A New Stereoselective Synthesis of (±)-Grandisol Based on the Remote Alkylation Protocol

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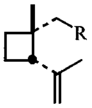
Keywords: Pheromones / Carbenoids / Natural products / Alkylation

A new stereoselective synthesis of (±)-grandisol (**1a**) has been developed. The synthesis starts with a simple cyclobutyl derivative to which the methyl group and the 1,2-*cis* disposed side chains were appended through a remote alkylation protocol.

Introduction

Grandisol [*cis*-2-(2-isopropenyl-1-methylcyclobutyl)ethanol, (**1a**)] is the major component of the pheromonal complex of the cotton boll weevil *Anthonomus grandis* Boheman, which is a very important pest in the cotton fields of the Americas.[1] The compound is also released by females of the ambrosia beetle *Trypodendron signatum*[2] and by males of the bark beetles *Pityophthorus pityographus*,[3] *Pityogenes quadridens* and *P. calcaratus*.[4] Grandisol, along with its corresponding aldehyde, grandisal (**1b**), is also the pheromone of weevils of the genus *Pissodes*.[5] More recently it has been found to be a component of the pheromonal mixture produced by the male pecan weevil *Curculio caryae*,[6] while its carboxylic derivative, grandisoic acid (**1c**), was found to be the aggregation pheromone of the plum curculio *Conotrachelus nenuphar* Herbst, a major pest of stone and pome fruits east of the Rocky Mountains.[7] Thus, it appears that several Coleoptera species use the same basic chemical structure to control their behaviour (Scheme 1).

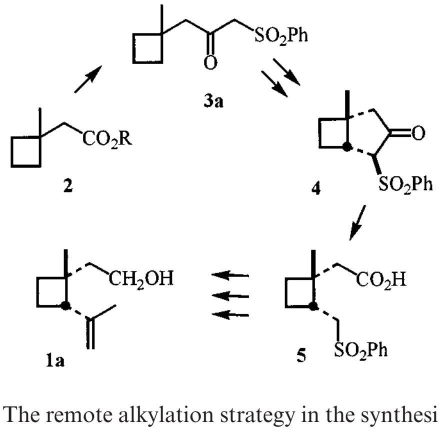


1a R = CH_2OH
1b R = CHO
1c R = CO_2H

Scheme 1. Grandisol and its oxidized derivative

Due to its high commercial value as a component of field monitoring traps and to its interesting cyclobutane structure, a large number of syntheses of racemic and optically active grandisol have already been described in the literature.[8] Since the cotton boll weevil *A. grandis* can only recognise the natural pheromone enantiomer [(+)-grandisol],[9] the synthesis of the racemic material becomes economically very attractive if the product is to be used in traps for control of that pest. Also, the finding that several economically important pests also use grandisol, or its oxidized derivatives, as pheromones is likely to provoke an increase in the future commercial demand for this class of compounds. Thus, a further search for new and cheaper methods of preparation of grandisol, or of its derivatives, seems justified.

Some years ago, one of us described a synthetic protocol which allowed the phenylsulfonylmethylation of a remote nonactivated γ-carbon atom of a carboxylic acid.[10] We felt that application of this protocol to (1-methylcyclobutyl)acetic acid (**2**) (R = H) should lead, via the bicycloheptanone **4**, to the *cis*-1,2-disubstituted acid **5**, which could then be readily converted into grandisol (**1a**) (Scheme 2). Thus, starting with a simple cyclobutane derivative, the proposed route would by-pass the conventional construction of the four-membered ring by photochemical or thermal [2+2] cycloadditions, which require either special equipment or an additional deoxygenation step. Furthermore, exploitation of the versatile chemistry of the benzenesulfonyl group, which exhibits leaving and anion-stabilizing behaviour, should allow a facile construction of the *cis*-2-isopropenyl side chain of **1a** by methanesulfonylation and methylation of the sulfonylated carbon atom of **5**, followed by a mild Ramberg–Bäcklund reaction.[11] This would also avoid stereochemically labile intermediates or the use of expensive reagents, which are found in many of the reported grandisol syntheses.



Scheme 2. The remote alkylation strategy in the synthesis of grandisol (**1a**)

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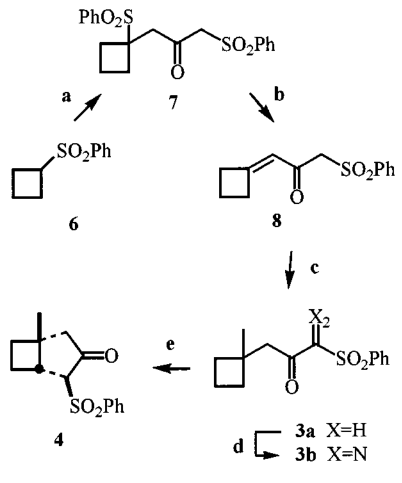
1434–193X/01/0714–2659 $ 17.50+.50/0

We now report on a new stereoselective and short synthesis of (±)-grandisol (**1a**) based on these concepts.

Results and Discussion

In our early investigations a modified Stetter condensation[12] of the sodium salt of (methylsulfonyl)benzene with methyl (1-methylcyclobutyl) acetate (**2**) (R = Me) was used for the preparation of the required β-ketosulfone **3a**. However, the ester **2** (R = Me) was not easily accessible,[13] and a direct and more convergent approach to **3a** was explored. Cyclobutyl derivatives are rather expensive chemicals, but (cyclobutylsulfonyl)benzene (**6**), while not commercially available, is easily prepared. It can be readily synthesized in multigram amounts by a modification of the Durst[14] procedure, and proved to be a cheap and very convenient starting material for our new route. Thus, conversion of the sulfone **6** to its anion with methyllithium and condensation with 2-(phenylsulfanylmethyl)oxirane[15] gave a crude reaction product, which was directly oxidized to the highly crystalline ketodisulfone **7**, in 87% isolated overall yield. Treatment of this compound with methanolic sodium hydroxide at room temperature gave a 97% yield of the expected[16] β-ketosulfone **8**, which was pure enough for the next step.

The quaternary centre in the key β-ketosulfone **3a** was now constructed by a 1,4-addition of a methyl group to **8**. As expected, the presence of the rather acidic, carbonyl- and phenylsulfonyl-flanked, methylene group in **8** precluded a conventional 1,4-addition with basic reagents such as copper-catalyzed methyl Grignard reagent or the usual organocopper reagents, the starting unsaturated β-ketosulfone **8** being recovered in quantitative yield. However, reaction of **8** with the Lewis acid trimethylaluminium and a catalytic amount of cuprous bromide[17] in THF at 0 °C smoothly gave the desired β-ketosulfone **3a** as a nicely crystalline material, in 80% yield.



Scheme 3. (a) i. MeLi, THF, −15 °C; ii. 2-(phenylsulfanylmethyl)oxirane; iii. H_2O_2, HOAc; iv. Jones reagent, room temp.; (b) NaOH, MeOH, room temp.; (c) $AlMe_3$, CuBr, THF, 0 °C; (d) 2-Chloro-1-ethylpyridinium tetrafluoroborate, NaN_3, NaOAc, MeOH, 0 °C; (e) $Rh_2(OAc)_4$, CH_2Cl_2, reflux

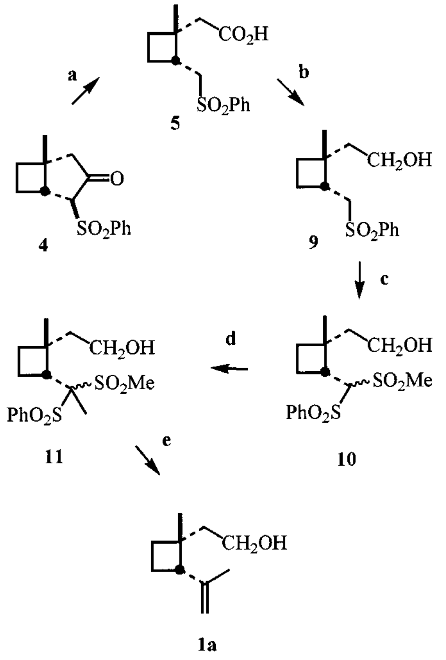
With an easy and efficient access to **3a** now available, the remote alkylation protocol could proceed. Diazotization of **3a** with the safe and very convenient 2-azido-1-ethylpyridinium tetrafluoroborate[18] (generated in situ) afforded the expected α-diazo-β-ketosulfone **3b** as an oil, in practically quantitative yield. Reflux of a dichloromethane solution of the crude diazo compound **3b** with a catalytic amount of rhodium acetate led to a smooth intramolecular carbenoid cyclization,[19] to afford crystalline 1-methyl-4-(phenylsulfonyl)bicyclo[3.2.0]heptan-3-one (**4**)[20] in 79% overall yield from **3a** (Scheme 3).

The construction of the *cis*-isopropenyl side-chain present in the grandisol molecule could now be initiated. To this end the bicyclic compound **4** was first cleaved by reflux of a methanolic sodium hydroxide solution to give the readily crystallized carboxylic acid **5**, in 96% yield. Reduction of **5** with borane−dimethyl sulfide complex in THF smoothly gave the alcohol **9** (95%) as a thick oil which slowly solidified to a crystalline mass. Transformation of the phenylsulfonylmethyl group of **9** into a *cis*-isopropylidene side chain by a Ramberg−Bäcklund reaction now required the successive introduction of methanesulfonyl and methyl groups onto its sulfone-activated methylene carbon atom. Consequently, the alcohol **9** was first converted into its dianion by treatment with methyllithium and quenched with 2.5 equivalents of dimethyl disulfide to yield an epimeric mixture of the expected methyl thioether (ca. 1:1.7 by NMR analysis of the crude product), which was directly converted into the corresponding epimeric mixture of disulfones **10** on oxidation with hydrogen peroxide in acetic acid (88% overall yield from **9**). No attempt was made to isolate the pure epimers, as the newly created asymmetric centre was to be destroyed later in the synthetic sequence.

Instead, crude **10** was treated with *tert*-butyldimethylsilyl chloride and triethylamine and the silyl ether isolated by flash chromatography to yield a resinous epimeric mixture which slowly set into a crystalline mass. The alkylation of this silyl ether was, as expected from the congested environment of its doubly sulfonyl-activated carbon atom, a rather slow reaction. The methylation was, however, conveniently carried out in practically quantitative yield by stirring the silyl ether with an excess of methyl iodide and concentrated sodium hydroxide under phase-transfer catalysis for seven days at room temperature. Subsequent treatment of the crude methylated product with Dowex 50 × 8 in methanol easily removed the protecting group to afford a crystalline epimeric mixture of the desired methylated disulfones **11** (78% overall yield from **10**). The synthesis was completed by treatment of **11** with methyllithium in THF, a Ramberg−Bäcklund reaction taking place after the initial attack on the methanesulfonyl group and extrusion of benzenesulfinate anion and sulfur dioxide to afford (±)-grandisol (**1a**) in 56.6% yield (Scheme 4).

Conclusion

We have described a new and efficient preparative route to (±)-grandisol (**1a**) starting with readily available (cyclo-



Scheme 4. (a) i. NaOH, MeOH, reflux; ii. H^+; (b) $Me_2S{\cdot}BH_3$; (c) i. MeLi, THF, −15 °C; ii. Me_2S_2; iii. H_2O_2, HOAc; (d) i. *t*BuMe$_2$SiCl, Et_3N, DMAP, CH_2Cl_2, room temp.; ii. NaOH, MeI, BTEAC, C_6H_6-H_2O; iii. Dowex 50x8, MeOH, room temp.; (e) MeLi, THF, 0 °C

butylsulfonyl)benzene (**6**), to which the quaternary methyl group and the two 1,2-*cis*-disposed side chains were appended in a stereoselective fashion through the application of the remote alkylation protocol.[10] The new synthetic route proceeds in 9 steps with ca. 18% overall yield from **6**, and since most of the synthetic intermediates are secured in good to excellent yields as crystalline compounds requiring no or minimal purification, it should be amenable to scale-up. Although a considerable loss of molecular mass occurs in steps **7**→**8** and **11**→**1a** due to the elimination of the benzenesulfinate anion, this can be efficiently compensated for in large runs by the recovery of benzenesulfinic acid from the aqueous phase of the reaction workup. After conversion into sodium benzenesulfinate this side product can be recycled by using it for the preparation of the starting (cyclobutylsulfonyl)benzene.

Experimental Section

General: ^1H spectra were recorded on a Bruker DPX 300 spectrometer (300 MHz) or Varian EM-390 (90 MHz), and ^{13}C spectra were recorded on a Bruker DPX 300 spectrometer (75.4 MHz) in $CDCl_3$ with TMS as internal standard. Infrared spectra were measured as KBr pellets, unless otherwise stated. Melting points were measured in an oil bath and are uncorrected. Anhydrous THF was distilled from sodium benzophenone ketyl. Extracts were dried with anhydrous Na_2SO_4 and evaporated under vacuum in a rotary evaporator. Thin layer chromatography, preparative or analytical, was run on SiO_2 FG_{257} plates, and detected with UV light or iodine vapour. Microanalyses were performed in the USP Microanalytical Laboratory. All reactions were run under argon.

1-Phenylsulfonyl-3-(1-phenylsulfonylcyclobutyl)acetone (7): A solution of (cyclobutylsulfonyl)benzene (**6**; 8.1 g, 41 mmol) in THF (100 mL) was cooled to −15 °C and a 1.4 M ethereal solution of methyllithium/lithium bromide (31 mL, 43.4 mmol) was slowly added. After 10 min. a solution of 2-(phenylsulfanylmethyl)oxirane (6.8 g, 40.9 mmol)[15] in THF (30 mL) was added dropwise during 25 min., care being taken to keep the temperature below −10 °C. After addition, the reaction was allowed to reach room temperature and was then quenched with saturated NaCl (25 mL). The organic layer was decanted and the aqueous phase further extracted with 25 mL of Et_2O. The pooled extracts were dried and evaporated to give 15.1 g of a crude product, which was redissolved in glacial HOAc (30 mL) and 1 mL of a 20% aqueous solution of sodium tungstate added. Hydrogen peroxide (30% H_2O_2, 11 mL) was then carefully added (*Care: exothermic*). After this addition, the reaction mixture was left at room temperature for 16 h and then most of the HOAc removed under vacuum. The residue was redissolved in Me_2CO (200 mL) and a 2.7 M Jones reagent (23 mL, 62.1 mmol) added in small portions under cooling with a water bath. After stirring at room temperature for 16 h, TLC analysis (solvent: EtOAc/*n*-C_6H_{14}, 2:3) showed complete reaction. The solvent was evaporated and the residue partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL). The organic layer was decanted, washed with saturated NaCl (2 × 25 mL) and dried. Solvent removal and crystallization of the residue from MeOH gave pure **7** (15.5 g, 96.6%), m.p. 130−132 °C. − IR: $\tilde{\nu}$ = 1711, 1320, 1290, 1142, 1072, 728 cm^{-1}. − ^1H NMR: δ = 1.87−2.07 (m, 2 H), 2.26−2.35 (m, 2 H), 2.69−2.79 (m, 2 H), 3.15 (s, 2 H), 4.28 (s, 2 H), 7.55−7.71 (m, 6 H), 7.85−7.88 (m, 4 H). − ^{13}C NMR: δ = 15.04, 27.60, 46.91, 64.72, 67.71, 128.21, 129.27, 129.45, 129.93, 134.17, 134.44, 134.99, 138.63, 194.51. − $C_{19}H_{20}O_5S_2$ (392.5): calcd. C 58.14, H 5.14; found C 57.96, H 5.27.

1-Cyclobutylidene-3-(phenylsulfonyl)acetone (8): The disulfone **7** (7.84 g, 20 mmol) was dissolved in 60 mL of a 1:1 mixture of MeOH and CH_2Cl_2 and warmed slightly. The stirred solution was then cooled in a water bath and treated with NaOH (0.87 g, 20.2 mmol) in MeOH (8 mL), added in small portions over 1 h. Occasionally, the disulfone separated as fine crystals which redissolved as more base was added. After stirring for an additional 2 h at room temperature, TLC analysis (solvent: Me_2CO/*n*-C_6H_{14}, 2:3) showed complete reaction. Most of the solvent was then removed under vacuum at room temperature and the pasty residue partitioned between Et_2O (150 mL) and H_2O (15 mL). The ethereal layer was decanted, the aqueous phase further extracted with Et_2O (2 × 25 mL), and the pooled extracts were washed with saturated NaCl (2 × 10 mL) and dried. Evaporation of the solvent yielded **8** (4.85 g, 97.1%) as a yellowish resin, which was pure enough for the next step. Preparative TLC (solvent: Me_2CO/*n*-C_6H_{14}, 2:3) gave an analytical sample, which crystallized on trituration with a few drops of MeOH. Recrystallization from MeOH gave material with m.p. 71−72 °C. − IR: $\tilde{\nu}$ = 1690, 1628, 1354, 1309, 1276, 1173, 1060, 895, 758 cm^{-1}. − ^1H NMR: δ = 2.13 (quint. *J* = 7.8 Hz, 2 H), 2.85−2.90 (m, 2 H), 3.08−3.15 (m, 2 H), 4.16 (s, 2 H), 6.21 (s, 1 H), 7.53−7.69 (m, 3 H), 7.88−7.90 (m, 2 H). − ^{13}C NMR: δ = 18.08, 33.26, 35.09, 67.40, 119.94, 128.30, 129.12, 129.43, 129.92, 134.14, 138.96, 172.94, 185.94. − $C_{13}H_{14}O_3S$ (250.3): calcd. C 62.38, H 5.64; found C 61.87, H 5.39.

Benzenesulfinic acid was recovered from the pooled aqueous workup phase by treatment with solid NH_4Cl (4 g), extraction with CH_2Cl_2 (2 × 15 mL) and acidification with concentrated H_2SO_4 to pH 1. Extraction with CH_2Cl_2 (4 × 15 mL), drying and evaporation of the solvent gave the acid (2.55 g, 89.8%), which could be converted into its sodium salt and recycled in the preparation of (cyclobutylsulfonyl)benzene (**6**).

1-(1-Methylcyclobutyl)-3-(phenylsulfonyl)acetone (3a): A 2 M toluene solution of Me_3Al (24 mL, 48 mmol) was added to a suspension of CuBr (0.48 g, 3.3 mmol) in THF (100 mL), cooled in an ice bath. The mixture was stirred for 10 min. and crude **5** (4.0 g, 16 mmol) in THF (80 mL) added dropwise during 1 h. After the addition, the reaction was carefully quenched with H_2O (copious gas evolution!) and then enough 6 M HCl was added to dissolve the precipitated aluminium hydroxide. The organic phase was decanted, the solvent evaporated and the residue redissolved in CH_2Cl_2 (80 mL). The solution was successively washed with 3 M NH_4OH (3 × 15 mL) and saturated NaCl (2 × 15 mL). Drying and evaporation of the solvent yielded a resin which readily crystallized from MeOH to give **3a** (3.4 g, 79.9%), m.p. 82−83 °C. − IR: $\tilde{\nu}$ = 1715, 1315, 1241, 1144, 745 cm^{-1}. − ^1H NMR: δ = 1.15 (s, 3 H), 1.76−1.94 (m, 6 H), 2.83 (s, 2 H), 4.11 (s, 2 H), 7.55 (m, 3 H), 7.86−7.89 (m, 2 H). − ^{13}C NMR: δ = 15.68, 25.80, 33.69, 36.76, 55.75, 67.44, 128.29, 129.31, 134.28, 138.63, 197.26. − $C_{14}H_{18}O_3S$ (266.4): calcd. C 63.13, H 6.81; found C 62.89, H 6.79.

(1*R,4*R**,5*S**)-1-Methyl-4-(phenylsulfonyl)bicyclo[3.2.0]heptan-3-one (4):** Sodium azide (4.38 g, 67.4 mmol) was added to an iced solution of 2-chloro-1-ethylpyridinium tetrafluoroborate[18] (15.4 g, 67.2 mmol) in MeOH (50 mL). After stirring for 10 min., finely ground **3a** (13.8 g, 51.8 mmol) and $NaOAc\cdot 3H_2O$ (7.05 g, 52 mmol) were added. The iced slurry was stirred until a clear yellow solution resulted and TLC monitoring (solvent: $Me_2CO/n\text{-}C_6H_{14}$, 1:4) showed complete disappearance of the starting material. Most of the solvent was then removed under vacuum at room temperature and the pasty residue partitioned between Et_2O (80 mL) and H_2O (40 mL). The separated ethereal phase was washed with saturated NaCl (25 mL), dried and evaporated under vacuum, also at room temperature, to give 15.01 g of practically pure (TLC) α-diazo-β-ketosulfone **3b** (oil; IR: $\tilde{\nu}$ (film) = 2109, 1665, 1448, 1337, 1156, 725 cm^{-1}). The crude diazo derivative was redissolved in CH_2Cl_2 (100 mL) and added dropwise over 8 h to a suspension of $Rh_2(OAc)_4$ (0.25 g, 0.57 mmol) in boiling CH_2Cl_2 (350 mL). After addition, the reaction mixture was further refluxed for 16 h, cooled and stirred with 3 M HCl (25 mL) for 1 h. The aqueous acid layer was decanted and saved for recovery of the rhodium salts. Evaporation of the organic phase under vacuum afforded a residue which was redissolved in Et_2O (250 mL) and filtered from any insoluble matter. Solvent removal yielded a resin, which readily crystallized on trituration with some MeOH. Recrystallization from MeOH gave **4** (10.8 g, 78.8% overall yield from **3a**), m.p. 114−115 °C. − IR: $\tilde{\nu}$ = 1745, 1305, 1144, 1080, 753, 730 cm^{-1}. − ^1H NMR: δ = 1.41 (s, 3 H), 1.53−1.63 (m, 2 H), 1.79−1.87 (m, 1 H), 1.89−2.03 (m, 1 H), 2.41 (d, J = 18 Hz, 1 H), 2.59 (d, J = 18 Hz, 1 H), 3.21 (dd, J = 14.5, 8.7 Hz, 1 H), 3.68 (s, 1 H), 7.29−7.71 (m, 3 H), 7.81−7.97 (m, 2 H). − ^{13}C NMR: δ = 21.51, 26.60, 32.07, 40.67, 41.24, 52.34, 78.85, 128.89, 129.27, 134.28, 137.60, 208.26. − $C_{14}H_{16}O_3S$ (264.3): calcd. C 63.61, H 6.10; found C 63.17, H 5.83.

(1*R,2*R**)-{1-Methyl-2-[(phenylsulfonyl)methyl]cyclobutyl}acetic Acid (5):** A mixture of **7** (4.0 g, 15 mmol) and 2 M NaOH (15 mL, 30 mmol) in MeOH (30 mL) was heated under reflux for 16 h. The solvent was removed, the residue redissolved in H_2O (25 mL), acidified to pH 1 with 6 M HCl and extracted with CH_2Cl_2 (3 × 20 mL). Drying and evaporation of the organic extracts gave acid **5** (4.1 g, 96%) as a resin, which readily crystallized on trituration with a few drops of Et_2O. Recrystallization from MeOH gave a pure material with m.p. 101−103 °C. − IR: $\tilde{\nu}$ = 3420 (br), 1702, 1306, 1144, 747 cm^{-1}. − ^1H NMR: δ = 1.24 (s, 3 H), 1.63−1.78 (m, 2 H), 1.97−2.04 (m, 2 H), 2.38 (d, J = 14.5 Hz, 1 H), 2.51 (d, J = 14.5 Hz, 1 H), 2.48−2.60 (m, 1 H), 3.10 (dd, J = 13.9, 9.3 Hz, 1 H), 3.31 (dd, J = 13.9, 5.3 Hz, 1 H), 7.54−7.68 (m, 3 H), 7.88−7.91 (m, 2 H). − ^{13}C NMR: δ = 22.25, 26.87, 31.02, 38.63, 39.61, 40.53, 57.47, 127.94, 129.32, 133.75, 139.60, 177.82. − $C_{14}H_{18}O_4S$ (282.4): calcd. C 59.55, H 6.43; found C 59.89, H 6.17.

(1*R,2*R**)-2-{1-Methyl-2-[(phenylsulfonyl)methyl]cyclobutyl}ethanol (9):** Acid **5** (3.83 g, 13.6 mmol) was dissolved in THF (30 mL) and carefully treated with 2.8 mL (28 mmol) of neat $Me_2S\cdot BH_3$ whilst stirring and cooling in an ice bath. After standing at room temperature for 16 h, the reaction was cautiously quenched with saturated NaCl (10 mL), and 2 M NaOH was added until the solution became strongly basic. The organic layer was decanted and the aqueous phase further extracted with Et_2O (2 × 30 mL). Drying and evaporation of the organic extracts afforded alcohol **9** as a thick oil that slowly crystallized on standing. An analytical sample, secured by preparative TLC (solvent: $Me_2CO/n\text{-}C_6H_{14}$, 2:3), showed m.p. 39−40 °C. − IR: $\tilde{\nu}$ = 3412 (br), 1303, 1143, 754 cm^{-1}. − ^1H NMR: δ = 1.07 (s, 3 H), 1.56−1.67 (m, 4 H), 1.70−1.77 (m, 1 H), 1.88−1.98 (m, 1 H), 2.25 (s, 1 H), 2.40−2.53 (m, 1 H), 3.11 (dd, J = 15.0, 9.2 Hz, 1 H), 3.26 (dd, J = 15.0, 5.4 Hz, 1 H), 3.61−3.67 (m, 2 H), 7.54−7.68 (m, 3 H), 7.87−7.90 (m, 2 H). − ^{13}C NMR: δ = 22.63, 26.90, 30.80, 37.50, 39.23, 40.50, 57.56, 59.39, 127.99, 129.37, 133.77, 139.84. − $C_{14}H_{20}O_3S$ (268.4): calcd. C 62.66, H 7.51; found C 62.39, H 7.36.

(1*R,2*R**)-2-{1-Methyl-2-[(methylsulfonyl)(phenylsulfonyl)methyl]-cyclobutyl}ethanol (10):** A solution of **9** (4.58 g, 17 mmol) in THF (40 mL) was cooled to −15 °C and a 1.57 M ethereal solution of methyllithium/lithium bromide (27.5 mL, 43.2 mmol) was added whilst stirring. After 10 min., Me_2S_2 (4.07 g, 43.2 mmol) was added and the reaction allowed to reach 0 °C, when it was quenched with saturated NaCl (15 mL). The organic layer was diluted with Et_2O (40 mL), decanted and dried. Evaporation of the solvents yielded the thioether (5.45 g) as an epimeric mixture (1:1.7, by NMR analysis). The crude material was redissolved in HOAc (30 mL) and 0.3 mL of 20% aqueous sodium tungstate was added, followed by cautious addition (*Care: exothermic*) of 30% H_2O_2 (4.0 mL, 46.5 mmol) whilst stirring and eventual cooling in a water bath. After addition, the reaction mixture was left at room temperature for 16 h, the HOAc removed under vacuum, the residue redissolved in CH_2Cl_2 (50 mL) and washed with 1 M NaOH (3 × 15 mL). Drying and solvent removal gave disulfone **10** (5.20 g, 87.9%) as a resin, which was pure enough for the next step. An analytical sample, secured by preparative TLC (solvent: $Me_2CO/n\text{-}C_6H_{14}$, 2:3), crystallized on trituration with a few drops of Et_2O to yield material with m.p. 160−162 °C. − IR: $\tilde{\nu}$ = 3549 (br), 1315, 1150, 1125, 1081, 755 cm^{-1}. − ^1H NMR: δ = 1.33 (s, 3 H), 1.73−1.87 (m, 1 H), 1.89−2.07 (m, 5 H), 2.54 (quintet-like, J = 10.8 Hz, 1 H), 2.94 (ddd, J = 15.1, 10.6, 8.5 Hz, 1 H), 3.07 (s, 3 H), 3.73−3.88 (m, 2 H), 4.63−4.66 (d, J = 10.8 Hz, 1 H), 7.53−7.69 (m, 3 H), 7.91−7.94 (m, 2 H). − ^{13}C NMR: δ = 22.56, 27.98, 30.26, 36.60, 39.74, 41.06, 42.54, 59.32, 82.34, 128.79, 128.88, 129.25, 129.45, 134.27, 139.00. − $C_{15}H_{22}O_5S_2$ (346.5): calcd. C 52.00, H 6.40; found C 51.76, H 6.38.

(1*R,2*R**)-2-{1-Methyl-2-[1-(methylsulfonyl)-1-(phenylsulfonyl)-ethyl]cyclobutyl}ethanol (11):** A solution of crude **10** (4.71 g, 13.6 mmol) in CH_2Cl_2 (25 mL) was treated sequentially with Et_3N (1.82 g, 18 mmol), 4-dimethylaminopyridine (0.165 g, 1.3 mmol) and *tert*-butyldimethylsilyl chloride (2.2 g, 14.6 mmol) whilst stirring in an ice bath. After standing at room temperature for 16 h, the reaction was quenched with saturated $NaHCO_3$ (15 mL), the organic layer decanted, washed with saturated NaCl (2 × 10 mL), dried and evaporated. Purification of the residue by flash chromatography (SiO_2; solvent: $Me_2CO/n\text{-}C_6H_{14}$, 1:9) gave the silyl ether (4.62 g, 81% based on used **10**) as a clear resin, which slowly set to a crystalline mass of m.p. 82−95 °C, along with 0.424 g of recovered **10**. The purified silyl ether (3.52 g, 7.64 mmol) was dissolved in benzene (30 mL) and vigorously stirred with 8 M NaOH (2.4 mL, 25 mmol), methyl iodide (3.76 g, 26.5 mmol) and benzyltriethylammonium chloride (0.1 g) for 7 days at room temperature. The organic layer was decanted, washed with saturated NaCl (2 × 10 mL), dried and evaporated to yield 3.58 g of a resin, which was redissolved in MeOH (30 mL) and stirred with Dowex 50x8 (0.1 g) for 16 h at room temperature. Filtration and solvent removal gave disulfone **11** (2.648 g, 96%) as an epimeric mixture which crystallized easily from CH_2Cl_2/Et_2O, m.p. 160−172 °C. − IR: $\tilde{\nu}$ = 3422 (br), 1318, 1302, 1148, 1072, 955 cm^{-1}. − ^1H NMR: δ = 1.38 (s, 3 H), 1.72 (s, 1 H), 1.82 (s, 3 H), 1.91−2.10 (m, 5 H), 2.28−2.38 (m, 2 H), 3.08−3.19 (dd, J = 11.6, 8.1 Hz, 1 H), 3.23 (s, 3 H), 3.61−3.67 (m, 1 H), 3.77−3.98 (m, 1 H), 7.50−7.55 (m, 2 H), 7.64−7.69 (m, 1 H), 7.89−7.92 (m, 2 H). − ^{13}C NMR: δ = 11.46, 22.18, 28.54, 30.87, 37.21, 38.32, 45.07, 59.87, 88.98, 128.24, 131.33, 134.36, 136.84. − $C_{16}H_{24}O_5S_2$ (360.5): calcd. C 53.31, H 6.71; found C 53.07, H 6.53.

(±)-*cis*-2-(2-Isopropenyl-1-methylcyclobutyl)ethanol (±-Grandisol, 1a): Disulfone **11** (1.282 g, 3.56 mmol) was dissolved in THF (12 mL) by gentle warming. The solution was then cooled in an ice bath and 1.57 M ethereal methyllithium/lithium bromide (7.2 mL, 11.3 mmol) was added whilst stirring. After the addition, the yellow solution was left standing in the bath for 1 h, and then quenched with saturated NaCl (10 mL), the organic layer diluted with 30 mL of petroleum ether and decanted. The aqueous phase was further extracted with petroleum ether (3 × 20 mL), the pooled extracts dried and concentrated by distillation through a short Vigreux column. Final distillation of the residue in a Hickmann still (125 °C/8 Torr, bath temperature) gave grandisol (**1a**) (0.3 g, 56.6%). The IR and ^1H NMR spectra were in agreement with those of an authentic sample: − IR: $\tilde{\nu}$ (film) = 3342 (br), 3080, 2949, 2867, 1646, 1454, 1376, 1054, 885 cm^{-1}. − ^1H NMR (90 MHz): δ = 1.20 (s, 3 H), 1.30−2.10 (m, 7 H), 1.70 (br. s, 3 H), 2.70 (unresolved t, 1 H, disappeared upon treatment with D_2O), 3.65 (t, J = 7.0 Hz), 4.70 (br. s, 1 H), 4.88 (br. s, 1 H).

Acknowledgments

Financial support by FAPDF to H. J. M. (grant no. 193171/95) and FAPESP to H. A. S. (grant no. 99/12182-7) is gratefully acknowledged.

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Received January 4, 2000
[O01005]