Enantiospecific syntheses of pseudopterosin aglycones. Part 2. Synthesis of pseudopterosin K–L aglycone and pseudopterosin A–F aglycone *via* a B→BA→BAC annulation strategy

Philip J. Kocienski,*[a] Alessandro Pontiroli[b] and Liu Qun[c]

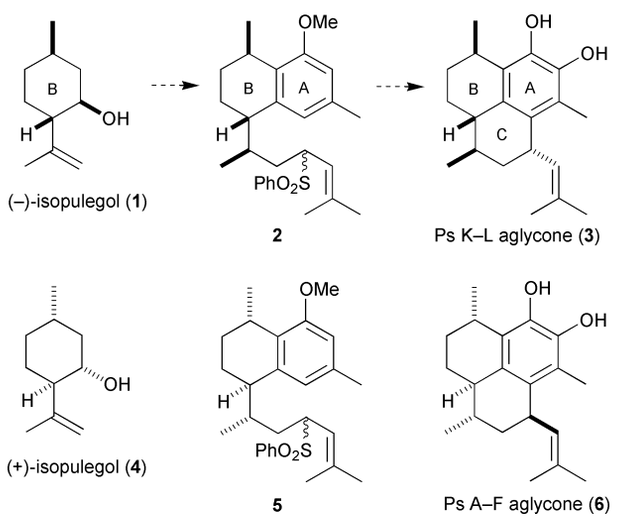
[a] *Department of Chemistry, Leeds University, Leeds, UK LS2 9JT*
[b] *Department of Chemistry, Glasgow University, Glasgow, UK G12 8QQ*
[c] *Department of Chemistry, Northeast Normal University, Changchun 130024, P. R. China*

Received (in Cambridge, UK) 2nd April 2001, Accepted 27th July 2001
First published as an Advance Article on the web 7th September 2001

The enantiomeric aglycones of pseudopterosins K–L and A–F are synthesised from (−)- and (+)-isopulegol respectively. Key features are (a) the construction of the C3 stereogenic centre by a directed epoxidation–reduction sequence (K–L); (b) the creation of the C3 stereogenic centre by a Pfaltz asymmetric conjugate reduction (A–F); (c) benzannulation of a cyclic ketone starting with an α-oxoketene-*S*,*S*-acetal to give a tetrahydronaphthol ether; and (d) a diastereoselective intramolecular electrophilic aromatic substitution using an allylic sulfone as the electrophilic trigger to complete the hexahydro-1*H*-phenalene core. An X-ray structure of compound **50** was determined.

Introduction

The pseudopterosins are a family of 12 diterpene glycosides whose aglycones are anti-inflammatory and analgesic.[1,2] The family comprises 3 sets based on the structure of the hexahydro-1*H*-phenalene core. In the preceding paper, we described a synthesis of the putative pseudopterosin G–J aglycone.[3] We now present complementary routes to the enantiomeric aglycones of pseudopterosins K–L (**3**, Scheme 1), the least



Scheme 1

abundant members of the family, and pseudopterosins A–F (**6**), the most abundant. The strategy we adopt (Scheme 1) is based on the annulation sequence B⟶BA⟶BAC beginning with the enantiomeric isopulegols **1** and **4**. The two routes share a number of key features including (a) the benzannulation chemistry whereby the aromatic ring A is appended to a monocyclic α-oxoketene-*S*,*S*-acetal intermediate and (b) the use of allylic sulfones **2** and **5** as the electrophilic trigger in the creation of ring C. The two routes differ primarily in the methods used to construct the stereogenic centre at C3.

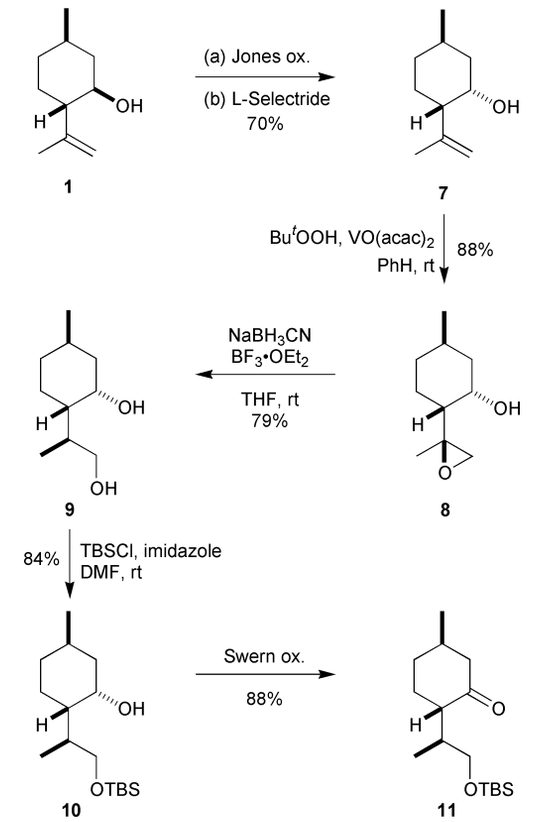
Results and discussion

Pseudopterosin K–L aglycone

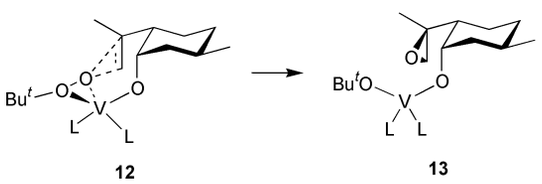
Construction of the C3 stereogenic centre. The principal attraction to the B⟶BA⟶BAC annulation strategy is the opportunity to use a cheap monoterpene for ring B which harbours two of the four stereogenic centres of the final target. A further enticement to begin with a monoterpene was the prospect of introducing a third stereogenic centre early in the synthesis. Schulte-Elte and Ohloff[4] had reported that (+)-neoisopulegol (**7**) undergoes diastereoselective hydroboration to give a mixture of diols (100%, dr 9 : 1) in favour of the diol **9** (Scheme 2) having the stereochemistry corresponding to C3, C4 and C6 of pseudopterosins K–L. (+)-Neoisopulegol was easily synthesised in 70% yield (dr ≥ 20 : 1) from technical grade isopulegol by Jones oxidation followed by stereoselective reduction with L-Selectride.[5] Unfortunately, in our hands the diastereoselectivity of the hydroboration was unfavourable (2.5 : 1 at best) despite extensive variations in time, temperature, solvent, order of addition and hydroborating agent. A further attempt at hydroboration of the corresponding methoxymethyl ether was likewise disappointing.[6]

We next investigated the possibility of introducing the C3 stereogenic centre by a sequence involving directed epoxidation followed by regioselective oxirane ring opening. Thus, treatment of (+)-neoisopulegol (**7**) with *tert*-butyl hydroperoxide in the presence of a catalytic amount of vanadyl bis(acetylacetonate)[7] returned the known[5] crystalline oxirane **8** in 88% yield. ^{1}H and ^{13}C NMR spectroscopic analysis of the crude product indicated >20 : 1 diastereoselectivity in the epoxidation in accord with a hydroxy-directed delivery of oxygen to the alkene as depicted in Scheme 3. The crucial reductive cleavage of the oxirane occurred with clean inversion of configuration by the procedure of Hutchins[8] involving addition of $BF_3{\cdot}OEt_2$ to a solution of the substrate, sodium cyanoborohydride and bromocresol green at a rate sufficient to maintain a yellow colour. The desired diol **9** was obtained as a single diastereoisomer in 79% yield. After protection of the primary hydroxy group as its TBS ether **10**, the secondary hydroxy group was oxidised to the ketone **11**.

 DOI: 10.1039/b102961b

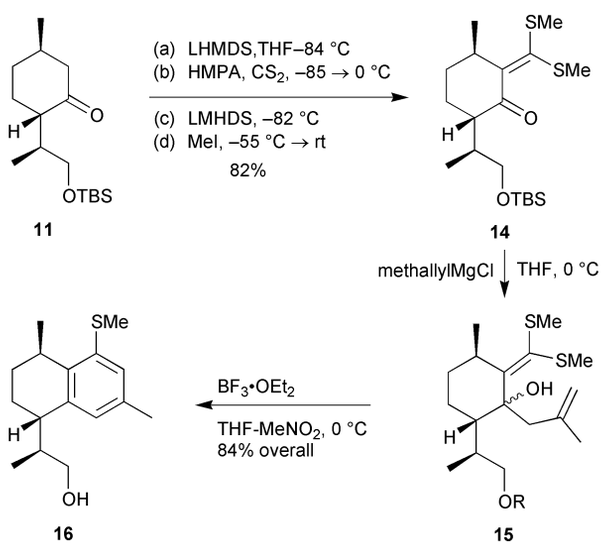


Scheme 2

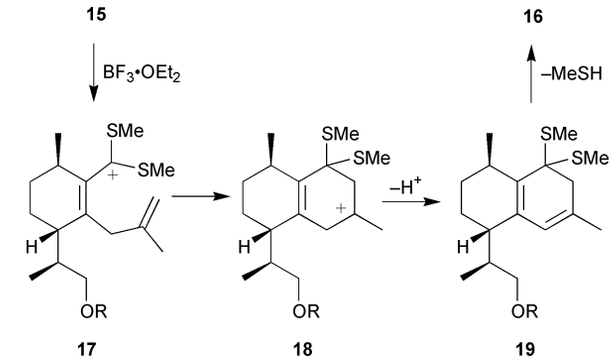


Scheme 3

Construction of the arene ring. In 1984 Dieter,[9] Junjappa and Ila[10] reported independently that 1,2-addition of methylallylmagnesium chloride to α-oxoketene-*S*,*S*-acetals followed by treatment of the carbinol with HBF_4 or a Lewis acid in THF leads to benzannulation reactions in good yield.[11,12] Application of the sequence to our ketone **11** (Scheme 4) gave the benzannulated product **16** in 69% overall yield. According to the



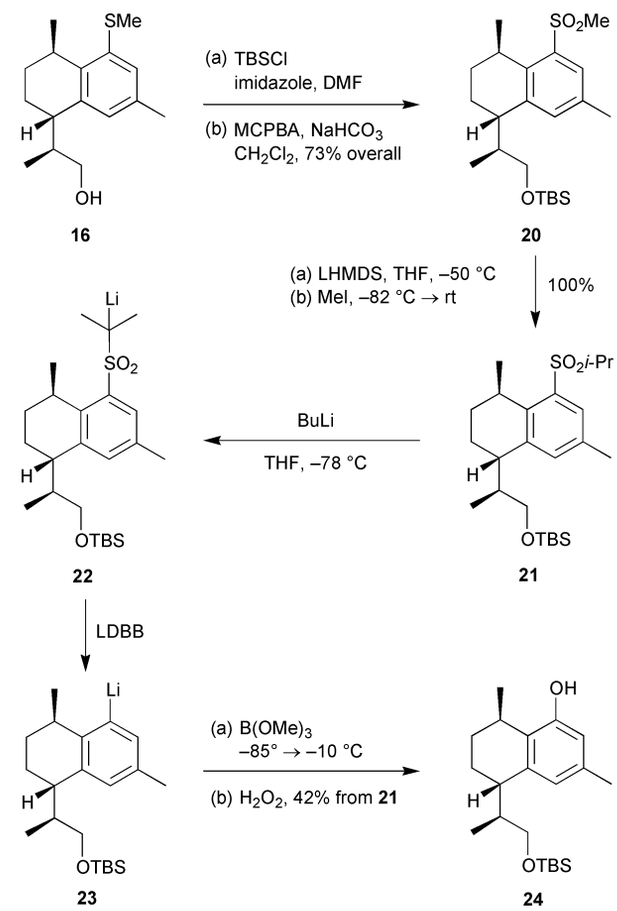
Scheme 4



Scheme 5

mechanism depicted in Scheme 5, the process depends on intramolecular capture of the carbocationic intermediate **17** by an alkene followed by loss of an alkylthio group with concomitant aromatisation. Since the corresponding methoxy analogue of **16** was our target, we tried to capture the carbocation intermediate **17** by conducting the benzannulation in methanol using a variety of protic and Lewis acid catalysts but in every case, the intramolecular cyclisation **17**⟶**18** was favoured.

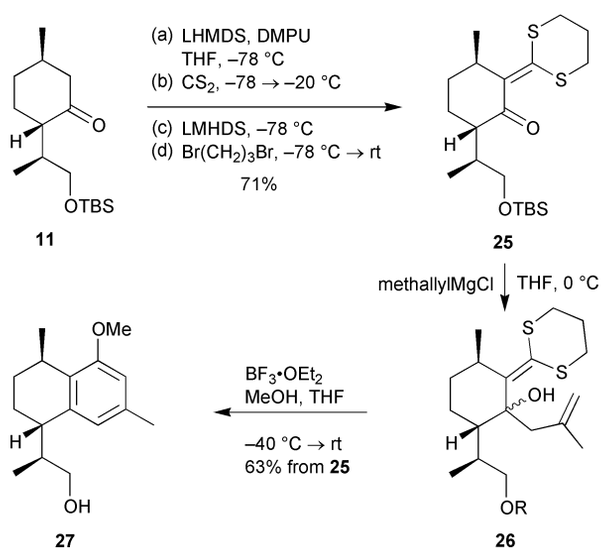
We tried a variety of methods ranging from the brutal to the exotic to replace the methylthio group in **16** with a methoxy or hydroxy group. Scheme 6 shows the most successful sequence



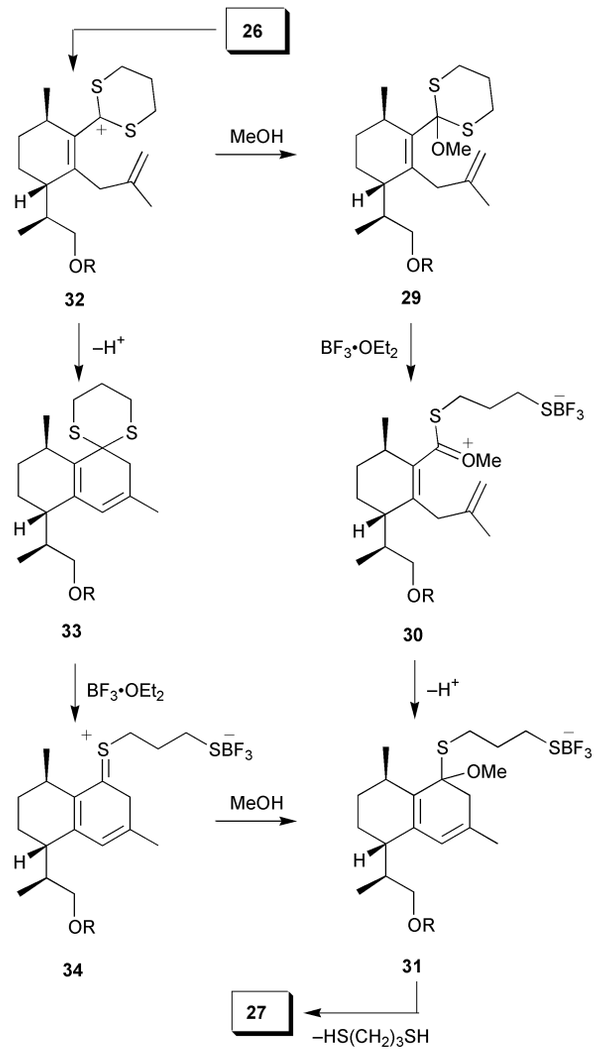
Scheme 6

based on reductive cleavage of an aryl–sulfone bond. Direct reductive cleavage of the methyl sulfone **20** was impossible owing to preferential cleavage of the alkyl–sulfur bond. A similar fate befell the isopropyl sulfone **21**. However, the lithiated sulfone **22** cleaved with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB)[13] to give the aryllithium **23** which could be converted to the phenol **24** by oxidation of a borate intermediate. The length of the route, its experimental difficulty and the low overall yield were good reasons to seek alternatives.

Relief came from an unexpected quarter. A fresh trek through the benzannulation chemistry discovered a trivial modification of the structure of the α-oxoketene-*S*,*S*-acetal that allowed a detour down paths leading to the desired methoxyarene **27** (Scheme 7). The lithium enolate of ketone **11** was condensed with carbon disulfide as before but this time, the adduct was quenched with 1,3-dibromopropane to give the dithianylidene derivative **25**. Addition of methylallylmagnesium chloride gave a sensitive adduct **26** which was immediately treated with $BF_3{\cdot}OEt_2$ in a mixture of THF and methanol to give the desired methoxyarene **27** shorn of its TBS protector. It would appear that the dithiane ring reduces the rate of cyclisation of **32** (Scheme 8) so that the intermediate carbocation can be captured by methanol to give the dithio orthoester intermediate **29**. Now cleavage of the dithiane ring leads to the oxonium ion **30** whose cyclisation is followed by expulsion of propane-1,3-dithiol leading to the desired product **27** in 63% yield for the two steps from the α-oxoketene-*S*,*S*-acetal **25**. An alternative mechanism which would account for the introduction of methanol allows an initial rapid cyclisation of carbocation **32** to the spirocyclic *S*,*S*-acetal **33**. Subsequent cleavage to the thionium ion **34** followed by addition of methanol leads to the same intermediate **31** and thence the methoxyarene **27**.



Scheme 7



Scheme 8

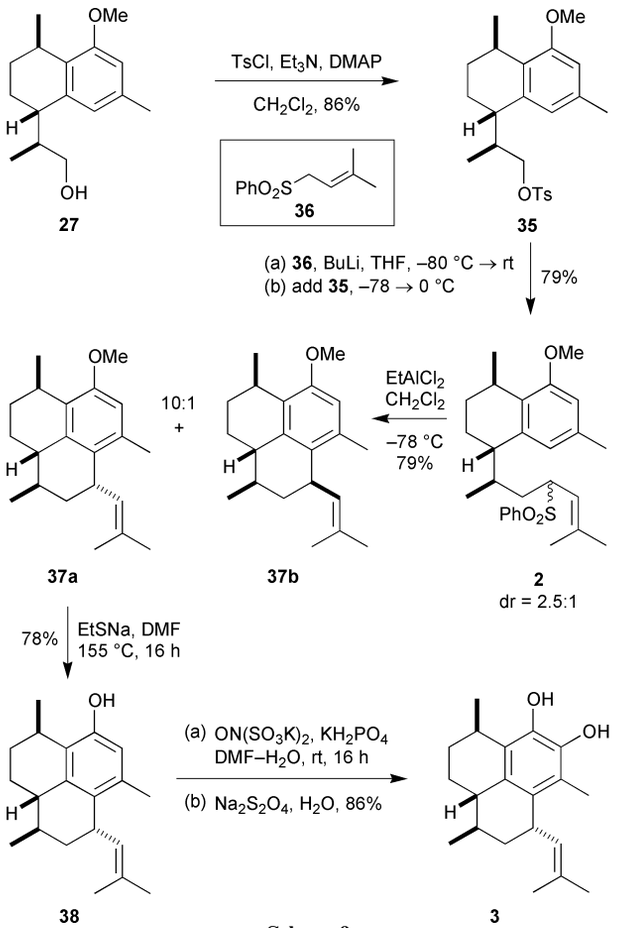
Construction of ring C. The third and final phase of the synthesis of the pseudopterosin K–L aglycone (Scheme 9) entailed construction of ring C using an allylic sulfone strategy described in our synthesis of the putative pseudopterosin G aglycone. Reaction of the crystalline toluene-*p*-sulfonate **35** with the lithiated sulfone derived from **36** afforded the allylic sulfone **2** in 76% yield. Without separation of the diastereoisomers (*ca.* 2.5 : 1), the mixture was treated with $EtAlCl_2$ (10 equiv.) in dichloromethane at low temperature to give the hexahydro-1*H*-phenalene ring system as a mixture of diastereoisomers (**37a** : **37b** = 10 : 1). The structure and stereochemistry of the major crystalline diastereoisomer **37a** were established by X-ray crystallography (see Experimental). The stereoselectivity of the electrophilic aromatic substitution reaction was sensitive to Lewis acid and solvent. For example, $AlCl_3$ (Et_2O, reflux) and Et_2AlCl (dichloromethane, −78 °C) both returned **37a**,**b** as a 1 : 1 mixture of diastereoisomers.

To complete the synthesis, cleavage of the methoxy group of **37a** was achieved in good yield using BBr_3 and 2,6-di-*tert*-butylpyridine over 30 min. Longer exposure to these reaction conditions resulted in partial epimerisation at the C6 benzylic centre. The epimerisation reaction could be suppressed by nucleophilic cleavage of the methyl ether using sodium ethanethiolate in hot DMF.[14] The final oxidation of the phenol **38** to the catechol in **3** was precedented in the work of McCombie *et al.*[15] but the best we could obtain was 22% yield using freshly prepared potassium nitrosodisulfonate (Fremy's salt) and KH_2PO_4 buffer in acetone–H_2O at rt followed by reduction of the red *o*-quinone with sodium dithionite.[16] Unreacted starting material and a number of side products were always recovered. Similar problems were encountered by Corey and Carpino[17] during their synthesis of pseudopterosin A. However, by simply using aqueous DMF as the solvent, the final step of the synthesis, oxidation of the phenol to the catechol, was achieved in a very satisfactory 86% yield.

Pseudopterosin A–F aglycone

All of the syntheses of the pseudopterosins reported thus far have identified the construction of the C3 stereogenic centre as an obstacle. Solutions to the problem have generally been inefficient or expensive. In our synthesis of pseudopterosin K–L aglycone described above, we presented a two-step procedure which was effective and cheap. We now suggest an alternative solution to the problem (Scheme 10) in the context of a synthesis of the pseudopterosin A–F aglycone **6**. As before, the synthesis began with isopulegol but we now require the (+)-enantiomer which is not available in a cheap commercial grade. However, (+)-isopulegol can be conveniently prepared in high yield and stereoselectivity by a $ZnCl_2$-catalysed intramolecular ene-reaction on (−)-citronellal according to the procedure of Nakatani and Kawashima.[18] After protection of the hydroxy group as its acetate derivative **39**, the alkene was ozonolysed

to afford the β-acetoxy ketone **40**. A Horner–Wadsworth–Emmons reaction then accomplished the synthesis of the α,β-unsaturated ester **41** in 64% yield as a mixture of isomers ($E : Z = 9 : 1$) which were easily separable by column chromatography. The key step of the sequence was an asymmetric conjugate reduction using sodium borohydride and $CoCl_2$ catalysed by Pfaltz's semicorrin **42**.[19,20] The reaction was very slow requiring up to 10 days at room temperature but the yield of **43** was 90% and the diastereoselectivity excellent (dr ≥ 97 : 3). The reaction requires rigorous exclusion of oxygen and our failure to do so was probably responsible for the long reaction time and the relatively high (8 mol%) catalyst loading. In more favourable circumstances as little as 1–2 mol% of catalyst is all that is required.

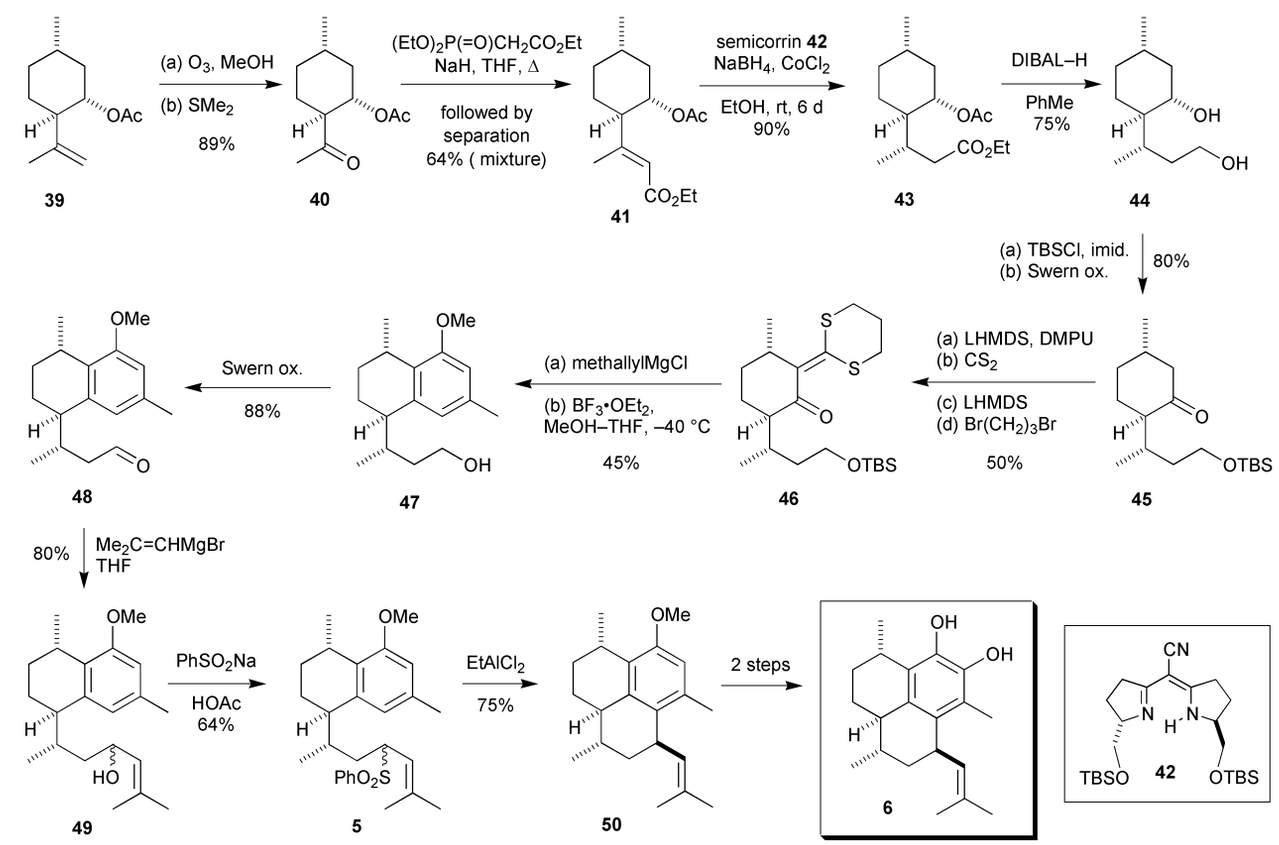


Scheme 9

Reduction of the ketoester **43** gave a crystalline diol **44** whose primary hydroxy was protected as its TBS ether **45** before oxidation of the secondary hydroxy was achieved in 80% yield using the Swern method. Thenceforth the synthesis bears a close resemblance to the route used to synthesise pseudopterosin K–L aglycone; *viz.* the arene was appended using an α-oxoketene-*S*,*S*-acetal benzannulation and ring C was constructed using the sulfone-based electrophilic aromatic substitution. The pseudopterosin A–F aglycone **6** thus obtained was identical to the one prepared as described in Scheme 9 except for the sign of the optical rotation.

Conclusions

Our syntheses of the pseudopterosin aglycones represent another rendition of the popular B⟶BA⟶BAC annulation strategy based on monoterpene precursors.[21–24] Pseudopterosin K–L aglycone was prepared in 7.8% overall yield (15 steps) from commercial (+)-isopulegol but the synthesis of pseudopterosin A–F aglycone was less efficient giving the target in only 2.3% overall yield from citronellal in 17 steps. An important milestone in our approach was the successful diversion of the Dieter–Junjappa–Ila benzannulation to produce a methoxyarene rather than the usual methylthioarene. Our solutions to the vexing problem of creating the C3 stereogenic centre are noteworthy too for their general efficiency and stereoselectivity. The reductive cleavage of the oxirane **8** has been applied



Scheme 10

in similar circumstances previously[25–27] but the Pfaltz asymmetric conjugate reduction has rarely been exploited in natural product synthesis.[28] It served our purposes well.

Experimental

For general experimental details see the previous paper in this issue.[3]

(+)-Neoisopulegol (7)

Technical grade isopulegol (Aldrich), a mixture of four diastereoisomers including (−)-isopulegol (*ca.* 65–80%) and (+)-neoisopulegol (*ca.* 10–25%), can be separated by column chromatography but the oxidation–reduction sequence of Friedrich and Bohlmann[5] is a more convenient procedure giving (+)-neoisopulegol in *ca.* 70% overall yield (120 mmol scale) and >90% purity. If necessary, the (+)-neoisopulegol can be further purified by crystallisation of its *p*-nitrobenzoate (mp 88–89 °C).[29]

(1*S*,2*R*,5*R*)-2-[(*R*)-1-Methyl-1,2-epoxyethyl]-5-methylcyclohexan-1-ol (8)

Epoxidation of (+)-isopulegol **7** (5.93 ml, 5.40 g, 35.0 mmol) by the procedure of Friedrich and Bohlmann.[5] gave the epoxide **8** (5.25 g, 30.8 mmol, 88%) as white crystals, mp 55–56 °C; $[\alpha]_D$ +3.2 (*c* 3, $CHCl_3$). Lit.[5] mp 56–58 °C.

(1*R*,2*S*,5*R*)-2-[(*S*)-2-Hydroxy-1-methylethyl]-5-methylcyclohexan-1-ol (9)

Sodium cyanoborohydride (4.47 g, 71.2 mmol, 3 equiv.) was added to a solution of epoxide **8** (4.04 g, 23.7 mmol) and a drop of bromocresol green in dry THF (5 ml). A solution of $BF_3{\cdot}OEt_2$ in dry THF (0.8 M) was added dropwise until the colour changed to yellow. The reaction mixture was stirred for 12 h maintaining the yellow colour by dropwise addition of the $BF_3{\cdot}OEt_2$ solution. The mixture was diluted with brine (35 ml) and extracted with EtOAc (5 × 35 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc–hexanes 1 : 1) to give the diol **9** (3.24 g, 18.8 mmol, 79%) as a pale yellow oil having $[\alpha]_D$, IR, ^{1}H NMR (300 MHz), and ^{13}C NMR (75 MHz) spectra consistent with data published by Schulte-Elte and Ohloff.[4]

(2*S*,5*R*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-5-methylcyclohexan-1-ol (10)

To a solution of the diol **9** (3.50 g, 20.3 mmol) and imidazole (3.18 g, 46.74 mmol, 2.3 equiv.) in dry DMF (15 ml) was added *tert*-butyldimethylsilyl chloride (3.37 g, 22.35 mmol, 1.1 equiv.). After 15 min the reaction mixture was poured into NH_4Cl (20 ml) and the product extracted into hexanes. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O–hexanes 1 : 25) to give the TBS ether **10** (4.89 g, 17.05 mmol, 84%) as a colourless oil: $[\alpha]_D$ +7.1 (*c* 3.9, $CHCl_3$); ν_{max} film/cm^{-1} 3440 br, 2927 s, 2858 s, 1472 m, 1461 m, 1354 s, 1071 s, 961 m, 937 m, 836 s, 776 s, 666 m; δ_H (270 MHz, $CDCl_3$) 4.07 (1H, m, C11H), 3.66 (2H, overlapping br s, OH, and dd, A portion of an ABX system, J_{AB} 10.4, J_{AX} 2.4, C2H$_A$), 3.52 (1H, dd, B portion of an ABX system, J_{AB} 10.4, J_{BX} 6.2, C2H$_B$), 1.92–1.59 (6H, m), 1.29–0.98 (3H, m), 0.94 (3H, d, *J* 6.4, C3Me), 0.91 (9H, s, *t*-Bu), 0.85 (3H, d, *J* 6.4, C6Me), 0.08 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 66.3 (2), 66.2 (1), 46.9 (1), 41.9 (2), 38.4 (1), 35.6 (2), 26.3 (1), 26.0 (3C, 3), 25.8 (2), 22.6 (3), 18.4 (0), 16.3 (3), −5.5 (2C, 3); *m*/*z* (CI mode, NH_3) 287 (MH^+, 100%), 137 (48); Found $(MH)^+$, 287.2414; $C_{16}H_{35}O_2Si$ requires *M*, 287.2406.

(2*S*,5*R*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-5-methylcyclohexan-1-one (11)

DMSO (1.0 g, 93 µl, 13.0 mmol, 2.5 equiv.) in CH_2Cl_2 (15 ml) was added dropwise to a solution of oxalyl chloride (0.8 g, 0.55 ml, 6.3 mmol, 1.2 equiv.) in dry CH_2Cl_2 (8 ml) at −72 °C over 7 min. After 5 min the alcohol **10** (1.50 g, 5.23 mmol) in CH_2Cl_2 (4 ml) was slowly added over 4 min at −65 °C. After 90 min stirring at −65 °C, Et_3N (2.18 g, 3 ml, 21.5 mmol, 4.1 equiv.) was added over 8 min and mixture allowed to warm to rt over 2 h. The white suspension was poured into vigorously stirred aq. NH_4Cl (15 ml) and extracted into hexanes (3 × 20 ml). The combined organic phases were washed with HCl (1.5 M, 10 ml) followed by brine (10 ml). The residue obtained on concentration *in vacuo* was purified by column chromatography (SiO_2, hexanes–Et_2O 95 : 5) to give the ketone **11** (1.31 g, 4.60 mmol, 88%) as a pale yellow oil: $[\alpha]_D$ −7.4 (*c* 2.5, $CHCl_3$); ν_{max} film/cm^{-1} 2955 s, 2857 s, 1710 s, 1471 m, 1387 m, 1256 m, 1087 s, 836 s, 776 s; δ_H (300 MHz, $CDCl_3$) 3.45 (2H, AB part of an ABX system, J_{AB} 9.9, J_{BX} 7.3, J_{AX} 5.5, C2H$_2$), 2.43–2.2 (3H, m), 2.05–1.80 (4H, m), 1.41–1.10 (2H, m), 1.02 (3H, d, *J* 6.2, C3Me), 0.88 (9H, s, *t*-Bu), 0.80 (3H, d, *J* 7.0, C5Me), 0.04 and 0.03 (3H each, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 212.6 (0), 66.0 (2), 51.0 (2), 50.0 (1), 35.4 (1), 34.1 (2), 33.3 (1), 27.0 (2), 26.1 (3C, 3), 22.5 (3), 18.4 (0), 12.9 (3), −5.4 (3), −5.5 (3); *m*/*z* (CI^+ mode, NH_3) 285 $[(M + H)^+$, 100%], 227 (66), 153 (33); Found $(M + H)^+$, 285.2249; $C_{20}H_{33}O_2Si$ requires *M*, 285.2250.

(2*S*,5*R*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-5-methyl-6-bis(methylsulfanyl)methylenecyclohexan-1-one (14)

To a solution of LHMDS in THF (6.0 ml, 1.0 M, 6 mmol) cooled to −85 °C was added a solution of ketone **11** (1.55 g, 5.47 mmol) in THF (10 ml) over 16 min. After 50 min, HMPA (0.5 ml, 3.2 mmol) and CS_2 (0.35 ml, 5.82 mmol) were added. The solution was allowed to warm to 0 °C over 100 min, stirred at 0 °C for 15 min and then cooled again to −82 °C whereupon LHMDS (6.0 ml, 1.0 M, 6 mmol) was added over 7 min. After 40 min, iodomethane (0.8 ml, 10.2 mmol) was added at −55 °C and the cooling bath removed. After 15 h, the reaction was quenched with saturated aqueous NH_4Cl (10 ml) and diluted with water (10 ml). The mixture was extracted into hexanes (50 ml) and the organic extract washed successively with 20 ml aliquots of water, HCl (2 M), water, and brine. The organic layer was dried over $MgSO_4$, concentrated *in vacuo*, and the residue purified by column chromatography (SiO_2, with ether–hexanes 5 : 95) to give the ketene-*S*,*S*-acetal **14** (1.74 g, 4.49 mmol, 82%) as a bright yellow oil: $[\alpha]_D$ +2.0 (*c* 2.36, $CHCl_3$); ν_{max} film/cm^{-1} 1683 s, 1259 s, 1098 s, 847 s; δ_H (270 MHz, $CDCl_3$) 3.55 (1H, dd, *J* 10.0, 6.0, CH_AH$_B$OSi), 3.54 (1H, apparent sextet, *J* 6.0), 3.35 (1H, dd, *J* 9.9, 7.4, CH$_A$H$_B$OSi), 2.36 and 2.29 (3 H each, s, SMe), 2.4–2.3 (1H, m), 2.17 (1H, apparent septet *J* 7.0), 2.02 (1H, ddt, *J* 15.2, 9.4, 3.0), 1.91–1.76 (1H, m), 1.71–1.58 (1H, m), 1.38–1.25 (1H, m), 1.06 (3H, d, *J* 6.9, C3Me), 0.88 (9H, s, Bu^t), 0.84 (3H, d, *J* 6.6, C6Me), 0.04 and 0.02 (3H each, s, $SiMe_2$); δ_C (67.5 MHz, $CDCl_3$) 206.1 (0), 148.6 (0), 140.4 (0), 66.4 (2), 52.1 (1), 37.2 (1), 36.4 (1), 30.0 (2), 26.1 (3), 22.0 (2), 20.7 (3), 18.4 (0), 17.75 (3), 17.7 (3), 13.2 (3), −5.25 (3), −5.2 (3); *m*/*z* (CI mode, NH_3) 389 $[(M + H)^+$, 100%], 331 $[(M - Bu^t)$, 76], 257 [(M − OTBS), 80].

(5*S*,8*R*)-1-Methylthio-3,8-dimethyl-5-[(*S*)-2-hydroxy-1-methylethyl]-5,6,7,8-tetrahydronaphthalene (16)

To a magnetically stirred solution of the ketene-*S*,*S*-acetal **14** (1.24 g, 3.19 mmol) in THF (7 ml) was added methylallylmagnesium chloride (5 ml, 0.9 M, 4.5 mmol) over 30 min at 0 °C. After 1 h, saturated aqueous NH_4Cl (10 ml) was added. The organic layer was extracted into Et_2O (30 ml) and washed with brine. After evaporation of the solvent the crude alcohol **15** was dissolved in THF (2 ml) and nitromethane (4 ml) and

cooled to 0 °C whereupon BF_3·OEt_2 (1.0 ml, 3.4 mmol) was added. The mixture was stirred at 0 °C for 1 h and then quenched by the addition of saturated aqueous NH_4Cl (10 ml). The organic material was extracted into Et_2O (30 ml) and washed with brine. The extract was dried over $MgSO_4$, concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, CH_2Cl_2) to give the methylthioarene **16** (0.71 g, 2.68 mmol, 84%) as a colourless oil: ν_{max} film/cm^{-1} 3356 br, 1598 m, 1560 m, 1040 s, 850 m; δ_H (270 MHz, $CDCl_3$) 6.84 and 6.68 (1H each, s), 3.65 (1H, dd, *J* 10.8, 5.0), 3.56 (1H, dd, *J* 10.8, 6.2), 3.25 (1H, quintet, *J* 5.7), 2.87 (1H, t, *J* 4.8), 2.47 and 2.31 (3H each, s), 2.1–2.0 (1H, m), 2.0–1.9 (2H, m), 1.75–1.55 (2H + OH, m), 1.2 (3H, d, *J* 6.75), 0.86 (3H, d, *J* 7.0); δ_C (67.5 MHz, $CDCl_3$) 138.9 (0), 137.9 (0), 137.2 (0), 135.05 (0), 126.9 (1), 123.8 (1), 66.9 (2), 42.1 (1), 37.6 (1), 29.4 (1), 27.3 (2), 21.42 (3), 21.39 (3), 18.8 (2), 16.0 (3), 14.25 (3); *m*/*z* (EI mode) 265 ($M^{+\bullet}$, 52%), 205 (100).

(5*S*,8*R*)-1-Methylsulfonyl-3,8-dimethyl-5-[(*S*)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-5,6,7,8-tetrahydronaphthalene (20)

To a solution of alcohol **16** (0.36 g, 1.35 mmol) in DMF (2 ml) were added imidazole (0.225 g, 3.31 mmol) and TBSCl (0.250 g, 1.66 mmol). After 1 h at rt, hexanes (5 ml) and water (5 ml) were added. The organic phase was diluted with hexanes (25 ml) and the organic layer washed with water and brine. The mixture was dried over $MgSO_4$ and concentrated *in vacuo* and the residue dissolved in CH_2Cl_2 (10 ml). $NaHCO_3$ (235 mg, 2.8 mmol) and *m*-chloroperbenzoic acid (0.60 g, *ca.* 80%, 2.8 mmol) were added and the mixture stirred at rt for 1 h whereupon water (10 ml) and saturated aqueous $NaHCO_3$ (10 ml) were added. The organic layer was diluted with CH_2Cl_2 (25 ml) and washed with $Na_2S_2O_3$ (1 M, 10 ml), $NaHCO_3$ (10 ml) and brine (10 ml). After drying over $MgSO_4$, the mixture was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, CH_2Cl_2) to give sulfone **20** (0.405 g, 0.99 mmol, 73%) as a pale yellow oil: ν_{max} film/cm^{-1} 1471 s, 1310 s, 1265 s, 1149 s, 1088 s, 958 s, 838 s, 777 s, 739 s; δ_H (270 MHz, $CDCl_3$) 7.72 (1H, s, C8H), 7.32 (1H, s, C10H), 3.90–3.75 (1H, m), 3.54 (2H, d, *J* 6.2, CH_2OSi), 3.2–3.1 (1H, m), 3.06 (3H, s, SO_2Me), 2.36 (3H, s, C9Me), 2.2–2.1 (1H, m), 2.06–1.6 (4H, m), 1.26 (3H, d, *J* 7, C3Me), 0.93 (9H, s, Bu^t), 0.71 (3H, d, *J* 7, C6Me), 0.09 (6H, s, $SiMe_2$); δ_C (67.5 MHz, $CDCl_3$) 142.2 (0), 140.1 (0), 137.5 (0), 135.6 (0), 135.2 (1), 128.3 (1), 66.2 (2), 45.3 (3), 42.0 (1), 35.3 (1), 29.5 (1), 27.0 (2), 26.1 (3), 24.0 (3), 21.15 (3), 18.5 (0), 17.3 (2), 12.6 (3), −5.2 (3), −5.1 (3); *m*/*z* (EI mode) 410 ($M^{+\bullet}$, 0.1%), 395 [($M^{+\bullet}$ − Me), 10], 353 [$M^{+\bullet}$ − Bu^t), 100].

(5*S*,8*R*)-5-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-3,8-dimethyl-1-(2-isopropylsulfonyl)-5,6,7,8-tetrahydronaphthalene (21)

To a solution of the methylsulfone **20** (97.5 mg, 0.24 mmol) in THF (2.5 ml) was added LHMDS (0.61 ml, 1.0 M, 0.61 mmol) at −50 °C. After 80 min, the solution was cooled to −78 °C whereupon iodomethane (0.1 ml, 1.6 mmol) was added and the mixture allowed to warm slowly to ambient temperature over 22 h. The reaction was quenched by adding saturated aqueous NH_4Cl (6 ml). The organic phase was extracted into Et_2O (20 ml) and washed with HCl (2 M) and brine. After drying over $MgSO_4$, the mixture was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, hexanes–CH_2Cl_2 1 : 1) to give the isopropylsulfone **21** (0.105 g, 0.24 mmol, 100%) as a colourless oil: ν_{max} film/cm^{-1} 1309 s, 1257 s, 1123 s, 1089 s, 1052 s, 837 s, 776 s, 677 s; δ_H (270 MHz, $CDCl_3$) 7.66 (1H, s, C8H), 7.31 (1H, s, C10H), 3.86–3.72 (1H, m), 3.60–3.49 (2H, m), 3.26–3.09 (1H, m), 2.35 (3H, s, C9Me), 2.15–1.60 (6H, m), 1.34 (3H, d, *J* 6.8), 1.23 (3H, d, *J* 6.95), 1.28 (3H, d, *J* 6.8), 0.93 (9H, s, Bu^t), 0.69 (3H, d, *J* 6.95), 0.08 (6H, s, $SiMe_2$); δ_C (67.5 MHz, $CDCl_3$) 142.0 (0), 141.9 (0), 135.4 (1), 135.3 (0), 133.8 (0), 130.1 (1), 66.30 (2), 55.95 (1), 42.6 (1), 35.5 (1), 29.8 (1), 27.0 (2), 26.1 (3), 24.5 (3), 21.1 (3), 18.5 (0), 17.2 (2), 16.2 (3), 15.1 (3), 12.7 (3), −5.1 (3), −5.2 (3); *m*/*z* (CI mode, NH_3) 456 [(M^+ + NH_4), 100%], 439 [(M^+ + H), 15], 381 [(M^+ − Bu^t, 27].

(5*S*,8*R*)-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-3,8-dimethyl-1-hydroxy-5,6,7,8-tetrahydronaphthalene (24)

To a solution of the isopropylsulfone **21** (0.140 g, 0.32 mmol) in THF (1.5 ml) was added BuLi (0.3 ml, 1.6 M, 0.48 mmol) dropwise at −78 °C. A deep yellow colour formed immediately. After 1 h, a solution of lithium 4,4-di-*tert*-butylbiphenylide in THF (3 ml, 0.25 M, 0.75 mmol) was added over 1 min. The solution changed from green to red–brown. Trimethyl borate (0.3 ml, 2.6 mmol) was added at −78 °C over 30 s. The solution was allowed to warm gradually to −10 °C over 2.5 h whereupon NaOH (2 ml, 2 M, 4 mmol) and H_2O_2 (3 ml, 15%) were added. After 16 h the solution was acidified with HCl (2 M) until the pH was approximately 1. The organic phase was extracted into ether (30 ml) and washed with water (20 ml) and brine (20 ml). After drying over $MgSO_4$, the mixture was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, ether–hexanes 4 : 96⟶10 : 90) to give the phenol **24** (0.047 g, 0.134 mmol, 42%) as a pale yellow oil: $[\alpha]_D$ 1.3 (*c* 4.35, $CHCl_3$); ν_{max} film/cm^{-1} 3586 m, 3418 br, 1618 s, 1579 s, 1264 s, 1088 s, 1036 s, 837 s, 776 s, 741 s; δ_H (270 MHz, $CDCl_3$) 6.67 (1H, s, C10H), 6.45 (1H, s, C8H), 3.56 (2H, d, *J* 5.8, CH_2OSi), 3.09 (1H, dquintets, *J* 6.0, 2.0), 2.91 (1H, dt, *J* 6.0, 3.0), 2.25 (3H, s), 2.08–1.87 (2H, m), 1.81 (1H, ddd, *J* 13.0, 5.9, 2.5), 1.75–1.66 (2H, m), 1.53 (1H, dquintets, *J* 12.5, 2.5), 1.22 (3H, d, *J* 7.0), 0.95 (9H, s), 0.83 (3H, d, *J* 7), 0.10 and 0.08 (3H each, s); δ_C (67.5 MHz, $CDCl_3$) 153.2 (0), 141.1 (0), 135.4 (0), 126.4 (0), 122.70 (1), 113.4 (1), 66.65 (2), 41.1 (1), 36.9 (1), 27.3 (2), 26.65 (1), 26.2 (3), 21.3 (3), 21.23 (3), 18.9 (2), 18.5 (0), 14.2 (3), −5.13 (3), −5.2 (3).

(2*S*,5*R*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-6-(1,3-dithian-2-ylidene)-5-methylcyclohexan-1-one (25)

A solution of HMDS (1.8 ml, 1.40 g, 8.7 mmol, 1.05 equiv.) in THF (7 ml) was cooled to −78 °C and BuLi (1.58 M in hexanes, 5.5 ml, 8.7 mmol, 1.05 equiv.) was added slowly over 7 min. The mixture was warmed to rt over 30 min, then the clear solution was cooled again to −78 °C and DMPU (1.06 ml, 1.11 g, 8.67 mmol, 1.05 equiv.) was added dropwise over 5 min. After stirring for 20 min at the same temperature, a solution of the ketone **11** (2.35 g, 8.26 mmol) in THF (12 ml) was added dropwise over 10 min and the solution stirred at −78 °C for a further 30 min before rapid addition of CS_2 (522 µl, 660 mg, 8.67 mmol, 1.05 equiv.). The orange solution was allowed to warm to −20 °C over 2 h, stirred at this temperature for 90 min, and cooled again to −78 °C before addition of a second portion of LHMDS solution in THF (1.05 equiv.) prepared as above. 1,3-Dibromopropane (885 µl, 1.75 g, 8.67 mmol, 1.05 equiv.) in THF (28 ml) was added after 30 min, the solution was allowed to warmed to rt over 13 h and then poured into aq. NH_4Cl (60 ml). The aqueous phase was separated, extracted with Et_2O (3 × 40 ml) and the combined organic layers washed with brine (20 ml) before drying over Na_2SO_4. The residue obtained on concentration *in vacuo* was purified by column chromatography (SiO_2, hexanes–Et_2O 4 : 1) to give the ketene-*S*,*S*-acetal **25** (2.35 g, 5.86 mmol, 71%) as a dark orange oil: $[\alpha]_D$ +14.3 (*c* 12, $CHCl_3$); ν_{max} film/cm^{-1} 2928 s, 2856 s, 1643s, 1472 s, 1418 m, 1281 m, 1255 m, 1087 s, 837 s, 775 s, 668 s; δ_H (300 MHz, $CDCl_3$) 3.40 (2H, m, AB portion of ABX system, J_{AB} 7.1, C3H_2), 3.21 (1H, app. sextet, *J* 6.4, C13H), 2.98 (2H, ddd, A_2 portion of $A_2BB'XY$ system, J_{AB} 13.9, S-CH_2), 2.83 (1H, ddd, B portion of $A_2BB'XY$ system, J_{AB} 13.9, J_{BX} 7.7, J_{BY} 7.3, S-CH_B), 2.75 (1H, ddd, B′ portion of $A_2BB'XY$ system, $J_{AB'}$ 13.9, $J_{B'X}$ 6.6, $J_{B'Y}$ 5.5, S-CH_B), 2.43 (1H, dd, *J* 12.9, 6.2, C4H or C5H), 2.35 (1H, dd, *J* 12.5, 6.6, C4H or C5H), 2.22–2.09 (2H,

m, S-C-CH_2), 2.03–1.93 (1H, m, C6H or C3H), 1.89–1.77 (1H, m, C6H or C13H), 1.61–1.49 (1H, m), 1.46–1.34 (1H, m), 1.11 (3H, d, *J* 7.2, C3Me), 0.86 (9H, s, Bu^t), 0.75 (3H, d, *J* 6.5, C6Me), 0.02 and 0.01 (3H each, s, $SiMe_2$); δ_C (67.5 MHz, $CDCl_3$) 200.4 (0), 150.8 (0), 137.1 (0), 66.1 (2), 48.7 (1), 36.1 (1), 33.9 (1), 29.3 (2), 29.1 (2), 28.9 (2), 26.1 (3), 23.9 (2), 20.3 (3), 19.8 (2), 18.4 (0), 12.7 (3), −5.2 (3), −5.3 (3); Found $(M + H)^+$, 401.2018; $C_{20}H_{36}O_2SiS_2$ requires *M*, 400.1926.

(5*S*,8*R*)-3,8-Dimethyl-5-[(*S*)-2-hydroxy-1-methylethyl]-1-methoxy-5,6,7,8-tetrahydronaphthalene (27)

To a solution of ketene-*S*,*S*-acetal **25** (4.09 g, 10.2 mmol) in THF (120 ml) was added dropwise methylallylmagnesium chloride [prepared from methylallyl chloride (7.03 ml, 6.46 g, 71.4 mmol, 7.0 equiv.) and Mg turnings (5.27 g, 217 mmol, 21 equiv.) in dry THF (286 ml)] over 15 min at 0 °C. The cooling bath was removed and the mixture stirred at ambient temperature for 90 min. The reaction mixture was poured into saturated aqueous NH_4Cl (200 ml), extracted with ether (3 × 40 ml) and dried over Na_2SO_4. Concentration *in vacuo* gave alcohol **26** as a pale yellow oil (4.46 g) which was used immediately in the next step.

To a solution of $BF_3{\cdot}OEt_2$ (11.1 g, 9.83 ml, 78.2 mmol, 8 equiv.) in methanol (40 ml) at −40 °C was added slowly crude alcohol **26** (4.46 g) in THF (10 ml). The mixture was allowed to warm to rt over 18 h. Saturated $NaHCO_3$ solution (45 ml) was added slowly and the mixture concentrated *in vacuo* to a slurry which was diluted with brine (15 ml) and extracted with ether (3 × 15 ml). The combined organic layers were dried over Na_2CO_3–Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes–Et_2O 7 : 3) to give the methoxyarene **27** (1.61 g, 6.48 mmol, 63% from **25**) as a yellow oil: $[\alpha]_D$ −25.0 (*c* 0.62, $CHCl_3$); ν_{max} film/cm^{-1} 3354 s, br (OH), 2954 s, 2869 s, 1612 s, 1579 s, 1462 s, 1373 m, 1344 m, 1272 s, 1096 s, 1029 s, 893 m, 832 m; δ_H (300 MHz, $CDCl_3$) 6.64 (1H, s, C10H), 6.53 (1H, s C8H), 3.82 (3H, s, OMe), 3.67 (1H, dd, *J* 10.7, 6.6, C2H), 3.56 (1H, dd, *J* 10.7, 5.9, C2H), 3.23–3.13 (1H, m), 2.84–2.74 (1H, m), 2.31 (3H, s, C9Me), 2.12–2.04 (1H, m), 1.91–1.65 (3H, m), 1.58–1.68 (2H, m), 1.15 (3H, d, *J* 6.8, C3Me), 0.89 (3H, d, *J* 7.0, C6Me); δ_C (75 MHz, $CDCl_3$) 157.4 (0), 139.9 (0), 135.3 (0), 128.9 (0), 122.1 (1), 109.0 (1), 67.0 (2), 55.2 (3), 41.4 (1), 38.4 (1), 27.1 (2), 26.6 (1), 21.7 (3), 21.6 (3), 19.5 (2), 14.7 (3); *m*/*z* (EI mode) 248 ($M^{+\bullet}$, 37), 189 [$(M - C_3H_7O)^{+\bullet}$, 100%], 175 (26); Found $M^{+\bullet}$, 248.1774; $C_{16}H_{24}O_2$ requires *M*, 248.1776.

(5*R*,8*R*)-3,8-Dimethyl-1-methoxy-5-[(*S*)-1-methyl-2-(*p*-tolylsulfonyl)oxyethyl]-5,6,7,8-tetrahydronaphthalene (35)

To a solution of alcohol **27** (1.45 g, 5.84 mmol, 1 equiv.), DMAP (0.78 g, 6.42 mmol, 1.1 equiv.) and NEt_3 (2.04 ml, 1.48 g, 14.6 mmol, 2.5 equiv.) in CH_2Cl_2 (40 ml) at 0 °C was added solid toluene-*p*-sulfonyl chloride (1.56 g, 8.18 mmol, 1.4 equiv.) portionwise over 10 min. The cooling bath was removed and the clear yellow solution stirred at rt for 18 h before pouring into saturated aqueous NH_4Cl (50 ml). The organic layer was separated, the aqueous phase extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers were washed with HCl (2 M, 10 ml) and brine (10 ml), dried over Na_2CO_3–Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes–CH_2Cl_2 1 : 4) to give the toluene-*p*-sulfonate **35** (2.02 g, 5.02 mmol, 86%) as colourless needles, mp 69–70 °C (hexanes): $[\alpha]_D$ +22.5 (*c* 1.25, $CHCl_3$); ν_{max} film/cm^{-1} 2932 s, 2870 s, 1612 m, 1579 m, 1463 s, 1360 s, 1274 m, 1176 s, 1097 s, 965 s, 836 s, 791 s, 666 s; δ_H (300 MHz, $CDCl_3$) 7.81 and 7.36 (2H each, d, *J* 8.3, Ar AA′BB′ system), 6.51 (1H, s, C10H), 6.44 (1H, s, C8H), 3.99 (2H, apparent d, *J* 5.9, $C2H_2$), 3.82 (3H, s, OMe), 3.12–3.08 (1H, m, C13H), 2.76–2.71 (1H, m, C6H), 2.47 (3H, s, ArMe), 2.25 (3H, s, C9Me), 2.10 (1H, m, C3H), 1.81–1.75 (2H, m), 1.58–1.44 (2H, m), 1.11 (3H, d, *J* 7.0, C3Me), 0.84 (3H, d, *J* 7.0, C6Me); δ_C (75 MHz, $CDCl_3$) 157.4 (0), 144.8 (0), 138.6 (0), 135.3 (0), 133.4 (0), 130.0 (2C, 1), 128.7 (0), 128.1 (2C, 1), 121.9 (1), 109.1 (1), 74.3 (2), 55.3 (3), 38.1 (1), 37.4 (1), 26.8 (2), 26.5 (1), 21.8 (3), 21.6 (3), 21.5 (3), 19.0 (2), 14.1 (3); *m*/*z* (EI mode) 402 ($M^{+\bullet}$, 59), 230 [$(M - C_7H_8O_3S)^{+\bullet}$, 35], 215 (41), 189 (100%), 173 (38), 91 (25); Found: C, 68.40; H, 7.7%. $C_{23}H_{30}O_4S$ requires C, 68.63; H, 7.51; O, 15.90; S, 7.96.

(4*RS*,5*S*,8*R*)-3,8-Dimethyl-5-[(1*S*)-1,5-dimethyl-3-phenylsulfonylhex-4-enyl]-1-methoxy-5,6,7,8-tetrahydronaphthalene (2)

To a solution of 3-methyl-1-(phenylsulfonyl)but-2-ene[30] (2.78 g, 13.2 mmol, 4 equiv.) in THF (40 ml) at −78 °C was added BuLi (1.58 M solution in hexanes, 8.36 ml, 13.2 mmol, 4 equiv.) over 10 min. The orange solution was warmed to −30 °C over 2 h, then cooled again to −78 °C, and a solution of toluene-*p*-sulfonate **35** (1.33 g, 3.30 mmol, 1 equiv.) in THF (24 ml) slowly added *via* a cannula. The solution was allowed to warm to rt over 4 h and then poured into vigorously stirred saturated aqueous NH_4Cl (80 ml). The product was extracted into Et_2O (3 × 50 ml), and the combined organic layers washed with brine (25 ml) and dried over $MgSO_4$. The residue obtained after filtration and concentration *in vacuo* was purified by column chromatography (SiO_2, Et_2O–hexanes 5 : 95) to give the sulfones **2** (1.10 g, 2.50 mmol, 76%) as a 2.5 : 1 mixture of epimers at C14 (^1H, ^{13}C NMR). Discernible signals attributed to the minor isomer are marked with an asterisk (*). $[\alpha]_D$ +13.2 (*c* 6, $CHCl_3$); ν_{max} film/cm^{-1} 3048 m, 2956 s, 2869 s, 1613 m, 1580 s, 1447 s, 1304 s, 1273 m, 1147 s, 1086 s, 743 s, 690 s; δ_H (300 MHz, $CDCl_3$) 7.90–7.78 (2H, m, Ph), 7.65–7.59 (1H, m, Ph), 7.58–7.48 (2H, m, Ph), 6.51 and 6.42* (2H, s, C8H and C10H), 5.00 and 4.92* (1H, dm, *J* 10.3, C14H), 3.88* and 3.79 (3H, s, OMe), 3.57 (1H, dt, *J* 10.3, 3.3, C1H), 3.05–2.98 (1H, m), 2.56–2.52* and 2.51–2.48 (1H, m), 2.30–2.10 (5H, m), 1.90–1.88 (1H, m, C3H), 1.73 and 1.69* (3H, s, $C16H_3$), 1.69 and 1.59* (2H, m), 1.52–1.46 (2H, m, $C2H_2$), 1.19* and 1.08 (3H, d, *J* 1.1, C17Me), 1.13* and 1.11 (3H, d, *J* 7.7, C3Me), 0.80 and 0.68* (3H, d, *J* 7.7, C6Me); δ_C (75 MHz, $CDCl_3$) 157.2* and 157.1 (0), 142.5* and 142.3 (0), 139.7 and 139.6* (0), 138.2 (0), 135.6 and 135.2* (0), 135.2 (0), 133.5* and 133.4, 133.4 (1), 129.4 (2C, 1), 128.8 (2C, 1), 121.8 (1), 117.8 and 117.5* (1), 108.8* and 108.7 (1), 64.0*, 63.3 (1), 55.3 (3), 41.8* and 38.1 (1), 36.5 and 36.2* (1), 33.4* and 32.0 (2), 29.9 (1), 27.6* and 27.4 (2), 26.0 (3), 21.9 (3), 21.2 (3), 19.2 (2), 18.7 and 18.1* (3), 17.9 and 15.7* (3); *m*/*z* (EI mode) 440 ($M^{+\bullet}$, 29%), 299 [$(M - PhSO_2)^{+\bullet}$, 100%], 216 [$(M - C_{10}H_{15}SO_2)^{+\bullet}$,48]; Found $M^{+\bullet}$, 440.2377; $C_{27}H_{36}O_3S$ requires *M*, 440.2385.

Cyclisation of the sulfones 2

To a solution of sulfones **2** (264 mg, 0.6 mmol) in CH_2Cl_2 (15 ml) cooled to −78 °C was added dropwise $EtAlCl_2$ (1 M in hexanes, 2.4 ml, 2.4 mmol, 4 equiv.) over 5 min. The brown solution was allowed to warm to rt overnight and then poured into HCl (2 M, 25 ml). The product was extracted into CH_2Cl_2 (3 × 25 ml) and the combined organic layers washed with saturated aqueous $NaHCO_3$ (5 ml), brine (5 ml) and dried over Na_2SO_4. After filtration and concentration *in vacuo*, ^1H NMR spectroscopic analysis of the crude reaction mixture before chromatography revealed a 10 : 1 mixture of C1 epimers. The isomers were isolated by column chromatography (SiO_2, hexanes) to give (1*S*,3*R*,6*R*,13*S*)-7-methoxy-1-(2-methylprop-1-enyl)-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-phenalene **37a** (142 mg, 0.48 mmol, 79%) as white needles, mp 95–96 °C (propan-2-ol); $[\alpha]_D$ +16.8 (*c* 0.57, $CHCl_3$); ν_{max} $CHCl_3$/cm^{-1} 2923 s, 2856 s, 1593 s, 1575 s, 1464 s, 1379 m, 1320 m, 1273 m, 1216 m, 1177 m, 1101 m, 836 s; δ_H (300 MHz, $CDCl_3$) 6.63 (1H, s, C8H), 5.19 (1H, dm, *J* 9.2, C14H), 3.86 (3H, s, OMe), 3.69–3.64 (1H, m, C1H), 3.43 (1H, app. sextet, *J* 7.0, C6H), 2.22 (3H, s, C9Me), 2.21–2.10 (3H, m), 1.80 (3H, d, *J* 1.3, $C15H_3$),

1.73–1.60 (6H, m), 1.58–1.45 (2H, m, C4H$_2$), 1.24 (3H, d, *J* 7.0, C6Me), 1.12 (3H, d, *J* 5.5, C3Me); δ_C (75 MHz, $CDCl_3$) 154.9 (0), 138.7 (0), 134.6 (0), 129.8 (1), 129.6 (2C, 0), 128.4 (0), 110.8 (1), 55.4 (3), 43.5 (1), 39.4 (2), 35.2 (1), 30.6 (2), 30.1 (1), 28.2 (2), 26.6 (1), 25.9 (3), 23.3 (3), 21.3 (3), 19.7 (3), 17.8 (3); *m*/*z* (EI mode) 298 ($M^{+\bullet}$, 87), 283 [$(M - CH_3)^{+\bullet}$, 100%], 242 [$(M - C_4H_8)^{+\bullet}$, 30], 227 [$(M - C_5H_{11})^{+\bullet}$, 33]; Found $M^{+\bullet}$, 298.2295; $C_{21}H_{30}O$ requires *M*, 298.2297.

A small amount of the minor isomer **37b** was obtained sufficiently pure (*ca.* 90%) to allow the following assignments:

δ_H (300 MHz, $CDCl_3$) 6.60 (1H, s, C8H), 4.99 (1H, dm, *J* 9.6, C14H), 3.86 (3H, s, OMe), 3.78–3.72 (1H, m, C1H), 3.43 (1H, app. sextet, *J* 7.0, C6H), 2.23 (3H, s, C9Me), 2.21–2.10 (3H, m), 1.77 (3H, d, *J* 1.5, C15Me), 1.73–1.60 (6H, m), 1.58–1.45 (2H, m, C4H$_2$), 1.26 (3H, d, *J* 6.6, C6Me), 1.08 (3H, d, *J* 5.9, C3Me); δ_C (75 MHz, $CDCl_3$) 155.6 (0), 140.7 (0), 135.1 (0), 131.3 (1), 130.0 (0) 129.8 (0), 127.9 (0), 111.1 (1), 55.2 (3), 45.0 (1), 40.2 (2), 36.7 (1), 34.2 (2), 31.9 (1), 28.3 (2), 27.8 (1), 25.6 (3), 23.8 (3), 20.8 (3), 20.3 (3), 17.7 (3).

(1*S*,3*R*,6*R*,13*S*)-7-Hydroxy-1-(2-methylprop-1-enyl)-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-phenalene (38)

A suspension of NaH (121 mg, 5 mmol, 20 equiv.) in dry DMF (2 ml) was added EtSH (311 mg, 0.37 ml, 5 mmol, 20 equiv.) in DMF (0.37 ml) at a rate sufficient to maintain slow gas evolution at 0 °C. After 30 min from the end of the addition, a solution of methoxyarene **37a** (75 mg, 0.25 mmol) in dry DMF (4 ml) was added *via* a cannula. The clear yellow solution was heated at 155 °C for 16 h before cooling to rt, diluting with Et_2O and pouring into saturated aqueous NH_4Cl (10 ml). After extraction of the aqueous phase with Et_2O (2 × 10 ml), and drying of the organic phase over Na_2SO_4, the solvent was removed *in vacuo* and column chromatography of the residue (SiO_2, hexanes–Et_2O 4 : 1) gave the phenol **38** (56 mg, 0.197 mmol, 78%) as a colourless oil.

A more expensive procedure which avoids the obnoxious smell of ethanethiol entailed dropwise addition of BBr_3 (1.0 M solution in CH_2Cl_2, 2.46 ml, 2.46 mmol, 2 equiv.) to methoxyarene **37a** (366 mg, 1.23 mmol) and freshly distilled 2,6-di-*tert*-butyl-4-methylpyridine (303 mg, 1.48 mmol, 1.2 equiv.) in CH_2Cl_2 (15 ml). The brown suspension was stirred for 30 min, whereupon the mixture was poured into H_2O (50 ml), extracted with Et_2O (3 × 25 ml) and dried over Na_2CO_3–Na_2SO_4. The mixture was filtered, concentrated *in vacuo*, and the residue purified by column chromatography (SiO_2, hexanes⟶hexanes–Et_2O 95 : 5) to give the phenol **38** (270 mg, 0.95 mmol, 77%) as a pale yellow oil: $[\alpha]_D$ +14.5 (*c* 0.5, $CHCl_3$); ν_{max} $CHCl_3$/cm^{-1} 3406 br (OH), 2922 s, 2868 s, 1585 s, 1455 s, 1096 m, 1043 m, 909 s, 843 s, 735 s; δ_H (300 MHz, $CDCl_3$) 6.49 (1H, s, C8H), 5.15 (1H, dm, *J* 8.0, C14H), 5.05 (1H, s, OH), 3.61–3.58 (1H, m, C1H), 3.32–3.28 (1H, app. sextet, *J* 7.0, C6H), 2.24–2.08 (6H, m), 1.81 (3H, s, C16H$_3$), 1.75–1.72 (5H, m), 1.60–1.42 (3H, m), 1.24 (3H, d, *J* 7.0, C6Me), 1.10 (3H, d, *J* 5.8, C3Me); δ_C (75 MHz, $CDCl_3$) 151.0 (0), 139.0 (0), 135.0 (0), 130.0 (2 C, 0 and 1), 129.7 (0), 126.0 (0), 115.4 (1), 43.6 (1), 39.3 (2), 35.1 (1), 30.8 (2), 29.9 (1), 28.1 (2), 26.9 (1), 25.8 (3), 23.1 (3), 21.1 (3), 19.1 (3), 17.7 (3); *m*/*z* (CI mode, NH_3) 285 [$(M + H)^+$, 100%], 134 (65), 35 (48); Found $M^{+\bullet}$, 284.2141; $C_{20}H_{28}O$ requires *M*, 284.2140.

(1*S*,2*S*,5*S*)-1-Acetoxy-2-acetyl-5-methylcyclohexane (40)

(+)-Isopulegyl acetate **39** [9.15 g, 46.1 mmol, $[\alpha]_D$ +17.3 (*c* 2, $CHCl_3$)] prepared from (+)-isopulegol[18] was dissolved in dry methanol (75 ml) and dry CH_2Cl_2 (25 ml), cooled to −78 °C and O_3 was bubbled through the solution until the formation of a persistent blue colour. The mixture was flushed with N_2 for 15 min at −78 °C before addition of SMe_2 (16.8 ml, 14.3 g, 230.5 mmol, 5 equiv.). The solution was allowed to warm to rt over 10 h and the solvent was removed under reduced pressure. After addition of water (150 ml) and Et_2O (150 ml) the aqueous phase was separated, extracted with Et_2O (2 × 60 ml) and the organic phase washed with brine (30 ml) and dried on $MgSO_4$. The mixture was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, hexanes–Et_2O 3 : 1) to give the ketone **40** (8.13 g, 41.0 mmol, 89%) as a colourless oil: $[\alpha]_D$ +76.3 (*c* 2, $CHCl_3$); ν_{max} film/cm^{-1} 2930 s, 2870 m, 1738 s, 1715 s, 1455 m, 1371 s, 1241 s, 1204 m; δ_H (360 MHz, $CDCl_3$) 4.91 (1H, td, *J* 11.0, 4.4, C11H), 2.55 (1H, ddd, *J* 10.9, 10.7, 3.8, C13H), 2.16–2.08 (4H, m), 1.97 (3H, s, OCOMe), 1.91 (1H, dq, *J* 13.4, 3.4, C5H or C4H), 1.79–1.69 (1H, m, C4H or C5H), 1.65–1.53 (1H, m, C6H), 1.33 (1H, app. dq, *J* 13.1, 3.6, C4H or C5H), 1.00–0.89 (2H, m), 0.93 (3H, d, *J* 6.6, C6Me); δ_C (90 MHz, $CDCl_3$) 210.0 (0), 170.3 (0), 73.4 (1), 55.7 (1), 39.6 (2), 33.5 (2), 31.0 (1), 29.2 (3), 27.9 (2), 22.0 (3), 21.3 (3); Found $(MH)^+$, 199.1332; $C_{11}H_{19}O_3$ requires *M*, 199.1334.

Ethyl 3-[(1*R*,2*S*,4*S*)-2-acetoxy-4-methyl-1-cyclohexyl]but-2-enoate (41)

NaH (60% suspension in mineral oil, 706 mg, 17.6 mmol, 3.5 equiv.) was washed with dry hexane to remove the oil, suspended in dry THF (25 ml) and cooled to 0 °C in an ice bath. Triethyl phosphonoacetate (4.0 ml, 4.52 g, 20.2 mmol, 4 equiv.) was slowly added over 35 min. The ice bath was removed and the clear solution stirred at rt for 20 min before addition *via* a cannula to a solution of ketone **40** (1.00 g, 5.04 mmol) in dry THF (25 ml). The solution was heated at reflux for 12 h, then poured into water (50 ml). The aqueous phase was extracted with ether (3 × 25 ml) and dried on $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, hexanes–ether 9 : 1) to give the α,β-unsaturated ester **41** (872 mg, 3.22 mmol, 64%) as a yellow oil: $[\alpha]_D$ −3.4 (*c* 2, $CHCl_3$). The compound was obtained as 9 : 1 mixture of isomers. The stereochemistry of the major product was confirmed by NOE experiments. ν_{max} film/cm^{-1} 2930, 2870 m, 1736 s, 1646 s, 1453 m, 1373 s, 1242 s, 1154 s, 1027 s, 868 s; δ_H (360 MHz, $CDCl_3$) 5.66 (1H, d, *J* 1.3, C2H), 4.83 (1H, dt, *J* 10.8, 4.4, C11), 4.11 (2H, q, *J* 7.2, CH_2CH$_3$), 2.18–2.08 (1H, m, C13H), 2.06 (3H, d, *J* 1.1, C3Me), 2.04–1.92 (4H, m, C12H + COOMe), 1.76–1.64 (2H, m), 1.61–1.35 (2H, m), 1.23 (3H, t, *J* 7.2, CH$_2$CH_3), 1.1–0.85 (1H, m), 0.98–0.80 (1H, m), 0.90 (3H, d, *J* 6.6, C6Me); δ_C (75 MHz, $CDCl_3$) 170.5 (0), 166.8 (0), 160.0 (0), 117.3 (1), 73.2 (2), 59.7 (2), 53.4 (1), 40.3 (2), 33.9 (2), 31.3 (1), 30.1 (2), 22.0 (3), 21.2 (3), 16.0 (3), 14.4 (3); Found $(M + H)^+$, 269.1769; $C_{15}H_{25}O_4$ requires *M*, 269.1753.

Data for the minor isomer: δ_H (270 MHz, $CDCl_3$) 5.65 (1H, s, C2H), 4.82 (1H, dt, *J* 10.6, 4.4, C11H), 4.15 (2H, q, *J* 7.1, CH_2CH$_3$), 2.18–2.08 (1H, m, C13H), 2.06 (3H, d, *J* 1.1, C$_3$Me), 2.04–1.92 (4H, m, C12H + COMe), 1.76–1.64 (2H, m), 1.61–1.35 (2H, m), 1.28 (3H, t, *J* 7.1, CH_3CH$_2$), 1.05–0.80 (2H, m), 0.92 (3H, d, *J* 6.6, C6Me); δ_C (75 MHz, $CDCl_3$) 170.7 (0), 166.2 (0), 160.0 (0), 118.5 (1), 73.3 (1), 59.7 (2), 53.4 (1), 43.8 (2), 33.8 (2), 31.4 (1), 29.5 (2), 22.0 (3), 20.4 (3), 15.3 (3), 14.4 (3).

(3*S*)-Ethyl 3-[(1*R*,2*S*,4*S*)-2-acetoxy-4-methyl-1-cyclohexyl]-butanoate (43)

In a flask fitted with a vacuum-tight Teflon stopper, a solution of the α,β-unsaturated ester **41** (670 mg, 2.5 mmol) in ethanol (1.0 ml) under N_2 was treated successively with $CoCl_2 \cdot 6H_2O$ (42 mg, 0.175 mmol, 0.07 equiv.) in EtOH (0.27 ml) and semicorrin ligand **42**[19,31] (93 mg, 0.2 mmol, 0.08 equiv.) in EtOH (0.52 ml) causing the colour to turn from blue–violet to dark blue. A solution of $NaBH_4$ (189 mg, 5.0 mmol, 2 equiv.) in DMF (1.5 ml) was then added whereupon the colour changed to brown. The suspension was then degassed at 0.01 mmHg by repeated (6) freeze–thaw cycles. The reaction mixture was stirred at 25 °C for 6 days in the vacuum-sealed flask, then water (10 ml) was added and the mixture extracted with CH_2Cl_2 (4 × 15 ml). The combined organic extracts were washed with

H_2O (15 ml) and dried over Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (SiO_2, hexanes–Et_2O 4 : 1) to give the diester **43** (592 mg, 2.2 mol, 90%) as a colourless oil: $[a]_D$ +35.7 (*c* 2.5, $CHCl_3$); ν_{max} film/cm^{-1} 2953 s, 2929 s, 2870 s, 1735 s, 1373 m, 1244 s, 1184 m, 1027 m; δ_H(300 MHz, $CDCl_3$) 4.63 (1H, dt, *J* 10.7, 4.4, C11H), 4.10 (2H, q, *J* 7.0, CH_2CH$_3$), 2.36 (1H, dd, *J* 14.9, 4.2, C5H), 2.27–2.19 (1H, m, C6H), 2.05 (3H, s, COCH_3), 2.03–1.93 (2H, m), 1.76–1.64 (2H, m), 1.53–1.40 (2H, m), 1.24 (3H, t, *J* 7.0, CH$_3$CH$_2$), 1.02–0.82 (3H, m), 0.93 (3H, d, *J* 7.0, C6Me or C3Me), 0.90 (3H, d, *J* 6.6, C6Me or C3Me); δ_C (75 MHz, $CDCl_3$) 173.8 (0), 170.8 (0), 73.6 (1), 60.6 (2), 46.6 (1), 40.7 (2), 37.5 (2), 34.4 (2), 31.4 (1), 29.3 (1), 25.8 (2), 22.9 (3), 21.4 (3), 17.6 (3), 14.4 (3); Found $(M + H)^+$, 271.1926; $C_{15}H_{27}O_4$ requires *M*, 271.1909.

(1*S*,2*R*,5*S*)-2-[(*S*)-3-Hydroxy-1-methylpropyl]-5-methylcyclohexan-1-ol (44)

Diester **43** (0.56 g, 2.08 mmol) was dissolved in dry CH_2Cl_2 (15 ml) and cooled to −70 °C. A 1.0 M solution of DIBAL-H in hexanes (11.3 ml, 11.3 mmol, 4.5 equiv.) was added dropwise over 15 min and the solution allowed to warm to 0 °C over 1 h. The mixture was then poured into an ice cold solution of sodium potassium tartrate (10.5 g, 3.3 equiv. with respect to DIBAL-H) in water (15 ml) and CH_2Cl_2 (5 ml) and vigorously stirred for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 ml), the combined organic extracts washed with brine (5 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, EtOAc–CH_2Cl_2 7 : 3) to give the diol **44** (0.29 g after recrystallisation from hexanes, 1.56 mmol, 75%) as a white crystalline solid, mp 93–94 °C: $[a]_D$ +75.2 (*c* 0.5, $CHCl_3$); ν_{max} $CHCl_3$/cm^{-1} 3265 br s, 2923 s, 2868 s, 1455 m, 1216 m, 1033 m, 758 s; δ_H (300 MHz, $CDCl_3$) 3.77 (1H, ddd, *J* 10.6, 5.9, 4.6, C1H_AH$_B$), 3.77 (1H, app. dt, *J* 9.9, 5.1, C1H$_A$$H_B$), 3.48 (1H, dt, *J* 10.4, 4.6, C11H), 2.90–2.50 (2H, br s, OH), 2.22–2.09 (1H, m, C6H), 2.01–1.95 (1H, m, C12H), 1.78–1.62 (3H, m), 1.50–1.38 (1H, m, C2H$_A$$H_B$), 1.29–1.12 (2H, m), 1.08–0.80 (3H, m), 0.95 (3H, d, *J* 7.0, C6Me or C3Me), 0.92 (3H, d, *J* 6.2, C6Me or C3Me); δ_C (90 MHz, $CDCl_3$) 71.0 (1), 61.4 (2), 50.5 (1), 44.7 (2), 34.8 (2), 33.7 (2), 31.9 (1), 27.7 (1), 24.2 (2), 22.4 (3), 18.4 (3); Found: C, 70.98; H, 11.75%. $C_{11}H_{22}O_2$ requires C, 70.92; H, 11.90; O, 17.18.

(1*S*,2*S*,5*R*)-2-[(*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-methylpropyl]-5-methylcyclohexan-1-one (45)

Diol **44** (4.2 g, 22.5 mmol) and imidazole (3.52 g, 51.7 mmol, 2.3 equiv.) were dissolved in dry DMF (35 ml) and solid *tert*-butyldimethylsilyl chloride (3.74 g, 24.8 mmol, 1.1 equiv.) was then added. After 15 min, the reaction mixture was poured into saturated aqueous NH_4Cl (40 ml) and the product extracted into hexanes (3 × 30 ml). The organic layer was washed with brine (5 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O–hexanes 1 : 25) to give (1*S*,2*S*,5*R*)-2-[(*R*)-3-(3-*tert*-butyldimethylsilyloxy)-1-methylpropyl]-5-methylcyclohexan-1-ol (6.42 g, 21.5 mmol, 95%) as a colourless oil which was used in the next step without further purification.

DMSO (4.36 g, 3.96 ml, 55.8 mmol, 2.6 equiv.) in CH_2Cl_2 (15 ml) was added dropwise to a solution of oxalyl chloride (3.54 g, 2.40 ml, 27.9 mmol, 1.3 equiv.) in dry CH_2Cl_2 (80 ml) at −72 °C over 10 min. After 20 min, the crude (1*S*,2*S*,5*R*)-2-[(*R*)-3-(3-*tert*-butyldimethylsilyloxy)-1-methylpropyl]-5-methylcyclohexan-1-ol (6.42 g, *ca.* 21,5 mmol) in CH_2Cl_2 (35 ml) was slowly added over 4 min at −65 °C. After 90 min stirring at −65 °C, Et_3N (8.90 g, 12.3 ml, 88.0 mmol, 4.1 equiv.) was added over 8 min and mixture allowed to warm to over 2 h. The white suspension was poured into vigorously stirred saturated aqueous NH_4Cl (50 ml) and extracted into hexanes (3 × 40 ml). The combined organic phases were washed with HCl (1.5 M, 30 ml) followed by brine (20 ml). The residue obtained on concentration *in vacuo* was purified by column chromatography (SiO_2, hexanes–Et_2O (95 : 5)) to give the ketone **45** (5.13 g, 17.2 mmol, 80%) as a pale yellow oil: $[a]_D$ +27.6 (*c* 1.1, $CHCl_3$); ν_{max} film/cm^{-1} 2928 s, 2858 s, 1712 s, 1462 s, 1255 s, 1104 s, 836 s, 775 s; δ_H (360 MHz, $CDCl_3$) 3.68–3.56 (2H, m, C_2H_2), 2.30 (1H, ddd, *J* 12.9, 3.7, 2.2, C13H), 2.15–2.09 (1H, m), 2.06–1.77 (5H, m), 1.64–1.56 (1H, m), 1.43 (1H, dq, *J* 12.6, 3.0, C3H), 1.33–1.22 (2H, m), 0.98 (3H, d, *J* 6.3, C6Me or C3Me), 0.90 (3H, d, *J* 6.9, C6Me or C3Me), 0.86 (9H, s, *t*-Bu), 0.03 and 0.02 (3H each, s, $SiMe_2$); δ_C (90 MHz, $CDCl_3$) 211.9 (0), 62.1 (1), 55.2 (2), 51.0 (2), 36.4 (2), 35.3 (1), 34.1 (2), 28.6 (2), 28.4 (1), 26.1 (3, 3C), 22.4 (3), 18.4 (0), 17.7 (3), −5.2 (3, 2C); *m*/*z* (CI mode, NH_3) 316 $[(M + NH_4)^+$, 15], 299 $[(M + H)^+$, 100%], 241 $[(M - C_4H_9)^+$, 15]; Found $(M + H)^+$, 299.2416; $C_{17}H_{35}O_2Si$ requires *M*, 299.2406.

(2*R*,5*S*)-2-[(*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-methylpropyl]-5-methyl-6-(1,3-dithian-2-ylidene)cyclohexan-1-one (46)

A solution of HMDS (4.30 ml, 3.33 g, 20.6 mmol, 1.1 equiv.) in THF (25 ml) was cooled to −78 °C and BuLi (1.38 M in hexanes, 14.9 ml, 20.6 mmol, 1.1 equiv.) was added slowly over 10 min. The mixture was warmed to rt over 30 min, then the clear solution was cooled again to −78 °C and DMPU (2.5 ml, 2.6 g, 20.6 mmol, 1.1 equiv.) was added dropwise over 5 min. After stirring for 20 min at the same temperature, a solution of ketone **45** (5.6 g, 18.8 mmol) in THF (20 ml) was added dropwise over 10 min and the solution stirred at −78 °C for a further 30 min before rapid addition of CS_2 (1.24 ml, 1.57 g, 20.6 mmol, 1.1 equiv.). The orange solution was allowed to warm to −20 °C over 2 h, stirred at this temperature for 90 min, and cooled again to −78 °C before addition of a second portion of LHMDS solution in THF (1.05 equiv.) prepared as above. 1,3-Dibromopropane (885 μl, 1.75 g, 8.67 mmol, 1.05 equiv.) in THF (28 ml) was added after 30 min at the same temperature, whereupon the solution was warmed to rt over 16 h and then poured into saturated aqueous NH_4Cl (80 ml). The aqueous phase was separated, extracted with Et_2O (3 × 40 ml) and the combined organic layers washed with brine (30 ml) before drying over Na_2SO_4. The residue obtained after concentration *in vacuo* was purified by column chromatography (SiO_2, hexanes–Et_2O 4 : 1) to give the ketene-*S*,*S*-acetal **46** (3.92 g, 9.45 mmol, 50%) as a dark orange oil: $[a]_D$ −46.2 (*c* 1.1, $CHCl_3$); ν_{max} film/cm^{-1} 2928 s, 2857 s, 1644 m, 1471 s, 1283 m, 1255 s, 1093 s, 836 s, 775 s; δ_H (360 MHz, $CDCl_3$) 3.64–3.50 (2H, m, C1H_2), 3.18 (1H, app. sextet, *J* 6.4, C13H), 3.01 (2H, AA′ part of an AA′BB′XY system, J_{AB} 13.8, $J_{A'B}$ 13.8, SCH_2), 2.91 (1H, ddd, B part of an AA′BB′XY system, J_{AB} 13.8, J_{BX} 8.6, J_{BY} 7.2, SCH_2), 2.71 (1H, ddd, B′ part of an AA′BB′XY system, J_{AB} 13.8, J_{BX} 6.6, J_{BY} 4.8, SCH), 2.19–2.10 (2H, m, SCH$_2$CH_2), 2.04–1.96 (1H, m), 1.90–1.71 (1H, m), 1.67–1.54 (3H, m), 1.42–1.24 (2H, m), 1.10 (3H, d, *J* 6.9, C3Me), 0.90–0.36 (13H, m), 0.03 and 0.02 (3H each, s, $SiMe_2$); δ_C (90 MHz, $CDCl_3$) 200.6 (01), 150.0 (0), 137.4 (0), 61.9 (2), 53.5 (1), 36.7 (2), 34.2 (1), 31.1 (1), 29.1 (2), 28.8 (2), 26.1 (3, 3C), 23.9 (2), 22.7 (2), 21.3 (2), 20.2 (3), 18.4 (0), 18.0 (3), −5.1 (3, 2C); *m*/*z* (ESI^+ mode, CH_3CN) 846 $[(2M + NH_4)^+$, 82], 415 $[(M + H)^+$, 100]; Found $(M + H)^+$, 415.2141; $C_{21}H_{39}O_2S_2Si$ requires *M*, 415.2161.

(5*R*,8*S*)-3,8-Dimethyl-5-[(*R*)-3-hydroxy-1-methylpropyl]-1-methoxy-5,6,7,8-tetrahydronaphthalene (47)

To a solution of ketene-*S*,*S*-acetal **46** (3.90 g, 9.4 mmol) in THF (100 ml) was added methylallylmagnesium chloride [prepared from methylallyl chloride (7.4 ml, 6.8 g, 75.2 mmol, 8.0 equiv.) and Mg turnings (5.4 g, 226 mmol, 24 equiv.) in dry THF (320 ml)] over 15 min at 0 °C *via* a cannula. The cooling bath was removed and the mixture stirred at rt for 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl (400 ml),

extracted with ether (3 × 80 ml) and dried over Na_2SO_4. Concentration *in vacuo* gave a pale yellow oil (4.80 g) which was dissolved in THF (40 ml) and added slowly to a solution of $BF_3{\cdot}OEt_2$ (13.3 g, 11.6 ml, 94 mmol, 10 equiv.) in methanol (40 ml) at −40 °C. The mixture was allowed to warm to rt over 18 h. Saturated aqueous $NaHCO_3$ (60 ml) was added slowly and the mixture concentrated *in vacuo* to a slurry which was diluted with brine (40 ml) and extracted with ether (3 × 45 ml). The combined organic layers were dried over Na_2CO_3–Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes–Et_2O 7 : 3) to give the methoxyarene **47** (1.12 g, 4.27 mmol, 45% over the two steps) as a pale yellow oil: $[\alpha]_D$ +32.9 (*c* 3.0, $CHCl_3$). The compound was contaminated with impurities (*ca*. 8%) that could not be removed by column chromatography.

ν_{max} film/cm^{-1} 3361 s, br, 2933 s, 2869 s, 1612 m, 1579 m, 1462 s, 1272 s, 1098 s, 1055 m, 832 m, 787 s, 764 m; δ_H (300 MHz, $CDCl_3$) 6.66 (1H, s, C10H), 6.53 (1H, s, C8H), 3.83 (3H, s, OMe), 3.64–3.56 (1H, A portion of an ABXY system, J_{AB} 10.5, J_{BY} 8.2, J_{AY} 5.1, C3H$_A$), 3.50–3.42 (1H, B portion of an ABXY system, J_{AB} 10.5, J_{BX}, J_{BY} 7.3, C3H$_B$), 3.20–3.17 (1H, m), 2.73–2.62 (1H, m), 2.33 (3H, s, C9Me), 2.22–1.70 (4H, m), 1.65–1.49 (2H, m), 1.41–1.28 (2H, m), 1.18 (3H, d, *J* 7.0, C3Me), 1.04 (3H, d, *J* 7.0, C6Me); δ_C (75 MHz, $CDCl_3$) 157.1 (1), 140.1 (0), 135.0 (0), 128.8 (0), 121.9 (1), 108.6 (1), 61.8 (2), 55.1 (3), 42.2 (1), 36.4 (2), 35.4 (1), 27.5 (2), 26.5 (1), 21.7 (3), 21.4 (3), 19.2 (3), 18.9 (2); Found M^+, 263.2028; $C_{17}H_{27}O_2$ requires *M*, 263.2011.

(5*R*,8*S*)-3,8-Dimethyl-5-[(*R*)-3-oxo-1-methylpropyl]-1-methoxy-5,6,7,8-tetrahydronaphthalene (48)

DMSO (204 mg, 0.19 ml, 2.6 mmol, 2.6 equiv.) in CH_2Cl_2 (0.5 ml) was added dropwise to a solution of oxalyl chloride (166 mg, 0.112 ml, 1.31 mmol, 1.3 equiv.) in dry CH_2Cl_2 (1.5 ml) at −70 °C over 5 min. After 20 min alcohol **47** (262 mg, 1.0 mmol) in CH_2Cl_2 (2.6 ml) was slowly added over 4 min at −65 °C. After 90 min stirring at −65 °C, Et_3N (417 mg, 0.575 ml, 4.12 mmol, 4.1 equiv.) was added over 8 min and the mixture was allowed to warm to rt over 2 h. The white suspension was poured into vigorously stirred saturated aqueous NH_4Cl (10 ml) and extracted into hexanes (3 × 10 ml). The combined organic phases were washed with HCl (2 M, 3 ml) followed by brine (2 ml). The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, hexanes–Et_2O 95 : 5); to give the aldehyde **48** (230 mg, 0.88 mmol, 88%) as a pale yellow oil: $[\alpha]_D$ +32.9 (*c* 3.0, $CHCl_3$); ν_{max} film/cm^{-1} 2928 s, 2870 s, 1725 s, 1612 m, 1579 m, 1463 s, 1273 s, 1098 s, 833 m, 733 m; δ_H (300 MHz, $CDCl_3$) 9.57 (1H, dd, *J* 3.1, 1.2, CHO), 6.65 (1H, s, C10H), 6.53 (1H, s, C8H), 3.82 (3H, s, OMe), 3.20–3.12 (1H, m), 2.74–2.69 (1H, m), 2.64–2.57 (1H, m), 2.34–2.29 (4H, m), 2.17 (1H, ddd, *J* 16.0, 10.3, 3.1, C2H), 1.97–1.68 (3H, m), 1.58–1.49 (1H, m), 1.14 (3H, d, *J* 6.9, C3H), 1.08 (3H, d, *J* 6.8, C6Me); δ_C (75 MHz, $CDCl_3$) 203.2 (0), 157.3 (0), 139.2 (0), 135.6 (0), 129.0 (0), 121.9 (1), 109.1 (1), 55.3 (3), 48.0 (2), 41.5 (1), 33.9 (1), 27.5 (2), 26.5 (1), 21.8 (3), 21.4 (3), 19.6 (3), 18.8 (2); *m*/*z* (EI mode) 260 ($M^{+\bullet}$, 22), 216 [$(M - C_2H_4O)^{+\bullet}$, 16], 189 [$(M - C_4H_7O)^{+\bullet}$,100]; Found $M^{+\bullet}$, 260.1781; $C_{17}H_{24}O_2$ requires *M*, 260.1776.

(2′*R*,5*R*,8*S*)-1-Methoxy-3,8-dimethyl-5-(1,5-dimethyl-3-hydroxyhex-4-enyl)-5,6,7,8-tetrahydronaphthalene (49)

To a solution of aldehyde **48** (153 mg, 0.59 mmol) in dry THF (2 ml) at 0 °C was added 2-methylprop-1-enylmagnesium chloride prepared from 1-bromo-2-methylprop-1-ene (398 mg, 2.95 mmol, 5 equiv.) and Mg turnings (142 mg, 5.9 mmol, 10 equiv.) in dry THF (2 ml) *via* a cannula over 5 min. The clear solution was allowed to warm to rt and stirred over 2 h; then saturated aqueous NH_4Cl (5 ml) was added and the aqueous phase separated and extracted with Et_2O (3 × 5 ml). The combined organic extracts were washed with brine (2 ml) and dried over Na_2SO_4 before removal of the solvent *in vacuo* and column chromatography of the residue (SiO_2, hexanes–NEt_2O 4 : 1⟶1 : 1). The title alcohol **49** (150 mg, 0.47 mmol, 80%) was obtained as a 2 : 1 mixture of epimers by ^{1}H and ^{13}C NMR spectroscopy. Discernible signals attributed to the minor isomer are marked with an asterisk (*).

ν_{max} film/cm^{-1} 3360 br (OH), 2927 s, 2863 s, 1612 s, 1580 s, 1462 s, 1416 s, 1370 m, 1344 m, 1271 s, 1097 s, 1043 s, 1016 s, 820 m, 800; δ_H (360 MHz, $CDCl_3$) 6.66 and 6.60* (1H, s, C10H), 6.51 (1H, s, C8H), 5.09 (0.67H, dt, *J* 8.5, 1.4, C14H), 4.86* (0.33H, dt, *J* 9.0, 1.4, C14H), 4.34–4.26 (1H, m, C1H), 3.82 (3H, s, OMe), 3.17–3.14 (1H, m), 2.69–2.60 (1H, m), 2.31 (3H, s, C9Me), 2.23–2.18 (1H, m), 1.94–1.86 (2H, m), 1.78–1.73 (2H, m), 1.72* and 1.69 (3H, d, *J* 1.2, C16H$_3$ or C17H$_3$), 1.67* and 1.66 (3H, d, *J* 1.2, C16H$_3$ or C17H$_3$), 1.50–1.43 and 1.40–1.33* (2H, m), 1.15 (3H, d, *J* 6.9, C3Me), 1.05 and 1.03* (3H, d, *J* 6.8, C6Me); δ_C (90 MHz, $CDCl_3$) 157.2 (0), 140.3* and 140.2 (0), 135.7 and 135.1 (0), 135.0 (0), 131.3 (0), 129.0 and 128.3* (1), 122.1 and 121.0* (1), 108.7 (1), 67.7* and 67.0 (1), 55.3 (3), 42.4 (1), 41.8 and 41.4* (2), 35.3* and 34.9 (1), 27.8* and 27.7 (2), 26.6 (1), 26.0* and 25.9 (3), 21.8 (3), 21.5 (3), 19.7 and 19.3* (3), 19.2* and 19.0 (2), 18.3* and 18.2 (3); *m*/*z* (EI mode) 298 [$(M - H_2O)^{+\bullet}$, 8], 216 [$(M - C_6H_{12}O)^{+\bullet}$, 67], 189 [$(M - C_8H_{15}O)^{+\bullet}$, 100]; Found $M^{+\bullet}$, 316.2402; $C_{21}H_{32}O_2$ requires *M*, 316.2402.

(2′*R*,5*R*,8*S*)-3,8-Dimethyl-5-(1,5-dimethyl-3-phenylsulfonylhex-4-enyl)-1-methoxy-5,6,7,8-tetrahydronaphthalene (5)

Solid $PhSO_2Na$ (579 mg, 3.52 mmol, 7.5 equiv.) was added to a solution of allylic alcohol **49** (150 mg, 0.47 mmol) in propan-2-ol (5 ml). Glacial AcOH (0.5 ml) was added dropwise over 2 min and the suspension stirred for 30 min at rt until all the solid had dissolved whereupon the mixture was heated at reflux for 16 h. The pale yellow solution was then allowed to cool to rt, diluted with EtOAc (6 ml) and neutralised with saturated aqueous $NaHCO_3$ (5 ml). The aqueous layer was extracted with EtOAc (2 × 5 ml) and the organic phases dried over $MgSO_4$ before concentrating *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes–Et_2O 1 : 1) to afford the title sulfones **5** (0.132 g, 0.3 mmol, 64%) as a 2 : 1 mixture of epimers giving ^{1}H and ^{13}C NMR spectroscopic data consistent with those reported for the enantiomers **2**.

(1*R*,3*S*,6*S*,13*R*)-7-Methoxy-1-(2-methylprop-1-enyl)-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-phenalene (50)

A mixture of sulfones **5** (110 mg, 0.25 mmol) in CH_2Cl_2 (10 ml) was treated with $EtAlCl_2$ (1 M in hexanes, 1.0 ml, 1.0 mmol) as described above for the synthesis of the enantiomer **37a**. The crude product was purified by column chromatography (SiO_2, hexanes) followed by crystallisation from propan-2-ol to give the title compound **50** (56 mg, 0.19 mmol, 75%) as white needles, mp 92–95 °C; $[\alpha]_D$ −17.0 (*c* 0.6, $CHCl_3$). Compound **50** was identical by ^{1}H and ^{13}C NMR spectroscopy with the data reported for the enantiomer **37a**. The relative configuration (Fig. 1) was established by X-ray diffraction on a Rigaku AFC7S diffractometer using Mo X-rays.

Crystal data† $C_{21}H_{30}O$, $M = 298.47$, monoclinic, $a = 10.653(5)$, $b = 9.082(7)$, $c = 18.57(1)$ Å, $\beta = 101.27(5)°$, $U = 1762(1)$ Å^3, $T = 150$ K, space group $P2_1/c$, $Z = 4$, μ(Mo-Kα) 0.066 mm^{-1}, 3083 reflections measured, 2894 unique, $R_{int} = 0.041$. Refinement on *F* using 1481 reflections with $I > 2.5\sigma(I)$ gave $R = 0.061$. Data were processed using the TeXsan Crystal Structure Analysis Package, Molecular4 Structure Corporation, New Trails Drive, The Woodlands, Texas 77381, USA, 1985 and 1992.

† CCDC reference number 144022.

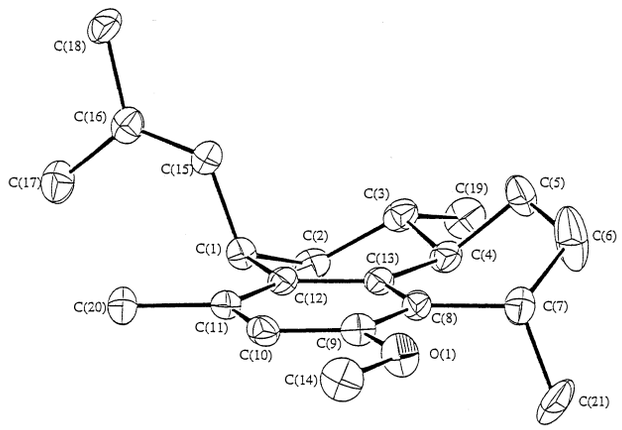


Fig. 1 Molecular drawing of **50** showing the atom numbering and 50% probability ellipsoids for non-hydrogen atoms.

(1*R*,3*S*,6*S*,13*R*)-7,8-Dihydroxy-1-[2-methylprop-1-enyl]-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-phenalene (pseudopterosins A–F aglycone) (6)

Compound **50** was converted to pseudopterosins A–F aglycone **6** by a 2-step procedure identical to that described above for the synthesis of the enantiomer. The catechol **6** was obtained as a yellow oil: $[\alpha]_D$ +30.5 (*c* 0.3, $CHCl_3$). IR and ^1H NMR data are in agreement with those reported by Carpino[32] and McCombie:[33] ν_{max} film/cm^{-1} 3449 br (OH), 2923 s, 2857 s, 1446 s, 1374 m, 1295 s, 1189 m, 1106 m, 1041 m, 810 m; δ_H (360 MHz, $CDCl_3$) 5.12 (1H, d, *J* 9.1, C14H), 5.07 (1H, br s, OH), 4.87 (1H, br s, OH), 3.62–3.55 (1H, m, C1H), 3.23 (1H, app. sextet, *J* 7.3, C6H), 2.25–2.13 (3H, m, $C5H_2$ and C13H), 2.04 (3H, s, C9Me), 1.76 (3H, s, $C16H_3$), 1.70 (3H, s, $C17H_3$), 1.71–1.41 (4H, m), 1.26 (3H, d, *J* 7.1, C6Me), 1.31–1.20 (1H, m, C3H), 1.05 (3H, d, *J* 6.1, C3Me); δ_C (90 MHz, $CDCl_3$) 140.0 (0), 139.9 (0), 130.4 (1), 130.3 (0), 130.0 (0), 126.0 (0), 125.7 (0), 120.0 (0), 43.3 (1), 39.7 (2), 35.5 (1), 31.1 (2), 30.1 (1), 28.4 (2), 27.5 (1), 25.8 (3), 23.2 (3), 21.2 (3), 17.8 (3), 11.0 (3); *m*/*z* (EI mode) 300 ($M^{+\bullet}$, 100), 285 [$(M - CH_3)^{+\bullet}$, 75], 245 [$(M - C_4H_7)^{+\bullet}$, 68], 244 [$(M - C_4H_8)^{+\bullet}$, 52], 229 [$(M - C_5H_{11})^{+\bullet}$, 36], 218 (28); Found $M^{+\bullet}$, 300.2071; $C_{20}H_{28}O_2$ requires *M*, 300.2089.

Acknowledgements

We thank GlaxoWellcome for financial support. We also thank the Collegio Ghislieri di Pavia and the Università di Pavia for a scholarship (A. P.) and Dr Andrew Kohler and Dr Simon Gill for crucial preliminary experiments.

References

1 S. A. Look, W. Fenical, G. K. Matsumoto and J. Clardy, *J. Org. Chem.*, 1986, **51**, 5140.
2 V. Roussis, Z. Wu, W. Fenical, S. A. Strobel, G. D. Van Duyne and J. Clardy, *J. Org. Chem.*, 1990, **55**, 4916.
3 Preceding paper: R. Chow, P. J. Kocienski, A. Kuhl, J.-Y. LeBrazidec, K. Muir and P. Fish, *J. Chem. Soc., Perkin Trans. 1*, 2001, DOI: 10.1039/b102960f.
4 K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, 1967, **50**, 153.
5 D. Friedrich and F. Bohlmann, *Tetrahedron*, 1988, **44**, 1369.
6 G. Schmid and W. Hofheinz, *J. Am. Chem. Soc.*, 1983, **105**, 624.
7 K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, 1973, **95**, 6136.
8 R. O. Hutchins, I. M. Taffer and W. Burgoyne, *J. Org. Chem.*, 1981, **46**, 5214.
9 R. K. Dieter, Y. J. Lin and J. W. Dieter, *J. Org. Chem.*, 1984, **49**, 3183.
10 G. Singh, H. Ila and H. Junjappa, *Tetrahedron Lett.*, 1984, **25**, 5095.
11 R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029.
12 H. Junjappa, H. Ila and C. V. Asokan, *Tetrahedron*, 1990, **46**, 5423.
13 P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924.
14 R. N. Mirrington and G. I. Feutrill, *Org. Synth.*, 1988, **Coll. Vol. VI**, 859.
15 S. W. McCombie, B. Cox, S.-I. Lin, A. K. Ganguly and A. T. McPhail, *Tetrahedron Lett.*, 1991, **32**, 2083.
16 H. Zimmer, D. C. Lankin and S. W. Morgan, *Chem. Rev.*, 1971, **71**, 229.
17 E. J. Corey and P. Carpino, *J. Am. Chem. Soc.*, 1989, **111**, 5472.
18 Y. Nakatani and K. Kawashima, *Synthesis*, 1978, 147.
19 A. Pfaltz, in *Modern Synthetic Methods*, ed. R. Scheffold, Springer Verlag, Berlin Heidelberg, 1989, pp. 198–448.
20 A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 339.
21 C. A. Broka, S. Chan and B. Peterson, *J. Org. Chem.*, 1988, **53**, 1584.
22 E. J. Corey and P. Carpino, *Tetrahedron Lett.*, 1990, **31**, 3857.
23 E. J. Corey and S. E. Lazerwith, *J. Am. Chem. Soc.*, 1998, **120**, 12777.
24 A. P. Kozikowski and J. P. Wu, *Synlett*, 1991, 465.
25 D. F. Taber and J. B. Houze, *J. Org. Chem.*, 1994, **59**, 4004.
26 H. Tone, T. Nishi, Y. Oikawa, M. Hikota and O. Yonemitsu, *Tetrahedron Lett.*, 1987, **28**, 4569.
27 H. B. Wood and B. Ganem, *Tetrahedron Lett.*, 1993, **34**, 1403.
28 B. W. Dymock, P. J. Kocienski and J.-M. Pons, *Synthesis*, 1998, 1655.
29 S. P. Chavan, P. K. Zubaidha and V. D. Dhondge, *Tetrahedron*, 1993, **49**, 6429.
30 B. M. Trost and N. R. Schmuff, *J. Am. Chem. Soc.*, 1985, **107**, 396.
31 U. Leutenegger, A. Madin and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 60.
32 P. Carpino, PhD Thesis, Harvard, Cambridge, MA, USA, 1989.
33 S. W. McCombie, B. Cox and A. K. Ganguly, *Tetrahedron Lett.*, 1991, **32**, 2087.