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SYNTHESIS OF THE BOTH ENANTIOMERS OF GRANDISOL, THE BOLL WEEVIL PHEROMONE†

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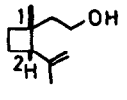
Abstract—Optically active forms of grandisol (2-isopropenyl-1-methylcyclobutane ethanol, **1** and **1'**) were synthesized from optically active 5-carboxybicyclo[3.2.0]heptan-2-one (**2** and its antipode), obtained by resolving the racemate. The optical purities of the synthetic products were determined by the NMR studies using a chiral shift reagent and shown to be 80%. The $[\alpha]_D$ values of our synthetic grandisols were ±20° (after correction) in accord with Magnus's synthetic (+)-grandisol (+18.5° after correction) and differed from that reported for the natural pheromone (+50 ± 10°).

(+)-Grandisol **1** is one of the four pheromones isolated from male boll weevils, *Anthonomus grandis* Boheman.[1,2] This cyclobutane compound attracted attention of many synthetic chemists and a number of syntheses were reported. The syntheses have been reviewed recently.[3] Among a dozen syntheses, there is only one of optically active grandisol: Hobbs and Magnus converted (−)-β-pinene of 90% optical purity into (+)-grandisol of 90% optical purity, establishing the (1*R*:2*S*)-absolute stereochemistry of the natural and levorotatory grandisol **1**.[4,5] However, the $[\alpha]_D$ value of Magnus's (+)-grandisol was reported to be +18.5°, while that of the natural pheromone was reported to be +50 ± 10°.[1,2] We undertook the synthesis of optically active grandisol to settle this discrepancy also bearing in mind the exploration of a new synthetic route suitable for the preparation of *the both enantiomers* of grandisol required for biological study.



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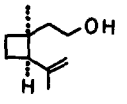
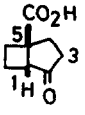


1'



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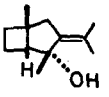

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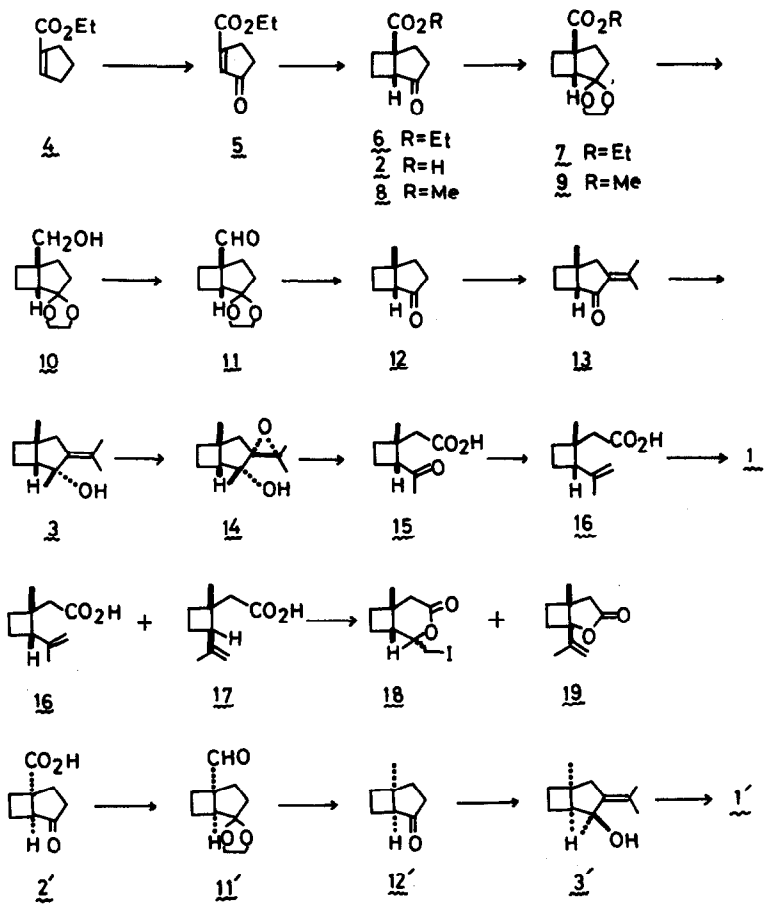
Our strategy was to employ a bicyclic carboxylic acid **2** as the resolvable key intermediate and convert the optically active **2** into an alcohol **3** with Me groups close to the asymmetric C atom bearing an OH group. The optical purity of **3** should be correctly measurable by means of NMR spectroscopy with the aid of a chiral shift reagent. This would enable us to know the correct $[\alpha]_D$ value of our final product, grandisol **1**. The execution of this plan is detailed below.

†Pheromone Synthesis—XVI. Part XV, K. Mori, *Agric. Biol. Chem.* **40**, 2499 (1976).

The photocycloaddition of ethylene to a keto ester **5** seemed to be the most feasible way leading to the key intermediate **2**. Therefore ethyl cyclopent-1-ene-1-carboxylate **4**[6] was chosen as our starting material. This was oxidized with t-butyl chromate[7] to give the required enone ester **5**. Irradiation of its benzene soln with a high-pressure mercury lamp with a continuous flow of ethylene gave the addition product **6** in 50–60% yield after distillation. Alkaline hydrolysis of this ester gave intractable material resulting from aldol condensation at the cyclopentanone portion of the molecule. To avoid this difficulty the ketone **6** was converted to an acetal **7** by acetal exchange with butanone ethylene acetal. Basic hydrolysis (NaOH) followed by acid treatment (HCl) of **7** gave a crystalline keto acid **2**. Optical resolution of this acid was not so easy as we initially thought to be. Crystalline salts of the acid **2** was obtained by treatment with EtOH soln of quinine, cinchonine and brucine, respectively. The separation of diastereomers, however, was rather difficult. After several recrystallizations the salts were decomposed by dissolving in dil. HCl and the partially resolved acid was recovered in ether. The quinine salt gave (−)-acid, while the cinchonine and brucine salts afforded (+)-acid. These partially resolved acids were recrystallized several times to remove less soluble racemic acid. The final mother liquors gave levorotatory ($[\alpha]_D^{20}$ − 136°) and dextrorotatory ($[\alpha]_D^{22}$ + 116°) acids, respectively, as low mleting solids (m.p. 20–23°). The absolute configuration of the (−)-acid was shown to be (1*R*:5*S*)-**2** by its later correlation with (1*R*:2*S*)-(+)-grandisol (*vide infra*). The optically active acids were esterified with CH_2N_2 to give the corresponding Me esters, **8** and its antipode **8'**. These were acetalized to **9** and **9'**, respectively, by treatment with butanone ethylene acetal.

The transformation of this acetal ester **9** to grandisol **1** was first tried with the racemate to optimize the reaction conditions. The acetal ester (±)-**7** was reduced with LAH to give a hydroxy acetal (±)-**10**. This was oxidized with the Corey chromic acid-pyridine reagent[8] to give an aldehyde (±)-**11**. The Huang-Minlon reduction of this aldehyde was followed by acid treatment to afford (±)-5-methylbicyclo[3.2.0]heptan-2-one **12**. Its IR and NMR data were in good accord with those reported previously.[9] The second key intermediate **3** was obtained



from **12** by the method of Cargill and Wright.[9] Thus the racemic ketone **12** was condensed with acetone in the presence of NaOMe to give (±)-**13**. This was treated with MeMgI to give (±)-**3** as crystals. Its epoxidation with *m*-chloroperbenzoic acid gave an epoxide (±)-**14**. Cleavage of the 5-membered ring was effected with HIO_4 to give the known keto acid (±)-**15**.[9,10] The Wittig methylenation of (±)-**15** (Ph_3PMeBr–NaH–DMSO) gave the known olefinic acid (±)-**16**,[10,11] contaminated with 10–20% of the *trans*-isomer (±)-**17**.[10] This was evident in the NMR spectrum of the crude product, since the C-1 Me protons of the *cis*-isomer exhibit a signal at δ 1.32 while those of the *trans*-isomer exhibit a peak at δ 1.04. The purification by iodolactonization-reduction was therefore attempted. Iodolactonization ($NaHCO_3$-I_2-KI)[12] of the mixture of olefinic acids [(±)-**16** + (±)-**17**] gave an iodolactone (±)-**18** and an unexpected by-product (±)-**19** which were separable by chromatography over SiO_2. The iodolactone **18** showed an IR band at 1740 cm^{-1}, while the γ-lactone **19** absorbed at 1780 cm^{-1} and showed signals in its NMR spectrum at δ 5.05 and 5.16 due to two olefinic protons. Reduction of the iodolactone (±)-**18** with Zn–AcOH[13] gave the pure *cis*-acid (±)-**16**. This was treated with LAH to give (±)-grandisol (1/2 **1** + 1/2 **1**′). The IR and NMR spectra of our material was identical with the authentic spectra kindly provided by Dr. C. A. Henrick.

The same sequence of transformations starting from the (−)-acid **2** and its antipode **2**′ afforded (+)-grandisol **1** and its antipode **1**′, respectively. The CD spectra of the intermediate bicyclic ketone **12** and its enantiomer **12**′ confirmed their antipodal nature: (−)-**12** showed a negative Cotton effect, $[\theta]_{298} - 3050$, while (+)-**12**′ showed a positive Cotton effect, $[\theta]_{298} + 3400$. The examination of a molecular model and application of the octant rule seemed to support the assignment of (1*R*:5*R*)-stereochemistry to **12** with a negative Cotton effect. The determination of the optical purities of the alcohol (−)-**3** and (+)-**3**′ was carried out employing the NMR optishift reagent, Eu(facam)$_3$.[14,15]† In the case of the racemic alcohol (±)-**3**, a 3H-singlet of C-5 Me was observed at δ 2.50 in the presence of Eu(facam)$_3$. However, signals due to other Me's were all observed as pairs of two 1.5 H-singlets. The resonance due to the Me at C-2, which is the closest to the OH, experienced the largest shift and appeared as a pair of singlets at δ 6.12 and 6.77. The signal due to one of the isopropylidene Me groups closer to the OH also suffered a large shift to down field and appeared as a pair of singlets at δ5.40 and 6.28. These resonance signals of two Me groups in the proximity of the OH group gave key informations for the determination of optical purities of (1*R*:5*R*)-(−)-**3** and (1*S*:5*S*)-(+)-**3**′. After the addition of Eu(facam)$_3$, three signals were observable in the low field region of the NMR spectrum of (−)-**3**: δ 5.28 (2.7 H, s, C=CMe), 6.04 (2.7 H, s, C(OH)Me) and 6.52 (0.3 H, s, C(OH)Me). Apparently the bigger signals were due to (1*R*:5*R*)-**3** while the smaller one was due to its antipode **3**′. The signal due to C=CMe of **3**′ was not recognizable.

†Tris[3 - trifluoromethylhydroxymethylene) - *d* - camphorato] - europium(III).

On the other hand, in the NMR spectrum of (+)-3' with Eu(facam)$_3$, three signals were observable: δ 5.20 (0.3 H, C=CMe), 5.72 (2.7 H, C=CMe) and 6.30 (2.7 H, C(OH)Me). In this case the signal due to C(OH)Me of 3 could not be observed. The optical purities of both 3 and 3' were therefore roughly estimated to be about 80%. This means that the resolution of the racemic acid (±)-2 was about 90% successful (90% (+)-2 + 10%(−)-2' and *vice versa*). As epimerization at the C-5 quaternary carbon atom of 3 or 3' was impossible during the remaining steps of the synthesis, our grandisol enantiomer (1 or 1') was of 80% optical purity.

(1*R*:2*S*)-(+)-Grandisol (1) had $[\alpha]_D^{20} + 19.6 \pm 2°$ (c = 0.23, n-hexane), which was corrected for the optical purity (80%) of 3. The antipode, (1*S*:2*R*)-(−)-grandisol (1'), had $[\alpha]_D^{20} - 20 \pm 3°$ (c = 0.14, n-hexane), which was also corrected. This led to the conclusion that the $[\alpha]_D$ value (+18.5°) of Magnus's synthetic grandisol[4,5] was correct, while "the optical rotation measured on 11 mg of the pure natural compound" ($[\alpha]_D + 50 \pm 10°$)[2] might be overestimated. Although we successfully synthesized the both enantiomers of grandisol, both the optical purities and yields of the final products were unsatisfactory for the biological study. We are currently surveying other routes to grandisol enantiomers which can provide materials satisfactory for entomological researches.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded as CCl_4 solns at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP-4 polarimeter. GLC analyses were performed on a Yanaco G 80 gas chromatograph. CD spectra were recorded on a Jasco J-20 spectropolarimeter.

Ethyl 3-oxocyclopent-1-ene-1-carboxylate **5**

Chromic anhydride (120 g) was added portionwise to t-BuOH (300 ml) under ice-cooling and shaking. The red soln was diluted with CCl_4 (900 ml), dried over $MgSO_4$ and filtered through a glass filter. The filtrate was concentrated *in vacuo* below 30° to a volume of *ca.* 300 ml. A soln of 4 (50 g) in CCl_4 (200 ml)–AcOH (80 ml)–Ac_2O (80 ml) was added to the oxidant. The mixture was ice-cooled, if necessary. Sometimes a sudden exothermic reaction took place resulting in a violent explosion. At the end of the exothermic reaction, the mixture was heated at 40–50° for 36 hr. Then it was poured into ice and aqueous oxalic acid (*ca.* 1l) to destroy excess of the oxidant. The mixture was stirred until the soln turned green with gas evolution. The organic layer was separated and the aq layer was extracted with $CHCl_3$. The combined organic soln was washed with water, $NaHCO_3$ aq and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was fractionally distilled with a 30 cm-Vigreux column to give 20.5 g of recovered 4, 12 g of a mixture of 4 and 5, b.p. 70–100°/5 mm and 11 g (34% conversion) of 5, b.p. 104–105°/5 mm, n_D^{21} 1.4756; ν_{max} 3080 (w), 2980 (m), 2930 (m), 1720 (vs), 1615 (m), 1440 (m), 1375(m), 1285 (m), 1260 (s), 1220 (s), 1165 (s), 1070 (s), 1000 (m), 740 (s) cm^{-1}; δ 1.38 (3H, t, J = 7 Hz), ~2.45 (2H, m), ~2.85 (2H, m), 4.35 (2H, q, J = 7 Hz), 6.72 (1H, t, J = 1.5 Hz). (Found: C, 62.14; H, 6.65. $C_8H_{10}O_3$ requires: C, 62.32; H, 6.54%).

(±)-5-*Carbethoxybicyclo*[3.2.0]*heptan-2-one* **6**

A soln of 5 (14.0 g) in C_6H_6 (350 ml) was irradiated through a Pyrex-filter with a 400-W high pressure mercury lamp (Osawa UV-Works, Tokyo, Model UV-HT) with a continuous flow of ethylene for 3.5 hr. The soln was concentrated *in vacuo* and the residue was distilled with a Vigreux column to give 9.3 g (55%) of 6, b.p. 90–96°/1 mm, n_D^{21} 1.4674; ν_{max} 2960 (m), 1740 (vs), 1300 (m), 1270 (m), 1250 (m), 1215 (m), 1170 (s), 1105 (m), 1040 (m) cm^{-1}; δ 1.26 (3H, t, J = 7 Hz), ~1.6–~3.0 (9H, m), 4.18 (2H, q, J = 7 Hz). (Found: C, 65.19; H, 7.64. $C_{10}H_{14}O_3$ requires: C, 65.91; H, 7.74%).

(±)-2-*Ethylenedioxy-5-carbethoxybicyclo*[3.2.0]*heptane* **7**

A soln of 6 (15.0 g) and *p*-TsOH (0.3 g) in butanone ethylene ketal (100 ml) was heated for 2 hr with removal of the low-boiling butanone through a Vigreux column. After cooling, the soln was washed with $NaHCO_3$ aq and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 13.0 g (70%) of 7, b.p. 112–118°/1.2 mm, n_D^{21} 1.4718; ν_{max} 2960 (s), 2880 (m), 1735 (vs), 1330 (s), 1290 (s), 1230 (s), 1210 (s), 1180 (s), 1120 (s), 1080 (m), 1040 (m), 1020 (m) cm^{-1}; δ 1.22 (3H, t, J = 7 Hz), ~1.5–~2.7 (9H, m), 3.80 (4H), 4.12 (2H, q, J = 7 Hz). (Found: C, 63.37; H, 7.92. $C_{12}H_{18}O_4$ requires: C, 63.70; H, 8.02%).

(±)-5-*Carboxybicyclo*[3.2.0]*heptan-2-one* **2**

Aqueous NaOH (10 g in 10 ml water) was added to a soln of 7 (12.0 g) in MeOH (200 ml) and the mixture was heated under reflux for 12 hr. Then it was concentrated *in vacuo* and acidified with N-HCl. After 30 min at 30–40°, the mixture was extracted with ether. The ether soln was washed with NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residual semi-solid was recrystallized from n-hexane–ether to give 4.8 g (59%) of 2. An analytical sample was obtained as prisms, m.p. 48–49°, by recrystallization from ether–n-hexane: ν_{max} ~3380 (m), 2560 (m), 1715 (vs), 1305 (s), 1280 (m), 1255 (m), 1215 (s), 1185 (m), 1000 (m) cm^{-1}. (Found: C, 61.96; H, 6.45. $C_8H_{10}O_3$ requires: C, 62.32; H, 6.54%).

Optical resolution of (±)-2

(a) *With quinine.* Quinine (17 g) and (±)-2 (8.0 g) were dissolved in hot 95% EtOH (70 ml). After cooling, the separated crystals were collected and recrystallized 4 times from EtOH to give 11.0 g of the quinine salt as prisms, m.p. 214–215°; $[\alpha]_D^{20}$ − 155° (c = 0.79, EtOH); ν_{max} ~3480 (w), ~2700 (m), ~2350 (m), 1740 (s), 1650 (w), 1625 (m), 1600 (m), 1520 (s), 1460 (s), 1440 (m), 1410 (s), 1255 (s), 1240 (s), 1040 (m), 860 (m) cm^{-1}. (Found: C, 70.12; H, 7.08; N, 5.82. $C_{28}H_{34}O_5N_2$ requires: C, 70.27; H, 7.16; N, 5.85%). This salt (11 g) was dissolved in N-HCl (50 ml). The soln was saturated with NaCl and thoroughly extracted with ether. The ether soln was washed with NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 3.0 g of crystalline acid (2), $[\alpha]_D^{20}$ − 54.2° (c = 0.929, EtOH). The resolution was repeated to give 7.0 g of the partially resolved acid. This was recrystallized from ether–pet. ether. The racemate was less soluble and separated first. The ppts were removed and the mother liquor was concentrated *in vacuo*. The residue was again dissolved in ether–pet. ether. This operation was repeated for 4 times to give 2.0 g of low melting acid (2), m.p. 20–22°, $[\alpha]_D^{20}$ − 136° (c = 0.66, EtOH). The IR spectrum was identical with that of the racemate. However, polymorphism was observed in some cases resulting in a different IR spectrum, ν_{max} ~3400 (m), ~3200 (m), ~2600 (m), 1740 (vs), 1700 (vs), 1270 (m), 1250 (m), 1240 (m), 1210 (m), 1180 (s), 1105 (m), 1005 (w), 940 (w) cm^{-1}.

(b) *With cinchonine.* Cinchonine (12 g) and (±)-2 (6.0 g) were dissolved in hot 95% EtOH (75 ml). After cooling, the separated crystals were collected and recrystallized 4 times from EtOH to give 6.1 g of the cinchonine salt as prisms, m.p. 189–191°, $[\alpha]_D^{20}$ + 159° (c = 0.74, EtOH); ν_{max} ~3150 (m), 1720 (vs), 1580 (m), 1560 (m), 1500 (m), 1380 (s), 1310 (m), 1280 (m), 1160 (m), 1100 (m), 800 (m), 780 (m), 765 (m), 750 (m) cm^{-1}. (Found: C, 71.99; H, 7.23; N, 6.28. $C_{27}H_{32}O_4N_2$ requires: C, 72.29; H, 7.19; N, 6.25%). This salt (6.0 g) was dissolved in N-HCl (50 ml). The soln was thoroughly extracted with ether. The ether soln was washed with NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 2.0 g of crystalline acid 2', $[\alpha]_D^{20}$ + 37.1° (c = 1.02, EtOH).

(c) *With brucine.* Brucine (15 g) and (±)-2 (7.5 g) were dissolved in hot 99% EtOH (60 ml). After cooling, the separated crystals were collected and recrystallized 3 times from EtOH to give 4.0 g of the brucine salt as prisms, m.p. 115–118°, $[\alpha]_D^{20}$ − 6.8° (c = 0.887, EtOH); ν_{max} 3550 (m), ~3400 (m), 1740 (s), 1650 (vs), 1620 (m), 1510 (vs), 1425 (m), 1380 (m), 1300 (m), 1215 (m), 1115 (m), 850 (m) cm^{-1}. (Found: C, 67.82; H, 6.65; N, 4.93. $C_{31}H_{36}O_7N_2$ requires: C, 67.86; H, 6.61; N, 5.11%). This was

dissolved in N-HCl (40 ml). The soln was thoroughly extracted with ether. The ether soln was washed with NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.0 g of oily acid **2'**, $[\alpha]_D^{22}$ + 83° (c = 0.762, EtOH). This crude **2'** was purified by fractional crystallization in the manner described for **2**. Thus 3.1 g of crude **2'** gave 1.9 g of purified **2'**, m.p. 20–23, $[\alpha]_D^{22}$ + 116° (c = 0.384, EtOH), The IR spectrum was identical with that of **2**.

(1R:5S) - 5 - *Carbomethoxybicyclo*[3.2.0]*heptan* - 2 - *one* **8** *and its* (1S:5R) - *isomer* **8'**

These were prepared by treating the acids (**2** and **2'**) with ethereal CH_2N_2. Thus 2.6 g of (−)-acid (**2**) gave 2.8 g of **8** as an oil, ν_{max} 1740 (vs), 1440 (m), 1340 (m), 1300 (m), 1270 (m), 1240 (m), 1210 (m), 1170 (s), 1110 (m), 1070 (w), 1025 (w), 965 (w), 885 (w), 790 (w), 760 (w) cm^{-1}; δ ~ 1.5–~3.0 (9H), 3.75 (3H, s). Similarly 2.7 g of (+)-acid (**2'**) gave 2.9 g of **8'**.

(1R:5S) - 2 - *Ethylenedioxy* - 5 - *carbomethoxybicyclo*[3.2.0]*heptane* **9** *and its* (1S:5R) - *isomer* **9'**

(a) (1R:5S)-*Isomer* **9**. A soln of **8** (2.8 g) and *p*-TsOH (0.1 g) in butanone ethylene ketal (30 ml) was heated for 3 hr with removal of the low-boiling butanone through a Vigreux column. After cooling, the soln was washed with $NaHCO_3$ aq and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 3.0 g of **9**, ν_{max} 2960 (m), 2890 (m), 1735 (vs), 1440 (m), 1350 (m), 1330 (s), 1290 (s), 1230 (m), 1210 (m), 1195 (m), 1175 (s), 1110 (s), 1080 (m), 1040 (m), 1020 (m) cm^{-1}. This was employed for the next step without further purification.

(b) (1S:5R)-*Isomer* **9'**. In the same manner 3.0 g of **8'** was converted to 3.5 g of **9'**. The IR spectrum was identical with that of **9**.

2 - *Ethylenedioxy* - 5 - *hydroxymethylbicyclo*[3.2.0]*heptane* **10**

(a) *Racemate*. A soln of (±)-**7** (8.0 g) in dry ether (50 ml) was gradually added to a suspension of LAH (2.0 g) in dry ether (50 ml) with stirring at 0–5°. The mixture was stirred overnight at room temp. Water (2 ml), 10% NaOH aq (2 ml) and water (6 ml) were added successively to the stirred and ice-cooled mixture. After stirring for 1 hr, the mixture was dried (K_2CO_3) and filtered. The solvent was removed *in vacuo*. The residue was distilled to give 5.6 g (86%) of racemic **10**, b.p. 122–124°/2 mm, n_D^{20} 1.4965; ν_{max} ~ 3400 (s), 2950 (s), 2870 (s), 1450 (m), 1350 (s), 1220 (s), 1145 (m), 1110 (s), 1060 (s), 1020 (s), 950 (m), 910 (m) cm^{-1}; δ ~ 1.3–~2.5 (9H, m), 2.70 (1H), 3.46 (2H, s), 3.88 (4H, s). (Found: C, 64.65; H, 8.73. $C_{10}H_{16}O_3$ requires: C, 65.19; H, 8.75%).

(b) (1R:5S)-*Isomer* **10**. In the same manner (1*R*:5*S*)-**9** (3.0 g) yielded 2.8 g of (1*R*:5*S*)-**10**. The IR and NMR spectra were identical with those of the racemate.

(c) (1S:5R)-*Isomer* **10'**. In the same manner (1*S*:5*R*)-**9'** (3.5 g) yielded 2.9 g of (1*S*:5*R*)-**10'**. The IR and NMR spectra were identical with those of the racemate.

2-*Ethylenedioxy*-5-*formylbicyclo*[3.2.0]*heptane* **11**

(a) *Racemate*. A soln of (±)-**10** (4.7 g) in CH_2Cl_2 (50 ml) was added to a stirred and ice-cooled suspension of CrO_3–$2C_5H_5N$–HCl (11.0 g) and NaOAc (1.0 g) in CH_2Cl_2 (20 ml). The mixture was stirred for 1.5 hr at room temp., diluted with dry ether (150 ml) and filtered through a Florisil column (20 g) in ether. The column was washed with ether. The filtrate and washings were combined and concentrated *in vacuo*. The residue was distilled to give 4.3 g (91%) of (±)-**11**, b.p. 112–114°/5 mm, n_D^{20} 1.4886; ν_{max} 2950 (s), 2890 (s), 2700 (w), 1720 (vs), 1230 (s), 1110 (vs), 1020 (s), 950 (m), 910 (m) cm^{-1}; δ ~ 1.4–~2.8 (9H), 3.88 (4H), 9.55 (1H, s). (Found: C, 65.66; H, 7.70. $C_{10}H_{14}O_3$ requires: C, 65.91; H, 7.74%).

(b) (1R:5S)-*Isomer* **11**. In the same manner, 2.8 g of (1*R*:5*S*)-**10** yielded 1.9 g of (1*R*:5*S*)-**11**, b.p. 110°/5 mm, n_D^{21} 1.4872; $[\alpha]_D^{20}$ − 13.5° (c = 1.36, ether). The IR and NMR spectra were identical with those of the racemate.

(c) (1S:5R)-*Isomer* **11'**. In the same manner, 2.9 g of (1*S*:5*R*)-**10'** afforded 2.2 g of (1*S*:5*R*)-**11'**, b.p. 108–110°/5 mm, n_D^{23} 1.4860; $[\alpha]_D^{24}$ + 12.3° (c = 1.33, ether). The IR and NMR spectra were identical with those of the racemate.

5-*Methylbicyclo*[3.2.0]*heptan*-2-*one* **12**

(a) *Racemate*. Hydrazine hydrate (85%; 4 ml) was added to a soln of (±)-**11** (4.0 g) in diethylene glycol (25 ml) and the mixture was heated under reflux for 30 min. Then KOH (3.5 g) in water (3.5 ml) was added and the mixture was heated under reflux for another 30 min. Then the bath temp was gradually raised to 210°, distilling off the excess N_2H_4, and kept there for 2 hr. After cooling, the mixture was diluted with water and extracted with ether. The ether soln was concentrated *in vacuo* to give a ketal, ν_{max} 2920 (s), 2870 (s), 1455 (m), 1350 (s), 1230 (m), 1140 (m), 1110 (s), 1020 (s), 950 (m), 900 (s) cm^{-1}. This was mixed with N-HCl (50 ml) and the mixture was stirred for 15 min at 30–40°. Then it was neutralized with solid $NaHCO_3$, saturated with NaCl and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated under atm press. The residue was distilled to give 2.0 g (73%) of (±)-**12**, b.p. 105–106°/80 mm, n_D^{20} 1.4633; ν_{max} 2960 (s), 2880 (s), 1740 (vs), 1460 (m), 1290 (m), 1170 (s), 1105 (m), 1040 (m), 940 (w) cm^{-1}; δ 1.31 (3H, s), ~1.5–~2.8 (9H). (Found: C, 77.00; H, 9.74. $C_8H_{12}O$ requires: C, 77.37, H, 9.74%).

(b) (1R:5R)-*Isomer* **12**. In the same manner, 1.9 g of (1*R*:5*S*)-**11** yielded 1.0 g of (1*R*:5*R*)-**12**, b.p. 100–105°/82 mm, n_D^{20} 1.4626; $[\alpha]_D^{20}$ − 165.5° (c = 0.562, acetone); CD (c = 0.13, MeOH) $[\theta]_{342}$ 0, $[\theta]_{298}$ − 3050, $[\theta]_{240}$ 0.

(c) (1S:5S)-*Isomer* **12'**. In the same manner, 2.0 g of (1*S*:5*R*)-**11'** gave 329 mg of (1*S*:5*S*)-**12**, b.p. 113°/90 mm, n_D^{23} 1.4613; $[\alpha]_D^{23}$ + 171.3° (c = 0.268, acetone); CD (c = 0.125, MeOH) $[\theta]_{342}$ 0, $[\theta]_{298}$ + 3400, $[\theta]_{240}$ 0.

3 - *Isopropylidene* - 5 - *methylbicyclo*[3.2.0]*heptan* - 2 - *one* **13**

(a) *Racemate*. A soln of (±)-**12** (2.35 g) in acetone (25 ml) was added to a stirred soln of NaOMe (from 2 g of Na) in MeOH (50 ml) at −5 ~ −10°. The soln was left to stand at 5° for 8 hr and then at room temp. (*ca* 15°) for 17 hr. This was neutralized with 2N-HCl, concentrated *in vacuo*, diluted with water and extracted with ether. The ether soln was washed with water and NaCl aq., dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 2.2 g (71%) of (±)-**13**, b.p. 62–65°/0.8 mm, n_D^{20} 1.4969; ν_{max} 2940 (s), 1700 (s), 1620 (s), 1280 (s), 1180 (s) cm^{-1}; δ 1.30 (3H, s), 1.82 (3H), 2.20 (3H). (Found: C, 79.67; H, 9.75. $C_{11}H_{16}O$ requires: C, 80.44; H, 9.83%).

(b) (1R:5R)-*Isomer* **13**. In the same manner, 1.0 g of (1*R*:5*R*)-**12** gave 1.0 g of (1*R*:5*R*)-**13** whose IR spectrum was identical with that of the racemate.

(c) (1S:5S)-*Isomer* **13'**. In the same manner, 0.33 g of (1*S*:5*S*)-**12'** yielded 0.4 g of (1*S*:5*S*)-**13'**. The IR spectrum was identical with that of the racemate.

2,5 - *Dimethyl* - 3 - *isopropylidenebicyclo*[3.2.0]*heptan* - 2 - *ol* **3**

(a) *Racemate*. A soln of (±)-**13** (2.1 g) in dry ether (20 ml) was gradually added to a stirred and ice-cooled soln of MeMgI (from 1.0 g of Mg and 6.0 g of MeI) in ether (20 ml). The mixture was stirred for 2 hr at room temp., poured into ice-NH_4Cl soln and extracted with ether. The ether soln was washed with NaCl soln, dried (K_2CO_3) and concentrated *in vacuo* to give 2.15 g of crude semi-solid (±)-**3**. This was recrystallized from pet. ether to give 1.35 g of prisms, m.p. 58–59°, ν_{max} 3390 (s), 2920 (vs), 2860 (s), 1670 (w), 1455 (m), 1380 (s), 1360 (m), 1120 (m), 1035 (m), 935 (m) cm^{-1}; δ ($CDCl_3$). 1.16 (3H, s), 1.31 (3H, s), 1.64 (3H, s), 1.96 (3H, s). δ (60 MHz, (±)-**3** (30 mg) + Eu(facam)$_3$ (81 mg) in 0.4 ml CCl_4) 2.50 (3H, s, Me at C-5), 3.28 (1.5H, s, C=CMe), 3.48 (1.5 H, s, C=CMe) 5.40 (1.5 H, s, C=CMe), 6.12 (1.5 H, s, C(OH)Me), 6.28 (1.5 H, s, C=CMe), 6.77 (1.5 H, s, C(OH)Me). (Found: C, 79.37; H, 11.01. $C_{12}H_{20}O$ requires: C, 79.94; H, 11.18%).

(b) (1*R*:5*R*)-*Isomer* **3**. In the same manner, 1 g of (1*R*:5*R*)-**13** afforded 1 g of crude alcohol (**3**). This was chromatographed over Al_2O_3 (Woelm neutral alumina, grade II, 30 g) in n-hexane. Elution with n-hexane and n-hexane–ether (3:1) gave alcohol **3** contaminated with some (±)-**3**. The racemate separated from the pet. ether soln as prisms (172 mg) and was removed by filtration. The mother liquor was concentrated to give **3** as an oil (583 mg), $[\alpha]_D^{20}$ − 25.5° (c = 0.47, ether): δ (60 MHz, **3** (30 mg) + Eu(facam)$_3$ (80 mg) in 0.4 ml CCl_4) 2.41 (3H, s, Me at C-5), 3.20 (3H, s, C=CMe), 5.28 (2.7H, s, C=CMe), 6.04 (2.7 H, s, C(OH)Me), 6.52

(0.3 H, s, C(OH)Me). This NMR measurement revealed the optical purity of **3** to be 80%.

(c) (1S:5S)-*Isomer* **3'**. In the same manner, 0.5 g of (1*S*:5*S*)-**13'** gave 0.4 g of crude **3'**. This was chromatographed over Al_2O_3 (Woelm neutral alumina, grade II, 15 g) in n-hexane. Elution with n-hexane gave 332 mg of **3'** contaminated with some (±)-**3**. The racemate (65 mg) was removed in the same manner as above. The mother liquor was concentrated to give 286 mg of oily **3'**, $[\alpha]_D^{22}$ + 23.8° (c = 0.357, ether); δ (60 MHz, **3'** (20 mg) + Eu (facam)$_3$ (60 mg) in 0.4 ml CCl_4) 2.38 (3H, s, Me at C-5), 3.28 (3H, s, C=C-Me), 5.20 (0.3 H, C=CMe), 5.72 (2.7 H, C=CMe), 6.30 (2.7 H, C(OH)Me). This NMR measurement revealed the optical purity of **3'** to be 80%.

2,5 - *Dimethyl* - 3 - *isopropylidenebicyclo*[3.2.0]*heptan* - 2 - *ol epoxide* **14**

(a) *Racemate.* A soln of *m*-chloroperbenzoic acid (85%, 1.4 g) in CH_2Cl_2 (30 ml) was added to a stirred and ice-cooled soln of (±)-**3** (1.117 g) in CH_2Cl_2 (20 ml). The mixture was left to stand for 3 hr at room temp. Then it was washed with Na_2CO_3 aq., dried (K_2CO_3) and concentrated *in vacuo* to give 1.1 g of crude (±)-**14**, ν_{max} ~3500 (m), 2940 (s), 2870 (m), 1385 (s), 1360 (m), 1200 (m), 1135 (m), 1105 (m) cm^{-1}; δ 1.14 (3H, s), 1.16 (3H, s), 1.27 (3H, s), 1.44 (3H, s). This was employed for the next step without further purification.

(b) (1R:5R)-*Isomer* **14**. In the same manner, 550 mg of (1*R*:5*R*)-**3** gave 560 mg of crude **14**, whose IR spectrum was identical with that of the racemate. This was employed for the next step without further purification.

(c) (1S:5S)-*Isomer* **14'**. In the same manner, 250 mg of (1*S*:5*S*)-**3'** gave 250 mg of crude **14'**, whose IR spectrum was identical with that of the racemate. This was employed for the next step without further purification.

2-*Acetyl*-1-*methylcyclobutane acetic acid* **15**.

(a) *Racemate.* A soln of (±)-**14** (1.1 g) in ether (80 ml) was added to a stirred and ice-cooled soln of $HIO_4 \cdot 2H_2O$ (3.0 g) in THF (10 ml). The mixture was stirred for 1 hr at room temp. and poured into water. The ether layer was separated, washed with NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.0 g (quantitative) of (±)-**15**, ν_{max} ~3400 (m), 2960 (s), ~2600 (m), 1730 (sh), 1710 (vs), 1370 (m), 1190 (m) cm^{-1}; δ 1.38 (~3H, s), 2.03 (3H, s), 2.45 (2H, d, J = 2 Hz), ~3.0 (1H, m). The product contained a small amount of the *trans*-isomer which showed the C-1 Me signal at δ 1.16. This was employed for the next step without further purification.

(b) (1R:2R)-*Isomer* **15**. In the same manner 550 mg of (1*R*:5*R*)-**14** gave 430 mg of **15**, whose IR spectrum was identical with that of the racemate. This was employed for the next step without further purification.

(c) (1S:2S)-*Isomer* **15'**. In the same manner 250 mg of (1*S*:5*S*)-**14'** gave 198 mg of **15'**, whose IR spectrum was identical with that of the racemate. This was employed for the next step without further purification.

2-*Isopropenyl* - 1 - *methylcyclobutane acetic acid* **16**

(a) *Racemate.* A DMSO soln of methylene triphenylphosphorane was prepared in the usual manner from 11 g of Ph_3PMeBr and 1.5 g of 50% NaH in DMSO (40 ml). This was gradually added to a stirred and ice-cooled soln of (±)-**15** (1.1 g) in dry THF (40 ml) under N_2. The mixture was stirred for 2 hr at room temp. and poured into ice-Na_2CO_3 aq. The mixture was extracted with ether to remove undesired neutral compounds. The aqueous layer was acidified with dil. HCl and extracted with ether. The ether soln was washed with NaCl aq., dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt AR 100 mesh, 7 g) in n-hexane. Elution with n-hexane–ether (4:1) gave 0.9 g (82%) of (±)-**16**, ν_{max} ~3800 (m), 2960 (s), ~2600 (m), 1710 (vs), 1645 (m), 890 (s) cm^{-1}; δ 1.04 (~0.5 H, s, Me at C-1 of the *trans*-isomer), 1.32 (2.5 H, s, Me at C-1 of 16), 1.65 (3H, s), 4.68 (1 H), 4.86 (1 H). This was purified by iodolactonization-reduction as described below.

(b) (1R:2S)-*Isomer* **16**. In the same manner 450 mg of (1*R*:2*R*)-**15** gave 220 mg of (1*R*:2*S*)-**16** after chromatographic purification. This also contained *ca.* 15% of the *trans*-isomer as judged by NMR and was purified by iodolactonization reduction.

(c) (1S:2R)-*Isomer* **16'**. In the same manner 198 mg of (1*S*:2*S*)-**15'** gave 130 mg of (1*S*:2*R*)-**16'** after chromatographic purification. This was contaminated with *ca.* 20% of the *trans*-isomer as judged by NMR and was purified by iodolactonization-reduction.

Purification of cis-2-*isopropenyl* - 1 - *methylcyclobutane carboxylic acid by iodolactonization-reduction*

(a) *Racemate.* A soln of crude (±)-**16** (0.9 g) in $NaHCO_3$ aq. (1.4 g $NaHCO_3$ in 25 ml H_2O) was mixed with 15 ml of KI_3 soln (12.6 g I_2 and 26 g KI in 150 ml H_2O). The mixture was left to stand overnight in a refrigerator and then extracted with ether. The ether soln was washed with $Na_2S_2O_3$ aq. and NaCl aq., dried ($MgSO_4$) and concentrated *in vacuo* to give 769 mg of neutral products. This was chromatographed over SiO_2 (Merck Kieselgel 60, 70–230 mesh, 20 g) in n-hexane. Elution with n-hexane and n-hexane–ether (9:1) gave 120 mg of (±)-**19**, b.p. 140–150°/15 mm, n_D^{23} 1.4797; ν_{max} 3100 (w), 2960 (m), 1780 (vs), 1650 (w), 1275 (m), 1240 (m), 1210 (s), 1135 (s), 1120 (m), 980 (s), 925 (m); δ 1.18 (3H, s), 1.70 (3H, s), 2.45 (2H, d, J = 4 Hz), 5.05 (1H), 5.16 (1H). Further elution with n-hexane–ether (9:1 ~ 4:1) gave 406 mg of (±)-iodolactone **18**, ν_{max} 2940 (s), 2860 (m), 1740 (vs), 1290 (s), 1220 (m), 1170 (s), 1150 (m), 1095 (m), 1020 (m). This was dissolved in AcOH (10 ml) and reduced by stirring with Zn dust (2 g). After 30 min, the mixture was diluted with ether and filtered through Celite. The filtrate was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 202 mg of pure (±)-*cis*-acid **16**, ν_{max} ~3800 (m), 2950 (s), 2870 (m), ~2600 (m), 1710 (s), 1640 (m), 1440(m), 1410 (m), 1380 (m), 1310 (m), 1290 (m), 1245 (m), 1220 (m), 1115 (w), 940 (m), 885 (m) cm^{-1}; δ 1.32 (3H, s), 1.65 (3H, s), 4.68 (1H), 4.86 (1H); MS (70 eV): *m/e* 168.1065 (M^+, $C_{10}H_{16}O_2$ requires: 168.1150).

(b) (1R:2S)-*Isomer* **16**. In the same manner 220 mg of crude **16** yielded 70 mg of pure (1*R*:2*S*)-acid (**16**) whose IR spectrum was identical with that of the racemate.

(c) (1S:2R)-*Isomer* **16'**. In the same manner 130 mg of crude **16'** yielded 30 mg of pure (1*S*:2*R*)-acid (**16'**) whose IR spectrum was identical with that of the racemate.

Grandisol (cis - 2 - *isopropenyl* - 1 - *methylcyclobutane ethanol*) **1**

(a) *Racemate.* A soln of (±)-**16** (180 mg) in dry ether (10 ml) was added to a stirred and ice-cooled suspension of LAH (200 mg) in dry ether (15 ml). The mixture was stirred overnight at room temp. Water (0.2 ml), 10% NaOH aq. (0.2 ml) and water (0.6 ml) were added successively to the stirred and ice-cooled mixture. After stirring for 30 min, the mixture was dried (K_2CO_3) and filtered. The solvent was removed *in vacuo* and the residue was distilled to give 100 mg of (±)-**1**, b.p. (bath temp.) 110–130°/18 mm, n_D^{22} 1.4739; ν_{max} ~3300 (s), 3800 (w), 2940 (vs), 2870 (s), 1650 (m), 1460 (m), 1380 (m), 1285 (w), 1245 (m), 1120 (w), 1100 (w), 1050 (s), 1020 (m), 1000 (m), 885 (s), 780 (w) cm^{-1}; δ 1.15 (3H, s), 1.65 (3H, s), 2.55 (1H, OH), 3.58 (2H, t, J = 7 Hz), 4.64 (1H), 4.84 (1H); MS (70 eV): *m/e* 154.1368 (M^+, $C_{10}H_{18}O$ requires: 154.1358); GLC (Column, 10% QF-1, 2.25 m at 100°; Carrier gas, N_2 at 0.75 kg/cm^2): R_t 10.9 min (100% pure): (Found: C, 77.75; H, 11.72. $C_{10}H_{18}O$ requires: C, 77.86; H, 11.76%). The IR and NMR spectra were identical with those of (±)-grandisol synthesized by the Zoecon group.[10]

(b) (1R:2S)-*Grandisol* **1**. In the same manner 70 mg of (1*R*:2*S*)-**16** afforded 23.6 mg of (1*R*:2*S*)-grandisol (**1**), n_D^{20} 1.4748, $[\alpha]_D^{20}$ + 15.7 ± 2° (c = 0.23, n-hexane); $[\alpha]_D^{20}$ (corrected for the optical purity (80%) of **3**) + 19.6 ± 2°. The IR spectrum was identical with that of the racemate.

(c) (1S:2R)-*Grandisol* **1'**. In the same manner 30 mg of (1*S*:2*R*)-**16'** afforded 15.0 mg of (1*S*:2*R*)-grandisol (**1'**), n_D^{22} 1.4760, $[\alpha]_D^{22}$ − 16 ± 3° (c = 0.14, n-hexane); $[\alpha]_D^{22}$ (corrected for the optical purity (80%) of **3'**) − 20 ± 3°.

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