NEW SYNTHESIS OF IMPORTANT PROSTANOID INTERMEDIATE

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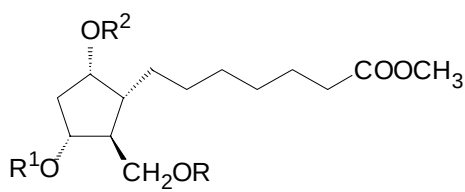
Dedicated to the memory of Dr Zdenek Arnold.

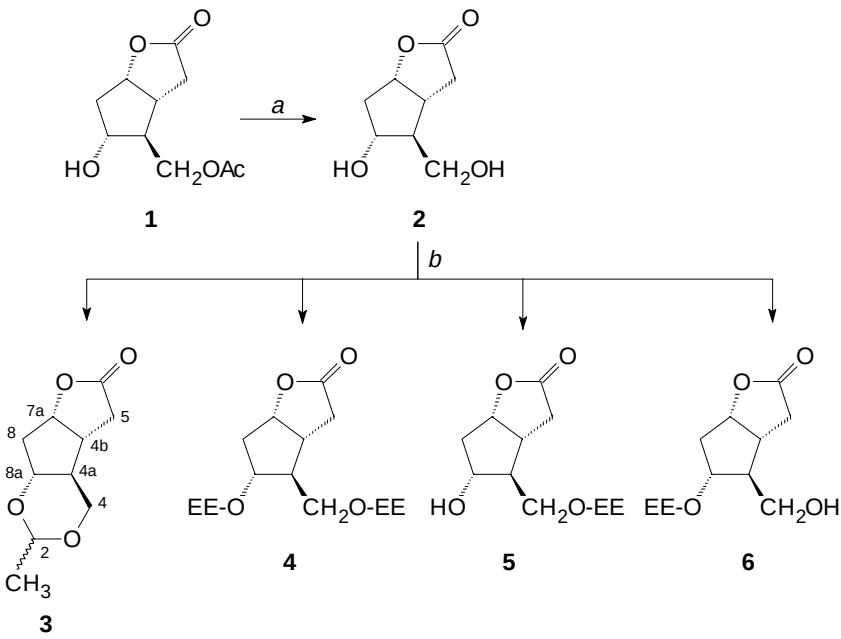
New synthesis of intermediates for the preparation of prostaglandin analogs of the E_1 series is described. The simple synthesis starts from commercially accessible Corey acetate **1** and makes use of simultaneous protection of the two hydroxy groups in the form of cyclic acetal. No expensive protecting reagents are required and the synthetic sequence leading to the end product is shorter.
Key words: Prostaglandins; Misoprostol; Acetals.

In the course of the last twenty years, the synthesis of prostanoids, particularly analogs of the E_1-series modified in the ω-chain, has been intensively studied[1]. This group of compounds exhibits significant cytoprotective activity and some analogues – Misoprostol[2], Riaprostol[3], and Mexiprostol[4] - are used for curing stomach and duodenal ulcers that represent an important medicinal problem[5]. The synthetic scheme for the preparation of prostaglandins of the series 2, introduced by Corey and coworkers[6,7], has not been successful for compounds of the series 1. These are often synthesized using the so-called "reversed approach"[8,9] that enables the synthesis of pharmacologically important E_1 prostaglandin analogs, modified in the bottom chain. Synthesis of important derivative *A*, used in these transformations, is described in several papers[6,7]. In the present communication we describe a new alternative approach to compounds of the type *A*, consisting in simultaneous protection of the two hydroxy groups in lactone **2** as cyclic acetal.



A

In the first step, the starting commercially accessible racemic (±)-(3aα,4α,5β,6aα)-4-(acetyloxymethyl)-5-hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-2-one (**1**) was converted almost quantitatively into (±)-(3aα,4α,5β,6aα)-5-hydroxy-4-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**2**) by transesterification with methanol in the presence of catalytic amount of sodium methoxide at room temperature (Scheme 1). Attempts to obtain the cyclic acetal by reaction with formaldehyde dimethyl acetal, catalyzed with *p*-toluenesulfonic acid were unsuccessful and led to complex mixtures of products. On the other hand, reaction of the diol **2** with acetaldehyde diethyl acetal in dichloromethane, catalyzed with *p*-toluenesulfonic acid, afforded in a high yield (87%) the desired (±)-(4aβ,4bα,7aα,8aα)-2-methylhexahydrofuro[3′,2′:3,4]cyclopenta[1,2-*d*]-1,3-dioxin-6(4*H*)-one (**3**) as a mixture of 2α- and 2β-diastereoisomers (**3a** and **3b**, respectively). One of the diastereoisomers (**3a**) was isolated in the crystalline state (m.p. 104–108 °C). As minor products, column chromatography of the reaction mixture afforded (±)-(3aα,4α,5β,6aα)-5-(1-ethoxyethoxy)-4-[(1-ethoxyethoxy)methyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**4**) (yield 5%), arising by reaction of diol **2** with two equivalents of the starting diethyl acetal, further the isomeric (±)-(3aα,4α,5β,6aα)-4-[(1-ethoxyethoxy)methyl]-5-hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-2-one (**5**) and



EE = 1-ethoxyethyl

a) CH_3OH, CH_3ONa; *b*) $CH_3CH(OC_2H_5)_2$

SCHEME 1

(±)-(3aα,4α,5β,6aα)-5-(1-ethoxyethoxy)-4-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**6**) in the yields of 2% and 1%, respectively. We found that even great excess of acetaldehyde diethyl acetal (200%) did not convert the side products **4–6** into the desired cyclic acetal **3**. The monoacetals **5** and **6** were not stable at room temperature and on standing for several days they turned into mixtures of acetals **3–6** and diol **2**.

The structure of compounds **4–6** was confirmed by independent syntheses. Treatment of diol **2** with ethyl vinyl ether in the presence of *p*-toluenesulfonic acid afforded the bisacetal **4**, reaction of acetate **1** with ethyl vinyl ether, followed by transesterification with methanol under the above-mentioned conditions, gave compound **6**. Analogous reaction starting from (±)-(3aα,4α,5β,6aα)-4-(hydroxymethyl)-5-[(*p*-phenylbenzoyl)-oxy]hexahydro-2*H*-cyclopenta[*b*]furan-2-one furnished selectively acetal **5**.

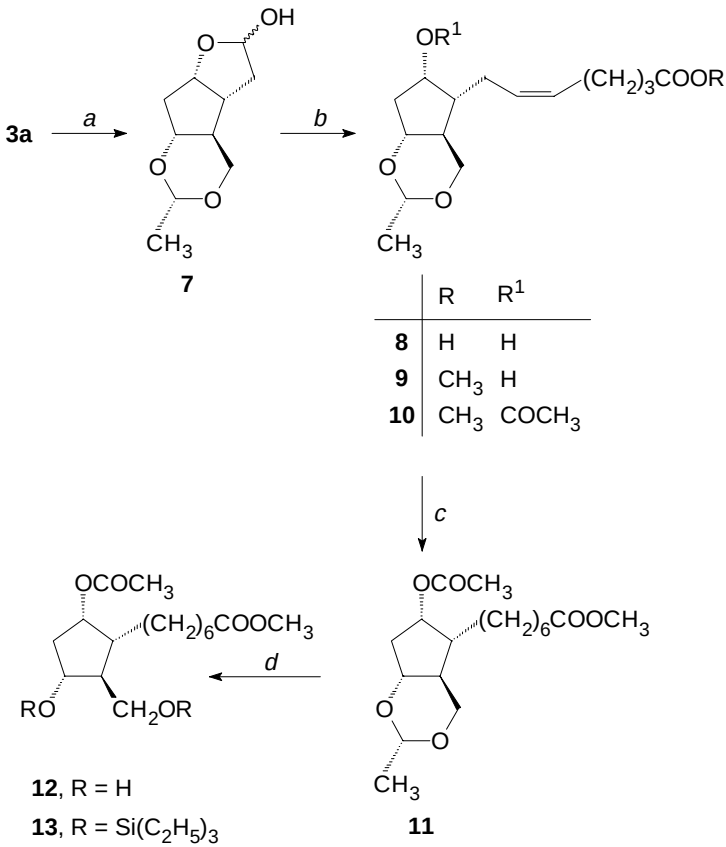
The presence of the 2α,2β-diastereoisomeric pair in the product **3** manifests itself by doubling of some proton signals in the ^{1}H NMR spectra, complicating thus their interpretation. Therefore, we performed a ^{1}H–^{1}H COSY study of the crystalline diastereoisomer **3a** and assigned unequivocally all the proton signals. By comparison with the spectrum of the diastereoisomeric mixture it was possible to assign also signals of the oily isomer **3b**. Both pairs differ practically only in the signals of the 1,3-dioxin ring protons and of the 2-methyl group. The configuration of the 2-methyl group (α or β) was assigned on the basis of the published ^{1}H NMR spectra and proton chemical shifts in *trans*-fused cyclopenta- and cyclohexa-1,3-dioxins[10,11]. Comparison of the shifts and coupling constants indicated that the 2-methyl group in the crystalline diastereoisomer **3a** occupies an equatorial position on the 1,3-dioxin ring and thus its configuration is 2α. Consequently, the isomer **3b** has configuration 2β.

Further synthetic transformations were performed both with mixtures of 2α,2β-diastereoisomers and with the pure diastereoisomer **3a** (for easier interpretation of spectral data). Since the results obtained in both synthetic sequences were identical, only the conversion of compound **3a** and its physicochemical data are described in the Experimental. The lactone grouping in compound **3a** was reduced with diisobutylaluminium hydride (DIBAH) in toluene at –78 °C (Scheme 2). The obtained (±)-(2α,4aβ,4bα,6αβ,7aα,8aα)-6-hydroxy-2-methylhexahydrofuro[3′,2′:3,4]cyclopenta[1,2-*d*] - 1,3(4*H*)-dioxin (**7**) was converted into (±)-(2α,4aβ,5α,6α,7aα)-[6-hydroxy-2-methylhexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]-5(*Z*)-heptenoic acid (**8**) by Wittig reaction with (4-carboxybutyl)triphenylphosphorane, generated from (4-carboxybutyl)triphenylphosphonium bromide with potassium *tert*-butoxide. The crude acid **8** was treated with anhydrous potassium carbonate and the resulting salt reacted with methyl iodide to give the corresponding methyl ester **9**.

The secondary hydroxyl in the ester **9** was protected by acylation with acetic anhydride in pyridine in the presence of catalytic amount of 4-dimethylaminopyridine and the obtained acetate **10** was hydrogenated over 10% Pd/C at atmospheric pressure to afford ester **11**.

Subsequent deprotection of the acetal with methanol in the presence of *p*-toluenesulfonic acid afforded smoothly methyl (±)-7-[(1α,2β,3α,5α)-5-acetyloxy-3-hydroxy-2-(hydroxymethyl)cyclopent-1-yl]heptanoate (**12**) in the yield of 90%. Standard reaction with chlorotriethylsilane[12] converted the diol **12** into the desired product, methyl (±)-7-[(1α,2β,3α,5α)-5-acetyloxy-3-(triethylsilyloxy)-2-[(triethylsilyloxy)methyl]cyclopent-1-yl]heptanoate (**13**). Selective oxidation of primary triethylsilyloxy group in the presence of a secondary one has already been described in detail[13–15].

In this study we also verified the approach (Scheme 3) consisting in introduction of the 9-oxo group (prostaglandin numbering), characteristic of prostaglandins of the E-series, under retention of the acetal protecting group. The aim of this approach was to circumvent the final oxidative conversion[16] of analogs of the F-series into those of



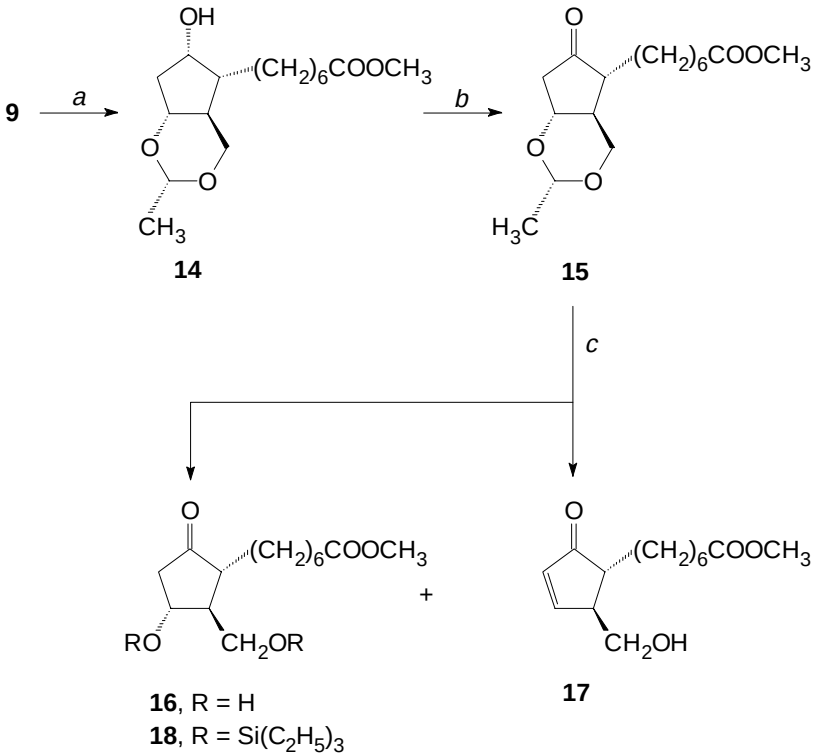
a) DIBAH; *b*) 1.$(C_6H_5)_3P{=}CH(CH_2)_3COOH$; 2. CH_3I, K_2CO_3; 3. $(CH_3CO)_2O$; *c*) H_2, Pd-C; *d*) 1. CH_3OH, TosOH; 2. $(C_2H_5)_3SiCl$

SCHEME 2

the E-series which often gives poor yields and is accompanied with side products of the A-series.

We made use of ester **9** which on standard hydrogenation at atmospheric pressure over 10% Pd/C in methanol afforded methyl (±)-(2α,4aβ,5α,6α,7aα)-[6-hydroxy-2-methylhexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]heptanoate (**14**) in an almost quantitative yield. The ester **14** was then oxidized with Jones reagent at –20 to –30 °C to give the desired methyl (±)-(2α,4aβ,5α,7aα)-[2-methyl-6-oxohexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]heptanoate (**15**) in the yield of 92%. Under the described reaction conditions, the acetal grouping in compounds **14** and **15** was stable.

However, this stability proved to be very disadvantageous in the next step, i.e., in the deprotection of both hydroxy groups. Commonly used reagents[12], such as pyridinium chloride, pyridinium fluoride, pyridinium trifluoracetate, iron(III) chloride, *p*-toluenesulfonic acid, or dilute hydrochloric or hydrobromic acid, were not effective and therefore we resorted to relatively strong acids: trifluroacetic or hydrofluoric acid. The



a) H_2, Pd-C; *b*) CrO_3 ,H_2SO_4; *c*) 1. aq. HF/SiO_2; 2. $(C_2H_5)_3SiCl$

SCHEME 3

deprotection of acetal **15** was accompanied with elimination of water and a considerable amount of methyl (±)-7-[(1α,2β)-2-(hydroxymethyl)-5-oxo-3-cyclopenten-1-yl]heptanoate (**17**) was isolated in addition to the desired methyl (±)-7-[(1α,2β,3α)-3-hydroxy-2-(hydroxymethyl)-5-oxocyclopent-1-yl]heptanoate (**16**). Only after using 40% aqueous hydrofluoric acid in the presence of silica gel in methanol we obtained the diol **16** in a very good yield (81%).

The diol **16** was converted into the corresponding methyl (±)-7-[(1α,2β,3α)-3-(triethylsilyloxy)-2-[(triethylsilyloxy)methyl]-5-oxocyclopent-1-yl]heptanoate (**18**), another important intermediate of the general formula *A*, suitable for the synthesis of prostanoids of the E-series.

We can conclude that we succeeded in elaboration of a novel and simple alternative preparation of important intermediates used in the synthesis of prostanoids of the series 1, modified in the ω-chain.

EXPERIMENTAL

The temperature data are uncorrected. The melting points were determined on a Boetius block. IR spectra were measured on a Nicolet 740 spectrometer in chloroform, wavenumbers are given in cm^{-1}. Proton and ^1H–^1H COSY NMR spectra (δ, ppm; *J*, Hz) were taken on a Bruker 400 instrument in deuteriochloroform. Mass spectra were obtained with a Jeol DX 300 spectrometer (electron energy 70 eV). The starting lactone **1** was a Spolana (Neratovice) product.

(±)-(3aα,4α,5β,6aα)-5-Hydroxy-4-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**2**)

To a solution of compound **1** (40.0 g, 0.187 mol) in dry methanol (250 ml) was added 1.5 M methanolic sodium methoxide (11 ml). The mixture was stirred at room temperature for 1 h and then neutralized with 0.85 M methanolic HCl (19.5 ml). The solid was filtered and the filtrate evaporated to dryness to yield 32.0 g (100%) of compound **2**, m.p. 116–117 °C (reported[17] m.p. 117–118 °C). Its IR and ^1H NMR spectra were identical with the published ones[18].

Reaction of Diol **2** with Acetaldehyde Diacetal

To a stirred suspension of diol **2** (31.3 g, 0.182 mol) in dry dichloromethane (310 ml) and acetaldehyde diethyl acetal (64.3 g, 0.545 mol) was added 40 ml of 0.2 M solution of anhydrous *p*-toluenesulfonic acid in dichloromethane. The mixture was stirred for 1 h at room temperature and then refluxed for 3.5 h. After cooling, the reaction was quenched by addition of solid potassium carbonate (5 g), the solid was filtered off and the filtrate was concentrated. The residue was dissolved in dichloromethane (200 ml), the solution washed with water and saturated solution of sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue crystallized from hexane–ethyl acetate to give 19.34 g (54%) of crystalline diastereoisomer **3a**, m.p. 104–108 °C. After concentration of the mother liquor, the residue was separated by column chromatography on silica gel in chloroform–methanol (1–5%). The chromatography afforded another portion (12.06 g) of compound **3** (mixture of diastereoisomers, total yield 87%), bisacetal **4** (2.70 g, 5%), monoacetal **5** (0.65 g, 2%) and monoacetal **6** (0.56 g, 1%).

Compound **3**: For $C_{10}H_{14}O_4$ (198.2) calculated: 60.59% C, 7.12% H; found: 60.47% C, 7.01% H. IR spectrum: 1 768 (CO). ^1H–^1H COSY NMR spectrum of diastereoisomer **3a**: 1.37 d, 3 H, *J* = 5.1

(CH_3); 1.69 dq, 1 H, J_1 = 4.2, J_2 = 10.8 (H-4a); 1.88 dt, 1 H, J_1 = 4.4, J_2 = 11.6 (H-8); 2.33 dtd, 1 H, J_1 = 1.5, J_2 = 7.4, J_3 = 13.7 (H-4b); 2.41 dd, 1 H, J_1 = 1.6, J_2 = 18.3 (H-5); 2.65 dt, 1 H, J_1 = 7.1, J_2 = 13.2 (H-5); 2.70 dd, 1 H, J_1 = 9.3, J_2 = 18.2 (H-8); 3.41 dt, 1 H, J_1 = 7.0, J_2 = 11.0 (H-8a); 3.58 t, 1 H, J = 10.7 (H-4); 4.29 dd, 1 H, J_1 = 4.3, J_2 = 10.7 (H-4); 4.70 q, 1 H (H-2); 4.90 dt, 1 H, J_1 = 4.4, J_2 = 7.2 (H-7a). ^{1}H NMR spectrum of diastereoisomer **3b**: 1.27 d, 3 H, J = 5.1 (CH_3); 1.64 m, 1 H, (H-4a); 1.88 dt, 1 H, J_1 = 4.4, J_2 = 11.6 (H-8); 2.33 dtd, 1 H, J_1 = 1.5, J_2 = 7.4, J_3 = 13.7 (H-4b); 2.41 dd, 1 H, J_1 = 1.6, J_2 = 18.3 (H-5); 2.65 dt, 1 H, J_1 = 7.1, J_2 = 13.2 (H-5); 2.70 dd, 1 H, J_1 = 9.3, J_2 = 18.2 (H-8); 3.41 dt, 1 H, J_1 = 7.0, J_2 = 11.0 (H-8a); 3.50 t, 1 H, J = 10.7 (H-4); 4.22 dd, 1 H, J_1 = 4.3, J_2 = 10.7 (H-4); 4.64 q, 1 H (H-2); 4.79 dt, 1 H, J_1 = 4.4, J_2 = 7.2 (H-7a).

Compound **4**: For $C_{16}H_{28}O_6$ (316.4) calculated: 60.74% C, 8.92% H; found: 60.46% C, 8.67% H. IR spectrum: 1 767 (CO). ^{1}H NMR spectrum: 1.18 dt, 6 H (CH_3); 1.27 dt, 6 H (CH_3); 2.11 m, 1 H; 2.18 m, 1 H; 2.36 m, 1 H; 2.55 m, 1 H; 2.70–2.85 m, 2 H; 3.38 m, 1 H; 3.45 m, 2 H; 3.57 m, 3 H; 3.98 m and 4.13 m, 1 H; 4.67 m, 1 H; 4.73 m, 1 H; 4.96 m, 1 H.

Compound **5**: For $C_{12}H_{20}O_5$ (244.3) calculated: 59.00% C, 8.25% H; found: 49.69% C, 8.07% H. IR spectrum: 3 609, 3 471 (OH), 1 767 (CO). ^{1}H NMR spectrum: 1.20 dt, 3 H (CH_3); 1.29 dd, 3 H (CH_3); 2.06 m, 2 H; 2.37 m, 1 H; 2.52 m, 2 H; 2.78 m, 2 H; 3.50 m, 1 H; 3.62 d, 2 H, J = 5.2; 4.05 q and 4.14 q, 1 H, J = 5.5; 4.74 q, 1 H, J = 5.5; 4.95 dt, 1 H, J_1 = 2.3, J_2 = 6.8.

Compound **6**: For $C_{12}H_{20}O_5$ (244.3) calculated: 59.00% C, 8.25% H; found: 49.77% C, 8.21% H. IR spectrum: 3 625, 3 480 (OH); 1 767 (CO). ^{1}H NMR spectrum: 1.21 t, 3 H, J = 7.2 (CH_3); 1.31 d, 3 H, J = 5.1 (CH_3); 1.79 s, 1 H (OH); 2.04 m, 2 H; 2.41 t, 1 H, J = 6.3; 2.47 m, 1 H; 2.64 m, 1 H; 2.82 t, 1 H, J = 8.3; 3.48 m, 2 H; 3.62 m, 2 H; 4.10 q, 1 H, J = 5.9; 4.70 dq, 1 H, J_1 = 2.8, J_2 = 6.9; 4.94 dt, 1 H, J_1 = 2.7, J_2 = 7.9.

(±)-(2α,4aβ,4bα,6αβ,7aα,8aα)-6-Hydroxy-2-methylhexahydrofuro[3′,2′:3,4]cyclopenta-[1,2-*d*]-1,3(4*H*)-dioxin (**7**)

A solution od DIBAH in toluene (26.5 ml of 1 M solution) was added during 20 min at –78 °C to a stirred solution of compound **3** (5.0 g, 25.2 mmol) in toluene (150 ml) under nitrogen. The mixture was stirred for 10 min and the reaction quenched by addition of methanol (7 ml). After warming to 0 °C, water (7 ml) was added dropwise and the mixture was stirred for 1.5 h. The solid was collected and washed with toluene (2 × 100 ml). The combined organic solutions were washed with saturated solution of sodium chloride (100 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 4.80 g (95%) of compound **7** as a nonvolatile oil. For $C_{10}H_{16}O_4$ (200.2) calculated: 59.98% C, 8.05% H; found: 59.86% C, 8.11% H. IR spectrum: 3 395, 3 264 (OH). ^{1}H NMR spectrum: 1.37 d, 3 H, J = 5.1 (CH_3); 1.70 m, 1 H; 1.96 dt, 1 H; 2.22 m, 1 H; 2.35 m, 1 H; 2.46 dt, 1 H; 3.38 dt, 1 H; 3.54 q, 1 H, J = 10.8; 4.30 dd, 1 H, J_1 = 4.3, J_2 = 10.7; 4.68 m, 2 H; 5.67 dd, 1 H, J_1 = 4.4, J_2 = 17.0 (CHOH).

Methyl (±)-7-[(2α,4aβ,5α,6α,7aα)-6-Hydroxy-2-methylhexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]-5(*Z*)-heptenoate (**9**)

A solution of potassium *tert*-butoxide (7.3 ml of 1.61 M solution) was added dropwise at 0 °C to a suspension of (4-carboxybutyl)triphenylphosphonium bromide (2.65 g, 6.0 mmol) in tetrahydrofuran (20 ml) under nitrogen. After 15 min, a solution of compound **7** (0.48 g, 2.4 mmol) in tetrahydrofuran (5 ml) was added in a single portion and the mixture was stirred at 0 °C for 3 h. The mixture was decomposed with water (5 ml), the organic layer was separated, washed with water (2 × 10 ml) and the combined aqueous layers were washed with benzene (10 ml). The aqueous solution was mixed with ether (30 ml) and the stirred mixture was adjusted to pH 5 by addition of saturated solution of sodium hydrogen sulfate. The ethereal layer was separated and the aqueous phase washed with

ether (2 × 20 ml). The combined ethereal solutions were dried over anhydrous magnesium sulfate and the solvent was evaporated. The obtained crude acid **8** was dissolved in acetone (25 ml), the solution was mixed with potassium carbonate (1.0 g) and methyl iodide (2 ml, 32 mmol), and the mixture was stirred at ambient temperature for 8 h. The solid was filtered and washed with acetone, the filtrate was concentrated and the residue was chromatographed on a column of silica gel in hexane–ethyl acetate (2 : 1) to give 0.61 g (85%) of oily ester **9**. For $C_{16}H_{26}O_5$ (298.4) calculated: 64.41% C, 8.78% H; found: 64.26% C, 8.93% H. IR spectrum: 3 613, 3 499 (OH), 1 731 (CO). ^{1}H NMR spectrum: 1.39 d, 3 H, J = 5.1 (CH_3); 1.46 m, 1 H; 1.59 m, 1 H; 1.72 m, 2 H; 2.12 m, 4 H; 2.20 m, 1 H; 2.32 t, 2 H, J = 7.4 (CH_2CO); 2.58 dt, 1 H, J_1 = 7.4, J_2 = 13.2; 3.27 dt, 1 H, J_1 = 7.6, J_2 = 11.0; 3.51 t, 1 H, J = 10.7; 3.68 s, 3 H (OCH_3); 4.25 dq, 2 H; 4.70 q, 1 H; 5.40 m, 2 H (CH=CH). Mass spectrum, *m/z* (%): 298 (M^+, 1), 280 (5), 267 (10), 255 (12), 225 (12), 205 (9), 187 (12), 154 (21), 109 (41), 95 (100), 81 (69), 69 (20), 55 (35).

Methyl (±)-7-[(2α,4aβ,5α,6α,7aα)-6-Acetyloxy-2-methylhexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]-5(*Z*)-heptenoate (**10**)

Acetic anhydride (5.5 g, 54 mmol) was added dropwise at 5 °C to a mixture of ester **9** (4.2 g, 14.1 mmol), pyridine (15 ml) and 4-dimethylaminopyridine (0.1 g). After stirring for 20 min at room temperature, the reaction mixture was diluted with ice-cold water (200 ml) and extracted with ethyl acetate (4 × 30 ml), the organic solution was washed with water, saturated solution of of sodium chloride, and dried over anhydrous magnesium sulfate. Evaporation of the solvent and filtration through a column of silica gel (eluent hexane–ethyl acetate 2 : 1) afforded 4.34 g (91%) of oily acetate **10**. For $C_{18}H_{28}O_6$ (340.4) calculated: 63.51% C, 8.29% H; found: 63.44% C, 8.13% H. IR spectrum: 1 733 (CO). ^{1}H NMR spectrum: 1.38 d, 3 H, J = 5.2 (CH_3); 1.58 m, 2 H; 1.68 m, 2 H; 1.79 m, 1 H; 2.06 s, 3 H (CH_3COO); 2.07 q, 2 H; 2.18 t (CH_2CO), 2 H, J = 6.4; 2.32 t, 2 H, J = 7.4; 2.65 dt, 1 H, J_1 = 7.3, J_2 = 13.6; 3.33 ddd, 1 H; 3.52 t, 1 H, J = 10.6; 3.67 s, 3 H (OCH_3); 4.27 dd, 1 H, J_1 = 4.1, J_2 = 10.6; 4.71 q, 1 H; 5.18 m, 1 H; 5.33 m, 2 H (CH=CH).

Methyl (±)-7-[(2α,4aβ,5α,6α,7aα)-6-Acetyloxy-2-methylhexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]-heptanoate (**11**)

Ester **10** (3.62 g, 10.6 mmol) was hydrogenated in methanol (50 ml) over 10% Pd/C (200 mg) at atmospheric pressure, using a standard apparatus. After consumption of the theoretical amount of hydrogen, the catalyst was filtered off and washed with methanol (10 ml). Evaporation of the solvent gave 3.35 g (92%) of oily ester **11**. For $C_{18}H_{30}O_6$ (342.4) calculated: 63.14% C, 8.83% H; found: 63.00% C, 8.77% H. IR spectrum: 1 732 (CO). ^{1}H NMR spectrum: 1.28 m, 6 H; 1.37 d, 3 H, J = 5.0 (CH_3); 1.46 m, 2 H; 1.58 m, 2 H; 1.78 m, 1 H; 2.05 s, 3 H (CH_3COO); 2.06 m, 2 H; 2.30 t, 2 H, J = 7.4 (CH_2CO); 2.66 dt, 1 H, J_1 = 7.3, J_2 = 13.6; 3.32 ddd, 1 H; 3.54 t, 1 H, J = 10.7; 3.66 s, 3 H (OCH_3); 4.27 dd, 1 H, J_1 = 4.1, J_2 = 10.5; 4.71 q, 1 H; 5.17 m, 1 H.

Methyl (±)-7-[(1α,2β,3α,5α)-5-Acetyloxy-3-hydroxy-2-(hydroxymethyl)cyclopent-1-yl]heptanoate (**12**)

Anhydrous *p*-toluenesulfonic acid (10 mg) was added at room temperature to a stirred solution of acetal **11** (1.06 g, 3.1 mmol) in methanol (10 ml). After stirring at room temperature for 12 h the mixture was partitioned between ethyl acetate (20 ml) and saturated solution of sodium chloride. The aqueous layer was extracted with ethyl acetate (2 × 10 ml) and the combined organic layers were washed with saturated solution of sodium hydrogen carbonate (10 ml) and saturated solution of sodium chloride. After drying over anhydrous magnesium sulfate and evaporation of the solvent, the residue was chromatographed on a silica gel column in chloroform containing 5% methanol. Yield 0.88 g

(90%) of oily diol **12**. For $C_{16}H_{28}O_6$ (316.4) calculated: 60.74% C, 8.92% H; found: 60.65% C, 8.55% H. IR spectrum: 3 630, 3 453 (OH), 1 730 (CO). ^{1}H NMR spectrum: 1.28 m, 6 H; 1.42 m, 1 H; 1.61 m, 4 H; 1.72 dd, 1 H, 1.95 m, 1 H; 2.06 s, 3 H (CH_3COO); 2.28 t, 2 H, J = 7.4; 2.38 t, 2 H; 3.56 dd, 1 H, J = 10.6; 3.68 s, 3 H (OCH_3); 3.91 dd, 1 H; 4.12 m, 1 H; 5.18 m, 1 H.

Methyl (±)-7-[(1α,2β,3α,5α)-5-Acetyloxy-3-triethylsilyloxy-2-[(triethylsilyloxy)methyl]cyclopent-1-yl]-heptanoate (**13**)

Chlorotriethylsilane (0.55 g, 3.6 mmol) was added dropwise at room temperature to a solution of diol **12** (0.48 g, 1.53 mmol) in pyridine (6 ml) and the mixture was stirred for 2 h. The reaction was quenched by addition of water (10 ml) and chloroform (10 ml). The aqueous layer was extracted with chloroform (3 × 10 ml) and the combined chloroform layers were washed with water (10 ml), saturated solution of sodium chloride (10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue chromatographed on a column of silica gel in hexane–ethyl acetate (4 : 1) to give 0.80 g (96%) of silylated product **13**. For $C_{28}H_{56}O_6Si_2$ (544.9) calculated: 61.72% C, 10.36% H; found: 61.55% C, 10.12% H. IR spectrum: 1 730 (CO). ^{1}H NMR spectrum: 0.58 m, 12 H (CH_2Si); 0.94 m, 18 H (CH_3); 1.27 m, 6 H; 1.39 m, 1 H; 1.61 m, 3 H; 1.77 m, 2 H; 2.03 s, 3 H (CH_3COO); 2.26 m, 3 H; 3.65 s, 3 H (OCH_3); 3.65 m, 2 H; 4.13 m, 1 H; 5.05 m, 1 H.

Methyl (±)-7-[(2α,4aβ,5α,6α,7aα)-6-Hydroxy-2-methylhexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]-heptanoate (**14**)

Ester **9** (0.72 g, 2.4 mmol) was hydrogenated in methanol (15 ml) at atmospheric pressure over 10% Pd/C (10 mg). After consumption of the theoretical amount of hydrogen, the mixture was filtered and the catalyst washed with methanol (10 ml). The filtrate was concentrated and the residue chromatographed on a column of silica gel in hexane–ethyl acetate (3 : 2) to give 0.71 g (98%) of ester **14**, m.p. 50.5–52.5 °C. For $C_{16}H_{28}O_5$ (300.4) calculated: 63.97% C, 9.40% H; found: 63.69% C, 9.34% H. IR spectrum: 3 610, 3 499 (OH), 1 730 (CO). ^{1}H NMR spectrum: 1.31 m, 5 H; 1.38 m, 2 H; 1.38 d, 3 H, J = 5.0 (CH_3); 1.50–1.64 m, 5 H; 1.74 m, 1 H; 2.30 t, 2 H, J = 7.4 (CH_2CO); 2.59 dt, 1 H, J_1 = 7.3, J_2 = 13.3; 3.27 dt, 1 H, J_1 = 7.4, J_2 = 11.0; 3.52 t, 1 H, J = 10.7; 3.67 s, 3 H (OCH_3); 4.24 m, 2 H; 4.70 q, 1 H. Mass spectrum, *m/z* (%): 300 (M^+, 2), 282 (2), 257 (12), 239 (7), 227 (8), 221 (11), 164 (35), 136 (21), 107 (15), 95 (100), 81 (45).

Methyl (±)-7-[(2α,4aβ,5α,7aα)-2-Methyl-6-oxohexahydrocyclopenta-1,3(4*H*)-dioxin-5-yl]-heptanoate (**15**)

Jones reagent (1.65 ml) was added dropwise at –20 to –30 °C to a stirred solution of ester **14** (0.71 g, 2.36 mmol) in acetone and the mixture was stirred for 10 min. The reaction was quenched by addition of 2-propanol (2 ml) and, after stirring for 5 min, the mixture was partitioned between chloroform (50 ml) and saturated solution of sodium chloride (200 ml). The organic phase was separated, washed with saturated sodium chloride solution (2 × 20 ml), dried over anhydrous magnesium sulfate, and the solvent was evaporated. Chromatography of the residue on a column of silica gel in benzene–ethyl acetate afforded 0.65 g (92%) of keto ester **15**. For $C_{16}H_{26}O_5$ (298.4) calculated: 64.41% C, 8.78% H; found: 64.34% C, 8.44% H. IR spectrum: 1 745 (CO). ^{1}H NMR spectrum: 1.30 m, 5 H; 1.40 d, 3 H, J = 5.1 (CH_3); 1.46 m, 2 H; 1.58–1.76 m, 4 H; 1.84 m, 1 H; 1.94 m, 1 H; 2.30 t, 2 H, J = 7.5 (CH_2CO); 2.33 dd, 1 H, J_1 = 11.7, J_2 = 17.7; 2.66 dd, 1 H, J_1 = 7.2, J_2 = 17.5; 3.68 s, 3 H (OCH_3), 3.75 t, 1 H, J = 10.5; 3.79 m, 1 H; 4.34 dd, 1 H, J_1 = 4.0, J_2 = 10.7; 4.92 q, 1 H. Mass spectrum, *m/z* (%): 298 (M^+, 2), 280 (2), 255 (5), 223 (15), 205 (11), 155 (20), 154 (33), 138 (21), 108 (25), 95 (100), 81 (37), 69 (39), 55 (50).

Methyl (±)-7-[(1α,2β,3α)-3-Hydroxy-2-(hydroxymethyl)-5-oxocyclopent-1-yl]heptanoate (**16**)

A solution of acetal **15** (2.79 g, 9.35 mmol) in methanol (30 ml) was mixed with silica gel (300 mg) and then hydrofluoric acid (4 ml of 40% solution) was added dropwise under stirring. The mixture was stirred at room temperature for 20 min, neutralized with triethylamine (6 ml) and diluted with chloroform (50 ml) and water (30 ml). The aqueous layer was extracted with chloroform (3 × 25 ml) and the combined organic solutions were washed with saturated solution of sodium hydrogen carbonate (30 ml) and saturated solution of sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue chromatographed on a column of silica gel in chloroform–methanol to give 2.07 g (81%) of oily compound **16**. Compound **17** (0.31 g, 13%; oil) was isolated as side product.

Compound **16**: For $C_{14}H_{24}O_5$ (272.3) calculated: 61.74% C, 8.88% H; found: 61.66% C, 8.47% H. IR spectrum: 3 623, 3 468 (OH), 1 737 (CO). ^{1}H NMR spectrum: 1.30 m, 5 H; 1.42 m, 1 H; 1.62 m, 4 H; 2.03 m, 2 H; 2.25 dd, 1 H, J_1 = 11.5, J_2 = 17.0; 2.31 t, 2 H, J = 7.5 (CH_2CO); 2.71 dd, 1 H, J_1 = 7.2, J_2 = 17.8; 3.68 s, 3 H (OCH_3); 3.75 m, 1 H; 3.97 d, 1 H, J = 10.2; 4.33 q, 1 H, J = 6.7. Mass spectrum, *m/z* (%): 272 (M^+, 1), 254 (1), 223 (1), 191 (1), 143 (20), 130 (40), 112 (24), 99 (100), 82 (27), 69 (20), 55 (35).

Compound **17**: For $C_{14}H_{22}O_4$ (254.3) calculated: 66.12% C, 8.72% H; found: 65.86% C, 8.54% H. IR spectrum: 3 625, 3 488 (OH), 1 729, 1 702 (CO), 1 590 (CH=CH). ^{1}H NMR spectrum: 1.28–1.47 m, 7 H; 1.61 m, 2 H; 1.74 m, 1 H; 2.11 m, 1 H; 2.31 t, 2 H, J = 7.5 (CH_2CO); 2.84 m, 1 H; 3.66 t, 1 H, J = 6.8; 3.68 s, 3 H (OCH_3); 3.81 dd, 1 H, J_1 = 5.3, J_2 = 10.5; 3.92 bs, 1 H (OH); 6.18 dd, 1 H, J_1 = 1.4, J_2 = 5.7 (CH=); 7.75 dd, 1 H, J_1 = 2.2, J_2 = 5.7 (=CHCO). Mass spectrum, *m/z* (%): 254 (M^+, 1), 223 (6), 192 (5), 181 (10), 121 (11), 112 (100), 94 (36), 83 (17), 66 (15), 55 (27).

Methyl (±)-7-[(1α,2β,3α)-5-Oxo-[(2-triethylsilyloxy)methyl]-3-(triethylsilyloxy)cyclopent-1-yl]-heptanoate (**18**)

Chlorotriethylsilane (2.08 g, 13.8 mmol) was added at 0–5 °C to a solution of ester **16** (1.57 g, 5.77 mmol) in pyridine (20 ml). After stirring at room temperature for 40 min, the reaction mixture was diluted with water (30 ml) and extracted with chloroform (3 × 30 ml). The extract was dried over anhydrous magnesium sulfate, the solvent evaporated, and the residue chromatographed on a column of silica gel in chloroform–methanol to give 2.56 g (89%) of oily silyl derivative **18**. For $C_{26}H_{52}O_5Si_2$ (500.9) calculated: 62.35% C, 10.46% H; found: 62.24% C, 10.23% H. IR spectrum: 1 735 (CO). ^{1}H NMR spectrum: 0.55 q, 12 H, J = 8.0 (CH_2Si); 0.91 t, 15 H (CH_3); 1.23 m, 5 H; 1.38 m, 1 H; 1.54 m, 4 H; 1.92 m, 1 H; 2.09 m, 1 H; 2.12 m, 1 H; 2.24 t, 2 H, J = 7.4 (CH_2CO); 2.57 ddd, 1 H, J_1 = 1.1, J_2 = 7.2, J_3 = 17.7; 3.58 dd, 1 H, J_1 = 3.8, J_2 = 10.2; 3.62 s, 3 H (OCH_3); 3.78 dd, 1 H, J_1 = 3.8, J_2 = 10.3; 4.27 q, 1 H, J = 6.9. Mass spectrum, *m/z* (%): 500 (M^+, 0.3), 471 (M – C_2H_5, 90), 339 (60), 217 (40), 205 (35), 189 (43), 161 (20), 151 (40), 133 (31), 117 (68), 115 (64), 103 (31), 87 (100), 75 (41), 67 (27), 59 (48).

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