Towards the Total Synthesis of Anthracimycin

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1. Abstract

In 2013 W. Fenical et al. reported the isolation of a natural product from a marine microorganism of *streptomyces* species, which possessed significant activity against Gram-positive pathogens *Bacillus anthracis*, methicillin-resistant and vancomycin resistant *Staphylococcus aureus* (MRSA). The compound responsible for the antibiotic activity was found to be the 14-membered macrolide named anthracimycin. The research detailed in this thesis describes the efforts towards the total synthesis of this natural product and specifically the formation of the core of anthracimycin in 12-steps. Direct palladium catalysed oxidation formed the enone used as a dienophile in a stereo- and regio-selective Diels–Alder/epimerisation sequence, which afforded the trans-decalin. A facial and stereoselective Hosomi–Sakurai 1,4-addition reaction, followed by a selective borylation/dihydroxylation sequence on the exocyclic alkene, allowed the formation of the core of anthracimycin (Scheme 1).

![Scheme 1. The formation of the decalin core of anthracimycin.](image-url)
2. Contents

1. Abstract ................................................................................................................................. 1
2. Contents ................................................................................................................................. 2
3. List of Figures .......................................................................................................................... 4
4. List of Schemes ....................................................................................................................... 5
5. List of Tables .......................................................................................................................... 8
6. Acknowledgements ............................................................................................................... 9
7. Declaration ............................................................................................................................. 10
8. Introduction ........................................................................................................................... 11
   8.1 Natural product synthesis ................................................................................................. 11
   8.2 The need for new antibiotics ........................................................................................... 12
     8.2.1 The mechanism of action of antibiotics ..................................................................... 15
   8.3 Anthracimycin: a new molecule active against MRSA bacteria .................................... 16
     8.3.1 The biosynthesis of anthracimycin ............................................................................. 18
     8.3.2 The biological effect of anthracimycin ................................................................. 20
   8.4 Isolation of an anthracimycin analogue 14 ....................................................................... 23
   8.5 A related polyketide: chlorotonil A 15 ............................................................................ 24
     8.5.1 The total synthesis of chlorotonil A 15 ..................................................................... 28
   8.6 Computational investigations into IMDA synthesis of anthracimycin ............................ 31
   8.7 Synthesis of functionalised decalin scaffold ..................................................................... 33
9. Results and discussion .......................................................................................................... 40
   9.1 The Robinson annulation to form a functionalised trans-decalin .................................... 40
     9.1.1 Retrosynthetic analysis ............................................................................................ 40
   9.2 Diels–Alder/epimerisation sequence to the trans-decalin ............................................. 45
     9.2.1 Retrosynthetic analysis ............................................................................................ 45
   9.3 Formation of the trans-decalin core of anthracimycin 114 ............................................. 61
     9.3.1 The synthetic plan .................................................................................................... 61
   9.4 Direct palladium catalysed oxidation studies ................................................................. 65
     9.4.1 Direct palladium catalysed oxidation studies: Stahl conditions ............................... 65
     9.4.2 Direct palladium catalysed oxidation studies: additives effect ............................... 67
     9.4.3 Direct palladium catalysed oxidation studies: the nitrate effect ............................. 70
     9.4.4 Direct palladium catalysed oxidation studies: substrate scope ................................ 72
   9.5 Enone 115 in the Diels–Alder reaction ............................................................................. 74
   9.6 Oxidation of trans-decalin 114 to enone trans-decalin 113 ........................................... 80
     9.6.1 The Ito–Saegusa oxidation ....................................................................................... 80
     9.6.2 The selenoxide elimination ....................................................................................... 84
9.6.3 The α-bromination/elimination sequence ................................................................. 85
9.6.4 The Rubottom oxidation ......................................................................................... 86
9.6.5 The oxidation in the presence of IBX ....................................................................... 88
9.7 Strategies to the core of anthracimycin 162 .............................................................. 92
  9.7.1 The Ireland–Claisen rearrangement ......................................................................... 92
  9.7.2 The Tsuji–Trost transformation ............................................................................. 103
  9.7.3 The Mukaiyama–Michael strategy ......................................................................... 106
  9.7.4 The Hosomi–Sakurai strategy .............................................................................. 109
  9.7.5 The Hosomi–Sakurai to the core of streptosetin A ............................................... 110
  9.7.6 The Hosomi–Sakurai approach towards anthracimycin core 162 .................. 111
  9.7.7 Functionalisation of the exocyclic double bond .................................................. 124
  9.7.8 The synthesis of the Still–Gennari reagent 92 .................................................. 131
10. Conclusions ............................................................................................................... 136
11. Future work .............................................................................................................. 138
12. Experimental ............................................................................................................. 140
  12.1 General experimental .......................................................................................... 140
  12.2 Methods and Characterisation of Compounds .................................................. 141
13. Abbreviations ........................................................................................................... 222
14. References ................................................................................................................ 226
3. List of Figures

Figure 1. Generations of different antibiotics. .............................................................. 13
Figure 2. Mode of action of different antibiotics. ....................................................... 15
Figure 3. The chemical structure of anthracimycin 1 ............................................... 17
Figure 4. Concentration effect of anthracimycin 1 .................................................... 22
Figure 5. The chemical structure of anthracimycin BII-2619 14 .................................. 23
Figure 6. The chemical structure of chlorotonil A 15 ................................................ 24
Figure 7. Computational calculation to study the biomimetic cycloaddition to form the decalin scaffold of anthracimycin, by Dr. Ian George ...................................................... 32
Figure 8. The transition of anthracimycin 11 ............................................................. 32
Figure 9. The X-ray diffraction single crystallography of the hydrazone 141 with thermal ellipsoids shown at 50%....................................................................................... 50
Figure 10. Ratio of cis- and trans-decalins 143 and 144 calculated on a quantitative $^{13}$C NMR spectrum based on ketone C-13 integration. ......................................................... 53
Figure 11. Ratio of cis- and trans-decalins 146 and 147 calculated on a $^1$H NMR spectrum based on methyl integration. ................................................................. 54
Figure 12. Ratio of cis- and trans-decalins 149 and 150 calculated on a $^1$H NMR spectrum based on integration of proton H-9 ........................................................................ 56
Figure 13. Ratio of cis- and trans-decalins 151 and 152 calculated on a quantitative $^{13}$C NMR spectrum based on ketone carbonyl integration. ........................................ 57
Figure 14. Ratio of cis- and trans-decalins 154 and 155 calculated on a quantitative $^{13}$C NMR spectrum based on ketone C-13 integration. .................................................... 58
Figure 15. Pyridine and bipyridine ligands used................................................................ 68
Figure 16. The re-addition of the catalyst restored the conversion rate of the oxidation .... 70
Figure 17. The effect of KNO$_3$ concentration on the oxidation rate of the formation of the enone 115 ................................................................. 71
Figure 18. The $^1$H NMR spectrum of 194 and the nOe analysis of H-12 ..................... 76
Figure 19. The nOe analysis of H-7 and H-6 ................................................................. 77
Figure 20. Single crystal X-ray diffraction of hydrazone 196 with thermal ellipsoids shown at 50% .................................................................................... 79
Figure 21. The $^1$H NMR spectrum of alcohol 224 in d$_6$ benzene................................. 96
Figure 22. The possible formation of the axial hydroxyl 231 ...................................... 99
Figure 23. The nOe correlation of compounds 232 and 215 ........................................ 102
Figure 24. The single crystal X-ray diffraction of 245 with thermal ellipsoids shown at 50% .... 108
Figure 25. The single crystal X-ray diffraction of 264 with thermal ellipsoids shown at 50% .... 112
Figure 26. The single crystal X-ray diffraction of compound 266 with thermal ellipsoids shown at 50% .......................................................................................... 114
Figure 27. The X-ray diffraction single crystallography of 281 and 282 with thermal ellipsoids shown at 50% .......................................................... 119
Figure 28. The $^1$H NMR data of the inseparable mixture of the two diastereoisomers of the Hosomi–Sakurai addition between 276 and 277 .................................................................. 122
Figure 29. The $^1$H NMR data of the inseparable mixture of the deprotected trans- and cis-decalins 278 and 279 (1 : 1 ratio) ................................................................. 123
Figure 30. The $^1$H NMR spectrum of 294 and 295 after the triflation/palladium reduction sequence .......................................................... 123
Figure 31. The $^1$H NMR and $^{13}$C NMR of the deprotection reaction ......................... 134
Figure 32. The $^1$H NMR and $^{13}$C NMR of the Dess–Martin oxidation ...................... 135
4. List of Schemes

**Scheme 1.** The formation of the decalin core of anthracimycin ........................................ 1
**Scheme 2.** The biosynthesis of anthracimycin 1 ................................................................. 19
**Scheme 3.** The biosynthesis of chlorotonil A 15 ................................................................. 26
**Scheme 4.** Total synthesis of chlorotonil A 15 by Kalesse et al. ................................................ 29
**Scheme 5.** Diels–Alder reaction without bromine: different ratio of products obtained ............ 30
**Scheme 6.** Transition state of endo-I and endo-II products .................................................... 30
**Scheme 7.** The disconnections strategy to form a decalin system ......................................... 33
**Scheme 8.** Allylation reaction as a type I A reaction for the formation of cis-decalin ............... 34
**Scheme 9.** Radical cyclopropane opening/annulation/elimination for the formation of decalin 60 35
**Scheme 10.** Photocatalytic Michael-aldol sequence for the enantioselective synthesis of decalin 63 35
**Scheme 11.** The Diels–Alder/carbocyclisation sequence reported by Zhang .............................. 36
**Scheme 12.** The total synthesis of rhodexin A 78 by Jung ....................................................... 37
**Scheme 13.** Pericyclic cyclisations as an example of a type I D disconnection .......................... 37
**Scheme 14.** The intramolecular Diels–Alder (type II A) in the total synthesis of kalihinol A 87 38
**Scheme 15.** Cationic cyclisation used as an example of type II B disconnection ....................... 39
**Scheme 16.** The retrosynthetic analysis of anthracimycin 1, using the Robinson annulation strategy ................................................................. 40
**Scheme 17.** The Robinson annulation/conjugate addition approach to the synthesis of the decalin core 94 ................................................................. 41
**Scheme 18.** The Robinson annulation of cyclohexanone 101 .................................................. 42
**Scheme 19.** The Robinson annulation of 4-methyl cyclohexanone 98 ....................................... 43
**Scheme 20.** The conjugate addition of 103 and the mechanism of the reaction ......................... 44
**Scheme 21.** The retrosynthetic analysis of anthracimycin 1 ...................................................... 45
**Scheme 22.** A two-steps “trans-Diels–Alder reaction” ............................................................ 46
**Scheme 23.** The epimerisation from a cis- to a trans-decalin via radical and photoredox startegy ... 47
**Scheme 24.** A Lewis acid-mediated Diels–Alder reaction to form the cis-decalin 134 ................ 48
**Scheme 25.** Palladium catalysed the synthesis of the sulfur-substituted diene 116 .................... 48
**Scheme 26.** A regioselective Diels–Alder to form cis-decalin 136 ......................................... 49
**Scheme 27.** The Diels–Alder cycloaddition between 131 and 133 ........................................... 49
**Scheme 28.** The epimerisation from the cis- to trans-decalin 139 ............................................ 50
**Scheme 29.** The derivatisation of the trans-decalin 139 into the hydrazone 141 ....................... 50
**Scheme 30.** The Diels–Alder/epimerisation reaction between 131 and 133 ............................ 53
**Scheme 31.** The Diels–Alder/epimerisation sequence between 131 and 145 ............................ 54
**Scheme 32.** The Diels–Alder/epimerisation sequence between 148 and 133 ............................ 55
**Scheme 33.** The Diels–Alder/epimerisation sequence between 148 and 142 ............................ 57
**Scheme 34.** The Diels–Alder reaction between 154 and 155 .................................................... 58
**Scheme 35.** The Diels–Alder/epimerisation sequence to form the trans-decalin 137 ................ 59
**Scheme 36.** The Raney-Nickel reduction of cis- and trans-decalins 156 and 137 ..................... 60
**Scheme 37.** The synthetic plan for anthracimycin 1 .............................................................. 61
**Scheme 38.** The formation of the enone 115 developed by Dr. Ian George ............................... 64
**Scheme 39.** Stahl reported condition of direct ketone oxidation ............................................ 65
**Scheme 40.** Proposed mechanism for Pd-catalysed oxidation of cyclic ketone ......................... 65
**Scheme 41.** Tsuji optimised condition of direct ketone oxidation ............................................ 68
**Scheme 42.** The optimised oxidation conditions to form the model enone trans-decalin 179 .... 72
**Scheme 43.** Palladium catalysed direct oxidation of cholesterone 180 ..................................... 72
**Scheme 44.** Palladium catalysed direct oxidation of allyl-substituted cyclohexanone 183 ............ 73
**Scheme 45.** Substrate scope using the optimised oxidation conditions ....................................... 73
**Scheme 46.** The Diels–Alder/epimerisation sequence between enone 115 and isoprene 133 .... 74
Scheme 47. The Diels–Alder cycloaddition between enone 115 and the sulfur substituted diene 116. ........................................................................................................................................................................ 75
Scheme 48. The formation of the trans-decalin core 114. ........................................................................................................ 79
Scheme 49. The conversion of the trans-decalin 114 to the enone trans-decalin 113 applying the optimised palladium oxidation conditions. .......................................................................................................................... 80
Scheme 50. The Ito–Saegusa oxidation conditions reported by Dirk Trauner. ........................................................................ 81
Scheme 51. The Ito–Saegusa oxidation to form the enone 179. ................................................................................................ 82
Scheme 52. The Ito–Saegusa oxidation of the model TES-enol ether trans-decalin 202. ......................................................... 83
Scheme 53. The Ito–Saegusa oxidation to form enone 113. ........................................................................................................ 84
Scheme 54. The selenoxide chemistry used for the oxidation of 139. ....................................................................................... 85
Scheme 55. The oxidation conditions reported by Baran and his group ................................................................................. 86
Scheme 56. The oxidation of 139 in the presence of NBS and DBU, as reported by Baran et al. ................................................. 86
Scheme 57. Literature reported Rubottom oxidation. ................................................................................................................ 87
Scheme 58. The Rubottom oxidation method to form the model enone trans-decalin. ............................................................. 87
Scheme 59. The oxidation of the model trans-decalin 139 using the reported literature conditions. ................................ 88
Scheme 60. The IBX oxidation of the model TES-enol trans-decalin 202. ................................................................................. 89
Scheme 61. The IBX oxidation to form the enone trans-decalin 113. ....................................................................................... 90
Scheme 62. Formation of the propionate ester trans-decalin 112. ............................................................................................ 92
Scheme 63. Proposal for stereocontrol in the Ireland–Claisen rearrangement. ......................................................................... 93
Scheme 64. Boat-like transition state in Ireland–Claisen rearrangement, in the total synthesis of Monensin. .................................................. 93
Scheme 65. The Z- and E-enolate formation. ........................................................................................................................ 94
Scheme 66. The two transition states in kinetic enolisation of esters. ....................................................................................... 94
Scheme 67. The Luche reduction of the model enone trans-decalin 179. ................................................................................ 95
Scheme 68. The esterification of 224 to understand the stereochemistry of H-13. ................................................................. 97
Scheme 69. The stereoselective reduction of ketone 229. .......................................................................................................... 98
Scheme 70. The 1,2-reduction of the enone trans-decalin 113. ................................................................................................. 101
Scheme 71. The attempted Ireland–Claisen rearrangement. ...................................................................................................... 103
Scheme 72. The stereocontrolled formation of cis-ring junction decalin by Tsuji. ................................................................. 103
Scheme 73. The proposal Tsuji–Trost reaction to the core of anthracimycin 162. ................................................................. 104
Scheme 74. The Tsuji–Trost transformation of esters 226 and 238, as substrates. ................................................................. 105
Scheme 75. The Mukaiyama–Michael 1,4-addition. .................................................................................................................. 106
Scheme 76. The model studies of the conversion of a ketone into an alkene. ........................................................................... 107
Scheme 77. The transformation of 241 to the tricyclic system 247. ......................................................................................... 108
Scheme 78. Mechanism of the Hosomi–Sakurai 1,4-addition. ................................................................................................. 109
Scheme 79. The Hosomi–Sakurai approach to streptosetin A 260. ......................................................................................... 110
Scheme 80. A possible explanation for the formation of the major syn-adduct. ................................................................. 111
Scheme 81. The deprotection/iodocyclisation sequence to determine the stereochemistry of 183. .......................................... 112
Scheme 82. The Hosomi–Sakurai addition between 113 and 250, and formation of hydrazone 268 from the major diastereoisomer 266. ......................................................................................................................... 113
Scheme 83. The TIPS-removal of 264 to test the antimicrobial activity. .............................................................................. 114
Scheme 84. An approach to the synthesis of E-crotyltrimethylsilane 272. ........................................................................... 115
Scheme 85. The attempted synthesis of E-crotyltrimethylsilane 272. ................................................................................... 115
Scheme 86. The synthesis of the E-crotyltrimethylsilane 272. ................................................................................................. 116
Scheme 87. The Hosomi–Sakurai addition between the enone trans-decalin 113 and E-crotyltrimethylsilane 272. ................. 117
Scheme 88. The TIPS-removal of the inseparable mixture of the major and the minor diastereoisomers 276 and 277. ....... 118
Scheme 89. The deprotection/iodocyclisation sequence used to establish the stereochemistry of the major diastereoisomer 276. ......................................................................................................................... 119
Scheme 90. The epimerisation of the model trans-decalin 139 to the cis-decalin 138. ..................... 120
Scheme 91. Epoxidation and dihydroxylation functionalised the endocyclic alkene preferentially. 124
Scheme 92. A selective dihydroxylation reaction of the exocyclic alkene. ............................. 126
Scheme 93. The periodate cleavage to the advanced precursor 290 and 291. .............................. 127
Scheme 94. Conversion of the carbonyl functionality into an alkene to form 294 and 295 128
Scheme 95. The formation of the core of anthracimycin 162 ...................................................... 130
Scheme 96. The synthesis of the Still–Gennari reagent 92 ...................................................... 131
Scheme 97. The attempted isolation of the major diastereoisomer 294 ................................. 133
Scheme 98. The formation of the core of anthracimycin 162 ................................................. 137
Scheme 99. The new strategy envisioned for the core of anthracimycin 162 ......................... 139
5. List of Tables

Table 1. Year of resistance observed.................................................................14
Table 2. MIC values against major classes of bacteria. .....................................21
Table 3. Biology activity of anthracimycin BII-2619 14 compared to anthracimycin 1………………23
Table 4. The biological activity of chlorotoniol A compared with the congeners………………….27
Table 5. The elimination conditions for the conversion of 102 into decalin 103…………………42
Table 6. The optimization of the Diels–Alder reaction between cyclohexanone 131 and 116……59
Table 7. Stahl’s conditions on target ketone 160.……………………………………….66
Table 8. Additive screening to increase the conversion to the desired enone 115…………………..67
Table 9. Pyridyl and bipyridyl ligand screening to improve the conversion to enone 115…………69
Table 10. The attempted Ito–Saegusa oxidation conditions........................................84
Table 11. The IBX oxidation of the model TES-enol intermediate 202………………………...89
Table 12. The IBX oxidation of the model TES-enol intermediate 203…………………………90
Table 13. The 1,2-reduction of the enone trans-decalin 179……………………………………100
Table 14. The reaction conditions tested for the borylation of 276 and 277……………………126
6. Acknowledgements

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The last thanks goes to my housemates Francesco, Mik and Miky of my last year in York. They have been enjoyable friends and true brothers and during the course of the year, we became a family.
7. Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text.
8. Introduction

8.1 Natural product synthesis

The role of total synthesis in the development of new natural product based drugs is of particular importance. In many cases new synthetic methodology has been developed to allow the synthesis of natural products. For example, the development of asymmetric alkylation and aldol methodology by Evans, gave access to the complex antibiotic cytovaricin. Hydroboration reactions have been used by Kishi to develop a new methodology to form propionate fragments for the total synthesis of monensin A. Plants and natural substances are used in traditional medicine to treat a wide range of illnesses. The active compounds, isolated from them, find use in conventional medicine such as taxol in the treatment of cancer, acetylsalicyclic acid as an anti-inflammatory drug and pilocarpine in the treatment of chronic and acute glaucoma. Mother Nature produces molecules which play an important role in drug discovery and development processes. These are continuing to expand the chemotherapeutic armory and organic chemists are devising new and ingenious strategies to develop synthesis of these natural products. The pharmaceutical industry seems to have recognised this trend and is shifting away from large libraries of simple compounds towards focused libraries of complex, natural product-like collections.

However, in many cases, supply issues have hindered the development of natural products into drugs. This can be because the source organism is not always known, and when it is known the active compound is often found in only miniscule quantities. The answer to these supply issues would seem to be total chemical synthesis.

It is generally accepted that the synthesis of compounds of any complexity can be achieved, given enough time and resources. However, the vast majority of the reported total synthesis provide only milligram quantities of the target compound. These amounts are insufficient for significant biological studies and therefore have little impact in drug development, especially when the compound can not be simplified without the loss of activity. Fortunately, in the last decades several groups have
successfully addressed this issue with an increased focus on scalability of the total synthesis. They have succeeded in the production of several highly complex natural products in multigram quantities for biological studies. They

With the excellent potential of natural products as biologically active molecules, and the increased focus on the scalability of the synthesis, one can only expect the role of total synthesis in chemistry, biology and medicine to increase in the coming years.

8.2 The need for new antibiotics

The Government and the World Health Organisation (WHO) have called for research into new anti-infective drugs, triggered by the rising threat of the methicillin resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* (C. Diff) and *Enterobacteriaceae*, as well as other resistant pathogens. These strongly antibiotic resistant bacteria or “superbugs” are untreatable with current antibiotics and new research in this area is necessary. Over the years, two parallel and different lines of antibiotic discovery and development have been explored: i) the antibacterial activity of natural products (such as cephalosporins, quinolones, macrolides and tetracyclines), and, ii) the antibiotic activity of synthetic aromatic sulfonamides. After “the golden age of antibiotics research” (1940-1960), different generations of the natural antibiotics were developed to overcome bacterial resistance, by modification of their chemical scaffolds (Figure 1).
<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Generation 1</th>
<th>Generation 2</th>
<th>Generation 3</th>
</tr>
</thead>
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<tr>
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<td><img src="image1" alt="Cephalosporin" /></td>
<td><img src="image2" alt="Cephalosporin" /></td>
<td><img src="image3" alt="Cephalosporin" /></td>
</tr>
<tr>
<td><strong>Quinolones</strong></td>
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<td><img src="image6" alt="Quinolone" /></td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
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<td><img src="image8" alt="Macrolide" /></td>
<td><img src="image9" alt="Macrolide" /></td>
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<tr>
<td><strong>Tetracyclines</strong></td>
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<td><img src="image11" alt="Tetracycline" /></td>
<td><img src="image12" alt="Tetracycline" /></td>
</tr>
</tbody>
</table>

**Figure 1.** Generations of different antibiotics.\(^8\)

**Figure 1** shows the different antibiotic classes, in which the lead structure has been modified to create different generations to overcome bacteria resistance.
The widespread introduction and the inappropriate use of antibiotics in human and veterinary contexts, led to an increase of resistant bacteria and the need of new antibiotic molecules. In 2014, a table to compare the year of antibiotics discovery with the year of resistance observed, was published showing how quick the clinical resistance has been developed by bacteria (Table 1).8

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Year Discovery</th>
<th>Clinical resistance observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>1930s</td>
<td>1940s</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1943</td>
<td>1946</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1943</td>
<td>1959</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1947</td>
<td>1959</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1948</td>
<td>1953</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1952</td>
<td>1988</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1956</td>
<td>1988</td>
</tr>
<tr>
<td>Methicillin</td>
<td>1960</td>
<td>1961</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1961</td>
<td>1973</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1960s</td>
<td>late 1960s</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>1962</td>
<td>1962</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>1980s</td>
<td>1980s</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1999</td>
<td>1999</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2003</td>
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</tr>
<tr>
<td>Retapamulin</td>
<td>2007</td>
<td>2007</td>
</tr>
<tr>
<td>Fidaxomycin</td>
<td>2011</td>
<td>2011</td>
</tr>
</tbody>
</table>

Table 1. Year of resistance observed.8
8.2.1 The mechanism of action of antibiotics

Different classes of antibiotics possess different mechanisms of action against bacteria and five major antibacterial targets/pathways have been studied: β–lactams and the vancomycin type glycopeptides target bacterial peptidoglycan/cell wall biosynthesis (Figure 2). Another target of antibiotics is bacterial protein synthesis, with macrolide-based drugs attacking the ribosome. Fluoroquinolones targets DNA replication and transcription to RNA. Two other targets are the folate biosynthetic pathway (sulfamides) and the disruption of bacterial membrane integrity (daptomycin). The resistance against these antibiotics is different for each class: for example, the substitution of the D-Ala-D-Ala sequence in the peptidoglycan wall with a D-Ala-D-lactate unit, represents the enterococci-type bacteria resistance against vancomycin. This causes the loss of one H-bond between the antibiotic and the target. Gene mutation in the sequence that encodes for DNA-gyrase enzyme, represents the mechanism of resistance against the fluoroquinolone antibiotics class.

Figure 2. Mode of action of different antiobiotics.
8.3 Anthracimycin: a new molecule active against MRSA bacteria

As mentioned in the previous section, the prevalence of methicillin-resistant *Staphylococcus aureus* infections and the slow development of new antibiotics, represents a major clinical challenge.\(^\text{10, 11}\) The availability of novel molecules for treating multi-resistant bacteria, is becoming a problem and new structures are needed.\(^\text{12}\) Natural products, such as secondary metabolites isolated from microorganisms, such as fungi and actinomycetes, were found to possess antimicrobial activities and this led to new lead structures for drug discovery.\(^\text{13}\) In some of these specific bioactive secondary metabolites such as monacolins, macrolides, pyrrolidine-2-one and 4-hydroxy-2-pyridone alkaloids, a common feature in the chemical structure was found to be a “decalin” motif, substituted with various functional groups. This peculiar scaffold could be biosynthesised by two different pathways: the mevalonate pathway for isoprenoids and the acetate pathway for polyketides.\(^\text{14}\) In 2013, Fenical and his group reported the isolation of a marine microorganism of *Streptomyces* species from near-shore marine sediments near Santa Barbara, CA.\(^\text{15}\) The culture extracts were found to possess significant activity against *Bacillus anthracis*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant of *Staphylococcus aureus*. The fractionations of the extract afforded a compound called anthracimycin 1, responsible for the antibiotic activity (Figure 3).\(^\text{15}\) The *Bacillus anthracis* disease is one of the most common infections in farm animals and has also been used as a bioterrorism weapon. In 2001, *Bacillus anthracis* spores were spread by someone sending letters through the US postal system, after the World Trade Center attack.\(^\text{15}\)

Anthracimycin was isolated as a white solid with a molecular formula of C\(_{25}\)H\(_{32}\)O\(_4\) and its structure was determined by NMR spectroscopy analysis and X-ray crystallographic data.\(^\text{15}\) Upon this analysis, the structure of this natural compound appeared to be a combination of a 14-, 6- and 6-membered rings of polyketide origin. The 14-membered ring is characterised by the presence of a lactone and an enolised β-diketone. The equidistant position of the proton between each oxygen, in the X-ray data, confirmed the keto-enol tautomerisation. Anthracimycin is also characterised by the presence of two double bonds in the 14-membered ring. One in a Z-configuration and the other as an E-alkene, which
was confirmed by the vicinal coupling constants of 10.5 Hz and 15.2 Hz, respectively. This molecule possesses a *trans*-decalin core scaffold, characterised by the presence of two double bonds. Anthracimycin also features stereogenic centers at C-2, C-6, C-7, C-12, C-15, C-16 and C-21 and a *cis*-orientation of A/B rings, as well as a *trans*-ring junction of B/C rings.

This polyketide belongs to the macrolide antibiotic class but is structurally distinct from the typical members of this group, by the presence of the tricyclic system characterised by a decalin scaffold and the absence of a deoxyhexose motif.\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{anthracimycin_structure.png}
\caption{The chemical structure of anthracimycin 1.\textsuperscript{15}}
\end{figure}
8.3.1 The biosynthesis of anthracimycin

In 2015, the biosynthesis of this polyketide was reported and a type I polyketide synthase (PKS) was found to be the enzyme responsible for chain assembly.\textsuperscript{16} Generally, three classes of PKSs have been reported: type I, iterative type II and the acyl-carrier protein type III. Type I PKSs contain a β-ketoacyl-ACP synthase, an acyltransferase and an acyl carrier protein domain, which are responsible for choosing and loading the carboxylic acid units for the successive condensation reactions in the chain assembly.\textsuperscript{17} This PKSs catalysed series of Claisen-like condensations, for the formation of metabolite intermediates in the chain elongation process (Scheme 2).\textsuperscript{17}

The biosynthetic pathway of anthracimycin may be initiated by decarboxylation of the malonyl residue 2, to form the acylated ACP\textsubscript{1} metabolite intermediate 3.\textsuperscript{18, 19} Chain elongation would proceed to provide ACP\textsubscript{2} 4, introducing a β,γ-double bond, which would also be introduced in fragment 5 to form a conjugated diene. Module 4 and 5 could be characterised by a chain elongation with the introduction of α,β-double bonds to form fragment 6.\textsuperscript{19} Then, α-methylation and β-keto reduction, followed by the introduction of a β,γ-shifted double bond with cis-geometry, would generate intermediate 8.\textsuperscript{20} Further chain elongation would allow the formation of the α,β-unsaturated compound 10, suitable for [4 + 2] cycloaddition, to generate the trans-decalin scaffold of the natural product. An endo-transition state of 10 could be envisioned for the formation of this trans-decalin core. The last two-step sequence of chain elongation, would be characterised by a TE domain to catalyse macrocyclisation and chain release (Scheme 2).\textsuperscript{16}

A small number of natural product biosynthetic pathways, are characterised by the presence of an enzyme that is able to catalyse intramolecular [4 + 2] cycloadditions, for the formation of decalin scaffolds.\textsuperscript{21-27} Recently, a FAD-dependent enzyme capable of generating a trans-decalin motif in the pyrroindomycin biosynthetic pathway has been identified,\textsuperscript{28} as well as the LovB PKS enzyme responsible for the [4 + 2] cycloaddition involved in the formation of the fungal metabolite lovastatin.\textsuperscript{25, 26, 29} Interestingly, in the case of anthracimycin biosynthesis, it is still unknown if the intramolecular Diels–Alder reaction for the formation of the trans-decalin is catalysed by the enzyme
or is spontaneous. In this cycloaddition reaction, fragment 10 is characterised by the presence of a dienophile double bond with $E$ geometry and a rigid orientation, due to the presence of the two $\beta,\gamma$-shifted double bonds. This leads to a diminished degree of freedom, aiding intramolecular cycloaddition by steric effects rather than stabilisation by any particular transition state.\textsuperscript{16}

Scheme 2. The biosynthesis of anthracimycin 1.\textsuperscript{16}
8.3.2 The biological effect of anthracimycin

In most macrolides, the mode of action is the inhibition of protein biosynthesis by binding the 50 S ribosomial subunit. However, macromolecular synthetic studies, suggested that the anthracimycin mechanism of action could involve inhibition of DNA and RNA synthesis, in the absence of DNA intercalation. These assays were performed by measuring the quantitative incorporation of radiolabelled precursors of DNA and RNA. Disruption effects of DNA and RNA synthesis occurred at the Minimum Inhibitory Concentration (MIC) value on [³H] thymidine and [³H] uridine. It was also observed an additional secondary effect of anthracimycin on protein synthesis, at higher concentration of the MIC value.

These assays also showed potent activity of the natural product against all groups of *Staphilococcus aureus* tested, with a MIC value of < 0.25 mgL⁻¹. Anthracimycin also inhibited vancomycin-resistant *Enterococcus faecalis*, MIC < 0.25 mgL⁻¹, but no relevant Gram-negative activity was found, MIC > 64 mgL⁻¹ (Table 2).
<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (mgL(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td></td>
</tr>
<tr>
<td>Sanger 252 (USA200)</td>
<td>0.063</td>
</tr>
<tr>
<td>TCH1516 (USA300)</td>
<td>0.125</td>
</tr>
<tr>
<td>ATCC 33591</td>
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</tr>
<tr>
<td>NRS192 (ST1)</td>
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</tr>
<tr>
<td>Non-S. aureus</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>0.25</td>
</tr>
<tr>
<td>Enterococcus faecalis isolate</td>
<td>0.125</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>0.03</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>&gt; 64</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>&gt; 64</td>
</tr>
</tbody>
</table>

Table 2. MIC values against major classes of bacteria.\(^{30}\)

A rapid bactericidal kinetics were also exhibited by this natural compound, with a > 4-log kill of USA 300 MRSA during a 3 hours period at > 5 x MIC. A minimal post-antibiotic effect, compared with vancomycin, and a minimal toxic effect to eukaryotic cells was also observed, having a half maximal inhibitory concentration (IC\(_{50}\)) = 70 mgL\(^{-1}\), against human carcinoma cells (Figure 4).\(^{30}\)

An effect below the MIC value and sensitisation of the host immune system at sub-MIC anthracimycin was also observed.\(^{32}\) The increased effect of human cathelicidin (antimicrobial peptides found in macrophages and involved in the innate human defense) on MSRA growth, occurred at 1/4 x MIC of anthracimycin. This synergy is without precedent and additional studies will investigate this interaction.\(^{32}\)
Another biological activity of anthracimycin has recently been discovered. In 2017, suppression of cell proliferation and motility and induction of apoptosis against hepatocellular carcinoma (HCC), was reported. This anticancer property of anthracimycin is associated with the mTOR-signalling activation. The serine/threonine kinase TOR phosphorylates the p70 S6 kinase, which is a protein involved in the regulation of cell growth, cell-cycle progression and metabolism. Playing such a pivotal role in cell metabolism, by activation of protein and lipid synthesis, for example, mTOR-signalling is induced by many types of cancer. The anthracimycin mechanism to deactivate this signalling is still unclear, but many biologists suspect that this natural product could inhibit the phosphorylation pathway of p70 S6 kinase. This anticancer effect has been observed with an IC$_{50}$ value of 2.5 µg/mL in the HCC cell lines.
8.4 Isolation of an anthracimycin analogue 14

In 2017, anthracimycin BII-2619 14 was isolated from *Nocardiopsis kunsanensis*, an actinobacterial microorganism (Figure 5). This natural product was purified as a white powder and was found to have the same molecular formula of anthracimycin 1. Via NMR spectroscopy analysis, the structure and relative configuration of 14 was assumed to be the same as anthracimycin, except for the presence of the methyl group at C-8 instead of C-2. This analogue of anthracimycin 14 was found to have antimicrobial activity against Gram-positive bacteria, but compared to data for anthracimycin the MIC values were found to be between 50 and 100-fold lower.

![Figure 5. The chemical structure of anthracimycin BII-2619 14.](image)

<table>
<thead>
<tr>
<th>Target Organism or Cell line</th>
<th>Activity (µg/ml) 1</th>
<th>Activity (µg/ml) 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram Positive bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MRSA (ATCC 33591)</em></td>
<td>0.06</td>
<td>0.125</td>
</tr>
<tr>
<td><em>MSSA (ATCC 25923)</em></td>
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<td>1</td>
</tr>
<tr>
<td><em>Bacillus subtilis (ATCC 6633)</em></td>
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<td>64</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
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<td>8</td>
</tr>
<tr>
<td>Gram Negative bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia Coli</em></td>
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<td>&gt;128</td>
</tr>
<tr>
<td><em>Pseudomonas aureginosa</em></td>
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<td>&gt;128</td>
</tr>
<tr>
<td>Mammalian cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Human lung carcinoma cells</em></td>
<td>-32</td>
<td>35</td>
</tr>
</tbody>
</table>

*Table 3. Biological activity of anthracimycin BII-2619 14 compared to anthracimycin 1.*
8.5 A related polyketide: chlorotonil A 15

A related tricyclic metabolite with a similar carbon skeleton was found in chlorotonil A 15, isolated from the myxobacteria Sorangium cellulosum (Figure 6). The pivotal feature of this polyketide is its pseudo-enantiomerism with anthracimycin 1. In fact, chlorotonil A 15 exhibits the opposite absolute configuration at C-2, C-6, C-7, C-12, C-25, C-21, C-15 and C-6 when compared to anthracimycin 1. Additional differences are represented by the presence of the methyl group at C-8 in the C-ring and by the presence of a dichloromethylene group at C-4, in the A-ring. In Nature, other examples of enantiomeric products are reported: a linear precursor geranylgeranyl pyrophosphate is cyclised into monoterpenes (+)-limonene and (-)-limonene; (+) notoamide B and (-)-notomamide B are enantiomers of the same intermediate precursors. In these cases, the enantiomeric products are formed by the cyclisation of achiral precursors, instead, in anthracimycin 1 and chlorotonil A 15, a pair of enantiomeric precursors generate highly modified related structures. These two secondary metabolites 1 and 15 share a similar carbon framework and this is a rare case, because anthracimycin 1 is produced by actinomycetes, whereas, chlorotonil A 15 is produced by myxobacteria. This is also the first reported example of pseudo-enantiomers polycyclic secondary metabolites derived from a type I PKS.

Figure 6. The chemical structure of chlorotonil A 15.
The molecular formula of chlorotonil A 15 is $\text{C}_{26}\text{H}_{32}\text{Cl}_2\text{O}_4$, and this polyketide features an unsaturated trans-decalin core scaffold between B/C-rings and an unusual gem-dichloro-1,3-dione functionality in the A-ring. A cis-relationship between the A/B rings is also observed, as well as the presence of stereogenic centers at C-2, C-6, C-7, C-12, C-25, C-21, C15, C-6 and C-8.

Compared to anthracimycin 1, chlorotonil A 15 exhibits potent bioactivity against Gram-negative bacteria, such as *Pseudomonas aeruginosa* and also against the malaria protozoan pathogen *Plasmodium falciparum*. The ability to penetrate external bacteria membranes, relies upon the presence of the gemdichloro-1,3-dione and on the methyl group at C-8, which enhance the lipophilicity of this polyketide.

The biosynthesis of chlorotonil A 15 was studied and biological data showed a PKS pathway responsible for the formation of this polyketide in parallel with the biosynthetic route of anthracimycin 1 (Scheme 3). This similarity, could explain the several homogeneity features in the structure of these two secondary metabolites.

Starting with a malonyl residue-ACP 16, chain elongation takes place via a series of Claisen condensation reactions, as reported in the biosynthesis of anthracimycin. Again, the key step in this pathway is the intramolecular Diels–Alder reaction to form the trans-decalin core of the molecule, intermediate 24. A hypothesis to explain the inversion of the stereocenters in the trans-decalin scaffold compared to anthracimycin, relies on the presence of the methyl group at C-8, which could play a role in “pre-organising” the structure of 23, during cycloaddition. After chain elongation, the advanced intermediate 27 is released by the PKS domain and an unprecedented double chlorination reaction at C-4, between the two carbonyl groups, and a methylation reaction at C-2 take place to form chlorotonil A 15 (Scheme 3).
Scheme 3. The biosynthesis of chlorotontil A 15.13
Interestingly, chlorotonil A congeners such as chlorotonil B 29, chlorotonil C 30 and chlorotonil C2 31 have also been isolated. Chlorotonil B 29 and chlorotonil C 30 differ from chlorotonil A by the lack of one chlorine atom at C-4, in the A-ring. Chlorotonil B 29 also differs from chlorotonil A by the lack of a double bond and the methyl group in the C-ring. In addition, chlorotonil C2 31 differs from chlorotonil C 30 by the lack of the methyl group at C-2 and the presence of no chlorine atom. These differences in the structure, made the congeners less potent towards bacteria, as highlighted by the MIC values (Table 4). This fact indicates that the presence of two chlorine atoms is pivotal for the biological activity.  

<table>
<thead>
<tr>
<th></th>
<th>MIC µg/ml</th>
<th>MIC µM</th>
<th>MIC µg/ml</th>
<th>MIC µM</th>
<th>MIC µg/ml</th>
<th>MIC µM</th>
<th>MIC µg/ml</th>
<th>MIC µM</th>
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<td>0.025</td>
<td>&gt; 3.2</td>
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<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>1.6</td>
<td>3.8</td>
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<td>B.subtilis DSM-10</td>
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<td>≤0.006</td>
<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>1.6</td>
<td>3.8</td>
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<td>&gt; 6.4</td>
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<td>&gt; 6.4</td>
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<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>&gt; 3.2</td>
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<td>&gt; 6.4</td>
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<td>&gt; 6.4</td>
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<tr>
<td>E.Coli</td>
<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td>&gt; 3.2</td>
<td>&gt; 6.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. The biological activity of chlorotonil A compared with the congeners.
8.5.1 The total synthesis of chlorotoniol A 15

In 2008, Kalesse et al. reported the total synthesis of chlorotoniol A 15, using a biomimetic and stereocontrolled strategy (Scheme 4). The synthesis started with derivatisation of the Roche ester to give the TBS-protected aldehyde 32, which was subjected to a Still-Gennari olefination and DIBAL-H reduction to afford allyl alcohol 33. Homologation and oxidation formed aldehyde 34, which was subjected to a Corey-Fuchs transformation, to generate the dibromoolefin 35. Suzuki coupling between the dibromoolefin 35 and the boronic ester 36 gave intermediate 37, which after deprotection, oxidation and chain elongation via a Wittig reaction, generated the key intermediate 38. A Lewis acid triggered the formation of the trans-decalin 39, with high diastereoselectivity due to the presence of the bromine atom (d.r. 13 : 1). Lac tone opening followed by esterification afforded compound 40, which was coupled with the novel allyl phosphonate reagent 41, to form 42 Z,E,E with a ratio of 3 : 1. Finally, dianion addition of ethyl-2-methylacetoacetate, followed by macrocyclisation in the presence of a Lewis acid, yielded chlorotoniol A 15, as a single isomer. To further explain the high selectivity obtained in the Diels–Alder cycloaddition reaction and the key role played by the bromine substituent, the dehalogenated intermediate 44 was prepared and subjected to the reaction conditions (Scheme 5). As a result, a mixture of the endo-I and endo-II products 45 and 46 were obtained in a 3 : 1 ratio, decreasing the selectivity of this cycloaddition reaction. The explanation of this result relied on the conformation of transition states 47 and 48, in which the presence of the bromine substituent disfavoured the endo-II transition state due to electronic and steric repulsion (Scheme 6).
Scheme 4. The total synthesis of chlorotonil A 15 by Kalesse et al.⁴⁴
Scheme 5. Diels–Alder reaction without bromine: different ratio of products obtained.

Scheme 6. Transition state of endo-I and endo-II products.
8.6 Computational investigations into IMDA synthesis of anthracimycin

The initial strategy considered towards the total synthesis of anthracimycin 1 was a biomimetic approach. The published total synthesis by Kalesse of chlorotonil A 15, utilised a bromine atom to direct the intramolecular Diels–Alder formation of the trans-decalin core in a biomimetic route. Computational studies were conducted to decide whether to follow a similar approach or whether a new total synthesis would be more appropriate. As highlighted in the biosynthetic pathway of anthracimycin 1, whilst the polyketide is still bound to the enzyme, a Diels–Alder reaction forms the trans-decalin scaffold. This intramolecular [4 + 2] cycloaddition could generate four possible decalin products, yet only one has been isolated.

Dr. Ian George (postdoctoral researcher in the Clarke group), conducted DFT computational studies to better understand the formation of the molecule via a biomimetic synthesis (Figure 7). Interestingly, these calculations showed the formation of two compounds 11 and 51 with a considerably lower activation barrier (ΔE) than the others. Compound 11 had a structure of the proposed anthracimycin intermediate and is both the kinetic and thermodynamic product, based on the activation energy value ΔE = 58 KJmol⁻¹ and the energy difference ΔH = -259.9 KJmol⁻¹ between the energy of the starting material precursor and the product. The exo-Diels–Alder product 51, generated from the diene approaching the opposite face of the dienophile, also appeared to have a low energy barrier (ΔE = 65 KJmol⁻¹). The exo-Diels–Alder compound 49, formed when the diene approached the same face of the dienophile, and the endo-Diels–Alder compound 50, instead, each showed a high activation energy value (ΔE = 335.36 KJmol⁻¹ and 268.55 KJmol⁻¹ respectively). The data suggests it would be unlikely for these two products 49 and 50 to form. However, as the ΔE of 11 and 51 showed similar values, the possibility of forming a mixture of decalin intermediates was potentially very likely and so, the biomimetic approach was not pursued any further.
**Figure 7.** Computational calculation to study the biomimetic cycloaddition to form the decalin scaffold of anthracimycin, by Dr. Ian George.

These studies also showed that the stereochemistry of the Diels–Alder cycloaddition reaction was determined by the methyl group, shown in red, presumably due to the steric clash generated in the transition state giving a higher barrier to the energy of activation for the disfavoured products 49 and 50 (Figure 8).

**Figure 8.** The transition of anthracimycin 11.
8.7 Synthesis of functionalised decalin scaffold

Computational studies showed that formation of a mixture of intramolecular Diels–Alder products was possible, therefore, an alternative strategy was explored for the synthesis of anthracimycin 1. In Natural product total synthesis, different strategies for the stereoselective formation of functionalised decalins have been reported. In general, there are two types of disconnection for the formation of these bicyclic systems. In the type I disconnection, functionalisation of the cyclohexane ring (cycle A or B) is followed by C-C bond formation, allowing the construction of the AB cycle. In the type II disconnection, a single process is involved in the formation of the AB decalin system (Scheme 7).

**Scheme 7.** The disconnection strategies to form a decalin system.
Type I A disconnection

Intramolecular allylation reactions are an example of a type I A disconnection, as reported by Anderson for the construction of the cis-decalin 55, in the total synthesis of popolohuanone E 56 (Scheme 8). An intramolecular Hosomi–Sakurai 1,4-addition, in the presence of TiCl₄ and allylsilane was used to generate the cis-decalin core of this natural product.⁵²

Scheme 8. Allylation reaction as a type I A reaction for the formation of cis-decalin.⁵²

Type I B and I E disconnection

Radical reactions are well established in the construction of decalin systems, as examples of type I B and I E disconnections. In 2013, Carreira et al. reported the total synthesis of ent-crotogoudin 61, in which the key step was a radical cyclopropane opening/annulation/elimination reaction promoted by SmI₂ (type I B) (Scheme 9).⁵³
Scheme 9. Radical cyclopropane opening/annulation/elimination for the formation of decalin 60.\textsuperscript{53}

In 2013, Hong reported a one-pot photocatalytic Michael-aldol sequence (type I E) for the enantioselective synthesis of the functionalised decalin system 63 (Scheme 10).\textsuperscript{54}

Scheme 10. Photocatalytic Michael-aldol sequence for the enantioselective synthesis of decalin 63.\textsuperscript{54}
Type I C disconnection

The intermolecular Diels–Alder cycloaddition reaction is an example of a type I C disconnection. In the synthesis of tricyclic ent-kaurenoid natural product 71 reported by Zhang, intermolecular Diels–Alder cycloaddition, followed by intramolecular carbocyclisation was developed to form a common building block 70, for the synthesis of this natural product (Scheme 11).55

Scheme 11. The Diels–Alder/carbocyclisation sequence reported by Zhang.55

The asymmetric version of the Robinson annulation reaction was reported by Jung in the total synthesis of rhodexin A 78 (Scheme 12).56 In this sequence, acetic acid and (S)-proline catalysed a condensation reaction to form compound 75, which was subsequently transformed into cis-decalin 77 using catalytic hydrogenation conditions.
Type I D disconnection

Pericyclic cyclisation reactions, such as 6π-electrocyclisation, were used by Williams for the formation of the cis-hydroxydecalin core of crotonsins, as an example of a type I D disconnection. A cross-coupling reaction between 79 and 80 afforded the intermediate 81, which was subjected to a thermal electrocyclisation reaction to form 82 in quantitative yield (Scheme 13).

Scheme 12. The total synthesis of rhodexin A 78, by Jung.

Scheme 13. Pericyclic cyclisations as an example of a type I D disconnection.
Type II A disconnection

In 2012, Miyaoka reported the synthesis of (+)-kalihinol A 87, a richly functionalised antimalarial diterpenoid. The synthetic sequence started with the construction of cis-decalin 86 in 20 steps using an intramolecular Diels–Alder cycloaddition, as an example of type II A disconnection (Scheme 14).

Scheme 14. The intramolecular Diels–Alder (type II A) in the total synthesis of kalihinol A 87.

Type II B disconnection

An example of a type II B disconnection is represented by cationic cyclisation, which has been used by Canesi et al., to form the trans-decalin intermediate 90 during the total synthesis of cassaic acid 91. In the presence of PhI(OAc)₂ and hexafluoroisopropanol, a phenol was transformed into a highly reactive electrophilic species 89 (aromatic ring umpolung). The presence of bromine atoms at the ortho-positions, promoted cyclisation at the para-position of the molecule to afford 90 in a 41% yield (Scheme 15).
As suggested by the computational studies, the intramolecular Diels–Alder cycloaddition reaction was not a useful strategy to selectively form the trans-decalin core of anthracimycin. Consequently, the intermolecular type I disconnections would be explored instead. The intermolecular Diels–Alder cycloaddition and the Robinson annulation (type I C) would be envisioned, as a versatile and common strategy to build bicyclic systems with angular substituents stereoselectively. As the trans-decalin core of anthracimycin presents two double bonds in the B and C ring, and two side chains in a syn-relationship, key disconnections of these two envisioned strategies will be proposed and discussed in detail in the next chapter.
9. Results and discussion

9.1 The Robinson annulation to form a functionalised \textit{trans}-decalin

9.1.1 Retrosynthetic analysis

The aim of this project was to complete the total synthesis of anthracimycin 1. The proposed retrosynthetic strategy (Scheme 16) involved dividing the molecule into three major fragments: the Still–Gennari reagent 92, the β-ketoester 93 and the highly functionalised \textit{trans}-decalin core 94. The desired Z-double bond was envisioned to be formed via Still–Gennari olefination, and a Weiler-dianion addition reaction would connect fragment 92 to the \textit{trans}-decalin core 94. Finally, a macrocyclisation would then generate the 14-membered macrocycle ring and form the desired natural product 1. Key disconnections for formation of this highly functionalised \textit{trans}-decalin core 94 would involve Wittig olefination and conjugate addition for the installation of the two side chains. A Robinson annulation reaction would be investigated for the synthesis of the decalin system 97.

\textbf{Scheme 16}. The retrosynthetic analysis of anthracimycin 1, using the Robinson annulation strategy.
As illustrated in the type I C disconnection, the Robinson annulation reaction is a three-step sequence, and due to its ability to form fused systems with angular substituents, it is one of the main reactions used for the construction of decalins in natural product synthesis. This reaction would be investigated for the synthesis of the trans-decalin 97. A conjugate addition reaction followed by enolate trapping with Mander’s reagent could be employed to install the methyl ester chain yielding 100. Further transformations of this compound 100, such as oxidation, Wittig olefination and reduction reactions would be explored to form the core of anthracimycin 94 (Scheme 17).

Scheme 17. The Robinson annulation/conjugate addition approach to the synthesis of the decalin core 94.

The annulation of cyclohexanone 101 in the presence of methylvinylketone 99 and KOH as a base was attempted, and the decalin product 103 was generated in a 3% yield (Scheme 18). The isolation of the hydroxyl-decalin intermediate 102 explained the low yield obtained from this cyclisation reaction, as a consequence of the incomplete transformation into the decalin final product 103. However, the conversion of 102 into the desired decalin 103 was investigated via an elimination reaction using a range of acidic and basic conditions. In the presence of strong acid, the desired compound 103 was isolated in high yields (Table 5, entry 1 and 2). Basic conditions, however, were not as effective for this transformation (Table 5, entry 3 and 4).
Scheme 18. The Robinson annulation of cyclohexanone 101.\textsuperscript{61}

<table>
<thead>
<tr>
<th>entry</th>
<th>condition</th>
<th>temperature</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>glacial AcOH, H₂SO₄</td>
<td>r.t.</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>HCl 4 M</td>
<td>r.t.</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>KOH, ethanol</td>
<td>r.t.</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>MsCl, Et₃N, 0 °C to r.t.</td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>

Then DBU CH₂Cl₂

Table 5. The elimination conditions for the conversion of 102 into decalin 103.\textsuperscript{52}

The annulation of 4-methyl cyclohexanone 98 in the presence of methylvinylketone 99 and KOH, generated decalin 105 in a 2% yield and the hydroxyl-decalin 104 in a 41% yield (Scheme 19). Acidic conditions-glacial acetic acid and sulfuric acid-were used to complete the conversion of 104 into the desired decalin 105, which was isolated in a 77% yield.
Having achieved the formation of decalins 103 and 105 via a two-step sequence, the conjugate addition reaction to functionalise these bicyclic compounds was explored. Treatment of 103 in the presence of allyl bromide 108, DMSO and NaH, formed the desired product 106 in a 26% yield. A doubly alkylated compound 107 was also generated and the decalin starting material 103 was recovered in a 5% yield (Scheme 20). A mechanism for this reaction was proposed: (i) the 1,4-addition of the DMSO ylide to the enone decalin 103 generated the enol-decalin 109, (ii) the alkylation of allyl bromide 108 generated intermediate 110, which after, (iii) a final elimination of DMSO formed the enone decalin alkylated product 106 (Scheme 20).
Scheme 20. The conjugate addition of 103 and the proposed mechanism of the reaction.\textsuperscript{53}

The conjugated addition of the Mander’s reagent instead of allyl bromide, using these conditions was attempted, but formation of the desired product was not observed and the starting material 103 was recovered unreacted. Due to the low yields and the formation of side-products during conjugate addition, this approach towards the synthesis of the highly functionalised trans-decalin core 94 was not pursued further.
9.2 Diels–Alder/epimerisation sequence to the \textit{trans}-decalin

9.2.1 Retrosynthetic analysis

The division of the natural product into three major fragments, the Still–Gennari reagent 92, the β-ketoester 93 and the highly-functionalised \textit{trans}-decalin core 94, remained the proposed retrosynthetic strategy (Scheme 21). Key reactions to form the highly functionalised \textit{trans}-decalin system 94 would involve a facially selective and diastereoselective Ireland–Claisen rearrangement on the face that presents the triisopropylsilylmethyloxy chain, and a Diels–Alder/epimerisation sequence starting form enone 115 and diene 116. The conjugated enone 115 would be synthesised \textit{via} an oxidation/reduction sequence of the commercially available keto-ester 117.

Scheme 21. The retrosynthesis analysis of anthracimycin 1.
The Diels–Alder cycloaddition reaction has left a special imprint in natural product total synthesis, due to the ability to construct polyfunctional and highly substituted molecules. This approach has been used as a key step in cascade sequences and has enabled synthetic chemists to obtain numerous scaffolds in total synthesis. Pericyclic reactions offer an efficient approach to the synthesis of six-membered rings and bicyclic systems, and have numerous advantages including stereochemical control (always a cis addition) and easy predictability of its regiochemistry, with the selectivity of the Diels–Alder cycloaddition rationalised using frontier molecular orbital theory. A classical method to enhance the rate of the reaction is the use of a Lewis acid-mediated Diels–Alder cycloaddition reaction to decrease the energy gap between the LUMO of the dienophile and the HOMO of the diene. As reported in the previous section, a range of natural products containing cis- and trans-decalins were formed by using this powerful cycloaddition. In 2009, Danishefsky and co-workers reported a two-step “trans-Diels–Alder reaction” with the use of nitrocycloalkenes to form bicyclic systems. This pericyclic reaction between diene and dienophile formed the cis-fused decalin adduct in a 62% yield. A radical reduction in the presence of AIBN and nBu3SnH, removed the nitro group and triggered the conversion from the cis- to the trans-fused system in a 71% yield and in a 5 : 1 ratio (Scheme 22).

Scheme 22. A two-step “trans-Diels–Alder reaction”.69
In 2010, Danishefsky et al. also described a Lewis acid catalysed Diels–Alder reaction between α-bromocyclohexenones 126 and various substituted dienes 127, to provide cis-fused bicyclic systems 128 (Scheme 23).\textsuperscript{70, 71} Removal of the bromine atom and the consequent epimerisation from cis- to trans-decalin, was performed by radical reduction using AIBN and \(n\text{Bu}_3\text{SnH}\). This conversion from α-halo cis-bicyclic systems to trans-decalins was also studied by Lee in 2015, who performed a new tin-free photoredox catalysis reaction.\textsuperscript{72}

\[ \text{Scheme 23. The epimerisation from cis- to trans-decalin via a radical and a photoredox strategy.} \textsuperscript{70-72} \]

With this idea in mind, the Diels–Alder strategy for the formation of the functionalised trans-decalin of anthracimycin was explored. The α-bromo-substituted cyclohexenone 132 was prepared from cyclohexanone 131 by treatment with molecular bromine and DMAP, using pyridine and chloroform as solvents.\textsuperscript{73, 74} A Lewis acid (EtAlCl\(_2\)) catalysed the Diels–Alder cycloaddition reaction between 132 and isoprene 133, afforded the cis-decalin 134 in a 62\% yield, as a single diastereoisomer (Scheme 24).\textsuperscript{72}
However, using isoprene 133, the position of the methyl group at C-9 in the cis-decalin 134 was incorrect for the decalin core of anthracimycin 94. This was not unexpected, due to the largest orbital coefficient of the HOMO of the alkene being next to the methyl group. To influence the regiochemistry of this cycloaddition and install the methyl group at C-10 as required, the sulfur-substituted diene 116 was synthesised, in order to exploit the greater electron-donating effect of the thiophenyl group compared to the methyl substituent. It is noteworthy that this diene 116 was freshly prepared in a quantitative yield before the Diels–Alder (Scheme 25). In this case, EtAlCl₂ catalysed the cycloaddition between 132 and 116 formed the cis-decalin 136 in a 54% yield as a single diastereoisomer (Scheme 26). Due to the instability of the α-bromo cis-decalin 136 to light and air, the conversion into the corresponding trans-diastereoisomer 137 was tested under radical conditions, but just unreacted starting material was recovered. However, the larger orbital coefficient of the HOMO of the alkene next to the thiophenyl group of diene 116, influenced the regiochemistry of this cycloaddition reaction and installed the methyl group at C-10 as required for anthracimycin 1.
Scheme 26. A regioselective Diels–Alder to form cis-decalin 136.\(^{72}\)

Due to the instability of the bromine-containing Diels–Alder adducts 134 and 136, it was decided to investigate the non-halogenated enone 131 as the dienophile in this reaction. The cycloaddition reaction of 131 and 133 was performed and generated two decalin products 138 and 139 in a 12 : 1 crude ratio (cis : trans) (Scheme 27).\(^{76}\) This result showed evidence of an epimerisation from a cis- to a trans-decalin under the reaction conditions. Treatment of 138, with further Lewis acid, generated the trans-diastereoisomer 139 in a 8 : 92 ratio (cis : trans), which confirmed the conversion via epimerisation observed during the cycloaddition (Scheme 28).

Scheme 27. The Diels–Alder cycloaddition between 131 and 133.\(^{76}\)
Scheme 28. The epimerisation from the cis- to trans-decalin 139.

In order to confirm the stereochemistry of the trans-decalin 139, the carbonyl was reacted with 2,4-dinitrophenyl hydrazine 140 to form the hydrazone 141 and facilitate the crystallisation of the molecule (Scheme 29). The structure of the hydrazone 141, isolated in a 54% yield, was confirmed unambiguously by single crystal X-ray diffraction (Figure 9).

Scheme 29. The derivatisation of the trans-decalin 139 into the hydrazone 141.

Figure 9. The X-ray diffraction single crystallography of the hydrazone 141 with thermal ellipsoids shown at 50%.
The X-ray crystal structure in Figure 9 confirmed the trans-ring junction between protons H-7 and H-12, which was obtained using a Diels–Alder/epimerisation sequence.

Armed with this knowledge, formation of the trans-diastereoisomer 139 in one-pot was attempted during the Diels–Alder cycloaddition reaction. Premixing the catalyst with cyclohexenone (131) over a period of 30 minutes, formed the two diastereoisomers 138 and 139 in a 0.85 : 1 ratio (cis : trans), which were isolated in a 37% and in a 40% yield, respectively. Increasing the amount of catalyst from 0.2 to 1.2 equivalents, did not significantly improve the formation of the trans-decalin 139. A 0.7 : 1 ratio (cis : trans) was achieved using stoichiometric amount of EtAlCl₂, whereas, a 0.6 : 1 ratio (cis : trans) was obtained by re-addition of the catalyst after the consumption of the cyclohexenone 131. The epimerisation to the trans-decalin 139 was, therefore, not performed in a one-pot reaction and its synthesis was achieved in a Diels–Alder/epimerisation sequence over two steps. However, to highlight the advantages of this method, different dienophiles and dienes were tested to form trans-bicyclic systems. The literature reported an AlCl₃-catalysed cycloaddition between different ring size enones in the presence of diverse dienes, to yield bicyclic adducts in various cis : trans ratio.⁷⁷, ⁷⁸

The Diels–Alder reaction between cyclohexenone (131) and 2,3-dimethyl-1,3-butadiene (142) formed cis- and trans-decals 143 and 144 in a 2 : 1 ratio as an inseparable mixture of products. After epimerisation, a 1 : 23 ratio (cis : trans) was observed (Scheme 30, Figure 10). The cycloaddition of cyclohexenone (131) in the presence of trans-1,3-pentadiene (145), formed the cis- and trans-decalins 146 and 147 in a 9.8 : 1 ratio (cis : trans). After epimerisation, the proportion of the trans-decalin 147 increased, but the diastereomeric ratio remained in favour of the cis-decalin 146, 1.92 : 1 ratio (cis : trans) (Scheme 31, Figure 11). The Diels–Alder reaction between cyclopentenone (148) and isoprene (133) formed the cis- and the trans-adducts 149 and 150 in a 1.34 : 1 ratio (cis : trans), which did not change under the epimerisation conditions (Scheme 32, Figure 12). In the presence of 2,3-dimethyl-1,3-butadiene 142, the cis- and the trans-bicyclic systems 151 and 152 were formed in a 4 : 1 ratio (cis : trans), which equilibrated to 1.47 : 1 after epimerisation (cis : trans) (Scheme 33, Figure 13). The cycloaddition between cycloheptenone (153) and isoprene (133) generated the cis- and trans-
diastereoisomers 154 and 155 in a 10 : 1 ratio (cis : trans), which were isolated in a 52% and 5% yields, respectively (Scheme 34, Figure 14).\textsuperscript{77, 78}

The Diels–Alder/epimerisation between enone 131 and diene 142, generated cis- and trans-decalins 143 and 144 in a 1 : 23 ratio (Scheme 30). Due to the presence of many overlapping peaks in the \textsuperscript{1}H NMR spectrum, the diastereomeric ratio of 143 and 144 before and after epimerisation was calculated using quantitative \textsuperscript{13}C NMR analysis. Using around 100 mg of compound and setting a long relaxation time (10 seconds) during a 16-hour analysis, it was possible to calculate an accurate diastereomeric ratio based on the integration of ketone peaks C-13 of 143 and 144, at \(\delta 212.5\) (cis) and at \(\delta 212.4\) (trans) ppm respectively (Figure 10).
Scheme 30. The Diels–Alder/epimerisation reaction between 131 and 133.

Figure 10. Ratio of cis- and trans-decalins 143 and 144 calculated on a quantitative $^{13}$C NMR spectrum based on ketone C-13 integration.

The Diels–Alder/epimerisation sequence between enone 131 and diene 145 afforded cis- and trans-decalins 146 and 147 in a 1.92 : 1 ratio (Scheme 31). The literature reported a similar ratio (1.8 : 1 cis : trans) using the same substrates in an AlCl₃-catalysed Diels–Alder reaction to form the decalin
products 146 and 147. As shown in the crude $^1$H NMR spectrum, the 1.92 : 1 diastereomeric ratio of 146 and 147 after epimerisation was calculated based on integration of methyl groups peaks; a doublet at $\delta$ 1.21 ppm (cis, 146) and a doublet at $\delta$ 0.94 ppm (trans, 147) (Figure 11). These data matched the literature assignments: methyl group of the cis-isomer 146 doublet at $\delta$ 1.27 ppm, and methyl group of the trans-adduct 147 doublet at $\delta$ 0.94 ppm.

![Scheme 31. The Diels–Alder/epimerisation sequence between 131 and 145.](image)

**Figure 11.** Ratio of cis- and trans-decalins 146 and 147 calculated on a $^1$H NMR spectrum based on methyl integration.
The cycloaddition between 148 and 133 was attempted and a 1.34 : 1 ratio cis : trans was obtained before and after epimerisation and the product was isolated as an inseparable mixture (Scheme 32). For these substrates, literature reported a 1.7 : 1 ratio cis : trans, calculated on integration of proton H-9 at δ 5.39 ppm (trans, 150) and at δ 5.36 ppm (cis, 149). As shown in the crude 1H NMR spectrum, the 1.34 : 1 diastereomeric ratio of 149 and 150 resulting from the Diels–Alder/epimerisation sequence, was calculated based on integration of H-9 protons, multiplets at δ 5.46–5.39 (trans, 150) and at δ 5.36–5.32 ppm (cis, 149) (Figure 12).

Scheme 32. The Diels–Alder/epimerisation sequence between 148 and 133.
Figure 12. Ratio of cis- and trans-decalins 149 and 150 calculated on a $^1$H NMR spectrum based on integration of proton H-9.

The Diels–Alder/epimerisation reaction between enone 148 and diene 142 afforded an inseparable mixture of decalins 151 and 152, isolated in a 1.47 : 1 ratio cis : trans (Scheme 33). Due to the presence of many overlapping peaks in the $^1$H NMR spectrum, the 1.47 : 1 diastereomeric ratio of 151 and 152 was calculated using a quantitative $^{13}$C NMR analysis. Using around 100 mg of compound and setting a long relaxation time (10 seconds) in a 16-hour experiment, integration of the ketone C-13 peaks of cis- and trans-decalins 151 and 152 of the crude reaction mixture allowed the determination of the diastereomeric ratio. The carbonyl peaks (C-13) of the cis- and trans-decalins were found at $\delta$ 219.7 (cis, 151) and at $\delta$ 218.9 (trans, 152) ppm (Figure 13).
Scheme 33. The Diels–Alder/epimerisation sequence between 148 and 142.

Figure 13. Ratio of cis- and trans-decalins 151 and 152 calculated on a quantitative $^{13}$C NMR spectrum based on ketone carbonyl integration.

The cycloaddition reaction between enone 153 and diene 133 generated decalins 154 and 155 in a 10 : 1 ratio cis : trans, isolated in a 52% and 5% yields respectively (Scheme 34). The diastereomeric ratio of these two products was calculated based on ketone integration C-13 of the crude reaction mixture.
using quantitative $^{13}$C NMR spectroscopic analysis. The carbonyl peaks (C-13) of the cis- and trans-decalins were found at $\delta$ 215.7 (cis, 154) and at $\delta$ 217.1 (trans, 155) ppm (Figure 14). The literature reported the formation of cis- and trans-diastereoisomers 154 and 155 in a 1 : 45 ratio (cis : trans), reporting carbonyl peaks (C-13) of the cis- and trans-decalins at $\delta$ 214.4 (cis, 154) and at $\delta$ 215.9 (trans, 155).

Scheme 34. The Diels–Alder reaction between enone 153 and diene 133.

Figure 14. Ratio of cis- and trans-decalins 154 and 155 calculated on a quantitative $^{13}$C NMR spectrum based on ketone C-13 integration.
After this screening, the Diels–Alder between cyclohexone (131) and the sulfur-substituted diene 116 was attempted, to correct the regioselectivity of the cycloaddition and install the methyl group at C-10. The literature reported an EtAlCl₂-catalysed cycloaddition between cyclohexone 131 and the sulfur substituted diene 116, to give the cis-decalin 156 in a 35% yield. Photoredox conditions then triggered the epimerisation from cis- to trans-decalin 137. Repeating the EtAlCl₂-catalysed Diels–Alder conditions, the cis-decalin 156 was generated as a single diastereoisomer in a 37% yield over a period of 3 hours at −10 °C (Scheme 35 and Table 6, entry 1). It was, however, observed that time and temperature had a key role in the formation of impurities, and in the isolation of the desired product 156 in a high yield. A period of 3 hours at room temperature afforded the cis-decalin 156 in a 51% yield (Table 6, entry 2), whereas, a 90% yield of 156 was obtained at room temperature over a period of 1.5 hours (Table 6, entry 3). Epimerisation, under the same reaction conditions, formed the trans-decalin 137 in a 68% yield over a two-step sequence, as observed in the previous studies (Scheme 35).

![Scheme 35](image_url)  
**Scheme 35.** The Diels–Alder/epimerisation sequence to form the trans-decalin 137.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temperature (°C)</th>
<th>time (h.)</th>
<th>yield of 156 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2 eq. EtAlCl₂</td>
<td>−10 °C</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>0.2 eq. EtAlCl₂</td>
<td>r.t.</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>0.2 eq. EtAlCl₂</td>
<td>r.t.</td>
<td>1.5</td>
<td>90</td>
</tr>
</tbody>
</table>

**Table 6.** The optimization of the Diels–Alder reaction between cyclohexanone 131 and diene 116.
A selective Raney-Nickel reduction was performed in an attempt to remove the thiophenyl group from compounds 156 and 137. However, the treatment of the cis-diastereoisomer 156 under these conditions generated 157 and 158 in a 23% and 11% yield respectively, where over-reduction to the hydroxyl had occurred. In contrast, Raney-Nickel reduction of the trans-diastereoisomer 137 selectively cleaved the thiophenyl bond, forming exclusively the model trans-decalin 159 that possesses the stereochemistry and regiochemistry required for the core of anthracimycin 94 (Scheme 36).^79

Scheme 36. The Raney-Nickel reduction of cis- and trans-decalins 156 and 137.\(^79\)

To summarise, a Lewis acid catalysed Diels–Alder/epimerisation sequence allowed the formation of a model trans-decalin in a good yield and selectivity as required for anthracimycin, without the need for a radical reduction of unstable bromine-containing Diels–Alder adducts. The scope of this cycloaddition was explored using different ring size enones in the presence of diverse dienes, to form trans-bicyclic products with a high diastereomeric ratio. The use of the sulfur-substituted diene 116 permitted us to influence the regiochemistry of the Diels–Alder cycloaddition reaction, exploiting the greater electron-donating effect of the thiophenyl group, and the cis-decalin 156 was obtained in a 90% yield, optimising the literature reported conditions. Epimerisation to the trans-decalin 137 in 68% yield was followed by a selective Raney-Nickel reduction to remove the thiophenyl group, which
generated 159 as a model trans-decalin system for that required for the total synthesis. Application of these conditions to form the trans-decalin core of anthracimycin will be discussed in the next section.

9.3 Formation of the trans-decalin core of anthracimycin 114

9.3.1 The synthetic plan

Based on the retrosynthetic plan (Scheme 21), the following synthetic route was proposed (Scheme 37). Starting with a lithium aluminium hydride reduction of the cheap and commercially available ethyl 4-oxocyclohexanecarboxylate 117, TIPS-protection of the primary alcohol and oxidation of the secondary alcohol would generate ketone 160. Oxidation of 160 to enone 115 would yield the dienophile suitable for the Diels–Alder/epimerisation sequence, optimised in the presence of the sulfur substituted diene 116. A selective Raney-Nickel reduction to remove the thiophenyl group would afford the required trans-decalin 114. Oxidation of this compound 114 to the enone trans-decalin 113, would yield a key α,β-unsaturated synthetic intermediate. A stereoselective 1,2-reduction of 113 to generate the axial hydroxyl group, followed by treatment with propionyl chloride would form the propionate ester of trans-decalin 112. The axial position of the propionate ester would ensure a facial and diastereoselective Ireland–Claisen rearrangement of 112 occurring from the same face of the triisopropylsilylmethyloxy chain, to afford the core of anthracimycin 162. Formation of the E-enolate of 112 in the presence of LDA should also provide the correct stereochemistry of the methyl group in 162. Esterification of 161 would be followed by DIBAL-H reduction to form aldehyde 162, setting the required functional group for a Still-Gennari olefination reaction to install fragment 92. Protecting group removal (TIPS) from 162, followed by an oxidation/esterification sequence would afford the highly functionalised trans-decalin core 94. Compound 94 represents the opposite enantiomer of the core of chlorotonil A 40 (except for the absence of the methyl group at C-8), reported by Kalesse. Following the published total synthesis of this chlorinated polyketide 15, 41
installation of fragment 92 would be performed by a Still-Gennari olefination reaction with the phosphonate reagent 92 and KHMD at −78 °C, to generate the advanced intermediate 163. Subsequent, Weiler dianion addition of the commercially available β-ketoester 93 with the use of LDA, as base would yield compound 164. Removal of the protecting group (PMB) by treatment with BF₃·Et₂O would also trigger the final macrocyclisation reaction, allowing the conclusion of the total synthesis in a total of 19 steps (Scheme 37).
Scheme 37. The synthetic plan for anthracimycin 1.
Dr. Ian George (postdoctoral researcher in the Clarke group) working on a related trans-decalin natural product called streptosetin A, had developed a scalable synthesis of enone 115. Reduction of commercially available compound 117, followed by TIPS-protection of the primary hydroxyl group, afforded a mixture of alcohols 165 and 166 in a 44% and 14% yield respectively. Swern oxidation, scalable to 10 g, was used to convert 165 and 166 into a single ketone 160 in excellent yield (99%). An Ito–Saegusa oxidation was used to transform 160 to enone 115 (Scheme 38). However, the instability of the silyl enol-ether intermediate and its unreliable conversion into 115 and the reaction sensitivity to scale, forced us to find a more predictable and scalable synthesis of this early intermediate 115.

Scheme 38. The formation of the enone 115 developed by Dr. Ian George.
9.4 Direct palladium catalysed oxidation studies

9.4.1 Direct palladium catalysed oxidation studies: Stahl conditions

A new palladium-catalysed direct oxidation of ketone 160 to enone 115, which obviated the need to go via the silyl enol-ether, was developed by Dr. Ian George (postdoctoral researcher in the Clarke group) and myself, in collaboration with the Fairlamb group. Inspired by the work of Stahl (Scheme 39), Dr. Ian George investigated conditions to perform the oxidation directly from the starting ketone 160. In the Stahl proposed oxidation mechanism (Scheme 40), the first step would require the formation of the α-Pd^{II}-ketone intermediate 170, which is in equilibrium with the Pd^{II}-enolate species 171. The β-hydride elimination would then afford the enone product 168. Oxidation of the Pd^{0} complex in the presence of oxygen, would regenerate the Pd^{II}-catalyst ready for the catalytic cycle.

Scheme 39. Stahl reported condition of direct ketone oxidation. 

Scheme 40. The proposed mechanism for Pd^{II}-catalysed oxidation of cyclic ketone.
Following Stahl’s reported conditions in the presence Pd(OAc)$_2$(DMSO)$_2$ and Pd(TFA)$_2$(DMSO)$_2$ as the catalyst, the direct oxidation of ketone $160$ to enone $115$ was tested. However, after 16 hours at room temperature or at 80 °C in AcOH only traces of the enone $115$ were formed (Table 7, entry 2-6). Using EtOAc, as the solvent, the conversion was not improved (Table 7, entry 7). A conversion of 5% to the desired product was observed over a period of 96 hours at room temperature in AcOH (Table 7, entry 1). As this conversion matched the catalyst loading (5 mol% of Pd(OAc)$_2$(DMSO)$_2$), the catalytic cycle was probably arrested and the addition of additives was tested to overcome this problem.

\[
\begin{array}{cccc}
\text{entry} & \text{Solvent} & \text{Temp} (°C) & \text{Time (h.)} & \text{Conversion} (\%) \\
1 & \text{AcOH} & \text{rt} & 96 & 5 \\
2 & \text{AcOH} & 80 & 16 & \text{trace} \\
3 & \text{AcOH} & \text{rt} & 16 & \text{trace} \\
4 & \text{AcOH} & 80 & 16 & \text{trace} \\
5 & \text{EtOAc} & \text{rt} & 16 & \text{trace} \\
6 & \text{AcOH} & 80 & 16 & \text{trace} \\
7 & \text{EtOAc} & \text{rt} & 16 & \text{trace} \\
\end{array}
\]

Table 7. Stahl’s conditions on target ketone $160$. 

PdX$_2$ = Pd(OAc)$_2$, Pd(OTFA)$_2$
ligand = DMSO
9.4.2 Direct palladium catalysed oxidation studies: additives effect

The use of additives was explored to improve the conversion. In most cross-coupling reactions, the presence of a base (K₂CO₃, Et₃N, NaHCO₃) generally helps the β-hydride elimination and improves the yield. The control experiment in the absence of an additive showed no conversion to the enone as expected (Table 8, entry 1). The use of 2 equivalents of K₂CO₃ and Et₃N, also showed no improvement in the conversion (Table 8, entry 2-3-4).

<table>
<thead>
<tr>
<th>entry</th>
<th>Temp (°C)</th>
<th>Additive</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>K₂CO₃</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>rt</td>
<td>K₂CO₃</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>NEt₃</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 8. Additive screening to increase the conversion to the desired enone 115.

In 2007, Tsuji reported the direct palladium-catalysed oxidation of cyclic ketones to conjugated enones, in chlorobenzene at 120 °C with the use of pyridine and bipyridine ligands as more efficient additives for this oxidation (Scheme 41). A stabilisation effect of the active palladium species, preventing aggregation and extending the catalyst lifetime, could be the role played by these bipyridine ligands.
Inspired by this work, the addition of pyridine and bipyridine ligands was tested for the oxidation of ketone 160 to the enone 115, using Pd(OAc)$_2$ and Pd(OAc)$_2$(DMSO)$_2$ complex as catalysts, in chlorobenzene at 120 °C (Figure 15). Little differences were observed in the conversion between the Pd(OAc)$_2$ and the Pd(OAc)$_2$(DMSO)$_2$ complex, using pyridine 174 as a ligand (Table 9, entry 1 and 5). The addition of 2,6-lutidine 175 and 1,10-phenathroline 176 did not lead to efficient oxidation by either catalyst complex (Table 9, entry 2-3 and 6-7). The use of 2,2’-bipyridyl 177 was found to be a highly effective ligand for the Pd(OAc)$_2$ catalyst, increasing the conversion to 58% (Table 9, entry 8). In contrast, the addition of this ligand to the Pd(OAc)$_2$(DMSO)$_2$ complex did not improve the level of conversion (Table 9, entry 4). A conversion of 76% to the desired enone 115 was finally obtained with the use of 4,4’-Bu-2,2’-dipyridyl ligand 178 with Pd(OAc)$_2$ as the catalyst (Table 9, entry 9).

Figure 15. Pyridine and bipyridine ligands used.
Table 9. Pyridyl and bipyridyl ligand screening to improve the conversion of ketone 160 into enone 115.

Having identified the oxidation conditions, the conversion of ketone 160 into the enone 115 was monitored over time. The rate of this transformation followed an exponential growth, slowing at approximately 35% conversion. To improve conversion, additional catalyst was added which restored the reaction rate. A 92% conversion to the desired enone 115 was achieved after two subsequent additions of catalyst and ligand: 15 mol% Pd(OAc)$_2$ and 15 mol% ligand total (Figure 16).
9.4.3 Direct palladium catalysed oxidation studies: the nitrate effect

In the proposed reaction mechanism reported by Stahl (Scheme 40), the Pd⁰-species was oxidised by oxygen to Pd⁴⁺ to re-start the catalytic cycle. However, during the reoxidation of palladium, aggregation and deactivation of the catalyst could take place arresting the cycle.⁸² The need of two subsequent additions of Pd(OAc)₂ and ligand to reach a 92% conversion to the enone 115, suggested that deactivation of the catalyst was occurring during the oxidation reaction. The Fairlamb group have previously reported the nitrate effect in a range of oxidative palladium mediated processes, highlighting the role of the NO₃⁻ anion as a co-catalyst of the palladium complex.⁸⁴, ⁸⁵ To progress the conversion without the need of subsequent additions of Pd(OAc)₂, the role of the nitrate was tested. In the presence of 19 mol% of KNO₃, a rate enhancement was indeed observed: over a period of 80 hours, a 60% conversion was seen (Figure 17). A conversion of 80% over the same period was observed with the use of 50 mol% of KNO₃, whereas, in the presence of stoichiometric KNO₃ a slower conversion was detected compared to the 50 mol% KNO₃ experiment. A possible poison effect of stoichiometric quantities of the NO₃⁻ anion to the Pd(OAc)₂ catalyst may explain this result (Figure 17).⁸⁴, ⁸⁵

Figure 16. The re-addition of the catalyst restored the conversion rate of the oxidation.
Figure 17. The effect of KNO₃ concentration on the oxidation rate of the formation of the enone 115.

The optimised reaction conditions, 5 mol% of Pd(OAc)₂, 5 mol% of 4,4’-‘Bu-2,2’-dipyridyl as a ligand and 50 mol% of KNO₃ as a co-catalyst, were performed on a 10 g scale oxidation of ketone 160 to the enone 115, which was isolated in an 85% yield (9.0 g).

In conclusion, a scalable and robust synthesis of the enone 115 was performed to afford the dienophile required for the Diels–Alder cycloaddition, for the formation of the trans-decalin core of anthracimycin. The reported Stahl and Tsuji direct palladium-catalysed oxidation conditions were tested with no success, and a new catalytic system was developed. The use of the nitrate anion as a co-catalyst was found to be pivotal for the rate of conversion of ketone 160 into the enone 115. However, more studies need to be performed to investigate the appropriate mechanism of this reaction, which is still unknown, and to obtain the same level of conversion and yield in a shorter period of time.
9.4.4 Direct palladium catalysed oxidation studies: substrate scope

To investigate if the optimised oxidation conditions were applicable to the formation of other enone systems, various ketone substrates were tested. A 50% conversion of the model trans-decalin 139 into the model enone trans-decalin 179, was achieved after 5 days. However, compound 179 was isolated in a 23% yield and unreacted ketone 139 was recovered in a 42% yield (Scheme 42). Purification issues explained the poor yield of 179, as enone 179 may remain coordinated to the Pd0 species.

Scheme 42. The optimised oxidation conditions to form the model enone trans-decalin 179.

The oxidation of cholesterol 180 generated enone 181 in 18% yield; compound 182 was also isolated in a 24% yield due to an unexpected addition of nucleophilic oxygen to the γ-alkene, and the consequent α,β migration of the double bond (Scheme 43).

Scheme 43. Palladium catalysed direct oxidation of cholesterol 180.
The allyl-substituted enone 184 was isolated in a 37% yield as a consequence of the direct oxidation of 183, occurring exclusively on the less hindered side of the molecule (Scheme 44). This selectivity was hypothesised to be due to the steric repulsion between the palladium complex and the allyl substituent, which directed the oxidation to the less hindered position, α to the carbonyl group of 184. However, the starting material 183 was recovered in a 31% yield.

Scheme 44. Palladium catalysed direct oxidation of allyl-substituted cyclohexanone 183.

The oxidation of ketones 185, 186, 187 and 189 did not yield any enone products. Ketones 185 and 186 exclusively formed polymerised material, whereas, the volatility of cyclopentanone 187 and heptanone 189 was responsible of the failure of these reactions (Scheme 45).

Scheme 45. Substrate scope using the optimised oxidation conditions.
In conclusion, the optimised palladium-catalysed direct oxidation conditions were not always applicable for the dehydrogenation of diverse substrates. Enones 179, 181 and 184 were formed in poor yields compared to the 85% isolated yield of enone 115. The reason is still unclear and more work is required to optimise and apply these conditions to the oxidation of various ketone substrates to enones in high yields.

9.5 Enone 115 in the Diels-Alder reaction

The power of this oxidation reaction allowed the synthesis of the enone 115 to be performed on a multi-gram scale and this compound was used as a dienophile in the Diels–Alder/epimerisation sequence. In the presence of isoprene 133 as a diene, cis- and trans-decalins 191 and 192 were formed in a 0.83 : 1 ratio (cis : trans) (Scheme 46). Determination of the stereochemistry at C-6 was required. To this end, the trans-diastereoisomer 191 was converted into the hydrazone 193 by treatment with 2,4-dinitrophenyhydrazine 140, in dry methanol and catalytic acetic acid. However, good quality single crystal X-ray diffraction could not be obtained.

Scheme 46. The Diels–Alder/epimerisation sequence between enone 115 and isoprene 133.
Following these results, the Diels–Alder cycloaddition between enone 115 and the sulfur-substituted diene 116 was attempted. After 10 minutes, diene 116 was consumed completely and the desired product 194 was isolated in a 10% yield. Under the standard conditions, the rate of decomposition of diene 116 was faster than the rate of product formation and this explained the poor yield. To solve this problem, a large excess of diene 116 (10 equivalents) was used and compound 194 was isolated in an 85% yield, as a single cis-diastereoisomer (Scheme 47). Determination of the stereochemistry of the ring junction protons C-12 and C-7 and between C-7 and C-6, was the key information needed to progress in the total synthesis (Figure 18). The nOe $^1$H NMR analysis showed a prominent through-space interaction between H-7 and H-12 (nOe = 2.66%), as well as a strong correlation between H-5 and both ring junctions protons (nOe = 2.22% and 2.14%, H-12 and H-7 respectively) (Figure 18). No through-space interaction was observed between H-6 and the ring junction proton H-12 (Figure 19). According to these nOe data, the structure of 194 was deduced to be a cis-decalin with an anti-relationship between protons H-6 and H-7. This stereochemical assignment was later confirmed by single crystal X-ray diffraction of derivative 196.

Scheme 47. The Diels-Alder cycloaddition between enone 115 and the sulfur substituted diene 116.
Figure 18. The $^1$H NMR spectrum of cis-decalin 194 and the nOe analysis of H-12.
Figure 19. The nOe analysis of H-7 and H-6.
Figure 18 shows the $^1$H NMR expansion between $\delta$ 4.3 and 0.7 ppm to highlight the key protons (H-5, H-12, H-7 and H-6) involved in the determination of the stereochemistry of the cis-decalin 194. The expansion between $\delta$ 4.3 and 0.7 ppm of the nOe spectrum of proton H-12 showed the through-space interaction with H-7 (nOe = 2.66%) and H-5 (nOe = 2.22%). Figure 19 shows the expansion between $\delta$ 4.3 and 0.7 ppm of the nOe of H-7, in which a correlation of 2.14% with H-5 and 2.18% with H-12 was observed, whereas, the nOe of H-6 showed no through-space interaction with H-12 (nOe = 0%) and a correlation with H-7 of 1.37%.

Consequently, EtAlCl$_2$-catalysed epimerisation of the cis-cycloadduct 194 gave the trans-diastereoisomer 195, after 3 days at room temperature in an 84% yield. The thiophenyl group was removed using selective Raney-Nickel reduction and the desired trans-decalin 114 was obtained in 77% yield (Scheme 48). To confirm the stereochemistry determined by nOe $^1$H NMR analysis, trans-decalin 114 was converted into the hydrazone 196 using 2,4-dinitrophenylhydrazine 140 in dry methanol and catalytic glacial acetic acid. Compound 196 was isolated in 70% yield as an orange solid and crystallised in a hexane/EtOAc, antisolvent-solvent system. Gratifyingly, single crystal X-ray diffraction confirmed the stereochemistry determined by nOe $^1$H NMR studies. An anti-relationship between the protons H-6 and H-7 and a trans-stereochemistry of the ring junction protons, H-12 and H-7, were observed (Figure 20). The $^1$H NMR spectroscopic analysis of the trans-decalins 114 and 192 were identical and it was concluded that both compounds had the same anti-relationship between protons H-6 and H-7 and a trans-stereochemistry of the ring junction protons, H-7 and H-12.
**Scheme 48.** The formation of the trans-decalin core 114.

**Figure 20.** Single crystal X-ray diffraction of hydrazone 196 with thermal ellipsoids shown at 50%.

**Figure 20** shows the structure of the hydrazone trans-decalin 196. A trans-relationship at the ring junction protons H-7 and H-12 and an anti-relationship between protons H-7 and H-6 is evident, as required for the trans-decalin core of anthracimycin.
9.6 Oxidation of trans-decalin 114 to enone trans-decalin 113

9.6.1 The Ito–Saegusa oxidation

To progress the synthesis, the conversion of the trans-decalin 114 into the enone trans-decalin 113 was required, but this transformation was very challenging and so various oxidation methods were explored. Firstly, this oxidation was attempted using the optimised conditions of the direct palladium-mediated oxidation. However, this transformation was particularly slow and the catalyst and the ligand had to be re-added every 24 hours. After 5 days, 87% conversion to the desired enone 113 was seen by $^1$H NMR analysis, but enone 113 was isolated in only 20% yield (Scheme 49). Purification issues could explain the poor yield of 113, because the enone trans-decalin 113 could have remained coordinated to the Pd$^0$ species formed during the reoxidation process of the catalyst. The presence of two double bonds in the product may be responsible for this coordination, because under the same oxidation conditions the model enone trans-decalin 179 was also isolated in poor yield (50% conversion, 23% yield).

Scheme 49. The conversion of the trans-decalin 114 to the enone trans-decalin 113 applying the optimised palladium oxidation conditions.
The Ito–Saegusa oxidation reaction was attempted in order to improve the yield of enone 113. In 1999, Dirk Trauner et al. reported the crystallisation and isolation of the Pd⁰-tetrolefin complex 199 to highlight the mechanism of this reaction.⁸⁶ Ketone 197 was converted into the silyl enol ether 198 using KHMDS and TMSCl, and subsequently oxidised in the presence of stoichiometric Pd(OAc)₂ in CH₃CN (Scheme 50).

**Scheme 50.** The Ito–Saegusa oxidation conditions reported by Dirk Trauner.⁸⁶

Inspired by these conditions,⁸⁶ the model trans-decalin 139 was converted into the TMS-enol ether intermediate 201 in the presence of LDA at −78 °C and TMSCl. Due to the propensity for hydrolysis of 201 to the ketone starting material 139 in water, air and any non-anhydrous solvent suitable for the work-up of the reaction, it was not possible to isolate this compound. However, the formation of this TMS-enol ether was detected by TLC and was subsequently oxidised in the presence of Pd(OAc)₂ to
form the model enone trans-decalin 179. Catalytic quantities of Pd(OAc)$_2$ did not produce the desired product, but in the presence of 1.5 equivalents of Pd(OAc)$_2$, the model enone trans-decalin 179 was generated in a 30% yield (Scheme 51). Hydrolysis of the TMS-enol ether 201 to the ketone starting material 139 occurred over time and this decomposition competed with the formation of the product 179. To avoid this hydrolysis, the use of a large excess (3.5 equivalents) of Pd(OAc)$_2$ was tested. A conversion of 82% to the model enone trans-decalin 179 was seen by $^1$H NMR analysis, but the desired product was isolated in just 25% yield (Scheme 51). Again, purification issues may explain the poor yield; elevated quantities of the catalyst may lead to high levels of Pd$^0$ species in the reoxidation process, causing coordination of 179 and reduction of the yield.

Scheme 51. The Ito–Saegusa oxidation to form the enone 179.

In 2011, Nishida et al. reported the Ito–Saegusa oxidation of various TES-enol ether substrates, highlighting the high stability of these silyl enol ethers for this transformation. $^{87}$ Inspired by this report, the model TES-enol ether trans-decalin 202 was formed and isolated in 78% yield. The ease of isolation was a consequence of the stability of the silyl enol ether in water and on silica chromatography. Treatment of 202 with stoichiometric Pd(OAc)$_2$ in CH$_3$CN formed the desired product 179, but only in
20% isolated yield (Scheme 52). The low yield was thought to be due to purification issues caused by the presence of the Pd\(^0\) species, and so this transformation was attempted using catalytic Pd(OAc)\(_2\) loading. However, the desired product 179 was not obtained after five days, and the starting TES-enol ether 202 was recovered unreacted. The use of DMSO as a solvent resulted in formation and isolation of the desired product 179 in variable yields, of between 40% and 50%, when 60 mol% of Pd(OAc)\(_2\) was used (Scheme 52).\(^{88}\)

\[ \begin{align*}
139 & \xrightarrow{1.2 \text{ eq. LDA}} 202, 78\% \text{ yield} \\
139 & \xrightarrow{1.5 \text{ eq. TESCI}} 202, 78\% \text{ yield} \\
& \xrightarrow{3.5 \text{ eq. Pd(OAc)}_2} 179, 20\% \text{ yield}
\end{align*} \]

\[ \begin{align*}
139 & \xrightarrow{1.2 \text{ eq. LDA}} 202, 78\% \text{ yield} \\
139 & \xrightarrow{1.5 \text{ eq. TESCI}} 202, 78\% \text{ yield} \\
& \xrightarrow{60 \text{ mol\% Pd(OAc)}_2} 179, 40-50\% \text{ yield}
\end{align*} \]

**Scheme 52.** The Ito–Saegusa oxidation of the model TES-enol ether *trans*-decalin 202.\(^{87,88}\)

Following these encouraging results, the conversion of the *trans*-decalin 114 to the enone *trans*-decalin 113 was attempted (Scheme 53). Formation of the TES-enol ether 203 in a 79% yield, was followed by the Ito–Saegusa oxidation, which had a similar outcome; enone 113 was isolated in variable yields (30%-50%) in the presence of 60 mol% of Pd(OAc)\(_2\) in DMSO (Table 10, entry 1). The use of CH\(_3\)CN as solvent did not increase the yield (Table 10, entry 2 and 3). The use of additives to increase the catalyst efficiency during the reoxidation process of the Pd\(^0\) species was tested. However, the presence of benzoquinone and Oxone\(^\text{®}\) had a negative effect on this transformation; enone 113 was isolated in 20% and 10% yield respectively (Table 10, entry 4 and 5).\(^{89,90}\)
Scheme 53. The Ito–Saegusa oxidation to form enone 113.\textsuperscript{89, 90}

<table>
<thead>
<tr>
<th>entry</th>
<th>additives</th>
<th>solvent</th>
<th>temperature (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>DMSO</td>
<td>40</td>
<td>30-50</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>CH\textsubscript{3}CN</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>CH\textsubscript{3}CN</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>benzoquinone</td>
<td>CH\textsubscript{3}CN</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Oxone\textsuperscript{a}</td>
<td>CH\textsubscript{3}CN</td>
<td>23</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 10. The attempted Ito–Saegusa oxidation conditions.\textsuperscript{89, 90}

9.6.2 The selenoxide elimination

Low yields had been obtained, and so the model \textit{trans}-decalin 139 was used to scope other oxidation methods suitable for this transformation. Treatment of \textit{trans}-decalin 139 in the presence of LDA at –78 °C and phenylselenium chloride formed the selenide intermediate 204, which was oxidised with an excess of 30% H\textsubscript{2}O\textsubscript{2} in water. The model enone \textit{trans}-decalin 179 was generated in yields of 10% and 33%, using CH\textsubscript{2}Cl\textsubscript{2} and THF as solvents respectively (Scheme 54).
This oxidation method formed the model enone *trans*-decalin 179 in low yields due to the formation of many impurities, (confirmed by $^1$H NMR analysis), and so the conversion of the *trans*-decalin 114 into the enone *trans*-decalin 113 under these conditions was not attempted.

### 9.6.3 The $\alpha$-bromination/elimination sequence

An oxidation method to progress in the total synthesis had to be identified and so, model studies were used to test other conditions. In 2002, Baran and his group reported a robust and high yielding method to form dienone 206, as a key intermediate in their concise synthesis of (−)-thapsigargin. The use of TMSOTf and Et$_3$N converted ketone 205 into the TMS-enol ether, which was subsequently $\alpha$-brominated in the presence of NBS. Treatment of this intermediated with DBU formed the desired dienone product 206 in an 85% yield (Scheme 55).

**Scheme 54.** The selenoxide chemistry used for the oxidation of 139.
Following the described method, the model trans-decalin 139 was converted to the model TMS-enol ether 201 by treatment with LDA at −78 °C and TMSCl. After formation of TMS-enol ether 201 had been established by TLC analysis, the α-bromination/elimination sequence in the presence of NBS and DBU generated tetralone 207 in a 13% yield (Scheme 56). The starting trans-decalin 139 was recovered in 40% yield, likely due to the hydrolysis of the TMS-enol ether 201. A possible explanation for the formation of tetralone 207, is equilibration of the kinetic to the thermodynamic enol ether, which occurred when the reaction was warmed to 0 °C in the α-bromination step.

9.6.4 The Rubottom oxidation

The α-functionalisation of ketone 139 with a leaving group suitable for elimination, and the subsequent formation of the enone 179 was investigated using the Rubottom oxidation reaction. Literature reported this mild method to synthesise α-hydroxy ketones, via formation of silyl enol ether
intermediates followed by oxidation in the presence of m-CPBA (Scheme 57). This approach would allow the formation of the α-hydroxy trans-decalin 214, which could be subjected to a mesylation/elimination sequence to yield the desired model enone 179.

Scheme 57. Literature examples of Rubottom oxidation.92

Treatment of the model trans-decalin 139 in the presence of LDA at −78 °C and TMSCl generated the TMS-enol ether 201. However, hydrolysis of the silyl enol ether 201 to the starting ketone trans-decalin 139 occurred in the oxidation step (Scheme 58). This oxidation method was therefore not pursued further.

Scheme 58. The Rubottom oxidation method to form the model enone trans-decalin.92
9.6.5 The oxidation in the presence of IBX

Model studies to discover a robust and reliable oxidation method continued to be explored to progress the total synthesis. In 2002 Nicolaou et al.,\textsuperscript{93} reported the direct oxidation of various ketone substrates to generate enones by treatment with 2-iodoxy benzoic acid (IBX) at elevated temperatures. Inspired by this work, the model trans-decalin 139 was treated with 1.5 equivalents of IBX at 95 °C, but after 16 hours only tetralone 207 was formed in a 23\% yield (Scheme 59). Presumably, generation of tetralone 207 was a consequence of the thermodynamic enol formation followed by oxidation/aromatisation, occurring at elevated temperature.

![Scheme 59. Oxidation of the model trans-decalin 139 using the reported literature conditions.\textsuperscript{93}](image)

To avoid the formation of the thermodynamic enol, the synthesis of the TES-enol ether trans-decalin 202 at a lower temperature was proposed. Treatment of the model trans-decalin 139 with LDA and TESCl at \(-78\) °C formed TES-enol ether 202 in a 78\% yield, which was then subjected to the IBX oxidation at 40 °C, the minimum temperature needed to dissolve IBX (Scheme 60). Interestingly, it was observed that the stoichiometry of IBX played an important role in the formation of the desired product in good yield. The use of 1.5 equivalents of IBX formed the model enone trans-decalin 179 and the ketone trans-decalin 139 in a 1 : 1 ratio (Table 11, entry 1). Increasing the stoichiometry of IBX to 2.5 equivalents formed 179 and 139 in a 1 : 0.37 ratio with the isolation of 179 in a 62\% yield (Table 11, entry 2). The use of a large excess of IBX (5 and 10 equivalents) did not improve the
conversion from 63%, as 179 and 139 were isolated in a 1 : 0.46 and 1 : 0.47 ratios respectively (Table 11, entry 3 and 4).

**Scheme 60.** The IBX oxidation of the model TES-enol trans-decalin 202.

<table>
<thead>
<tr>
<th>entry</th>
<th>equivalents of IBX</th>
<th>crude ratio</th>
<th>combined yield of 179 and 139 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>1 : 1</td>
<td>78 (a)</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>1 : 0.37</td>
<td>62 (b)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1 : 0.46</td>
<td>80 (a)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>1 : 0.47</td>
<td>75 (a)</td>
</tr>
</tbody>
</table>

(a) crude yield, (b) isolated yield of enone trans-decalin 179

**Table 11.** The IBX oxidation of the model TES-enol intermediate 202.

The formation of the model enone trans-decalin 179 in a good yield under IBX oxidation, prompted the application of these conditions to convert the trans-decalin 114 to the enone trans-decalin 113. After formation of the TES-enol ether intermediate 203 in a 79% yield, oxidation of TES-enol ether 203 in the presence of 2.5 equivalents of IBX formed the desired enone 113 in a 65% conversion and a 63% yield (Scheme 61, Table 12, entry 2). The amount of IBX played an important role in the formation of enone 113 in a good ratio and yield. The use of 1.5 equivalents of IBX formed 113 and 114 in a 1 : 1
ratio (Table 12, entry 1), whereas, a large excess of IBX (5 equivalents) did not improve the conversion and yield from 65% and 63% respectively (Table 12, entry 3).

Scheme 61. The IBX oxidation to form the enone trans-decalin 113.

<table>
<thead>
<tr>
<th>entry</th>
<th>equivalents of IBX</th>
<th>crude ratio 113 : 114</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>1 : 1</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>1 : 0.35</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1 : 0.42</td>
<td>62</td>
</tr>
</tbody>
</table>

Table 12. The IBX oxidation of the model TES-enol intermediate 203.

In conclusion, the formation of the enone trans-decalin 113 was found to be very challenging and several oxidation methods were studied to afford 113 in a good yield to progress the total synthesis. The model trans-decalin 139 was therefore used to scope an appropriate strategy. The direct palladium-oxidation method developed by Dr. Ian George and the Ito–Saegusa reaction, formed the desired enone products in a good conversion. Nevertheless, purification issues explained the low
yields of 113 and 179. Model studies involving selenoxide chemistry were not successful and afforded the desired product in low yields with many impurities.

The strategies used by Baran and Rubottom to α-functionalise the model trans-decalin 139 with a suitable leaving group prone to elimination were found to be unreliable. The Nicolaou IBX oxidation protocol, generated tetralone 207 due to the formation of the thermodynamic enol followed by an oxidation/aromatisation reaction. In contrast, the formation of the model TES-enol ether intermediate 202 allowed the IBX-mediated formation of the model enone trans-decalin 179 to be accomplished in a good yield. The identification of this reliable, consistent and robust oxidation method permitted the isolation of the desired enone trans-decalin 113 in a good yield, allowing progression of the total synthesis.

Stereoselective 1,2 reduction of this key intermediate 113 followed by treatment with propionyl chloride to form the propionate ester trans-decalin 112, suitable for the facial and diastereoselective Ireland–Claisen rearrangement will be discussed in the next section.
9.7 Strategies to the core of anthracimycin 162

9.7.1 The Ireland–Claisen rearrangement

The use of an Ireland–Claisen rearrangement was the reaction envisioned for functionalisation to give the core of anthracimycin 162. This approach would start with a stereoselective Luche reduction of 113,95 followed by treatment with propionyl chloride to provide 112, an allylic ester suitable for the rearrangement reaction (Scheme 62).

![Scheme 62. Formation of the propionate ester trans-decalin 112.](image)

The axial position of the propionate ester would ensure the rearrangement occurring from the same face of the triisopropylsilylmethyloxy side chain, to install the double bond and the side chain in the correct positions. Rearrangement of the $E$-enolate would proceed via chair-like or boat-like transition states I and II. A chair-like transition state I would form 161a with the stereochemistry of the methyl group opposite to anthracimycin, whereas, a boat-like transition state II would install the methyl group with the required stereochemistry for the natural product (Scheme 63). In his synthesis of Monensin, Ireland amply demonstrated the formation of substituted cyclohexenyl fragments by using the Ireland-Claisen rearrangement, which proceeded via a boat-like transition state (Scheme 64).96, 97, 98, 99, 100, 101, 102
Methods to control the formation of the $E$-enolates were investigated for the synthesis of the core of anthracimycin 162. In 1991, Ireland and his group reported kinetically controlled enolate formation for the stereoselective formation of both $Z$- and $E$-silyl ketene acetals in THF and THF/dipolar solvent system with the use of LDA. According to their studies, various ratios of $Z$- and $E$-enolates 220 and 221 were formed depending on the solvent effect. A 6 : 94 ratio ($Z$- : $E$-) was produced in THF, whereas in the presence of additives, such as DMPU (30% in THF) and HMPA (23% in THF) ratios of 98 : 2 and a 85 : 15 ($Z$- : $E$-) respectively were observed (Scheme 65).
The 6-membered ring transition states IV and V were rationalised to explain the stereochemical control during enolate formation (Scheme 66). The transition state IV permitted a close interaction between the lithium cation, carbonyl oxygen and the base; in the presence of HMPA as an additive, transition state V was preferred. The transition state V is characterised by a 1,3-diaxial interaction between the N-isopropyl group and the R enolate group. However, this strain was reduced in the presence of DMPU or HMPA due to the greater degree of solvation of the lithium cation. As a result, in transition state V the association between ester and base diminished minimising the 1,3-diaxial interaction, whereas, the transition state IV is still destabilised by the 1,3-diaxial strain.

Scheme 65. The Z- and E-enolate formation.

Scheme 66. The two transition states in kinetic enolisation of esters.
Stereoselective 1,2-reduction was investigated with the use of the model enone trans-decalin 179 as the substrate. Luche conditions were tested in the presence of equimolar amounts of CeCl₃·7H₂O and NaBH₄ in MeOH, in order to favour 1,2-reduction over possible 1,4-reduction. This reaction produced the allylic alcohol 224 in a 62% yield as a single diastereoisomer (Scheme 67). The nOe ¹H NMR analysis was used to assign the stereochemistry of 224 at H-13. However, the only prominent through-space interaction (nOe = 0.16%) was found between protons H-13 and H-12 and one of the two H-11 (Scheme 67, Figure 21). Due to this ambiguous nOe result and the absence of other clear evidence, the stereochemistry of 224 was tentatively assigned based on the known mechanism of the sodium borohydride reduction. Wigfield amply demonstrated that hydrides preferentially attack from a pseudo-axial trajectory in unhindered cyclohexanones, to give the hydroxyl group in the equatorial position. As the model enone trans-decalin 179 was considered an unhindered cyclohexanone, the hydroxyl was tentatively assigned as having an equatorial position, as a result of pseudo-axial attack of the hydride on the carbonyl group.

Scheme 67. The Luche reduction of the model enone trans-decalin 179.
Figure 21. The $^{1}$H NMR spectrum of alcohol 224 in d$_6$ benzene.
The expansion of the $^1$H NMR spectrum between $\delta$ 4.44-1.32 ppm showed the key peaks H-13 and H-12 needed to be irradiated to determine the stereochemistry of 224. The expansion between $\delta$ 4.31-1.32 ppm of the nOe analysis of H-13 showed the through-space interaction with H-12 (nOe = 0.16%), which was in a multiplet with H-11. Due to the overlap of these two protons (H-12 and H-11) it was not possible to determine the stereochemistry of 224 at H-13 unambiguously (Figure 21).

The allylic alcohol 224 was derivatised to produce the propionate and acetate esters 226 and 227, in order to clarify the stereochemistry of H-13 by nOe $^1$H NMR analysis (Scheme 68). However, the formation of these two esters did not help to establish the configuration of 224, due to the overlap of key peaks in the $^1$H NMR spectrum. In the acetate ester 226, H-12 was overlapping with H-6 between $\delta$ 1.80-1.75 ppm, whereas, in the propionate ester 227 H-12 was in a multiplet with H-11, H-7 and H-8 between $\delta$ 1.93-1.84 ppm.

Scheme 68. The esterification of 224 to understand the stereochemistry of H-13.

Pseudo axial attack of the hydride onto the model enone trans-decalin 179 with consequent formation of the equatorial hydroxyl-substituted trans-decalin 224 was expected, so various reducing agents
were tested to explore their influence on the selectivity of this reduction reaction. In 2000, De Groot reported the stereoselective 1,2-reduction of ketone 229 to give alcohol 230 by the use of DIBAL-H. The presence of the methyl group at the ring junction of the trans-decalin system 229 ensured the high selectivity of this reduction reaction. In this case, attack of hydride from the equatorial face of the ketone, ensured formation of the axial hydroxyl group in 230 (Scheme 69).

\[
\begin{align*}
\text{OTBS 228} & \xrightarrow{TBAF, THF} \text{229, 60\% yield} \\
\text{229} & \xrightarrow{\text{DIBAL-H, THF}} \text{230, 94\% yield}
\end{align*}
\]

Scheme 69. The stereoselective reduction of ketone 229.

The use of DIBAL-H as the reducing agent produced the alcohol 224 as the major product, but in the \(^1\text{H}\) NMR spectrum of 224, other related decalin peaks were seen (Figure 22). A possible explanation for the presence of these peaks was formation of the axial alcohol 231, because the bulkier reducing agent influenced the selectivity of the 1,2-reduction, directing pseudo-equatorial hydride attack. However, it was not possible to unambiguously determine this because the two possible diastereoisomers, 224 and 231, were isolated as an inseparable mixture.
Figure 22. The $^1$H NMR spectrum of the possible formation of the axial hydroxyl 231.
Figure 22 shows the $^1$H NMR spectrum of alcohol 224 formed as a single compound under the Luche conditions, and the $^1$H NMR spectrum of alcohol 224 under DIBAL-H reduction, in which the presence of extra-olefin peaks between $\delta$ 6.00-5.31 ppm suggested formation of the axial alcohol 231 as the minor diastereoisomer.

Nevertheless, DIBAL-H 1,2-reduction of the model enone 179 generated the equatorial and axial alcohols 224 and 231 as an inseparable mixture, in an 8 : 2 ratio in toluene and in a 9 : 1 ratio in THF (Table 13, entry 2 and 3). The use of a bulkier reducing agent such as Red-Al® also formed the alcohol 224, as the major diastereoisomer in an 8 : 2 ratio (Table 13, entry 4). Interestingly, Al(iOPr)$_3$ and IPA formed alcohol 224 exclusively, whereas, with L-selectride only the model ketone 139 was isolated, as a consequence of a 1,4-reduction (Table 13, entry 1 and 5). These results showed that the substrate controlled 1,2-reduction of 179, biases hydride to attack from the axial face of 179.

![Chemical structures](image)

<table>
<thead>
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<th>entry</th>
<th>reagent</th>
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<th>solvent</th>
<th>time (minutes)</th>
<th>selectivity</th>
<th>yield (%)</th>
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<td>THF</td>
<td>30</td>
<td>139</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
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<td>−78</td>
<td>Toluene</td>
<td>30</td>
<td>8 : 2</td>
<td>74</td>
</tr>
<tr>
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<td>THF</td>
<td>30</td>
<td>9 : 1</td>
<td>76</td>
</tr>
<tr>
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<td>−78</td>
<td>THF</td>
<td>30</td>
<td>8 : 2</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
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<td>50</td>
<td>IPA/Toluene</td>
<td>5 days</td>
<td>224</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 13. The 1,2-reduction of the enone trans-decalin 179.\textsuperscript{106}
In conclusion, the Luche reduction of ketone 179 generated the alcohol trans-decalin 224 in which the stereochemistry of H-13 was assigned tentatively based on the mechanism of sodium borohydride reduction of unhindered cyclic ketones, and the nOe 1H NMR analysis. Inversion of the selectivity, forcing the hydride attack from the equatorial face of ketone 179, was attempted with the use of a bulkier reducing agents such as DIBAL-H, Red-Al, L-selectride and Al(iOPr)3 in IPA. Under these conditions, alcohol 224 was formed as the major product and in the 1H NMR spectrum new key olefin decalin peaks were indeed observed, suggesting the possible formation of the axial alcohol 231. However, it was not possible to prove this outcome unambiguously because alcohols 224 and 231 were isolated as an inseparable mixture of products.

As the literature reported the 1,2-reduction of a related decalin system similar to the enone 228 by the use of DIBAL-H,105 treatment of this compound under these conditions was attempted with the hope of achieving the correct stereoselectivity. However, the 1,2-reduction of ketone 113 in the presence DIBAL-H generated the diastereoisomeric alcohols 232 and 215 in a 5 : 1 ratio in toluene, and in a 3 : 1 ratio in THF (Scheme 70).

\[ \text{Scheme 70. The 1,2-reduction of the enone trans-decalin 113.}^{105} \]
The stereochemistry of the alcohols 232 and 215 was determined by nOe $^1$H NMR analysis. In the major diastereoisomer 232, a significant through-space interaction (nOe = 0.74%) between H-13 and axial H-7 was detected, whereas, no interaction (nOe = 0%) between protons H-13 and H-6 was observed (Figure 23). In the minor diastereoisomer 215 a significant through-space interaction (nOe = 1.03%) between H-13 and H-6 was detected, as well as between protons H-13 and H-12 (nOe = 1.32%). This nOe analysis allowed tentative assignment of the stereochemistry of the major and minor alcohols 232 and 215 (Figure 23).

![nOe correlation of compounds 232 and 215](image)

Figure 23. The nOe correlation of compounds 232 and 215.

These reduction conditions were found to be non-selective for formation of the desired axial alcohol 215, which was isolated as the minor diastereoisomer. As shown in the model studies, the use of Red-Al, L-selectride and Al(iOPr)$_3$ in IPA did not improve the selectivity, and favoured formation of the equatorial hydroxyl group, and so other conditions were not tested.

After separation and isolation of the alcohols trans-decalins 232 and 215, the minor diastereoisomer 215 was converted into the propionate ester 112 to test the Ireland–Claisen rearrangement reaction (Scheme 71). However, in the presence of LDA and TMSCI, compound 112 did not rearrange to form the expected compound 161.103
In conclusion, due to the low selectivity of the 1,2-reduction reaction to give the alcohol 215 and the difficulties encountered when attempting to form compound 161 via the Ireland–Claisen rearrangement, this approach to the synthesis of the core of anthracimycin was not taken further.

9.7.2 The Tsuji–Trost transformation

In 1993, Tsuji reported a stereocontrolled method to generate cis-ring junctions in decalins, in which compound 233 was converted into the cis-bicyclic product 236 in a 79% yield by use of a Tsuji–Trost reaction. This approach to the synthesis of the core of the natural product was explored (Scheme 72).

[Scheme 71. The attempted Ireland–Claisen rearrangement.]

[Scheme 72. The stereocontrolled formation of cis-ring junction decalin by Tsuji.]
A second strategy was therefore envisioned to generate the core of anthracimycin 162. The major diastereoisomeric alcohol 232 was derivatised to give the acetate 238, and used as a substrate for the Tsuji–Trost transformation (Scheme 73).

Following this strategy, the model allylic alcohol 224 was converted into the corresponding acetate 224 in a 72% yield. In the presence of Pd(OAc)$_2$, PPh$_3$ and dimethylmethylmalonate, as a soft nucleophile, unreacted model acetate 224 was recovered in 80% yield (Scheme 74). Acetylation of the allylic alcohol 232 formed the acetate ester 238, which under the Tsuji–Trost conditions generated the enone 113 and the alcohol 232 in yields of 40% and 30% respectively (Scheme 74).$^{108, 109, 110, 111, 112}$ The presence of water, in the solvent and/or in the atmosphere of the reaction, may explain the formation of these products. Once the Pd$^{	ext{II}}$ π-decalin system had formed, water could have added as a nucleophile to generate the alcohol trans-decalin 232, which could then oxidised to the enone 113 under the reaction conditions.
Scheme 74. The Tsuji–Trost transformation of esters 226 and 238, as substrates.\textsuperscript{108, 109, 110, 111, 112}

In conclusion, the 1,2-reduction of the enone 113 afforded the desired alcohol 215 as the minor diastereoisomer. This compound 215 was converted to the ester 112, which did not rearrange to form the core of anthracimycin 162, using the Ireland–Claisen transformation. The major alcohol diastereoisomer 232 was converted to the acetate 238 and subjected to the Tsuji–Trost conditions. However, this strategy also failed to deliver the core of anthracimycin 162 and, hence, a new approach to functionalise the enone 113 was required.
9.7.3 The Mukaiyama–Michael strategy

The Mukaiyama–Michael approach to synthesise the core of anthracimycin 162 was next explored. To this end, *E*-ethyl-propanoate silyl ketene acetal 240 was synthesised and used as a nucleophile to accomplish 1,4-addition to the enone 113. When TiCl₄ was employed as a Lewis acid, compound 241 was isolated as a single diastereoisomer in a 45% yield (Scheme 75). When Yb(OTf)₃ was used to promote the addition reaction, compound 242 was obtained in quantitative crude yield and was converted into 241 under acidic conditions (Scheme 75). The instability of 241 on silica explained the poor yield.¹¹⁴ ¹¹⁵ ¹¹⁶

![Scheme 75. The Mukaiyama–Michael 1,4-addition.](image)

Determination of the stereochemistry of 241 was required and the conversion of this compound into the tricyclic system 247 was proposed (Scheme 77), in order to determine its configuration via nOe ¹H NMR analysis. To this end, the ketone of Mukaiyama–Michael adduct 241 needed to be converted into an alkene by use a triflation-enol formation/palladium reduction sequence reported by Ishibashi.¹¹⁶ In the first instance, these conditions were studied using the model trans-decalin 139 as the substrate. Treatment of ketone 139 in the presence of LDA and *N*-phenyl-*bis*-trifluoromethanesulfonimide 243 formed the triflate enol trans-decalin 244 in a 36% yield.
Palladium-mediated reduction in the presence of Pd(OAc)$_2$(PPh$_3$)$_2$, Bu$_3$N and formic acid completed this transformation to form the alkene between C-13 and C-14, to generate the diene 245 (Scheme 76).\textsuperscript{117}

![Scheme 76. The model studies of the conversion of a ketone into an alkene.\textsuperscript{117}](image)

Following these studies, the triflation of the Mukaiyama–Michael adduct 241 in the presence of LDA and N-phenyl-bis-trifluoromethanesulfonimide 243, was followed by TIPS-removal using TBAF to generate the tricycle system 246, which was isolated in 67% yield over two-steps (Scheme 77). Palladium reduction conditions converted enol triflate 246 into alkene 247 in a 51% yield (Scheme 77, Figure 24). The single crystal X-ray diffraction of the tricycle lactone 247, showed that the addition of the $\varepsilon$-ethyl-propanoate silyl ketene acetal 240 had occurred selectively opposite to the face of the bicyclic system 113 presenting the triisopropylsilylmethyloxy group. The methyl group at C-25 had the required stereochemistry for the core of the natural product (Figure 24)
Scheme 77. The transformation of 239 to the tricyclic system 245.\textsuperscript{117}

Figure 24. The single crystal X-ray diffraction of 247 with thermal ellipsoids shown at 50%.

Figure 24 shows the \textit{anti}-relationship between protons H-15 and H-6, and shows that addition of the \textit{E}-ethyl-propanoate silyl ketene acetal 240 occurred from the face opposite to that presenting the triisopropylsilylmethyloxy chain. The stereochemistry of the methyl group at C-25 was instead correct for the core of the natural product.

In conclusion, the Mukaiyama‒Michael strategy formed the “\textit{epi}-core of anthracimycin 247”, upon selective 1,4-addition to 113 from the face of the decalin opposite to that presenting the
triisopropylsilylmethyloxy chain. However, contemporaneous studies towards the decalin-core of streptosetin A 260 performed by Dr. Ian George, showed an Hosomi–Sakurai approach might be the answer to the problem of selectivity in this 1,4-addition reaction and might allow continuation of the total synthesis.

9.7.4 The Hosomi–Sakurai strategy

The Hosomi–Sakurai transformation was explored to synthesise the core of anthracimycin 162. As reported in the literature, this 1,4-addition process involves a Lewis acid-promoted allylation of various electrophiles such as aldehydes, ketones and enones in the presence of allyltrimethylsilane 250. This strategy is recognised as a mild method for C-C bond formation, and has the possibility to generate new stereogenic centres. Generally, the reaction proceeds by the addition of the alkene of the allyltrimethylsilane 250 to the carbon electrophile 249, leading to the formation of a carboxylation intermediate 251 stabilised by the presence of the β-silicon atom. Stabilisation arises from the orbital overlap between the empty orbital on the carboxylation and the co-planar C–Si σ-bond (Scheme 78).  

Scheme 78. The mechanism of the Hosomi–Sakurai 1,4-addition.
9.7.5 The Hosomi–Sakurai to the core of streptosetin A

This 1,4-addition reaction was studied by the group, during the synthesis of the core of streptosetin A 260 (Dr. Ian George). The decalin core of this natural product was synthesised using the Hosomi–Sakurai transformation between allyltrimethylsilane 250 and the enone 115, followed by an aldol addition reaction in the presence of aldehyde 255. The reaction sequence generated a mixture of 256 and 257 in a 3 : 1 ratio (Scheme 79). An alkene metathesis reaction of 255 and 257 formed decalins 258 and 259, which were crystallised to confirm the stereochemistry of the two diastereoisomers. The single crystal X-ray diffraction of 258 and 259, showed a syn-selective addition of allyltrimethylsilane 250 to enone 115, as highlighted by the syn-relationship of protons H-7 and H-6 in both compounds (Figure 25). The aldol addition reaction, instead, generated the two diastereoisomers 256 and 257 at C-11 in a 3 : 1 crude ratio (Scheme 79).

Scheme 79. The Hosomi–Sakurai approach to streptosetin A 260.
In compounds 258 and 259, a syn-relationship of protons H-7 and H-6 was observed, whereas, the diastereoselectivity at C-11, is a consequence of the aldol addition reaction (Figure 25).

A possible hypothesis based on the transition state conformation of the titanium-complex 261 was used to rationalise these results. The addition of allyltrimethylsilane 250 from the same face of the triisopropylsilylmethyloxy chain of 261, led to a favoured “chair” intermediate 261a, forming the syn-adduct. If the addition of 250, instead, occurred from the opposite face of the triisopropylsilylmethyloxy chain, a disfavoured “twist boat” intermediate 261b was formed, leading to the anti-adduct 262 (Scheme 80).

9.7.6 The Hosomi–Sakurai approach towards anthracimycin core 162

Inspired by this work, model studies of the Hosomi–Sakurai 1,4-addition between enone 115 and allyltrimethylsilane 250 were performed, and compound 183 was generated as a single product in a 60% yield. The determination of the stereochemistry of 183 was achieved following a deprotection/iodoetherification sequence. Removal of the TIPS-group of the allyl-substituted cyclohexanone 183 under HF/pyridine conditions generated alcohol 263, which was subjected to
cyclisation by an iodoetherification reaction upon treatment with I₂ and NaHCO₃. This formed two bicyclic products 264 and 265 in a 2.7 : 1 crude ratio (Scheme 81). The major diastereoisomer 264 was crystallised and the single crystal X-ray diffraction showed a syn-relationship between protons H-6 and H-15, as required for anthracimycin (Figure 26).

Scheme 81. Formation of 183 and the use of a deprotection/iodocyclisation sequence to determine its stereochemistry.¹²⁰

Figure 25. The single crystal X-ray diffraction of 264 with thermal ellipsoids shown at 50%.

Figure 25. Structure of 264 established by single crystal X-ray diffraction showing the syn-relationship between protons H-6 and H-15.
Following these studies, the 1,4-addition reaction between allyltrimethylsilane 250 and the enone trans-decalin 113 was tested and two diastereoisomeric products 266 and 267 were generated in a 61% and 7% yield, respectively (Scheme 82). Derivatisation of the major diastereoisomer 266 to give the hydrazone 268 by treatment with 2,4-dinitrophenylhydrazine 140 and acetic acid, allowed the determination of the stereochemistry of the addition reaction (Scheme 82). The single crystal X-ray diffraction of 268 showed a syn-relationship between protons H-15 and H-6, which confirmed the outcome of the Hosomi–Sakurai 1,4-addition of allyltrimethylsilane 250 (Figure 27).

Scheme 82. The Hosomi–Sakurai addition between 113 and 250, and formation of hydrazone 268 from the major diastereoisomer 266.
Figure 26. The single crystal X-ray diffraction of compound 268 with thermal ellipsoids shown at 50%.

Figure 26. Single crystal X-ray diffraction of hydrazone 268 produced from the product of the Hosomi–Sakurai 1,4 addition reaction.

Following determination of the stereochemistry of the major diastereoisomer 266, the biological activity of compound 269 was tested by the biologist collaborators in this project: Dr. Gavin Thomas and Dr. Emmanuele Severi. To this end, TIPS-removal of the major diastereoisomer allyl trans-decalin 266 was performed under HF/pyridine conditions and compound 269 was isolated in a 98% yield (Scheme 83). However, this advanced intermediate in the synthesis of the core of anthracimycin did not possess antimicrobial activity.

Scheme 83. The TIPS-removal of 266 to test the antimicrobial activity.
To install the methyl group at C-25 via this strategy, the use of the $E$-crotyltrimethylsilane 272, as a nucleophile, was envisioned, but the synthesis of this compound was found to be challenging. The literature reported a number of different approaches to synthesise the $E$-crotyltrimethylsilane 272: in one of them, the treatment of propargyl trimethylsilane 270 with methyl lithium and iodomethane formed compound 271 in a 48% yield. Conversion of 271 into $E$-crotyltrimethylsilane 272 was achieved by treatment with Ni(OAc)$_2$·4H$_2$O and NaBH$_4$ under H$_2$ atmosphere (Scheme 84).

![Scheme 84. An approach to the synthesis of $E$-crotyltrimethylsilane 272.](image)

Inspired by this work, the formation of the $E$-crotyltrimethylsilane 272 was explored. Commercially available methyl propargyl bromide 274 was converted into methyl propargyl trimethylsilane 271, following the conditions reported by Xiao et al. by treatment with stoichiometric quantities of Mg and TMSCl, and a catalytic amount of HgCl. However, 271 was isolated in just 10% yield due to the volatility of this compound (Scheme 85). Conversion of 271 into 272 was attempted by treatment with Ni(OAc)$_2$·4H$_2$O and NaBH$_4$, but crude $^1$H NMR analysis, showed that the desired compound 272 was not formed and only polymerisation was detected (Scheme 85).

![Scheme 85. The attempted synthesis of $E$-crotyltrimethylsilane 272.](image)
In order to synthesise $E$-crotyltrimethylsilane 272, another strategy involving a two-step sequence was explored. In the first step, the trans-crotylchloride 274 was converted into intermediate 275 by reaction with Et₃N, CuCl and Cl₃SiH. This was followed by the methylation of 275 using MeMgl to form the desired $E$-crotyltrimethylsilane 272 in a 59% yield. Following these conditions, the $E$-crotyltrimethylsilane 272 was isolated in only 30% yield when working on a large scale and under rigorously inert atmospheric conditions (N₂). The low yield was attributed to the instability in air of 276 and the volatility of the desired product 272 (Scheme 86).

![Scheme 86. The synthesis of the $E$-crotyltrimethylsilane 272.](image)

With compound 272 in hand, the 1,4-addition between the enone trans-decalin 113 and the $E$-crotyltrimethylsilane 272 was investigated. When this reaction was performed at −78 °C, the product was not formed and the starting material 113 was recovered unreacted. When the temperature was increased to −40 °C, an inseparable mixture of two diastereoisomers 276 and 277 was generated in a 2 : 1 ratio (43% yield) (Scheme 87). The instability of 276 and 277 on silica explained the poor yield, as all of the enone 113 was consumed to form the products.
Scheme 87. The Hosomi–Sakurai addition between the enone trans-decalin 113 and E-crotyltrimethylsilane 272.

This 1,4-addition reaction generated an inseparable mixture of two diastereoisomeric products, and two new stereogenic centres at C-15 and C-16 were created. Determination of the stereochemistry of the major and the minor diastereoisomers 276 and 277 was needed to progress in the total synthesis. To this end, a deprotection/iodocyclisation sequence was envisioned to separate and derivatise these two diastereoisomers to form two tricyclic systems, facilitating the determination of the stereochemistry by nOe 1H NMR analysis. It was hoped that the TIPS-removal of 276 and 277 would allow the separation of the major and the minor diastereoisomers, and so this inseparable mixture of compounds was treated with HF/pyridine (Scheme 88). The reaction, however, produced multiple products. The major diastereoisomer 276 was fully deprotected and generated an inseparable mixture of two diastereoisomer alcohols 278 and 279 in a 1 : 1 ratio, as a consequence of an epimerisation from a trans- to a cis-decalin (Scheme 88). Partial deprotection of the minor diastereoisomer 277 was accomplished, and alcohol 280 was isolated in just 13% yield after a 16-hour reaction (Scheme 88). Unreacted minor diastereoisomer 277 was recovered in 41% yield. Treatment of 277 over an extended period of time (2 days) under HF/pyridine conditions, allowed the isolation of alcohol 280 in a 78% yield (Scheme 88).
Scheme 88. The TIPS-removal of the inseparable mixture of the major and the minor diastereoisomers 276 and 277.

After TIPS-removal and the separation of the major and minor diastereoisomers 276 and 277, an iodoetherification cyclisation reaction was used to derivatise these compounds. Treatment of the inseparable mixture of alcohol products 278 and 279, isolated from the deprotection of the major diastereoisomer 276, in the presence of I₂ and NaCHO₃, generated two tricyclic systems 281 and 282 in a 27% and 29% yields respectively (Scheme 89). Both products 281 and 282 were isolated as solids and the presence of iodine facilitated the crystallisation of these molecules. The X-ray diffraction single crystallography of 281 and 282 allowed the determination of the stereochemistry of the major diastereoisomer 276 (Scheme 89, Figure 28). As shown in the crystal structures of 281 and 282, the major diastereoisomer 276 had the required syn-relationship between protons H-15 and H-6, as well as the correct stereochemistry at the methyl-bearing stereocentre C-25 needed for anthracimycin. However, in compound 282 a cis-decalin ring junction was observed, indicating that epimerisation
from a trans- to a cis-decalin had occurred during the deprotection of the major diastereoisomer 276 under HF/pyridine conditions.

**Scheme 89.** The iodocyclisation reaction used to establish the stereochemistry of the major diastereoisomer 276.

**Figure 27.** The X-ray diffraction single crystallography of 281 and 282 with thermal ellipsoids shown at 50%.

**Figure 27** shows the stereochemistry of the derivatives of the major diastereoisomer 281 and 282 of the Hosomi–Sakurai reaction, which was what was required for the synthesis of anthracimycin. A syn-
relationship between protons at H-15 and H-6 was observed, as well as the correct stereochemistry of the methyl group at C-25 required for the core of anthracimycin 162.

The epimerisation from a trans- to a cis-decalin was also studied using the model trans-decalin 139, as the substrate. Treatment of trans-decalin 139 with 40 equivalents of 70% HF in pyridine, triggered the epimerisation from the trans-decalin 139 to the cis-cycloadduct 138 in an 8 : 2 ratio, over the same period of time as the deprotection reaction (16-hour) (Scheme 90).

![Scheme 90. The epimerisation of the model trans-decalin 139 to the cis-decalin 138.](image)

Having established the stereochemistry of the major diastereoisomer 276, the deprotected minor diastereoisomer 280 was treated under the iodoetherification conditions to determine its configuration. However, no iodocyclisation occurred and compound 280 was recovered unreacted, which meant that it was impossible to determine the stereochemistry of the minor diastereoisomer 277 using this approach.
To summarise, the Hosomi–Sakurai 1,4-addition reaction between the enone 113 and the E-crotyltrimethylsilane 272 generated an inseparable mixture of products 276 and 277 in a 2 : 1 ratio (Scheme 88). A deprotection/iodoetherification sequence allowed the determination of the stereochemistry of the major diastereoisomer 276, which confirmed that the stereochemistry at both stereogenic centres C-15 and C-25 had been established correctly for the core of anthracimycin.

Scheme 87. The Hosomi–Sakurai addition between the enone trans-decalin 113 and E-crotyltrimethylsilane 272.

As highlighted in Figure 28, 276 and 277 were isolated as an inseparable mixture of diastereoisomers in a 2 : 1 ratio. Due to the presence of many overlapping peaks in the ¹H NMR spectrum, the diastereomeric ratio was calculated based on the integration of resolved resonances for proton H-5. The expansion between δ 4.01 and 3.70 ppm shows a major 276 doublet-doublet at δ 3.77 and a doublet-doublet at δ 3.74 ppm, as well as a minor 277 multiplet at δ 3.95–3.89 ppm. The methyl groups at C-25 were also resolved peaks: a major 276 doublet at δ 0.99 ppm, and a minor 277 doublet at δ 0.94 ppm.
Figure 28. The $^1$H NMR data of the inseparable mixture of the two diastereoisomers of the Hosomi–Sakurai addition between 276 and 277.

The $^1$H NMR spectrum of the inseparable mixture (1 : 1 ratio) of 278 and 279, generated during the TIPS-removal of the major diastereoisomer 276 under HF/pyridine conditions was obtained (Figure 29). Due to the 1 : 1 ratio and the presence of many overlapping peaks in the $^1$H NMR spectrum, analysis of the $^1$H-H COSY was too challenging to determine which resolved proton peaks belonged to which isomer.
Figure 29. The $^1$H NMR data of the inseparable mixture of the deprotected *trans*- and *cis*-decalins 278 and 279 (1 : 1 ratio).

Figure 29 shows the $^1$H NMR spectrum of the *trans*- and *cis*-decalins 278 and 279, isolated as inseparable mixture of deprotected products. The 1 : 1 ratio of these two diastereoisomers was calculated based on the integration of resolved resonances for proton H-17, doublet-doublet-doublet at δ 5.79 and at δ 5.68 ppm; protons H-9 multiplets at δ 5.38–5.33 and at δ 5.33–5.28 ppm; protons H-5 doublet-doublet at δ 4.05, at δ 3.93, at δ 3.75 and at δ 3.66 ppm; methyl groups of H-25 doublet at δ 1.01 and at δ 0.98 ppm.
9.7.7 Functionalisation of the exocyclic double bond

Now that the stereochemistry of the major diastereoisomer 276 had been established, selective functionalisation of the exocyclic alkene became the new challenge. Epoxidation and dihydroxylation reactions were attempted, with the hope that the less sterically demanding exocyclic double bond would react preferentially. In the presence of catalytic OsO₄ (5 mol%) and 1 equivalent of NMO, diols 283 and 284 were formed exclusively by reaction of the endocyclic alkene (Scheme 91). Determination of the reactivity was established by the ¹H NMR analysis of the crude reaction mixture, in which the absence of the olefin peak of proton H-9 was seen. The exocyclic peaks of H-17 and H-18 remained unchanged. Treatment of the inseparable mixture of diastereoisomers 276 and 277 with m-CPBA, also formed epoxide at the endocyclic alkene as a consequence of the higher reactivity of this alkene (Scheme 91). Determination of the selectivity of this epoxidation reaction was again established by ¹H NMR analysis of the crude reaction mixture, in which the absence of proton H-9 was seen.

Scheme 91. Epoxidation and dihydroxylation functionalised the endocyclic alkene preferentially.
Under these conditions, electronic effects predominated over steric hindrance and epoxide and diols were formed selectively at the endocyclic double bond, as a consequence of the higher reactivity of this alkene. Other conditions were therefore explored to selectively functionalise the exocyclic double bond. In the last few years, Morken and his group have focused their chemistry research on the enantioselective diborylation and hydroboration of alkenes, forming enantioriched diols.\textsuperscript{124, 125, 126} The selective functionalisation of the exocyclic alkene was attempted by use of this borylation/dihydroxylation sequence in the presence of a boronic ester reagent, trans-cyclohexanediol and Cs\textsubscript{2}CO\textsubscript{3}, followed by the addition of 3 M NaOH and 30% H\textsubscript{2}O\textsubscript{2} aqueous solutions. Under these conditions, selective functionalisation of the exocyclic alkene was possible and diols 288 and 289 were generated (Scheme 92). The formation of these products was determined by \textsuperscript{1}H NMR analysis of the crude mixture; the NMR spectrum showed an absence of the olefin peaks (protons H-17 and H-18), whereas, the endocyclic alkene (proton H-9) remained unchanged. The use of 1 equivalent of B\textsubscript{2}pin\textsubscript{2} and methanol formed diols 288 and 289 in a 56% conversion and in a 40% yield, along with the recovery of the starting material 276 and 277 in a 37% yield (Table 14, entry 1). In the presence of 1 equivalent of B\textsubscript{2}pin\textsubscript{2} and 0.3 equivalents of trans-cyclohexanediol 287, the diols 288 and 289 were instead formed with 53% conversion, whereas, with the use of 1 equivalent of trans-cyclohexanediol 287 90% conversion into the desired products 288 and 289 was achieved (Table 14, entry 2 and 3). The use of a catalyst such as Pt\textsubscript{2}(dba)\textsubscript{3} was also tested to increase the level of conversion and the yield. A conversion of 80% was obtained, but diols 288 and 289 were isolated in just 39% yield (Table 14, entry 4).\textsuperscript{124, 125, 126}
Scheme 92. A selective dihydroxylation reaction of the exocyclic alkene.¹²⁴,¹²⁵,¹²⁶

Morken’s conditions allowed the selective functionalisation of the less sterically demanding and less electronically reactive exocyclic alkene of the molecule. The use of 1 equivalent of B₂pin₂ and trans-cyclohexanediol 287 allowed the formation of diols 288 and 289 with 90% conversion, but a 41% yield was obtained upon isolation of the products (Table 14, entry 3). The instability on silica of 288 and 289, was responsible for the low yield and these dihydroxylated intermediates were carried into the next step without silica chromatography purification. A periodate cleavage reaction was used to

Table 14. The reaction conditions tested for the borylation of 276 and 277.¹²⁴,¹²⁵,¹²⁶
convert the diol into an aldehyde, the functionality required for the subsequent Still–Gennari olefination. Treatment of the crude reaction mixture of diols 288 and 289 with NaIO₄ in CH₂Cl₂ : H₂O (1 : 1), delivered the aldehydes 290 and 291 in 30% and 16% yield respectively (Scheme 93). Instability on silica chromatography again explained the low yields.

Scheme 93. The periodate cleavage to the advanced precursor 290 and 291.

The presence of the ketone at C-13 made 290 and 291 unstable to silica chromatography and could give rise to selectivity issues in the Still–Gennari olefination with the phosphonate reagent 92, competing with the aldehyde functionality. To this end, the previously studied conditions that had been used to convert the carbonyl group into an alkene, were used to avoid these problems. The inseparable mixture of diastereoisomers 276 and 277 produced by the Hosomi–Sakurai 1,4-addition reaction was treated with LDA and N-phenyl-bis-trifluoromethanesulfonimide 243. This reaction yielded the enol triflates 292 and 293 with quantitative conversion, as evident by ¹³C NMR analysis of the crude reaction mixture.¹¹⁶ Palladium-mediated reduction of the enol triflates with Pd(OAc)₂(PPh₃)₃, Bu₃N and formic acid completed the transformation to form the alkene, between C-13 and C-14, and generated the trans-decalins 294 and 295 in a 56% yield as an inseparable mixture of isomers in a 2 : 1 ratio (Scheme 94, Figure 30).¹¹⁷
The 56% yield of 294 and 295 was the highest yield obtained in the enol triflate formation/palladium reduction sequence. As the second step always gave full conversion into the desired products 294 and 295, the triflation of 276 and 277 was identified as the problematic-step. The purity of the N-phenyl-bis-trifluoromethanesulfonimide (243), a small scale reaction in which it was difficult to prevent moisture and water destroying freshly prepared LDA solution, and the purity of 276 and 277 isolated as a crude mixture due to the instability on silica, are factors that could have led to decrease in the yield. To solve these problems, Comin’s reagent was used instead of N-phenyl-bis-trifluoromethanesulfonimide (243), and the crude mixture of 276 and 277 was concentrated in vacuo with benzene to azeotrope any residual water. However, the yield could not be increased from 56%.
Figure 30. The $^1$H NMR spectrum of 294 and 295 after the triflation/palladium reduction sequence.

Figure 30 shows the $^1$H NMR spectrum of 294 and 295 after the triflation/palladium reduction sequence. The region between $\delta$ 4.00 and 3.59 ppm contained the only resolved resonances for proton H-5 of the major and the minor diastereoisomers 294 and 295. Based on the integration of these peaks it was possible to measure an unchanged 2 : 1 ratio of 294 and 295 after the two-step sequence.

Following conversion of the carbonyl functionality into an alkene, as the B-ring of anthracimycin required, selective functionalisation of the exocyclic double bond was performed using the borylation/dihydroxylation sequence. Reaction of trienes 294 and 295 with 1 equivalent of B$_2$pin$_2$ and trans-cyclohexanediol 287 and 0.15 equivalents of Cs$_2$CO$_3$ as a base, followed by the addition of aqueous solutions of NaOH and H$_2$O$_2$, resulted in selective dihydroxylation of the exocyclic alkene. These conditions allowed the selective functionalisation of the less reactive double bond based
on steric hindrance. The formation of diols 296 and 297 at the exocyclic alkene was confirmed by $^1$H NMR analysis, which showed the absence of the olefin peak of protons H-17 and H-18. Cleavage of diols 296 and 297 to afford the aldehyde functionality was attempted by reaction with NaIO$_4$. These conditions formed the aldehyde 162 corresponding to the core of anthracimycin 162, which was isolated as an inseparable mixture with 298 (2 : 1 ratio) in a 60% isolated yield b.r.s.m. (Scheme 95).

Scheme 95. The formation of the core of anthracimycin 162.

In conclusion, the Hosomi‒Sakurai 1,4-addition reaction between the E-crotyltrimethylsilane 272 and the enone 113, allowed the formation of all the C-C bonds with the required stereochemistry for the core of anthracimycin 162. Subsequent selective borylation/dihydroxylation of the exocyclic alkene and periodate cleavage of diols 296 and 297 delivered the desired core of the molecule. The aldehyde 162 was isolated as an inseparable mixture with 298 in a 2 : 1 ratio in a 45% yield (60% yield b.r.s.m.). Overall, the aldehyde 162 was obtained in 12-steps.
9.7.8 The synthesis of the Still–Gennari reagent 92

To progress the total synthesis, the formation of the side chain 92 was prepared following Kalesse’s procedure. To this end, PMB protection of the enantiopure D-(+)-lactate methyl ester (299) afforded the ester 301, which was converted into the aldehyde 302 by DIBAL-H reduction. This was followed by Wittig methylenation and an alkene metathesis reaction between 303 and 304 using Grubbs-II catalyst, which generated side chain 92 in a 34% yield (Scheme 96).

![Scheme 96. The synthesis of the Still–Gennari reagent 92.](image-url)
To summarise, different strategies were explored for the synthesis of the core of anthracimycin 162. The 1,2-reduction of key intermediate 113 was found to be non-selective and two diastereoisomeric alcohols 232 and 215 were isolated and used to scope the Ireland–Claisen rearrangement reaction and the Tsuji–Trost reaction. However, these two approaches did not yield the core of anthracimycin 162.

The Mukaiyama–Michael addition afforded the lactone 247 corresponding to the C-15 epimer of the core of the natural product, suitable for the synthesis of analogues.

Inspired by previous work in the group towards the synthesis of the core of streptosetin A, the Hosomi–Sakurai 1,4-addition reaction was explored to yield the desired core of anthracimycin 162. This approach introduced the allyl side chain with a high syn-selectivity forming compound 266, but the synthesis of the E-crotyltrimethylsilane 272 was needed. In the presence of this nucleophile, the Hosomi–Sakurai 1,4-addition reaction gave products 276 and 277 as an inseparable mixture in a 2 : 1 ratio, with the major diastereoisomer 276 having the stereochemistry necessary for the core of anthracimycin. Selective functionalisation of the exocyclic alkene was performed using Morken’s diborylation/hydroxylation conditions, which allowed the selective functionalisation of the exocyclic double bond. This strategy permitted the formation of the core of anthracimycin 162, which was isolated with 298, as an inseparable mixture of products in a 2 : 1 ratio.

Having achieved the synthesis of 162, the phosphonate reagent 92 was formed following the synthetic route reported by Kalesse. However, the Still–Gennari olefination could not be explored due to the difficulty in the separation of 162 and 298.
The core of anthracimycin was formed as an inseparable mixture of diastereoisomers, which hindered the progression of the total synthesis.

Removal of the TIPS-group of compounds 294 and 295 was performed in order to convert the major diastereoisomer 294 into the core of anthracimycin 162 and test the Still–Gennari olefination reaction. However, deprotection followed by Dess-Martin oxidation yielded a mixture of products, which was impossible to interpret by $^1$H NMR and $^{13}$C NMR analysis or to separate by silica chromatography (Scheme 97, Figure 31). Identification of the major diastereoisomer was not possible. The $^1$H NMR and $^{13}$C NMR analysis of the products obtained from the Dess-Martin oxidation reaction showed the presence of multiple unexpected aldehyde peaks, in the region between $\delta$ 10.0 and 9.48 ppm in the $^1$H NMR spectrum, as well as in the region between $\delta$ 207.5 and 203.5 ppm in the $^{13}$C NMR spectrum (Figure 32).

**Scheme 97.** The attempted isolation of the major diastereoisomer 294.
Figure 31. The $^1$H NMR and $^{13}$C NMR spectrum of the deprotection reaction.
Figure 32. The $^1$H NMR and $^{13}$C NMR spectrum of the Dess-Martin oxidation.
10. Conclusions

The formation of the core of anthracimycin 162 was achieved in a 12-step sequence. The development of the direct palladium oxidation conditions in the presence of Pd(OAc)$_2$, 4,4’-Bu-2,2’-dipyridyl and KNO$_3$, allowed the formation of enone 115, suitable for the Diels–Alder cycloaddition to generate the cis-decalin 194 in an 85% yield. This was followed by epimerisation and Raney-Nickel reduction to afford the trans-decalin 114, which was oxidised to 113 in the presence of IBX. The planned Luche reduction/Ireland–Claisen rearrangement sequence failed to deliver the core of the natural product. However, the Hosomi–Sakurai 1,4-addition between the enone 113 and the E-crotyltrimethylsilane 272, allowed the installation of the crotyl chain and delivered 276 and 277 as an inseparable mixture of diastereoisomers in a 2 : 1 ratio. The major diastereoisomer 276 had the stereochemistry required for the core of anthracimycin, which was determined by a deprotection/iodoetherification sequence. Conversion of the ketone carbonyl group of 276 and 277 into an alkene was performed via a triflation/palladium reduction sequence, which afforded 294 and 295 in a 56% yield. Morken’s conditions allowed the selective dihydroxylation of the exocyclic double bond in the presence of two potentially reactive endocyclic alkenes, using B$_2$pin$_2$, trans-cyclohexanediol and Cs$_2$CO$_3$. This was followed by diol cleavage with the use of NaIO$_4$, which formed the core of anthracimycin 162 in an inseparable mixture with 298 in a 2 : 1 ratio in a 45% yield (60% yield b.r.s.m.). (Scheme 98).
Scheme 98. The formation of the core of anthracimycin 162.
11. Future work

The inability to separate the major and the minor diastereoisomers 294 and 295 and the difficulties in interpretation of the NMR spectrum of the deprotection and Dess-Martin oxidation products 305 and 306, represented a real challenge of this strategy. This has forced the redesign of the Hosomi–Sakurai 1,4-addition approach to give the core of the natural product as a single compound. The new route will involve a Hosomi–Sakurai reaction between allyltrimethylsilane 250 and the enone 113, to generate compound 266 as the major diastereoisomer. This compound could be derivatised to give the core of the natural product, by converting the carbonyl group into an alkene 307, via enol-triflation formation and palladium reduction. Selective dihydroxylation of the exocyclic alkene followed by periodate cleavage could form aldehyde 309, which would then be converted into the methyl ester 310. Removal of the TIPS-group, would yield the tricyclic system 311. Installation of the methyl group as required for the core of the natural product, could be achieved with the use of LDA and methyl iodide (Scheme 99). The concave shape of the A/B-ring, as a cis-decalin, should ensure installation of the methyl group with the required stereochemistry, forming the core of anthracimycin as a single diastereoisomer 312.
Scheme 99. The new strategy envisioned for the core of anthracimycin 162.

Compound 312 would then be used to complete the synthesis. Subsequent functionalisation would involve DIBAL-H reduction, Still–Gennari olefination and a Weiler dianion addition reaction after oxidation of the hydroxyl methylene to an ester. Macrocyclisation would then allow the completion of anthracimycin 1.
12. Experimental

12.1 General experimental

Melting points were determined using a Stuart SMP3 apparatus. Optical rotations were carried out using a JASCO-DIP370 polarimeter and $[\alpha]_D$ values are given in $10^3 \text{deg.cm}^2\cdot\text{g}^{-1}$. Infra-red spectra were acquired on a ThermoNicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECX-400, a Jeol ECS-400, Bruker DRX 500 at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: CDCl$_3$ 7.27 ppm, C$_6$D$_6$ 7.16 ppm for $^1$H NMR; CDCl$_3$ 77.0 ppm, central line of triplet, C$_6$D$_6$ 128.4 ppm, central line of triplet for $^{13}$C NMR.$^{13}$C NMR spectra were assigned using DEPT experiments. Coupling constants ($J$) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI), electron ionization (EI) and atmospheric pressure chemical ionization (APCI) techniques. All the Mass-spectra data were in a 5 ppm error. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich. Hexane, CH$_2$Cl$_2$, toluene, THF and Et$_2$O were all purified using Innovative Technology Solvent Purification System; diisopropylamine was distilled from calcium hydride. All other solvents and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to IUPAC rules. Compounds numbers are reported in relation to anthracimycin numbers.$^{15}$
12.2 Methods and Characterisation of Compounds

7-Hydroxyoctahydronaphthalen-15(1H)-one, 102

To a solution of cyclohexanone 101 (5.28 mL, 50.9 mmol) in dry THF (63.3 mL) at 0 °C, a solution of KOH/MeOH (0.74 M, 7.79 mmol, 1.04 mL) and a solution of methylvinyl ketone 99 (2.07 mL, 25.5 mmol) in dry THF (63.3 mL) were added slowly over 30 minutes. The reaction was stirred at room temperature for 2 days. After this time, the solvent was removed in vacuo and the residue was dissolved with EtOAc (60 mL) and the organic phase was washed with water (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was triturated with hexane (30 mL), filtered and the desired product 102 was isolated, without further purification, as a white solid (1.41 g, 34% yield).

Melting point = 142‒144 °C. Rf = 0.11 (EtOAc : hexane 10% : 90%). IR (ATR): ν max 3353 (C-OH), 2952, 2854, 1706 (C=O), 1451, 1346, 1296, 958, 656 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 2.47‒2.27 (4H, m), 1.89‒1.62 (5H, m), 1.53‒1.47 (4H, m), 1.39‒1.24 (2H, m) ppm. ¹³C NMR (400 MHz, CDCl₃): δ 210.6 (C=O), 73.9 (C-OH), 55.3 (CH₂), 42.6 (CH), 41.4 (CH₂), 39.6 (CH₂), 28.6 (CH₂), 27.7 (CH₂), 25.7 (CH₂), 20.8 (CH₃) ppm. MS (ESI): m/z 191 (M+Na⁺); HRMS: found: (M+Na⁺) 191.1042. C₅₀H₃₆NaO₂ requires (M+Na⁺) 191.1043.
To a solution of hydroxyl decalin 102 (720 mg, 4.23 mmol) in glacial acetic acid (11.5 mL), was added H$_2$SO$_4$ 98% solution in water (1.0 mL) and the reaction was stirred at 50 °C for 30 minutes. After this time, the reaction was quenched with cold water (10 mL) and saturated aqueous solution of NaHCO$_3$ (20 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The desired product 103 was obtained without further purification as an orange oil (570 mg, 90% yield). $^{62}$ Rf = 0.23 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 2926, 2855, 1667 (C=O), 1205, 858 cm$^{-1}$. $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.82 (1H, s), 2.48–2.40 (1H, m), 2.40–2.36 (1H, m), 2.35–2.25 (2H, m), 2.25–2.15 (1H, m), 2.09 (1H, dddd, $J = 13.3, 4.9, 4.9, 4.9$ Hz), 2.00–1.79 (3H, m), 1.63 (1H, dddd, $J = 13.3, 13.3, 9.0, 4.9$ Hz), 1.55–1.33 (2H, m), 1.28–1.4 (1H, m) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 200.1 (C=O), 167.4 (C=C), 124.3 (CH), 37.6 (CH), 36.6 (CH$_2$), 35.4 (CH$_2$), 34.4 (CH$_2$), 29.3 (CH$_2$), 26.8 (CH$_2$), 25.5 (CH$_2$) ppm. MS (ESI): m/z 173 (M+Na$^+$); HRMS: found: (M+Na$^+$) 173.0937. C$_{10}$H$_{14}$NaO requires (M+Na$^+$) 173.0937. m/z 151 (M+H$^+$); HRMS: found: (M+H$^+$) 151.1113. C$_{10}$H$_{15}$O requires (M+H$^+$) 151.1117. Characterisation of this compound matched the compound reported in the literature.$^{61}$

7-Hydroxy-10-methyloctahydronaphthalen-15(1H)-one, 104

To a solution of 4-methyl-cyclohexanone 98 (5.40 mL, 44.6 mmol) in dry THF (65.5 mL) at 0 °C, a solution of KOH/MeOH (0.74 M, 8.22 mmol, 1.20 mL) and a solution of methylvinyl ketone 99 (1.86 mL, 22.4 mmol) in dry THF (65.5 mL) were added slowly over 30 minutes. The reaction was stirred at
room temperature for 2 days. After this time, the solvent was removed \textit{in vacuo} and the residue was dissolved with EtOAc (60 mL) and the organic phase was washed with water (10 mL) and brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The crude product was triturated with hexane (30 mL), filtered and the desired product \textbf{104} was isolated, without further purification, as a white solid (1.67 g, 41% yield). \textbf{Melting point} = 137–139 °C. \textbf{Rf} = 0.11 (EtOAc : hexane 10% : 90 %). \textbf{IR} (ATR): $v_{\text{max}}$ 3358 (C-OH), 2925, 2856, 1709 (C=O), 1458, 1402, 1268, 1252, 960, 640 cm$^{-1}$. \textbf{H NMR} (400 MHz, CDCl$_3$): $\delta$ 2.49–2.28 (3H, m), 2.13–2.08 (1H, m), 1.96–1.56 (4H, m), 1.55–1.53 (5H, m), 1.48–1.40 (1H, m), 1.30 (3H, d, $J$ = 7.8 Hz) ppm. \textbf{C NMR} (400 MHz, CDCl$_3$): $\delta$ 210.8 (C=O), 74.1 (C-OH), 55.3 (CH$_2$), 41.5 (CH$_2$), 36.5 (CH), 33.9 (CH$_2$), 33.2 (CH$_3$), 28.6 (CH$_2$), 26.8 (CH), 25.8 (CH$_2$), 17.5 (CH$_3$) ppm. \textbf{MS} (ESI): m/z 205 (M+Na$^+$); HRMS: found: (M+Na$^+$) 205.1201. C$_{11}$H$_{18}$NaO$_2$ requires (M+Na$^+$) 205.1199.

10-Methyl-13,12,11,10,9,8-hexahydropyronaphthalen-15(3H)one, \textbf{105}

![Structure of 10-Methyl-13,12,11,10,9,8-hexahydropyronaphthalen-15(3H)one](structure.png)

To a solution of hydroxyl decalin \textbf{104} (100 mg, 0.560 mmol) in glacial acetic acid (1.50 mL), was added H$_2$SO$_4$ 98% solution in water (0.50 mL). The reaction was stirred at 50 °C for 30 minutes. After this time, the reaction was quenched with cold water (10 mL) and saturated aqueous solution of NaHCO$_3$ (20 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The desired product \textbf{105} was obtained without further purification as an orange oil (71.0 mg, 77% yield). \textbf{Rf} = 0.21 (EtOAc : hexane 10% : 90 %). \textbf{IR} (ATR): $v_{\text{max}}$ 2922, 2856, 1664 (C=O), 1503, 1455, 1329, 1256, 1243, 894, 848 cm$^{-1}$. \textbf{H NMR} (400 MHz, CDCl$_3$): $\delta$ 5.83 (1H, s), 2.49–2.40 (2H, m), 2.40–2.25 (3H, m), 2.09 (1H, ddd, $J$ = 13.3, 9.6, 5.0 Hz), 1.95–1.82 (2H, m), 1.73–1.56 (3H, m), 1.17–1.03 (1H, m), 0.95 (3H, d, $J$ = 6.4 Hz) ppm. \textbf{C NMR} (400 MHz, CDCl$_3$): $\delta$ 200.2 (C=O), 166.9 (C=C), 124.3 (CH), 42.8 (CH$_2$), 37.5 (CH), 36.7 (CH$_2$), 35.3 (CH$_2$), 35.0 (CH$_2$), 31.9 (CH), 29.2 (CH$_2$), 21.9 (CH$_3$) ppm. \textbf{MS} (ESI): m/z 187 (M+Na$^+$);
HRMS: found: (M+Na') 187.1095. C_{11}H_{16}NaO requires (M+Na') 187.1093. m/z 165 (M+H'); HRMS: found: (M+H') 165.1268. C_{11}H_{17}O requires (M+H') 165.1274.

6-Allyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)-one, **106**

[Chemical structure image]

14-Diallyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)-one, **107**

[Chemical structure image]

Anhydrous DMSO (1.50 mL) was added to a NaH (60% dispersion in mineral oil, 28.0 mg, 0.72 mmol) and the mixture was stirred at 50 °C for 1 hour. After this time, it was cooled to room temperature and dry THF (1.50 mL) was added and then the reaction was cooled to 0 °C. A solution of decalin **103** (100 mg, 0.610 mmol) in dry THF (1.50 mL) was added dropwise (5 minutes) and stirred at 0 °C for 2 hours. Allyl bromide (0.060 mL, 0.72 mmol) was added and the reaction was warmed to room temperature and stirred for 16 hours. The reaction was quenched with saturated aqueous solution of NH_{4}Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_{2}SO_{4}, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield **106** as a pale yellow oil (30.0 mg, 26% yield) and **107** as a pale yellow oil (20.0 mg, 15% yield).\(^6\) 6-Allyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)-one, **106**; Rf = 0.62 (EtOAc : hexane 10% : 90%). **IR (ATR):** ν\(_{\text{max}}\) 2925, 2855, 1667 (C=O), 1450, 1363, 1194, 910 cm\(^{-1}\). **\(^1\)H NMR (400 MHz, CDCl\(_3\)):** δ 5.85‒5.70 (1H, m), 4.96‒4.89 (2H, m), 3.13‒3.06 (1H, m), 2.88‒2.77 (1H, m), 2.52‒2.39 (2H, m), 2.37‒2.27 (2H, m), 2.07 (1H,
dddd, J = 13.7, 5.4, 5.4, 5.4 Hz), 2.01–1.77 (3H, m), 1.70–1.54 (2H, m), 1.49 (1H, dddd, J = 13.7, 13.7, 3.2, 3.2 Hz), 1.42–1.20 (2H, m) ppm. 13C NMR (400 MHz, CDCl3): δ 198.8 (C=O), 161.6 (C=C), 136.3 (CH), 130.5 (C=C), 114.4 (CH2), 38.9 (CH), 36.4 (CH2), 35.0 (CH2), 31.4 (CH2), 28.8 (CH2), 28.7 (CH2), 26.9 (CH2), 25.5 (CH2) ppm. MS (ESI): m/z 213 (M+Na+); HRMS: found: (M+Na+) 213.1249. C13H18NaO requires (M+Na+) 213.1250.

In a pressure vessel were placed Pd(OAc)2 (134 mg, 0.600 mmol), dry THF (15.2 mL), 2-methyl-1-buten-3-yne 135 (2.88 mL, 30.2 mmol) and thiophenol (3.10 mL, 30.2 mmol) were added. The reaction was stirred at 60 °C for 16 hours. After this period, the mixture was filtrated through celite with EtOAc (50 mL) and the solvent was concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield 116 as a pale yellow liquid (5.32 g, quantitative yield).75 Rf = 0.66 (100% hexane). IR (ATR): νmax 2978, 2952, 1617, 1574, 1478, 1458, 1440, 1375, 1119,
1025 cm$^{-1}$.  $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34–7.16 (5H, m, Ar-H), 5.55 (1H, s, H-11), 5.51 (1H, s, H-11), 5.22 (1H, d, $J = 1.4$ Hz, H-7), 5.05 (1H, d, $J = 1.4$ Hz, H-7), 1.96 (3H, s, H-24) ppm.  $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 143.8 (C-9), 140.4 (C-10), 134.4 (ar), 130.9 (Ar-H), 128.7 (Ar-H), 126.7 (Ar-H), 117.1 (C-11), 116.4 (C-7), 20.9 (C-24) ppm.  MS (APCI): m/z 177 (M+H$^+$); HRMS: found: (M+H$^+$) 177.0736.  C$_{11}$H$_{13}$S requires (M+H$^+$) 177.0732.  Characterisation of this compound matched the compound reported in the literature.$^{75}$

12-Bromocyclohex-13-enone, 132$^{74}$

![12-Bromocyclohex-13-enone](image)

To a solution of cyclohexenone 131 (0.500 mL, 5.21 mmol) in pyridine : CHCl$_3$ (1 : 1, 4.0 mL) at 0 °C, were added DMAP (127 mg, 1.04 mmol) and a solution of bromine (0.500 mL, 10.4 mmol) in pyridine : CHCl$_3$ (1 : 1, 4.0 mL) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was diluted with EtOAc (100 mL), washed with aqueous solution of 2 M HCl (20 mL), water (10 mL) and brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield 132 as a white solid (360 mg, 40% yield).$^{74}$ Melting point = 75–76 °C.  RF = 0.24 (EtOAc : hexane 10% : 90%).  IR (ATR): $\nu_{\text{max}}$ 2942, 2872, 1678 (C=O), 1461, 1424, 1315, 1124, 971, 813 cm$^{-1}$.  $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 (1H, dd, $J = 4.6$, 4.6 Hz, H-7), 2.65 (2H, ddd, $J = 6.4$, 3.2, 3.2 Hz, H-14), 2.45–2.43 (2H, m, H-6), 2.14 (2H, ddd, $J = 6.4$, 6.4, 4.6 Hz, H-15) ppm.  $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 191.3 (C-13), 151.1 (C-7), 123.9 (C-12), 38.3 (C-14), 28.4 (C-15), 22.7 (C-6) ppm.  MS (ESI): m/z 196 (M+Na$^+$), 198 (M+Na$^+$); HRMS: found: (M+Na$^+$) 196.9568.  C$_7$H$_7$BrNaO requires (M+Na$^+$) 196.9572.  Characterisation of this compound matched the compound reported in the literature$^{74}$
To a solution of 2-bromocyclohexenone 132 (173 mg, 1.00 mmol) in dry CH₂Cl₂ (5.0 mL) at −10 °C, were sequentially added a 1.0 M solution of EtAlCl₂ in hexane (0.20 mL, 0.20 mmol) and isoprene 133 (1.00 mL, 10.0 mmol) and the reaction was stirred at −10 °C for 2 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and the mixture was stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield 134 as pale yellow oil (150 mg, 62% yield). Rf = 0.44 (EtOAc : hexane 5% : 95%). IR (ATR): ν max 2912, 1714 (C=O), 1447, 1424, 1310, 1168, 1071, 783 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.28–5.23 (1H, m, H-10), 3.20 (1H, ddd, J = 15.1, 10.5, 7.3 Hz, H-14), 3.18–3.10 (1H, m, H-11), 2.71–2.58 (2H, m, H-14 + H-7), 2.45–2.34 (2H, m, H-15 + H-11), 2.15 (1H, dd, J = 17.4, 6.9 Hz, H-8), 2.08–1.58 (4H, m, H-8 + H-15 + H-6), 1.63 (3H, s, H-24) ppm. ¹³C NMR (400 MHz, CDCl₃): δ 204.0 (C-13), 131.7 (C-9), 118.2 (C-10), 70.6 (C-12), 43.5 (C-7), 36.3 (C-14), 36.3 (C-11), 33.0 (C-8), 26.7 (C-15), 23.0 (C-24), 22.5 (C-6) ppm. MS (ESI): m/z 265 (M+Na⁺), 267 (M+Na⁺); HRMS: found: (M+Na⁺) 265.0197. C₁₂H₁₅BrNaO requires (M+Na⁺) 265.0198. Characterisation of this compound matched the compound reported in the literature.
To a solution of 2-bromocyclohexenone 132 (36.0 mg, 0.210 mmol) in dry CH$_2$Cl$_2$ (0.50 mL) at −10 °C, was added a 1.0 M solution of EtAlCl$_2$ in hexane (0.04 mL, 0.04 mmol) and stirred for 10 minutes. A solution of sulfur substituted diene 116 (150 mg, 0.850 mmol) in dry CH$_2$Cl$_2$ (0.55 mL) was then added and the reaction was stirred at −10 °C for 2 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 5% EtOAc in hexanes) to yield 136 as a pale yellow oil (40.0 mg, 54% yield).$^{72}$ Rf = 0.56 (EtOAc : hexane 5% : 95%).

**IR (ATR):** ν$_{max}$ 2931, 1716 (C=O), 1477, 15852, 1477, 1233, 1024, 741, 760 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.22–7.13 (2H, m, Ar-H), 7.09–7.00 (3H, m, Ar-H), 3.24 (1H, d, J = 17.9 Hz, H-11), 3.16 (1H, ddd, J = 15.1, 9.2, 9.2 Hz, H-14), 2.74 (1H, d, J = 17.9, Hz, H-11), 2.64–2.57 (1H, m, H-7), 2.37–2.23 (3H, m, H-14 + H-15 + H-6), 2.22–2.11 (1H, m, H-6), 1.90 (3H, s, H-24), 1.81–1.75 (2H, m, H-8), 1.53–1.45 (1H, m, H-15) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): δ 203.7 (C-13), 139.5 (C-9), 135.8 (Ar), 129.0 (Ar-H), 128.0 (Ar-H), 125.6 (Ar-H), 120.7 (C-10), 68.8 (C-12), 44.5 (C-7), 43.0 (C-11), 36.0 (C-14), 34.1 (C-6), 26.1 (C-15), 22.2 (C-8), 20.9 (C-24) ppm. MS (ESI): m/z 373 (M+Na$^+$), 375 (M+Na$^+$); HRMS: found: (M+Na$^+$) 373.0229. C$_{13}$H$_{13}$BrNaOS requires (M+Na$^+$) 373.0232. Characterisation of this compound matched the compound reported in the literature.$^{72}$
To a solution of thiophenyl cis-declalin 156 (100 mg, 0.370 mmol) in dry CH₂Cl₂ (2.0 mL), was added a 1.0 M solution of EtAlCl₂ in hexane (0.07 mL, 0.07 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH₂Cl₂ (3 × 10 mL). The reunited organic layers were washed with water (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield 137 as a white solid (68.0 mg, 68% yield). Melting point = 76–79 °C. Rf = 0.45 (EtOAc : hexane 10% : 90%). IR (ATR): νmax 2923, 1709 (C=O), 1581, 1476, 1438, 1370, 1085, 740, 691 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.29–7.25 (2H, m, Ar-H), 7.21–7.13 (3H, m, Ar-H), 2.52–2.39 (1H, m, H-11), 2.42 (1H, ddddd, J = 13.8, 4.4, 2.5, 1.9 Hz, H-14), 2.41–2.29 (4H, m, H-14 + H-12 + H-8 + H-11), 2.21–2.13 (1H, m, H-8), 2.11–2.05 (1H, m, H-15), 2.01 (3H, s, H-24), 1.83 (1H, dddd, J = 13.3, 6.6, 3.4, 1.6 Hz, H-6), 1.78–1.72 (1H, m, H-7), 1.68–1.59 (1H, m, H-15), 1.42 (1H, dddd, J = 13.3, 13.3, 11.7, 3.7 Hz, H-6) ppm. ¹³C NMR (500 MHz, CDCl₃): δ 211.3 (C-13), 140.5 (C-9), 136.0 (Ar), 128.7 (Ar-H), 127.9 (Ar-H), 125.2 (Ar-H), 121.2 (C-10), 50.7 (C-12), 42.1 (C-14), 41.9 (C-7), 39.9 (C-8), 32.3 (C-6), 32.1 (C-11), 26.3 (C-15), 21.8 (C-24) ppm. MS (ESI): m/z 295 (M+Na⁺); HRMS: found: (M+Na⁺) 295.1119. C₁₇H₂₄NaOS requires (M+Na⁺) 295.1127.

Characterisation of this compound matched the compound reported in the literature."
To a solution of cyclohexeneone 131 (0.50 mL, 5.0 mmol) in dry CH₂Cl₂ (25.0 mL), was added a 1.0 M solution of EtAlCl₂ in hexane (1.0 mL, 1.0 mmol) and stirred at room temperature for 30 minutes. Isoprene 133 (5.0 mL, 50 mmol) was then added, and the reaction was stirred at 30 °C for 8 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 138 as a pale yellow oil (305 mg, 37% yield) and 139 as a pale yellow oil (371 mg, 40% yield). (12R*, 7S*)-9-Methyl-15,6,7,8,11,12-hexahydonaphthalen-13(2H)-one, 138

(12S*, 7R*)-9-Methyl-15,6,7,8,11,12-hexahydonaphthalen-13(2H)-one, 139

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\text{IR (ATR): } \nu_{\text{max}} \text{ 2922, 2866, 1708 (C=O), 1444, 1377, 1310, 1234, 1179, 919, 889 cm}^{-1}. \]

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\text{H NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 5.31‒5.27 (1H, m, H-10), 2.63 (1H, ddd, } J = 10.9, 4.5, 2.0 \text{ Hz, H-12), 2.47‒2.45 (1H, m, H-11), 2.43‒2.31 (2H, m, H-14 + H-7), 2.24 (1H, ddd, } J = 15.1, 9.2, 5.7, 1.3 \text{ Hz, H-14), 2.02‒1.90 (2H, m, H-8 + H-11), 1.89‒1.66 (4H, m, H-8 + H-6 + H-15), 1.74‒1.67 (1H, m, H-6), 1.59 (3H, s, H-24) \text{ ppm.} \]

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\text{C NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 213.1 (C-13), 131.9 (C-9), 118.2 (C-10), 48.0 (C-12), 40.0 (C-14), 36.3 (C-7), 32.2 (C-15), 28.5 (C-6), 24.2 (C-8), 24.1 (C-11), 23.8 (C-24) ppm. MS (ESI): } m/z \text{ 187 (M+Na\textsuperscript{+}); HRMS: found: (M+Na\textsuperscript{+}) 187.1090. C}_{13}\text{H}_{16}\text{NaO} \]
requires (M+Na\(^+\)) 187.1093. m/z 165 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 165.1273. C\(_{11}\)H\(_{17}\)O requires (M+H\(^+\)) 165.1274. Characterisation of this cis-decalin 138 matched the compound reported in the literature\(^76\) (125\(^*\), 75\(^*\))-9-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 139; \(\text{Rf} = 0.48\) (EtOAc : hexane 5% : 95%). IR (ATR): \(\nu_{\text{max}}\) 2921, 1705 (C=O), 1439, 1378, 1340, 1310, 1149, 1060, 824 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.39–5.34 (1H, m, H-10), 2.04 (1H, dddd, \(J = 13.7, 4.5, 2.8, 1.7\) Hz, H-14), 2.34 (1H, dddd, \(J = 13.7, 13.7, 5.7, 0.7\) Hz, H-14), 2.40–2.11 (3H, m, H-12 + H-11), 2.10–2.01 (2H, m, H-8 + H-15), 1.93–1.84 (2H, m, H-8 + H-6), 1.76–1.66 (2H, m, H-7 + H-15), 1.64 (3H, s, H-24), 1.45 (1H, dddd, \(J = 13.2, 13.2, 11.7, 3.4\) Hz, H-6) ppm. \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta\) 212.1 (C-13), 132.1 (C-9), 118.7 (C-10), 50.0 (C-12), 41.8 (C-14), 40.2 (C-7), 38.1 (C-8), 32.4 (C-6), 25.9 (C-15), 24.4 (C-11), 22.9 (C-24) ppm. MS (ESI): m/z 187 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 187.1091. C\(_{11}\)H\(_{16}\)NaO requires (M+Na\(^+\)) 187.1093. m/z 165 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 165.1221. C\(_{11}\)H\(_{17}\)O requires (M+H\(^+\)) 165.1274. Characterisation of this trans-decalin 139 matched the compound reported in the literature\(^70\)

**Epimerisation Method**

To a solution of cis-decalin 138 (326 mg, 1.99 mmol), in dry CH\(_2\)Cl\(_2\) (10.0 mL), was added a 1.0 M solution of EtAlCl\(_2\) in hexane (0.40 mL, 0.40 mmol) and stirred for 16 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and the reaction was stirred vigorously for 1 hour. The mixture was diluted with water (10 mL) and the organic phase was extracted with CH\(_2\)Cl\(_2\) (3 \times 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na\(_2\)SO\(_4\), filtered and concentrated \textit{in vacuo}. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 139 as a pale yellow oil (245 mg, 75% yield).
To a solution of trans-decalin 139 (40.0 mg, 0.270 mmol) in methanol (1.0 mL), were added 2,4-dinitrophenyl hydrazine 140 (120 mg, 0.540 mmol), glacial acetic acid (0.50 mL) and H$_2$SO$_4$ 98% solution in water (0.10 mL). The reaction was stirred at 50 °C for 2 hours and after this period the reaction was cooled to room temperature and then quenched with cold water (10 mL) and saturated aqueous solution of NaHCO$_3$ (20 mL). The mixture was extracted with CH$_2$Cl$_2$ (4 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 141 as an orange solid (50.0 mg, 54% yield). Crystallized using solvent/antisolvent system: EtOAc/hexane. **Melting point** = 192–194 °C. **Rf** = 0.55 (EtOAc : hexane 10% : 90%). **IR** (ATR): $\nu_{max}$ 3328, 2927, 1615 (C=N), 1587, 1514, 1500, 1264, 1296, 741 cm$^{-1}$. **$^1$H NMR** (500 MHz, CDCl$_3$): $\delta$ 11.29 (1H, s, NH), 9.14 (1H, d, $J$ = 2.5 Hz, Ar-H), 8.31 (1H, dd, $J$ = 9.6, 2.5 Hz, Ar-H), 7.98 (1H, d, $J$ = 9.6 Hz, Ar-H), 5.51–5.47 (1H, m, H-10), 2.95–2.92 (1H, m, H-14), 2.41–2.32 (2H, m, H-11), 2.19 (1H, ddd, $J$ = 11.4, 7.8, 6.5 Hz, H-12), 2.14–2.04 (3H, m, H-14 + H-8 + H-15), 1.95–1.91 (1H, m, H-6), 1.92–1.84 (1H, m, H-8), 1.69 (3H, s, H-24), 1.64–1.60 (1H, m, H-7), 1.55–1.51 (1H, m, H-15), 1.33 (1H, dddd, $J$ = 13.1, 13.1, 11.2, 3.1 Hz, H-6) ppm. **$^{13}$C NMR** (500 MHz, CDCl$_3$): $\delta$ 162.1 (C=N), 145.7 (C-9), 137.5 (Ar), 132.5 (Ar), 128.9 (Ar-H), 128.4 (Ar), 123.7 (Ar-H), 120.2 (C-10), 116.5 (Ar-H), 44.9 (C-12), 40.1 (C-7), 38.6 (C-8), 33.0 (C-6), 27.5 (C-14), 26.8 (C-11), 25.3 (C-15), 23.4 (C-24) ppm. **MS** (ESI): m/z 367 (M+Na$^+$); HRMS: found: (M+Na$^+$) 367.1375. C$_{17}$H$_{20}$N$_2$NaO$_4$ requires (M+Na$^+$) 367.1377.
(12R*, 75*)-9,10-Dimethyl,15,6,7,8,11,12-hexahydronaphthalen-13-(2H)-one, 143

(12S*, 77*)-9,10-Dimethyl,15,6,7,8,11,12-hexahydronaphthalen-13-(2H)-one, 144

To a solution of cyclohexanone 131 (0.10 mL, 1.0 mmol) in dry CH$_2$Cl$_2$ (5.0 mL), was added a 1.0 M solution of EtAlCl$_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. 2,3-Dimethyl-1,3-butadiene 142 (1.20 mL, 10.0 mmol) was added and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and the mixture was stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture 143 and 144 in a 2:1 ratio as pale yellow oil (178 mg, 99% yield).

Epimerisation

To a solution of the inseparable mixture of cis-decalin 143 and trans-decalin 144 2:1 ratio (178 mg, 1.00 mmol) in dry CH$_2$Cl$_2$ (5.0 mL), was added a 1.0 M solution of EtAlCl$_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, filtered and
concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield 144 as a pale yellow oil in a 23 : 1 ratio (166 mg, 93% yield). Data reported for the *trans*-diastereoisomer 144 only, after epimerization. \( \text{RF} = 0.52 \) (EtOAc : hexane 10% : 90%). IR (ATR): \( \nu_{\text{max}} 2911, 1708 \) (C=O), 1445, 1380, 1237, 1180, 1131, 515 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 2.40 (1H, dddd, \( J = 13.7, 4.3, 2.6, 1.6 \) Hz, H-14), 2.33 (1H, dddd, \( J = 13.7, 13.7, 5.6, 0.9 \) Hz, H-14), 2.21–2.13 (2H, m, H-11 + H-12), 2.10–1.98 (3H, m, H-15 + H-7), 1.97–1.86 (2H, m, H-11 + H-6), 1.72–1.63 (2H, m, H-8), 1.61 (3H, s, H-24), 1.57 (3H, s, H-25), 1.41 (1H, dddd, \( J = 13.0, 13.0, 11.9, 3.7 \) Hz, H-6) ppm. \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \( \delta \) 212.5 (C-13), 124.5 (C-9), 123.9 (C-10), 51.0 (C-12), 41.8 (C-14), 40.9 (C-7), 40.2 (C-8), 32.3 (C-6), 30.7 (C-11), 26.1 (C-15), 18.8 (C-24), 18.6 (C-25) ppm. MS (ESI): m/z 179 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 179.1441. \( \text{C}_{12}\text{H}_{19}\text{O} \) requires (M+H\(^+\)) 179.1430.

\((125^{*}, 75^{*})\)-10-Methyl,15,6,7,8,11,12-hexahydroronaphthalen-13-(2H)-one, 146

To a solution of cyclohexanone 131 (0.10 mL, 1.0 mmol) in dry CH\(_2\)Cl\(_2\) (5.0 mL), was added a 1.0 M solution of EtAlCl\(_2\) in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. *trans*-1,3-Pentadiene 145 (1.00 mL, 10.0 mmol) was added and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na\(_2\)SO\(_4\), filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield 146 as a pale yellow oil (164 mg, 99% yield). \( \text{RF} = 0.54 \) (EtOAc : hexane 10% : 90%). IR (ATR): \( \nu_{\text{max}} 2899, 1710 \) (C=O), 1444, 1367, 1212, 1139, 1063, 803 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.57–5.53 (2H, m, H-10 + H-9), 2.83 (1H, dd, \( J = 4.6, 4.6 \) Hz, H-12), 2.60–2.52 (1H, m, H-7), 2.44–2.31 (2H, m, H-14 + H-
11), 2.29–2.21 (1H, m, H-14), 2.05–1.88 (5H, m, H-15 + H-6 + H-8), 1.76–1.68 (1H, m, H-8), 1.21 (3H, d, J = 7.3 Hz, H-24) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 211.3 (C-13), 131.2 (C-10), 123.8 (C-9), 53.8 (C-12), 43.3 (C-14), 39.6 (C-7), 32.7 (C-11), 30.0 (C-15), 26.2 (C-8), 24.9 (C-6), 17.9 (C-24) ppm. MS (APCI): m/z 165 (M+H$^+$); HRMS: found: (M+H$^+$) 165.1277. $C_{11}H_{17}O$ requires (M+H$^+$) 165.1274. Characterisation of this compound matched the compound reported in the literature. $^{77}$

(12R*, 7S*)-10-Methyl,15,6,7,8,11,12-hexahydonaphthalen-13-(2H)-one, 147$^{77}$

To a solution of cis-decalin 146 (164 mg, 1.00 mmol) in dry CH$_2$Cl$_2$ (5.0 mL), was added a 1.0 M solution of EtAlCl$_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The reunited organic layers were washed with water (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 147 as a pale yellow oil (38.0 mg, 23% yield). $R_f$ = 0.56 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\max}$ 2924, 2870, 1707 (C=O), 1447, 1363, 1278, 1109, 895 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.57 (1H, dddd, $J = 10.0, 5.0, 2.7, 2.3$ Hz, H-9), 5.55–5.45 (1H, m, H-10), 2.59 (1H, dqdd, $J = 9.1, 6.9, 4.5, 2.7$ Hz, H-11), 2.44–2.37 (2H, m, H-14), 2.20–2.06 (2H, m, H-8 + H-6), 2.00–1.85 (3H, m, H-12 + H-15 + H-8), 1.80–1.63 (2H, m, H-15 + H-7), 1.47 (1H, dddd, $J = 13.0, 13.0, 11.9, 3.7$ Hz, H-6), 0.98 (3H, d, $J = 6.9$ Hz, H-24) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 212.2 (C-13), 133.0 (C-10), 123.5 (C-9), 58.2 (C-12), 43.0 (C-14), 41.0 (C-7), 33.1 (C-6), 33.0 (C-8), 29.1 (C-11), 27.2 (C-15), 21.1 (C-24) ppm. MS (APCI): m/z 165 (M+H$^+$); HRMS: found: (M+H$^+$) 165.1278. $C_{11}H_{17}O$ requires (M+H$^+$) 165.1274. Characterisation of this compound matched the compound reported in the literature. $^{77}$
To a solution of cyclopenteone 148 (0.10 mL, 1.2 mmol) in dry CH$_2$Cl$_2$ (6.0 mL), was added a 1.0 M solution of EtAlCl$_2$ in hexane (0.24 mL, 0.24 mmol) and stirred at room temperature for 30 minutes. Isoprene 133 (1.20 mL, 12.0 mmol) was added and the reaction was stirred at room temperature for 3 days. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture 149 and 150 in a 1.34 : 1 ratio as a pale yellow oil (41.0 mg, 23% yield). $R_f = 0.51$ (EtOAc : hexane 10% : 90%). On a mixture IR (ATR): $\nu_{\text{max}}$ 2923, 1738 (C=O), 1438, 1377, 1172, 1125, 886, 783 cm$^{-1}$. Integration of the $^1$H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.46–5.39 (1H, m, 150), 5.36–5.32 (1H, m, 149), 2.57–2.48 (1H, m, 149), 2.47–2.39 (1H, m, 149), 2.38–2.29 (3H, m, 2H x 149 + 1H x 150), 2.28–2.23 (3H, m, 1H x 149 + 2H x 150), 2.23–2.12 (4H, m, 1H x 149 + 3H x 150), 2.11–1.93 (5H, m, 3H x 149 + 2H x 150), 1.85–1.76 (3H, 3H x 149 + 2H x 150), 1.71 (3H, s, 150), 1.63 (3H, s, 149) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 219.8 (C=O), 218.5 (C=O), 134.3 (C=CC), 132.3 (C=CC), 120.3 (CH), 118.7 (CH), 51.2 (CH$_2$), 46.6 (CH), 39.4 (CH), 37.7 (CH), 37.3 (CH$_2$), 34.2 (CH$_3$), 32.8 (CH), 30.8 (CH$_2$), 27.8 (CH$_2$), 26.5 (CH$_2$), 24.8 (CH$_2$), 23.9 (CH$_3$), 1
23.6 (CH₃), 21.7 (CH₂) ppm. On a mixture MS (ESI): m/z 173 (M+Na⁺); HRMS: found: (M+Na⁺) 173.0938. C₁₀H₁₄NaO requires (M+Na⁺) 173.0937. Characterisation of this compound matched the compound reported in the literature.

Epimerisation

To a solution of the inseparable mixture of cis-decalin 149 and trans-decalin 150 1.34 : 1 (41.0 mg, 0.270 mmol) in dry CH₂Cl₂ (2.0 mL), was added a 1.0 M solution of EtAlCl₂ in hexane (0.05 mL, 0.05 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle’s salt 10% aqueous solution (10 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture 149 and 150 in an unchanged 1.34 : 1 ratio as a pale yellow oil (39.0 mg, 99% yield).

(12R*, 7S*)-9,10-Dimethyl,14,15,7,8,11,12-hexahydro-1H-inden-13-one, 151

(12S*, 7S*)-9,10-Dimethyl,14,15,7,8,11,12-hexahydro-1H-inden-13-one, 152

To a solution of cyclopenteone 148 (0.10 mL, 1.2 mmol) in dry CH₂Cl₂ (6.0 mL), was added a 1.0 M solution of EtAlCl₂ in hexane (0.24 mL, 0.24 mmol) and the reaction was stirred at room temperature for 30 minutes. 2,3-Dimethyl-1,3-butadiene 142 (1.40 mL, 12.0 mmol) was added and the reaction was
stirred at room temperature for 3 days. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and the mixture was stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, filtered and concentrated _in vacuo_. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture **151** and **152** in a 4 : 1 ratio as a pale yellow oil (149 mg, 76% yield).

**Epimerisation**

To a solution of the inseparable mixture of _cis-decalin_ **151** and _trans-decalin_ **152** 4 : 1 (149 mg, 0.910 mmol) in dry CH$_2$Cl$_2$ (4.50 mL), was added a 1.0 M solution of EtAlCl$_2$ in hexane (0.18 mL, 0.18 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle’s salt 10% aqueous solution (10 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, filtered and concentrated _in vacuo_. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture **151** and **152** in a 1.47 : 1 ratio as a pale yellow oil (113 mg, 75% yield). \[ \text{Rf} = 0.54 \text{ (EtOAc : hexane 10% : 90%).} \] On a mixture IR (ATR): $\nu_{\text{max}}$ 2914, 2831, 1737 (C=O), 1439, 1380, 1274, 1249, 1128, 1020 cm$^{-1}$. Integration of the $^1$H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.49–2.41 (1H, m), 2.41–2.34 (1H, m), 2.33–2.24 (2H, m), 2.23–2.11 (6H, m), 2.10–1.88 (6H, m), 1.84–1.64 (4H, m), 1.62 (6H, s), 1.59 (3H, s), 1.56 (3H, s) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 219.7 (C=O, **151**), 218.9 (C=O, **152**), 125.6 (C=C, **152**), 124.9 (C=C, **152**), 123.9 (C=C, **151**), 123.4 (C=C, **151**), 51.9 (CH, **152**), 47.6 (CH, **151**), 39.4 (CH, **152**), 38.8 (CH$_2$, **152**), 37.5 (CH$_2$, **152**), 34.2 (CH$_2$, **151**), 32.8 (CH, **151**), 32.7 (CH$_2$, **151**), 31.0 (CH$_2$, **152**), 27.8 (CH$_2$, **151**), 27.7 (CH$_2$, **152**), 26.4 (CH$_2$, **151**), 19.3 (CH$_3$, **151**), 19.2 (CH$_3$, **152**), 19.1 (CH$_3$, **152**), 18.7 (CH$_3$, **151**) ppm. On a mixture MS (ESI): m/z 187 (M+Na$^+$); HRMS: found: (M+Na$^+$) 187.1099. C$_{11}$H$_{16}$NaO
requires (M+Na\(^+\)) 187.1093. m/z 165 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 165.1276. C\(_{11}\)H\(_{17}\)O requires (M+H\(^+\)) 165.1274.

\((12R^*, 7S^*)\)-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, \textbf{154}\(^{77}\)

\[(12S^*, 7S^*)\]-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, \textbf{155}\(^{77}\)

To a solution of cycloheptenone \textbf{153} (0.10 mL, 1.0 mmol) in dry CH\(_2\)Cl\(_2\) (5.0 mL), was added a 1.0 M solution of EtAlCl\(_2\) in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. Isoprene \textbf{133} (1.00 mL, 10.0 mmol) was added and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na\(_2\)SO\(_4\), filtered and concentrated \textit{in vacuo}. The crude product (10 : 1 \textit{cis} : \textit{trans}) was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield \textbf{154} as a pale yellow oil (92.0 mg, 52% yield) and \textbf{155} as a pale yellow oil (8.0 mg, 5% yield).

\((12R^*, 7S^*)\)-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, \textbf{154}; \textit{Rf} = 0.48 (EtOAc : hexane 10% : 90%). \textbf{IR} (ATR): \(\nu_{\text{max}}\) 2920, 2854, 1693 (C=O), 1436, 1377, 1145, 942 cm\(^{-1}\). \textbf{\textit{\(^1\)H NMR}} (400 MHz, CDCl\(_3\)): \(\delta\) 5.39–5.34 (1H, m, H-10), 2.71–2.60 (2H, m, H-12 + H-14) 2.50–2.40 (1H, m, H-14), 2.32–2.23 (3H, m, H-15 + H-6 + H-7), 2.17–2.06 (1H, m, H-8), 1.97–1.86 (4H, m, H-8 + H-6a + H-11), 1.67–1.59 (6, m, H-24 + H-6 + H-6a + H-15) ppm. \textbf{\textit{\(^{13}\)C NMR}} (400 MHz, CDCl\(_3\)): \(\delta\) 215.7 (C-13), 132.3
(C-9), 119.1 (C-10), 49.5 (C-12), 43.8 (C-14), 36.9 (C-8), 34.2 (C-7), 33.1 (C-11), 27.6 (C-6), 26.1 (C-15),
24.2 (C-6a), 23.7 (C-24) ppm. **MS (ESI):** m/z 201 (M+Na⁺); HRMS: found: (M+Na⁺) 201.1254. C₁₂H₁₈NaO
requires (M+Na⁺) 201.1250. m/z 179 (M+H⁺); HRMS: found: (M+H⁺) 179.1435. C₁₂H₁₅O requires (M+H⁺)
179.1430. (12S*, 7S*)-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, **155**;
**Rf = 0.51 (EtOAc : hexane 10% : 90%).** **IR (ATR):** ν<sub>max</sub> 2920, 1698 (C=O), 1444, 1340, 1150,
521 cm⁻¹. **¹H NMR (400 MHz, CDCl₃):** δ 5.39‒5.34 (1H, m), 2.72‒2.61 (2H, m), 2.51‒2.40 (1H, m), 2.39‒2.34 (1H, m),
2.29‒2.17 (2H, m), 2.12‒2.04 (3H, m), 2.02‒1.87 (5H, m), 1.66 (3H, s) ppm. **¹³C NMR (400 MHz, CDCl₃):**
δ 217.1 (C=O), 134.2 (C=C), 119.3 (CH), 54.9 (CH), 41.1 (CH₂), 38.6 (CH₂), 36.9 (CH), 35.4 (CH₂), 29.7
(CH₂), 29.1 (CH₂), 26.4 (CH₂), 23.2 (CH₃) ppm. **MS (ESI):** m/z 201 (M+Na⁺); HRMS: found: (M+Na⁺)
201.1253. C₁₂H₁₈NaO requires (M+Na⁺) 201.1250. m/z 179 (M+H⁺); HRMS: found: (M+H⁺) 179.1431. C₁₂H₁₅O requires (M+H⁺)
179.1430. Characterisation of this compound matched the compound reported in the literature.⁷⁷

(12R*, 7S*)-10-Methyl-9-(phenylthio)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **156**⁷²

![Chemical structure](image)

To a solution of cyclohexenone **131** (0.10 mL, 1.0 mmol) in dry CH₂Cl₂ (2.5 mL), was added a 1.0 M
solution of EtAlCl₂ in hexane (0.20 mL, 0.20 mmol). After 15 minutes, a solution of sulfur substituted
diene **116** (704 mg, 4.00 mmol) in dry CH₂Cl₂ (2.5 mL) was added and the reaction was stirred at room
temperature for 1.5 hours. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added
and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic
phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with water
(10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude product
was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **156** as a
pale yellow solid (242 mg, 90% yield). Melting point = 95–97 °C. Rf = 0.43 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 2922, 1698 (C=O), 1580, 1370, 1138, 1023, 737 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.25–7.21 (3H, m, Ar-H), 7.14–7.07 (2H, m, Ar-H), 2.81–2.76 (1H, m, H-12), 2.70 (1H, dd, J = 18.7, 2.3 Hz, H-11), 2.48–2.43 (1H, m, H-7), 2.39 (1H, dddd, J = 9.9, 9.9, 5.1, 1.5 Hz, H-14), 2.33–2.25 (1H, m, H-14), 2.19–2.12 (1H, m, H-11), 2.10–2.07 (2H, m, H-8), 1.97 (3H, s, H-24), 1.95–1.80 (3H, m, H-15 + H-6), 1.73–1.65 (1H, m, H-6) ppm. $^{13}$C NMR (500 MHz, CDCl$_3$): $\delta$ 211.9 (C-13), 139.9 (C-9), 136.6 (Ar), 128.9 (Ar-H), 127.7 (Ar-H), 125.3 (Ar-H), 120.8 (C-10), 48.6 (C-12), 40.4 (C-14), 37.4 (C-7), 33.6 (C-8), 31.3 (C-11), 28.4 (C-6), 23.9 (C-15), 21.4 (C-24) ppm. MS (ESI): m/z 295 (M+Na$^+$); HRMS: found: (M+Na$^+$) 295.1119. C$_{17}$H$_{20}$NaOS requires (M+Na$^+$) 295.1127. m/z 273 (M+H$^+$); HRMS: found: (M+H$^+$) 273.1310. C$_{17}$H$_{21}$OS requires (M+H$^+$) 273.1308. Characterisation of this compound matched the compound reported in the literature.$^{72}$

(12R$^*$, 7S$^*$)-10-Methyl-15,6,7,8,11,12-hexahydroronaphalen-13(2H)-one, 157$^{72}$

(12R$^*$, 7S$^*$)-10-Methyl-13,14,15,6,7,8,11,12-octahydroronaphalen-13-ol, 158

To a solution of thiophenyl cis-decalin 156 (75.0 mg, 0.280 mmol) in acetone (30.0 mL), was added an excess of unwashed Raney Nickel (0.240 mg, 2.80 mmol) and the reaction was stirred at room temperature for 45 minutes under H$_2$ atm. After this time, the reaction was filtered through a pad of celite with CH$_2$Cl$_2$ (50 mL) and the filtrate was dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in
hexanes) to yield 157 as a pale yellow oil (10.0 mg, 23% yield) and 158 as a white solid (5.0 mg, 11% yield).\(^72\) (12\(R^*\), 75\(S^*\))-10-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 157; \(\text{Rf} = 0.48\) (EtOAc : hexane 10% : 90%). IR (ATR): \(\nu_{\text{max}}\) 2911, 1709 (C=O), 1444, 1375, 1225, 1135, 1024, 597, 497 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.35–5.31 (1H, m, H-9), 2.74–2.68 (1H, m, H-12), 2.39 (1H, dddd, \(J = 14.2, 5.8, 5.8, 0.9\) Hz, H-14), 2.36–2.23 (3H, m, H-11 + H-7 + H-14), 2.07–1.84 (5H, m, H-11 + H-6 + H-15), 1.81–1.68 (2H, m, H-8), 1.69 (3H, s, H-24) ppm. \(^13\)C NMR (500 MHz, CDCl\(_3\)): \(\delta\) 212.9 (C-13), 131.4 (C-10), 119.1 (C-9), 48.9 (C-12), 40.0 (C-14), 35.7 (C-7), 28.6 (C-11), 28.5 (C-8), 27.6 (C-15), 24.3 (C-6), 23.5 (C-24) ppm. MS (ESI): \(m/z\) 187 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 187.1093. \(C_{11}H_{16}NaO\) requires (M+Na\(^+\)) 187.1093. \(m/z\) 165 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 165.1257. \(C_{11}H_{17}O\) requires (M+H\(^+\)) 165.1274. Characterisation of this compound matched the compound reported in the literature.\(^72\) (12\(R^*\), 75\(S^*\))-10-Methyl-13,14,15,6,7,8,11,12-octahydronaphthalen-13-ol, 158; **Melting point** = 74–77 °C. \(\text{Rf} = 0.22\) (EtOAc : hexane 10% : 90%). IR (ATR): \(\nu_{\text{max}}\) 3338 (C=OH), 2923, 2855, 1377, 1447, 1088, 1034, 571 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.37–5.31 (1H, m), 3.82 (1H, ddd, \(J = 10.9, 4.6, 4.6\) Hz), 2.31–2.20 (1H, m), 2.01–1.90 (2H, m), 1.89–1.73 (2H, m), 1.67 (3H, s), 1.64–1.48 (1H, m), 1.47–1.40 (2H, m), 1.39–1.23 (4H, m) ppm. \(^13\)C NMR (400 MHz, CDCl\(_3\)): \(\delta\) 131.3 (C=C), 119.3 (CH), 73.3 (CH), 38.7 (CH), 33.2 (CH\(_2\)), 31.5 (CH), 30.3 (CH\(_2\)), 29.1 (CH\(_2\)), 26.1 (CH\(_2\)), 23.7 (CH\(_2\)), 20.3 (CH\(_3\)) ppm. MS (ESI): \(m/z\) 189 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 189.1251. \(C_{11}H_{18}NaO\) requires (M+Na\(^+\)) 189.1250.
(12S*, 7S*)-10-Methyl-15,6,7,8,11,12-hexahydronaphthalen13(2H) one, 159

To a solution of thiophenyl trans-declalin 137 (171 mg; 0.630 mmol) in acetone (66.0 mL), was added an excess of unwashed Raney Nickel (540 mg, 6.30 mmol) and the reaction was stirred at room temperature for 45 minutes under H₂ atm. After this time, the reaction was filtered through a pad of celite with CH₂Cl₂ (50 mL) and the filtrate was dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield 159 as a white solid (61.0 mg, 60% yield). Melting point = 49‒51 °C. Rf = 0.51 (EtOAc : hexane 10% : 90%). IR (ATR): ν max 2902, 2844, 2828, 1701 (C=O), 1428, 1374, 1236, 1182, 845 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 5.36–5.29 (1H, m, H-9), 2.47–2.41 (1H, dddd, J = 13.5, 4.6, 2.6, 1.8 Hz, H-14), 2.36 (1H, dddd, J = 13.5, 13.5, 5.0, 0.9 Hz, H-14), 2.28–2.13 (3H, m, H-12 + H-8), 2.12–2.02 (2H, m, H-6 + H-11), 1.96–1.85 (2H, m, H-15), 1.76–1.69 (1H, m, H-7), 1.68 (3H, s, H-24), 1.65–1.56 (1H, m, H-11), 1.44 (1H, dddd, J = 13.5, 13.5, 11.4, 3.5 Hz, H-6) ppm. ¹³C NMR (400 MHz, CDCl₃): δ 212.5 (C-13), 133.1 (C-9), 119.3 (C-10), 50.7 (C-12), 42.0 (C-14), 40.4 (C-7), 33.7 (C-8), 32.2 (C-6), 29.2 (C-11), 26.1 (C-15), 23.5 (C-24) ppm. MS (ESI): m/z 187 (M+Na⁺); HRMS: found: (M+Na⁺) 187.1084. C₁₁H₁₆NaO requires (M+Na⁺) 187.1093. Characterisation of this compound matched the compound reported in the literature.⁷²
To a suspension of lithium aluminium hydride (2.07 g, 54.4 mmol) in dry THF (200 mL) at 0 °C, ethyl 4-oxocyclohexane carboxylate 117 (10.0 mL, 54.6 mmol) was added dropwise (10 minutes). The reaction was stirred for 45 minutes and then quenched with water (2.10 mL), followed by 15% sodium hydroxide aqueous solution (2.10 mL), and then more water (4.20 mL) and stirred for a further 30 minutes. MgSO₄ was added and filtered through celite, which was washed with copious amounts of Et₂O and concentrated in vacuo to give the title compound as a white sticky residue which was used directly in the next reaction without further purification.

To a solution of the title compound (8.23 g, 63.2 mmol) in dry CH₂Cl₂ (250 mL), were added imidazole (6.46 g, 94.8 mmol), DMAP (772 mg, 6.30 mmol) and triisopropylsilyl chloride (15.0 mL, 70.1 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, an aqueous solution of 2 M HCl (100 mL) was added and the organic phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried with Na₂SO₄ and concentrated in vacuo to give a mixture of diastereoisomers as a colourless oil. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 165 as a pale yellow oil (8.01 g, 44%) and 166 as a colourless oil (2.50 g, 14%). (13S*, 6S*)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanol, 165; Rf = 0.28 (EtOAc : hexane 10% : 90%). IR (ATR): νmax

(13S*, 6S*)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanol, 165

(13R*, 6S*)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanol, 166
3350 (C-OH), 2924, 2890, 1463, 1254, 881, 679 \text{ cm}^{-1}.^1\text{H NMR} (400 MHz, CDCl$_3$): \delta 3.56 (1H, dddd, J = 10.5, 10.5, 4.1, 4.1 Hz, H-13), 3.52–3.49 (2H, m, H-5), 2.04–1.96 (2H, m, H-12), 1.88–1.79 (3H, m, H-12 + H-7), 1.52–1.40 (1H, m, H-6), 1.33–1.19 (3H, m, H-7), 1.15–0.96 (21H, m, OSiCH(CH$_3$)$_2$) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): \delta 67.9 (C-13), 67.1 (C-5), 39.4 (C-6), 32.0 (C-12), 23.4 (C-7), 18.0 (OSiCH(CH$_3$)$_2$), 12.0 (OSiCH(CH$_3$)$_2$) ppm. MS (ESI): m/z 309 (M+Na$^+$); HRMS: Found (M+Na$^+$) 309.2216. C$_{16}$H$_{34}$NaO$_2$Si requires (M+Na$^+$) 309.2220. m/z 287 (M+H$^+$); Found (M+H$^+$), 287.2392. C$_{16}$H$_{35}$O$_2$Si requires (M+H$^+$) 287.2401. (13R*, 6S*)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanone, 166; Rf = 0.26 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 3261 (C-OH), 2924, 2864, 1463, 1383, 1254, 1111, 1064, 881, 679 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): \delta 4.03–3.97 (1H, m, H-13), 3.56–3.53 (2H, m, H-5), 1.77–1.68 (2H, m, H-12 + H-7), 1.61–1.50 (5H, m, H-12 + H-7 + H-6), 1.46–1.32 (2H, m, H-12 + H-7), 1.13–1.00 (21H, m, OSiCH(CH$_3$)$_2$) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): \delta 68.0 (C-13), 67.1 (C-5), 39.4 (C-6), 32.2 (C-12), 23.4 (C-7), 18.0 (OSiCH(CH$_3$)$_2$), 12.0 (OSiCH(CH$_3$)$_2$) ppm. MS (ESI): m/z 309 (M+Na$^+$); HRMS: Found (M+Na$^+$), 309.2216. C$_{16}$H$_{34}$NaO$_2$Si requires (M+Na$^+$) 309.2220. m/z 287 (M+H$^+$); Found (M+H$^+$), 287.2392. C$_{16}$H$_{35}$O$_2$Si requires (M+H$^+$) 287.2401.

(6S*)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanone, 160

Dimethyl sulfoxide (3.30 mL, 46.9 mmol) was added slowly to a stirred solution of oxalyl chloride (3.81 mL, 45.0 mmol) in dry CH$_2$Cl$_2$ (360 mL) at $-78 \, ^\circ\text{C}$ and stirred for 1 hour. A solution of cyclohexanols 165 and 166 (10.7 g, 37.5 mmol) in dry CH$_2$Cl$_2$ (40.0 mL) was added slowly and the reaction stirred at $-78 \, ^\circ\text{C}$ for 1 hour. After this time, Et$_3$N (26.0 mL, 188 mmol) was added and the mixture was warmed to room temperature and after a further 2.5 hours, water (20 mL) was added, followed by aqueous solution of 2 M HCl (100 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 100 mL) and the
combined organic layers were washed with aqueous solution of 2 M HCl (50 mL) and brine (20 mL), dried with Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 160 as a pale yellow oil (10.6 g, 98% yield). Rf = 0.39 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 2942, 2865, 1716 (C=O), 1463, 1120, 1103, 881, 680, 658 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.66‒3.64 (2H, m, H-5), 2.42 (2H, dddd, $J = 14.8, 4.7, 3.3, 1.8$ Hz, H-12), 2.35 (2H, ddd, $J = 14.8, 12.9, 6.1$ Hz, H-12), 2.11 (2H, dddd, $J = 13.2, 6.2, 6.1, 3.3$ Hz, H-7), 1.95 (1H, dddddd, $J = 12.9, 12.9, 6.2, 6.2, 3.3, 3.3$ Hz, H-6), 1.47 (2H, dddd, $J = 13.2, 12.9, 12.9, 4.7$ Hz, H-7), 1.15‒1.03 (21H, m, OSiCH(CH$_3$)$_2$) ppm. $^{13}$C NMR (500 MHz, CDCl$_3$): $\delta$ 212.4 (C-13), 67.3 (C-5), 40.6 (C-12), 39.0 (C-6), 29.2 (C-7), 18.0 (OSiCH(CH$_3$)$_2$), 11.9 (OSiCH(CH$_3$)$_2$) ppm. MS (ESI): m/z 307 (M+Na$^+$); HRMS: Found (M+Na$^+$), 307.2070. C$_{16}$H$_{32}$NaO$_2$Si requires (M+Na$^+$) 307.2064. m/z 285 (M+H$^+$); Found (M+H$^+$), 285.2249. C$_{16}$H$_{33}$O$_2$Si requires (M+H$^+$) 285.2244.

(6S*)-6-(((Triisopropylsilyl)oxy)methyl)cyclohex-13-enone, 115

[Image of the compound]

Example procedure for re-addition experiment

To a solution of cyclohexanone 160 (1.67 g, 5.88 mmol) in chlorobenzene (60.0 mL) were added Pd(OAc)$_2$ (66.0 mg, 0.290 mmol) and 4,4’-Bu-2,2’-dipyridyl (79.0 mg, 0.290 mmol) and the reaction was stirred at 120 °C in an aluminium drysyn® under a O$_2$ balloon. After 72 hours, additional Pd(OAc)$_2$ (66.0 mg, 0.290 mmol) and 4,4’-di-tert-butyl-2,2’-dipyridyl (79.0 mg, 0.290 mmol) were added and the O$_2$ balloon refreshed. After a further 44 hours, additional Pd(OAc)$_2$ (66.0 mg, 0.290 mmol) and 4,4’-di-tert-butyl-2,2’-dipyridyl (79.0 mg, 0.290 mmol) were added and the O$_2$ balloon refreshed. The reaction was stirred for a further 45 hours, then concentrated in vacuo to give a brown oil (2.50 g). The crude
product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) and by kugelrohr distillation to yield 115 as a pale yellow oil (1.17 g, 70% yield).

Example reaction for nitrate experiment

To a solution of cyclohexanone 160 (10.6 g, 37.5 mmol) in chlorobenzene (375 mL), were added Pd(OAc)₂ (420 mg, 1.88 mmol), 4,4'-Bu-2,2'-dipyridyl (510 mg, 1.88 mmol) and KNO₃ (1.90 g, 18.8 mmol) and the reaction was stirred at 120 °C in an aluminium drysyn® under a balloon of O₂. After 48 hours, additional Pd(OAc)₂ (420 mg, 1.88 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (510 mg, 1.88 mmol) were added and the O₂ balloon refreshed. The O₂ balloon was refreshed every 24 hours and after a further 5 days, the reaction was cooled to room temperature and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) and by kugelrohr distillation to yield 115 as a pale yellow oil (9.0 g, 85% yield, 92% conversion).

B.P. 147 °C @ 0.6 mbar; Rf = 0.38 (EtOAc : hexane 10% : 90%). IR (ATR): νmax 2942, 2891, 2865, 1682 (C=O), 1462, 1389, 1110, 881, 783, 681 cm⁻¹.¹H NMR (400 MHz, CDCl₃): δ 7.00 (1H, ddd, J = 10.2, 2.7, 1.4 Hz, H-7), 6.05 (1H, dd, J = 10.2, 2.5 Hz, H-12), 3.76 (1H, dd, J = 9.6, 6.4 Hz, H-5), 3.68 (1H, dd, J = 9.6, 6.9 Hz, H-5), 2.63 (1H, dddddd, J = 9.6, 6.9, 6.4, 4.6, 2.7, 2.5 Hz, H-6), 2.54 (1H, ddd, J = 16.5, 4.6, 4.6 Hz, H-14), 2.39 (1H, ddd, J = 16.5, 12.8, 5.0 Hz, H-14), 2.10 (1H, dddddd, J = 13.3, 5.0, 4.6, 4.6, 1.4 Hz, H-15), 1.79 (1H, ddddd, J = 13.3, 12.8, 9.6, 4.6 Hz, H-15), 1.15–1.00 (21H, m, OSiCH(CH₃)₂) ppm. ¹³C NMR (400 MHz, CDCl₃): δ 199.9 (C-13), 152.1 (C-7), 129.8 (C-12), 65.8 (C-5), 29.4 (C-14), 36.7 (C-6), 25.4 (C-15), 17.9 (OSiCH(CH₃)₂), 11.8 (OSiCH(CH₃)₂) ppm. MS (ESI): m/z 305 (M+Na⁺); HRMS: Found (M+Na⁺), 305.1899 C₁₆H₃₁NaO₂Si requires (M+Na⁺) 305.1907. m/z 283 (M+H⁺); Found (M+H⁺), 283.2083. C₁₆H₂₂O₂Si requires (M+H⁺) 283.2088.
To solution of enone 115 (282 mg, 1.00 mmol) in dry CH$_2$Cl$_2$ (5.0 mL), was added a 1.0 M solution of EtAlCl$_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. After this time, isoprene 133 (1.00 mL, 10.0 mmol) was added and the reaction was stirred at 30°C for a further 8 hours. Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 191 as a pale yellow oil (61.0 mg, 17% yield) and 192 as a pale yellow oil (80.0 mg, 23% yield). (12R*, 7R*, 6S*)-9-Methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahyronaphthalen-13(2H)-one 191; $R_f$ = 0.34 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 2866, 1707 (C=O), 1110, 905, 729, 646, 597 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.38–5.35 (1H, m, H-10), 3.88 (1H, dd, $J = 9.3, 5.3$ Hz, H-5), 3.84 (1H, dd, $J = 9.3, 3.2$ Hz, H-5), 2.77–2.68 (1H, m, H-12), 2.52–2.44 (1H, m, H-11), 2.42–2.32 (3H, m, H-14 + H-6), 2.01–1.81 (5H, m, H-8 + H-11 + H-7 + H-15), 1.76–1.65 (1H, m, H-15), 1.63 (3H, s, H-24), 1.15–1.11 (21H, m, OSiCH(CH$_3$)$_2$) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 213.5 (C-13), 132.0 (C-9), 118.7 (C-10), 65.5 (C-5), 45.2 (C-12), 42.6 (C-7), 39.0 (C-14), 37.4 (C-6), 36.5 (C-8), 33.1 (C-11), 25.9 (C-15), 23.7 (C-24), 18.0
To a solution of trans-decalin 192 (15 mg, 0.040 mmol) in dry methanol (2.0 mL) and 3Å molecular sieves, were added 2,4-dinitrophenylhydrazine 140 (15 mg, 0.080 mmol) and glacial acetic acid (0.25 mL). The reaction was stirred at 50 °C for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of NaHCO₃ (5 mL) and the organic layer was extracted with CH₂Cl₂ (3 × 10 mL) dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 20% EtOAc in hexane) to yield 193 as an orange solid (14 mg, 67% yield). Crystalization method attempted: slow evaporation of solvent from a solution of 193 in a
minimum amount of CHCl₃ and solvent/antisolvent system such as EtOAc/hexane and CH₂Cl₂/hexane.

**Melting point** = 140–142 °C. **Rf** = 0.61 (EtOAc : hexane 10% : 90%). **IR** (ATR): vₐₘₐₓ 3323, 2940, 2864, 1616 (C=N), 1518, 1461, 1116, 871 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃): δ 11.28 (1H, s, N-H), 9.14 (1H, d, J = 2.3 Hz, Ar-H), 8.31 (1H, dd, J = 9.6, 2.3 Hz, Ar-H), 7.98 (1H, d, J = 9.6 Hz, Ar-H), 5.52–5.48 (1H, m, H-10), 3.84 (1H, dd, J = 9.6, 3.4 Hz, H-5), 3.66 (1H, dd, J = 9.6, 5.0 Hz, H-5), 2.98 (1H, ddd, J = 14.7, 3.7, 3.7 Hz, H-14), 2.48–2.32 (2H, m, H-11), 2.31–2.19 (3H, m, H-12 + H-8 + H-14), 2.18–2.08 (2H, m, H-15), 1.94–1.82 (1H, m, H-8), 1.70 (3H, s, H-24), 1.65–1.49 (2H, m, H-6 + H-7), 1.15–0.99 (21H, m, OSiCH(CH₃)₂) ppm. **¹³C NMR** (400 MHz, CDCl₃): δ 161.9 (C=N), 145.6 (C-9), 137.5 (Ar), 132.1 (Ar), 129.9 (Ar), 128.9 (Ar-H), 123.6 (Ar-H), 120.0 (C-10), 116.4 (Ar-H), 64.6 (C-5), 45.2 (C-6), 43.6 (C-12), 40.3 (C-7), 36.4 (C-8), 28.5 (C-15), 26.9 (C-11), 26.5 (C-14), 23.4 (C-24), 18.0 (OSiCH(CH₃)₂), 11.9 (OSiCH(CH₃)₂) ppm. **MS** (ESI): m/z 529 (M-H⁺); HRMS: found: (M-H⁺) 529.2863. C₂₇H₄₁N₄O₅Si requires (M-H⁺) 529.2852.

(12R*, 7R*, 6S*)-10-Methyl-9-(phenylthio)-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 194

To a solution of enone 115 (854 mg, 3.02 mmol) in dry CH₂Cl₂ (7.5 mL), was added a 1.0 M solution of EtAlCl₂ in hexane (0.60 mL, 0.60 mmol). After 10 minutes, a solution of sulfur substituted diene 116 (5.30 g, 30.2 mmol) in dry CH₂Cl₂ (7.5 mL) was added and the reaction was stirred at room temperature for 1 hour. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified.
by silica gel flash column chromatography (2% to 5% EtOAc in hexane) to yield 194 as a yellow oil (1.18 g, 85% yield). \( \text{Rf} = 0.48 \) (EtOAc : hexane 10% : 90%). \( \text{IR (ATR): } \nu_{\text{max}} 2925, 2864, 1703 \text{ (C=O), 1582, 1476, 1104, 1068, 882, 739 cm}^{-1} \). \( ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.26‒7.22 \) (2H, m, Ar-\( H \)), 7.17‒7.10 (3H, m, Ar-\( H \)), 3.82 (1H, dd, \( J = 9.9, 5.9 \text{ Hz, H-5} \)), 3.78 (1H, dd, \( J = 9.9, 6.1 \text{ Hz, H-5} \)), 2.90 (1H, ddd, \( J = 6.1, 5.8, 3.2 \text{ Hz, H-12} \)), 2.71 (1H, dd, \( J = 17.2, 3.2 \text{ Hz, H-11} \)), 2.47 (1H, ddd, \( J = 9.5, 9.5, 6.1, 4.9 \text{ Hz, H-7} \)), 2.40‒2.30 (2H, m, H-14), 2.21‒2.12 (3H, m, H-8 + H-11), 2.00 (3H, s, H-24), 1.98‒1.87 (2H, m, H-15), 1.78‒1.72 (1H, m, H-6), 1.11‒0.98 (21H, m, OSiCH(CH\(_3\))\(_2\)) ppm. \( ^{13}\text{C NMR (500 MHz, CDCl}_3\text{): } \delta 212.4 \) (C-13), 140.1 (C-9), 136.4 (Ar), 128.9 (Ar-\( H \)), 127.9 (Ar-\( H \)), 125.3 (Ar-\( H \)), 121.1 (C-10), 65.1 (C-5), 45.4 (C-12), 38.9 (C-6), 37.4 (C-7), 37.4 (C-14), 35.0 (C-8), 31.2 (C-11), 25.4 (C-15), 21.3 (C-24), 18.0 (OSiCH(CH\(_3\))\(_2\)), 11.9 (OSiCH(CH\(_3\))\(_3\)) ppm. \( \text{MS (ESI): } m/z \) 481 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 481.2552. C\(_{27}\)H\(_{42}\)NaO\(_2\)SSi requires (M+Na\(^+\)) 481.2567. m/z 459 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 459.2750. C\(_{27}\)H\(_{43}\)O\(_2\)SSi requires (M+H\(^+\)) 459.2748.

(125\(^*\), 7R\(^*\), 6S\(^*\))-10-Methyl-9-((phenylthio)-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12 hexahydonaphthalen-13(2H)-one, 195

To a solution of thiophenyl cis-decalin 194 (542 mg, 1.18 mmol) in dry CH\(_2\)Cl\(_2\) (6.0 mL), was added a 1.0 M solution of EtAlCl\(_2\) in hexane (0.30 mL, 0.30 mmol) and the reaction was stirred at room temperature for 3 days. After this time, Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 195 as an
orange oil (459 mg, 84% yield). \( \text{Rf} = 0.48 \) (EtOAc : hexane 10% : 90%). \( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.27–7.21 (2H, m, Ar-H) 7.20–7.11 (3H, m, Ar-H), 3.65 (1H, dd, \( J \) = 10.1, 3.2 Hz, H-5), 3.61 (1H, dd, \( J \) = 10.1, 5.0 Hz, H-5), 2.57–2.42 (4H, m, H-14 + H-8 + H-11), 2.41–2.23 (2H, m, H-12 + H-11), 2.19–2.08 (2H, m, H-15 + H-8), 2.00 (3H, s, H-24), 1.87–1.70 (2H, m, H-15 + H-7), 1.70–1.60 (1H, m, H-6), 1.01–0.89 (21H, m, OSiCH(CH\(_3\))\(_2\)) ppm. \( ^{13} \text{C NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 211.6 (C-13), 140.5 (C-9), 136.0 (Ar), 128.9 (Ar-H), 128.1 (Ar-H), 125.5 (Ar-H), 121.5 (C-10), 64.1 (C-5), 48.9 (C-12), 44.6 (C-6), 41.5 (C-7), 41.1 (C-14), 37.9 (C-8), 32.3 (C-11), 29.8 (C-15), 21.5 (C-24), 17.9 (OSiCH(CH\(_3\))\(_2\)), 11.8 (OSiCH(CH\(_3\))\(_2\)) ppm. \( \text{MS} \) (ESI): m/z 481 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 481.2572. C\(_{27}\)H\(_{42}\)NaO\(_2\)SSi requires (M+Na\(^+\)) 481.2567. m/z 459 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 459.2753. C\(_{27}\)H\(_{43}\)O\(_2\)SSi requires (M+H\(^+\)) 459.2748.

(125*, 7R*, 6S*)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **114**

To a solution of sulfur trans-decalin **195** (401 mg, 0.880 mmol) in acetone (88.0 mL), was added an excess of unwashed Raney Nickel (0.754 mg, 8.80 mmol) and the reaction was stirred at room temperature for 40 minutes under H\(_2\) atm. After this time, the reaction was filtered through celite with CH\(_2\)Cl\(_2\) (50 mL) and the filtrate was dried with Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (1% to 2% EtOAc in hexane) to yield **114** as a white solid (238 mg, 77% yield). **Melting point** = 51–53 °C. \( \text{Rf} = 0.58 \) (EtOAc : hexane 10% : 90%). \( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 5.37–5.26 (1H, m, H-9), 3.83 (1H, dd, \( J \) = 9.9, 2.5 Hz, H-5), 3.65 (1H, dd, \( J \) = 9.9, 5.5 Hz, H-5), 2.47–2.45 (2H, m, H-14), 2.38–2.14 (5H, m, H-12 + H-11 + H-15 + H-7 + H-8), 2.08–2.04 (1H, m, H-11),
1.94‒1.83 (1H, m, H-8), 1.68 (3H, s, H-24), 1.66‒1.59 (1H, m, H-6 + H-15), 1.10‒1.02 (21H, m, OSiCH(CH$_3$)$_2$) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): δ 212.5 (C-13), 132.9 (C-10), 119.0 (C-9), 64.6 (C-5), 49.3 (C-12), 45.0 (C-6), 41.2 (C-14), 40.1 (C-7), 31.6 (C-8), 29.9 (C-11), 29.5 (C-15), 23.4 (C-24), 18.0 (OSiCH(CH$_3$)$_2$), 11.9 (OSiCH(CH$_3$)$_2$) ppm. MS (ESI): m/z 373 (M+Na$^+$); HRMS: found: (M+Na$^+$) 373.2527. C$_{21}$H$_{38}$NaO$_2$Si requires (M+Na$^+$) 373.2533.

To a solution of trans-decalin 114 (25 mg, 0.070 mmol) in dry methanol (4.0 mL) and 3Å molecular sieves, were added 2,4-dinitrophenylhydrazine 140 (28 mg, 0.14 mmol) and glacial acetic acid (0.50 mL). The reaction was stirred at 50 °C for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of NaHCO$_3$ (5 mL) and the organic layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL) dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 20% EtOAc in hexane) to yield 196 as an orange solid (26 mg, 70% yield). Crystallization method: slow evaporation of solvent from a solution of 196 in a minimum amount of CHCl$_3$. Melting point = 71‒73 °C. Rf = 0.61 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 3006, 2942, 2864, 1617 (C=N), 1518, 1422, 1333, 1119, 1092 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 11.29 (1H, s, N-H), 9.15 (1H, d, J = 2.8 Hz, Ar-H), 8.34 (1H, dd, J = 9.6, 2.8 Hz, Ar-H), 8.00 (1H, d, J = 9.6 Hz, Ar-H), 5.41‒5.37 (1H, m, H-9), 3.83 (1H, dd, J = 10.1, 2.8 Hz, H-5), 3.64 (1H, dd, J = 10.1, 5.5 Hz, H-5), 3.01 (1H, ddd, J = 14.2, 3.2, 3.2 Hz, H-14), 2.45‒2.30 (4H, m, H-12 + H-11 + H-8), 2.29‒2.20 (1H, m, H-14), 2.18‒
2.03 (1H, m, H-15), 1.94–1.82 (1H, m, H-8), 1.78 (3H, s, H-24), 1.57–1.49 (3H, m, H-6 + H-7 + H-15), 1.09–1.02 (21H, m, OSiCH(CH3)2) ppm. $^{13}$C NMR (400 MHz, CDCl3): δ 162.1 (C=N), 145.6 (C-10), 137.5 (Ar), 132.9 (Ar), 130.0 (Ar), 128.9 (Ar-H), 123.4 (Ar-H), 119.2 (C-9), 116.4 (Ar-H), 64.6 (C-5), 45.2 (C-6), 44.0 (C-12), 39.8 (C-7), 31.7 (C-8), 31.5 (C-11), 28.6 (C-15), 26.5 (C-14), 23.7 (C-24), 18.0 (OSiCH(CH3)2), 11.9 (OSi(CH3)2) ppm. MS (ESI): m/z 529 (M-H+); HRMS: found: (M-H+) 529.2847. C$_{27}$H$_{41}$N$_4$O$_5$Si requires (M-H+) 529.2852.

Triethyl-(((8S*, 7S*)-9-methyl,15,6,7,8,11,12-hexahydronaphthalen-13-yl)oxy)silane, 202

To a solution of freshly distilled diisopropylamine (0.12 mL, 0.83 mmol) in dry THF (0.80 mL) at −78 °C, was added n-BuLi (0.390 mL, 2.11 M) and the solution was stirred at −78 °C for 30 minutes. A solution of the model trans-decalin 139 (106 mg, 0.640 mmol) in dry THF (2.41 mL) was added to the LDA solution and stirred at −78 °C for 1 hour. After this time, freshly distilled TESCl (0.15 mL, 0.89 mmol) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to warm to room temperature for 30 minutes. The reaction was then quenched with water (2 mL), extracted with Et$_2$O (20 mL) and the organic layer was dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield 202 as a pale yellow oil (138 mg, 78% yield). $R_f = 0.88$ (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 2954, 2875, 1412, 1243, 1196 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl3): δ 5.45–5.41 (1H, m, H-10), 4.81–4.78 (1H, m, H-14), 2.38 (1H, ddd, $J = 17.4, 4.7, 4.7$ Hz, H-11), 2.17–1.89 (5H, m, H-12 + H-6 + H-15 + H-7), 1.85–1.73 (3H, m, H-11 + H-8), 1.68 (3H, s, H-24), 0.68 (9H, t, $J = 8.1$ Hz, OSiCH$_2$CH$_3$), 0.52 (6H, q, $J = 8.1$ Hz, OSi(CH$_2$CH$_3$) ppm. $^{13}$C NMR (400 MHz, CDCl3): δ 152.6 (C-13), 133.9 (C-9), 121.3 (C-10), 102.9 (C-14), 41.2 (C-12), 38.1 (C-8), 37.5 (C-7), 29.3 (C-11), 29.2 (C-6), 23.7 (C-15), 23.2 (C-24), 6.4 (OSiCH$_2$CH$_3$), 4.4
(OSi(CH₂)₃) ppm. MS (ESI): m/z 279 (M+H⁺); HRMS: found: (M+H⁺) 279.2141. C₁₇H₃₁O requires (M+H⁺) 279.2139.

(125°, 75°)-9-Methyl-7,8,11,12-tetrahydronaphthalen-13(4H)-one, 179

**Ito-Saegusa conditions**

To a solution of TES-enol trans-decalin 202 (781 mg, 2.81 mmol) in dry DMSO (14.0 mL), was added Pd(OAc)₂ (378 mg, 1.69 mmol) and the reaction was stirred at room temperature for 1 day under an O₂ atm. After this time, the reaction was diluted with water (10 mL) and extracted with hexane (4 × 50 mL). The reunited organic layers were washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexane) to yield 179 as an orange oil (234 mg, 52% yield).

**IBX conditions**

To a solution of TES-enol trans-decalin 202 (122 mg, 0.440 mmol) in dry DMSO (7.0 mL), was added IBX (616 mg, 2.20 mmol) and the reaction was stirred at 40 °C for 16 hours. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of NaHCO₃ (10 mL) and extracted with hexane (4 × 10 mL). The reunited organic layers were washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexane) to yield 179 as an orange oil (88.0 mg, 62% yield).

**Direct palladium oxidation conditions**

To a solution of trans-decalin 139 (100 mg, 0.610 mmol) in dry chlorobenzene (6.0 mL), were added Pd(OAc)₂ (7.0 mg, 3.0 μmol), 4,4’-Bu-2,2’-dipyridyl (8.0 mg, 3.0 μmol) and KNO₃ (31 mg, 0.030 mmol)
and the reaction was stirred at 120 °C for 7 days under an O₂ atm. After this time, the solvent was removed in vacuo and the crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexane) to yield 179 as an orange oil (23.0 mg, 23% yield).

**Rf** = 0.39 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν max 2923, 1668 (C=O), 1549, 1434, 1386, 1291, 1115, 772 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃): δ 6.97 (1H, ddd, J = 10.1, 6.2, 1.6 Hz, H-15), 6.05 (1H, dd, J = 10.1, 3.2 Hz, H-14), 5.49–5.38 (1H, m, H-10), 2.56–2.45 (2H, m, H-6 + H-11), 2.27–1.91 (6H, m, H-11 + H-12 + H-8 + H-7 + H-6), 1.67 (3H, s, H-24) ppm. **¹³C NMR** (400 MHz, CDCl₃): δ 201.2 (C-13), 148.8 (C-15), 132.0 (C-9), 129.8 (C-14), 120.1 (C-10), 46.3 (C-12), 37.4 (C-8), 35.6 (C-7), 33.0 (C-6), 25.3 (C-11), 23.2 (C-24) ppm. **MS** (ESI): m/z 185 (M+Na⁺); HRMS: found: (M+Na⁺) 185.0930. C₁₁H₁₄NaO requires (M+Na⁺) 185.0937. m/z 163 (M+H⁺); HRMS: found: (M+H⁺) 163.1120. C₁₁H₁₃O requires (M+H⁺) 163.1117.

(13S*, 12S*, 7S*)-9-Methyl-13,6,7,8,11,12-hexahydronaphthalen-13-ol, 224

To a solution of enone trans-decalin 179 (47.0 mg, 0.290 mmol) in dry MeOH (3.0 mL) at 0 °C, was added CeCl₃·7H₂O (108 mg, 0.290 mmol) and stirred for 10 minutes. Solid NaBH₄ (11.0 mg, 0.290 mmol) was added and the mixture was stirred for further 10 minutes. After this time, the reaction was quenched with saturated aqueous solution of NH₄Cl (7 mL) at 0 °C and allowed to warm to room temperature for 40 minutes at which time the mixture was diluted further with water (5 mL) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield 224 as a white solid (30.0 mg, 62% yield). **Melting point** = 73–75°C. **Rf** = 0.35 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν max 3348 (C-OH), 2922, 1435, 1178, 1089, 1026, 959, 772 cm⁻¹. **¹H NMR** (400 MHz, C₆D₆): δ 5.65 (1H, ddd, J = 10.1, 3.3,
1.5 Hz, H-14), 5.55 (1H, dddd, J = 10.1, 4.8, 2.0, 2.0 Hz, H-15), 5.41–5.37 (1H, m, H-10), 3.77–3.71 (1H, m, H-13), 2.64–2.55 (1H, m, H-11), 1.97–1.89 (1H, m, H-7), 1.81–1.66 (2H, m, H-8), 1.57 (3H, s, H-24), 1.52–1.48 (2H, m, H-6), 1.39–1.31 (2H, m, H-12 + H-11) ppm. $^{13}$C NMR (400 MHz, C$_6$D$_6$): $\delta$ 132.9 (C-9), 132.5 (C-14), 127.7 (C-15), 121.2 (C-10), 74.7 (C-13), 42.8 (C-12), 38.3 (C-8), 33.4 (C-6), 33.2 (C-7), 31.4 (C-11), 24.2 (C-24) ppm. 

MS (ESI): m/z 187 (M+Na$^+$); HRMS: found: (M+Na$^+$) 187.1095. C$_{11}$H$_{16}$NaO requires (M+Na$^+$) 187.1093.

(13$^S$, 12$^S$, 7$^S$)-9-Methyl-13,6,7,8,11,12-hexahyronaphthalen-13-yl propionate, 227

To a solution of hydroxyl trans-decalin 224 (24.0 mg, 0.150 mmol) in pyridine (1.50 mL), were added DMAP (4.0 mg, 0.030 mmol) and propionyl chloride 216 (0.13 mL, 1.5 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the reaction was diluted with EtOAc (10 mL) and the pyridine was removed by washing with saturated aqueous solution of Cu$_2$SO$_4$ (3 × 10 mL). The organic layer was washed with water (4 × 10 mL) and brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield 227 as a pale yellow oil (20.0 mg, 61% yield). Rf = 0.82 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{max}$ 2913, 2849, 1735 (C=O), 1179, 597 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.82 (1H, dddd, J = 10.1, 5.0, 2.0, 2.0 Hz, H-14), 5.56 (1H, dddd, J = 10.1, 3.2, 1.5, 1.5 Hz, H-15), 5.42–5.32 (1H, m, H-10), 5.21–5.16 (1H, m, H-13), 2.36 (2H, q, J = 7.4 Hz, H-16), 2.31–2.20 (2H, m, H-6), 2.09–2.05 (1H, m, H-11), 1.93–1.84 (5H, m, H-11 + H-7 + H-8 + H-12), 1.65 (3H, s, H-24), 1.16 (3H, t, J = 7.4 Hz, H-25) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 174.6 (C-17), 132.7 (C-9), 129.4 (C-15), 126.8 (C-14), 119.6 (C-10), 76.1 (C-13), 34.1 (C-12), 30.1 (C-11), 29.5 (C-6), 29.4 (C-7), 27.9 (C-8), 23.4 (C-16), 22.7 (C-25), 25.0 ppm.
9.3 (C-24) ppm. **MS** (ESI): m/z 243 (M+Na⁺); HRMS: found: (M+Na⁺) 243.1365. C₁₄H₂₀NaO₂ requires (M+Na⁺) 243.1356.

(135*, 125*, 7S*)-9-Methyl-13,6,7,8,11,12-hexahyronaphthalen-13-yl acetate, **226**

To a solution of hydroxyl *trans*-decalin **224** (17.0 mg, 0.110 mmol) in pyridine (1.0 mL), were added DMAP (3.0 mg, 0.020 mmol) and acetyl chloride **225** (0.10 mL, 1.0 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the reaction was diluted with EtOAc (10 mL) and the pyridine was removed by washing with saturated aqueous solution of Cu₂SO₄ (3 × 10 mL). The organic layer was washed with water (4 × 10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield **226** as a pale yellow oil (17.0 mg, 76% yield). **Rf** = 0.80 (EtOAc : hexane 10% : 90%). **IR** (ATR): νₘₐₓ 2962, 2907, 2830, 1731 (C=O), 1435, 1370, 1235, 1020 cm⁻¹. **¹H NMR** (400 MHz, C₆D₆): δ 5.73 (1H, dddd, J = 10.1, 3.5, 2.0, 1.3 Hz, H-14), 5.59 (1H, dddd, J = 10.1, 5.0, 2.0, 2.0 Hz, H-15), 5.39–5.33 (1H, m, H-13), 5.32–5.29 (1H, m, H-10), 2.40–2.33 (1H, m, H-11), 1.87 (1H, dddd, J = 17.6, 5.0, 5.0, 1.7, 1.7 Hz, H-7), 1.80–1.75 (2H, m, H-12 + H-6), 1.77 (3H, s, H-16), 1.73–1.67 (2H, m, H-11 + H-8), 1.53 (3H, s, H-24), 1.51–1.41 (2H, m, H-8 + H-6) ppm. **¹³C NMR** (400 MHz, C₆D₆): δ 170.3 (C-17), 132.4 (C-9), 129.2 (C-15), 127.5 (C-14), 120.0 (C-10), 76.3 (C-13), 38.8 (C-12), 37.4 (C-8), 32.9 (C-6), 32.5 (C-7), 30.5 (C-11), 23.4 (C-24), 20.8 (C-16) ppm. **MS** (ESI): m/z 229 (M+Na⁺); HRMS: found: (M+Na⁺) 229.1204. C₁₃H₁₆NaO₂ requires (M+Na⁺) 229.1199.
To a solution of freshly distilled diisopropylamine (0.200 mL, 1.42 mmol) in dry THF (1.42 mL) at –78 °C, was added n-BuLi (0.72 mL, 1.97 M) and the solution was stirred at –78 °C for 30 minutes. A solution of trans-decalin 114 (414 mg, 1.18 mmol) in dry THF (4.48 mL) was added and the mixture was stirred at –78 °C for 1 hour. After this time, distilled TESCl (0.260 mL, 1.53 mmol) was added and the reaction was stirred at –78 °C for a further 30 minutes and then allowed to warm to room temperature for 30 minutes. The reaction was then quenched with water (2 mL) and extracted with of Et₂O (20 mL). The organic layer was dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield 203 as a colourless oil (401 mg, 79% yield). Rf = 0.91 (EtOAc : hexane 10% : 90%). IR (ATR): νmax 2957, 1462, 1378, 1199, 1092, 904, 649 cm⁻¹. 1H NMR (400 MHz, CDCl₃): δ 5.41–5.33 (1H, m, H-9), 4.84 (1H, ddd, J = 5.6, 1.6, 1.6 Hz, H-14), 3.77 (1H, dd, J = 9.6, 3.4 Hz, H-5), 3.59 (1H, dd, J = 9.6, 6.1 Hz, H-5), 2.31–2.27 (1H, m, H-11), 2.24–1.97 (4H, m, H-8 + H-15 + H-12), 1.80–1.71 (2H, m, H-15 + H-11), 1.68 (3H, s, H-24), 1.53–1.40 (2H, m, H-7 + H-6), 1.11–1.03 (21H, m, OSiCH(CH₃)₂), 0.99 (9H, t, J = 8.1 Hz, OSiCH₂CH₃), 0.69 (6H, q, J = 8.1 Hz, OSiCH₂CH₃) ppm. 13C NMR (400 MHz, CDCl₃): δ 151.9 (C-13), 134.1 (C-10), 120.3 (C-9), 102.2 (C-14), 65.1 (C-5), 41.4 (C-12), 41.1 (C-6), 38.2 (C-7), 34.1 (C-11), 30.2 (C-8), 27.7 (C-15), 23.7 (C-24), 18.1 (OSiCH(CH₃)₂), 11.9 (OSiCH₂(CH₃)₂), 6.8 (OSiCH₂CH₃), 5.1 (OSiCH₂CH₃) ppm. MS (ESI): m/z 487 (M+Na⁺); HRMS: found: (M+Na⁺) 487.3375. C₂₇H₅₉NaO₃Si₂ requires (M+Na⁺) 487.3398. m/z 465 (M+H⁺); HRMS: found: (M+H⁺) 465.3579. C₂₇H₅₉O₃Si₂ requires (M+H⁺) 465.3578.
(12S*, 7R*, 6S*)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-7,8,11,12-tetrahydronaphthalen-13(4H)-one, 113

Ito-Saegusa oxidation

To a solution of TES-enol trans-decalin 203 (234 mg, 0.500 mmol) in dry DMSO (2.5 mL), was added Pd(OAc)$_2$ (67 mg, 0.30 mmol) and the reaction was stirred at room temperature for 2 days under O$_2$ atm. After this time, the reaction was diluted with water (10 mL) and extracted with MTBE (3 × 30 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexane) to yield 113 as a yellow solid (82.0 mg, 47% yield).

Direct oxidation

To a solution of trans-decalin 114 (100 mg, 0.290 mmol) in dry chlorobenzene (3.0 mL), were added Pd(OAc)$_2$ (3 mg, 0.02 mmol), 4,4’-tBu-2,2’-dipyridyl (4 mg, 0.02 mmol) and KNO$_3$ (12 mg, 0.15 mmol) and the reaction was stirred at 120 °C for 7 days under O$_2$ atm. After this time, the solvent was removed in vacuo and the crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexane) to yield 113 as a yellow solid (20 mg, 20% yield).

IBX oxidation

To a solution of TES-enol trans-decalin 203 (401 mg, 0.860 mmol) in dry DMSO (7.2 mL), was added IBX (605 mg, 2.16 mmol) and the reaction was stirred at 40 °C for 2 days. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of NaHCO$_3$ (5 mL) and extracted with MTBE (5 × 30 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexane) to yield 113 as a yellow solid (188 mg, 63% yield). **Melting point** = 48–50 °C. **Rf** = 0.56 (EtOAc : hexane 10% : 90%). IR
(ATR): \( \nu_{\text{max}} \) 2942, 2891, 2865, 1671 (C=O), 1462, 1112, 1068, 731 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.09 (1H, dd, \( J = 10.2, 1.8 \) Hz, H-15), 6.09 (1H, dd, \( J = 10.2, 2.8 \) Hz, H-14), 5.37–5.34 (1H, m, H-9), 3.98 (1H, dd, \( J = 9.8, 4.1 \) Hz, H-5), 3.66 (1H, dd, \( J = 9.8, 7.1 \) Hz, H-5), 2.47–2.30 (4H, m, H-11 + H-6 + H-12), 2.09–1.84 (3H, m, H-7 + H-8), 1.71 (3H, s, H-24), 1.13–1.01 (21H, m, OSiCH(CH\(_3\))\(_2\)) ppm. \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \( \delta \) 201.2 (C-13), 152.1 (C-15), 133.2 (C-10), 129.1 (C-14), 118.7 (C-9), 63.7 (C-5), 45.9 (C-12), 45.8 (C-6), 36.1 (C-7), 31.0 (C-8), 30.1 (C-11), 23.4 (C-24), 17.9 (OSiCH(CH\(_3\))\(_2\)), 11.9 (OSiCH(CH\(_3\))\(_2\)) ppm. MS (ESI): m/z 371 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 371.2356. \( \text{C}_{21}\text{H}_{36}\text{NaO}_2\text{Si} \) requires (M+Na\(^+\)) 371.2377. m/z 349 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 349.2538. \( \text{C}_{21}\text{H}_{37}\text{O}_2\text{Si} \) requires (M+H\(^+\)) 349.2557.

**Tsuji Trost conditions**

To a solution of Pd(OAc)\(_2\) (1.0 mg, 2.0 \( \mu \)mol) and PPh\(_3\) (1.0 mg, 3.0 \( \mu \)mol) in dry THF (0.20 mL), was added a solution of acetate trans-decalin 236 (11 mg, 0.030 mmol) in dry THF (0.20 mL) and the reaction was stirred at room temperature for 10 minutes. After this time, a pre-cooled solution at 0 °C of dimethylmalonate (4 \( \mu \)L, 0.04 mmol) and NaH (60% dispersion in mineral oil, 6.0 mg, 0.10 mmol) in dry THF (0.20 mL) was added and the reaction was stirred at 60 °C for 16 hours. The reaction was cooled to room temperature and diluted with Et\(_2\)O (10 mL), washed with water (2 × 10 mL) and brine (10 mL), dried with Na\(_2\)SO\(_4\), filtered and concentrated \( \text{in vacuo} \). The crude product was purified by silica gel flash column chromatography (3% to 20% EtOAc in hexanes) to yield 113 as a yellow solid (4.0 mg, 38% yield) and 232 as a pale yellow oil (3.0 mg, 29% yield).
To a solution of enone *trans*-decalin 113 (30 mg, 0.090 mmol) in dry THF (0.90 mL) at −78 °C, was added a 1.0 M solution of Dibal-H in toluene (0.09 mL, 0.09 mmol) and the reaction was stirred at −78 °C for 30 minutes. After this time, the reaction was quenched with acetone (1.20 mL) at −78 °C, warmed to room temperature and then Rochelle’s salt 10% aqueous solution (10 mL) was added and stirred for 16 hours. The mixture was diluted with water (5 mL), extracted with EtOAc (4 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield 232 as a pale yellow oil (25.0 mg, 79% yield) and 215 as a pale yellow oil (5.0 mg, 16% yield). (13S*, 12S*, 7R*, 6S*)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-ol, 232; Rf = 0.41 (EtOAc : hexane 20% : 80%). IR (ATR): ν_{max} 3318 (C-OH), 2941, 2863, 1462, 1390, 1114, 1091, 881 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.84 (1H, ddd, J = 10.1, 2.3, 2.3 Hz, H-14), 5.72 (1H, ddd, J = 10.1, 2.3, 2.3 Hz, H-15), 5.39–5.34 (1H, m, H-9), 3.91–3.87 (1H, m, H-13), 3.81 (1H, dd, J = 9.6, 4.1 Hz, H-5), 3.51 (1H, dd, J = 9.6, 7.3 Hz, H-5), 2.45 (1H, dd, J = 15.1, 5.5 Hz, H-11), 2.40–2.31 (1H, m, H-8), 2.08–1.99 (1H, m, H-6), 1.86–1.75 (2H, m, H-11 + H-8), 1.68 (3H, s, H-24), 1.52–1.45 (1H, m, H-12), 1.43–1.37 (1H, m, H-7), 1.14–0.99 (21H, m, OSi(CH₃)₂) ppm. ¹³C NMR (400 MHz, CDCl₃): δ 132.7 (C-10), 130.8 (C-14), 130.6 (C-15), 119.8 (C-9), 73.9 (C-13),
65.6 (C-5), 45.9 (C-6), 42.3 (C-12), 34.9 (C-11), 33.3 (C-7), 31.3 (C-8), 23.4 (C-24), 18.0 (OSi(CH₃)₂), 11.9 (OSi(CH₂)₃) ppm. MS (ESI): m/z 373 (M+Na⁺); HRMS: found: (M+Na⁺) 373.2517. C₂₁H₃₈NaO₂Si requires (M+Na⁺) 373.2533. m/z 351 (M+H⁺); HRMS: found: (M+H⁺) 351.2677. C₂₁H₃₉O₂Si requires (M+H⁺) 351.2714. (13R*, 12S*, 6S*)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-ol, 215; Rf = 0.38 (EtOAc : hexane 20% : 80%). IR (ATR): νmax 3386 (C- OH), 2922, 2864, 1462, 1379, 1093, 1013, 930 cm⁻¹. ¹H NMR (500 MHz, C₆D₆): δ 6.04 (1H, ddd, J = 9.7, 5.6, 2.4 Hz, H-14), 5.94 (1H, dd, J = 9.7, 2.4 Hz, H-15), 5.43–5.37 (1H, m, H-9), 3.78–3.72 (1H, m, H-13), 3.68 (1H, dd, J = 9.4, 3.9 Hz, H-5), 3.49 (1H, dd, J = 9.4, 6.7 Hz, H-5), 2.62–2.53 (1H, m, H-11), 2.41–2.32 (1H, m, H-8), 1.89–1.82 (1H, m, H-6), 1.72–1.69 (3H, m, H-11 + H-7 + H-8), 1.68 (3H, s, H-24), 1.62–1.58 (1H, m, H-12), 1.12–1.02 (21H, m, OSiCH(CH₃)₂) ppm. ¹³C NMR (500 MHz, C₆D₆): δ 133.8 (C-10), 132.9 (C-14), 130.1 (C-15), 119.3 (C-9), 65.8 (C-13), 64.9 (C-5), 46.9 (C-6), 38.9 (C-12), 32.4 (C-8), 32.1 (C-11), 28.6 (C-7), 23.8 (C-24), 18.2 (OSi(CH₃)₂), 12.3 (OSi(CH₃)₂) ppm. MS (ESI): m/z 373 (M+Na⁺); HRMS: (ESI): m/z (M+Na⁺) 373.2518, C₂₁H₃₈NaO₂Si requires (M+Na⁺) 373.2533.

(13S*, 12S*, 7R*, 6S*)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-yl acetate, 238

To a solution of hydroxyl trans-decalin 232 (25 mg, 0.080 mmol) in pyridine (1.0 mL), were added DMAP (2 mg, 0.01 mmol) and acetyl chloride 225 (0.050 mL, 0.80 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the mixture was diluted with EtOAc (20 mL), washed with saturated aqueous solution of Cu₂SO₄ (3 × 10 mL), water (2 × 10 mL) and brine (2 × 10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield 238 as a pale yellow oil (18.0 mg,
58% yield. $\text{Rf} = 0.83$ (EtOAc : hexane 10% : 90%). $\text{IR}$ (ATR): $\nu_{\text{max}}$ 2942, 2922, 2865, 1728 (C=O), 1462, 1368, 1238, 732 cm$^{-1}$. $^1\text{H NMR}$ (400 MHz, CDCl$_3$): $\delta$ 5.91 (1H, ddd, $J$ = 10.1, 2.3, 2.3 Hz, H-14), 5.62 (1H, ddd, $J$ = 10.1, 2.3, 2.3 Hz, H-15), 5.43–5.37 (1H, m, H-9), 5.19–5.11 (1H, m, H-13), 3.81 (1H, dd, $J$ = 9.6, 4.6 Hz, H-5), 3.52 (1H, dd, $J$ = 9.6, 7.3 Hz, H-5), 2.39 (1H, ddd, $J$ = 16.9, 6.0, 6.0 Hz, H-8), 2.20–2.13 (1H, m, H-11), 2.11 (3H, s, H-16), 2.05 (1H, ddd, $J$ = 9.6, 7.3, 4.6, 2.3, 2.3 Hz, H-6), 1.80–1.78 (3H, m, H-11 + H-8 + H-12), 1.65 (3H, s, H-24), 1.55 (1H, ddd, $J$ = 12.4, 9.6, 9.6, 6.0 Hz, H-7), 1.13–0.99 (21H, m, OSiCH(CH$_3$)$_2$) ppm. $^{13}\text{C NMR}$ (400 MHz, CDCl$_3$): $\delta$ 171.2 (C-17), 132.4 (C-10), 132.2 (C-14), 126.6 (C-15), 119.3 (C-9), 76.1 (C-13), 65.5 (C-5), 45.7 (C-6), 38.6 (C-12), 34.6 (C-11), 33.3 (C-7), 31.2 (C-8), 23.3 (C-24), 21.3 (C-16), 18.0 (OSiCH(CH$_3$)$_2$), 11.9 (OSiCH(CH$_3$)$_2$) ppm. $\text{MS}$ (ESI): m/z 415 (M+Na$^+$); HRMS: found: (M+Na$^+$) 415.2642. C$_{23}$H$_{40}$NaO$_3$Si requires (M+Na$^+$) 415.2639. m/z 393 (M+H$^+$); HRMS: found: (M+H$^+$) 393.2842. C$_{23}$H$_{40}$O$_3$Si requires (M+H$^+$) 393.2819.

(13$R^*$, 12$S^*$, 7$R^*$, 6$S^*$)-10-Methyl-6-{((triisopropylsilyl)oxy)methyl}-13,6,7,8,11,12-hexahydronaphthalen-13-yl propionate, 112

To a solution of hydroxyl $\text{trans}$-decalin 215 (8.0 mg, 0.023 mmol) in pyridine (1.0 mL), were added DMAP (1.0 mg, 0.050 mmol) and propionyl chloride 216 (0.05 mL, 0.23 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the mixture was diluted with EtOAc (20 mL), washed with saturated aqueous solution of Cu$_2$SO$_4$ (3 × 10 mL), water (2 × 10 mL) and brine (2 × 10 mL), dried with Na$_2$SO$_4$, filtered and concentrated $\text{in vacuo}$. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield 112 as a pale yellow oil (5.0 mg, 62% yield). $\text{Rf} = 0.83$ (EtOAc : hexane 10% : 90%). $\text{IR}$ (ATR): $\nu_{\text{max}}$ 2941, 2865, 1724 (C=O), 1462, 1189, 1066, 907, 731 cm$^{-1}$. $^1\text{H NMR}$ (400 MHz, CDCl$_3$): $\delta$ 6.08 (1H, dd, $J$ = 10.1, 2.4 Hz, H-14), 5.95 (1H,
ddd, \( J = 10.1, 5.0, 2.4 \text{ Hz, H-15} \), 5.39–5.33 (1H, m, H-9), 5.17–5.13 (1H, m, H-13), 3.85 (1H, dd, \( J = 9.5, 4.4 \text{ Hz, H-5} \)), 3.58 (1H, dd, \( J = 9.5, 7.4 \text{ Hz, H-5} \)), 2.46–2.39 (1H, m, H-8), 2.31 (2H, q, \( J = 7.6 \text{ Hz, H-16} \)), 1.99–1.97 (2H, m, H-8 + H-11), 1.83–1.80 (3H, m, H-11 + H-12 + H-6), 1.79–1.70 (1H, m, H-7), 1.67 (3H, s, H-24), 1.14 (3H, t, \( J = 7.6 \text{ Hz, H-25} \)), 1.08–1.05 (21H, m, OSiCH(CH\(_3\)\(_2\)) ppm. \( ^{13}\text{C NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 174.3 (C-17), 135.3 (C-10), 132.9 (C-14), 124.5 (C-15), 119.3 (C-9), 67.9 (C-13), 65.5 (C-5), 46.8 (C-6), 36.7 (C-12), 31.9 (C-8), 31.3 (C-11), 29.0 (C-7), 27.8 (C-16), 23.5 (C-24), 18.0 (OSiCH(CH\(_3\)\(_2\))), 11.9 (OSiCH(CH\(_3\)\(_2\))), 9.2 (C-25) ppm. MS (ESI): m/z 429 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 429.2788. C\(_{24}\)H\(_{42}\)NaO\(_3\)Si requires (M+Na\(^+\)) 429.2795.

\((15S^*, 6R^*)\)-15-Allyl-6-(((triisopropylsilyl)oxy)methyl)cyclohexanone, 183

To a solution of enone 115 (50 mg, 0.18 mmol) in dry CH\(_2\)Cl\(_2\) (1.8 mL) at –78 °C, was added TiCl\(_4\) (0.030 mL, 0.25 mmol) and the orange solution was stirred for 5 minutes. Allyltrimethylsilane 250 (0.030 mL, 0.24 mmol) was added and the reaction was stirred at –78 °C for a further 30 minutes. After this time, saturated aqueous solution of NaHCO\(_3\) (8 mL) was added at –78 °C and then allowed to warm to room temperature for 30 minutes. The aqueous phase was then extracted with CH\(_2\)Cl\(_2\) (3 \( \times \) 10 mL) and the combined organic layers were washed with saturated aqueous solution of NaHCO\(_3\) (10 mL) and brine (10 mL), dried with Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 183 as a pale yellow oil (34.0 mg, 59% yield). Rf = 0.52 (EtOAc : hexane 10% : 90%). IR (ATR): \( \nu_{\text{max}} \) 2941, 2864, 1714 (C=O), 1462, 1382, 1246 cm\(^{-1}\). \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 5.72 (1H, dddd, \( J = 16.5, 10.6, 8.2, 5.5 \text{ Hz, H-17} \)), 5.08–5.05 (1H, m, H-18), 5.04–5.01 (1H, m, H-18), 3.86–3.74 (2H, m, H-5), 2.48–2.39 (2H, m, H-14), 2.37–2.30 (3H, m, H-12 + H-7), 2.19–2.16 (2H, m, H-6 + H-16), 1.88–1.78 (3H, m, H-16 + H-17), 1.14 (3H, t, \( J = 7.6 \text{ Hz, H-25} \)).
In a plastic vial, to a solution of allyl-cyclohexanone 183 (30 mg, 0.090 mmol) in dry pyridine (0.90 mL), was added hydrogen fluoride 70% in pyridine (0.070 mL, 3.6 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, the reaction was quenched with saturated aqueous solution of NaHCO₃ and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with 2 M HCl (2 × 10 mL) and brine (10 mL), dried with Na₂SO₄ filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (20% to 50% EtOAc in hexanes) to yield 263 as a pale yellow oil (13.0 mg, 98% yield). \( R_f = 0.25 \) (EtOAc : hexane 20% : 80%). IR (ATR): \( \nu_{\text{max}} \) 3405 (C-OH), 2923, 1702 (C=O), 1035, 913, 597 cm⁻¹. \(^1\text{H NMR}\) (400 MHz, CDCl₃): \( \delta \) 5.73 (1H, dddd, \( J = 16.5, 10.6, 8.2, 5.5 \text{ Hz, H-17}) \), 5.11–5.06 (1H, m, H-18), 5.06–5.02 (1H, m, H-18), 3.76 (1H, dd, \( J = 10.6, 6.9 \text{ Hz, H-5}) \), 3.71 (1H, dd, \( J = 10.6, 7.1 \text{ Hz, H-5}) \), 2.47–2.35 (3H, m, H-14 + H-12), 2.34–2.23 (2H, m, H-12 + H-15), 2.23–2.13 (2H, m, H-16 + H-6), 1.94–1.78 (3H, m, H-7 + H-16) ppm. \(^{13}\text{C NMR}\) (400 MHz, CDCl₃): \( \delta \) 211.9 (C-13), 136.2 (C-17), 117.3 (C-18), 62.9 (C-5), 44.9 (C-14), 40.6 (C-6), 39.6 (C-12), 30.1 (C-15), 33.8 (C-16), 25.4 (C-7) ppm. \textbf{MS} (APCI): m/z 169 (M+H⁺); HRMS: found: (M+H⁺) 169.1226. C₁₀H₁₇O₂ requires (M+H⁺) 169.1223.
To a solution of allyl-hydroxyl-cyclohexanone 263 (13 mg, 0.090 mmol) in dry CH₃CN (0.90 mL) at 0 °C, were added iodine (28 mg, 0.11 mmol) and solid NaHCO₃ (15 mg, 0.18 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of Na₂SO₃ (2 mL) and extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with 2 M HCl (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (20% to 40% EtOAc in hexanes) to yield 264 as a white solid (14.0 mg, 54% yield) and 265 as a pale yellow oil (8.0 mg, 31% yield).

120 (17R*, 15S*,6R*)-15-Iodomethyl-octahydro-isochromen-13-one, 264; Crystallized using a solvent/antisolvent system: EtOAc/hexane. Rf = 0.44 (EtOAc : hexane 20% : 80%). Melting point = 57–59 °C. IR (ATR): νmax 2925, 2853, 1709 (C=O), 1463, 1376, 1108, 1095, 904 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 3.92 (1H, dd, J = 11.4, 0.6 Hz, H-5), 3.72 (1H, dd, J = 11.4, 2.6 Hz, H-5), 3.30 (1H, dddd, J = 11.2, 6.3, 4.4, 2.1 Hz, H-17), 3.22 (1H, dd, J = 10.6, 4.4 Hz, H-18), 3.17 (1H, dd, J = 10.6, 6.3 Hz, H-18), 2.66 (1H, dd, J = 14.3, 6.3 Hz, H-14), 2.46–2.38 (3H, m, H-16 + H-12), 2.35–2.21 (3H, m, H-16 + H-15 + H-7), 2.18 (1H, ddd, J = 14.3, 1.6, 1.6 Hz, H-14), 2.03–1.96 (2H, m, H-6 + H-7) ppm. ¹³C NMR (500 MHz, CDCl₃): δ 210.7 (C-13), 76.9 (C-17), 71.6 (C-5), 46.6 (C-14), 40.5 (C-12), 36.4 (C-6), 34.5 (C-15), 32.8 (C-
To a solution of enone trans-decalin 113 (40 mg, 0.12 mmol) in dry CH₂Cl₂ (1.2 mL) at −78 °C, was added TiCl₄ (0.020 mL, 0.14 mmol). After 5 minutes allyltrimethylsilane 250 (0.020 mL, 0.13 mmol) was also added and the reaction was stirred at −78 °C for 30 minutes. After this time, saturated aqueous solution of NaHCO₃ (4.5 mL) was added at −78 °C, stirred for 45 minutes and then allowed to warm to room temperature for 30 minutes. The aqueous phase was then extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of NaHCO₃ (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was
purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 266 as a pale yellow oil (25.0 mg, 61% yield) and 267 as a pale yellow oil (3.0 mg, 7% yield). (15S*, 12S*, 7R*, 6S*)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydropthalenc-13(2H)-one, 266; \( RF = 0.52 \) (EtOAc : hexane 10% : 90%). \( ^{1}H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.72 (1H, dddd, \( J = 16.5, 10.6, 8.2, 5.5 \) Hz, H-17), 5.14–5.12 (1H, m, H-9), 5.07–5.01 (2H, m, H-18), 3.76 (1H, dd, \( J = 9.9, 1.4 \) Hz, H-5), 3.62 (1H, dd, \( J = 9.9, 9.9 \) Hz, H-5), 2.60–2.51 (2H, m, H-15 + H-14), 2.45–2.40 (1H, m, H-14), 2.32–2.23 (2H, m, H-12 + H-16), 2.18–2.12 (2H, m, H-8 + H-11), 1.94–1.84 (1H, m, H-8), 1.68 (3H, s, H-24), 1.65–1.56 (2H, m, H-16 + H-7), 1.10–1.02 (21H, m, OSiCH(CH\(_3\))\(_2\)) ppm. \( ^{13}C \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 212.2 (C-13), 136.5 (C-17), 133.2 (C-10), 119.1 (C-9), 116.9 (C-18), 62.6 (C-5), 49.7 (C-12), 47.3 (C-6), 44.7 (C-14), 36.9 (C-15), 36.8 (C-7), 31.8 (C-16), 31.9 (C-8), 29.4 (C-11), 23.4 (C-24), 18.1 (OSiCH(CH\(_3\))\(_2\)), 11.9 (OSiCH(CH\(_3\))\(_2\)) ppm. MS (ESI): m/z 413 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 413.2830. C\(_{24}\)H\(_{42}\)NaO\(_2\)Si requires (M+Na\(^+\)) 413.2846. m/z 391 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 391.3033. C\(_{24}\)H\(_{43}\)O\(_2\)Si requires (M+H\(^+\)) 391.3027. (15R*, 12S*, 7R*, 6S*)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydropthalenc-13(2H)-one, 267; \( RF = 0.54 \) (EtOAc : hexane 10% : 90%). \( ^{1}H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 5.77 (1H, dddd, \( J = 16.5, 10.6, 8.2, 5.5 \) Hz, H-17), 5.34–5.32 (1H, m, H-9), 4.99–4.97 (2H, m, H-18), 4.19–4.16 (1H, dd, \( J = 9.2, 4.9 \) Hz, H-5), 3.60 (1H, dd, \( J = 9.2, 9.2 \) Hz, H-5), 2.65–2.60 (1H, m, H-15), 2.53 (1H, dd, \( J = 13.2, 3.2 \) Hz, H-14), 2.45 (1H, dd, \( J = 13.2, 5.8 \) Hz, H-14), 2.28–2.15 (3H, m, H-16 + H-12 + H-8), 2.12–2.05 (2H, m, H-11), 1.93–1.81 (1H, m, H-6), 1.86–1.80 (1H, m, H-8), 1.75–1.70 (1H, m, H-16), 1.68 (3H, s, H-24), 1.66–1.58 (1H, m, H-7), 1.10–1.05 (21H, m, OSiCH(CH\(_3\))\(_2\)) ppm. \( ^{13}C \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 212.2 (C-13), 137.0 (C-17), 133.2 (C-10), 119.3 (C-9), 116.1 (C-18), 62.6 (C-5), 49.7 (C-12), 48.1 (C-6), 45.1 (C-14), 39.8 (C-16), 37.2 (C-7), 34.2 (C-15), 33.7 (C-8), 32.1 (C-11), 29.7 (C-24), 18.1 (OSiCH(CH\(_3\))\(_2\)), 11.9 (OSiCH(CH\(_3\))\(_2\)) ppm. MS (ESI): m/z 413 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 413.2842. C\(_{24}\)H\(_{43}\)NaO\(_2\)Si requires (M+Na\(^+\)) 413.2846.
13-((15S*, 12S*, 7S*, 6S*)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-ylidene)-14-(2,4-dinitrophenyl)hydrazine, 268

To a solution of allyl-trans-decalin 266 (10 mg, 0.030 mmol) in dry MeOH (1.0 mL) and 3Å molecular sieves, were added 2,4-dinitrophenyl hydrazine 140 (12 mg, 0.060 mmol) and glacial acetic (0.50 mL) and the reaction was stirred at 50 °C with for 16 hours. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 268 as an orange solid (4.0 mg, 24% yield). Crystallization method: slow evaporation of CH₂Cl₂ from a solution of 268 in CH₂Cl₂. Melting point = 135‒137 °C. Rf = 0.58 (EtOAc : hexane 10% : 90%). IR (ATR): νₘₐₓ 2923, 1617 (C=N), 1334, 1099 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 11.23 (1H, s, N-H), 9.15 (1H, d, J = 2.6 Hz, Ar-H), 8.33 (1H, d, J = 9.6, 2.6 Hz, Ar-H), 8.00 (1H, d, J = 9.6 Hz, Ar-H), 5.82–5.72 (1H, m, H₁₁), 5.41–5.38 (1H, m, H₉), 5.07–4.87 (2H, m, H₁₈), 3.91 (1H, dd, J = 9.7, 5.5 Hz, H₅), 3.01 (1H, dd, J = 9.7, 9.7 Hz, H₅), 3.01 (1H, dd, J = 14.8, 3.8 Hz, H₁₄), 2.61–2.52 (1H, m, H₁₅), 2.46–2.41 (1H, m, H₁₂), 2.39–2.33 (3H, m, H₁₆ + H₁₄ + H₁₁), 2.27–2.26 (2H, m, H₈), 1.91–1.88 (2H, m, H₆ + H₁₁), 1.77 (3H, s, H₂₄), 1.71–1.58 (2H, m, H₁₆ + H₇), 1.13–1.02 (21H, m, OSi(CH₃)₂) ppm. ¹³C NMR (500 MHz, CDCl₃): δ 160.9 (C=N), 145.4 (Ar), 137.5 (C-17), 137.3 (C-10), 133.3 (Ar), 129.9 (Ar), 128.8 (Ar-H), 123.7 (C-9), 119.2 (Ar-H), 117.3 (Ar-H), 116.3 (C-18), 62.7 (C-5), 47.5 (C-6), 44.2 (C-12), 37.1 (C-8), 35.9 (C-15), 32.2 (C-7), 31.6 (C-16),
30.7 (C-11), 29.7 (C-14), 23.6 (C-24), 18.1 (OSi(CH₃)₂), 11.9 (OSi(CH₃)₂) ppm. **MS** (ESI): m/z 569 (M-H⁺); HRMS: found: (M-H⁺) 569.3209. C₃₀H₄₅N₄O₅Si requires (M-H⁺) 569.3165.

(15S*, 12S*, 7R*, 6S*)-15-Allyl-6-(hydroxymethyl)-10-methyl-1,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 269

In a plastic vial, to a solution of allyl-trans-decalin 266 (20 mg, 0.050 mmol) in pyridine (1.0 mL), was added hydrogen fluoride 70% in pyridine (0.200 mL, 1.47 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of NaHCO₃ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 2 M HCl (20 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 40% EtOAc in hexanes) to yield 269 as a pale yellow oil (10.0 mg, 85% yield). **RF** = 0.28 (EtOAc : hexane 20% : 80%). **IR** (ATR): νₚₓₚ 3417 (C-OH), 2919, 2852, 1704 (C=O), 1436, 1376, 1027, 911 cm⁻¹. **¹H NMR** (500 MHz, CDCl₃): δ 5.80–5.71 (1H, m, H-17), 5.36–5.31 (1H, m, H-9), 5.10–5.01 (2H, m, H-18), 3.90 (1H, dd, J = 10.8, 4.9 Hz, H-5), 3.65 (1H, dd, J = 10.8, 9.2 Hz, H-5), 2.56 (1H, dd, J = 12.8, 2.7 Hz, H-14), 2.53–2.43 (3H, m, H-15 + H-14 + H-16), 2.39–2.13 (5H, m, H-12 + H-6 + H-8 + H-11 + H-16), 2.12–2.04 (2H, m, H-7 + H-11), 2.00–1.87 (1H, m, H-8), 1.71–1.65 (3H, s, H-24) ppm. **¹³C NMR** (500 MHz, CDCl₃): δ 211.7 (C-13), 136.4 (C-17), 133.2 (C-10), 119.1 (C-9), 117.2 (C-18), 62.3 (C-5), 49.8 (C-12), 47.1 (C-6), 45.0 (C-14), 37.1 (C-15), 37.1 (C-7), 31.8 (C-11), 29.7 (C-16), 29.4 (C-8), 23.4 (C-24) ppm. **MS** (ESI): m/z 257 (M+Na⁺); HRMS: found: (M+Na⁺) 257.1503. C₁₅H₂₂NaO₂ requires (M+Na⁺) 257.1512. m/z 235 (M+H⁺); HRMS: found: (M+H⁺) 235.1672. C₁₅H₂₃O₂ requires (M+H⁺) 235.1693.
But-2-yn-1-yl(trimethyl)silane, \textit{271}^{123}

\begin{center}
\includegraphics[width=0.5\textwidth]{TMS.png}
\end{center}

To a suspension of magnesium (290 mg, 11.9 mmol) in dry Et\textsubscript{2}O (2.71 mL), was added mercurydichloride (40 mg, 0.15 mmol) and stirred for 30 minutes. The grey mixture was cooled to 0 °C and a solution of 1-bromo-2-butylene \textit{273} (0.50 mL, 5.9 mmol) in dry Et\textsubscript{2}O (5.50 mL) was added over 10 minutes. The resulting mixture was stirred at room temperature for 30 minutes and then re-cooled to 0 °C before the addition of TMSCl (0.75 mL, 5.9 mmol). The resulting reaction was stirred vigorously at room temperature for 16 hours. The reaction was then filtrated through celite with Et\textsubscript{2}O (10 mL) and the filtrate was distilled at atmospheric pressure (80‒90 °C) to yield the desired compound \textit{271} as a colourless liquid (50.0 mg, 6% yield).\textsuperscript{123} ¹H NMR (400 MHz, CDCl\textsubscript{3}): δ 1.78 (3H, t, \textit{J} = 2.8 Hz), 1.40 (2H, q, \textit{J} = 2.8 Hz), 0.08 (9H, s, Si(CH\textsubscript{3})\textsubscript{3}) ppm. ¹³C NMR (400 MHz, CDCl\textsubscript{3}): δ 76.7 (CH), 74.1 (CH), 7.2 (CH\textsubscript{3}), 3.9 (CH\textsubscript{2}), 1.8 (Si(CH\textsubscript{3})\textsubscript{3}) ppm. This compound was characterized only by ¹H NMR due to its volatility and instability, and the data matched the literature.\textsuperscript{123}

9-methyl-15,6-dihydronaphthalen-13(2H)-one, \textit{207}^{94}

To a solution of freshly distilled diisopropylamine (0.150 mL, 1.09 mmol) in dry THF (1.09 mL) at −78 °C, was added \textit{n}-BuLi (0.510 mL, 2.15 M) and the resulting solution was stirred at −78 °C for 30 minutes. At this time, a solution of model \textit{trans}-decalin \textit{139} (89 mg, 0.54 mmol) in dry THF (1.61 mL) was introduced and the resulting solution was stirred for 1 hour at −78 °C. Freshly distilled TMSCl (0.210 mL, 1.62 mmol) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to warm to room temperature for 1 hour. The reaction was cooled to 0 °C and NBS (recrystallised, 125 mg, 0.710 mmol) was added as a solid, and the resulting reaction was stirred at 0
°C for 3 hours. The reaction was allowed to warm to room temperature and DBU (0.81 mL, 5.40 mmol) was added and the reaction was stirred at 50 °C for 16 hours. A solution of 2 M HCl (10 mL) was added and stirred for 2 hours and then the mixture was washed with saturated aqueous solution of NaHCO₃ (3 × 10 mL) and brine (20 mL) dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield 207 as a pale yellow oil (11.0 mg, 14% yield).³¹

**IBX oxidations**

To a solution of IBX (207 mg, 0.740 mmol) in dry DMSO (2.0 mL) at 40 °C, was added a solution of model *trans*-decalin 139 (61 mg, 0.37 mmol) in dry DMSO (0.47 mL) and the reaction was stirred at 95 °C for 16 hours. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of NaHCO₃ (10 mL) and extracted with MTBE (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 207 as a pale yellow oil (12.0 mg, 20% yield).⁹³ *Rf* = 0.38 (EtOAc : hexane 10% : 90%).

**IR** (ATR): νₘₐₓ 2923, 2854, 1680 (C=O), 1435, 1347, 1284, 1184, 817 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃): δ 7.94 (1H, d, *J* = 8.0 Hz, Ar-H), 7.12 (1H, d, *J* = 8.0 Hz, Ar-H), 7.07 (1H, s, Ar-H), 2.93 (2H, t, *J* = 6.2 Hz, H-14), 2.64 (2H, t, *J* = 6.4 Hz, H-6), 2.40 (3H, s, H-24), 2.19–2.08 (2H, m, H-15) ppm. **¹³C NMR** (500 MHz, CDCl₃): δ 198.2 (C-13), 144.6 (Ar), 144.2 (Ar), 130.3 (Ar), 129.2 (Ar-H), 127.6 (Ar-H), 127.3 (Ar-H), 39.1 (C-14), 29.7 (C-6), 23.3 (C-15), 21.7 (C-24) ppm. **MS** (ESI): m/z 161 (M+H⁺); HRMS: found: (M+H⁺) 161.0968. C₁₁H₁₃O requires (M+H⁺) 161.0961. Characterisation of this compound matched the compound reported in the literature.⁹⁴
To a solution of freshly distilled diisopropylamine (0.13 mL, 0.92 mmol) in dry THF (0.92 mL) at −78 °C, was added n-BuLi (0.390 mL, 2.38 M) and the solution was stirred at −78 °C for 30 minutes. A solution of trans-decalin 139 (100 mg, 0.610 mmol) in dry THF (1.33 mL) was added and stirred for a further 1 hour at −78 °C. After this time, a solution of N-phenylbistrifluoromethanesulfonimide 243 (327 mg, 0.920 mmol) in dry THF (1.33 mL) was added at −78 °C and the reaction was allowed to warm to room temperature for 2 hours. After this time, the reaction was quenched with water (5 mL) and the aqueous phase was extracted with Et$_2$O (2 × 20 mL). The combined organic layers were dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 244 as a pale yellow oil (66.0 mg, 36% yield). Rf = 0.75 (EtOAc : hexane 10% : 90%). IR (ATR): $\nu_{\text{max}}$ 2918, 1414, 1247, 1203, 1141, 1033, 877 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.80–5.70 (1H, m, H-14), 5.46–5.38 (1H, m, H-10), 2.40–2.29 (2H, m, H-12 + H-11), 2.27–2.22 (2H, m, H-15), 2.01 (1H, dd, $J$ = 15.1, 5.0 Hz, H-8), 1.95–1.80 (3H, m, H-7 + H-6 + H-11), 1.80–1.72 (1H, m, H-8), 1.70 (3H, s, H-24), 1.46–1.24 (1H, m, H-6) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 151.8 (C-13), 134.1 (C-9), 119.7 (C-10), 118.4 (C-14), 39.7 (C-12), 37.7 (C-7), 37.2 (C-8), 28.3 (C-11), 27.8 (C-6), 23.8 (C-15), 23.3 (C-24) ppm. $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -70.5, -73.9, -75.8 ppm. MS (APCI): m/z 297 (M+H$^+$); HRMS: found: (M+H$^+$) 297.0755. C$_{12}$H$_{16}$F$_3$O$_3$S requires (M+H$^+$) 297.0767.
To a solution of triflate-enol trans-decalin 244 (66 mg, 0.20 mmol) in dry DMF (12.5 mL), were added Bu$_3$N (0.17 mL, 0.70 mmol), bis(acetato)bis(triphenylphosphine)palladium (II) (14 mg, 0.020 mmol) and formic acid (0.020 mL, 0.47 mmol) and the reaction was heated at 50 °C for 3 hours. After this time, the reaction was cooled to room temperature and Et$_2$O (10 mL) was added and it was filtrated through a celite pad. The filtrate was washed with water (5 × 20 mL), brine (20 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 245 as a pale yellow oil (13.0 mg, 45% yield). \( R_f = 0.89 \) (EtOAc : hexane 10% : 90%). \( \text{IR (ATR): } \nu_{\text{max}} 2911, 2852, 1449, 1376, 1047, 915, 873, 800, 735 \text{ cm}^{-1} \). \( ^1{\text{H NMR}} \) (400 MHz, CDCl$_3$): \( \delta \) 5.69–5.64 (1H, m, H-14), 5.55–5.49 (1H, m, H-13), 5.42–5.38 (1H, m, H-10), 2.14–2.04 (3H, m, H-12 + H-11), 1.97–1.86 (2H, m, H-8), 1.82–1.70 (3H, m, H-15 + H-7), 1.67 (3H, s, H-24), 1.50–1.36 (2H, m, H-6) ppm. \( ^{13}{\text{C NMR}} \) (400 MHz, CDCl$_3$): \( \delta \) 134.4 (C-10), 131.3 (C-13), 126.6 (C-14), 121.1 (C-9), 38.0 (C-8), 37.5 (C-12), 36.5 (C-7), 32.5 (C-15), 29.3 (C-6), 25.7 (C-11), 23.6 (C-24) ppm. \( \text{MS (EI): } m/z 148 \) (M+H$^+$); HRMS: found: (M+H$^+$) 148.1256. C$_{11}$H$_{16}$ requires (M+H$^+$) 148.1252.

\[(E)-\text{But-2-en-1-yltrimethylsilane, 272}\]

To a suspension of CuCl (980 mg, 10.0 mmol) and Et$_3$N (4.60 mL, 33.0 mmol) in dry Et$_2$O (7.0 mL) at 0 °C, a solution of trans-crotyl chloride 274 (3.0 mL, 33.0 mmol) and Cl$_3$SiH (3.30 mL, 33.0 mmol) in dry Et$_2$O (3.0 mL) was transferred over 10 minutes. The reaction was stirred at room temperature for 3
hours and was then diluted with Et₂O (50 mL) and filtered under nitrogen. The resulting ethereal solution was transferred into a solution of MeMgI (63.5 mL, 140 mmol) in dry Et₂O (60 mL) at 0 °C, and the reaction was stirred at 50 °C for 16 hours. After this time, the reaction was cooled to 0 °C and quenched with a pre-cooled saturated aqueous solution of NH₄Cl (30 mL) and the aqueous phase was extracted with Et₂O (3 × 20 mL). The combined organic layers were dried with Na₂SO₄, filtered and the ether was evaporated at 45 °C and the orange liquid was distilled at ambient pressure (112‒115 °C) to yield 272 as a colourless liquid (1.44 g, 34% yield). IR (ATR): v max 2953, 2891, 1452, 1398, 1244, 1038, 962, 834 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.44‒5.34 (1H, m), 5.31‒5.21 (1H, m), 1.65 (3H, dtd, J = 7.0, 1.3, 1.2 Hz), 1.39 (2H, dqd, J = 7.8, 1.3, 1.0 Hz), 0.04 (9H, s, Si(CH₃)₃) ppm. ¹³C NMR (400 MHz, CDCl₃): δ 127.0 (CH), 123.1 (CH), 22.6 (CH₂), 18.0 (CH₃), 2.0 (Si(CH₃)₃) ppm. MS (EI): m/z 128 (M+H⁺); HRMS: found: (M+H⁺) 128.1024. C₁₅H₁₆Si requires (M+H⁺) 128.1021.

Characterisation of this compound matched the compound reported in the literature.

(15R*, 12S*, 7R*, 6S*)-15-((R*)-But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 276

(12S*, 7R*, 6S*)-15-((But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 277

To a solution of enone trans-decalin 113 (100 mg, 0.290 mmol) in dry CH₂Cl₂ (2.90 mL) at −40 °C, was added TiCl₄ (0.040 mL, 0.37 mmol). After 5 minutes, E-crotyltrimethylsilane 272 (0.060 mL, 0.13 mmol)
was added and the reaction was stirred at −40 °C for 1.5 hours. After this time, saturated aqueous solution of NaHCO$_3$ (4.5 mL) was added at −40 °C, stirred for 45 minutes and then allowed to warm to room temperature and stirred for an additional 30 minutes. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of NaHCO$_3$ (10 mL) and brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 276 and 277 as an inseparable mixture in a 2 : 1 ratio as a pale yellow oil (50.0 mg, 43% yield). Rf = 0.58 (EtOAc : hexane 10% : 90%). On a mixture IR (ATR): ν$_{max}$ 2922, 2865, 1711 (C=O), 1461, 1379, 1247, 1067, 911 cm$^{-1}$. Integration of the $^1$H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. $^1$H NMR (400 MHz, CDCl$_3$): δ 5.82–5.72 (2H, m, 276 + 277), 5.37–5.31 (2H, m, 276 + 277), 5.06–4.92 (4H, m, 276 + 277), 3.95–3.89 (2H, m, 277), 3.77 (1H, dd, $J = 9.8$, 6.1 Hz, 276), 3.74 (1H, dd, $J = 9.8$, 4.9 Hz, 276), 2.77–2.70 (1H, m, 276), 2.49–2.40 (3H, m, 276 + 277), 2.39–2.32 (2H, m, 276 + 277), 2.30–2.04 (11H, m, 276 + 277), 1.99–1.80 (5H, m, 276 + 277), 1.69 (6H, 276 + 277), 1.10–1.03 (42H, m, OSiCH(CH$_3$)$_2$), 0.99 (3H, d, $J = 6.3$ Hz, 276), 0.94 (3H, d, $J = 6.9$ Hz, 277) ppm. Major (15$^R$*, 12$S$*, 7$R$*, 6$S$*)-15-((R*)-But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 276; $^{13}$C NMR (400 MHz, CDCl$_3$): δ 213.5 (C=O), 143.8 (CH), 133.4 (C=C), 120.0 (CH), 113.5 (CH$_2$), 65.9 (CH$_2$), 48.5 (CH), 45.5 (CH), 42.6 (CH$_2$), 40.1 (CH), 38.7 (CH), 38.5 (CH), 37.2 (CH$_2$), 33.9 (CH$_2$), 23.4 (CH$_3$), 19.4 (CH$_3$), 18.1 (OSiCH(CH$_3$)$_2$), 11.9 (OSiCH(CH$_3$)$_2$); Minor (12$S$*, 7$R$*, 6$S$*)-15-(-But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 277; $^{13}$C NMR (400 MHz, CDCl$_3$): δ 212.9 (C=O), 142.7 (CH), 132.9 (C=C), 119.2(CH), 113.8 (CH$_3$), 59.3 (CH$_2$), 49.6 (CH), 46.4 (CH), 41.7 (CH), 40.5 (CH$_2$), 38.5 (CH), 35.9 (CH), 32.0 (CH$_2$), 31.9 (CH$_3$), 23.4 (CH$_3$), 18.1 (OSiCH(CH$_3$)$_2$), 11.9 (OSiCH(CH$_3$)$_2$), 11.0 (CH$_3$) ppm. On a mixture MS (ESI): m/z 427 (M+Na$^+$); HRMS: found: (M+Na$^+$) 427.3012. C$_{25}$H$_{44}$NaO$_2$Si requires (M+Na$^+$) 427.3003.
(12S*, 7R*, 6S*)-15-(But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 277

Exclusively the minor diastereoisomer 277 was recovered unreacted in the deprotection reaction using HF 70% in pyridine and was characterized as single a compound. Pale yellow oil (15.0 mg, 41% yield). 

Rf = 0.58 (EtOAc : hexane 10% : 90%). IR (ATR): ν_max 2923, 1713 (C=O), 1507, 1102 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.82–5.72 (1H, m), 5.37–5.31 (1H, m), 5.06–4.92 (2H, m), 3.95–3.89 (2H, m), 2.77–2.70 (1H, m), 2.49–2.40 (1H, m), 2.39–2.32 (1H, m), 2.30–2.04 (6H, m), 1.99–1.80 (2H, m), 1.69 (3H, s), 1.10–1.03 (21H, m, OSiCH(CH₃)₂), 0.94 (3H, d, J = 6.9 Hz, CH₃) ppm. ¹³C NMR (400 MHz, CDCl₃): δ 212.9 (C=O), 142.7 (CH), 132.9 (C=C), 119.2(CH), 113.8 (CH₂), 59.3 (CH₂), 49.6 (CH), 46.4 (CH), 41.7 (CH), 40.5 (CH₂), 38.5 (CH), 35.9 (CH), 32.0 (CH₂), 31.9 (CH₂), 23.4 (CH₃), 18.1 (OSiCH(CH₃)₂), 11.9 (OSiCH(CH₃)₂), 11.0 (CH₃) ppm. MS (ESI): m/z 427 (M+Na⁺); HRMS: found: (M+Na⁺) 427.3007. C₂₅H₴₄NaO₂Si requires (M+Na⁺) 427.3003.

(12S*, 7R*, 6S*)-3-(But-17-en-16-yl)-6-(hydroxymethyl)-10-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 280

In a plastic vessel, to a solution of minor crotyl-trans-decalin 277 (15 mg, 0.040 mmol) in pyridine (0.10 mL), was added hydrogen fluoride 70% in pyridine (0.030 mL, 1.6 mmol) and the reaction was stirred at room temperature for 2 days. After this time, the reaction was quenched with saturated aqueous
solution of NaHCO₃ (5 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous solution of 2 M HCl (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (20% to 30% EtOAc in hexanes) to yield **280** as a pale yellow oil (7.0 mg, 78% yield).

**Rf = 0.35** (EtOAc : hexane 20% : 80%). **IR (ATR):** ν<sub>max</sub> 3402 (C-<OH>), 2915, 1704 (C=O), 911 cm<sup>–1</sup>. **1H NMR** (500 MHz, CDCl₃): δ 5.80 (1H, ddd, J = 17.5, 10.6, 5.6 Hz, H-17), 5.37–5.35 (1H, m, H-9), 5.06 (1H, ddd, J = 10.6, 1.5, 1.5 Hz, H-18), 5.02 (1H, ddd, J = 17.5, 1.5, 1.5 Hz, H-18), 3.99–3.86 (2H, m, H-5), 2.72–2.66 (1H, m, H-16), 2.51–2.42 (1H, m, H-11), 2.37 (1H, dd, J = 12.9, 3.4 Hz, H-14), 2.32–2.24 (1H, m, H-12), 2.23–2.15 (2H, m, H-8), 2.14–2.06 (2H, m, H-14 + H-15), 1.93–1.85 (1H, m, H-11), 1.82 (1H, dddd, J = 12.1, 12.1, 10.5, 4.1 Hz, H-7), 1.69 (3H, s, H-24), 1.50 (1H, dddd, J = 10.5, 10.5, 2.3, 2.3 Hz, H-6), 0.94 (3H, d, J = 5.9 Hz, H-25) ppm. **13C NMR** (500 MHz, CDCl₃): δ 212.2 (C-13), 142.4 (C-17), 133.1 (C-10), 119.1 (C-9), 114.1 (C-18), 58.7 (C-5), 49.6 (C-12), 45.8 (C-6), 41.6 (C-16), 40.8 (C-14), 38.4 (C-7), 36.3 (C-15), 31.8 (C-8), 30.0 (C-11), 23.3 (C-24), 11.3 (C-25) ppm. **MS (ESI):** m/z 271 (M+Na⁺); HRMS: found: (M+Na⁺) 271.1678. C₁₆H₂₄NaO₂ requires (M+Na⁺) 271.1669.
(15*R*, 12S*, 7R*, 6S*)-15-((R*)-But-17-en-16-yl)-6-(hydroxymethyl)-10-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 278

\[
\begin{align*}
\text{O} &
\end{align*}
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(15*R*, 12R*, 7R*, 6S*)-15-((R*)-But-17-en-16-yl)-6-(hydroxymethyl)-10-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, 279

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\begin{align*}
\text{O} &
\end{align*}
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In a plastic vessel, to a solution of a 2 : 1 inseparable mixture of crotyl-trans-decalin 276 and 277 (52 mg, 0.13 mmol) in pyridine (0.31 mL), was added hydrogen fluoride 70% in pyridine (0.10 mL, 5.2 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of NaHCO₃ (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous solution of 2 M HCl (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (20% to 30% EtOAc in hexanes) to yield 278 and 279 as an inseparable mixture in a 1 : 1 ratio as a pale yellow oil (13.0 mg, 62% yield).

Due to the 1 : 1 ratio and the presence of many overlapping peaks in the ¹H NMR, it was impossible to determine which resolved proton peaks belonged to the trans-isomer and which was instead generated from the cis-compound. Rf = 0.32 (EtOAc : hexane 20% : 80%). IR (ATR): νmax 3417 (C-OH), 2910, 1703 (C=O), 1436, 1376, 1039, 912, 786 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.79 (1H, ddd, J = 17.5, 10.2, 9.0 Hz), 5.68 (1H, ddd, J = 17.5, 10.2, 9.0 Hz), 5.38–5.33 (1H, m), 5.33–5.28 (1H, m), 5.11–4.98 (4H, m), 4.05 (1H, dd, J = 10.7, 4.4 Hz), 3.93 (1H, dd, J = 10.7, 9.5 Hz), 3.75 (1H, dd, J = 10.7, 6.7 Hz), 2.00
To a solution of crotyl-hydroxyl-trans-decalin 278 and 279 (12 mg, 0.060 mmol) in dry CH$_3$CN (0.60 ml) at 0 °C, were added iodine (15 mg, 0.060 mmol) and solid NaHCO$_3$ (8.0 mg, 0.12 mmol) and the reaction was allowed to stir at room temperature for 24 hours. After this time, the reaction was quenched with saturated aqueous solution of Na$_2$SO$_3$ (1 mL) and the aqueous phase was extracted.
with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous solution 2 M HCl (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield 281 as a white solid (6.0 mg, 27% yield) and 282 as a white solid (9.0 mg, 29% yield).

(17S*, 16R*, 15R*, 12S*, 7R*, 6S*)-17-(Iodomethyl)-16,10-dimethyl-17,16,15,14,12,11,8,7-octahydro-1H-benzo[h]isochromen-13(6H)-one, 281; Crystallization method solvent/antisolvent system: EtOAc/hexane. Melting point = 110‒113 °C. Rf = 0.65 (EtOAc : hexane 30% : 70%). IR (ATR): ν max 2923, 2854, 1706 (C=O), 1465, 1357, 1161, 817 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.38‒5.35 (1H, m, H-9), 3.85 (1H, ddd, J = 10.7, 4.5, 4.5 Hz, H-17), 3.76‒3.66 (2H, m, H-5), 3.46 (1H, dd, J = 10.7, 10.7 Hz, H-18), 3.23 (1H, dd, J = 10.7, 4.5 Hz, H-18), 2.58 (1H, dd, J = 14.6, 7.7 Hz, H-14), 2.48 (1H, dd, J = 14.6, 4.9 Hz, H-14), 2.37‒2.35 (2H, m, H-12 + H-8), 2.28‒2.22 (1H, m, H-15), 2.19‒2.13 (1H, m, H-11), 2.11‒2.04 (1H, m, H-8), 1.97‒1.86 (3H, m, H-16 + H-11 + H-7), 1.86‒1.82 (1H, m, H-6), 1.68 (3H, s, H-24), 0.96 (3H, d, J = 7.1 Hz, H-25) ppm. ¹³C NMR (500 MHz, CDCl₃): δ 211.7 (C-13), 133.1 (C-10), 19.3 (C-9), 76.9 (C-17), 62.8 (C-5), 48.2 (C-12), 42.2 (C-14), 39.5 (C-6), 38.1 (C-15), 35.1 (C-7), 33.4 (C-16), 32.9 (C-11), 29.6 (C-8), 23.3 (C-24), 14.2 (C-25), 3.7 (C-18) ppm. MS (ESI): m/z 397 (M+Na⁺); HRMS: found: (M+Na⁺) 397.0633. C₁₆H₂₃INaO₂ requires (M+Na⁺) 397.0635.

(17S*, 16R*, 15R*, 12R*, 9R*, 8R*, 7R*, 6S*)-10-Hydroxy-9-iodo-17-(iodomethyl)-4,10-dimethyldecahydro-1H-benzo[h]isochromen-13(6H)-one, 282; Crystallization method solvent/antisolvent system: EtOAc/hexane. Melting point = 104‒107 °C. Rf = 0.62 (EtOAc : hexane 30% : 70%). IR (ATR): ν max 3417 (C-OH), 2922, 2852, 1659 (C=O), 1430, 1374, 1141, 1081, 597 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 4.40 (1H, dd, J = 5.5, 2.6 Hz, H-9), 3.96‒3.91 (2H, m, H-5), 3.88 (1H, ddd, J = 7.8, 6.8, 2.3 Hz, H-17), 3.23 (1H, dd, J = 10.0, 7.8 Hz, H-18), 3.05 (1H, dd, J = 10.0, 6.8 Hz, H-18), 2.90 (1H, dd, J = 13.2, 13.2 Hz, H-14), 2.73‒2.71 (1H, m, H-12), 2.62‒2.58 (1H, m, H-7), 2.37‒2.25 (3H, m, H-14 + H-8 + H-15), 2.14‒2.02 (3H, m, H-11 + H-6), 1.97‒1.92 (1H, m, H-8), 1.76 (1H, ddq, J = 13.7, 7.6, 2.3 Hz, H-16), 1.69 (3H, s, H-24), 1.02 (3H, d, J = 7.6 Hz, H-25) ppm. ¹³C NMR (500 MHz, CDCl₃): δ 216.4 (C-13), 81.8 (C-10), 75.3 (C-17), 67.7 (C-5), 46.0 (C-12), 42.0 (C-14), 41.7 (C-9), 41.6 (C-15), 37.2 (C-7), 35.8 (C-16), 35.2 (C-11), 34.4 (C-
6), 31.2 (C-8), 22.7 (C-24), 12.6 (C-25), 5.5 (C-18) ppm. MS (ESI): m/z 540 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 540.9707. \(C_{16}H_{24}I_2NaO_3\) requires (M+Na\(^+\)) 540.9707.

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\text{(E)-(1-Ethoxyprop-1-en-1-yl)oxy} \text{trimethylsilane, 240}^{113}
\]

![Image of (E)-(1-Ethoxyprop-1-en-1-yl)oxytrimethylsilane]

To a solution of freshly distilled diisopropylamine (1.47 mL, 10.4 mmol) in dry THF (10.4 mL) at −78 °C, was added \(n\)-BuLi (4.42 mL, 2.36 M) and the solution was stirred at −78 °C for 30 minutes. A solution of ethyl-propionate (1.0 mL, 8.7 mmol) in dry THF (11.3 mL) was added to the LDA solution and stirred for 1 hour at −78 °C. After this time, freshly distilled TMSCl (1.32 mL, 10.4 mmol) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to stir at room temperature for 2 hours. The solvent was concentrated \textit{in vacuo} and the residue was dissolved with pentane (10 mL) and filtered through a sinter funnel and the pentane was concentrated \textit{in vacuo}. The crude was purified by kugelrohr distillation pressure 0.2 mmbar at room temperature to yield 240 as a colourless liquid (767 mg, 51% yield).\(^{113}\) \(^1\)H NMR (400 MHz, \(C_6D_6\)): \(\delta\) 3.90 (1H, q, \(J = 6.5\) Hz, CH), 3.79 (2H, q, \(J = 7.0\) Hz), 1.74 (3H, d, \(J = 6.5\) Hz), 1.10 (1H, t, \(J = 7.0\) Hz), 0.17–0.13 (9H, m, OSi(CH\(_3\))\(_3\)). This compound was characterized only by \(^1\)H NMR due to its volatility and instability and the data matched the literature.\(^{113}\)
(R*)-Ethyl-15-((15R*, 12S*, 7R*, 6R*)-10-methyl-13-oxo-6-(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphthalen-15-yl)propanoate, 241

Method A

To a solution of enone trans-decalin 113 (25 mg, 0.072 mmol) in dry CH₂Cl₂ (0.72 mL) at −78 °C was added TiCl₄ (0.010 mL, 0.10 mmol). After 5 minutes, TMS-silyl keten acetal 240 (0.020 mL, 0.14 mmol) was added and the reaction was stirred at −78 °C for 30 minutes. After this time, the reaction was quenched with saturated aqueous solution of NaHCO₃ (1.5 mL) at −78 °C, stirred for 45 minutes and then warmed to room temperature for a further 30 minutes. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of NaHCO₃ (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 241 as a pale yellow oil (15.0 mg, 48% yield).

Method B

A solution of TMS-enol trans-decalin 242 (20 mg, 0.048 mmol) in THF (0.48 mL) and aqueous solution of 2 M HCl (0.48 mL) was stirred at room temperature for 30 minutes. After this time, the reaction was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product 241 was used in the next step without further purification as a pale yellow oil (18.0 mg, 99% crude yield). Rf = 0.45 (EtOAc : hexane 10% : 90%). IR (ATR): νmax 2924, 2865, 1725 (C=O ester), 1713 (C=O ketone), 1462, 1380, 1146, 881 cm⁻¹. ¹H NMR (500 MHz, C₆D₆): δ 5.36–5.31 (1H, m, H-9), 4.15 (1H, dd, J = 10.8, 2.5 Hz, H-5), 3.98–3.87 (2H, m, H-18), 3.85 (1H, dd, J = 10.8, 2.1 Hz, H-5), 3.07 (1H, qd, J = 7.4, 3.7 Hz, H-16), 2.77 (1H, dd, J = 13.5, 3.9 Hz, H-14), 2.54 (1H, dd, J = 13.5, 13.5 Hz, H-14), 2.46–2.34 (2H, m, H-8 + H-11),
2.21–2.09 (2H, m, H-15 + H-11), 1.96–1.82 (2H, m, H-12 + H-7), 1.71–1.63 (1H, m, H-8), 1.61–1.58 (1H, m, H-6), 1.57 (3H, s, H-24), 1.08 (3H, d, J = 7.4 Hz, H-25), 1.04–0.99 (21H, m, OSiCH(CH$_3$)$_2$), 0.93 (3H, t, J = 7.2 Hz, H-19) ppm. $^{13}$C NMR (500 MHz, C$_6$D$_6$): $\delta$ 208.7 (C-13), 173.6 (C-17), 133.0 (C-10), 118.9 (C-9), 59.6 (C-18), 59.4 (C-5), 49.2 (C-12), 47.2 (C-6), 41.8 (C-15), 41.1 (C-14), 39.2 (C-16), 38.3 (C-7), 31.9 (C-8), 30.2 (C-11), 23.1 (C-24), 17.8 (OSiCH(CH$_3$)$_2$), 15.3 (C-25), 13.9 (C-19), 11.9 (OSiCH(CH$_3$)$_2$) ppm. MS (ESI): m/z 473 (M+Na$^+$); HRMS: found: (M+Na$^+$) 473.3070. C$_{26}$H$_{46}$NaO$_4$Si requires (M+Na$^+$) 473.3058. m/z 451 (M+H$^+$); HRMS: found: (M+H$^+$) 451.3250. C$_{26}$H$_{47}$O$_4$Si requires (M+H$^+$) 451.3238.

(R*)-Ethyl-15-((15S*, 12S*, 7R* 6R*)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-13-((trimethylsilyl)oxy)-6,15,12,11,8,7-hexahydonaphthalen-15-yl)propanoate, 242

To a solution of enone trans-decalin 113 (25 mg, 0.072 mmol) in dry CH$_2$Cl$_2$ (0.72 mL) at −78 °C, was added Yb(OTf)$_3$ (56 mg, 0.072 mmol). After 5 minutes, TMS-silyl keten acetal 240 (0.020 mL, 0.14 mmol) was added and the reaction was stirred at −78 °C for 2 hours. After this time, the reaction was quenched with saturated aqueous solution of NaHCO$_3$ (1.5 mL) at −78 °C, stirred for 45 minutes and then the mixture was warmed to room temperature and stirred for an additional 30 minutes. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of NaHCO$_3$ (10 mL) and brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product 242 was used in the next step without further purification as a pale yellow oil (36.0 mg, 99% crude yield). Rf = 0.58 (EtOAc : hexane 10% : 90%). IR (ATR): ν$_{max}$ 2866, 1725 (C=O ester), 1462, 1379, 1264, 1191, 876, 704 cm$^{-1}$. $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 5.41–5.36 (1H, m, H-9), 4.86 (1H, dd, J = 2.7, 2.7 Hz, H-14), 4.16–4.00 (2H, m, H-18), 3.97 (1H, dd, J = 10.5, 2.3 Hz,
H-5), 3.87 (1H, dd, J = 10.5, 2.8 Hz, H-5), 2.87 (1H, qd, J = 6.9, 5.6 Hz, H-16), 2.49 (1H, ddd, J = 10.6, 5.6, 2.7 Hz, H-15), 2.38–2.29 (1H, m, H-11), 2.27–2.17 (1H, m, H-8), 2.09–1.94 (1H, m, H-12), 1.78–1.71 (3H, m, H-8 + H-11 + H-7), 1.69 (3H, s, H-24), 1.52 (1H, dddd, J = 10.6, 10.6, 2.8, 2.3 Hz, H-6), 1.21 (3H, t, J = 7.3 Hz, H-19), 1.19 (3H, d, J = 6.9 Hz, H-25), 1.10–1.03 (21H, m, OSi(CH(CH₃)₂), 0.20 (9H, s, OSi(CH₃)₃) ppm. ^^13^C NMR (500 MHz, C₆D₆): δ 174.7 (C-17), 152.9 (C-13), 133.7 (C-10), 120.4 (C-9), 102.7 (C-14), 60.0 (C-18), 59.9 (C-5), 43.5 (C-6), 40.7 (C-12), 40.0 (C-16), 39.9 (C-15), 36.6 (C-7), 33.9 (C-8), 30.6 (C-11), 23.6 (C-24), 18.1 (OSiCH(CH₃)₂), 15.7 (C-25), 14.4 (C-19), 12.0 (OSiCH(CH₃)₂), 0.17 (OSi(CH₃)₃) ppm. MS (ESI): m/z 545 (M+Na⁺); HRMS: found: (M+Na⁺) 545.3476. C₂₉H₅₄NaO₄Si₂ requires (M+Na⁺) 545.3453.

(16R*, 15S*, 7R*, 6R*)-16,10-Dimethyl-17-oxo-17,16,15,12,11,8,7,6-octahydro-1H-benzo[h]isochromen-13-yl trifluoromethanesulfonate, 246

To a solution of freshly distilled diisopropylamine (0.020 mL, 0.12 mmol) in dry THF (0.12 mL) at −78 °C, was added n-BuLi (0.0510 mL, 2.36 M) and the solution was stirred at −78 °C for 30 minutes. A solution of ethylester-trans-decalin 241 (47 mg, 0.10 mmol) in dry THF (0.4 mL) was added and stirred at −78 °C for 1 hour. After this time, N-phenyl-bis-(trifluoromethanesulfonimide) 243 (43 mg, 0.12 mmol) in dry THF (1 mL) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to warm to room temperature for 1 hour. The reaction was then quenched with water (2 mL) and extracted with Et₂O (20 mL) and the organic layer was dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product (48 mg, 83% crude yield) was carried into the next step without further purification.

To a solution of this crude (40 mg, 0.071 mmol) in dry THF (0.71 mL), was added a 1.0 M solution of TBAF in THF (0.20 mL, 0.70 mmol) and the reaction was stirred at room temperature for 16 hours.

206
After this time, the reaction was diluted with EtOAc (10 mL), and washed with water (2 × 10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield 246 as a pale yellow oil (14.0 mg, 54% yield). \( \text{RF} = 0.25 \) (EtOAc : hexane 30% : 70%). IR (ATR): \( \nu_{\text{max}} \) 2919, 1735 (C=O), 1416, 1209, 1141, 1057, 825, 624 cm⁻¹. \(^1\)H NMR (500 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta \) 5.07–5.02 (1H, m, H-9), 4.92–4.89 (1H, dd, \( J = 11.8 \), 10.7 Hz, H-5), 3.15 (1H, dd, \( J = 11.8 \), 10.7 Hz, H-5), 2.31 (1H, qd, \( J = 7.5 \), 5.5 Hz, H-16), 2.12–2.04 (3H, m, H-12 + H-7 + H-11), 1.71–1.65 (1H, m, H-15), 1.61–1.49 (3H, m, H-8 + H-11), 1.43 (3H, s, H-24), 1.15–1.05 (1H, m, H-6), 0.94 (3H, d, \( J = 7.5 \) Hz, H-25) ppm. \(^{13}\)C NMR (500 MHz, \( \text{C}_6\text{D}_6 \)) : \( \delta \) 171.4 (C-17), 151.6 (C-13), 132.7 (C-10), 120.0 (C-9), 118.4 (C-14), 71.5 (C-5), 39.6 (C-12), 38.6 (C-7), 38.5 (C-15), 38.1 (C-16), 32.7 (C-11), 32.5 (C-6), 28.3 (C-8), 23.4 (C-24), 13.8 (C-25) ppm. \(^{19}\)F NMR (376 MHz, CDCl₃) : \( \delta \) -73.9 ppm. MS (APCI): m/z 381 (M+H⁺); HRMS: found: (M+H⁺) 381.0968. C₁₆H₂₀F₃O₅S requires (M+H⁺) 381.0978.

(16R*, 15R*, 12R*, 7S*, 6R*)-16,10-Dimethyl-16,10,15,12,11,8,7-hexahydro-1H-benzo[h]isochromen-17(6H)-one, 247

To a solution of triflate enol -trans-decalin 246 (14 mg, 0.040 mmol) in dry DMF (2.50 mL), were added \( \text{Bu}_3\text{N} \) (0.030 mL, 0.14 mmol), bis(acetate)bis(triphenylphosphine)palladium (II) (3.0 mg, 3.8 μmol) and formic acid (3.39 μL, 0.090 mmol) and the reaction was heated at 50 °C for 3 hours. After this time, the reaction was cooled to room temperature and diluted with Et₂O (10 mL), washed with water (5 × 10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield 247 as a pale yellow solid (5.0 mg, 51% yield). Melting point = 89–91 °C. \( \text{RF} = 0.31 \) (EtOAc : hexane 10% : 90%). IR
(ATR): $\nu_{\text{max}}$ 2923, 1736 (C=O), 1459, 1217, 1057, 790, 597 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.69 (1H, ddd, $J = 9.9, 2.2, 2.2$ Hz, H-13), 5.41 (1H, ddd, $J = 9.9, 2.2, 2.2$ Hz, H-14), 5.39–5.36 (1H, m, H-9), 4.50 (1H, dd, $J = 10.9, 5.0$ Hz, H-5), 4.01 (1H, dd, $J = 11.8, 10.9$ Hz, H-5), 2.86 (1H, qd, $J = 7.5, 5.6$ Hz, H-16), 2.64–2.58 (1H, m, H-15), 2.21–2.12 (1H, m, H-12), 2.09–2.00 (2H, m, H-8 + H-11), 1.95–1.74 (3H, m, H-6 + H-8 + H-11), 1.68 (3H, s, H-24), 1.40–1.32 (1H, m, H-7), 1.20 (3H, d, $J = 7.5$ Hz, H-25) ppm. $^{13}$C NMR (500 MHz, CDCl$_3$): $\delta$ 174.4 (C-17), 134.4 (C-10), 133.2 (C-13), 125.6 (C-9), 119.9 (C-14), 73.4 (C-5), 39.6 (C-15), 38.7 (C-16), 37.6 (C-12), 37.6 (C-7), 36.7 (C-11), 33.7 (C-6), 29.2 (C-8), 23.4 (C-24), 13.6 (C-25) ppm. MS (APCI): m/z 233 (M+H$^+$); HRMS: found: (M+H$^+$) 233.1531. C$_{15}$H$_{21}$O$_2$ requires (M+H$^+$) 233.1536.

$p$-methoxybenzyl 2,2,2-trichloroacetimidate, 300

To a solution of $p$-methoxybenzylalcohol (3.30 g, 12.0 mmol) in dry Et$_2$O (9 mL) at room temperature, was added NaH (60% dispersion in mineral oil, 241 mg, 6.06 mmol) and the mixture was stirred at room temperature for 30 minutes. After this time, the mixture was cooled to 0 °C and Trichloroacetonitrile (2.40 mL, 12.02 mmol) was added, and the reaction was stirred for 2 hours at room temperature. The reaction was then quenched with saturated solution of NaHCO$_3$ (10 mL) and extracted with Et$_2$O (4 × 20 mL). The combined organic layers were dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product 300 was used into the next step without further purification as a pale yellow oil (3.39 g, >99% crude yield). IR (ATR): $\nu_{\text{max}}$ 2955, 2836, 1661, 1612, 1514, 1175, 1033, 819 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.37 (1H, br. s.), 7.38 (2H, d, $J = 8.70$ Hz), 6.92 (2H, d, $J = 8.70$ Hz), 5.28 (2H, s), 3.82 (3H, s) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 162.8 (C), 159.8 (C), 129.8 (CH), 114.0 (CH), 70.8 (CH$_3$), 55.47 (CH$_3$) ppm. MS (ESI): m/z 303 (M+Na$^+$), m/z 305 (M+Na$^+$); HRMS: found:
(M+Na•) 303.9652 C_{10}H_{10}{^35}Cl_{3}NNaO_{2} requires (M+Na•) 303.9669. Characterisation of this compound matched the compound reported in the literature^{127}

(R*)-Methyl-21-((methoxybenzyl)oxy)propanoate, 301

To a solution of (+)-methyl-D-lactate 299 (1.15 mL, 12.0 mmol) in dry CH_{2}Cl_{2} (60.0 mL), were added 4-methoxybenzyl-2,2,2-trichloroacetimidate 300 (6.76 g, 12.0 mmol) in dry CH_{2}Cl_{2} (60.0 mL) followed by CSA (279 mg, 1.20 mmol). The reaction was stirred at room temperature for 24 hours. After this time, the reaction was diluted with CH_{2}Cl_{2} (50 mL) and quenched with saturated aqueous solution of NaHCO_{3} (10 mL). The aqueous phase was extracted with CH_{2}Cl_{2} (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL), dried with Na_{2}SO_{4}, filtered and concentrated \textit{in vacuo}. The crude product was purified by silica gel flash column chromatography (10% to 20% EtOAc in hexanes) to yield 301 as a pale yellow oil (2.45 g, 91% yield). [α]_{20}^{D} +76.45 (c 0.50, CHCl_{3}). \textbf{Rf} = 0.25 (EtOAc : hexane 20% : 80%). \textbf{IR} (ATR): \nu_{\text{max}} 2952, 1747 (C=O), 1586, 1444, 1205, 1174, 755 cm^{-1}. \textbf{^1H NMR} (500 MHz, CDCl_{3}): \delta 7.30 (2H, d, J = 8.7 Hz, Ar-H), 6.89 (2H, d, J = 8.7 Hz, Ar-H), 4.62 (1H, d, J = 11.5 Hz, H-26), 4.40 (1H, d, J = 11.5 Hz, H-26), 4.06 (1H, q, J = 6.8 Hz, H-21), 3.81 (3H, s, H-28), 3.76 (3H, s, H-27), 1.43 (3H, d, J = 6.8 Hz, H-22) ppm. \textbf{^13C NMR} (500 MHz, CDCl_{3}): \delta 173.9 (C-20), 159.5 (Ar), 129.8 (Ar-H), 129.7 (Ar), 113.9 (Ar-H), 73.7 (C-21), 71.8 (C-26), 55.4 (C-28), 52.1 (C-27), 18.9 (C-22) ppm. \textbf{MS} (ESI): m/z 247 (M+Na•); HRMS: found: (M+Na•) 247.0944. C_{12}H_{16}NaO_{4} requires (M+Na•) 247.0941.
(R*)-Methyl 21-((methoxybenzyl)oxy)propanal, 302

To a solution of PMB-ester 301 (270 mg, 1.20 mmol) in dry CH₂Cl₂ (12.0 mL) at −78 °C, was added a 1.0 M solution of Dibal-H in toluene (1.20 mL, 1.20 mmol) and the reaction was stirred at −78 °C for 1 hour. After this time, the reaction was quenched with dry acetone (1.2 mL) at −78 °C and allowed to warm to room temperature and then Rochelle’s salt 10% aqueous solution (20 mL) was added and stirred for 16 hours. The aqueous phase was then extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 20% EtOAc in hexanes) to yield 302 as a pale yellow oil (232 mg, 99% yield). [α]²⁰ D +39.89 (c 0.50, CHCl₃); Rf = 0.25 (EtOAc : hexane 20% : 80%). IR (ATR): ν max 2951, 1730 (C=O), 1612, 1513, 1450, 1371, 1175, 821 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 9.64 (1H, d, J = 1.9 Hz, H-20), 7.30 (2H, d, J = 8.7 Hz, Ar-H), 6.89 (2H, d, J = 8.7 Hz, Ar-H), 4.58 (1H, d, J = 11.5 Hz, H-26), 4.55 (1H, d, J = 11.5 Hz, H-26), 3.88 (1H,qd, J = 6.9, 1.9 Hz, H-21), 3.82 (3H, s, H-28), 1.32 (3H, d, J = 6.9 Hz, H-22) ppm. ¹³C NMR (500 MHz, CDCl₃): δ 203.6 (C-20), 159.6 (Ar), 129.7 (Ar-H), 129.4 (Ar), 114.0 (Ar-H), 79.1 (C-21), 71.7 (C-26), 55.3 (C-28), 15.3 (C-22) ppm. MS (ESI): m/z 217 (M+Na⁺); HRMS: found: (M+Na⁺) 217.0840. C₁₁H₁₄NaO₃ requires (M+Na⁺) 217.0835. Characterisation of this compound matched the compound reported in the literature.⁴⁴
To a suspension of methylphenylphosphonium bromide (405 mg, 1.13 mmol) in dry THF (4.0 mL) at 0 °C, was added n-BuLi (0.50 mL, 2.25 M) and the yellow solution was stirred for 1 hour. A solution of PMB-aldehyde 302 (182 mg, 0.930 mmol) in dry THF (2.0 mL) was added and the reaction was stirred at 0 °C for 2 hours. After this time, the reaction was filtered through a pad of silica with MTBE (10 mL) and the solvent was evaporated under nitrogen flow. The crude product 303 was used in the next reaction without further purification as a pale yellow oil (178 mg, >99% crude yield). \([\alpha]_{D}^{20} +1.21 \text{ (c 0.50, CHCl}_3); \text{Rf} = 0.62 \text{ (EtOAc : hexane 10% : 90%)}.\) IR (ATR): \(\nu_{\text{max}}\) 2923, 2853, 1588, 1611, 1462, 1246, 1071, 997 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.28 (2H, d, \(J = 8.5\) Hz, Ar-H), 6.88 (2H, d, \(J = 8.5\) Hz, Ar-H), 5.80 (1H, ddd, \(J = 17.3, 10.2, 7.4\) Hz, H-20), 5.21 (1H, ddd, \(J = 17.3, 1.5, 1.5\) Hz, H-19), 5.18 (1H, ddd, \(J = 10.2, 1.5, 1.5\) Hz, H-19), 4.51 (1H, d, \(J = 11.5\) Hz, H-26), 4.33 (1H, d, \(J = 11.5\) Hz, H-26), 3.93–3.89 (1H, m, H-21), 3.81 (3H, s, H-28), 1.28 (3H, d, \(J = 6.4\) Hz, H-22) ppm. \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta\) 159.1 (Ar), 140.9 (C-20), 130.9 (Ar), 129.3 (Ar-H), 115.9 (C-19), 113.8 (Ar-H), 75.7 (C-21), 69.6 (C-26), 55.3 (C-28), 21.4 (C-22) ppm. MS (ESI): \(m/z\) 215 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 215.1045. \(C_{12}H_{16}NaO_2\) requires (M+Na\(^+\)) 215.1043. Characterisation of this compound matched the compound reported in the literature.\(^{44}\)

**Allyl phosphonate, 304\(^{44}\)**

A mixture of TBAI (81 mg, 0.22 mmol), tris(2,2,2 trifluoroethyl)phosphite (0.810 mL, 3.62 mmol) and allylbromide (0.50 mL, 5.96 mmol) was stirred in a microwave at 180 °C for 3 hours. After this time,
the crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield 304 as a pale yellow oil (620 mg, 60% yield). Rf=0.25 (EtOAc : hexane 30% : 70%). IR (ATR): ν \text{max} 2659, 1506, 1439, 1210, 1126, 1094, 1004, 943 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 5.85–5.69 (1H, m), 5.41–5.27 (2H, m), 4.47–4.30 (4H, m), 2.80 (2H, dd, J = 22.9) ppm. \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}): δ 124.8 (d, J = 11.9 Hz), 122.5 (qd, J = 277.6, 7.3 Hz), 122.1 (d, J = 15.1 Hz), 62.3 (qd, J = 37.8, 5.8 Hz), 31.9 (d, J = 141.1 Hz) ppm. \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}): δ -75.3 (t, J = 7.9 Hz), -75.2 (t, J = 7.9 Hz), -75.1 (t, J = 7.9 Hz) ppm. MS (ESI): m/z 309 (M+Na\textsuperscript{+}); HRMS: found: (M+Na\textsuperscript{+}) 309.0084.

C\textsubscript{7}H\textsubscript{9}F\textsubscript{6}NaO\textsubscript{3}P requires (M+Na\textsuperscript{+}) 309.0086. Characterisation of this compound matched the compound reported in the literature.\textsuperscript{44}

\[(R^*, E)-\text{Bis}(2,2,2,\text{-trifluoroethyl})-(((21\text{-methoxybenzyl})\text{oxy})\text{pent-19-en-18-yl})\text{phosphonate}, 92\textsuperscript{44}\]

\[
\begin{array}{c}
\text{P(O(CH\textsubscript{2}CF\textsubscript{3})\textsubscript{2}}} \\
\text{18} \\
\text{19} \\
\text{20} \\
\text{21} \\
\text{22} \\
\text{23} \\
\text{24} \\
\text{25} \\
\text{26} \\
\text{27} \\
\text{28} \\
\text{29} \\
\end{array}
\]

To a solution of PMB-alkene 303 (30.7 mg, 0.160 mmol) and allyl phosphonate 304 (45.8 mg, 0.160 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (2.5 mL), was added Grubbs II generation catalyst (7.0 mg, 8.0 μmol) and the reaction was stirred under reflux for 36 hours. After this time, the solvent was concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10% to 40% EtOAc in hexane 30% : 70%). IR (ATR): ν \text{max} 2928, 1613, 1586, 1513, 1296, 1249, 1102 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.25 (2H, d, J = 8.9 Hz), 6.88 (2H, d, J = 8.9 Hz), 5.76–5.66 (1H, m), 5.64 (1H, m), 4.48 (1H, d, J = 11.5 Hz), 4.45–4.34 (4H, m), 4.31 (1H, d, J = 11.5 Hz), 3.97–3.89 (1H, m), 3.81 (3H, s), 2.83 (2H, dd, J = 22.0, 7.3 Hz), 1.26 (3H, d, J = 6.6 Hz) ppm. \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}): δ 159.1 (C=C), 139.7 (d, J = 15.0 Hz).
Hz, CH), 130.5 (C=C), 129.2 (CH), 121.2 (qd, \( J = 27.7, 6.9 \) Hz), 118.2 (d, \( J = 12.5 \) Hz, CH), 113.8 (CH), 74.5 (d, \( J = 2.3 \) Hz, CH), 69.4 (CH₂), 62.2 (qdd, \( J = 37.9, 6.2, 4.2 \) Hz, CH₂), 55.2 (CH), 29.6 (d, \( J = 141.1 \) Hz, CH₂), 21.2 (d, \( J = 3.1 \) Hz, \( \text{CH}_3 \)) ppm. \(^9\)F NMR (376 MHz, CDCl₃): \( \delta = -75.3 \) (q, \( J = 7.8 \) Hz) ppm. MS (ESI): m/z 473 (M+Na⁺); HRMS: found: (M+Na⁺) 473.0924. \( \text{C}_{17}\text{H}_{21}\text{F}_6\text{NaO}_5\text{P} \) requires (M+Na⁺) 473.0923.

Characterisation of this compound matched the compound reported in the literature.\(^{44}\)

\[ R^*\text{-15-}((15S^*, 12S^*, 7R^*, 6S^*)\text{-10-Methyl-13-oxo-6((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydonaphthalen-15yl)propanal, 290 } \]

\[ 15-((12S^*, 7R^*, 6S^*)\text{-10-Methyl-13-oxo-6((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydonaphthalen-15yl)propanal, 291 } \]

To a solution of crotyl-substituted \textit{trans}-decalins 276 and 277 (227 mg, 0.560 mmol) in dry THF (0.56 mL), were added B₂pin₂ (156 mg, 0.620 mmol), \textit{trans}-cyclohexanediol 287 (64.9 mg, 0.560 mmol) and Cs₂CO₃ (26.9 mg, 0.080 mmol). The reaction was stirred at 60 °C for 5 days and then cooled to 0 °C and an aqueous solution of 3 M NaOH (2.20 mL) was added, followed by addition of an 30% aqueous solution of H₂O₂ (1.10 mL) and the resultant mixture was stirred for 4 hours. Saturated aqueous solution of Na₂SO₃ (4.40 mL) was then added and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated \textit{in vacuo}. The crude product mixture of diols 288 and 289 was directly used in the next step without further purification.
To a solution of the mixture of diol intermediates **288** and **289** (53 mg, 0.12 mmol) in CH$_2$Cl$_2$ : H$_2$O (1 : 1, 1.20 mL) at 0 °C, was added NaO$_4$ (25.7 mg, 0.120 mmol) and the reaction was allowed to stir at room temperature for 24 hours. After this time, the mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated in *vacuo*. The crude product was purified by silica gel flash column chromatography (5% EtOAc in hexanes) to yield **290** as a pale yellow oil (14.0 mg, 30% yield) and **291** as a pale yellow oil (8.0 mg, 16% yield). *R*-15-((15S*, 12S*, 7R*, 6S*)-10-Methyl-13-oxo-6(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphtalen-15yl)propanal, **290**; *RF* = 0.38 (EtOAc : hexane 20% : 80%).

**IR (ATR):** \( \nu_{\text{max}} = 2922, 2864, 1714 \) (C=O, aldehyde + ketone), 1461, 1379, 1066, 917 cm$^{-1}$. **$^1$H NMR** (500 MHz, CDCl$_3$): \( \delta \) 9.62 (1H, d, J = 2.7 Hz, H-17), 5.33–5.29 (1H, m, H-9), 4.07 (1H, dd, J = 10.4, 5.4 Hz, H-5), 4.00 (1H, dd, J = 10.4, 6.5 Hz, H-5), 3.05–3.01 (1H, m, H-15), 2.64 (1H, dqq, J = 8.3, 5.2, 2.7 Hz, H-16), 2.61–2.56 (1H, m, H-12), 2.55–2.50 (1H, m, H-7), 2.49–2.43 (2H, m, H-11), 2.39 (1H, dd, J = 14.3, 4.6 Hz, H-14), 2.35–2.25 (1H, m, H-14), 1.95–1.83 (3H, m H-8 + H-6), 1.70 (3H, s, H-24), 1.11 (3H, d, J = 5.2 Hz, H-25), 1.08–1.02 (21H, m, OSiCH(CH$_3$)$_3$) ppm. **$^{13}$C NMR** (500 MHz, CDCl$_3$): \( \delta \) 210.3 (C-17), 203.3 (C-13), 132.0 (C-10), 118.9 (C-9), 63.2 (C-5), 48.2 (C-16), 44.7 (C-15), 41.6 (C-6), 41.5 (C-14), 38.0 (C-12), 37.5 (C-7), 27.9 (C-11), 27.7 (C-8), 23.4 (C-24), 18.1 (OSiCH(CH$_3$)$_3$), 12.6 (C-25), 11.9 (OSiCH(CH$_3$)$_3$) ppm. **MS (ESI):** m/z 429 (M+Na$^+$); HRMS: found: (M+Na$^+$) 429.2811. C$_{23}$H$_{24}$NaO$_3$Si requires (M+Na$^+$) 429.2795. m/z 407 (M+H$^+$); HRMS: found: (M+H$^+$) 407.2979. C$_{24}$H$_{25}$O$_3$Si requires (M+H$^+$) 407.2976. 15-((12S*, 7R*, 6S*)-10-Methyl-13-oxo-6(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphtalen-15yl)propanal, **291**; *RF* = 0.41 (EtOAc : hexane 20% : 80%). **IR (ATR):** \( \nu_{\text{max}} = 2864, 1714 \) (C=O, aldehyde + ketone), 1462, 1094, 788, 680 cm$^{-1}$. **$^1$H NMR** (400 MHz, CDCl$_3$): \( \delta \) 9.57 (1H, d, J = 2.9 Hz, H-17), 5.35–5.29 (1H, m, H-9), 3.88 (1H, dd, J = 10.7, 5.1 Hz, H-5), 3.58 (1H, dd, J = 10.7, 9.4 Hz, H-5), 3.00–2.94 (1H, m, H-15), 2.57–2.52 (1H, m, H-16), 2.51–2.44 (2H, m, H-14), 2.32 (1H, ddd, J = 11.8, 7.9, 7.5 Hz, H-12), 2.20–2.14 (1H, m, H-8), 2.14–2.10 (2H, m, H-11), 2.10–2.03 (1H, m, H-6), 1.94–1.86 (1H, m, H-8), 1.76 (1H, dddd, J = 12.1, 11.8, 10.3, 3.9, H-7), 1.68 (3H, s, H-24), 1.09 (3H, d, J = 5.3 Hz, H-25), 1.09–1.02 (21H, m, OSiCH(CH$_3$)$_3$) ppm. **$^{13}$C NMR** (400 MHz, CDCl$_3$): \( \delta \) 211.9 (C-17), 204.3 (C-
13), 133.3 (C-10), 119.1 (C-9), 62.4 (C-5), 49.1 (C-12), 46.5 (C-16), 45.9 (C-6), 42.7 (C-14), 37.1 (C-7),
35.5 (C-15), 32.5 (C-8), 29.6 (C-11), 23.4 (C-24), 18.0 (OSiCH(CH3)2), 12.6 (C-25), 11.9 (OSiCH(CH3)2)
ppm. MS (ESI): m/z 429 (M+Na+); HRMS: found: 429.2805 (M+Na+). C24H42NaO3Si requires (M+Na+)
429.2795.

(((15R*, 12R*, 7S*, 6R*)-15-((S*)But-14-en-15yl)-10-methyl-6,15,12,11,8,7-hexahydronaphthalen-6-
yl)methoxy)triisopropylsilane, 294

(((12R*, 7S*, 6R*)-15-(But-14-en-15yl)-10-methyl-6,15,12,11,8,7-hexahydronaphthalen-6-
yl)methoxy)triisopropylsilane, 295

To a solution of freshly distilled diisopropylamine (0.10 mL, 0.65 mmol) in dry THF (0.65 mL) at −78 °C,
was added n-BuLi (0.31 mL, 2.15 M) and the solution was stirred at −78 °C for 30 minutes. A solution
of trans-decalin 276 and 277 (220 mg, 0.54 mmol) in dry THF (1 mL) was added and stirred for 1 hour.
After this time, N-phenyl-bis-(trifluoromethanesulfonylimide) 243 (232 mg, 0.650 mmol) in dry THF (1
mL) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to
warm to room temperature for 1 houd. The reaction was then quenched with water (2 mL) and
extracted with Et2O (20 mL). The organic layer was dried with Na2SO4, filtered and concentrated in vacuo. The crude product (401 mg, 79% yield) was carried out into the next step, without further
purification.

To a solution of model enol triflate trans-decalin 292 and 293 (286 mg, 0.530 mmol) in dry DMF (33.1
mL), were added Bu3N (0.440 mL, 1.86 mmol), bis(acetato)bis(triphenylphosphate)palladium (II) (38
mg, 0.050 mmol) and formic acid (0.050 mL, 1.86 mmol) and the reaction was heated at 50 °C for 2 hours. After this time, the reaction was cooled to room temperature and MTBE (10 mL) was added and washed with water (5 x 20 mL) and brine (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield 294 and 295 as an inseparable mixture in a 2 : 1 ratio as a pale yellow oil (115 mg, 56% yield over 3 steps). Rf = 0.95 (EtOAc : hexane 10% : 90%). On a mixture IR (ATR): νmax 2923, 2865, 1461, 1097, 907, 881, 791, 680 cm⁻¹. Integration of the ¹H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. ¹H NMR (400 MHz, CDCl₃) Major 294 + Minor 295: δ 6.01–5.90 (1H, m, 294), 5.85–5.44 (5H, m, 294 + 295), 5.43–5.29 (2H, m, 295), 5.02–4.94 (4H, m, 294 + 295), 3.94 (1H, dd, J = 10.1, 4.6 Hz, 294), 3.87–3.82 (2H, m, 295), 3.72 (1H, dd, J = 10.1, 10.1 Hz, 294), 2.79–2.72 (1H, m, 294), 2.64–2.56 (2H, m, 294 + 295), 2.13–1.93 (8H, m, 294 + 295), 1.92–1.82 (2H, m, 294 + 295), 1.79–1.73 (2H, m, 294 + 295), 1.67 (6H, s, 294 + 295), 1.53–1.35 (3H, m, 294 + 295), 1.13–1.01 (42H, OSiCH(CH₃)₂), 0.95 (6H, d, J = 6.9 Hz, 294 + 295) ppm. ((15R*, 12R*, 7S*, 6R*)-15-(((5*)-But-14-en-15yl)-10-methyl,-6,15,12,11,8,7-hexahyronaphthalen-6-yl)methoxy)triisopropylsilane, 294; ¹³C NMR (400 MHz, CDCl₃): δ 145.3 (CH), 134.2 (C=C), 132.3 (CH), 126.9 (CH), 120.7 (CH), 112.0 (CH₂), 62.6 (CH₂), 45.0 (CH), 40.1 (CH), 38.7 (CH), 35.6 (CH), 34.6 (CH), 31.9 (CH₂), 30.8 (CH₂), 23.4 (CH₃), 18.1 (OSiCH(CH₃)₂), 16.2 (CH₃), 11.9 (OSiCH(CH₃)₂) ppm. ((12R*, 7S*, 6R*)-15-(But-14-en-15yl)-10-methyl,-6,15,12,11,8,7-hexahyronaphthalen-6-yl)methoxy)triisopropylsilane, 295; ¹³C NMR (400 MHz, CDCl₃): δ 143.9 (CH), 133.8 (C=C), 131.0 (CH), 128.7 (CH), 120.9 (CH), 112.0 (CH₂), 60.4 (CH₂), 45.2 (CH), 43.4 (CH), 41.3 (CH), 38.9 (CH), 37.9 (CH), 31.6 (CH₂), 29.4 (CH₂), 23.5 (CH₃), 18.1 (OSiCH(CH₃)₂), 14.1 (CH₃), 12.0 (OSiCH(CH₃)₂) ppm. On a mixture MS (APCI): m/z 389 (M+H⁺); HRMS: found: (M+H⁺) 389.3228. C₂₅H₄₅OSi requires (M+H⁺) 389.3234.
To a solution of crotyl-substituted trans-decalin 294 and 295 (115 mg, 0.280 mmol) in dry THF (0.31 mL), were added \( \text{B}_2\text{pin}_2 \) (76 mg, 0.31 mmol), trans-cyclohexanediol 287 (35 mg, 0.31 mmol) and \( \text{Cs}_2\text{CO}_3 \) (17 mg, 0.040 mmol). The reaction was stirred at 60 °C for 5 days and then cooled to 0 °C and an aqueous solution of 3 M NaOH (1.20 mL) was added, followed by addition of an 30% aqueous solution of \( \text{H}_2\text{O}_2 \) (0.60 mL) and the resultant mixture was stirred for 4 hours. Saturated aqueous solution of \( \text{Na}_2\text{SO}_3 \) (2.40 mL) was added and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with \( \text{Na}_2\text{SO}_4 \), filtered and concentrated \textit{in vacuo}. The crude product mixture of diols 296 and 297 was directly used in the next step without further purification.

To a solution of the mixture of diol intermediates 296 and 297 (162 mg, 0.280 mmol) in \( \text{CH}_2\text{Cl}_2: \text{H}_2\text{O} \) (1 : 1, 3.0 mL) at 0 °C, was added \( \text{NaIO}_4 \) (128 mg, 0.560 mmol) and the reaction was allowed to stir at room temperature for 24 hours. After this time, the mixture was extracted with \( \text{CH}_2\text{Cl}_2 \) (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with \( \text{Na}_2\text{SO}_4 \), filtered and concentrated \textit{in vacuo}. The crude product was purified by silica gel flash column chromatography (5% EtOAc in hexanes) to yield 162 and 298 as an inseparable mixture in a 2 : 1 ratio as a pale yellow oil (49.0 mg, 60% yield b.r.s.m.). \( R_f = 0.57 \) (EtOAc : hexane 10% : 90%). On a mixture IR (ATR): \( \nu_{\text{max}} \) 2924,
2865, 1725 (C=O), 1462, 1096, 882, 796 cm\(^{-1}\). Integration of the \(^1\)H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. \(^1\)H NMR (500 MHz, CDCl\(_3\)): Major \textbf{162} + Minor \textbf{298}: \(\delta\) 9.76 (1H, d, \(J = 5.8\) Hz, \textbf{298}), 9.70 (1H, d, \(J = 0.9\) Hz, \textbf{162}), 5.68 (1H, d, \(J = 10.4, 1.2, 1.2\) Hz, \textbf{162}), 5.60 (1H, d, \(J = 10.2, 1.2, 1.2\) Hz, \textbf{298}), 5.43–5.40 (1H, m, \textbf{298}), 5.16 (1H, d, \(J = 10.2, 2.3\) Hz, \textbf{298}), 3.97 (1H, d, \(J = 10.5, 4.8\) Hz, \textbf{162}), 3.87–3.81 (2H, m, \textbf{162}), 3.60 (1H, m, \textbf{298}), 3.21–3.18 (2H, m, \textbf{162} + \textbf{298}), 2.85–2.76 (3H, m, \textbf{162} + \textbf{298}), 2.37–2.27 (3H, m, \textbf{162} + \textbf{298}), 2.09–1.95 (7H, m, \textbf{162} + \textbf{298}), 1.79–1.70 (3H, m, \textbf{162} + \textbf{298}), 1.67 (6H, s, \textbf{162} + \textbf{298}), 1.14–1.00 (42H, OSiCH(\(\text{CH}_3\)_2), \textbf{162} + \textbf{298}), 0.98–0.96 (6H, d, \(J = 6.7\) Hz, \textbf{162} + \textbf{298}) ppm. \(R^*\)-15-(((triisopropylsilyl)oxy)methyl)-6,15,12,11,8,7-hexahydonaphthalen-15-yl)propanal, \textbf{162}; \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta\) 205.5 (C=O), 134.3 (C=C), 133.5 (CH), 125.8 (CH), 120.5 (CH), 62.4 (\(\text{CH}_2\)), 46.2 (CH), 44.1 (CH), 38.4 (CH), 37.2 (\(\text{CH}_2\)), 34.5 (CH), 34.5 (\(\text{CH}_3\)), 30.4 (CH), 23.4 (\(\text{CH}_3\)), 18.1(OSiCH(\(\text{CH}_3\)_2)), 14.1 (\(\text{CH}_3\)), 11.9 (OSiCH(\(\text{CH}_3\)_2)) ppm; \(15-((\text{12R}^*, \text{7S}^*, 6\text{R}^*)\)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-6,15,12,11,8,7-hexahydonaphthalen-15-yl)propanal, \textbf{298}; \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta\) 205.3 (C=O), 133.7 (C=C), 133.6 (CH), 125.9 (CH), 120.8 (CH), 60.9 (\(\text{CH}_3\)), 47.6 (CH), 42.9 (CH), 37.4 (\(\text{CH}_2\)), 37.2 (CH), 36.4 (CH), 36.3 (\(\text{CH}_2\)), 30.3 (CH), 23.4 (\(\text{CH}_3\)), 18.1(OSiCH(\(\text{CH}_3\)_2)), 14.2 (\(\text{CH}_3\)), 11.9 (OSiCH(\(\text{CH}_3\)_2)) ppm. On a mixture MS (ESI): m/z 413 (M+Na\(^+\)); HRMS: found: (M+Na\(^+\)) 413.2829. \(\text{C}_{24}\text{H}_{42}\text{NaO}_2\text{Si}\) requires (M+Na\(^+\)) 413.2846. m/z 391 (M+H\(^+\)); HRMS: found: (M+H\(^+\)) 391.3020. \(\text{C}_{24}\text{H}_{43}\text{O}_2\text{Si}\) requires (M+H\(^+\)) 391.3027.
(15S*, 6S*)-15-Allyl-6-(((triisopropylsilyl)oxymethyl)cyclohex-13-enone, 184

In a microwave tube, to a solution of allyl-cyclohexanone 183 (75.7 mg, 0.230 mmol) in chlorobenzene (2.3 mL), were added Pd(OAc)$_2$ (2.25 mg, 0.010 mmol), 4-4’ditertbutyl-2-2’bypiridyl (2.68 mg, 0.010 mmol) and KNO$_3$ (12.1 mg, 0.121 mmol). The reaction was stirred at 120 °C for 5 days under O$_2$ atm. After this time, the reaction was cooled to room temperature and the solvent was evaporated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 184 as a pale yellow oil (23.0 mg, 31% yield, starting material recovered 28.0 mg, 37% yield, 68% yield b.r.s.m.). **RF** = 0.48 (EtOAc : hexane 10% : 90%). **IR** (ATR): $\nu_{\text{max}}$ 2941, 2865, 1680 (C=O), 1462, 1382, 1247, 1067, 995 cm$^{-1}$.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 6.95 (1H, dd, $J$ = 10.5, 4.6 Hz, H-7), 6.10 (1H, dd, $J$ = 10.5, 1.8 Hz, H-12), 5.75 (1H, dddd, $J$ = 15.6, 12.5, 7.3, 5.5 Hz, H-17), 5.10–5.03 (2H, m, H-18), 3.94 (1H, dd, $J$ = 9.8, 6.4 Hz, H-5), 3.87 (1H, dd, $J$ = 9.8, 5.5 Hz, H-5), 2.71–2.65 (1H, m, H-15), 2.58 (1H, dd, $J$ = 17.4, 11.3 Hz, H-14), 2.39 (1H, dd, $J$ = 17.4, 4.1 Hz, H-14), 2.36–2.32 (1H, m, H-6), 2.26 (1H, dddddd, $J$ = 13.7, 6.4, 5.5, 1.4, 1.4 Hz, H-16), 2.10 (1H, dddddd, $J$ = 13.7, 7.3, 7.3, 0.9, 0.9 Hz, H-16), 1.14–1.04 (21H, m, OSi(CH$_3$)$_3$) ppm. **$^{13}$C NMR** (400 MHz, CDCl$_3$): $\delta$ 199.9 (C-13), 151.4 (C-7), 135.9 (C-17), 130.2 (C-12), 117.1 (C-18), 62.5 (C-5), 41.5 (C-6), 41.4 (C-14), 35.9 (C-15), 35.3 (C-16), 18.0 (OSiCH(CH$_3$)$_3$), 11.8 (OSiCH(CH$_3$)$_3$) ppm. **MS (ESI)**: m/z 345 (M+Na$^+$); HRMS: found: (M+Na$^+$) 345.2224. **C$_{39}$H$_{54}$NaO$_2$Si** requires (M+Na$^+$) 345.2220. m/z 323 (M+H$^+$); HRMS: found: (M+H$^+$) 323.2402. **C$_{30}$H$_{34}$O$_2$Si** requires (M+H$^+$) 323.2401.
In a microwave tube, to a solution of cholesterol 180 (115 mg, 0.300 mmol) in chlorobenzene (3.0 mL), were added Pd(OAc)$_2$ (4.49 mg, 0.020 mmol), 4-4’ditertbutil-2-2’bypiridyl (5.37 mg, 0.020 mmol) and KNO$_3$ (15.2 mg, 0.150 mmol). The reaction was stirred at 120 °C for 3 days under O$_2$ atm. After this time, the reaction was cooled to room temperature and the solvent was evaporated in vacuo. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield 181 as a pale yellow oil (21.0 mg, 18% yield) and 182 as a pale yellow solid (28.0 mg, 24% yield).

(S, S, R, R, S)-Dimethyl-((R)-methylheptan-yl)dodecahydrocyclopenta[a]phenanthren-one, 181


1H NMR (400 MHz, CDCl$_3$): $\delta$ 6.18‒6.06 (2H, m), 5.69‒5.65 (1H, m, CH), 2.71‒2.52 (1H, m), 2.49‒2.39 (1H, m), 2.23‒2.15 (1H, m), 2.07 (1H, ddd, $J$ = 12.5, 2.9, 2.9 Hz), 2.00 (1H, ddd, $J$ = 13.2, 5.4, 2.1 Hz), 1.96‒1.85 (2H, m), 1.84–1.76 (1H, m), 1.71 (1H, ddd, $J$ = 13.7, 13.7, 5.0 Hz), 1.58–1.47 (3H, m), 1.46–1.29 (5H, m), 1.28–1.13 (7H, m), 1.11 (3H, s), 0.92 (3H, d, $J$ = 6.4 Hz), 0.88 (3H, d, $J$ = 1.8 Hz), 0.86 (3H, d, $J$ = 1.8 Hz), 0.76 (3H, s) ppm. $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 199.8 (C=O), 164.2 (C-C), 141.7 (CH), 127.7 (CH), 123.4 (CH), 56.0 (CH), 53.4 (CH), 50.6 (CH), 43.4 (C-C), 39.5 (CH$_3$), 39.4 (CH$_3$), 37.7 (CH), 36.1 (C-C), 36.0 (CH$_3$), 35.8 (CH), 33.9 (CH$_3$), 33.8 (CH$_3$), 28.1 (CH$_3$), 27.9 (CH), 23.8 (CH$_3$), 23.7(CH$_3$), 22.8 (CH$_3$), 22.5 (CH$_3$), 20.6 (CH$_2$), 18.6 (CH$_3$), 16.3 (CH$_3$), 11.9 (CH$_3$).
ppm. **MS** (ESI): m/z 405 (M+Na⁺); HRMS: found: (M+Na⁺) 405.3111. C₂₇H₄₂NaO requires (M+Na⁺) 405.3128. m/z 383 (M+H⁺); HRMS: found: (M+H⁺) 383.3302. C₂₇H₄₃O requires (M+H⁺) 383.3308. (S, S, R, R, S, R)-Dimethyl-((R)-methylheptanyl)-decahydro-cyclopenta[a]phenanthrene-dione, **182**; [α]²₀ = 13.9 (c 1.00, CHCl₃). **Melting point** = 81–83 °C. **Rf** = 0.28 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν max 2946, 2867, 1683 (C=O), 1465, 1415, 1381, 1327, 1219, 1082, 915 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃): δ 6.16 (1H, s), 2.68 (1H, dd, J = 15.8, 3.9 Hz), 2.61–2.41 (2H, m), 2.18–2.06 (2H, m), 2.05–2.02 (1H, m), 1.95–1.82 (4H, m), 1.68–1.58 (2H, m), 1.57–1.44 (3H, m), 1.41–1.19 (6H, m), 1.16 (3H, s), 1.13–1.08 (5H, m), 0.92 (3H, d, J=6.4 Hz), 0.87 (3H, d, J=1.5 Hz), 0.85 (3H, d, J = 1.5 Hz), 0.72 (3H, s) ppm. **¹³C NMR** (400 MHz, CDCl₃): δ 202.4 9 (C=O), 199.5 (C=O), 161.1 (C-C), 125.4 (CH), 56.5 (CH), 55.9 (CH), 50.9 (CH), 46.8 (CH₂), 42.5 (C-C), 39.8 (C-C), 39.4 (CH₃), 39.1 (CH₃), 36.0 (CH₂), 35.6 (CH), 35.5 (CH₂), 34.1 (CH), 33.9 (CH₂), 27.6 (CH + CH₂), 23.9 (CH₃), 23.7 (CH₃), 22.8 (CH₃), 22.5 (CH₃), 20.8 (CH₂), 18.6 (CH₃), 17.5 (CH₃), 11.8 (CH₃) ppm. **MS** (ESI): m/z 421 (M+Na⁺); HRMS: found: (M+Na⁺) 421.3080. C₂₇H₄₂NaO₂ requires (M+Na⁺) 421.3077.
13. Abbreviations

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<td>microwaves</td>
</tr>
<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>sodium bicarbonate</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear overhauser effect</td>
</tr>
<tr>
<td>O₂</td>
<td>oxygen</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>palladium acetate</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
</tbody>
</table>
Pd(PPh$_3$)$_4$  palladium tetrakis(triphenylphosphine)
Ph  phenyl
PhI(OAc)$_2$  diacetoxyiodo benzene
PhSH  thiophenyl
PKS  polyketide synthase
PPh$_3$  triphenylphosphine
PMB  $p$-methoxybenzyl
Py  pyridine
RNA  ribonucleic acid
rt  room temperature
SmI$_2$  samarium diodide
SiO$_2$  silica
TBAF  tetra-$n$-butylammonium fluoride
TBS  $t$-butyldimethylsilyl
TES  triethylsilyl
Tf  triflate
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TLC  thin layer chromatography
TMS  trimethylsilyl
TS  transition state
$\nu$  vibration frequency (cm$^{-1}$)
14. References


