The Total Syntheses of (−)-Occidentalol and Its C_7-Epimer. The Stereochemical Assignment of (+)-Occidentalol[1,2]

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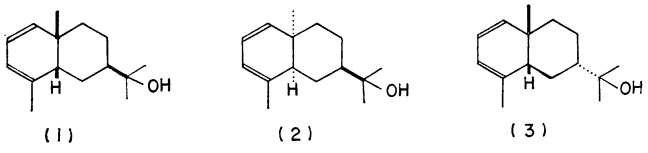
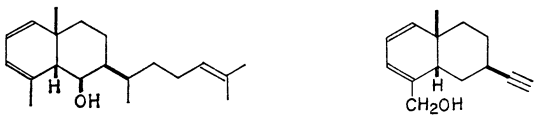
The total syntheses of (−)-occidentalol and its C_7-epimer are reported with the object of establishing the structure of naturally occurring (+)-occidentalol.

The sesquiterpene alcohol (+)-occidentalol was first isolated from the wood of Eastern white cedar (*Thuja occidentalis* L.) by Nakatsuka and Hirose.[3] Subsequent reports from various laboratories lead to the acceptance of the structure **1**.[4–7] In 1969, Hortmann and De Roos reported a careful analysis of 100 MHz NMR spectrum of (+)-occidentalol and suggested the structure **2** for (+)-occidentalol.[8] In 1970, we established the structure **2** for (+)-occidentalol by the syntheses of compound **1** and (−)-occidentalol (**3**).[2] After our syntheses had been completed, several other syntheses of (+) or (±)-occidentalol were reported.[9–14] Recent isolation and characterization of dehydrochamaecynenol[15] and dictyolene,[16] which possess similar structures to compound **1**, is interesting matter from the biosynthetic point of view. This paper details the total syntheses of **1** and (−)-occidentalol (**3**) with the object of establishing the structure of naturally occurring (+)-occidentalol and the stereochemical consideration of their related compounds.



(1) (2) (3)

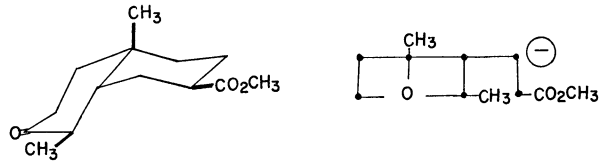


Dictyolene Dehydrochamaecynenol

Syntheses

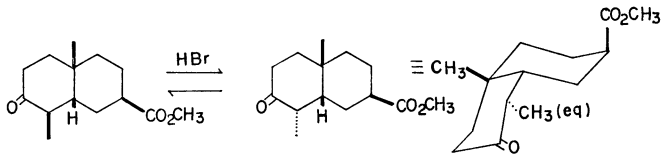
We chose an olefinic ketone (**4**) as the starting material since **4** was easily available from l-α-santonin by means of the previously reported method[17] and conveniently functionalized as the starting material of both **1** and **3**. We envisioned an approach which consisted of the transformation of the terminal olefine at C_7 of **4** to a methoxycarbonyl group (**4**→**7**), the introduction of a homoannular 1,3-diene unit (**7**→**14**), and its transformation to **1**, or the epimerization of the methoxycarbonyl group from β to α (**14**→**17**), and its transformation to **3**.

The treatment of **4** with four equivalent of $NaIO_4$ in the presence of a catalytic amount of OsO_4 gave a 1:1 mixture of a carboxylic acid (**6**) and an aldehyde (**5**). The latter was oxidized with Ag_2O to **6**. The compound (**6**) was methylated with CH_2N_2 to give the ester (**7**). In agreement with the structure of a *cis*-decalin derivative possessing the steroid conformation, the CD curve exhibited a negative Cotton effect.[18]



7 Steroid conformation $[\theta]_{270} = -1980$

Fig. 1.



7 **18** Non-steroid conformation

Fig. 2.

The bromination of **7** with Br_2 in acetic acid in the presence of HBr afforded two kinds of oily monobromides (**8** and **9**). The splitting patterns of the NMR signals due to the bromomethine protons, δ 4.72 (q, J=6.0 and 14.0 Hz) and δ 4.73 (q, J=6.0 and 12.0 Hz) for **8** and **9** respectively, indicated that both **8** and **9** were α-bromo ketones bearing the equatorial bromine atoms. Judging from the reaction conditions, both C_4–Me groups of **8** and **9** were deduced to be thermodynamically the more stable equatorial configuration. In addition, the β(*eq*)-configuration of the C_4–Me group of **8** and the α(*eq*)-configuration of the C_4–Me group of **9** were confirmed by the transformation of these compounds to the α,β-unsaturated ketones, **10** and **11**, respectively. The formation of the bromides **8** and **9** starting from **7** can be reasonably explained as follows. The ketone **7** was epimerized at C_4 in the presence of HBr to give an equilibrium mixture of **7** and its C_4-epimer, **18**. The bromination of **7** and **18** in the reaction mixture at the C_2-position gave **8** and **9**, respectively.

The dehydrobromination of **8** with LiBr–Li_2CO_3 in DMF produced an oily α,β-unsaturated ketone (**10**). In accordance with the stereo-structure **10** with the steroid conformation, as is shown in Fig. 3, the NMR spectrum (CCl_4, 100 MHz) did not show a long-range coupling between C_1–H and C–H.[19,20] The half-

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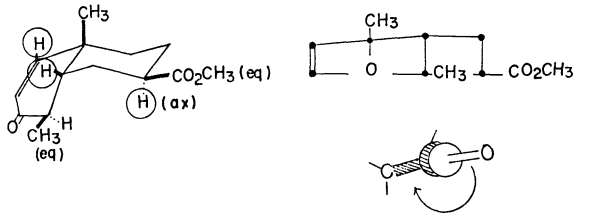
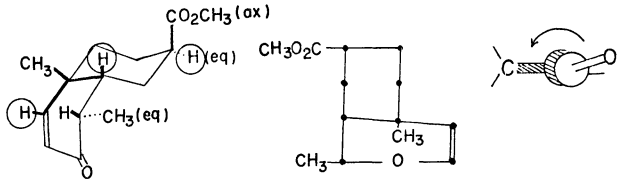


10 Steroid conformation $n\rightarrow\pi^*$ $[\theta]_{320}=-2580$
$\pi\rightarrow\pi^*$ $[\theta]_{225}=+33900$

Fig. 3.



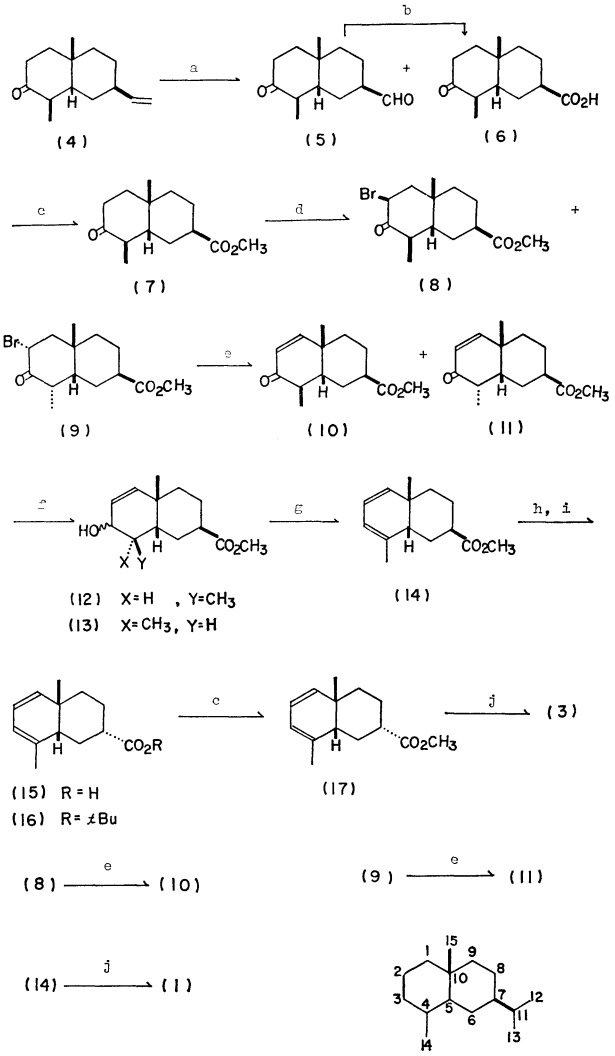
11 Non-steroid conformation $n\rightarrow\pi^*$ $[\theta]_{310}=+1200$
$\pi\rightarrow\pi^*$ $[\theta]_{225}=-12600$

Fig. 4.

band width of C_7–H was *ca.* 20 Hz, which agreed with the expected value of $\alpha(ax)$ C_7–H.[19] The β-equatorial configuration of the C_4–Me group of **10** was suggested from the solvent effect in the NMR spectrum on passing from CCl_4 to benzene ($\delta_{CCl_4}-\delta_{C_6H_6}=+0.01$ ppm)[21] and was confirmed from the coupling constant between C_4–H and C_5–H ($J=12.5$ Hz). The CD curve of **10** showed a negative Cotton effect at 320 nm for the $n\rightarrow\pi^*$ transition and a positive Cotton effect at 225 nm for the $\pi\rightarrow\pi^*$ transition[22] which agreed with the signs expected from the stereo-structure **10** with the steroid conformation bearing a $\beta(eq)$-methyl group at C_4 and a $\beta(eq)$-methoxycarbonyl group at C_7.

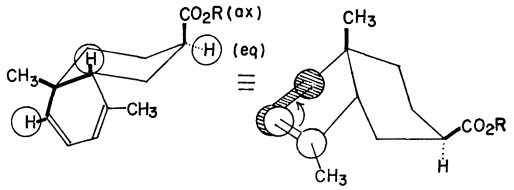
The dehydrobromination of **9** with LiBr–Li_2CO_3 in DMF gave an oily α,β-unsaturated ketone (**11**). In agreement with the stereo-structure **11**, as is shown in Fig. 4, the NMR (CCl_4, 100 MHz) spectrum showed a long-range coupling ($J=2.5$ Hz) between C_1–H and C_5–H.[19,20] The half-band width of C_7–H was *ca.* 10 Hz which agreed with the expected value of $\alpha(eq)$ C_7–H.[19] The α-equatorial configuration of the C_4–Me group of **11** was suggested from the solvent effect in the NMR spectrum on passing from CCl_4 to benzene ($\delta_{CCl_4}-\delta_{C_6H_6}=-0.09$ ppm)[21] and was confirmed from the coupling constant between C_4–H and C_5–H ($J=3.8$ Hz). The CD curve of **11** showed a positive Cotton effect at 310 nm for $n\rightarrow\pi^*$ transition and a negative Cotton effect at 225 nm for $\pi\rightarrow\pi^*$ transition[22] which agreed with the signs expected from the stereo-structure **11** with the non-steroid conformation bearing an $\alpha(eq)$-methyl group at C_4 and a $\beta(ax)$-methoxycarbonyl group at C_7.

The reduction of **10** and **11** with $NaBH_4$ gave an oily mixture of epimeric alcohols (**12**) and of epimeric alcohols (**13**), respectively. On being heated at 210 °C in the presence of alumina containing 4% of pyridine,[23] both mixtures of alcohols gave the same oily diene (**14**). The diene (**14**) was conveniently prepared from **7** by the same method described above, without the



a: OsO_4, $NaIO_4$; b: Ag_2O; c: CH_2N_2; d: HBr, Br_2; e: LiBr, Li_2CO_3, DMF; f: $NaBH_4$; g: Al_2O_3–Py; h: *t*-BuOK/*t*-BuOH; i: hydrolysis; j: MeMgI

Scheme 1.



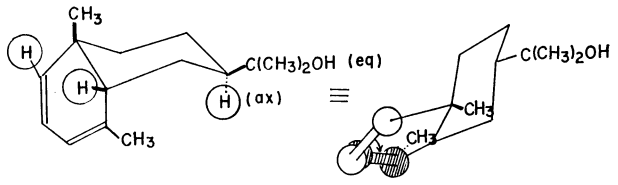
14 $R=CH_3$ $[\theta]_{259}=-33800$
19 $R=CH(CH_3)_2$ $[\theta]_{260}=-34200$
Non-steroid conformation

Fig. 5.

separation of the epimers in each step. The non-steroid conformation bearing the $\beta(ax)$-methoxycarbonyl group at C_7 for **14**, as is shown in Fig. 5, was revealed from the NMR spectrum which showed the long-range coupling between C_1–H and C_5–H ($J=1.0$ Hz)[8,19,20] and a rather small magnitude of the half-band width ($W_{h/2}=11$ Hz) of C_7–H.[19] The CD curve of **14** showed a negative Cotton effect at 259 nm due to the skewing of the *s-cis* butadiene moiety in the sense of a left-hand helix[24] which agreed with

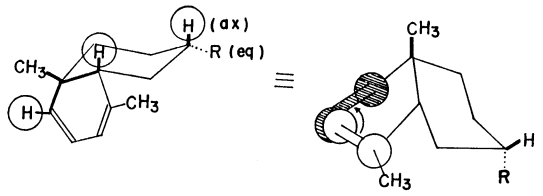
Table 1. The NMR spectral data of *s-cis* diene derivatives

Compound	Conformation	Chemical shifts of hydrogens (δ)						The orientation of the functional groups at C_7
		C_1-H	C_2-H	C_3-H	C_7-H	C_4-CH_3	C_{10}-CH_3	
1	Steroid	5.2—5.8 (3H, m)				1.80	1.10	β (*eq*)
2, 3	Non-steroid	5.21 (d)	5.74 (dd)	5.49 (m)		1.79	0.85	α (*eq*)
14	Non-steroid	5.22 (d)	5.76 (dd)	5.52 (m)	2.49 ($W_{h/2}$=11 Hz)	1.80	0.86	β (*ax*)
16	Non-steroid	5.27 (d)	5.80 (dd)	5.55 (m)		1.79	0.85	α (*eq*)
17	Non-steroid	5.28 (d)	5.81 (dd)	5.50 (m)		1.79	0.86	α (*eq*)
19[25]	Non-steroid	5.22 (d)	5.75 (dd)	5.51 (m)	2.44 ($W_{h/2}$=12 Hz)	1.79	0.85	β (*ax*)



1 Steroid conformation $[\theta]_{261}$= +27600

Fig. 6.



17 R=CO_2Me $[\theta]_{262}$= −49200
3 R=$C(CH_3)_2OH$ $[\theta]_{260}$= −56900
Non-Steroid conformation

Fig. 7.

the stereo-structure **14** with the non-steroid conformation bearing a β(*ax*)-methoxycarbonyl group at C_7.

The treatment of **14** with methylmagnesium bromide gave an unstable oily alcohol (**1**), which exhibited completely different IR (in $CHCl_3$), NMR (in CCl_4), CD (in MeOH), and MS (at 70 eV) from those of naturally occurring occidentalol. In accordance with the stereo-structure **1** with the steroid conformation, as is shown in Fig. 6, the CD curve of **1** showed a positive Cotton effect due to the skewing of *s-cis* butadiene moiety in the sense of right-hand helix.[24]

Since the structure **1**, the Rudloff's structure of (+)-occidentalol, was not identical with naturally occurring "(+)-occidentalol", our attention was focused on the synthesis of **3**, the C_7-epimer of **1**.

The treatment of **14** with 1 M (1 M=1 mol dm^{-3}) *t*-BuOK in *t*-BuOH under refluxing temperature for 2 h gave a mixture of a carboxylic acid (**15**) and the corresponding *t*-butyl ester (**16**). The hydrolysis of the latter with aqueous alkali and the combined acidic part was methylated subsequently with diazomethane to give a 1:22 mixture of **14** and **17**. The NMR spectrum of **17** was quite similar to that of **14** except the signal of C_7–H which was shifted to higher field than the corresponding signal of **14** and was overlapped with those of other protons. These NMR data

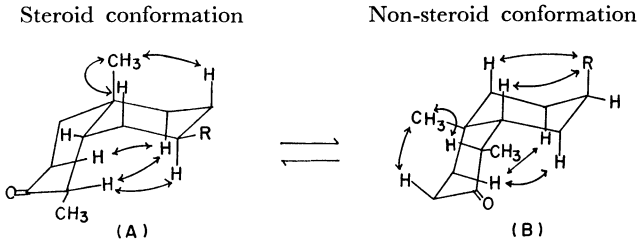


Fig. 8.

Table 2. Equilibration data for the **A**⇌**B** reaction at 25 °C

R	K (**B**/**A**)	ΔG/kcal mol^{-1}
-C≡CH	1.58	−0.27[17]
$-CO_2CH_3$	0.45	0.46
$-CH=CH_2$	0.16	1.09[17]
$-CH_2-CH_3$	(0)	[17]

strongly suggest that compounds **14** and **17** are stereoisomeric at C_7 position with each other and have the same non-steroid conformation. The CD curve of **17** showed a negative Cotton effect at 262 nm due to the skewing of the *s-cis* butadiene moiety in the sense of a left-hand helix[24] which agreed with the conclusion from the NMR data.

The treatment of **17** with methylmagnesium bromide gave an alcohol (**3**), which was identical with naturally occurring (+)-occidentalol in the NMR, IR, and MS but showed the opposite sign in the CD curves. These results indicate that the structure of naturally occurring "(+)-occidentalol" must be represented by the structure (**2**) and the alcohol (**3**) is its antipodal (−)-occidentalol (**3**).

The Stereochemical Studies of the Synthetic Intermediates

Equilibration of ***7***⇌***18*** *and* ***10***⇌***11***. The keto ester (**7**) was treated with a 2% KOH solution of ethanol for 6 h at 25 °C and then quenched by the use of aqueous acetic acid solution to give a 2.2:1.0 equilibrium mixture of **7** and **18**. The ΔG value of this equilibration at 25 °C was determined to be 0.46 kcal mol^{-1}. This ΔG value was compared with those of three pairs of *cis*-decalone derivatives possessing the different functional groups at C_7-position and summarized in Table 2. The examination of Dreiding models showed that the observed ΔG values

Steroid conformation Non-steroid conformation

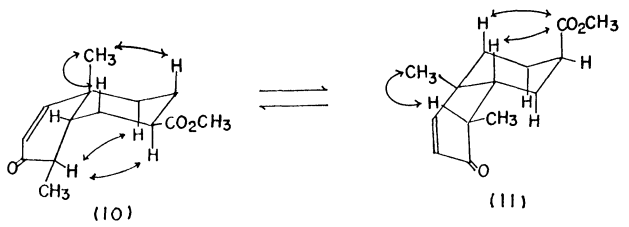


Fig. 9.

Steroid conformation Non-steroid conformation

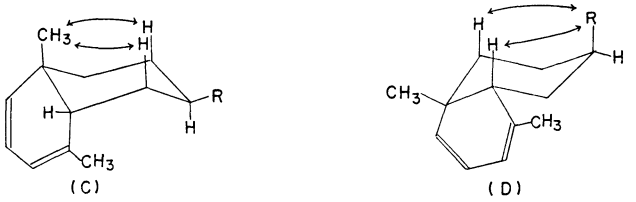


Fig. 10.

should reflect the difference between the one inner H–H interaction in the A-series compounds and the two R–H 1,3-diaxial interactions in the B-series compounds since two Me–H 1,3-diaxial interactions and two inner H–H interactions existed in both series compounds, as depicted in the stereo-structures **A** and **B**. Actually, the observed ΔG values, summarized in Table 2, reflect well the order of the bulkiness of R at C_7, $-CH_2CH_3 \gg -CH{=}CH_2 > -CO_2Me > -C{\equiv}CH$. The equilibrium reaction of α,β-unsaturated ketones **10** and **11** gave a tendency similar to that of the equilibrium reaction of **7** and **18**. The ΔG value is 0.37 kcal mol^{-1}, smaller than the latter case, because in **11** one Me–H interaction and two inner H–H interactions are eliminated compared with **18** by the introduction of a double bond at C_1, whereas in **10** one inner H–H interaction is eliminated compared with **7**.

The Stereochemistry of s-cis *Diene Derivatives.* For *s-cis* diene derivatives (**1**, **14**, and **19**) bearing a β-oriented substituent at C_7 there are two possible conformations, steroid conformation (**C**) and non-steroid conformation (**D**). The examination of Dreiding models showed there to be two Me–H 1,3-diaxial interactions in the conformer (**C**) as depicted by the arrows. On the other hand, in the conformer (**D**) there are two R–H 1,3-diaxial interactions as depicted by the arrows. Since the R–H 1,3-diaxial interaction is far bigger than that of Me–H in the case of R=–C-$(CH_3)_2OH$, the compound (**1**) exists exclusively in the steroid conformation (**C**).

When R is methoxycarbonyl or isopropoxycarbonyl group, the non-steroid conformation **D** may be expected to be the favored conformer by the following reasons. The methoxycarbonyl and isopropoxycarbonyl groups are planar and the magnitudes of the 1,3-diaxial interactions of these groups at C_7 and the two hydrogen atoms at C_5 and C_9 in the conformer **D** are smaller than those of the angular methyl group and two hydrogen atoms at C_6 and C_8 in the conformer (**C**). Actually **14** and the corresponding isopropyl ester (**19**)[25] exist exclusively in the non-steroid conformation (**D**).

Steroid conformation Non-steroid conformation

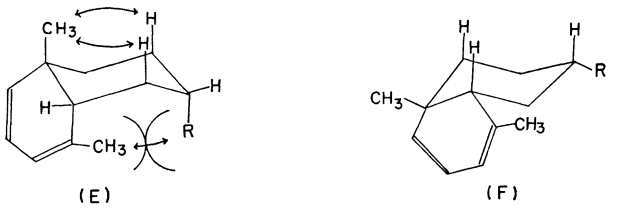


Fig. 11.

For *s-cis* diene derivatives (**3**, **16**, and **17**) bearing an α-oriented substituent at C_7 there are two possible conformations, the steroid conformation (**E**) and the non-steroid conformation (**F**). In the conformer **E** there is a big interaction between the axial substituent at C_7 and the A-ring in addition to two Me–H 1,3-diaxial interactions as depicted by the arrows, whereas there is no remarkable interaction in the conformer **F**. Actually all of the compounds **3**, **16**, and **17** exist exclusively in the non-steroid conformation (**F**).

Experimental

All the melting points are uncorrected. The IR spectra were recorded on Shimadzu IR-27 spectrophotometers. The NMR spectra were recorded on Varian A-60, Nichiden-Varian T-60, and Varian HA-100 spectrometers, employing tetramethylsilane as the internal reference. The CD spectra were recorded on a Nihonbunko ORD/UV-5 spectrometer. Mass spectra were recorded on a Hitachi RMu-6D spectrometer with a direct inlet system operating at 70 eV.

Methyl 3-Oxo-4αH,*5*β*-12,13-bisnoreudesman-11-oate (7).* A mixture of 4α*H*,5β-13-noreudesm-11-en-3-one (**4**, 2.90 g, 14.1 mmol), $NaIO_4$ (12.1 g, 56.6 mmol), and OsO_4 (13.3 mg, 0.05 mmol) in 50 ml of dioxane–H_2O (4:1) was stirred for 2 h at room temperature and filtered. The filtrate was poured into a saturated aq soln of NaCl (200 ml) and extracted with ether (100 ml×3). The combined extracts were washed successively with a 2 M aq soln of Na_2CO_3 (20 ml×3), and a saturated aq soln of NaCl, dried and concentrated to give an oily neutral product (1.94 g). The combined washings of Na_2CO_3 were acidified with 6 M HCl and extracted with ether (50 ml×3). The combined extracts were washed with a saturated soln of NaCl, dried ($MgSO_4$), and concentrated to give 745 mg of an oily acidic product. The neutral part was stirred with Ag_2O, which was freshly prepared from 17 g of $AgNO_3$, in 50 ml of THF–H_2O (4:1) for 70 h at room temperature to give further 785 mg of acidic part. The combined acidic product (1.52 g) was methylated with 12 ml of CH_2N_2–ether soln (0.6 mmol/ml) to give 1.62 g of crude methyl ester, which was chromatographed over silica gel (Merck, finer than 230 mesh, 80 g) and eluted with CCl_4–$CHCl_3$ (1:1) to give 804 mg (24%) of spectroscopically pure **7**. This was recrystallized from pentane to give colorless prisms; mp 71 °C. IR (KBr): 1730 and 1698 cm^{-1}. NMR (CCl_4): δ 0.97 (3H, d, J=6.5 Hz, C_4–Me), 1.07 (3H, s, C_{10}–Me), and 3.61 (3H, s, –OMe) ppm. CD (MeOH): $[\theta]_{270} = -1980$. Found: C, 70.54; H, 9.26%. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31%.

Methyl 5β*-12,13-Bisnoreudesma-1,3-dien-11-oate (14) from 7 without Separation of Stereoisomers in Each Step.* Into a solution of **7** (1.645 g, 6.90 mmol) and HBr (0.1 ml) in AcOH

(15 ml) was added a solution of Br_2 (1.20 g, 7.5 mmol) in AcOH (5 ml). The mixture was stirred for 30 min at room temperature, poured into a saturated aq soln of NaCl (200 ml) and extracted with ether (50 ml×3). The combined extracts were washed successively with a saturated aq soln of Na_2CO_3 and a saturated aq soln of NaCl dried ($MgSO_4$), and concentrated to give 2.26 g of the crude bromides as the epimeric mixture of C_2 and C_4, which was employed in the following reaction without any purification.

A mixture of the crude bromides (2.26 g), dry DMF (30 ml), LiBr (2.36 g, 27.2 mmol), and Li_2CO_3 (2.36 g, 31.9 mmol) was heated at 153 °C under stirring for 8 h. The mixture was poured into a saturated aq soln of NaCl (200 ml) and extracted with ether (50 ml×3). The combined extracts were washed successively with a 2 M aq soln of HCl (30 ml) and a saturated aq soln of NaCl, dried and concentrated to give a mixture of **10** and **11** (2:1, 863 mg), which was employed in the next step without any purification.

The mixture of **10** and **11** (863 mg) was reduced with $NaBH_4$ (140 mg, 3.70 mmol) in ether–MeOH (2:1, 27 ml) and treated in the usual way to give a mixture of allylic alcohols as a epimeric mixture at C_3 and C_4, which was employed without any purification in the next step.

The resultant allylic alcohols were passed through the column packed with basic alumina†† (2.6 g), which was preheated at 220 °C, with the flow of nitrogen. The product was trapped in a flask cooled with Dry Ice–acetone bath to give spectroscopically pure **14** (264 mg, 17.4% overall yield from **7**) as an oily material, which was chromatographed over silica gel (Merck, finer than 230 mesh) and eluted with $CHCl_3$–CCl_4 (1:1) to give the analytical sample as an oil. IR (neat): 1730 and 1645 cm^{-1}. NMR (CCl_4): δ 0.86 (3H, s, C_{10}–Me), 1.80 (3H, broad s, C_4–Me), 2.49 (1H, m, $W_{h/2}$=11.0 Hz, C_7–H), 3.64 (3H, s, –OMe), 5.22 (1H, ddd, $J_{1,3}$=1.0 Hz, $J_{1,5}$=1.0 Hz, and $J_{1,2}$=9.5 Hz, C_1–H), 5.52 (1H, dqd, $J_{1,3}$=1.0 Hz, $J_{3,14}$=1.8 Hz, and $J_{2,3}$=5.0 Hz, C_3–H), and 5.76 (1H, dd, $J_{2,3}$=5.0 Hz and $J_{1,2}$=9.5 Hz, C_2–H) ppm. CD (MeOH): $[\theta]_{259}=-33800$. MS (70 eV) *m/e* (rel intensity): 220 (19, M^+), 173 (15), 160 (24), 145 (100), 119 (35), 105 (23), 91 (20). Found: C, 76.12; H, 9.27%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

Methyl 2β-Bromo-3-oxo-4αH,5β-12,13-bisnoreudesman-11-oate (8) and Methyl 2α-Bromo-3-oxo-4βH,5β-12,13-bisnoreudesman-11-oate (9). A mixture of the crude bromide (253 mg) which was prepared from **7** was chromatographed over silica gel (Merck, finer than 230 mesh) and eluted with CCl_4–$CHCl_3$ (2:1) to give 19 mg of spectroscopically pure **9** from the first fraction and 42 mg of spectroscopically pure **8** from the last fraction. NMR (CCl_4) of **8**: δ 1.05 (3H, d, J=6.5 Hz, C_4–Me), 1.10 (3H, s, C_{10}–Me), 3.58 (3H, s, –OMe), and 4.72 (1H, q, J=6.0 and 14.0 Hz, C_2–H) ppm. NMR (CCl_4) of **9**: δ 1.03 (3H, d, J=6.5 Hz, C_4–Me), 1.33 (3H, s, C_{10}–Me), 3.61 (3H, s, –OMe), and 4.73 (1H, q, J=6.0 and 12.0 Hz) ppm.

Methyl 3-Oxo-4αH,5β-12,13-bisnoreudesm-1-en-11-oate (10) and Methyl 3-Oxo-4βH,5β-12,13-bisnoreudesm-1-en-11-oate (11). The crude mixture of α,β-unsaturated ketones (**10** and **11**, 572 mg) which was prepared by the previously mentioned method was chromatographed over silica gel (60 g, Merck, finer than 230 mesh) and eluted with CCl_4–$CHCl_3$ (1:1). The first fraction gave **11** (85 mg). IR (neat): 1732 and 1680 cm^{-1}. NMR (CCl_4): δ 1.05 (3H, d, J=7.0 Hz, C_4–Me), 1.24 (3H, s, C_{10}–Me), 2.63 (1H, m, $W_{h/2}$=*ca.* 10 Hz, C_7–H), 2.88 (1H, dq, J=3.8 and 7.0 Hz, C_4–H), 3.65 (3H, s, –OMe), 5.79 (1H, d, J=10.0 Hz, C_2–H), and 6.34 (1H, dd, J=2.5 and 10.0 Hz, C_1–H) ppm. NMR (C_6H_6): δ 0.88 (3H, s, C_{10}–Me) and 1.14 (3H, d, J=7.0 Hz, C_4–Me). CD (MeOH): $[\theta]_{225}=-12600$, $[\theta]_{310}=+1200$. MS (70 eV) *m/e* (rel intensity): 236 (91, M^+), 221 (21), 189 (32), 177 (34), and 161 (100). The second fraction gave a mixture of **10** and **11**. The third fraction gave **10** (120 mg). IR (neat): 1736 and 1680 cm^{-1}. NMR (CCl_4): δ 1.10 (3H, d, J=6.5 Hz, C_4–Me), 1.23 (3H, s, C_{10}–Me), 2.34 (1H, m, $W_{h/2}$=*ca.* 20 Hz, C_7–H), 2.42 (1H, qd, J=6.5 and 12.5 Hz, C_4–H), 3.62 (3H, s, –OMe), 5.76 (1H, d, J=10.0 Hz, C_2–H), and 6.45 (1H, d, J=10.0 Hz, C_1–H) ppm. NMR (C_6H_6): δ 0.80 (3H, s, C_{10}–Me) and 1.09 (3H, d, J=6.5 Hz, C_4–Me). CD (MeOH): $[\theta]_{225}=+33900$, $[\theta]_{320}=-2580$. MS (70 eV): *m/e* (rel intensity), 236 (97, M^+), 221 (28), 189 (28), 177 (44), 161 (79), 82 (100).

Preparation of 11 from 9. A mixture of **9** (19 mg, 0.06 mmol), LiBr (20 mg, 0.23 mmol), Li_2CO_3 (24 mg, 0.32 mmol) in dry DMF was stirred at 160 °C for 6 h and treated in a usual way to give spectroscopically pure **11** (8 mg, 57%).

Preparation of 10 from 8. A mixture of **8** (42 mg, 0.13 mmol), LiBr (20 mg, 0.23 mmol), Li_2CO_3 (24 mg, 0.32 mmol) was stirred at 160 °C for 6 h and treated in a usual way to give spectroscopically pure **10** (22 mg, 70%).

Preparation of 14 from 10. The α,β-unsaturated ketone **10** (100 mg, 0.42 mmol) was reduced with $NaBH_4$ (16 mg, 0.42 mmol) in ether–MeOH (2:1, 1.5 mmol) and treated in a usual way to give methyl 3-hydroxy-4α*H*,5β-12,13-bisnoreudesm-1-en-11-oate (**12**) as an epimeric mixture at C_3. This mixture was passed through the column packed with basic alumina (300 mg), which was preheated at 220 °C, with N_2 flow to give **14** (31 mg, 33%).

Preparation of 14 from 11. The α,β-unsaturated ketone **11** (40 mg, 0.17 mmol) gave **14** (12 mg, 33%) in the same procedure above mentioned.

5β-Eudesma-1,3-dien-11-ol (1). Into a dry ether solution of methylmagnesium iodide [prepared from magnesium (73 mg, 3.00 mmol), methyl iodide (426 mg, 3.00 mmol), and dry ether (4 ml)] was added **14** (150 mg, 0.68 mmol) in dry ether (2 ml). This mixture was refluxed under N_2 for 1 h, poured into an aq soln of ammonium chloride, and extracted with ether (20 ml×3). The combined extracts were washed with a saturated aq soln of NaCl, dried ($MgSO_4$) and concentrated to give **1** (110 mg, 73%). IR (neat): 3350, 756, and 732 cm^{-1}. NMR (CCl_4): δ 1.10 (3H, s, C_{10}–Me), 1.13 (6H, s, C_{11}–Me), 1.80 (3H, broad s, C_4–Me), and 5.2—5.8 (3H, m) ppm. CD (MeOH): $[\theta]_{261}=27600$. MS (70 eV): *m/e* 220.

Methyl 5β,7βH-12,13-Bisnoreudesma-1,3-dien-11-oate (17). A mixture of **14** (80 mg, 0.36 mmol) and 1 M *t*-BuOK/*t*-BuOH (5 ml) was refluxed for 1.5 h under N_2, allowed to stand at room temperature for 2 h, poured into a saturated aq soln of NaCl, and extracted with ether (15 ml×3). The combined extracts were washed with a saturated aq soln of NaCl, dried ($MgSO_4$) and concentrated to give 57 mg of oily material as a neutral part, which mainly consisted of *t*-butyl 5β,7β*H*-12,13-bisnoreudesma-1,3-dien-11-oate (**16**). NMR (CCl_4): δ 0.85 (3H, s, C_{10}–Me), 1.39 (9H, s, *t*-Bu), 1.79 (3H, broad s, C_4–Me), 5.27 (1H, broad d, J=9.5 Hz, C_1–H), 5.55 (1H, m, C_3–H), 5.80 (1H, dd, J=5.0 and 9.5 Hz, C_2–H) ppm.

The aq layer was acidified by 2 M HCl and extracted with ether (15 ml×3). The combined extracts were wash-

†† The mixture of neutral alumina (active grade I, 5 g) and pyridine (0.4 ml) was shaken and evaporated at room temperature under reduced pressure (20 mmHg) for 7 h to give 5.23 g of basic alumina.

ed with a saturated aq soln of NaCl, dried ($MgSO_4$) and concentrated to give 28 mg of crystalline material, which mainly consisted of 5β,7β*H*-12,13-bisnoreudesma-1,3-dien-11-oic acid (**15**).

The neutral part was dissolved in a mixture of MeOH (5 ml) and a 10% aq soln of NaOH (2 ml). The mixture was refluxed for 40 min under N_2, cooled, poured into a saturated aq soln of NaCl, and extracted with ether. The aq layer was acidified by 2 M HCl and extracted with ether (15 ml×3). The combined ether layer was treated in a usual way to give 24 mg of a crystalline material, which mainly consisted of **15**.

The combined acidic part (52 mg) was methylated with a slight excess of diazomethane in ether to give 55 mg of oily material, which was ascertained to be a mixture of **14** and **17** (1:22) by the analysis of GLPC.

In another experiment a mixture of **14** (50 mg, 0.23 mmol) and 1 M *t*-BuOK/*t*-BuOH (3 ml) was refluxed for 2 h under N_2, poured into a saturated aq soln of NaCl, and extracted with ether to eliminate the neutral part. The aq layer was acidified by 2 M hydrochloric acid and extracted with ether (15 ml×3). The combined extracts were washed with a saturated aq soln of NaCl, dried ($MgSO_4$) and concentrated to give a crystalline material, which was recrystallized from ether to give 37 mg of **15** (mp 113 °C). This material was methylated by diazomethane to give **17** (40 mg, 80%). IR (neat): 1735, 1705 (sh), and 728 cm^{-1}. NMR (CCl_4): δ 0.86 (3H, s, C_{10}–Me), 1.79 (3H, broad s, C_4–Me), 3.57 (3H, s, –OMe), 5.28 (1H, broad d, J= 9.5 Hz, C_1–H), 5.50 (1H, m, C_3–H), and 5.81 (1H, dd, J=5.5 and 9.5 Hz, C_2–H) ppm. CD (MeOH): $[\theta]_{262}$= −49200. Found: C, 76.75; H, 9.11%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

(−)-Occidentalol (3). Into an ether solution of methylmagnesium iodide [prepared from magnesium powder (25 mg, 1.0 mmol) and methyl iodide (182 mg, 1.0 mmol) in dry ether (10 ml)] was added **17** (37 mg, 0.17 mmol) in dry ether (7 ml). The solution was stirred at room temperature for 40 min, then refluxed for 30 min under N_2. The reaction mixture was poured into a saturated aq soln of NH_4Cl, and extracted with ether. The combined extracts was washed with a saturated aq soln of NaCl, dried ($MgSO_4$) and concentrated to give an oily material (34 mg), which was purified by preparative TLC (silica gel GF_{254}, thickness 0.25 mm, $CHCl_3$) to give 20 mg (54%) of spectroscopically pure (−)-occidentalol (**3**), mp 83—85 °C.

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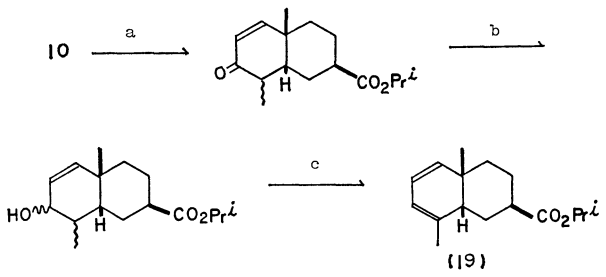
25) The isoproyl ester (**19**) was prepared in 47% yield as the following procedures.



a: $Al(i\text{-}PrO)_3$, *i*-PrOH; b: $NaBH_4$; c: Al_2O_3–Py