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TOTAL SYNTHESIS OF 11-OXAPROSTAGLANDIN $F_2\alpha$ AND $F_2\beta$*

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ABSTRACT

1,4-Anhydro-D-glucitol has been used as a chiral template for the synthesis of 11-oxaprostaglandin $F_2\alpha$ and $F_2\beta$. Methodology was also developed to provide access to chiral, *C*-branched tetrahydrofuran derivatives.

INTRODUCTION

Since the publication of the first total syntheses of prostaglandins[1,2], the field of prostaglandin research has expanded rapidly[3]. Many elegant syntheses of the naturally occurring members of this class of hormones have now been reported, and further developments have focused mostly on structural and functional variations, based on emerging biological data. The diverse biological responses to structural variations in the prostaglandin skeleton are impressive and, at times, enigmatic. This has further intensified the already well-established and on-going analog program in several pharmaceutical research laboratories.

Some years ago, we initiated a program aimed at the total synthesis of 11-oxaprostaglandins[4] from carbohydrate precursors as part of our studies on the utilization of carbohydrates in the total synthesis of natural products and their analogs[5,6]. At that time, our interest in the 11-oxaprostaglandins was motivated by the close structural resemblance between such analogs and their naturally occurring counterparts (Scheme 1). Our premise was that replacement of C-11 in $PGF_2\alpha$, for example, by oxygen might affect a biological parameter and hence confer a different profile of activity. It was also argued that, except for the ring component, the conformation of the whole molecule[7] would not be significantly different from that of the natural product. It was also known that 11-deoxyprostaglandins exhibited biological activity[8]. Inspection of molecular models demonstrated the quasi-juxtaposition of the 11-oxa atom in the region of the HO-11 in the prostaglandin F_2 series, thus possibly simulating the stereoelectronic requirements at that position in the absence of a protic group.

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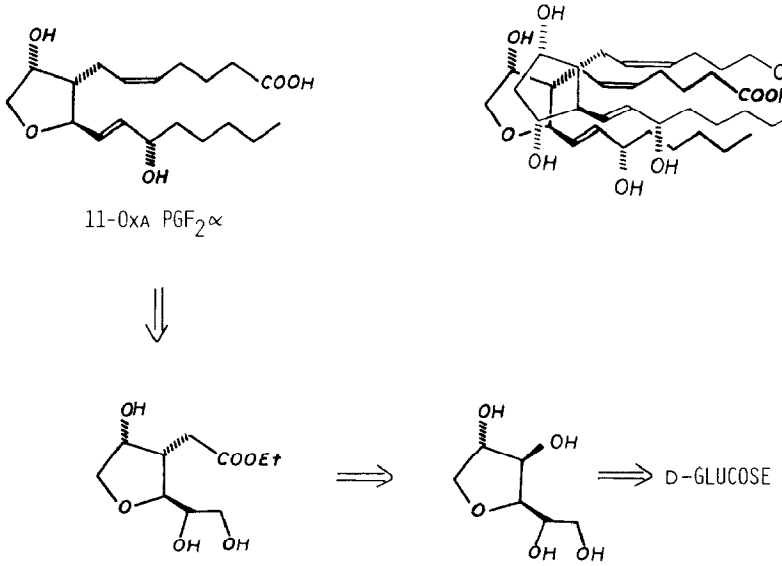


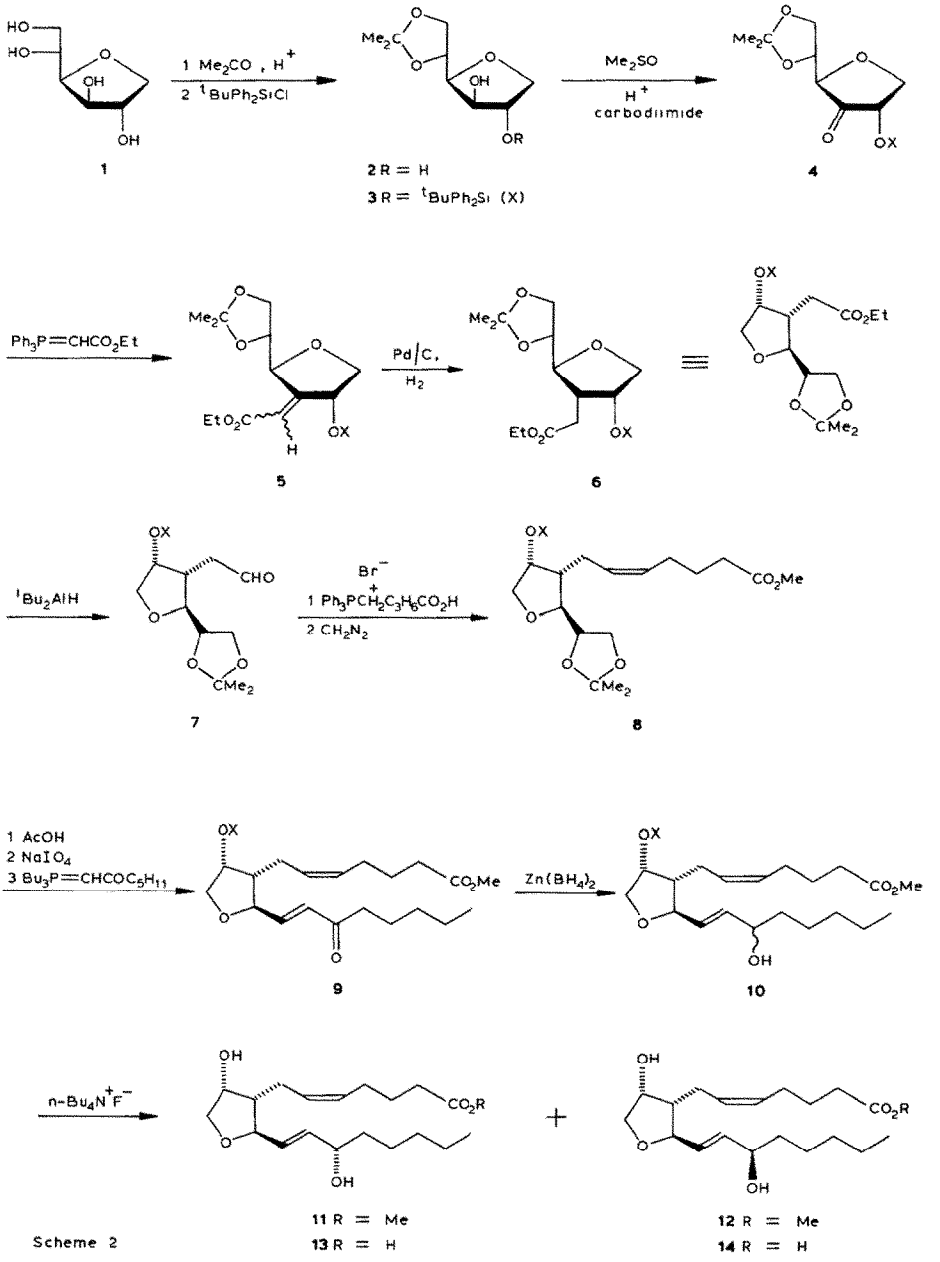
Scheme 1

Thus, the targets for synthesis were 11-oxaprostaglandin $F_2\alpha$ and $F_2\beta$. Moreover, we had devised a synthesis scheme that provided access to the two target compounds from 1,4-anhydro-D-glucitol[9]. While our work was in progress, several syntheses of racemic 11-oxaprostaglandins were reported[10] as well as syntheses from D-glucose and D-xylose[11].

1,4-Anhydro-D-glucitol (**1**) was chosen as a chiral template since it provided the necessary ring, and the side-chain diol could be considered as a latent aldehyde function. The sense of chirality at C-2 and C-4 of **1** corresponded to that of C-9 and C-12, respectively, in $PGF_2\alpha$. Therefore, the synthesis required the regio- and stereo-controlled introduction of an acetic acid side-chain at C-3 in **1**, which could be elaborated into the C-1/C-8 acyclic segment of the target compounds.

Preferential acetonation of **1** gave the 5,6-acetal **2**, the less-hindered HO-2 of which was *tert*-butyldiphenylsilylated[12] to give **3**. The crystalline ether **3** was oxidized using a carbodiimide method (see Experimental) to give the syrupy 3-keto derivative **4** in excellent yield (Scheme 2). Treatment of **4** with the appropriate phosphorane derivative led to the 3-(ethoxycarbonyl)methylene derivative **5**, catalytic hydrogenation of which was stereoselective (*cf.* ref. 13), and gave the desired branched-chain derivative **6** (74% from **4**).

For reasons of compatibility of reaction conditions, it was decided to introduce the acid side-chain first. Thus, treatment of **6** with di-isobutylaluminum hydride gave the aldehyde **7**, which, after reaction with (4-carboxybutyl)triphenylphosphorane and then diazomethane, gave **8** containing the *cis*-olefinic side-chain. The wine-red ylid was best generated by using lithium hexamethylsilazide in hexamethylphosphoric triamide[14]. Continuation of the synthesis followed a



protocol well established in prostaglandin chemistry. Thus, selective acid hydrolysis of the acetal group in **8** followed by periodate oxidation and Wittig reaction of the resulting aldehyde gave the desired enone **9** (62% from **8**). The stereochemistry of the olefinic linkages in **9** was ascertained by ^{1}H- and ^{13}C-n.m.r. studies and comparison with data[16] for authentic $PGF_2\alpha$ (130.2 and 128.1 p.p.m. for C-5 and C-6,

TABLE I

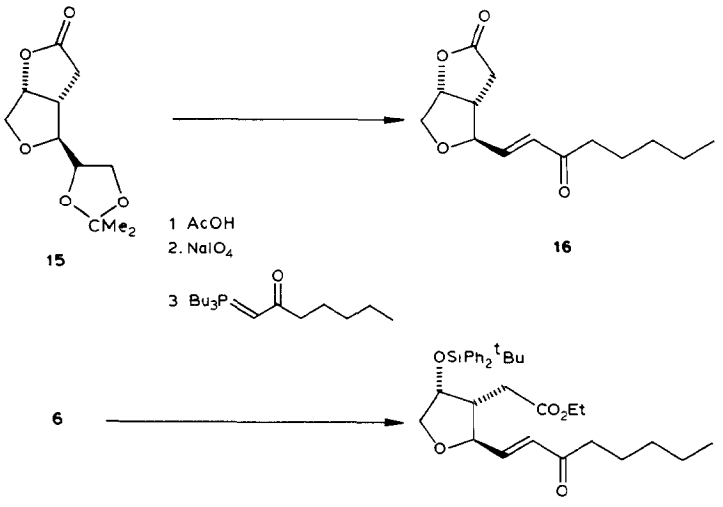
^{13}C-N M R CHEMICAL SHIFTS FOR 11-OXAPROSTAGLANDIN METHYL ESTERS[a]

Atom	*11-oxa PGF$_2\alpha$ (15R)*	*11-oxa PGF$_2\beta$ (15R)*
C-1	174.3	174.3
C-2	33.3	33.3
C-3	24.7	24.7
C-4	26.7	26.6
C-5	130.2	129.8
C-6	127.5	128.3
C-7	28.1	28.1
C-8	54.4	54.4
C-9	84.3	82.5
C-10	74.1	72.8
C-11	—	—
C-12	77.2	76.5
C-13	130.8	130.2
C-14	136.0	137.0
C-15	72.0	72.1
C-16	37.2	37.1
C-17	25.1	25.1
C-18	31.8	31.8
C-19	22.6	22.6
C-20	14.0	14.0
CO_2Me	51.6	51.2

[a]Prostaglandin numbering, with CO_2H as C-1.

respectively). Reduction of the ketone function in **9** with zinc borohydride gave a mixture of C-15 epimers **10**, which could be fractionated by preparative t.l.c. (the 15-*S* isomers are consistently the more polar[15]). The undesired 15-*S* epimer could be then recycled by an oxidation–reduction sequence. Treatment of the individual C-15 isomers with tetrabutylammonium fluoride gave the corresponding esters **11** and **12** as syrups and saponification then afforded crystalline 11-oxa PGF$_2\alpha$ **13**, and its syrupy 15-*S* isomer **14**. The ^{13}C-n.m.r. spectrum of **13** accorded with published data[16] on PGF$_2\alpha$ (Table I). Scheme 3 illustrates additional transformations from **6** and **15**, leading to the potential synthetically useful intermediates **16** and **17**, respectively.

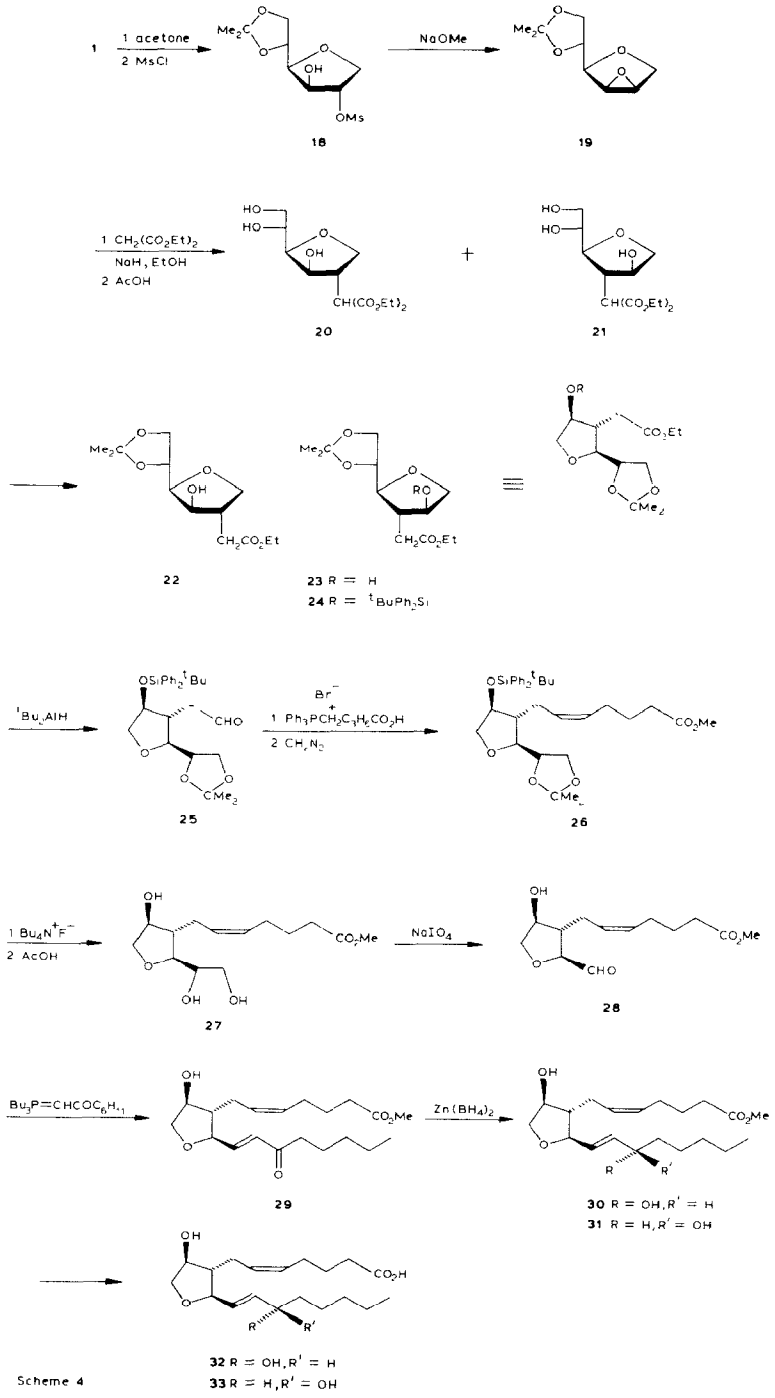
The synthesis of 11-oxa PGF$_2\beta$ required a regioselective chain-branching reaction that would also secure the β-disposition of the HO-2 in **1** (C-9 in the target molecule) (see Scheme 4). Thus, acetonation of 1,4-anhydro-D-glucitol (**1**) followed by selective mesylation gave the 2-mesylate **18**, which was then converted into the desired epoxide **19**. Although the reaction of conformationally biased epoxides with malonate anion is highly regioselective[17], such selectivity was not expected for **19**. Indeed, reaction of **19** with the sodium derivative of diethyl malonate in refluxing ethanol gave a ~1:1 mixture of C-2 and C-3 branched derivatives **20** and **21**, which



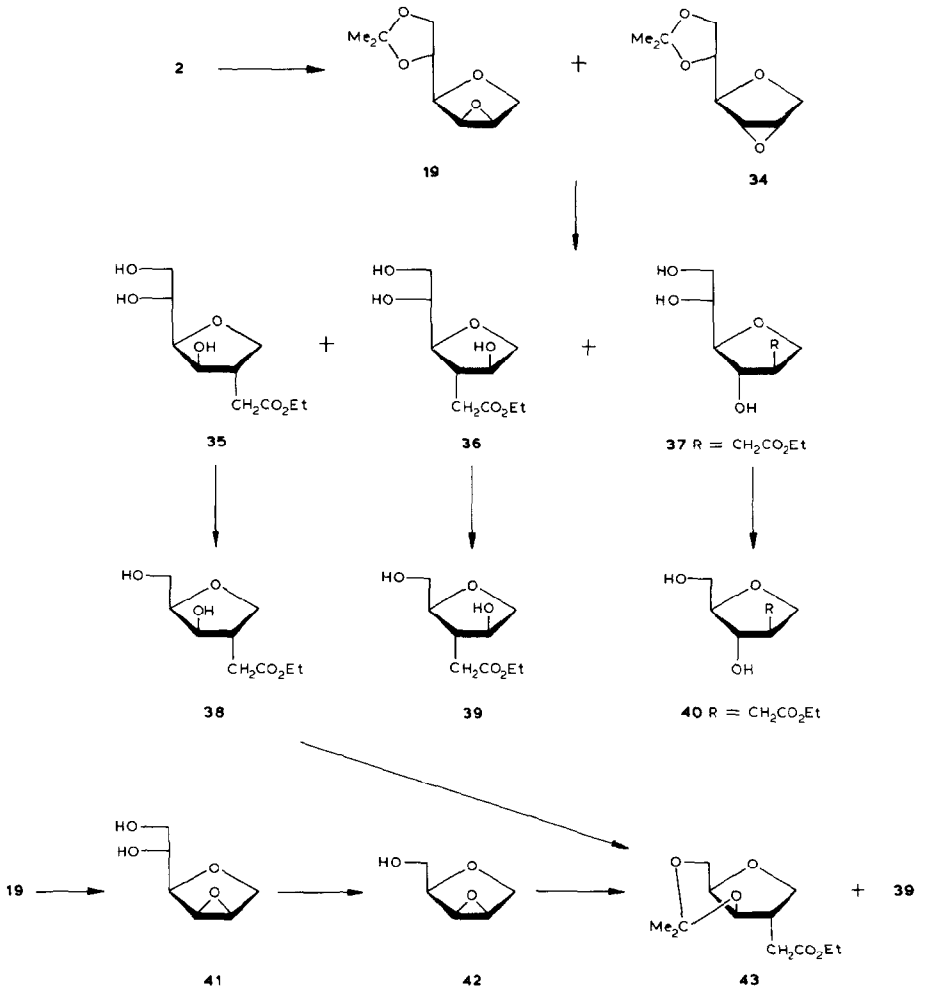
Scheme 3

were isolated by chromatography and decarboxylated to give **23** and **22**, respectively. The functional groups in **23** were then manipulated as described above and shown in Scheme 4, to give the C-15 epimeric 11-oxa $PGF_2\beta$ derivatives **30** and **31**. Again, the 15-*S* isomer had the higher R_F value compared to the 15-*R* isomer. 11-Oxa $PGF_2\beta$ had ^{13}C-n.m.r. characteristics in accord with its structure (Table I), but, unlike the α isomer, it was obtained as a syrup.

In seeking to improve the preparation of the epoxide **19**, a procedure[18] for selective sulfonylation using *N*-toluene-*p*-sulfonylimidazole, as used by Fraser-Reid and Hicks[19] in another series, was adapted. Although sulfonylation and epoxidation occurred as anticipated, it was subsequently found that the epoxide **34** was also formed as a result of indiscriminate esterification (Scheme 5). Since **19** and **34** were inseparable by chromatography and possessed similar spectroscopic properties, the initial results of epoxide-ring opening with malonate ion were puzzling since, in addition to the expected **20** and **21**, a third isomer was formed. Only after its identity was established as **37** was it possible to deduce that the original sulfonylation–epoxidation sequence had produced two epoxides, namely, **19** and **34**. Thus, cleavage of the epoxide ring with malonate, followed by hydrolysis of the acetal group, saponification, decarboxylation, and re-esterification, gave a mixture of three *C*-branched products **35–37** (Scheme 5). Chromatography on silica gel impregnated with boric acid gave **35** and **36** as crystalline compounds. Each of the *C*-branched-chain products was transformed readily into the *C*-branched 1,4-anhydro-D-pentitols **38–40** by the sequence of reactions shown in Scheme 5. Compound **40** did not form an isopropylidene derivative upon treatment with 2,2-dimethoxypropane and toluene-*p*-sulfonic acid. Of the three products, and as expected, only **38** gave an isopropylidene derivative. In order to secure independent proof of the identity of **38, 39,** and **43**, the dianhydropentitol **42** was synthesized by an unambiguous route



Scheme 4



Scheme 5

TABLE II

^{13}C-N M R CHEMICAL SHIFTS OF 11-OXAPROSTAGLANDIN ANALOGS[a]

Atom	**8**	**15**	**17**
C-1	73.7	75.1	74.5
C-2	82.7	85.6	81.4
C-3	28.1	41.5	47.1
C-4	78.1	83.8	75.5
C-5	74.2	76.5	—
C-6	66.8	66.9	—

[a]Numbering according to a 1,4-anhydroalditol.

TABLE III

^{13}C-N M R CHEMICAL SHIFTS OF SOME 1,4-ANHYDRO-HEXITOL AND -PENTITOL INTERMEDIATES[a]

Atom	**1**	**3**	**4**	**5**	**24**	**34**	**37**	**38**	**40**
C-1	73.5	73.4	69.0	73.2	71.6	74.1	74.3	71.1	66.5
C-2	76.5	78.0	74.6	77.3	87.7	76.8	76.8	45.0	54.7
C-3	76.8	76.2	—	—	45.6	45.2	45.5	78.1	55.5
C-4	80.0	80.4	77.6	77.3	79.9	84.6	84.4	80.2	76.5
C-5	69.1	72.6	73 0	70.3	75.8	73.3	63.4	61.8	69.1
C-6	63.7	67.5	63.5	64.8	66.7	64 0			62.8

[a]Numbers refer to carbon atoms in the ring and the side chain of the alditol

from **41**. Reaction of **42** with malonate anion, followed by decarboxylation and esterification, gave only **38** (isolated after conversion into **43**) and **39**. Compound **37** must have therefore arisen from a regioselective opening of the epoxide ring in **34**. ^{13}C-N.m.r. data for some of the intermediates are listed in Tables II and III.

Although neither 11-oxa $PGF_2\alpha$ or β showed smooth-muscle-contracting activity using $PGF_2\alpha$ as a standard, the methodology developed in this work will be useful in the elaboration of natural products containing functionalized tetrahydrofuran rings.

EXPERIMENTAL

Melting points are uncorrected. N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise stated at 60 or 90 MHz (^{1}H), and 22.6 MHz (^{13}C), using a Bruker WP-80 instrument. I.r. spectra were recorded with a Beckman IR-8 spectrometer. Optical rotations were measured at room temperature (25°) with a Perkin–Elmer Model 141 automatic spectropolarimeter. Mass spectra (70 eV) were obtained using Hitachi–Perkin–Elmer medium-resolution and MS-902 high-resolution mass spectrometers and the direct insertion technique. T.l.c. and column chromatography were performed on silica gel GF_{254} (Merck) unless stated otherwise. Convential processing signified the drying of organic solutions (Na_2SO_4), filtration, and concentration under diminished pressure. Some of the syrupy products were characterized by mass spectrometry after purification by chromatography and not by microanalysis.

*1,4-Anhydro-2-*O*-tert-butyldiphenylsilyl-5,6-*O*-isopropylidene-*D*-glucitol* (**3**). — A solution of 1,4-anhydro-D-glucitol[9] (**1**; 2.2 g, 13.4 mmol) in dry *N,N*-dimethylformamide (15 mL) and 2,2-dimethoxypropane (5 mL, containing a few drops of ethanolic acetyl chloride) was stirred at room temperature for 6 h and then neutralized with solid sodium hydrogencarbonate, the suspension was filtered, and the filtrate was concentrated. The oily residue was extracted with dichloromethane, the extract was filtered and concentrated, and the oily residue (**2**) was treated with M *tert*-butyldiphenylsilyl chloride in *N,N*-dimethylformamide (14.7 mL) and

imidazole (2 g, 29.5 mmol). After storage for 3 h at room temperature, the solution was concentrated to dryness below 40° under reduced pressure. A solution of the residue in chloroform (150 mL) was washed with water and then processed conventionally. Trituration of the product with cold hexane gave **3** (3.5 g). Column chromatography (10:2 benzene–EtOAc) of the material in the mother liquors gave more (1.1 g) **3** (total yield, 78%). Recrystallization from light petroleum gave material having m.p. 88.5–89.5°, $[\alpha]_D$ −13° (*c* 1.4, chloroform). Mass spectrum: *m/z* 427 (M^+ − Me), 385 (M^+ − CMe_3).

Anal. Calc. for $C_{25}H_{34}O_5Si$: C, 67.84; H, 7.74. Found: C, 67.93; H, 8.07.

*1,4-Anhydro-2-*O-tert-*butyldiphenylsilyl-3-deoxy-3-*C-*(ethoxycarbonylmethyl)-5,6-*O-*isopropylidene-*D-*allitol* (**6**). — To a solution of **3** (2.2 g, 5 mmol) in anhydrous methyl sulfoxide (20 mL) was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodi-imide hydrochloride[20,21] (2.9 g, 15 mmol) and dichloroacetic acid (0.2 mL). The solution was stirred at room temperature for 3 h, then poured into ice–water, and extracted with di-isopropyl ether, and the extracts were combined and processed conventionally. The resulting, chromatographically homogeneous, syrupy 1,4-anhydro-2-*O-tert*-butyldiphenyl-5,6-*O*-isopropylidene-D-*ribo*-3-hexulose (**4**; 2.15 g, 98%), λ_{max}^{film} 1770 cm^{-1} (C=O), was used as such in the next step.

A solution of **4** (2.1 g, 4.8 mmol) in dichloromethane (40 mL) was stirred with ethoxycarbonylmethylenetriphenylphosphorane (3.48 g, 10 mmol) at room temperature for 12 h. After evaporation of the solvent, the oily residue was triturated twice with light petroleum to remove triphenylphosphine oxide. The final residue (3.3 g) contained traces of triphenylphosphine oxide, but was otherwise chromatographically homogeneous and was used in the next step. A portion, purified by preparative t.l.c., gave 1,4-anhydro-2-*O-tert*-butyldiphenylsilyl-3-deoxy-3-*C*-(ethoxycarbonylmethylene)-5,6-*O*-isopropylidene-D-*ribo*-hexitol (**5**) as a syrup, λ_{max}^{film} 1725 (COEt), 1690 cm^{-1} (C=C). Mass spectrum: *m/z* 510 (M^+), 495 (M^+ − Me), 453 (M^+ − CMe_3).

A solution of **5** (3.2 g) in ethanol (200 mL) was hydrogenated in the presence of 10% Pd/C. After 16 h, the suspension was filtered through Celite and then concentrated to dryness. The resulting syrup was purified by column chromatography (benzene–EtOAc, 10:1.5), to give **6** as colorless crystals (2.04 g, 79% from **4**). Recrystallization from hexane gave material having m.p. 63–64°, $[\alpha]_D$ +46° (*c* 1.3, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 1.1 (s, ^{t}Bu), 1.2 (t, CH_2CH_3), 1.27, 1.35 (2 s, CMe_2), 2.7 (m, CH_2Et), 4.05 (m, CH_2CH_3). Mass spectrum: *m/z* 497 (M^+ − Me), 455 (M^+ − CMe_3).

Anal. Calc. for $C_{29}H_{40}O_6Si$: C, 67.94; H, 7.64. Found: C, 67.97; 7.34.

*1,4-Anhydro-2-*O-tert-*butyldiphenylsilyl-3-deoxy-3-*C-*(formylmethyl)-5,6-*O-*isopropylidene-*D-*allitol* (**7**). — To a solution of **6** (1.5 g, 3 mmol) in anhydrous toluene (35 mL) was added 1.4M di-isobutylaluminum hydride in hexane (3.2 mL, 4.5 mmol) at −78° under nitrogen. After stirring at −78° for 30 min, the solution was diluted with ether (25 mL) and aqueous ammonium chloride (25 mL). The mixture was allowed to attain 25° and then poured into ethyl acetate (200 mL), and

the suspension was filtered through Celite. The organic layer was processed conventionally to give a colorless syrup (1.37 g, 97%) that was chromatographically homogeneous and suitable for use in the next step. A portion, purified by preparative t.l.c. (benzene–EtOAc, 10:1), gave **7**, $[\alpha]_D$ +51.2° (*c* 1.8, chloroform). Mass spectrum: *m/z* 468 (M^+), 453 (M^+ − Me). ^{1}H-N.m.r. data: δ 1.07 (s, ^{t}Bu), 1.27, 1.35 (2 s, CMe_2), 2.3 (m, H-3), 2.8 (m, CH_2CHO), 9.6 (s, CHO).

*Methyl {2S-[2α(1E),3β(Z),4β]}-7-[4-(*tert*-butyldiphenylsilyloxy)-tetrahydro-2-(3-oxo-1-octenyl)-furan-3-yl]-5-heptenoate* (**9**). — 2.41M Butyl-lithium in hexane (7.1 mL) was added under nitrogen to a solution of bis(trimethylsilyl)amine (2.87 g) in ether (30 mL) at 0°. The mixture was stirred at room temperature for 1 h, the solvent was then evaporated in a stream of nitrogen, and a solution of the solid residue in hexamethylphosphoric triamide (15 mL) was added to (4-carboxybutyl)triphenylphosphonium bromide (3.9 g, 8.8 mmol) (previously dried at 110° for 5 h) followed by a solution of **7** (1.1 g, 2.3 mmol) in hexamethylphosphoric triamide (10 mL). The solution was stirred at room temperature for 40 h, and then diluted with ether (30 mL) and water (30 mL). 0.2M Sodium hydrogensulfite was added to pH ~2, the aqueous phase was extracted with ether (3 × 150 mL), and the combined extracts were washed with water and then processed conventionally.

A solution of the product in ether (100 mL) was treated with excess of diazomethane. After 6 h, the excess of reagent was destroyed by the addition of silica, and the solution was processed conventionally. The product was purified by preparative t.l.c. (benzene–EtOAc, 10:1) to give methyl {2*S*-[2α(4*R*),3β(*Z*),4β]}-7-[4-(*tert*-butyldiphenylsilyloxy)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-3-yl]-5-heptenoate (0.8 g, 60%) as a homogeneous syrup, $[\alpha]_D$ +6.5° (*c* 2.45, chloroform). Mass spectrum: *m/z* 551 (M^+ − Me).

A solution of **8** (0.68 g, 1.2 mmol) in aqueous 80% acetic acid (15 mL) was stirred overnight, and the resulting diol was isolated and oxidized with sodium periodate (0.38 g) in aqueous methanol. The resulting aldehyde derivative (0.49 g, 92.5%) was a chromatographically homogeneous syrup, and a solution of a portion (0.48 g, 0.97 mmol) in ether (10 mL) was stirred with a solution of 1-tributylphosphoranylidene-2-heptanone (0.6 g, 1.91 mmol) in ether (4 mL) at room temperature for 1 h. The solution was then concentrated to dryness and the residue was purified by preparative t.l.c. (benzene–EtOAc, 10:1) to give **9** (0.44 g, 76.8%; 62% from **8**) as a colorless syrup, $[\alpha]_D$ +29° (*c* 1.7, chloroform). Mass spectrum: *m/z* 559 (M^+ − Me), 533 (M^+ − C_4H_{10}). ^{1}H-N.m.r. data (90 MHz): δ 6.76 (dd, $J_{13,14}$ 17.5, $J_{13,12}$ 7 Hz, H-13), 6.32 (dd, $J_{14,13}$ 17.5, $J_{14,12}$ 2 Hz, H-14).

Anal. Calc. for $C_{36}H_{50}O_5Si$: C, 73.18; H, 8.53; M^+, 590.3388. Found: C, 73.21; H, 8.35; M^+, 590.3371.

O-tert-*Butyldiphenylsilyl-15(*R,S*)-11-oxaprostaglandin $F_2\alpha$ methyl ester* (**10**). — To a solution of **9** (0.31 g) in ether (10 mL) was added ~2.5M zinc borohydride in 1,2-dimethoxyethane (8 mL) at 0°, and the mixture was stirred for 4.5 h. After the addition of saturated aqueous ammonium chloride (40 mL), the organic phase was processed conventionally to give **10** (0.28 g, 90%). Mass spectrum: *m/z* 592

(M^+). The residue was purified by preparative t.l.c. (benzene–EtOAc, 10:3) to give the 15-*S* isomer (higher R_F), $[\alpha]_D$ +6° (*c* 0.5, chloroform). Mass spectrum: *m/z* 592.354 (M^+; calc. 592.3519). The 15-*R* isomer (lower R_F) had $[\alpha]_D^{25}$ +16.5° (*c* 0.4, chloroform).

Anal. Calc. for $C_{36}H_{52}O_5Si$ (15-*S*-**10**): C, 72.94; H, 8.94. Found: C, 72.90; H, 8.81.

11-Oxaprostaglandin $F_2\alpha$ methyl ester (**11**) *and its 15-β isomer* (**12**). — A solution of 15-(*R,S*)-**10** (0.237 g, 0.4 mmol) in M tetrabutylammonium fluoride in tetrahydrofuran (1.5 mL) was stirred overnight and then concentrated to dryness, and the residue was purified by column chromatography ($CHCl_3$–MeOH, 100:2) to give a 1:1 mixture (0.12 g, 85%) of 15-*R,S* isomers. Mass spectrum: *m/z* 336.2296 ($M^+ - H_2O$) (calc. 336.2311).

Preparative t.l.c. (chloroform–methanol, 10:2) gave the 15-*R* isomer **11** (50 mg), m.p. 61–61.5°, $[\alpha]_D$ +31° (*c* 1.4, chloroform), and the 15-*S* isomer **12** as a colorless syrup (48 mg), $[\alpha]_D$ +20° (*c* 0.5, chloroform).

Anal. Calc. for $C_{20}H_{34}O_5$ (**11**): C, 67.75; H, 9.66. Found: C, 67.42; H, 9.55.

11-Oxaprostaglandin $F_2\alpha$ (**13**) *and its 15-S epimer* (**14**). — A solution of **11** (36 mg) in 0.1M sodium hydroxide (1.5 mL) was stirred for 8 h at room temperature, acidified with Dowex 50 (H^+ resin, filtered, and extracted with ethyl acetate. Processing the extract conventionally, followed by preparative t.l.c. (EtOAc–AcOH, 10:0.1), gave **13** (24 mg, 60%), m.p. 64–66°, $[\alpha]_D$ +52° (*c* 0.4, chloroform); lit.[11] m.p. 66–67°, $[\alpha]_D$ +57° (chloroform).

Anal. Calc. for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.84; H, 9.22.

Treatment of **12** (14 mg) under similar conditions gave **14** as a colorless syrup (10 mg, 68%), $[\alpha]_D$ +32° (*c* 0.5, chloroform).

1,4-Anhydro-3-C-(carboxymethyl)-3-deoxy-5,6-O-isopropylidene-D-allitol 3^2,2-lactone (**15**). — A solution of **6** (0.44 g, 0.85 mmol) in tetrahydrofuran (2 mL) was stirred with 0.5M tetrabutylammonium fluoride in tetrahydrofuran (4 mL) at room temperature overnight, and then concentrated to dryness. Preparative t.l.c. (benzene–EtOAc, 10:1) of the residue gave **15** as colorless crystals (0.166 g, 85%). Recrystallization from ether–light petroleum gave material having m.p. 86–87°, $[\alpha]_D$ −6° (*c* 0.7, chloroform), λ_{max}^{KBr} 1770 cm^{-1} (C=O). Mass spectrum: *m/z* 213 (M^+ − Me).

Anal. Calc. for $C_{11}H_{15}O_5$: C, 57.89; H, 7.07. Found: C, 57.97; H, 7.17.

1,4-Anhydro-3-C-(carboxymethyl)-3,5-dideoxy-5-C-(2-oxoheptylidene)-D-ribitol 3^2,2-lactone (**16**). — A solution of **15** (0.153 g) in aqueous 50% acetic acid (5 mL) was stirred at room temperature for 12 h and then concentrated to dryness. A solution of the resulting syrup in toluene was concentrated to dryness and this procedure was repeated several times. The solid residue was then recrystallized from 2-propanol to give the deacetalated lactone (0.115 g, 90%), m.p. 133–134°, $[\alpha]_D$ −23° (*c* 0.55, chloroform).

A solution of a portion (43 mg, 0.25 mmol) of this product in water (2 mL) was stirred with a solution of sodium periodate (67 mg, 0.31 mmol) in water (1.5

mL) at 0° for 30 min and then concentrated to dryness. The residue was extracted with ether, the extract was concentrated, and toluene was repeatedly evaporated from the residue. The resulting syrup was chromatographically homogeneous and showed a ^{1}H-n.m.r. signal for an aldehyde proton (δ 9.4).

A solution of the preceding compound in ether (5 mL) was stirred with a solution of 1-tributylphosphoranylidene-2-heptanone (0.144 g) in ether (2 mL) at room temperature for 1 h and then concentrated to dryness. The residue was purified by preparative t.l.c. (benzene–EtOAc, 10:3) to give **16** (43 mg, 75%), m.p. 67–68°, $[\alpha]_D$ +33° (*c* 1.2, chloroform); lit.[11] m.p. 67°, $[\alpha]_D^{25}$ +34° (chloroform).

Anal. Calc. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.83; H, 7.96.

*1,4 - Anhydro - 2 - O - tert - butyldiphenylsilyl - 3,5 - dideoxy - 3 - C - (ethoxycarbonylmethyl)-5-C-(2-oxo-*trans*-heptylidene)-D-ribitol* (**17**). — A solution of **6** (0.18 g) in aqueous 70% acetic acid (8 mL) was stirred at room temperature for 10 h and then concentrated, and toluene was repeatedly evaporated from the residue. A solution of the resulting syrup in dichloromethane was washed with water, dried, and concentrated to give the diol as a chromatographically homogeneous syrup (0.16 g, 92%).

A solution of the diol (0.14 g) in water (3 mL) and methanol (4 mL) at 0° was treated with a solution of sodium metaperiodate (40 mg) in water (1 mL) for 30 min at 0° and then concentrated to dryness. The residue was extracted with ether, and the extract was filtered and concentrated to dryness to give the aldehyde as a chromatographically homogeneous syrup (0.13 g).

A solution of the aldehyde (70 mg, 0.15 mmol) in ether (10 mL) was stirred with a solution of 1-tributylphosphoranylidene-2-heptanone (100 mg) in ether (1 mL) at room temperature for 30 min and then concentrated to dryness. The residue was purified by preparative t.l.c. (CCl_4–acetone, 20:1.5) to give **17** (71 mg, 83%) as a colorless syrup, $[\alpha]_D$ +51° (*c* 1.3, chloroform). Mass spectrum: *m/z* 536 (M^+) 491 ($M^+ - Et$).

The same product was also obtained from the reaction of the aldehyde derivative with dimethyl (2-oxoheptyl)phosphonate, but the yield was lower (40%).

*1,4-Anhydro-5,6-*O*-isopropylidene-2-*O*-methanesulfonyl-*D*-glucitol* (**18**). — A solution of 1,4-anhydro-D-glucitol (22 g, 0.134 mol) in *N,N*-dimethylformamide (150 mL) was stirred with 2,2-dimethoxypropane (30 mL) and a solution of ethanolic hydrogen chloride (from 0.5 mL of ethanol and 0.2 mL of acetyl chloride) for 5 h, and then neutralized with solid sodium hydrogen carbonate, The solids were filtered off, and the filtrate was processed conventionally. The resulting syrup was dissolved in pyridine (250 mL) at 0°, and the solution was treated with methanesulfonyl chloride (11 mL, 0.142 mol) dropwise with vigorous stirring. The mixture was stored for 20 h at 0°, more reagent (3 mL, 38.7 mmol) was added, and the solution was stirred for 4 h at 0° and then poured into ice–water (2.5 L). The crystalline precipitate was recrystallized from ethanol to give the dimesylate (2.3 g, 4.7%), m.p. 159–160°. Recrystallization gave material with m.p. 163–163.5° (from ethanol), $[\alpha]_D$ −4° (*c* 4.6, methyl sulfoxide).

Anal. Calc. for $C_{11}H_{20}O_9S_2$: C, 36.66; H, 5.59. Found: C, 36.54; H, 5.52.

The aqueous phase was extracted with ethyl acetate (5 × 200 mL), and the combined extracts were processed conventionally to give **18** (10 g, 26%), m.p. 140–141° (from ethanol), $[\alpha]_D$ +1.3° (*c* 1, methyl sulfoxide).

Anal. Calc. for $C_{10}H_{18}O_7S$: C, 42.54; H, 6.42; S, 11.36. Found: C, 42.41; H, 6.40; S, 11.22.

*1,4-Anhydro-2-deoxy-2-*C*-di(ethoxycarbonyl)methyl-*D*-glucitol* (**20**) *and 1,4-anhydro-3-deoxy-3-*C*-di(ethoxycarbonyl)methyl-*D*-altritol* (**21**). — A solution of **18** (2 g, 7.4 mmol) in chloroform (100 mL) was treated at 0° with ethanol (20 mL) containing sodium ethoxide [from 0.18 g (7.8 mmol) of sodium] at 0° for 24 h. The solution was then diluted with water and the organic phase was processed conventionally to give 1,4:2,3-dianhydro-5,6-*O*-isopropylidene-D-mannitol (**19**) as a syrup (1.35 g, 98%).

Compound **19** was also obtained from the mixture of **18** and the corresponding dimesylate. Thus, the preparation of **18** was repeated, and the pyridine solution was poured into ice–water (500 mL) and extracted with chloroform to give **18** and the dimesylate. Treatment with methanolic sodium methoxide (from 3.1 g of sodium and 150 mL of methanol) and processing as described above gave **19** (14.22 g, 57% from **1**), b.p. 53–54°/0.015 Torr. The residue consisted of the dimesylate (8.8 g, 18%), m.p. 162–163°.

Sodium metal (3.77 g, 0.16 mol) was added to dry ethanol (300 mL) and the resulting solution was added to diethyl malonate (30 mL, 0.2 mol). After the mixture had been heated at 40° for 2 h, a solution of **19** (8 g, 43 mmol) in dry ethanol (100 mL) was added and the solution was heated at reflux for 18 h under dry nitrogen. The cooled solution was added to aqueous acetic acid and extracted with ether (4 × 100 mL), and the extracts were combined and processed conventionally to give a mobile liquid. Excess of diethyl malonate was removed by distillation at 40–45°/0.05 mmHg. A solution of the syrupy residue in hot water (200 mL) containing glacial acetic acid (30 mL) was stirred overnight, then neutralized with solid sodium hydrogencarbonate, and extracted with hot ethyl acetate. The extract was processed conventionally to give a residue which was crystallized from the minimum volume of ethyl acetate to yield **20** (2.32 g, 18%), m.p. 75–76°. The mother liquor was concentrated and the residue was eluted from a column (2.5 × 12 cm) of silica gel impregnated with 2% boric acid, using $CHCl_3$–EtOAc (85:15). Better separation could be achieved by preparative t.l.c. using the same support and $CHCl_3$–MeOH. (150:20), to give **20** (1.07 g, 26% total), m.p. 76–77°, $[\alpha]_D$ −1.5° (*c* 2.1, ethyl acetate), and **21** (2.66 g, 20%). Mass spectrum: *m/z* 306 (M^+), 270 ($M^+ - 2\,H_2O$).

Anal. Calc. for $C_{13}H_{22}O_8$ (**20**): C, 50.97; H, 7.24. Found: 50.39; H, 7.09.

*1,4-Anhydro-2-deoxy-2-*C*-(ethoxycarbonylmethyl)-5,6-*O*-isopropylidene-*D*-glucitol* (**22**) *and 1,4-anhydro-3-deoxy-3-*C*-(ethoxycarbonylmethyl)-5,6-*O*-isopropylidene-*D*-altritol* (**23**). — A solution of **20** (0.44 g, 1.44 mmol) in 0.1M sodium hydroxide (18 mL) was stirred for 23 h and then neutralized with Rexyn-101 (H^+)

resin, the suspension was filtered, and the filtrate was concentrated to dryness. A solution of the residue in pyridine (15 mL) was heated to reflux for 5 h and then concentrated to dryness, and toluene was repeatedly distilled from the residue which consisted of a mixture of an ester and an acid. The mixture was treated with ethanol (20 mL) containing conc. sulfuric acid (0.1 mL) for 24 h, then neutralized with sodium hydrogencarbonate, and processed conventionally. Preparative t.l.c. (silica gel impregnated with 2% boric acid; $CHCl_3$–MeOH, 150:20) gave the triol **35** (77%), m.p. 72–73° (from chloroform–isopropyl ether), $[\alpha]_D$ +11° (*c* 1.2, ethanol).

Anal. Calc. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.14; H, 7.72.

The triol **36** was obtained (87%) from **21**, by the same procedure, as a syrup, $[\alpha]_D$ −6° (*c* 3.6, ethanol). Mass spectrum: *m/z* 235.1180 (M + 1) (calc. 235.1182).

Treatment of each triol (0.5 g, 2.14 mmol) in acetone containing ethanolic (10%) hydrogen chloride gave **22** and **23**, as chromatographically homogeneous, colorless syrups which were used as such.

*1,4-Anhydro-2-*O*-*tert*-butyldiphenylsilyl-3-deoxy-3-*C*-(ethoxycarbonylmethyl)-5,6-*O*-isopropylidene-*D*-altritol* (**24**). — A solution of **23** (0.5 g, 2.14 mmol) in *N,N*-dimethylformamide (15 mL) was stirred with a M solution of *tert*-butyldiphenylsilyl chloride in *N,N*-dimethylformamide (2.5 mL) and imidazole (0.41 g, 6 mmol) for 3 h, then diluted with ether, and washed with water, and the organic layer was processed conventionally. Column chromatography (benzene–EtOAc, 10:1) of the syrupy product gave **24** (1 g, 91%) as a syrup, $[\alpha]_D$ +14° (*c* 1.1, chloroform). Mass spectrum: *m/z* 497 (M^+ − Me), 455 (M^+ − ^{t}Bu).

*Methyl {2S-[2α(4R),3β(Z),4α]}-7-[4-(*tert*-butyldiphenylsilyloxy)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-3-yl]-5-heptenoate* (**26**). — A solution of **24** (1 g, 1.95 mmol) in toluene (20 mL) was stirred with M di-isobutylaluminum hydride in hexane (2 mL, 3 mmol) at −78° for 30 min, then diluted with ether, washed with saturated aqueous ammonium chloride, filtered through Celite, and diluted with ethyl acetate. Conventional processing gave a syrup from which toluene and then dichloromethane were evaporated, to give the aldehyde **25** as a chromatographically homogeneous syrup, which was used as such. Mass spectrum: *m/z* 453 (M^+ − Me).

1.58M Butyl-lithium in hexane (7.6 mL, 12 mmol) was added dropwise at 0° to a solution of bis(trimethylsilyl)amine (1.93 g, 12 mmol) in ether (10 mL). The solvent was evaporated by a stream of dry nitrogen, and a solution of the crystalline lithium salt in hexamethylphosphoric triamide (15 mL) was added to a solution of (4-carboxybutyl)triphenylphosphonium bromide (2.7 g, 6 mmol; previously dried at 110°/0.02 mmHg, 6 h) in the same solvent (15 mL). The deep-red solution was added dropwise to a solution of **25** (0.87 g, 1.85 mmol) in hexamethylphosphoric triamide (13 mL) at 0°. After stirring at room temperature under nitrogen for 20 h, the solution was diluted with ether (150 mL), cooled, and acidified with 0.2M sodium hydrogensulfate. The organic layer was separated and processed conventionally. A solution of the syrupy product in ether–dichloromethane–methanol

(1:1:0.5, 25 mL) was treated with excess of diazomethane in ether. After 20 min, the excess of reagent was neutralized with silica, and the suspension was filtered and concentrated to dryness. Preparative t.l.c. (benzene–EtOAc, 10:1) then gave **26** (0.84 g, 81%) as a syrup, $[\alpha]_D$ +7° (*c* 1, chloroform). Mass spectrum: *m/z* 551 (M^+ – Me), 509 (M^+ – ^{t}Bu).

Methyl {2S-[2α(1S),3β(Z),4α]}-7-[2-(1,2-dihydroxyethyl)-tetrahydro-4-hydroxyfuran-3-yl]-5-heptenoate (**27**). — A solution of **26** (0.78 g, 1.37 mmol) in tetrahydrofuran (4 mL) was stirred with M tetrabutylammonium fluoride in the same solvent (3 mL) for 1 h and then concentrated. Chromatography (benzene–EtOAc, 1:1) (1.93 g, 12 mmol) gave a syrup (0.427 g, 95%), $[\alpha]_D$ +14° (*c* 1, chloroform). A solution of a portion (0.33 g, 1 mmol) in aqueous 20% acetic acid (4 mL) was stirred for 8 h and then concentrated to dryness, and toluene was repeatedly evaporated from the residue. A solution of the residue in ethyl acetate was processed conventionally. Preparative t.l.c. ($CHCl_3$–MeOH, 10:2) of the product gave **27** (0.29 g) as a syrup, $[\alpha]_D$ +12° (*c* 1.6, chloroform). Mass spectrum: *m/z* 239 (M^+ – MeO – H_2O).

Methyl {2S-[2α(1E),3β(Z),4α]}-7-[tetrahydro-4-hydroxy-2-(3-oxo-1-octenyl)-furan-3-yl]-5-heptenoate (**29**). — A solution of **27** (0.29 g, 1 mmol) in water (4 mL) was treated with sodium metaperiodate (0.23 g, 1 mmol) for 30 min and then extracted with ethyl acetate, and the extract was processed conventionally to give the aldehyde **28** (0.25 g, 98%) as a syrup. A solution of 1-tributylphosphoranylidene-2-heptanone (0.47 g, 1.5 mmol) in ether–dichloromethane (3:1, 24 mL) was stirred with **28** at room temperature for 3 h and then concentrated to dryness. Preparative t.l.c. (benzene–EtOAc, 1:1) of the residue gave **29** (0.29 g, 83%) as a syrup, $[\alpha]_D$ +35° (*c* 1.2, chloroform). Mass spectrum: *m/z* 352 (M^+ – MeO – H_2O).

Anal. Calc. for $C_{20}H_{32}O_5$: C, 69.28; H, 9.15. Found: C, 68.97; H, 9.03.

11-Oxaprostaglandin $F_2\beta$ methyl ester (**30**) *and its 15-epimer* (**31**). — 0.5M Zinc borohydride (4 mL) in 1,2-dimethoxyethane was stirred with a solution of **29** (0.275 g, 0.78 mmol) in ether (20 mL) for 6 h. Ethyl acetate and ammonium chloride were then added successively and the organic phase was processed conventionally to give a crude mixture (0.27 g, 98%) of C-15 epimeric alcohols. Column chromatography (benzene–EtOAc, 1:1) of the mixture gave the 15-*R* isomer **30** (74 mg, 26.8%), $[\alpha]_D$ +10° (*c* 1, chloroform), R_F 0.51 ($CHCl_3$–MeOH, 10:2). Mass spectrum: *m/z* 336 (M^+ – H_2O), 332 (M^+ – MeOH). The 15-*S* isomer **31** (76 mg, 27.5%) was alkso obtained; $[\alpha]_D$ +11° (*c* 1.1, chloroform), R_F 0.46.

11-Oxaprostaglandin $F_2\beta$ (**32**) *and its 15-epimer* (**33**). — A solution of **30** (62 mg, 0.17 mmol) in 0.1M sodium hydroxide (2 mL) and methanol (2 mL) was stirred for 8 h, concentrated below 35° to a small volume, and acidified with Dowex 50 (H^+) resin, the suspension was filtered, and the filtrate was diluted with ethyl acetate. The organic phase was concentrated and column chromatography (EtOAc–AcOH, 10:0.1) of the residue gave **32** (50 mg, 85%) as a colorless syrup, $[\alpha]_D$ +23° (*c* 0.9, ethyl acetate), R_F 0.3 (EtOAc–AcOH, 99:1). Mass spectrum: *m/z* 322 (M^+ – H_2O), 304 (M^+ – 2 H_2O).

Anal. Calc. for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.70; H, 9.18.

Treatment of **31** under similar conditions gave **33** (5.1 mg, 88%), $[\alpha]_D$ +18° (*c* 1.2, chloroform), R_F 0.41.

*1,4-Anhydro-2-deoxy-2-*C*-(ethoxycarbonylmethyl)-*D*-glucitol* (**35**), *1,4-anhydro-3-deoxy-3-*C*-(ethoxycarbonylmethyl)-*D*-altritol* (**36**), *and 1,4-anhydro-2-deoxy-2-*C*-(ethoxycarbonylmethyl)-*D*-altritol* (**37**). — A solution of 1,4-anhydro-D-glucitol (22 g, 0.14 mol) in *N,N*-dimethylformamide (75 mL) was stirred with 2,2-dimethoxypropane (5 mL), dry ethanol (1 mL), and 4 drops of acetyl chloride for 6 h and then neutralized with solid sodium hydrogencarbonate, the solids were filtered off, and the filtrate was concentrated to dryness. A suspension of the residue in dichloromethane was filtered, the filtrate was concentrated, and to a solution of the syrupy residue in *N,N*-dimethylformamide (50 mL) was added sodium hydride (6.5 g, 0.29 mol, previously washed with pentane) at 0° followed by *N*-toluene-*p*-sulfonylimidazole (33 g, 0.15 mol). The mixture was stirred for 2 h, diluted with methanol, and neutralized with Rexyn-102 (H^+) resin, the suspension was filtered, and the filtrate was concentrated to dryness. Distillation of the residue gave 1,4:2,3-dianhydro-5,6-*O*-isopropylidene-D-mannitol (**19**) and -D-iditol (**34**) as a mixture (15.3 g, 61.5%), b.p. 53–54°/0.015 mmHg.

Diethyl malonate (46 mL, 0.3 mol) was added to a solution of sodium ethoxide [from 6 g of sodium (0.2 mol) and 500 mL of dry ethanol]. After 2 h, a solution of the mixture of **19** and **34** (12.1 g, 65 mmol) in ethanol (250 mL) was added, and the mixture was boiled under reflux for 18 h and then neutralized with Rexyn-102 (H^+) resin. Excess of reagent was distilled off (60°/0.01 mmHg), and a solution of the residue in 3:1 acetic acid–water (200 mL) was stirred overnight and then concentrated to dryness. The residue was treated with M sodium hydroxide (150 mL) at 50° overnight, and the solution was cooled, acidified with Dowex 50 (H^+) resin, filtered, concentrated to a small volume, and applied to a column of Amberlite IR-45 (HO^-) resin. Elution with water gave products resulting from the opening of the epoxides with ethoxide ion. Elution with 0.1M sodium hydroxide (1 L, 50-mL fractions), followed by acidification of the appropriate fractions with Dowex 50 (H^+) resin and concentration, gave the malonic acid derivatives. Decarboxylation of a solution of these products in pyridine (150 mL, 10 h, at reflux), followed by concentration, acidification with Dowex 50 (H^+) resin, and esterification (EtOH, *p*-TsOH, reflux, 15 h), gave a syrupy mixture (6.6 g, 46%) of **35–37**. Chromatography on silica containing 2% boric acid ($CHCl_3$–MeOH, 10:1) gave, first, **36** (2.3 g, 16.5%), m.p. 72–73° (from ethyl acetate–isopropyl ether), $[\alpha]_D$ +10° (*c* 1, ethanol); and then a mixture (3.02 g, 21%) of **35** and **37**, from which **35** (1.11 g, 7.7%) could be fractionally crystallized, m.p. 70–71° (from ethyl acetate–isopropyl ether), $[\alpha]_D$ −5° (*c* 1, ethanol).

Anal. Calc. for $C_{10}H_{18}O_6$ (**35**): C, 51.27; H, 7.75. Found: C, 51.17; H, 7.98.

*1.4-Anhydro-2-deoxy-2-*C*-(ethoxycarbonylmethyl)-*D*-xylitol* (**38**) *and* -D-*arabinitol* (**40**). — A solution of the syrupy mixture (0.35 g, 1.5 mmol) of **35** and **37** and sodium periodate (0.34 g, 1.6 mmol) in water (10 mL) was stirred for 5 min and

then extracted with ethyl acetate. Conventional processing gave a mixture of aldehydes (0.3 g), a solution of which in ethanol (15 mL) was treated with sodium borohydride (0.1 g) at 0° for 2 h, then neutralized with Rexyn-102 (H^+) resin, filtered, and processed conventionally. Chromatography ($CHCl_3$–MeOH, 10:1) of the syrupy residue (0.22 g) gave **38** (63 mg, 21%), $[\alpha]_D$ +21° (*c* 0.2, ethanol). Mass spectrum: *m/z* 173 ($M^+ - CH_2OH$), 168 ($M^+ - 2\ H_2O$). Compound **40** (96 mg, 31%) was also obtained; $[\alpha]_D$ +24° (*c* 1.3, chloroform). Mass spectrum: *m/z* 173 ($M^+ - CH_2OH$).

*1,4-Anhydro-3-deoxy-3-*C*-(ethoxycarbonylmethyl)-*D*-arabinitol* (**39**) *and 1,4-anhydro-2-deoxy-2-*C*-(ethoxycarbonylmethyl)-3,5-*O*-isopropylidene-*D*-xylitol* (**43**). — A solution of **36** (0.23 g, 1 mmol) in water (5 mL) was treated with sodium periodate (0.23 g, 1 mmol), the mixture was processed, and the product was reduced, as described above, to give **39** as a syrup (0.12 g, 59%), $[\alpha]_D$ +5° (*c* 1.1, chloroform). Mass spectrum: *m/z* 204 (M^+), 173 ($M^+ - CH_2OH$).

Compound **19** was hydrolyzed with aqueous 80% acetic acid (80°, 3 h) to give 1,4:2,3-dianhydro-D-mannitol (**41**, 96%), m.p. 101.5–102.5°, $[\alpha]_D$ −49.5° (*c* 1, ethanol). To a solution of **41** (0.88 g, 6 mmol) in water (20 mL) was added sodium metaperiodate (1.35 g, 6.3 mmol), and the mixture was stirred at 0° for 10 min and then processed as described above to give an aldehyde which was reduced with sodium borohydride (0.15 g) in ethanol at 0°. Conventional processing then gave 1,4:2,3-dianhydro-D-lyxitol (**42**; 0.58 g, 84%) as a colorless syrup, $[\alpha]_D$ −54.5° (*c* 1.7, chloroform).

A solution of **42** (0.77 g, 6.5 mmol) in ethanol (30 mL) was treated with the sodium derivative of diethyl malonate [from 0.6 g of sodium (26 mmol), 5.2 mL of the diester (32.5 mmol), and 50 mL of ethanol], as described above for **19** and **34**, to give a syrup (0.36 g) consisting mainly of the esters **38** and **39**. Treatment of the mixture with acetone (20 mL) and toluene-*p*-sulfonic acid (2 mg) for 6 h, followed by neutralization, conventional processing, and column chromatography ($CHCl_3$–MeOH, 10:1), gave **39** (0.13 g, 10% from **41**), $[\alpha]_D$ +21° (*c* 1.6, chloroform), and **43** (0.17 g), syrup, $[\alpha]_D$ +7.2° (*c* 1.2, chloroform). Mass spectrum: *m/z* 229 (M^+ – EtO).

Compound **43** (0.17 g, 0.7 mmol) was treated with aqueous 80% acetic acid (18 h) and the solution was concentrated with toluene several times. Column chromatography ($CHCl_3$–MeOH, 10:1) of the residue gave **38** (0.14 g, 96%; 10.3% from **42**), $[\alpha]_D$ +5.25° (*c* 1, chloroform).

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