PROSTANOIDS: SYNTHESIS OF ENANTIOMERS OF 15-DEOXY-16-HYDROXY-16-METHYLPROSTAGLANDIN E_1

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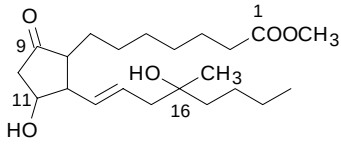
Dedicated to Dr Jaromir Plesek on the occasion of his 70th birthday.

Four optically pure isomers of methyl 11,16-dihydroxy-16-methyl-9-oxoprost-13-enoate (**1a**–**1d**) were synthesized using an approach reverse to the classical Corey procedure, the key intermediates being the easily accessible (–)- and (+)-enantiomers of the Corey lactone, **2a** and **2b**.
Key words: Prostaglandins; Enantiomeric resolution.

Cytoprotective analogues of prostaglandin E_1 modified in the ω-chain are recently used as active components in preparations controlling the secretion of gastric juice and preventing or curing gastric intestinal tract (GIT) ulcers induced by nonsteroidal antiinflammatory drugs (NSAIDs)[1–5]. In this group of compounds, methyl ester of (+/–)-15-deoxy-(16*RS*)-16-hydroxy-16-methylprostaglandin E_1 (INN misoprostol, **1**)[1,2] plays an important role. This derivative is a mixture of four enantiomers **1a** (8*R*,11*R*,12*R*,16*R*), **1b** (8*S*,11*S*,12*S*,16*R*), **1c** (8*R*,11*R*,12*R*,16*S*) and **1d** (8*S*,11*S*,12*S*,16*S*), however, only the enantiomer **1c** (with the natural PG E_1 configuration) bears the main biological activity.



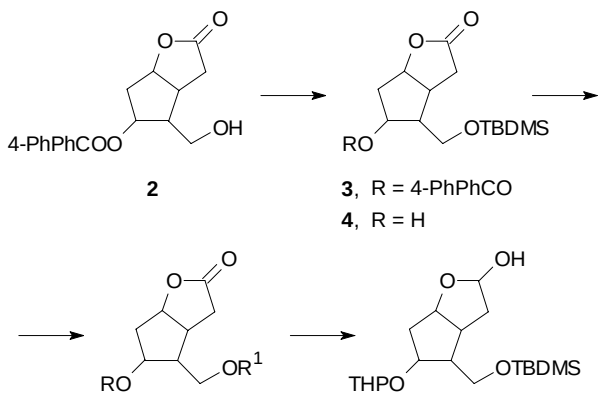
1

a, (8*R*, 11*R*, 12*R*, 16*R*) **c**, (8*R*, 11*R*, 12*R*, 16*S*)
b, (8*S*, 11*S*, 12*S*, 16*R*) **d**, (8*S*, 11*S*, 12*S*, 16*S*)

During the last 15 years much effort has been devoted to the synthesis of these compounds using two- or three-component conjugate additions of organocuprate reagents with modified ω-chain to the corresponding cyclopentene system[2,6–8]. These at the first

glance simple and convergent procedures suffer from several drawbacks. In addition to relatively complicated synthesis of intermediates, these methods do not allow to prepare the biologically active enantiomer **1c** in the required 98–99.5% enantiomeric excess[9,10]. The aim of our present study was to synthesize the said enantiomers **1a–1d** using an approach "reverse" to the classical highly stereoselective and flexible Corey synthesis[11]. This approach had not been fully realized even using racemic intermediates[12,13]. Contrary to previous syntheses[11–13] we prepared the pure enantiomers **1a–1d** starting from the easily accessible (–)-enantiomer (natural) of lactone **2a** and from the (+)-enantiomer of the Corey lactone **2b**. We employed standard procedures which in several steps were modified and optimized. For the sake of clarity, the reaction pathway is depicted only for the levorotatory lactone **2a** as the starting compound.

This lactone was almost quantitatively converted into the corresponding derivative **3a** by reaction with *tert*-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole (Scheme 1). Removal of the 4-phenylbenzoyl protecting group by treatment with sodium methoxide in methanol gave hydroxy derivative **4a** which was converted into a mixture of diastereoisomers **5a** by reaction with 3,4-dihydro-2*H*-pyran catalyzed with *p*-toluenesulfonic acid. In addition to the desired product (62%) we isolated also the starting compound **4a** (10–12%), the bistetrahydropyranyl derivative **6a** (17%) and the diol **7a** (4–6%). Therefore, we tried to optimize this step using other catalysts[14] (Dowex 8 WX, Amberlyst H-15, pyridinium *p*-toluenesulfonate) and varying the reaction conditions. An excellent result (about 90% of **5a**, without **4a**, **6a** and **7a**) was



2

3, R = 4-PhPhCO
4, R = H

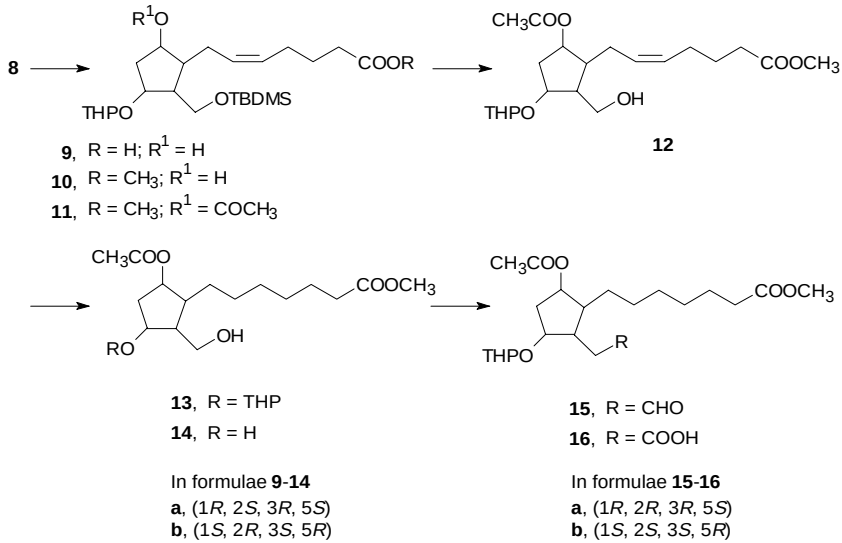
5, R = 4-THP; R^1 = TBDMS
6, R = THP; R^1 = THP
7, R = H; R^1 = H

8

In formulae **2**-**8**
a, (3a*R*, 4*S*, 5*R*, 6a*S*)
b, (3a*S*, 4*R*, 5*S*, 6a*R*)

SCHEME 1

achieved with anhydrous pyridinium *p*-toluenesulfonate as catalyst. The lactone **5a** was reduced with diisobutylaluminium hydride (DIBAL) in toluene at a temperature below –75 °C and the obtained lactol **8a** (90–95%) was converted into acid **9a** by treatment with ylide generated *in situ* from 4-(carboxybutyl)triphenylphosphonium bromide with potassium *tert*-butoxide. Without isolation, the acid **9a** was reacted with methyl iodide and anhydrous potassium carbonate in acetone to give methyl ester **10a** (Scheme 2) in overall yield over 80%.

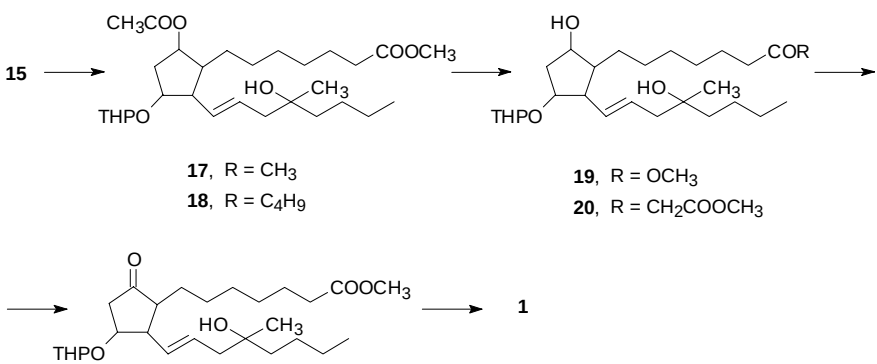


SCHEME 2

In the next step, the free C-9 hydroxy group (PG-numbering) was acetylated with acetic anhydride in pyridine in the presence of catalytic amount of 4-dimethylaminopyridine. The acetyl derivative **11a** was obtained in high yield (about 90%). Attempted catalytic hydrogenation of acetate **11a** over 10% Pd/C in ethyl acetate was unsuccessful because of immediate deactivation (precipitation) of the catalyst. Only after removal of the *tert*-butyldimethylsilyl protecting group with tetrabutylammonium fluoride in tetrahydrofuran, the primary alcohol **12a** was smoothly hydrogenated under the described conditions. After consumption of the theoretical amount of hydrogen we isolated the saturated alcohol **13a** in high yield (95%) and purity. We found that prolonged hydrogenation resulted in higher consumption of hydrogen due to hydrogenolysis of the tetrahydropyranylgroup[14] under formation of diol **14a**. To obtain an optimal yield of the relatively little stable aldehyde **15a**, we tried to oxidize the primary C-13 hydroxy group in alcohol **13a** with various reagents. Application of the chromium trioxide–pyridine complex (Collins reagent[15]; sixfold molar excess, dichloromethane, 0 °C, 30 min) gave the product **15a** in about 45% yield, oxidation with *in situ* prepared *N*-chlorosuccin-

imide–thioanisole complex (Corey reagent[16], threefold molar excess, dichloromethane, 20 °C, 210 min) afforded only 15% of the aldehyde and mainly the acid **16a** (35%), and reaction with periodate (Dess–Martin[17], dimethyl sulfoxide, 1.5 molar excess, 20 °C, 40 min) furnished 67% of the product. On the other hand, oxidation with the *in situ* prepared complex of dimethyl sulfoxide and oxalyl chloride (Swern reagent[18], threefold molar excess, dichloromethane, –75 °C, 60 min) gave very pure product **15a** in 92% yield (Scheme 2).

In the next step, the bottom chain was introduced by reaction of aldehyde **15a** with ylide, generated *in situ* from (3-hydroxy-3-methylheptyl)triphenylphosphonium iodide and butyl lithium in tetrahydrofuran. Surprisingly, in addition to the expected methyl esters **17a** + **17c**, this reaction gave also the butyl esters **18a** + **18c** whose structure was unequivocally confirmed by elemental analysis and spectral (IR, ^{1}H NMR and MS) methods (Scheme 3). The amount of the butyl esters increased with increasing reaction time. So far, we are not able to explain this side reaction. Removal of the acetyl protecting group by treatment of these esters with excess of anhydrous methanol and calcined potassium carbonate was accompanied by simultaneous transesterification and the desired mixture of methyl esters **19a** + **19c** was obtained in very good yield (86%). In addition, preparative chromatography of the reaction mixture afforded minor quantity of another product whose molecular formula was $C_{29}H_{50}O_7$, according to its elemental analysis and molecular ion (*m/z* 510). As followed from ^{1}H NMR, ^{13}C NMR and IR spectral analysis, this side product may be the Claisen condensation product **20a** + **20c**.



In formulae **17-20**

a, (8*R*, 9*S*, 11*R*, 12*R*, 16*R*) **c**, (8*R*, 9*S*, 11*R*, 12*R*, 16S)
b, (8*S*, 9*R*, 11*S*, 12*S*, 16*R*) **d**, (8*S*, 9*R*, 11*S*, 12*S*, 16*S*)

In formulae **21**

a, (8*R*, 11*R*, 12*R*, 16*R*) **c**, (8*R*, 11*R*, 12*R*, 16S)
b, (8*S*, 11*S*, 12*S*, 16*R*) **d**, (8*S*, 11*S*, 12*S*, 16*S*)

SCHEME 3

The C-9 secondary hydroxyl in **19a** + **19c** was oxidized with chromium trioxide–pyridine complex in dichloromethane and the resulting oxo derivatives **21a** + **21c** were obtained in 80–90% yield. The tetrahydropyranyl protecting group was removed by treatment with 1 M hydrochloric acid in tetrahydrofuran and the reaction gave the diastereoisomeric pair (11*R*,16*R*)-**1a** and (11*R*,16*S*)-**1c**, together with minor quantity (about 3–5%) of the corresponding isomers PG A_1. Preparative HPLC afforded individual highly pure epimers **1a** and **1c**. The other two diastereoisomers **1b** and **1d** were prepared analogously starting from the (+)-enantiomer **2b** (see Experimental).

The spectral data of the prepared compounds **1a**–**1d** are in good accord with the published ones[9,19,20]. The observed small differences in the optical rotation values (Table I) can be explained by different enantiomeric purity and conditions of the measurements. We assigned configuration to individual isomers on the basis of these data and configuration of the starting lactone **2**. The structure of all the prepared compounds is in accord with the elemental analyses (Table I), infrared spectra (Table II) and ^{1}H NMR spectra (Table III) and in some cases was also verified by ^{13}C NMR and mass spectra (see Experimental).

EXPERIMENTAL

The temperature data are uncorrected. Melting points were determined on a Boetius block. Infrared spectra were measured on a Nicolet 740 FT-IR spectrometer in chloroform (unless stated otherwise), ^{1}H and ^{13}C NMR spectra were obtained with Varian 300 and Bruker 400 instruments in deuteriochloroform (unless stated otherwise). The chemical shifts are given in δ (ppm) and coupling constants *J* in Hz. Optical rotations were determined on a Jasco digital polarimeter DIP-370. Mass spectra were measured on a Finnigan MAT-90 spectrometer, using FAB or ES (electrospray) methods; the ion species are described by *m/z* units (relative intensity, %). Column chromatography was performed on Kieselgel 60 (Merck, 0.063–0.100 mm), TLC analyses were carried out on plates coated with Kieselgel GF_{254} (Fluka); spots were detected by UV light or spraing with 1% solution of cerium(IV) ammonium nitrate in 10% sulfuric acid and subsequent heating. The mixtures of isomers **1a** + **1c** or **1b** + **1d** were separated by high pressure liquid chromatography on a Thermo Separation Products instrument, using a P 1000 gradient pump, a Spectra Monitor 3200 UV-detector, and a Rheodyne 7125 injection valve. Preparative chromatography was carried out on a Biospher SI 100 column (7 μm, 25 × 250 mm) in hexane–ethanol (96 : 4); analytical separation was done on a Separon SGX column (7 μm, 4 × 250 mm) in hexane–ethanol (95 : 5).

Chemicals. Optically pure (–)-enantiomer of Corey lactone **2a** (m.p. 128–130 °C, $[\alpha]_D^{20}$ = –86.8° ($CHCl_3$, *c* 1.0)) and the (+)-enantiomer **2b** (m.p. 133–135 °C, $[\alpha]_D^{20}$ = +88.5° ($CHCl_3$, *c* 0.2)) was obtained by resolution of the racemic lactone **2** (Spolana, Neratovice) according to a described procedure[21]. (3-Hydroxy-3-methylheptyl)triphenylphosphonium iodide was prepared as described in a patent[22].

(–)-(3a*R*,4*S*,5*R*,6a*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-(4-phenylbenzoyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**3a**)

Imidazole (11.01 g, 162 mmol) and *tert*-butyldimethylsilyl chloride (9.96 g, 66.1 mmol) were added to a solution of lactone **2a** (13.6 g, 38.6 mmol) in *N*,*N*-dimethylformamide (20 ml). The reaction

TABLE I
Optical rotations and elemental analyses of compounds **1–21**

Compound	Formula M.w.	$[\alpha]_D^{20}$, °($CHCl_3$) *c*, g/100 ml	Calculated/Found	
			% C	% H
3a	$C_{27}H_{34}O_5Si$	–81.5	69.49	7.34
	466.7	0.8	68.95	7.09
3b	$C_{27}H_{34}O_5Si$	+81.3[a]	69.49	7.34
	466.7	0.8	69.65	7.60
4a	$C_{14}H_{26}O_4Si$	–14.7	58.70	9.15
	286.4	0.9	58.58	9.19
4b	$C_{14}H_{26}O_4Si$	+12.6[b]	58.70	9.15
	286.4	0.8	58.82	9.43
5a	$C_{19}H_{34}O_5Si$	–66.2	61.58	9.25
	370.6	0.7	61.93	9.45
5b	$C_{19}H_{34}O_5Si$	+27.2	61.58	9.25
	370.6	0.7	61.87	9.04
6a	$C_{18}H_{28}O_6$	–	63.51	8.29
	340.4		63.32	8.08
6b	$C_{18}H_{28}O_6$	–	63.51	8.29
	340.4		63.20	8.11
7a	$C_8H_{12}O_4$	–	55.81	7.02
	172.2		55.72	6.88
7b	$C_8H_{12}O_4$	–	55.81	7.02
	172.2		55.56	7.11
8a	$C_{19}H_{36}O_5Si$	–19.7[c]	61.25	9.74
	372.6	0.3	61.33	9.27
8b	$C_{19}H_{36}O_5Si$	+25.6	61.25	9.74
	372.6	0.4	61.35	9.82
9a	$C_{24}H_{44}O_6Si$	+25.6	63.12	9.71
	456.7	0.7	63.54	9.73
9b	$C_{24}H_{44}O_6Si$	–26.9	63.12	9.71
	456.7	0.2	63.65	9.68
10a	$C_{24}H_{46}O_6Si$	+27.8[d]	63.79	9.85
	470.7	0.2	63.40	9.95

TABLE I
(*Continued*)

Compound	Formula M.w.	$[\alpha]_D^{20}$, °($CHCl_3$) *c*, g/100 ml	Calculated/Found	
			% C	% H
10b	$C_{24}H_{46}O_6Si$	–23.7[e]	63.79	9.85
	470.7	0.3	63.74	9.84
11a	$C_{27}H_{48}O_7Si$	+24.6	63.25	9.44
	512.8	0.3	62.72	8.97
11b	$C_{27}H_{48}O_7Si$	–26.7	63.25	9.44
	512.8	0.3	63.55	9.49
12a	$C_{21}H_{34}O_7$	+37.1	63.30	8.60
	398.5	0.4	63.72	8.67
12b	$C_{21}H_{34}O_7$	–42.5	63.30	8.60
	398.5	0.5	63.35	8.85
13a	$C_{21}H_{36}O_7$	+29.7	62.98	9.06
	400.5	0.1	62.38	9.25
13b	$C_{21}H_{36}O_7$	–49.2	62.98	9.06
	400.5	0.4	63.26	9.35
14a	$C_{16}H_{26}O_6$	–	61.13	8.34
	314.4		59.84	8.11
14b	$C_{16}H_{26}O_6$	–	61.13	8.34
	314.4		59.66	8.06
15a	$C_{21}H_{34}O_7$	+42.7	63.30	8.60
	398.5	0.4	63.08	8.57
15b	$C_{21}H_{34}O_7$	–47.3	63.30	8.60
	398.5	0.3	62.31	8.70
17a + **17c**	$C_{29}H_{50}O_7$	+59.8	68.20	9.87
	510.7	0.2	68.68	10.06
17b + **17d**	$C_{29}H_{50}O_7$	–53.6	68.20	9.87
	510.7	0.1	68.76	10.03
18a + **18d**	$C_{32}H_{58}O_7$	+44.5	69.28	10.54
	554.8	0.2	68.83	10.34
18b + **18d**	$C_{32}H_{58}O_7$	–40.9	69.28	10.54
	554.8	0.1	69.62	10.05

TABLE I
(*Continued*)

Compound	Formula M.w.	$[\alpha]_D^{20}$, °($CHCl_3$) *c*, g/100 ml	Calculated/Found	
			% C	% H
19a + **19c**	$C_{27}H_{48}O_6$	+13.1	69.19	10.32
	468.7	0.1	68.79	10.34
19b + **19d**	$C_{27}H_{48}O_6$	–19.9	69.19	10.32
	468.7	0.9	68.60	10.31
20a + **20c**	$C_{29}H_{50}O_7$	–	68.20	9.87
	510.7		68.02	10.12
20b + **20d**	$C_{29}H_{50}O_7$	–	68.20	9.87
	510.7		67.94	9.92
21a + **21c**	$C_{27}H_{46}O_6$	–8.4	69.49	9.94
	466.7	0.2	69.57	9.79
21b + **21d**	$C_{27}H_{46}O_6$	+50.1	69.49	9.94
	466.7	1.0	68.94	10.29
1a	$C_{22}H_{38}O_5$	–57.8[f]	69.08	10.01
	382.5	0.5	68.31	9.92
1b	$C_{22}H_{38}O_5$	+80.4[g]	69.08	10.01
	382.5	0.4	68.20	10.14
1c	$C_{22}H_{38}O_5$	–75.1[h]	69.08	10.01
	382.5	0.2	68.24	9.99
1d	$C_{22}H_{38}O_5$	+62.5[i]	69.08	10.01
	382.5	1.0	68.30	9.84

$[\alpha]_D^{20}$, °: [a] Ref.[23] +78.0 ($CHCl_3$). [b] Ref.[23] +13.6 ($CHCl_3$). [c] Ref.[24] –28.0 (*c* 1.98, $CHCl_3$). [d] Ref.[24] +22.0 (*c* 1.84, CH_3OH). [e] Ref.[23] –26.0 ($CHCl_3$). [f] Ref.[9] –55.5 (CH_3OH). [g] Ref.[9] +47.5 (CH_3OH). [h] Ref.[9] –71.8 (*c* 1.0, CH_3OH). [i] Ref.[9] +56.5 (CH_3OH).

mixture was stirred at room temperature under exclusion of air for 1 h. After partition between toluene (150 ml) and water (100 ml), the organic layer was washed with saturated solution of sodium hydrogen carbonate (2 × 80 ml), water (2 × 80 ml), dried over anhydrous magnesium sulfate and the solvent was evaporated. Crystallization of the crude residue (17.9 g) from ethyl acetate–hexane (1 : 7) afforded 16.9 g (94%) of silyl ether **3a**; white crystals, m.p. 74–76 °C (reported[23] m.p. 83–84.5 °C (ether–hexane).

(+)-(3a*S*,4*R*,5*S*,6a*R*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-(4-phenylbenzoyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**3b**)

Silyl ether **3b** was obtained analogously in 97% yield; white crystals, m.p. 81–83 °C.

(–)-(3a*R*,4*S*,5*R*,6a*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**4a**)

Freshly prepared sodium methoxide (62.6 mmol) in methanol (80 ml) was added to a solution of compound **3a** (16.2 g, 34.7 mmol) in anhydrous methanol (30 ml). After stirring under nitrogen at room temperature for 80 min, the reaction mixture was partitioned between chloroform (150 ml) and water (150 ml). The chloroform layer was washed with saturated solutions of calcium chloride (2 × 80 ml) and sodium chloride (2 × 80 ml), dried over anhydrous magnesium sulfate and the solvent was evaporated. Pressure chromatography (0.5% triethylamine in chlorofom with gradient 2–4% methanol) of the residue (14.2 g) afforded 6.69 g of the product which was crystallized from toluene–hexane (1 : 10) to give 6.44 g (65%) of alcohol **4a** as white crystals, m.p. 57–59 °C (reported[23] m.p. 61–62.5 °C).

(+)-(3a*S*,4*R*,5*S*,6a*R*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**4b**)

The title alcohol was prepared in the same manner as described above in 65% yield. White crystals, m.p. 57–59 °C.

(–)-(3a*R*,4*S*,5*R*,6a*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**5a**)

To a solution of alcohol **4a** (5.65 g, 19.7 mmol) in 1,2-dichloroethane (40 ml) were successively added 3,4-dihydro-2*H*-pyran (10.9 ml, 120 mmol) and pyridinium *p*-toluenesulfonate (3.74 g, 14.9 mmol). The suspension was stirred at room temperature in an inert atmosphere for 2 h and then partitioned between 1,2-dichloroethane (40 ml) and water (40 ml). The organic layer was washed with saturated sodium hydrogen carbonate solution (3 × 70 ml), water (2 × 70 ml) and saturated sodium chloride solution (2 × 70 ml). After drying over anhydrous magnesium sulfate the solvent was evaporated and the crude residue (6.97 g) was column chromatographed (pressure, eluent toluene–*tert*-butyl methyl ether (6 : 1) with 0.5% triethylamine). Yield 6.56 g (90%) of pure lactone **5a** as a viscous oil.

(+)-(3a*S*,4*R*,5*S*,6a*R*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**5b**)

The title lactone **5b** was prepared in the same manner as lactone 5a. Yield 82%, yellow oil.

(–)-(2*RS*,3a*R*,4*S*,5*R*,6a*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (**8a**)

A solution of diisobutylaluminium hydride (1 M, 24.0 ml, 24.0 mmol) was added dropwise under nitrogen at –75 °C during 10 min to a solution of compound **5a** (3.39 g, 9.15 mmol) in toluene (40 ml). After stirring at –70 °C for 45 min under nitrogen, anhydrous methanol (4.5 ml) was added and the mixture was allowed to warm to about 5 °C. Water (26 ml) was added and the mixture was stirred for 80 min at 5 °C. The precipitated aluminium salts were filtered off and washed with toluene (3 × 25 ml), the combined organic filtrates were washed with saturated solution of sodium chloride (2 × 90 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 3.20 g (94%) of pure lactol **8a** as a yellowish viscous oil.

TABLE II
Absorption maxima in IR spectra of compounds **1–21**

Compound	ν(OH)	ν(C–H)	ν(C=O)	ν(C–O)
3a	–	3 027 w, 2 956 w, 2 888 w, 2 858 w	1 769 s, 1 712 s	1 277 s
3b	–	3 026 w, 2 956 w, 2 898 w, 2 859 w	1 769 s, 1 712 s	1 279 s
4a	3 607 w, 3 523 w	3 025 w, 2 956 m, 2 900 m, 2 859 m	1 768 s	–
4b	3 608 w, 3 507 w	3 024 w, 2 956 m, 2 899 w, 2 859 m	1 766 s	–
5a	–	3 013 w, 2 954 m, 2 932 m, 2 858 m	1 765 s	–
5b	–	3 024 w, 2 954 m, 2 932 m, 2 858 m	1 785 s	–
6a	–	2 985 w, 2 935 m, 2 892 w	1 750 s	1 212 s
6b	–	2 990 w, 2 940 m, 2 890 w	1 755 s	1 210 s
7a	3 365 m	2 978 w, 2 935 m, 2 887 w	1 737 s	1 205 s
7b	3 368 m	2 980 w, 2 938 m, 2 889 w	1 739 s	1 208 s
8a	3 600 w, 3 385 w	3 012 m, 2 952 s, 2 932 s, 2 858 m	–	–
8b	3 600 w, 3 389 w	3 011 m, 2 952 s, 2 932 s, 2 858 m	–	–
9a	3 519 w	3 017 m, 2 952 s, 2 930 s, 2 857 m	1 709 m	–
9b	3 518 w	3 010 m, 2 952 s, 2 932 s, 2 857 s	1 709 s	–
10a	3 523 w	3 005 w, 2 953 s, 2 931 s, 2 857 m	1 731 m	–
10b	3 522 w	3 010 m, 2 953 s, 2 932 s, 2 858 m	1 731 m	–
11a	–	3 025 w, 2 953 m, 2 932 m, 2 858 m	1 729 s	1 255 s
11b	–	3 023 w, 2 953 m, 2 932 m, 2 858 w	1 729 s	1 255 s
12a	3 460 w	3 023 w, 2 951 m, 2 869 w	1 730 s	1 254 m
12b	3 508 w, 3 448 w	3 022 m, 2 951 m, 2 869 w	1 729 s	1 255 m
13a	3 460 w	3 023 w, 2 938 m, 2 860 w	1 729 s	1 256 m
13b	3 447 w	3 022 m, 2 939 m, 2 860 w	1 729 s	1 257 m
14a	3 450 w	3 024 w, 2 935 m, 2 859 w	1 730 s	1 254 m
14b	3 453 w	3 026 w, 2 935 m, 2 861 w	1 730 s	1 253 m
15a	–	3 023 w, 2 941 m, 2 860 w	1 731 s	1 250 m
15b	–	3 023 m, 2 942 m, 2 860 w	1 729 s	1 250 m
17a + **17c**	3 486 w	3 014 w, 2 934 s, 2 860 m	1 730 s	1 253 m
17b + **17d**	3 474 w	3 013 m, 2 936 s, 2 862 m	1 730 s	1 260 m
18a + **18c**	3 486 w	3 012 w, 2 935 m, 2 861 w	1 727 s	1 254 m
18b + **18d**	3 482 w	3 012 w, 2 935 s, 2 861 m	1 727 s	1 260 m
19a + **19c**	3 607 w, 3 521 w	3 011 m, 2 934 s, 2 859 m	1 731 m	–
19b + **19d**	3 606 w, 3 515 w	3 019 m, 2 934 s, 2 859 m	1 731 s	–
20a + **20c**[a]	3 607 w, 3 512 w	3 019 m, 2 935 m, 2 860 m	1 740 m, 1 717 m	–
20b + **20d**[a]	3 606 w, 3 514 w	3 018 m, 2 934 m, 2 860 m	1 741 m, 1 718 m	–
21a + **21c**	3 605 w, 3 479 w	3 017 w, 2 936 m, 2 860 w	1 737 s	–
21b + **21d**	3 606 w, 3 477 w	3 019 w, 2 936 m, 2 860 w	1 737 s	–

TABLE II
(*Continued*)

Compound	ν(OH)	ν(C–H)	ν(C=O)	ν(C–O)
1a	3 601 w, 3 407 w	3 019 w, 2 935 m, 2 860 w	1 737 s	–
1b	3 605 w, 3 403 w	3 018 w, 2 935 m, 2 860 w	1 738 s	–
1c	3 603 w, 3 407 w	3 020 w, 2 935 m, 2 861 w	1 738 s	–
1d	3 602 w, 3 405 w	3 018 w, 2 935 m, 2 861 w	1 738 s	–

[a] Neat.

(+)-(2*RS*,3a*S*,4*R*,5*S*,6a*R*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (**8b**)

Lactol **8b** was prepared in the same manner as compound **8a**, yield 91%, viscous oil.

Methyl-(+)-7-{(1*R*,2*S*,3*R*,5*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-hydroxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopent-1-yl]}hept-5(*Z*)-enoate (**10a**)

A solution of potassium *tert*-butoxide in tetrahydrofuran (2.26 mol l^{-1}; 43.1 ml, 97.4 mmol) was added dropwise at about 5 °C (external cooling with ice) to a suspension of 4-(carboxybutyl)triphenylphosphonium bromide (21.6 g, 48.7 mmol) in tetrahydrofuran (80 ml). The reaction mixture, containing the deep orange ylide, was stirred at 5 °C for 15 min. Then a solution of lactol **8a** (5.20 g, 14.0 mol) in tetrahydrofuran (30 ml) was added in one portion. The reaction mixture was stirred at the same temperature for 60 min and then mixed with a solution of potassium carbonate (0.850 g, 6.15 mmol) in water (50 ml), ether (30 ml), ethyl acetate (30 ml) and benzene (60 ml). After separation, the aqueous layer was extracted with ether–ethyl acetate (1 : 1) (2 × 60 ml) and the combined organic layers were washed with water (3 × 60 ml). The aqueous phases, containing the salt of acid **9a** (TLC), were combined, cooled (ice) to about 5 °C, and under constant stirring acidified with saturated solution of sodium hydrogen sulfate (to pH about 6). The reaction mixture was extracted with diethyl ether (3 × 60 ml), the combined ethereal phases were washed with water (20 ml) and saturated sodium chloride solution (20 ml) and dried over anhydrous magnesium sulfate. A part of the filtrate was evaporated and subjected to column chromatography (gradient elution with 5–10% methanol in chloroform) which gave 0.086 g of acid **9a** for analytical purposes. The rest of the filtrate was coevaporated with potassium carbonate (7.66 g, 55.4 mmol) and the obtained crude potassium salt of acid **9a** (14.5 g) was slurried in acetone (60 ml). Methyl iodide (20.5 ml, 329 mmol) was added and the reaction mixture was stirred at room temperature under exclusion of moisture. After 15 h the separated inorganic salts were removed by filtration and washed with acetone (3 × 20 ml) and the combined acetone washings were evaporated on a rotatory evaporator *in vacuo*. The crude residue was diluted with diethyl ether–ethyl acetate (1 : 1, 30 ml), the precipitated crystals were collected and washed with the same solvent mixture (2 × 20 ml). The combined organic portions were evaporated and the residue (5.52 g) was subjected to column chromatography. Yield 5.25 g (80% from the lactol **8a**) of methyl ester **10a** as a yellowish oil.

TABLE III
Characteristic shifts of signals in the ^{1}H NMR spectra of compounds **1–21**

Compound	^{1}H NMR spectrum, ppm
3a	0.08 s, 6 H (2 × CH_3); 0.91 s, 9 H ((CH_3)$_3$C); 7.39–8.09 m, 9 H (H-arom)
3b	0.08 s, 6 H (2 × CH_3); 0.91 s, 9 H ((CH_3)$_3$C); 7.40–8.09 m, 9 H (H-arom)
4a	0.07 s, 6 H (2 × CH_3); 0.89 s, 9 H ((CH_3)$_3$C); 2.28 d, 1 H (OH)
4b	0.07 s, 6 H (2 × CH_3); 0.89 s, 9 H ((CH_3)$_3$C); 2.24 d, 1 H (OH)
5a	0.04 s, 6 H (2 × CH_3); 0.88 s, 9 H ((CH_3)$_3$C)
5b	0.04 s, 6 H (2 × CH_3); 0.88 s, 9 H ((CH_3)$_3$C)
6a	3.90 m, 1 H (CH–O); 4.83 dt, 1 H (CH–O)
6b	3.88 m, 1 H (CH–O); 4.82 dt, 1 H (CH–O)
7a[a]	3.92 m, 1 H (CH–O); 4.63 t, 1 H (OH); 4.74 d, 1 H (OH); ; 4.90 dt, 1 H (CH–O)
7b[a]	3.90 m, 1 H (CH–O); 4.61 t, 1 H (OH); 4.73 d, 1 H (OH); 4.87 dt, 1 H (CH–O)
8a	0.05 s, 6 H (2 × CH_3); 0.89 s, 9 H ((CH_3)$_3$C)
8b	0.04 s, 6 H (2 × CH_3); 0.89 s, 9 H ((CH_3)$_3$C)
9a	0.04 s, 6 H (2 × CH_3); 0.89 s, 9 H ((CH_3)$_3$C); 2.36 t, 2 H (CH_2–CO); 5.40–5.49 m, 2 H (CH=CH)
9b	0.05 s, 6 H (2 × CH_3); 0.89 s, 9 H ((CH_3)$_3$C); 2.36 t, 2 H (CH_2–CO); 5.40–5.48 m, 2 H (CH=CH)
10a	0.04 s, 6 H (2 × CH_3); 0.89 s, 9 H ((CH_3)$_3$C); 2.33 t, 2 H (CH_2–CO); 3.67 s, 3 H (OCH_3); 5.40–5.49 m, 2 H (CH=CH)
10b	0.03 s, 6 H (2 × CH_3); 0.87 s, 9 H ((CH_3)$_3$C); 2.31 t, 2 H (CH_2–CO); 3.65 s, 3 H (OCH_3); 5.38–5.47 m, 2 H (CH=CH)
11a	0.04 s, 6 H (2 × CH_3); 0.88 s, 9 H ((CH_3)$_3$C); 2.03 s, 3 H (CO–CH_3); 2.30 t, 2 H (CH_2–CO); 3.67 s, 3 H (OCH_3); 5.29–5.42 m, 2 H (CH=CH)
11b	0.02 s, 6 H (2 × CH_3); 0.85 s, 9 H ((CH_3)$_3$C); 2.00 s, 3 H (CO–CH_3); 2.27 t, 2 H (CH_2–CO); 3.63 s, 3 H (OCH_3); 5.23–5.41 m, 2 H (CH=CH)
12a	2.04 s, 3 H (CO–CH_3); 2.31 t, 2 H (CH_2–CO); 3.67 s, 3 H (O–CH_3); 5.29–5.44 m, 2 H (CH=CH)
12b	2.02 s, 3 H (CO–CH_3); 2.29 t, 2 H (CH_2–CO); 3.65 s, 3 H (O–CH_3); 5.24–5.41 m, 2 H (CH=CH)
13a	2.04 s, 3 H (CO–CH_3); 2.29 t, 2 H (CH_2–CO); 3.66 s, 3 H (O–CH_3)
13b	2.04 s, 3 H (CO–CH_3); 2.29 t, 2 H (CH_2–CO); 3.66 s, 3 H (O–CH_3)
14a	2.06 s, 3 H (CO–CH_3); 2.30 t, 2 H (CH_2–CO); 3.66 s, 3 H (O–CH_3); 5.29–5.45 m, 2 H (CH=CH)
14b	2.06 s, 3 H (CO–CH_3); 2.29 t, 2 H (CH_2–CO); 3.67 s, 3 H (O–CH_3); 5.22–5.40 m, 2 H (CH=CH)
15a	2.06 s, 3 H (CO–CH_3); 2.28 t, 2 H (CH_2–CO); 3.65 s, 3 H (O–CH_3); 9.77 dd, 1 H (CH=O)
15b	2.04 s, 3 H (CO–CH_3); 2.26 t, 2 H (CH_2–CO); 3.63 s, 3 H (O–CH_3); 9.75 dd, 1 H (CH=O)

TABLE III
(*Continued*)

Compound	^{1}H NMR spectrum, ppm
17a + **17c**	0.92 t, 3 H (CH_3); 1.16 s, 3 H (CH_3); 2.05 s, 3 H (CO–CH_3); 2.29 t, 2 H (CH_2–CO); 3.67 s, 3 H (O–CH_3); 5.31–5.64 m, 2 H (CH=CH)
17b + **17d**	0.90 t, 3 H (CH_3); 1.13 s, 3 H (CH_3); 2.03 s, 3 H (CO–CH_3); 2.26 t, 2 H (CH_2–CO); 3.64 s, 3 H (O–CH_3); 5.25–5.62 m, 2 H (CH=CH)
18a + **18c**	0.94 t, 3 H (CH_3); 1.16 s, 3 H (CH_3); 2.05 s, 3 H (CO–CH_3); 2.29 t, 2 H (CH_2–CO); 4.07 t, 2 H (O–CH_2); 5.32–5.64 m, 2 H (CH=CH)
18b + **18d**	0.93 t, 3 H (CH_3); 1.15 s, 3 H (CH_3); 2.04 s, 3 H (CO–CH_3); 2.27 t, 2 H (CH_2–CO); 4.06 t, 2 H (O–CH_2); 5.31–5.63 m, 2 H (CH=CH)
19a + **19c**	0.92 t, 3 H (CH_3); 1.15 s, 3 H (CH_3); 2.30 t, 2 H (CH_2–CO); 3.67 s, 3 H (O–CH_3); 5.34–5.61 m, 2 H (CH=CH)
19b + **19d**	0.92 t, 3 H (CH_3); 1.15 s, 3 H (CH_3); 2.30 t, 2 H (CH_2–CO); 3.67 s, 3 H (O–CH_3); 5.35–5.61 m, 2 H (CH=CH)
20a + **20c**	0.92 t, 3 H (CH_3); 1.15 s, 3 H (CH_3); 2.51 t, 2 H (CH_2–CO); 3.44 s, 3 H (O–CH_3); 3.74 s, 2 H (CO–CH_2–CO); 5.35–5.58 m, 2 H (CH=CH)
20b + **20d**	0.92 t, 3 H (CH_3); 1.15 s, 3 H (CH_3); 2.52 t, 2 H (CH_2–CO); 3.45 s, 3 H (O–CH_3); 3.74 s, 2 H (CO–CH_2–CO); 5.35–5.58 m, 2 H (CH=CH)
21a + **21c**	0.92 t, 3 H (CH_3); 1.16 s, 3 H (CH_3); 2.29 t, 2 H (CH_2–CO); 3.66 s, 3 H (O–CH_3); 5.44–5.75 m, 2 H (CH=CH)
21b + **21d**	0.91 t, 3 H (CH_3); 1.16 s, 3 H (CH_3); 2.28 t, 2 H (CH_2–CO); 3.66 s, 3 H (O–CH_3); 5.42–5.72 m, 2 H (CH=CH)
1a	0.92 t, 3 H (CH_3); 1.18 s, 3 H (CH_3); 3.67 s, 3 H (O–CH_3); 5.39–5.80 m, 2 H (CH=CH)
1b	0.90 t, 3 H (CH_3); 1.16 s, 3 H (CH_3); 3.65 s, 3 H (O–CH_3); 5.36–5.74 m, 2 H (CH=CH)
1c	0.92 t, 3 H (CH_3); 1.18 s, 3 H (CH_3); 3.67 s, 3 H (O–CH_3); 5.39–5.80 m, 2 H (CH=CH)
1d	0.90 t, 3 H (CH_3); 1.16 s, 3 H (CH_3); 3.65 s, 3 H (O–CH_3); 5.36–5.74 m, 2 H (CH=CH)

[a] Measured in $(CD_3)_2CO$.

Methyl (–)-7-{(1*S*,2*R*,3*S*,5*R*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-hydroxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopent-1-yl]}hept -5(*Z*)-enoate (**10b**)

The title methyl ester **10b** was prepared as a yellowish oil from the lactol **8b** in 79% yield in the same manner as described for **10a**.

Methyl (+)-7-{(1*R*,2*S*,3*R*,5*S*)-5-acetyloxy-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopent-1-yl]}hept-5(*Z*)-enoate (**11a**)

Freshly distilled acetic anhydride (6.10 ml, 64.7 mmol) was added at 5 °C (external cooling) to a mixture of alcohol **10a** (5.06 g, 10.7 mmol), 4-dimethylaminopyridine (0.096 g, 0.786 mmol) and dry pyridine (40 ml). The solution was stirred under exclusion of moisture at diminished temperature for 10 min and then at room temperature for 60 min. The reaction mixture was cooled, decomposed with water (50 ml) and extracted with ethyl acetate (4 × 50 ml). The combined organic extracts were subsequently washed with water (50 ml), 0.5 M hydrochloric acid (50 ml), saturated solution of sodium

hydrogen carbonate (3 × 50 ml), water (50 ml) and saturated sodium chloride solution (50 ml). After drying over anhydrous magnesium sulfate and evaporation of the solvent, the crude product (5.19 g) was repeatedly coevaporated with toluene (5 × 10 ml) to remove the remaining pyridine. Column chromatography in hexane–ethyl acetate (4 : 1) afforded 4.94 g of ester **11a** (90%) as a yellowish oil.

Methyl (–)-7-{(1*S*,2*R*,3*S*,5*R*)-5-acetyloxy-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopent-1-yl]}hept-5(*Z*)-enoate (**11b**)

The title ester was obtained as a viscous oil from alcohol **10b** in 88% yield in the same manner as described for **11a**.

Methyl (+)-7-{(1*R*,2*S*,3*R*,5*S*)-5-acetyloxy-2-(hydroxymethyl)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-cyclopent-1-yl]}hept-5(*Z*)-enoate (**12a**)

To a solution of silyl ether **11a** (4.92 g, 9.60 mmol) in tetrahydrofuran (60 ml) 1 M tetrabutylammonium fluoride in tetrahydrofuran (50.0 ml, 50.0 mmol) was added at 5 °C (external ice-cooling) in the course of 5 min. After stirring under nitrogen at 10 °C for 2 h, the reaction mixture was diluted with ethyl acetate (100 ml), the solution was washed with water (4 × 50 ml) and saturated sodium chloride solution (2 × 50 ml), and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue (4.56 g) purified by column chromatography in hexane–ethyl acetate (1 : 1) to give 3.55 g of unsaturated alcohol **12a** (93%) as a viscous oil. Mass spectrum (ES): 421.0 ($[M + Na]^+$, 100).

Methyl (–)-7-{(1*S*,2*R*,3*S*,5*R*)-5-acetyloxy-2-(hydroxymethyl)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-cyclopent-1-yl]}hept-5(*Z*)-enoate (**12b**)

The title compound was prepared as a yellowish oil in 98% yield from **11b** as described above.

Methyl (+)-7-{(1*R*,2*S*,3*R*,5*S*)-5-acetyloxy-2-(hydroxymethyl)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-cyclopent-1-yl]}heptanoate (**13a**)

Unsaturated alcohol **12a** (3.39 g, 8.51 mmol) was hydrogenated in ethyl acetate (110 ml) over 10% Pd/C (0.443 g) at atmospheric pressure and room temperature in a standard apparatus. After consumption of the theoretical amount of hydrogen, the catalyst was filtered off and washed with ethyl acetate (3 × 50 ml). The combined filtrates were evaporated and the crude product (3.30 g) was column chromatographed in hexane–ethyl acetate (1 : 1) to give 3.28g (96%) of saturated alcohol **13a** as a yellow oil. Mass spectrum (ES): 423.1 ($[M + Na]^+$, 100), 439.1 ($[M + K]^+$, 10).

Methyl (–)-7-{(1*S*,2*R*,3*S*,5*R*)-5-acetyloxy-2-(hydroxymethyl)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-cyclopent-1-yl]}heptanoate (**13b**)

The saturated alcohol **13b** was obtained from **12b** as a yellowish oil in 86% yield using an analogous procedure.

Methyl (+)-7-{(1*R*,2*S*,3*R*,5*S*)-5-acetyloxy-2-formyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopent-1-yl]}-heptanoate (**15a**)

A solution of dimethyl sulfoxide in dichloromethane (5.64 mol l^{-1}, 5.10 ml, 28.8 mmol) was added at –75 °C to a solution of oxalyl chloride in dichloromethane (1.16 mol l^{-1}, 7.50 ml, 8.70 mmol). After 10 min at –75 °C, a solution of alcohol **13a** (3.28 g, 8.19 mmol) in dichloromethane (7 ml) was

added and the reaction mixture was stirred at –75 °C for 1 h. The complex was decomposed with triethylamine (6.40 ml, 45.9 mmol), the mixture was allowed to warm to room temperature and then was diluted with ether (50 ml). The solution was washed with saturated solutions of ammonium chloride (2 × 30 ml) and sodium chloride (2 × 30 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue (3.16 g) subjected to column chromatography in hexane–ethyl acetate (1 : 1) to afford 3.01 g (92%) of aldehyde **15a** as an oil. In addition, 0.030 g (1%) of the starting alcohol **13a** was recovered.

Methyl (–)-7-{(1*S*,2*R*,3*S*,5*R*)-5-acetyloxy-2-formyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopent-1-yl]}-heptanoate (**15b**)

The title aldehyde **15b** (yellow oil) was prepared analogously in 85% yield. Small amount (2%) of the starting alcohol **13b** was also recovered.

Methyl (+)-(8*R*,9*S*,11*R*,12*R*,16*RS*)-9-acetyloxy-16-hydroxy-16-methyl-11-[(tetrahydro-2*H*-pyran-2-yl)-oxy]prost-13-enoate (**17a** + **17c**)

A solution of butyllithium in hexane (1.86 mol l^{-1}, 15.4 ml, 28.6 mmol) was added dropwise at –75 °C during 5 min to a suspension of (3-hydroxy-3-methylheptyl)triphenylphosphonium iodide (7.45 g, 14.4 mmol) in tetrahydrofuran (30 ml) in a nitrogen atmosphere. After addition, the cooling bath was removed and the suspension was stirred at room temperature for 2 h. The mixture was cooled to –40 °C, stirred at this temperature for 10 min and then a solution of aldehyde **15a** (2.81 g, 7.05 mmol) in tetrahydrofuran (20 ml) was added in one portion. The reaction mixture was stirred under nitrogen at –30 to –20 °C for 2 h and partitioned between ethyl acetate (80 ml) and water (80 ml). The aqueous phase was washed with ethyl acetate (2 × 60 ml) and the combined organic phases were washed with water (50 ml), saturated solutions of ammonium chloride (50 ml) and sodium chloride (50 ml) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude residue (8.2 g) was subjected to column chromatography in hexane–ethyl acetate (2 : 1) to give 1.04 g (29%) of methyl esters **17a** + **17c** and 0.861 g (22%) of butyl esters **18a** + **18c**, both as viscous oils.

Methyl (–)-(8*S*,9*R*,11*S*,12*S*,16*RS*)-9-acetyloxy-16-hydroxy-16-methyl-11-[(tetrahydro-2*H*-pyran-2-yl)-oxy]prost-13-enoate (**17b** + **17d**)

The title methyl esters were obtained as a yellow oil in 28% yield, together with the corresponding butyl esters **18b** + **18d** (oil, 22%).

Methyl (+)-(8*R*,9*S*,11*R*,12*R*,16*RS*)-9,16-dihydroxy-16-methyl-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]-prost-13-enoate (**19a** + **19c**)

Freshly calcined potassium carbonate (2.85 g, 20.6 mmol) was added to a solution of a mixture of **17a** + **17c** (0.846 g, 1.66 mmol) and **18a** + **18c** (0.575 g, 1.04 mmol) in anhydrous methanol (80 ml). After stirring under nitrogen at 45 °C for 3 h, the suspension was diluted with ethyl acetate (80 ml) and washed with saturated ammonium chloride solution (70 ml). The aqueous layer was extracted with ethyl acetate (2 × 30 ml) and the combined organic phases were washed with saturated solution of sodium chloride (2 × 50 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the crude product (1.22 g) was subjected to column chromatography to give 0.887 g (68%) of product **19a** + **19c** as a viscous oil, together with the Claisen condensation product **20a** + **20c** (0.128 g; 9%; oil). Mass spectrum of **19a** + **19c** (FAB): 469.4 ($[M]^{\ddagger}$, 6), 85.1 (THP, 100), 385.4 ($[M - THP]^{\ddagger}$, 23), 367.4 ($[M - THP - H_2O]^{\ddagger}$, 85), 349.4 ($[M - THP - 2H_2O]^{\ddagger}$, 64), 331.3 ($[M - THP - 3H_2O]^{\ddagger}$, 52).

Mass spectrum of **20a** + **20c** (ES): 533.2 ($[M + Na]^+$, 100). ^{13}C NMR spectrum of **20a** + **20c** (characteristic shifts): 167.98 s ($^{(CH_2}COCH_2$); 203.04 s (CH_2COOCH_3).

Methyl (–)-(8*S*,9*R*,11*S*,12*S*,16*RS*)-9,16-dihydroxy-16-methyl-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]-prost-13-enoate (**19b** + **19d**)

Prepared as a yellowish oil in 65% yield in the same manner as above. The Claisen condensation product **20b** + **20d** was isolated in 11% yield as an oil.

Methyl (–)-(8*R*,11*R*,12*R*,16*RS*)-16-hydroxy-16-methyl-9-oxo-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]-prost-13-enoate (**21a** + **21c**)

Collins reagent (2.12 g, 8.21 mmol) was added in one portion at 0 °C (external cooling) to a solution of **19a** + **19c** (0.515 g, 1.10 mmol) in dichloromethane (50 ml). The cooling bath was removed and the suspension was stirred under exclusion of moisture at room temperature for 2 h. The inorganic salts were removed by filtration and washed with chloroform (3 × 15 ml). The combined filtrates were evaporated on a rotatory evaporator, the residue was codistilled with toluene (3 × 20 ml) and the obtained crude product (0.540 g) was purified by column chromatography in hexane–ethyl acetate (1 : 1). Yield 0.435 g (85%) of oily product **21a** + **21c**.

Methyl (+)-(8*S*,9*R*,11*S*,12*S*,16*RS*)-16-hydroxy-16-methyl-9-oxo-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]-prost-13-enoate (**21b** + **21d**)

Prepared in the same manner as above in 83% yield as a viscous oil.

Methyl (8*R*,11*R*,12*R*,16*R*)-(–)-11,16-Dihydroxy-16-methyl-9-oxo-prost-13-enoate (**1a**) and
Methyl (8*R*,11*R*,12*R*,16*S*)-(–)-11,16-Dihydroxy-16-methyl-9-oxo-prost-13-enoate (**1c**)

Dilute hydrochloric acid (1 mol l^{-1}; 13.4 ml, 13.4 mmol) was added during 5 min to a solution of acetal **21a** + **21c** (0.364 g, 0.780 mmol) in tetrahydrofuran (8 ml). The solution was stirred at room temperature for 30 min and then partitioned between ethyl acetate (25 ml) and water (25 ml). The aqueous phase was extracted with ethyl acetate (3 × 15 ml), the combined organic layers were washed with water (20 ml), saturated sodium hydrogencarbonate solution (20 ml), again water (20 ml), and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue (0.284 g) was subjected to column chromatography (eluent 3% methanol + 1% triethylamine in chloroform). The chromatography afforded 0.260 g (87%) of oily alcohol **1a** + **1c** (mixture of epimers **1a** and **1c** of misoprostol **1**), 0.014 g (5%) of prostaglandin A derivative formed by elimination of water, and 0.013 g (4%) of the starting acetal **21a** + **21c**. Preparative HPLC in hexane–ethanol (95 : 5) separated the mixture **1a** + **1c** into the individual desired epimers **1a** (0.117 g) and **1c** (0.122 g).

Methyl (8*S*,11*S*,12*S*,16*R*)-(+)-11,16-Dihydroxy-16-methyl-9-oxo-prost-13-enoate (**1b**) and
Methyl (8*S*,11*S*,12*S*,16*S*)-(+)-11,16-Dihydroxy-16-methyl-9-oxo-prost-13-enoate (**1d**)

The title compounds (mixture of epimers **1b** and **1d** of misoprostol **1**) were prepared in 85% yield analogously. A prostaglandin A derivative was also isolated (7%) and some of the starting acetal **21b** + **21d** was recovered (7%). Preparative HPLC in hexane–ethanol (95 : 5) afforded the individual epimers **1b** and **1d**.

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