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

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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 hexa-hydro-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



Pseudopterosin K-L aglycone

Construction of the C3 stereogenic centre. The principal attraction to the $B \rightarrow BA \rightarrow BAC$ 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 Ohloff⁴ 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 known⁵ crystalline oxirane 8 in 88% yield. ¹H and ¹³C 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 Hutchins⁸ involving addition of BF₃·OEt₂ 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.

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 $B \rightarrow BA \rightarrow BAC$ 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.





Construction of the arene ring. In 1984 Dieter,⁹ Junjappa and Ila¹⁰ reported independently that 1,2-addition of methylallylmagnesium chloride to α -oxoketene-*S*,*S*-acetals followed by treatment of the carbinol with HBF₄ 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





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 $17 \rightarrow 18$ 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



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.

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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 BF₃·OEt₂ 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.



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 EtAlCl₂ (10 equiv.) in dichloromethane at low temperature to give the hexahydro-1H-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, AlCl₃ (Et₂O, reflux) and Et₂AlCl (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 BBr₃ 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 Carpino¹⁷ 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 ZnCl₂-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 CoCl₂ 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 \ge 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

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

Our syntheses of the pseudopterosin aglycones represent another rendition of the popular $B \rightarrow BA \rightarrow BAC$ 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





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in similar circumstances previously²⁵⁻²⁷ 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 Bohlmann⁵ 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

(1S,2R,5R)-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; $[a]_{\rm D}$ + 3.2 (*c* 3, CHCl₃). Lit.⁵ mp 56–58 °C.

(1*R*,2*S*,5*R*)-2-[(*S*)-2-Hydroxy-1-methylethyl]-5methylcyclohexan-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 BF₃·OEt₂ 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 BF₃·OEt₂ solution. The mixture was diluted with brine (35 ml) and extracted with EtOAc (5 × 35 ml). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, EtOAc–hexanes 1 : 1) to give the diol **9** (3.24 g, 18.8 mmol, 79%) as a pale yellow oil having $[a]_D$, IR, ¹H NMR (300 MHz), and ¹³C 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 NH₄Cl (20 ml) and the product extracted into hexanes. The organic layer was washed with brine, dried over MgSO4 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: $[a]_{D}$ +7.1 (c 3.9, CHCl₃); v_{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; $\delta_{\rm H}$ (270 MHz, CDCl₃) 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, JAB 10.4, JBX 6.2, C2HB), 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, SiMe₂); δ_C (75 MHz, CDCl₃) 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, NH₃) 287 (MH⁺, 100%), 137 (48); Found (MH)⁺, 287.2414; C₁₆H₃₅O₂Si 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 CH₂Cl₂ (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 CH₂Cl₂ (8 ml) at -72 °C over 7 min. After 5 min the alcohol 10 (1.50 g, 5.23 mmol) in CH₂Cl₂ (4 ml) was slowly added over 4 min at -65 °C. After 90 min stirring at -65 °C, Et₃N (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. NH₄Cl (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 (SiO₂, hexanes- Et_2O 95 : 5) to give the ketone 11 (1.31 g, 4.60 mmol, 88%) as a pale yellow oil: $[a]_D$ -7.4 (c 2.5, CHCl₃); v_{max} film/ cm⁻¹ 2955 s, 2857 s, 1710 s, 1471 m, 1387 m, 1256 m, 1087 s, 836 s, 776 s; $\delta_{\rm H}$ (300 MHz, CDCl₃) 3.45 (2H, AB part of an ABX system, J_{AB} 9.9, J_{BX} 7.3, J_{AX} 5.5, C2H₂), 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, SiMe₂); δ_C (75 MHz, CDCl₃) 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, NH₃) 285 $[(M + H)^+, 100\%], 227$ (66), 153 (33); Found $(M + H)^+,$ 285.2249; C₂₀H₃₃O₂Si 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 CS₂ (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 NH₄Cl (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 MgSO4, concentrated in vacuo, and the residue purified by column chromatography (SiO₂, with etherhexanes 5:95) to give the ketene-S,S-acetal 14 (1.74 g, 4.49 mmol, 82%) as a bright yellow oil: $[a]_D$ +2.0 (c 2.36, CHCl₃); $v_{\rm max}$ film/cm⁻¹ 1683 s, 1259 s, 1098 s, 847 s; $\delta_{\rm H}$ (270 MHz, CDCl₃) 3.55 (1H, dd, J 10.0, 6.0, CH_AH_BOSi), 3.54 (1H, apparent sextet, J 6.0), 3.35 (1H, dd, J 9.9, 7.4, CH_AH_BOSi), 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'), 0.84 (3H, d, J 6.6, C6Me), 0.04 and 0.02 (3H each, s, SiMe₂); δ_{C} (67.5 MHz, CDCl₃) 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, NH₃) 389 [(M + H)⁺, 100%], 331 [(M - Bu'), 76], 257 [(M - OTBS), 80].

(5*S*,8*R*)-1-Methylthio-3,8-dimethyl-5-[(*S*)-2-hydroxy-1methylethyl]-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 NH₄Cl (10 ml) was added. The organic layer was extracted into Et₂O (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 BF₃·OEt₂ (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 NH₄Cl (10 ml). The organic material was extracted into Et₂O (30 ml) and washed with brine. The extract was dried over MgSO₄, concentrated in vacuo and the residue purified by column chromatography (SiO₂, CH₂Cl₂) to give the methylthioarene 16 (0.71 g, 2.68 mmol, 84%) as a colourless oil: v_{max} film/cm⁻¹ 3356 br, 1598 m, 1560 m, 1040 s, 850 m; $\delta_{\rm H}$ (270 MHz, CDCl₃) 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, CDCl₃) 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⁺, 52%), 205 (100).

(5*S*,8*R*)-1-Methylsulfonyl-3,8-dimethyl-5-[(*S*)-2-(*tert*-butyl-dimethylsilyloxy)-1-methylethyl]-5,6,7,8-tetrahydro-naphthalene (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 TBSCI (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 MgSO4 and concentrated in vacuo and the residue dissolved in CH₂Cl₂ (10 ml). NaHCO₃ (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 NaHCO₃ (10 ml) were added. The organic layer was diluted with CH₂Cl₂ (25 ml) and washed with Na₂S₂O₃ (1 M, 10 ml), NaHCO₃ (10 ml) and brine (10 ml). After drying over MgSO₄, the mixture was concentrated in vacuo and the residue purified by column chromatography (SiO₂, CH₂Cl₂) to give sulfone **20** (0.405 g, 0.99 mmol, 73%) as a pale yellow oil: v_{max} film/cm⁻¹ 1471 s, 1310 s, 1265 s, 1149 s, 1088 s, 958 s, 838 s, 777 s, 739 s; $\delta_{\rm H}$ (270 MHz, CDCl₃) 7.72 (1H, s, C8H), 7.32 (1H, s, C10H), 3.90-3.75 (1H, m), 3.54 (2H, d, J 6.2, CH₂OSi), 3.2-3.1 (1H, m), 3.06 (3H, s, SO₂Me), 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, J7, C6Me), 0.09 (6H, s, SiMe₂); $\delta_{\rm C}$ (67.5 MHz, CDCl₃) 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) $410(M^{+}, 0.1\%), 395$ $[(M^{+\bullet} - Me), 10], 353 [M^{+\bullet} - Bu'), 100].$

(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 NH₄Cl (6 ml). The organic phase was extracted into Et₂O (20 ml) and washed with HCl (2 M) and brine. After drying over MgSO₄, the mixture was concentrated in vacuo and the residue purified by column chromatography (SiO2, hexanes-CH2Cl2 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; $\delta_{\rm H}$ (270 MHz, CDCl₃) 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, SiMe₂); $\delta_{\rm C}$ (67.5 MHz, CDCl₃) 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, NH₃) 456 [(M⁺ + NH₄), 100%], 439 [(M⁺ + H), 15], 381 [(M⁺ - Bu^t, 27].

(5*S*,8*R*)-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-3,8dimethyl-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 H₂O₂ (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 MgSO₄, the mixture was concentrated in vacuo and the residue purified by column chromatography (SiO₂, ether-hexanes $4:96 \rightarrow 10:90$) to give the phenol 24 (0.047 g, 0.134 mmol, 42%) as a pale yellow oil: $[a]_{D}$ 1.3 (c 4.35, CHCl₃); v_{max} film/cm⁻¹ 3586 m, 3418 br, 1618 s, 1579 s, 1264 s, 1088 s, 1036 s, 837 s, 776 s, 741 s; $\delta_{\rm H}$ (270 MHz, CDCl₃) 6.67 (1H, s, C10H), 6.45 (1H, s, C8H), 3.56 (2H, d, J 5.8, CH₂OSi), 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); $\delta_{\rm C}$ (67.5 MHz, CDCl₃) 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. NH₄Cl (60 ml). The aqueous phase was separated, extracted with Et₂O $(3 \times 40 \text{ ml})$ and the combined organic layers washed with brine (20 ml) before drying over Na₂SO₄. The residue obtained on concentration in vacuo was purified by column chromatography $(SiO_2, hexanes-Et_2O4: 1)$ to give the ketene-S,S-acetal 25 (2.35) g, 5.86 mmol, 71%) as a dark orange oil: $[a]_{D}$ +14.3 (c 12, CHCl₃); v_{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; $\delta_{\rm H}$ (300 MHz, CDCl₃) 3.40 (2H, m, AB portion of ABX system, J_{AB} 7.1, C3H₂), 3.21 (1H, app. sextet, J 6.4, C13H), 2.98 (2H, ddd, A₂ portion of A2BB'XY system, JAB 13.9, S-CH2), 2.83 (1H, ddd, B portion of A₂BB'XY system, J_{AB} 13.9, J_{BX} 7.7, J_{BY} 7.3, S-CH_B), 2.75 (1H, ddd, B' portion of A₂BB'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-CH₂), 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'), 0.75 (3H, d, J 6.5, C6Me), 0.02 and 0.01 (3H each, s, SiMe₂); $\delta_{\rm C}$ (67.5 MHz, CDCl₃) 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; C₂₀H₃₆O₂SiS₂ 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 NH₄Cl (200 ml), extracted with ether (3×40 ml) and dried over Na₂SO₄. 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 BF₃·OEt₂ (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 NaHCO3 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 $(3 \times 15 \text{ ml})$. The combined organic layers were dried over Na₂CO₃-Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, hexanes- $Et_2O 7: 3$) to give the methoxyarene 27 (1.61 g, 6.48 mmol, 63%) from **25**) as a yellow oil: $[a]_D - 25.0$ (*c* 0.62, CHCl₃); v_{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; $\delta_{\rm H}$ (300 MHz, CDCl₃) 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); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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^{+•}, 37), 189 $[(M - C_3H_7O)^+, 100\%]$, 175 (26); Found M⁺, 248.1774; C₁₆H₂₄O₂ requires *M*, 248.1776.

(5*R*,8*R*)-3,8-Dimethyl-1-methoxy-5-[(*S*)-1-methyl-2-(*p*-tolyl-sulfonyl)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 NEt₃ (2.04 ml, 1.48 g, 14.6 mmol, 2.5 equiv.) in CH₂Cl₂ (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 NH₄Cl (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 Na₂CO₃-Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, hexanes-CH₂Cl₂ 1:4) to give the toluene-p-sulfonate 35 (2.02 g, 5.02 mmol, 86%) as colourless needles, mp 69–70 °C (hexanes): [a]_D +22.5 (c 1.25, CHCl₃); v_{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; $\delta_{\rm H}$ (300 MHz, CDCl₃) 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, C2H₂), 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); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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⁺⁺, 59), 230 [(M - C₇H₈O₃S)⁺⁺, 35], 215 (41), 189 (100%), 173 (38), 91 (25); Found: C, 68.40; H, 7.7%. C₂₃H₃₀O₄S 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-ene³⁰ (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-psulfonate 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 NH₄Cl (80 ml). The product was extracted into Et₂O $(3 \times 50 \text{ ml})$, and the combined organic layers washed with brine (25 ml) and dried over MgSO4. The residue obtained after filtration and concentration in vacuo was purified by column chromatography (SiO₂, Et₂O-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, ¹³C NMR). Discernible signals attributed to the minor isomer are marked with an asterisk (*). $[a]_{D}$ +13.2 (c 6, CHCl₃); v_{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; $\delta_{\rm H}$ (300 MHz, CDCl₃) 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, C16H₃), 1.69 and 1.59* (2H, m), 1.52-1.46 (2H, m, C2H₂), 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, CDCl₃) 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⁺⁺, 29%), 299 [(M – PhSO₂)⁺⁺, 100%], 216 [(M – C₁₀H₁₅SO₂)⁺⁺,48]; Found M⁺⁺, 440.2377; C₂₇H₃₆O₃S requires M, 440.2385.

Cyclisation of the sulfones 2

To a solution of sulfones 2 (264 mg, 0.6 mmol) in CH₂Cl₂ (15 ml) cooled to -78 °C was added dropwise EtAlCl₂ (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 CH₂Cl₂ $(3 \times 25 \text{ ml})$ and the combined organic layers washed with saturated aqueous NaHCO₃ (5 ml), brine (5 ml) and dried over Na₂SO₄. 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 (SiO₂, hexanes) to give (1S,3R,6R,13S)-7-methoxy-1-(2-methylprop-1enyl)-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydro-1H-phenalene 37a (142 mg, 0.48 mmol, 79%) as white needles, mp 95-96 °C (propan-2-ol); $[a]_D$ +16.8 (c 0.57, CHCl₃); v_{max} CHCl₃/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; $\delta_{\rm H}$ (300 MHz, CDCl₃) 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, J7.0, C6H), 2.22 (3H, s, C9Me), 2.21-2.10 (3H, m), 1.80 (3H, d, J 1.3, C15H₃),

1.73–1.60 (6H, m), 1.58–1.45 (2H, m, C4H₂), 1.24 (3H, d, *J* 7.0, C6Me), 1.12 (3H, d, *J* 5.5, C3Me); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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⁺⁺, 87), 283 [(M – CH₃)⁺⁺, 100%], 242 [(M – C₄H₈)⁺⁺, 30], 227 [(M – C₅H₁₁)⁺⁺, 33]; Found M⁺⁺, 298.2295; C₂₁H₃₀O requires *M*, 298.2297.

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

 $\delta_{\rm H}$ (300 MHz, CDCl₃) 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, C4H₂), 1.26 (3H, d, J 6.6, C6Me), 1.08 (3H, d, J 5.9, C3Me); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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)-3,6,9trimethyl-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 Et₂O and pouring into saturated aqueous NH₄Cl (10 ml). After extraction of the aqueous phase with Et₂O (2×10 ml), and drying of the organic phase over Na₂SO₄, the solvent was removed *in vacuo* and column chromatography of the residue (SiO₂, hexanes–Et₂O 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 BBr₃ (1.0 M solution in CH₂Cl₂, 2.46 ml, 2.46 mmol, 2 equiv.) to methoxyarene 37a (366 mg, 1.23 mmol) and freshly distilled 2,6-ditert-butyl-4-methylpyridine (303 mg, 1.48 mmol, 1.2 equiv.) in CH₂Cl₂ (15 ml). The brown suspension was stirred for 30 min, whereupon the mixture was poured into H₂O (50 ml), extracted with Et₂O (3 × 25 ml) and dried over Na₂CO₃-Na₂SO₄. The mixture was filtered, concentrated in vacuo, and the residue Et₂O 95 : 5) to give the phenol **38** (270 mg, 0.95 mmol, 77%) as a pale yellow oil: $[a]_{D}$ +14.5 (c 0.5, CHCl₃); v_{max} CHCl₃/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, CDCl₃) 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, C16H₃), 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); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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, NH₃) 285 [(M + H)⁺, 100%], 134 (65), 35 (48); Found M⁺⁺, 284.2141; C₂₀H₂₈O requires M, 284.2140.

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

(+)-Isopulegyl acetate **39** [9.15 g, 46.1 mmol, $[a]_{\rm D}$ +17.3 (*c* 2, CHCl₃)] prepared from (+)-isopulegol¹⁸ was dissolved in dry methanol (75 ml) and dry CH₂Cl₂ (25 ml), cooled to -78 °C and O₃ was bubbled through the solution until the formation of a persistent blue colour. The mixture was flushed with N₂ for 15 min at -78 °C before addition of SMe₂ (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 Et₂O (150 ml) the aqueous phase was separated, extracted with Et₂O (2×60 ml) and the organic phase washed with brine (30 ml) and dried on MgSO4. The mixture was concentrated in vacuo and the residue purified by column chromatography (SiO₂, hexanes-Et₂O 3:1) to give the ketone 40 (8.13 g, 41.0 mmol, 89%) as a colourless oil: $[a]_{D}$ +76.3 (c 2, CHCl₃); v_{max} film/cm⁻¹ 2930 s, 2870 m, 1738 s, 1715 s, 1455 m, 1371 s, 1241 s, 1204 m; $\delta_{\rm H}$ (360 MHz, CDCl₃) 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); $\delta_{\rm C}$ (90 MHz, CDCl₃) 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-2enoate (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 $(3 \times 25 \text{ ml})$ and dried on MgSO₄. The solvent was removed in vacuo and the residue purified by column chromatography (SiO₂, hexanes-ether 9:1) to give the α , β -unsaturated ester 41 (872 mg, 3.22 mmol, 64%) as a yellow oil: $[a]_{D}$ -3.4 (c 2, CHCl₃). The compound was obtained as 9:1 mixture of isomers. The stereochemistry of the major product was confirmed by NOE experiments. v_{max} film/cm⁻¹ 2930, 2870 m, 1736 s, 1646 s, 1453 m, 1373 s, 1242 s, 1154 s, 1027 s, 868 s; $\delta_{\rm H}$ (360 MHz, CDCl₃) 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, CH₂CH₃), 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, CH₂CH₃), 1.1–0.85 (1H, m), 0.98–0.80 (1H, m), 0.90 (3H, d, J 6.6, C6Me); δ_C (75 MHz, CDCl₃) 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: $\delta_{\rm H}$ (270 MHz, CDCl₃) 5.65 (1H, s, C2H), 4.82 (1H, dt, *J* 10.6, 4.4, C11H), 4.15 (2H, q, *J* 7.1, CH₂CH₃), 2.18–2.08 (1H, m, C13H), 2.06 (3H, d, *J* 1.1, C₃Me), 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, CH₃CH₂), 1.05–0.80 (2H, m), 0.92 (3H, d, *J* 6.6, C6Me); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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 N₂ was treated successively with CoCl₂·6H₂O (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 NaBH₄ (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 CH₂Cl₂ (4 × 15 ml). The combined organic extracts were washed with H₂O (15 ml) and dried over Na₂SO₄. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (SiO₂, hexanes–Et₂O 4 : 1) to give the diester **43** (592 mg, 2.2 mol, 90%) as a colourless oil: $[a]_D$ +35.7 (*c* 2.5, CHCl₃); v_{max} film/cm⁻¹ 2953 s, 2929 s, 2870 s, 1735 s, 1373 m, 1244 s, 1184 m, 1027 m; δ_H (300 MHz, CDCl₃) 4.63 (1H, dt, *J* 10.7, 4.4, C11H), 4.10 (2H, q, *J* 7.0, CH₂CH₃), 2.36 (1H, dd, *J* 14.9, 4.2, C5H), 2.27–2.19 (1H, m, C6H), 2.05 (3H, s, COCH₃), 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, CH₃CH₂), 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, CDCl₃) 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; C₁₅H₂₇O₄ 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 CH₂Cl₂ (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 CH₂Cl₂ (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 Na₂SO₄. The solvent was removed in vacuo and the residue purified by column chromatography (SiO₂, EtOAc-CH₂Cl₂ 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, CHCl₃); v_{max} CHCl₃/cm⁻¹ 3265 br s, 2923 s, 2868 s, 1455 m, 1216 m, 1033 m, 758 s; $\delta_{\rm H}$ (300 MHz, CDCl₃) 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_AH_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_AH_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); $\delta_{\rm C}$ (90 MHz, CDCl₃) 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%. C₁₁H₂₂O₂ 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 NH₄Cl (40 ml) and the product extracted into hexanes (3×30 ml). The organic layer was washed with brine (5 ml), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, Et₂O– 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 CH₂Cl₂ (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 CH₂Cl₂ (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-methyl-cyclohexan-1-ol (6.42 g, *ca.* 21,5 mmol) in CH₂Cl₂ (35 ml) was slowly added over 4 min at -65 °C. After 90 min stirring at -65 °C, Et₃N (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 NH₄Cl (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 (SiO₂, hexanes-Et₂O (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, CHCl₃); v_{max} film/cm⁻¹ 2928 s, 2858 s, 1712 s, 1462 s, 1255 s, 1104 s, 836 s, 775 s; $\delta_{\rm H}$ (360 MHz, CDCl₃) 3.68–3.56 (2H, m, C₂H₂), 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, SiMe₂); $\delta_{\rm C}$ (90 MHz, CDCl₃) 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 CS₂ (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 NH₄Cl (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 Na₂SO₄. The residue obtained after concentration in vacuo was purified by column chromatography (SiO₂, 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, CHCl₃); v_{max} film/ cm⁻¹ 2928 s, 2857 s, 1644 m, 1471 s, 1283 m, 1255 s, 1093 s, 836 s, 775 s; $\delta_{\rm H}$ (360 MHz, CDCl₃) 3.64–3.50 (2H, m, C1H₂), 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, SCH₂), 2.91 (1H, ddd, B part of an AA'BB'XY system, J_{AB} 13.8, J_{BX} 8.6, J_{BY} 7.2, SCH₂), 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, SCH₂CH₂), 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, SiMe₂); $\delta_{\rm C}$ (90 MHz, CDCl₃) 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, CH₃CN) 846 [(2M + NH₄)⁺, 82], 415 [(M + H)⁺, 100]; Found $(M + H)^+$, 415.2141; $C_{21}H_{39}O_2S_2S_1$ 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 NH₄Cl (400 ml),

extracted with ether $(3 \times 80 \text{ ml})$ and dried over Na₂SO₄. 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 BF₃·OEt₂ (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 NaHCO₃ (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 Na₂CO₃-Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, hexanes-Et₂O 7 : 3) to give the methoxyarene **47** (1.12 g, 4.27 mmol, 45% over the two steps) as a pale yellow oil: $[a]_D + 32.9$ (*c* 3.0, CHCl₃). The compound was contaminated with impurities (*ca.* 8%) that could not be removed by column chromatography.

 $v_{\rm max}$ 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; $\delta_{\rm H}$ (300 MHz, CDCl₃) 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, $J_{\rm AB}$ 10.5, $J_{\rm BY}$ 8.2, $J_{\rm AY}$ 5.1, C3H_A), 3.50–3.42 (1H, B portion of an ABXY system, $J_{\rm AB}$ 10.5, $J_{\rm BY}$ 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); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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; C₁₇H₂₇O₂ 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 CH₂Cl₂ (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 CH₂Cl₂ (1.5 ml) at -70 °C over 5 min. After 20 min alcohol 47 (262 mg, 1.0 mmol) in CH₂Cl₂ (2.6 ml) was slowly added over 4 min at -65 °C. After 90 min stirring at -65 °C, Et₃N (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 NH₄Cl (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 (SiO₂, hexanes-Et₂O 95 : 5); to give the aldehyde 48 (230 mg, 0.88 mmol, 88%) as a pale yellow oil: $[a]_{D}$ +32.9 (c 3.0, CHCl₃); v_{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, CDCl₃) 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); $\delta_{\rm C}$ (75 MHz, CDCl₃) 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⁺⁺, 22), 216 [(M - C₂H₄O)⁺⁺, 16], 189 [(M - C₄H₇O)⁺⁺, 100]; Found M⁺⁺, 260.1781; C₁₇H₂₄O₂ requires M, 260.1776.

(2'*R*,5*R*,8*S*)-1-Methoxy-3,8-dimethyl-5-(1,5-dimethyl-3hydroxyhex-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 NH₄Cl (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 (SiO₂, hexanes–NEt₂O 4 : 1 \rightarrow 1 : 1). The title alcohol **49** (150 mg, 0.47 mmol, 80%) was obtained as a 2 : 1 mixture of epimers by ¹H and ¹³C NMR spectroscopy. Discernible signals attributed to the minor isomer are marked with an asterisk (*).

 v_{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; $\delta_{\rm H}$ (360 MHz, CDCl₃) 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, C16H₃ or C17H₃), 1.67* and 1.66 (3H, d, J 1.2, C16H₃ or C17H₃), 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); $\delta_{\rm C}$ (90 MHz, CDCl₃) 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 $[(M - H_2O)^+, 8]$, 216 $[(M - C_6H_{12}O)^+, 67]$, 189 $[(M - C_8H_{15}O)^{+*}, 100];$ Found $M^{+*}, 316.2402; C_{21}H_{32}O_2$ 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 PhSO₂Na (579 mg, 3.52 mmol, 7.5 equiv.) was added to a solution of allylic alcohol **49** (150 mg, 0.47 mmol) in propan-2ol (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 NaHCO₃ (5 ml). The aqueous layer was extracted with EtOAc (2 × 5 ml) and the organic phases dried over MgSO₄ before concentrating *in vacuo*. The residue was purified by column chromatography (SiO₂, hexanes–Et₂O 1 : 1) to afford the title sulfones **5** (0.132 g, 0.3 mmol, 64%) as a 2 : 1 mixture of epimers giving ¹H and ¹³C 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)-3,6,9trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-phenalene (50)

A mixture of sulfones **5** (110 mg, 0.25 mmol) in CH₂Cl₂ (10 ml) was treated with EtAlCl₂ (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 (SiO₂, 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; $[a]_D - 17.0$ (*c* 0.6, CHCl₃). Compound **50** was identical by ¹H and ¹³C 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, $\beta = 101.27(5)^{\circ}$, U = 1762(1) Å³, T = 150 K, space group $P2_1/c$, Z = 4, μ (Mo-K α) 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]-3,6,9trimethyl-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: $[a]_{D}$ +30.5 (c 0.3, CHCl₃). IR and ¹H NMR data are in agreement with those reported by Carpino³² and McCombie: ³³ v_{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; $\delta_{\rm H}$ (360 MHz, CDCl₃) 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, C5H₂ and C13H), 2.04 (3H, s, C9Me), 1.76 (3H, s, C16H₃), 1.70 (3H, s, C17H₃), 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); $\delta_{\rm C}$ (90 MHz, CDCl₃) 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 $(M^{+*}, 100), 285 [(M - CH_3)^{+*}, 75], 245 [(M - C_4H_7)^{+*}, 68], 244$ $[(M - C_4H_8)^+, 52], 229 [(M - C_5H_{11})^+, 36], 218 (28);$ Found M⁺, 300.2071; C₂₀H₂₈O₂ requires *M*, 300.2089.

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