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Synthesis of (+)-trixagol and its enantiomer, the terpenoid side chain of (−)-agelasine E

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Abstract—The naturally occurring γ-cyclogeranylgeraniol called (+)-trixagol has been synthesised for the first time. Trixagol was readily available in five steps from (*S*)-2,2-dimethyl-6-methylene-1-cyclohexanemethanol. The enantiomer of trixagol, which equates to the terpenoid side chain of the naturally occurring 7,9-dialkylpurinium salt (−)-agelasine E, was prepared from the (*R*) enantiomer of the cyclohexanemethanol. Both trixagol enantiomers were moderately active against *Mycobacterium tuberculosis*.

1. Introduction

In 1975, 7,9-dialkylpurinium salts were isolated from the marine sponge *Agelas dispar*,[1] and at the present a total of 11 9-methyladeninium salts, agelasine A-I, epiagelasine C and agelin B, has been isolated from *Agelas* species.[2–8] All of these compounds carry a diterpenoid side chain in the adenine 7-position. At the present time, only (−)-agelasine A,[9] (−)-agelasine B,[10] and (±)-agelasine F,[11] have been synthesised. The Agelasines are associated with bio-activities like antimicrobial and cytotoxic effects as well as contractive responses of smooth muscles and inhibition of Na, K-ATPase. Furthermore in vitro activity against *Mycobacterium tuberculosis* has recently been reported for agelasine F.[12] The terpenoid side chain of agelasine E (Fig. 1) is the enantiomer of the γ-cyclogeranylgeraniol, called trixagol, found in the plant *Bellardia trixago* (L).[13] In connection with our projects directed towards the synthesis of naturally occurring bioactive purinium salts,[14] as well as antimycobacterial purines,[15–17] we are now working towards the synthesis of agelasine E. We herein report the first synthesis of (+)-trixagol and its enantiomer, the terpenoid part of (−)-agelasine E.

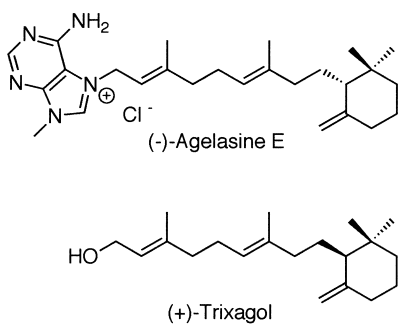

Figure 1.

2. Results and discussion

As a model substance for trixagol, we first chose to prepare the geraniol derivative **5** (Scheme 1). Geraniol was converted to the allylic alcohol **1** essentially as described before,[18] and the alcohol was reacted with diphenyldisulfide in the presence of tributylphosphine to give the sulfide **2** in high yield. Deprotonation of compound **2** with *n*-BuLi and DABCO, and subsequent reaction with bromomethylcyclohexane gave the cyclohexyl derivative **3** and the phenylthio group was easily removed with Raney-Nickel or sodium in *tert*-butanol, but compound **4** was formed as an essentially 1:1 *E*/*Z*-mixture. In order to avoid this isomerisation, we decided to move the sulfur substituent away from the allylic position.[19] The allylic alcohol **1** was converted to the tosylate **6**. Reaction between the alcohol **1** and tosyl chloride (TsCl) in pyridine was slow and the chloride was formed rather than the desired product. When the reaction was performed in the presence of trimethylammonium chloride and triethylamine,[20] however, the tosylate **6** was formed essentially quantitatively. Cyclohexylmethane-sulfonylbenzene **9**, prepared from cyclohexylmethanol **7** and diphenyldisulfide followed by oxone (89% yield) or *m*-CPBA (80% yield) oxidation of the sulfide **8**, was deprotonated with *n*-BuLi in the presence of DMPU and reacted with the tosylate **6** to give compound **10**. The sulfonyl group was removed with sodium-amalgam in methanol to give compound **4** as the pure *E*,*E* isomer, and finally the THP-protecting group was removed under mild

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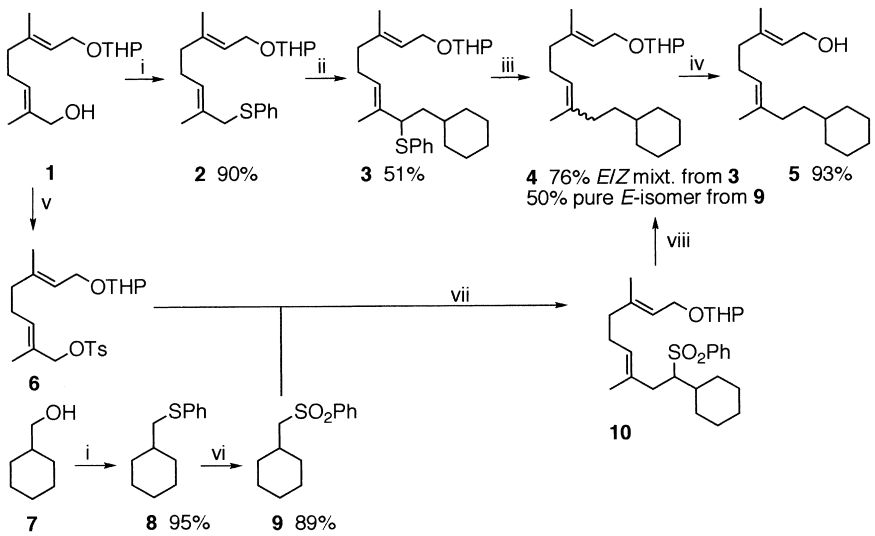
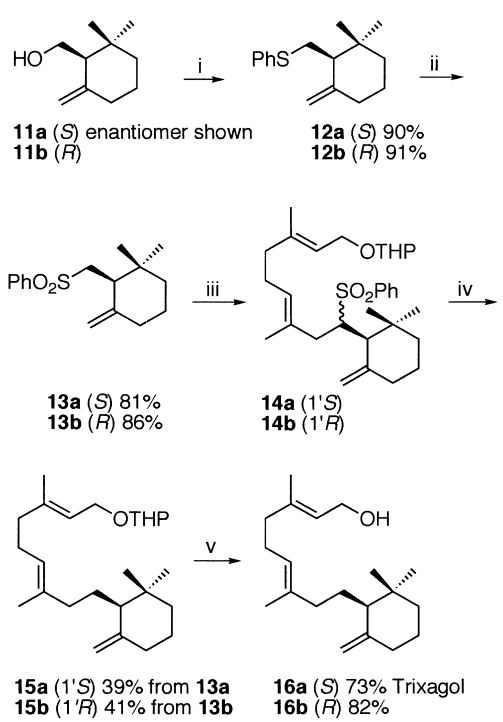


Scheme 1. *Reagents and conditions*: (i) PhSSPh, Bu_3P, pyridine; (ii) *n*-BuLi, DABCO, bromomethylcyclohexane, THF, 0°C; (iii) Raney-Ni, EtOH, 0°C; (iv) PPTS, EtOH, 55°C; (v) TsCl, Me_3NHCl, Et_3N, toluene; (vi) oxone, MeOH, H_2O, 0°C to rt; (vii) *n*-BuLi, DMPU, THF, 0°C; (viii) NaHg, Na_2HPO_4, MeOH.

conditions employing pyridinium *p*-toluenesulfonate (PPTS).[21]

The enantiomeric sulfones **13a** and **13b** required for the introduction of the cyclohexyl part of (+)-trixagol and (−)-agelasine E, were prepared from the alcohols **11** (Scheme 2). Both enantiomers of compound **11** are available from 4-methylpent-3-en-2-one and dimethyl malonate by literature methods.[22–24] The alcohols **11** were converted to the sulfides **12** in one step and compounds **12** were oxidised selectively to the corresponding sulfones **13** by applying oxone.[25] When we attempted the previously reported *m*-CPBA oxidation of (±)-**12**,[26] we were only able to isolate the desired product in 33 % yield due to concurrent epoxidation of the exocyclic double bond. The sulfones **13** were coupled with the geraniol part as described for the synthesis of compound **4** above. In the sodium mediated reduction of the sulfones **14** to compounds **15**, Na_2HPO_4 was included in order to minimise unwanted elimination.[27] The desired compounds **15** could be separated from small amounts of elimination products on silica gel impregnated with silver nitrate. Reductions with metallic sodium gave better results than with sodium-amalgam and attempts to remove the sulfonyl group with lithium metal and ethylamine[28] met with little success. After PPTS mediated protecting group cleavage, we isolated (+)-trixagol **16a** or its enantiomer **16b** in high yields. We found the optical rotations of the synthetic trixagol enantiomers to be numerically considerably higher than what has been reported for naturally occurring trixagol. This might indicate that natural trixagol is formed largely through non-enzymic processes. Both enantiomers of trixagol **16** were tested as potential antimycobacterials; at 6.25 mg/mL the inhibition of *M. tuberculosis* was 36% for (+)-trixagol **16a** and 61% for the agelasine E side chain **16b**. In the same assay, the alcohol **5** exhibited 49% inhibition.



Scheme 2. *Reagents and conditions*: (i) PhSSPh, Bu_3P, pyridine; (ii) oxone, MeOH, H_2O, 0°C to rt; (iii) *n*-BuLi, DMPU, comp. **6**, THF, 0°C to rt; (iv) Na, Na_2HPO_4, EtOH, THF; (v); (vi) PPTS, EtOH, 55°C.

3. Experimental

3.1. General

The ^1H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 Mz instrument, and the ^1H decoupled ^{13}C NMR spectra were recorded at 50 MHz using a Bruker Avance DPX 200 Mz instrument. Assignments of ^1H and ^{13}C resonances are based on APT, DEPT and / or on 2D NMR experiments (COSY, HMBC, HMQC NOESY). Mass spectra under electron impact conditions (EI) were recorded at 70 eV ionising voltage with a VG Prospec instrument, and are presented as *m/z* (% rel. int.). CH_4 was employed as the ionisation gas for chemical ionisation (CI). IR spectra were recorded on a Nicolet

Magna 550 instrument. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). Analytical thin layer chromatography was performed with E. Merck silica gel $60F_{254}$ 0.25 mm plates (Merck No. 1.05554). THF was distilled from sodium-benzophenone. DMF was distilled from BaO and DMPU from CaH_2 and stored over 4 Å molsieve. Pyridine in Sure/Seal™ bottles was purchased from Aldrich, Buchs, Switzerland. (2*E*,6*E*)-3,7-Dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-octadien-8-ol,[18] and (*S*) and (*R*)-(+)-2,2-dimethyl-6-methylene-1-cyclohexanemethanol (%ee≥98; GC)[22–24] were prepared according to literature procedures. All other reagents were commercially available and used as received. Screening of antimycobacterial activity was performed as previously reported.[17]

3.1.1. (2*E*,6*E*)-3,7-Dimethyl-8-phenylthio-1-(tetrahydro-2-pyranyloxy)-2,6-octadiene 2. A mixture of (2*E*,6*E*)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-octadien-8-ol **1** (538 mg, 2.11 mmol) and diphenyldisulfide (1.393 g, 6.19 mmol) in dry pyridine (1 mL) was stirred at ambient temperature under N_2-atm. for 30 min. Tributylphosphine (1.6 mL, 6.16 mmol) was added and the resulting mixture was stirred for an additional 2.5 h, before EtOAc (100 mL) and water (25 mL) were added. The phases were separated and the organic layer was washed with 10% HCl(aq) (25 mL), 10% NaOH(aq) (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with EtOAc–hexane (1:15); yield 657 mg (90%), colourless liquid [Found: C, 73.00; H, 8.60. $C_{21}H_{30}O_2S$ requires C, 72.80; H, 8.73%]; ν_{max}(liquid film): 3056, 2939–2849 (br) cm^{-1} δ_H (500 MHz, $CDCl_3$) 1.50–1.62 (5H, m, THP), 1.64 (3H, br s, CH_3), 1.66–1.75 (1H, m, THP), 1.73 (3H, br s, CH_3), 1.95 (2H, m, H-4), 2.09 (2H, m, H-5), 3.48 (2H, br s, H-8), 3.52 (1H, m, H-6_a in THP), 3.89 (1H, m, H-6_b in THP), 4.00 (1H, dd, J=12.0, 7.3 Hz, CH_aH$_b$OTHP), 4.22 (1H, dd, J=12.0, 6.5 Hz, CH$_a$$H_b$OTHP), 4.62 (1H, dd, J=4.6, 3.1 Hz, H-2 in THP), 5.21 (1H, t, J=7.0 Hz, H-6), 5.31 (1H, dd, J=7.3, 6.5 Hz, H-2), 7.17 (1H, m, Ph), 7.2–7.3 (2H, m, Ph), 7.32 (2H, m, Ph); δ_C (50 MHz, $CDCl_3$) 15.2 (CH_3), 16.3 (CH_3), 19.6 (CH_2 in THP), 25.5 (CH_2 in THP), 26.3 (C-5), 30.7 (CH_2 in THP), 39.1 (C-4), 44.2 (C-8), 62.3 (C-6 in THP), 63.6 (C-1), 97.9 (C-2 in THP), 120.8 (C-2), 126.2 (CH in Ph), 128.4 (CH in Ph), 128.6 (C-6), 130.5 (CH in Ph), 136.5 (C-7), 139.7 (C-3), 1 signal was hidden; *m*/*z* (EI) 346 (2, M^+), 177 (20), 176 (18), 135 (20), 110 (15), 109 (16), 93 (14), 85 (100), 84 (17), 67 (20).

3.1.2. (2*E*,6*E*)-9-Cyclohexyl-3,7-dimethyl-8-phenylthio-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene 3. A mixture of (2*E*,6*E*)-3,7-dimethyl-8-phenylthio-1-(tetrahydro-2-pyranyloxy)-2,6-octadiene **2** (173 mg, 0.50 mmol) and DABCO (224 mg, 2.0 mmol) in dry THF (5 mL) was stirred at ambient temperature under N_2-atm. for 30 min and cooled to 0°C, before *n*-BuLi (1.25 mL of a 1.6 M solution in hexane, 2.0 mmol) was added dropwise. After 30 min at 0°C, a solution of bromomethylcyclohexane (90 mg, 0.51 mmol) in dry THF (3 mL) was added dropwise. The resulting mixture was stirred at 0°C for 3 h and allowed to reach ambient temperature before diethyl ether (50 mL) was added and the mixture was washed with water (2×25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with EtOAc–hexane (1:15); yield 113 mg (51%), colourless liquid; δ_H (500 MHz, $CDCl_3$) 0.82–0.96 (3H, m), 1.09–1.36 (5H, m), 1.49–1.75 (10H, m), 1.607 (3H, br s, CH_3), 1.614 (3H, br s, CH_3), 1.80–1.85 (3H, m), 1.98–2.02 (2H, dd, J=15.0, 7.6 Hz, H-5), 3.49–3.53 (1H, m, THP), 3.70–3.74 (1H, dd, J=8.9, 6.8 Hz, H-8), 3.86–3.91 (1H, m, THP), 3.98 (1H, dd, J=11.8, 7.3 Hz, CH_aH$_b$OTHP), 4.21 (1H, dd, J=11.8, 6.4 Hz, CH$_a$$H_b$OTHP), 4.60–4.62 (1H, m, H-2 in THP), 4.98 (1H, t, J=7.0 Hz, H-6), 5.27 (1H, dd, J=7.3, 6.4 Hz, H-2), 7.17–7.28 (3H, m, Ph), 7.30–7.33 (2H, m, Ph); δ_C (50 MHz, $CDCl_3$) 11.5 (CH_3), 16.3 (CH_3), 19.6 (CH_2 in THP), 25.5 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 30.7 (CH_2), 32.7 (CH_2), 33.6 (CH_2), 35.3 (C-10), 39.0 (C-4), 40.0 (CH_2), 56.1 (C-8), 62.2 (C-6 in THP), 63.6 (C-1), 97.8 (C-2 in THP), 120.6 (C-2), 126.7 (CH in Ph), 127.9 (C-6), 128.4 (CH in Ph), 132.8 (CH in Ph), 133.5 (C-7), 135.7 (C in Ph), 139.8 (C-3); *m*/*z* (CI, CH_4) 443 (3, MH^+), 442 (5, M^+), 342 (25), 341 (100), 273 (11), 249 (11), 232 (14), 231 (75), 163 (10), 135 (14), 85 (72), 61 (13).

3.1.3. (2*E*,6*E*)-9-Cyclohexyl-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene 4. *Method A*: A solution of (2*E*,6*E*)-9-cyclohexyl-3,7-dimethyl-8-phenylthio-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene **3** (261 mg, 0.59 mmol) in abs. EtOH (15 mL) was added dropwise to a stirred mixture of Raney-Nickel (3.551 g of a 50% suspension in water) in abs. EtOH (20 mL) at 0°C. The reaction mixture was stirred at 0°C for 40 min and filtered through celite. The celite was washed with EtOH (50 mL) and the combined EtOH solutions were evaporated in vacuo. The product was purified by flash chromatography eluting with EtOAc–hexane (1:15); yield 150 mg (76%) as a ca. 1:1 mixture of the 6*E*,6*E* and 6*Z*,2*E* isomers; colourless liquid.

Method B. To a mixture of (2*E*,6*E*)-9-benzenesulfonyl-9-cyclohexyl-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene **10** (405 mg, cont. ca. 25% of comp. **9**) and Na_2HPO_4 (545 mg, 3.8 mmol) in methanol (10 mL) was added NaHg 5% (2.508 g, 5.5 mmol Na) and the resulting mixture was stirred at ambient temperature for 2 h. Water (25 mL) and diethyl ether (50 mL) was added, the mixture was decanted and the phases separated. The ethereal layer was washed with sat. NH_4Cl(aq) (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with EtOAc–hexane (1:15); yield 192 mg (50%) in two steps from comp. **9**, colourless liquid [Found: C, 79.00; H, 11.54. $C_{22}H_{38}O_2$ requires C, 78.99; H, 11.45%]; δ_H (500 MHz, $CDCl_3$) 0.80–0.88 (1H, m), 1.01–1.25 (6H, m), 1.49–1.74 (11H, m), 1.55 (3H, br s, CH_3), 1.65 (3H, br s, CH_3), 1.78–1.85 (1H, m), 1.91–1.95 (2H, m, H-8), 2.00–2.05 (2H, m, H-4), 2.05–2.11 (2H, m, H-5), 3.47–3.51 (1H, m, H-6_a in THP), 3.85–3.89 (1H, m, H-6_b in THP), 4.01 (1H, dd, J=12.0, 7.6 Hz, CH_aH$_b$OTHP), 4.21 (1H, dd, J=12.0, 6.3 Hz, CH$_a$$H_b$OTHP), 4.59–4.61 (1H, m, H-2 in THP), 5.07 (1H, t, J=7.0 Hz, H-6), 5.34 (1H, dd, J=7.6, 6.3 Hz, H-2); δ_C (50 MHz, $CDCl_3$) 16.0 (CH_3), 16.4 (CH_3), 19.6 (CH_2), 25.4

(C-5), 26.3 (CH_2), 26.4 (CH_2), 26.7 (CH_2), 30.7 (CH_2), 33.3 (CH_2), 35.8 (C-9), 37.0 (C-8), 37.4 (C-10), 39.6 (CH_2), 62.2 (C-6 in THP), 63.6 (C-1), 97.7 (C-2 in THP), 120.6 (C-2), 123.4 (C-6), 135.9 (C-7), 140.2 (C-3); *m/z* (CI, CH_4) 335 (0.1, MH^+), 233 (28), 232 (10), 137 (10), 121 (8), 109 (20), 95 (19), 85 (100).

3.1.4. (2*E*,6*E*)-9-Cyclohexyl-3,7-dimethyl-2,6-nonadien-1-ol 5. A mixture of (2*E*,6*E*)-9-cyclohexyl-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene **4** (56 mg, 0.17 mmol) and pyridinium *p*-toluenesulfonate (11 mg, 0.04 mmol) in ethanol (2 mL) was stirred at 55°C under N_2-atm. for 13 h, before the mixture was evaporated in vacuo and the residue was purified by flash chromatography eluting with acetone–hexane (1:5); yield 39 mg (93%), pale yellow oil [Found C, 81.28; H, 11.66. $C_{17}H_{30}O$ requires C, 81.54; H, 12.08]; δ_H (500 MHz, $CDCl_3$) 0.80–0.88 (2H, m), 1.00–1.25 (5H, m, H-9 and cyclohexyl), 1.29 (1H, br s, OH), 1.56 (3H, br s, CH_3), 1.65 (3H, br s, CH_3), 1.59–1.69 (6H, m, cyclohexyl), 1.92–1.95 (2H, m, H-8), 1.99–2.02 (2H, m, H-4), 2.06–2.10 (2H, m, H-5), 4.12 (2H, d, *J*=6.9 Hz, H-1), 5.07 (1H, t, *J*=6.9 Hz, H-6), 5.39 (1H, t, *J*=6.9 Hz, H-2); δ_C (50 MHz, $CDCl_3$) 15.9 (CH_3), 16.2 (CH_3), 26.3 (C-5), 26.4 (CH_2), 26.7 (CH_2), 33.3 (CH_2), 35.8 (C-9), 37.0 (C-8), 37.3 (C-10), 39.5 (C-4), 59.3 (C-1), 123.25 (C-6), 123.30 (C-2), 136.1 (C-7), 139.8 (C-3); *m/z* (EI): 250 (7, M^+), 123 (24), 109 (87), 95 (94), 93 (46), 83 (78), 81 (54), 69 (46), 67 (40), 55 (100).

3.1.5. (2*E*,6*E*)-3,7-Dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-octadien-8-yl 4-methylbenzenesulfonate 6. A solution of tosyl chloride (314 mg, 1.6 mmol) in toluene (3 mL), was added to a stirred solution of (2*E*,6*E*)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-octadien-8-ol **1** (382 mg, 1.5 mmol), trimethylammonium hydrochloride (142 mg, 1.5 mmol) and triethylamine (0.52 mL, 3.7 mmol) in toluene (3 mL) under N_2-atm. The resulting mixture was stirred for 2 h, diluted with diethyl ether (100 mL), washed with water (2×25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo; yield 572 mg, pale yellow oil which was used directly without further purification; δ_H (500 MHz, $CDCl_3$, 0°C) 1.50–1.61 (4H, m), 1.58 (3H, s, $-C_4H_6-CH_3$), 1.66 (3H, br s, CH_3), 1.71–1.76 (1H, m), 1.80–1.85 (1H, m), 1.99–2.02 (2H, m, H-4), 2.08–2.13 (2H, m, H-5), 2.46 (3H, br s, CH_3), 3.50–3.53 (1H, m), 3.87–3.92 (1H, m,), 4.00 (1H, dq, *J*=11.7, 7.5 Hz), 4.25 (1H, dq, *J*=11.7, 6.5 Hz), 4.40 (2H, br s, H-8), 4.61–4.63 (1H, m), 5.32–5.35 (1H, H-2), 5.40–5.43 (1H, m, H-6), 7.36 (2H, d, *J*=8.1 Hz, Ar), 7.84 (2H, d, *J*=8.1 Hz, Ar); δ_C (50 MHz, $CDCl_3$) 13.6 ($-C_4H_6-CH_3$), 16.3 (CH_3), 19.5 (CH_2); 21.7 (CH_3), 25.3 (CH_2), 25.8 (C-5), 30.5 (CH_2), 38.4 (CH_2), 62.3 (CH_2O–THP), 63.5 (C-1), 76.8 (CH_2OTs), 97.9 (CHO–THP), 120.7 (C-2), 127.8 (CH in Ph), 128.3 (C in Ph); 129.7 (CH in Ph), 132.3 (C-6), 133.0 (C in Ph), 139.4 (C-3), 144.6 (C-7); *m/z* (CI, CH_4): 335 (0.1, MH^+), 233 (28), 232 (10), 165 (19), 137 (10), 121 (8), 109 (20), 95 (19), 85 (100), 83 (11).

3.1.6. Cyclohexylmethyl)thiobenzene 8. Tributylphosphine (7.6 mL, 29.3 mmol) was added to a stirred mixture of cyclohexylmethanol **7** (1.3 mL, 10.6 mmol) and diphenyldisulfide (6.598 g, 31.2 mmol) in pyridine (4.3 mL) at ambient temperature under N_2-atm. The resulting mixture was stirred for 13 h, diluted with ethyl acetate (100 mL), washed with 10% HCl(aq) (25 mL), 10% NaOH(aq) (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone–hexane (1:100); yield 2.303 g (95%), colourless liquid; Spectral data were in good agreement with those reported before.[29]

3.1.7. Cyclohexylmethyl)sulfonylbenzene 9. A solution of oxone (8.260 g, 13.4 mmol) in water (35 mL) was added to a stirred solution of (cyclohexylmethyl)thiobenzene **8** (1.848 g, 8.95 mmol) in methanol (35 mL) at 0°C. When the addition was complete, the cooling bath was removed and the reaction mixture was stirred for 19 h at ambient temperature before diethyl ether (200 mL) was added and the resulting mixture was washed with water (100 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone–hexane (1:5); yield 1.896 g (89%), colourless liquid which solidified upon standing, mp 56–57°C (lit.[30] 53–54°C).

3.1.8. (2*E*,6*E*)-9-Benzenesulfonyl-9-cyclohexyl-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene 10. *n*-Butyllithium (2.5 mL, 1.4 M sol., 3.5 mmol) was added dropwise to a stirred solution of cyclohexylmethanesulfonylbenzene **9** (414 mg, 1.74 mmol) in THF (10 mL) at 0°C under N_2-atm. and the resulting mixture was stirred at 0°C for 30 min before a solution of crude (2*E*,6*E*)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-octadien-8-yl 4-methylbenzenesulfonate **6** (710 mg, ca. 1.74 mmol) and DMPU (2.5 mL, 21 mmol) in THF (3 mL) was added. The reaction mixture was stirred for 20 h while reaching ambient temperature. Diethyl ether (50 mL) was added and the mixture was washed with sat. NH_4Cl(aq) (25 mL), water (3×25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was partly purified by flash chromatography eluting with acetone–hexane (1:5); yield 608 mg (diastereomeric mixture of the compounds **10** cont. ca 25% starting material **9**), colourless oil. Further purification gave an analytical sample [Found: C, 70.77 H, 8.79. $C_{28}H_{42}O_4S$ requires C, 70.85; H, 8.92%]. Spectral data for the diastereomeric mixture: δ_H (500 MHz, $CDCl_3$) 1.00–1.10 (1H, m), 1.14–1.25 (2H, m), 1.26 (3H, br s, CH_3), 1.31–1.41 (2H, m), 1.43–1.58 (6H, m), 1.62 (3H, br s, CH_3), 1.57–1.65 (1H, m), 1.66–1.75 (2H, m), 1.77–1.86 (2H, m), 1.89–1.98 (4H, m, H-4 and H-5), 2.14–2.21 (1H, m), 2.36–2.46 (2H, m, H-8), 3.01–3.04 (1H, t, *J*=6.8 Hz, H-9), 3.46–3.50 (1H, m, H-6_a in THP), 3.83–3.88 (1H, m, H-6_b in THP), 3.97 (1H, dd, *J*=11.8, 7.4 Hz, CH_aH_bOTHP), 4.20 (1H, dd, *J*=11.8, 6.4 Hz, CH_aH_bOTHP), 4.58 (1H, m, H-2 in THP), 5.12 (1H, br s, H-6), 5.30 (1H, dd, *J*=7.4, 6.4 Hz, H-2), 7.48–7.51 (2H, m, Ph), 7.57–7.60 (3H, m, Ph); δ_C (50 MHz, $CDCl_3$) 15.0 (CH_3), 16.35 and 16.37 (CH_3), 19.61 and 19.60 (CH_2 in THP), 25.4 (CH_2 in THP), 26.1 (CH_2), 26.2 (C-5), 26.4 (CH_2), 27.1 (CH_2), 28.3 (CH_2), 30.7 (CH_2), 31.3 (CH_2), 35.3 (CH_2), 37.4 (C-10), 39.0 (C-4), 62.28 and 62.29 (C-6 in THP), 63.61 and 63.62 (C-1), 66.7 (C-9), 97.90 and 97.92 (C-2 in THP), 120.8 (C-2), 128.2 (C-6), 128.5 (CH in Ph), 128.9 (CH in Ph), 130.2 (C-7), 133.2 (CH in Ph), 139.6 (C in Ph), 139.8 (C-3); *m/z* (EI) 474 (0.3 M^+), 389 (28), 231 (47), 230 (51), 229 (28), 163 (39), 135 (23), 121 (22), 93 (18), 85 (100).

3.1.9. (*S*)-(−)-2,2-Dimethyl-6-methylene-1-[1′-(phenylthio)methyl]cyclohexane 12a. A mixture of (*S*)-(+)-2,2-dimethyl-6-methylene-1-cyclohexanemethanol **11a** (639 mg, 4.1 mmol) and diphenyldisulfide (1.174 g, 5.4 mmol) in pyridine (8 mL) was stirred at ambient temperature for 1 h before tributylphosphine (1.4 mL, 5.4 mmol) was added. After stirring for an additional 15 h, diethyl ether (100 mL) and water (25 mL) were added and the phases separated. The organic extract was washed with 10% HCl(aq) (25 mL), 10% NaOH(aq) (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone–hexane (1:100); yield 923 mg (90%), colourless liquid [Found: C, 78.17; H, 9.02. $C_{16}H_{22}S$ requires C, 77.99; H, 9.00%]; $[\alpha]_D=-55.1$ (*c* 2.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.82 (3H, s, CH_3), 0.90 (3H, s, CH_3), 1.11–1.25 (2H, m, H-3 or H-4), 1.35–1.45 (2H, m, H-3 or H-4), 1.97–2.11 (3H, m, H-1 and H-5), 2.94 (1H, t, *J*=11.4 Hz, CH_aH_bS), 3.09 (1H, dd, *J*=11.4, 3.7 Hz, CH_aH_bS), 4.61 (1H, d, *J*=1.3 Hz, $=CH_aH_b$), 4.82 (1H, br s, $=CH_aH_b$), 7.06–7.09 (1H, m, Ph), 7.17–7.20 (2H, m, Ph), 7.24–7.26 (2H, m, Ph); δ_C (50 MHz, $CDCl_3$) 23.5 (CH_2), 25.4 (CH_3), 28.4 (CH_3), 32.0 (CH_2S), 32.7 (C-5), 35.5 (C-2), 36.9 (CH_2), 53.1 (C-1), 110.3 ($=CH_2$), 125.5 (CH in Ph), 128.68 (CH in Ph), 128.73 (CH in Ph), 137.8 (C in Ph), 147.3 (C-6); *m*/*z* (EI) 246 (137, M^+), 137 (22), 136 (53), 123 (100), 121 (19), 109 (16), 95 (17), 93 (18), 81 (32).

3.1.10. (*R*)-(+)-2,2-Dimethyl-6-methylene-1-[1′-(phenylthio)methyl]cyclohexane 12b. The title compound was prepared from (*R*)-(−)-2,2-dimethyl-6-methylene-1-cyclohexanemethanol **11b** as described for the enantiomer **12a** above; yield 91% [Found: C, 78.06; H, 9.11. $C_{16}H_{22}S$ requires C, 77.99; H, 9.00%]; $[\alpha]_D=+56.5$ (*c* 2.0, $CHCl_3$).

3.1.11. (*S*)-(+)-1-[1′-(Benzenesulfonyl)methyl]-2,2-dimethyl-6-methylenecyclohexane 13a. A solution of oxone (3.241 g, 10.5 mmol) in water (15 mL) was added to a stirred solution of (*S*)-(−)-2,2-dimethyl-6-methylene-1-[1′-(phenylthio)methyl]cyclohexane **12a** (886 mg, 3.5 mmol) in methanol (15 mL) at 0°C. When the addition was complete, the cooling bath was removed and the reaction mixture was stirred for 3 h at ambient temperature before diethyl ether (100 mL) was added and the resulting mixture was washed with water (75 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone–hexane (1:5); yield 796 mg (81%), colourless crystals, mp 38–39°C [Found: C, 68.76; H, 7.85. $C_{16}H_{22}O_2S$ requires C, 69.02; H, 7.96%]; $[\alpha]_D=+10.8$ (*c* 2.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.75 (3H, s, CH_3), 0.87 (3H, s, CH_3), 1.27–1.29 (2H, m, H-3), 1.46–1.48 (2H, m, H-4), 1.92–2.00 (2H, m, H-5), 2.40–2.42 (1H, dd, *J*=9.5, 2.5 Hz, H-1), 3.22 (1H, dd, *J*=14.8, 2.5 Hz, $CH_aH_bSO_2$), 3.32 (1H, *J*=14.8, 9.5 Hz, $CH_aH_bSO_2$), 4.53 (1H, br s, $=CH_aH_b$), 4.71 (1H, br s, $=CH_aH_b$), 7.49–7.52 (2H, m, Ph), 7.58–7.62 (1H, m, Ph), 7.85–7.87 (2H, m, Ph); δ_C (50 MHz, $CDCl_3$) 23.2 (C-4), 24.9 (CH_3), 27.8 (CH_3), 32.9 (C-5), 35.3 (C-2), 37.2 (C-3), 47.7 (C-1), 54.4 (CH_2SO_2), 110.9 ($CH_2=$), 128.2 (CH in Ph), 129.0 (CH in Ph), 133.4 (CH in Ph), 140.0 (C in Ph), 145.6 (C-6); *m*/*z* (EI) 278 (0.12, M^+), 137 (51), 136 (100), 121 (34), 107 (12), 95 (22), 93 (35), 81 (34), 77 (21), 69 (28).

3.1.12. (*R*)-(−)-1-[1′-(Benzenesulfonyl)methyl]-2,2-dimethyl-6-methylenecyclohexane 13b. The title compound was prepared from (*R*)-(+)-2,2-dimethyl-6-methylene-1-[1′-(phenylthio)methyl]cyclohexane **12b** as described for the enantiomer **13a** above; yield 86% [Found: C, 69.36; H, 7.94. $C_{16}H_{22}O_2S$ requires C, 69.02; H, 7.96%]; $[\alpha]_D=-10.9$ (*c* 3.9, $CHCl_3$).

3.1.13. (1′*S*)-(2*E*,6*E*)-9-Benzenesulfonyl-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene 14a and the 1′*R*-isomer 14b. *n*-Butyllithium (1.20 mL, 1.5 M sol., 1.80 mmol) was added dropwise to a stirred solution of (*S*)-(+)-1-[1′-(benzenesulfonyl)methyl]-2,2-dimethyl-6-methylenecyclohexane **13a** or (*R*) enantiomer **13b** (240 mg, 0.86 mmol) in THF (10 mL) at 0°C under N_2-atm. and the resulting mixture was stirred at 0°C for 1 h before a solution of crude (2*E*,6*E*)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-octadien-8-yl 4-methylbenzenesulfonate **6** (420 mg, ca. 1.00 mmol) and DMPU (1.3 mL, 10.8 mmol) in THF (5 mL). The reaction mixture was stirred for 16 h while reaching ambient temperature. Diethyl ether (50 mL) was added and the mixture was washed with sat. NH_4Cl(aq) (25 mL), water (10 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone–hexane (1:5); to give the compounds **14a** or **14b** as a mixture of stereoisomers containing ca. 20% of starting material **13a** or **13b**. Further purification gave analytical samples as colourless liquids [**14a**: Found: C, 72.34; H, 8.97; **14b**: [Found: C, 72.18; H, 8.85 $C_{31}H_{46}O_4S$ requires C, 72.33; H, 9.01%]. Spectral data for the isomeric mixtures: δ_H (500 MHz, $CDCl_3$) 0.80–0.88 (m), 0.96 (s, CH_3) 0.97 (s, CH_3), 1.00 (s, CH_3), 1.07 (s, CH_3), 1.09 (s, CH_3), 1.12 (s, CH_3), 1.16–1.26 (m), 1.35–1.40 (m), 1.47–1.56 (m), 1.61 (s, CH_3), 1.66–1.71 (m), 1.76–1.85 (m), 1.88–2.04 (m), 2.12–2.23 (m), 2.28–2.34 (m), 2.45–2.51 (m, H-10), 2.59–2.62 (m), 2.67–2.73 (m), 3.14 (bs, H-10), 3.45–3.51 (m, CH_2O in THP and $CH_aH_bSO_2Ph$), 3.68–3.71 (m, $CH_aH_bSO_2Ph$) 3.83–3.88 (m, CH_2O in THP), 3.93–3.99 (m, H-1), 4.17–4.22 (m, H-1), 4.58–4.59 (m, CHO in THP), 4.73 (br s, $CH_2=$), 5.01 (br s, $CH_2=$), 5.03 (br s, $CH_2=$), 5.08–5.10 (m, H-6), 5.16 (m, H-6), 5.28–5.32 (m, H-2), 7.44–7.47 (m, Ph), 7.49–7.54 (m, Ph), 7.55–7.59 (m, Ph), 7.76–7.77 (m, Ph), 7.82–7.83 (m, Ph); δC (50 MHz, $CDCl_3$) 14.6 (CH_3, H-7), 15.3 (CH_3, H-7), 16.29 (CH_3, H-3 or H-7), 16.31 (CH_3, H-3 or H-7), 16.4 (CH_3, H-3 or H-7), 19.55 (CH_2), 19.60 (CH_2), 19.62 (CH_2), 22.2, (CH_2), 23.2 (CH_2), 25.4 (CH_2), 26.11 (CH_2), 26.14 (CH_2), 26.2 (CH_2), 27.5 (CH_3), 28.6 (CH_3), 29.1 (CH_3), 29.9 (CH_3), 30.64 (CH_2), 30.7, (2×CH_2), 33.3 (CH_2), 34.0 (CH_2), 34.3 (C-11), 34.85 (C-11), 34.86 (C-11), 34.87 (C-11), 35.8 (CH_2), 36.8 (CH_2), 37.43 (CH_2), 37.44 (CH_2), 38.7 (CH_2), 38.9 (CH_2), 39.1 (CH_2), 47.8 (C-10), 51.9 (C-10), 62.20 (C-6 in THP), 62.29 (C-6 in THP), 62.31 ($CHSO_2Ph$), 62.33 ($CHSO_2Ph$), 62.4 ($CHSO_2Ph$), 63.56 (C-1), 63.59 (C-1), 63.62 (C-1), 63.64 (C-1), 97.87 (C-2 in THP), 97.91 (C-2 in THP), 97.92 (C-2 in THP), 98.0 (C-2 in THP), 114.1 ($CH_2=$), 116.2 ($CH_2=$), 120.9 (C-2), 121.0 (C-2), 127.6 (C-6), 128.1 (CH in Ph), 128.5 (CH in Ph), 128.8 (CH in Ph), 128.9 (CH in Ph), 129.6 (C-6), 129.7 (C-6), 129.99 (C-7), 130.00 (C-7), 130.01 (C-7), 130.6 (C-7), 132.8 (CH in Ph), 133.0 (CH in Ph), 139.4 (C-3), 139.5 (C-3), 139.6 (C-3), 139.7 (C-3), 141.05 (C in Ph), 141.06 (C in Ph), 144.4 ($C=CH_2$), 146.3

(C═CH_2); *m*/*z* (EI) 514 (0.22, M^+), 271 (31), 238 (54), 193 (43), 166 (27), 165 (100), 147 (44), 93 (28), 85 (43), 81 (34), 55 (30).

3.1.14. (1′*S*)-(2*E*,6*E*)-9-(2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene 15a. A mixture of (1′*S*)-(2*E*,6*E*)-9-benzenesulfonyl-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene **14a** (333 mg, cont. ca. 20% of comp. **13a**), Na_2HPO_4 (2.755 g, 19.4 mmol), sodium (617 mg, 26.8 mmol) and ethanol (2.3 mL, 39 mmol) in THF (50 mL) was stirred at ambient temperature for 16 h, before the mixture was filtered and the filtrate was diluted with diethyl ether (100 mL). The resulting mixture was washed with water (100 mL), sat. NH_4Cl(aq) (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel containing 20%(w/w) $AgNO_3$ eluting with EtOAc–hexane (1:15); yield 126 mg (39% from compound **13a**), of the title compound as a diastereomeric mixture, colourless liquid [Found: C, 79.91 H, 11.27. $C_{25}H_{42}O_2$ requires C, 80.16; H, 11.30%]; δ_H (500 MHz, $CDCl_3$) 0.81 (3H, s, CH_3), 0.88 (3H, s, CH_3), 1.15–1.23 (1H, m), 1.56 (3H, br s, CH_3), 1.33–1.63 (10H, m), 1.66 (3H, br s, CH_3), 1.63–1.75 (3H, m), 1.77–1.85 (m, 1 H), 1.85–2.00 (2H, m), 2.01–2.05 (2H, m), 2.05–2.11 (2H, m, H-5), 3.47–3.51 (1H, m, H-6_a in THP), 3.85–3.89 (1H, m, H-6_b in THP), 4.01 (1H, dd, J=11.9, 7.5 Hz, CH_aH$_b$OTHP), 4.21 (1H, dd, J=11.9, 6.4 Hz, CH$_a$$H_b$OTHP), 4.51 (1H, d, J=2.5 Hz, ═CH_aH$_b$), 4.59–4.61 (1H, t, J=3.8 Hz, H-2 in THP), 4.72 (1H, br s, ═CH$_a$$H_b$), 5.05–5.08 (1H, t, J=6.6 Hz, H-6), 5.33–5.35 (1H, dd, J=7.5, 6.4 Hz, H-2); δ_C (50 MHz, $CDCl_3$) 16.1 (CH_3), 16.4 (CH_3), 19.6 (CH_2 in THP), 23.7 (CH_2), 24.7 (CH_2), 25.5 (CH_2 in THP), 26.3 (CH_2 and CH_3), 28.4 (CH_3), 30.7 (CH_2), 32.5 (CH_2), 34.8 (CCH$_3$), 36.3 (CH_2), 38.2 (C-8), 39.7 (C-4), 53.6 (C-1 in cyclohexyl), 62.3 (C-6 in THP), 63.6 (C-1), 97.8 (C-2 in THP), 108.8 (CH_2═), 120.5 (C-2), 123.6 (C-6), 135.8 (C-7), 140.3 (C-3), 149.3 (C═CH_2); *m*/*z* (EI) 374 (1, M^+), 272 (13), 177 (20), 175 (19), 149 (16), 123 (13), 109 (16), 95 (17), 85 (100), 81 (26), 69 (16).

3.1.15. (1′*R*)-(2*E*,6*E*)-9-(2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene 15b. The title compound was prepared from (1′*R*)-(2*E*,6*E*)-9-benzenesulfonyl-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene **14b** as described for the enantiomer **15a** above; yield 41% from compound **13b**.

3.1.16. (*S*)-(+)-(2*E*,6*E*)-9-(2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-ol (trixagol) 16a. A mixture of (1′*S*)-(2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene **15a** (126 mg, 0.34 mmol) and pyridinium *p*-toluenesulfonate (8.5 mg, 0.03 mmol) in ethanol (3 mL) was stirred at 55°C under N_2-atm. for 3 h, before the mixture was evaporated in vacuo and the residue was purified by flash chromatography eluting with acetone–hexane (1:5); yield 72 mg (73%), colourless oil; $[\alpha]_D$=+14 (*c* 2.6, $CHCl_3$); (lit.[12] $[\alpha]_D$=+8.0; *c* 0.76, $CHCl_3$). Spectral data were in good agreement with those reported before.[12]

3.1.17. (*R*)-(−)-(2*E*,6*E*)-9-(2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-ol 16b. The title compound was prepared from (2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-1-(tetrahydro-2-pyranyloxy)-2,6-nonadiene **15b** as described for the enantiomer **16a** above; yield 82% [Found: C, 82.93; H, 11.91. $C_{20}H_{34}O$ requires C, 8269; H, 11.80%]; $[\alpha]_D$=−15 (*c* 2.6, $CHCl_3$).

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