## 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)- $\alpha$ -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),<sup>2</sup> two potent antibiotics isolated from the aminoglycoside complex nebramycin<sup>3</sup> produced by *Streptomyces tenebrarius*, have been shown<sup>2,4</sup> to contain a unique amino-octodiosyl component which exists as a rigid, *trans*-decalin-like system. Previous investigations from this laboratory<sup>5</sup> 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 twocarbon 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-butyl-dimethylsilyl ether [Bu<sup>t</sup>Me<sub>2</sub>SiCl, 4-(dimethylamino)pyridine, dimethylformamide (DMF)]. Benzoylation of the resulting



(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 <sup>1</sup>H n.m.r. spectrum<sup> $\dagger$ </sup> and the

 $<sup>\</sup>dagger$  <sup>1</sup>H and <sup>13</sup>C N.m.r. spectra were recorded at 200 and 50.307 MHz, respectively, on a Bruker CXP-200 spectrometer.  $\delta$  Values are in p.p.m. from SiMe<sub>4</sub>.



chemical-shift difference between H-1 ( $\delta$  4.52, CDCl<sub>3</sub>) and H-3 ( $\delta$  3.67). The 6'-O-silyl group of (6) then was cleaved under mildly acidic conditions [tetrahydrofuran (THF)–AcOH-H<sub>2</sub>O, 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<sub>3</sub>) 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<sub>2</sub>SO-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<sub>3</sub>P=CHCO<sub>2</sub>Et 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) ( $\alpha$ -D-threo-D-gluco) and (11) ( $\beta$ -Lthreo-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,<sup>8</sup> an interesting and useful result providing selective access to one or the other isomer.

Base-catalysed debenzoylation (MeONa in MeOH-CH<sub>2</sub>Cl<sub>2</sub>) 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.); v(C=O) 1735 cm<sup>-1</sup>,  $\delta$ (<sup>13</sup>CO) 175.78 (CD<sub>3</sub>)<sub>2</sub>SO], 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; [ $\alpha$ ]<sup>26</sup><sub>2</sub> + 32.6°, c 0.95, MeOH; v(C=O) 1735 cm<sup>-1</sup>;  $\delta$ (<sup>13</sup>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<sub>2</sub>Na) is retained. The behaviour of (12) is thus in obvious contrast with that of the well known hexofuranurono-6,3-lactones.<sup>9</sup>

Attempted perbenzoylation of (12) afforded as the sole product the enol-lactone benzoate (14) arising most probably from a  $\beta$ -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],<sup>11</sup> the best results for the key reduction of (12) to the expected amino-octodialdose derivative were obtained with lithium aluminium hydride.<sup>12</sup> 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;  $[\alpha]_{25}^{25} -10.1^{\circ}$ , c 0.74, MeOH), the structure of which has been established by its <sup>1</sup>H n.m.r. spectrum ( $\delta$  H-1's 5.27, 5.33;  $\delta$  H-7' $\alpha$  3.50,  $J_{6'\alpha7'\alpha}$  9.0 Hz;  $\delta$  H-8' $\alpha$  5.09,  $J_{7'\alpha8'\alpha}$  3.5 Hz;

 $\delta$  H-8' $\beta$  4.45,  $J_{7'\beta,8'\beta}$  7.5 Hz; CD<sub>3</sub>OD). 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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