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Chemical Transformation of Terpenoids. III.[1] Syntheses of (3*R*)-1-Vinyl-, (3*R*)-1-Hydroxypropenyl-, and (3*R*)-1-Epoxyethyl-5-methoxy-1,2,2-trimethylcyclopentane Derivatives from *d*-Camphor *via* 5-Oxo-*d*-bornyl Acetate

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As a continuation of our transformation studies on terpenoids, three optically active 5-methoxy-1,2,2-trimethylcyclopentane derivatives, *i.e.*, (+)-(1*R*,3*R*,5*S*)-3-acetoxymethyl-5-methoxy-1,2,2-trimethyl-1-vinylcyclopentane (**7**), (+)-(1*R*,3*R*,5*S*)-3-acetoxymethyl-1-(3′-hydroxypropenyl)-5-methoxy-1,2,2-trimethylcyclopentane (**8**), and (−)-(1*R*,3*R*,5*S*,1′*R*)-3-acetoxymethyl-1-(1′,2′-epoxyethyl)-5-methoxy-1,2,2-trimethylcyclopentane (**9**), were synthesized from *d*-camphor (**1**) *via* 5-oxo-*d*-bornyl acetate (**6**). All three compounds (**7**, **8**, **9**) retain the C-4 configuration of *d*-camphor at their C-3 positions.

Keywords——*d*-camphor; 5-oxo-*d*-bornyl acetate; 5-methoxy-1-vinyl-1,2,2-trimethylcyclopentane; 1-hydroxypropenyl-5-methoxy-1,2,2-trimethylcyclopentane; 1-epoxyethyl-5-methoxy-1,2,2-trimethylcyclopentane; Horeau's method

In a previous paper,[2] we reported syntheses of four (3*S*)-1,2,2-trimethylcyclopentane derivatives from *d*-camphor (**1**), *i.e.*, (+)-(1*S*, 3*S*)-3-acetoxymethyl-1,2,2-trimethyl-1-vinylcyclopentane (**2**) [referred to as (+)-(3*S*)-vinylcyclopentane], (+)-(1*S*, 3*S*)-3-acetoxymethyl-1-(3′-hydroxypropenyl)-1,2,2-trimethylcyclopentane (**3**) [= (+)-(3*S*)-hydroxypropenylcyclopentane], (+)-(1*R*, 3*S*, 1′*S*)-3-acetoxymethyl-1-(1′,2′-epoxyethyl)-1,2,2-trimethylcyclopentane (**4**)[= (+)-(3*S*)-(1′*S*,2′)-epoxyethylcyclopentane], and (+)-(1*R*, 3*S*, 1′*R*)-3-acetoxymethyl-1-(1′,2′-epoxyethyl)-1,2,2-trimethylcyclopentane (**5**) [= (+)-(3*S*)-(1′*R*, 2′)-epoxyethylcyclopentane]. In the subsequent report,[1] the structural elucidation of the reaction products, which were obtained by acid treatment of these (3*S*)-1,2,2-trimethylcyclopentane derivatives (**2**—**5**), was described. It was found that **2** and **5** gave the ring-enlarged cyclohexane derivatives (**B**) which retained the C-3 configuration of **A** (*via* path b), while **4** furnished the cyclopentane derivatives which were derivable *via* path c and C.

As a continuation of these studies, we synthesized three (3*R*)-1,2,2-trimethylcyclopentane derivatives having a 5-methoxyl residue, *i.e.*, (+)-(1*R*, 3*R*, 5*S*)-3-acetoxymethyl-5-methoxy-1,2,2-trimethyl-1-vinylcyclopentane (**7**) [referred to hereafter as (+)-(3*R*)-vinylcyclopentane], (+)-(1*R*,3*R*,5*S*)-3-acetoxymethyl-1-(3′-hydroxypropenyl)-5-methoxy-1,2,2-trimethylcyclopentane (**8**) [= (+)-(3*R*)-hydroxypropenylcyclopentane], (−)-(1*R*, 3*R*, 5*S*, 1′*R*)-3-acetoxymethyl-1-(1′,2′-epoxyethyl)-5-methoxy-1,2,2-trimethylcyclopentane (**9**) [= (−)-(3*R*)-(1′*R*, 2′)-epoxyethylcyclopentane] and examined their behavior upon acid treatment under various conditions. This paper is a report on the synthesis of **7**, **8**, and **9** from 5-oxo-*d*-bornyl acetate (**6**), which was prepared from *d*-camphor (**1**) according to the known procedure.[3]

Our initial approach for the synthesis of (3*R*)-5-methoxy-1,2,2-trimethylcyclopentane derivatives was realized by cleavage of the C-5,6 bond of the 5-oxo-*d*-bornyl derivative (**11**) by use of the Baeyer–Villiger reaction. Thus, the keto-alcohol (**10**), which was prepared quantitatively from 5-oxo-*d*-bornyl acetate (**6**) by alkaline hydrolysis, was methylated to furnish the methyl ether (**11**) [infrared (IR) spectrum: no OH; proton nuclear magnetic resonance (^{1}H NMR) spectrum: δ 3.28 (3H, s)] in 74% yield. Oxidation of **11** with 9% peracetic acid in

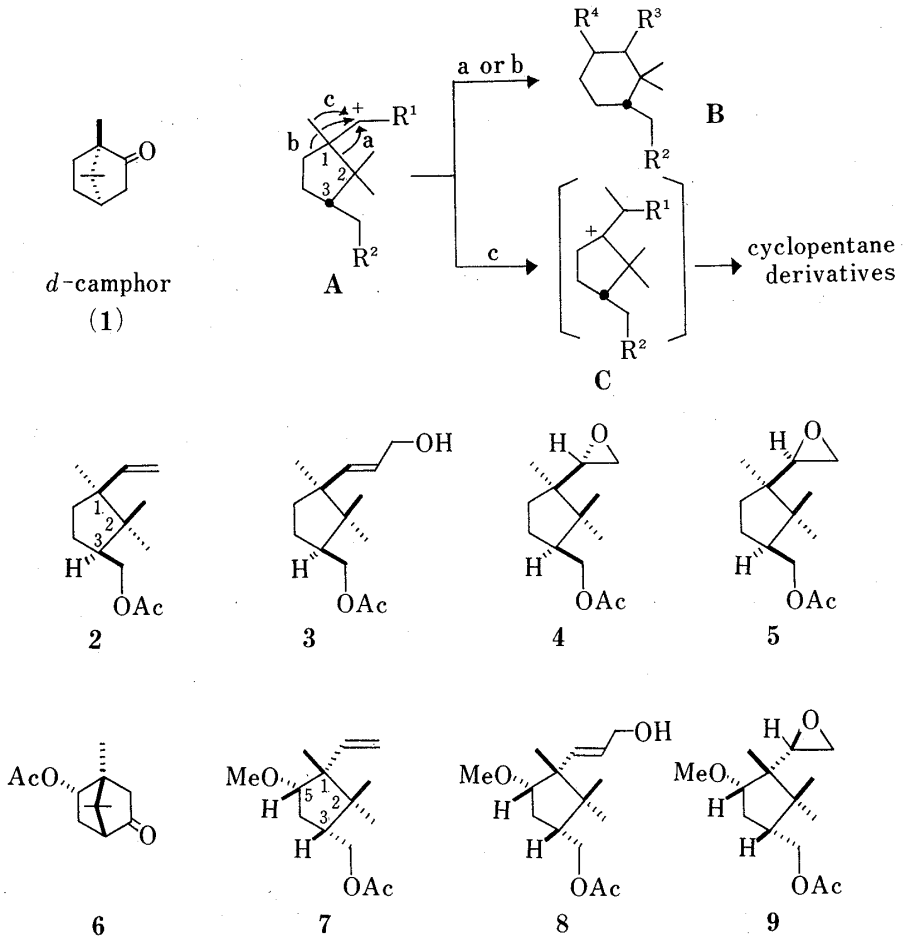

Chart 1

acetic acid[4] for 10 d yielded a mixture of two lactones, which, without isolation of each, product, was treated with lithium aluminum hydride to furnish two diols, **12** (41%) and **13** (14%), IR: 3300 cm^{-1} (OH) for both. The ^1H NMR spectra of both compounds clearly support their assigned structures: signals due to three tertiary methyl groups for **12** and **13** and signals due to protons on carbons bearing an oxygen function (5H, m, δ 3.3—4.0 for **12**; 1H, t-like at δ 3.34, 2H, m, at δ 3.66, and 1H, t-like at δ 3.95 for **13**).

Acetylation of the desired diol (**12**) gave two acetates, **14** (50%) and **15** (33%). The structure of the major monoacetate (**14**) was substantiated by its IR spectrum: 3470 (OH), 1740 (OAc) cm^{-1} and ^1H NMR spectrum: δ 1.97 (3H, s, OAc), 3.23 (3H, s, OMe), 3.27 ,3.75 (2H, ABq, J=10 Hz, a hydroxymethyl group attached to a quaternary carbon), 3.9—4.2 (2H, AB in ABX, an acetoxymethyl group attached to a tertiary carbon). The IR and ^1H NMR spectra of the minor diacetate are consistent with the structure **15**. Hydorlysis of the diacetate (**15**) with methanolic potassium hydroxide regenerated the parent diol (**12**) quantitatively.

The monoacetate (**14**) was then oxidized with pyridinium chlorochromate (PCC)[5] to quantitatively afford the aldehyde (**16**), which, on methylenation with methyltriphenylphosphonium bromide and dimsyl sodium, was converted to the vinylcyclopentane derivative: (+)-(3*R*)-vinylcyclopentane (**7**), our first target compound, in 91% yield. The IR spectrum of **7** shows the presence of a vinyl group (3080, 1633 cm^{-1}) and an acetoxyl group (1748 cm^{-1}), while the ^1H NMR spectrum shows signals due to three tertiary methyl groups, an acetoxyl group, a methoxyl group, an acetoxymethyl group attached to a tertiary carbon (δ 3.9—4.1, 2H, AB in ABX), and a vinyl group (δ 4.8—6.4, 3H, ABC).

Formylolefination[6] of the aldehyde (**16**) by treatment with diethyl 2-(cyclohexylimino)-ethylphosphonate and sodium hydride followed by acidic hydrolysis yielded the α,β-unsaturated

aldehyde (**17**) in 64% yield. The formation of the *E*-α,β-unsaturated aldehyde moiety in **17** was corroborated by the physical properties, the ultraviolet (UV) maximum at 226 nm (ε 15000); IR: 2730, 1695, and 1625 cm^{-1}; ^1H NMR: δ 5.94 (1H, A in ABX, J_{AB}=16 Hz, J_{AX}=8 Hz), δ 7.08 (1H, B in ABX, J_{AB}=16 Hz, J_{BX}=0 Hz), and δ 9.51 (1H, X in ABX, J_{AX}=8 Hz, J_{BX}=0 Hz). Reduction of **17** with sodium borohydride in methanol gave the hydroxypropenyl derivative: (+)-(3*R*)-hydroxypropenylcyclopentane (**8**), our second target compound, in 96% yield. The IR spectrum shows hydroxyl and acetoxyl absorption bands (3425, 1745 cm^{-1}), whereas the ^1H NMR spectrum shows signals due to three tertiary methyl groups, an acetoxyl group, and a methoxyl group together with signals ascribable to a methine-proton geminal to a methoxyl group (δ 3.25, 1H, t, J=5 Hz), four protons attached to the carbons bearing oxygen functions (δ 3.9—4.2, 4H, m), and two *E*-olefinic protons (δ 5.52 and 5.95, AB in ABX_2, J_{AB}=16 Hz, J_{BX}=5 Hz, J_{AX}=0 Hz).

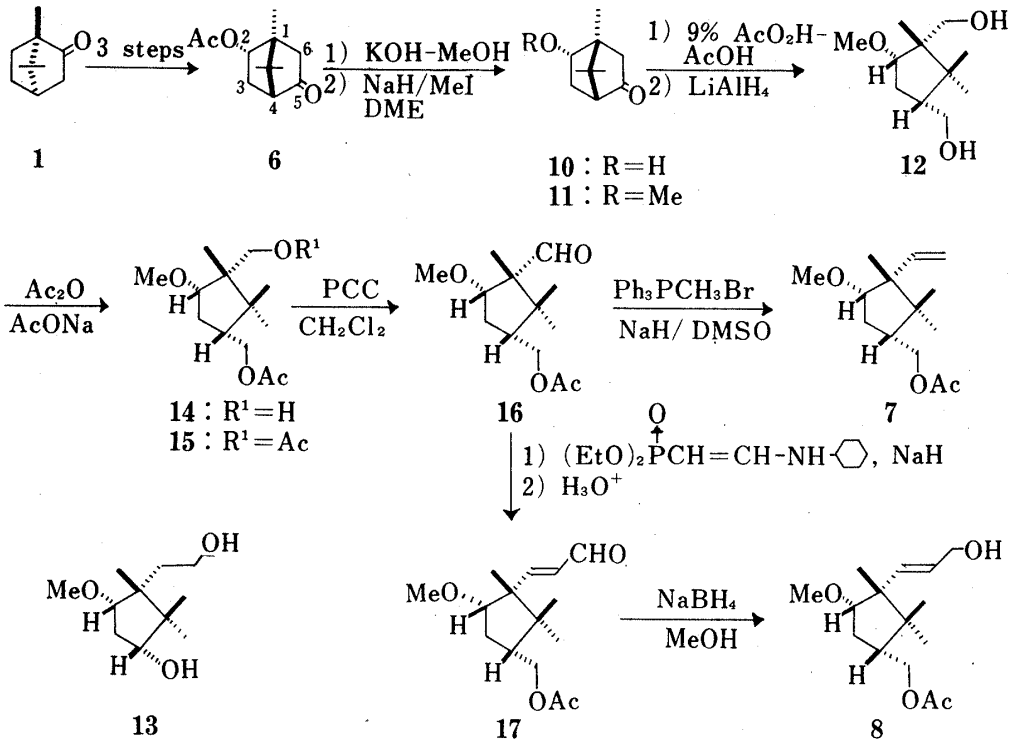

Chart 2

The hydroxypropenyl derivative (**8**) was more conveniently synthesized from 5-oxo-*d*-bornyl methyl ether (**11**) *via* the allyl derivative (**18**). During the course of this synthetic pathway, high regioselectivity was observed in the Baeyer-Villiger reaction from the ketone (**20**) to the lactone (**21**) and in the acetylation of the diol (**22**) to give the monoacetate (**23**).

After examination of the allylation of **11** under various conditions (Table I), the best result was obtained by the reaction of **11** with *n*-butyl lithium and allyl iodide in hexamethylphosphoramide (HMPA)-tetrahydrofuran (THF). The IR spectrum of the allyl derivative (**18**) thus obtained shows the presence of a vinyl group (3080, 1645 cm^{-1}) and a ketone moiety (1750 cm^{-1}), while the ^1H NMR spectrum shows signals due to vinyl protons (δ 4.8—6.1, 3H, ABC) and a methine-proton (2-H) geminal to a methoxyl group (δ 3.63, 1H, dd, J=9, 4 Hz). The long-range coupling, which is observed between 2β-H and 6β-H (both *exo*, $J_{2,6}$=2 Hz) in the ^1H NMR spectrum of **11**, is not observed in the spectrum of **18**. Thus, the *exo* configuration of the newly introduced allyl group in **18** has been proved.

Ozone oxidation of **18** followed by reductive degradation of the ozonide yielded the keto-aldehyde (**19**) in 85% yield. The structure is supported by the IR spectrum (2710, 1729,

Table I. Allylation of **11** under Various Reaction Conditions Using *n*-BuLi as the Base

Run[a]	Solvent	Allyl halide	Yield (%)	
			18	Recovered **11**
1	THF	Allyl bromide	20	45
2	5(v/v)% HMPA–THF	Allyl bromide	54	31
3	20(v/v)% HMPA–THF	Allyl bromide	40	40
4	50(v/v)% HMPA–THF	Allyl bromide	37	46
5	THF	Allyl iodide	25	41
6	5(v/v)% HMPA–THF	Allyl iodide	63	22

a) Reactions were carried out as described for run 6 (see "Experimental").

1748 cm^{-1}) and the ^1H NMR spectrum (no vinyl proton and 1H at δ 9.44, narrow m, $W_{h/2}$= 6 Hz). The keto-aldehyde (**19**) was then converted through the ordinary procedure to the monoketal (**20**), IR: no aldehyde, 1752 cm^{-1}; ^1H NMR: 4H, m, at δ3.7—3.9, 1H, t, J=5 Hz, at δ 4.91, in 84% yield. The retention of the C-6 configuration during the conversion from **18** to **20** is shown by the signal pattern of 2-H in the ^1H NMR spectrum of **20** (1H, dd, J=10, 4 Hz, at δ 3.66, no long-range coupling between 2-H and 6-H).

Baeyer–Villiger oxidation of **20** with 9% peracetic acid in acetic acid gave the lactone (**21**) in 31% yield together with unchanged **20** (57%). Although the yield of **21** was low, the oxidation proceeded regioselectively. The IR spectrum of **21** shows the lactone absorption band (1750 cm^{-1}), while the ^1H NMR spectrum shows signals ascribable to a methine proton on the ketal ring (δ 4.91, 1H, dd, J=9, 3 Hz) and another methine proton (6-H) on the lactone ring (δ 5.00, 1H, dd, J=4, 2 Hz). Reduction of **21** with lithium aluminum hydride quantitatively yielded a diol (**22**), whose IR spectrum demonstrates the loss of the ester function but shows a broad hydroxyl absorption band (3460 cm^{-1}).

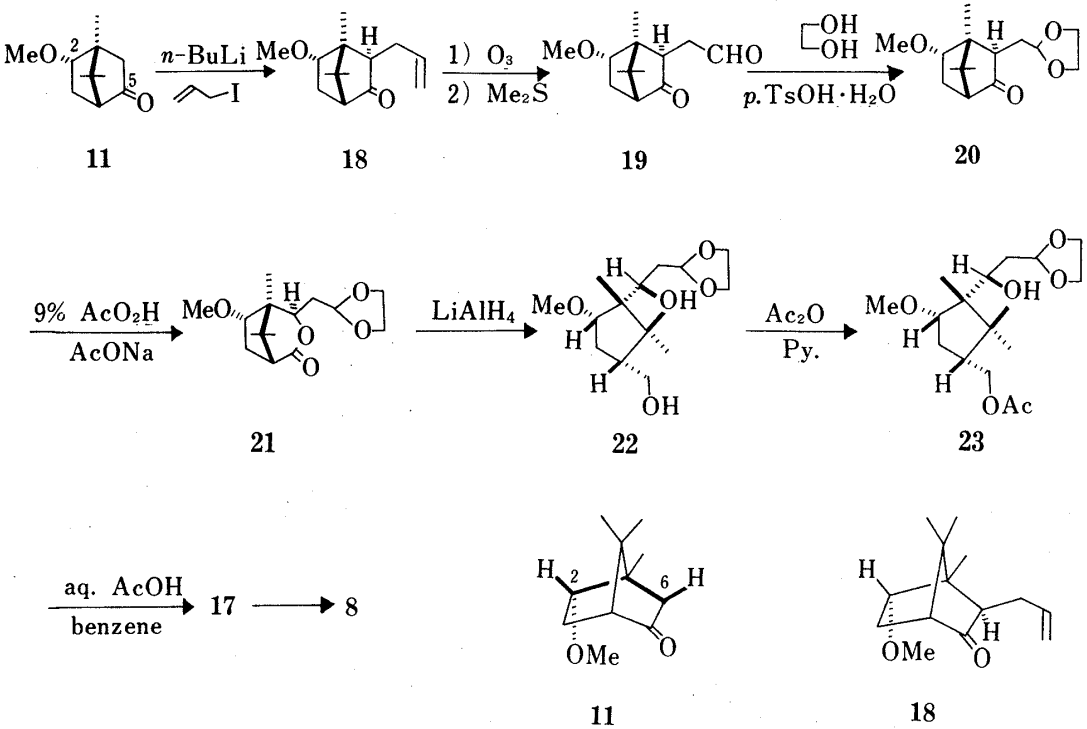

Chart 3

Acetylation of the diol (**22**) with acetic anhydride and pyridine selectively gave the monoacetate (**23**) (IR: 3570, 1745 cm^{-1}; ^1H NMR: δ 1.94, 3H, s), which, on heating under reflux with aqueous acetic acid in benzene, was converted to the α,β-unsaturated aldehyde (**17**) in 80% yield. Reduction of **17** gave **8** as described above.

(—)-(3*R*)-(1′*R*,2′)-Epoxyethylcyclopentane (**9**), the third target compound in this study, was synthesized from (—)-(3*R*)-vinylcyclopentane (**7**) by *m*-chloroperbenzoic acid oxidation. The epoxidation furnished **9** in 68% yield together with unchanged **7** (22%). The IR spectrum of this *levo*-rotatory epoxide (**9**) shows the acetoxyl absorption band (1745 cm^{-1}), and the ^1H NMR spectrum indicates the loss of vinyl protons and shows signals ascribable to three protons on the epoxide ring (δ 2.5—2.7, ABC).

The 1′*R* configuration in **9** was determined by the application of Horeau's method[7] to the monoacetyl derivative (**25**), which was derivable from **9** by lithium aluminum hydride reduction (giving **24**) then quantitative acetylation. The structure of **25** is supported by the physical properties, IR: 3550, 1735 cm^{-1}; ^1H NMR: δ 1.14 (3H, d, J=6 Hz, 1′-CH_3), 2.04 (3H, s, OAc), 3.24 (3H, s, OMe). Treatment of **25** with (±)-α-phenylbutyric anhydride in pyridine furnished the α-phenylbutyrate (**26**) together with α-phenylbutyric acid of $[\alpha]_D$ —2.2° (benzene). Thus, the 1′*S* configuration of **25** and consequently the 1′*R* configuration of the parent epoxide (**9**) has been determined.

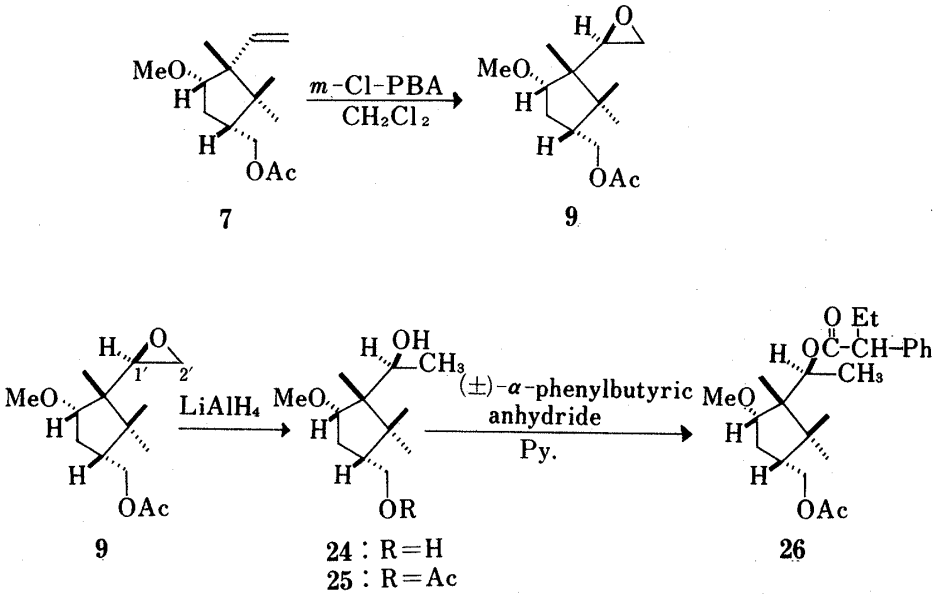

Chart 4

Thus, three optically active 5-methoxy-1,2,2-trimethylcyclopentane derivatives, *i.e.*, (+)-(3*R*)-vinylcyclopentane (**7**), (+)-(3*R*)-hydroxypropenylcyclopentane (**8**), and (—)-(3*R*)-(1′*R*, 2′)-epoxyethylcyclopentane (**9**), have been synthesized from *d*-camphor (**1**) *via* 5-oxo-*d*-bornyl acetate (**6**). Each compound possesses the 3*R* configuration which arises from the C-4 of *d*-camphor (**1**) in the turned-over manner. Chemical transformation studies on these compounds (**7**—**9**) will be reported in the following paper.[8]

Experimental

The instruments used to obtain physical data and the experimental conditions for chromatography were the same as described in our previous paper.[2]

Alkaline Hydrolysis of 5-Oxo-d-bornyl Acetate (6)——A solution of **6** (2.95 g)[3] in 5% KOH–MeOH (18 g) was stirred at room temperature for 1 h. After dilution with water (60 ml), the reaction mixture was concentrated under reduced pressure to remove MeOH. The resulting residue was extracted with EtOAc and work-up of the EtOAc extract in the usual manner gave **10** (2.29 g, 97%). **10**, colorless prisms (ether), dec. 70—75°C, $[\alpha]_D^{20}$ +80° (c=5.5, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.62. Found: C, 71.28; H, 9.62. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3630, 3460, 1755. ^1H NMR (CCl_4, δ): 0.91, 0.95, 0.98 (3H each, all s), 1.18 (1H, dd, J=14, 4 Hz, 3α-H), 2.01 (1H, d, J=6 Hz, 4-H), 1.75, 2.53 (1H each, ABq, J=18 Hz, 6-H_2), 4.12 (1H, m, 2β-H). MS m/z (%): 168 (45, M^+), 124 (100).

Methylation of 10 giving 11——A suspension of NaH (890 mg, 50% in oil, washed with n-pentane beforehand) in DME (40 ml) was treated dropwise with a solution of **10** (2.85 g) in DME (10 ml) and the whole mixture was stirred at room temperature for 1.5 h. The reaction mixture was cooled to 0°C then treated with CH_3I (3.5 ml) and stirred at room temperature for 3 h. The whole mixture was poured into ice-water and extracted with ether. The ether extract was dried over $MgSO_4$ and removal of the solvent under reduced pressure gave a product (3 g) which was purified by column chromatography (SiO_2, 270 g, n-hexane–EtOAc=3:1) to furnish **11** (2.34 g, 74%). **11**, $bp_{0.01}$ 48°C, colorless oil, $[\alpha]_D^{20}$ +115° (c=5.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1755. ^1H NMR (CCl_4, δ): 0.88, 0.91, 0.99 (3H each, all s), 3.28 (3H, s), 3.64 (1H, ddd, J=10, 4, 2 Hz, >C<u>H</u>–OMe). High resolution MS (m/z): Calcd for $C_{11}H_{18}O_2$: 182.127. Found: 182.128. MS m/z (%): 182 (50, M^+), 99 (100).

Peracetic Acid Oxidation followed by Reduction of 11 giving 12 and 13——A solution of **11** (11.7 g) in 9% AcO_2H–AcOH (92 ml) was treated with AcONa (5.4 g) and the whole mixture was left to stand at room temperature for 10 d. After dilution with EtOAc (500 ml), the reaction mixture was washed successively with aq. sat. $NaHCO_3$ and aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (12.5 g), which was purified by column chromatography (SiO_2, 500 g, n-hexane–EtOAc=3:2) to furnish a mixture of lactones (8.5 g). The mixture (8.5 g) was dissolved in THF (80 ml) and the solution was added dropwise to a suspension of $LiAlH_4$ (2.0 g) in THF (150 ml), then the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of aq. ether and acidified with aq. 5% H_2SO_4, then the mixture was extracted with EtOAc. The EtOAc extract was washed successively with aq. sat. $NaHCO_3$ and aq. sat. NaCl and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a product (8.5 g) which was purified by column chromatography (SiO_2, 600 g, n-hexane–EtOAc=2:1) to furnish **12** (5.4 g, 41%) and **13** (1.8 g, 14%). **12**, mp 94—95°C (colorless rods from $CHCl_3$), $[\alpha]_D^{20}$ +28° (c=1.0, EtOH). *Anal.* Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.13; H, 10.87. IR ν_{max}^{KBr} cm^{-1}: 3300. ^1H NMR ($CDCl_3$, δ): 0.84, 0.94, 0.99 (3H each, all s), 3.28 (3H, s), 3.3—4.0 (5H, m, >C<u>H</u>–OMe, –C<u>H_2</u>–OH×2). MS m/z (%): 170 (3, M^+−MeOH), 84 (100). **13**, mp 94—96°C (colorless plates from $CHCl_3$), $[\alpha]_D^{20}$ +35° (c=1.1, EtOH). *Anal.* Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.06; H, 10.93. IR ν_{max}^{KBr} cm^{-1}: 3300. ^1H NMR ($CDCl_3$, δ): 0.83, 0.86, 0.87 (3H each, all s), 3.24 (3H, s), 3.34 (1H, t-like, >C<u>H</u>–OMe), 3.66 (2H, m, –CH_2–C<u>H_2</u>–OH), 3.95 (1H, t-like, >C<u>H</u>–OH). MS m/z (%): 202 (0.3, M^+), 87 (100).

Acetylation of 12 giving the Monoacetate (14) and the Diacetate (15)——A solution of **12** (1.3 g) in CH_2Cl_2 (10 ml) was treated with AcONa (1.5 g) and Ac_2O (2 ml) and the whole mixture was stirred at room temperature for 10 h. The reaction mixture was poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract as usual and removal of the solvent under reduced pressure gave a product (1.8 g), which was subjected to column chromatography (SiO_2, 100 g, n-hexane–EtOAc=1:1) to furnish **14** (0.76 g, 50%) and **15** (0.6 g, 33%). **14**, colorless oil, $[\alpha]_D^{24}$ +41° (c=3.4, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.79; H, 10.15. IR ν_{max}^{film} cm^{-1}: 3470, 1740. ^1H NMR (CCl_4, δ): 0.88 (3H, s), 0.96 (6H, s), 1.97 (3H, s), 3.23 (3H, s), 3.2—3.5 (1H, m, >C<u>H</u>–OMe), 3.27, 3.75 (1H each, ABq, J=10 Hz, –C(CH)–C<u>H_2</u>–OH), 3.9—4.2 (2H, AB in ABX, >CH–C<u>H_2</u>–OAc). MS m/z (%): 184 (7, M^+−AcOH), 43 (100). **15**, colorless oil, $[\alpha]_D^{24}$ +25° (c=0.2, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.85; H, 9.29. IR ν_{max}^{film} cm^{-1}: 1738. ^1H NMR (CCl_4, δ): 0.92, 0.94, 0.99 (3H each, all s), 1.96, 1.98 (3H each, both s), 3.20 (3H, s), 3.2—3.4 (1H, m, >C<u>H</u>–OMe), 3.8—4.2 (4H, m, –C<u>H_2</u>–OAc×2). MS m/z (%): 226 (2, M^+−AcOH), 43 (100).

Alkaline Hydrolysis of 15 Regenerating 12——**15** (5 g) was dissolved in 10% KOH–MeOH (5 g) and the solution was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave a product (3.5 g, 99%) which was identical with **12** as judged by TLC, $[\alpha]_D$ (EtOH), IR (KBr), and ^1H NMR ($CDCl_3$) comparisons.

PCC Oxidation of 14 giving the Aldehyde (16)——A solution of **14** (1.51 g) in CH_2Cl_2 (8 ml) was treated with PCC (2.0 g) and the whole was stirred at room temperature for 1.5 h. After dilution with ether (100 ml), the whole mixture was passed through a Florisil column (70—100 mesh, 10 g). Removal of the solvent from the eluate under reduced pressure gave an aldehyde (**16**) (1.5 g, 97%), colorless oil, $[\alpha]_D^{15}$ +15° (c=2.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2730, 1718 (CHO), 1735 (OAc). ^1H NMR (CCl_4, δ): 0.94, 0.98, 1.07 (3H each, all s), 1.96 (3H, s), 3.23 (3H, s), 3.42 (1H, dd, J=7, 5 Hz, >C<u>H</u>–OMe), 3.9—4.1 (2H, m, –C<u>H_2</u>–OAc), 9.86 (1H, s, –CHO). High resolution MS (m/z): Calcd for $C_{13}H_{22}O_4$: 242.152. Found: 242.151 MS m/z (%): 242 (0.2, M^+), 84 (100).

(+)-(3*R*)-Vinylcyclopentane (7) from 16——A dimsyl carbanion-DMSO solution [prepared from 0.35 g of NaH (7.3 mmol) and 3.6 ml of DMSO] was mixed with a solution of methyltriphenylphosphonium bromide (2.75 g, 7.8 mmol) in DMSO (7.2 ml) and the whole was stirred at room temperature for 1 h. The mixture was then treated with a solution of **16** (1.1 g, 4.6 mmol) in DMSO (2 ml) and the whole was stirred for a further 10 h. The mixture was poured into ice-water and extracted with *n*-hexane. The *n*-hexane extract was washed successively with aq. 5% HCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (1.2 g) which was purified by column chromatography (SiO_2, 30 g, *n*-hexane–EtOAc=4: 1) to furnish **7** (1.0 g, 91%), colorless oil, $[\alpha]_D^{23}$ +17° (*c*=1.8, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.06; H, 10.01. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3080, 1633 (vinyl), 1748 (OAc). ^1H NMR (CCl_4, δ): 0.81, 0.87, 0.92 (3H each, all s), 1.94 (3H, s), 3.20 (3H, s), 3.9—4.1 (2H, AB in ABX, >CH–C<u>H</u>$_2$–OAc), 4.8—6.4 (3H, ABC, vinyl protons). MS *m/z* (%): 208 (35, M^+ − AcOH), 43 (100).

Formylmethylenation of 16 giving the Unsaturated Aldehyde (17)——An ice-cooled suspension (0°C) of NaH (0.56 g, 50% in oil, 11.5 mmol, washed with *n*-hexane beforehand) in THF (5 ml) was treated dropwise over a period of 15 min with a solution of diethyl 2-(cyclohexylimino)ethylphosphonate (3.0 g, 11.5 mmol) in THF (8 ml). The mixture was stirred at 0°C for 45 min, and a solution of **16** (2.4 g, 9.9 mmol) in THF (16 ml) was added. The whole was stirred at room temperature for 24 h then poured into ice-water. The mixture was extracted with EtOAc and the extract was washed with aq. sat. NaCl and worked up in the usual manner to give an oily product (4.0 g). A benzene (50 ml) solution of the product was mixed with aq. 0.8% oxalic acid (60 ml) and heated under reflux for 1 h. After cooling, the organic phase was separated. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with aq. sat. $NaHCO_3$ and aq. sat. NaCl then dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a product (2.6 g) which was purified by column chromatography (SiO_2, 90 g, *n*-hexane–EtOAc=3: 1) to furnish **17** (1.8 g, 64%), colorless oil, $[\alpha]_D^{20}$ +3.3° (*c*=0.7, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2730, 1745, 1695, 1625. UV λ_{max}^{MeOH} nm (ε): 226 (15000). ^1H NMR (CCl_4, δ): 0.88, 0.93, 1.02 (3H each, all s), 1.96 (3H, s), 3.22 (3H, s), 3.99 (2H, d, *J*=6 Hz, –C<u>H</u>$_2$–OAc), 5.94 (1H, A in ABX, J_{AB}=16 Hz, J_{AX}=8 Hz), 7.08 (1H, B in ABX, J_{AB}=16 Hz, J_{BX}=0 Hz), 9.51 (1H, X in ABX, J_{AX}=8 Hz, J_{BX}=0 Hz) (–CH_B=CH_A–CH_XO). High resolution MS (*m/z*): Calcd for $C_{15}H_{24}O_4$: 268.167. Found: 268.166. MS *m/z* (%): 268 (0.5, M^+), 84 (100).

$NaBH_4$ Reduction of 17 giving (+)-(3*R*)-Hydroxypropenylcyclopentane (8)——A solution of **17** (1.06 g, 4 mmol) in MeOH (30 ml) was treated with $NaBH_4$ (150 mg, 4 mmol) at 0°C and the mixture was stirred for 30 min. The reaction mixture was poured into ice-water and extracted with EtOAc. Work-up of the EtOAc extract in the usual manner and removal of the solvent under reduced pressure gave a product (**8**) (1.02 g, 96%), colorless oil, $[\alpha]_D^{13}$ +27° (*c*=4.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3425, 1745. ^1H NMR (CCl_4, δ): 0.83, 0.86, 0.96 (3H each, all s), 1.97 (3H, s), 3.21 (3H, s), 3.25 (1H, t, *J*=5 Hz, –C<u>H</u>–OMe), 3.9—4.2 (4H, m, –C<u>H</u>$_2$–OAc, –CH=CH–C<u>H</u>$_2$OH), 5.52 (1H, B in ABX_2, J_{AB}=16 Hz, J_{BX}=5 Hz), 5.95 (1H, A in ABX_2, J_{AB}=16 Hz, J_{AX}=0 Hz) (–CH_A=CH_B–CH_{X_2}OH). High resolution MS (*m/z*): Calcd for $C_{15}H_{26}O_4$: 270.183. Found: 270.183. MS *m/z* (%): 270 (0.1, M^+), 93 (100).

Allylation of 11 giving 18——A solution of **11** (1.0 g, 5.5 mmol) in 5(v/v)% HMPA–THF (40 ml) was treated dropwise at 0°C over a period of 5 min with a 1.7 N *n*-hexane solution of *n*-BuLi (5.5 ml, 9.35 mmol) and the whole was stirred for 30 min. The reaction mixture was stirred further at room temperature for 6 h and treated with allyl iodide (7.5 ml, 83 mmol, freshly distilled before use). Then the reaction mixture was stirred for 8 h and poured into ice-water. The whole mixture was extracted with EtOAc. Work-up of the EtOAc extract and removal of the solvent under reduced pressure gave a product (1.5 g) which was purified by column chromatography (SiO_2, 100 g, benzene–$CHCl_3$=1: 2) to furnish **18** (0.77 g, 63%) and **11** (0.22 g, 22%, recovered). **18**, mp 36.5—37.5°C (colorless needles from *n*-hexane), $[\alpha]_D^{20}$ +150° (*c*=2.0, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.38; H, 9.94. IR ν_{max}^{film} cm^{-1}: 3080, 1645 (terminal methylene), 1750 (ketone). ^1H NMR (CCl_4, δ): 0.84, 0.91, 0.98 (3H each, all s), 3.31 (3H, s), 3.63 (1H, dd, *J*=9, 4 Hz, >C<u>H</u>–OMe), 4.8—6.1 (3H, ABC, vinyl protons). MS *m/z* (%): 222 (5, M^+), 181 (100).

Ozone Oxidation of 18 giving the Aldehyde (19)——A solution of **18** (610 mg) in *n*-pentane (50 ml) was bubbled through with a stream of ozonated oxygen at −78°C for 90 min (10 ml/min). Excess ozone was flushed out with a nitrogen stream and the whole mixture was gradually allowed to come to room temperature. Removal of the solvent by evaporation under reduced pressure gave a product (700 mg) which was dissolved in MeOH (8 ml) and cooled to −10°C. The solution was treated with Me_2S (8 ml) and stirred for 1 h. The whole mixture was then stirred at room temperature for 5 h. Removal of the solvent under reduced pressure gave a product (600 mg) which was purified by column chromatography (SiO_2, 30 g, *n*-hexane–EtOAc=2: 1) to furnish **19** (520 mg, 85%), colorless oil, $[\alpha]_D^{20}$ +160° (*c*=0.55, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2710, 1729 (CHO), 1748 (ketone). ^1H NMR (CCl_4, δ): 0.82, 0.91, 0.93 (3H each, all s), 3.37 (3H, s), 3.72 (1H, dd, *J*=10, 4 Hz, >C<u>H</u>–OMe), 9.44 (1H, narrow m, $W_{h/2}$=6 Hz, –CHO). High resolution MS (*m/z*): Calcd for $C_{13}H_{20}O$: 224.140. Found: 224.140. MS *m/z* (%): 224 (1, M^+), 138 (100).

Ketalization of 19 giving the Monoketal (20)——A solution of **19** (2.27 g, 10 mmol) in benzene (150 ml) was treated with ethylene glycol (0.8 ml, 13 mmol) and *p*-TsOH·H_2O (one microspatulafull) and the whole mixture was heated under reflux for 1.5 h while removing water azeotropically. After cooling, the reaction mixture was washed with aq. sat. $NaHCO_3$ and aq. sat. NaCl then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave **20** (2.26 g, 84%). **20**, mp 107—108°C (colorless rods from EtOAc), $[\alpha]_D^{20}$ +127°

(c=3.6, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.06; H, 9.01. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1752. ^1H NMR (CCl_4, δ): 0.80, 0.91,1.00 (3H each, all s), 3.30 (3H, s), 3.66 (1H, dd, J=10, 4 Hz, –C<u>H</u>–OMe), 3.7—3.9 (4H, m, –O–C<u>H</u>$_2$C<u>H</u>$_2$–O–), 4.91 (1H, t, J=5 Hz, –C<u>H</u>$\langle^{O}_{O}\rangle$). MS m/z (%); 268 (2, M^+), 73 (100).

Baeyer-Villiger Oxidation of 20 giving the Lactone (21)——A solution of **20** (400 mg, 1.5 mmol) in 9% AcO_2H–AcOH (14.5 ml, 18 mmol) was treated with AcONa (500 mg, 6.1 mmol) and the whole was left to stand in the dark at room temperature for 24 h. The reaction mixture was poured into ice-water and the whole was neutralized with $NaHCO_3$ powder and extracted with EtOAc. Work-up of the EtOAc extract in the usual manner and removal of the solvent under reduced pressure gave a product (410 mg) which was purified by column chromatography (SiO_2, 20 g, n-hexane–EtOAc=1: 1) to furnish **21** (130 mg, 31%) and **20** (230 mg, 57%, recovered). **21**, mp 76.5—77°C (colorless needles from ether), $[\alpha]_D^{20}$ +152° (c=2.6, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.19; H, 8.45. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1750. ^1H NMR (CCl_4, δ): 0.90, 0.96, 1.06 (3H each, all s), 3.33 (3H, s), 3.5—4.0 (5H, m, –O–C<u>H</u>$_2$C<u>H</u>$_2$–O–, >C<u>H</u>–OMe), 4.91 (1H, dd, J=9, 3 Hz), 5.00 (1H, dd, J=4, 2 Hz). MS m/z (%): 284 (1, M^+), 73 (100).

LiAlH$_4$ Reduction of 21 giving the Diol (22)——A solution of **21** (890 mg, 3.2 mmol) in ether (40 ml) was added dropwise over a period of 10 min to a suspension of $LiAlH_4$ (180 mg, 4.8 mmol) in ether (20 ml) and the whole was stirred at room temperature for 30 min. After decomposition of the excess reagent with EtOAc, the reaction mixture was poured into ice-water and extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave **22** (900 mg, >99%), amorphous, $[\alpha]_D^{20}$ +5.0° (c=1.6, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3460 (br). ^1H NMR (CCl_4, δ): 0.84, 0.97, 1.04 (3H each, all s), 3.13 (3H, s), 3.0—4.3 (8H, m, >C<u>H</u>$_2$–OH, –C<u>H</u>–OH, –C<u>H</u>–OMe, –O–C<u>H</u>$_2$C<u>H</u>$_2$–O–), 4.94 (1H, dd, J=6, 3 Hz, –C<u>H</u>$\langle^{O}_{O}\rangle$). High resolution MS (m/z): Calcd for $C_{15}H_{28}O_5$: 288.193. Found: 288.192. MS m/z (%): 288 (0.1, M^+), 73 (100).

Acetylation of 22 giving the Monoacetate (23)——A solution of **22** (1.1 g) in pyridine (10 ml) was treated with Ac_2O (2 ml) and left to stand at room temperature for 12 h. The mixture was poured into ice-water and extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave a product (**23**) (1.15 g, 92%), colorless oil, $[\alpha]_D^{20}$ +12° (c=1.0, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3570, 1745. ^1H NMR (CCl_4, δ): 0.86, 1.03, 1.09 (3H each, all s), 1.94 (3H, s), 3.12 (3H, s), 3.8—4.1 (7H, m, >C<u>H</u>–OMe, –C<u>H</u>$_2$–OAc, –O–C<u>H</u>$_2$C<u>H</u>$_2$–O–), 4.21 (1H, dd, J=8, 2 Hz, –C–C<u>H</u>(OH)–CH$_2$–), 4.91 (1H, dd, J=6, 3 Hz, –C<u>H</u>$\langle^{O}_{O}\rangle$). High resolution MS (m/z): Calcd for $C_{17}H_{30}O_6$: 330.204. Found: 330.204. MS m/z (%): 330 (0.5, M^+), 73 (100).

Acid Treatment of 23 giving the Unsaturated Aldehyde (17)——A solution of **23** (660 mg) in benzene (30 ml) was treated with AcOH (30 ml) and water (1.8 ml) and heated under reflux for 40 h. After cooling, the reaction mixture was poured into ice-water and extracted with EtOAc. Work-up of the EtOAc extract gave a product (510 mg) which was purified by column chromatography (SiO_2, 50 g, benzene–EtOAc=2: 1) to furnish the unsaturated aldehyde (430 mg, 80%), which was identical with **17** as judged by TLC, $[\alpha]_D$ ($CHCl_3$), IR (CCl_4), and ^1H NMR (CCl_4) comparisons.

Epoxidation of 7 giving (–)-(3*R*)-(1′*R*,2′)-Epoxyethylcyclopentane (9)——A solution of **7** (1.0 g, 4.16 mmol) in CH_2Cl_2 (20 ml) was treated with 80% m-chloroperbenzoic acid (1.4 g, 6.24 mmol) and the mixture was stirred at 0°C for 6 h. After addition of aq. 5% Na_2SO_3, the whole was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed successively with aq. sat. $NaHCO_3$ and aq. sat. NaCl then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (1.1 g) which was chromatographed on a silica gel column (SiO_2, 50 g) with n-hexane–EtOAc (4: 1) to furnish **9** (0.72 g, 68%) and **7** (0.22 g, 22%, recovered). **9**, colorless oil, $[\alpha]_D^{20}$ −30° (c=1.8, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3035, 1745. ^1H NMR (CCl_4, δ): 0.56, 0.91, 1.03 (3H each, all s), 1.94 (3H, s), 2.5—2.7 (3H, ABC, –C<u>H</u>$\langle^{O}$–CH$_2$), 3.31 (3H, s), 3.8—4.2 (2H, AB in ABX, >CH–C<u>H</u>$_2$–OAc). High resolution MS (m/z): Calcd for $C_{14}H_{24}O_4$: 256.167. Found: 256.167. MS m/z (%): 256 (0.2, M^+), 85 (100).

LiAlH$_4$ Reduction of 9 giving the Diol (24)——A solution of **9** (150 mg, 0.60 mmol) in THF (8 ml) was added dropwise to a suspension of $LiAlH_4$ (60 mg, 1.6 mmol) in THF (2 ml) and the whole was heated under reflux for 6 h, then cooled. Excess reagent was decomposed with EtOAc and the reaction mixture was treated with aq. 5% NaOH (0.5 ml). The resulting gray precipitate was filtered off and the filtrate was dried over $MgSO_4$. Removal of the solvent under reduced pressure gave **24** (120 mg, 95%). **24**, mp 86—87°C (colorless needles from n-hexane), $[\alpha]_D^{20}$ +52° (c=3.8, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.38; H, 11.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3615, 3420. ^1H NMR ($CDCl_3$, δ): 0.87, 0.89, 0.98 (3H each, all s), 1.13 (3H, d, J=6 Hz), 3.24 (3H, s), 3.3—3.9 (3H, m, >C<u>H</u>–OMe, >CH–C<u>H</u>$_2$–OH), 4.22 (1H, q, J=6 Hz, –C<u>H</u>(OH)–CH$_3$). MS m/z (%): 216 (1, M^+), 125 (100).

Acetylation of 24 giving the Monoacetate (25)——A solution of **24** (80 mg, 0.37 mmol) in pyridine (2 ml) was treated with Ac_2O (0.2 ml, 2.1 mmol) and left to stand at 0°C for 6 h. The mixture was poured into ice-water and extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave a product (110 mg), which was purified by column chromatography (SiO_2, 5 g, n-hexane–EtOAc=3: 1) to furnish **25** (90 mg, 94%), colorless oil, $[\alpha]_D^{19}$ +46° (c=1.5, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 64.87; H, 10.07. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3550, 1735. ^1H NMR ($CDCl_3$, δ): 0.92 (6H, s), 1.00 (3H, s), 1.14 (3H,

d, J=6 Hz), 2.04 (3H, s), 3.24 (3H, s), 3.3—3.6 (1H, m, >C<u>H</u>–OMe), 3.9—4.3 (3H, m, –C<u>H</u>(OH)–CH_3, –$C\underline{H}_2$–OAc). MS m/z (%): 258 (1, M^+), 122 (100).

α-Phenylbutylation of 25 giving 26——A solution of **25** (25 mg, 0.10 mmol) in pyridine (0.5 ml) was treated with (±)-α-phenylbutyric anhydride (190 mg, 0.62 mmol) and the whole was stirred at 55°C for 91 h. After addition of water (5 ml), the whole was left to stand for 30 min and extracted with EtOAc. The organic phase was separated and washed with aq. sat. $NaHCO_3$. The combined aqueous phase and washing was washed again with EtOAc, and acidified with aq. 5% HCl. Work-up in the usual manner furnished α-phenylbutyric acid (140 mg), $[\alpha]_D^{19}$ −2.2° (c=5.6, benzene). The organic phase was washed successively with aq. 5% HCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl and worked up in the usual manner to give a product (35 mg). Purification of the product by column chromatography (SiO_2, 3 g, n-hexane–EtOAc=5: 1) furnished α-phenylbutyrate (**26**) (20 mg, 51%) and **25** (10 mg, 40%, recovered). **26**, colorless oil, $[\alpha]_D^{19}$ +42° (c=1.5, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3075, 3030, 1743, 1601. High resolution MS (m/z): Calcd for $C_{24}H_{36}O_5$: 404.256. Found: 404.257. MS m/z (%): 404 (0.6, M^+), 261 (100). Recovered α-phenylbutyric acid: $[\alpha]_D^{19}$ −2.2° (c=5.6, benzene).

References and Notes

1) Part II: I. Kitagawa, H. Shibuya, H. Fujioka, A. Kajiwara, Y. Yamamoto, S. Tsujii, and K. Murakawa, *Chem. Pharm. Bull.*, **29**, 2548 (1981).
2) Part I: I. Kitagawa, H. Shibuya, H. Fujioka, A. Kajiwara, Y. Yamamoto, A. Takagi, and M. Hori, *Chem. Pharm. Bull.*, **29**, 2540 (1981).
3) J. Meinwald, J.C. Shelton, G.L. Buchannan, and A. Courtin, *J. Org. Chem.*, **33**, 99 (1968).
4) R.R. Sauers, *J. Am. Chem. Soc.*, **81**, 925 (1959).
5) E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, **1975**, 2647.
6) W. Nagata and Y. Hayase, *J. Chem. Soc.* (*C*), **1969**, 460.
7) A. Horeau, *Tetrahedron Lett.*, **1961**, 506; **1962**, 965.
8) H. Shibuya, H. Fujioka, Y. Yamamoto, K. Suzuki, and I. Kitagawa, *Chem. Pharm. Bull.*, **30**, 1280 (1982).