1: Several examples of diazoesters synthesised from glycine esters using sodium nitrite



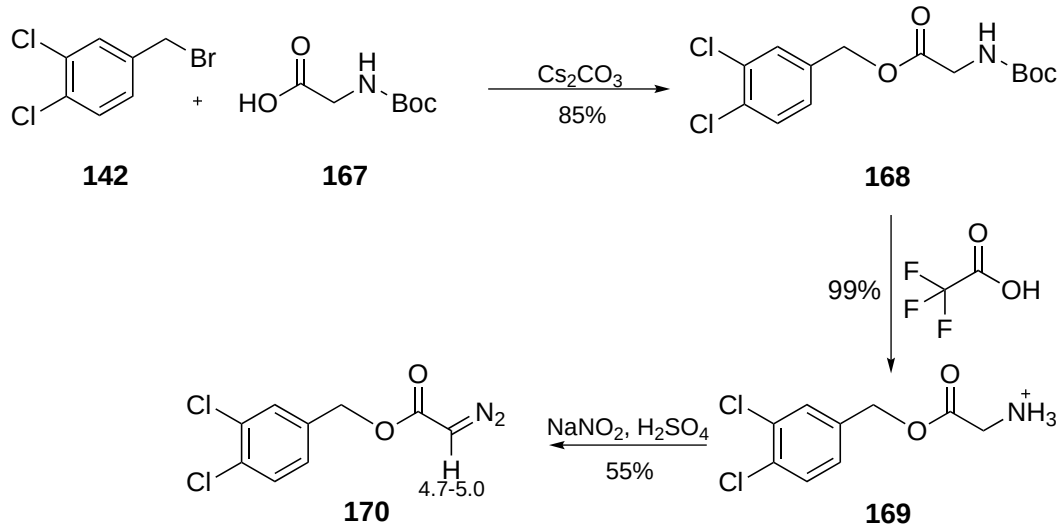
Scheme 3.1: Potential path for the synthesis of cordytropolone **37** using the Buchner ring expansion and nucleophilic aromatic subtitution



Scheme 3.2: Scott *et al.* Intramolecular Buchner ring expansion[124]

The synthesis of benzyl diazoacetate ester **170** was reasonably straight forward. BOC

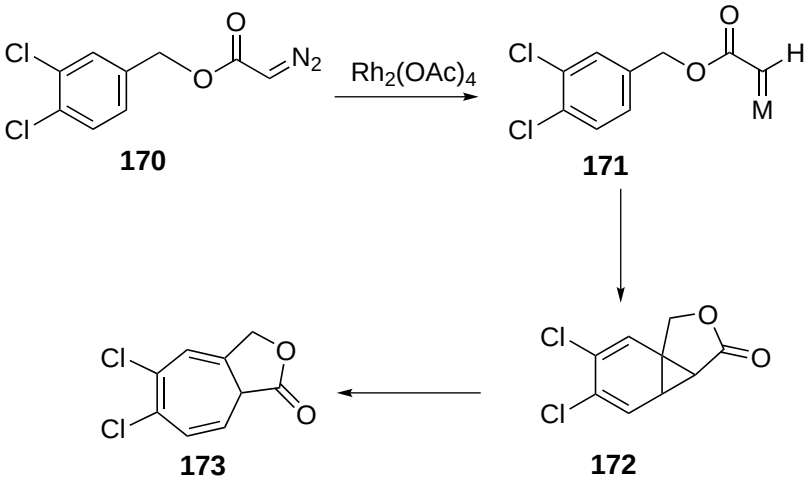
protected glycine **167** was deprotonated with caesium carbonate to afford the caesium salt, which then reacted with **142** to produce benzyl ester **168**. The removal of the BOC protecting group using trifluoroacetic acid gave the water soluble ammonium salt **169**. Finally, diazotisation was conducted using nitrous acid generated *in situ*. The product from this reaction was a straw yellow colour consistant with diazo compounds. The ^{1}H NMR spectrum showed a broad peak between 4.7-5.0 ppm indicative of the hydrogen attached to the carbon adjacent to the diazo group and, there was a signal present on the IR spectrum at 1691 cm^{-1}representative of the N=N bond.[149] From this evidence it was concluded that the synthesis of **170** was successful.



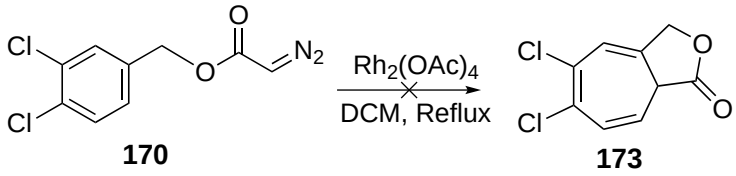
Scheme 3.3: Synthesis of diazoacetate **170**

The next step of the synthesis was to attempt the Buchner ring expansion (Scheme 3.4). This reaction involves using a catalytic amount of $Rh_2(OAc)_4$ to produce metal carbenoid **171** *in situ* which would then undergo a cyclopropanation with the benzene ring to produce **172**. The cyclopropane ring would then break apart due the ring strain into the desired bicyclic product **173**. A catalytic amount of $Rh_2(OAc)_4$ was dissolved into a solution of DCM which was heated under reflux (Scheme 3.5). The diazoacetate was then slowly introduced via a dropping funnel. This reaction produced a complex mixture of products over several attempts. The ^{1}H NMR spectrum of these attempts showed no signals in 5.50-7.00 ppm range which is where the vinyl signals for the cycloheptratriene ring were

expected to appear.



Scheme 3.4: Buchner ring expansion of **170**

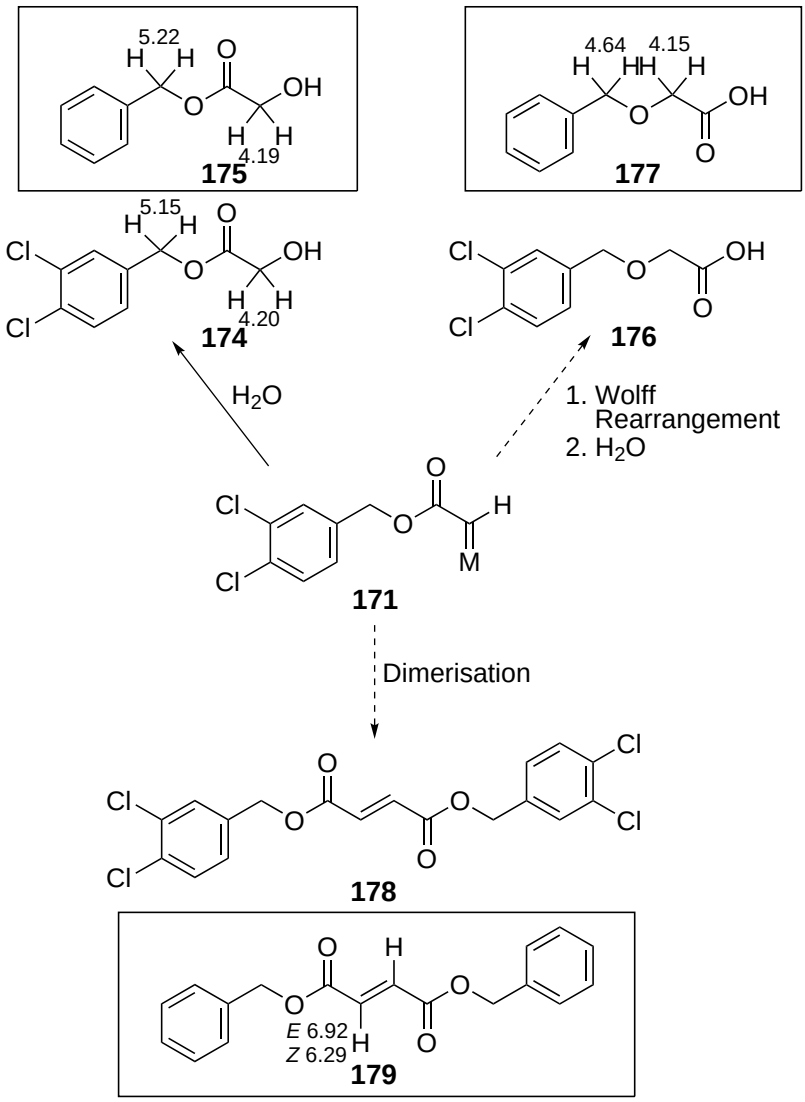


Scheme 3.5: Unsuccessful ring expansion of **170**

After exhaustive chromatography four products in trace amounts were isolated. One of these products had aromatic signals present on the ^{1}H NMR spectrum between 7.0-7.5ppm integrating for 3H, as well as a singlet integrating for 2H at 5.15 ppm indicating benzyl hydrogens. There was also another singlet at 4.20 ppm integrating for 2H representing the 2H alpha to the carbonyl. The ^{13}C NMR spectrum showed two signals between 60-70 ppm which is the appropriate chemical shift for carbons that are single bonded with oxygens. The ^{1}H NMR spectrum is also consistant with benzyl glycolate **175**.[150] Based on this evidence the isolated compound appeared to be the C-H insertion product with water **174** (Scheme 3.6). There was insufficient material to obtain an IR spectrum to confirm the presence of an OH group.

The three other products that were isolated were unable to be identified based on the gathered ^{1}H NMR and ^{13}C NMR spectra. However, the ^{1}H NMR spectrum of all of the

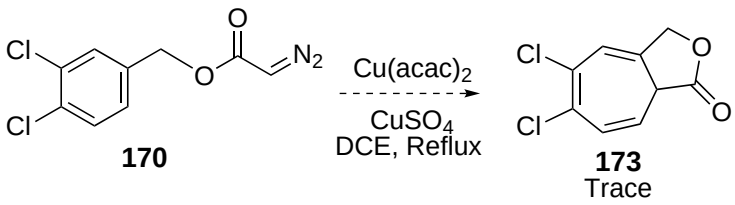
isolated products contained signals in the aromatic region (7-7.5 ppm) that were integrating for 3H. Based on this it is evident that the dichlorobenzene ring remains intact in each of these products. Metal carbenoids are highly reactive. This reactivity may lead to several side reactions occuring resulting in the observed complex mixture. A reaction that may be occuring is a Wolff rearrangement. In this reaction the diazocarbonyl is converted into a ketene. The ketene can then undergo a reaction with a nucleophile such as water to give carboxylic acid **176**. However, there was no signal around 4.15 ppm for the hydrogens adjacent to the carboxylic acid and no signal at 4.64 ppm representative of the benzyl hydrogens as would be expected when compared to the ^{1}H NMR spectrum of benzyloxy acetic acid.[151] The carbene may also react in an intermolecular fashion with itself, dimerising to form an alkene **178**, but there were no signals present in the vinyl region between 6-7 ppm that would be consistant with dibenzyl maleate or fumarate **179**.[152,153]



Scheme 3.6: Potential reactions that could be occuring in the mixture

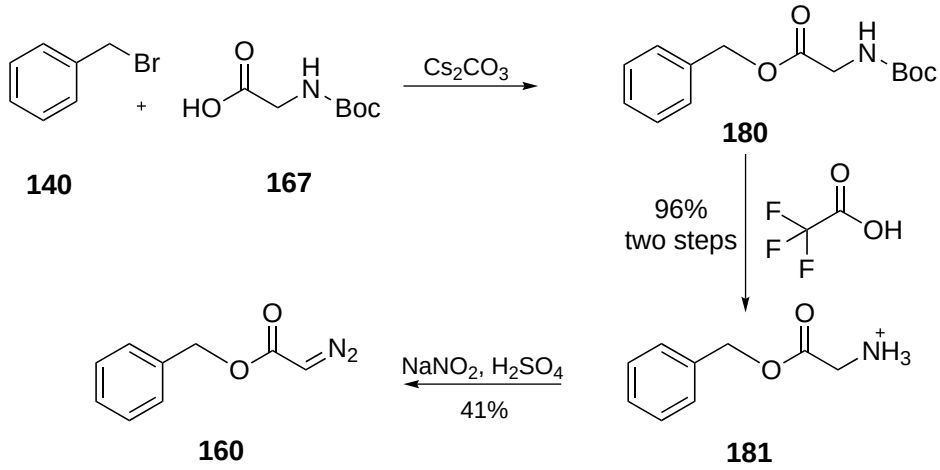
The cyclopropanation was also attempted on the dichlorobenzyl diazoacetate **170** using a Cu catalyst Scheme 3.7. Previous studies done by Mander *et al.* and backed up by Reisman *et al.* reported that Cu catalysts favoured the aryl cyclopropanation product, albeit at lower yields.[154,155] Based on a procedure from Langer,[156] $Cu(acac)_2$ and $CuSO_4$ was attempted as the catalytic system. DCE was used as the solvent in the hope that the higher reflux temperature would overcome the effect of the electron withdrawing chlorines and induce the desired reaction with the aromatic ring. The reaction once again produced a complex mixture, however after tedious chromatography a trace amount of an impure substance was

identified with potential vinyl signals in the 6.0-7.5 ppm range on the ^{1}H NMR spectrum. This substance was unable to be further purified or characterised but did indicate that the desired ring expansion product may have been forming in trace amounts.



Scheme 3.7: Attempt at ring expansion using an alternative catalyst

In order to determine whether or not the chlorines were having a detrimental effect on the Buchner ring expansion the synthesis of an alternative diazoacetate **160** without the electron withdrawing chlorines present was devised (Scheme 3.8). Benzyl bromide was reacted with BOC-glycine **167** and caesium carbonate to give the ester **180**. This crude ester was used without purification in the next step and the BOC group was removed using trifluoroacetic acid. As the amine salt **181** was water soluble and was isolated by extraction the salt was sufficiently pure for the subsequent diazotisation. Diazotisation of the salt with sodium nitrite and sulfuric acid gave diazoacetate **160**. The ^{1}H NMR spectrum of this compound matched those reported.[157]



Scheme 3.8: Synthetic pathway for synthesis of **160**

With the benzyl diazoacetate obtained, the ring expansion was once again attempted with

$Rh_2(OAc)_4$ in DCM. This reaction once again produced a complex mixture but minor signals were identified at 6.0-7.5 ppm in the ^1H NMR spectrum of the crude material. These signals could indicate that the ring expansion may be occuring, but in a low yield. Unfortunately, no compounds relating to these signals could be isolated by chromatography.

High dilution is a known method to improve the yields of these reactions.[158] Increasing the dilution would favour intramolecular reactions over intermolecular reactions. Previous reactions involved the slow dripping of the diazoacetate into a stirred solution of the catalyst however this procedure produced the results described in Scheme 3.6. To increase the dilution of the reaction a new reaction setup was devised. The diazoacetate was injected using a syringe pump into a solvent reservoir dilution the reactant prior to dripping into a main solution containing the catalyst. (Figure 3.0.2).

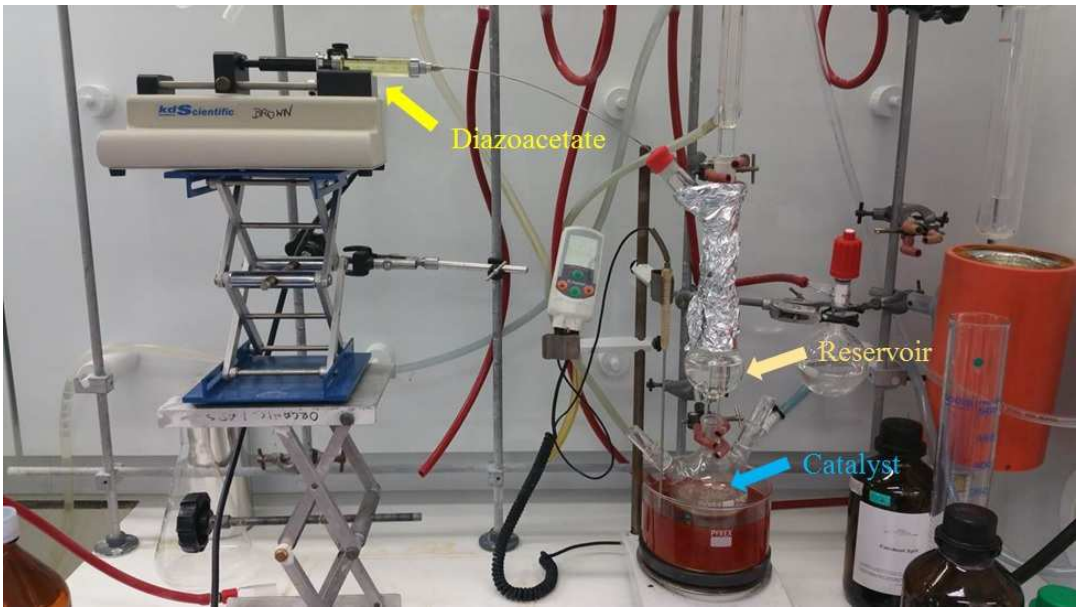


Figure 3.0.2: The sample is injected using the syringe pump into a reservoir which then slowly drips into the bottom flask containing the catalyst

This method was attempted with the $Rh_2(OAc)_4$ as the catalyst to no avail. However, when attempted with the $Cu(acac)_2$/ $CuSO_4$ catalyst[156,159] a product was identified in a trace amount as a potential ring expansion product. Based on the ^1H NMR spectrum of several fractions eluted from the purification column it was determined that product integrated for a total of 8H. This is consistent with the desired cycloheptatriene-lactone system. There was a singlet (H_e) at 4.77 ppm that integrated for 2H that likely belongs to the two former benzylic hydrogens. The benzylic hydrogens appear at around 5.2 ppm in the diazoacetate so a shift upfield would be consistent with the loss of aromaticity. There is one signal (H_f) integrating for 2H at 2.90 ppm, this signal could correlate to an aliphatic signal on the cycloheptatriene ring. The four remaining signals each integrate for 1H and appear at 6.73 (H_a), 6.59 (H_b), 6.17 (H_c) and, 5.4 (H_d) ppm. The position of these signals is consistent with what be expected for the vinyl signals on a cycloheptatriene ring. The *J*-coupling values as well the ^1H COSY spectrum indicate that these hydrogens are positioned around the ring and connected in the pattern a-b-c-d-f. There is long range coupling on the ^1H COSY between f-e indicating that these may be nearby each other. Based on this information it appears that the product is the ring expansion **162** (Figure 3.0.3). Despite extensive chromatography the pure product could not be isolated.

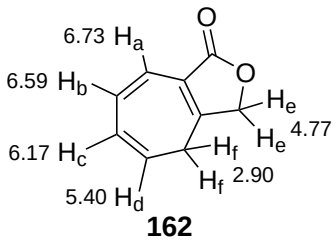
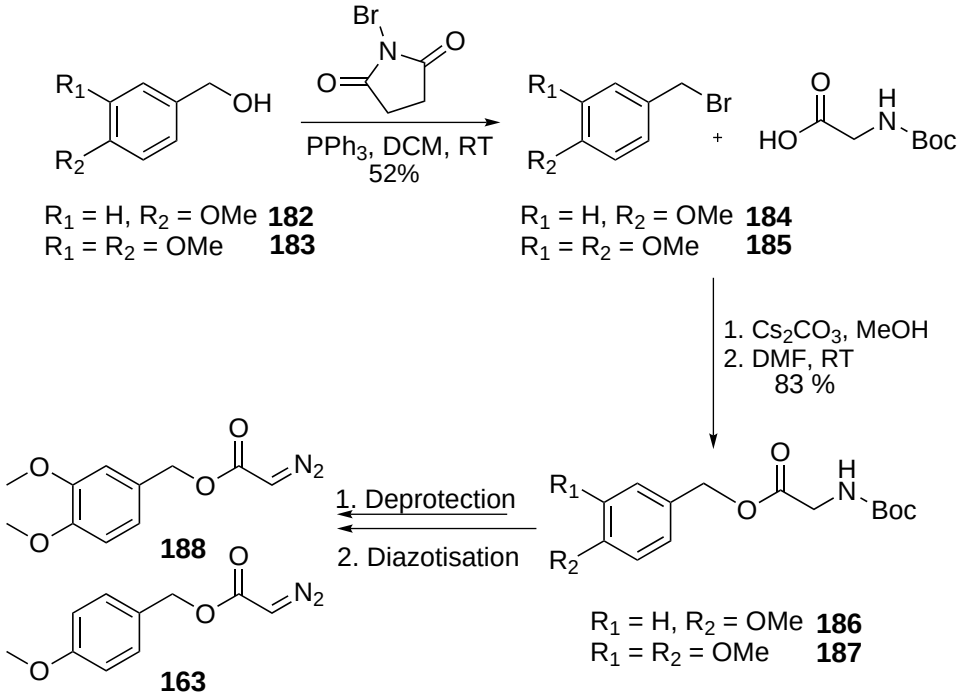


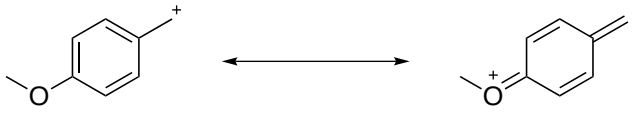
Figure 3.0.3: Proposed structure of identified benzyl ring expansion product

As a metal carbenoid is electron deficient, an electron rich aryl ring was used to promote the reaction. The addition of methoxy groups on the aromatic ring would improve the reactivity of the benzene ring towards the cyclopropanation product. Thus, the methoxy derivatives **163** and **188** were the next focus of study (Scheme 3.9). The two methoxy derivatives **163** and **188** were made by an approach similar to **170** (Scheme 3.3). The synthesis started with the readily available 4-methoxybenzyl alcohol **182** and 3,4-dimethoxybenzyl alcohol **183** (Scheme 3.9). An Appel reaction using triphenylphosphine and *N*-bromosuccinimide was performed to convert the alcohol to the benzyl bromides **184** and **185**. These benzyl bromides were then reacted with the BOC-Gly caesium salt to produce the two Boc-protected benzyl esters **186** and **187**.



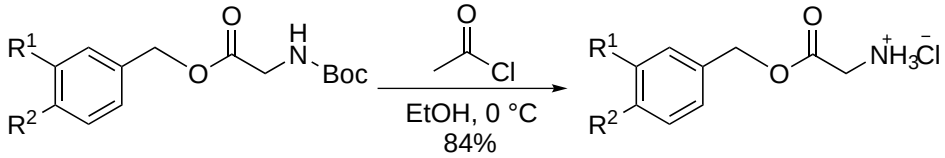
Scheme 3.9: Partial synthesis of methoxy benzyldiazoacetates **163** and **188**

When the deprotection of the Boc group was done using trifluoroacetic acid a complex mixture was obtained. It is likely that increased reactivity afforded by the methoxy groups coupled with the acidic nature of trifluoroacetic acid was causing side reactions to occur. With the methoxy group present, the carbonium ion that would be formed after hydrolysis of the ester is stabilised by resonance (Figure 3.0.4). The carbonium ion has also been shown to polymerise under acidic conditions.[160] An alternative method of deprotection could be performed using hydrochloric acid (Scheme 3.10). As reaction with aqueous HCl may have led to the hydrolysis of the ester, the deprotection was done using *in situ* generation of anhydrous HCl in anhydrous ethanol using acetyl chloride. This produced water soluble chloride salts **191** and **192** that were sufficiently pure for the diazotisation. The clean products obtained by these reaction conditions could be attributed to the rapid deprotection of the BOC group, avoiding side reactions caused by the formation of the benzyl cation **189**.



189 **190**

Figure 3.0.4: Formation of the carbonium ion can lead to polymerisation or other undesired side reactions



R^1 = H, R^2 = OMe **186**
R^1 = R^2 = OMe **187**

R^1 = H, R^2 = OMe **191**
R^1 = R^2 = OMe **192**

Scheme 3.10: Deprotection of the BOC group to afford choride salts **191** and **192**

When diazotisation of **192** was attempted using the previous conditions of sulfuric acid and sodium nitrite, only a minimal amount of the desired product was isolated. The additional acid added to the reaction mixture may cause the formation of the carbonium ion as previously described. The reaction was then attempted without the addition of any of the sulfuric acid (Scheme 3.11). This reaction was successful and produced the diazoacetates **163** and **188** which were purified with minimal chromatography. Traditionally, diazotization reactions including sulfuric acid complete quite quickly,[161,162] however the reaction instead took several hours to complete. In aqueous media the nitrite ion naturally forms nitrous acid which would allow the reaction proceed at a slower rate (Figure 3.0.5). The addition of ammonium ions has also shown to increase the rate of reaction.[163]

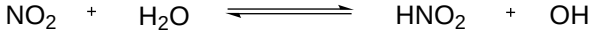
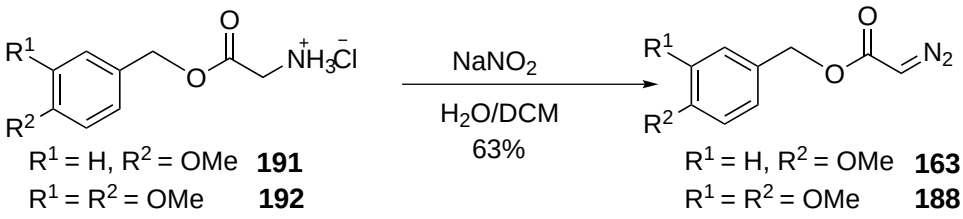
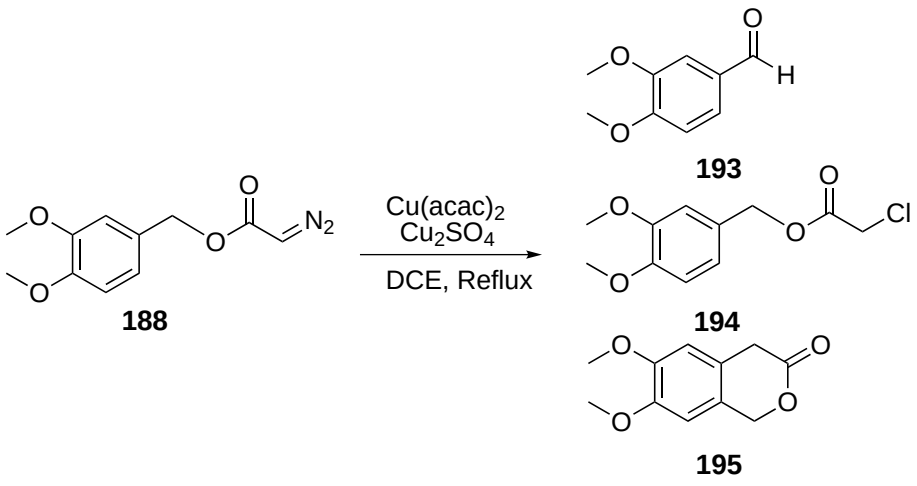


Figure 3.0.5: The nitrite ion naturally dissociates water in aqueous media to form nitrous acid



Scheme 3.11: Formation of diazoacetates **163** and **188**

The Buchner ring expansion was attempted on the dimethoxybenzyl diazoacetate **188**. Using the $Cu(acac)_2/CuSO_4$ catalyst system which favours the intramolecular reaction. A complex mixture was obtained but several major compounds, including starting material were isolated (Scheme 3.12). The isolated compounds include the benzaldehyde **193**, evident by the aldehyde signal on the ^1H NMR spectrum at 9.84 ppm and, 190.88 ppm on the ^{13}C NMR spectrum. The C-H insertion product with chlorine **194** was also identified. The signal relating to the hydrogens alpha to the carbonyl now integrate for as a singlet for 2H and the signal has moved from 4.75 ppm on the ^1H NMR spectrum of the starting material to 4.08 ppm. This signal and the signal relating to benzylic hydrogens are consistent with the chemical shift of the similar compound **196**. There is also a signal at 40.97 ppm on the ^{13}C NMR spectrum relating to the carbon alpha to the carbonyl which is at a chemical shift consistent with that of a carbon bonded to a chlorine and confirmed by the ^{13}C NMR spectrum of **196** which has a similar signal at 40.10 ppm (Figure 3.0.6).



Scheme 3.12: Isolated products from attempted ring expansion reaction

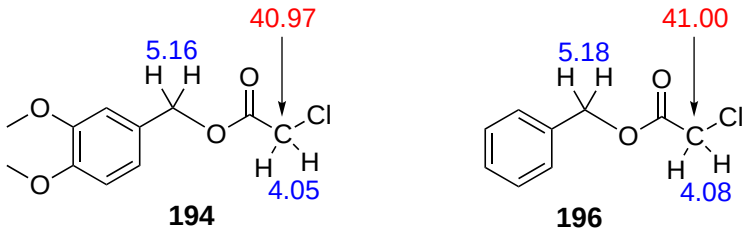


Figure 3.0.6: Isolated products from attempted ring expansion reaction

To confirm the structure of **194**, synthesis of the compound was undertaken. 3,4-dimethoxybenzyl alcohol **183** was reacted with chloroacetyl chloride **197** in the presence of triethylamine (Figure 3.0.7). After purification, **194** was isolated with characterisation data matching the compound previously isolated (Figure 3.0.6). This confirms that a C-H insertion reaction was occuring.

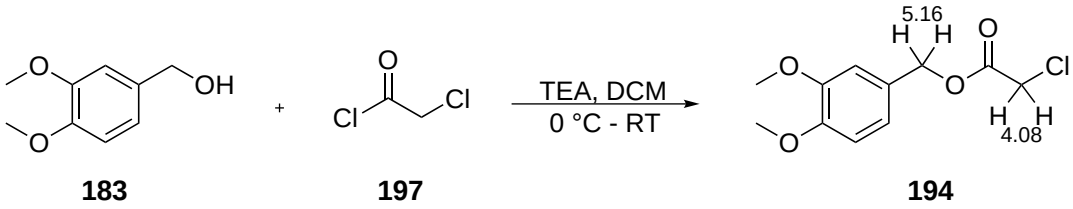
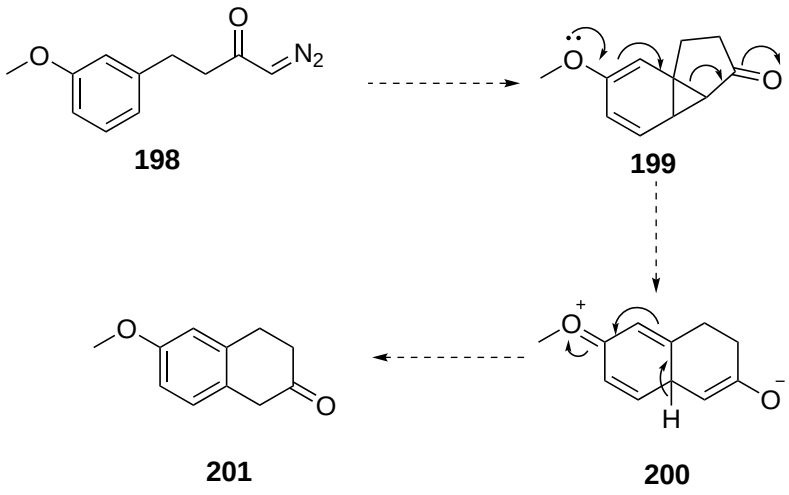


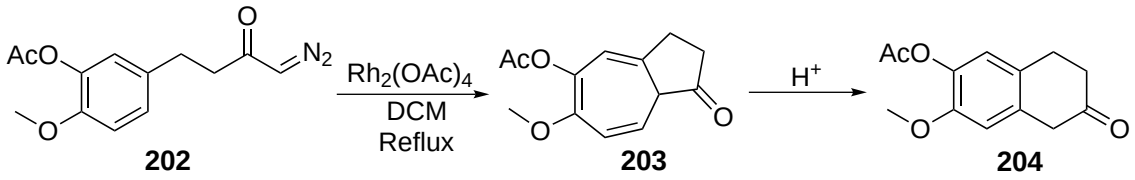
Figure 3.0.7: Synthesis of **194** confirmed the characterisation data

The last and major product could not be isolated as a pure compound as it co-eluted with another, unidentifiable dimethoxybenzyl compound. However, the ^{1}H NMR spectrum shows two singlets in the aromatic region at 6.71 and 6.68 ppm which integrate for 1H. There is also a singlet at 5.22 ppm integrating for 2H which would correlate with the hydrogens usually at the benzylic position. The signal for the hydrogens that appear alpha to the carbonyl usually appear around 4.20 ppm, but on this spectrum the signal had shifted to 3.60 ppm. It was concluded that the compound was likely the lactone **195**. The number and form of the signals on the ^{1}H NMR spectrum matched those given in literature but the chemical shifts of each of the signals was slightly different. However, when comparing the ^{13}C NMR spectra, all of the signals matched up with those that appear on the impure spectrum almost exactly. Based on this it was concluded that the compound was lactone **195**.

There is some precedence for the formation of the 6-membered lactone **195** in this Buchner ring expansion. In 2001, Maguire *et al*. investigated products of intramolecular additions of diazoketones to aryl rings with methoxy substituents.[164] Maguire *et al*. discovered that when a methoxy is present in the 3-position of the benzene ring the tetralone is produced as a single product (Scheme 3.13). Maguire proposed that the cyclopropane intermediate **199** was forming but due to the resonance provided by the methoxy at the 3-position the compound always reconfigured into the tetralone **201**. This backed up a similar report by Kennedy *et al.* who observed a similar outcome in their reactions of similar compounds.[126] Kennedy found that while exchanging a methoxy group for an acetoxy group at the three position on the diazoketone **202** did produce the cycloheptatriene **203** as the ring expansion product, it still converted to the tetralone **204** in the presence of acid (Scheme 3.14).

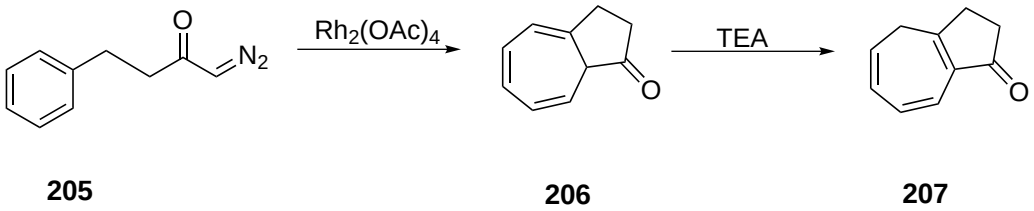


Scheme 3.13: Proposed mechanism by Maguire *et al.*[164]



Scheme 3.14: By replacing the methoxy at the 3-position with an acetyoxy Kennedy formed the cycloheptatriene **203**[126]

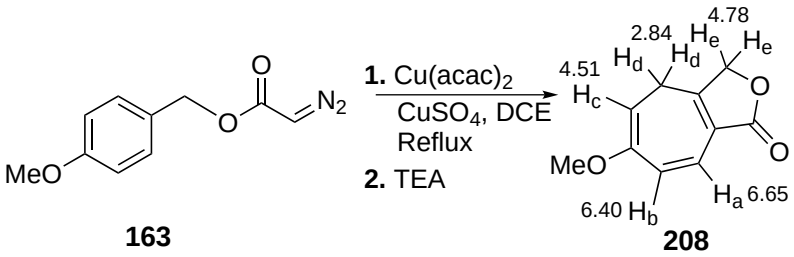
It is also possible that multiple isomers were forming in the reaction mixture and this was reducing yield and making purification difficult. In a reaction by Kennedy *et al.*[126] (Scheme 3.15) diazoketone **205** was reacted with $Rh_2(OAc)_4$ to produce enone **206**, TEA was then added to the reaction mixture to force the enone to isomerise to **207**. TEA was added to subsequent reactions to facilitate the formation of a single product.



205 **206** **207**

Scheme 3.15: Isomerisation of **206** to **207** using TEA

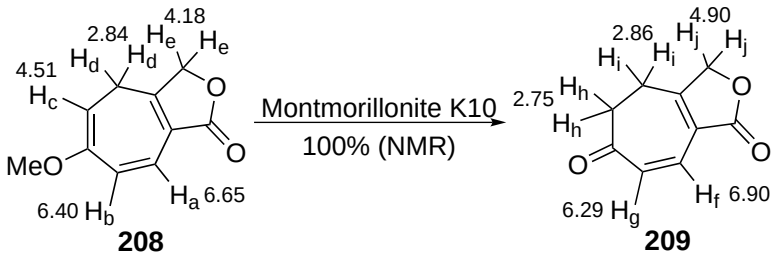
The reaction was attempted with 4-methoxybenzyl diazoacetate **163** using the dilution system as described in Figure 3.0.2 (Scheme 3.16). The ^{1}H NMR spectrum of the reaction mixture had some minor signals in the 6.0-7.0 ppm region, the region that vinyl signals from a cycloheptatriene ring would be expected. Chromatography yielded a trace amount of the compound relating to some of these signals. Analysis of the ^{1}H NMR spectrum led to the conclusion that the compound was ring expansion product **208**. There were two doublets at 6.65 and 6.40 ppm integrating for 1H each which likely correlate to the vinyl signals H_a and H_b. A singlet at 4.78 ppm for 2H is likely to be the hydrogens present on the lactone (H_e), the signal has shifted slightly upfield from the starting material due to the loss of aromaticity. A triplet at 4.51 ppm integrating for 1H is likely H_c. A singlet at 3.52 ppm integrating for 3H is consistent with the methoxy signals. A doublet (H_d) at 2.84 ppm integrating for 2H indicates that this signal is not part of a vinyl environment and is not part of the lactone ring. H_d also has long range coupling on the ^{1}H COSY with H_e indicating that these two environments are near each other and thus, the carbonyl in the lactone is as described in Scheme 3.16.



163 **208**

Scheme 3.16: Successful Buchner ring expansion of **163**

When a sample of **208** was left in the NMR tube overnight a new compound was observed in the ^{1}H NMR spectrum. This indicated that the enol ether of compound **208** is likely hydrolysing to give the ketone **209** (Scheme 3.17). There were still two signals present in the vinyl region relating to H_f and H_g but these had shifted slightly and were now at 6.89 and 6.29 ppm. The signals for the hydrogens on the lactone were still present but had shifted down-field slightly to 4.90 ppm. Two new multiplets that integrate for 2H each were present at 2.86 and 2.75 ppm. The multiplet at 2.86 is likely the signal relating to H_i as the chemical shift has not changed from the previous isomer. As this has turned into a multiplet is likely that the adjacent hydrogens have changed. The new signal at 2.75 ppm is likely to be that of H_h which has shifted due to gaining a hydrogen and no longer being vinylic. There is also no methoxy signal that could be attributed to this compound. This was confirmed by hydrolysing freshly isolated **208** with Montmorillonite K 10 clay in DCM at RT to give the ketone **209** in 100% yield by NMR. (Subsequent ^{1}H NMR analysis of this product confirmed they were the same.)

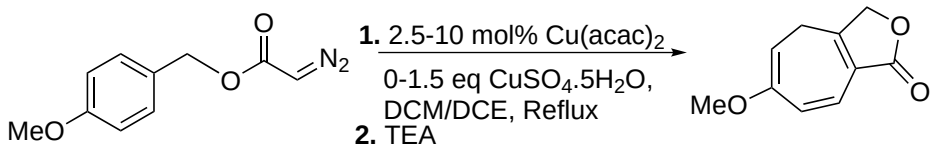


208 **209**

Scheme 3.17: Acid catalysed hydrolysis of **208**

Having identified the Buchner ring expansion product **208** in the reaction mixture, a brief optimisation study was undertaken. The reaction was repeated several times with differ-

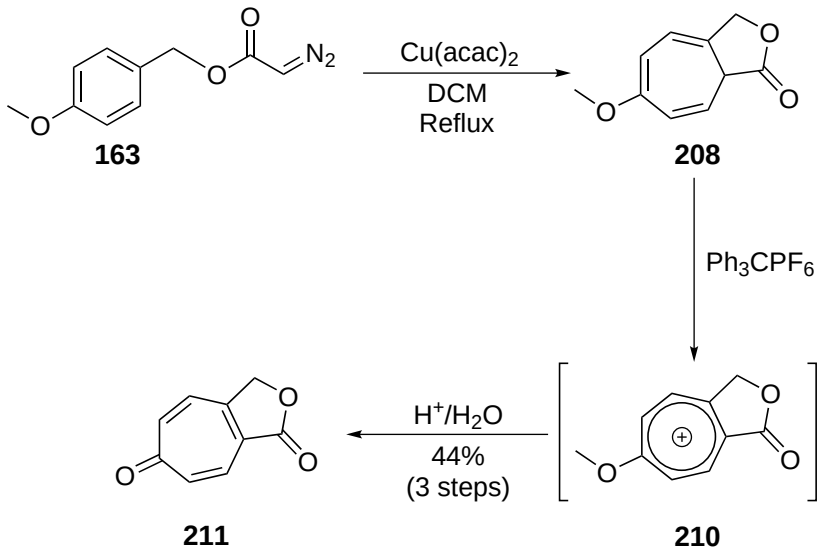
ning amounts of reagents in the process of generating more material. Eventually it was found that omitting $CuSO_4.5H_2O$ and using 5 mol% of $Cu(acac)_2$ produced the best results. The higher temperatures afforded by using DCE were also determined to not be required. The solvent was changed to DCM for subsequent reactions. The likely conclusion is that the yield of the ring expansion product improved as more potential water sources were eliminated from the reaction.



163 **208**

Scheme 3.18: The reaction conditions were briefly investigated in order to determine the optimum conditions

To avoid the issues with hydrolysis/isomerisation of the enol ether, **208** could be converted to the tropone **211**. One of the ways to do is through hydride abstraction using a triphenylmethyl cation. The reaction was attempted using triphenylmethyl hexafluorophosphate on ring expansion product **208** reaction in order to see if the tropylium cation **210** could be formed (Scheme 3.19). When the crude reaction mixture was subjected to chromatography the entire column turned the same dark green colour. This reaction did not occur in the flask. The increased surface area provided by the silica appeared to catalyse a reaction occuring on exposure to light. Chromatography was performed in a darkened environment and the compound was isolated and identified. This compound had three signals in the aromatic region on the ^1H NMR spectrum at 7.58, 7.32 and 7.21 ppm integrating for a total of 4H. These signals would likely relate to the four vinyl hydrogens present around the aromatic tropone ring. There is also a signal at 5.27 ppm integrating for 2H which is consistent with the two hydrogens present on the lactone. Based on this it can be concluded the reaction was successful in producing tropone **211**.



Scheme 3.19: Buchner ring expansion followed by oxidation by hydrogen traction to produce tropone **211**

The similarities between the target cordytropolone **37** and tropone **211** are obvious. Cordytropolone **37** contains two hydroxyl groups on the seven-membered ring and lacks the carbonyl present on the five membered ring. Moving towards the final goal, attempts were made to substitute substituent groups on the seven-membered ring of tropone **211**.

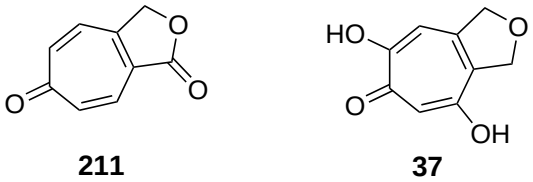
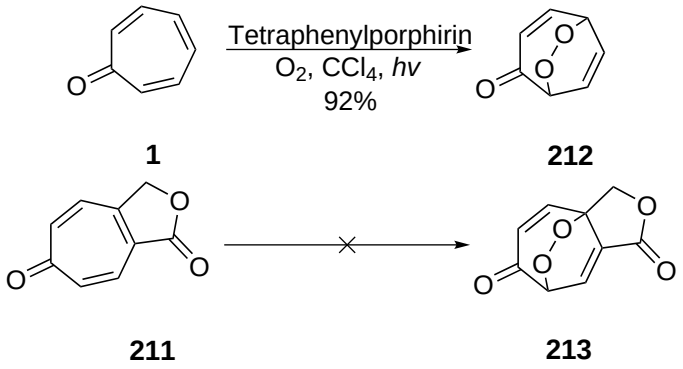


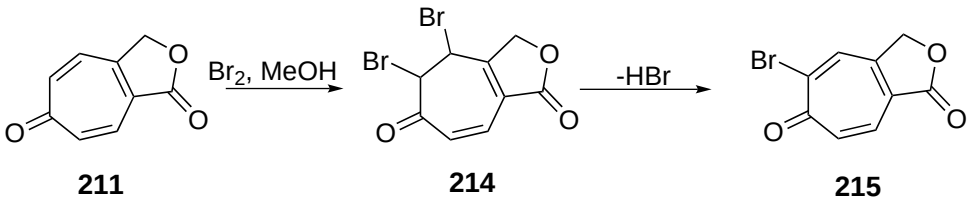
Figure 3.0.8: Comparison of tropone **211** and the target cordytropolone **37**

There are very few methods for oxgenating tropone in the literature. One report by Secen *et al.* (Scheme 3.20),[165] reacted tropone **1** with oxygen in the presence triphenylporphyrin under a 150 W projection lamp to produce the endoperoxide **212**. Unfortunately, the same reaction attempted on tropone **211** using triphenylporphyrin, LED lights and air bubbling through the reaction mixture only returned starting material and did not produce the expected endoperoxide **213**.



Scheme 3.20: Conversion of tropone **1** to tropone endoperoxide **212** as described by Secen *et al.*[165] This reaction attempted on **211** did not produce expected **213**

An attempt was also made to introduce a halogen onto the tropone ring, the halogen could then be substituted later for another functional group. The reaction was attempted using bromine in methanol stirred at room temperature. TLC of the reaction indicated a new product forming that was less polar than the starting material and also reacted with light on the TLC to produce a coloured compound. The crude ^{1}H NMR spectrum contained signals indicating that a new compound had been formed. There were two signals at 6.44 and 6.22 ppm integrating for 1H each, this is consistent with the vinyl signals in a cycloheptatriene ring. There was a singlet at 4.98 ppm integrating for 2H consistent with the hydrogens on the 5-membered lactone ring. The final two signals were at 4.72 and 4.51 ppm for 1H each and would indicate two non-vinyl signals on the cycloheptatriene ring. Based on this it is likely that the product is **214** (Scheme 3.21).

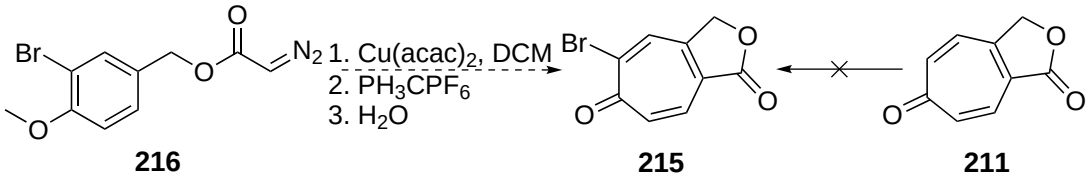


Scheme 3.21: Product formed as a result of attempted substitution of **211**

To form the tropone **215** from **214** an elimination reaction was attempted (Scheme 3.21). It was expected that by eliminating HBr from the molecule the double bond would be regained and the tropone reformed. The elimination was first attempted using triethylamine,

which was ineffective. The ^{1}H NMR spectrum showed no change in the two vinyl signals at 6.44 and 6.22 ppm and there were no signals that would indicate the desired product. The elimination was also unsuccessfully attempted by adding $CaCO_3$ and washing the reaction mixture with K_2CO_3.

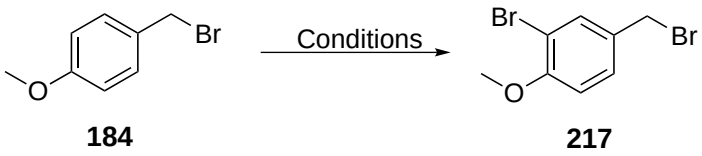
Although the bicyclic framework of cordytropolone had been obtained, functionalistion of it was not possible. Another method of obtaining the brominated tropone **215** was devised. Instead of attempting substitution on the tropone a bromine could be added at an earlier step in the synthesis (Scheme 3.22). The best way to produce diazoacetate **216** was to substitute the additional bromine earlier in the reaction sequence due to the ease of acquiring the starting material. Using the same starting material as used in Scheme 3.9, 4-methoxybenzyl alcohol **182** once again underwent an Appel reaction with NBS to produce **184**. Bromination of the 3-position was then attempted on **184** (Scheme 3.23). Several brominating reagents and conditions were tested (Table 3.0.1). Potassium bromide with tetrabutylammonium bromide and, potassium bromide with sodium perborate returned mostly starting material. The best result came from using a combination of NBS and triflic acid, producing crude 3-bromo-4-methoxybenzyl bromide **217**. The product was confirmed by matching signals from the literature with those on the crude ^{1}H NMR spectrum. Due to the unstable nature of the benzyl bromides during column chromatography **217** was immediately reacted with Boc-glycine **167** and caesium carbonate. This produced benzyl ester **218**. The signals from the ^{1}H NMR spectrum of **218** matched those with similar, previously synthesised compounds, but only containing three aromatic signals integrating for 1H each. This is consistant with the disubstituted benzene ring.



216 **215** **211**

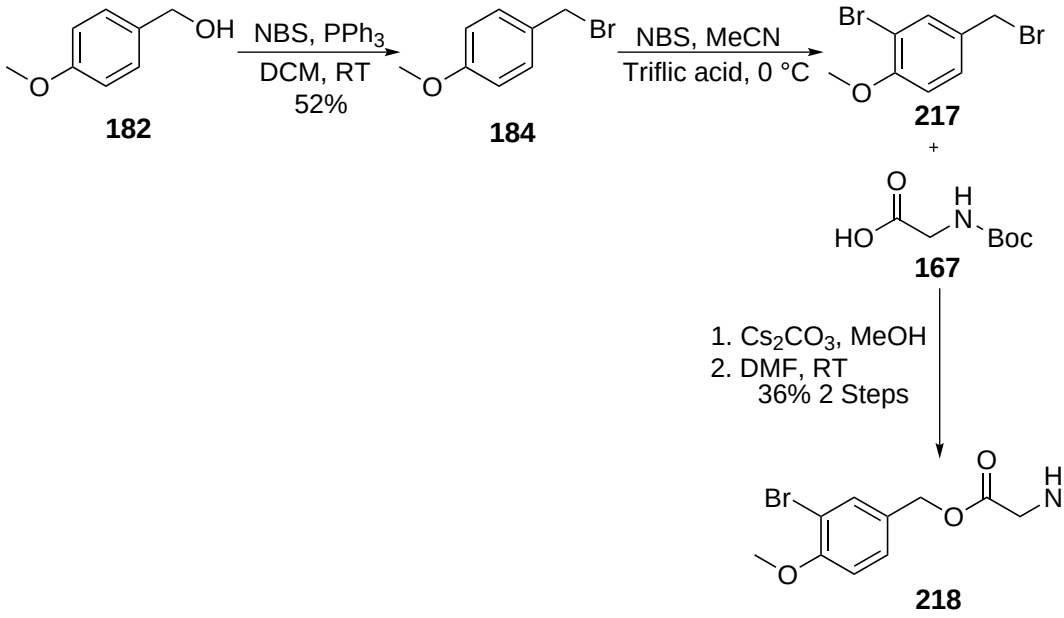
Scheme 3.22: Bromotropone **215** could not be formed directly from **211** so synthesis of diazoacetate **216** was devised

Table 3.0.1: Attempts to brominate 3-position of 3,4-dimethoxybenzyl bromide



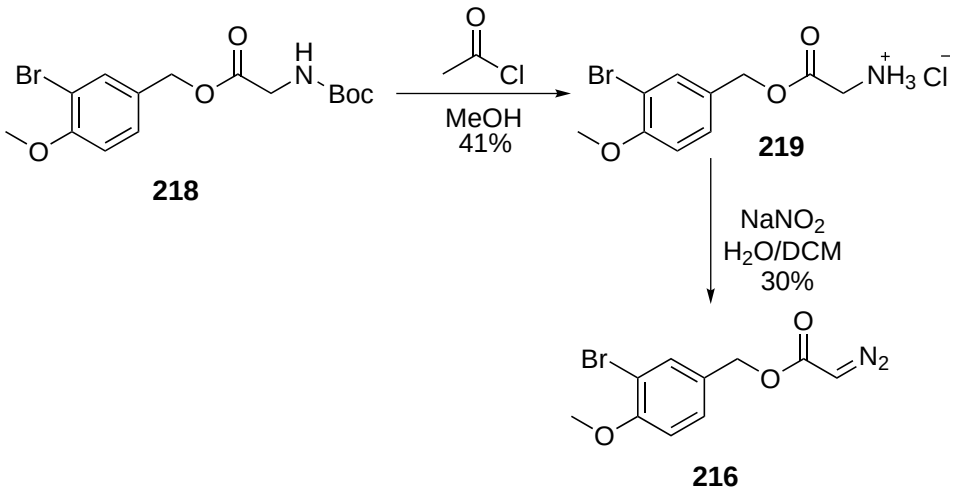
184 **217**

Entry	Conditions	Solvent	Result
1	KBr, Bu_4NBr, HNO_3 21%	DCE	Mostly Starting Material, No **217** present
2	KBr, $NaBO_3.4H_2O$	AcOH	Recovered Starting Material
3	NBS, Triflic acid	MeCN	**217**



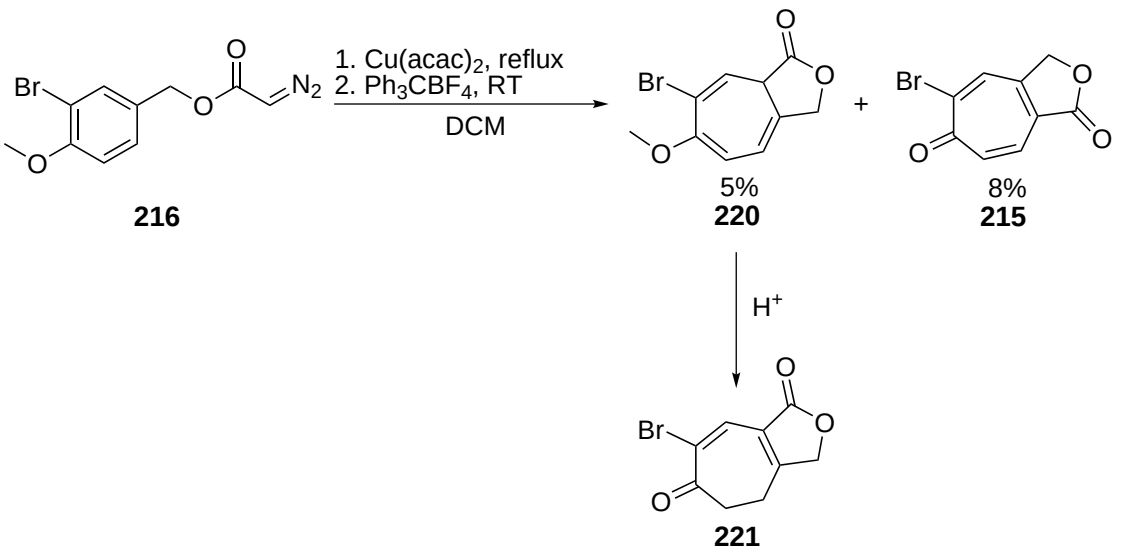
Scheme 3.23: Bromination of the 3-position to eventually produce **218**

The BOC-protected compound **218** was then deprotected using acetyl chloride to afford the HCl salt **219** (Scheme 3.24) which then underwent diazotisation using sodium nitrite to produce the diazoacetate **216**. Again, the ^{1}H NMR spectrum showed signals that were consistent with the benzyl hydrogens and the hydrogens alpha to the carbonyl in similar compounds. Three aromatic signals integrating for 1H each indicate that the bromine is still present on the benzene ring.



Scheme 3.24: Synthesis of 3-bromo-4-methoxybenzyl diazoacetate **216**

The ring expansion was then attempted ensuring that concentration of reagents was kept similar to the conditions that were successful previously. 5 mol% $Cu(acac)_2$ was used with diazoacetate **216** injected at 0.07 ml/min. Once the dilution reservior had become colourless the reaction was let cool to room temperature and triphenylmethyl tetrafluoroborate was added. During purification of the product, the chromatography column became coloured despite being performed in a darkened environment but a small amount of the compound was isolated. The compound was not pure but key signals on the ^{1}H NMR spectrum were identified. There were no signals in the vinyl region that would indicate that it was any of the cycloheptatriene compounds. There was the usual signal at 5.17 ppm representing the two hydrogens on the five-membered lactone ring and there was no signal for any methoxy groups. There was a singlet at 8.09 ppm integrating for 1H that was shifted downfield compared to the other aromatic signals. Literature research on similar compounds indicated that it was likely representative of the hydrogen adjacent to the bromine on the tropone ring. Sims and Wege made the tropone **222** (Figure 3.0.9)[166] and the signal for hydrogen adjacent to the bromine appears at 8.18 ppm on the ^{1}H NMR spectrum. It is likely the electron withdrawing nature of the bromine deshields these signals, shifting them downfield when compared to tropone signals without the bromine present. Based on this evidence it was concluded that the synthesis of **215** was successful.



Scheme 3.25: The ring expansion of diazoacetate **216** produced two isolateable compounds, **220** and **215**

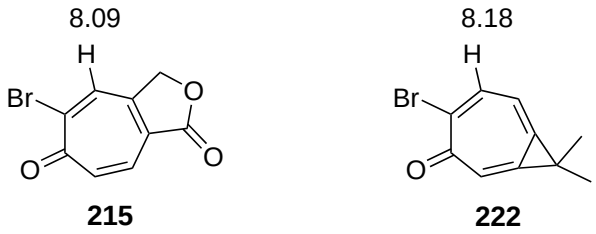
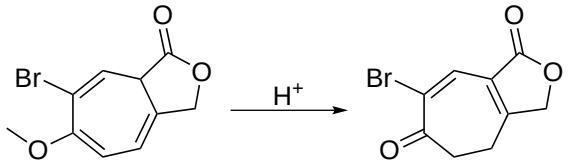


Figure 3.0.9: The two compounds show similar chemical shifts for the hydrogen adjacent to the bromine on the tropone ring

In addition to tropone **215** another compound was isolated. This compound did not produce a coloured spot on the TLC and the ^{1}H NMR spectrum resembled that of **208**. There was a signal at 3.72 ppm integrating for 3H indicating that the methoxy group is present. There were three signals in the vinyl region from 5.8-6.1 ppm, each integrating for 1H. These would be from the vinylic hydrogens on a cycloheptatriene ring. There was a multiplet at 3.26 ppm integrating for 1H, based on the experience with the similar compound **208** it is likely that this is a non-vinylic hydrogen present on the cycloheptatriene ring. This most obvious change on the ^{1}H NMR spectrum is the signal relating to the hydrogens on the five-membered lactone ring. The signal is present at 5.01 ppm and instead of being a singlet, as is the case on nearly all other spectra, the signal has split into a multiplet.

This indicates that the lactone environment is dissimilar from the previous synthesised compounds. Based on this it was concluded that this compound was cycloheptatriene **220** (Scheme 3.25) where the carbonyl is on the opposite side of the lactone compared to compounds like cycloheptatriene **208** and tropone **215**.

A ^{1}H NMR spectrum of cycloheptatriene **220** taken after the initial analysis showed that new signals had formed. It was suspected that **220** underwent hydrolysis in the same way that cycloheptatriene **208** does (Scheme 3.17). Scrutiny of the ^{1}H NMR spectrum confirmed this. A singlet at 7.62 ppm integrating for 1H likely relates to the hydrogen adjacent to the bromine similar to the signals on ^{1}H NMR spectrum of **215** and **222** (Figure 3.0.9). However, this signal is shifted slightly upfield which may indicate the absence of aromaticity. The multiplet relating to the hydrogens on the five-membered furan ring have shifted upfield to 4.87 ppm and returned to a singlet. There are no signals in the vinyl region but two new multiplets have occurred at 3.04 and 2.77 ppm integrating for 2H each. The form and location of these multiplets is very similar to the non vinyl cycloheptatriene signals that appear on the ^{1}H NMR spectrum of **209** (Scheme 3.17). Based on this information, and the comparison with the ^{1}H NMR spectrum of compound **209**, cycloheptatriene **220** is being hydrolysed into compound **221** (Scheme 3.26). This has the added bonus of confirming the structure of **220**.

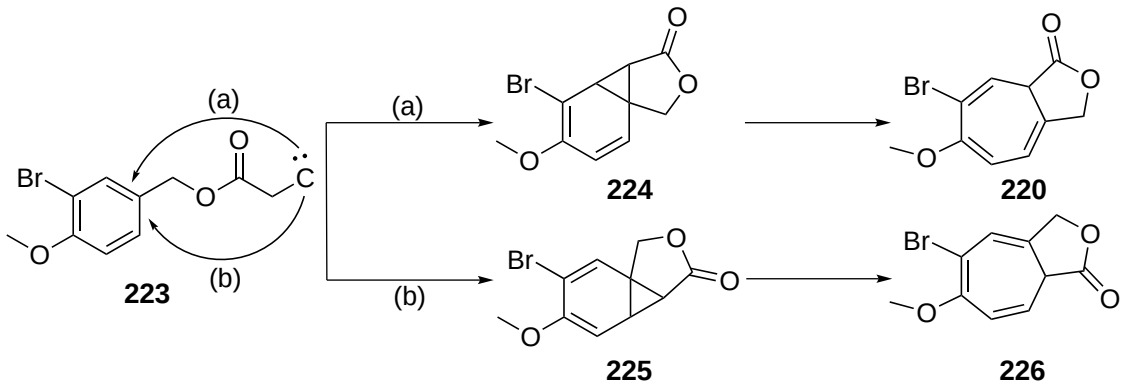


220 **221**

Scheme 3.26: Acid catalysed hydrolysis of **220**

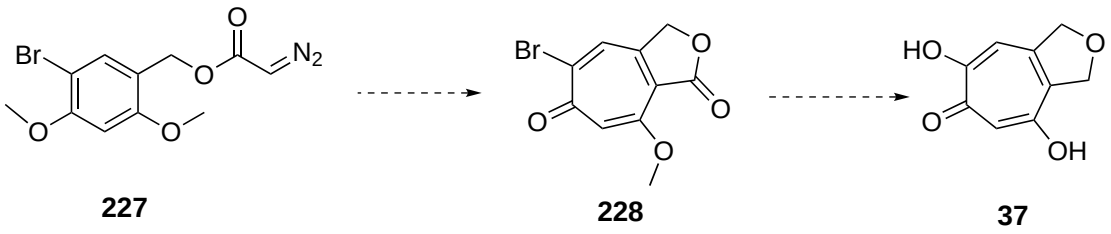
The carbene **223** formed as part of the ring expansion can react at one of two positions on the benzene ring to form the two intermediates **224** and **225**. These intermediates then expand to form the products **220** and **226** (Scheme 3.27). As **220** had not been previously isolated, it is possible the bromine may have some affect on which direction the carbene reacts. It is important to note that **220** was isolated as the cycloheptatriene

and not the tropolone, despite the addition of oxidant (Scheme 3.25). The addition of functional groups has been known to change the conformation of cycloheptatriene.[167,168] These confirmational changes have also been shown to affect the reactivity and position of the H atoms present on the ring.[169] It is possible the position on the carbonyl and bromine on **220** is causing a conformational change in the cycloheptatriene ring that makes it less reactive towards oxidation into the corresponding tropolone.



Scheme 3.27: The carbene **223** formed as part of the ring expansion can react at two positions on the benzene ring to form cyclopropanes **224** and **225**. These intermediates then expand to form the products **220** and **226**

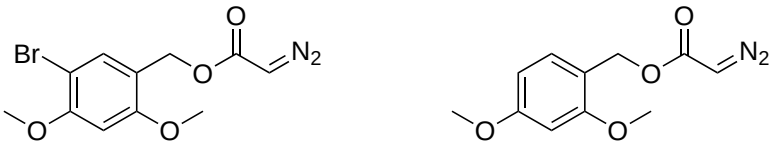
With the substitution of the bromine at the 3-position of the benzene and the subsequent ring expansion successfully undertaken, the synthesis moved to produce a compound that was also substituted at the 2-position of the benzene ring such as diazoester **227** (Scheme 3.28). If the ring expansion was successful on this product, producing tropone **228**, the synthesis would only be a few steps away from the target cordytropolone **37**.



Scheme 3.28: Proposed synthesis of cordytropolone **37** from diazoacetate **227**

Due to the issues in the ring expansion in regards to having a methoxy at the 3-position

Scheme 3.13, it was decided to attempt the synthesis of 2,4-dimethoxybenzyl diazoacetate **229** before committing time and expensive starting material to the synthesis of the tri-substituted **227** (Figure 3.0.10).



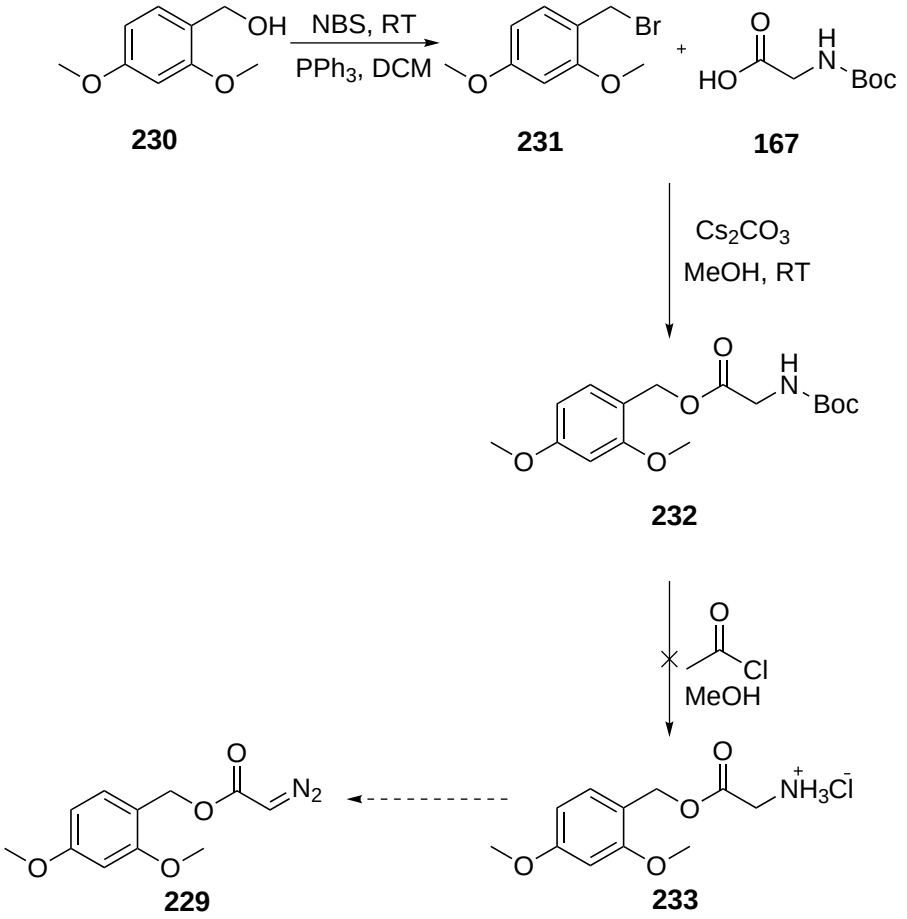
227 **229**

Figure 3.0.10: Synthesis of diazoacetate **229** was attempted before the synthesis of the more complicated **227**

The synthesis of **229** was undertaken in the same sequence as previous described in Scheme 3.3 and Scheme 3.11. Starting with 2,4-dimethoxybenzyl alcohol **230** an Appel reaction was performed to produce the benzyl bromide **231** (Scheme 3.29). This was then reacted with the BOC-glycine carboxylate salt formed from reaction with caesium carbonate, producing the benzyl ester **232**. Initial attempts at the Appel reaction to produce benzyl bromide **231** showed the compound decomposing quite quickly. It is likely that the addition of the methoxy at the 2-position increases the reactivity of the adjacent benzyl position by donation of electrons into the benzene ring. To combat this, the crude reaction mixture was immediately reacted with the BOC-glycine carboxylate salt to form the more stable ester **232**.

With the benzyl ester **232** in hand the next steps in the synthesis involved the deprotection of the BOC group to produce the HCl salt **233**, followed by the diazotisation to form desired diazoacetate **229**. This was done using *in situ* generation of HCl using acetyl chloride in methanol at 0 °C (Scheme 3.29). The reaction was monitored by TLC, and while it appeared to produce the salt the TLC contained several products, many more than is the usual for this deprotection. The salts produced as a result of this reaction are usually water soluble and purified by extraction. Workup of the reaction by extraction with water and DCM, produced an immiscible white solid that present in both aqueous and organic phases. A ^{1}H NMR spectrum of the aqueous phase showed no products present and ^{1}H NMR spectrum of the DCM phase showed a complex mixture of multiple products with

no signals indicating that the desired product had formed. Based on this it was concluded that the additional methoxy group at the 2-position, and its ability to donate electrons into the benzene ring next to the benzyl carbon, rendered the molecule too reactive to be successfully used. The synthesis of diazoacetates **227** and **229** was abandoned for this reason.



Scheme 3.29: Reaction pathway to produce desired diazoacetate **229**.

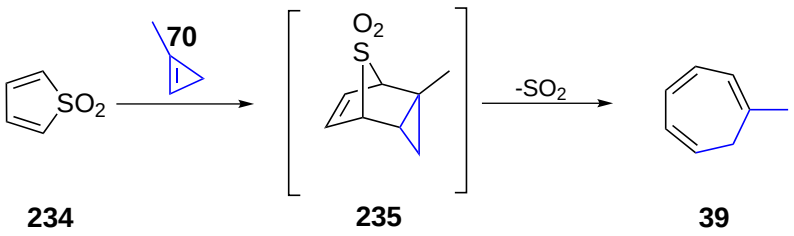
While this pathway to cordytropolone **37** did show some promise with the successful synthesis of **211** and **215**, it was determined to be too limited. The need for the large dilution conditions limited the scale of the key step, the Buchner ring expansion. This in turn made purification and attempts at subsequent reactions on the ring expansion products difficult. The Buchner ring expansion itself was inconsistant, the reaction was sensitive to the presence of water in the reaction mixture and success was highly dependant on the substituents on the benzene ring. For these reasons, research into the Buchner ring

expansion was halted, and focus turned towards more versatile methods of synthesising seven-membered rings.

Chapter 4

Diels-Alder Reaction of 3,4-Dichlorothiophene-1,1-dioxide and Substituted Cyclopropenes

The key challenge in the synthesis of cordytropolone **37** is formation of the seven membered ring. An overlooked method for preparing cycloheptatrienes is a Diels-Alder reaction between a thiophene-1,1-dioxide and a cyclopropene (Scheme 4.1).[170] The initial Diels-Alder reaction between thiophene-1,1-dioxide **234** and 1-methylcyclopropene **70** forms the adduct **235** which spontaneously emliminates sulfur dioxide to form cycloheptatriene **39**. Reinhoudt *et al*. successfully employed substituted thiophene-1,1-dioxides and substituted cyclopropenes to produce a wide range of cycloheptatrienes (Figure 4.0.1).[109,110]



Scheme 4.1: The Diels-Alder reaction between thiophene-1,1-dioxide and 1-methylcyclopropene.

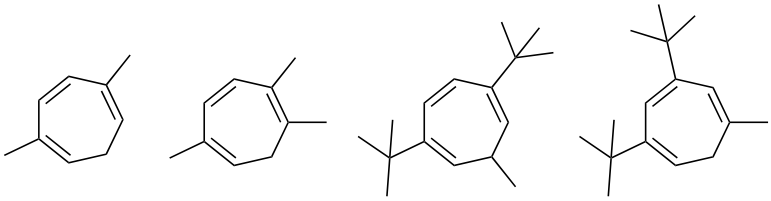
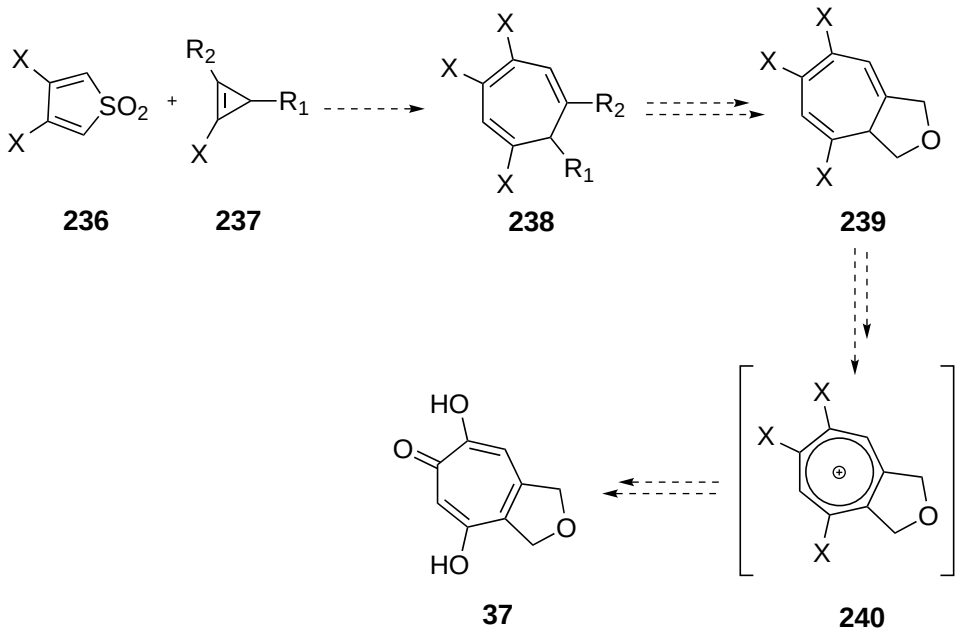


Figure 4.0.1: Some example of the cyclohetatrienes produced by Reinhoudt[109]

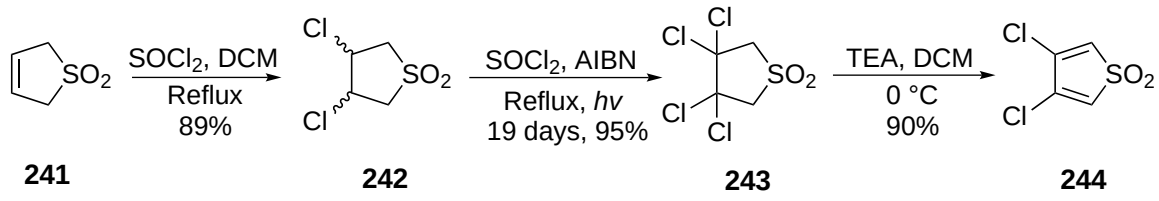
Cordytropolone **37** could be synthesised by a pathway similar to that shown in Scheme 4.2 using a thiophene-1,1-dioxide substituted with halogens such as **236**. The thiophene-1,1-dioxide **236** could then react with cyclopropene **237** to produce the highly substituted cycloheptatriene **238**. With appropriate functional groups at the R_1 and R_2 positions, the substitutents could be converted into a furan ring to produce the bicyclic ring system of cordytropolone **239**. Following this, the tropylium ion **240** could be formed and then the halogen groups replaced using nucleophillic aromatic substitution to form cordytropolone **37**.



Scheme 4.2: A potential pathway to cordytropolone **37** using thiophene-1,1-dioxides and cyclopropenes

An excellent candidate for the substituted thiophene-1,1-dioxide **236** was 3,4-dichlorothiophene-1,1-dioxide **244**. This compound is synthesised from 3,3,4,4-tetrachlorosulfolane **243**

which is produced on a large scale for the agriculture industry. 3,3,4,4-tetrachlorosulfolane **243** synthesised using radical chlorination and the synthesis can be replicated in the lab using chlorine gas and a suitable solvent such as CCl_4.[171] Recently our research group discovered that the same reaction could be performed using sulfuryl chloride as both the solvent and source of chlorine (Scheme 4.3).[172] Sulfuryl chloride is a source of Cl_2 and when paired with an appropriate initiator can be used to chlorinate compounds under free radical conditions.[173] 3-Sulfolene **241** was chlorinated with sulfuryl chloride to produce 3,4-dichlorosulfolane **242**. 3,4-dichlorosulfolane **242** is then converted to 3,3,4,4-tetrachlorosulfolane **243** via a radical chlorination. Previously, the reaction to produce 3,3,4,4-tetrachlorosulfolane **243** had been successful with 2,2´-azobis(2-methylpropionitrile) (AIBN) as the initiator. Catalytic amounts of AIBN were added daily to a solution of 3,4-dichlorosulfolane **242** in sulfuryl chloride, heated to reflux by a halogen lamp. The reaction proceeded slowly, taking approximately 19 days to go to completion. 3,3,4,4-tetrachlorosulfolane **243** then underwent an elimination using TEA to give 3,4-dichlorothiophene-1,1-dioxide **244**.

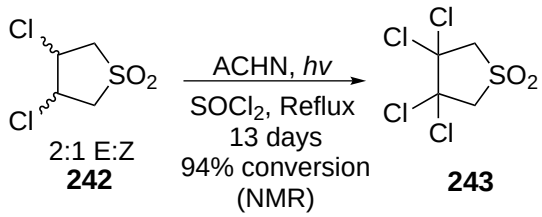


Scheme 4.3: Previous work in the research group produced 3,4-dichlorothiophene-1,1-dioxide **244** via a radical chlorination of **243** using AIBN[172]

Unfortunately, AIBN became only avalaiable as a solution with solvents which were incompatable with the reaction, so a new initiator was required. Benzoyl peroxide has been used as an inititator in the chlorination of 3-sulfolene **241** to 3,3,4,4-tetrachlorosulfolane **243** using Cl_2.[174] The reaction was attemtped with the same conditions as in Scheme 4.3 but with benzyl peroxide as the radical initiator. After a few days had elapsed, the reaction turned a dark brown colour. ^{1}H NMR analysis of the reaction mixture showed that progress had stalled, additional benzoyl peroxide did not increase the amount of **243** present. The reaction only continued to proceed after purification by recrystalisation or

column chromatography.

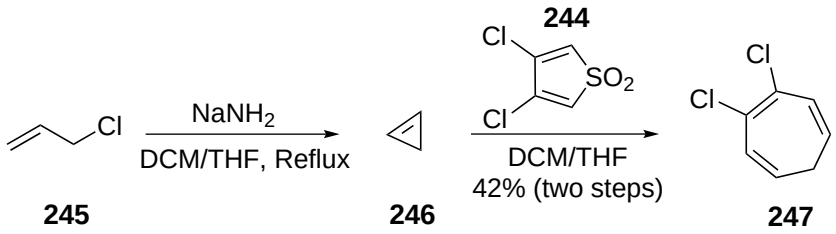
Assuming it was an issue with the benzyl peroxide, the initiator was changed to 1,1´-azobis(cyclohexanecarbonitrile) (ACHN). The reaction turned black at a faster rate compared to benzoyl peroxide and additional ACHN did not increase the amount of **243** present in the reaction mixture. Visual inspection of the condenser attached to the reaction mixture showed that a liquid had condensed on the inner wall. The byproduct of the chlorination reaction is hydrogen chloride gas which was thought to be condensing into hydrochloric acid in the condenser and re-entering the reaction mixture causing it go black. A nitrogen stream was passed through the reaction mixture to vent any hydrogen chloride from the reaction mixture and prevent water from the atmosphere entering the reaction vessel. With a constant nitrogen stream the reaction was much cleaner and completed in 13 days (Scheme 4.4). The 10 hour half-life of ACHN is 88 °C while benzoyl peroxide is 70 °C and AIBN 60 °C, ACHN would decompose less quickly, lasting longer in the reaction mixture allowing the reaction to be more successful.[175]



Scheme 4.4: Optimised synthesis of **243** using ACHN

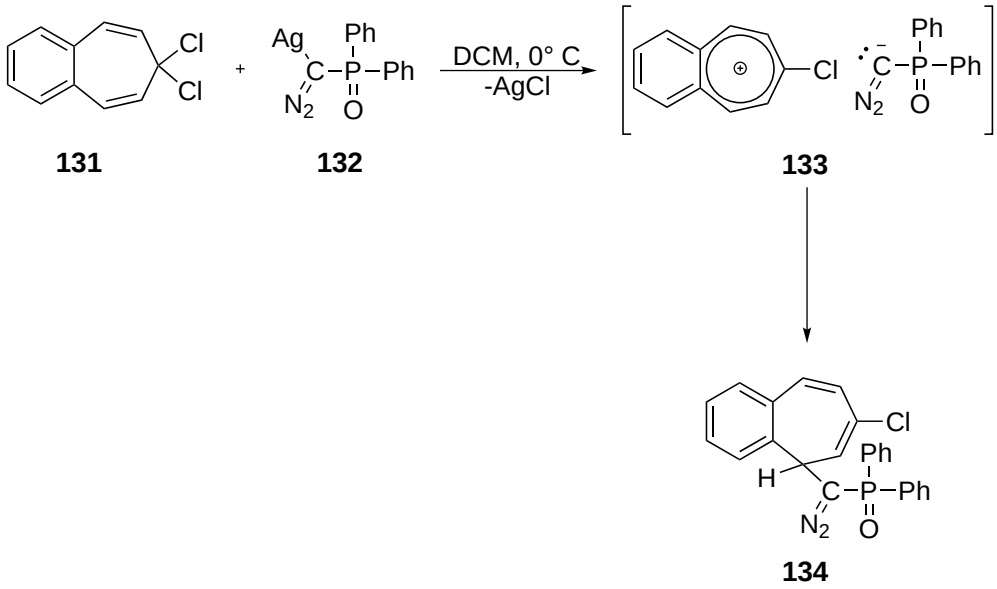
While Reinhoudt *et al.* successfully performed the Diels-Alder reaction with a range of thiophene-1,1-dioxides, it had yet to be performed with a halogen substitued thiophene-1,1-dioxide such as **244**. A model reaction was undertaken to evaluate the feasibility of the sequence. Cyclopropene was prepared by the method described by Fisher and, Closs (Scheme 4.5).[176,177] Sodium amide was suspended in THF and allyl chloride **245** added. The reaction was heated to 80 °C and a nitrogen stream used to force any produced gas into a collection flask cooled with liquid nitrogen containing 3,4-dichloro-1,1-thiophenedioxide **244**. As cyclopropene is highly volatile it needed to be reacted immediately. Once the reaction was complete, 3,4-dichlorocycloheptatriene **247** was isolated.

There were three signals on the ^{1}H NMR spectrum. Two signals integrating for 2H each in the 5.40-6.30 ppm range which is where the alkene signals on the cycloheptatriene are expected. There was also a triplet at 2.4 ppm integrating for 2H, the chemical shift and splitting of this signal indicates that it refers to the allylic hydrogens at the 7-position. As there were only three signals total, it was determined that the compound is likely symmetrical. This indicates that compound is **247** and not a different arrangement of the double bonds.



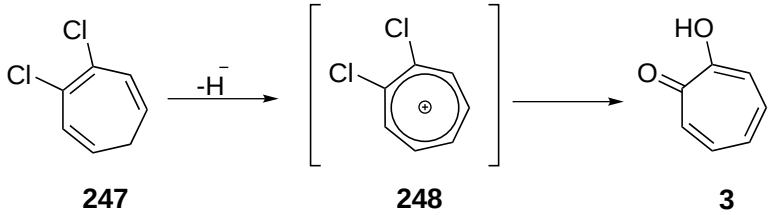
Scheme 4.5: Synthesis of 3,4-dichlorocycloheptatriene **247**

Having successfully made 3,4-dichlorocycloheptatriene **247**, its conversion to tropolone was then investigated. There are two steps involved in this process, the formation of the tropylium ion and the nucleophillic aromatic substitution reaction. Although the two individual steps of the synthesis are known, there are very few reported instances of the two occuring in combination. As reported in Chapter 1 (Scheme 1.35) Regitz *et al*. were able to form the tropylium ion from dichlorobenzocycloheptatriene **131** and then substitute it in combination.[139] Reacting dichlorobenzocycloheptatriene **131** with silver diazomethylphosphoryl compound **132** caused silver chloride to eliminate and the tropylium ion **133** to form. The diazomethylphosphoryl compound then adds to the tropylium ion to give benzyocycloheptatriene **134** (Scheme 4.6).

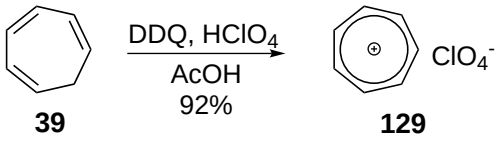


Scheme 4.6: Regitz *et al*. formed the tropylium cation **133** and then added a nucleophile

Using 3,4-dichlorocycloheptatriene **247**, the first step would be to form the tropylium ion **248**, then after substituting, tropolone **3** could be formed (Scheme 4.7). To form the tropylium ion, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) could be used. DDQ has been shown to react with cycloheptatriene to form stable tropylium salts.[178] By reacting DDQ with cycloheptatriene **39** in acetic acid and perchloric acid, cycloheptatrienyllium perchlorate **129** was isolated in 92% yield (Scheme 4.8). This reaction was also perfomed with other quinones such as chloranil and several other counter ion sources, including picric acid, sodium iodide and phosphoric acid.

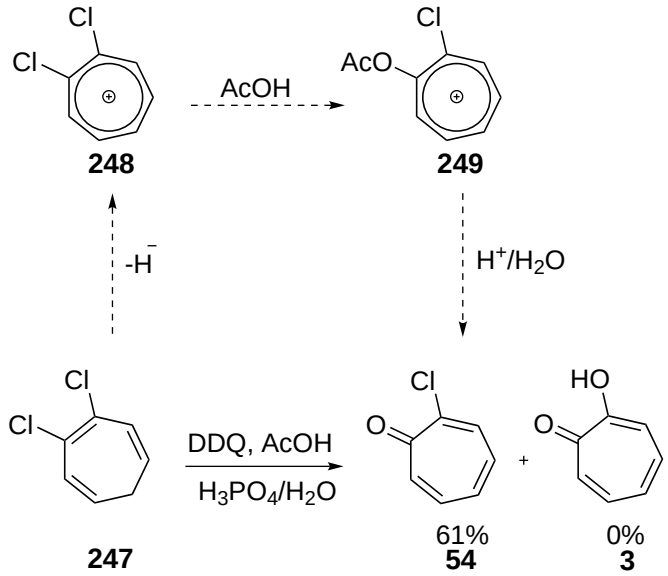


Scheme 4.7: By forming the tropylium ion **248** and then using nucleophlic substitution troplone **3** could be formed



Scheme 4.8: Reaction of cycloheptatriene **39** with DDQ

Instead of isolating the tropylium salt, the addition of water in the workup should cause the tropylium ion to undergo nucleophillic aromatic substitution to form tropone. When 3,4-dichlorocycloheptatriene **247** and DDQ were heated in acetic acid for two hours. The ^{1}H NMR spectrum indicated that one major product formed after workup. There were four aromatic signals present integrating for 4H between 6.9-7.3 ppm, there was an additional signal shifted slightly further than anticipated integrating for 1H at 7.77 ppm. Aromatic signals totalling for 4H is consistant with the expected product tropolone. While the ^{1}H NMR spectrum did not match that of tropolone, it was thought that it the product may be the intermediate, 2-chlorotropone **54** (Scheme 4.9). 2-Chlorotropone has been reported but it was difficult to get an exact match with the literature. The ^{1}H NMR spectrum of the compound run in C_6D_6 did not match the simulated spectrum of 2-chlorotropone proposed by Bertelli *et al.*[179] but the ^{13}C NMR spectrum matched that provided by Bagli and St-Jacques[180]. There was also a ^{1}H NMR spectrum in CD_3COCD_3 by Zhang and Petoud[181] with similar chemcial shifts to the spectrum run in $CDCl_3$(Table 4.0.1). HRMS analysis gave a spectrum for ion C_7H_5OCl with mass 140.00242 corresponding to **54** the result also matched that reported by Zhang and Petoud.[181]



Scheme 4.9: Formation of 2-chlorotropone from **247**

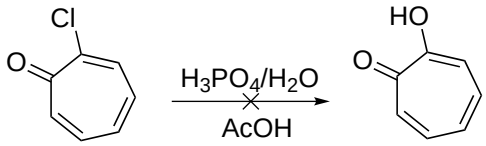
Table 4.0.1: Comparison of ^{1}H and ^{13}C NMR data of 2-chlorotropone **54**

Experimental		Bertelli *et al.*[179]*	Zhang and Petoud[181]
^{1}H	^{1}H	^{1}H	^{1}H
$CDCl_3$	C_6D_6	C_6D_6	CD_3COCD_3
7.77	6.96	8.21	7.93
7.26-7.19	6.84	8.05	7.41-7.34
7.16	6.14	7.90	7.25-7.04
7.08	5.98	7.46	
6.94	5.85-5.72	7.02	
*Converted from data given in Hz			

Experimental	Bagli and St-Jaques[180]
^{13}C	^{13}C
C_6D_6	$CDCl_3$
179.4	179.9
149.4	148.7
138.6	135.3
134.7	131.2
134.5	133.9
133.0	138.6
130.6	135.6

With 2-chlorotropone **54** in hand, the next step to form tropolone **3** would be the replacement of the chlorine group with a hydroxy group. This was initially attempted by acid hydrolysis with a water/phosphoric acid mixture. While phosphoric acid was present in the initial reaction Scheme 4.9 it was thought that there may not have been enough water present to fully hydrolise the compound. 2-Chlorotropone was dissolved in AcOH followed by 42.5% phosphoric acid solution. The reaction was then heated under reflux for 2 hours (Scheme 4.10). Unfortunately only starting material was recovered from the

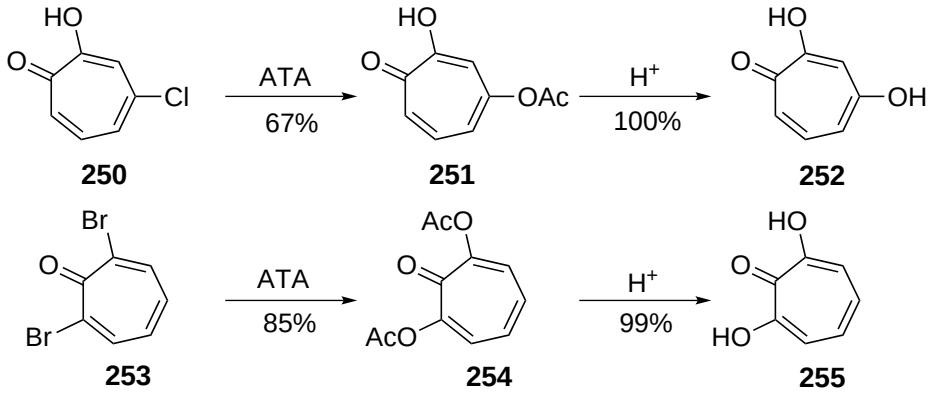
reaction.



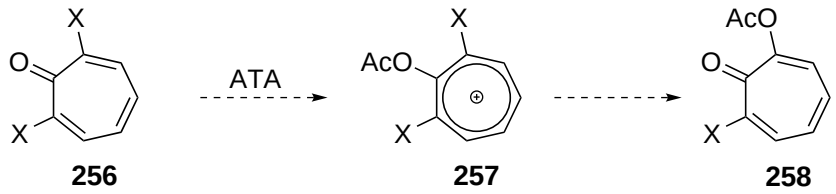
54 **3**

Scheme 4.10: Attempted acid hydrolysis to produce tropolone

Takeshita *et al.*[182,183] were able to produce a wide range of acetoxy and hydroxytropolones from halogenated tropones and tropolones using acetolysis Scheme 4.11. Chlorotropolone **250** and dibromotropone **253** were heated in a solution of acetyl trifluoroacetate (ATA) to give the acetylated products **251** and **254**. The acetate groups were then hydrolysed using a 50% aqueous AcOH mixture at 100 °C to give the two hydroxy tropolones **252** and **255**. The mechanism is throught to proceed via the tropylium ion **257** where, after substitution of the halogen has occured, the tropone is reformed by hydrolysis of the acetate (Scheme 4.12).



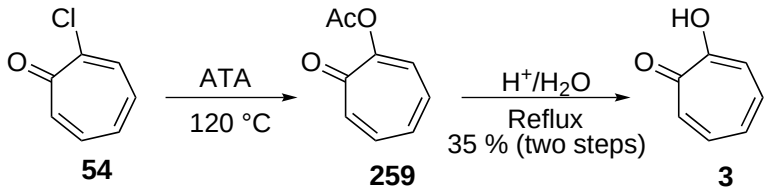
Scheme 4.11: Acetolysis of tropones and tropolones to form hydroxytropolones by Takeshita *et al*.



256 **257** **258**

Scheme 4.12: Proposed mechanism for acetolysis of halogenated tropones by Takeshita *et al.*[183]

When 2-chlorotropone **54** was dissolved in the ATA mixture and heated to 120 °C overnight, the ^{1}H NMR spectrum was different compared to that of the starting material. The signals in the aromatic region were shifted slightly compared to the starting material and there was a singlet integrating for 3H present at 2.35 ppm strongly indicating the presence of an acetyl group. This was determined to be sufficiently indicative that the acetyltropone **259** had been formed. The compound was redisolved in 50% aqueous acetic acid and heated under reflux for five hours. The solvent was removed and the ^{1}H and ^{13}C NMR spectrum indicated one compound which matched the literature spectra for tropolone **3** in 35% yield (two steps).



54 **259** **3**

Scheme 4.13: Acetolysis of chlorotropone **54** to acetyltropone **259** followed by hydrolysis to form tropolone **3**

With a viable path to for the synthesis of tropolone now laid down, other reagents for the transformation of 3,4-dichlorocycloheptatriene **247** to 2-chlorotropone **54** were investigated. In addition to DDQ other quinones such as *p*-chloranil and *o*-chloranil (Figure 4.0.2) have also been used to form tropylium salts (Scheme 4.8).[178] 3,4-dichlorocycloheptatriene **247**, was dissolved in AcOH with *o*-chloranil. The reaction was then heated to 100 °C for four hours. The ^{1}H NMR spectrum gave a single product, matching the spectrum for **54** in 28% yield (Scheme 4.15).

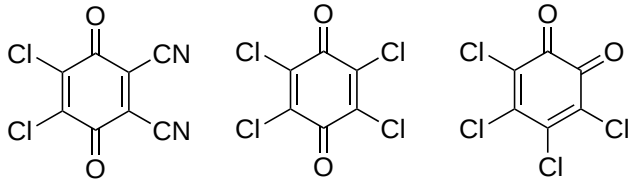
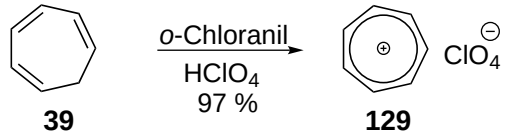
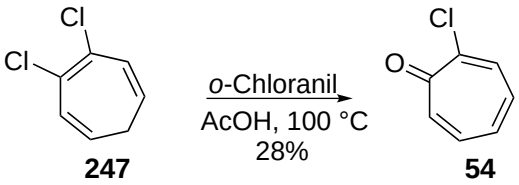


Figure 4.0.2

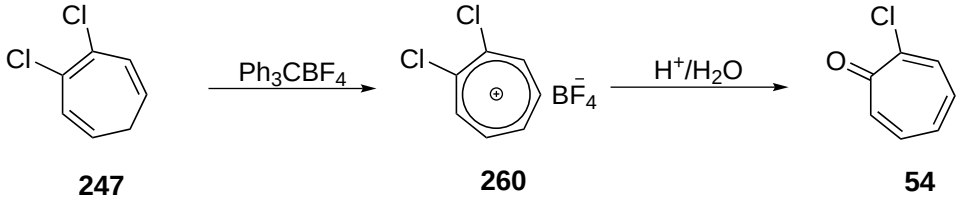


Scheme 4.14: *o*-Chloranil can also be used to form tropylium salts



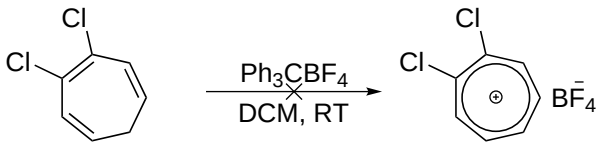
Scheme 4.15: Oxidation of **247** to **54** using *o*-chloranil

Work described in a previous chapter had some success forming tropones using triphenylmethyl salts (Scheme 3.19). While 3,4-dichlorocycloheptatriene **247** does not contain an oxygen like the cycloheptatriene described in Scheme 3.19, reaction with triphenylmethyl tetrafuloroborate should still form the tropylium salt **290**. The tropylium salt **290** could then be substituted by a nucleophile such as water to form the chlorotropone **54** Scheme 4.16.



Scheme 4.16: Reaction with triphenylmethyl tetrafluoroborate could form the tropylium salt **260** which could then be substituted to form the chlorotropone **54**

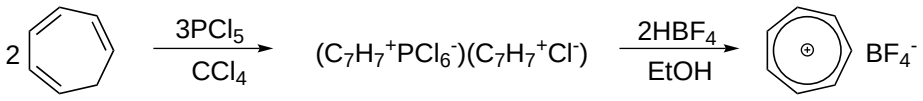
3,4-dichlorocycloheptatriene **247** was dissolved in DCM with Ph_3CBF_4. The reaction was left at room temperature for 18 hours before being quenched by the addition of water. The ^{1}H NMR spectrum of the crude reaction mixture showed no indication of any chlorotropone present but did show that a large amount of starting material had been left unreacted (Scheme 4.17).



247 **260**

Scheme 4.17: Oxidation using a triphenylmethyl salt was unsuccessful

The reaction of cycloheptatriene with PCl_5 was first reported in 1957 by Kursanov and Volpin[184] with a follow up study done by Bryce-Smith and Perkins[185] in 1962. Organic Synthesis reports a method submitted by Conrow based on this research. Tropylium fluroborate was synthesised via formation of tropylium di-salt using PCl_5 (Scheme 4.18).[186] To a suspension of PCl_5 in carbon tetrachloride, cycloheptatriene **39** was added. This forms the tropylium di-salt **261**[185] which was collected and immediately added to a solution of absolute ethanol followed by fluroboric acid. The tropylium furoborate salt **262** was then collected as a white precipitate in 80-89%.



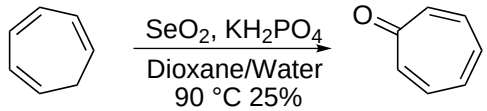
39 **261** **262**

Scheme 4.18: Conrow's procedure for the synthesis of tropylium fluroborate **262**

The reaction with PCl_5 was applied to 3,4-dichlorocycloheptatriene **247**. As the goal was to form 2-chlorotropone **54**, water was added to substitute to the tropylium ion and quench the reaction. 3,4-Dichlorocycloheptatriene **247** was dissolved in DCM and heated to reflux for 18 hours. Upon cooling to room temperature, water was added and left to stir for an additional 30 minutes. The ^{1}H NMR spectrum of the crude material indicated the reaction

had been successful but had not gone to completion. 2-Chlorotropone **54** had been formed in a 1:0.6 ratio when compared to the starting material on the ^{1}H NMR spectrum. However there was low mass recovery from the reaction, making this method unviable.

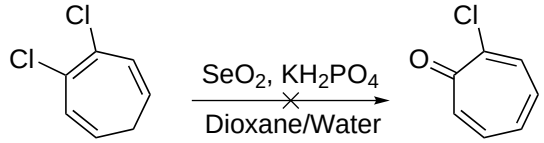
Another reported method of producing tropone from cycloheptatriene is oxidation using selenium dioxide.[187] The reaction was performed in a biphasic solution of aqueous potassium dihydrogenphosphate and dioxane. Cycloheptatriene **39** was dissolved in solution followed by selenium dioxide. After heating at 90 °C for 15 hours, tropone **1** was obtained in 25% yield.



39 **1**

Scheme 4.19: Selenium dioxide oxidation of cycloheptatriene **39** to tropone **1**

A solution of 3,4-dichlorocycloheptatriene **247** in a mixture of dioxane/water with potassium dihydrogenphosphate was prepared. Selenium dioxide was added and the reaction heated to 90 °C for 18 hours. The ^{1}H NMR spectrum of the crude material only indicated starting material. There was no indiciation of any kind of aromatic product (Scheme 4.20).

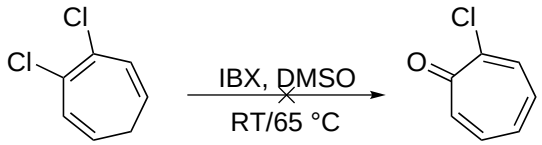


247 **54**

Scheme 4.20: There was no reaction between **247** and selenium dioxide

More traditional oxidants were also tested. 2-Iodoxybenzoic acid (IBX) is an oxidising agent commonly used in organic synthesis. Like the reaction with selenium dioxide Scheme 4.19 it was thought that 3,4-dichlorocycloheptatriene **247** might be oxidised to 2-chlorotropone **54**. 3,4-Dichlorocycloheptatriene **247** was dissolved in DMSO, IBX was added and the reaction left at room temperature for 18 hours (Scheme 4.21). The ^{1}H NMR spectrum showed a large amount of starting material with a minor aromatic product. The minor aromatic product was confirmed to be 2-iodobenzoic acid, a bi-product

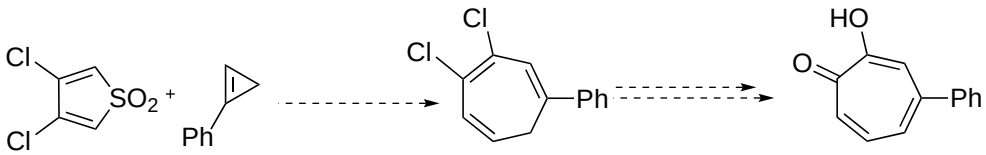
of IBX. Due to the non-reaction of 3,4-dichlorocycloheptatriene **247** at room temperature, the reaction was attempted again heating to 65 °C for 18 hours. The signals on the ^{1}H NMR spectrum relating to 2-iodobenzoic acid had increased relative to the starting material **247**, but there did not appear to be any new products forming. The resistance of 3,4-dichlorocycloheptatriene **247** to various methods of oxidation compared to **39** is likely due to the additional chlorines present on the ring. Chlorines are electron withdrawing and are likely deactivating the ring towards oxidation.



247 **54**

Scheme 4.21: The unsuccessful oxidation of **247** using IBX

With success in producing tropolone **3** from 3,4-dichlorocycloheptatriene **247** a new synthesis was undertaken with phenyl cycloheptatriene **264** as the target. Again, thiophene dixoide **244** would be used in a Diels-Alder reaction but in this case it would be reacted with 1-phenylcyclopropene **263**. The reaction would give phenyl cycloheptatriene **264** which could be converted into the tropolone **265** (Scheme 4.22).

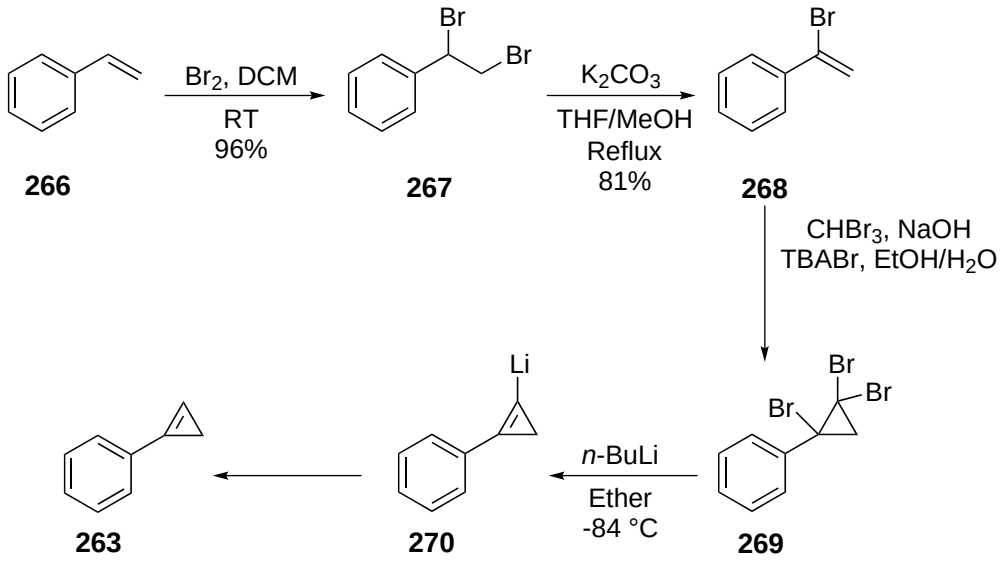


244 **263** **264** **265**

Scheme 4.22: A diels alder reaction between **244** and **263** should produce cycloheptatriene **264** which could then be converted into tropolone **265**

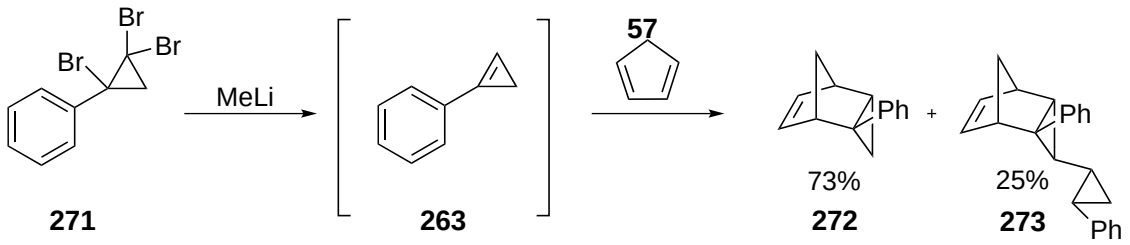
The synthesis of the phenyl cyclopropene **263** first started by the bromination of styrene using Br_2 to give the dibromide **267**.[188,189] Potassium carbonate in THF/MeOH under reflux caused elimination of the primary bromine to give the bromovinyl benzene **268**.[190] The reaction of **268** with a dibromocarbene generated from bromoform and sodium hydroxide, gave the cyclopropane **269**. The cyclopropane **269** was then reacted with 2.8

eq. *n*-BuLi at -84 °C before being quenched with saturated ammonium chloride. It was expected that the *n*-BuLi would lithiate the halogen positions followed by elimination to produce the desired cyclopropene **263** (Scheme 4.23).[191,192] However, the ^{1}H NMR spectrum of the obtained product indicated an absence of cyclopropene **263**.



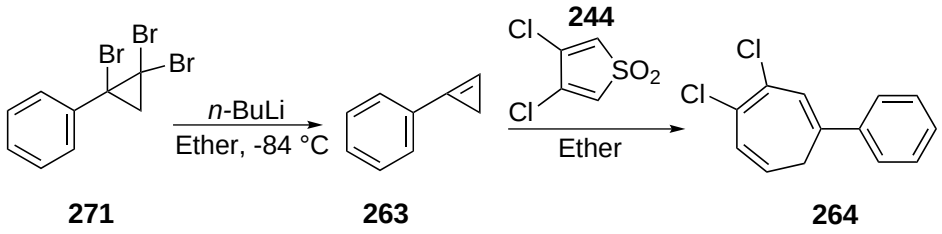
Scheme 4.23: Attempted synthetic pathway for the synthesis of cyclopropene **263**

1-Phenylcyclopropene was likely degrading through an ene reaction. Lee *et al.* were able to trap and isolate an ene dimer by forming phenyl cyclopropene in solution and then immediately adding cyclopentadiene **57** to form the Diels-Alder adducts (Scheme 4.24).[192] This formed the expected phenyl adduct **272** and the ene dimer adduct **273** in a 73:25 ratio, indicating that dimerisation happens rapidly. It is likely that when the reaction with tribromocyclopropane **269** and *n*-BuLi warmed to room temperature it underwent ene dimerisation or trimerisation. The reaction by Lee et al. also proves that a Diels-Alder reaction with the phenyl cyclopropene is possible. By forming the phenyl cyclopropene **263** in solution at -84 °C and adding thiophene-1,1-dioxide **244** it should form the phenylcycloheptatriene **264**.



Scheme 4.24: Lee /emphet al. trapped the cyclopropene **263** with cyclopentadiene[192]

When the cyclopropane **271** was dissolved in ether at -84 °C and 3.1 eq. *n*-BuLi was added dropwise. The reaction was left to warm over 2 hours then cooled back down to -84 °C and quenched by saturated ammonium chloride. Thiophene-1,1-dioxide **244** was then added and the reaction was left to warm to room temerpature. The ^{1}H NMR spectrum showed the formation of a cycloheptatriene. There was a singlet at 6.51 ppm integrating for 1H, a doublet at 6.30 ppm for 1H and a multiplet at 5.63 ppm for 1H. These signals are consistant with the vinyl signals of a cycloheptatriene. There was a doublet at 2.91 ppm for 2H which is consistant with the allylic hydrogens on the cycloheptatriene and there were signals in the aromatic region integrating for a total of 5H. This confirms the synthesis of phenyl cycloheptatriene **264** (Scheme 4.25).



Scheme 4.25: Synthesis of the cycloheptatriene **264**

When the reaction described in Scheme 4.25 was not allowed to heat up sufficiently after the addition of *n*-BuLi, an additional cycloheptatriene product was isolated alongside phenylcycloheptatriene **264**. The ^{1}H NMR of this compound had aromatic signals integrating for 5H the same as **264** but the signals normally associated with a cycloheptatriene were slightly different. Instead of 3 vinyl signals there were two singlets present at 6.64 and 6.58 ppm each integrating for 1H and instead of a doublet for the allylic signals there

was a singlet integrating for 2H at 3.41 ppm. The absence of the multiplet usually associated with H-6 and changing of splitting to all singlets indicated that the H-6 position had been substituted (Figure 4.0.3). As this product was only found when the reaction was not sufficiently warmed it is likely that formation of this compound is due to an incomplete reaction of tribromocyclopropane **271** with *n*-BuLi to give the cyclopropane **274**. A Diels-Alder reaction with thiophene-1,1-dioxide **244** and **274** would give cycloheptatriene **275**. The HRMS (Orbitrap) spectrum showed an ion of weight 313.9258 which is consistant with $C_{13}H_9Cl_2Br$ corresponding to **275**.

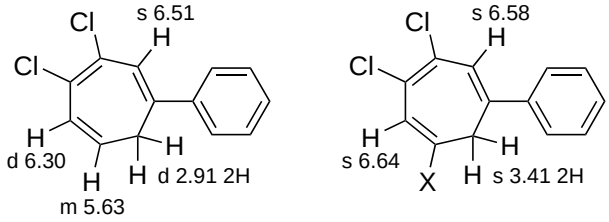
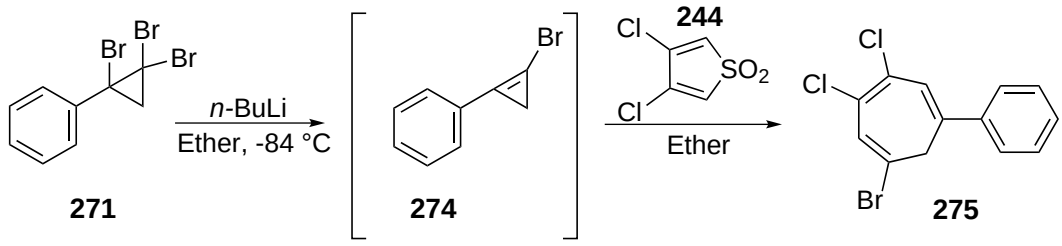
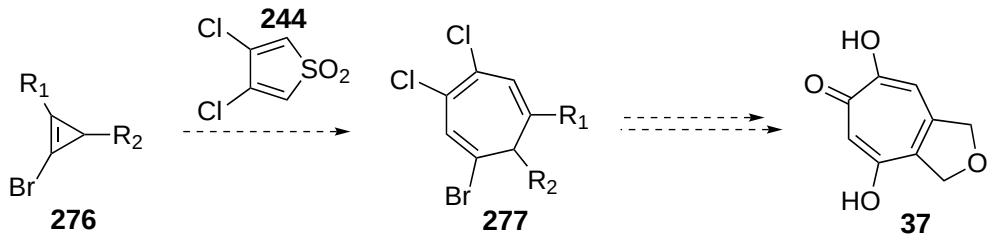


Figure 4.0.3: ^{1}H NMR spectra comparison to the substituted cycloheptatriene



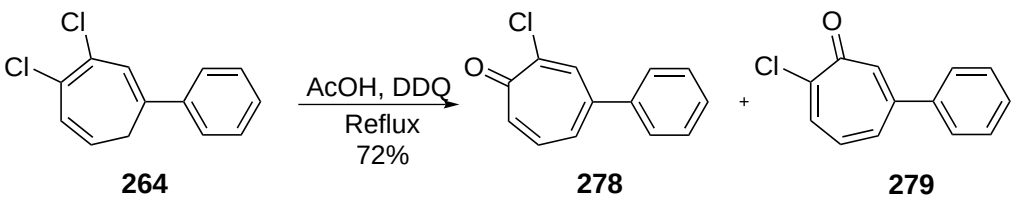
Scheme 4.26: Incomplete reaction with BuLi produced cyclopropene **274** which gave **275**

The disovery of 6-substituted cycloheptatriene **275** (Scheme 4.26) is significant as it shows that a Diels-Alder reaction with a cyclopropene which has a halogen substituted at the 2-position is possible. In order to produce cordytropolone **37** a cyclopropene with a halogen present at the 2-position of the cyclopropene **276** would be needed in order to substitute for the hydroxy present at the 6-position on cordytropolone. The Diels-Alder reaction between **276** and **244** would produce cycloheptatriene **277**. **277** has three halogens present which, after forming the tropylium ion could be substituted to form cordytropolone **37** as described in Scheme 4.2 (Scheme 4.27)



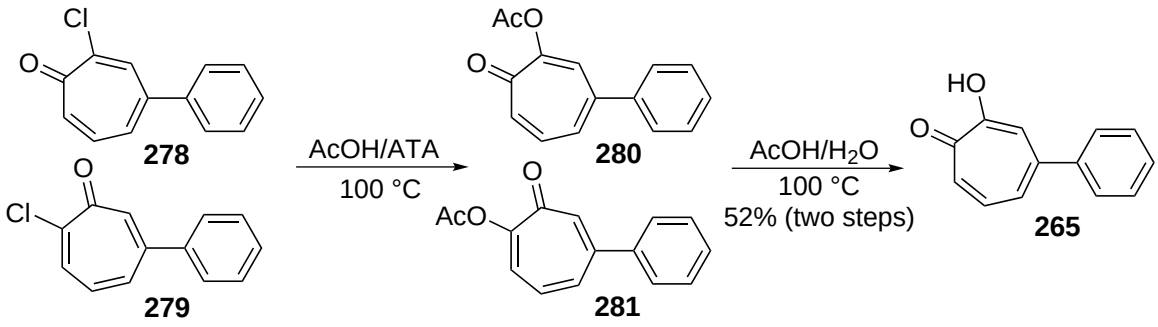
Scheme 4.27: A cyclopropene substituted at the 2-position as in **276** is essential in the synthesis of cordytropolone **37**

With the phenylcycloheptatriene **264** successfuly obtained the DDQ aromatisation to form the tropone was attempted. **264** was dissolved in AcOH with DDQ and heated at 100 °C for 4 hours, the isolated material showed no cycloheptatriene signals and several aromatic signals in the ^{1}H NMR spectrum. These signals were quite messy and unable to be resolved. In total there appeared to be two compounds as two sets signals were integrating for 1:1 ratio with each other. There was also a large multiplet from 7.33-7.45 ppm which integrated for aprroximately 10H, it is likely that this multiplet is two sets of 5H from the phenyl ring. The ^{13}C NMR at 179.61 and 179.54 ppm which are characteristic of the carbonyl carbon on a tropone. In total there were 22 signals on ^{13}C NMR spectrum which is consistant with there being two isomers of the expected phenylchlorotropone. Each isomer would display 11 carbons on the ^{13}C NMR instead of the expected 13C, as the phenyl ring is symmetrical. From this evidence it was concluded that the reaction was successful and produced a mix of phenylchlorotropones **278** and **279**. The reaction was also repeated with *o*-chloranil as the oxidant under the same conditions. The ^{1}H NMR spectrum of the crude reaction mixture showed both **278** and **279**. However, due to the small amount of crude residue recovered a purified yield was not obtained.



Scheme 4.28: The aromatisation with DDQ was successful producing two chlorotropone isomers **278** and **279**

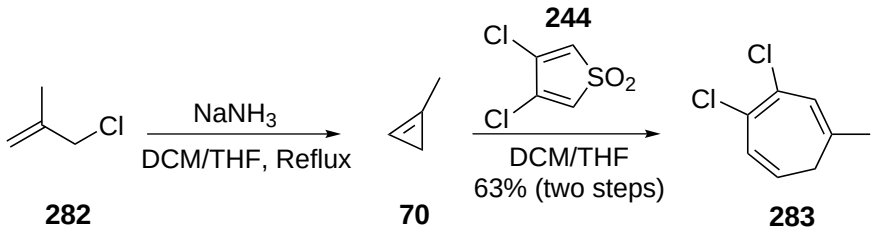
The mixture of phenylchlorotropones **278** and **279** was dissolved in the ATA/AcOH mixture and heated to 100 °C overnight. The ^{1}H NMR spectrum of the product showed one major aromatic product with a signal at 2.39 ppm integrating for 3H relative to the major aromatic signals. This is likely the CH_3 carbon on the acetyl group. There was a minor aromatic product which also had a signal integrating for 3H relative to it at 2.25 ppm. From this it was concluded that the acetolysis was successful and had again produced two isomers **280** and **281** but the ratio had shifted to one major product instead of the approximate 1:1 ratio of the starting material. This crude residue was immediately hydrolysed by dissolving in 50% aqueous AcOH and heating to 100 °C for 4 hours (Scheme 4.29). This produced a single product with signals only present in the aromatic region 7.2-7.65 ppm integrating for a total of 9H. Based on this it was concluded that the product was likely the expected phenyl tropolone which was confirmed with HRMS. The HRMS (HESI Q exactive MS) spectrum gave an ion of weight 199.0754 consistant with $C_{13}H_{12}O_2^{+}$, corresponding to **265**.



Scheme 4.29: Acetolysis followed by hydrolysis successfully produced 4-phenyltropolone **265**

With two successful synthesis of tropolone complete, 1-methylcyclopropene **70** was selected as the next candidate (Scheme 4.5). 1-Methylcyclopropene **70** was synthesised using sodium amide and methyl allyl chloride using the method developed by Fisher and Applequist.[176] The gaseous cyclopropene was collected at -196 °C and reacted with a solution of 3,4-dichloro-1,1-thiophene dioxide **244** in DCM at RT to give 1-methyl,-3,4-dichlorocycloheptatriene **283** (Scheme 4.30). The ^{1}H NMR spectrum showed the methyl signal at 1.98 ppm integrating for 3H. The other signals were consistant with a cyclo-

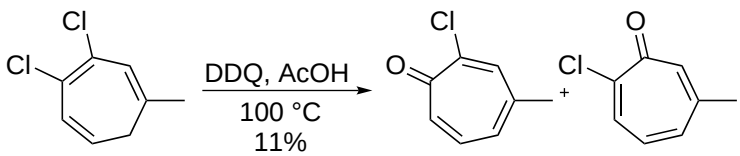
heptatriene, three vinyl signals were present form 5.5-6.2 ppm integrating for 1H each. One signal was present at 2.45 ppm integrating for 2H representative of the two allylic hydrogens on the cycloheptatriene ring.



282 **70** **283**

Scheme 4.30: Synthesis of dichloromethylcycloheptatriene **283** =from 1-methylcyclopropene **70**

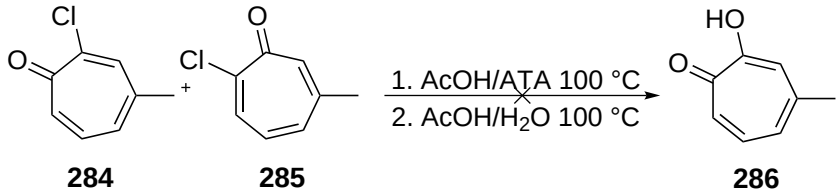
The reaction to form a tropone from the cycloheptatriene **283** was attempted under similar conditions as described above. The compound was dissolved in AcOH with DDQ and left to react at 100 °C for two hours. However, the ^{1}H NMR spectrum of the reaction mixture was a complex mixture. There were a multitude of signals in the aromatic region. Column chromatogrpahy of the crude product gave a small amount a material tentatively assigned as methylchlorotropone **284**. There were two potential methyl signals that integrated betwen 3.26-2.42 ppm that integrated for 3H each relative to signals in the aromatic region but not to each other. There were several signals in the aromatic region with four signals integrating in 1:1:1:1 ratio indicating potentially the four aromatic signals that would be expected with with the chlorotropone. These integrated in a 1:3 ratio with one of the potential methyl signals. Several other signals in the aromatic region also appeared to integrate in a 1:1:1:1 ratio, with a 1:3 ratio to the other methyl signal. This information lead to the conclusion that two isomers **284** and **285** had been produced (Scheme 4.31).



283 **284** **285**

Scheme 4.31: The reaction with DDQ produce a complex mixture but a small amount of what appeared to be compounds **284** and **285** was able to be isolated

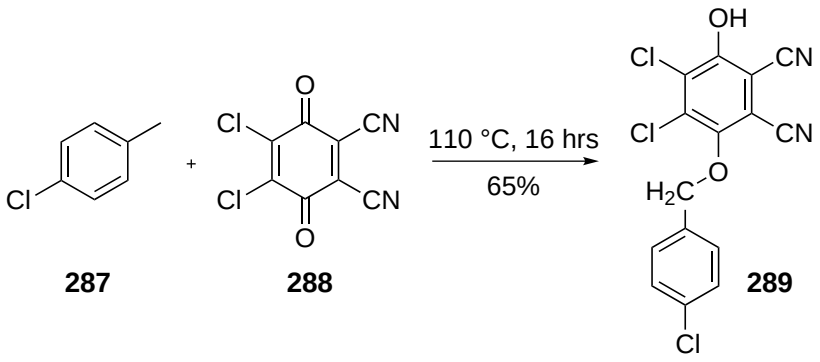
Chlorotropones **284** and **285** should form the same methyltropolone **286** (Scheme 4.32) as was the case with the phenyltropolones **280** and **281** (Scheme 4.29). To confirm the structures of the mixture of isomers, the mixture was subjected to ATA acetyloysis followed by hydrolysis as per the chlorotropone previously described in Scheme 4.13. Unfortunately this pathway was not successful, reactions resulted in an increasingly complex aromatic region and loss of any methyl signals in the ^{1}H NMR spectrum.



284 **285** **286**

Scheme 4.32: Formation of the tropolone by acetolysis was not successful

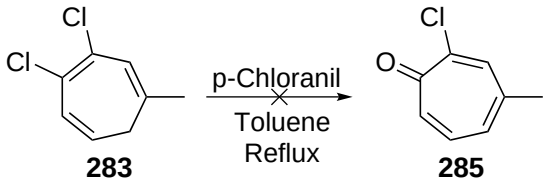
The other fractions resulting from the aromatisation of methyl cycloheptatriene **283** by DDQ (Scheme 4.31) were analysed by ^{1}H NMR spectroscopy. There were no other products with any visibile signals relating to the methyl group other than those that could be attributed to the compounds **284** and **285**. It is likely a competing oxidation reaction with DDQ at the allylic/benzylic position. There are several reported cases of toluene reacting with DDQ.[193] Batista *et al.*[194] reported oxidation of the methyl group of toluene as well as other toluene compounds such as 4-chlorotoluene **287** to produce compound **289** (Scheme 4.33).



287 **288** **289**

Scheme 4.33: Oxidation of the benzyl position of 4-chlorotoluene **287** with DDQ reported by Batista *et al.*[194]

As the methylcycloheptatriene **283** appeared to be highly reactive, a reaction using *p*-chloranil was attempted as it is a milder oxidant. Methylcycloheptatriene **283** was dissolved in toluene and chloranil was added. Toluene was chosen as the solvent over AcOH to ensure that AcOH was not substituting at the benzyl position of cycloheptatriene. The reaction was heated under reflux overnight. 85% phosphoric acid was added in order to form the tropylium salt and the reaction cooled to RT (Scheme 4.34). Analysis of the ^{1}H NMR spectrum of the crude material showed that most of the starting material had not reacted and there were no signals relating to **285** present.



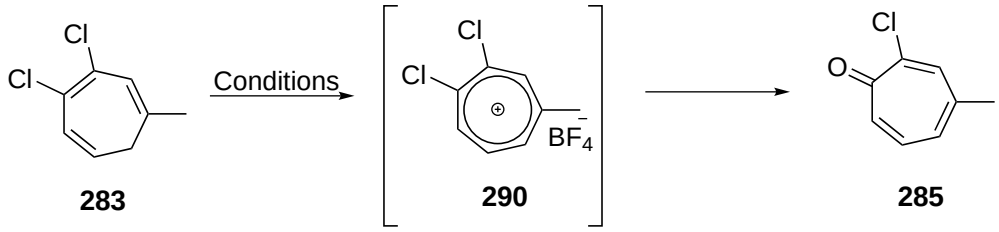
Scheme 4.34: p-Chloranil reaction of **283** yielded nearly entirely starting material

Forming a tropylium salt via hydrogen abstraction as decribed in Scheme 4.16 was also attempted on **283** and the results represented in Table 4.0.2. **283** was dissolved in the solvent and then reacted for the listed time and temperature. Sodium acetate was then added before workup to attempt to form the chlorotropone **285**. Entries 1 and 2 only recovered starting material, heating the reaction higher (Entry 3) gave some new additional signals on the crude ^{1}H NMR spectrum but on purification no desired products were found. There were several examples in the literature of tropylium salts being formed at low temperatures so this was also attempted (Entry 5). In this case the reaction was performed at -40 °C and allowed to warm to RT over 30 minutes. The reaction was then cooled back down and water added to quench the reaction and form the tropone. Only starting material was recovered.

Several other oxidants were also tested in an attempt to convert the methylcycloheptatriene **283** to the methylchlorotropone **291**. Each of these oxidants had previously been tested on 3,4-dichlorocycloheptatriene **247** and the results are listed in Table 4.0.3

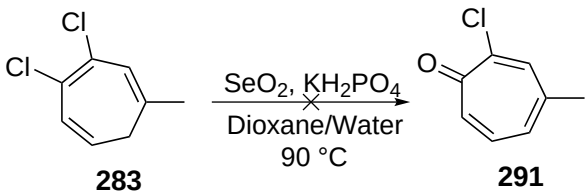
In the reaction of methyl cycloheptatriene **283** with selenium dioxide (Table 4.0.3, Entry 7) the ^{1}H NMR spectrum of the crude material showed many minor signals throughout the

Table 4.0.2: Attempts to produce chlorotropone **291** via formation of tropylium salts



Entry	Solvent	Reagent	Conditions	Additional Reagent	Result
1	MeCN	1 eq. Ph_3CBF_4	RT, 0.5 hrs	NaOAc	NR
2	MeCN	1 eq. Ph_3CBF_4	RT, 18 hrs	NaOAc	NR
3	MeCN	2 eq. Ph_3CBF_4	40 °C, 2 hrs	NaOAc	No tropolones found
5	MeCN	2 eq. Ph_3CBF_4	-40 °C - RT, 0.5 hrs	None	NR

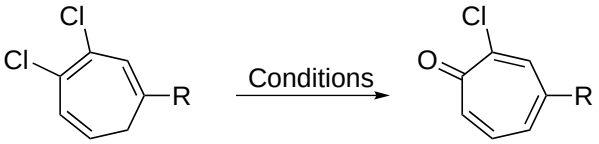
spectrum, particularly in the 6.00-8.15 region. None of these signals appeared to indicate that a tropolone or tropone had formed. However, there were two signals at 10.19 and 10.69 ppm. There were also several signals in this region on the oxidations of methyl cycloheptatriene **283** involving DDQ. Unfortunately, in either of these cases, the compound relating to these signals were unable to be isolated. The high chemical shift of these signals indicates that they may possibly be related to the hydrogen present on an aldehyde. This is significant as it may indicate that the cycloheptatriene **283** is transforming into a benzaldehyde.



Scheme 4.35: Attempted selenium dioxide oxidation

While the presence of chlorine facilitiates nucleophilic aromatic substitution on the 7-membered ring system, there are examples of ring contraction occuring instead. In the

Table 4.0.3: Summary of attempts to convert dichlorocycloheptatrienes to the corresponding 2-chlorotropone



R = H **247**
R = Me **283**
R = Ph **264**

R = H **54**
R = Me **291**
R = Ph **278**

Entry	Reagent	Conditions	**247**	**283**	**264**
1	DDQ	AcOH, 100 °C	61%	Minor Conversion	72%
2	*o*-chloranil	AcOH, 100 °C	28%	Complex Mixture	15%
3	*p*-chloranil	Toluene, reflux	-	NR	-
4	PCl_5	DCM, reflux	Partial Conversion	NR	-
5	Ph_3CBF_4	DCM, RT./H_2O	NR	-	-
6	Ph_3CBF_4	See Table 4.0.2	-	Table 4.0.2	-
7	SeO_2	H_2O/dioxane, KH_2PO_4, 90 °C	NR	NR	-
8	IBX	DMSO, 65 °C	NR	-	-

presence of alkaline conditions, 2-halotropones have been shown to give both benzoic acid and salicylaldehyde.[195,196] Benzoic acid formation occurs through a mechanism whereby a norcaradiene intermediate is formed and C1 extruded[197]. While salicylaldehyde occurs through extrustion of C3[198] under dilute alkaline conditions. It is possible that the small amounts of the cycloheptatriene are being oxidised to the chlorotropone or tropylium ion and then going through the ring contraction to give an aldehyde or acid due to the heat. The signals at 10.19 and 10.69 ppm on ^{1}H NMR spectrum of the crude residue do not match the ^{1}H NMR spectrum of either the benzoic acid, benzaldehyde or salicylaldehyde. Despite this, the large amount of starting material remaining and the tiny ratio of these signals to the starting material indicated that the reaction was not successful.

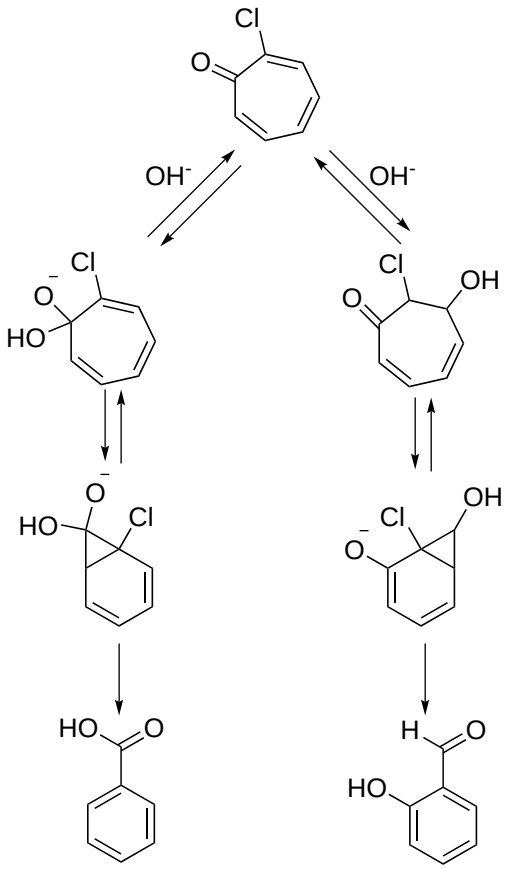
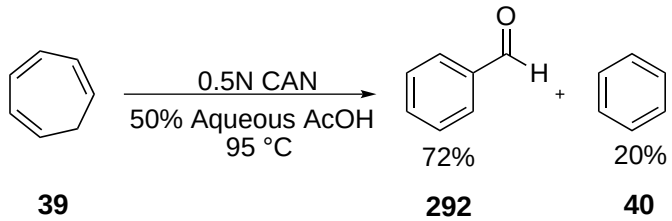


Figure 4.0.4: Ring contraction of halotropones[196] through C1 extrusion to give benzoic acid[197] (left) and C3 to give saliciladehyde[198] (right)

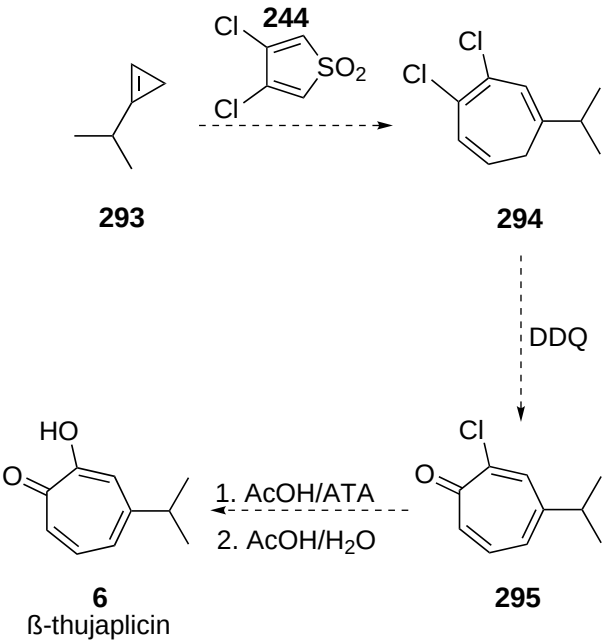
There is also precident for ring contractions occuring via oxidation. In a study done by Young,[199] cerric ammonium nitriate (CAN) was used to oxidise cycloheptatriene **39** and the products of this reaction investigated. Young found that when cycloheptatriene **39** was oxidised using 4 eq. CAN in aqueous solvents, the products were varying ratios of benzaldehyde **292** and benzene **40** (Scheme 4.36). A followup study by Robbins[200] showed that similar products were observed when substituted cycloheptatrienes were used. The reaction of methylcycloheptatriene with CAN in aqueous acetonitrile produced benzophenone, diphenylmethanol and, diphenylmethyl acetate. In anhydrous acetonitrile the sole product was *N*-diphenylmethyl acetamide. When the reaction was performed with phenylcycloheptatriene the products were biphenyl, benzophenone and phenylbenzaldehydes. These results eliminated CAN as an oxidant and also explains the trace aromatic and aldehyde signals appearing in reactions of cycloheptatriene **317** with other oxidants. There is

also evidence that oxidation via hydrogen peroxide can also cause a ring contraction[201] and that oxidation of cycloheptatriene carboxylic acid gives benzaldehyde.[202]



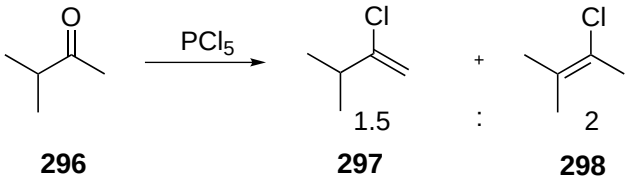
Scheme 4.36: Oxidation of cycloheptatriene using CAN results in benzene and benzaldehyde

The method for producing tropolones was then applied to some known natural products. As described previously β-thujaplicin **6**, also known as hinokitiol is a natural product derived from the Western Red Cedar tree. It has been shown to have antifungal activity and has some inhibitory effects against the Chlamydia bacteria. Hinokitol is a tropolone with an isopropyl group at the 4-position. Using the method to make tropolones described in this chaper, an isopropyl cyclopropene **293** could be reacted with thiophene-1,1-dioxide **244** to give isopropyl cycloheptatriene **294**. Which could then be converted into β-thujaplicin **6** using the developed oxidation/hydrolysis conditions (Scheme 4.37).



Scheme 4.37: Proposed synthesis of β-thujaplcin **6** from isopropylcyclopropene **293**

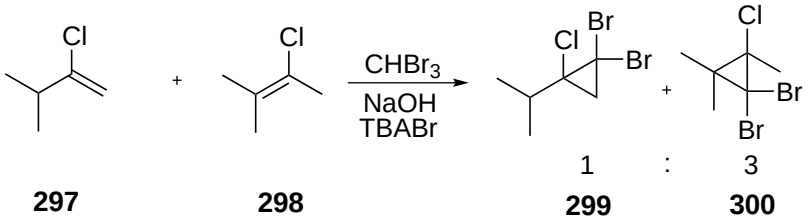
The synthesis of the isopropylcyclopropene **293** required the preparation of 2-chloro-3-methyl-1-butene **297**. 3-methyl-2-butanone **296** was chlorinated by addition of PCl_5 then heating under reflux for 1 hours.[203] Due to the volatility of the product the crude mixture was unable to be purified by column chromatography. The ^{1}H NMR spectrum of the crude residue indicated that two products were present, 2-chloro-3-methylbut-2-ene **298** and the desired product 2-chloro-3-methylbut-1-ene **297** (Scheme 4.38). Both of these compounds have been reported previously.[203–205]



Scheme 4.38: Chlorination by phosphorus pentachloride gave **298** and **297**

The mixture of butenes **297** and **298** was then subjected to a dibromocarbene reaction based on a procedure by Hopf *et al.*[206] The mixture of **298** and **297** were dissolved in bromoform followed by the additon of EtOH, TBABr and NaOH. The reaction was

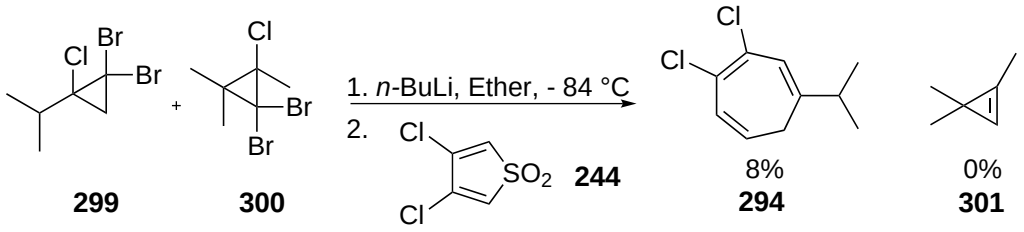
then left overnight at RT After purification a mixture of two compounds was once again obtained. 1,1-dibromo-2-chloro-2,3,3-trimethylcyclopropane **300** and the desired 1,1-dibromo-2-chloro-2-isopropylcyclopropane **299** (Scheme 4.39. 1,1-dibromo-2-chloro-2-isopropylcyclopropane **299** is a reported compound[203,207] so was easily identified. Baird *et al.* have reported 1,1,2-tribromo-2,3,3-trimethylcyclopropane and 1,1,2-trichloro-2,3,3-trimethylcyclopropane to have the same ^{1}H NMR spectrum, which also matches 1,1-dibromo-2-chloro-2,3,3-trimethylcyclopropane **300**.[207]



Scheme 4.39: Preparation of cyclopropanes **300** and **299**

The next step is a lithiation/elimination using *n*-BuLi. As isopropyl cyclopropene **293** is volatile and due to the possibly of an ene reaction, the idea was to form the cyclopropene in solution and then immediately react with thiophene-1,1-dioxide **244**. This would form the cycloheptatriene **294** in the same way as described for phenyl cyclopropene **263** (Scheme 4.25). The mixture of cyclopropanes **300** and **299** were dissolved in ether at -84 °C and *n*-BuLi was added dropwise. The reaction was left to warm up for one hour then cooled back down to -84 °C to be quenched by saturated ammonium chloride solution. After quenching, thiophene-1,1-dioxide **244** was added and the reaction was stirred at RT for 3 hours. The ^{1}H NMR spectrum showed only one set of cycloheptatriene signals. There was a singlet at 6.14 ppm for 1H, a doublet at 5.99 ppm for 1H and a multiplet at 5.46 ppm for 1H. There was also a doublet present at 2.41 ppm for 2H. These signals are consistant with the three vinyl and two allylic hydrogens on the cycloheptatriene as described previously in Figure 4.0.3. Upon purification, the signals relating to the isopropyl group were able to be elucidated with a doublet at 1.08 ppm integrating for 6H. From this it was concluded that the synthesis of isopropyl cycloheptatriene **294** was successful (Scheme 4.40). The elimation product of cyclopropane **300**,

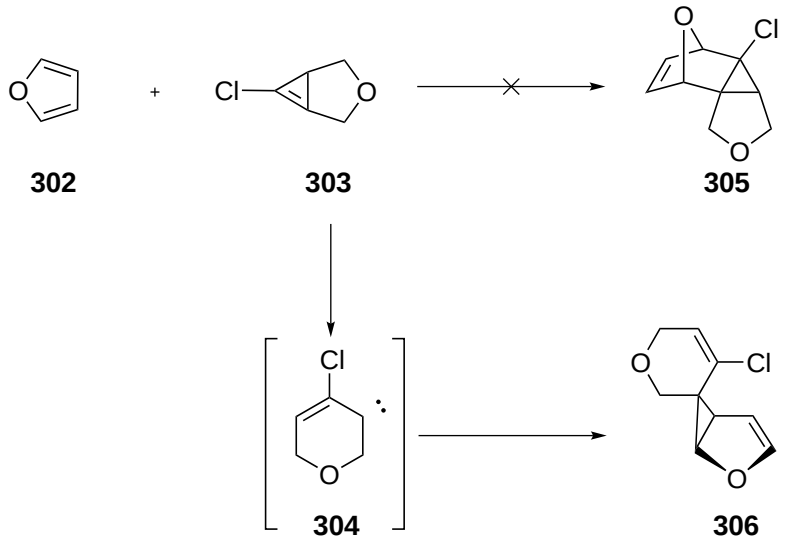
1,3,3-trimethylcyclopropene **301** has been reported to be unreactive towards a Diels-Alder reaction with thiophene-1,1-dioxide[109] likely due to the steric hinderance of the methyl groups. 1,3,3-trimethylcyclopropene **301** itself was also not detected on the ^{1}H NMR spectrum, with a reported boiling point of 45 °C it is likely to have evaporated during solvent removal.



Scheme 4.40: Reaction of the cyclopropene mixture yeilded only the desired cycloheptatriene **294**

The reaction to form the isopropyl chlorotropone **295** from the isopropyl cycloheptatriene **294** was attempted using DDQ. Cycloheptatriene **294** was dissolved in AcOH with DDQ and left to react at 100 °C for four hours. The ^{1}H NMR spectrum of the crude residue was highly complex and resemebled that of attempted DDQ oxidations performed on **283**. There were no signals present on the ^{1}H NMR spectrum that would indicate that isopropyl chlorotropone **295** had formed. As in the case with methyl cycloheptatriene **283** it is likely that the allylic position is highly reactive, leading to many undesired side reactions.

With two successful synthesies of tropolones **3** and **265**, research turned to producing the tropolone core of cordytropolone **37**. The five-membered ring of cordytropolone cannot be produced directly through a Diels-Alder reaction with 3,4-dichlorothiophene-1,1-dioxide **244**. Halton *et al.* reported that the bicyclic cyclopropene **303** did not react with furan **302** to give Diels-Alder adduct **305** in the manner expected. Instead Halton *et al.* disovered spyrocycle **306** had formed. The cyclopropene **303** had rearranged to the more stable vinyl carbene **304** before reaction with furan **302**.[208] Any cyclopropene with the five-membered ring already formed would unsuitable for forming cordytropolone as the same rearrangement would be likely to occur.

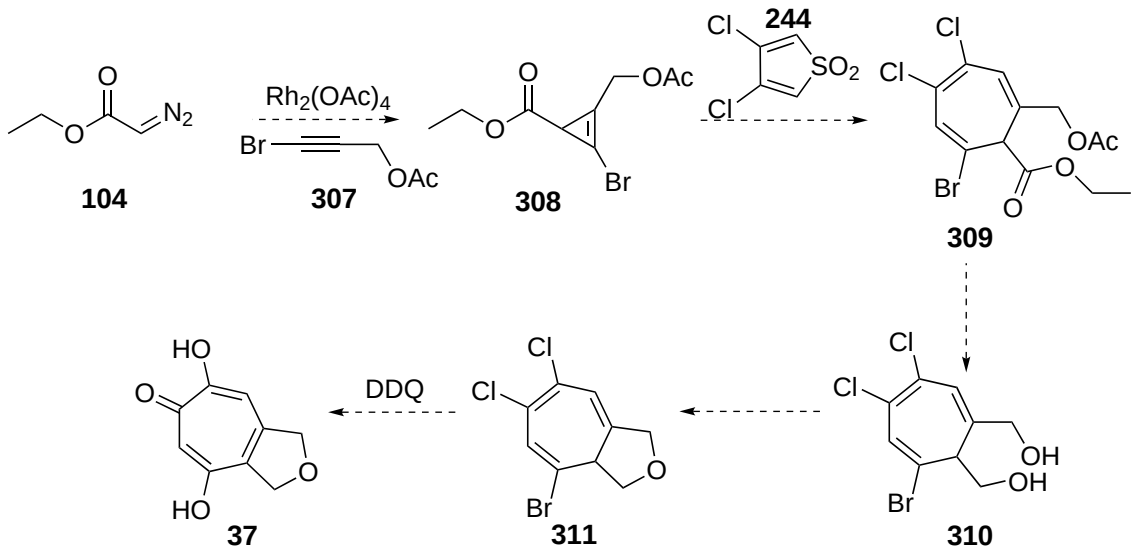


302 **303** **305**

304 **306**

Scheme 4.41: Halton *et al*. discovered that cyclopropene **303** would rearrange to less strained **304** before reaction

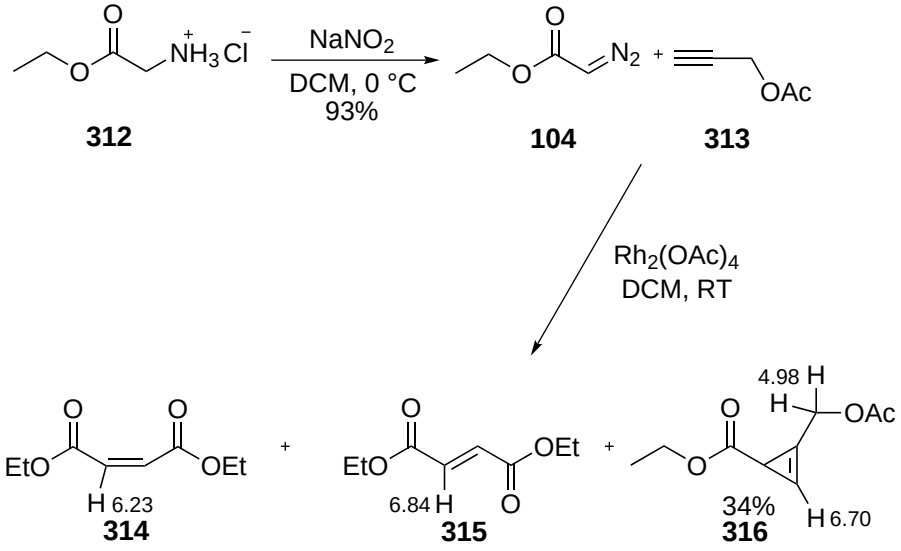
As described in Scheme 4.2 and Scheme 4.27 a trisubstituted cyclopropene with substituents that could be used to form the five membered ring of cordytropolone would be needed. A cyclopropene like **308** could be synthesised through the rhodium catalysed cyclopropanation of ethyl diazoacetate **104** and bromo propargyl acetate **307**. After the Diels-Alder reaction with thiophene-1,1-dioxide **244** to give the cycloheptatriene **309** the esters could be reduced to a diol **310**. The diol could then be cyclysed to form the five membered ether ring, giving the bicyclic cycloheptatriene **311**. **311** could then be converted into cordytropolone **37** through DDQ and acetolysis/hydrolysis (Scheme 4.42).



Scheme 4.42: Proposed synthesis of cordytropolone via Diels-Alder reaction of cyclopropene **308** and thiophene-1,1-dioxide **244**

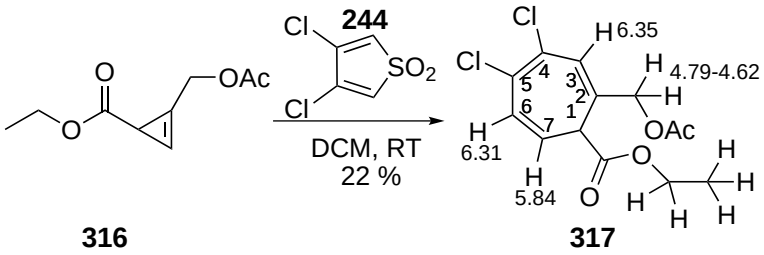
Having previously established that the Diels-Alder reaction between a 1,2-substituted cyclopropene **274** and thiophene-1,1-dioxide **244** was possible (Scheme 4.26) a 1,3-substituted cyclopropene was synthesised in order to model the synthetic plan in Scheme 4.42. Propargyl acetate **313** was chosen as the starting alkyne as this can be easily substituted with a bromine later. Ethyl diazoacetate **104** was synthesised by the diazotisation of ethyl glycine ester hydrochloride **312** using sodium nitrite via the same methods described in Chapter 2.[148] The crude ethyl diazoacetate **104** was condensed under reduced pressure and used immediately by injecting slowly into a solution of propargyl acetate **313** and rhodium acetate in DCM at room temperature (Scheme 4.43). The ^{1}H NMR spectrum of the crude reaction mixture showed several products, however some key signals were indentified. There were three signals in the vinyl region: a singlet at 6.84 ppm, a quartet at 6.70 ppm and a singlet at 6.23 ppm. The two singlets are a result of ethyl ester dimers of ethyl diazoacetate, the lack of splitting in the signal reinforces this. The signal at 6.84 ppm matches with vinyl hydrogen present in diethyl fumarate **315**[209] while the signal at 6.23 ppm matches with diethyl maleate **314**.[210] These to products are consistant with the dimerisation of the metal carbenoid formed from reaction of ethyl diazoacetate **104** with rhodium acetate. The third signal, the quartet at 6.70 ppm is from the hydrogen present

at the 2-position of the cyclopropene. After purification it was confirmed that this was the product and thus the desired cyclopropene **316** had been produced. The signal at 6.70 ppm for 1H was present, indicating the vinyl hydrogen on the cyclopropene. There was a doublet of doublets at 4.98 ppm for 2H, the chemical shift indicates this is likely the hydrogens on the carbon adjacent to the cyclopropene. There was another doublet of doublets at 4.07 ppm for 2H, the chemical shift for this signal is consistant with a CH_2 present on the ethyl chain. There were two signals integrating for 3H each, a singlet at 2.05 ppm consistant with a methyl on the acetate and, a triplet at 1.19 ppm, consistant with a CH_3 on the ethyl chain. The cyclopropene was isolated but in poor yield after column chromatography (34 %, impure). It is probable that the acidic nature of the silica is causing the cyclopropene to decompose.



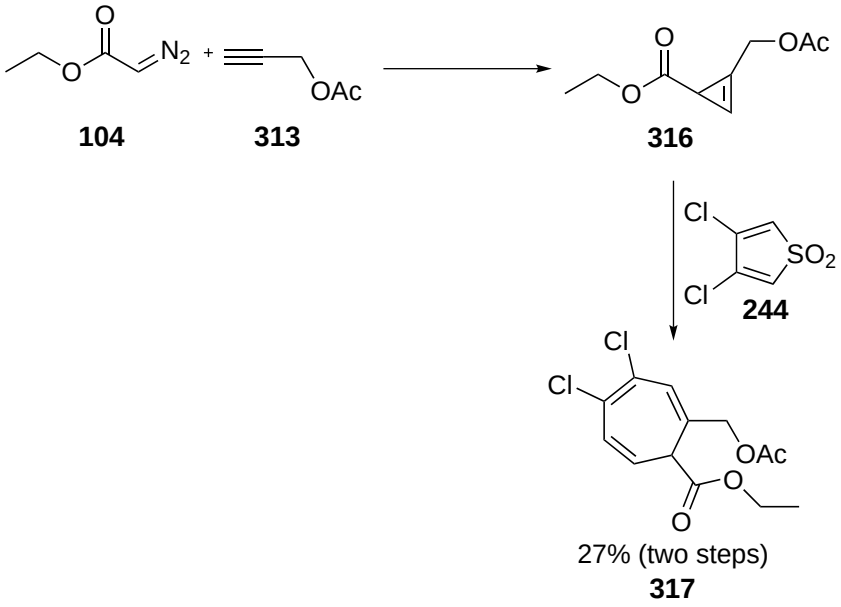
Scheme 4.43: Synthesis of cyclopropene **316** from the rhodium catalysed cyclopropantion of ethyl diazoacetate **104** and propargyl acetate **313**

The cyclopropene **316** was then reacted with 3,4-dichlorothiophene-1,1-dioxide **244** in DCM at room temperature to give cycloheptatriene **317**. The presence of the cycloheptatriene was obvious on the ^{1}H NMR spectrum. The three characteristic vinyl signals were present at 6.35, 6.31 and 5.84 ppm. There were also signals relating to the acetate and the ethyl ester as with the allylic hydrogen of the cycloheptatriene present 3.30 ppm (Scheme 4.44).



Scheme 4.44: Synthesis of cycloheptatriene **317** via Diels-Alder reaction of **316** and **244**

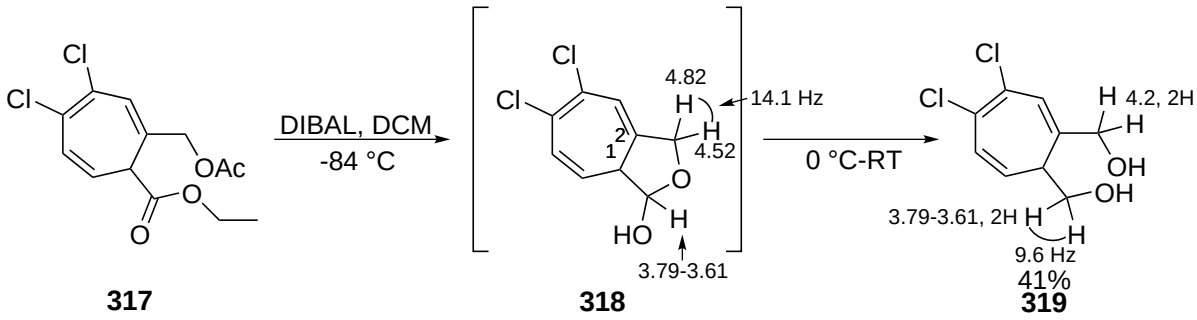
Due to the poor yields resulting from the purification of the cyclopropene **316** it was thought that performing the Diels-Alder reaction in the same reaction flask would garner a better yield. When the addition of diazoacetate **104** to propargyl acetate **313** was complete, the reaction mixture was cooled in an ice bath and thiophene-1,1-dioxide **244** added, and the reaction mixture left to warm to room temperature. The ^{1}H NMR spectrum of the crude material showed only one Diels-Alder adduct was present, **317** which was isolated in 27% yield (two steps) (Scheme 4.45). This indicated that thiophene-1,1-dioxide **244** selectively reacts with cyclopropene **316** over the fumarate **315** and maleate **314** that were present in the reaction mixture. This is likely because the electron withdrawing effects of the carbonyls present on the diethyl esters deactives the molecule towards an inverse demand Diels-Alder reaction.



Scheme 4.45: Performing the reaction in the same reaction flasks gives cycloheptatriene **317** as the sole Diels-Alder adduct

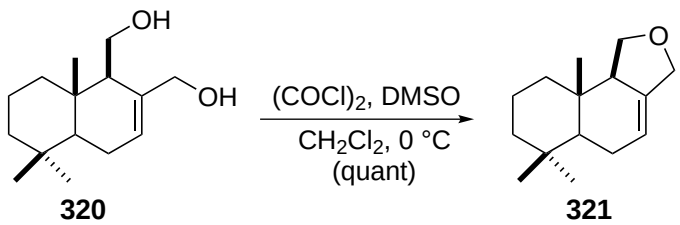
With the cycloheptatriene **317** obtained the next process was to form the furan ring from the esters. The esters were first reduced to the diol **318** using DIBAL. When the cycloheptatriene **317** was dissolved in DCM at 0 °C and DIBAL was added dropwise, the reaction warmed to room temperature and left for 5 hours, the diol **318** was obtained in 41% yield. The signals on the ^{1}H NMR spectrum relating to the acetyl and ethyl ester had dissappeared and there was now a singlet present at 4.20 ppm integrating for 2H this is likely the two hydrogens at the alcohol at the 2-position as there are no adjacent hydrogens at this position. There is a new signal integrating for 2H at 3.79-3.61 ppm as a multiplet. The integation for 2H, multiplicity and slightly lower chemical shift indicate that this is likely the two hydrogens now present at an alcohol at 1-position. When the reduction of **317** with DIBAL was performed at -84 °C and not allowed to warm for an extended period, a new cycloheptatriene was obtained. It was identified as the lactol **318** from the spectral data. The ^{1}H NMR The singlet relating to the hydrogens on the acetyl at the 2-position had split and were now two multiplets integrating for 1H each at 4.78-4.86 and 4.52 ppm. The compound appeared to be a cycloheptatriene that integrageted for a total of 7H, indicating that the compound was possibly an incomplete reduction of **317**. Based on this

information it was concluded that compound was likely the lactol **318** (Scheme 4.46). This was confirmed by the HRMS spectrum (Orbitrap), gave an ion of mass 217.98958 which is consistant with formula $C_9H_8O_2Cl_2$, corresponding to **318**.

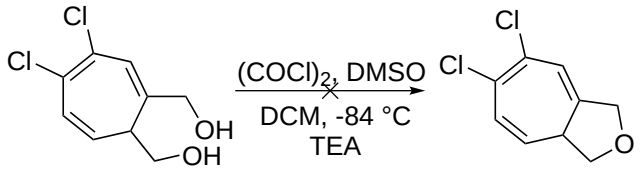


Scheme 4.46: DIBAL reduction of **317** gave lactol **318** and diol **319**

With the diol **319** obtained, the next step was to convert the two alcohols into the 5-membered ether ring. Matsuda *et al.* were able to convert drimendiol **320** into the hydrofuran **321** in quantitative yield via a Swern oxidation (Scheme 4.47).[211] Drimendiol **320** was reacted with a cooled (0 °C) solution of$(COCl)_2$and DMSO in DCM to give hydrofuran **321**. The diol **319** was reacted under Swern conditions, the ^{1}H NMR spectrum of the crude material did not show any cycloheptatriene signals but there were a multitude of new aromatic signals between 7.30-8.15 ppm. There were also several singlets between 9.00-10.05 ppm. As these signals are in the region assoicated with aldehyde formation it indicated that the reaction conditions did not form the cyclic ether ring as expected, rather products from oxidation. The new aromatic signals coupled with the aldehyde signals also indicate that the compound may also be going through the ring contraction as described previously, the spectrum are similar (Scheme 4.48).



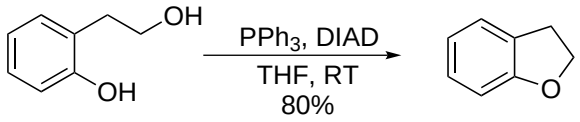
Scheme 4.47: Matsuda's Swern conditions to produce ether **321**



319 **322**

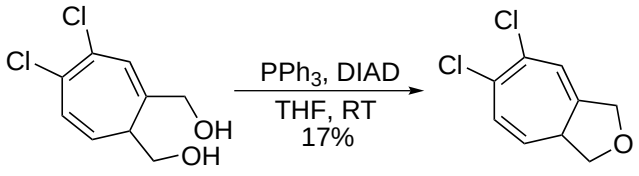
Scheme 4.48: Swern oxidation to produce ether **322** was unsuccesful.

Kuznetsov and Gevorgyan reported a cyclisation of hydroxyphenethyl alcohol **323** into the benzofuran **324** via Mitsunobu conditions (Scheme 4.49).[212]



Scheme 4.49: Cyclisation done by Kuznetsov and Gevorgyan under Mitsunobu conditions.[212]

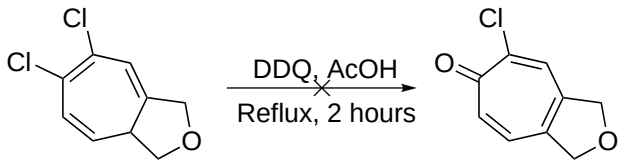
When a solution of the diol **319**, triphenylphosphine and DIAD in THF was stirred at room temperature for 3 hours, the ether **322** was obtained in 17% yield. The new tetrahydrofuran ring had a distinctive ^{1}H NMR spectrum. There was a singlet for 2H relating to the carbon attached to the 2-position but this had shifted slightly to 4.43. The multiplet relating to the hydrogens on the carbon attached to the 1-position had now split and was present as two doublet of doublets for 1H each at 4.08 and 4.22 ppm. The coupling constant of these hydrogens (J = 9.6 Hz) is also consistant with geminal coupling of a tetrahydrofuran ring.[213] The change in chemicals shifts and splitting of these carbons indicated that a reaction had taken place that had affected both alcohols. It was suspected that this was the desired cordytropolone core **322** (Scheme 4.50). The formula of **322** was confirmed by the HRMS spectrum (Orbitrap) which gave an ion of weight 201.99474 which is consistant with formula $C_9H_8OCl_2$.



319 **322**

Scheme 4.50: Cycloheptatriene **319** was converted to **322** using Mitsunobu conditions

Having made the cycloheptatriene **322**, its conversion to the tropone **325** was attempted. As with previous cycloheptatrienes, conversion into the chlorotropone was attempted using DDQ. A solution of ether **322** and, DDQ in AcOH was heated under reflux for 2 hours. Disappointingly the ^{1}H NMR spectrum showed that mostly starting material remained. There were some additional signals forming in the aromatic region but nothing that was able to be resolved. There were also signals appearing at 9.54 and 10.48 ppm indicating that ring contraction may be occuring. Additional heating or DDQ did not improve the reaction and caused decomposition of the compound with less being recovered each time (Scheme 4.51).



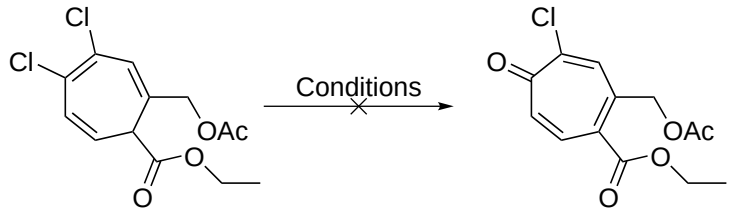
322 **325**

Scheme 4.51: Attempted conversion of ether **322** to chlorotropone **325** was unsuccessful

Due to the small amount of ether **322** avaliable, work on aromatisation of this compound moved to using the ester cycloheptatriene **317** which was avaliable in larger quantities. The conversion of this compound into chlorotropone **326** was attempted using DDQ, however this did not react at all and only starting material was recovered (Entry 1, Table 4.0.4). Due to the lack of reactivity in AcOH under reflux, the reaction was attempted using a sealed tube to gain a higher temperature. DCE was chosen as the solvent as it is aprotic and non acidic and it was thought that acetic acid at such a high temperature may cause

side reactions or decomposition (Entry 2). The cycloheptatriene **317** was dissolved in DCE with DDQ in a sealed tube. The reaction was heated to 130 °C for 3 hours. Once again the reaction mixture only contained starting material. There were some very minor signals that resembled signals previously noted on other unsuccesful aromatisations. Overall, the compound was unreactive even at this temperature. The conversion of cycloheptatriene **317** into a tropolone was also attempted using the ATA mixture as the solvent (Entry 3). Cycloheptatriene **317** was dissolved in the ATA solution with DDQ and heated to 100 °C. After 3 hours ^{1}H NMR spectroscopy of the reaction mixture indicated a large amount of starting material remaining. The reaction was then left under reflux overnight. The ^{1}H NMR spectrum of the crude residue showed no signals relating to the starting materials. There were some minor aromatic signals but none that would indicate a tropolone had formed.

Table 4.0.4: Summary of attempts to convert cycloheptatriene **317** to tropone **326** using DDQ



317 **326**

Entry	Oxidant	Solvent	Time/Temp	Notes	Results
1	DDQ	AcOH	Reflux, 3 hours	-	NR
2	DDQ	DCE	130 °C, 3 hours	Sealed Tube	NR
3	DDQ	ATA/AcOH	Reflux, 2 hours	-	Decomposition

The lack of reactivity of the cycloheptatriene **317** towards hydrogen abstraction by DDQ is likely due to the abstracted hydrogen (H-1) being adjacent to the ethyl ester. Keto-enol tautomerism at this position would cause the hydrogen to become more acidic reducing its reactivity as a hydride (Figure 4.0.5).

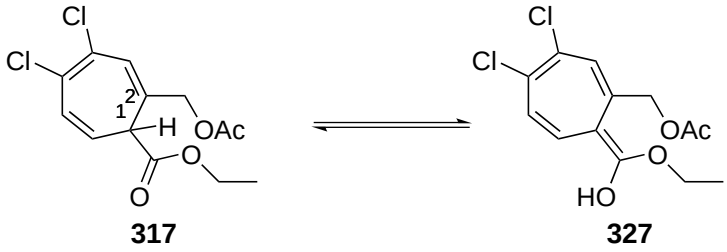
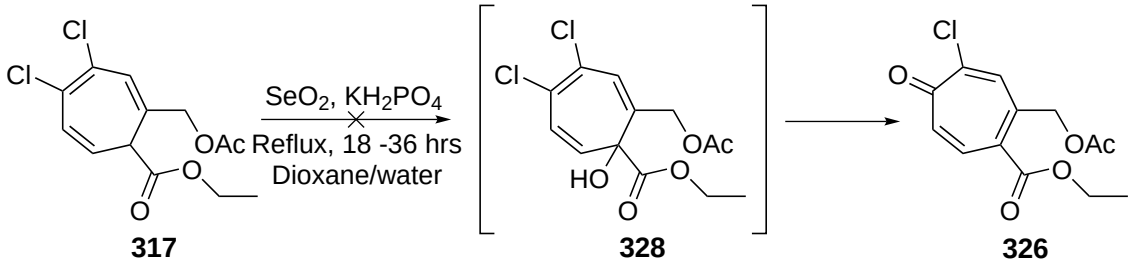


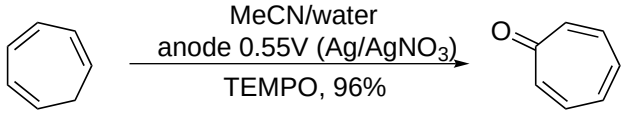
Figure 4.0.5: Keto **317** and enol **327** forms of cycloheptatriene **317** the hydrogen at the 1-position is slightly acidic due to the enol tautomer

An oxidation using selenium dixoide was attempted on the cycloheptatriene **317**. Cyclohepatriene **317** was dissolved in a solution of dioxane and aqueous KH_2PO_4, selenium dioxide was added and the reaction heated under reflux for 36 hours. ^{1}H NMR spectrum of the reaction mixture showed starting material. There were some aromatic signals but none that would indicate the chlorotropone **326**. There were also signals between 9.95-10.15 so it is likely that the aromatic signals are related to aldehyde products. From this information it was determined that the reaction was unsuccessful (Scheme 4.52.



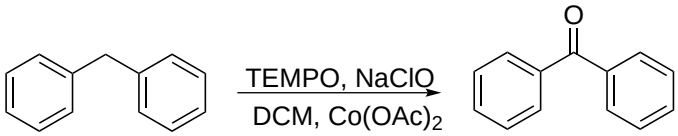
Scheme 4.52: Attempted oxidation by selenium dioxide

Several other oxidation methods were investigated. Breton *et al.*[214] converted a wide range of alkenes into their corresponding alkenone using TEMPO at a controlled electrochemical potential. They were able to successfully convert cycloheptatriene to tropone in a 96% yield (Scheme 4.53). This lead the investigation into reactions involving TEMPO that may be suitable without the use of an electrochemical potential. Jin *et al.*[215]reported a similar reaction where they oxidised diphenylmethane **329** to benzophenone **330** using TEMPO and NaClO with a $Co(OAc)_2$ catalyst (Scheme 4.54).



39 **1**

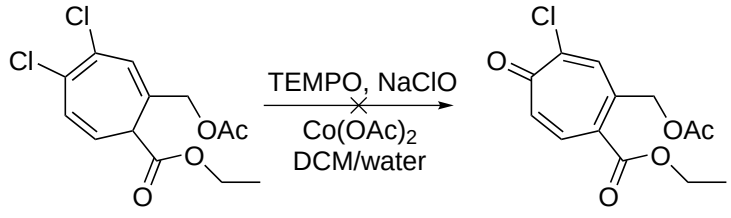
Scheme 4.53: TEMPO oxidation of cycloheptatriene **39** to tropone **1** using an electrochemical potential by Breton *et al.*[214]



329 **330**

Scheme 4.54: TEMPO oxidation using a cobalt co-catalyst by Jin *et al.*[215]

To a cooled (0 °C) solution of cycloheptatriene **317** in DCM, TEMPO was added followed by $Co(OAc)_2$ and NaOCl. The ^1H NMR spectrum of the crude residue showed almost entirely starting material. There were some barely visible aromatic signals as well as some signals around 9.50 ppm and a signal at 10.42 ppm. There was nothing that indicated oxidation to a tropone or tropolone was successful (Scheme 4.55).

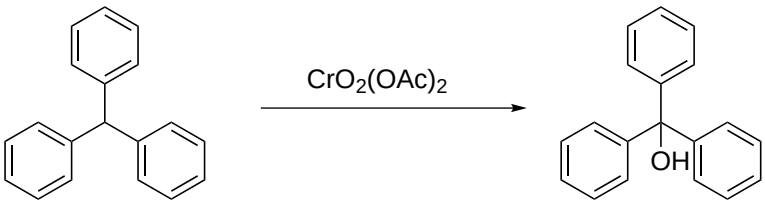


317 **326**

Scheme 4.55: Attempted TEMPO oxidation using sodium hypochlorite and a cobalt co-catalyst

Another oxidation method that was investigated was chromyl acetate. Chromyl acetate has successfully been used to oxidise bicyclic alkanes to alcohols and ketones. It has also been shown oxidise the benzylic position of aromatic compounds and can convert alkenes to epoxides and oxiranes. The Encyclopedia of Reagents for Organic Synthesis reported

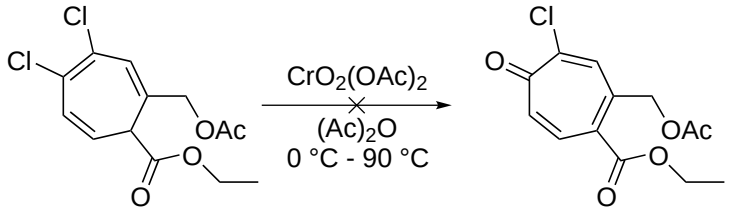
unpublished work by Freeman *et al*. where triphenylmethane **331** was converted to triphenylcarbinol **332** using chromyl acetate.\cite{doi:10.1002/9780470842898.rc176.pub2} As triphenylmethane **331** can also form a cation similar to tropones and tropolones it was thought this method may have merit.



331 **332**

Scheme 4.56: Oxidation of **331** to **332** reported in EROS based on unpublished work by Freeman *et al*.

Chromyl acetate was prepared by reaction of chromium trioxide with excess acetic acid. This was added dropwise to a cooled solution of cycloheptatriene **317** dissolved in acetic anhydride. The reaction was allowed to warm to RT then left to react overnight. The ^{1}H NMR spectrum of the crude material showed mostly starting material once again. The residue was redissolved in acetic anhydride and additional chromyl acetate was prepared and added. The reaction was heated to 90 °C overnight (Scheme 4.57). The ^{1}H NMR spectrum now showed the starting material had been consumed but there were no signals present that would indicate a tropone or topolone. The same signals that was present 10.42 ppm in the reaction with TEMPO was also present in the reaction with chromyl acetate. The structure of the compound relating to this signal was unable to be resolved.

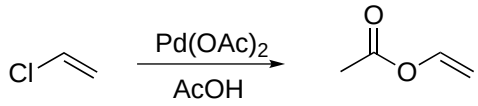


317 **326**

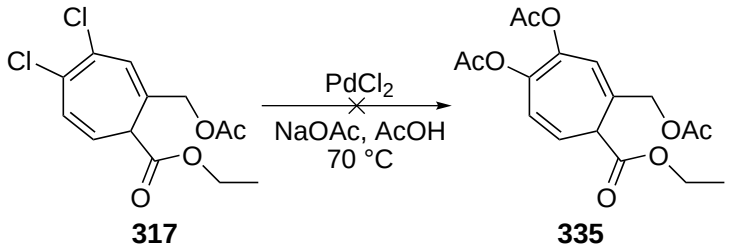
Scheme 4.57: Attempted oxidation using chromyl acetate

Direct oxidation of **317** appeared to be not possible so other synthetic methods were inves-

tigated. A cross-coupling using the chlorines on the cycloheptatriene ring may circumvent the issues with oxidation. One such method by Kohll and Helden, was the palladium (II) catalysed cross-coupling of vinyl chloride **333** with acetic acid to give vinyl acetate **334**.[216] Vinyl chloride was flushed into a vessel containing sodium acetate in AcOH, saturating the AcOH solution. The palladium (II) chloride catalyst was then added. After the reaction was stopped, vinyl acetate was observed in 94% yield. Cycloheptatriene **317** was dissolved in acetic acid with sodium acetate. Palladium (II) chloride was added and the reaction heated to 70 °C and left overnight. The reaction was unsuccessful and only starting material was recovered (Scheme 4.59).

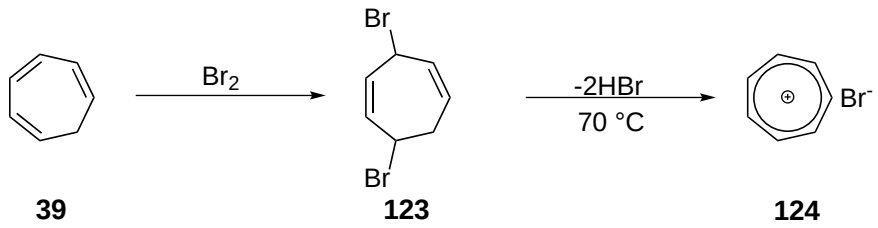


Scheme 4.58: Kohll and Helden[216] were able to acetylate vinyl chloride using a palladium catalyst



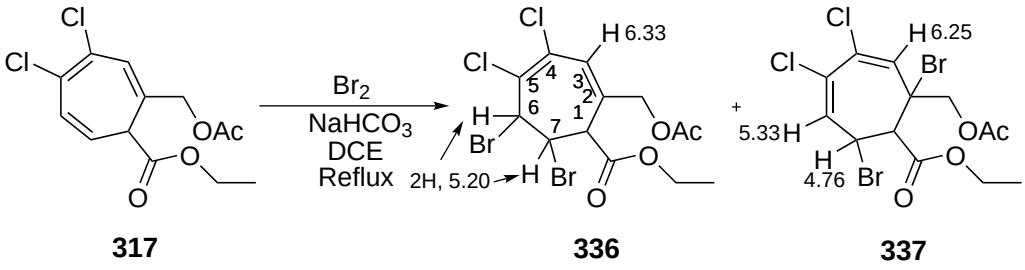
Scheme 4.59: Attempted coupling using palladium (II) chloride

Doering and Knox[134,135] were one of the first to investigate the formation of the tropylium ion. Their method involved brominating cycloheptatriene **39** to form the dibromide **123** and then eliminating HBr through heating to form the tropylium bromide salt **124** (Scheme 4.60). If this could be done on **317** it could form the cation so that it could be substituted.



Scheme 4.60: Deoring and Knox[134] formed tropylium bromide via elimination of HBr

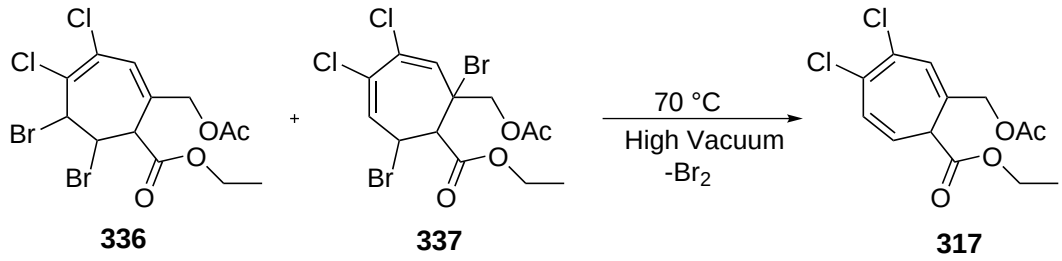
Cycloheptatriene **317** was dissolved in DCE and oven dried solid sodium bicarbonate was added. Bromine was then added until the colour persisted and the reaction was heated under reflux for 1.5 hours. The ^{1}H NMR spectrum indicated that there were two products present. The signals for each product were indentified using ^{1}H COSY NMR spectroscopy. One compound had a signal at 6.33 ppm and the other at 6.25 ppm, these are consistant with vinyl hydrogens present on the cycloheptatriene, the lower number of total vinyl signals is consistant with a brominated compound. The other signals on the 7-membered ring were determined to be between 4.73-5.36 ppm, from correlations on the ^{1}H COSY spectrum. The two structures were tentatively assigned as two cycloheptatrienes brominated at different positions; 5,6-dibromocycloheptatriene **336** and 1,6-dibromocycloheptatriene **337** (Scheme 4.61). The small amount recovered indicates that the product is likely unstable on silica gel.



Scheme 4.61: Bromination of **317** with solid sodium bicarbonate was confirmed to give **336** and **337**

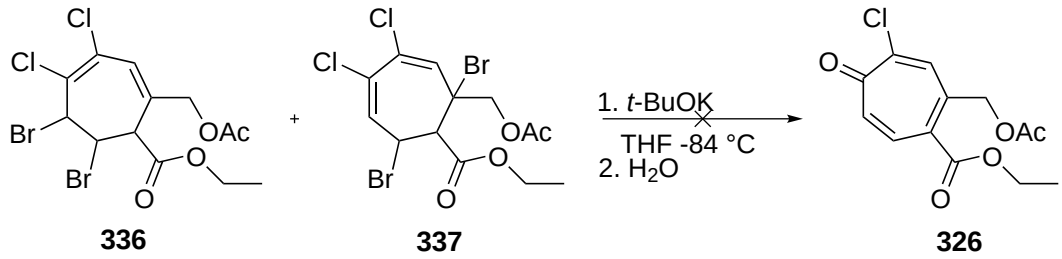
Following the conditions of Doering and Knox (Scheme 4.60) the mixture of compounds **336** and **337** was then heated to 70 °C under vaccuum overnight in order to form the tropylium salt. The vaccuum should remove any HBr formed to promote formation of

the tropylium bromide salt. Water was then added in order to form the tropone. The ^{1}H NMR spectrum of this crude residue showed that the compound had reverted back to cycloheptatriene **317** (Scheme 4.62). This also indicated that compound was likely eliminating bromine to return to the starting material and not eliminating HBr to form the tropylium ion.



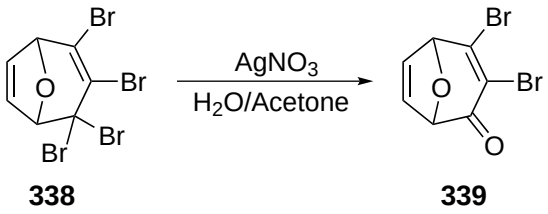
Scheme 4.62: Attempting to form the tropylium bromide **124** in the same way as Doering and Knox (Scheme 4.60) resulted in debromination back to give **317**

A base elimination using a strong base was also attempted, the mixture of **336** and **337** was dissolved in dry THF at -84 °C and *t*-BuOK was added. The reaction was stirred for 1.5 hrs followed by the addition of water. The ^{1}H NMR spectrum of the crude material showed that there had been some consumption of one of the dibromo products and new signals had formed. There was an obvious signal at 10.46 ppm which indicated that the product was likely going through a ring contraction to the aldehyde. The residue was redissolved in THF at 0 °C and additional *t*-BuOK was added. After quenching, the ^{1}H NMR spectrum of the residue showed that the brominated compounds had been completely consumed. The signal at 10.46 ppm was still present. It is likely that the compound is going through a ring contraction which is consistant with previously reported literature results whereby a ring contraction occured in basic media (Figure 4.0.4).

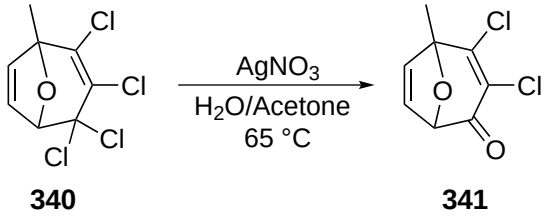


Scheme 4.63: Attempting to eliminate HBr using *t*-BuOK

If an oxygen could be introduced to the cycloheptatriene ring of **317** or on the dibromo variants **336** and **337** the conversion to the chlorotropone **326** would be much more favoured. There are numerous cases of tropolone formation on a seven membered ring with an oxygen already present. Oblak *et al.*[217] were able to use a Diels-Alder reaction to form a cycloheptatdiene with a geminal dibromide **338**. The geminal dibromide was then reacted with silver nitrate to form ketone **339** (Scheme 4.64). The was also used in patent by Jeanmart *et al.*[218] on a cycloheptatdiene with a geminal dichloride **340** (Scheme 4.65.



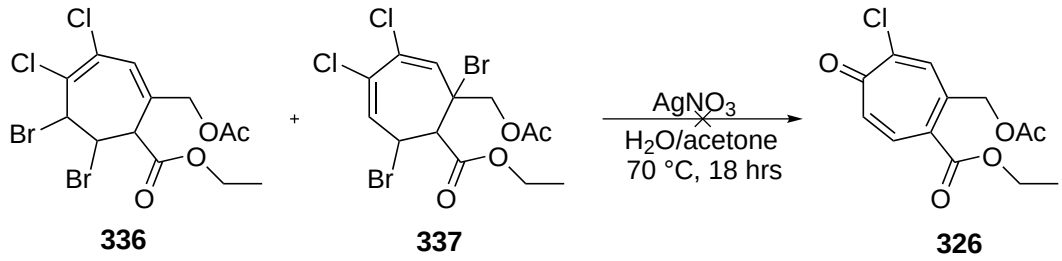
Scheme 4.64: Oblak *et al.*[217] were able to form a ketone from geminal dibromide using silver nitrate



Scheme 4.65: A patent by Jeanmart *et al.*[218] shows the geminal dichloride **340** was converted into **341** using silver nitrate

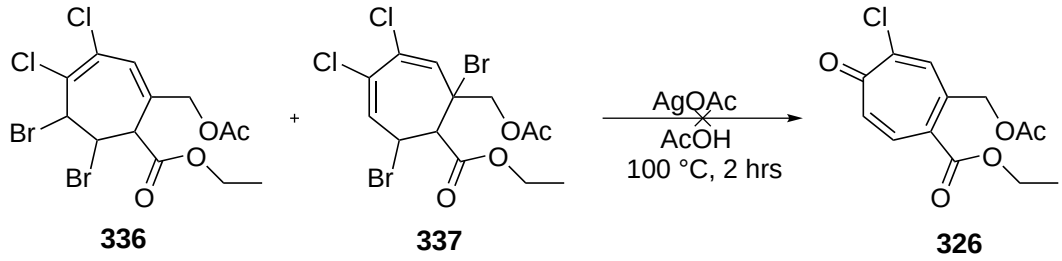
As the dibromo compounds **336** and **337** decomposed during purification they were used as a crude mixture for subsequent reactions. The mixture was dissolved in 1:1 water/acetone.

Silver nitrate was added and the reaction heated to 70 °C overnight. The ^{1}H NMR spectrum of the crude material showed the starting materials had been consumed and there were no signals that would indicate a tropolone had been formed. Once again there was a siginal present in the aldehyde region, this time at 10.51 ppm. Performing the reaction in acetonitrile/water was also unsuccessful.



Scheme 4.66: Attempted de-halogenation using silver nitrate

As an alternative to silver nitrate, a similar reaction was attempted using silver acetate. The cycloheptatriene mixture of **336** and **337** was dissolved in AcOH. Silver acetate was added, and the reaction heated to 100 °C for 2 hours. The ^{1}H NMR spectrum of the crude residue looked promising despite the several signals in the 10.30-10.70 ppm region. There were signals in the aromatic region that integrated in a 1:1:1 ratio possibly indicating a tropone. Purification was undertaken by column chromatography. None of the fractions isolated from the purification indicated a tropone. The reaction was also attempted in a mixture of water\acetone 1:3, producing a similar product to that of the reaction with silver nitrate. There were no signals indicating a tropone and there were several signals in the aldehyde region between 10.40-10.55 ppm.

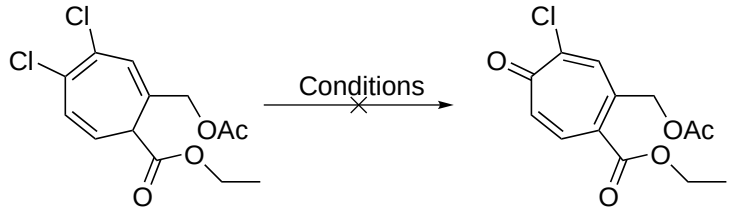


Scheme 4.67: Dehalogenation using silver acetate

A summary of methods attempted on cycloheptatriene **317** are collated in Table 4.0.5.

Attempts to oxidise **317** using standard reagents (entries 4-7) resulted in no reactivity or mixtures with indications of an aldehyde. Attempts to use DDQ (entries 1-3), which had been successful in other systems, resulted in complex mixtures. It is likely that the substitutents present on the seven-membred ring are sufficiently electron withdrawing to deactivate the compound towards reaction. Cycloheptatriene **317** was also brominated (Scheme 4.61) and there were several attempts made to form the tropone by elimination of HBr (Table 4.0.6).

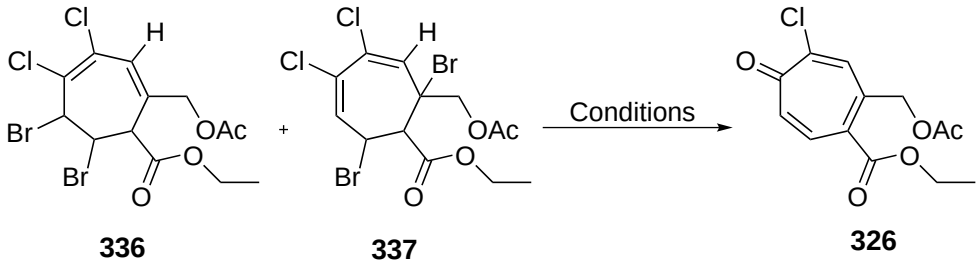
Table 4.0.5: Attempts at converting cycloheptatriene **317** into chlorotropone **326**



317 **326**

Entry	Reagents	Solvent	Conditions	Scheme
1	DDQ	AcOH	Reflux, 3 hrs	Table 4.0.4
2	DDQ	DCE	130 °C, 3 hrs	Table 4.0.4
3	DDQ	ATA/AcOH	100 °C, 3 hrs	Table 4.0.4
4	SeO_2 KH_2PO_4	Dioxane/H_2O	Reflux, 24 hrs	Scheme 4.52
5	TEMPO NaClO $Co(OAc)_2$	DCM/H_2O	RT 3 hrs	Scheme 4.55
6	$CrO_2(OAc)_2$	$(Ac)_2O$	0-90 °C, 18 hrs	Scheme 4.57
7	$PdCl_2$ NaOAc	AcOH	70 °C, 18 hrs	Scheme 4.59

Table 4.0.6: Attempts at eliminating dibromo cycloheptatrienes **336** and **337** into chlorotropone **326**



336 **337** **326**

Entry	Reagents	Solvent	Conditions	Scheme
1	Na_2CO_3	DCE	Reflux, 1.5 hrs	Scheme 4.61
2	High Vacuum	None	70 °C 18 hrs	Scheme 4.62
3	t-BuOK	THF	-84 °C-RT 1.5 hrs	Scheme 4.63
4	$AgNO_3$	H_2O/Acetone	70 °C, 18 hrs	Scheme 4.66
5	AgOAc	AcOH	100 °C, 2 hrs	Scheme 4.67

In summary, a new approach to tropolones has been developed. 3,4-dichlorothiophene-1,1-dioxide **244** was succesfully used as a reagent in Diel-Alder reactions with various subtitutued cyclopropenes to produce functionalised cycloheptatrienes (Figure 4.0.6). Through the formation of the tropylium ion via oxidation using DDQ, these cycloheptatrienes were able to be substituted via nucleophillic aromatic substitution and formed into chlorotropones and tropolones (Figure 4.0.6). However oxidation was not suitable for all subtrates. Several substituted cycloheptatrienes that were prepared could not be converted into their corresponding chlorotropone (Figure 4.0.7). All of these compounds have allylic hydrogens which are likely to compete in oxidation reactions.

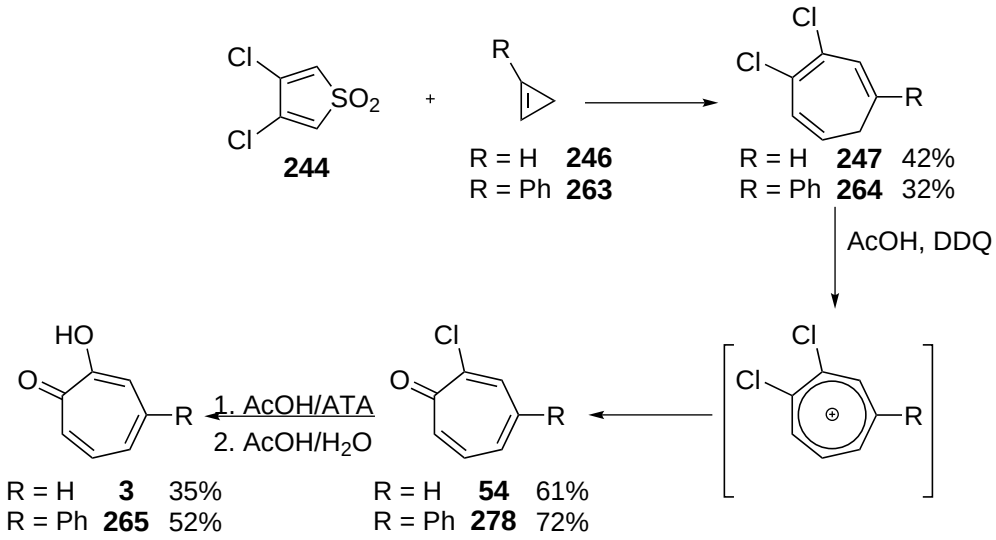


Figure 4.0.6: A new approach to tropolones has been developed invloving a Diels-Alder reaction and substitution to the tropylium ion

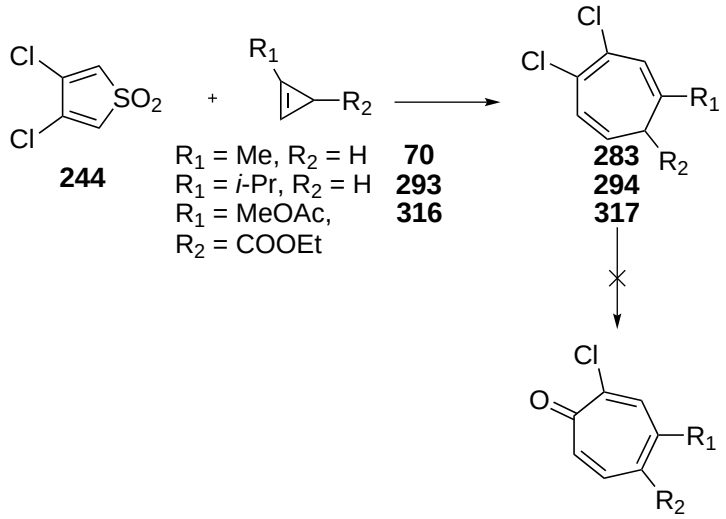
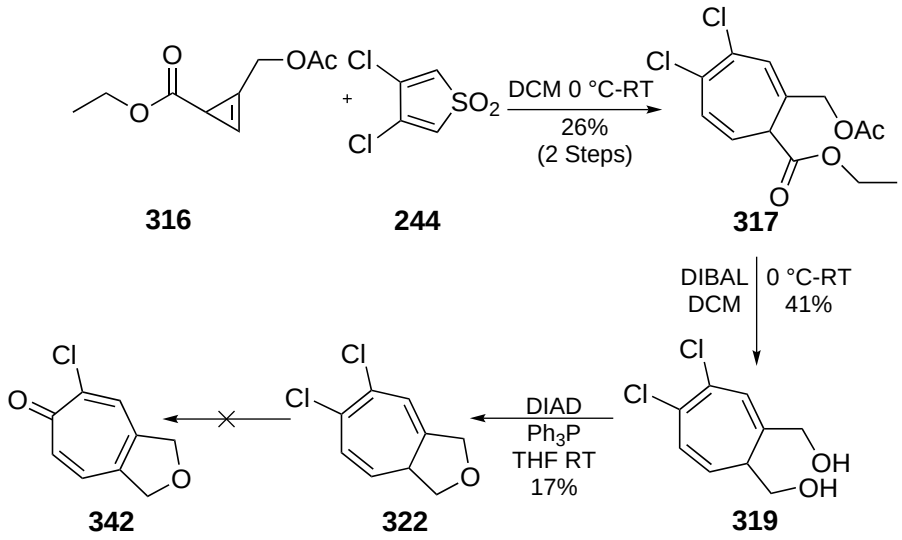


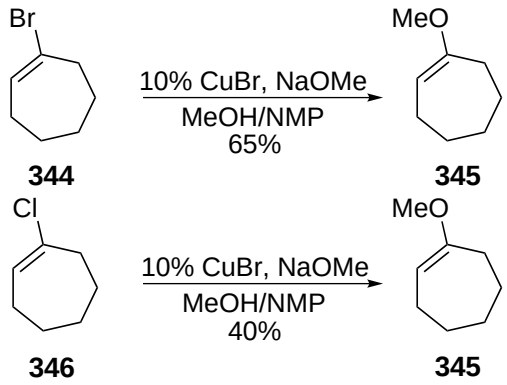
Figure 4.0.7: The formation of tropolones via oxidation does not work in all cases

Using this new approach towards the synthesis of cordytropolone **37**, cyclopropene **316** was synthesised and successfully underwent a Diels-Alder reaction with 3,4-dichlorothiophene-1,1-dioxide **244** to give cycloheptatriene **317**. Cycloheptatriene **317** was reduced to the diol **319**. Diol **319** was then converted to the bicyclic cycloheptatriene **322** mirroring the seven and five-membered ring system of cordytropolone (Scheme 4.68). Unfortunately, cycloheptatriene **322** could not be converted to the corresponding tropolone **343**.



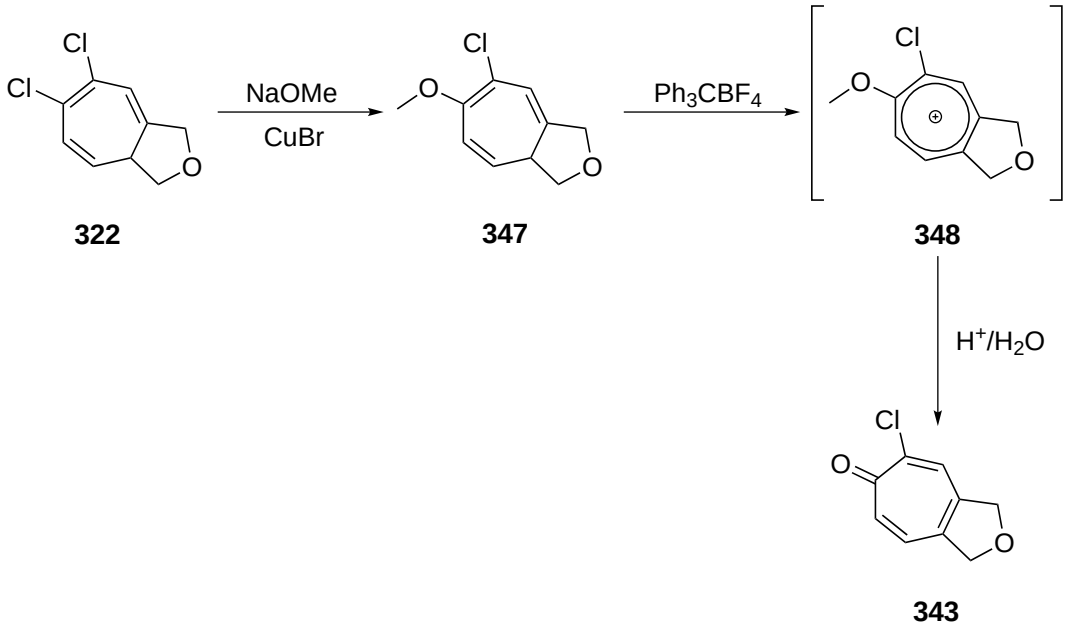
Scheme 4.68: A bicyclic cycloheptatriene was able to be synthesised but not able to be converted to the corresponding tropolone

Future research into the synthesis of cordytropolone could utilise one of the halogens present on the 7-membered in a cross coupling reaction to introduce an oxygen onto the 7-membered ring. This is a similar approach to the cross coupling reaction attempted in Scheme 4.59 using a Pd catalyst. Reasearch in Chapter 3 (Scheme 3.19) indicated that if an oxygen substituent could be introduced to the cycloheptatriene ring on cycloheptatriene **317** or **322** the conversion to the chlorotropone would be much more favoured . Keegstra developed a reaction whereby vinyl halides were converted to vinyl methoxides using sodium methoxide and a copper catalyst.[219] Keegstra was able to convert 1-bromocycloheptene **344** and 1-chlorocycloheptene **345** to 1-methoxycycloheptene **346** in 65% and 40% yield respectively (Scheme 4.69). A similar reaction also using copper catalysis was also reported by Buchwald *et al.*[220]



Scheme 4.69: Formation of vinyl methoxide via vinyl halogens by Keegstra[219]

The reaction by Keegstra could be used to introduce an oxygen to the 7-membered ring of **322** which would make the conversion to tropolone able to be completed under much milder conditions. In Chapter 3, cycloheptatrienes with a methoxy substituent were easily converted to the corresponding tropolones using triphenylmethyl salts (Scheme 3.19). Cycloheptatriene **322** could be converted into dimethoxycycloheptatriene **347** which could then form tropolone **343** via the tropylium ion (Scheme 4.70).

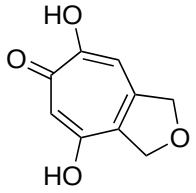


Scheme 4.70: If an oxygen could be introduced to the 7-membered ring the conversion to chlorotropone **343** should be much more favourable

Chapter 5

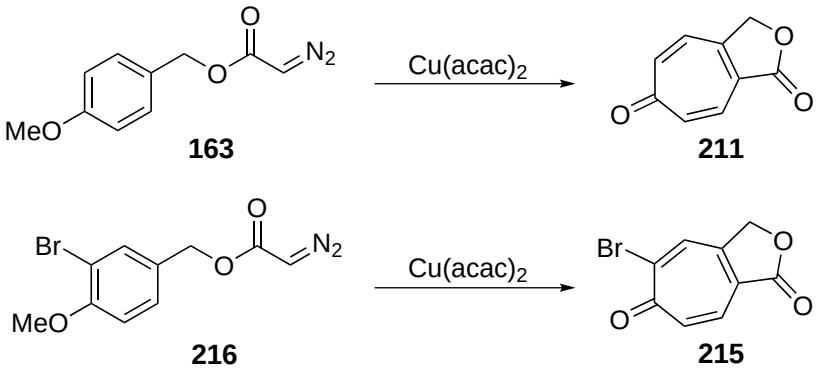
General Conclusions

The aim of this project was the first total synthesis of the naturally occuring, bicyclic tropolone, cordytropolone **37** (Figure 5.0.1). Several methods towards this goal were investigated. The Buchner ring expansion was one such method investigated. The diazoesters, **163** and **216** were synthesised. Facilitated by a $Cu(acac)_2$ catalyst, the diazoesters underwent a Buchner ring expansion followed by oxidation using the triphenylmethyl cation to give tropolones **211** and **215** in modest yield. These tropones contain the same bicyclic framework as cordytropolone **37**.



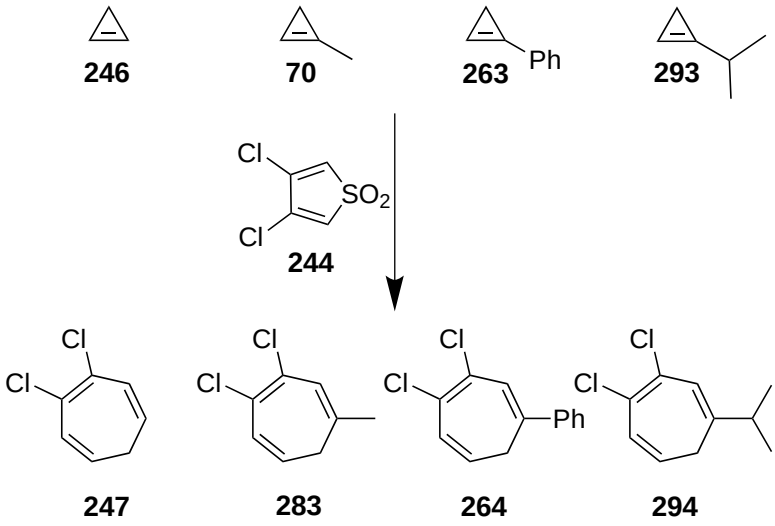
37

Figure 5.0.1: Cordytropolone



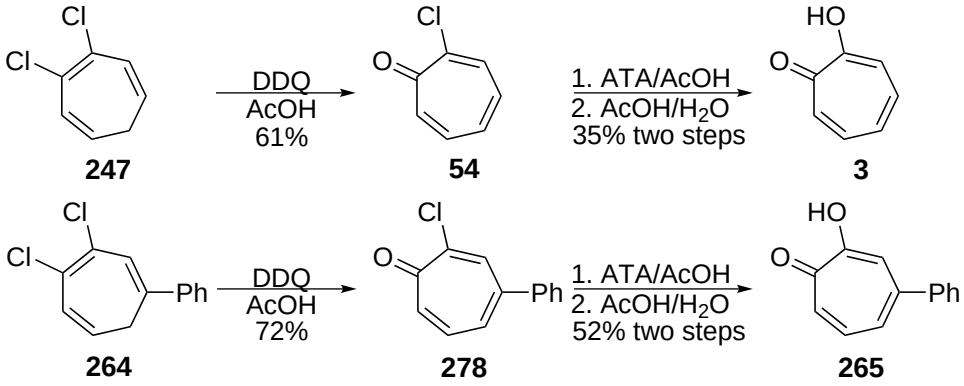
Scheme 5.1: Intramolecular Buchner ring expansion, tropolones **211** and **215** were synthesised

In the search to find an alternative method to synthesise cordytropolone **37**, a versatile method to prepare substituted cycloheptatrienes and tropolones was developed. By reacting a cyclopropene, such as 1-methylcyclopropene **70** with 3,4-dichlorothiophene-1,1-dioxide **244**, 1-methyl-3,4-dichlorocycloheptatriene **283** was formed through a Diels-Alder reaction followed by a cheleotropic elimination of sulfur dioxide. This method was expanded to produce several different cycloheptatrienes including 3,4-dichlorocycloheptatriene **247**, 1-phenyl-3,4-dichlorocycloheptatriene **264** and 1-isopropyl-3,4-dichlorocycloheptatriene **294** (Scheme 5.2).



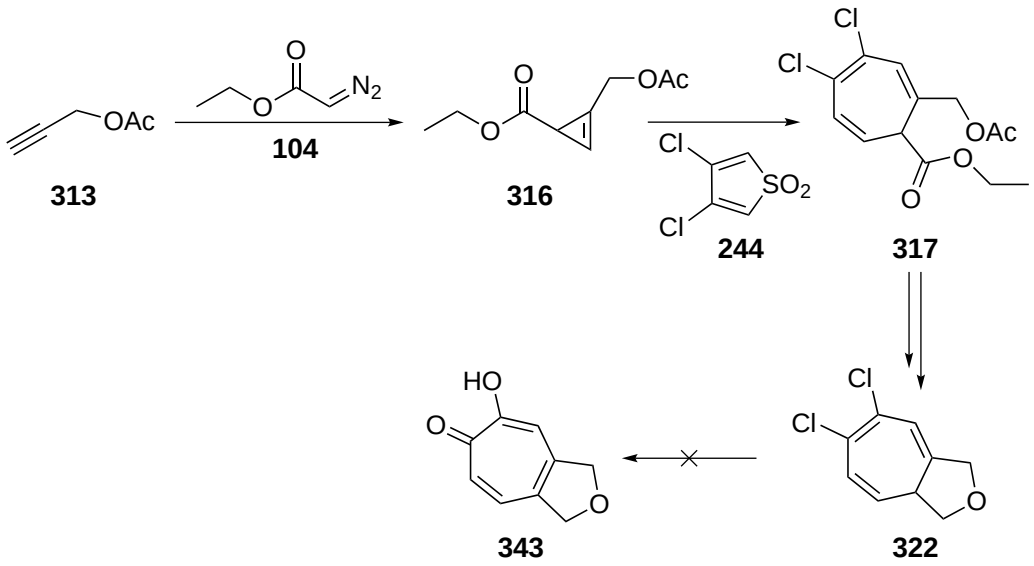
Scheme 5.2: Synthesis of cycloheptatrienes by the Diels-Alder reaction between 3,4-dichlorothiophene-1,1-dioxide **244** and substituted cyclopropenes

Some of these cycloheptatrienes could be converted to 2-chlorotropones and tropolones by oxidising the seven-membered ring to a tropylium ion. Of all the methods tested, PCl_5, *o*-chloranil and DDQ gave 2-chlorotropone **54** with DDQ giving the best results. Chlorotropones **54** and **278** were then substituted with acetates and hydrolysed to give tropolones **3** and **265** (Scheme 5.3). However, compounds that contain an allylic hydrogen had competing reactions that lead to many undesired side reactions.



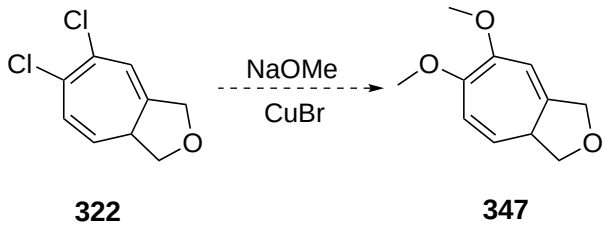
Scheme 5.3: Cycloheptatrienes **247** and **264** converted into tropolone **3** and phenyl-tropolone **265**

The bicyclic framework of cordytropolone was prepared using the cycloheptatriene chemistry developed earlier. The cyclopropene **316** was synthesised by the cyclopropanation of propargyl acetate **313** and ethyl diazoacetate **104** catalysed by rhodium acetate. The cyclopropene **316** was then reacted with 3,4-dichlorothiophene-1,1-dioxide **244** to give cycloheptatriene **317** in modest yield. The cycloheptatriene was converted to the bicyclic cycloheptatriene **322**. However, despite numerous efforts, cycloheptatriene **322** could not be converted to the corresponding tropolone **343** (Scheme 5.4). Again, likely due to the apparent limitation of an allylic hydrogen present in the molecule.



Scheme 5.4: Bicyclic cycloheptatriene **322** was synthesised but could not be converted to the tropolone **343**

To conclude, the Diels-Alder reaction of cyclopropenes with 3,4-dichlorothiophene-1,1-dioxide is a versatile method for the development of substituted cycloheptatrienes, including cycloheptatrienes with a similar bicyclic framework to cordytropolone. Two of the cycloheptatrienes developed by this method were converted into tropolones. The allylic hydrogens present on the other cyclohpetatrienes appears to be hindering conversion in the other cases. Reasearch in Chapter 3 of this study indicated that the conversion of cycloheptatrienes into tropolones is much more favoured if there is an oxygen present on the seven-membered ring, possibly overcoming the issues with allylic carbon. Future work on this subject would involve attempts to introduce an oxygen to the seven-membered ring for this reason. A reaction described in Chapter 4 by Keegstra (Scheme 4.69) could be suitable for introducing an oxygen using a copper promoted reaction (Scheme 5.5).



Scheme 5.5: Possible reaction to introduce an oxygen based on work by Keegstra[219]

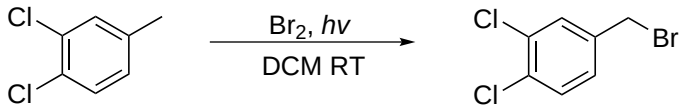
Chapter 6

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 120ºC 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}H, 400 MHz; ^{13}C, 101 MHz). Chemical shifts (δ) are expressed in ppm with reference to the solvent resonances of chloroform-*d* (^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm) and benzene-*d6* (^{1}H, 7.16 ppm; ^{13}C, 128.06 ppm). HRMS spectra were recorded at the School of Science, Edith Cowan University, Joondalup WA, using a Q Exactive™ Focus Hybrid Quadrupole-Orbitrap™ Mass Spectrometer (Thermo Fisher Scientific Corporation, US). Analytes ionisation was achieved using a heated electrospray ionisation source (HESI) operated in negative (-eV) mode. Samples were introduced into the HESI using a syringe pump operated at a flow rate of 5 µl min^{-1}. The Q Exactive mass spectrometer was operated in full-scan mode from 70–1000 m/z followed by isolation and full MS2 fragmentation of the parent compound in the HDC cell at variable collision energy. 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 cm^{-1}. 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. TLC was completed on Merck aluminium backed silica gel 60 F254 sheets and visualised by using short-wave UV light (λ = 254 nm). The solvents tetrahydrofuran, dichloromethane, diethyl ether and acetonitrile are saturated with nitrogen and dried over activated alumina columns, *N*,*N*-dimethylformamide is saturated with nitrogen and dried over (5Å) molecular sieve columns (Innovative Technology PS-MD-5). Petroleum spirits 40-60 refers to the fraction of alkanes that boils between 40- 60°C. $Cu(acac)_2$was prepared similar to the procedure by Shahid *et al.*[221] $Rh_2(OAc)_4$was prepared according to the procedure by Wang *et al.*[222]

4-(bromomethyl)-1,2-dichlorobenzene 142

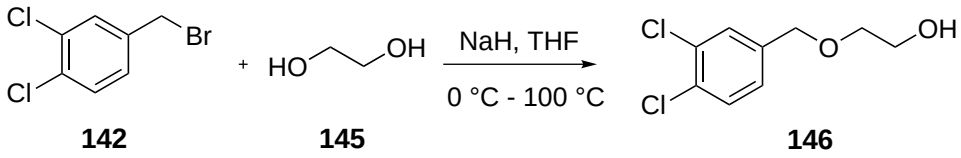


141 **142**

3,4-dichlorotoluene **141** (16.1 g, 100 mmol) was dissolved in DCM (100 mL) and heated under reflux using a tungsten lamp. Br_2 (5.0 ml, 98 mmol) was added dropwise to the reaction mixture at a rate such the reaction mixture did not become too dark in colour. After addition had completed the reaction was left for an additional 30 minutes under the tungsten lamp. The lamp was then removed and the mixture was stirred at RT for an additional hour. The solution was washed with water (2x 100 mL) then brine (1x 100 mL). The organic layer was dried, filtered and concentrated under reduced pressure to afford the crude residue as a yellow oil. The crude residue was purified by flash chromatography (eluent: petroleum spirits 40-60) to obtain 4-(bromomethyl)-1,2-dichlorobenzene **142** (22.02 g, 94% yield) as a pale yellow oil .

Characterisation data matches literature.[223]

2-((3,4-dichlorobenzyl)oxy)ethanol



142 **145** **146**

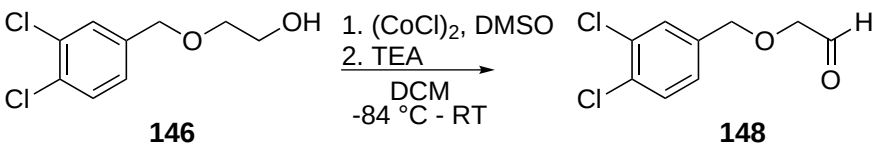
Ethylene glycol **145** (5.2 g, 84 mmol) was dried by azeotropic removal of water with toluene and then cooled to 0 °C. Sodium hydride (60%, 408 mg, 10 mmol) was added in small portions over 30 minutes. This was then left to react for 1 hour before being taken out of the ice bath and left until the solution was clear. Dichlorobenzyl bromide **142** (1.36 g, 8 mmol) was added dropwise and the reaction left at RT for 1 hour. The reaction was then heated to 100 °C overnight. After cooling, the mixture was diluted with water (40 mL) and extracted with DCM (4x 40 mL). The organic extracts were washed with water (3x 40 mL) and brine (1x 50 ml). The organic layer was dried using sodium sulfate, filtered and concentrated under reduced pressure to obtain crude residue as a dark orange oil. The residue was purified by flash chromatography (eluent: EtOAc/Petroleum Spirits 1:1) to obtain 2-((3,4-dichlorobenzyl)oxy)ethanol **146** (632 mg, 37%) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.13 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.46 (s, 2H), 3.76 – 3.69 (m, 2H), 3.59 – 3.52 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 138.4 (C), 132.5 (C), 131.6 (C), 130.4 (CH), 129.5 (CH), 126.8 (CH), 71.8 (CH_2), 71.8 (CH_2), 61.7 (CH_2).

FTIR-ATR(cm^{-1}): 3400 (OH)

2-((3,4-dichlorobenzyl)oxy)acetaldehyde 148



146 **148**

Oxalyl chloride (0.4 mL) was dissolved in dry DCM (6 mL) at -83 °C. Dry DMSO (0.8 mL) was dissolved in dry DCM (2 mL) and added to the reaction mixture which was

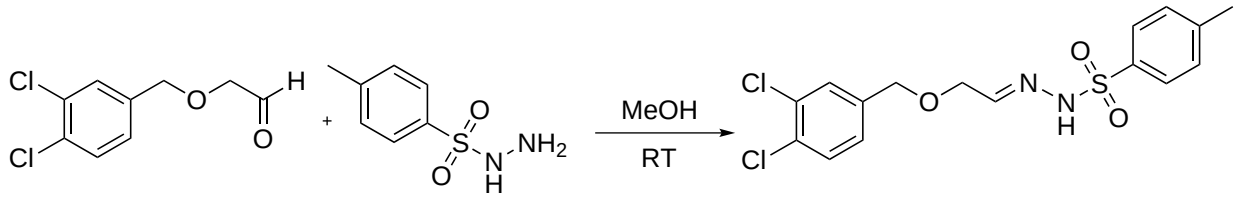
left to react for 15 minutes. 2-((3,4-dichlorobenzyl)oxy)ethanol **146** (498 mg, 2.3 mmol) was dissolved in dry DCM (3 mL) and added before being left to react for 30 minutes. Triethylamine (2 mL) was added to quench and the reaction allowed to warm to RT. The mixture was diluted with petroleum spirits (20 mL) and ether (20 mL) then filtered through magnesium sulfate. The combined filtrates were then concentrated under reduced pressure. Excess DMSO was removed by nitrogen stream. The crude residue was purified by flash chromatography (eluent: EtOAc/Petroleum spirits 1:3) to obtain 2-((3,4-dichlorobenzyl)oxy)acetaldehyde **148** (152 mg, 30%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.20 – 7.15 (m, 1H), 4.55 (s, 2H), 4.12 (s, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.6 (C), 137.4 (C), 132.7 (C), 132.1 (C), 130.6 (CH), 129.6 (CH), 127.0 (CH), 75.6 (CH_2), 72.2 (CH_2).

FTIR-ATR(cm^{-1}): 1736 (C=O)

(*E*/*Z*)-*N*'-(2-((3,4-dichlorobenzyl)oxy)ethylidene)-4-methylbenzenesulfonohydrazide 144



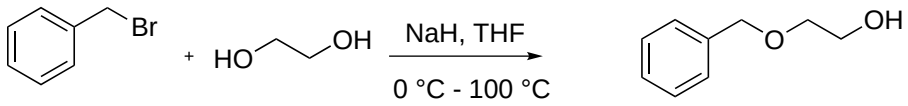
148 **150** **144**

A solution of 2-((3,4-dichlorobenzyl)oxy)acetaldehyde **148** (122 mg, 0.56 mmol) in MeOH (1 mL) was added was added dropwise to a suspension of toluene sulfonyl hydrazide (112 mg, 0.60 mmol) **150**. Once addition was complete the reaction was stirred vigourously at RT for 4 hours. The solvent was removed and the reaction purified by flash chromatography (eluent: EtOAc:DCM 5:95) to obtain (*E*/*Z*)-*N*'-(2-((3,4-dichlorobenzyl)oxy)ethylidene)-4-methylbenzenesulfonohydrazide **144** as yellow crystals (10 mg, 5%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.80 (m, 2H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.20 – 7.15 (m, 1H), 7.09 – 7.05 (m, 1H), 4.35 (s, 2H), 4.09 (d, *J* = 5.1

Hz, 2H), 2.42 (s, 3H).

2-(benzyloxy)ethanol 147

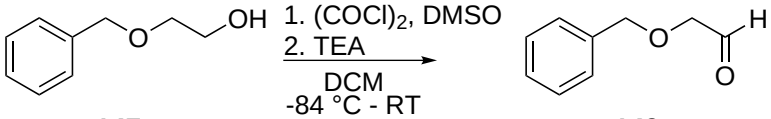


140 **145** **147**

Ethylene glycol **145** (19.5 g, 315 mmol) was dried by azeotropic removal of water with toluene and then cooled to 0 °C. Sodium hydride (60%, 1.34 g, 33 mmol) was added in small portions over 2 hours. Dichlorobenzyl bromide **140** (10.0 g, 18 mmol) was added dropwise and the reaction left at RT for 30 minutes. The reaction was then heated to 100 °C overnight. After cooling, the mixture was diluted with water (40 mL) and extracted with DCM (4x 40 mL). The organic extracts were washed with water (3x 40 mL) and brine (1x 50 ml). The organic layer was dried using sodium sulfate, filtered and concentrated under reduced pressure to obtain crude residue as a dark orange oil. The residue was purified by flash chromatography (eluent: EtOAc/Petroleum Spirits 1:1) to obtain 2-(benzyloxy)ethanol **147** (2.717 g, 54%) as a yellow oil.

Characterisation data matches literature.[224]

Benzyloxy acetaldehyde 149



147 **149**

Dry DMSO (1 mL) in dry DCM (5 mL) was added to a solution of oxalyl chloride (0.8 mL) was dissolved in dry DCM (10 mL) at -83 °C. After 15 minutes, a solution of 2-(benzyloxy)ethanol **147** (468 mg, 3.08 mmol) in dry DCM (5 mL) was added dropwise to the reaction mixture and the reaction stirred for 1 hour. Triethylamine (2.5 mL) was added

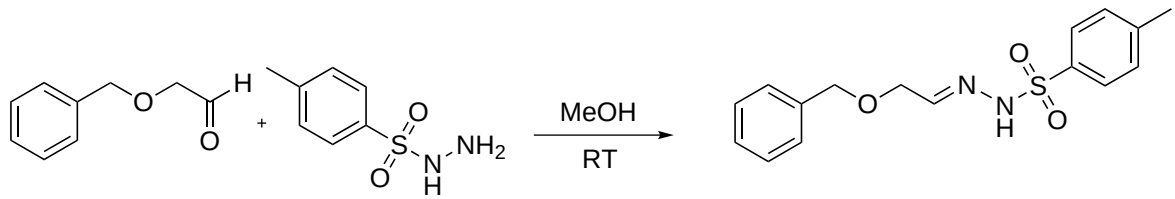
and the reaction allowed to warm to room temperature. Tthe reaction mixture was diluted in DCM (20 mL), washed with water (5x 20 mL) and brine (1x 20 mL). The organic phase was dried with sodium sulfate and concentrated under reduced pressure. Excess DMSO was removed by nitrogen stream. The crude residue was purified by flash chromatography (eluent: EtOAc/DCM 5:95) to obtain benzyloxy acetaldehyde **149** (373 mg, 81%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.38 – 7.34 (m, 5H), 4.63 (s, 2H), 4.10 (s, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.4, 136.8, 128.6, 128.2, 128.0, 75.3, 73.7.

Characterisation data matches literature.[225,226]

(*E*/*Z*)-*N*'-(2-(benzyloxy)ethylidene)-4-methylbenzenesulfonohydrazide 143



149 **150** **143**

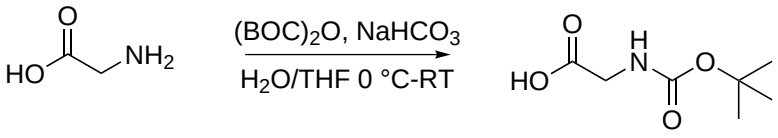
A solution of benzyloxy acetaldehyde **149** (373 mg, 2.48 mmol) in MeOH (1 mL) and added dropwise to a suspension of toluene sulfonyl hydrazide (468 mg, 3.11 mmol) was suspended in MeOH (1 mL). Once addition was complete the reaction was stirred vigorously for 4 hours. The solvent was removed and the reaction purified by flash chromatography (eluent: EtOAc:DCM 5:95) to obtain (*E*/*Z*)-*N*'-(2-(benzyloxy)ethylidene)-4-methylbenzenesulfonohydrazide **143** as white crystals (117 mg, 15% *E*/*Z* 1:2).

Z:^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.79 (m, 2H), 7.38 – 7.21 (m, 7H), 7.16 (t, *J* = 5.1 Hz, 1H), 4.40 (s, 2H), 4.09 (d, *J* = 5.1 Hz, 2H), 2.41 (s, 3H).

E:^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 – 7.74 (m, 2H), 7.38 – 7.21 (m, 7H), 6.70 (t, *J* = 3.5, 2.9 Hz, 1H), 4.47 (s, 2H), 4.16 (d, *J* = 3.3 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.4, 144.5, 144.2, 142.9, 137.5, 136.1, 135.7, 135.3, 129.9, 129.8, 128.9, 128.7, 128.6, 128.1, 128.1, 128.1, 128.0, 128.0, 73.7, 72.9, 69.0, 67.0, 21.7.

***N*-(*tert*-Butoxycarbonyl)glycine 167**

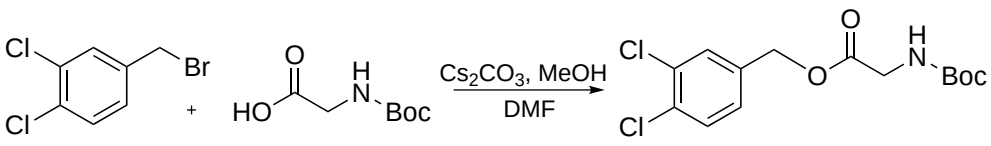


349 **167**

BOC anhydride (7.706 g, 35.30 mmol) was dissolved in THF (60 ml) and cooled in an ice bath. Glycine **349** (2.36 g, 31.43 mmol) and $NaHCO_3$ (7.440 g, 88.56 mmol) were added to the reaction flask followed by water (60 mL). Finally, a catalytic amount of DMAP was added and the reaction left overnight at room temperature under N_2. The cloudy solution was extracted with EtOAc (3x 100 mL) and the aqueous layer acidified to pH 4 by citric acid solution. The acidified solution was then extracted with DCM (3x 100 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford *N*-(*tert*-butoxycarbonyl)glycine **167** (1.804 g, 33%) as white crystals sufficiently pure for subsequent steps.

Characterisation data matches literature.[227]

3,4-dichlorobenzyl (*tert*-butoxycarbonyl)glycinate 168



142 **167** **168**

A 20% (w/v) solution of Cs_2CO_3 was added dropwise to a solution of *N*-(*tert*-butoxycarbonyl)-glycine **167** (919 mg, 5.25 mmol) in MeOH (30 mL) until the reaction mixture reached

pH 7. The solvent was evaporated and the solvent suspended in anhydrous DMF (5 mL), the solvent was evaporated again and the residue was resuspended in anhydrous DMF (15 mL). 4-(Bromomethyl)-1,2-dichlorobenzene **142** (1.37 g, 5.70 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature. Solvent was removed by a stream of nitrogen and the residue suspended in water (30 mL). The suspension was extracted with EtOAc (4x 30 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL) then dried with sodium sulfate. The solution was filtered and concentrated under reduced pressure to afford the crude residue as a yellow oil. The residue was purified by flash chromatography (EtOAc:petroleum spirits 0:1-1:4) to afford 3,4-dichlorobenzyl (*tert*-butoxycarbonyl)glycinate **168** as a slightly yellow oil (1.49 g, 85%).

MP: 42-45 °C

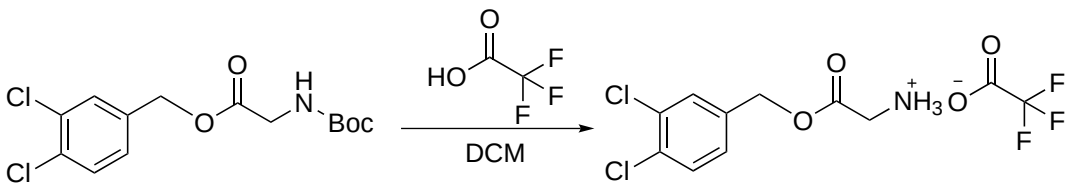
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.39 (m, 2H), 7.17 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.10 (s, 2H), 3.94 (s, 2H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2 (C), 155.8 (C), 135.6 (C), 132.9 (C), 132.7 (C), 130.7 (CH), 130.3 (CH), 127.6 (CH), 80.3 (C), 65.5 (CH_2), 42.6 (CH_2), 28.4 (CH_3).

FTIR-ATR (cm^{-1}): 3321 (NH), 1746 (C=O), 1687 (C=O)

HRMS (ESI): $[M+1]^+$ $C_{14}H_{18}NO_4Cl_{2^+}$ requires 334.0535; found 334.0605.

3,4-dichlorobenzyl glycinate trifluroacetate 169



168 **169**

A solution of trifluoroacetic acid (3.5 mL, 45.6 mmol) dissolved in DCM (3 mL) was added dropwise to a cooled (0 °C) solution of 3,4-dichlorobenzyl (*tert*-butoxycarbonyl)glycinate **168** (751 mg, 2.25 mmol) in DCM (17 mL). After 2 hours, the solvent was evaporated

and the residue dissolved in water (50 mL). The aqueous phase was washed with chloroform (3x 30 mL). The aqueous phase was concentrated under reduced pressure to give 3,4-dichlorobenzyl glycinate trifluroacetate salt **169** as white crystals (780 mg, 99%) sufficiently pure for subsequent steps.

MP: 154-157 °C

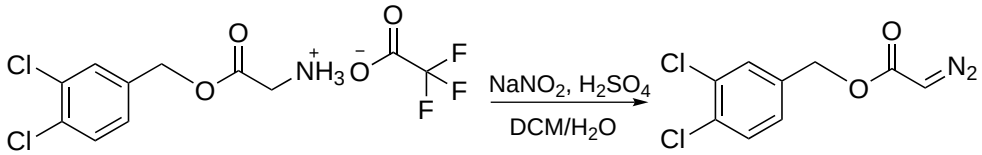
^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.60 (dq, *J* = 2.1, 0.5 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.33 (ddt, *J* = 8.3, 2.1, 0.6 Hz, 1H), 5.25 (s, 2H), 3.95 (s, 2H).

^{13}C NMR (101 MHz, Deuterium Oxide) δ 170.4 (C), 137.6 (C), 134.6 (C), 134.4 (C), 133.2 (CH), 132.7 (CH), 130.5 (CH), 69.3 (CH_2), 42.7 (CH_2).

HRMS (ESI): $[M+1]^+$ $C_9H_{10}Cl_2NO_{2^+}$ requires 234.0010; found 234.0082.

FTIR-ATR(cm^{-1}): 1762 (C=O), 1675 (C=O)

3,4-dichlorobenzyl 2-diazoacetate 170



169 **170**

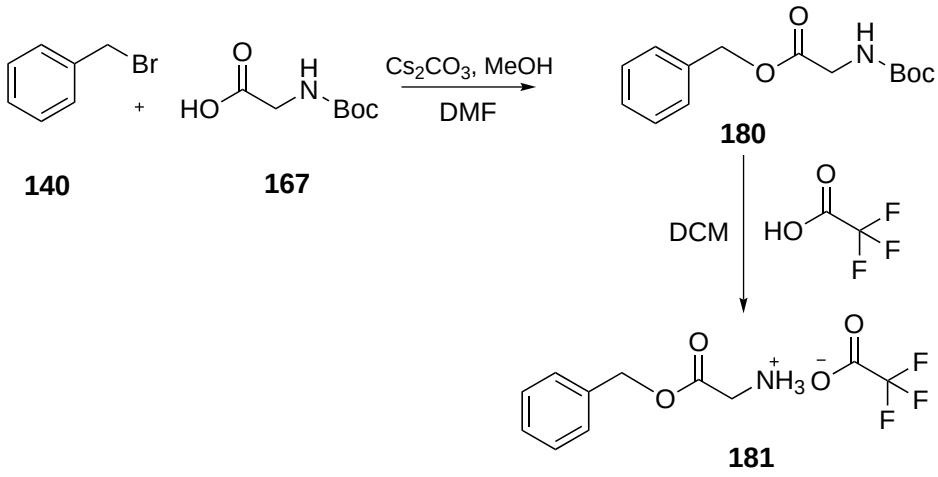
A solution of sodium nitrite (659 mg, 9.6 mmol) in water (80 mL) was added to a cooled (0 °C) suspension of 3,4-dichlorobenzyl (tert-butoxycarbonyl)glycinate trifluroacetate salt **169** (2.22 g, 6.4 mmol) in DCM (50 mL). Sulfuric acid (4 mL, 10 % w/w) was added dropwise and the reaction left for one hour. The organic layer was seperated and the aqueous layer was returned to the reaction flask. To the aqueous phase, DCM (50 mL) was added followed by sodium nitrite (252 mg, 3.6 mmol) and sulfuric acid (3 mL, 10 % w/w) dropwise which was stirred for an additional hour. The organic layers were each washed with water (50 mL) and brine (50 mL) before being dried with sodium sulfate. The organic extracts were combined and reduced under pressure to yield a crude yellow oil which was purified by flash chromatography (eluent: EtOAc/Petroleum Spirits 1:9) to yield 3,4-dichlorobenzyl 2-diazoacetate **170** (858 mg, 55%) as a straw yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.40 (m, 2H), 7.18 (ddt, *J* = 8.2, 2.1, 0.6 Hz, 1H), 5.13 (d, *J* = 0.6 Hz, 2H), 4.81 (s, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.3 (C), 132.8 (C), 132.6 (C), 130.7 (CH), 130.2 (CH), 127.5 (CH), 65.0 (CH_2), 46.5 (CH).

FTIR-ATR(cm^{-1}): 2108 (C=N=N), 1685 (C=O)

Benzyl aminoacetate trifluoroacetate 181



140 **167** **180** **181**

A solution of Cs_2CO_3 (20% w/v) was added to solution of BOC glycine **167** (1.480 g, 8.4 mmol) in methanol (35 mL) and water (5 mL) until the reaction mixture reached pH 7. The solvent was evaporated and the residue was suspended in DMF (25 mL). Benzyl bromide **140** (1.1 mL, 9.3 mmol) was added dropwise the reaction mixture. The reaction was left to stir at RT for 5 hours. The solvent was removed and the residue dissolved in EtOAc/water (40/40 mL) and the organic extract run off. The aqueous layer was then extracted with additional EtOAc (3x 40 mL). The organic extracts were combined and dried with sodium sulfate, filtered and concentrated under reduced pressure to obtain crude benzyl 2-((tert-butoxycarbonyl)amino)acetate **180**.

The crude product was dissolved in DCM (40 mL) then cooled in an ice bath. Trifluoroacetic acid (8 mL) was added dropwise and the reaction left for 2hrs. The reaction

mixture was concentrated under reduced pressure to obtain benzyl aminoacetate trifluroacetate salt **181** as white crystals (2.27 g, 96% two steps). Which was sufficiently pure for subsequent reactions.

Benzyl 2-((tert-butoxycarbonyl)amino)acetate

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.33 (m, 5H), 5.18 (s, 2H), 3.96 (d, *J* = 5.6 Hz, 2H), 1.55 (s, 3H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.3 (C), 155.7 (C), 135.3 (C), 128.1 (CH), 128.5 (CH), 128.4 (CH), 80.0 (C), 67.0 (CH_3), 42.5 (CH_2), 28.3 (CH_3).

Characterisation data matches literature.[228]

Benzyl aminoacetate trifluroacetate salt

MP: 103-105 °C

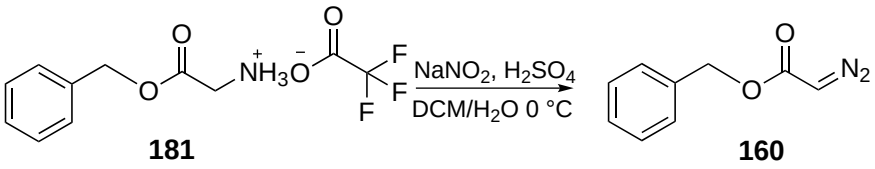
^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.55 – 7.46 (m, 5H), 5.35 (s, 2H), 4.00 (s, 2H).

^{13}C NMR (101 MHz, Deuterium Oxide) δ 168.0 (C), 134.7 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 68.4 (CH_2), 40.2 (CH_2).

HRMS (ESI): $[M+1]^+$ $C_9H_{12}NO_{2^+}$ requires 166.0790; found 166.086.

FTIR-ATR(cm^{-1}): 1746 (C=O), 1673 (C=O)

Benzyl diazoacetate 160



181 **160**

A solution of sodium nitrite (1.278 g, 18.5 mmol) in water (80 mL) and added to a cooled (0 °C) solution of benzyl aminoacetate trifluroacetate salt **181** (3.407 g, 12.2 mmol) in DCM (50 mL). H_2SO_4 (10 % w/w, 5 mL) was added dropwise to the reaction mixture and the reaction left for 2 hrs. The organic layer extracted was extracted and the aqueous layer

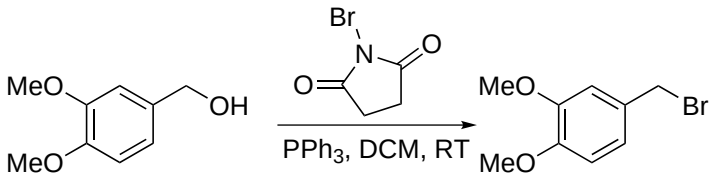
was returned to the reaction vessel. The organic layer was washed with brine (50 mL) dried with sodium sulfate and concentrated.

To the aqueous layer in the reaction vessel, DCM (50 mL) was added followed by sodium nitrite (400 mg, 5.8 mmol) and H_2SO_4 (10% w/w, 2 mL) was added dropwise. The reaction was left to react in the ice bath for 1 hour. The organic layer was then removed, washed with brine (50 mL) and dried with sodium sulfate. The organic extracts were then combined and concentrated under reduced pressure before being purified by flash chromatography (eluent: EtOAc/Petroleum Spirits 1:3) to obtain benzyl diazoacetate **160** (871 mg, 41%) as a straw yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.30 (m, 6H), 5.32 (d, *J* = 4.9 Hz, 1H), 5.21 (s, 2H), 4.80 (s, 1H).

Characterisation data matches literature.[149,157]

3,4-dimethoxybenzyl bromide 185



183 **185**

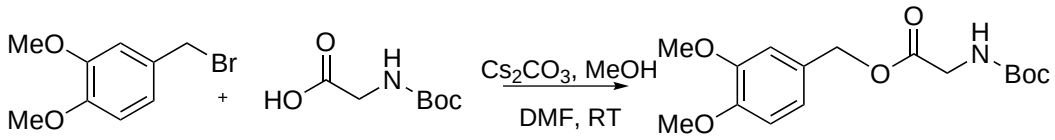
N-bromosuccinimide (11.78 g, 65.7 mmol) was added portion-wise to a solution of 3,4-dimethoxybenzyl alcohol **183**(10.02 g, 59.5 mmol) and triphenyl phosphine (23.0 g, 87.7 mmol) in dry DCM (240 mL) at room temperature. Once addition was complete the reaction was stirred at room temperature for two hours. The solvent was then removed under reduced pressure and the product was trituated using petroleum spirits 40-60. The trituate was filtered and concentrated under reduced pressure to obtain 3,4-dimethoxybenzyl bromide **185** as a colourless oil (7.145 g, 52%). An analytical sample was purified by flash chromatography (eluent: EtOAc/Petroleum Spirits 1:9).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.95 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.50 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.3, 149.1, 130.3, 121.6, 112.1, 111.1, 55.9, 55.9, 34.4.

Characterisation data matches literature.[229]

3,4-dimethoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate 187



185 **167** **187**

A 20% (w/v) solution of Cs_2CO_3 was added dropwise to a solution of BOC-glycine **167** (6.01 g, 34.3 mmol) in methanol (50 mL) and water (5 mL) until pH 8. The solvent was then removed under reduced pressure and the residue dissolved in DMF (50 mL). To this mixuture, the forgoing crude 3,4-dimethoxybenzyl bromide (7.145 g, 30.9 mmol) was added and the reaction stirred for 70 hours at room temperature. The solvent was removed under reduced pressure, the residue dissolved in water (50 mL) and extracted with EtOAc (4x 50 mL). The combined organic extracts were dried with sodium sulfate and concentrated under reduced pressure to obtain crude 3,4-dimethoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate **187** (9.872 g, 89%) as a colourless oil sufficiently pure for subsequent reactions. An analytical sample was purified by flash chromatography (eluent: EtOAc:petroleum spirits 40-60 4:7)

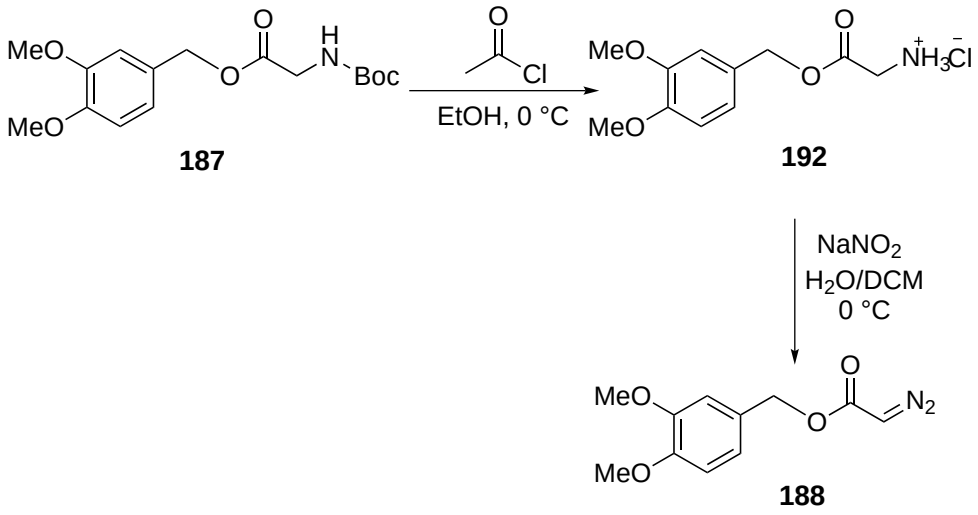
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.90 – 6.82 (m, 2H), 6.79 (d, *J* = 8.1 Hz, 1H), 5.06 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.4 (C), 155.8 (C), 149.4 (C), 149.2 (C), 127.9 (C), 121.6 (CH), 112.0 (CH), 111.2 (CH), 80.1 (C), 67.3 (CH_2), 56.0 (CH_3), 42.6 (CH_2), 28.4 (CH_3).

FTIR-ATR(cm^{-1}): 3382 (NH), 1709 (C=O), 1516 (C=O).

HRMS (ESI): $[M+1]^+$ $C_{16}H_{24}NO_6^+$ requires 326.1525; found 326.1594.

3,4-dimethoxybenzyl 2-aminoacetate hydrochloride 192 and 3,4-dimethoxybenzyl 2-diazoacetate 188



187 **192** **188**

Acetyl chloride (0.6 mL) was added dropwise to a cooled (0 °C) solution of 3,4-dimethoxy benzylboc glycine **187** (950 mg, 2.9 mmol), in dry ethanol (20 mL), the resulting solution was stirred for 3 hours. After concentrating the reaction mixture, the residue was dissolved in water (20 mL) and washed with DCM (3x 10mL). The aqueous phase containing 3,4-dimethoxybenzyl 2-aminoacetate hydrochloride **192** was used immediately for the next reaction. DCM (30 mL) was added to the aqueous mixture which was then cooled to 0 °C. Sodium nitrite (344mg, 4.98 mmol) was added and the reaction left to warm to room temperature over 5 hours.

The organic layer was seperated and the aqueous layer washed with an additional (2x 20 mL) DCM. The combined organic extracts were dried using sodium sulfate and concentrated under reduced pressure to give a yellow oil. The oil was purified using flash chromatography (eluent: EtOAc:Petroleum spirits 40-60 1:4) to obtain 3,4-dimethoxybenzyl 2-diazoacetate **188** (289 mg, 41% two steps) as yellow crystals.

3,4-dimethoxybenzyl 2-aminoacetate hydrochloride **192**

MP: 131-140 °C

^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.13 (d, *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 7.08 (d, *J* = 0.5 Hz, 1H), 5.26 (s, 2H), 3.97 (s, 2H), 3.89 (s, 6H).

^{13}C NMR (101 MHz, Deuterium Oxide) δ 167.9 (C), 148.6 (C), 148.1 (C), 127.6 (C), 122.2 (CH), 112.5 (CH), 111.8 (CH), 68.3 (CH_2), 55.7 (2x CH_3), 40.2 (CH_2).

HRMS (ESI): $[M+1]^+$ $C_{11}H_{16}NO_4^+$ requires 226.1001; found 226.1073.

FTIR-ATR(cm^{-1}): 1745 (C=O)

3,4-dimethoxybenzyl 2-diazoacetate **188**

MP: 69-71°C

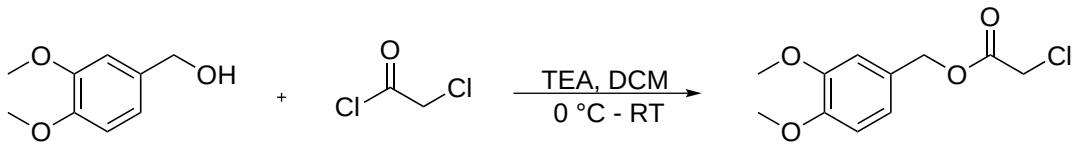
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.93 (ddd, J = 8.2, 1.6, 1.0 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 5.13 (s, 2H), 4.78 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.6 (C), 149.3 (C), 149.1 (C), 128.5 (C), 121.4 (CH), 111.9 (CH), 111.1 (CH), 66.7 (CH_2), 56.0 (CH_3), 56.0 (CH_3).

HRMS (ESI): $[M+1-N_2]^+$ $C_{11}H_{13}O_4^+$ requires 209.0813; found $C_{11}H_{13}O_4$ 209.0890.

FTIR-ATR(cm^{-1}): 2119 (C=N=N), 1679 (C=O)

3,4-Dimethoxybenzyl 2-chloroacetate 194



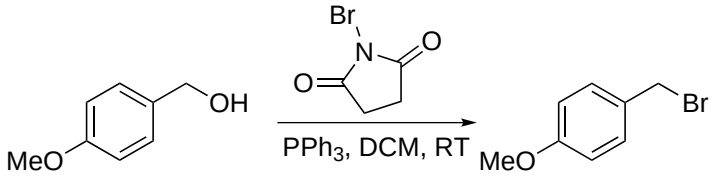
183 **197** **194**

Triethylamine (2.2 mL, 15.8 mmol) was added dropwise to a cooled (0 °C) solution of 3,4-dimethoxybenzyl alcohol **183** (2.6 mL, 17.8 mmol) in DCM (130 mL). Once addition was complete, chloroacetyl chloride **197** (1.0 mL, 12.6 mmol) was added dropwise and the reaction mixture stirred for 1.5 hours. Water (10 mL) was added and the reaction left to stirr for an additional 1 hour. The organic layer was removed and washed with water (2x 50 mL), brine (50 mL) then dried with sodium sulfate, filtered and concentrated under reduced pressure to give an oil. The oil was purified using flash chromatography (eluent: EtOAc:Petroleum spirits 40-60 1:4) to give 3,4-Dimethoxybenzyl 2-chloroacetate **194** (1.236g, 28%) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.95 (dd, J = 8.2, 2.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.16 (s, 2H), 4.08 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.4, 149.6, 149.2, 127.5, 121.8, 112.1, 111.2, 68.2, 56.1, 41.1.

4-Methoxybenzyl bromide 184



182 **184**

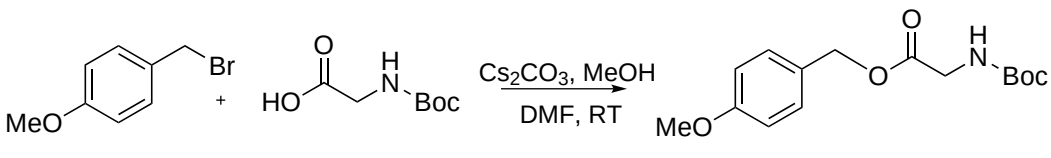
N-bromosuccinimide (11.86g, 66.6 mmol) was added portion-wise to a solution of 4-methoxybenzyl alcohol **182** (10.13 g, 73.25 mmol) and triphenyl phosphine (22.73 g, 86.66 mmol) in dry DCM (260 mL) at room temperature. Once addition was complete the reaction was stirred at room temperature for 2 hours. The solvent was then removed and the residue was trituated using petroleum spirits 40-60. The titruate was then filtered and concentrated to obtain crude 4-methoxybenzyl bromide **184** (7.649 g, 57%) as a colourless oil. This was sufficiently pure for subsequent steps.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 2H), 6.93 – 6.80 (m, 2H), 4.51 (s, 2H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.8, 130.6, 130.1, 114.4, 55.5, 34.1.

Characterisation data matches literature.[230]

4-methoxybenzyl 2-((*tert*-butoxycarbonyl)amino)acetate 186



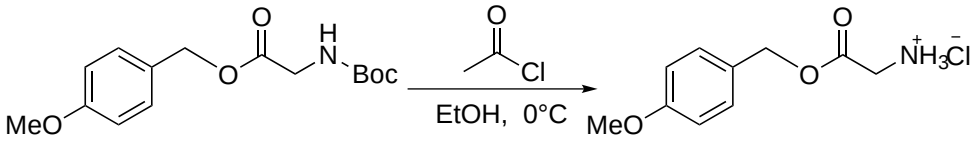
184 **167** **186**

A 20% (w/v) solution of Cs_2CO_3 was added dropwise to a solution of BOC-glycine **167** (7.58 g, 43.3 mmol) in MeOH (50 mL) and water (5 mL) until pH 8. The solvent was then removed under reduced pressure and the residue dissolved in DMF (25 mL). The DMF was removed under reduced pressure and the residue redissolved in DMF (50 mL). To this mixuture, the forgoing crude 4-methoxybenzyl bromide (7.647 g, 38.0 mmol) was added and the reaction stirred for 16 hours at room temperature. The solvent was removed under reduced pressure, dissolved in water (100 mL) and then extracted with EtOAc (3x 60 mL). The combined organic extracts were washed with brine (1x 100 mL), then dried with sodium sulfate, filtered and concentrated under reduced pressure to obtain crude 4-methoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate **186** (9.347 g, 83%) as a viscous yellow oil sufficiently pure for subsequent reactions. An analytical sample was purified by flash chromatography (eluent: EtOAc:petroleum spirits 40-60 3:7)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.27 (m, 2H), 6.91 – 6.86 (m, 2H), 5.11 (s, 2H), 3.81 (s, 3H), 1.44 (s, 9H).

Characterisation data matches literature.[148,231]

4-methoxybenzyl 2-aminoacetate hydrochloride 191



186 **191**

A solution of 4-methoxybenzyl BOC-glycine **186** (408 mg, 1.38 mmol) in dry ethanol (10 mL) was cooled (0 °C) and acetyl chloride (0.35 mL, 4.9 mmol) was added drop-wise. After addition was completed, the reaction mixture was stirred for 3 hours. The solvent was removed under reduced pressure. The residue was dissolved in water (15 mL) and washed with dichloromethane (3x 5 mL). The aqueous phase was concentrated under reduced pressure to afford 4-methoxybenzyl 2-aminoacetate hydrochloride **191** as white crystals (261 mg, 84%) sufficiently pure for subsequent reactions.

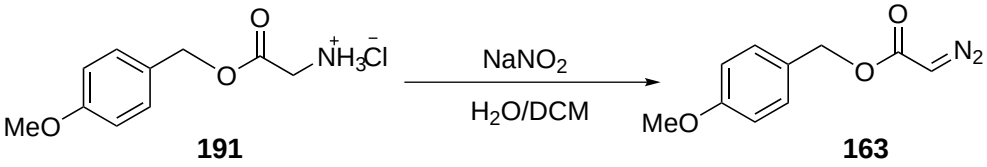
^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.42 – 7.31 (m, 2H), 7.02 – 6.86 (m, 2H), 5.18 (s, 2H), 3.88 (s, 2H), 3.78 (s, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide) δ 167.9 (C), 159.3 (C), 130.6 (CH), 127.2 (C), 114.2 (CH), 68.1 (CH_2), 55.4 (C), 40.2 (CH_2).

HRMS (ESI): $[M+1]^+$ $C_{10}H_{14}NO_3^+$ requires 196.0895; found 196.0964.

Compound previously reported.[148]

4-methoxybenzyl 2-diazoacetate 163



191 **163**

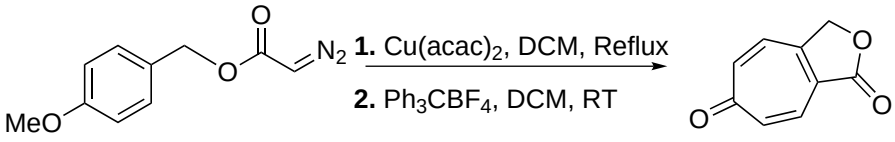
4-methoxybenzyl aminoacetate hydrochloride **191** (11.5 g, 49.6 mmol) was dissolved in a mixture of DCM and water (1:1, 200 ml) and stirred in an ice bath. To the reaction mixture sodium nitrite (4.79 g, 69.4 mmol) was added and the mixture was left to react for 5 hours. The organic layer was removed and washed with water (3x 50 mL) followed by brine (1x 50 mL). The organic layer was dried with sodium sulfate and then concentrated under reduced pressure to afford the crude residue as a yellow oil. The residue was purified by flash chromatography (eluent EtOAc:Petroleum spirits 40-60 1:9-1:4) to obtain 4-methoxybenzyl diazoacetate **163** (4.3 g, 42%) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 2H), 6.92 – 6.86 (m, 2H), 5.13 (s, 2H), 4.76 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.8 (C), 130.3 (CH), 128.1 (C), 114.1 (CH), 66.5 (CH_2), 55.4 (CH_3), 46.4 (CH).

Compound previously reported.[148]

1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione 211



163 **211**

A suspension of $Cu(acac)_2$ (11 mg) in dry DCM (50 mL) was heated under reflux with a dilution reservoir containing DCM (70 mL) (see Figure 3.0.2). A solution of 4-methoxybenzyl diazoacetate **163** (308 mg, 1.49 mmol) in DCM (10 mL) was injected into the dilution reservoir over 2 hours using a syringe pump. Once addition was complete, the reaction was heated under reflux for 1 hour and then left to cool to room temperature. Triphenylmethyl hexafluorophosphate (460 mg, 1.18 mmol) was added and the reaction stirred for an additional hour. The reaction mixture was washed with water (4x 30 mL), dried with sodium sulfate, filtered and concentrated under reduced pressure. The oil was purified by flash chromatography (eluent: EtOAc/Petroleum spirits 1:1-1:0) to obtain pure product 1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione **211** (105 mg, 44%) as a slightly yellow oil.

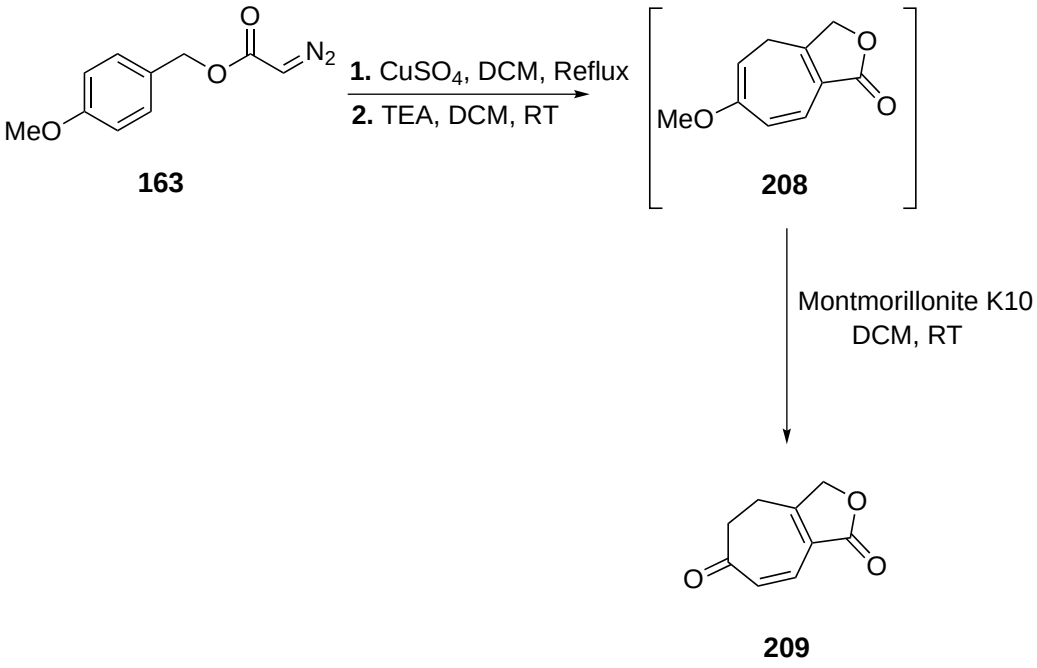
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (dd, J = 11.9, 0.6 Hz, 1H), 7.20 (dd, J = 11.9, 2.5 Hz, 1H), 7.12 (d, J = 11.9 Hz, 1H), 7.08 (ddt, J = 11.9, 2.4, 1.0 Hz, 1H), 5.15 (s, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 187.0 (C), 171.1 (C), 155.3 (C), 146.3 (CH), 142.3 (CH), 129.9 (CH), 128.8 (C), 128.7 (CH), 70.5 (CH_2).

FTIR-ATR: 1755 (C=O), 1582 (C=O).

HRMS (ESI): $[M+1]^+$ $C_9H_7O_3^+$ requires 163.0317; found 163.0391.

4,5-Dihydro-1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione 209



163 **208** **209**

A suspension of $Cu(acac)_2$ (48 mg) in DCM (110 mL) was heated under reflux with a dilution reservoir containing DCM (70 mL) (see Figure 3.0.2). A solution of 4-methoxybenzyl diazoacetate **163** (1.11 g, 53.9 mmol) was dissolved in DCM (10 mL) and injected into the dilution reservoir over 4 hours using a syringe pump. Once addition was complete the reaction wasallowed to react for 1 hour and then left to cool to room temperature. TEA (1.5 mL) was added and the reaction was stirred for an additional 30 minutes. The reaction mixture was washed with HCl (1 M, 50 mL), water (2x 50 mL) and brine (1x 50 mL), dried with sodium sulfate, and concentrated under reduced pressure to give an oil containing 6-methoxy-3,4-dihydro-1*H*-cyclohepta[*c*]furan-1-one **208**. The oil was diluted in DCM (70 mL) and montmorillonite K10 was added to the reaction mixture in portions until the desired product had formed (TLC). The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The oil was purified by flash chromatography (eluent: EtOAc:Petroleum Spirits 1:1) to afford 4,5-dihydro-1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione **209** (120 mg, 15%) as a slightly brown oil.

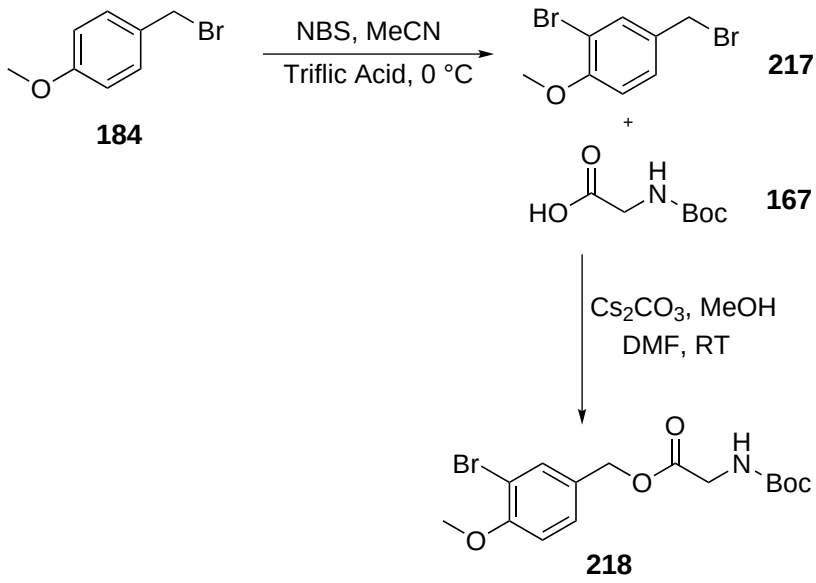
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.90 (dd, *J* = 12.2, 0.8 Hz, 1H), 6.29 (dd, *J* = 12.2, 0.8 Hz, 1H), 4.88 (s, 2H), 2.86 – 2.79 (m, 2H), 2.77 – 2.70 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.4 (C), 172.0 (C), 167.1 (C), 133.7 (CH), 128.9 (CH), 124.1 (C), 71.6 (CH_2), 38.9 (CH_2), 22.3 (CH_2).

FTIR-ATR(cm^{-1}): 1752 (C=O), 1652 (C=O).

HRMS (ESI): $[M+1]^+$ $C_9H_9O_3^+$ requires 165.0473; found 165.0547.

3-Bromo-4-methoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate 218



To a cooled (-5 °C) solution of 4-methoxybenzyl bromide **184** (4.76 g, 23.8 mmol) in dry MeCN (50 mL), triflic acid (2.4 mL) was added, followed by *N*-bromosuccinimide (5.05 g, 28.4 mmol) portion-wise over 20 minutes. The reaction was monitored by TLC until starting material was consumed. The reaction was diluted with aqueous sodium metabisulfate (5%, 100 mL) and extracted with DCM (3x 50 mL). The combined organic extracts were washed with brine (50 mL), dried with sodium sulfate and concentrated under reduced pressure to afford 3-bromo-4-methoxy benzylbromide **217** as a golden orange oil.

To a soultion of BOC-Glycine (4.58 g, 26.1 mmol) in MeOH (60 mL) and water (30 mL) solid $Cs_2CO_3$was added until the reaction mixture reached pH 8. Solvent was removed under reduced pressure and the residue dissolved in DMF (30 mL). To this mixture, a solution of 3-bromo-4-methoxybenzylbromide **217** in DMF (3 mL) was added

dropwise. The reaction was stirred at room temperature overnight. The resulting mixture was concentrated under reduced pressure, diluted with water (100 mL) and extracted with EtOAc (3x 50 mL). The combined organic extracts dried with sodium sulfate and concentrated under reduced pressure to yield viscous golden orange oil. The oil was purified by flash chromatography (eluent: EtOAc:Petroleum Spirits 40-60 1:3) to afford 3-bromo-4-methoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate **218** (3.20 g, 36% two steps) as white crystals.

MP: 67-70 °C

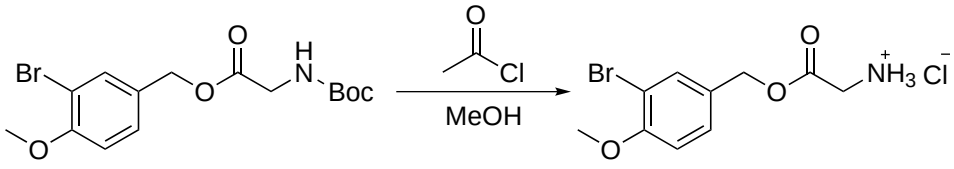
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 2.1 Hz, 1H), 7.30 – 7.26 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.08 (s, 2H), 3.93 (dd, *J* = 6.8, 3.0 Hz, 2H), 3.90 (s, 3H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.3 (C), 156.2 (C), 155.8 (C), 133.8 (CH), 129.2 (CH), 129.0 (C), 111.9 (CH), 111.8 (C), 80.1 (C), 66.0 (CH_2), 56.4 (CH_3), 42.6 (CH_2), 28.4 (CH_3).

HRMS (ESI): $[M+1]^+$ $C_{15}H_{21}NO_5Br^+$ requires 374.0525; found 374.0594.

FTIR-ATR(cm^{-1}): 1760 (C=O), 1670 (C=O)

3-bromo-4-methoxybenzyl 2-aminoacetate hydrochloride 219



218 **219**

To a cooled (0 °C) solution of 3-bromo-4-methoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate **218** (2.79 g, 7.46 mmol) in dry ethanol (40 mL) acetyl chloride (2.1 mL) was added dropwise and the reaction mixture was stirred for 2 hours. The solvent was removed under reduced pressure. The residue was dissolved in water (50 mL) and washed with DCM (3x 20). The aqueous phase was concentrated under reduced pressure to obtain 3-bromo-4-methoxybenzyl 2-aminoacetate hydrochloride **219** (952 mg, 41%) as a white solid, sufficiently pure for subsequent reactions.

MP: 186-188 °C

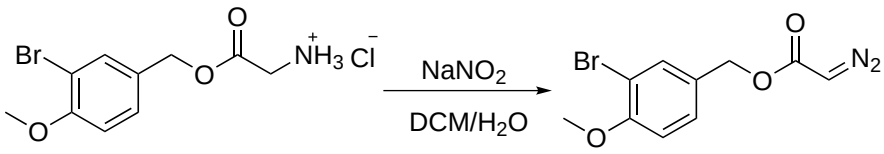
^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.61 (m, 1H), 7.36 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.04 (dd, *J* = 8.6, 1.0 Hz, 1H), 5.15 (s, 2H), 3.89 (s, 2H), 3.85 (s, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide) δ 167.9 (C), 155.5 (C), 133.5 (CH), 129.7 (CH), 128.6 (C), 112.7 (CH), 110.7 (C), 67.3 (CH_2), 56.3 (CH_3), 40.2 (CH_2).

HRMS (ESI): $[M+1]^+$ $C_{10}H_{13}NO_3{}^+Br$ requires 274.0001; found 274.0070.

FTIR-ATR(cm^{-1}): 1755 (C=O)

3-bromo-4-methoxybenzyl 2-diazoacetate 216



219 **216**

To a cooled (0 °C) mixture of 3-bromo-4-methoxybenzyl 2-aminoacetate hydrochloride **219** (931 mg, 3.00 mmol) in water (10 mL) and DCM (20 mL), sodium nitrite (290 mg, 4.20 mmol) was added and the reaction mixture stirred for 1 hour. The organic phase was separated, dried with sodium sulfate and concentrated under reduced pressure to obtain an oil. The oil was purified by flash chromatography (eluent: EtOAc:Petroleum Spirits 40-60 1:9 followed by 1:4) to obtain 3-bromo-4-methoxybenzyl 2-diazoacetate (253 mg, 30%) **216** as a viscous yellow oil.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 (d, *J* = 2.1 Hz, 1H), 7.30 – 7.25 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.09 (s, 2H), 4.78 (s, 1H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.5 (C), 156.0 (C), 133.7 (CH), 129.6 (C), 129.1 (CH), 111.9 (CH), 111.8 (C), 65.5 (CH_2), 56.4 (CH_3), 46.5 (CH).

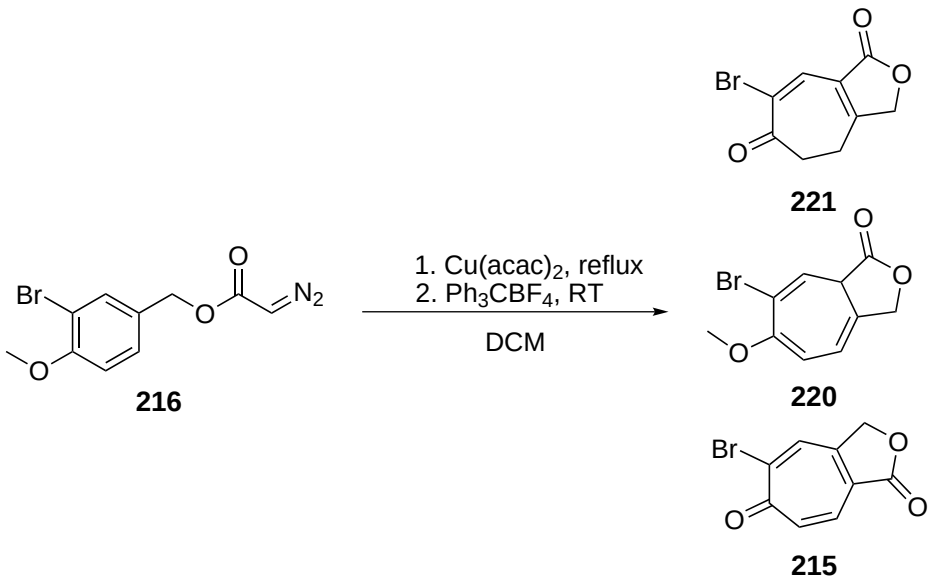
HRMS (ESI): $[M+1-N_2]^+$ $C_{10}H_{10}O_3Br$ requires 256.9813; found $C_{10}H_{10}O_3Br$ 256.9808

FTIR-ATR(cm^{-1}): 2108 (C=N=N), 1687 (C=O)

5-bromo-1H-cyclohepta[c]furan-1,6(3H)-dione 215

7-bromo-6-methoxy-3,8-dihydro-1H-cyclohepta[c]furan-1-one 220

7-bromo-4,5-dihydro-1H-cyclohepta[c]furan-1,6(3H)-dione 221



A suspension of $Cu(acac)_2$ (25 mg) in DCM (110 mL) was heated under reflux with a dilution reservoir containing DCM (70 mL) (see Figure 3.0.2). A solution of 3-bromo-4-methoxybenzyl diazoacetate **216** (313 mg, 1.10 mmol) in DCM (8 mL) was injected into the dilution reservoir over 2 hours using a syringe pump. Once addition was complete the reaction was heated under reflux until the dilution reservoir become colourless and then left to cool to room temperature. Triphenylcarbenium tetrafluoroborate (772 mg, 2.34 mmol) was added and the reaction stirred for 45 minutes. The reaction mixture was washed with water (3x 40 mL) and brine (1x 50 mL), dried with sodium sulfate and concentrated under reduced pressure to give an oil. The oil was purified by flash chromatography (eluent: EtOAc:Petroleum spirits 40-60 1:3-1:1) to obtain 5-bromo-1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione **215** (20 mg, 8%) and, 7-bromo-6-methoxy-3,8-dihydro-1*H*-cyclohepta[*c*]furan-1-one **220** which rapidly hydrolysed to 7-bromo-4,5-dihydro-1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione **221** (14 mg, 5%) as a yellow oil.

5-bromo-1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione **215**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (s, 1H), 7.53 – 7.49 (m, 1H), 7.25 – 7.21 (m, 1H), 5.18 – 5.16 (m, 2H).

HRMS (ESI): $[M+1]^{+}$ $C_9H_6O_3Br$ requires 240.9422; found 240.9493.

7-bromo-6-methoxy-3,8-dihydro-1*H*-cyclohepta[*c*]furan-1-one **220**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.05 (dq, *J* = 6.8, 2.3 Hz, 1H), 5.90 – 5.86 (m, 1H), 5.83 (d, *J* = 5.1 Hz, 1H), 5.02 (dtd, *J* = 5.1, 2.1, 1.3 Hz, 2H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-^{d}) δ 175.7, 155.93, 128.0, 122.9, 117.6, 116.9, 105.2, 70.6, 55.8, 43.3.

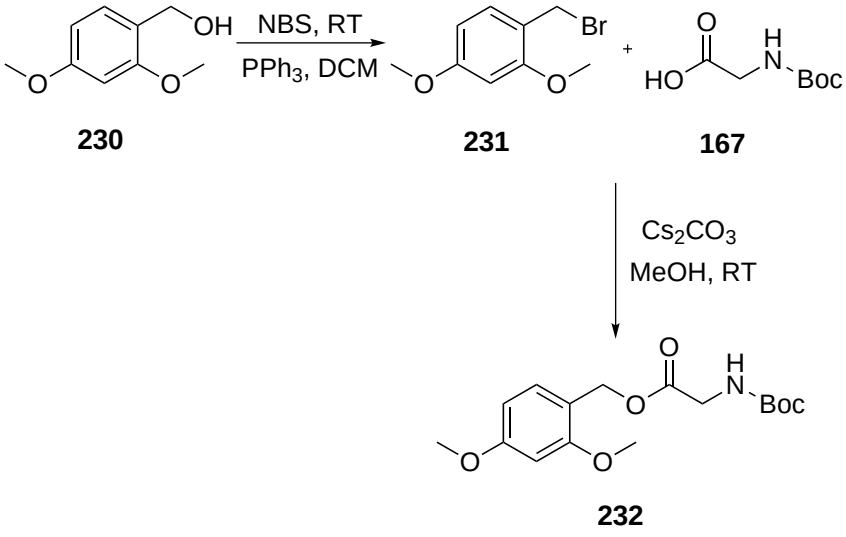
HRMS (ESI): $[M+1]^{+}$ $C_{10}H_{10}O_3Br$ requires 256.9735; found 256.9807.

7-bromo-4,5-dihydro-1*H*-cyclohepta[*c*]furan-1,6(3*H*)-dione **221**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (s, 1H), 4.87 (s, 2H), 3.07 – 3.01 (m, 2H), 2.80 – 2.74 (m, 2H).

HRMS (ESI): $[M+1]^{+}$ $C_9H_9O_3Br$ requires 242.9579; found 242.9650.

2,4-dimethoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate 232



N-bromosuccinimide (5.89 g, 33.1 mmol) was added portion-wise to a cooled (0 °C) solution of 2,4-dimethoxybenzyl alcohol **230** (5.06 g, 30.1 mmol) and triphenylphosphene

(9.50 g, 36.2 mmol) in dry DCM and the reaction stirred for 1 hour. The reaction mixture was trituated using petroleum spirits 40-60, the trituant was filtered and concentrated under reduced pressure to give 2,4-dimethoxybenzyl bromide as an orange oil **231**.

To a solution of BOC-glycine **167** (5.80 g, 8.5 mmol) in MeOH (30 mL) and H_2O (15 mL), solid $Cs_2CO_3$was added until the reaction mixture reached pH 8. The solvent was removed under reduced pressure and the residue dissolved in DMF (35 mL). 2,4-dimethoxybenzyl bromide **231** in DMF (5 mL) was added dropwise to the reaction mixture and stirred for 18 hours. The solvent was removed under reduced pressure and the oil diluted in water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried with sodium sulfate and concentrated under reduced pressure to give an oil. The oil was purified using flash chromatography (eluent: EtOAc:Petroleum Spirits 40-60 1:4) to obtain 2,4-dimethoxybenzyl 2-((tert-butoxycarbonyl)amino)acetate **232** (1.2 g, 12% two steps) as white crystals.

MP: 92-97 °C

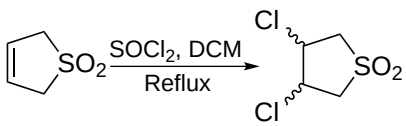
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.21 (m, 1H), 6.46 (dq, *J* = 4.7, 2.4 Hz, 2H), 5.16 (s, 2H), 3.92 (d, *J* = 5.5 Hz, 2H), 3.81 (d, *J* = 1.9 Hz, 6H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.4 (C), 161.5 (C), 159.1 (C), 155.6 (C), 131.7 (CH), 116.0 (C), 104.1 (CH), 98.6 (CH), 79.9 (C), 62.6 (CH_2), 55.5 (CH_3), 55.4 (CH_3), 42.5 (CH_2), 28.3 (3x CH_3).

HRMS (ESI): $[M+1]^+$ $C_{16}H_{24}NO_6^+$ requires 326.1525; found 326.1594

FTIR-ATR(cm^{-1}): 3319 (NH), 1753 (C=O), 1681 (C=O)

3,4-Dichlorosulfolane 242



241 **242**

Sulfuryl chloride (45 mL, 560 mmol) was added dropwise to a solution of 3-sulfolene (20.1 g, 170 mmol) **241** in dry DCM (160 mL) and the mixture heated under reflux for 18 hours. The reaction was cooled to room temperature then cooled to 0 °C to promote crystal formation. The solution was filtered to obtain 3,4-dichlorosulfolane (28.6g, 89%, 2:1 *E*:*Z*) **242** as offwhite crystals.

MP: 57-65 °C

E:^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.72 (m, 2H), 3.96 – 3.87 (m, 2H), 3.50 – 3.41 (m, 2H).

Z:^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.82 – 4.75 (m, 2H), 3.74 – 3.66 (m, 2H), 3.65 – 3.56 (m, 2H).

E/Z mix: ^{13}C NMR (101 MHz, Chloroform-d) δ 58.42 (CH_2), 57.73 (CH), 57.56 (CH_2), 56.83 (CH).

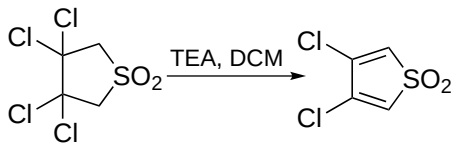
3,3,4,4-Tetrachlorosulfolane 243

242 **243**

3,4-dichlorosulfolane **242** (5.01g, 26.5 mmol) was dissolved in sulfuryl chloride (250 mL) under a positive nitrogen atmosphere. The reaction was heated under reflux using a halogen lamp and a spatula of 1,1´-azobis(cyclohexanecarbonitrile) was added twice a day for 13 days. Bulk sulfuryl chloride was removed by distillation and the residue dissolved in DCM (200 mL). The solution was added to ice water (400 mL) and the mixture stirred for two hours. The organic layer was separated and washed with water (2x 200 mL) and brine (3x 200 mL). The organic phase was dried with sodium sulfate concentrated under reduced pressure to afford 3,3,4,4-Tetrachlorosulfolane (6.5g, 94% conversion by ^{1}H NMR) as off white crystals sufficiently pure for subsequent steps.

Characterisation data matches literature.[172,232]

3,4-Dichloro-1,1-thiophenedioxide 244

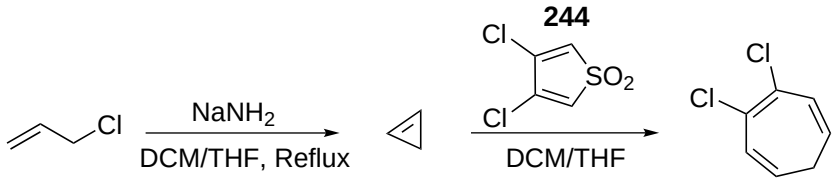


243 **244**

A solution of 3,3,4,4-tetrachlorosulfolane **243** in DCM (50 mL) was cooled to 0 °C. TEA (10 mL) was added to the reaction and stirred for 3 hours, allowing to warm to room temperature. The reaction mixture was washed with water (3x 30 mL) and brine (1x 30 mL). The organic layer was dried with sodium sulfate, filtered and concentrated under reduced pressure to afford the crude reside. The residue was purified by silica gel filtration (eluent: EtOAc/Petroleum spirits 40-60 1:3) to afford 3,4-dichloro-1,1-thiophenedioxide **244** (5.70g, 93%) as orange crystals, sufficiently pure for subsequent steps.

Characterisation data matches literature.[172]

3,4-Dichlorocyclohepta-1,3,5-triene 247



245 **246** **247**

Allyl chloride **245** (23 mL, 280 mmol) was added dropwise to a solution of sodium amide (9.9 g, 254 mmol) in dry THF (100 mL) and the reaction heated under reflux. A gentle flow of nitrogen gas was pumped through the reaction flask carrying the produced gas into a collection flask cooled at - 196 °C. The collection flask was periodically warmed to - 84 °C to clear blockages. After 1 hour, a solution of 3,4-dichlorothiophene-1,1-dioxide **244** (907 mg, 4.9 mmol) in DCM (5 mL) was added to the collection flask and the reaction left for an additional two hours. The collection flask was allowed to warm to room temperature

and the checked for unreacted thiophene-1,1-dioxide **244** by ^{1}H NMR spectroscopy. Once the thiophene-1,1-dioxide **244** had been consumed additional 3,4-dichloro thiophene-1,1-dioxide (661 mg, 3.57 mmol) was added, the reaction was restarted and left to run for an additional 2 hours.

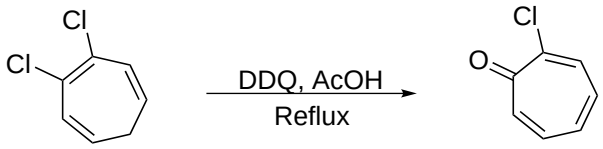
The contents of the collection flask were concentrated under reduced pressure then dissolved in water (20 mL). The aqueous mixture was extracted with DCM (3x 10 mL). The combined organic extracts were washed with water (2x 10 mL) and brine (1x 10 mL), dried with sodium sulfate, and concentrated under reduced to pressure to afford 3,4-dichlorocyclohepta-1,3,5-triene **247** (569 mg, 42%) as a yellow oil sufficiently pure for subsequent steps.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.23 (d, *J* = 9.1 Hz, 2H), 5.57 – 5.49 (m, 2H), 2.40 (t, *J* = 7.0 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 132.8 (C), 127.9 (CH), 124.6 (CH), 27.3 (CH_2).

HRMS (Orbitrap): $[M]^+$ $C_7H_6Cl_2^+$ requires 159.9847; found 159.9842.

2-Chlorotropone 54



247 **54**

DDQ (1.99 g, 8.8 mmol) was added to a solution of 3,4-dichlorocyclohepta-1,3,5-triene **247** (453 mg, 2.81 mmol) in AcOH (8 mL) and the reaction heated under reflux for 2 hours. Phosphoric acid (85%, 0.6 mL) was added and the reaction stirred at room temperature for 30 minutes. The reaction mixture was diluted with water and extracted with DCM (3 x10 mL). The combined organic extracts were washed with water (3x 10mL), NaOH (2x 50ml) and brine (1x 10mL). The organic phase was dried with sodium sulfate and concentrated under reduced pressure to give the crude residue. The reaction mixture was

purified by column chromatography (eluent: EtOAc/petroleum spirits 40-60 1:3) to afford 2-chlorotropone **54** (240 mg, 61%) as a slightly brown solid.

MP: 57-65 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 9.4, 0.8 Hz, 1H), 7.26 – 7.16 (m, 2H), 7.08 (m, 1H), 6.94 (m, 1H).

^{1}H NMR (400 MHz, Benzene-*d6*) δ 6.96 (dd, *J* = 9.4, 0.8 Hz, 1H), 6.84 (dt, *J* = 12.2, 0.8 Hz, 1H), 6.14 (ddd, *J* = 12.2, 8.2, 1.2 Hz, 1H), 5.98 (ddt, *J* = 10.9, 8.2, 0.9 Hz, 1H), 5.85 – 5.72 (m, 1H).

^{13}C NMR (101 MHz, Benzene-*d6*) δ 179.4 (C), 149.4 (C), 138.6 (CH), 134.7 (CH), 134.5 (CH), 133.0 (CH), 130.6 (CH).

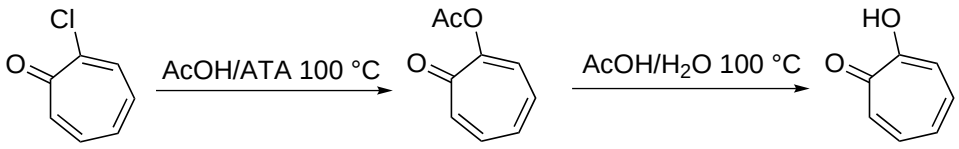
^{13}C NMR (101 MHz, Chloroform-*d*) δ 180.5 (C), 149.5 (C), 139.0 (CH), 135.9 (CH), 135.7 (CH), 134.2 (CH), 131.6 (CH)

HRMS (Orbitrap): $[M]^+$ $C_7H_5OCl^+$ requires 140.0029; found 140.00242.

FTIR-ATR(cm^{-1}): 1576 (C=O)

2-Acetyl tropone 259

Tropolone 3



54 **259** **3**

2-Chlorotropone **54** (219 mg, 1.6 mmol) was added to a solution of ATA (10 mL) prepared by the procedure of Takeshita *et al.*[183] and the reaction mixture heated to 120 °C for 18 hours. The solvent was removed under reduced pressure to afford 2-Acetyl tropone **259** which was immediately in disolved in AcOH (5 mL) and water (5mL) and heated to 100 °C for 5 hours. The reaction mixture was then stirred at room temperature overnight. The

solvent was removed under reduced pressure and residue purified by column chromatography (eluent: petroleum spirits 40-60) to give tropolone **3** (44 mg, 35% two steps) as a slightly yellow solid.

2-Acetyltropone

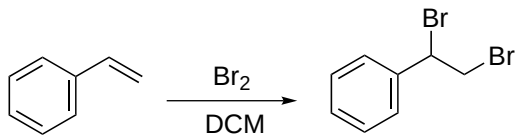
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 (m, 2H), 7.14 (t, *J* = 9.8 Hz, 2H), 7.10 – 7.03 (m, 1H), 2.35 (s, 3H).

The NMR spectral data matches those reported in literature.[233]

Tropolone:

The NMR spectral data matches those reported in literature.[234,235]

(1,2-Dibromoethyl)benzene 267

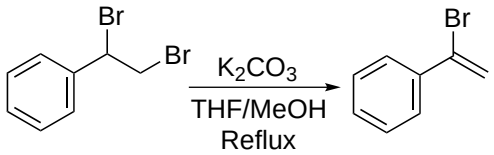


266 **267**

Bromine (6 mL, 533 mmol) was added dropwise to a cooled (0 °C) solution of styrene **266** (10.06 g, 9.66 mmol) in DCM (200 mL) and the reaction stirred for 1.5 hours. Sodium metabisulfate solution (5%, 100 mL) was added and the reaction mixture stirred for 2 hours. The organic layer was seperated then washed with brine (1x 50 mL), dried with sodium sulfate concentrated under reduced pressure to afford (1,2-dibromoethyl)benzene **267** (24.44 g, 96%) as a white powder sufficiently pure for subsequent steps.

Characterisation data matches literature.[236]

(1-Bromovinyl)benzene 268

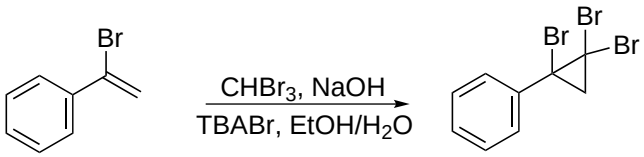


267 **268**

Potassium carbonate (13.85 g, 100 mmol) was added to a solution of (1,2-Dibromoethyl)benzene **267** (15.98 g, 60.5 mmol) in MeOH 100 mL and THF (100 mL) and reaction mixture was heated under reflux for 2 hours. The reaction was diluted with ether (200 mL), washed with sodium hydroxide solution (5%, 50 mL) and brine (2x 50 mL), dried with sodium sulfate and concentrated under reduced pressure to afford (1-bromovinyl)benzene **268** (8.948 g, 81%) as a slightly yellow oil sufficiently pure for subsequent steps.

Characterisation data matches literature.[237]

(1,2,2-Tribromocyclopropyl)benzene 269



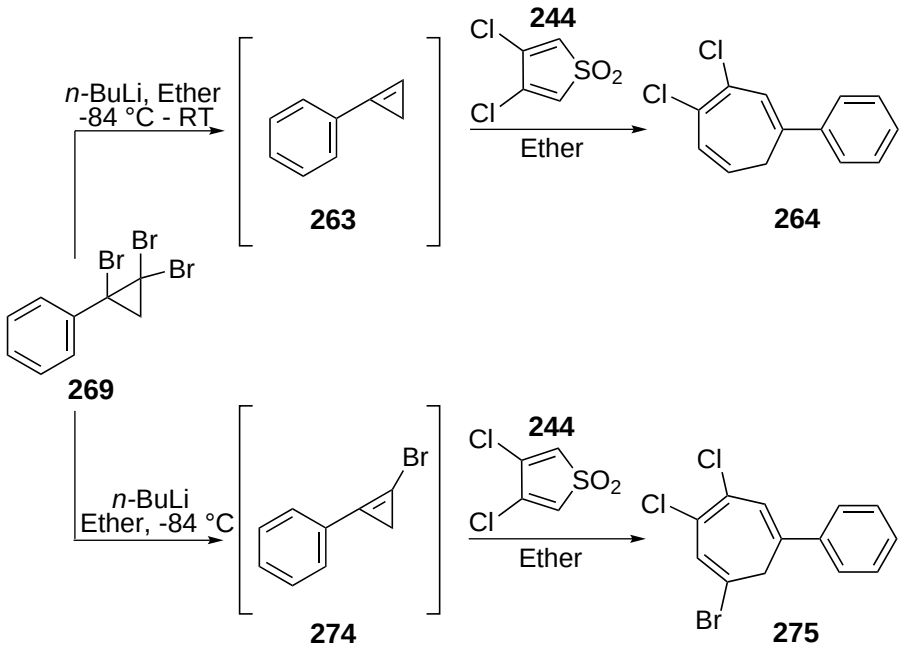
268 **269**

Tetrabutylammonium bromide (278 mg) and EtOH (0.5 mL) was added to a cooled (0 °C) solution of bromide **268** (1.21 g, 6.6 mmol) in bromoform (3 mL). To the reaction mixture, a solution of sodium hydroxide (1.14 g, 28 mmol) in water (6 mL) was added dropwise and the reaction mixture heated to 80 °C overnight. The reaction mixture was diluted with DCM (20 mL), washed with water (3x 20 mL) and brine (20 mL). The organic phase was dried with sodium sulfate, concentrated under reduced pressure and purified by flash chromatography (eluent: petroleum spirits 40-60) to give (1,2,2-tribromocyclopropyl)benzene **269** (418 mg, 18%) as a slightly yellow oil.

Characterisation data matches literature.[191]

3,4-Dichloro-1-phenylcyclohepta-1,3,5-triene 264

3,4-Dichloro-6-bromo-1-phenylcyclohepta-1,3,5-triene 275



A suspension of *n*-BuLi (1.6 M, 6.8 mL) in hexanes was added dropwise to a cooled (-84 °C) solution of (1,2,2-tribromocyclopropyl)benzene **269** (1.23 g, 3.5 mmol) in ether (20 ml) over 10 minutes, the reaction was stirred for 2 hours allowing to warm to room temperature. The reaction mixture was cooled to 0 °C and ammonium chloride solution (sat. 10 mL) was added, after 15 minutes 3,4-dichloro-1,1-thiophene dioxide **244** (494 mg, 2.67 mmol) was added and the reaction stirred overnight.

The organic layer was separated and washed with water (3x 20 mL) and brine (1x 20 mL), dried with sodium sulfate and concentrated under reduced pressure to afford the crude residue. The residue was purified by flash chromatography (eluent: petroleum spirits 40-60) to afford 3,4-dichloro-1-phenylcyclohepta-1,3,5-triene **264** (201 mg, 32% two steps) as a slightly brown oil..

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.44 (m, 2H), 7.40 – 7.32 (m, 3H), 6.51 (s, 1H), 6.30 (d, *J* = 9.5 Hz, 1H), 5.63 (m, *J* = 9.5, 7.3, 0.5 Hz, 1H), 2.91 (d, *J* = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 139.3 (C), 137.2 (C), 133.0 (C), 132.1 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 124.5 (CH), 123.7 (CH), 31.4 (CH_2).

HRMS (Orbitrap): $[M]^+$ $C_{13}H_{10}Cl_2$ $^+$requires 236.016; found 236.01537

The incomplete reaction product 3,4-dichloro-6-bromo-1-phenylcyclohepta-1,3,5-triene **275** was also identified in trace amounts.

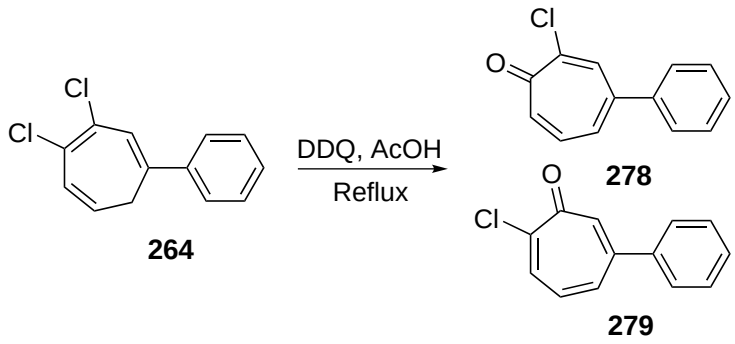
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.53 (m, 2H), 7.44 – 7.35 (m, 3H), 6.64 (s, 1H), 6.58 (s, 1H), 3.41 (s, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 138.3 (C), 136.8 (C), 133.3 (C), 130.4 (C), 129.1 (CH), 129.0 (CH), 128.9 (CH), 127.0 (CH), 124.0 (CH), 115.2 (C), 42.0 (CH_2).

HRMS (Orbitrap): $[M+1]^+$ $C_{13}H_{10}Cl_2Br^+$ requires 314.2965; found 313.9258.

2-Chloro-4-phenyl tropone 278

2-Chloro-6-phenyl tropone 279



264 **278** **279**

DDQ (385 mg, 1.7 mmol) was added to a solution of 3,4-dichloro-1-phenylcyclohepta-1,3,5-triene **264** (201 mg) in AcOH (5 mL) and the reaction mixture heated to 100 °C for 4 hours. The reaction mixture was cooled to room temperature and phosphoric acid (85%, 0.2 mL) was added and the reaction mixture stirred overnight. The solvent was removed under reduced pressure and the residue dissolved in DCM (50 mL), washed with 5% sodium hydroxide solution (3 x 30 mL) and brine (30 mL). The organic phase was dried with sodium solvent and concentrated under reduced pressure to give the crude oil

which was purified by flash chromatography (eluent: EtOAc/petroleum spirits 40-60 1:9) to give a mixture of 2-chloro-4-phenyl tropone **278** and 2-chloro-6-phenyl tropone **279** (133 mg, 72%) as a yellow oil.

Mixture of both isomers:

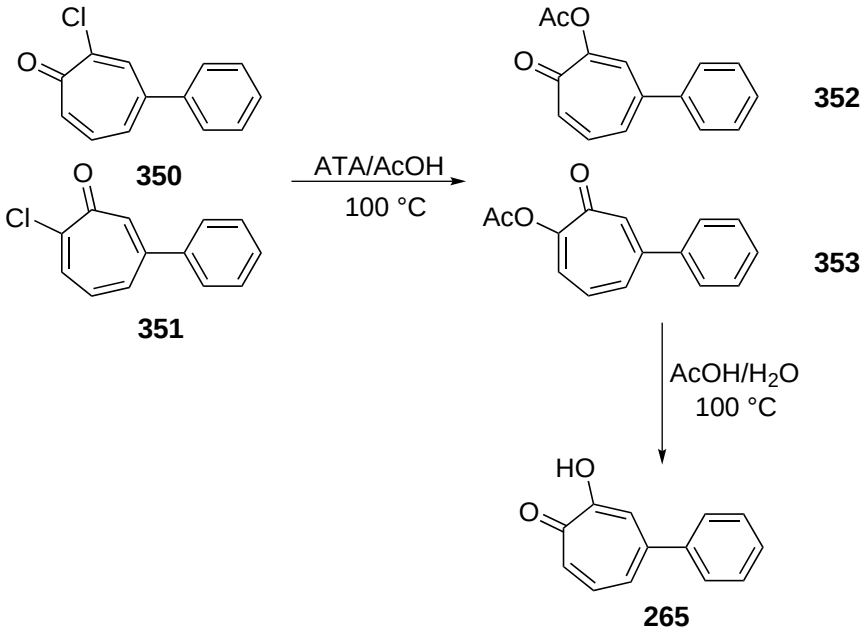
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 1.5 Hz, 1H), 7.78 (d, *J* = 9.5 Hz, 1H), 7.53 – 7.43 (m, 10H), 7.35 – 7.29 (m, 2H), 7.28 (s, 1H), 7.25 – 7.19 (m, 2H), 6.97 (dd, *J* = 11.4, 9.5 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 179.6 (C), 179.5 (C), 149.3 (C), 149.2 (C), 148.8 (C), 145.7 (C), 141.7 (C), 141.5 (C), 137.7 (CH), 137.7 (CH), 137.2 (CH), 136.5 (CH), 136.0 (CH), 135.1 (CH), 132.5 (CH), 130.7 (CH), 129.4 (CH), 129.2 (CH), 129.2 (CH), 129.1 (CH), 127.8 (CH), 127.6 (CH).

HRMS (ESI): $[M+1]^+$ $C_{13}H_{11}OCl^+$ requires 217.0342; found 217.0412

FTIR-ATR(cm^{-1}): 1626 (C=O), 1588 (C=O)

4-Phenyltropolone 265



A mixture of 2-Chloro-4-phenyl tropone **350** and 2-Chloro-6-phenyl tropone **351** (100 mg, 0.5 mmol) was added to a solution of ATA (5 mL) prepared by the procedure of Takeshita *et al.*[183] and the reaction mixture heated at 85 °C overnight. The solvent was removed under reduced pressure to give a mixture of 2-acetyl-4-phenyltropolone **352** and 2-acetyl-4-phenyl tropolone **353** which were immediately hydrolysed using a solution of water (5 mL) and AcOH (5 mL) heated to 100 °C overnight. The solvent was removed under reduced pressure and the residue purified by flash chromatography (eluent: EtOAc/petroleum spirits 40-60 1:9) to give 4-phenyltropolone **265** (63 mg, 52%) as a slightly yellow solid.

Acetylphenyltroplone:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (t, *J* = 10.5 Hz, 1H), 8.30 – 8.23 (m, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 7.99 (d, *J* = 10.2 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.37 – 7.30 (m, 3H), 1.95 (s, 3H).

Other isomer unable to be elucidated.

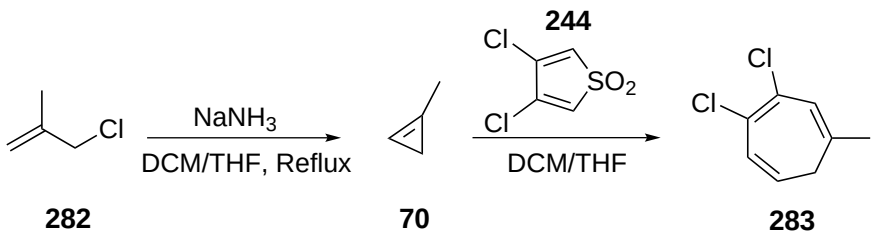
4-Phenyltropolone

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 1.6 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.50 – 7.43 (m, 4H), 7.36 (s, 1H), 7.27 – 7.23 (m, 1H).

HRMS (HESI Q exactive MS): $[M+1]^+$ $C_{13}H_{12}O_2^+$ requires 199.061; found 199.0754

The NMR spectral data matches those reported in literature.[217]

3,4-Dichloro-1-methylcyclohepta-1,3,5-triene 283



Methyl allyl chloride **282** (30 mL, 304 mmol) was added slowly to a solution of sodium amide (11.06 g, 284 mmol) in dry THF (100 mL) and the reaction heated under reflux.

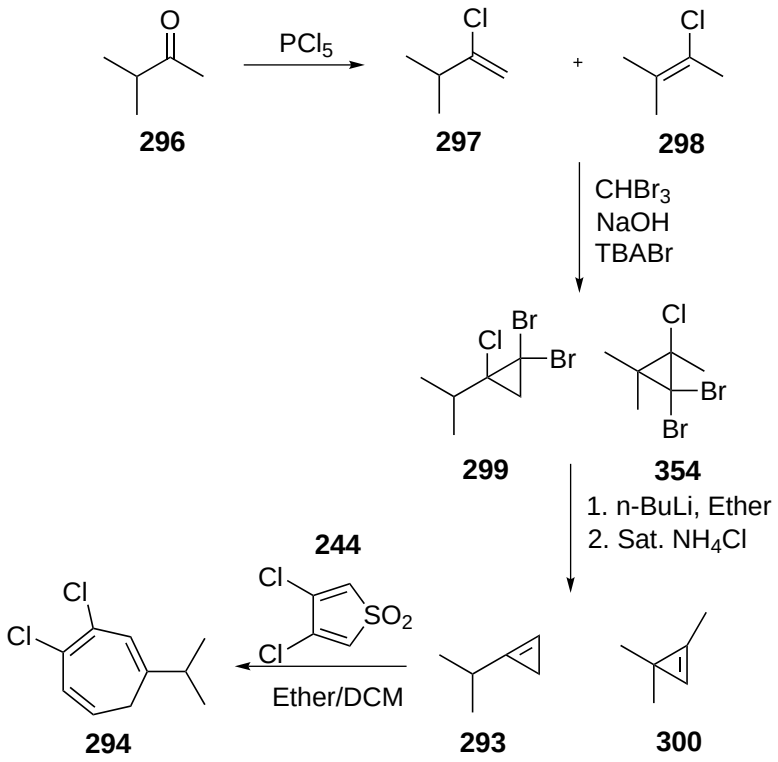
A gentle flow of nitrogen gas was passed through the reaction flask to collect the 1-methylcyclopropene **70** in a - 196 °C trap containing a solution of 3,4-dichloro thiophene-1,1-dioxide **244** (507 mg, 2.7 mmol) in DCM (5 mL). The trap was periodically warmed to - 84 °C to clear blockages. After three hours the solvent from the collection flask was removed and the residue dissolved in water (20 mL). The aqueous mixture was then extracted with (3x 20 mL) DCM. The combined organic extracts were washed with water (3x 10 mL) and brine (1x 20 mL), dried with sodium sulfate and concentrated under reduce pressure to afford an oil. The oil was purified by flash chromatography (elutent: petroleum spirits 40-60) to afford 3,4-dichloro-1-methylcyclohepta-1,3,5-triene **283** (300 mg, 63%) as a slightly yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.16 (d, *J* = 9.5 Hz, 1H), 6.02 (q, *J* = 1.5 Hz, 1H), 5.54 (dt, *J* = 9.5, 7.2 Hz, 1H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.98 (d, *J* = 1.5 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.4 (C), 132.7 (C), 130.6 (C), 127.9 (CH), 124.5 (CH), 123.2 (CH), 33.4 (CH_2), 23.9 (CH_3).

HRMS (Orbitrap): $[M]^+$ $C_8H_8Cl_2^+$ requires 174.0003; found 173.9998.

3,4-Dichloro-1-isopropylcyclohepta-1,3,5-triene 294



3-methyl-2-butanone **296** (6.98 g, 8.11 mmol) was added to cooled (0 °C) PCl_5(20.05 g, (9.63 mmol) neat. After addition was complete, the reaction was heated under reflux for 1 hour. Once cool, the reaction mixture was added to ice water (300 mL) and gently stirred for 30 minutes. The organic layer was seperated, and dried with sodium sulfate to give an oil containing two isomers; 2-chloro-3-methylbut-2-ene **298** and the desired product 2-chloro-3-methylbut-1-ene **297** (4.47 g, 53% crude, both isomers) as a yellow oil.

2-chloro-3-methylbut-1-ene **297**:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.13 (dd, *J* = 1.4, 0.9 Hz, 1H), 5.09 (d, *J* = 1.4 Hz, 1H), 2.56 (h, *J* = 6.8, 0.9 Hz, 1H), 1.14 (s, 3H), 1.13 (s, 3H).

2-chloro-3-methylbut-2-ene **298**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.15 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H).

Characterisation data matches literature.[203–205]

Ethanol (1 mL) and TBABr (278 mg) were added to a cooled (0 °C) solution of the forgoing butene mixture (4.47 g, 42.7 mmol) in bromoform (11 mL, 126 mmol). NaOH (7.93 g, 198 mmol) in water (12 mL) was added dropwise to the reaction mixture, once addition completed the reaction mixture was stirred overnight while warming to room temperature. Water (100 mL) was added and extracted with DCM (3x 30 mL). The combined organic extracts were dried with sodium sulfate and concentrated under reduced pressure to give an oil. The oil was purified by flash chromatography (eluent: petroleum spirits 40-60) to get a mixture of two isomers 1,1-dibromo-2-chloro-2,3,3-trimethylcyclopropane **300** and the desired 1,1-dibromo-2-chloro-2-isopropylcyclopropane **299** (3.11 g, 26% both isomers 4:1) as colourless crystals.

1,1-dibromo-2-chloro-2-isopropylcyclopropane **299**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.97 (h, *J* = 13.2, 6.6 Hz, 1H), 1.92 (d, *J* = 9.0 Hz, 1H), 1.79 (d, *J* = 9.0 Hz, 1H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H).

Characterisation data matches literature.[203,207]

1,1-dibromo-2-chloro-2,3,3-trimethylcyclopropane **300**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.81 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H).

Baird *et al.* have reported 1,1,2-tribromo-2,3,3-trimethylcyclopropane and 1,1,2-trichloro-2,3,3-trimethylcyclopropane to have the same ^{1}H NMR spectrum, which also matches 1,1-dibromo-2-chloro-2,3,3-trimethylcyclopropane **300**.[207]

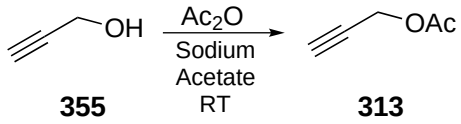
n-BuLi (1.6 M, 20 mL) diluted in ether (10 mL) was added dropwise to a cooled solution (- 84 °C) of the cyclopropane isomer mixture (3.11 g, 11.3 mmol) in ether (30 ml) over 20 minutes. Once addition was complete the reaction mixtured stirred for 1 hour while allowing to warm to room temperature. The reaction was cooled to - 84 °C, ammonium chloride solution (sat. 20 mL) was added and the reaction stirred for 15 minutes. The organic layer was separated, to which, 3,4-dichloro-1,1-thiophene dioxde (632 mg, 3.4 mmol) dissolved in DCM (40 mL) was added and the reaction stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to give an oil which was purified by flash chromatography (eluent: petroleum spirits 40-60) to afford 3,4-dichloro-1-isopropylcyclohepta-1,3,5-triene **294** (184 mg, 8% two steps) as a slighly yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.15 (d, *J* = 9.5 Hz, 1H), 6.00 (dt, *J* = 1.0, 0.5 Hz, 1H), 5.47 (dtd, *J* = 9.5, 7.2, 0.5 Hz, 1H), 2.48 (pd, *J* = 6.8, 1.1 Hz, 1H), 2.42 (d, *J* = 7.2 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.5 (C), 132.7 (C), 130.6 (C), 127.6 (CH), 124.8 (CH), 120.6 (CH), 35.4 (CH), 30.2 (CH_2), 22.2 (CH_3).

HRMS (Orbitrap): $[M]^+$ $C_{10}H_{12}Cl_2^+$ requires 202.0316; found 202.0358.

Propargyl Acetate 313

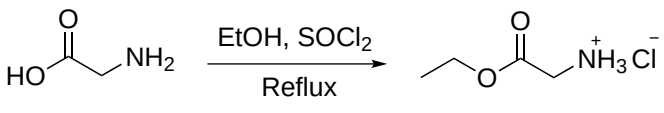


355 **313**

A solution of propargyl alcohol **355** (20.06 g, 360 mmol) and sodium acetate trihydrate (4.87 g, 35.8 mmol) in acetic anhydride (40 mL) was stirred at room temperature for 2 hours. The reaction was diluted with ether (200 mL) and, washed with water (100 mL), saturated $NaHCO_3$ solution (3x 50 mL). The organic layer was dried with sodium sulfate, filtered and concentrated under reduced pressure to afford the crude as a slightly yellow liquid. The crude was purified by vacuum distillation to afford propargyl acetate **313** (23.80 g, 68%) as a colourless liquid.

Characterisation data matches literature.[238]

Glycine ethyl ester hydrochloride 312



349 **312**

Thionyl chloride (30 mL, 414 mmol) was added dropwise to a cooled (0 °C) solution of glycine (20.04 g, 267 mmol) **349** in ethanol (200 mL). Once addition was complete

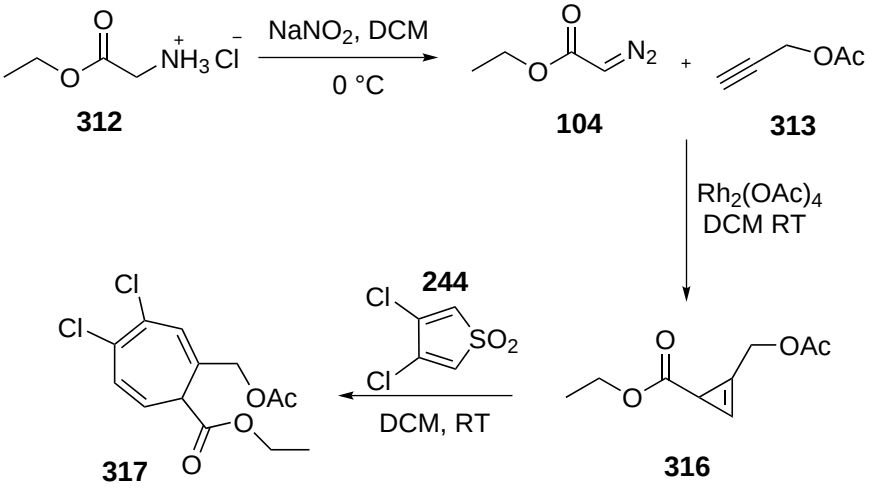
additional glycine **349** (19.97 g, 266 mmol) was added and the reaction heated under reflux for 2 hours. After the reaction had cooled to 60 °C the stirrer was removed and the reaction left to sit overnight to allow crystal formation. The crystals were collected by vacuum filtration then dried under reduced pressure to obtain Glycine ethyl ester hydrochloride **312** (57.347 g, 99%) as white crystals.

Characterisation data matches literature.[239]

Ethyl diazoacetate 104

Ethyl 2-(acetoxymethyl)cycloprop-2-enecarboxylate 316

Ethyl 2-(acetoxymethyl)-4,5-dichlorocyclohepta-2,4,6-trienecarboxylate 317



Sodium nitrite (7.45 g, 108 mmol) was added to a cooled (0 °C) solution of glycine ethyl ester hydrochloride **312** (10.123 g, 72.5 mmol) in DCM (200 mL) and water (100 mL) and the reaction mixture stirred for 4 hours. The organic layer was seperated and washed with water (1x 50 mL) and brine (1x 50 mL), dried with sodium sulfate and concentrated under reduced pressure at room temperature to afford crude ethyl diazoacetate **104** (7.62 g, 66.8 mmol) as a brightly coloured yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.72 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

The crude ethyl diazoacetate **104** solution was diluted to 12 mL in dry DCM and injected using a syringe pump at a rate of 0.14 mL/min into a solution of propargyl acetate (2.135 g, 21.8 mmol) and Rh_2OAc_4 (95 mg) in dry DCM (25 mL). The reaction was stirred at room temperature for 18 hours including injection time.

3,4-dichloro-1,1-thiophene dioxide **244** (4.40 g, 23.8 mmol) was added to the cooled (0 °C) crude mixture containting ethyl 2-(acetoxymethyl)cycloprop-2-enecarboxylate **316** and the reaction left stirred while warming to room temperature over 3 hours. The mixture was concentrated under reduced pressure and the crude residue purified by flash chromatography (eluent: EtOAc:petroleum spirits 40-60 1:9) to obtain ethyl 2-(acetoxymethyl)-4,5-dichlorocyclohepta-2,4,6-trienecarboxylate **317** (1.785 g, 27 % two steps) as a slightly yellow oil.

2-(acetoxymethyl)cycloprop-2-enecarboxylate **316**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.70 (q, *J* = 1.6 Hz, 1H), 5.05 (dd, *J* = 4.3, 1.6 Hz, 2H), 4.16 – 4.13 (m, 2H), 2.32 (d, *J* = 1.5 Hz, 1H), 2.11 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).

HRMS (ESI): $[M+1]^+$ $C_9H_{14}O_4^+$ requires 185.0736; found 185.0807

Ethyl 2-(acetoxymethyl)-4,5-dichlorocyclohepta-2,4,6-trienecarboxylate **317**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.35 (td, *J* = 1.3, 0.7 Hz, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 5.84 (ddd, *J* = 9.8, 7.5, 0.6 Hz, 1H), 4.79 – 4.62 (m, 2H), 4.18 (q, *J* = 7.1, 1.3 Hz, 2H), 3.30 (d, *J* = 7.5 Hz, 1H), 2.05 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

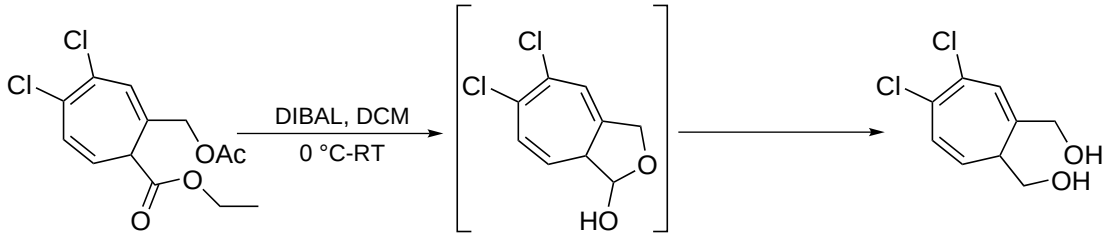
^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.18 (C), 169.73 (C), 133.28 (C), 132.04 (C), 131.68 (C), 127.49 (CH), 125.61 (CH), 124.66 (CH), 64.35 (CH_2), 61.71 (CH_2), 45.79 (CH), 20.90 (CH_3), 14.21 (CH_3).

ATR-FTIR(cm^{-1}): 1740 (C=O)

HRMS (ESI): $[M+1]^+$ $C_{13}H_{16}O_4Cl_2^+$ requires 305.0269; found 305.0340

(4,5-Dichlorocyclohepta-2,4,6-triene-1,2-diyl)dimethanol 319

5,6-dichloro-3,8α-dihydro-1*H*-cyclohepta[*c*]furan-1-ol 318



317 **318** **319**

A suspension of DIBAL (1M, 14 mL) in THF was added dropwise was added to a cooled (0 °C) solution of ethyl 2-(acetoxymethyl)-4,5-dichlorocyclohepta-2,4,6-trienecarboxylate (1.01 g, 3.3 mmol) **317** in dry DCM (50 mL). Once addition was complete the reaction was stirred for 1.5 hours while warming to room temperature. The reaction mixture was cooled to 0 °C and water (3 mL) was added, followed by NaOH (5%, 9 mL), the mixture was diluted with ether (60 mL) and stirred at room temperature for 15 minutes. Magnesium sulfate was added and the reaction mixture stirred for an additional 15 minutes. The reaction mixture was filtered and the magnesium sulfate residue washed with DCM (50 mL). The fitrate was concentrated under reduced pressure to obtain the crude residue which was purified by flash chromatography (eluent: EtOAc:petroleum spirits 40-60 1:1) to obtain (4,5-dichlorocyclohepta-2,4,6-triene-1,2-diyl)dimethanol **319** (458 mg, 63%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.33 (s, 1H), 6.26 (d, *J* = 10.0 Hz, 1H), 5.50 (dd, *J* = 10.0, 7.9 Hz, 1H), 4.23 (s, 2H), 3.79 – 3.61 (m, 2H), 3.28 (s, 2H, OH), 2.95 – 2.80 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.4, 132.2, 131.3, 128.1, 126.0, 124.7, 65.4, 60.0, 42.9.

FTIR-ATR(cm^{-1}): 3416 (OH).

The incomplete reduction product 5,6-dichloro-3,8α-dihydro-1*H*-cyclohepta[*c*]furan-1-ol **318** was also isolated in trace amountsc as a slightly brown solid:

MP: 136-142 °C

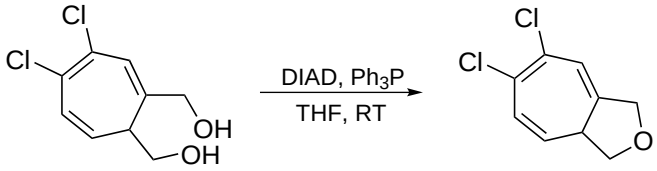
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.27 – 6.07 (m, 2H), 5.34 (dd, *J* = 9.7, 4.8 Hz, 1H), 4.82 (d, *J* = 14.1 Hz, 1H) , 4.53 (dtd, *J* = 14.1, 1.9, 0.6 Hz, 1H). 4.68 – 4.44 (m, 1H), 2.65 (ddt, *J* = 6.9, 5.1, 2.5 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.35 (C), 127.35 (CH), 127.15 (C), 124.31 (CH), 116.59 (CH), 103.13 (CH), 68.47 (CH_2), 49.83 (CH), 46.60 (CH).

FTIR-ATR(cm^{-1}): 3390 (OH-C-O)

HRMS (Orbitrap): $[M]^+$ $C_9H_8O_2Cl_2^+$ requires 217.9907; found 217.98958.

6,7-Dichloro-3,3a-dihydro-1H-cyclohepta[c]furan 322



319 **322**

Triphenylphosphene (548 mg, 2.09 mmol), followed by DIAD (540 μL, 2.7 mmol) were added to a cooled (0 °C) solution of (4,5-dichlorocyclohepta-2,4,6-triene-1,2-diyl)dimethanol **319** (305 mg , 1.38 mmol) in dry THF (6 mL) and the reaction stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue purified by flash chromatography (eluent: EtOAc:petroleum spirits 40-60 0:1-1:4) to obtain 6,7-dichloro-3,3a-dihydro-1*H*-cyclohepta[*c*]furan **322** (63 mg, 23%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.20 – 6.15 (m, 2H), 5.29 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.43 (s, 2H), 4.22 (dd, *J* = 9.2, 6.8 Hz, 1H), 4.08 (dd, *J* = 9.2, 3.9 Hz, 1H), 2.83 – 2.74 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.9 (C), 133.0 (C), 131.4 (C), 127.9 (CH), 127.4 (CH), 116.2 (CH), 74.2 (CH_2), 70.1 (CH_2), 42.7 (CH).

HRMS (Orbitrap): $[M]^+$ $C_9H_8OCl_2^+$ requires 201.9952; found 201.99474.

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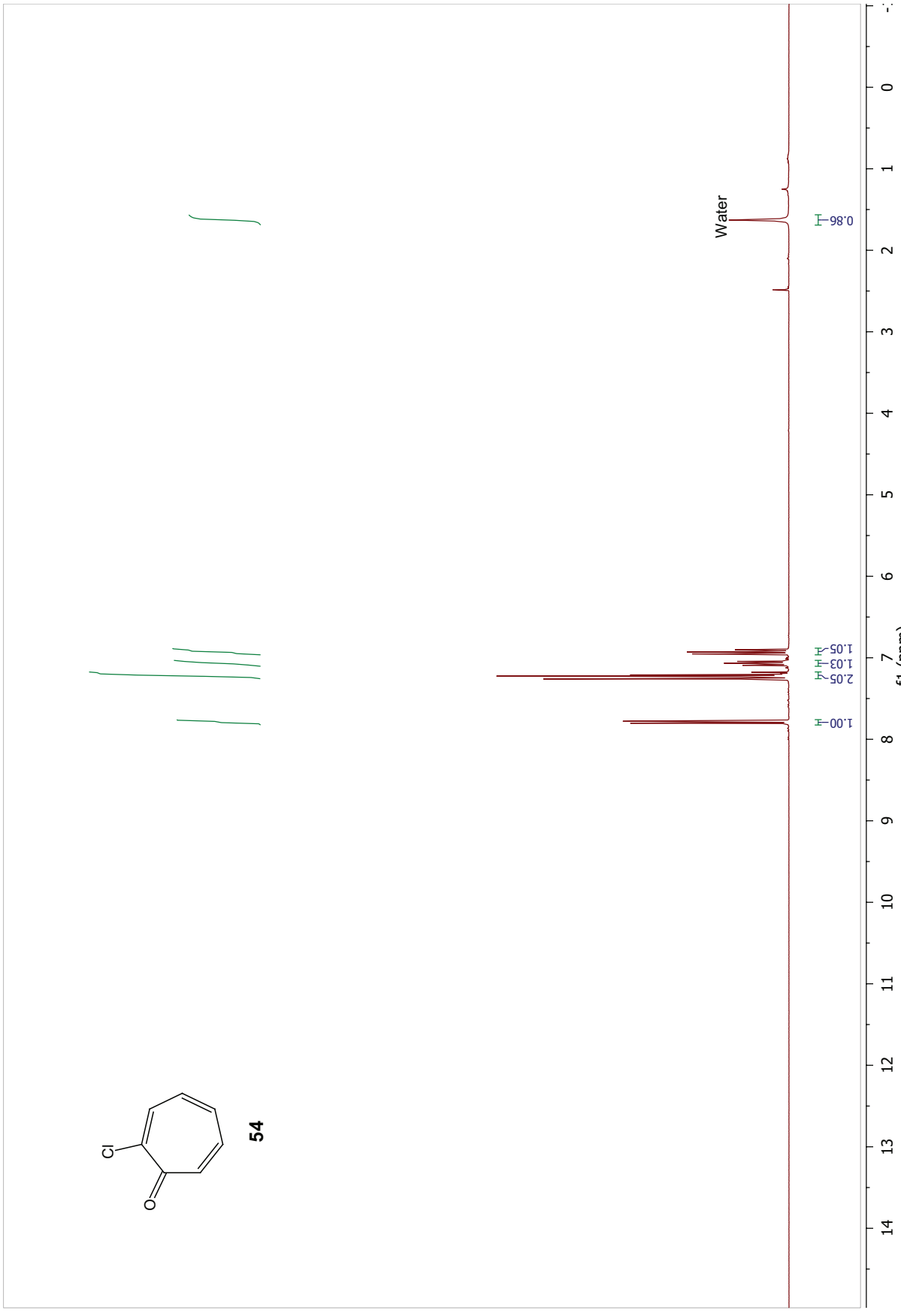
Appendix A

NMR Spectra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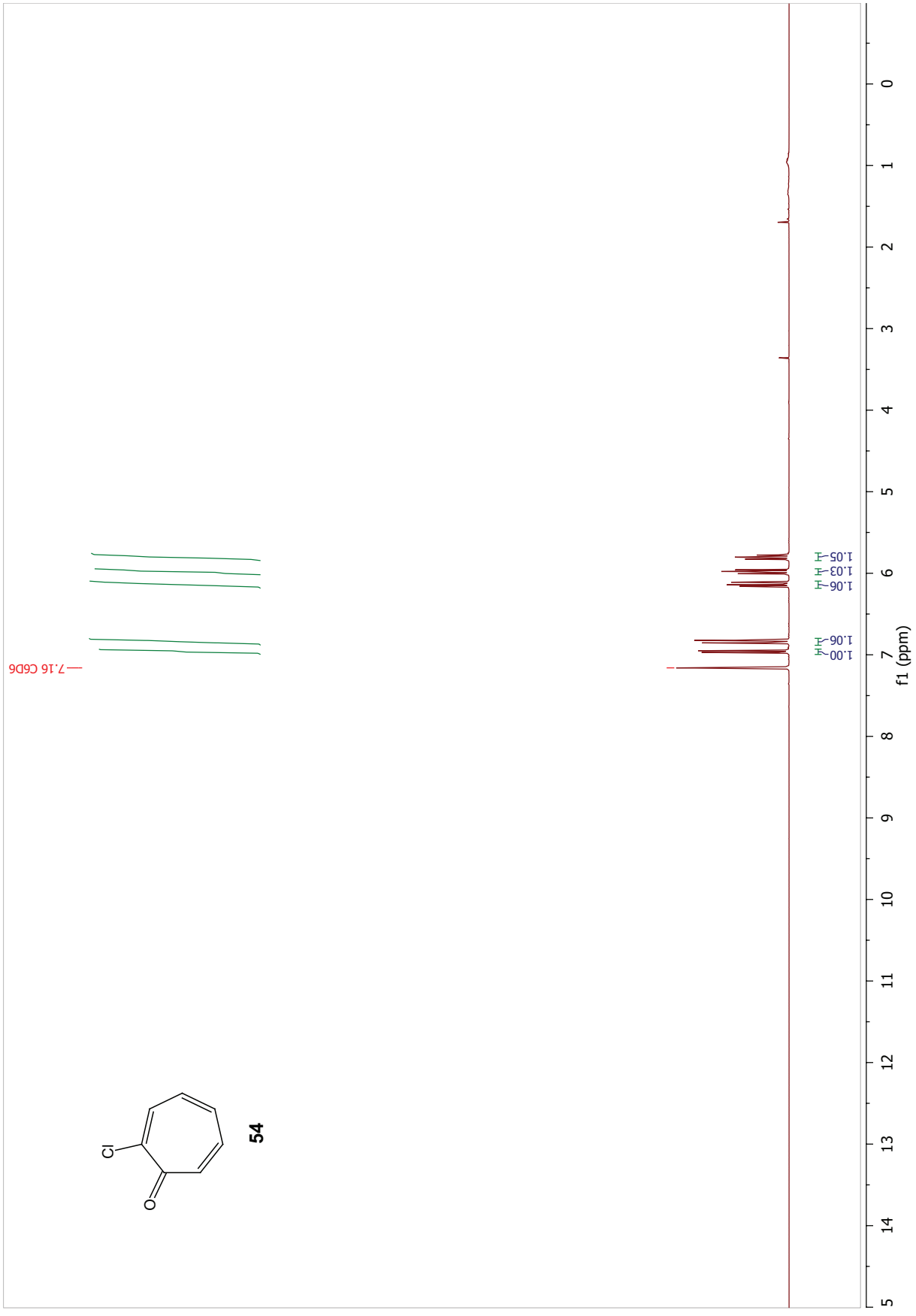
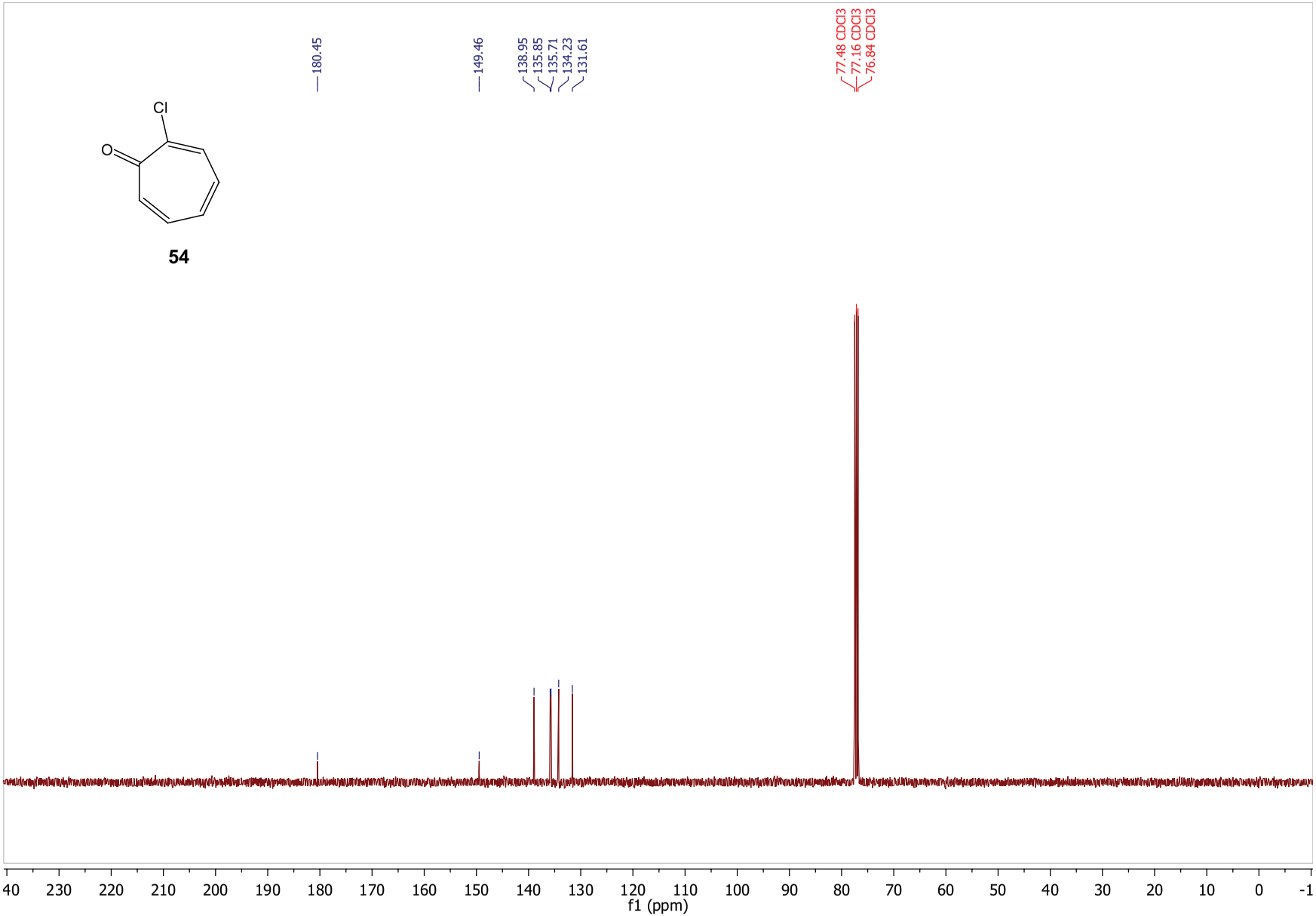
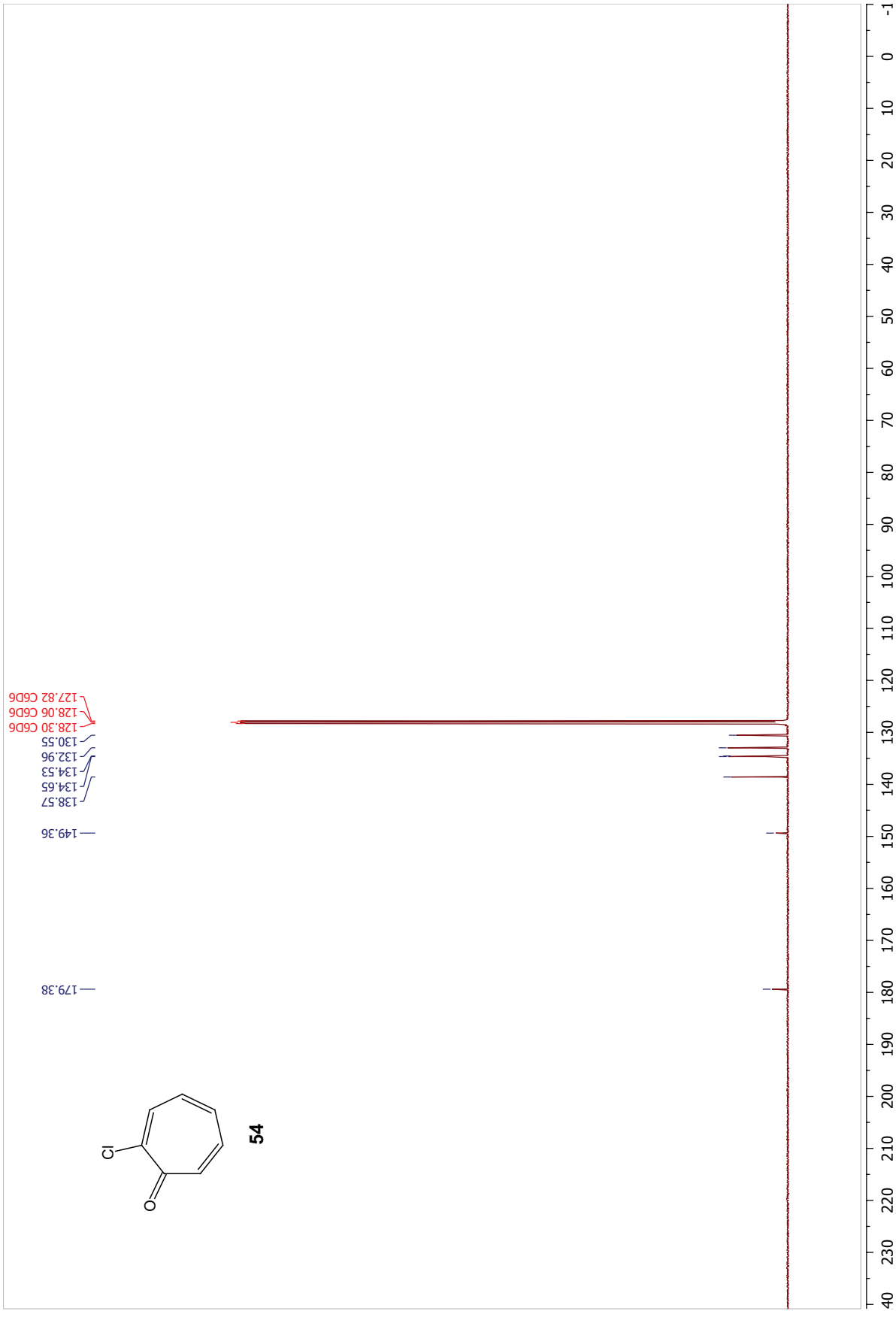
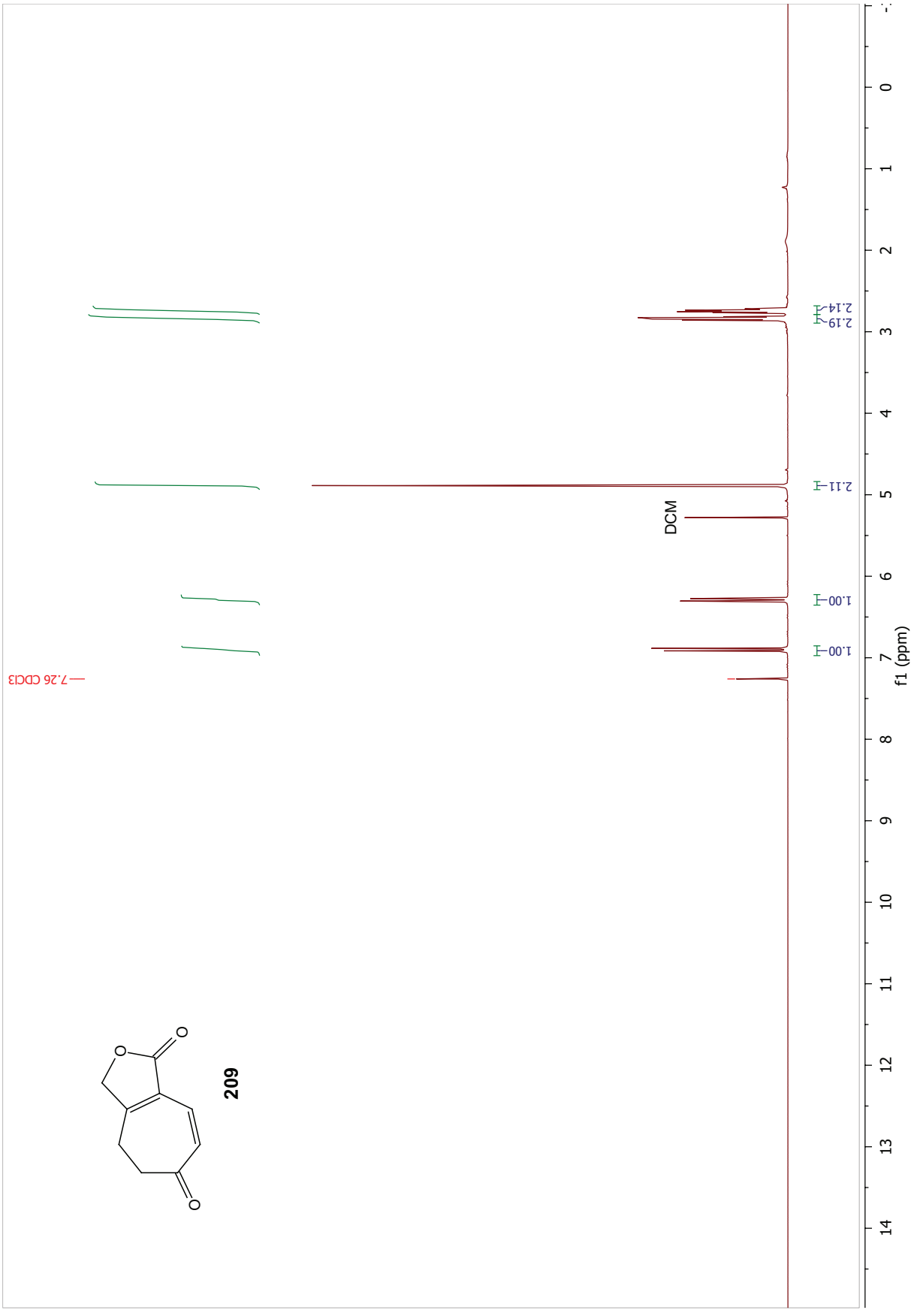
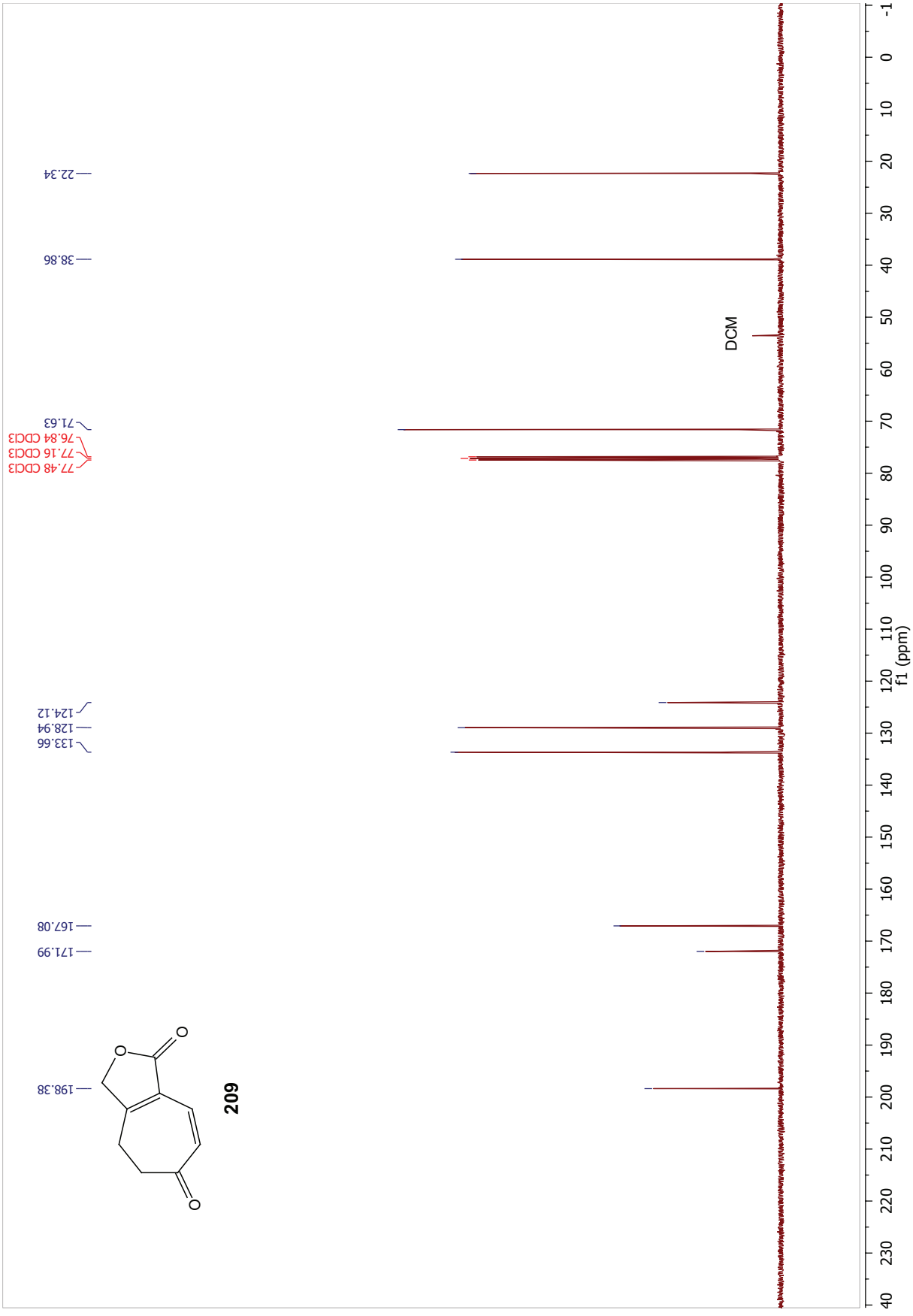
1.03
2.05
1.00
f1 (ppm)
Cl
O
54

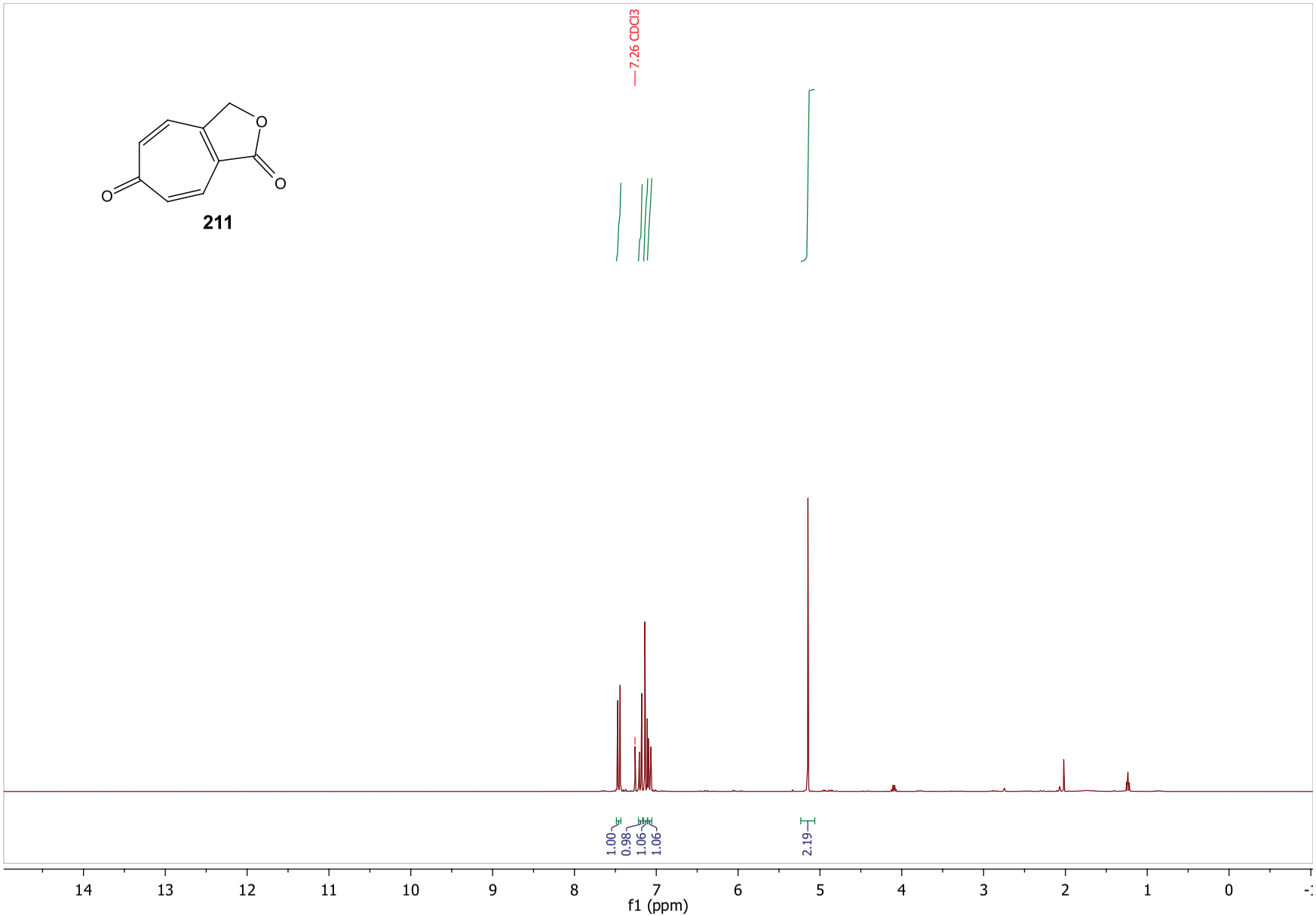

7.16 C6D6
1.00
1.06
1.06
1.03
1.05
f1 (ppm)
Cl
O
54

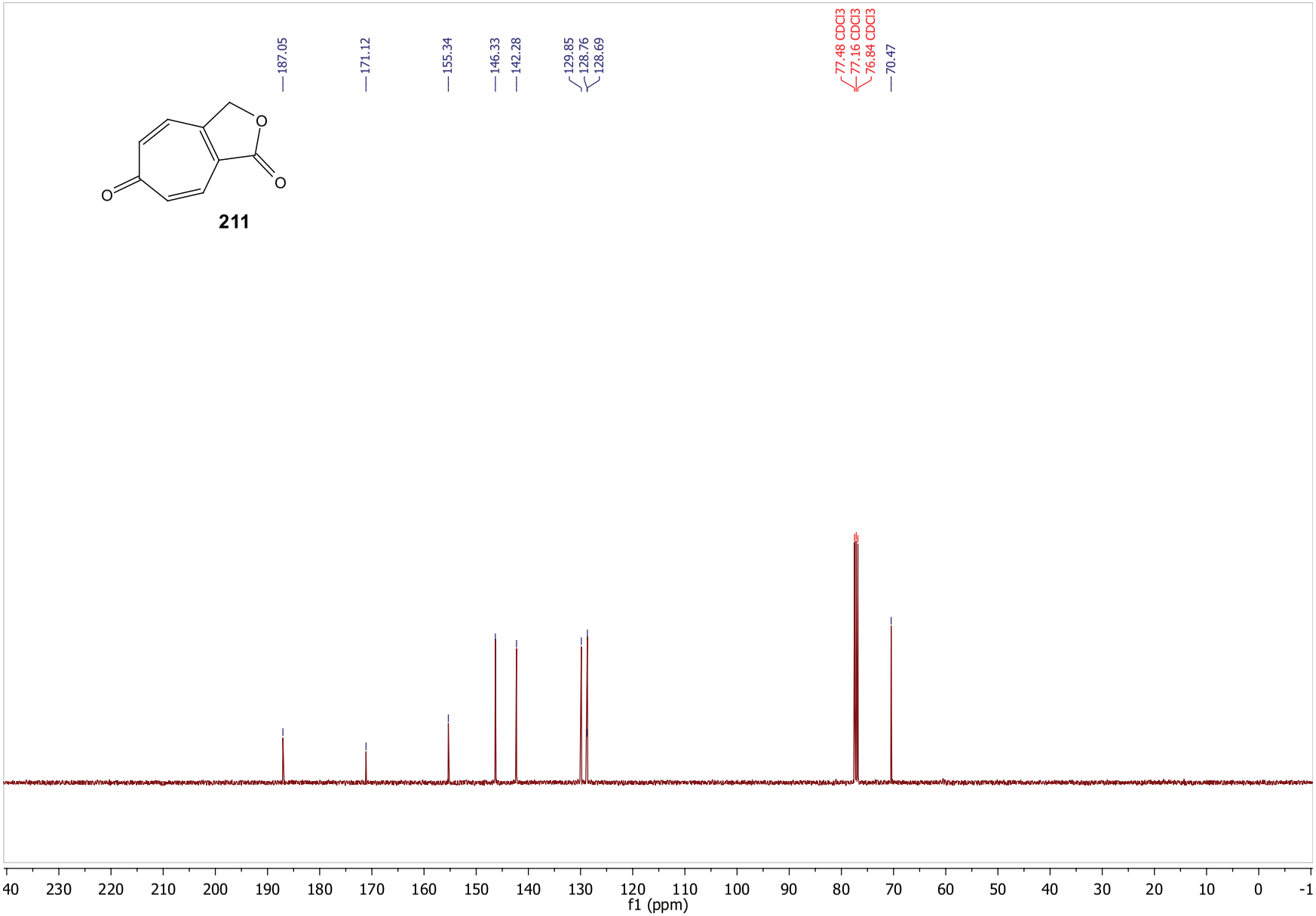

180.45
149.46
138.95
135.85
135.71
134.23
131.61
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
Cl
O
54
f1 (ppm)


179.38
149.36
138.57
134.65
134.53
132.96
130.55
128.30 C6D6
128.06 C6D6
127.82 C6D6
f1 (ppm)
Cl
O
54


209
7.26 CDCl3
DCM
2.19
2.14
2.11
1.00
1.00
f1 (ppm)


198.38
171.99
167.08
133.66
128.94
124.12
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.63
38.86
22.34
DCM
209
f1 (ppm)


7.26 CDCl3
O
O
O
211
1.00
0.98
1.06
1.06
2.19
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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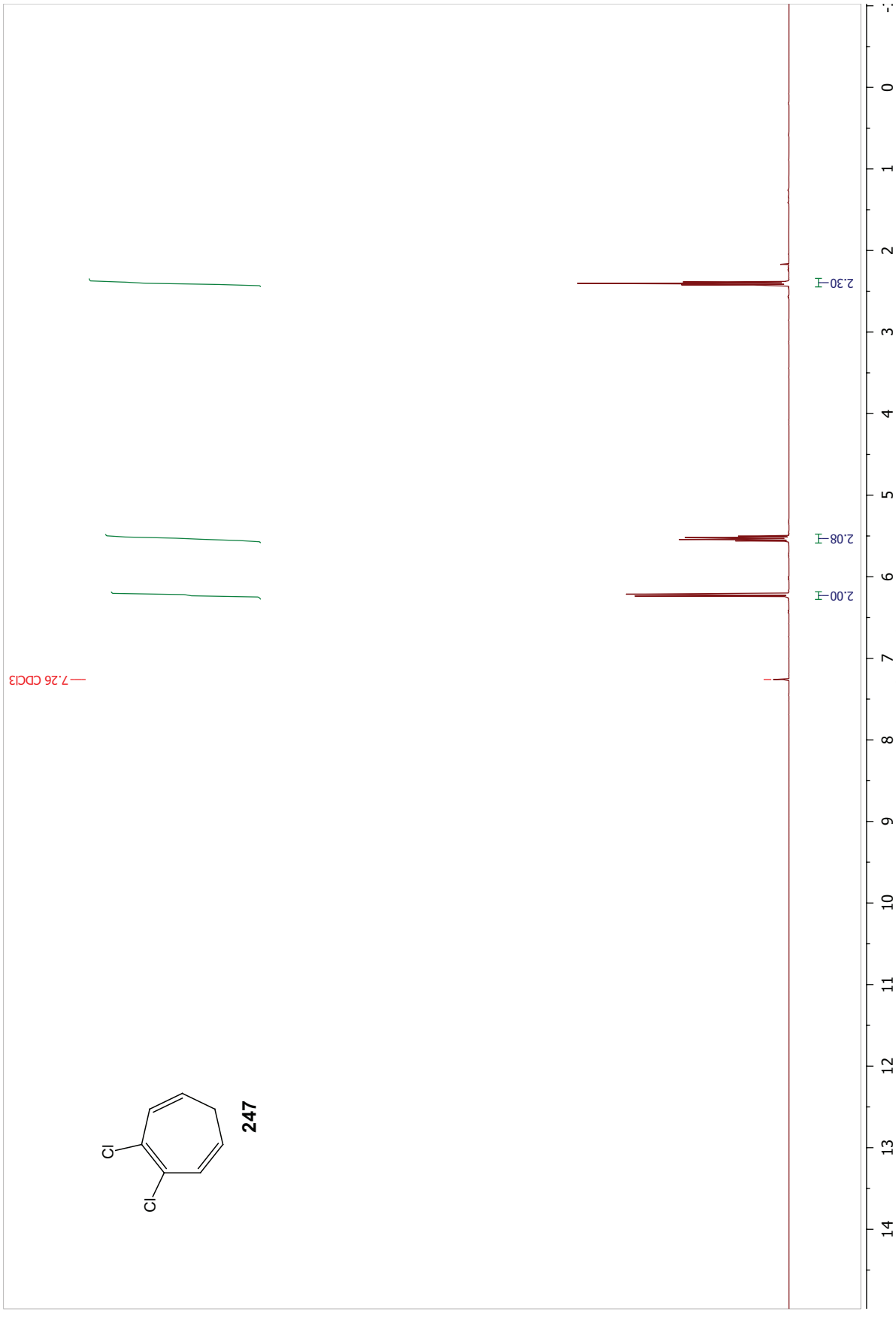
171.12
155.34
146.33
142.28
129.85
128.76
128.69
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
70.47
O
O
O
211
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)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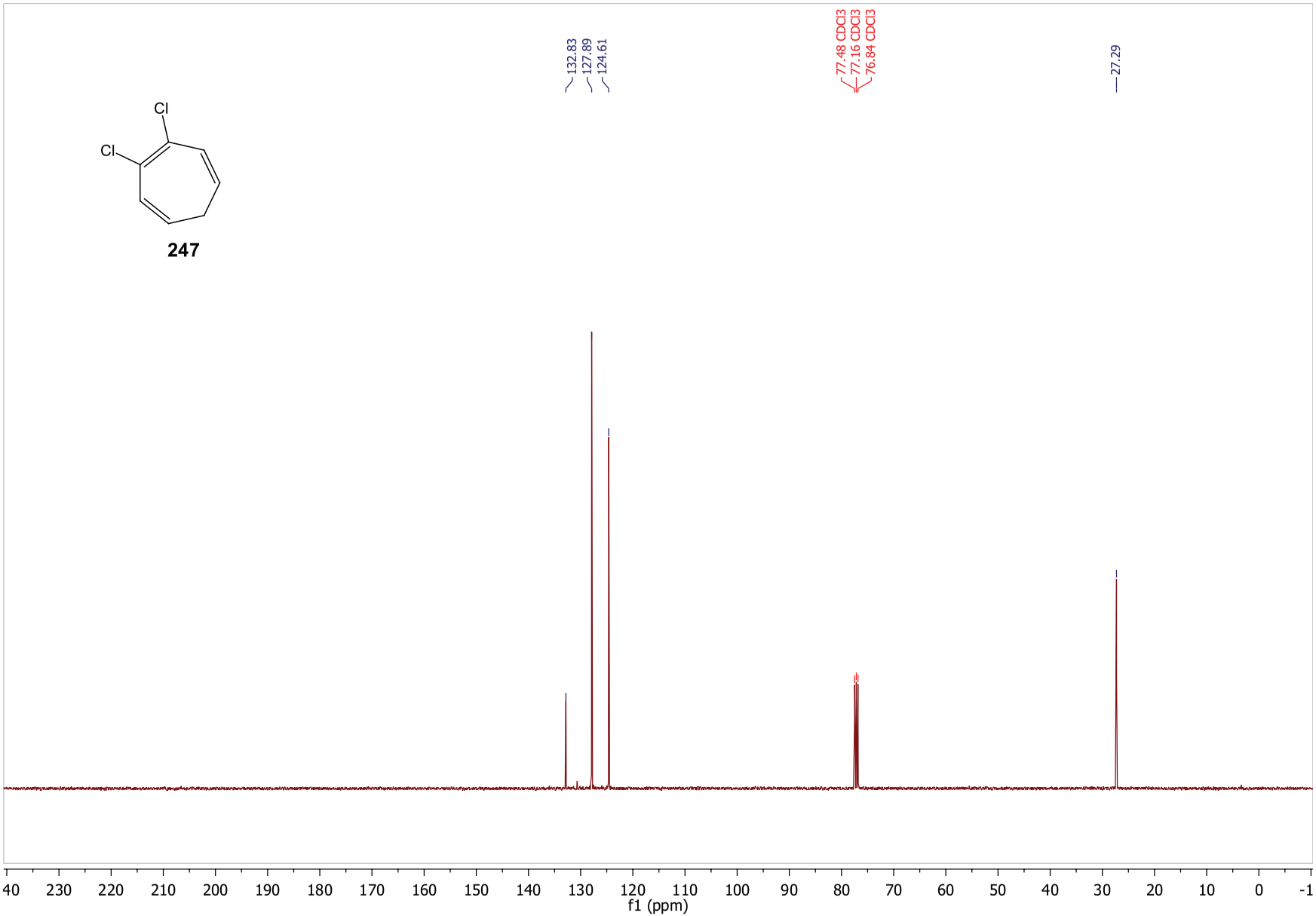
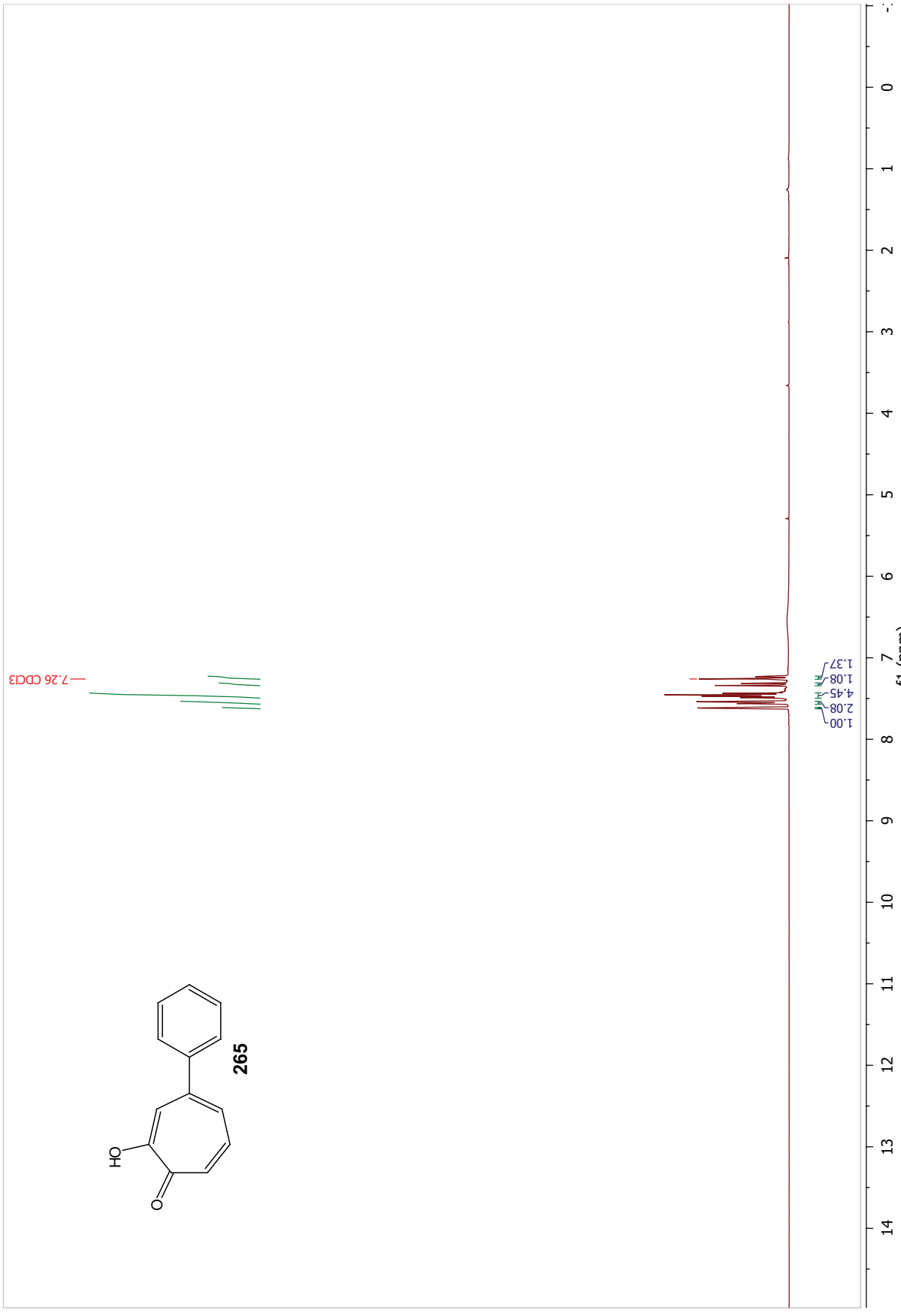
2.30
2.08
2.00
f1 (ppm)
Cl
Cl
247


Cl
Cl
247
132.83
127.89
124.61
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
27.29
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)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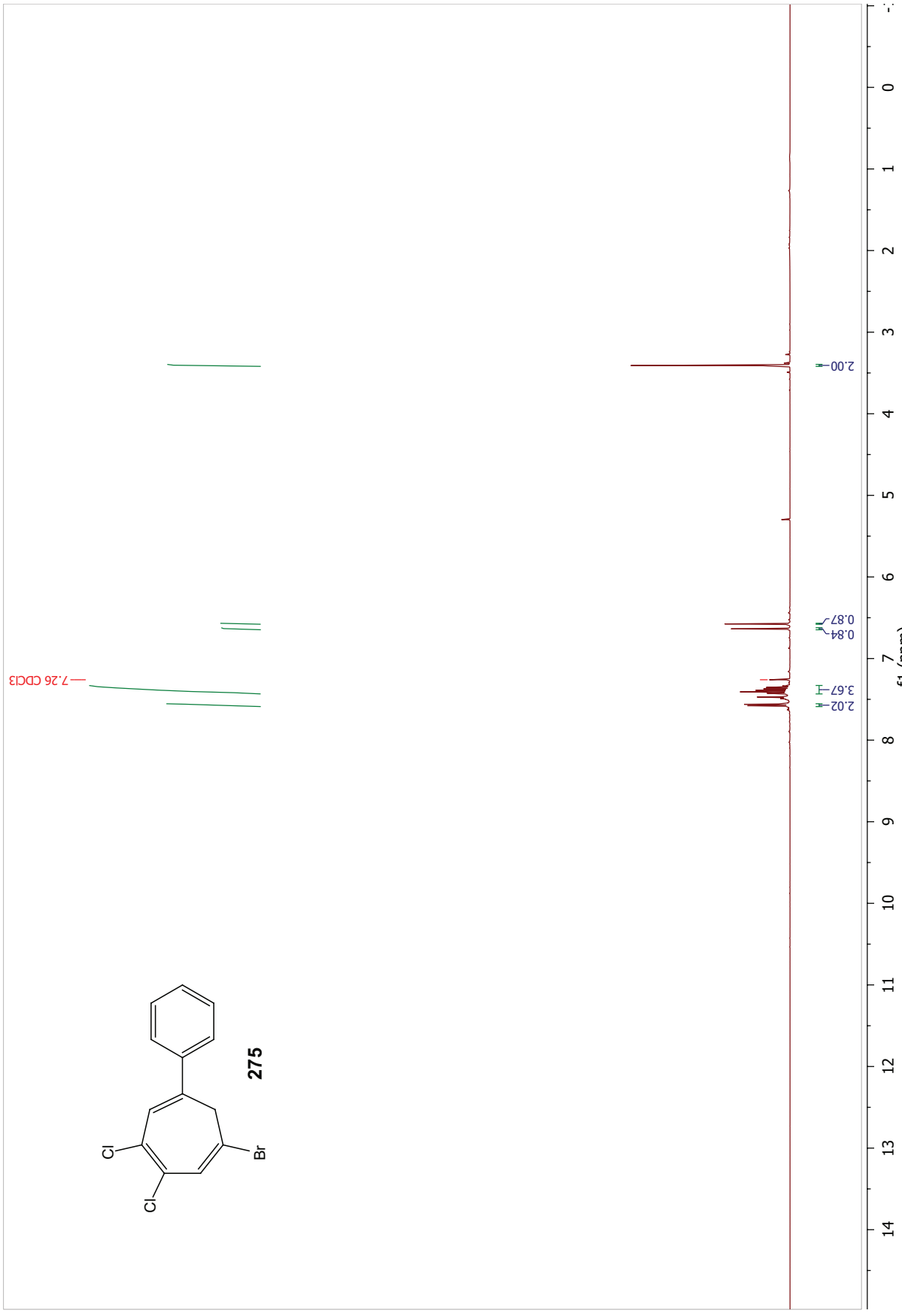
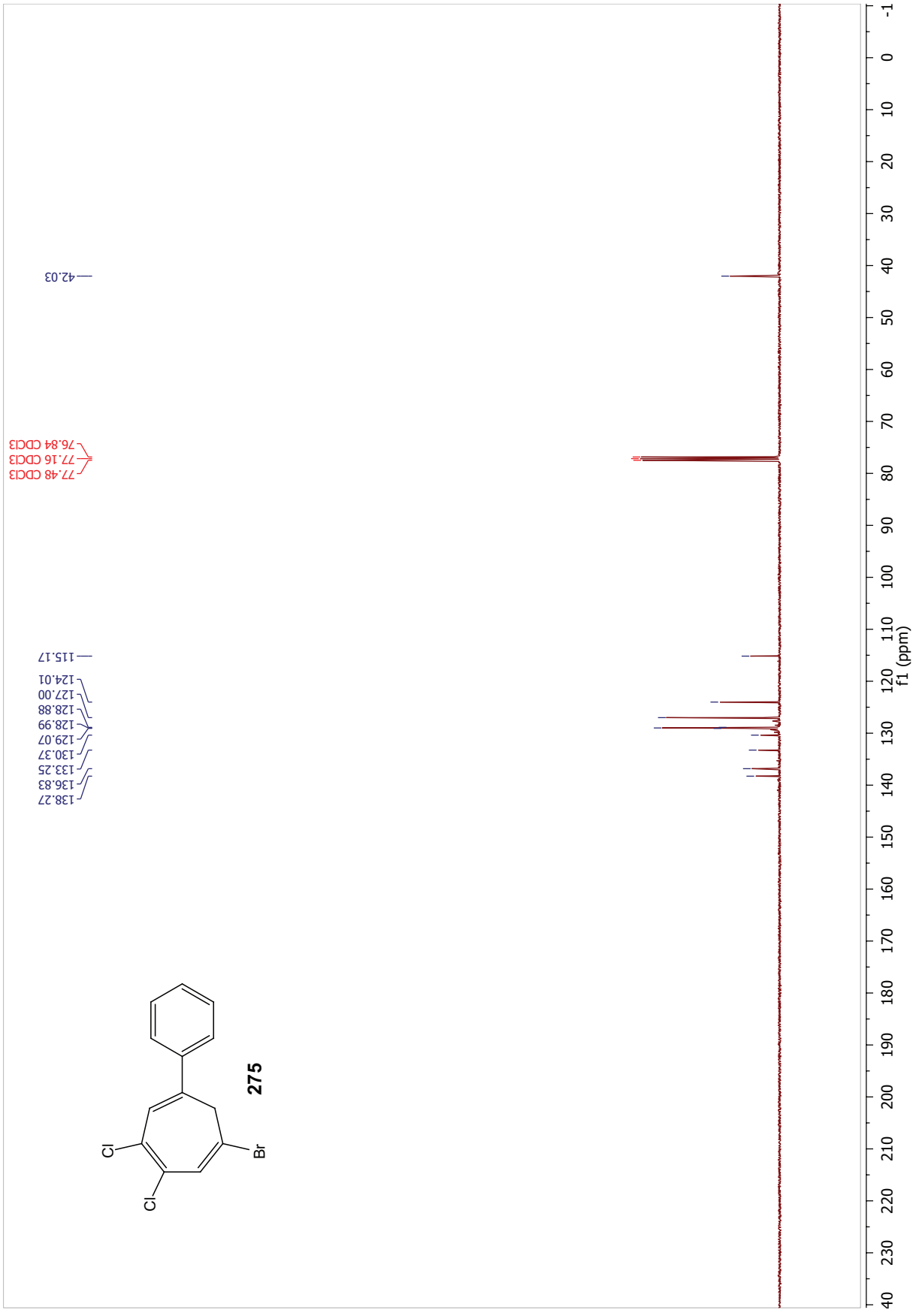
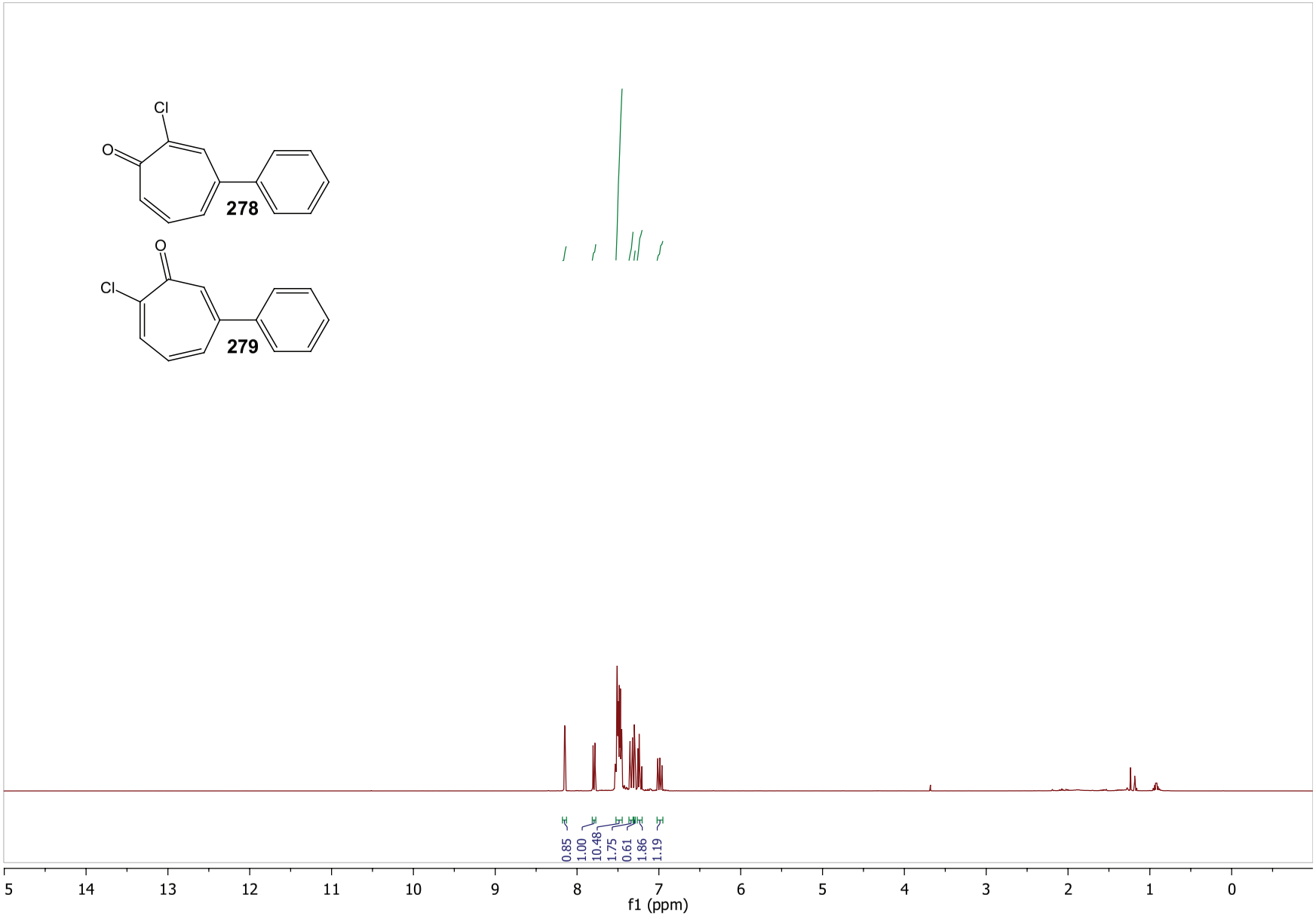
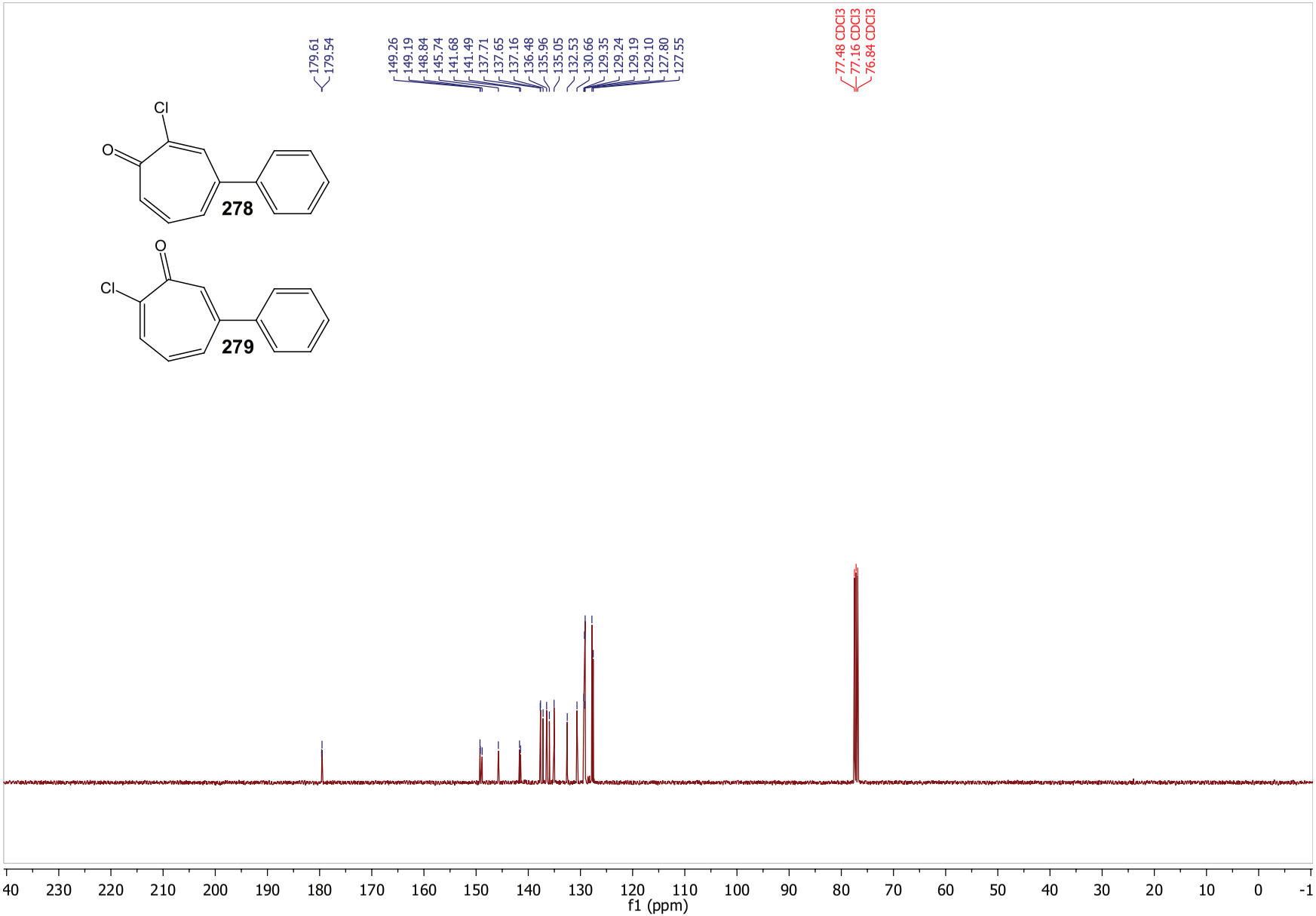
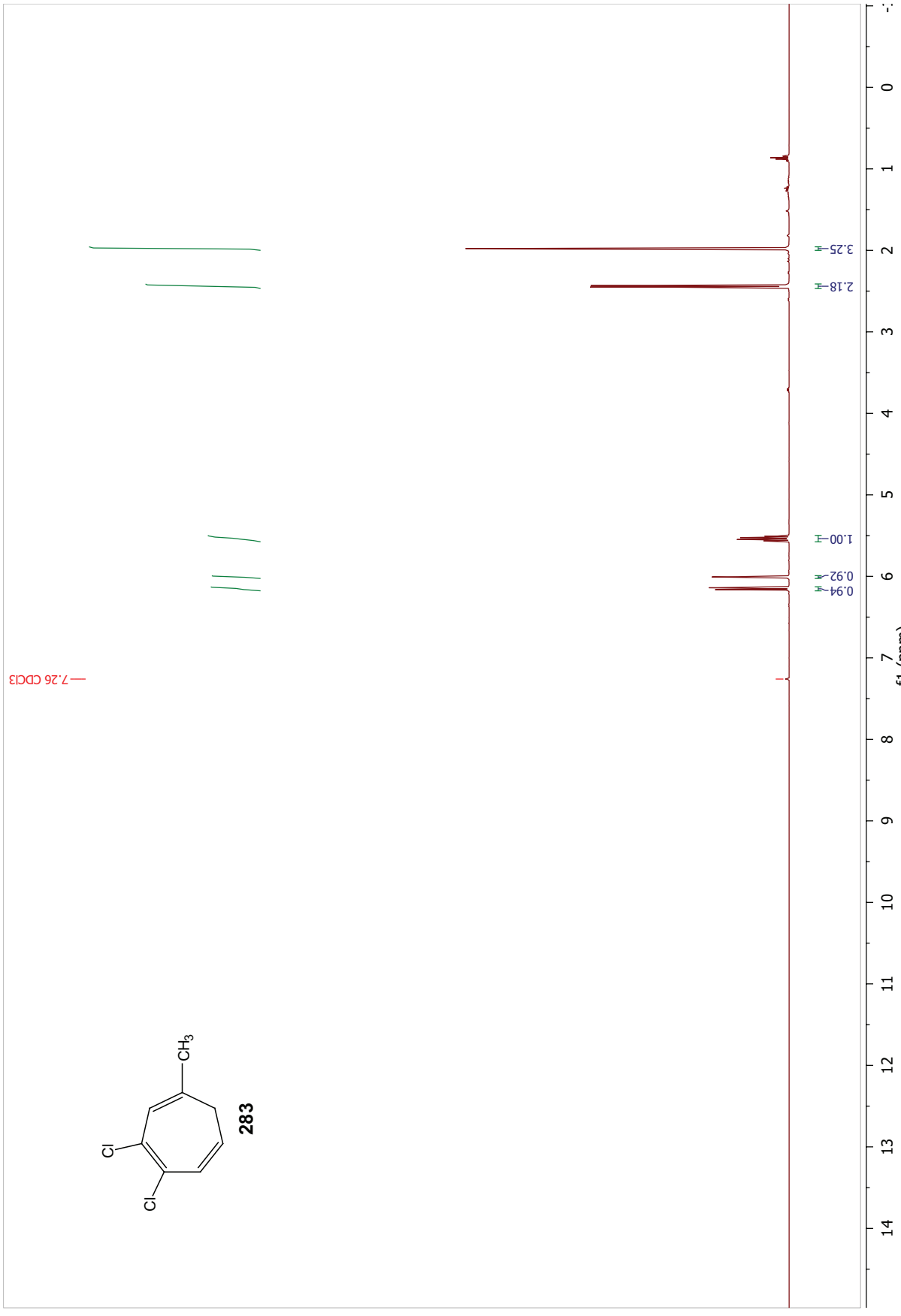
1.00
2.08
4.45
1.08
1.37
f1 (ppm)
HO
O
265

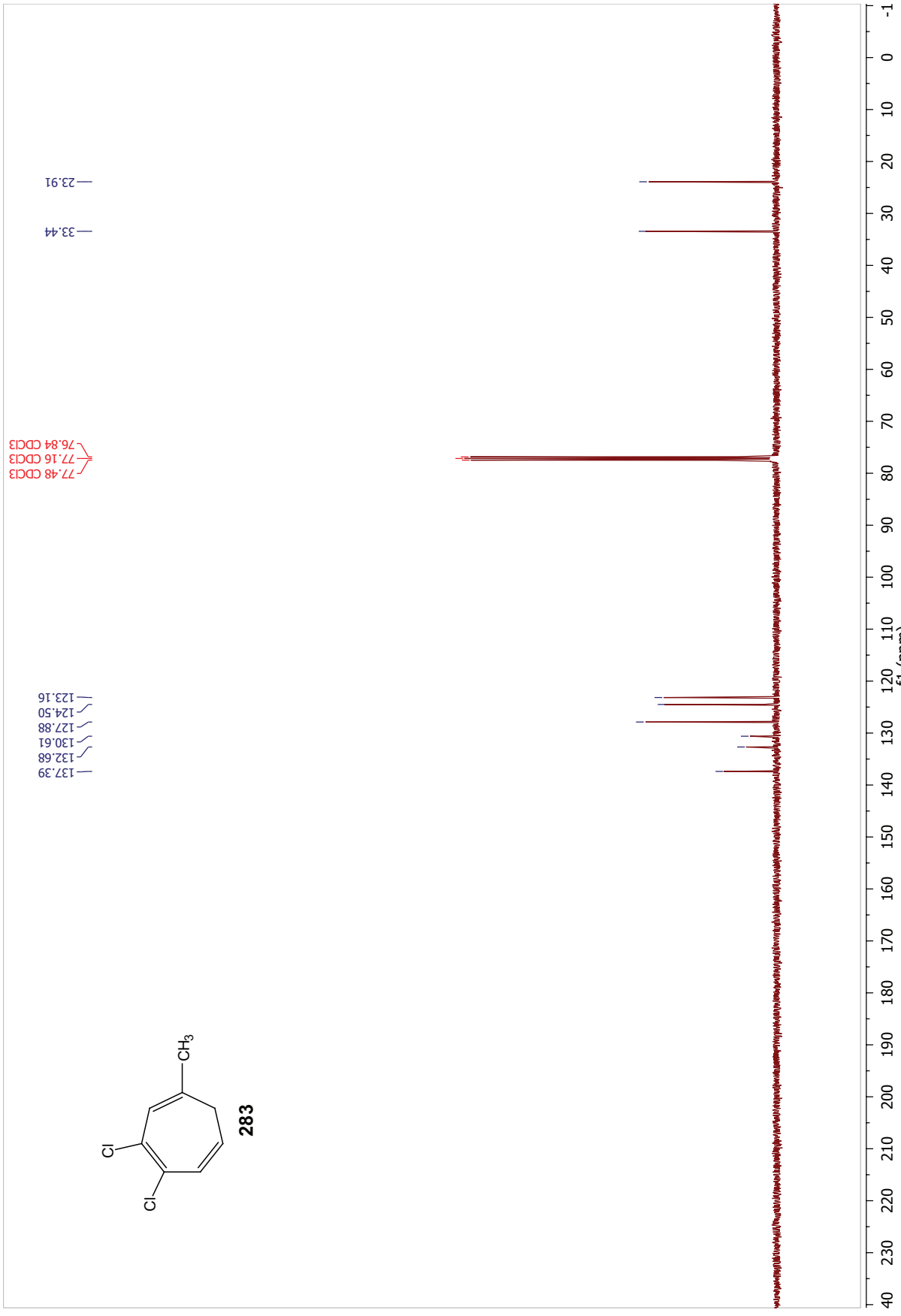

7.26 CDCl3
2.00
0.84
0.87
3.67
2.02
f1 (ppm)
275
Cl
Cl
Br

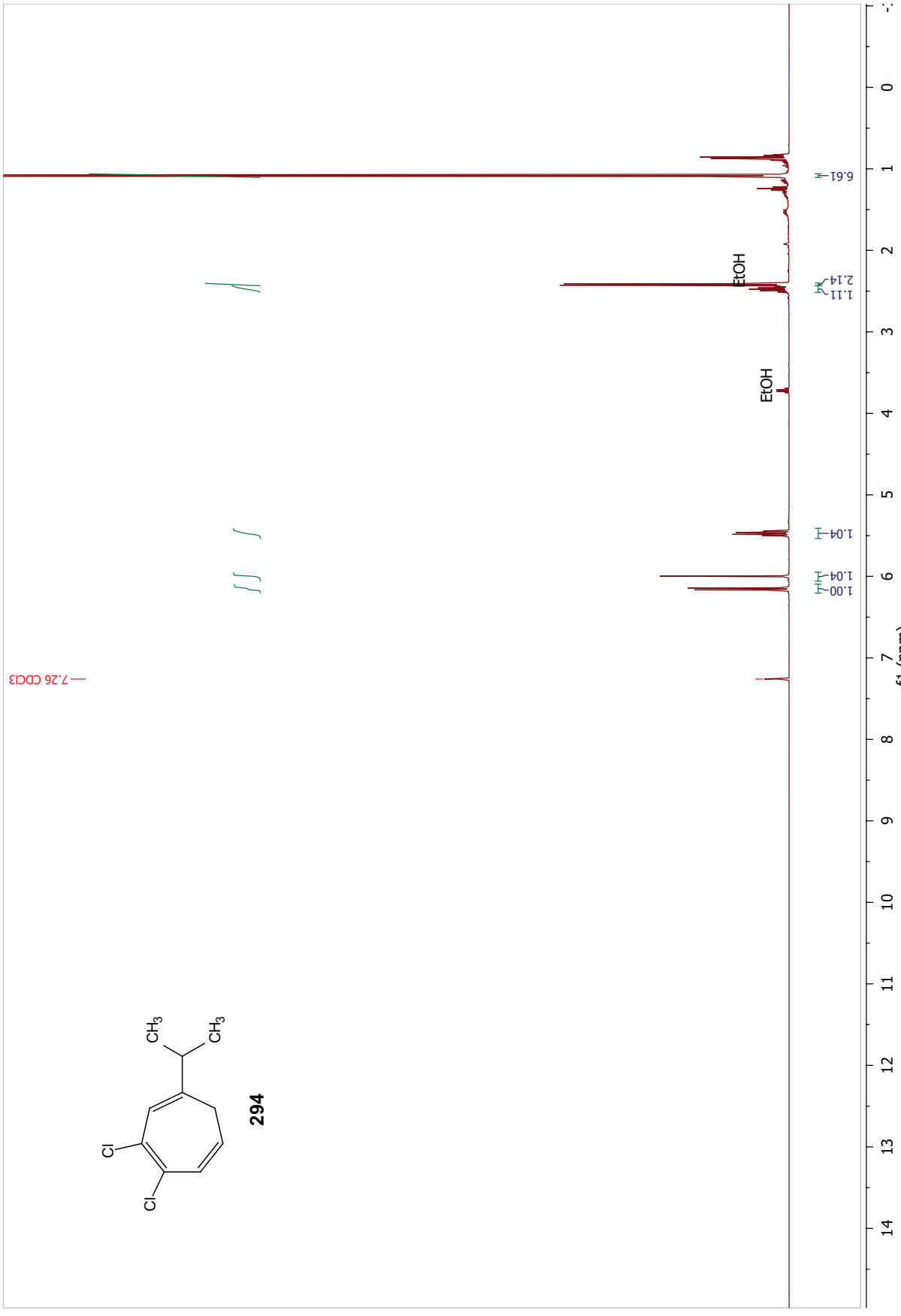

138.27
136.83
133.25
130.37
129.07
128.99
128.88
127.00
124.01
115.17
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
42.03
f1 (ppm)
Cl
Cl
Br
275

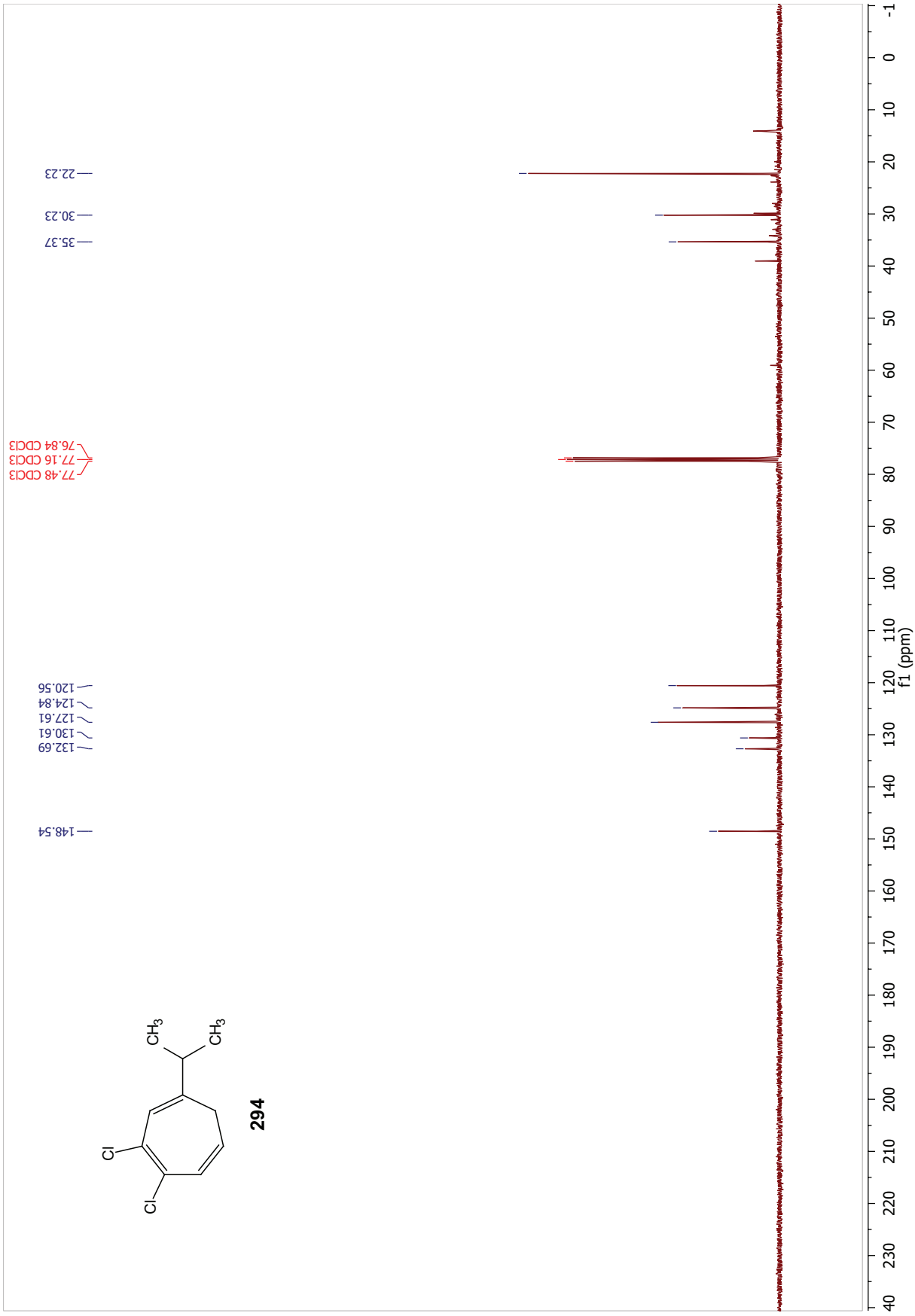

Cl
O
278
O
Cl
279
0.85
1.00
10.48
1.75
0.61
1.86
1.19
5
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

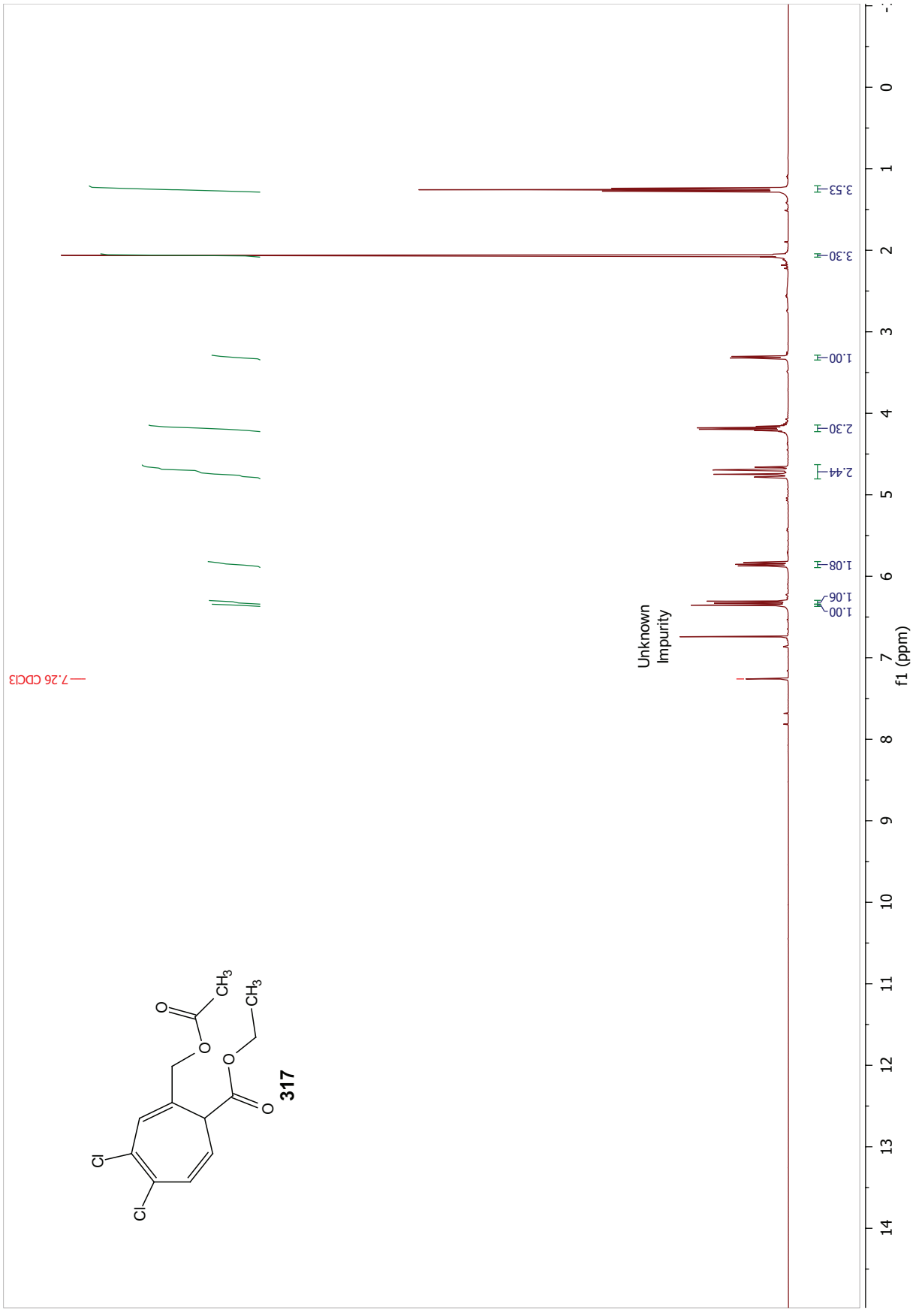

179.61
179.54
149.26
149.19
148.84
145.74
141.68
141.49
137.71
137.65
137.16
136.48
135.96
135.05
132.53
130.66
129.35
129.24
129.19
129.10
127.80
127.55
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
Cl
O
278
O
Cl
279
40
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

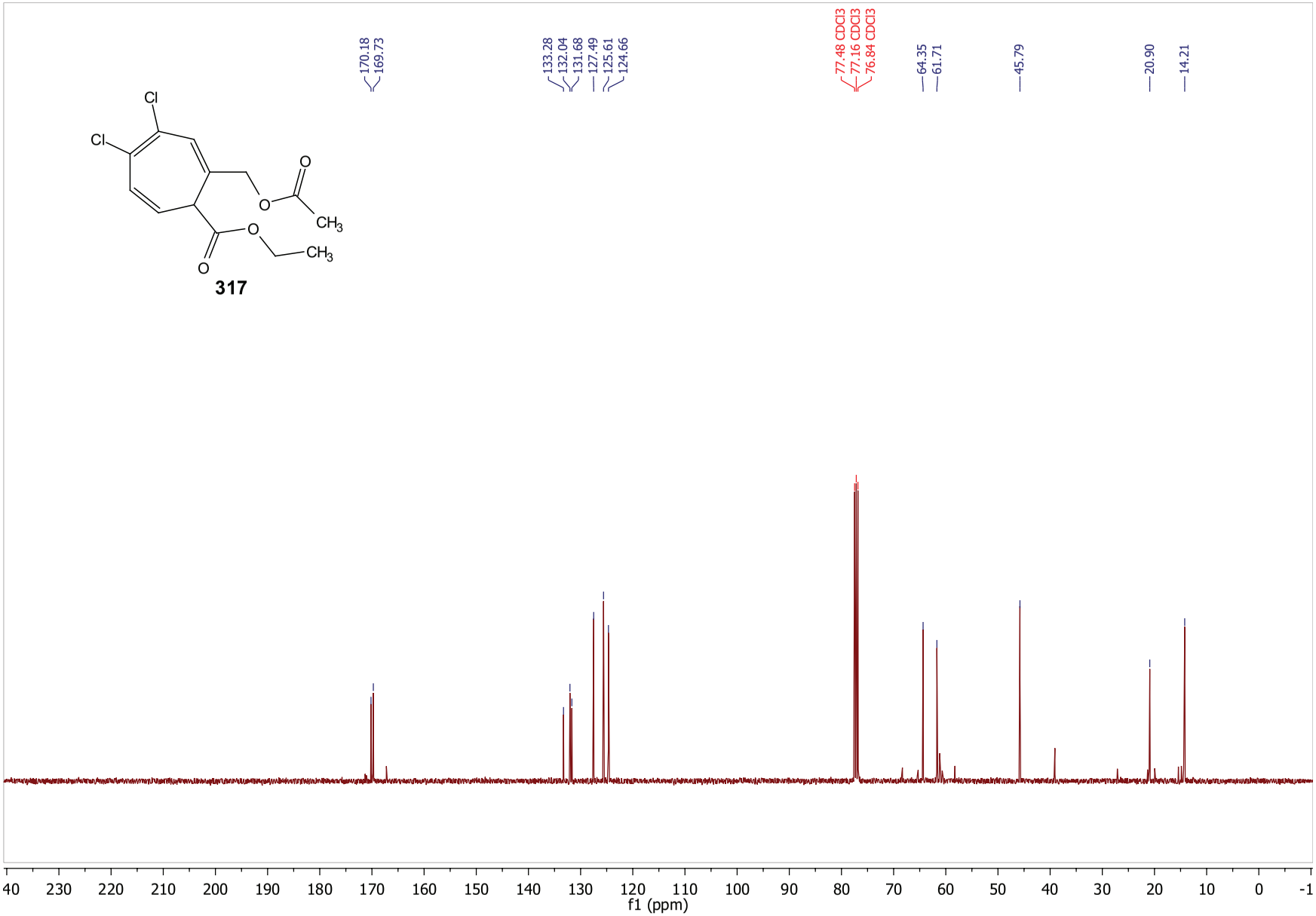

7.26 CDCl3
3.25
2.18
1.00
0.92
0.94
f1 (ppm)
283
CH3
Cl
Cl

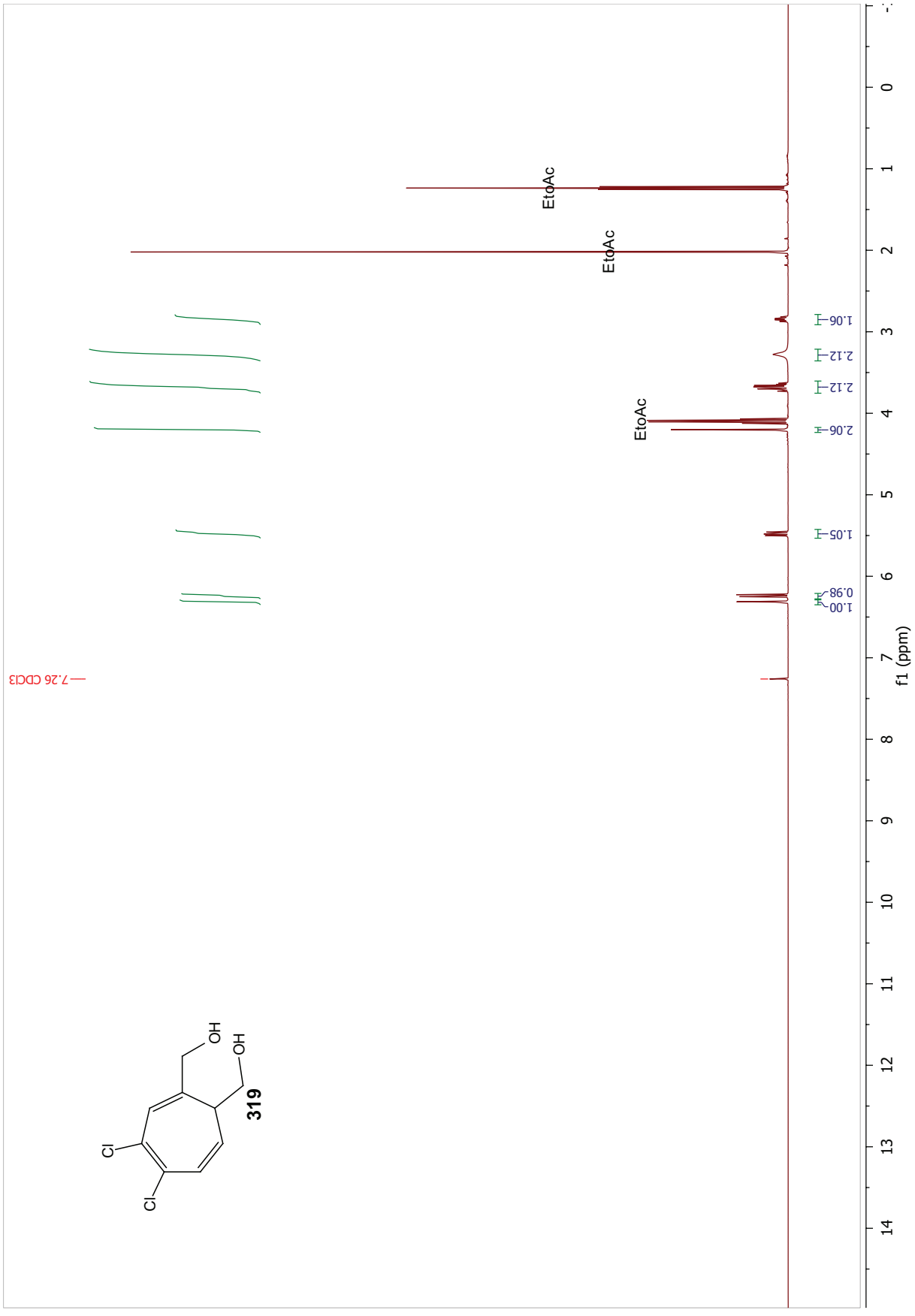

283
Cl
Cl
CH3
137.39
132.68
130.61
127.88
124.50
123.16
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
33.44
23.91
f1 (ppm)

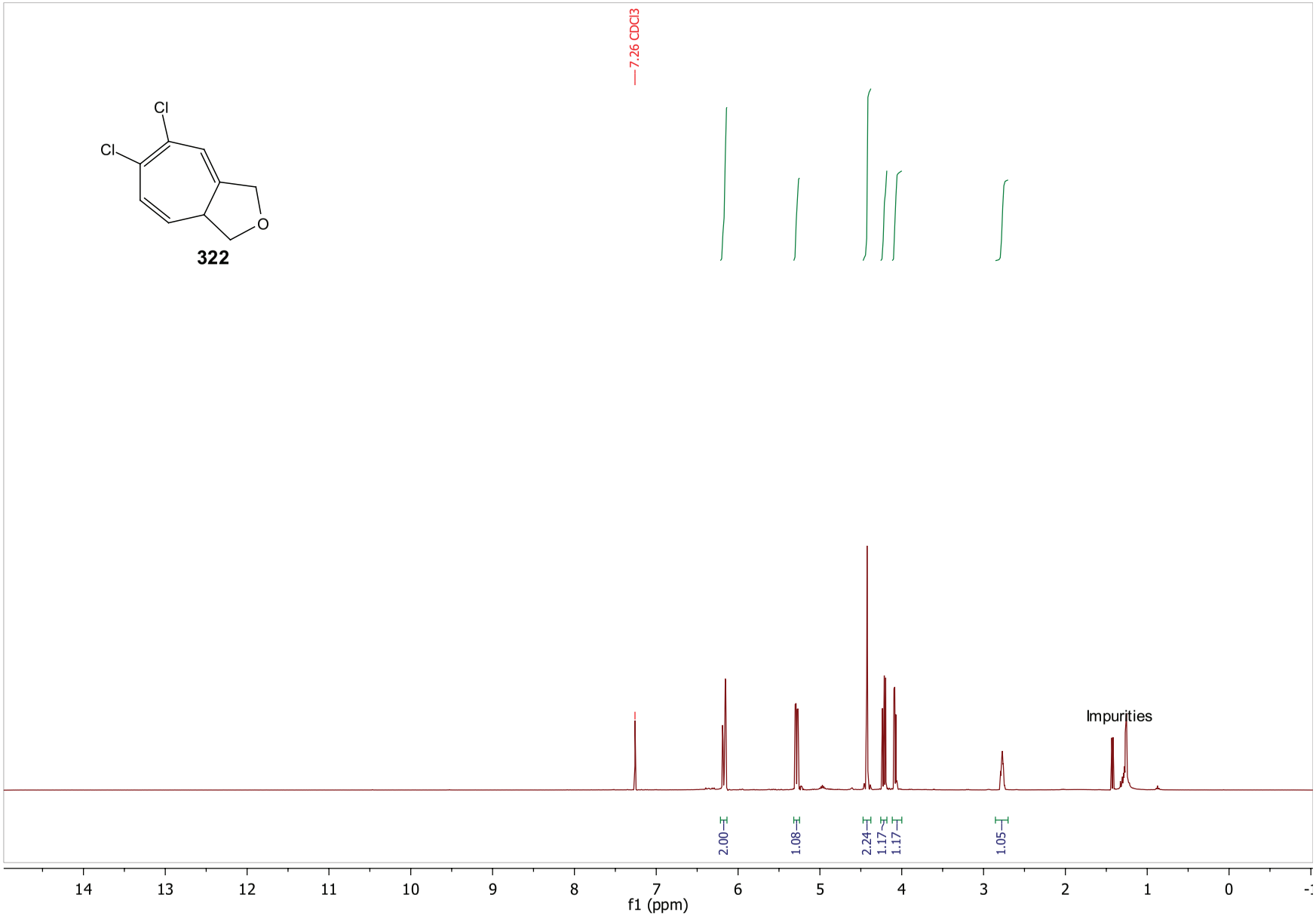

7.26 CDCl3
EtOH
EtOH
6.61
2.14
1.11
1.04
1.00
1.04
f1 (ppm)
294

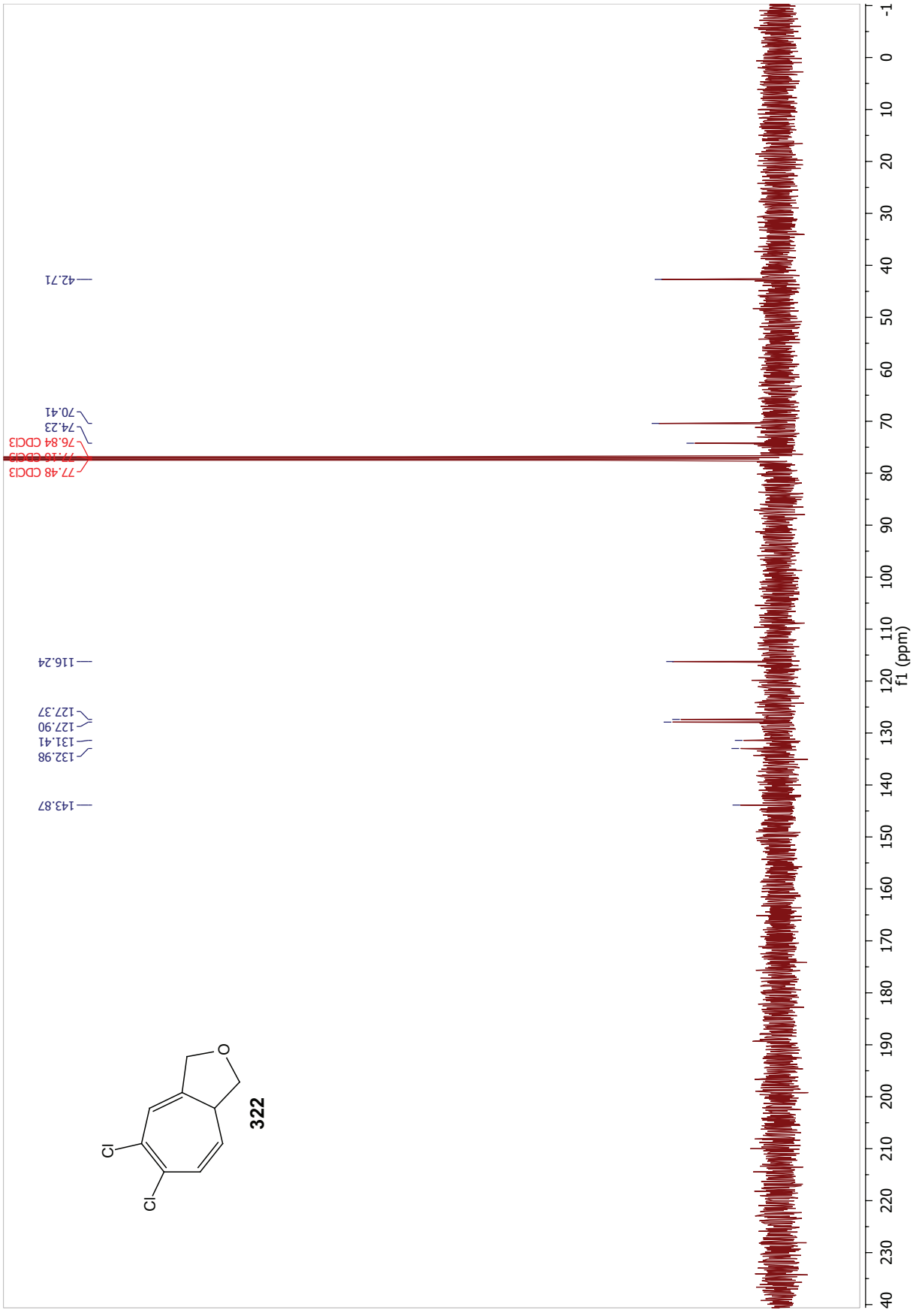

22.23
30.23
35.37
76.84 CDCl3
77.16 CDCl3
77.48 CDCl3
120.56
124.84
127.61
130.61
132.69
148.54
f1 (ppm)
294
CH3
CH3
Cl
Cl


7.26 CDCl3
Unknown
Impurity
3.53
3.30
1.00
2.30
2.44
1.08
1.06
1.00
f1 (ppm)
317


Cl
Cl
O
O
CH3
O
O
CH3
317
170.18
169.73
133.28
132.04
131.68
127.49
125.61
124.66
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.35
61.71
45.79
20.90
14.21
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


7.26 CDCl3
EtoAc
EtoAc
EtoAc
1.06
2.12
2.12
2.06
1.05
0.98
1.00
f1 (ppm)
OH
OH
Cl
Cl
319


Cl
Cl
O
322
7.26 CDCl3
Impurities
2.00
1.08
2.24
1.17
1.17
1.05
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


42.71
70.41
74.23
76.84 CDCl3
77.16 CDCl3
77.48 CDCl3
116.24
127.37
127.90
131.41
132.98
143.87
Cl
Cl
O
322
f1 (ppm)