for determination of its ^{13}C NMR spectrum, $[\alpha]^{25}_D$ 0.0 ± 1° (c 0.1, 95% EtOH). Other alkaloids were isolated: anabasine (463 mg), 1.61 × 10^4 dpm/mmol, $[\alpha]^{25}_D$ −0.3 ± 0.4° (c 4.3, $CHCl_3$); nicotine (1.5 mg), 1.3 × 10^3 dpm/mmol, $[\alpha]^{25}_D$ −102 ± 2° (75% MeOH);[27] nornicotine (8.5 mg), 1.8 × 10^4 dpm/mmol, $[\alpha]^{25}_D$ −51°[28] (c 0.4, $CHCl_3$); and anatabine (2.8 mg), 5.3 × 10^3 dpm/mmol, $[\alpha]^{25}_D$ −43° (95% EtOH).

That part of the TLC plate where 5-fluoronicotine would be expected to occur was extracted with methanol and diluted with inactive 5-fluoronicotine, which was then reisolated and crystallized as its perchlorate and dipicrate. The amount of activity in these derivatives was not significant.

N. glauca plants growing out of doors (July) were also fed 5-fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic acid (18.2 mg, 5.32 × 10^7 dpm/mmol). The plants were harvested after 14 days. The distribution of activity in the various fractions from the plant was essentially the same as that found in plants cultivated in a greenhouse: crude alkaloids, 9.75 × 10^6 dpm; aqueous ammoniacal layer, 1.71 × 10^7 dpm.

Registry No.—**1**, 22620-29-7; **2**, 3553-93-3; **3**, 68258-30-0; **5** dipicrate, 68258-31-1; **6**, monopicrate, 68258-32-2; 5-fluoro[5-^{13}C,6-^{14}C]nicotinic acid, 68258-33-3; 5-fluoro[5-^{14}C,6-^{13}C]nicotinic acid, 68317-60-2; 5-fluoro[5,6-$^{14}C_2$]nicotinic acid, 35286-42-1; (±)-5-fluoro[5-^{13}C,6-^{14}C]anabasine, 68258-34-4; (±)-5-fluoro[5-^{14}C,6-^{13}C]-anabasine, 68258-35-5; (±)-5-fluoro[5,6-$^{14}C_2$]anabasine, 68258-36-6.

References and Notes

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(28) This represents a 56% optical purity.

Synthesis of 9-Deoxy-11-oxoprostaglandins. Selective Reduction of an 11,15-Dione[1]

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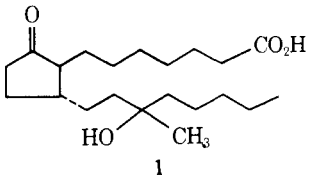
Prostaglandins containing an oxygen function at C-9 but not at C-11 have been reported to show a separation of biological activity. This prompted the synthesis of a 9-deoxy-11-oxoprostaglandin for evaluation. In this synthesis, which began with 4,7-dioxo-7-(*p*-methoxyphenyl)heptanoic acid (**5**), the 20 carbon atoms were assembled to afford a mixture of acyclic compounds, **17** and **18**. The five-membered ring of the prostaglandin system was obtained by coupling C-8 to C-12. The resultant 11,15-dioxoprostanoid **19** possesses an asymmetric center at C-4. Reduction by the Meerwein–Ponndorf–Verley procedure proceeded regioselectively but not stereoselectively at C-15.

The prostaglandins are extremely potent substances, and they display an extensive range of biological activities. Although they are flexible molecules, some have preferred conformations in solution as well as in the solid state.[2-6] The prostaglandins are usually unstable oils or low-melting solids. Hopes have been entertained that through structural modification stability can be imparted to them and a separation of biological activity can be achieved.

Beginning in the late 1960's Bagli et al.[7-9] reported the synthesis of several 9-oxygenated 15-hydroxyprostanoic acids (e.g., 1) without an oxygen function at C-11. A significant



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dissociation of activity was achieved with these compounds. Since the primary natural prostaglandins are oxygenated at both C-11 and -9, conceivably a similarly interesting separation of activity could be found in prostaglandins bearing an

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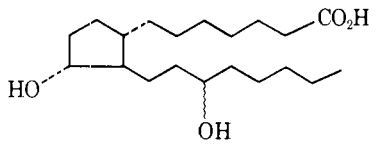
oxygen function at C-11 but not at C-9. This prompted us to undertake the synthesis of certain 9-deoxy-11-oxygenated prostanoids and to determine their biological effects. The observations of Caton et al.[10] that the 11,15-dihydroxyprostanoic acid **2** reduced pentagastrin-induced gastric secretions in rats gave added impetus to our investigation.

Compounds **2** with double bonds in various positions have also been synthesized.[11-13] The 11,15-dihydroxyprostenoic acids **3** and **4** were found to have the same activity as PGE_2 in



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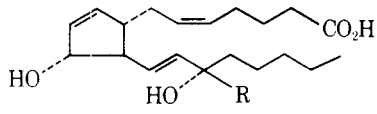


3, R = H
4, R = CH_3

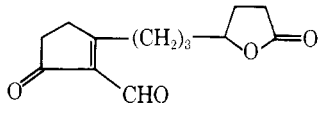
the isolated rat uterus preparation but less than 10% the activity of PGE_2 in the guinea pig ileum and the rat stomach fundus tests.[12]

The starting compound for our synthesis was 4,7-dioxo-7-(*p*-methoxyphenyl)heptanoic acid (**5**), which was prepared according to the procedure of Robinson and Koebner.[14,15] The benzoyl group was selectively reduced by catalytic hydrogenation. Although consideration was given to transforming the carbonyl group at C-4 also into a methylene group, it was decided for the intial phase of this work to reduce it merely to the alcohol stage. This would allow protection of the carboxyl group as the lactone. In addition, reduction to a hydroxyl group would generate a center of asymmetry which could have a directing influence on subsequent transformations.

Reduction of **6** was accomplished with sodium borohydride. Careful acidification furnished the hydroxy acid **7** instead of the corresponding lactone. Birch reduction[16,17] of the hydroxy acid, followed again by careful acidification, provided mainly the β,γ-unsaturated ketone **8**, which retained the hydroxy acid side chain. When a benzene solution of **8** was heated to reflux, the lactone **9** was obtained without migration of the double bond into the α,β position. Subsequently, it was found that 7-(*p*-methoxyphenyl)-4-oxoheptanoic acid (**6**) could be converted into the lactone **9** by Birch reduction followed by acid treatment and heating in benzene.

The β,γ-unsaturated ketone **9** was cleaved by ozonolysis to give the β-keto aldehyde **10**, which was found to be in equilibrium with the *s*-cis enol **11** in deuteriochloroform. The same equilibrium mixture was obtained by hydroxylating the β,γ-unsaturated ketone with osmium tetroxide and cleaving the resultant mixture of glycols with periodic acid. The ^1H NMR spectrum showed the presence of the vinyl protons of the enol as a pair of doublets. The magnitude of the coupling constant of the vinyl protons (J_{ab} = 5 Hz) was indicative that the enol **11** had the *s*-cis conformation.[18,19]

Attempted cyclization of the mixture of β-keto aldehyde **10** and its enol **11** under a variety of conditions failed to furnish the desired cyclopentenone aldehyde **12**. The prostanoid system was, however, successfully prepared by an alternate route. The carbonyl group of **9** was first protected. Although protection could be accomplished by conversion to either the ethylene ketal **13** or the dimethyl ketal **14**, the latter was



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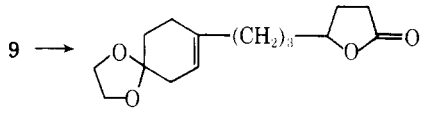

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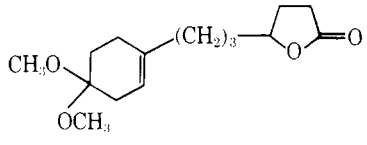

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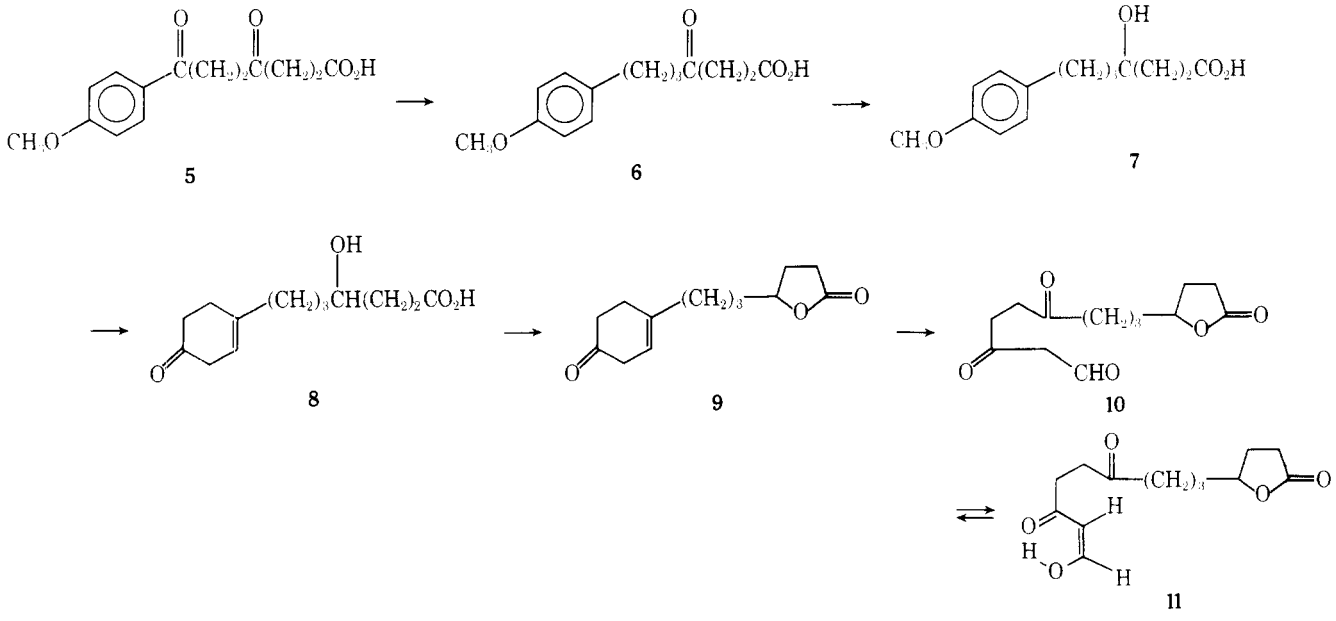
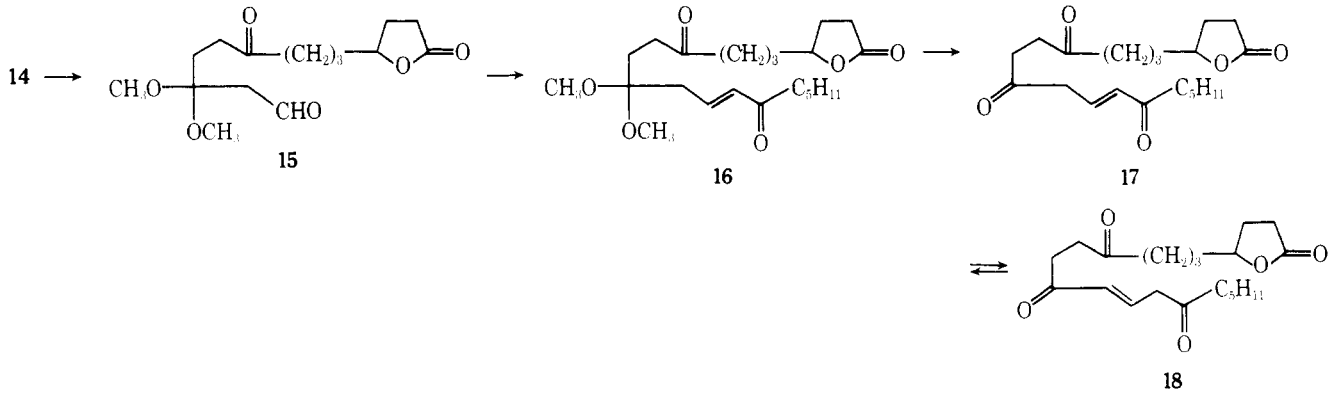
chosen for further elaboration because of the relative ease with which its protecting group could be subsequently removed. The dimethyl ketal was prepared by treating **9** with methanol in the presence of malonic acid.[22] Cleavage of the double bond in **14** was attempted with a variety of reagents with variable success. The best procedure consisted of ozonolysis in ethanol at 0 °C followed by hydrogenation[23] of the ozonized mixture over 5% palladium on charcoal at the same temperature to afford **15**. Conversion of **15** to the C-20 intermediate **16** was





15 16 17 18

accomplished by a Wittig condensation employing a slight excess of either 2-oxoheptyltriphenylphosphorane or dimethyl 2-oxoheptylphosphonate.[20,21] The phosphonate was the preferred reagent as triphenylphosphine oxide generated from the phosphorane interfered with the isolation of the product **16.**

Removal of the dimethyl ketal group in **16** was achieved with dilute hydrochloric acid in dioxane at room temperature. The crystalline product, obtained in 66% yield, was a 1:1 equilibrium mixture of the Δ^{13} and Δ^{12} isomers, **17** and **18.**

The α-methylene groups (C-12 and C-14) of the β,γ-unsaturated keto systems appeared as two sets of doublets in the NMR spectrum. One doublet was centered at δ 3.45 and the other at δ 3.40. In both sets of doublets the coupling constant was 7 Hz. Particularly illuminating was the olefinic proton pattern which appeared further downfield. In one of the isomers, the proton at C-13 was a doublet of triplets centered at δ 7.02 with coupling constants of 16, 7, and 7 Hz. The adjoining vinyl proton was a doublet centered at δ 6.20 with a coupling constant of 16 Hz. In the other isomer, the C-13 proton was likewise a doublet of triplets, but centered at δ 6.95 with coupling constants also of 16, 7, and 7 Hz. The adjacent vinyl proton was a doublet centered at δ 6.20 with a coupling constant of 16 Hz, as with the other isomer.

With all 20 carbon atoms of the prostaglandin system assembled, an effort was made to join C-8 to C-12. The two most active methylene groups in the acyclic mixture **17** and **18** are C-12 and C-14, respectively. Condensation between C-8 and C-14 would give rise to a seven-membered ring compound. Although, a priori, cyclization would favor formation of the five-membered ring system, conditions were sought which would not only minimize formation of the seven-membered ring compound but would also suppress a Michael addition of either C-7, C-9, or the solvent across the conjugated double bond.

These conditions were met by conducting the cyclization in dilute aqueous sodium hydroxide at room temperature. Within a short time, the mixture of ketones **17** and **18** cyclized preferentially to afford the 11,15-dioxoprostaglandin derivative **19** in greater than 60% yield. The course of the reaction was followed by observing the development of the ultraviolet absorption maximum characteristic of the desired compound **19.** The pure crystalline product displayed an absorption maximum at 275 nm.

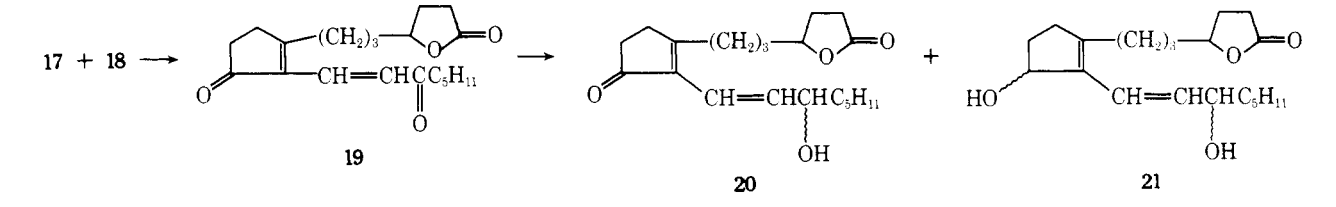
The olefinic protons appeared as a pair of doublets with a coupling constant of 16 Hz, which indicated that the double bond had the *E* configuration and that cyclization had proceeded in the desired manner. Had cyclization involved C-14 instead of C-12, the double bond would have been endocyclic and part of the dihydrotropone system, in which case it would have had the *Z* configuration, and the coupling constant would have been substantially less than 16 Hz.[24]

Application of the Meerwein–Ponndorf–Verley procedure[25,26] resulted in a selective reduction of the carbonyl group at C-15. Either freshly prepared aluminum isopropoxide or aluminum *sec*-butoxide in refluxing isopropyl alcohol could be employed. The yield of the major product **20** was 80%. A byproduct of the reduction was the 11,15-diol **21.** No product was obtained in which the C-11 carbonyl group was reduced exclusively. The identity of the major product was established by NMR spectroscopy. The C-14 proton was found to be coupled not only to the proton at C-13 but also to that at C-15.

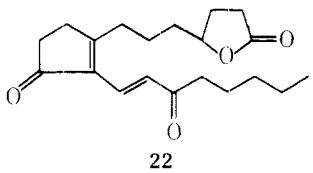
The Meerwein–Ponndorf–Verley reduction proceeded regioselectively. Conceivably, the reagent had formed a complex with the lactone ring prior to the reduction of the carbonyl group at C-15. The apparent juxtaposition of C-15 to the chiral center at C-4 suggested the possibility of asymmetric induction at C-15, in which case the reduction would not only be regioselective but stereoselective as well.

Although the ^{1}H NMR spectrum, as well as the TLC and VPC results, suggested that the 15-hydroxy compound **20** was homogeneous, studies employing the europium shift reagent Eu(fod)$_3$ clearly indicated the presence of two diastereomeric racemates in an approximate ratio of 1:1. The europium reagent altered the position of the chemical shift of the C-14 olefinic proton in the two racemates to different extents. In the absence of the shift reagent, the proton at C-13 appeared as a doublet while that at C-14 appeared as a doublet of doublets. In the presence of the europium shift reagent, there was one set of doublets but two sets of doublet of doublets for the C-13 and C-14 protons, respectively. Thus, the Meerwein–Ponndorf–Verley reaction proceeded regioselectively but not stereoselectively in the reduction of the 11,15-dione **19.**

Failure to achieve stereoselective reduction at C-15 suggests that the dione **19** may not have the hairpin conformation **22** of some of the natural primary prostaglandins.[2-6] In order for **19** to have this conformation, the diene system of **19** would have to assume the *s*-cis conformation. Thermodynamically, the more stable conformation of 1,3-butadiene is *s*-trans.[27-29] If it is assumed that the $\Delta^{8(12),13}$-diene system of **19** is *s*-trans and that the C-15 carbonyl group is turned inwardly so that the oxygen atom is syn periplanar with C-13, then the ω side chain of **23** would be perpendicular to the α side chain. The



19 20 21



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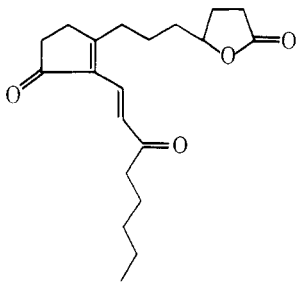

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compound would have the L-shape conformation which was postulated for PGB_1 by DeTitta on the basis of X-ray diffraction studies.[5] This latter substance is also a $\Delta^{8(12),13}$-prostaglandin.

If, on the other hand, the C-15 carbonyl group is directed outwardly, then the ω side chain beyond C-15 would turn back toward the α side chain so that it would be more or less aligned with the α chain. In either event,[30] the carbonyl group at C-15 would be expected to be at a distance from the lactone ring. Hence, complexation of the aluminum alkoxide to the lactone ring does not appear likely to be the reason for the preferential reduction of the C-15 carbonyl group of the 11,15-dione **19**. Other factors will have to be considered.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were taken in deuteriochloroform on a Varian A-60A or a Varian EM-390 90-MHz spectrometer with tetramethylsilane used as an internal standard. IR and UV spectra were determined in chloroform and methanol, respectively. Compounds containing an asymmetric center are racemic.

4-Oxo-7-(*p*-methoxyphenyl)heptanoic Acid (6). A solution of 50.0 g (189.3 mmol) of 4,7-dioxo-7-(*p*-methoxyphenyl)heptanoic acid (**5**) in 500 mL of 95% ethanol was hydrogenated over 8.0 g of palladium black at 49 psi and 50 °C. After 5 h, the catalyst was removed by filtration. The filtrate was distilled to dryness under reduced pressure. The residue was crystallized from methylene chloride–hexane to afford 43 g (90%) of **6**: mp 88–89 °C; IR 1715, 1700, 1615, 1585 cm^{-1}; NMR δ 3.78 (s, 3 H, OCH_3); UV 224 nm (ϵ 10 800). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.18; H, 7.17.

4-Hydroxy-7-(*p*-methoxyphenyl)heptanoic Acid (7). To a stirred suspension of 7.9 g (31.6 mmol) of **6** in 400 mL of isopropyl alcohol, cooled in an ice bath, was added portionwise over 0.5 h 8 g of sodium borohydride. The reaction mixture was stirred in the ice bath for 3.5 h. Then it was diluted with water and carefully acidified with 10% hydrochloric acid. The resultant mixture was extracted with cold methylene chloride. The methylene chloride extract was washed with water and dried over sodium sulfate. The solvent was removed by distillation under reduced pressure at a temperature below 40 °C. The residue was crystallized from cold ether–hexane to furnish 6.7 g (84%) of **7**: mp 67–68 °C; IR 3630, 3520, 1715 cm^{-1}; NMR δ 3.75 (s, 3 H, OCH_3). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.68; H, 8.14.

4-Hydroxy-7-(4-oxo-1-cyclohexenyl)heptanoic Acid γ-Lactone (9). A. A solution of 20.0 g (79.3 mmol) of **7** in 500 mL of dry isopropyl alcohol was added to 1 L of ammonia which had been distilled over sodium. To this stirred mixture was added portionwise 10 g of lithium metal over a period of 10 min. When the reaction mixture turned white, an additional 5 g of lithium was added in small portions. The mixture was stirred until it turned colorless (ca. 20 min). To this mixture was slowly added 150 mL of ethanol followed by 240 mL of water. The ammonia was removed by evaporation, and the residue was cooled in an ice bath and carefully acidified with concentrated hydrochloric acid. The acidified mixture was extracted with cold methylene chloride. The methylene chloride extract was washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure to afford an oily product which consisted mainly of **8**. In a separate run, 1.0 g of **7** furnished 0.89 g of **8** also as an oil: IR 3700, 3620, 3520, 1770 (weak), 1720 cm^{-1}; NMR showed no lactone proton at δ 4.5.

The hydroxy acid **8** from the larger run was dissolved in ca. 600 mL of benzene and heated to reflux, using a Dean-Stark trap, for 2.5 h. The reaction mixture was concentrated under reduced pressure to give 18 g of a red oil that was chromatographed on 360 g of silica gel. Elution with 20% ethyl acetate–benzene gave 11 g (62%) of **9** as an oil: IR 1775, 1720 cm^{-1}; NMR δ 5.50 (m, 1 H, olefin H), 4.51 (m, 1 H, lactone H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.84; H, 8.32.

B. The same product **9** was obtained when 4-oxo-7-(*p*-methoxyphenyl)heptanoic acid (**6**) was used in place of the corresponding 4-hydroxy compound **7** following the aforesaid procedure.

4-Hydroxy-8,11,13-trioxotridecanoic Acid γ-Lactone (10). A. A solution of 0.5 g (2.25 mmol) of **9** in 10 mL of dioxane was added to a solution of 1.0 g of osmium tetroxide in 10 mL of dioxane. The reaction mixture was stirred for 20 h, after which hydrogen sulfide was bubbled into the mixture for 40 min. Celite was added, and the resultant mixture was filtered. The filter cake was washed with ethanol. The combined filtrate and washings were distilled to dryness under reduced pressure to afford as an oil 0.5 g (83%) of the corresponding diastereomeric mixture of diols: IR 3620, 3580, 3490, 1775, 1720 cm^{-1}; NMR δ 4.51 (m, 1 H, lactone H).

To a solution of 0.18 g (0.7 mmol) of the diol mixture in 2 mL of methanol and 0.1 mL of pyridine was added 0.19 g of periodic acid in 0.8 mL of water. The reaction mixture was stirred for 15 min at room temperature, after which it was diluted with water and extracted with methylene chloride. The extract was successively washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure to give 0.14 g (78%) of a tautomeric mixture of **10** and **11** in the form of an oil: IR 1775, 1725, 1645, 1600 cm^{-1}; NMR δ 9.79 (t, CHO, J_{ax} = 2 Hz), 7.56 (d, olefin H, J_{ab} = 5 Hz), 5.57 (d, olefin H, J_{ab} = 5 Hz), 4.50 (m, lactone H).

B. A solution of 1.4 g (6.3 mmol) of **9** in 75 mL of methylene chloride was treated with a stream of ozone and oxygen at −70 °C until a blue color appeared. Zinc dust (2.5 g) and 25 mL of 75% acetic acid in water was added, and the reaction mixture was stirred in an ice bath for 1.5 h. The mixture was filtered, and the filtrate was diluted with cold methylene chloride. The organic phase was separated and successively washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure to afford 1.2 g (75%) of an oil which consisted of **10** in equilibrium with its enol tautomer **11**. The product proved to be identical with that afforded by the preceding procedure.

4-Hydroxy-7-(4,4-dimethoxy-1-cyclohexenyl)heptanoic Acid γ-Lactone (14). To a solution of 4.1 g (18.4 mmol) of **9** in 40 mL of methanol was added a solution of 2.0 g of malonic acid in 20 mL of methanol.[22] The reaction mixture was stirred at room temperature for 7 h. Then it was cooled in an ice bath and made basic with 5% sodium bicarbonate. The alkaline mixture was extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure. The residue was chromatographed on 200 g of silica gel. Elution with 50% ethyl acetate–hexane afforded 3.8 g (84%) of the dimethyl ketal **14** as an oil: IR 1775 cm^{-1}; NMR δ 3.20 (s, 6 H, OCH_3), 4.50 (m, 1 H, lactone H).

11-Dimethoxy-8,13-dioxo-4-hydroxytridecanoic Acid γ-Lactone (15). A solution of 5.0 g (20.5 mmol) of the ketal **14** in 250 mL of ethanol was cooled in an ice bath, and the calculated amount of ozone was bubbled into the solution. The reaction mixture was flushed with nitrogen. After 0.62 g of 5% palladium on charcoal was added, the mixture was hydrogenated at 45 psi at 0 °C.[23] The catalyst was removed by filtration after 45 min. The filtrate was distilled nearly to dryness under reduced pressure, and the residue was extracted with benzene. The benzene extract was dried over sodium sulfate and then distilled to dryness under reduced pressure to afford 4.99 g (79%) of **15** as an oil: NMR δ 9.70 (t, 1 H, CHO), 3.23 (s, 6 H, OCH_3). Without further purification the oil was used for the next step.

(*E*)-11,11-Dimethoxy-8,15-dioxo-4-hydroxyeicos-13-enoic Acid γ-Lactone (16). A solution of a phosphonate ylide was prepared by adding 5.52 g (25 mmol) of dimethyl 2-oxoheptylphosphonate to a solution of sodium methylsulfinyl methide prepared from 0.975 g (20.3 mmol) of 50% sodium hydride dispersed in mineral oil and 15 mL of dimethyl sulfoxide.

The ylide solution was diluted with an additional 15 mL of dimethyl sulfoxide, after which it was added dropwise over a period of 1 h under nitrogen to a solution of 5.0 g (16.7 mmol) of the aldehyde **15** in 30 mL of dimethoxyethane cooled in an ice bath. The reaction mixture was stirred in the ice bath for 5 min. Then it was poured into ice water. The resultant mixture was extracted with benzene. The benzene extract was successively washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure. The residue was chromatographed on 160 g of silica gel. Elution with 75% ethyl acetate–hexane gave 2.9 g (44%) of **16** as an oil: IR 1775, 1720, 1675, 1635 cm^{-1}; NMR δ 6.80 (dt, 1 H, C-13 H, J_{ab} = 16 Hz, J_{ax} = 5 Hz), 6.12 (d, 1 H, C-14 H, J_{ab} = 16 Hz), 4.50 (m, 1 H, lactone H), 3.20 (s, 6 H, OCH_3). Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.26; H, 8.90.

In other runs, 16 could be obtained in yields as high as 89%, but the product was always contaminated with traces of dimethyl 2-oxoheptylphosphonate, which could be removed only after repeated chromatography.

(*E*)-4-Hydroxy-8,11,15-trioxoeicos-13-enoic Acid γ-Lactone (17) and (*E*)-4-Hydroxy-8,11,15-trioxoeicos-12-enoic Acid γ-Lactone (18). To a solution of 4.8 g (12.1 mmol) of the ketal **16** in 320 mL of dioxane was added 115 mL of 0.1 N hydrochloric acid. The reaction mixture was concentrated on a rotatory evaporator at room temperature under reduced pressure. After 2 h the residue was extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure. The product was crystallized from ether–hexane to furnish 2.8 g (66%) of a 1:1 mixture of **17** and **18**: mp 48–50 °C; IR 1770, 1725, 1680, 1635 cm^{-1}; UV 224 nm (ε 10 800); NMR δ 7.02 (dt, C-13 H, J_{ab} = 16 Hz, J_{ax} = 7 Hz; first isomer), 6.95 (dt, C-13 H, J_{ab} = 16 Hz, J_{ax} = 7 Hz; second isomer), 6.20 (d, C-12 H of one isomer and C-14 H of the other, J_{ax} = 7 Hz), 3.45 (d, α-CH_2, J_{ax} = 7 Hz), 3.40 (d, α-CH_2, J_{ax} = 7 Hz). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.66; H, 8.29.

(*E*)-11,15-Dioxo-4-hydroxyprosta-8(12),13-dienoic Acid γ-Lactone (19). To a suspension of 4.6 g (13.13 mmol) of the isomeric acyclic, unsaturated diones **17** and **18** in 120 mL of water under a nitrogen atmosphere was added 120 mL of 0.2% aqueous sodium hydroxide. The reaction mixture was stirred for 0.5 h at room temperature. Then it was cooled in an ice bath, acidified with 2% aqueous citric acid, and extracted with methylene chloride. The extract was in turn successively washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from ether to furnish 2.7 g (62%) of **19**: mp 55–56 °C; IR 1770, 1715, 1625, 1590 cm^{-1}; NMR δ 7.52 (d, 1 H, C-13 H, J_{ab} = 16 Hz), 7.20 (d, 1 H, C-14 H, J_{ab} = 16 Hz); UV 275 nm (ε 22 600). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.62.

(*E*)-4,15-Dihydroxy-11-oxoprosta-8(12),13-dienoic Acid γ-Lactone (20). A solution of aluminum isopropoxide was prepared by heating together for 24 h 0.203 g of aluminum in 75 mL of anhydrous isopropyl alcohol (distilled over calcium hydride) containing 0.013 g of mercuric chloride and three drops of carbon tetrachloride.[31] To this solution of aluminum isopropoxide, heated under reflux, was added dropwise a solution of 0.5 g (1.5 mmol) of the dioxoprostanoid **19** in 25 mL of anhydrous isopropyl alcohol over a period of 10 min. The isopropyl alcohol was distilled slowly through a short-path distillation apparatus over a period of 1 h while the volume in the reaction flask was kept constant by the addition of fresh anhydrous isopropyl alcohol. The reaction mixture was cooled, acidified with 10% aqueous tartaric acid, and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure to give 0.7 g of an oil. The oil was chromatographed on 7 g of silica gel. Elution with 50% ethyl acetate–benzene afforded 0.4 g (80%) of **20** as an oil: IR 3610, 1775, 1700, 1625, 1600 cm^{-1}; UV 228 (ε 13 300), 236 sh (10 000), 263 nm (10 200); NMR δ 6.87 (dd, C-14 H, J_{ab} = 16 Hz, J_{ax} = 5 Hz), 6.25 (d, C-13 H, J_{ab} = 16 Hz); NMR [**20** (50 mg) + $Eu(fod)_3$ (25 mg)] δ 8.33 (dd, C-14 H, J_{ab} = 16 Hz, J_{ax} = 5 Hz), 8.28 (dd, C-14 H, J_{ab} = 16 Hz, $J_{ax} \simeq$ 5 Hz), 7.39 (d, C-13 H, J_{ab} = 16 Hz). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.42; H, 8.74.

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References and Notes

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