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# Synthesis of some further C-3 branched 3-amino-2,3,6-trideoxy sugars, related to daunosamine, as potential components for structurally modified anthracyclines

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ABSTRACT

A Hofmann-type, oxidative rearrangement of methyl 4,6-*O*-benzylidene-3-*C*-carbamoyl-3-*C*-cyano-3-deoxy-α-D-glucopyranoside (**1**) by mercuric acetate and *N*-bromosuccinimide resulted in a 2-oxazolidinone ring fused to the pyranoside. Deoxygenation by tributylstannane of the 2-*O*-phenoxythiocarbonyl derivative of **1** led to its 2,3-dideoxy analog. The latter was subjected to Hofmann rearrangement with lead tetraacetate followed by reduction of the cyano group, with simultaneous *N*-*tert*-butoxycarbonylation in both steps, to give methyl 4,6-*O*-benzylidene-3-*tert*-butoxycarbonylamino-3-*C*-*tert*-butoxycarbonylaminomethyl-2,3-dideoxy-α-D-glucopyranoside. Hanessian reaction of this acetal yielded the corresponding 6-bromo-6-deoxy 4-benzoate which by dehydrobromination with DBU produced a blocked 3-*C*-aminomethyl-2,3,6-trideoxy-3,6-iminohexopyranoside.

Methyl 3-amino-3,6-dideoxy-3-*C*-methoxycarbonyl-α-L-galactopyranoside was partially blocked at $NH_2$-3 and OH-4 by *N*-*tert*-butoxycarbonylation and *N*,*O*-isopropylidenation, and then converted into a 2-xanthate. Subsequent Barton deoxygenation followed by hydride reduction of the methyl ester function and methylation of the resulting primary alcohol gave 3,4-protected derivatives of 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose (L-daunosamine) branched at C-3 by methoxycarbonyl, hydroxymethyl, and methoxymethyl groups.

## INTRODUCTION

Our laboratories are currently engaged in a project of synthesis[1] of amino sugars bearing two branches at C-3, some of which are considered as possible building blocks for use in planned extensions of our studies[2] concerning the preparation of structurally modified anthracycline antibiotics. In a preceding paper[3] the synthesis of several 3-*C*-carbamoyl-3-*C*-cyano-3-deoxyhexopyranosides

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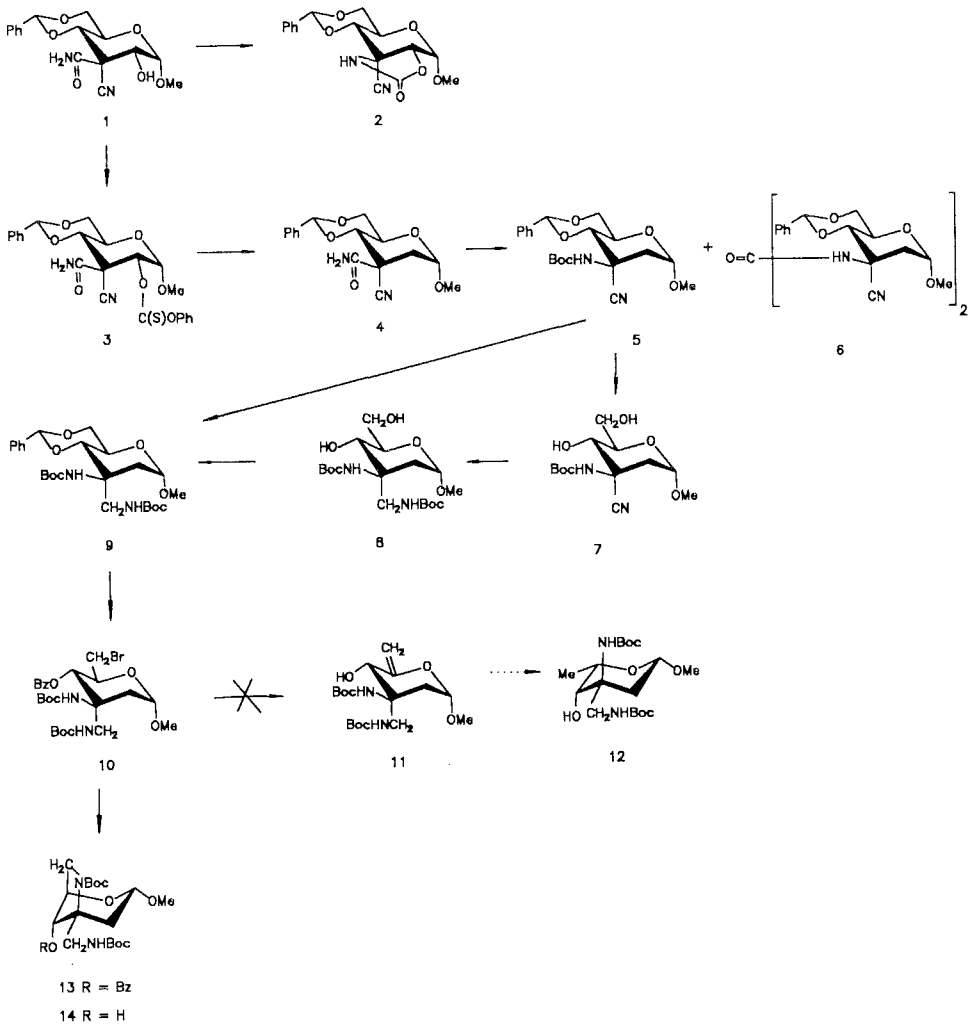
was reported, and subsequently the conversion of such carbamoyl-cyano derivatives into 3-amino-3-*C*-aminomethyl-3-deoxy sugars by Hofmann rearrangement of the amide, followed by reduction of the cyano group, was described[4]. Similar syntheses of 3,6-dideoxyhexopyranosides doubly branched at C-3 were also accomplished[5]. The present paper discloses some results of further investigations in this area.

## RESULTS AND DISCUSSION

In our preceding studies[4,5], Hofmann-type oxidative rearrangements of 3-*C*-carbamoyl glycosides having protected neighboring hydroxyl functions were performed by the lead tetraacetate procedure[6], with added *tert*-butyl alcohol to trap the intermediate isocyanates as *tert*-butyl carbamates, that is, to produce 3-*N*-(*tert*-butoxycarbonyl)amino sugars. We have now achieved a Hofmann rearrangement of the amide[3] **1**, which bears a free OH-2 group, using a new method recently described[7]. It employs the reagent system mercuric acetate–*N*-bromosuccinimide–*N*,*N*-dimethylformamide and is normally performed with added methanol for trapping the engendered isocyanate. However, we omitted the alcohol, and trapping occurred internally to give the cyclic carbamate **2** in 40% yield (unoptimized). It was interesting to note the formation of a five-membered cyclic carbamate that is *trans*-fused to a pyranoside ring; this complements the previous observation[4] of a (quantitative) formation of such a carbamate *trans*-fused to a seven-membered ring, occurring when a 3-*tert*-butoxycarbonylamino-heptoseptanoside was treated with sodium methoxide. Compound **2**, with its relatively stable protection of positions 2 and 3 may be a potentially useful intermediate for the preparation of products structurally modified at C-4 and (or) C-6.

Chief targets of the present study were C-3 branched diamino sugars of the 2,3,6-trideoxy-L-hexopyranose type, that is, analogs of L-daunosamine, in view of their special interest in connection with synthesis of modified anthracyclines. Thus, the reaction sequence depicted in Scheme 1 was devised. Compound **1** was deoxygenated at C-2 by a variant of the Barton deoxygenation elaborated by Robins and coworkers[8], involving conversion into the 2-phenoxythiocarbonyl ester **3** by treatment with phenyl chlorothionoformate, and subsequent reaction with tributylstannane in boiling benzene, to furnish methyl 4,6-*O*-benzylidene-3-*C*-carbamoyl-3-*C*-cyano-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**4**). Both reactions gave > 80% yields *. The primary amide **4** was then subjected to Hofmann rearrangement using lead tetraacetate in the presence of *tert*-butyl alcohol[6c], which afforded a 76% yield of the desired *tert*-butoxycarbonylamino glycoside **5**, together with the symmetrical *N*,*N*′-bisglycosid-3-yl urea **6** isolated as a byproduct (19%). The structure of **6** was ascertained by elemental analysis, NMR spectra that

* It was not necessary to use isomerically pure **1** as a starting material. More conveniently obtainable crude **1**, which contained a substantial proportion of its D-*manno* epimer[3], was employed in large-scale preparations, without diminution in yields of **3** (containing its 2-epimer) or **4**.



Scheme 1.

indicated the presence of benzylidene, cyano, and amide carbonyl groups in a symmetrical molecule possessing no *tert*-butyl groups, and by the mass spectrum showing a strong $M^+ + 1$ peak at $m/z$ 607 (70%) and a base peak at $m/z$ 317 corresponding to $M^+ - C_{15}H_{17}N_2O_4$ (loss of one complete amino glycoside moiety from the disubstituted urea). Formation of *N,N'*-dialkylureas in this kind of reaction has been observed before[6a] and is attributed to partial hydrolysis of intermediate isocyanate, by water inadvertently present or generated through dehydration of *tert*-butyl alcohol, and addition of the resulting amine to another isocyanate molecule[6c].

*O*-Debenzylidenation of **5** by iodine in methanol[9] gave the diol **7**, the cyano group of which was reduced[10] with sodium borohydride–cobaltous chloride in the

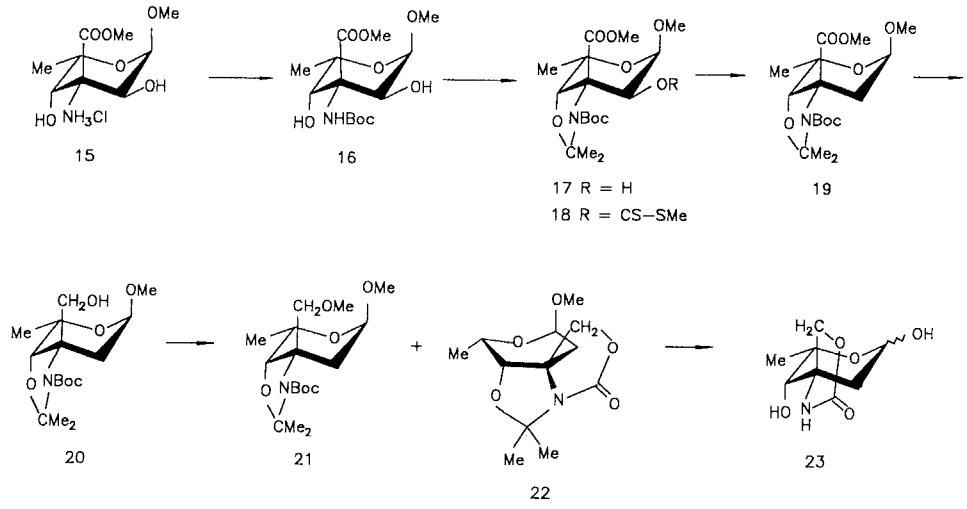
presence of di-*tert*-butyl dicarbonate, to afford methyl 3-*tert*-butoxycarbonylamino-3-*C*-*tert*-butoxycarbonylaminomethyl-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**8**). This 4,6-diol was rebenzylidenated to give the acetal **9**. The overall yield of **9** from **5** via **7** and **8** was 38%, but it was subsequently discovered that **5** can be reduced to **9** directly *, with a yield of 68% and recovery of 18% of unchanged **5**.

Hanessian reaction of **9** provided the 6-bromo-6-deoxy-4-benzoate **10** in almost quantitative yield. The product was characterized by spectral data (IR, $^1$H NMR, and MS), but attempted purification by column chromatography to remove traces of slow-moving byproducts (TLC) led to decomposition, and the material was therefore used in crude form. The aim of the next step was to effect dehydrobromination in **10** to procure the alkene **11**, thought to be convertible into the target compound **12** by catalytic hydrogenation as performed successfully in previous, similar instances[2]. For dehydrobromination, **10** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene in refluxing benzene, and it was hoped that the bulky *N*-Boc substituent would discourage a competitive, internal nucleophilic displacement of the bromine by the amide function, an event that had occurred in similar instances in 6-bromo-6-deoxy pyranosides bearing a 3-acetamido[11a,b], 3-methoxycarbonylamino[11c], or 3-*p*-toluenesulfonamido[11d] substituent. Disappointingly the product, isolated in 72% yield, was not the desired alkene **11** but in fact the isomeric pyrrolidine **13**; its methanolysis (Zemplén) gave the alcohol **14**. The chemical-ionization mass spectra of **13** and **14** displayed intense $M^+ + 1$ peaks at *m/z* 493 and 389, respectively, which of course provided no distinction between the alkene and putative pyrrolidine structures. However, the NMR spectra lacked signals attributable to a vinyl ether structure comprising C-5,6; there were no $^1$H signals in the appropriate low-field region, and the $^{13}$C spectra (ADEPT) exhibited three methine carbon signals (C-1,4,5) and three saturated methylene carbon signals (C-2,3′,6 in the δ 30–50 region), but no low-field methylidene carbon signal (see Tables I and II). Preliminary experiments performed similarly with the 3-*C*-cyano analog of **10**, obtained by Hanessian reaction of **5** (unpublished) also appeared to give a pyrrolidine according to $^1$H NMR evidence, which reinforced the conclusion that a *tert*-butoxycarbonyl substituent is not capable of preventing N-3 → C-6 cyclization. It may be more promising to attempt 5,6-elimination in a phthalimido analog of **10**, if obtainable, for which there is a precedent[11c] in the literature †. In the meantime, an alternative approach to the desired 2,3,6-trideoxy derivatives was sought.

The second approach (see Scheme 2) started with methyl 3-amino-3,6-dideoxy-3-*C*-methoxycarbonyl-α-L-galactopyranoside hydrochloride (**15**), available[5] from methyl α-L-rhamnopyranoside by nitromethane methodology. The compound was

* Initial trials at reduction of **5**, carried out without addition of di-*tert*-butyl dicarbonate to the medium, proceeded unsatisfactorily. This prompted us to pursue the described detour, but the experiences gained in preparing **8** were then successfully applied to the reduction of **5**.

† We thank a referee for this suggestion.




Scheme 2.

first protected as the *tert*-butoxycarbonylamide **16** and then acetonated with 2,2-dimethoxypropane to give the 3-*N*,4-*O*-isopropylidene derivative **17**, which was transformed into the 2-*O*-[(methylthio)thiocarbonyl] derivative **18** by treatment with carbon disulfide, methyl iodide, and sodium hydride. Barton deoxygenation[12] of this xanthate furnished the corresponding 2-deoxy glycoside **19**. Selective reduction of the methyl carboxylate function in **19** by lithium borohydride (which does not attack the carbamate group) gave methyl 3-*tert*-butoxycarbonylamino-2,3,6-trideoxy-3-*C*-hydroxymethyl-3-*N*,4-*O*-isopropylidene-α-L-*lyxo*-hexopyranoside (**20**), a derivative of hitherto unknown 3′-hydroxyvancosamine. Yields in the steps **15** → **16** and **19** → **20** were 65–68%, and those in **16** → **17** → **18** → **19** were 90–95%.

Vancosamine (3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose) has been coupled to daunomycinone by way of an acid-catalyzed addition of the aglycon to a glycal derived from the amino sugar[13]. For an application of the same method to **20**, or alternatively, for its conversion into a derivative having a suitably activated anomeric center, to be used in a Koenigs–Knorr type coupling, the compound requires appropriate protection of its hydroxymethyl group. This posed a problem as the protecting group would have to be removable under basic conditions; an anthracycline generated would not tolerate acidic, hydrogenolytic or oxidative conditions, and a silyl group on O-3′ might not resist an acid solvolysis of the methyl glycoside needed to convert protected **20** into a glycosyl donor. Because of these constraints it was decided to *methylate* OH-3′ for a first approach to modified anthracyclines, considering that a methoxymethyl analog might also be a worthwhile target whose biological activity should be interesting to compare with that reported[13] for 3′-*C*-methyldaunorubicin.

Therefore, compound **20** was treated with methyl iodide and sodium hydride in oxolane. There was obtained in a 2:1 ratio the expected ether **21** and a crystalline

TABLE I

$^1$H NMR data [a] for **2–10**, **13**, **14**, and **16–22**

| Compound | Chemical shifts ($\delta$) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H-1 | H-2*eq* | H-2*ax* | H-4 | H-5 | H-6*eq* | H-6*ax* | *Ph*CH [b] | $OCH_3$ [b] | $CCH_3$ | N*H* | Others [c,d] |
| **2** | 5.19d | | 4.27d | 3.92d | 4.22td | 4.34dd | 3.84t | 5.57 | 3.58 | | 6.06s | |
| **3** [c] | 5.37d | | 5.80d | 4.03d | 4.25td | 4.39dd | 3.79t | 5.56 | 3.55 | | 6.58, 5.84 (2 bs) | |
| **4** | 4.82dd | 2.28dd | 2.46dd | 3.93d | 4.20td | 4.30dd | 3.76t | 5.57 | 3.41 | | 6.55, 5.92 (2 bs) | |
| **5** | 4.77d | 3.31d | 1.99dd | 3.63d | 4.23td | 4.32dd | 3.73t | 5.55 | 3.39 | | 5.34bs | 1.44 (*t*-Bu) |
| **6** | 4.37dd | 3.01d | 1.53 d | ⊢—— 4.25–4.05m, 3.75–3.65m ——⊣ | | | | 5.58 | 3.24 | | 5.94s | |
| **7** | 4.77d | 2.91dd | 1.83dd | 3.73d | ⊢—— 4.03–3.8m ——⊣ | | | | 3.34 | | | 5.2, 5.1 (2 OH); 1.45 (*t*-Bu) |
| **8** | 4.70dd | 2.00dd, | 1.94dd | 3.37m | 3.65td | ⊢3.87dd, 3.80dd⊣ | | | 3.30 | | 5.10bs, 4.92 b | 3.94m (NHC$H_2$); 1.43, 1.42 (2 *t*-Bu) |
| **9** | 4.73 ~ d | 2.02 ~ d | 2.80 ~ dd | 4.60d | 3.86td | 4.23dd | 3.74t | 5.53 | 3.31 | | 5.78bs, 5.16t | 3.83, 3.53 (2 dd, NHC$H_2$); 1.42, 1.39 (2 *t*-Bu) |
| **10** | 4.85d | 3.00dd | 2.00d | 6.03d | 4.1m | ⊢3.85–3.3m (4 H) [f]⊣ | | | 3.41 | | 5.86bs, 5.00m | 1.41, 1.36 (2 *t*-Bu) |
| **13** [g] | 4.72dd | 2.18m | 1.99dd | 4.77bs | 4.63nm | ⊢3.54 (AB-q, 2 H)⊣ | | | 3.44 | | 5.30bs | 1.48, 1.35 (2 *t*-Bu) |
| **14** | 4.61dd | 1.95dd | 1.84dd | *h* | 4.30nm | ⊢3.85–3.33m (6 H) [h]⊣ | | | 3.46 | | 5.01t | 1.45, 1.35 (2 *t*-Bu) |
| **16** | 4.67d | | 3.88m | ⊢4.48–4.40m (2 H)⊣ | | | | | 3.34, 3.77 | 1.30d | 5.39bs | |
| **16** [i] | 4.44d | | 3.77dd | 3.97d | 4.37q | | | | 3.17, 3.54 | 1.00d | 6.66bs | 4.93d (OH-4), 4.19d (OH-2), 1.34 (2 *t*-Bu) |
| **17** [i] | 4.49d | | 4.40m | 4.29d | 4.19dq | | | | 3.30, 3.67 | 1.12d | | 4.95d (OH); 1.57, 1.46 ($CMe_2$); 1.38 (*t*-Bu) |
| **18** | 4.75d | | 6.66d | 4.22dq | | | | | 3.40, 3.74 | 1.30d | | 2.58s (*S*Me); 1.72, 1.61 ($CMe_2$); 1.41 (*t*-Bu) |
| **19** [j] | 4.74dd | 2.33dd | 2.47dd | 4.00bs | 3.94bq | | | | 3.39, 3.75 | 1.24d | | 1.63 and 1.39 (*t*-Bu) [k] 1.67 and 1.46 ($CMe_2$) [l] |
| **20** [m] | 4.70dd | 2.47 | 1.80 | ⊢4.0–3.4m (4 H) [n]⊣ | | | | | 3.32 | 1.30d | | 4.30 (b, OH); 1.60 [3 H] and 1.42 [12H] ($CMe_2$ and *t*-Bu) |
| **21** [g] | 4.66t | 2.18bm [o] | 1.87bm [o] | ⊢4.0–3.4m (4H) [n,p]⊣ | | | | | 3.33, 3.31 | 1.28d | | 1.62, 1.48 ($CMe_2$); 1.46 (*t*-Bu) |
| **22** [m] | 4.76t | 1.97dt | 2.13dd | 3.55nm | 3.91dq | | | | 3.28 | 1.31 | | 4.18 (AB-q, 2 H, $CH_2O$); 1.63, 1.54 ($CMe_2$) |

| | Coupling constants (Hz) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $J_{1,2ax}$ | $J_{1,2eq}$ | $J_{4,5}$ | $J_{5,6ax}$ | $J_{5,6eq}$ | $J_{6ax,6eq}$ | $J_{2ax,2eq}$ | $J_{5,Me}$ | Others |
| **2** | 2.9 | | 9.3 | 9.5 | 4.9 | 10.4 | | | |
| **3** | 3.4 | | 9.7 | ~10.3 | 5.0 | 10.3 | | | |
| **4** | 3.75 | 1.0 | 9.5 | ~10.2 | 5.1 | ~10.2 | 14.3 | | |
| **5** | 4.0 | ~0 | 9.3 | ~10.0 | 5.25 | ~10.0 | 14.4 | | |
| **6** | 2 | ~0 | | | | | 13.8 | | |
| **7** | 3.8 | ~0 | 9.4 | | | | 14.0 | | |
| **8** | 3.8 | 1.9 | 9.9 | ⊢——4.3, 4.1——⊣ | | 11.5 | 14.1 | | |
| **9** | ~3.8 | ~0 | | 10.0 | 4.5 | 10.0 | 14 | | $J_{3'a,NH}$ 8.8, $J_{3'b,NH}$ 6.6, $J_{3'a,3'b}$ 14.7 |
| **10** | ~0 | 3.8 | 10.3 | | | | 14.4 | | |
| **13** [g] | 8 | 4 | ~1 | 3 | 3 | 10 | | | |
| **14** | 8.4 | 4.3 | | | | | | | |
| **16** | 3.2 | | 1.3 | | | | | 6.6 | |
| **16** [i] | 3.2 | | 0 | | | | | 6.6 | $J_{2,OH}$ 8.9, $J_{4,OH}$ 6.2 |
| **17** [i] | 3.7 | | 2.1 | | | | | 6.6 | $J_{2,OH}$ 6.9 |
| **18** | 4.1 | | 1.8 | | | | | 6.6 | |
| **19** | 6.8 | 4.9 | <1 | | | | | ~6.5 | |
| **20** | | | | | | | | | |
| **21** [g] | | 8.5 [q] | | | | | 15 | 6.6 | |
| **22** [m] | 2.9 | ~1.7 | 2.3 | | | | 13.6 | 6.6 | $J_{2eq,4}$ ~1 |

[a] At 300 MHz for $CDCl_3$ solutions unless otherwise indicated. [b] Singlets. [c] All compounds containing phenyl groups showed 5-proton multiplets at δ 7.5–7.3 (7.5–7.1, 10 H, for **3**). [d] All *tert*-butyl signals were 9-proton singlets. [e] Pure *gluco* isomer. The epimeric mixture showed additional signals for the minor, *manno* component at δ 6.03 (d, *J* 1.4 Hz, H-2), 5.69 (s, PhC*H*), 4.99 (d, *J* 1.4 Hz, H-1), and 3.53 (s, $OCH_3$). The remaining signals were largely overlapped by those of the *gluco* component. [f] Also containing $CH_2NH$ signals. [g] At 55°C. [h] 5 H after $D_2O$ exchange (OH-4); the complex multiplet contains also H-4 and $CH_2NH$ signals. [i] In $Me_2SO$-$d_6$. [j] Most signals were accompanied by satellites of ~2/3 intensity due to existence of amide tautomerism. The signals listed are those of the major tautomer. [k] Two singlets in 2:3 ratio, integrating together to 9 H. [l] Two singlets in 2:3 ratio, integrating to 6 H. [m] At 200 MHz. [n] Contains also $CH_2O$ signals. [o] At room temperature, H-2*ax* gave two independent AB-quartets (for 2 tautomers) at δ 2.18 (*J* 4.8 and 15 Hz) and 1.98 (*J* 4.5 and 15 Hz), and H-2*eq* gave AB-quartets at δ 1.90 (*J* 3.8 and 15 Hz) and 1.84 (*J* 3.4 and 15 Hz). [p] At room temperature the $CH_2O$ signals were observed as two independent AB systems, δ 3.68, 3.51 (*J* 10 Hz) and 3.87, 3.60 (*J* 10 Hz). [q] $J_{1,2ax} + J_{1,2eq}$.

TABLE II

$^{13}C$ NMR data [a]

| Compound | Chemical shifts (δ) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | C-1 | C-2 | C-4 | C-5 | C-6 | C-3 | PhC | $OCH_3$ | Others [b] |
| **2** | 95.8 | 78.1 | 80.7 | 63.8 | 68.5 | 59.3 | 102.2 | 56.5 | 156.1 (CO), 114.9 (CN) |
| **3** [c] | 95.1 | ⊢77.7, 77.0⊣ | | 60.8 | 68.7 | 51.4 | 102.3 | 56.1 | 193.3 (CS), 164.5 (CO), 115.8 (CN) |
| **4** | 96.6 | 35.7 | 78.0 | 61.0 | 68.9 | 45.0 | 102.3 | 55.2 | 167.0 (CO), 118.3 (CN) |
| **5** | 97.1 | 39.3 | 80.0 | 60.5 | 68.8 | 51.2 | 102.7 | 55.3 | 154.1 (CO), 117.5 (CN); 81.8, 28.3 (*t*-Bu) |
| **6** | 96.8 | 37.0 | 78.5 | 60.6 | 66.7 | 51.1 | 102.3 | 55.0 | 155.6 (CO), 118.5 (CN) |
| **7** | 96.8 | 38.5 | ⊢70.7, 69.2⊣ | | 61.8 | 54.4 | | 55.1 | 155.2 (CO), 118.2 (CN); 82.3, 28.3 (*t*-Bu) |
| **8** | 97.7 | 35.9 | ⊢72.2, 69.7⊣ | | 63.8 | 58.1 | | 55.0 | 156.0 (CO), 42.6 (C-3′); 80.2, 79.8, 28.4 (2 *t*-Bu) |
| **9** | 98.8 | 34.8 | 79.1 | 61.3 | 69.4 | 56.1 | 101.9 | 54.9 | 157.3, 154.2 (CO); 44.3 (C-3′); 79.6, 28.3, 28.2 (2 *t*-Bu) |
| **13** | 97.9 | 32.1 | ⊢70.7, 70.5⊣ | | 50.4 | 63.3 | | 56.6 | 165.7 (*Ph*CO); 155.9, 153.8 (*NH*CO); 42.3 (C-3′); 80.6, 28.3, 28.2 (2 *t*-Bu) |
| **14** | 97.7 | 32.0 | ⊢72.7, 69.5⊣ | | 50.1 | 63.9 | | 56.5 | 41.6 (C-3′); 80.1, 79.9, 28.4, 28.2 (2 *t*-Bu) |
| **16** | 99.1 | ⊢69.2, 64.8⊣ | | | 16.6 | 61.4 | | 55.5, 52.6 | 171.3 (*MeO*CO), 155.1 (*NH*CO); 81.2, 28.2 (*t*-Bu) |
| **17** [d] | 97.4 | 64.4 | 78.7 | 68.5 | 15.8 | 80.2 | | 54.7, 52.2 | 169.9 (*MeO*CO), 95.8 ($Me_2$C); 27.6 (*t*-Bu) [e]; 26.5, 24.8 ($CMe_2$) |
| **18** | 96.6 | ⊢78.0 (2 C)⊣ | | 64.0 | 16.2 | 67.0 | | 55.9, 52.7 | 216.5 (CS), 168.1 (*MeO*CO), 96.5 ($Me_2$C); 81.5, 28.3 (*t*-Bu); 26.5, 25.7 ($CMe_2$) |
| **19** | 97.2 | 32.3 | 79.2 | 64.4 | 16.5 | 80.9 | | 55.1, 52.8 | 172.5 (*MeO*CO), 96.8 ($Me_2$C), 28.3 (*t*-Bu) [e]; 26.9, 24.3 ($CMe_2$) |
| **20** | 97.6 | 31.9 | 74.9 | 61.8 | 16.7 | 62.8 | | 54.9 | 93.9 ($Me_2$C); 80.9, 28.5 (*t*-Bu); 66.6 (C-3′); 28.1, 25.7 ($CMe_2$) |
| **21** [f] | 97.5, 97.3 | 34.6, 32.9 | 75.2, 75.1 | 62.7, 62.3 | 16.5, 16.4 | 61.9, 60.6 | | 59.0, 54.7 | 151.5 (CO); 94.4, 93.9 ($Me_2$C); 79.7, 28.5, 79.6, 28.4 (*t*-Bu); 73.0, 71.8 (C-3′); 27.9, 25.6, 26.7, 24.3 ($CMe_2$) |
| **21** [g] | 97.6 | 33.5 [h] | 75.8 | 63.0 | 16.3 | 62 [h] | | 59.0, 54.5 | 151.6 (CO); 94.4 ($Me_2$C); 79.7, 28.5 (*t*-Bu); 72.9 (C-3′); 27.7 [h], 25.2 [h] ($CMe_2$) |
| **22** | 97.6 | 36.9 | 77.8 | 61.4 | 16.6 | 64.1 | | 55.0 | 156.7 (CO); 94.4 ($Me_2$C); 61.8 (C-3′); 29.3, 23.7 ($CMe_2$) |

[a] At 75.4 MHz for $CDCl_3$ solutions unless otherwise indicated. [b] All compounds possessing phenyl groups gave the expected Ph signals in the δ 137–127 region. [c] Pure *gluco* isomer. The epimeric mixture showed additional signals for the *manno* component at δ 193.2 (CS), 163.9 (CO), 113.9 (CN), 102.9 (*Ph*C), 97.5 (C-1), 78.0 and 74.9 (C-2,4), 61.4 (C-5), 55.8 ($OCH_3$), and 47.2 (C-3). [d] In $Me_2SO$-$d_6$. [e] The quaternary carbon signal presumably coincided with the C-3 signal. [f] At room temperature. [g] At 55°C. [h] Weak, broad signal.

tricyclic compound (**22**), separable by chromatography. The less-polar **21** gave a molecular-ion peak at $m/z$ 346 in the mass spectrum, a sharp amide band (1694 $cm^{-1}$) in the IR spectrum, and a correct microanalysis. The $^1H$ NMR spectrum taken at 55°C showed a clear triplet for H-1 and single resonances for two $OCH_3$ and two isopropylidene $CH_3$ groups, the $C(CH_3)_3$ group, and the terminal $C$-$CH_3$ group (see Table I). Taken at room temperature, the spectrum exhibited multiple substituent resonances and also some other signals (including those for H-2*ax* and H-2*eq*) were duplicated, which was regarded as a reflection of hindered rotation due to amide resonance. The phenomenon was particularly well observable in $^{13}C$ spectra: At room temperature, all carbon atoms except those of the carbonyl and the two methoxyl groups gave two resonances, some of them separated by as little as 0.08, others by as much as 2 ppm (see Table II); at 38°C, the narrow ones of these doublets became sharp singlets whereas the wider ones persisted (but with line broadening), and at 55°C they became broad single peaks. For a discussion of similar spectral phenomena recently observed in some *N*-acylated aminocyclitols, see ref. 14. The structure of the more polar **22** was assigned on the basis of microanalysis, a sharp amide carbonyl band shifted to 1759 $cm^{-1}$ (signifying a 5-membered, cyclic carbamate), and the following NMR parameters. The $^{13}C$ spectrum displayed 12 signals attributable by ADEPT to quaternary, tertiary, secondary, and primary carbon atoms as required for **22** (Table II). The $^1H$ spectrum showed a doublet of doublets (H-1), an AB quartet ($CH_2O$), an octet (H-5), a narrow multiplet (H-4), a three-proton singlet (OMe), and a doublet of doublets as well as a doublet of triplets (due to long-range coupling with H-4) for H-2 and H-2′ (Table I).

Compound **22** arose from intramolecular transesterification of the carbamic ester, and it may well prove to be a useful intermediate since it represents a molecule having OH-3′ protected in a non-permanent way. Preliminary experiments indicated that its glycosidic and isopropylidene groups can be cleaved efficiently by hydrolysis with trifluoroacetic acid, with retention of the cyclic carbamate. Although only NMR and mass-spectroscopic evidence for this is available at present, it is hoped that the partially blocked sugar **23** can be elaborated on a preparative scale and will prove suitable for coupling with anthracyclinones.

## EXPERIMENTAL

*General methods.*—General preparative procedures and instrumental techniques were the same as those employed previously[2–5]. The following solvent combinations (v/v) were used for thin-layer chromatography (TLC) and column chromatography on silica gel: ether–hexane, (*A*) 3:1, (*B*) 2:1, (*C*) 1:1, and (*D*) 1:2; MeOH–$CHCl_3$ (*E*) 1:10; and EtOAc–hexane (*F*) 1:3. Optical rotations ($[\alpha]_D$) were measured at room temperature in $CHCl_3$ ($c \sim 1$), unless otherwise indicated. Infrared data ($\nu_{max}$) were obtained with a Perkin–Elmer IR 983 spec-

trometer; only bands of special structural significance are listed. The NMR data listed in Tables I ($^1$H) and II ($^{13}$C) were recorded with Bruker AM 300 and Varian XL-300 instruments, except those denoted as 200 (or 50.3) MHz, which were obtained by a Varian Gemini 200 instrument. Mass spectral data ($m/z$) were obtained by the chemical ionization mode using ether as the ionizing gas, unless otherwise specified.

*Methyl 3-amino-4,6-O-benzylidene-2-O,3-N-carbonyl-3-C-cyano-3-deoxy-α-D-glucopyranoside* (**2**).—A mixture of methyl 4,6-*O*-benzylidene-3-*C*-carbamoyl-3-*C*-cyano-3-deoxy-α-D-glucopyranoside[3] (**1**, 250 mg), *N*-bromosuccinimide (200 mg), and $Hg(OAc)_2$ (490 mg) in dry *N*,*N*-dimethylformamide (5 mL) was stirred for 1 week at room temperature; TLC (ether; double irrigation) then showed that **1** ($R_F$ 0.3) was replaced by **2** ($R_F$ 0.7). The mixture was diluted with toluene (30 mL) and ether (15 mL), washed with water (2 × 20 mL), dried, and evaporated. The residue was chromatographed (solvent *B*) on a short column, to give crystalline **2** (120 mg, 48%), mp 115–116°C, $[\alpha]_D$ +103°; $\nu_{max}^{Nujol}$ 3276, (NH), 1786 (cyclic carbamate CO), and 1660 (amide II) cm$^{-1}$; mass spectrum (CI, $CH_4$): $m/z$ 333 ($M^+ + 1$), 306 ($M^+ + 1 - HCN$), 301 ($M^+ + 1 - MeOH$), 289 ($M^+ + 1 - CO_2$), 255 ($M^+ + 1 - C_6H_6$). *Anal.* Calcd for $C_{16}H_{16}N_2O_6$ (332.3): C, 57.83; H, 4.85; N, 8.43. Found: C, 57.71; H, 5.17; N, 8.57.

*Methyl 4,6-O-benzylidene-3-C-carbamoyl-3-C-cyano-3-deoxy-2-O-phenoxythiocarbonyl-α-D-glucopyranoside* (**3**).—To a solution of 8.34 g of a mixture[3] (~ 2.5 : 1) of **1** and its α-D-*manno* epimer in dry MeCN (100 mL), stirred at −15°C, was added 4-dimethylaminopyridine (6.0 g) followed by phenyl chlorothionoformate (6.5 g). Cooling was stopped after 10 min and stirring continued for 30 min at ambient temperature. The solution was diluted with $CH_2Cl_2$ (200 mL), washed sequentially with 5% HCl, aq $NaHCO_3$, water, dried, and evaporated. The residue was crystallized from ether–hexane, affording 8.9 g of a mixture of **3** and its 2-epimer, and an additional 0.6 g was obtained upon chromatographic processing (solvent *C*) of the mother liquor, for a total yield of 81%. This material was used for the preparation of **4**.

For characterization of **3**, the procedure just described was performed with pure, recrystallized[3] **1** on a 350-mg scale. Crystalline **3** obtained in 83% yield had mp 203–204°C, $[\alpha]_D$ +122°; $\nu_{max}^{KBr}$ 3426, 3251, and 3195 (OH, $NH_2$), 1717 and 1688 (amide I and II), 1278 (Ph–O–C stretch), and 1217 (C=S) cm$^{-1}$; mass spectrum (CI, $CH_4$): $m/z$ 471 ($M^+ + 1$), 439 ($M^+ + 1 - MeOH$), 393 ($M^+ + 1 - C_6H_6$), 319 ($M^+ + 1 - C_7H_4O_2S$), 213 ($M^+ + 1 - C_7H_4O_2S - PhCHO$). *Anal.* Calcd for $C_{23}H_{22}N_2O_7S$ (470.5): C, 58.71; H, 4.71; N, 5.95. Found: C, 58.34; H, 4.72; N, 6.25.

*Methyl 4,6-O-benzylidene-3-C-carbamoyl-3-C-cyano-2,3-dideoxy-α-D-arabino-hexopyranoside* (**4**).—A solution of **3** (18.4 g, epimer mixture), $Bu_3SnH$ (31 mL), and α,α′-azobis(isobutyronitrile) (300 mg) in dry benzene (390 mL) was boiled under reflux for 4 h and then concentrated. A solution of the residue in $CH_2Cl_2$ (250 mL) was washed with aq $NaHCO_3$ (2 × 100 mL) and water (2 × 100 mL), and evaporated. A solution of the product in MeCN (200 mL) was then extracted with

hexane (3 × 50 mL) for removal of tin-containing by-products (see ref. 12b, p 37) and evaporated again. Crystallization from solvent *C* gave **4** (9.40 g), and another 1.2 g was elaborated chromatographically (solvent *B*) from the mother liquor, for a total yield of 85%; mp 190–193°C, $[\alpha]_D$ +112°; $\nu_{max}^{Nujol}$ 3389 and 3274 ($NH_2$), 2251 (CN), 1717 and 1679 (amide I), 1621 and 1598 (amide II) $cm^{-1}$; *m/z* 319 (base peak, $M^+ + 1$), 287 ($M^+ + 1 - MeOH$), 271 (unassigned), 213 ($M^+ + 1 - PhCHO$), 181 ($M^+ + 1 - MeOH - PhCHO$), 169 (unassigned). *Anal.* Calcd for $C_{16}H_{18}N_2O_5$ (318.3): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.28; H, 5.85; N, 8.74.

*Methyl 4,6-O-benzylidene-3-*tert*-butoxycarbonylamino-3-C-cyano-2,3-dideoxy-α-*D*-*arabino*-hexopyranoside* (**5**) *and* N,N′*-bis(methyl 4,6-O-benzylidene-3-C-cyano-2,3-dideoxy-α-*D*-*arabino*-hexopyranosid-3-yl)urea* (**6**).—A mixture of **4** (7.95 g), $Pb(OAc)_4$ (52 g), *N,N*-dimethylformamide (40 mL), and *tert*-butyl alcohol (100 mL) was boiled under reflux for 40 min, with efficient stirring and protection from atmospheric moisture. The cooled mixture was then diluted with toluene (200 mL) and ether (50 mL), and filtered. The filtrate was washed with water (2 × 100 mL), dried, and evaporated. Column chromatography of the residue using ether as the eluant gave **5** (7.454 g, 76.4%) followed by **6** (2.86 g, 19%).

Compound **5** had mp 183–185°C, $[\alpha]_D$ +115°; $\nu_{max}^{Nujol}$ 3346 (NH), 1717, 1684, and 1513 $cm^{-1}$.

Compound **6** had mp 239–242°C (dec, with sintering from >200°C), $[\alpha]_D$ +142°; $\nu_{max}^{Nujol}$ 3361 (NH), 1675 and 1544 (amide I and II) $cm^{-1}$; *m/z* (CI, $CH_4$) 607 ($M^+ + 1$), 580 ($M^+ + 1 - HCN$), 575 ($M^+ + 1 - MeOH$), 501 ($M^+ + 1 - PhCHO$), 317 (base peak; $M^+ - C_{15}H_{17}N_2O_4$ [A]), 290 (A − HCN), 285 (A − MeOH), 264 ($C_{15}H_{18}N_2O_4$ [B] + 1 − HCN), 239 (A − $C_6H_6$), 232 (B + 1 − HCN − MeOH), 211 (A − PhCHO), 126 (B + 1 − HCN − MeOH − PhCHO), 107 (PhCHO + $H^+$), 79 ($C_6H_6 + H^+$), 61 ($H_2NCONH_2 + H^+$). Only the fragments with >10% of base peak intensity are listed. *Anal.* Calcd for $C_{31}H_{34}N_4O_9 \cdot H_2O$ (624.6): C, 59.61; H, 5.81; N, 8.97. Found: C, 59.75; H, 5.65; N, 8.98.

*Methyl 3-*tert*-butoxycarbonylamino-3-C-cyano-2,3-dideoxy-α-*D*-arabino-hexopyranoside* (**7**).—A solution of **5** (2.0 g) and $I_2$ (1 g) in MeOH (100 mL) was boiled under reflux for 17 h and then evaporated. The residue dissolved in EtOAc was freed from $I_2$ by extraction with aq $Na_2S_2O_3$ solution. The organic phase, which contained **7** ($R_F$ 0.3) and unreacted **5** ($R_F$ 0.7; TLC with solvent *E*) was evaporated. Separation of the components by column chromatography (solvent *E*) gave **7** (0.75 g) and **5** (0.68 g); the latter was recycled to give another 0.25 g of **7** (total yield, 65%). It was a solid foam, $[\alpha]_D$ −95.5°; $\nu_{max}^{Nujol}$ 3350 (OH, NH), 2249 (weak, CN), and 1716 (carbamate CO) $cm^{-1}$. *Anal.* Calcd for $C_{13}H_{22}N_2O_6$ (302.3): C, 51.65; H, 7.33; N, 9.26. Found: C, 51.56; H, 6.95; N, 9.04.

*Methyl 3-*tert*-butoxycarbonylamino-3-C-*tert*-butoxycarbonylaminomethyl-2,3-dideoxy-α-*D*-arabino-hexopyranoside* (**8**).—To a stirred solution of **7** (3.1 g), $CoCl_2$ (16 g), and di-*tert*-butyl dicarbonate (10 g) in MeOH (620 mL) was added $NaBH_4$ (16 g) in small portions in the course of 30 min, after which stirring was continued for 30 min. A 20% aq solution of $NH_4Cl$ (120 mL) was then added and the mixture

was concentrated to remove most of the MeOH. The remaining aqueous solution was extracted with EtOAc (3 × 50 mL), and the dried extract was evaporated and purified by column chromatography (ether), to give **8** (2.5 g, 60%) as a dry foam, $[\alpha]_D$ +85°; $\nu_{max}^{Nujol}$ 3353 (OH, NH), 1699 and 1507 (amide I and II) $cm^{-1}$. *Anal.* Calcd for $C_{18}H_{34}N_2O_8$ (406.3): C, 53.20; H, 8.43; N, 6.89. Found: C, 53.33; H, 8.29; N, 6.71.

*Methyl 4,6-*O*-benzylidene-3-*tert*-butoxycarbonylamino-3-*C*-tert-butoxycarbonylaminomethyl-2,3-di-deoxy-α-*D*-arabino-hexopyranoside* (**9**).—*A. From* **5**. The cyano derivative **5** (240 mg), $CoCl_2$ (500 mg), and di-*tert*-butyl dicarbonate (300 mg) were dissolved in MeOH (30 mL), and $NaBH_4$ (500 mg) was added portionwise during 10 min. After continued stirring for 4 h the solids were removed by centrifugation, and the supernatant was evaporated to give a residue that was taken up in EtOAc and washed with water (2 × 25 mL). The organic phase, which showed a strong spot for **9** ($R_F$ 0.5) and a trace spot for **5** ($R_F$ 0.2; TLC with solvent *C*) was concentrated, and the product purified by column chromatography (solvent *F*), to furnish crystalline **9** (207 mg, 68%) and unchanged **5** (45 mg, 19%). Compound **9** had mp 134–135°C, $[\alpha]_D$ −15°; $\nu_{max}^{Nujol}$ 3443, 3306, 1707, 1528, and 1507 $cm^{-1}$; *m/z* 495 ($M^+ + 1$, base peak), 463 ($M^+ + 1 - MeOH$), 439 ($M^+ + 1 - C_4H_8$), 407 ($M^+ + 1 - MeOH - C_4H_8$), 395 ($M^+ + 1 - C_4H_8 - CO_2$), 383 ($M^+ + 1 - 2\ C_4H_8$), 351 ($M^+ + 1 - MeOH - 2\ C_4H_8$), 339 ($M^+ + 1 - 2\ C_4H_8 - CO_2$), 307 ($M^+ + 1 - MeOH - 2\ C_4H_8 - CO_2$), 295 ($M^+ + 1 - 2\ C_4H_8 - 2\ CO_2$), 264 ($M^+ + 1 - MeOH - 2\ C_4H_8 - 2\ CO_2$). *Anal.* Calcd for $C_{25}H_{38}N_2O_8$ (494.6): C, 60.71; H, 7.74; N, 5.66. Found: C, 60.55; H, 7.75; N, 5.56.

*B. From* **8**. The 4,6-diol **8** (200 mg) was benzylidenated in MeCN solution by treatment (30 min) with α,α-dimethoxytoluene in the presence of a catalytic amount of *p*-TsOH, as described[2b,3] for similar examples. The solvent was evaporated at 35°C to one-half its volume, the solution carefully neutralized with $Et_3N$, and solvent evaporation was then completed. Purification of the solid product by column chromatography using solvent *D* followed by solvent *C* gave **9** (230 mg, 95%), identical ($^1H$ NMR, TLC) with **9** prepared from **5**.

*Methyl-4-*O*-benzoyl-6-bromo-3-*tert*-butoxycarbonylamino-3-*C*-tert-butoxycarbonylaminomethyl-2,3,6-trideoxy-α-*D*-arabino-hexopyranoside* (**10**).—A mixture of **9** (1.71 g), *N*-bromosuccinimide (0.7 g), $BaCO_3$ (1.41 g, dried at 180°C for 4 h), and $CCl_4$ (170 mL, freshly distilled from $P_2O_5$) was vigorously stirred and heated under reflux for 1 h, after which TLC (solvent *C*) indicated complete replacement of **9** ($R_F$ 0.4) by **10** ($R_F$ 0.5). The mixture was filtered through Celite, the filter cake washed with hot $CCl_4$, and the filtrate evaporated. An ethereal solution of the residue was washed with aq $NaHCO_3$ solution, brine, and water, dried, and evaporated, to give crude, syrupy **10** (2.0 g, 100%, after drying in a high vacuum); $\nu_{max}^{film}$ 3382 (NH), 1710 and 1518 (CO and amide II) $cm^{-1}$; *m/z* 575, 573 ($M^+ + 1$), 543, 541 ($M^+ + 1 - MeOH$), 519, 517 ($M^+ + 1 - C_4H_8$), 487, 485 ($M^+ + 1 - MeOH - C_4H_8$), 475, 473 ($M^+ + 1 - C_4H_8 - CO_2$), 474 (unassigned), 463, 461 ($M^+ + 1 - 2\ C_4H_8$), 431, 429 ($M^+ + 1 - MeOH - 2\ C_4H_8$), 419, 417 ($M^+ + 1 - 2\ C_4H_8 -$

$CO_2$), 393 ($M^+ + 1 - HBr - C_4H_8 - CO_2$), 387, 385 ($M^+ + 1 - MeOH - 2\ C_4H_8 - CO_2$), 293 ($M^+ + 1 - HBr - 2\ C_4H_8 - 2\ CO_2$), 261 ($M^+ + 1 - MeOH - HBr - 2\ C_4H_8 - 2\ CO_2$). Purification by chromatography was dispensed with as **10** proved unstable towards $SiO_2$.

*Methyl 4-O-benzoyl-3-C-*tert*-butoxycarbonylaminomethyl-3,6-(*N*-tert-butoxycarbonyl)imino-2,3,6-trideoxy-α-*D*-arabino-hexopyranoside* (**13**).—A solution of bromo derivative **10** (2.0 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 mL) in dry benzene (100 mL) was boiled under reflux for 11 h, then cooled, washed sequentially with 5% HCl (3 × 70 mL), aq $NaHCO_3$ (2 × 50 mL), and water, dried ($Na_2SO_4$), and evaporated. TLC showed a strong spot for **13** ($R_F$ 0.3), and **10** ($R_F$ 0.4) was absent (solvent *C*). Column chromatography (solvent *D*) of the crude product removed a small amount of an unidentified byproduct (not seen in TLC of the reaction mixture) in forefractions and then gave pure **13** (1.23 g, 69%) as a solid foam analyzing as a monohydrate; $[\alpha]_D$ −37.5°; $\nu_{max}^{film}$ 3390 (br, NH and OH of water), 1706 and 1504 (CO and amide II) $cm^{-1}$; *m/z* 493 ($M^+ + 1$, base peak), 461 ($M^+ + 1 - MeOH$), 437 ($M^+ + 1 - C_4H_8$), 393 ($M^+ + 1 - C_4H_8 - CO_2$), 381 ($M^+ + 1 - 2\ C_4H_8$), 337 ($M^+ + 1 - 2\ C_4H_8 - CO_2$), 305 ($M^+ + 1 - MeOH - 2\ C_4H_8 - CO_2$), 293 ($M^+ + 1 - 2\ C_4H_8 - 2\ CO_2$), 261 ($M^+ + 1 - MeOH - 2\ C_4H_8 - 2\ CO_2$). *Anal.* Calcd for $C_{25}H_{36}N_2O_8 \cdot H_2O$ (510.6): C, 58.80; H, 7.50; N, 5.49. Found: C, 58.92; H, 7.13; N, 5.35.

*Methyl 3-C-*tert*-butoxycarbonylaminomethyl-3,6-(*N*-tert-butoxycarbonyl)imino-2,3,6-trideoxy-α-*D*-arabino-hexopyranoside* (**14**).—Benzoate **13** (1.17 g) was debenzoylated in methanolic, 0.06 M $NaOCH_3$ solution (48 mL) during 1 h at 25°C. After deionization by cation exchange, evaporation of the solution, and column chromatography (solvent *B*) of the residue, **14** (770 mg, 86.5%) was obtained as a solid foam, $[\alpha]_D$ +78°; $\nu_{max}^{Nujol}$ 3396, 1696 $cm^{-1}$; $\nu_{max}^{film}$ 3359, 1682 $cm^{-1}$; *m/z* 389 ($M^+ + 1$), 357 ($M^+ + 1 - MeOH$), 333 ($M^+ + 1 - C_4H_8$), 301 ($M^+ + 1 - MeOH - C_4H_8$), 289 ($M^+ + 1 - C_4H_8 - CO_2$), 283 ($M^+ + 1 - MeOH - C_4H_8 - H_2O$), 257 ($M^+ + 1 - MeOH - C_4H_8 - CO_2$), 245 ($M^+ + 1 - MeOH - 2\ C_4H_8$), 227 ($M^+ + 1 - MeOH - 2\ C_4H_8 - H_2O$), 201 ($M^+ + 1 - MeOH - 2\ C_4H_8 - CO_2$), 183 ($M^+ + 1 - MeOH - 2\ C_4H_8 - CO_2 - H_2O$). *Anal.* Calcd for $C_{18}H_{32}N_2O_7$ (388.4): C, 55.65; H, 8.30; N, 7.21. Found: C, 55.79; H, 8.13; N, 7.03.

*Methyl 3-*tert*-butoxycarbonylamino-3,6-dideoxy-3-C-methoxycarbonyl-α-L-galactopyranoside* (**16**).—A solution of methyl 3-amino-3,6-dideoxy-3-*C*-methoxycarbonyl-α-L-galactopyranoside[5] (**15**, 1.28 g) and di-*tert*-butyl dicarbonate (4 g) in dry $CH_2Cl_2$ (50 mL), rendered basic against moist indicator paper by addition of $Et_3N$, was stored for 3 days at room temperature, washed with 5% HCl and water, dried ($Na_2SO_4$), and evaporated. The product was chromatographed (solvent *A*), to furnish pure **16** (1.07 g, 68%) as a colorless, amorphous solid, mp 64–65°C, $[\alpha]_D$ −13°; $\nu_{max}^{Nujol}$ 3486 (OH, NH), 1753 (ester CO), 1716 (carbamate CO), and 1516 (amide II) $cm^{-1}$. Mass spectrum (CI, $CH_4$): *m/z* 336 ($M^+ + 1$), 304 ($M^+ + 1 - MeOH$), 280 ($M^+ + 1 - C_4H_8$), 276 ($M^+ - CO_2Me$), 248 ($M^+ + 1 - C_4H_8 -$

MeOH), 204 ($M^+ + 1 - C_4H_8 - CO_2$). *Anal.* Calcd for $C_{14}H_{25}NO_8$ (335.4): C, 50.14; H, 7.51; N, 4.18. Found: C, 50.08; H, 7.65; N, 3.91.

*Methyl 3-*tert*-butoxycarbonylamino-3,6-dideoxy-3-*N*,4-O-isopropylidene-3-C-methoxycarbonyl-α-*L*-galactopyranoside* (**17**).—A solution of **16** (1.053 g) in a mixture of dry MeCN (15 mL) and 2,2-dimethoxypropane (10 mL) containing a catalytic amount of *p*-TsOH was kept for 3 h at room temperature, then basified with $Et_3N$ and evaporated to dryness. The material was taken up in $CH_2Cl_2$, washed with aq $NaHCO_2$, recovered by solvent evaporation, and chromatographed (solvent *C*), to give syrupy **17** (1.103 g, 94%), $[\alpha]_D$ +98.7°; $\nu_{max}^{film}$ 3523 (OH), 1742 (ester CO), 1698 (carbamate CO) $cm^{-1}$; *m/z* 376 ($M^+ + 1$), 346, 344 ($M^+ + 1$ – MeOH), 320 ($M^+ + 1 - C_4H_8$), 288 ($M^+ + 1$ – MeOH – $C_4H_8$), 276 ($M^+ + 1 - C_4H_8 - CO_2$), 244 ($M^+ + 1$ – MeOH – $C_4H_8 - CO_2$). Exact mass calcd for $C_{17}H_{29}NO_8$: 375.18931. Found: 375.18762.

*Methyl 3-*tert*-butoxycarbonylamino-3,6-dideoxy-3-*N*,4-O-isopropylidene-3-C-methoxycarbonyl-2-O-(methylthio)thiocarbonyl-α-*L*-galactopyrano* (**18**).—To a solution of **17** (486 mg) in oxolane (25 mL, freshly distilled from $LiAlH_4$) was added $CS_2$ (10 mL) and NaH (60 mg). The mixture was stored at room temperature overnight, boiled under reflux for 45 min, cooled to room temperature and, after addition of $CH_3I$ (1 mL), allowed to stand for 3 h. It was then diluted with $CH_2Cl_2$ (150 mL), washed with water (2 × 100 mL), dried, and concentrated. Column chromatography (solvent *D*) of the residue gave **18** (569 mg, 95%) as a syrup, $[\alpha]_D$ +60.2°; $\nu_{max}^{film}$ 1772, 1736, and 1694 (ester and carbamate CO), 1135, 1098, and 1048 (C=S) $cm^{-1}$; *m/z* 466 ($M^+ + 1$), 434 ($M^+ + 1$ – MeOH), 410 ($M^+ + 1 - C_4H_8$), 378 ($M^+ 1$ – MeOH – $C_4H_8$), 366 ($M^+ + 1 - C_4H_8 - CO_2$), 334 ($M^+ + 1$ – MeOH – $C_4H_8 - CO_2$), 302 ($M^+ + 1 - C_4H_8$ – MeS–CS–OH). *Anal.* Calcd for $C_{19}H_{31}NO_8S_2$ (465.6): C, 49.01; H, 6.71; N, 3.01. Found: C, 49.04; H, 6.84; N, 3.05.

*Methyl 3-*tert*-butoxycarbonylamino-2,3,6-trideoxy-3-*N*,4-O-isopropylidene-3-C-methoxycarbonyl-α-*L*-lyxo-hexopyranoside* (**19**).—A solution of **18** (508 mg), $Bu_3SnH$ (1 mL), and a catalytic amount of α,α-azobis(isobutyronitrile) in dry benzene (25 mL) was boiled under reflux for 4 h. The solvent was evaporated and the residue subjected to column chromatography (solvent *D*), to give syrupy **19** (375 mg, 95%), $[\alpha]_D$ −2°; $\nu_{max}^{film}$ 1744 (ester CO) and 1705 (carbamate CO) $cm^{-1}$. Mass spectrum (CI, ether): *m/z* 360 (7%, $M^+ + 1$), and peaks due to the principal fragmentation pathway, initiated by α-cleavage of the methyl ester, at *m/z* 328 (68%, $M^+ + 1$ – MeOH), 272 (100%, $M^+ + 1$ – MeOH – $C_4H_8$), 228 (86%, $M^+ + 1$ – MeOH – $C_4H_8 - CO_2$), 200 (5%, $M^+ + 1$ – MeOH – $C_4H_8 - CO_2$ – CO), and 168 (7%, $M^+ + 1 - 2$ MeOH – $C_4H_8 - CO_2$ – CO); two series of additional, minor peaks (generally 1–7%) were attributable to less important fragmentation modes initiated by loss of an isopropylidene $CH_3$ group from $M^+$ (*m/z* 344, 288, 244 [16%], 212, and 185), and by loss of $CO_2CH_3$ from $M^+$ (*m/z* 300, 244, 212, 200, and 168). Note that some of the peaks are not pathway-specific. Exact mass calcd for $C_{17}H_{29}NO_7$: 359.1944. Found: 359.1915.

*Methyl 3-*tert*-butoxycarbonylamino-2,3,6-trideoxy-3-C-hydroxymethyl-3-*N*,4-O-*

*isopropylidene-α-*L*-lyxo-hexopyranoside* (**20**).—A solution of **19** (328 mg) and $LiBH_4$ (120 mg) in rigorously dried oxolane (38 mL) was stored overnight at room temperature, after which TLC (solvent *C*) indicated the complete replacement of **19** ($R_F$ 0.5) by **20** ($R_F$ 0.3). After careful addition of MeOH the solvents were evaporated. Column chromatography (solvent *C*) of the residue gave **20** (200 mg, 66%) as a syrup that crystallized slowly on standing, mp 82–83°C, $[\alpha]_D$ −41.5°; $\nu_{max}^{film}$ 3471 (OH), 1693 (carbamate CO) $cm^{-1}$; *m/z* 332 ($M^+ + 1$), 300 ($M^+ + 1 -$ MeOH), 244 ($M^+ + 1 -$ MeOH $- C_4H_8$), 232 ($M^+ + 1 - C_4H_8 - CO_2$), 200 ($M^+ + 1 -$ MeOH $- C_4H_8 - CO_2$). Exact mass calcd for $C_{16}H_{29}NO_6$: 331.1995. Found: 331.2135.

*Methyl 3-*tert*-butoxycarbonylamino-2,3,6-trideoxy-3-*N*,4-O-isopropylidene-3-C-methoxymethyl-α-*L*-lyxo-hexopyranoside* (**21**) *and methyl 3-amino-3-*N*,3′-O-carbonyl-2,3,6-trideoxy-3-C-hydroxymethyl-3-*N*,4-O-isopropylidene-α-*L*-lyxo-hexopyranoside* (**22**).—To a stirred solution of **20** (413 mg) in dry oxolane (50 mL) was added NaH (200 mg of a 62% mineral oil suspension), followed after 30 min by $CH_3I$ (0.175 mL). After 20 h, a small volume of MeOH was added and the solvent was evaporated. A solution of the residue in EtOAc was washed with water, dried, and evaporated, to give a crude product showing a major ($R_F$ 0.4) and a minor ($R_F$ 0.2) spot in TLC (solvent *C*). Separation by column chromatography (solvent *D*) yielded syrupy **21** (230 mg, 53.4%), followed by crystalline **22** (81 mg, 25%).

Compound **21** had $[\alpha]_D$ −36°, $[\alpha]_{436}$ −68.5°; $\nu_{max}^{film}$ 1694 (carbamate CO) $cm^{-1}$; *m/z* 346 ($M^+ + 1$), 314 ($M^+ + 1 -$ MeOH), 300 ($M^+ + 1 - Me_2O$), 290 ($M^+ + 1 - C_4H_8$), 258 ($M^+ + 1 -$ MeOH $- C_4H_8$), 230 (unassigned), 214 ($M^+ + 1 -$ MeOH $- C_4H_8 - CO_2$), 200 ($M^+ + 1 - Me_2O - C_4H_8 - CO_2$). *Anal.* Calcd for $C_{17}H_{31}NO_6$ (345.4): C, 59.11; H, 9.05; N, 4.05. Found: C, 59.81; H, 8.77; N, 3.94.

Compound **22** had mp 115–116°C, $[\alpha]_D$ −99°; $\nu_{max}^{film}$ 1759 (cyclic carbamate CO) $cm^{-1}$; *m/z* 258 ($M^+ + 1$), 242 ($M^+ + 1 - CH_4$), 226 ($M^+ + 1 -$ MeOH), 214 ($M^+ + 1 - CO_2$), 200 ($M^+ + 1 - Me_2CO$), 168 ($M^+ + 1 -$ MeOH $- Me_2CO$). *Anal.* Calcd for $C_{12}H_{17}NO_5$ (257.3): C, 56.02; H, 7.44; N, 5.44. Found: C, 55.84; H, 7.27; N, 5.36.

In a preliminary trial, **22** (70 mg) was boiled for 25 min with aq 30% trifluoroacetic acid (10 mL). Removal of the acid by coevaporation with toluene and chromatography of the product with 1:5 MeOH–$CHCl_3$ gave 48 mg of a white solid, presumably **23**. Definitive characterization requires further purification; however, in accord with this structure the product lacked methoxy and isopropylidene resonances in its $^1H$ and $^{13}C$ NMR spectra, and it showed *m/z* 204 ($M^+ + 1$), 186 ($M^+ + 1 - H_2O$), and 160 ($M^+ + 1 - CO_2$).

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