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## Note

# Synthesis of aminoglycal derivatives, precursors of glycosidic moieties of antitumor anthracyclines*

JEAN-CLAUDE FLORENT, JOËL UGHETTO-MONFRIN, AND CLAUDE MONNERET†
*Département de Pharmacognosie, Associé au C.N.R.S., U.A. 484, Faculté des Sciences Pharmaceutiques et Biologiques, 4, Avenue de l'Observatoire, 75270 Paris 06 (France)*
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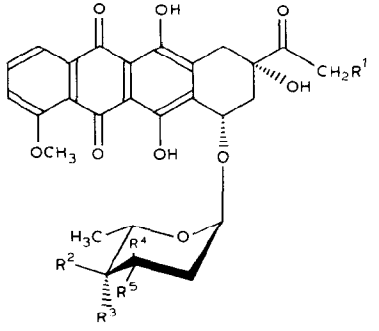
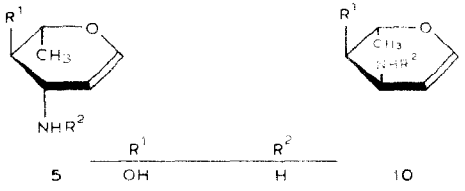
The anthracycline antibiotics, doxorubicin **1** and daunorubicin **2** are active against a wide variety of experimental tumors and some human cancers[1]. Unfortunately the dose-limiting toxicity includes alopecia, nausea, myelosuppression, and cardiotoxicity[2] with congestive heart failure, so that there is great interest in synthetic analogs having improved therapeutic indices. Among numerous analogs are those in which positions 3 and 4 in the amino sugar moiety have been modified, giving compounds generally with improved pharmacological properties and/or a wider spectrum of activity. For example, epirubicin **3**, in which the daunosaminyl residue has been replaced by the acosaminyl residue, is less myelosuppressive and less cardiotoxic than doxorubicin and is used in the treatment of breast cancer.

The glycal corresponding to 2,3-dideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*arabino*-hexopyranose was an appropriate synthon for glycosidation with daunomycinone in the presence of TsOH[4]. Moreover, glycal derivatives of

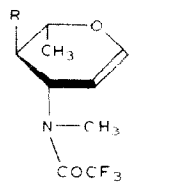


| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| 1 | OH | H | OH | H | $NH_2$ |
| 2 | H | H | OH | H | $NH_2$ |
| 3 | H | OH | H | H | $NH_2$ |
| 4 | H | OH | H | $NH_2$ | H |

*Dedicated to Professor Rezső Bognár in the year of his 75th birthday.
†Author for correspondence.



| | $R^1$ | $R^2$ | |
|---|---|---|---|
| 5 | OH | H | 10 |
| 6 | OH | $COCF_3$ | 11 |
| 7 | $OCS(SCH_3)$ | $COCF_3$ | 12 |
| 8 | H | $COCF_3$ | 13 |
| 9 | OH | $CH(CN)CH_3$ | 14 |



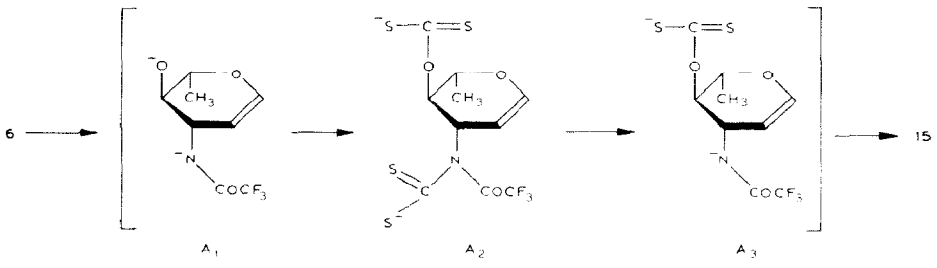
15 R = $OCS(SCH_3)$

16 R = H

3-amino-2,3,6-trideoxy-L-*arabino*-hexopyranose (acosamine derivative **5**) and of the corresponding L-*ribo* isomer (ristosamine) **10** have been synthesized in two steps from 3,4-di-*O*-acetyl-L-rhamnal, giving access after protection of HO-4 and NH-3 to 4′-epi- (**3**) and 3′,4′-di-epi-daunorubicin[5] (**4**), respectively, after glycosidation with daunomycinone. We now report on the conversion of the glycals **5** and **10** or their corresponding *N*-trifluoroacetyl derivatives **6** and **11** into 4-deoxy, 3-cyanoalkyl, and 3-morpholino derivatives.

Since 4′-deoxydaunorubicin and 4′-deoxydoxorubicin have high activity with lower toxicity[6], deoxygenation of **6** and **11** was attempted. The respective methyl thiocarbonate derivatives **7** and **12** were obtained by treatment at 0° in sequence with NaH, $CS_2$, and MeI (2 equiv. of each) followed by reduction with tributyltin hydride[7] to give the 4-deoxyglycals **8** and **13** (68% and 70% overall yields, respectively, after chromatography). Reduction[8] of methyl 3-azido-2,3,6-trideoxy-4-*O*-(methylthio)thiocarbonyl-α-L-*ribo*-hexopyranoside with the same reagent gave an oxazoline derivative. The non-formation of an oxazoline from **12** can be explained by the weaker nucleophilicity of the trifluoroacetamido function. If, in the first stage of the reaction of **6**, the mixture was allowed to reach room temperature before the addition of MeI (see Experimental), 75% of the *N*-methylglycal **15** was obtained. Radical-mediated deoxygenation of **15** led to **16**.

The formation of **15** from **6** can be explained as follows. The dianion $A_1$ formed by treatment of **6** with 2 equiv. of NaH at 0° reacts with carbon disulfide to give the bis-*O*,*N*-dithiocarbonate anion $A_2$. When the temperature increases, $A_2$ decomposes to afford the anion $A_3$ which reacts with methyl iodide to give **15**. In contrast, at 0°, $A_2$ reacts with MeI and *N*-methylation is prevented.



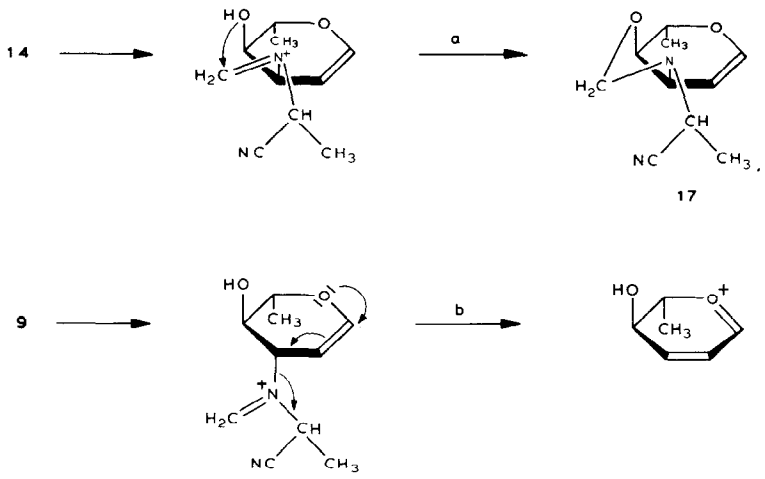
Since replacement of the 3-amino group in daunorubicin and doxorubicin by 3-morpholino[9], cyanomorpholino[10], or *N*-cyanoalkyl groups[11] yields potent anthracyclines, glycals bearing such substituents at C-3 were synthesized.

The aminonitrile derivatives **9** and **14** were obtained in almost quantitative yield as mixtures of diastereoisomers from **5** and **10**, respectively, using a modified Strecker reaction[12] with acetaldehyde and trimethylsilyl cyanide. The diastereoisomers were isolated pure, but the absolute configurations were not determined.

The *cis* vicinal relationship of the 3-amino or the 3-alkylamino group and HO-4 in the L-*ribo* series (*i.e.*, **10** or **14**) could explain differences in some of their reactions compared with those of their isomers **5** and **9**. Thus, treatment of the crude aminonitrile derivative **9** with a large excess of formaldehyde in the presence of sodium borohydride caused decomposition and gave water-soluble products, whereas, under similar conditions, **14** gave the bicyclic derivative **17**. Similarly, as reported, the reaction of *N*-*p*-tolyl-D-fructosylamine with benzaldehyde yields an oxazoline derivative[13]. The structural determination of **17** was based essentially on its 270-MHz $^1$H-n.m.r. spectrum which contained two doublets for O–$CH_2$–N between 4 and 5 p.p.m. Proton attributions in the isomers **17a** and **17b** were assigned by double irradiation procedures (see Experimental). Mass spectra and microanalyses were in full agreement with these structures.

This difference in the reactions of **9** and **14** can be explained as follows. The first step probably involved the formation of an unstable iminium salt derivative followed by either an intramolecular attack of the *cis* vicinal OH (*i.e.*, **14**) (route *a*) to give **17**, or, for a *trans* vicinal OH (*i.e.*, **9**), by an elimination reaction giving an enoxonium ion (route *b*) which is hydrolyzed during the work-up.

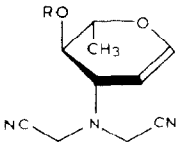
Different behaviour was observed during the condensation of >2 equiv. of iodoacetonitrile with **5** and **10**. With the former compound, 50% of the bis(cyanomethyl) compound **18** was isolated, whereas 72% of the monocyanomethyl



derivative **20** was formed from the latter, probably because bis-alkylation was sterically hindered.

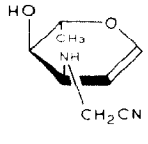
The morpholino derivative **21** was also prepared from **5** by condensation with 2,2′-oxydiacetaldehyde prepared from 1,4-anhydro-erythritol[14] and then converted into its 4-*p*-nitrobenzoate **22** ready for glycosidation.

When the *p*-nitrobenzoate **19** of **18** was treated with methanol in the presence of trimethylsilyl triflate, the methyl glycoside **23** was obtained (70% yield after chromatography). The coupling of the above glycal derivatives with new aglycons, recently synthesized in our laboratory[15,16], is now being studied.

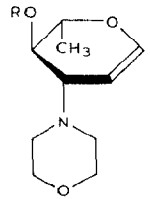



**18** R = H

**19** R = *p*-$NO_2$Bz

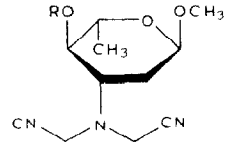



**20**




**21** R = H

**22** R = *p*-$NO_2$Bz




**23** R = *p*-$NO_2$Bz

## EXPERIMENTAL

*General methods.* — Melting points (Kofler hot-stage microscope) are uncorrected. I.r. spectra were recorded with a Perkin–Elmer Model 257 spectrophotometer. $^1$H-N.m.r. spectra (270 MHz) were recorded with a Bruker HX 270 spectrometer for solutions in $CDCl_3$ (internal $Me_4Si$). Mass spectra [c.i. (ammonia) or e.i. (70 eV)] were recorded on a Nermag R 1010 instrument. Flash column chromatography was performed on Silica Gel H-60 (Merck 7736) and t.l.c. on Silica Gel 60 $F_{254}$ (Merck). Ether-type solvents were dried over sodium benzophenone and distilled. Microanalyses were performed by the Laboratoire de Microanalyse du C.N.R.S. (Gif-sur-Yvette and Lyon).

*1,5-Anhydro-2,3,6-trideoxy-3-(trifluoroacetamido)-4-*O*-[(methylthio)thiocarbonyl]*-L-arabino-*hex-1-enitol* (**7**). — To a solution of **6** (990 mg, 4 mmol) in tetrahydrofuran (50 mL) at 0° were added sodium hydride (80% suspension in oil, 256 mg, 8.2 mmol), then, after 30 min, freshly distilled carbon disulfide (0.56 mL, 8.2 mmol), and, after 3 h, methyl iodide (0.56 mL, 8.2 mmol). The final mixture was stirred for 2 h at 0°, water (50 mL) was added, and the product was extracted with ether and crystallized from hexane to afford **7** (960 mg, 72%), m.p. 145°, $[\alpha]_D^{20}$ −170° (*c* 2, chloroform); $\nu_{max}^{Nujol}$ 3260 (NH), 1690 ($COCF_3$), and 1650 $cm^{-1}$ (C=C). Mass spectrum (e.i.): *m/z* 315 ($M^+$, trace), 207 (80%), 192 (40), 95 (100), 91. For $^1$H-n.m.r. data, see Table I and δ 2.57 (s, SMe).

*Anal.* Calc. for $C_{10}H_{12}F_3NO_3S_2$ (315.15): C, 38.11; H, 3.82; N, 4.44. Found: C, 38.30; H, 3.90; N, 4.40.

TABLE I

270-MHz $^1$H-N.M.R. DATA FOR **7**, **8** AND **12–23** IN $CDCl_3$

| *Compound* | *Chemical shifts (δ)* | | | | | | | *Coupling constants (Hz)* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *H-1* | *H-2* | *H-3* | *H-4a* | *H-4e* | *H-5* | *$CH_3$-6* | $J_{1,2}$ | $J_{1,3}$ | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{5,6}$ |
| **7** | 6.40 dd | 4.68 dd | 4.88 dd | 5.89 t | | 4.18 m | 1.32 d | 5.5 | 1.8 | 2 | 9 | 9 | 6.5 |
| **8** | 6.42 dd | 4.55 dd | 4.67 m | 1.48 m | 2.32 m | 4.06 m | 1.30 d | 5.5 | 1.8 | 2 | 9.5 | 10 | 6.5 |
| **9a** | 6.25 d | 4.76 dd | 3.40 m | 3.26 t | | 3.80 m | 1.36 d | 5.5 | <1 | 2 | 9 | 9 | 6.5 |
| **9b** | 6.28 dd | 4.73 d | 3.45–3.33 m | 3.36 t | | 3.82 m | 1.38 d | 6.0 | <1 | 4.5 | | 8 | 6.5 |
| **12** | 6.58 dd | 4.73 dd | 4.92 m | 5.86 | | 4.25 m | 1.35 d | 5.5 | <0.5 | 5 | 4.8 | 8 | 6.5 |
| **13** | 6.49 d | 4.75 dd | 4.33 m | 1.78 m | 1.95 m | 3.85 m | 1.33 d | 5.5 | <0.5 | 5 | 4.8 | 10 | 6.5 |
| **14** | 6.33 d | 5.01 dd | ←3.75 m→ | | | 3 | 1.36 d | 6.0 | | 6 | 2.5 | 2.5 | 6.5 |
| **15** | 6.46 dd | 4.46 dd | 5.50 m | 5.94 t | | 4.18 m | 1.32 d | 5.5 | 2.5 | 2.5 | 9.5 | 9.5 | 6.5 |
| **16** | 6.49 dd | 4.68 dd | 4.44 m | 2.05–1.50 m | | 4.07 m | 1.32 d | 6.0 | 2 | 2.5 | | | 6.5 |
| **17a** | 6.44 d | 4.80 dd | 3.18 m | 3.77 dd | | 3.59 m | 1.34 d | 6.0 | | 4.5 | 6.5 | 8 | 6.5 |
| **17b** | 6.36 d | 4.75 dd | 3.53 m | 3.92 dd | | 3.84 m | 1.33 d | 6.0 | | 5.5 | 6.5 | 6.5 | 6.5 |
| **18** | 6.53 dd | 4.91 dd | 3.79 dd | 5.10 dd | | 4.20 m | 1.34 d | 6.0 | 1.5 | 1.5 | 8 | 8 | 6 |
| **19** | 6.35 d | 4.53 d | 3.49 d | 3.74–3.67 m | | 3.74–3.67 m | 1.31 d | 6.0 | | <1 | 8 | | 6 |
| **20** | 6.31 d | 4.92 dd | 3.22 dd | ←3.70–3.40 m→ | | | 1.34 d | 6.0 | | 5 | 5 | | 6.5 |
| **21** | 6.34 dd | 4.73 dd | 3.21 d | 3.48 dd | | 3.92–3.59 m | 1.39 d | 6.0 | 1.5 | 1.5 | 8.5 | 8.5 | 6 |
| **22** | 6.38 dd | 4.77 dd | | 5.23 dd | | 4.09 m | 1.32 d | 6.0 | 2.5 | 1.5 | 8.5 | 8.5 | 6 |
| **23** | 4.80 d | 2.34 dd<br>1.69 m | 3.88 m | 4.91 dd | | 3.75 m | 1.22 d | 2.5 | | | 10 | 10 | 6 |

*1,5-Anhydro-2,3,4,6-tetradeoxy-3-trifluoroacetamido*-L-threo-*hex-1-enitol* (**8**). — To a solution of **7** (700 mg, 2.2 mmol) in toluene (100 mL) were added azabis(isobutyronitrile) (50 mg) and tributyltin hydride (1 mL, 3.4 mmol). The mixture was stirred overnight under argon and then concentrated, and the residue was adsorbed on silica gel (1 g). Flash chromatography (hexane–$CH_2Cl_2$, 2:1) gave **8** (440 mg, 95%), m.p. 89–90° (from hexane), $[\alpha]_D^{20}$ −29° (*c* 1, chloroform); $\nu_{max}^{Nujol}$ 1690 ($COCF_3$) and 1650 $cm^{-1}$ (C=C). Mass spectrum (e.i.): *m/z* 209 ($M^+$, 30%), 194 ($M^+$ −15, 10), 166 (10), 140, 112, 96, 81, and 69. For $^1$H-n.m.r. data, see Table I and δ 2.32 (m, *J* 14.5, and 1 Hz, H-4*e*).

*Anal.* Calc. for $C_8H_{10}F_3NO_2$ (209.16): C, 45.94; H, 4.81; N, 6.69. Found: C, 46.01; H, 4.87; N, 6.65.

*1,5-Anhydro-3-(1-cyanoethyl)amino-2,3,6-trideoxy*-L-arabino-*hex-1-enitol* (**9a** *and* **9b**). — To a solution of **5** (129 mg, 1 mmol) in methanol (20 mL) at 0–5° were added acetaldehyde (0.53 mL, 1 mmol) and trimethylsilyl cyanide (0.27 mL, 2 mmol). The resulting solution was allowed to reach room temperature, then heated under reflux for 1 h, and concentrated *in vacuo* to dryness. Chromatography (dichloromethane–methanol–$NH_3$, 99:1) of the residue (140 mg) gave **9a** (45 mg), a mixture (200 mg) of **9a** and **9b**, and then **9b** (46 mg) (overall yield, 82%).

Compound **9a** was a syrup, $[\alpha]_D^{20}$ +23° (*c* 1, chloroform); $\nu_{max}^{film}$ 3300 (OH), 2240 (CN), and 1640 $cm^{-1}$ (C=C). For $^1$H-n.m.r. data, see Table I and δ 3.82 [q, C*H*(CN)$CH_3$], 1.52 [d, *J* 6.5 Hz, CH(CN)C*H*$_3$].

*Anal.* Calc. for $C_6H_{14}N_2O_2$ (182.21): C, 59.32; H, 7.74; N, 15.36. Found: C, 59.40; H, 7.80; N, 15.25.

Compound **9b** was a syrup, $[\alpha]_D^{20}$ +70° (*c* 2.2, chloroform); $\nu_{max}^{film}$ as for **9a**. For $^1$H-n.m.r. data, see Table I and δ 3.76 [q, C*H*(CN)$CH_3$], 1.51 [d, *J* 6.5 Hz, CH(CN)C*H*$_3$]. Mass spectrum (c.i.): *m/z* 190 ($M + NH_4^+$), 183 ($M + H^+$), 156 (M − CN)$^+$ (base peak), 113 [M − NHCH(CN)$CH_3$]$^+$, 98, 95.

*1,5-Anhydro-2,3,6-trideoxy-4-O-(methylthio)thiocarbonyl-3-trifluoroacetamido*-L-ribo-*hex-1-enitol* (**12**). — Treatment of **11** (1.5 g, 6.6 mmol), as described for the preparation of **7**, afforded **12** (1.5 g, 75%), m.p. 92° (from dichloromethane), $[\alpha]_D^{20}$ −73° (*c* 1, chloroform); $\nu_{max}^{Nujol}$ as for **7**.

*Anal.* Calc. for $C_{10}H_{12}F_3NO_3S_2$ (315.15): C, 38.11; H, 3.82; N, 4.44. Found: C, 38.27; H, 3.87; N, 4.50.

*1,5-Anhydro-2,3,4,6-tetradeoxy-3-trifluoroacetamido*-L-erythro-*hex-1-enitol* (**13**). — Treatment of **12** (700 mg, 2.2 mmol), as described for the synthesis of **8**, gave **13** (450 mg, 95%), m.p. 110–112° (from hexane), $[\alpha]_D^{20}$ −76° (*c* 1, chloroform). Mass spectrum (e.i.): *m/z* 209 ($M^+$, 30%), 194 ($M^+$ −15, 10). For $^1$H-n.m.r. data, see Table I and δ 1.95 (m, *J* 14, 2.5, and 2.5 Hz, H-4*e*).

*Anal.* Calc. for $C_8H_{10}F_3NO_2$ (209.16): C, 45.94; H, 4.81; N, 6.69. Found: C, 45.97; H, 4.75; N, 6.73.

*1,5-Anhydro-3-(1-cyanoethyl)amino-2,3,6-trideoxy*-L-ribo-*hex-1-enitol* (**14**). — Compound **10** was treated, as described for the preparation of **9a** and **9b**[10], to give **14** as a mixture (95%) of diastereoisomers. Column chromatography (di-

chloromethane–methanol, 99.5:0.5) or crystallization from hexane gave **14a**, m.p. 92–95°, $[\alpha]_D^{20}$ −205° (*c* 1.6, chloroform); $\nu_{max}^{Nujol}$ 3400, 3260 (OH, NH), 2220 (CN), and 1640 $cm^{-1}$ (C=C). For $^1$H-n.m.r. data, see Table I and δ 1.52 [d, *J* 4.5 Hz, $CH(CN)CH_3$]. Mass spectrum (c.i.): *m/z* 200 ($M + NH_4^+$), 183 ($M + H^+$), 156 ($M - C{\equiv}N)^+$, 130, 113.

*Anal.* Calc. for $C_9H_{14}N_2O_2$ (182.21): C, 59.32; H, 7.74; N, 15.36. Found: C, 59.42; H, 7.82; N, 15.25.

*1,5-Anhydro-2,3,6-trideoxy-3-(*N*-methyltrifluoroacetamido)-4-*O*-[(methylthio)thiocarbonyl]*-L-arabino-*hex-1-enitol* (**15**). — A solution of **6** (225 mg, 1 mmol) in tetrahydrofuran (25 mL) was treated as for the preparation of **7**, but the reaction mixture was allowed to reach room temperature before the addition of methyl iodide. The same work-up followed by column chromatography (dichloromethane) afforded **15** (250 mg, 76%) as a syrup, $[\alpha]_D^{20}$ −158° (*c* 2, chloroform); $\nu_{max}^{film}$ 1690 ($NHCOCF_3$) and 1650 $cm^{-1}$ (C=C). Mass spectrum (e.i.): *m/z* 330 ($M^+ + 1$, 50%), 222 (100), 206 (95). For $^1$H-n.m.r. data, see Table I and δ 2.97 (s, NMe), 2.50 (s, SMe).

*Anal.* Calc. for $C_{11}H_{14}F_3NO_3S_2$ (329.32): C, 40.14; H, 4.28; N, 4.25. Found: C, 40.22; H, 4.35; N, 4.15.

*1,5-Anhydro-2,3,4,6-tetradeoxy-3-(*N*-methyltrifluoroacetamido)-*L-threo-*hex-1-enitol* (**16**). — Treatment of **15** (800 mg), as described for **7**, afforded, after chromatography (dichloromethane), **16** (620 mg), which contained traces of tin salts; $\nu_{max}^{film}$ 1690 ($COCF_3$) and 1650 $cm^{-1}$ (C=C). Mass spectrum (c.i.): *m/z* 241 ($M + NH_4^+$), 224 ($M + H^+$). For $^1$H-n.m.r. data, see Table I and δ 2.92 (s, NMe).

No satisfactory analysis could be obtained for this compound.

*1,5-Anhydro-3-(1-cyanoethyl)amino-2,3,6-trideoxy-3,4-*N,O*-methylene-*L-ribo-*hex-1-enitols* (**17a** *and* **17b**). — A solution of **14** (510 mg) in acetonitrile (50 mL) at 0–5° was stirred for 30 min in the presence of aqueous 37% formaldehyde (3 mL). Sodium borohydride (700 mg) was then carefully added in order to avoid an exothermic reaction, stirring was maintained for 1 h at 0–5°, water (50 mL) was added, and the mixture was concentrated under reduced pressure. Column chromatography (dichloromethane–MeOH, 99.5:0.5) of the residue afforded **17a** and then **17b**.

Diastereoisomer **17a** had m.p. 84° (from hexane), $[\alpha]_D^{20}$ −198° (*c* 1, chloroform); $\nu_{max}^{Nujol}$ 2230 (CN) and 1640 $cm^{-1}$ (C=C). For $^1$H-n.m.r. data, see Table I and δ 4.55 and 4.15 (2 d, *J* 2.5 Hz, $OCH_2N$), 1.48 [d, *J* 6.5 Hz, $CH(CN)CH_3$]: irradiation of the doublet at δ 1.34 ($CH_3$-5) transformed the signal at δ 3.59 (m, H-5) into a doublet ($J_{4,5}$ 8.5 Hz). The quadruplet at δ 3.97 [$CH(CN)CH_3$] was converted into a singlet by irradiation of the doublet at δ 1.48 [$CH(CN)CH_3$]. Mass spectrum (c.i.): *m/z* 195 ($M + H^+$) (base peak), 168 ($M - CN)^+$, 113.

*Anal.* Calc. for $C_{10}H_{14}N_2O_2$ (194.21): C, 61.84; H, 7.26; N, 14.41. Found: C, 61.56; H, 7.16; N, 14.67.

Diastereoisomer **17b** was a syrup, $[\alpha]_D^{20}$ −82° (*c* 0.4, chloroform); $\nu_{max}^{film}$ as for **17a**. For $^1$H-n.m.r. data, see Table I and δ 4.58 and 4.26 (d, *J* 4.5 Hz, $OCH_2N$),

1.55 [d, CH(CN)C$H_3$)]. Irradiation of the doublet at $\delta$ 1.33 ($CH_3$-5) transformed the signal at $\delta$ 3.84 (m, H-5) into a doublet ($J_{4,5}$ 6.5 Hz); the quadruplet at $\delta$ 3.74 [C*H*(CN)$CH_3$] was converted into a singlet by irradiation of the signal (d) at $\delta$ 1.55; finally, the signal at $\delta$ 3.62 (dd ~ t, H-4) was transformed into a doublet by irradiation of the multiplet at $\delta$ 3.53 (H-3). Mass spectrum (c.i.): *m/z* 212 ($M + NH_4^+$), 195 ($M + H^+$) (base peak), 181, 168, 113.

*1,5-Anhydro-3-bis(cyanomethyl)amino-2,3,6-trideoxy*-L-arabino-*hex-1-enitol* (**18**). — To a solution of **5** (130 mg, 1 mmol) in *N,N*-dimethylformamide (5 mL) were added triethylamine (1 mL) and acetonitrile (0.5 mL, 7 mmol). The mixture was stirred for 48 h in the dark, water was added, and the mixture was extracted with EtOAc. The combined extracts were washed with aqueous sodium thiosulfate, and the usual work-up afforded a syrup. Flash chromatography (dichloromethane–MeOH, 95:5) gave **18** (105 mg, 50%). Mass spectrum (c.i.): *m/z* 225 ($M + NH_4^+$) (base peak), 208 ($M + H^+$), 130 and 113 [$M^+ - N(CH_2CN)_2$]. For $^1$H-n.m.r. data, see Table I and $\delta$ 3.76 (s, 4 H, 2 $CH_2CN$).

*Anal.* Calc. for $C_{10}H_{13}N_3O_2$ (207.21): C, 57.96; H, 6.32; N, 20.22. Found: C, 57.80; H, 6.35; N, 20.15.

*1,5-Anhydro-3-bis(cyanomethyl)amino-2,3,6-trideoxy-4-*O-p-*nitrobenzoyl*-L-arabino-*hex-1-enitol* (**19**). — A solution of **18** (210 mg, 1 mmol) in pyridine (5 mL) was stirred overnight with *p*-nitrobenzoyl chloride (500 mg, 2.7 mmol) and then diluted with water. Extraction with dichloromethane in the usual way afforded a product (400 mg) which was recrystallized from hexane–acetone to give **19** (325 mg, 95%), m.p. 118–120°, $[\alpha]_D^{20}$ +33.5° (*c* 0.5, chloroform); $\nu_{max}^{Nujol}$ 1725 (ester), 1640 cm$^{-1}$ (C=C). For $^1$H-n.m.r. data, see Table I and $\delta$ 3.76 and 3.65 (2 d, *J* 17 Hz, $CH_2CN$).

*Anal.* Calc. for $C_{17}H_{16}N_4O_5$ (336.32): C, 57.30; H, 4.52; N, 15.72. Found: C, 57.24; H, 4.40; N, 15.47.

*1,5-Anhydro-3-cyanomethylamino-2,3,6-trideoxy*-L-ribo-*hex-1-enitol* (**20**). — Treatment of **10** (130 mg, 1 mmol), as described in the preparation of **18**, gave **20** (100 mg, 72%), m.p. 78° (from hexane–acetone), $[\alpha]_D^{20}$ −254° (*c* 0.8, chloroform); $\nu_{max}^{Nujol}$ 3300–3100 (OH), 2230 (CN), and 1640 cm$^{-1}$ (C=C). For $^1$H-n.m.r. data, see Table I and $\delta$ 3.70 and 3.52 (2 d, *J* 16 Hz, $CH_2CN$). Mass spectrum (c.i.): *m/z* 186 ($M + NH_4^+$), 169 ($M + H^+$) (base peak), 142 $(M - CN)^+$, 130, 113 $(M - NHCH_2CN)^+$.

*Anal.* Calc. for $C_8H_{12}N_2O_2$ (168.18): C, 57.12; H; 7.19; N, 16.64. Found: C, 57.24; H, 7.03; N, 16.40.

*1,5-Anhydro-2,3,6-trideoxy-3-morpholino*-L-arabino-*hex-1-enitol* (**21**). — A solution of 2,2′-oxydiacetaldehyde prepared[10] from 1,4-anhydro-erythritol (3.12 g) was reacted with **5** (130 mg, 1 mmol). Flash chromatography (dichloromethane–methanol, 95:5) of the product gave **21** (70 mg, 35%) as a syrup, $[\alpha]_D^{20}$ +68° (*c* 1.15, methanol); $\nu_{max}^{CHCl_3}$ 1640, 1600 cm$^{-1}$. For $^1$H-n.m.r. data, see Table I and $\delta$ 3.92–3.59 (m, $CH_2O$), 2.68–2.55 (m, $CH_2N$). Mass spectrum (e.i.): *m/z* 200 ($M^+$, 1.5%), 143 (100), 141 (RDA, 70).

*1,5-Anhydro-2,3,6-trideoxy-3-morpholino-4*-O-p-*nitrobenzoyl*-L-arabino-*hex-1-enitol* (**22**). — Treatment of **21** (70 mg, 0.3 mmol), under the conditions used to prepare **19** from **18**, gave **22** (90 mg, 82%) as a syrup, $[\alpha]_D^{20}$ +57° (*c* 1.6, methanol); $\nu_{max}^{film}$ 1725 (ester) and 1640 $cm^{-1}$ (C=C). For $^1$H-n.m.r. data, see Table I and δ 3.56–3.43 (m, $CH_2O$), 2.72–2.40 (m, $CH_2N$). Mass spectrum (c.i.): *m/z* 349 ($M + H^+$) (base peak).

*Anal.* Calc. for $C_{17}H_{20}N_2O_6$ (348.34): C, 58.61; H, 5.78; N, 8.03. Found: C, 58.25; H, 5.81; N, 8.10.

*Methyl 3-bis(cyanomethyl)amino-2,3,6-trideoxy-4*-O-p-*nitrobenzoyl*-α-L-arabino-*hexopyranoside* (**23**). — To a solution of **21** (60 mg, 0.17 mmol) in benzene (5 mL) and dichloromethane (5 mL) at −10° were added methanol (0.5 mL) and then trimethylsilyl triflate (0.5 mL). The mixture was stirred overnight and then quenched with saturated aqueous $NaHCO_3$. Extraction with dichloromethane and the usual work-up gave, after flash chromatography (hexane–acetone, 2:1), **23** (50 mg, 76%) as a syrup, $[\alpha]_D^{20}$ −56° (*c* 0.4, chloroform); $\nu_{max}^{film}$ 1720 (ester) and 1600 $cm^{-1}$ (Ar). For $^1$H-n.m.r. data, see Table I and δ 8.40–8.20 (m, aromatic), 3.35 (s, 4 H, 2 $CH_2$), 3.28 (s, 3 H, OMe); $J_{1,2e}$ <1, $J_{1,2a}$ 4.5, $J_{2a,2e}$ 13, $J_{2a,3a}$ 10, $J_{2e,3a}$ 4.5 Hz.

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