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STEREOSELECTIVE SYNTHESIS OF A 13-AZAPROSTACYCLIN METHYL ESTER

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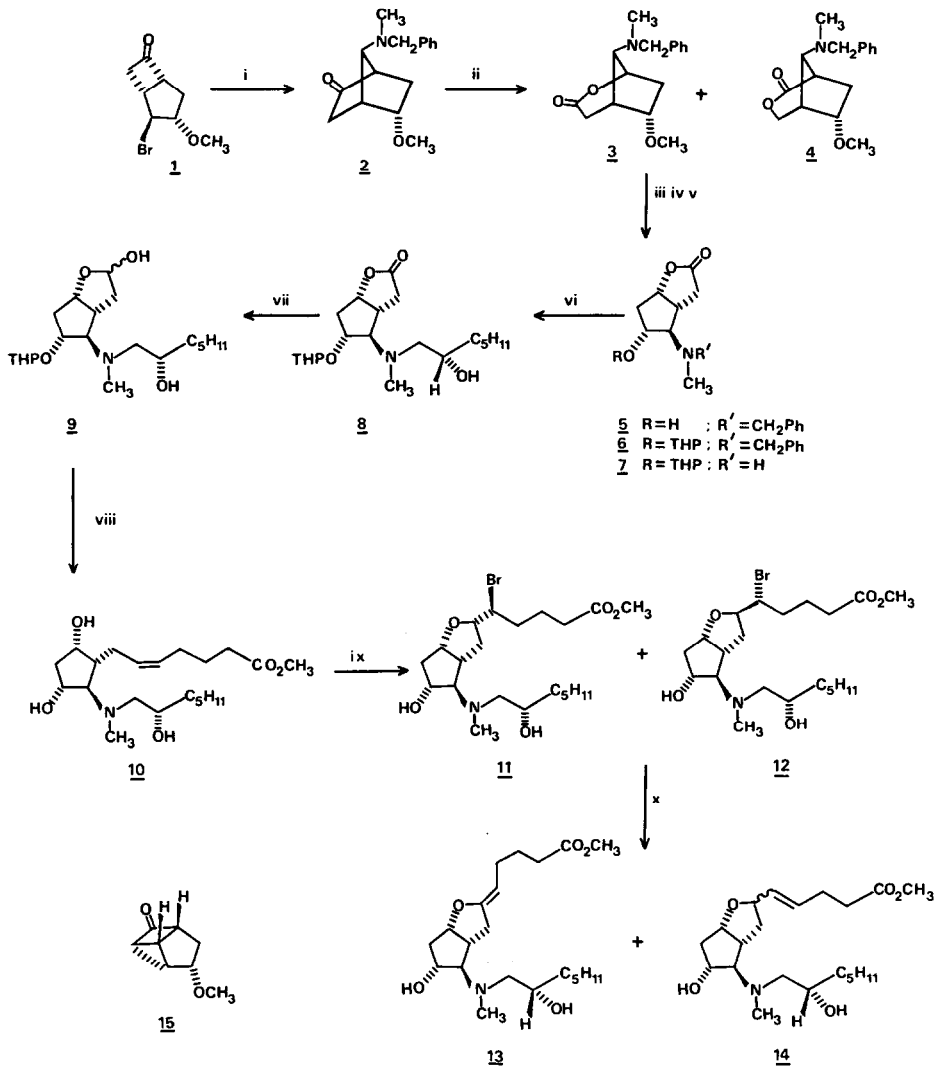
Summary: The synthesis of 13-azaprostacyclin methyl ester 13 in ten steps from the readily available 2-exo-bromo-3-endo-methoxybicyclo[3.2.0]heptan-6-one 1 is described.

Inhibition of platelet aggregation and vasodilation are two well recognised properties of prostacyclin and based on these effects it has generated immense interest in the fields of thrombosis and vascular disease. However, its potential therapeutic usefulness is limited by its instabilty and poor degree of tissue selectivity with the result that increasing numbers of analogues have been made[1] in the search for a compound with the desired properties. We now wish to describe the stereoselective synthesis of a 13-aza methyl ester analogue 13 of this important biomolecule.

Treatment of the bromoketone 1 with an excess of N-methylbenzylamine in ether gave the bicyclo[2.2.1]heptan-2-one 2 (m.p. 58-62°, 77%)[2]. The structure of ketone 2 was established on the basis of its IR ($CHBr_3$,1745cm^{-1} C=O) and ^{1}H n.m.r. spectra [($CDCl_3$) δ 1.43 (1H,bd,6-endo H), 2.04 (1H,dd,6-exo H), 2.09 (3H,s,NCH_3), 2.5-2.8 (4H,m,H1,H3,H7), 2.93 (1H,m,H4), 3.3 (3H,s,OCH_3), 3.5 (2H,AB,J=15Hz,N-CH_2Ph), 4.3 (1H,m,H5), 7.3 (5H,m,Ph)]. The appearance of W coupling between the 6-endo H and the 7-H (J=1.5Hz) established the configuration of the amino group as being 7-anti. Formation of the norbornanone 2 takes place through the tricyclic intermediate 15 which undergoes regiospecific nucleophilic cleavage at C-1[3].

Baeyer-Villiger oxidation of ketone 2 employing 40% peracetic acid in dichloromethane gave an isomeric mixture of lactones 3 and 4 which after purification by silica gel column chromatography (ether as eluent) gave the required isomer 3[4a] (m.p. 48-49°) in 46% yield. Exposure of lactone 3 to 45%w/v HBr/CH_3CO_2H at 100° cleaved the methyl ether with concomitant rearrangement of the δ-lactone to the ϑ-lactone 5[4b] (m.p. 76-77°, 69%).

Scheme



Reagents: i) $PhCH_2NHCH_3$ / Ether / 5h ii) CH_3CO_3H/CH_2Cl_2 / 24h iii) 45% HBr / CH_3CO_2H / 100°/ 15h iv) 4eq DHP/PTSA / CH_2Cl_2 / -10° v) H_2 / 10%PdO-C vi) C_5H_{11} / CH_3OH / reflux 18h vii) Dibah / -70° / CH_2Cl_2 viii) $Ph_3P^+(CH_2)_4CO_2H\,Br^-$ / KO^tBu / THF / 20°/3h then CH_3OH/H_2SO_4 /18h ix) a) anhydrous HCl b) 1·1eq NBS / CH_3CN / 0°/1·5h x) neat DBU / 90°/0·5h

The alcohol 5 was protected as the tetrahydropyranyl ether 6 (m.p. 60-61°, 97%) and then hydrogenated in ethanol over palladium catalyst to afford the oily secondary amine 7 [100%, IR($CHBr_3$) 3330 (NH), 1765 (C=O)cm^{-1}] which was not purified.

Introduction of the ω-chain into amine 7 was carried out by reaction with (S)-pentyloxirane[5] in methanol under reflux[6]. Reduction of the lactone 8 with diisobutylaluminium hydride (dibah) to the corresponding lactol 9 (99%), followed by first condensation with the potassium salt of the ylid derived from 4-(carboxybutyl)triphenylphosphonium bromide (KO^tBu/THF) and then exposure to 10% methanolic sulphuric acid gave the triol 10[7] in 60% yield after purification by chromatography (ether-methanol, 93:7 as eluent).

Triol 10, as its hydrochloride salt, was converted into the intermediate bromo ethers 11 and 12 (ratio endo:exo = 3:1, 39%)[8], using N-bromosuccinimide (NBS) in dry acetonitrile. Attempts to haloetherify compound 10 (as its free base) with either NBS or N-iodosuccinimide gave complex mixtures of polar by-products. Dehydrohalogenation of both isomers 11 and 12 proceeded readily in neat 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford a chromatographically separable mixture of the desired prostacyclin methyl ester 13 (61%) [IR($CHBr_3$) 3580, 3440 (br) (OH), 1725 (C=O), 1695 (C=C), cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 4.05-4.25 (2H,m,H5,H11), 4.58 (1H,m,H9), 3.68 (3H,s,OCH_3)][11] and the 4E isomer 14[12] (7%) as viscous oils.

Aza analogue 13 (10μg/ml) was inactive against both ADP- and collagen-induced aggregation of human platelet rich plasma.

References and Notes

1. See for example K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz and W. E. Barnette, J. Chem. Soc. Chem. Comm., 1978, 1067. K. C. Nicolaou, W. E. Barnette, G. P. Gasic and R. L. Magolda, J. Amer. Chem. Soc., 1977, 99, 7736. M. Shibasaki and S. Ikegami, Tetrahedron Lett., 1978, 19, 559. G. L. Bundy and J. M. Baldwin, Tetrahedron Lett., 1978, 19, 1371. W. Bartmann, G. Beck, J. Knolle and R. H. Rupp, Angew. Chem. Int. Ed. Engl., 1980, 19, 819. R. H. Bradbury and K. A. M. Walker, Tetrahedron Lett., 1982, 23, 1335. L. Novak, J. Aszodi and C. Szantay, Tetrahedron Lett., 1982, 23, 2135.
2. The composition of all new compounds was confirmed by elemental analysis (2-7, 10-13) or high resolution mass spectrometry (8, 9).
3. S. M. Roberts, J. Chem. Soc. Chem. Comm., 1974, 948.
4. a) IR($CHBr_3$) 1730cm^{-1} (C=O). b) IR($CHBr_3$) 3580, 1773cm^{-1} (OH,C=O).

5. F. Bartkowiak, U. Schmidt, J. Talbiersky and J. Wild, Angew. Chem. Int. Ed. Engl., 1980, 19, 198.

6. Purification by silica gel chromatography using ether followed by ether-methanol (9:1) as eluent; (83%).

7. ^{1}H n.m.r. ($CDCl_3$) δ 0.89 (3H,t,CH_3), 1.2-1.6(8H,m,H16-19), 1.6-2.7 (13H,m), 2.27 and 2.39 (3H,2xs,NCH_3 diastereoisomers), 2.95 (1H,m,H12), 3.1-3.8 (4H,br m,3xOH,H15), 3.67 (3H,s,OMe), 4.1-4.25 (2H,m,H9,H11), 5.32-5.58 (2H,m,CH=CH). IR ($CHBr_3$) 3590, 1728cm^{-1} (OH,C=O).

8. Purified by alumina chromatography using ether through to ether-methanol (95:5) as eluent. The endo:exo ratio (3:1) was confirmed by ^{1}H n.m.r.[9,10], H^9-endo δ 4.32 and H^9-exo δ 4.53. Additional supporting data was obtained from ^{13}C n.m.r. studies[9] on the product mixture. As yet we are unable to explain this unexpected stereochemical outcome of the haloetherification reaction.

9. G. Galambos, G. Kovacs, V. Simonidesz and I. Tomoskozi, Tetrahedron Lett., 1977, 18, 2627.

10. G. Galambos, G. Kovacs, L. Radics and I. Tomoskozi, Tetrahedron Lett., 1978, 19, 581.

11. Prostacyclins 13 and 14 were separated by chromatography on alumina with ether-methanol (19:1) as eluent. T.l.c. (Al_2O_3: column eluent) 13 (Rf 0.71), 14 (Rf 0.61). ^{13}C n.m.r. indicated that compound 13 existed as two diastereoisomers (ratio 1:1).

12. High field (250MHz) ^{1}H n.m.r. spectrum was in accord with the assigned structure.

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