Tetrahedron Vol. 44, No. 10, pp. 2835 to 2842, 1988
Printed in Great Britain.

0040-4020/88 \$3.00+.00

SYNTHESIS AND ABSOLUTE CONFIGURATION OF (-)-PENTALENOLACTONE E METHYL ESTER†

KENJI MORI* and **MASAHIRO TSUJI**††

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

(*Received in Japan* 11 *January* 1988)

Abstract -- The naturally occurring enantiomer of pentalenolactone E was synthesized as its levorotatory Me ester **1** starting from (+)-2-ethoxycarbonyl-7,7-ethylenedioxy-bicyclo[3.3.0]octan-3-one **3**, which was obtained by treating (±)-**3** with baker's yeast. The absolute configuration of pentalenolactone E Me ester was established as depicted in **1**.

Pentalenolactone E, isolated as its Me ester 1 from cultures of Streptomyces UC 5319, is a sesquiterpene antibiotic with a unique tricyclic ring system.[1] Although there exist six published syntheses of (±)-1,[2-7] no enantioselective synthesis of the optically active form of **1** has been reported. We became interested in synthesizing the optically active pentalenolactone E Me ester to confirm the stereostructure as depicted in 1, which was proposed in analogy with the established stereostructures of other microbial metabolites related to 1.[1]

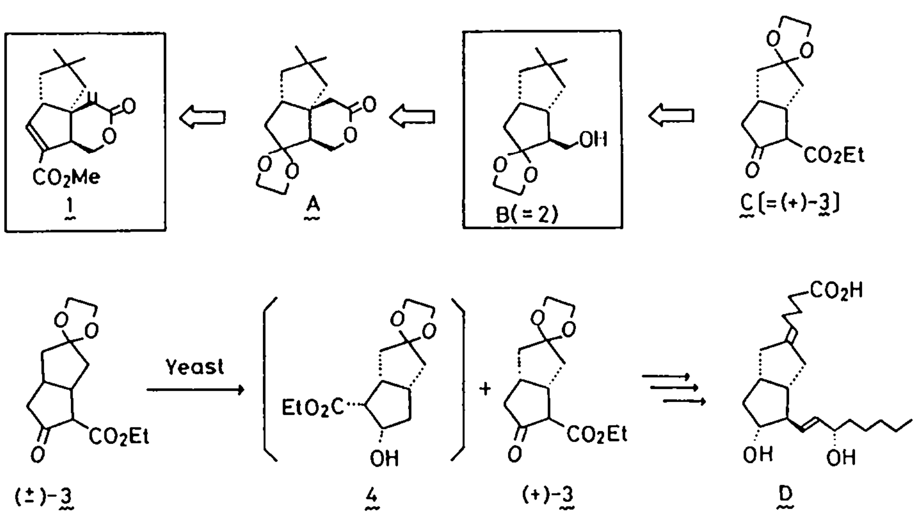


Fig.1. Synthetic plan of (-)-pentalenolactone E Me ester.

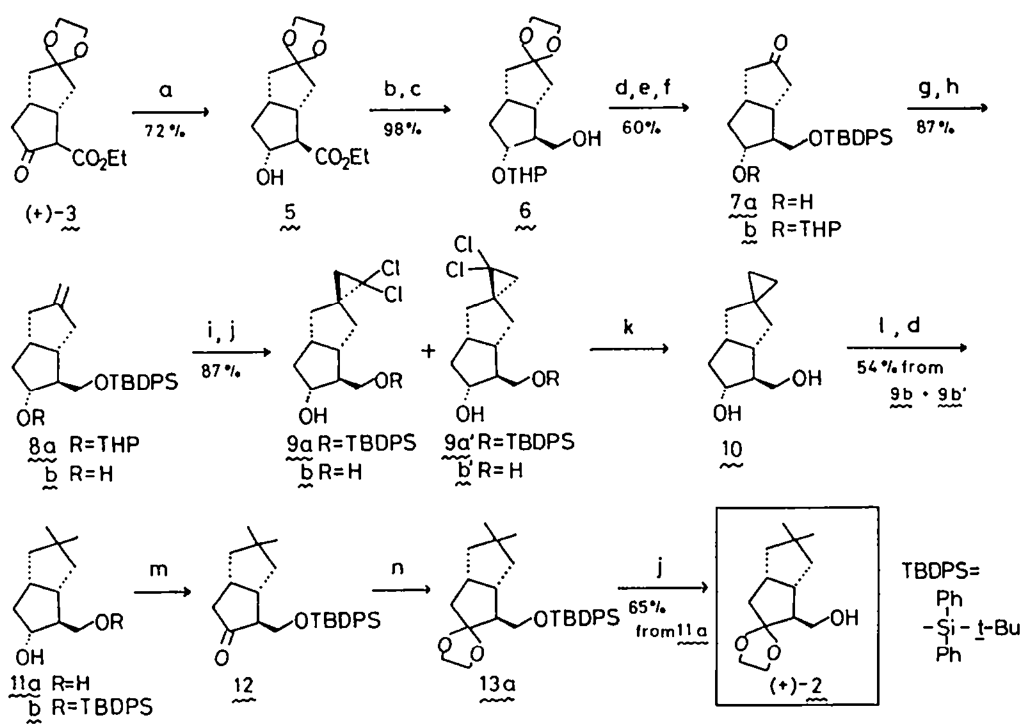
†Synthesis of mono- and sesquiterpenoids -- 11. Part 10, K. Mori and H. Tamura, Liebigs Ann. Chem. in the press.

††Present address: Central Research Laboratory, Nisshin Flour Milling Co., Ltd., Oimachi, Saitama 354, Japan.

In Fig.1 is shown our synthetic plan. Conversion of lactone **A** to (±)-pentalenolactone E Me ester **1** is a known process.[2,4] The lactone **A**, in turn, is derivable from a bicyclic intermediate **B** (=**2**).[4] Therefore, the preparation of enantiomerically pure **2** would enable us to synthesize enantiomerically pure **1**. We selected the keto ester **C**[=(+)-**3**] as our chiral starting material. This ester [(+)-**3**] was prepared previously by us by reducing its racemate (±)-**3** with yeast.[8] The reduction yielded a mixture of (+)-**3** and **4**, which could be readily separated.[8] Because the absolute configuration of (+)-**3** is established as depicted by its conversion to (+)-6a-carbaprostaglandin I_2 (**D**), our planned synthesis of pentalenolactone E Me ester from (+)-**3** _via_ **2** will lead to the enantiomer as depicted in **1**. Herein we report in detail our synthesis of the enantiomerically pure and crystalline (+)-**2** together with its conversion to (-)-pentalenolactone E Me ester **1**.

Synthesis of the bicyclic intermediate (2). Fig.2 shows the route by which (+)-**3** was converted into the key-intermediate (+)-**2**. The crucial introduction of the _gem_-Me_2 group to the bicyclo[3.3.0]octane ring system was executed by the hydrogenolysis of a cyclopropane compound **10**.

As reported previously, reduction of (±)-**3** with _Saccharomyces bailii_ KI 0116 yielded unchanged (+)-**3** of 92-94% e.e., while dry baker's yeast gave (+)-**3** of 62% e.e.[8] This reduction with _S. bailii_, however, was more time-consuming than the reduction with baker's yeast (_S. cerevisiae_), because the precultivation of _S. bailii_ was necessary to secure a sufficient amount of yeast cells to achieve the kinetic resolution _via_ asymmetric reduction. Baker's yeast was more convenient to be handled with. Fortunately in our prelimi-



a) $NaBH_4$; b) DHP, PPTS; c) LAH; d) TBDPSCl, imidazole; e) AcOH-THF-H_2O (3:1:1); f) DHP, TsOH; g) $Ph_3P=CH_2$; h) TsOH/MeOH; i) $CHCl_3$, NaOH, $PhCH_2NEt_3Cl$; j) ($\underline{n}$-Bu)$_4$NF/THF; k) Li/$\underline{t}$-BuOH-THF; l) H_2, PtO_2/AcOH; m) PCC; n) $HOCH_2CH_2OH$, TsOH.

Fig.2. Synthesis of the key bicyclic intermediate 2.

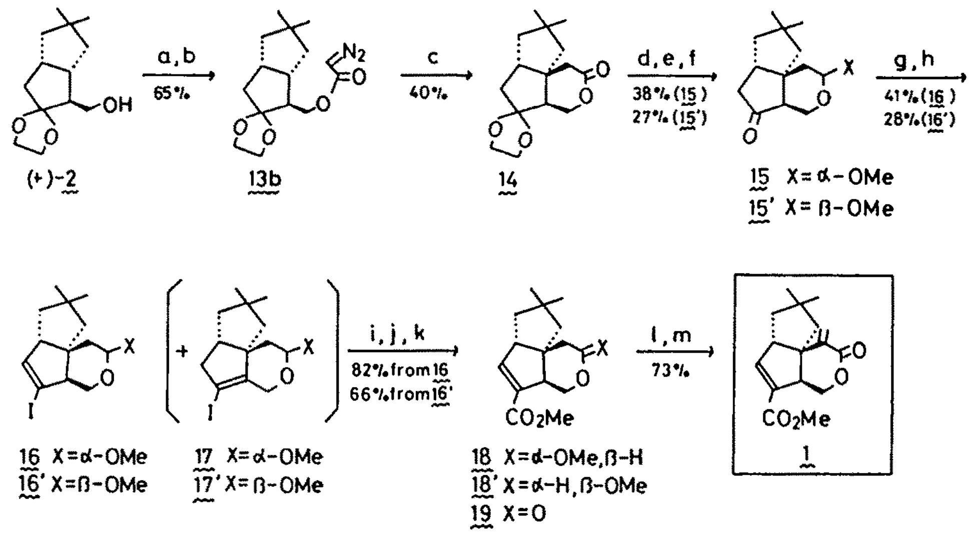
nary survey, the silyl ether **7a** was found to be so highly crystalline that its recrystallization could serve to increase the e.e. of enantiomerically impure **7a**. Consequently, even slightly optically impure (+)-**3** could be employed as the starting material, if we could incorporate **7a** as one of our intermediates. We therefore reinvestigated the kinetic resolution of (±)-**3** with baker's yeast. When wet and fresh baker's yeast was employed, the reduction of (±)-**3** in 0.1 M phosphate buffer (pH 7) proceeded smoothly to give (+)-**3** in 34% yield together with 35% yield of **4** (98.8% e.e.; see Experimental). The optical purity of (+)-**3**, $[\alpha]_D^{24}$ +20.7° ($CHCl_3$), was estimated to be over 80% on the basis of the previously reported $[\alpha]_D$ value (25.2°) for (+)-**3** of 100% e.e.[8] It thus became clear that the reduction of (±)-**3** with fresh baker's yeast was more enantioselective than that with dry baker's yeast. A sufficient amount of (+)-**3** was secured by reducing (±)-**3** with fresh baker's yeast, and was employed for the transformation as described below.

Reduction of (+)-**3** with $NaBH_4$ gave **5** [84.2% e.e. as determined by the HPLC analysis of the corresponding (R)-MTPA ester[9]], which was further manipulated to give **6**.[8] Treatment of **6** with t-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in DMF was followed by the removal of the THP and the acetal protective groups to give **7a**. After a single recrystallization, the enantiomeric purity of **7a** was found to be 98.8% e.e. as estimated by the HPLC analysis of the corresponding (R)-MTPA ester. The conversion of (+)-**3** as described above was useful in providing **7a** to be employed in the syntheses of not only the present target molecule **1** but also (+)-6a-carbaprostaglandin I_2.[8]

The next task was to convert the C=O group of **7a** into CMe_2 group. This was done by a series of reactions to achieve methylenation, cyclopropanation, and the reductive cleavage of the cyclopropane ring. Prior to the methylenation, the OH group of **7a** was protected as THP ether to give **7b**. Treatment of **7b** with $Ph_3P{=}CH_2$ gave **8a**. Cyclopropanation of **8a** or **8b** was attempted under the conditions previously reported by others.[10,11] Neither of the two methods was successful. We then attempted the addition of dichlorocarbene to **8b**. This was successful under the phase-transfer condition employing $PhCH_2NEt_3Cl$ as the catalyst.[12] The product was a stereoisomeric mixture of **9a** and **9a'**, which was treated with $(n\text{-}Bu)_4NF$ to give a separable mixture of **9b** and **9b'** in 87% combined yield. A portion of the mixture was separated to give analytical samples of the less polar isomer (presumably **9b**) and the more polar isomer (probably **9b'**), both as crystals. Reductive dechlorination of a mixture of **9b** and **9b'** was best carried out with Li and t-BuOH in THF[13] to give **10** as the major product. With $(n\text{-}Bu)_3SnH$ as the reducing agent, only partial dechlorination was observed yielding an isomeric mixture of monochloro derivatives. Hydrogenolytic cleavage of the cyclopropane ring of **10** was smoothly effected with H_2 and PtO_2 in AcOH giving **11a** as needles. Conversion of **11a** to **2** was straightforward as follows. Protection of the primary OH group of **11a** as TBDPS ether gave **11b**, which was oxidized with $CrO_3 \cdot C_5H_5N \cdot HCl$ (PCC)[14] to give **12**. Acetalization of **12** to **13a** was followed by the removal of the TBDPS group to give the crystalline key-intermediate (+)-**2**. The ^1H and ^{13}C NMR spectra of (+)-**2** were in good accord with those reported for oily (±)-**2**.[4] The overall yield of (+)-**2** from (+)-**3** was 11.2% in 16 steps.

Synthesis of (−)-pentalenolactone E Me ester (1). Although the conversion of (±)-**2** into (±)-**1** was a known process,[2,4] we carried out the synthesis of (−)-**1** from (+)-**2** as shown in Fig.3. We did this in order to establish the absolute configuration of natural **1**. The assignment of the absolute configuration was made possible by kind cooperation of Prof. D.E. Cane to reisolate natural **1** in an amount sufficient to measure both its specific rotation and CD spectrum.

According to Cane and Thomas,[4] (+)-**2** was converted to the diazoacetate **13b**, which was treated with $Rh_2(OAc)_4$ to effect the carbene insertion reaction giving the δ-lactone **14** as crystals. Reduction of **14** with DIBAL was followed by acetal removal and another acetal



a) TsNHN=CHCOCl, AgCN/C_6H_6; b) Et_3N/CH_2Cl_2; c) $Rh_2(OAc)_4$/Freon TF; d) DIBAL/Et_2O; e) TsOH/An-H_2O; f) HCl/MeOH; g) N_2H_4-Et_3N/EtOH; h) I_2, Me_3N/THF; i) $Ni(CO)_4$, MeONa/MeOH; j) dil H_2SO_4/An; k) Jones CrO_3/An; l) MMC/DMF; m) CH_2O, Et_2NH, AcONa/AcOH.

Fig.3. Synthesis of (−)-pentalenolactone E methyl ester.

formation to give a mixture of **15** and **15'**. These two acetals were separated, and the structures **15** and **15'** were assigned to the less polar and the more polar isomers, respectively, as reported by Cane and Thomas.[4]

For the conversion of **15** and **15'** to **1**, we adopted the route developed by Paquette *et al.*[2] Accordingly, **15** and **15'** were separately converted to the iodides **16** and **16'**, respectively. The unwanted isomers **17** and **17'** were also generated in the amount almost equal to **16** and **16'**. However, they could be removed by chromatographic purification. Following the procedure of Paquette as shown in Fig.3, **16** and **16'** was converted to the oily lactonic ester **19** *via* **18** and **18'**. Finally, methylenation of **19** yielded **1**. The overall yield of **1** was 3.4% in 13 steps from (+)-2, 0.4% in 29 steps from (+)-3, or 0.1% in 32 steps from bicyclo[3.3.0]octane-3,7-dione.

The specific rotation of our synthetic pentalenolactone E Me ester **1** was $[\alpha]_D^{22}$ −70.2° ($CHCl_3$). This value was in good accord with that of the natural **1**, $[\alpha]_D^{23}$ −70.6° ($CHCl_3$).[15] The CD as well as the ^1H and ^{13}C NMR and IR spectra of the synthetic **1** were identical to those of an authentic sample kindly sent to us by Professor Cane. Additionally, the synthetic **1** was indistinguishable from the natural **1** upon TLC analysis. We therefore conclude that the Me ester derived from natural pentalenolactone E possesses the absolute configuration as depicted in **1**.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on a Jasco IRA-102 spectrometer or a Jasco IR-810 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard and $CDCl_3$ as a solvent at 200 MHz on a JEOL JNM-FX 200 spectrometer unless otherwise stated. ^{13}C NMR spectra were recorded with $CDCl_3$ as an internal standard and a solvent at 50 MHz on a JEOL JNM-FX 200 spectrometer. Optical rotations were measured with $CHCl_3$ as a solvent on a Jasco DIP-140 polarimeter or a Jasco DIP-4 polarimeter unless otherwise stated. CD spectra were measured on a Jasco J-20C polarimeter. Mass spectra were recorded on a Hitachi M-80 spectrometer at 70 eV. Merck Kieselgel 60 (Art 7734, 70-230 mesh) or Fuji Davison BW-820 MH were used for SiO_2 column chromatography unless otherwise stated. TLC analyses were performed on a Merck Kieselgel 60 F-254 (0.25 mm, Art 5715).

Reduction of (±)-3 with baker's yeast: (1S,5R)-2-ethoxycarbonyl-7,7-ethylenedioxybicyclo[3.3.0]octan-3-one (+)-3 and (1R,2R,3S,5S)-2-ethoxycarbonyl-7,7-ethylenedioxy-3-hydroxybicyclo[3.3.0]octane 4. Compressed baker's yeast (100 g, Oriental Yeast Co., Ltd.) was dispersed in 0.1 M phosphate buffer (pH 7, 1000 ml) containing glucose (100 g) in a 2000-ml Sakaguchi flask at 30°C. The flask was shaken for 30 min at 30°C, when brisk fermentation took place. An emulsion of (±)-3 (5.0 g, 20 mmol) in 0.2% Triton X-100 soln (50 ml) was added to the fermentation mixture and the shaking culture was continued at 30°C. Glucose (50 g) was added to the mixture after 7 h and the fermentation was continued for 17 h. The total fermentation period was 24 h. The fermentation broth was mixed with a small amount of ether and Celite, and filtered through Celite. The filtrate was saturated with NaCl and extracted with EtOAc (500 ml x 3). The combined EtOAc soln was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue resulting from nine fermentations [45.0 g of (±)-3 in sum total] was chromatographed over SiO_2 (600 g). The fraction earlier eluted with n-hexane-EtOAc (6:1) gave 15.3 g (34%) of (+)-3, $[\alpha]_D^{24}$ +20.7° (c=1.53). Its IR and ^{1}H NMR spectra were identical with those reported previously.[8] The fraction later eluted with n-hexane-EtOAc (6:1) gave 15.8 g (35%) of 4, $[\alpha]_D^{24}$ +3.8° (c=1.73). Its IR and ^{1}H NMR spectra were identical with those reported previously.[8] A small amount of 4 described above was converted to the corresponding (R)-MTPA ester in the conventional manner, which was analyzed by HPLC. HPLC (column, Nucleosil® 50-5, 25 cm x 4.6 mm; solvent, n-hexane-THF (10:1), 1.0 ml/min; detected at 254 nm) Rt 41.3 min (0.6%), 43.1 min (99.4%). Therefore the optical purity of 4 was 98.8% e.e.

(1S,2R,3R,5R)-2-Ethoxycarbonyl-7,7-ethylenedioxy-3-hydroxybicyclo[3.3.0]octane 5. In the same manner as reported previously,[8] (+)-3 was converted to 5, $[\alpha]_D^{23}$ +23.1° (c=1.56). A small amount of 5 was converted to the corresponding (R)-MTPA ester in the conventional manner, which was analyzed by HPLC under the same condition as described for the (R)-MTPA ester of 4: Rt 23.3 min (92.1%), 27.0 min (7.9%). The optical purity of 5 was therefore 84.2% e.e.

(1R,5S,6S,7R)-6-t-Butyldiphenylsilyloxymethyl-7-hydroxybicyclo[3.3.0]octan-3-one 7a. To a stirred and water-cooled soln of 6 (12.0 g, 40.3 mmol, prepared from 5 in the same manner as reported previously[8]) t-butylchlorodiphenylsilane (11.6 g, 42.0 mmol) in dry DMF (60 ml) was added imidazole (6.5 g, 0.10 mol) and the mixture was stirred for 30 min at room temp. Then the mixture was poured into water, and extracted with ether. The ether soln was washed with water, and concentrated *in vacuo*. The residue was dissolved in AcOH-water-THF (3:1:1, 270 ml), and the soln was stirred for 1.5 h at 90°C. After cooling, the mixture was poured into water, and extracted twice with EtOAc. The combined EtOAc soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (180 g). Elution with n-hexane-EtOAc (4:1-2:1) gave 13.2 g (80%) of 7a. This was recrystallized from n-hexane-EtOAc to give 9.8 g (60%) of 7a as needles, m.p. 100-101°C; $[\alpha]_D^{24}$ +9.7° (c=1.97); vmax 3450 (m) 1730 (s), 1590 (w), 1430 (m), 1130 (m), 1115 (m), 1105 (s), 1095 (m) cm^{-1}; ^{1}H NMR δ 1.06 (9H, s), 1.49-2.63 (10H, m), 3.67 (1H, dd, J=10.1 and 7.6 Hz), 3.82 (1H, dd, J=10.1 and 5.1 Hz), 4.10-4.21 (1H, m), 7.37-7.46 (6H, m), 7.64-7.69 (4H, m). (Found: C, 72.97; H, 7.83. Calc for $C_{25}H_{32}O_3Si$: C, 73.48; H, 7.89%). A small amount of 7a was converted to the corresponding (R)-MTPA ester in the conventional manner, which was analyzed by HPLC under the same condition as described for the (R)-MTPA ester of 4: Rt 21.8 min (99.4%), 25.9 min (0.6%). The optical purity of 7a was therefore 98.8% e.e.

(1S,2S,3R,5S)-2-t-Butyldiphenylsilyloxymethyl-3-hydroxy-7-methylenebicyclo[3.3.0]octane 8b. A soln of 7a (14.5 g, 35.6 mmol), dihydropyran (4.5 g, 53.3 mmol), and p-TsOH·H_2O (80 mg, 0.42 mmol) in dry CH_2Cl_2 (200 ml) was stirred for 20 min at room temp. Then the mixture was poured into sat $NaHCO_3$ soln. The CH_2Cl_2 layer was separated and washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 19.3 g of crude 7b, vmax 1745 (s), 1590 (w), 1430 (m), 1115 (s), 1080 (m) cm^{-1}. This was employed in the next step without further purification.

A soln of $NaCH_2SOMe$ (71.2 mmol) was prepared from NaH (2.84 g, 60% dispersion in mineral oil, 71.2 mmol) and dry DMSO (42 ml). To this was added a soln of methyltriphenylphosphonium bromide (25.4 g, 71.2 mmol) in dry DMSO (55 ml) at such a rate as to maintain the soln at 25°C under Ar. The mixture was stirred for 30 min at room temp to yield the red soln of ylide. To this ylide soln was added dropwise over 10 min a soln of 7b (19.3 g) in dry DMSO (30 ml) and the mixture was stirred for 1 h at room temp under Ar. Then the mixture was poured into ice, and extracted twice with ether. The combined ether soln was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was passed through SiO_2 [70 g, n-hexane-ether (9:1)] to give 16.3 g of crude 8a, vmax 1660 (w), 1595 (w), 1475 (m), 1435 (m), 1115 (s), 1085 (m) cm^{-1}. This was employed in the next step without further purification.

A soln of 8a (16.3 g), p-TsOH·H_2O (0.8 g, 4.2 mmol) in MeOH (250 ml) was stirred for 4 h at room temp. Then the mixture was neutralized with K_2CO_3 and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was extracted with EtOAc. The EtOAc soln was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (200 g). Elution with n-hexane-EtOAc (19:1) gave 12.6 g (87% from 7a) of 8b, n_D^{23} 1.5538; $[\alpha]_D^{23}$ +49.7° (c=1.79); vmax 3430 (m), 1660 (w), 1590 (w), 1430 (s), 1115 (s) cm^{-1}; ^{1}H NMR δ 1.06 (9H, s), 1.20-1.35 (1H, m), 1.58-1.65 (1H, m), 1.83-2.02 (3H, m), 2.22-2.50 (2H, m), 2.90 (1H, br.s), 3.66 (1H, dd, J=10.1 and 8.5 Hz), 3.83 (1H, dd, J=10.1 and 4.7 Hz), 3.87-4.00 (1H, m), 4.81 (1H, br.s), 4.83 (1H, br.s), 7.36-7.48 (6H,m), 7.66-7.71 (4H, m). (Found: C, 76.46; H, 8.33. Calc for $C_{26}H_{34}O_2Si$: C,76.79; H, 8.42%).

(1S,3S,5S,6S,7R)- and (1S,3R,5S,6S,7R)-Spiro[7-hydroxy-6-hydroxymethylbicyclo[3.3.0]octane-3,1'-(2',2'-dichlorocyclopropane)] 9b and 9b'. To a stirred suspension of 8b (12.2 g, 30.1 mmol), powdered NaOH (4.0 g, 99.5 mmol) in $CHCl_3$ (60 ml) was added benzyltriethylammonium chloride (69 mg, 0.30 mmol) at room temp. After 2 min, a vigorous reflux took place and continued for 3 min. The mixture was stirred for further 10 min, then filtered through Celite. The filtrate was concentrated *in vacuo* to give 14.8 g of a crude mixture of 9a and 9a', vmax 3450 (m), 1590 (w), 1430 (s), 1115 (s), 1075 (s), 1050 (s) cm^{-1}. This was employed in the next step without further purification.

To a stirred soln of the crude mixture of 9a and 9a' (14.8 g) in THF (120 ml) was addded dropwise a soln of $(n\text{-}Bu)_4NF$ in THF (1M, 33.2 ml, 33.2 mmol) at room temp and the mixture was stirred for 15 min at room temp. Then THF was removed *in vacuo* from the reaction mixture, and the residue was extracted with EtOAc. The EtOAc soln was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (150 g). Elution with n-hexane-EtOAc (1:1-1:2) gave 6.6 g (87% from 8b) of a mixture of 9b and 9b'. Although the separation of 9b and 9b' was not necessary, a few fractions of chromatographically pure less polar isomer and those of more polar isomer were obtained. These were recrystallized to give pure samples.

Less polar isomer (the structure 9b was tentatively assigned.): m.p. 107-109°C (from n-hexane-EtOAc, needles); $[\alpha]_D^{23}$ +14.5° (c=1.01, MeOH); vmax 3260 (s), 1355 (m), 1145 (m), 1080 (s), 1055 (s) cm^{-1}. ^{1}H NMR δ 1.37 (2H, s), 1.48-2.63 (9H, m), 2.43 (2H, s), 3.68 (1H, dd, J=10.5 and 8.5 Hz), 3.85-3.98 (2H, m); TLC (n-hexane-EtOAc=1:3) Rf 0.31. (Found: C, 52.47; H, 6.46. Calc for $C_{11}H_{16}O_2Cl_2$: C, 52.60; H, 6.42%).

More polar isomer (the structure **9b'** was tentatively assigned.): m.p. 184-186°C (from MeOH, rods); $[\alpha]_D^{23}$ -9.0° (c=1.10, MeOH); νmax 3280 (s), 1360 (m), 1135 (m), 1085 (s), 1055 (s) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.58 (2H, s), 1.20-2.50 (9H, m), 3.35-3.70 (3H, m), 4.32 (1H, br.t, J=5.1 Hz), 4.55 (1H, br.d, J=5.9 Hz); TLC (n-hexane-EtOAc=1:3) Rf 0.22. (Found: C, 52.20; H, 6.45. Calc for $C_{11}H_{16}O_2Cl_2$: C, 52.60; H, 6.42%).

(1S,5S,6S,7R)-Spiro[7-hydroxy-6-hydroxymethylbicyclo[3.3.0]octane-3,1'-cyclopropane] **10.** To a soln of a mixture of **9b** and **9b'** (9.4 g, 37.4 mmol) in dry t-BuOH (27.7 g, 0.37 mol) and dry THF (140 ml) was added finely cut Li (5.2 g, 0.75 mol) at room temp, and the mixture was stirred at room temp under Ar. After 15 min, a vigorous reflux took place and continued for 5 min, then a gentle reflux continued for 50 min. Then the mixture was stirred at reflux temp for 15 h. After cooling, the mixture was poured into ice, and extracted twice with EtOAc. The combined EtOAc soln was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from n-hexane-EtOAc to give 5.5 g of **10** containing a small amount of impurities, which were presumably monochloro derivatives. This was employed in the next step without further purification. An analytical sample of **10** was prepared as follows. SiO_2 chromatography [Merck Art. 9385, 230-400 mesh, n-hexane-EtOAc (1:1)] followed by recrystallization from n-hexane-EtOAc gave pure **10** as needles, m.p. 87.5-89.0°C; $[\alpha]_D^{24}$ +20.4° (c=1.54); νmax 3270 (s), 1455 (m), 1360 (m), 1135 (m), 1075 (s), 1045 (s), 1010 (m) cm^{-1}; ^1H NMR δ 0.29-0.37 (2H, m), 0.51-0.59 (2H, m), 1.14-1.21 (2H, m), 1.41-1.57 (1H, m), 1.80-2.55 (6H, m), 3.00 (2H, br.s), 3.63 (1H, dd, J=10.5 and 8.6 Hz), 3.81-3.94 (2H, m). (Found: C, 71.93; H, 10.03. Calc for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%).

(1S,2S,3R,5S)-3-Hydroxy-2-hydroxymethyl-7,7-dimethylbicyclo[3.3.0]octane **11a.** A mixture of **10** containing a small amount of monochloro derivatives (5.5 g) and PtO_2 (550 mg) in AcOH (80 ml) was shaken for 2 h at room temp under atmospheric pressure of hydrogen. Then the mixture was filtered through Celite, and AcOH was removed in vacuo from the filtrate. The residue was diluted with sat $NaHCO_3$ soln and extracted with EtOAc. The EtOAc soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Art. 9385, 250 g). Elution with n-hexane-EtOAc (1:1) gave 4.5 g of **11a.** Recrystallization from n-hexane-EtOAc gave 3.7 g (54% from **9b** and **9b'**) of **11a** as needles, m.p. 89.0-90.0°C; $[\alpha]_D^{24}$ +16.8° (c=1.52); νmax 3270 (s), 1465 (m), 1380 (m), 1360 (m), 1130 (m), 1080 (s), 1035 (s) cm^{-1}; ^1H NMR δ 0.87 (3H, s), 1.06 (3H, s), 1.15-1.42 (3H, m), 1.62-1.81 (3H, m), 2.03-2.45 (3H, m), 2.51 (2H, br.s), 3.61 (1H, dd, J=10.5 and 8.8 Hz), 3.85 (1H, dd, J=10.5 and 4.7 Hz), 3.92-4.05 (1H, m). (Found: C, 71.39; H, 11.03. Calc for $C_{11}H_{20}O_2$: C, 70.70; H, 10.94%).

(1S,2S,3R,5S)-2-t-Butyldiphenylsilyloxymethyl-3-hydroxy-7,7-dimethylbicyclo[3.3.0]octane **11b.** To a stirred and ice-cooled soln of **11a** (3.6 g, 19.4 mmol) and t-butylchlorodiphenylsilane (5.6 g, 20.4 mmol) in dry DMF (18 ml) was added imidazole (2.64 g, 38.8 mmol) and the mixture was stirred for 1.5 h at that temp. Then the mixture was poured into water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (120 g). Elution with n-hexane-EtOAc (9:1) gave 7.2 g (88%) of **11b**, n_D^{23} 1.5403; $[\alpha]_D^{23}$ +32.2° (c=2.31); νmax 3420 (m), 1590 (w), 1465 (m), 1430 (m), 1115 (s) cm^{-1}; ^1H NMR δ 0.82 (3H, s), 1.03 (3H, s), 1.06 (9H, s), 1.14-2.54 (9H, m), 3.02 (1H, br.s), 3.63 (1H, dd, J=10.0 and 8.8 Hz), 3.84 (1H, dd, J=10.0 and 4.8 Hz), 3.98-4.11 (1H, m), 7.34-7.43 (6H, m), 7.66-7.74 (4H, m). (Found: C, 76.32; H, 9.02. Calc for $C_{27}H_{38}O_2Si$: C, 76.72; H, 9.06%).

(1S,2S,5S)-3,3-Ethylenedioxy-2-hydroxymethyl-7,7-dimethylbicyclo[3.3.0]octane **(+)-2.** To a soln of **11b** (7.1 g, 16.8 mmol) in dry CH_2Cl_2 (100 ml) was added PCC (7.3 g, 33.6 mmol) at room temp and the mixture was stirred for 3 h at room temp. Then the CH_2Cl_2 layer was decanted and the residue was washed with ether. The combined organic soln was passed through a short column of Florisil, and concentrated in vacuo to give 7.2 g of crude **12**, νmax 1740 (s), 1590 (w), 1465 (m), 1430 (m), 1115 (s) cm^{-1}. This was employed in the next step without further purification.

A mixture of **12** (7.2 g), ethylene glycol (20 ml), a catalytic amount of p-TsOH·H_2O, and benzene (200 ml) was stirred for 18 h at reflux temp with azeotropic removal of water by Dean-Stark apparatus. After cooling, the mixture was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo to give 7.9 g of **13a**, νmax 1590 (w), 1465 (m), 1430 (m), 1115 (s) cm^{-1}. This was employed in the next step without further purification.

To a stirred soln of **13a** (7.9 g) in THF (100 ml) was added $(n\text{-}Bu)_4NF$ in THF (1M, 18.5 ml, 18.5 mmol) at room temp and the mixture was stirred for 2 h at room temp. Then THF was removed in vacuo from the reaction mixture. The residue was poured into water and extracted with EtOAc. The EtOAc soln was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (120 g). Elution with n-hexane-EtOAc (4:1) gave 2.8 g (74% from **11b**) of **(+)-2**, which crystallized on standing. Recrystallization from n-hexane gave **(+)-2** as plates, m.p. 38.5-39.5°C; $[\alpha]_D^{24}$ +23.6° (c=1.58); νmax 3510 (s), 1465 (m), 1285 (m), 1175 (m), 1070 (m), 1045 (s), 1025 (m) cm^{-1}; ^1H NMR δ 0.90 (3H, s), 1.05 (3H, s), 1.15-1.31 (2H, m), 1.47 (1H, dd, J=13.4 and 6.0 Hz), 1.63-1.80 (2H, m), 1.90-1.98 (1H, m), 2.08 (1H, dd, J=13.3 and 8.5 Hz), 2.44-2.58 (2H, m), 2.77 (1H, br.s), 3.65-3.68 (2H, m), 3.86-3.98 (4H, m); ^{13}C NMR δ 27.2, 28.9, 38.3, 41.5, 42.2, 42.7, 47.9, 48.8, 53.6, 61.8, 64.1, 64.6, 120.8; MS: m/z 226.1578 (M^+). Calc for $C_{13}H_{22}O_3$: 226.1569. (Found: C, 68.71; H, 9.80. Calc for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80%).

(1S,2S,5S)-2-(Diazoacetoxy)methyl-3,3-ethylenedioxy-7,7-dimethylbicyclo[3.3.0]octane **13b.** This was prepared from **(+)-2** (4.2 g) in 65% yield (3.5 g) according to Cane and Thomas[4]; $[\alpha]_D^{23}$ +14.0° (c=1.51); νmax 2120 (s), 1710 (s), 1400 (m), 1370 (m), 1240 (m), 1190 (m) cm^{-1}; ^1H NMR δ 0.90 (3H, s), 1.05 (3H, s), 1.10-1.79 (5H, m), 1.99-2.59 (4H, m), 3.81-3.97 (4H, m), 4.14 (1H, dd, J=11.0 and 7.8 Hz), 4.27 (1H, dd, J=11.0 and 6.1 Hz), 4.75 (1H, s); MS: m/z 294.1551 (M^+). Calc for $C_{15}H_{22}O_4N_2$: 294.1579.

(4aS,6aS,9aR)-Octahydro-5,5-ethylenedioxy-8,8-dimethyl-2-oxopentaleno[1,6a-c]pyran **14.** This was prepared from **13b** (795 mg) in 40% yield (288 mg) as an oil according to Cane and Thomas.[4] This sample crystallized on standing. Recrystallization from n-hexane-ether gave pure **14** as prisms, m.p. 62.4-63.0°C; $[\alpha]_D^{23}$ +0.7±0.1° (c=1.06); νmax 1745 (s), 1285 (m), 1255 (m), 1160 (m), 1135 (m), 1085 (m), 1070 (m) cm^{-1}; ^1H NMR δ 1.01 (3H, s), 1.05 (3H, s), 1.56-1.80 (5H, m), 2.04 (1H, dd, J=13.7 and 8.5 Hz), 2.14 (1H, t, J=7.1 Hz), 2.30-2.43 (1H, m), 2.60 (2H, s), 3.79-3.99 (4H, m), 4.22 (2H, d, J=7.1 Hz); ^{13}C NMR δ 27.9, 29.8, 39.4, 40.6, 42.5, 47.2, 47.9, 50.8, 54.1, 56.2, 64.1, 64.3, 66.5, 117.8, 172.8; MS: m/z 266.1533 (M^+). Calc for $C_{15}H_{22}O_4$: 266.1518. (Found: C, 67.35; H, 8.38. Calc for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%).

(2R,4aS,6aS,9aR)- and (2S,4aS,6aS,9aR)-Octahydro-2-methoxy-8,8-dimethylpentaleno[1,6a-c]pyran-5(6H)-one **15** and **15'.** The lactone **14** (1.42 g) was converted to **15** (483 mg, 38%), a mixture of **15** and **15'** (121 mg, 10%) and **15'** (348 mg, 27 %) according to Cane and Thomas.[4]

15: m.p. 53.7-54.5°C (from n-hexane, needles); $[\alpha]_D^{22}$ -254° (c=1.01); νmax 1740 (s), 1370 (m), 1195 (m), 1130 (s), 1095 (m), 1055 (s) cm^{-1}; ^1H NMR δ 1.06 (3H, s), 1.10 (3H, s), 1.30-2.47 (10H, m), 3.33 (3H, s), 3.77 (1H, dd, J=11.7 and 4.2 Hz), 4.01 (1H, d, J=11.7 Hz), 4.61 (1H, br. s); ^{13}C NMR δ 30.8, 31.3, 38.5, 40.2 (2C), 44.4, 45.9, 46.9, 53.0, 53.1, 54.2, 54.8, 97.4, 217.4. MS: m/z 238.1596 (M^+). Calc for $C_{14}H_{22}O_3$: 238.1569. (Found: C, 70.55; H, 9.39. Calc for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30%).

15': $[\alpha]_D^{22}$ -93.4° (c=0.99); νmax 1745 (s), 1450 (m), 1390 (m), 1140 (s), 1110 (s), 1070 (s) cm^{-1}; ^1H NMR δ 1.09 (3H, s), 1.12 (3H, s), 1.32-2.52 (10H, m), 3.41 (3H, s), 3.62 (1H, dd, J=12.2 and 4.6 Hz), 4.23 (1H, dd, J=9.3 and 2.2 Hz), 4.38 (1H, dd, J=12.2 and 2.2 Hz); ^{13}C NMR δ 30.4, 31.1, 40.4, 40.6, 41.2, 44.2, 47.5, 49.1, 53.2, 53.9, 55.7, 59.7, 100.4, 216.7. MS: m/z 238.1576 (M^+). Calc for $C_{14}H_{22}O_3$: 238.1569.

(2R,4aS,6aS,9aR)-1,2,4,4a,6a,7,8,9- and (2R,6aS,9aS)-1,2,4,6,6a,7,8,9-Octahydro-5-iodo-2-methoxy-8,8-dimethylpentaleno[1,6a-c]pyran **16** and **17**. According to Paquette et al.,[2] **15** (474 mg) was converted to 533 mg of a mixture of **16** and **17**. This mixture was chromatographed over SiO_2 (Merck Art. 9385, 25 g). Elution with n-hexane-EtOAc (40:1) gave 259 mg (41% from **15**) of a less polar isomer **17**, which was recrystallized from n-hexane to give rods, and 263 mg (41% from **15a**) of a more polar isomer **16**.

16: $[\alpha]_D^{23}$ -78.0° (c=1.08); νmax 1615 (w), 1445 (m), 1115 (m), 1075 (s), 1050 (m) cm^{-1}; ^1H NMR δ 1.02 (3H, s), 1.03 (3H, s), 1.42 (1H, dd, J=12.9 and 4.4 Hz), 1.56-1.79 (4H, m), 2.03 (1H, dd, J=14.4 and 5.1 Hz), 2.50-2.57 (1H, m), 2.86-3.00 (1H, m), 3.36 (3H, s), 3.70 (1H, dd, J=12.2 and 1.7 Hz), 3.83 (1H, dd, J=12.2 and 3.7 Hz), 4.55 (1H, dd, J=7.8 and 5.1 Hz), 6.16 (1H, br); MS: m/z 348.0562 (M^+). Calc for $C_{14}H_{21}O_2I$: 348.0588.

17: m.p. 70.1-71.6°C; $[\alpha]_D^{23}$ -151° (c=1.08); νmax 1655 (w), 1455 (m), 1370 (m), 1205 (m), 1110 (s), 1045 (s) 960(s) cm^{-1}; ^1H NMR δ 0.97 (3H, s), 0.98 (3H, s), 1.22 (1H, dd, J=12.7 and 6.6 Hz), 1.56-1.97 (5H, m), 2.39-2.50 (2H, m), 2.89-3.03 (1H, m), 3.37 (3H, s), 4.08 (1H, d, J=11.7 Hz), 4.27 (1H, d, J=11.7 Hz, with additional fine coupling), 4.67 (1H, m). (Found: C, 48.36; H, 6.11. Calc for $C_{14}H_{21}O_2I$: C, 48.29; H, 6.08%).

(2S,4aS,6aS,9aR)-1,2,4,4a,6a,7,8,9- and (2S,6aS,9aR)-1,2,4,6,6a,7,8,9-Octahydro-5-iodo-2-methoxy-8,8-dimethylpentaleno[1,6a-c]pyran **16'** and **17'**. According to Paquette et al.,[2] **15'** (320 mg) was converted to a mixture (341 mg) of **16'** and **17'**; This mixture was chromatographed over SiO_2 (Merck Art. 9385, 50 g). Elution with n-hexane-ether (40:1) gave 131 mg (28% from **15'**) of a less polar isomer **16'**, 79 mg (17% from **15'**) of a mixture of **16'** and **17'**, and 114 mg (24% from **15'**) of a more polar isomer **17'**.

16': $[\alpha]_D^{22}$ +61.9° (c=1.26); νmax 1605 (w), 1465 (m), 1120 (s), 1075 (s), 1020 (m) cm^{-1}; ^1H NMR δ 1.01 (3H, s), 1.04 (3H, s), 1.28 (1H, dd, J=12.7 and 8.0 Hz), 1.58-1.90 (5H, m), 2.74-2.89 (2H, m), 3.38 (3H, s), 3.52 (1H, dd, J=11.7 and 10.0 Hz), 3.80 (1H, dd, J=11.7 and 6.8 Hz), 4.64 (1H, dd, J=8.3 and 5.1 Hz), 6.20 (1H, br); MS: m/z 348.0547 (M^+). Calc for $C_{14}H_{21}O_2I$: 348.0588.

17': $[\alpha]_D^{22}$ +27.8° (c=1.08); νmax 1660 (w), 1460 (m), 1145 (s), 1075 (s), 1060 (s), 1035 (m) cm^{-1}; ^1H NMR δ 1.00 (3H, s), 1.01 (3H, s), 1.24 (1H, dd, J=12.7 and 8.0 Hz), 1.50-1.97 (5H, m), 2.38-2.58 (2H, m), 2.90-3.15 (1H, m), 3.47 (3H, s), 4.04 (1H, d, J=12.7 Hz, with additional fine coupling), 4.39 (1H, d, J=12.7 Hz), 4.53 (1H, dd, J=9.0 and 2.6 Hz). (Found: C, 48.25; H, 6.03. Calc for $C_{14}H_{21}O_2I$: C, 48.29; H, 6.07%).

Methyl (2R,4aS,6aS,9aR)-1,2,4,4a,6a,7,8,9-octahydro-2-methoxy-8,8-dimethylpentaleno[1,6a-c]pyran-5-carboxylate **18** According to Paquette et al.,[2] **16** (338 mg) was converted to **18** (269 mg, 99%); $[\alpha]_D^{23}$ -85.4° (c=1.03); νmax 1715 (s), 1635 (w), 1440 (m), 1280 (m), 1235 (m), 1120 (m), 1060 (s) cm^{-1}; ^1H NMR δ 0.99 (3H, s), 1.04 (3H, s), 1.46 (1H, dd, J=13.3 and 4.5 Hz), 1.57-1.87 (4H, m), 2.02 (1H, dd, J=14.4 and 5.1 Hz), 2.81 (1H, br.s), 3.08-3.20 (1H, m), 3.37 (3H, s), 3.73 (3H, s), 3.79 (1H, dd, J=12.0 and 2.0 Hz), 3.96 (1H, dd, J=12.0 and 3.9 Hz), 4.64 (1H, dd, J=8.4 and 5.0 Hz), 6.78 (1H, br.s). MS: m/z 280.1670 (M^+). Calc for $C_{16}H_{24}O_4$: 280.1674. (Found: C, 68.75; H, 8.74. Calc for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63%).

Methyl (2S,4aS,6aS,9aR)-1,2,4,4a,6a,7,8,9-octahydro-2-methoxy-8,8-dimethylpentaleno[1,6a-c]pyran-5-carboxylate **18'**. According to Paquette et al.,[2] **16'** (116 mg) was converted to **18'** (79 mg, 85%); $[\alpha]_D^{23}$ +91.0° (c=0.82); νmax 1720 (s), 1630 (w), 1440 (m), 1275 (m), 1260 (m), 1120 (m), 1070 (s) cm^{-1}; ^1H NMR δ 1.02 (3H, s), 1.03 (3H, s), 1.25-1.92 (6H, m), 2.93-3.10 (2H, m), 3.36 (3H, s), 3.55 (1H, dd, J=11.6 and 10.5 Hz), 3.71 (3H, s), 4.08 (1H, dd, J=11.6 and 7.1 Hz), 4.69 (1H, dd, J=7.6 and 5.4 Hz), 6.82 (1H, br). MS: m/z 280.1664 (M^+). Calc for $C_{16}H_{24}O_4$: 280.1674. (Found: C, 68.91; H, 8.77. Calc for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63%).

Methyl (4aS,6aS,9aR)-1,2,4,4a,6a,7,8,9-octahydro-2-oxo-8,8-dimethylpentaleno[1,6a-c]pyran-5-carboxylate **19**. According to Paquette et al.,[2] **18** (247 mg) was converted to 193 mg (83%) of **19**. Similarly **18'** (71 mg, 0.25 mmol) was converted to 52 mg (78%) of **19**; $[\alpha]_D^{24}$ -58.3° (c=1.06); νmax 1755 (s), 1715 (s), 1635 (m), 1435 (m), 1355 (m), 1270 (m), 1255 (m), 1220 (m), 1120 (m), 1080 (m) cm^{-1}; ^1H NMR δ 1.02 (3H, s), 1.06 (3H, s), 1.37 (1H, dd, J=12.9 and 5.9 Hz), 1.67-1.93 (3H, m), 2.55 (1H, d, J=14.4 Hz), 2.66 (1H, d, J=14.4 Hz), 3.07-3.21 (2H, m), 3.75 (3H, s), 4.43 (1H, dd, J=11.7 and 4.2 Hz), 4.50 (1H, dd, J=11.7 and 4.2 Hz), 6.84 (1H, br). MS: m/z 264.1352 (M^+). Calc for $C_{15}H_{20}O_4$: 264.1361.

(-)-Pentalenolactone E methyl ester **1**. According to Paquette et al.,[2] **19** (164 mg) was converted to 96 mg (56%; 73% based on the consumed **19**) of **1**; $[\alpha]_D^{22}$ -70.2° (c=1.04) [natural **1**[15]: $[\alpha]_D^{23}$ -70.6° (c=1.37, $CHCl_3$)]; CD (c=1.3 x 10^{-3} mol/l, n-hexane) [θ] (nm) +3.8 x 10^4 (219.0) [natural **1** CD (c=1.3 x 10^{-3} mol/l, n-hexane) +3.6 x 10^4 (218.5)]; νmax ($CHCl_3$ soln) 3020 (m), 3010 (w), 2950 (m), 2940 (w), 2900 (w), 2860 (w), 1730 (sh), 1710 (s), 1635 (w), 1550 (w), 1470 (w), 1440 (m), 1385 (w), 1355 (m), 1335 (w), 1320 (w), 1265 (m), 1255 (sh), 1195 (w), 1165 (w), 1135 (m), 1110 (w), 1090 (w), 1075 (w), 1055 (w), 1040 (w), 1000 (w), 985 (w), 970 (w), 940 (w) cm^{-1}; ^1H NMR δ 1.06 (3H, s), 1.07 (3H, s), 1.44 (1H, dd, J=12.9 and 6.0 Hz), 1.74 (1H, d, J=13.9 Hz), 1.90 (1H, dd, J=12.9 and 8.9 Hz), 2.16 (1H, d, J=13.9 Hz), 3.15-3.36 (2H, m), 3.76 (3H, s), 4.25-4.40 (2H, m), 5.58 (1H, s), 5.91 (1H, s), 6.85 (1H, br); ^{13}C NMR δ 29.5, 29.7, 40.7, 46.3, 51.6, 53.5, 55.2, 57.0, 58.1, 67.4, 120.0, 131.1, 144.6, 149.9, 164.4, 170.1. Its IR and NMR spectra were identical with those of the natural product **1** MS: m/z 276.1345 (M^+). Calc for $C_{16}H_{20}O_4$: 276.1362. (Found: C, 69.27; H, 7.17. Calc for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29%).

Acknowledgement -- We thank Professor D. E. Cane, Brown University, for his kind cooperation to reisolate pentalenolactone E Methyl ester. Financial support of this work by Nisshin Flour Milling Co., Ltd. is acknowledged with thanks.

REFERENCES

1 D. E. Cane and T. Rossi, Tetrahedron Lett. 2973 (1979).
2 L. A. Paquette, G. D. Annis and H. Schostarez, J. Am. Chem. Soc. **104**, 6646 (1982).
3 T. Ohtsuka, H. Shirahama and T. Matsumoto, Tetrahedron Lett. **24**, 3851 (1983).
4 D. E. Cane, and P. J. Thomas, J. Am. Chem. Soc. **106**, 5295 (1984).
5 D. F. Taber and J. L. Schuchardt, J. Am. Chem. Soc. **107**, 5289 (1985); Idem, Tetrahedron **43**, 5677 (1987).
6 J. P. Marino, C. Silveira, J. Comasseto and N. Petragnani, J. Org. Chem. **52**, 4139 (1987).
7 D. H. Hua, M. J. Coulter and L. Badejo, Tetrahedron Lett. **28**, 5465 (1987).
8 K. Mori and M. Tsuji, Tetrahedron **42**, 435 (1986).
9 J. A. Dale and H. S. Mosher, J. Am. Chem. Soc. **95**, 512 (1973).
10 R. J. Rawson and I. T. Harrison, J. Org. Chem. **35**, 2057 (1970).
11 K. Maruoka, Y. Fukutani and H. Yamamoto, J. Org. Chem. **50**, 4412 (1985).
12 S. Juliá and A. Ginebreda, Synthesis 682 (1979).
13 P. G. Gassman and P. G. Pape, J. Org. Chem. **29**, 160 (1964).
14 E. J. Corey and J. W. Suggs, Tetrahedron Lett. 2647 (1975).
15 D. E. Cane, personal communication to K.M. dated April 22, 1987.