Synthetic Routes to Amino Sugars. Efficient Syntheses of 4-Amino- and 4,6-Diamino-hexopyranosides and Forosamine *via* Hex-2-enopyranosides

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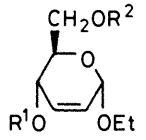
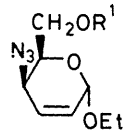
4-Amino-, and 4,6-diamino-hexopyranosides of the *threo*- and *erythro*-series have been synthesized from D-glucose *via* hex-2-enopyranosides. Further work along these lines led to an effective synthesis of forosamine, a 4-deoxy-4-amino sugar moiety of the spiramycin antibiotics.

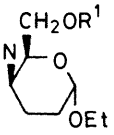
The 4- and 6-amino sugars are widely distributed in nature in free or combined forms, and some of them constitute the essential parts of highly effective antibiotics.[1-7] The diamino sugars have also been identified in potential antibiotics such as prumycin,[8] neomycin C,[9] and zygomycin A.[10] From the viewpoint of medicinal chemistry, it has become of interest to investigate the syntheses and biological activities of such compounds. In a previous communication we described a convenient one-pot synthesis of 4-amino pentopyranosides.[1] We now report the details of our preliminary investigations [11] of the synthetic route to 4-amino- and 4,6-diamino-hexopyranosides of both the *threo*- and *erythro*-configuration *via* hex-2-enoses. Prior to this work there was no reference in the literature to the synthesis of 4,6-diamino sugars. Forosamine (2,3,4,6-tetradeoxy-4-dimethylamino-α-D-*erythro*-hexopyranose) is the amino sugar moiety of the spiramycin antibiotics [12] and the total synthesis of this potential compound has also been developed *via* 2-eno sugars. This constitutes a short and more efficient route than that cited in the literature which proceeds through intervening saturated hexopyranosides.[12]



(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = COC_6H_4NO_2-p$
(3) $R^1 = Ts$, $R^2 = COC_6H_4NO_2-p$



(4) $R^1 = COC_6H_4NO_2-p$
(5) $R^1 = H$



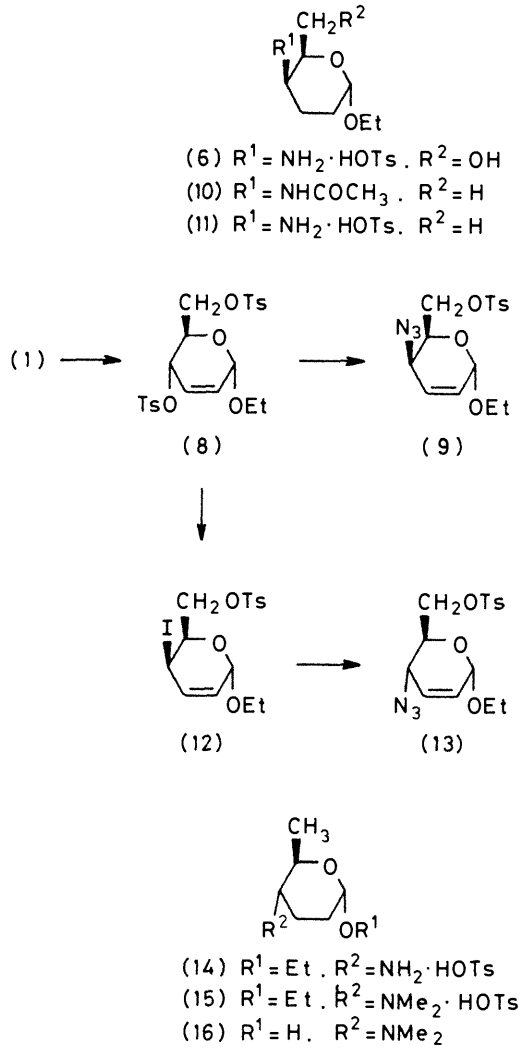
(6) $R^1 = H$
(7) $R^1 = COC_6H_4NO_2-p$

Ts = Tosyl

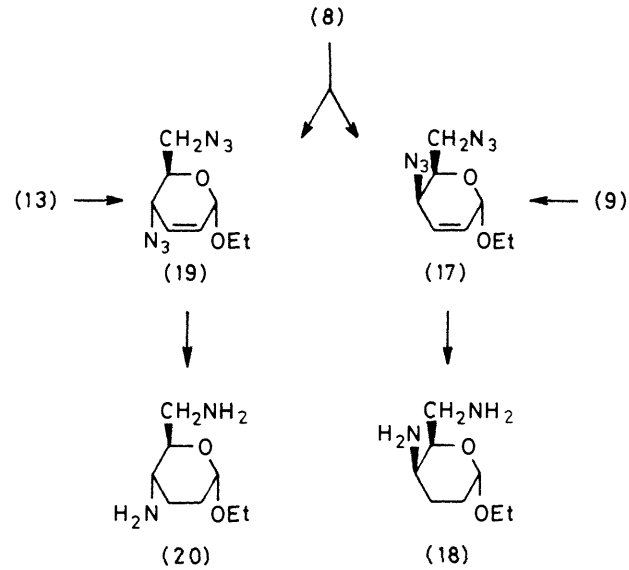
Results and Discussion

Syntheses of 4-*Amino Sugars*.—Ethyl 4-amino-2,3,4-trideoxy-α-D-*threo*-hexopyranoside (6) and its 6-*O*-*p*-nitrobenzoyl derivative (7) were obtained by the reaction sequence outlined below. Following the traditional procedures ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (1) [13,14] was prepared in three steps from D-glucose. The 6-hydroxy group of (1) was protected through preferential esterification with *p*-nitrobenzoyl chloride,[13] and tosylation of the resulting compound (2) gave the toluene-*p*-sulphonate (3). Displacement of the tosyl group with sodium azide in dimethylformamide (DMF) at room temperature caused inversion at C-4 to afford the *threo*-azide (4). Brief treatment with 5% alcoholic potash removed the *p*-nitrobenzoyl group from C-6 to give compound (5), which on catalytic hydrogenation provided the 4-amino derivative, isolated and characterized as its toluene-*p*-sulphonate salt (6). On the other hand, direct catalytic hydrogenation of compound (4), followed by treatment with toluene-*p*-sulphonic acid, furnished the toluene-*p*-sulphonate (7). Ethyl 4-amino-2,3,4,6-tetradeoxy-α-D-*threo*-hexopyranoside hydrogen toluene-*p*-sulphonate (11), its *erythro*-analogue (14), and forosamine (16) were synthesized as illustrated in Scheme 1. Reaction of compound (1) with toluene-*p*-sulphonyl chloride in pyridine–dichloromethane at −30 °C gave the 4,6-ditosyldiester (8) [14] which reacted with sodium azide in DMF at room temperature to yield the *threo*-monoazide (9). The displacement of the secondary tosyl group, occurring in preference to that of the primary tosyl group, is opposite to that observed for saturated pyranosides. The rate enhancement of the nucleophilic displacement reaction in allylic systems can be attributed to the stabilisation of the reaction transition state by the double bond.[15] Catalytic hydrogenation of the azide (9) simultaneously removed the primary tosyl group and acetylation of the reduction product provided ethyl 4-acetamido-2,3,4,6-tetradeoxy-α-D-*threo*-hexopyranoside (10). The reduction of primary tosyl esters by lithium aluminium hydride yields, in most cases, the corresponding deoxy sugars but we have discovered that such a conversion can also be effected under favourable conditions by catalytic hydrogenation over 10% palladium–charcoal. *N*-Deacetylation of (10) with barium hydroxide afforded the free amino sugar [12] which was isolated and characterized as its toluene-*p*-sulphonate salt (11). The trideoxy amino sugar (6) could also be obtained by reductive alkaline hydrolysis of the primary tosyl group in (9) with sodium amalgam, followed by catalytic hydrogenation and similar work-up as described in the foregoing account. The yield of compound (6) was lower than that recorded above but it provides a short route for this compound.

Entry into the *erythro*-series was made possible by effecting double inversion of configuration at C-4 of the ditosyldiester (8). Treatment of (8) with sodium iodide in acetone at room temperature gave the *threo*-4-iodo derivative (12) which was used, without extensive purification, to minimise loss of material. Reaction of compound (12) with sodium azide in refluxing acetone, followed by silica-gel column chromatography, provided the *erythro*-monoazide (13) from which the



Scheme 1.



Scheme 2.

corresponding amino sugar was obtained (by catalytic hydrogenation) as its toluene-*p*-sulphonate salt (14).[12] Reductive dimethylation of (14) cleanly afforded the toluene-*p*-sulphonate salt of the 4-dimethylamino derivative (15), which, on acidic hydrolysis with dilute sulphuric acid (pH 3.1, 90 °C), gave forosamine (16).[12]

Syntheses of 4,6-*Diamino Sugars*.—The azido sugar (9) reacted with an excess of sodium azide in dimethyl sulphoxide (DMSO) at 120 °C for 2 h to yield a mixture of products from which the major compound could be isolated by silica-gel column chromatography and identified as the *threo*-4,6-diazido sugar (17). Catalytic hydrogenation cleanly afforded the corresponding diamino sugar (18). Similar reactions with the azido sugar (13) provided the *erythro*-4,6-diazido sugar (19) and the related diamino sugar (20), respectively. The diazido sugars (18) and (19) could also be obtained directly from the *erythro*-4,6-ditosyldiester (8). Reaction of (8) with an excess of sodium azide in absolute DMSO at 140 °C for 4 h gave a mixture of four products comprising epimeric pairs of monoazido sugars, (9) and (13), and diazido sugars, (17) and (19). The formation of monoazido sugars was, however, appreciably depressed under the reaction conditions used and silica-gel column chromatography furnished in 50% combined yield the diazido sugars (17) and (19) in the ratio 3 : 2 (Scheme 2).

All the compounds obtained in the present work gave accurate analyses which are described along with physical data in Table 1.

Since the nucleophilic displacements at C-4 with the *erythro*- and *threo*-compounds invariably lead to products of inverted configuration at allylic centres, they probably involve an S_N2 or ion-pair mechanism. All these reactions, however, occur readily in DMF in which the anionic nucleophiles are less solvated and are thus free to react, whereas the polar transition states are stabilised by solvation compared with the analogous reactions in protic solvents.[16] This, along with the observation that the reaction rates varied considerably with the nature and concentration of nucleophiles, suggested strongly the operation of an S_N2 mechanism rather than a unimolecular process.

The configurations of various compounds were determined by ^{1}H n.m.r. spectroscopy. The α-D-hex-2-enopyranosides have already been shown to adopt the $^0H_5$ conformation [17,18] in which the anomeric effect is favourable while C-6 adopts the preferred equatorial orientation. For the *erythro*-compounds 4-H and 5-H have the quasi-axial, axial relationship and the calculated $^{19}J_{4,5}$ value is 9.2 Hz whereas in *threo*-compounds 4-H and 5-H have the quasi-equatorial, axial relationship and the corresponding $J_{4,5}$ value is *ca.* 2 Hz. $J_{3,4}$ Values of *ca.* 2 and 4.5 Hz obtained for *erythro*- and *threo*-compounds were found to be in good agreement with those calculated by Gabish.[20] The $J_{1,2}$ values observed for the ethyl 2,3-dideoxy-α-D-hex-2-enopyranosides where 1-H is equatorial varied from 0—2.5 Hz and were found to depend on the configuration at the other allylic centre (C-4). For the *threo*-compounds (substituent at C-4 quasi-axial) $J_{1eq,2}$ values of *ca.* 1.5—2.5 Hz and for the *erythro*-analogues (substituent at C-4 quasi-equatorial) $J_{1eq,2}$ values of *ca.* 0—1.8 Hz were obtained. This observation served as an additional means of diagonising the *erythro* and *threo* configurations. A summarized account of the ^{1}H n.m.r. spectra of the unreported compounds obtained in the present work is given in Table 2.

The ^{13}C n.m.r. spectra of these compounds were also recorded (Table 3), not only to lend further support to the assigned structures, but also because of the fact that the ^{13}C

Table 1. Physical data and analyses [a] of compounds (3)—(7), (9)—(11), and (13)—(20)

Compd.	Yield (%)	M.p. (°C) (solvent)	$[\alpha]_D^{20}$ (°) [b] (solvent)	Formula	Found (%) (Required) C	H	N	S
(3)	68	114—115 (Et_2O)	+23.4 ($CHCl_3$)	$C_{22}H_{23}NO_9S$	55.9 (55.34	4.7 4.82	2.8 2.93	6.8 6.7)
(4)	83	58 (EtOH)	−153.8 ($CHCl_3$)	$C_{15}H_{16}N_4O_6$	51.5 (51.72	4.7 4.59	15.95 16.09	— —)
(5)	98	36—37 (n-Hexane)	−265.7 ($CHCl_3$)	$C_8H_{13}N_3O_3$	48.3 (48.24	6.6 6.53	21.2 21.1	— —)
(6)	73	151—152 (decomp.) ($CHCl_3$–n-Hexane)	+54.1 (water)	$C_{15}H_{25}NO_6S$	51.9 (51.87	7.1 7.2	4.1 4.03	9.3 9.22)
(7)	71	171—172 (decomp.) (EtOAc–Et_2O)	+28.1 (water)	$C_{22}H_{28}N_2O_9S$	53.3 (53.22	5.7 5.64	5.6 5.64	6.5 6.45)
(9)	83	57 (MeOH–water)	−55 (CH_2Cl_2)	$C_{15}H_{19}N_3O_5S$	50.7 (50.99	5.3 5.38	11.85 11.89	8.9 9.06)
(10)	79	151 (EtOAc–Et_2O)	+60.6 ($CHCl_3$)	$C_{10}H_{19}NO_3$	59.55 (59.7	9.55 9.45	7.05 6.96	— —)
(11) [12]	72	146—147 (Et_2O)	+80.7 ($CHCl_3$)	$C_{15}H_{25}NO_5S$	54.4 (54.38	7.45 7.52	4.3 4.23	9.6 9.66)
(13)	71	Oil	+88 (CH_2Cl_2)	$C_{15}H_{19}N_3O_5S$	50.6 (50.99	5.4 5.38	11.85 11.89	9.0 9.06)
(14) [12]	74	130—131 (Et_2O)	+77.2 (MeOH)	$C_{15}H_{25}NO_5S$	54.3 (54.38	7.6 7.52	4.3 4.23	9.55 9.66) *
(15) [12]	81	90—92 (EtOAc–Et_2O)	+91.1 (MeOH)	$C_{17}H_{29}NO_5S$	56.75 (56.82	8.1 8.07	3.9 3.89	8.9 8.91)
(16) [12]	61	60 (sublimation)	+87.3 (MeOH)	$C_8H_{17}NO_2$	60.5 (60.37	10.6 10.69	8.85 8.8	— —)
(17)	38	Oil	−276 (CH_2Cl_2)	$C_8H_{12}N_6O_2$	42.8 (42.85	5.3 5.35	37.9 37.5	— —)
(18)	78	Oil	+53 (MeOH)	$C_8H_{18}N_2O_2$	55.2 (55.17	10.25 10.34	16.1 16.01	— —)
(19)	33	Oil	+309 (CH_2Cl_2)	$C_8H_{12}N_6O_2$	42.75 (42.85	5.35 5.35	37.6 37.5	— —)
(20)	74	Oil	+109 (MeOH)	$C_8H_{18}N_2O_2$	55.1 (55.17	10.3 10.34	16.2 16.09	— —)

[a] Elemental analyses were carried out with a Carlo Erba Elemental Analyser, Model 1 104. [b] The optical rotations were measured on a Digital polarimeter OLD 5, Zeiss.

* Calc. for known compound.

Table 2. ^1H N.m.r. data [a] of compounds (3)—(7), (9)—(10), (13), and (17)—(20)

Compd.	ArH [b]	Pyranoside ring	1-O-CH_2 [c]	1-O-CH_2CH_3 [d]	Other signals	Coupling constants (Hz) $J_{1,2}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
(3) [e]	8.22 (4 H, dd), 7.34 (4 H, dd)	5.87 (2 H, m, 2- and 3-H), 5.16 (1 H, d, 1-H), 4.98 (1 H, dd, 4-H), 4.34—4.16 (3 H, m, 5-H and 6-H_2)	3.6 (m)	1.17 (t)	2.3 (3 H, s, $CH_3C_6H_4$)	1.7	1.8	9.5	*
(4) [e]	8.24 (4 H, dd)	6.13 (2 H, m, 2- and 3-H), 5.08 (1 H, d, 1-H), 4.64 (1 H, m, 4-H), 4.51 (2 H, m, 6-H_2), 3.4 (1 H, t, 5-H)	3.6 (m)	1.13 (t)		2.2	4.4	2.1	2.7
(5) [e]		5.91 (2 H, m, 2- and 3-H), 5.09 (1 H, d, 1-H), 4.68 (1 H, dd, 4-H), 3.9 (2 H, m, 6-H_2), 3.35 (1 H, t, 5-H)	3.56 (m)	1.12 (t)		2.5	4.2	2.5	2.8
(6) [f]	7.55 (4 H, dd)	4.91 (1 H, m, 1-H), 4.67 (1 H, m, 4-H), 3.94—3.66 (3 H, m, 5-H and 6-H_2), 1.94 (2 H, m, 2-H_2), 1.67 (2 H, m, 3-H_2)	3.61 (m)	1.14 (t)	2.12 (3 H, s, $CH_3C_6H_4$)	*	*	*	*

Table 2 (*continued*)

Compd.	ArH [b]	Pyranoside ring	1-O-CH_2 [c]	1-O-CH_2CH_3 [d]	Other signals	Coupling constants (Hz) $J_{1,2}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
(7) [f]	8.2 (4 H, dd), 7.55 (4H, dd)	4.85 (1 H, m, 1-H), 4.67 (1 H, m, 4-H), 4.01—3.64 (3 H, m, 5-H and 6-H_2), 1.98 (2 H, m, 2-H_2), 1.65 (2 H, m, 3-H_2)	3.55 (m)	1.12 (t)	2.14 (3 H, s, $CH_3C_6H_4$)	*	*	*	*
(9) [e]	7.44 (4 H, dd)	6.06 (2 H, m, 2- and 3-H), 4.90 (1 H, d, 1-H), 4.28 (1 H, dd, 4-H), 4.19 (2 H, m, 6-H_2), 3.31 (1 H, t, 5-H)	3.62 (m)	1.18 (t)	2.43 (3 H, s, $CH_3C_6H_4$)	2.1	4.4	2.2	2.4
(10) [e]		4.76 (1 H, m, 1-H), 4.1 (1 H, m, 4-H), 3.31 (1 H, q, 5-H), 1.79 (2 H, m, 2-H_2), 1.61 (2 H, m, 3-H_2), 1.04 (3 H, d, 6-H_3)	3.61 (m)	1.19 (t)	5.93 (1 H, br s, $NHCOCH_3$), 2.1 (3 H, s, $COCH_3$)	*	*	*	7.1
(13) [e]	7.55 (4 H, dd)	5.96 (2 H, m, 2- and 3-H), 5.09 (1 H, d, 1-H), 4.31 (1 H, dd, 4-H), 4.11 (2 H, m, 6-H_2), 3.35 (1 H, m, 5-H)	3.62 (m)	1.17 (t)	2.24 (3 H, s, $CH_3C_6H_4$)	1.7	2	9.5	*
(17) [e]		6.1 (2 H, m, 2- and 3-H), 4.87 (1 H, d, 1-H), 3.89 (1 H, dd, 4-H), 3.38 (3 H, m, 5-H and 6-H_2)	3.71 (m)	1.21 (t)		2.5	4.5	2.3	*
(18) [e]		4.9 (1 H, m, 1-H), 4.09 (1 H, m, 4-H), 3.31 (2 H, m, 6-H_2), 3.04 (1 H, t, 5-H), 2.01 (2 H, m, 2-H_2), 1.69 (2 H, m, 3-H_2)	3.66 (m)	1.22 (t)		*	*	*	4.7
(19) [e]		6.12 (2 H, m, 2- and 3-H), 5.09 (1 H, d, 1-H), 4.22 (1 H, dd, 4-H), 3.5 (3 H, m, 5-H and 6-H_2)	3.7 (m)	1.24 (t)		1.8	1.9	9.1	*
(20) [e]		4.88 (1 H, m, 1-H), 4.01 (1 H, m, 4-H), 3.34 (2 H, m, 6-H_2), 3.08 (1 H, t, 5-H), 1.99 (2 H, m, 2-H_2), 1.68 (2 H, m, 3-H_2)	3.64 (m)	1.2 (t)		*	*	*	4.6

[a] At 100 MHz on a Varian HA 100 spectrometer. Chemical shifts are quoted in δ units relative to Me_4Si. [b] The aromatic protons of the *p*-nitrobenzoyl group were observed at δ 8—8.3, J_{ortho} 8.1 Hz. The aromatic protons of the tosyl group came at δ 7.3—7.6, J_{ortho} 8 Hz. [c] $J(CH_3)$ 6.8—6.9 Hz. [d] $J(CH_2)$ 7—7.1 Hz. [e] $CDCl_3$. [f] D_2O.

* Could not be calculated due to complex pattern.

n.m.r. data of such compounds are not frequently available in the literature.

Experimental

M.p.s were recorded in glass capillaries and are uncorrected. Field desorption mass spectra were determined with a 311 A Varian instrument, and i.r. spectra with a Perkin-Elmer Infracord 2221 spectrometer. The catalytic hydrogenations were performed at 1 atmosphere and room temperature over 10% palladium–charcoal. The compounds (1), (2), and (8) were prepared in reproducible yields according to reported procedures.[13,14] The physical data and ^1H and ^{13}C n.m.r. spectra of various compounds are given in Tables 1—3.

Ethyl 2,3-*Dideoxy*-6-O-p-*nitrobenzoyl*-4-O-*tosyl*-α-D-erythro-*hex*-2-*enopyranoside* (3).—Toluene-*p*-sulphonyl chloride (6.1 g, 30.2 mmol) was added to a solution of ethyl 2,3-

Table 3. ^{13}C N.m.r. data * of compounds (3)—(7), (9), (10), (13), and (17)—(20)

Compd.	C-1	C-2	C-3	C-4	C-5	C-6	1-O-CH_2	1-O-CH_2CH_3	Other signals
(3) [a]	94.1 (d)	129.2 (d)	127.81 (d)	66.33 (d)	71.41 (d)	64.75 (t) [c]	64.1 (t) [c]	15.13 (q)	21.52 (q, $CH_3C_6H_4$)
(4) [a]	93.9 (d)	130.7 (d)	123.61 (d)	52.43 (d)	68.15 (d)	65.03 (t) [c]	63.99 (t) [c]	15.19 (q)	
(5) [a]	93.82 (d)	130.23 (d)	123.49 (d)	52.57 (d)	68.01 (d)	64.81 (t) [c]	64.01 (t) [c]	15.11 (q)	
(6) [b]	97.89 (d)	25.31 (t)	24.52 (t)	49.89 (d)	68.86 (d)	65.39 (t)	64.51 (t)	16.12 (q)	23.2 (q, $CH_3C_6H_4$)
(7) [b]	97.82 (d)	25.29 (t)	24.81 (t)	49.77 (d)	69.84 (d)	65.89 (t)	64.31 (t)	16.38 (q)	22.9 (q, $CH_3C_6H_4$)
(9) [a]	93.69 (d)	129.61 (d)	123.54 (d)	51.87 (d)	68.86 (d)	67.83 (t)	64.07 (t)	15.04 (q)	22.6 (q, $CH_3C_6H_4$)
(10) [a]	96.85 (d)	23.77 (t)	23.37 (t)	46.9 (d)	62.62 (d)	17.52 (q)	64.92 (t)	15.01 (q)	170.04 (s, C=O), 24.44 (q, CH_3CO)
(13) [a]	98.48 (d)	131.19 (d)	121.36 (d)	54.61 (d)	70.69 (d)	66.26 (t)	64.25 (t)	14.89 (q)	22.2 (q, $CH_3C_6H_4$)
(17) [a]	93.85 (d)	131.14 (d)	121.81 (d)	52.68 (d)	69.42 (d)	51.84 (t)	64.08 (t)	15.09 (q)	
(18) [a]	95.63 (d)	20.68 (t)	20.26 (t)	47.28 (d)	63.59 (d)	42.95 (t)	64.32 (t)	14.31 (q)	
(19) [a]	98.52 (d)	131.21 (d)	120.77 (d)	54.75 (d)	67.60 (d)	54.26 (t)	64.27 (t)	14.92 (q)	
(20) [a]	96.63 (d)	20.76 (t)	20.36 (t)	45.54 (d)	61.37 (d)	43.24 (t)	64.62 (t)	14.43 (q)	

* At 22.6 MHz on an HFX 90, Bruker-Physik AG machine. Chemical shifts are in p.p.m. from Me_4Si. Signal multiplicity obtained by off-resonance decoupling experiments. The carbonyl and aromatic carbons of the *p*-nitrobenzoyl and tosyl groups are not described for the sake of simplicity.

[a] $CDCl_3$. [b] D_2O. [c] The assignments of these signals may be reversed.

dideoxy-6-*O*-*p*-nitrobenzoyl-α-D-*erythro*-hex-2-enopyranoside (2) (9.69 g, 30 mmol) in pyridine (15 ml). The reaction mixture was stirred at room temperature for 12 h then poured onto crushed ice and extracted with chloroform. The extract was washed in turn with dilute hydrochloric acid, water, dilute aqueous sodium hydrogencarbonate, and again with water and was dried (Na_2SO_4). Removal of solvent gave a thick oily residue which was taken up in diethyl ether from which the tosyl ester (3) crystallized as needles, $\nu_{max.}$ 1 730 (CO), 1 615 (C=C), 1 555 (NO_2), 1 340, 1 320, 1 175, and 1 155 cm^{-1} (SO_2); *m/z* 477 (M^+), 432 ($M - OCH_2CH_3)^+$, 268 ($M - CH_2OCOC_6H_4NO_2 - CHO)^+$, and 155 ($CH_3C_6H_4SO_2^+$).

Ethyl 4-*Azido*-2,3,4-*trideoxy*-6-O-p-*nitrobenzoyl*-α-D-threo-*hex*-2-*enopyranoside* (4).—A solution of compound (3) (9.54 g, 20 mmol) in DMF (15 ml) was stirred with sodium azide (8 g) at room temperature for 24 h. The solvent was removed under reduced pressure and the residue extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and freed of solvent. The residue crystallized from ethanol to yield the *azide* (4) as needles, $\nu_{max.}$ 2 100 (N_3), 1 728 (C=O), 1 610 (C=C), and 1 555 cm^{-1} (NO_2); *m/z* 348 (M^+), 303 ($M - OEt)^+$, 287 ($M - OEt - O)^+$, and 274 ($M - OEt - CHO)^+$.

Ethyl 4-*Azido*-2,3,4-*trideoxy*-α-D-threo-*hex*-2-*enopyranoside* (5).—A solution of the nitrobenzoate (4) (3.48 g, 10 mmol) in 5% alcoholic potash was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. Usual work-up of the organic phase provided the *alcohol* (5) which crystallized from n-hexane as fine needles, $\nu_{max.}$ 3 300 (OH), 2 110 (N_3), and 1 615 cm^{-1} (C=C).

Ethyl 4-*Amino*-2,3,4-*trideoxy*-α-D-threo-*hexopyranoside Hydrogen Toluene*-p-*sulphonate* (6).—To a solution of the azide (5) (398 mg, 2 mmol) in absolute ethanol (4 ml) was added 10% Pd–C catalyst (0.3 g) and a slow stream of hydrogen was passed through the mixture for 3 h. The catalyst was filtered off, the solvent was removed under reduced pressure, and the residue was taken up in diethyl ether and treated with an ethereal solution of toluene-*p*-sulphonic acid until acidic. The crude salt thereby obtained was recrystallized from chloroform–n-hexane to give needles of the *salt* (6), $\nu_{max.}$ 3 420 and 3 250 (OH, $\overset{+}{N}H_3$), 2 020, 1 590, and 1 515 ($\overset{+}{N}H_3$), 1 372—1 337, and 1 194—1 164 cm^{-1} (SO_2); *m/z* 333 (M^+).

Ethyl 4-*Amino*-2,3,4-*trideoxy*-6-O-p-*nitrobenzoyl*-α-D-threo-*hexopyranoside Hydrogen Toluene*-p-*sulphonate* (7).—To a solution of the azide (4) (348 mg, 1 mmol) in absolute ethanol (4 ml) was added 10% Pd–C catalyst (0.3 g) and the mixture was hydrogenated for 3 h. Similar work-up as for compound (6) provided the *salt* (7) which crystallized from ethyl acetate–diethyl ether as slender needles, $\nu_{max.}$ 3 250 ($\overset{+}{N}H$), 2 020, 1 590, and 1 515 ($\overset{+}{N}H_3$), 1 720 (C=O), 1 555 (NO_2), 1 340, 1 320, 1 175, and 1 152 cm^{-1} (SO_2); *m/z* 496 (M^+).

Ethyl 4-*Azido*-2,3,4-*trideoxy*-6-O-*tosyl*-α-D-threo-*hex*-2-*enopyranoside* (9).—A solution of compound (8) [14] (2 g, 5.15 mmol) in DMF (10 ml) was stirred with sodium azide (300 mg, 10 mmol) at room temperature for 12 h. The reaction mixture was poured onto crushed ice and repeatedly extracted with dichloromethane. The extract was dried (Na_2SO_4) and freed of solvent. The residue was taken up in methanol; a little water was added and the solution was cooled to give the *azide* (9) which crystallized as long needles, $\nu_{max.}$ 2 120 (N_3), 1 610 (C=C), 1 372—1 337, and 1 194—1 164 cm^{-1} (SO_2); *m/z* 353 (M^+), 292 ($M - OCH_2CH_3 - O)^+$, 279 ($M - OCH_2CH_3 - CHO)^+$, and 217 ($M - OCH_2CH_3 - C_6H_4CH_3)^+$.

Ethyl 4-*Acetamido*-2,3,4,6-*tetradeoxy*-α-D-threo-*hexopyranoside* (10).—To a solution of the azide (9) (3.53 g, 10 mmol) in absolute ethanol was added 10% Pd–C catalyst (0.5 g) and a slow stream of hydrogen was passed through the mixture for 6 h. The solution was filtered, the filtrate freed of

solvent, and the residue was acetylated with pyridine and acetic anhydride. Usual work-up afforded the *amide* (10) as fine tapering needles, $\nu_{max.}$ 3 290 (NH), 1 635 (amide I), 1 545 (amide II), 1 250, and 1 227 cm^{-1} (acetate C–O–C); *m/z* 195 (M^+).

Ethyl 4-*Amino*-2,3,4,6-*tetradeoxy*-α-D-threo-*hexopyranoside Hydrogen Toluene*-p-*sulphonate* (11).—A solution of the amide (10) (195 mg, 1 mmol) and barium hydroxide monohydrate (350 mg) in water (4 ml) was refluxed for 40 h, neutralized with dilute sulphuric acid, and filtered. The filtrate was freed of solvent and the residue was taken up in methanol and passed through a column of anion-exchange resin [Dowex 1 ($^-$OH)]. Evaporation of the methanol left a syrup which was taken up in diethyl ether to which was added an ethereal solution of toluene-*p*-sulphonic acid until the mixture was acidic. The solution was cooled and the salt (11) crystallized as prismatic plates, m.p. 146—147 °C; $[\alpha]_D^{20}$ +80.5° (*c* 1.1 in MeOH). The physical data are in accord with those reported in the literature.[12]

Reductive Alkaline Hydrolysis of the Azide (9) *with Sodium Amalgam.*—To a solution of the monoazide tosylate (9) (3.53 g, 10 mmol) in 80% aqueous methanol (184 ml) was added 4% sodium amalgam (46 g) and the mixture was stirred at room temperature for 14 h. The solution was filtered and carbon dioxide was bubbled into the filtrate until the alkalinity was neutralized. The solution was decanted from the mercury and the mercury was washed several times with water; the washings were added to the main solution. The solvent was completely removed under reduced pressure with the help of absolute ethanol. The residue was extracted with diethyl ether and chromatographic purification of the ethereal extract provided a uniform carbohydrate compound which, when hydrogenated and worked up as usual, afforded needles which could be identified as those of compound (6) through mixed m.p. and superimposable spectral data.

Ethyl 4-*Azido*-2,3,4-*trideoxy*-6-O-*tosyl*-α-D-erythro-*hex*-2-*enopyranoside* (13).—A solution of the 4-tosyl ester (8) (2 g, 4.15 mmol) in absolute acetone (20 ml) was stirred with sodium iodide (3 g) at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was partitioned between chloroform and water. The organic phase was washed in turn with water, dilute aqueous sodium thiosulphate, and water. Removal of the solvent left crude, syrupy ethyl 2,3,4-trideoxy-4-iodo-6-*O*-tosyl-α-D-*threo*-hex-2-enopyranoside (12). This was taken up in acetone (20 ml) to which was added sodium azide (1 g), and the mixture was refluxed gently for 24 h. Similar work-up and chromatographic purification over silica gel provided the azide (13) as a syrup, homogenous on t.l.c. The i.r. and mass spectra were quite similar to those of its epimer (9).

Ethyl 4-*Amino*-2,3,4,6-*tetradeoxy*-α-D-erythro-*hexopyranoside Hydrogen Toluene*-p-*sulphonate* (14).—A solution of the azide (13) (353 mg, 1 mmol) in absolute ethanol containing 10% Pd–C catalyst (200 mg) was hydrogenated for 4 h and worked up as for compound (6). Crystallization from diethyl ether provided prismatic plates of the salt (14), m.p. 130—131 °C; $[\alpha]_D^{20}$ +77.2° (*c* 1.0 in MeOH). The physical data are in accord with those reported in the literature.[12]

Ethyl 2,3,4,6-*Tetradeoxy*-4-*dimethylamino*-α-D-erythro-*hexopyranoside Hydrogen Toluene*-p-*sulphonate* (15).—To a solution of the primary amine salt (14) (400 mg, 1.2 mmol) in absolute ethanol (20 ml) is added 38% formalin solution (330 μl) and 10% Pd–C (200 mg). The solution was stirred in an atmosphere of hydrogen until hydrogen uptake reached the theoretical value. The catalyst was filtered off and the filtrate was evaporated to yield a thick syrup which was dissolved in water and treated with charcoal. Following reflux and filtration, the water was completely removed under diminished pressure with the help of absolute ethanol. The resulting syrup was crystallized from ethyl acetate–diethyl ether to give plates of the tertiary amine salt (15), m.p. 90—92 °C; $[\alpha]_D^{20}$ +91° (*c* 0.75 in MeOH). The physical data are in accord with those reported in the literature.[12]

2,3,4,6-*Tetradeoxy*-4-*dimethylamino*-α-D-erythro-*hexopyranose* (16).—A solution of the glycoside salt (15) (150 mg, 0.415 mmol) in water (5ml) was adjusted to pH 3.1 with dilute sulphuric acid and was then heated at 90 °C for 92 h. The stirred aqueous solution was then made basic with an excess of Dowex 1 ($^-$OH) anion-exchange resin during 1 h. The resulting solution was filtered and freed of solvent to give a sticky solid which could be sublimed at 60—80 °C at 0.05 Torr to give the pure crystalline compound (16), m.p. 60 °C; $[\alpha]_D^{20}$ +87.3° (*c* 1.0 in MeOH); picrate, m.p. 159 °C; methiodide, m.p. 181—182 °C. The physical data are in accord with those reported in the literature for natural forosamine.[12]

Ethyl 4,6-*Diazido*-2,3,4,6-*tetradeoxy*-α-D-threo-*hex*-2-*enopyranoside* (17).—A solution of the 6-tosyl ester (9) (3.53 g, 10 mmol) in absolute DMSO (20 ml) was heated and stirred with sodium azide (4 g, 60 mmol) at 120 °C for 2 h. Removal of solvent left a crude mixture of products which was chromatographed on a silica-gel column (Lobar B, Si 60, Merck). Elution was carried out with chloroform–n-hexane–ethyl acetate (2 : 2 : 0.1). The diazide (17) was obtained as a syrup which was homogeneous on t.l.c. [SiO_2; $CHCl_3$–n-hexane–EtOAc (2 : 2 : 0.1] (R_F 0.4), $\nu_{max.}$ 2 160 (N_3) and 1 620 cm^{-1} (C=C); *m/z* 224 (M^+), 168 ($M - CH_2N_3$)$^+$, 139 ($M - CH_2N_3 - CHO$)$^+$, 94 ($M - OCH_2CH_3 - CH_2N_3 - CHO$)$^+$, and 81 ($M - OCH_2CH_3 - CH_2N_3 - N_3$)$^+$.

Ethyl 4,6-*Diamino*-2,3,4,6-*tetradeoxy*-α-D-threo-*hexopyranoside* (18).—To a solution of the diazide (17) (200 mg, 0.89 mmol) in absolute methanol was added 10% Pd–C catalyst (100 mg) and a slow stream of hydrogen was passed through the mixture for 1.5 h. Filtration and removal of solvent gave the *diamine* (18) which was purified on a silica-gel column and formed a syrup, homogenous on t.l.c.; $\nu_{max.}$ 3 450, 3 320, and 1 590 cm^{-1} (NH_2); *m/z* 174 (M^+) and 129 ($M - OCH_2CH_3$)$^+$.

Ethyl 4,6-*Diazido*-2,3,4,6-*tetradeoxy*-α-D-erythro-*hex*-2-*enopyranoside* (19).—This compound was prepared in exactly the same manner as its 4-epimer (17), and was obtained as a *syrup*, homogenous on t.l.c. [SiO_2; $CHCl_3$–n-hexane–EtOAc (2 : 2 : 0.1)] (R_F 0.36). The i.r. and mass spectra were quite similar to those of compound (17).

Ethyl 4,6-*Diamino*-2,3,4,6-*tetradeoxy*-α-D-erythro-*hexopyranoside* (20).—The *diamino sugar* (20), which was obtained from the diazide (19) by following a similar procedure to that for compound (18), formed a syrup, homogenous on t.l.c., with i.r. and mass spectra quite similar to those of its 4-epimer (18).

Reaction of the Ditosyl Ester (8) *with Sodium Azide in DMSO.*—To a solution of compound (8) (3.5 g, 7.3 mmol) in absolute DMSO (20 ml) was added sodium azide (4 g, 60 mmol) and the mixture was heated and stirred at 140 °C for 4 h. The reaction mixture was cooled, poured onto crushed ice,

and extracted with dichloromethane. The extract was dried (Na_2SO_4), freed of solvent, and the resulting oil was subjected to column chromatography over silica gel (Lobar B, Si 60, Merck). Elution was carried out with chloroform–n-hexane–cyclohexane–ethyl acetate (1 : 1 : 1 : 0.1). The epimeric diazides (17) and (19) were obtained in 50% combined yield as faster moving products in the ratio 3 : 2. Further elution of the column provided the epimeric monoazides (9) and (13) in comparatively minor concentrations.

Acknowledgements

One of us (A. M.) expresses his gratitude to DAAD and to the Ministerium für Wissenschaft und Kunst Baden-Württemberg for the award of scholarships during the course of this work.

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Received 3rd *February* 1983; *Paper* 3/156