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A Stereoselective Synthesis of a Stable Prostacyclin Analogue; *dl*-3-Oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1

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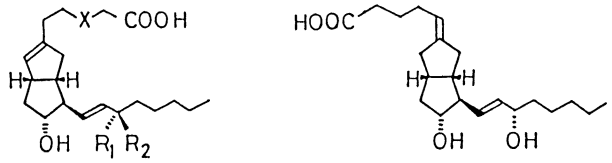
A prostacyclin analogue, *dl*-3-oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (**1a**), has been synthesized. The key step for this synthesis is a new, one-step conversion reaction of the (hydroxymethyl)cyclopropylketone group in **8** and **21** to the γ,δ-unsaturated ketone **9** and **22**, respectively, with iodotrimethylsilane.

Keywords——isocarbacyclin; prostacyclin analogue; iodotrimethylsilane; cyclopropane ring; bicyclo[3.3.0]octane

Many prostacyclin analogues have been synthesized in attempts to develop therapeutically useful agents.[1] In 1983, Shibasaki *et al.*[2a,b] reported the synthesis of 9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (isocarbacyclin) (**2**), which was found to be more potent than well-known 9(*O*)-methanoprostacyclin (carbacyclin) (**3**) in inhibiting platelet aggregation.[2a] Since then, many syntheses of **2** and its derivatives have been reported.[2c-g] We[3] have also described the synthesis of *dl*-isocarbacyclin (**2**) and its derivatives *via* a different route. Aiming at



1a: X=O, R_1=OH, R_2=H
1b: X=O, R_1=H, R_2=OH
2: X=CH_2, R_1=OH, R_2=H

3

Chart 1

synthesizing a biologically more stable isocarbacyclin analogue, we thought of blocking the β-oxidation reaction of the carboxylic acid side chain (α-side chain) by replacement of the C-3 methylene group with an oxygen atom. The β-oxidation reaction of the α-side chain is well-known as one of the main metabolic pathways of prostaglandins, and results in the loss of biological activity. 3-Oxa analogues of both PGE_1[4a] and carbacyclin[4b] have already been synthesized. We now report the synthesis of a 3-oxa analogue of isocarbacyclin, *dl*-3-oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (**1a**), using a new, one-step conversion reaction.

For the synthesis of 3-oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (**1a**), we investigated a new, regioselective method for the introduction of the 6(9α)-double bond (prostaglandin numbering). Our basic approach was as follows; if the (hydroxymethyl)cyclopropylketone group could be converted to the γ,δ-unsaturated ketone group in one step, the double bond at the 6(9α) position would be introduced regioselectively (**21**→**22**). In order to realize this

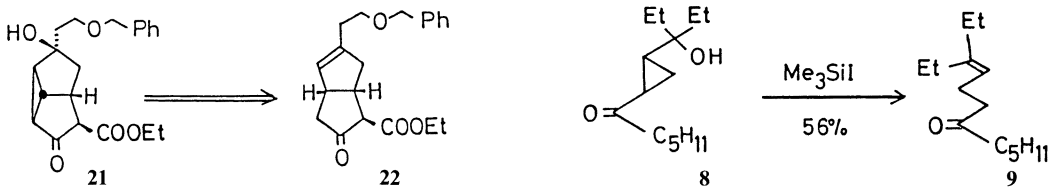


Chart 2

approach, we firstly investigated a model reaction using the simple acyclic compound (**8**) with iodotrimethylsilane (Me_3SiI). Treatment of **8** with 2.5 eq of Me_3SiI in toluene at 25 °C afforded the desired γ,δ-unsaturated ketone (**9**), together with liberation of iodine, in 56% yield[5] (Chart 2). Compound **8** was synthesized from methyl 4-oxo-2-nonenoate (**4**)[6] as illustrated in Chart 3.

As for the mechanism of this reaction, two routes (route A and B) might be possible (Chart 4). Route A: The cyclopropane ring in **8** was cleaved[7] by Me_3SiI and the hydroxy

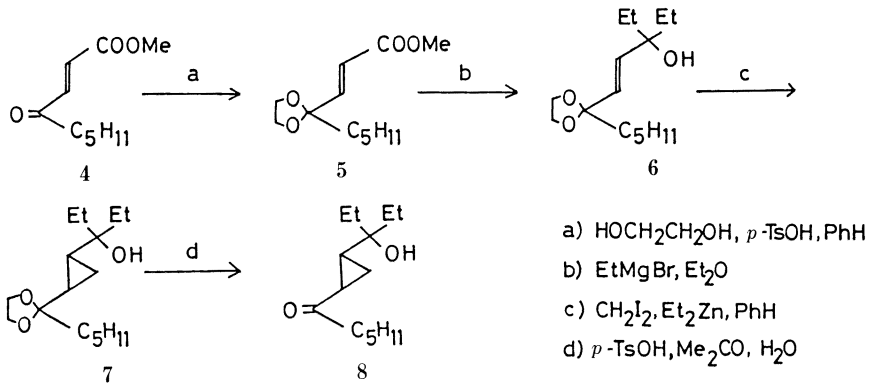


Chart 3

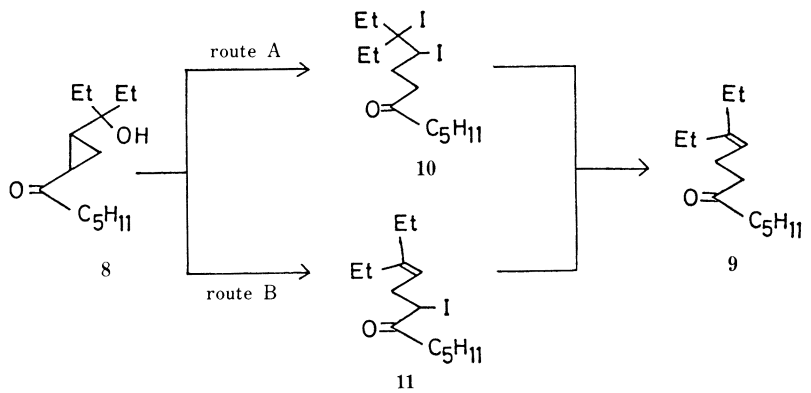
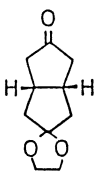


Chart 4

group was substituted[8] by iodide ion to afford the 1,2-diiodide (**10**), which might be converted[9] to the olefin (**9**). Route B: The cyclopropyl carbinol moiety in **8** was converted[10] to the γ-iodo olefin (**11**) by treatment with Me_3SiI, and **11** might be converted[11] to **9** with further Me_3SiI. The following results indicate that route A is more probable than route B.

Similar reaction of **8** with Me_3SiI under ice-cooling in place of room temperature, followed by quenching of the reaction mixture with aqueous sodium thiosulfate solution after 10 min, gave a crude mixture of **9** and a new, more polar product. All attempts to isolate this new product failed. However, thin layer chromatographic (TLC) analysis of the crude mixture obtained above in chloroform at room temperature showed that the more polar product was slowly converted to the olefin (**9**) with liberation of iodine. It is known that a 1,2-diiodide is unstable and loses iodine to afford an olefin.[9] Thus, we assigned this new product as the 1,2-diiodide (**10**), namely an intermediate of this reaction.

Now, we have applied this new, one-step conversion reaction to the synthesis of *dl*-3-oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (**1a**). The key compound **21** was easily synthesized from the mono-acetal (**12**)[12] as follows (Chart 5). The Wittig–Honer reaction of **12** with



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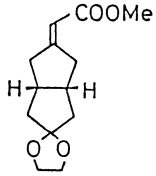
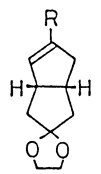
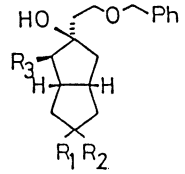


13 **14**: R=CH_2COOMe **15**: R=CH_2CH_2OH **16**: R=$CH_2CH_2OCH_2Ph$



17: R_1,R_2=OCH_2CH_2O, R_3=OH **18**: R_1,R_2=O, R_3=OH **19**: R_1,R_2=O, R_3=OMs



20: R=H **21**: R=COOEt

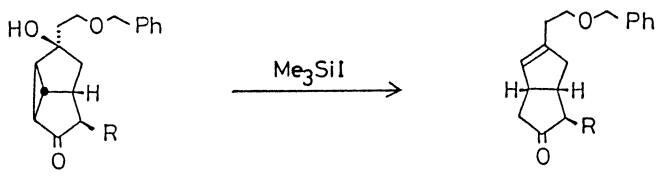
Chart 5

trimethyl phosphonoacetate [$(MeO)_2P(O)CH_2COOMe$] and sodium hydride in 1,2-dimethoxyethane (DME) gave the α,β-unsaturated ester (**13**). Isomerization of the *exo*-double bond in **13** to the *endo*-double bond was easily accomplished by treatment with lithium diisopropylamide (LDA) and hexamethylphosphoric triamide (HMPA)[13] in tetrahydrofuran (THF) at $-78\,^{\circ}C$ to give **14**. Reduction of the ester group in **14** with lithium aluminum hydride ($LiAlH_4$) gave the alcohol (**15**), which was treated with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide (DMF) to give the benzyl ether (**16**) in 85% yield from **12**. Oxidation of the double bond in **16** with *N*-methylmorpholine *N*-oxide[14] and a catalytic amount of osumiun tetroxide (OsO_4) gave the β-diol (**17**) in 95% yield. Treatment of **17** with HCl aq. in acetone gave the ketone (**18**), which was then converted to the mono-mesylate (**19**) with methanesulfonyl chloride (MsCl) and triethylamine (Et_3N) in methylene chloride. Cyclopropanation of the mono-mesylate (**19**) with potassium *tert*-butoxide (*tert*-BuOK) in THF at room temperature afforded the tricyclic compound **20** in 73% yield. Finally, treatment of **20** with LDA and then ethoxyformylimidazole[15] in THF at $-78\,^{\circ}C$ yielded the desired tricyclic β-ketoester (**21**) in 84% yield.

We then investigated the key step, the one step conversion reaction (Chart 6). Similar treatment of the tricyclic β-ketoester (**21**) with Me_3SiI in toluene at $25\,^{\circ}C$ afforded the desired olefin (**22**) in 45% yield. Under the reaction conditions used, the benzyl group in **21** remained intact. The bicyclo[3.3.0]octane structure of **22** was confirmed by synthesizing **22** through the following reactions: acid treatment of **16** gave the ketone (**23**), which was treated with diethyl carbonate and sodium hydride in 1,4-dioxane to give **22** along with the isomeric β-ketoester after chromatographic separation.

Similar treatment of the tricyclic ketone (**20**) afforded the olefin (**23**) in 43% yield.

We now had the desired intermediate (**22**), which was then converted into *dl*-3-oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (**1a**) by the following sequence of reactions (Chart 7). Reduction of the ketone group in **22** with sodium borohydride ($NaBH_4$) in ethanol,[3] followed by protection of the hydroxy group as the tetrahydropyranyl ether, afforded **25** in 79% yield.



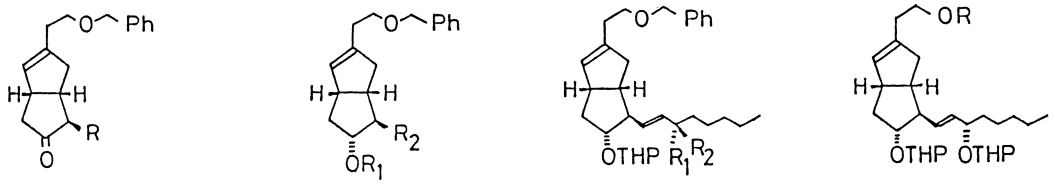
20: R=H
21: R=COOEt

22 45%
23 43%

Chart 6

After reduction of the ester group in **25** with $LiAlH_4$ in THF, the obtained alcohol (**26**) was oxidized to the aldehyde (**27**) with excess sulfur trioxide (SO_3) pyridine complex and Et_3N in dimethylsulfoxide (DMSO). The Wittig reaction of **27** with tributyl 2-oxoheptylidenephosphorane [$Bu_3P=CHCOC_5H_{11}$] in ether at room temperature gave the α,β-unsaturated ketone (**28**) in 86% yield from the ester (**25**). Reduction of the ketone group in **28** with $NaBH_4$ in the presence of cerium(III) chloride ($CeCl_3$) in methanol gave the more polar 15α-alcohol (**29a**) (PG numbering) and the less polar 15β-alcohol (**29b**) in 65% and 33% yields, respectively. Protection of the hydroxy group in the 15α-alcohol (**29a**) with dihydropyran (DHP) and *p*-toluenesulphonic acid (*p*-TsOH) in methylene chloride, followed by treatment with excess sodium metal in liquid ammonia at $-78\,^{\circ}C$ gave the alcohol (**31**) in 88% yield from **29a**. Alkylation of the alcohol (**31**) with lithium chloroacetate ($ClCH_2COOLi$) afforded the carboxylic acid **32** in 85% yield. Finally, removal of the protective groups of **32** with camphorsulphonic acid in aqueous acetone gave *dl*-3-oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (**1a**), mp 72—74 °C, in 74% yield.

By using a sequence of reactions similar to that described for the synthesis of **1a**, the 15β-alcohol (**29b**) was led to the 15β-isomer (**1b**).



22: R=COOEt
23: R=H

24: R_1=H, R_2=COOEt
25: R_1=THP, R_2=COOEt
26: R_1=THP, R_2=CH_2OH
27: R_1=THP, R_2=CHO

28: R_1,R_2=O
29a: R_1=OH, R_2=H
29b: R_1=H, R_2=OH

30: R=CH_2Ph
31: R=H
32: R=CH_2COOH

Chart 7

dl-3-Oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (**1a**) (IC_{50}: 23 ng/ml) was found to be a more potent inhibitor of adenosine diphosphate-induced platelet aggregation than (+)-carbacyclin (**3**), using rabbit platelet-rich plasma. In a preliminary experiment, **1a** was found to be more stable than isocarbacyclin (**2**) in an *in vitro* experimental model for β-oxidation using liver homogenate. Details will be published elsewhere.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO A-102 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Varian T-60A (60 MHz) or EM-390 (90 MHz) spectrometer in deuteriochloroform, with tetramethylsilane as internal reference. Mass spectra (MS) were

obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer. Removal of solvents *in vacuo* was accomplished with a rotating flash evaporator at 20—30 mmHg and usually at 35—50 °C. Plates for thin layer chromatography (TLC) were Silica gel 60 F-254 (E. Merck AG) and spots were visualized by spraying a solution of 0.5% vanillin in 20% ethanol in sulfuric acid (v/v), followed by heating. Columns for ordinary chromatography were prepared with Silica gel 60 (70—230 mesh or 230—400 mesh, E. Merck AG). In general, reactions were carried out under a nitrogen stream.

Methyl 4,4-Ethylenedioxy-2-nonenoate (5)——A mixture of methyl 4-oxo-2-nonenoate (**4**)[6] (4.860 g), ethyleneglycol (15 ml) and *p*-TsOH (150 mg) in benzene (60 ml) was heated under reflux using a Dean–Stark apparatus for 5 h. The reaction mixture was diluted with benzene, washed with 5% $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 2—3% AcOEt in hexane (v/v) afforded **5** (6.020 g) as a colorless oil. IR (neat): 1725, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.76 (3H, s, COOMe), 3.92 (4H, s, OCH_2CH_2O), 6.06 (1H, d, J=16 Hz, olefinic-H), 6.80 (1H, d, J=16 Hz, olefinic-H). MS *m/z*: 229 (M^++1), 197, 157.

3-Ethyl-6,6-ethylenedioxy-4-undecen-3-ol (6)——A solution of **5** (6.020 g) in Et_2O (60 ml) was added to stirred EtMgBr reagent [prepared from Mg metal (3.20 g) and EtBr (9.9 ml) in Et_2O (160 ml)] at room temperature. The reaction mixture was stirred for 30 min, quenched with NH_4Cl aq., and then extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 4—6% AcOEt in hexane (v/v) afforded **6** (4.140 g) as a colorless oil. IR (neat): 3300, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (4H, s, OCH_2CH_2O), 5.45 (1H, d, J=16 Hz, olefinic-H), 5.80 (1H, d, J=16 Hz, olefinic-H). MS *m/z*: 257 (M^++1), 227, 185.

1-(1-Ethyl-1-hydroxypropyl)-2-(1,1-ethylenedioxyhexyl)cyclopropane (7)——CH_2I_2 (3.9 ml) was added to a stirred solution of **6** (4.140 g) and Et_2Zn (1 M solution in hexane, 48.5 ml) in benzene (90 ml) at room temperature, and the whole was stirred for 12 h. The reaction mixture was poured into water and extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 6—8% AcOEt in hexane (v/v) afforded **7** (2.460 g) as a colorless oil. IR (neat): 3510, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (4H, s, OCH_2CH_2O). MS *m/z*: 241 (M^+ − Et), 199.

1-(1-Ethyl-1-hydroxypropyl)-2-(1-oxohexyl)cyclopropane (8)——A solution of **7** (2.460 g) and *p*-TsOH (50 mg) in a mixture of acetone (50 ml) and water (25 ml) was stirred at room temperature for 30 min. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 5—7% AcOEt in hexane (v/v) afforded **8** (1.770 g) as a colorless oil. IR (neat): 3500, 1685, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (2H, t, J=6 Hz, $COC\underline{H}_2CH_2$). MS *m/z*: 197 (M^+ − Et).

3-Ethyl-7-oxo-3-dodecene (9)——Me_3SiI (0.31 ml) was added dropwise to a stirred solution of **8** (200 mg) in toluene (20 ml) at 25 °C, and the whole was stirred for 1 h. Sodium thiosulfate aq. was added to the reaction mixture, and which was extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 1% AcOEt in hexane (v/v) afforded **9** (105 mg) as a colorless oil. IR (neat): 1710, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (4H, t, J=6 Hz, $C\underline{H}_2COC\underline{H}_2CH_2$), 4.90—5.40 (1H, m, olefinic-H). MS *m/z*: 210 (M^+), 154, 127.

(1*S,5*R**)-3-Methoxycarbonylmethyliden-7,7-ethylenedioxybicyclo[3.3.0]octane (13)**——A solution of **12** (20.00 g) in DME (60 ml) was added to a stirred ylide solution [prepared from trimethyl phosphonoacetate (20.00 g) and 55% NaH in oil (3.83 g) in DME (900 ml)] under ice-cooling, and the whole was stirred for 29 h at room temperature. The reaction mixture was poured into brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 3—8% AcOEt in hexane (v/v) afforded **13** (23.60 g) as a colorless oil. IR (neat): 1720, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, COOMe), 3.88 (4H, s, OCH_2CH_2O), 5.80 (1H, m, olefinic-H). MS *m/z*: 238 (M^+), 207.

(1*S,5*R**)-3-Methoxycarbonylmethyl-7,7-ethylenedioxybicyclo[3.3.0]oct-2-ene (14)**——A solution of **13** (15.26 g) in THF (86 ml) was added to a stirred solution of LDA [prepared from 15% *n*-BuLi in hexane solution (56 ml), diisopropylamine (13.5 ml) and HMPA (16.7 ml) in THF (66 ml)] at −78 °C, and the whole was stirred for 40 min at the same temperature. The reaction mixture was quenched with NH_4Cl aq., poured into brine, and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 4—20% AcOEt in hexane (v/v) afforded **14** (15.05 g) as a colorless oil. IR (neat): 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, COOMe), 3.88 (4H, s, OCH_2CH_2O), 5.47 (1H, m, olefinic-H). MS *m/z*: 238 (M^+), 188, 166.

(1*S,5*R**)-3-(2-Hydroxyethyl)-7,7-ethylenedioxybicyclo[3.3.0]oct-2-ene (15)**——A solution of **14** (14.96 g) in THF (250 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (3.57 g) in THF (125 ml) under ice-cooling. The reaction mixture was stirred for 25 min, then quenched with 4% NaOH aq. (15 ml). The reaction mixture was stirred at room temperature for another 1 h, and then the precipitate was filtered off. Removal of the solvent of the filtrate *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 25—55% AcOEt in hexane (v/v) afforded **15** (12.42 g) as a colorless oil. IR (neat): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (4H, s,

OCH_2CH_2O), 5.35 (1H, m, olefinic-H). MS *m/z*: 210 (M^+), 180.

(1*S,5*R**)-3-(2-Benzyloxyethyl)-7,7-ethylenedioxybicyclo[3.3.0]oct-2-ene (16)**——A solution of **15** (15.00 g) in DMF (25 ml) was added dropwise to a stirred suspension of 55% NaH in oil (4.60 g) in DMF (50 ml) under ice-cooling. The reaction mixture was stirred for 30 min at room temperature. Benzyl bromide (10 ml) was added dropwise to the reaction mixture, and the whole was stirred for 20 min at room temperature. The reaction mixture was poured into water and extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 3—10% AcOEt in hexane (v/v) afforded **16** (21.40 g) as a colorless oil. IR (neat): 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (4H, s, OCH_2CH_2O), 4.50 (2H, s, OCH_2Ph), 5.31 (1H, br s, olefinic-H), 7.35 (5H, s, arom.-H). MS *m/z*: 300 (M^+).

(1*S,2*R**,3*R**,5*R**)-3-(2-Benzyloxyethyl)-7,7-ethylenedioxybicyclo[3.3.0]octane-2,3-diol (17)**——A solution of **16** (20.00 g) in acetone (100 ml) was added to a solution of OsO_4 (100 mg) and *N*-methylmorpholine *N*-oxide (10.00 g) in a mixture of *tert*-BuOH (150 ml), acetone (100 ml) and water (100 ml) at room temperature, and the whole was stirred for 6 h. $Na_2S_2O_4$ was added to the reaction mixture and filtered off. The filtrate was evaporated *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 3—10% AcOEt in hexane (v/v) afforded **17** (20.90 g) as crystals. Recrystallization from AcOEt–hexane gave an analytical sample, mp 56—58 °C. *Anal.* Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.97; H, 7.78. IR (KBr): 3440, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (4H, s, OCH_2CH_2O), 4.52 (2H, s, OCH_2Ph), 7.36 (5H, s, arom.-H). MS *m/z*: 334 (M^+), 316.

(1*R,5*S**,6*R**,7*R**)-7-(2-Benzyloxyethyl)-6,7-dihydroxybicyclo[3.3.0]octan-3-one (18)**——A solution of **17** (20.80 g) in a mixture of acetone (100 ml), water (50 ml) and conc. HCl (3 ml) was stirred for 30 min at room temperature. The reaction mixture was poured into brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 3—10% AcOEt in hexane (v/v) afforded **18** (18.00 g) as crystals. Recrystallization from AcOEt–hexane gave an analytical sample, mp 91—93 °C. *Anal.* Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.11; H, 7.69. IR (KBr): 3440, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 7.36 (5H, s, arom.-H). MS *m/z*: 290 (M^+), 272, 216.

(1*R,5*S**,6*R**,7*R**)-7-(2-Benzyloxyethyl)-7-hydroxy-5-methanesulphonyloxybicyclo[3.3.0]octan-3-one (19)**——MsCl (5.5 ml) was added to a stirred solution of **18** (17.90 g) and Et_3N (13 ml) in CH_2Cl_2 (350 ml) under ice-cooling, and the whole was stirred for 50 min. The reaction mixture was poured into brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave **19** (22.51 g) as crystals. Recrystallization from AcOEt–hexane gave an analytical sample, mp 90—92 °C. *Anal.* Calcd for $C_{18}H_{24}O_6S$: C, 58.67; H, 6.57. Found: C, 58.49; H, 6.50. IR (KBr): 3400, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (3H, s, CH_3SO_2), 4.52 (2H, s, OCH_2Ph), 7.36 (5H, s, arom.-H). MS *m/z*: 368 (M^+).

(1*R,4*S**,5*S**,6*R**,7*R**)-7-(2-Benzyloxyethyl)-7-hydroxytricyclo[3.3.0.0^{4,6}]octan-3-one (20)**——*tert*-BuOK (3.51 g) was added to a stirred solution of **19** (7.681 g) in THF (300 ml) at room temperature, and the whole was stirred for 20 min at room temperature. After neutralization of the reaction mixture with AcOH, the whole was poured into water and extracted with AcOEt. The extracts were washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 30—60% AcOEt in hexane (v/v) afforded **20** (4.170 g) as a colorless oil. IR (neat): 3455, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.55 (2H, s, OCH_2Ph), 7.35 (5H, s, arom.-H). MS *m/z*: 272 (M^+), 254.

Ethyl(1*S,2*R**,3*S**,5*S**,6*R**,7*R**)-7-(2-Benzyloxyethyl)-7-hydroxy-3-oxotricyclo[3.3.0.0^{4,6}]octane-2-carboxylate (21)**——A solution of **20** (4.002 g) in THF (70 ml) was added dropwise to a stirred solution of LDA [prepared from diisopropylamine (5.3 ml) and 15% solution of *n*-BuLi in hexane (22.0 ml) in THF (240 ml)] at −78 °C. The mixture was stirred for 20 min, a solution of ethoxyformylimidazole[15] (4.00 g) in THF (45 ml) was added, and the whole was stirred for 15 min at −78 °C. After neutralization with AcOH, the reaction mixture was poured into water, and extracted with AcOEt. The extracts were washed with 5% HCl aq. and brine, and then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 25—50% AcOEt in hexane (v/v) afforded **21** (4.262 g) as a colorless oil. IR (neat): 3500, 1735, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.11 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.49 (2H, s, OCH_2Ph), 7.28 (5H, s, arom.-H). MS *m/z*: 344 (M^+), 326.

Ethyl (1*S,2*R**,5*S**)-7-(2-Benzyloxyethyl)-3-oxobicyclo[3.3.0]oct-6-en-2-carboxylate (22)**——Me_3SiI (3.1 ml) was added dropwise to a stirred solution of **21** (3.010 g) in toluene (200 ml) over 30 min at 25 °C. The mixture was stirred for 30 min, and sodium thiosulfate aq. was added. The reaction mixture was extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 4—5% AcOEt in hexane (v/v) afforded **22** (1.290 g) as a colorless oil. IR (neat): 1755, 1720, 1655, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.46 (2H, s, OCH_2Ph), 5.20 (1H, br s, olefinic-H), 7.25 (5H, s, arom.-H). MS *m/z*: 328 (M^+), 283, 238.

(1*R,5*S**)-7-(2-Benzyloxyethyl)bicyclo[3.3.0]oct-6-en-3-one (23)**——A solution of **16** (2.600 g) in a mixture of acetone (20 ml), water (8 ml) and conc. HCl (0.5 ml) was stirred for 1 h at room temperature. The reaction mixture was poured into brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal

of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 7—10% AcOEt in hexane (v/v) afforded **23** (2.100 g) as a colorless oil. IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.46 (2H, s, OCH_2Ph), 5.28 (1H, br s, olefinic-H), 7.30 (5H, s, arom.-H). MS *m/z*: 256 (M^+), 166.

Treatment of 23 with $(EtO)_2CO$ and NaH——A solution of **23** (1.102 g) in dioxane (10 ml) was added dropwise to a stirred mixture of 55% NaH in oil (940 mg) and $(EtO)_2CO$ (17 ml) in dioxane (30 ml) at 80 °C, and the whole was stirred for 30 min at the same temperature. After neutralization, the reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 5% AcOEt in hexane (v/v) afforded **22** (280 mg), and elution with 6% AcOEt in hexane (v/v) afforded the isomeric ester (226 mg) as a colorless oil.

Treatment of 20 with Me_3SiI——Similar treatment of **20** (200 mg) with Me_3SiI (0.25 ml) in toluene (20 ml) afforded the olefin **23** (80 mg) as a colorless oil.

Ethyl (1*S,2*R**,3*R**,5*S**)-7-(2-Benzyloxyethyl)-3-hydroxybicyclo[3.3.0]oct-6-ene-2-carboxylate (24)**——$NaBH_4$ (330 mg) was added to a stirred solution of **22** (1.281 g) in ethanol (25 ml) under ice-cooling, and the whole was stirred for 30 min. The reaction mixture was poured into brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 15—20% AcOEt in hexane (v/v) afforded **24** (1.060 g) as a colorless oil. IR (neat): 3450, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.09 (2H, q, J=7 Hz, $OCH_2\underline{CH_3}$), 4.46 (2H, s, OCH_2Ph), 5.26 (1H, br s, olefinic-H), 7.30 (5H, s, arom.-H). MS *m/z*: 330 (M^+), 312.

Ethyl (1*S,2*R**,3*R**,5*S**)-3-(2-Benzyloxyethyl)-3-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-6-ene-2-carboxylate (25)**——A mixture of **24** (2.201 g), DHP (0.93 ml) and a catalytic amount of *p*-TsOH in CH_2Cl_2 (60 ml) was stirred under ice-cooling for 30 min. The reaction mixture was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 5—10% AcOEt in hexane (v/v) afforded **25** (2.620 g) as a colorless oil. IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=6 Hz, $C\underline{H_3}CH_2O$), 4.14 (2H, q, J=6 Hz, $CH_3C\underline{H_2}O$), 4.52 (2H, s, OCH_2Ph), 4.65 (1H, br s, OCHO), 5.35 (1H, br s, olefinic-H), 7.36 (5H, s, arom.-H). MS *m/z*: 414 (M^+), 330.

(1*S,5*S**,6*S**,7*R**)-3-(2-Benzyloxyethyl)-6-hydroxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (26)**——A solution of **25** (2.580 g) in THF (15 ml) was added to a stirred suspension of $LiAlH_4$ (400 mg) in THF (50 ml) under ice-cooling, and the whole was stirred for 30 min, and then quenched with 4% NaOH aq. (1.6 ml). The reaction mixture was stirred at room temperature for another 1 h, and the precipitate was filtered off. Removal of the solvent of the filtrate *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 20—25% AcOEt in hexane (v/v) afforded **26** (2.620 g) as a colorless oil. IR (neat): 3470, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 5.37 (1H, br s, olefinic-H), 7.35 (5H, s, arom.-H). MS *m/z*: 372 (M^+), 354, 288.

(1*S,5*S**,6*R**,7*R**)-3-(2-Benzyloxyethyl)-6-formyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (27)**——A solution of SO_3 pyridine complex (2.500 g) in DMSO (15 ml) was added to a stirred mixture of **26** (2.140 g) and Et_3N (10.0 ml) in DMSO (20 ml) at room temperature. After being stirred for 45 min, the reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave almost pure aldehyde (**27**) (2.061 g) as a pale yellow oil. The crude material was used for the subsequent step without purification. IR (neat): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 4.65 (1H, br s, OCHO), 5.37 (1H, br s, olefinic-H), 7.37 (5H, s, arom.-H), 9.77 (1H, d, J=4 Hz, CHO). MS *m/z*: 370 (M^+), 286, 268.

(1*S,5*S**,6*S**,7*R**)-3-(2-Benzyloxyethyl)-6-[3-oxo-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]oct-2-ene (28)**——Tributyl 2-oxoheptylidenephosphorane (2.36 g) in Et_2O (10 ml) was added to a solution of **27** (2.032 g) in Et_2O (20 ml), and the mixture was stirred for 5 h at room temperature, then evaporated to dryness. The residue was purified by silica gel column chromatography. Elution with 4—6% AcOEt in hexane (v/v) afforded **28** (2.358 g) as a colorless oil. IR (neat): 1695, 1670, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 5.37 (1H, br s, olefinic-H), 6.17 (1H, dd, J=3, 12 Hz, olefinic-H), 6.75—7.05 (1H, m, olefinic-H), 7.36 (5H, s, arom.-H). MS *m/z*: 382 ($M^+ - 84$), 364.

(1*S,5*S**,6*S**,7*R**)-3-(2-Benzyloxyethyl)-6-[3(*S**)-hydroxyoct-1(*E*)-enyl]-7-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]oct-2-ene (29a) and (1*S**,5*S**,6*S**,7*R**)-3-(2-Benzyloxyethyl)-6-[3(*R**)-hydroxyoct-1(*E*)-enyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (29b)**——$NaBH_4$ (280 mg) was added to a stirred solution of **28** (2.318 g) and $CeCl_3 \cdot 7H_2O$ (2.22 g) in methanol (40 ml) under ice-cooling. After 30 min of stirring, the excess reagent was decomposed by adding AcOH, and the reaction mixture was diluted with brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 10% AcOEt in hexane (v/v) afforded **29b** (762 mg) as a colorless oil, and then elution with 12% AcOEt in hexane (v/v) afforded **29a** (1.510 g) as a colorless oil. Compound **29a**; IR (neat): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 4.68 (1H, br s, OCHO), 5.35 (1H, br s, olefinic-H), 5.60 (2H, m, olefinic-H), 7.36 (5H, s, arom.-H). MS *m/z*: 468 (M^+), 450, 406. Compound **29b**; IR (neat): 3440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 4.70 (1H, br s, OCHO), 5.36 (1H, br s, olefinic-H), 5.60 (2H,

m, olefinic-H), 7.36 (5H, s, arom.-H). MS *m/z*: 468 (M^+), 450, 406.

(1*S,5*S**,6*S**,7*R**)-3-(2-Benzyloxyethyl)-6-[3(*S**)-(tetrahydropyran-2-yl)oxyoct-1(*E*)-enyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (30)**——A mixture of **29a** (1.489 g), DHP (0.44 ml) and a catalytic amount of *p*-TsOH in CH_2Cl_2 (15 ml) was stirred under ice-cooling for 1 h. The reaction mixture was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ aq. and water, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel chromatography. Elution with 6—10% AcOEt in hexane (v/v) afforded **30** (1.721 g) as a colorless oil. IR (neat): 2950, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.53 (2H, s, OCH_2Ph), 4.73 (2H, br s, OCHO), 5.37 (1H, br s, olefinic-H), 5.60 (2H, m, olefinic-H), 7.37 (5H, s, arom.-H). MS *m/z*: 450 ($M^+ - 102$), 406.

(1*S,5*S**,6*S**,7*R**)-3-(2-Hydroxyethyl)-6-[3(*S**)-(tetrahydropyran-2-yl)oxyoct-1(*E*)-enyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (31)**——Excess sodium metal was added to a stirred solution of **30** (1.690 g) in a mixture of liquid ammonia (80 ml) and THF (30 ml) at −78 °C until a blue color persisted, and the whole was stirred for 20 min. The reaction was quenched by the addition of NH_4Cl, and ammonia was evaporated off at room temperature under a stream of N_2. Water was added to the residue and extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 20—30% AcOEt in hexane (v/v) afforded **31** (1.273 g) as a colorless oil. IR (neat): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.71 (2H, br s, OCHO), 5.43 (1H, br s, olefinic-H), 5.60 (2H, m, olefinic-H). MS *m/z*: 360 ($M^+ - 102$), 316, 276.

***dl*-3-Oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 11,15-Bis(tetrahydropyran-2-yl)ether (32)**——A 15% solution of *n*-BuLi in hexane (3.1 ml) was added to a stirred solution of **31** (1.240 g) in THF (6 ml) under ice-cooling. The mixture was stirred for 10 min, DMF (3 ml), DMSO (3 ml), $ClCH_2COOLi$ (540 mg) and NaI (2.00 g) were added to the reaction mixture, and the whole was stirred for 8 h at room temperature. The reaction mixture was diluted with water, acidified with 3% HCl aq. and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by acid-washed silica gel column chromatography. Elution with 20—30% AcOEt in hexane (v/v) afforded **32** (1.186 g) as a colorless oil. IR (neat): 1760, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.12 (2H, s, OCH_2COOH), 4.74 (2H, br s, OCHO), 5.38 (1H, br s, olefinic-H), 5.60 (2H, m, olefinic-H), 8.17 (1H, s, COOH). MS *m/z*: 418 ($M^+ - 102$), 374, 334.

***dl*-3-Oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (1a)**——A mixture of **32** (528 mg) and camphorsulphonic acid (50 mg) in acetone (20 ml) and water (10 ml) was stirred at 40 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave a crystalline residue, which was recrystallized from AcOEt–hexane to give **1a** (265 mg), mp 72—74 °C. *Anal.* Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.01; H, 8.97. IR ($CHCl_3$): 3400, 1730, 972 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.70—3.20 (1H, m, C_9-H), 3.67 (2H, t, J=6 Hz, OCH_2CH_2), 4.07 (2H, s, OCH_2COOH), 5.40—5.55 (3H, m, olefinic-H). MS *m/z*: 334 ($M^+ - 18$), 316, 290. TLC: Rf=0.48 [AcOEt : AcOH = 10 : 1 (v/v)].

15β-Isomer (1b) of 1a——Similar treatment of the 15β-alcohol (**29b**) through the reaction sequence described for the synthesis of **1a** gave **1b** as a colorless viscous oil. IR (neat): 3350, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (2H, t, J= 6 Hz, OCH_2CH_2), 4.09 (2H, s, OCH_2COOH), 5.40—5.55 (3H, m, olefinic-H). MS *m/z*: 334 ($M^+ - 18$), 316, 290. TLC: Rf=0.56 [AcOEt : AcOH = 10 : 1 (v/v)].

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