Pergamon

Tetrahedron, Vol. 52, No. 11, pp. 3879-3888, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00175-5

A NEW PRACTICAL SYNTHESIS OF (+)-GRANDISOL FROM (+)-CITRONELLOL USING AN INTRAMOLECULAR CARBENOID CYCLIZATION

Hugo J. Monteiro[†*] and Julio Zukerman-Schpector[‡]

[†]*Departamento de Química, Universidade de Brasília, 70910-900, Brasília, DF, Brasil*
[‡]*Departamento de Química, Universidade Federal de São Carlos, São Carlos, São Paulo, Brasil*

Abstract: A new practical 10 step synthesis of (1S,2R)-2-acetyl-1-methylcyclobutaneacetic acid **15** is reported, which has as a key step a rhodium catalyzed intramolecular carbenoid cyclization of the α-diazo-β-ketosulfone **5**, readily available from (+)-citronellol **2**. Since **15** has already been converted into (+)-grandisol **1**, the major pheromone of the cotton boll-weevil *Anthonomus grandis*, the described preparation constitutes a new formal synthesis of the optically active pheromone.

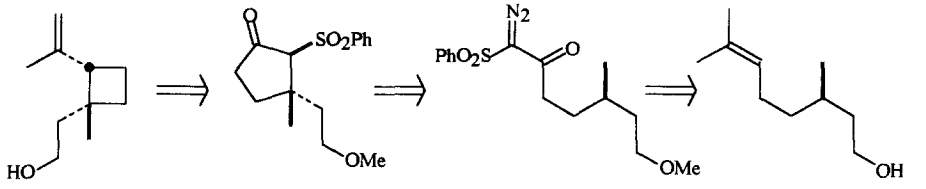
The cotton boll weevil (*Anthonomus grandis* Boheman) is a serious pest responsible for heavy damage to cotton crops in USA and Central America. In 1983 the pest was first detected in Brazilian cotton fields, and since then it has also become a major cause of losses to local cotton farmers. The male weevil produces an aggregation pheromone mixture whose principal component is the terpene (+)-*cis*-2-isopropenyl-1-methylcyclobutaneethanol (**1**), named (+)-grandisol.[1] Grandisol, as well as the corresponding aldehyde, grandisal, is also found in the pheromonal secretion of several other beetles.[2]

The terpene has been a popular target for the synthetic organic chemist, not only due to its commercial importance, but also because of its interesting cyclobutane structure. The potential use of (+)-grandisol in traps for monitoring crop infestation in integrated pest management control prompted us to search for an efficient preparation of the more active[3] (+)-enantiomer. Among the large number of preparations of **1** published to date many were devised to produce the pure (+)-enantiomer.[4] However, most of the preparations of enantiomerically pure grandisol require photochemical reactors to construct the cyclobutane ring, while others may additionally need tedious resolution, purification steps and/or use starting materials which are not easily accessible. A synthesis adequate for the production of (+)-grandisol in gram scale must obviously by-pass these limitations. Mori[4c] has recently disclosed a synthetic route to (+)-**1** which avoids sophisticated reactions and uses the readily available (+)-carvone as starting material, but purification steps and low overall yield still detract from its efficiency.

We now wish to describe a practical preparation of (+)-grandisol, which starts with the easily available[5] (+)-citronellol **2**, uses conventional chemistry to make the cyclobutane ring, and avoids complicated purification procedures, since most of the intermediates are solids readily purified by simple crystallizations. Although not described in detail, the same synthetic sequence and experimental conditions were also carried out with racemic citronellol, with identical results. The key step in our approach is

a rhodium acetate catalyzed intramolecular carbenoid cyclization[6] of the diazoketosulfone **A** to the 2-phenylsulfonyl-cyclopentanone **B**. The carbenoid C-H insertion at the C-5 carbon atom of **A** proceeds stereospecifically to create a quaternary center[7] which, after proper reorganization of the remaining atoms, will possess the same absolute stereochemistry as that found in (+)-grandisol (Scheme 1).

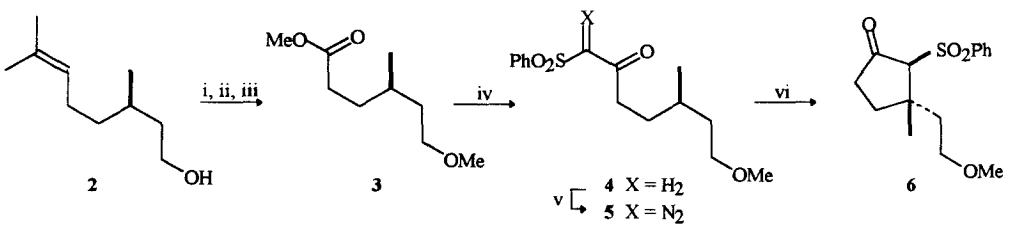
Scheme 1



1 **B (= 6)** **A (= 5)** **2**

Accordingly, R-(+)-citronellol **2** was successively submitted to etherification, oxidative cleavage of the double bond, and esterification of the resulting carboxylic acid to afford the ester **3** in 81% overall yield. Treatment of **3** with the phenylsulfonylmethyde anion, according to a slightly modified Stetter procedure,[8] gave a 92% yield of the β-ketosulfone **4** as a thick oil, homogeneous by tlc, spectroscopic, and analytical criteria. Next, the ketosulfone **4** was diazo-transferred to **5** under neutral conditions,[9] and the crude oily diazo derivative cyclized under rhodium acetate catalysis to the desired 2-phenylsulfonyl-cyclopentanone **6** (Scheme 2). β-Ketosulfones such as **4** and **6** are rather acidic substances,[10] and generally dissolve in dilute alkali from which they are easily recovered intact by acidification, provided the exposure to base is kept to a minimum.[11] This property was put to practical use in the isolation of **6**. Thus, simple extraction of the cyclization reaction mixture with dilute sodium hydroxide, and immediate treatment of the basic extracts with solid ammonium chloride precipitated the fairly pure cyclopentanone **6**. Further purification by crystallization gave the pure epimer at C-2 (60% yield from **4**), the stereochemistry of which, although completely irrelevant for our purposes, was confirmed by single crystal X-ray analysis[12] (Fig. 1).

Scheme 2



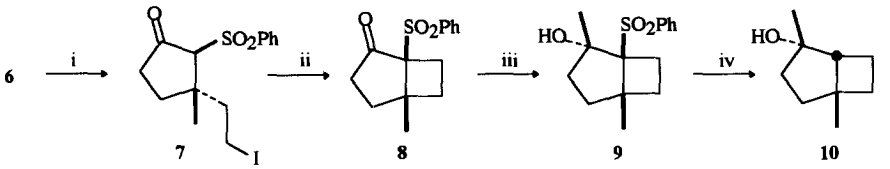
2 **3** **6**

Reagents and conditions: i. NaH, MeI, DME, reflux; ii. CrO_3, OsO_4, Me_2CO, rt; iii. MeOH, H^+, CH_2Cl_2, reflux; iv. $PhSO_2CH_2Na$, THF/DMSO, rt; v. 2-Chloro-1-ethylpyridinium fluoroborate, NaN_3, NaOAc, MeOH, rt; vi. $Rh_2(OAc)_4$, C_6H_6, 35-40°.

With the cyclopentanone **6** in hand the construction, using routine chemistry, of the cyclobutane ring of **1** could now be initiated. To this end, **6** was refluxed with sodium iodide/chlorotrimethylsilane[13] in acetonitrile to afford the iodide **7** (71% yield), which upon treatment with sodium hydride in THF at room temperature smoothly cyclized to the desired bicycloheptane derivative **8** with 94% yield . To build the *cis*-1-ethanol-2-isopropylidene side chains system of grandisol it was now necessary to

cleave the cyclopentanone ring of the bicycloheptane **8**. Accordingly, **8** was first treated with methyl Grignard, whereupon a single alcohol **9**, resulting from attack of the nucleophile at the less hindered *exo*-face of **8**, could be isolated (94% yield). At this stage it was desirable to confirm the structure of the alcohol **9**. This was readily accomplished by its treatment with sodium amalgam in methanol, when quantitative desulfonylation[14] took place to yield the known (-)-alcohol **10**, previously prepared by Rosini[15] (Scheme 3).

Scheme 3



Reagents and conditions: i. NaI, Me_3SiCl, MeCN, reflux; ii. NaH, THF, rt; iii. MeMgI, THF/Et_2O, rt; iv. Na/Hg, MeOH, rt.

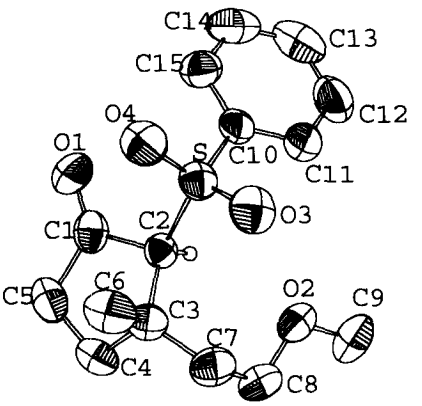
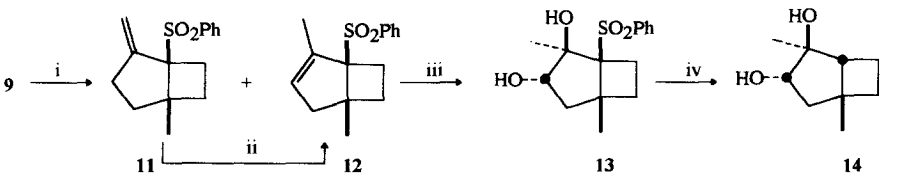


Fig. 1 X-ray structure of **6**

The next step required dehydration of **9** to the alkene **12**. Despite its tertiary nature, the alcohol **9** proved to be fairly resistant to dehydration under acid catalysis, presumably due to the presence of the vicinal electron withdrawing phenylsulfonyl group which hinders the formation of the incipient tertiary carbocation required for dehydration. Smooth elimination of water was, however, achieved by its reaction with thionyl chloride/pyridine at room temperature, when a 99% yield of a mixture of the olefins **11** and **12** was secured (approximately 1:1.4 ratio, by nmr analysis). The crystalline isomeric alkenes could only be separated by a very careful column chromatography, but this difficulty was avoided by equilibrating the mixture with potassium *tert*-butoxide in DMSO at room temperature. Under these conditions the exocyclic alkene **11** was completely converted into its endocyclic and more stable[16] isomer **12**, which could be secured as a pure material in 96% yield. Construction of the *cis*-side chains of **1** could now be completed. Our strategy required a dihydroxylation of the double bond of **12**, followed by removal of the phenylsulfonyl group and cleavage of the glycol moiety, in order to ensure the thermodynamically less stable *cis*-arrangement of

the side chains present in **1**. Thus, dihydroxylations of the double bond of **12** with osmium tetroxide or potassium permanganate were attempted, but the reactions were, as expected from these sterically demanding reagents and the hindered nature of the substrate, very sluggish and preparatively useless. However, smooth *trans*-dihydroxylation could be achieved by reaction with hot, *in situ* generated, performic acid, followed by treatment with methanolic alkali, when the diol **13** was the major product formed. Separation of **13** from minor non-identified products was easily accomplished by simple crystallization, to give the pure material in 73% yield. An X-ray analysis[12] performed on a single crystal of **13**, secured in the *racemic* series, firmLy established its stereochemistry (Fig. 2). Its preferential formation can be rationalized as resulting from an initial epoxidation of the alkene **12** at its *exo*-face, followed by nucleophilic opening of the epoxide ring at its least hindered site. Desulfonylation[14] of **13** then gave the desired diol **14** in 66% yield (Scheme 4).

Scheme 4



Reagents and conditions: i. $SOCl_2$, C_5H_5N, CH_2Cl_2, rt; ii. $KOCMe_3$, DMSO, rt; iii. 30% H_2O_2, HCO_2H, 100°, then NaOH, MeOH, rt; iv. Na/Hg, MeOH, rt.

The synthetic route was completed with the cleavage of the diol **14** with ruthenium chloride/sodium periodate to produce the *cis*-2-acetyl-1-methylcyclobutaneacetic acid **15** (83% yield), slightly contaminated with the *trans* isomer, presumably produced during work up. Since the conversion in two steps of the acid **15** to (+)-grandisol **1** has already been reported,[18a,b] its preparation as described here constitutes a new practical formal synthesis of the enantiomerically pure pheromone (Scheme 5).

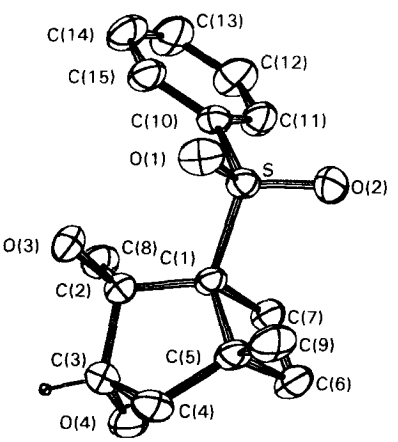
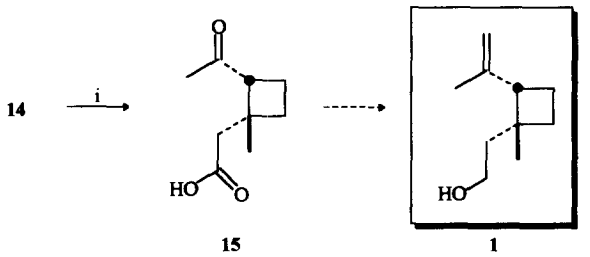


Fig. 2 X-ray structure of **13**

Scheme 5



Reagents and conditions: i. $NaIO_4$, $RuCl_3$, H_2O, rt.

In conclusion, we have demonstrated the usefulness of an α-diazo-β-ketosulfone as synthetic intermediate in the enantioselective construction of a quaternary center, such as that in (+)-grandisol. The chemically versatile sulfone group is easily introduced and removed, and confers a high degree of crystallinity to most of the compounds in which it is present, thus simplifying purification procedures.

Experimental

All air and moisture sensitive reactions were run under argon atmosphere. All solvents were distilled before use. Dry THF, Et_2O and DME were distilled from Na-benzophenone ketyl. Dry DMSO was distilled from CaH_2. Extracts were dried over anhydrous sodium sulfate. (+)-Citronellol ($[\alpha]_D$ +5.3, neat) was obtained as described in the literature.[5] Melting points are uncorrected. Infrared spectra were measured on a Nicolet ZDX-5 FT instrument; comparison spectra were made with the *racemic series* as chloroform solution. Microanalyses were made by Analytische Laboratorien H. Malissa and G. Reuter GmbH, Germany. ^{1}H-Nmr spectra were measured on a Varian EM-390 (90 MHz), and ^{13}C-nmr on Varian FT-80 (20 MHz) or Varian Gemini (75 MHz) instruments, using deuterochloroform as solvent and Me_4Si as internal standard. Mass spectra were taken on an Extrel-U1272 instrument (EI, 70 eV). Optical rotations were measured on a Zeiss LEP A1 photoelectric polarimeter.

(4R)-Methyl 6-methoxy-4-methyl-hexanoate (3):

A three necked flask provided with mechanical stirrer, dropping funnel, and condenser was charged with 4.8 g (0.12 mol) of 60% oil dispersed sodium hydride suspended in 80 mL of dry DME. (+)-Citronellol **2** (15.6 g, 0.10 mol) was then carefully added. After the hydrogen evolution subsided 17.2 g (0.12 mol) of iodomethane was slowly added. When the addition was complete the reaction mixture was heated under reflux for 2 h, followed by removal of most of the DME through a small Vigreux. The pasty residue was cooled in a water bath and water carefully added to just dissolve the sodium iodide. The oily material was decanted, the aqueous phase extracted with petroleum ether (2 x 25 mL), the extracts combined with the decanted oil and distilled to give 16.1 g (95%) of citronellylmethyl ether,[19] bp 101-102°C/25torr. For the oxidative cleavage of the double bond the procedure described by Weinreb[20] was used. Thus, to a cooled and well stirred solution of 15.6 g (0.092 mol) of the methyl ether in 300 mL of Me_2CO, 0.16 g (0.63 mmol) of osmium tetroxide was added. The solution was then treated with 88 mL of Jone's reagent, added in small amounts during a period of 72 h. The reaction was quenched with 5 g of $NaHSO_3$ and stirred overnight. The solids were filtered, washed with 5 x 20 mL of Me_2CO, and the solvent distilled (Vigreux). The oily residue was carefully treated with 35 mL of 2.5M NaOH and any insoluble material extracted with Et_2O. The basic solution was cautiously acidified with 20 mL of 6M HCl and the crude carboxylic acid extracted with Et_2O (3 x 30 mL). The ether was removed by distillation (Vigreux) and the remaining crude

oily acid (about 12.6 g) immediately esterified by refluxing in 100 mL of CH_2Cl_2 containing 12 g of methanol and 1 mL of concentrated H_2SO_4. Usual work up gave 13.7 g (86%) of the methyl ester **3**, bp 109-111°C/25torr; $[\alpha]_D$ +5.3, neat; $ir^{film}(cm^{-1})$: 1740; ^{1}H-nmr(δ): 0.90(3H,d,J=5), 1.20-1.80(5H,m), 2.32(2H,t,J=7.5), 3.29(3H,s), 3.38(2H,t,J=6.5), 3.64(3H,s); ^{13}C-nmr(δ): 19.2, 29.5, 31.8, 31.9, 36.4, 51.5, 58.6, 70.8, 174.4; ms(*m/z*): 159(6), 143(12), 142(22), 127(18), 110(28), 98(34), 87(26), 74(23), 69(31), 59(35), 55(80), 45(100).

$C_9H_{18}O_3$: MW 174.24; calcd.: C 62.04, H 10.41; found: C 62.16, H 10.53.

Starting from *racemic* citronellol a comparable yield of the *racemic* ester was obtained, spectrally identical with the optically active product.

(5R)-7-Methoxy-5-methyl-1-(phenylsulfonyl)-2-heptanone (4):

A variation of the procedure described by Stetter[8] was used. A solution of sodium dimsyl was prepared by dissolving 5.0 g (0.125 mol) of hexane-washed 60% oil dispersed sodium hydride in 35 mL of dry dimethylsulfoxide at 65°C. The solution was cooled, diluted with 40 mL of dry THF, and 19.5 g (0.125 mol) of phenylmethylsulfone added. After stirring for 5 min, the mixture was cooled in an ice bath and 10.8 g (0.062 mol) of the ester **3** in 10 mL of THF added dropwise. After addition the thick reaction mixture was left stirring at rt for 0.5 h, again iced, and treated sucessively with 30 mL of saturated NH_4Cl solution, 20 mL of 6M HCl, and 50 mL of Et_2O. The organic layer was decanted and the aqueous phase further extracted with Et_2O (2 x 40 mL). The combined extracts were evaporated *in vacuo* to give a thick oil which was redissolved into 100 mL of Et_2O. The ethereal solution was then extracted with iced 1M NaOH (3 x 25 mL), and the organic phase saved for recovery of unreacted phenylmethylsulfone. The basic aqueous extracts were immediately treated with 15 g of solid NH_4Cl and the resulting oily precipitate extracted with Et_2O (3 x 30 mL). The extracts were washed with 30 mL of saturated aqueous sodium chloride, dried, and evaporated *in vacuo* to afford 18.9 g (theoretical: 18.49 g) of crude ketosulfone **4**. Nmr analysis of the material showed it to be contaminated with about 10% of phenylmethylsulfone. The product was used as such in the next step. An analytical sample was secured as an oil by preparative tlc and multiple elution with 95:5 hexane:acetone; $[\alpha]_D$ +3.2 (c 17.47, MeOH); $ir^{film}(cm^{-1})$: 1721, 1449, 1320, 1154, 1113; ^{1}H-nmr(δ): 0.81(3H,d,J=5), 1.15-1.80(5H,m), 2.62(2H,t,J=7.5), 3.27(3H,s), 3.33(2H,t,J=6.5), 4.20(2H,s), 7.40-8.00(5H,m); ^{13}C-nmr(δ): 19.9, 29.2, 29.9, 36.2, 42.1, 58.5, 66.7, 70.6, 128.2, 129.3, 134.2, 138.7, 198.3; ms(*m/z*): 157(17), 156(17), 141(29), 125(64), 107(26), 98(24), 97(27), 83(41), 77(100), 69(61), 55(70), 45(91).

$C_{15}H_{22}O_4S$: MW 298.41; calcd.: C 60.37, H 7.43; found: C 60.46, H 7.51.

The *racemic* form, secured in comparable yield, showed identical spectroscopic data.

(2S,3S)-3-(2-Methoxyethyl)-3-methyl-2-(phenylsulfonyl)cyclopentanone (6):

A solution of 1-ethyl-2-azido-pyridinium fluoroborate was prepared *in situ* by mixing 15.3 g (0.068 mol) of 1-ethyl-2-chloro-pyridinium fluoroborate with 4.34 g (0.068 mol) of sodium azide in 50 mL of cold methanol. After stirring for 10 min 17 g (0.051 mol) of 90% **4** was added, followed by 9.0 g (0.068 mol) of sodium acetate. The mixture was stirred at rt with tlc monitoring (elution solvent n-hexane:acetone 8:2) until disappearance of the starting material (about 2 h). The MeOH was evaporated *in vacuo* at 30-35 °C, and the residue partitioned between 50 mL of Et_2O and 25 mL of saturated aqueous sodium chloride. The ethereal solution was successively washed with 15 mL of water, 15 mL of saturated aqueous sodium chloride, and dried. Evaporation in a rotary evaporator at rt and final drying in high vacuum gave the crude α-diazo-β-ketosulfone **5** as a yellow oil, contaminated with 10-15% of phenylmethylsulfone and minor colored impurities; $ir^{film}(cm^{-1})$: 2109, 1670, 1340, 1156. The crude diazo compound was dissolved into 100 mL of dry benzene (*carcinogen!*) and added dropwise during 3 h to a stirred suspension of 0.23 g (0.51 mmol) of rhodium acetate in 300 mL of benzene at 35-45°C. The mixture was left stirring at rt until complete reaction (tlc monitoring). The dirty green solution was then carefully stirred with 20 mL of 3M HCl to remove

most of the rhodium salts, the organic phase decanted, and the solvent removed in a rotary evaporator. The residue was redissolved into 150 mL of Et_2O and any insoluble material filtered. The cyclopentanone **6** was then isolated by extraction of the ethereal solution with 3 x 25 mL of iced 1M NaOH and processing the basic extracts as described above for **4**. Crystallization from Et_2O (freezer) gave 9.1 g (60%) of the pure product; mp 74-75°C; $[\alpha]_D$ +58.4 (c 0.941, Me_2CO); $ir^{KBr}(cm^{-1})$: 1747, 1450, 1313, 1150, 1110; ^{1}H-nmr(δ): 1.53(3H,s), 1.80-2.60(6H,m), 3.32(3H,s), 3.58(2H,t,J=6.5), 4.04(1H,s), 7.40-8.10(5H,m); ^{13}C-nmr(δ): 22.3, 33.5, 36.1, 40.0, 44.6, 58.6, 69.3, 77.27, 128.8, 128.9, 133.6, 207.3; ms(*m/z*): 296(1), 237(72), 159(16), 155(15), 149(13), 141(16), 122(32), 97(100), 81(41), 77(40), 69(54), 67(39), 55(33), 45(65).

$C_{15}H_{20}O_4S$: MW 296.40; calcd.: C 60.78, H 6.80; found: C 60.54, H 6.76.

X-Ray analysis,[12] see Fig.1.

The *racemic* form, mp 64-65°C , secured in comparable yield, showed identical spectroscopic data.

(2S,3S)-3-(2-Iodoethyl)-3-methyl-2-(phenylsulfonyl)cyclopentanone (7):

The cyclopentanone **6** (7.47 g, 0.025 mol) was heated with 15 g (0.1 mol) of oven-dried sodium iodide and 11 g (0.1 mol) of chlorotrimethylsilane in 75 mL of dry acetonitrile under reflux, with stirring and moisture exclusion. After 20 h the reaction was practically complete. The solvent was removed *in vacuo*, and the residue partitioned between 35 mL of water and 70 mL of CH_2Cl_2. The organic phase was decanted, washed with 25 mL of saturated aqueous sodium chloride containing some $NaHSO_3$, dried, and evaporated in the rotary evaporator to give 9.5 g of the crude iodide. Trituration of the brownish resin with some Et_2O and standing in the freezer gave 5.4 g of practically pure **7**. An additional 1.6 g of product could be secured from the mother liquors by flash chromatography and fractional crystallization, giving **7** in a total yield of 71%; mp 109-110°C; $[\alpha]_D$ +108.6, falls to +89.7 after *ca.* 45 min by mutarotation, (c 0.741, Me_2CO); $ir^{KBr}(cm^{-1})$: 1754, 1448, 1300, 1143; ^{1}H-nmr(δ): 1.40(3H,s), 1.50-2.70(6H,m), 3.00-3.30(2H,m), 3.45(1H,s), 7.35-8.00(5H,m); ^{13}C-nmr(δ): -2.4, 20.4, 33.4, 46.7, 47.2, 77.4, 128.9, 129.0, 133.9, 140.1, 206.3; ms(*m/z*): 265(53), 237(100), 159(30), 141(46), 123(71), 95(50), 81(52), 77(93), 69(60), 67(74), 55(50), 41(60).

$C_{14}H_{17}IO_3S$: MW 392.25; calcd.: C 42.86, H 4.36; found: C 42.64, H 4.29.

The racemic form, mp 95-97°C, secured in comparable yield, showed identical spectroscopic data.

(1S,5S)-5-Methyl-1-(phenylsulfonyl)bicyclo[3.2.0]heptan-2-one (8):

A solution of 7.1 g (0.018 mol) of the iodide **7** in 80 mL of dry THF was cooled in an ice bath and 0.8 g (0.02 mol) of 60% oil-dispersed sodium hydride carefully added with stirring (foam!). After addition the bath was removed and the mixture stirred at rt for 16 h. The reaction was quenched with 0.5 mL of glacial acetic acid, the solvent removed *in vacuo*, and the residue partitioned between 50 mL of CH_2Cl_2 and 30 mL of saturated aqueous sodium chloride containing some $NaHSO_3$. Usual workup of the organic phase and crystallization from CH_2Cl_2-hexane gave 4.5 g of pure **8** (94%); mp 183-184°C; $[\alpha]_D$ -70.4 (c 0.944, Me_2CO); $ir^{KBr}(cm^{-1})$: 1741, 1446, 1298, 1262, 1142, 1074; ^{1}H-nmr(δ): 1.75(3H,s), 1.40-2.35(5H,m), 2.40-3.00(3H,m), 7.40-8.00 (5H,m); ^{13}C-nmr(δ): 22.9, 24.2, 28.9, 34.4, 38.0, 51.7, 71.9, 128.6, 129.4, 133.8, 138.8, 211.8; ms(*m/z*): 264(4), 123(100), 95(26), 77(25), 67(25), 55(15).

$C_{14}H_{16}O_3S$: MW 264.35; calcd.: C 63.60, H 6.10; found: C 63.52, H 6.05.

The *racemic* form, mp 144-145°C, secured in comparable yield, showed identical spectroscopic properties.

(1S,2S,5S)-2,5-Dimethyl-1-(phenylsulfonyl)bicyclo[3.2.0]heptan-2-ol (9):

The ketone **8** (4.5 g, 0.015 mol) in 70 mL of dry THF was added to an iced and stirred solution of 4.75 g (0.029 mol) of methylmagnesium iodide in 120 mL of Et_2O. After 0.5 h the reaction was carefully quenched with 20 mL of H_2O, followed by 20

mL of 2M HCl and 20 mL of saturated aqueous sodium chloride containing some $NaHSO_3$. Usual workup of the organic phase gave a crystalline product still contaminated with some starting ketone. Fractional crystallization from benzene-hexane gave 3.4 g of pure **9**. From the mother liquors an additional 0.7 gm of **9** and 0.4 g of **8** could be recovered by consecutive fractional crystallization from MeOH and benzene-hexane (94%, based on consumed ketone); mp 107-108°C; $[\alpha]_D$ +21.5 (c 1.00, Me_2CO); $ir^{KBr}(cm^{-1})$: 3495, 1288, 1187, 1140; ^1H-nmr(δ): 1.43(3H,s), 1.52(3H,s), 1.50-2.50(9H,m), 7.40-8.10(5H,m); ^{13}C-nmr(δ): 21.9, 25.1, 26.8, 30.4, 38.3, 39.5, 50.1, 80.6, 129.0, 129.3, 133.6, 139.9; ms(*m/z*): 280(3), 262(10), 237(23), 211(13), 143(20), 138(26), 137(24), 121(100), 105(52), 95(37), 93(52), 77(39), 43(97).

$C_{15}H_{20}O_3S$: MW 280.40; calcd.: C 64.25, H 7.19; found: C 64.47, H 7.22.

The *racemic* form, mp 149-150°C, secured in comparable yield, showed identical spectroscopic data.

(1R,2S,5R)-2,5-Dimethyl-bicyclo[3.2.0]heptan-2-ol (10):

A solution of 0.280 g (1 mmol) of the alcohol **9** in 10 mL of methanol was stirred with 1.50 g (3.9 mmol) of 6% sodium amalgam, added in small portions with eventual cooling and monitoring by tlc. After disappearance of the starting material the solution was decanted and the residual mercury washed with 5 mL of methanol. The methanol was then removed with help of a small Vigreux, the residue dissolved into 1 mL of water and saturated with sodium sulfate. Extraction with Et_2O (6 x 5 mL) and usual workup of the ethereal extracts gave 0.140 g of crude **10** (100%). Sublimation yielded the pure product, mp 76-78°C (closed capillary); $[\alpha]_D$ -25.6 (c 1.622 MeOH). Direct comparison with an authentic sample[15] confirmed its identity.

The *racemic* form, mp 56-57°C (literature:[18c] mp 56-57°C), secured in comparable yield, showed identical spectroscopic data.

(1S,5R)-2,5-Dimethyl-bicyclo[3.2.0]hept-2-ene (12):

A cold solution of 7.04 g (0.025 mol) of **9** in 60 mL of CH_2Cl_2 was successively treated with 2.65 g (0.033 mol) of pyridine and 3.93 g (0.033 mol) of thionyl chloride. After standing at rt for 1.5 h the reaction was washed (2 x 15 mL) with H_2O and saturated $NaHCO_3$ (15 mL). Usual workup gave 6.52 g (99%) of a crystalline mixture of the alkenes **11** and **12** (1:1.4 ratio, by nmr). The crude product (6.44 g , 0.024 mol) was dissolved into 45 mL of dry DMSO with gentle heating, the solution cooled to rt, and 0.47 g (4.2 mmol) of freshly sublimed potassium *tert*-butoxide added. After 48 h at rt the dark brown reaction mixture was diluted with 120 mL of H_2O and extracted with Et_2O (6 x 25 mL). Usual proccessing of the extracts gave 6.20 g (96%) of pure **12**; mp 129-131°C; $[\alpha]_D$ -132.4 (c 2.862 MeOH); $ir^{KBr}(cm^{-1})$: 1446, 1283, 1139, 1075; ^1H-nmr(δ): 1.46(3H,s), 1.74(3H,br.s), 1.60-2.30(5H,m), 2.80-3.28(1H,m), 5.61(1H,br.s), 7.40-8.00(5H,m); ^{13}C-nmr (δ): 14.0, 21.5, 24.5, 31.4, 45.1, 51.3, 128.6, 133.2, 133.6, 136.9, 139.1; ms(*m/z*): 121(100), 105(21), 93(34), 91(33), 79(19), 77(28).

$C_{15}H_{18}O_2S$: MW 262.36; calcd.: C 68.66, H 6.91; found: C 68.79, H 7.05.

The *racemic* form, mp 107-108°C, secured in comparable yield, showed identical spectroscopic data.

(1S,2R,3S,5R)-2,5-Dimethyl-1-(phenylsulfonyl)bicyclo[3.2.0]heptan-2,3-diol (13):

The alkene **12** (6.14 g, 0.023 mol) was dissolved into 55 mL of 90% formic acid, and the solution treated with 6.8 mL (0.08 mol) of 30% hydrogen peroxide. After standing at rt for 24 h the reaction was treated with water (10 mL) and the mixture heated for 1 h in the steam bath. The volatiles were then removed *in vacuo*, the residue redissolved into 25 mL of methanol, and adjusted to pH 8 with 2M NaOH. After 0.5 h the solvent was evaporated and the crystalline product secured further purified by recrystallization from CH_2Cl_2-Et_2O to give 5.06 g (73%) of pure **13**; mp 158-159°C; $[\alpha]_D$ +15.3 (c 2.619 MeOH); $ir^{KBr}(cm^{-1})$: 3522, 3430, 1448, 1285, 1130, 1077; ^1H-nmr(δ): 0.62(3H,s), 1.62(3H,s), 1.60-2.85(7H,m), 3.57(1H,d,J=6), 3.80-4.80(1H, very br.s, exchanges with D_2O), 7.40-8.10(5H,m); ^{13}C-nmr(δ): 17.2, 21.7, 26.2, 29.9, 47.3, 52.8, 76.6, 83.2, 83.9, 128.8, 129.4, 133.7, 140.0; ms(*m/z*): 296(2), 235(7), 211(10), 154(52), 143(30), 137(47), 126(25), 125(53) 109(25), 95(22),

93(23), 77(27), 69(26), 55(22), 43(100).

$C_{15}H_{20}O_4S$: MW 296.4; calcd.: C 60.78, H 6.80; found: C 60.86, H 6.93.

The *racemic* form, mp 175-176°C, secured in comparable yield, showed identical spectroscopic data.

X-Ray analysis,[12] see Fig.2.

(1S,2R,3S,5R)-2,5-Dimethyl-bicyclo[3.2.0]heptan-2,3-diol (14):

A stirred solution of 1.0 g (3.38 mmol) of **13** in 20 mL of methanol was treated with 4.6 g (12 mmol) of 6% sodium amalgam added in small portions with eventual cooling. After the reaction was complete (tlc) the methanol was removed in a rotary evaporator and the residue dissolved into 2 mL of water. The solution was saturated with Na_2SO_4 and extracted with Et_2O (5 x 10 mL). Usual processing of the extracts gave a resin which crystallized on standing. Recrystallization from benzene-hexane yielded 0.35 g (66%) of pure **14**; mp 79-80°C; $[\alpha]_D$ +12.9 (c 3.415 MeOH); ir^{KBr} (cm^{-1}): 3353, 1122, 1027; ^{1}H-nmr(δ): 1.22(3H,s), 1.32(3H,s), 1.60-2.20(7H,m), 2.44(2H,s, exchanges with D_2O), 4.00(1H,br.d,J=6); ^{13}C-nmr(δ): 16.5, 19.0, 29.0, 31.4, 44.7, 47.9, 55.4, 84.3, 84.5; ms(*m/z*): 138(16), 97(30), 95(36), 81(58), 69(100), 57(54), 55(69), 43(92), 42(88).

$C_9H_{16}O_2$: MW 156.23; calcd.: C 69.19, H 10.32; found: C 69.02, H 10.46.

The *racemic* form, mp 68-69°C, secured in comparable yield, showed identical spectroscopic data.

(1S,2R)-2-Acetyl-1-methylcyclobutaneacetic acid (15):

Sodium periodate (2.393 g, 11.2 mmol) was added to a solution of 0.580 g (3.7 mmol) of the diol **14** and 0.004 g of ruthenium trichloride in 20 mL of water. Monitoring by tlc showed complete reaction after 5 h at rt. The solution was then adjusted to pH 3 with 2M sulfuric acid and extracted with dichloromethane (5 x 10 mL). The extracts were dried, the solvent removed in a rotary evaporator, and the remaining dark residue distilled at 120°C(bath)/0.5torr in a Hickman still to give 0.523 g (83% yield) of **15** slightly impurified by the *trans* isomer (small peak for the quaternary methyl at 1.13ppm in the nmr spectrum). Spectral data in agreement with the literature;[18] $[\alpha]_D$ -41.0 (c 8.446 EtOAc).

The *racemic* form, secured in comparable yield, gave a tosylhydrazone, mp 191-192°C (literature:[18c] mp 192-193°C) and showed identical spectroscopic data.

Acknowledgement

We thank the Conselho Nacional de Pesquisas (Proc. 300003/89-7) and FAPESP (Proc. 94/1213-5) for financial spport.

References and Notes

1. TumLinson, J. H., Gueldner, R. C., Hardee, D. D., Thompson, A. C., Hedin, P. A., and Minyard, J. P. *J. Org. Chem.*, **1971**, *36*, 2616.
2. Franke, W., Bartels, J., Krohn, S., Schultz, S., Baader, E., Tengo, J., and Schneider, D. *Pure & Appl. Chem.*, **1989**, *61*, 539.
3. Dickens, J. C. and Mori, K. *J. Chem. Ecol.*, **1989**, *15*, 517.
4. a) Martin, T., Rodriguez, C. M., and Martin, V. S. *Tetrahedron: Asymmetry*, **1995**, *6*, 1151; b) Alibés, R., Bourdelande, J. L., and Font, J. *Tetrahedron Lett.*, **1993**, *34*, 7455; c) Mori, K. and Fukumatsu, K.

Liebigs Ann. Chem., **1992**, 489; d) Narasaka, K., Kusama, H., and Hayashi, Y. *Bull. Chem. Soc. Jpn.*, **1991**, *64*, 1471; for references to earlier enantioselective grandisol syntheses, see Hoffmann, N. and Scharf, H. -D. *Liebigs Ann. Chem.*, **1991**, 1273.

5. Enantiomerically pure (+)-citronellol is readily secured from (+)-pulegone, see Overberger, C. G. and Kaye, H. J. *J. Am. Chem. Soc.*, **1968**, *89*, 5640; or by enzymatic resolution, see Cambou, B. and Klibanov, A. M. *J. Am. Chem. Soc.*, **1984**, *106*, 2687; for other methods and use in natural products synthesis, see Ho, T. -L. *Enantioselective Synthesis. Natural Products from Chiral Terpenes*, **1992**, John Wiley & Sons, New York.
6. Monteiro, H. J. *Tetrahedron Lett.*, **1987**, *28*, 3459.
7. For an elegant example of construction of a quaternary center with retention of configuration by means of an intramolecular carbenoid cyclization see Taber, D. F., Petty, E. H., and Raman, K. *J. Am. Chem. Soc.*, **1985**, *107*, 196.
8. Stetter, H. and Hesse, R. *Monatsh. Chem.*, **1967**, *98*, 755.
9. Monteiro, H. J. *Synth. Commun.*, **1987**, *17*, 983.
10. Truce, W. E., Bannister, W. W., and Knospe, R. H. *J. Org. Chem.*, **1962**, *27*, 2821.
11. Monteiro, H. J. *Synlett*, **1992**, 990.
12. A full crystallographic report on **6** and **13** has been submitted to *Acta Crystallographica, Section C*.
13. Olah, G. A., Narang, S. C., Gupta, B. G. B., and Malhotra, R. *J. Org. Chem.*, **1979**, *44*, 1247.
14. Trost, B. M., Arndt, H. C., Strege, P. E., and Verhoeven, T. R. *Tetrahedron Lett.*, **1976**, 3477.
15. a) Rosini, G., Marotta, E., Raimondi, A., and Righi, P. *Tetrahedron: Asymmetry*, **1991**, *2*, 123; b) Rosini, G., Carloni, P., Iapalucci, M. C., and Marotta, E. *Tetrahedron: Asymmetry*, **1990**, *1*, 751. The melting point of the enantiomerically pure alcohol **10** has erroneously been reported as 56-57°C in these publications; the correct melting point is 75-77°C (personal communication from Prof. Rosini, to whom the authors are indebted for a generous sample of the product).
16. Calculations using PM3 implemented in the AMPAC/MOPAC program package, version 6.0[17] suggest that **12** is about 13.5 kJ mol^{-1} more stable than **11**. We thank Prof. Elaine R. Maia for performing the calculations.
17. Stewart, J. J. P. *J. Comput. Chem.*, **1989**, *10*, 201.
18. Pure enantiomer : a) Mori, K. *Tetrahedron*, **1978**, *34*, 915; b) Webster, F. X. and Silverstein, R. M. *J. Org. Chem.*, **1986**, *51*, 5226; for the racemic form, see: c) Rosini, G., Marotta, E., Petrini, M., and Ballini, R. *Tetrahedron*, **1985**, *41*, 4633; d) Confalonieri, G., Marotta, E., Rama, F., Righi, P., Rosini, G., Serra, R., and Venturelli, F. *Tetrahedron*, 1994, *50*, 3235.
19. Phadnis, A. P., Nanda, B., Patwardhan, S., Powar, P., and Sharma, R. N. *Indian J. of Chem., Section B*, **1988**, *27B*, 867.
20. Henry, J. R. and Weinreb, S. M. *J. Org. Chem.*, **1993**, *58*, 4745.

(*Received in USA* 20 *December* 1995; *accepted* 5 *February* 1996)