Tetrahedron Letters,Vol.25,No.19,pp 1979-1982,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A VERSATILE TOTAL SYNTHESIS OF α-D-PURPUROSAMINIDES C

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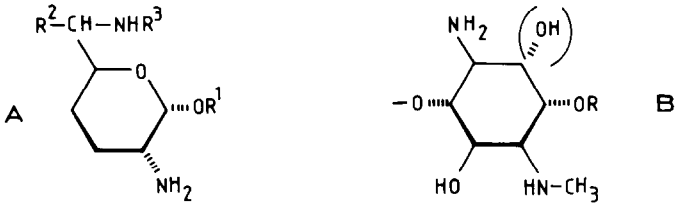
A convenient synthesis of methyl α-D-purpurosaminide C has been developed starting from dimeric acrolein (25-30 % overall yield of each enantiomer). Key steps are the efficient separation of intermediate diastereomeric amines and the stereospecific reduction of 2-oximino-α-hexopyranosides.

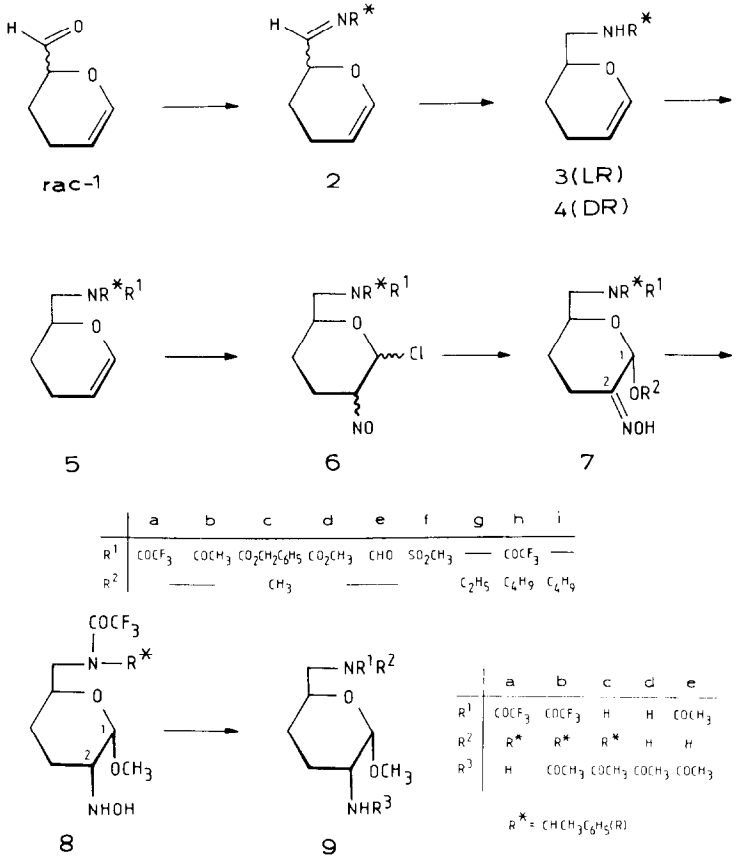
Purpurosamines (A) are components of many natural and semisynthetic antibiotics (e.g. gentamicins, fortimicins, sporaricins, dibekacin). Specifically for purpurosamine C several syntheses with chiral and achiral sources have been reported[1-9]; yields are usually low except in the procedures starting from neamine[1] and glucosamine[4,7].

For the total synthesis of chemically modified aminoglycoside antibiotics of the fortimicin (istamicin, sannamicin) type A (R^1=B) - efficient syntheses for appropriately protected precursors of the cis-1,4-(deoxy)inosadiamine aglycons (BH) have been worked out[10] - we have developed a syn-



thesis for methyl α-D-purpurosaminide C with the objective that intermediates should be applicable to glycosidation reactions without extensive functional group manipulations. Noticeable features of our approach are the easy availability of the educt, the high efficiency of the optical resolution, the stereospecific reduction of 2-oximino-α-hexopyranosides, and the relatively high yields. Starting material is the racemic acrolein dimer [11]

14 Hz), 2.99 (m,2-H), 3.24 (dd, 6-H', $J_{5,6'} \simeq 2$ Hz), 3.34 (s, OCH_3), 4.86 (d, 1-H, $J_{1,2} = 3.5$ Hz), which by Pd/C (HOAc, rt, 1 atm, 2d) is quantitatively reduced to 9a (94% from 7a, isolated as acetate 9b, colourless oil, $\delta(CDCl_3)$:



	a	b	c	d	e	f	g	h	i
R^1	$COCF_3$	$COCH_3$	$CO_2CH_2C_6H_5$	CO_2CH_3	CHO	SO_2CH_3	—	$COCF_3$	—
R^2	—		CH_3	—			C_2H_5	C_4H_9	C_4H_9

	a	b	c	d	e
R^1	$COCF_3$	$COCF_3$	H	H	$COCH_3$
R^2	R*	R*	R*	H	H
R^3	H	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_3$

R* = $CH(CH_3)C_6H_5$(R)

1.95 (s, $NHCOCH_3$), 2.68 (dd, 6-H, $J_{5,6} = 8.5$, $J_{6,6'} = 14$ Hz), 3.22 (dd, 6-H', $J_{5,6'} \simeq 2$ Hz), 3.31 (s, OCH_3), 3.9-4.1 (m, 2-,5-H), 4.56 (d, 1-H, $J_{1,2} = 3.5$ Hz) $[\alpha]_{578}^{23}$ +88° (c=0.93, CH_2Cl_2)). In 9b the trifluoracetamide bond is stable towards bases (NH_3, $CH_3ONa(CH_3OH)$) and acids (HCl/CH_3OH, CF_3COOH), but is cleaved by $NaBH_4$/EtOH (95%, 9c), whereupon the phenethylgroup can be eliminated by hydrogenolysis ($Pd(OH)_2$, $MeOH/H_2O$ 1:1, 25°C, 1 atm, 24 h). 9d is characterised as the known methyl 2,6-diacetamido-2,3,4,6-tetradeoxy-α-D-erythro-hexopyranoside (9e, methyl N,N'-diacetyl-α-D-purpurosaminide C, 90% from 9c) and the corresponding bis-ethylthioacetal [2,16].

1 which had been used by Brimacombe et al. [3] for the synthesis of racemic purpurosaminide C (4% overall yield).

After treatment of rac-1 with an equimolar amount of R(+)-1-phenylethylamine (0°C) and reduction ($NaBH_4$/EtOH,0°C) of the crude diastereomeric imines 2 the amines 3/4 are obtained in 90-95% yield. Their basicities are sufficiently different to allow selective protonation; with one equivalent (with respect to 4) of 3,5-dinitrobenzoic acid 55% salt of the desired 4 (m.p. 185°C, m.p. of the more soluble 3-salt 155°C) crystallises from acetonitrile. Separation of the remaining mixture (as the free bases) is effected on a large scale by "flash" chromatography [12] (ethyl acetate/ligroin (60-70°C) 1:10, 1% NEt_3, R_F(4) = 0.19, R_F(3) = 0.28). In this way the pure diastereomers are isolated in 80-85% yield (3,$[\alpha]_D^{24}$ +1° (c=1.9, benzene), 4,$[\alpha]_D^{24}$ +63° (c=1.1, benzene)). They are easily distinguishable, inter alia, by their high-field ^{1}H-nmr-spectra (CD_3CN, (3): δ= 2.42 (dd, 6'-H), 2.58 (dd, 6-H); (4): δ= 2.46 (dd, 6-H), 2.54 (dd, 6'-H); $J_{5,6}$= 8, $J_{5,6'}$= 4, $J_{6,6'}$= 11 Hz). 4 is transformed into the N-protected derivatives 5a-f by standard procedures ($(CF_3CO)_2O$/Py/CH_2Cl_2/0°C, Ac_2O/Py/0°C, $C_6H_5CH_2$-OCOCl(ClCOOMe)/NEt_3/toluene/0°C, HCOOMe/17 h/110°C/pressure, CH_3SO_2Cl/Py/0°C). Their reaction with NOCl [13] under standardised, strictly anhydrous conditions (CH_2Cl_2, -70°C, 5 min, evaporation i. vac.) leads to colourless-bluish solids (6a,f) or oils (6b-e). After immediate addition of 1.2 equiv. absol. methanol (DMF), preferably in the presence of the HCl-buffer 1,3,5-trimethyl-pyrazole, and purification the methyl α-D-oximinoglycosides 7a-f are obtained in yields which depend strongly on the group R^1 (e.g. 67% for 7c, 94% for 7a). 7a-f are rather unexpectedly [14] stable towards bases, but they rapidly exchange the aglycon in excess ethanol, 2-butanol, tert-butanol/HCl (e.g. 7g-i from 7a). After numerous unsuccessful attempts to achieve one-pot oximino → amine reduction (Pd/C, with variation of solvent, of pressure, with addition of acid, with Pd/N_2H_4,Zn/Cu/HOAc,LAH [15] this problem was solved by the following two-step procedure: $NaBH_3CN$/HOAc/25°C reduces 7a stereospecifically (DC, ^{1}H-nmr) and quantitatively to the stable methyl α-D-erythro-2-hydroxylamino-glycoside 8 (colourless oil, δ($CDCl_3$):2.7 (dd, 6-H, $J_{5,6}$= 8.5, $J_{6,6'}$=

Support from the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the BASF AG is gratefully acknowledged. We thank Dr. D. Hunkler for the nmr measurements.

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(Received in Germany 7 February 1984)