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SYNTHESIS OF 12-AZAPROSTACYCLIN ANALOGUES

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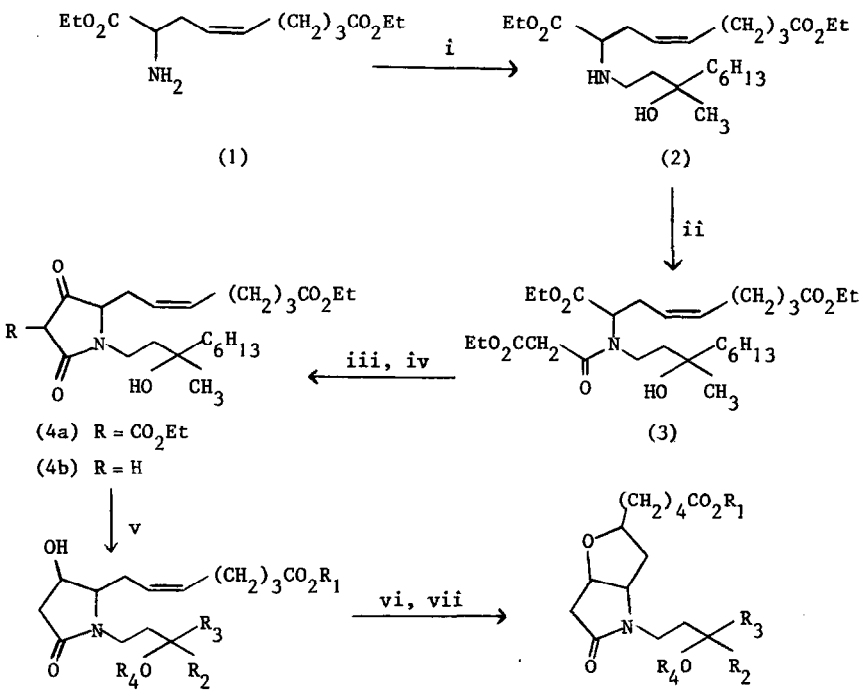
Abstract : Synthetic routes for the preparation of 12-azaprostacyclin analogues are described.

Since the discovery[1] of prostacyclin, PGI_2, a number of prostacyclin analogues with modifications to the tetrahydrofuran ring have been reported, for example, 6,9-thiaprostacyclin, carboprostacyclin and various aza analogues[2]. In this communication, we wish to report the synthesis of analogues of prostacyclin in which the carbocyclic ring has been modified, namely dl-12-aza-11-dehydro-5,6,13,14-tetrahydroprostacyclin methyl ester (6c) and related compounds[3].

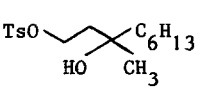
Two approaches were used to prepare 12-aza-13,14-dihydro PGD_2 analogues (5), which were cyclised subsequently to the 12-azaprostacyclin analogues (6). In the first approach (Scheme 1), based on our earlier synthesis of 12-azaprostaglandins[4], the amine (1), prepared in 70% yield from N-benzylidene glycine ethyl ester[5] and ethyl 7-bromohept-5-enoate[6], was treated with 1-(toluene-p-sulphonyloxy)-3-methylnonan-3-ol[7] in acetonitrile to yield (2, 55%). Acylation of (2) with monoethyl malonate in the presence of dicyclohexylcarbodiimide gave (3, 45% after purification[8]). Cyclisation of (3) with potassium t-butoxide in refluxing tetrahydrofuran gave (4a) which yielded (4b, 65% from 3) on treatment with anhydrous magnesium sulphate in ether. Reduction of (4b) with sodium borohydride afforded (5a, 60%). (IR : ν max (film), 3350, 1730, 1670 cm^{-1}. Mass spectrum : m/e ($M^{+\cdot}$) requires 411.2982; found 411.2960). Cyclisation of (5a) was achieved by treatment with mercuric trifluoroacetate and subsequent reduction with sodium borohydride[9] to yield the 12-azaprostacyclin analogue (6a, 47%).[3]

Scheme 1



	R_1	R_2	R_3	R_4
(5a)	Et	CH_3	C_6H_{13}	H
(5b)	CH_3	H	C_5H_{11}	$CH_2C_6H_5$

	R_1	R_2	R_3	R_4
(6a)	Et	CH_3	C_6H_{13}	H
(6b)	CH_3	H	C_5H_{11}	$CH_2C_6H_5$
(6c)	CH_3	H	C_5H_{11}	H

Reagents : i. 

ii. $EtO_2CCH_2CO_2H$, DCC, CH_2Cl_2, 18 hr.

iii. KO^tBu, reflux in THF under N_2, 1-1.5 hr.

iv. $MgSO_4$, Et_2O, 18 hr.

v. $NaBH_4$, EtOH.

vi. $Hg(OCOCF_3)_2$, $CaCO_3$, THF, 1 hr.

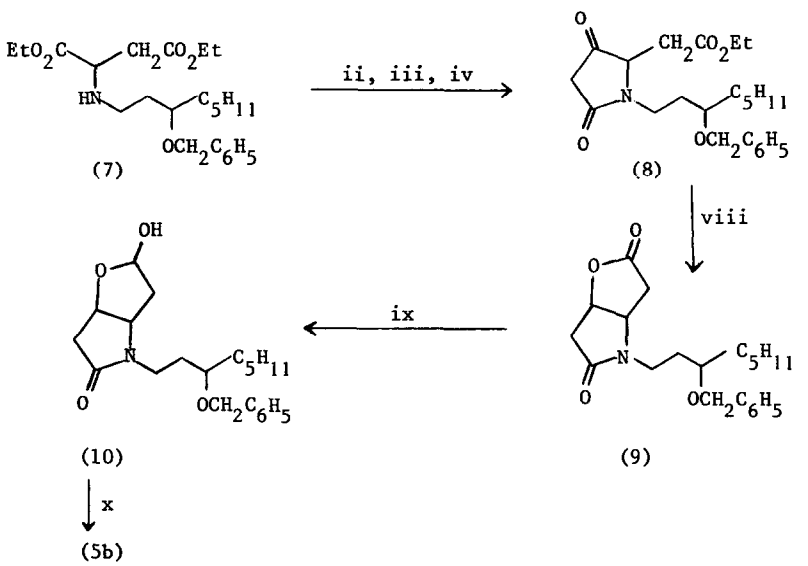
vii. $NaBH_4$, EtOH, -20^o, 1 hr.

In the second approach (Scheme 2), alkylation of 3-benzyloxyoctylamine[4] with diethyl bromosuccinate gave the amine (7, 80%) which was converted to (8, 82%) by the methods used in Scheme 1. Hydrolysis of (8) to the potassium salt of the acid followed by reduction in situ with sodium borohydride yielded the bicyclic lactone (9, 60%). (IR : ν max (film), 1785, 1690 cm^{-1}. Mass spectrum : m/e (MH^+) requires 360.2175; found 360.2168). When reduction of (9) to the lactol was attempted with di-isobutylaluminium hydride a complex mixture was obtained, but treatment of (9) with lithium tri-t-butoxyaluminium hydride afforded the lactol (10, 63%). (IR : ν max (film), 3360, 1665 cm^{-1}. Mass spectrum : m/e (MH^+) requires 362.2331; found 362.2326).

Reaction of (10) with the ylid (2 moles) derived from 4-carboxybutyltriphenylphosphonium bromide, followed by esterification of the crude product with diazomethane and purification afforded (5b, 57% from 10). (IR : ν max (film), 1735, 1670 cm^{-1}. Mass spectrum : m/e ($M^{+\cdot}$) requires 459.2985; found 459.3009). Cyclisation of (5b) to (6b) and subsequent hydrogenolysis over 10% palladium on charcoal catalyst gave the 12-azaprostacyclin analogue (6c, 50% from 5b).[3]

Preliminary biological results indicate that (6a) and (6c) are potent inhibitors of collagen- and ADP-induced platelet aggregation in human platelet-rich plasma.

Scheme 2



Reagents : viii. KOH, EtOH, 18 hr; then $NaBH_4$, 0-5°, 1 hr, aq. acid work-up.
ix. $LiAl(O^tBu)_3H$, THF, 0-20°, 3 hr.
x. $Ph_3P{=}CH(CH_2)_3CO_2^-$, DMSO, THF, N_2; then CH_2N_2, Et_2O, CH_3OH.

Data for Compounds (6a) and (6c)

Compound (6a). IR : ν max (film), 3400, 1730, 1670 cm^{-1}. Mass spectrum : m/e ($M^{+\cdot}$) requires 411.2982; found 411.2979. PMR[10] : τ ($CDCl_3$), 9.40-8.98 (m, 3H, $(CH_2)_5\underline{CH_3}$); 8.95-8.11 (m, 25H, $(\underline{CH_2})_3CH_2CO_2CH_2\underline{CH_3}$, $C(OH)\underline{CH_3}$, $NCH_2\underline{CH_2}$, $(CH_2)_5$, $\frac{1}{2}NCHC\underline{H_2}$); 8.00-7.35 (m, 5H, $\underline{CH_2}CO_2Et$, CH_2CON, $\frac{1}{2}NCHC\underline{H_2}$); 7.35-5.55 (m, 7H, NCH_2, $OC\underline{H}(CH_2)_4$, $CO_2\underline{CH_2}CH_3$, OH, NCH); 5.35 (m, 1H, OCH).

Compound (6c). IR : ν max (film), 3410, 1735, 1670 cm^{-1}. Mass spectrum : m/e ($M^{+\cdot}$) requires 369.2515; found 369.2520. PMR[10] : τ ($CDCl_3$), 9.30-9.00 (m, 3H, $(CH_2)_4\underline{CH_3}$); 9.00-8.10 (m, 17H, $NCH_2\underline{CH_2}$, $(CH_2)_4$, $(\underline{CH_2})_3CH_2CO_2CH_3$, $\frac{1}{2}NCHC\underline{H_2}$); 8.03-7.30 (m, 5H, $\underline{CH_2}CO_2CH_3$, CH_2CON, $\frac{1}{2}NCHC\underline{H_2}$); 7.30-5.20 (m, 10H, NCH_2, $C\underline{H}OH$, $OC\underline{H}(CH_2)_4$, CO_2CH_3 (6.40), OH, NCH, OCH).

References and Notes

1. S. Moncada, R. Gryglewski, S. Bunting and J.R. Vane, Nature, 263, 663 (1976).
2. K.C. Nicolaou, W.E. Barnette and R.L. Magolda, J. Amer. Chem. Soc., 101, 766 (1979); M. Shibasaki, J. Ueda and S. Ikegami, Tetrahedron Letters, 433 (1979); and references cited therein.
3. The analogues were obtained as oils consisting of mixtures of racemic diastereoisomers. Physical data (PMR and/or HPLC) for (6a) and (6c) indicated each contained unequal amounts of 6(S) and 6(R) epimers, although it could not be ascertained which predominated (see Reference 9).
4. British Patents 1524818 and 1524819 (1978); Chem. Abs., 85, 192576s and 91, 39150c.
5. G. Stork, A.Y.W. Leong and A.M. Touzin, J. Org. Chem., 41, 3491 (1976).
6. British Patent 1355991 (1974); Chem. Abs., 76, 24712d.
7. Prepared by Reformatsky reaction of ethyl bromoacetate with octan-2-one, reduction and subsequent tosylation.
8. Where necessary, purification was carried out by column chromatography on Merck Kieselgel 60.
9. R.A. Johnson, F.H. Lincoln, E.G. Nidy, W.P. Schneider, J.L. Thompson and U. Axen, J. Amer. Chem. Soc., 100, 7690 (1978).
10. NMR spectrum of (6a) was determined on a Varian CFT-20 (79.5 MHz) instrument and that of (6c) on a Varian EM-390 (90 MHz) instrument, both using TMS as internal standard.

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