Stereocontrolled routes to *cis*-hydroxyamino sugars. Part VII.[1] A synthesis of holacosamine[2]

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Methyl 4,6-di-*O*-*p*-toluenesulfonyl-α-D-*threo*-hex-2-enopyranoside **4***b* reacts with methylamine at room temperature to displace the allylic sulfonate only, and the ethyl urethane of the resulting 4-*N*-methylamino sugar is cyclized with iodonium ion to give the 2-iodo-oxazolidinone, **13**. This substance, upon treatment with sodium iodide in acetone, gives the 2,6-diiodide **14***a*. Deiodination, followed by base hydrolysis, gives the *cis*-hydroxyamino precursor, which upon *N*-acetylation and *O*-methylation affords the previously known holacosaminide **1***b*.

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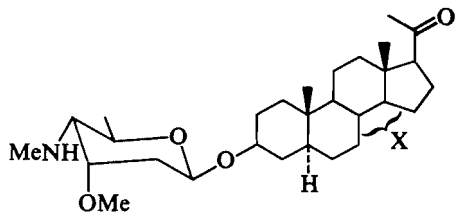
Le di-*O*-*p*-toluènesulfonyl-4,6 α-D-*thréo*-hexèno-2 pyrannoside de méthyle (**4***b*) réagit avec la méthylamine à la température ambiante pour déplacer uniquement le sulfonate allylique; l'éthyl uréthane du sucre *N*-méthylamino-4 qui en résulte se cyclise avec l'ion iodonium pour donner l'iodo-2 oxazolidinone (**13**). Cette substance, sous l'action de l'iodure de sodium dans l'acétone, conduit au dérivé diiodo-2,6 (**14***a*). L'élimination de l'iode, suivie d'une hydrolyse alcaline, conduit au précurseur amino-alcool-*cis* qui, par *N*-acétylation et *O*-méthylation, fournit l'holacosaminide déjà connu, **1***b*.

[Traduit par le journal]

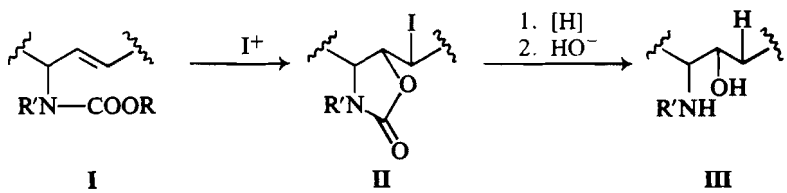
In the accompanying paper (1) we gave full details of a new synthesis of garosamine in which the troublesome *cis*-hydroxyamino moiety and the tertiary hydroxyl group were established simultaneously by means of iodonium ion-induced cyclization of an allylic amide, for example **I**–**III**, Scheme 1. A secondary feature of this crucial process of the introduction of the iodine atom which opens the way for several additional transformations, of which reductive deiodination is one of the more obvious. Thus, a ready route to polydeoxyamino sugars is suggested, and in order to develop this chemistry we looked at the trideoxyamino sugar, holacosamine **1***a*. In this paper we give full details of this study, which was reported previously in preliminary form (2).

Holacosamine, **1***a* (Scheme 3), was first obtained from the amino glycosteroids, holacurtin, **2***a*, and holarosine, **2***b*, isolated from the leaves of *Holarrhena curtisii* which is a native plant of Malaysia (3). The sugar was subsequently isolated from the corticosteroid, mitiphylline, extracted from the leaves of *Holarrhena mitis* from Sri Lanka (4). These compounds have cardiotonic activity, and there is also some interest in them as anti-cancer drugs in view of the discovery that some glycosteroids have significant inhibitory activity against human carcinoma of the nasopharynx (5). An early synthesis of holacosamine was reported by Gero and co-workers (6), but the number of epimerizations needed to establish the proper stereorelationships, the harsh conditions for most of these reactions, and their low yield illustrate the problems associated with even such a relatively simple *cis*-hydroxyamino sugar.



2

a X = 8β-H 14β-OH, holacurtin
b X = $\Delta^{8\text{-}14}$, holarosine



I **II** **III**

SCHEME 1

[1]For Part VI see accompanying paper, ref. 1.
[2]For a preliminary account of this work see ref. 2.
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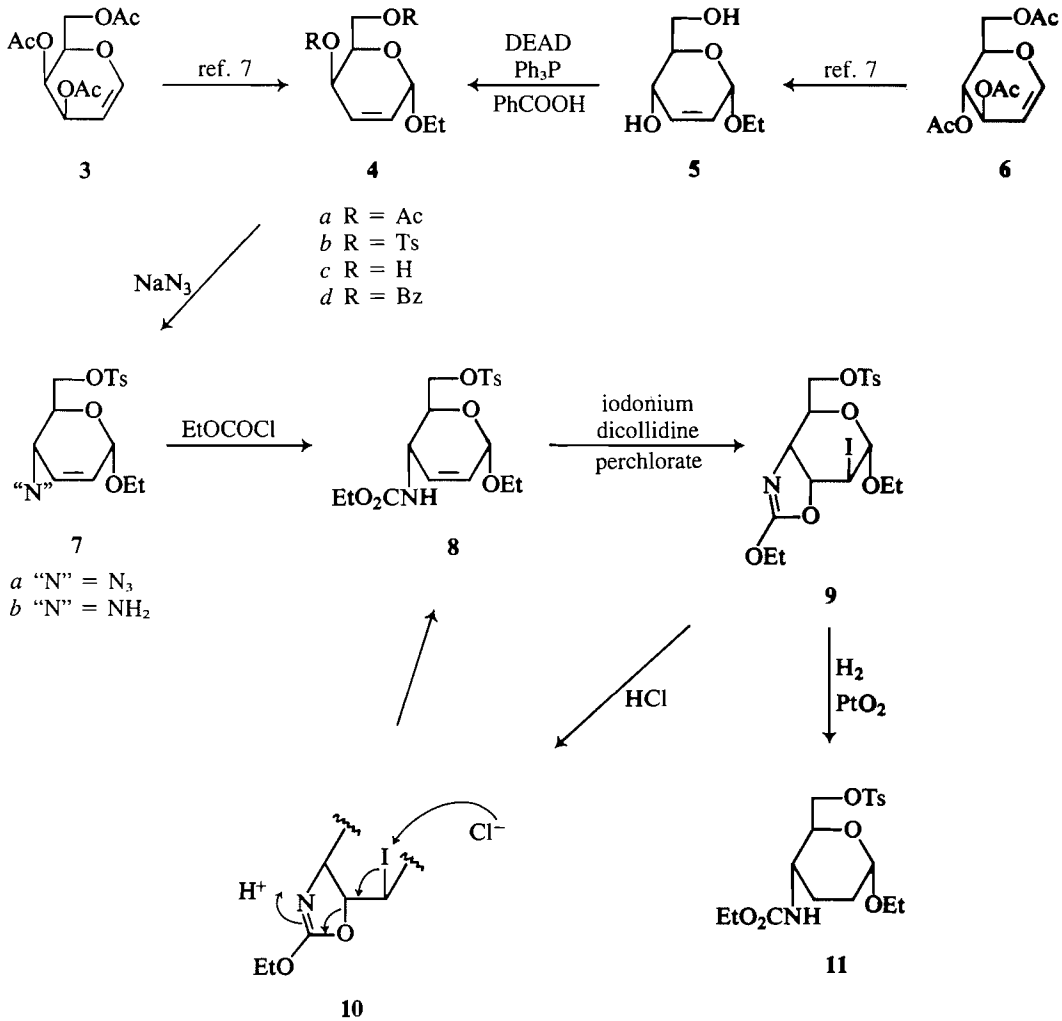
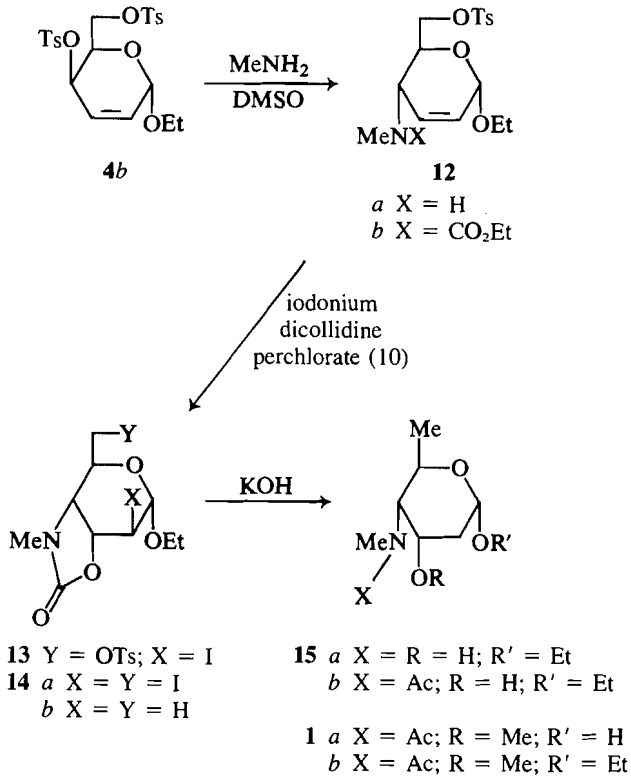
Application of the process depicted in **I** → **II** → **III**, Scheme 1, would require the unsaturated amino sugar **7** whose preparation from the *threo*-hex-2-eno-pyranoside **4***b* is apparent. Although the corresponding diacetate **4***a* is obtainable in one step from "triacetyl galactal" by the Ferrier rearrangement (7), considerations of economy and efficiency make the three-step sequence beginning with commercially available "triacetyl glucal", **6**, more attractive (7). As was the case in Gero's synthesis (6), we faced a double inversion sequence to establish the C-4 nitrogen in **7**. However, since our reactions would be occurring at an allylic site, much milder conditions would be required.



SCHEME 2

Reaction of the diol **5** under the Mitsunobu conditions (8), as modified by Galynker and Still (9), allowed for direct conversion into the disulfonate **4***b*. Although this modification (9) saves two steps in the sequence, the necessity of using five equivalents of diethyl azodicarboxylate per hydroxyl group did not make it very practical for large scale preparations and conventional sulfonation was therefore preferred. Accordingly, **5** was converted into the dibenzoate **4***d* by the Mitsunobu reaction (8), and the latter was converted into the disulfonate **4***b* via diol **4***c*. Reaction of **4***b* with sodium azide in dimethyl sulfoxide at room temperature displaced only the allylic sulfonate, and the structure of the product **7***a* was apparent from the value $J_{3,4}$ = 1 Hz. The azide was reduced to the amine **7***b* with lithium aluminium hydride in ether at −25°C. Treatment of the derived urethane, **8**, with iodonium dicollidine perchlorate (10) in methylene chloride gave the oxazoline **9**, instead of an oxazolidinone as in the garosamine synthesis (1).

Very surprisingly, hydrolysis of **9** with 0.5 *N* hydrochloric acid at room temperature for 1.5 h regenerated the allylic urethane **8**. We rationalized that this course of reaction was triggered by protonation of the nitrogen with the eventual collapse depicted in **10**. Removal of the C-2 iodine should, therefore, prevent this process, but reductive deiodination of **9** proved remarkably difficult. Hydrogenolysis did not occur with palladium as catalyst, and with platinum, two products in the ratio 7:1 were obtained, the major of which proved to be **11**. Compound **11** is probably formed by a homolytic fragmentation comparable to the heterolytic process depicted in **10**, followed by hydrogenation of the double bond.



4*b*

12
a X = H
b X = CO_2Et

13 Y = OTs; X = I
14 *a* X = Y = I
b X = Y = H

15 *a* X = R = H; R′ = Et
b X = Ac; R = H; R′ = Et

1 *a* X = Ac; R = Me; R′ = H
b X = Ac; R = Me; R′ = Et

SCHEME 3

The difficulties experienced with **9** contrasted with the smooth process in the garosamine case (1), and suggested that at least part of our problem might be due to the fact that our intermediate **9** was a 2-ethoxy oxazolidine instead of an oxazolidinone. The presence of a C-4 *N*-methyl substituent, ultimately required at C-4 of **1**, would preclude the formation of such a 2-ethoxy oxazolidine, and so the ammonolysis of **4***b* was examined. The pressure vessel method used in our earlier work (1) led to decomposition, but use of dimethyl sulfoxide saturated with methylamine at room temperature afforded a 71% yield of **12***a*. Reaction of the derived urethane **12***b* with iodonium dicollidine perchlorate (10) at room temperature did give the desired oxazolidone **13**, but a second, unstable product obtained in 25% yield vitiated this result. The structure of the latter material was not determined, but patient experimentation showed that its formation could be avoided by adding the iodonium salt in small portions to **12***b* in refluxing dioxane.

When **13** was heated in refluxing acetone containing sodium iodide, the diiodourethane **14***a* was obtained and this was reduced with tri-*n*-butyltin hydride in refluxing benzene to afford the trideoxy sugar **14***b*. Hydrolysis of the oxazolidone with 5% potassium hydroxide proceeded smoothly to yield the *cis* vicinal hydroxyamine, **15***a*. *N*-Acetylation of the latter followed by *O*-methylation of the product, **15***b*, yielded *N*-acetyl holacosamine **1***b*. An attempt to procure an authentic sample of holacosamine from Gero (6) was unsuccessful. However, the synthetic sample of **1***b* gave compatible 400 MHz ^{1}H nmr and ir spectra, as well as microanalytical data (see Experimental).

Experimental

General methods

Melting points were determined in capillary tubes in a Buchi Model 510 and are uncorrected. Elemental analyses were performed by Guelph Chemical Labs, Guelph, Ontario and by Dr. F. Kasler, Department of Chemistry, University of Maryland. The ^{1}H nmr spectra were determined in deuteriochloroform with internal tetramethylsilane as the standard, unless otherwise stated, on one of the following spectrometers: Varian T-60, Bruker WP-80, or Bruker WH-400. Coupling constants were measured directly from the spectra or calculated from the peak listings. The ir spectra were determined on either a Beckman IR-10 or a Perkin–Elmer 298 spectrometer. Neat samples were smeared on sodium chloride plates and solutions were placed in sodium chloride cells. Low resoltuion ms were run on a Hitachi/Perkin–Elmer RMH-2. Optical rotations were determined on a Perkin–Elmer 241 polarimeter.

Thin layer chromatography (tlc) was performed using aluminum plates precoated with silica gel (HF-254, 0.2 mm thickness) containing a fluorescent indicator (E. Merck, CAT. 5539). The chromatograms were viewed under a uv light (254 nm), sprayed with concentrated sulfuric acid, and heated until charring occurred.

Column chromatography was carried out using silica gel (E. Merck 70–230 mesh A.S.T.M. or 230–500 mesh A.S.T.M.).

*Ethyl 2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside,* **4***c*

To a solution of **5** (11) (1.74 g, 10 mmol) triphenylphosphine (5.76 g, 22 mmol), and benzoic acid (2.68 g, 22 mmol) in dry tetrahydrofuran (50 mL) at 23°C under argon was added, over a period of 5 min, diethyl azodicarboxylate (3.82 g, 22 mmol). The reaction mixture was stirred for 30 min, after which time the solvent was removed *in vacuo*. The resulting oily mixture was purified by medium pressure chromatography on silica gel (30:70 diethyl ether – petroleum ether 30–60°C, R_f 0.57) to afford 3.31 g (85%) of the known (12) **4***d* dibenzoate as a colourless oil; ir ($CHCl_3$) ν_{max}: 2910, 1715 (benzoate), 1614, 1600, 1310–1160, 1110–950 cm^{-1}; ^{1}H nmr (80 MHz) δ: 1.23 (t, 3H, OCH_2CH_3), 3.39–4.06 (m, 2H, OCH_2CH_3), 4.42–4.78 (m, 3H, H5, H6, H6), 5.17 (d, J = 3 Hz, 1H, H1), 5.38 (bd, J = 5.3 Hz, 1H, H4), 6.09 (dd, J = 3, 10 Hz, 1H, H2), 6.31 (dd, J = 5.1, 10 Hz, 1H, H3), 7.30–7.60 (m, 6H, aromatic), 7.94–8.13 (m, 4H, aromatic).

To a solution of **4***d* (4.36 g, 11mmol) in methanol (50 mL) at 23°C was added a catalytic amount of sodium methoxide (100 mg). The reaction mixture was stirred for 2 h, after which time the solvent was removed *in vacuo*. The resulting mixture was chromatographed on silica gel (7:93 methanol – methylene chloride, R_f 0.32) to afford 1.51 g (75%) of an oil that crystallized upon standing. Recrystallization from methylene chloride – hexane afforded the known diol **4***c* as a crystalline material, mp 75–76°C (lit. (11) mp 76–77°C).

*Ethyl 2,3-dideoxy-4,6-di-*O*-p-toluenesulfonyl-α-D-*threo*-hex-2-enopyranoside,* **4***b*

To a solution of **4***c* (4.00 g, 23 mmol) in dry pyridine (30 mL) cooled to −40°C, *p*-toluenesulfonyl chloride (8.70 g, 46 mmol) and dry pyridine (20 mL) were added over 20 min. After 48 h at 0°C the reaction mixture was poured into ice water, carefully neutralized with 1 *N* HCl, and extracted with methylene chloride (1 × 75, 2 × 25 mL). The methylene chloride fractions were combined, washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo* to yield an oil. Medium pressure chromatography on silica gel (2:98 methanol – methylene chloride) followed by recrystallization (ether–hexane) afforded 9.52 g (86%) of pure **4***b* mp 78–79°C; R_f 0.36 (methylene chloride); $[\alpha]_D^{23}$ −11.3° (*c* 0.7, in $CHCl_3$); ir ν_{max} ($CHCl_3$): 2920, 1594 (C=C), 1464 (SO_2), 1168 (SO_2), 1097, 1000, 972 cm^{-1}; ^{1}H nmr (80 MHz) δ: 1.20 (t, 3H, OCH_2CH_3), 2.48 (s, 6H, tosyl CH_3), 3.25, 4.00 (m, 2H, OCH_2CH_3), 4.12 (2d, J = 2, 2.5, 6 Hz, 2H, H6, H6), 4.31 (ddd, J = 2.5, 6 Hz, 1H, H5), 4.67 (dd, J = 2.5, 5 Hz, 1H, H4), 4.97 (d, J = 2.5 Hz, 1H, H1), 5.82 (dd, J = 5, 10 Hz, 1H, H3), 6.03 (dd, J = 2.5, 10 Hz, 1H, H2), 7.33 (d, 4H, aromatic), 7.78 (d, 4H, aromatic). *Anal.* calcd. for $C_{22}H_{26}O_8S_2$: C 54.76, H 5.43; found: C 54.90, H 5.17.

*Ethyl 4-azido-2,3,4-trideoxy-6-*O*-p-toluenesulfonyl-α-D-*erythro*-hex-2-enopyranoside,* **7***a*

To a solution of **4***b* (12.7 g, 26 mmol) in dry dimethyl sulfoxide

(20 mL) under argon at 23°C was added sodium azide (2.40 g, 37 mmol). The reaction mixture was stirred for 45 min, poured into 100 mL of ice water, and extracted with ethyl acetate (1 × 100, 1 × 30 mL). The ethyl acetate fractions were combined, washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo* to afford 7.20 g (77%) of **7***a* as a colourless oil; R_f 0.69 (methylene chloride); ir ν_{max} ($CHCl_3$): 2900, 2100 (N_3), 1585 (tosylate), 1430, 1350, 1270, 1220, 1155, 1100, 1084, 990, 955, 910 cm^{-1}; ^1H nmr (80 MHz) δ: 1.19 (t, 3H, OCH_2CH_3), 2.46 (s, 3H, ϕCH_3), 3.30–3.95 (m, 4H, OCH_2CH_3, H4, H5), 4.25 (bs, 2H, H6, H6), 4.95 (s, 1H, H1), 5.93 (s, 2H, H2, H3), 7.35 (bd, 2H, aromatic), 7.82 (bd, aromatic); *m/e*: 325 ($M^+ - N_2$).

*Ethyl 4-amino-2,3,4-trideoxy-6-*O-p-*toluenesulfonyl-α-D-*erythro-*hex-2-enopyranoside,* **7**b

To a suspension of lithium aluminum hydride (380 mg, 10 mmol) in dry ether (150 mL) at −25°C under an atmosphere of argon was added, over 10 min, **7***a* (7.20 g, 20 mmol) in dry ether (50 mL). The reaction mixture was stirred for 20 min. The excess lithium aluminum hydride was destroyed by the slow addition of sodium sulfate decahydrate. The resulting precipitate was removed by filtration. The filtrate was concentrated *in vacuo* to afford 6.00 g (90%) of **7***b* as a clear oil; R_f 0.52 (110:90 methanol − methylene chloride); ir ν_{max} ($CHCl_3$): 3410, 3320 (amine), 2985, 2900, 1600 (tosylate, amine), 1455, 1320, 1120, 975, 970 cm^{-1}; ^1H nmr (80 MHz) δ: 1.19 (dt, 3H, OCH_2CH_3), 1.39 (s, 2H, NH_2), 2.45 (s, 3H, CH_3), 3.21–3.87 (m, 4H, OCH_2CH_3, H4, H5), 4.26 (d, 2H, H6, H6), 4.87 (bs, 1H, H1), 5.66–5.77 (m, 2H, H2, H3), 7.32 (bd, 4H, aromatic), 7.71 (bd, 4H, aromatic); *m/e*: 283 (($M^+ + 1$)-OC_2H_5), 282 ($M^+ - OC_2H_5$).

*Ethyl 2,3,4-trideoxy-4-*N-*ethoxycarbonylamino-6-*O-p-*toluenesulfonyl-α-D-*erythro-*hex-2-enopyranoside,* **8**

To a solution of **7***b* (790 mg, 2.4 mmol) and triethylamine (0.42 mL, 3 mmol) in dry methylene chloride (15 mL) at 0°C under argon was added, over 5 min, ethyl chloroformate (0.25 mL, 2.6 mmol) in dry methylene chloride (3 mL). The mixture was stirred for 30 min and then methanol (~0.5 mL) was added to destroy any remaining ethyl chloroformate. The reaction mixture was washed with water, dried over sodium sulfate, and concentrated *in vacuo*. Purification by medium pressure chromatography on silica gel (2:3 diethyl ether − methylene chloride, R_f 0.82) afforded 828 mg (86%) of **8** as a colourless oil; ir ν_{max} ($CHCl_3$): 3440 (NH), 2900, 1725 (urethane), 1610, 1590, 1375, 1310, 1185, 1108, 1005, 985 cm^{-1}; ^1H nmr (80 MHz) δ: 1.21 (dt, 6H, OCH_2CH_3), $CO_2CH_2CH_3$), 2.45 (s, 3H, CH_3), 3.38–4.70 (m, 9H, OCH_2CH_3, $CO_2CH_2CH_3$, H4, H5, H6, H6, NH), 4.94 (s, 1H, H1), 5.77 (s, 2H, Hs, H3), 7.32 (d, 2H, aromatic), 7.80 (d, 2H, aromatic); *m/e*: 355 (($M^+ + 1$)-OC_2H_5), 354 ($M^+ - OC_2H_5$).

*2′-Ethoxy (ethyl 2,4-dideoxy-2-iodo-6-*O-p-*toluenesulfonyl-α-D-altropyranosido)-[3,4:5′,4′]-Δ²-oxazoline,* **9**

A solution of **8** (399 mg, 1 mmol) and iodonium dicollidine perchlorate (10) (702 mg, 1.5 mmol) in dry methylene chloride (7 mL) was stirred under argon at 23°C in the dark. After 6 h an additional 350 mg (0.75 mmol) of iodonium dicollidine perchlorate were added and the reaction was allowed to continue for 18 h. The reaction mixture was poured into diethyl ether (25 mL) and filtered. The filtrate was concentrated *in vacuo* to yield a reddish coloured oil. Purification by medium pressure chromatography on silica gel (10:90 diethyl ether − methylene chloride) followed by recrystallization (diethyl ether − hexane) afforded 320 mg (61%) of **9**; R_f 0.76 (3:7 diethyl ether − methylene chloride); ir ν_{max} ($CHCl_3$): 2900, 1658 (C=N), 1595, 1362, 1324, 1170, 1100, 990, 915 cm^{-1}; ^1H nmr (80 MHz) δ: 1.08–1.40 (m, 6H, 2(OCH_2CH_3)), 2.45 (s, 3H, ϕCH_3), 3.48–4.34 (m, 10 H, C2, C3, C5, C6, C6, 2(OCH_2CH_3)), 5.13 (d, 1H, H1), 7.26–7.38 (bd, 2H, aromatic), 7.73–7.86 (bd, 2H, aromatic); *m/e*: 526 ($M^+ + 1$), 525 (M^+).

*Ethyl 4-*N-*ethoxycarbonylamino-2,3,4-trideoxy-6-*O-p-*toluenesulfonyl-α-D-*erythro-*hexopyranoside,* **11**

Product **9** (120 mg, 0.20 mmol) in methanol (10 mL) and triethylamine (0.25 mL) was hydrogenated over platinum oxide (10 mg). After 2 h the reaction mixture was filtered through a bed of Celite. The filtrate was evaporated to dryness *in vacuo*. Purification by medium pressure chromatography (30:70 diethyl ether − chloroform, R_f 0.65) followed by recrystallization (methylene chloride − hexane) afforded 35 mg (38%) of **11** as crystals, mp 116–117°C; ir ν_{max}: 3418 (NH), 1710 (urethane), 1600, 1450 (tosylate), 1290, 1117, 973, 951 cm^{-1}; ^1H nmr (80 MHz) δ: 1.21 (dt, 6H, OCH_2CH_3, $CO_2CH_2CH_3$), 1.60 (s, 1H, NH), 1.68–1.86 (m, 4H, H2, H2, H3, H3), 2.43 (s, 3H, ϕCH_3), 3.22–4.57 (m, 9H, H4, H5, H6, H6, OCH_2CH_3, $CO_2CH_2CH_3$), 4.77 (bs, 1H, H1), 7.36 (2bs, 2H, aromatic), 7.79 (2bs, 2H, aromatic). *Anal.* calcd. for $C_{18}H_{27}N\,O_7S$: C 53.86, H 6.73, N 3.49; found: C 54.20, H 7.05, N 3.30.

*Ethyl 2,3,4-trideoxy-4-*N-*methylamino-6-*O-p-*toluenesulfonyl-α-D-*erythro-*hex-2-enopyranoside,* **12**a

To a solution of dry dimethyl sulfoxide saturated with methylamine (1 mL) was added **4***b* (110 mg, 0.2 mmol). The reaction mixture was allowed to stand at room temperature for 1.5 h, during which time the colour changed from light yellow to wine red. The reaction mixture was diluted with 3 mL of ice water and extracted with ethyl acetate (3 × 5 mL). The ethyl acetate fractions were combined, washed with a saturated aqueous sodium chloride solution, dried, and concentrated *in vacuo* to afford an orange-red oil. Purification by medium pressure chromatography on silica gel (8:92 methanol − methylene chloride, R_f 0.50) afforded 55 mg (71%) of **12***a* as a colourless oil: $[\alpha]_D^{23}$ +160.5° (*c* 1.1, in $CHCl_3$) ir ν_{max}: ($CHCl_3$) 3680 (NH), 3460 (NH), 2880, 2480, 1598 (C=C), 1425, 1355 (S[=O]$_2$), 1100, 995, 925 cm^{-1}; ^1H nmr (80 MHz) δ: 1.00 (s, 1H, NH), 1.22 (t, 3H, OCH_2CH_3), 1.38 (s, 3H, ϕCH_3), 1.48 (s, 3H, NCH_3), 2.48 (bd, 1H, H4), 3.34–3.95 (m, 3H, OCH_2CH_3, H5), 4.28–4.48 (m, 2H, H6, H6), 4.94 (bs, 1H H1), 5.88 (dt, J = 2 Hz, 10 Hz, 1H, H3), 6.08 (bd, J = 10 Hz, 1H, H2), 7.35 (2bs, 2H, aromatic), 7.83 (2s, 2H aromatic); *m/e*: 297 (($M^+ + 1$)-OC_2H_5), 296 ($M^+ - OC_2H_5$).

*Ethyl 2,3,4-trideoxy-4-*N-*ethoxycarbonyl-*N-*methylamino)-6-*O-p-*toluenesulfonyl-α-D-*erythro-*hex-2-enopyranoside,* **12**b

To a solution of **12***a* (1.90 g, 5.6 mmol) and triethylamine (606 mg, 6 mmol) in dry methylene chloride (35 mL) under argon at 0°C was added, over 5 min, ethyl chloroformate (0.57 mL, 6 mmol) in dry methylene chloride (10 mL). The reaction mixture was stirred for 2 h, quenched with 1 mL of methanol, washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo*. Purification by medium pressure chromatography on silica gel (3:97 methanol − methylene chloride, R_f 0.73) afforded 1.80 g (79%) of **12***b* as a colourless oil: $[\alpha]_D^{23}$ +34.3° (*c* 1.1, in $CHCl_3$); ir ν_{max} ($CHCl_3$): 2887, 1680 (urethane), 1593, 1357, 1291, 1127, 959 cm^{-1}; ^1H nmr (80 MHz) δ: 1.25 (dt, 6H, OCH_2CH_3, $CO_2CH_2CH_3$), 2.46 (s, 3H, ϕCH_3), 2.75 (s, 3H, NCH_3), 3.37–3.88 (m, 2H, H4, H5), 3.88–4.31 (m, 6H, H6, H6, OCH_2CH_3, $CO_2CH_2CH_3$), 4.95 (bs, 1H, H1), 6.70 (bd, J = 10.6 Hz, 1H, H3), 6.93 (dt, J = 2.4, 10.6 Hz, 1H, H2); *m/e*: 370 (($M^+ + 2$]-OC_2H_5), 369 (($M^+ + 1$)-OC_2H_5), 368 (M^+-OC_2H_5).

*3′-*N-*methyl-2′-oxo-(ethyl 2,4-dideoxy-2-iodo-6-*O-p-*toluenesulfonyl-α-D-altropyranosido)-[3,4:5[,4′]-oxazolidone,* **13**

To a solution of **12***b* (1.20 g, 2.5 mmol) in 15 mL of refluxing dioxane under argon was added iodonium dicollidine perchlorate (1.75 g, 3.7 mmol). After 15 min a second addition of iodonium dicollidine perchlorate (0.88 g, 1,9 mmol) was made, followed by a third addition (0.88 g, 1.9 mmol) 15 min later. The reaction mixture was refluxed another 10 min, then cooled and concentrated *in vacuo*. The resulting dark oil was diluted with 75 mL of methylene chloride, washed with ice-cold 0.5 *N* hydrochloric acid, 0.5 *M* sodium thiosulfate, saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. Further purification by medium pressure chromatography (diethyl ether, R_f 0.43) afforded 1.03 g (72%) of **13** as a colourless oil; $[\alpha]_D^{23}$ −2.9° (*c* 0.3, in $CHCl_3$); ir ν_{max} ($CHCl_3$): 2900, 1760 (urethane), 1590, 1600 (C=C tosylate), 1460 (tosylate), 1435 (R_2NCH_3), 1100, 995 cm^{-1}; ^1H nmr (80 MHz) δ: 1.19 (t, 3H, OCH_2CH_3), 2.48 (s, 3H, ϕCH_3), 2.85 (s, 3H, NCH_3), 3.29–4.38 (m, 7H, H2, H4, H5, H6, H6, OCH_2CH_3), 4.73 (dd, J = 8.0, 9.3 Hz, 1H,

H3), 5.12 (d, J = 6.0 Hz, 1H, H1), 7.30 (d, 2H aromatic), 7.82 (d, 2H, aromatic); *m/e*: 479 (M^+).

*3'-N-Methyl-2'-oxo-(ethyl 2,4,6-trideoxy-2,6-diiodo-α-D-altropyranosido)-[3,4:5',4]-oxazolidone, **14**a*

A solution of **13** (400 mg, 0.8 mmol) and sodium iodide (180 mg, 1.2 mmol) in dry acetone (10 mL) was refluxed for 6 h. The reaction mixture was cooled and concentrated *in vacuo*. The residue was diluted with methylene chloride (25 mL), washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated again *in vacuo* to give a clear oil. Purification by medium pressure chromatography on silica gel (diethyl ether) followed by recrystallization (methylene chloride − hexane) afforded 280 mg (76%) of **14***a* as crystals, mp 109−110°C; R_f 0.53 (diethyl ether); $[\alpha]_D^{23}$ +7.5° (*c* 1, in $CHCl_3$); ir ν_{max} ($CHCl_3$): 3510 (carbonyl overtone), 2900, 1755 (urethane), 1590, 1421, 1373, 1348, 1125, 1098, 992, 955 cm^{-1}; ^1H nmr (400 MHz) δ: 1.24 (t, 3H, OCH_2CH_3), 2.92 (s, 3H, NCH_3), 3.29 (dd, J = 6.9, 11.2 Hz, 1H, H6), 3.52 (dd, J = 2.3, 11.2 Hz, 1H, H6), 3.58 (m, 1H, $OCH\,CH_3$), 3.78 (m, $J_{4,5}$ = 16.6 Hz, H4, H5), 3.95 (m, 1H, $OCH\,CH_3$), 4.08 (dd, J = 6.1, 9.4 Hz, 1H, H2), 4.76 (dd, J = 9.4, 8.0 Hz, 1H, H3), 5.20 (d, J = 6.1 Hz, 1H, H1). *Anal.* calcd. for $C_{10}H_{15}NO_4I_2$: C 25.71, H 3.24, N 3.00, I 54.34; found: C 25.75, H 3.30, N 3.00, I 54.92.

*3'-N-Methyl-2'-oxo-(ethyl 2,4,6-trideoxy-α-D-*ribo-hexapyranosido)-[3,4:5',4']-oxazolidone, ***14**a*

To a solution of **14***b* (250 mg, 0.5 mmol) in dry benzene (10 mL) under argon was added tri-*n*-butyltin hydride (0.4 mL, 1.5 mmol) and a catalytic amount of benzoyl peroxide. The reaction mixture was refluxed for 30 min, cooled, and concentrated *in vacuo*. The resulting oil was dissolved in acetonitrile (25 mL) and washed with hexane (1 × 15, 1 × 5 mL). The acetonitrile layer was concentrated *in vacuo* to afford an oil that crystallized upon standing. Recrystallization from methylene chloride − hexane afforded 70 mg (59%) of **14***b* as crystals, mp 67−68°C; R_f 0.35 (diethyl ether); $[\alpha]_D^{23}$ +107.1° (*c* 0.5, in $CHCl_3$); ν_{max} ($CHCl_3$): 3485 (carbonyl overtone), 2895, 1747 (urethane), 1595, 1425, 1373, 1105, 1045, 1005 cm^{-1}; ^1H nmr (80 MHz) δ: 1.25 (t, 3H, OCH_2C_3), 1.37 (d, J = 6.3 Hz, 3H, CH_3), 1.71−2.48 (m, 2H, H3, H2), 2.90 (s, 3H, NCH_3), 3.27−4.13 (m, 4H, H5, OCH_2CH_3), 4.42−4.94 (m, 2H, H1, H3). *Anal.* calcd. for $C_{10}H_{17}NO_4$: C 55.81, H 7.92, N 6.51; found: C 56.10, H 8.12, N 6.77.

*Ethyl-4-(N-methylacetamido)-2,4,6-trideoxy-α-D-*ribo-*hexopyranoside, **15**b*

A solution of **14***b* (175 mg, 0.8 mmol) in 5 mL of 5% potassium hydroxide was refluxed for 30 min. The reaction mixture was cooled and concentrated *in vacuo*. The resulting oily material was extracted with hot ethyl acetate (3 × 5 mL). The ethyl acetate fractions were combined and concentrated *in vacuo* to afford 110 mg (71%) of crude **15***a* as a clear oil; ^1H nmr (80 MHz) δ: 1.08−1.44 (m, 6H, OCH_2CH_3, CH_3), 1.80−2.33 (m, 4H, H2, H2, OH, NH), 2.45 (s, 3H, NCH_3), 3.30−4.18 (m, OCH_2CH_3, H3, H4), 4.90 (bd, 1H, H1).

To a solution of impure **15***a* (55 mg, 0.3 mmol) in dry methanol (2 mL) at 23°C under argon was added 0.25 mL of acetic anhydride. After 24 h the solvents were removed *in vacuo* to give an oil. Purification by medium pressure chromatography on silica gel (5:95 methanol − methylene chloride, R_f 0.38) afforded 55 mg (82%) of **15***b* as a colourless oil; $[\alpha]_D^{23}$ +194° (*c* 1.1, in $CHCl_3$); ir ν_{max} ($CHCl_3$): 3500 (OH), 3400, 1620 (amide), 1380, 1310, 950 cm^{-1}; ^1H nmr (80 MHz) δ: 1.10−1.30 (m, 6H, OCH_2CH_3, C—CH_3), 1197−2.23 (m, 6H, H2, OH, CH_3CO), 3.08 (d, 3H, NCH_3), 3.22−4.54 (m, 6H, OCH_2CH_3, H3, H4, H5), 4.96 (bs, 1H, H1); *m/e*: 232 (M^+ +1), 231 M^+.

*Ethyl-4-(N-methylacetamido)-3-O-methyl-2,4,6-trideoxy-α-D-*ribo-hexopyranoside, ***1**b*

To a suspension of sodium hydride (prewashed with hexane) (20 mg, 50% oil dispersion, 0.4 mmol) in dry tetrahydrofuran (3 mL) at 23°C under argon was added **15***b* (55 mg, 0.2 mmol) in dry tetrahydrofuran (2 mL). Tetra-*n*-butylammonium iodide (10 mg) was added, followed 10 min later by the addition of methyl iodide (1 mL). The reaction mixture was stirred for 2 h, quenched with sodium sulfate decahydrate, and filtered. The filtrate was concentrated *in vacuo* and then diluted with 5 mL of a saturated aqueous sodium chloride solution. The aqueous solution was extracted with diethyl ether (3 × 5 mL). The diethyl ether fractions were combined, washed with water, dried over sodium sulfate, and concentrated *in vacuo* to give an oil that crystallized upon standing. Recrystallization from hexane afforded 46 mg (79%) of **1***b* as granular crystals, mp 83−84°C; $[\alpha]_D^{23}$ +29.6° (*c* 0.6, in $CHCl_3$); R_f 0.31 (2:98 methanol − diethyl ether); ir ν_{max}: ($CHCl_3$) 3396, 1623 (amide), 1380, 1316, 943 cm^{-1}; ^1H nmr (400 Mhz, $CDCl_3$) δ: 1.17−1.84 (m, 6H, OCH_2CH_3, CH_3), 1.81 (dt, J = 4.1, 14.4 Hz, H2), 2.11 (d, 3H, $COCH_3$), 2.16 (2dd, J = 1.0, 14.2 Hz), 2.76 (d, 3H, NCH_3), 3.33 (d, 3H, OCH_3), 3.38−3.76 (m, 3H, H4, OCH_2CH_3), 4.22−4.32 (m, 2H, H3, H5), 4.80 (d, J = 4.2, 1H, H1). *Anal.* calcd. for $C_{12}H_{23}NO_4$: C 58.78, H 9.93, N 5.71; found: C 58.84, H 9.50, N 5.92.

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1. H. W. PAULS and B. FRASER-REID. Can. J. Chem. **62**, 0000 (1984).
2. M. GEORGES and B. FRASER-REID. Tetrahedron Lett. **22**, 4635 (1981).
3. M. M. JANOT, P. H. DEVISSAGUET, Q. KHUONG-HUU, J. PARELLO, N. G. BISSET, and R. GOUTAREL. C. R. Acad. Sci. Ser. C, **266**, 388 (1968).
4. M. M. JANOT, M. LEBOEUF, A. CAVE, R. O. B. WIJESEKERA, and R. GOUTAREL. C. R. Acad. Sci. Ser. C, **267**, 1050 (1968).
5. S. M. KUPCHAN, R. J. HEMINGWAY, and R. W. DOSKOTCH. J. Med. Chem. **7**, 803 (1964).
6. J. HILDESHEIM, S. D. GERO, G. KHUONG-KUU, and C. MONNERET. Tetrahedron Lett. 2849 (1969).
7. R. J. FERRIER and N. PRASAD. J. Chem. Soc. C, 570 (1969).
8. O. MITSUNOBU. Synthesis, 1 (1981).
9. I. GALYNKER and W. C. STILL. Tetrahedron Lett. **23**, 4461 (1982).
10. R. U. LEMIEUX and A. R. MORGAN. Can. J. Chem. **43**, 2199 (1965).
11. R. J. FERRIER and N. VETHAVIYASER. J. Chem. Soc. C, 1907 (1971).
12. B. FRASER-REID, S. Y.-K. TAM, and B. RADATUS. Can. J. Chem. **53**, 2005 (1975).