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Synthesis of 6a-Carbaprostaglandin I_3

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A synthesis of 6a-carbaprostaglandin I_3 (**2**) was achieved in which the ω-chain was introduced by Wittig reaction of the optically active aldehyde (**3**) with the β-oxido ylid (**4**), followed by removal of the protecting groups to afford a chromatographically separable mixture of the 13(*E*)-product (**8**) and its 13(*Z*)-isomer (**7**). The geometry of the double bond was determined by direct comparison of **8** with a standard sample synthesized by an alternative route (Chart 2). Compound **8** was easily transformed into **2** by a 6-step sequence of reactions (Chart 3). By using a similar technique, (13*Z*)-6a-carbaprostaglandin I_3 (**1A**) was also synthesized from the 13(*Z*)-isomer (**6**).

Keywords——β-oxido ylid; Wittig reaction; prostaglandin; carbacyclin; 13(*Z*)-6a-carbaprostaglandin I_3

Prostacyclin [prostaglandin(PG)I_2] is a potent inhibitor of platelet aggregation as well as being a powerful vasodilator, and it appears to have an important role in preventing stroke, thrombosis, and heart attack. PGI_3 is a metabolite of *cis*-5,8,11,14,17-eicosapentaenoic acid and is equivalent to PGI_2 in its ability to inhibit platelet aggregation.[1] Other biological properties of PGI_3 are also known to be very similar to those of PGI_2. However, beccause of the presence of a labile enol ether linkage, PGI_2 and PGI_3 are both unstable. Therefore, our research has been focused on the synthesis of a stable carba-analogue of PGI_3. The present paper describes the synthesis of 6a-carbaprostaglandin I_3 (**2**) and its 13(*Z*)-isomer (**1A**).

Wittig reaction of the aldehyde[6] (**3**) with the β-oxido ylid reagent (**4**), which was prepared from (2*S*,4*Z*)-2-hydroxy-4-heptenyltriphenylphosphonium iodide[3] and MeLi, afforded in 38% yield a mixture of the 13(*E*)-product (**5**) and an unexpected product,[2,3] the 13(*Z*)-isomer (**6**) (PG numbering). The isomers could be separated after removal of the protecting group by treatment with aq. AcOH followed by column chromatography on silica gel to give the more polar **8** and the less polar **7** in almost equal amounts (Chart 1). The geometry of the double bond at C_{13} was established by direct comparison of **8** with a sample[4] obtained from **3** by an alternative route involving 3 steps (Chart 2): Wittig reaction of **3** with the keto ylid (**9**), followed by reduction with $NaBH_4$ and hydrolysis of the tetrahydropyranyl ether with aq. AcOH. The ylid **9** employed here was easily prepared from the phosphonium salt (**25**) which was obtained by the reaction of the chloroketone (**24**) with triphenylphosphine (Chart 3).

Compound **8** was converted into the bis-tetrahydropyranyl ether (**17**) by treatment with dihydropyran in the presence of *p*-toluenesulfonic acid in 77% yield. In order to introduce the α-chain, **17** was subjected to Wittig reaction with (4-sodiocarboxybutylidene)triphenylphosphorane in DMSO, followed by treatment of the product with CH_2N_2 to give the ester (**18**) as a mixture of 5(*E*) and 5(*Z*)isomers. Hydrolysis of the tetrahydropyranyl group in **18** afforded a mixture of diols (**19** and **20**) in 81% yield. The mixture was acetylated and the resulting diacetate isomers were separated by silica gel chromatography in 18% (**22**) and

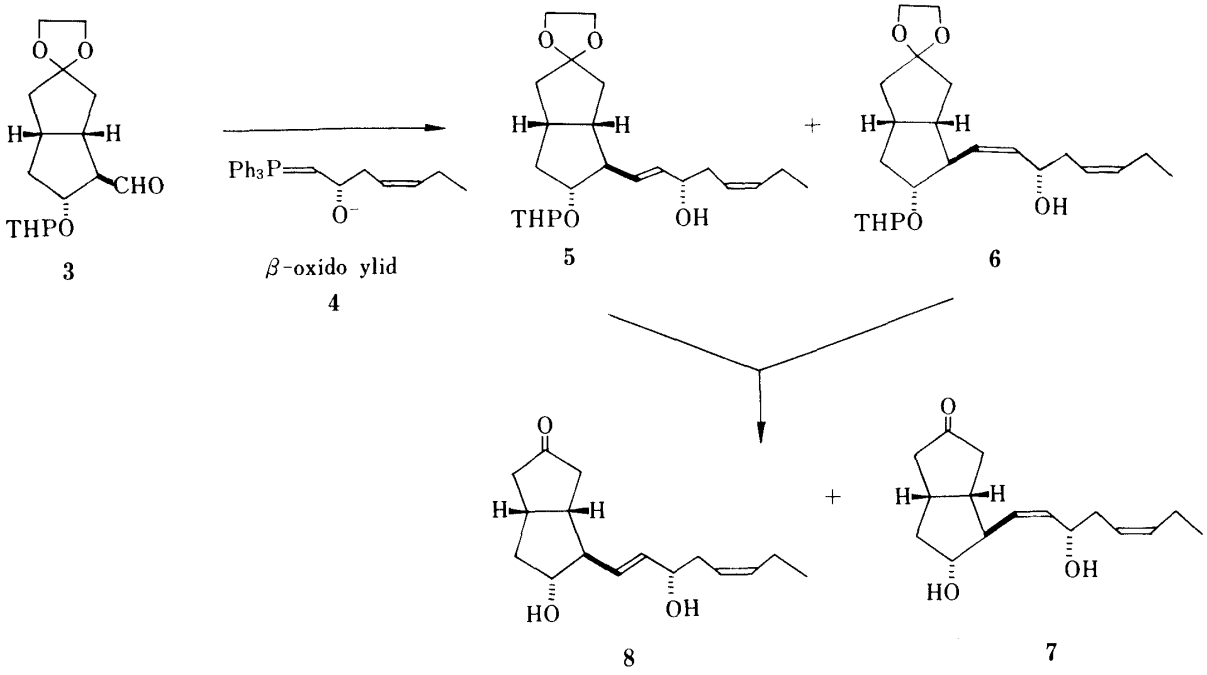

Chart 1

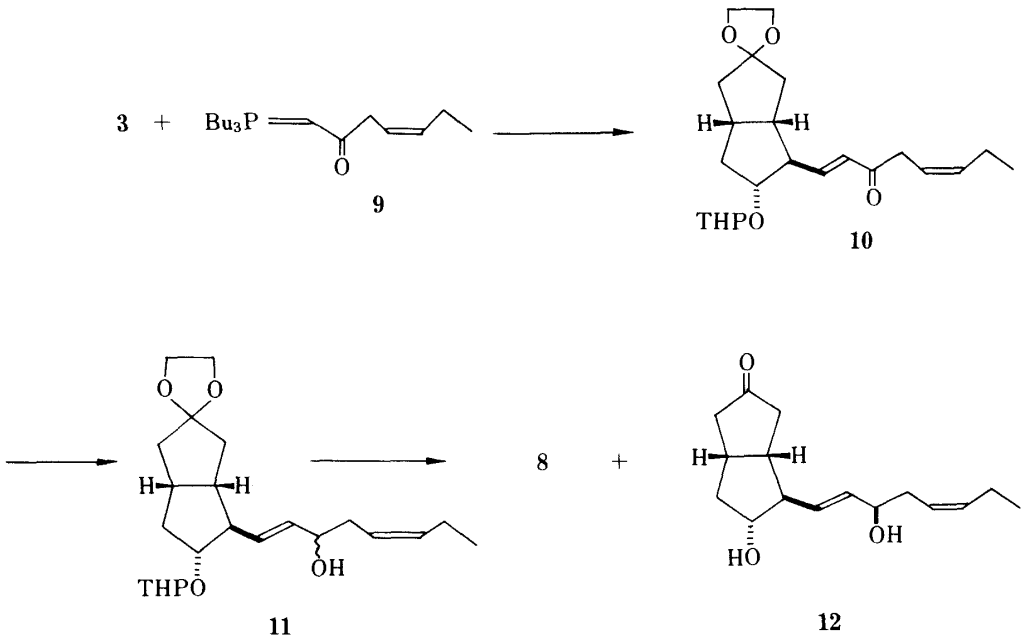

Chart 2

59% (**21**) yields. The more polar isomer **21** was identified as the 5(*E*)-diacetate and the less polar isomer as the 5(*Z*)-diacetate **22** on the basis of the thin layer chromatography (TLC) behavior[8] as in the case of carbacyclin and its 5(*Z*)-isomer. The 5(*E*)-diacetate **21** was subjected to hydrolysis with methanolic NaOH, giving 6a-carbaprostaglandin I_3 (**2**) in 95% yield from **21** (Chart 3). The product was identical with an authentic sample[5] on the basis of TLC and proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectral comparisons. (13*Z*)-6a-Carbaprostaglandin I_3 (**1A**) and (5*Z*,13*Z*)-6a-carbaprostaglandin I_3 (**1B**)

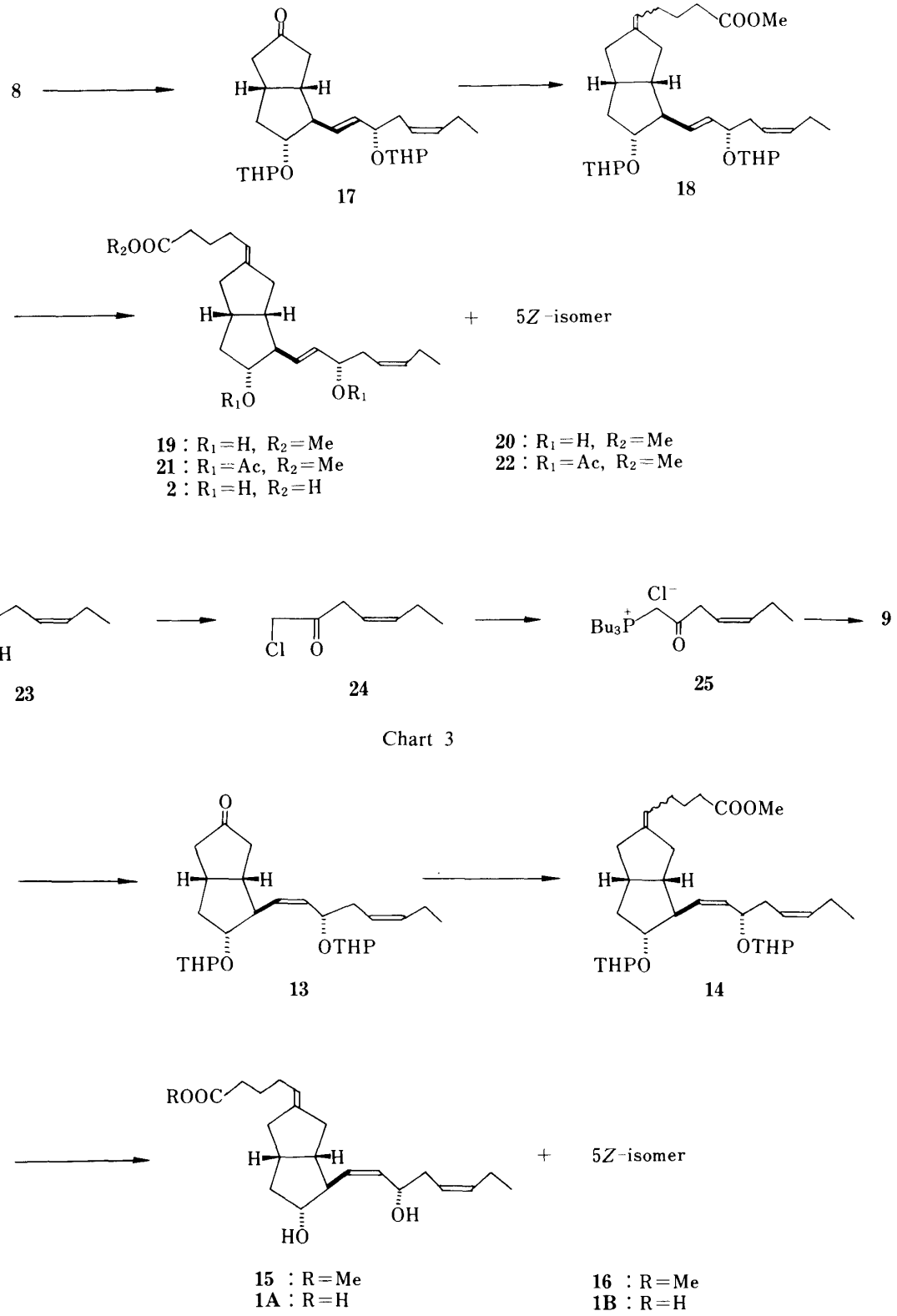

Chart 3

Chart 4

were similarly synthesized from **7**, as shown in Chart 4.

In a preliminary biological test, **2** was found to be a potent inhibitor of platelet aggregation induced by collagen, but **1A** was appreciably less active than **2**. The details will be published elsewhere.

Experimental

IR spectra were taken on a Jasco IRA-2 spectrometer, ^{1}H-NMR spectra on a Varian T-60, and mass spectra (MS) on a JEOL O1SG. For column chromatography, Kanto Chemical silica gel (60—100 mesh) was used. Thin layer chromatography was carried out on Silica gel 60 F_{254} plates (Merck). Optical rotations were measured with a Perkin-Elmer model 141 polarimeter. All organic solvent extracts were washed with brine and dried on anhydrous sodium sulfate.

(1*S*,2*R*,3*R*,5*R*)-7,7-Ethylenedioxy-2-[(1*E*,3*S*,5*Z*)-3-hydroxy-octa-1,5-dienyl]-3-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (5) and (1*S*,2*R*,3*R*,5*R*)-7,7-Ethylenedioxy-2-[(1*Z*,3*S*,5*Z*)-3-hydroxy-octa-1,5-dienyl]-3-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (6)——The aldehyde **3** (2.272 g) in anhydrous tetrahydrofuran (THF) (10 ml) was added dropwise to a stirred solution of the *β*-oxido ylid [derived from (2*S*,4*Z*)-2-hydroxy-4-heptenyltriphenylphosphonium iodide (10.00 g)][3] at −78 °C under an Ar atmosphere. After 0.5 h, the reaction mixture was poured into ice water (500 ml) and extracted with ether (300 ml × 3). The combined extracts were washed with brine (500 ml × 2) and dried. After removal of the solvent *in vacuo*, ether (500 ml) was added, and the resulting precipitate was filtered off. The filtrate was evaporated to dryness *in vacuo* to afford an oily residue (5.15 g), which was purified by column chromatography on silica gel (150 g). The fractions eluted with 45—50% AcOEt in hexane (v/v) afforded the starting material **3** (0.752 g). The fractions eluted with 55—70% AcOEt in hexane (v/v) afforded a mixture (0.753 g, 38%) of **5** and **6**. IR (neat): 3450, 1120, 1020, 980, 910 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 0.95 (3H, t, *J*= 7 Hz, $-CH_2C\underline{H}_3$), 3.83 (4H, s, OCH_2CH_2O), 5.20—5.60 (4H, m, olefinic H).

(1*S*,2*R*,3*R*,5*R*)-2-[(1*Z*,3*S*,5*Z*)-3-Hydroxy-octa-1,5-dienyl]-3-hydroxy-bicyclo[3.3.0]octan-7-one (7) and (1*S*,2*R*,3*R*,5*R*)-2-[(1*E*,3*S*,5*Z*)-3-Hydroxy-octa-1,5-dienyl]-3-hydroxy-bicyclo[3.3.0]octan-7-one (8)——The mixture of **5** and **6** (1.472 g) was dissolved in AcOH (16 ml) and H_2O (200 ml). The solution was stirred for 5 h at 30—40 °C, then poured into H_2O (200 ml). The whole was extracted with AcOEt (200 ml × 2). The combined extracts were washed with brine (100 ml × 3), and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (45 g). The fractions eluted with 50% AcOEt in hexane (v/v) were collected, and the solvent was removed *in vacuo* to afford the 13(*Z*) compound **7** (331 mg, 33%) as a colorless oil. The fractions eluted with 80—90% AcOEt in hexane (v/v) afforded the 13(*E*) compound **8** (291 mg, 29%) as a colorless oil. **7**: $[\alpha]_D^{22}$ −41.3° (*c*=1.25, $CHCl_3$). IR (neat): 3400, 1735, 1160, 1030, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 0.95 (3H, t, *J*= 7 Hz, $CH_2C\underline{H}_3$), 3.70—4.20 (2H, m, olefinic H). *Anal.* Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.55; H, 9.28. **8**: $[\alpha]_D^{22}$ −23.1° (*c*=1.09, $CHCl_3$). IR (neat): 3400, 1740, 1160, 1090, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 0.95 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 3.70—4.30 (4H, m, olefinic H). *Anal.* Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.73; H, 9.19.

(1*S*,2*R*,3*R*,5*R*)-7,7-Ethylenedioxy-2-[(1*E*,5*Z*)-3-oxo-octa-1,5-dienyl]-3-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (10)——The ylid **9** (719 mg) in ether (10 ml) was added dropwise to a stirred solution of **3** (395 mg) in ether (7 ml) at room temperature. The mixture was stirred for 3 h, then the solvent was removed *in vacuo* to afford an oily residue (1.203 g), which was purified by column chromatography on silica gel (25 g). The fractions eluted with 15—20% AcOEt in hexane (v/v) were collected, and concentrated to dryness *in vacuo* to afford **10** (422 mg, 81%) as a colorless oil. IR (neat): 1700, 1670, 1630, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.83 (4H, s, $-OCH_2CH_2O$), 5.50 (2H, m, olefinic H), 6.15 (1H, d, *J*=16 Hz, C_{14}–H), 6.85 (1H, dd, *J*=16, 7 Hz, C_{13}–H). *Anal.* Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.88; H, 8.79.

(1*S*,2*R*,3*R*,5*R*)-7,7-Ethylenedioxy-2-[(1*E*,3*ξ*,5*Z*)-3-hydroxy-octa-1,5-dienyl]-3-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (11)——$NaBH_4$ (400 mg) was added portionwise to a stirred solution of **10** (443 mg) in MeOH (15 ml) at 0—5 °C, and the reaction mixture was stirred for 20 min, then diluted with H_2O (100 ml) containing 7% HCl (2 ml) and extracted with AcOEt (100 ml × 2). The combined extracts were washed with brine (100 ml × 2) and dried. Removal of the solvent *in vacuo* afforded an oily residue (466 mg), which was subjected to column chromatography on silica gel (20 g). The fractions eluted with 30—40% AcOEt in hexane (v/v) were collected, and removal of the solvent *in vacuo* afforded **11** (229 mg, 52%) as a colorless oil. IR (neat): 3450, 1120, 1020, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.80 (4H, s, OCH_2CH_2O), 4.57 (1H, br, OCHO), 5.10—5.60 (4H, m, olefinic H). *Anal.* Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.51; H, 9.36.

(1*S*,2*R*,3*R*,5*R*)-2-[(1*E*,3*R*,5*Z*)-3-Hydroxy-octa-1,5-dienyl]-3-hydroxy-bicyclo[3.3.0]octan-7-one (12) and 8——In a manner similar to that described for **7** and **8**, the hydrolysis of **11** (211 mg) in aq. AcOH afforded a mixture of **12** and **8** (158 mg), which was subjected to column chromatography on silica gel (15 g). The fractions eluted with 50% AcOEt in hexane (v/v) afforded the 13(*E*)-15*β*-alcohol (**12**) (39 mg, 28%) as a colorless oil. The fractions eluted with 60—80% AcOEt in hexane (v/v) afforded the 13(*E*)-15*α*-alcohol (**8**) (32 mg, 23%) as a colorless oil, which was identical with the sample obtained by the reaction of **3** with the *β*-oxido ylid (**4**). **12**: IR (neat): 3400, 1740, 1160, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 0.97 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 3.70—4.30 (2H, m, –CH–O × 2), 5.05—5.80 (4H, m, olefinic H). *Anal.* Calcd for $C_{16}H_{24}O_3$; C, 72.69; H, 9.15. Found; C, 72.75; H, 9.11.

(1*S*,2*R*,3*R*,5*R*)-2-[(1*E*,3*S*,5*Z*)-3-(Tetrahydropyran-2-yl)oxy-octa-1,5-dienyl]-3-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octan-7-one (17)——2,3-Dihydropyran (0.30 ml) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of **8** (290 mg) in CH_2Cl_2 (8 ml) in the presence of *p*-toluenesulfonic acid (*ca.* 10 mg) at 0—5 °C. The reaction

mixture was stirred for 0.5 h, diluted with 5% aq. $NaHCO_3$ (30 ml) and then extracted with AcOEt (50 ml × 3). The combined extracts were washed with brine (50 ml × 3) and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (4.0 g). The fractions eluted with 15—30% AcOEt in hexane (v/v) were collected and removal of the solvent *in vacuo* afforded **17** (453 mg, 96%) as a colorless oil. $[\alpha]_D^{22}$ −31.3° (c=1.71, $CHCl_3$). IR (neat): 1740, 1130, 1075, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 4.64 (2H, br s, OCHO × 2), 5.25—5.66 (4H, m, olefinic H). *Anal.* Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.30; H, 9.40.

(5ξ)-6a-Carbaprostaglandin I_3 Methyl Ester 11,15-Bis(tetrahydropyran-2-yl)ether (18)——(4-Sodiocarboxybutylidene)triphenylphosphorane was prepared by the reaction of (4-carboxybutyl)triphenylphosponium bromide (2.50 g) with sodium methyl sulfinylmethide [prepared from DMSO (50 ml) and NaH (50% content, 0.52 g) in the usual manner]. A solution of **17** (470 mg) in DMSO (5 ml) was added dropwise to the above Wittig reagent with stirring at room temperature under an Ar atmosphere. The reaction mixture was stirred for 15 h, then poured into ice water (200 ml) containing AcOH (3 ml) and extracted with ether (200 ml × 3). The combined extracts were washed with brine (100 ml × 3) and dried. Removal of the solvent *in vacuo* afforded an oily residue (1.22 g), which was treated with CH_2N_2 in the usual manner. The resulting crude methyl ester was subjected to column chromatography on silica gel (40 g). The fractions eluted with 15—20% AcOEt in hexane (v/v) were concentrated to dryness *in vacuo* to afford **18** (292 mg, 51%) as a colorless oil. $[\alpha]_D^{22}$ +18.6° (c=0.98, $CHCl_3$). IR (neat): 1743, 1135, 1076, 1035, 978 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 3.60 (3H, s, COOMe), 5.20—5.70 (5H, m, olefinic H). *Anal.* Calcd for $C_{32}H_{50}O_6$: C, 72.41; H, 9.50. Found: C, 72.29; H, 9.41.

6a-Carbaprostaglanidin I_3 Methyl Ester (19) and (5*Z*)-6a-Carbaprostaglandin I_3 Methyl Ester (20)——Bis(tetrahydropyran-2-yl)ether **18** (285 mg) was dissolved in 50% aq. AcOH (10 ml). The solution was stirred at 30—40 °C for 3 h, diluted with H_2O (100 ml), and extracted with AcOEt (100 ml × 3). The combined extracts were washed with brine (50 ml × 3) and dried. The solvent was removed *in vacuo* to afford an oily residue (161 mg), which was subjected to column chromatography on silica gel (10 g). The fractions eluted with 40—90% AcOEt in hexane (v/v) were collected, and removal of the solvent *in vacuo* afforded an inseparable mixture of **19** and **20** (161 mg, 83%) as a colorless oil. $[\alpha]_D^{22}$ +49.1° (c=1.10, $CHCl_3$). IR (neat): 3370, 1740, 1170, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.67 (3H, s, COOMe), 5.10—5.65 (5H, m, olefinic H). *Anal.* Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.79; H, 9.55.

11,15-Diacetoxy-6a-carbaprostaglandin I_3 Methyl Ester (21) and (5*Z*)-11,15-Diacetoxy-6a-carbaprostaglandin I_3 Methyl Ester (22)——A mixrure of Ac_2O (1 ml), pyridine (2 ml), **19** and **20** (142 mg) was stirred at room temperature. After 10 h, the reaction mixture was diluted with H_2O (20 ml) and extracted with AcOEt (30 ml × 3). The combined extracts were washed with brine (50 ml × 3) and dried. Removal of the solvent *in vacuo* afforded the diacetates **21** and **22** (179 mg), which were subjected to column chromatography on silica gel (20 g). The fractions eluted with 8% AcOEt in hexane (v/v) were concentrated to dryness *in vacuo* to afford the 5(*Z*) compound **22** (36 mg, 21%) as a colorless oil, and the fractions eluted with 10% AcOEt in hexane (v/v) similarly afforded the 5(*E*) compound **21** (117 mg, 67%) as a colorless oil. **21**: $[\alpha]_D^{22}$ +24.2° (c=1.01, $CHCl_3$). IR (neat): 1740, 1240, 1060, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.00 (3H, s, COMe), 2.05 (3H, s, COMe), 3.70 (3H, s, COOMe), 4.60—5.10 (2H, m, C_{11}–H, C_{15}–H), 5.20—5.75 (5H, m, olefinic H). *Anal.* Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found; C, 70.01; H, 8.62. **22**: $[\alpha]_D^{22}$ −1.5° (c=1.35, $CHCl_3$). IR (neat): 1735, 1240, 1060, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 2.00 (3H, s, COMe), 2.05 (3H, s, COMe), 3.72 (3H, s, COOMe), 4.60—5.10 (2H, m, C_{11}–H, C_{15}–H), 5.20—5.75 (5H, m, olefinic H). *Anal.* Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.99; H, 8.69.

6a-Carbaprostaglandin I_3 (2)——A solution of the diacetate **21** (102 mg) in 5% NaOH (3 ml) and MeOH (5 ml) was stirred at room temperature for 1 h, then diluted with H_2O (50 ml), made acidic with 7% HCl, and extracted with AcOEt (50 ml × 2). The combined extracts were washed with brine (50 ml × 2) and dried. Removal of the solvent *in vacuo* afforded **2** (76 mg, 95%) as a colorless oil. $[\alpha]_D^{22}$ +83.0° (c=1.42, MeOH). IR (neat): 3350, 1705, 1240, 1070, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.30—4.20 (2H, m, C_{11}–H, C_{15}–H), 5.10—5.80 (5H, m, olefinic H). *Anal.* Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.39; H, 9.33. MS m/e: 348 (M^+), 330, 312, 261.

(1*S*,2*R*,3*R*,5*R*)-2-[(1*Z*,3*S*,5*Z*)-3-(Tetrahydropyran-2-yl)oxy-octa-1,5-dienyl]-3-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octan-7-one (13)——In a manner similar to that described for **17**, **7** (405 mg) afforded **13** (510 mg, 77%) as a colorless oil. $[\alpha]_D^{22}$ −22.5° (c=0.89, $CHCl_3$). IR (neat): 1740, 1130, 1075, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.65 (2H, br, OCHO × 2), 5.20—5.65 (4H, m, olefinic H). *Anal.* Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.30; H, 9.39.

(5ξ,13*Z*)-6a-Carbaprostaglandin I_3 Methyl Ester 11,15-Bis(tetrahydropyran-2-yl)ether (14)——In a manner similar to that described for **18**, **13** (772 mg) afforded **14** as a crude oil (915 mg), which was purified by column chromatography on silica gel (70 g). The fractions eluted with 15—20% AcOEt in hexane (v/v) were collected, and the solvent was removed *in vacuo* to afford **14** (631 mg, 62%) as a colorless oil. $[\alpha]_D^{22}$ +8.0° (c=1.75, $CHCl_3$). IR (neat): 1740, 1135, 1120, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.65 (3H, s, COOMe), 4.65 (2H, br, OCHO × 2), 5.10—5.65 (5H, m, olefinic H).

(13*Z*)-6a-Carbaprostaglandin I_3 Methyl Ester (15) and (5*Z*,13*Z*)-6a-Carbaprostaglandin I_3 Methyl Ester (16)——In a manner similar to that described for the deprotection in **18**, **14** (590 mg) afforded a mixture (496 mg) of **15** and **16**,

which was subjected to column chromatography on silica gel (20 g). The fractions eluted with 20—25% AcOEt in hexane (v/v) afforded **16** (90 mg, 22%) as a colorless oil and the fractions eluted with 25—30% AcOEt in hexane (v/v) afforded **15** (182 mg, 45%) as a colorless oil. **15**: $[\alpha]_D^{22}$ +18.4° (c=1.48, $CHCl_3$). IR (neat): 3430, 1730, 1250, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.62 (3H, s, COOMe), 5.10—5.70 (5H, m, olefinic H). *Anal.* Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.77; H, 9.39. **16**: $[\alpha]_D^{22}$ −11.9° (c=1.34, $CHCl_3$). IR (neat): 3440, 1740, 1725, 1250, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.60 (3H, s, COOMe), 5.10—5.75 (5H, m, olefinic H). *Anal.* Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.92; H, 9.48.

(13*Z*)-6a-Carbaprostaglandin I_3 (1A) and (5*Z*,13*Z*)-Carbaprostaglandin I_3 (1B)——In a manner similar to that described for **2**, **15** (128 mg) afforded a crude oil (144 mg), which was purified by column chromatography on silica gel (6 g). The fractions eluted with 30—60% AcOEt in hexane (v/v) afforded **1A** (105 mg, 85%). Similarly, **16** (77 mg) afforded **1B** (45 mg, 58%) as a colorless oil. **1A**: $[\alpha]_D^{22}$ +19.9° (c=1.83, $CHCl_3$), +9.41° (c=1.04, MeOH). IR (neat): 3370, 1710, 1240, 1030, 900 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.70 (1H, m, C_{11}–H), 4.35 (1H, q, J=6 Hz, C_{15}–H), 5.05—5.70 (5H, m, olefinic H). MS *m/e*: 348 (M^+), 330, 312, 261. *Anal.* Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.51; H, 9.29. **1B**: $[\alpha]_D^{22}$ +0.34° (c=1.0, $CHCl_3$), −25.1° (c=1.63, MeOH). IR (neat): 3370, 1710, 1240, 1030, 900 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.62 (1H, m, C_{11}–H), 4.37 (1H, br q, J=6 Hz, C_{15}–H), 5.10—5.70 (5H, m, olefinic H). MS *m/e*: 348 (M^+), 330, 312, 261. *Anal.* Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.41; H, 9.34.

(4*Z*)-2-Oxo-4-heptenyl Chloride (24)——Jones reagent (3 ml) was added dropwise to a stirred solution of **23** (320 mg)[7] in acetone (10 ml) at 5—10 °C. After 1.5 h, isopropanol (1 ml) was added to decompose excess reagent. The reaction mixture was poured into ice water (150 ml), and extracted with ether (100 ml × 2). The combined extracts were washed with brine (100 ml × 2) and dried. The solvent was evaporated off *in vacuo* to afford an oily residue (310 mg), which was subjected to column chromatography on silica gel (5.0 g). The fraction eluted with 2% AcOEt in hexane (v/v) was collected, and removal of the solvent *in vacuo* yielded **24** (240 mg, 75%) as a colorless oil. IR (neat): 1735, 1400, 1063 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 3.37 (2H, d, J=5 Hz, $COCH_2CH$), 4.09 (2H, s, $ClCH_2CO$), 5.20—5.90 (2H, m, olefinic H).

(4*Z*)-2-Oxo-4-heptenylidene-tributylphosphorane (9)——The mixture of the chloroketone **24** (232 mg) and tributylphosphine (500 mg) in $CHCl_3$ (5 ml) was stirred at room temperature. After 1 h, 4% aq. NaOH (15 ml) was added to the reaction mixture over 2 min under vigorous stirring. The resulting ylid was extracted with ether (30 ml × 3). The combined extracts were washed with brine (20 ml × 2) and dried. Removal of the solvent *in vacuo* afforded **9** (719 mg) as an oil, which was used for the Wittig reaction with **3** without further purification.

References and Notes

1) *a*) P. Needleman, A. Raz, M. S. Minkes, J. A. Ferrendelli and H. Sprecher, *Proc. Natl. Acad. Sci., U.S.A.*, **76**, 944 (1979); *b*) R. A. Johnson, F. H. Lincoln, E. G. Nidy, W. P. Schneider, J. L. Thompson and U. Axen, *J. Am. Chem. Soc.*, **100**, 7690 (1978); *c*) E. G. Nidy and R. A. Johnson, *Tetrahedron Lett.*, **1978**, 2375.
2) This result is clearly different from that of Corey in the synthesis of PGE_3 and $PGF_{3\alpha}$,[3] in which only the 13(*E*)-form was obtained with the β-oxido ylid.
3) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu and T. K. Schaaf, *J. Am. Chem. Soc.*, **93**, 1490 (1971).
4) Like the Wittig reaction of 2-oxo-heptylidene-tributylphosphorane, the stable ylid **9** afforded only the 13(*E*)-form, as determined from the ^{1}H-NMR data (J=16 Hz, C_{13}–H and C_{14}–H).
5) K.Kojima, S. Amemiya, K. Koyama and K. Sakai, *Chem. Pharm. Bull.*, **31**, 3775 (1983).
6) A report on the synthesis of the optically active aldehyde (**3**) is in preparation.
7) (2*S*, 4*E*)-2-Hydroxy-4-hexenyl chloride (**23**) was synthesized from (*S*)-(−)-malic acid by a slight modification of Corey's method.[3]
8) D. R. Morton, Jr. and F. C. Brokaw, *J. Org. Chem.*, **44**, 2880 (1979).