Tetrahedron Letters No. 9, pp 805 - 808.
0040-4039/79/0222-0805$02.00/0

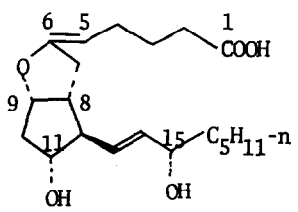
SYNTHESIS OF NITROGEN-CONTAINING PROSTAGLANDIN I_1 ANALOGS

Hisao NAKAI, Yoshinobu ARAI, Nobuyuki HAMANAKA and Masaki HAYASHI*

Research Institute, Ono Pharmaceutical Co., Ltd.,

Shimamoto-cho, Mishima-gun, Osaka, Japan 618

Since the discovery of prostacyclin(PGI_2), much attention has been payed on its very potent activity in inhibition of blood platelet aggregation. Although chemical synthesis of PGI_2 1 has been achieved by various researchers, its instability is an undesirable factor for a potential drug for treatment of thrombosis, stroke and heart attack[1]. We directed our efforts to the synthesis of stable PGI_2 analogs having comparable physiological activities to natural PGI_2. In this paper we report the synthesis of dl-6-aza-6,9-methano-PGI_1 analogs, 2, 3, 4, 5 and 6[2].



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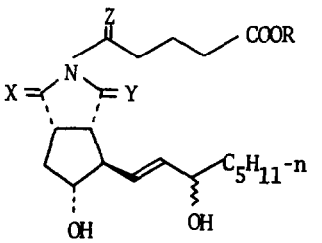


2 X=Y=O, Z=$<^{H}_{H}$, R=H

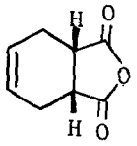
3 X=Y=O, Z=$<^{H}_{H}$, R=CH_3

4 X=Y=$<^{H}_{H}$, Z=O, R=H

5 X=Y=$<^{H}_{H}$, Z=O, R=CH_3

6 X=Y=Z=$<^{H}_{H}$, R=CH_3

Reduction of the anhydride 7[3] with $LiAlH_4$ in THF(reflux, 3 hr) followed by the reaction with 2,2-dimethoxypropane in DMF(p-TsOH, reflux, 4 hr) gave the acetonide 8[4] (bp 75-85°/4 mm, 68% from 7). Oxidative cleavage of 8 with $KMnO_4$[5] followed by the treatment with CH_2N_2 yielded the diester 9[40%; m/e 274(M^+)]. Dieckmann condensation of 9(NaH-THF) gave the β-ketoester 10[6] [93%; ν_{max} 1760, 1730, 1660, 1620 cm-1]. Reduction of 10 with $NaBH_4$ afforded 11[6] [quant; ν_{max}



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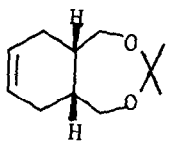

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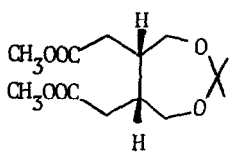

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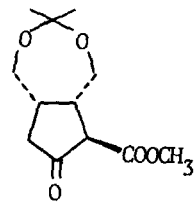

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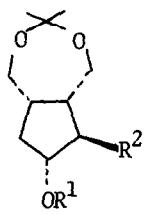
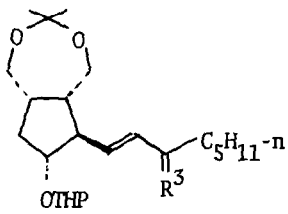


11 R^1=H, R^2=$COOCH_3$

12 R^1=THP, R^2=$COOCH_3$

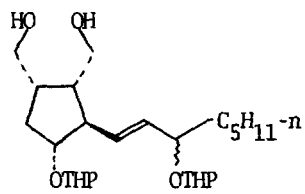
13 R^1=THP, R^2=CH_2OH



14 R^3=O

15 R^3= 

16 R^3= 



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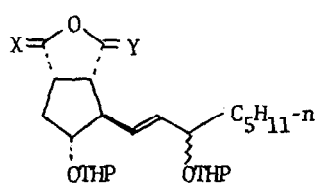
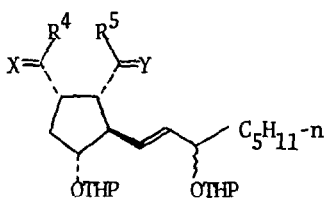


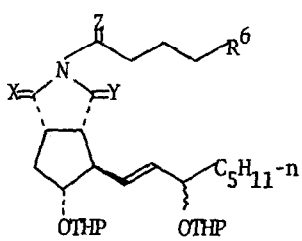
18a X=O, Y= 

18b X=, Y=O



19a R^4=NH_2, R^5=OH, X=O, Y=

19b R^4=OH, R^5=NH_2, X=, Y=O



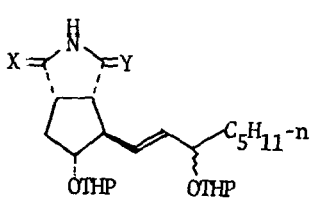
22 X=Y=O, Z=, R^6=CH_2OH

23 X=Y=O, Z=, R^6=COOH

24 X=Y=, Z=O, R^6=$COOCH_3$

25 X=Y=Z=, R^6=CH_2OH

26 X=Y=Z=, R^6=$COOCH_3$



20 X=Y=O

21 X=Y=

3400 cm-1; m/e 244(M^+)]. Protection of 11 with THP group followed by reduction with i-Bu_2AlH in toluene(25°, 1 hr) gave the alcohol 13[quant; ν_{max} 3450 cm-1; m/e 300(M^+)]. Oxidation(Corey-Kim method)[7] of 13, followed by condensation with dimethyl 2-oxoheptylphosphonate provided the enone 14(85% from 13). Reduction of 14 with $NaBH_4$ gave C-15(prostanoic acid numbering) epimeric mixture 15, which was converted into 16(quant from 14) without separation. Treatment of 16 with pyridinium p-toluenesulphonate in MeOH[8] (25°, 1.5 hr) gave the diol 17[67%; ν_{max} 3400 cm-1; m/e 422(M^+-H_2O)]. Sarett oxidation of 17 gave a mixture of two isomeric γ-lactones 18a and 18b[94%; ν_{max} 1775 cm-1], which was treated with NH_3 in MeOH(50°, 4 hr) to give a mixture of the amide alcohols 19a and 19b[69%; ν_{max} 3400, 1670, 1620 cm-1]. Sarett oxidation of the mixture of 19a and 19b without separation afforded the imide 20[98%; ν_{max} 1780, 1730 cm-1]. Treatment of 20 with 5-aminopentanol(120°, 4 hr) gave the imide alcohol 22[75%; ν_{max} 3400, 1780, 1700 cm-1; m/e 433(M^+-THPOH)] which was oxidized(Sarett oxidation) to give the imide acid 23[79%; ν_{max} 3500-2500, 1780, 1705 cm-1]. Removal of THP groups of 23 with aq AcOH in THF(60°, 3 hr) gave 2[60%; δ 5.65-5.45 ppm(2H, m); ν_{max} 3500-2500, 1780, 1700 cm-1; m/e 363(M^+-H_2O)]. Esterification with CH_2N_2 and deprotection of 23 gave the corresponding ester 3[58% from 23; δ 5.63-5.50(2H, m), 3.65 ppm(3H, s); ν_{max} 3450, 1780, 1740, 1695 cm-1; m/e 377(M^+-H_2O)]. Reduction of 20 with $LiAlH_4$ in THF(reflux, 2 hr) gave the cyclic amine 21[quant; m/e 421(M^+)], which was treated with glutaric anhydride in pyridine(25°, 1 hr) followed by esterification(CH_2N_2) to give the amide ester 24[quant from 21; ν_{max} 1740, 1650 cm-1]. Removal of THP groups of 24 gave 5[72%; δ 5.66-5.45(2H, m), 3.68 ppm(3H, s); ν_{max} 3400, 1740, 1630 cm-1; m/e calcd for $C_{21}H_{35}O_5N_1$(M^+) 381.251, obserbed 381.253]. Hydrolysis with aqueous alcoholic base and deprotection of 24 afforded 4[82% from 24; δ 5.65-5.48 ppm(2H, m); ν_{max} 3500-2300, 1720, 1620 cm-1; m/e 367(M^+)]. Reduction of 24 with $LiAlH_4$ in THF(reflux, 15 min) gave the amino alcohol 25(quant), which was subjected to Jones oxidation and esterification(CH_2N_2) to give the amino ester 26[20% from 27; m/e 367(M^+)]. Removal of THP groups of 26 gave 6[59%; δ 5.25-5.40(2H, m), 4.15-3.90(2H, m), 3.66 ppm(3H, s); ν_{max} 3400, 1740 cm-1; m/e 367(M^+)].

All of these compounds(2, 3, 4, 5 and 6) showed weak inhibitory activity in blood platelet aggregation.

References and Notes

1) K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, Angew. Chem. Int. Ed. Engl., 17, 293(1978) and references cited.

2) All of these compounds were obtained as C-15 epimeric mixture(ca 1:1).

3) A. C. Cope and E. C. Herrick, J. Amer. Chem. Soc., 72, 983(1950).

4) Satisfactory infrared, ^{1}H NMR and mass spectral data were obtained for all synthetic intermediates.

5) C. M. Starks, J. Amer. Chem. Soc., 93, 195(1971).

6) Compound 10 was obtained as a tautomeric mixture with its enol form. But reduction of 10 gave single product 11 which was confirmed by tlc(homogeneous in several solvent systems) and shift reagent[$Eu(fod)_3$] technique.

Similar results were reported in

(a) K. G. Paul and F. Johnson, J. Amer. Chem. Soc., 98, 1285(1976) and (b) K. Kojima and K. Sakai, Tetrahedron Lett., 3337(1972).

7) E. J. Corey and C. U. Kim, J. Org. Chem., 38, 1233(1973).

8) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, J. Org. Chem., 42, 3772(1977).

(Received in Japan 18 November 1978)