Tetrahedron Letters Vol. 21, pp 1255 - 1258 0040-4039/80/0322-1255$02.00/0

THE SYNTHESIS OF NEW AROMATIC PROSTACYCLIN ANALOG

Katsuichi SHIMOJI and Masaki HAYASHI
ONO Pharmaceutical Co. Ltd., Research Institute
3-1-1, Sakurai, Shimamoto-cho, Mishima-gun, Osaka 618, Japan

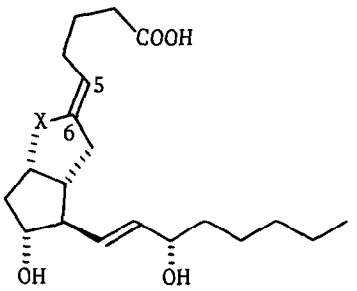
The new aromatic prostacyclin analog 3a and 3b were synthesized from the allylic alcohol 5 in high regio- and stereoselectivity.

Prostacyclin (PGI_2, 1) possesses the remarkable biological property of inhibiting the fatal effects caused by thromboxane A_2.[1] There is, however, an obstacle to the use of PGI_2 (1) as a therapeutic agent, owing to its instability.[1] To achieve tissue selectivity and metabolic stability, several stable PGI_2-analogs have been prepared.[2] The 9(O)-methano-PGI_2 (2) is the most stable analog of those reported, and possesses a potency comparable to the natural PGI_2 (1).[2a]

Introduction of an aromatic ring to the 9(O)-methano-PGI_2 (2), retaining the sp^2 character of C-5 and C-6, would afford important information on the structure-activity relationship between PGI_2 (1) and its analogs. We, therefore, prepare the aromatic PGI_2-analog 3a and 3b.

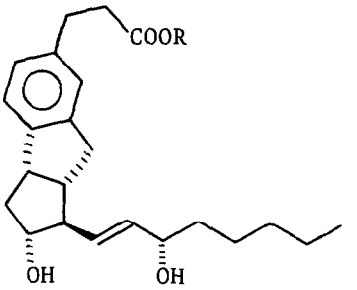
The readily available regioisomeric mixture of the β-keto ester 4[3] was converted to the desired allylic alcohol 5 in 58% yield, along with the isomer 6 in 35% yield,[4] in 4-steps: (1) $NaBH_4$, MeOH, -20 °C; (2) $MeSO_2Cl$-Et_3N, CH_2Cl_2, 0 °C; (3) DBU, benzene, RT; (4) DIBAL, toluene, -40 °C. The structures of compound 5 and its isomer 6 were confirmed by Pmr spectra using double resonance method.[4]

Pyridinium dichromate oxidation[5] of the allylic alcohol 5 in methylene chloride at room temperature yielded the ene-aldehyde 7 (Pmr ($CDCl_3$) δ 9.75 (s, 1H), 6.72 (m, 1H), and 4.00 (m, 1H) ppm; ir (liquid film), 1680, 1620, and 1610 cm^{-1}) in 80% yield. Condensation of 7 with methoxymethylidenetriphenylphosphorane in DMSO-THF (1 : 1) at 0 °C gave the conjugated enol-



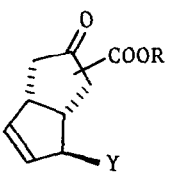
1 X = O

2 X = CH_2

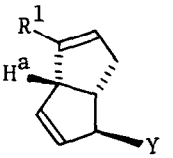


3a R = CH_3

3b R = H



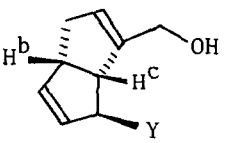
4



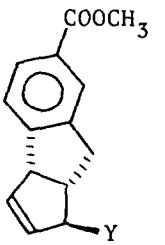
5 R^1 = CH_2OH

7 R^1 = CHO

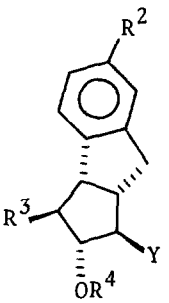
8 R^1 = $CH=CHOCH_3$



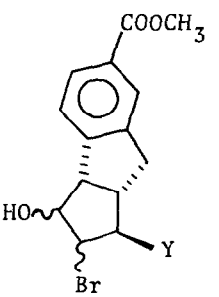
6



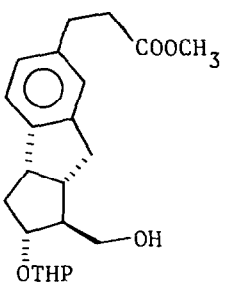
9



	R^2	R^3	R^4
10	$COOCH_3$	Br	H
12	$COOCH_3$	H	H
13	$COOCH_3$	H	THP



11



14

Y = CH_2OCH_2Ph

ether 8 as a stereoisomeric mixture (Pmr ($CDCl_3$) δ 3.64 and 3.58 (2s, 3H, OCH_3 for E- and Z-isomer respectively) ppm; ir (liquid film), 1640 and 1600 cm^{-1} (enol-ether double bond)) in 95% yield in a ratio of ca. E : Z = 7 : 3. The Diels-Alder reaction of 8 with methyl propiolate in toluene at 100 °C, followed by aromatization (SiO_2, CH_2Cl_2, RT) gave exclusively the desired product 9 (Pmr ($CDCl_3$) δ 7.85 (m, 2H), 7.22 (d, 1H), and 3.88 (s, 3H) ppm; ir (KBr), 1710 cm^{-1}) in 65% yield.

Introduction of 11α-OH to 9 was effected with high regio- and stereoselectivity by treatment with N-bromosuccinimide in 1% aq-DMSO to give the desired bromohydrin 10 (R_f 0.46 (5% ethyl acetate in CH_2Cl_2); Pmr ($CDCl_3$) δ 4.26-3.77 (m, 2H) and 3.88 (s, 3H) ppm) in 96% yield along with a small amount of the position-isomer 11 (R_f 0.26; Pmr ($CDCl_3$) δ 4.65 (m, 1H), 4.42 (m, 1H), and 3.88 (s, 3H) ppm).[6] Debromination of 10 (Bu_3SnH, AIBN, hν, benzene, 15 °C), followed by tetrahydropyranylation (DHP, CH_2Cl_2, p-TsOH, RT) gave the compound 13 in quantitative yield. Lastly, the resultant ester 13 could be transformed to the alcohol 14 by the standard method: (1) DIBAL, toluene, -40 °C; (2) pyridinium dichromate, CH_2Cl_2, RT;[5] (3) Bu_3P=CHCOOMe, $CHCl_3$, RT; (4) H_2/Pd-C, EtOAc-MeOH).

The aromatic PGI_2 analog 3a[7] was readily prepared from the alcohol 14 by the previously reported sequence: (1) SO_3-Pyridine complex, Et_3N, DMSO, RT; (2) dimethyl 2-oxoheptylphosphonate, aq-NaOH, toluene, 50 °C; (3) $NaBH_4$, MeOH, -40 °C; (4) AcOH-H_2O-THF = 2 : 1 : 1, 50 °C).[8] Hydrolysis of the methyl ester 3a in aqueous methanolic sodium hydroxide solution produced the acid 3b[9] quantitatively.

Contrary to expectations, the aromatic PGI_2-analog 3a and 3b did not show any PGI_2-like biological properties.

References and Footnotes

1. S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, Nature (London), 263, 663 (1976); R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, Prostaglandins, 12, 915 (1976); K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, Angew. Chem. Int. Ed. Engl., 17, 293 (1978).

2. a) For 9(O)-methano-PGI_2: K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz, and W. E. Barnette, J. Chem. Soc. Chem. Commun., 1067, (1978); K. Kojima and K. Sakai,

Tetrahedron Lett., 3743 (1978); M. Shibasaki, J. Uda, and S. Ikegami, Tetrahedron Lett., 443 (1979). b) For 9(O)-thia-PGI_2: K. Shimoji, Y. Arai, and M. Hayashi, Chem. Lett., 1375 (1978); K. C. Nicolaou, W. E. Barnette, G. P. Gasic, and R. L. Magolda, J. Am. Chem. Soc., 99, 7736 (1977); M. Shibasaki and S. Ikegami, Tetrahedron Lett., 559 (1978). c) For 6,9-aza-PGI_2: G. L. Bundy and J. M. Baldwin, Tetrahedron Lett., 1371 (1978). d) For aromatic PGI_2: K. C. Nicolaou, W. E. Barnette, and R. L. Magolda, J. Am. Chem. Soc., 101, 766 (1979).

3. Y. Konishi, M. Kawamura, Y. Arai, and M. Hayashi, Chem. Lett., 1437 (1979).

4. The compound 5: Pmr ($CDCl_3$) δ 7.32 (m, 5H), 5.88 (d of t, 1H), 5.66 (d of t, 1H), 5.48 (m, 1H), 4.53 (s, 2H), 4.16 (d, 2H), 3.70 (m, 1H, H^a), and 3.40 (m, 2H) ppm; ir (liquid film), 3370, 1492, and 738 cm^{-1}; MS m/e 256 ($\dot{M}$); R_f 0.20 (ethyl acetate-cyclohexane, 1 : 3). The isomer 6: Pmr ($CDCl_3$) δ 7.33 (m, 5H), 5.70 (d 0f t, 1H), 5.44 (d of t, 1H), 5.36 (m, 1H), 4.55 (s, 2H), 4.20 (s, 2H), 3.58 (d of d, 1H), 3.50 (m, 1H, H^b or H^c), 3.23 (m, 1H, H^b or H^c), and 3.21 (d of d, 1H) ppm; ir (liquid film), 3400, 1493, and 730 cm^{-1}; MS m/e 256 ($\dot{M}$); R_f 0.27.

5. E. J. Corey and G. Schmidt, Tetrahedron Lett., 399 (1979).

6. Initially, the bromonium cation should approach from the less steric hindered β-site, and secondary, the hydroxide anion should attack the 11-carbon, because of 1,2-cis repulsion in cyclopentane ring, from α-site. Similar selectivity was also observed in the synthesis of the 9(O)-methano-PGI_2 from the β-keto ester 4.[3]

7. Pmr ($CDCl_3$) δ 7.04 (m, 3H), 5.50 (m, 2H), 4.05 (m, 1H), 3.86 (m, 1H), 3.68 (s, 3H), and 3.51 (m, 1H)ppm; ir (KBr) 3420, 1732, 1715, 1490, 1438, 1080, 973, 908, 890, and 820 cm^{-1}; MS m/e 386 ($\dot{M}$).

8. The diastereoisomeric mixture of the allylic alcohol 3a and its isomer was easily separated by column chromatography on silica gel. The less polar isomer (R_f 0.30, EtOAc-cyclohexane = 3 : 2) was assigned as the 15β-isomer and the more polar one as the 15α-isomer (3a) on the basis of the known chromatographic behavior of the natural prostaglandins, see N. H. Andersen, J. Lipid Res., 40, 316 (1969).

9. Pmr ($CDCl_3$) δ 7.06 (m, 3H), 5.57 (m, 2H), 4.08 (m, 1H), 3.92 (m, 1H), and 3.51 (m, 1H) ppm; ir (KBr) 3400, 1702, 1490, 1090, 1080, 978, 915, 895, and 838 cm^{-1}; MS m/e 372 ($\dot{M}$).

(Received in Japan 14 December 1979)