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A SYNTHESIS OF 9(O)-METHANOPROSTACYCLIN

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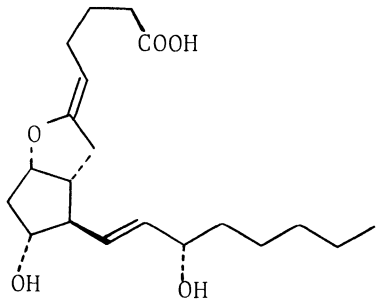
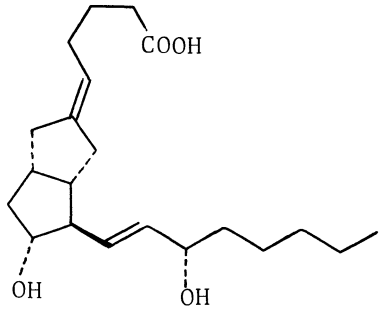
The optically active 9(O)-methanoprostacyclin was synthesized from 1-2-oxa-3-oxo-6-syn-benzyloxymethyl-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3.3.0]octane or d-(2β-benzyloxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)acetic acid, which are the general synthetic intermediates for natural prostaglandins.

The significant biological importance of prostacyclin (PGI_2, 1)[1] has prompted an intence research for the chemical modification of its structure[1c),2)] since its enol-ether linkage is readily hydrolyzed, even at pH 7.48.[3] We report herein a simple synthesis of the optically active 9(O)-methanoprostacyclin 2, which embraces all the characteristic functionalities of prostacyclin 1 except that 6,9-oxybridge has been replaced by methylenebridge.



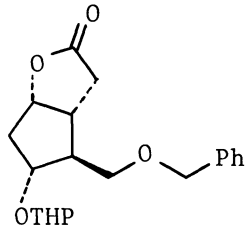
1



2

The crucial synthetic intermediate 8 was prepared as follows. The optically active and readily available lactone 3, a general synthetic intermediate for natural prostaglandins,[4] was converted to the alcohol 4 (first with NaOH then CH_2N_2), and thence to the ketone 5 by reaction with chromyl chloride-t-butyl alcohol-pyridine complex[5] in 79% overall yield from 3. Treatment of the ketone 5 with excess methyl lithiotrimethylsilylacetate[6] in THF at -78 °C for 1.5 h afforded the α,β-unsaturated ester 6 (46% yield, 69% based on the consumed 5), which was hydrogenated over palladium on carbon to a mixture of the diester 7 quantitatively.

Ring closure of the diester 7 was effected by exposure with potassium t-butoxide (4 equiv) in benzene at 75 °C for 4 h (48% yield),[7] and demethoxycarbonylation of the resulting keto-esters proceeded smoothly at 175 °C for 15 min in HMPA to give a mixture of ketones 8 and 9. The desired α-ketone 8 (54% yield, more polar) was separated from its β-isomer 9 (37% yield, less polar) by chromato-



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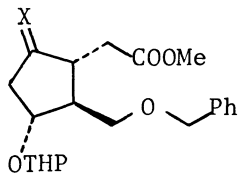
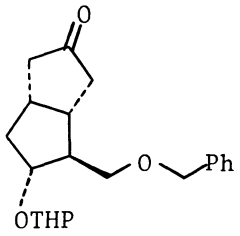


4: X=H, OH
5: X=O
6: X=CHCOOMe
7: X=H, CH_2COOMe



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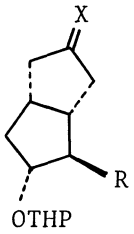
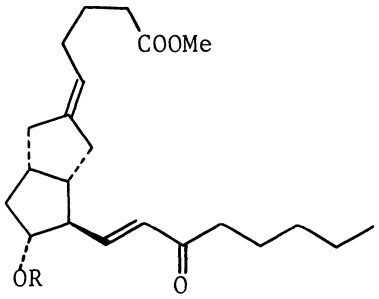
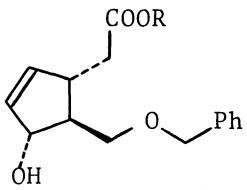


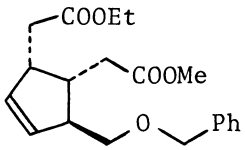
10: R=CH_2OH, X=O
11: R=$CH_2OC(CH_3)_2OCH_3$, X=O
12: R=CH_2OH, X=$CH(CH_2)_3COOMe$
13: R=CHO, X=$CH(CH_2)_3COOMe$



14: R=THP
15: R=H



16: R=H
17: R=Me



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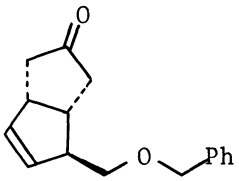

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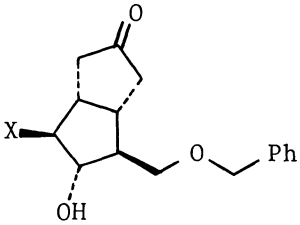
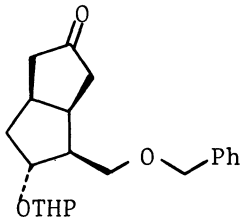


20: X=Br
21: X=H



9

graphy on silica gel. The stereochemistry of 8, a crucial element in the synthesis, was confirmed, after deprotection of THP group in 8, by circular dichroisms[8] as well as chemical evidence.[9]

A second route to the ketone 8 was achieved starting with the optically active and readily available hydroxy acid 16,[10] a general synthetic intermediate for the synthesis of the natural prostaglandins. Esterification of 16 with methyl iodide in the presence of K_2CO_3 in acetone at reflux temperature provided the hydroxy ester 17 which was converted stereospecifically to the diester 18 by Claisen rearrangement (triethyl orthoacetate, hydroquinone, 140 °C)[11] in 53% yield from 16. Dieckmann condensation of the diester 18 (potassium-t-butoxide in benzene) followed by dealkoxycarbonylation (175 °C, HMPA) led to the ketone 19 in 84% yield.

The bromohydrin 20 could be obtained in high regio- and stereoselectivity by treatment of the resulting 19 with N-bromosuccinimide at room temperature in DMSO-water (100:1) in 74% yield. Irradiation of 20 with the high pressure mercury lamp in the presence of n-Bu_3SnH and AIBN (as a sensitizer) in benzene produced 21 in 70% yield, which was identical with the detetrahydropyranylation product of 8 in NMR, IR, and MS spectra and TLC behabior on silica gel.

The ketone 8, thus prepared, could be converted to 2 straightforwardly using methodology previously developed by Corey for the synthesis of natural prostaglandins.[12] Deprotection of benzyl ether group was accomplished by hydrogenolysis using palladium on carbon in ethanol-acetic acid (10:1) to yield the hydroxy ketone 10 (96% yield). The hydroxy function in 10 was protected with a methoxypropyl unit by treatment of 2-methoxypropene to furnish 11 quantitatively. Conversion of 11 to the methyl ester 12 was effected by the following sequence: (1) Wittig reaction with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide in DMSO at 35 °C for 15 h, (2) esterification with CH_2N_2, (3) selective deprotection of 2-methoxypropyl unit with 0.5N-HCl in THF at 0 °C (overall 76% yield). The alcohol 12 was oxidized to the aldehyde 13 using SO_3-pyridine complex[13] and thence transformed to a mixture of enone 14 and its 5Z-isomer by Emmons-Horner method[14] (97% yield from 12).

Hydrolysis of THP group in a mixture of enone 14 and 5Z-isomer, produced a mixture of alcohol 15 [42% yield, R_f 0.28 (ethyl acetate-cyclohexane 1:2, twice developments)] and 5Z-isomer 15' (40% yield, R_f 0.32), which were readily separated by chromatography on silica gel.[15] Stereoselective reduction of the enone 15 with diisobutylaluminum 2,6-di-t-butyl-4-methylphenoxide[16] in toluene at -78 to -10 °C furnished 15S-alcohol (82% yield) and 15R-alcohol (12% yield) after separation by chromatography on silica gel. 15S-Isomer was saponified with KOH in aqueous ethanol to the desired 2[17] in 98% yield. By the same procedure, 5Z-isomer 2'[17] was obtained from 15'.

An interesting biological property for 2 and 2' was indicated by biological investigation: 2 was 2 times more potent than PGE_1, whereas 2' was 50 times less potent in inhibitory effect on ADP-induced rat platelet aggregation *in vitro*. Full biological data will be published in due course.

Acknowledgment. The authors wish to express their thanks to Professor Hisashi Yamamoto of University of Hawaii for his valuable suggestions.

References and Notes

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6) K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., 96, 5675 (1974).
7) In addition to the desired ketoester 8, unidentified compound was formed as the major by-product (30-40%), the structure of which is under investigations.
8) The α-isomer: IR (liquid film) 3450, 1740 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (5H, s), 4.11 (1H, m); MS m/e 260 (M^+); CD (c 7.07×10^{-3}, methanol) [θ] (nm) 0 (245), -6.40×10^{2} (289, 297), -4.34×10^{2} (sh, 307), -0.88×10^{2} (sh, 319), 0 (330).
The β-isomer: IR (liquid film) 3450, 1740 cm^{-1}; NMR ($CDCl_3$) δ 7.31 (5H, s), 4.34 (1H, m); MS m/e 260 (M^+); CD (c 7.60×10^{-3}, methanol) [θ] (nm) 0 (235), $+1.51\times10^{4}$ (sh, 287), $+1.66\times10^{4}$ (295), $+1.27\times10^{4}$ (sh, 305), $+0.46\times10^{4}$ (sh, 316), 0 (330). This β-isomer might be produced by epimerization in the Wittig type reaction of 5 with the silyl reagent or in hydrogenation of 6.
9) The structure of 8 was further confirmed by the following chemical transformations: (1) deprotection of THP group in the diester 7, (2) hydrolysis (KOH), (3) intramolecular lactonization (p-TsOH, benzene) followed by separation (33%), (4) hydrolysis (KOH), (5) esterification (CH_2N_2), (6) tetrahydropyranylation, (7) Dieckmann condensation, and (8) demethoxycarbonylation to form the α-isomer 8 as a sole product.
10) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, J. Am. Chem. Soc., 93, 1491 (1971).
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15) The Wittig reaction of 10 containing the hydroxy group gave a 1:2 mixture of 5E and 5Z-isomers, which were readily separated from each other by chromatography on silica gel after Emmons-Horner reaction.
16) S. Iguchi, H. Nakai, M. Hayashi, and H. Yamamoto, J. Org. Chem., 44, 1363 (1979).
17) 2: mp 59-61°C; $[\alpha]^{25}_D$ +66.8° (c 1.13, THF); Rf 0.25 (ethyl acetate-cyclohexane-acetic acid 75:25:2, twice developments, silica gel); IR (KBr) 3330, 1720, 1675 cm^{-1}; NMR ($CDCl_3$) δ 5.47 (2H, m), 5.23 (1H, m), 4.02 (1H, m), 3.68 (1H, m), 0.89 (3H, m); MS m/e 332 (M^+-H_2O), 314, 288, 218, 165.
High-resolution MS calcd for $C_{21}H_{32}O_3$ (dehydration peak from molecular ion), m/e 332.23513, found 332.23413.
2': mp 112-114°C; $[\alpha]^{25}_D$ +35.3° (c 1.01, THF); Rf 0.29; IR (KBr) 3360, 1700 cm^{-1}; NMR ($CDCl_3$) δ 5.51 (2H, m), 5.25 (1H, m), 4.00 (1H, m), 3.70 (1H, m), 0.91 (3H, m); MS m/e 332 (M^+-H_2O), 314, 288, 218, 165.
High-resolution MS calcd for $C_{21}H_{32}O_3$ (dehydration peak from molecular ion), m/e 332.23513, found 332.23377.

Note added in proof: D. R. Morton, Jr., and F. C. Brokaw, J. Org. Chem., 44, 2880 (1979), have recently reported the synthesis of optically active 9(O)-methanoprostacyclin.

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