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Vitamin D_3 Synthetic Studies. Intramolecular Diels–Alder Approaches to the CD-Ring Fragment

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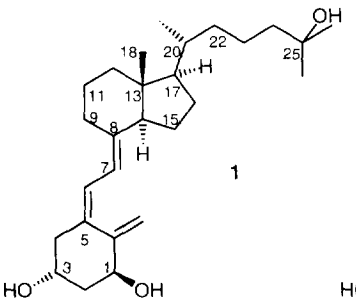
Abstract: The enantiospecific synthesis of the vitamin D_3 CD ring fragment **3** is reported. Key steps are the diastereoselective allylation of a norephedrine/dihydrocitronellic acid-derived oxazolidinone, and the intramolecular Diels–Alder reaction of a sulfonyl-substituted dienyne. The analogous cycloaddition reaction of a trienylsulfone substrate is shown to give products having the incorrect stereochemistry for vitamin D_3 synthesis.

INTRODUCTION

The importance of the vitamin D family of steroidal molecules as regulators of calcium and phosphorus metabolism has long been recognised. The more recent discovery that 1α,25-dihydroxy-vitamin D_3 **1** and analogues exhibit significant therapeutic utility and potential in a wide range of human diseases has stimulated a renaissance in studies of its chemical synthesis, biochemistry, and biological and medicinal characteristics.[1] We have begun a programme directed towards the development of total synthetic approaches and methods for the assembly of vitamin D_3 **2** and structural analogues thereof, including oxygenated congeners such as **1**. Such strategies are uniquely equipped to deliver analogues of **1** and **2** having extremely subtle structural variations, which are considerably less easily accessible using semi-synthetic or degradative routes. We communicated recently an enantiospecific synthesis of the key bicyclic sulfone **3** corresponding to the CD ring fragment of **1**,[2] and an improved degradative procedure which enables ready preparation of **3** from natural vitamin D_3.[3] We now describe in full the results of these studies.



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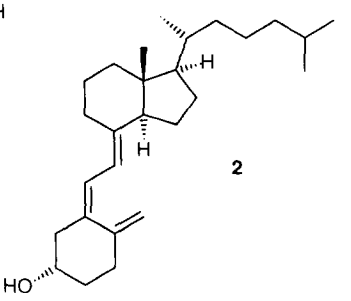

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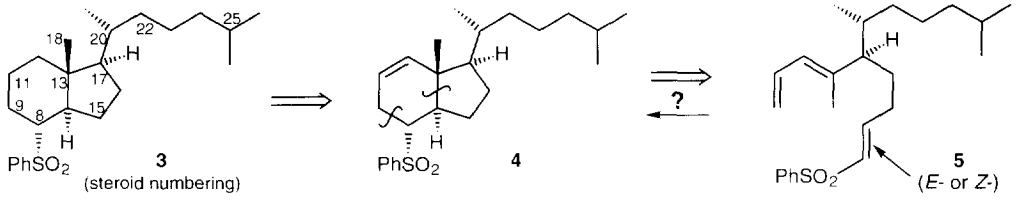
RESULTS AND DISCUSSION

Retrosynthetic analysis and synthetic strategy

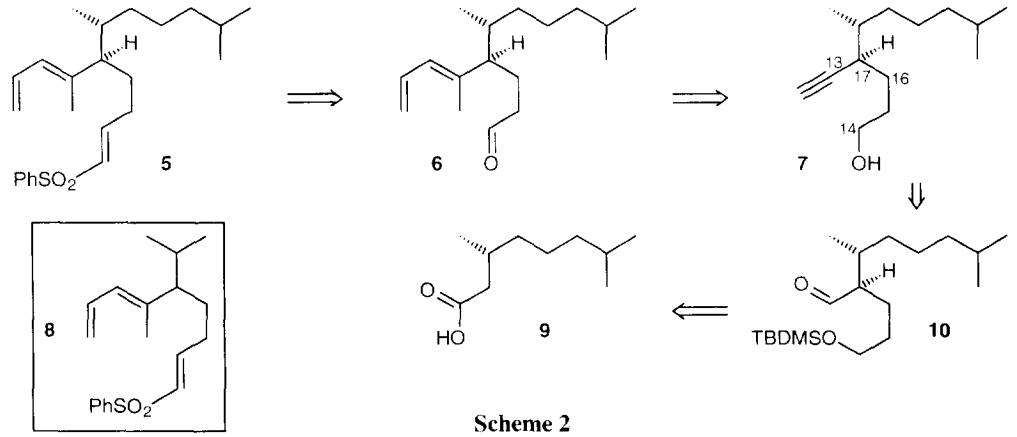
Sulfones such as **3** are established as viable intermediates in vitamin D_3 synthetic strategies involving coupling of a pre-fabricated bicyclic CD ring fragment which is nucleophilic at C-8 with an A-ring segment possessing a C-7 electrophile.[4] In light of our studies on the intramolecular Diels–Alder (IMDA) reactions of trienes substituted with sulfone[5] and sulfoximine[6] groups, we reasoned that **3** might be accessible via hydrogenation of the putative product **4** of IMDA reaction of triene **5** (Scheme 1). IMDA Reactions have previously been employed for the synthesis of vitamin D_3 CD ring fragments,[7] but these approaches invariably involved the concerted formation of the C11–C12 and C13–C14 and not the C8–C9 and C13–C14 bonds as



Scheme 1

was the case in our planned route. The IMDA reaction-based strategy we envisaged was especially attractive in that it was anticipated that the 1,1-disubstituted 1,3-diene unit in **5** would inherently be an unreactive cycloaddition component on account of its expected preferred transoid conformation; as such triene **5** would provide a stringent test of our previously developed IMDA methodology.

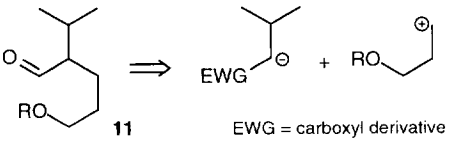
It was decided to pursue a strategy for the synthesis of **5** which would enable access also to the *Z*- isomer and related substrates from a common late-stage intermediate. Whilst the synthesis of dienophile *E*-isomers had been considerably more straightforward in our earlier work,[5] the *Z*-substrates had shown greater selectivity for trans-fused bicyclo[4.3.0] products. These studies indicated aldehyde **6** as the key precursor of triene **5**. The diene unit would be assembled from alkyne **7** by successive transition-metal-mediated transformations. The key precursor **10** would be constructed from (+)-[*R*]-dihydrocitronellic acid **9** via a route involving asymmetric alkylation as the key C16–C17 bond-forming step (Scheme 2).



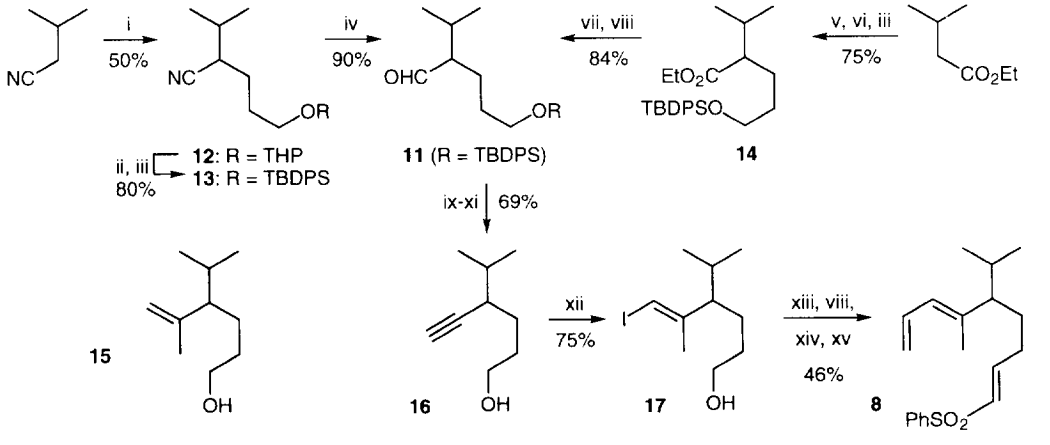
Scheme 2

As a preliminary study, it was decided to synthesise a model substrate **8**, and to subject it to IMDA reaction conditions. It was felt that this sequence of operations would provide valuable tactical insights for the construction of **5**, and crucial information concerning the IMDA reactivity and selectivity of this previously unreported triene system.

Synthesis and IMDA reaction of model triene 8



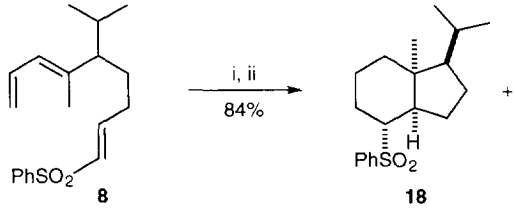
Application to the model triene **8** of the retrosynthetic analysis presented in Scheme 2 indicated protected hydroxyaldehyde **11** as a key precursor. This would be available by α-alkylation of 3-methylbutanoic acid or a derivative with a three-carbon electrophilic reagent possessing a masked 3-hydroxyl group. Two approaches were pursued in this context. In the first of these, alkylation of the lithio-anion of isovaleronitrile with THP-protected 3-iodo-1-propanol in THF–DMPU gave in moderate yield the α-substituted intermediate **12**. Reduction using DIBAL-H gave the corresponding aldehyde **11** (R = THP). Attempted one-carbon homologation of **11** using carbon tetrabromide–triphenylphosphine[8] or iodomethylenetriphenylphosphorane[9] was inefficient, apparently because of the instability of the aldehyde. Therefore, nitrile **12** was deprotected, and reprotected with the *tert*-butyldiphenylsilyl group to give **13**.[10] Reduction of **13** gave a stable aldehyde **11** (R = *t*-BuSiPh$_2$). The second route to **11** (R = *t*-BuSiPh$_2$) started from ethyl isovalerate, and was carried out as a more representative model of the sequence planned for the construction of **5**. Allylation of the lithium enolate of ethyl isovalerate, followed by hydroboration–oxidation and protection gave the silyloxyester **14**. Reduction and re-oxidation using DMSO activated with oxalyl chloride[11] gave the target aldehyde. Exposure of **11** (R = *t*-BuSiPh$_2$) to iodomethylenetriphenylphoshorane in THF at low temperature[9] gave exclusively the *Z*-iodoalkene, which was subjected to elimination[12] followed by fluoride-mediated deprotection to give alkynol **16**. Construction of the 1,3-diene group was accomplished using sequential zirconium(IV)- and palladium(0)-mediated transformations. Thus, syn-specific iodomethylation[13] of **16** gave the *E*-iodoalkene **17** contaminated with the non-iodinated olefin **15** as an inseparable ca. 10:1 mixture.[14] Exposure of this mixture to vinylmagnesium bromide in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0)[15] gave the expected dienol together with unreacted **15**. Oxidation gave the corresponding aldehyde; this was coupled with lithio(phenylsulfonyl)-methane and the adduct dehydrated as described previously[5] to give **8** as a 97:3 *E*:*Z* mixture of dienophile olefin isomers. The syntheses of **8** from isovaleronitrile and ethyl isovalerate are summarised in Scheme 3.



Reagents and conditions: (i) Add isovaleronitrile to LDA–THF, -78°C, add I(CH$_2$)$_3$OTHP, -78°C→rt; (ii) cat. CSA, MeOH, rt; (iii) TBDPSCl, cat. DMAP, Et$_3$N, CH$_2$Cl$_2$, rt; (iv) DIBAL-H, PhMe, -78°C; (v) add ethyl isovalerate to LDA–THF, -78°C, add BrCH$_2$CH=CH$_2$; (vi) 9-BBN, THF, rt; NaOH–H$_2$O$_2$; (vii) LiAlH$_4$, Et$_2$O, rt; (viii) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, -60°C; (ix) add **11** (R = TBDPS) to ICH$_2$PPh$_3$$^+I^-$, NaHMDS, THF, -78°C; (x) *t*-BuOK, THF, -78°C; (xi) *n*-Bu$_4$NF, THF, rt; (xii) Cp$_2$ZrCl$_2$, Me$_3$Al, Cl(CH$_2$)$_2$Cl, -40°C; I$_2$, THF; (xiii) cat. Pd(PPh$_3$)$_4$, PhMe, CH$_2$=CHMgBr, THF, 0°C; (xiv) PhSO$_2$CH$_2$Li, THF, -78°C; AcOH quench; (xv) MsCl, Et$_3$N, CH$_2$Cl$_2$, -6°C.

Scheme 3

As expected, triene **8** was a relatively unreactive substrate. Heating of a rigorously dried, degassed toluene solution in a Carius tube at 240°C for 48 hours gave in 89% yield after chromatography a 1:1 mixture of two major cycloadducts, together with a small amount (<5%) of a third, minor component. The minor isomer could be separated by HPLC. All attempts to separate the mixture of major isomers by HPLC or fractional crystallisation met with failure. In spite of the somewhat inconclusive nature of the IMDA reaction of **8** it was decided at this stage to proceed with the synthesis of the enantiomerically pure triene **5**, and to assess its IMDA reaction. The route developed for diene assembly was efficient and high-yielding, and since the desired sulfone **3** was a known compound[4(ii)] it was felt that comparison of its nmr characteristics with those of the hydrogenated cycloadducts of **5** would allow unequivocal structural assignment of the latter. Also, the route used for the preparation of **5** was flexible: because the dienophile was introduced at a late stage in the synthetic sequence a variety of related IMDA substrates could in principle be accessed. These investigations are described in detail below. Subsequent to these studies, we undertook a reinvestigation of the IMDA reaction of model triene **8**. Hydrogenation of the mixture followed by separation by HPLC gave pure samples of two bicyclic sulfones in excellent yield. X-Ray crystallographic analysis of one of these showed it to be **18**, having the 1*R**,2*R**,6*S**,7*R** configuration (Figure 1). The second hydrogenated isomer resisted all attempts to generate a crystal suitable for X-ray diffraction studies. However, nOe studies strongly suggested the structure **19**: in particular, enhancement of the ring junction proton was observed on irradiation of the quaternary methyl group. The IMDA reaction of **8** and the subsequent derivatisation reaction are depicted in Scheme 4.



8 **18** **19**

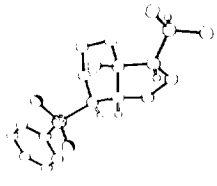


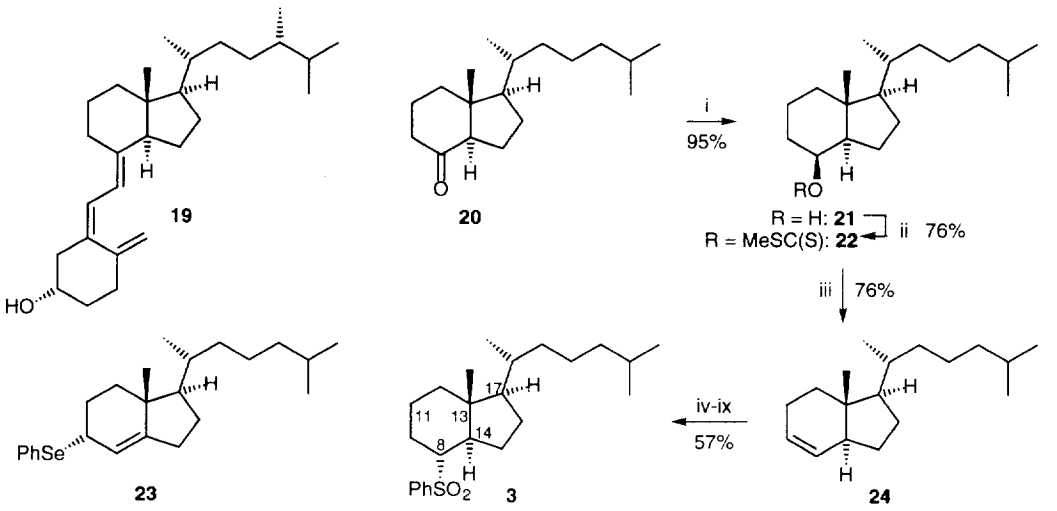
Figure 1
X-ray structure of **18**

Reagents and conditions: (i) PhMe, 240°C, 48 h; HPLC; (ii) H_2, 10% Pd(C), EtOAc; HPLC.

Scheme 4

Synthesis of CD ring fragment 3

Degradative synthesis of 3 from vitamin D_3. In order to obtain reliable, high-field ^1H nmr data for **3** it was decided to prepare an authentic sample from commercially available vitamin D_3 via Windaus–Grundmann ketone **20**.[16] This was carried out initially using a modification of the degradative sequence from vitamin D_4 **19** reported[4(i)] by Lythgoe and Kocienski. Thus, reduction of **20** mediated by DIBAL-H gave exclusively the axial secondary alcohol **21**. In the original route[4(i)] regiospecific elimination of the elements of water from the analogous alcohol had been carried out by thermolysis at 370°C of the derived benzoate, giving the $\Delta_{8,9}$ alkene (steroid numbering). In an effort to define milder conditions for this key step, we looked at the related Chugaev reaction[17] of the xanthate ester **22** derived from **21**. Formation of the ester was effected by treatment of **21** with *n*-butyllithium in THF followed by sequential exposure to carbon disulfide and iodomethane; the presence of DMPU as co-solvent was essential to obtain good yields of **22**. Syn-elimination of **22** was carried out by brief thermolysis at 220°C in the absence of solvent. Attempted trans-diaxial addition of $PhSeSO_2Ph$[18] across the $\Delta_{8,9}$ linkage with a view to effecting oxidation–syn-elimination to give the allylic sulfone precursor of **3** directly gave instead the allylic selenide **23** in low yield. Therefore, α-selective epoxidation as before,[4(i)] followed by trans-diaxial ring-opening with thiophenoxide, benzoylation, oxidation and base-mediated elimination gave the required precursor in good overall yield from **22**. Finally, hydrogenation provided the target bicyclic sulfone **3** (Scheme 5). Compound **3** prepared in this way had ^1H and ^{13}C nmr and melting point properties in agreement with those reported.[4(ii)] The triplet of doublets at 3.03 ppm corresponding to H-8, and

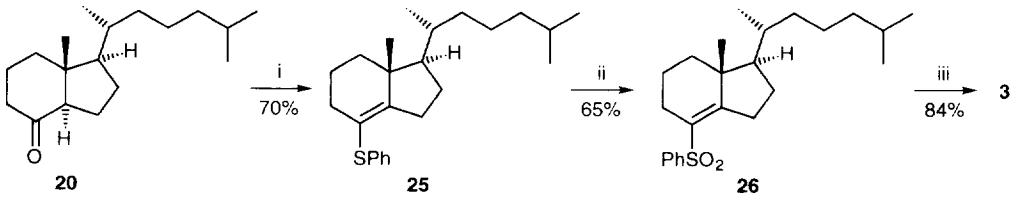


Reagents and conditions: (i) DIBAL-H, PhMe, -78°C; (ii) *n*-BuLi, CS_2, MeI, THF–DMPU, 0°C; (iii) 220°C, 6 min; (iv) *m*-CPBA, CH_2Cl_2, 0°C; (v) PhSNa, EtOH, reflux; (vi) PhCOCl, cat. DMAP, py, rt; (vii) CH_3CO_3H, NaOAc, CH_2Cl_2, 0°C; (viii) *t*-BuOK, *t*-BuOH, THF, rt; (ix) H_2, Pd(C), EtOAc, rt.

Scheme 5

the angular C13 methyl singlet at 0.69 ppm were distinctive resonances. While low, the measured specific rotation of **3** was substantially greater than that quoted by the same authors.

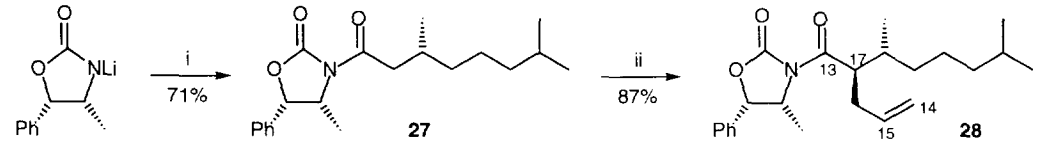
In view of the rather lengthy nature of the route to **3** described above (nine steps from **20**), we sought a shorter sequence which would be amenable to the generation of quantities of material suitable for model CD-ring–A-ring coupling studies. A three-step route from **20** was developed in which the key transformations were Lewis acid-catalysed enol thioetherification[19] to give vinylsulfide **25**, followed by α-face selective reduction of the derived sulfone **26** (Scheme 6). These studies have been described in detail elsewhere.[3]



Reagents and conditions: (i) PhSH, $BF_3{\cdot}OH_2$, CH_2Cl_2, 0°C; (ii) CH_3CO_3H, NaOAc, CH_2Cl_2, 0°C; (iii) $LiAlH_4$, THF, reflux, 20 min; *t*-BuOK, *t*-BuOH, THF, rt (on minor C8 epimer).

Scheme 6

Synthesis and IMDA reaction of triene 5. With the method for diene and dienophile assembly established in the model system as outlined in Scheme 2, the synthesis of the enantiomerically pure triene **5** centred on the formation of the C16–C17 bond with incorporation of the masked 3-hydroxypropyl fragment in such a way as to guarantee the *R*-configuration at C17 (steroid numbering). We selected the Evans oxazolidone approach[20] as being the most reliable and practicable. The correct *R*-configuration at C20 was present in the (+)-[*R*]-dihydrocitronellic acid starting material **9**, which was readily synthesised on a one-mole scale from (+)-[*R*]-pulegone using a literature procedure.[21] Acylation using [*R*]-dihydrocitronellyl chloride of the lithio-anion of the commercially available[22] oxazolidone derived from (+)-norephedrine gave the crystalline alkylation substrate**27**. Allylation was carried out by the addition of allyl bromide to a THF solution of sodio-**27** under carefully controlled conditions, giving the oily product **28** in high yield and with ca. 19:1 selectivity for the re-

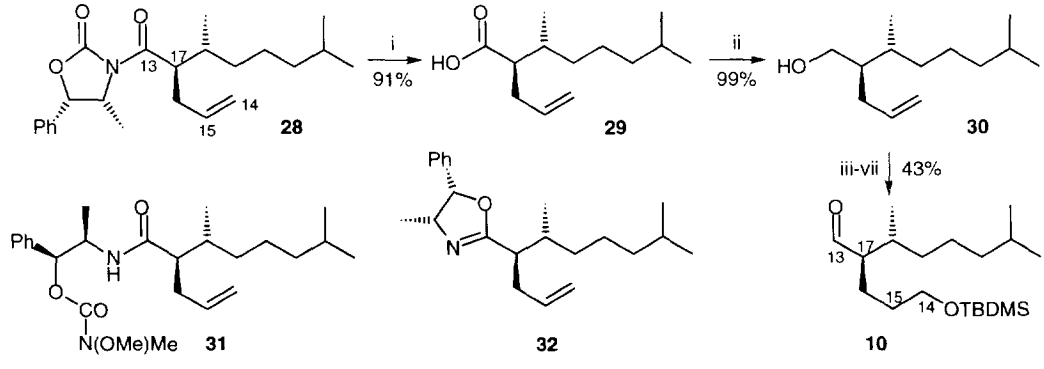


Reagents and conditions: (i) Add [*R*]-dihydrocitronellyl chloride, THF, -78°C→rt; (ii) NaHMDS, THF, -78°C; add $BrCH_2CH{=}CH_2$, -78°C→-50°C, 5 h; -50°C, 12 h.

Scheme 7

quired *R*-configuration at the newly-formed stereocentre (Scheme 7). Allylation of the lithium enolate of **27** gave material of similar diastereomeric excess, but in much lower yield. Disappointingly, 1-(*tert*-butyldiphenylsilyloxy)-3-iodopropane was insufficiently reactive with respect to the sodium enolate of **27** for more direct introduction of the C14-C16 fragment to be realised.

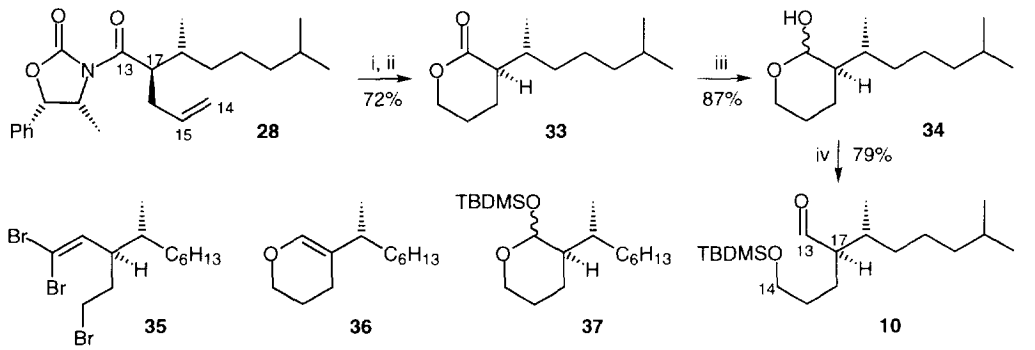
With the allylated compound **28** in hand, it was necessary (i) to remove the oxazolidone auxiliary group, (ii) to adjust the oxidation level at C13 in readiness for conversion to the alkyne-containing diene precursor, and (iii) to transform the terminal olefinic linkage into the oxygen functionality required ultimately for elaboration of the dienophilic unit. Two conceptually different sequences were developed for the synthesis of the key intermediate **10**. The first of these involved auxiliary removal prior to hydration of the C14-C15 bond. In practice however, compound **28** proved to be inert to many of the auxiliary-cleaving reactions developed for this class of substrates. For example, attempts to effect steps (i) and (ii) above in a single operation by direct reductive cleavage[23] using $LiAlH_4$ gave low yields of the alcohol **30**. Transesterification of **28** with lithium benzyloxide[23] was low-yielding; the use of the more reactive sodium salt in this reaction resulted in up to 20% epimerisation at the α-stereocentre. Attempted conversion of **28** into the corresponding *N*-methoxy-*N*-methylamide[24] gave the amidocarbamate **31** when three equivalents of $Me_2AlN(OMe)Me$ were used; with two equivalents of the reagent 75% of **28** was recovered, along with 12% of the oxazoline **32** arising by cleavage of the carbamoyl instead of the amide linkage. The latter findings were in accord with those of Evans, who has noted[25] that in sterically demanding cases nucleophilic attack can occur preferentially at the 'endocyclic' oxazolidone carbonyl carbon atom. In the course of this work Evans found that lithium hydroperoxide was in many cases highly effective for the removal of oxazolidone auxiliary groups from hindered substrates. Treatment of **28** with this reagent duly gave the desired carboxylic acid **29** in excellent yield, with 89% recovery of the chiral auxiliary. Reduction to the alcohol **30** followed by benzyl protection, regioselective hydroboration with oxidative work-up, C14-OH protection, deprotection of the C13 benzyl ether and oxidation gave the aldehyde **10**. The seven-step sequence from **28** is summarised in Scheme 8.



Reagents and conditions: (i) LiOH, H_2O_2, THF–H_2O, 10°C; (ii) $LiAlH_4$, Et_2O, 0°C; (iii) NaH, BnBr, DMF, rt; (iv) $BH_3{\cdot}SMe_2$, hexane, 0°C→rt; H_2O_2, NaOH, EtOH, 0°C; (v) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt; (vi) Na, liq NH_3; (vii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60°C.

Scheme 8

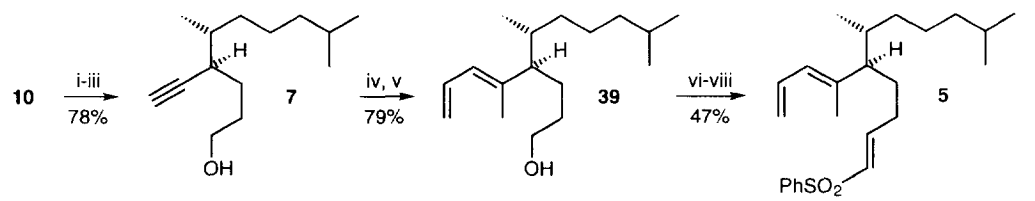
We were keen to shorten the sequence from **28** to **10** presented in Scheme 8. In particular, we wanted to identify a method for the direct reduction of C13 to the aldehyde oxidation level; this would save three steps by avoiding the need for both the C13 alcohol protection–deprotection reactions and the final re-oxidation to the aldehyde. In this second approach it was considered essential to convert the C14-C15 olefin to the primary alcohol *prior to* cleavage of the chiral auxiliary. Thus, hydroboration of **28** using 9-BBN followed by oxidative work-up under carefully controlled conditions gave the expected C14 alcohol together with the lactone **33**; the crude product was converted into pure **33** by brief treatment with potassium *tert*-butoxide. In agreement with published observations,[26] care had to be exercised in the lactonisation step because of the epimerisation at C17 which occurred readily at elevated pH. Reduction of **33** using DIBAL-H gave lactols **34**. Since **34** is the cyclic tautomer of unprotected **10**, we investigated methods for the direct introduction of the haloalkene functionality required for conversion to the alkyne. Attempted iodomethylenation[9] of **34** gave no identifiable products, while application of the Corey–Fuchs dibromomethylenation procedure[8] gave tribromide **35** in moderate yield. Attempted silyl protection of the open-chain form of **34** using TBDMSCl[27] gave in low yield the dihydropyran **36**. In contrast, treatment of **34** with TBDMSOTf gave **10** in high yield, together with a small amount of the lactol ether **37**. This shortened route proceeded in 49.5% overall yield from **28**, and is depicted in Scheme 9.



Reagents and conditions: (i) 9-BBN, THF, rt; H_2O_2, NaOH, 10°C; (ii) cat. *t*-BuOK, *t*-BuOH, THF, 0°C; (iii) DIBAL-H, PhMe, -78°C; (iv) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C.

Scheme 9

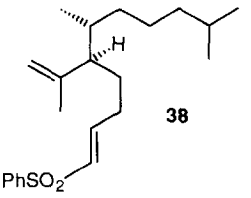
The stage was now set for final elaboration of **10** to the triene **5**. This followed exactly the sequence established for the conversion of **11** to the model substrate **8**. Thus, Wittig reaction of **10** with iodomethylenetriphenylphosphorane followed by base-mediated elimination and deprotection gave the alkynol **7**. This was subjected to syn-iodomethylation and palladium(0)-mediated coupling with vinylmagnesium bromide

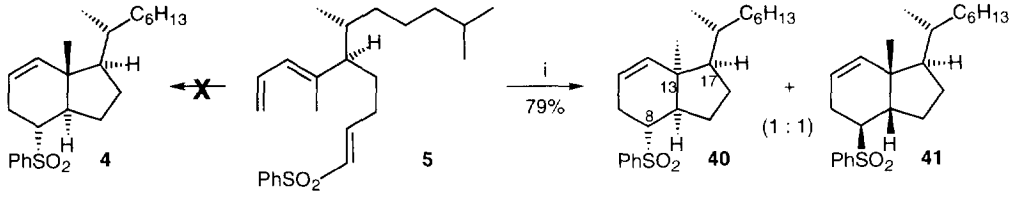


Reagents and conditions: (i) Add **10** to $ICH_2PPh_3^+I^-$, NaHMDS, THF, -78°C; (ii) *t*-BuOK, THF, -78°C; (iii) *n*-Bu_4NF, THF, rt; (iv) Cp_2ZrCl_2, Me_3Al, THF, rt; add **7**, $Cl(CH_2)_2Cl$, 0°C; add I_2, THF, -30°C; (v) cat. $Pd(PPh_3)_4$, CH_2=CHMgBr, PhMe, rt; (vi) $(COCl)_2$ DMSO, Et_3N, CH_2Cl_2, -60°C; (vii) $PhSO_2CH_2Li$, THF, -78°C, AcOH quench; (viii) MsCl, Et_3N, CH_2Cl_2, -6°C.

Scheme 10

as before to give the dienol **39**. Oxidation to the aldehyde **6**, followed by addition of lithio(phenylsulfonyl)methane and mesylation with in situ elimination gave triene **5** contaminated with ca. 25% of the diene **38** arising from protolysis during the iodomethylation step as previously observed. The dienophile double bond was again formed as a 97:3 isomeric mixture. The completion of the synthesis of **5** from **10** is presented in Scheme 10. Thermolysis of the 3:1 mixture of triene **5** and diene **38** at 240°C for 48 hours followed by silica gel chromatography gave in 79% yield (based on **5** present in the reactant) a 1:1 mixture of two products. Separation by reversed-phase HPLC gave milligram quantities of isomerically pure cycloadducts. One of these had a signal for H-8 which resembled closely the corresponding resonance in the crystalline model compound **18**. This strongly suggested that **40** was one of the products (Scheme 11). Hydrogenation of the other component proceeded in excellent yield to give a saturated product. However, comparison of its high-field (500 MHz) ^{1}H nmr spectrum with that of authentic **3** revealed two significant differences. Firstly, the H-8 signal appeared at 2.95 instead of 3.03 ppm, and possessed additional fine structure superimposed on the basic triplet of doublets. Secondly, the three-proton singlet assigned to the angular C13 methyl group appeared at 0.89 ppm, some 0.2 ppm downfield from the same signal in the spectrum of **3**. These observations proved conclusively that compound **4** was not formed in the IMDA reaction of **5**. We defer unequivocal comment on the identity of the second cycloadduct, but the nOe studies of the hydrogenated products of IMDA reaction of the model triene **8** (see above) indicate **41** as the most likely option (Scheme 11). In light of our studies on IMDA reactions of sulfonyl-substituted trienes,[5] this complete cis-selectivity is highly unusual.

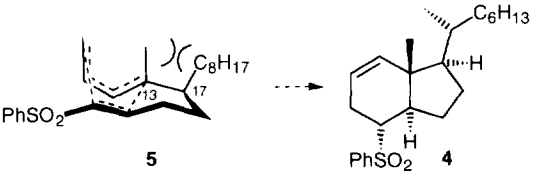




Reagents and conditions: (i) PhMe, 240°C, 48 h; HPLC.

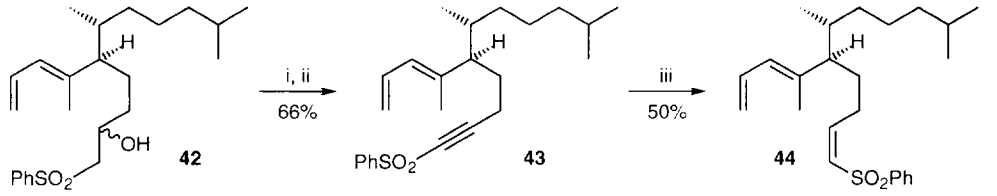
Scheme 11

The failure of IMDA reaction of **5** to deliver the cycloadduct **4** required for vitamin D_3 synthesis was completely unexpected. We speculate that formation of **4** is disfavoured by steric interactions between the incipient angular C13 methyl group and the bulky α-branched C17 side-chain (Scheme 12). Rotation through 180° about the C13–C17 bond would place sp^2-hybridised C12 in proximity with the C17 substituent, leading to the observed product **40**.



Scheme 12

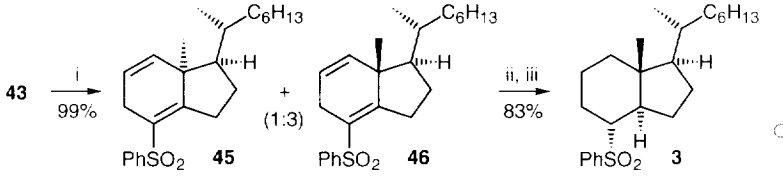
Synthesis and IMDA reactions of modified substrates. The unsuccessful IMDA reaction of triene **5** prompted a search for alternative substrates. In light of our observations of highly trans-selective IMDA reactions of sulfonyl-substituted trienes possessing *Z*-dienophilic groups,[5] we turned our attention first to the *Z*-analogue **44** of the original substrate **5**. Our earlier work had demonstrated that the preparation of such substrates was frequently problematic because of the lack of direct methods for the fabrication of the *Z*-vinylic sulfone dienophilic unit, and the difficulties often encountered in separating mixtures of geometric isomers. It was decided to attempt to synthesise **44** by partial hydrogenation of the corresponding alkyne **43**, which was accessible using our previously developed method.[28] Thus, PDC-mediated oxidation of the intermediate **42** formed previously by addition of lithio(phenylsulfonyl)methane to aldehyde **6** gave a β-ketosulfone which was



Reagents and conditions: (i) PDC, 4Å mol. sieves, CH_2Cl_2, rt; (ii) *i*-Pr_2NEt, Tl_2O, CH_2Cl_2, 0°C; (iii) H_2, Lindlar catalyst, EtOAc, rt.

Scheme 13

subjected to our standard alkynylsulfone-forming conditions. Partial hydrogenation of **43** formed in this way gave substrate **44** in moderate yield (Scheme 13). Triene **44** was heated in toluene solution at 180°C for 24 hours, at which point all of the starting material had been consumed. ^1H Nmr analysis of the crude product in the usual way indicated a complex mixture of components, with evidence of substantial decomposition. It occurred to us that the dienynylsulfone **43** itself might be a viable IMDA substrate: alkynylsulfones have been reported to show useful levels of reactivity and selectivity in these transformations.[29] To our delight, on heating in toluene solution at 115°C for 9 hours dienyne **43** underwent near-quantitative IMDA reaction to give a 3:1 mixture of cycloadducts **46** and **45** which were separated by normal-phase HPLC. Subjection of the **46** to partial hydrogenation gave in excellent yield the bicyclic vinylic sulfone **26**, identical in all respects to material prepared from Windaus–Grundmann ketone (Scheme 6). Finally, reduction with $LiAlH_4$ in hot THF followed by base-mediated epimerisation of the minor product as before delivered the target bicycle **3**, whose ^1H and ^{13}C nmr spectra and all other measured physical properties matched exactly those of the authentic sample prepared from vitamin D_3. The final elaboration of **43** to **3** is depicted in Scheme 14; the X-ray crystal structure of **3** is depicted in Figure 2.



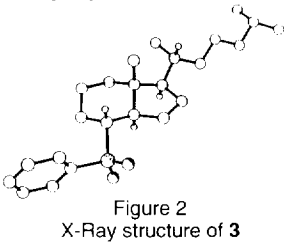


Figure 2
X-Ray structure of **3**

Reagents and conditions: (i) PhMe, 115°C, 9 h; HPLC; (ii) H_2, Pd(C), EtOAc; (iii) as for Scheme 6.

Scheme 14

CONCLUSIONS

The above results demonstrate conclusively that the IMDA reaction of alkynylsulfone-containing dienynes such as **43** is a powerful and efficient strategy for the construction of vitamin D_3 CD ring fragments. We are currently engaged in the synthesis of analogues of **43** possessing functionality suitable for the construction of side-chain analogues of vitamin D_3, and are actively exploring new methods for A-ring synthesis and coupling reactions. We are looking also at IMDA reactions of alkynylsulf*oximine*-substituted analogues of **43** with a view to improving the selectivity of the key cycloaddition step. The results of these studies will be reported in due course.

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EXPERIMENTAL

General procedures

^{1}H nmr spectra were recorded in $CDCl_3$ on either Bruker AM-500, Bruker DRX-300, Jeol GX-270Q or Bruker WM-250 spectrometers, using residual isotopic solvent ($CHCl_3$, δ_H 7.26 ppm; $PhCD_2H$, δ_H 2.03 ppm) as internal reference. Infrared spectra were recorded on Perkin-Elmer 881 or Mattson 5000 FTIR spectrophotometers. Mass spectra were obtained using Jeol SX-102, VG-7070B, VG 12-253, VG ZAB-E and VG Autospec Q instruments. Elemental combustion analyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Optical rotation measurements were carried out using an Optical Activity AA-100 polarimeter. Air- and moisture-sensitive reagents were transferred via syringe or cannula, and reactions involving these materials were carried out in oven-dried flasks under a positive pressure of argon or nitrogen. Liquid reagents were transferred via syringe. Chromatography refers to column chromatography on Merck Kieselgel 60 (230-400 mesh) or Matrex Silica 60 (35-70 micron) under pressure unless otherwise stated. Tlc refers to analytical thin-layer chromatography performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised with ultraviolet light, iodine and acidic ammonium molybdate(IV), vanillin or potassium permanganate solutions as appropriate. Petrol refers to redistilled 40°–60° petroleum ether, and ether to diethyl ether. Ether and tetrahydrofuran were distilled from sodium–benzophenone ketyl, dichloromethane from phosphorus pentoxide, and toluene from sodium. Other solvents and reagents were purified according to standard procedures.[30]

Preparation of (±)-2-(4-cyano-5-methylhexyloxy)tetrahydro-2*H*-pyran (12).

To a stirred solution of diisopropylamine (11.5 ml, 81.7 mmol, 1.1 eq) in THF (200 ml) under argon at -78°C was added *n*-BuLi (33 ml of a 2.5M solution in hexanes, 81.5 mmol, 1.1 eq). After 20 min, isovaleronitrile (8.6 ml, 81.7 mmol, 1.1 eq) was added dropwise via syringe. The anion solution was added via cannula at -78°C to a stirred solution of 2-(3-iodopropoxy)tetrahydro-2*H*-pyran (20 g, 74.3 mmol) in THF (200 ml) at -78°C over a period of 90 min. After a further 20 min at -78°C the reaction was allowed to warm to rt, by which time it had taken on a red colour. Water (300 ml) was added, discharging the colour and the organic phase was separated. The aqueous phase was extracted with ether (2 x 200 ml), the organic layers were combined and washed with water (3 x 200 ml), brine (200 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (10%→30% ether–petrol gradient, 5% increments) to give the *nitrile* **12** (8.43 g, 50%) as a colourless oil; υ_{max} (film) 2943, 2875, 2237, 1559, 1470, 1373, 1353, 1324, 1261, 1201, 1122, 1078, 1035, 991, 905, 869, 815 cm^{-1}; δ_H (270 MHz) 4.56 (1H, t, J 3.0 Hz, H-2), 3.90-3.70 (2H, m, H-1', H-6), 3.55-3.35 (2H, m, H-1, H-6'), 2.47 (1H, q, J 4.0 Hz, H-4), 1.95-1.60 (7H, m) and 1.60-1.45 (4H, m, all comprising H-2, H-3, H-5, H-3', H-4', H-5'), 1.05 (6H, d, J 7.0 Hz, H-6, H-5''); *m/z* (EI) 225 (M^+), 224 (M^+-H), 183, 142, 124, 85, 82 (Found: (M^+-H), 224.1653. $C_{13}H_{23}NO_2$ requires (M^+-H), 224.1657).

Preparation of (±)-1-(*tert*-butyldiphenylsilyloxy)-4-cyano-5-methylhexane (13).

(±)-2-(4-Cyano-5-methylhexyloxy)tetrahydro-2*H*-pyran **12** (7.053 g, 31.3 mmol) was dissolved in dry methanol (150 ml) with a catalytic amount of CSA and stirred at rt for 18 h, after which time tlc (40% ether–

petrol) showed complete deprotection of the alcohol. The solution was concentrated to 1/4 of the original volume, dissolved in ether (100 ml) and filtered through a pad of silica gel, rinsing with more ether (700 ml), to give, after removal of the solvents under reduced pressure, a near-colourless oil (4.81 g). This was used crude in the next, reprotection step. A small portion was purified by chromatography (20%→100% ether–petrol) to give *(±)-4-cyano-5-methylhexanol* as a colourless oil; υ_{max} (film) 3438 (br), 2960, 2235, 1464, 1389, 1373, 1349, 1262, 1233, 1176, 1135, 1062, 1002, 967, 931 cm^{-1}; δ_H (270 MHz) 3.75-3.60 (2H, m, H-1), 2.45 (1H, dt, J 7.0, 5.5 Hz, H-4), 1.85 (1H, m, H-5), 1.75-1.60 (4H, m, H-2, H-3), 1.06 (6H, d, 7.0 Hz, H-6, H-5'); *m/z* (EI) 140 (M^+-H), 126, (M^+-Me), 122 (M^+-H_2O), 111, 108 (M^+-H_2O-Me) 99, 96, 83, 81, 71, 69, 43 (Found: C, 68.15; H, 10.74; N, 9.89. $C_8H_{15}NO$ requires C, 68.05; H, 10.71; N, 9.92%). To a solution of the crude alcohol (4.81 g, ca. 31.3 mmol) in CH_2Cl_2 together with DMAP (38 mg, 0.31 mmol, 0.01 eq) under argon at 0°C was added triethylamine (5.3 ml, 37.6 mmol, 1.2 eq) followed by *tert*-butylchlorodiphenylsilane (9.8 ml, 37.6 mmol, 1.2 eq). The reaction was allowed to stir for 30 min, then warmed to rt and stirred for a further 4 h after which time more triethylamine (436 µl, 3.13 mmol, 0.1 eq) and *tert*-butyldiphenylchlorosilane (814 µl, 3.13 mmol, 0.1 eq) were added. The reaction was quenched after another hour by the addition of saturated aqueous sodium hydrogencarbonate (100 ml) and the aqueous phase extracted with CH_2Cl_2 (3 x 70 ml). The combined organic layers were washed with saturated aqueous ammonium chloride (3 x 100 ml), water (3 x 50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (2%→20% ether–petrol gradient elution; 5% increments) to give the *nitrile* **13** (9.44 g, 80% from **12**) as a colourless oil; υ_{max} (film) 3076, 2963, 2862, 2237, 1540, 1472, 1391, 1362, 1113, 998, 824 cm^{-1}; δ_H (270 MHz) 7.66 (4H, dd J 8.0, 2.0 Hz, ortho Ph), 7.45-7.35 (6H, m, meta and para Ph), 3.71 (2H, t, J 5.5 Hz, H-1), 2.42 (1H, m, H-4), 1.84 (1H, m, J 6.0 Hz, H-5), 1.75-1.60 (4H, m, H-2, H-3), 1.08 (9H, s, *t*-Bu), 1.05 (6H, d, J 7.0 Hz, H-6, H-5); *m/z* (EI) 379 (M^+), 322 (M^+-C_4H_9), 225, 199, 183, 148, 135, 105, 91, 77 (Found: (M^+-*t*-Bu), 322.1627. $C_{24}H_{33}NOSi$ requires (M^+-*t*-Bu), 322.1627).

Preparation of (±)-1-(*tert*-butyldiphenylsilyloxy)-5-methyl-4-(oxomethyl)hexane (11; R = TBDPS).

To a stirred solution of nitrile **13** (12.46 g, 32.8 mmol) in toluene (330 ml) under argon at -78°C was added DIBAL-H (66 ml of a 1.5 M solution in toluene, 98.5 mmol, 3 eq) dropwise via cannula. After 20 min the reaction was quenched by the addition of aqueous THF (59 ml of a 10% v/v solution, 328 mmol, 10 eq) (**CAUTION:** large volume of gas evolved). The reaction was allowed to stir while warming to rt. At ca. 0°C an exothermic reaction was observed and the mixture assumed a paste-like consistency. The mixture was poured onto solid sodium hydrogencarbonate and diluted with EtOAc (800 ml). After stirring vigorously for 30 min the now freely-flowing solid was removed by filtration through a pad of Celite® and the solution concentrated under reduced pressure. The residue was purified by chromatography (5%→10% ether–petrol) to give the *aldehyde* **11** (R = TBDPS) (11.24 g, 90%) as a colourless oil; υ_{max} (film) 3072, 2959, 2859, 1726, 1591, 1539, 1473, 1429, 1390, 1362, 1114, 999, 823, 742, 702 cm^{-1}; δ_H (250 MHz) 9.60 (1H, d, J 3.0 Hz, H-4'), 7.68 (4H, dd, J 8.0, 2.0 Hz, ortho Ph), 7.45-7.30 (6H, m, meta and para Ph), 3.65 (2H, t, J 5.5 Hz, H-1), 2.10-1.90 (2H, m, H-4, H-5), 1.70-1.40 (4H, m, H-2, H-3), 1.07 (9H, s, *t*-Bu), 0.97 and 0.96 (both 3H, d, J 6.5 Hz, CH*Me*$_2$); *m/z* (EI) 381 (M^+-H), 325 (M^+-*t*-Bu), 295, 269, 199, 183, 139, 109, 105, 91, 77 (Found C, 75.48; H, 9.22. $C_{24}H_{34}O_2Si$ requires C, 75.48; H, 8.96%) (Found: (M^+-*t*-Bu), 325.1626. $C_{24}H_{34}O_2Si$ requires (M^+-*t*-Bu), 325.1624).

Preparation of (±)-ethyl 2-(prop-2-yl)-4-pentenoate.

To a stirred solution of diisopropylamine (23.7 ml, 168.98 mmol, 1.1 eq) in THF (180 ml) at -78°C was added *n*-BuLi (67.6 ml, 168.98 mmol, 1.1 eq). The resultant pale yellow solution was left to stir at -78°C for 30 min. A solution of ethyl isovalerate (23 ml, 153.62 mmol) in THF (30 ml + 2 x 10 ml rinses) was added and

the mixture stirred for 2.5 h. Allyl bromide (14 ml, 161.30 mmol, 1.05 eq) was added and the mixture was stirred for a further 2.5 h. The reaction mixture was then quenched with aqueous HCl (2M, 200 ml) and extracted with ether (3 x 80 ml). The organic extracts were combined and washed with aqueous sodium hydrogencarbonate (5%; 65 ml), and dried with brine (100 ml) and $MgSO_4$. Concentration under reduced pressure followed by distillation gave the *ester* (26.43 g, 92%) as a colourless liquid, $bp_{1.2}$ 100°C; υ_{max} (CH_2Cl_2) 3079, 2964, 2840, 1734, 1641, 1465, 1372, 1180, 1038, 914 cm^{-1}; δ_H (500 MHz) 5.74 (1H, ddt, J 17.0, 10.5, 7.0 Hz, C*H*=CH_2), 5.04 (1H, dd with additional fine structure, J 16.5, 1.5 Hz, trans CH=CH_2), 4.98 (1H, dd with additional fine structure, J 11.0, 1.0 Hz, cis CH=CH_2), 4.12 (2H, q, J 4.0 Hz, OCH_2Me), 2.27 (2H, m, H-2, C*H*Me_2), 1.87 (2H, m, H-3), 1.24 (3H, t, J 7.0 Hz, OCH_2*Me*), 0.95 and 0.92 (both 3H, d, J 7.0 Hz, CH*Me*$_2$); *m/z* (EI) 171 (MH^+), 155 (M^+-Me), 127 (*i*-Pr^+), 41 (CH_2=$CHCH_2^+$), 29 (Et^+) (Found: C, 70.40; H, 10.69. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.70%).

Preparation of (±)-ethyl 5-hydroxy-2-(prop-2-yl)pentanoate.

To a stirred solution of (±)-ethyl 2-(prop-2-yl)-4-pentenoate (5.08 g, 29.84 mmol) in THF (150 ml) at rt was added 9-BBN (117 ml of a 0.5M solution in THF, 58.5 mmol, 1.96 eq). The resultant colourless solution was stirred at rt for 1.5 h. The reaction mixture was then cooled to -5°C. Aqueous NaOH (1M; 59 ml, 59 mmol, 1.98 eq) was added, keeping the internal temperature below 10°C. H_2O_2 (24 ml of a 30% w/w solution, 211.47 mmol, 7.2 eq) was then added, keeping the internal temperature below 20°C. The mixture was left to stir for another 1 h, after which it was quenched with HCl (0.5M; 160 ml) and extracted into ether (3 x 100 ml). The organic extracts were combined and washed with water (2 x 125 ml), saturated aqueous NH_4Cl (3 x 125 ml), water (2 x 125 ml), brine (125 ml) and dried ($MgSO_4$). Concentration under reduced pressure gave the crude *alcohol* (5.59 g, 100%) as a pale yellow liquid; υ_{max} (CH_2Cl_2) 3404 (br), 2961, 2874, 1729, 1030, 1120, 1252 cm^{-1}; δ_H (270 MHz) 4.14 (2H, q, J 7.5 Hz, OCH_2Me), 3.62 (2H, t, J 6.5 Hz, H-5), 2.12 (1H, td, J 9.0, 4.0 Hz, H-2), 1.86 (1H, octet, J 7.0 Hz, C*H*Me_2), 1.59 (5H, m, H-3, H-4, OH), 1.28 (3H, t, J 7.0 Hz, OCH_2*Me*), 0.93 and 0.91 (both 3H, d, J 6.5 Hz, CH*Me*$_2$); *m/z* (EI) 155 (M^+-Me), 127 (*i*-Pr^+), 31 (CH_2OH^+), 29 (Et^+) (Found: (MH^+), 189.1487. $C_{10}H_{20}O_3$ requires (MH^+), 189.1491).

Preparation of (±)-ethyl 5-(*tert*-butyldiphenylsilyloxy)-2-(prop-2-yl)pentanoate (14).

To a stirred solution of crude (±)-ethyl 5-hydroxy-2-(prop-2-yl)pentanoate (5.0 g, 26.56 mmol) and DMAP (0.130 g, 1.06 mmol, 0.04 eq) in CH_2Cl_2 (53 ml) at rt was added Et_3N (11.2 ml, 79.68 mmol, 3 eq), followed by TBDPSCl (7.6 ml, 29.21 mmol, 1.1 eq). The resultant cloudy mixture was stirred at rt for 2 h, after which the reaction was quenched with saturated aqueous sodium hydrogencarbonate (300 ml) and extracted with CH_2Cl_2 (3 x 80 ml). The organic extracts were combined and washed with saturated aqueous sodium hydrogencarbonate (80 ml), water (80 ml), brine (80 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (5% ether–petrol) gave the *ester* **14** (9.29 g, 82%) as a pale yellow liquid; υ_{max} (CH_2Cl_2) 2959, 2859, 1729, 1448, 1472, 1257, 1176, 1031, 998, 702 cm^{-1}; δ_H (270 MHz) 7.66 (4H, d, J 6.5 Hz, ortho Ph) 7.5-7.3 (6H, m, meta and para Ph), 4.12 (1H, dq, J 13.0, 7.0 Hz, OCH_2Me), 4.11 (1H, dq, J 13.0, 7.0 Hz, OCH_2Me), 3.65 (2H, t, J 6.0 Hz, H-5), 2.10 (1H, ddd, J 10.0, 7.5, 4.5 Hz, H-2), 1.84 (1H, octet, J 7.0 Hz, C*H*Me_2), 1.7-1.4 (4H, m, H-3, H-4), 1.24 (3H, t, J 7.0 Hz, OCH_2*Me*), 1.04 (9H, s, *t*-Bu), 0.93 and 0.91 (both 3H, d, J 6.5 Hz, CH*Me*$_2$); *m/z* (EI) 381 (M^+-OEt), 369 (M^+-*t*-Bu), 349 (M^+-Ph) (Found: C, 73.09; H, 8.69. $C_{26}H_{38}O_3Si$ requires C, 73.19; H, 8.98%) (Found: (MH^+), 427.2661. $C_{26}H_{38}O_3Si$ requires (MH^+), 427.2668).

Preparation of (±)-5-(*tert*-butyldiphenylsilyloxy)-2-(prop-2-yl)pentanol.

To a stirred solution of ester **14** (0.05 g, 0.12 mmol) in ether (0.732 ml) was added $LiAlH_4$ (0.018 g, 0.47 mmol, 4 eq). Rapid effervescence was observed. After stirring at rt for 10 min, the reaction was

quenched with dropwise addition of water (0.017 ml), aqueous NaOH (15%, 0.017 ml) and finally water (0.053 ml). The reaction was left to stir at rt for another 5 min until all excess $LiAlH_4$ had been quenched, giving a gelatinous white precipitate. The mixture was filtered and the residue washed with ether until tlc indicated no further product in the filtrate. Concentration under reduced pressure gave the crude *alcohol* (0.046 g, 100%) as a colourless oil; υ_{max} (CH_2Cl_2) 3350, 2868, 3000, 1658, 1567, 1427, 1470, 1261, 1042, 937, 854, 823 cm^{-1}; δ_H (270 MHz) 7.66 (4H, d, J 6.5 Hz, ortho Ph), 7.5-7.4 (6H, m, meta and para Ph), 3.65 (2H, t, J 6.5 Hz, H-5), 3.55 (2H, dd, J 5.5, 4.0 Hz, H-1), 1.7-1.6 (1H, m, H-2), 1.6-1.2 (6H, m, OH, C*H*Me_2, H-3, H-4), 1.04 (9H, s, *t*-Bu), 0.88 and 0.85 (both 3H, d, J 7.0 Hz, CH*Me*$_2$); *m/z* (EI) 327 (M^+-*t*-Bu), 255 ($OTBDPS^+$), 128 (M^+-TBDPSOH) (Found: (MH^+), 385.2554. $C_{24}H_{36}O_2Si$ requires (MH^+), 385.2563).

Preparation of (±)-1-(*tert*-butyldiphenylsilyloxy)-5-methyl-4-(oxomethyl)hexane (11; R = TBDPS).

To a solution of $(COCl)_2$ (1.57 ml, 17.55 mmol, 1.5 eq) in CH_2Cl_2 (17.5 ml) at -60°C was added a solution of DMSO (2.5 ml, 35.10 mmol, 3 eq) in CH_2Cl_2 (23.4 ml). After 5 min, a solution of (±)-5-(*tert*-butyldiphenylsilyloxy)-2-(prop-2-yl)pentanol (4.5 g, 11.70 mmol) in CH_2Cl_2 (20 ml + 3 rinses: total volume 58 ml) was added. Et_3N (6.6 ml, 46.80 mmol, 4 eq) was added to the resultant cloudy solution after 20 min. The reaction mixture was then allowed to warm to rt and quenched with water (70 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with saturated aqueous NH_4Cl (50 ml) and brine (50 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (3% ether–petrol) gave the aldehyde **11** (R = TBDPS) (3.73 g, 84%) as a pale yellow oil; spectroscopic data were in agreement with those obtained previously.

Preparation of (±)-(Z)-6-(*tert*-butyldiphenylsilyloxy)-1-iodo-3-(prop-2-yl)hexene.

To a stirred suspension of iodomethyltriphenylphosphonium iodide (31.15 g, 58.8 mmol, 2.0 eq) in THF (250 ml) at rt under argon was added NaHMDS (58.8 ml of a 1.0M solution in THF, 58.8 mmol, 2.0 eq) via cannula. After 20 min the deep red solution of the phosphorane was cooled to -78°C and a solution of aldehyde **11** (R = TBDPS) (11.24 g, 29.4 mmol, 1.0 eq) in THF (50 ml) was added via cannula. After 15 min the reaction was allowed to warm to rt and was quenched after a further 30 min with saturated aqueous ammonium chloride (300 ml). The aqueous phase was extracted with ether (3 x 150 ml) and the combined organic layers filtered to remove triphenylphosphine oxide. The filtrate was washed with 5% aqueous sodium metabisulfite (3 x 200 ml), water (3 x 200 ml), brine (3 x 200 ml), dried ($MgSO_4$) and concentrated to give a yellow oil. This oil was triturated with 5% ether–petrol and the white solid removed by filtration through a short pad of silica gel. After removal of the solvents under reduced pressure the product was purified by chromatography (3%→10% ether–petrol) to give the *iodoalkene* (11.96 g, 80%) as a colourless oil; υ_{max} (film) 3070, 2958, 2860, 1624, 1570, 1559, 1541, 1458, 1429, 1387, 1301, 1266, 1112, 702 cm^{-1}; δ_H (270 MHz) 7.78 (4H, m, ortho Ph), 7.45-7.32 (6H, m, meta and para Ph), 6.25 (1H, d, J 7.5 Hz, H-1), 5.89 (1H, dd, J 9.5, 7.5 Hz, H-2), 3.64 (2H, t, J 6.0 Hz, H-6), 2.25 (1H, m, H-3), 1.70-1.25 (5H, m, H-4, H-5, C*H*Me_2), 1.05 (9H, s, *t*-Bu), 0.91 and 0.87 (both 3H, d, 7.0 Hz, CH*Me*$_2$); *m/z* (EI) 449 (M^+-*t*-Bu), 309, 199 (Ph_2SiOH^+), 183, 123, 105, 81, 77 (Found: (M^+-*t*-Bu), 449.0798. $C_{25}H_{35}IOSi$ requires (M^+-*t*-Bu), 449.0798).

Preparation of (±)-6-(*tert*-butyldiphenylsilyloxy)-4-(prop-2-yl)hexyne.

To a stirred solution of (±)-(Z)-6-(*tert*-butyldiphenylsilyloxy)-1-iodo-3-(prop-2-yl)hexene (8.55 g, 16.88 mmol) in THF (170 ml) under argon at -78°C was added potassium *tert*-butoxide (34 ml of a 2.0M solution in THF, 33.76 mmol, 2 eq). The mixture was allowed to warm to rt during 30 min and stirred for a further 10 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (200 ml). The aqueous phase was extracted with ether (3 x 150 ml) and the combined organic layers washed with water (3 x

100 ml), brine (2 x 100 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography (1%→10% ether–petrol) provided the *alkyne* (5.57 g, 87%) as a colourless oil; υ_{max} (film) 3305 (sharp), 3072, 2960, 2932, 2863, 1653, 1559, 1463, 1429, 1358, 1112, 823, 740, 702 cm^{-1}; δ_H (270 MHz) 7.66 (4H, dd, J 8.0, 2.0 Hz, ortho Ph), 7.45-7.32 (6H, m, meta and para Ph), 3.68 (2H, t, J 4.5 Hz, H-6), 2.20 (1H, m, H-3), 2.02 (1H, d, J 2.5 Hz, H-1), 1.80 (1H, m, C*H*Me_2), 1.70-1.40 (4H, m, H-4, H-5), 1.05 (9H, s, *t*-Bu), 0.95 (6H, d, J 7.0 Hz, CH*Me*$_2$); *m/z* (EI) 321 (M^+-C_4H_9), 279, 265, 243, 217, 199, 183, 163, 105, 77 (Found: C, 79.27; H, 9.22. $C_{25}H_{34}OSi$ requires C, 79.31; H, 9.05%) (Found: (M^+-*t*-Bu), 321.1675. $C_{25}H_{34}OSi$ requires (M^+-*t*-Bu), 321.1674).

Preparation of (±)-4-(prop-2-yl)-5-hexyn-1-ol (16).

To a stirred solution of (±)-6-(*tert*-butyldiphenylsilyloxy)-4-(prop-2-yl)hexyne (6.41 g, 16.92 mmol) in THF (17 ml) under argon was added TBAF (34 ml of a 1.0M solution in THF, 33.83 mmol, 2.0 eq) at rt. After 15 min, tlc (30% ether–petrol) indicated complete desilylation and the reaction was quenched by the addition of saturated aqueous ammonium chloride (100 ml). The aqueous phase was extracted with ether (3 x 50 ml) and the combined organic layers washed with water (3 x 50 ml), brine (2 x 50 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography gave the *alcohol* **16** (2.36 g, 99%) as a colourless oil; υ_{max} (film) 3609 (br), 3308 (sharp), 2962, 2874, 1557, 1539, 1457, 1370, 1060 cm^{-1}; δ_H (270 MHz) 3.68 (2H, t, J 6.0 Hz, H-1), 2.24 (1H, m, H-4), 2.04 (1H, d, J 2.5 Hz, H-6), 1.80 (1H, m, C*H*Me_2), 1.70-1.40 (4H, m, H-2, H-3), 0.96 and 0.94 (both 3H, d, J 6.0 Hz, CH*Me*$_2$); *m/z* (EI) 123 (M^+-OH), 100, 81 (C_6H_9) (Found: C, 77.38; H, 11.60. $C_9H_{16}O$ requires C, 77.09; H, 11.50%) (Found: (M^+-OH), 123.1174. $C_9H_{16}O$ requires (M^+-OH), 123.1174).

Preparation of (±)-(*E*)-6-iodo-5-methyl-4-(prop-2-yl)-5-hexenol (17).

To a stirred solution of zirconocene dichloride (1.97 g, 6.75 mmol, 0.4 eq) in 1,2-dichloroethane (25 ml) under argon was added trimethylaluminium (26 ml of a 2.0M solution in hexanes, 50.61 mmol, 3.0 eq). After 10 min the reaction was cooled to 0°C and treated with a solution of alcohol **16** (2.37 g, 16.87 mmol) in 1,2-dichloroethane (25 ml) via cannula. The yellow solution was allowed to warm to rt and stirred overnight, after which time it had assumed an orange colour. The solution was then cooled to -30°C and a solution of iodine (4.71 g, 18.56 mmol, 1.1 eq) in THF (20 ml + 2 x 5 ml rinse) was added via cannula. After stirring for a further 30 min the reaction was allowed to warm to 0°C whereupon it was quenched by the addition of saturated aqueous potassium carbonate (5 ml) with rapid stirring (**CAUTION**: large volume of gas evolved). The mixture was poured onto solid sodium hydrogencarbonate and diluted with EtOAc (200 ml). After 30 min stirring the free-flowing white solid was removed by filtration through Celite® and the residue washed thoroughly with EtOAc. The combined filtrate and washings were concentrated under reduced pressure to give a yellow oil. Purification by chromatography (25%→75% ether–petrol) gave a 10:1 mixture of the *alcohols* **17** and **15** (3.95 g, 83%) as a colourless oil; **17**: υ_{max} (film) 3334 (br), 2957, 2870, 1613, 1469, 1386, 1270, 1150, 1063, 911, 771, 663 cm^{-1}; δ_H (270 MHz) 5.83 (1H, d, J 1.0 Hz, H-6), 3.60 (2H, dt, J 6.5, 1.0 Hz, H-1), 1.87 (1H, dt, J 10.0, 4.0 Hz, H-4), 1.67 (3H, d, J 1.0 Hz, C-5 Me), 1.64-1.20 (6H, m, H-2, H-3, C*H*Me_2, OH), 0.91 and 0.75 (both 3H, d, J 6.5 Hz, CH*Me*$_2$); *m/z* (EI) 282 (M^+), 239 (M^+-*i*-Pr), 221, 195, 181, 155 (M^+-I), 128, 94, 91, 71 (Found: (M^+-*i*-Pr), 238.9927. $C_{10}H_{19}IO$ requires (M^+-*i*-Pr), 238.9933); **15**: υ_{max} (film) 3313 (br), 3073, 2936, 1645, 1456, 1376, 1166, 1063, 1001, 975, 888 cm^{-1}; δ_H (270 MHz) 4.74 (1H, dt, J 2.0, 1.5 Hz, H-6), 4.64 (1H, dd, J 2.0, 0.5 Hz, H-6), 3.60 (2H, td, J 6.5, 2.0 Hz, H-1), 1.57 (3H, d, J 1.5 Hz, C-5 Me), 1.65-1.15 (7H, m, H-2, H-3, H-4, C*H*Me_2, OH), 0.90 and 0.80 (both 3H, d, J 6.35 Hz, CH*Me*$_2$); *m/z* (EI) 156 (M^+), 138 (M^+-H_2O), 141 (M^+-Me), 123, 112, 109, 97, 95, 81, 69, 67, 57, 55, 43, 41 (Found: (M^+), 156.1516. $C_{10}H_{20}O$ requires (M^+), 156.1514).

Preparation of (±)-(*E*)-5-methyl-4-(prop-2-yl)-5,7-octadienol.

A solution of alcohol **17** (3.27 g, 11.58 mmol) in toluene (100 ml + 20 ml rinse) was added via cannula to a flask containing tetrakis(triphenylphosphine)palladium (0) (670 mg, 0.579 mmol, 5 mol %) under argon and stirred for 20 min. To this mixture was added vinylmagnesium bromide (34.7 ml of a 1M solution in THF, 34.7 mmol, 3 eq) at 0°C. After 20 min tlc indicated that the reaction was complete, and it was quenched with saturated aqueous ammonium chloride (100 ml). The aqueous phase was extracted with ether (3 x 100 ml) and the combined organic layers were washed with water (3 x 75 ml), brine (2 x 75 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a red oil. Chromatography (20%→70% ether–petrol gradient; 10% increments) gave a pale yellow oil which was decolourised by dissolution in 1:1 ether–petrol (75 ml), treatment with activated charcoal and filtration through a pad of Celite®. Further chromatography (30%→60% ether–petrol) gave the *dienol* (1.713 g, 81%) as a colourless oil; υ_{max} (film) 3382 (br), 3084, 2956, 1647, 1559, 1508, 1456, 1385, 1166, 1063, 988, 898 cm^{-1}; δ_H (500 MHz) 6.59 (1H, ddd, J 17.0, 11.0, 10.5 Hz, H-7), 5.82 (1H, br d, J 11.0 Hz, H-6); 5.08 (1H, dd, J 17.0, 2.0 Hz, H-8_{trans}), 4.98 (1H, dd, J 10.0, 2.0 Hz, H-8_{cis}), 3.60 (2H, m, J 6.0 Hz, H-1), 1.62 (3H, d, J 1.0 Hz, C-5 Me), 1.65-1.50 (2H, m, H-4, C*H*Me_2), 1.45 and 1.33 (both 1H, m, H-3), 1.35-1.25 (2H, m, H-2), 1.20 (1H, br s, OH), 0.92 and 0.78 (both 3H, d, J 6 Hz, CH*Me*$_2$); *m/z* (EI) 182 (M^+), 123 (M^+-C_3H_6), 121, 105 ($C_9H_{16}O$-H_2O), 95, 93, 79, 77, 55, 41 (C_3H_5) (Found: (M^+), 182.1671. $C_{12}H_{22}O$ requires (M^+), 182.1671).

Preparation of (±)-(*E*)-5-methyl-4-(prop-2-yl)-5,7-octadienal.

To a stirred solution of oxalyl chloride (351 µl, 4.03 mmol, 2 eq) in CH_2Cl_2 at -60°C under argon was added DMSO (572 µl, 8.05 mmol, 4 eq) as a solution in CH_2Cl_2 (5 ml). After 5 min a solution of (±)-(*E*)-5-methyl-4-(prop-2-yl)-5,7-octadienol (367 mg, 2.013 mmol) in CH_2Cl_2 (5 ml + 2 ml rinse) was added via cannula. After 20 min, triethylamine (1.4 ml, 10.06 mmol, 5 eq) was added via syringe; the reaction was stirred for 10 min at -60°C, then allowed to warm to rt over a period of 45 min. The mixture was poured into ether–water (1:1, 100 ml), the layers separated and the aqueous phase extracted with ether (2 x 50 ml). The combined organic layers were washed with saturated aqueous ammonium chloride (3 x 50 ml), water (3 x 50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Chromatography (3%→8%→15%→20% ether–petrol) gave the *dienal* (307 mg, 85%) as a colourless oil; υ_{max} (film) 3085, 2958, 1727, 1645, 1598, 1570, 1539, 1470, 1386, 989, 900 cm^{-1}; δ_H (500 MHz) 9.74 (1H, t, J 1.5 Hz, H-1), 6.58 (1H, dt, J 16.5, 11.0 Hz, H-7), 5.80 (1H, br d, J 11.0 Hz, H-6), 5.11 (1H, dd, J 17.0, 2.0 Hz, H-8_{trans}), 5.00 (1H, dd, J 10.0, 2.0 Hz, H-8_{cis}), 2.30 (2H, m, H-2), 1.94 (1H, m, H-4), 1.61 (3H, d, J 1.0 Hz, C-5 Me), 1.58-1.46 (3H, m, H-3, C*H*Me_2), 0.95 and 0.79 (both 3H, d, J 6.0 Hz, CH*Me*$_2$); *m/z* (EI) 180 (M^+), 162 (M^+-H_2O), 121 (M^+-H_2O-C_3H_5), 119, 109, 95, 93, 81, 79, 67, 55, 41 (Found: (M^+), 180.1511. $C_{12}H_{20}O$ requires (M^+), 180.1514).

Preparation of (±)-(*E*)-6-methyl-1-(phenylsulfonyl)-5-(prop-2-yl)-6,8-nonadien-2-ol.

To a stirred solution of (phenylsulfonyl)methane (398 mg, 2.55 mmol, 1.1 eq) in THF (15 ml) under argon at -78°C was added dropwise *n*-BuLi (1.11 ml of a 2.30M solution in hexanes, 2.55 mmol, 1.1 eq) to give a slightly yellow anion. After 10 min a solution of (±)-(*E*)-5-methyl-4-(prop-2-yl)-5,7-octadienal (422 mg, 2.315 mmol) in THF (10 ml + 5 ml rinse) was added via cannula. After 20 min tlc (50% ether–petrol) showed complete consumption of the aldehyde and the reaction was quenched at -78°C by the addition of acetic acid (2.7 ml of a 1.75M solution in THF (10% v/v), 4.63 mmol, 2.0 eq) and allowed to warm to rt. Saturated aqueous sodium hydrogencarbonate (30 ml) was added and the aqueous phase extracted with CH_2Cl_2 (3 x 30 ml). The combined organic layers were washed with saturated aqueous ammonium chloride solution (3 x 50 ml), water (3 x 50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (10%→55% ether–petrol gradient, 5% increments) furnished a diastereomeric

mixture of the *alcohols* (653 mg, 84%) as a colourless oil; υ_{max} (film) 3526 (br), 2953, 1646, 1448, 1385, 1305, 1149, 1088, 901, 785, 747, 719, 689 cm^{-1}; δ_H (500 MHz) 7.92 (2H, dd, J 7.5, 1.5 Hz, ortho Ph), 7.72-7.55 (3H, m, meta and para Ph), 6.53 (1H, dt, J 16.5, 11.0 Hz, H-8), 5.73 and 5.71 (both 1H, d, J 11.0 Hz, H-7, two diastereomers), 5.07 and 5.00 (both 1H, dd, J 7.0, 2.0 Hz, H-9_{cis} two diastereoisomers), 4.95 (1H, br d, J 11.0 Hz, H-9_{trans} both diastereomers), 4.20-4.06 (1H, m, H-2), 3.37-3.31 (1H, m, OH both diastereomers), 3.18 (1H, dd, J 7.5, 3.5 Hz) and 3.15 (1H, dd, J 7.5, 2.0 Hz; H-1 both diastereomers), 1.80-1.10 (6H, m, H-3, H-4, H-5, C*H*Me_2), 1.56 (3H, s, C-6 Me), 0.90, 0.88, 0.75, 0.73 (all 3H, d, J 6.5 Hz, CH*Me*$_2$ both diastereoisomers); *m/z* (EI) 336 (M^+), 293, 275, 199, 195, 133, 123, 93, 81, 77 (Found: (M^+), 336.1766. $C_{19}H_{28}O_3S$ requires (M^+), 336.1759).

Preparation of (±)-(*E*,*E*)-6-methyl-1-(phenylsulfonyl)-5-(prop-2-yl)-1,6,8-nonatriene (8).

To a rapidly stirred solution of (±)-(*E*)-6-methyl-1-(phenylsulfonyl)-5-(prop-2-yl)-6,8-nonadien-2-ol (653 mg, 1.941 mmol) in CH_2Cl_2 (20 ml) at -6°C under argon was added triethylamine (2.7 ml, 19.41 mmol, 10 eq) followed by methanesulfonyl chloride (378 µl, 5.82 mmol, 3 eq). A white precipitate developed and after 30 min tlc (50% ether–petrol) showed no starting material to be present. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate (50 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 40 ml) and the combined organic layers were washed with water (3 x 20 ml), dried ($MgSO_4$) and concentrated under reduced pressure to a yellow oil. Purification by chromatography (15%→30% ether–petrol) gave the *triene* **8** (425 mg, 69%) as a colourless oil; υ_{max} (film) 2958, 1641, 1448, 1385, 1320, 1148, 1087, 989, 901, 818, 754, 716, 689 cm^{-1}; δ_H (270 MHz) 7.88 (2H, dd, J 8.0, 1.5 Hz, ortho Ph), 7.60-7.48 (3H, m, meta and para Ph), 6.95 (1H, ddd, J 14.5, 7.0, 6.0 Hz, H-2), 6.52 (1H, ddd, J 16.5, 11.0, 10.5 Hz, H-8), 6.27 (1H, dt, J 15.0, 1.5 Hz, H-1), 5.68 (1H, br d, J 11.0 Hz, H-7), 5.05-4.93 (2H, m, H-9), 2.14 (1H, m, H-5), 2.01 (1H, septet, J 6.5 Hz, C*H*Me_2), 1.80-1.30 (4H, m, H-3, H-4), 1.58 (3H, s, C-6 Me), 0.89 and 0.75 (both 3H, d, J 6.0 Hz, CH*Me*$_2$); *m/z* (EI) 318 (M^+), 275, 133, 123, 95, 81 (Found: (M^+), 318.1660. $C_{19}H_{26}O_2S$ requires (M^+), 318.1654).

IMDA reaction of (±)-(*E*,*E*,*E*)-6-methyl-1-(phenylsulfonyl)-5-(prop-2-yl)-1,6,8-nonatriene (8).

An azeotropically dried, degassed solution of triene **8** (250 mg, 0.78 mmol)) in toluene (10 ml) in a Carius tube was heated at 240°C for 48 h. Concentration under reduced pressure followed by chromatography (15%→20% etherpetrol) gave the adduct mixture (223 mg, 89%) as a colourless oil; υ_{max} (CH_2Cl_2) 2980, 2840, 1651, 1634, 1621, 1351, 1146 cm^{-1}; δ_H (270 MHz) 7.80-8.00 (2H, m, ortho Ph), 7.5-7,7 (3H, m, meta and para Ph), 5.3-6.2 (2H, m, H-1, H-2; 3 diastereomers), 3.0-3.5 (1H, m, H-4, 3 diastereomers), 2.2-2.5 (1H, m, H-5, 3 diastereomers), 1.2-2.2 (14H, m, H-3, H-6, H-7, H-8, H-9, 3 diastereomers), 1.2-1.3 (3H, s, H-1'), 0.8-1.1 (6H, m, H-10); m/z (CI) 177 (M^+-$PhSO_2$), 150 (M^+-$PhSO_2$-Et), 135 (M^+-$PhSO_2$-*i*-Pr). (Found: (M^++NH_4), 336.1990. $C_{19}H_{26}O_2S$ requires (M^++NH_4), 336.1997). A solution of the chromatographed mixture of cycloadducts (14 mg, 0.04 mmol) in EtOAc (0.5 ml) was stirred overnight with 10% Pd(C) (4 mg) under an atmosphere of H_2. The mixture was filtered through a silica gel pad and the filtrate concentrated under reduced pressure to yield the crude product (12 mg, 94%) as a pale yellow oil. This was separated by reversed-phase HPLC (ODS2 column, UV detection @ 230 nm; mobile phase: 0.1% TFA in water (solvent A) and 0.05% TFA in MeCN (solvent B); gradient elution, using 20:80 solvent A:solvent B→pure solvent B; flow rate 40 ml min^{-1}) to give *[1R*,5S*,6S*,9R*]-1-methyl-5-(phenylsulfonyl)-9-(prop-2-yl)bicyclo[4.3.0]nonane* **19** (retention time 17.8 min) followed by *[1R*,5S*,6S*,9S*]-1-methyl-5-(phenylsulfonyl)-9-(prop-2-yl)bicyclo[4.3.0]nonane* **18** (retention time 19.1 min); **18**: υ_{max} ($CHCl_3$) 3064, 2924, 2852, 1465, 1446, 1301, 1146, 731 cm^{-1}; δ_H (500 MHz and 250 MHz COSY) 7.90 (2H, d, J 8.5 Hz, ortho Ph), 7.63 (1H, t, J 7.5 Hz, para Ph), 7.54 (2H, t, J 8.0 Hz, meta Ph), 3.03 (1H, m, H-5), 2.40 (1H, td, J 9.0, 3.0 Hz, H-6), 1.89 (1H, m, H-4), 1.75 (1H, m, H-7), 1.64 (3H, m, H-4, H-8), 1.45 (2H, m, H-7, H-

9), 1.35 (5H, m, H-2, H-3, H-2'), 1.31 (3H, s, C-1 Me), 0.97 and 0.84 (both 3H, d, J 6.5 Hz, H-1', H-3'); *m/z* (CI) 338 (M^++NH_4), 321 (MH^+), 179 (M^+-$PhSO_2$) (Found: (M^++NH_4), 338.2147. $C_{19}H_{28}O_2S$ requires (M^++NH_4), 338.2154); **19**: δ_H (500 MHz nOe, 400MHz HetCor and 500 MHz COSY) 7.69 (2H, d, J 7.0 Hz, ortho Ph), 6.9-7.1 (3H, m, meta and para Ph), 2.67 (1H, ddd, J 12.5, 11.0, 4.0 Hz, H-5), 2.25 (1H, m, H-8), 1.60-1.80 (4H, m, H-4, H-8, H-9), 1.45 (2H, dt, J 14.0, 4.0 Hz, H-2), 1.10-1.40 (4H, m, H-6, H-7, H-2'), 1.00 (3H, m, H-3), 0.90 (1H, m, H-3), 0.74 (6H, d, J 6.5 Hz, H-1', H-3'), 0.60 (3H, s, C-1 Me).

Preparation of (+)-[1*R*,2'*R*,5*S*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)bicyclo[4.3.0]nonan-5-ol (21).

To a stirred solution of Windaus–Grundmann ketone **20**[16] (0.76 g, 2.88 mmol) in toluene (28.1 ml) at -78°C was added DIBAL-H (2.88 ml of a 1.5 M solution toluene, 4.32 mmol, 1.5 eq) dropwise over 20 min. The reaction mixture was stirred for a further 30 min when tlc indicated complete consumption of starting material. Water (1.86 ml) was then added dropwise, and the resultant gelatinous mixture was allowed to warm to rt. The mixture was diluted with EtOAc (60 ml), solid sodium hydrogencarbonate (2.88 g) added and the mixture stirred vigorously for 30 min giving a granular white precipitate. The mixture was filtered and the residue washed with EtOAc until tlc indicated no more product to be present in the filtrate. The combined filtrates were concentrated and the residue chromatographed (20% ether–petrol) to give *alcohol* **21** (0.731 g, 95%) as a colourless oil; $[\alpha]_D^{20}$ +48.6 (*c* 0.87, $CHCl_3$); υ_{max} (film) 3410, 2949, 1467, 1367, 1268, 1166, 1065, 991, 942, 887, 858 cm^{-1}; δ_H (500 MHz) 4.07 (1H, m, H-5), 1.99 (1H, m), 1.86-1.79 (3H, m) and 1.60-0.95 (17H, m, all comprising H-2, H-3, H-4, H-6, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.92 (3H, s, C-1 Me), 0.89 (3H, d, J 6.5 Hz, H-1'), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, H-7' and C-6' Me); *m/z* (EI) 266 (M^+), 251 (M^+-Me), 249 (M^+-OH), 248 (M^+-H_2O), 43 ($C_3H_7^+$).

Preparation of (+)-[1*R*,2'*R*,5*S*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-[(methylthio)thiocarbonyloxy]bicyclo[4.3.0]nonane (22).

To a stirred solution of alcohol **21** (0.731 g, 2.75 mmol), in THF (6 ml) at -78°C was added *n*-BuLi (1.21 ml of a 2.5 M solution in hexanes, 3.02 mmol, 1.1 eq) dropwise. After a further 5 min at -78°C the mixture was allowed to warm to rt. DMPU (3 ml) followed by carbon disulfide (0.331 ml, 5.5 mmol, 2 eq) was added and after 15 min tlc indicated complete consumption of alcohol. Iodomethane (0.342 ml, 2.25 mmol, 1 eq) was added to give a yellow solution. The mixture was stirred for a further 15 min when saturated aqueous ammonium chloride (20 ml) was added. The aqueous layer was extracted with ether (3 x 20 ml) and the combined organic extracts were alternately washed with H_2O/brine (3 x 20 ml each) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (petrol) gave the *xanthate ester* **22** (0.744 g, 76%) as a colourless oil; $[\alpha]_D^{20}$ +39.5 (*c* 0.62, $CHCl_3$); υ_{max} (film) 3363, 2950, 2137, 1590, 1468, 1380, 1220, 1150, 1052, 873 cm^{-1}; δ_H (500 MHz) 5.98 (1H, br d, J 2.5 Hz, H-5), 2.55 (3H, s, SMe), 207 (2H, m) and 1.89-1.75 (1H, m, all comprising H-4, H-6), 1.75-1.68 (1H, m) and 1.58-0.94 (16H, m, all comprising H-2, H-3, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.92 (6H, overlapping s and d, J 6.5 Hz, C-1 Me, H-1'), 0.86 and 0.85 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'); *m/z* (EI) 249 (M^+- $C_2H_3OS_2$), 248 (M^+-$C_2H_4OS_2$), 233 (M^+-$C_2H_4OS_2$-Me), 135 (M^+-$C_2H_4OS_2$-C_8H_{17}) , 43 (C_3H_7) (Found: (M^+-$C_2H_3OS_2$), 249.2582. $C_{20}H_{36}OS_2$ requires (M^+-$C_2H_3OS_2$), 249.2582).

Preparation of (+)-[1*S*,2'*R*,6*R*,7*R*]-6-methyl-7-(6-methylhept-2-yl)bicyclo[4.3.0]-2-nonene (24).

A flask containing xanthate ester **22** (744 mg, 2.09 mmol) was fitted with a reflux condenser and heated to 215°C for 6 min. The residue was chromatographed (petrol) to give the *olefin* **24** (396 mg, 76%) as a colourless oil; $[\alpha]_D^{20}$ +89.8 (*c* 0.56, $CHCl_3$); υ_{max} (film) 3019, 2952, 2872, 1636, 1590, 1465, 1379, 1117,

1045, 925, 901, 857, 767, 669 cm^{-1}; δ_H (270 MHz) 5.64-5.50 (2H, m, H-2, H-3) , 2.15-1.82 (5H, m) and 1.75-0.95 (13H, m, all comprising H-1, H-4, H-5, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.93 (3H, d, J 6.5 Hz, H-1'), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'), 0.68 (3H, s, C-6 Me); *m/z* (EI) 248 (M^+), 233 (M^+-Me), 135 (M^+-C_8H_{17}), 43 ($C_3H_7^+$) (Found: (M^+), 248.2504. $C_{18}H_{32}$ requires (M^+), 248.2504).

Preparation of [1*R*,2'*R*,4*R*,5*S*,6*R*,9*R*]-4,5-epoxy-1-methyl-9-(6-methylhept-2-yl)bicyclo-[4.3.0]nonane.

To a stirred solution of *m*-CPBA (838 mg, 2.26 mmol, 1.5 eq) in CH_2Cl_2 (4 ml) at 0°C was added a solution of olefin **24** (375.6 mg, 1.51 mmol) in CH_2Cl_2 (4 ml + 2 ml rinse). After 20 min tlc indicated complete consumption of starting material. The reaction mixture was diluted to 60 ml with additional CH_2Cl_2. The mixture was washed with 10% sodium thiosulfate (3 x 20 ml), NaOH (3 x 20 ml), water (3 x 20 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (10% ether–petrol) gave the *epoxide* (355 mg, 89%) as a colourless oil; $[\alpha]_D^{20}$ +45.0 (*c* 0.99, $CHCl_3$); υ_{max} (film) 2955, 1464, 1380, 1168, 939, 882, 832, 777 cm^{-1}; δ_H (270 MHz) 3.15 (1H, br t, J 3.5 Hz, H-4), 2.96 (1H, br d, J 4.0 Hz, H-5), 2.07-1.70 (4H, m) and 1.60-0.94 (14H, m, all comprising H-2, H-3, H-6, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.92 (3H, J 6.5 Hz, H-1'), 0.87 and 0.85 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'), 0.67 (3H, s, C-1 Me); *m/z* (EI) 265 (MH^+), 250 (MH^+-Me), 248 (M^+-O), 151 (M^+-C_8H_{17}), 43 (C_3H_7) (Found: C, 81.59; H, 11.97. $C_{18}H_{32}O$ requires C, 81.74; H, 12.19%).

Preparation of (+)-[1*R*,2'*R*,4*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylthio)-bicyclo[4.3.0]nonan-4-ol.

To ethanol (7.1 ml) was added freshly cut sodium with stirring. Once all the sodium had been consumed PhSH (0.79 ml) was added. After stirring for 10 min a solution of [1*R*,2'*R*,4*R*,5*S*,6*R*,9*R*]-4,5-epoxy-1-methyl-9-(6-methylhept-2-yl)bicyclo[4.3.0]nonane (345 mg, 1.31 mmol) in ethanol (2 ml) was added. The resultant solution was heated to reflux for 16 h when tlc indicated complete consumption of starting material. The mixture was allowed to cool to rt and water (30 ml) was cautiously added. The aqueous mixture was extracted with ether (3 x 30 ml) and the combined organic extracts washed with NaOH (3 x 30 ml of a 1M solution), water (3 x 30 ml), brine (3 x 30 ml), and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (10% ether–petrol) gave the *hydroxysulfide* (446 mg, 92%) as a colourless oil; $[\alpha]_D^{20}$ +27.8 (*c* 1.31, $CHCl_3$); υ_{max} (neat) 3295, 2952, 1585, 1474, 1370, 1262, 1087, 997, 959, 919, 804, 737, 691 cm^{-1}; δ_H (270 MHz) 7.50-7.10 (5H, m, Ph), 4.08 (1H, br d, J 2.5 Hz, H-4), 3.43 (1H, m, H-5), 2.26-2.13 (2H, m, H-3), 1.90-0.95 (16H, m, H-2, H-6, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.91 (3H, d, J 6.5 Hz, H-1'), 0.89-0.83 (9H, m, C-1 Me, C-6' Me, H-7'); *m/z* (EI) 374 (M^+), 265 (M^+-PhS), 264 (M^+-PhSH), 247 (M^+-PhS-H_2O), 134 (M^+-H_2O-C_8H_{17}), 77 (Ph^+) (Found: (M^+), 374.2643. $C_{24}H_{38}OS$ requires (M^+), 374.2643).

Preparation of (-)-[1*R*,2'*R*,4*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylthio)-bicyclo[4.3.0]non-4-yl benzoate.

To a stirred solution of (+)-[1*R*,2'*R*,4*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylthio)-bicyclo[4.3.0]nonan-4-ol (386 mg, 1.03 mol) in pyridine (2 ml) at rt was added DMAP (6.3 mg, 5 mol %) followed by benzoyl chloride (131 µl, 1.13 mmol, 1.1 eq). After stirring for 6 h tlc indicated complete comsumption of starting material. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate (20 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extracts were washed with water (3 x 20 ml), saturated aqueous $CuSO_4$ (3 x 20 ml), water (3 x 20 ml), and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (5% ether–petrol) gave

the *ester* (425 mg, 86%) as a colourless oil; $[\alpha]_D^{20}$ -39.9 (*c* 0.74, $CHCl_3$); υ_{max} (film) 3312, 3061, 2951, 1718, 1584, 1446, 1342, 1266, 1174, 1110, 1069, 1025, 982, 948, 912, 887, 802, 738, 710 cm^{-1}; δ_H (500 MHz) 8.04-8.02 (2H, m, ortho protons on $PhCO_2$), 7.57-7.54 (1H, m, para protons on $PhCO_2$), 7.50-7.45 (4H, m), 7.34-2.27 (2H, m, all comprising meta protons on $PhCO_2$, ortho and meta protons on PhS), 7.21-7.18 (1H, m, para protons on PhS), 5.37 (1H, br d, J 2.5 Hz, H-4), 3.63 (1H, m, H-5), 2.34-2.20 (2H, m, H-3), 1.98-1.78 (4H, m) and 1.66-1.00 (12H, m, all comprising H-2, H-6, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.95 (3H, s, C-1 Me), 0.93 (3H, d, J 6.5 Hz, H-1'), 0.88 and 0.87 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'); *m/z* (EI) 356 (M^+-$PhCO_2H$), 247 (M^+-$PhCO_2H$-PhS), 243 (M^+-$PhCO_2H$-C_8H_{17}), 122 ($PhCO_2H^+$), 105 ($PhCO^+$), 77 (Ph^+), 43 (C_3H_7) (Found: C, 77.74; H, 9.09. $C_{31}H_{42}O_2S$ requires C, 77.77; H, 8.84%).

Preparation of (-)-[1*R*,2'*R*,4*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]non-4-yl benzoate.

To a stirred solution of (-)-[1*R*,2'*R*,4*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylthio)-bicyclo[4.3.0]non-4-yl benzoate (400 mg, 0.837 mmol) in CH_2Cl_2 at 0°C buffered with NaOAc (75 mg, 0.92 mmol, 1.1 eq) was added peracetic acid (385 µl of a 33% (by wt) solution, 2.51 mmol, 3 eq). After stirring for 6 h tlc indicated complete consumption of starting material. The mixture was diluted with CH_2Cl_2 (30 ml) and washed with NaOH (3 x 10 ml of a 1M solution), water (3 x 10 ml), and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (20% ether–petrol) gave the *sulfone* (390 mg, 91%) as a colourless oil; $[\alpha]_D^{20}$ -57.1 (*c* 0.61, $CHCl_3$); υ_{max} (film) 3334, 2953, 1722, 1600, 1448, 1382, 1263, 1150, 1108, 1025, 987, 741, 710 cm^{-1}; δ_H (270 MHz) 7.98 (2H, m, ortho protons on $PhCO_2$) 7.89-7.85 (2H, m, ortho protons on $PhSO_2$), 7.68-7.50 (4H, m, meta and para protons on $PhCO_2$, para protons on $PhSO_2$), 7.43-7.36 (2H, m, meta protons on $PhSO_2$), 5.38 (1H, m, H-4), 3.65 (1H, br d, J 6.0 Hz, H-5), 2.55-2.43 (2H, m) and 2.20 (1H, m, all comprising H-3, H-6), 2.03-1.00 (15H, m, H-2, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 1.19 (3H, s, C-1 Me), 0.97 (3H, d, J 6.5 Hz, H-1'), 0.89 and 0.88 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'); *m/z* (EI) 388 (M^+-$PhCO_2H$), 275 (M^+-$PhCO_2H$-C_8H_{17}), 247 (M^+-$PhCO_2H$-$PhSO_2$), 105 ($PhCO^+$), 77 (Ph^+), 43 (C_3H_7) (Found: C, 72.75; H, 8.47. $C_{31}H_{42}O_4S$ requires C, 72.90; H, 8.29%).

Preparation of (-)-[1*R*,2'*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)-bicyclo[4.3.0]-3-nonene.

To a stirred solution of (-)-[1*R*,2'*R*,4*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)-bicyclo[4.3.0]non-4-yl benzoate (363 mg, 0.71 mmol) in THF (4 ml) at rt was added *t*-BuOH (2.4 ml) followed by *t*-BuOK (2.84 ml of a 1M solution in THF, 2.84 mmol, 4 eq). There was immediate formation of a white precipitate and after 5 h the reaction was quenched by the addition of saturated aqueous ammonium chloride (10 ml). The aqueous layer was extracted with ether (3 x 10 ml) and the combined organic extracts washed with water (3 x 10 ml), brine (3 x 10 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (20% ether–petrol) gave the *sulfone* (262 mg, 95%) as a colourless oil; $[\alpha]_D^{20}$ -22.8 (*c* 0.70, $CHCl_3$); υ_{max} (film) 3032, 2954, 2317, 1640, 1466, 1447, 1380, 1311, 1212, 1146, 1086, 1022, 868, 758, 731, 709, 690, 668 cm^{-1}; δ_H (500 MHz) 7.85 (2H, m, ortho $PhSO_2$), 7.65-7.62 (2H, m, para $PhSO_2$), 7.55-7.52 (2H, m, meta $PhSO_2$) 5.88-5.83 (1H, m, H-3), 5.78-5.69 (1H, m, H-4), 3.60 (1H, m, H-5), 2.19 (1H, dd with additional fine structure, J 17.5, 5.5 Hz, H-2), 2.07-2.00 (1H, m, H-2), 1.90-1.80 (2H, m) and 1.56-1.05 (12H, m, all comprising H-6, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.87 (3H, d, J 6.5 Hz, H-1'), 0.86 (3H, s, C-1 Me), 0.85 and 0.84 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'); *m/z* (EI) 388 (M^+), 275 (M^+-C_8H_{17}), 247 (M^+-$PhSO_2$), 77 (Ph^+), 43 ($C_3H_7^+$) (Found: C, 73.88; H, 9.27. $C_{24}H_{36}O_2S$ requires C, 74.18; H, 9.34%).

Preparation of (+)-[1*R*,2'*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)-bicyclo[4.3.0]nonane (3).

To a flask containing Pd(C) (10 mg) in EtOAc (5 ml) at rt was added a solution of (-)-[1*R*,2'*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]-3-nonene (205 mg, 0.53 mmol) in EtOAc (5 ml). The mixture was stirred vigorously under an atmosphere of hydrogen for 16 h. The hydrogen was displaced with argon and the mixture filtered through a pad of Celite®, washing with EtOAc until tlc indicated no more product to be present in the filtrate. The combined filtrates were evaporated to dryness under reduced pressure and the residue chromatographed (20% ether–petrol) to give the sulfone **3** (195 mg, 95%) as a colourless solid, mp 117-118°C (petrol) (lit.,[4(ii)] 116.5-118°C); $[\alpha]_D^{20}$ +0.76 (*c* 1.32, $CHCl_3$) (lit.,[4(ii)] $[\alpha]_D^{20}$ +0.06 (*c* 0.2, $CHCl_3$)); υ_{max} (CH_2Cl_2) 2951, 2319, 1446, 1383, 1306, 1283, 1141, 1085, 790, 756, 689 cm^{-1}; δ_H (500 MHz) 7.86 (2H, m, ortho Ph), 7.65-7.61 (1H, m, para Ph), 7.56-7.53 (2H, m, meta Ph), 3.03 (1H, td, J 12.0, 3.5 Hz, H-5), 2.09-2.01 (1H, m) and 1.96-1.84 (3H, m, H-4, H-6), 1.65-0.95 (17H, m, H-2, H-3, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.89 (3H, d, J 6.5 Hz, H-1'), 0.86 and 0.85 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'), 0.69 (3H, s, C-1 Me); δ_C (500 MHz) 138.5 (quarternary C on Ph), 133.4 (ortho C on Ph), 129.0 (para C on Ph), 128.8 (meta C on Ph) , 63.9 (C-5), 55.2 (CH), 48.2 (CH), 44.7 (C-1), 39.5 (CH_2), 38.2 (CH_2), 26.2 (CH_2), 35.6 (CH), 28.0 (CH), 27.9 (CH_2), 27.4 (CH_2), 25.4 (CH_2), 23.8 (CH_2), 22.8 (Me), 22.6 (Me), 21.2 (CH), 18.8 (Me), 11.9 (Me); *m/z* (EI) 390 (M^+), 288 (M^+-H_2), 347 (M^+-C_3H_7), 277 (M^+-C_8H_{17}), 249 (M^+-$PhSO_2$), 77 (Ph^+), 43 ($C_3H_7^+$).

Preparation of (+)-[2'*R*,6*R*,7*R*]-6-methyl-7-(6-methylhept-2-yl)-2-(phenylsulfonyl)bicyclo-[4.3.0]-1-nonene (26) from Windaus–Grundmann ketone.

To a stirred solution of Windaus–Grundmann ketone **20** (1.23 g, 4.67 mmol) in CH_2Cl_2 (18.7 ml) at 0°C was added thiophenol (4.8 ml, 46.7 mmol, 10 eq) followed by $BF_3{\cdot}H_2O$ (0.554 ml, 5.6 mmol 1.2 eq). The mixture was stirred for 6 h when tlc indicated complete consumption of starting material. The mixture was poured into water (25 ml) and the aqueous layer extracted with CH_2Cl_2 (3 x 25 ml). The combined organic extracts were washed with NaOH (3 x 25 ml of a 1M solution), water (3 x 25 ml) and dried ($MgSO_4$). Concentration under reduced pressure gave the crude product. A small sample of the *sulfide* **25** was chromatographed (petrol): $[\alpha]_D^{20}$ +15.2 (*c* 0.75, $CHCl_3$); υ_{max} (film) 3067, 2928, 1941, 1648, 1583, 1474, 1371, 1334, 1205, 1171, 1087, 1025, 983, 860, 811, 739, 693 cm^{-1}; δ_H (500 MHz) 7.40-7.05 (5H, m, Ph), 2.63-2.54 (1H, m), 2.43-2.34 (1H, m) and 2.14-2.06 (2H, m, all comprising H-3, H-9), 2.01 (1H, dt, J 13.0, 3.5 Hz) and 1.90-1.05 (14H, m, all comprising H-4, H-5, H-7, H-8, H-2', H-3', H-4', H-5', H-6'), 0.98 (3H, s, C-6 Me), 0.96 (3H, d, J 6.5 Hz, H-1'), 0.88 and 0.87 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'); *m/z* (EI) 356 (M^+), 341 (M^+-Me), 279 (M^+-Ph), 247 (M^+-PhS), 243 (M^+-C_8H_{17}), 77 (Ph^+), 43 ($C_3H_7^+$) (Found: (M^+), 356.2538. $C_{24}H_{36}S$ requires (M^+), 356.2538). The crude sulfide was redissolved in CH_2Cl_2. NaOAc (421 mg, 5.14 mmol, 1.1 eq) was added and the mixture cooled to 0°C. Peracetic acid (3.24 ml of a 33% wt solution in AcOH, 14 mmol, 3 eq) was added dropwise and the mixture stirred at rt for 16 h when tlc indicated complete consumption of starting material. The mixture was poured into water (50 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with NaOH (3 x 60 ml of a 1M solution), water (3 x 60 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (20% ether–petrol) gave sulfone **26** (1.17 g, 65%) identical in all respects to the sample prepared previously.[3]

Preparation of (+)-[1*R*,2'*R*,5*R*,6*R*,9*R*]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)-bicyclo[4.3.0]nonane (3) from sulfone (26).

To a stirred solution of sulfone **26** (1.14 g, 2.94 mmol) in THF (19 ml) ar rt was added $LiAlH_4$ (2.94 ml of a 1M solution in THF, 2.94 mmol, 1 eq) dropwise. The resulting yellow solution was then heated at reflux

for 20 min to give a golden brown solution. After cooling to rt water (114 µl) was added dropwise, followed by NaOH (114 µl of a 3M solution) and finally water (342 µl). The resulting solution was stirred vigorously at rt for 20 min giving a white precipitate. The solution was filtered and the residue washed with ether until tlc indicated no more product to be present in the filtrate. The combined filtrates were concentrated and the residue chromatographed (10→20% ether–petrol) to give, in order of elution, 5-epi **3** (100 mg, 9%) as a colourless solid, mp 250°C (dec.); $[\alpha]_D^{20}$ +21.5 (*c* 1.0, $CHCl_3$); υ_{max} (CH_2Cl_2) 2948, 2353, 2316, 1650, 1444, 1380, 1297, 1134, 1083, 742, 690 cm^{-1}; δ_H (500 MHz) 7.93-7.90 (2H, m, ortho Ph), 7.63-7.56 (1H, m, para Ph), 7.55-7.51 (2H, m, meta Ph), 3.42 (1H, br t, J 5.5 Hz, H-5), 2.35 (1H, m), 2.21-2.11 (1H, m) and 2.07 (1H, br dt, J 13.0, 3.5 Hz, all comprising H-4, H-6), 1.97 (1H, br d, J 15 Hz), 1.84-1.74 (2H, m), 1.71-1.64 (1H, m) and 1.58-1.00 (13H, m, all comprising H-2, H-3, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 1.13 (3H, s, C-1 Me), 0.92 (3H, d, J 6.5 Hz, H-1'), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, C-6' Me and H-7'); *m/z* (EI) 388 (M^+-H_2), 249 (M^+-$PhSO_2$), 141 ($PhSO_2^+$), 77 (Ph^+), 43 ($C_3H_7^+$) (Found: (M^+-H_2), 388.2461. $C_{24}H_{36}O_2S$ requires (M^+-H_2), 388.2436), followed by sulfone **3** (0.877 g, 76%) identical in all respects to the sample prepared as described above. To a stirred solution of 5-epi **3** (13.6 mg, 35.0 µmol) in THF (350 µl) at rt was added *t*-BuOH (132 µl, 1.4 mmol, 40 eq) followed by *t*-BuOK (140 µl of a 1M solution in THF, 0.14 mmol, 4 eq) to give a pale yellow solution. After stirring for 30 min saturated aqueous ammonium chloride (5 ml) was added and the aqueous layer was extracted with ether (3 x 5 ml). The combined organic extracts were washed with water (3 x 5 ml), brine (3 x 5 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (20% ether–petrol) gave further sulfone **3** (13 mg, 9%; total yield 85%).

Preparation of (+)-[3'*R*,4*R*,5*S*]-4-methyl-3-(1-oxo-3,7-dimethyloctyl)-5-phenyl-1,3-oxazolidin-2-one (27).

(+)-[*R*]-Dihydrocitronellic acid **9**[21] (25 ml, 22.4 g, 130 mmol, 1 eq) was heated at reflux with thionyl chloride (14.2 ml, 23.2 g, 195 mmol, 1.5 eq) under argon for 45 min. Excess thionyl chloride was removed by distillation at atmospheric pressure and the resultant oil distilled at reduced pressure to give dihydrocitronellyl chloride as a pungent, citrus-flavoured oil, $bp_{0.1}$ 45-46°C, υ_{max} (film) inter alia 1808 cm^{-1}. To a stirred solution of [4*R*,5*S*]-4-methyl-5-phenyl-1,3-oxazolidin-2-one[31] (23.0 g, 130 mmol) in dry THF (430 ml) at -78°C was added, dropwise via syringe *n*-BuLi (56.4 ml of a 2.3 M solution in hexanes, 130 mmol 1.0 eq) giving a blood-red anion. To this mixture was added a solution of the freshly prepared dihydrocitronellyl chloride in THF (50 ml) and the reaction was allowed slowly to warm to rt, giving a pale yellow solution. The reaction was quenched by the addition of saturated aqueous ammonium chloride (100 ml). The aqueous phase was extracted with ether (3 x 200 ml) and the combined organic layers washed with 1M aqueous sodium hydroxide (2 x 100 ml), water (3 x 200 ml), brine (200 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale solid. This was dissolved in benzene (100 ml) and filtered through a 2" pad of silica gel, eluting with 20% ether–petrol until no more material could be detected in the filtrate by tlc (40% ether–petrol). The solvents were removed to give a colourless solid which was recrystallised to give *(+)-[3'R,4R,5S]-4-methyl-3-(1-oxo-3,7-dimethyloctane)-5-phenyl-2-oxazolidinone* **27** (30.51 g, 71%) as large plates, mp 90-93°C (EtOH); $[\alpha]_D^{20}$ +37.7 (*c* 1.03, $CHCl_3$); υ_{max} (film) 3038, 2959, 1781, 1701, 1457, 1348, 1226, 1200, 792, 775, 765, 744 cm^{-1}; δ_H (500 MHz) 7.44-7.35 (5H, m, Ph), 5.66 (1H, d, J 7.5 Hz, H-5), 4.78 (1H, quintet, J 7.0 Hz, H-4), 2.99 (1H, dd, J 16.0, 5.5 Hz, H-2'), 2.70 (1H, dd, J 16.0, 8.5 Hz, H-2'), 2.08 (1H, m, H-3'), 1.53 (1H, septet, J 6.5 Hz, H-7'), 1.36-1.10 (6H, m, H-4', H-5', H-6'), 0.97 (3H, d, J 6.5 Hz, C-4 Me), 0.89, 0.87 and 0.86 (all 3H, d, J 6.5 Hz, C-3' Me, C-7' Me, H-8'); *m/z* (EI) 332 (MH^+), 316, 288, 272, 268, 246, 219, 202, 178, 160, 134, 118, 107, 71, 57, 43 (Found: C, 72.20; H, 8.90; N, 4.10. $C_{20}H_{29}NO_3$ requires C, 72.47; H, 8.82; N, 4.23%).

Preparation of (+)-[2'*R*,3'*R*,4*R*,5*S*]-4-methyl-3-[1-oxo-2-(2-propenyl)-3,7-dimethyloctyl]-5-phenyl-1,3-oxazolidin-2-one (28).

To a stirred solution of oxazolidinone **27** (20.04 g, 60.5 mmol) in THF (200 ml) at -78°C under argon was added NaHMDS (66.5 ml of a 1M solution in THF, 66.5 mmol, 1.1 eq). After 30 min freshly distilled allyl bromide (21 ml, 242 mmol, 4.0 eq) was added via syringe. The reaction was allowed to warm to -50°C during 5 h and then stirred at this temperature for 12 h. After this period of time tlc (20% ether–petrol) indicated complete consumption of the starting material, so the reaction was allowed to warm to 0°C during a further 3 h, whereupon it was quenched by the addition of saturated aqueous ammonium chloride (150 ml). The organic layers were separated and the aqueous phase extracted with ether (3 x 100 ml). The combined organic extracts were washed with 0.5M hydrochloric acid (3 x 100 ml), water (3 x 100 ml), brine (100 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (5%→8%→15%→25% ether–petrol) to give the *oxazolidinone* **28** (19.62 g, 87%) as a colourless syrup containing <5% of the [2'*S*,3'*R*,4*R*,5*S*] diastereoisomer by ^1H nmr; $[\alpha]_D^{20}$ +12.5 (*c* 1.99, $CHCl_3$); υ_{max} (film) 3068, 2958, 1789, 1697, 1643, 1457, 1345, 1193, 1148, 1120, 1090, 1068, 1032, 993, 916, 887, 768, 722, 700, 638; δ_H (500 MHz) 7.43-7.28 (5H, m, Ph), 5.78 (1H, m, H-2''), 5.61 (1H, d, J 7.0 Hz, H-5), 5.03 (1H, ddd, J 17.0, 1.5, 1.5 Hz, H-3''$_{trans}$), 4.95 (1H, dd with fine structure, J 10.5, 1.5 Hz, H-3''$_{cis}$), 4.79 (1H, quintet, J 6.5 Hz, H-4), 3.94 (1H, ddd, J 10.0, 7.0, 4.5 Hz, H-2'), 2.25 (2H, m, H-1''), 1.82 (1H, m, H-3'), 1.53 (1H, septet, J 6.5 Hz, H-7'), 1.48 (1H, m, H-4'), 1.38 (1H, m, H-4'), 1.26-1.10 (4H, m, H-5', H-6'), 0.97 (3H, d, J 7.0 Hz, C-3' Me), 0.88 and 0.87 (both 3H, d, J 6.5 Hz, C-7' Me and H-8'), 0.85 (3H, d, J 6.5 Hz, C-4 Me); *m/z* (EI) 371 (M^+), 356 (M^+-Me), 330, 286, 259, 194 (M^+-$C_9H_{10}NO_2$), 178, 134, 118, 109, 81, 69, 55, 41 (Found: C, 74.0; H, 9.0; N, 3.74. $C_{23}H_{33}NO_3$ requires C, 74.36; H, 8.95; N, 3.77%) (Found: (M^+), 371.2460. $C_{23}H_{33}NO_3$ requires (M^+), 371.2460). Nmr data for the [2'*S*,3'*R*,4*R*,5*S*] diastereoisomer: δ_H (500 MHz) inter alia 7.25-7.15 (5H, m, Ph), 5.08 (1H, ddd, J 17.0, 2.0, 1.5 Hz, H-3''$_{trans}$), 4.98 (1H, m, H-3''$_{cis}$), 3.87 (1H, ddd, J 10, 6.0, 3.5 Hz, H-2'), 2.25 (2H, m, H-1''), 1.90 (1H, m, H-3'), 0.90 (3H, d, J 7.0 Hz, Me).

Preparation of (-)-[2*R*,3*R*]-3,7-dimethyl-2-(2-propenyl)octanoic acid (29).

To a solution of oxazolidinone **28** (15.22 g, 0.041 mol) in a mixture of THF (614 mol) and water (215 ml) at 0°C was added H_2O_2 (33.6 ml, 0.328 mmol, 8 eq) followed by LiOH (3.44 g, 0.082 mmol, 2 eq). The reaction mixture was stirred at 10°C for 15 h. After cooling to 0°C the reaction was quenched with saturated aqueous Na_2SO_3 (240 ml of a 1.5M solution, 0.361 mmol, 8.8 eq) and allowed to warm to rt. The aqueous layer was acidified to pH 1 and extracted with CH_2Cl_2 (3 x 800 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an oily solid. This solid was dissolved in CH_2Cl_2 (300 ml) and shaken with NaOH (0.985 g in 300 ml of H_2O, 0.041 mmol, 1 eq). The aqueous layer was extracted with CH_2Cl_2 (3 x 300 ml) and the combined organic layers dried ($MgSO_4$). Concentration under reduced pressure gave a white solid which was recrystallised (CH_2Cl_2–ether–petrol) to give recovered [4*R*,5*S*]-4-methyl-5-phenyl-1,3-oxazolidin-2-one as colourless crystals (1st crop: 4.25 g; 2nd crop: 2.22 g; total recovered yield: 89%). The aqueous layer was reacidified with HCl (100 ml of a 2M solution), extracted with CH_2Cl_2 (3 x 400 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (25% ether–petrol) gave the *acid* **29** (7.9 g, 91%) as a colourless oil; $[\alpha]_D^{19}$ -1.15 (*c* 1.0, $CHCl_3$); υ_{max} (film) 3067, 2954, 2868, 1706, 1639, 1463, 1439, 1380, 1365, 1284, 1244, 1211, 1169, 993, 915, 828, 730, 643 cm^{-1}; δ_H (500 MHz) 5.77 (1H, m, H-2'), 5.08 (1H, d with additional fine structure, J 16.5 Hz, H-3'$_{trans}$), 5.02 (1H, d with additional fine structure, J 10 Hz, H-3'$_{cis}$), 2.45-2.35 (2H, m, H-1'), 2.32-2.22 (1H, m, H-2), 1.58-1.57 (1H, m, H-3), 1.52 (1H, septet, J 6.5 Hz, H-7), 1.5-1.12 (6H, m, H-4, H-5, H-6), 0.95 (3H, d, J 7.0 Hz, C-3 Me), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, C-7 Me and H-8); *m/z* (EI) 213 (MH^+), 194 (M^+-H_2O), 171 (M^+-C_3H_5), 99 (M^+-C_8H_{17}), 45 (CO_2H^+), 43 ($C_3H_7^+$), 41 ($C_3H_5^+$) (Found: C, 73.42; H, 11.60. $C_{13}H_{24}O_2$ requires C, 73.53; H, 11.39%).

Preparation of (+)-[2*R*,3*R*]-3,7-dimethyl-2-(2-propenyl)octanol (30).

To a stirred suspension of $LiAlH_4$ (3 g, 0.0179 mol, 2 eq hydride) in ether (90 ml) at 0°C was added a solution of acid **29** (7.6 g, 0.0357 mol), in ether (90 ml) dropwise. The mixture was stirred at rt for 3 h and then cooled to 0°C. Water (3 ml) was added dropwise followed by NaOH (3 ml of a 3M aqueous solution) and finally water (7.5 ml). The resulting mixture was stirred vigorously at rt for 20 min, the resulting granular white solid removed by filtration, and the residue washed with ether until tlc indicated no more product to be present in the filtrate. The combined filtrates were concentrated and the resultant oil chromatographed (25% ether–petrol) to give the *alcohol* **30** (7.19 g, 99%) as a colourless oil; $[\alpha]_D^{19}$ +9.8 (*c* 1.06, $CHCl_3$); υ_{max} (film) 3337, 3067, 2955, 2927, 1823, 1639, 1463, 1382, 1366, 1209, 1169, 1132, 1037, 993, 910, 734 cm^{-1}; δ_H (500 MHz) 5.84 (1H, m, H-2'), 5.10-4.99 (2H, m, H-3'), 3.68-3.52 (2H, m, H-1), 2.13 (2H, br dd, J 7.0, 1.5 Hz, H-1'), 1.65-1.50 (2H, m, H-2, H-7), 1.37-1.10 (7H, m, H-3, H-4, H-5, H-6), 0.87 (6H, d, J 6.5 Hz, C-7 Me and H-8), 0.86 (3H, d, J 6.5 Hz, C-3 Me); *m/z* (EI) 198 (M^+), 180 (M^+-H_2O), 57 ($C_4H_9^+$), 43 ($C_3H_7^+$) (Found: ($M+NH_4^+$), 216.2330. $C_{13}H_{26}O$ requires ($M+NH_4^+$), 216.2327).

Preparation of (+)-[4*R*,5*R*]-4-(benzyloxymethyl)-5,9-dimethyl-1-decene.

To a stirred suspension of NaH (1.72 g of a 60% dispersion in mineral oil, 1.2 eq) washed with dry petrol (3 x 50 ml) in DMF (60 ml) at 0°C was added a solution of the alcohol **30** (7.09 g, 0.036 mol) in DMF (50 ml + 10 ml rinse) dropwise. Effervesence was observed and after stirring for 30 min BnBr (4.26 ml, 1 eq) was added dropwise. After stirring at rt for 3 h tlc indicated complete consumption of starting material. The mixture was added to an ether/H_2O bilayer (300 ml of each) and the aqueous layer extracted with ether (3 x 300 ml). The combined organic layers were washed with saturated aqueous ammonium chloride (3 x 300 ml), water (3 x 300 ml), brine (3 x 300 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (10→50% ether–petrol) gave the *ether* (8.96 g, 84%) as a colourless oil; $[\alpha]_D^{19}$ +5.4 (*c* 1.1, $CHCl_3$); υ_{max} (film) 3064, 3027, 2952, 2923, 2864, 1637, 1493, 1451, 1411, 1388, 1363, 1306, 1253, 1204, 1100, 1028, 993, 910, 734, 697, cm^{-1}; δ_H (500 MHz) 7.40-7.27 (5H, Ph), 5.78 (1H, m, H-2), 5.04-4.95 (2H, m, H-1), 4.49 and 4.46 (both 1H, AB quartet, J 12.0 Hz, PhCH_2), 3.45 (1H, dd, J 9.5, 5.5 Hz, H-1'), 3.33 (1H, dd, J 9.5, 6.5 Hz, H-1'), 2.20-2.04 (2H, m, H-3), 1.51 (1H, septet, J 6.5 Hz, H-9), 1.71-1.61 (2H, m) and 1.35-1.06 (6H, m, H-4, H-5, H-6, H-7, H-8), 0.87 (6H, d, J 6.5 Hz, C-9 Me and H-10), 0.86 (3H, d, J 7.0 Hz, C-5 Me); *m/z* (EI) 288 (M^+), 197 (M^+-C_7H_7), 180 (M^+-C_7H_7OH), 175 (M^+-C_8H_{17}), 118 ($C_7H_7OCH_2^+$), 107 ($C_7H_7O^+$), 91 ($C_7H_7^+$), 43 ($C_3H_7^+$) (Found: C, 83.01; H, 10.95. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%).

Preparation of (+)-[4*R*,5*R*]-4-(benzyloxymethyl)-5,9-dimethyldecanol.

To a stirred solution of (+)-[4*R*,5*R*]-4-(benzyloxymethyl)-5,9-dimethyl-1-decene (9.52 g, 0.033 mol) in hexane (11 ml) at 0°C was added BH_3·DMS (1.09 ml, 0.011 mol, 0.33 eq). The mixture was stirred at room temperature for 3 h. Ethanol (11 ml) was added followed by aqueous NaOH (3.63 ml of a 3M solution) and the mixture was cooled to 0°C. Hydrogen peroxide (4.22 ml of a 30% aqueous solution, 0.037 mol, 1.12 eq) was added dropwise and after stirring for 10 min tlc indicated complete conversion. Water (300 ml) was added and the mixture extracted with ether (4 x 300 ml). The combined organic extracts were washed with water (3 x 300 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (10→50% ether–petrol) gave, in order of elution a 1:1 diastereomeric mixture of *[2R*,4R,5R]-4-(benzyloxymethyl)-5,9-dimethyldecan-2-ol* (451 mg, 4.5%) as a colourless oil; υ_{max} (film) 3412, 3030, 2958, 2353, 1603, 1459, 1367, 1206, 1096, 736, 698 cm^{-1}; δ_H (270 MHz) 7.38-7.27 (5H, m, Ph), 4.53 (2H, s) and 4.50 (2H, s, PhCH_2), 3.95-3.70 (2H, m, H-2), 3.60-3.34 (2H, m, H-1'), 2.94 (1H, br s, OH), 1.86-1.09 (11H, m, H-3, H-4, H-5, H-6, H-7, H-8, H-9), 1.18 (3H, d, J 6.5 Hz, H-1), 0.86 (6H, d, J 6.5 Hz, C-9 Me), 0.83 (3H, d, J 6.5 Hz) and 0.81 (3H, d, J 6.5 Hz, C-5 Me); *m/z* (EI) 306 (M^+), 288 (M^+-H_2O), 215 (M^+-C_7H_7), 197 (M^+-

C_7H_7-H_2O), 107 ($C_7H_7O^+$), 91 ($C_7H_7^+$), 43 ($C_3H_7^+$) (Found: (M^+), 306.2259. $C_{20}H_{34}O_2$ requires (M^+), 306.2259), followed by *(+)-[4*R*,5*R*]-4-(benzyloxymethyl)-5,9-dimethyldecanol* (10.68 g, 85%) as a colourless oil; $[\alpha]_D^{19}$ +3.1 (*c* 1.0, $CHCl_3$); υ_{max} (film) 3343, 3061, 3027, 2950, 2926, 2864, 1603, 1493, 1451, 1380, 1363, 1204, 1098, 1072, 1028, 907, 734, 697 cm^{-1}; δ_H (500 MHz) 7.35-7.20 (5H, m, Ph), 4.48 (2H, s, PhC*H*$_2$), 3.63 (2H, t, J 6.5 Hz, H-1), 3.45 (1H, dd, J 9.5, 5.0 Hz, H-1'), 3.32 (1H, dd, J 9.5, 6.5 Hz, H-1'), 1.65-1.05 (13H, m, H-2, H-3, H-4, H-5, H-6, H-7, H-8, H-9), 0.77 (6H, d, J 7.0 Hz, H-10 and C-9 Me), 0.73 (3H, d, J 7.0 Hz, C-5 Me); *m/z* (EI) 306 (M^+), 215 (M^+-C_7H_7), 197 (M^+-C_7H_7-H_2O), 107 ($C_7H_7O^+$), 91 ($C_7H_7^+$), 43 ($C_3H_7^+$) (Found: C, 78.13; H, 10.92. $C_{20}H_{34}O_2$ requires C, 78.37; H, 11.18%).

Preparation of (+)-[4*R*,5*R*]-4-(benzyloxymethyl)-1-(*tert*-butyldimethylsilyloxy)-5,9-dimethyldecane.

To a stirred solution of (+)-[4*R*,5*R*]-4-(benzyloxymethyl)-5,9-dimethyldecanol (8.26 g, 0.027 mol) in CH_2Cl_2 (54 ml) at 0°C was added a mixture of TBDMSCl (4.47 g, 0.030 mol, 1.1 eq) and DMAP (165 mg, 1.5 mmol, 5 mol %) in CH_2Cl_2 (27 ml). The mixture was stirred for 1 h at rt when tlc indicated complete consumption of starting material. Saturated aqueous ammonium chloride (200 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 ml). The combined organic extracts were washed with water (3 x 250 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (1→5% ether–petrol) gave the *silyl ether* (11.03 g, 97%) as a colourless oil; $[\alpha]_D^{19}$ +4.9 (*c* 1.09, $CHCl_3$); υ_{max} (film) 2951, 2926, 2855, 1493, 1460, 1382, 1360, 1253, 1203, 1099, 1028, 1005, 938, 836, 813, 775, 733, 697, 661 cm^{-1}; δ_H (500 MHz) 7.33-7.31 (5H, m, Ph), 4.49 and 4.46 (2H, AB quartet, J 12.0 Hz, PhC*H*$_2$), 3.64-3.56 (2H, m, H-1), 3.44 (1H, dd, J 9.5, 5.5 Hz, H-1'), 3.31 (1H, dd, J 9.5, 6.5 Hz, H-1'), 1.65-1.00 (13H, m, H-2, H-3, H-4, H-5, H-6, H-7, H-8, H-9), 0.89 (9H, s, *t*-Bu), 0.85 (6H, d, J 7.0 Hz, C-9 Me), 0.82 (3H, s, J 7 Hz, C-5 Me), 0.05 (6H, s, *t*-BuSi*Me*$_2$); *m/z* (EI) 420 (M^+), 329 (M^+-C_7H_7), 288 (M^+-TBDMSOH), 91 ($C_7H_7^+$), 57 (*t*-Bu) (Found: C, 73.94; H, 11.60. $C_{26}H_{48}O_2Si$ requires C, 74.22; H, 11.49%).

Preparation of (+)-[2*R*,3*R*]-2-[3-(*tert*-butyldimethylsilyloxy)propyl]-3,7-dimethyloctanol.

To liquid ammonia (400 ml) was added a solution of (+)-[4*R*,5*R*]-4-(benzyloxymethyl)-1-(*tert*-butyldimethylsilyloxy)-5,9-dimethyldecane (10.9 g, 0.033 mol) in ether (20 ml). Freshly cut sodium was then added with stirring until the solution remained dark blue during 1.5 h. Solid ammonium chloride was then added until effervescence ceased. Ether (200 ml) was added and the ammonia was allowed to evaporate. Water (300 ml) was then added and the aqueous layer was extracted with ether (3 x 300 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride (3 x 300 ml), water (3 x 300 ml), brine (3 x 300 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (10→50% ether–petrol) gave the *alcohol* (7.4 g, 86%) as a colourless oil; $[\alpha]_D^{19}$ +6.1 (*c* 1.07, $CHCl_3$); υ_{max} (film) 3344, 2951, 2927, 2857, 2735, 1461, 1381, 1363, 1254, 1100, 1030, 938, 836, 813, 775, 712, 661 cm^{-1}; δ_H (500 MHz) 3.65-3.48 (4H, m, H-1, H-3'), 1.65-1.10 (13H, m, H-2, H-3, H-4, H-5, H-6, H-7, H-1', H-2'), 0.89 (9H, s, *t*-Bu), 0.92-0.85 (9H, m, H-8, C-3 Me, C-7 Me), 0.05 (6H, s, *t*-BuSi*Me*$_2$); *m/z* (EI) 273 (M^+-*t*-Bu), 255 (M^+-*t*-Bu-H_2O), 131 (TBDMSO$^+$), 115 (TBDMS$^+$), 57 (*t*-Bu), 43 ($C_3H_7^+$) (Found: C, 68.86; H, 12.85. $C_{19}H_{42}O_2Si$ requires C, 69.02; H, 12.80%).

Preparation of (-)-[2*R*,3*R*]-2-[3-(*tert*-butyldimethylsilyloxy)propyl]-3,7-dimethyloctanal (10).

To a stirred solution of oxalyl chloride (217 µl, 2.48 mmol, 2.2 eq), in CH_2Cl_2 (2 ml) at -60°C was added a solution of DMSO (176 µl, 2.48 mmol, 2.2 eq) in CH_2Cl_2 (2 ml) dropwise. After stirring for 15 min a solution of (+)-[2*R*,3*R*]-2-[3-(*tert*-butyldimethylsilyloxy)propyl]-3,7-dimethyloctanol (373 mg, 1.13 mmol) in CH_2Cl_2 (1.65 ml) was added dropwise and the mixture stirred at -60°C for 30 min. Triethylamine (0.693 ml,

4.97 mmol, 4.4 eq) was added dropwise to give a cloudy white solution. The mixture was stirred at -60°C for a further 10 min and then allowed to warm to rt. Saturated aqueous ammonium chloride was added (15 ml) and the aqueous layer was extracted with ether (3 x 15 ml). The combined organic extracts were washed with HCl (3 x 15 ml of a 0.5M solution), saturated aqueous sodium hydrogencarbonate solution (3 x 15 ml), water (3 x 15 ml), brine (3 x 15 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (1→5% ether–petrol) gave the *aldehyde* **10** (267 mg, 72%) as a colourless oil; $[\alpha]_D^{19}$ -9.9 (*c* 1.21, $CHCl_3$); υ_{max} (film) 2952, 2927, 2857, 2708, 1722, 1461, 1382, 1254, 1100, 1006, 937, 836, 776, 714, 660 cm^{-1}; δ_H (500 MHz) 9.64 (1H, d, J 3.5 Hz, H-1), 3.60 (2H, m, H-3'), 2.17 (1H, m, H-2), 1.83-1.80 (1H, m), 1.72-1.66 (1H, m) and 1.58-1.10 (10H, m, all comprising H-3, H-4, H-5, H-6, H-7, H-1', H-2'), 0.95 (3H, d, J 7.0 Hz, C-3 Me), 0.88 (9H, s, *t-Bu*$SiMe_2$), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, H-8 and C-7 Me), 0.04 (6H, s, *t*-BuSi*Me*$_2$), *m/z* (EI) 327 (M^+-H), 313 (M^+-Me), 271 (M^+-*t*-Bu), 197 (M^+-TBDMSO), 131 (TBDMSO$^+$), 57 (*t*-Bu$^+$) (Found: (M^++H_2O), 346.2903. $C_{19}H_{40}O_2Si$ requires (M^++H_2O), 346.2870).

Preparation of (+)-[2'*R*,3*R*]-3-(6-methylhept-2-yl)tetrahydro-2*H*-pyran-2-one (33).

To a stirred solution of alkene **28** (17.28 g, 46.51 mmol) in THF (230 ml) under argon at rt was added a solution of 9-BBN (186 ml of a 0.5M THF solution, 93.03 mmol, 2.0 eq). The reaction was allowed to stir for 5 hours at rt, after which time tlc (75% ether–petrol) indicated complete consumption of starting material. The solution was cooled to 0°C and quenched cautiously with aqueous sodium hydroxide (93 ml of a 1M solution, 93.0 mmol, 2.0 eq), maintaining the internal temperature below 10°C. Hydrogen peroxide (38 ml of a 30% w/v solution, 335 mmol, 7.2 eq) was added dropwise to the cloudy solution, maintaining the temperature below 20°C. The reaction was quenched after 45 min by the addition of 0.5M aqueous hydrochloric acid (ca. 250 ml) and the aqueous phase was extracted with ether (3 x 150 ml). The combined organic layers were washed with water (2 x 200 ml), saturated aqueous ammonium chloride (3 x 200 ml), water (2 x 100 ml), brine (200 ml), dried ($MgSO_4$) and concentrated under reduced pressure with ice-cooling to give a colourless oil. This was redissolved in 60% ether–petrol (100 ml) and the solution filtered through a pad of silica gel, rinsing with further 60% ether–petrol (750 ml). The solvents were removed under reduced pressure to give a ca. 1:1 mixture (by ^1H nmr) of the expected primary alcohol and the derived lactone **33** as a colourless oil (16 g). This was dissolved in THF (450 ml), and redistilled *tert*-butanol (88 ml, 930 mmol, 20 eq) was added via cannula. The mixture was cooled to 0°C and treated with potassium *tert*-butoxide (930 µl of a 1.0M solution in THF, 0.930 mmol, 2 mol%). After 20 min, tlc (50% ether–petrol; visualized using $KMnO_4$ spray) indicated complete lactonisation and the reaction was immediately quenched by the addition of 0.5M aqueous hydrochloric acid (10 ml). Water (250 ml) was added and the organic layers were separated. The aqueous phase was extracted with ether (3 x 150 ml) and the combined organic layers were washed with saturated aqueous ammonium chloride (3 x 200 ml), water (3 x 200 ml), brine (2 x 200 ml), dried ($MgSO_4$) and concentrated under reduced pressure with ice-cooling to give a near-colourless oil. Purification by chromatography (40%→60% ether–petrol) furnished *(+)-[2'R,3R]-3-(6-methylhept-2-yl)-2-oxotetrahydro-2H-pyran* **33** (7.11 g, 72% from **28**) as a colourless, mobile oil; $[\alpha]_D^{19}$ +48.0 (*c* 1.11, $CHCl_3$), 95% d.e. (500 MHz ^1H nmr). Material of greater than 98% d.e. had $[\alpha]_D^{19}$ +52.8 (*c* 1.15, $CHCl_3$); υ_{max} (film) 2956, 1737, 1464, 1383, 1271, 1153, 1085, 953 cm^{-1}; δ_H (500 MHz) 4.33 (1H, ddt, J 11.0, 5.0, 1.5 Hz, H-6_{eq}), 4.23 (1H, ddd, J 11.0, 9.0, 4.5 Hz, H-6_{ax}), 2.45 (1H, ddd, J 11.0, 7.0, 4.0 Hz, H-3), 2.18 (1H, m, H-2'), 1.95 (1H, ddd, J 12.5, 5.0, 1.5 Hz, H-4_{eq}), 1.92-1.80 (2H, m, H-4_{ax}, H-5_{ax}), 1.66-1.58 (1H, m, H-5_{eq}), 1.52 (1H, septet, J 6.5 Hz, H-6'), 1.38-1.30 and 1.25-1.08 (6H, m, all comprising H-3', H-4', H-5'), 0.96 (3H, d, J 7.0 Hz, H-1'), 0.86 and 0.85 (both 3H, d, J 6.5 Hz, H-7' and C-6' Me); *m/z* (EI) 213 (MH$^+$), 211 (M^+-H), 197 (M-Me$^+$), 141, 127, 100, ($C_5H_8O_2^+$), 84, 69, 55 (Found: (MH$^+$), 213.1855. $C_{13}H_{24}O_2$ requires (MH$^+$), 213.1855).

Preparation of (+)-[2*R,2'*R*,3*R*]-2-hydroxy-3-(6-methylhept-2-yl)tetrahydro-2*H*-pyran (34).**

To a stirred solution of lactone **33** (717 mg, 3.38 mmol) in toluene (30 ml) at -78°C under argon was added DIBAL-H (2.7 ml of a 1.5M solution in toluene, 4.05 mmol, 1.2 eq). The mixture was allowed to react for 20 min before it was quenched with aqueous THF (6 ml of a 10% v/v solution of water in THF, 34 mmol, 10 eq). The reaction was warmed to rt, then the pasty mixture was diluted with EtOAc (50 ml) and solid sodium hydrogencarbonate added. After stirring for 30 min the free-flowing solid was removed by filtration through a pad of Celite® and the filtrate was concentrated under reduced pressure to give a colourless oil. This residue was redissolved in 1:1 ether–petrol (25 ml) and filtered through a pad of silica gel, eluting with 50% ether–petrol (150 ml) to give, after removal of the solvents, *lactol* **34** (633 mg, 87%) as a colourless oil; $[\alpha]_D^{20}$ +8.5 (*c* 1.07, $CHCl_3$); υ_{max} (film) 3397, 2953, 1725 (weak), 1540, 1466, 1367, 1073, 981, 910 cm^{-1}; δ_H (500 MHz) 5.23 (1H, t, J 2.5 Hz, H-6 axial anomer), 4.63 (1H, t, J 6.5 Hz, H-6 equatorial anomer), 4.00-3.90 (2H, m, H-2 both anomers), 3.58-3.53 (1H, m, H-6 one anomer), 3.48-3.42 (1H, m, H-6 one anomer), 3.10 (1H, d, J 6.0 Hz, OH axial anomer), 2.62 (1H, dd, J 3.0, 1.0 Hz, OH equatorial anomer), 1.80-1.00 (13H, m, H-3, H-4, H-5, H-2', H-3', H-4', H-5', H-6'), 0.92 (3H, d, J 6.0 Hz, H-1' one anomer), 0.91 (3H, d, J 7.0 Hz, H-1' one anomer), 0.86 and 0.85 (both 6H, d, J 6.5 Hz, H-7', C-6' Me, both anomers); *m/z* (EI) 214 (M^+, weak), 196 (M^+-H_2O), 181 (M^+-H_2O-Me), 140, 111, 84, 70, 55, 43, 41; (CI) 215 (MH^+), 197 (MH^+-H_2O), 140, 129, 111, 84, 69 (Found: (MH^+), 215.2011. $C_{13}H_{26}O_2$ requires (MH^+), 215.2011).

Silylation of lactol (34).

To a stirred solution of triethylamine (1.51 ml, 10.84 mmol, 1.1 eq) and lactol **34** (2.11 g, 9.86 mmol) in CH_2Cl_2 (19.7 ml) at 0°C was added TBDMSOTf (2.5 ml, 1.08 mmol, 1.1 eq) dropwise. The mixture was stirred for 2 h when tlc indicated complete consumption of starting material. Saturated aqueous ammonium chloride was added (100 ml) and the aqueous layer was extracted with ether (3 x 100 ml). The combined organic extracts were washed with HCl (3 x 100 ml of a 0.1M solution), saturated aqueous sodium hydrogencarbonate (3 x 100 ml), water (3 x 100 ml), brine (3 x 100 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (2→10% ether–petrol) gave, in order of elution, *(+)-[2R*,2'R,3R]-2-(*tert*-butyldimethylsilyloxy)-3-(6-methylhept-2-yl)tetrahydro-2H-pyran* **37** (347 mg, 11%) as a colourless oil; $[\alpha]_D^{20}$ +27.7 (*c* 1.13, $CHCl_3$); υ_{max} (film) 2955, 2930, 2858, 2713, 1030, 1721, 1658, 1462, 1386, 1364, 1274, 1253, 1222, 1189, 1162, 1138, 1081, 1040, 1021, 1005, 995, 953, 939, 917, 882, 837, 779, 736, 670 cm^{-1}; δ_H (270 MHz) 4.59 (1H, d, J 5.5 Hz, H-1), 3.60 (1H, br t, J 5.5 Hz, H-6), 3.37 (1H, m, H-6), 2.02-1.07 (13H, m, H-3, H-4, H-5, H-2', H-3', H-4', H-5', H-6'), 0.98 (9H, s, *t-Bu*$SiMe_2$), 0.95 (3H, d, J 6.5 Hz, H-1'), 0.86 (6H, d, J 6.5 Hz, H-7' and C-6' Me), 0.12 and 0.09 (both 3H, s, *t*-Bu$SiMe_2$); *m/z* (EI) 328 (M^+), 313 (M^+-Me), 271 (M^+-*t*-Bu), 197 (M^+-TBDMSO), 131 (TBDMSO$^+$), 57 (*t*-Bu$^+$) (Found: (M^+), 328.2770. $C_{19}H_{40}O_2Si$ requires (M^+), 328.2787), followed by the aldehyde **10** (2.57 g, 79%) as a colourless oil, identical in all respects to the sample prepared previously.

Preparation of (+)-[3*R*,4*R*]-(*Z*)-3-[3-(*tert*-butyldimethylsilyloxy)propyl]-4,8-dimethyl-1-iodo-1-nonene.

To a stirred solution of iodomethyltriphenylphosphonium iodide (8.3 g, 15.7 mmol, 2 eq) in THF at rt was added NaHMDS (15.7 ml of a 1M solution in THF, 15.7 mmol, 2 eq) dropwise to give a deep red solution. The mixture was stirred at rt for 30 min and cooled to -78°C, whereupon a solution of aldehyde **10** (2.57 g, 7.83 mmol) in THF (13 ml + 13 ml rinse) was added. The mixture was stirred at -78°C for a further 10 min then allowed to warm to rt. Saturated aqueous ammonium chloride (100 ml) was added and the aqueous layer was extracted with petrol (3 x 100 ml). The combined organic extracts were washed with 5% sodium metabisulfite solution (3 x 100 ml), water (3 x 100 ml), brine (3 x 100 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (petrol) gave the *iodoalkene* (2.91 g, 82%) as a colourless

oil; $[\alpha]_D^{19}$ +1.55 (*c* 1.35, $CHCl_3$); υ_{max} (film) 2956, 1607, 1465, 1384, 1254, 1102, 1005, 938, 836, 776, 709, 662 cm^{-1}; δ_H (500 MHz) 6.25 (1H, d, J 7.5 Hz, H-1), 5.94 (1H, dd, J 10.0, 7.5 Hz, H-2), 3.64-3.57 (2H, m, H-3'), 2.42-2.35 (1H, m, H-3), 1.55-1.10 (12H, m, H-4, H-5, H-6, H-7, H-8, H-1', H-2'), 0.89 (9H, s, *t-Bu*Me_2Si), 0.87 (3 x 3H, overlapping d, J 6.5 Hz, H-9, C-4 Me, C-8 Me), 0.04 (6H, s, *t*-Bu*Me*$_2$Si); *m/z* (EI) 451 (M^+-H), 437 (M^+-Me), 395 (M^+-*t*-Bu), 57 (*t*-Bu^+), 43 ($C_3H_7^+$) (Found: (MH^+), 453.2050. $C_{20}H_{41}OSiI$ requires (MH^+), 453.2050.).

Preparation of (+)-[3*R*,4*R*]-3-[3-(*tert*-butyldimethylsilyloxy)propyl]-4,8-dimethyl-1-nonyne.

To a stirred solution of (+)-[3*R*,4*R*]-3-[3-(*tert*-butyldimethylsilyloxy)propyl]-4,8-dimethyl-1-iodo-1-nonene (2.91 g, 6.44 mmol) in THF (64 ml) at -78°C was added *t*-BuOK (12.9 ml of a 1M solution in THF, 12.9 mmol, 2 eq). After stirring at -78°C for 15 min the mixture was allowed to warm to rt. Saturated aqueous ammonium chloride (75 ml) was added and the aqueous layer extracted with petrol (3 x 75 ml). The combined organic extracts were washed alternately with water (3 x 100 ml) and brine (3 x 100 ml), and then dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (petrol) gave the *alkyne* (2.03 g, 97%) as a colourless oil; $[\alpha]_D^{19}$ +1.06 (*c* 0.93, $CHCl_3$); υ_{max} (film) 3311, 2956, 2112, 1714, 1465, 1385, 1254, 1102, 1004, 837, 776, 627 cm^{-1}; δ_H (500 MHz) 3.63 (2H, m, H-3'), 2.45-2.35 (1H, m, H-3), 2.01 (1H, d, J 2.5 Hz, H-1), 1.80-1.15 (12H, m, H-4, H-5, H-6, H-7, H-8, H-1', H-2'), 0.92 (3H, d, J 6.5 Hz, C-4 Me), 0.89 (9H, s, *t-Bu*Me_2Si), 0.86 (6H, d, J 6.5 Hz, H-9 and C-8 Me), 0.05 (6H, s, *t*-Bu*Me*$_2$Si); *m/z* (EI) 309 (M^+-Me), 267 (M^+-*t*-Bu), 57 (*t*-Bu^+), 43 ($C_3H_7^+$) (Found: C, 73.88; H, 12.51. $C_{20}H_{40}OSi$ requires C, 74.00; H, 12.41%).

Preparation of (-)-[4*R*,5*R*]-4-ethynyl-5,9-dimethyldecanol (7).

To a stirred solution of (+)-[3*R*,4*R*]-3-[3-(*tert*-butyldimethylsilyloxy)propyl]-4,8-dimethyl-1-nonyne (2.03 g, 6.17 mmol) in THF (13.16 ml) at rt was added TBAF (12.34 ml of a 1M solution in THF, 12.34 mmol, 2 eq) dropwise. After stirring for 1 h tlc indicated complete consumption of starting material. Saturated aqueous ammonium chloride was added (100 ml) and the aqueous layer was extracted with ether (3 x 100 ml). The combined organic extracts were washed with water (3 x 100 ml), brine (3 x 100 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (20→50% ether–petrol) gave the *alkynol* **7** (1.28 g, 98%) as a colourless oil; $[\alpha]_D^{19}$ -2.52 (*c* 1.15, $CHCl_3$); υ_{max} (film) 3308, 2930, 2110, 1709, 1463, 1382, 1234, 1170, 1058, 626 cm^{-1}; δ_H (500 MHz) 3.69 (2H, t, J 6.5 Hz, H-1), 2.37 (1H, ddd, J 10.0, 4.5, 2.5 Hz, H-4), 2.03 (1H, d, J 2.5 Hz, H-2'), 1.85-1.75 (1H, m, H-5), 1.70-1.36 (6H, m) and 1.35-1.10 (5H, m, all comprising H-2, H-3, H-6, H-7, H-8, H-9), 0.93 (3H, d, J 6.5 Hz, C-5 Me), 0.86 (6H, d, J 6.5 Hz, H-10 and C-9 Me); *m/z* (EI) 210 (M^+), 195 (M^+-Me), 192 (M^+-H_2O), 185 (M^+- C_2H), 167 (M^+-C_3H_7), 43 (C_3H_7) (Found: C, 79.82; H, 12.58. $C_{14}H_{26}O$ requires C, 79.93; H, 12.45%).

Preparation of [4*R*,5*R*]-(*E*)-4-(1-iodopropen-2-yl)-5,9-dimethyldecanol.

To a stirred solution of zirconocene dichloride (1.31 g, 4.5 mmol, 0.4 eq) in THF (16 ml) at rt was added trimethylaluminium (16.76 ml of a 2M solution in hexanes, 33.5 mmol, 3 eq) dropwise. The mixture was cooled to 0°C and a solution of alkynol **7** (2.35 g, 11.2 mmol) in dichloroethane was added. The mixture was allowed to warm to rt and stirred at rt for a further 16 h. The mixture was cooled to -30°C and a solution of iodine (3.12 g, 12.3 mmol, 1.1 eq) in THF (16 ml, dried over 4Å molecular sieves prior to addition) was added. After stirring for a further 15 min the mixture was allowed to warm to 0°C. Saturated aqueous K_2CO_3 (8 ml) was added dropwise. The resulting gelatinous mixture was diluted with EtOAc (300 ml) and stirred vigorously with solid sodium hydrogencarbonate for 20 min. The resultant solid was removed by filtration, washing with EtOAc until tlc indicated no more product to be present in the filtrate. Concentration under reduced pressure followed by chromatography (20→40% ether–petrol) gave the *iodoalkene* contaminated with

ca. 10 mol% [4*R*,5*R*]-5,9-dimethyl-4-(propen-2-yl)decanol (total yield 3.4 g, 88%) as a colourless oil. Data for the iodoalkene: υ_{max} (film) 3310, 2960, 2110, 1609, 1463, 1380, 1265, 1172, 1060, 774, 730, 627 cm^{-1}; δ_H (500 MHz) 5.83 (1H, d, J 1.0 Hz, H-1'), 3.64-3.57 (2H, m, H-1), 1.98 (1H, dt, J 11.0, 4.0 Hz, H-4), 1.67 (3H, d, J 1.0 Hz, C-5 Me), 1.65-1.08 (11H, m) and 1.05-0.80 (1H, m, all comprising H-2, H-3, H-5, H-6, H-7, H-8, H-9), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, H-10 and C-9 Me), 0.74 (3H, d, J 6.5 Hz, C-5 Me); *m/z* (EI) 239 (M^+-C_8H_{17}), 225 (M^+-I), 221, 194, 141, 96, 81 (Found: (M^+-C_8H_{17}), 238.9933. $C_{15}H_{29}IO$ requires (M^+-C_8H_{17}), 238.9933).

Preparation of [4*R*,5*R*]-(*E*)-5,9-dimethyl-4-(1-methyl-1,3-butadienyl)decanol (39).

To a stirred solution of tetrakis(triphenylphosphine)palladium(0) (0.56 g, 0.49 mmol, 5 mol%) in toluene (15 ml) in darkness was added a solution of [4*R*,5*R*]-(*E*)-4-(1-iodopropen-2-yl)-5,9-dimethyldecanol (contaminated with 9% of [4*R*,5*R*]-5,9-dimethyl-4-(propen-2-yl)decanol) (3.45 g, 9.8 mmol) in toluene (68 ml + 15 ml rinse). After 20 min vinylmagnesium bromide (29.4 ml of a 1M solution in toluene, 29.4 mmol, 3 eq) was added dropwise. The reaction mixture was stirred for a further 50 min in the dark. Saturated aqueous ammonium chloride was added (150 ml) and the aqueous layer was extracted with ether (3 x 150 ml). The combined organic extracts were washed with water (3 x 150 ml), brine (3 x 150 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (25→40% ether–petrol) gave the *dienol* **39** contaminated with ca.15 mol% of [4*R*,5*R*]-5,9-dimethyl-4-(propen-2-yl)decanol (total yield 2.22 g, 90%) as a colourless oil. Data for the dienol: υ_{max} (film) 3318, 2954, 2931, 2869, 1466, 1381, 1366, 1061, 897, 658 cm^{-1}; δ_H (270 MHz) 6.59 (1H, dt, J 17.0, 10.5 Hz, H-3'), 5.81 (1H, d, J 10.5 Hz, H-2'), 5.09 (1H, dd, J 17.0, 2.0 Hz, H-4'$_{trans}$), 4.98 (1H, dd, J 10.5, 2.0 Hz, H-4'$_{cis}$), 3.68-3.55 (2H, m, H-1) 1.78-0.95 (13H, m, H-2, H-3, H-4, H-5, H-6, H-7, H-8, H-9), 1.62 (3H, s, C-1' Me), 0.87 (6H, d, J 6.5 Hz, H-10 and C-9 Me), 0.76 (3H, d, J 6.5 Hz, C-5 Me); *m/z* (EI) 252 (M^+), 234 (M^+-H_2O), 209 (M^+-C_3H_7), 184 (M^+-C_5H_8), 139 (M^+-C_8H_{17}), 43 ($C_3H_7^+$) (Found: (M^+), 252.2453. $C_{17}H_{32}O$ requires (M^+), 252.2453).

Preparation of [4*R*,5*R*]-(*E*)-5,9-dimethyl-4-(1-methyl-1,3-butadienyl)decanal.

To a stirred solution of oxalyl chloride (1.68 ml, 19.1 mmol, 2.2 eq) in CH_2Cl_2 (36.4 ml) at -60°C was added a solution of DMSO (2.72 ml, 38.28 mmol, 4.4 eq) in CH_2Cl_2 (36.4 ml) dropwise. After stirring for 15 min a solution of dienol **39** (contaminated with ca. 15 mol% of [4*R*,5*R*]-5,9-dimethyl-4-(propen-2-yl)decanol) (2.1 g, 1.13 mmol) in CH_2Cl_2 (30 ml + 6 ml rinse) was added dropwise and the mixture stirred at -60°C for 30 min. Triethylamine (6.69 ml, 47.8 mmol, 5.5 eq) was added dropwise to give a cloudy colourless mixture. The mixture was stirred at -60°C for a further 10 min and allowed to warm to rt. The reaction mixture was poured into an ether/H_2O bilayer (300 ml each) and the aqueous layer was extracted with ether (3 x 300 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride (3 x 15 ml), water (3 x 15 ml), brine (3 x 15 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (2→5% ether–petrol) gave *[4R,5R]-(E)-5,9-dimethyl-4-(1-methyl-1,3-butadienyl)decanal* contaminated with ca. 15 mol% of [4*R*,5*R*]-5,9-dimethyl-4-(propen-2-yl)decanal (total yield 1.7 g, 79%) as a colourless oil. Data for the dienal: υ_{max} (film) 3083, 3040, 2958, 2870, 2715, 1724, 1641, 1465, 1412, 1382, 1366, 1171, 988, 899, 735, 660 cm^{-1}; δ_H (500 MHz) 9.74 (1H, t, J 1.5 Hz, H-1), 6.56 (1H, dt, J 17.0, 10.5 Hz, H-3'), 5.80 (1H, d, J 10.5 Hz, H-2'), 5.10 (1H, dd, J 17.0, 2.0 Hz, H-4'$_{trans}$), 5.00 (1H, dd, J 10.5, 2.0 Hz, H-4'$_{cis}$), 2.35-2.25 (2H, m, H-2), 1.97-1.90 (1H, m, H-4), 1.76-1.78 (1H, m), 1.60-1.31 (6H, m) and 1.23 (3H, m, all comprising H-3, H-5, H-6, H-7, H-8, H-9), 1.60 (3H, s, C-1' Me), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, H-10 and C-9 Me), 0.76 (3H, d, J 6.5 Hz, C-5 Me); *m/z* (EI) 250 (M^+), 209 (M^+-C_3H_7), 137 (M^+-C_8H_{17}), 67 ($C_5H_7^+$).

Preparation of [2*R,5*R*,6*R*]-(*E*)-6,10-dimethyl-5-(1-methyl-1,3-butadienyl)-1-(phenylsulfonyl)-2-undecanol (42).**

To a stirred solution of (phenylsulfonyl)methane (1.14 g, 7.35 mmol, 1.1 eq) in THF (45 ml) at -78°C was added *n*-BuLi (2.94 ml of a 2.5M solution in hexanes, 7.35 mmol, 1.1 eq) dropwise giving a pale yellow solution. The mixture was stirred for 10 min at -78°C, whereupon a solution of [4*R*,5*R*]-(*E*)-5,9-dimethyl-4-(1-methyl-1,3-butadienyl)decanal (contaminated with 14 mol% of [4*R*,5*R*]-5,9-dimethyl-4-(propen-2-yl)decanal) (1.67 g, 6.68 mmol) in THF (15 ml + 7 ml rinse) was added dropwise. The mixture was allowed to stir at -78°C for a further 20 min when tlc indicated complete consumption of starting materials. Acetic acid (4.2 ml of a 1.75M solution in THF, 7.35 mmol, 1.1 eq) was added. The mixture was stirred at -78°C for a further 10 min and allowed to warm to rt. The reaction mixture was poured into a CH_2Cl_2/saturated aqueous sodium hydrogencarbonate bilayer (100 ml of each) and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with water (3 x 100 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (2→5% ether–petrol) gave *hydroxysulfones* **42** contaminated with ca. 15 mol% of [2*R**,5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)-2-undecanol (total yield 2.49 g, 90%) as a colourless oil. Data for the dienol: υ_{max} (film) 3521, 3067, 2954, 2869, 1640, 1586, 1447, 1382, 1305, 1147, 1085, 1024, 990, 898, 843, 789, 748, 720, 687 cm^{-1}; δ_H (500 MHz) 7.93 (2H, m, ortho Ph), 7.68-7.65 (1H, m, para Ph), 7.62-7.56 (2H, m meta Ph), 6.52 (1H, dt, J 17.0, 10.5 Hz, H-3'), 5.71 (1H, d, J 10.5 Hz, H-2'), 5.04 (1H, m, H-4'$_{trans}$), 4.96 (1H, m, H-4'$_{cis}$), 4.18-4.08 (1H, m, H-2), 3.32 (1H, m, OH), 3.20-3.18 (2H, m, H-1), 1.72-1.25, 1.22-1.05 and 1.00-0.90 (13H, m, all comprising H-3, H-4, H-5, H-6, H-7, H-8, H-9, H-10), 1.56 (3H, s, C-1' Me), 0.86 and 0.85 (both 3H, d, J 6.5 Hz, H-11 and C-10 Me), 0.76 and 0.70 (3H, d, J 6.5 Hz, C-6 Me); *m/z* (EI) 293 (M^+-C_8H_{17}), 247 (M^+-$PhSO_2$-H_2O), 141 ($PhSO_2^+$), 43 ($C_3H_7^+$) (Found: (M^+), 406.2542. $C_{24}H_{38}O_3S$ requires (M^+), 406.2542).

Preparation of [5*R*,6*R*]-(*E*,*E*)-6,10-dimethyl-5-(1-methyl-1,3-butadienyl)-1-(phenylsulfonyl)-1-undecene (5).

To a stirred solution of alcohols **42** (contaminated with ca. 15 mol% of [2*R**,5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)-2-undecanol) (718 mg, 1.77 mmol) in CH_2Cl_2 (17 ml) under argon at -6°C was added triethylamine (2.5 ml, 17.7 mmol, 10 eq) followed by methanesulfonyl chloride (344 µl, 5.3 mmol, 3 eq). After 30 min tlc (40% ether–petrol) indicated complete reaction and saturated aqueous sodium hydrogencarbonate (30 ml) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml) and the combined organic layers were washed with saturated aqueous ammonium chloride (3 x 10 ml), water (3 x 10 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography gave *[5R,6R]-(E,E)-6,10-dimethyl-5-(1-methyl-1,3-butadienyl)-1-(phenylsulfonyl)-1-undecene* **5** contaminated with ca. 15 mol% [5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(2-propenyl)undecene (total yield 454 mg, 66%) as a colourless oil. Data for the triene: υ_{max} (film) 2951, 2866, 1637, 1445, 1379, 1318, 1147, 1086, 987, 901, 816, 752, 715, 687 cm^{-1}; δ_H (500 MHz) 7.87 (2H, dd, J 7.0, 1.5 Hz, ortho protons on Ph), 7.65-7.50 (3H, m, meta and para protons on Ph), 6.96 (1H, ddd, J 14.0, 7.5, 6.5 Hz, H-2), 6.53 (1H, dt, J 17.0, 10.5 Hz, H-3'), 6.28 (1H, tt, J 15.0, 1.5 Hz, H-1), 5.68 (1H, d, J 11.0 Hz, H-2'), 5.01 (1H, dd, J 17.0, 2.0 Hz, H-4'$_{trans}$), 4.97 (1H, dd, J 10.0, 2.0 Hz, H-4'$_{cis}$), 2.22-2.10 (1H, m, H-3), 2.02 (1H, m, H-5), 1.74-1.62 (2H, m, H-3, H-6), 1.52 (1H, m, H-10), 1.48-1.28 (4H, m), 1.20-1.08 (3H, m) and 1.05-0.95 (1H, m, all comprising H-4, H-7, H-8, H-9), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, H-11, C-10 Me), 0.73 (3H, d, J 6.5 Hz, C-6 Me); *m/z* (EI) 388 (M^+), 373 (M^+-Me), 359, 345, 331, 321 (M^+-C_5H_7), 303, 276, 247, 218, 182, 135, 95 (Found: (M^+), 388.2436. $C_{24}H_{36}O_2S$ requires (M^+), 388.2436).

IMDA Reaction of triene (5).

A solution of a 3:1 mixture of triene **5** and diene **38** (azeotropically dried with toluene [2 x 10 ml]; 162 mg, 0.417 mmol) in dry toluene (10 ml) was degassed as previously described and transferred to a dry, argon-filled Carius tube via cannula. The tube was evacuated, cooled in liquid nitrogen, sealed using a flame and allowed to warm to rt behind a safety screen. The tube was then heated in a Carius oven at 240°C for 48 h. After cooling to rt, the tube was opened and the solvent removed under reduced pressure to give a pale yellow/brown oil. ^{1}H Nmr analysis of the crude mixture showed the presence of a 1:1 mixture of two major products, assigned as **40** and **41** (see Results and Discussion section) together with a third, unidentified compound. Chromatography (15%→20% ether-petrol) gave a 1:1 mixture of *[1S,2'R,5R,6R,9R]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]-2-nonene* **40** and *[1R,2'R,5S,6S,9R]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]-2-nonene* **41** (96 mg, 79% based on **5**) as a colourless oil; υ_{max} (film) 3043, 2955, 1539, 1508, 1466, 1446, 1385, 1306, 1144, 1086, 690 cm^{-1}; δ_H (500 MHz) both diastereoisomers: 7.88 (2H, m, ortho protons on Ph), 7.63 (1H, m, para protons on Ph), 7.55 (2H, m, meta protons on Ph); **40** inter alia: 5.80 (1H, ddd, J 10.0, 2.5, 1.5 Hz, H-2), 5.43 (1H, ddd, J 10.0, 5.5, 3.0 Hz, H-3), 3.12-3.03 (1H, m, H-5), 0.96 (3H, s, C-1 Me); **41** inter alia 5.71 (1H, dt, J 10.0, 2.0 Hz, H-2), 5.63 (1H, dt, J 10.5, 4.5 Hz, H-3), 3.16-3.00 (1H, m, H-5), 1.20 (3H, s, C-1 Me); both diastereoisomers, not assigned: 0.94 (3H, d, J 6.5 Hz, H-1'), 0.92 (3H, d, J 6.5 Hz, H-1'), 0.86 and 0.84 (both 3H, d, J 6.5 Hz, H-7' or C-6' Me), 0.84 (6H, d, J 6.5 Hz, C-6' Me or H-7', both isomers); *m/z* (EI) 388 (M^+), 362, 246, 220, 205, 135, 107, 93, 77 (Found: (M^++NH_4) 406.2780. $C_{24}H_{36}O_2S$ requires (M^++NH_4), 406.2780.

Hydrogenation of bicyclic sulfone (41).

To a flask containing 10% Pd(C) (2 mg) in EtOAc (0.5 ml) at rt was added a solution of the bicyclic sulfone **41** (5 mg, 12.88 μmol) in EtOAc (0.5 ml). The mixture was stirred vigorously under an atmosphere of H_2 for 16 h. The hydrogen was displaced with argon and the mixture filtered through a pad of Celite®, washing with EtOAc until tlc indicated no more product to be present in the filtrate. The combined filtrates were concentrated and the residue chromatographed (20% ether–petrol) to give the product assigned as *[1R,2'R,5S,6S,9R]-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]nonane* (5 mg, 99%) as a colourless oil; υ_{max} (film) 2954, 1728, 1588, 1449, 1380, 1303, 1144, 1086, 749, 690 cm^{-1}; δ_H (500 MHz) 7.85 (2H, m, ortho Ph), 7.66-7.60 (1H, m, para Ph), 7.57-7.52 (2H, m, meta Ph), 2.95 (1H, td with additional fine structure, J 11.0, 4.5 Hz, H-5), 2.12-2.03 (1H, m) and 1.97-1.74 (2H, m, all comprising H-4, H-6), 1.72-0.91 (17H, m, H-2, H-3, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 0.89 (6H, overlapping s and d, J 6.5 Hz, C-1 Me, H-1'), 0.86 and 0.85 (both 3H, d, J 6.5 Hz, H-7' and C-6' Me); *m/z* (EI) 249 (M^+-$PhSO_2$), 77 (Ph^+), 43 ($C_3H_7^+$) (Found: (M^+-$PhSO_2$), 249.2582. $C_{24}H_{38}O_2S$ requires (M^+-$PhSO_2$), 249.2582).

Preparation of [5*R*,6*R*]-(*E*)-6,10-dimethyl-5-(1-methyl-1,3-butadienyl)-1-(phenylsulfonyl)-undecan-2-one.

To a stirred slurry of PDC (1.35 g, 3.65 mmol, 1.5 eq) and powdered 4Å molecular sieves (4.86 g) in CH_2Cl_2 (16 ml) was added a solution of hydroxysulfones **42** (contaminated with ca. 15 mol% of [2*R**,5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)-2-undecanol) (0.987 g, 2.43 mmol) in CH_2Cl_2 (4 ml + 2 ml rinse). The dark brown reaction mixture was stirred for 4 h when tlc indicated complete consumption of starting material. The mixture was filtered through a 3-cm pad of silica gel, washing with EtOAc until tlc indicated no more product to be present in the filtrate. The combined filtrates were concentrated and the resulting brown oil chromatographed (30% ether–petrol) to give *[5R,6R]-(E)-6,10-dimethyl-5-(1-methyl-1,3-butadienyl)-1-(phenylsulfonyl)undecan-2-one* contaminated with ca. 18 mol% [5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)undecan-2-one (total yield 0.7 g, 71%) as a colourless oil. Data for the

dienone: υ_{max} (film) 3066, 2955, 1722, 1642, 1589, 1541, 1448, 1379, 1324, 1229, 1155, 1084, 993, 898, 735, 688 cm^{-1}; δ_H (500 MHz) 7.88 (2H, m, ortho Ph), 7.70-7.65 (1H, m, para Ph), 7.58-7.54 (2H, m meta Ph), 6.55 (1H, dt, J 17.0, 10.5 Hz, H-3'), 5.78 (1H, d, J 10.5 Hz, H-2'), 5.10 (1H, dd, J 17.0, 1.0 Hz, H-$4'_{trans}$), 4.96 (1H, dd, J 10.5, 1.0 Hz, H-$4'_{cis}$), 4.11 and 4.04 (both 1H, d, J 14.0 Hz, AB quartet, H-1), 2.53-2.49 (2H, m, H-3), 1.92-1.81 (1H, m), 1.73-1.64 (1H, m) and 1.59-0.98 (9H, m, all comprising H-4, H-5, H-6, H-7, H-8, H-9, H-10), 1.58 (3H, s, C-1' Me), 0.89 and 0.88 (both 3H, d, J 6.5 Hz, H-11 and C-10 Me), 0.75 (3H, d, J 6.5 Hz, C-6 Me); *m/z* (EI) 405 (MH^+), 291 (M^+-C_8H_{17}), 77 (Ph^+), 43 ($C_3H_7^+$) (Found: (MH^+), 405.2463. $C_{24}H_{36}O_3S$ requires (MH^+), 405.2463).

Preparation of [5*R*,6*R*]-(*E*)-6,10-dimethyl-5-(1-methyl-1,3-butadienyl)-1-(phenylsulfonyl)-1-undecyne (43).

To a stirred solution of [5*R*,6*R*]-(*E*)-6,10-dimethyl-5-(1-methyl-1,3-butadienyl)-1-(phenylsulfonyl)-undecan-2-one contaminated with ca. 18 mol% [5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)undecan-2-one (469 mg, 1.16 mmol) in CH_2Cl_2 (6 ml) at 0°C was added *N*,*N*-diisopropylethylamine (449 mg, 3.48 mmol, 3 eq) followed by triflic anhydride (327 mg, 1.16 mmol, 1 eq). The mixture was stirred at 0°C during 4 h, and then poured into saturated aqueous ammonium chloride (15 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 ml) and the combined organic layers washed with saturated aqueous ammonium chloride (2 x 15 ml), water (3 x 15 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography (15% ether–petrol) gave the *dienyne* **43** contaminated with ca. 20 mol% [5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)-1-undecyne (416 mg, 93%) as a colourless oil. Data for the dienyne: υ_{max} (film) 2956, 2200, 1640, 1447, 1381, 1332, 1164, 1091, 988, 901, 757, 728, 686, 639 cm^{-1}; δ_H (500 MHz) 8.00 (2H, m, ortho Ph), 7.68-7.65 (1H, m, para Ph), 7.59-7.55 (2H, m meta Ph), 6.52 (1H, dt, J 17.0, 10.5 Hz, H-3'), 5.72 (1H, d, J 10.5 Hz, H-2'), 5.06 (1H, dd, J 17.0, 2.0 Hz, H-$4'_{trans}$), 5.00 (1H, dd, J 10.5, 2.0 Hz, H-$4'_{cis}$), 2.31-2.24 (1H, m), 2.14 (1H, m), 1.85-1.76 (1H, m), 1.75-1.67 (1H, m) and 1.55-0.92 (9H, m, all comprising H-3, H-4, H-5, H-6, H-7, H-8, H-9, H-10), 1.56 (3H, s, C-1' Me), 0.88 and 0.87 (both 3H, d, J 6.5 Hz, H-11, C-10 Me), 0.73 (3H, d, J 6.5 Hz, C-6 Me) (Found: (M^+), 386.2280. $C_{24}H_{34}O_2S$ requires (M^+), 386.2279).

IMDA Reaction of (43).

A solution of dienyne **43** contaminated with ca. 20 mol% [5*R*,6*R*]-(*E*)-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)-1-undecyne (400 mg, 0.84 mmol) in toluene (15 ml) was degassed as described previously and transferred to a resealable Carius tube. The solution was heated at 115°C for 9 h. The solution was allowed to cool to rt, the tube opened and the mixture concentrated under reduced pressure to give a yellow oil. Chromatography (10% ether–petrol) gave, in order of elution, unchanged *(+)-[5*R*,6*R*]-6,10-dimethyl-1-(phenylsulfonyl)-5-(propen-2-yl)-1-undecyne* (60.7 mg, 76% based on ratio of starting materials) as a colourless oil; $[\alpha]_D^{25}$ +18.7 (*c* 1.0, $CHCl_3$); υ_{max} (film) 3069, 2955, 2201, 1644, 1585, 1448, 1378, 1330, 1309, 1164, 1091, 1049, 1024, 999, 896, 757, 729, 687, 638 cm^{-1}; δ_H (500 MHz) 8.00 (2H, m, ortho Ph), 7.68-7.65 (1H, m, para Ph), 7.58-7.55 (2H, m, meta Ph), 4.77 and 4.58 (both 1H, s, H-1'), 2.33 (1H, ddd, J 17.5, 8.0, 4.5 Hz) and 2.16 (1H, m, H-3), 1.82-1.70 (2H, m, H-4), 1.55 (3H, s, H-3'), 1.54-0.95 (9H, m, H-5, H-6, H-7, H-8, H-9, H-10), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, H-11 and C-10 Me), 0.76 (3H, d, J 6.5 Hz, C-6 Me); *m/z* (EI) 360 (M^+), 345 (M^+-Me), 317 (M^+-C_3H_7), 219 (M^+-$PhSO_2$), 218 (M^+-$PhSO_2H$), 77 (Ph^+), 43 ($C_3H_7^+$), 41 ($C_3H_5^+$) (Found: (M^+-$PhSO_2H$) 218.2034. $C_{22}H_{32}O_2S$ requires (M^+-$PhSO_2H$), 218.2034), followed by a mixture 3:1 of bicycles **46** and **45** (324 mg, 99% based on ratio of starting materials). These were separated by HPLC (Dynamax 60A column, 200 mm x 41.4 mm; mobile phase 5% 2-propanol–petrol) to give, in order of elution, *(+)-[2'*R*,6*R*,7*R*]-6-methyl-7-(6-methylhept-2-yl)-2-(phenylsulfonyl)bicyclo[4.3.0]-1,4-nonadiene* **46** (235.7 mg, 97% recovery) as a colourless oil; $[\alpha]_D^{20}$ +59.0 (*c* 0.31, $CHCl_3$); υ_{max} (film) 3054, 2954, 1717, 1663, 1630, 1586, 1448, 1368, 1312, 1226, 1151, 1109,

1087, 1026, 999, 975, 897, 788, 754, 714, 655 cm^{-1}; δ_H (500 MHz) 7.85 (2H, m, ortho Ph), 7.60-7.57 (1H, m, para Ph), 7.53-7.49 (2H, m meta Ph), 6.09 (1H, dd, J 9.5, 3.0 Hz, H-5), 5.67 (1H, ddd, J 9.5, 5.5, 2.0 Hz, H-4), 3.05-2.75 (4H, m, H-3, H-9), 2.04-1.97 (1H, m) and 1.60-1.06 (10H, m, H-7, H-8, H-2', H-3', H-4', H-5', H-6'), 1.03 (3H, d, J 6.0 Hz, H-1'), 0.94 (3H, s, C-6 Me), 0.87 and 0.86 (both 3H, d, J 6.5 Hz, H-7', C-6' Me); *m/z* (EI) 386 (M^+), 371 (M^+-Me), 273 (M^+-C_8H_{17}), 245 (M^+-$PhSO_2$), 141 ($PhSO_2^+$), 77 (Ph^+), 43 ($C_3H_7^+$) (Found: (M^+), 386.2280. $C_{24}H_{34}O_2S$ requires (M^+), 386.2279), followed by *(+)-[2'R,6S,7R]-6-methyl-7-(6-methylhept-2-yl)-2-(phenylsulfonyl)bicyclo[4.3.0]-1,4-nonadiene* **45** (74.5 mg, 92% recovery) as a colourless oil; $[\alpha]_D^{20}$ +80.6 (*c* 0.54, $CHCl_3$); υ_{max} (film) 3065, 2956, 2201, 1712, 1664, 1631, 1587, 1465, 1449, 1382, 1311, 1211, 1151, 1087, 1026, 977, 933, 859, 811, 752, 718, 689 cm^{-1}; δ_H (500 MHz) 7.85 (2H, m, ortho Ph), 7.58-7.52 (1H, m, para Ph), 7.51-7.48 (2H, m meta Ph), 5.82 (1H, dd, J 10.5, 2.5 Hz, H-5), 5.64 (1H, ddd, J 10.5, 4.5, 2.0 Hz, H-4), 3.04-2.75 (4H, m, H-3, H-9), 2.05-0.80 (11H, m, H-7, H-8, H-2', H-3', H-4', H-5', H-6'), 1.08 (3H, s, C-6 Me), 0.79, 0.76 and 0.73 (all 3H, d, J 6.5 Hz, H-1', H-7' and C-6' Me); *m/z* (EI) 384 (M^+-H_2), 273 (M^+-C_8H_{17}), 245 (M^+-$PhSO_2$), 141 ($PhSO_2^+$), 77 (Ph^+), 43 ($C_3H_7^+$) (Found: (M^+-$PhSO_2$), 245.2269. $C_{24}H_{34}O_2S$ requires (M^+-$PhSO_2$), 245.2269).

Preparation of (+)-[2'*R*,6*R*,7*R*]-6-methyl-7-(6-methylhept-2-yl)-2-(phenylsulfonyl)bicyclo-[4.3.0]-1-nonene.

A solution of sulfone **46** (18.2 mg, 47.1 μmol) in EtOAc (1 ml) was stirred vigorously with 10% Pd(C) (4.5 mg) under an atmosphere of H_2 for 16 h. The hydrogen was displaced with argon and the mixture filtered through a pad of Celite®, washing with EtOAc until tlc indicated no more product to be present in the filtrate. The combined filtrates were then evaporated to dryness under reduced pressure and the residue purified by chromatography (20% ether–petrol) to give sulfone **26** (18.1 mg, 99%) as a colourless oil, identical in all respects to the previously prepared sample.[3]

X-Ray crystal data[32]

All data were corrected for Lorentz and polarisation factors; the non-hydrogen atoms were refined anisotropically. Unless stated otherwise, the positions of all hydrogen atoms were idealised, C–H = 0.96Å, assigned isotropic thermal parameters, $U(H) = 1.2U_{eq}(C)$, and allowed to ride on their parent carbon atoms. All methyl groups were refined as rigid bodies. All computations were carried out using the SHELXTL programme system.[33]

Compound **3**: data were measured using a Siemens P4/PC diffractometer, using Cu-K_α radiation (λ = 1.54178 Å, graphite monochromator), using ω-scans, with $0° \leq 2\theta \leq 116°$. $C_{24}H_{38}O_2S$, M = 390.6, monoclinic, a = 8.033(5), b = 9.433(3), c = 15.941(7) Å, β = 104.29(4)°, V = 1171 $Å^3$, space group $P2_1$, Z = 2, D_c = 1.11 g cm^{-3}, μ(Cu-K_α) = 13.3 cm^{-1}, $F(000)$ = 428. 1752 Independent reflections were measured of which 1644 had $|F_o| > 4\sigma(|F_o|)$, and were considered to be observed. Refinement was by full-matrix least squares to give R = 0.049, R_w = 0.054 [$w^{-1} = \sigma^2(F) + 0.0005F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.25 and -0.26 $eÅ^{-3}$ respectively. The maximum and mean shift/error ratios in the final refinement cycle were 0.069 and 0.013 respectively. The absolute stereochemistry was confirmed by refinement of a free variable, η, which multiplies all f''. This parameter refined to a value of 1.2(2) provided definitive assignment.

Compound **18**: data were measured using a Siemens P4/PC diffractometer, using Cu-K_α radiation (λ = 1.54178 Å, graphite monochromator), using ω-scans, with $3° \leq 2\theta \leq 120°$. $C_{19}H_{28}O_2S$, M = 320.5, monoclinic, a = 10.676(2), b = 11.123(2), c = 14.923(4) Å, β = 100.22(2)°, V = 1744 $Å^3$, space group $P2_1/c$, Z = 4, D_c = 1.22 g cm^{-3}, μ(Cu-K_α) = 16.8 cm^{-1}, $F(000)$ = 696. 2589 Independent reflections were measured of which 2245 had $|F_o| > 4\sigma(|F_o|)$, and were considered to be observed. Refinement was by full-matrix least squares to give R = 0.043, R_w = 0.053 [$w^{-1} = \sigma^2(F) + 0.0005F^2$]. A face-indexed numerical absorption

correction was applied; the minimum and maximum transmissions were 0.6326 and 0.7831. The maximum and minimum residual electron densities in the final ΔF map were 0.25 and -0.22 $eÅ^{-3}$ respectively. The maximum and mean shift/error ratios in the final refinement cycle were 0.004 and 0.001 respectively.

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