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# Investigations of the stereoselectivity of the intramolecular Diels–Alder reaction of a spiculoic acid model system

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**Abstract**

Model linear precursors to the spiculoic acids were prepared and underwent thermally induced IMDA reactions. The configuration of C5 in the stereotriad was found to dominate any inherent *endo*/*exo* selectivity of the IMDA reaction. The isomer **(2*E*,5*S*)-20** underwent the IMDA to give the spiculoic acid stereochemistry in 84% yield and 94% ds. The required stereotriads were synthesised using stereoselective substrate-controlled aldol reactions; an *anti*-boron aldol reaction, controlled by the π-facial preference of (*S*)-2-benzoyloxypentan-3-one ((***S*)-27**) led to **(5*R*)-(22)** and a *syn*-titanium aldol reaction, under the stereocontrol of a chiral *N*-acylthiazolidinethione (**42**) led to **(5*S*)-(22)**. Chain extension using standard Wittig, HWE and 'modified' Julia olefinations installed the diene and dienophile components giving the linear precursors to the IMDA reactions.

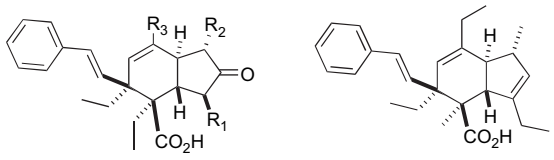

*Keywords:* Intramolecular Diels–Alder reaction; Substrate-controlled aldol reaction; Spiculoic acids

## 1. Introduction

The spiculoic acids (**1**–**5**)[1,2] are a family of polyketide derived compounds, which are among the rich variety of secondary metabolites that have been isolated from sponges of the genus *Plakortis* (Fig. 1). Andersen et al. reported the isolation of spiculoic acids A (**1**) and B (**2**) from the methanol extracts of a Caribbean sponge *Plakortis angulospiculatus*.[1] Subsequent studies by Amade et al. identified the derivatives *iso*-, nor- and dinor-spiculoic acids (**3**–**5**) from the sponge *Plakortis zyggompha*, collected off the coast of Martinique Island.[2]

Spiculoic acid A (**1**) was found to be mildly cytotoxic against the tumor cell line MCF-7 (human breast cancer),[1] while isospiculoic acid (**3**) and nor-spiculoic acid (**4**) exhibited mild cytotoxicity against both tumor cell lines A549 (lung carcinoma) and HT29 (colon carcinoma).[2] The spiculoic acids possess a previously unreported spiculane skeleton featuring a [4.3.0] bicyclic core. Of interest is the proposed biogenesis of spiculoic acid A (**1**) involving incorporation of four butyrate units (which is relatively uncommon) and one propionate unit to construct a linear precursor, which then undergoes an enzyme-catalysed intramolecular Diels–Alder (IMDA) reaction.[1–4]

The IMDA cycloaddition of the potential linear precursors to the spiculoic acids (**6**), possessing an *E*,*E*-diene and an *E*-dienophile, can proceed through four alternative transition states to give four possible stereoisomeric cycloadducts (**7**–**10**) (Fig. 2).




**1,3-5** **2**

spiculoic acid A (**1**); $R_1$ = Et, $R_2$ = Me, $R_3$ = Et
spiculoic acid B (**2**)
isospiculoic acid A (**3**); $R_1$ = Me, $R_2$ = Et, $R_3$ = Et
*nor*-spiculoic acid A (**4**); $R_1$ = Me, $R_2$ = Me, $R_3$ = Et
*dinor*-spiculoic acid A (**5**); $R_1$ = Me, $R_2$ = Me, $R_3$ = Me

Figure 1.

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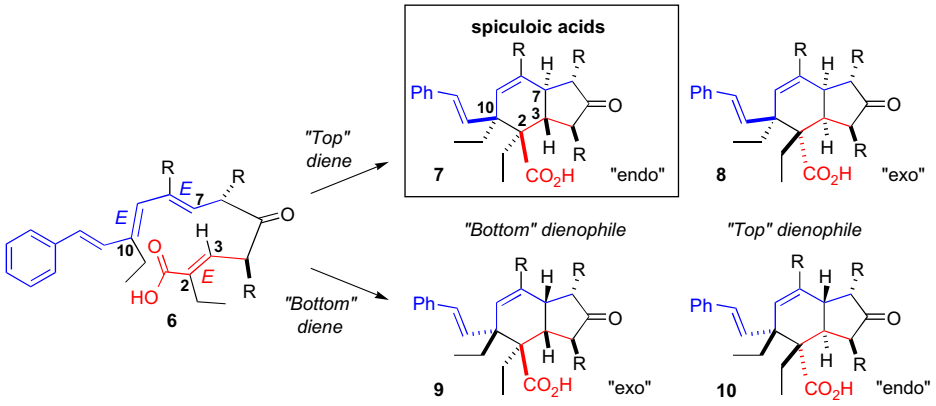
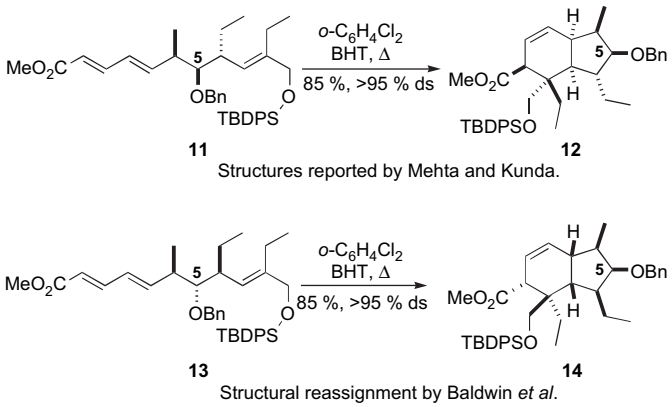



Figure 2.

There are a number of examples of natural products, which appear to be products of Diels–Alder type cycloaddition reactions.[4] Evidence suggests that during biosynthesis Diels–Alder reactions are occurring under both non-enzymatic and enzymatic (i.e., Diels–Alderase) control. Isolation and characterisation of the Diels–Alderase enzyme has been achieved in some systems including solanapyrone synthase,[5] lovastatin nonaketide synthase[6] and macrophomate synthase,[7] but this is a difficult and time consuming task. Biomimetic total syntheses can be used to give an indication as to whether the Diels–Alder reaction is likely to be facilitated by enzymes. If the non-enzymatic cyclisation product(s) achieved synthetically does not match the natural product (including the enantiomeric/diastereomeric ratios) then enzymatic involvement is likely. Alternatively if the non-enzymatic laboratory cyclisation product(s) (including the enantiomeric/diastereomeric ratios) obtained synthetically matches the natural product this suggests that enzymatic involvement is not necessary. However, biomimetic total syntheses cannot prove or disprove enzyme involvement in the biosynthesis.

During the course of our work these compounds have attracted synthetic attention. Mehta and Kunda[8] published the synthesis and subsequent IMDA cycloaddition of a model linear precursor **11** to give cycloadduct **12** selectively, but their stereochemical assignment was found to be incorrect (Scheme 1).[9] Incorrect transposition of the C5 stereocentre from their linear precursor **11** to the cycloadduct **12** is apparent. An in-depth examination by Baldwin et al.[10] revealed an erroneous stereochemical assignment of the product of a stereoselective Sharpless epoxidation, synthesised earlier in the reaction sequence with the resulting reassignment of the linear precursor **11** as compound **13**. Subsequent analysis of Mehta and Kunda's NOE results led to assignment of the Diels–Alder adduct **12** as cycloadduct **14** (Scheme 1). While cycloadduct **14** does contain the desired [4.3.0] bicyclic core, the relative orientation of the six stereocentres is different from the natural products. The C4 and C6 stereocentres present in the linear precursor, which were stereoselectively installed are not in the correct *anti*-orientation. The protons at the bridgehead have a cis rather than a trans orientation, suggesting an *exo* rather than an *endo* transition state geometry. The linear precursor **13** has an electron withdrawing group (EWG) attached to the diene facilitating an inverse electron demand IMDA reaction. While potentially synthetically useful this approach is not biomimetic with regards to the IMDA where the potential linear precursors to the spiculoic acids have the EWG on the dienophile, activating a normal electron demand IMDA reaction.

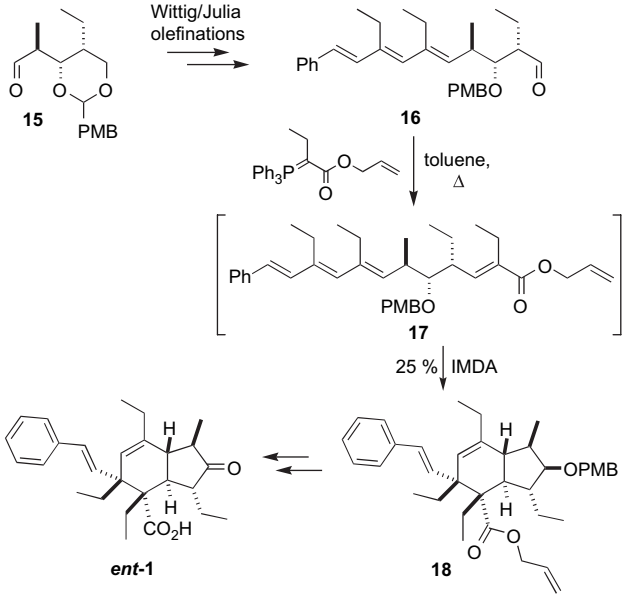



Scheme 1.

In 2006, Baldwin et al. reported the total synthesis of *ent*-spiculoic acid A, employing a biomimetic IMDA reaction (Scheme 2).[11] Following stereoselective synthesis of a chiral aldehyde **15**, via a highly stereoselective aldol cross-coupling reaction utilising chiral oxazolidinone derivatives, sequential Wittig and Julia olefination reactions were employed to generate the conjugated triene **16**. A Wittig olefination reaction installed the dienophile component (**17**) and spontaneous IMDA cycloaddition formed cycloadduct **18** (25% yield) leading to *ent*-spiculoic acid A (***ent*-1**).

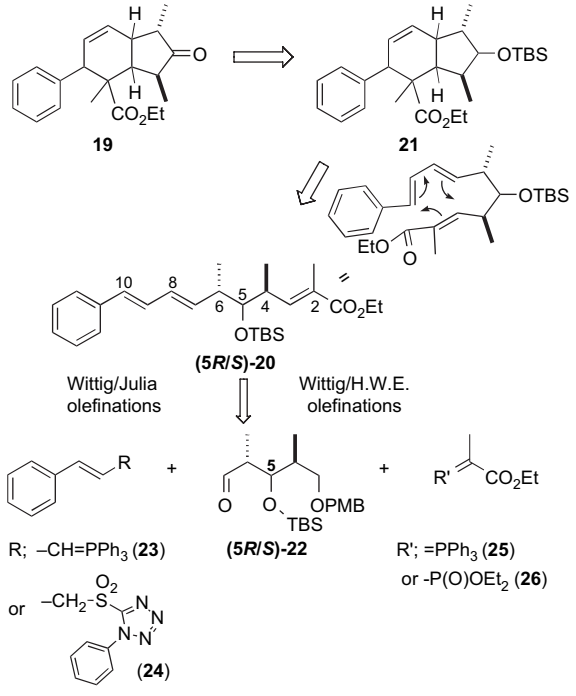
## 2. Retrosynthetic analysis of a model system

We proposed to investigate the use of a thermally induced IMDA reaction to construct the [4.3.0] spiculane skeleton. Prior to commencement of this study no synthetic studies towards the spiculoic acids had been reported. The model system was designed to investigate the stereoselectivity of the thermally induced IMDA, especially the effect of the configuration of the C5 stereocentre.




Scheme 2.

The model **19** has a simplified side chain (−Ph instead of −CH=CHPh), no ethyl groups at C8 or C10, the ethyl groups at C2 and C4 are replaced with methyl groups and the carboxylic acid is masked as the ethyl ester (Scheme 3). To avoid problems during the synthesis of the linear precursor **20**, we chose to prepare **20** with C5 protected at the alcohol oxidation state. The C5 alcohol was protected as the TBS ether in both the *R* and *S* configurations in order to examine whether this centre imparts any control over the stereochemical outcome of the IMDA. IMDA reaction of **20** gives **21**, which can be deprotected (at C5) and oxidised to give **19**. This approach



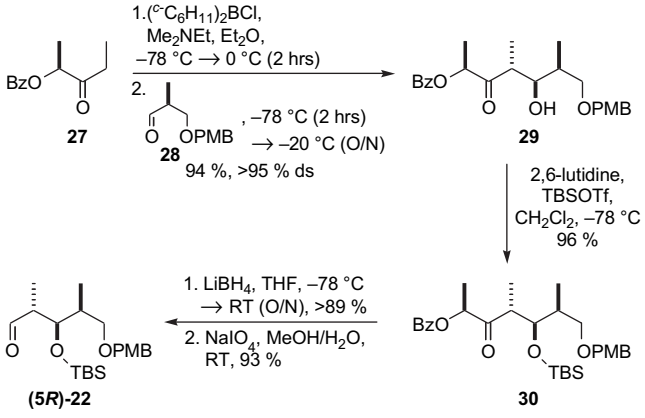

Scheme 3.

potentially offered some flexibility as deprotection and oxidation of C5 could be performed prior to the IMDA reaction. Central chiral fragment **(5*R*/*S*)-22**[9] was extended via either Wittig or Julia olefination reactions with ylide **23** and sulfone **24** to install the diene moiety. Subsequent installation of the dienophile functionalities employing Wittig and HWE olefination reactions with ylide **25** and phosphonates **26** produced the linear precursor **20**.

## 3. Results and discussion

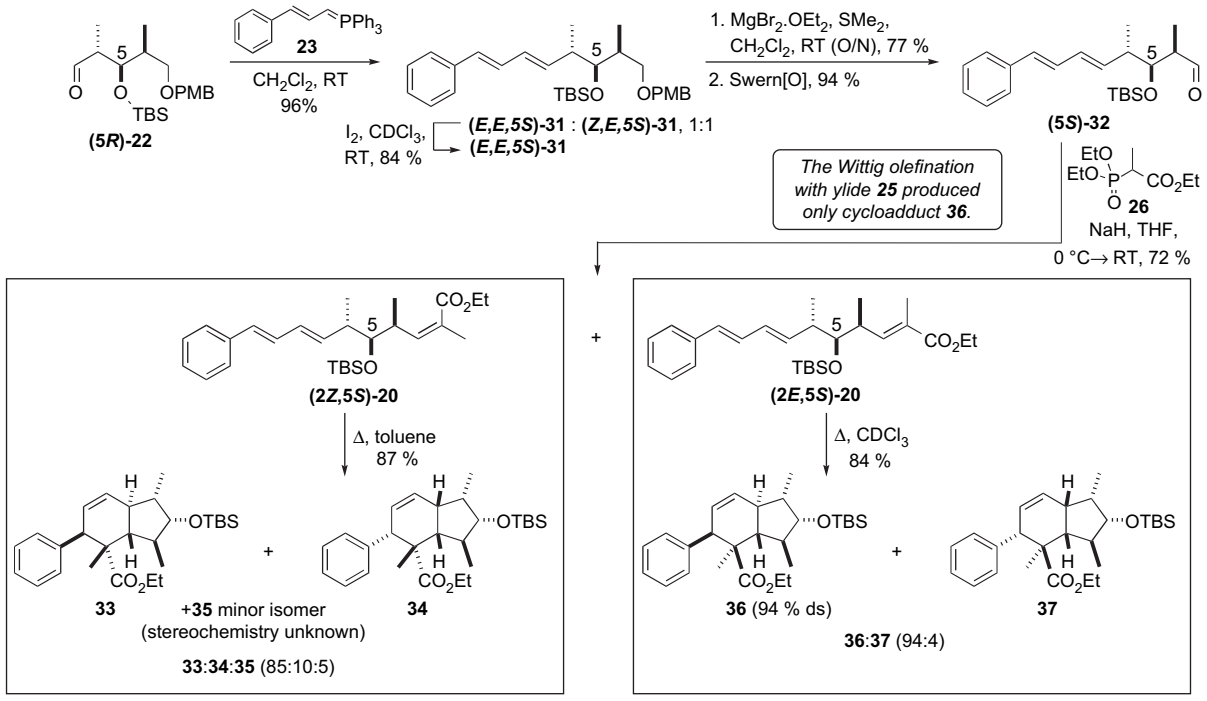
### 3.1. Synthesis

Synthesis of the required stereotriad in aldehyde **(5*R*)-22** was achieved by employing a substrate-controlled aldol coupling procedure reported by Paterson et al.[12] An *anti*-selective double stereodifferentiating[13] aldol coupling reaction between ketone **27** and aldehyde **28**[14] (Scheme 4) produces adduct **29** in >95% ds (minor component not characterised). The facial preference of the enolate of chiral ketone **27** is matched with the Felkin preference of chiral aldehyde **28** accounting for this high diastereoselectivity. The alcohol was protected as the TBS ether **30**[15] and reduction of both the ketone and ester functionalities with $LiBH_4$ gave the 1,2-diol. Oxidative cleavage using periodate gave the aldehyde **(5*R*)-22** in good yield (>75% over four steps).




Scheme 4.

Synthesis of the full linear precursor was now possible through Wittig and HWE couplings with the central chiral fragment **(5*R*)-22** (Scheme 5). A Wittig coupling[16] of the ylide **23** (available in a four-step sequence from cinnamaldehyde; $NaBH_4$ reduction to the alcohol,[17] conversion to the allyl chloride,[18] formation of the phosphonium salt[16] and deprotonation) with the chiral aldehyde **(5*R*)-22** gave an inseparable 1:1 mixture of the **(*E*,*E*)-31** and **(*Z*,*E*)-31** isomers in good yield (96%). Isomerisation of **(*Z*,*E*)-31** to the thermodynamically favoured **(*E*,*E*)-31** was achieved with catalytic $I_2$.[19] Cleavage of the PMB ether proved troublesome due to the sensitivity of diene **(*E*,*E*)-31**. Conventional methods (DDQ[20] and CAN[21]) resulted in decomposition of the starting material and attempts at achieving cleavage using a variety of acids



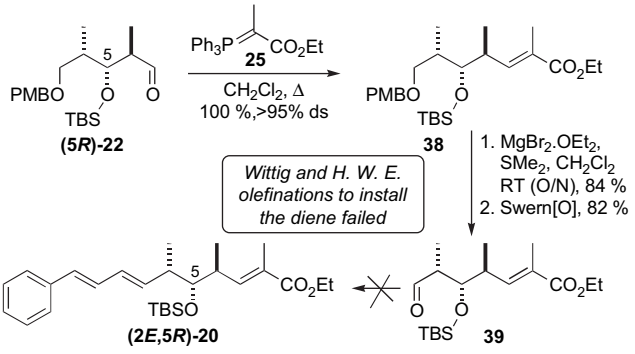

Scheme 5.

(e.g., *p*-TsOH, TFA, amberlyst resin) yielded only starting material. Fortunately, a method by Iwasaki et al.[22] using $MgBr_2 \cdot OEt_2$ and $SMe_2$ in $CH_2Cl_2$ was successful giving the alcohol in 77% yield. Swern oxidation[23] of the generated alcohol gave the desired aldehyde **32** in good yield (94%).

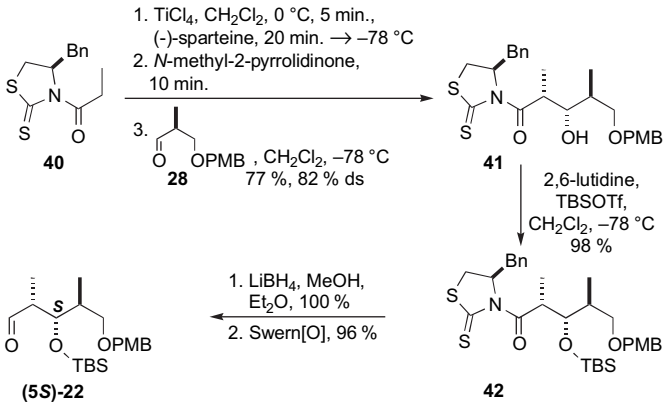
A HWE coupling[24] of phosphonate **26** with aldehyde **32** gave the linear triene as a 1:2.75 mixture of **(2*E*,5*S*)-20/(2*Z*,5*S*)-20** isomers. Upon purification on silica gel the minor isomer **(2*E*,5*S*)-20** spontaneously begins to undergo the IMDA cyclisation to give adducts **36** and **37**. Heating gently to 50 °C drives the reaction to completion giving the major product **36** with 94% ds. Due to the spontaneity of the cyclisation the reaction could not be attempted with the C5 hydroxyl or the C5 carbonyl in place. The major triene **(2*Z*,5*S*)-20**, was much slower to cyclise but heating overnight under reflux in toluene gives the inseparable IMDA adducts **33/34/35** (ratio 85:10:5). Aldehyde **32** was also coupled to ylide **25** in a Wittig olefination[25] to install the dienophile moiety. In this case following reaction at 40 °C for 5 days only cycloadduct **36** was isolated (40% yield due to incomplete reaction).

Attempts were made at generating the linear precursor **20** with the 5*R* configuration using **(5*R*)-22** by first incorporating the dienophile moiety giving alkene **38** and then the diene end (Scheme 6). However, the substrate possessing the dienophile **39** proved to be extremely sensitive and decomposed under the conditions used to attempt to install the diene in **(2*E*,5*R*)-20**.[26]

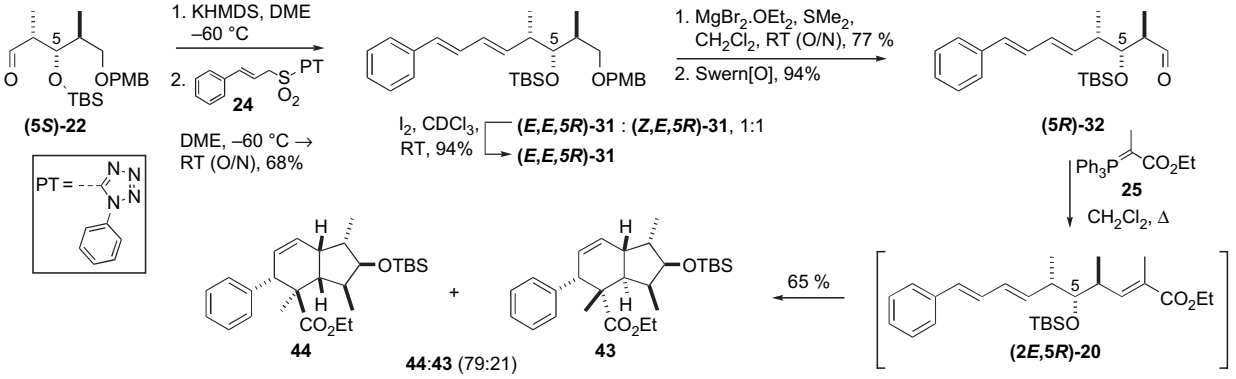
Alternatively an isomer of aldehyde **22** with the *S* stereochemistry at C5 would allow synthesis of the linear precursor **(5*R*)-20** (NB: change in priority of groups means 5*R* stereochemistry) in an analogous manner to that described in Scheme 5. Synthesis of the required stereotriad was achieved via a *syn*-selective substrate-controlled aldol coupling[27] between chiral thiazolidinethione **40** and aldehyde **28** (77% yield, 82% ds) (Scheme 7). The stereochemical assignment of the separable major adduct **41** was based on the literature precedent,[28] while the two minor isomers were not characterised. The major




Scheme 6.




Scheme 7.

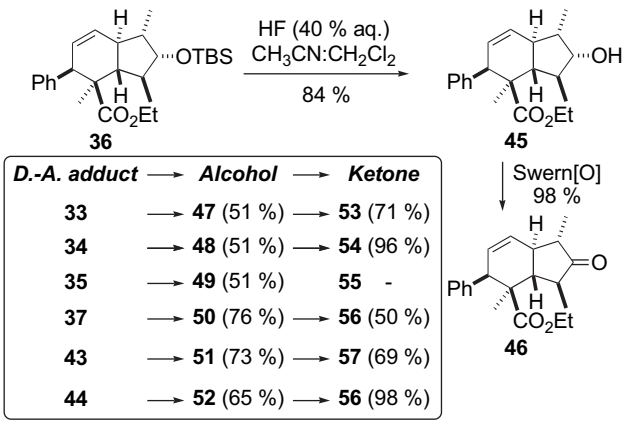



Scheme 8.

product from this double stereodifferentiating aldol coupling, adduct **41**, results from a matched reaction involving *anti*-Felkin addition to aldehyde **28**, the favoured face for addition of a *Z*-enolate to an α-chiral aldehyde.[13] The alcohol **41** was protected as the TBS ether **42**[15] (98%) and the chiral auxiliary cleaved, in quantitative yield, with $LiBH_4$[29] to give the primary alcohol. Subsequent oxidation under Swern conditions[23] yielded aldehyde **(5*S*)-22** in excellent yield (96%).

Again a two directional olefination approach analogous to that described in Scheme 5 was proposed to generate the alternative linear triene with the 5*R* stereochemistry. Unfortunately both Wittig[16] and HWE[30] olefination reactions were unsuccessful at installing the diene moiety due to the susceptibility of the C5 TBS ether, in this configuration, to undergo elimination. The 'modified' Julia olefination reaction[31] of PT sulfone **24** with aldehyde **(5*S*)-22** proceeded in reasonable yield (68%) producing an inseparable mixture (1:1) of **(*E*,*E*,5*R*)-31** and **(*Z*,*E*,5*R*)-31**. In an identical method to that described in Scheme 5, **(*Z*,*E*,5*R*)-31** was isomerised with catalytic $I_2$[19] to the thermodynamically favoured **(*E*,*E*,5*R*)-31**. Following PMB ether cleavage[22] and Swern oxidation[23] aldehyde **(5*R*)-32** was isolated (66% yield, over three steps). The next step involved generation of the dienophile moiety, which was attempted via both HWE and Wittig olefinations. In this instance the HWE olefination[24] was unsuccessful at installing the dienophile moiety and starting materials were recovered. The Wittig olefination reaction with ylide **25**[25] proceeded with high *E*-selectivity forming triene **(2*E*,5*R*)-20**, which spontaneously cyclised under the reaction conditions to give two cycloadducts **43** and **44** (21:79) (Scheme 8).

Deprotection of IMDA product **36** with aqueous HF[32] gave alcohol **45** (84% yield) and subsequent Swern oxidation[22] gave ketone **46** with the spiculoic acid stereochemistry. The other cycloadducts (**33**–**35**, **37**, **43** and **44**) were similarly deprotected with aqueous HF[32] to give the corresponding alcohols (**47**–**52**) and subsequent Swern oxidation[22] gave the ketones (**53**–**57**), as depicted in Scheme 9.




Scheme 9.

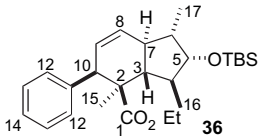
### 3.2. Stereochemical assignment of the cycloadducts

Extensive 1D and 2D NMR studies enabled the stereochemical assignment of the cyclic products. Following structural assignment, NOESY and ROESY correlations using the sterotriad C4–C6, of known stereochemical orientation, enabled the configuration of the stereocentres generated via the IMDA cycloaddition reaction to be assigned. In each instance (except cycloadducts **34** and **35**, which were inseparable from the major isomer **33**) the stereochemistry of the cyclic products with the TBS, OH and carbonyl groups in place were all analyzed in order to confirm the stereochemical assignment. For cycloadducts **34** and **35**, separation was achieved following silyl ether cleavage and alcohol **48** and its corresponding ketone **54** were thoroughly analysed. Alcohol **49**, from **35** the smallest (5%) component, was isolated in very small quantities and remained impure after repeated attempts at purification.

Molecular modelling studies were performed to predict the low energy conformations of each stereoisomer and in each case the NOESY and ROESY correlations observed could be explained considering the predicted low energy conformers.[25] In general the cycloadducts with a trans-bridgehead were relatively planar with the *pseudo* chair conformation of the cyclohexene ring unable to ring flip. Conversely, the cycloadducts with a cis-bridghead, which experience a bend in the bicyclic core, were free to ring flip.

The NMR data for cycloadduct **36** is summarised in Table 1 and the assignments are based on extensive 2D NMR experiments. The ROESY correlations, which were instrumental in the stereochemical assignment of cycloadduct **36** are shown

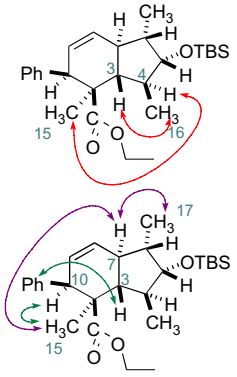
Table 1
NMR data for cycloadduct **36**




| Carbon no. | $^{13}$C NMR $\delta$[a,b] | $^{1}$H NMR $\delta$(m) $J$ in Hz[a,b] |
|---|---|---|
| 1 | 175.3 | — |
| 2 | 49.6 | — |
| 3 | 47 | 1.80 (dd) 11.2, 10.2 |
| 4 | 44.3 or 44.2 | 1.59–1.54 (m) |
| 5 | 82.9 | 3.70 (dd) 6.6, 1.8 |
| 6 | 40.4 | 1.70 (dq) 12.0, 6.6 |
| 7 | 44.3 or 44.2 | 2.02 (ddddd) 11.2, 11.2, 2.4, 2.4, 2.4 |
| 8 | 128 | 5.99 (ddd) 10.2, 1.8, 1.8 |
| 9 | 128.3 | 5.54 (ddd) 10.2, 3.6, 3.0 |
| 10 | 54.3 | 3.31 (m) |
| 11 | 142 | — |
| 12, 13, 14 | 129.6, 127.7, 126.7 | 7.24–7.11 (m) |
| 15 | 26.1 | 1.34 (m) |
| 16 | 18.3 or 18.2 | 0.86 (d) 7.2 |
| 17 | 12.5 | 1.03 (d) 6.6 |
| 18 | 59.7 | 3.54 (dq) 10.8, 7.2 and 3.21 (dq) 10.8, 7.2 |
| 19 | 13.2 | 0.69 (t) 7.2 |
| $SiC(CH_3)_3$ | 25.9 | 0.88 (s) |
| $SiC(CH_3)_3$ | 18.3 or 18.2 | — |
| $Si(CH_3)_A$ | −4.3 | 0.03 (s) |
| $Si(CH_3)_B$ | −4.6 | 0.02 (s) |

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments were assisted by $^{1}$H–$^{13}$C HMBC, $^{1}$H–$^{13}$C HMQC, $^{1}$H–$^{1}$H COSY, $^{1}$H–$^{1}$H ROESY.
[b] Chemical shifts in parts per million referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm.

Table 2
ROESY correlations and stereochemical assignment of cycloadduct **36**




| H no. | $^{1}$H–$^{1}$H ROESY[a] |
|---|---|
| 3 | H4*, H7*, H16, ArH |
| 4 | H3*, H15, H16* |
| 5 | H6*, H16 |
| 6 | H5*, H7*, H17* |
| 7 | H3*, H6*, H15, H17 |
| 8 | H9*, H17 |
| 9 | H8*, H10*, H17 (wk) |
| 10 | H9*, H15, ArH |
| 15 | H4, H7, H10 |
| 16 | H3, H4*, H5 |
| 17 | H6*, H7, H8, H9 (wk) |
| ArH | H3, H10 |

* Indicates $^{1}$H–$^{1}$H COSY correlations.
[a] NMR spectrometer (600 MHz, $CDCl_3$).

in Table 2. The correlations involving the C4 stereocentre, of known stereochemical orientation, enabled assignment of both the C2 and C3 stereocentres. A correlation between the bridgehead proton on C3 and the C16 protons (in red) indicated the C3 configuration shown. Similarly, a correlation between the C4 and C15 protons suggested the absolute stereochemistry at C2, as shown. The relative relationship between these two centres is consistent with the *E*-geometry of the dienophile in the linear precursor. Moving around the ring system, the C3 proton correlates to the aromatic protons while the C15 protons correlate to the C10 proton (in green), providing supporting evidence for the absolute stereochemistry depicted for C10. Finally, the stereochemical orientation of C7 was assigned based on the correlations between the C7 and both the C10 and C17 protons (in purple). The *E*,*E*-diene geometry has been conserved in the cycloadduct thus supporting this stereochemical assignment. In addition the protons at the bridgehead have a trans-relationship, suggested by the relatively large coupling constant, $J_{a,b}$=11.2 Hz, which is indicative of an *anti*-periplanar orbital overlap.[33]

The stereochemical assignment of all the other cycloadducts and the corresponding alcohols and ketones was similarly carried out. Tables of NMR data, including structural assignments are available in Supplementary data for cycloadducts (**33**, **36**, **37** and **43**, **44**), alcohols (**45**, **47**, **48**, **50**–**52**) and ketones (**46**, **53**, **54**, **56**, **57**).

### 3.3. Comparison of the isomers

The linear precursor **20** was synthesised with both the *R* and *S* configurations at the C5 stereocentre as proposed in Scheme 3. In addition the dienophile at C2 was prepared in both the *E* and *Z* geometries, in the linear precursor with the 5*S* configuration. This provided the opportunity to examine the effect of the orientation of the C5 stereocentre and the dienophile geometry on the resulting IMDA transition states (there are four diastereomeric alternative transition states for each precursor as described in Fig. 2).

The effect of the dienophile geometry on the outcome of the IMDA reaction can be seen by comparing cycloadducts **36** and **37**, from linear precursor **(2*E*,5*S*)-20**, and cycloadducts **33** and **34**, from linear precursor **(2*Z*,5*S*)-20**. Figure 3 illustrates the faces of reaction of the diene and dienophile and the *endo* or *exo* orientation of the corresponding transition state.

Notably both the major adducts, **36** and **33**, are formed via reaction at the same faces of the addends (i.e., the diene and dienophile) producing cycloadducts differing only at the C2 stereocentre. This difference arises from the dienophile geometry and results in two transition states, leading to cycloadducts **33** and **36**, being *exo* and *endo*, respectively. Similarly the two minor cycloadducts **34** and **37** are also formed through reaction of the same faces of the addends. Again the orientation of the C2 stereocentre is opposite and the two transition states, leading to **34** and **37**, are *endo* and *exo*, respectively.

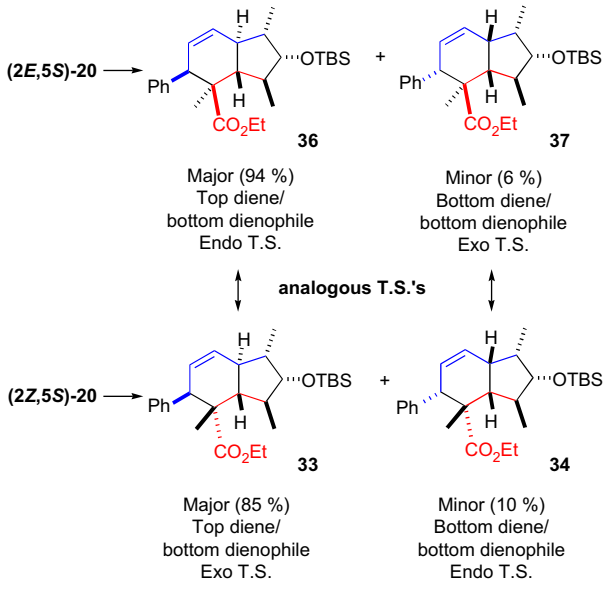



Figure 3.

This implies that the inherent *endo*/*exo* selectivity has little control over the transition state geometry, instead the C4–C6 stereotriad dictates the stereoselectivity.

The stereochemical outcome of the IMDA reaction of the linear precursor **(2*E*,5*S*)-20** compared to **(2*E*,5*R*)-20** reveals the effect of the configuration of the C5 stereocentre (Fig. 4). The major cycloadduct **36** from **(2*E*,5*S*)-20** and the major cycloadduct **44** from **(2*E*,5*R*)-20** are formed through different transition states with formation of **36** by the reaction of the top face of the diene and the bottom face of the dienophile via an *endo* transition state whereas **44** is formed by reaction of the bottom face of the diene and the bottom face of the dienophile via an *exo* transition state.

Interestingly the major cycloadduct **44**, from **(2*E*,5*R*)-20**, and the minor cycloadduct **37**, from **(2*E*,5*S*)-20**, proceed through analogous *exo* transition states with the same faces

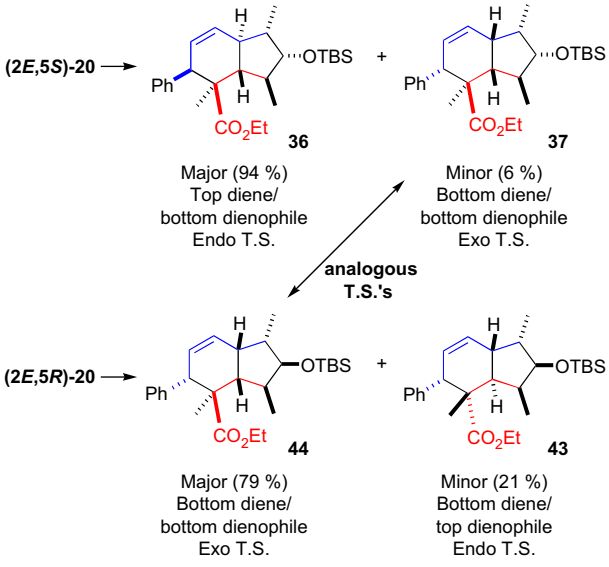



Figure 4.

of each addend undergoing reaction. These two compounds, **44** and **37**, ultimately give the same ketone **56** (Scheme 9). But the major adduct **36** from the 5*S* precursor and the minor adduct **43** from the 5*R* precursor are generated via different *endo* transition states with the opposite faces of each addend participating in the reaction. These results suggest that the orientation of the C5 stereocentre is of fundamental importance in controlling the stereochemical outcome of the cycloaddition reaction, dominating any inherent *endo*/*exo* selectivity of the IMDA reaction.

## 4. Conclusion; implications to the natural product synthesis/biosynthesis

In summary, a model system for the spiculoic acids was synthesised in order to explore the stereoselectivity of the intramolecular Diels–Alder reaction required to generate the spiculane skeleton. The thermally induced IMDA reaction of each of the linear precursors proceeded in generally high yield with moderate to good diastereoselectivity (>70% yield, >79% ds).

Comparison of each of the cycloadducts to the natural products reveals that cycloadduct **36**, formed with high diastereoselectivty (94%) from the **(2*E*,5*S*)-20** linear precursor, has stereochemistry matching the natural product at all six stereocentres (Fig. 5). This suggests that the total synthesis of the natural products may be achieved in high diastereoselectivity from a linear precursor with the C5 carbonyl masked as the TBS ether in the *S* configuration. This is consistent with the results of the IMDA reaction of the C5 benzyl ether protected substrate **17** in Baldwin's total synthesis of *ent*-spiculoic acid A. Currently we are exploring the extension of this methodology to the total synthesis of *dinor*-spiculoic acid A (**5**).

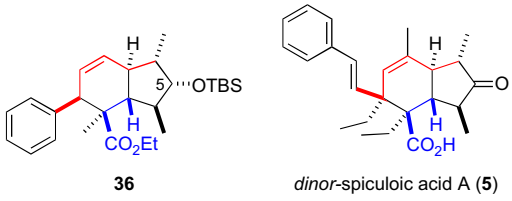



Figure 5.

These results suggest that the IMDA reaction can occur stereoselectively under non-enzymatic control and thus an enzyme may not be necessary in the biosynthesis of the spiculoic acids. However, in the natural system the C5 carbon centre possesses a carbonyl functionality (or possibly a hydroxyl group if oxidation occurs following cyclisation) not the C5 TBS ether as present in these systems. Thus the possible involvement of a Diels–Alderase in the biosynthesis cannot be discarded. Investigation of cyclisation of the linear precursors to the spiculoic acids possessing either a C5 carbonyl or hydroxyl group would provide further information to support or refute the involvement of a Diels–Alderase in the biosynthesis.

## 5. Experimental procedures

### 5.1. General details

All reactions were carried out under an atmosphere of nitrogen in oven dried glassware. Dichloromethane, triethylamine and dimethylethylamine were distilled over calcium hydride; and tetrahydrofuran and ether were distilled over sodium and benzophenone. Analytical thin layer chromatography was performed on Merck Keiselgel $60F_{254}$ silica aluminium backed sheets and were developed in potassium permanganate, anisaldehyde or monitoring by a UV lamp. Column chromatography was performed on Merck Keiselgel (particle size: 0.04–0.063 mm) 230–400 mesh silica. All optical rotations were measured on a PolA AR 21 polarimeter referenced to the sodium D line (589 nm) at 20 °C, using the spectroscopic grade solvents specified and at the concentrations (*c*, g/100 mL) indicated. Electron Impact (EI) mass spectra and Electrospray Ionisation (ESI) mass spectra were recorded using a Bruker 4.7T FTMS Ultra High Resolution spectrometer. ESIMS/MS were recorded on a Micromass Quattro micro spectrometer. High resolution mass spectral data are presented as molecular formula, molecular ion ($M^+$, $Na^+$ or $K^+$), calculated and measured masses to 4 significant figures. Low resolution mass spectral data are reported as mass to charge ratio (*m*/*z*) with intensity relative to the base peak indicated. LCMS were recorded on a Micromass Quattro micro, tandem quadrupole mass spectrometer with positive ion electrospray ionisation. Mass spectral data are presented as the molecular formula, molecular ion and calculated and measured masses to 3 significant figures. Infrared spectra were recorded on a BIO-RAD FTS-40A Fourier Transform spectrophotometer with the absorptions recorded in wavenumbers ($cm^{-1}$). Samples were analysed as thin films on NaCl discs. UV–vis spectra were recorded using a Varian Cary 50 Scan spectrophotometer using the spectroscopic grade solvents specified. Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected.

$^1H$ NMR spectra were recorded at either 200, 300 or 600 MHz on a Varian Mercury, Varian Gemini, Varian Unity Inova or Bruker Avance II 600 Spectrometer. $^{13}C$ NMR spectra were recorded at either 50, 75 or 151 MHz on a Varian Mercury, Varian Gemini, Varian Unity Inova or Bruker Avance II 600 Spectrometer. $CDCl_3$ was used as the solvent and internal lock, and referenced to $CHCl_3$ ($\delta$ 7.26) for $^1H$ NMR and $CDCl_3$ ($\delta$ 77) for $^{13}C$ NMR. Chemical shift vales are reported in parts per million, coupling constants are reported in hertz. Abbreviations used; Ar=aromatic, apt=apparent, br=broad, s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet. Structural and stereochemical assignments were made using $^1H-^1H$ COSY, $^1H-^1H$ TOCSY, $^1H-^{13}C$ HETCOR, $^1H-^{13}C$ HMQC, $^1H-^{13}C$ HMBC, $^1H-^1H$ NOESY and $^1H-^1H$ ROESY spectra. Details of 2D NMR experiments are included in Supplementary data.

#### 5.1.1. (2S,4R,5R,6S)-2-Benzoyloxy-5-hydroxy-7-(4′-methoxybenzyloxy)-4,6-dimethylheptane-3-one (**29**)

To a solution of dicyclohexylboron chloride (0.57 g, 0.58 mL, 2.69 mmol) in $Et_2O$ (7 mL) at −78 °C was added $Me_2NEt$ (0.24 g, 0.35 mL, 3.22 mmol), dropwise, followed by ketone **(*S*)-27** (0.36 g, 1.75 mmol) in $Et_2O$ (7 mL), via a cannula. The resulting solution was allowed to warm slowly to 0 °C and stirred for 2 h. The solution was again cooled to −78 °C and aldehyde **28** (0.55 g, 2.64 mmol) added in $Et_2O$ (3 mL) via a cannula. The resulting solution was stirred at −78 °C for 2 h before placing overnight in the freezer. The reaction was warmed to 0 °C for 30 min before quenching with MeOH (7 mL), pH 7 buffer (7 mL) and $H_2O_2$ (30% aq, 7 mL). The solution was stirred for a further 1 h at room temperature. The product was extracted with $CH_2Cl_2$ (3×75 mL) and the combined extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (5% $Et_2O/CH_2Cl_2$, $R_f$=0.30) yielded 0.69 g (94% yield, 90% ds) of adduct **29** as a white solid (mp 74–76 °C).

$^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.08 (2H, d, *J*=6.9 Hz, Ar*H*); 7.60–7.55 (1H, m, Ar*H*); 7.45 (2H, m, Ar*H*); 7.21 (2H, d, *J*=8.7 Hz, Ar*H*); 6.87 (2H, d, *J*=8.7 Hz, Ar*H*); 5.43 (1H, q, *J*=6.9 Hz, BzOC*H*($CH_3$)); 4.44 (1H, d, *J*=11.4 Hz, C$H_A$$H_B$Ar); 4.38 (1H, d, *J*=11.4 Hz, C$H_A$$H_B$Ar); 4.07 (1H, dd, *J*=9.3, 2.1 Hz, C*H*(OH)); 3.80 (3H, s, O$CH_3$); 3.54 (1H, dd, *J*=9.0, 4.2 Hz, C$H_A$$H_B$OPMB); 3.49 (1H, dd, *J*=9.0, 4.2 Hz, C$H_A$$H_B$OPMB); 3.00 (1H, dq, *J*=9.3, 7.2 Hz, C(=O)C*H*($CH_3$)CH(OH)); 1.91–1.84 (1H, m, CH(OH)C*H*($CH_3$)CH(OPMB)); 1.53 (3H, d, *J*=6.9 Hz, BzOCH($CH_3$)); 1.21 (3H, d, *J*=7.2 Hz, C(=O)CH($CH_3$)-CH(OH)); 0.95 (3H, d, *J*=6.9 Hz, CH(OH)CH($CH_3$)-$CH_2$(OPMB)). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 211.1; 165.9; 159.2; 133.2; 130.0; 129.8; 129.6; 129.2; 128.4; 113.8; 75.1; 74.6; 73.0; 55.2; 45.7; 34.4; 15.5; 13.8; 9.5 (one signal missing). IR (film, $cm^{-1}$) 3512; 2968; 2938; 1718; 1613; 1514; 1453; 1301; 1269; 1250; 1116; 1072; 1034; 1006; 713. $[\alpha]_D^{20}$ +11.3 (*c* 0.7, $CHCl_3$). HRMS (ESI) $C_{24}H_{30}O_6Na^+$ requires 437.1935, found 437.1936. LRGCMS 208 (3.7%); 137 (74%); 121 (100%); 109 (8.9%); 91 (3.7%); 77 (8.9%).

#### 5.1.2. (2S,4R,5R,6S)-2-Benzoyloxy-5-(tert-butyldimethylsilyloxy)-7-(4′-methoxybenzyloxy)-4,6-dimethylheptane-3-one (**30**)

To a solution of alcohol **29** (6.02 g, 14.5 mmol) in $CH_2Cl_2$ (145 mL) at −78 °C was added 2,6-lutidine (3.4 mL, 29 mmol) followed immediately by TBSOTf (4.9 mL, 22 mmol). The resulting solution was stirred for 1 h at −78 °C before warming to −50 °C for a further hour. TLC analysis showed that the reaction was almost complete so the solution was warmed to 0 °C before quenching. The reaction mixture was poured onto $NaHCO_3$ (satd aq, 200 mL) and extracted with $CH_2Cl_2$ (3×200 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (100% $CH_2Cl_2$ → 5% $Et_2O/CH_2Cl_2$, $R_f$ ($CH_2Cl_2$)=0.38) yielded 7.37 g (96%) of silyl ether **30** as a clear colourless oil.

$^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.08 (2H, m, Ar*H*); 7.59 (1H, m, Ar*H*); 7.46 (2H, m, Ar*H*); 7.23 (2H, m, Ar*H*); 6.86 (2H, m, Ar*H*); 5.48 (1H, q, *J*=6.9 Hz, $CH_3$(BzO)C*H*(C=O)); 4.44 (1H, d, *J*=11.4 Hz, OC$H_A$$H_B$Ar); 4.36 (1H, d, *J*=11.4 Hz, OC$H_A$$H_B$Ar); 4.21 (1H, dd, *J*=8.7, 1.5 Hz,

C*H*(OTBS)); 3.80 (3H, s, $OCH_3$); 3.39 (1H, dd, *J*=9.0, 7.2 Hz, C$H_AH_B$OPMB); 3.24 (1H, dd, *J*=9.0, 6.9 Hz, $CH_AH_B$OPMB); 3.10 (1H, dq, *J*=8.1, 7.2 Hz, C(=O)C*H*($CH_3$)CH(OTBS)); 1.93 (1H, m, CH(OTBS)C*H*($CH_3$)$CH_2$OPMB); 1.51 (3H, d, *J*=6.9 Hz, C$H_3$CH(OBz)C(=O)); 1.11 (3H, d, *J*=7.2 Hz, C(=O)CH(C$H_3$)CH(OTBS)); 0.89 (3H, d, *J*=6.9 Hz, CH(OTBS)CH(C$H_3$)$CH_2$OPMB); 0.83 (9H, s, SiC(C$H_3$)$_3$); 0.02 (3H, s, Si(C$H_3$)$_A$($CH_3$)$_B$); −0.09 (3H, s, Si($CH_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 209.0; 165.6; 159.1; 133.2; 130.6; 129.8; 128.4; 113.7; 75.0; 72.9; 72.8; 72.5; 55.3; 46.9; 36.1; 26.2; 25.6; 18.6; 15.6; 14.0; 10.5; −3.6; −5.1. IR (film, $cm^{-1}$) 2954; 2928; 2855; 1721; 1613; 1513; 1462; 1452; 1250; 1115; 1039; 833; 711. $[\alpha]_D^{20}$ −6.5 (*c* 0.77, $CHCl_3$). HRMS (ESI) $C_{30}H_{44}O_6NaSi^+$ requires 551.2799, found 551.2797. LREIMS 241 (4.2%); 207 (4.2%); 179 (6.7%); 137 (11%); 121 (100%); 105 (26%); 85 (15%); 71 (23%); 57 (34%); 55 (22%).

### *5.1.3. (2S,3R/S,4R,5R,6S)-5-(tert-Butyldimethylsilyloxy)-7-(4′-methoxybenzyloxy)-4,6-dimethylheptan-2,3-diol (**58**)*

To a cooled (−78 °C) solution of benzoate **30** (5.71 g, 10.8 mmol) in THF (130 mL) was added a solution of $LiBH_4$ (2 M in THF, 108 mL, 0.216 mol). The reaction mixture was placed in an ice/$H_2O$ bath for 10 min before warming slowly to room temperature and the stirring continued overnight. The solution was cooled to 0 °C for 10 min before quenching with $H_2O$ (200 mL). The mixture was extracted with $Et_2O$ (4×200 mL), washed with brine (200 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (30% mixed hexanes/$Et_2O$, $R_f$=0.29) yielding 4.10 g (89%) of an inseperable mixture of isomers of diol **58** (ratio ~2:1) as a clear colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.26−7.22 (2H, m, Ar*H*); 6.91−6.86 (2H, m, Ar*H*); 4.44 (2H, m, OC$H_2$Ar); 3.99 (1H, dd, *J*=4.5, 2.7 Hz), 3.81−3.25 (4H, m, C*H*(OH), C*H*(OH), C*H*(OTBS), C$H_2$(OPMB)); 3.81 (3H, s, OC$H_3$); 2.47 (2H, br s, O*H*, O*H*); 2.10−1.95 and 1.70−1.63 (2H, m, CH(OH)C*H*($CH_3$)-CH(OTBS), CH(OTBS)C*H*($CH_3$)$CH_2$(OPMB)); 1.15−0.79 (18H, m, C$H_3$CH(OH), CH(OH)CH(C$H_3$)CH(OTBS), CH(OTBS)CH(C$H_3$)$CH_2$(OPMB), SiC(C$H_3$)$_3$); 0.12−0.00 (6H, m, Si(C$H_3$)$_2$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ showed a complex mixture of isomers. IR (film, $cm^{-1}$) 3449; 2957; 2932; 2886; 2858; 1613; 1514; 1463; 1249; 1099; 1061; 1037; 837. HRMS (ESI) $C_{23}H_{42}O_5SiNa^+$ requires 449.2694, found 449.2694. LREIMS 323 (2.5%); 243 (2.5%); 187 (4.2%); 173 (2.5%); 137 (5.1%); 122 (14%); 121 (100%); 115 (6.7%); 91 (2.5%); 75 (10%); 73 (11%).

### *5.1.4. (2R,3R,4S)-3-(tert-Butyldimethylsilyloxy)-5-(4′-methoxybenzyloxy)-2,4-dimethylpentanal ((**5R**)-**22**)*

To a stirred solution of diols **58** (1.18 g, 2.77 mmol) in methanol (27.7 mL) and $H_2O$ (13.9 mL) at room temperature was added $NaIO_4$ (3.56 g, 8.08 mmol) and the resulting suspension stirred for 15 min (after this time TLC analysis showed consumption of SM). The reaction mixture was diluted with $H_2O$ (100 mL) and extracted with $Et_2O$ (3×100 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (30% mixed hexanes/$CH_2Cl_2$, $R_f$=0.39) yielding 0.37 g (93%) of aldehyde **(5*R*)-22** as a clear, colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ 9.70 (1H, d, *J*=2.7 Hz, C*H*(O)); 7.24 (2H, d, *J*=8.7 Hz, Ar*H*); 6.88 (2H, d, *J*=8.7 Hz, Ar*H*); 4.37 (2H, s, C$H_2$Ar); 4.05 (1H, dd, *J*=5.7, 4.2 Hz, C*H*(OTBS)); 3.81 (3H, s, OC$H_3$); 3.35 (1H, dd, *J*=9.0, 6.9 Hz, C$H_AH_B$(OPMB)); 3.26 (1H, dd, *J*=9.0, 5.7 Hz, $CH_AH_B$(OPMB)); 2.61−2.51 (1H, m, CH(O)C*H*($CH_3$)); 1.99−1.91 (1H, m, CH(OTBS)C*H*($CH_3$)$CH_2$(OPMB)); 1.07 (3H, d, *J*=6.9 Hz, CH(O)CH(C$H_3$)); 0.93 (3H, d, *J*=6.6 Hz, CH(OTBS)CH(C$H_3$)$CH_2$(OPMB)); 0.87 (9H, s, Si(C(C$H_3$)$_3$)); 0.05 (3H, s, Si(C$H_3$)$_A$($CH_3$)$_B$); 0.04 (3H, s, Si($CH_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 204.8; 159.2; 130.4; 129.2; 113.7; 74.1; 72.5; 72.0; 55.3; 50.9; 37.7; 25.9; 18.3; 12.2; 11.5; −4.2; −4.3. IR (film, $cm^{-1}$) 2956; 2931; 2884; 2857; 1725; 1613; 1514; 1463; 1361; 1249; 1173; 1088; 1037; 837; 775. $[\alpha]_D^{20}$ −19.9 (*c* 1.0, $CHCl_3$). HRMS (ESI) $C_{21}H_{36}O_4NaSi$ requires 403.2275, found 403.2286. LRGCMS 137 (2.2%); 122 (9.6%); 121 (100%); 116 (2.2%); 91 (0.7%); 75 (2.9%); 73 (3.7%); 59 (2.2%).

### *5.1.5. (2S,3S,4S,5E,7E)-3-(tert-Butyldimethylsilyloxy)-1-(4′-methoxybenzyloxy)-2,4-dimethyl-8-phenylocta-5,7-diene ((**E,E,5S**)-**31**)*

To a solution of triphenylcinnamylphosphonium chloride (2.48 g, 5.99 mmol) and aldehyde **(5*R*)-22** (0.455 g, 1.20 mmol) in EtOH (2 mL) was added a solution of NaOEt (1 M, 30 mL) in EtOH. The solution immediately turned red indicating formation of the ylide. The reaction mixture was stirred at room temperature for a few days until TLC analysis showed consumption of starting material. The reaction was quenched by the addition of $H_2O$ (25 mL) and the EtOH was removed in vacuo. The product was extracted with $Et_2O$ (3×50 mL) and the combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (50% $CH_2Cl_2$/mixed hexanes, $R_f$=0.44) yielding 0.551 g (96%) of a clear colourless oil as a mixture of **(*E,E*)-31** and **(*Z,E*)-31** isomers. To a solution of mixture of isomers **(*Z,E*)-31** and **(*E,E*)-31** in $CDCl_3$ was added a few crystals of $I_2$ and the reaction monitored by $^1$H NMR to see complete conversion of **(*Z,E*)-31** to **(*E,E*)-31** isomers. The reaction mixture was diluted with $CH_2Cl_2$ (20 mL) and washed with sodium metabisulfite (satd aq, 10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2×20 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (50% $CH_2Cl_2$/mixed hexanes, $R_f$=0.44) yielding 0.461 g (84%) of **(*E,E,5S*)-31** as a clear colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 and 6.89−6.85 (9H, m, Ar*H*); 6.74 (1H, dd, *J*=15.9, 10.5 Hz, ArCH=C*H*); 6.43 (1H, dd, *J*=15.9 Hz, ArC*H*); 6.15 (1H, dd, *J*=15.3, 10.5 Hz, ArCH=CHC*H*=CH); 5.80 (1H, dd, *J*=15.3, 8.4 Hz, ArCH=CHCH=C*H*); 4.43 (1H, d, *J*=11.4 Hz, C$H_AH_B$Ar); 4.37 (1H, d, *J*=11.4 Hz, $CH_AH_B$Ar); 3.78 (3H, s, OC$H_3$); 3.70−3.67 (1H, m, C*H*(OTBS)); 3.38 (1H, dd, *J*=9.0, 6.6 Hz, C$H_AH_B$OPMB); 3.21 (1H, dd, *J*=9.0, 6.9 Hz, $CH_AH_B$OPMB);

2.49–2.40 (1H, m, =CHC*H*($CH_3$)CH(OTBS)); 2.00–1.91 (1H, m, CH(OTBS)C*H*($CH_3$)$CH_2$OPMB); 1.04 (3H, d, $J$=6.9 Hz, =CHCH(C$H_3$)); 0.92–0.89 (12H, m, SiC(C$H_3$)$_3$, CH(OTBS)CH(C$H_3$)$CH_2$OPMB); 0.032 (3H, s, Si(C$H_3$)$_A$-($CH_3$)$_B$); 0.025 (3H, s, Si($CH_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 159.1; 138.9; 137.7; 130.2; 130.0; 129.6; 129.2; 129.1; 128.5; 127.1; 126.1; 113.7; 76.2; 73.3; 72.5; 55.2; 42.1; 37.3; 26.1; 18.4; 17.7; 12.3; −3.7; −4.1. IR (film, cm$^{-1}$) 3024; 2957; 2930; 2856; 1613; 1514; 1471; 1463; 1362; 1249; 1172; 1086; 1057; 1037; 990; 836; 773; 746; 691. $[\alpha]_D^{20}$ −20.5 (*c* 0.1, $CHCl_3$). HRMS (ESI) $C_{30}H_{44}NaO_3Si^+$ requires 503.2952, found 503.2953. LREIMS 323 (4.3%); 187 (11%); 121 (100%); 85 (26%); 83 (58%); 57 (24%); 55 (16%).

### *5.1.6. (2S,3S,4S,5E,7E)-3-(tert-Butyldimethylsilyloxy)-2,4-dimethyl-8-phenylocta-5,7-diene-1-ol (**59**)*

To a solution of PMB ether **(*E*,*E*,5*S*)-31** (0.106 g, 0.22 mmol) in dry $CH_2Cl_2$ (3.7 mL) at room temperature were added $Me_2S$ (164 μL, 2.2 mmol) and powdered $MgBr_2\cdot OEt_2$ (0.170 g, 0.66 mmol). The mixture was stirred at room temperature overnight after which time TLC analysis showed consumption of the SM. The reaction was quenched by the addition of $NH_4Cl$ (satd aq, 10 mL) and the product extracted with $CH_2Cl_2$ (3×15 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (30% mixed hexanes/$CH_2Cl_2$, $R_f$=0.27) yielded 0.061 g (77%) of alcohol **59** as a clear colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40–7.18 (5H, m, Ar*H*); 6.67 (1H, dd, $J$=15.6, 10.2 Hz, ArCH=C*H*); 6.45 (1H, d, $J$=15.6 Hz, ArC*H*); 6.20 (1H, dd, $J$=15.3, 10.2 Hz, ArCH=CHC*H*); 5.87 (1H, dd, $J$=15.3, 7.8 Hz, ArCH=CHCH=C*H*); 3.72–3.58 (2H, m, C$H_A$H$_B$OH, C*H*(OTBS)); 3.47 (1H, dd, $J$=10.5, 5.7 Hz, $CH_AH_B$OH); 2.59–2.46 (1H, m, =CHC*H*($CH_3$)); 2.00–1.87 (1H, m, CH(OTBS)C*H*($CH_3$)$CH_2$OH); 1.70 (1H, br s, O*H*); 1.07 (3H, d, $J$=6.9 Hz, =CHCH(C$H_3$)); 0.93–0.89 (12H, m, SiC(C$H_3$)$_3$, CH(OH)CH(C$H_3$)); 0.09 (3H, s, Si-(C$H_3$)$_A$($CH_3$)$_B$); 0.07 (3H, s, Si($CH_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 138.2; 137.6; 130.5; 130.3; 129.5; 128.5; 127.1; 126.2; 77.3; 65.9; 41.1; 39.8; 26.1; 18.4; 16.6; 12.2; −3.9; −4.1. IR (film, cm$^{-1}$) 3400; 3023; 2958; 2929; 2856; 1472; 1461; 1251; 1029; 989; 858; 836; 773; 745; 691. $[\alpha]_D^{20}$ −10.2 (*c* 0.1, $CHCl_3$). HRMS (ESI) $C_{22}H_{36}NaO_2Si^+$ requires 383.2377, found 383.2375. LREIMS 259 (1.7%); 203 (11%); 185 (8.5%); 173 (8.5%); 157 (77%); 145 (100%); 131 (15%); 115 (38%); 111 (26%); 85 (35%); 75 (100%); 55 (21%).

### *5.1.7. (2R,3S,4S,5E,7E)-3-(tert-Butyldimethylsilyloxy)-2,4-dimethyl-8-phenylocta-5,7-dienal ((**5S**)-**32**)*

Oxalyl chloride (126 μL, 0.25 mol) was added dropwise to a solution of DMSO (36 μL, 0.50 mmol) in $CH_2Cl_2$ (720 μL) at −78 °C. The resulting solution was stirred at −78 °C for 30 min before dropwise addition of a solution of alcohol **59** (0.031 g, 0.085 mmol) in $CH_2Cl_2$ (0.25 mL, wash 2×0.25 mL) via a cannula. The resulting mixture was stirred for 45 min at −78 °C. $Et_3N$ (140 μL, 1.01 mmol) was added dropwise over several minutes and stirred at −78 °C for 30 min before warming to 0 °C and stirring for 30 min. The reaction mixture was quenched by addition of $NaHSO_4$ (1 M, 10 mL), and the product extracted with $Et_2O$ (3×10 mL). The combined extracts were concentrated in vacuo. The product was taken up in $Et_2O$ (30 mL) and washed with $NaHSO_4$ (1 M, 10 mL), $H_2O$ (10 mL), $NaHCO_3$ (satd aq, 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (50% mixed hexanes/$CH_2Cl_2$, $R_f$=0.53) yielding 28.4 mg (94%) of aldehyde **(5*S*)-32** as a clear colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.76 (1H, d, $J$=1.2 Hz, C*H*O); 7.40–7.18 (5H, m, Ar*H*); 6.73 (1H, dd, $J$=15.6, 10.2 Hz, ArCH=C*H*); 6.46 (1H, d, $J$=15.6 Hz, ArC*H*); 6.17 (1H, dd, $J$=15.3, 10.5 Hz, ArCH=CHC*H*); 5.73 (1H, dd, $J$=15.3, 8.7 Hz, ArCH=CHCH=C*H*); 4.03 (1H, dd, $J$=4.5, 4.5 Hz, C*H*(OTBS)); 2.57–2.46 (2H, m, C*H*($CH_3$)CH(OTBS)-CH($CH_3$)C(=O), CH($CH_3$)CH(OTBS)C*H*($CH_3$)C(=O)); 1.11 (3H, d, $J$=6.9 Hz, C(=O)CH(C$H_3$) or CH(C$H_3$)CH=); 1.09 (3H, d, $J$=6.9 Hz, C(=O)CH(C$H_3$) or CH(C$H_3$)CH=); 0.91 (9H, s, SiC(C$H_3$)$_3$); 0.09 (3H, s, Si(C$H_3$)$_A$($CH_3$)$_B$); 0.05 (3H, s, Si($CH_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 Hz, $CDCl_3$) $\delta$ 204.6; 137.4; 136.0; 132.0; 131.3; 128.9; 128.5; 127.3; 126.3; 75.8; 51.0; 41.5; 25.9; 18.2; 17.8; 9.4; −4.1; −4.2. IR (film, cm$^{-1}$) 2932; 2855; 1724; 1653; 1559; 1472; 1257; 1078; 1031; 991; 837; 776; 747; 692. $[\alpha]_D^{20}$ −71.6 (*c* 1.2, $CHCl_3$). HRMS (ESI) $C_{22}H_{34}NaO_2Si^+$ requires 381.2220, found 381.2222. LREIMS 301 (4.3%); 201 (31%); 173 (31%); 145 (17%); 115 (59%); 85 (40%); 83 (44%); 75 (44%); 73 (100%); 59 (21%).

### *5.1.8. (2E/Z,4S,5S,6S,7E,9E)-5-(tert-Butyldimethylsilyloxy)-2,4,6-trimethyl-10-phenyldeca-2,7,9-trieneoic acid ethyl esters ((**2Z,5S**)-**20** and (**2E,5S**)-**20**)*

To a solution of NaH (washed X4 and dried under $N_2$) (93 mg, 3.83 mmol) in THF (5.8 mL) at 0 °C was added the phosphonate **26** (0.80 mL, 3.7 mmol), dropwise. The solution was stirred at room temperature for 1 h before cooling to 0 °C and addition of aldehyde **(5*S*)-32** (0.42 g, 1.17 mmol). The solution was warmed slowly to room temperature and after 30 min no further reaction occurred so the reaction was quenched by pouring on to $NH_4Cl$ (satd aq, 30 mL). The product was extracted with $Et_2O$ (3×30 mL) and the combined extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (40% $CH_2Cl_2$/mixed hexanes, $R_f$ (2*E*)=0.41, $R_f$ (2*Z*)=0.3) to give 120 mg (23%) of **(2*Z*,5*S*)-20** and 373 mg (72%) of **(2*E*,5*S*)-20** isomer. The **(2*E*,5*S*)-20** isomer spontaneously undergoes a [4π+2π] cycloaddition reaction and was therefore not characterised.

Compound **(2*Z*,5*S*)-20**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.39–7.17 (5H, m, Ar*H*); 6.73 (1H, dd, $J$=15.6, 10.2 Hz, ArCH=C*H*); 6.42 (1H, d, $J$=15.6 Hz, ArC*H*); 6.10 (1H, dd, $J$=15.3, 10.2 Hz, ArCH=CHC*H*); 5.82–5.71 (2H, m, ArCH=CHCH=C*H*, C*H*=C($CH_3$)$CO_2$Et); 4.24–4.10 (2H, m, $CO_2CH_2$); 3.52–3.42 (1H, m, C*H*(OTBS)); 3.38–3.27 (1H, m, CH(OTBS)C*H*($CH_3$)CH=); 2.44–2.34 (1H, m, CH=CHC*H*($CH_3$)); 1.89 (3H, d, $J$=1.5 Hz, CH=C(C$H_3$)$CO_2$Et);

1.27 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$); 1.05 (3H, d, $J$=6.9 Hz, =CHCH($CH_3$)CH(OTBS)); 0.99 (3H, d, $J$=6.6 Hz, CH(OTBS)-CH($CH_3$)CH=); 0.92 (9H, s, SiC($CH_3$)$_3$); 0.04 (3H, s, Si-($CH_3$)$_A$($CH_3$)$_B$); 0.03 (3H, s, Si($CH_3$)$_A$($CH_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 168.1; 146.1; 138.3; 130.7; 130.3; 130.2; 129.6; 128.5; 127.7; 127.0; 126.1; 79.9; 60.1; 42.5; 37.4; 26.1; 20.9; 18.4; 17.3; 15.9; 14.3; −3.5; −3.8. IR (film, cm$^{-1}$) 3025; 2960; 2928; 2857; 1716; 1253; 1219; 1092; 1030; 836; 773; 691; 667. $[\alpha]_D^{20}$ +58.3 ($c$ 1.0, $CHCl_3$). HRMS (ESI) $C_{27}H_{42}NaO_3Si^+$ requires 465.2795, found 465.2800. LREIMS 385 (57%); 339 (9.6%); 310 (14%); 285 (26%); 239 (33%); 237 (73%); 221 (16%); 195 (31%); 181 (1%); 157 (26%); 153 (15%); 129 (19%); 115 (24%); 103 (19%); 91 (40%); 84 (74%); 75 (94%); 73 (100%); 57 (23%); 51 (34%).

### *5.1.9. (1S,2S,3S,3aS,4R,5R,7aR)-2-(tert-Butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (**36**)*

A solution of aldehyde **32** (96 mg, 0.27 mmol) and ylide **25** (116 mg, 0.32 mmol) in $CH_2Cl_2$ (1.8 mL) was heated under reflux for 6 days. TLC analysis of the reaction mixture failed to reveal anything about the reaction progress as the starting material and product had similar $R_f$ values. The solvent was removed in vacuo and the product was triturated with mixed hexanes to remove the triphenylphosphine oxide. Purification by column chromatography (50% $CH_2Cl_2$/mixed hexanes, $R_f$=0.45) yielded 47 mg (40%) of the IMDA cycloadduct **36** and some recovered starting material.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.24−7.11 (5H, m, Ar$H$); 5.99 (1H, dt, $J$=10.2, 1.8 Hz, PhCHCH=C$H$); 5.54 (1H, ddd, $J$=10.2, 3.6, 3.0 Hz, PhCHC$H$); 3.70 (1H, dd, $J$=6.6, 1.8 Hz, C$H$(OTBS)); 3.54 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.31 (1H, m, PhC$H$); 3.21 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2CH_AH_B$); 2.04−1.99 (1H, m, CH=CHC$H$); 1.80 (1H, dd, $J$=11.2, 10.2 Hz, $EtO_2CC(CH_3)CHCH(CH_3)$); 1.70 (1H, ddd, $J$=12.0, 6.6, 6.6 Hz, CH=CHCHC$H$($CH_3$)); 1.59−1.54 (1H, m, $Et_2OC(CH_3)CHCH(CH_3)$); 1.34 (3H, s, $Et_2OCC(CH_3)$); 1.03 (3H, d, $J$=6.6 Hz, CH=CHCHCH($CH_3$)); 0.88 (9H, s, SiC($CH_3$)$_3$); 0.86 (3H, d, $J$=7.2 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 0.69 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$); 0.03 (3H, s, Si($CH_3$)$_A$-($CH_3$)$_B$); 0.02 (3H, s, Si($CH_3$)$_A$($CH_3$)$_B$). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 175.3; 142.0; 129.6; 128.3; 128.0; 127.7; 126.7; 82.9; 59.7; 54.3; 49.6; 47.0; 44.3; 44.2; 40.4; 26.1; 25.9; 18.3; 18.2; 13.2; 12.5; −4.3; −4.6. IR (film, cm$^{-1}$) 3026; 2954; 2929; 2885; 2856; 1720; 1473; 1460; 1256; 1092; 1060; 1028; 834; 773; 701; 669. HRMS (ESI) $C_{27}H_{42}O_3Si^+$ requires 443.2976, found 443.2979. LREIMS 385 (22%); 310 (11%); 285 (62%); 237 (35%); 235 (22%); 206 (23%); 195 (16%); 181 (12%); 157 (23%); 129 (17%); 125 (41%); 116 (24%); 105 (14%); 91 (41%); 75 (90%); 73 (100%); 57 (40%).

### *5.1.10. (1S,2S,3S,3aS,4R,5R,7aR)- and (1S,2S,3S,3aS,4R,5S,7aS)-2-(tert-Butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (**36** and **37**)*

A solution of triene **(2*Z*,5*S*)-20** (120 mg, 0.28 mmol) in $CDCl_3$ (4 mL) was warmed to 50 °C overnight. After this time the product was concentrated in vacuo and the product purified by column chromatography (50% $CH_2Cl_2$/mixed hexanes, $R_f$=0.52 and 0.45) yielding two steroisomers, cycloadduct **37** (5.1 mg, 4.3% yield) and cycloadduct **36** (95 mg, 84% yield, 94% ds) as clear colourless oils.

Compound **36**: data is identical to the cycloadduct from the Wittig olefination reaction above.

Compound **37**: $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 7.29−7.10 (5H, m, Ar$H$); 5.88 (1H, ddd, $J$=9.9, 2.8, 2.8 Hz, =C$H$CHAr); 5.83 (1H, ddd, $J$=9.9, 2.8, 2.1 Hz, PhCHCH=C$H$); 4.08−4.07 (1H, m, C$H$Ph); 3.97 (1H, qd, $J$=7.2, 6.8 Hz, $OCH_AH_BCH_3$); 3.94 (1H, dq, $J$=10.8, 7.2 Hz, $OCH_AH_BCH_3$); 3.52 (1H, dd, $J$=3.2, 3.2 Hz, CHOTBS); 2.77 (1H, dd, $J$=10.3, 7.4 Hz, $EtO_2CC(CH_3)CHCH(CH_3)$); 2.64 (1H, ddddd, $J$=10.3, 10.3, 3.2, 3.2, 3.2 Hz, CH=CHC$H$); 1.95 (1H, qdd, $J$=7.0, 4.3, 3.2 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 1.50 (1H, dqd, $J$=6.6, 6.6, 3.2 Hz, CH=CHCHC$H$($CH_3$)); 1.13 (3H, s, $Et_2OCC(CH_3)$); 1.02 (3H, d, $J$=7.0 Hz, CH=CHCHCH($CH_3$)); 1.01 (9H, s, SiC($CH_3$)$_3$); 0.96 (3H, d, $J$=6.6 Hz, CH=CHCHCH($CH_3$)); 0.92 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$); 0.0349 (3H, s, Si-($CH_3$)$_A$($CH_3$)$_B$); 0.0347 (3H, s, Si($CH_3$)$_A$($CH_3$)$_B$). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 176.5; 142.5; 130.1; 129.8; 129.5; 128.3; 127.0; 79.7; 60.3; 50.9; 50.2; 48.8; 44.6; 43.7; 40.1; 26.3; 18.6; 16.1; 14.2; 13.4; 12.9; −3.8; −3.9. IR (film, cm$^{-1}$) 2956; 2928; 1712; 1462; 1257; 1160; 1096; 1061; 1028; 862; 834; 773. $[\alpha]_D^{20}$ +11 ($c$ 0.45, $CHCl_3$).

### *5.1.11. (1S,2S,3S,3aS,4S,5R,7aR)-2-(tert-Butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl esters (**33**–**35**)*

A solution of triene **(2*E*,5*S*)-20** (80.9 mg, 0.18 mmol) was heated under reflux in toluene (4 mL) overnight. The solvent was then removed in vacuo and the product purified by column chromatography (5% $Et_2O$/mixed hexanes, $R_f$=0.31) yielding 70.7 mg (87% yield, 85% ds) of an inseparable mixture of three isomers **33**–**35** (ratio 85:10:5) as a clear colourless oil. Characterisation of the major isomer was achieved.

Compound **33**: $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 7.16−7.03 (5H, m, Ar$H$); 5.93 (1H, apt ddd, $J$=9.6, 1.8, 1.8 Hz, PhCHCH=C$H$); 5.72 (1H, ddd, $J$=9.6, 6.6, 2.4 Hz, PhCHC$H$); 4.27 (1H, apt qn, $J$=1.8 Hz, PhC$H$); 4.06 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.99 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2$-$CH_AH_B$); 3.52 (1H, dd, $J$=5.4, 1.8 Hz, C$H$OTBS); 2.39 (1H, dqd, $J$=9.6, 7.2, 1.8 Hz, $Et_2OCCHCH(CH_3)CH(OTBS)$); 2.24 (1H, ddddd, $J$=11.4, 11.4, 1.8, 1.8, 1.8 Hz, CH=CHC$H$); 1.43 (1H, dq, $J$=6.6, 6.6 Hz, CH=CHCHC$H$($CH_3$)); 1.36 (1H, dd, $J$=11.4, 9.6 Hz, $Et_2OCC(CH_3)CH$); 1.02 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$); 1.01 (3H, d, $J$=6.6 Hz, CH=CHCHCH($CH_3$)); 0.95 (9H, s, SiC($CH_3$)$_3$); 0.92 (3H, s, $Et_2OCC(CH_3)$); 0.87 (3H, d, $J$=7.2 Hz, $Et_2OC(CH_3)$-$CHCH(CH_3)$); 0.03 (3H, s, Si($CH_3$)$_A$($CH_3$)$_B$); 0.01 (3H, s, Si-($CH_3$)$_A$($CH_3$)$_B$). $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 175.7; 141.7; 131.0; 130.7; 128.8; 128.1; 127.0; 84.5; 60.4; 52.8; 51.1; 49.1; 45.7; 43.9; 42.6; 26.2; 23.9; 21.2; 18.4; 14.4; 12.2; −4.0; −4.6. IR (film, cm$^{-1}$) 3018; 2956; 2928; 2886; 2856; 1724; 1463; 1452; 1251; 1207; 1102; 1089; 1021; 875; 773; 703; 674. $[\alpha]_D^{20}$ +55.6 ($c$ 0.36, $CHCl_3$). HRMS (ESI)

$C_{27}H_{42}NaO_3Si^+$ requires 465.2795, found 465.2796. LREIMS 385 (74%); 339 (13%); 310 (17%); 285 (18%); 237 (84%); 221 (19%); 195 (35%); 181 (17%); 157 (27%); 129 (20%); 115 (26%); 103 (19%); 91 (43%); 86 (45%); 84 (69%); 75 (100%); 73 (87%); 57 (30%).

Compound **34–35** (two isomers): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.22–7.21 (Ar*H*); 5.88 (1H, ddd, $J$=9.6, 2.4, 2.4 Hz); 5.83 (1H, m); 4.29 (1H, m); 3.89 (1H, dq, $J$=10.8, 7.2 Hz); 2.67 (1H, dq); 2.15 (1H, apt sex, $J$=7.2 Hz); 1.96 (1H, dd, $J$=12.6, 9.0 Hz); 1.90 (m); 1.87 (m); 0.92 (9H, s) (Note: data incomplete due to overlap with major isomer obscuring some resonances.). Minor isomers were not able to be identified in the $^{13}$C NMR spectrum.

### *5.1.12. (1-(4′R)-2R,3S,4S)-1-(4′-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentan-1-one (**41**)*

To a solution of the *N*-acylthiazolidinethione **40** (2.29 g, 8.65 mmol) in $CH_2Cl_2$ (55 mL) at 0 °C was added $TiCl_4$ (9 mL, 9.07 mmol) dropwise. The solution was allowed to stir for 5 min at 0 °C before (−)-sparteine (2 mL, 2.03 g, 8.65 mmol) was added dropwise to the suspension. The dark red enolate was stirred for 20 min at 0 °C before cooling to −78 °C and addition of *N*-methyl-2-pyrrolidinone (0.83 mL, 8.65 mmol) dropwise. The solution was stirred for 10 min at −78 °C before addition of the aldehyde **28** (0.90 g, 4.32 mmol) in $CH_2Cl_2$ (3 mL, 1 mL×2). The resulting mixture was stirred at −78 °C to −50 °C for 2.5 h before placing overnight in the −80 °C freezer. The next morning the reaction was warmed to −50 °C for 3 h, however, TLC analysis showed no further reaction. The reaction was quenched by addition of $NH_4Cl$ (half satd aq, 80 mL). The product was extracted with $CH_2Cl_2$ (2×100 mL) and the combined extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (100% $CH_2Cl_2$→ 2.5% $Et_2O/CH_2Cl_2$, $R_f$ (2.5% $Et_2O/CH_2Cl_2$)=0.28 (*iso* 1), 0.17 (*iso* 2 and 3)) yielded 1.29 g (63%) of isomer **41** (desired isomer) and 0.29 g (14%) of a mixture of two minor isomers as clear yellow oils.

Major isomer **41**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36–7.23 (8H, m, Ar*H*); 6.87 (2H, d, $J$=8.4 Hz, Ar*H*); 5.27 (1H, ddd, $J$=10.5, 6.6, 3.3 Hz, C*H*Bn); 4.57 (1H, apt qn, $J$=6.9 Hz, C(=O)C*H*($CH_3$)); 4.44 (1H, d, $J$=12.6 Hz, OC$H_A$H$_B$Ar); 4.39 (1H, d, $J$=12.6 Hz, OCH$_A$$H_B$Ar); 3.97 (1H, dd, $J$=6.3, 4.8 Hz, C*H*OTBS); 3.80 (3H, s, OC$H_3$); 3.44 (2H, m, C$H_2$OPMB); 3.35 (1H, dd, $J$=11.4, 6.9 Hz, CHC$H_A$H$_B$Ar); 3.21 (1H, dd, $J$=13.2, 3.9 Hz, SC$H_A$H$_B$); 3.03 (1H, dd, $J$=13.2, 10.5 Hz, SCH$_A$$H_B$); 2.89 (1H, d, $J$=11.4 Hz, CHCH$_A$$H_B$Ar); 1.79 (1H, m, C*H*($CH_3$)$CH_2$OPMB); 1.33 (3H, d, $J$=6.9 Hz, C(=O)CH(C$H_3$)); 1.00 (3H, d, $J$=7.2 Hz, CH(C$H_3$)$CH_2$OPMB). $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 200.9; 177.9; 159.2; 136.4; 130.2; 129.4; 129.2; 129.0; 127.2; 113.8; 75.2; 73.9; 73.1; 68.7; 55.3; 41.9; 36.7; 36.4; 32.1; 13.1; 12.2. IR (film, cm$^{-1}$) 3483; 2932; 1684; 1653; 1612; 1558; 1513; 1456; 1341; 1299; 1249; 1165; 1135; 1031; 820; 702. $[\alpha]_D^{20}$ +143.6 ($c$ 1.5, $CHCl_3$). HRMS (ESI) $C_{25}H_{31}NNaO_4S_2^+$ requires 496.1587, found 496.1582. LREIMS 352 (7.1%); 276 (12%); 264 (56%); 210 (100%); 121 (71%); 117 (14%).

Minor isomers: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36–7.21 (7H, m, ArH); 6.86 (2H, d, $J$=8.7 Hz, ArH); 5.25 (1H, ddd, $J$=10.5, 6.6, 3.9 Hz, C*H*Bn); 4.76 (1H, qd, $J$=6.6, 3.6 Hz, C(=O)C*H*($CH_3$)); 4.44 (2H, s, OC$H_2$Ar); 3.90 (1H, dd, $J$=8.1, 3.6 Hz, CH(OH)); 3.80 (3H, s, $OCH_3$); 3.59–3.29 (4H, m); 3.05 (1H, dd, $J$=12.9, 10.8 Hz); 2.86 (1H, d, $J$=11.4 Hz, C$H_2$OPMB, C$H_2$S, CHC$H_2$Ar); 1.95–1.86 (1H, m, C*H*($CH_3$)$CH_2$OPMB); 1.24 (3H, d, $J$=6.6 Hz, C(=O)CH(C$H_3$)); 0.89 (3H, d, $J$=6.9 Hz, CH(C$H_3$)-$CH_2$OPMB). $^{13}$C NMR (75.5 MHz, $CDCl_3$) 201.2; 201.1; 177.8; 177.4; 159.3; 159.2; 152.4; 136.6; 136.5; 130.1; 129.7; 129.4; 129.4; 129.3; 129.3; 128.9; 127.2; 127.1; 113.9; 113.8; 76.3; 74.9; 74.3; 74.2; 73.2; 73.1; 69.8; 69.1; 65.8; 55.2; 42.2; 41.7; 37.1; 36.6; 36.1; 36.0; 32.0; 31.7; 15.2; 13.9; 13.6; 10.6; 9.6.

### *5.1.13. (1(4′R),2R,3S,4S)-1-(4′-Benzyl-2-thioxothiazolidin-3-yl)-3-(tert-butyldimethylsilyloxy)-5-(4″-methoxybenzyloxy)-2,4-dimethylpentan-1-one (**42**)*

To a solution of the alcohol **41** (0.82 g, 1.74 mmol) in $CH_2Cl_2$ (17.4 mL) at −78 °C was added 2,6-lutidine (0.30 mL, 0.28 g, 2.61 mmol), followed immediately by TBSOTf (0.59 mL, 0.69 g, 2.61 mmol). The solution was stirred at −78 °C for 30 min, after which time TLC analysis indicated consumption of SM. The reaction was quenched by the addition of $NaHCO_3$ (satd aq, 20 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×40 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (10% mixed hexanes/ $CH_2Cl_2$, $R_f$=0.49) yielding 0.99 g (98%) of TBS ether **42** as a clear colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.34–7.24 (7H, m, Ar*H*); 6.86 (2H, d, $J$=8.4 Hz, Ar*H*); 5.21 (1H, ddd, $J$=10.2, 6.6, 3.9 Hz, C*H*Bn); 4.50 (1H, qd, $J$=8.4, 6.9 Hz, C(=O)C*H*($CH_3$)); 4.43 (1H, d, $J$=11.7 Hz, OC$H_A$H$_B$Ar); 4.38 (1H, d, $J$=11.7 Hz, OCH$_A$$H_B$Ar); 4.09 (1H, dd, $J$=8.4, 2.1 Hz, C*H*(OTBS)); 3.78 (3H, s, OC$H_3$); 3.40 (1H, dd, $J$=9.3, 6.6 Hz, C$H_A$H$_B$OPMB); 3.31 (1H, dd, $J$=11.7, 7.2 Hz, C$H_A$H$_B$Ar); 3.25–3.17 (2H, m, CH$_A$$H_B$OPMB, SC$H_A$H$_B$); 3.03 (1H, dd, $J$=13.2, 10.2 Hz, SCH$_A$$H_B$); 2.86 (1H d, $J$=11.7 Hz, CH$_A$$H_B$Ar); 1.82–1.75 (1H, m, CH(OTBS)C*H*($CH_3$)$CH_2$OPMB); 1.26 (3H, d, $J$=6.6 Hz, C(=O)CH(C$H_3$)); 0.89–0.87 (12H, m, SiC(C$H_3$)$_3$, CH(C$H_3$)$CH_2$OPMB); 0.09 (3H, s, Si(C$H_3$)$_A$(CH$_3$)$_B$); 0.03 (3H, s, Si(CH$_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 200.8; 177.3; 159.1; 136.6; 130.7; 129.5; 129.2; 128.9; 127.2; 113.7; 75.0; 72.8; 72.6; 69.0; 55.3; 43.1; 38.9; 36.6; 32.1; 26.1; 18.4; 15.5; 11.6; −3.7; −4.1. IR (film, cm$^{-1}$) 2930; 2856; 1693; 1613; 1513; 1462; 1362; 1341; 1250; 1062; 1109; 1032; 838; 775. $[\alpha]_D^{20}$ +119.6 ($c$ 0.9, $CHCl_3$). HRMS (ESI) $C_{31}H_{45}NO_4S_2SiNa^+$ requires 610.2456, found 610.2451. LREIMS 530 (21%); 482 (21%); 466 (22%); 330 (39%); 319 (20%); 286 (16%); 276 (33%); 264 (90%); 228 (44%); 201 (14%); 135 (15%); 121 (100%).

*5.1.14. (2R,3S,4S)-3-(tert-Butyldimethylsilyloxy)-(4′-methoxybenzyloxy)-2,4-dimethylpentan-1-ol (**60**)*

To a solution of the thione **42** (0.51 g, 8.5 mmol) and methanol (45 μL, 36 mg, 1.1 mmol) in $Et_2O$ (5 mL) was added a solution of $LiBH_4$ (2 M in THF, 0.56 mL, 1.1 mmol). Evolution of $H_2$ was observed and after 15 min at 0 °C the solution was warmed to room temperature and the reaction progress monitored by TLC. After 15 min the starting material had been consumed and the reaction was quenched carefully with NaOH (5 M, 4 mL). The biphasic mixture was stirred for 30 min at room temperature to ensure complete hydrolysis of the borates. The layers were separated and the aqueous layer was back-extracted with $Et_2O$ (20 mL). The organic layers were concentrated and the crude product filtered through a silica plug yielding 0.33 g (crude yield ~100%) of the alcohol **60** as a clear colourless oil, which was used without further purification.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.25 (2H, d, $J$=8.7 Hz, Ar*H*); 6.87 (2H, d, $J$=8.7 Hz, Ar*H*); 4.41 (2H, s, $OCH_2Ar$); 3.86 (1H, apt t, $J$=3.6 Hz, C*H*(OTBS)); 3.80 (3H, s, $OCH_3$); 3.66 (1H, dd, $J$=10.8, 8.1 Hz, $CH_AH_BO$); 3.48 (1H, dd, $J$=10.8, 6.0 Hz, $CH_AH_BO$); 3.36 (1H, dd, $J$=9.0, 7.2 Hz, $CH_AH_BO$); 3.23 (1H, dd, $J$=9.0, 6.3 Hz, $CH_AH_BO$); 2.04–1.90 (3H, m, O*H*, C*H*($CH_3$)$CH_2$(OH), C*H*($CH_3$)$CH_2$OPMB); 0.94 (3H, d, $J$=6.9 Hz, CH(C$H_3$)); 0.89 (9H, s, SiC(C$H_3$)$_3$); 0.84 (3H, d, $J$=7.2 Hz, CH(C$H_3$)); 0.07 (3H, s, Si(C$H_3$)$_A$($CH_3$)$_B$); 0.03 (3H, s, Si($CH_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 159.2; 130.7; 129.1; 113.8; 74.5; 73.5; 72.6; 66.3; 55.3; 40.3; 36.2; 26.0; 18.3; 12.9 (2); −4.2; −4.4. IR (film cm$^{-1}$) 3419; 2956; 2929; 2856; 1613; 1514; 1463; 1361; 1302; 1249; 1173; 1096; 1036; 837; 773. $[\alpha]_D^{20}$ +1.6 (*c* 0.6, $CHCl_3$). HRMS (ESI) $C_{21}H_{38}NaO_4Si^+$ requires 405.2432, found 405.2430. LREIMS 203 (1.6%); 187 (1.6%); 145 (5.4%); 137 (1.6%); 121 (100%); 115 (3.1%); 89 (3.1%); 75 (16%); 59 (1.6%); 45 (1.6%).

*5.1.15. (2R,3S,4S)-3-(tert-Butyldimethylsilyloxy)-5-(4′-methoxybenzyloxy)-2,4-dimethylpentanal ((**5S**)-**22**)*

To a solution of DMSO (26 μL, 28 mg, 0.37 mmol) in $CH_2Cl_2$ (0.5 mL) at −78 °C, was added a solution of oxalyl chloride (2 M in $CH_2Cl_2$, 92 μL, 0.18 mmol) and the resulting solution stirred at −78 °C for 30 min. A solution of the alcohol **60** (0.328 g, 8.59 mmol) in $CH_2Cl_2$ (3×0.3 mL) was added and the resulting solution stirred at −78 °C for 45 min. $NEt_3$ (102 μL, 74 mg, 0.73 mmol) was added and the solution stirred at −78 °C for 30 min before warming to 0 °C and stirring for a further 30 min. The reaction was quenched by the addition of $NaHSO_4$ (1 M, 10 mL), the product extracted with $Et_2O$ (3×10 mL) and concentrated in vacuo. The product was taken up in $Et_2O$ (20 mL), washed with $NaHSO_4$ (1 M, 10 mL), $H_2O$ (10 mL), $NaHCO_3$ (satd aq, 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (100% $CH_2Cl_2$, $R_f$=0.45) yielding 0.27 g (96%) of the aldehyde **(5S)-22** as a clear colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.85 (1H, apt s, C*H*(=O)); 7.24 (2H, d, $J$=8.7 Hz, Ar*H*); 6.87 (2H, d, $J$=8.7 Hz, Ar*H*); 4.43 (1H, d, $J$=11.4 Hz, $OCH_AH_BAr$); 4.37 (1H, d, $J$=11.4 Hz, $OCH_AH_BAr$); 4.22 (1H, dd, $J$=4.8, 3.6 Hz, C*H*(OTBS)); 3.80 (3H, s, $OCH_3$); 3.37 (1H, dd, $J$=9.0, 7.2 Hz, $CH_AH_BOPMB$); 3.23 (1H, dd, $J$=9.0, 5.7 Hz, $CH_AH_BOPMB$); 2.54 (1H, apt qn, $J$=6.9 Hz, CH(=O)C*H*($CH_3$)); 1.94 (1H, m, C*H*($CH_3$)$CH_2$OPMB); 1.04 (3H, d, $J$=6.9 Hz, CH(=O)-CH(C$H_3$)); 0.88 (9H, s, SiC(C$H_3$)$_3$); 0.85 (3H, d, $J$=6.9 Hz, CH(C$H_3$)$CH_2$OPMB); 0.06 (3H, s, Si(C$H_3$)$_A$($CH_3$)$_B$); 0.04 (3H, s, Si($CH_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 205.3; 130.5; 129.2; 113.8; 72.64; 72.57; 72.4; 55.3; 51.4; 37.1; 25.9; 18.2; 12.2; 9.3; −4.0; −4.6 (one aromatic signal missing). IR (film, cm$^{-1}$) 2930; 2856; 1721; 1613; 1514; 1463; 1361; 1302; 1249; 1172; 1093; 1036; 836; 774. $[\alpha]_D^{20}$ +36.5 (*c* 1.9, $CHCl_3$). HRMS (ESI) $C_{21}H_{36}NaO_4Si^+$ requires 403.2275, found 403.2276. LREIMS 143 (1.6%); 137 (1.6%); 132 (1.6%); 121 (100%); 115 (3.9%); 112 (8.5%); 97 (1.6%); 91 (1.6%); 78 (3.9%); 75 (51%); 67 (1.6%); 59 (3.1%); 55 (1.6%); 47 (3.1%).

*5.1.16. (2R,3R,4S,5E,7E)-3-(tert-Butyldimethylsilyloxy)-1-(4′-methyoxybenzyloxy)-2,4-dimethyl-8-phenylocta-5,7-diene ((**E,E,5R**)-**31**)*

To a solution of sulfone **24** (0.99 g, 3.03 mmol) in anhydrous DME (7.6 mL) at −60 °C was added a solution of KHMDS in toluene (0.5 M, 5.4 mL, 2.72 mmol) dropwise. The solution turned deep red and was stirred at −60 °C for 30 min before the addition of aldehyde **(5S)-22** (0.576 g, 1.51 mmol) in DME (3×0.5 mL). The solution was stirred at −60 °C for 30 min before warming to room temperature and stirring overnight. The reaction was quenched by the addition of $H_2O$ (30 mL) and diluted with $Et_2O$ (50 mL). The layers were shaken well, separated and the organic layer dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (50% mixed hexanes/$CH_2Cl_2$, $R_f$=0.55) yielding 0.494 g (68%) of a mixture of dienes **(E,E)-41** and **(Z,E)-41** as a pale yellow oil. The product was dissolved in $CDCl_3$ (1 mL) and few crystals of $I_2$ added. The isomerisation reaction was monitored by $^1$H NMR and after 44 min isomerisation of the **(Z,E)-41** to **(E,E)-41** was complete. The solution was diluted with $CH_2Cl_2$ (50 mL) and washed with sodium metabisulfite solution (satd aq, 20 mL) and $H_2O$ (20 mL). The organics were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (50% mixed hexanes/$CH_2Cl_2$, $R_f$=0.55) yielded 0.464 g (94%) of **(E,E,5R)-31** as a single isomer.

$^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.40–7.19 (7H, m, Ar*H*); 6.88 (2H, dt, $J$=9.0, 2.4 Hz, Ar*H*); 6.73 (1H, dd, $J$=15.6, 10.2 Hz, ArCH=C*H*); 6.43 (1H, d, $J$=15.6 Hz, ArC*H*); 6.16 (1H, dd, $J$=15.4, 10.2 Hz, ArCH=CHC*H*); 5.78 (1H, dd, $J$=15.4, 8.0 Hz, ArCH=CHCH=C*H*); 4.44 (1H, d, $J$=11.8 Hz, $OCH_AH_BAr$); 4.36 (1H, d, $J$=11.8 Hz, $OCH_AH_BAr$); 3.80 (3H, s, $OCH_3$); 3.68 (1H, dd, $J$=6.8, 2.4 Hz, C*H*(OTBS)); 3.36 (1H, dd, $J$=9.2, 7.6 Hz, $CH_AH_BOPMB$); 3.19 (1H, dd, $J$=9.2, 6.6 Hz, $CH_AH_BOPMB$); 2.44 (1H, apt qn, $J$=6.8 Hz, =CHC*H*($CH_3$)); 1.98 (1H, apt qnd, $J$=6.6, 2.4 Hz, C*H*($CH_3$)$CH_2$OPMB); 1.04 (3H, d, $J$=6.8 Hz, =CHCH(C$H_3$)); 0.91 (9H, s, SiC(C$H_3$)$_3$); 0.85 (3H, d,

$J$=6.6 Hz, CH(C$H_3$)CH$_2$OPMB); 0.06 (3H, s, Si(C$H_3$)$_A$(CH$_3$)$_B$); 0.03 (3H, s, Si(CH$_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 138.9; 137.6; 130.8; 130.2; 129.6; 129.5; 129.2; 128.5; 127.1; 126.1; 113.7; 75.8; 73.4; 72.5; 55.3; 41.9; 36.8; 26.9; 18.4; 17.2; 11.2; −3.6; −4.1 (note: two coincident signals in vinyl region). $[\alpha]_D^{20}$ 0 ($c$ 0.4, $CHCl_3$). IR (film, cm$^{-1}$) 2956; 2928; 2855; 1731; 1612; 1513; 1462; 1385; 1248; 1173; 1111; 1038; 990; 837; 773; 747; 693. HRMS (ESI) $C_{30}H_{44}NaO_3Si^+$ requires 503.2952, found 503.2944. LREIMS 323 (57%); 277 (41%); 251 (31%); 229 (20%); 199 (21%); 187 (100%); 131 (16%); 121 (41%).

### 5.1.17. (2R,3R,4S,5E,7E)-3-(tert-Butyldimethylsilyloxy)-2,4-dimethyl-8-phenylocta-5,7-dien-1-ol (**61**)

To a solution of PMB ether (**E,E,5R**)-**31** (0.464 g, 0.96 mmol) in dry $CH_2Cl_2$ (16 mL) at room temperature were added $Me_2S$ (0.72 mL, 9.74 mmol) and powdered $MgBr_2\cdot OEt_2$ (0.747 g, 2.89 mmol). The mixture was stirred at room temperature overnight after which time TLC analysis showed consumption of SM. The reaction was quenched by the addition of $NH_4Cl$ (satd aq, 40 mL) and the product extracted with $CH_2Cl_2$ (3×40 mL). The combined extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (20% mixed hexanes/$CH_2Cl_2$, $R_f$=0.35) yielded 0.292 g (84%) of alcohol **61** as a clear colourless oil.

$^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.31−7.10 (5H, m, Ar$H$); 6.65 (1H, dd, $J$=15.8, 10.2 Hz, ArCH=C$H$); 6.37 (1H, d, $J$=15.8 Hz, ArC$H$); 6.10 (1H, dd, $J$=15.4, 10.4 Hz, ArCH=CHC$H$); 5.68 (1H, dd, $J$=15.4, 8.2 Hz, ArCH=CHCH=C$H$); 3.60 (1H dd, $J$=7.2, 2.6 Hz, C$H$(OTBS)); 3.52 (1H, dd, $J$=10.4, 8.4 Hz, C$H_A$H$_B$OH); 3.38 (1H, dd, $J$=10.5, 5.7 Hz, CH$_A$$H_B$OH); 2.42 (1H, apt sex., $J$=6.8 Hz, =CHC$H$(CH$_3$)); 1.87−1.62 (1H, m, C$H$(CH$_3$)CH$_2$OH); 1.00 (3H, d, $J$=6.8 Hz, =CHCH(C$H_3$)); 0.84 (9H, s, SiC(C$H_3$)$_3$); 0.76 (3H, d, $J$=6.8 Hz, CH(C$H_3$)-CH$_2$(OH)); 0.00 (6H, s, Si(C$H_3$)$_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 138.6; 137.5; 130.5; 129.6; 129.4; 128.5; 127.2; 126.1; 76.7; 66.1; 41.3; 39.6; 26.1; 18.3; 17.4; 11.5; −3.8; −4.2. IR (film, cm$^{-1}$) 3362; 2957; 2929; 2883; 2856; 1472; 1459; 1252; 1095; 1025; 988; 859; 837; 773; 746; 690; 669. $[\alpha]_D^{20}$ +39.4 ($c$ 2.9, $CHCl_3$).

### 5.1.18. (2R,3R,4S,5E,7E)-3-(tert-Butyldimethylsilyloxy)-2,4-dimethyl-8-phenylocta-5,7-dienal ((**5R**)-**32**)

A solution of oxalyl chloride in $CH_2Cl_2$ (2 M, 0.61 mL, 1.21 mmol) was added dropwise to a solution of DMSO (0.172 mL, 2.43 mmol) in $CH_2Cl_2$ (3.5 mL) at −78 °C. The resulting solution was stirred at −78 °C for 30 min. A solution of alcohol **61** (0.292 g, 0.81 mmol) in $CH_2Cl_2$ (0.5 mL, 0.25 mL×2) was added via a cannula to the reaction mixture, dropwise. The resulting mixture was stirred for 45 min at −78 °C. $Et_3N$ (0.67 mL, 4.86 mmol) was added dropwise over several minutes and stirred at −78 °C for 30 min before warming to 0 °C and stirring for 30 min. The reaction mixture was quenched by addition of $NaHSO_4$ (1 M, 30 mL) and the product extracted with $Et_2O$ (3×30 mL). The combined extracts were concentrated in vacuo. The product was taken up in $Et_2O$ (50 mL) and washed with $NaHSO_4$ (1 M, 20 mL), $H_2O$ (20 mL), $NaHCO_3$ (satd aq, 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (100% $CH_2Cl_2$, $R_f$=0.41) yielding 0.243 g (84%) of aldehyde (**5R**)-**32** as a clear colourless oil.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.75 (1H, s, C$H$O); 7.41−7.22 (5H, m, Ar$H$); 6.75 (1H, dd, $J$=15.6, 10.5 Hz, ArCH=C$H$); 6.50 (1H, d, $J$=15.6 Hz, ArC$H$); 6.23 (1H, dd, $J$=15.3, 10.5 Hz, ArCH=CHC$H$); 5.75 (1H, dd, $J$=15.3, 8.4 Hz, ArCH=CHCH=C$H$); 4.09 (1H, dd, $J$=7.2, 2.7 Hz, C$H$(OTBS)); 2.60−2.42 (2H, m, =CHC$H$(CH$_3$), C$H$(CH$_3$)C(=O)); 1.14 (3H, d, $J$=7.2 Hz, C(=O)CH(C$H_3$) or CH(C$H_3$)CH=); 1.10 (3H, d, $J$=6.9 Hz, C(=O)CH(C$H_3$) or CH(C$H_3$)CH=); 0.91 (9H, s, SiC(C$H_3$)$_3$); 0.11 (3H, s, Si(C$H_3$)$_A$(CH$_3$)$_B$); 0.01 (3H, s, Si(CH$_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (75.5 Hz, $CDCl_3$) $\delta$ 205.2; 137.3; 137.2; 131.3; 130.7; 128.9; 128.6; 127.3; 126.2; 75.0; 50.8; 41.9; 26.0; 18.3; 16.9; 7.8; −4.1 (2C). IR (film, cm$^{-1}$) 3024; 2956; 2930; 2884; 2857; 1725; 1491; 1462; 1447; 1253; 1104; 1028; 990; 837; 775; 747; 691; 672. $[\alpha]_D^{20}$ +135 ($c$ 1.1, $CHCl_3$).

### 5.1.19. (1S,2R,3S,3aS,4R,5S,7aS)- and (1S,2R,3S,3aS,4R,5R,7aR)-2-(tert-Butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (**44** and **43**)

To a solution of the aldehyde (**5R**)-**32** (0.243 g, 0.678 mmol) in $CH_2Cl_2$ (5 mL) at room temperature was added the ylide **25** (1.23 g, 3.39 mmol) carefully with stirring and the resulting yellow solution heated under reflux for 60 h. The solvent was removed in vacuo and the product triturated with mixed hexanes. The residue was a mixture of two cycloadducts **44** and **43**, separable by column chromatography (50% $CH_2Cl_2$/mixed hexanes, $R_f$ (**44**)=0.5, $R_f$ (**43**)=0.36) yielding 0.187 g (65%) of adduct **44** and 0.049 g (17%) of adduct **43** (overall yield 82%).

Compound **44**: $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 7.24−7.07 (5H, m, Ar$H$); 5.80 (2H, ABq, $J$=11.4 Hz, PhCHC$H$=C$H$); 4.12 (1H, m, PhC$H$); 3.89 (2H, q, $J$=7.2 Hz, CO$_2$C$H_2$CH$_3$); 3.12 (1H, dd, $J$=9.0, 7.8 Hz, C$H$(OTBS)); 2.56 (1H, dd, $J$=10.2, 6.6 Hz, EtO$_2$CC(CH$_3$)C$H$CH(CH$_3$)); 2.05 (1H, apt br sex, $J$=6.6 Hz, Et$_2$OC(CH$_3$)CHC$H$(CH$_3$)); 1.95 (1H, m, CH=CHC$H$); 1.76 (1H, ddq, $J$=12.6, 9.0, 6.6 Hz, CH=CHCHC$H$(CH$_3$)); 1.19 (3H, s, Et$_2$OCC(C$H_3$)); 1.13 (3H, d, $J$=6.6 Hz, CH=CHCHCH(C$H_3$)); 1.03 (3H, d, $J$=6.6 Hz, Et$_2$OC(CH$_3$)CHCH(C$H_3$)); 0.99 (9H, s, SiC(C$H_3$)$_3$); 0.87 (3H, t, $J$=7.2 Hz, CO$_2$CH$_2$C$H_3$); 0.11 (3H, s, Si(C$H_3$)$_A$(CH$_3$)$_B$); 0.09 (3H, s, Si(CH$_3$)$_A$(C$H_3$)$_B$). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 176.4; 142.4; 129.0; 128.4; 130.0; 128.3; 127.0; 88.2; 60.4; 50.1; 50.5; 49.2; 45.8; 42.8; 42.3; 26.2; 20.0; 18.3; 16.4; 13.5; 14.2; −3.5; −3.6. IR (film, cm$^{-1}$) 2956; 2929; 2856; 1717; 1463; 1386; 1255; 1111; 892; 835; 774; 752; 704. $[\alpha]_D^{20}$ −6.0 ($c$ 0.8, $CHCl_3$).

Compound **43**: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.25−7.11 (5H, m, Ar$H$); 5.91 (1H, dt, $J$=10.2, 1.8 Hz, PhCHCH=C$H$); 5.59 (1H, ddd, $J$=9.6, 4.2, 3.0 Hz, PhCHC$H$=CH); 3.57 (1H, dq, $J$=10.8, 7.2 Hz, CO$_2$C$H_A$H$_B$); 3.35 (1H, dd, $J$=6.6, 1.8 Hz, C$H$(OTBS)); 3.29 (1H, m, PhC$H$); 3.23 (1H, dq,

$J$=10.8, 7.2 Hz, $CO_2CH_AH_B$); 2.53 (1H, ddddd, $J$=10.8, 7.8, 4.8, 3.0, 1.8 Hz, CH=CHC*H*CH($CH_3$)); 2.04 (1H, dqd, 7.8, 7.8, 1.8 Hz, CH=CHCHC*H*($CH_3$)); 2.02 (1H, apt t, $J$=12.0 Hz, $Et_2OCC(CH_3)CH$); 1.57 (1H, ddq, $J$=13.2, 6.6, 6.6 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 1.36 (3H, s, $Et_2OCC(CH_3)$); 1.07 (3H, d, $J$=7.8 Hz, CH=CHCHCH($CH_3$)); 0.89 (9H, s, $SiC(CH_3)_3$); 0.79 (3H, d, $J$=6.6 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 0.69 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$); 0.07 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.05 (3H, s, $Si(CH_3)_A(CH_3)_B$). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 175.2; 141.9; 129.5; 128.5; 127.7; 127.5; 126.7; 89.1; 59.7; 53.6; 49.0; 45.1; 41.3; 41.2; 41.1; 25.9; 18.0; 17.6; 16.9; 16.0; 13.2; −4.2; −4.5. IR (film, $cm^{-1}$) 2956; 2928; 2856; 1721; 1456; 1377; 1258; 1204; 1105; 1074; 866; 836; 774; 700. $[\alpha]_D^{20}$ +143 ($c$ 0.4, $CHCl_3$).

### *5.1.20. (1S,2S,3S,3aS,4R,5R,7aR)-2-Hydroxy-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (**45**)*

To a solution of the TBS ether **36** (47 mg, 0.106 mmol) in $CH_3CN/CH_2Cl_2$ (1:1, 2 mL) in a Teflon® screw cap jar was added aqueous HF (40%, 200 μL) at room temperature. The resulting solution was stirred at room temperature and the reaction monitored by TLC. Successive additions of aqueous HF (200 μL) was performed over 3 h until the starting material was consumed. The reaction was quenched by the addition of $H_2O$ (30 mL) and the product was extracted with EtOAc (3×20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (10% $Et_2O/CH_2Cl_2$, $R_f$=0.25) yielding 29 mg (84%) of alcohol **45** as a clear colourless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.25−7.23 (2H, m, Ar*H*); 7.21−7.18 (1H, m, Ar*H*); 7.13−7.12 (2H, m, Ar*H*); 5.99 (1H, ddd, $J$=9.6, 1.8, 1.8 Hz, PhCHCH=C*H*); 5.59 (1H, ddd, $J$=9.6, 3.6, 2.4 Hz, PhCHC*H*=CH); 3.80 (1H, dd, $J$=7.8, 5.4 Hz, C*H*(OH)); 3.57 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.34 (1H, apt qn, $J$=2.4 Hz, C*H*(Ph)); 3.22 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2CH_AH_B$); 1.91 (1H, dq, $J$=11.4, 1.8 Hz, CH=CHC*H*); 1.86 (1H, apt t, $J$=11.4 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 1.82−1.75 (1H, m $CH(CH_3)CHCH$=CH); 1.60−1.54 (2H, m, OH, CCHC*H*($CH_3$)); 1.36 (3H, s, $CH_3C$); 1.13 (3H, d, $J$=7.2 Hz, CH($CH_3$)CHCH=CH); 0.92 (3H, d, $J$=7.2 Hz, CCHCH($CH_3$)); 0.69 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 175.1; 141.8; 129.5; 128.3; 127.7; 127.5; 126.8; 82.0; 59.7; 54.2; 49.1; 45.8; 44.8; 44.7; 39.9; 17.9; 17.6; 13.2; 11.7. IR (film, $cm^{-1}$) 3450; 3020; 2961; 2930; 2905; 2875; 1720; 1453; 1381; 1268; 1242; 1167; 1088; 1029; 760; 701. $[\alpha]_D^{20}$ +120 ($c$ 0.3, $CHCl_3$).

### *5.1.21. (1S,3S,3aR,4R,5R,7aR)-1,3,4-Trimethyl-2-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (**46**)*

To a solution of DMSO (0.27 mmol, 21 mg, 19 μL) in $CH_2Cl_2$ (700 μL) at −78 °C was added a solution of oxalyl chloride in $CH_2Cl_2$ (2 M, 0.13 mol, 66 μL), dropwise. The solution was stirred at −78 °C for 30 min before the addition of alcohol **45** (29 mg, 0.088 mmol) in $CH_2Cl_2$ via a cannula (200 μL, 200 μL, 100 μL). The resulting mixture was stirred at −78 °C for 45 min before the addition of $NEt_3$ (0.53 mmol, 54 mg, 74 μL) over several minutes. The mixture was stirred at −78 °C for 30 min before warming to 0 °C and the stirring continued for 30 min. The reaction was quenched by the addition of $NH_4Cl$ (satd aq, 15 mL) and the product extracted with $CH_2Cl_2$ (3×15 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (100% $CH_2Cl_2$, $R_f$=0.42) yielding 29 mg (98%) of ketone **46** as a clear colourless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.28−7.21 (3H, m, Ar*H*); 7.15 (2H, d, $J$=7.2 Hz, Ar*H*); 6.11 (1H, d, $J$=9.6 Hz, CH(Ph)-CH=C*H*); 5.72 (1H, dt, $J$=9.6, 3.6 Hz, CH(Ph)C*H*=CH); 3.58 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2CH_AH_BCH_3$); 3.43 (1H, m, C*H*(Ph)); 3.23 (1H, dq, $J$=10.8, 7.2 Hz, $CO_2CH_AH_BCH_3$); 2.22 (1H, apt t, $J$=11.4 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 2.04 (1H, apt qn, $J$=7.2 Hz, $CH(CH_3)CHCH$=CH); 2.00−1.92 (2H, m, CCHC*H*($CH_3$), CH=CHC*H*); 1.41 (3H, s, $C(CH_3)(CO_2Et)$); 1.25 (3H, d, $J$=7.2 Hz, $CH(CH_3)$-CHCH=CH); 0.93 (3H, d, $J$=7.2 Hz, CCHCH($CH_3$)); 0.69 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 219.8; 174.4; 141.0; 129.5; 129.0; 127.9; 127.1; 125.9; 60.1; 53.6; 48.9; 47.7; 46.3; 44.9; 43.0; 17.7; 13.5; 13.1; 12.5. IR (film, $cm^{-1}$) 3026; 2961; 2929; 2874; 1721; 1453; 1379; 1266; 1241; 1157; 701; 672. $[\alpha]_D^{20}$ +191 ($c$, 0.2 $CHCl_3$).

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## Supplementary data

Experimental procedures and data for compounds **47**−**54**, **56** and **57**, Tables of NMR data for compounds **33**, **36**, **37**, **45**−**48** and **50**−**56** and $^1$H and $^{13}$C NMR spectra for compounds **33**, **36**, **37**, **43**−**48** and **53**, **54**, **56** and **57** are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.109.

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