A Stereoselective Route to the Prostaglandin Intermediate from Norbornadiene

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Tricyclic compound **2** which was prepared from norbornadiene (**1**) was shown to be an excellent starting material for the preparation of prostaglandins. **2** was transformed reductively into the bicyclic ketene dichloride **3** with zinc and acetic acid which on tosylation followed by solvolysis afforded the epimeric tricyclic acetate **5**. Hydrolysis, followed by Jones oxidation, of **5** afforded the tricyclic ketone **9** in an excellent yield. The cyclopropane ring of **9** was cleaved regio- and stereoselectively with hydrobromic acid to give the bromo ketone **11** which upon the Baeyer–Villiger oxidation, followed by heating with ethanol, provided the monocyclic ester **13**. **13** was treated with mercuric acetate or silver perchlorate under the solvolytic condition to form the lactone **16** stereoselectively. The Corey prostaglandin aldehyde (**18**) was prepared in two steps by acylation with 4-phenylbenzoyl chloride and subsequent ozonolysis.

Corey's group[1] and Sutherland's group[2] have independently described the synthesis of the synthon for all the primary prostaglandins from norbornadiene (**1**). We wish to report here an alternative synthesis of the synthon **18**[3] from norbornadiene (**1**) by a stereoselective sequence which would allow a practical production of the prostaglandins. Special practical values of this synthesis are mild reaction conditions employed, dispensability of chromatographic purifications,

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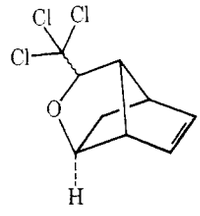

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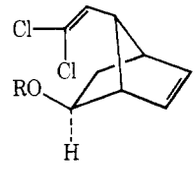
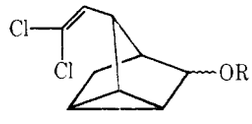


3, R = H
4, R = *p*-tosyl



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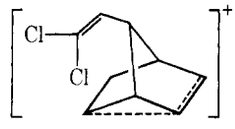
6, R = H



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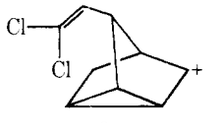

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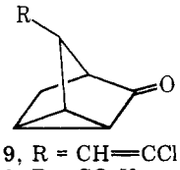
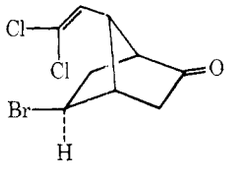


9, R = CH=CCl$_2$
10, R = CO$_2$H



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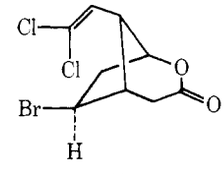

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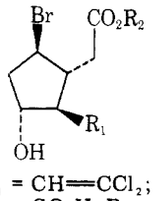
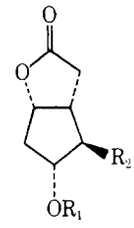


13, R$_1$ = CH=CCl$_2$; R$_2$ = Et
14, R$_1$ = CO$_2$H; R$_2$ = H



15, R$_1$ = H; R$_2$ = CO$_2$H
16, R$_1$ = H; R$_2$ = CH=CCl$_2$
17, R$_1$ = PB; R$_2$ = CH=CCl$_2$
18, R$_1$ = PB; R$_2$ = CHO
19, R$_1$ = PB; R$_2$ = CH$_2$OH
20, R$_1$ = H; R$_2$ = CH=CH—C(OH)H—*n*-C$_5$H$_{11}$

PB = *p*-phenylbenzoyl

and a good overall conversion. Further, this approach would be applied to the synthesis of the Fried prostaglandin synthon (**20**),[4] since the key intermediate (**16**) of the synthon **18** possessed a potential acetylenic function at the right position as a ketene dichloride group.[5]

The tricyclic compound **2**, prepared by following Fritz et al.,[6] from norbornadiene (**1**) and chloral in the presence of aluminum chloride, was treated with zinc and acetic acid to give the bicyclic ketene dichloride **3** in a 74.2% yield. This was tosylated with *p*-toluenesulfonyl chloride in pyridine affording the tosylate **4**, which on treatment with potassium acetate in acetic acid at 50–52 °C gave the tricyclic acetate **5** as an 1:1 epimeric mixture in an excellent overall yield. In the solvolysis a bulky dichloroketene group would control the regioselectivity leading to the exclusive formation of a localized carbonium ion (**8**) through a nonclassical carbonium ion (**7**) and the stability of the ion **8** would allow the nonstereoselective nucleophilic attack from both endo and exo sides to form an epimeric mixture of the acetates (**5**). However, the nonstereoselectivity was not an important problem from the synthetic point of view, since the epimeric center was lost in the later stage. Hydrolysis of this mixture with ethanolic potassium carbonate afforded an epimeric mixture of the alcohols (**6**), quantitatively, which on oxidation by means of the Jones reagent gave rise to the tricyclic ketone **9** as a sole product in a 95.8% yield. The structure and stereochemistry of the products was established by transforming **6** into the known keto acid **10**[1,2] through a two-stage oxidation by ozonolysis, followed by Jones oxidation. Electrophilic regio- and stereochemical ring opening of the cyclopropyl ketone system in **9** was accomplished cleanly to give an 87.6% yield of the bicyclic bromo ketone **11** by hydrobromic acid in hot acetic acid which has been successfully applied to the keto acid **10** by Sutherland's

group.[2] By use of 1.2 molar equiv of *m*-chloroperbenzoic acid in chloroform or methylene chloride at room temperature, the bromo ketone **11** was oxidized chemo- and regioselectively to yield the δ-lactone **12** as a sole product. Susceptibility of the lactone **12** to the alcoholic solvent made us isolate the product as the monocyclic ethyl ester **13** after a brief heating of the reaction mixture with ethanol in the presence of *p*-toluenesulfonic acid. Since intramolecular lactonization catalyzed by hydroxide ion, which has been successfully employed to convert the similar compounds (**14**[1] and **14**[2], Br = Cl) into the lactone **15**, was ineffective to our compound (**13**), an alternative method was developed. Initially we selected mercuric acetate as a catalyst to convert **13** into the lactone **16** under the solvolytic condition. This choice was based on the observation by McKillop and Ford[7] that mercuric salts catalyzed the solvolytic nucleophilic substitution of aliphatic halides. The bromo ester **13** was treated with 1 molar equiv of mercuric acetate in the presence of perchloric acid in aqueous dimethoxyethane at room temperature to yield the lactone **16** in a 79.0% yield. A substitution of poisonous mercuric acetate was simply achieved by using silver salt instead. Thus, the treating of the bromo ester **13** with 1 molar equiv of silver perchlorate under the same condition as the mercuric salt gave rise to **16** in an 82.8% yield with a precipitation of a recoverable solid silver by-product. The conversion of the lactone **16** into the prostaglandin synthon (the Corey aldehyde) (**18**) was completed by a two-step sequence by acylating with *p*-phenylbenzoyl chloride, followed by ozonolysis in an excellent overall yield. The unstable aldehyde **18** was reduced with sodium borohydride to give the known alcohol **19** which was completely identical with the authentic material. Conversion of the lactone **16** into the Fried prostaglandin synthon **20** is now under investigation.

Experimental Section[8]

7-(2,2-Dichlorovinyl)-5-hydroxy-2-norbornene (3). To a stirred suspension of 5-trichloromethyl-4-oxatricyclo[4.3.0.0^{3,7}]non-8-ene (**2**,[6] 11.98 g, 50 mmol) and zinc powder (22.88 g, 0.35 g-atom) in ether (300 ml) was added a solution of acetic acid (50 ml) in ether (200 ml) at 0 °C and the mixture was stirred for 8 h at room temperature. The organic layer was filtered and the insoluble material was washed thoroughly with ether. The combined ethereal solution was washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left crude **3** (9.43 g), which on crystallization from petroleum ether yielded pure **3** (7.6 g, 74.2%) as colorless needles: mp 35–37 °C; ν_{max} (neat) 3300, 3050, 1605, 1570, 1050 cm^{-1}; δ 1.65 (2 H, m), 1.76 (1 H, s, disappeared with D_2O), 2.80 (3 H, br s), 3.96 (1 H, m), 6.16 (1 H, m), 6.00 (1 H, m), 6.44 (1 H, d, J = 9.5 Hz); *m/e* 208, 206, 204, 160 (100). Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91; Cl, 34.57. Found: C, 52.45; H, 4.80; Cl, 34.35.

3-Acetoxy-7-(2,2-dichlorovinyl)tricyclo[2.2.1.0^{2,6}]heptane (5). A solution of **3** (2.05 g, 10 mmol) in dry pyridine (20 ml) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (6.30 g, 33 mmol) with stirring under nitrogen for 2 h. After 24 h at room temperature, the reaction mixture was diluted with water and extracted with benzene. The organic layer was washed with 10% HCl and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a practically pure oily tosylate (**4**, 3.55 g, 98.9%) which was used without further purification: ν_{max} (neat) 3050, 1605, 1595, 1570, 1355, 1185, 1170 cm^{-1}; δ 1.72 (2 H, m), 2.44 (3 H, s), 2.82 (3 H, m), 4.56 (1 H, m), 6.00 (2 H, m), 6.06 (1 H, d, J = 9.5 Hz), 7.32 (2 H, d, J = 8.5 Hz), 7.79 (2 H, d, J = 8.5 Hz).

Crude **4** (3.59 g, 10 mmol) and fused potassium acetate (1.96 g, 20 mmol) were dissolved into acetic acid (80 ml) and the mixture was heated at 50–52 °C for 42 h with stirring under nitrogen. After cooling, the reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a practically pure oily **5** (2.47 g, 87.1%) as a 1:1 epimeric mixture, which was used without further purification. A preparative GLC (10% SE-30, 1-m column) purification afforded an analytically pure endo isomer: ν_{max} (neat) 1730, 1605, 1235 cm^{-1}; δ 1.43 (6 H, m), 2.07 (3 H, s), 2.67 (1 H, d, J = 6.0 Hz), 4.72 (1 H, br s), 5.65 (1 H, d, J = 6.0 Hz); *m/e* 250, 248, 246, 43 (100). Anal. Calcd for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.89. Found: C, 53.65; H, 5.09. Exo isomer: ν_{max} (neat) 1730, 1605, 1235 cm^{-1}; δ 1.43 (6 H, m), 2.09 (3 H, s), 3.11 (1 H, d, J = 6.0 Hz), 4.75 (1 H, br s), 5.81 (1 H, d, J = 6.0 Hz); *m/e* 250, 248, 246, 43 (100). Anal. Calcd for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.89. Found: C, 53.70; H, 5.12.

7-(2,2-Dichlorovinyl)-3-hydroxytricyclo[2.2.1.0^{2,6}]heptane (6). A solution of an epimeric mixture of **5** (1.65 g, 6.68 mmol) in ethanol (120 ml) was treated with anhydrous potassium carbonate (1.26 g, 7.35 mmol) and stirred under nitrogen for 3.5 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was extracted with methylene chloride. The extract was washed with 10% HCl and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a practically pure oily **6** (1.37 g, 100%) as a 1:1 epimeric mixture, which was used without further purification. A preparative TLC (silica gel) purification afforded an analytically pure endo isomer: ν_{max} (neat) 3275, 3050, 1608, 1065 cm^{-1}; δ 1.25 (3 H, br s), 1.73 (3 H, m), 2.50 (1 H, br d, J = 9.0 Hz), 3.09 (1 H, s, disappeared with D_2O), 3.78 (1 H, br s), 5.63 (1 H, d, J = 9.0 Hz); *m/e* 208, 206, 204, 66 (100). Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 53.04; H, 5.11. Exo isomer: ν_{max} (neat) 3275, 3050, 1608, 1068 cm^{-1}; δ 1.30 (5 H, br d), 1.81 (1 H, br s), 2.94 (1 H, s, disappeared with D_2O), 3.11 (1 H, br d J = 9.0 Hz), 3.86 (1 H, br s), 5.74 (1 H, d, J = 9.0 Hz); *m/e* 208, 206, 204, 66 (100). Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 52.73; H, 5.26.

7-(2,2-Dichlorovinyl)tricyclo[2.2.1.0^{2,6}]hept-3-one (9). A solution of an epimeric mixture of **6** (4.10 g, 20 mmol) in acetone (21 ml) was added to the Jones reagent, prepared by mixing CrO_3 (2.2 g, 22 mmol) in H_2O (21 ml) with 98% H_2SO_4 (2.51 ml) at 0 °C, with stirring at 0 °C and the mixture was kept stirring for 2.5 h at room temperature. The reaction was quenched by addition of isopropyl alcohol (ca. 1 ml) and the reaction mixture was extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to leave a crystalline residue, which was recrystallized from petroleum ether to give **9** (3.89 g, 95.81%) as colorless needles: mp 29–30 °C; ν_{max} (neat) 3020, 1750, 1608 cm^{-1}; δ (CCl_4) 1.36 (1 H, t, J = 6.5 Hz), 1.91 (3 H, br s), 2.15 (2 H, br d, J = 6.5 Hz), 3.07 (1 H, d, J = 9.0 Hz), 5.78 (1 H, d, J = 9.0 Hz); *m/e* 206, 204, 202, 103 (100). Anal. Calcd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97. Found: C, 53.29; H, 4.32.

7-Carboxytricyclo[2.2.1.0^{2,6}]hept-3-one (10) from 6. An epimeric mixture of **6** (1.18 g, 5.76 mmol) in acetone (60 ml) was treated with ozone at −78 °C with stirring until the reaction mixture became blue. After excess ozone was bubbled out with nitrogen, the Jones reagent, prepared by mixing CrO_3 (6.3 g, 63 mmol) in H_2O (60 ml) with 98% H_2SO_4 (7.2 ml) at 0 °C, was added to the reaction mixture and the stirring was continued for 2 h at room temperature. The reaction was quenched by addition of isopropyl alcohol (ca. 2 ml) and the reaction mixture was extracted with ether. The ethereal layer was extracted with saturated $NaHCO_3$ and the aqueous layer was reextracted with ether after acidification with 10% HCl. The ethereal extract was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a crystalline residue, which was recrystallized from a mixture of *n*-hexane and benzene to give **10** (0.65 g, 74.3%) as colorless needles: mp 142–143 °C (lit.[9] 143–144 °C); ν_{max} (Nujol) 3300–2500, 1730–1710 cm^{-1}; δ ($CDCl_3$ + CF_3CO_2H) 1.58 (1 H, m), 2.01 (2 H, br s), 2.39 (3 H, m), 3.08 (1 H, br s); *m/e* 152, 79 (100). Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.26; H, 5.22.

5-Bromo-7-(2,2-dichlorovinyl)norbornan-2-one (11). A solution of **9** (3.78 g, 18.6 mmol) in a mixture of 47% HBr (3.53 g, 20.5 mmol) and acetic acid (74.5 ml) was refluxed for 2 h under nitrogen. The reaction mixture was poured into ice–water (ca. 200 ml) and extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to leave a crystalline residue, which was recrystallized from *n*-hexane to give **11** (4.63 g, 87.55%) as pale yellow needles: mp 66–67 °C; ν_{max} (Nujol) 1745, 1610 cm^{-1}; δ 2.03 (2 H, m), 2.49 (3 H, m), 2.94 (1 H, br s), 3.05 (1 H, br d, J = 9.0 Hz), 4.05 (1 H, br t, J = 4.0 Hz), 6.44 (1 H, d, J = 9.0 Hz); *m/e* 288, 286, 284, 282, 139 (100). Anal. Calcd for $C_9H_9BrCl_2O$: C, 38.07; H, 3.19. Found: C, 38.04; H, 3.10.

6-Bromo-8-(2,2-dichlorovinyl)-2-oxabicyclo[3.2.1]oct-3-one (12). A solution of **11** (0.284 g, 1 mmol) in methylene chloride (10 ml) was stirred with 70% *m*-chloroperbenzoic acid (0.296 g, 1.2 mmol) at room temperature for 24 h. The reaction mixture was washed with 2% $Na_2S_2O_4$, saturated $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a crystalline residue, which on recrystallization from *n*-hexane gave **12** (0.267 g, 89.0%) as colorless needles: mp 80–81 °C; ν_{max} (Nujol) 3030, 1730, 1607, 1150 cm^{-1}; δ 2.80 (5 H, m), 3.22 (1 H, br d, J = 9.0 Hz), 4.29 (1 H, m), 4.70 (1 H, m), 6.24 (1 H, d, J = 9.0 Hz); *m/e* 304, 302, 300, 298, 113 (100). Anal. Calcd for $C_9H_9BrCl_2O_2$: C, 36.03; H, 3.02. Found: C, 36.03; H, 3.03.

Ethyl 5β-Bromo-3α-hydroxy-2β-(2,2-dichlorovinyl)cy-

clopentane-1α-acetate (13). A solution of **11** (2.84 g, 10 mmol) in chloroform (30 ml) was stirred with 70% *m*-chloroperbenzoic acid (2.96 g, 12 mmol) at room temperature for 24 h. To the reaction mixture ethanol (5 ml) was added, the mixture was refluxed for 4 h, and the solvent was removed in vacuo. The residue was extracted with methylene chloride and the extract was washed with 2% $Na_2S_2O_4$, saturated $NaHCO_3$, and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left practically pure **13** (3.46 g, 100%) as a pale yellow oil, which was used without further purification. A preparative TLC (silica gel) purification afforded analytically pure **13** as pale yellow oil: ν_{max} (neat) 3400, 1720, 1608, 1170, 1030 cm^{-1}; δ (CCl_4) 1.31 (3 H, t, J = 7.5 Hz), 2.56 (6 H, m), 3.14 (1 H, br s, disappeared with D_2O), 4.18 (2 H, q, J = 7.5 Hz), 4.32 (2 H, m), 5.79 (1 H, d, J = 9.0 Hz); *m/e* 350, 348, 346, 344, 173 (100). Anal. Calcd for $C_{11}H_{15}BrCl_2O_3$: C, 38.18; H, 4.37. Found: C, 38.82; H, 4.25.

3α,5α-Dihydroxy-2β-(2,2-dichlorovinyl)cyclopentane-1α-acetic Acid γ-Lactone (16). A. $Hg(OAc)_2$-Catalyzed Reaction. A solution of **13** (2.955 g, 8.54 mmol) in 1,2-dimethoxyethane (10 ml) was added to a mixture of 98.5% $Hg(OAc)_2$ (2.763 g, 8.54 mmol), 70% $HClO_4$ (2.14 ml), water (1.71 ml), and 1,2-dimethoxyethane (15.6 ml) with stirring at room temperature under nitrogen. After stirring for 2 h, the reaction mixture was evaporated in vacuo and the residue was extracted with methylene chloride. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to leave a crystalline residue, which was recrystallized from a mixture of *n*-hexane and benzene to give **16** (1.61 g, 79%) as colorless needles: mp 106–107 °C; ν_{max} (Nujol) 3450, 1755, 1615, 1200, 1080 cm^{-1}; δ 2.30 (3 H, m), 2.76 (3 H, m), 3.21 (1 H, br s, disappeared with D_2O), 4.16 (1 H, m), 5.03 (1 H, br s), 5.68 (1 H, d, J = 9.0 Hz); *m/e* 240, 238, 236, 115 (100). Anal. Calcd for $C_9H_{10}Cl_2O_3$: C, 45.60; H, 4.25; Cl, 29.91. Found: C, 45.79; H, 4.21; Cl, 29.77.

B. $AgClO_4$-Catalyzed Reaction. A solution of **13** (2.46 g, 7.11 mmol) in 1,2-dimethoxyethane (15 ml) was added to a mixture of $AgClO_4$ (1.55 g, 7.11 mmol), water (1.5 ml), and 1,2-dimethoxyethane (10 ml) with stirring at room temperature under nitrogen. After stirring for 30 min, insoluble precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was extracted with methylene chloride and the extract was washed with saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a crystalline residue, which on recrystallization from a mixture of *n*-hexane and benzene gave **16** (1.41 g, 82.84%).

2β-(2,2-Dichlorovinyl)-5α-hydroxy-3-(4-phenylbenzoyloxy)cyclopentane-1α-acetic Acid γ-Lactone (17). A solution of **16** (0.237 g, 1 mmol) in a mixture of ether (10 ml) and methylene chloride (10 ml) was mixed with a solution of 4-phenylbenzoyl chloride (0.473 g, 1.1 mmol) in ether (10 ml) in the presence of triethylamine (0.2 ml) under stirring at room temperature. After stirring for 24 h, separating triethylamine hydrochloride was filtered off and the filtrate was evaporated in vacuo. The residue was extracted with methylene chloride and the extract was washed with 5% HCl, saturated $NaHCO_3$, and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a crystalline residue, which on recrystallization from a mixture of *n*-hexane and benzene afforded **17** (0.36 g, 86.12%) as colorless needles: mp 133–134 °C; ν_{max} (Nujol) 1755, 1705, 1610, 1600, 1270, 745, 690 cm^{-1}; δ 2.18–3.36 (6 H, m), 5.09 (1 H, br s), 5.32 (1 H, m), 5.78 (1 H, d, J = 9.0 Hz), 7.33–7.68 (7 H, m), 8.07 (2 H, d, J = 8.0 Hz); *m/e* 420, 418, 416, 181 (100). Anal. Calcd for $C_{22}H_{18}Cl_2O_4$: C, 63.32; H, 4.35; Cl, 16.99. Found: C, 63.57; H, 4.50; Cl, 16.76.

2β-Formyl-5α-hydroxy-3α-(4-phenylbenzoyloxy)cyclopentane-1α-acetic Acid γ-Lactone (18). To a stirring solution of **17** (0.105 g, 0.25 mmol) in a mixture of methanol (20 ml) and methylene chloride (10 ml) was bubbled ozone at −20 to −15 °C until the no starting material was detected by TLC. After an excess of ozone was bubbled out by means of nitrogen, NaI (0.083 g, 0.55 mmol) and acetic acid (0.15 ml) was added and the stirring was continued for 30 min at room temperature; during the reaction 10% $Na_2S_2O_3$ was added dropwise to remove liberating iodine. The reaction mixture was extracted with methylene chloride and the extract was washed with saturated $NaHCO_3$, 10% $Na_2S_2O_3$, and saturated NaCl, dried over Na_2SO_4, and evaporated in vacuo to yield practically pure **18** (0.087 g, 98.86%) as a colorless foam, which was used without further purification: ν_{max} ($CHCl_3$) 1770, 1720, 1610 cm^{-1}; δ 2.03–3.29 (6 H, m), 5.14 (1 H, br s), 5.79 (1 H, m), 7.33–7.80 (7 H, m), 8.07 (2 H, d, J = 8.0 Hz), 9.85 (1 H, s); *m/e* 350, 198 (100). In order to confirm its structure, unstable **18** was reduced with sodium borohydride in methanol to yield the stable alcohol **19**:[10] mp 123–124 °C (from *n*-hexane–CH_2Cl_2) (lit.[3,11] 130–131 °C); ν_{max} ($CHCl_3$) 3650, 3500, 1770, 1710, 1610, 1280 cm^{-1}; δ 2.08 (1 H, s, disappeared with D_2O), 2.18–3.04 (6 H, m), 3.71 (2 H, d, J = 6.0 Hz), 5.08 (1 H, br s-), 5.41 (1 H, m), 7.34–7.72 (7 H, m), 8.04 (2 H, d, J = 8.0 Hz); *m/e* 352, 181 (100).

5α-Hydroxy-2β-hydroxymethyl-3α-(4-phenylbenzoyloxy)-cyclopentane-1α-acetic Acid γ-Lactone (19) from 17. To a stirring solution of **17** (0.105 g, 0.25 mmol) in a mixture of methanol (20 ml) and methylene chloride (10 ml) was bubbled ozone at −20 to −15 °C until no starting material was detected by TLC. After an excess of ozone was bubbled out by means of nitrogen, sodium borohydride (ca. 1 g) was added dividedly into the reaction mixture and the stirring was continued for 1 h at room temperature. The reaction mixture was extracted with methylene chloride and the extract was washed with saturated NaCl, dried over Na_2SO_4, and evaporated in vacuo to leave a crystalline residue which was recrystallized from a mixture of *n*-hexane and methylene chloride to yield **19** (0.065 g, 73.86%) as colorless needles, mp 123–124 °C.

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Registry No.—**2,** 61046-12-6; **3,** 61009-51-6; **4,** 61009-52-7; **5** isomer A, 61091-84-7; **5** isomer B, 61047-20-9; **6** isomer A, 61047-21-0; **6** isomer B, 61091-83-6; **9,** 61047-22-1; **10,** 52730-40-2; **11,** 61009-53-8; **12,** 61009-54-9; **13,** 61009-55-0; **16,** 61009-56-1; **17,** 61009-57-2; **18,** 38754-71-1; **19,** 31752-99-5; *p*-toluenesulfonyl chloride, 98-59-9; HBr, 10035-10-6; 4-phenylbenzoyl chloride, 14002-51-8.

References and Notes

(1) J. S. Bindra, A. Grodski, T. K. Schaaf, and E. J. Corey, *J. Am. Chem. Soc.*, **95,** 7522 (1973).
(2) R. Peel and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 151 (1974).
(3) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93,** 1491 (1971).
(4) J. Fried and J. C. Sih, *Tetrahedron Lett.*, 3899 (1973).
(5) J. Villieras, P. Perriot, and J. F. Normant, *Synthesis,* 458 (1975).
(6) H. Fritz, C. D. Weis, and T. Winkler, *Helv. Chim. Acta,* **58,** 1345 (1975).
(7) A. McKillop and M. E. Ford, *Tetrahedron,* **30,** 2467 (1974).
(8) Infrared spectra were recorded with a Shimadzu IR 400 grating spectrometer or a Hitachi EPI-3 grating spectrometer. NMR spectra were obtained with Hitachi H-60 or JEOL PS-100 instruments in deuteriochloroform with Me_4Si as internal standard unless otherwise indicated. Mass spectra were recorded on a Hitachi RMU-7 spectrometer.
(9) P. A. Grieco and Y. Masaki, *J. Org. Chem.*, **40,** 150 (1975).
(10) The infrared spectrum in chloroform solution, NMR spectrum, and mass spectrum were superimposable on those of an authentic optically active sample. The R_f value of the synthetic product on TLC was identical with that of an authentic sample.
(11) Recorded with optically active sample.