

**Towards the Total Synthesis of  
 $1\alpha,25$ -dihydroxylumisterol**

A. Simon Partridge

*Julia Laboratory, Department of Chemistry, Imperial College London,  
South Kensington Campus, London SW7 2AZ, United Kingdom*

**September 2012**

A thesis submitted as partial fulfilment of the requirements for the degree of Doctor of Philosophy, Imperial College London.

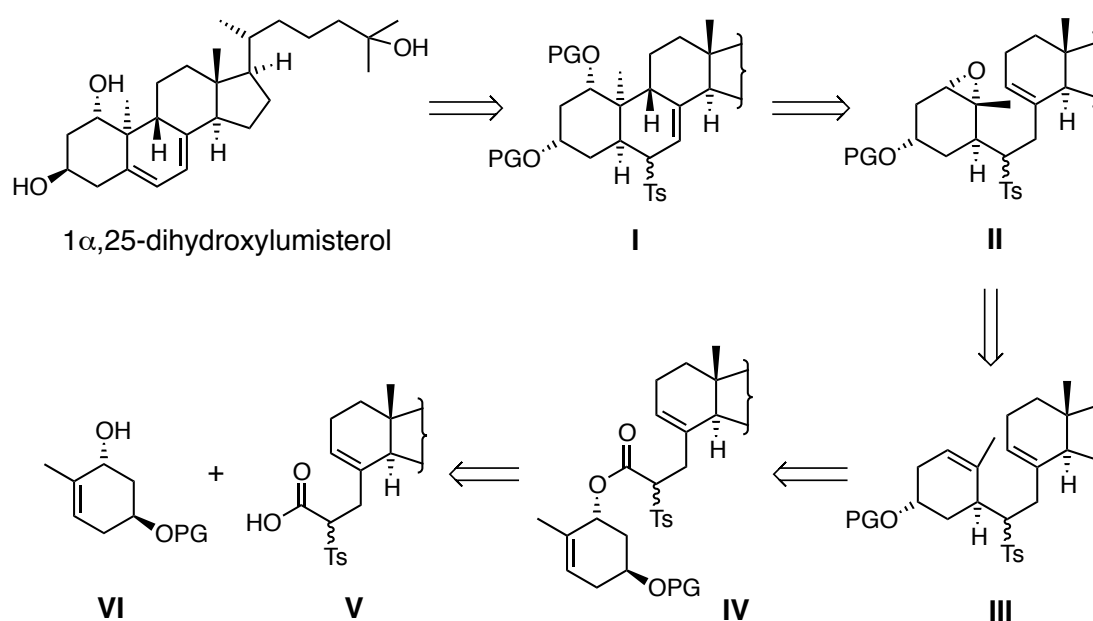
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## Abstract

This thesis is divided into three chapters.

The first chapter provides a brief review on recent work in the application of cascade cyclisations to the total synthesis of natural products. This is followed by a review of the decarboxylative Claisen rearrangement (dCr), a novel variant of the Ireland-Claisen reaction in which tosylacetic esters of allylic alcohols are transformed into homoallylic sulfones using BSA and potassium acetate, and its applications.

The second chapter discusses the results of our studies towards the total synthesis of  $1\alpha,25$ -dihydroxylumisterol *via* a proposed route containing two key steps; a cascade-inspired, Lewis-acid mediated cyclisation to form the steroid B-ring in **I**, and the dCr reaction of tosylacetic ester **IV** to give diene **III**. Successful syntheses, as well as problems encountered along this route will be discussed, as well as the measures taken to adapt the synthesis to circumvent these problems.



The third and final chapter contains experimental procedures and characterisation data for the prepared compounds.

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## **Declaration**

I certify that all work in this thesis is solely my own, except where explicitly stated and appropriately referenced. No part of this thesis has been submitted previously for a degree at this, or any other academic institution.

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*“Everybody has a book in them, but in most cases that’s where it should stay”*

Christopher Hitchens

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## Acknowledgements

Thanks firstly to Professor Don Craig for providing me with this research project, for his support, ideas and enthusiasm throughout, and for being a thoroughly decent bloke.

I would also like to thank my GSK industrial supervisors, Dr. Amanda Lucas and Dr. Dave Macpherson, for their advice, assistance and support.

Many thanks to the stores boys, Paul and Jame, for big hugs, good chat and, of course, sound chemical services. Thanks also to spectroscopic services; Peter Haycock, Dick Sheppard, Jason Barton and Lisa Haigh. Particular thanks goes to Pete for going beyond the call of duty to aid structure elucidation.

A whole bunch of love and thanks must go to the DC group. To my guys (Rich, Joe, Toby, Niels, Alex, Kiyo, Jason C), my girls (Shu, Claire, Jas, Sophie) and my underlings (Marc, Guto, Signe, Shan<sup>2</sup>), we had more fantastic/hilarious/ridiculous times than I can even recall. Special thanks is reserved for my lab family, Claire, Joe, and Niels, who were forced to put up with me more than most. Thanks also to the PP group members; Lee, Alex, Lewis and Jason W.

The biggest thanks of all must go to the most unexpected, peculiar and rewarding find of my entire PhD – Jenny. Words can't adequately express my gratitude for her support, love, and patience over the last few years. Laughing with you every day made this possible.

Finally, thank you to my family, who, as ever, have been the epitome of unconditional love and support.

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## Abbreviations

|         |                                           |
|---------|-------------------------------------------|
| Ac      | acetyl                                    |
| acac    | acetylacetonate                           |
| Alloc   | allyloxycarbonyl                          |
| Ar      | aryl                                      |
| Bn      | benzyl                                    |
| Boc     | <i>tert</i> -butyloxycarbonyl             |
| BSA     | <i>N,O</i> -bis(trimethylsilyl)acetamide  |
| Bu      | butyl                                     |
| Bz      | benzoyl                                   |
| cat.    | catalytic                                 |
| Cp      | cyclopentadiene                           |
| CSA     | camphorsulfonic acid                      |
| d       | doublet                                   |
| DBU     | 1,8-diazabicycloundec-7-ene               |
| DCC     | dicyclohexylcarbodiimide                  |
| dCr     | decarboxylative Claisen rearrangement     |
| DDQ     | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL-H | diisobutylaluminium hydride               |
| DIC     | diisopropylcarbodiimide                   |
| DIPA    | diisopropylamine                          |

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|       |                                         |
|-------|-----------------------------------------|
| DMAP  | 4-(dimethylamino)pyridine               |
| DMDO  | dimethyldioxirane                       |
| DMF   | <i>N,N</i> -dimethylformamide           |
| DMSO  | dimethylsulfoxide                       |
| dr    | diastereomeric ratio                    |
| ee    | enantiomeric excess                     |
| Et    | ethyl                                   |
| HMDS  | hexamethyldisilazide                    |
| HMPA  | hexamethylphosphoramide                 |
| Hz    | Hertz                                   |
| LCMS  | liquid-chromatography mass spectrometry |
| LDA   | lithium diisopropylamide                |
| LG    | leaving group                           |
| mCPBA | 3-chloroperoxybenzoic acid              |
| Me    | methyl                                  |
| MIP   | 2-methoxyisopropyl                      |
| MOM   | methoxymethyl                           |
| MS    | mass spectrometry                       |
| MW    | microwave                               |
| nap   | naphthyl                                |
| NMP   | <i>N</i> -methyl-2-pyrrolidone          |
| NMR   | nuclear magnetic resonance spectrometry |
| Ns    | 4-nitrobenzenesulfonyl                  |

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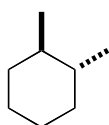
|                |                                         |
|----------------|-----------------------------------------|
| PG             | protecting group                        |
| Ph             | phenyl                                  |
| PMB            | <i>p</i> -methoxybenzyl                 |
| PPTS           | pyridinium <i>p</i> -toluenesulfonate   |
| Pr             | propyl                                  |
| <i>p</i> -TSA  | <i>p</i> -toluenesulfonic acid          |
| q              | quartet                                 |
| R <sub>f</sub> | retention factor                        |
| rt             | room temperature                        |
| s              | singlet                                 |
| t              | triplet                                 |
| TBAF           | tetra- <i>n</i> -butylammonium fluoride |
| TBS            | tert-butyldimethylsilyl                 |
| TES            | triethylsilyl                           |
| Tf             | trifluoromethanesulfonyl                |
| TFA            | trifluoroacetic acid                    |
| THF            | tetrahydrofuran                         |
| TIPS           | triisopropylsilyl                       |
| TLC            | thin layer chromatography               |
| TMS            | trimethylsilyl                          |
| Tris           | 2,4,6-triisopropylphenylsulfonyl        |
| Ts             | <i>p</i> -toluenesulfonyl               |

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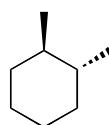
## Stereochemical Notation

The Maehr convention for indicating relative and absolute stereochemistry has been used throughout this report.<sup>1</sup> Therefore, solid and broken lines are used to denote racemates, and solid and broken wedges denote absolute configuration.



Racemate

Relative stereochemistry

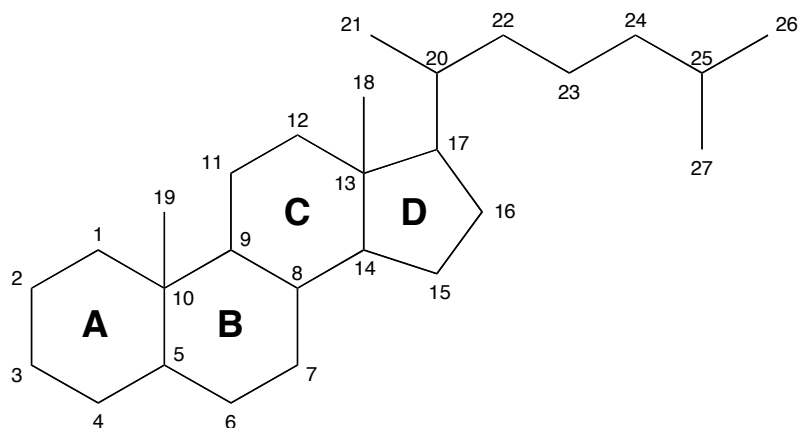


Single enantiomer

Absolute stereochemistry

## Steroid Notation

During this report the following steroidal numbering system will be used.



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<sup>1</sup> Maehr, H. *J. Chem. Ed.* **1985**, 62, 114.

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## Chapter 1

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# *Introduction*

## **1.1 *Cascade cyclisations in natural product synthesis***

### **1.1.1 Introduction**

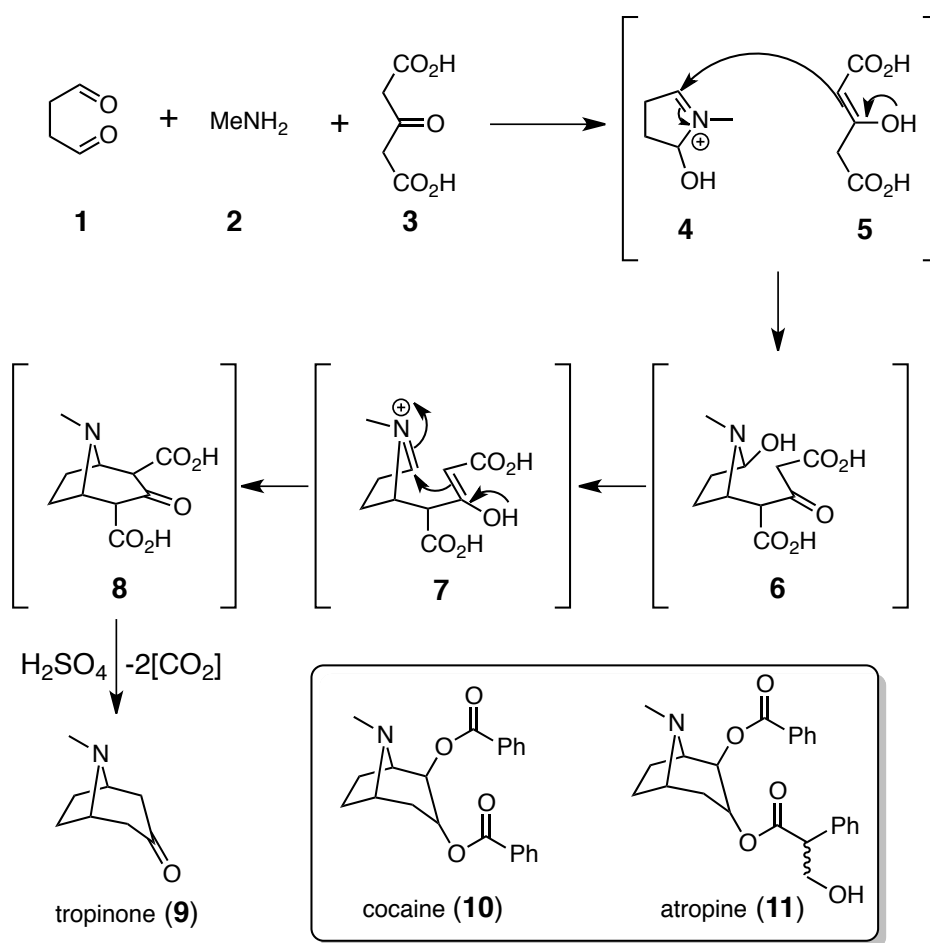
Traditionally, the pursuit of chemical synthesis has involved combining individual bond-forming processes into reaction sequences, with workup, and often purification, required between each step. Advances made over decades of modern chemical research have provided us with a range of synthetic tools that enable the construction of almost any complex molecule. But, in addition, a modern chemist must also consider the efficiency of their work, both to limit environmental impact and maximise the economic viability of a synthetic process.<sup>1</sup> There are many ways in which to approach improved efficiency in chemical synthesis,<sup>2</sup> but arguably one of the most academically exciting and burgeoning areas is the development of processes in which multiple, often chemically distinct, bonds are installed in a controlled sequential fashion in a single synthetic procedure. These cascade (or domino) processes have received a great deal of attention in recent years,<sup>3</sup> with the most impressive examples allowing multiple stereocentres and complex cyclic structures to be installed in a single step. Although there is some argument in the literature as to how best to describe and differentiate between these processes, for the purposes of this piece, the terms “cascade” and “domino” will be used interchangeably under the definition provided by Tietze as “two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond-forming reactions”.<sup>4</sup> This type of cascade is not to be confused with other distinctly different processes such as photochemical, biochemical or electronic cascades.

The following mini-review is not intended as a comprehensive discussion of the work in this fascinating area; a number of excellent recent reviews already provide greater scope.<sup>1</sup> Instead, it highlights interesting examples of ring-forming cascades incorporated into natural product syntheses since 2006.

### 1.1.2 Background

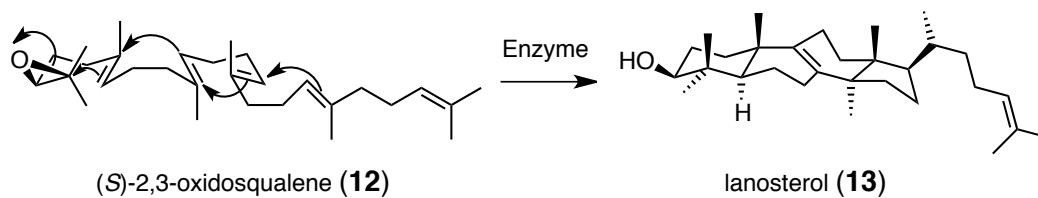
Whilst cascade reactions are becoming more commonplace in natural product synthesis, they are by no means a new concept. Nature, of course, utilises enzyme-catalyzed cascades in biosynthesis. As understanding of these biosyntheses developed, so did the work of chemists looking to recreate these cascades in biomimetic approaches to total syntheses. Interestingly, the first biomimetic cascade total synthesis was achieved before knowledge of the biosynthesis was revealed; Robinson's one-pot synthesis of tropinone (**9**, Scheme 1).<sup>5</sup> Tropinone contains the bicyclic tropane motif, a feature shared with several other alkaloids such as cocaine (**10**) and atropine (**11**). The cascade involves the double Mannich reaction of succinaldehyde (**1**), methylamine (**2**) and acetonedicarboxylic acid (**3**) to give tropinone (**9**) in good yield, and in a considerably more concise synthesis than those achieved previously.<sup>6</sup>

**Scheme 1.** Robinson's total synthesis of tropinone (**9**).



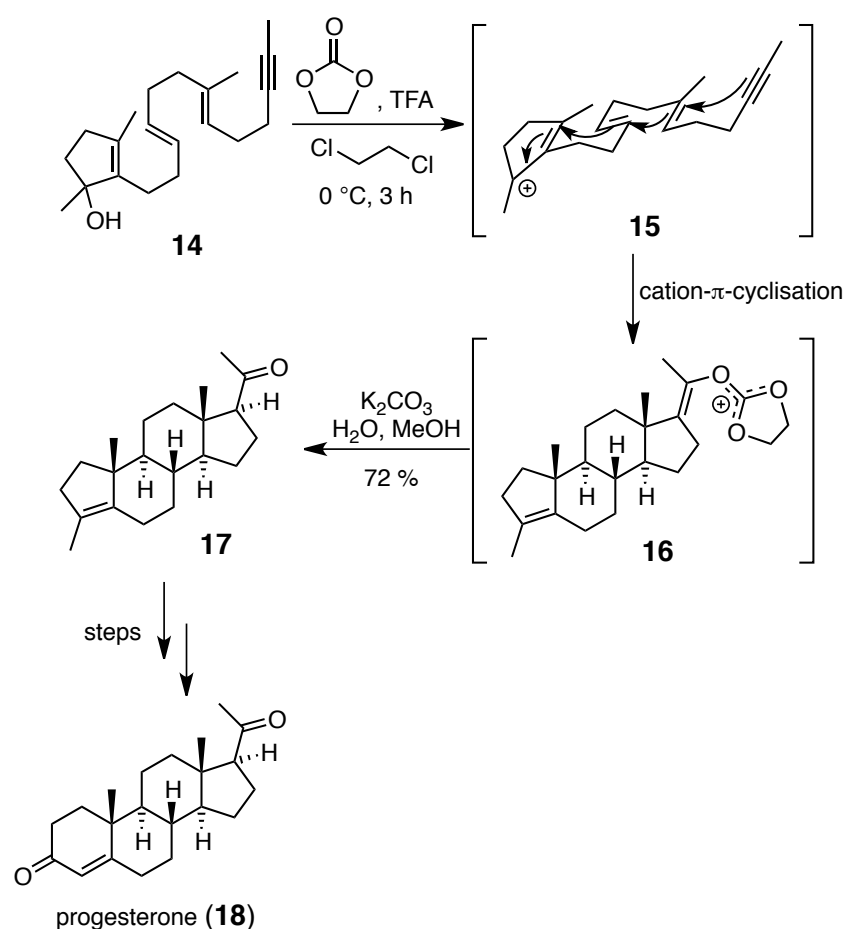
In 1955 Stork<sup>7,8a</sup> and Eschenmoser<sup>8</sup> rationalised that polyalkenes undergo cyclisation in well-defined conformations, dependent only upon the alkene geometry. The biosynthesis of lanosterol (**13**, Scheme 2) from 2,3-oxidosqualene (**12**) is just one example of this type of stereospecific transformation.

**Scheme 2.** Biosynthesis of lanosterol (**13**).



An improved understanding of steroid biosynthesis inspired the first forays into biomimetic syntheses of steroidal structures by van Tamelen<sup>9</sup> and Corey,<sup>10</sup> leading to Johnson's classic total synthesis of progesterone (**18**, Scheme 3).<sup>11</sup> The key step in this synthesis was the acid-catalyzed polycyclisation cascade of polyalkene **14**, achieved in the presence of cation-trapping agent ethylene carbonate. The reaction yielded the desired tetracycle **17** as a 5:1 mixture of C-17 epimers, with subsequent oxidative scission and intramolecular aldol/dehydration delivering progesterone in high yield.

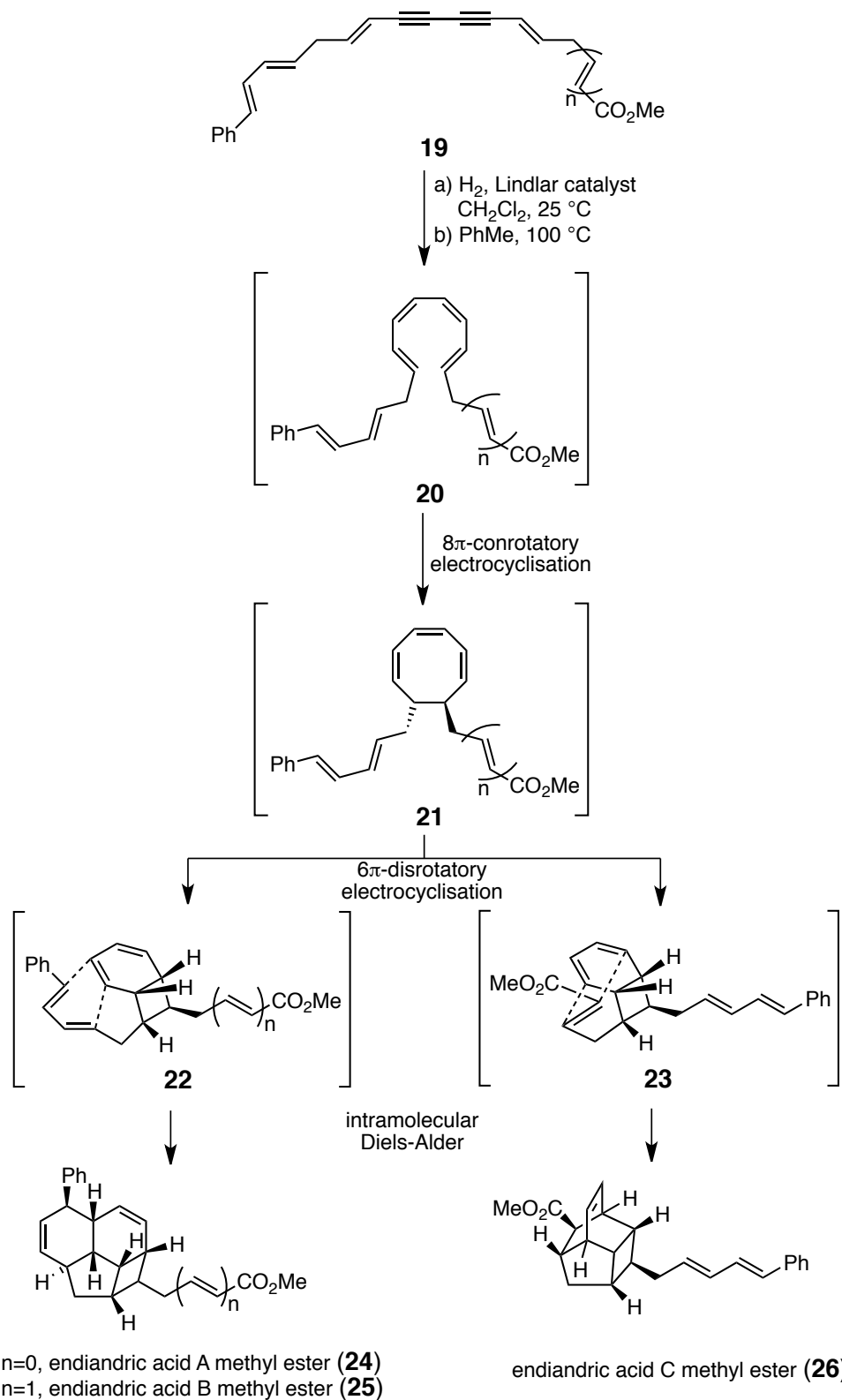
**Scheme 3.** Johnson's total synthesis of progesterone (**18**).



Another classic example is Nicolaou's biomimetic synthesis of the tetracyclic endiandric acids from a simple achiral polyalkene (**20**, Scheme 4).<sup>12</sup> Endiandric acids are unusual in that they are found in nature as racemates. To account for this, Black proposed the biosynthesis of these compounds through an electrocyclisation cascade.<sup>13</sup> Nicolaou put this hypothesis into practice, hydrogenating diacetylene precursor **19** with Lindlar catalyst and quinoline, before thermal initiation of the

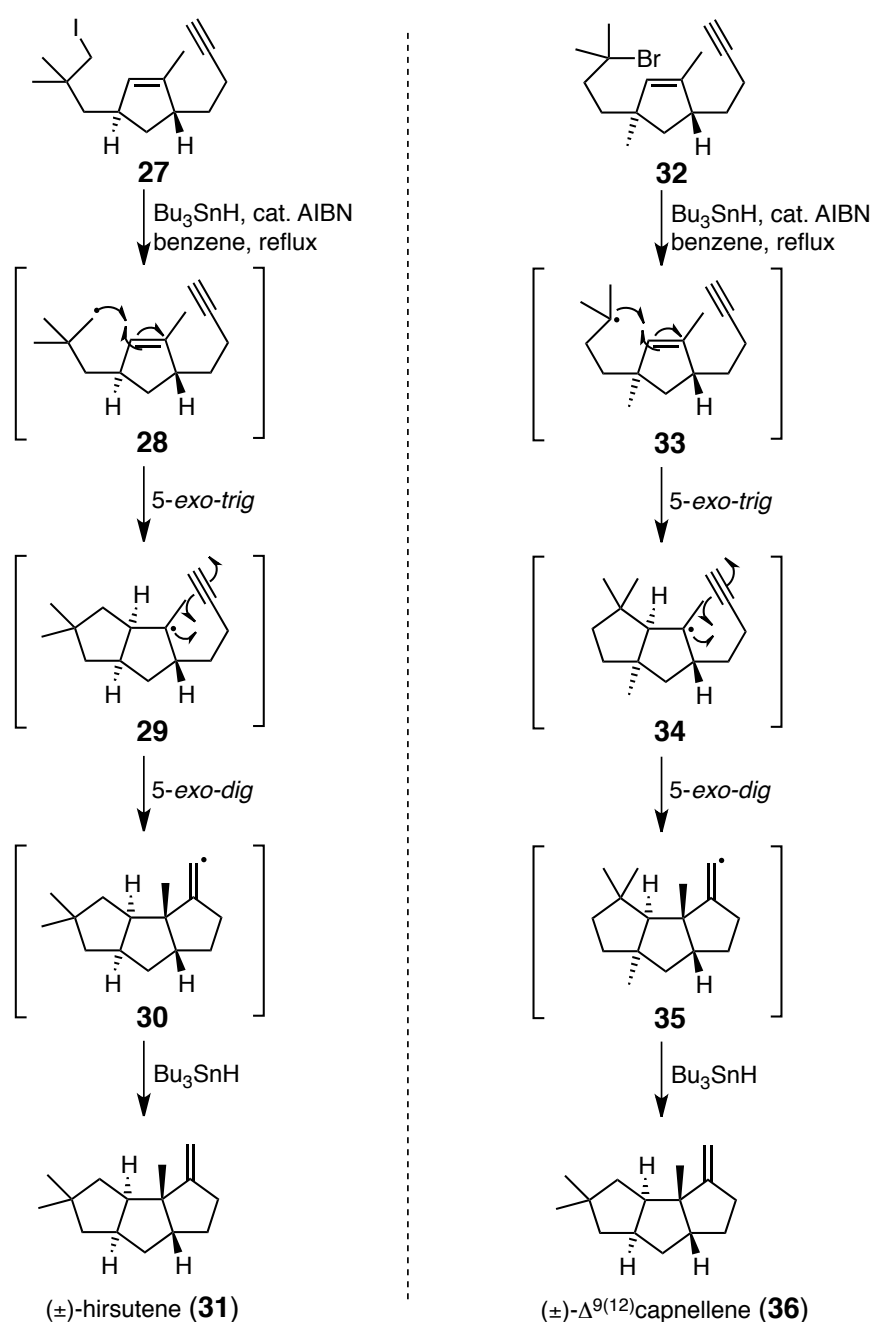
cascade, which terminates with a Diels-Alder cycloaddition to give endiandric acid methyl esters **24**, **25** and **26** in good yield.

**Scheme 4.** Biomimetic synthesis of Endiandric acid A, B and C methyl esters.



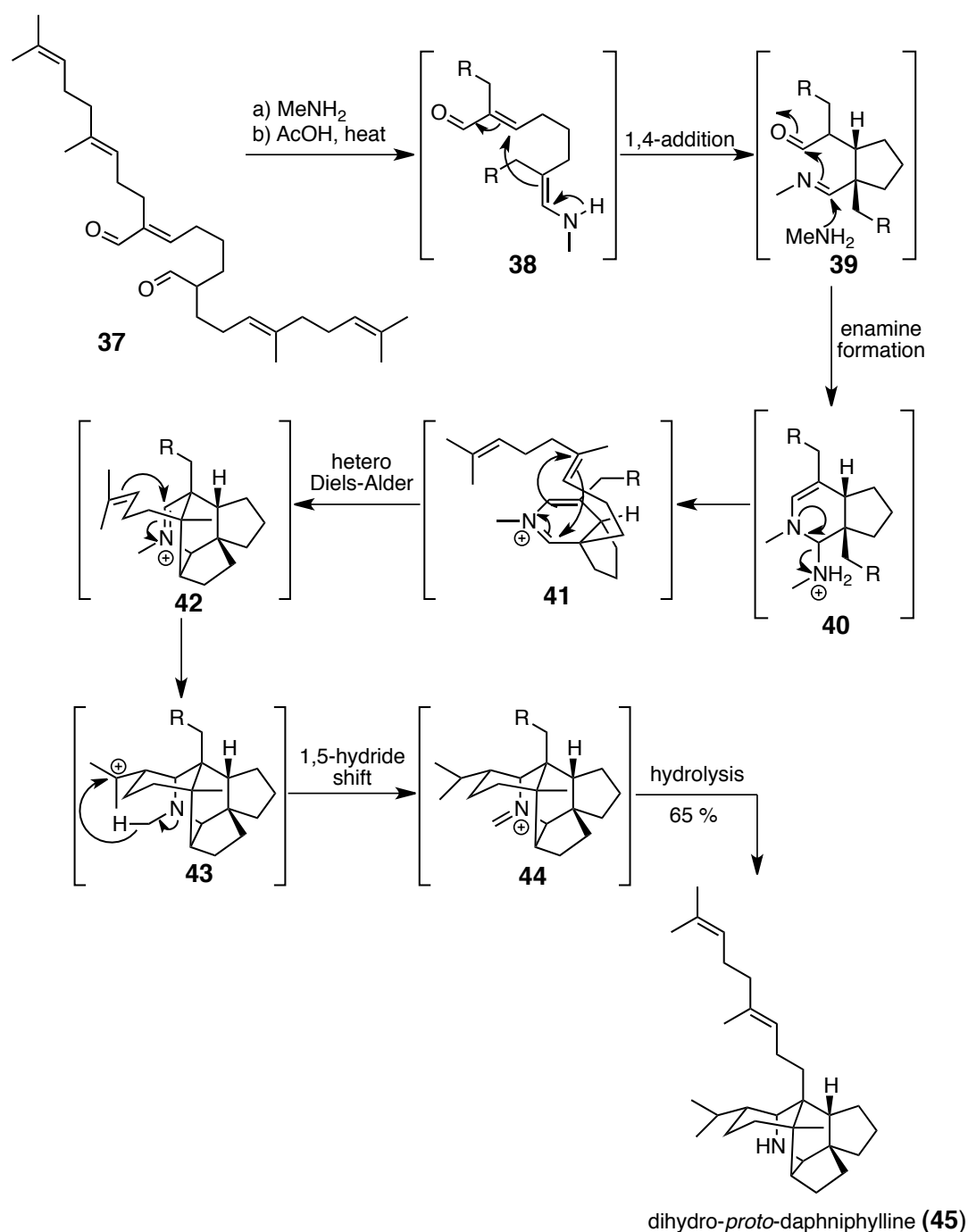
Later, in one of the landmark developments in synthetic radical chemistry, Curran demonstrated the power of controlled, tandem cascade radical cyclisations as key steps in the synthesis of hirsutene<sup>14</sup> (**31**, Scheme 5) and  $\Delta^{9(12)}$ -capnellene (**36**).<sup>15</sup> Cyclopentene precursors **27** and **32** were treated with tributyltin hydride and catalytic AIBN to form radical intermediates **28** and **33** that undergo tandem 5-*exo* cyclisations which, due to conformational constraints, proceed in a *cis* fashion to give the desired products in excellent yield.

**Scheme 5.** Synthesis of ( $\pm$ )-hirsutene (**31**) and ( $\pm$ )- $\Delta^{9(12)}$ -capnellene (**36**) via a radical cyclisation cascade.



Finally, Heathcock's total synthesis of dihydro-*proto*-daphniphylline (**45**, Scheme 6),<sup>16</sup> a biosynthetic precursor to several members of the *Daphniphyllum* alkaloid family, is a classic demonstration of an iminium-mediated cascade. Dihydrosqualene dialdehyde **37** was treated with methylamine, then acetic acid, and heated to give the target **45** in excellent yield *via* a 1,4 addition/hetero Diels-Alder cascade. In just one process eight new stereocentres and five rings were installed in a diastereoselective fashion.

**Scheme 6.** Heathcock's synthesis of dihydro-*proto*-daphniphylline (**45**).



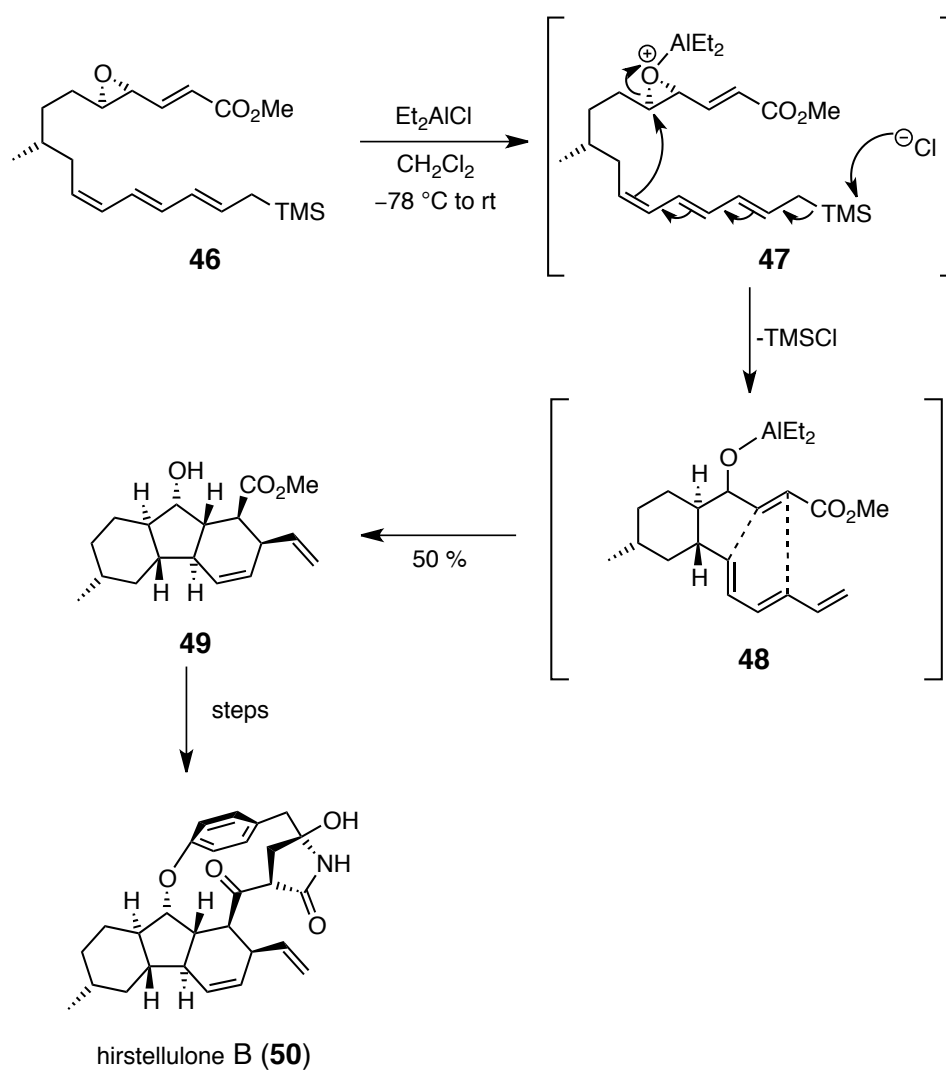
### 1.1.3 Recent examples of cascade cyclisations in natural product synthesis

For convenience, the following examples have been grouped according to what is considered the main theme of the cascade, although the intrinsic multi-faceted nature of cascades means that they may also contain other reaction types.

#### 1.1.3.1 Pericyclic cascades

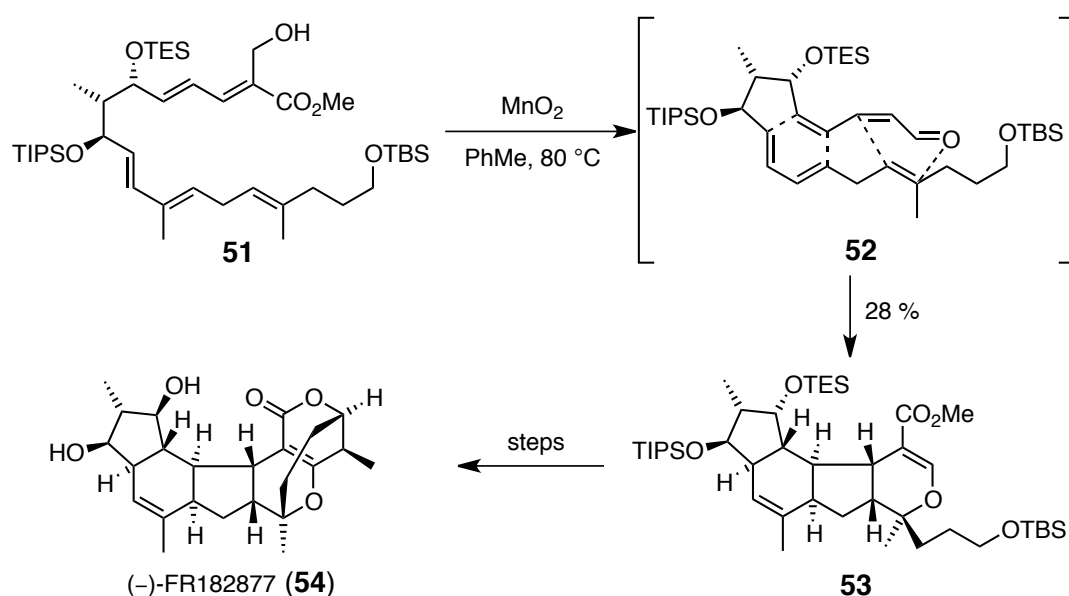
As can be seen from examples in Section 1.1.2, pericyclic reactions have been prevalent in the pioneering cascade cyclisations for natural product synthesis. This is no coincidence, as electrocyclisations and cycloadditions are particularly suited to installing multiple rings sequentially in a single process.

Hirsutellone B (**50**, Scheme 7), a fungal secondary metabolite, shows impressive activity against the pathogen that leads to tuberculosis. Of synthetic interest was the enantioselective construction of the tricyclic core. The groups of Sorensen,<sup>17</sup> Liu,<sup>18</sup> and Nicolaou<sup>19</sup> each independently approached this construction *via* a key intramolecular Diels-Alder (IMDA) reaction. Nicolaou's approach utilised a cascade intramolecular epoxide-opening/Diels-Alder reaction of TMS-epoxy tetraene **46**. Lewis acid activation of epoxide **46** with Et<sub>2</sub>AlCl gave rise to the first six-membered ring and the triene moieties in **48**, which were then in close enough proximity to undergo the IMDA reaction to give **49** exclusively as the *endo* product in 50 % yield. **49** was converted to hirsutellone B (**50**) in further steps.

**Scheme 7.** Nicolaou's approach to hirsutellone B (**50**).

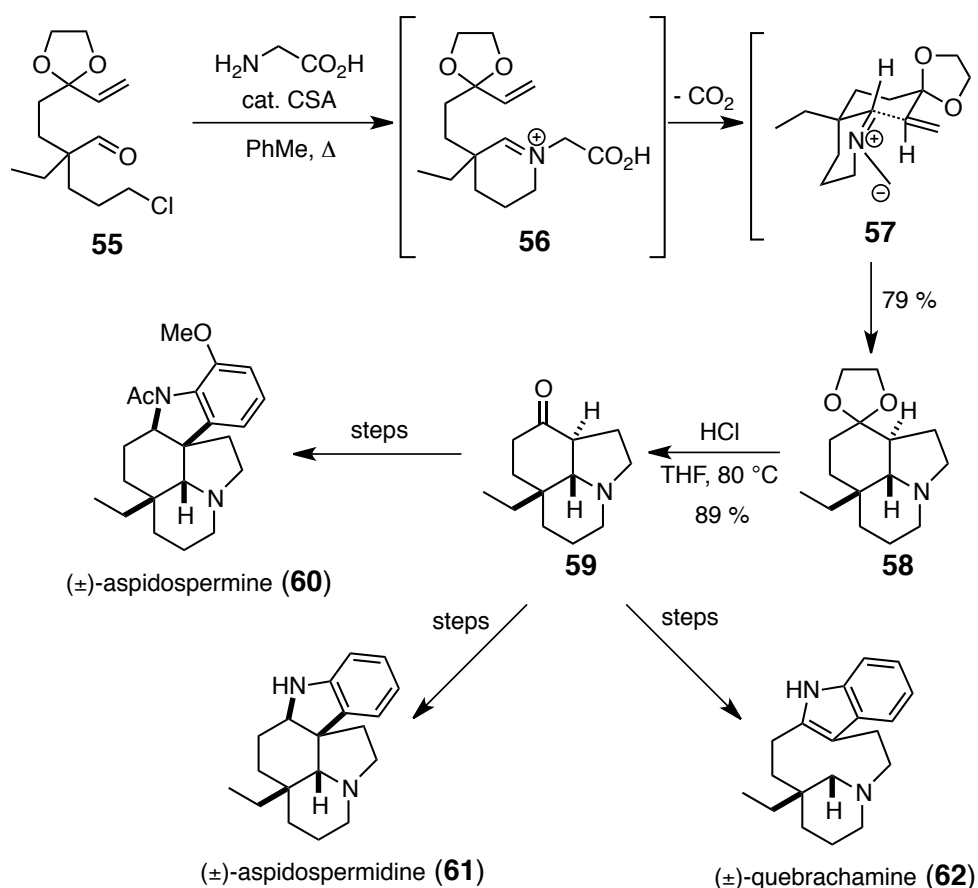
Another impressive use of Diels-Alder chemistry was demonstrated by Nakada and co-workers in the total synthesis of polyketide-derived (–)-FR182877 (**54**, Scheme 8),<sup>20</sup> a potent anticancer agent. A biomimetic intramolecular Diels-Alder/hetero-Diels-Alder (IMDA/HDA) cascade of acyclic pentaene substrate **51** was used to install the four rings and seven stereocentres in tetracycle **53**. The cascade was triggered by MnO<sub>2</sub> allylic oxidation of **51**, giving rise to transient dienal **52** that underwent IMDA/HDA cascade cyclisation to give **53** in 28 % yield. A subsequent 13 steps led to natural product (–)-FR182877 (**54**).

**Scheme 8.** Nakada's total synthesis of (–)-FR182877 (**54**).



Coldham and co-workers recently reported the total synthesis of three *Aspidosperma* alkaloids, namely (±)-aspidospermine (**60**, Scheme 9), (±)-aspidospermidine (**61**), and (±)-quebrachamine (**62**), using a cyclisation/cycloaddition cascade to install the tricyclic amine core **59** shared by this class of alkaloids.<sup>21</sup> Inspired by the work of Pearson *et al.*,<sup>22</sup> they prepared substrate **55**, and treated it with glycine under acidic conditions to give condensation/alkylation intermediate **56**. Concomitant decarboxylation gave rise to azomethine ylide **57** which then underwent [3+2]-cycloaddition with the dipolarophilic alkene to give the desired tricycle **58**. Acetal removal delivered ketoamine **59**, which was in turn converted to (±)-aspidospermine (**60**), (±)-aspidospermidine (**61**), and (±)-quebrachamine (**62**).

**Scheme 9.** Total synthesis of *Aspidosperma* alkaloids **60**, **61** and **62**.

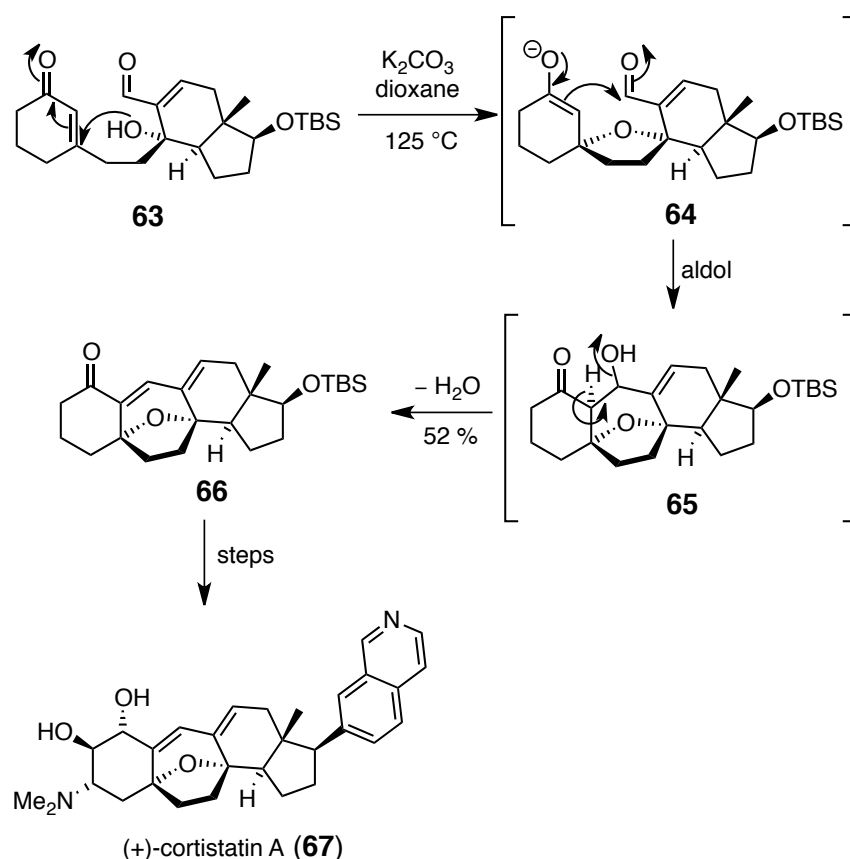


### 1.1.3.2 Heteroatom-mediated cascades

Cascade cyclisations that give rise to heterocyclic natural products have also received a lot of attention in the literature recently.

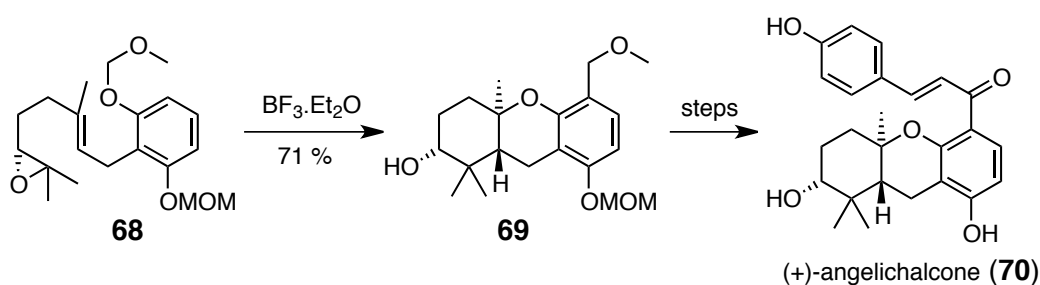
Nicolaou *et al.* were able to install the pentacyclic framework in substrate **66** (Scheme 10) en route to the total synthesis of (+)-cortistatin A (**67**),<sup>23</sup> using a unique intramolecular 1,4-addition/aldol/dehydration cascade. The cascade proceeds by treatment of enone-enal **63** with  $K_2CO_3$  at reflux in dioxane, to deliver **66** in 52 % yield, presumably through the pathway of intermediates **64** and **65**. Synthesis of (+)-cortistatin A (**67**) was completed in a further 13 steps.

**Scheme 10.** Nicolaou's total synthesis of (+)-cortistatin A (**67**).

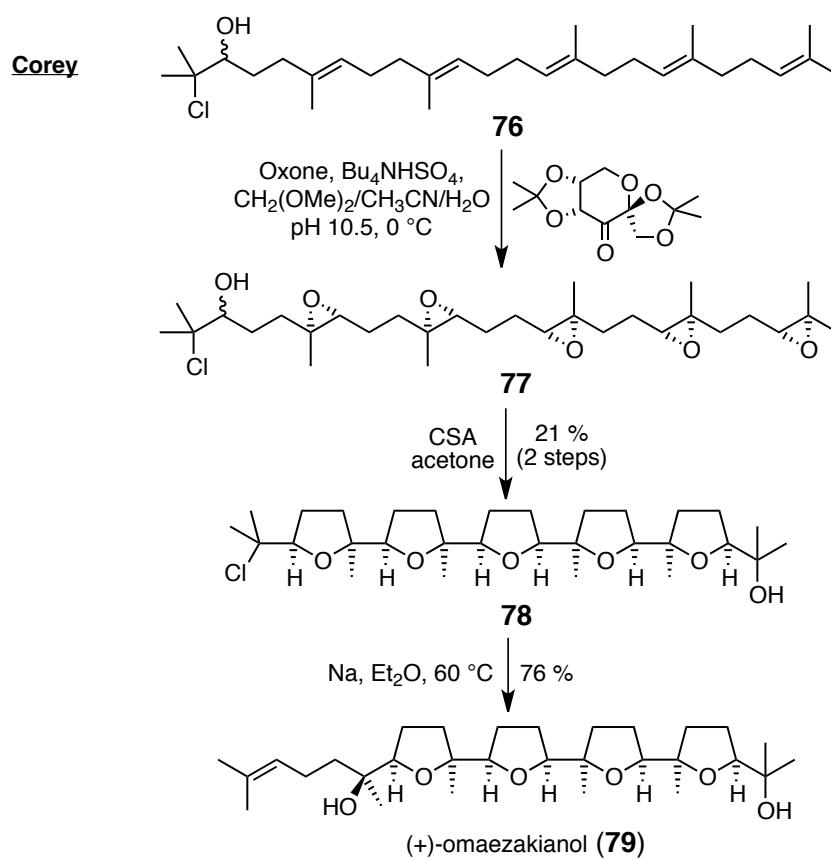
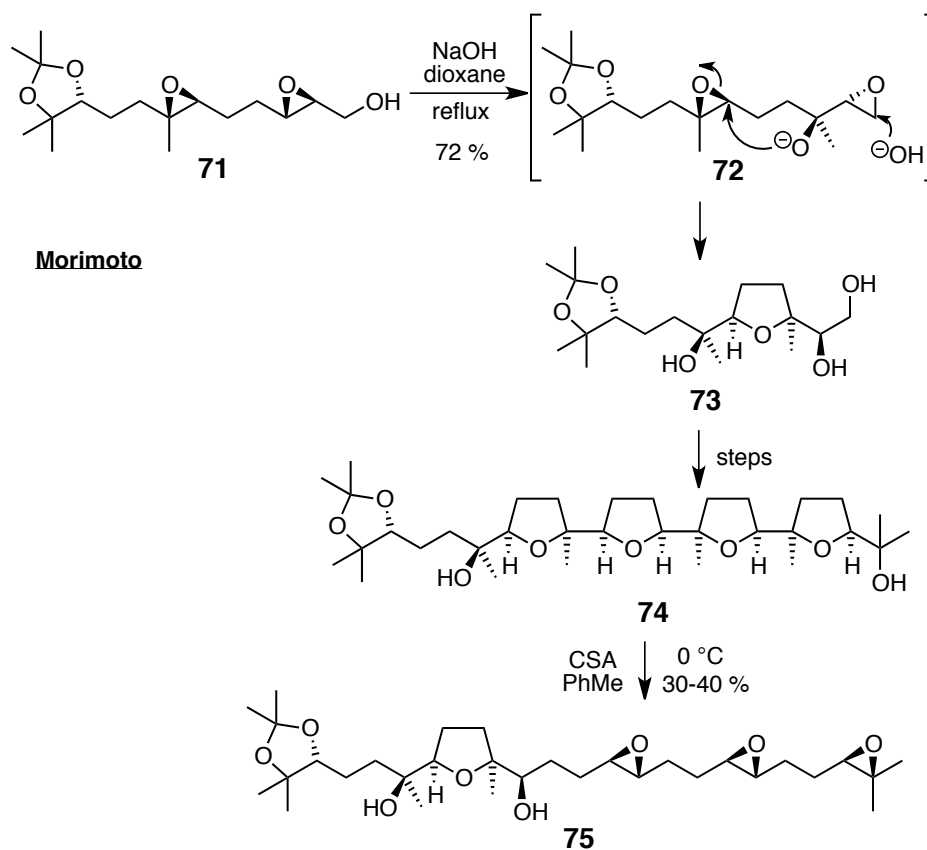


Another simple but powerful cascade was used to install the carbocycle and heterocycle of (+)-angelichalcone (**70**, Scheme 11) by Wiemer *et al.*<sup>24</sup> MOM-protected phenol **68**, when treated with  $\text{BF}_3 \cdot \text{OEt}_2$  underwent a rapid stereoselective cyclization/electrophilic aromatic substitution cascade to deliver tricycle **69** in which a new C-C bond had formed between the arene and transient MOM cation. Further embellishment of the newly installed benzylic methyl ether over 5 steps led to (+)-angelichalcone (**70**) in good yield.

**Scheme 11.** Wiemer's total synthesis of (+)-angelichalcone (**70**).

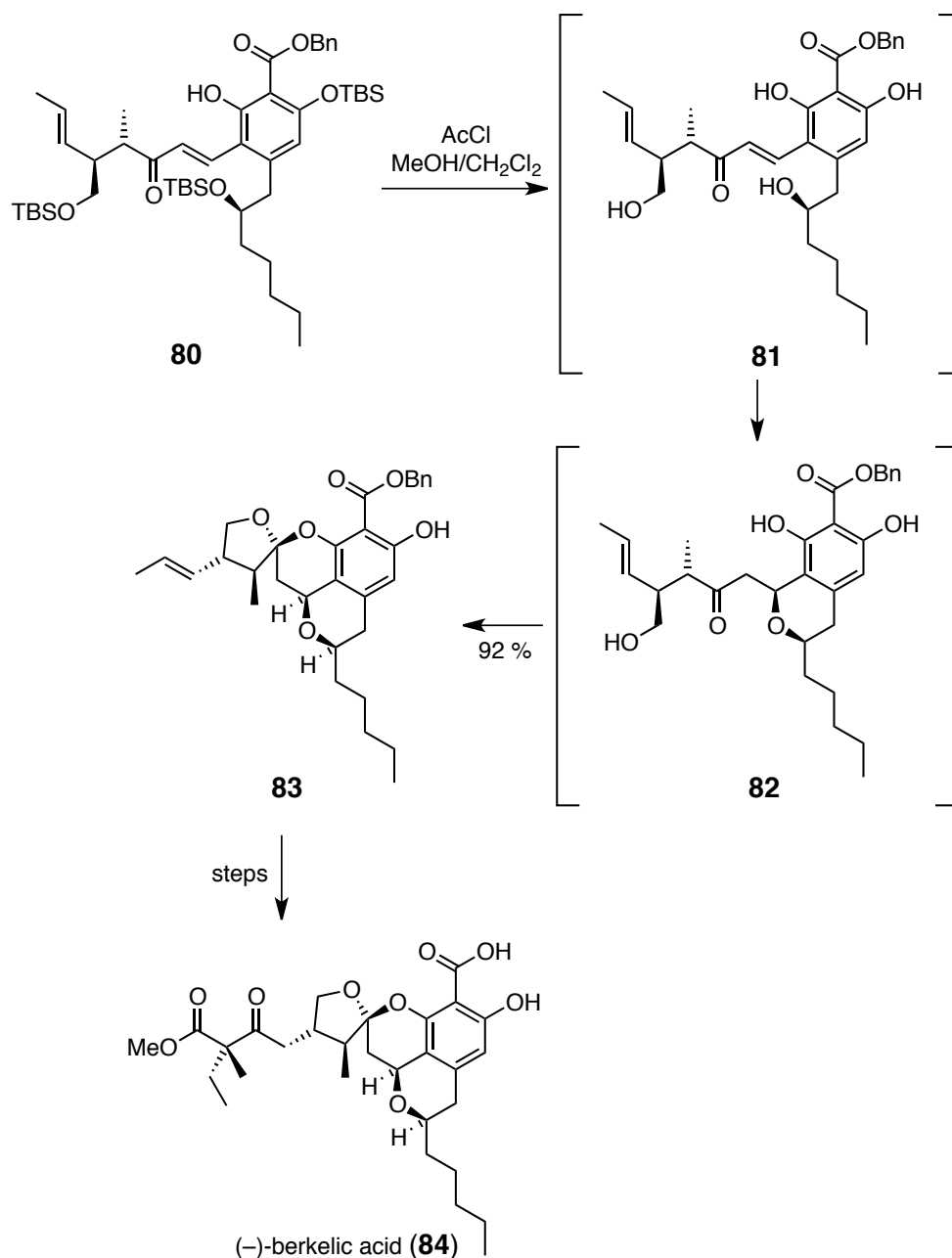


A more advanced implementation of epoxide-opening cascades has been demonstrated by Corey<sup>25</sup> and Morimoto<sup>26</sup> in their biomimetic syntheses of (+)-omaezakianol (**79**, Scheme 12). Morimoto utilises firstly a base-mediated Payne rearrangement/epoxide-opening cascade to construct intermediate **73**, then later an acid-mediated epoxide-opening cascade to give advanced tetrahydrofuran intermediate **75**. Alternatively, Corey's approach reduces the synthetic effort considerably by accessing pentaepoxide **77** via Shi asymmetric epoxidation of easily accessible chlorohydrin **76**. Cascade cyclisation of **77** under acidic conditions, followed by reductive olefination gave the natural product **79**.

**Scheme 12.** Total syntheses of (+)-omaezakianol (**79**).

An example of cascade synthesis of spiroketals is demonstrated by Fürstner *et al.* in their synthesis of (–)-berkelic acid<sup>27</sup> (**84**, Scheme 13). Treatment of enone **80** with acid triggered, what Fürstner proposed to be, a well-orchestrated triple deprotection/1,4-addition/spirocyclisation cascade to give tetracyclic product **83** in 92 % yield. Further steps yielded (–)-berkelic acid (**84**).

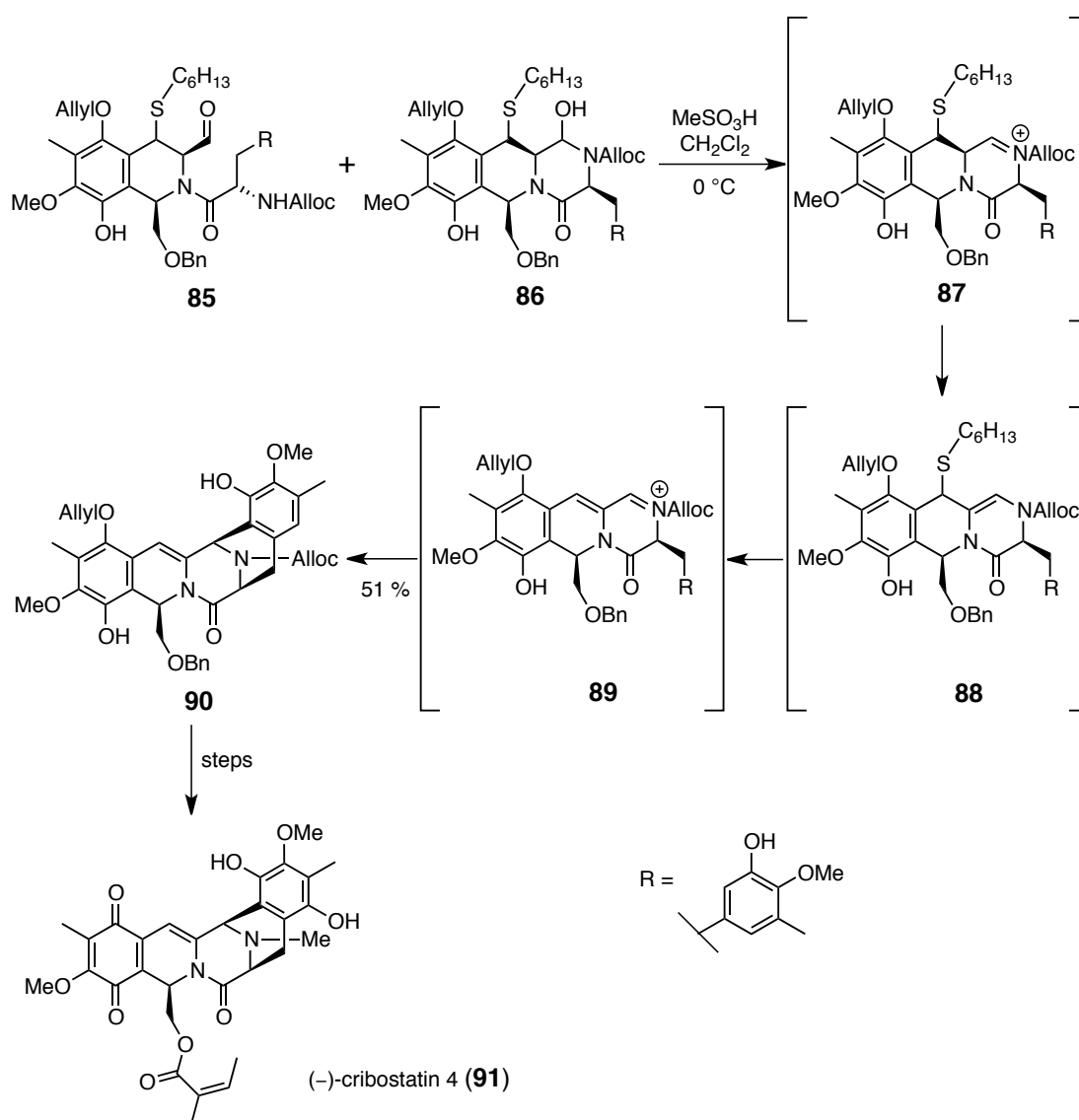
**Scheme 13.** Fürstner's total synthesis of berkelic acid (**84**).



### 1.1.3.3 Cation-mediated cascades

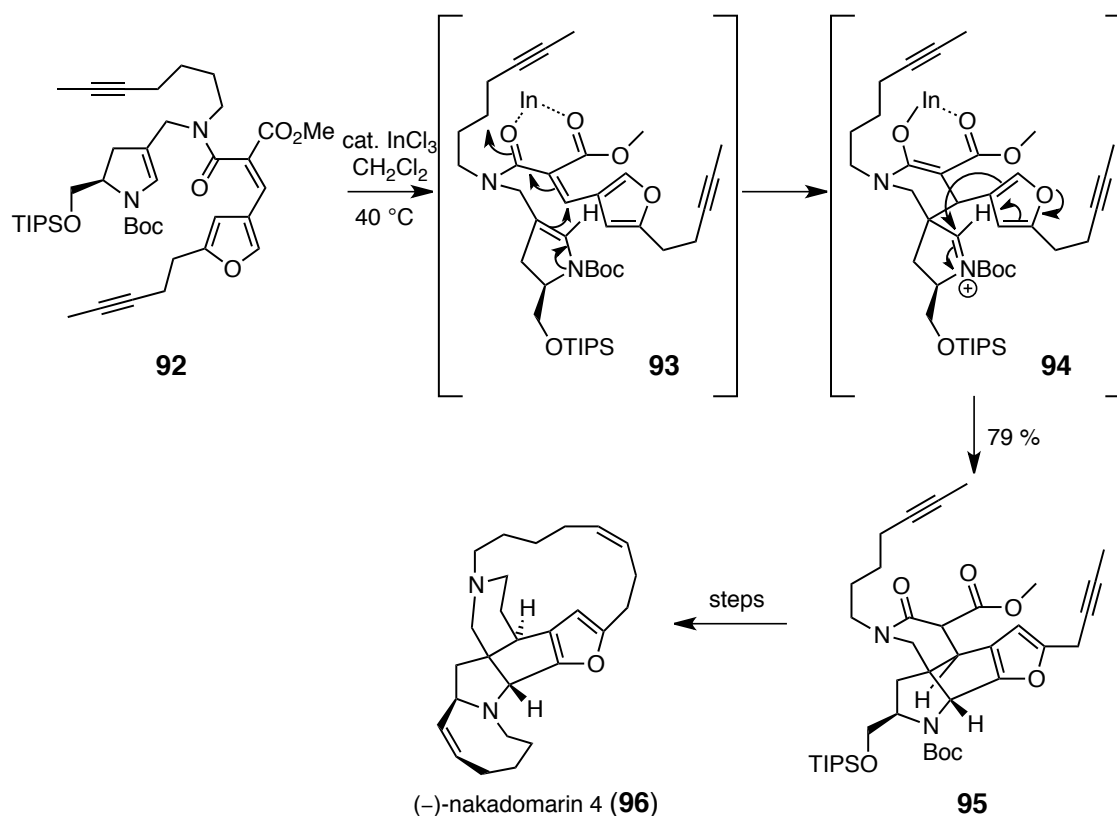
Another common motif in cascade chemistry is the utilisation of iminium/enamine intermediates in ring formation. As a first example, Chen and Xhu completed the total synthesis of tetrahydroisoquinoline natural product (–)-cribostatin 4 (**91**, Scheme 14).<sup>28</sup> An acyliminium-mediated cascade cyclisation of a mixture of aldehyde **85** and cyclic hemiaminal **86** led to pentacyclic core **90** in 51 % yield (with a further 15 % of a regioisomer). The authors rationalise that the process occurs *via*  $\beta$ -elimination of enamide **88** to give conjugated iminium species **89** that underwent nucleophilic addition to the tethered arene to give pentacycle **90**. Increased concentration of the mesic acid reagent led to reduced regioselectivity in this step. A subsequent eight steps delivered (–)-cribostatin 4 (**91**) in 4.3 % yield, and 26 steps overall.

**Scheme 14.** Cascade approach to (–)-cribostatin 4 (**91**).

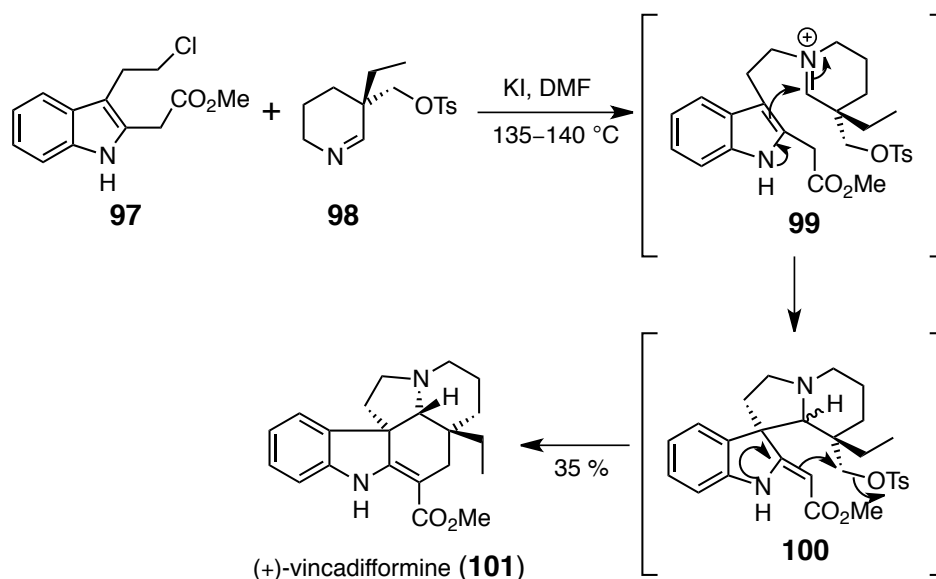


A Michael/Mannich cascade sequence was used by Funk *et al.* as a key feature in the total synthesis of (–)-nakadomarin A (**96**, Scheme 15).<sup>29</sup> Activation of the enoate moiety in substrate **92** with catalytic indium trichloride led to intramolecular attack of the enamide portion. Nucleophilic addition of the resultant iminium species **94** to the furan gave desired tetracycle **95**.

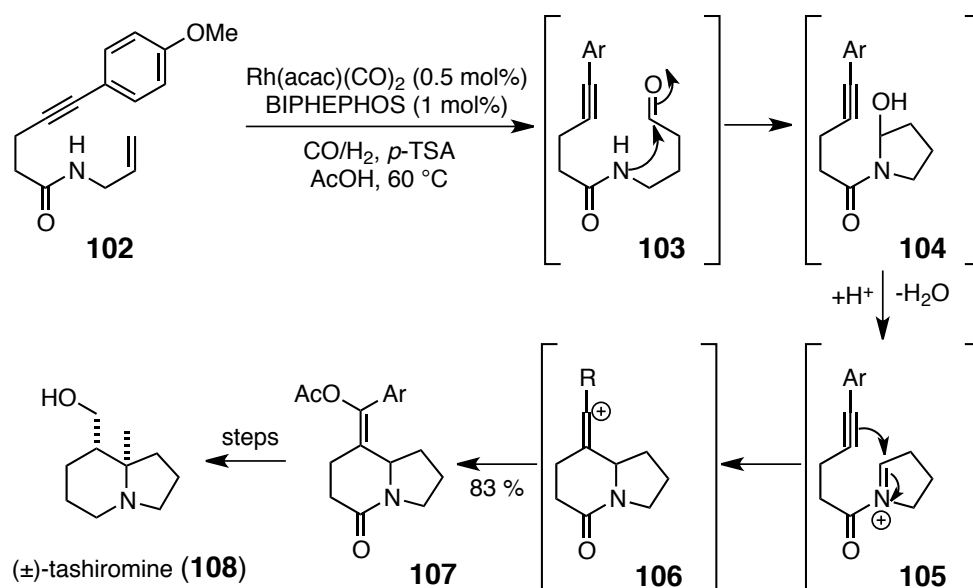
**Scheme 15.** Funk's total synthesis of (–)-nakadomarin A (**96**).



Another *Aspidosperma* alkaloid, (+)-vincadifformine (**101**, Scheme 16), containing a conformationally rigid pentacyclic core, was prepared using a non-biomimetic cascade cyclisation of iminium species **99**, resulting from coupling of chiral imine **98** and easily prepared indole derivative **97**.<sup>30</sup> Heating the coupling partners with potassium iodide in DMF gave the desired transformation in 35 % yield, delivering (+)-vincadifformine (**101**) in 99 % *ee*, and 4 % yield overall.

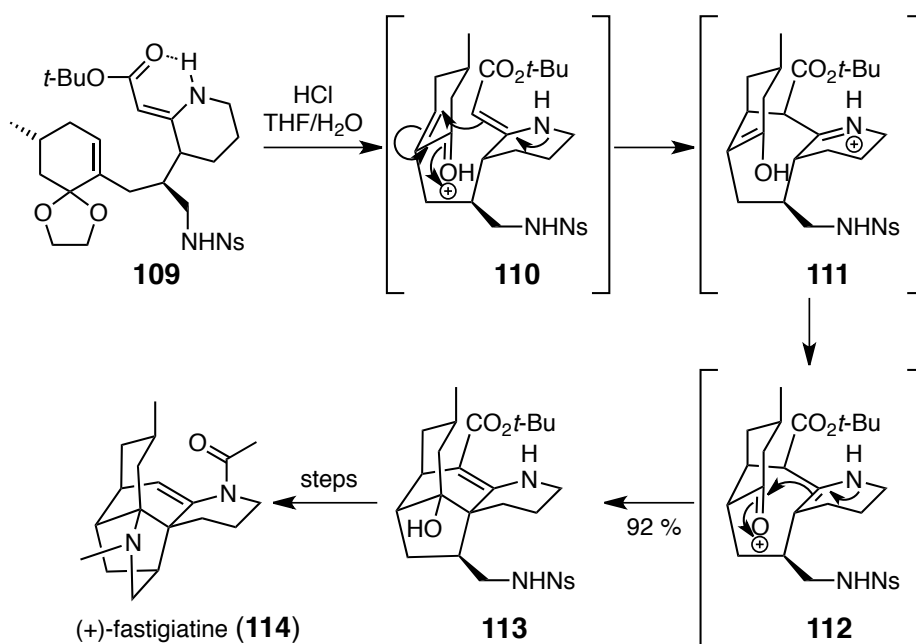
**Scheme 16.** Non-bimimetic cascade approach to (+)-vincadifformine (**101**).

Chiou *et al.* recently published the concise synthesis of simple indolizidine (±)-tashiromine (**108**, Scheme 17) in 33 % yield over four steps.<sup>31</sup> Their cascade strategy involved a one-step, alkyne-mediated Rh-catalysed hydroformylation/double cyclisation to construct the bicycle **107** from *N*-allylamide **102**. Hydroformylation of **102** afforded aldehyde **103** which under the acidic conditions underwent intramolecular condensation to iminium species **105**. Intramolecular cyclisation with the nucleophilic alkene (enhanced by electron donating phenyl moiety) gave enol acetate **107** in excellent yield, with subsequent steps furnishing (±)-tashiromine (**108**).

**Scheme 17.** Cascade total synthesis of (±)-tashiromine (**108**).

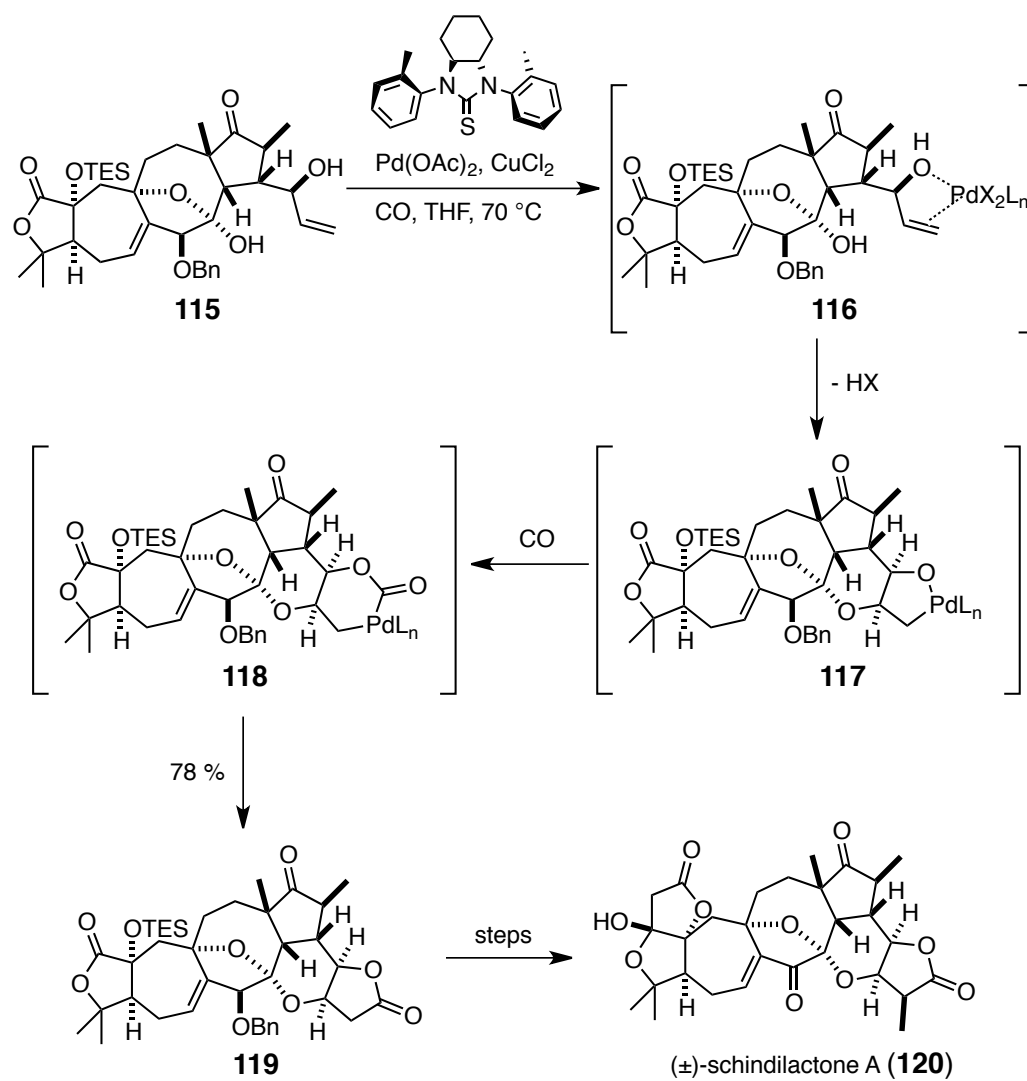
In the final example, Shair and co-workers reported the first synthesis of *Lycopodium* alkaloid (+)-fastigiatine (**114**, Scheme 18).<sup>32</sup> Treatment of ketal with acid furnished activated enone **110**. The first C-C bond is formed by 1,4-addition of the enamine to give enol-iminium species **111**, which in turn tautomerises to activated ketone-enamine **112** that undergoes a second C-C bond forming reaction to complete the formal [3+3] cycloaddition to give **113**. (+)-Fastigiatine (**114**) is furnished in a further four steps.

**Scheme 18.** Total synthesis of (+)-fastigiatine (**114**).



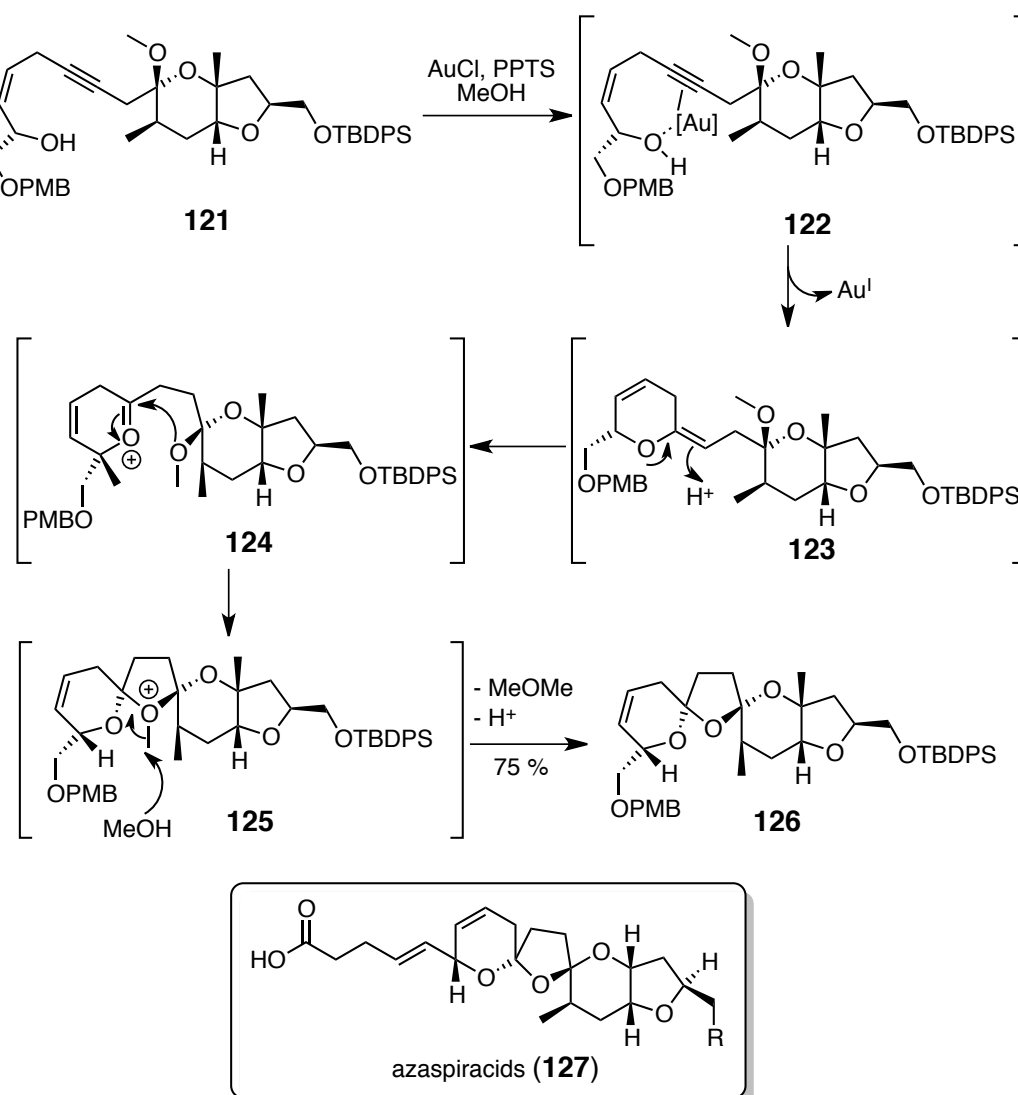
#### 1.1.3.4 Transition metal-mediated cascades

The continuing development of new transition metal-catalysed reactions makes this one of the most exciting areas of cascade chemistry, offering a catalytic approach to a host of regioselective and stereoselective transformations. Palladium-catalysed cascades have so far dominated this field due to the diversity of C-C bonds they are capable of installing. A recent example allowed the total synthesis of (±)-schindilactone A (**120**, Scheme 19) to be achieved using a Pd-catalysed carbonylative annulation cascade construction of the GH ring.<sup>33</sup> Diol **115** was treated with Pd<sup>II</sup> and a chiral thiourea catalyst under a CO atmosphere to deliver only lactone **119** in 78 % yield. (±)-Schindilactone A (**120**) was furnished in a further six steps. The key step is initiated by the formation of allylic alcohol derived Pd-complex **116**, which undergoes intramolecular nucleophilic attack across the double bond to give alkoxy-Pd species **117**. CO-insertion followed by reductive elimination delivered the lactone product **119**.<sup>34</sup>

**Scheme 19.** Pd-catalyzed cascade for the synthesis of (±)-schindilactone A (**120**).

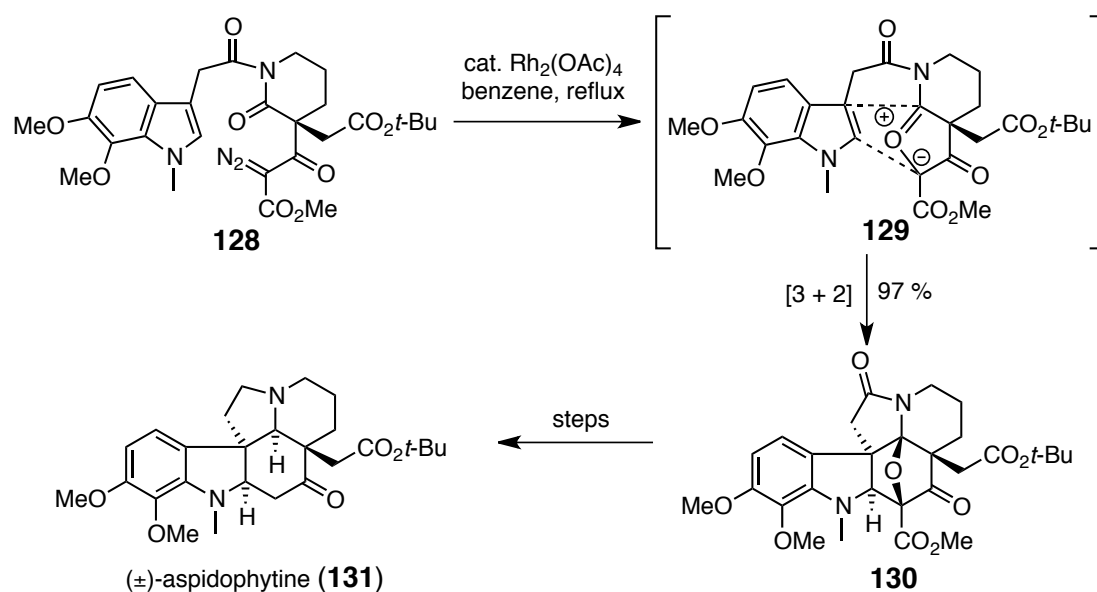
$\pi$ -Acid catalysis, particularly gold catalysis, has become increasingly popular in recent years, leading to the development of numerous new methodologies, including cyclisations.  $\pi$ -Acid catalysis has been particularly effective in spiroketal synthesis. One recent deployment of this reactivity was in the study of Forsyth *et al.* towards the total synthesis of azaspiracids (**127**, Scheme 20).<sup>35</sup> Bis-spiroketalisation of ynol **121** was achieved by treating with AuCl and PPTS in MeOH to give spiroketal **126** in 75 % yield. The reaction is presumed to proceed *via* enol ether **123**, the result of hydroxyl addition to the  $\pi$ -coordinated alkyne-Au<sup>I</sup> complex.

**Scheme 20.** Gold-catalysed spiroketalisation for the total synthesis of azaspiracids.



The rhodium-catalysed degradation of diazocarbonyl compounds to give 1,3-dipoles has been utilised by the Padwa group in their recent racemic synthesis of alkaloid aspidophytine (**131**, Scheme 21).<sup>36</sup> Treatment of diazo compound **128** with Rh<sup>II</sup> generated carbonyl ylide **129** which underwent an intramolecular 1,3-dipolar cycloaddition to give pentacycle **130** in excellent yield. Subsequent steps led to the natural product **131**.

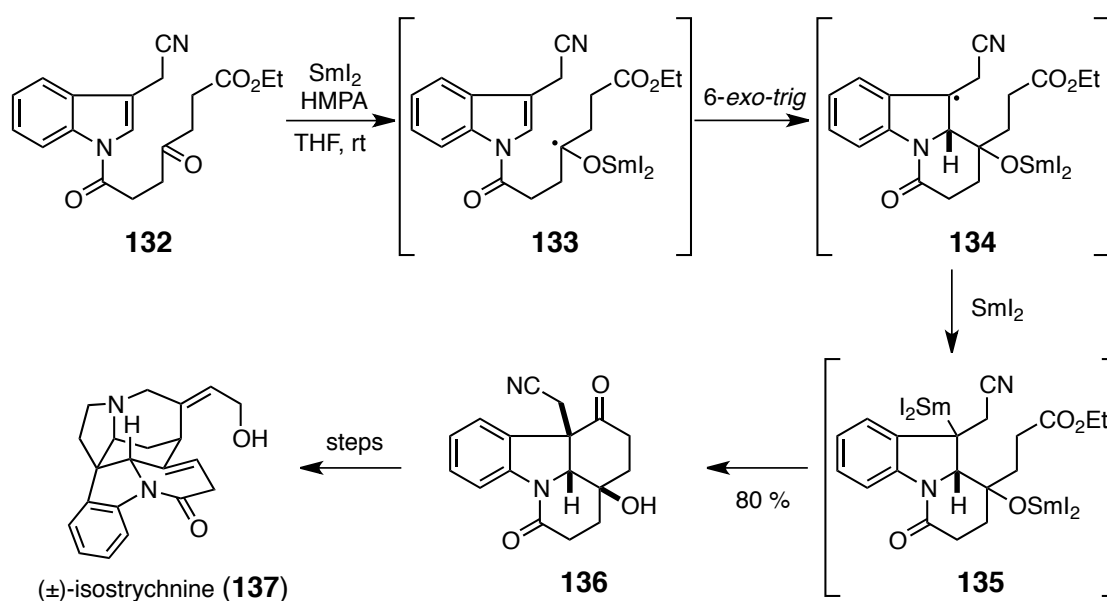
**Scheme 21.** Padwa's route to (±)-aspidophytine (**131**).



### 1.1.3.5 Radical cascades

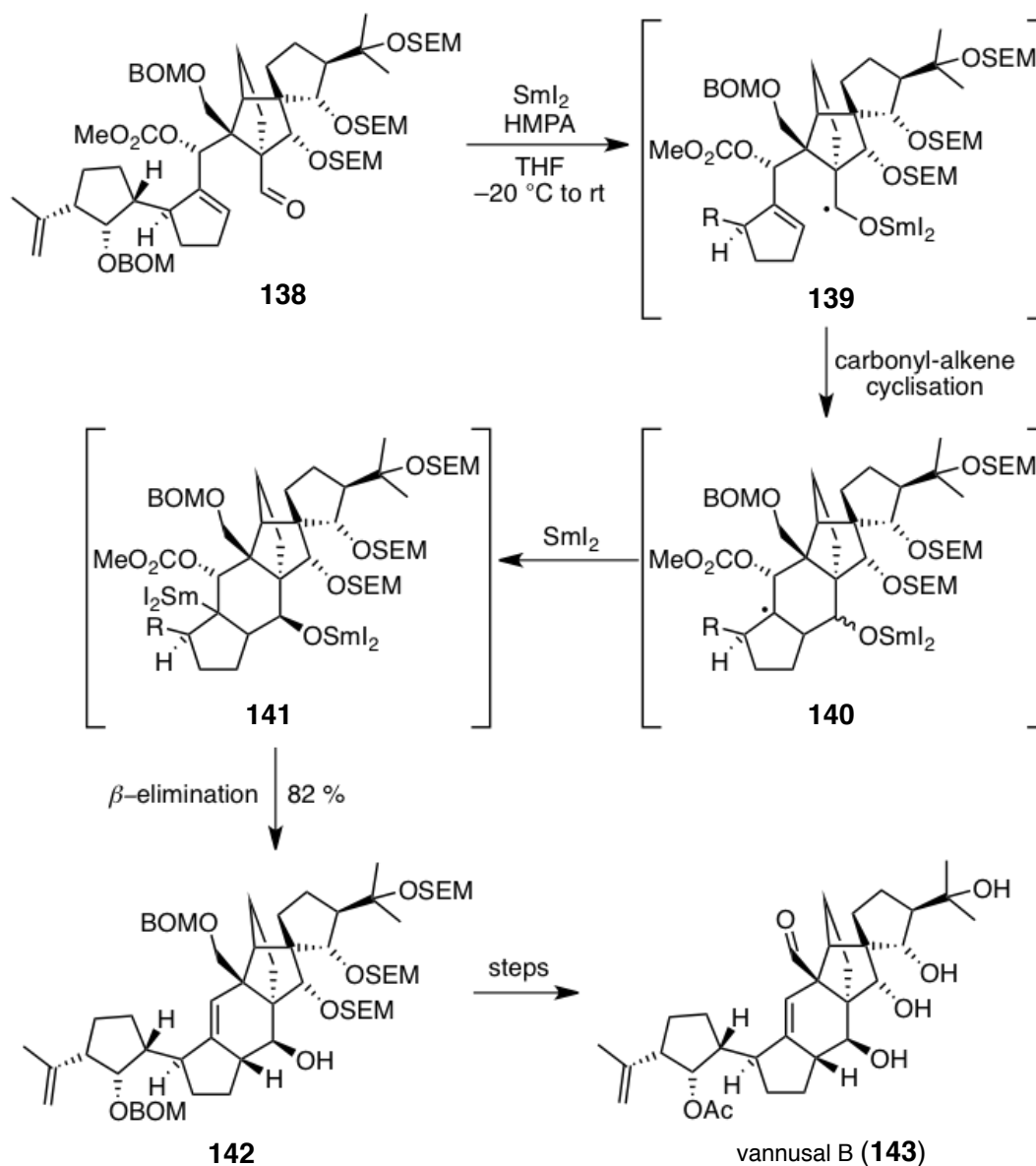
As seen with the examples of ( $\pm$ )-hirsutene and ( $\pm$ )- $\Delta^{9(12)}$ -capnellene (Section 1.1.2), organic radicals are well suited to cascade chemistry, and have been utilised extensively. Samarium-promoted radical cascades have been used extensively in total synthesis.<sup>37</sup> One recent example is Reissig's formal synthesis of ( $\pm$ )-strychnine.<sup>38</sup> Tetracyclic intermediate **136** (Scheme 22) was prepared by a samarium-mediated ketyl-radical cyclisation cascade of amide **132**. Ketyl radical **133** was generated by treatment of **132** with  $\text{SmI}_2$  and HMPA and underwent a 6-*exo-trig* cyclisation to give benzyl radical intermediate **134**. Reduction to alkylsamarium intermediate **135**, followed by intramolecular acylation gave tetracyclic product **136** in 80 % yield. Subsequent steps led to ( $\pm$ )-isostrychnine (**137**) *via* Rawal's intermediate.<sup>39</sup>

**Scheme 22.** Reissig's formal synthesis of ( $\pm$ )-strychnine.



A SmI<sub>2</sub>-induced ketyl radical cascade was also utilised by Nicolaou *et al.* in the total synthesis of vannusal B (**143**, Scheme 23). Aldehyde **138** gave intermediate ketyl radical **139** when treated with SmI<sub>2</sub> and HMPA. Ketyl-alkene cyclisation gave tertiary radical **140**, which underwent reduction followed by carbonate elimination to deliver **142** in good yield as a 2:1 mixture of epimers.

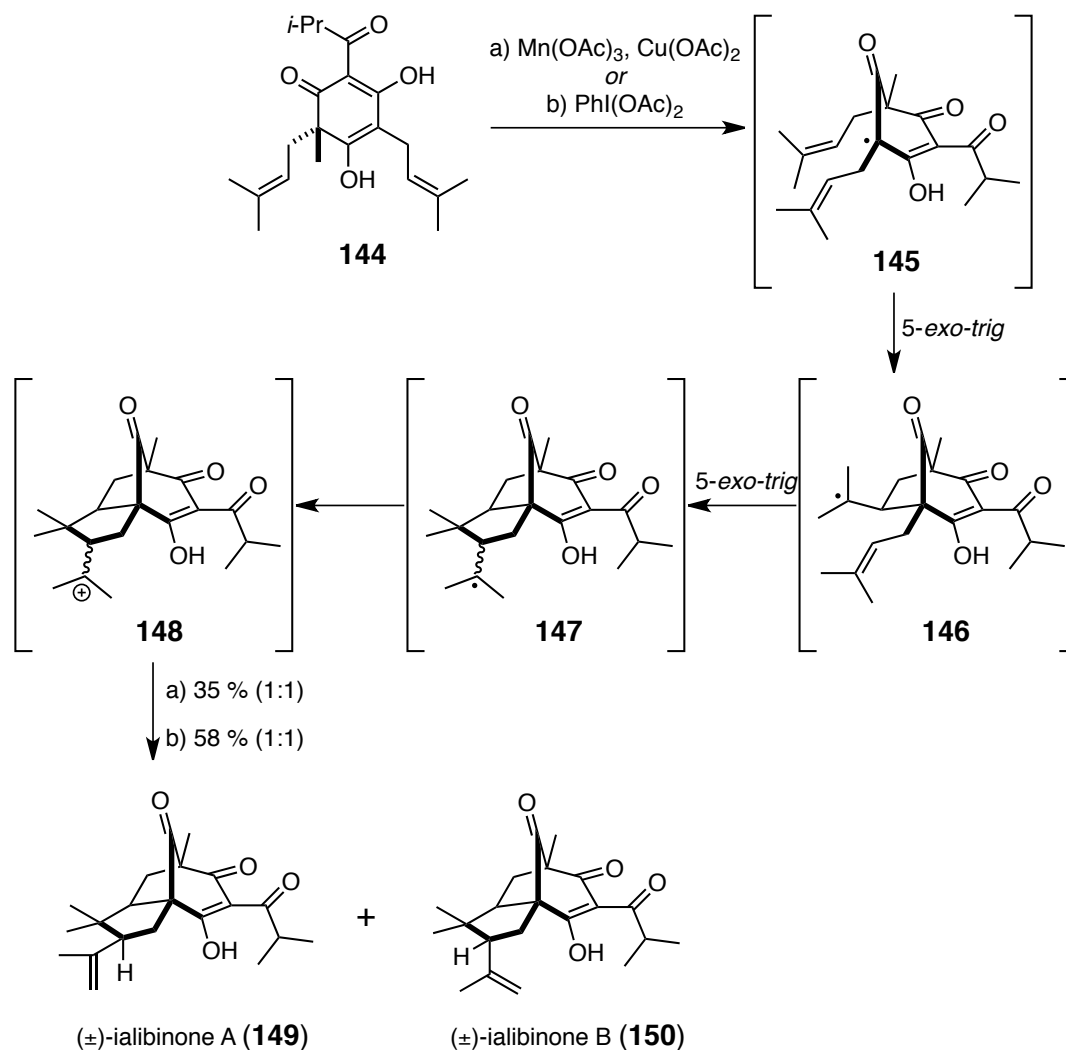
**Scheme 23.** SmI<sub>2</sub>-mediated ring closure cascade in the synthesis of vannusal B (**143**).



Radical cascades have also recently been utilised in the total synthesis of polycyclic polyprenylated acylphloroglucinol (PPAP) natural products ialibinone A (**149**, Scheme 24) and ialibinone B (**150**) by Simpkins<sup>40</sup> and George.<sup>41</sup> Simpkins achieved the synthesis through a biomimetic Mn<sup>III</sup>-mediated radical cascade cyclisation of

acylphloroglucinol **144**, involving two sequential *5-exo-trig* cyclisations, to deliver ialibinones A (**149**) and B (**150**) in 35 % yield. Independently, George *et al.* published an identical strategy, using alternative oxidant  $\text{PhI}(\text{OAc})_2$ , that afforded an improved yield (58 %) of ialibinones A (**149**) and B (**150**) as a 1:1 mixture.

**Scheme 24.** Radical cascade polycyclisation for the total synthesis of ialibinones.

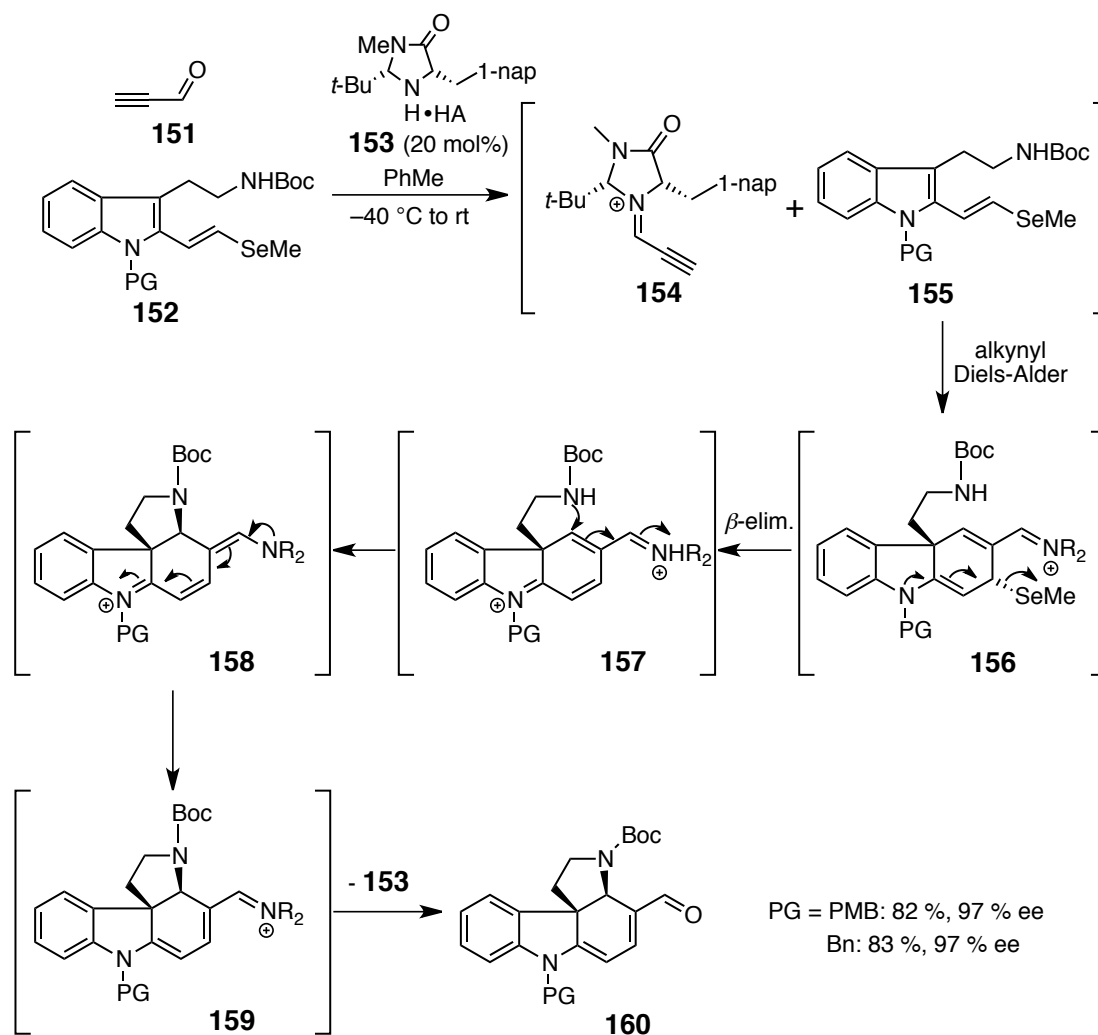


### 1.1.3.6 Organocatalysed cascades

Over the last decade the research area of organocatalysis has quickly grown to become a powerful third mode of asymmetric catalysis, alongside metal catalysis and biocatalysis. As knowledge and methodologies in this fledgling area have improved, it is no surprise that interest in developing asymmetric organocatalysed cascade processes has exploded.<sup>3c</sup> Naturally, applications of these cascades have followed in

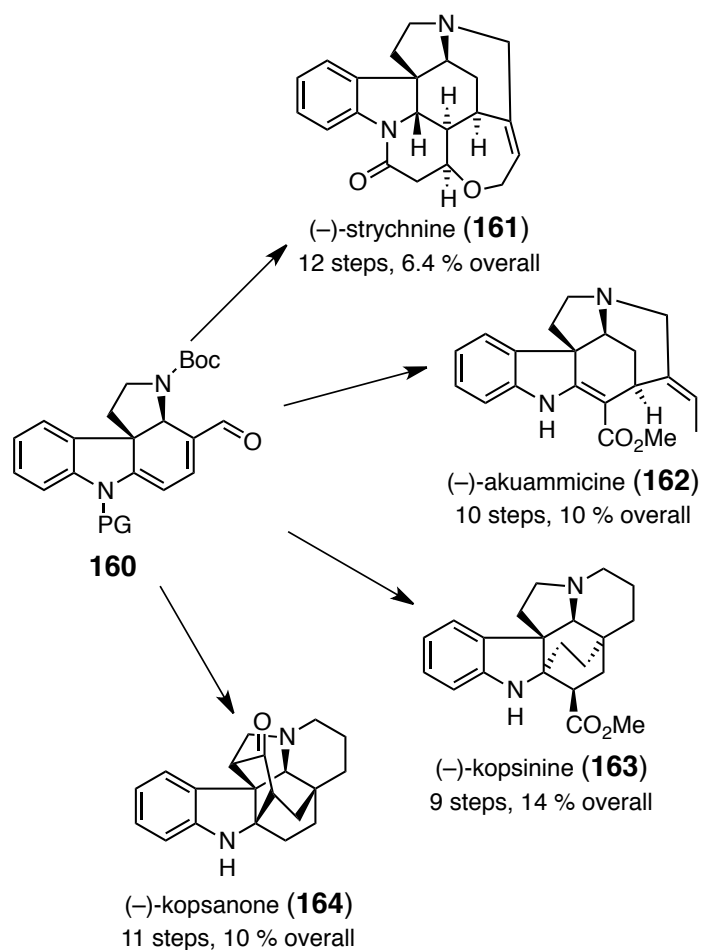
short succession. The Macmillan group has been particularly active in this area, with an impressive recent publication demonstrating a powerful asymmetric organocatalytic cascade approach to a common intermediate in the synthesis of various members of the *Strychnos*, *Aspidosperma* and *Kopsia* families of alkaloids.<sup>42</sup> Synthesis of this spiroindoline intermediate (**160**, Scheme 25) is achieved from vinyl indole **152** and propynal (**151**) using imidazolidinone catalyst **153**, and is understood to proceed *via* an organocatalysed Diels-Alder/ $\beta$ -elimination/conjugate addition sequence.

**Scheme 25.** Proposed mechanism for the organocatalysed cascade generation of tetracyclic intermediate **160**.



Intermediate **160** was then elaborated in different synthetic sequences to deliver the aforementioned alkaloids in excellent yield, and with unprecedentedly short routes. (Scheme 26)

**Scheme 26.** Synthesis of *Strychnos*, *Aspidosperma* and *Kopsia* alkaloids from common spiroindoline intermediate **160**.



#### 1.1.4 Summary

Although designing cascades for natural product syntheses requires careful thought and precise execution - doubtless the successes reported here are the snow cap atop a mountain of failed cascades - the economies afforded by cascade reactions when applied successfully to total syntheses are clear to see in the examples shown above. The ability to install multiple carbo- or heterocycles stereoselectively is an invaluable synthetic tool. As the field matures, and more methodologies/combinations of methodologies are developed for these complex reactions, they will bring the capabilities of the synthetic chemist closer still to the mastery of Nature. Asymmetric cascade processes where selectivity is defined by the catalyst (metal, organic or biological) rather than the substrate will become increasingly important as chemists continue to push the state of the art.

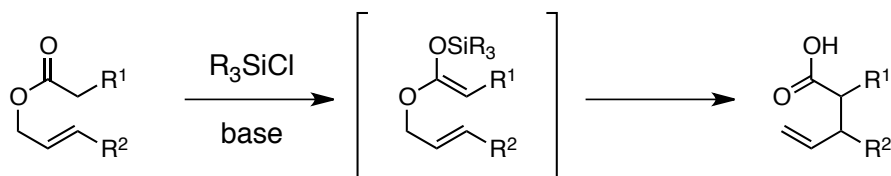
## 1.2 The decarboxylative Claisen rearrangement

### 1.2.1 Introduction

Since its discovery nearly a century ago, the Claisen rearrangement<sup>43</sup> has remained one of the most powerful carbon-carbon bond forming reactions in organic synthesis.<sup>44</sup> This [3,3]-sigmatropic process delivers new C-C bonds in a regiospecific, and often stereoselective, manner from synthetically readily accessible substrates. These assets, as well as a compatibility with a wide range of functionalities, make the Claisen rearrangement particularly suited to total synthesis.

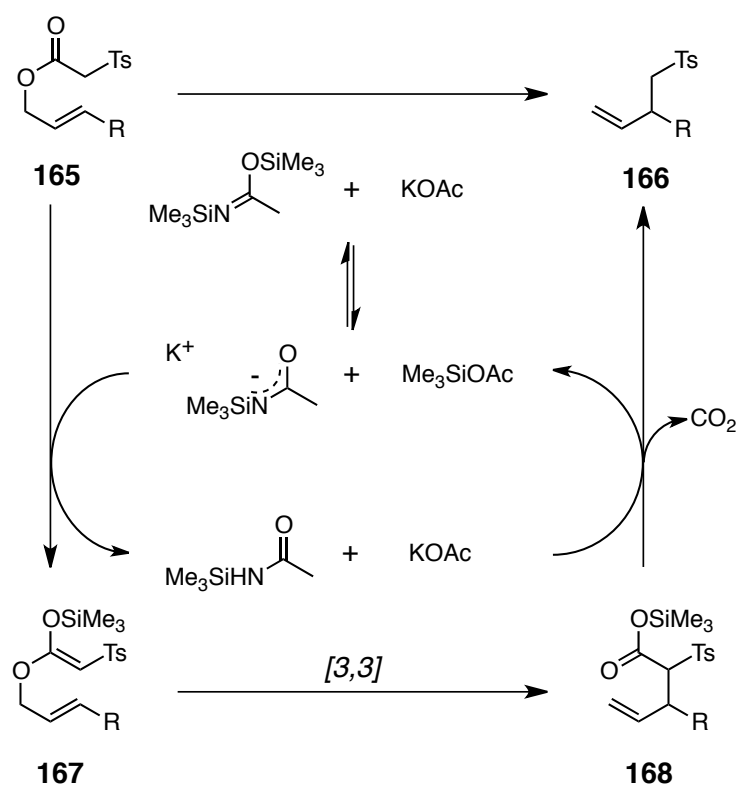
Of the many variations of the original method, the Ireland-Claisen rearrangement of silyl ketene acetals has become one of the most versatile and widely used.<sup>45</sup> These species, formed by the treatment of allylic esters with a silylating agent in the presence of base, undergo facile sigmatropic rearrangement under mild conditions to give  $\gamma,\delta$ -unsaturated carboxylic acids after silyl ester hydrolysis. (Scheme 27)

**Scheme 27.** The Ireland-Claisen rearrangement.



The Craig group has recently introduced a novel variant of the Ireland-Claisen rearrangement, termed the decarboxylative Claisen rearrangement (dCr).<sup>46</sup> Tosylacetic esters of allylic alcohols are transformed into homoallylic sulfones upon exposure to sub-stoichiometric amounts of *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate under thermal or microwave conditions. The proposed catalytic cycle is initiated by the reversible reaction of KOAc and BSA to generate trimethylsilyl acetate.<sup>47</sup> The conjugate base of *N*-trimethylacetamide deprotonates ester **165** to give silyl ketene acetal **167**, with regeneration of KOAc. Following [3,3]-sigmatropic rearrangement to give silyl ester **168**, nucleophilic acetate desilylates **168** resulting in decarboxylation. Proton abstraction from either *N*-trimethylsilylacetamide or another molecule of substrate **A** gives homoallylic sulfone **166**. (Scheme 28)

**Scheme 28.** The proposed catalytic cycle of the dCr reaction.

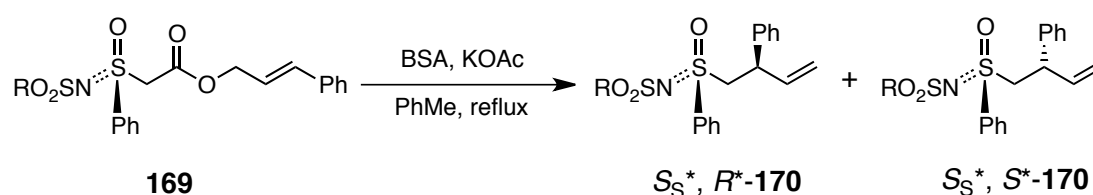


The dCr substrates can be derived from both primary and secondary allylic alcohols, and rearrangement occurs regardless of the level of olefin substitution.<sup>47</sup>

### 1.2.2 Diastereoselectivity in the dCr reaction

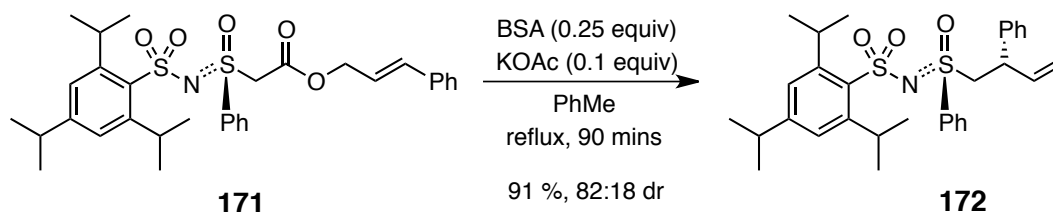
A diastereoselective version of the dCr reaction has been achieved using *N*-arylsulfonyl sulfoximine groups instead of tosyl groups.<sup>48</sup> Enantiopure sulfoximines are readily accessible from the racemate and are an ideal functionality for mimicking tosyl reactivity. A variety of different nitrogen substituents were investigated and the diastereomeric ratios of their dCr products recorded. (Scheme 29)

**Scheme 29.** dCr reaction of racemic sulfoximine-substituted esters.

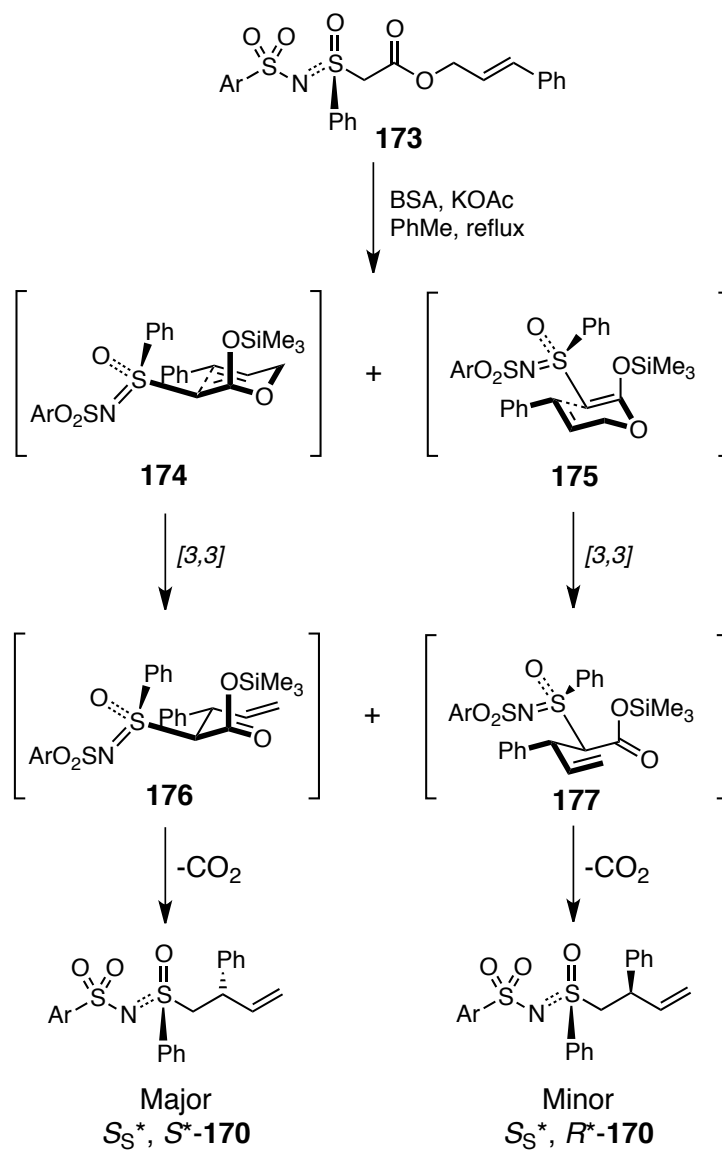


Of the substituents investigated, *N*-(2,4,6-triisopropylphenylsulfonyl)-*S*-phenyl sulfoximine (Tris) gave the best diastereomeric ratio of 82:18. (Scheme 30)

**Scheme 30.** dCr of Tris-sulfoximine **171**.



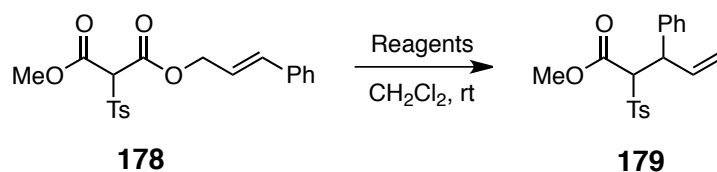
A transition-state model has been proposed to rationalise the stereochemical outcome observed. The pseudo-chair conformation shows that when the bulky  $\text{ArSO}_2\text{N}$  group sits antiperiplanar to the ketene-acetal double bond, as in transition state **174** (Scheme 31), the most stable conformation is achieved. The preferred trajectory of approach for the allylic moiety is *syn* with respect to the sulfoximine oxygen and *anti* to the phenyl group, hence explaining why bulky aryl groups improve selectivity.

**Scheme 31.** Proposed transition state model.<sup>48</sup>

### 1.2.3 dCr reactions of allylic malonate substrates

The effect of an electron-withdrawing substituent at the  $\alpha$ -position of the allylic tosylates has been investigated.<sup>49</sup> Methyl allyl 2-tosylmalonates were prepared, and underwent dCr reaction at ambient temperature in the presence of stoichiometric BSA. The reactions were also successful with alternative reagents TBSOTf and DBU. (Table 1)

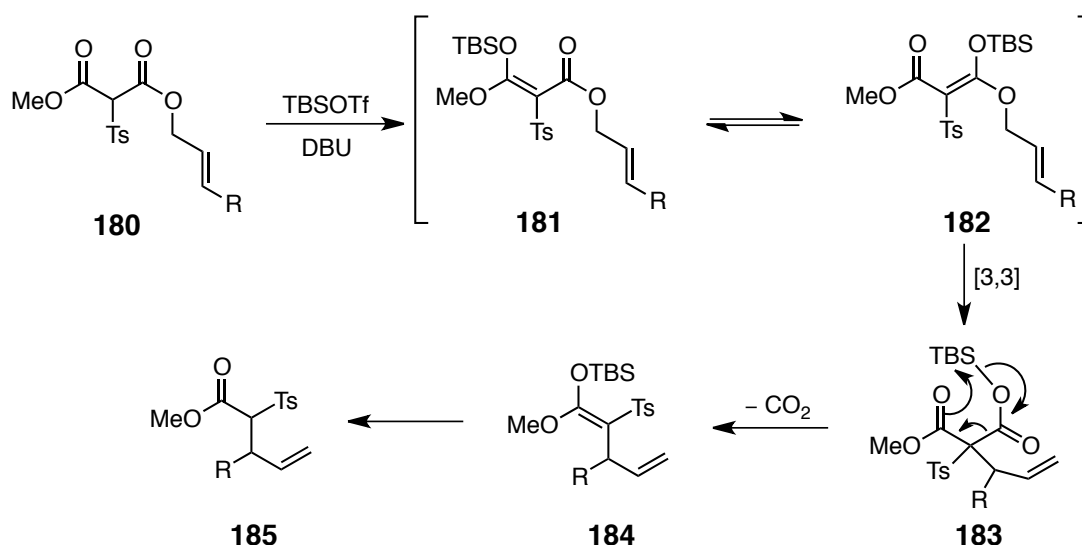
**Table 1.** dCr reaction of **178** at ambient temperature.



|   | Reagents                            | Yield of <b>179</b> |
|---|-------------------------------------|---------------------|
| 1 | TBSOTf (2.1 equiv), DBU (2.1 equiv) | 83 %                |
| 2 | BSA (1.0 equiv), KOAc (0.1 equiv)   | 81 %                |

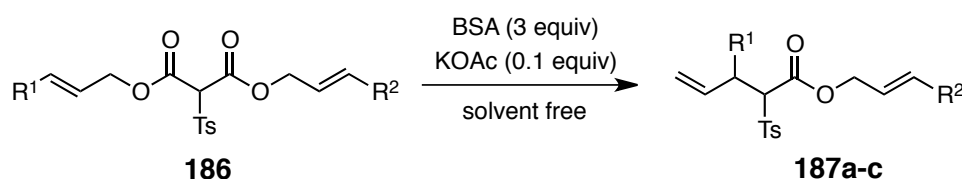
Due to the lack of a nucleophilic species to facilitate desilylation in the TBSOTf-DBU system, the normal mode of desilylation-decarboxylation as seen with BSA-KOAc could not be occurring, and an alternative mechanism was proposed. (Scheme 32)

**Scheme 32.** Proposed mechanism of decarboxylation mediated by TBSOTf-DBU.<sup>49</sup>



The dCr reaction of unsymmetrical diallyl tosylmalonates (**186**) at ambient temperature has also been demonstrated.<sup>50</sup> Only mono-rearrangement occurs under these conditions to give allylic tosyl esters **187**. These species no longer bear the electron-withdrawing group required for rearrangement under such mild conditions and so no further reaction takes place. In general, electron-rich allylic side chains were observed to react preferentially. (Table 2)

**Table 2.** Examples of the dCr reaction of unsymmetrical diallyl tosylmalonates **186**.

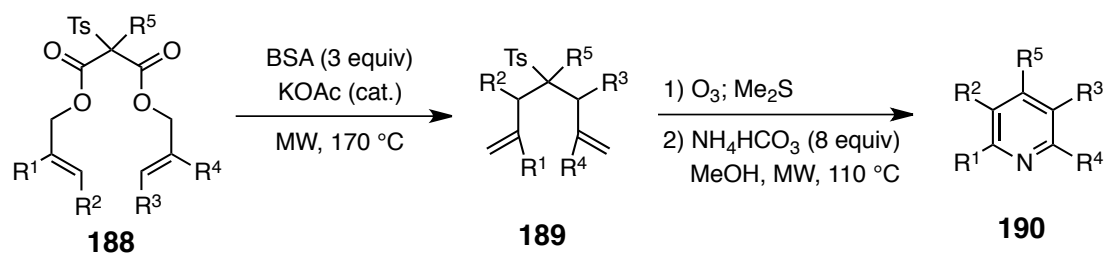


| Entry | Substrate   | R <sup>1</sup>                     | R <sup>2</sup>    | T (°C) | t (h) | Product (%)      |
|-------|-------------|------------------------------------|-------------------|--------|-------|------------------|
| 1     | <b>186a</b> | 4-MeOC <sub>6</sub> H <sub>4</sub> | <i>E</i> -MeCH=CH | 0      | 2     | <b>187a</b> (95) |
| 2     | <b>186b</b> | 4-MeOC <sub>6</sub> H <sub>4</sub> | Ph                | 25     | 2     | <b>187b</b> (81) |
| 3     | <b>186c</b> | <i>E</i> -MeCH=CH                  | Ph                | 25     | 16    | <b>187c</b> (79) |

It was subsequently shown that the first-order rate constants for dCr reactions were dependent upon the electron density of the aryl group attached to the allylic portion.<sup>51</sup> This indicates that there is a significant build-up of positive charge at the benzylic position during rearrangement. The effect is greater than that found in investigations into other [3,3]-sigmatropic processes.<sup>52</sup>

The double dCr reaction of unsymmetrical diallyl tosylmalonates can be achieved using BSA-KOAc under microwave conditions. This has been applied in the *de novo* synthesis of pyridines.<sup>53</sup> (Scheme 33)

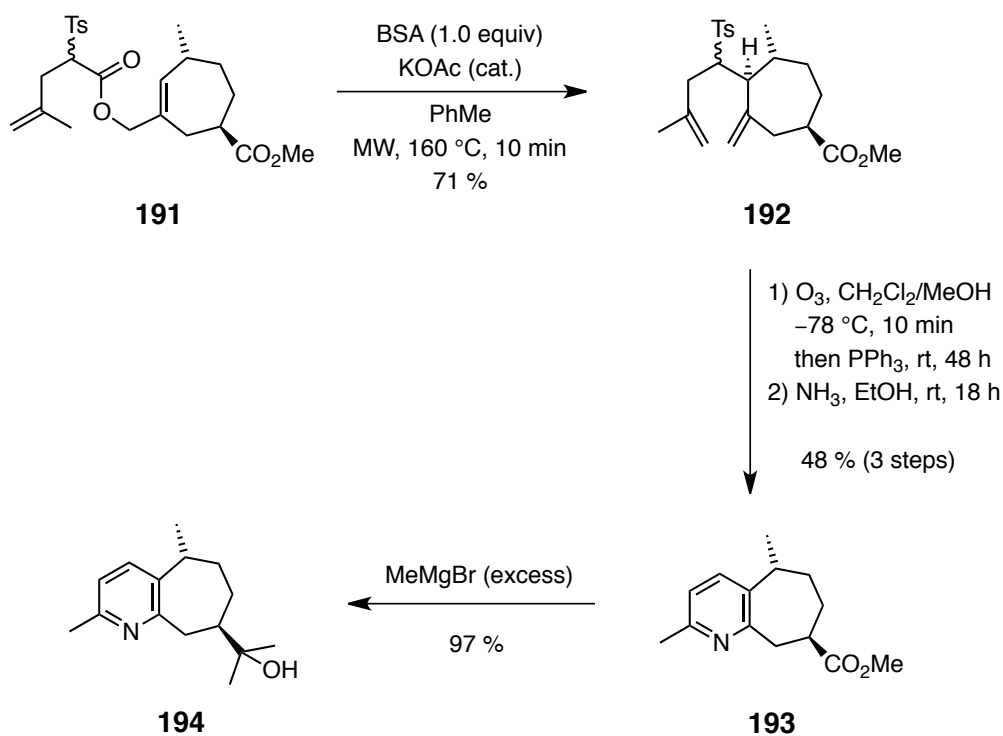
**Scheme 33.** Synthesis of pyridines using diallyl 2-tosylmalonates.



### 1.2.4 Application of dCr to the total synthesis of (+)-cananodine

The dCr reaction has also been used as a key step in the total synthesis of (+)-cananodine (**194**, Scheme 34).<sup>54</sup> Intermediate **191** was treated under microwave-assisted dCr conditions to give diene **192** as a mixture of two epimers in 71% yield. Ozonolysis, then exposure to ethanolic ammonia gave pyridine intermediate **193** in 48% yield. Exposure of **193** to excess methylmagnesium bromide gave (+)-cananodine **194** in 97% yield.

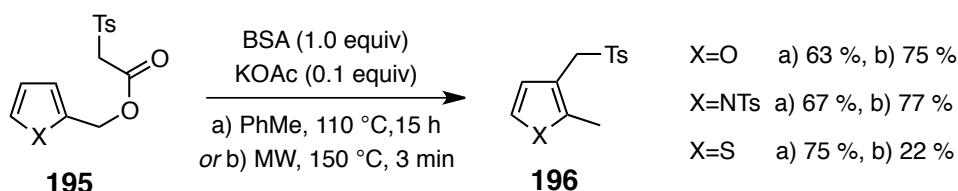
**Scheme 34.** Application of the dCr reaction in the synthesis of (+)-cananodine (**194**).



### 1.2.5 dCr reactions of heteroaromatic substrates

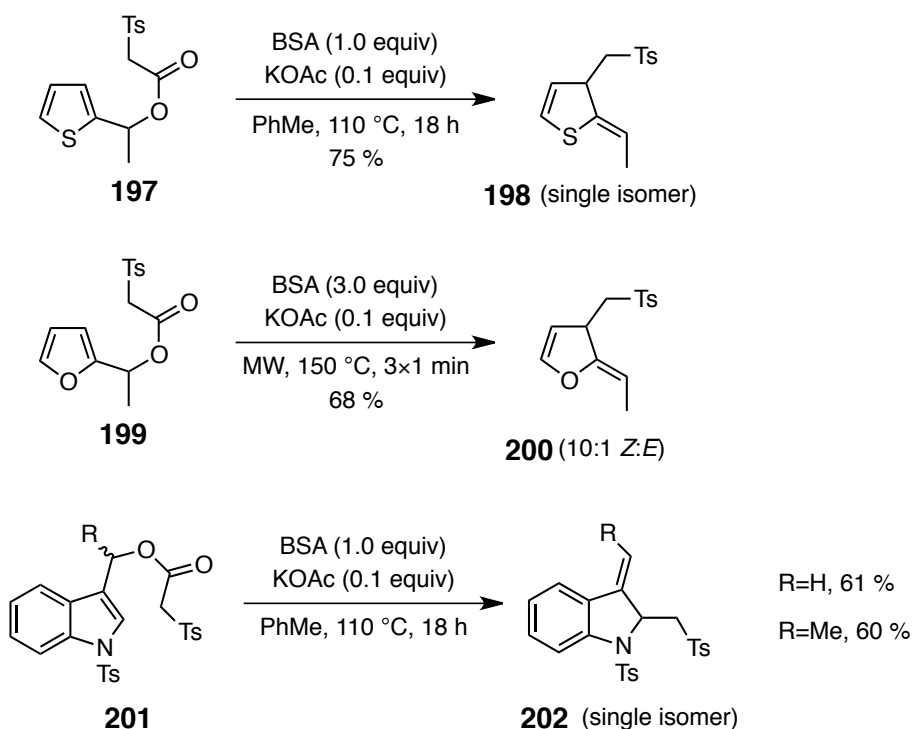
Furan-2-ylmethyl, thien-2-ylmethyl and pyrrol-2-ylmethyl 2-tosylacetates have undergone dCr reactions under microwave or thermal conditions to deliver corresponding 2,3-disubstituted heteroaromatic products (Scheme 35).<sup>55</sup>

**Scheme 35.** dCr reaction of heteroaromatic substrates.



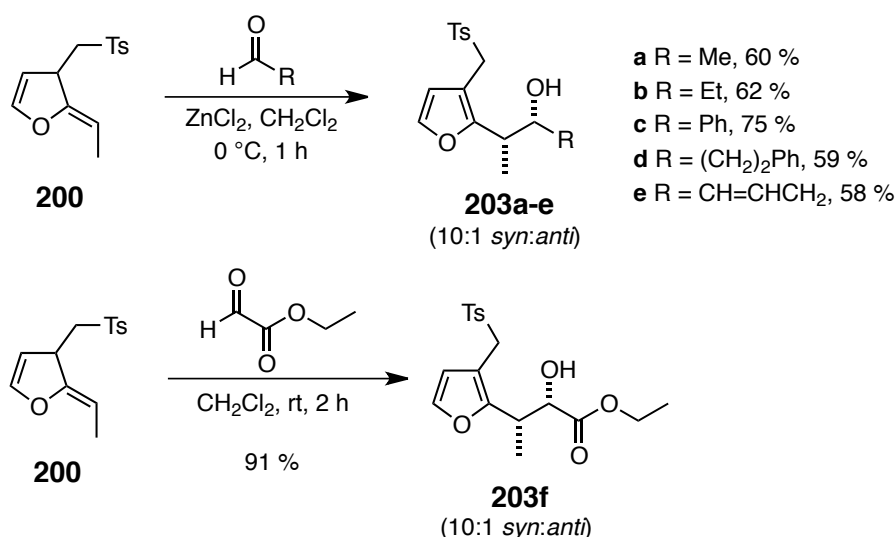
Conversely, 1-(thien-2-yl)ethyl (**197**) and 1-(furan-2-yl)ethyl (**199**) 2-tosylacetates, do not undergo rearomatisation.<sup>55,56</sup> This was reasoned to be a result of both higher substitution of the exocyclic alkenes in **197** and **199** and greater steric buttressing in the product of the non-observed rearomatisation. The same was true of 3-(hydroxyalkyl)indoles **201**, which gave stable indolines **202** that failed to rearomatise even when subjected to acidic or basic conditions (Scheme 36).<sup>55</sup> The corresponding 2-substituted indole did not undergo Claisen rearrangement due to lower electron density at this position.

**Scheme 36.** Dearomatising dCr reactions of heteroaromatic substrates.



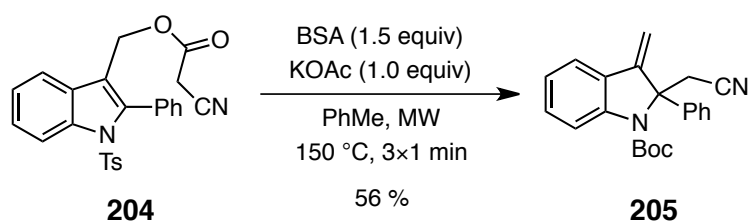
Further investigations have shown these dearomatised products to be highly useful substrates for further synthetic embellishment. Novel dearomatised furan **203** was found to react diastereoselectively with a variety of aldehydes under relatively mild conditions.<sup>56</sup> (Scheme 37)

**Scheme 37.** Diastereoselective reaction of dearomatised furan dCr products with electrophiles.



Reactivity and versatility of the dearomatised indoline dCr products was demonstrated by derivatisation with a variety of oxidation, reduction and addition methods.<sup>57</sup> Of particular interest was the dCr of cyanoacetate ester **204** under standard conditions, which gave dearomatised substrate **205** possessing a C-2 quaternary centre in good yield (Scheme 38).<sup>57</sup> Work to develop an asymmetric version of this process, including potential applications in natural product synthesis, is ongoing.

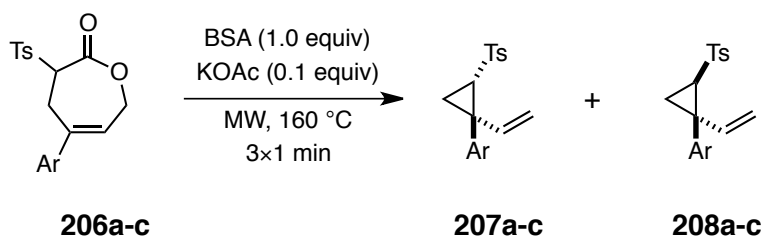
**Scheme 38.** Dearomatising dCr of ester **204**.



### 1.2.6 Transannular dCr reactions

Finally, ring contraction of  $\epsilon$ -lactones was achieved using a transannular dCr reaction, giving access to cyclopropanes possessing quaternary centres.<sup>58</sup> A modest degree of diastereoselectivity was observed when bulkier aromatic groups were used to increase steric demand in the allylic moiety (Table 3).

**Table 3.** Transannular dCr reactions of  $\alpha$ -tosyl- $\gamma$ -aryl- $\epsilon$ -lactones **206a-c**.<sup>58</sup>



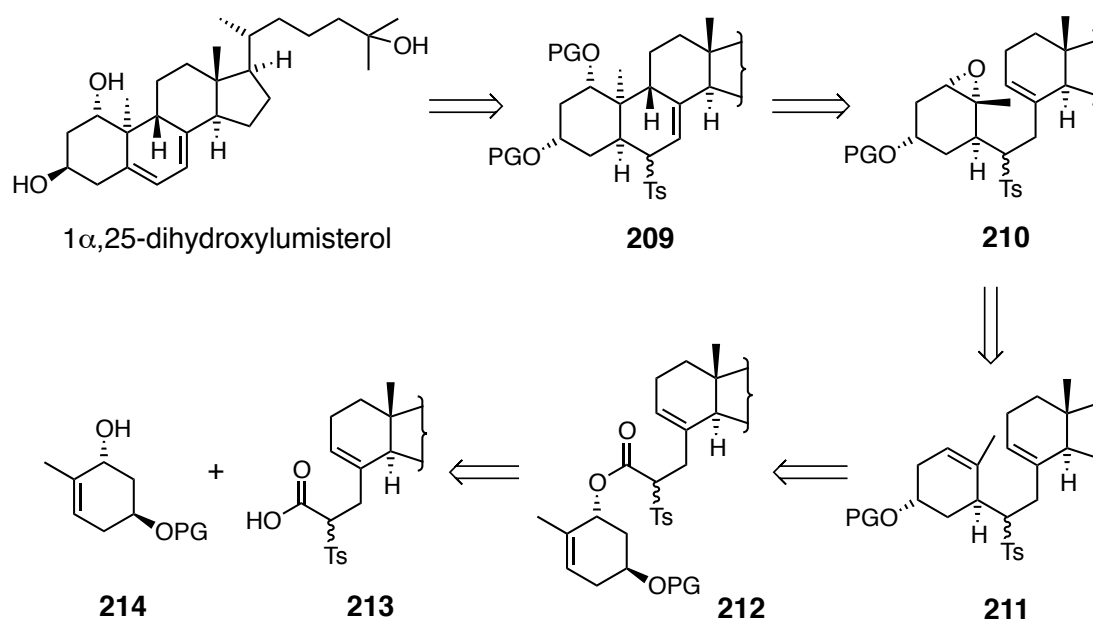
| Substrate   | Ar                                               | Products           | Ratio <b>207:208</b> <sup>a</sup> | Yield (%) |
|-------------|--------------------------------------------------|--------------------|-----------------------------------|-----------|
| <b>206a</b> | Ph                                               | <b>207a + 208a</b> | 1 : 1                             | 87        |
| <b>206b</b> | 2,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | <b>207b + 208b</b> | 1.3 : 1                           | 75        |
| <b>206c</b> | 2,6-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | <b>207c + 208c</b> | 2.2 : 1                           | 82        |

a) Determined by <sup>1</sup>H NMR analysis of crude products.

### 1.3 Proposed synthesis of 1 $\alpha$ ,25-dihydroxylumisterol

Workers at the Wellcome Centre for Research in Clinical Tropical Medicine have investigated the immunomodulatory properties of vitamin D in tuberculosis infection.<sup>59</sup> They have shown that Vitamin D stimulates macrophage superoxide burst by rapid membrane-initiated signalling; as well as down-regulating protective cytokine responses *in vitro*.<sup>60</sup> 6-*s-cis*-locked calcitriol analogues, such as 1 $\alpha$ ,25-dihydroxylumisterol (Scheme 39), are proposed as potential candidates for selective stimulation of membrane-initiated macrophage anti-mycobacterial activity without affecting cytokine response.<sup>61</sup> This presents a potential area for the development of novel agents for tuberculosis treatment. Currently, no synthetic route to 1 $\alpha$ ,25-dihydroxylumisterol exists.

Our proposed synthetic route to calcitriol analogue 1 $\alpha$ ,25-dihydroxylumisterol intends to make use of a dCr reaction of ester **212** as a key step. C-3 hydroxy-directed epoxidation of the resultant 1,6-heptadiene **211** will deliver  $\omega$ -epoxyalkene **210**, the substrate for the second key step; a Lewis acid-mediated cyclisation in which the nucleophilic C-ring olefin intercepts the A-ring epoxide in a stereospecific manner akin to, and inspired by, the squalene epoxide ring-closure cascade.<sup>62</sup> Completion of the synthesis will involve elimination of TsH under basic conditions, Mitsunobu inversion of the C-1 alcohol, and deprotection steps to give the desired natural product (Scheme 39).

**Scheme 39.** Retrosynthetic approach to 1 $\alpha$ ,25-dihydroxylumisterol.

The synthetic challenge is thus reduced to the fabrication of simple allylic alcohol **214** and carboxylic acid **213**.

## 1.4 References

- 
- <sup>1</sup> Sorensen, E. J.; Davies, H. M. L. *Chem. Soc. Rev.* **2009**, 38 (11), special issue on rapid formation of molecular complexity in organic synthesis.
- <sup>2</sup> Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, 38, 3010.
- <sup>3</sup> For recent reviews, see: a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, **2009**, Wiley-VCH, Weinheim; b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, 45, 7134; c) Pellissier, H. *Adv. Synth. Catal.* **2012**, 354, 237; d) Anderson, E. A. *Org. Biomol. Chem.* **2011**, 9, 3997.
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- <sup>5</sup> Robinson, R. *J. Chem. Soc. Trans.* **1917**, 762.
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## Chapter 2

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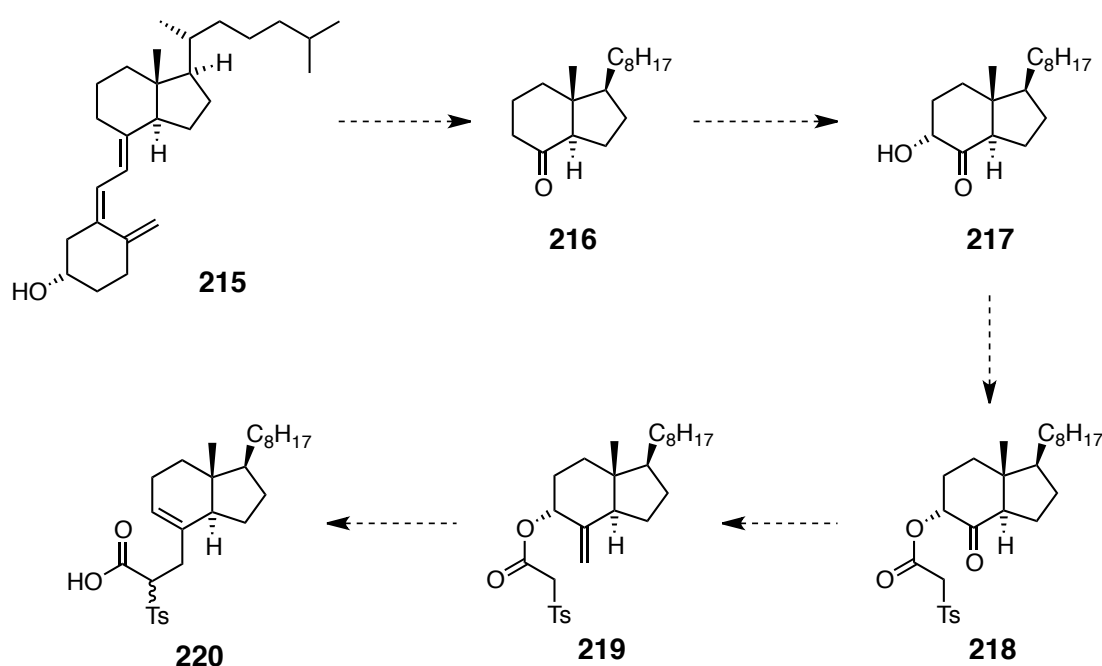
# *Results & Discussion*

## 2.1 Progress towards the synthesis of 1 $\alpha$ ,25-dihydroxylumisterol

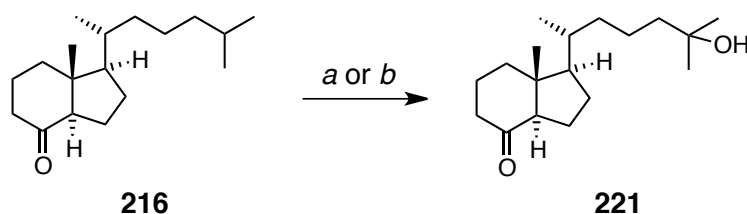
### 2.1.1 Synthesis of carboxylic acid **220**

For the synthesis of carboxylic acid **220** it was envisaged that known  $\alpha$ -hydroxyketone **217**<sup>1</sup> could be coupled with commercially available 2-tosylacetic acid, then methylenated to give allylic ester **219**. Subsequent rearrangement under Ireland-Claisen conditions would deliver desired acid **220**. (Scheme 40)

**Scheme 40.** Proposed synthesis of carboxylic acid **220**.



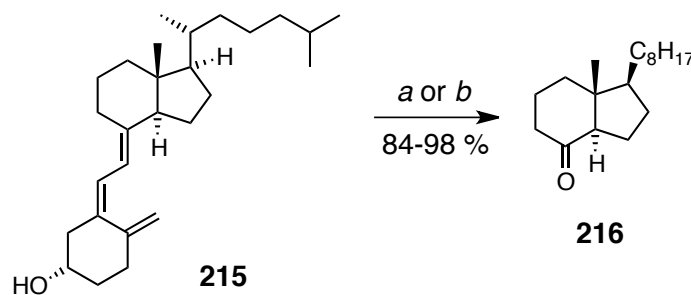
During these initial studies we chose to omit the 25-hydroxy moiety from our synthesis. The early incorporation of this moiety, *via* oxidation of the Windaus-Grundmann ketone **216**<sup>2</sup> with dioxirane reagents<sup>3</sup> or RuO<sub>4</sub><sup>4</sup> is well established (Scheme 41), but due to the poor scalability of the former method, and the expense of the latter, we felt the chemistry did not lend itself to early-stage synthesis. Also, given the relative distance of this moiety from the other reactive centres in the molecule, its omission was unlikely to lead to a synthetic route to the natural product that could not be repeated upon its inclusion, protected as either a silyl or benzyl ether.

**Scheme 41.** Oxidation of Grundmann's ketone to 25-hydroxy analogue **221**.

a)  $\text{RuCl}_3$  (0.15 equiv),  $\text{NaIO}_4$  (3.6 equiv),  $\text{H}_2\text{O}/\text{CCl}_4/\text{CH}_3\text{CN}$ , rt, 120 h, 43 %; b) DMDO (3 equiv),  $\text{CH}_2\text{Cl}_2/\text{acetone}$ , 20 °C, 48 h, 86%.

**2.1.1.1 Synthesis of  $\alpha$ -hydroxyketone 217**

There are numerous literature procedures for the ozonolysis of vitamin- $\text{D}_3$  to Grundmann's ketone but we chose to follow a procedure that had previously been used successfully in the Craig group.<sup>5</sup> Thus, bubbling ozone through a  $\text{CH}_2\text{Cl}_2$  solution of (+)-vitamin  $\text{D}_3$  (**215**) at  $-78$  °C, followed by addition of  $\text{PPh}_3$  to reduce the intermediate ozonide gave **216** in 84% yield after chromatography. On scale-up we found that alternative conditions, using MeOH as solvent and  $\text{Me}_2\text{S}$  as reductant,<sup>6</sup> facilitated an easier work-up, and gave **216** in up to 98% yield. (Scheme 42)

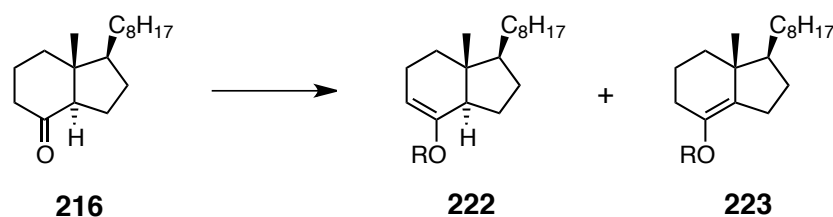
**Scheme 42.** Ozonolysis of vitamin  $\text{D}_3$  to give Windaus-Grundmann ketone **216**.

a)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78$  °C; then  $\text{PPh}_3$ , 84% or b)  $\text{O}_3$ , MeOH,  $-78$  °C; then  $\text{Me}_2\text{S}$ , 98%.

Oxidation of ketone **216** to  $\alpha$ -hydroxyketone **217** has been reported using oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) ( $\text{MoOPH}$ ) to oxidise the kinetic lithium enolate of **216** in 75% yield.<sup>1</sup> Given the poor atom economy of this stoichiometric reagent, and the toxic reagents involved in its preparation, we decided to look at other methods.

We first investigated forming **217** by oxidising silyl enol ether **222** under Rubottom conditions (Table 4).<sup>7</sup> Unfortunately, forming the desired silyl enol ether proved more

challenging than expected. Initial attempts using Et<sub>3</sub>N and TESOTf<sup>8</sup> favoured the silylated thermodynamic enolate as the major product (1:2 **222/223**) in quantitative yield (Table 4, Entry 1). It was thought we could make the kinetic enolate more favoured by changing solvent from CH<sub>2</sub>Cl<sub>2</sub> to Et<sub>2</sub>O as the reduced solubility of triflic acid salt in Et<sub>2</sub>O may have helped to limit reversibility of enol ether formation. In practice this change had the opposite effect and gave **223** as the only product, quantitatively (Table 4, Entry 2). We expected switching the base to LDA would improve selectivity, but the reaction failed to go to completion, with NMR analysis of the crude mixture showing a 6:1 mixture of starting material and silyl enol ether **222** respectively (Table 4, Entry 3). We suspected that this poor conversion might be a result of acidic impurities in TMSCl causing hydrolysis of the lithium enolate, or perhaps even the silyl enol ether product, so the reaction was repeated, this time using Et<sub>3</sub>N-treated solution of TMSCl in THF. This gave only a small improvement (5:2 **216/222**) (Table 4, Entry 4). Another attempt, using a larger excess of base, still gave only a 2:1 **216/222** mixture (Table 4, Entry 5). Clearly any acidic entity present was reacting with the lithium enolate before it could be neutralised by base. With this in mind, we reversed the addition of ketone and TMSCl to the reaction mixture. And so, to an excess of LDA in THF was added TMSCl followed by ketone **216**. The workup gave pure silyl enol ether **222** in quantitative yield without chromatography (Table 4, Entry 6). On repeat we found that the same result could be achieved using only a small excess of base (Table 4, Entry 7).

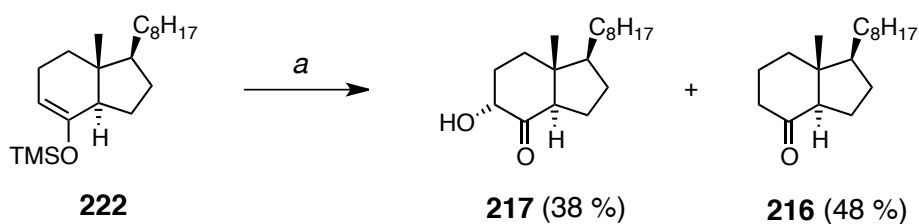
**Table 4.** Synthesis of silyl enol ethers **222/223**.

| Entry | Conditions                                                          | R   | Ratio 216/222/223 <sup>a</sup> |
|-------|---------------------------------------------------------------------|-----|--------------------------------|
| 1     | Et <sub>3</sub> N, TESOTf, CH <sub>2</sub> Cl <sub>2</sub> , -78 °C | TES | 0 : 1 : 2                      |
| 2     | Et <sub>3</sub> N, TESOTf, Et <sub>2</sub> O, -78 °C                | TES | <b>223</b> (>99%)              |
| 3     | LDA (1.2 equiv), TMSCl (1.1 equiv), THF, -78 °C                     | TMS | 6 : 1 : 0                      |
| 4     | LDA (1.2 equiv), base-treated TMSCl (1.1 equiv), THF, -78 °C        | TMS | 5 : 2 : 0                      |
| 5     | LDA (2 equiv), TMSCl (1.1 equiv), THF, -78 °C                       | TMS | 2 : 1 : 0                      |
| 6     | LDA (3 equiv), TMSCl (1.1 equiv), THF, -78 °C, ketone added last    | TMS | <b>222</b> (>99%)              |
| 7     | LDA (1.2 equiv), TMSCl (1.1 equiv), THF, -78 °C, ketone added last  | TMS | <b>222</b> (>99%)              |

a) All reactions gave a quantitative recovery; ratios determined from the <sup>1</sup>H-NMR spectrum of the mixture.

Oxidation of silyl enol ether **222** under Rubottom conditions also proved problematic. The susceptibility of bicyclic silyl enol ethers to hydrolysis by the *m*-chlorobenzoic acid present in mCPBA is known and can be negated by using non-polar solvents, and pre-stirring mCPBA with NaHCO<sub>3</sub> for a short time.<sup>9</sup> Accordingly, treatment of silyl enol ether **216** in CH<sub>2</sub>Cl<sub>2</sub> at -30 °C with a pre-stirred mixture of mCPBA and NaHCO<sub>3</sub> in pentane followed by acid hydrolysis,<sup>10</sup> gave a best yield of 38 % **217**, with a 48% recovery of ketone **216**. (Scheme 43)

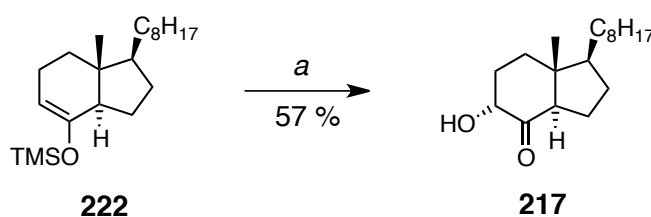
**Scheme 43.** Rubottom oxidation of silyl enol ether **222**.



a) mCPBA (2 equiv), excess  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ /pentane, 0 °C, 3 h, then AcOH/ $\text{H}_2\text{O}$ /THF.

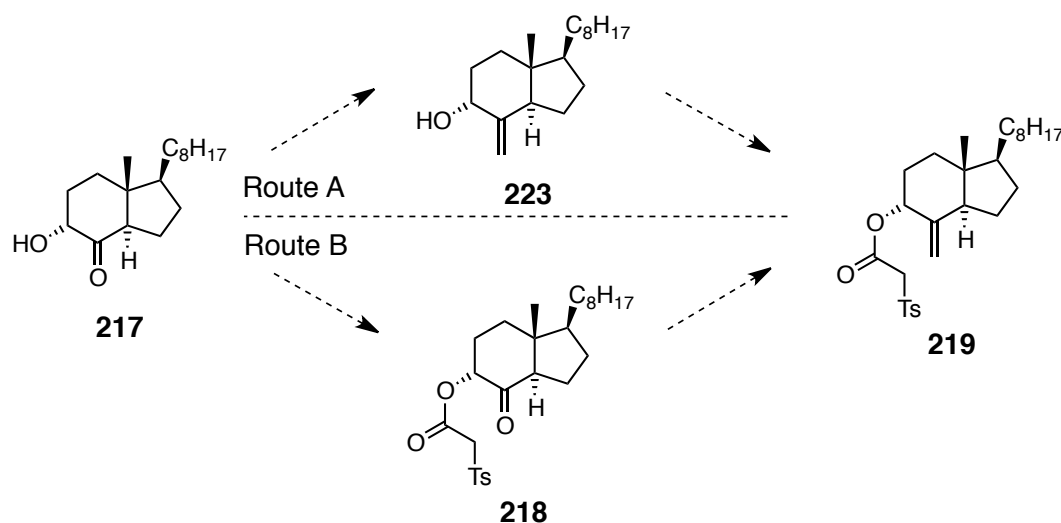
Given that, despite measures taken, hydrolysis was still an issue, it was decided instead to use ozone to achieve this oxidation step.<sup>11</sup> Silyl enol ether **222** in CH<sub>2</sub>Cl<sub>2</sub>/pyridine at -78 °C was treated with ozone. After acidic workup  $\alpha$ -hydroxyketone **217** was isolated in 65 % yield. Unfortunately on scale-up the yield of this reaction fell to below 50 %, but it was found that performing ozonolysis in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, and using a reductive workup,<sup>12</sup> we could isolate **217** in a 54% yield that remained consistent on large scale. (Scheme 44)

**Scheme 44.** Oxidation of silyl enol ether **222** to  $\alpha$ -hydroxyketone **217** with ozone.

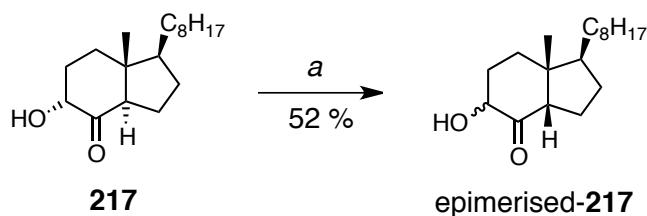


a) O<sub>3</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub> (4:1), -78 °C, 15 min; then Me<sub>2</sub>S, -78 °C→rt, o/n.

Allylic ester **219** was the next target, requiring methylenation and esterification with 2-tosylacetic acid, although it was not obvious in which order these steps would be most effective. (Scheme 45)

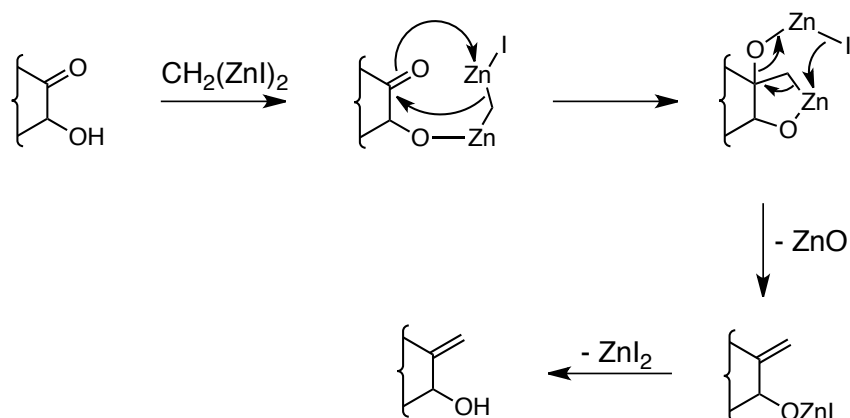
**Scheme 45.** Two possible routes to allylic ester **219** from  $\alpha$ -hydroxyketone **217**.

Route A was the first to be explored. Methylenation was first attempted under Wittig conditions. Ketone **217** was treated with  $\text{Ph}_3\text{PCH}_2$  in THF at 0 °C. Although starting material appeared to be consumed, the only isolated product was the C-14 epimer of **217** in 52 % yield, produced as result of the basic conditions. The stereochemistry of the C-9 position in the product was not determined. (Scheme 46)

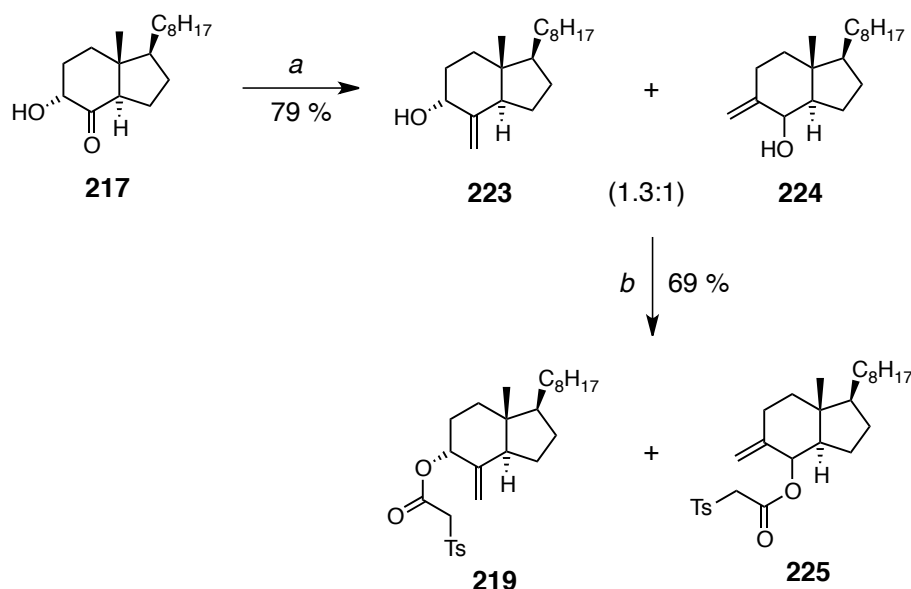
**Scheme 46.** Attempted Wittig reaction of  $\alpha$ -hydroxyketone **217**.

a)  $\text{Ph}_3\text{PCH}_3\text{I}$  (2 equiv),  $n\text{-BuLi}$  (2 equiv), THF, 0 °C  $\rightarrow$  rt, 2 h.

Hydroxyketones have been successfully methylenated using *gem*-dimetallic reagent  $\text{CH}_2(\text{ZnI})_2$  (made using Zn-Cu couple and diiodomethane).<sup>13,14</sup> A proposed mechanism is shown in Scheme 47.

**Scheme 47.** Methylenation of hydroxyketones using  $\text{CH}_2(\text{ZnI})_2$ .<sup>13</sup>

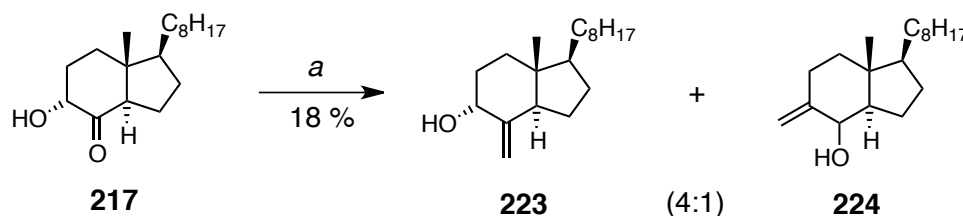
On treatment with  $\text{CH}_2(\text{ZnI})_2$ , hydroxyketone **217** gave a mixture of two inseparable isomers of the desired product **223** (isomer ratio 1.3:1) in 79% yield. The isomers were initially considered to be diastereomers as both seemed to have NMR spectra consistent with the desired product. By coupling the mixture with 2-tosylacetic acid, the resultant allylic ester products could be separated by chromatography. Analysis by NMR spectroscopy showed that the major isomer was the desired allylic ester **219**. Further analysis using a variety of 2D NMR techniques showed strong support for the minor product being isomer **225** rather than another diastereomer of **219** (Scheme 48).

**Scheme 48.** Synthesis of isomers **219** and **225** from  $\alpha$ -hydroxyketone **217**.

a)  $\text{CH}_2(\text{ZnI})_2$  (9 equiv),  $\text{Et}_2\text{O}$ , rt, 3 h; b) 2-tosylacetic acid (1 equiv), DCC (1.1 equiv), DMAP (0.1 equiv),  $\text{CH}_2\text{Cl}_2$ , rt, o/n.

Another attempted methylenation, treating **217** with the Petasis reagent ( $\text{Cp}_2\text{TiMe}_2$ )<sup>15</sup> at reflux in THF/PhMe gave a similar result to the dimetallic zinc reagent, delivering an inseparable 4:1 mixture of **223** and **224** in only 18% yield (Scheme 49).

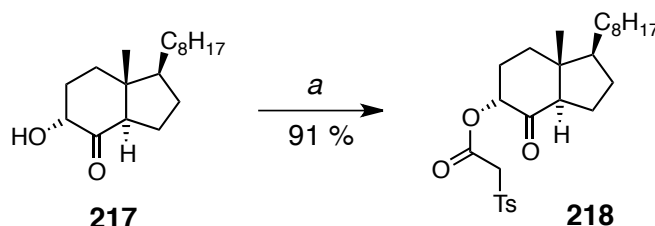
**Scheme 49.** Methylenation of  $\alpha$ -hydroxyketone **217** with the Petasis reagent.



a)  $\text{Cp}_2\text{TiMe}_2$  (3 equiv), PhMe/THF, 70 °C, 18 h.

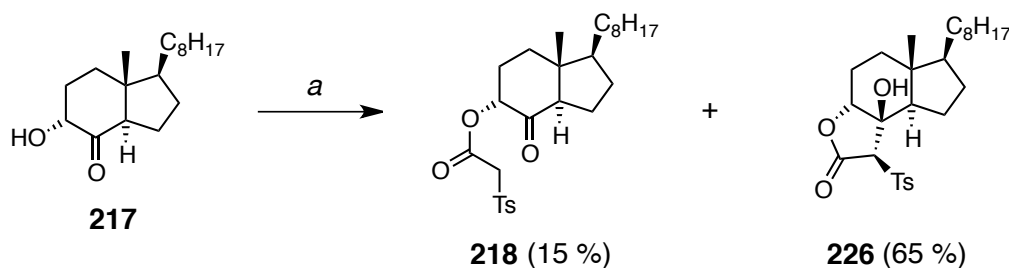
Given the problems with Route A, Route B was explored (Scheme 45). **217** was coupled to 2-tosylacetic acid by treatment with DIC and DMAP to give **218** in 91% yield on a 100 mg scale (Scheme 50).

**Scheme 50.** Small-scale coupling of  $\alpha$ -hydroxyketone **217** with 2-tosylacetic acid.



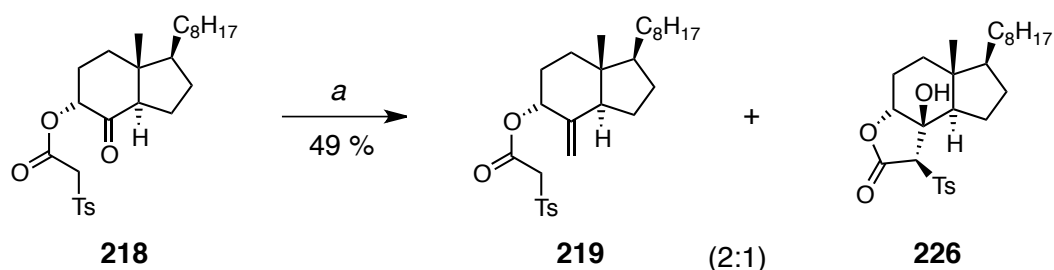
a) 2-tosylacetic acid (1 equiv), DIC (1.1 equiv), DMAP 0.1 equiv),  $\text{CH}_2\text{Cl}_2$ , 0 °C  $\rightarrow$  rt, 15 min.

However, when repeated on a larger scale (700 mg) an unexpected reaction occurred. Although TLC assay showed that the majority of starting material had been consumed and the desired product forming after 15 min, after a further 15 min the initial product had been mostly consumed to give a new product with a higher  $R_f$ . After immediate workup and chromatography, the desired product **218** was isolated in just 15% yield, with  $\gamma$ -lactone **226**, as the major product (65 %), most probably formed by DMAP-catalysed intramolecular aldol reaction of the ketoester (Scheme 51). **218** was also observed to undergo partial cyclisation to **226** during chromatography and whilst being stored. As such the prospect of improving the yield of **218** by halting the coupling reaction before cyclisation could occur was deemed not to be a viable option.

**Scheme 51.** Synthesis of  $\gamma$ -lactone **226** from  $\alpha$ -hydroxyketone **217**.

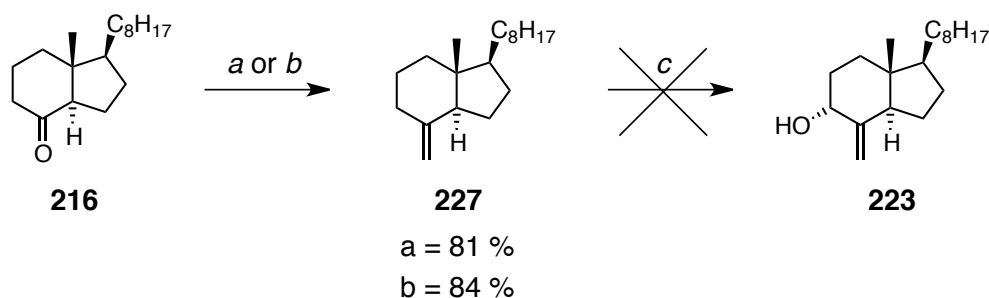
a) 2-tosylacetic acid (1 equiv), DIC (1.1 equiv), DMAP (0.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 30 min.

When Wittig methylenation of ketoester **218** was attempted it led, unsurprisingly given the basic conditions, to a mixture of the desired allylic ester **219** and  $\gamma$ -lactone **226** as a 2:1 mixture in 49 % yield (Scheme 52). Attempts to achieve the same methylenation with Cp<sub>2</sub>TiMe<sub>2</sub> led to total decomposition of starting material over 72 h.

**Scheme 52.** Synthesis of allylic ester **219** and  $\gamma$ -lactone **226** from **218**.

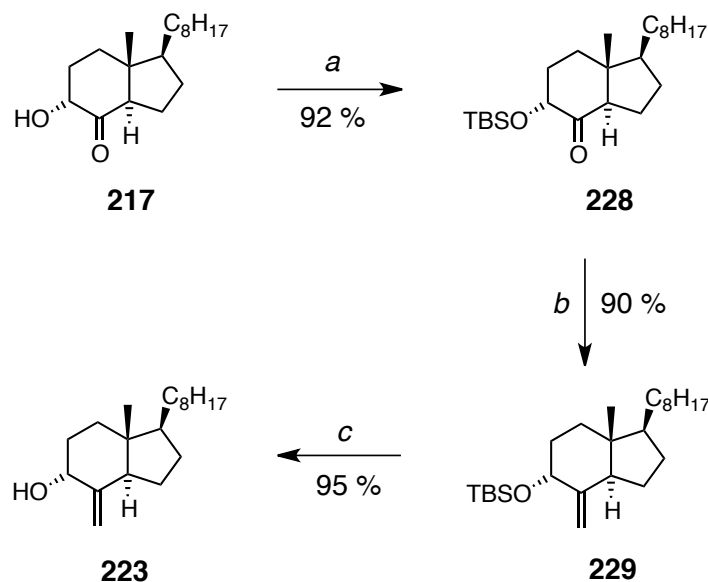
a) Ph<sub>3</sub>PCH<sub>3</sub>I (1.3 equiv), *n*-BuLi (1.1 equiv), THF, 0 °C→rt, 2 h.

Another potential route to allylic alcohol **223** was by methylenation of Grundmann's ketone **216** followed by a Riley oxidation. Methylenation was successfully achieved with under both Wittig<sup>16</sup> and Petasis conditions, giving olefin **227** in 81% and 84% respectively. Selenium dioxide oxidation of a C-17 analogue of **227** (R=OAc instead of C<sub>8</sub>H<sub>17</sub>) had been reported in 55% yield.<sup>17</sup> Unfortunately a procedure for transformation was not included within the paper and attempted oxidation gave only an intractable mixture of products.<sup>18</sup> (Scheme 53)

**Scheme 53.** Methylenation and attempted Riley oxidation.

a)  $\text{Ph}_3\text{PCH}_3\text{I}$  (1.3 equiv),  $n\text{-BuLi}$  (1.1 equiv), THF,  $0\text{ }^\circ\text{C} \rightarrow \text{rt}$ , 4 h; b)  $\text{Cp}_2\text{TiMe}_2$ ,  $\text{PhMe/THF}$ ,  $65\text{ }^\circ\text{C}$ , 48 h; c)  $\text{SeO}_2$  (0.3 equiv),  $t\text{BuOOH}$  (2 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C} \rightarrow \text{rt}$ , 24 h.

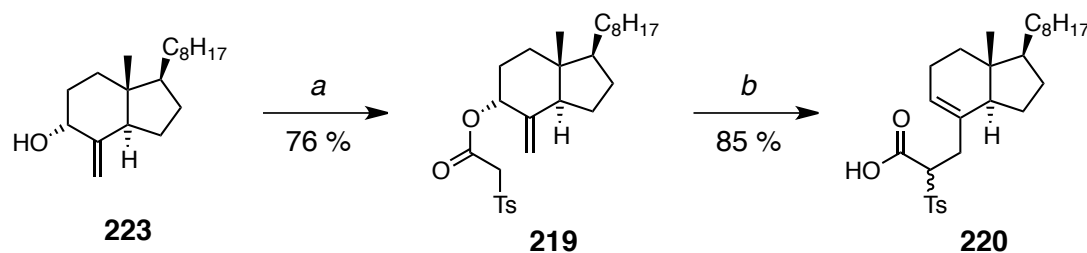
After these failed attempts to access allylic ester **219** we decided to proceed by protecting  $\alpha$ -hydroxyketone **217**, followed by methylenation, deprotection and then esterification. Consequently, TBS protection of the alcohol, carried out under standard conditions,<sup>19</sup> followed by Wittig methylenation and TBS removal with TBAF gave **223** in 78 % yield over 3 steps. Furthermore, the yield of this sequence was only modestly diminished (74 %) when purification was omitted from all but the final step. (Scheme 54)

**Scheme 54.** Synthesis of allylic alcohol **223**.

a)  $\text{TBSCl}$  (3 equiv), imidazole (3 equiv),  $\text{CH}_2\text{Cl}_2$ , 18 h, rt; b)  $\text{Ph}_3\text{PCH}_3\text{I}$  (1.3 equiv),  $n\text{-BuLi}$  (1.1 equiv), THF,  $0\text{ }^\circ\text{C}$ , 1 h; c)  $\text{TBAF} \cdot 3\text{H}_2\text{O}$  (3 equiv) THF, rt, 72 h.

Coupling of **223** with 2-tosylacetic acid under standard Steglich conditions<sup>20</sup> was rapid and gave allylic ester **219** in 76 % yield. Ireland-Claisen rearrangement of **219** to give carboxylic acid **220** was achieved under mild conditions by treatment with BSA and Et<sub>3</sub>N in acetonitrile.<sup>21</sup> The rearrangement proved facile and high-yielding, giving **220** as a mixture of C-Ts epimers. (Scheme 55)

**Scheme 55.** Synthesis of carboxylic acid **220**.

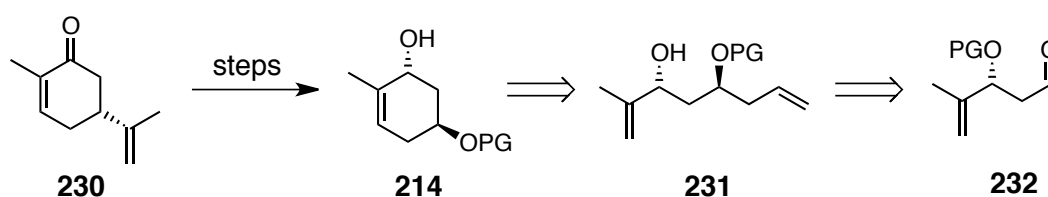


a) 2-tosylacetic acid (1 equiv), DIC (1.1 equiv), DMAP (0.05 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min; b) BSA (3 equiv), Et<sub>3</sub>N (1.2 equiv), CH<sub>3</sub>CN, 60 °C, 30 min.

### 2.1.2 Synthesis of racemic alcohol **214**

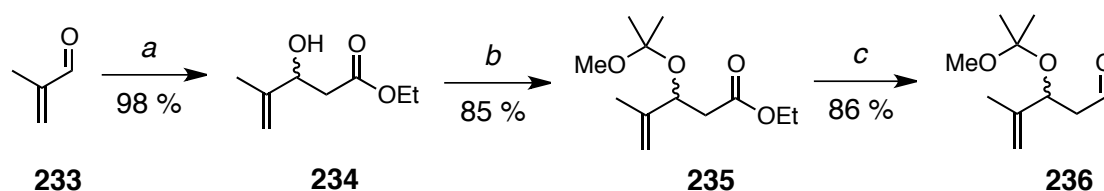
Differentially protected cyclohexenediols such as **214** have been synthesised *via* multi-step sequences from (*R*)-carvone (**230**).<sup>22</sup> Despite this, we envisaged a simpler route *via* 1,3-*anti*-diol derivative **231** that would provide **214** when subjected to ring-closing metathesis. We intended to make **231** itself by the diastereoselective allylation of aldehyde **232**. (Scheme 56)

**Scheme 56.** Literature approach<sup>22</sup> and our proposed approach to **214**.



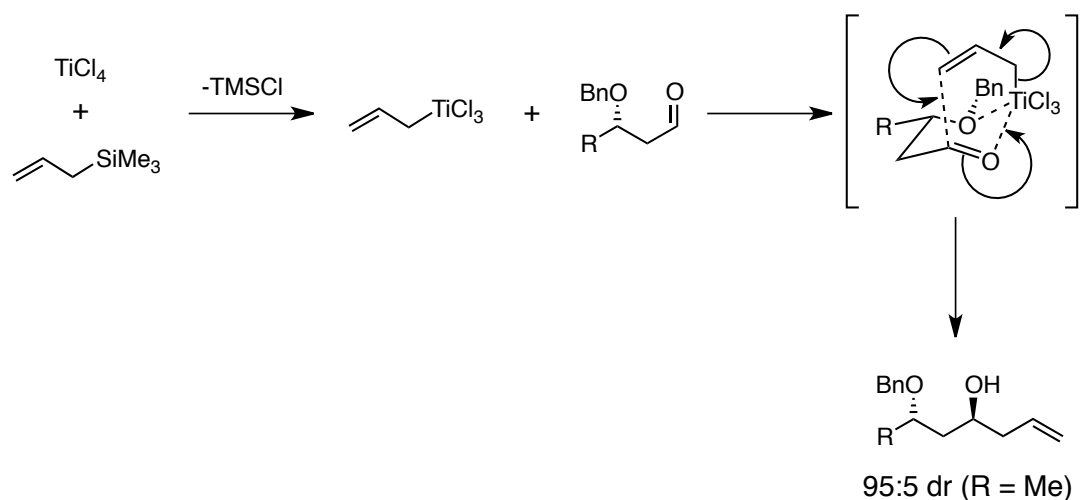
Our synthesis of **236** began with an aldol addition of EtOAc to methacrolein (**233**) to give racemic  $\beta$ -hydroxyester **234**. The kinetic resolution of **234** to its (*R*)-enantiomer in 98 % *ee* by Sharpless epoxidation was known in the literature and was key to our planned strategy for the asymmetric synthesis of **214**,<sup>23</sup> but during early investigations we chose to continue with the racemate. Hydroxy protection followed by DIBAL-H reduction gave aldehyde **236** in good yield (Scheme 57). Compounds **235** and **236** could not be stored for longer than 24 h otherwise significant loss of the MIP protecting group was observed.

**Scheme 57.** Synthesis of aldehyde **236** from methacrolein.

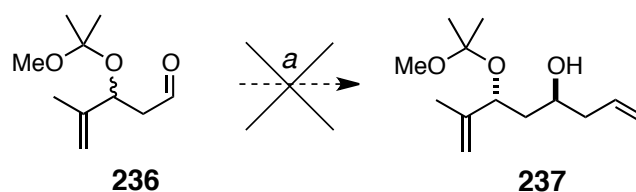


a) LDA (1.1 equiv), EtOAc (1.1 equiv), THF,  $-78\text{ }^{\circ}\text{C}$ , 90 min; b) PPTS (5 mol%), 2-methoxypropene,  $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$ , 90 min; c) DIBAL-H (1.05 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^{\circ}\text{C}$ , 1 h.

Chelation-controlled 1,3-asymmetric induction is well studied.<sup>24</sup> Allylic addition to protected  $\beta$ -hydroxyaldehydes using  $\text{TiCl}_4$  and allyltrimethylsilane can be used to give differentially protected *anti*-1,3-diols with good diastereoselectivity.<sup>25</sup> (Scheme 58)

**Scheme 58.** Chelate-controlled addition to  $\beta$ -alkoxyaldehydes.

This approach gives the best results for benzyl-protected alcohols. At this stage we chose not to use this protecting group as we had intended to use benzyl protection on the other hydroxy moiety in *anti*-1,3-diol **231**. We had believed MIP-protection to be a suitable alternative, but when aldehyde **236** was treated with  $\text{TiCl}_4$  and trimethylallylsilane at  $-78^\circ\text{C}$ , the starting material was consumed immediately, with only baseline material visible by TLC. The desired product **237** was not observed in the crude isolate by NMR or mass analysis. (Scheme 59)

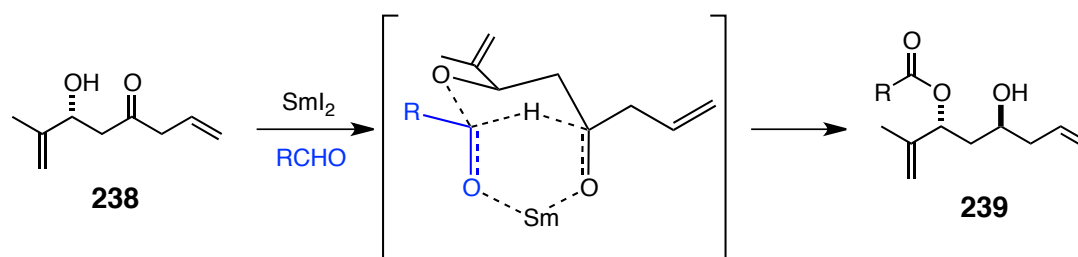
**Scheme 59.** Attempted synthesis of differentially-protected *anti*-1,3-diol **237**.

a)  $\text{TiCl}_4$  (0.5 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C} \rightarrow -78^\circ\text{C}$ , then allylSiMe<sub>3</sub> (1 equiv), 5 min.

At this stage we realised we had overlooked a potentially more convenient and diastereoselective route to **231** involving an Evans-Tishchenko reaction of allylketone **238**. This methodology generally delivers differentially protected *anti*-1,3-diols in high yield and excellent diastereoselectivities (often  $>99:1$  dr).<sup>26</sup> It is proposed that this reaction proceeds by coordination of the aldehyde and ketone to the samarium catalyst, followed by hemiacetal formation and donation of aldehydic hydride to reduce the ketone. The highly-ordered transition state contributes to the high diastereoselectivity of the reaction and the favoured product is that of the

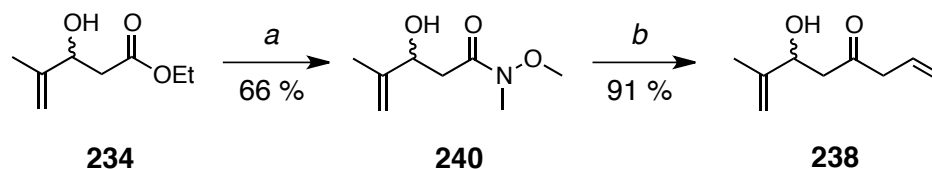
intermediate in which all alkyl/aryl substituents are equatorial (Scheme 60).<sup>26</sup>

**Scheme 60.** Potential Evans-Tishchenko reaction of **238**.



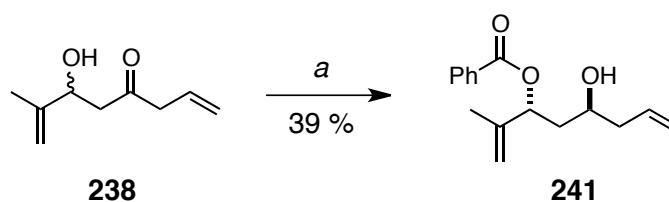
For the synthesis of allylketone **238**,  $\beta$ -hydroxyester **234** was converted to the corresponding Weinreb amide **240** using isopropylmagnesium chloride and *N,O*-dimethylhydroxylamine hydrochloride.<sup>27</sup> Subsequent treatment with allylmagnesium chloride gave crude **238** in excellent yield (Scheme 61). **238** was not further purified as this led to significant isomerisation to its  $\alpha,\beta$ -unsaturated analogue. This degradation was also observed if crude **238** was stored for more than 2 h in the freezer.

**Scheme 61.** Synthesis of allylic ketone **238**.



a) MeONHMe.HCl (3 equiv), iPrMgCl (5.95 equiv), THF,  $-30\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$ , 3 h; b) allylMgCl (2 equiv),  $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$ , 2 h.

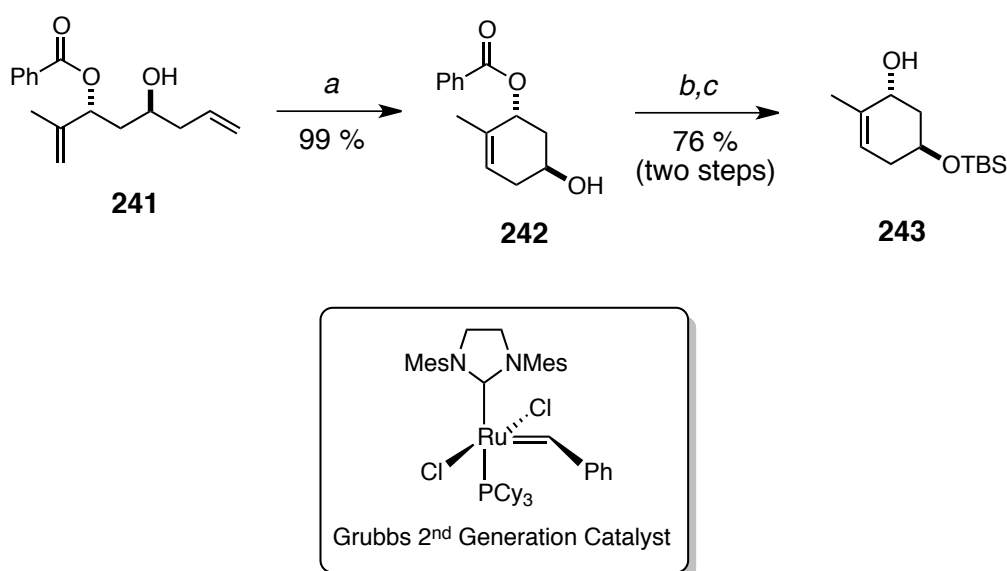
The Evans-Tishchenko reaction was initially performed using 15 mol%  $\text{SmI}_2$ .<sup>26</sup> After stirring overnight, completion was observed, but the desired product **241** was recovered in only 18% yield, albeit with excellent diastereoselectivity (only one diastereomer was present in the NMR spectrum). Doubling the catalyst loading to 30 mol% gave an improved 39 % yield after only 1 h with no drop in selectivity (Scheme 62).

**Scheme 62.** Evans-Tishchenko reaction of allylketone **282**.

a)  $\text{SmI}_2$  (0.3 equiv),  $\text{PhCHO}$  (4 equiv), THF,  $-10^\circ\text{C}$ , 1 h.

Further investigations, in which concentration, temperature, benzaldehyde equivalents and catalyst loading were altered gave no further improvement. In all cases, the major by-product was observed to be a viscous gum that we were unable to identify by conventional analysis, although we suspect it to have been a result of polymerisation of the starting material.

Attempted ring-closing metathesis of **241** using Grubbs 2<sup>nd</sup> generation catalyst<sup>28</sup> showed no conversion at room temperature, but when heated to  $40^\circ\text{C}$ , the reaction proceeded quickly to give **242** in almost quantitative yield. Subsequent TBS protection of the free alcohol, followed by ester cleavage under basic conditions<sup>29</sup> gave the desired allylic alcohol **243** in good yield (Scheme 63).

**Scheme 63.** Synthesis of **243** from *anti*-1,3-diol **241**.

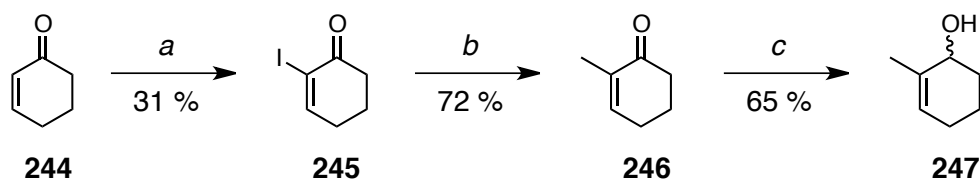
a) Grubbs 2<sup>nd</sup> generation catalyst (0.05 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $40^\circ\text{C}$ , 2 h; b) TBSCl (1.2 equiv), imidazole (2.5 equiv), DMF, rt, 3 h, 82 %; c) KOH (1.5 equiv), MeOH, rt, o/n, 93 %.

### 2.1.3 Synthesis of a generic analogue of allylic alcohol **243**

As carboxylic acid **220** and allylic alcohol **243** both required multi-step syntheses, the decision was taken to conserve material by using a simple structural analogue of **243** in the initial investigation and optimisation of the coupling with acid **220** and the subsequent dCr reaction.

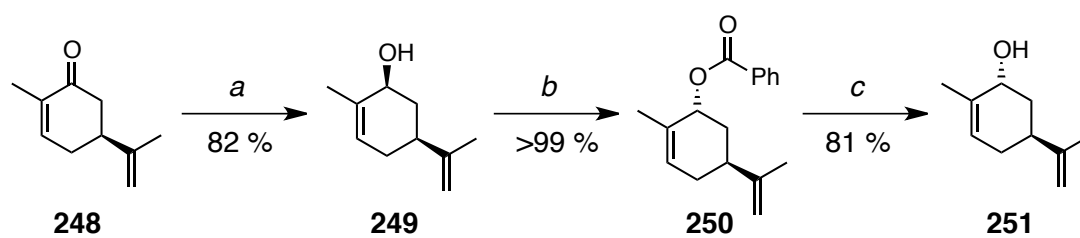
The simplest potential analogue, 2-methyl-2-cyclohexenol (**247**) was chosen as it had previously been prepared in the Craig group.<sup>30</sup> Thus, treatment of commercially available cyclohexenone **244** with I<sub>2</sub> in Et<sub>2</sub>O/pyridine gave 2-iodo-2-cyclohexenone **245** in 31% yield after recrystallisation. Methylation using Fe(acac)<sub>3</sub> and methylmagnesium chloride gave 2-methyl-2-cyclohexenone **246** in 72 % yield. Asymmetric reduction using (*S*)-methyl CBS (Corey-Bashi-Shibata) reagent<sup>31</sup> had previously furnished alcohol (*S*)-**247** in up to 84 % ee,<sup>30</sup> but we observed no conversion, probably due to poor quality of the CBS reagent. As **246** was beginning to decompose in storage we converted it to the more stable *rac*-**247** in 65 % yield by standard NaBH<sub>4</sub> reduction. (Scheme 64)

**Scheme 64.** Synthesis of *rac*-**247**.



a) I<sub>2</sub> (2.1 equiv), Et<sub>2</sub>O/pyridine, 0 °C→rt, 2 h; b) Fe(acac)<sub>3</sub> (5 mol%), MeMgCl (1.1 equiv), NMP/THF, 15 °C, 1 h; c) NaBH<sub>4</sub> (1.1 equiv), MeOH, 0 °C→rt, o/n.

As we had originally intended to use an optically pure allylic alcohol in our synthetic studies, in an effort to best mimic our real system, we decided to prepare another analogue. In accordance with the literature, Luche reduction<sup>32</sup> of (*S*)-carvone (**248**) gave (+)-carveol **249** with 95:5 dr (determined by <sup>1</sup>H-NMR spectroscopy). Inversion of the hydroxyl stereocentre under Mitsunobu conditions<sup>33</sup> and subsequent ester methanolysis delivered the desired analogue, (+)-carveol (**251**), in good yield and 9:1 dr (determined by <sup>1</sup>H-NMR spectroscopy).<sup>34</sup> (Scheme 65)

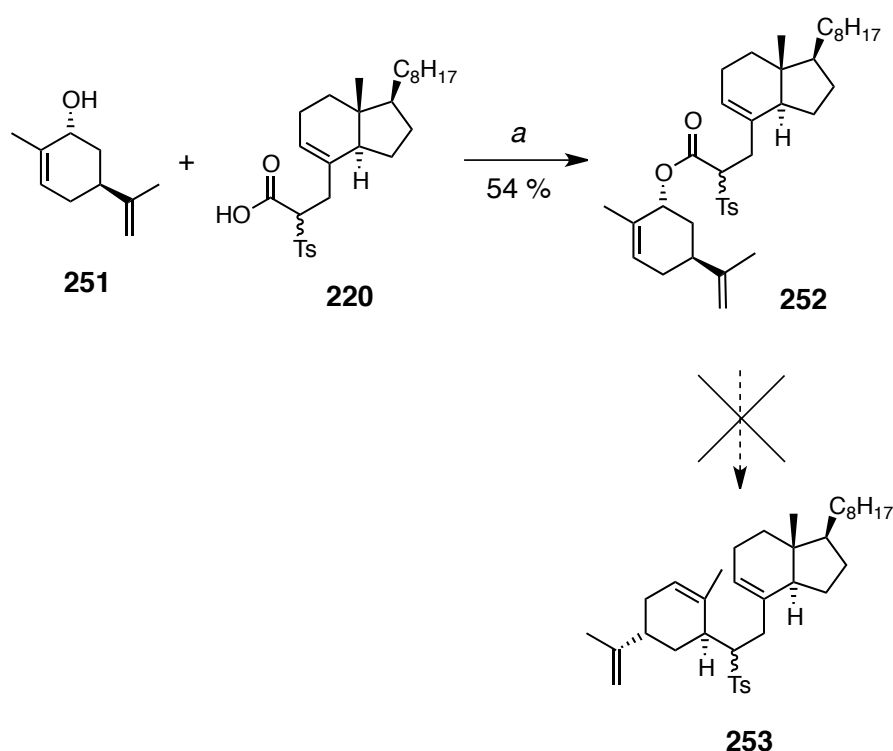
**Scheme 65.** Synthesis of (4*S*,6*R*)-(+)-carveol (**251**).

a)  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (1 equiv),  $\text{NaBH}_4$  (1 equiv), MeOH, rt, 10 min; b) DIAD (3 equiv),  $\text{PPh}_3$  (3 equiv),  $\text{PhCOOH}$  (3 equiv), THF,  $0\text{ }^\circ\text{C} \rightarrow \text{rt}$ , 20 h; c) 2M KOH in MeOH (1.5 equiv), rt, 14 h.

### 2.1.4 Synthesis and attempted dCr of ester **252**

Coupling of the allylic alcohol analogue **251** and carboxylic acid **220** with DIC/DMAP proceeded very slowly, even at high concentration ( $\sim 2$  M in  $\text{CH}_2\text{Cl}_2$ ). A first attempt, gave ester **252** in just 23% yield with 76% recovery of starting material after 24 h. Increasing the reaction time to 96 h gave a 54% yield of **252** (33% recovery of starting material). Despite the poor conversion observed for this step, with material in hand we attempted the key dCr reaction. Under standard thermal conditions using BSA (3 equiv) and KOAc (0.2 equiv) in PhMe at reflux starting material was unchanged. Investigation was continued using microwave irradiation, making use of a pulse sequence previously found to be optimal within our group.<sup>35</sup> Thus, **252** was treated with KOAc (0.2 equiv) neat in BSA (6 equiv). After heating at 180 °C in a 3×1 min cycle (cooling between each heat cycle) TLC showed significant starting material consumption, but numerous products. Silica gel chromatography of the crude reaction mixture yielded an intractable mixture, none of which could be identified as the desired product **253** by NMR or MS analysis. Subsequent attempts in the microwave at lower temperature yielded no conversion whatsoever (Scheme 66).

**Scheme 66.** Synthesis and attempted dCr of ester **252**.

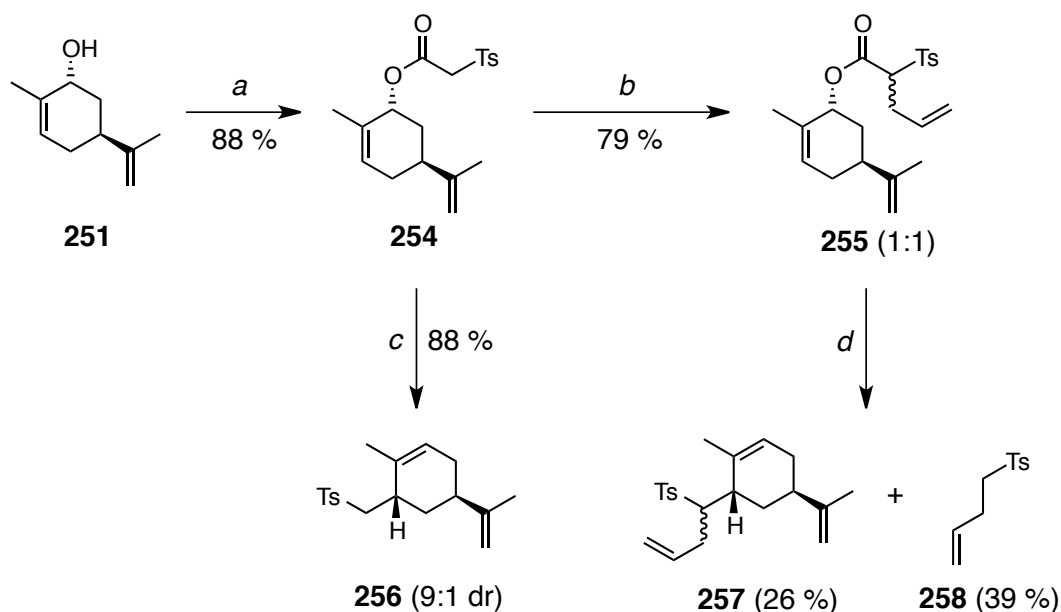


a) DIC (1.1 equiv), DMAP (0.1 equiv),  $\text{CH}_2\text{Cl}_2$ , rt, 4 days.

### 2.1.5 Testing the reactivity of model dCr substrates

In order to assess the reactivity of the carveyl moiety as the allylic portion in the dCr reaction, simple tosyl acetates **254** and **255** were prepared and subjected to dCr conditions (Scheme 67). Thus, **251** was coupled with 2-tosylacetic acid to give ester **254** in good yield. Next, **254** was treated with DBU and *in-situ* generated allyl iodide to give the desired mono-allyl product **255** in 79 % yield, alongside 15 % of the unwanted bis-allylation product.<sup>36</sup> Ester **254** was heated at 180 °C for 3×1 min under microwave irradiation to give homoallylic sulfone **256** in 88 % yield. Heating at lower temperatures significantly slowed conversion, though no other products were observed. In contrast, when **255** was subjected to the same reaction conditions only 26 % of the desired dCr product **257** was isolated, with allyl *p*-tolyl sulfone **258** the major product in 39 % yield. Again, reducing the reaction temperature resulted in reduced conversion, but with little change in the product distribution.

**Scheme 67.** dCr reactions of tosylacetic esters **254** and **255**.



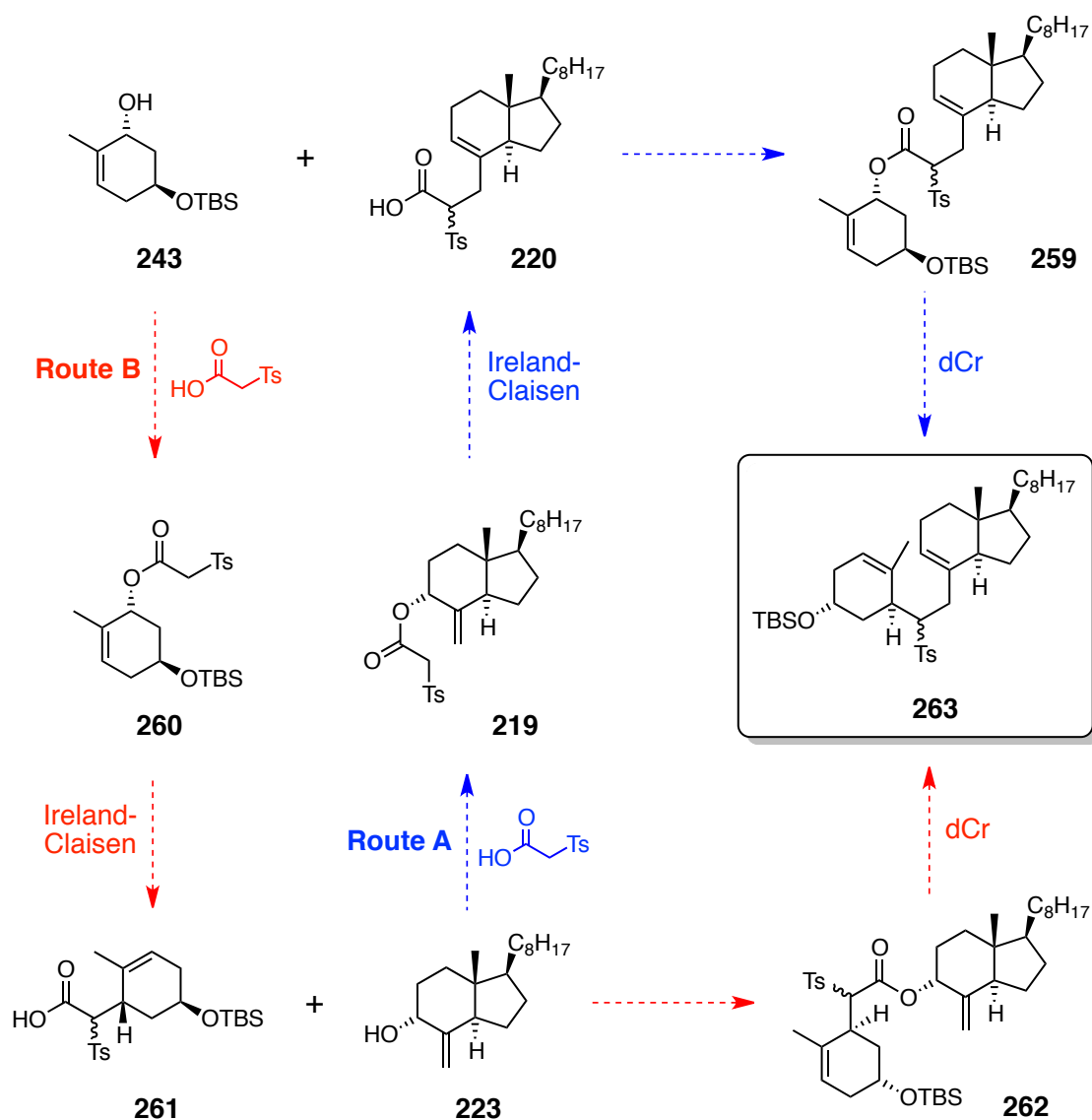
a) 2-tosylacetic acid (1 equiv), DIC (1.1 equiv), DMAP (0.1 equiv), rt, 2 h; b) allyl bromide (1 equiv), *n*-Bu<sub>4</sub>Ni (1 equiv), DBU (2 equiv), DMF, rt, 2 h; c) KOAc (0.1 equiv) BSA (5 equiv), microwave (3×1 min, 180 °C); d) KOAc (0.2 equiv), BSA (5 equiv), microwave (3 x 1 min, 180 °C).

Clearly, the poor recovery of the desired products when model substrates were subjected to dCr conditions did not bode well for our original synthetic strategy. However, there was an alternative route available to 1,6-heptadiene **253**, simply

requiring the sequence of the two Claisen reactions currently in the synthesis to be switched.

In the original route (Route A, Scheme 68), carboxylic acid **220** is formed by an Ireland-Claisen reaction, with the reacting allylic portion in **219** containing the exocyclic methylene group of the C,D-ring system. After coupling **220** with allylic alcohol **243** a dCr reaction of the resulting ester **259** would furnish diene **263**. An alternative route (Route B) would see Ireland-Claisen reaction of easily accessible ester **260** deliver carboxylic acid **261**, which could then be coupled with allylic alcohol **223** to give a dCr substrate **262** in which the reacting allylic portion is now the exocyclic methylene.

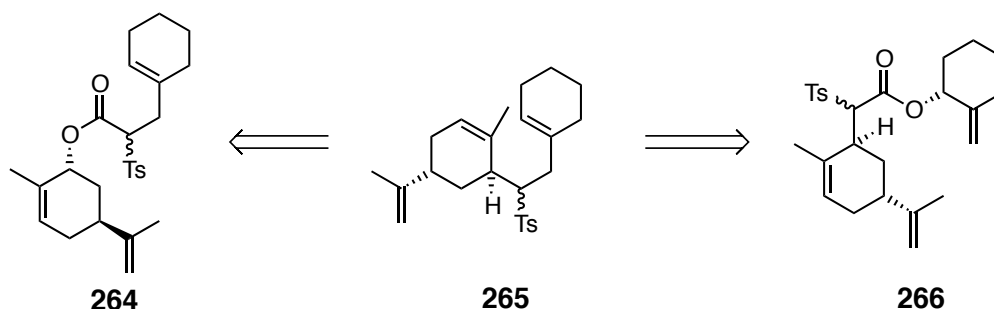
**Scheme 68.** Original and alternative routes to key 1,6-heptadiene **263**.



### 2.1.6 Feasibility study of alternative dCr on model substrates

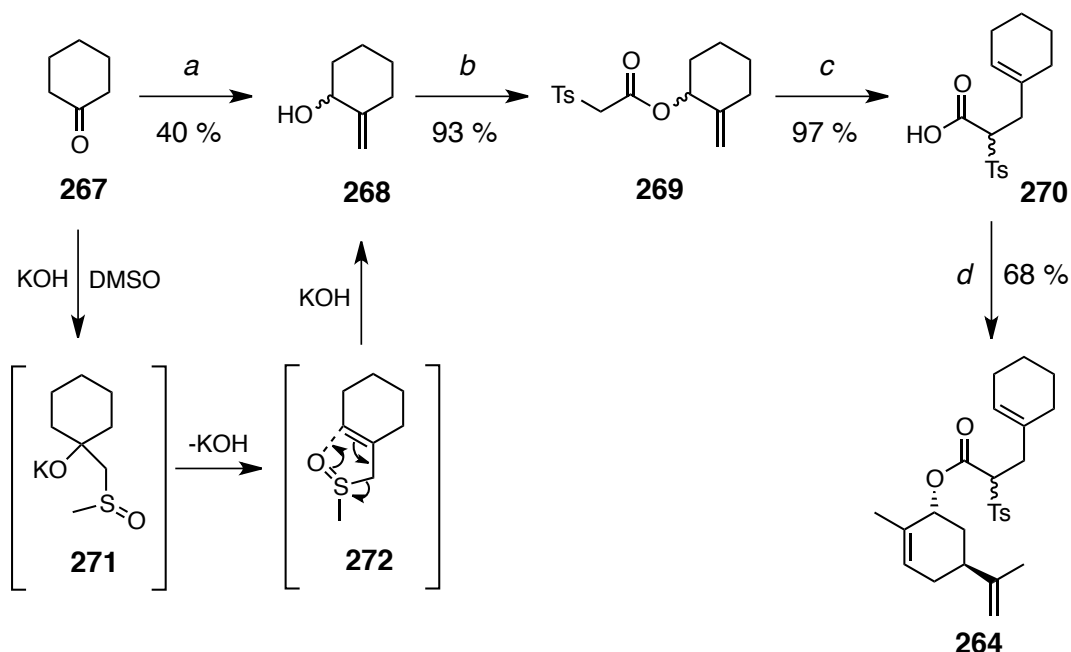
The most efficient strategy to assess whether this alternative approach would be facile was to investigate model substrates for both routes and compare them directly. Substrates **264** and **266** were selected for their similarity to the desired dCr substrates and relative ease of synthesis (Scheme 69).

**Scheme 69.** Model investigation of alternative routes to dCr product **265**.



Substrate **264**, representative of Route A (Scheme 68), was prepared in four steps from cyclohexanone. In accordance with the literature, one-step transformation of cyclohexanone to allylic alcohol **268** in modest yield was achieved by heating with superbasic KOH in DMSO (Scheme 70).<sup>37</sup> This reaction is believed to occur *via* dimsyl anion attack on the ketone, followed by elimination to give allyl sulfoxide **272**, then [2,3]-sigmatropic rearrangement and subsequent hydrolysis to give allylic alcohol **268**. Coupling with 2-tosylacetic acid, achieved under conditions described previously, gave ester **269**, which underwent Ireland-Claisen rearrangement to carboxylic acid **270** in 97 % yield under conditions identical to those used previously (BSA, Et<sub>3</sub>N, CH<sub>3</sub>CN, 60 °C). Another DIC/DMAP coupling, with allylic alcohol **251**, furnished the desired model dCr substrate **264** in good yield.

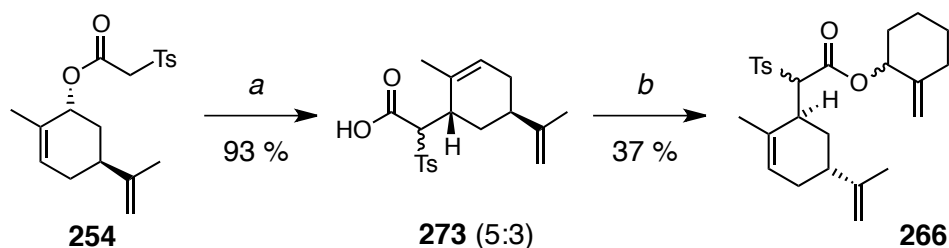
**Scheme 70.** Preparation of model dCr substrate **264**, including the proposed mechanism for synthesis of **268**.



a) KOH (3 equiv), DMSO, 110 °C, 90 min; b) 2-tosylacetic acid (1 equiv), DMAP (0.1 equiv), DIC (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; c) Et<sub>3</sub>N (1.2 equiv), BSA (3 equiv), CH<sub>3</sub>CN, 60 °C, 30 min; d) **251** (1 equiv), DMAP (0.1 equiv), DIC (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 1 h.

Substrate **266** (Scheme 71), representative of Route B (Scheme 68), was prepared in a further two steps. Ireland-Claisen rearrangement of previously synthesised ester **254** was achieved in excellent yield, but required slightly more forcing conditions (reflux in CH<sub>3</sub>CN, compared with 60 °C) than the Ireland-Claisen in Route A. DIC/DMAP coupling of the resultant carboxylic acid **273** with allylic alcohol **268** furnished the second desired model dCr substrate **266** in modest yield.

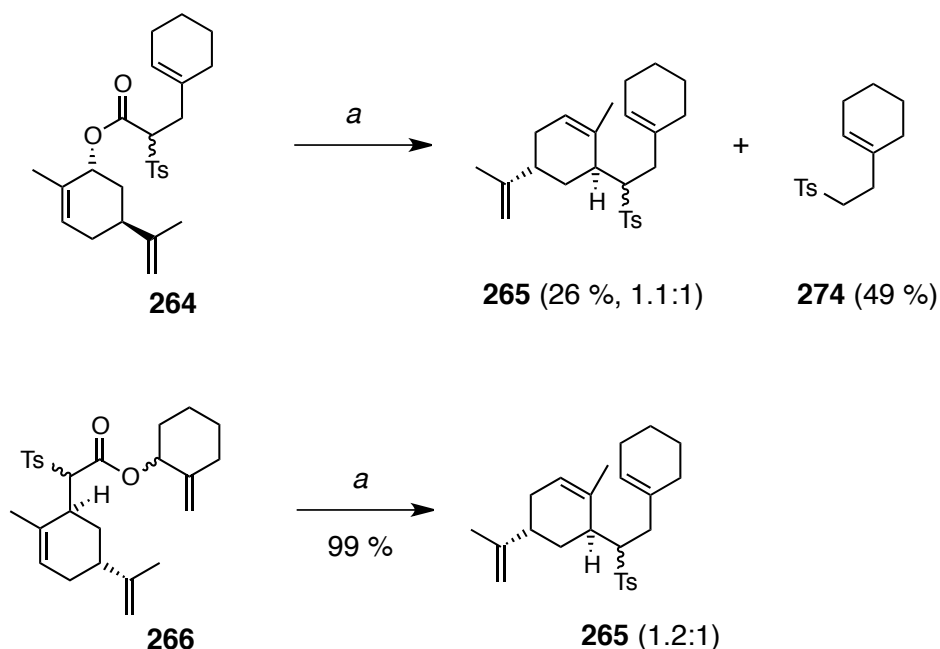
**Scheme 71.** Preparation of model alternative dCr substrate **266**.



a) Et<sub>3</sub>N (1.2 equiv), BSA (3 equiv), CH<sub>3</sub>CN, reflux, 2 h; b) **268** (1.0 equiv), DMAP (0.1 equiv), DIC (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 18 h.

With both ester substrates in hand, dCr reactions were attempted as previously described, using catalytic KOAc and excess BSA in the absence of solvent under microwave irradiation at 180 °C for 3 x 1 min. After the reaction period ester **264** was consumed to furnish the desired product **265** in only 26 % yield, with the major product the homoallylic sulfone **274** in 49 % yield (Scheme 72). As found previously, reducing the reaction temperature only served to reduce conversion and had little effect on the relative distribution of products. In contrast, and to our delight, when substrate **266** was subjected to the aforementioned conditions it was fully consumed, giving desired **265** as the sole product in essentially quantitative yield.

**Scheme 72.** dCr reactions of substrates **264** and **266**.

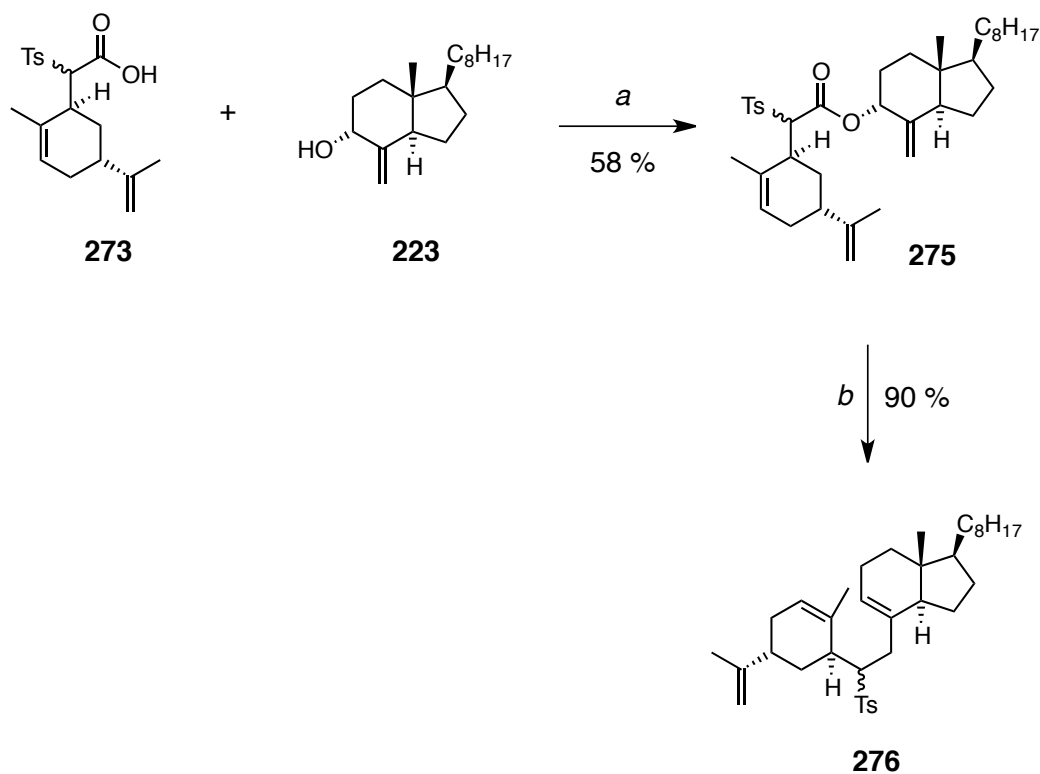


a) KOAc (0.2 equiv), BSA (5 equiv), microwave (3×1 min, 180 °C).

In summary, substrate **266** possessing the allylic portion containing the exocyclic methylene was demonstrably more reactive in the Claisen rearrangement than that containing the cyclohexenyl moiety, under both Ireland and decarboxylative conditions. Given that rearrangement of both moieties could be achieved in excellent yield under Ireland-Claisen conditions, we had good reason to believe that the new alternative pathway to substrate **263** was worth pursuing. To confirm this, previously synthesised allylic alcohol **223** was coupled with carveol-derived carboxylic acid **273** in modest yield to give ester **275**, an even more representative model dCr substrate,

that subsequently underwent dCr reaction in the microwave to afford the desired dCr product **276** in 90 % yield (Scheme 73).

**Scheme 73.** dCr of model substrate **275**.

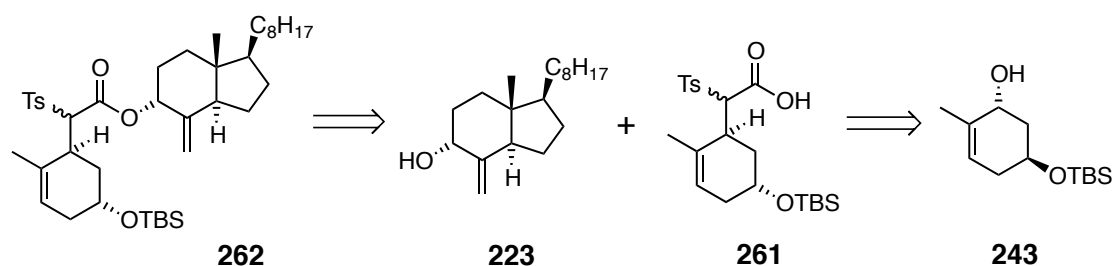


a) DMAP (0.1 equiv), DIC (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 6 h; b) KOAc (0.2 equiv), BSA (5 equiv), microwave (3×1 min, 180 °C).

### 2.1.7 Asymmetric synthesis of carboxylic acid **261**

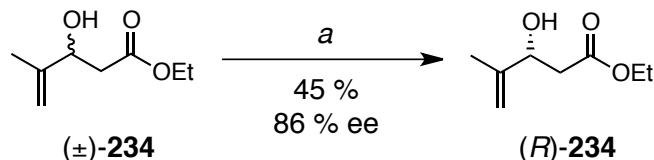
In order to apply this alternative dCr to our actual system **262**, the asymmetric synthesis of allylic alcohol **243** had to be completed before coupling with 2-tosylacetic acid and Ireland-Claisen rearrangement would furnish desired carboxylic acid **261**. (Scheme 74)

**Scheme 74.** Retrosynthetic approach to dCr substrate **262**.



As previously discussed in Section 2.1.2, our already-developed synthesis of racemic **243** could be rendered asymmetric by the known kinetic resolution of  $\beta$ -hydroxyester **234** using a Sharpless asymmetric epoxidation.<sup>23</sup> Following the literature procedure, **234** was treated with sub-stoichiometric  $\text{Ti}(\text{O}i\text{-Pr})_4$  and L-(+)-DIPT, and stoichiometric  $t\text{-BuOOH}$ , in the presence of 4 Å molecular sieves. Tracking conversion quantitatively by GC or LCMS was found to be somewhat unreliable, hence reaction progress was followed by workup and purification of small aliquots at 8-15 h intervals, assessing the *ee* by addition of chiral lanthanide shift reagent tris[3-[(trifluoromethyl)hydroxymethylene]-(+)-camphorato]europium(III) to the  $^1\text{H}$ -NMR sample. The reaction was stopped once the *ee* increase had levelled off. As a result (*R*)-**234** was afforded in 45 % yield and 86 % *ee* after 96 h, a moderate result compared with the literature value of 49 %, 98 % *ee* after 24 h.<sup>23</sup> Despite efforts to improve this result, these reaction conditions remained the most effective, with difficulty in quantitative monitoring of reaction progression perhaps limiting our ability to improve the *ee* further. (Scheme 75)

**Scheme 75.** Kinetic resolution of  $\beta$ -hydroxyester **234**.

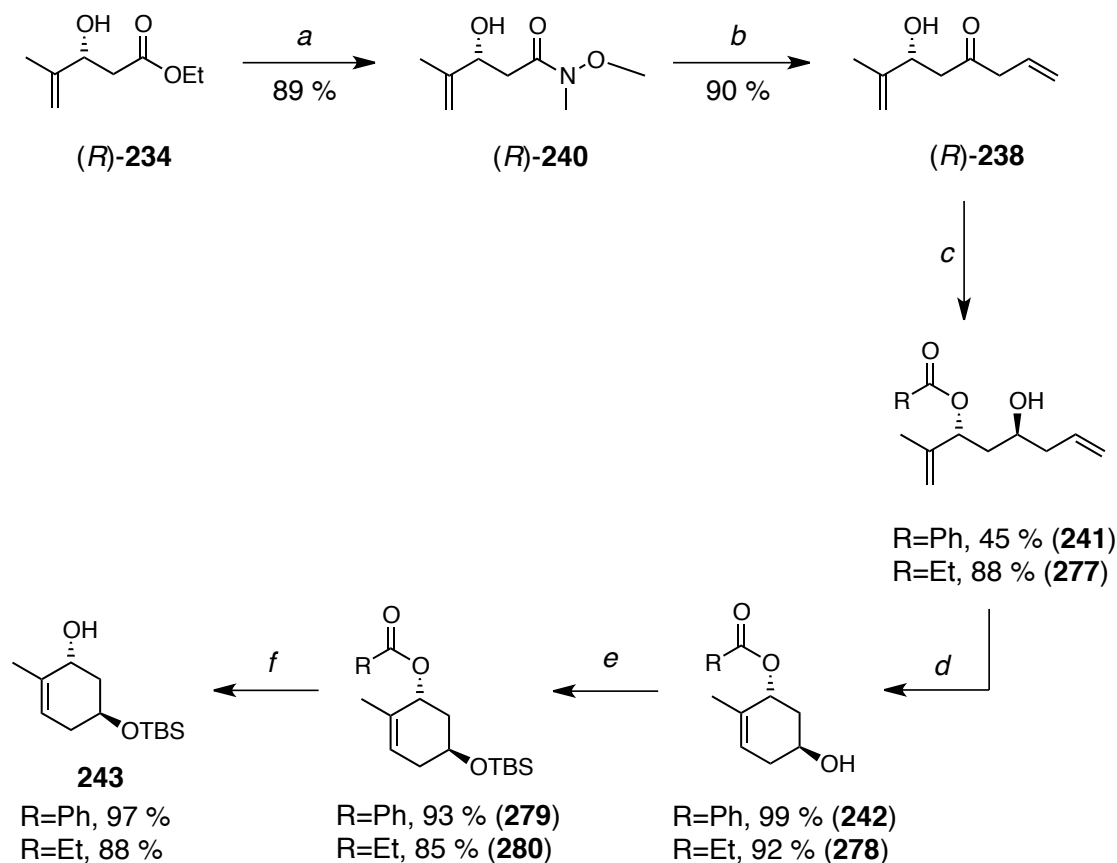


a) L-(+)-DIPT (0.45 equiv),  $\text{Ti}(\text{O}i\text{-Pr})_4$  (0.4 equiv),  $t\text{-BuOOH}$  (1 equiv), 4 Å MS,  $\text{CH}_2\text{Cl}_2$ ,  $-25^\circ\text{C}$ , 96 h.

The synthetic sequence to allylic alcohol **243** employed the same chemistry as the racemic synthesis (see Section 2.1.2), but entailed some optimisation to improve yields. Conditions for generation of Weinreb amide **240** were changed to the more commonly-used method of treating of *N,O*-dimethylhydroxylamine hydrochloride with  $\text{AlMe}_3$ , rather than isopropylmagnesium chloride (Scheme 76). This resulted in an improved yield of 89 % from 66 %. Inspired by the Evans-Tishchenko reaction of a structure very similar to **238** (an ethyl moiety in place of our isopropenyl moiety) published in the interim,<sup>38</sup> we assessed the use of propionaldehyde instead of benzaldehyde in our reaction. To our delight the alternative aldehyde improved the yield from 45 % to 88 %, affording propionate ester **277**. When **277** was subjected to ring-closing metathesis, it was found that a reduced catalyst loading of 3 mol%,

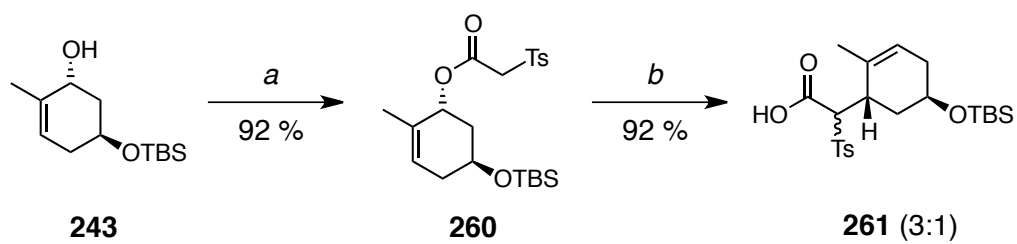
added in three portions at hourly intervals, gave only a slight reduction in yield. All other reaction conditions in the sequence remained unchanged from those used for the racemate, with similar yields.

**Scheme 76.** Synthesis of cyclohexenol (*R*)-**243**.



a) MeONHMe.HCl (2.2 equiv), AlMe<sub>3</sub> (2.2 equiv), THF, rt, 45 min; b) allylMgCl (2 equiv), THF, 0 °C, 2 h; c) RCHO (4 equiv), SmI<sub>2</sub> (0.1 equiv), THF, -10 °C, 1 h; d) R=Ph: Grubbs II (0.05 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 90 min; R=Et: Grubbs II (0.03 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 3 h; e) TBSCl (2 equiv), imidazole (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 5-15 h; f) KOH (3 equiv), MeOH, 0 °C→rt, 12-16 h.

Coupling of **243** with 2-tosylacetic acid using DIC and DMAP gave the desired ester **260** in 92 % yield (Scheme 77). When **260** was subjected to the Ireland-Claisen conditions used previously for the corresponding model substrate **273** (see Scheme 71), it underwent full conversion in 3 h to furnish desired carboxylic acid **261** in 92 % yield.

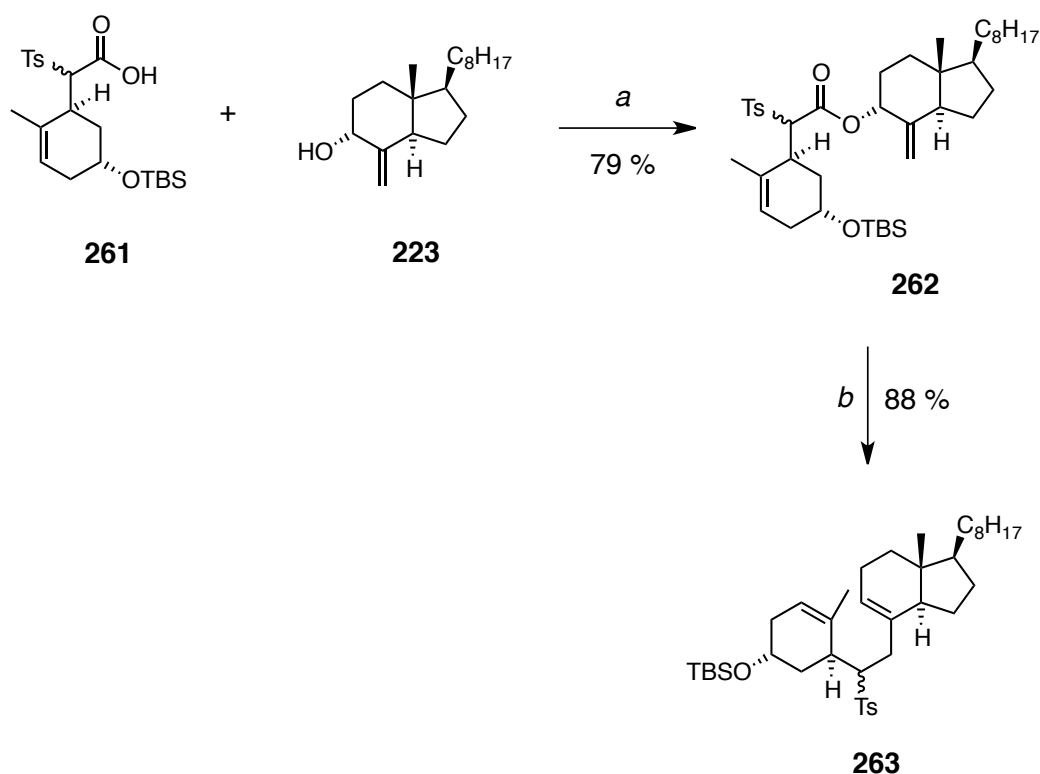
**Scheme 77.** Synthesis of carboxylic acid **261**.

a) 2-tosylacetic acid (1 equiv), DMAP (0.1 equiv), DIC (1.1 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C} \rightarrow \text{rt}$ , 2 h; b)  $\text{Et}_3\text{N}$  (1.2 equiv), BSA (3 equiv),  $\text{CH}_3\text{CN}$ , reflux, 3 h.

### 2.1.8 Synthesis and dCr of ester **262**

Carboxylic acid **261** and allylic alcohol **223** coupled more readily under DIC/DMAP conditions than some of the model substrates, to give dCr substrate **262** in 79 % yield after 6 h (Scheme 78). When **262** was treated with KOAc and BSA in the microwave, it underwent complete conversion to the desired product **263**, isolated in 88 % yield after chromatography as a mixture of C-Ts epimers. Pleasingly, a second round of careful chromatography allowed the epimers to be separated, delivering the less polar major epimer **263a** in 56 % yield, and more polar minor epimer **263b** in 30 % yield. The stereochemistry of the C-Ts centres was not determined.

**Scheme 78.** Synthesis and dCr reaction of ester **262**.

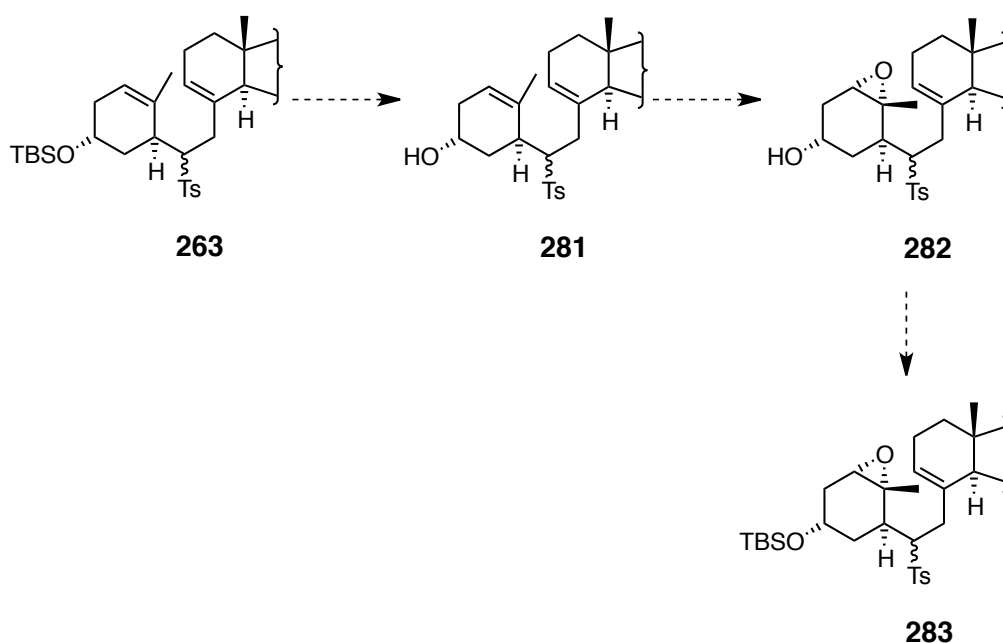


a) DMAP (0.1 equiv), DIC (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 6 h; b) KOAc (0.1 equiv), BSA (3.5 equiv), microwave (5×1 min, 180 °C).

### 2.1.9 Synthesis of epoxide **283**

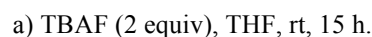
With our desired dCr product in hand we continued with the next stages of our synthetic strategy, namely the preparation of epoxide **283**, the substrate for our key acid-mediated cyclisation step. Our intention was to prepare **283** by a facially-selective, hydroxy-directed epoxidation of homoallylic alcohol **281**. (Scheme 79)

**Scheme 79.** Proposed synthesis of epoxide **283**.

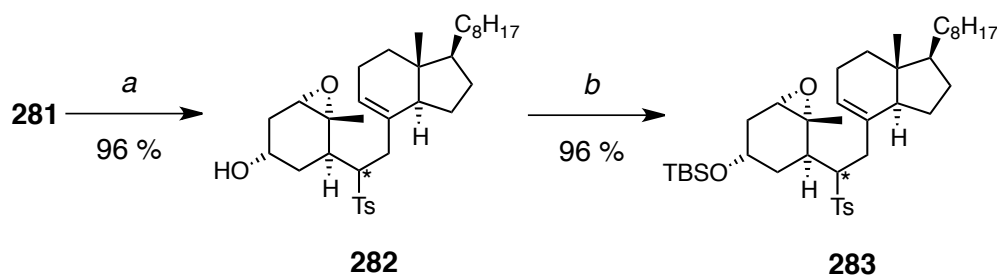


In order to simplify the characterisation of compounds made in the continuing synthesis, we elected to take only major epimer **263a** through subsequent investigations.

Desilylation of **263a** with excess TBAF trihydrate was slow, taking 3 days to go to completion, but nevertheless delivered homoallylic alcohol **281** in 86 % yield. We found that using anhydrous TBAF improved both the reaction time and yield of **281** to 15 h and 95 % respectively. (Scheme 80)



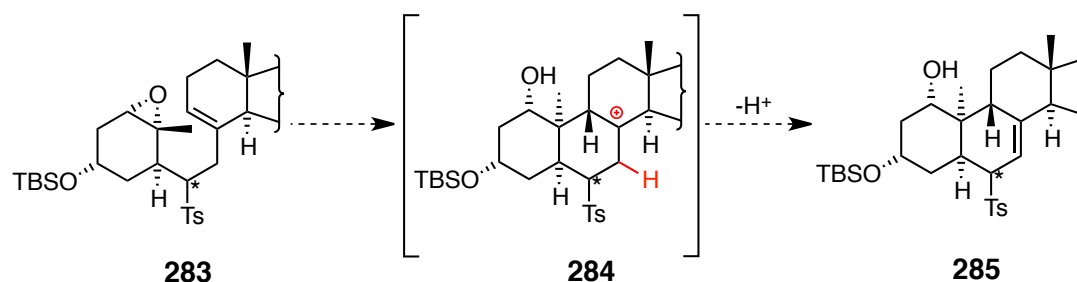
With **282** in hand, reprotection of the free alcohol with TBS was achieved under standard conditions to give our cyclisation substrate **283** in excellent yield. (Scheme 81)

**Scheme 81.** Synthesis of key epoxide substrate **283**.

a) VO(acac)<sub>2</sub> (0.03 equiv), *t*-BuOOH (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -10 °C, 4 h; b) TBSCl (2 equiv), imidazole (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 18 h.

### 2.1.10 Attempted cyclisation of epoxide **283**

As the second key step of our synthesis we predicted that Lewis acid activation of epoxide **283** would initiate intramolecular attack of the C-8(9) alkene, giving rise to a transient tertiary carbocation **284** that would be spontaneously quenched by elimination of a proton. Our hope was that this elimination would be favoured from the adjacent methylene, as opposed to the two adjacent methynes, to give desired tetracycle **285**. The stereochemistry observed in **285** is predicted as a result of back face of the nucleophilic alkene preferentially attacking into the activated epoxide. This assumption is based on huge degree of steric hindrance that would need to be overcome in order for the top face of the alkene to attack (Scheme 82).

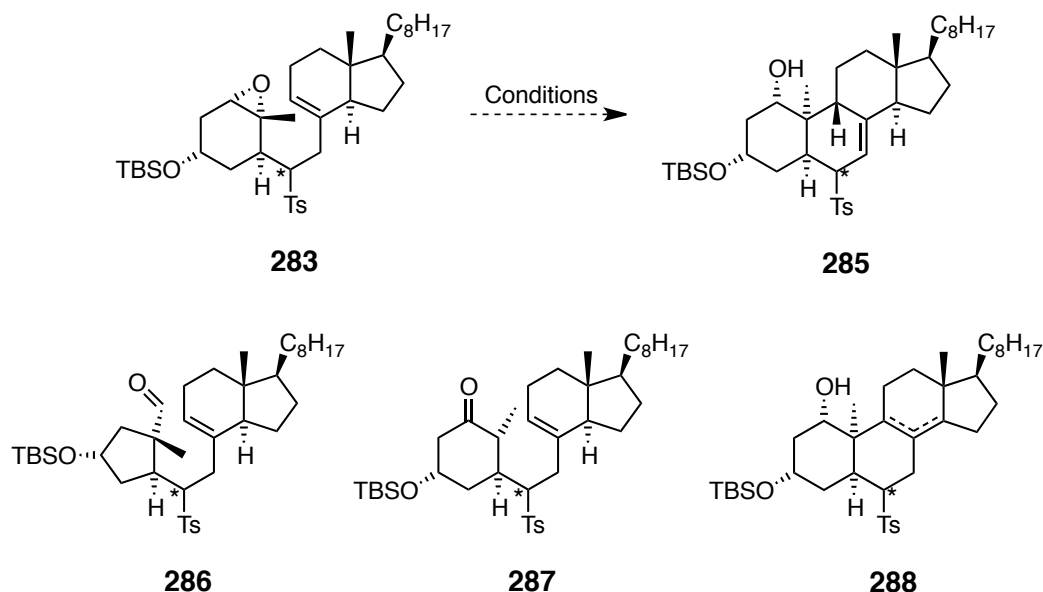
**Scheme 82.** Predicted regiochemistry and stereochemistry of the desired intramolecular cyclisation of **283**.

This reaction was attempted under numerous conditions, summarised in Table 5 below. Strong Lewis acids such as MeAlCl<sub>2</sub><sup>42</sup>, BF<sub>3</sub>·Et<sub>2</sub>O<sup>43</sup> and SnCl<sub>4</sub><sup>44</sup> are commonly employed to activate epoxides to nucleophilic attack by weak nucleophiles such as alkenes. When our substrate was treated with MeAlCl<sub>2</sub> (Table 5, Entry 1), starting material was consumed instantly, but no cyclisation products were observed. The

major product was identified as aldehyde **286**, the product of a 1,2-shift (also known as a Meinwald rearrangement<sup>45</sup>) of the alkyl group attached to the tertiary epoxide carbon, resulting in ring contraction. Treatment with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (Table 5, Entry 2) again resulted in a fast reaction, with some aldehyde **286** isolated, but with new product ketone **287** isolated as the major product. **287** could be rationalised as a result of another Meinwald rearrangement in which hydride had undergone a 1,2-shift. When  $\text{SnCl}_4$  was employed (Table 5, Entry 3), no aldehyde product was isolated, and only a little of the undesired ketone. The major product was identified as cyclised substrate **288** as a single stereoisomer and regioisomer, containing a tetra-substituted alkene as opposed to the to the desired tri-substituted isomer. After extensive NMR studies we were unable to determine conclusively whether the double bond was positioned between the C-8 and C-14 centres or the C-8 and C-9 centres. Using  $\text{TiCl}_4$  gave a similar result to  $\text{SnCl}_4$ , but gave better recovery of the products (Table 5, Entry 4). Yamamoto's hindered dialkylaluminium amides have been effective reagents for the rearrangement of epoxides to allylic alcohols,<sup>46</sup> but it was hoped that we could utilise the bulky basic amide ligand to direct post-cyclisation deprotonation from the methylene centre. As it transpired,  $\text{Me}_2\text{AlN}(i\text{-Pr})_2$ , prepared from LDA and  $\text{Me}_2\text{AlCl}$ , gave a very similar result to  $\text{MeAlCl}_2$ , delivering aldehyde **286** as the sole product (Table 5, Entry 5). With strong Lewis acids giving a large degree of unwanted 1,2-rearrangement, as well as some cyclisation, focus shifted to milder Lewis acids that might promote preferential cyclisation. Metal triflates are effective mild Lewis acids used in a variety of transformations.<sup>47</sup> A variety of triflates were tested in cyclisation of **283** (Table 5, Entries 6-12). The  $\text{M}^{3+}$  triflates were ineffective in favouring cyclisation over alkyl/hydride migration, with only  $\text{Yb}(\text{OTf})_3$  delivering cyclisation product, albeit as a minor product and still as the undesired regioisomer **288** (Table 5, Entry 6).  $\text{Zn}(\text{OTf})_2$  was more effective, delivering almost equal amounts of cyclisation and migration products in good recovery (Table 5, Entry 10). Monovalent triflates  $\text{AgOTf}$  and  $\text{LiOTf}$  were not sufficiently Lewis acidic to activate the epoxide substrate, with no starting material consumed after stirring for a long period. With desired cyclisation product **285** still not observed, our attention turned to utilising Brønsted acids to activate the epoxides instead. Phosphoric acid has been used to achieve similar cyclisations.<sup>48</sup> When employed here (Table 5, Entry 13),  $\text{H}_3\text{PO}_4$  again gave a mixture of the three previously observed products, slightly favouring cyclised **288**. In contrast CSA, a slightly stronger organic acid, gave only

migration products (Table 5, Entry 14). An even stronger organic acid, TFA, gave the best result yet, with cyclisation product **288** delivered in 65 % yield, almost three times more abundant than the combined migration products (Table 5, Entry 15). Finally, the best result was achieved using organic superacid triflic acid, delivering **288** in 68 % yield, and as the sole product (Table 5, Entry 16).

**Table 5.** Reaction conditions investigated for the intramolecular cyclisation of **283** and products **286**, **287**, **288**.

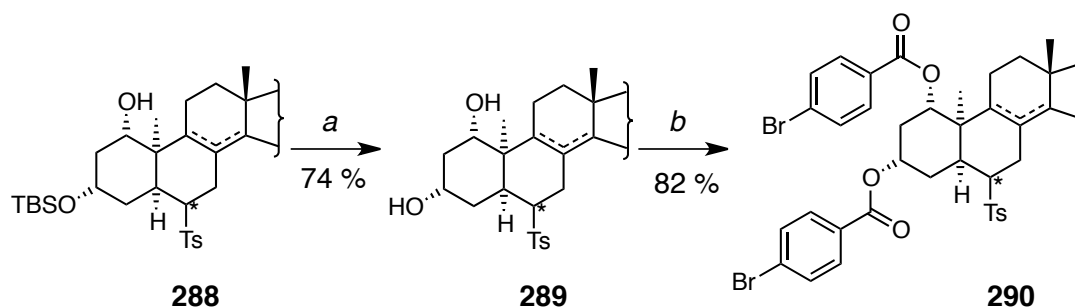


| Entry | Reagent <sup>a</sup>                                         | Conditions                                       | Isolated Products                                   |
|-------|--------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------|
| 1     | MeAlCl <sub>2</sub>                                          | CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 5 min  | 30 % <b>286</b>                                     |
| 2     | BF <sub>3</sub> ·Et <sub>2</sub> O <sup>b</sup>              | CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 5 min  | 35 % <b>286</b> , 50 % <b>287</b>                   |
| 3     | SnCl <sub>4</sub>                                            | CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 5 min  | 18 % <b>287</b> , 34 % <b>288</b>                   |
| 4     | TiCl <sub>4</sub>                                            | CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 1 h    | 32 % <b>287</b> , 51 % <b>288</b>                   |
| 5     | Me <sub>2</sub> AlN( <i>i</i> -Pr) <sub>2</sub> <sup>b</sup> | PhMe, -78 °C→rt, 2 h                             | 59 % <b>286</b>                                     |
| 6     | Yb(OTf) <sub>3</sub>                                         | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 1 h      | 18 % <b>286</b> , 43 % <b>287</b> , 22 % <b>288</b> |
| 7     | Sc(OTf) <sub>3</sub>                                         | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 30 min   | 55 % <b>287</b>                                     |
| 8     | Bi(OTf) <sub>3</sub>                                         | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 10 min   | 12 % <b>286</b> , 49 % <b>287</b>                   |
| 9     | In(OTf) <sub>3</sub>                                         | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 30 min   | 62 % <b>287</b>                                     |
| 10    | Zn(OTf) <sub>2</sub>                                         | CH <sub>2</sub> Cl <sub>2</sub> , rt, 18 h       | 10 % <b>286</b> , 36 % <b>287</b> , 42 % <b>288</b> |
| 11    | AgOTf                                                        | CH <sub>2</sub> Cl <sub>2</sub> , rt, 18 h       | No reaction                                         |
| 12    | LiOTf                                                        | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C→rt, 24 h  | No reaction                                         |
| 13    | H <sub>3</sub> PO <sub>4</sub> <sup>c</sup>                  | CH <sub>2</sub> Cl <sub>2</sub> , rt, 18 h       | 19 % <b>286</b> , 29 % <b>287</b> , 35 % <b>288</b> |
| 14    | (-)-CSA                                                      | CH <sub>2</sub> Cl <sub>2</sub> , -78 °C→rt, 2 h | 22 % <b>286</b> , 9 % <b>287</b>                    |
| 15    | TFA                                                          | CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 2 h    | 17 % <b>286</b> , 6 % <b>287</b> , 65 % <b>288</b>  |
| 16    | TfOH                                                         | CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 2 h    | 68 % <b>288</b>                                     |

a) 1 equivalent unless otherwise stated; b) 2 equivalents; c) in excess as an 85 % aqueous solution.

Derivatives of **288** were synthesised in an attempt to produce compounds more suited to crystallisation, so that the cyclised structure could be unambiguously determined by X-ray crystallography (Scheme 83).

**Scheme 83.** Synthesis of **288** derivatives **289** and **290**.



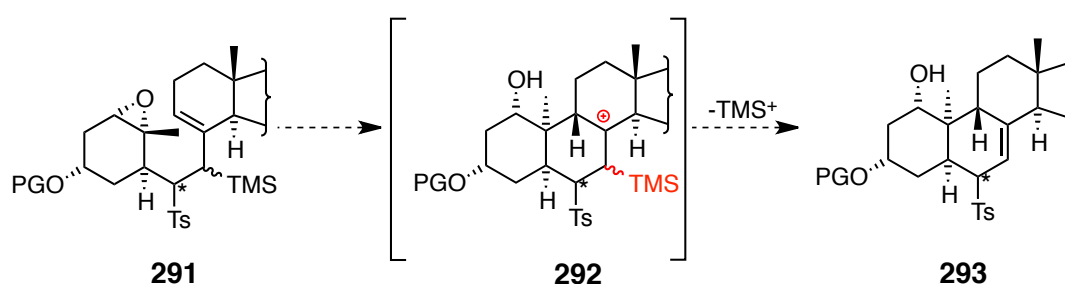
a) TBAF (2 equiv), THF, rt, 18 h; b) *p*-BrPhCOOH (2.0 equiv), DMAP (0.1 equiv), DIC (2.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, o/n.

Unfortunately, after numerous attempts under various conditions, crystals of **289** or **290** could not be grown. Despite this disappointment we believed that the spectroscopic evidence obtained provided robust support for our assigned structure and so we continued under the assumption that our assignment was correct. In addition, we strongly suspected, though could not prove outright, that the isomer of **288** in hand contained the C-C double bond between C8 and C14. Any attempts to isomerise this compound to the desired C8-C7 double bond would have resulted in an unwanted *cis*-fused ring system in the product, so the decision was taken to explore other routes.

### 2.1.11 Investigation of an alternative route to cyclised product 285

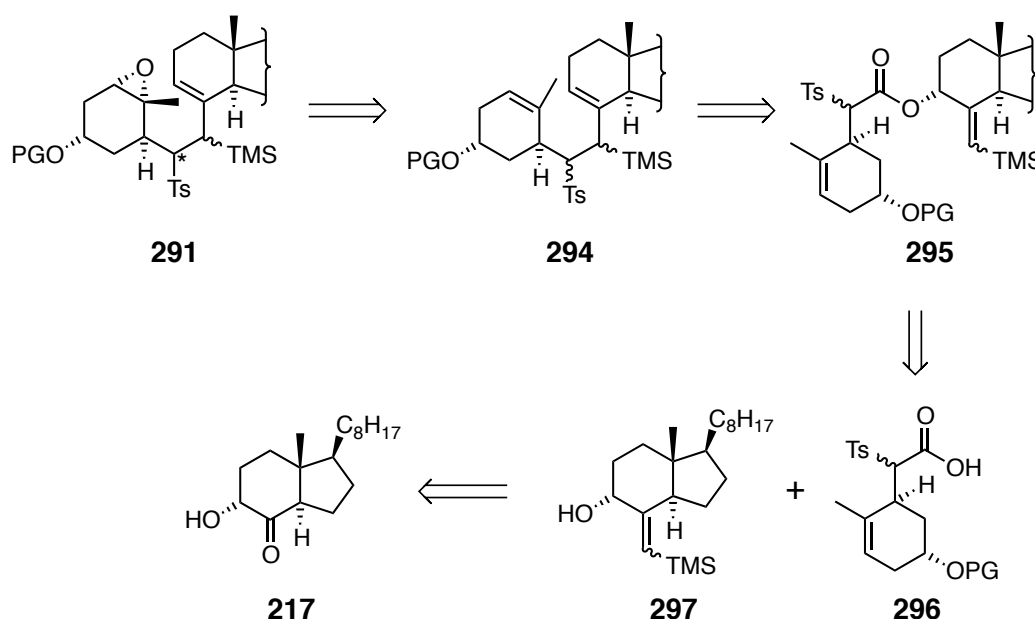
Now that suitable conditions for preferential cyclisation of our epoxide substrate had been identified, measures had to be taken in order to direct the cyclised substrate to undergo proton elimination at the desired carbon centre. Silylated substrate **291** was proposed as a potential cyclisation substrate. It was predicted that if substrate **291** underwent cyclisation, the silyl moiety would not only stabilise the transient  $\beta$ -carbocation **292**, but preferentially act as the leaving group, given the greater capacity of a TMS group to stabilise positive charge. The result would be the desired cyclisation substrate **293** (Scheme 84).

**Scheme 84.** Predicted regiochemistry of the intramolecular cyclisation of **291**.



Cyclisation substrate **292** could be prepared using a same route as before, incorporating exocyclic silylalkene **297**, prepared from protected hydroxyketone **217**, in place of the exocyclic methylene group incorporated previously (Scheme 85).

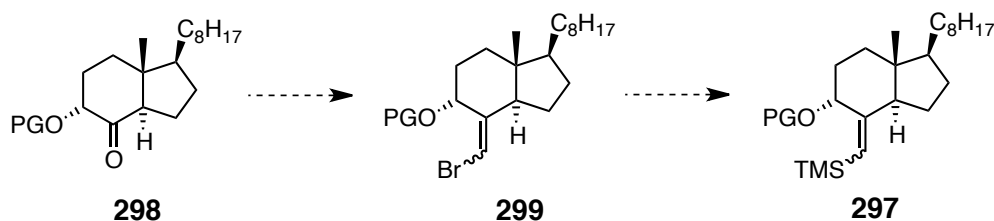
**Scheme 85.** Retrosynthesis of epoxide **291**.



### 2.1.11.1 Synthesis of allylic alcohol **297**

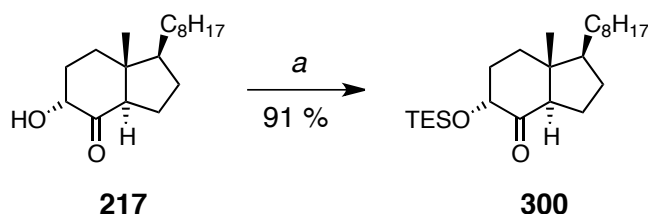
Literature precedent for converting ketones directly to silylalkenes is limited, and so our immediate proposal was to prepare **297** *via* lithiation of the bromoalkene **299**, and subsequent treatment with TMSCl; compound **299** would be prepared from ketone **298** under Wittig conditions. (Scheme 86)

**Scheme 86.** Proposed synthesis of exocyclic silylalkene **297**.



We began by TES-protecting  $\alpha$ -hydroxyketone **217** in excellent yield (Scheme 87). We chose TES-protection as this group could be later removed under mild oxidative conditions<sup>49</sup> that would be more compatible with the silylalkene than the more strongly basic conditions required for TBS-removal.

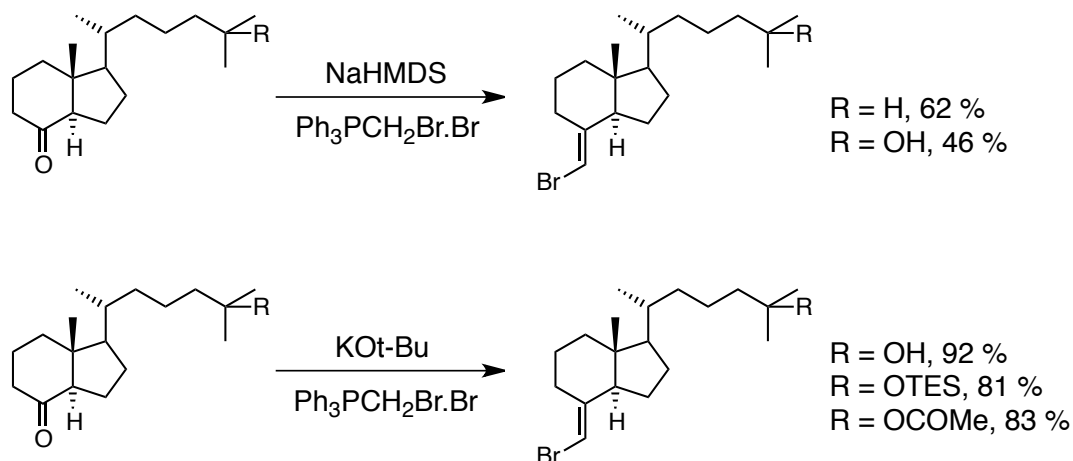
**Scheme 87.** TES-protection of  $\alpha$ -hydroxyketone **217**.



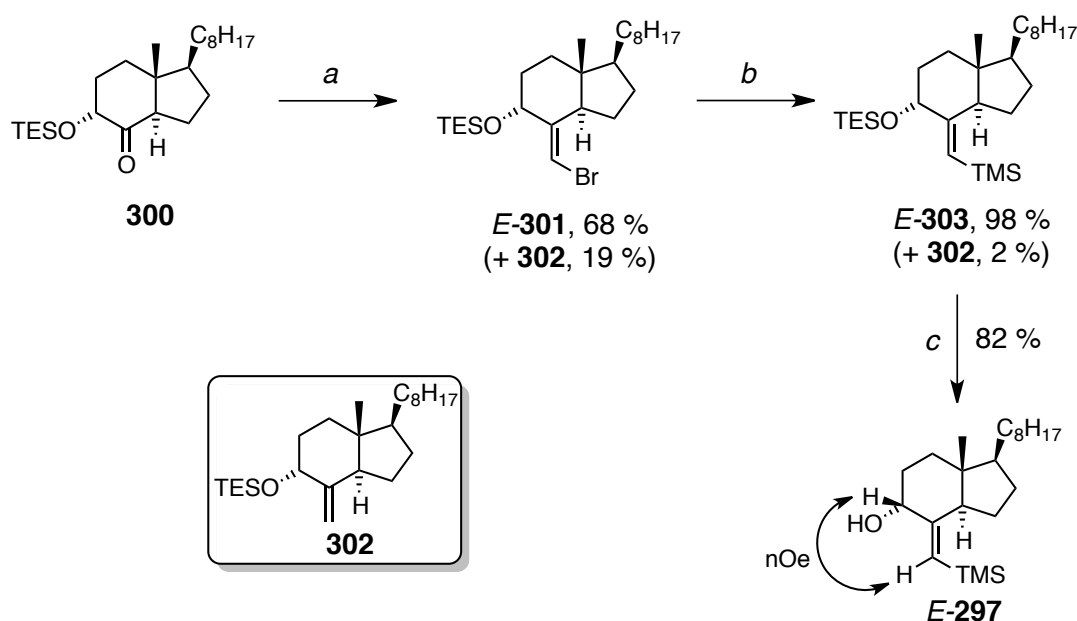
a) TESCl (2 equiv), imidazole (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0°C→rt, 1 h.

The synthesis of bromoalkenes from C-25 analogues of Grundmann's ketone has been reported,<sup>50</sup> giving products as the *E*-isomer only. (Scheme 88)

**Scheme 88.** Bromomethylenation of Grundmann's ketone analogues.<sup>50</sup>

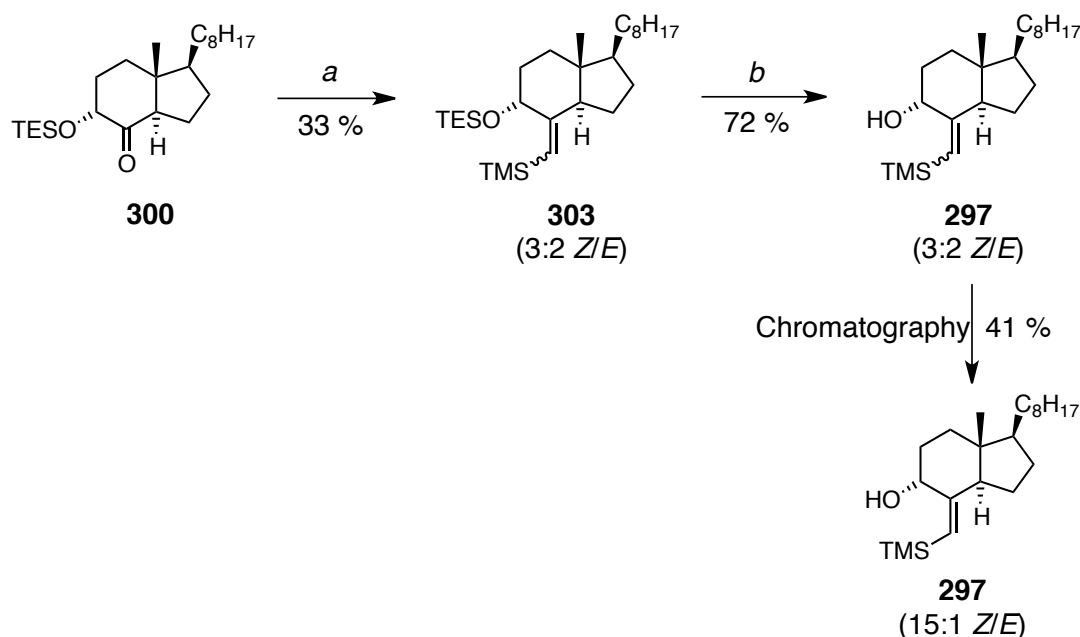


We first tried bromomethylenation with bromomethyltriphenylphosphonium bromide and KOtBu as base, as these conditions had achieved the best results for other ketone analogues.<sup>50b</sup> Unfortunately, under these conditions we observed no conversion at all, perhaps due to greater hindrance of the ketone at the  $\alpha$ -position. When the reaction was repeated using Trost's original conditions<sup>50a</sup> using NaHMDS as base, an inseparable mixture of desired bromoalkene **301** (as only one isomer) and alkene **302** (68 % and 19 % yield respectively, determined by  $^1\text{H}$ -NMR) was obtained. This mixture was then treated with *t*-BuLi, then TMSCl, to furnish the desired silylalkene **303** in 98 % yield, still as an inseparable mixture with alkene **302**, of which a further 2 % yield had been produced during this step. Removal of the TES protecting group using catalytic DDQ in aqueous THF furnished pure silylallylic alcohol **297** after chromatography. This reaction is believed to be a single electron transfer process, going *via* an intermediate *O*-centred radical cation.<sup>49</sup> At this stage, nOe studies showed that the isomer obtained was the unexpected *E*-isomer, with the alkenyl proton shown to be close in space to the equatorial H-9 proton (Scheme 89).

**Scheme 89.** Synthesis of *E*-silylalkene **297**.

a) bromomethyltriphenylphosphonium bromide (3 equiv), NaHMDS (2.75 equiv), THF,  $-60 \rightarrow -5^\circ\text{C}$ , 15 h; b) *t*-BuLi (2 equiv), TMSCl (2 equiv),  $\text{Et}_2\text{O}$ /pentane,  $-78^\circ\text{C} \rightarrow \text{rt}$ , o/n; c) DDQ (0.1 equiv), 10 %  $\text{H}_2\text{O}$  in THF,  $0^\circ\text{C} \rightarrow \text{rt}$ , o/n.

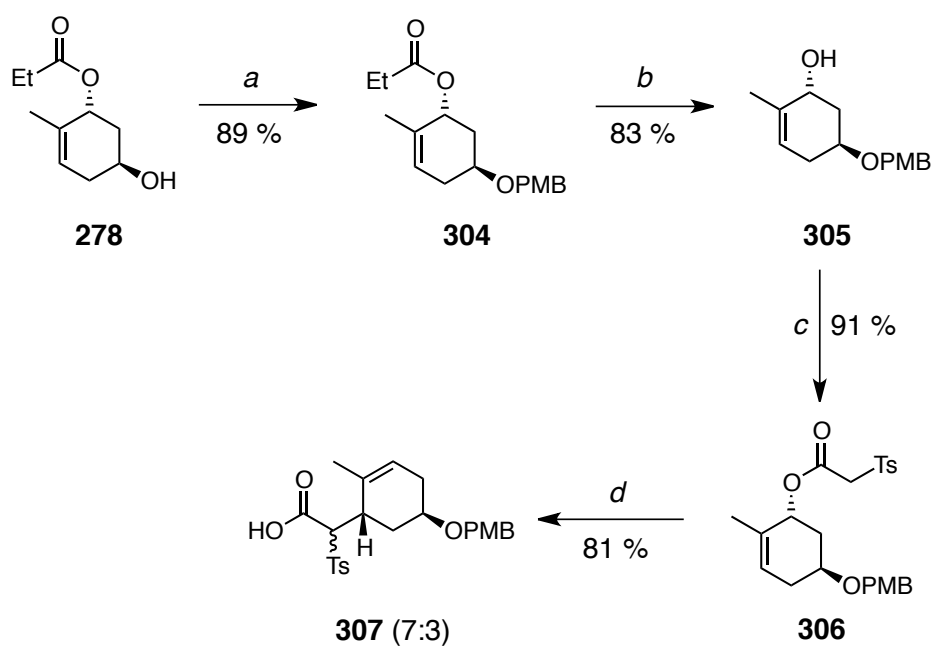
The only literature example of direct conversion of exocyclic ketones to silyl alkenes found was achieved by employing an easily prepared  $\alpha$ -lithioalkoxysilane Peterson reagent.<sup>51</sup> When we attempted the reaction, starting material was consumed after stirring at rt overnight, but crude NMR of the isolate showed no alkenyl protons. The original paper postulates that endocyclic isomers of the desired products can be removed by heating at  $100^\circ\text{C}$  for 2 h. To our delight, after two hours in an oven at that temperature, two strong alkenyl peaks had begun to appear in the  $^1\text{H}$ -NMR spectrum. After chromatography, the desired silylalkene **303** was isolated cleanly in 26 % yield as a 5:1 mixture of *Z/E* isomers. When repeated on a larger scale the yield was improved to 33 %, although the selectivity dropped to 3:2 *Z/E*. Heating the crude product at  $100^\circ\text{C}$  for longer than 2 h only succeeded in diminishing the yield. Again, TES-deprotection using DDQ was achieved in 72 % yield. Further careful chromatography allowed the mixture to be enriched further, providing **297** in 41 % yield and 15:1 *Z/E* ratio, with a remaining 17:10 *E/Z* mixture in 31 % yield. (Scheme 90)

**Scheme 90.** Synthesis of *Z*-silylalkene **297**.

a)  $\text{TMSCH}_2\text{SiMe}_2\text{OMe}$  (1.2 equiv), *t*-BuLi (1.2 equiv), pentane,  $-78^\circ\text{C} \rightarrow \text{rt}$ , o/n; b) DDQ (0.1 equiv), 10 %  $\text{H}_2\text{O}$  in THF,  $0^\circ\text{C} \rightarrow \text{rt}$ , 18 h.

**2.1.11.2 Synthesis of carboxylic acid 307**

Again, our concern for the compatibility of the chemistry required to cleave a TBS-ether with the silylalkene moiety resulted in a change to the protection used on our carboxylic acid substrate. The PMB protecting group was selected as a suitable alternative. Attempted alkylation of alcohol **278** with sodium hydride and *in situ* generated *p*-methoxybenzyl iodide resulted in ester cleavage, with no PMB-ether formed. A second attempt using a catalytic amount of Lewis acid  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , and the trichloroacetimidate of *p*-methoxybenzyl alcohol (PMBTCA) resulted in an intractable mixture of numerous products. A milder variant of this method was ultimately successful, using 3 mol%  $\text{La}(\text{OTf})_3$  and PMBTCA<sup>52</sup> to give the desired PMB-ether **304** in 89 % yield. A similar result could also be achieved with  $\text{Sc}(\text{OTf})_3$ . With the differentially protected diol **304** in hand we were in a position to use the same chemistry as for TBS ether **280** in order to complete the synthesis of carboxylic acid **261**. Thus, ester methanolysis, coupling with 2-tosylacetic acid and Ireland-Claisen rearrangement provided acid **307** in high yield. (Scheme 91)

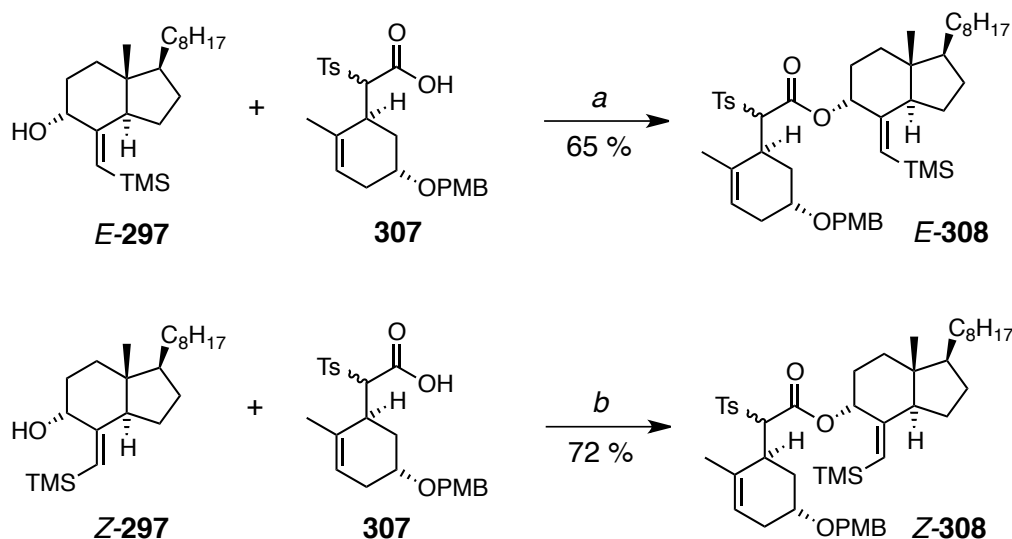
**Scheme 91.** Synthesis of carboxylic acid **307**.

a)  $\text{La}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$  (0.05 equiv), PMBTCA (1.5 equiv), PhMe, rt, 40 min; b) KOH (2 equiv), MeOH, rt, 15 h; c) 2-tosylacetic acid (1 equiv), DMAP (0.1 equiv), DIC (1.1 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 3 h; d)  $\text{Et}_3\text{N}$  (1.2 equiv), BSA (3 equiv),  $\text{CH}_3\text{CN}$ , reflux, 6 h.

### 2.1.11.3 Synthesis of dCr substrates *E/Z*-308

With both *E* and *Z* isomers of **297** in hand, silylalkene dCr substrates *E*-**308** and *Z*-**308** were prepared separately by coupling with carboxylic acid **307** using DIC/DMAP, delivering the desired esters in good yield. (Scheme 92)

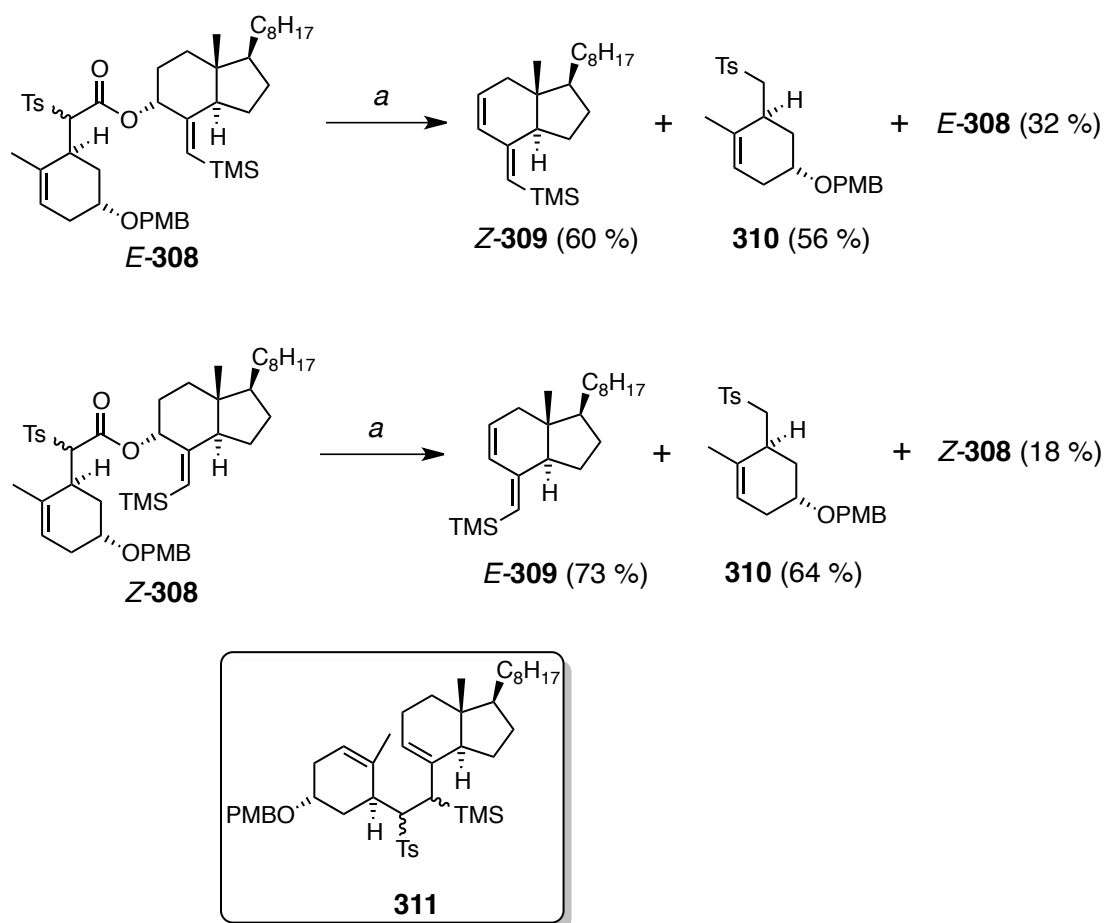
**Scheme 92.** Synthesis of esters *E*-**308** and *Z*-**308**.



a) DMAP (0.1 equiv), DIC (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 48 h; b) DMAP (0.1 equiv), DIC (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 96 h.

### 2.1.11.4 Attempted rearrangement of ester **308**

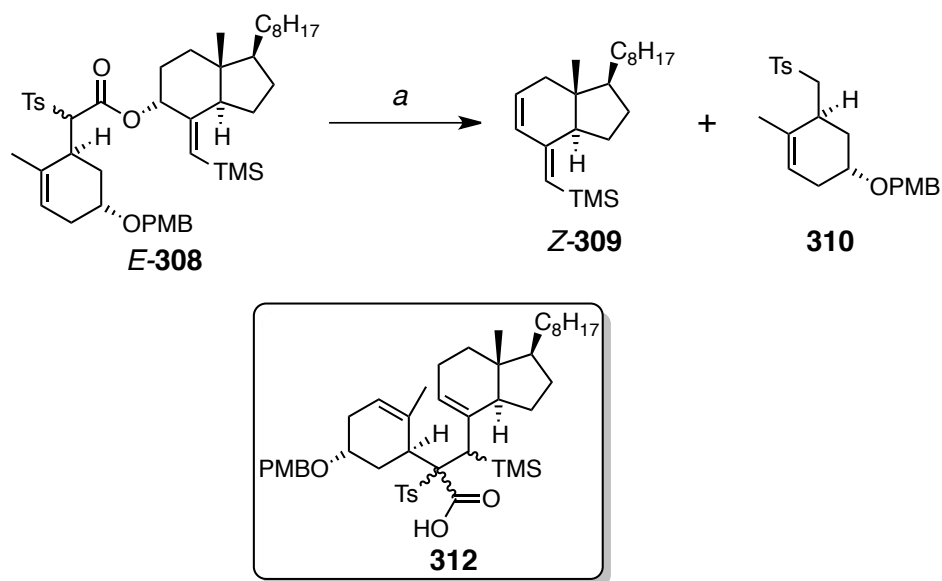
With the ester substrates in hand, the dCr reaction was attempted. *E*-**308** was treated with BSA and KOAc before heating in the microwave. After 3×1 min at 120 °C, no starting material had been consumed. A further 3×1 min at 150 °C showed small amounts of new products forming in the TLC assay, but the reaction mixture still consisted predominantly of starting material. A further 3×1 min at 180 °C showed that *E*-**308** had been largely consumed. Disappointingly, the desired rearrangement product **311** was not present. The two products isolated from this reaction were the result of elimination (**309** in 60 % yield) followed by decarboxylation (**310** in 56 % yield), with some remaining starting material. When the same reaction conditions were applied to *Z*-**308**, similar products were observed, with some remaining starting material. (Scheme 93)

**Scheme 93.** Attempted dCr of *E*-**308** and *Z*-**308**.

a) KOAc (0.25 equiv), BSA (15 equiv), microwave (3 x 1 min, 180 °C).

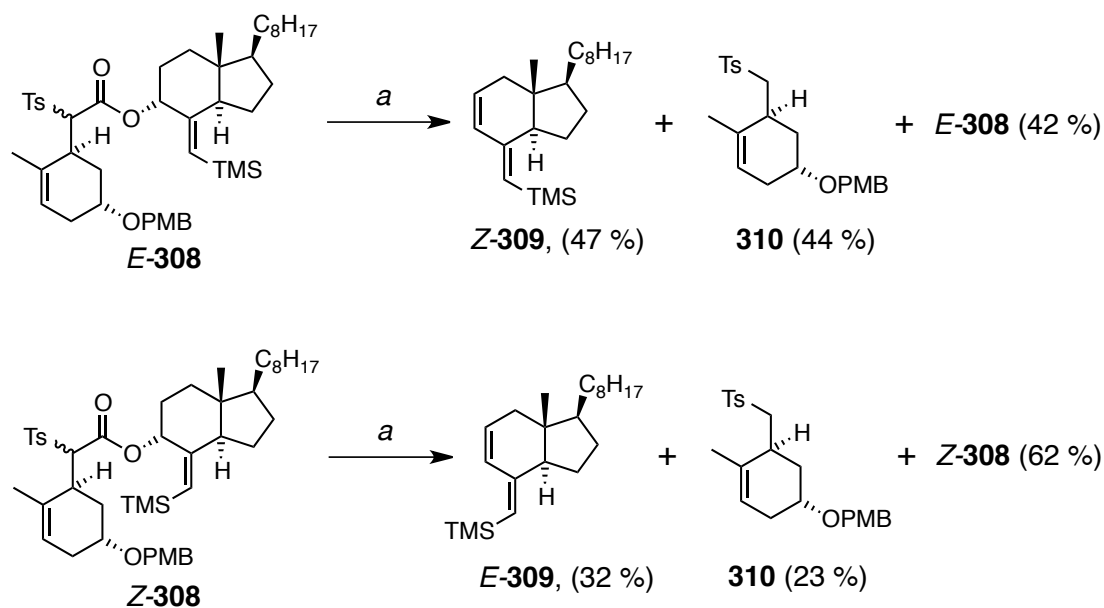
*E*-**308** was heated in the microwave in DMF in the presence of 0.2 equivalents of KOAc to assess whether the same unwanted reaction would occur. After heating for 3×1 min at 180 °C, only starting material was returned.

The rearrangement of **308** to carboxylic acid **312**, under the Ireland-Claisen conditions used previously, was also attempted. **312** would then be subjected to a separate decarboxylation step to furnish the desired product **311**. After heating *E*-**308** at 60 °C for 2 h, then under reflux for 2 h, no starting material had been consumed. An aliquot was taken from the reaction and subjected to microwave heating at 160 °C for 10 min, after which still no reaction was observed. A further 10 min at 180 °C saw *E*-**308** consumed, but <sup>1</sup>H-NMR analysis of the crude reaction mixture after workup showed only a mixture of unwanted by-products *Z*-**309** and **310** (Scheme 94).

**Scheme 94.** Attempted Ireland-Claisen rearrangement of *E*-**308**.

a) Et<sub>3</sub>N (1.2 equiv), BSA (3 equiv), CH<sub>3</sub>CN, microwave (160 °C, 3×1 min, then 180 °C 3×1 min).

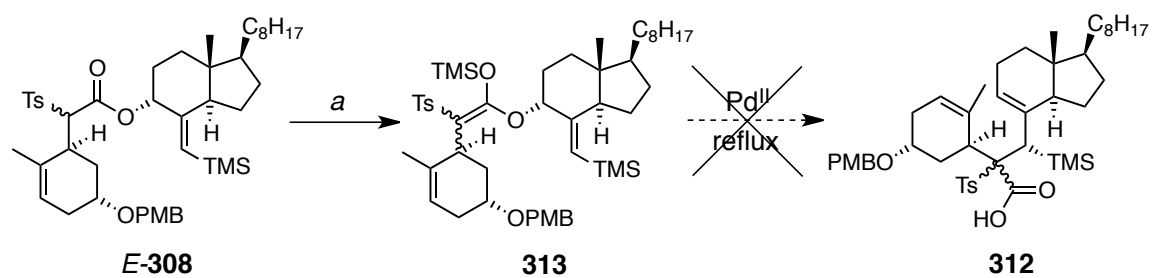
Intramolecular decarboxylative allylations of simple allyl  $\alpha$ -sulfonylesters, essentially Pd-allyl variant of the dCr, have been reported.<sup>53</sup> Rearrangement was attempted under the reported best conditions; heating the substrate in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> and ligand BINAP at 95 °C in PhMe. After 2 days, the reactions were stopped. Again, the only products isolated were **309** and **310** along with the return of remaining starting materials (Scheme 95).

**Scheme 95.** Attempted decarboxylative allylation of *E*-**308** and *Z*-**308**.

a)  $\text{Pd}_2(\text{dba})_3$  (0.05 equiv), BINAP (0.1 equiv), PhMe, 95 °C, 48 h.

Decarboxylative allylation was also attempted using  $\text{Pd}(\text{PPh}_3)_4$  at reflux in THF for 48 h, both with and without pre-treatment of the substrate with NaH. Under both conditions, and for both isomers of **308**, only starting material was returned.

A report in the literature described  $\text{Pd}^{\text{II}}$ -catalysed Ireland-Claisen rearrangement of a pre-formed silyl ketene acetal, using  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ .<sup>54</sup> Therefore, *E*-**308** was submitted to these conditions, pre-treating with LDA and TMSCl to pre-form silyl ketene acetal **313**, and subsequent treatment with  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ , followed by heating at reflux for 24 h. TLC assay showed some conversion. After workup and purification 36 % starting material was recovered, along with a complex mixture of products from the baseline equating to a 42 % mass recovery. Analysis by NMR spectroscopy and MS did not indicate the presence in this mixture of any of the desired carboxylic acid **312**, or the decarboxylated form, **311** (Scheme 96).

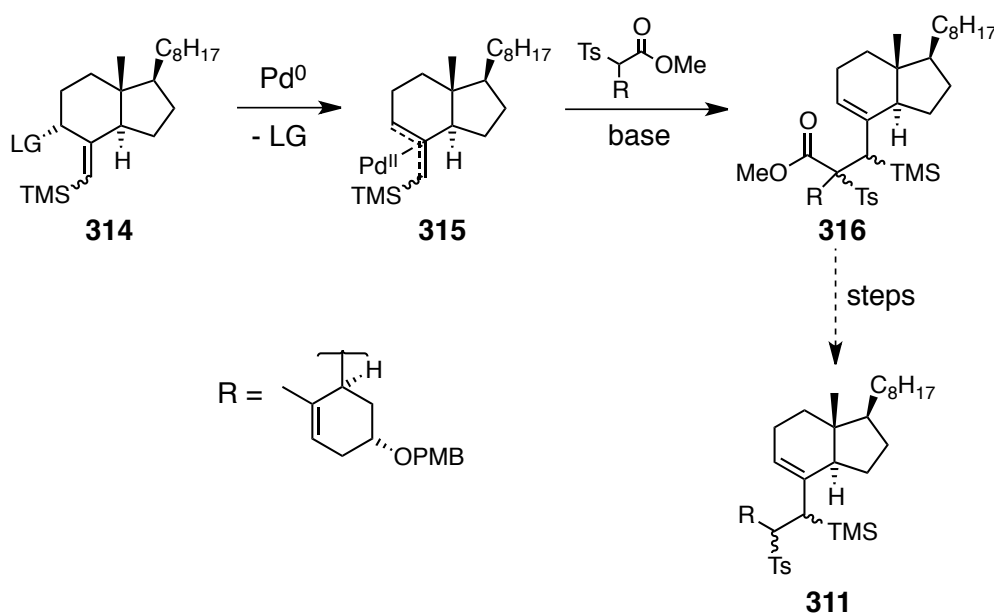
**Scheme 96.** Attempted Pd-catalysed Ireland-Claisen rearrangement of **308**.

a) DIPA (1 equiv), *n*-BuLi (1 equiv), TMSCl, (1.1 equiv), THF,  $-78\text{ }^{\circ}\text{C} \rightarrow \text{rt}$ .

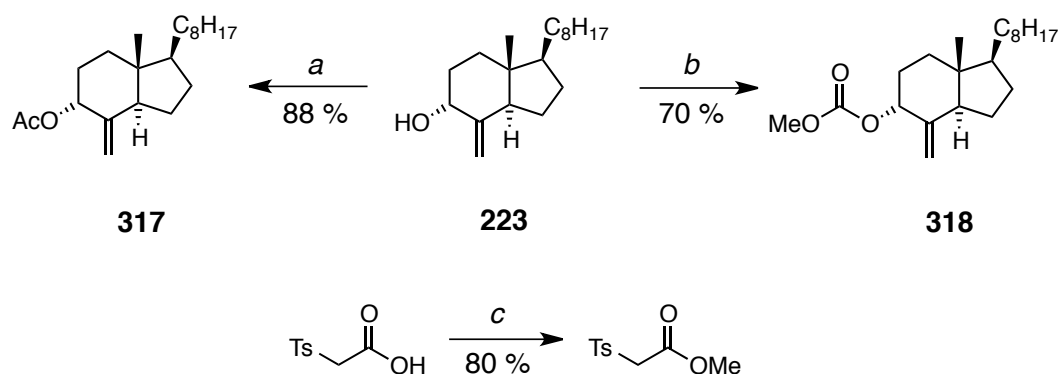
### 2.1.12 Investigation of Tsuji-Trost approach to **311**

With intramolecular palladium-catalysed allylations failing to yield the desired product, we decided to explore the intermolecular alternative under classic Tsuji-Trost allylation conditions.<sup>55</sup>  $\alpha$ -Sulfonylesters have been shown to act as competent nucleophiles in reactions with  $\pi$ -allyl palladium complexes to deliver homoallylic  $\alpha$ -sulfonylesters.<sup>56</sup> We proposed treating substrate **314** with  $\text{Pd}^0$  to produce  $\pi$ -allyl complex **315** that would react with an  $\alpha$ -sulfonylester in the presence of base to give **316** regioselectively. Subsequent ester hydrolysis and decarboxylation would deliver desired substrate **311** (Scheme 97)

**Scheme 97.** Proposed Tsuji-Trost approach to homoallylic sulfone **311**.

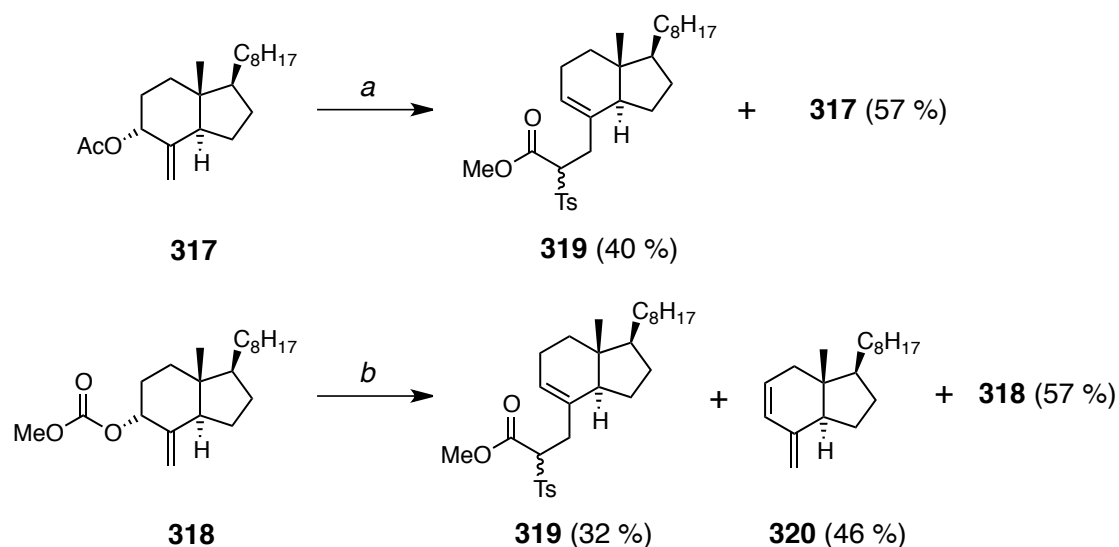


In order to test this hypothesis on a simple model substrate we prepared acetate ester **317** and methyl carbonate **318** of allylic alcohol **223** under standard conditions. Methyl 2-tosylacetate was also prepared in good yield. (Scheme 98)

**Scheme 98.** Synthesis of Tsuji-Trost test substrates **317** and **318**.

a) pyridine (4 equiv), DMAP (0.05 equiv), Ac<sub>2</sub>O (1.2 equiv), rt, 3 h; b) pyridine (3 equiv), DMAP (0.05 equiv), methyl chloroformate (1.2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 48 h; c) H<sub>2</sub>SO<sub>4</sub>, MeOH, reflux, 8 h.

Firstly, acetate **317** in the presence of catalytic Pd(PPh<sub>3</sub>)<sub>4</sub> was treated with the sodium salt of deprotonated methyl 2-tosylacetate (generated by pre-treating with NaH). After refluxing the mixture in THF for 48 h the reaction was stopped, with starting material still present in the TLC assay. The desired product **319** was isolated in 40 % yield, with 57 % starting material remaining. Carbonate **318**, a more reactive substrate under Tsuji-Trost conditions, was treated with Pd(PPh<sub>3</sub>)<sub>4</sub> in the presence of methyl 2-tosylacetate (pre-treatment with base was not required as formation of the  $\pi$ -allyl complex produces methoxide *in situ*). After refluxing for 5 h, TLC assay appeared to show reaction completion. The desired product **319** was isolated in 32 % yield, however the major product was elimination product **320** in 46 % yield, with 22 % starting material also remaining. (Scheme 99)

**Scheme 99.** Tsuji-Trost reaction of **317** and **318** with methyl 2-tosylacetate.

a) Pd(PPh<sub>3</sub>) (0.05 equiv), PPh<sub>3</sub> (0.1 equiv), NaH (1.1 equiv), methyl 2-tosylacetate (1.1 equiv), THF, reflux, 48 h; b) Pd(PPh<sub>3</sub>) (0.05 equiv), methyl 2-tosylacetate (1.1 equiv), THF, reflux, 5 h.

Given the slow conversion of acetate **317** under these conditions, we chose to pursue optimisation of the reaction of carbonate **318**. It was believed that performing the reaction at milder temperatures might improve the yield. However, when repeated at 60 °C no conversion was observed. To our dismay, we were also unable to repeat the previous result either. When treated at reflux as previously, **318** underwent no conversion at all. Despite preparing fresh methyl 2-tosylacetate, repurifying **318**, using new samples of Pd(PPh<sub>3</sub>)<sub>4</sub>, and even preparing Pd(PPh<sub>3</sub>)<sub>4</sub> *in situ* from Pd(OAc)<sub>2</sub> and PPh<sub>3</sub>, failed to give conversion. At this stage there was no time left in the laboratory to continue investigating this new approach and the reaction was abandoned.

## 2.2 Summary

Our initial proposal for the total synthesis of  $1\alpha,25$ -dihydroxylumisterol involved two late-stage key steps. The first, a dCr reaction to give 1,6-heptadiene **263**, was ultimately successful, albeit *via* an alternative ester substrate to that initially anticipated. The interesting study of model dCr substrates that led to this success gave us some insight into the relative reactivities of different allyl moieties under dCr conditions. The dCr substrate, ester **262**, was prepared in good yield *via* the convergent coupling of allylic alcohol **223** and carboxylic acid **261**, both having been prepared in high-yielding synthetic routes.

The continuation of the synthesis to epoxide substrate **283** was also successful and, through reagent screening, we were able to identify suitable conditions for the second key step, a cyclisation to form the steroid B-ring, although the product delivered was an undesired isomer **288**. A proposal to direct this reaction to yield the desired isomer led to the successful, if challenging, synthesis of silylated ester substrates *E*-**308** and *Z*-**308**. Attempts were made to get them to undergo sigmatropic rearrangement to deliver the desired silyl-1,6-heptadiene **311** under dCr and a variety of other conditions, however none were successful.

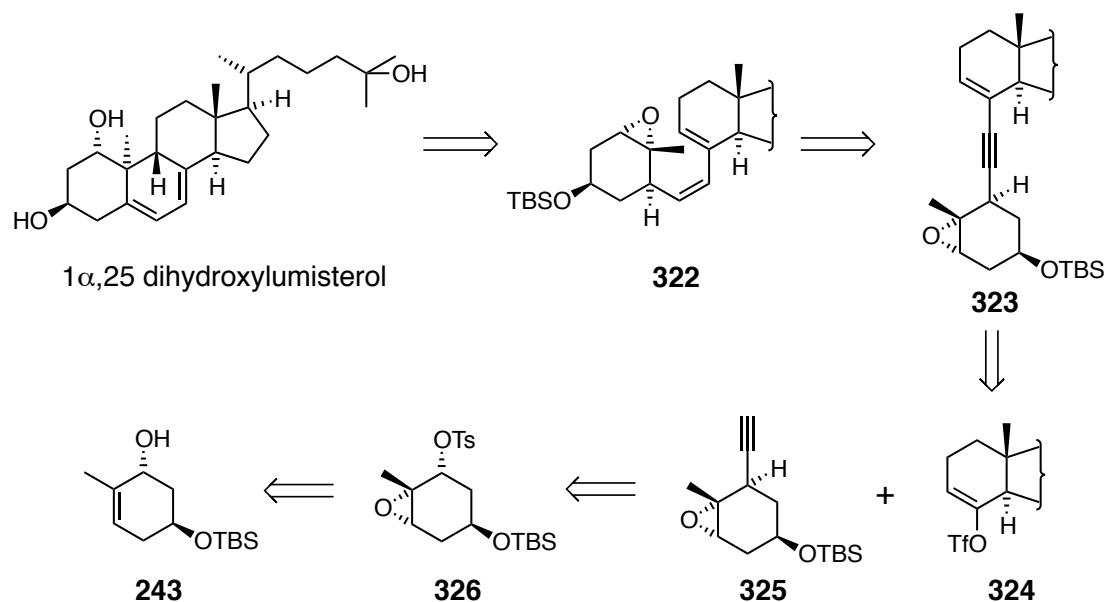
Finally, preliminary investigations into forming desired TMS-diene **311** *via* Pd-catalysed intermolecular allylation chemistry showed some promise, but more investigation would be required for a full conclusion to be drawn.

### 2.3 Future Work

Had the intermolecular allylation chemistry failed to deliver the desired product, an alternative approach to 1 $\alpha$ ,25-dihydroxylumisterol was proposed that circumvented the use of a Claisen rearrangement altogether, but there was not sufficient laboratory time left to test the hypothesis.

It was proposed that alternative cyclisation substrate **322** (Scheme 100) could be prepared from Sonogashira coupling of vinyl triflate **324** and alkyne **325**, followed by selective *cis*-hydrogenation of intermediate enyne **323**. It was hoped that the cyclisation would lead to the desired alkene isomer, driven by formation of the conjugated diene in 1 $\alpha$ ,25-dihydroxylumisterol. Vinyl triflate **324** would be easily accessible from Grundmann's ketone **216**, and synthesis of alkynyl epoxide **325** could be envisioned from previously made allylic alcohol **243** by a pathway using hydroxy-directed epoxidation followed by conversion of alcohol to tosylate **326**. Treatment with an ethynyl organometallic reagent would yield **325**.

**Scheme 100.** Proposed alternative synthesis of 1 $\alpha$ ,25-dihydroxylumisterol.



## 2.4 References

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## Chapter 3

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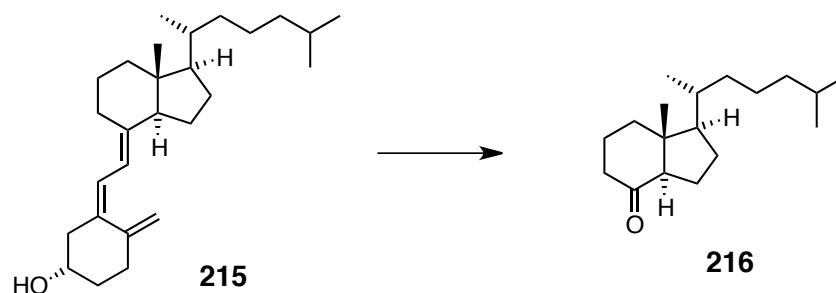
# *Experimental*

### 3.1 General Laboratory Procedures

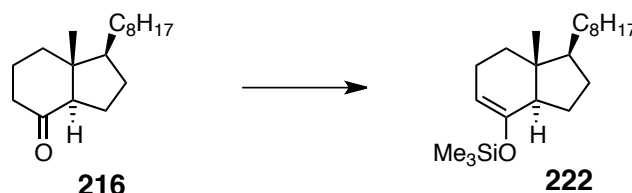
All reactions were performed under an atmosphere of nitrogen unless otherwise stated. Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Proton ( $^1\text{H}$ ) and carbon ( $^{13}\text{C}$ ) nuclear magnetic resonance spectra were recorded on a Bruker AV-400 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced relative to the residual proton-containing solvent ( $^1\text{H}$  NMR: 7.26 ppm for  $\text{CDCl}_3$ ;  $^{13}\text{C}$  NMR: 77.0 ppm for  $\text{CDCl}_3$ ) or in the case of  $^{31}\text{P}$  NMR, to an external standard ( $\text{H}_3\text{PO}_4$ ). Coupling constants ( $J$ ) are reported to the nearest 0.5 Hertz. Infrared spectra were recorded on a Perkin-Elmer Spectrum RX FT-IR System spectrometer with samples prepared as thin films on NaCl plates. Mass spectra (CI, ES and ESI) were recorded using Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier instruments. Elemental analyses were performed at the microanalytical laboratories of the London Metropolitan University. Optical rotation were determined on an Optical Activity AA-10 Automatic polarimeter at 589nm (Na D-line) with a path length of 1 dm. Concentrations ( $c$ ) are quoted in g/100 mL and specific rotations ( $[\alpha]_{\text{D}}^{\text{T}}$ ) are quoted in  $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$  at the specified temperature. Analytical thin layer chromatography (TLC) was performed on aluminium plates pre-coated with silica gel (0.2 mm, Merck 60 F<sub>254</sub>) and development was effected with UV light or potassium permanganate as appropriate. Flash column chromatography was performed using BDH (40-63  $\mu\text{m}$ ) silica gel according to the method of W.C Still *et al.*<sup>1</sup> Kugelrohr distillations were performed using a Büchi D56 Kugelrohr oven and controller system. Standard solvents were distilled under nitrogen prior to use; THF from sodium-benzophenone ketyl,  $\text{CH}_2\text{Cl}_2$  and acetonitrile from  $\text{CaH}_2$  and toluene from sodium. All other solvents used were distilled prior to use. Petrol refers to petroleum ether b.p. 40–60 °C. Potassium acetate was oven-dried at 120 °C for several days prior to use. Microwave reactions were performed in a Biotage Initiator and cooled using compressed air (4 bar). Ozone gas was generated from oxygen gas using a Triogen LAB2B ozone generator.

### 3.2 Individual Procedures

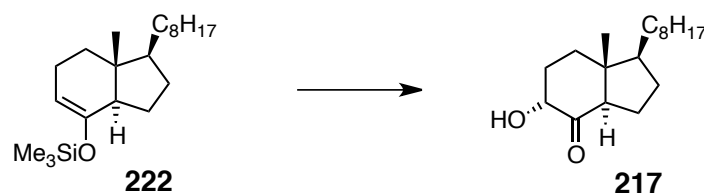
#### De-A,B-cholestan-8-one (Windaus-Grundmann ketone) (**216**)



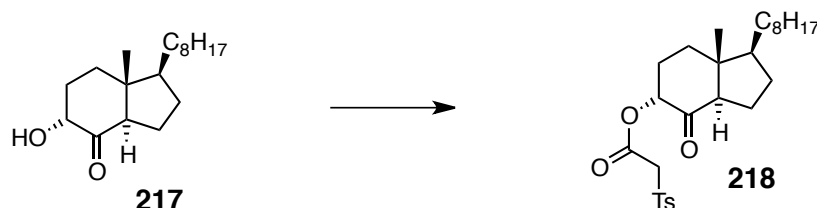
Ozone was bubbled through a solution of (+)-vitamin D<sub>3</sub> (**215**) (10.0 g, 26.0 mmol, 1 equiv) in MeOH (520 mL) at  $-78\text{ }^{\circ}\text{C}$  until a blue colour persisted ( $\sim 90$  min). The solution was flushed with nitrogen until the blue colour abated. Me<sub>2</sub>S (9.50 mL, 130 mmol, 7 equiv) was added and the mixture allowed to warm to rt overnight. MeOH was removed under reduced pressure, and the remaining oil taken up in Et<sub>2</sub>O (600 mL) and washed with H<sub>2</sub>O (3 x 200 mL). The aqueous layers were back-extracted with Et<sub>2</sub>O (2 x 200 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Silica gel chromatography (5 % Et<sub>2</sub>O in petrol) gave **216** as a colourless oil (6.74 g, 98 %);  $R_f$  0.50 (10 % Et<sub>2</sub>O in petrol);  $[\alpha]_D^{25} +6.1$  ( $c$  0.89, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 2955, 2870, 1715, 1464, 1380  $\text{cm}^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 2.46 (1H, m, H-14), 2.34–0.99 (22H, m), 0.96 (3H, d,  $J$  6.0 Hz, H-21), 0.89 (3H, d,  $J$  2.0 Hz, H-26/27), 0.87 (3H, d,  $J$  2.0 Hz, H-26/27), 0.66 (3H, s, H-18);  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 212.2 (C-8), 62.0 (C-14), 56.7 (C-9), 49.9 (C-13), 41.0, 39.4, 39.0, 36.0, 35.5, 28.0, 27.5, 24.1, 23.8, 22.8, 22.5, 19.1, 18.7 (C-21), 12.5 (C-18);  $m/z$  (EI) 264 [M]<sup>+</sup>, 249, 221. In agreement with published data.<sup>2</sup>

8-[(Trimethylsilyl)oxy]des-A,B-8(9)-cholestene (**222**)

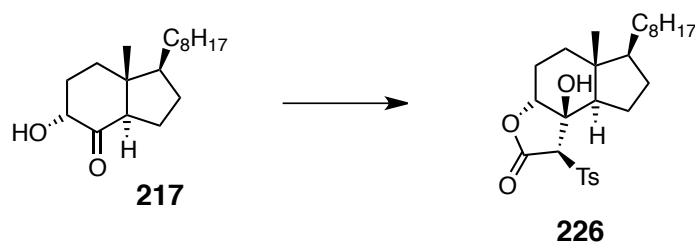
To diisopropylamine (0.35 mL, 2.46 mmol, 1.3 equiv) in THF (10 mL) at  $-78^{\circ}\text{C}$  was added *n*-BuLi (0.91 mL, 2.50 M in hexanes, 2.27 mmol, 1.2 equiv). After 45 min stirring, TMSCl (0.26 mL, 2.08 mmol, 1.1 equiv) was added. After a further 5 min, a solution of **216** (500 mg, 1.89 mmol, 1 equiv) in THF (1 mL) was added dropwise. Stirring was continued at  $-78^{\circ}\text{C}$  for 1 h. After warming to rt the reaction mixture was diluted with Et<sub>2</sub>O (100 mL) and washed with sat. NaHCO<sub>3</sub> (50 mL) and brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give **222** as a colourless oil (628 mg, >99 %); *R*<sub>f</sub> 0.95 (5 % Et<sub>2</sub>O in petrol);  $\nu_{\text{max}}$  (film) 2951, 1716, 1658, 1378, 1252, 1206  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 4.66 (1H, m, H-9), 2.28–0.98 (18H, m), 0.95 (3H, d, *J* 6.5 Hz, H-21), 0.90 (3H, d, *J* 2.0 Hz, H-26/27), 0.88 (3H, d, *J* 2.0 Hz, H-26/27), 0.75 (3H, s, H-18), 0.19 (9H, s, CH<sub>3</sub>Si);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 151.3 (C-9), 101.6 (C-8), 54.8 (C-14), 51.8, 43.7 (C-13), 39.5, 36.2, 36.1, 28.4, 28.0, 23.9, 23.4, 22.8, 22.6, 22.1, 18.7 (C-21), 11.3 (C-18), 0.4 (CH<sub>3</sub>Si); *m/z* (EI) 337 [M+H]<sup>+</sup>. In agreement with published data.<sup>3</sup>

**De-A,B-9 $\alpha$ -hydroxycholestan-8-one (217)**

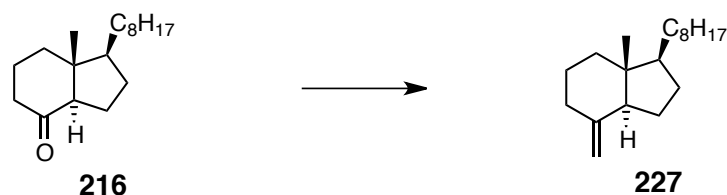
Ozone was bubbled through a solution of **222** (17.3 g, 51.4 mmol, 1 equiv) in MeOH (700 mL) and CH<sub>2</sub>Cl<sub>2</sub> (150 mL) at  $-78^{\circ}\text{C}$  until a blue colour persisted. The solution was flushed with nitrogen until the blue colour abated. Me<sub>2</sub>S (19.1 mL, 260 mmol, 5 equiv) was added and the mixture allowed to warm to rt overnight. MeOH was removed under reduced pressure, and the remaining oil taken up in Et<sub>2</sub>O (400 mL) and washed with H<sub>2</sub>O (3 x 150 mL). The aqueous layers were back-extracted with Et<sub>2</sub>O (2 x 250 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Silica gel chromatography (10 % EtOAc in petrol) gave **217** as a colourless oil (8.24 g, 57 %);  $R_f$  0.50 (10 % EtOAc in petrol);  $[\alpha]_D^{25} -22.4$  ( $c$  1.20, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3418, 2954, 2926, 2868, 1719, 1466, 1383, 1260, 1014  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 4.01 (1H, t,  $J$  3.5 Hz, H-8), 3.15 (1H, dd,  $J$  12.0, 4.5 Hz, H-14), 2.58 (1H, bs, OH), 2.08–1.00 (17H, m), 0.96 (3H, d,  $J$  6.5 Hz, H-21), 0.90 (3H, d,  $J$  2.0 Hz, H-26/27), 0.88 (3H, d,  $J$  2.0 Hz, H-26/27), 0.65 (3H, s, H-18);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 212.3 (C-8), 74.4 (C-9), 56.8 (C-14), 50.2 (C-13), 39.4, 35.9, 35.5, 34.1, 31.4, 28.0, 27.6, 23.8, 22.8, 22.5, 18.6 (C-21), 12.9 (C-18);  $m/z$  (EI) 280  $[\text{M}]^+$ , 221, 168. In agreement with published data.<sup>4</sup>

De-A,B-cholestan-8-onyl-9 $\alpha$ -2-tosylacetate (**218**)

To **217** (110 mg, 0.39 mmol, 1 equiv) and 2-tosylacetic acid (85 mg, 0.39 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at 0 °C was added DMAP (2 mg, 0.02 mmol, 0.05 equiv) followed by DIC (67  $\mu$ L, 0.43 mmol, 1.1 equiv) dropwise. After 15 min the reaction mixture was filtered through Celite<sup>®</sup> and the filtrate concentrated under reduced pressure. Silica gel chromatography (10 % EtOAc in petrol) gave **218** as a colourless oil (170 mg, 91 %); *R*<sub>f</sub> 0.25 (10 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -11.4 (*c* 0.95, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2955, 2932, 2870, 1747, 1729, 1598, 1469, 1385, 1330, 1267, 1151, 1085 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.79 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.39 (2H, d, *J* 8.0 Hz, *m*-Ts), 4.90 (1H, t, *J* 3.0 Hz, H-9), 4.15 (2H, s, TsCH<sub>2</sub>), 2.92, (1H, dd, *J* 12.0, 4.5 Hz, H-14), 2.48 (3H, s, CH<sub>3</sub>Ar), 2.16–1.00 (17H, m), 0.96 (3H, d, *J* 6.5 Hz, H-21), 0.89 (3H, d, *J* 2.0 Hz, H-26/27), 0.87 (3H, d, *J* 2.0 Hz, H-26/27), 0.64 (3H, s, H-18);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 205.2 (C-8), 161.3 (CO-ester), 145.7 (Ar), 135.5 (Ar), 130.0 (*m*-Ts), 128.4 (*o*-Ts), 78.4 (C-9), 61.1 (TsCH<sub>2</sub>), 58.2 (C-14), 56.8, 51.1 (C-13), 39.4, 35.9, 35.5, 34.3, 29.6, 28.0, 27.5, 23.8, 22.8, 22.5, 21.7 (CH<sub>3</sub>Ar), 18.7, 18.5, 12.3 (C-18); *m/z* (CI) 494 [M+NH<sub>4</sub>]<sup>+</sup>, 476 [M]<sup>+</sup>, 322, 174 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 494.2944. C<sub>27</sub>H<sub>40</sub>O<sub>5</sub>S requires [M+NH<sub>4</sub>]<sup>+</sup>, 494.2935).

**$\gamma$ -Lactone (226)**

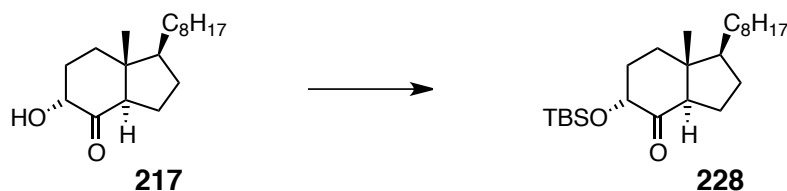
To **217** (675 mg, 2.41 mmol, 1 equiv) and 2-tosylacetic acid (516 mg, 2.41 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added DMAP (15 mg, 0.12 mmol, 0.05 equiv) followed by DIC (412  $\mu\text{L}$ , 2.65 mmol, 1.1 equiv) dropwise. After 30 min the reaction mixture was filtered through Celite<sup>®</sup> and the filtrate concentrated under reduced pressure. Silica gel chromatography (10 % EtOAc in petrol) gave **226** as a white powder (743 mg, 65 %);  $R_f$  0.60 (10 % EtOAc in petrol); mp 180-182 °C (decomp.);  $[\alpha]_D^{25} +52.6$  ( $c$  0.57,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3486, 2950, 2926, 2867, 1760, 1597, 1470, 1330, 1214, 1184, 1140, 1084, 1008  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.83 (2H, d,  $J$  8.0Hz, *o*-Ts), 7.41 (2H, d,  $J$  8.0 Hz, *m*-Ts), 4.80 (1H, m, H-9), 3.90 (1H, s, OH), 3.75 (1H, s, TsCH), 2.50 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.11–0.96 (14H, m), 0.94 (3H, s, C-18), 0.91 (3H, d,  $J$  6.5 Hz, C-21), 0.89 (3H, d,  $J$  2.0 Hz, H-26/27), 0.87 (3H, d,  $J$  2.0 Hz, H-26/27);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 166.5 (CO), 146.4 (Ar), 135.0 (Ar), 130.0 (*m*-Ts), 129.2 (*o*-Ts), 82.3 (C-9), 78.6 (C-8), 71.2 (TsCH), 56.3 (C-14), 52.1, 41.8, 39.4, 35.8, 35.2, 33.0, 28.0, 26.4, 23.7, 22.8, 22.5, 21.9 ( $\text{CH}_3\text{Ar}$ ), 18.8, 18.5, 12.1 (C-18);  $m/z$  (CI) 494  $[\text{M}+\text{NH}_4]^+$ , 476  $[\text{M}]^+$ , 322, 174 (Found  $[\text{M}+\text{NH}_4]^+$ , 494.2944.  $\text{C}_{27}\text{H}_{40}\text{O}_5\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 494.2935).

**De-A,B-8-methylenecholestane (227)**

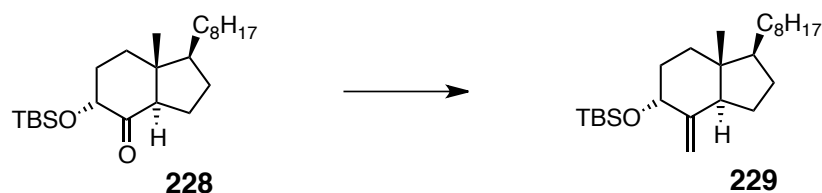
Method A: To a slurry of methyltriphenylphosphonium iodide (397 mg, 0.98 mmol, 1.3 equiv) in THF (4 mL) at 0 °C was added *n*-BuLi (425  $\mu$ L, 0.83 mmol, 1.1 equiv) dropwise. After 30 min, **216** (200 mg, 0.76 mmol, 1 equiv) in THF (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min, then rt for 4 h. Water (5 mL) was added and the mixture extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude oil was passed through a short silica gel plug, eluting with petrol, to afford **227** as a colourless oil (162 mg, 81 %).

Method B: A round-bottomed flask fitted with reflux condenser and covered in foil was charged with **216** (200 mg, 0.76 mmol, 1 equiv) and Cp<sub>2</sub>TiMe<sub>2</sub> (7.3 mL, 5 % in PhMe/THF, 1.52 mmol, 2 equiv). The reaction mixture was heated at 65 °C for 48 h. Petrol (25 mL) was added and the reaction mixture filtered through Celite<sup>®</sup> to remove titanium solids. The filtrate was passed through a silica gel plug, eluting with petrol, to afford **227** as a colourless oil (167 mg, 84 %).

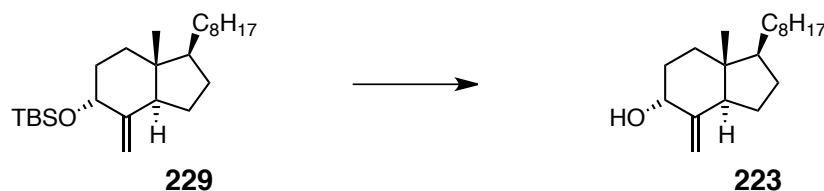
R<sub>f</sub> 1.00 (petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +68.4 (*c* 0.93, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2951, 2930, 2869, 1651, 1468, 1378 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 4.75 (1H, s, C=CH<sub>2</sub>), 4.48 (1H, s, C=CH<sub>2</sub>), 2.34–2.24 (1H, m), 2.06–1.83 (4H, m), 1.69–0.99 (15H, m), 0.95 (3H, d, *J* 6.0 Hz, H-21), 0.89 (3H, d, *J* 2.0 Hz, H-26/27), 0.87 (3H, d, *J* 2.0 Hz, H-26/27), 0.58 (3H, s, H-18);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 149.7 (C-8), 105.0 (C=CH<sub>2</sub>), 56.4 (C-17), 55.4 (C-14), 45.1 (C-13), 40.2, 39.5, 36.2, 36.1, 35.5, 28.0, 27.7, 23.9, 23.8, 22.8, 22.6, 22.3, 18.8 (C-21), 11.7 (C-18); *m/z* (CI) 280 [M+NH<sub>4</sub>]<sup>+</sup>, 263 [M]<sup>+</sup>, 149 (Found [M+H]<sup>+</sup>, 263.2732. C<sub>19</sub>H<sub>34</sub> requires [M+H]<sup>+</sup>, 263.2739). In agreement with published data.<sup>5</sup>

**De-A,B-9 $\alpha$ -(*tert*-butyldimethylsilyloxy)cholestan-8-one (228)**

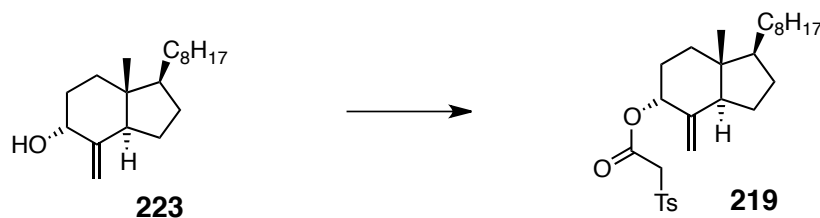
To **217** (4.00 g, 14.3 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (50 mL) at 0 °C was added imidazole (2.92 g, 42.79 mmol, 3 equiv), followed after 5 min by *tert*-butyldimethylsilylchloride (6.45 g, 42.8 mmol, 3 equiv). The reaction mixture was stirred at rt for 18 h then diluted with  $\text{CH}_2\text{Cl}_2$  (200 mL), washed with  $\text{H}_2\text{O}$  (100 mL) and brine (100 mL), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (0-20 % EtOAc in heptane) afforded **228** as a colourless oil (5.20 g, 92 %);  $R_f$  0.90 (5 % EtOAc in petrol);  $[\alpha]_D^{24}$   $-19.0$  ( $c$  1.40,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2954, 2929, 2858, 1724, 1464, 1384, 1363, 1252, 1083, 1034  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 3.89 (1H, bm, H-9), 3.13 (1H, dd,  $J$  12.0, 7.0 Hz, H-14), 1.98-1.80 (5H, m), 1.78-1.65 (1H, m), 1.56-0.97 (11H, m), 0.94 (3H, d, H-21), 0.88 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 0.87 (6H, m, H-26/27), 0.59 (3H, s, H-18), 0.06 (3H, s,  $\text{CH}_3\text{Si}$ ), 0.00 (3H, s,  $\text{CH}_3\text{Si}$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 211.06 (C-8), 75.5 (C-9), 56.8 (C-14), 56.5 (C-17), 39.5 (C-13), 36.1, 35.6, 34.2, 32.9, 31.9, 29.0, 28.0, 27.6, 25.7 ( $(\text{CH}_3)_3\text{CSi}$ ), 23.9, 22.8, 22.7, 22.6, 18.7, 18.5, 18.0, 14.1, 12.1 (C-18),  $-4.9$  ( $\text{CH}_3\text{Si}$ ),  $-5.0$  ( $\text{CH}_3\text{Si}$ );  $m/z$  (CI) 412  $[\text{M}+\text{NH}_4]^+$ , 395  $[\text{M}+\text{H}]^+$ , 337, 280  $[\text{M}+\text{NH}_4-\text{TBSOH}]^+$  (Found  $[\text{M}+\text{H}]^+$ , 395.3358.  $\text{C}_{24}\text{H}_{46}\text{O}_2\text{Si}$  requires  $[\text{M}+\text{H}]^+$ , 395.3345).

**De-A,B-9 $\alpha$ -(*tert*-butyldimethylsilyloxy)-8-methylenecholestane (229)**

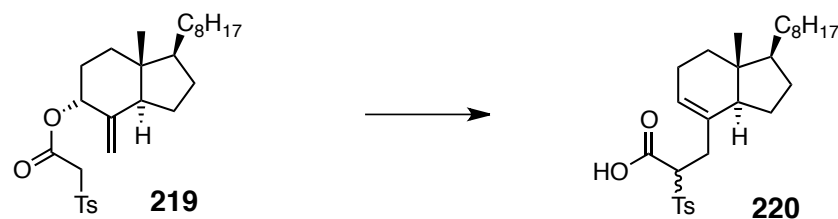
To a suspension of methyltriphenylphosphonium iodide (1.29 g, 3.20 mmol, 1.3 equiv) in THF (12 mL) at 0 °C was added *n*-BuLi (1.26 mL, 2.15 M in hexanes, 2.71 mmol, 1.1 equiv) dropwise. The mixture was stirred at 0 °C for 30 mins before dropwise addition of **228** (971 mg, 2.46 mmol, 1 equiv) in THF (5 mL). The reaction mixture was stirred at 0 °C for 1 h then diluted with Et<sub>2</sub>O (200 mL), washed with H<sub>2</sub>O (200 mL) then brine (200 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (Petrol) afforded **229** as a colourless oil (865 mg, 90 %); *R*<sub>f</sub> 1.00 (5 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>22</sup> +9.5 (*c* 1.40, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2951, 2930, 2858, 1655, 1470, 1379, 1361, 1341, 1251, 1070, 1036 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 4.79 (1H, s, C=CH<sub>2</sub>), 4.48 (1H, s, C=CH<sub>2</sub>), 4.12 (1H, m, H-9), 2.44 (1H, m, H-14), 1.86 (1H, m), 1.69-1.56 (3H, m), 1.53-0.93 (13H, m), 0.89 (3H, d, *J* 6.0 Hz, H-21), 0.84 (6H, m, H-26/27) 0.83 (9H, s, (CH<sub>3</sub>)<sub>3</sub>Si), 0.49 (3H, s, H-18), 0.00 (3H, s, CH<sub>3</sub>Si), -0.05 (3H, s, CH<sub>3</sub>Si);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 151.3 (C-8), 106.7 (C=CH<sub>2</sub>), 73.1 (C-9), 56.3 (C-17), 49.4 (C-14), 45.1 (C-13), 39.5, 36.2, 34.7, 32.1, 28.0, 27.8 ((CH<sub>3</sub>)<sub>3</sub>CSi), 25.8, 24.0, 22.9, 22.6, 21.8, 18.8, 18.1, 11.2 (C-18), -4.6 (CH<sub>3</sub>Si), -5.1 (CH<sub>3</sub>Si); *m/z* (CI) 410 [M+NH<sub>4</sub>]<sup>+</sup>, 335, 261, 230 (Found [M+H]<sup>+</sup>, 393.3548. C<sub>25</sub>H<sub>48</sub>OSi requires [M+H]<sup>+</sup>, 393.3552).



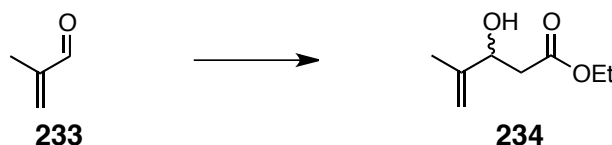
120

**De-A,B-8-methylenecholestan-9 $\alpha$ -yl 2-tosylacetate (**219**)**

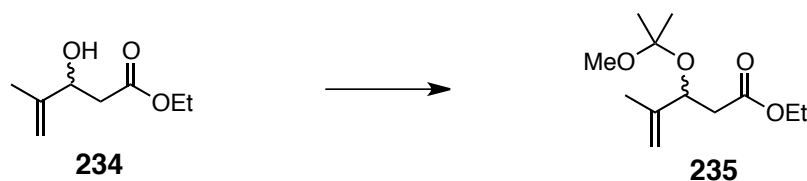
To a solution of **223** (725 mg, 2.60 mmol, 1 equiv) and 2-tosylacetic acid (560 mg, 2.60 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0 °C was added DMAP (15 mg, 0.13 mmol, 0.05 equiv) followed by dropwise addition of DIC (450  $\mu$ L, 2.86 mmol, 1.1 equiv). The reaction mixture was stirred at 0 °C for 30 mins before diluting with Et<sub>2</sub>O (50 mL) and filtering through Celite®, further washing the solids with Et<sub>2</sub>O (10 mL). The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (10% EtOAc in petrol) to afford **219** as a colourless oil (943 mg, 76 %); *R*<sub>f</sub> 0.60 (10% EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>23</sup> +32.3 (*c* 1.10, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2953, 2932, 2870, 1736, 1654, 1598, 1466, 1332, 1275, 1151, 1086 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.82 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.36 (2H, d, *J* 8.0 Hz, *m*-Ts), 5.33 (1H, s, H-9), 5.08 (1H, s, C=CH<sub>2</sub>), 4.76 (1H, s, C=CH<sub>2</sub>), 4.10 (2H, s, TsCH<sub>2</sub>), 2.47 (3H, s, CH<sub>3</sub>Ar), 2.17 (1H, m, H-14), 1.98–0.99 (17H, m), 0.93 (3H, d, *J* 6.0 Hz, H-21), 0.90 (3H, d, *J* 2.0 Hz, H-26/27), 0.88 (3H, d, *J* 2.0 Hz, H-26/27), 0.55 (3H, s, H-18);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 161.6 (CO), 145.3 (C=CH<sub>2</sub>), 145.0 (Ar), 135.8 (Ar), 129.8 (*m*-Ts), 128.5 (*o*-Ts), 112.4 (C=CH<sub>2</sub>), 77.1 (C-9), 61.4 (TsCH<sub>2</sub>), 56.0, 50.3 (C-14), 44.6, 39.5, 36.1, 34.9, 28.2, 28.0, 27.6, 23.9, 22.8, 22.6, 21.9, 21.8 (CH<sub>3</sub>Ar), 18.8, 11.1 (C-18); *m/z* (CI) 492 [M+NH<sub>4</sub>]<sup>+</sup>, 476 [M+H]<sup>+</sup>, 391, 338, 261, 188, 174 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 492.3138. C<sub>28</sub>H<sub>42</sub>O<sub>4</sub>S requires [M+NH<sub>4</sub>]<sup>+</sup>, 492.3148).

**3-(Des-A,B-8(9)-cholesten-8-yl)-2-tosylpropanoic acid (220)**


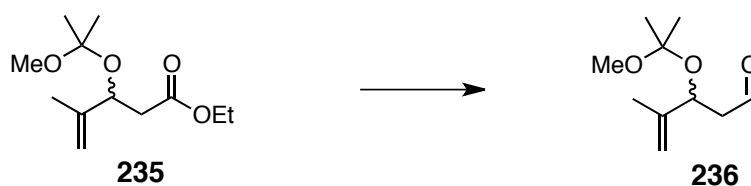
To **219** (500 mg, 1.05 mmol, 1 equiv) in CH<sub>3</sub>CN (3.5 mL) was added Et<sub>3</sub>N (176  $\mu$ L, 1.26 mmol, 1.2 equiv) and BSA (773  $\mu$ L, 3.16 mmol, 3 equiv). The mixture was heated to 60 °C and stirred for 30 min. The mixture was then diluted with EtOAc (20 mL) and washed with 2 N HCl (5 mL), then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petrol + 10 % MeOH + 1 % AcOH) afforded a 2:1 mixture of C-Ts epimers of **220** as a white foamy solid (423 mg, 85 %); *R*<sub>f</sub> 0.70 (15 % EtOAc in petrol + 10% MeOH + 1 % AcOH); mp 58-60 °C;  $\nu_{\text{max}}$  (film) 3419, 2955, 1732, 1598, 1468, 1381, 1322, 1149, 1086 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.81 (2H, m, *o*-Ts), 7.37 (2H, m, *m*-Ts) 5.30 (1H, s, H-9 major), 5.26 (1H, s, H-9 minor), 4.12 (1H, m, CHTs major), 4.08 (1H, m, CHTs minor); 2.47 (3H, s, CH<sub>3</sub>Ar), 2.71–2.44 (2H, m), 2.10–1.81 (5H, m), 1.64–0.90 (13H, m), 0.92 (3H, d, *J* 6.5 Hz, H-21), 0.90 (3H, d, *J* 2.0 Hz, H-26/27), 0.88 (3H, d, *J* 2.0 Hz, H-26/27), 0.62 (3H, s, H-18);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 170.0 (CO), 145.6 (Ar), 133.9 (Ar), 132.8 (C-8 major), 132.3 (C-8 minor), 129.8 (*m*-Ts), 128.4 (*o*-Ts), 124.3 (C-9 major), 123.3 (C-9 minor), 69.8 (CH-Ts), 54.3, 51.1, 49.4, 42.4, 42.3, 36.1, 35.8, 32.9, 31.5, 28.2, 28.0, 24.6, 23.8, 22.8, 22.5, 21.7 (CH<sub>3</sub>Ar), 18.7 (C-21), 11.1 (C-18); *m/z* (CI) 448 [M-CO<sub>2</sub>+NH<sub>4</sub>]<sup>+</sup>, 174 (Found C, 70.74; H, 8.84%. C<sub>28</sub>H<sub>42</sub>O<sub>4</sub>S requires C, 70.85; H, 8.92%).

**(±)-Ethyl 3-hydroxy-4-methylpent-4-enoate (234)**

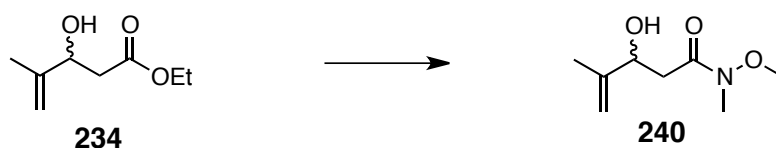
To a stirred solution of diisopropylamine (10.6 mL, 75.8 mmol, 1.2 equiv) in THF (60 mL) at  $-78\text{ }^{\circ}\text{C}$  was added *n*-BuLi (29.6 mL, 2.25 M in hexanes, 66.7 mmol, 1.1 equiv) dropwise. After 15 min EtOAc (6.50 mL, 66.70 mmol, 1.1 equiv) was added dropwise. After a further 30 min methacrolein (**233**) (5.00 mL, 60.64 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred for 90 min, allowing it to warm to  $-30\text{ }^{\circ}\text{C}$ , before being poured onto an ice-cold mixture of sat.  $\text{NH}_4\text{Cl}$  (100 mL) and EtOAc (200 mL). After 10 min vigorous stirring the organic layer was separated, and the aqueous layer further extracted with EtOAc (2 x 100 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated under reduced pressure to give a yellow oil which was distilled under reduced pressure to give **234** (9.42 g, 98 %) as a colourless oil;  $R_f$  0.45 (10 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 3459, 2982, 1738, 1651, 1372, 1163, 1023  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 5.03 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.88 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.48 (1H, m,  $\text{CHOH}$ ), 4.18 (2H, q,  $J$  7.0 Hz,  $\text{CH}_2\text{O}$ ), 3.05 (1H, br s, OH), 2.57 (2H, m,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 1.76 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ ), 1.28 (3H, t,  $J$  7.0 Hz,  $\text{CH}_3\text{CH}_2$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 172.6 (CO), 145.5 ( $\text{C}=\text{CH}_2$ ), 111.4 ( $\text{C}=\text{CH}_2$ ), 71.6 ( $\text{CHOH}$ ), 60.9 ( $\text{CH}_2\text{O}$ ), 40.2 ( $\text{CH}_2\text{CO}_2\text{Et}$ ), 18.3 ( $\text{CH}_3\text{C}=\text{C}$ ), 14.3 ( $\text{CH}_3\text{CH}_2$ );  $m/z$  (CI) 334, 246, 176  $[\text{M}+\text{NH}_4]^+$ , 159  $[\text{M}+\text{H}]^+$ , 141. In agreement with published data.<sup>6</sup>

**(±)-Ethyl 3-(2-methoxy-2-propyloxy)-4-methylpent-4-enoate (235)**

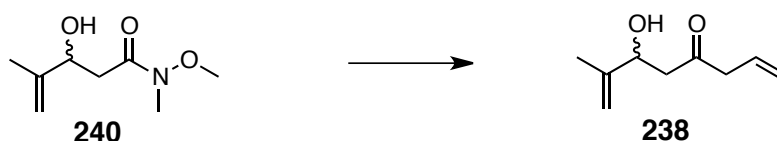
To **234** (1.00 g, 6.32 mmol, 1 equiv) in 2-methoxypropene (32 mL) at 0 °C was added PPTS. The reaction was allowed to warm to rt and stirred for 90 min. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and washed with water (50 mL) and brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Silica gel chromatography (5 % EtOAc in petrol) gave **235** as a colourless oil (1.24 g, 85 %); *R<sub>f</sub>* 0.80 (10 % EtOAc in petrol); *v*<sub>max</sub> (film) 2988, 2943, 1739, 1651, 1446, 1372, 1209, 1156, 1075, 1030 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 4.96 (1H, s, C=CH<sub>2</sub>), 4.84 (1H, s, C=CH<sub>2</sub>), 4.48 (1H, t, *J* 7.0 Hz, CHOMIP), 4.12 (2H, dq, *J* 7.0, 2.0 Hz, CH<sub>2</sub>O), 3.18 (3H, s, CH<sub>3</sub>O), 2.55 (2H, m, CH<sub>2</sub>CO<sub>2</sub>Et), 1.76 (3H, s, CH<sub>3</sub>C=C), 1.36 (3H, s, Me), 1.33 (3H, s, Me), 1.26 (3H, t, *J* 7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 171.0 (CO), 145.9 (C=CH<sub>2</sub>), 112.4 (C=CH<sub>2</sub>), 101.1 (C(CH<sub>3</sub>)<sub>2</sub>OMe), 72.0 (CHOMIP), 60.4 (CH<sub>2</sub>O), 49.3 (CH<sub>3</sub>O), 41.2 (CH<sub>2</sub>CO<sub>2</sub>Et), 25.2 (Me), 25.0 (Me), 17.1 (CH<sub>3</sub>C=C), 14.2 (CH<sub>3</sub>CH<sub>2</sub>).

**(±)-Ethyl 3-(2-methoxy-2-propyloxy)-4-methylpent-4-enal (236)**

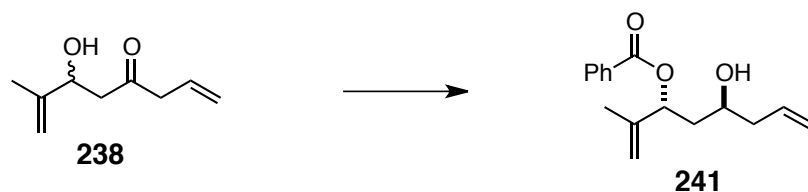
To **235** (250 mg, 1.09 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at  $-78^\circ\text{C}$  was added DIBAL-H (0.95 mL, 1.2 M in PhMe, 1.14 mmol, 1.05 equiv). After stirring for at  $-78^\circ\text{C}$  for 1 h the reaction mixture was poured into Rochelle's salt (10 mL).  $\text{Et}_2\text{O}$  (20 mL) and  $\text{H}_2\text{O}$  (3 mL) were added. The resultant biphasic mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer was further extracted with  $\text{Et}_2\text{O}$  (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give **236** as a colourless oil (175 mg, 86 %). No further purification required;  $R_f$  0.65 (10 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 2991, 2946, 1730, 1458, 1382, 1374, 1262, 1210, 1184, 1150, 1075, 1059, 1034  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 9.76 (1H, s, CHO), 5.05 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.90 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.68 (1H, t,  $J$  6.0 Hz, CHOMIP), 3.20 (3H, s,  $\text{CH}_3\text{O}$ ), 2.60 (2H, m,  $\text{CH}_2\text{CHO}$ ), 1.77 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ ), 1.38 (3H, s, Me), 1.34 (3H, s, Me);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 201.6 (CHO), 145.9 ( $\text{C}=\text{CH}_2$ ), 112.2 ( $\text{C}=\text{CH}_2$ ), 101.4 ( $\text{C}(\text{CH}_3)_2\text{OMe}$ ), 70.0 (CHOMIP), 49.4 ( $\text{CH}_3\text{O}$ ), 48.6 ( $\text{CH}_2\text{CHO}$ ), 25.2 (Me), 24.9 (Me), 17.8 ( $\text{CH}_3\text{C}=\text{C}$ ).

**(±)-3-Hydroxy-*N*-methoxy-*N*,4-dimethylpent-4-enamide (240)**

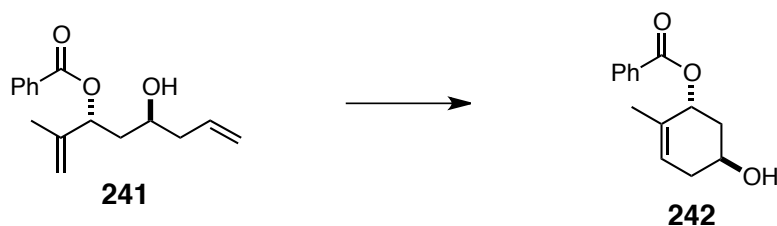
To **234** (5.00 g, 31.6 mmol, 1 equiv) and *N,O*-dimethylhydroxylamine hydrochloride (9.21 g, 94.8 mmol, 3 equiv) in THF (160 mL) at  $-30\text{ }^{\circ}\text{C}$  was added *i*-PrMgCl (94.0 mL, 2 M in THF, 188.0 mmol, 5.95 equiv) dropwise. The reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 3 h before being poured into sat.  $\text{NH}_4\text{Cl}$  (100 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 200 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Silica gel chromatography (20–50% EtOAc in petrol) gave **240** as a colourless oil (3.59 g, 66 %);  $R_f$  0.35 (50 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 3430, 2972, 2942, 1651, 1443, 1389, 1179, 1106, 998  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 5.07 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.90 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.49 (1H, m,  $\text{CHOH}$ ), 3.88 (1H, d,  $J$  3.0 Hz, OH), 3.71 (3H, s,  $\text{OCH}_3$ ), 3.22 (3H, s,  $\text{NCH}_3$ ), 2.66 (2H, m,  $\text{CH}_2$ ), 1.79 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 173.6 (CO), 145.8 ( $\text{C}=\text{CH}_2$ ), 111.2 ( $\text{C}=\text{CH}_2$ ), 71.3 ( $\text{CHOH}$ ), 61.3 ( $\text{OCH}_3$ ), 36.9 ( $\text{NCH}_3$ ), 31.9 ( $\text{CH}_2$ ), 18.5 ( $\text{CH}_3\text{C}=\text{C}$ ).  $m/z$  (CI) 191  $[\text{M}+\text{NH}_4]^+$ , 174  $[\text{M}+\text{H}]^+$ , 156 (Found  $[\text{M}+\text{H}]^+$ , 174.1131.  $\text{C}_8\text{H}_{15}\text{NO}_3$  requires  $[\text{M}+\text{H}]^+$ , 174.1130).

**(±)-6-Hydroxy-7-methyl-1,7-octadien-4-one (238)**

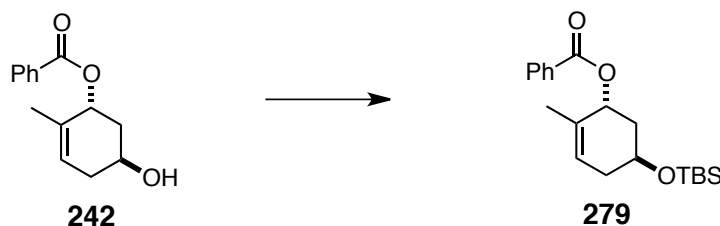
To **240** (300 mg, 1.73 mmol, 1 equiv) in THF (17 mL) at 0 °C was added allylmagnesium chloride (1.73 mL, 2 M in THF, 3.46 mmol, 2 equiv) dropwise. The mixture was stirred at 0 °C for 30 min, then rt for 2 h before being poured into sat.  $\text{NH}_4\text{Cl}$  (20 mL), the organic layer was separated and the aqueous layer was further extracted with DCM (6 x 20 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give **238** as a yellow oil (243 mg, 91 %). No further purification;  $R_f$  0.30 (10 % EtOAc in petrol),  $\nu_{\text{max}}$  (film) 3427, 2975, 2921, 1713, 1652, 1393, 1080  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 6.00–5.89 (1H, m,  $\text{CH}=\text{CH}_2$ ), 5.27–5.15 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.04 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.89 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.54 (1H, t,  $J$  6.0 Hz,  $\text{CHOH}$ ), 3.25 (2H, d,  $J$  6.0 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 2.92 (1H, bs, OH), 2.71 (2H, d,  $J$  6.0 Hz,  $\text{CH}_2\text{C}=\text{O}$ ), 1.77 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 209.2 (CO), 145.6 ( $\text{C}=\text{CH}_2$ ), 129.2 ( $\text{CH}=\text{CH}_2$ ), 119.4 ( $\text{CH}=\text{CH}_2$ ), 111.3 ( $\text{C}=\text{CH}_2$ ), 71.0 ( $\text{CHOH}$ ), 48.5 ( $\text{CH}_2\text{C}=\text{C}$ ), 47.2 ( $\text{CH}_2\text{CO}$ ), 18.3 ( $\text{CH}_3\text{C}=\text{C}$ ).  $m/z$  (CI) 172  $[\text{M}+\text{NH}_4]^+$ , 155  $[\text{M}+\text{H}]^+$ , 137 (Found  $[\text{M}+\text{H}]^+$ , 155.1071.  $\text{C}_9\text{H}_{14}\text{O}_2$  requires  $[\text{M}+\text{H}]^+$ , 155.1072).

**(±)-5-Hydroxy-2-methyl-1,7-octadien-3-yl benzoate (241)**

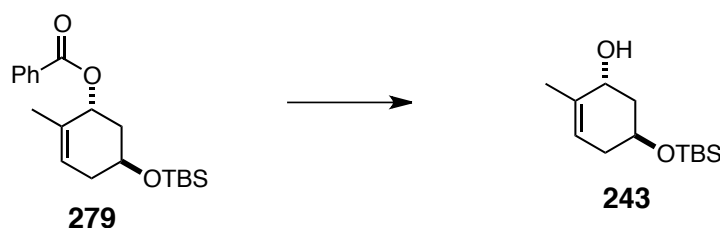
To crude **238** (90 mg, 0.58 mmol, 1 equiv) in THF (1.7 mL) was added benzaldehyde (240  $\mu$ L, 2.33 mmol, 4 equiv). The mixture was cooled to  $-10\text{ }^{\circ}\text{C}$  and  $\text{SmI}_2$  (1.9 mL, 0.1 M in THF, 0.19 mmol, 0.3 equiv) was added over 2 min. The reaction mixture was stirred at  $-10\text{ }^{\circ}\text{C}$  for 30 min. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (10 mL) and washed with sat.  $\text{NaHCO}_3$  (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Silica gel chromatography (5–10 %  $\text{EtOAc}$  in petrol) gave **241** as a yellow oil (57 mg, 38 %, >99:1 *anti/syn*);  $R_f$  0.50 (10 %  $\text{EtOAc}$  in petrol);  $\nu_{\text{max}}$  (film) 3489, 307600, 2920, 1719, 1654, 1451, 1315, 1269, 1111, 1070  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 8.12–8.06 (2H, m, *o*-Ph), 7.65–7.58 (1H, m, *p*-Ph), 7.53–7.45 (2H, m, *m*-Ph), 5.92–5.80 (1H, m,  $\text{CH}=\text{CH}_2$ ), 5.73 (1H, dd,  $J$  10.5 Hz, 3.0 Hz,  $\text{CHOBz}$ ), 5.16 (1H, s,  $\text{CH}=\text{CH}_2$ ), 5.14 (1H, s,  $\text{CH}=\text{CH}_2$ ), 5.12 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.96 (1H, s,  $\text{C}=\text{CH}_2$ ), 3.78–3.68 (1H, m,  $\text{CHOH}$ ), 2.79 (1H, d,  $J$  3.5 Hz, OH), 2.33–2.27 (2H, m,  $\text{CH}_2$ ), 2.02–1.78 (2H, m,  $\text{CH}_2\text{C}=\text{C}$ ), 1.88 (3H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 166.6 (CO), 143.5 ( $\text{C}=\text{CH}_2$ ), 134.6 ( $\text{CH}=\text{CH}_2$ ), 133.2 (*p*-Ph), 130.0 (*ipso*-Ph), 129.7 (*o*-Ph), 128.5 (*m*-Ph), 117.9 ( $\text{CH}=\text{CH}_2$ ), 112.6 ( $\text{C}=\text{CH}_2$ ), 74.9 ( $\text{CHOBz}$ ), 66.8 ( $\text{CHOH}$ ), 41.8 ( $\text{CH}_2\text{C}=\text{C}$ ), 40.9 ( $\text{CH}_2$ ), 18.7 ( $\text{CH}_3\text{C}=\text{C}$ ).  $m/z$  (CI) 278  $[\text{M}+\text{NH}_4]^+$ , 261  $[\text{M}+\text{H}]^+$ , 243, 230 (Found  $[\text{M}+\text{H}]^+$ , 261.1493.  $\text{C}_{16}\text{H}_{20}\text{O}_3$  requires  $[\text{M}+\text{H}]^+$ , 261.1491).

**(±)-5-Hydroxy-2-methylcyclohex-2-enyl benzoate (242)**

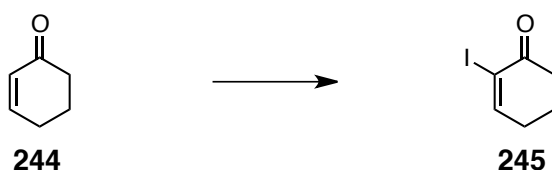
To **241** (100 mg, 0.38 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) was added Grubbs 2<sup>nd</sup> generation catalyst (16 mg, 0.019 mmol, 0.05 equiv). The reaction mixture was heated to 40 °C for 2 h, before being cooled, filtered through Celite® and concentrated under reduced pressure. Purification by silica gel chromatography (10% EtOAc in petrol) afforded **242** as a brown oil (95 mg, >99 %); *R*<sub>f</sub> 0.20 (15 % EtOAc in petrol); *v*<sub>max</sub> (film) 3416, 2920, 1715, 1452, 1338, 1316, 1269, 1110, 1025 cm<sup>-1</sup>; *δ*<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 8.10–8.04 (2H, m, *o*-Ph), 7.61–7.55 (1H, m, *p*-Ph), 7.50–7.42 (2H, m, *m*-Ph), 5.69–5.61 (2H, m, C=CH + CHOBz), 4.23–4.11 (1H, m, CHOH), 2.57–2.47 (1H, m, ring CH<sub>2</sub>), 2.24–2.16 (1H, m, ring CH<sub>2</sub>), 2.11–2.00 (1H, m, ring CH<sub>2</sub>), 1.99–1.89 (1H, m, ring CH<sub>2</sub>), 1.77 (1H, bs, OH), 1.76 (3H, s, CH<sub>3</sub>); *δ*<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 166.2 (CO), 133.0 (*p*-Ph), 131.8 (C=CH), 130.5 (*ipso*-Ph), 129.6 (*o*-Ph), 128.4 (*m*-Ph), 125.1 (CH=C), 71.9 (CHOBz), 64.4 (CHOH), 37.8 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>), 20.2 (CH<sub>3</sub>); *m/z* (CI) 482, 360, 250 [M+NH<sub>4</sub>]<sup>+</sup> (Found [M+H]<sup>+</sup>, 233.1181. C<sub>14</sub>H<sub>16</sub>O<sub>3</sub> requires [M+H]<sup>+</sup>, 233.1177).

**(±)-5-(*Tert*-butyldimethylsilyloxy)-2-methylcyclohex-2-enyl benzoate (**279**)**

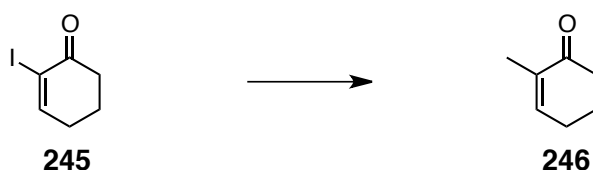
To **242** (95 mg, 0.41 mmol, 1 equiv) in DMF (0.5 mL) at 0 °C was added imidazole (70 mg, 1.02 mmol, 2.5 equiv) followed, after 5 min, by *tert*-butyldimethylsilylchloride (74 mg, 0.49 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 3 h then diluted with Et<sub>2</sub>O (25 mL), washed with H<sub>2</sub>O (4x10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded **279** as a colourless oil (117 mg, 82 %); *R*<sub>f</sub> 0.65 (20 % EtOAc in petrol); *v*<sub>max</sub> (film) 2954, 2928, 2857, 1717, 1264, 1098 cm<sup>-1</sup>; *δ*<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 8.11–8.05 (2H, m, *o*-Ph), 7.61–7.55 (1H, m, *p*-Ph), 7.50–7.43 (2H, m, *m*-Ph), 5.67–5.60 (2H, m, C=CH + CHOBz), 4.21–4.12 (1H, m, CHOTBS), 2.45–2.35 (1H, m, ring CH<sub>2</sub>), 2.14–2.00 (2H, m, ring CH<sub>2</sub>), 1.99–1.88 (1H, m, ring CH<sub>2</sub>), 1.75 (3H, s, CH<sub>3</sub>C=C), 0.90 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.08 (6H, s, Si(CH<sub>3</sub>)<sub>2</sub>); *δ*<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 166.2 (CO), 132.9 (*p*-Ph), 131.6 (C=CH), 130.6 (*ipso*-Ph), 129.6 (*o*-Ph), 128.3 (*m*-Ph), 125.8 (CH=C), 72.4 (CHOBz), 65.0 (CHOTBS), 38.3 (CH<sub>2</sub>), 35.3 (CH<sub>2</sub>), 25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 20.3 (CH<sub>3</sub>C=C), 18.2 (C(CH<sub>3</sub>)<sub>3</sub>), -4.70 (SiCH<sub>3</sub>), -4.74 (SiCH<sub>3</sub>); *m/z* (ESI) 347 [M+H]<sup>+</sup>, 328, 300, 284 (Found [M+H]<sup>+</sup>, 347.2038. C<sub>20</sub>H<sub>30</sub>O<sub>3</sub>Si requires [M+H]<sup>+</sup>, 347.2032).

**(±)-5-(*Tert*-butyldimethylsilyloxy)-2-methylcyclohex-2-enol (**243**)**

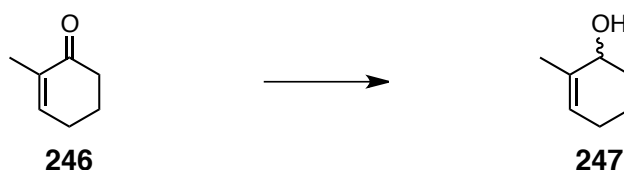
To **279** (117 mg, 0.34 mmol, 1 equiv) in MeOH (0.5 mL) at 0 °C was added KOH (28 mg, 0.51 mmol, 1.5 equiv). The reaction was allowed to warm to rt and stirred overnight. 1 N HCl (3 mL) was added and the reaction mixture diluted with Et<sub>2</sub>O (10 mL). The aqueous layer was separated and further extracted with Et<sub>2</sub>O (2 x 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure before purification by silica gel chromatography (20 % EtOAc in petrol) afforded **243** as a colourless oil (77 mg, 93 %); *R*<sub>f</sub> 0.20 (10 % EtOAc in petrol); *v*<sub>max</sub> (film) 3319, 2928, 2857, 1472, 1463, 1447, 1376, 1252, 1101 cm<sup>-1</sup>; *δ*<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 5.37–5.32 (1H, m, CH=C), 4.09–4.02 (1H, m, *CHOH*), 4.02–3.93 (1H, m, *CHOTBS*), 2.26–2.16 (1H, m, ring CH<sub>2</sub>), 1.92–1.81 (2H, m, ring CH<sub>2</sub>), 1.74–1.64 (1H, m, ring CH<sub>2</sub>), 1.71 (3H, s, CH<sub>3</sub>C=C), 1.42 (1H, d, *J* 6.0 Hz, OH), 0.82 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.01 (3H, s, SiCH<sub>3</sub>), 0.00 (3H, s, SiCH<sub>3</sub>); *δ*<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 134.8 (C=CH), 123.1 (C=CH), 69.6 (*CHOH*), 64.6 (*CHOTBS*), 41.3 (CH<sub>2</sub>), 35.5 (CH<sub>2</sub>), 25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 20.3 (CH<sub>3</sub>C=C), –4.61 (SiCH<sub>3</sub>), –4.66 (SiCH<sub>3</sub>); *m/z* (CI) 260 [M+NH<sub>4</sub>]<sup>+</sup>, 242 [M]<sup>+</sup>, 225, 202, 185 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 260.2046. C<sub>13</sub>H<sub>26</sub>O<sub>2</sub>Si requires [M+NH<sub>4</sub>]<sup>+</sup>, 260.2051).

**2-Iodo-2-cyclohexenone (245)**

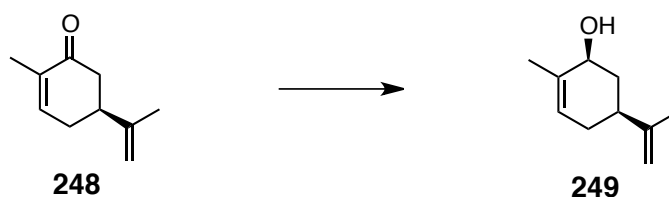
To Et<sub>2</sub>O (40 mL) and pyridine (40 mL) at rt was added I<sub>2</sub> (27.7 g, 109.2 mmol, 2.1 equiv) slowly. After allowing the resulting dark brown mixture to stir for 20 min it was cooled to 0 °C before dropwise addition of 2-cyclohexen-1-one (**244**) (5.00 g, 52.0 mmol, 1 equiv). The reaction mixture was the allowed to stir at rt for 2 h before being diluted with Et<sub>2</sub>O (200 mL) and washed with 2 N HCl (2 x 100 mL), 20 % Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (3 x 100 mL) and brine (100 mL). The organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give a yellow solid. Recrystallisation (2:1 Et<sub>2</sub>O/pentane) afforded **245** as a pale yellow solid (3.60 g, 31 %); R<sub>f</sub> 0.35 (10 % EtOAc in petrol); mp 46–47 °C;  $\nu_{\text{max}}$  (film) 2932, 1676, 1583 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.80 (1H, t, *J* 4.5 Hz, C=CH), 2.70 (2H, m, CH<sub>2</sub>CO), 2.47 (2H, m, CH<sub>2</sub>CH=C), 2.12 (2H, m, CH<sub>2</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 192.2 (CO), 159.4 (C=CH), 103.9 (C=CI), 37.3 (CH<sub>2</sub>CO), 29.9 (CH<sub>2</sub>CH=C), 22.9 (CH<sub>2</sub>); *m/z* (ESI) 240 [M+NH<sub>4</sub>]<sup>+</sup>, 223 [M+H]<sup>+</sup>, 194, 114, 97. In agreement with published data.<sup>7</sup>

**2-Methyl-2-cyclohexenone (246)**

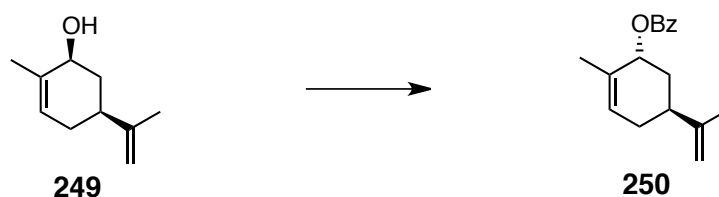
To 2-iodo-2-cyclohexenone (**245**) (500 mg, 2.25 mmol, 1 equiv), Fe(acac)<sub>3</sub> (40 mg, 0.11 mmol, 0.05 equiv) and *N*-methylpyrrolidone (2 mL) in THF (3 mL) at 15 °C was added methylmagnesium chloride (0.83 mL, 2.48 mmol, 1.1 equiv, 3M in THF) dropwise. After 1 h, 2 N HCl (5 mL) was added and the mixture extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layers were washed with sat. NaHCO<sub>3</sub> (10 mL) then brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give a brown oil. Purification by silica gel chromatography (5 % EtOAc in petrol) afforded **246** as a yellow oil (178 mg, 72 %); R<sub>f</sub> 0.50 (10 % EtOAc in petrol); δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 6.75 (1H, m, CH=CCH<sub>3</sub>), 2.42 (2H, m, CH<sub>2</sub>CO), 2.32 (2H, m, CH<sub>2</sub>C=C), 1.99 (2H, m, CH<sub>2</sub>), 1.77 (3H, s, CH<sub>3</sub>); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 200.1 (CO), 145.6 (C=CH), 135.7 (C=CCH<sub>3</sub>), 38.3 (CH<sub>2</sub>CO), 26.0 (CH<sub>2</sub>CH=C), 23.3 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>). In agreement with published data.<sup>8</sup>

**(±)-2-Methyl-2-cyclohexenol (251)**

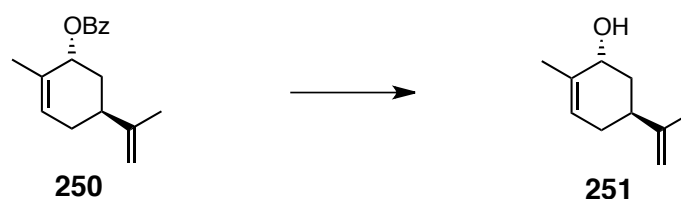
To 2-methyl-2-cyclohexenone (**246**) (360 mg, 3.27 mmol, 1 equiv) in MeOH (16 mL) at 0 °C was added NaBH<sub>4</sub> (136 mg, 3.60 mmol, 1.1 equiv). The reaction was stirred overnight at rt. H<sub>2</sub>O (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL) were added, and the mixture poured into brine (20 mL). The organic layer was separated, and the aqueous layer further extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Silica gel chromatography afforded **247** as a yellow oil (238 mg, 65 %); R<sub>f</sub> 0.25 (10 % EtOAc in petrol); ν<sub>max</sub> (film) 3563, 3523, 3386, 3060, 2989, 2923, 1469, 1452, 1284, 1242, 1227, 1161, 1030 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 5.52 (1H, m, CH=CCH<sub>3</sub>), 3.97 (1H, m, CHOH), 3.17 (1H, q, *J* 7.5 Hz, OH), 2.10–1.83 (2H, m, ring CH<sub>2</sub>), 1.81–1.32 (2H, m, ring CH<sub>2</sub>), 1.77 (3H, s, CH<sub>3</sub>); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 135.2 (C=CMe), 125.4 (C=CH), 68.4 (CHOH), 32.2 (CH<sub>2</sub>CHOH), 25.4 (CH<sub>2</sub>CH=C), 20.6 (CH<sub>2</sub>), 18.1 (CH<sub>3</sub>); *m/z* (CI) 130 [M+NH<sub>4</sub>]<sup>+</sup>. In agreement with published data.<sup>9</sup>

**(4*S*,6*S*)-(+)-Carveol (249)**

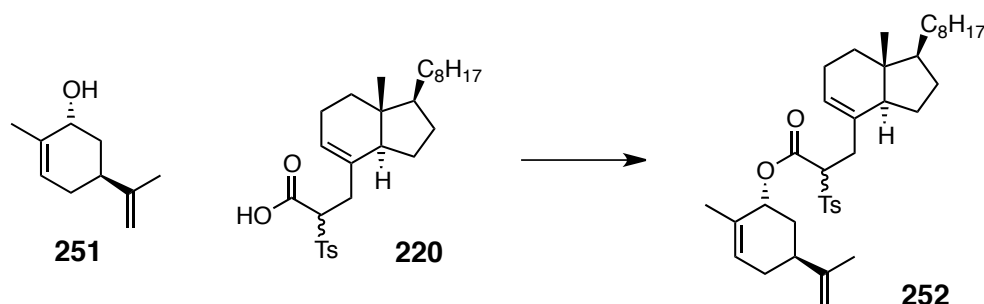
To  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (4.96 g, 13.3 mmol, 1 equiv) in MeOH (35 mL) was added (*S*)-carvone (**248**) (2.00 g, 13.3 mmol, 1 equiv), followed by slow portion-wise addition of  $\text{NaBH}_4$  (505 mg, 13.3 mmol, 1 equiv). After stirring for 10 min the reaction mixture was poured into  $\text{H}_2\text{O}$  (35 mL) and the mixture extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Silica gel chromatography (10 % EtOAc in petrol) gave **249** as a colourless oil (1.65 g, 82 %, 95:5 *syn/anti*);  $R_f$  0.45 (10 % EtOAc in petrol);  $[\alpha]_D^{25} +33.7$  ( $c$  1.16,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3325, 2920, 1645, 1453, 1438, 1038  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 5.61 (1H, m,  $\text{C}=\text{CH}$  *anti*), 5.52 (1H, m,  $\text{C}=\text{CH}$  *syn*), 4.75 (2H, s,  $\text{C}=\text{CH}_2$ ), 4.21, (1H, m,  $\text{CHOH}$  *syn*), 4.04 (1H, m,  $\text{CHOH}$  *anti*), 2.29 (1H, m, ring CH), 2.22–2.05 (2H, m, ring  $\text{CH}_2$ ), 2.03–1.93 (1H, m, ring  $\text{CH}_2$ ) 1.78 (3H, s,  $\text{CH}_3$ ), 1.76 (3H, s,  $\text{CH}_3$ ), 1.63 (1H, bs, OH), 1.58–1.47 (1H, m, ring  $\text{CH}_2$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 149.0 ( $\text{C}=\text{CH}_2$ ), 136.2 ( $\text{C}=\text{CH}$ ), 123.9 ( $\text{C}=\text{CH}$ ), 109.2 ( $\text{C}=\text{CH}_2$ ), 70.9 ( $\text{CHOH}$ ), 40.4 (ring CH), 38.0 (ring  $\text{CH}_2$ ), 31.0 (ring  $\text{CH}_2$ ), 20.7 ( $\text{CH}_3$ ), 19.0 ( $\text{CH}_3$ );  $m/z$  (CI) 152  $[\text{M}]^+$ , 135  $[\text{M}-\text{OH}]^+$ . In agreement with published data.<sup>10</sup>

**(4*S*,6*R*)-(+)-Carvyl benzoate (250)**

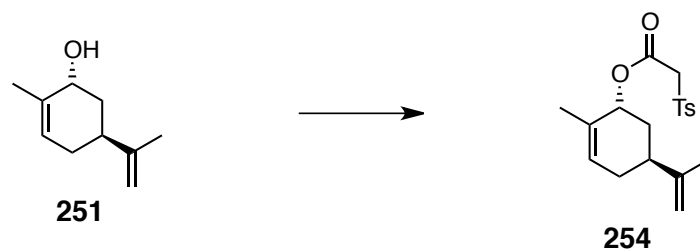
To **249** (1.00 g, 6.56 mmol, 1 equiv), benzoic acid (2.41 g, 19.7 mmol, 3 equiv) and  $\text{PPh}_3$  (5.17 g, 19.7 mmol, 3 equiv) in THF (50 mL) at 0 °C was added DIAD (3.91 mL, 19.7 mmol, 3 equiv) dropwise. The reaction mixture was stirred for 20 h at rt before diluting with  $\text{Et}_2\text{O}$  (150 mL), and washing with sat.  $\text{NaHCO}_3$  (2 x 50 mL). The combined aqueous layers were then further extracted with  $\text{Et}_2\text{O}$  (100 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. To the resulting orange oil was added 50%  $\text{Et}_2\text{O}$  in petrol (20 mL) and the resultant precipitate removed by filtration. The filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (5 %  $\text{EtOAc}$  in petrol) afforded **250** as a yellow oil (1.69 g, >99%, 9:1 *anti/syn*);  $R_f$  0.45 (10 %  $\text{Et}_2\text{O}$  in petrol);  $[\alpha]_D^{25} +14.1$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2918, 1715, 1644, 1602, 1451, 1268, 1109, 1025  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 8.10 (2H, d,  $J$  7.5 Hz, *o*-Ph), 7.59 (1H, dd,  $J$  7.5, 7.5 Hz, *p*-Ph), 7.47 (2H, dd,  $J$  7.5, 7.5 Hz, *m*-Ph), 5.82 (1H, m,  $\text{C}=\text{CH}$  *anti*), 5.73 (1H, m,  $\text{C}=\text{CH}$  *syn*) 5.69 (1H, m,  $\text{CHOBz}$  *syn*), 5.54 (1H, m,  $\text{CHOBz}$  *anti*), 4.77 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.75 (1H, s,  $\text{C}=\text{CH}_2$ ), 2.45 (1H, m, ring CH), 2.34–2.24 (1H, m, ring  $\text{CH}_2$ ), 2.16–2.08 (1H, m, ring  $\text{CH}_2$ ), 2.00–1.89 (1H, m, ring  $\text{CH}_2$ ), 1.76 (6H, s,  $\text{CH}_3 \times 2$ ) 1.75 (1H, m, ring  $\text{CH}_2$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 166.4 (CO), 148.7 ( $\text{C}=\text{CH}_2$ ), 132.9 ( $\text{C}=\text{CH}$ ), 131.1 (*p*-Ph), 129.7 (*o*-Ph), 128.9 (*ipso*-Ph), 128.4 (*m*-Ph), 127.9 ( $\text{C}=\text{CH}$ ), 109.3 ( $\text{C}=\text{CH}_2$ ), 71.3 ( $\text{CHOBz}$ ), 36.0 (CH), 33.8 (ring  $\text{CH}_2$ ), 31.0 (ring  $\text{CH}_2$ ), 20.9 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ );  $m/z$  (CI) 408, 378, 274  $[\text{M}+\text{NH}_4]^+$ , 256  $[\text{M}]^+$ , 244, 152, 135 (Found  $[\text{M}+\text{NH}_4]^+$ , 274.1811.  $\text{C}_{17}\text{H}_{20}\text{O}_2$  requires  $[\text{M}+\text{NH}_4]^+$ , 274.1807).

**(4*S*,6*R*)-(+)-Carveol (251)**

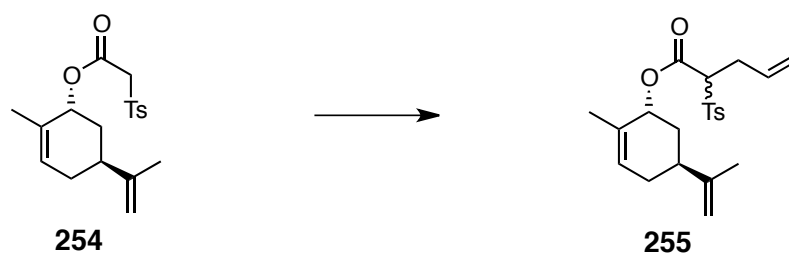
To **250** (500 mg, 1.95 mmol, 1 equiv) was added a methanolic solution of KOH (1.5 mL, 2 M, 2.92 mmol, 1.5 equiv). The mixture was stirred for 14 h at rt. The reaction was neutralized with 1 N HCl and extracted with Et<sub>2</sub>O (3 x 20 mL). The combined organic layers were washed with sat. NaHCO<sub>3</sub> (20 mL) and brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification of the crude oil by silica gel chromatography (5 % EtOAc in petrol) gave **251** as a colourless oil (239 mg, 81 %, 9:1 *anti/syn*); *R*<sub>f</sub> 0.45 (10 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +108.7 (*c* 0.87, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3326, 2915, 1645, 1440, 1055, 1032 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 5.61 (1H, m, CH=C *anti*), 5.52 (1H, m, CH=C *syn*), 4.77 (1H, s, C=CH<sub>2</sub>), 4.75 (1H, s, C=CH<sub>2</sub>) 4.22 (1H, m, CHOH *syn*), 4.05 (1H, m, CHOH *anti*), 2.35 (1H, m, CH), 2.22–2.11 (1H, m, ring CH<sub>2</sub>), 1.99–1.85 (2H, m, ring CH<sub>2</sub>), 1.82 (3H, s, CH<sub>3</sub>), 1.77 (3H, s, CH<sub>3</sub>), 1.63–1.57 (1H, m, ring CH<sub>2</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 149.2 (C=CH<sub>2</sub>), 134.3 (C=CH), 125.4 (C=CH), 109.1 (C=CH<sub>2</sub>), 68.6 (CHOH), 36.7 (ring CH), 35.2 (ring CH<sub>2</sub>), 31.0 (ring CH<sub>2</sub>), 20.9 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>); *m/z* (CI) 152 [M]<sup>+</sup>, 135 [M-OH]<sup>+</sup>. In agreement with published data.<sup>10</sup>

**(4*S*,6*R*)-Carvyl 3-(des-A,B-8(9)-cholesten-8-yl)-2-tosylpropanoate (**252**)**

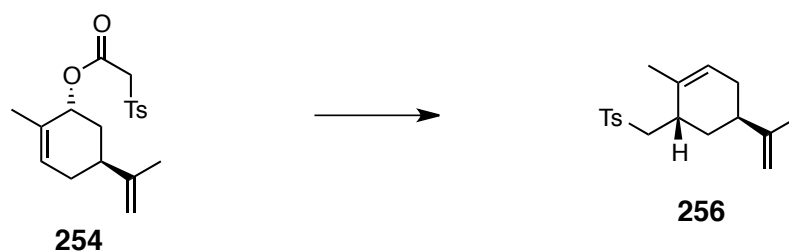
To **220** (192 mg, 0.40 mmol, 1 equiv) and **251** (62 mg, 0.40 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (1 mL) at rt was added DMAP (5 mg, 0.04 mmol, 0.1 equiv) followed by DIC (70  $\mu\text{L}$ , 0.44 mmol, 1.1 equiv). The reaction mixture was stirred for 4 days before being subjected directly to silica gel chromatography (5% EtOAc in petrol) to afford **252** as a colourless oil (130 mg, 54 %);  $R_f$  0.90 (15 % EtOAc in petrol;  $\nu_{\text{max}}$  (film) 2955, 1732, 1598, 1442, 1323, 1262, 1147, 1085, 1021  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.80–7.76 (2H, m, *o*-Ts), 7.40–7.33 (2H, m, *m*-Ts), 5.77 (1H, s,  $\text{CH}=\text{C}$  carveyl), 5.32–5.20 (2H, m,  $\text{CH-ester}$  + H-9), 4.81–4.66 (2H, m,  $\text{C}=\text{CH}_2$ ), 4.16–4.05 (1H, m,  $\text{CHTs}$ ), 2.75–2.50 (2H, m,  $\text{CH}$ ), 2.49–2.45 (3H, m,  $\text{CH}_3\text{Ar}$ ), 2.33–0.96 (23H, m), 1.75 (3H, s,  $\text{CH}_3\text{C}=\text{CH}_2$ ), 1.65 (3H, s,  $\text{CH}_3\text{C}=\text{CH}$ ), 0.96–0.87 (9H, m, H-21 + H-26/27), 0.67–0.61 (3H, m, H-18);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 165.5 (CO), 148.5 ( $\text{C}=\text{CH}_2$ ), 145.3 (Ar), 130.4 ( $\text{C}=\text{CH}$ ), 130.2 ( $\text{C}=\text{CH}$ ), 129.7 (*m*-Ts), 129.4 (*o*-Ts), 128.5 (Ar), 128.4 ( $\text{C}=\text{CH}$ ), 124.4 ( $\text{C}=\text{CH}$ ), 109.2 ( $\text{C}=\text{CH}_2$ ), 72.4 ( $\text{CH-ester}$ ), 69.7 ( $\text{CHTs}$ ), 54.3, 49.4, 42.3, 39.4, 36.1, 35.5, 33.4, 33.2, 30.9, 28.2, 28.0, 24.6, 24.5, 23.8, 22.8, 22.6, 21.7, 21.0, 20.2, 18.7, 11.2 (C-18);  $m/z$  (CI) 626  $[\text{M}+\text{NH}_4]^+$ , 448, 174, 152, 135 (Found  $[\text{M}+\text{NH}_4]^+$ , 626.4244.  $\text{C}_{38}\text{H}_{56}\text{O}_4\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 626.4243) (Found C, 75.06; H, 9.18%.  $\text{C}_{38}\text{H}_{56}\text{O}_4\text{S}$  requires C, 74.95; H, 9.27%).

**(4*S*,6*R*)-(+)-Carvyl 2-tosylacetate (**254**)**

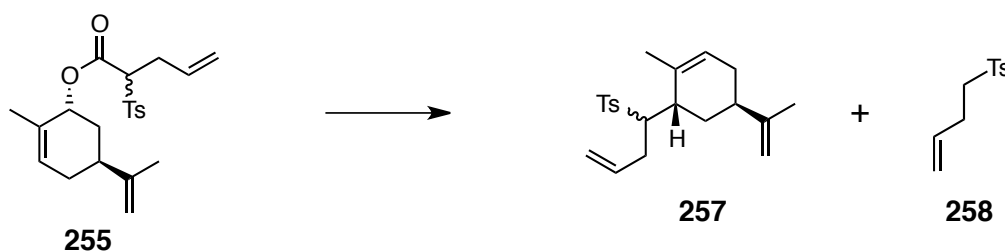
To **251** (500 mg, 3.28 mmol, 1 equiv) and 2-tosylacetic acid (704 mg, 3.28 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at rt was added DMAP 40 mg, 0.33 mmol, 0.1 equiv) then DIC (562  $\mu$ L, 3.61 mmol, 1.1 equiv) dropwise. The mixture was stirred for 20 min before filtering through Celite<sup>®</sup>, washing the solids with Et<sub>2</sub>O (20mL), and concentrating the filtrate under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded **254** as a colourless oil (1.00 g, 88 %, 10:1 *anti/syn*);  $R_f$  0.50 (10% EtOAc in petrol);  $[\alpha]_D^{25} +143.0$  ( $c$  1.54, CHCl<sub>3</sub>)  $\nu_{max}$  (film) 2954, 1733, 1466, 1598, 1441, 1325, 1141, 1085 cm<sup>-1</sup>;  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 7.83 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.37 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.77 (1H, m, C=CH *anti*), 5.62 (1H, m, C=CH *syn*), 5.44 (1H, m, CH-O *syn*), 5.27 (1H, m, CH-O *anti*), 4.77 (1H, m, C=CH<sub>2</sub> *anti*), 4.75 (1H, m, C=CH<sub>2</sub> *syn*), 4.69 (1H, m, C=CH<sub>2</sub>), 4.13 (2H, s, CH<sub>2</sub>Ts), 2.47 (3H, s, CH<sub>3</sub>Ar), 2.24-2.14 (2H, m, ring CH), 1.90-1.79 (2H, m, ring CH), 1.73 (3H, s, CH<sub>3</sub>), 1.68 (3H, s, CH<sub>3</sub>), 1.63–1.57 (1H, m, ring CH);  $m/z$  (CI) 366 [M+NH<sub>4</sub>]<sup>+</sup>, 152 [M-TsCH<sub>2</sub>CO<sub>2</sub>]<sup>+</sup>, 135 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 366.1739. C<sub>19</sub>H<sub>24</sub>O<sub>4</sub>S requires [M+NH<sub>4</sub>]<sup>+</sup>, 366.1739).

**(4*S*,6*R*)-(+)-Carvyl 2-tosylpenten-4-enoate (255)**

To **254** (300 mg, 0.86 mmol, 1 equiv), *n*-Bu<sub>4</sub>NI (318 mg, 0.86 mmol, 1 equiv) and DBU (258  $\mu$ L, 1.72 mmol, 2 equiv) in DMF (1.0 mL) was added a solution of allyl bromide (75  $\mu$ L, 0.86 mmol, 1 equiv) in DMF (2.5 mL) dropwise. After stirring at rt for 2 h the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with 1 N HCl (5 mL). The aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 mL), the combined organics dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (5-10 % EtOAc in petrol) afforded a 1:1 mixture of C-Ts epimers of **255** as a colourless oil (265 mg, 79 %); *R*<sub>f</sub> 0.70 (10 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 2968, 2919, 1732, 1644, 1598, 1441, 1327, 1239, 1176, 1148, 1086, 914 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.82–7.75 (2H, m, *o*-Ts), 7.40–7.34 (2H, m, *m*-Ts), 5.76 (1H, m, C=CH), 5.74–5.64 (1H, m, CH=CH<sub>2</sub>), 5.26 and 5.22 (1H, m, CH-O), 5.20–5.07 (2H, m, CH=CH<sub>2</sub>), 4.78–4.75 (1H, m, C=CH<sub>2</sub>), 4.72–4.67 (1H, m, C=CH<sub>2</sub>), 4.05 and 4.02 (1H, d, *J* 3.5 Hz, CH<sub>2</sub>Ts), 2.87–2.78 (1H, m, ring CH), 2.77–2.65 (1H, m, ring CH<sub>2</sub>), 2.47 and 2.46 (3H, s, CH<sub>3</sub>Ar), 2.27–2.13 (2H, m, ring CH), 1.93–1.82 (1H, m, ring CH), 1.73 (3H, s, CH<sub>3</sub>), 1.70–1.65 (2H, m, ring CH), 1.61 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 165.3 (CO), 148.4 (C=CH<sub>2</sub>), 145.5 (C=CH), 145.4 (C=CH), 131.7, 131.6, 130.1, 130.0, 129.8 (*m*-Ts), 129.4 (*o*-Ts), 128.8, 128.7, 119.1 and 119.0 (CH=C), 109.4 and 109.3 (C=CH<sub>2</sub>), 73.3 and 72.8 (CH-ester), 70.1 and 69.9 (CHTs), 35.6, 35.5, 33.4, 33.2, 31.2, 31.1, 30.8, 30.7, 21.7, 20.9, 20.7, 20.6, 20.5; *m/z* (CI) 406 [M+NH<sub>4</sub>]<sup>+</sup>, 252, 228, 174, 152, 135 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 406.2057. C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>S requires [M+NH<sub>4</sub>]<sup>+</sup>, 406.2052) (Found C, 68.16; H, 7.37%. C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>S requires C, 68.01; H, 7.26%).

**(4*R*,6*S*)-(-)-Limonen-6-yl tosylmethane (256)**

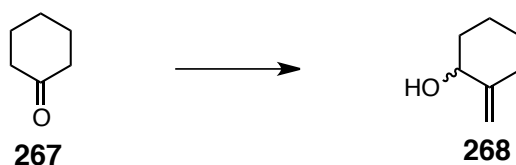
To **254** (100 mg, 0.29 mmol, 1 equiv) and KOAc (3 mg, 0.03 mmol, 0.1 equiv) in a capped microwave vial was added BSA (355  $\mu$ L, 1.45 mmol, 5 equiv). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for  $3 \times 1$  min (including a 1 min cooling period between each 1 min heating period). Purification of the crude reaction mixture by silica gel chromatography (10 % EtOAc in petrol) afforded **256** as a white solid (78 mg, 88 %, 9:1 *anti/syn*);  $R_f$  0.30 (5 % EtOAc in petrol); mp 89–91  $^{\circ}$ C;  $[\alpha]_D^{24}$   $-38.1$  ( $c$  0.70,  $\text{CHCl}_3$ );  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 7.83 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.38 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.55 (1H, m, C=CH *syn*), 5.48 (1H, m, C=CH *anti*), 4.73 (1H, m, C=CH<sub>2</sub>), 4.68 (1H, m, C=CH<sub>2</sub>), 3.13 (1H, m, TsCH<sub>2</sub>), 3.11 (1H, s, TsCH<sub>2</sub>), 2.62–2.56 (1H, m, ring CH), 2.47 (3H, s, CH<sub>3</sub>Ar), 2.12–2.00 (3H, m, ring CH), 1.91–1.81 (1H, m, ring CH), 1.70 (3H, s, CH<sub>3</sub>), 1.60–1.54 (1H, m, ring CH), 1.53 (3H, s, CH<sub>3</sub>);  $\delta_C$  ( $\text{CDCl}_3$ , 100 MHz) 148.7 (C=CH<sub>2</sub>), 144.6 (Ar), 136.8 (Ar), 132.8 (C=CH), 129.9 (*m*-Ts), 128.0 (*o*-Ts), 124.6 (C=CH), 109.1 (C=CH<sub>2</sub>), 58.3 (CH<sub>2</sub>Ts), 35.6, 34.4, 31.6, 30.6, 21.8 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>);  $m/z$  (CI) 322  $[\text{M}+\text{NH}_4]^+$ , 148 (Found  $[\text{M}+\text{NH}_4]^+$ , 322.1854.  $\text{C}_{18}\text{H}_{24}\text{O}_2\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 322.1841) (Found C, 71.14; H, 8.05%.  $\text{C}_{18}\text{H}_{24}\text{O}_2\text{S}$  requires C, 71.01; H, 7.95%).

**1-(4*R*,6*S*)-Limonen-6-yl-1-tosylbut-3-ene (257) and 4-tosylbut-1-ene (258)**


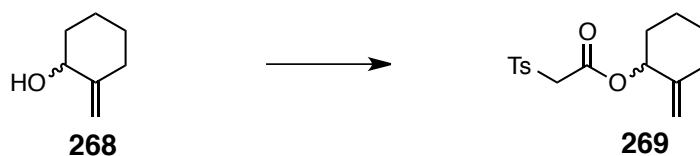
To **255** (80 mg, 0.21 mmol, 1 equiv) and KOAc (4 mg, 0.04 mmol, 0.2 equiv) in a capped microwave vial was added BSA (252  $\mu$ L, 1.03 mmol, 5 equiv). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for  $3 \times 1$  min (including a 1 min cooling period between each heating period). Purification of the crude reaction mixture by silica gel chromatography (5 % EtOAc in petrol) afforded **257** as a white solid (20 mg, 26 %) and **258** as a colourless oil (17 mg, 39 %).

Data for **257**:  $R_f$  0.40 (5 % EtOAc in petrol); mp 70–72  $^{\circ}$ C;  $\nu_{\max}$  (film) 2921, 1726, 1643, 1598, 1446, 1314, 1302, 1287, 1144, 1087  $\text{cm}^{-1}$ ;  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 7.83–7.77 (2H, m, *o*-Ts), 7.40–7.34 (2H, m, *m*-Ts), 5.75–5.46 (2H, m,  $\text{C}=\text{CH} + \text{CH}=\text{CH}_2$ ), 5.13–4.86 (2H,  $\text{CH}=\text{CH}_2$ ), 4.86–4.71 (1H,  $\text{C}=\text{CH}_2$ ), 4.71–4.65 (1H,  $\text{CH}=\text{CH}_2$ ), 3.50–3.38 and 3.18–3.10 (1H, m, CHTs), 3.02–1.19 (9H, m), 2.47 (3H, s,  $\text{CH}_3\text{Ar}$ );  $\delta_C$  ( $\text{CDCl}_3$ , 100 MHz) 148.8 (Ar), 144.5 ( $\text{C}=\text{CH}_2$ ), 135.3 and 135.1 ( $\text{CH}=\text{CH}_2$ ), 132.4 (Ar), 131.2 ( $\text{C}=\text{CH}$ ), 129.8 (*m*-Ts), 128.9 (*o*-Ts), 128.6 (Ar), 126.2 and 125.2 ( $\text{C}=\text{CH}$ ), 117.4 and 117.2 ( $\text{CH}=\text{CH}_2$ ), 109.3 and 109.1 ( $\text{C}=\text{CH}_2$ ), 68.2 and 65.7 (CHTs), 40.8 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 37.4, 37.2, 36.4, 33.3, 31.3, 30.4, 29.5, 29.4, 29.0, 27.3, 23.4, 21.7, 21.5, 21.4 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ );  $m/z$  (CI) 362  $[\text{M}+\text{NH}_4]^+$ , 240 (Found  $[\text{M}+\text{NH}_4]^+$ , 362.2148.  $\text{C}_{21}\text{H}_{28}\text{O}_2\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 362.2154).

Data for **258**:  $R_f$  0.20 (5 % EtOAc in petrol);  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 7.81 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.39 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.81–5.68 (1H, m,  $\text{CH}=\text{CH}_2$ ), 5.11–5.02 (2H, m,  $\text{CH}=\text{CH}_2$ ), 3.20–3.13 (2H, m,  $\text{CH}_2\text{Ts}$ ), 2.51–2.43 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 2.48 (3H, s,  $\text{CH}_3\text{Ar}$ );  $\delta_C$  ( $\text{CDCl}_3$ , 100 MHz) 144.8 (Ar), 136.0 (Ar), 133.9 ( $\text{CH}=\text{CH}_2$ ), 130.0 (*m*-Ts), 128.1 (*o*-Ts), 117.1 ( $\text{CH}=\text{CH}_2$ ), 55.5 ( $\text{CH}_2\text{Ts}$ ), 27.0 ( $\text{CH}_3\text{Ar}$ ), 21.7 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ).

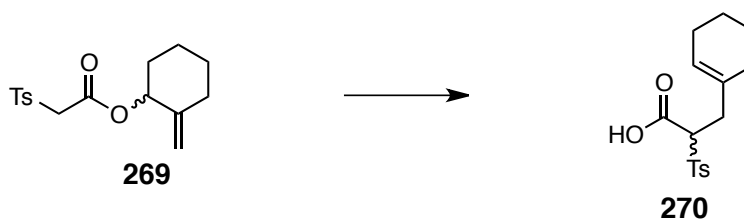
**2-Methylenecyclohexanol (268)**

To KOH (1.85 g, 46.3 mmol, 3 equiv) in DMSO (30 mL) at rt was added cyclohexanone (**267**) (1.60 mL, 15.4 mmol, 1 equiv). The mixture was heated to 110 °C for 90 min. The reaction mixture was cooled, diluted with Et<sub>2</sub>O (200 mL) and washed with 1 N HCl (3 x 30 mL). The aqueous layer was further extracted with Et<sub>2</sub>O (100 mL), the combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded **268** as an orange oil (697 mg, 40 %); *R<sub>f</sub>* 0.50 (15 % EtOAc in petrol); *v*<sub>max</sub> (film) 3552, 2934, 1858, 1655, 1448, 1344, 1288, 1080, 897 cm<sup>-1</sup>; *δ*<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 4.91 (1H, s, C=CH<sub>2</sub>), 4.78 (1H, s, C=CH<sub>2</sub>), 4.15–4.09 (CHOH), 2.48–2.38 (1H, m, ring CH), 2.09–1.95 (2H, m, ring CH), 1.88–1.78 (1H, m, ring CH), 1.72–1.58 (2H, m, ring CH and OH), 1.55–1.34 (3H, m, ring CH); *δ*<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 151.6 (C=CH<sub>2</sub>), 105.0 (C=CH<sub>2</sub>), 72.6 (CHOH), 36.7 (ring CH<sub>2</sub>), 33.5 (ring CH<sub>2</sub>), 27.7 (ring CH<sub>2</sub>), 23.8 (ring CH<sub>2</sub>); *m/z* (CI) 175, 130 [M+NH<sub>4</sub>]<sup>+</sup>, 112 [M]<sup>+</sup>, 95 [M-H<sub>2</sub>O]<sup>+</sup>, 52 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 130.1235. C<sub>7</sub>H<sub>12</sub>O requires [M+NH<sub>4</sub>]<sup>+</sup>, 130.1232). In agreement with published data.<sup>11</sup>

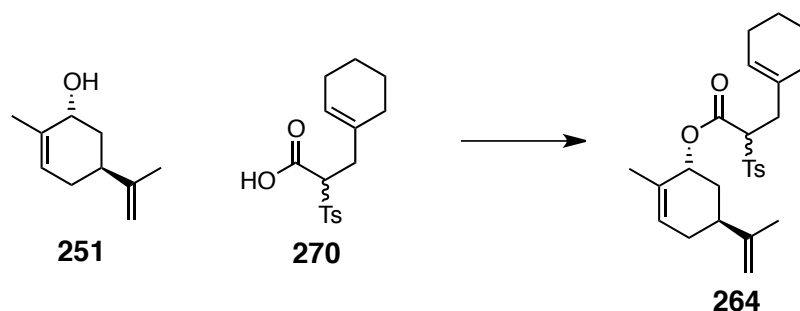
**2-Methylenecyclohexyl 2-tosylacetate (269)**

To **268** (200 mg, 1.78 mmol, 1 equiv) and 2-tosylacetic acid (382 mg, 1.78 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (6 mL) at 0 °C was added DMAP (22 mg, 0.18 mmol, 0.1 equiv) then DIC (305  $\mu\text{L}$ , 1.96 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 1 h then filtered through Celite®. The solids were washed with  $\text{Et}_2\text{O}$  (20 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded **269** as a colourless oil (511 mg, 93 %);  $R_f$  0.40 (15 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 2939, 1739, 1658, 1598, 1448, 1402, 1330, 1278, 1157, 1086  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.84 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.38 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.26–5.21 (1H, m, CH-O), 4.82 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.80 (1H, s,  $\text{C}=\text{CH}_2$ ), 4.15 (2H, s,  $\text{CH}_2\text{Ts}$ ), 2.48 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.36–2.27 (1H, m, ring  $\text{CH}_2$ ), 2.13–2.04 (1H, m, ring  $\text{CH}_2$ ), 1.85–1.45 (6H, m, ring  $\text{CH}_2$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 161.6 (CO), 145.4 ( $\text{C}=\text{CH}_2$ ), 145.1 (Ar), 135.7 (Ar), 129.9 (*m*-Ts), 128.6 (*o*-Ts), 108.9 ( $\text{C}=\text{CH}_2$ ), 76.6 (CH-O), 61.3 ( $\text{CH}_2\text{Ts}$ ), 32.9 (ring  $\text{CH}_2$ ), 32.8 (ring  $\text{CH}_2$ ), 27.2 (ring  $\text{CH}_2$ ), 22.7 (ring  $\text{CH}_2$ ), 21.7 ( $\text{CH}_3\text{Ar}$ );  $m/z$  (ESI) 372, 326  $[\text{M}+\text{NH}_4]^+$ , 224 (Found  $[\text{M}+\text{NH}_4]^+$ , 326.1432.  $\text{C}_{16}\text{H}_{20}\text{O}_4\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 326.1426) (Found C, 62.38; H, 6.64%.  $\text{C}_{16}\text{H}_{20}\text{O}_4\text{S}$  requires C, 62.31; H, 6.54%).

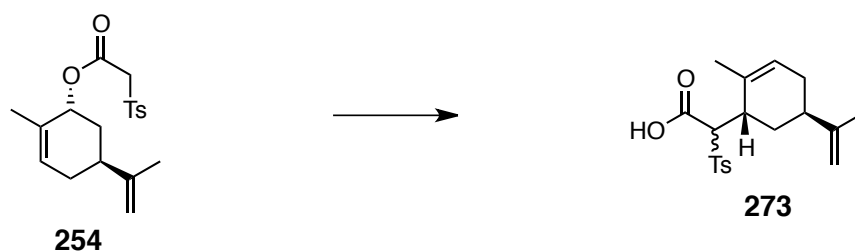
### 3-Cyclohexenyl-2-tosylpropionic acid (**270**)



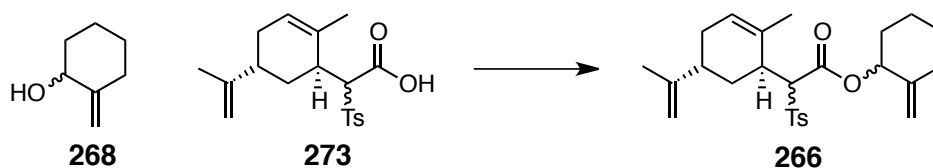
To a solution of **269** (300 mg, 0.97 mmol, 1 equiv) in CH<sub>3</sub>CN (3.5 mL) was added Et<sub>3</sub>N (177 μL, 1.17 mmol, 1.2 equiv) then BSA (714 μL, 2.92 mmol, 3 equiv). The reaction mixture was heated to 60 °C for 30 min, before being cooled, diluted with EtOAc (30 mL), washed with 1 N HCl (15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol + 10 % MeOH + 1 % AcOH) afforded **270** as an off-white solid (290 mg, 97 %); *R*<sub>f</sub> 0.60 (15 % EtOAc in petrol); mp 48-49 °C; *v*<sub>max</sub> (film) 3381, 2927, 1770, 1614, 1381, 1289, 1143, 1085 cm<sup>-1</sup>; *δ*<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 7.83 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.34 (2H, d, *J* 8.0 Hz, *m*-Ts), 4.53 (1H, s, CH=C), 4.19 (1H, s, CHTs), 2.70–2.51 (2H, m, CH<sub>2</sub>), 2.45 (3H, s, CH<sub>3</sub>Ar), 1.96–1.67 (4H, m, ring CH<sub>2</sub>), 1.60–1.33 (4H, m, ring CH<sub>2</sub>); *δ*<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 145.36 (Ar), 134.0 (Ar), 131.8 (C=CH), 129.8 (*m*-Ts), 129.4 (*o*-Ts), 125.0 (CH=C), 69.5 (CHTs), 35.2 (CH<sub>2</sub>CHTs), 27.9 (ring CH<sub>2</sub>), 25.1 (ring CH<sub>2</sub>), 22.6 (ring CH<sub>2</sub>), 21.9 (ring CH<sub>2</sub>), 21.7 (CH<sub>3</sub>Ar); *m/z* (CI) 340, 326 [M+NH<sub>4</sub>]<sup>+</sup>, 324, 322, 282 [M+NH<sub>4</sub>-CO<sub>2</sub>]<sup>+</sup>, 174.

**(4*R*,6*S*)-(+)-Carvyl 3-cyclohexenyl-2-tosylpropanoate (264)**

To **251** (128 mg, 0.84 mmol, 1 equiv) and **270** (260 mg, 0.84 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at 0 °C was added DMAP (10 mg, 0.08 mmol, 0.1 equiv) then DIC (145  $\mu\text{L}$ , 0.92 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 1 h then filtered through Celite®. The solids were washed with  $\text{Et}_2\text{O}$  (20 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (5 %  $\text{EtOAc}$  in petrol) afforded a 1:1 mixture of C-Ts epimers of **264** as a colourless oil (252 mg, 68 %);  $R_f$  0.75 (15 %  $\text{EtOAc}$  in petrol);  $\nu_{\text{max}}$  (film) 2928, 1732, 1645, 1598, 1440, 1324, 1155, 1085, 915  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.81–7.75 (2H, m, *o*-Ts), 7.39–7.33 (2H, m, *m*-Ts), 5.78–5.72 (1H, m, C=CH), 5.48–5.41 (1H, m, CH-ester), 5.28–5.22 (1H, m, C=CH), 4.79–4.73 (1H, m, C=CH<sub>2</sub>), 4.71–4.66 (1H, m, C=CH<sub>2</sub>), 4.14 (1H, dd,  $J$  11.0, 4.5 Hz, CHTs), 2.70–2.55 (2H, m), 2.47 and 2.46 (3H, s, CH<sub>3</sub>Ar), 2.33–2.13 (2H, m), 2.00–1.41 (10H, m), 1.74 (3H, s, CH<sub>3</sub>), 1.60 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 165.9 and 165.7 (CO), 148.5 and 148.5 (C=CH), 145.3 (Ar), 134.2 and 134.1 (C=CH), 131.8 and 131.7 (C=CH<sub>2</sub>), 130.3 and 130.1 (Ar), 129.7 (*m*-Ts), 129.5 and 129.4 (*o*-Ts), 128.6 and 128.5 (C=CH), 125.1 and 125.0 (C=CH), 109.3 and 109.2 (C=CH<sub>2</sub>), 72.8 and 72.5 (CH-ester), 69.4 and 69.3 (CHTs), 35.6, 35.5, 35.3, 35.2, 33.2, 33.1, 28.0, 25.1, 25.0, 22.6, 22.0, 21.9, 21.7 (CH<sub>3</sub>Ar), 20.9 and 20.8 (CH<sub>3</sub>), 20.5 and 20.3 (CH<sub>3</sub>);  $m/z$  (ESI) 506, 481, 460  $[\text{M}+\text{NH}_4]^+$ , 224 (Found  $[\text{M}+\text{NH}_4]^+$ , 460.2529.  $\text{C}_{26}\text{H}_{34}\text{O}_4\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 460.2522) (Found C, 70.69; H, 7.86%.  $\text{C}_{26}\text{H}_{34}\text{O}_4\text{S}$  requires C, 70.55; H, 7.74%).

2-(4*R*,6*S*)-Limonen-6-yl-2-tosylacetic acid (**273**)

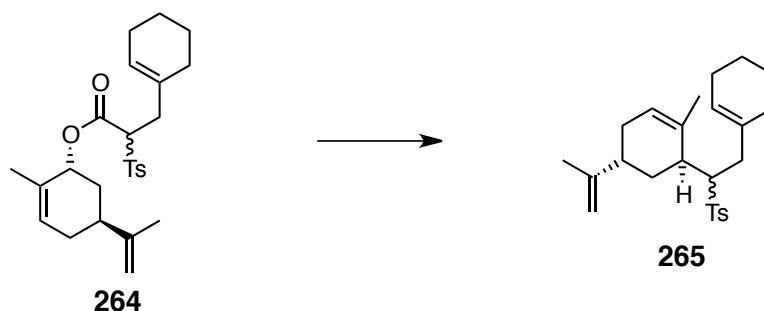
To a solution of **254** (478 mg, 1.37 mmol, 1 equiv) in CH<sub>3</sub>CN (5 mL) was added Et<sub>3</sub>N (250  $\mu$ L, 1.65 mmol, 1.2 equiv) then BSA (1.00 mL, 4.12 mmol, 3 equiv). The reaction mixture was heated to reflux for 2 h, before being cooled, diluted with EtOAc (50 mL), washed with 1 N HCl (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol + 10 % MeOH + 1 % AcOH) afforded a 5:3 mixture of C-Ts epimers of **273** as an off-white solid (444 mg, 93 %); *R*<sub>f</sub> 0.65 (15 % EtOAc in petrol; mp 57-58 °C;  $\nu_{\text{max}}$  (film) 3476, 2921, 1714, 1644, 1598, 1453, 1379, 1304, 1144, 1086, 912 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.86 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.37 (2H, d, *J* 8.0 Hz, *m*-Ts major), 7.33 (2H, d, *J* 8.0 Hz, *m*-Ts minor), 5.62 (1H, s, CH=C major), 5.52 (1H, s, CH=C minor), 4.70 (1H, s, CH<sub>2</sub>=C), 4.65 (1H, s, CH<sub>2</sub>=C minor), 4.60 (1H, s, CH<sub>2</sub>=C major), 4.24 (1H, s, CHTs major), 4.14 (1H, d, *J* 7.5 Hz, CHTs minor), 2.92 (1H, m, CHCHTs major), 3.01 (1H, m, CHCHTs minor), 2.39–1.76 (5H, m), 2.46 (3H, s, CH<sub>3</sub>Ar major), 2.43 (3H, s, CH<sub>3</sub>Ar minor), 1.69 (3H, s, CH<sub>3</sub> minor), 1.67 (3H, s, CH<sub>3</sub> major), 1.62 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 175.0 (CO), 148.9 and 148.5 (C=CH), 145.2 and 144.9 (Ar), 135.7 and 135.2 (C=CH<sub>2</sub>), 129.8 and 129.7 (*m*-Ts), 129.3 and 129.2 (*o*-Ts), 126.3 (C=CH), 109.0 and 108.8 (C=CH<sub>2</sub>), 70.1 (CHTs), 39.0, 37.1, 36.5, 35.0, 30.8, 29.7, 28.6, 23.4, 22.6, 21.7 (CH<sub>3</sub>Ar), 21.4 and 21.2 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>); *m/z* (CI) 364 [M+NH<sub>4</sub>]<sup>+</sup>, 322, 242, 228.

**2-Methylenecyclohexyl 2-(4*S*,6*R*)-limonen-6-yl-2-tosylacetate (266)**

To **268** (77 mg, 0.68 mmol, 1 equiv) and **273** (240 mg, 0.68 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at 0 °C was added DMAP (8 mg, 0.07 mmol, 0.1 equiv) then DIC (118  $\mu\text{L}$ , 0.76 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 18 h then filtered through Celite®. The solids were washed with  $\text{Et}_2\text{O}$  (20 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (5 %  $\text{EtOAc}$  in petrol) afforded a complex mixture of stereoisomers of **266** as a colourless oil (110 mg, 37 %);  $R_f$  0.75 (15 %  $\text{EtOAc}$  in petrol);  $\nu_{\text{max}}$  (film) 2936, 2861, 1740, 1646, 1598, 1449, 1327, 1142, 1086  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.89–7.81 (2H, m, *o*-Ts), 7.38–7.29 (2H, m, *m*-Ts), 5.63–5.51 (1H, m, C=CH), 5.28–5.03 (1H, m, CH-ester), 4.89–4.47 (4H, m, C=CH<sub>2</sub>), 4.25–4.05 (1H, m, CHTs), 3.32–2.98 (1H, m, CHCHTs), 2.46–2.43 (3H, m, CH<sub>3</sub>Ar), 2.36–1.07 (19 H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 165.5 (CO) 165.1 (CO), 164.6 (CO), 148.9, 148.4, 148.3, 145.1, 145.0, 144.9, 135.4, 135.3, 135.2, 130.7, 130.6, 129.7, 129.6, 129.5, 129.4, 129.1, 129.0, 126.9, 126.7, 126.6, 126.5, 126.4, 109.4, 109.3, 109.0, 108.9, 108.6, 108.5, 76.1, 76.0, 74.5, 74.3, 70.6, 70.4, 70.1, 70.0, 41.1, 39.9, 39.8, 38.6, 38.4, 37.4, 37.3, 36.2, 35.9, 35.1, 33.8, 33.1, 32.8, 32.6, 32.4, 30.9, 30.8, 30.5, 30.0, 29.8, 28.5, 28.4, 27.1, 23.8, 23.5, 22.8, 22.6, 22.5, 22.4, 21.6, 21.5, 21.2, 21.0, 20.8, 20.6;  $m/z$  (ESI) 506, 481, 460  $[\text{M}+\text{NH}_4]^+$  (Found  $[\text{M}+\text{NH}_4]^+$ , 460.2525.  $\text{C}_{26}\text{H}_{34}\text{O}_4\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 460.2522) (Found C, 70.69; H, 7.86%.  $\text{C}_{26}\text{H}_{34}\text{O}_4\text{S}$  requires C, 70.55; H, 7.74%).

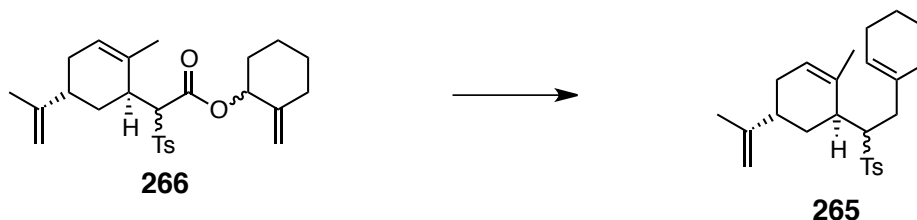
**1-(2-Cyclohexenyl-1-(4*S*,6*R*)-limonen-6-ylethylsulfonyl)-4-methylbenzene (265)**

Method A:



To **264** (100 mg, 0.23 mmol, 1 equiv) and KOAc (4.5 mg, 0.05 mmol, 0.2 equiv) in a capped microwave vial was added BSA (276  $\mu$ L, 1.13 mmol, 5 equiv). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for  $3 \times 1$  min (including a 1 min cooling period between each 1 min heating period). Purification of the crude reaction mixture by silica gel chromatography (5 % EtOAc in petrol) afforded a 1.1:1 mixture of C-Ts epimers of **265** as a colourless oil (24 mg, 26 %).

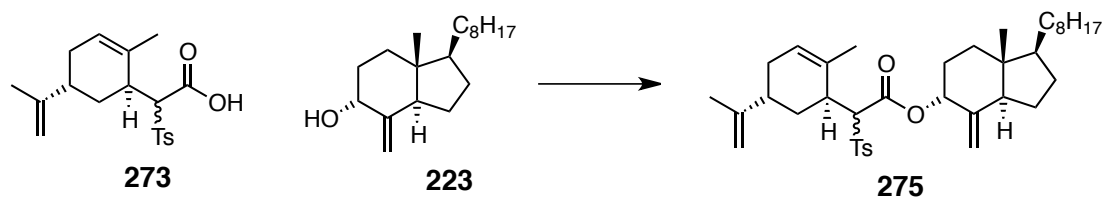
Method B:



To **266** (43 mg, 0.10 mmol, 1 equiv) and KOAc (2 mg, 0.02 mmol, 0.2 equiv) in a capped microwave vial was added BSA (119  $\mu$ L, 0.49 mmol, 5 equiv). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for  $3 \times 1$  min (including a 1 min cooling period between each 1 min heating period). Purification of the crude reaction mixture by silica gel chromatography (5 % EtOAc in petrol) afforded a 1.2:1 mixture of C-Ts epimers of **265** as a colourless oil (40 mg, >99 %).

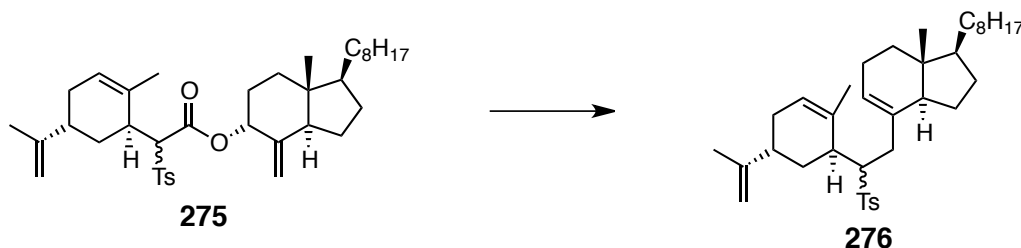
$R_f$  0.45 (5 % EtOAc in petrol);  $\nu_{\max}$  (film) 2924, 1644, 1598, 1447, 1312, 1300, 1142, 1086  $\text{cm}^{-1}$ ;  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 7.78 (2H, d  $J$  8.0 Hz, *o*-Ts major), 7.73 (2H, d  $J$  8.0 Hz, *o*-Ts minor), 7.34 (2H, d  $J$  8.0 Hz, *m*-Ts major), 7.31 (2H, d  $J$  8.0 Hz, *m*-Ts minor), 5.67 (1H, s, CH=C minor), 5.59 (1H, s, CH=C major), 5.42 (1H, s, CH=C minor), 5.39 (1H, s, CH=C major), 4.80–4.74 (1H, m, C=CH<sub>2</sub>), 4.71 (1H, s, C=CH<sub>2</sub>),

3.69–3.56 (1H, m, CHTs major), 3.41–3.33 (1H, m, CHTs minor), 3.15 (1H, s, *CH*CHTs minor), 2.80 (1H, s, *CH*CHTs major), 2.76–2.67 (1H, m, CH major), 2.51 – 0.83 (14H, m), 2.46 (3H, s, CH<sub>3</sub>Ar major), 2.45 (3H, s, CH<sub>3</sub>Ar minor), 1.80 (3H, s CH<sub>3</sub>C=CH major), 1.77 (3H, s CH<sub>3</sub>C=CH<sub>2</sub> minor), 1.76 (3H, s CH<sub>3</sub>C=CH<sub>2</sub> major), 1.65 (3H, s CH<sub>3</sub>C=CH minor);  $\delta_c$  (CDCl<sub>3</sub>, 100 MHz) 148.9, 148.3, 144.2, 143.8, 138.5, 136.8, 132.8, 132.4, 131.1, 129.5 (Ar), 129.2 (Ar), 128.7 (Ar), 128.6 (Ar), 126.7, 125.6, 125.5, 124.6, 109.2 and 109.0 (C=CH<sub>2</sub>), 64.1 and 62.1 (CHTs), 37.5, 36.8, 36.7, 34.5, 31.9, 30.3, 29.7, 28.1, 27.3, 27.1, 25.2, 25.1, 23.1, 22.6, 22.3, 22.0, 21.6 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 21.3 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>); *m/z* (ESI) 462, 416 [M+NH<sub>4</sub>]<sup>+</sup>, 399 [M+H]<sup>+</sup> (Found [M+H]<sup>+</sup>, 399.2361. C<sub>25</sub>H<sub>34</sub>O<sub>2</sub>S requires [M+H]<sup>+</sup>, 399.2358).

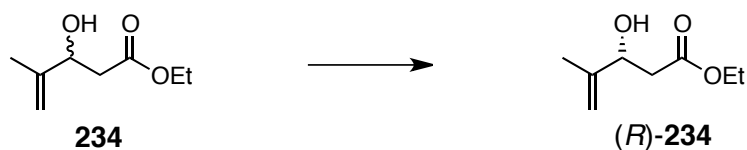
**De-A,D-8-methylenecholestan-9-yl 2-(4*S*,6*R*)-limonen-6-yl-2-tosylacetate (**275**)**

To **223** (140 mg, 0.50 mmol, 1 equiv) and **273** (175 mg, 0.50 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at 0 °C was added DMAP (6 mg, 0.05 mmol, 0.1 equiv) then DIC (86  $\mu\text{L}$ , 0.55 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 6 h then filtered through Celite®. The solids were washed with  $\text{Et}_2\text{O}$  (20 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (5 % EtOAc in petrol) afforded an epimeric mixture of **275** as a colourless oil (176 mg, 58 %);  $R_f$  0.90 (15 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 2954, 2870, 1739, 1646, 1598, 1453, 1329, 1139 1086  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.88–7.77 (2H, m, *o*-Ts), 7.38–7.27 (2H, m, *m*-Ts), 5.65–4.54 (6H, m,  $\text{CH}=\text{C}$ , 2 x  $\text{C}=\text{CH}_2$ , H-9), [1H, 4.18 (d,  $J$  3.0 Hz) and 4.02 (d,  $J$  6.0 Hz), CHTs], 3.11–2.96 (1H, m,  $\text{CHCHTs}$ ), 2.43(3H, s,  $\text{CH}_3\text{Ar}$ ), 2.36–0.96 (32H, m), 0.94–0.86 (H-21 + H-26/27), 0.54–0.48 (3H, s, H-18);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 165.2, 164.5, 149.0, 148.1, 145.0, 144.9, 144.8, 135.7, 135.2, 132.1, 131.0, 129.7, 129.6, 129.6, 129.5, 129.2, 126.3, 126.2, 112.1, 111.9, 109.0, 108.9, 76.5, 76.4, 74.4, 70.4, 56.1, 50.5, 50.4, 44.5, 39.5, 38.4, 37.1, 36.2, 36.1, 35.9, 35.3, 35.1, 34.9, 33.9, 31.1, 29.8, 28.4, 28.2, 28.0, 27.5, 27.5, 23.9, 23.7, 23.3, 22.8, 22.6, 21.9, 21.8, 21.7, 21.6, 21.3, 20.6, 18.8, 11.1, 11.0;  $m/z$  (ESI) 672, 626  $[\text{M}+\text{NH}_4]^+$  (Found  $[\text{M}+\text{NH}_4]^+$ , 626.4236.  $\text{C}_{38}\text{H}_{56}\text{O}_4\text{S}$  requires  $[\text{M}+\text{NH}_4]^+$ , 626.4243) (Found C, 74.80; H, 9.20%.  $\text{C}_{38}\text{H}_{56}\text{O}_4\text{S}$  requires C, 74.95; H, 9.27%).

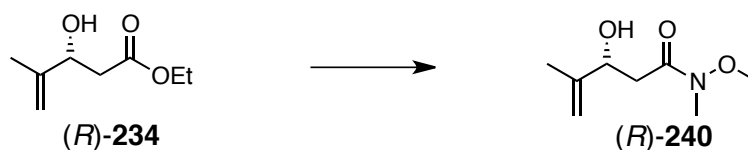
**1-(2-(Des-A,B-8(9)-cholesten-8-yl)-1-(4*S*,6*R*)-limonen-6-ylethylsulfonyl)-4-methylbenzene (276)**



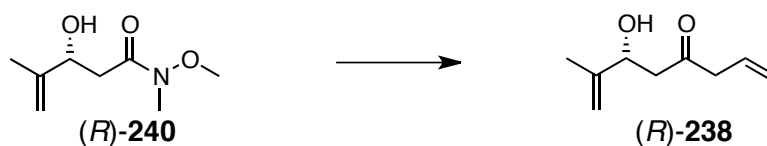
To **275** (70 mg, 0.11 mmol, 1 equiv) and KOAc (2 mg, 0.02 mmol, 0.2 equiv) in a capped microwave vial was added BSA (150  $\mu$ L, 0.55 mmol, 5 equiv). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for 3  $\times$  1 min (including a 1 min cooling period between each 1 min heating period). Purification of the crude reaction mixture by silica gel chromatography (5 % EtOAc in petrol) afforded an epimeric mixture of **276** as a colourless oil (56 mg, 90 %);  $R_f$  0.90 (5 % EtOAc in petrol);  $\nu_{\max}$  (film) 2928, 1452, 1302, 1144  $\text{cm}^{-1}$ ;  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 7.80–7.71 (2H, m, *o*-Ts), 7.36–7.29 (2H, m, *m*-Ts), 5.68–5.51 (1H, m, CH=C), [1H, 5.28–5.51 (m) and 5.04–4.95 (m), CH=C], 4.80–4.66 (2H, m, C=CH<sub>2</sub>), [1H, 3.65–3.58 (m) and 3.47–3.40 (m), CHTs), 2.91 (1H, bs, CHCHTs), 2.67–0.82 (40H, m), 2.45 (CH<sub>3</sub>Ar), 0.60–0.48 (3H, m, H-18);  $m/z$  (ESI) 582  $[\text{M}+\text{NH}_4]^+$ , 565  $[\text{M}+\text{H}]^+$ , 479 (Found  $[\text{M}+\text{H}]^+$ , 565.4093.  $\text{C}_{37}\text{H}_{56}\text{O}_2\text{S}$  requires  $[\text{M}+\text{H}]^+$ , 565.4079).



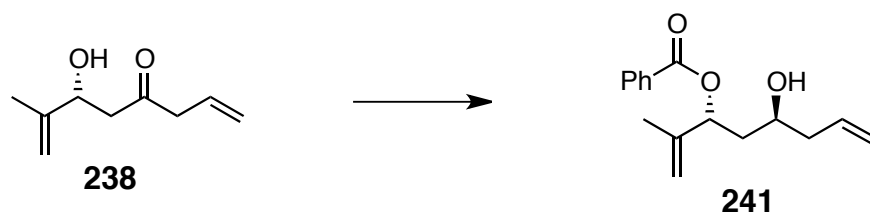
153

**(*R*)-3-Hydroxy-*N*-methoxy-*N*,4-dimethylpent-4-enamide (**240**)**

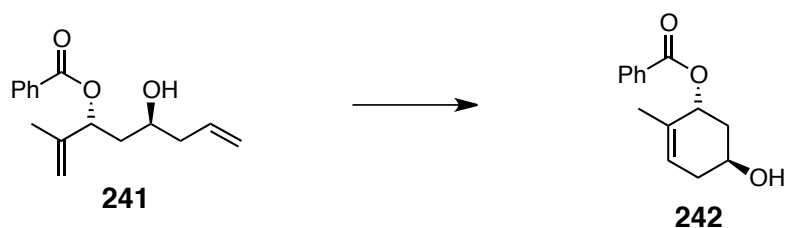
To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (7.32 g, 75.1 mmol, 2.2 equiv) in THF (70 mL) at -10 °C was added AlMe<sub>3</sub> (37.5 mL, 2 M in heptane, 75.1 mmol, 2.2 equiv) dropwise. The mixture was stirred at rt for 1 h before adding a solution of (*R*)-**234** (5.40 g, 34.1 mmol, 1 equiv) in THF (35 mL) dropwise. The resulting mixture was stirred at rt for 45 min. before slow addition of sat. NH<sub>4</sub>Cl (50 mL) (CAUTION - HIGHLY EXOTHERMIC QUENCH), Rochelle's salt (50 mL), and EtOAc (100 mL). The mixture was stirred overnight at rt before separating and further extracting the aqueous layer with EtOAc (2 x 200 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Silica gel chromatography (30%-70% EtOAc in heptane) afforded (*R*)-**240** as a colourless oil (5.26 g, 89 %);  $[\alpha]_D^{24} +48.9$  (*c* 1.50, CHCl<sub>3</sub>). All other data as for racemic **240**.

**(R)-6-Hydroxy-7-methyl-1,7-octadien-4-one (238)**

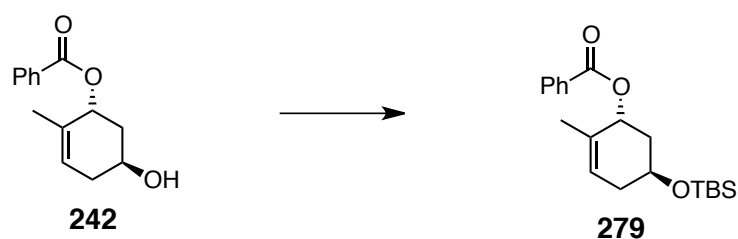
To **(R)-240** (4.65 g, 26.9 mmol, 1 equiv) in THF (135 mL) at 0 °C was added allylmagnesium chloride (26.9 mL, 2 M in THF, 53.7 mmol, 2 equiv) dropwise. The mixture was stirred at 0 °C for 30 min, then rt for 2 h before being poured into sat.  $\text{NH}_4\text{Cl}$  (200 mL), the organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 300 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give **(R)-238** as a yellow oil (3.73 g, 90 %). No further purification required;  $[\alpha]_{\text{D}}^{25} +62.1$  ( $c$  1.25,  $\text{CHCl}_3$ ). All other data as for racemic **238**.

**(3*R*,5*S*)-5-Hydroxy-2-methyl-1,7-octadien-3-yl benzoate (241)**

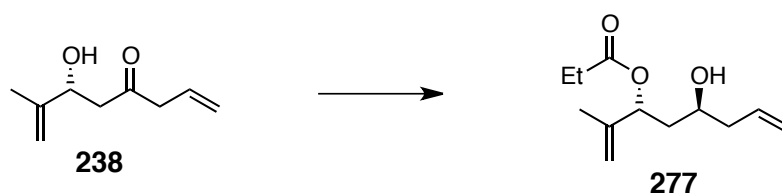
To crude (*R*)-**238** (~26.9 mmol, 1 equiv) in THF (90 mL) was added benzaldehyde (10.9 mL, 108 mmol, 4 equiv). The mixture was cooled to  $-10\text{ }^{\circ}\text{C}$  and  $\text{SmI}_2$  (81 mL, 0.1 M in THF, 8.1 mmol, 0.3 equiv) was added over 2 min. The reaction mixture was stirred at  $-10\text{ }^{\circ}\text{C}$  for 30 min. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (100 mL) and washed with sat.  $\text{NaHCO}_3$  (100 mL), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Silica gel chromatography (5-20%  $\text{EtOAc}$  in heptane) gave (*3R,5S*)-**241** as a colourless oil (3.15 g, 45 % over two steps, >99:1 *anti/syn*);  $[\alpha]_{\text{D}}^{25} +10.0$  ( $c$  1.00,  $\text{CHCl}_3$ ). All other data as for racemic **241**.

**(1*R*,5*S*)-5-Hydroxy-2-methylcyclohex-2-enyl benzoate (242)**

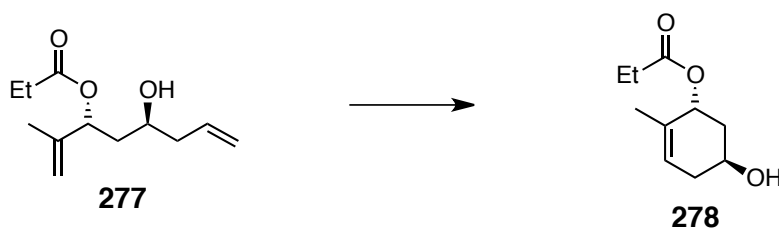
To (3*R*,5*S*)-**241** (1.90 g, 7.30 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was added Grubbs 2<sup>nd</sup> generation catalyst (310 mg, 0.36 mmol, 0.05 equiv). The reaction mixture was heated to 40 °C for 90 min, before being cooled, filtered through Celite® and concentrated under reduced pressure. Purification by silica gel chromatography (10-30 % EtOAc in heptane) afforded (1*R*,5*S*)-**242** as a brown oil (1.68 g, 99 %);  $[\alpha]_{\text{D}}^{25} +150.0$  (*c* 0.60, CHCl<sub>3</sub>). All other data as for racemic **242**.

**(1*R*,5*S*)-5-(*Tert*-butyldimethylsilyloxy)-2-methylcyclohex-2-enyl benzoate (279)**

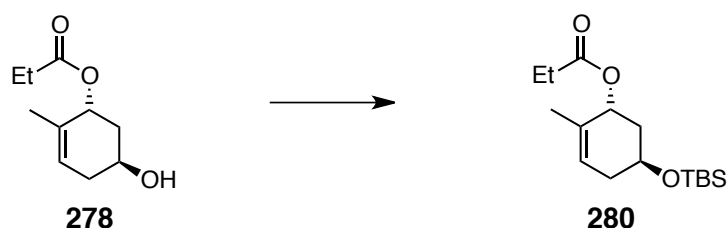
To (1*R*,5*S*)-**242** (2.51 g, 10.8 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at 0 °C was added imidazole (1.48 g, 21.7 mmol, 2 equiv), followed after 5 min by *tert*-butyldimethylsilylchloride (3.24 g, 21.7 mmol, 2 equiv). The reaction mixture was stirred at rt for 15 h then diluted with CH<sub>2</sub>Cl<sub>2</sub> (300 mL), washed with H<sub>2</sub>O (200 mL) and brine (200 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (0-10 % EtOAc in heptane) afforded (1*R*,5*S*)-**279** as a colourless oil (3.48 g, 93 %); [ $\alpha$ ]<sub>D</sub><sup>24</sup> +0.43 (*c* 1.30, CHCl<sub>3</sub>). All other data as for racemic **279**.

**(3*R*,5*S*)-5-Hydroxy-2-methyl-1,7-octadien-3-yl propionate (277)**

To (*R*)-**238** (1.30 g, 8.43 mmol, 1 equiv) in THF (22 mL) at  $-10\text{ }^{\circ}\text{C}$  was added propionaldehyde (2.42 mL, 33.7 mmol, 4 equiv). After 5 min stirring,  $\text{SmI}_2$  (25.2 mL, 0.1 M in THF, 2.52 mmol, 0.3 equiv) was added over 1 min. After the green/blue colour had abated ( $\sim 2$  min) the reaction mixture was stirred for a further 30 min before adding sat.  $\text{NaHCO}_3$  (20 mL) and extracting with  $\text{Et}_2\text{O}$  (3 x 50 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (0-10 %  $\text{EtOAc}$  in petrol) afforded **277** as a yellow oil (1.57 g, 88 %);  $R_f$  0.60 (10 %  $\text{EtOAc}$  in petrol);  $[\alpha]_D^{24} +42.9$  ( $c$  0.70,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3443, 2360, 1723, 1642, 1438, 1365, 1277, 1191, 1082  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 5.92–5.79 (1H, m,  $\text{CH}=\text{CH}_2$ ), 5.45 (1H, dd,  $J$  10.0, 3.0 Hz, CH-ester), 5.17–5.09 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.02–5.00 (1H, m,  $\text{CH}_2=\text{C}$ ), 4.92–4.90 (1H, m,  $\text{CH}_2=\text{C}$ ), 3.68–3.59 (1H, m,  $\text{CHOH}$ ), 2.62 (1H, d,  $J$  4.0 Hz, OH), 2.40 (2H, q,  $J$  7.5 Hz,  $\text{CH}_3\text{CH}_2$ ), 2.29–2.24 (2H, m,  $\text{CH}_2$ ), 1.85–1.66 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 1.77 (3H, s,  $\text{CH}_3$ ), 1.18 (3H, t,  $J$  7.5 Hz,  $\text{CH}_3\text{CH}_2$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 174.6 (CO), 143.6 ( $\text{C}=\text{CH}_2$ ), 134.6 ( $\text{CH}=\text{CH}_2$ ), 117.8 ( $\text{CH}=\text{CH}_2$ ), 112.2 ( $\text{C}=\text{CH}_2$ ), 74.1 (CH-ester), 66.8 ( $\text{CHOH}$ ), 41.7 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 40.6 ( $\text{CH}_2$ ), 27.8 ( $\text{CH}_2\text{CH}_3$ ), 18.6 ( $\text{CH}_3\text{C}=\text{C}$ ), 9.2 ( $\text{CH}_3\text{CH}_2$ );  $m/z$  (CI) 230  $[\text{M}+\text{NH}_4]^+$ , 213  $[\text{M}+\text{H}]^+$ , 139, 121 (Found  $[\text{M}+\text{NH}_4]^+$ , 230.1757.  $\text{C}_{12}\text{H}_{20}\text{O}_3$  requires  $[\text{M}+\text{NH}_4]^+$ , 230.1756).

**(1*R*,5*S*)-5-Hydroxy-2-methylcyclohex-2-enyl propionate (278)**

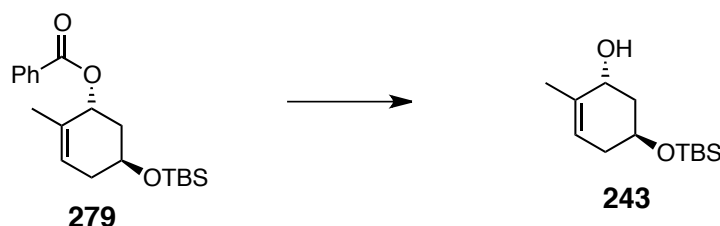
To **277** (900 mg, 4.24 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (85 mL) at 40 °C was added Grubbs 2<sup>nd</sup> generation catalyst (108 mg, 0.13 mmol, 0.03 equiv) in three equal portions separated by 45 min intervals. After addition was complete the reaction mixture was stirred for a further 3 h, before being cooled, filtered through Celite® and concentrated under reduced pressure. Purification by silica gel chromatography (20–30 % EtOAc in petrol) afforded **278** as a brown oil (715 mg, 92 %); *R*<sub>f</sub> 0.25 (15 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>23</sup> +114.8 (*c* 0.90, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3338, 2972, 2921, 1732, 1452, 1365, 1274, 1187, 1082, 1061, 1023 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 5.62–5.57 (1H, m, CH=C), 5.42–5.37 (1H, m, CH-ester), 4.12–4.01 (1H, m, CHOH), 2.52–2.43 (1H, m, ring CH<sub>2</sub>) 2.37 (2H, q, *J* 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>), 2.09–1.94 (2H, m, ring CH<sub>2</sub>), 1.88–1.76 (1H, m, ring CH<sub>2</sub>), 1.75 (1H, bs, OH), 1.70 (3H, s, CH<sub>3</sub>C=C), 1.18 (3H, t, *J* 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 174.2 (CO), 131.8 (C=CH), 124.9 (CH=C), 71.0 (CH-ester), 64.2 (CHOH), 37.7 (ring CH<sub>2</sub>), 34.6 (ring CH<sub>2</sub>), 27.9 (CH<sub>2</sub>CH<sub>3</sub>), 20.1 (CH<sub>3</sub>C=C), 9.2 (CH<sub>3</sub>CH<sub>2</sub>); *m/z* (CI) 202 [M+NH<sub>4</sub>]<sup>+</sup>, 185 [M+H]<sup>+</sup>, 153, 128 (Found [M+H]<sup>+</sup>, 185.1183. C<sub>10</sub>H<sub>16</sub>O<sub>3</sub> requires [M+H]<sup>+</sup>, 185.1177).

**(1*R*,5*S*)-5-(*Tert*-butyldimethylsilyloxy)-2-methylcyclohex-2-enyl propionate (280)**

To **278** (520 mg, 2.82 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0 °C was added imidazole (384 mg, 5.64 mmol, 2 equiv), followed after 5 min by *tert*-butyldimethylsilylchloride (850 mg, 5.64 mmol, 2 equiv). The reaction mixture was stirred at rt for 5 h then diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), washed with H<sub>2</sub>O (50 mL) and brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (0-10 % EtOAc in petrol) afforded **280** as a colourless oil (718 mg, 85 %); R<sub>f</sub> 0.55 (10 % EtOAc in petrol); [α]<sub>D</sub><sup>24</sup> +58.9 (*c* 1.30, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 2955, 2929, 2857, 1737, 1463, 1361, 1255, 1183, 1106 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 5.61–5.56 (1H, m, CH=C), 5.39–5.34 (1H, m, CH-ester), 4.66–3.97 (1H, m, CHOTBS), 2.40–2.28 (3H, m, CH<sub>3</sub>CH<sub>2</sub> + ring CH<sub>2</sub>), 2.04–1.92 (2H, m, ring CH<sub>2</sub>), 1.85–1.73 (1H, m, ring CH<sub>2</sub>), 1.69 (3H, s, CH<sub>3</sub>C=C), 1.19 (3H, t, *J* 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>), 0.90 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.08 (3H, s, SiCH<sub>3</sub>), 0.07 (3H, s, SiCH<sub>3</sub>); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 174.2 (CO), 131.5 (C=CH), 125.8 (CH=C), 71.6 (CH-ester), 64.8 (CHOH), 38.3 (CH<sub>2</sub>), 35.3 (CH<sub>2</sub>), 27.9 (CH<sub>3</sub>CH<sub>2</sub>), 25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 20.2 (CH<sub>3</sub>C=C), 18.2 (C(CH<sub>3</sub>)<sub>3</sub>), 9.4 (CH<sub>3</sub>CH<sub>2</sub>), –4.7 (SiCH<sub>3</sub>), –4.8 (SiCH<sub>3</sub>); *m/z* (CI) 316 [M+NH<sub>4</sub>]<sup>+</sup>, 299 [M+H]<sup>+</sup>, 242, 225, 167 (Found [M+H]<sup>+</sup>, 299.2036. C<sub>16</sub>H<sub>30</sub>O<sub>3</sub>Si requires [M+H]<sup>+</sup>, 299.2042).

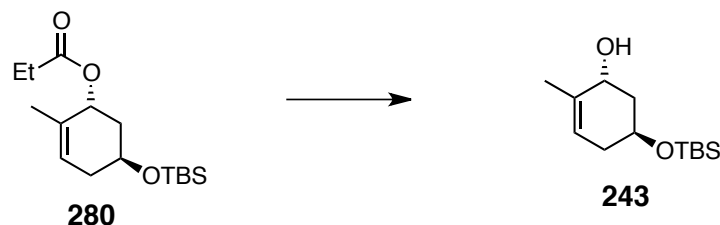
**(1*R*,5*S*)-5-(*Tert*-butyldimethylsilyloxy)-2-methylcyclohex-2-enol (243)**

Method A:



To (1*R*,5*S*)-**279** (1.00 g, 2.89 mmol, 1 equiv) in MeOH (13 mL) at 0 °C was added methanolic KOH (8.67 mL, 1 M in MeOH, 8.67 mmol, 3 equiv). The reaction was allowed to warm to rt and stirred for 12 h. 1 N HCl (20 mL) was added and the reaction mixture diluted with Et<sub>2</sub>O (150 mL). The aqueous layer was separated and further extracted with Et<sub>2</sub>O (2 x 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure before purification by silica gel chromatography (5-25 % EtOAc in heptane) afforded (1*R*,5*S*)-**243** as a colourless oil (677 mg, 97 %).

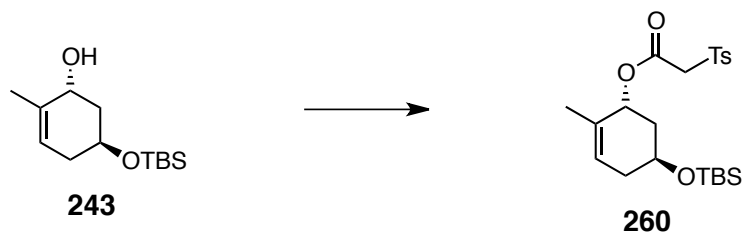
Method B:



To **280** (658 mg, 2.20 mmol, 1 equiv) in MeOH (6 mL) at 0 °C was added methanolic KOH (5 mL, 1 M in MeOH, 5 mmol, 2.3 equiv). The reaction was allowed to warm to rt and stirred for 16 h. 1 N HCl (15 mL) and the resulting mixture extracted with Et<sub>2</sub>O (3 x 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure before purification by silica gel chromatography (20 % EtOAc in petrol) afforded (1*R*,5*S*)-**243** as a colourless oil (468 mg, 88 %);

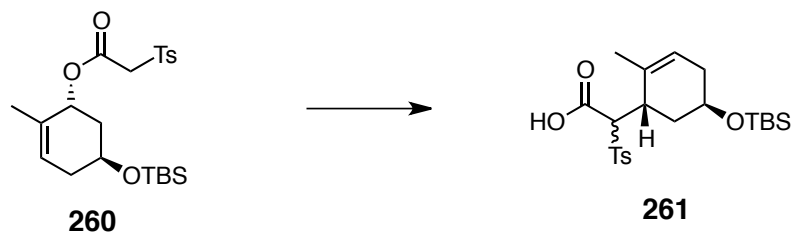
$[\alpha]_D^{23} +83.3$  (*c* 1.00, CHCl<sub>3</sub>). All other data as for racemic **243**.

**(1*R*,5*S*)-5-(*Tert*-butyldimethylsilyloxy)-2-methylcyclohex-2-enyl 2-tosylacetate**  
**(260)**

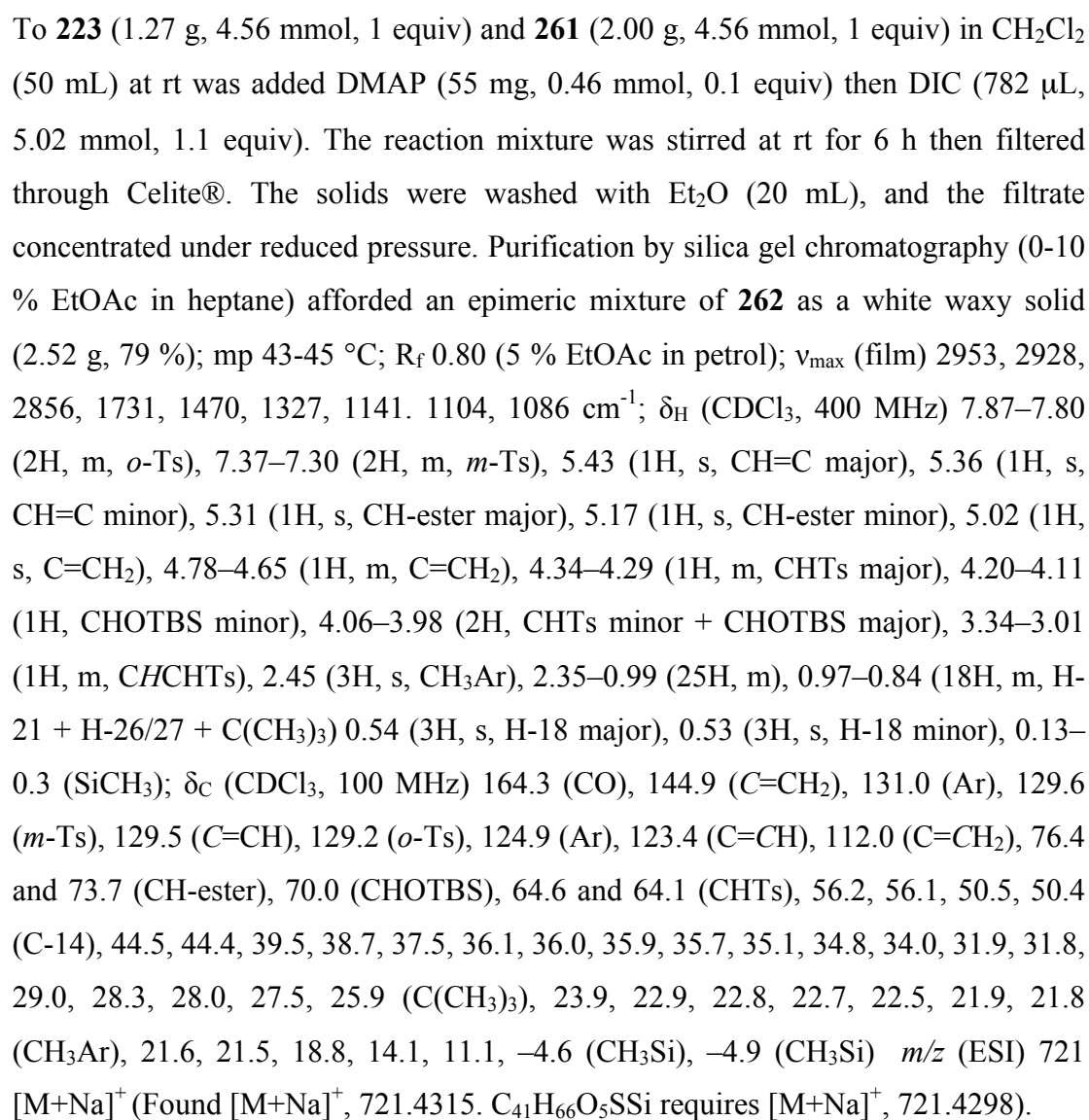


To (1*R*,5*S*)-**243** (1.34 g, 5.53 mmol, 1 equiv) and 2-tosylacetic acid (1.18 g, 5.53 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at 0 °C was added DMAP (68 mg, 0.55 mmol, 0.1 equiv) then DIC (950 µL, 6.08 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 2 h then filtered through Celite®. The solids were washed with Et<sub>2</sub>O (20 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (5–20 % EtOAc in heptane) afforded **260** as a colourless oil 2.23 g, 92 %; *R*<sub>f</sub> 0.15 (15 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>23</sup> +60.6 (*c* 1.10, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2928, 2856, 1734, 1598, 1472, 1387, 1329, 1261, 1156, 1103, 1083 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.78 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.32 (2H, d, *J* 8.0 Hz, *m*-Ts), 5.55–5.50 (1H, m, CH=C), 5.33–5.28 (1H, m, CH-ester), 4.05 (2H, s, CH<sub>2</sub>Ts), 3.93–3.84 (1H, m, CHOTBS), 2.41 (3H, s, CH<sub>3</sub>Ar), 2.30–2.19 (1H, ring CH<sub>2</sub>), 1.96–1.82 (2H, m, ring CH<sub>2</sub>), 1.76–1.67 (1H, m, ring CH<sub>2</sub>), 1.59 (3H, s, CH<sub>3</sub>C=C), 0.82 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.00 (6H, s, SiCH<sub>3</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 162.2 (CO), 145.4 (C=CH), 136.0 (Ar), 130.4 (Ar), 129.9 (*m*-Ts), 128.6 (*o*-Ts), 126.7 (CH=C), 74.3 (CH-ester), 64.4 (CHOTBS), 61.2 (CH<sub>2</sub>Ts), 37.8 (CH<sub>2</sub>), 35.2 (CH<sub>2</sub>), 25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 21.7 (CH<sub>3</sub>Ar), 20.1 (CH<sub>3</sub>C=C), 18.1 (C(CH<sub>3</sub>)<sub>3</sub>), -4.7 (SiCH<sub>3</sub>), -4.8 (SiCH<sub>3</sub>); *m/z* (ESI) 502, 477, 461 [M+Na]<sup>+</sup>, 456 [M+NH<sub>4</sub>]<sup>+</sup> (Found [M+Na]<sup>+</sup>, 461.1795. C<sub>22</sub>H<sub>34</sub>O<sub>5</sub>SSi requires [M+Na]<sup>+</sup>, 461.1794).

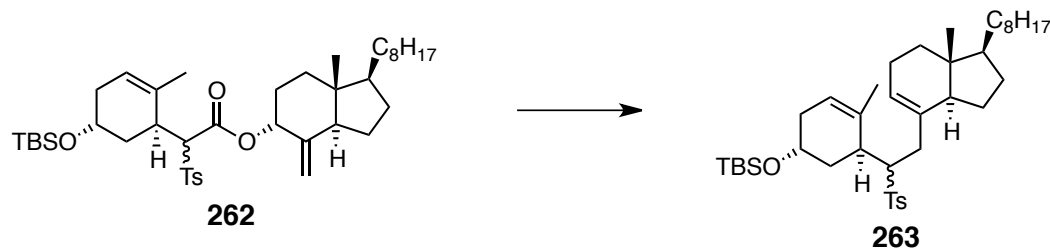
**2-((1*S*,5*R*)-5-(*Tert*-butyldimethylsilyloxy)-2-methylcyclohex-2-enyl)-2-tosylacetic acid (**261**)**



To a solution of **260** (2.08 g, 4.74 mmol, 1 equiv) in CH<sub>3</sub>CN (16 mL) was added Et<sub>3</sub>N (795  $\mu$ L, 5.69 mmol, 1.2 equiv) then BSA (3.48 mL, 14.22 mmol, 3 equiv). The reaction mixture was heated to reflux for 3 h, before being cooled, diluted with EtOAc (150 mL), washed with 1 N HCl (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Purification by silica gel chromatography (10–30 % EtOAc in heptane + 10 % MeOH + 1 % AcOH) afforded a 3:1 mixture of C-Ts epimers of **261** as an off-white foamy solid (1.91 g, 92 %); *R*<sub>f</sub> 0.55 (10 % EtOAc in petrol + 10 % MeOH + 1 % AcOH); mp 60–61 °C;  $\nu_{\text{max}}$  (film) 3450, 3182, 2955, 2929, 2857, 1739, 1598, 1382, 1324, 1255, 1148, 1086 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.84–7.77 (2H, m, *o*-Ts), 7.37–7.30 (2H, m, *m*-Ts), 5.42 (1H, s, CH=C), 4.31 (1H, d, *J* 3.0 Hz, CHTs major), 4.20–4.09 (1H, m, CHOTBS minor), 4.11 (1H, d, *J* 5.5 Hz, CHTs minor), 4.00–3.93 (1H, m, CHOTBS major), 3.22–3.14 (1H, m, CHCHTs major), 3.09–3.03 (1H, m, CHCHTs minor), 2.44 (3H, s, CH<sub>3</sub>Ar), 1.61 (3H, s, CH<sub>3</sub>C=C), 0.86 (9H, s, C(CH<sub>3</sub>)<sub>3</sub> minor), 0.84 (9H, s, C(CH<sub>3</sub>)<sub>3</sub> major), 0.06 (3H, s, SiCH<sub>3</sub> minor), 0.02 (3H, s, SiCH<sub>3</sub> major), 0.00 (3H, s, SiCH<sub>3</sub> major), –0.02 (3H, s, SiCH<sub>3</sub> minor);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 170.3 (CO major), 169.2 (CO minor), 145.5 (Ar), 135.3 (Ar major), 135.2 (Ar minor), 131.2 (C=CH minor), 130.1 (C=CH major), 130.0 (*m*-Ts major), 129.8 (*m*-Ts minor), 129.4 (*o*-Ts minor), 129.2 (*o*-Ts major), 125.2 (CH=C minor), 124.1 (CH=C major), 72.9 (CHTs minor), 69.8 (CHTs major), 64.5 (CHOTBS major), 64.1 (CHOTBS minor), 38.8 (CHCHTs minor), 36.4 (CHCHTs major), 36.3 (CH<sub>2</sub> minor), 35.3 (CH<sub>2</sub> minor), 34.1 (CH<sub>2</sub> major), 32.1 (CH<sub>2</sub> major), 25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 22.7 (CH<sub>3</sub>Ar minor), 21.7 (CH<sub>3</sub>Ar major), 21.3 (CH<sub>3</sub>C=C), 18.1 (C(CH<sub>3</sub>)<sub>3</sub>), –4.5 (SiCH<sub>3</sub> minor), –4.6 (SiCH<sub>3</sub> major), –4.7 (SiCH<sub>3</sub> minor), –4.8 (SiCH<sub>3</sub> major); *m/z* (ESI) Found [M+Na]<sup>+</sup>, 461.1798. C<sub>22</sub>H<sub>34</sub>O<sub>5</sub>SSi requires [M+Na]<sup>+</sup>, 461.1794).



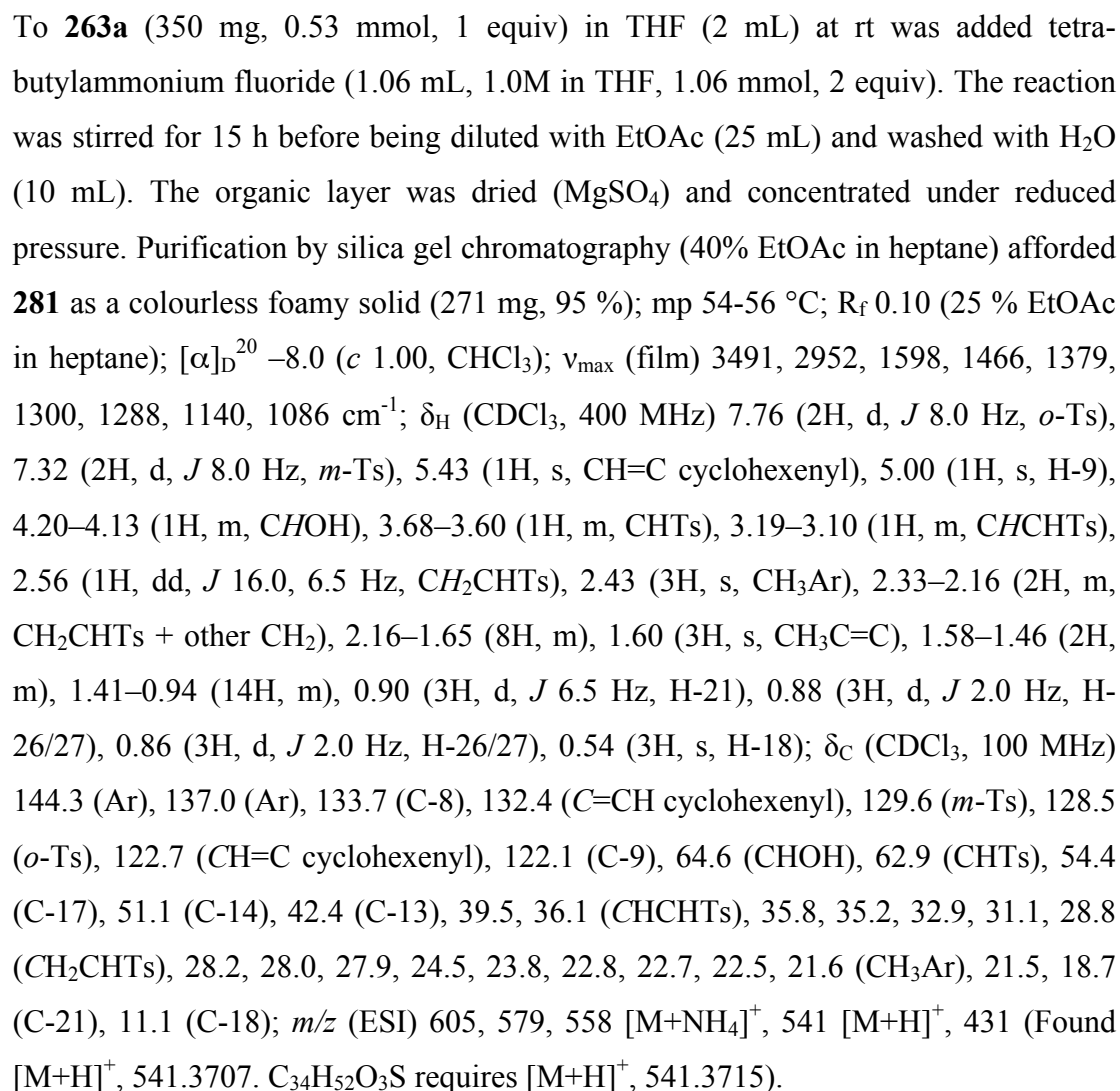
***Tert*-butyldimethyl((1*R*,5*S*)-4-methyl-5-(2-(des-A,B-8(9)-cholesten-8-yl)-1-tosylethyl)cyclohex-3-enyloxy)silane (**263**)**



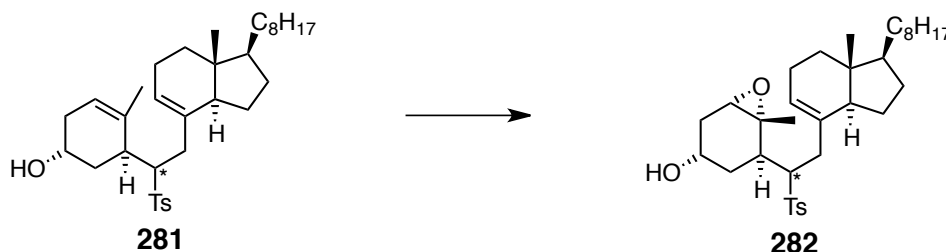
To **262** (411 mg, 0.59 mmol, 1 equiv) and KOAc (6 mg, 0.06 mmol, 0.1 equiv) in a capped microwave vial was added BSA (500  $\mu$ L, 2.05 mmol, 3.5 equiv). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for 5  $\times$  1 min (including a 1 min cooling period between each 1 min heating period). Purification of the crude reaction mixture by silica gel chromatography (0-5 % EtOAc in heptane) afforded **263** as a colourless oil (340 mg, 88 %). Further silica gel chromatography (5% Et<sub>2</sub>O in heptane) furnished separate epimers **263a** (217 mg, 56%) and **263b** (113mg, 30%).

Data for major epimer **263a**:  $R_f$  0.65 (25 % EtOAc in heptane);  $[\alpha]_D^{25}$   $-19.3$  ( $c$  1.45, CHCl<sub>3</sub>);  $\nu_{max}$  (film) 2953, 2927, 1463, 1378, 1341, 1301, 1251, 1143, 1088  $cm^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 7.74 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.30 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.37 (1H, s, CH=C cyclohexenyl), 5.02 (1H, s, H-9), 4.12–4.04 (1H, m, CHOTBS), 3.65–3.58 (1H, m, CHTs), 3.10–3.01 (1H, m, CHCHTs), 2.59 (1H, dd,  $J$  16.0, 7.0 Hz, CH<sub>2</sub>CHTs), 2.42 (3H, s, CH<sub>3</sub>Ar), 2.27 (1H, dd,  $J$  16.0 Hz, 5.0 Hz, CH<sub>2</sub>CHTs), 2.04–0.93 (22H, m), 1.56 (3H, s, CH<sub>3</sub>C=C), 0.90 (3H, d,  $J$  6.5 Hz, H-21), 0.88–0.84 (15H, m, H-26/27 + C(CH<sub>3</sub>)<sub>3</sub>), 0.55 (3H, s, H-18), 0.08 (3H, s, SiCH<sub>3</sub>), 0.05 (3H, s, SiCH<sub>3</sub>);  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 144.1 (Ar), 137.3 (Ar), 134.1 (C-8), 131.9 (C=CH cyclohexenyl), 129.6 (*m*-Ts), 128.5 (*o*-Ts), 123.1 (CH=C cyclohexenyl), 122.1 (C-9), 65.3 (CHOTBS), 63.3 (CHTs), 54.4 (C-17), 51.2 (C-14), 42.4 (C-13), 39.5, 36.1 (CHCHTs), 36.0, 35.8, 34.1, 31.7, 28.9 (CH<sub>2</sub>CHTs), 28.3, 28.0, 25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 24.5, 23.9, 22.8, 22.6, 21.6 (CH<sub>3</sub>Ar), 21.5, 18.8 (C-21), 18.1 (C(CH<sub>3</sub>)<sub>3</sub>), 11.1 (C-18),  $-4.5$  (SiCH<sub>3</sub>),  $-4.8$  (SiCH<sub>3</sub>);  $m/z$  (ESI) 713, 693, 672 [M+NH<sub>4</sub>]<sup>+</sup>, 655 [M+H]<sup>+</sup>, 523 (Found [M+H]<sup>+</sup>, 655.4594. C<sub>40</sub>H<sub>66</sub>O<sub>3</sub>SSi requires [M+H]<sup>+</sup>, 655.4580).

Data for minor epimer **263b**:  $R_f$  0.60 (25 % EtOAc in heptane);  $[\alpha]_D^{25} -12.9$  ( $c$  0.93,  $\text{CHCl}_3$ );  $\nu_{\max}$  (film) 2953, 2927, 1463, 1378, 1312, 1301, 1250, 1142, 1087  $\text{cm}^{-1}$ ;  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 7.75 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.32 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.37 (1H, s, CH=C cyclohexenyl), 5.26–5.22 (1H, m, C-9), 4.28–4.22 (1H, m, CHOTBS), 3.61–3.53 (1H, m, CHTs), 3.04–2.96 (1H, m, CHCHTs), 2.45 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.41–2.28 (3H, m), 2.20–2.11 (1H, m), 2.10–0.92 (23H, m), 0.92–0.84 (18H, m, H-21 + H-26/27 +  $\text{C}(\text{CH}_3)_3$ ), 0.56 (3H, s, H-18), 0.00 (6H, s,  $\text{SiCH}_3$ );  $\delta_C$  ( $\text{CDCl}_3$ , 100 MHz) 144.1 (Ar), 137.7 (Ar), 133.7 (C-8), 133.3 (C=CH cyclohexenyl), 129.5 (*m*-Ts), 128.5 (*o*-Ts), 125.2 CH=C cyclohexenyl), 120.9 (C-9), 65.2 (CHOTBS), 63.3 (CHTs), 54.1 (C-17), 51.5 (C-14), 42.3 (C-13), 39.5, 36.1, 36.1, 35.9, 35.7, 34.4, 32.6, 32.2, 29.7, 28.2, 28.0, 25.9 ( $\text{C}(\text{CH}_3)_3$ ), 24.5, 23.8, 22.8, 22.6, 22.5, 21.6 ( $\text{CH}_3\text{Ar}$ ), 18.8 (C-21), 18.2 ( $\text{C}(\text{CH}_3)_3$ ), 11.4 (C-18), –4.5 ( $\text{SiCH}_3$ ), –4.7 ( $\text{SiCH}_3$ );  $m/z$  (CI) 718, 693, 672  $[\text{M}+\text{NH}_4]^+$ , 655  $[\text{M}+\text{H}]^+$ , 523 (Found  $[\text{M}+\text{H}]^+$ , 655.4604.  $\text{C}_{40}\text{H}_{66}\text{O}_3\text{SSi}$  requires  $[\text{M}+\text{H}]^+$ , 655.4580).

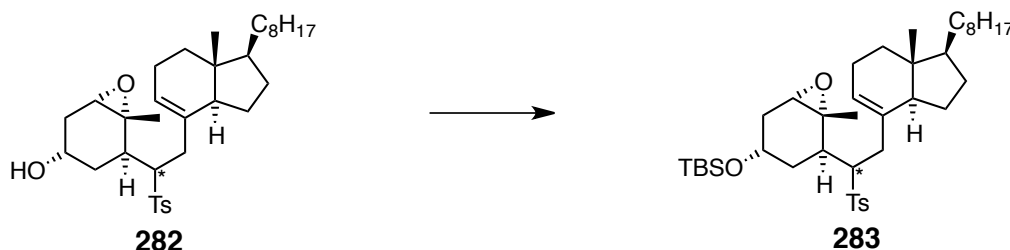


**(1*S*,3*S*,5*S*,6*R*)-6-Methyl-5-(2-(des-A,B-8(9)-cholesten-8-yl)-1-tosylethyl)-7-oxabicyclo[4.1.0]heptan-3-ol (282)**



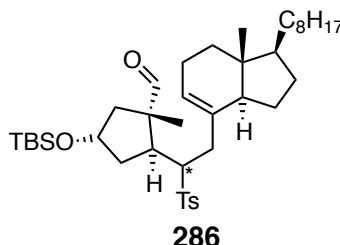
To **281** (326 mg, 0.60 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at –10 °C was added VO(acac)<sub>2</sub> (5 mg, 0.02 mmol, 3 mol %) followed by dropwise addition of *t*-BuOOH (208 μL, 4.33 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.90 mmol, 1.5 equiv). The resulting red reaction mixture was stirred at –10 °C for 4 h before diluting with EtOAc (50 mL) and washed with sat. NaHCO<sub>3</sub> (20 mL) then brine (20 mL). The organic layer was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (20–50 % EtOAc in heptane) afforded **282** as a colourless foamy solid (319 mg, 96 %); R<sub>f</sub> 0.10 (25 % EtOAc in heptane); mp 53–55 °C; [α]<sub>D</sub><sup>20</sup> +21.8 (*c* 1.10, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 3510, 2953, 1598, 1454, 1381, 1314, 1301, 1289, 1145, 1086, 1052 cm<sup>–1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 7.76 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.34 (2H, d, *J* 8.0 Hz, *m*-Ts), 5.03 (1H, s, H-9), 4.00–3.89 (1H, m, CHOH), 3.62–3.54 (1H, m, CHTs), 3.18–3.04 (3H, m, OH + CH(epoxide) + CHCHTs), 2.72 (1H, dd, *J* 17.0, 6.5 Hz, CH<sub>2</sub>CHTs), 2.45 (3H, s, CH<sub>3</sub>Ar), 2.32–2.22 (2H, m, CH<sub>2</sub>CHTs + cyclohexyl CH<sub>2</sub>), 2.21–2.12 (1H, m, cyclohexyl CH<sub>2</sub>), 2.06–0.94 (20H, m), 1.30 (3H, s, CH<sub>3</sub>(epoxide)), 0.90 (3H, d, *J* 6.5 Hz, H-21), 0.88 (3H, d, *J* 2.0 Hz, H-26/27), 0.86 (3H, d, *J* 2.0 Hz, H-26/27), 0.57 (H-18); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 144.7 (Ar), 136.9 (Ar), 133.4 (C-8), 129.8 (*m*-Ts), 128.6 (*o*-Ts), 122.1 (C-9), 64.5 (CHOH), 63.3 (CHTs), 62.0 (CHO), 60.2 (CH<sub>3</sub>CO), 54.4 (C-14), 51.3 (C-17), 42.4 (C-13), 39.5, 36.1, 35.7, 33.8 (CHCHTs), 31.2, 30.1, 29.7, 28.2, 28.0, 24.6, 23.8, 22.8, 22.7, 22.6, 22.4, 21.6 (CH<sub>3</sub>Ar), 18.8 (C-21), 11.2 (C-18); *m/z* (ESI) 557 [M+H]<sup>+</sup>, 540 [M–O]<sup>+</sup>, 401 (Found [M+H]<sup>+</sup>, 557.3663. C<sub>34</sub>H<sub>52</sub>O<sub>4</sub>S requires [M+H]<sup>+</sup>, 557.3664).

***Tert*-butyldimethyl((1*S*,3*S*,5*S*,6*R*)-6-methyl-5-(2-(des-A,B-8(9)-cholesten-8-yl)-1-tosylethyl)-7-oxabicyclo[4.1.0]heptan-3-yloxy)silane (**283**)**



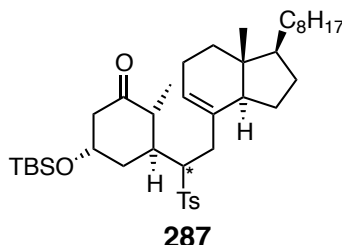
To **282** (174 mg, 0.31 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) at 0 °C was added imidazole (43 mg, 0.62 mmol, 2 equiv), followed after 5 min by *tert*-butyldimethylsilylchloride (94 mg, 0.62 mmol, 2 equiv). The reaction mixture was stirred at rt for 18 h then diluted with  $\text{Et}_2\text{O}$  (25 mL), washed with  $\text{H}_2\text{O}$  (20 mL) and brine (20 mL), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (5-10 %  $\text{EtOAc}$  in petrol) afforded **283** as a colourless oil (200 mg, 96 %);  $R_f$  0.55 (30 %  $\text{EtOAc}$  in heptane);  $[\alpha]_D^{25} +13.7$  ( $c$  1.30,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2953, 2929, 1598, 1463, 1382, 1315, 1300, 1255, 1146, 1104, 1088  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.75 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.32 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.00 (1H, s, H-9), 4.05–3.95 (1H, m, CHOTBS), 3.56–3.49 (1H, m, CHTs), 2.97–2.88 (2H, m, CH(epoxide) + CHCHTs), 2.72 (1H, dd,  $J$  16.5, 7.5 Hz,  $\text{CH}_2\text{CHTs}$ ), 2.44 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.35–2.15 (2H, m,  $\text{CH}_2\text{CHTs}$  + cyclohexyl  $\text{CH}_2$ ), 2.05–0.96 (24H, m), 1.17 (3H, s,  $\text{CH}_3(\text{epoxide})$ ), 0.95–0.82 (15H, m,  $\text{C}(\text{CH}_3)_3$  + H-21 + H-26/27), 0.58 (3H, s, H-18), 0.00 (6H,  $\text{CH}_3\text{Si}$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 143.5 (Ar), 136.4 (Ar), 132.7 (C-8), 128.7 (*m*-Ts), 127.5 (*o*-Ts), 120.9 (C-9), 63.1 (CHTs), 62.1 (CHOTBS), 58.7 (CHO), 57.2 ( $\text{CH}_3\text{CO}$ ), 53.4 (C-14), 50.3 (C-17), 41.4 (C-13), 38.5, 35.9 (CHCHTs), 35.1, 34.7, 32.3, 30.9, 29.9, 29.5, 27.2, 27.0, 24.9 ( $\text{C}(\text{CH}_3)_3$ ), 23.6, 22.8, 21.8, 21.7, 21.6 ( $\text{CH}_3\text{Ar}$ ), 21.5, 17.8 (C-21), 17.0 ( $\text{C}(\text{CH}_3)_3$ ), 13.1, 10.2 (C-18), –5.4 ( $\text{CH}_3\text{Si}$ ), –5.8 ( $\text{CH}_3\text{Si}$ );  $m/z$  (ESI) 693  $[\text{M}+\text{Na}]^+$ , 671  $[\text{M}+\text{H}]^+$  (Found  $[\text{M}+\text{Na}]^+$ , 693.4355.  $\text{C}_{40}\text{H}_{66}\text{O}_4\text{SSi}$  requires  $[\text{M}+\text{Na}]^+$ , 693.4349).

**(1*S*,2*S*,4*S*)-4-(*Tert*-butyldimethylsilyloxy)-1-methyl-2-(2-(des-A,B-8(9)-cholesten-8-yl)-1-tosylethyl)cyclopentanecarbaldehyde (286)**

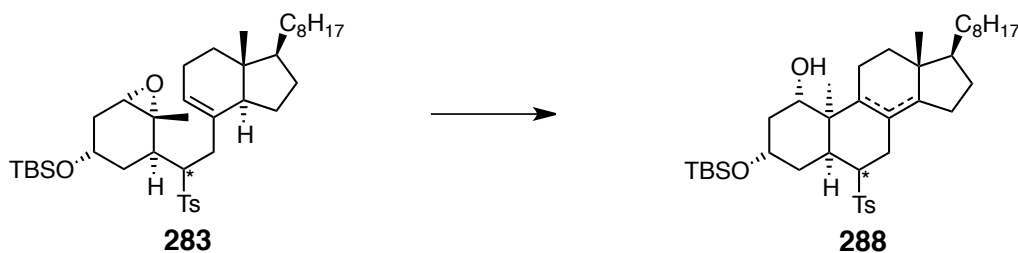


$R_f$  0.60 (20 % EtOAc in heptane);  $[\alpha]_D^{25} +19.5$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 9.40 (1H, s, CHO), 7.74 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.32 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.19 (1H, s, H-9), 4.37–4.32 (1H, m, CHOTBS), 3.44–3.37 (1H, m, CHTs), 3.00–2.92 (1H, m, CHCHTs), 2.72–2.63 (1H, m,  $\text{CH}_2\text{CHTs}$ ), 2.44 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.28 (1H, dd,  $J$  14.0, 5.5 Hz,  $\text{CH}_2\text{CCHO}$ ), 2.13–0.95 (25H, m), 0.93–0.89 (12H, m,  $\text{C}(\text{CH}_3)_3$  + H-21), 0.88 (3H, d,  $J$  2.0 Hz, H-26/27), 0.86 (3H, d,  $J$  2.0 Hz, H-26/27), 0.59 (3H, s, H-18), 0.07 (3H, s,  $\text{SiCH}_3$ ), 0.04 (3H, s,  $\text{SiCH}_3$ );  $\delta_C$  ( $\text{CDCl}_3$ , 100 MHz) 203.6 (CHO), 143.5 (Ar), 134.0 (Ar), 132.9 (C-8), 128.6 (*m*-Ts), 128.2 (*o*-Ts), 121.9 (C-9), 70.4 (CHOTBS), 58.8 (CHTs), 53.7 (CCHO), 53.3, 49.5, 45.4 (CHCHTs), 43.4 ( $\text{CH}_2\text{CCHO}$ ), 41.4 (C-13), 38.5, 37.1, 35.1, 34.6, 30.9, 29.9, 28.7, 27.2, 27.0, 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 23.6, 22.8, 21.8, 21.5, 20.8, 20.6, 17.7, 16.9, 10.3 (C-18), –5.8 ( $\text{SiCH}_3$ ), –5.9 ( $\text{SiCH}_3$ );  $m/z$  (ESI) 693  $[\text{M}+\text{Na}]^+$  (Found  $[\text{M}+\text{Na}]^+$ , 693.4311.  $\text{C}_{44}\text{H}_{66}\text{O}_4\text{SSi}$  requires  $[\text{M}+\text{Na}]^+$ , 693.4349).

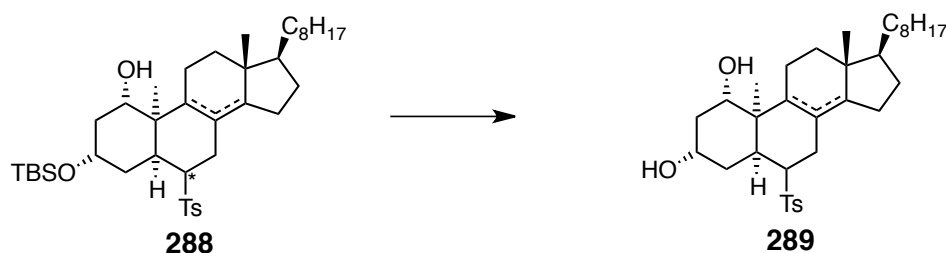
**(2*R*,3*S*,5*S*)-5-(*Tert*-butyldimethylsilyloxy)-2-methyl-3-(2-(des-A,B-8(9)-cholesten-8-yl)-1-tosylethyl)cyclohexanone (287)**



$R_f$  0.65 (30 % EtOAc in heptane);  $[\alpha]_D^{24} +6.9$  ( $c$  0.50,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2954, 2930, 2857, 1720, 1598, 1464, 1316, 1302, 1148  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.76 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.34 (2H, d,  $J$  8.0 Hz, *m*-Ts), 5.44 (1H, s, H-9), 4.49 (1H, s, CHOTBS), 3.36 (1H, dd,  $J$  10.5, 2.5 Hz, CHTs), 2.81–2.69 (2H, m,  $\text{CHCHTs} + \text{CH}_2\text{CHTs}$ ), 2.63–2.51 (1H,  $\text{CH}_2\text{CHTs}$ ), 2.49–2.28 (5H, m), 2.46 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.15–1.84 (7H, m), 1.63–0.82 (32H, m), 1.23 (3H, s,  $\text{CH}_3\text{CHC=O}$ ), 0.62 (3H, s, H-18), 0.12 (3H, s,  $\text{SiCH}_3$ ), 0.08 ( $\text{SiCH}_3$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 209.0 (CO), 144.5 (Ar), 135.5 (Ar), 134.8 (C-8), 129.8 (*m*-Ts), 128.7 (*o*-Ts), 124.4 (H-9), 68.3 (CHOTBS), 61.9 (CHTs), 54.3, 50.6, 49.4, 47.5, 42.7, 39.5, 37.1, 36.1, 36.0, 35.9, 33.6, 30.0, 29.7, 28.2, 28.0, 25.8 ( $\text{C}(\text{CH}_3)_3$ ), 24.7, 23.9, 23.8, 22.8, 22.5, 22.4, 21.6, 18.7, 18.0, 12.2, 11.1 (C-18),  $-4.8$  ( $\text{SiCH}_3$ ),  $-5.1$  ( $\text{SiCH}_3$ );  $m/z$  (ESI) 734, 709, 693  $[\text{M}+\text{Na}]^+$ , 688  $[\text{M}+\text{NH}_4]^+$ , 671  $[\text{M}+\text{H}]^+$ , 539 (Found  $[\text{M}+\text{H}]^+$ , 671.4536.  $\text{C}_{40}\text{H}_{66}\text{O}_4\text{SSi}$  requires  $[\text{M}+\text{H}]^+$ , 671.4529).

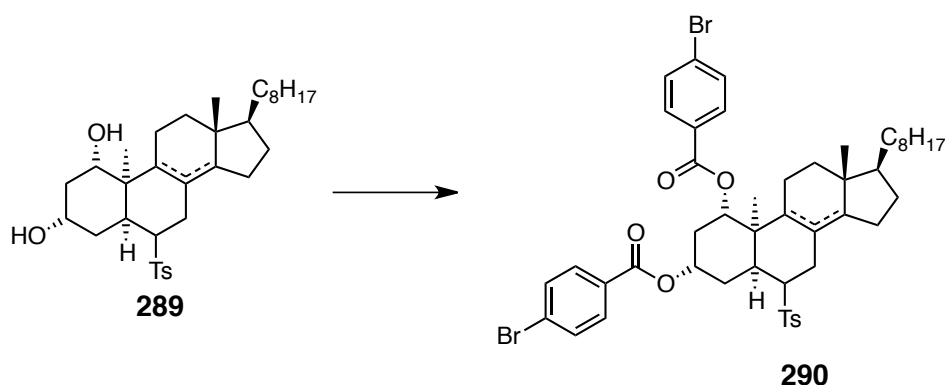
3-(*Tert*-butyldimethylsilyloxy)-6-tosylcholestenol (**288**)

To **283** (40 mg, 65  $\mu$ mol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.3 mL) at  $-78^\circ\text{C}$  was added a pre-prepared solution of trifluoromethanesulfonic acid (6  $\mu$ L, 1 % v/v in  $\text{CH}_2\text{Cl}_2$ , 65  $\mu$ mol, 1 equiv). The reaction mixture was stirred vigorously and allowed to warm to  $-40^\circ\text{C}$  over 2 h before being diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL) and washed with brine (5 mL), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded **288** as a colourless oil (27 mg, 68 %);  $R_f$  0.60 (30 % EtOAc in heptane);  $[\alpha]_D^{25} +54.0$  ( $c$  1.25,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3493, 2954, 2929, 2858, 1598, 1464, 1384, 1366, 1314, 1302, 1286, 1259, 1147, 1087, 1056  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.77 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.35 (2H, d,  $J$  8.0 Hz, *m*-Ts), 4.34 (1H, d,  $J$  9.0 Hz, OH), 4.32–4.26 (1H, m, H-3), 3.81–3.74 (1H, m, H-1), 3.37–3.29 (1H, m, H-6), 2.65–2.57 (1H, m, H-5), 2.46 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.46–2.36 (2H, m, allyl  $\text{CH}_2$  + H-7), 2.25–2.10 (3H, m, contains H-4 + H-2), 1.98–1.03 (H, m), 0.97 (3H, s, H-18), 0.95–0.91 (12H, m, H-21 +  $\text{C}(\text{CH}_3)_3$ ), 0.86 (3H, d,  $J$  2.5 Hz, H-26/27), 0.84 (3H, d,  $J$  2.5 Hz, H-26/27), 0.16 (3H, s,  $\text{SiCH}_3$ ), 0.14 (3H, s,  $\text{SiCH}_3$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 144.2 (Ar), 139.8 (olefin C), 136.1 (olefin C), 135.4 (Ar), 129.8 (*m*-Ts), 128.2 (*o*-Ts), 73.3 (C-1), 68.7 (C-3), 61.7 (C-6), 50.3 (C-10), 48.1 (C-17), 39.0 (C-13), 37.9, 35.7, 35.2, 32.6, 31.9 (C-5), 31.5 (allyl-CH), 29.7, 28.6, 28.0, 27.8, 26.5, 25.8 ( $\text{C}(\text{CH}_3)_3$ ), 25.4, 23.1, 22.7, 22.6, 21.6 ( $\text{CH}_3\text{Ar}$ ), 20.3, 20.2, 19.5, 18.0, 17.9,  $-4.8$  ( $\text{SiCH}_3$ ),  $-5.4$  ( $\text{SiCH}_3$ );  $m/z$  (ESI) 693  $[\text{M}+\text{Na}]^+$ , 671  $[\text{M}+\text{H}]^+$  (Found  $[\text{M}+\text{H}]^+$ , 671.4525.  $\text{C}_{40}\text{H}_{66}\text{O}_4\text{S}$  requires  $[\text{M}+\text{H}]^+$ , 671.4529).

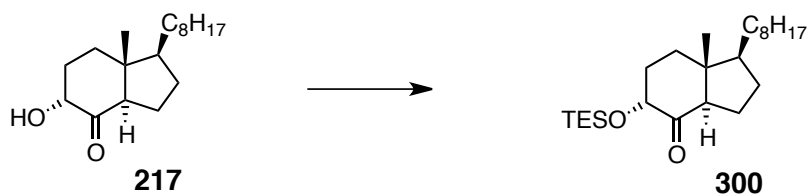


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### 6-Tosylcholestenyl bis-1,3-(4-bromo)benzoate (**290**)

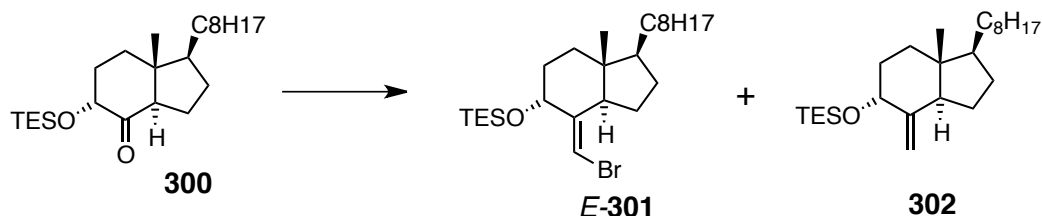


To **289** (33 mg, 0.06 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was added 4-bromobenzoic acid (24 mg, 0.12 mmol, 2 equiv) and DMAP (1.5 mg, 0.012 mmol, 0.1 equiv), followed after 5 mins with DIC (20  $\mu\text{L}$ , 0.126 mmol, 2.1 equiv). The reaction was stirred at rt overnight. The mixture was directly submitted to purification by silica gel chromatography (5 % EtOAc in petrol) to afford **290** as an off-white foamy solid (45 mg, 82 %);  $R_f$  0.45 (5 % EtOAc in petrol);  $[\alpha]_D^{23} +18.5$  ( $c$  0.40,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2928, 1718, 1591, 1452, 1398, 1286, 1148, 1119, 1103, 1013  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 7.77 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.55 (2H, d,  $J$  8.0 Hz, *o*-Ar), 7.51 (2H, d,  $J$  8.0 Hz, *o*-Ar), 7.41 (2H, d,  $J$  8.0 Hz, *m*-Ts), 7.28 (2H, d,  $J$  8.0 Hz, *m*-Ar), 7.18 (2H, d,  $J$  8.0 Hz, *m*-Ar), 5.40–5.35 (1H, m, H-3), 5.30–5.25 (1H, m, H-1), 3.50–3.41 (1H, m, H-6), 2.58–2.38 (5H, m), 2.42 (3H, s,  $\text{CH}_3\text{Ar}$ ), 2.23–2.06 (4H, m), 2.00–1.74 (6H, m), 1.56–0.82 (9H, m), 1.06 (3H, s, H-18), 0.97 (3H, d,  $J$  6.0 Hz, H-21), 0.92 (3H, s, H-19), 0.89 (3H, d,  $J$  2.5 Hz, H-26/27), 0.87 (3H, d,  $J$  2.5 Hz, H-26/27);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 146.2 (Ar), 144.3 (Ar), 141.3 (Ar), 139.2 (olefin C), 136.1 (olefin C), 135.4 (Ar), 131.6 (Ar), 131.3 (Ar), 131.0 (Ar), 130.9 (Ar), 129.8 (Ar), 129.1 (Ar), 128.3 (Ar), 127.8 (Ar), 74.9 (C-1), 68.5 (C-3), 61.2 (C-6), 50.5 (C-10), 47.7 (C-17), 40.1, 39.0 (C-13), 38.0, 35.7, 34.6, 33.8, 31.5 (allyl-CH), 28.2, 28.0, 27.8, 26.9, 25.4, 24.9, 23.0, 22.8, 22.7, 22.6, 21.7, 20.2, 19.6, 19.1 (C-19), 17.9 (C-18);  $m/z$  (ESI) 945  $[\text{M}+\text{Na}]^+$  (Found  $[\text{M}+\text{Na}]^+$ , 945.2228.  $\text{C}_{48}\text{H}_{58}\text{O}_6\text{SBr}^{81}\text{Br}^{79}$  requires  $[\text{M}+\text{Na}]^+$ , 945.2198).

**De-A,B-9 $\alpha$ -(triethylsilyloxy)cholestan-8-one (300)**

To **217** (1.88 g, 6.70 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (35 mL) at 0 °C was added imidazole (912 mg, 13.40 mmol, 2 equiv), followed after 5 min by triethylsilyl chloride (2.25 mL, 13.40 mmol, 2 equiv). The reaction mixture was stirred at rt for 1 h then diluted with  $\text{CH}_2\text{Cl}_2$  (200 mL), washed with  $\text{H}_2\text{O}$  (100 mL) and brine (100 mL), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (2 % EtOAc in petrol) afforded **300** as a colourless oil (2.32 g, 91 %);  $R_f$  0.60 (2 % EtOAc in petrol);  $[\alpha]_D^{24}$   $-15.4$  ( $c$  1.30,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2955, 1724, 1467, 1384, 1239, 1085  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 3.94–3.90 (1H, m, H-9), 3.21 (1H, dd,  $J$  12.0, 7.0 Hz, H-14), 2.00–1.83 (5H, m), 1.80–1.68 (1H, m), 1.61–0.99 (11H, m), 0.99–0.91 (12H, m, H-21 +  $\text{CH}_3\text{CH}_2\text{Si}$ ), 0.90 (3H, d,  $J$  2.0 Hz, H-26/27), 0.88 (3H, d,  $J$  2.0 Hz, H-26/27), 0.63–0.56 (9H, m, H-18 +  $\text{CH}_2\text{Si}$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 211.4 (CO), 75.3 (C-9), 56.7 (C-17), 56.4 (C-14), 51.1 (C-17), 39.5, 36.0, 35.6, 34.0, 33.0, 28.0, 27.6, 23.8, 22.8, 22.6, 18.7, 18.5, 12.1 (C-18), 6.7 ( $\text{CH}_3\text{CH}_2\text{Si}$ ), 4.6 ( $\text{CH}_2\text{Si}$ );  $m/z$  (CI) 412  $[\text{M}+\text{NH}_4]^+$ , 395  $[\text{M}+\text{H}]^+$ , 365, 132 (Found  $[\text{M}+\text{H}]^+$ , 395.3342.  $\text{C}_{24}\text{H}_{46}\text{O}_2\text{Si}$  requires  $[\text{M}+\text{H}]^+$ , 395.3345).

**(*E*)-De-A,B-9 $\alpha$ -(triethylsilyloxy)-8-bromomethylenecholestane (303) and De-A,B-9 $\alpha$ -(triethylsilyloxy)-8-methylenecholestane (302)**



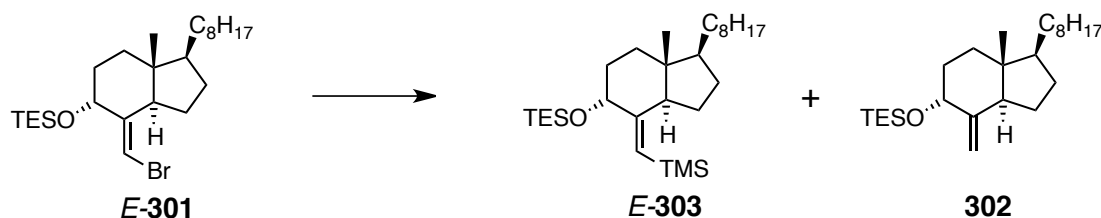
To bromomethyltriphenylphosphonium bromide (3.31 g, 7.60 mmol, 3 equiv) in THF (13 mL) at  $-60^{\circ}\text{C}$  was added NaHMDS (3.49 mL, 2 M in THF, 6.97 mmol, 2.75 equiv) dropwise. After 2 h stirring, **300** (1.00 g, 2.53 mmol, 1 equiv) in THF (2 mL) was added dropwise. The reaction mixture was stirred at  $-60^{\circ}\text{C}$  for 3 h,  $-40^{\circ}\text{C}$  for 2 h, then  $-5^{\circ}\text{C}$  for 15 h. After allowing to warm to rt, the reaction mixture was poured into sat.  $\text{NH}_4\text{Cl}$  (25 mL) and extracted with  $\text{Et}_2\text{O}$  (2 x 75 mL). The combined organic layers were washed with brine (50 mL), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (Petrol) afforded an inseparable mixture of desired product *E*-**301** (809 mg, 68 %) and methylene-derivative **302** (188 mg, 19%) as a colourless oil.

Data for mixture:  $R_f$  1.00 (5 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 2954, 2875, 1466, 1380, 1083, 1038  $\text{cm}^{-1}$ ;  $m/z$  (CI) 490, 488  $[\text{M}(\textbf{301})+\text{NH}_4]^+$ , 443, 392  $[\text{M}(\textbf{302})]^+$ , 391  $[\text{M}(\textbf{301})-\text{Br}]^+$ , 276, 261, 259 (Found  $[\text{M}+\text{NH}_4]^+$ , 488.2913.  $\text{C}_{25}\text{H}_{47}\text{BrOSi}$  requires  $[\text{M}(\textbf{301})+\text{NH}_4]^+$ , 488.2924).

NMR data for *E*-**301**:  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) *inter alia* 6.18 (1H, d,  $J$  1.5 Hz,  $\text{CH}=\text{C}$ ), 4.16–4.12 (1H, m, H-9), 2.61 (1H, ddd,  $J$  13.0, 6.5, 1.0 Hz, H-14), 2.46–2.33 (1H, m), 1.98–0.99 (16H, m), 0.99–0.92 (12H, m, H-21 +  $\text{CH}_3\text{CH}_2\text{Si}$ ), 0.90 (3H, d,  $J$  2.0 Hz, H-26/27), 0.88 (3H, d,  $J$  2.0 Hz, H-26/27), 0.71 (3H, s, H-18), 0.58 (6H, q,  $J$  8.0 Hz,  $\text{CH}_2\text{Si}$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) *inter alia* 145.7 ( $\text{C}=\text{CHBr}$ ), 100.0 ( $\text{CH}=\text{C}$ ), 74.5 (C-9), 55.1 (C-14), 49.8 (C-17), 46.4, 39.5, 36.2, 24.7, 32.2, 28.2, 28.0, 24.0, 23.7, 22.8, 22.6, 19.0, 11.8 (C-18), 6.8 ( $\text{CH}_2\text{Si}$ ), 4.8 ( $\text{CH}_3\text{Si}$ ).

NMR data for **302**:  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) *inter alia* 4.87–4.85 (1H, m,  $\text{CH}_2=\text{C}$ ),

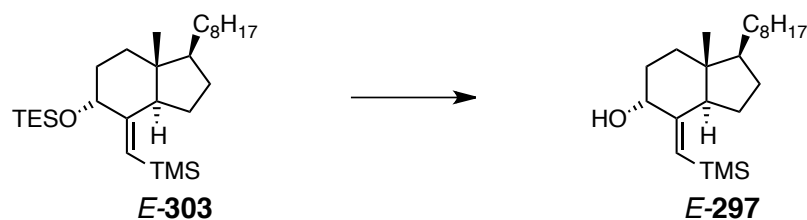
4.55–4.52 (1H, m, CH<sub>2</sub>=C), 4.20–4.17 (1H, m, H-9), 2.56–2.50 (1H, m, H-14), 1.98–0.99 (15H, m), 0.99–0.92 (12H, m, H-21 + CH<sub>3</sub>CH<sub>2</sub>Si), 0.90 (3H, d, *J* 2.0 Hz, H-26/27), 0.88 (3H, d, *J* 2.0 Hz, H-26/27), 0.71 (3H, s, H-18), 0.58 (6H, q, *J* 8.0 Hz, CH<sub>2</sub>Si); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) *inter alia* 151.4 (C=CH<sub>2</sub>), 106.7 (CH<sub>2</sub>=C), 72.8 (C-9), 56.2 (C-14), 49.3 (C-17), 45.1, 39.5, 36.2, 34.7, 32.2, 27.7, 23.9, 23.7, 22.8, 22.6, 21.8, 18.8, 11.2 (C-18), 6.9 (CH<sub>2</sub>Si), 4.9 (CH<sub>3</sub>Si)



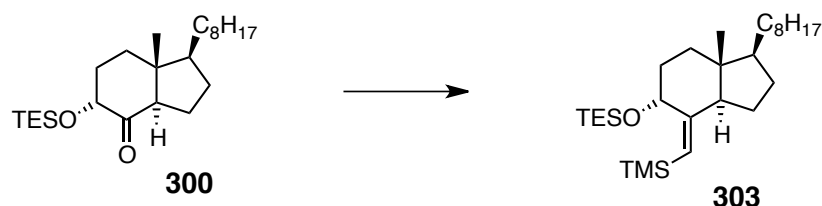
A mixture of *E*-**301** (773 mg, 1.64 mmol, 1 equiv) and **302** (179 mg) in Et<sub>2</sub>O (3.5 mL) at -78 °C was added *t*-BuLi (2.11 mL, 1.55M in pentane, 3.28 mmol, 2 equiv) dropwise. After stirring for 2 h at -78 °C, TMSCl (416 µL, 3.28 mmol, 2 equiv) was added dropwise and the reaction allowed to warm to rt overnight. The reaction mixture was poured into sat. NH<sub>4</sub>Cl (25 mL) and extracted with petrol (2 x 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Purification by silica gel chromatography (Petrol) gave an inseparable mixture of the desired product *E*-**303** (747 mg, 98%) and methylene-derivative **302** (191 mg; 12 mg, 2 % from this step).

Data for **302** as reported above.

Data for **E-303**:  $R_f$  0.90 (Petrol);  $v_{max}$  (film) 2953, 1625, 1467, 1378, 1248, 1078, 1037  $\text{cm}^{-1}$ ;  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) *inter alia* 5.40 (1H, CH=C), 4.06–4.02 (1H, m, H-9), 2.79–2.68 (1H, m, H-14), 2.00–1.84 (1H, m), 1.78–1.00 (16H, m), 0.98–0.86 (18H, m,  $\text{CH}_3\text{CH}_2\text{Si}$  + H-21, 26, 27), 0.62–0.54 (9H, m,  $\text{CH}_2\text{Si}$  + H-18), 0.13 (9H, s,  $\text{CH}_3\text{Si}$ );  $\delta_C$  ( $\text{CDCl}_3$ , 100 MHz) *inter alia* 160.4 (C=CH), 122.4 (CH=C), 79.8 (C-9), 55.8 (C-14), 51.0 (C-17), 46.6, 45.0, 39.5, 36.0, 34.9, 32.5, 28.0, 27.9, 24.2, 23.9, 22.8, 22.5, 21.8, 18.9, 11.7 (C-18), 6.9 ( $\text{CH}_3\text{CH}_2\text{Si}$ ), 4.9 ( $\text{CH}_2\text{Si}$ ) 2.0 ( $\text{CH}_3\text{Si}$ );  $m/z$  (CI) 465  $[\text{M}+\text{H}]^+$ , 350, 333, 261 (Found  $[\text{M}+\text{H}]^+$ , 465.3953.  $\text{C}_{28}\text{H}_{56}\text{OSi}_2$  requires  $[\text{M}+\text{H}]^+$ , 465.3948).

**(*E*)-De-A,B-9 $\alpha$ -hydroxy-8-(trimethylsilyl)methylenecholestane (297)**

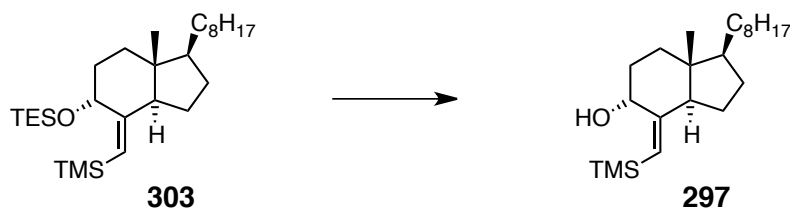
To a *E*-**303** (85 mg, 0.18 mmol, 1 equiv) in 10% H<sub>2</sub>O/THF (1.2 mL) cooled to 0 °C was added DDQ (4 mg, 0.02 mmol, 0.1 equiv). The reaction was allowed to warm to rt and stirred overnight. The reaction mixture was directly purified by silica gel chromatography (1-5 % EtOAc in petrol) to afford *E*-**297** as a colourless oil (52 mg, 82 %); *R*<sub>f</sub> 0.45 (5 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>24</sup> +36.3 (*c* 1.15, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3334, 2952, 1623, 1468, 1381, 1248, 1014 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 5.53 (1H, s, CH=C), 4.17–4.10 (1H, m, H-9), 2.75–2.63 (1H, m, H-14), 2.01–1.01 (18H, m), 0.96 (3H, d, *J* 6.0 Hz, H-21), 0.92–0.85 (6H, m, H-26-27), 0.62 (3H, s, H-18), 0.15 (9H, CH<sub>3</sub>Si);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 158.8 (C=CH), 126.4 (CH=C), 79.8 (C-9), 55.7 (C-14), 50.9 (C-17), 46.7, 39.5, 36.1, 35.9, 34.7, 30.7, 28.0, 27.8, 24.6, 23.8, 22.8, 22.6, 18.9, 11.7 (C-18), 1.52 (CH<sub>3</sub>Si); *m/z* (CI) 368 [M+NH<sub>4</sub>]<sup>+</sup>, 350 [M]<sup>+</sup>, 333 [M–OH]<sup>+</sup>, 261 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 368.3346. C<sub>22</sub>H<sub>42</sub>OSi requires [M+NH<sub>4</sub>]<sup>+</sup>, 368.3349).

**(Z)-De-A,B-9 $\alpha$ -(triethylsilyloxy)-8-(trimethylsilyl)methylenecholestane (303)**

To  $\text{Me}_3\text{SiCH}_2\text{SiMe}_2(\text{OMe})$  (1.12 g, 6.34 mmol, 1.2 equiv) in pentane (18 mL) at rt was added  $t\text{-BuLi}$  (4.10 mL, 1.55 M in pentane, 6.34 mmol, 1.2 equiv) dropwise. After 2 h stirring at rt the reaction mixture was cooled to  $-78^\circ\text{C}$  and **300** (2.09 g, 5.28 mmol, 1 equiv) in pentane (5 mL) added dropwise. The reaction was allowed to warm to rt overnight, then poured into sat.  $\text{NH}_4\text{Cl}$  (25 mL) and extracted with petrol (2 x 100 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. The crude oil obtained was placed in an oven set at  $110^\circ\text{C}$  for 3 h. Purification by silica gel chromatography (Petrol) afforded **303** as a colourless oil (811 mg, 33 %, 3:2 *Z/E*).

Data for *E*-**303** as reported above.

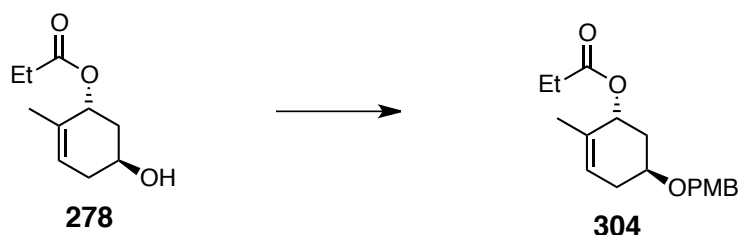
Data for *Z*-**303**:  $R_f$  0.90 (Petrol);  $\nu_{\text{max}}$  (film) 2953, 2875, 1625, 1466, 1248, 1080, 1048, 836  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 4.99 (1H, s,  $\text{CH}=\text{C}$ ), 4.52–4.48 (1H, m, H-9), 2.81–2.69 (1H, m, H-14), 1.97–1.86 (1H, m), 1.77–0.99 (16H, m), 0.99–0.85 (18H, m, H-21, 26, 27,  $\text{CH}_3\text{CH}_2\text{Si}$ ), 0.61 (6H, q,  $J$  8.0 Hz,  $\text{CH}_2\text{Si}$ ), 0.52 (3H, s, H-18), 0.15 (9H, s,  $(\text{CH}_3)_3\text{Si}$ );  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 160.0 ( $\text{C}=\text{CHTMS}$ ), 118.3 ( $\text{CH}=\text{C}$ ), 71.0 (C-9), 56.7 (C-14), 51.2 (C-17), 46.1, 39.5, 36.2, 36.1, 34.7, 32.5, 28.0, 27.7, 24.0, 22.9, 22.6, 21.7, 18.8, 11.2 (C-18), 7.0 ( $\text{CH}_3\text{CH}_2\text{Si}$ ), 5.3 ( $\text{CH}_2\text{Si}$ ), 0.8 ( $(\text{CH}_3)_3\text{Si}$ );  $m/z$  (CI) 465  $[\text{M}+\text{H}]^+$ , 333 (Found  $[\text{M}+\text{H}]^+$ , 465.3937.  $\text{C}_{28}\text{H}_{56}\text{OSi}_2$  requires  $[\text{M}+\text{H}]^+$ , 465.3948).

**(Z)-De-A,B-9 $\alpha$ -hydroxy-8-(trimethylsilyl)methylenecholestane (297)**

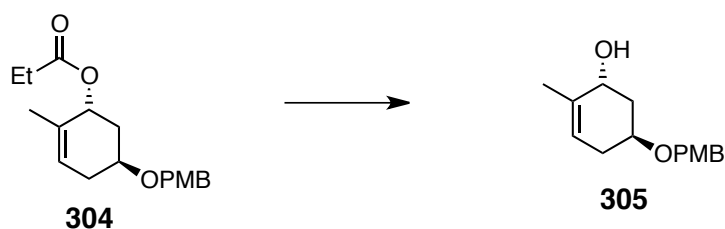
To **303** (790 mg, 1.69 mmol, 1 equiv, 3:2 *Z/E*) in 10% H<sub>2</sub>O/THF (11 mL) cooled to 0 °C was added DDQ (39 mg, 0.17 mmol, 0.1 equiv). The reaction was allowed to warm to rt and stirred for 18 h. The reaction mixture was directly purified by silica gel chromatography (1-5 % EtOAc in petrol) to afford **297** as a colourless oil (240 mg, 41 %, 15:1 *Z/E*).

Data for *E*-**297** as reported above.

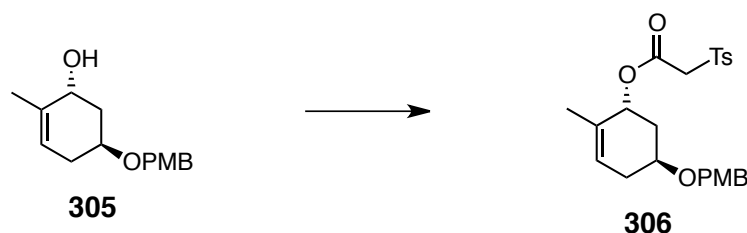
Data for *Z*-**297**: *R*<sub>f</sub> 0.50 (5 % EtOAc in petrol); *v*<sub>max</sub> (film) 3334, 2952, 1623, 1468, 1380, 1248, 1014 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 5.20 (1H, d, *J* 2.0 Hz, CH=C), 4.54–4.51 (1H, m, *CHOH*), 2.61–2.54 (1H, m, H-14), 1.97–1.85 (1H, m), 1.86–0.99 (17H, m), 0.95 (3H, d, *J* 6.0 Hz, H-21), 0.90 (3H, d, *J* 2.0 Hz, H-26/27), 0.88 (3H, d, *J* 2.0 Hz, H-26/27), 0.54 (3H, s, H-18), 0.16 (9H, s, (CH<sub>3</sub>)<sub>3</sub>Si);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 159.5 (C=CH), 122.9 (CH=C), 70.2 (C-9), 56.5 (C-14), 51.5 (C-17), 45.7, 39.5, 36.1, 34.7, 30.3, 28.0, 27.4, 23.9, 22.8, 22.6, 22.1, 18.8, 11.1 (C-18), 0.6 ((CH<sub>3</sub>)<sub>3</sub>Si); *m/z* (CI) 350 [M]<sup>+</sup>, 333 [M–OH]<sup>+</sup>, 261, 90 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 368.3341. C<sub>22</sub>H<sub>42</sub>OSi requires [M+NH<sub>4</sub>]<sup>+</sup>, 368.3349).

**(1*R*,5*S*)-5-(4-Methoxybenzyloxy)-2-methylcyclohex-2-enyl propionate (304)**

To **278** (574 mg, 3.11 mmol, 1 equiv) and PMBTCA (1.32 g, 4.67 mmol, 1.5 equiv) in PhMe (62 mL) at rt was added lanthanum trifluoromethanesulfonate hydrate (91 mg, 0.16 mmol, 0.05 equiv). The reaction mixture was stirred for 40 min before pouring onto a silica gel plug, eluting first with petrol to remove PhMe, then Et<sub>2</sub>O to elute the crude product containing some *p*-methoxybenzylalcohol. Further purification by silica gel chromatography (5–10 % EtOAc in petrol) afforded **304** as a colourless oil (842 mg, 89 %); *R*<sub>f</sub> 0.70 (10 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>23</sup> +39.4 (*c* 1.10, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2940, 1838, 1732, 1613, 1514, 1462, 1358, 1248, 1183 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.30–7.26 (2H, m, *m*-PMB), 6.91–6.87 (2H, m, *o*-PMB), 5.61–5.57 (1H, m, CH=C), 5.42–5.38 (1H, m, CH-ester), 4.53 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub>), 4.49 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub>), 3.82 (3H, s, CH<sub>3</sub>O), 3.80–3.71 (1H, m, CHOPMB), 2.52–2.43 (1H, m, ring CH<sub>2</sub>), 2.35 (2H, dq, *J* 7.5, 1.5 Hz, CH<sub>3</sub>CH<sub>2</sub>), 2.14–1.99 (2H, m, ring CH<sub>2</sub>), 1.90–1.82 (1H, m, ring CH<sub>2</sub>), 1.68 (3H, s, CH<sub>3</sub>), 1.17 (3H, t, *J* 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 174.2 (CO), 159.2 (Ar), 131.8 (C=CH), 130.7 (Ar), 129.3 (*m*-PMB), 125.1 (C=CH), 113.8 (*o*-PMB), 71.0 (CH-ester), 70.4 (CHOPMB), 69.9 benzyl CH<sub>2</sub>), 55.3 (CH<sub>3</sub>O), 34.4 (ring CH<sub>2</sub>), 32.0 (ring CH<sub>2</sub>), 27.9 (CH<sub>2</sub>CH<sub>2</sub>), 20.1 (CH<sub>3</sub>C=C), 9.2 (CH<sub>3</sub>CH<sub>2</sub>); *m/z* (CI) 442, 322 [M+NH<sub>4</sub>]<sup>+</sup>, 231, 138, 121 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 322.2011. C<sub>18</sub>H<sub>24</sub>O<sub>4</sub> requires [M+NH<sub>4</sub>]<sup>+</sup>, 322.2019).

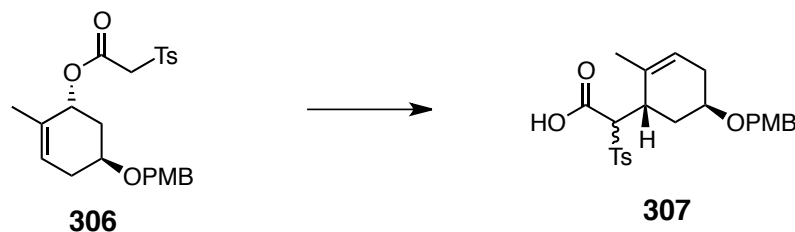
**(1*R*,5*S*)-5-(4-Methoxybenzyloxy)-2-methylcyclohex-2-enol (305)**

To **304** (825 mg, 2.71 mmol, 1 equiv) in MeOH (7 mL) at 0 °C was added methanolic KOH (5.4 mL, 1 M in MeOH, 5.40 mmol, 2 equiv). The reaction was allowed to warm to rt and stirred for 15 h before diluting with Et<sub>2</sub>O (100 mL) and washing with 1 N HCl (10 mL) then sat. NaHCO<sub>3</sub> (20 mL). The organic layer was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure before purification by silica gel chromatography (10–25 % EtOAc in petrol) afforded **305** as a colourless oil (557 mg, 83 %); *R<sub>f</sub>* 0.15 (10 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>23</sup> +50.0 (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3400, 2915, 1613, 1514, 1452, 1356, 1302, 1248, 1172, 1095, 1033 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.32–7.27 (2H, m, *m*-PMB), 6.93–6.87 (2H, m, *o*-PMB), 5.49–5.44 (1H, m, CH=C), 4.53 (2H, s, benzyl CH<sub>2</sub>), 4.21–4.16 (1H, m, CHOH), 3.85–3.77 (1H, m, CHOPMB), 3.83 (3H, s, CH<sub>3</sub>O), 2.50–2.40 (1H, m, ring CH<sub>2</sub>), 2.18–2.11 (1H, m, ring CH<sub>2</sub>), 2.08–1.98 (1H, m, ring CH<sub>2</sub>), 1.87–1.78 (1H, m, ring CH<sub>2</sub>), 1.81 (2H, s, CH<sub>3</sub>C=C);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 159.1 (Ar), 135.0 (C=CH), 130.9 (Ar), 129.2 (*m*-PMB), 122.7 (C=CH), 113.8 (*o*-PMB), 70.4 (CHOPMB), 69.9 (benzyl CH<sub>2</sub>), 69.2 (CHOH), 55.3 (CH<sub>3</sub>O), 37.6 (ring CH<sub>2</sub>), 32.1 (ring CH<sub>2</sub>), 20.3 (CH<sub>3</sub>C=C); *m/z* (CI) 266 [M+NH<sub>4</sub>]<sup>+</sup>, 248 [M]<sup>+</sup>, 231, 138, 121 (Found [M+NH<sub>4</sub>]<sup>+</sup>, 266.1748. C<sub>15</sub>H<sub>20</sub>O<sub>3</sub> requires [M+NH<sub>4</sub>]<sup>+</sup>, 266.1756).

**(1*R*,5*S*)-5-(4-Methoxybenzyloxy)-2-methylcyclohex-2-enyl 2-tosylacetate (306)**

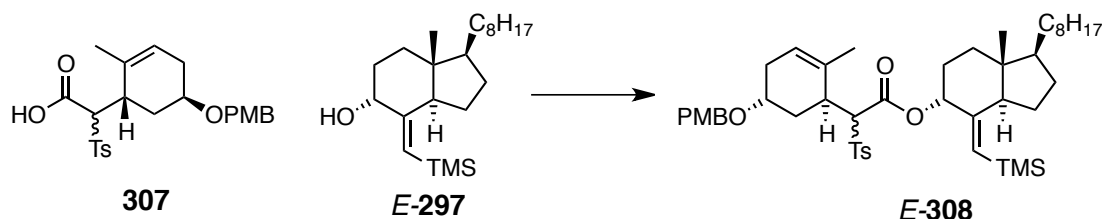
To **305** (524 mg, 2.11 mmol, 1 equiv) and 2-tosylacetic acid (452 mg, 2.11 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (11 mL) at 0 °C was added DMAP (26 mg, 0.21 mmol, 0.1 equiv) then DIC (361 μL, 2.32 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 3 h then filtered through Celite®. The solids were washed with Et<sub>2</sub>O (20 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded **306** as a colourless oil (858 mg, 91 %); *R*<sub>f</sub> 0.20 (10 % EtOAc in petrol); [ $\alpha$ ]<sub>D</sub><sup>24</sup> +39.4 (*c* 1.10, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2924, 1735, 1613, 1514, 1328, 1248, 1156, 1085 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.84 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.38 (2H, d, *J* 8.0 Hz, *m*-Ts), 7.31–7.26 (2H, m, *m*-PMB), 6.91–6.87 (2H, m, *o*-PMB), 5.645.59 (1H, m, CH=C), 5.40–5.36 (1H, m, CH-ester), 4.50 (2H, s, benzyl CH<sub>2</sub>), 4.12 (2H, s, CH<sub>2</sub>Ts), 3.82 (3H, s, CH<sub>3</sub>O), 3.76–3.68 (1H, m, CHOPMB), 2.50–2.41 (1H, m, ring CH<sub>2</sub>), 2.46 (3H, s, CH<sub>3</sub>Ar), 2.14–1.98 (2H, m, ring CH<sub>2</sub>), 1.86–1.78 (1H, m, ring CH<sub>2</sub>), 1.65 (3H, s, CH<sub>3</sub>C=C);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 162.2 (CO), 159.2 (Ar), 145.4 (Ar), 135.9 (C=CH), 130.7 (Ar), 130.6 (Ar), 129.9 (*m*-Ts), 129.3 (*m*-PMB), 128.5 (*o*-Ts), 126.3 (CH=C), 113.8 (*o*-PMB), 73.9 (CH-ester), 70.3 (benzyl CH<sub>2</sub>), 70.1 (CHOPMB), 61.2 (CH<sub>2</sub>Ts), 55.3 (CH<sub>3</sub>O), 34.2 (ring CH<sub>2</sub>), 31.9 (ring CH<sub>2</sub>), 21.7 (CH<sub>3</sub>Ar), 20.1 (CH<sub>3</sub>C=C); *m/z* (ESI) 504, 483, 467 [M+Na]<sup>+</sup>, 462 [M+NH<sub>4</sub>]<sup>+</sup> (Found [M+Na]<sup>+</sup>, 467.1503. C<sub>24</sub>H<sub>28</sub>O<sub>6</sub>S requires [M+Na]<sup>+</sup>, 467.1505).

**2-((1*S*,5*R*)-5-(4-Methoxybenzyloxy)-2-methylcyclohex-2-enyl)-2-tosylacetic acid (307)**



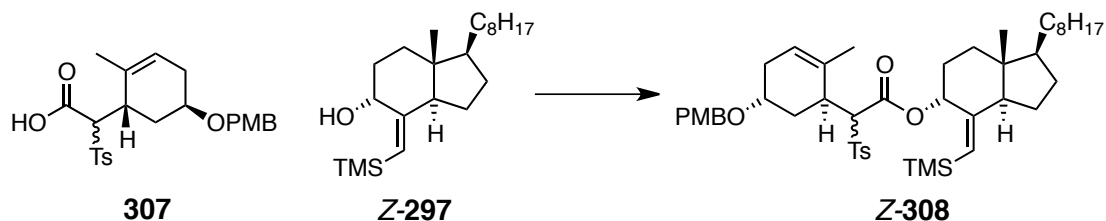
To a solution of **306** (770 mg, 1.73 mmol, 1 equiv) in CH<sub>3</sub>CN (6 mL) was added Et<sub>3</sub>N (290 μL, 2.07 mmol, 1.2 equiv) then BSA (1.27 mL, 5.19 mmol, 3 equiv). The reaction mixture was heated to reflux for 6 h, before being cooled, diluted with EtOAc (75 mL), washed with 1 N HCl (20 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol + 10 % MeOH + 1 % AcOH) afforded a 7:3 mixture of epimers of **307** as a white solid (620 mg, 81 %); R<sub>f</sub> 0.30 (10 % EtOAc in petrol); mp 69–70 °C; ν<sub>max</sub> (film) 3440, 2924, 1732, 1613, 1514, 1318, 1304, 1248, 1146, 1086, 1035 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 7.89–7.82 (2H, m, *o*-Ts), 7.38–7.33 (2H, m, *m*-Ts), 7.32–7.25 (2H, m, *m*-PMB), 6.91–6.86 (2H, m, *o*-PMB), 5.47 (1H, s, CH=C), 4.57 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub> major), 4.41 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub> major), 4.35 (2H, d, *J* 2.5 Hz, benzyl CH<sub>2</sub> minor), 3.82 (CH<sub>3</sub>O), 3.76–3.70 (1H, m, CHOPMB), 3.25–3.16 (1H, m, CHTs major), 3.16–3.09 (1H, m, CHTs minor). 2.58–2.00 (5H, m, ring CH<sub>2</sub>), 2.47 (3H, s, CH<sub>3</sub>Ar major), 2.45 (3H, s, CH<sub>3</sub>Ar minor), 1.65 (3H, s, CH<sub>3</sub>C=C minor), 1.64 (3H, s, CH<sub>3</sub>C=C major); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 168.6 (CO), 159.1 (Ar), 145.6 (Ar), 135.2 (C=CH), 130.8 (Ar), 130.7 (Ar), 130.0 (*m*-Ts), 129.8 (*m*-PMB), 129.4 (*m*-PMB major), 129.4 (*m*-PMB minor), 129.1 (*o*-Ts), 125.0 (CH=C minor), 124.0 (CH=C major), 113.8 (*o*-PMB), 72.5 (CHTs minor), 70.2 (CHOPMB), 69.8 (CHTs major), 69.5 (benzyl CH<sub>2</sub>), 53.3 (CH<sub>3</sub>O), 38.7 (CHCHTs minor), 35.8 (CHCHTs major), 31.2 (ring CH<sub>2</sub>), 27.8 (ring CH<sub>2</sub>), 22.7, 21.7 (CH<sub>3</sub>Ar), 21.3 (CH<sub>3</sub>C=C); *m/z* (ESI) 467 [M+Na]<sup>+</sup>, 462 [M+NH<sub>4</sub>]<sup>+</sup>, 423 [M+Na–CO<sub>2</sub>]<sup>+</sup> (Found [M+Na]<sup>+</sup>, 467.1512. C<sub>24</sub>H<sub>28</sub>O<sub>6</sub>S requires [M+NH<sub>4</sub>]<sup>+</sup>, 467.1505).

**(*E*)-De-A,B-8-(trimethylsilyl)methylenecholestan-9 $\alpha$ -yl 2-((1*S*,5*R*)-5-(4-methoxybenzyloxy)-2-methylcyclohex-2-enyl)-2-tosylacetate (**308**)**



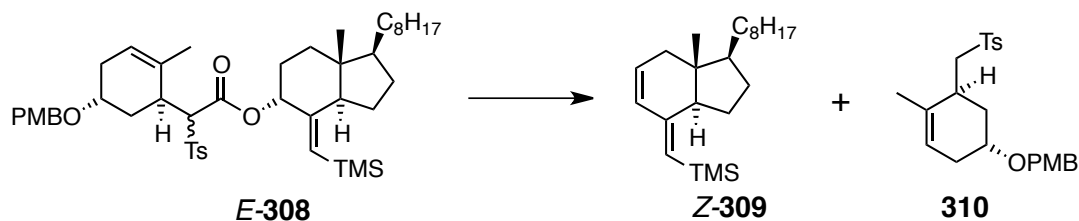
To *E*-**297** (237 mg, 0.67 mmol, 1 equiv) and **307** (300 mg, 0.67 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) at rt was added DMAP (8 mg, 0.07 mmol, 0.1 equiv) then DIC (115  $\mu$ L, 0.74 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 48 h then filtered through Celite®. The solids were washed with Et<sub>2</sub>O (10 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded *E*-**308** as a colourless oil (338 mg, 65 %); *R*<sub>f</sub> 0.65 (10 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 2952, 1738, 1598, 1514, 1328, 1248, 1145, 1087 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.89–7.81 (2H, m, *o*-Ts), 7.37–7.26 (4H, m, *m*-Ts, *m*-PMB), 6.92–6.86 (2H, m, *o*-PMB), 5.58–5.54 (1H, m, H-9), 5.50–5.39 (1H, m, CH=C), 5.25–5.17 (1H, m, TMSCH=C), 4.63 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub>), 4.43 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub>), 4.35 (1H, d, *J* 2.5 Hz, CHTs), 3.83–3.79 (3H, m, CH<sub>3</sub>O), [1H, 3.78–3.72 (m) and 3.40–3.30 (m), CHCHTs], 2.44 (3H, s, CH<sub>3</sub>Ar), 2.57–0.96 (23H, m), 1.70 (3H, m, CH<sub>3</sub>C=C), 0.97–0.84 (9H, m, H-21, H-26/27), 0.52–0.47 (3H, m, H-18), 0.09–0.05 (9H, m, CH<sub>3</sub>Si);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 164.1 (CO), 159.1 (C=CTMS), 153.0 (C=CH), 144.9 (Ar), 135.9 (Ar), 131.2 (Ar), 130.9 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 129.3 (Ar), 129.2 (Ar), 125.6 (TMSCH=C), 123.7 (CH=C), 113.7 (Ar), 75.1 (C-9), 70.3, 70.1 (CHCHTs), 69.5 (CHTs), 69.4 (benzyl CH<sub>2</sub>), 56.6, 55.3, 52.8, 45.1, 40.9, 39.5, 36.0, 35.2, 34.6, 31.3, 28.4, 28.3, 28.0, 27.7, 27.4, 23.9, 22.8, 22.6, 22.0, 21.7, 21.6, 20.8, 18.8, 17.4, 17.3, 14.7, 11.2 and 11.1 (C-18), 7.9, 0.3 (CH<sub>3</sub>Si), 0.2 (CH<sub>3</sub>Si); *m/z* (ESI) 799 [M+Na]<sup>+</sup> (Found [M+Na]<sup>+</sup>, 799.4429. C<sub>46</sub>H<sub>68</sub>O<sub>6</sub>SSi requires [M+Na]<sup>+</sup>, 799.4404).

**(Z)-De-A,B-8-(trimethylsilyl)methylenecholestan-9 $\alpha$ -yl 2-((1*S*,5*R*)-5-(4-methoxybenzyloxy)-2-methylcyclohex-2-enyl)-2-tosylacetate (**308**)**



To **Z-297** (240 mg, 0.68 mmol, 1 equiv) and **307** (304 mg, 0.68 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) at rt was added DMAP (8 mg, 0.07 mmol, 0.1 equiv) then DIC (117  $\mu$ L, 0.74 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 96 h then filtered through Celite®. The solids were washed with Et<sub>2</sub>O (10 mL), and the filtrate concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petrol) afforded **Z-308** as a colourless oil (380 mg, 72 %); *R*<sub>f</sub> 0.60 (10 % EtOAc in petrol);  $\nu_{\text{max}}$  (film) 2953, 1736, 1627, 1613, 1598, 1514, 1466, 1326, 1249, 1146, 1086 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz) 7.89–7.81 (2H, m, *o*-Ts), 7.37–7.26 (4H, m, *m*-Ts, *m*-PMB), 6.92–6.86 (2H, m, *o*-PMB), 5.60–5.55 (1H, m, H-9), 5.50–5.39 (1H, m, CH=C), 5.25–5.20 (1H, m, TMSCH=C), 4.63 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub>), 4.43 (1H, d, *J* 11.5 Hz, benzyl CH<sub>2</sub>), 4.35 (1H, d, *J* 2.5 Hz, CHTs), 3.83–3.79 (3H, m, CH<sub>3</sub>O), [1H, 3.78–3.72 (m) and 3.40–3.30 (m), CHCHTs], 2.44 (3H, s, CH<sub>3</sub>Ar), 2.57–0.96 (23H, m), 1.70 (3H, m, CH<sub>3</sub>C=C), 0.97–0.84 (9H, m, H-21, H-26/27), 0.52–0.47 (3H, m, H-18), 0.09–0.05 (9H, m, CH<sub>3</sub>Si);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz) 164.1 (CO), 159.1 (C=CTMS), 153.0 (C=CH), 144.9 (Ar), 135.9 (Ar), 131.2 (Ar), 130.9 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 129.3 (Ar), 129.2 (Ar), 125.6 (TMSCH=C), 123.7 (CH=C), 113.7 (Ar), 75.1 (C-9), 70.3, 70.1 (CHCHTs), 69.5 (CHTs), 69.4 (benzyl CH<sub>2</sub>), 56.6, 55.3, 52.8, 45.1, 40.9, 39.5, 36.0, 35.2, 34.6, 31.3, 28.4, 28.3, 28.0, 27.7, 27.4, 23.9, 22.8, 22.6, 22.0, 21.7, 21.6, 20.8, 18.8, 17.4, 17.3, 14.7, 11.2 and 11.1 (C-18), 7.9, 0.3 (CH<sub>3</sub>Si), 0.2 (CH<sub>3</sub>Si).

**(Z)-De-A,B-8-(trimethylsilyl)methylenecholest-9(11)-ene (309) and 1-Methoxy-4-(((1*R*,5*S*)-4-methyl-5-(tosylmethyl)cyclohex-3-enyloxy)methyl)benzene (310)**

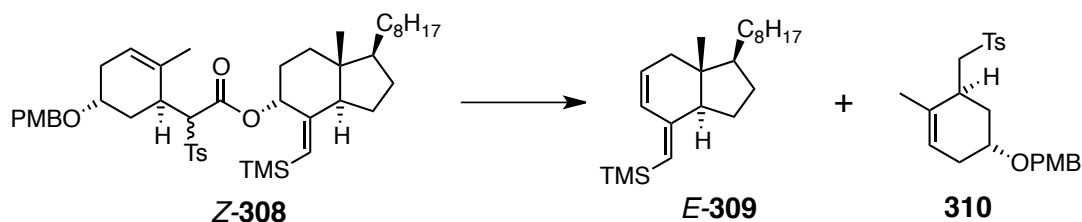


To *E*-**308** (31 mg, 0.04 mmol, 1 equiv) and KOAc (0.5 mg, 0.004 mmol, 0.1 equiv) in a capped microwave vial was added BSA (190  $\mu$ L). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for 3  $\times$  1 min (including a 1 min cooling period between each 1 min heating period). Purification of the crude reaction mixture by silica gel chromatography (5–10 % EtOAc in petrol) afforded *Z*-**309** as a colourless oil (8 mg, 60 %) and **310** as a white solid (90 mg, 56 %) along with returned starting material *Z*-**308** (10 mg, 32 %).

Data for *Z*-**309**:  $R_f$  1.00 (5 % EtOAc in petrol);  $[\alpha]_D^{26} +25.9$  ( $c$  0.90,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2954, 2870, 1624, 1574, 1467, 1378, 1248  $\text{cm}^{-1}$ ;  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 6.37–6.31 (1H, m, H-9), 5.79–5.71 (1H, m, H-11), 5.23 (1H, s, CH=C), 2.36 (1H, dd,  $J$  18.0, 5.5 Hz, H-12), 2.34–2.26 (1H, m, H-14), 2.24–2.15 (1H, m, H-12), 2.02–1.87 (1H, m), 1.78–0.98 (18H, m), 0.95 (3H, d,  $J$  6.0 Hz, H-21), 0.91 (3H, d,  $J$  2.0 Hz, H-26/27), 0.89 (3H, d,  $J$  2.0 Hz, H-26/27), 0.59 (3H, s, H-18), 0.16 (9H, s,  $\text{CH}_3\text{Si}$ );  $\delta_C$  ( $\text{CDCl}_3$ , 100 MHz) 142.0 (C-8), 128.4 (C-11), 122.7 (C-9), 122.0 (C=CHTMS), 57.7, (C-14) 43.3, 39.5, 38.9, 36.0, 34.3, 28.0, 27.8, 26.6, 23.8, 22.8, 22.6, 22.2, 18.8, 15.7 (C-18), 0.89 ( $\text{CH}_3\text{Si}$ );  $m/z$  (EI) 332  $[\text{M}]^+$ , 260  $[\text{M-TMS}]^+$ , 147 (Found  $[\text{M}]^+$ , 332.2906.  $\text{C}_{22}\text{H}_{40}\text{Si}$  requires  $[\text{M}]^+$ , 332.2899).

Data for **310**:  $R_f$  0.30 (10% EtOAc in petrol);  $[\alpha]_D^{23} -16.7$  ( $c$  0.40,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2926, 1613, 1513, 1454, 1302, 1248, 1145, 1088, 1035  $\text{cm}^{-1}$ ;  $\delta_H$  ( $\text{CDCl}_3$ , 400 MHz) 7.84 (2H, d,  $J$  8.0 Hz, *o*-Ts), 7.40 (2H, d,  $J$  8.0 Hz, *m*-Ts), 7.30 (2H, d,  $J$  8.5 Hz, *m*-PMB) 6.91 (2H, d,  $J$  8.5 Hz, *o*-PMB), 5.37 (1H, m, C=CH), 4.52 (1H, d,  $J$  11.5 Hz, benzyl- $\text{CH}_2$ ), 4.45 (1H, d,  $J$  11.5 Hz, benzyl- $\text{CH}_2$ ), 3.84 (3H, s,  $\text{OCH}_3$ ), 3.59 (1H,

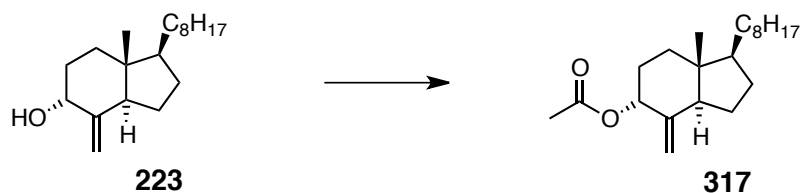
m, *CHOPMB*), 3.17 (1H, dd, *J* 14.5, 1.5 Hz, TsCH<sub>2</sub>), 3.00 (1H, dd, *J* 14.5, 10.0 Hz, TsCH<sub>2</sub>) 2.70 (1H, m, *CHCH*<sub>2</sub>Ts), 2.48 (3H, s, Ts-CH<sub>3</sub>), 2.38-2.22 (2H, m, ring-CH<sub>2</sub>), 2.02 (1H, m, ring-CH<sub>2</sub>), 1.78 (1H, m, ring-CH<sub>2</sub>), 1.53 (3H, s, C=CCH<sub>3</sub>); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 159.1 (Ar), 144.8 (Ar), 136.7, 133.0, 130.7, 130.0 (*m*-Ts), 129.3 (*m*-PMB), 128.0 (*o*-Ts), 122.7 (*o*-PMB), 113.8 (C=CH), 69.6 (OCH<sub>3</sub>), 69.5 (benzyl-CH<sub>2</sub>), 58.4 (TsCH<sub>2</sub>), 55.3 (1/3), 34.4 (*CHCH*<sub>2</sub>Ts), 32.1 (ring-CH<sub>2</sub>), 31.9 (ring-CH<sub>2</sub>), 21.7 (Ts-CH<sub>3</sub>), 21.0 (C=CCH<sub>3</sub>); *m/z* (ESI) 423 [M+Na]<sup>+</sup> (Found [M+NH<sub>4</sub>]<sup>+</sup>, 423.1603. C<sub>23</sub>H<sub>28</sub>O<sub>4</sub>S requires [M+Na]<sup>+</sup>, 423.1606).



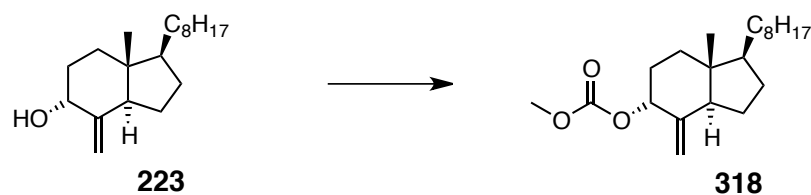
To **Z-308** (64 mg, 0.08 mmol, 1 equiv) and KOAc (2 mg, 0.02 mmol, 0.25 equiv) in a capped microwave vial was added BSA (200  $\mu$ L, 1.18 mmol, 15 equiv). The mixture was heated by microwave irradiation at 180  $^{\circ}$ C for  $3 \times 1$  min (including a 1 min cooling period between each 1 min heating period). Purification of the crude reaction mixture by silica gel chromatography (0–20 % EtOAc in petrol) afforded *E*-**309** as a colourless oil (20 mg, 73 %) and **310** as a white solid (21 mg, 64 %) along with returned starting material **Z-308** (12 mg, 18 %).

Data for ***E*-309**: R<sub>f</sub> 1.00 (5 % EtOAc in petrol); [α]<sub>D</sub><sup>26</sup> +6.3 (*c* 0.80, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 2954, 2870, 1623, 1573, 1467, 1379, 1248 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 6.04 (1H, dd, *J* 9.5, 2.5 Hz, H-9), 5.68–5.61 (1H, m, H-11), 5.41 (1H, s, CH=C), 2.39–2.27 (1H, m, H-14), 2.37 (1H, dd, *J* 17.5, 5.5 Hz, H-12), 2.19–2.10 (1H, m H-12), 2.02–1.87 (2H, m), 1.82–0.72 (20H, m), 0.64 (3H, s, H-18), 0.18 (9H, s, CH<sub>3</sub>Si); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 154.8 (C-8), 134.7 (C-11), 127.8 (C-9), 127.6 (C=CHTMS), 55.6, 52.7, 44.0, 42.3, 39.5, 36.1, 35.8, 28.1, 28.0, 24.9, 23.8, 22.8, 22.6, 18.5, 11.9 (C-18), 1.9 (CH<sub>3</sub>Si); *m/z* (EI) 332 [M]<sup>+</sup>, 317, 260 [M-TMS]<sup>+</sup>, 147 (Found [M]<sup>+</sup>, 332.2894. C<sub>22</sub>H<sub>40</sub>Si requires [M]<sup>+</sup>, 332.2899).

Data for **310** as reported above.

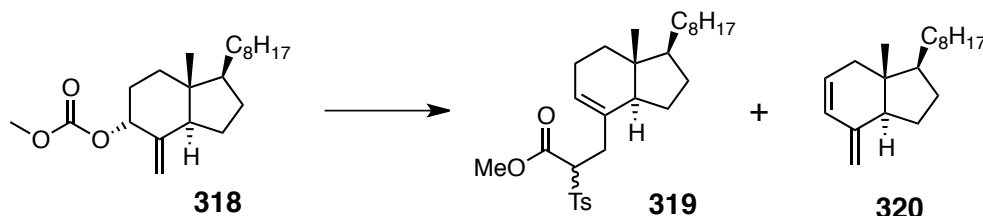
**De-A,B-8-methylenecholestan-9 $\alpha$ -yl acetate (317)**

To **223** (198 mg, 0.71 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at rt was added pyridine (230  $\mu\text{L}$ , 2.84 mmol, 4 equiv), then DMAP (5 mg, 0.04 mmol, 0.05 equiv), then  $\text{Ac}_2\text{O}$  (80  $\mu\text{L}$ , 0.85 mmol, 1.2 equiv). The reaction mixture was stirred for 3 h.  $\text{H}_2\text{O}$  (20 mL) was added, and the mixture extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). The combined organic layers were further washed with  $\text{H}_2\text{O}$  (20 mL), 10 %  $\text{CuSO}_4$  (20 mL) and brine (20 mL), then dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (2 %  $\text{EtOAc}$  in petrol) afforded **317** as a yellow oil (211 mg, 88 %);  $R_f$  0.85 (10 %  $\text{EtOAc}$  in petrol);  $[\alpha]_D^{22} +58.6$  ( $c$  2.10,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2952, 2869, 1737, 1657, 1468, 1368, 1238, 1016  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 5.35–5.32 (1H, m, H-9), 5.13–5.10 (1H, m,  $\text{CH}_2=\text{C}$ ), 4.76–4.74 (1H, m,  $\text{CH}_2=\text{C}$ ), 2.40–2.32 (1H, m, H-14), 2.05 (3H, s,  $\text{CH}_3\text{CO}$ ), 2.00–1.72 (4H, m), 1.65–0.99 (13H, m), 0.95 (3H, d,  $J$  6.0 Hz, H-21), 0.90 (3H, d,  $J$  2.0 Hz, H-26/27), 0.88 (3H, d,  $J$  2.0 Hz, H-26/27), 0.59 (3H, s, H-18);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 170.3 (CO), 146.1 ( $\text{C}=\text{CH}_2$ ), 111.4 ( $\text{C}=\text{CH}_2$ ), 74.6 (C-9), 56.1, 50.5, 44.2, 39.5, 36.1, 36.0, 35.2, 28.5, 28.0, 27.6, 23.8, 22.8, 22.6, 21.9, 21.6, 18.8, 11.2 (C-18);  $m/z$  (CI) 338  $[\text{M}+\text{NH}_4]^+$ , 321  $[\text{M}+\text{H}]^+$ , 261 (Found  $[\text{M}+\text{NH}_4]^+$ , 338.3053.  $\text{C}_{21}\text{H}_{36}\text{O}_2$  requires  $[\text{M}+\text{NH}_4]^+$ , 338.3059).

**De-A,B-8-methylenecholestan-9 $\alpha$ -yl methyl carbonate (318)**

To **223** (200 mg, 0.72 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added pyridine (173  $\mu\text{L}$ , 2.15 mmol, 3 equiv), then DMAP (5 mg, 0.04 mmol, 0.05 equiv), then methyl chloroformate (67  $\mu\text{L}$ , 0.86 mmol, 1.2 equiv) dropwise. The reaction mixture was allowed to warm to rt and stirred for 48 h.  $\text{H}_2\text{O}$  (20 mL) was added, and the mixture extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). The combined organic layers were further washed with  $\text{H}_2\text{O}$  (20 mL), 10 %  $\text{CuSO}_4$  (20 mL) and brine (20 mL), then dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification by silica gel chromatography (5 %  $\text{EtOAc}$  in petrol) afforded **318** as a yellow oil (170 mg, 70 %);  $R_f$  0.90 (10 %  $\text{EtOAc}$  in petrol);  $[\alpha]_D^{22} +5.0$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2953, 2869, 1748, 1658, 1442, 1327, 1264  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 400 MHz) 5.20–5.16 (2H, m,  $\text{CH}_2\text{C}=\text{C}$  + H-9), 4.81–4.78 (1H, m,  $\text{CH}_2\text{C}=\text{C}$ ), 3.78 ( $\text{CH}_3\text{O}$ ), 2.42–2.33 (1H, m, H-14), 2.99–1.77 (4H, m), 1.70–0.99 (13H, m), 0.94 (3H, d,  $J$  6.0 Hz, H-21), 0.90 (3H, d,  $J$  2.0 Hz, H-26/27), 0.88 (3H, d,  $J$  2.0 Hz, H-26/27), 0.59 (3H, s, H-18);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 100 MHz) 155.1 (CO), 145.4 ( $\text{C}=\text{CH}_2$ ), 112.1 ( $\text{CH}_2=\text{C}$ ), 78.7 (C-9), 56.0, 54.4 ( $\text{CH}_3\text{O}$ ), 50.2, 44.7, 39.5, 36.1, 36.0, 34.9, 28.5, 28.0, 27.5, 28.0, 27.5, 23.7, 22.8, 22.6, 21.9, 18.8, 11.1 (C-18);  $m/z$  (CI) 354  $[\text{M}+\text{NH}_4]^+$ , 261, 147 (Found  $[\text{M}+\text{NH}_4]^+$ , 354.3003.  $\text{C}_{21}\text{H}_{36}\text{O}_3$  requires  $[\text{M}+\text{NH}_4]^+$ , 354.3008).

**Methyl 3-(des-A,B-8(9)-cholesten-8-yl)-2-tosylpropionate (319) and De-A,B-8-methylenecholest-9(11)-ene (320)**



To **318** (100 mg, 0.30 mmol, 1 equiv) and methyl 2-tosylacetate (75 mg, 0.33 mmol, 1.1 equiv) in THF (5 mL) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (17 mg, 0.015 mmol, 0.05 equiv). The reaction mixture was heated to reflux for 5 h. Sat. NH<sub>4</sub>Cl (5 mL) was added, and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give an orange residue. Purification by silica gel chromatography (5–10 % EtOAc in petrol) afforded **319** as a colourless oil (47 mg, 32 %) and **320** as a colourless oil (36 mg, 46 %).

Data for **319**: isolated as a 3:2 mixture of C-Ts epimers; R<sub>f</sub> 0.45 (10 % EtOAc in petrol); ν<sub>max</sub> (film) 2953, 2869, 1746, 1598, 1438, 1328, 1148, 1085 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 7.77 (2H, d, *J* 8.0 Hz, *o*-Ts), 7.38 (2H, d, *J* 8.0 Hz, *m*-Ts), 5.25 (1H, m, H-9 major) 5.21 (1H, m, H-9 minor); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 166.4 and 166.1 (CO), 145.3 (Ar), 134.2 (Ar), 134.1 (Ar), 133.1 and 132.6 (C-8), 129.7 (*m*-Ts), 129.4 (*o*-Ts), 124.4 and 123.4 (C-9), 69.9 and 69.8 (CHTs), 54.3, 54.2, 52.8 and 52.7 (CH<sub>3</sub>O), 51.3, 49.5, 42.4, 42.3, 39.5, 36.16, 36.1, 35.9, 35.9, 32.9, 31.6, 28.3, 28.2, 28.0, 24.6, 23.9, 23.8, 22.9, 22.8, 22.6, 21.7 (CH<sub>3</sub>Ar), 18.8 and 18.7 (C-21), 11.2 and 11.1 (C-18); *m/z* (ESI) 506 [M+NH<sub>4</sub>]<sup>+</sup>, 489 [M+H]<sup>+</sup> (Found [M+H]<sup>+</sup>, 489.3033. C<sub>29</sub>H<sub>44</sub>O<sub>4</sub>S requires [M+H]<sup>+</sup>, 489.3039).

Data for **320**: R<sub>f</sub> 0.95 (petrol); [α]<sub>D</sub><sup>25</sup> +90.0 (*c* 1.00, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 2954, 2869, 1639, 1600, 1467, 1379 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 6.13 (1H, dd, *J* 9.5, 2.5 Hz, H-9), 5.68 (1H, m, H-11), 4.88 (1H, s, C=CH<sub>2</sub>), 4.73 (1H, s, C=CH<sub>2</sub>), 2.35 (1H, dd, *J* 17.5, 5.5 Hz, H-12), 2.27 (1H, m, H-14), 2.17 (1H, d, *J* 17.5 Hz, H-12) 1.61–1.01 (13H, m) 0.96 (3H, d, *J* 6.5 Hz, H-21), 0.91 (3H, d, *J* 2.0 Hz, H-26/27), 0.89 (3H, d, *J* 2.0 Hz, H-26/27), 0.61 (3H, s, H-18); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 146.4 (C-8), 129.1 (C-11), 128.6

(C-9), 109.3 (C=CH<sub>2</sub>), 56.4 (C-14), 51.3 (C-13), 43.0, 42.5, 39.5 (C-12), 36.1, 35.9, 28.0, 27.9, 23.9, 22.8, 22.7, 22.6, 18.4, 11.6 (C-18); *m/z* (EI) 260 [M]<sup>+</sup>, 147 (Found [M]<sup>+</sup>, 260.2507. C<sub>19</sub>H<sub>32</sub> requires [M]<sup>+</sup>, 260.2504).

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