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AN APPLICATION OF THE PALLADIUM-CATALYZED, ALLYLIC AMINATION OF UNSATURATED SUGARS: A NEW SYNTHESIS OF D-FOROSAMINE

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ABSTRACT

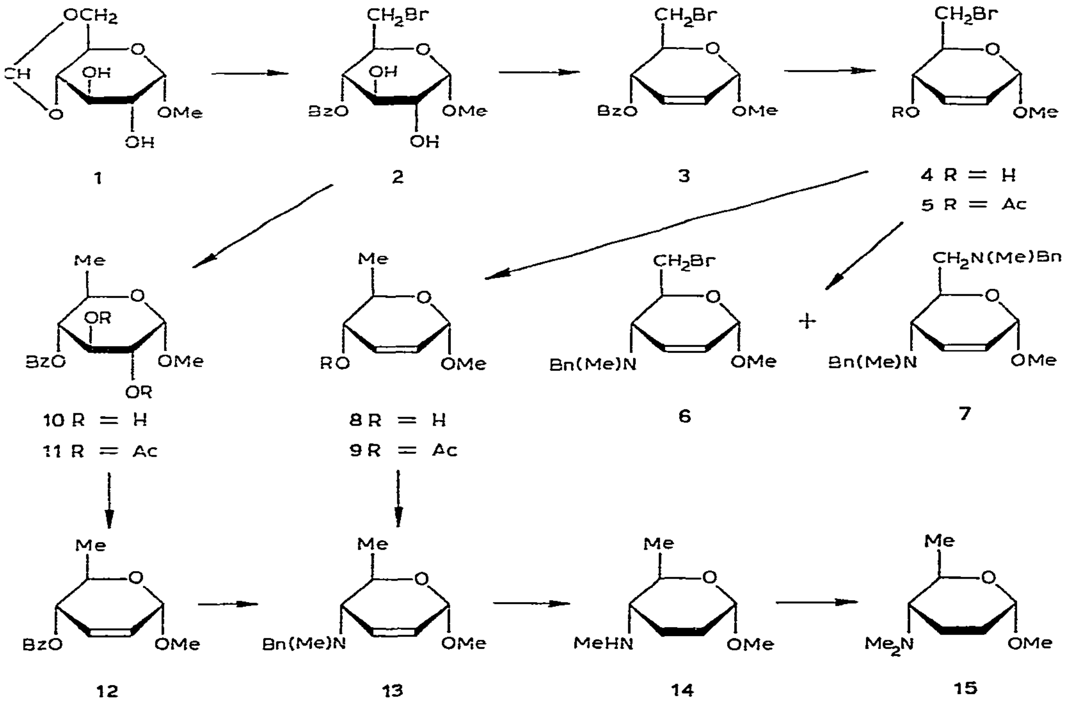
Methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside, obtainable from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**), was converted into the 2,3-unsaturated 4-benzoate (**3**) by application of the triiodoimidazole method. Debenzoylation of **3**, followed by acetylation, afforded crystalline methyl 4-*O*-acetyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**5**). Treatment of **5** with benzylmethylamine under conditions of palladium-catalyzed, allylic substitution gave a separable mixture of the corresponding 4-(*N*-benzyl)methylamino-6-bromo-2-enoside (37%) and the 4,6-di-[(*N*-benzyl)methylamino]-2-enoside (55%). Debromination of **5** with lithium triethylborohydride, proceeding with simultaneous deacetylation, readily yielded methyl 2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**8**). The 4-acetate of **8** (obtained by reacetylation), and also its 4-benzoate (prepared by a different synthetic route), furnished high yields (~80%) of methyl 4-[(*N*-benzyl)-methylamino]-2,3,4,6-tetradeoxy-α-D-*erythro*-hex-2-enopyranoside (**13**) upon palladium-catalyzed amination with benzylmethylamine. Catalytic hydrogenation of **13** effected saturation of the alkenic double bond and removal of the *N*-benzyl group, to afford methyl 2,3,4,6-tetradeoxy-4-methylamino-α-D-*erythro*-hexopyranoside, which was subsequently *N*-methylated with formaldehyde and sodium borohydride, to give its *N*,*N*-dimethyl analog, methyl α-D-forosaminide (**15**). The overall yield of **15** from **1** was 24%. Hydrolysis of **15** to the free sugar has been described previously.

INTRODUCTION

In continuation of our studies[1] on the synthesis of amino and branched-chain sugars by palladium-catalyzed, allylic substitution[2] of unsaturated sugar acetates, we have applied this method to perform a key step in a convenient, new route to an aminopolydeoxy sugar, D-forosamine, and some related derivatives. D-Forosamine is one of the three carbohydrate entities present in the spiramycin (foromacidin) group of macrolide antibiotics isolated from *Streptomyces ambofaciens*[3]; it has been established[4,5] to be 2,3,4,6-tetradeoxy-4-(dimethylamino)-D-*erythro*-hexose. Early, multistep syntheses departing formally from D-glucose were reported by Stevens *et al.*[5] and by Albano and Horton[6], but they furnished the amino sugar in very low overall yields. More recently, Dyong and co-workers[7] accomplished an elegant, total synthesis, starting from 2,4-hexadienoic acid (sorbic acid), that provided the sugar in seven steps (including a racemate resolution) with 12% overall yield. The present approach appears to compare favorably with these previous syntheses. In addition, it provides facile access to analogs of forosamine structurally modified at the nitrogen atom.

RESULTS

The point of departure was methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (**2**), conveniently prepared[8] from the readily available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) by the Hanessian–Hullar reaction. The plan of synthesis obviously called for replacement of the bromine atom at C-6 by hydrogen at some stage on the route to the target molecule, and it was recognized that this could have been performed at the outset, by a reduction as described[8b]. However, we decided for two reasons to postpone this step until later on. First, from the viewpoint of assessing the scope and general utility of the palladium-catalyzed, allylic amination in different kinds of carbohydrate derivatives, we wished to examine whether the method is compatible with the presence of a 6-halogeno substituent. An encouragement in this regard was the recent article by Trost and Verhoeven[2b],



who reported that 3-acetoxy-8-bromo-1-octene can be allylically alkylated with retention of the bromine atom; on the other hand, we did not find in the literature any similar precedent for amination. Secondly, it was considered that, should such amination be successful, the required removal of the halogen atom might advantageously be combined, in a single operation, with a subsequent reductive step that would be necessary for preparing the desired aminopolydeoxy sugar.

Consequently, the bromo diol **2** was first converted into the bromoalkene **3**. This was accomplished, in >90% yield, by application of the excellent procedure of Garegg and Samuelsson[9], which employs the reagent system triphenylphosphine–2,4,5-triiodoimidazole–imidazole. On performing the reaction on a 20-g scale, we found preparation of **3** in an entirely pure state, *i.e.*, free from triphenylphosphine oxide, to be somewhat cumbersome; complete removal of the contaminant from an analytical sample required use of preparative, thin-layer chromatography (p.t.l.c.). However, this difficulty was of little consequence, as thorough purification proved unnecessary for performance of the next step; actually, it was found advisable to proceed without undue delay, using partially purified **3**, because the isolated compound showed only limited stability on the shelf. The benzoic ester group in **3** was replaced by an acetate group through *O*-debenzoylation with triethylamine followed by acetylation of the intermediary alcohol **4** (which was not characterized). The acetate **5** was obtained crystalline, and its structure and purity were confirmed by spectroscopy; although this ester, too, was rather unstable at room temperature, it could be stored for prolonged periods at —20°. The overall yield of **5** from **1** was* ~60%.

Treatment of the allylic acetate **5** with benzylmethylamine in the presence of triphenylphosphine and a catalytic proportion of tetrakis(triphenylphosphine)-palladium(0) by the method previously delineated in detail[1b] gave a mixture of two aminated compounds that were separated by p.t.l.c. The less-polar product proved to be the desired 6-bromo-4-[(*N*-benzyl)methylamino] glycoside **6**, and it was isolated in 37% yield. The more-polar product, revealed to be the bromine-free, 4,6-di-[(*N*-benzyl)methylamino] derivative **7**, was obtained in 55% yield. Two unidentified by-products having intermediate chromatographic mobility were removed during the procedure; their amounts were negligible. The experiment thus indicated that a very high degree of regio- and stereo-selective, allylic amination at C-4 can be achieved in the bromo glycoside **5**, in full analogy to the 6-acetoxy derivatives previously[1] studied. However, the large extent of nucleophilic substitution that concurrently took place at C-6 defeated use of this venue as a high-yielding approach to monoamino sugars of the forosamine type, and further work along this line (which may provide a useful route to certain 4,6-diamino sugars) was held in abeyance. In view

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*The reaction **1**→**2** proceeds[8c] almost quantitatively, although only part of the product is isolable by direct crystallization. When all of the crude **2** was used for the next step, the yield of crude **3** was 92% (based on **1**). Therefrom was obtained an 80% crude yield of **5**, decreasing to 65% on purification by column chromatography.

of the moderate yield of **6**, it was decided to perform a reductive debromination prior to amination.

To this end, the unsaturated bromo glycoside **5** was treated with lithium triethylborohydride in oxolane, readily removing the bromine[10] atom (and the 4-*O*-acetyl group) while leaving the alkene function intact. The known[11,12] methyl 2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**8**) was obtained in 93% yield (or 56% overall yield from **1**)**. This facile synthesis of **8** superseded an alternative approach that we concurrently examined in a preliminary way. Compound **2** was hydrogenolyzed with a zinc–copper couple in warm acetic acid, to give the 6-deoxy-D-glucoside **10** (65%), spectroscopically characterized as its 2,3-diacetate **11**, but side-products tended to arise in this reaction. The diol **10** was then subjected to olefination[9], producing the unsaturated, 4-benzoate **12**, but the yield was disappointing (~30%) in the one experiment that was performed. Nevertheless, in view of the highly successful conversion **2** → **3**, as well as the olefinations reported[9], appropriate trials might well be expected to lead to improved results. We did not pursue this avenue, however, as in the meantime, the desired, key compound **8** had become conveniently available through **3** and **5**, as already outlined. A confirmatory, Zemplén deacylation correlated the crystalline benzoate **12** with the liquid alcohol **8** (from which it had previously been obtained[12] by benzoylation). Physical and spectral data for **8** and **12** were in accord with those reported for L enantiomers[14–16] and racemic forms[17].

The alcohol **8** was almost quantitatively acetylated, and the resulting 4-acetate **9** was subjected to palladium-catalyzed amination with benzylmethylamine. The reaction readily gave the unsaturated, tertiary amine **13**, essentially as a single product which, upon purification from traces of contaminants by column chromatography, was isolated in 81% yield. The same reaction proceeded equally well with the benzoate **12**; this is noteworthy, in so far as there seem to be few examples for the use of allylic benzoates as substrates in such substitutions[2]. Catalytic hydrogenation of **13** in the presence of palladium-on-carbon simultaneously saturated the alkenic bond and removed the *N*-benzyl group, affording a 72% yield of methyl 2,3,4,6-tetradeoxy-4-methylamino-α-D-*erythro*-hexopyranoside (**14**; methyl *N*-monodemethyl-α-D-forosaminide). This compound was *N*-methylated (74%) by use of formaldehyde and sodium borohydride[18], to give methyl 2,3,4,6-tetradeoxy-4-(dimethylamino)-α-D-*erythro*-hexopyranoside (**15**; methyl α-D-forosaminide). The n.m.r. data for this liquid glycoside agreed fully with those reported by Albano and Horton[6a], who have also described its conversion by acid hydrolysis into the free dimethylamino sugar. The overall yield of **15** from **1** was 24%.

On account of the results of our previous work[1], it could be anticipated that

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Compound **8 had previously been prepared[12] from **1**, in 15–20% overall yield, *via* the dimesylate of **1**, in a sequence involving the Hanessian–Hullar reaction, reduction by a zinc–copper couple, and reductive elimination employing a modified, Tipson–Cohen procedure[13]. The ethyl glycoside analogous to **8** has been synthesized[12] in 3 steps (and 70% yield) from the corresponding 4,6-diol, but the latter needs first to be prepared, by the Ferrier method, from tri-*O*-acetyl-D-glucal, which is considerably more expensive than **1**.

TABLE I

PROTON MAGNETIC RESONANCE DATA[a]

Compound	*Chemical shifts (δ)*									*Coupling constants (Hz)*					
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6,6′ or C-Me*	*OMe*	*N-Me*	*Others*	$J_{2,3}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*Others*
3[b]	4.97nm	5.86s		5.40dnm	4.07sx	3.44dd, 3.17dd	3.56s		8.00m, 7.45m (OBz)		9	8	3	11	
5	4.94nm	5.82nm		5.14dd	3.89ddd	3.41dd, 3.16dd	3.56s		2.10s (OAc)		9.5	8.3	2.7	10.8	
6	4.87nm	5.86dt	6.07dt		4.1–3.1m		3.51s	2.24s	7.28s (Ph), ~3.5 (*N*-CH$_2$-*Ph*)	10.5					c
7	4.83nm	5.89dt	6.12dt	3.10ddd	4.11sp	3.05dd, 2.56dd	3.49s	2.32s, 2.20s	7.31nm, 7.24s (Ph), 3.66s (*N*-CH$_2$-*Ph*), 3.71d, 3.49d (AB system of *N*′-CH$_2$-*Ph*)	10.5	9.7	8.0	1.7	13.7	c, d
8[e]	4.81nm	5.71dt	5.91dt	3.9–3.5m		1.31d	3.42s		2.6 (broad, exchangeable, OH)	10.0		6			c
11[b]	5.65m (1H), 5.2–4.8m (3H)				4.00dq	1.25d	3.42s		7.95m, 7.40m (OBz), 2.04s, 1.86s (OAc)		~10	6.5			
12[f]	4.92nm	5.86ddd	5.99dnm	5.34ddd	4.14dq	1.31d	3.48s		8.0 m, 7.45m (OBz)	10.2	9.2	6.5			c
9	4.87nm	5.84nm		5.07dnm	3.92dq	1.24d	3.46s		2.10s (OAc)		9.2	6.3			c
13	4.79nm	5.86dt	6.12dt	2.99ddd	3.95dq	1.34d	3.42s	2.24s	7.29s (Ph), 3.72d, 3.54d (AB system of *N*-CH$_2$-*Ph*)	10.5	9.5	6.3			c, g
14	4.65dd	2.3–1.4m			3.57dq	1.24d	3.34s	2.44s	1.57s (exchangeable, NH)		9.2	6.3			
15[b,h]	4.70m	2.0–1.5m		~2.3m	3.80dq	1.23d	3.35s	2.26s				6.5			

[a] From 100-MHz spectra, measured at 250-Hz sweep-width, for solutions in CDCl$_3$ containing tetramethylsilane as the internal standard (unless specified otherwise). Signal multiplicities: d, doublet; m, multiplet; nm, narrow multiplet; q, quartet; s, singlet; sp, septet; sx, sextet; and t, triplet. [b] Measured at 60 MHz. [c] The small splittings present in the signals of H-1 to H-4, which represented vicinal ($J_{1,2}$ and $J_{3,4}$), allylic ($J_{1,3}$ and $J_{2,4}$), and homoallylic ($J_{1,4}$) couplings, were nearly the same as those reported[1b] for analogous α-D-*erythro*-2-enopyranosides. [d] J_{gem} 14 Hz (*N*′-CH$_2$-*Ph*). [e] Data in good agreement with those of L enantiomer[16], except for reversed assignment of H-2 and H-3; also in good agreement with those of DL form[17] measured in CCl$_4$ solution (where all δ values were lower by 0.1–0.15 p.p.m.). [f] Data in good agreement with those of L enantiomer[14]. [g] J_{gem} 13.5 Hz (*N*-CH$_2$-*Ph*). [h] Data in full agreement with those reported[9a] for 60-MHz spectrum.

TABLE II

^{13}C-CHEMICAL SHIFTS (P.P.M. FROM TETRAMETHYLSILANE)[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OMe*	*NMe*	*NCH$_2$Ph*	*C=O*	*COMe*	*Ph*
3	95.8	128.5	129.8	68.9	70.0	5.5	56.6			165.8		128–129, 133.5
5	95.7	127.9	128.8	68.8	69.6	5.4	56.5			170.2	21.0	
6	95.7	128.4	128.6	61.6	67.9	9.1	56.0	38.1	58.8			127–129, 139.1
7	95.4	128.1	128.6	59.1	67.5	62.6	56.0	38.0, 43.2	58.5, 59.1			127–129, 139.5
8	95.4	126.2	133.9	68.0	69.5	18.0	55.6					
12	95.5	128.4	129.7	65.0	71.3	18.1	55.8			166.0		128–130, 133.2
9	95.4	127.7	129.8	64.8	70.9	18.0	55.8			170.6	21.1	
13	95.5	128.2	128.6	62.8	64.4	18.9	55.4	38.2	58.6			127–130, 139.7
14	97.5	24.2	29.6	61.2	68.9	18.7	54.3	33.7				

[a] From spectra of chloroform solutions. The signal multiplicities observed in proton-coupled spectra were taken into account in making assignments. In the compounds bearing an aromatic substituent, the two signals of highest intensity in the range of 127–130 p.p.m. were attributed to the alkenic atoms C-2 and C-3, and the remaining signals were assigned to the aromatic-ring carbon atoms. For the other compounds, C-2 and C-3 gave similar, high-intensity signals.

the products of amination obtained from **5** and **9** would possess the α-D-*erythro* 2-enoside structure, as formulated for **6**, **7**, and **13**. Spectral and optical-rotation data provided structural proof for **6** and **7**, and also corroborated the assignment of **13** which, of course, rested independently on the unambiguous transformation of the latter compound into the known **15**. All of the data were entirely consistent with those gathered previously for numerous analogs, and, for a closer evaluation of the significance of individual values, we refer to the detailed discussion presented[1b]. The following, decisive, spectral features may be noted.

The 2,3-position of the alkenic double bond was indicated by mass spectra showing strong peaks that arose from retrodienic fragmentation. Thus, **6** gave a prominent fragment (*m/z* 203) resulting from loss of bromoacetaldehyde. The same fragment was given by **7** (loss of benzylmethylaminoacetaldehyde) and **13** (loss of acetaldehyde). The precursor **5**, as well as **8**, **9**, and **12**, all gave the corresponding fragments due to loss of bromoacetaldehyde and acetaldehyde, respectively. Peaks corresponding to loss of methyl formate (m/z = M — 60), which would have signified 3,4-unsaturation, were absent, or very weak. The ^{1}H-n.m.r. data (see Table I) were in excellent accord with those of relevant analogs[1b]. The large value of $J_{4,5}$ for **7** (9.7 Hz) and **13** (9.5 Hz) proved an axial orientation of H-4 and, hence, the D-*erythro* configuration. (For **6**, unfortunately, the H-4 and H-5 signals were insufficiently resolved to permit analysis.) Compounds **6**, **7**, and **13** displayed the same, characteristic, AB patterns for their olefinic protons (H-2 and H-3) as were found typical for the 4-aminated, α-D-*erythro* 2-enopyranosides prepared earlier, with each signal component showing multiplicities due to vicinal ($J_{1,2}$ and $J_{3,4}$) and allylic coupling ($J_{1,3}$ and $J_{2,4}$) as described[1b]. (In the esters **3**, **5**, and **9**, the olefinic proton signals coincided, as did those of ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside.) The assignments were corroborated by ^{13}C-n.m.r. data (see Table II) that were also fully consistent with those obtained[1b] for structural analogs. Noteworthy in particular was the narrow range in which the C-1 chemical shifts of all of the unsaturated glycosides listed in Table II appeared (δ 95.4–95.8). This parameter, which appears to be rather sensitive, suggested equality with respect to the position of the double bond and to the overall configuration in these compounds. Finally, but not least significantly, the molecular rotations of **6** ($[M]_D$ +584°), **7** ($[M]_D$ +560°), and **13** ($[M]_D$ +521°) agreed satisfactorily with that of ethyl 6-*O*-acetyl-4-[(*N*-benzyl)methylamino]-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[1b] ($[M]_D$ +527°). This fact alone precluded the opposite configuration at C-4, as alkyl α-D-*threo*-hex-2-enopyranosides exhibit strong levorotation.

EXPERIMENTAL

General methods. — General, preparative, and chromatographic procedures, as well as instrumental techniques, were the same as those previously employed[1b]. Special reference is made to the procedure for palladium-catalyzed, allylic amination already described in detail[1b]. Optical rotations were measured at 25°. The following solvent combinations (v/v) were used for t.l.c. and column chromatography, unless stated otherwise: (*A*) 1:2 ethyl acetate–petroleum ether; (*B*) the same solvents, but 1:3; (*C*) the same, but 1:6; (*D*) the same, but 1:10; (*E*) 1:1 ethyl acetate–ether; (*F*) 1:1:1 ethyl acetate–ether–petroleum ether; and (*G*) 1:2 methanol–dichloromethane. Petroleum ether refers to the fraction having b.p. 30–60°. Mass spectra were recorded with an A.E.I. MS 902 mass spectrometer fitted with a direct-inlet probe, at an ionizing potential of 50–55 eV.

*Methyl 4-O-benzoyl-6-bromo-2,3,6-trideoxy-α-*D-erythro-*hex-2-enopyranoside* (3). — A mixture of methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside[8] (**2**; 6.3 g, 17.5 mmol), triphenylphosphine (19.8 g, 75 mmol), 2,4,5-triiodoimidazole (18.0 g, 40 mmol), and imidazole (3.43 g, 50 mmol) in toluene (360 mL) was boiled under reflux for 2 h, after which time, the slow-moving **2** was replaced by fast-moving **3**, R_F ~0.8 (t.l.c. with solvent *A*). After the mixture had been cooled, the solution was decanted from a gummy residue which was washed well with several portions of ether. The organic solutions were combined, washed once with saturated, aqueous sodium hydrogencarbonate solution, twice with saturated sodium thiosulfate solution, and once with water, and then dried ($MgSO_4$), and evaporated *in vacuo*, to give a brownish mixture of products that was triturated with ether. Evaporation of the extract gave a syrup from which some crystalline triphenylphosphine oxide was separated by renewed trituration with ether. The ethereal solution was evaporated to a syrup which was chromatographed on a column of silica gel (30 g per g of syrup), elution being started with 1:20 ethyl acetate–petroleum ether (50 mL). When most of the remaining triphenylphosphine had been eluted, the eluting solvent ratio was changed to 1:10 (50 mL) and then to 1:5 (250 mL). The syrupy **3** (3.5 g, 61.4%) obtained on evaporation was suitable for use in the subsequent step, although it still contained a small amount of triphenylphosphine oxide.

A higher yield of **3** was achieved when crude **2** (24 g, as produced from 20 g of the benzylidene derivative **1** before crystallization, and processing of mother liquors[8b]) was dehydroxylated as just described, with proportionate quantities of the reagents, and a reflux time of 2.5 h. Processing was performed in the foregoing manner, except that the aqueous washings of the reaction mixture were subsequently combined (650 mL) and, as they were revealed by t.l.c. to contain a considerable amount of **3**, extracted with dichloromethane (3 × 100 mL) followed by ether (2 × 100 mL). These extracts were combined with the original toluene–ether phase before proceeding as described, and there was obtained 21.3 g (91.8%) of crude **3**.

For spectral analysis, a sample of the material was purified by preparative t.l.c. on silica gel (solvent *D*). The band visible under u.v. light was eluted with ethyl acetate, and evaporation of the eluate gave colorless, syrupy **3** whose n.m.r. spectra (Table I and II), taken immediately, established its structure and purity. Isolated **3** tended to decompose rather rapidly at room temperature, so that elemental analysis had to be dispensed with.

*Methyl 4-O-acetyl-6-bromo-2,3,6-trideoxy-α-*D-erythro-*hex-2-enopyranoside* (5). — Crude **3** (21.0 g) was stirred at room temperature in a mixture of methanol (150 mL), water (65 mL), and triethylamine (30 mL). A small amount of triphenylphosphine oxide precipitated in the course of time. The debenzoylation, which was surprisingly slow (requiring about 3 days for completion), was monitored by t.l.c. with solvent *A*; replacement of **3** (R_F 0.8) by the alcohol **4** (R_F 0.6) was observed. After completion, the precipitated contaminant was filtered off, the filtrate was evaporated, and several portions of ethanol were added and evaporated. Small amounts of solid material that separated during this operation were removed. Finally, the solution was evaporated, to give a residue which was freed of a trace of ethanol by evaporation with ethyl acetate followed by dichloromethane. The vacuum-dried, syrupy **4** (13.3 g, 93%) was dissolved in acetic anhydride (10 mL), and to the cooled (—5°) solution was added pyridine (12 mL). The acetylation, allowed to proceed at room temperature, was complete after 2 h. The mixture was evaporated at 40° (bath temperature) under an oil-pump vacuum, and 2 portions of toluene were added to, and evaporated from, the product. The crude acetate **5** (13.65 g) appeared relatively unstable on storage; it was immediately passed through a column of silica gel (175 g) by means of ethyl acetate–petroleum ether in the ratio 1:20 (420 mL) and, subsequently, 1:15 (1.2 L). The fractions containing pure **5** yielded 10.9 g (64%) as crystals, m.p. 70–71°, $[\alpha]_D$ +136.8° (*c* 3.5, chloroform); ν_{max}^{Nujol} 1740 (OAc) and 735 cm^{-1} (*cis*-alkene); *m/z* 235, 233 (M^+ — OMe), 175, 173 (M^+ — OMe — HOAc), and 142 (M^+ — $BrCH_2CHO$). The compound could be stored only at —20° or below.

*Methyl 4-[(*N*-benzyl)methylamino]-6-bromo-2,3,4,6-tetradeoxy-α-*D-erythro*-hex-2-enopyranoside* (**6**) *and methyl 4,6-di[(*N*-benzyl)methylamino]-2,3,4,6-tetradeoxy-α-*D-erythro*-hex-2-enopyranoside* (**7**). — A solution of crystalline **5** (265 mg, 1 mmol), triphenylphosphine (185 mg, 0.7 mmol), and tetrakis(triphenylphosphine)palladium (82 mg, 0.07 mmol) in oxolane (20 mL: dried by refluxing over, and distillation from, potassium) was stirred for 30 min at room temperature, under nitrogen. Benzylmethylamine (1 mL) was then added by syringe, and the mixture was boiled under reflux for 36 h. T.l.c. with solvent *B* then showed 2 major spots (R_F ~0.5 and ~0.8) and 2 minor ones (R_F ~0.55 and ~0.7), and no change was observed after an additional 6 h of heating. The solution was then cooled, and partitioned between ether and water, the aqueous phase was extracted with dichloromethane (4 × 30 mL), and the organic phases were combined, dried ($MgSO_4$), and evaporated, to give a yellow oil (0.8 g). The oil was subjected to p.t.l.c. (solvent *C*), which furnished **6** (R_F 0.8 in solvent *B*; 120 mg, 36.8%) and **7** (R_F 0.5 in solvent *B*; 200 mg, 54.6%) as colorless syrups. The intermediate fractions that contained the minor products yielded only a few milligrams of material (unidentified).

Compound **6** showed $[\alpha]_D$ +179.1° (*c* 1, chloroform); *m/z* 327, 325 (M^+), 296, 294 (M^+ — OMe), 246 (M^+ — Br), and 203 (M^+ — $BrCH_2CHO$).

Compound **7** showed $[\alpha]_D$ +153.1° (*c* 1, chloroform); *m/z* 366 (M^+), 335 (M^+ — OMe), 306 (weak), 275 (M^+ — Bn), 246 (M^+ — BnNMe), and 203 (strong; M^+ — $BnMeNCH_2CHO$).

The i.r. spectra (liquid films) of **6** and **7**, which were very similar, agreed with the proposed constitutions. Noticeable differences were seen below 800 cm^{-1}, where

6 exhibited strong bands at 790, 765 (with a shoulder at 750), and 700 cm^{-1}, whereas **7** showed strong bands at 735 (broadened) and 695 cm^{-1} (sharp).

*Methyl 2,3,6-trideoxy-α-*D-erythro-*hex-2-enopyranoside* (**8**). — To a solution of the bromo sugar **5** (200 mg) in oxolane (5 mL; dried over potassium) was added dropwise, at room temperature, 3 mL of an M solution of lithium triethylborohydride in oxolane (Superhydride® solution, Aldrich Chemical Co.). The mixture was kept for 24 h, whereupon **5** (R_F 0.55) was seen to be absent (t.l.c., solvent *B*). The strong spot of the reduction product **8** (R_F ~0.2) was accompanied by a very faint, marginally faster-moving spot of an unidentified by-product. The mixture was cooled to 0°, stirred for 30 min with added methanol, in order to decompose the excess of hydride, and evaporated, and the residue was placed onto a short column of silica gel by means of a little ethyl acetate. Elution with solvent *B* produced **8** (101 mg, 93%) as a colorless syrup, $[\alpha]_D$ +110° (*c* 2.4, chloroform). A similar value, $[\alpha]_D$ +107°, was obtained when a sample of the benzoate **12** in chloroform was catalytically *O*-debenzoylated with a drop of sodium methoxide solution, with subsequent neutralization by ion exchange; lit.[11] +75°; for the L enantiomer[15], —94° and[16] —115° (all in chloroform). Compound **8** showed ν_{max}^{film} 3400 (OH), 1660 (weak) and 725 (strong) for *cis*-alkene, 1200–970 (multiple bands), 890, and 830 cm^{-1}; *m/z* 143 (weak, $M^+ - H$), 127 (weak, $M^+ - OH$), 113 (strong, $M^+ - OMe$), and 100 (very strong, $M^+ - CH_3CHO$). The ^{1}H-n.m.r. spectrum of **8** (see Table I) and that of a sample prepared by a different route[12] proved their identity.

*Methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-*D-erythro-*hex-2-enopyranoside* (**12**). — A solution of the bromo sugar **2** (8.0 g) in glacial acetic acid (100 mL) was mechanically stirred with zinc–copper couple (10 g), the reductive debromination of **2** (R_F ~0.5) to give **10** (R_F ~0.4) being monitored by t.l.c. (solvent *E*). The reaction was promoted by gentle to moderate heating of the mixture in such a way that the spots of two fast-moving side-products (R_F 0.8 and 0.9) did not become prominent. (These were the chief products when, in a pilot experiment, the reaction was performed at reflux temperature.) Additional reductant (10 g) was introduced after 1 h, and all of **2** had reacted within ~2 h. The warm mixture was filtered through sintered glass, and the filtrate was evaporated (oil-pump vacuum, 40° bath temperature) to a thick syrup which was subsequently passed through a short column of silica (10 cm × 5 cm) by flash chromatography, with ether as the eluant. The fast-moving by-products were thereby removed, and crude **10** was obtained as a pale-yellow syrup (~4 g). A small sample of it was treated with acetic anhydride and pyridine (1 h, 25°) to give, upon customary processing, the 2,3-diacetate **11**; t.l.c. with solvent *F*: R_F 0.2 (**10**) and 0.8 (**11**). The ^{1}H-n.m.r. data (60 MHz) of **11** in $CDCl_3$: δ 7.95 (m, 2 H) and 7.4 (m, 3 H) (OBz), 5.65 (m, 1 H) and 5.2–4.8 (m, 3 H) (H-1–4), 4.00 (o, 1 H, H-5), 3.42 (s, 3 H, OMe), 2.04 and 1.86 (s, 2 × 3 H, 2 OAc), and 1.25 (d, 3 H, *C*-Me).

A mixture of crude **10** (2.2 g), triphenylphosphine (5.2 g), 2,4,5-triiodoimidazole (4.7 g), imidazole (0.9 g) in dry toluene (100 mL), and dry oxolane (20 mL) was boiled for 1.5 h under reflux. The product (**12**) showed R_F 0.9 (t.l.c. with solvent *B*). The reaction mixture was processed as described for **3**, and separation of **12** from a slow-moving by-product that was present in major proportion was achieved by flash chromatography on a short column of silica gel by use of petroleum ether as the eluant. Evaporation of the eluate yielded **12** as a colorless syrup (0.6 g, 31%) that crystallized rapidly upon refrigeration. Recrystallized from moist methanol, the long needles showed m.p. 50–50.5°, whereas, from petroleum ether containing a small proportion of ether, crystals of m.p. 52–53° were obtained on strong cooling: $[\alpha]_D$ +214° (*c* 0.5, chloroform); lit.[12] m.p. 47–48°, $[\alpha]_D$ +104.8°; for the L enantiomer[14], m.p. 43–45°, $[\alpha]_D$ −215° and[15] m.p. 53–54°, $[\alpha]_D$ −225°. The mass spectrum showed peaks at *m/z* 217 (M^+ − OMe) and 204 (strong, M^+ − CH_3CHO).

*Methyl 4-O-acetyl-2,3,6-trideoxy-α-*D-erythro-*hex-2-enopyranoside* (**9**). — To a cooled (0°) solution of the alcohol **8** (600 mg) in dichloromethane (6 mL) containing triethylamine (0.7 mL) was added acetic anhydride (0.44 mL). The solution was kept overnight at room temperature, whereafter t.l.c. (solvent *B*) indicated complete conversion of **8** (R_F 0.2) into the acetate **9** (R_F 0.7), and evaporated, and the residue passed through a small column of silica gel by means of ethyl acetate, in order to separate **9** from triethylammonium salt. Evaporation of the effluent (30° bath temperature) gave **9** as a colorless liquid weighing 0.75 g after brief drying at room temperature and 1 torr; $[\alpha]_D$ +165° (*c* 1.6, chloroform); reported[15] for a distilled sample of the L enantiomer, −187°. For spectral analysis, samples were freed of traces of solvent by prolonged drying *in vacuo*, although this led to some loss of the compound owing to its volatility. The mass spectrum had peaks at *m/z* 185 (weak, M^+ − H), 155 (strong, M^+ − OMe), 142 (strong, M^+ − CH_3CHO), and 100 (very strong, M^+ − CH_3CHO − CH_2CO).

*Methyl 4-[(N-benzyl)methylamino]-2,3,4,6-tetradeoxy-α-*D-erythro-*hex-2-enopyranoside* (**13**). — *A. From* **9**. A mixture of the acetate **9** (600 mg), triphenylphosphine (570 mg), tetrakis(triphenylphosphine)palladium (200 g), and dry oxolane (30 mL) was stirred for 0.5 h at room temperature. Benzylmethylamine (3 mL) was then added, and the mixture was boiled under reflux until **9** (R_F 0.7) had disappeared (t.l.c. with solvent *B*). The reaction time required varied (24–48 h), possibly owing to variations in catalyst quality. The aminated product **12** (R_F 0.85) was accompanied only by traces of slow-moving by-products. Processing as described for **6** and **7** gave **13** as a colorless syrup. The yield, after purification by column chromatography, was 645 mg (81%); $[\alpha]_D$ +211° (*c* 3.8, chloroform): *m/z* 247 (weak, M^+), 232 (weak, M^+ − Me), 216 (weak, M^+ − OMe), 203 (very strong, M^+ − CH_3CHO), and 188 (strong, M^+ − CH_3CHO − Me). The i.r. spectrum closely resembled that of **7**.

Anal. Calc. for $C_{15}H_{21}NO_2$ (247.3): C, 72.84; H, 8.56; N, 5.66. Found: C, 72.60; H, 8.55; N, 5.45.

B. From **12**. The benzoate **12** (200 mg) was allowed to react with triphenylphosphine (186 mg), tetrakis(triphenylphosphine)palladium (82 mg), and benzylmethylamine (1 mL) in oxolane (20 mL) as just described for **9**. The reaction time was 20 h. Although **12** and **13** have almost identical R_F values (0.85–0.9 in solvent *B*, 0.7 in 1:4 ethyl acetate–petroleum ether), they are readily distinguished by the color of the spots produced on heating the t.l.c. plates after spraying with 5% ethanolic sulfuric acid, namely, light yellowish-brown (**13**) and nearly black (**12**). The crude reaction-product showed one major spot (**13**), together with several, slow-moving (trace) spots. Processing and chromatographic purification gave 160 mg (80%) of **13**, whose ^{1}H-n.m.r. spectrum was identical with that of the product prepared from **9**.

*Methyl 2,3,4,6-tetradeoxy-4-methylamino-α-*D-erythro-*hexopyranoside* (**14**). — Compound **13** (260 mg) and 10% palladium-on-carbon catalyst (200 mg) in 99% ethanol (10 mL) were shaken for 24 h under hydrogen at ambient temperature and pressure. T.l.c. indicated complete conversion of **13** into a material that was immobile in solvent *B*, and gave an elongated spot (R_F ~0.4) in solvent *G*. The suspension was filtered, and the filtrate evaporated, to give **14** as a colorless oil that crystallized on refrigeration; m.p. 161° after recrystallization from methanol–ether–petroleum ether. The yield, 121 mg (72%), was low, possibly because of the considerable volatility shown by the compound *in vacuo*; *m/z* 159 (M^+) and 128 (M^+ — OMe); ν_{max}^{Nujol} 3400 (broad) and 1600 (weak, N–H), 1125, 1065, 1020, 983, 900, 860, 840, and 810 cm^{-1}.

*Methyl 2,3,4,6-tetradeoxy-4-dimethylamino-α-*D-erythro-*hexopyranoside* (**15**). — A mixture of the methylamino derivative **14** (100 mg), methanol (3 mL), and 37% aqueous formaldehyde solution (1 mL) was boiled for 1 h under reflux, effecting replacement of **14** by an almost immobile material (t.l.c. with solvent *G*). Sodium borohydride (135 mg) was then added, which caused within 1 h the conversion of the immobile product into **15**, R_F 0.3–0.4 (not readily distinguishable from **14**). The mixture was diluted with water, and extracted with dichloromethane (3 × 15 mL), and the extracts were combined, dried ($MgSO_4$), and evaporated at 25° (bath) to afford **15** (80 mg, 74%) as a colorless, rather volatile liquid. The n.m.r. spectrum (see Table I) was in agreement with published[6a] data.

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REFERENCES

1 H. H. BAER AND Z. S. HANNA, (a) *Carbohydr. Res.*, 78 (1980) c11–c14; (b) *Can. J. Chem.*, 59 (1981) 889–906.

2 (a) B. M. TROST, *Acc. Chem. Res.*, 13 (1980) 385–393; (b) B. M. TROST AND T. R. VERHOEVEN, *J. Am. Chem. Soc.*, 102 (1980) 4730–4743; (c) see further references cited in ref. 1b.

3 S. PINNERT-SINDICO, L. NINET, J. PREUD'HOMME, AND C. COSAR, *Antibiot. Ann.*, (1954) 724–727; R. CORBAZ, L. ETTLINGER, E. GÄUMANN, W. KELLER-SCHIERLEIN, F. KRADOLFER, E. KYBURZ, L. NEIPP, V. PRELOG, W. WETTSTEIN, AND H. ZÄHNER, *Helv. Chim. Acta*, 39 (1956) 304–317; W. KELLER-SCHIERLEIN, *Fortschr. Chem. Org. Naturst.*, 30 (1973) 313–460.

4 R. PAUL AND S. TCHELITCHEFF, *Bull. Soc. Chim. Fr.*, (1957) 734–737.

5 C. L. STEVENS, G. GUTOWSKI, K. G. TAYLOR, AND C. P. BRYANT, *Tetrahedron Lett.*, (1966) 5717–5721.

6 E. L. ALBANO AND D. HORTON, (a) *Carbohydr. Res.*, 11 (1969) 485–495; (b) *J. Org. Chem.*, 34 (1969) 3519–3522.

7 I. Dyong, R. Knollmann, and N. Jersch, *Angew. Chem.*, 88 (1976) 301–302; I. Dyong, R. Knollmann, N. Jersch, and H. Luftmann, *Chem. Ber.*, 111 (1978) 559–565.
8 S. Hanessian and N. R. Plessas, *J. Org. Chem.*, (a) 34 (1969) 1035–1044; (b) 1045–1053; (c) S. Hanessian, *Methods Carbohydr. Chem.*, 6 (1972) 183–189.
9 P. J. Garegg and B. Samuelsson, *Synthesis*, (1979) 813–814.
10 H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, 95 (1973) 1669–1671.
11 T. D. Inch, *Carbohydr. Res.*, 21 (1972) 37–43.
12 M. B. Yunker, S. Y.-K. Tam, D. R. Hicks, and B. Fraser-Reid, *Can. J. Chem.*, 54 (1976) 2411–2416.
13 R. S. Tipson and A. Cohen, *Carbohydr. Res.*, 1 (1965) 338–340.
14 K. Bock, J. K. Christiansen, and C. Pedersen, *Carbohydr. Res.*, 20 (1971) 73–81.
15 J. S. Brimacombe, L. W. Doner, and A. J. Rollins, *J. Chem. Soc., Perkin Trans. 1*, (1972) 2977–2979.
16 D. M. Clode, D. Horton, and W. Weckerle, *Carbohydr. Res.*, 49 (1976) 305–314.
17 O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska, and A. Zamojski, *Tetrahedron*, 27 (1971) 1973–1996.
18 B. L. Sondengam, J. Hentchoya Héno, and G. Charles, *Tetrahedron Lett.*, (1973) 261–264.