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# A NOVEL SYNTHESIS OF CARBACYCLIN ANALOGS VIA A STEREOSELECTIVE INTRODUCTION OF 15α-HYDROXY GROUP

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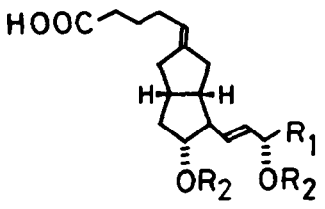
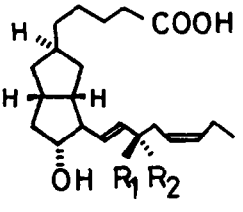
Abstract --- (+/-)-6,9α-Methanoprostaglandin $I_3$ (2) and (+/-)-5,6-dihydro-6,9α-methano-6β-prostaglandin $I_3$ (4a) have been synthesized using a new method for the stereoselective introduction of the 15α-hydroxy group *via* a stereoselective electrophilic addition of phenylsulfenyl chloride to the enol ether (6) and (23) respectively.

Carbacyclin [9(O)-methanoprostacyclin] (1), a stable carba-analog of prostaglandin $I_2$ (prostacyclin), is of interest owing to its potent platelet anti-aggregation activity. The synthesis of carbacyclin has already been accomplished *via* various routes.[1] In the course of our studies on the stereoselective synthesis of carbacyclin analogs, we herein describe the synthesis of (+/-)-6,9α-methanoprostaglandin $I_3$ (2) and (+/-)-5,6-dihydro-6,9α-methano-6β-prostaglandin $I_3$ (4a) using a new and stereoselective method for the introduction of the 15α-hydroxy group.

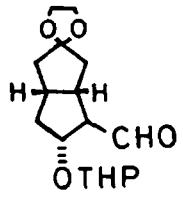
A general plan for the stereoselective introduction of the 15α-hydroxy group is shown in chart 1 in the case of the enol ether (6). The sulfide (8) is transformed to the desired 15α-alcohol (10) *via* a [2,3]-sigmatropic rearrangement. The sulfide (8) is in turn accessible by cis-olefination of the aldehyde (7), which is derived from the enol ether (6) by a stereoselective addition of phenylsulfenyl chlorid (PhSCl).



1 : $R_1 = C_5H_{11}$, $R_2 = H$
2 : $R_1$ =  , $R_2 = H$
3 : $R_1$ =  , $R_2$ = THP



4a: $R_1 = H$, $R_2 = OH$
4b: $R_1 = OH$, $R_2 = H$



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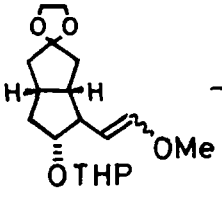

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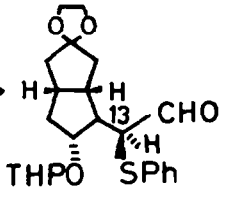

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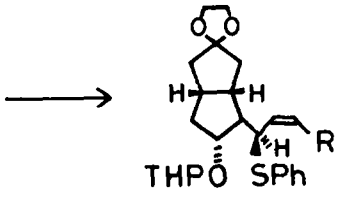
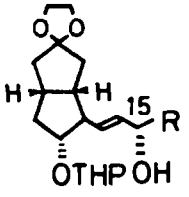
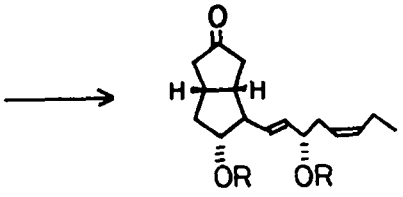


8 : R = $C_5H_{11}$
11 : R = 



10 : R = $C_5H_{11}$
12 : R = 



13 : R = H
14 : R = THP

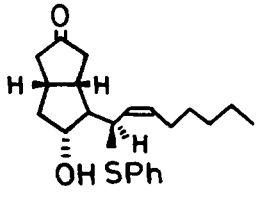


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Chart 1

A SYNTHESIS OF (+/-)-6,9α-METHANOPROSTAGLANDIN $I_3$ (2)[2)]

First we investigated the electrophilic addition reaction of PhSCl to the enol ether (6), which was synthesized by treatment of the aldehyde (5)[1a)] with methoxymethylenetriphenylphosphorane ($Ph_3P=CHOCH_3$). Thus, treatment of 6 with PhSCl at -78°C and then hydrolysis with 10% sodium hydrogen carbonate solution yielded the aldehyde (7) stereoselectively in 91% yield.

The S*-configuration at C-13 (PG numbering) in the aldehyde (7) was determined through the following reactions. Treatment of the aldehyde (7) with hexylidenetriphenylphosphorane ($Ph_3P=CHC_5H_{11}$) in tetrahydrofuran (THF)/dimethyl sulfoxide (DMSO) at -78°C and then ambient temperature afforded the sulfide (8). Deprotection of 8 with aqueous acetic acid gave the alcohol (9). The IR spectrum of 9 has no signal of 970 $cm^{-1}$ characteristic to the trans double bond. Moreover the coupling constant (J=10.5 Hz) of the olefinic protons in the $^1$H-NMR ($CDCl_3$, 400 MHz, decoupling experiment) supported the cis structure of the double bond in the alcohol (9) and hence that of the sulfide (8). Treatment of the sulfide (8) with m-chloroperbenzoic acid (mCPBA) in methanol at -30°C, followed by the addition of trimethylphosphite [$(MeO)_3P$] at -30°C and then ambient temperature gave the 15α-alcohol (10) in 89% yield,[3)] which was identified with an authentic sample[1a)] (TLC, IR, $^1$H-NMR, MS). The stereoselectivity of the 15α-hydroxy group intoruction (6 to 10) was 92-95% based on HPLC.

Now we have the aldehyde (7) with the desired 13S*-configuration. So we then converted the aldehyde (7) into (+/-)-6,9α-methanoprostaglandin $I_3$ (2) through the following reactions. The aldehyde (7) was treated with 3(Z)-hexenylidenetriphenylphosphorane [(Z)-$Ph_3P=CHCH_2CH=CHCH_2CH_3$], derived from 3(Z)-hexenyltriphenylphosphonium iodide to give the sulfide (11) in 73% yield. The phosphonium salt, mp 158°C, was prepared from 3(Z)-hexen-1-ol through the following reactions i) tosylation with p-toluenesulfonyl chrolide (p-TsCl) in pyridine; ii) iodination with sodium iodide in acetone; iii) reaction with triphenylphosphine in acetonitrile. Treatment of the sulfide (11) with mCPBA in methanol, followed by the addition of $(MeO)_3P$ afforded the alcohol (12) in 95% yield. Treatment of 12 with aqueous acetic acid yielded the diol (13). The hydroxy groups in 13 were protected with dihydropyran (DHP) to afford 14. The Wittig reaction of 14 with (4-sodiocarboxybutylidene)triphenylphosphorane in DMSO and separation of $\Delta^5$-isomers by silica gel column chromatography yielded the acid 3 (more polar) and the 5(Z)-isomer (less polar) of 3. The stereochemistry of the double bond at C-5 was assigned on the basis of TLC behavior.[1a)] Treatment of the 3 with aqueous acetic acid at room temperature afforded (+/-)-6,9α-methanoprostaglandin $I_3$ (2).[4)]

A SYNTHESIS OF (+/-)-5,6-DIHYDRO-6,9α-METHANO-6β-PROSTAGLANDIN $I_3$ (4a)

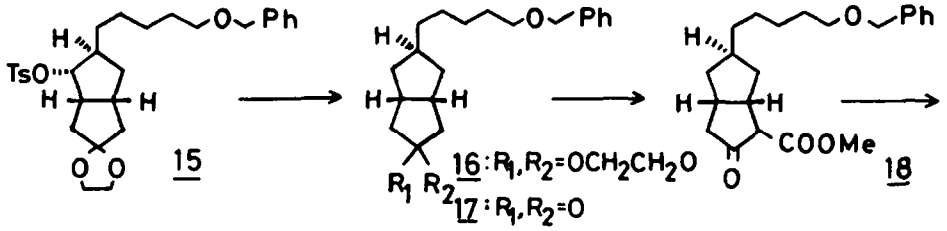
We then applied this methodology to the synthesis of (+/-)-5,6-dihydro-6,9α-methano-6β-prostaglandin $I_3$ (4a). Accordingly we studied a key reaction, namely the addition reaction of PhSCl to the enol ether (23) having a long chain alkyl substituent in place of the ethylenedioxy group in 6. The starting enol

ether (23) was prepared as illustrated in chart 2. The tosylate (15), which was prepared as described in the previous communication,[5] was reduced with lithium aluminum hydride ($LiAlH_4$) in diethyl ether at reflux temperature yielding the deoxygenated compound 16. After removing the acetal group in 16 with 10% aqueous HCl in acetone, the resulting ketone (17) was treated with dimethyl carbonate and sodium hydride (NaH) in 1,4-dioxane at 80°C for 2 hours to afford the β-ketoester (18). Reduction of 18 with sodium borohydride ($NaBH_4$) in ethanol gave the trans-alcohol (19a) as main product (64%) together with cis-alcohol (19b, 11%). The cis-alcohol (19b) could be converted to 19a by treatment with potassium carbonate in refluxing methanol, followed by esterification with diazomethane. The hydroxy group in 19a was protected with DHP affording the tetrahydropyranyl ether (20), which was then reduced with $LiAlH_4$ in THF to give the alcohol (21). The alcohol (21) was converted to the aldehyde (22) with excess sulfur trioxide pyridine complex[6] and triethylamine ($Et_3N$) in DMSO. Treatment of the aldehyde (22) with $Ph_3P{=}CHOCH_3$ in toluene gave the desired enol ether (23) as an inseparable mixture of geometrical isomers (E:Z=ca. 2:1).

Now we were ready for the electrophilic addition reaction of PhSCl to the enol ether (23). Thus treatment of 23 in a similar manner described for the synthesis of 7 afforded stereoselectively the compound 24a along with a small amount of the isomeric compound 24b (Chart 3). The ratio of 24a to 24b was about 10 to 1. The configuration at C-13 was assigned by an analogy to the similar reaction of 6; the major aldehyde (24a) has the desired $13S^*$-configuration and the minor aldehyde (24b) has $13R^*$-configuration.

The major aldehyde (24a) was then treated with (Z)-$Ph_3P{=}CHCH_2CH{=}CHCH_2CH_3$ in THF/DMSO at -78°C and then ambient temperature to give a single product 25a in 92% yield. Treatment of the sulfide (25a) with mCPBA in methanol, followed by the addition of $(MeO)_3P$ gave the 15α-alcohol (26a) in 90% yield. Similar treatment of the minor aldehyde (24b) afforded the corresponding 15β-alcohol (26b) in 70% overall yield. Both alcohol (26a) and (26b) gave the same ketone (27) by oxidation with the Jones reagent ($CrO_3$-$H_2SO_4$)[7] in acetone at -20°C. This suggested that 26a and 26b are isomeric pairs at the C-15 position. The more polar alcohol (26a) was assigned as the 15α-hydroxy compound and hence the less polar alcohol (26b) as the 15β-hydroxy compound on the basis of the general rule for prostaglandin chemistry. These results also supported the previous assignment of the configuration at C-13 in 24a and 24b.

The 15α-alcohol (26a) was then converted into (+/-)- 5,6-dihydro-6,9α-methano-6β-prostaglandin $I_3$ (4a) through the following sequence of reactions. The 15α-hydroxy group in 26a was protected by reaction with DHP and p-toluenesulfonic acid in $CH_2CH_2$ to afford the compound 28. Treatment of 28 with excess sodium metal in liquid ammonia[8] at -78°C gave the alcohol (29). Oxidation of 29 with the Jones reagent in acetone at -20°C afforded the carboxylic acid (30). Finally, removal of the protecting groups of 30 with camphorsulfonic acid in aqueous acetone at 40°C gave the crystalline (+/-)-5,6-dihydro-6,9α-methano-6β-prostaglandin $I_3$ (4a)[9], mp 62-65°C, in 51% yield from 26a.



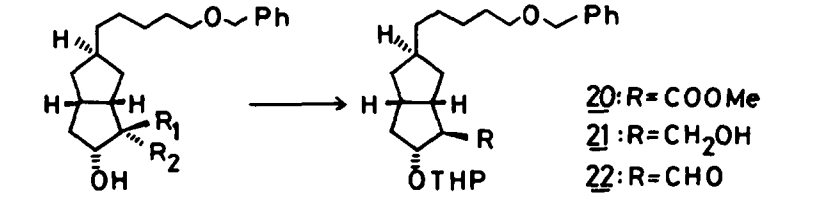
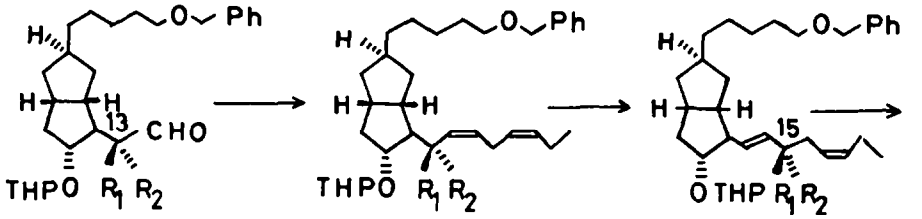




Chart 2



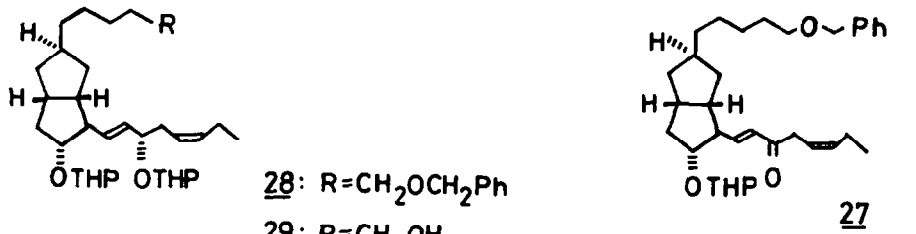




Chart 3

Similarly, the 15β-alcohol (26b) was converted to the 15β-isomer (4b), which was less polar than the 15α-isomer (4a) on a thin layer chromatogram.

STEREOSELECTIVITY OF PhSCl ADDITION REACTION

The addition reaction of PhSCl to the enol ether (6), followed by hydrolysis yielded 13S*-aldehyde (7) stereoselectively. Similar treatment of the enol ether (6) with PhSCl and then hydrolysis with 10% sodium hydrogen carbonate in $D_2O$ gave the same aldehyde (7) without incorporation of deuterium. This indicates that 13S*-configuration in 7 was generated in the addition step of PhSCl. So the stereoselectivity for the addition reaction of PhSCl to 6 and 23 might be explained as follows (chart 4); the stable conformation of 6 and 23 is assumed to be 31. The addition reaction of PhSCl to the enol ether (6 and 23) would take place from the sterically less hindered side through the transition state (32)[10] to give the β-chlorosulfide intermediate (33) and/or episulfonium ion intermediate (34), which upon hydrolysis gave the aldehyde (7 and 24a).

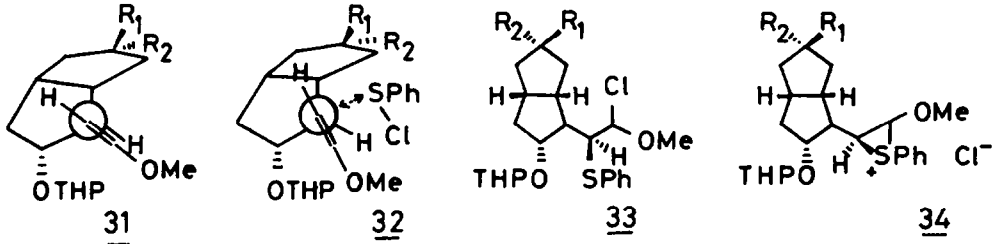



Chart 4

EXPERIMENTAL

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO A-102 spectrophotometer. $^1$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. Low-resolution mass spectra (LR-MS) were obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer and high-resolution mass spectra (HR-MS) with a JEOL JMS-HX100 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 nitrogen stream.

7,7-Ethylenedioxy-2β-(2-methoxyvinyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]-octane (6)

Methoxymethyltriphenylphosphonium chloride (22.4 g) was added to a solution of sodium methyl sulfinylmethide [prepared from 55% NaH in oil (2.36 g) and DMSO (200 ml) in the usual manner] under ice cooling, and stirred for 30 min at the same temperature. A solution of the aldehyde (5)[1a] (7.20 g) in DMSO (30 ml) was added to the reaction mixture. After being stirred for 1 hr at the same temperature, the reaction mixture was diluted with ice-water, 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 10-20% AcOEt in hexane (v/v) afforded the colorless, oily enol ether (6) (5.29 g) as an inseparable mixture of geometrical isomers [E:Z=ca. 1:1]. IR (neat) ν: 2950, 1665, 1325, 1260, 1205, 1120, 1020 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.50, 3.55 (each 3/2 H, s, OMe), 3.80(4H, s, $OCH_2CH_2O$), 4.70(1H, br.s, OCHO), 5.92(1/2H, m, olefinic-H), 6.34(1/2H, dd, J=12.0, 6.0Hz, olefinic-H). LR-MS m/z: 239($M^+$-85), 224, 223, 222, 190, 166.

7,7-Ethylenedioxy-2β-(2-oxo-1β-phenylthioethyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (7)

PhSCl[11] (4.0 ml) was added to a stirred mixture of the enol ether (6) (1.606 g) and $K_2CO_3$ (3.3 g) in toluene (100 ml) at -78°C, and stirred for 50 min at the same temperature. The reaction mixture was poured into 10% $NaHCO_3$ aq. (100 ml), vigorously stirred for 30 min at room temperature, and then 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 10-20% AcOEt in hexane (v/v) afforded the compound 7 (1.882 g) as a colorless oil. IR (neat) ν: 2950, 2880, 2720, 1710, 1585, 1440, 1325, 1125, 1020 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.91(4H, s, $OCH_2CH_2O$), 4.71(1H, br.s, OCHO), 7.32(5H, m, arom.-H), 9.27(1H, dd, J=10.5, 6.0 Hz, CHO). LR-MS m/z: 418($M^+$), 334, 316, 306, 288, 207. HR-MS m/z: 418.1826 (Calcd for $C_{23}H_{30}O_5S$, 418.1814 $M^+$).

7,7-Ethylenedioxy-2β-(1β-phenylthio-2(Z)-octenyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (8)

Hexyltriphenylphosphonium bromide (8.0 g) was added to a solution of sodium methyl sulfinylmethide [prepared from 55% NaH in oil (650 mg) and DMSO (30 ml) in the usual manner] under ice cooling. After 10 min stirring at same temperature, resulting red-colored solution was diluted with THF (240 ml). A solution of the aldehyde (7) (800 mg) in THF (10 ml) was added to this reaction mixture at -78°C, and stirred for 30 min. Then the reaction mixture was warmed up to room temperature, and stirred for another 1 hr. After neutralization of the reaction mixture with acetic acid, 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 10% AcOEt in hexane (v/v) afforded the compound 8 (517 mg) as a colorless oil. IR (neat) ν: 2930, 2860, 1585, 1120, 1010 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=6.0Hz, $CH_2CH_3$), 3.86 (4H, s, $OCH_2CH_2O$), 4.68(1H, br.s, OCHO), 5.28(2H, m, olefinic-H), 7.20(5H, m, arom.-H). LR-MS m/z: 486($M^+$), 384, 293, 278, 275.

2β-(1β-Phenylthio-2(Z)-octenyl)-3α-hydroxy-7-oxobicyclo[3.3.0]octane (9)

A mixture of the compound 8 (10 mg), AcOH (2 ml) and water (1 ml) was stirred for 4 hr at 50°C. The reaction mixture was diluted with AcOEt, washed with $NaHCO_3$ aq., and then brine, and dried over $Na_2SO_4$. The solvent was removed *in vacuo*, and purification of the residue by silica gel preparative TLC [developed with hexane:AcOEt = 1:1(v/v)] afforded the compound 9 (4 mg) as a colorless oil. IR (neat) ν: 3440, 2920, 2880, 1735, 740, 690 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=6.0Hz, $CH_2CH_3$), 4.18(1H, m, CHOH), 5.44(2H, m, olefinic-H), 7.34(5H, m, arom.-H). LR-MS m/z: 358($M^+$), 250, 249, 232, 109.

7,7-Ethylenedioxy-2β-(3α-hydroxy-1(E)-octenyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (10)

To a solution of the sulfide (8) (876 mg) in methanol (40 ml) was added mCPBA (205 mg) at -30°C and stirred for 1 hr at -30°C. $(MeO)_3P$ (2.0 ml) was added to this reaction mixture at the same temperature, gradually warmed up to the room temperature, and then stirred over night. The reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with brine, 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 8-20% AcOEt in hexane (v/v) afforded the alcohol (10) (659 mg) as a colorless oil. IR (neat)

ν: 3450, 2930, 2860, 1120, 1010 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.90(3H, t, J=6.0Hz, $CH_2\underline{CH_3}$), 3.90(4H, s, $OCH_2CH_2O$), 4.67(1H, m, OCHO), 5.58(2H, m, olefinic-H). LR-MS m/z: 292($M^+$-102), 274, 190.

3(Z)-Hexenyltriphenylphosphonium Iodide

TsCl (49.5 g) was added to a stirred solution of 3(Z)-hexen-1-ol (21.3 g) in pyridine (200 ml) under ice-cooling and the mixture was kept at -10°C for 14 hr. The reaction mixture was poured into ice-water and extracted with AcOEt. The extracts were washed with brine, dil. HCl, $NaHCO_3$ aq. and brine, and then dried over $Na_2SO_4$. Removal of the solvent *in vacuo* gave the crude tosylate (51.9 g). A mixture of the tosylate and NaI (100 g) in acetone (400 ml) was refluxed for 1 hr. Concentration of the solvent afforded the residue, to which water was added, and extracted with $Et_2O$. The extracts were washed with brine, dried over $Na_2SO_4$. Evaporation of the solvent gave an oily residue, which was distilled at reduced pressure to give the iodide as a colorless oil (36.8 g, bp 70-71°C/17 mmHg). A mixture of the iodide (36 g) and triphenylphosphine (45 g) in acetonitrile (100 ml) was refluxed for 17 hr. $Et_2O$ was added to the reaction mixture and the precipitate was collected. Recrystallization from acetonitrile-$Et_2O$ gave the phosphonium salt (52.7 g) as colorless crystals, mp 158°C. IR (nujol) ν: 1445, 1440, 1115, 750 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.82 (3H, t, J=7.0Hz, $CH_2\underline{CH_3}$), 5.45(2H, m, olefinic-H), 7.80(15H, m, arom.-H).

7,7-Ethylenedioxy-2β-(1β-phenylthio-2(Z),5(Z)-octadienyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (11)

3(Z)-Hexenyltriphenylphosphonium iodide (7.52 g) was added to a solution of sodium methyl sulfinylmethide [prepared from 55% NaH in oil (650 mg) and DMSO (25 ml) in the usual manner] under ice cooling. After 10 min stirring at same temperature, resulting red-colored solution was diluted with THF (200 ml). A solution of the aldehyde (7) (1.711 g) in THF (10 ml) was added to this reaction mixture at -78°C, and stirred for 30 min. Then the reaction mixture was warmed up to room temperature, and stirred for another 1 hr. After neutralization of the reaction mixture with acetic acid, 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 9-10% AcOEt in hexane (v/v) afforded the compound 11 (1.458 g) as a colorless oil. IR (neat) ν: 2950, 2880, 1585, 1325, 1125, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.90(3H, t, J=7.0Hz, $CH_2\underline{CH_3}$), 3.88(4H, s, $OCH_2CH_2O$), 5.28(4H, m, olefinic-H), 7.30(5H, m, arom.-H). LR-MS m/z: 485($M^+$+1), 484($M^+$), 414, 400, 382, 372, 274.

7,7-Ethylenedioxy-2β-(3α-hydroxy-1(E),5(Z)-octadienyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (12)

Treatment of 11 (168 mg) in a similar manner described for the synthesis of 10 gave 12 (132 mg) as a colorless oil. IR (neat) ν: 3450, 2960, 2890, 1120, 1030 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.95(3H, t, J=6.0Hz, $CH_2\underline{CH_3}$), 3.86(4H, s, $OCH_2CH_2O$), 4.64(1H, br.s, OCHO), 5.50(4H, m, olefinic-H). LR-MS m/z: 290($M^+$-102), 272, 238, 220, 190.

2β-(3α-Hydroxy-1(E),5(Z)-octadienyl)-3α-hydroxy-7-oxobicyclo[3.3.0]octane (13)

A mixture of the compound 12 (125 mg), AcOH (2 ml) and water (4 ml) was stirred for 4 hr at 40°C. The reaction mixture was diluted with AcOEt, washed with $NaHCO_3$ 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 50-100% AcOEt in hexane (v/v) afforded 13 (78 mg). IR (neat) ν: 3380, 1740, 970 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.97(3H, t, J=7.0Hz, $CH_2\underline{CH_3}$), 4.00(2H, m, $C\underline{H}OHx2$), 5.50(4H, m, olefinic-H). LR-MS m/z: 246($M^+$-18), 195, 177.

7-Oxo-2β-[3α-(tetrahydropyran-2-yl)oxy-1(E),5(Z)-octadienyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (14)

A mixture of the alcohol (13) (140 mg), DHP (0.4 ml) and catalytic amount of p-TsOH in $CH_2CH_2$ (4 ml) was stirred under ice cooling for 30 min. The reaction mixture was diluted with $NaHCO_3$ 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 silica gel column chromatography. Elution with 3-6% AcOEt in hexane (v/v) afforded the compound 14 (176 mg) as a colorless oil. IR (neat) ν: 1740, 1130, 1075, 1030, 970 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.95(3H, t, J=7.0Hz, $CH_2\underline{CH_3}$), 4.64(2H, br.s, OCHOx2), 5.45(4H, m, olefinic-H). LR-MS m/z: 433($M^+$+1), 330, 248. HR-MS m/z: 433.2990 (Calcd for $C_{26}H_{41}O_5$,

433.2954 $M^+$+1).

(+/-)-6,9α-Methanoprostaglandin $I_3$ 11,15-Bis(tetrahydropyran-2-yl) ether (3) (4-Carboxybutyl)triphenylphosphonium bromide (4.8 g) was added to a solution of sodium methyl sulfinylmethide [prepared from 55% NaH in oil (722 mg) and DMSO (40 ml) in the usual manner] at 15-20°C. After 30 min stirring, resulting red-colored solution was treated with the ketone (14) (190 mg) in DMSO (2 ml). The reaction mixture was stirred at room temperature overnight, then poured into ice-water, acidified with conc. HCl (1 ml), and extracted with cyclohexane. The extracts were washed with brine and dried over $Na_2SO_4$. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 10-15% AcOEt in hexane (v/v) afforded the 5(Z)-compound (27 mg) as a colorless oil, and then elution with 15-30% AcOEt in hexane (v/v) afforded the compound 3 (55 mg) as a colorless oil.
5(E)-compound (3); IR (neat) ν: 2950, 1730, 1710, 1440, 1020 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.93(3H, t, J=7.0Hz, $CH_2CH_3$), 4.62(2H, br.s, OCHOx2), 5.32(5H, m, olefinic-H). LR-MS m/z: 414($M^+$-102), 330, 312, 280.
5(Z)-isomer of 3; IR (neat) ν: 2950, 1730, 1710, 1440, 1020 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.93(3H, t, J=7.0Hz, $CH_2CH_3$), 4.62(2H, br.s, OCHOx2), 5.32(5H, m, olefinic-H). LR-MS m/z: 414($M^+$-102), 330, 312, 280.

(+/-)-6,9α-Methanoprostaglandin $I_3$ (2) A mixture of the compound 3 (39 mg), AcOH (15 ml) and water (9 ml) was stirred at room temperature overnight. 12% NaOH aq. (50 ml) was added to the reaction mixture, and extracted with AcOEt. The extracts were washed with brine, dried over $Na_2SO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel (acid washed, 3 g) column chromatography. Elution with 40-50% AcOEt in hexane (v/v) afforded the (+/-)-6,9α-methanoprostaglandin $I_3$ (2) (21 mg) as a colorless oil. IR (neat) ν: 3350, 1705, 1075, 970 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.97(3H, t, J=7.0Hz, $CH_2CH_3$), 3.70, 4.10(each 1H, m, CHOH), 5.45(5H, m, olefinic-H). LR-MS m/z: 330($M^+$-18), 262, 244.

7β-(5-Benzyloxypentyl)-3,3-ethylenedioxybicyclo[3.3.0]octane (16) A solution of the tosylate (15)[5] (2.000 g) in diethyl ether (20 ml) was added to a suspension of $LiAlH_4$ (0.75 g) in diethyl ether (100 ml) at room temperature. The mixture was heated at reflux for 4 hr and then quenched by the addition of 4% NaOH aq. (3 ml). The reaction mixture was stirred at room temperature for another 2 hr, and the white precipitate was filtered off. The filtrate was evaporated to dryness *in vacuo* to give an oily residue, which was purified by silica gel column chromatography. Elution with 2-4% AcOEt in hexane (v/v) afforded the compound 16 (0.800 g) as a colorless oil. IR (neat) ν: 2935, 2860, 1330, 1105, 1020, 735, 695 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.46(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 3.89(4H, s, $OCH_2CH_2O$), 4.51(2H, s, $CH_2Ph$), 7.37(5H, s, arom.-H). LR-MS m/z: 344 ($M^+$), 301, 253, 167, 91. HR-MS m/z: 344.2333 (Calcd for $C_{22}H_{32}O_3$, 344.2351 $M^+$).

7β-(5-Benzyloxypentyl)-3-oxo-bicyclo[3.3.0]octane (17) A mixture of the acetal (16) (0.700 g) and 10% HCl aq. (5 ml) in acetone (10 ml) was stirred at room temperature for 30 min. Water was added to the reaction mixture 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 5-8% AcOEt in hexane (v/v) afforded the ketone (17) (0.490 g) as a colorless oil. IR (neat) ν: 2935, 2855, 1740, 1450, 1400, 1360, 1100, 735, 695 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.45(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.50(2H, s, $OCH_2Ph$), 7.36(5H, s, arom.-H). LR-MS m/z: 300 ($M^+$), 282, 210, 196, 108, 91. HR-MS m/z: 300.2076 (Calcd for $C_{20}H_{28}O_2$, 300.2089 $M^+$).

7β-(5-Benzyloxypentyl)-2β-(methoxycarbonyl)-3-oxobicyclo[3.3.0]octane (18) A solution of the ketone (17) (2.323 g) in 1,4-dioxane (30 ml) was added dropwise to a suspension of 55% NaH in oil (2.30 g) in a mixture of dimethyl carbonate (35 ml) and 1,4-dioxane (70 ml) and a few drops of EtOH at 80°C. The reaction mixture was stirred for 1 hr at same temperature, then neutralize with acetic acid under ice-cooling, poured into water 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 3-6% AcOEt in hexane (v/v) afforded the β-ketoester (18) (2.597 g) as a colorless oil. IR (neat) ν: 2940, 2860, 1755, 1730, 1665, 1625, 1445, 1360, 1255, 1230 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 3.74, 3.77 (each 3/2H, s, keto- and enol-form COOMe), 4.52(2H, s, $CH_2Ph$), 7.37(5H, s,

arom.-H), 10.48(1/2H, s, enol-form enol-OH). LR-MS m/z: 358 ($M^+$), 326, 300, 236, 91. HR-MS m/z: 358.2114 (Calcd for $C_{22}H_{30}O_4$, 358.2144 $M^+$).

7β-(5-Benzyloxypentyl)-3α-hydroxy-2β-methoxycarbonylbicyclo[3.3.0]octane (19a) and 7β-(5-Benzyloxypentyl)-3α-hydroxy-2α-methoxycarbonylbicyclo[3.3.0]octane (19b) $NaBH_4$ (0.40 g) was added to a solution of the β-ketoester (18) (2.550 g) in ethanol (50 ml) at -40°C, and the reaction mixture was stirred at -40°C for 30 min. The reaction was quenched by the addition of acetic acid. The reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with brine, 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 10-12% AcOEt in hexane (v/v) afforded the compound 19b (0.290 g) as a colorless oil and then elution with 18-20% AcOEt in hexane (v/v) afforded the compound 19a (1.640 g) as a colorless oil.
compound 19a;
IR (neat) ν: 3450, 2940, 2860, 1735, 1455, 1435, 1200, 1170, 1105 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.46(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 3.73(3H, s, COOMe), 4.20(1H, m, CHOH), 4.52(2H, s, $CH_2Ph$), 7.37(5H, s, arom.-H). LR-MS m/z: 360 ($M^+$), 300, 282, 192, 91. HR-MS m/z: 360.2293 (Calcd for $C_{22}H_{32}O_4$, 360.2301 $M^+$).
compound 19b;
IR (neat) ν: 3540, 2940, 2860, 1720, 1460, 1440, 1200, 1180, 1105 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.45(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 3.72(3H, s, COOMe), 4.40(1H, m, CHOH), 4.50(2H, s, $CH_2Ph$), 7.37(5H, s, arom.-H). LR-MS m/z: 360 ($M^+$), 282, 220, 192, 91.

Conversion of cis-hydroxyester (19b) to trans-hydroxyester (19a) A mixture of cis-hydroxyester (19b) (16 mg) and anhydrous $K_2CO_3$ (100 mg) in methanol (1.0 ml) was heated at reflux for 2 hr. The reaction mixture was diluted with brine, acidified with 10% HCl and extracted with AcOEt. The extracts were washed with brine, dried over $Na_2SO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was dissolved in ether (1.0 ml) and treated with excess $CH_2N_2$ in ether under ice cooling. The solvent was removed *in vacuo*, and purification of the residue by silica gel preparative TLC [developed with hexane:AcOEt = 1:1 (v/v)] afforded trans-hydroxyester (19a) (10 mg) as a colorless oil.

7β-(5-Benzyloxypentyl)-2β-methoxycarbonyl-3α-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]octane (20) A mixture of the alcohol (19a) (1.600 g) and DHP (0.61 ml) and catalytic amount of p-TsOH in $CH_2Cl_2$ (30 ml) was stirred under ice cooling for 30 min. The reaction mixture was diluted with $CH_2Cl_2$ and washed with 5% $NaHCO_3$ aq., 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 6-9% AcOEt in hexane (v/v) afforded the compound 20 (1.580 g) as a colorless oil. IR (neat) ν: 2940, 2860, 1735, 1455, 1435, 1200, 1120, 1075, 1035, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.47(2H, t, J=6.0Hz, $CH_2COH_2Ph$), 3.70(3H, s, COOMe), 4.20(1H, m, CHOTHP), 4.52(2H, s, $CH_2Ph$), 4.63(1H, br.s, OCHO), 7.37(5H, s, arom.-H). LR-MS m/z: 444 ($M^+$), 360, 332, 282, 91. HR-MS m/z: 444.2860 (Calcd for $C_{27}H_{40}O_5$, 444.2876 $M^+$).

7β-(5-Benzyloxypentyl)-2β-hydroxymethyl-3α-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]octane (21) A solution of the ester (20) (1.550 g) in THF (10 ml) was added to a suspension of $LiAlH_4$ (0.200 g) in THF (30 ml) under ice cooling. The reaction mixture was stirred for 15 min at the same condition, then quenched with 4% NaOH aq. (0.8 ml). The reaction mixture was stirred at room temperature for another 2 hr, then the precipitate was filtered off. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 12-20% AcOEt in hexane (v/v) afforded the alcohol (21) (1.306 g) as a colorless oil. IR (neat) ν: 3450, 2940, 2860, 1455, 1120, 1075, 1035, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.45(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.52(2H, s, $CH_2Ph$), 4.63(1H, br.s, OCHO), 7.37(5H, s, arom.-H). LR-MS m/z: 415($M^+$+1), 330, 316, 298, 224, 208, 206, 91. HR-MS m/z: 415.2848 (Calcd for $C_{26}H_{39}O_4$, 415.2848 $M^+$+1).

7β-(5-Benzyloxypentyl)-2β-formyl-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]-octane (22) A solution of pyridine-$SO_3$ complex (2.070 g) in DMSO (10 ml) was added to a stirred mixture of the alcohol (21) (0.650 g) and $Et_3N$ (5.9 ml) in DMSO (7 ml) at room temperature. After being stirred for 1 hr, 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*

afforded almost pure aldehyde (22) (0.653 g) as a pale yellow oil. The crude material was used for the subsequent step without purification. IR (neat) ν: 2940, 2860, 1720, 1455, 1120, 1075, 1035 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.52(2H, s, $CH_2Ph$), 4.65(1H, br.s, OCHO), 7.37(5H, s, arom.-H), 9.73(1H, d, J=3.0Hz, CHO).

7β-(5-Benzyloxypentyl)-2β-(2-methoxyvinyl)-3α-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]octane (23) A LDA solution [prepared from 15% n-butyl lithium in hexane solution (4.66 ml) and diisopropylamine (1.13 ml) in THF (9.2 ml)] was added to a stirred suspension of methoxymethyltriphenylphosphonium chloride (3.010 g) in toluene (20 ml) under ice cooling, and stirred for 30 min at the same temperature, then cold to -15°C. A solution of the aldehyde (22) (0.640 g) in toluene (6 ml) was added to this reaction mixture. After being stirred for 20 min at the same temperature, warmed up to room temperature and stirred for additional 1 hr. The reaction mixture was neutralized with acetic acid under ice cooling and poured into water, 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 4-6% AcOEt in hexane (v/v) afforded the colorless oily enol ether (23) (0.486 g) as an inseparable mixture of geometrical isomers [E:Z=Ca. 2:1]. IR (neat) ν: 1655, 1455, 1210, 1120, 1075 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 3.52(3x2/3H, s, OMe), 3.55(3x1/3H, s, OMe), 4.52(2H, s, $CH_2Ph$), 4.72(1H, br.s, OCHO), 5.97(1/3H, m, olefinic-H), 6.35(2/3H, dd, J=12.0, 6.0Hz, olefinic-H), 7.37(5H, s, arom.-H). LR-MS m/z: 340($M^+$-102), 252, 250, 236, 160, 91. HR-MS m/z: 340.2392 (Calcd for $C_{23}H_{32}O_2$, 340.2402 $M^+$-$C_5H_{10}O_2$).

7β-(5-Benzyloxypentyl)-2β-(2-oxo-1β-phenylthioethyl)-3α-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (24a) and 7β-(5-Benzyloxypentyl)-2β-(2-oxo-1α-phenyl-thioethyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (24b) Excess PhSCl[11] was added to a stirred mixture of the enol ether (23) (0.350 g) and $K_2CO_3$ (1.40 g) in toluene (7 ml) at -78°C, and stirred for 50 min at the same temperature. The reaction mixture was poured into 10% $NaHCO_3$ aq. (15 ml), vigorously stirred for 30 min at room temperature, and then 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% AcOEt in hexane (v/v) afforded the compound 24b (27 mg) as a colorless oil, and then elution with 5% AcOEt in hexane (v/v) afforded the compound 24a (0.264 g) as a colorless oil.
compound 24a;
IR (neat) ν: 2950, 2870, 1720, 1455, 1440, 1125, 1080, 1030, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.48(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.53(2H, s, $CH_2Ph$), 4.75(1H, br.s, OCHO), 7.37(10H, m, arom.-H), 9.33(1H, dd, J=9.0, 5.5Hz, CHO). LR-MS m/z: 452($M^+$-84), 434, 406, 342, 91. HR-MS m/z: 452.2368 (Calcd for $C_{28}H_{36}O_3S$, 452.2385 $M^+$-$C_5H_8O$).
compound (24b);
IR (neat) ν: 2940, 2860, 1715, 1455, 1440, 1125, 1080, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.52(2H, s, $CH_2Ph$), 4.73(1H, br.s, OCHO), 7.37(10H, m, arom.-H), 9.65(1H, dd, J=18.0, 5.5Hz, CHO). LR-MS m/z: 452($M^+$-84), 434, 406, 342, 91.

7β-(5-Benzyloxypentyl)-2β-(1β-phenylthio-2(Z),5(Z)-octadienyl)-3α-(tetrahydro-pyran-2-yl)oxybicyclo[3.3.0]octane (25a) 3(Z)-Hexenyltriphenylphosphonium iodide (3.42 g) was added to a solution of sodium methyl sulfinylmethide [prepared from 55% NaH in oil (0.286 g) and DMSO (10 ml) in the usual manner] under ice cooling. After 10 min stirring at same temperature, resulting red-colored solution was diluted with THF (80 ml). A solution of the aldehyde (24a) (0.370 g) in THF (10 ml) was added to this reaction mixture at -78°C, and stirred for 30 min. Then the reaction mixture was warmed up to room temperature, and stirred for another 1 hr. After neutralization of the reaction mixture with acetic acid, 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 3-4% AcOEt in hexane (v/v) afforded the compound 25a (0.383 g) as a colorless oil. IR (neat) ν: 2940, 2860, 1455, 1120, 1075, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.91(3H, t, J=6.0Hz, $CH_2CH_3$), 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.52(2H, s, $CH_2Ph$), 4.62(1H, br.s, OCHO), 5.30(4H, m, olefinic-H), 7.37(10H, m, arom.-H). LR-MS m/z: 602($M^+$), 408, 392, 391, 390, 302, 300. HR-MS m/z: 602.3818 (Calcd for $C_{39}H_{54}O_3S$,

602.3794 $M^+$).

7β-(5-Benzyloxypentyl)-2β-(3α-hydroxy-1(E),5(Z)-octadienyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (26a) To a solution of the sulfide (25a) (103 mg) in methanol (15 ml) was added mCPBA (42 mg) at -30°C and stirred for 1 hr at -30°C. $MeO_3P$ (2.0 ml) was added to this reaction mixture at the same temperature, gradually warmed up to the room temperature, and then stirred over night. The reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with brine, 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 8-10% AcOEt in hexane (v/v) afforded the alcohol (26a) (81 mg) as a colorless oil [TLC (hexane:AcOEt=3:1) Rf = 0.46]. IR (neat) ν: 3440, 2940, 2860, 1455, 1120, 1075, 1035, 1020 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.97(3H, t, J=6.0Hz, $CH_2CH_3$), 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.51(2H, s, $CH_2Ph$), 4.70 (1H, br.s, OCHO), 5.57(4H, m, olefinic-H), 7.37(5H, m, arom.-H). LR-MS m/z: 408($M^+$-102), 390, 364, 358, 318, 91. HR-MS m/z: 408.3020 (Calcd for $C_{28}H_{40}O_2$, 408.3028 $M^+$-$C_{10}H_{20}O_4$).

7β-(5-Benzyloxypentyl)-2α-(1α-phenylthio-2(Z),5(Z)-octadienyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (25b) Treatment of the aldehyde (24b) (82 mg) in a similar manner described for the synthesis of 25a gave 25b (74 mg) as a colorless oil. IR (neat) ν: 2940, 2850, 1455, 1440, 1120, 1075, 1035, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.91(3H, t, J=6.0Hz, $CH_2CH_3$), 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.52(2H, s, $CH_2Ph$), 4.66(1H, br.s, OCHO), 5.30(4H, m, olefinic-H), 7.36(10H, m, arom.-H). LR-MS m/z: 602($M^+$), 408, 392, 391, 318, 302, 300.

7β-(5-Benzyloxypentyl)-2α-(3β-hydroxy-1(E),5(Z)-octadienyl)-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (26b) Treatment of 25b (27 mg) in a similar manner described for the synthesis of 26a afforded 26b (20 mg) as a colorless oil. [TLC (hexane:AcOEt=3:1 (v/v)) Rf=0.51]. IR (neat) ν: 3440, 2940, 2860, 1455, 1120, 1075, 1040, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.97(3H, t, J=6.0Hz, $CH_2CH_3$), 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.50(2H, s, $CH_2Ph$), 4.70(1H, br.s, OCHO), 5.57(4H, m, olefinic-H), 7.37(5H, m, arom.-H). LR-MS m/z: 408($M^+$-102), 390, 364, 358, 318, 91. HR-MS m/z: 408.3029 (Calcd for $C_{28}H_{40}O_2$, 408.3028 $M^+$-$C_5H_{10}O_2$).

7β-(5-Benzyloxypentyl)-2α-(3-oxo-1(E),5(Z)-octadienyl)-3α-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (27) Jones Reagent (0.2 ml) was added to a solution of the alcohol (26a) (73 mg) in acetone (5 ml) at -30°C. The reaction mixture was stirred for 30 min at the same condition, then neutralized with 5% $NaHCO_3$ aq., extracted with diethyl ether. The extracts were washed with brine, 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 6-7% AcOEt in hexane (v/v) afforded the ketone (27) (32 mg) as a colorless oil. IR (neat) ν: 2930, 2860, 1695, 1670, 1625, 1455, 1120, 1075 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.96(3H, t, J=6.0Hz, $CH_2CH_3$), 4.42(2H, s, $CH_2Ph$), 4.56(1H, br.s, OCHO), 5.47(2H, m, olefinic-H), 6.06(1H, dd, J=15.0, 3.0Hz, olefinic-H), 6.65(1H, m, olefinic-H), 7.23(5H, m, arom.-H). LR-MS m/z: 424($M^+$-84), 406, 380, 356, 91. HR-MR m/z: 424.2971 (Calcd for $C_{28}H_{40}O_3$, 424.2977 $M^+$-$C_5H_8O$).

7β-(5-Benzyloxypentyl)-2β-[3α-(tetrahydropyran-2-yl)oxy-1(E),5(Z)-octadienyl]-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (28) A catalytic amount of p-TsOH was added to a mixture of the alcohol (26a) (298 mg) and DHP (0.1 ml) in $CH_2Cl_2$ (4 ml) under ice cooling. After being stirred for 40 min, the reaction mixture was diluted with $CH_2Cl_2$, washed with 5% $NaHCO_3$ aq. then water, 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 3-5% AcOEt in hexane (v/v) afforded the compound 28 (312 mg) as a colorless oil. IR (neat) ν: 2950, 2860, 1455, 1205, 1120, 1080, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.96(3H, t, J=6.0Hz, $CH_2CH_3$), 3.47(2H, t, J=6.0Hz, $CH_2OCH_2Ph$), 4.52(2H, s, $CH_2Ph$), 4.75(2H, br.s, OCHO), 5.52(4H, m, olefinic-H), 7.37(5H, m, arom.-H). LR-MS m/z: 408($M^+$-102-84), 390, 364, 357, 91. HR-MS m/z: 408.3030 (Calcd for $C_{28}H_{40}O_2$, 408.3028 $M^+$-$C_{10}H_{18}O_3$).

7β-(5-Hydroxypentyl)-2β-[3α-(tetrahydropyran-2-yl)oxy-1(E),5(Z)-octadienyl]-3α-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (29) Excess sodium metal was added to a solution of the compound 28 (302 mg) in liquid ammonia (20 ml) and THF (16 ml) at -78°C and stirred for 40 min. The reaction was quenched by the addition of $NH_4Cl$, and ammonia was evaporated at room temperature.

Water was added to the residue and extracted with diethyl ether. 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 10-14% AcOEt in hexane afforded the alcohol (29) (235 mg) as a colorless oil. IR (neat) ν: 3440, 2930, 2850, 1195, 1115, 1075, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.96(3H, t, J=6.0Hz, $CH_2CH_3$), 4.74(2H, br.s, OCHO), 5.50(4H, m, olefinic-H). LR-MS m/z: 403($M^+$-101), 351, 319, 302, 301, 300. HR-MS m/z: 403.3204 (Calcd for $C_{26}H_{43}O_3$, 403.3212 $M^+$-$C_5H_2O_4$).

(+/-)-5,6-Dihydro-6,9α-methano-6β-prostaglandin $I_3$ 11,15-Bis(tetrahydropyran-2-yl)ether (30) Jones Reagent (0.5 ml) was added to a solution of the alcohol (29) (222 mg) in acetone (20 ml) at -20 to -25°C. The reaction mixture was stirred for 1.5 hr at the same condition, then neutralized with 5% $NaHCO_3$ aq., extracted with diethyl ether. The extracts were washed with brine, dried over $Na_2SO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatogrpahy. Elution with 20-50% AcOEt in hexane (v/v) afforded the carboxylic acid (30) (162 mg) as a colorless oil. IR (neat) ν: 3120, 2940, 2850, 1740, 1710, 1035, 1025 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.96(3H, t, J=6.0Hz, $CH_2CH_3$), 4.72(2H, br.s, OCHO), 5.50(4H, m, olefinic-H), 8.90(1H, br.s, COOH). LR-MS m/z: 417($M^+$-101), 332, 290, 282, 264, 246. HR-MS m/z: 417.3000 (Calcd for $C_{24}H_{41}O_4$, 417.3005 $M^+$-$C_5H_9O_2$).

(+/-)-5,6-Dihydro-6,9α-methano-6β-prostaglandin $I_3$ (4a) A mixture of the compound (30) (152 mg) and camphorsulfonic acid (20 mg) in acetone (8 ml) and water (3 ml) was stirred at 40 to 45°C for 2.5 hr. 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 *in vacuo* gave a crystalline residue, which was recrystallized from AcOEt-hexane mixture to give the (+/-)-5,6-dihydro-6,9α-methano-6β-prostaglandin $I_3$ (4a) (89 mg), mp 62-65°C, [TLC (AcOEt:hexane:AcOH=10:5:0.25 (v/v/v)) Rf=0.28]. *Anal.* Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.92; H, 9.80. IR (KBr) ν: 3380, 2950, 1705, 1435, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.96(3H, t, J=6.0Hz, $CH_2CH_3$), 3.60(1H, m, CHOH), 4.10(1H, m, CHOH), 5.53(4H, m, olefinic-H). LR-MS m/z: 332($M^+$-18), 314, 282, 264, 246.

15β-Isomer (4b) of compound 4a Similar treatment of 15β-alcohol (26b) (23 mg) through the reaction sequence for the synthesis of 4a gave the compound 4b (6.5 mg) as a colorless viscous oil [TLC (AcOEt:hexane:AcOH=10:5:0.25 (v/v/v)) Rf=0.42]. IR (neat) ν: 3350, 2935, 2850, 1705, 1460, 1070 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.97(3H, t, J=6.0Hz, $CH_2CH_3$), 3.66(1H, m, CHOH), 4.13(1H, m, CHOH), 5.50(4H, m, olefinic-H). LR-MS m/z: 332($M^+$-18), 314, 282, 264, 246. HR-MS m/z: 332.2340 (Calcd for $C_{21}H_{32}O_3$, 332.2351 $M^+$-$H_2O$).

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