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A NOVEL APPROACH TO THE SYNTHESIS OF 8-METHYL PROSTAGLANDINS

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Abstract—A synthesis of 8-methyl prostaglandins is described. Starting from a chiral cyclic keto lactone, C_1-homologation with dimethyl oxosulfonium methylide is used as key reaction in the sequence. 8-Methyl prostaglandin C_2 and its methyl ester proved to be quite unstable due to double-bond migration and dehydration.

Prostaglandins of type A (**1**) show considerable vasodilative action.[1] Unfortunately, the clinical use of prostaglandin A (**1**), particularly in patients with fixed essential hypertension, renal insufficiency or decreased blood flow in extremities[2] suffers from rapid deactivation into the practically inactive prostaglandins of the B-series (**3**).[3,4]

This metabolic pathway was found by Jones[5] to proceed via prostaglandin C (**2**), which displayed hypotensive activity three times higher than that of prostaglandin A (**1**) itself.[6]

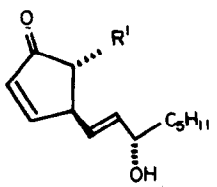
The transformation of C-prostaglandins (**2**) into those of the B-type (**3**) is blocked, if prostaglandin C bears a substituent at position 8, a methyl group being sufficient. Therefore, compounds such as 8-methyl prostaglandin C_2 (**4b**) may be expected to exhibit increased biological half-life period compared with prostaglandins A (**1**).

In 1973, Corey and Sachdev described the first, and up to now the only, synthesis of 8-methyl prostaglandin C_2 (**4b**) from achiral 2-methylcyclopentane-1,3-dione. In the course of this synthesis a resolution of diastereomeric (8R, 15S)- and (8S, 15S)-intermediates was necessary towards the end of the sequence to obtain optically active compounds, the configuration of the final product (**4b**), however, being provisionally assigned on the basis of biological data.[7]

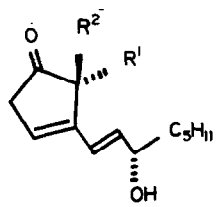
We have also been working on 8-methyl prostaglandin C_2 (**4b**) and now present a detailed report on a novel approach to the synthesis of 8-methyl prostaglandins, starting from the chiral keto lactone **10**, which was obtained originally[8] from secosteroid **5**,[9] an optically active intermediate in steroid total synthesis.[10]. Since the chirality of carbon atom 13 of secosteroid **5** is well established,[10,11] the configuration of the angular methyl group of keto lactone **10** is defined. Consequently, 8-methyl prostanoids prepared from keto lactone **10** have a "natural" configuration of carbon atom 8.

Recently, an improved synthesis of keto lactone **10** was realized by microbial reduction of either the allyl diketone **6**[12] or the propargyl diketone **7**[13] giving rise to the chiral hydroxy ketones **8** and **9**, respectively[14,15] which can be oxidized by potassium permanganate to afford keto lactone **10**.[16]

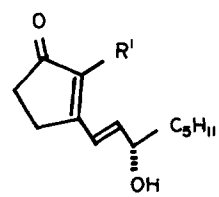
Keto lactone **10**, when treated with dimethyl oxosulfonium methylide (**11**)[17] generated from trimethyl oxosulfonium iodide and sodium hydride in dimethyl sulfoxide, yielded a 3:1 mixture of γ-lactone alcohol **16** and δ-lactone alcohol **17**. This mixture was equilibrated



1



2: R^2=H
4: R^2=CH_3



3

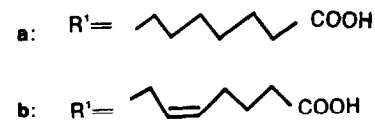
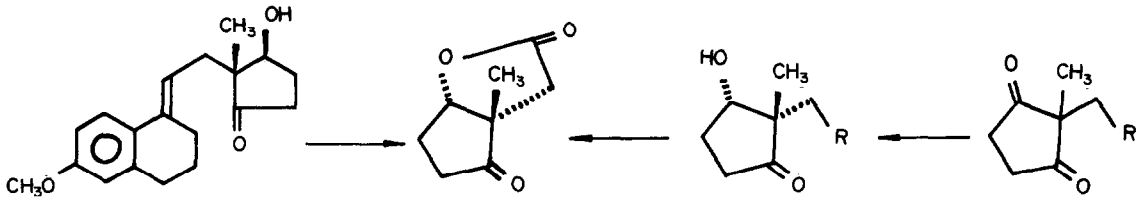


Chart 1.



5 10 8,9 6,7

6, 8: R=CH=CH2
7, 9: R=C≡CH

Chart 2.

with 1N aqueous potassium hydroxide to give the more stable γ-lactone alcohol **16** as single product (60–65% yield from **10**).

When alkali hydroxide was used as the base instead of sodium hydride to prepare oxosulfonium methylide **11**, the γ-lactone alcohol **16** could be obtained directly from keto lactone **10** in a 60% yield. Other applications of the alkali hydroxide/dimethyl sulfoxide system have been described[18]. The formation of the lactone alcohols **16** and **17** is thought to proceed via the initially formed spiroxiranes **12** and **13**, which undergo further rearrangement. The anticipated transition states of these epoxide rearrangements are schematically shown in **14** and **15**. As may be seen from the pictures, the alkoxide groupings, which arise by fission of α-epoxide **12** and β-epoxide **13** are clearly different in their spatial arrangements. In **15**, the alkoxide can attack the near γ-lactone carbonyl group, in **14**, the alkoxide group cannot. Thus, **15** may

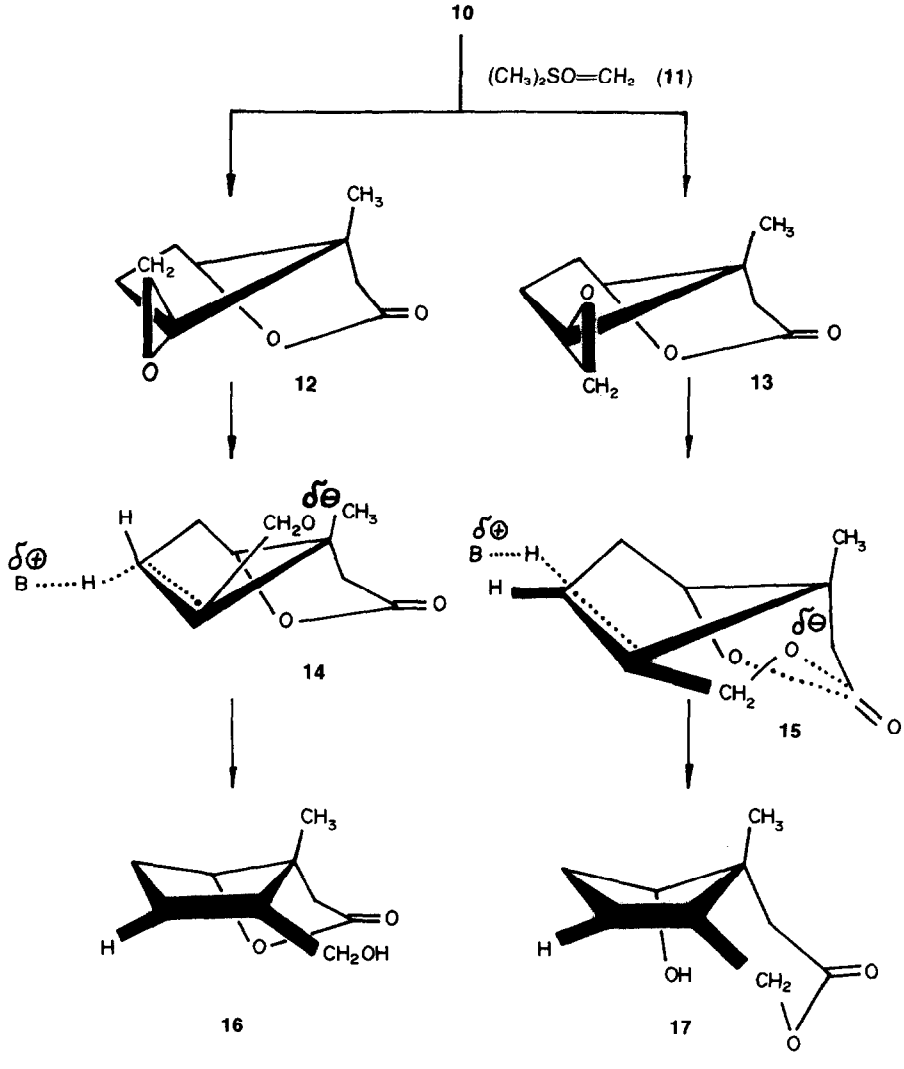


Chart 3.

lead to δ-lactone alcohol **17**, whereas **14** may afford γ-lactone alcohol **16**.

γ-Lactone alcohol **16** was oxidized by pyridinium chlorochromate in methylene chloride[19] or by the Jones reagent[20] to achieve aldehyde **18** (90% yield). Horner-Wadsworth-Emmons olefination[21,22] of aldehyde **18**, using the sodium salt of dimethyl 2 - oxo - heptylphosphonate **19**[23], then provided dienone **20** in 45–56% yield. This reaction could be performed either conventionally in dimethoxyethane with sodium hydride as base,[22] or simply with powdered alkali hydroxide as base in methylene chloride. Obviously, the latter reaction is a solid–liquid two-phase transfer process, self-catalyzed by the alkali salt of phosphonate **19**. Horner-Wadsworth-Emmons olefinations as self-catalyzed *liquid–liquid* two-phase transfer reactions were first described by Mikolajczyk *et al.*[24] After we had completed our own studies, Texier-Boullet and Fouchaud[25] published on *solid–liquid* phase transfer-catalyzed Horner-Wadsworth-Emmons reactions.

Dienone **20** was reduced with sodium borohydride in methanol at −20°C to give the (15-RS)-alcohol **21** (97% yield). Alternatively, alcohol **21** could be obtained in a low yield (12%), when aldehyde **18** was treated with the ylide derived from phosphonium iodide **22**. Crystalline phosphonium iodide **22**, was readily synthesized in a 72% yield when neat iodoheptyl ether **23** was allowed to react with triphenylphosphine under argon at 45°C for 16 days. Under these conditions no appreciable decomposition of phosphonium salt **22** occurred,[26] which was thought to be due to a favourable overlapping of phosphonium salt formation and thermal ether cleavage. An approach to the synthesis of (S)-chiral phosphonium salt **22**[27]: chloroheptan - 2 - one → (S) - chloroheptan - 2 - ol (microbiologically) → (S)-iodoheptan - 2 - ol → (S) - iodoheptan - 2 - ol, (α-ethoxy)ethylether → (S)-**22** is under study. Hitherto, on a preparative scale, the microbiological step of this sequence yielded products of 60% enantiomeric excess only.

Alcohol **21**, prepared either via dienone **20** or by use of phosphonium iodide **22**, was then treated with ethyl vinyl ether in the presence of catalytic amounts of pyridinium p-toluenesulfonate[28] to give the α-ethoxy ethylether **24** in 98% yield. This ether, when reduced with diisobutyl aluminium hydride[29] in hexane solution at −70°C, afforded lactol **25** practically quantitative.

To complete the upper prostaglandin side chain, lactol **25** was allowed to react with ylide **26** generated from 4-carboxybutyl triphenyl phosphonium bromide and sodium methyl sulfinylmethide in dimethyl sulfoxide.[30] Hydrolysis of the resulting prostaglandin ether **27** (obtained from **25** in a 78% yield) with pyridinium para-toluenesulfonate in ethanolic solution and purification of the product by layer chromatography furnished (15-RS)-8-methyl prostaglandin **28** as a pale yellow oil in 50% yield.

Oxidation of ether **27** by the Collins reagent[31] provided oxo-compound **29** in a moderate yield (40–65% without purification), converted into (15-RS)-8-methyl prostaglandin C_2 (**30**) upon ether cleavage by pyridinium p-toluenesulfonate in ethanol and chromatographic purification (40% yield). Compound **30** could be separated into two components by layer chromatography on silica gel, using two developments with the solvent system benzene (90), dioxane (10), acetic acid (1).[7] However, spectral investigations of the more polar isomer to which (15-S)-configuration[32] was assigned displayed that this chromatography was accompanied by an isomerization process (*vide infra*).

In order to increase the yield in the Collins oxidation, ether **27** was transformed into methyl ester **31** with etheral diazomethane solution. Oxidation of ether **31** to compound **32** succeeded in a 97% yield (without purification). The sequence was accomplished as described above by ether cleavage and chromatography, affording (15-RS)-8-methyl prostaglandin C_2 methylester **33** as a nearly colourless oil (50% yield).

Dienone **20** and the 9-oxo prostaglandins **29**, **30**, **32**, **33** proved to be considerably unstable. The low stability of 8-methyl prostaglandin **30** followed from spectral data in particular: The UV-spectrum of compound **30** beside the characteristic maximum at 235 nm[5,7] revealed a shoulder near 280 nm, which evolved to a new maximum at 283–285 nm, when the sample was stored or was subjected to thin-layer chromatography, e.g. to obtain the (15-S)-component (**4b**) (*vide supra*). After treatment with 0.01 N hydrochloric acid in methanol, 8-methyl prostaglandin **30** showed an additional long wavelength band at 328 nm (Figure).

Complementarily, samples of compound **30**, which showed intensive UV-absorption at 283–285 nm, displayed in their IR-spectra a decreased carbonyl stretching at 1750 cm^{-1} and an increase in the 1715 cm^{-1} band. These spectral results may be interpreted best by the assumption that the incompletely conjugated 9-oxo-11,13-diene system of compound **30** is transformed partially into the fully conjugated 9-oxo-10,12-diene structure **34**, which in turn undergoes dehydration to the 9-oxo-10,12,14-triene **35** under drastic conditions. (The

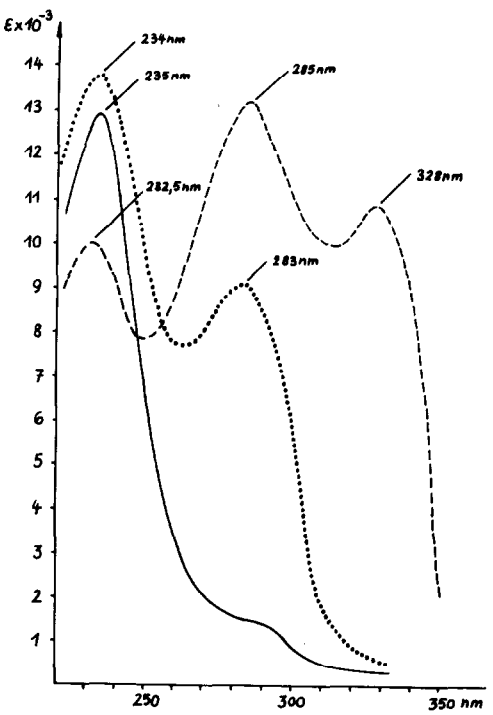


Fig. 1. ——, (15 - RS) - 8 - Methyl prostaglandin C_2, methyl ester (**33**); . . . , (15 - RS) - 8 - Methyl prostaglandin C_2 (**30**) after two-fold layer chromatography on silica gel; – – –, (15 - RS) - 8 - Methyl prostaglandin C_2 (**30**) in 0.01 N aqueous methanolic hydrochloric acid after 23 hr at room temp.

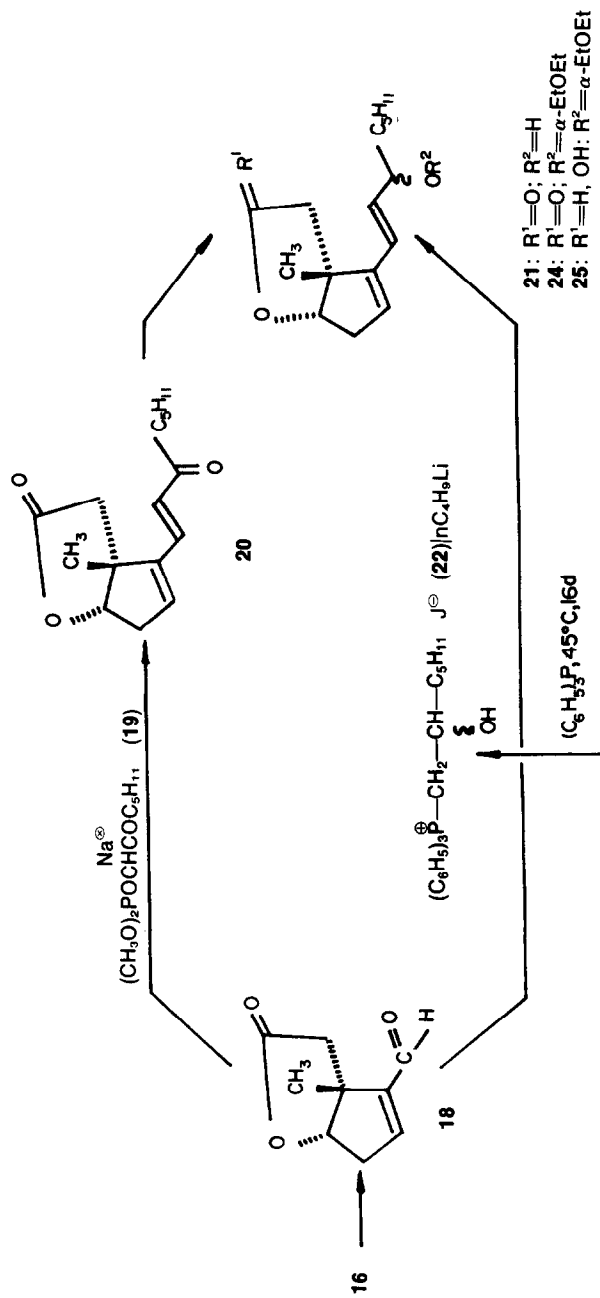
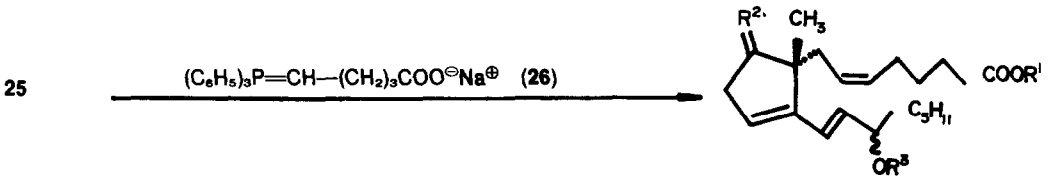
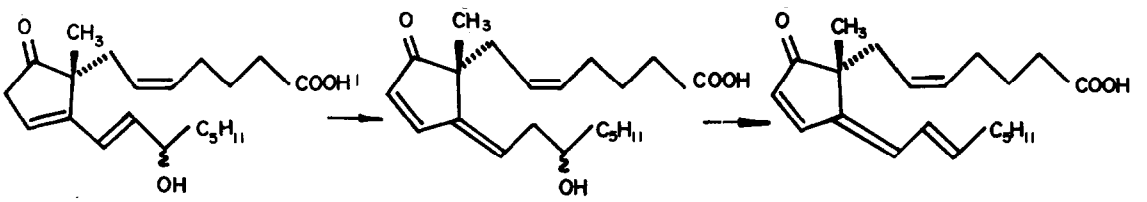

16
18
20
21: R¹=O; R²=H
24: R¹=O; R²=α-EtOEt
25: R¹=H, OH: R²=α-EtOEt
(α-EtOEt: α-Ethoxy-ethyl)

Chart 4.



27: R^1=H; R^2=α-OH, β-H; R^3=α-EtOEt
28: R^1=R^3=H; R^2=α-OH, β-H
29: R^1=H; R^2=O; R^3=α-EtOEt
30: R^1=R^3=H; R^2=O
31: R^1=CH_3; R^2=α-OH, β-H; R^3=α-EtOEt
32: R^1=CH_3; R^2=O; R^3=α-EtOEt
33: R^1=CH_3; R^2=O; R^3=H

Chart 5.



30 **34** **35**

Chart 6.

UV-absorption maximum of the 8-desmethyl derivative of compound **35** is located near 325 nm.[33])

(15-RS)-8-Methyl prostaglandin C_2 methyl ester (**33**) follows the same line in principle. Although its stability proved high enough to obtain practically pure samples for analytical and pharmacological purposes, chromatography of ester **33** to isolate the (15-S)-isomer or storage of the compound causes a spectral behaviour like that of acid **30**.

It is unknown yet, whether the isomerization of 8-methyl prostaglandin **30** into compound **34** will occur also in biological systems which, however, may be expected for energetic reasons. The published biological data of 8-methyl prostaglandin C_2 (**4b**)[7] as well as our own disappointing results obtained from screening tests of compound **30** and its methyl ester **33** (Unpublished results from our Department of Pharmacology, D. Hübler, A. Heinze and K.-H. Chemnitius) probably are related to such a transformation.

EXPERIMENTAL

Melting points were determined with a Mettler FP5. Optical rotations were measured with the photoelectric polarimeter Polamat A (VEB Carl Zeiss Jena); solvent chloroform, concentration 1 g per 100 ml, temperature +20°C, unless stated otherwise. UV-spectra were taken with UV-Specord and UV-VIS (VEB Carl Zeiss Jena) for methanolic solutions. IR-spectra were run with the UR 20 (VEB Carl Zeiss Jena). ^{1}H-NMR-spectra were recorded with the 80 MHz spectrometer BS 487c (Tesla, CSSR), using $CDCl_3$ solutions (unless stated otherwise) with tetramethylsilane as internal standard; ppm in δ-scale. Mass spectra were obtained with a Jeol mass spectrometer D 100 (Japan); the *m/e* values of molecular ions and characteristic fragment ions were determined by peak matching. Layer chromatography was performed using Kieselgel GF_{254} or PF_{254} (E. Merck, FRG).

[(1*S*,2*R*) - 1 - *Hydroxy* - 3 - *hydroxymethyl* - 2 - *methyl* - *cyclopent* - 3 - *en* - 2 - *yl*] - *acetic acid*, *γ-lactone* (**16**)

(A) The following reaction was run under an atmosphere of argon and under rigorously anhydrous conditions. A solution of dimethyl oxosulfoniummethylide (**11**) was prepared from sodium hydride (2.16 g, 90 mmol), trimethyl oxosulfonium iodide (19.8 g, 90 mmol), and dry dimethyl sulfoxide (100 ml) by stirring these components for 1 hr at room temp. [(1S, 2S) - 1 - Hydroxy - 2 - methyl - 3 - oxo - cyclopent - 2 - yl] - acetic acid, γ-lactone (**10**, 9.25 g, 60 mmol),[16] dissolved in dry dimethyl sulfoxide (50 ml) was added to the ylide **11** within 20 min at +7 to +10°C. The resulting mixture was stirred for 4 h, while the reaction temperature was allowed to reach room temp. After having cooled the solution again to 10°C, the reaction mixture was quenched with water (150 ml) and acidified with 1 M aqueous potassium hydrogen sulfate (pH 3–4). This solution was saturated with sodium chloride and extracted 10 times with ethyl acetate. The combined extracts, after having been dried over anhydrous sodium sulfate, were evaporated *in vacuo* giving rise to an oily mixture (9.0–9.6 g) of [(1S, 2S) - 1 - hydroxy - 3 - hydroxymethyl - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**16**) and [(1S, 2S) - 1 - hydroxy - 3 - hydroxymethyl - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, δ-lactone (**17**), which contained residual dimethyl sulfoxide. IR (film): 3340 (OH); (carbon tetrachloride) 1785, 1750 (CO) cm^{-1}. ^{1}H-NMR: 1.16 (s); 1.34 (s); 4.13 (m); 4.25 (m); 4.72 (m); 4.97 (m); 5.60 (1H, m)ppm. The mixture of the lactones **16** and **17** was dissolved in aqueous 1N sodium hydroxide (230 ml) at room temp. After 2 hr, the solution was thoroughly extracted with chloroform, then acidified with solid potassium hydrogen sulfate to pH 3 and extracted 10 times with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give [(1S, 2R) - 1 - hydroxy - 3 - hydroxymethyl - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**16**, 6.0–6.6 g, 60–65% yield) as a yellow oil which slowly crystallized. m.p. 49–52.5°C (diethyl ether); $[\alpha]_D$: +34.5°; IR (chloroform): 3620, 3490 (OH), 1770 (CO) cm^{-1}. ^{1}H-NMR: 1.29 (3H, s); 2.65 (AB, J_{AB} = 18.5 Hz, δ_{AB} = 0.42 ppm); 4.19 (2H, m); 4.67 (1H, m);

5.61 (1H, m). Found: C, 64.33; H, 7.15. $C_9H_{12}O_3$ requires: C, 64.27; H, 7.19%.

(B) The following reaction was run under an atmosphere of argon. 49.52 g (225 mmol) Trimethyloxosulfonium iodide and 9 g (225 mmol) powdered sodium hydroxide were stirred at room temp. in 110 ml dimethyl sulfoxide for 1 hr. To the suspension was added a solution of 23.12 g (150 mmol) keto lactone **10** in 100 ml dimethyl sulfoxide within 1 hr. Stirring was continued for 3.5 hr at room temp., followed by addition of 150 ml water. The resulting solution was acidified (pH 3) with 75 ml aqueous 1 M potassium hydrogen sulfate, saturated with sodium chloride and extracted 10 times with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to obtain 15.2 g (60% yield) [(1S, 2R) - 1 - hydroxy - 3 - hydroxymethyl - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone **16** as a yellow oil, which slowly crystallized. The IR- and ^{1}H-NMR-spectra of this substance were identical with the corresponding spectra of compound **16**, prepared by method A.

[(1S, 2R) - 3 - Formyl - 1 - hydroxy - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**18**)

(A) To a stirred solution of pyridinium chlorochromate (0.81 g, 3.75 mmol) in dry methylene chloride {3 ml, distilled over phosphorus (V)-oxide} was added a solution of [(1S, 2R) - 1 - hydroxy - 3 - hydroxymethyl - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**16**, 0.42 g, 2.5 mmol) in dry methylene chloride (3 ml). After having stirred the dark brown mixture at room temp. for 2 hr, the reaction was quenched with water (3 ml). The organic layer was separated and the aqueous phase was extracted 3 times with methylene chloride. All organic solutions were combined, washed with brine and dried over anhydrous sodium sulfate. The resulting solution was filtered through silica gel and evaporated *in vacuo* to give [(1S, 2R) - 3 - formyl - 1 - hydroxy - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**18**, 0.4 g, 96% yield) as a pale yellow oil. UV: 228.5 nm ($\log \epsilon = 3.96$); IR (chloroform): 2827, 2727 (=C–H), 1775 (lactone CO), 1685 (aldehyde CO), 1617 (C=C) cm^{-1}; ^{1}H-NMR: 1.44 (3H, s), 2.87 (AB, $J_{AB} = 18.5$ Hz, $\delta_{AB} = 0.45$ ppm), 4.74 (1H, m), 6.89 (1H, m), 9.74 (1H, s) ppm.

(B) At 15°C, Jones reagent (1.3 ml, 3.5 mmol) was added dropwise, with stirring, to a solution of γ-lactone alcohol **16** (0.85 g, 5 mmol) in acetone (2 ml). Stirring was continued for 2 hr. Then the reaction was quenched with water (5 ml) and the resulting solution saturated with sodium chloride. Extraction with ethyl acetate, drying of the extract with anhydrous sodium sulfate and evaporating *in vacuo* gave oily [(1S, 2R) - 3 - formyl - 1 - hydroxy - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**18**, 0.75 g, 89% yield), identical in all respects with aldehyde **18** prepared by method A.

[(1*S*, 2*R*) - 1 - *Hydroxy* - 2 - *methyl* - 3 - (3 - *oxo* - *oct* - (*E*) - *enyl*) - *cyclopent* - 3 - *en* - 2 - *yl*] - *acetic acid*, γ-*lactone* (**20**)

(A) The following reaction was run under an atmosphere of argon and under rigorously anhydrous conditions. A suspension of sodium hydride (42.5 mg, 1.77 mmol) and dimethyl - (2 - oxo - heptyl) - phosphonate (393 mg, 1.76 mmol) in dimethoxyethane (6 ml, freshly distilled over lithium aluminium hydride) was stirred at room temp. After 1 h, the evolution of hydrogen ceased and a thick white precipitate (**19**) was formed. To this mixture a solution of [(1S, 2R) - 3 - formyl - 1 - hydroxy - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**18**, 294 mg, 1.77 mmol) in dimethoxyethane (6 ml, freshly distilled over lithium aluminium hydride) was added dropwise. The reaction mixture was refluxed and stirred for 2 hr, then cooled to +5°C and carefully quenched with water (10 ml). The resulting solution was saturated with sodium chloride and extracted 5 times with 5 ml portions of ethyl acetate. All extracts were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a yellow oil (0.44 g), which was purified by layer chromatography on silica gel {ethyl acetate (9), isooctane (5), acetic acid (2) and water (10) were equilibrated and the upper phase was used as solvent system[34]}. Thus [(1S, 2R) - 1 - hydroxy - 2 - methyl - 3 - (3 - oxo - oct - (E) - enyl) - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**20**, 209 mg, 45% yield) was obtained as a nearly colourless oil.

(B) The following reaction was run under an atmosphere of argon. Lactone aldehyde **18** (3.0 g, 18 mmol), dimethyl - (2 - oxo - heptyl) - phosphonate (6.03 g, 27 mmol) and powdered potassium hydroxide (1.52 g, 27 mmol) in dry methylene chloride (30 ml) were stirred for 2 h at room temp. The resulting dark brown mixture was washed with 3N aqueous hydrochloric acid (cooling), with aqueous sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford 6.23 g brown oil. This oil was chromatographed as described in procedure (A) to give [(1S, 2R) - 1 - hydroxy - 2 - methyl - 3 - (3 - oxo - oct - (E) - enyl) - cyclopent - 3 - en - 2 - yl] acetic acid, γ-lactone (**20**, 2.65 g, 56% yield) as a pale yellow oil, which was kept at −70°C to crystallize after several weeks. m.p. 32.5–33.5°C (methanol); $[\alpha]_D$ +116°; UV: 274 nm ($\log \epsilon = 4.2$); IR (carbon tetrachloride): 1785 (lactone CO), 1695, 1675 (CO), 1615, 1590 (C=C), 985 (=C–H) cm^{-1}; ^{1}H-NMR: 0.87 (3H, t), 1.40 (3H, s), 2.56 (2H, t, J = 7.5 Hz), 2.72 (AB, $J_{AB} = 18$ Hz, $\delta_{AB} = 0.33$ ppm), 4.71 (1H, m), 6.12 (1H, m), 6.17 (1H, d), 7.17 (1H, d) ppm. Found: C, 73.32; H, 8.42. $C_{16}H_{22}O_3$ requires: C, 73.25; H, 8.45%.

{(1*S*, 2*R*) - 1 - *Hydroxy* - 3 - [(*RS*) - 3 - *hydroxy* - *oct* - (*E*) - *enyl*] - 2 - *methylcyclopent* - 3 - *en* - 2 - *yl*} - *acetic acid*, γ-lactone (**21**)

(A) To a solution of [(1S, 2R) - 1 - hydroxy - 2 - methyl - 3 - (3 - oxo - oct - (E) - enyl) - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**20**, 0.7 g, 2.64 mmol) in methanol (40 ml) was added sodium borohydride (160 mg, 4.23 mmol) at −20°C under stirring. Stirring was continued for 1 hr at −20°C. The reaction was then quenched with a few drops of acetic acid (pH 6) and the solution was concentrated *in vacuo*. The resulting residue was distributed between brine and ethyl acetate. After having separated the organic layer the aqueous phase was well extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give {(1S, 2R) - 1 - hydroxy - 3 - [(RS) - 3 - hydroxy - oct - (E) - enyl] 2 - methylcyclopent - 3 - en - 2 - yl} - acetic acid, γ-lactone (**21**, 0.685 g, 97% yield) as a colourless oil. $[\alpha]_D$: +67°; UV: 235 nm ($\log \epsilon$ 4.29); IR (carbon tetrachloride): 3625, 3490 (OH), 1785 (CO), 1655, 1625 (C=C), 975 (=C–H) cm^{-1}; ^{1}H-NMR: 0.93 (3H, t), 1.45 (3H, s), 2.82 (AB, $J_{AB} = 18$ Hz, $\delta_{AB} = 0.42$ ppm); 2.81 (AB, $J_{AB} = 18$ Hz, $\delta_{AB} = 0.39$ ppm); 4.21 (1H, m), 4.72 (1H, m), 5.69 (1H, m), 5.77 (1H, dd, J = 15.5 Hz, J = 5.5 Hz), 6.20 (1H, d, J = 15.5 Hz) ppm. MS: found *m/e* 264.1746 (M^+); $C_{16}H_{24}O_3$ calculated 264.1725.

(B) The following reaction was run under an atmosphere of argon and under rigorously anhydrous conditions. To a suspension of [(RS) - 2 - Hydroxy - heptyl] - triphenyl phosphonium iodide (**22**, 1.44 g, 2.85 mmol) in dry tetrahydrofuran (11.5 ml, freshly distilled over lithium aluminium hydride) was added at −70°C, with stirring, 5.7 mmol butyl lithium in n-hexane (nearly 20%). After stirring for 15 min at −25°C, a dark red brown, homogeneous solution of the ylide was formed, which again was cooled to −70°C. Then [(1S, 2R) - 3 - formyl - 1 - hydroxy - 2 - methyl - cyclopent - 3 - en - 2 - yl] - acetic acid, γ-lactone (**18**, 0.474 g, 2.85 mmol) in dry tetrahydrofurane (1.5 ml) was added dropwise. Stirring was continued for 15 min at −70°C and 1 h at 0°C. The yellow crystals formed were filtered off and washed with tetrahydrofurane. The tetrahydrofuran solutions were added to citrate buffer of pH 4 (40 ml) and this mixture was extracted with 25, 20 and 15 ml of methylene chloride. The methylene chloride extracts were combined, washed with 30 ml water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain a semicrystalline product (0.872 g), which after layer chromatography on silica gel (solvent system methylene chloride (8), ether (1)) gave {(1S, 2R) - 1 - hydroxy - 3 - [(RS) - 3 - hydroxy - oct - (E) - enyl] - 2 - methyl - cyclopent - 3 - en - 2 - yl} - acetic acid, γ-lactone (**21**, 90.5 mg, 12% yield), identical in all respects with compound **21** prepared by method A.

{(1*S*, 2*R*) - 1 - *Hydroxy* - 3 - [(*RS*) - 3 - (α - *ethoxy*)*ethoxy* - *oct* - (*E*) - *enyl*] - 2 - *methyl* - *cyclopent* - 3 - *en* - 2 - *yl*} - *acetic acid*, γ - *lactone* (**24**)

A mixture of {(1S, 2R) - 1 - hydroxy - 3 - [(RS) - 3 - hydroxy -

oct - (E) - enyl] - 2 - methyl - cyclopent - 3 - en - 2 - yl} - acetic acid, γ - lactone (**21**, 1.12 g, 4.24 mmol), pyridinium p-toluenesulfonate (0.35 g, 1.39 mmol), and ethyl vinyl ether (18 ml, freshly distilled) was stirred at room temp., until the solution turned homogeneous, the mixture was set aside for 1 hr, then diluted with ether (50 ml), washed with saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate and concentrated *in vacuo*, affording {(1S, 2R) - 1 - hydroxy - 3 - [(RS) - 3 - (α - ethoxy)ethoxy - oct - (E) - enyl] - 2 - methyl - cyclopent - 3 - en - 2 - yl} - acetic acid, γ-lactone (**24**, 1.40 g, 98% yield) as a yellow oil. $[\alpha]_D$ +89.5° (pyridine); UV: 235 nm (log ε 4.29); IR (film): 1780 (CO), 1655 (C=C), 1125, 1095, 1035 (C–O) cm^{-1}; ^{1}H-NMR (benzene-d_6): 2.30 (AB, J_{AB} = 18 Hz, δ_{AB} = 0.69 ppm), 2.30 (AB, J_{AB} = 18 Hz, δ_{AB} = 0.74 ppm); 3.39 (2H, q, J = 7 Hz); 4.00 (2H, m); 4.34–4.81 (1H, m); 5.10 (1H, m); 5.19–5.69 (1H, m); 5.91 (1H, d, J = 16.5 Hz) ppm; MS: found *m/e* 336.2299 (M^+), $C_{20}H_{32}O_4$ calculated: 336.2300.

{(1S, 2R) - 1 - Hydroxy - 3 - [(RS) - 3 - (α - ethoxy)ethoxy - oct - (E) - enyl] - 2 - methyl - cyclopent - 3 - en - 2 - yl} - acetaldehyde, γ - lactol (**25**)

The following reaction was run under an atmosphere of argon and under rigorously anhydrous conditions. To a mixture of {(1S, 2R) - 1 - hydroxy - 3 - [(RS) - 3 - (α - ethoxy)ethoxy–oct - (E) - enyl] - 2 - methyl - cyclopent - 3 - en - 2 - yl} - acetic acid, γ-lactone (**24**, 2.03 g, 6.04 mmol) and dry n-hexane (25 ml, freshly distilled over lithium aluminium hydride) was added with stirring, at −70°C, di-isobutyl aluminium hydride (10 mmol) in dry n-hexane (20.5 ml). After 10 min, a clear yellow solution was formed, which was stirred for a further 50 min. The reaction mixture then was quenched with methanol (5 ml) and allowed to reach room temp. A small portion of brine was added and the resulting precipitate filtered off after stirring for a further 45 min. The precipitate was washed with diethyl ether and the ether solutions were combined with the filtrate. The solution was dried over anhydrous sodium sulfate and evaporated *in vacuo*, to give {(1S, 2R) - 1 - hydroxy - 3 - [(RS) - 3 - (α - ethoxy)ethoxy - oct - (E) - enyl] - 2 - methyl - cyclopent - 3 - en - 2 - yl} - acetaldehyde, γ-lactol (**25**, 1.99 g, 97% yield) as a yellow oil. ^{1}H-NMR: 0.87 (3H, t); 1.39 (3H, s); 3.17–4.39 (3H, m); 4.51(1H, m); 4.71 (1H, m); 5.25–6.30 (4H, m) ppm.

(15-RS) - 15 - (α - Ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11, 13(E) - trienoic acid (**27**)

The following reaction was run under an atmosphere of argon and under rigorously anhydrous conditions. To a solution of sodium methylsulfinyl methide in dimethyl sulfoxide, prepared from sodium hydride (0.319 g, 13.3 mmol) and dry dimethyl sulfoxide (6 ml) was added dropwise, at room temp., a solution of (4 - carboxy)butyl - triphenylphosphonium bromide (2.94 g, 6.64 mmol) in dry dimethyl sulfoxide (10 ml). The dark red mixture (**26**) was stirred for 15 min and then treated with {(1S, 2R) - 1 - hydroxy - 3 - [(RS) - 3 - (α - ethoxy)ethoxy - oct - (E) - enyl] - 2 - methylcyclopent - 3 - en - 2 - yl} - acetaldehyde, γ-lactol (**25**, 0.56 g, 1.66 mmol) in dry dimethyl sulfoxide (5 ml). After stirring for 3 h and standing for 15 hr at room temp., the reaction was quenched by slowly adding the mixture dropwise to a vigorously stirred mixture of 2M aqueous potassium hydrogen sulfate solution (50 ml) and diethylether (50 ml) at 0°C. The phases were separated, the aqueous phase was well extracted with cold diethylether and the combined etheral extracts were carefully concentrated *in vacuo* up to 10 ml, followed by two intensive washings, at 0°C, with 1N aqueous sodium hydroxide solution (each time 25 ml). To the combined alkaline extracts, which were twice re-extracted with cold diethyl ether, were added diethylether (50 ml) and, under stirring and cooling (0°C), solid potassium hydrogen sulfate, to adjust pH 3–4. The organic layer was separated and the aqueous solution well extracted with cold diethylether. The combined solutions were washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*, achieving (15 - RS) - 15 - (α - ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11,13(E)-trienoic acid (**27**, 0.549 g, 78.5% yield) as a pale yellow oil pure enough for the next steps. An analytical sample was obtained by layer chromatography on silica gel (solvent system: cylohexane (1), ethyl acetate (1)). UV: 240 nm (log ε 4.10); IR (carbon tetrachloride): 3600–2400 (OH, COOH); 1715 (CO) cm^{-1}. ^{1}H-NMR: 0.91 (3H, s); 1.15 (3H, s); 1.75 (2H, t, J = 7 Hz); 3.34–4.31 (4H, m); 4.57–4.94 (1H, m); 5.30–6.0 (4H, m); 6.09 (1H, d, J = 15 Hz); 6.27 (m, absent after H/D-exchange). MS: found *m/e* 422 (M^+, weak); 376.2622 (M^+–C_2H_5OH; calculated 376.2617).

(15 - RS) - 9α, 15 - Dihydroxy - 8 - methyl - prosta - 5(Z), 11, 13(E) - trienoic acid (**28**)

(15 - RS) - 15 - (α - Ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11, 13(E)-trienoic acid (**27**, 0.17 g, 0.4 mmol) and pyridinium paratoluenesulfonate (11 mg, 0.047 mmol) in dry ethanol (3.4 ml) were stirred for 2 hr at room temp. The mixture was then diluted with diethyl ether (20 ml), the solution washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* affording a pale yellow oil (0.14 g), which was purified by layer chromatography on silica gel (solvent system: benzene (90), dioxane (10), acetic acid (1)) to give (15-RS) - 9α, 15 - dihydroxy - 8 - methylprosta - 5(Z), 11, 13(E) - trienoic acid (**28**, 71 mg, 50% yield) as a colourless oil. UV: 240 nm (log ε 4.1); IR (carbon tetrachloride) 3670–2400 (OH, COOH); 1715 (CO) cm^{-1}. ^{1}H-NMR (after H/D-exchange): 0.91 (3H, t); 1.12, 1.14 (3H); 3.93–4.37 (2H, m); 4.88–5.94 (4H, m); 6.07 (1H, d, J = 16 Hz) ppm. MS: found *m/e* 350 (M^+, weak); 332.2353 (M^+-H_2O; calculated 332.2351).

(15 - RS) - 8 - Methyl prostaglandin C_2 (**30**)

(15 - RS) - 15 - (α - Ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11, 13 (E)-trienoic acid (**27**, 0.95 g, 2.25 mmol) and freshly prepared chromium(VI) oxide/pyridine complex (3.53 g, 13.7 mmol) were stirred in dry methylene chloride (17 ml, distilled over phosphorus-V-oxide) at room temp. for 3 hr. Subsequently the dark brown complex was filtered off and carefully washed with ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a dark brown tar, which was well triturated with diethyl ether. Filtration of the combined etheral solutions over silica gel and evaporation *in vacuo* afforded (15 - RS) - 15 - (α - ethoxy)ethoxy - 8 - methyl - 9 - oxo - prosta - 5(Z), 11, 13(E) - trienoic acid (**29**, 0.38 g, 40% yield). IR (carbon tetrachloride): 1750 (CO), 1710 (COOH) cm^{-1}. Ether **29** (0.38 g, 0.9 mmol) and pyridinium p-toluenesulfonate, (30 mg, 0.12 mmol) were stirred in dry ethanol (8 ml) at room temp. for 4 hr. The reaction mixture was diluted with diethyl ether (50 ml), washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to obtain a pale yellow oil (0.35 g), which was purified by layer chromatography on silica gel (solvent system as used for compound **20**), affording (15 - RS) - 8 - methyl prostaglandin C_2 (**30**, 0.13 g, 41% yield) as a nearly colourless oil. UV: 235 nm (288 sh) (log ε 3.87); IR (carbon tetrachloride): 1750 (CO), 1710 (COOH), 1620 (C=C), 975 (=C–H) cm^{-1}; ^{1}H-NMR: 0.86 (3H, t); 1.19, 1.20 (3H); 2.29 (2H, t, J = 7 Hz); 2.84 (2H, m); 4.0–4.42 (1H, m); 4.75–6.06 (4H, m); 6.18 (1H, d, J = 16 Hz); 6.37–7.16 (m, absent after H/D-exchange) ppm. MS: found *m/e* 348.2320 (M^+), $C_{21}H_{32}O_4$ calculated 348.2300.

(15 - RS) - 15 - (α - Ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11, 13(E) - trienoic acid, methyl ester (**31**)

To a solution of (15 - RS) - 15 - (α - ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11, 13(E) - trienoic acid (**27**, 0.68 g, 1.6 mmol) in diethylether (2 ml) was added etheral diazomethane solution, until the evolution of nitrogen ceased. Excess diazomethane was destroyed by acetic acid followed by evaporation *in vacuo*, affording (15 - RS) - 15 - (α - ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11, 13(E) - trienoic acid, methyl ester (**31**, 0.7 g, practically quantitative yield). UV: 240 nm (log ε 4.16). IR (carbon tetrachloride): 3634 (OH), 1743 (CO) cm^{-1}. ^{1}H-NMR: 0.86 (m); 1.09, 1.10 (3H); 3.21–4.19 (3H, m); 3.64 (3H, s); 4.37–4.87 (1H, m); 5.42 (1H, m); 5.63 (1H, dd, J = 16 Hz, J = 7 Hz); 6.00 (1H, d, J = 16 Hz) ppm.

(15 - RS) - 8 - Methyl prostaglandin C_2 methyl ester (**33**)

(15 - RS) - 15 - (α - Ethoxy)ethoxy - 9α - hydroxy - 8 - methyl - prosta - 5(Z), 11, 13(E) - trienoic acid, methyl ester (**31**, 0.4 g, 0.92 mmol) was oxidized with freshly prepared chromium (VI)

oxide/pyridine complex (1.44 g, 5.6 mmol) in dry methylene chloride (5 ml, distilled over phosphorus (V) oxide) by analogy with the oxidation of acid **27**. After a reaction time of 2 hr and work up, methyl(15-RS)-15-(α-ethoxy)ethoxy-8-methyl-9-oxo-prosta-5(Z), 11, 13(E)-trienoic acid (**32**, 0.39 g, 97% yield) was obtained and treated, as described for compound **29**, with pyridinium paratoluenesulfonate (41 mg, 0.16 mmol) in dry ethanol (10 ml), followed by layer chromatography (solvent system as used for compound **20**) to achieve (15-RS)-8-methyl prostaglandin C_2 methyl ester (**33**, 0.16 g, 50% yield). UV: 235 nm (log ε 4.10). IR (carbon tetrachloride): 3625, 3535 (OH); 1745 (CO); 1725 (sh, CO); 1620 (C=C); 970 (=C-H) cm^{-1}. ^{1}H-NMR: 0.89 (3H, t); 1.22 (3H, s); 2.29 (2H, t, J = 7–8 Hz); 2.84 (2H, m); 3.65 (3H, s); 3.91–4.37 (1H, m); 4.95–5.60 (2H, m); 5.92 (1H, dd, J = 16.5 Hz, J = 5.5 Hz); 6.20 (1H, d, J = 16.5 Hz) ppm. MS: found *m/e* 362.2439 (M^+), $C_{22}H_{34}O_4$ calculated 362.2457).

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