Approach to the Pseudodisaccharides Present in (Oxy)apramycin. Synthesis of a 4-*O*-Amino-octodiosyl-2-deoxystreptamine from Paromamine

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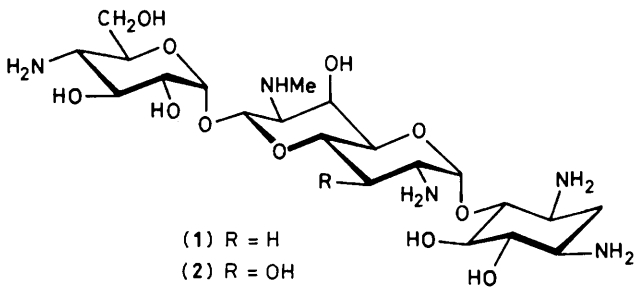
The synthesis of an *N*-protected 2′-amino-2′-deoxy-1′-*O*-(2-deoxystreptamin-4-yl)-α-D-*threo*-D-*gluco*-octo-1′,5′ : 4′,8′-dipyranose in nine steps from paromamine is described; the key steps are the conversion of paromamine into a protected octuronic acid derivative, followed by its 8′,4′-lactonization upon removal of the *O*-protecting groups, and partial reduction of the resulting '*trans*-decalone-like' lactone.

Apramycin (**1**)[1] and oxyapramycin (**2**),[2] two potent antibiotics isolated from the aminoglycoside complex nebramycin[3] produced by *Streptomyces tenebrarius*, have been shown[2,4] to contain a unique amino-octodiosyl component which exists as a rigid, *trans*-decalin-like system. Previous investigations from this laboratory[5] have already led to the first examples of octodioses adopting a bipyranoid structure. In this communication, we describe the first synthesis of a pseudodisaccharide containing an amino-octodiose, a close analogue of the pseudodisaccharide present in oxyapramycin (**2**).

Starting from paromamine (**3**), our strategy involves a two-carbon chain elongation to an octuronic acid derivative, functionalization of positions 6′ and 7′, lactonization of the octuronic ester, and reduction of the lactone to an octodialdose derivative.

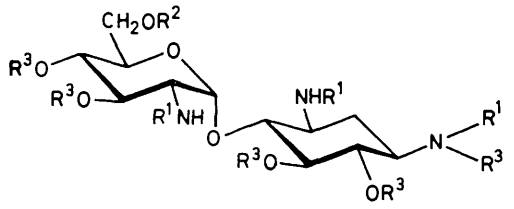
Thus, paromamine (**3**)[6] was selectively *N*-tosylated using toluene-*p*-sulphonyl chloride in water–dioxane (1 : 2 v/v) in the presence of sodium carbonate to give (**4**), and the primary hydroxy-function of (**4**) then was protected as its t-butyldimethylsilyl ether [Bu^{t}Me$_2$SiCl, 4-(dimethylamino)pyridine, dimethylformamide (DMF)]. Benzoylation of the resulting



(**1**) R = H
(**2**) R = OH

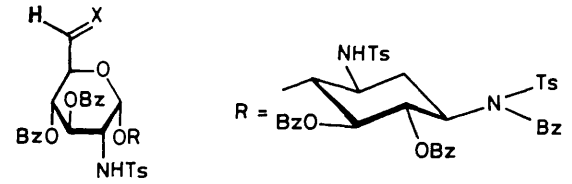
(**5**) under standard conditions afforded compound (**6**) in which the toluene-*p*-sulphonamido group at position 1 exclusively is *N*-benzoylated, as indicated by the presence of only two NH signals in its ^{1}H n.m.r. spectrum† and the

† ^{1}H and ^{13}C N.m.r. spectra were recorded at 200 and 50.307 MHz, respectively, on a Bruker CXP-200 spectrometer. δ Values are in p.p.m. from SiMe$_4$.

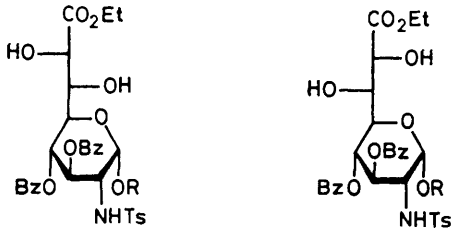


(3) $R^1 = R^2 = R^3 = H$
(4) $R^1 = Ts$, $R^2 = R^3 = H$
(5) $R^1 = Ts$, $R^2 = SiMe_2Bu^t$, $R^3 = H$
(6) $R^1 = Ts$, $R^2 = SiMe_2Bu^t$, $R^3 = Bz$
(7) $R^1 = Ts$, $R^2 = H$, $R^3 = Bz$

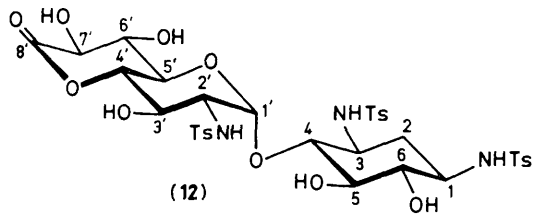
Ts = *p*-$MeC_6H_4SO_2$, Bz = PhCO



(8) X = O
(9) X = *E*-$CHCO_2Et$

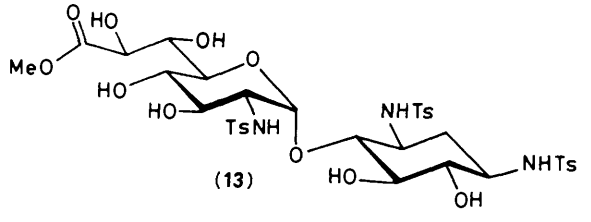


(10) (11)



(12)

MeOH, H^+ ⇅ MeOH, MeONa



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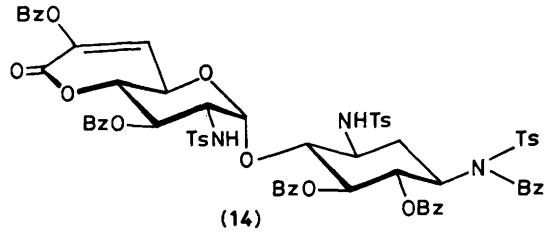
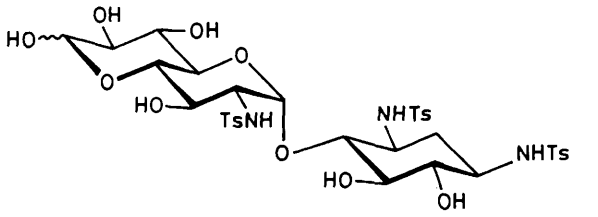


(14)



(15)

chemical-shift difference between H-1 (δ 4.52, $CDCl_3$) and H-3 (δ 3.67). The 6′-*O*-silyl group of (**6**) then was cleaved under mildly acidic conditions [tetrahydrofuran (THF)–AcOH–H_2O, 4:2:1 v/v, 3 h at 90 °C] to give the suitably protected precursor (**7**) (m.p. 153—156 °C; $[\alpha]_D^{23}$ −32.8°, *c* 1.0, $CHCl_3$) in a 62% overall yield from paromamine.

Oxidation of (**7**) to the key *aldehydo* intermediate (**8**) could be achieved under neutral conditions using Moffatt's original procedure (C_6H_6–Me_2SO–pyridine–trifluoroacetic acid, 100:10:2:1 v/v, dicyclohexylcarbodi-imide; see ref. 7). The highly base-sensitive (**8**) was isolated with a very satisfactory degree of purity upon aqueous processing of the mixture and used without further purification for the subsequent steps. Thus, condensation of (**8**) with $Ph_3P{=}CHCO_2Et$ gave the expected unsaturated octuronic ester (**9**) (*E*-isomer only) in excellent yield [80% from (**7**)]. As an initial approach to the 7′-hydroxy-analogues of the natural pseudodisaccharides, compound (**9**) was submitted to *cis*-hydroxylation. The two possible stereoisomers (**10**) (α-D-*threo*-D-*gluco*) and (**11**) (β-L-*threo*-D-*gluco*) were obtained in a 3:1 ratio (70—85%) using pure osmium tetroxide in pyridine, and in a 1:4 ratio (51%) using osmium tetroxide as a catalyst and t-butyl hydroperoxide as the main oxidant,[8] an interesting and useful result providing selective access to one or the other isomer.

Base-catalysed debenzoylation (MeONa in MeOH–CH_2Cl_2) of compound (**10**) was found to lead simultaneously to 8′,4′-lactonization and gave quantitatively the bicyclic lactone (**12**) [m.p. 187—195 °C (decomp.); ν(C=O) 1735 cm^{-1}, δ(^{13}CO) 175.78 $(CD_3)_2SO$], the first example of a bicyclic uronolactone having two fused six-membered rings. Alcoholysis of (**12**), however, is exceedingly easy and, for example, the corresponding methyl octuronate (**13**) {m.p. 160—167 °C; $[\alpha]_D^{26}$ + 32.6°, *c* 0.95, MeOH; ν(C=O) 1735 cm^{-1}; δ(^{13}CO) 173.35} is rapidly formed in methanol containing a trace of an acidic catalyst. Hence, isolation of (**12**) from its methanol solution is critical and can be achieved only if a base (*e.g.* $MeCO_2Na$) is retained. The behaviour of (**12**) is thus in obvious contrast with that of the well known hexofuranurono-6,3-lactones.[9]

Attempted perbenzoylation of (**12**) afforded as the sole product the enol-lactone benzoate (**14**) arising most probably from a β-elimination of benzoic acid from the saturated perbenzoate of (**12**), a common reaction of simple acylated aldonolactones (*e.g.* see ref. 10).

Although free aldonolactones have been converted usually efficiently into the corresponding free sugars using disiamylborane [bis(1,2-dimethylpropyl)borane],[11] the best results for the key reduction of (**12**) to the expected amino-octodialdose derivative were obtained with lithium aluminium hydride.[12] Thus, treatment of (**12**) [or of (**13**)] with this reagent in a 1:1 mixture of dry pyridine and THF [(**13**) in THF only] at low temperature and then at 0 °C (overnight) afforded the reducing compound (**15**) (*ca.* 30%) (m.p. 208—214 °C; $[\alpha]_D^{25}$ −10.1°, *c* 0.74, MeOH), the structure of which has been established by its ^{1}H n.m.r. spectrum (δ H-1's 5.27, 5.33; δ H-7′α 3.50, $J_{6'\alpha,7'\alpha}$ 9.0 Hz; δ H-8′α 5.09, $J_{7'\alpha,8'\alpha}$ 3.5 Hz;

δ H-8′β 4.45, $J_{7'\beta,8'\beta}$ 7.5 Hz; CD_3OD). The further elaboration of (**15**) and of isomer (**11**), as well as a new approach to the 7′-aminopseudodisaccharide, are being studied.

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