

## A New Approach to Functionalized Cyclobutanes: Stereoselective Synthesis of the Enantiomers of Grandisol and Fraganol

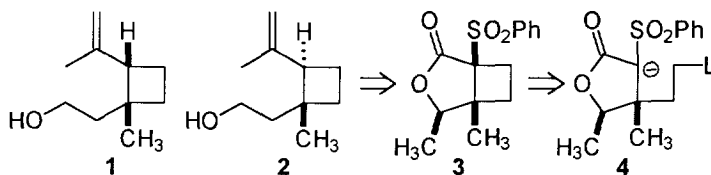
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**Abstract:** Enantiomerically enriched (+)-grandisol and (+)-fraganol were synthesized using as the key step a new stereoselective synthesis of cyclobutanes fused to  $\gamma$ -lactones by a stereochemically-controlled intramolecular alkylation of  $\alpha$ -benzenesulfonyl- $\gamma$ -lactones. This method provides a way to synthesize the enantiomers in a straightforward manner.

The cyclobutane ring is frequently encountered in the structure of natural products.<sup>1</sup> (+)-grandisol **1** has been found to be an active component of the sex pheromone of male cotton boll weevils, *Anthonomus grandis* Boheman<sup>2</sup> and other species.<sup>3</sup> The *trans*-isomer fraganol **2**, a natural product isolated from the roots of *Artemisia fragrans* Willd.,<sup>2</sup> was found to be 100- to 200-times less active than the *cis*-compound in the laboratory assay of weevil attraction. Although several syntheses of both enantiomers of grandisol have been developed in order to study the stereochemistry-pheromone activity relationship,<sup>3</sup> we are not aware of any enantiomeric synthesis of fraganol. Most of the syntheses reported to date obtain the key cyclobutane ring by stereoselective [2+2] cycloaddition.<sup>4</sup> The asymmetric synthesis of the four-membered ring by the intramolecular attack of a nucleophilic carbon to an electrophilic position has scarcely been used in light of the difficulty of ensuring the stereochemistry on the ring.<sup>5</sup>

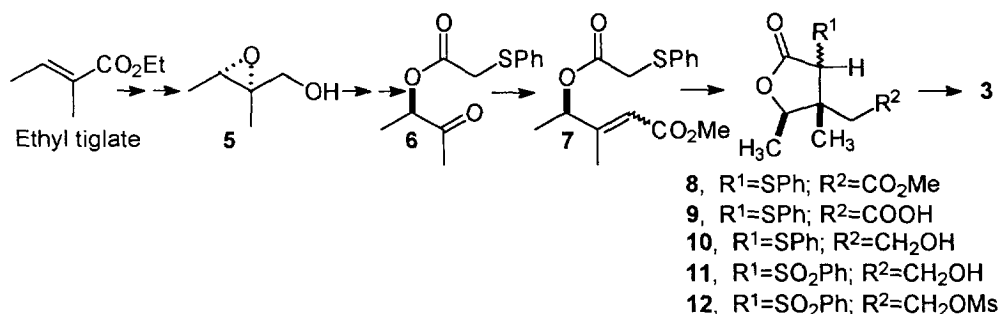
In this paper we report on the synthesis of the enantiomers of both grandisol **1** and fraganol **2**, in which the cyclobutane ring is obtained by an intramolecular carbon-carbon bond formation based on our recently reported diastereoselective alkylation of enantiomerically enriched  $\alpha$ -benzenesulfonyl- $\gamma$ -lactones (**Scheme 1**).<sup>6</sup>



**Scheme 1**

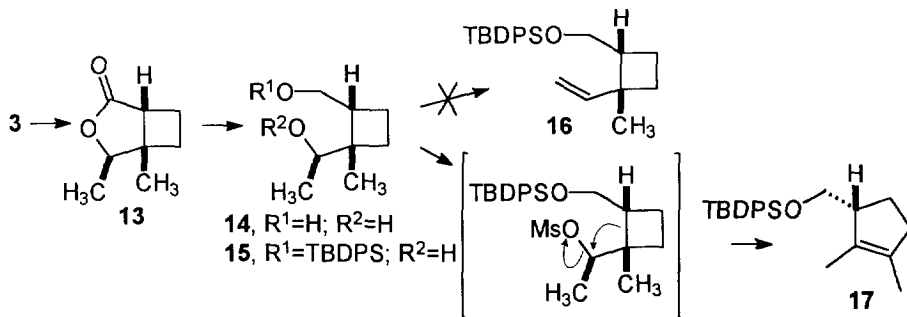
Our synthetic plan as shown in **Scheme 1** was based on the intramolecular reaction of the enolate **4** with a suitable leaving group located in the side chain of a  $\gamma$ -lactone ring, expecting that the stereochemistry of the newly created stereocenter would be controlled by two major factors: the relative stereochemistry in the fused ring system and the observed stereochemical course in the intermolecular alkylations.<sup>6</sup>

In order to obtain the precursor of **4** we prepared **8** by application of our recently reported methodology of the enantiomeric synthesis of  $\gamma$ -lactones based on the intramolecular Michael addition of  $\gamma$ -[(phenylthio)acyl]oxy  $\alpha$ - $\beta$ -unsaturated esters.<sup>7</sup> Thus, the asymmetric epoxidation<sup>8</sup> of tiglic alcohol obtained from reduction of ethyl tiglate yielded the epoxy alcohol **5** (75%, 90% ee)<sup>9</sup> which was regioselectively opened with (phenylthio)acetic acid and the obtained diol was oxidatively cleaved to give the methyl ketone **6** (80%). Treatment of **6** with the sodium salt of trimethylphosphonoacetate yielded the unsaturated ester **7** (75%) which when submitted to basic treatment provided the epimeric (4 : 1)  $\gamma$ -lactone **8** (95%). The *cis*-relative configuration of the *vic*-dimethyls in such a  $\gamma$ -lactone has been well established by n.O.e studies.

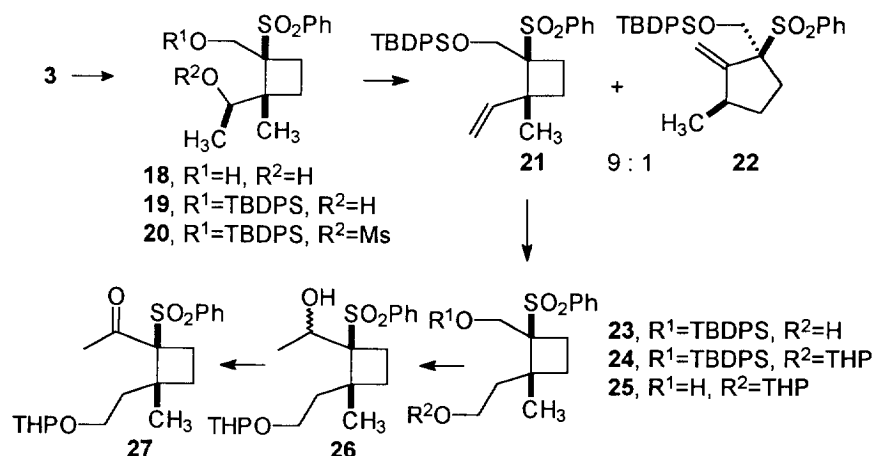


In order to obtain the desired activation in the side chain, **8** was saponified and the obtained carboxylic acid **9** (87%) reduced with the complex BH<sub>3</sub>·SMe<sub>2</sub> in THF to the primary alcohol **10** (91%) which was oxidized to the corresponding sulfone **11** by Oxone<sup>®</sup> (93%).<sup>10</sup> The activation of the hydroxy group was performed by preparing the corresponding mesylate **12** (MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C) which under basic treatment yielded the fused cyclobutane **3** in 75% overall yield with the desired stereochemistry. It should be pointed out that the mesylation reaction needed to be performed at the indicated temperature in order to avoid the competitive C-sulfonation in the  $\alpha$ -carbonyl carbon.

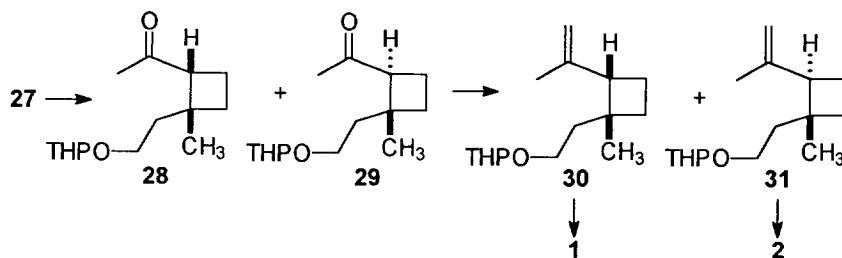
With the cyclobutane **3** in our hands we directed our attention to the cleavage of the benzenesulfonyl group, which was smoothly performed using Na(Hg)/Na<sub>2</sub>HPO<sub>4</sub> in THF : MeOH (1 : 1),<sup>11</sup> obtaining the cyclobutane **13** in 92% yield. In order to transform the  $\gamma$ -lactone unit in suitable functionalities to afford the natural products, **13** was reduced with LiAlH<sub>4</sub> in THF to the diol **14** (97%), which was selectively monoprotected as the silyl ether **15** (90%). However, when we attempted to transform the secondary alcohol into a methanesulfonate to produce the elimination product **16** the rearranged cyclopentene **17** was obtained as the sole product in 75% yield.



This result induced us to postpone the elimination of the benzenesulfonic group to a later stage in the synthesis. Thus, the above-mentioned sequence of reactions applied to **3** yielded **20** with similar overall yields which, when submitted to heating with DBU, afforded the vinyl derivative **21** (76%), contaminated with a small amount of the rearranged product **22** (8%). The addition to **21** of the complex  $\text{BH}_3 \cdot \text{SMe}_2$  in THF, and oxidative cleavage of the alkyl borane yielded the primary alcohol **23** (77%) which was protected as the tetrahydropyranyl ether **24** (87%) and desilylated ( $n\text{-Bu}_4\text{NF}$ , THF) to the hydroxymethyl derivative **25** (85%). Oxidation with PCC and treatment without purification of the formed aldehyde with methyl magnesium chloride gave the diastereoisomeric mixture **26** (85%) which was again oxidized (PCC,  $\text{CH}_2\text{Cl}_2$ ) to the methyl ketone **27** (92%).



Any attempt to transform **27** into the corresponding isopropenyl derivative using  $\text{Ph}_3\text{P}=\text{CH}_2$  took place with poor yields probably due to the steric encumbrance of the ketone. As a synthetic alternative, we decided to remove the sulfone group at this stage of the synthesis. Consequently, **27** was submitted to reductive desulfonation with  $\text{Na}(\text{Hg})/\text{Na}_2\text{HPO}_4$ <sup>11</sup> at room temperature yielding a 1 : 10 epimeric mixture of **28** and **29**. The stereochemistry of **29** is the correct one necessary to achieve the synthesis of fraganol. However, this result is unsatisfactory to obtain grandisol. Fortunately, we found that the stereochemistry in the desulfonation reaction is temperature-dependent. Thus, when such a reaction was performed at  $-40\text{ }^\circ\text{C}$  (the lowest temperature to achieve any transformation) a synthetically useful 1 : 1 mixture of **28** and **29** was obtained in 92% overall yield.



In order to check the possibility of obtaining both natural products we observed that once the benzenesulfonyl group was removed, the Wittig methylenation ( $\text{Ph}_3\text{P}=\text{CH}_2$ )<sup>12</sup> of **28** and **29** gave the

tetrahydropyranyl protected products **30** and **31** (87%) in a smooth manner. Final THP-cleavage under mild conditions (Dowex 50Wx8, MeOH) to avoid disturbing the isopropenyl group yielded after chromatographic separation on silica gel the natural enantiomer of grandisol **1** (39% from **27**) [ $[\alpha]_D^{25} +18.4$  (c 0.5, *n*-hexane)<sup>13</sup> [lit.<sup>14</sup> [ $[\alpha]_D^{25} +20.4$  (c 0.6, *n*-hexane)] and fraganol **2** (38% from **27**) [ $[\alpha]_D^{25} +5.5$  (c 1.16, CHCl<sub>3</sub>). Obviously, the use of the product obtained by desulfonation at room temperature produced fraganol in almost pure form.

The presented synthesis is a convenient route to the enantiomers of grandisol and fraganol since although only those directed to one enantiomer have been described the choice of the proper stereoisomer of the epoxy alcohol of **5** permits the control of the absolute configuration in the final products. On the other hand, we describe herein a new methodology that could be applied to the stereoselective synthesis of those products containing in their structure a substituted cyclobutane ring.

## Experimental Section

**Materials and Methods.** <sup>1</sup>H and <sup>13</sup>C-NMR spectra were recorded on a Bruker AMX 400 and/or Bruker AC 200 spectrometer in CDCl<sub>3</sub> as solvent, and chemical shifts are reported relative to Me<sub>4</sub>Si. Low- and high-resolution mass spectra were taken using a Hewlett-Packard Model 257 and VG Micromass ZAB-2F spectrometer, respectively. Optical rotations were determined for solutions in chloroform or dichloromethane with a Perkin-Elmer Model 241 polarimeter. Infrared spectra were recorded on a Perkin-Elmer Model 257 and Perkin-Elmer Model 1605 FTIR spectrophotometer. GC analyses were performed on a Hewlett-Packard HP-5890 instrument with a capillary column, OV-1, 25 m. Melting points were determined on a Büchi model 535 melting point apparatus and are uncorrected. HPLC chromatography was performed using a LKB PUMP Model 2248 with a LKD 2MD RAPID SPECTRAL detector using a  $\mu$ -Porasil Silica 10  $\mu$ m WATERS column. Column chromatography was performed on silica gel, 0.015-0.04 and 0.04-0.063 mm, and TLC and PLC were performed on silica gel, all Merck products. Visualization of spots was effected with UV light and/or phosphomolybdic acid in ethanol stain. All solvents were purified by standard techniques. Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

**Preparation of (*E*)-2-Methyl-2-buten-1-ol (Tiglic Alcohol).** To a solution of LiAlH<sub>4</sub> (102.4 mL, 0.102 mol, 1 M in ether) in ether (600 mL), at 0 °C was added slowly AlCl<sub>3</sub> (4.5 g, 0.034 mol). After complete addition the mixture was stirred for 15 min and the ethyl tiglate (25 g, 0.195 mol) dissolved in ether (50 mL) was added dropwise. The reaction mixture was stirred for 30 min, after which time TLC showed complete conversion. The reaction was quenched with water (3.9 mL), NaOH aqueous solution (15% w/v, 3.9 mL) and water (11.7 mL), diluted with ether (300 mL) and dried. The mixture was filtered through a pad of Celite and washed with ether (3 x 100 mL). The resulting solution was concentrated and the obtained crude was purified by distillation (bp 133-135 °C) affording the alcohol as a colorless oil (13.6 g, 81% yield): <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.57 (d, *J* = 5.4 Hz, 3 H), 1.58 (s, 3 H), 2.86 (br s, 1 H), 3.69 (s, 2 H), 5.41 (q, *J* = 5.4 Hz, 1 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 12.8 (q), 13.1 (q), 68.4 (t), 120.0 (d), 135.3 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3611, 3435, 3017, 2920, 1453, 1385, 995.

**Preparation of (2*S*,3*S*)-2,3-Epoxy-2-methyl-1-butanol **5**.** Crushed, activated 3 Å molecular sieves (20% w) were added to stirred CH<sub>2</sub>Cl<sub>2</sub> (600 mL) under argon. The flask was cooled to -20 °C and Ti(OP*r*-*i*)<sub>4</sub> (4.7 mL, 0.0157 mol), (*R,R*)-(+)-diisopropyl tartrate (4.3 mL, 0.0188 mol), and (*E*)-2-methyl-2-buten-1-ol (13.5 g,

0.157 mol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) were added sequentially with stirring. The mixture was stirred for 25 min, and then cooled to  $-78^\circ\text{C}$ . After 10 min, *tert*-butyl hydroperoxide (39.2 mL, 7.2 M in *iso*-octane, 0.283 mol) was added slowly. After the addition, the reaction was maintained with stirring for 12 h and carefully treated with tributylphosphine (31.3 mL, 0.1256 mol), added over a period of 1 h. The mixture was then treated with citric acid monohydrate (3.3 g, 0.01 mol) dissolved in 250 mL of acetone-ether (1 : 9). The cooling bath was removed, and the mixture was stirred for 20-30 min. The organic phase was filtered through a pad of Celite, dried and concentrated. The crude product was purified by distillation (bp<sub>2.5mm</sub> 60-65  $^\circ\text{C}$ ) affording **5** as a colorless oil (12 g, 75% yield, 90% ee by  $^1\text{H-NMR}$  analysis of the Mosher's ester<sup>15</sup>):  $[\alpha]_{\text{D}}^{25} -19.9$  (*c* 0.68,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.26 (s, 3 H), 1.31 (d,  $J = 5.6$  Hz, 3 H), 2.26 (br s, 1 H), 3.14 (q,  $J = 5.6$  Hz, 1 H), 3.54 (d,  $J = 12.2$  Hz, 1 H), 3.66 (d,  $J = 12.2$  Hz);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 13.4 (q), 13.8 (q), 55.9 (d), 60.9 (s), 65.5 (t); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 3420, 3000, 2971, 1460, 1380, 1031, 855.

**Preparation of (1*R*)-1-Methyl-2-oxo-propyl (Phenylthio)acetate 6.** To a stirred solution of (2*S*,3*S*)-2,3-epoxy-2-methyl-1-butanol **5** (10 g, 0.098 mol) in dry  $\text{CH}_2\text{Cl}_2$  (980 mL, 0.1 M) was added (phenylthio)acetic acid (19.7 g, 0.117 mol) under argon at  $0^\circ\text{C}$ . The mixture was stirred for 15 min, and  $\text{Ti}(\text{OPr-}i)_4$  (32.1 mL, 0.108 mol) was added. After the addition, the mixture was allowed to warm to room temperature and the solution was stirred for 2 h. Tartaric acid aqueous solution (15% w/v, 800 mL) was added, and stirred until clear phases were reached (30 min). The phases were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 300 mL). The combined organic phases were washed with a saturated aqueous solution of  $\text{NaHCO}_3$  (300 mL) and brine (300 mL), dried and concentrated, yielding the diol, which was used without purification. To a stirred solution of the crude diol dissolved in  $\text{MeOH} : \text{H}_2\text{O}$  (20 : 1, 490 mL) was added  $\text{NaIO}_4$  (41.9 g, 0.196 mol) and a catalytic amount of *tetra*-butylammonium periodate at rt. After 1 h, the mixture was filtered through a pad of Celite and washed with ether (3 x 200 mL). The resulting solution was dried, concentrated and purified by column chromatography to give the ketone **6** (22.1 g, 80% yield from **5**):  $[\alpha]_{\text{D}}^{25} +22.7$  (*c* 1.45,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.36 (d,  $J = 6.9$  Hz, 3 H), 2.10 (s, 3 H), 3.73 (s, 2 H), 5.08 (q,  $J = 6.9$  Hz, 1 H), 7.35 (m, 5 H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 15.9 (q), 25.5 (q), 36.3 (t), 75.8 (d), 127.1 (d), 129.1 (d), 130.0 (d), 134.6 (s), 169.1 (s), 179.7 (s); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 2060, 3020, 2939, 1735, 1728, 1358, 1267, 1091, 984; MS *m/z* (relative intensity): 240 ( $\text{M} + 2$ )<sup>+</sup> (5), 239 ( $\text{M} + 1$ )<sup>+</sup> (12), 238 ( $\text{M}$ )<sup>+</sup> (71), 150 (72), 123 (100), 109 (63), 77 (68); HRMS calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_3\text{S}$  ( $\text{M}$ )<sup>+</sup> 238.06637, found 238.06625.

**Preparation of Methyl (4*R*)-3-Methyl-4-[(phenylthio)acetoxy]-pent-2-enoate 7.** Crushed, activated 4Å molecular sieves (20% w) were added to a suspension of sodium hydride (3.2 g, 0.106 mol, 80% in mineral oil) in dry benzene (800 mL) at  $0^\circ\text{C}$ . Trimethylphosphonoacetate (18.7 mL, 0.115 mol) in benzene (50 mL) was added slowly to this mixture. After complete addition the mixture was stirred for 5 min and the ketone **6** (22 g, 0.092 mol) dissolved in benzene (30 mL) was added dropwise. The reaction mixture was stirred for 2 h, after which time TLC showed complete conversion to the unsaturated ester. The reaction was diluted in  $\text{CH}_2\text{Cl}_2$  (100 mL), filtered through a pad of Celite and washed with 5% (w/v) HCl aqueous solution (2 x 50 mL). The aqueous phase was extracted with ether (3 x 100 mL) and the combined organic phases were washed with saturated aqueous solution of brine (200 mL), dried, filtered and concentrated. Flash-chromatography provided the ester **7** (20.4 g, 75% yield), as a isomeric mixture *E* : *Z*, 2 : 1:  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.29 (d,  $J = 5.5$  Hz, 6 H), 1.33 (d,  $J = 5.6$  Hz, 3 H), 1.74 (d,  $J = 1.5$  Hz, 3 H), 2.08 (d,  $J = 1.3$  Hz, 3 H), 3.63 (s, 2 H), 3.65 (s, 2 H), 3.69 (s, 6 H), 5.22 (q,  $J = 5.5$  Hz, 1 H), 5.65 (q,  $J = 1.5$  Hz, 1 H), 5.83 (q,  $J = 1.3$  Hz, 1 H), 6.51 (q,  $J = 5.6$

Hz, 1 H), 7.32 (m, 10 H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 14.9 (q), 18.4 (q), 18.7 (q), 18.9 (q), 36.5 (t), 36.7 (t), 51.0 (q), 51.1 (q), 70.9 (d), 74.8 (d), 115.3 (d), 116.8 (d), 126.9 (d), 127.0 (d), 129.01 (d), 129.9 (d), 130.1 (d), 134.6 (s), 134.9 (s), 156.2 (s), 157.2 (s), 165.7 (s), 166.7 (s), 168.5 (s), 168.6 (s); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 3063, 3023, 2953, 1731, 1718, 1440, 1276, 1163, 1074; MS  $m/z$  (relative intensity): 296 ( $\text{M} + 2$ )<sup>+</sup> (2), 295 ( $\text{M} + 1$ )<sup>+</sup> (6), 294 ( $\text{M}$ )<sup>+</sup> (33), 168 (18), 150 (25), 123 (100), 95 (63); HRMS calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}_4\text{S}$  ( $\text{M}$ )<sup>+</sup> 294.09258, found 294.09159.

**Preparation of Methyl (2*R*,3*R*,4*S*)- and (2*R*,3*R*,4*R*)-(2,3-Dimethyl-5-oxo-4-phenylthio-tetrahydro-furan-3-yl)-acetate 8.** To a suspension of sodium hydride (2.24 g, 0.075 mol, 80% in mineral oil) in dry DMF (600 mL) under argon was added dropwise the unsaturated ester 7 (20 g, 0.068 mol) in dry DMF (80 mL) at -50 °C. The reaction mixture was stirred for 4 h, after which time TLC showed complete conversion into the lactone. The reaction was poured into HCl aqueous solution (15% w/v, 500 mL), ice and ether (500 mL) and vigorously stirred. After 10 min, the mixture was extracted with ether (2 x 200 mL) and the combined organic phases were washed with a saturated aqueous solution of  $\text{NaHCO}_3$  (200 mL) and brine (200 mL), dried and concentrated. Purification by column chromatography gave the lactone 8 (19 g, 95% yield) as an epimeric mixture in  $\text{C}_4$  ( $S : R$ , 4 : 1):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.08 (s, 3 H), 1.20 (s, 3 H), 1.27 (d,  $J = 6.6$  Hz, 3 H), 1.33 (d,  $J = 6.4$  Hz, 3 H), 2.42 (d,  $J = 15.2$  Hz, 1 H), 2.43 (d,  $J = 16.4$  Hz, 1 H), 2.54 (d,  $J = 15.2$  Hz, 1 H), 2.78 (d,  $J = 16.4$  Hz, 1 H), 3.58 (s, 3 H), 3.70 (s, 3 H), 3.76 (s, 1 H), 4.28 (s, 1 H), 4.47 (q,  $J = 6.6$  Hz, 1 H), 4.55 (q,  $J = 6.4$  Hz, 1 H), 7.30 (m, 6 H), 7.58 (m, 4 H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 13.7 (q), 13.9 (q), 15.9 (q), 18.6 (q), 37.7 (t), 38.7 (t), 44.7 (s), 45.7 (s), 51.8 (q), 57.1 (d), 57.6 (d), 79.9 (d), 81.1 (d), 127.8 (d), 128.5 (d), 128.9 (d), 129.1 (d), 132.3 (d), 133.9 (d), 133.8 (s), 170.5 (s), 170.6 (s), 174.0 (s); MS  $m/z$  (relative intensity): 296 ( $\text{M} + 2$ )<sup>+</sup> (3), 295 ( $\text{M} + 1$ )<sup>+</sup> (7), 294 ( $\text{M}$ )<sup>+</sup> (38), 221 (20), 141 (26), 109 (100); HRMS calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}_4\text{S}$  ( $\text{M}$ )<sup>+</sup> 294.09258, found 294.09296.

**Preparation of (2*R*,3*R*,4*S*)- and (2*R*,3*R*,4*R*)-(2,3-Dimethyl-5-oxo-4-phenylthio-tetrahydro-furan-3-yl)-acetic Acid 9.** To a stirred solution of lactone 8 (15 g, 0.05 mol) in THF :  $\text{H}_2\text{O}$  (4 : 1, 510 mL) was added NaOH (20.4 g, 0.51 mol). The reaction was stirred for 1 h, after which time TLC showed that the starting material had disappeared, and then concentrated HCl was added at 0 °C until pH  $\approx$  1 was reached and the aqueous layer was extracted with AcOEt (4 x 150 mL). The combined organic phases were washed with 150 mL of a saturated solution of brine, dried, evaporated in vacuo and purified by column chromatography to give 9 (12.4 g, 87% yield) as an oil:  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.24 (s, 3 H), 1.29 (d,  $J = 6.5$  Hz, 3 H), 2.49 (d,  $J = 17.1$  Hz, 1 H), 2.89 (d,  $J = 17.1$  Hz, 1 H), 3.77 (s, 1 H), 4.47 (q,  $J = 6.5$  Hz, 1 H), 7.35 (m, 3 H), 7.59 (m, 2 H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 13.8 (q), 18.6 (q), 37.7 (t), 44.7 (s), 57.0 (d), 81.2 (d), 128.8 (d), 129.3 (d), 131.5 (s), 133.6 (d), 174.1 (s), 175.7 (s); MS  $m/z$  (relative intensity): 282 ( $\text{M} + 2$ )<sup>+</sup> (3), 281 ( $\text{M} + 1$ )<sup>+</sup> (7), 280 ( $\text{M}$ )<sup>+</sup> (46), 177 (16), 127 (20), 110 (38), 69 (100); HRMS calcd. for  $\text{C}_{14}\text{H}_{16}\text{O}_4\text{S}$  ( $\text{M}$ )<sup>+</sup> 280.07693, found 280.07634.

**Preparation of (3*S*,4*R*,5*R*)- and (3*R*,4*R*,5*R*)-4-(2-Hydroxy-ethyl)-4,5-dimethyl-3-phenylthio-dihydro-furan-2-one 10.** To a stirred solution of 9 (12 g, 0.043 mol) in dry THF (214 mL, 0.2M) under argon was added dropwise the complex  $\text{BH}_3 \cdot \text{SMe}_2$  2 M in THF (26 mL, 0.05 mol) at -10 °C. The mixture was allowed to warm slowly to rt and stirred additionally for 6-8 h until TLC showed the end of the reaction. Then the mixture was cooled to 0 °C and quenched by careful addition of MeOH (16 mL, 0.43 mol). The resulting solution was evaporated in vacuo and the obtained crude was purified by column chromatography to give the alcohol 10 (10.4 g, 91% yield):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.05 (s, 3 H), 1.12 (s, 3 H), 1.29 (d,  $J = 6.5$  Hz, 3 H), 1.34 (d,  $J =$

6.4 Hz, 3 H), 1.64 (br s, 2 H), 1.79 (dd,  $J = 6.3, 6.3$  Hz, 4 H), 3.59 (s, 1 H), 3.77 (dd,  $J = 6.3, 6.0$  Hz, 4 H), 3.91 (s, 1 H), 4.45 (q,  $J = 6.4$  Hz, 1 H), 4.46 (q,  $J = 6.5$  Hz, 1 H), 7.29 (m, 6 H), 7.61 (m, 4 H); MS  $m/z$  (relative intensity): 268 ( $M + 2$ )<sup>+</sup> (8), 267 ( $M + 1$ )<sup>+</sup> (23), 266 ( $M$ )<sup>+</sup> (100), 221 (82), 177 (58), 135 (36), 109 (75), 69 (49); HRMS calcd. for  $C_{14}H_{18}O_3S$  ( $M$ )<sup>+</sup> 266.09767, found 266.09776.

**Preparation of (3*S*,4*R*,5*R*)- and (3*R*,4*R*,5*R*)-3-Benzenesulfonyl-4-(2-Hydroxy-ethyl)-4,5-dimethyl-dihydro-furan-2-one 11.** To a stirred solution of the lactone **10** (10 g, 0.037 mol) in MeOH (125.3 mL, 0.3 M) was added  $KHSO_5$  (34.7 g, 0.056 mol) in  $H_2O$  (112 mL, 0.5 M) at 0 °C. The mixture was vigorously stirred for 5 h, until TLC showed completion. Then it was diluted with AcOEt (250 mL) and the organic phase was washed with  $H_2O$  (150 mL) and brine (150 mL), dried, concentrated and purified by column chromatography, yielding **11** (10.4 g, 93% yield) as a epimeric mixture in  $C_3$  ( $S : R, 1 : 1$ ):  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  : 1.17 (s, 3 H), 1.30 (d,  $J = 6.4$  Hz, 6 H), 1.43 (s, 3 H), 1.68 (m, 1 H), 1.79 (m, 1 H), 2.25 (m, 1 H), 2.77 (m, 1 H), 2.91 (br s, 2 H), 3.84 (m, 2 H), 3.85 (s, 1 H), 3.95 (m, 2 H), 4.48 (q,  $J = 6.4$  Hz, 1 H), 4.79 (s, 1 H), 5.01 (q,  $J = 6.4$  Hz, 1 H), 7.62 (m, 6 H), 7.85 (m, 2 H), 8.06 (m, 2 H);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 12.9 (q), 13.1 (q), 17.0 (q), 18.9 (q), 32.9 (t), 37.2 (t), 47.4 (s), 47.5 (s), 58.6 (t), 58.7 (t), 69.5 (d), 74.1 (d), 79.9 (d), 83.1 (d), 128.8 (d), 129.0 (d), 129.1 (d), 134.1 (d), 134.7 (d), 137.3 (s), 139.6 (s), 167.5 (s), 167.8 (s); MS  $m/z$  (relative intensity): 299 ( $M + 1$ )<sup>+</sup> (1), 253 (12), 234 (22), 189 (59), 113 (86), 77 (100); HRMS calcd. for  $C_{14}H_{19}O_5S$  ( $M + 1$ )<sup>+</sup> 299.09532, found 299.09657.

**Preparation of (1*S*,4*R*,5*R*)-1-Benzenesulfonyl-4,5-dimethyl-3-oxa-bicyclo-[3.2.0]-heptan-2-one 3.** To a stirred solution of **11** (10 g, 0.033) in dry  $CH_2Cl_2$  (335 mL, 0.1 M) under argon was slowly added  $Et_3N$  (5.6 mL, 0.04 mol) at -20 °C. After 15 min of vigorous stirring, methanesulfonyl chloride was added (2.6 mL, 0.033 mol) and stirring continued for 15 min. Then the reaction mixture was poured into ice and extracted with ether (3 x 100 mL) and the organic layer was washed with  $H_2O$  (100 mL) and brine (100 mL), dried and concentrated to obtain the crude mesylate **12**, which was used without purification.

The mesylate **12** was dissolved in dry DMF (335 mL, 0.1 M) under argon, and NaH (1.2 g, 0.04 mol, 80% in mineral oil) was added at 0 °C, with stirring. The reaction was allowed to warm to rt and monitored for TLC until complete conversion (4 H). The reaction was poured into HCl aqueous solution (15% w/v, 200 mL), ice and ether (200 mL) and vigorously stirred. After 10 min, the mixture was extracted with ether (2 x 100 mL) and the combined organic phases were washed with a saturated aqueous solution of  $NaHCO_3$  (100 mL) and brine (100 mL), dried and concentrated. The crude obtained was purified by flash chromatography, yielding **3** (7.05 g, 75% yield) as a white solid: mp 201-203 °C;  $[\alpha]_D^{25} +25.7$  ( $c$  2.26,  $CHCl_3$ ),  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 1.40 (d,  $J = 6.6$  Hz, 3 H), 1.65 (s, 3 H), 2.01 (m, 1 H), 2.10 (m, 2 H), 2.99 (m, 1 H), 4.38 (q,  $J = 6.6$  Hz, 1 H), 7.56 (m, 2 H), 7.69 (m, 1 H), 7.85 (m, 2 H);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 16.9 (q), 17.8 (q), 25.7 (t), 30.1 (t), 52.3 (s), 68.2 (s), 84.3 (d), 129.2 (d), 130.3 (d), 134.7 (d), 137.3 (s), 172.2 (s); IR ( $CHCl_3$ ) ( $cm^{-1}$ ): 3072, 3024, 2939, 1766, 1321, 1309, 1219, 1159, 1087; MS  $m/z$  (relative intensity): 281 ( $M + 1$ )<sup>+</sup> (1), 253 ( $M - C_2H_5$ )<sup>+</sup> (2), 139 ( $M - SO_2P H$ )<sup>+</sup> (100), 93 (30), 77 (78); HRMS calcd. for  $C_{14}H_{17}O_4S$  ( $M + 1$ )<sup>+</sup> 281.08476, found 281.08326.

**Preparation of (1*R*,4*R*,5*S*)-4,5-dimethyl-3-oxa-bicyclo-[3.2.0]-heptan-2-one 13.** To a stirred solution of sulfone **3** (1 g, 3.6 mmol) and anhydrous  $Na_2HPO_4$  (2.03 g, 14.4 mmol) in THF : MeOH, 1 : 1 (71 mL, 0.05 M) was added pulverized 6% sodium amalgam (5.4 g) at 0 °C. The reaction mixture was vigorously stirred for 1 h, until TLC showed complete conversion. The mixture was poured into water (50 mL) and extracted with ether (3 x 50 mL). The resulting solution was dried, concentrated and the obtained crude was purified by flash-

chromatography, to yield **13** (460 mg, 92% yield) as a sole product:  $[\alpha]_D^{25} -30.5$  (*c* 0.44, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.20 (d, *J* = 6.6 Hz, 3 H), 1.27 (s, 3 H), 1.90 (m, 1 H), 2.07 (m, 1 H), 2.26 (m, 1 H), 2.50 (m, 1 H), 2.68 (m, 1 H), 4.44 (q, *J* = 6.6 Hz, 1 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 17.7 (q), 18.3 (q), 20.8 (t), 32.0 (t), 42.9 (d), 44.3 (s), 84.6 (d), 180.1 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 2925, 2850, 1751, 1460, 1380.6, 1334, 1306, 1170, 1048; MS *m/z* (relative intensity): 140 (M)<sup>+</sup> (6), 113 (34), 81 (38), 69 (100), 67 (58); HRMS calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub> (M)<sup>+</sup> 140.08373, found 140.08336.

**Preparation of (1R)-1-[(2R)-2-Hydroxymethyl-(1S)-1-methyl-cyclobutyl]-ethanol 14.** To a suspension of LiAlH<sub>4</sub> (146 mg, 3.85 mmol) in dry THF (30 mL) was added slowly the bicyclo **13** (450 mg, 3.21 mmol) in dry THF (2 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 0.5 h. The reaction mixture was cooled at 0 °C and quenched with sequential addition of water (146 μL), NaOH aqueous solution (15% w/v, 146 μL) and water (440 μL) and stirred for 1 h. To the resulting mixture were added ether (30 mL), and MgSO<sub>4</sub> with additional stirring for 15 min. The solid was filtered through a pad of Celite and washed with ether (3 x 30 mL). The resulting solution was concentrated and the obtained crude was purified by flash-chromatography, to yield **14** (461 mg, 97% yield): <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (d, *J* = 6.4 Hz, 3 H), 1.17 (s, 3 H), 1.30 (m, 1 H), 1.60 (m, 2 H), 1.98 (m, 1 H), 2.26 (m, 1 H), 3.56 (dd, *J* = 11.3, 4.5 Hz, 1 H), 3.63 (br s, 2 H), 3.86 (dd, *J* = 11.3, 11.3 Hz, 1 H), 4.14 (q, *J* = 6.4 Hz, 1 H).

**Preparation of (1R)-1-[(2R)-2-(tert-Butyl-diphenyl-silanyloxymethyl)-(1S)-1-methyl-cyclobutyl]-ethanol 15.** To a stirred solution of the diol **14** (450 mg, 3.13 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (31.3 mL, 0.1 M) under argon was added imidazole (248.4 mg, 3.65 mmol) and *tert*-butylchlorodiphenylsilane (811 μL, 3.13 mmol) at 0 °C. The reaction was allowed to warm to rt and stirred for 0.5 h, poured into water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 25 mL). The combined organic phases were washed with brine (50 mL), dried, filtered and concentrated. The crude obtained was purified by flash chromatography, yielding **15** (1.04 g, 90% yield): <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.06 (s, 9 H), 1.08 (d, *J* = 6.5 Hz, 3 H), 1.15 (m, 1 H), 1.26 (s, 3 H), 1.59 (m, 2 H), 1.85 (m, 1 H), 2.28 (m, 1 H), 3.54 (dd, *J* = 11.3, 4.6 Hz, 1 H), 3.98 (dd, *J* = 11.3, 11.3 Hz, 1 H), 4.24 (q, *J* = 6.5 Hz, 1 H), 4.29 (br s, 1 H), 7.45 (m, 6 H), 7.70 (m, 4 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 15.3 (q), 16.6 (t), 19.0 (s), 20.9 (q), 26.7 (q), 28.4 (t), 44.5 (s), 45.3 (d), 65.3 (t), 69.4 (d), 127.8 (d), 127.8 (d), 129.9 (d), 132.8 (s), 135.5 (d); MS *m/z* (relative intensity): 383 (M + 1)<sup>+</sup> (1), 239 (13), 199 (100), 181 (51), 135 (60), 109 (100), 67 (100).

**Preparation of *tert*-Butyl-[(1R)-2,3-dimethyl-cyclopent-2-enylmethoxy]-diphenyl-silane 17.** To a stirred solution of **15** (1 g, 2.6 mmol) in dry pyridine (26 mL, 0.1 M) was added methanesulfonyl chloride (401 μL, 5.2 mmol) at 40 °C. The reaction mixture was vigorously stirred for 3 h, until TLC showed complete conversion. The mixture was poured into HCl aqueous solution (15% w/v, 50 mL), ice and ether (50 mL) and vigorously stirred, and the organic layer was extracted with ether (2 x 50 mL). The combined organic phases were washed with a saturated aqueous solution of NaHCO<sub>3</sub> (50 mL) and brine (50 mL), dried and concentrated. The crude obtained was purified by silica gel column chromatography, giving **17** (714.6 mg, 75% yield) as a sole product:  $[\alpha]_D^{25} +13.8$  (*c* 2.41, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.08 (s, 9 H), 1.56 (s, 3 H), 1.64 (s, 3 H), 1.75 (m, 1 H), 1.96 (m, 1 H), 2.19 (m, 1 H), 2.31 (m, 1 H), 2.70 (m, 1 H), 3.55 (dd, *J* = 9.8, 6.5 Hz, 1 H), 3.74 (dd, *J* = 9.8, 4.7 Hz, 1 H), 7.42 (m, 6 H), 7.70 (m, 4 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 12.9 (q), 14.3 (q), 19.7 (s), 26.4 (t), 27.3 (q), 37.2 (t), 52.8 (d), 66.9 (t), 127.9 (d), 129.9 (d), 131.6 (s), 133.4 (s), 134.5 (s), 134.7 (s), 136.0 (d), 136.1 (d); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3075, 3019, 2935, 2860, 1470, 1427, 1114, 1006, 823; MS *m/z* (relative intensity): 308 (M



+ 1 - <sup>1</sup>Bu)<sup>+</sup> (31), 307 (M - <sup>1</sup>Bu)<sup>+</sup> (96), 229 (82), 199 (100), 183 (52), 107 (66), 67 (52); HRMS calcd. for C<sub>20</sub>H<sub>23</sub>OSi (M - <sup>1</sup>Bu)<sup>+</sup> 307.15182, found 307.15318.

**Preparation of (1R)-1-[(2S)-2-Benzenesulfonyl-2-Hydroxymethyl-(1R)-1-methyl-cyclobutyl]-ethanol 18.**

The LiAlH<sub>4</sub> reduction used above to obtain **14** was applied to **3** on a 6 g (0.021 mol) scale, yielding **18** (5.78 g, 95% yield) as a white solid: mp 147-149 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> -29.0 (c 1.35, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.07 (d, *J* = 6.4 Hz, 3 H), 1.46 (ddd, *J* = 12.0, 8.4, 3.8 Hz, 1 H), 1.68 (s, 3 H), 1.73 (m, 2 H), 2.76 (ddd, *J* = 12.0, 9.6, 9.6 Hz, 1 H), 3.25 (br s, 1 H), 3.27 (d, *J* = 13.4 Hz, 1 H), 4.01 (br s, 1 H), 4.10 (q, *J* = 6.4 Hz, 1 H), 4.11 (d, *J* = 13.4 Hz, 1 H), 7.54 (m, 2 H), 7.65 (m, 1 H), 7.9 (m, 2 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 16.0 (q), 16.4 (q), 23.5 (t), 28.0 (t), 51.7 (s), 63.1 (t), 71.3 (d), 71.6 (s), 129.4 (d), 129.5 (d), 134.1 (d), 138.3 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3491, 3406, 3032, 2985, 2872, 1448, 1298, 1139, 1037; MS *m/z* (relative intensity): 285 (M + 1)<sup>+</sup> (1), 239 (M - C<sub>2</sub>H<sub>5</sub>O)<sup>+</sup> (3), 143 (M - SO<sub>2</sub>P H)<sup>+</sup> (46), 125 (96), 81 (96); HRMS calcd. for C<sub>14</sub>H<sub>17</sub>O<sub>3</sub>S (M - H<sub>3</sub>O)<sup>+</sup> 265.08984, found 265.09077.

**Preparation of (1R)-1-[(2S)-2-Benzenesulfonyl-2-(tert-Butyl-diphenyl-silyloxy)methyl-(1R)-1-methyl-cyclobutyl]-ethanol 19.**

The TBDPS-protection used above to obtain **15** was applied to **18** on a 5.5 g (0.019 mol) scale, yielding **19** (9.1 g, 90% yield): [ $\alpha$ ]<sub>D</sub><sup>25</sup> -1.53 (c 0.72, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.76 (d, *J* = 6.4 Hz, 3 H), 1.05 (s, 9 H), 1.43 (m, 2 H), 1.54 (m, 1 H), 1.64 (s, 3 H), 2.84 (m, 1 H), 2.87 (br s, 1 H), 3.53 (q, *J* = 6.4 Hz, 1 H), 3.74 (d, *J* = 12.2 Hz, 1 H), 3.91 (d, *J* = 12.2 Hz, 1 H), 7.43 (m, 10 H), 7.60 (m, 3 H), 7.82 (m, 2 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 14.6 (q), 15.5 (q), 19.0 (s), 23.4 (t), 27.2 (q), 27.5 (t), 52.1 (s), 63.1 (t), 69.0 (d), 71.3 (s), 127.6 (d), 127.7 (d), 128.5 (d), 128.9 (d), 129.8 (d), 130.1 (d), 131.6 (s), 133.2 (d), 135.7 (d), 135.9 (d), 139.2 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3528, 3069, 2938, 1467, 1302, 1139, 1078; MS *m/z* (relative intensity): 465 (M - <sup>1</sup>Bu)<sup>+</sup> (12), 323 (58), 259 (83), 199 (100), 135 (64); HRMS calcd. for C<sub>26</sub>H<sub>29</sub>O<sub>4</sub>SSi (M - <sup>1</sup>Bu)<sup>+</sup> 465.15558, found 465.15598.

**Preparation of (1R)-1-[(2S)-2-Benzenesulfonyl-2-(tert-Butyl-diphenyl-silyloxy)methyl-(1R)-1-methyl-cyclobutyl]-ethyl Methanesulfonate 20.**

The mesylation procedure used above to obtain **17** was applied to **19** on a 9 g (0.017 mol) scale, yielding **20** (9.4 g, 91% yield): [ $\alpha$ ]<sub>D</sub><sup>25</sup> +6.1 (c 2.41, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.01 (s, 9 H), 1.39 (d, *J* = 6.4 Hz, 3 H), 1.54 (ddd, *J* = 9.5, 9.5, 1.9 Hz, 1 H), 1.75 (s, 3 H), 1.85 (ddd, *J* = 10.0, 9.5, 1.9 Hz, 1 H), 2.06 (ddd, *J* = 9.5, 9.5, 9.5 Hz, 1 H), 2.80 (ddd, *J* = 10.0, 9.5, 9.5 Hz, 1 H), 3.00 (s, 3 H), 3.57 (d, *J* = 11.2 Hz, 1 H), 4.33 (d, *J* = 11.2 Hz, 1 H), 5.61 (q, *J* = 6.4 Hz, 1 H), 7.33 (m, 10 H), 7.53 (m, 5 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 15.0 (q), 17.2 (q), 19.2 (s), 21.9 (t), 26.8 (q), 28.3 (t), 39.1 (q), 50.5 (s), 62.7 (t), 69.9 (s), 78.3 (d), 127.7 (d), 128.4 (d), 128.9 (d), 129.8 (d), 129.9 (d), 131.9 (s), 131.9 (s), 133.3 (d), 135.4 (d), 135.8 (d), 138.8 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3069, 3013, 2947, 1471, 1326, 1302, 1171, 1073; MS *m/z* (relative intensity): 543 (M - <sup>1</sup>Bu)<sup>+</sup> (1), 323 (81), 263 (94), 259 (100), 199 (100); HRMS calcd. for C<sub>24</sub>H<sub>31</sub>O<sub>3</sub>S (M - MsO - SO<sub>2</sub>Ph - H)<sup>+</sup> 363.21442, found 363.21336.

**Preparation of [(1S)-1-Benzenesulfonyl-(2R)-2-methyl-2-vinyl-cyclobutylmethoxy]-tert-butyl-diphenyl-silane 21.**

A solution of **20** (9 g, 0.015 mol) in DBU (44.9 mL, 0.3 mol) at 120 °C was vigorously stirred for 5 h, until TLC showed complete conversion. The reaction was poured into HCl aqueous solution (15% w/v, 100 mL), ice and ether (100 mL) at 0 °C and vigorously stirred. After 15 min, the mixture was extracted with ether (2 x 100 mL) and the combined organic phases were washed with a saturated aqueous solution of NaHCO<sub>3</sub> (100 mL) and brine (100 mL), dried and concentrated. The crude obtained was purified by column chromatography, yielding **21** as a white solid: mp 92-94 °C (5.74 g, 76% yield) and **22** as a white solid: mp

111–113 °C (604.8 mg, 8% yield). Compound **21**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> –4.7 (*c* 2.33, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85 (s, 9 H), 1.56 (ddd, *J* = 9.9, 9.9, 2.9 Hz, 1 H), 1.64 (ddd, *J* = 9.9, 9.9, 9.9 Hz, 1 H), 1.70 (s, 3 H), 2.03 (ddd, *J* = 9.9, 9.9, 2.9 Hz, 1 H), 2.78 (ddd, *J* = 9.9, 9.9, 9.9 Hz, 1 H), 3.80 (d, *J* = 12.4 Hz, 1 H), 3.92 (d, *J* = 12.4 Hz, 1 H), 4.63 (d, *J* = 17.4 Hz, 1 H), 4.87 (d, *J* = 10.6 Hz, 1 H), 5.91 (dd, *J* = 17.4, 10.6 Hz, 1 H), 7.41 (m, 10 H), 7.45 (m, 1 H), 7.72 (m, 2 H), 7.81 (m, 2 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 19.0 (s), 21.0 (t), 24.9 (q), 26.9 (q), 27.0 (t), 50.8 (s), 62.4 (t), 70.7 (s), 113.6 (t), 127.6 (d), 127.7 (d), 128.8 (d), 128.8 (d), 129.6 (d), 129.7 (d), 129.8 (d), 132.6 (s), 132.7 (s), 133.1 (d), 134.8 (d), 135.6 (d), 135.8 (d), 140.5 (s), 142.1 (d); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3069, 2929, 1471, 1429, 1298, 1143, 1115; MS *m/z* (relative intensity): 379 (1), 259 (8), 199 (82), 121 (21), 77 (100), 57 (100); HRMS calcd. for C<sub>26</sub>H<sub>28</sub>O<sub>3</sub>SiS (M + 1 – <sup>t</sup>Bu)<sup>+</sup> 448.15285, found 448.15285; Compound **22**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> +31.7 (*c* 1.57, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.95 (d, *J* = 6.7 Hz, 3 H), 1.00 (s, 9 H), 1.06 (m, 1 H), 1.68 (m, 1 H), 2.17 (m, 1 H), 2.36 (m, 1 H), 2.46 (m, 1 H), 3.94 (d, *J* = 10.2 Hz, 1 H), 4.17 (d, *J* = 10.2 Hz, 1 H), 5.22 (d, *J* = 2.5 Hz, 1 H), 5.41 (d, *J* = 2.5 Hz, 1 H), 7.35 (m, 4 H), 7.37 (m, 4 H), 7.45 (m, 5 H), 7.55 (m, 2 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 18.4 (q), 19.3 (s), 26.8 (q), 29.9 (t), 31.8 (t), 40.4 (d), 66.0 (t), 77.0 (s), 112.6 (t), 127.6 (d), 127.7 (d), 128.4 (d), 129.8 (d), 130.8 (d), 132.8 (s), 132.9 (s), 133.4 (d), 135.6 (d), 135.7 (d), 137.8 (s), 151.3 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3075, 2963, 2860, 1469, 1427, 1301, 1146, 1114; MS *m/z* (relative intensity): 363 (2), 323 (15), 259 (45), 199 (53), 77 (100); HRMS calcd. for C<sub>26</sub>H<sub>28</sub>O<sub>3</sub>SiS (M + 1 – <sup>t</sup>Bu)<sup>+</sup> 448.15285, found 448.15285.

**Preparation of 2-[(2*S*)-2-Benzenesulfonyl-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-(1*R*)-1-methylcyclobutyl]-ethanol **23**.** To a stirred solution of **21** (5 g, 9.92 mmol) in dry THF (99.2 mL, 0.1 M) under argon at 0 °C was added dropwise the complex BH<sub>3</sub>•SMe<sub>2</sub> 2 M in THF (6 mL, 11.9 mmol). The reaction was allowed to warm slowly to rt and stirred additionally for 12 h until TLC showed the end of the reaction. The reaction mixture was cooled to 0 °C and H<sub>2</sub>O<sub>2</sub> (30% w/v, 4.2 mL), NaOH (3 M, 1.8 mL) and H<sub>2</sub>O (1.8 mL) were added sequentially with stirring. The mixture was allowed to warm to rt and stirred. After 0.5 h the mixture was extracted with ether (3 x 50 mL) and the combined organic solutions were washed with brine (100 mL), dried, evaporated in vacuo and purified by column chromatography, giving the alcohol **23** (3.99 g, 77% yield): [ $\alpha$ ]<sub>D</sub><sup>25</sup> –1.25 (*c* 1.12, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.92 (s, 9 H), 1.35 (m, 1 H), 1.60 (m, 2 H), 1.70 (s, 3 H), 2.06 (m, 2 H), 2.49 (br s, 1 H), 2.85 (m, 1 H), 3.52 (m, 1 H), 3.77 (m, 1 H), 3.81 (d, *J* = 11.8 Hz, 1 H), 4.12 (d, *J* = 11.8 Hz, 1 H), 7.28 (m, 3 H), 7.44 (m, 10 H), 7.71 (m, 2 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 19.5 (s), 22.6 (t), 23.6 (q), 27.3 (q), 31.6 (t), 41.5 (t), 46.9 (s), 59.2 (t), 62.8 (t), 71.4 (s), 128.1 (d), 128.1 (d), 129.0 (d), 129.3 (d), 130.2 (d), 130.3 (d), 132.2 (s), 133.7 (d), 135.9 (d), 136.1 (d), 140.0 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3491, 3070, 2938, 1429, 1293, 1115, 1073; MS *m/z* (relative intensity): 465 (M – <sup>t</sup>Bu)<sup>+</sup> (4), 323 (33), 259 (56), 199 (100), 107 (66); HRMS calcd. for C<sub>26</sub>H<sub>29</sub>O<sub>4</sub>SiS (M – <sup>t</sup>Bu)<sup>+</sup> 465.15558, found 465.15624.

**Preparation of {(1*S*)-1-Benzenesulfonyl-(2*R*)-2-methyl-2-[2-(tetrahydro-pyran-(2*R* and 2*S*)-2-yloxyethyl]-cyclobutylmethoxy}-*tert*-butyl-diphenyl-silane **24**.** To a stirred solution of the alcohol **23** (3.9 g, 7.5 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (75 mL, 0.1 M) under argon was added dihydropyran (1.02 mL, 11.2 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate at 0 °C. The reaction was allowed to warm to rt and stirred for 6 h. The reaction mixture was poured into ice and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL). The combined organic phases were washed with brine (100 mL), dried and concentrated. The crude obtained was purified by flash chromatography, yielding **24** (3.94 g, 87% yield): <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.95 (s, 9 H), 1.55 (m, 4 H), 1.61 (s, 3 H), 1.68 (m, 4 H), 1.81 (m, 1 H), 1.96 (m, 1 H), 2.03 (m, 1 H), 2.80 (m, 1 H), 3.41 (m, 2 H), 3.74 (m, 2

H), 3.77 (d,  $J = 11.5$  Hz, 1 H), 3.98 (d,  $J = 11.5$  Hz, 1 H), 4.52 (m, 1 H), 7.41 (m, 13 H), 7.66 (m, 2 H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 19.2 (s), 19.4 (t), 19.5 (t), 22.5 (t), 23.2 (q), 23.3 (q), 25.5 (t), 26.9 (q), 30.7 (t), 31.0 (t), 37.1 (t), 37.2 (t), 46.7 (s), 46.9 (s), 61.9 (t), 62.1 (t), 62.8 (t), 63.8 (t), 71.1 (s), 71.2 (s), 98.5 (d), 98.7 (d), 127.7 (d), 127.7 (d), 128.6 (d), 128.8 (d), 129.7 (d), 129.6 (d), 132.4 (s), 132.5 (s), 133.0 (d), 135.6 (d), 135.7 (d), 139.9 (s); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 3069, 3013, 2947, 1429, 1298, 11438, 1115, 1078; MS  $m/z$  (relative intensity): 465 ( $\text{M} - ^t\text{Bu} - \text{C}_5\text{H}_8\text{O}$ ) $^+$  (1), 323 (12), 259 (34), 199 (85), 77 (100), 57 (100); HRMS calcd. for  $\text{C}_{31}\text{H}_{37}\text{O}_5\text{SiS}$  ( $\text{M} - ^t\text{Bu}$ ) $^+$  549.21310, found 549.21670.

**Preparation of {(1*S*)-1-Benzenesulfonyl-(2*R*)-2-methyl-2-[2-(tetrahydro-pyran-(2*R* and 2*S*)-2-yloxy)-ethyl]-cyclobutyl}-methanol **25**.** To a stirred solution of **24** (3.9 g, 6.4 mmol) in dry THF (32.2 mL, 0.2 M) under argon was added tetrabutylammonium fluoride 1 M in THF (7.7 mL, 7.7 mmol) at 0 °C. The reaction was allowed to warm to rt and stirred for 2 h. The reaction mixture was poured into  $\text{H}_2\text{O}$  (100 mL) and extracted with ether (2 x 30 mL). The combined organic solutions were washed with brine (50 mL) and dried. The resulting solution was concentrated and purified by column chromatography, yielding the alcohol **25** (2.01 g, 85% yield):  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.58 (m, 10 H), 1.67 (s; 3 H), 1.69 (s, 3 H), 1.87 (m, 8 H), 2.03 (m, 1 H), 2.11 (m, 1 H), 2.24 (m, 1 H), 2.54 (m, 1 H), 2.72 (m, 2 H), 3.31 (m, 1 H), 3.39 (m, 1 H), 3.42 (m, 1 H), 3.51 (m, 2 H), 3.63 (m, 1 H), 3.83 (m, 4 H), 4.05 (m, 3 H), 4.35 (m, 1 H), 4.57 (m, 1 H), 4.64 (m, 1 H), 7.56 (m, 4 H), 7.65 (m, 2 H), 7.90 (m, 4 H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 19.3 (q), 19.4 (t), 22.0 (s), 22.5 (q), 22.9 (t), 23.4 (s), 25.4 (t), 30.2 (t), 30.5 (t), 30.5 (t), 30.7 (t), 38.0 (t), 38.2 (t), 45.1 (s), 45.7 (s), 62.2 (t), 62.3 (t), 62.5 (t), 62.6 (t), 63.6 (t), 64.0 (t), 70.7 (s), 99.2 (d), 99.2 (d), 128.9 (d), 129.0 (d), 129.1 (d), 133.6 (d), 133.7 (d), 139.9 (s); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 3491, 3359, 2947, 1448, 1293, 1134, 1077.8, 1026; MS  $m/z$  (relative intensity): 265 (1), 199 (3), 139 (30), 85 (100), 71 (87); HRMS calcd. for  $\text{C}_{13}\text{H}_{17}\text{O}_3\text{S}$  ( $\text{M} - \text{C}_6\text{H}_{11}\text{O}_2$ ) $^+$  253.08984, found 253.09128.

**Preparation of (1*R* and 1*S*)-1-[(1*S*)-1-Benzenesulfonyl-(2*R*)-2-methyl-2-[2-(tetrahydro-pyran-(2*R* and 2*S*)-2-yloxy)-ethyl]-cyclobutyl]-ethanol **26**.** Crushed, activated 3 Å molecular sieves (20% w) were added to stirred NaOAc (133.7 mg, 1.6 mmol) and the alcohol **25** (2 g, 5.4 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (27 mL, 0.2 M) under argon. The flask was cooled to 0 °C and pyridinium chlorochromate (2.3 g, 10.9 mmol) was added. The reaction was allowed to warm to rt and stirred for 3 h. After dilution with ether (75 mL) the mixture was filtered through a pad of Celite and silica gel and washed with ether (2 x 10 mL). The resulting solution was concentrated, yielding an oil of the crude aldehyde, which was used without purification.

To a stirred solution of the crude aldehyde dissolved in dry THF (54.3 mL, 0.1 M) under argon was added methyl magnesium chloride 3 M in THF (2.17 mL, 6.5 mmol) at -20 °C. After the addition, the reaction was maintained with stirring for 2 h. The reaction mixture was partitioned between ether and  $\text{H}_2\text{O}$ , and the aqueous layer extracted with ether (2 x 50 mL). The combined organic phases were washed with saturated aqueous solution of ammonium chloride (100 mL), dried and concentrated. Purification by column chromatography gave the alcohol **26** (1.76 g, 85% yield) as a diastereoisomeric mixture:  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.66 (d,  $J = 7.2$  Hz, 3 H), 0.78 (d,  $J = 6.8$  Hz, 3 H), 1.56 (m, 10 H), 1.71 (s, 3 H), 1.73 (s, 3 H), 1.86 (m, 10 H), 2.21 (m, 2 H), 2.94 (m, 2 H), 3.42 (m, 1 H), 3.53 (m, 2 H), 3.63 (m, 1 H), 3.75 (br s, 1 H), 3.84 (m, 2 H), 3.97 (m, 2 H), 4.49 (m, 3 H), 4.62 (m, 1 H), 4.71 (m, 1 H), 7.53 (m, 4 H), 7.61 (m, 2 H), 7.91 (m, 4 H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 17.9 (q), 18.4 (q), 19.1 (t), 19.4 (t), 23.3 (q), 23.4 (q), 25.0 (t), 25.2 (t), 25.4 (t), 30.1 (t), 30.5 (t), 30.8 (t), 31.0 (t), 38.5 (t), 38.6 (t), 48.1 (s), 48.4 (s), 61.9 (t), 62.2 (t), 63.7 (t), 64.0 (t), 66.7 (d), 67.4

(d), 76.2 (s), 76.3 (s), 99.1 (d), 99.3 (d), 128.7 (d), 128.8 (d), 128.8 (d), 129.6 (d), 129.8 (d), 133.4 (d), 133.5 (d), 141.9 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3444, 3022, 2947, 1729, 1448, 1284, 1134, 1076; MS *m/z* (relative intensity): 279 (M - H<sub>2</sub>O - C<sub>5</sub>H<sub>9</sub>O)<sup>+</sup> (1), 254 (4), 139 (20), 85 (100), 67 (38); HRMS calcd. for C<sub>15</sub>H<sub>19</sub>O<sub>3</sub>S (M - H<sub>2</sub>O - C<sub>5</sub>H<sub>9</sub>O)<sup>+</sup> 279.10212, found 279.10492.

**Preparation of (1*S*)-1-Benzenesulfonyl-(2*R*)-2-methyl-2-[2-(tetrahydro-pyran-(2*R* and 2*S*)-2-yloxy)-ethyl]-cyclobutyl methyl ketone 27.** Crushed, activated 3 Å molecular sieves (20% w) were added to stirred AcONa (109.5 mg, 1.33 mmol) and **26** (1.7 g, 4.45 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (22.2 mL, 0.2 M) under argon. The flask was cooled to 0 °C and pyridinium chlorochromate (1.9 g, 8.9 mmol) was added. The reaction was allowed to warm to rt and stirred for 3 h. After dilution with ether (75 mL) the mixture was filtered through a pad of Celite and silica gel and washed with ether (2 x 10 mL). The resulting solution was concentrated, and purified by flash-chromatography, yielding the ketone **27** (1.55 g, 92% yield): <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.53 (m, 4 H), 1.66 (m, 3 H), 1.73 (s, 3 H), 1.86 (m, 2 H), 2.23 (m, 1 H), 2.33 (s, 3 H), 2.51 (m, 1 H), 2.64 (m, 1 H), 3.44 (m, 2 H), 3.80 (m, 2 H), 4.52 (m, 1 H), 7.49 (m, 2 H), 7.61 (m, 1 H), 7.72 (m, 2 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 19.5 (t), 22.2 (q), 22.2 (q), 23.1 (t), 25.4 (t), 28.4 (t), 28.4 (t), 30.3 (q), 30.6 (t), 37.6 (t), 37.7 (t), 49.2 (s), 62.4 (t), 63.2 (t), 63.2 (t), 82.9 (s), 82.9 (s), 99.0 (d), 99.0 (d), 128.9 (d), 128.9 (d), 133.9 (d), 137.9 (s), 201.6 (s), 201.6 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3028, 2953, 1769, 1699, 1446, 1306, 1156, 1076; MS *m/z* (relative intensity): 211 (5), 109 (6), 85 (100), 67 (34), 55 (23); HRMS calcd. for C<sub>15</sub>H<sub>19</sub>O<sub>4</sub>S (M - C<sub>5</sub>H<sub>9</sub>O)<sup>+</sup> 295.10041, found 295.10143.

**Preparation of (1*R* and 1*S*)-(2*R*)-2-methyl-2-[2-(tetrahydro-pyran-(2*R* and 2*S*)-2-yloxy)-ethyl]-cyclobutyl methyl ketones 28 and 29.** The desulfonation used above to obtain **13** was applied to **27** on a (1.5 g, 3.9 mmol) scale for 3 h at -40 °C, yielding **28** and **29** (871.5 mg, 92% yield) as a 1 : 1 epimeric mixture (when such reduction was performed for 0.5 h at rt, a 1 : 10 mixture of **28** and **29** was obtained): <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.97 (s, 6 H), 1.27 (s, 3 H), 1.28 (s, 3 H), 1.48 (m, 20 H), 1.61 (m, 6 H), 1.76 (m, 14 H), 1.86 (m, 4 H), 2.00 (s, 6 H), 2.02 (s, 6 H), 2.26 (m, 4 H), 2.94 (m, 2 H), 3.04 (m, 2 H), 3.30 (m, 2 H), 3.43 (m, 6 H), 3.69 (m, 2 H), 3.79 (m, 6 H), 4.49 (m, 2 H), 4.54 (m, 2 H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 16.3 (t), 16.4 (t), 16.4 (t), 19.4 (t), 19.5 (t), 19.6 (t), 19.6 (t), 20.9 (q), 21.0 (q), 25.4 (t), 25.4 (t), 27.9 (q), 28.0 (q), 29.5 (t), 29.6 (t), 29.9 (q), 30.2 (t), 30.3 (t), 30.5 (q), 30.6 (t), 30.7 (t), 30.7 (t), 34.6 (t), 34.7 (t), 42.2 (s), 42.3 (t), 42.5 (t), 42.5 (t), 42.5 (s), 42.6 (s), 54.5 (d), 54.5 (d), 56.9 (d), 62.1 (t), 62.2 (t), 62.4 (t), 62.4 (t), 63.7 (t), 63.8 (t), 64.1 (t), 98.7 (d), 98.8 (d), 99.0 (d), 99.1 (d), 208.3 (s); IR (CHCl<sub>3</sub>) (cm<sup>-1</sup>): 3010, 2953, 1699, 1357, 1184, 1137, 1025; MS *m/z* (relative intensity): 155 (M - C<sub>5</sub>H<sub>9</sub>O)<sup>+</sup> (36), 139 (17), 95 (41), 85 (100), 67 (68); HRMS calcd. for C<sub>14</sub>H<sub>24</sub>O<sub>3</sub> (M)<sup>+</sup> 240.17254, found 240.17425.

**Preparation of (2*R* and 2*S*)-2-[2-[(2*R* and 2*S*)-2-Isopropenyl-(1*R*)-1-methyl-cyclobutyl]-ethoxy]-tetrahydro-pyran 30 and 31.** A solution of *n*-BuLi (1.98 mL, 4.9 mmol, 2.5 M in *n*-hexane) was added dropwise to a stirred and ice-cooled suspension of methyltriphenylphosphonium bromide (1.9 g, 5.3 mmol) in dry THF (30 mL) under argon. The mixture was stirred at 0 °C for 1 h and allowed to settle. The salt-free supernatant was taken up in another flask, and a solution of **28** and **29** (850 mg, 3.5 mmol) in dry THF (5.4 mL) was added dropwise to the mixture. The reaction was allowed to warm to rt and stirred. After 2 h, the mixture was poured into water (35 mL) and extracted with ether (3 x 30 mL). The resulting solution was dried, concentrated and the obtained crude was purified by flash-chromatography, yielding **30** and **31** (733.3 mg, 87% yield): <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.92 (s, 6 H), 1.16 (s, 3 H), 1.17 (s, 3 H), 1.49 (m, 18 H), 1.64 (s, 6 H), 1.66 (s, 6

H), 1.69 (m, 6 H), 1.73 (m, 18 H), 1.95 (m, 6 H), 2.56 (m, 4 H), 3.38 (m, 4 H), 3.50 (m, 4 H), 3.80 (m, 4 H), 3.86 (m, 4 H), 4.56 (m, 4 H), 4.61 (s, 2 H), 4.63 (s, 2 H), 4.82 (s, 4 H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 19.1 (t), 19.5 (q), 19.6 (q), 19.7 (t), 23.0 (q), 23.2 (q), 25.5 (t), 28.3 (q), 28.4 (q), 29.1 (t), 29.2 (t), 29.9 (t), 30.0 (t), 30.8 (t), 33.3 (t), 41.0 (s), 41.3 (s), 43.3 (t), 50.4 (d), 50.4 (d), 52.5 (d), 62.2 (t), 62.3 (t), 64.4 (t), 64.5 (t), 64.6 (t), 98.9 (d), 98.9 (d), 98.9 (d), 99.0 (d), 109.5 (t), 109.7 (t), 145.1 (s), 145.7 (s); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 3010, 2944, 2869, 1455, 1441, 1132, 1025; MS  $m/z$  (relative intensity): 165 (4), 108 (13), 85 ( $\text{C}_5\text{H}_9\text{O}$ ) (100), 67 (95), 57 (54); HRMS calcd. for  $\text{C}_{15}\text{H}_{26}\text{O}_2$  ( $\text{M}$ ) $^+$  238.19328, found 238.19458.

**Preparation of 2-[(2S and 2R)-2-Isopropenyl-(1R)-1-methyl-cyclobutyl]-ethanol 1 and 2.** To a stirred solution of **30** and **31** (700 mg, 2.94 mmol) in MeOH (19.6 mL, 0.15 M) was added Dowex 50Wx8 (210 mg, 30% (w)) at rt. The reaction mixture was vigorously stirred for 15 h, until TLC showed complete conversion. After filtration, the solution was concentrated and purified by flash-chromatography, yielding **1** (220 mg, 49% yield) and **2** (220 mg, 47% yield). Compound **1**:  $[\alpha]_{\text{D}}^{25} +18.4$  (c 0.5, *n*-hexane);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.17 (s, 3 H), 1.45 (ddd,  $J = 6.1, 9.2, 13.5$  Hz, 1 H), 1.58 (br s, 1 H), 1.61 (ddd,  $J = 8.8, 10.2, 10.9$  Hz, 1 H), 1.68 (s, 3 H), 1.69 (ddd,  $J = 2.6, 9.0, 10.9$  Hz, 1 H), 1.76 (ddd,  $J = 5.8, 9.2, 13.5$  Hz, 1 H), 1.81 (dddd,  $J = 2.6, 8.8, 9.0, 11.2$  Hz, 1 H), 1.97 (dddd,  $J = 9.0, 9.0, 10.2, 11.2$  Hz, 1 H), 2.55 (dd,  $J = 9.0, 9.0$  Hz, 1 H), 3.66 (ddd,  $J = 5.8, 9.2, 10.2$  Hz, 1 H), 3.69 (ddd,  $J = 6.1, 9.2, 10.2$  Hz, 1 H), 4.65 (s, 1 H), 4.84 (s, 1 H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 19.1 (t), 23.2 (q), 28.4 (q), 29.3 (t), 36.9 (t), 41.3 (s), 52.5 (d), 59.9 (t), 109.7 (t), 145.2 (s); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 3625, 3462, 3004, 2946, 1646, 1455, 1374; MS  $m/z$  (relative intensity): 154 ( $\text{M}$ ) $^+$  (1), 139 ( $\text{M} - \text{CH}_3$ ) $^+$  (2), 121 (10), 109 (36), 93 (26), 79 (30), 68 (100), 53 (93); HRMS calcd for  $\text{C}_{10}\text{H}_{18}\text{O}$  ( $\text{M}$ ) $^+$  154.13577, found 154.13602. Compound **2**:  $[\alpha]_{\text{D}}^{25} +5.5$  (c 1.16,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.94 (s, 3 H), 1.32 (br s, 1 H), 1.43 (m, 1 H), 1.65 (s, 3 H), 1.81 (m, 4 H), 1.98 (m, 1 H), 2.58 (m, 1 H), 3.70 (m, 2 H), 4.62 (s, 1 H), 4.84 (s, 1 H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 19.5 (q), 19.7 (t), 23.0 (q), 30.2 (t), 40.9 (s), 46.7 (t), 50.5 (d), 59.9 (t), 109.8 (t), 145.6 (s); IR ( $\text{CHCl}_3$ ) ( $\text{cm}^{-1}$ ): 3623, 3446, 3032, 2966, 1645, 1457, 1377, 1038; MS  $m/z$  (relative intensity): 139 ( $\text{M} - \text{CH}_3$ ) $^+$  (1), 109 (16), 91 (14), 79 (22), 67 (100), 56 (23); HRMS calcd. for  $\text{C}_{10}\text{H}_{18}\text{O}$  ( $\text{M}$ ) $^+$  154.13577, found 154.13678.

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## References and notes:

1. Thomas, A.F.; Bessiere, Y. *The Total Synthesis of Natural Products*, Ed. by John ApSimon, Wiley, NY, **1981**, Vol IV, 488.
2. a) Katzenellenbogen, J.A. *Science*, **1976**, *194*, 139; b) *Dictionary of Natural Products*, C. Djerassi, Ed. by Chapman and Hall, London, **1994**, Vol 3, 2984.
3. Rosini, G.; Marotta, E.; Raimondi, A.; Righi, P. *Tetrahedron: Asymmetry*, **1991**, *2*, 123.
4. Alibés, R.; Bourdelande, J.L.; Font, J. *Tetrahedron Lett.*, **1994**, *35*, 2587, and references cited therein.
5. a) Mori, K; Fukamatsu, K. *Liebigs. Ann. Chem.* **1992**, *489*, b) For a recently reported synthesis of ( $\pm$ )-grandisol see: Kim, D.; Kwak, Y.S.; Shin, K. J. *Tetrahedron Lett.*, **1994**, *35*, 9211.

6. Rodríguez, C.M.; Ramírez, M.A.; Martín, V.S. *Tetrahedron Lett.*, **1992**, *33*, 3039.
7. Rodríguez, C.M.; Martín, T.; Ramírez, M.A.; Martín, V.S. *J. Org. Chem.*, **1994**, *59*, 4461.
8. a) Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1980**, *102*, 5976; b) Martín, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1981**, *103*, 6237; c) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1987**, *109*, 5765.
9. Evans, D.A.; Bender, S.L.; Morris, J. *J. Am. Chem. Soc.*, **1988**, *110*, 2501.
10. a) Trost, B.M.; Curran, D.P. *Tetrahedron Lett.*, **1981**, *22*, 1287; b) Trost, B.M.; Braslau, R. *J. Org. Chem.*, **1988**, *53*, 532.
11. Trost, B.M.; Arndt, H.C.; Strege, P.E.; Verhoeven, T.R. *Tetrahedron Lett.*, **1976**, 3477.
12. Stork, G.; Cohen, J.F. *J. Am. Chem. Soc.*, **1974**, *96*, 5270.
13. This specific rotation is in agreement with a product of 90% ee in accordance with the observed optical purity of the epoxy alcohol **5**. Although we have not attempted to optimize the optical purities in the series of described compounds we found that the sulfone **3** can be obtained as a pure enantiomer by two recrystallisations in *n*-hexane/chloroform,  $[\alpha]_D^{25} +28.5$  (*c* 2.2, CHCl<sub>3</sub>). The use of this material should produce optically pure grandisol and fraganol.
14. Mori, K.; Fukamatsu, K. *Liebigs. Ann. Chem.* **1992**, 489.
15. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.*, **1969**, *34*, 2543.

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