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

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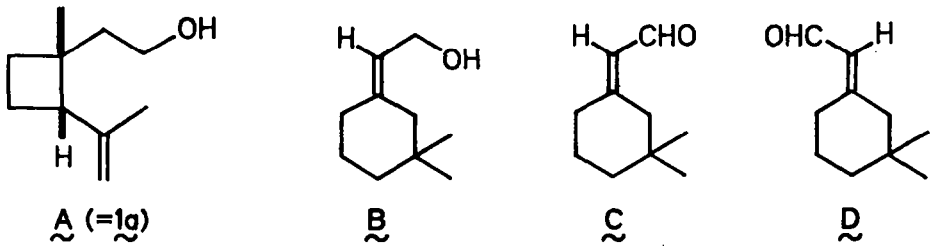
Abstract - The pure enantiomers of grandisol (2-isopropenyl-1-methylcyclobutaneethanol), the pheromone component of Anthonomus grandis Boheman, were synthesized employing ethyl (R)-3-hydroxybutanoate as the single chiral source.

In 1967 Tumlinson et al. isolated four new monoterpenes **A** (=**1a**), **B**, **C** and **D** (Fig. 1) as the components of the male-produced pheromone of the boll weevil, Anthonomus grandis Boheman.[1,2] The chiral cyclobutane derivative (2-isopropenyl-1-methylcyclobutaneethanol) **1a** was named grandisol, which attracted attention of many synthetic chemists due to its



A (=1a) B C D

Fig. 1. The components of the boll weevil pheromone.

unique structure. A number of syntheses of (±)-**1a** was reported to date.[3-8] The absolute configulation of the naturally occurring (+)-grandisol **1a** was determined to be 1R,2S by its synthesis from (-)-β-pinene as reported by Hobbs and Magnus.[9] Since then several chiral syntheses of grandisol were accomplished resulting in the preparation of both (+)-**1a**[10] and (-)-**1a'**[10,11], (+)-**1a**[12], (-)-**1a'**[13] and both (+)-**1a** and (-)-**1a'**.[14]

Our own synthesis of both the enantiomers of grandisol enabled us to evaluate their pheromone activity.[10,11] Unexpectedly, even the unnatural (-)-grandisol was found to be fully bioactive.[11] This was indeed quite an unusual case among bioactive natural products. So as to know more about the pheromone activity of grandisol enantiomers,

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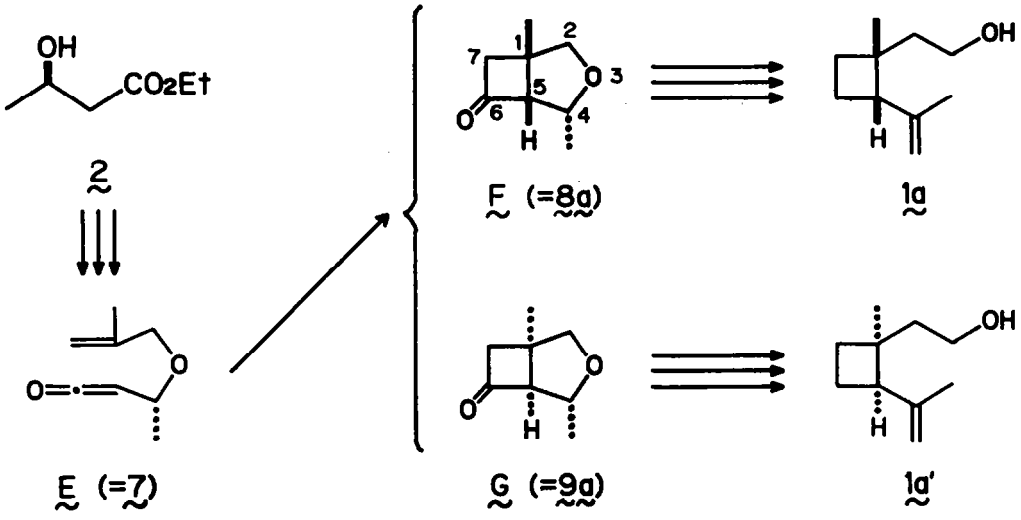


Fig. 2. Synthetic plan.

highly pure (+)-**1a** and (-)-**1a'** were in urgent need. We therefore decided to develop a new synthesis by which sufficient amounts of grandisol enantiomers would be supplied.

Our synthetic plan as shown in Fig. 2 is based on the use of a chiral building block **2** of microbial origin. Enantiomerically pure ethyl (R)-3-hydroxybutanoate **2** is readily available by ethanolysis of poly(3-hydroxybutanoate) (PHB) produced by *Zoogloea ramigera*.[15,16] The key-reaction in our synthesis is the intramolecular cycloaddition of olefinic ketene **E** to give a mixture of bicyclic cyclobutanones **F** and **G**. The usefulness of intramolecular cycloadditions of olefinic ketenes has recently been established in alicyclic chemistry.[17-19] The cyclobutanone **F** is to be converted to (+)-grandisol **1a**, while the isomer **G** leads to (-)-**1a'**. This plan was realized as detailed below resulting in the preparation of the pure enantiomers of grandisol.

The first phase of our work was the preparation of the key bicyclic intermediates **8a** (=**F**) and **9a** (=**G**) as shown in Fig. 3. Reduction of **2** with LAH gave the known diol **3a**,[20,21] whose primary OH group was protected as trityl ether **3b**. Treatment of **3b** with NaH in DMF was followed by etherification with CH_2=$CMeCH_2Cl$ to give **4a**. The trityl group of **4a** was removed by treatment with 80 % AcOH to give **4b**. Oxidation of **4b** with Jones reagent furnished **5** in 56 % overall yield from **2** in 5 steps. Attempts to prepare **5** by direct 3-O-β-methallylation of (R)-3-hydroxybutanoic acid or **2** were unsuccessfull. Acyl chloride **6** was prepared from **5** by treatment with oxalyl chloride. Subsequently, the key cycloaddition reaction *via* **7** (=**E**) was executed by slowly adding Et_3N to a refluxing soln of **6** in a large volume of CH_2Cl_2[17-19] yielding a 3.4:1 mixture of two bicyclic ketones whose structures were later assigned as **8a** and **9a**, respectively (*vide infra*). The cycloaddition was thus moderately stereoselective giving the *endo*-Me isomer **8a** as the major product.

Although these two ketones were separable by GLC, their purification by conventional SiO_2 chromatography was rather difficult. The mixture of ketones **8a** and **9a** was therefore converted to the corresponding mixture of alcohols **10** and **11** by reduction with LiBH(*s*-Bu)$_3$. Reduction of a fused bicyclic cyclobutanone like **8a** and **9a** with LiBH(*s*-Bu)$_3$ was known to give an *endo*-alcohol.[22] The diastereomeric alcohols **10** and **11** were readily separable by SiO_2 chromatography at this stage. The structure **10** was assigned to the less polar alcohol (obtained in 51.0 % yield from the mixture of **8a** and **9a**) on the basis of its ^{1}H NMR spectrum in which the 3 H doublet due to the Me group at C-4 was observed at δ 1.58. In the ^{1}H NMR spectrum of the more polar alcohol **11** (obtained in 13.8 % yield), the

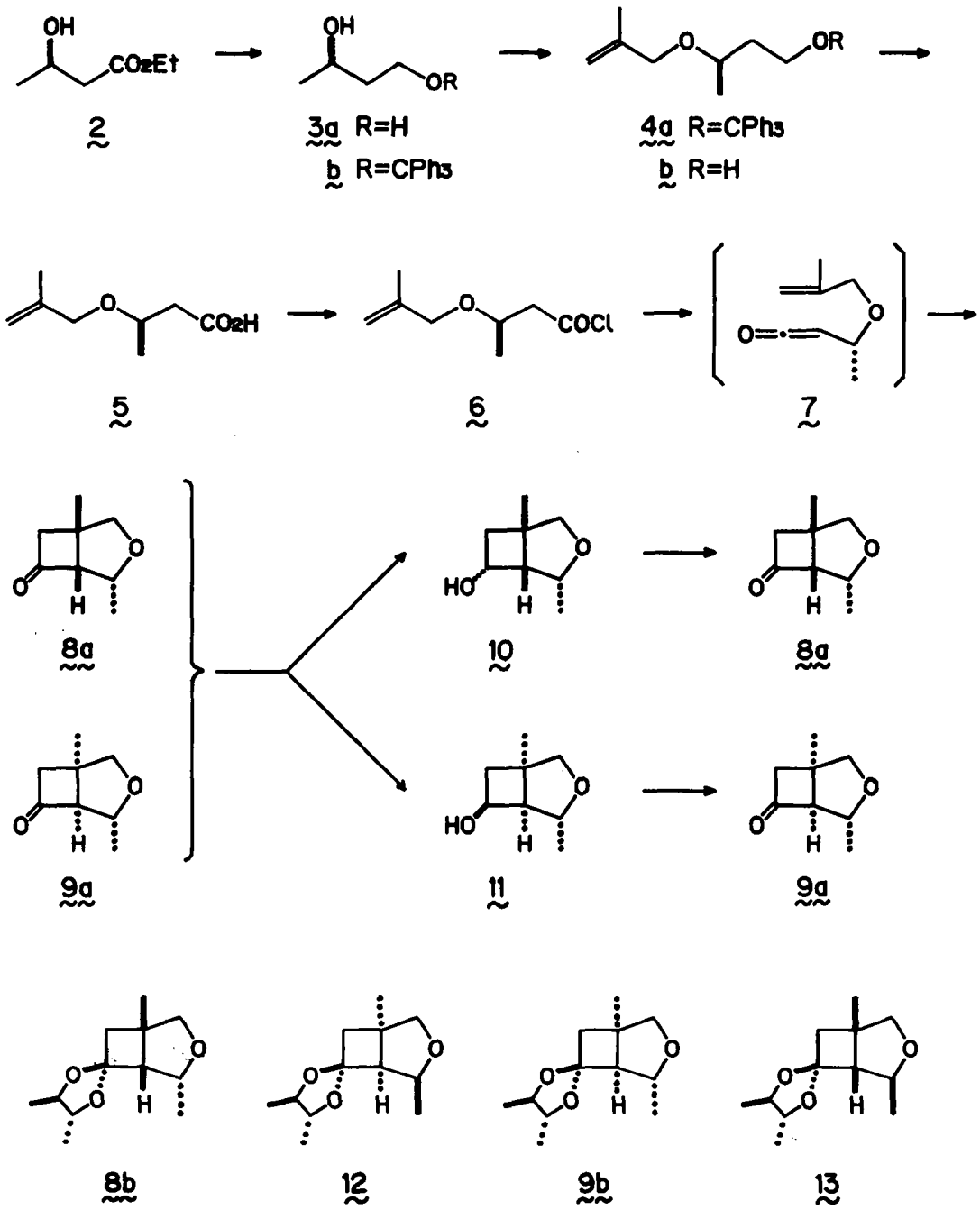


Fig. 3. Synthesis of the bicyclic intermediates.

3 H doublet due to C-4 Me group appeared at δ 1.16. The down-field shift of the signal due to C-4 Me group in the case of 10 must be due to the shielding effect of the OH group at C-6, which is in cis-relationship to the Me group at C-4. The signal due to the methine proton at C-4 was observed at δ 3.94 (1 H, dq, J=5.3, 7.0 Hz) in the case of 10, while in the case of 11 that signal appeared at δ 4.56 (1 H, br.q, J=6.7 Hz). The above observation indicated that the methine proton at C-4 of 11 absorbing at a lower field than

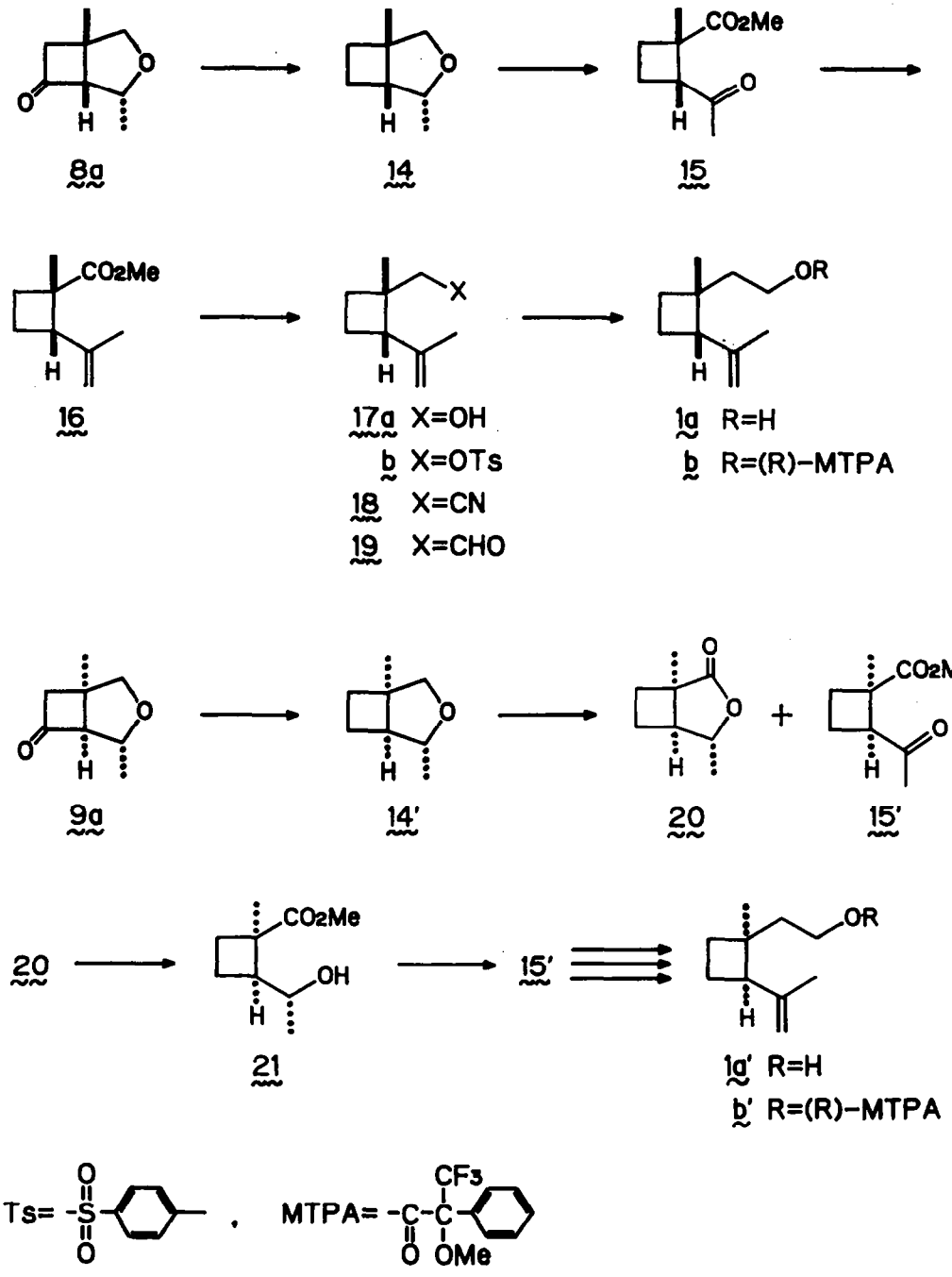


Fig. 4. Synthesis of the enantiomers of grandisol.

that of **10** must be in cis-relationship to the OH group at C-6. The coupling constant between the proton at C-4 and that at C-5 was almost zero in the case of **11** in accord with the assigned stereochemistry. Considering all of the above observation, the less polar alcohol was thought to be (1S,4R,5S,6R)-**10**, while the more polar alcohol must be (1R,4R,5R,6S)-**11**. These assignments were proved to be true by the later conversion of **10** and **11** to (+)-**1a** and (-)-**1a'**, respectively. Having solved the separation problem, what

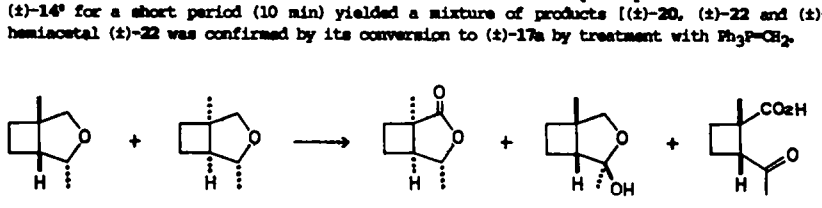
should be done next was to give back the ketones **8a** and **9a** by oxidizing the alcohols **10** and **11**, respectively, under the Swern condition using DMSO and oxalyl chloride in CH_2Cl_2.[23] The overall yield of **8a** from **5** was 31 %, while that of **9a** from **5** was 9.7 % in 4 steps.

At this stage we thought it appropriate to estimate the enantiomeric purity of **8a** and **9a**. This was achieved by the GLC analyses of the acetals **8b** and **9b** prepared from (2R,3R)-2,3-butanediol and the ketones **8a** and **9a**. Acetal prepared from chiral ketones and (2R,3R)-2,3-butanediol were frequently employed for the purpose of the separation of enantiomeric ketones by GLC.[24,25] To secure a reference sample, (±)-**8a**, which was separately prepared from (±)-**3a**, was acetalized with (2R,3R)-2,3-butanediol to give a mixture of **8b** and **12**. This mixture was cleanly separable by capillary GLC. The acetal **8b** derived from **8a** showed a single peak upon GLC analysis. The acetal **8b** was therefore diastereomerically pure, and hence the ketone **8a** was enantiomerically pure. Similarly (±)-**9a**, which was also synthesized from (±)-**3a**, was acetalized to a mixture of **9b** and **13**. These acetals were also separable by capillary GLC, while the acetal **9b** prepared from **9a** exhibited only a single peak. The ketone **9a** was therefore of 100 % e.e., too.

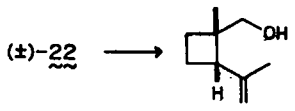
The conversion of the ketones **8a** and **9a** to the enantiomers (**1a** and **1a'**) of grandisol was executed as shown in Fig. 4. The synthesis of (+)-grandisol **1a** will be discussed first. The Wolff-Kishner reduction of **8a** with N_2H_4 and KOH in diethylene glycol gave bicyclic ether **14**. Treatment of **14** with RuO_4-$NaIO_4$[26] followed by CH_2N_2 yielded keto ester **15**, whose antipode **15'** was previously prepared by Meyers and Fleming.[13] Their route was followed to convert **15** to the final product **1a**. The keto ester **15** was treated with $Ph_3P{=}CH_2$ in 1,2-dimethoxyethane to give olefinic ester **16**. LAH reduction of **16** yielded alcohol **17a**, which was tosylated to give **17b** as crystals in our case. Treatment of **17b** with NaCN in wet HMPA[27] furnished nitrile **18**. Reduction of **18** with $(i\text{-Bu})_2AlH$ to **19** was followed by further reduction of **19** with LAH to afford (+)-grandisol **1a** in 12 % overall yield in 8 steps from **8a**. The IR and ^1H NMR spectra of (+)-**1a** were identical with those reported previously.[10] The detailed ^1H and ^{13}C NMR data are listed in the Experimental Section as Table 2.

Similarly, the ketone **9a** was converted to (-)-grandisol **1a'**. Thus **9a** was first reduced to give **14'**. Oxidation of **14'** with RuO_4-$NaIO_4$, however, took a course slightly different from the case with **14**. The H atom at C-4 was with endo-orientation in the case of **14'**, contrary to the exo-orientation in the case of **14**. Therefore in the case of **14'**, the H atom at C-4 was more resistant to the oxidation than that of **14**.† Thus RuO_4-$NaIO_4$ oxidation of **14'** furnished, after methylation with CH_2N_2, a mixture of **20** and **15'** in the ratio of ca. 2:1. As the separation of the mixture was rather difficult, it was directly

† The C-4 position of **14** was readily oxidizable. In fact, RuO_4-$NaIO_4$ oxidation of a diastereomeric mixture of (±)-**14** and (±)-**14'** for a short period (10 min) yielded a mixture of products [(±)-**20**, (±)-**22** and (±)-**23**]. The structure of the new hemiacetal (±)-**22** was confirmed by its conversion to (±)-**17a** by treatment with $Ph_3P{=}CH_2$.



(±)-**14** (±)-**14'** (±)-**20** (±)-**22** (±)-**23**



(±)-**17a**

treated with $Ph_3P=CH_2$ to give a separable mixture of 16' (25.5 % yield from 14') and 20 (42.9 % yield from 14'). The lactone 20 was then converted to 21 by hydrolysis with KOH followed by esterification (CH_2N_2) of the resulting hydroxy acid. The Swern oxidation of 21 with DMSO and oxalyl chloride in CH_2Cl_2 gave 15', which was submitted to the Wittig reaction yielding 16', identical to 16' prepared by the direct route (14' → 15' → 16'). The combined olefinic ester 16' was then reduced to 17a', which yielded (-)-grandisol 1a' via 17b', 18' and 19'. The overall yield of 1a' from 9a was 9.7 %. The spectral data of 1a' were indistinguishable from those of 1a, although its plain positive ORD curve was antipodal to that of 1a.

To confirm the high enantiomeric purity of our grandisol enantiomers, 1a and 1a' were converted to the corresponding (R)-α-methoxy-α-trifluoromethylphenylacetates (MTPA esters)[28] 1b and 1b'. Their 400 MHz ^1H NMR spectra firmly established the satisfactory enantiomeric purity (100 % e.e.) of our 1a and 1a'. In the case of 1b, a 3 H singlet due to the Me group at C-1 appeared at δ 1.152, while in the case of 1b', it was observed at δ 1.142. Neither contamination of 1b with 1b' nor that of 1b' with 1b could be detected.

Finally, a comment should be made on the specific rotations of grandisol enantiomers. Optical rotations of the enantiomers of grandisol reported to date are listed in Table 1.

Table 1. Optical rotations of the enantiomers of grandisol.*

Compound		$[\alpha]_D$ of (+)-1a	$[\alpha]_D$ of (-)-1a'
Magnus's	1a[9]	+16.7°(c= 1, at 21.5°)	
Mori's	1a[10]	+15.7°(c= 0.23, at 20°)	
Mori's	1a'[10]		-16°(c= 0.14, at 22°)
Mori's	1a'[11]		-18.2°(c= 1.3, at 22°)
Jones's	1a[12]	+14.8°(c= 1, at 25°)	
Meyers's	1a'[13]		-16°(c= 1, temp not specified)
Silverstein's	1a[14]	+18.4°(c= 1.1, at 25°)	
Silverstein's	1a'[14]		-18.1°(c= 1.2, at 25°)
The present samples**		+20.5°(c= 0.585, at 24.2°)	-20.0°(c= 0.535, at 23.8°)

* measured as n-hexane soln.

** The values were calibrated by measuring the $[\alpha]_D$-value (+66.9° and +67.0°) of pure saccharose in water (c= 1.001 and 1.000, at 24°)

Magnus estimated the specific rotation of pure (+)-grandisol 1a to be +18.5° basing on the enantiomeric purity (90 % e.e.) of his starting material.[9] We estimated it to be +20° basing on the direct determination by ^1H NMR of the enantiomeric purity of a synthetic intermediate.[10] Meyers's (-)-1a' was reported to be of 88 % e.e., and accordingly his estimation for the $[\alpha]_D$ value of pure (-)-1a' was -18.2°. Jones regarded his (+)-1a as pure as 100 % e.e.,[12] although his specific rotation value was slightly smaller than the values reported by others. The present samples of our grandisol enantiomers after distillation showed the $[\alpha]_D$ values of ca. ±20°, which were in good accord with the values predicted by us.[10] The $[\alpha]_D$ values (+18.4° and -18.1°)[14] of Silverstein's pure 1a and 1a' are slightly smaller than our present values. It is not clear whether the values recorded by Silverstein refer to those obtained with distilled samples or not, since no b.ps were reported for their grandisol enantiomers.[14]

In conclusion, we were able to synthesize pure enantiomers of grandisol in amounts (290 mg of 1a and 81 mg of 1a') sufficient for the biological test. The overall yield of (+)-grandisol 1a from ethyl (R)-3-hydroxybutanoate 2 was 1.9 % in 16 steps, while that of (-)-1a' was 0.5 %. The bioassay of our samples is now under way by Dr. J. C. Dickens of the U.S. Department of Agriculture.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrophotometer unless otherwise stated. ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard at 100 MHz on a JEOL JNM FX-100 spectrometer unless otherwise stated. ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as an internal standard at 25 MHz on a JEOL JNM FX-100 spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP 140 polarimeter. ORD spectra were measured on a Jasco J-20C spectropolarimeter. Mass spectra were recorded on a JEOL JMS DX-303 spectrometer at 70 eV. Fuji-Davison BW-820 MH were used for SiO_2 column chromatography.

(R)-1,3-Butanediol 3a. A soln of ethyl (R)-3-hydroxybutanoate 2 [66 g, 0.5 mol, $[\alpha]_D^{18.6}$ -44.4° (c=1.39, $CHCl_3$)] in dry ether (400 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (19 g, 0.5 mol) in dry ether (600 ml). The mixture was stirred for 1 h at room temp. The usual alkaline work-up gave an oil, which was distilled to give 39 g (86 %) of 3a, b.p. 86°/4.5 Torr; $n_D^{21.5}$ 1.4354; $[\alpha]_D^{21.5}$ -30.7° (c=1.47, EtOH) [lit.[20] $[\alpha]_D^{25}$ -30.5° (c=1.51, EtOH)]; MS: m/z 72 (M^+-18). Its IR and ^{1}H NMR spectra were identical with authentic ones.[21]

(R)-4-Trityloxy-2-butanol 3b. A soln of 3a (38.5 g, 0.428 mol) and trityl chloride (123 g, 0.44 mol) in dry pyridine (400 ml) was stirred overnight at room temp. The mixture was then poured into ice-conc. HCl and extracted with ether. The ether soln was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried (K_2CO_3) and concentrated in vacuo to give crude 3b (150 g). This was employed in the next step without further purification. A small portion of it was purified by SiO_2 chromatography to give an analytical sample, n_D^{22} 1.5911; $[\alpha]_D^{22}$ -2.5° (c=1.12, EtOH); νmax 3420 (s), 3170 (s), 2950 (s), 1600 (m), 1495 (s), 1450 (s), 1070 (s), 900 (s), 770 (s), 760 (s), 745 (s), 710 (s) cm^{-1}; ^{1}H NMR δ 1.16 (3H, d, J=6.2 Hz), 1.60-1.90 (2H, m), 2.82 (1H, OH), 3.05-3.50 (2H, m), 3.80-4.15 (1H, m), 7.10-7.50 (15H, m). (Found: C, 83.40; H, 7.26. Calc for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28 %).

(R)-3-(2-Methyl-2-propenyloxy)-1-trityloxybutane 4a. A soln of crude 3b (148 g) in dry DMF (300 ml) was added dropwise to a suspension of NaH (22.8 g, 60 % dispersion in mineral oil, 0.57 mol) in dry DMF (400 ml). The mixture was stirred at room temp for 2 h. To this was added dropwise a soln of CH_2=$CMeCH_2Cl$ (51.6 g, 0.57 mol) in dry DMF (100 ml) with external ice-cooling. After stirring at room temp for 20 min, the mixture was poured into ice-water and extracted with ether. The ether soln was washed with water and brine, dried (K_2CO_3) and concentrated in vacuo to give crude 4a (174 g). This was employed in the next step without further purification. A small portion of it was purified by SiO_2 chromatography to give an analytical sample, n_D^{22} 1.5668; $[\alpha]_D^{22}$ -13.2° (c=2.22, n-hexane); νmax 1660 (w), 1600 (w), 1495 (m), 1450 (s), 1070 (s), 900 (m), 760 (m), 745 (s), 710 (s) cm^{-1}; ^{1}H NMR δ 1.14 (3H, d, J=6.3 Hz), 1.65 (3H, s), 1.60-2.10 (2H, m), 3.00-3.30 (2H, m), 3.30-4.10 (3H, m), 4.60-5.00 (2H, m), 7.10-7.50 (15H, m). (Found: C, 83.60; H, 7.82. Calc for $C_{27}H_{32}O_2$: C, 83.90; H, 7.82 %). This sample of 4a solidified after leaving at room temp for several weeks, m.p. 31.7-32.5°.

(R)-3-(2-Methyl-2-propenyloxy)-1-butanol 4b. A soln of crude 4a (172 g) in 80 % AcOH aq soln (900 ml) was stirred overnight at 30°C. The precipitate was filtered off, and the filtrate was concentrated in vacuo. The residue was poured into water, neutralised with NaOH soln, saturated with NaCl and extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln, water and brine, dried (K_2CO_3) and concentrated in vacuo. The residue was distilled over K_2CO_3 to give 47.9 g (77.7 % from 3a) of 4b, b.p. 77°/6.5 Torr; n_D^{23} 1.4362; $[\alpha]_D^{23}$ -47.4° (c=1.25, EtOH); νmax 3400 (s), 3100 (w), 1660 (m), 1100 (m), 1055 (s), 900 (s) cm^{-1}; ^{1}H NMR δ 1.19 (3H, d, J=6.3 Hz), 1.77 (3H, s), 1.60-1.90 (1H, m), 2.68 (1H, OH), 3.40-4.30 (5H, m), 4.89 (1H, m), 5.00 (1H, m); MS: m/z 144 (M^+).

(R)-3-(2-Methyl-2-propenyloxy)butanoic acid 5. Jones reagent (8 N, 125 ml) was added dropwise to a stirred and ice-cooled soln of 4b (43.2 g, 0.3 mol) in acetone (600 ml). 2-Propanol was added to destroy the excess Jones reagent. Acetone soln was decanted and concentrated in vacuo. The green residue was dissolved in brine and extracted with ether. The combined organic layer was washed with brine and extracted with 1 M K_2CO_3 soln. Aqueous layer was acidified with 6 N HCl, saturated with NaCl and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give 39.3 g (83 %) of crude 5. This was employed in the next step without further purification. A small portion of it was purified by SiO_2 chromatography to give an analytical sample, n_D^{21} 1.4369; $[\alpha]_D^{21}$ -20.5° (c=0.945, EtOH); νmax 3100 (br. s), 1720 (s), 1660 (m), 1140 (s), 1090 (s), 1060 (s), 905 (s) cm^{-1}; ^{1}H NMR δ 1.27 (3H, d, J=6.2 Hz), 1.75 (3H, s), 2.51 (1H, dd, J=15.5, 5.8 Hz), 2.61 (1H, dd, J=15.5, 6.9 Hz), 3.75-4.10 (3H, m), 4.89 (1H, m), 5.00 (1H, m), 8.40 (1H, br, COOH); MS m/z 158 (M^+).

Diastereomeric mixture of (1S,4R,5R)-1,4-dimethyl-3-oxabicyclo[3.2.0]heptan-6-one 8a and its (1R,4R,5S)-isomer 9a. Oxalyl chloride (5.24 ml, 7.62 g, 60 mmol) was added to a stirred and ice-cooled soln of 5 (6.3 g, 40 mmol) in n-hexane (20 ml). The mixture was stirred at room temp until the disappearance of 5 as checked by IR (ca. 4 h). The mixture was then concentrated in vacuo to give crude 6, νmax 3110 (w), 1805 (s), 1660 (w), 1110 (m), 985 (m), 910 (m), 740 (m) cm^{-1}. This

was dissolved in CH_2Cl_2 (1.4 l) and the soln was stirred and heated under reflux. To this was added dropwise a soln of Et_3N (5.09 g, 50 mmol) in CH_2Cl_2 (400 ml) over a period of 4 h. After cooling, the mixture was concentrated in vacuo at 0°. The products of six batches were combined and diluted with n-pentane. The n-pentane soln was washed with dil. HCl, 1 M K_2CO_3 soln and brine, dried ($MgSO_4$) and concentrated in vacuo at 0°. The residue was distilled to give 23.7 g (70.4 %) of a mixture of 8a and 9a, vmax 1780 (s) cm^{-1}; GLC (Column, 5 % FFAP, 2 m x 4 mm at 80°+3°/min; Carrier gas, N_2, 1.0 kg/cm^2): Rt 8a 17.4 (75 %), 9a 18.3 (22 %) min. This was employed in the next step without further purification.

(1S,4R,5S,6R)-1,4-Dimethyl-3-oxabicyclo[3.2.0]heptan-6-ol 10 and its (1R,4R,5R,6S)-isomer 11. A soln of the mixture of 8a and 9a (23.6 g, 0.169 mol) in dry THF (70 ml) was added dropwise to a stirred and cooled soln of LiBH(s-Bu)$_3$ (L-selectride®, 1 M in THF, 330 ml, 0.33 mol) at -70° under Ar. After stirring at -70° for 2 h, NaOAc soln (1 M, 33 ml) followed by H_2O_2 (35 %, 160 ml) was added dropwise to the mixture below 10°, and the mixture was stirred at room temp for 30 min. This was diluted with ether, washed with brine, 20 % $Na_2S_2O_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 900 g, n-hexane:ether=4:1).

Fractions eluted earlier gave 12.2 g (51.0 %) of pure 10, b.p. 81°/7.5 Torr; n_D^{21} 1.4673; $[\alpha]_D^{21}$ -40.0° (c=1.10, EtOH); vmax 3450 (s), 1160 (m), 1075 (m), 1040 (s), 850 (m) cm^{-1}; ^1H NMR δ 1.22 (3H, s), 1.58 (3H, d, J=7.0 Hz), 1.65-2.00 (1H, m), 2.20-2.50 (2H, m), 2.40 (1H, OH), 3.34 (1H, d, J=9.5 Hz), 3.83 (1H, d, J=9.5 Hz), 3.94 (1H, dq, J=5.3, 7.0 Hz), 4.40 (1H, m); ^{13}C NMR δ 15.6, 21.5, 41.0, 43.3, 52.9, 65.7, 79.6, 80.1; GLC (Column, 5 % FFAP, 2 m x 4 mm at 80°+3°/min; Carrier gas, N_2, 1.0 kg/cm^2): Rt 23.2 (single peak) min; TLC (Merck Kieselgel 60 F-254, Art 5715, n-pentane:ether=1:3): Rf 0.41. HRMS: m/z Found: 142.1068. Calc for $C_8H_{14}O_2$: 142.0994.

Fractions eluted later gave a mixture of 10 and 11 (1.0 g, 4.2 %).

Fractions eluted still later gave 3.3 g (13.8 %) of pure 11, b.p. 87.5°/5 Torr; $n_D^{23.5}$ 1.4493; $[\alpha]_D^{23.5}$ +21.0° (c=0.80, EtOH); vmax 3430 (s), 1165 (s), 1115 (s), 1080 (s), 1040 (s), 855 (m), 810 (m) cm^{-1}; ^1H NMR δ 1.16 (3H, d, J=6.7 Hz), 1.28 (3H, s), 1.82 (1H, dd, J=7.0, 13.5 Hz), 2.10-2.50 (3H, m), 3.48 (1H, d, J=8.9 Hz), 3.60 (1H, d, J=8.9 Hz), 4.27 (1H, q, J=7.7 Hz), 4.56 (1H, br.q, J=6.7 Hz); ^{13}C NMR δ 20.0, 21.8, 40.7, 42.7, 57.1, 61.7, 74.4, 76.7; GLC (Column, 5 % FFAP, 2 m x 4 mm at 80°+3°/min; Carrier gas, N_2, 1.0 kg/cm^2): Rt 26.6 (single peak) min; TLC (Merck Kieselgel 60 F-254, Art 5715, n-pentane:ether=1:3): Rf 0.30. HRMS: m/z Found: 142.0974. Calc for $C_8H_{14}O_2$: 142.0994.

1,4-Dimethyl-3-oxabicyclo[3.2.0]heptan-6-one.

(a) (1S,4R,5R)-isomer 8a. A soln of DMSO (6.2 ml, 80 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise to a stirred and cooled soln of $(COCl)_2$ (3.49 ml, 5.08 g, 40 mmol) in dry CH_2Cl_2 (80 ml) at -60° under Ar. To this mixture was added dropwise a soln of 10 (3.9 g, 27.5 mmol) in dry CH_2Cl_2 (30 ml) at -60°. After stirring at -60° for 2 h, Et_3N (8.4 ml, 6.12 g, 60 mmol) was added to the mixture. The reaction temp was allowed to raise to 0° and this temp was maintained for 1 h. Water was added and the mixture was diluted with n-pentane. The organic soln was washed with water, dil. HCl and brine, dried ($MgSO_4$) and concentrated in vacuo at 0° to give 3.4 g (87.3 %) of crude 8a. This was employed in the next step without further purification. An analytical sample was purified by distillation, b.p. 92°/16 Torr; $n_D^{17.5}$ 1.4504; $[\alpha]_D^{17.5}$ +165° (c=0.62, n-hexane); vmax 1775 (vs), 1250 (m), 1220 (m), 1120 (m), 1100 (m), 1070 (s), 1030 (s), 950 (m), 850 (m) cm^{-1}; ^1H NMR δ 1.35 (3H, d, J=6.0 Hz), 1.46 (3H, s), 2.80-3.20 (3H, m), 3.60 (1H, d, J=9.5 Hz), 4.07 (1H, d, J=9.5 Hz), 3.85-4.15 (1H, m). HRMS: m/z Found: 140.0859. Calc for $C_8H_{12}O_2$: 140.0837.

(b) (1R,4R,5S)-isomer 9a. In the same manner as described above, 2.13 g (15 mmol) of 11 yielded crude 9a quantitively. This was employed in the next step without further purification. An analytical sample was purified by distillation, b.p. 72°/12 Torr; n_D^{24} 1.4479; $[\alpha]_D^{24}$ -123° (c=0.44, n-hexane); vmax 1785 (s), 1265 (m), 1235 (m), 1110 (s), 1040 (s), 995 (m), 865 (m), 850 (m) cm^{-1}; ^1H NMR δ 1.16 (3H, d, J=6.7 Hz), 1.55 (3H, s), 2.7-3.2 (3H, m), 3.77 (1H, d, J=9.3 Hz), 4.01 (1H, d, J=9.3 Hz), 4.52 (1H, br.q, J=6.7 Hz). HRMS: m/z Found: 140.0798. Calc for $C_8H_{12}O_2$: 140.0837.

Determination of the enantiomeric purity of 8a and 9a.

(a) Racemate. A soln of a mixture of (±)-8a and (±)-9a (ca. 3:1, 42 mg, 0.3 mmol), (2R,3R)-2,3-butanediol (Aldrich, 45 mg, 0.5 mmol) and p-TsOH (catalytic amount) in C_6H_6 (0.5 ml) was refluxed for 2 h with azeotropic removal of water by using MS-3A. The mixture was directly purified by prep. TLC (Merck Kieselgel 60 F-254, Art 5744, n-hexane:EtOAc=4:1) to give two components. Less polar component, TLC (Merck Kieselgel 60 F-254, Art 5715, n-hexane:EtOAc=4:1): Rf 0.48, GLC (Column, OV-101, 50 m x 0.25 mm at 140°; Carrier gas, N_2, 1.6 kg/cm^2): Rt 36.6 (8b, 55.4 %), 40.2 (12, 43.7 %) min. More polar component, TLC (under the same condition as described above): Rf 0.43. GLC (under the same condition as described above): Rt 37.7 (13, 50.9 %), 39.1 (9b, 43.3 %) min.

(b) 8a. A soln of 8a (14 mg, 1 mmol), (2R,3R)-2,3-butanediol (18 mg, 2 mmol) and p-TsOH (catalytic amount) in C_6H_6 (0.3 ml) was refluxed for 2 h with azeotropic removal of water by using MS-3A. The mixture was diluted with ether, and washed with water, sat. $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was directly employed for the GLC analysis. GLC (under the same condition as described above): Rt 36.7 (8b, single peak) min. This peak coincided with the former peak of the less polar component by the co-injection test. Therefore, the enantiomeric purity of 8a was proved to be 100 % e.e. In addition, the diastereomeric purity of 8a was proved to be 100 %.

(c) 9a. In the same manner as described above, 9a was converted to the corresponding acetal. GLC (under the same condition as described above): Rt 44.7 (9b, single peak) min. This peak coincided with the latter peak of the more polar component by the co-injection test. Therefore, the enantiomeric purity of 9a was proved to be 100 % e.e. The diastereomeric purity of 9a was also proved to be 100 %.

1,4-Dimethyl-3-oxabicyclo[3.2.0]heptane.

(a) (1S,4R,5R)-Isomer 14. A soln of 8a (3.4 g, 24 mmol) and $N_2H_4 \cdot H_2O$ (3.6 g, 72 mmol) in diethylene glycol (36 ml) was heated at 100° for 2 h. Then, KOH (4.03 g, 72 mmol) and water (5 ml) was added to the mixture and the reaction temp was raised to 180°. During the reaction, the product was removed from the reaction mixture by means of steam distillation. The distillate was saturated with NaCl and extracted with n-pentane. The n-pentane soln was washed with brine, dried ($MgSO_4$) and concentrated at atmospheric pressure. The residue was distilled to give 2.0 g (56.3 % from 10) of 14, b.p. 127-128°; $[\alpha]_D^{18.5}$ -66.0° (c=0.50, n-hexane); vmax 2710 (w), 2640 (w), 1085 (m), 1040 (s), 850 (m) cm^{-1}; ^1H NMR δ 1.22 (3H, s), 1.23 (3H, d, J=7.0 Hz), 1.60-1.90 (4H, m), 2.15-2.40 (1H, m), 3.28 (1H, d, J=9.0 Hz), 3.75 (1H, d, J=9.0 Hz), 3.87 (1H, dq, J=7.0, 7.0 Hz); MS: m/z 126 (M^+).

(b) (1R,4R,5S)-Isomer 14'. In the same manner as described above, 2.1 g (15 mmol) of 9a yielded 1.8 g (95.8 % from 11) of 14' before distillation. An analytical sample was purified by distillation, b.p. 79°/145 Torr; $[\alpha]_D^{22}$ +19.1° (c=0.86, n-hexane); vmax 2700 (w), 1140 (m), 1105 (m), 1030 (s), 990 (m), 840 (m) cm^{-1}; ^1H NMR δ 1.09 (3H, d, J=6.6 Hz), 1.28 (3H, s), 1.50-2.20 (5H, m), 3.52 (1H, d, J=9.1 Hz), 3.70 (1H, d, J=9.1 Hz), 4.07 (1H, br.q, J=6.6 Hz); MS: m/z 126 (M^+).

RuO_4 oxidation study on the diastereomeric mixture of (±)-1,4-dimethyl-3-oxabicyclo[3.2.0]heptane. A two-phase mixture of (±)-1,4-dimethyl-3-oxabicyclo[3.2.0]heptane [ca. 3:1 mixture of (±)-14 and (±)-14', 1.26 g, 10 mmol], $NaIO_4$ (10.7 g, 50 mmol), RuO_2 (66.5 mg, 0.5 mmol), CCl_4 (20 ml), MeCN (20 ml) and phosphate buffer (pH 7, 0.05 M, 30 ml) was stirred for 10 min. To this mixture was added ether and the precipitate was filtered off. The aqueous layer was separated and extracted with ether. The combined organic soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give 4 components [starting materials, (±)-20, (±)-22 and (±)-23]. The hemiacetal (±)-22 was isolated by SiO_2 column chromatography, and treated with $Ph_3P{=}CH_2$ in DME. The reaction mixture was directly purified by prep. TLC. The resulting olefinic alcohol was submitted to NMR analysis [^{1}H NMR δ 1.22 (3H, s), 1.77 (3H, br.s), 2.63 (1H, br.t, J=8.9 Hz), 3.49 (1H, d, J=11.4 Hz), 3.60 (1H, d, J=11.4 Hz), 4.77 (1H, m), 4.87 (1H, m).], and identified as (±)-17a.

Methyl (1R,2R)-2-acetyl-1-methylcyclobutanecarboxylate 15. A two-phase mixture of 14 (1.95 g, 15.5 mmol), RuO_2 (133 mg, 1 mmol), $NaIO_4$ (21.4 g, 0.1 mol), CCl_4 (31 ml), MeCN (31 ml) and phosphate buffer (pH 7, 0.05 M, 47 ml) was stirred at room temp for 12 h. To this mixture was added ether and the precipitate was filtered off. The aqueous layer was separated and extracted with ether, and the combined organic soln was washed with brine. A soln of CH_2N_2 in ether was added to the organic soln and it was stirred at room temp for 30 min. AcOH was added to destroy the excess CH_2N_2. After the addition of some amount of CH_2N_2 in ether, the mixture was dried ($MgSO_4$) and concentrated in vacuo to give 2.35 g (89.2 %) of crude 15, vmax 1715 (s), 1300 (s), 1140 (s) cm^{-1}; ^{1}H NMR δ 1.52 (3H, s), 2.10 (3H, s), 1.70-2.50 (4H, m), 3.07 (1H, br.t, J=7.3 Hz), 3.67 (3H, s). This was employed in the next step without further purification.

Methyl (1R,2S)-2-isopropenyl-1-methylcyclobutanecarboxylate 16. A soln of n-BuLi (1.57 N in n-hexane, 31.8 ml, 50 mmol) was added dropwise to a stirred and ice-cooled suspension of Ph_3PMeBr (19.6 g, 55 mmol) in dry DME (120 ml) under Ar. The mixture was stirred at 0° for 1 h and allowed to settle. The salt-free supernatant (50 ml) was taken up in an another flask, and a soln of 15 (2.4 g) in dry DME (20 ml) was added dropwise to the mixture. After stirring at room temp for 2 h, water (1 ml) was added and the mixture was concentrated in vacuo. The residue was filtered through SiO_2 to remove Ph_3PO to give crude 16 (2.0 g). vmax 3110 (m), 1725 (s), 1650 (m), 995 (m), 890 (s) cm^{-1}; ^{1}H NMR δ 1.45 (3H, s), 1.69 (3H, br.s), 1.60-2.50 (4H, m), 2.81 (1H, br.t, J=9.3 Hz), 3.63 (3H, s), 4.66 (1H, m), 4.78 (1H, m). Only a trace amount of trans-isomer was detected by ^{1}H NMR. This was employed in the next step without further purification.

A mixture of methyl (1R,2S)-2-acetyl-1-methylcyclobutanecarboxylate 15' and (1R,4R,5S)-1,4-dimethyl-3-oxabicyclo[3.2.0]-heptan-2-one 20. In the same manner as described for the preparation of 15, 1.76 g (14 mmol) of 14' yielded a mixture of 15' and 20 (ca. 1:2 by ^{1}H NMR). ^{1}H NMR δ 1.31 (d, J=6.6 Hz), 1.42 (s), 1.52 (s), 2.10 (s), 3.07 (br.t, J=7.3 Hz), 3.67 (s), 4.47 (br.q, J=6.6 Hz). Because the separation of 15' and 20 was somewhat difficult, the mixture was employed in the next step without further purification.

Methyl (1R,2R)-2-isopropenyl-1-methylcyclobutanecarboxylate 16' and (1R,4R,5S)-1,4-dimethyl-3-oxabicyclo[3.2.0]heptan-2-one 20. In the same manner as described for the preparation of 16, the mixture of 15' and 20 yielded a mixture of 16' and 20. This was further purified by SiO_2 chromatography.

Fractions eluted earlier gave 600 mg (25.5 % from 14') of 16', b.p. 80-110°/33 Torr (bath temp); n_D^{24} 1.4459; $[\alpha]_D^{24}$ +73.7° (c=0.55, n-hexane) [lit.[13] $[\alpha]_D$ +24.3° (c=1, n-hexane)]. IR and ^{1}H NMR spectra were identical with those of 16. A small amount of the trans-isomer (~5 %) was detected by ^{1}H NMR (δ 1.17 and 3.70). This was employed in the next step without further purification.

Fractions eluted later gave 840 mg (42.9 % from 14') of 20, n_D^{22} 1.4474; $[\alpha]_D^{22}$ -65.3° (c=0.50, n-hexane); vmax 1760 (s), 1235 (m), 1150 (s), 1105 (s), 1020 (s), 930 (s) cm^{-1}; ^{1}H NMR δ 1.31 (3H, d, J=6.6 Hz), 1.42 (3H, s), 1.70-2.60 (5H, m), 4.47 (1H, br.q, J=6.6 Hz). HRMS: m/e Found: 140.0878. Calc for $C_8H_{12}O_2$: 140.0837.

Conversion of 20 to 16'.

Methyl (1R,2S,1'R)-2-(1'-hydroxyethyl)-1-methylcyclobutanecarboxylate 21. A mixture of 20 (70 mg, 0.5 mmol), 2 N KOH aq soln (1 ml) and MeOH (10 ml) was heated at 50° for 7 h. After cooling, the mixture was concentrated in vacuo, and the alkaline residue was diluted with ether. AcOH (0.3 ml) was added with vigorous stirring, and the mixture was stirred for 2 min. A soln of CH_2N_2 in ether was added to the mixture. After stirring for 15 min, AcOH was added to destroy the excess CH_2N_2. The mixture was dried ($MgSO_4$) and concentrated in vacuo to give 21 (95 mg) quantitivly, vmax 3500 (s), 1720 (s) cm^{-1}; ^{1}H NMR δ 1.04 (3H, d, J=6.2 Hz), 1.45 (3H, s), 1.50-2.70 (6H, m), 3.64 (1H, dq, J=9.7, 6.2 Hz), 3.77 (3H, s). This was employed in the next step without further purification.

Methyl (1R,2S)-2-acetyl-1-methylcyclobutanecarboxylate 15'. A soln of DMSO (213 μl, 3 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise to a stirred and cooled soln of $(COCl)_2$ (131 μl, 1.5 mmol) in dry CH_2Cl_2 (3 ml) at -60° under Ar. To this mixture was added dropwise a soln of crude 21 (95 mg) in dry CH_2Cl_2 (1 ml) at -60°. After stirring at -60° for 1 h, Et_3N (354 μl, 5 mmol) was added to the mixture. The reaction temp was allowed to raise to 0° and this temp was maintained for 3 h. Water was added, and the mixture was diluted with ether. The organic soln was washed with water, dil. HCl and brine, dried ($MgSO_4$) and concentrated in vacuo to give crude 15' (90 mg). Its IR and ^{1}H NMR spectra were identical with those of 15. This was employed in the next step without further purification.

Methyl (1R,2R)-2-isopropenyl-1-methylcyclobutanecarboxylate 16'. In the same manner as described for the preparation of 16, crude 15' (90 mg) yielded 51.5 mg (61.3 % from 20) of 16'. Its IR and ^{1}H NMR spectra were identical with those of 16. The trans-isomer was not detected by ^{1}H NMR.

2-Isopropenyl-1-methylcyclobutanemethanol.

(a) (1R,2S)-Isomer 17a. A soln of 16 (2.0 g, 11.9 mmol) in dry ether (20 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (380 mg, 10 mmol) in dry ether (20 ml). The mixture was stirred at room temp for 1 h. The usual alkaline work-up gave crude 17a (quant.), vmax 3400 (s), 3110 (m), 1650 (m), 1030 (s), 890 (s) cm^{-1}; ^{1}H NMR δ 1.22 (3H, s), 1.77 (3H, br.s), 1.60-2.20 (5H, m), 2.63 (1H, br.t, J=8.9 Hz), 3.49 (1H, d, J=11.4 Hz), 3.60 (1H, d, J=11.4 Hz), 4.77 (1H, m), 4.87 (1H, m). This was employed in the next step without further purification.

(b) (1R,2R)-Isomer 17a'. In the same manner as described above, 580 mg (3.45 mmol) of 16' yielded crude 17a', which was purified by column chromatography (Lobar® Grosse B, n-pentane:ether=20:1) to give 330 mg (68.3 %) of pure 17a' (100 % cis by GLC), $[\alpha]_D^{24}$ -3° (c=0.245, n-hexane) [lit.[13] $[\alpha]_D$ -8±3° (c=1, n-hexane)]; GLC (Column, 10 % PEG-20M, 2 m x 4 mm at 80°+3°/min; Carrier gas, N_2, 1.0 kg/cm^2): Rt 16.5 (single peak) min; MS: m/e 140 (M^+). Its IR and ^{1}H NMR spectra were identical with those of 17a.

2-Isopropenyl-1-methylcyclobutaneethyl p-toluenesulfonate.
(a) (1R,2S)-Isomer 17b. p-TsCl (4.2 g, 22 mmol) was added to a stirred and ice-cooled soln of crude 17a (1.66 g) in dry pyridine (30 ml). The mixture was stirred overnight at room temp. Water (1 ml) was added, and the mixture was stirred for 1 h. The mixture was poured into ice-dil. HCl and extracted with ether. The ether soln was washed with water, sat. $CuSO_4$ soln, water, sat. $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 2.55 g (72.7 % from 16) of 17b as an oil, νmax 3100 (w), 1645 (w), 1600 (m), 1360 (m), 1190 (s), 1180 (s), 1100 (m), 960 (s), 840 (s), 670 (m) cm^{-1}. This crystallized after storage in a freezer. It was then recrystallized from n-pentane (80 % recovery) to give pure 17b, m.p. 50.5-50.9°. Due to its instability even at low temp, this was employed in the next step without delay.
(b) (1R,2R)-Isomer 17b'. In the same manner as described above, 310 mg (2.2 mmol) of 17a' yielded 530 mg (82 %) of 17b' as crystals. This was recrystallized from n-pentane (89 % recovery) to give pure 17b', m.p. 50.5-50.9°. Due to its instability even at low temp, this was employed in the next step without delay. Its IR spectrum was identical with that of 17b. Analytical sample: $[\alpha]_D^{24}$ +23° (c=0.66, n-hexane); ^1H NMR δ 1.20 (3H, s), 1.63 (3H, br.s), 1.50-2.10 (4H, m), 2.45 (3H, s), 2.63 (1H, br.t, J=8.4 Hz), 3.84 (1H, d, J=9.6 Hz), 3.97 (1H, d, J=9.6 Hz), 4.57 (1H, m), 4.73 (1H, m), 7.35 (2H, br.d, J=8.4 Hz), 7.77 (2H, br.d, J=8.4 Hz).

2-Isopropenyl-1-methylcyclobutaneacetonitrile.
(a) (1R,2S)-Isomer 18. A soln of 17b (2.05 g, 6.97 mmol), NaCN (0.85 g, 17.3 mmol) and water (0.04 ml) in HMPA (7.5 ml) was stirred at 80° for 7 h.[cf. 27] The mixture was poured into water and extracted with n-pentane. The n-pentane soln was washed with water, sat. $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo at 0°. The residue was purified by SiO_2 column chromatography to give 800 mg (77 %) of 18, b.p. 81°/8 Torr; $n_D^{24.2}$ 1.4582; $[\alpha]_D^{24.2}$ +47.3° (c=0.68, n-hexane); νmax 3100 (m), 2260 (m), 2150 (trace, isonitrile), 1645 (s), 1300 (m), 1240 (m), 890 (s) cm^{-1}; ^1H NMR δ 1.37 (3H, s), 1.69 (3H, br.s), 1.70-2.10 (4H, m), 2.14 (1H, d, J=16.5 Hz), 2.45 (1H, d, J=16.5 Hz), 2.71 (1H, br.t, J=8.8 Hz), 4.71 (1H, m), 4.93 (1H, m); GLC (Column, OV-101, 50 m x 0.25 mm at 80°+2°/min; Carrier gas, N_2, 1.5 kg/cm^2): Rt 40.53 (single peak) min. MS: m/z 149 (M^+).
(b) (1S,2R)-Isomer 18'. In the same manner as described above, 470 mg (1.6 mmol) of 17b' yielded 190 mg (80 %) of 18', b.p. 82.5°/8.5 Torr; n_D^{25} 1.4594; $[\alpha]_D^{25}$ -44.6° (c=0.275, n-hexane) [lit.[13] $[\alpha]_D$ -20.3° (c=1, n-hexane)]; MS: m/z 149 (M^+). Its IR and ^1H NMR spectra were identical with those of 18.

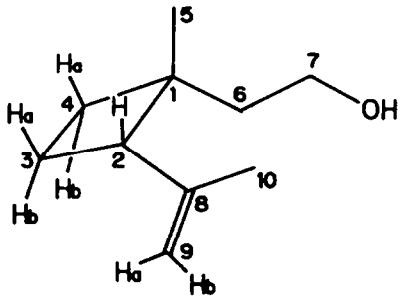
2-Isopropenyl-1-methylcyclobutaneethanol (Grandisol).
(a) (1R,2S)-Isomer [(+)-Grandisol] 1a. $(i\text{-Bu})_2AlH$ (DIBAL-H, 1 M in n-hexane, 7 ml, 7 mmol) was added dropwise to a stirred and ice-cooled soln of 18 (700 mg, 4.7 mmol) in dry n-pentane (20 ml). The mixture was stirred at room temp for 2 h. L-Tartaric acid aq soln (1 M, 7 ml) was added, and the mixture was stirred at room temp for 1 h. The mixture was filtered, and the aqueous layer was extracted with ether. The combined organic soln was washed with sat. $NaO_2CCH(OH)CH(OH)CO_2K$ soln, sat. $NaHCO_3$ soln and brine and dried ($MgSO_4$). To this soln (ca. 50 ml) was added portionwise LAH (180 mg, 4.7 mmol) with external ice-cooling, and the mixture was stirred at room temp for 2 h. The usual alkaline work-up gave an oil, which was purified by SiO_2 column chromatography followed by distillation to give 290 mg (40 %) of 1a, b.p. 103°/9 Torr; $n_D^{24.2}$ 1.4671; $[\alpha]_D^{24.2}$ +20.6° (c=0.585, n-hexane, non-calibrated); $[\alpha]_D^{24.2}$ +20.5° (c=0.585, n-hexane, calibrated); ORD (c=1.3x10^{-2}, n-hexane, at 24°) [[α], ν (nm)] -2.90x10^3 (210), 0 (242), +77 (589); νmax 3350 (s), 3110 (m), 2970 (s), 2890 (s), 1645 (m), 1450 (m), 1380 (m), 1240 (w), 1055 (s), 1015 (m), 890 (s) cm^{-1}; νmax (CCl_4 soln) 3660 (m), 3100 (w), 2990 (s), 2975 (s), 2890 (m), 1645 (m), 1450 (m), 1377 (m), 1235 (w), 1115 (w), 1050 (m), 995 (w), 890 (s) cm^{-1} (This was identical with an authentic spectrum.); ^1H NMR (100MHz, CCl_4, JEOL JNM FX-100 spectrometer, C_6D_6 was used as an external lock signal) δ 0.85 (1H, OH), 1.17 (3H, s), 1.66 (3H, br.s), 1.20-2.20 (6H, m), 2.51 (1H, br.t, J=8.5 Hz), 3.57 (2H, t, J=7.4 Hz), 4.60 (1H, m), 4.79 (1H, m) (This was identical with an authentic spectrum.); ^{13}C NMR (complete decoupled and INEPT were carried out) δ 19.2 (t), 23.2 (q), 28.4 (q), 29.3 (t), 36.9 (t), 41.4 (s), 52.5 (d), 59.9 (t), 109.8 (t), 145.2 (s); GLC (Column, PEG-20M, 50 m x 0.25 mm at 120°; Carrier gas, N_2, 1.2 kg/cm^2): Rt 22.7 (single peak) min; HRMS: m/z Found: 154.1356. Calc for $C_{10}H_{18}O$: 154.1358. In addition, 61 mg (8.5 %) of (1R,2S)-2-isopropenyl-1-methylcyclobutaneacetaldehyde (19) was recovered. B.p. 94°/26 Torr; $n_D^{23.6}$ 1.4596; $[\alpha]_D^{23.6}$ +63.8° (c=0.87, n-hexane); νmax 3100 (m), 2960 (s), 2840 (m), 2740 (m), 1725 (s), 1645 (m), 890 (s) cm^{-1}; ^1H NMR δ 1.33 (3H, s), 1.68 (3H, br.s), 1.70-2.20 (4H, m), 2.21 (1H, dd, J=15.5, 3.1 Hz), 2.50 (1H, dd, J=15.5, 2.4 Hz), 2.64 (1H, br.t, J=7.9 Hz), 4.70 (1H, m), 4.86 (1H, m), 9.80 (1H, dd, J=2.4, 3.1 Hz). MS: m/z 152 (M^+).
(b) (1R,2R)-Isomer [(-)-Grandisol] 1a'. $(i\text{-Bu})_2AlH$ (DIBAL-H, 1 M in n-hexane, 1.5 ml, 1.5 mmol) was added dropwise to a stirred and ice-cooled soln of 18' (180 mg, 1.2 mmol) in dry n-pentane (5 ml). The mixture was stirred at room temp for 2 h. L-Tartaric acid aq soln (1 M, 1.5 ml) was added and the mixture was stirred at room temp for 1 h. The mixture was filtered, and the aqueous layer was extracted with ether. The combined organic soln was washed with sat. $NaO_2CCH(OH)CH(OH)CO_2K$ soln, sat. $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo at 0°. The residue was diluted with dry ether (5 ml). To this was added portionwise LAH (180 mg, 4.7 mmol) with external ice-cooling, and the mixture was stirred at room temp for 2 h. NaOH (2 μl) was added and the mixture was stirred at room temp for 20 min. The usual alkaline work-up gave an oil, which was purified by column chromatography followed by distillation to give 81 mg (43.8 %) of 1a', b.p. 84°/6 Torr; $n_D^{23.8}$ 1.4682; $[\alpha]_D^{23.8}$ -20.1° (c=0.535, n-hexane, non-calibrated); $[\alpha]_D^{23.8}$ -20.0° (c=0.535, n-hexane, calibrated); ORD (c=1.3x10^{-2}, n-hexane, at 24°) [[α], ν (nm)] +2.90x10^3 (210), 0 (242), -120 (589); GLC (Column, PEG-20M, 50 m x 0.25 mm at 120°; Carrier gas, N_2, 1.2 kg/cm^2): Rt 22.7 (single peak) min; HRMS: m/z Found: 154.1325. Calc for $C_{10}H_{18}O$: 154.1358. Its IR and ^1H NMR spectra were identical with those of 1a.

Determination of the enantiomeric purity of Grandisol.
1a and 1a' were converted to the corresponding (R)-MTPA[28] ester (1b and 1b'). 400 MHz ^1H NMR spectra (JEOL JNM GX-400 spectrometer) of 1b, 1b' and the mixture were measured in $CDCl_3$. The signal due to $-C_1-CH_3$ was observed at difference position. Mixture of 1b and 1b': δ 1.142 (s), 1.152 (s); 1b: δ 1.152 (s, 100 %); 1b': δ 1.142 (s, 100 %). Therefore, the enantiomeric purity of 1a and 1a' was proved to be 100 % e.e., respectively.

NMR studies on grandisol.

With detailed decoupling experiments, all the protons and carbons of grandisol were assigned as shown in Table 2. [500 MHz (^{1}H) and 126 MHz (^{13}C), Bruker AM-500 spectrometer, $CDCl_3$]

Table 2. ^{1}H and ^{13}C NMR data of grandisol



No.	^{13}C δ	J_{C-H} (Hz)	^{1}H δ	J_{H-H} (Hz)
1	41.4 (s)			
2	52.5 (d)	130	2.55 (dddddq)	0.9, 1.0, 1.9, 8.2, 10.2, 0.8
3 a	19.2 (t)	131	1.81 (dddd)	2.6, 8.2, 8.8, 11.2
b			1.97 (dddd)	9.1, 10.2, 10.2, 11.2
4 a	29.3 (t)	130	1.61 (dddd)	1.3, 8.8, 10.2, 10.9
b			1.68 (dddd)	0.9, 2.6, 9.1, 10.9
5	23.2 (q)	123	1.19 (s)	
6 a	36.9 (t)	123	1.45 (dddd)	1.3, 6.1, 9.2, 13.5
b			1.76 (ddd)	5.8, 9.2, 13.5
7 a	59.9 (t)	142	3.66 (ddd)	5.8, 9.2, 10.2
b			3.69 (ddd)	6.1, 9.2, 10.2
8	145.2 (s)			
9 a	109.8 (t)	155	4.84 (ddq)	1.0, 1.9, 1.6
b			4.65 (ddq)	1.9, 1.9, 0.8
10	28.4 (q)	125	1.68 (ddd)	0.8, 0.8, 1.6
-OH			1.57	

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