Carbohydrate Research, 63 (1978) 77–89

THE SYNTHESIS OF 3-AMINO-2,3,6-TRIDEOXY-L-*xylo*-HEXOPYRANOSE DERIVATIVES*

TAK-MING CHEUNG, DEREK HORTON, RODERICK J. SORENSON, AND WOLFGANG WECKERLE
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (U.S.A.)
(Received August 8th, 1977; accepted for publication, August 25th, 1977)

ABSTRACT

Derivatives (the 3-acetamido-4-benzoate **12**, the 3-acetamido-4-acetate **13**, and the *N*-acetyl derivative **14**) of the methyl glycoside of the title sugar were prepared in a sequence of high-yielding steps from methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**4**). *N*-Bromosuccinimide converted **4** into the crystalline 4-*O*-benzoyl-6-bromide **5**, which was treated with silver fluoride to afford the 5,6-unsaturated glycoside **6**. Catalytic hydrogenation of **6** led, essentially, to a 7:1 mixture of **12** and its 5-epimeric D-*arabino* isomer **7**. Alternatively, **6** was debenzoylated to **10**, and the latter treated with lithium aluminum hydride to give crystalline methyl 3-amino-2,3,6-trideoxy-α-D-*threo*-hex-5-enopyranoside (**11**). Reduction of **11** (as its salt) by hydrogen, with subsequent *N*-acetylation, furnished the methyl β-L-*xylo*-glycoside **13** almost exclusively, with net inversion at C-5. Compound **13** was readily converted into the crystalline target compound **14**. When dehydrobromination by silver fluoride was attempted with the 3-acetamido analog (**2**) of **5**, a 3,6-anhydro product (**1**) was obtained, instead of the expected 5,6-alkene **3**.

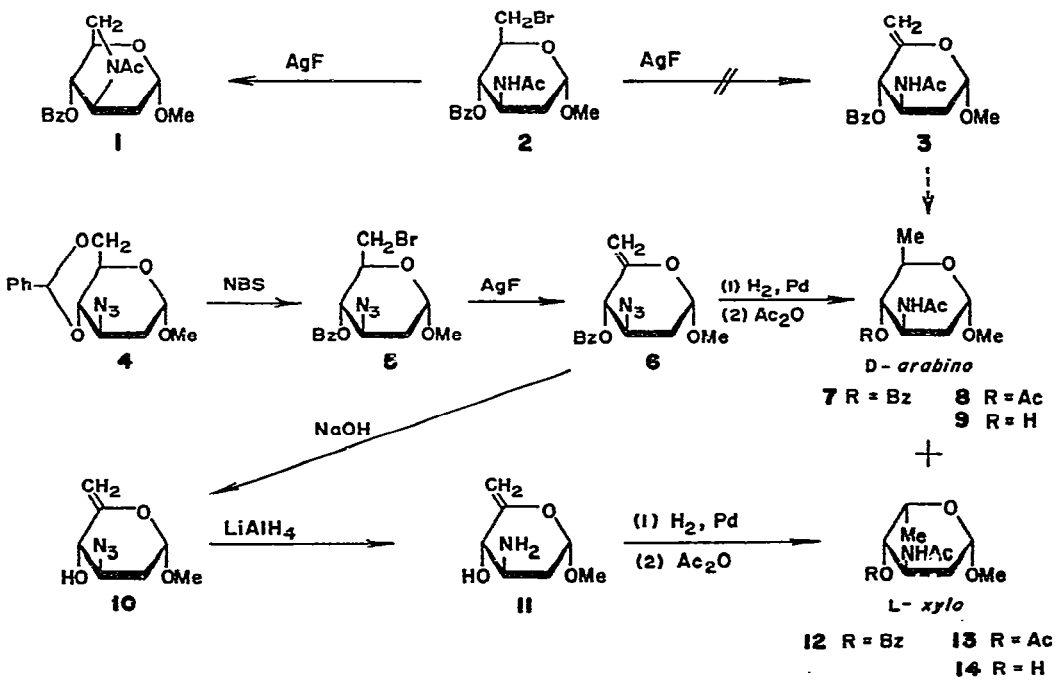
INTRODUCTION

3-Amino-2,3,6-trideoxyhexoses have received much attention during the past few years because of their presence[2] in many antibiotic agents. Thus, daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) is the sugar constituent of the antineoplastic anthracycline glycosides daunorubicin[3], adriamycin[4], and carminomycin[5]. Ristosamine (L-*ribo* stereochemistry) forms part[6] of the vancomycin-type antibiotic ristomycin, and acosamine (L-*arabino* stereochemistry) as well as its 4-methyl ether actinosamine are found[7] in the antibiotic actinoidin. In addition, *N*,*N*-dimethyl derivatives having the D-*arabino* (angolosamine) and L-*lyxo* (rhodosamine) configuration occur in Nature as constituents of the macrolide angolamycin[8] and of such anthracycline antibiotics[9] as cinerubins, pyrromycins, and rhodomycins, respectively. D-Rhodosamine has been shown[10] to be part of the macrolide-type megalomicins.

*For a preliminary report, see ref. 1.

In continuation of our work concerned[11] with the synthesis of aminopolydeoxy sugars, we now report the preparation of several derivatives of 3-amino-2,3,6-trideoxy-L-*xylo*-hexose. This isomer (and its D enantiomer) is thus far unknown in Nature and, to the best of our knowledge, has not yet been synthesized*† in either enantiomeric form, despite considerable interest in various analogs of daunosamine. Such analogs may be coupled[15c,17,19] to daunomycinone or adriamycinone to furnish compounds that are configurationally and/or functionally modified in the carbohydrate residue with respect to the parent antibiotics, and which, therefore, might display decreased toxicity and possibly an even broader spectrum of antitumor activity than daunorubicin and adriamycin.

With this goal in mind, we designed a synthetic route for converting a readily available 2-deoxy-D-*ribo*-hexose precursor into derivatives of 3-amino-2,3,6-trideoxy-L-*xylo*-hexose, which is the 3-epimer of daunosamine. The major features of the route involve generation of the terminal *C*-methyl group with concomitant stereochemical inversion at C-5 by exploiting the elimination–hydrogenation sequence successfully used before in analogous systems[11a,20], and introduction, only late in the sequence, of the 3-amino group by reducing the azido group introduced at the



*In contrast, the six other diastereoisomers (or derivatives thereof) have been prepared repeatedly; for daunosamine, its D enantiomer, and the racemic form, see refs. 11a and 12, ref. 13, and ref. 14, respectively; for ristosamine and its D enantiomer, see ref. 15 and refs. 11b and 16; for acosamine and its D enantiomer, see refs. 15d and 17 and refs. 11c, 13, and 18.

†Note added in proof. Since this article was submitted for publication, a report of the preparation of methyl 3-amino-2,3,6-trideoxy-β-L-*xylo*-hexopyranoside has been presented[15e].

TABLE I

100-MHz, ^{1}H-N.M.R. SPECTRAL DATA FOR COMPOUNDS 1, 5–8, 10, AND 12–14

Compound[a]	*Chemical shifts* (δ)[b] *(first-order couplings, Hz, in parentheses)*												
	H-1 ($J_{1,2a}$)	*H-2e* ($J_{1,2e}$)	($J_{2e,2a}$)	*H-2a* ($J_{2a,3}$)	*H-3* ($J_{2e,3}$)	*H-4* ($J_{3,4}$)	*H-5* ($J_{4,5}$)	*H-6* ($J_{5,6}$)	*H-6′* ($J_{5,6'}$)	*OMe-1*	*OR-4* ($J_{4,OH}$)	*NH* ($J_{3,NH}$)	*NAc*
1[c]	4.45 m (~7)	← 2.40–1.86 m → (2.5)			← 5.05–4.60 and 3.95–3.50 m →					3.47 s 3.45 s	8.20–7.35 m	—	2.10 s 2.04 s
5[d]	4.34 dd (3.5)	1.78 ddd (1.3)	(13.5)	1.30 ddd (12.3)	3.78 ddd (5.0)	5.02 t (9.8)	3.84 ddd (9.8)	← 3.39–2.94 m → (3.3)	(7.8)	3.08 s	8.05–6.98 m	—	—
6[d, e]	4.39 dd (3.2)	1.86 ddd (1.7)	(13.5)	1.44 ddd (11.7)	4.02 ddd (5.0)	5.69 dt (10.0)	—	4.63 t	4.54 t	3.08 s	8.20–6.98 m	—	—
7	4.73 dd (3.5)	2.26 ddd (1.3)	(13.8)	1.69 m[f] (11.2)	4.57 m (4.5)	4.80 t (10.0)	4.05 dq (9.0)	1.19 d (6.4)	—	3.34 s	8.15–7.30 m	6.19 d (7.8)	1.78 s
8	4.69 dd (3.0)	2.19 ddd (1.0)	(13.5)	1.58 ddd (11.5)	← 4.20–4.67 m → (3.0)		3.88 dq (9.0)	1.15 d (6.5)	—	3.31 s	2.03 s	5.86 d (7.0)	1.88 s
10[g]	5.21 dd (3.5)	2.38 ddd (1.7)	(14.0)	2.03 ddd (11.5)	← 4.26–3.88 m → (4.8)		—	5.11 d	4.93 d	3.65 s	6.32 d (5.0)	—	—
12[h]	4.71 dd (7.5)	← 2.45–1.68 m[f] → (2.8)			4.46 m	5.05 m (4.5)	4.15 dq (2.4)	1.25 d (6.5)	—	3.44 s	8.20–7.26 m	6.76 d (6.8)	1.94 s
13	4.72 dd (7.4)	← 2.20–1.65 m[f] → (3.3)			4.13 m	4.81 dd (4.0)	4.08 dq (2.2)	1.18 d (6.3)	—	3.45 s	2.08 s	7.73 d (7.7)	1.99 s
14[i]	4.64 dd (8.5)	← 2.05–1.52 m[f] → (3.0)	(13.6)		4.02 m	3.27 m	3.80 dq (2.0)	1.15 d (6.2)	—	3.38 s	4.70[f]	7.82 d	1.88 s

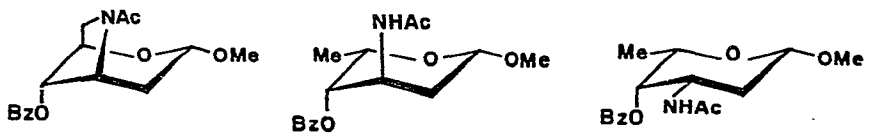
[a]In chloroform-*d*, unless otherwise stated. [b]Signal multiplicities: d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet. [c]The signals for OMe-1 and NAc are split into two peaks of unequal intensities, the ratio being ~3:1 in favor of the peaks at lower field. [d]In benzene-d_6. [e]$J_{6,6'} \approx J_{4,6} \approx J_{4,6'} \approx 1.8$ Hz. [f]Partially obscured signal. [g]In methyl sulfoxide-d_6; $J_{6,6'}$ 1.5 Hz. [h] $^4J_{2,4} \sim 2$ Hz. [i]In 3:1 chloroform-*d*–methyl sulfoxide-d_6.

very beginning. When, according to the original synthetic plan, the elimination reaction was attempted with a 3-acetamido sugar precursor, an unexpected 3,6-anhydro product was encountered.

RESULTS AND DISCUSSION

Methyl 3-acetamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**2**) has recently been prepared[11c] as a key intermediate in the synthesis of 3-amino-2,3,6-trideoxy-D-*arabino*-hexose, which is the D enantiomer of the antibiotic sugar acosamine. It was soon realized that this compound (**2**) might well be suited as a precursor for another stereochemical variant of daunosamine, namely, that having the L-*xylo* configuration. Therefore, in order to invert the configuration at C-5 and to generate the terminal *C*-methyl group, the elimination–hydrogenation sequence (by the route **2** → **3** → **7** + **12**) was to be applied; this sequence had proved very successful in the synthesis of daunosamine[11a] and its 3-hydroxy analog[20]. However, when **2** was treated with silver fluoride[21] by the established, general procedure[22] to afford the 5,6-unsaturated derivative **3**, a different, crystalline product (**1**) was obtained in high yield. Its i.r. spectrum indicated the absence of an alkenic group (confirmed by a negative test with permanganate) and it lacked the characteristic absorption-band for the N–H stretching vibration near 3300 cm^{-1}; instead, it suggested a disubstituted amide group (strong C=O stretching absorption at 1640 cm^{-1}). The complex p.m.r. spectrum (see Table I) of **1** in chloroform-*d* verified the presence of a benzoyl and a methoxyl group and one acetyl substituent [the signals for the last two being split into two singlets of unequal intensities (3 : 1) because of the chiral character of the trisubstituted nitrogen atom]. The observed coupling-constants ($J_{1,2a}$ ~7 Hz, $J_{1,2e}$ 2.5 Hz) for the H-1 signal were typical of an axially disposed proton, and indicated a conformation other than $^4C_1$(D) for the pyranose ring, if anomerization during the reaction had not taken place. All of this information led to the formulation of the 3,6-anhydro structure assigned to **1**, which was further substantiated by elemental composition and mass-spectrometric data (*m/e* 305, M^+; see Experimental section).

The 3,6-anhydro glycoside **1** closely resembles the original L-*xylo* target sugar [compare the conformational formulas of **1** and the corresponding L-*xylo* (**12**) and L-*lyxo* (daunosamine) derivatives] and is considered an interesting, novel candidate in the quest of developing new, anthracycline-type antitumor agents because of its rigid conformation, in contrast to the rather flexible chairs of daunosamine and all of its stereochemical analogs.



3,6-anhydro-D-*arabino* (**1**) L-*xylo* (**12**) L-*lyxo*

The 3,6-anhydro derivative **1** obviously arises through intramolecular, nucleophilic attack of the 3-acetamido nitrogen atom on C-6, and this reaction could not be suppressed by modifying the reaction conditions (solvent, temperature). In consequence, an alternative approach to the desired 3-amino-L-*xylo* sugar was chosen that employed the azido group as a latent amino function in the critical elimination-reaction. The required 3-azido-6-bromo derivative **5** was obtained crystalline (in contrast to a literature report[23]) in good yield (75%) by treating the corresponding 4,6-benzylidene acetal[13a,24] **4** with *N*-bromosuccinimide. Compound **5** constitutes the common precursor for the synthesis of the title sugar as well as its 5-epimer (D-*arabino* stereochemistry), as reduction of **5** with Raney nickel or lithium aluminum hydride, followed by acetylation, would provide the D-*arabino* derivatives **7**, **8**, or **9**. This sequence of reactions, however, is closely related to another one, recently reported[11c] from this laboratory, and is, therefore, not described in detail herein.

Treatment of the bromide **5** with silver fluoride[21] furnished the 5,6-unsaturated derivative **6** as a homogeneous (by t.l.c.) syrup in high yield. Compound **6** gave an excellent, first-order p.m.r. spectrum (see Table I), and the observed, large values for $J_{2a,3}$ and $J_{3,4}$ (11.7 and 10.0 Hz, respectively) clearly indicated the presence of three consecutive, *trans*-diaxially disposed protons (at C-2–C-4), suggesting that the $^4C_1$(D) conformation is strongly favored, as expected from conformational analysis[25].

Catalytic hydrogenation of **6** in the presence of palladium-on-carbon, followed by acetylation, afforded a rather complex mixture of products. No attempt was made to separate any of the numerous, minor components, but two major fractions were isolated by column chromatography on silica gel. The faster-moving one was obtained crystalline in 6.3% yield, and appeared to be, by t.l.c. comparison, methyl 3-acetamido-4-*O*-benzoyl-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**7**). This conclusion was substantiated by direct comparison (physical and spectroscopic data) with an authentic sample[11c] of **7** available in this laboratory.

The other product (**12**), isolated crystalline in 40% yield, gave, in chloroform-*d*, a 100-MHz p.m.r. spectrum (see Table I) that was essentially of first order. It displayed, in particular, a 3-proton doublet at high field (δ 1.25, *C*-Me) and a well-resolved, doubled doublet (δ 4.71; $J_{1,2e}$ 2.8, $J_{1,2a}$ 7.5 Hz) for H-1, clearly indicating the equatorial disposition of the anomeric methoxyl group. This information, and the small values for $J_{3,4}$ and $J_{4,5}$ (4.5 and 2.4 Hz, respectively), unequivocally established the β-L-*xylo* stereochemistry for the product (**12**) obtained. Mass spectrometry (*m/e* 307, M^+; see Table II), i.r. spectroscopy, and elemental composition provided additional evidence for the structure proposed.

The numerous side-products encountered in the hydrogenation reaction are believed to arise partly from participation of the benzoyloxy group on C-4 in the reaction. Similar difficulties were experienced[26] in the attempted hydrogenation of the D-*erythro* analog of **3** to give the corresponding daunosamine derivative. As, in that instance, the problem was completely overcome by subjecting the debenzoylated analog to hydrogenation, the benzoic ester **6** was converted, by catalytic transesterification, into the crystalline, unprotected glycoside **10**. Treatment of **10**, or its 3-amino

TABLE II

MASS-SPECTRAL DATA FOR THE L-*xylo* DERIVATIVES **12**, **13**, AND **14**

m/e *of principal fragments*[a] *(% of base peak)*								
Compound **12**[c]	**13**[c]	**14**	*Assignment*[b]	*Compound* **12**[c]	**13**[c]	**14**	*Assignment*[b]
308 (0.04)	246 (0.8)	204 (0.06)	M + 1	163 (1)	101^1 (61)	59^1 (100)	D_3
307 (0.09)	245 (0.2)	203 (0.05)	M$^+$	249 (0.1)	187 (0.7)	145 (0.8)	E_1^2
306 (0.3)	244 (0.7)	202 (0.24)	M − 1	58 (0.7)	58 (16)	58 (27)	E_1^1
275 (0.1)	213 (0.8)	171 (6.7)	A_1	129 (0.7)	129 (4.4)	129 (17)	F_1^1
153 (19)	153^1 (27)	153 (11)	A_2	114^1 (0.5)	114^1 (4.4)	114^1 (9.2)	F_2^1
138^1 (4.7)	138^1 (5)	138 (1.9)	A_3	128 (8)	128 (23)	128 (5)	F_1^2
185 (6)	185 (7)	185 (0.6)	B_1	86 (3.5)	86 (33)	86 (5.4)	G_1^1
142^1 (17)	142^1 (36)	142 (9)	B_2	72 (1.5)	72 (9.5)	72 (25)	G_1^2
276 (1.9)	214 (6)	172 (4.4)	C_1	—	—	86 (5.4)	H_1
217^1 (0.8)	155^1 (3.3)	113^1 (8)	C_2	105 (100)	—	—	$PhCO^+$
95^1 (8)	95 (22)	95^1 (4.5)	C_3	77 (18)	—	—	Ph^+
263 (1.4)	201 (2.6)	159 (2.4)	D_1	43 (12)	43 (100)	43 (62)	Ac^+
205^1 (3.7)	143^1 (22)	101^1 (75)	D_2	—	[d]	[e]	other

[a]Prominent, metastable fragments observed in the spectra are indicated by a superscript number 1 at the daughter ion of the process involved; deviations between observed and calculated values are less than ±0.1 mass units. [b]For details, see ref. 11c. [c]Metastable peak observed for $B_1 \rightarrow A_2$. [d]*m/e* 59^1 (22%, D_2 − ketene); 44^1 (18%, G_1^1 − ketene). [e]*m/e* 129^1 (17%, A_1 − ketene); 60 (28%, $AcNH_3^+$).

analog **11** (obtained from **10** by reduction with lithium aluminum hydride), with palladium-on-carbon under a variety of conditions did not, however, give satisfactory results. In another attempt, therefore, the amino glycoside **11** was first treated with an equimolar amount of *p*-toluenesulfonic acid prior to catalytic hydrogenation in aqueous solution; this procedure afforded, after selective *N*-acetylation, essentially a single, crystalline product (**14**). As **14** proved difficult to purify by recrystallization, and had a chromatographic mobility on silica gel almost identical to that of the very minor side-product (**9**), the mixture was acetylated* and the product subjected to column chromatography. The faster-moving, minor (4.5% yield) component was obtained crystalline, and was subsequently identified as methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**8**); it was identical, by all characteristics (physical and spectroscopic data, X-ray powder pattern), with an authentic[11c] sample.

The main product (83% yield) proved to be the expected L-*xylo* derivative **13**. Although a syrup, it gave an acceptable elemental analysis, and its p.m.r. spectrum (see Table I) resembled that of **12**, except that H-3 and H-4 resonated at somewhat higher field because of the lack of the deshielding effect of the benzoyloxy group (on C-4 in **12**). I.r.-spectroscopic, microanalytical, and mass spectrometric data (*m/e* 245, M^{+}; see Table II) fully supported the structure indicated.

Catalytic transesterification (Zemplén) of **13** gave crystalline methyl 3-acetamido-2,3,6-trideoxy-β-L-*xylo*-hexopyranoside (**14**) in high yield. The fairly well-resolved p.m.r. spectrum (see Table I) of **14** closely resembled that of **12** and **13**, except for the expected diamagnetic shift of the H-4 resonance attributable to removal of the deshielding acyl group on O-4. The splittings of the well-resolved, doubled doublet for H-1 ($J_{1,2e}$ 3.0, $J_{1,2a}$ 8.5 Hz) suggested that the $^{1}C_{4}$(L) conformation is preponderant, despite two axial substituents (at C-3 and C-4) and the anomeric effect, which generally operates to favor the axial orientation of the glycosidic methoxyl group[25].

The foregoing synthesis affords the crystalline methyl acetamidoglycoside **14** from **4** in 44% overall yield, with all of the steps amenable to scaled-up operation. The further preparation of derivatives of **14** bearing suitable, temporary protecting-groups would be useful in the synthesis of anthracycline antibiotics in which the stereochemistry of the natural sugar (α-L-*lyxo*) would be altered (α- and/or β-L-*xylo*).

Details of the 100-MHz, ^{1}H-n.m.r. spectra of intermediates and target compounds are recorded in Table I, and electron-impact mass-spectrometric data and probable assignments for the L-*xylo* derivatives **12**–**14** are summarized in Table II.

---

*Attempted benzoylation (benzoyl chloride–pyridine, 12 h, 0°) in order to prepare the more readily separable (by chromatography on silica gel) derivatives **7** and **12**, led invariably to the *N*-acetyl-3-benzamido analogs of **7** and **12** (compare ref. 27).

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure at bath temperatures below 50°. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. A Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r. spectra were recorded with a Perkin–Elmer Model 457 grating i.r. spectrophotometer, with solids dispersed in potassium bromide, and syrups as films on sodium chloride discs. ^{1}H-N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer; chemical shifts refer to an internal standard of tetramethylsilane ($\delta = 0.00$), and are listed, together with spin-coupling values (Hz) in Table I. In most instances, the assignments were confirmed by decoupling experiments. T.l.c. was performed on precoated plates of Silica Gel 60 (E. Merck, Darmstadt); zones were detected by u.v. light, and by spraying with sulfuric acid and subsequent heating. Solvent volumes are v/v. Column chromatography was performed with silica gel (Merck No. 7734; 63–200 μm). Microanalyses were performed by W. N. Rond. Mass spectra were recorded by C. R. Weisenberger with an AEI MS-9 double-focusing, high-resolution spectrometer operating at an ionizing potential of 70 eV and an accelerating potential of 8 kV; the source temperature (direct-inlet system) was 120°. The notations in the assignments are adopted from fragmentation pathways proposed[11c] for D-acosamine derivatives. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

*Methyl 3-acetamido-3,6-anhydro-4-O-benzoyl-2,3-dideoxy-α-*D-arabino-*hexopyranoside* (**1**). — A mixture of methyl 3-acetamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside[11c] (**2**; 5 g, 12.95 mmol) and dry, technical-grade silver fluoride[21] (5.8 g) in dry pyridine (100 ml) was thoroughly stirred for 24 h at room temperature, after which time t.l.c. (2:3 benzene–acetone) indicated that **2** had all reacted. The dark solution was poured into ether (500 ml), the resultant mixture filtered, and the filtrate evaporated. Toluene (three 20-ml portions) was added to and evaporated from the residue, which was then dissolved in methanol and treated with activated charcoal. The yellow residue obtained upon evaporation of the solvent was placed on a small column (250 × 20 mm) of silica gel, and eluted with acetone in order to remove the last traces of silver salts. The effluent afforded a crystalline product (3.28 g, 83%), a sample of which was recrystallized from hexane (or isopropyl ether†) to give analytically pure **1**; m.p. 127–128°, $[\alpha]_D^{21}$ −61° (*c* 0.6, chloroform); ν_{max}^{KBr} no absorption near 3300 (NH), 1720 (ester C=O), 1640 (disubstituted amide), 1600 and 1580 cm^{-1} (monosubstituted phenyl); *m/e* (rel. intensity): 305 (M^+, 2.3), 274 (1, C_1), 273 (1, A_1), 247 (0.8, E_1^2), 184 (17, M − BzO·), 183 (3.5,

†This solvent is prone to generation of explosive peroxides, and should be tested before use to ensure that peroxides are absent.

B_1; m* at 109.8, calc. 109.80), 152 (3.6, 184 – MeOH; m* at 125.6, calc. 125.57), 151 (1.5, A_2), 140 (13, B_2; m* at 107.1, calc. 107.10), 105 (100, $PhCO^+$), 77 (30, Ph^+), 58 (2.5, E_1^1), and 43 (25, Ac^+); X-ray powder diffraction data: 12.99 w, 9.87 s (1), 8.34 w, 7.31 w, 5.86 m, 5.47 s (2,2), 5.15 s (3), 4.67 s (2,2), 4.37 m, and 4.06 w.

Anal. Calc. for $C_{16}H_{19}NO_5$ (305.33): C, 62.94; H, 6.27; N, 4.59. Found: C, 63.10; H, 6.46; N, 4.66.

Similar experiments employing (as the solvent) acetone, acetone–hexamethylphosphoric triamide, acetonitrile, and dimethyl sulfoxide afforded the same product (**1**). Treatment of **2** with sodium methoxide (1.5 molar equiv.) in refluxing methanol led to the corresponding product debenzoylated at O-4, as verified by t.l.c. comparison with a sample prepared from **1** by catalytic transesterification.

*Methyl 3-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-*D-arabino-*hexopyranoside* (**5**). — A mixture of methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside[13a,24] {**4**; m.p. 83–84° (2-propanol–water), $[\alpha]_D^{22}$ +110.4° (*c* 1.4, chloroform); lit.[13a] m.p. 82–83°, $[\alpha]_D$ +111° in chloroform} (13.69 g, 47 mmol), *N*-bromosuccinimide (8.72 g, 49 mmol), and barium carbonate (11 g) in dry carbon tetrachloride (320 ml) was boiled for 3 h with stirring under reflux. T.l.c. (9:1 benzene–ether) then revealed the reaction to be complete. The precipitate was filtered off and thoroughly washed with dichloromethane. The filtrates were combined and successively washed with aqueous solutions of sodium hydrogensulfite and sodium hydrogencarbonate, dried (magnesium sulfate), and evaporated to dryness. The resulting solid (17.2 g) was recrystallized from 2-propanol (60 ml), to give analytically pure **5**; yield 13.03 g (75%), m.p. 63–64°, $[\alpha]_D^{22}$ +44.1° (*c* 1.3, chloroform); ν_{max}^{KBr} 2100 (azide), 1715 (ester C=O), 1598 and 1580 cm^{-1} (monosubstituted phenyl); *m/e* (rel. intensity): 339 (0.03, C_1), 338 (0.15, A_1), 248 (0.03, B_1), 216 (0.04, A_2), 122 (4.1, A_3 or $BzOH^+$), 105 (100, $PhCO^+$), 77 (25, Ph^+), and 58 (7, E_1^1); X-ray powder diffraction data: 12.18 s (3), 8.34 m, 5.88 w, 5.11 m, 4.60 s (2), 4.37 m, 4.21 m, 3.95 w, 3.77 w, 3.57 vs (1), 3.41 m, 3.31 m, and 3.22 m.

Anal. Calc. for $C_{14}H_{16}BrN_3O_4$ (370.21): C, 45.42; H, 4.36; Br, 21.59; N, 11.35. Found: C, 45.12; H, 4.27; Br, 21.70; N, 11.23.

Hanessian and Plessas[23] described compound **5** as a syrup having $[\alpha]_D$ +52.7° in chloroform.

*Methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-α-*D-threo-*hex-5-enopyranoside* (**6**).— A mixture of the 6-bromide **5** (14.52 g, 39.22 mmol) and dry, technical-grade silver fluoride[21] (15 g) in dry pyridine (200 ml) was vigorously stirred for 16 h at room temperature, after which time g.l.c. [Hewlett–Packard Gas Chromatograph Series 5720A, equipped with a flame-ionization detector and a glass column (1.83 m × 3 mm) packed with 2% of OV-1 on Chromosorb, at 230° (isothermal), with helium as the carrier gas at a flow rate of 25 $ml.min^{-1}$] revealed that all of the **5** had reacted. The dark solution was poured into ether (800 ml), and stirred briefly, and the mixture was filtered. The filtrate was concentrated, and toluene (three 20-ml portions) was added to and evaporated from the residue. The resulting, dark syrup was passed through a small column (500 × 30 mm) of silica gel, using dichloromethane as the

eluant to remove residual silver salts. Evaporation of the effluent afforded syrupy **6**, sufficiently pure for the following step; yield 10.85 g (96%), $[\alpha]_D^{24}$ +37.4° (*c* 2, chloroform); ν_{max}^{film} 2100 (azide), 1725 (ester C=O), 1660 (C=C), 1600 and 1585 cm^{-1} (monosubstituted phenyl); *m/e* (rel. intensity): 289 (0.04, M^+), 271 (0.01, B_1), 258 (0.2, C_1), 257 (0.02, A_1), 247 (21, M − N_3·/ketene), 215 (28, C_2 or 247 − MeOH; m* at 187.1, calc. for 247 → 215: 187.15), 122 (5.8, $BzOH^+$), 112 (3.9, F_1^2), 105 (100, $PhCO^+$), 84 (10), 77 (45, Ph^+), and 58 (14, E_1^1).

Although the product migrated as a single zone in t.l.c. (R_F 0.7, 2:3 benzene–acetone) and no signals due to impurities were detected in its p.m.r. spectrum, an elemental analysis within acceptable limits could not be obtained.

*Catalytic hydrogenation of methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-α-*D*-threo-hex-5-enopyranoside* (**6**). — The unsaturated, syrupy sugar **6** (900 mg, 3.11 mmol) from the foregoing experiment, dissolved in methanol (25 ml), was hydrogenated (4.2 $kg.cm^{-1}$) in the presence of 5% palladium-on-carbon (300 mg) for 1 h at ~25°. The catalyst was then removed by filtration, and the filtrate evaporated to a syrup that was treated with 1:2 acetic anhydride–pyridine (9 ml) for 18 h at room temperature. After conventional processing, a syrupy product was obtained that was shown by t.l.c. (2:3 benzene–acetone) to consist of a mixture of two major products (R_F 0.58 and 0.49), together with a number of minor components. These were fractionated by chromatography on a column (450 × 30 mm) of silica gel, with 1:1 benzene–acetone as the eluant.

The component having R_F 0.58 crystallized on evaporation of the solvent, and was identified as *methyl 3-acetamido-4-*O*-benzoyl-2,3,6-trideoxy-α-*D*-arabino-hexopyranoside* (**7**) by comparison with an authentic[11c] sample; yield 60 mg (6.3%), m.p. 133–134°, $[\alpha]_D^{22}$ +134° (*c* 0.8, chloroform). Compound **7** was indistinguishable by chromatography (t.l.c., g.l.c.), spectroscopy (i.r., n.m.r.), and mass spectrometry from a product prepared earlier[11c] in this laboratory.

Evaporation of the fractions containing the product having R_F 0.49 gave crystalline *methyl 3-acetamido-4-*O*-benzoyl-2,3,6-trideoxy-β-*L*-xylo-hexopyranoside* (**12**); yield 380 mg (40%). After recrystallization from dichloromethane–isopropyl ether, it had m.p. 185–187°, $[\alpha]_D^{22}$ +16.4° (*c* 0.5, chloroform); ν_{max}^{KBr} 3340 (NH), 1730 (ester C=O), 1655 and 1545 (amide), 1605 and 1585 cm^{-1} (monosubstituted phenyl); for m.s. data, see Table II; X-ray powder diffraction data: 11.55 m, 7.43 s (2), 6.91 vw, 5.71 s (3), 5.26 w, 4.95 w, 4.62 s (1), 4.50 m, 3.91 s, 3.59 s, 3.44 m, and 3.29 w.

Anal. Calc. for $C_{16}H_{21}NO_5$ (307.35): C, 62.53; H, 6.89; N, 4.56. Found: C, 62.64; H, 6.90; N, 4.40.

*Methyl 3-azido-2,3,6-trideoxy-α-*D*-threo-hex-5-enopyranoside* (**10**). — To a suspension of the 4-benzoate **6** (9.72 g, 33.60 mmol) in a mixture of methanol (40 ml) and water (10 ml) was added M aqueous sodium hydroxide (50 ml). After stirring for 18 h at ~25°, t.l.c. (chloroform) indicated the saponification to be complete. The product was extracted with dichloromethane (three 50-ml portions), and the extract was washed with water, dried (magnesium sulfate) and evaporated, to afford crude, crystalline **10**; yield 5.66 g (91%). For analytical purposes, a sample was recrystallized

from dichloromethane–hexane; m.p. 86–88°, $[\alpha]_D^{22}$ +102.6° (*c* 1, chloroform); ν_{max}^{KBr} 3300 (broad, OH), 2105 (azide), and 1655 cm^{-1} (C=C); *m/e* (rel. intensity): 185 (0.2, M^+), 154 (10, C_1), 153 (14, A_1), 142 (1.2, M − HN_3), 111 (1.4, C_2), 96 (45), 84 (28), 69 (13), 58 (100, E_1^1), 43 (75, HN_3^+); X-ray powder diffraction data: 9.06 m, 6.48 m, 6.10 s (i,1), 5.45 vw, 5.02 s (2), 4.69 m, 4.30 s (3), 4.41 w, 3.98 m, 3.85 m, and 3.60 s (1,1).

Anal. Calc. for $C_7H_{11}N_3O_3$ (185.18): C, 45.40; H, 5.99; N, 22.69. Found: C, 45.30; H, 6.15; N, 22.38.

The white, crystalline product (**10**) could be kept in a desiccator in the dark for an extended period, but without these precautions, it turned yellow after a few days.

*Methyl 3-amino-2,3,6-trideoxy-α-*D-threo-*hex-5-enopyranoside* (**11**). — A mixture of the azido compound **10** (4.10 g, 22.14 mmol) and lithium aluminum hydride (3.8 g, 100 mmol) in ether (250 ml) was boiled under reflux for 4 h, after which time the unreacted reducing agent was decomposed by the conventional procedure[28]. The inorganic precipitate was filtered off, and repeatedly resuspended in dichloromethane. The filtrate and washing solutions were combined, and evaporated, to give crystalline **11**; yield 2.96 g (84%). A small sample was recrystallized from dichloromethane–hexane to afford analytically pure **11**; m.p. 146–148°, $[\alpha]_D^{22}$ +74.7° (*c* 0.8, chloroform); ν_{max}^{KBr} 3400–3100 (OH, NH_2) and 1650 cm^{-1} (C=C); *m/e* (rel. intensity): 143 (0.8, M − ·NH_2), 142 (4.5, M − ·OH), 128 (7.5, C_1), 127 (3.2, A_1), 111 (1.1, C_2), 109 (0.7, A_2), 101 (85, E_1^2), 86 (35), 59 (100, E_1^2 − ketene), 58 (9, E_1^1), 56 (28), and 43 (56); X-ray powder diffraction data: 7.40 vw, 5.90 w, 5.40 s (2), 4.75 vs (1), 3.98 s (3), 3.53 m, 3.40 w, 3.26 m, and 3.03 w.

Anal. Calc. for $C_7H_{13}NO_3$ (159.19): C, 52.82; H, 8.23; N, 8.80. Found: C, 52.76; H, 8.60; N, 8.66.

Catalytic hydrogenation of **11**: *methyl 3-acetamido-4-O-acetyl-2,3,6-trideoxy-β-*L-xylo-*hexopyranoside* (**13**) *and its α-*D-arabino *analog* (**8**). — A mixture of the amino glycoside **11** (1.37 g, 8.64 mmol) and *p*-toluenesulfonic acid monohydrate (1.64 g, 8.62 mmol) in water (50 ml) was hydrogenated under pressure (2.1 $kg.cm^{-2}$; 30 $lb.in.^{-2}$) in the presence of 10% palladium-on-carbon (100 mg) for 5 h at 25°. The catalyst was filtered off, and the filtrate was treated with Amberlite IRA-400 (OH^-) anion-exchange resin (15 ml) for 1 h at 0°. Acetic anhydride (8 ml) then was added, and the mixture was kept for 3 h at 0°, after which time the excess of reagent was decomposed by the addition of pyridine. The solvent was evaporated off, and pyridine and toluene (three 10-ml portions each) were added to and evaporated from the residue (~1.6 g); this slowly crystallized on being kept. T.l.c. analysis (2:3 benzene–acetone) revealed the presence of a very minor component (**9**; R_F 0.23) along with the principal product (**14**; R_F 0.19); these were separated, after conventional acetylation, by column chromatography on silica gel with 19:1 ethyl acetate–acetone as the eluant.

The faster-moving component (R_F 0.22) crystallized after evaporation of the solvent, and was identified as the α-D-*arabino* derivative **8**, identical by m.p. (161–162°

after recrystallization from isopropyl ether), optical rotation {$[\alpha]_D^{22}$ +172° (*c* 0.8, chloroform)}, and powder diffraction pattern with an authentic[11c] sample; yield 95 mg (4.5%).

When the corresponding fractions containing the major component, having R_F 0.15, were combined and concentrated, the *β*-L-*xylo* derivative **13** was obtained as a syrup; yield 1.75 g (83%). To secure an analytical sample, an ethereal solution of **13** was treated with activated charcoal, and, after evaporation of the solvent, the colorless syrup was kept over phosphorus pentaoxide, potassium hydroxide, and paraffin in a desiccator for several days; it had $[\alpha]_D^{22}$ +41.7° (*c* 0.8, chloroform); ν_{max}^{film} 3300 (NH), 1740 (ester C=O), 1660, and 1550 cm^{-1} (amide); for m.s. data, see Table II.

Anal. Calc. for $C_{11}H_{19}NO_5$ (245.28): C, 53.87; H, 7.81; N, 5.71. Found: C, 53.79; H, 7.84; N, 5.38.

*Methyl 3-acetamido-2,3,6-trideoxy-β-*L-xylo-*hexopyranoside* (**14**). — To a solution of the protected glycoside **13** (500 mg, 2.04 mmol) in abs. methanol (10 ml) was added M sodium methoxide (250 µl), and the mixture was kept for 12 h at 25°, after which time t.l.c. (2:3 benzene–acetone) indicated that the transesterification was complete. De-ionization [Amberlite IRC-50 (H^+), 2 ml; 30 min, 0°], followed by evaporation of the solvent, afforded crude **14** as a syrup that crystallized upon trituration with ether; yield 400 mg (97%). After recrystallization from ethanol–ether, **14** had m.p. 136–138°, $[\alpha]_D^{22}$ +41.4° (*c* 0.7, methanol); ν_{max}^{KBr} 3500–3200 (OH, NH), 1655 and 1540 cm^{-1} (amide); for m.s. data, see Table II; X-ray powder diffraction data: 8.11 m, 7.05 m, 6.43 vs (1), 5.75 m, 5.45 w, 5.24 m, 5.03 w, 4.68 vw, 4.06 s (3), and 3.73 s (2).

Anal. Calc. for $C_9H_{17}NO_4$ (203.24): C, 53.19; H, 8.43; N, 6.89. Found: C, 52.97; H, 8.76; N, 6.77.

ACKNOWLEDGMENT

This work was supported by Contract No. NO1-CM-57015 (The Ohio State University Research Foundation Project 784226) from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md. 20014.

REFERENCES

1 D. HORTON, T.-M. CHEUNG, R. J. SORENSON, W. WECKERLE, AND B. WINTER, *Abstr. Pap. Chem. Inst. Can., Am. Chem. Soc. Joint Conf., 2nd*, (1977) CARB-39.
2 For a review, see S. HANESSIAN AND T. H. HASKELL, in W. PIGMAN AND D. HORTON (Eds.), *The Carbohydrates*, Vol. IIA, Academic Press, New York, 1970, pp. 139–211.
3 F. ARCAMONE, G. CASSINELLI, G. FRANCESCHI, R. MONDELLI, P. OREZZI, AND S. PENCO, *Gazz. Chim. Ital.*, 100 (1970) 949–989.
4 F. ARCAMONE, G. FRANCESCHI, S. PENCO, AND A. SELVA, *Tetrahedron Lett.*, (1969) 1007–1010; A. DI MARCO, F. ARCAMONE, AND F. ZUNINO, in J. W. CORCORAN AND F. E. HAHN (Eds.), *Antibiotics*, Vol. III, Springer Verlag, New York, 1975, pp. 101–128.

5 M. G. BRAZHNIKOVA, V. B. ZBARSKY, V. L. PONOMARENKO, AND N. B. POTAPOVA, *J. Antibiot.*, 27 (1974) 254–259; G. F. GAUSE, M. G. BRAZHNIKOVA, AND V. A. SHORIN, *Cancer Chemother. Rep.*, 58 (1974) 255–256; M. C. WANI, H. L. TAYLOR, M. E. WALL, A. T. MCPHAIL, AND K. D. ONAN, *J. Am. Chem. Soc.*, 97 (1975) 5955–5956.
6 N. N. LOMAKINA, I. A. SPIRIDONOVA, R. BOGNÁR, M. PUSKÁS, AND F. SZTARICSKAI, *Antibiotiki*, 13 (1968) 975–978; R. BOGNÁR, F. SZTARICSKAI, M. E. MUNK, AND J. TAMAS, *J. Org. Chem.*, 39 (1974) 2971–2974.
7 N. N. LOMAKINA, I. A. SPIRIDONOVA, YU. N. SHEINKER, AND T. F. VLASOVA, *Khim. Prir. Soedin.*, 9 (1973) 101–107; *Chem. Abstr.*, 78 (1973) 148,170*m*.
8 M. BRUFANI AND W. KELLER-SCHIERLEIN, *Helv. Chim. Acta*, 49 (1966) 1962–1970.
9 See, for example, H. BROCKMANN, E. SPOHLER, AND T. WAEHNELDT, *Chem. Ber.*, 96 (1963) 2925–2936.
10 A. K. MALLAMS, *J. Am. Chem. Soc.*, 91 (1969) 7505–7506.
11 (a) D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 44 (1975) 227–240; (b) *ibid.*, 46 (1976) 227–235; (c) D. HORTON, R. J. SORENSON, AND W. WECKERLE, *ibid.*, 58 (1977) 125–138.
12 J. P. MARSH, JR., C. W. MOSHER, E. M. ACTON, AND L. GOODMAN, *Chem. Commun.*, (1967) 973–975.
13 (a) A. C. RICHARDSON, *Carbohydr. Res.*, 4 (1967) 422–428; (b) H. H. BAER, K. ČAPEK, AND M. C. COOK, *Can. J. Chem.*, 47 (1969) 89–97.
14 C. M. WONG, T.-L. HO, AND W. P. NIEMCZURA, *Can. J. Chem.*, 53 (1975) 3144–3145.
15 (a) F. SZTARICSKAI, I. PELYVÁS, R. BOGNÁR, AND G. BUJTAS, *Tetrahedron Lett.*, (1975) 1111–1114; (b) W. W. LEE, H. Y. WU, J. P. MARSH, JR., C. W. MOSHER, E. M. ACTON, L. GOODMAN, AND D. W. HENRY, *J. Med. Chem.*, 18 (1975) 767–768; (c) F. ARCAMONE, A. BARGIOTTI, G. CASSINELLI, S. PENCO, AND S. HANESSIAN, *Carbohydr. Res.*, 46 (1976) C3–C5; (d) K. HEYNS, M.-J. LIM, AND J. I. PARK, *Tetrahedron Lett.*, (1976) 1477–1480; (e) J. BOIVIN, M. PAIS, AND C. MONNERET, *Abstr. VII*[es] *Journées des Glucides*, Pont-à-Mousson, France, October 23–26, 1977, abstr. 46.
16 I. PELYVÁS, F. SZTARICSKAI, R. BOGNÁR, AND G. BUJTAS, *Carbohydr. Res.*, 53 (1977) C17–C19; H. H. BAER AND F. F. Z. GEORGES, *ibid.*, 55 (1977) 253–258.
17 (a) S. K. GUPTA, *Carbohydr. Res.*, 37 (1974) 381–383; W. W. LEE, H. Y. WU, J. E. CHRISTENSEN, L. GOODMAN, AND D. W. HENRY, *J. Med. Chem.*, 18 (1975) 768–769; (b) F. ARCAMONE, S. PENCO, A. VIGEVANI, S. REDAELLI, G. FRANCHI, A. DI MARCO, A. M. CASAZZA, T. DASDIA, F. FORMELLI, A. NECCO, AND C. SORANZO, *ibid.*, 18 (1975) 703–707.
18 H. H. BAER AND F. F. Z. GEORGES, *Can. J. Chem.*, 53 (1977) 1100–1103.
19 F. ARCAMONE, A. BARGIOTTI, G. CASSINELLI, S. REDAELLI, S. HANESSIAN, A. DI MARCO, A. M. CASAZZA, T. DASDIA, A. NECCO, P. REGGIANI, AND R. SUPINO, *J. Med. Chem.*, 19 (1976) 733–734; F. ARCAMONE, S. PENCO, S. REDAELLI, AND S. HANESSIAN, *ibid.*, 19 (1976) 1424–1425; E.-F. FUCHS, D. HORTON, AND W. WECKERLE, *Carbohydr. Res.*, 57 (1977) C36–C39.
20 T.-M. CHEUNG, D. HORTON, AND W. WECKERLE, *Carbohydr. Res.*, 58 (1977) 139–151.
21 W. KWASNIK, in G. BRAUER (Ed.), *Handbuch der praeparativen anorganischen Chemie*, Vol. 1, F. Enke Verlag, Stuttgart, 1960, pp. 224–225; *Handbook of Preparative Inorganic Chemistry*, Vol. I, Academic Press, New York, 1963, pp. 240–241.
22 B. HELFERICH AND E. HIMMEN, *Ber.*, 61 (1928) 1825–1835; M. J. BLAIR, *Methods Carbohydr. Chem.*, 2 (1963) 415–418; compare J. LEHMANN AND A. A. BENSON, *J. Am. Chem. Soc.*, 86 (1964) 4469–4472; J. LEHMANN AND W. WECKERLE, *Carbohydr. Res.*, 42 (1975) 275–295.
23 S. HANESSIAN AND N. R. PLESSAS, *J. Org. Chem.*, 34 (1969) 1045–1053.
24 R. D. GUTHRIE AND D. MURPHY, *J. Chem. Soc.*, (1965) 6956–6960; J. KOVÁŘ, V. DIENSTBIEROVÁ, AND J. JARÝ, *Collect. Czech. Chem. Commun.*, 32 (1967) 2498–2503.
25 P. L. DURETTE AND D. HORTON, *Adv. Carbohydr. Chem. Biochem.*, 26 (1971) 49–125.
26 D. HORTON AND W. WECKERLE, *Abstr. Pap. Am. Chem. Soc. Meet.*, 170 (1975) CARB-4; compare ref. 11a.
27 T. D. INCH AND H. G. FLETCHER, JR., *J. Org. Chem.*, 31 (1966) 1815–1820, 1821–1825; T. D. INCH, J. R. PLIMMER, AND H. G. FLETCHER, JR., *ibid.*, 31 (1966) 1825–1830.
28 L. F. FIESER AND M. FIESER, *Reagents for Organic Synthesis*, Wiley, New York, 1967, pp. 583–584.