Synthesis of Amino Sugars from Tri-*O*-acetyl-D-glucal via Epoxides[1]

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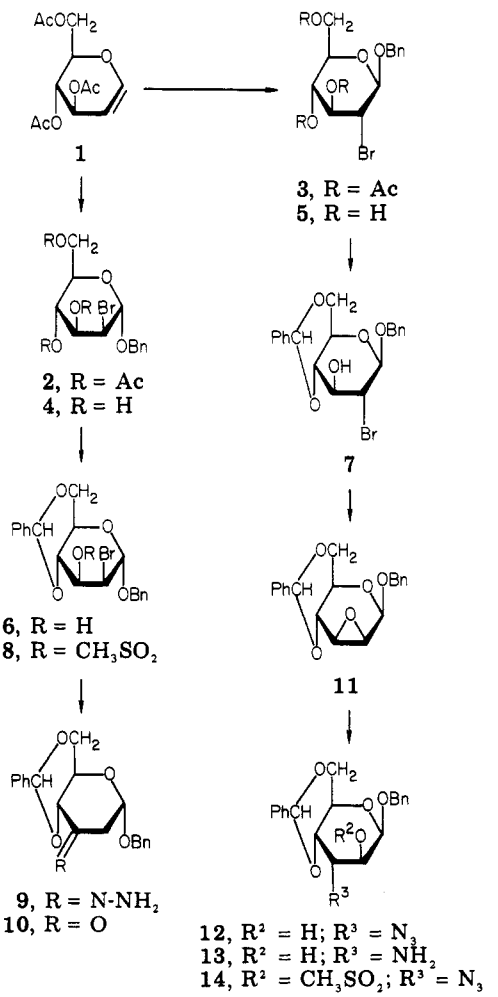
Simultaneous stereospecific trans addition of the benzyloxy and bromo residues with *N*-bromosuccinimide in benzyl alcohol to tri-*O*-acetyl-D-glucal (3,4,6-tri-*O*-acetyl-1,2-dideoxy-D-*arabino*-1-hexenopyranose; **1**) gave a mixture of benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside (**2**) and benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside (**3**). Their de-*O*-acetyl derivatives (**4** and **5**, respectively) were used to prepare the 4,6-*O*-benzylidene derivatives (**6** and **7**). The 3-*O*-mesyl derivative (**8**) of **6** was converted into benzyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**10**). The D-gluco derivative (**7**) was converted by base into benzyl 2,3-anhydro-4,6-*O*-benzylidene-β-D-mannopyranoside (**11**). Epoxide cleavage of **11** by sodium azide in hexamethylphosphoric triamide (HMPT) under carbon dioxide gave only benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranoside (**12**), which was subsequently reduced to benzyl 3-amino-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranoside (**13**). The 3-*O*-mesyl derivative (**14**) of **12** did not react with sodium azide under a variety of conditions. Epoxide cleavage of benzyl-2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**15**) gave benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (**16**) and mostly benzyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (**17**). The 2-*O*-mesyl gluco derivative (**18**) of **16** failed to react with NaN_3 in HMPT, but the 3-*O*-mesyl altro derivative (**19**) gave benzyl 2,3-diazido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranoside (**20**) and benzyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-3-hexenopyranoside (**21**). The azido sugars **16**, **17**, **20**, and **21** were all reduced by lithium aluminum hydride to the amino sugars **22–25** and N-acetylated to give **22a**, **23a**, and **25a**. From the diamino manno derivative **24** were prepared the cyclic urea **26** and the cyclic oxamide **27**. The reactivities of the *O*-mesyl groups in **14**, **18**, and **19** are discussed in mechanistic terms.

The chemistry of glycals has been comprehensively reviewed by Ferrier.[2] Fischer's work[3] on the addition of Br_2 to D-glucal was extended by Lemieux and Fraser-Reid[4] to the direct haloalkoxylation of a variety of unsaturated sugars and to the synthesis of 2-deoxy-2-halo disaccharides.

Halide at C(2) of an aldose derivative is often difficult to displace directly by a nitrogen function, but a neighboring *trans*-OH group at C(3) reacts easily to give an epoxide. While 1,2-epoxycyclohexane was cleaved with NaN_3 in aqueous dioxane,[5] the cleavage of the more stable sugar epoxides[6] with NaN_3 in aqueous 2-methoxyethanol[7,8] required the presence of NH_4Cl. The mildly acidic medium led to low yields in the cases of 4,6-*O*-benzylidene derivatives, presumably due to partial cleavage of this function. Methylsulfonylation of the *trans*-azido hydrins resulting from epoxide cleavage and S_N2 displacement of the mesyloxy group by a second azido group led to *cis*-diazido sugars which were subsequently reduced to *cis*-diamino sugars.[9] Unfortunately, this sequence is not generally applicable because some sulfonate groups fail to react. In this paper we report some new methods and results concerning possible synthetic sequences leading from glycals to amino sugars.

Scheme I



Discussion

Bromoalkoxylations of alkenes with *N*-bromo amides in alcohols have been known for a long time.[10,11] We have

(1) (a) Partially from the M.S. thesis of T.C.T., University of the Pacific, Stockton, CA, 1972, and the Staatsprüfungsarbeit of Detlef Rebentisch, Freie Universität, West Berlin, Germany, 1979. (b) Preliminary partial versions were presented in 1974 at the 167th National Meeting of the American Chemical Society, Los Angeles, CA (No. CARB 6, on the addition reactions with 1) and in 1979 at the ACS/CSJ Chemical Congress, Honolulu, HI (No. CARB 65). (c) P.H.G. gratefully acknowledges a sabbatical grant by the University of the Pacific and a visiting professorship by Freie Universität. (d) We thank Professor H. H. Baer (Ottawa) and Professor M. J. Minch (Stockton) for valuable discussions.

(2) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199.

(3) Fischer, E.; Bergman, M.; Schotte, H. *Ber.* **1920**, *53*, 509.

(4) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1967**, *42*, 532, 1473, **1965**, *43*, 1460, 2190.

(5) Van der Werf, C. A.; Heisler, R. Y.; McEven, W. E. *J. Am. Chem. Soc.* **1954** *76*, 1231.

(6) Newth, F. H. *Q. Rev., Chem. Soc.* **1959**, *13*, 30.

(7) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1963**, 5288.

(8) Guthrie, R. D.; Prior, A. M.; Creasey, S. E. *J. Chem. Soc. C* **1970**, 1961.

(9) Guthrie, R. D.; Murphy D. *Chem. Ind. (London)* **1962**, 1473; *J. Chem. Soc. C* **1965**, 6956.

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reported[1b] that *N*-bromosuccinimide (NBS)/benzyl alcohol gave benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside (**2**) and -β-D-glucopyranoside (**3**) by trans halo benzoxylation of tri-*O*-acetyl-D-glucal (**1**; see Scheme I). Our report was apparently not noticed. Later Tatsuta et al.[12] found that the haloalkoxylation of glycals, with NBS and alcohols generally gave only one product in acetonitrile. Their paper led to several applications.[13-15] Benzyl glycosides have apparently not been prepared in this way, and our working with the undiluted alcohol was perhaps significant. Even if some benzyl alcohol became oxidized by NBS, the large excess provided for sufficient nucleophile to attack C(1) of the intermediate bromonium ion(s).[4] Rapid opening by alcohol could occur in either *trans*-diaxial or *trans*-diequatorial fashion, to give both **2** and **3** (Scheme I). A large proportion of the D-gluco configuration was observed by Tatsuta et al.[12] only with methanol as the reagent.

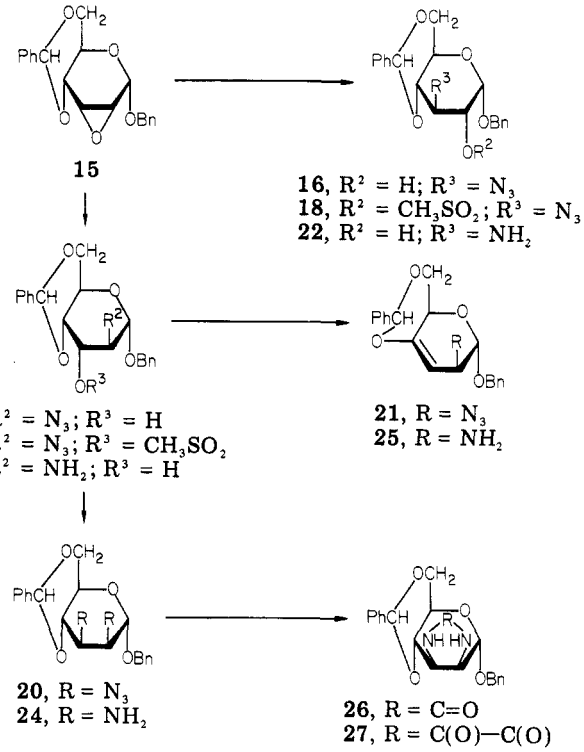
After succinimide had been precipitated by ether, the less soluble β-D-gluco isomer **3** was crystallized from ethanol. The liquid α-D-manno isomer **2** was de-O-acetylated[4] to give crystalline compound **4**. Compound **4** and any benzyl 2-bromo-2-deoxy-β-D-glucopyranoside (**5**) which at this point was still present were then isolated by fractional crystallization. From compounds **4** and **5** (2:1; 90% based on **1**) were obtained the 4,6-*O*-benzylidene derivatives (**6** and **7**, respectively) by conventional methods. The α-D-manno derivative **6** was methylsulfonylated to give **8**. The dehydrobromination and hydrazinolysis[16] of **8**, to give the hydrazone **9** and subsequently the 3-ulose derivative **10**, provide an unequivocal structure proof for the whole sequence (**2**–**10**). The keto sugar **10** had been prepared by an independent route.[17]

Similarly, the structures **3**–**7** were proved by the preparation of the β-D-manno epoxide **11** from the β-D-gluco bromohydrin **7**. This epoxide (**11**) could be *trans*-diaxially opened by the new reagent NaN_3/CO_2/hexamethylphosphoric triamide (HMPT) to give only benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranoside (**12**, 91%). The presence of CO_2 in the liquid phase appears to be necessary for a good yield. Probably HMPT at 70 °C (procedure A) is a better solvent for CO_2 than aqueous dioxane at 100 °C (procedure B). In procedure A ($HMPT/CO_2$), compound **11** was completely consumed in 1 day. Procedure C ($HMPT/N_2$) gave starting material **11** (80%) after 5 days and at least five other products, possibly by alkaline degradation of the initially formed oxyanion of **12**.

Carbon dioxide neutralizes this oxyanion by forming the much less basic carbonic acid half-ester anion. The weakly electrophilic CO_2 could also associate with the epoxide oxygen atom to reduce coulombic effects during cleavage of the epoxide C–O bond. Finally, a possibly very stable six-membered cyclic chelate of sodium ion with HMPT and CO_2 could release azide ion from ion pairs.

An attempt to prepare **12** directly from **7** (procedure D) by generating the intermediate epoxide **11** in situ with ethyldiisopropylamine had little success (**12**, 17%). The reduction of **12** with $LiAlH_4$ gave the 3-aminoaltro derivative **13**. The methylsulfonyl derivative (**14**) of **12** was treated with 10 equiv of sodium azide in HMPT (100 °C, 21 days) or Me_2SO (120 °C, 14 days). In the experiment with HMPT, **14** was reclaimed (70%); in Me_2SO at least seven products were formed.

Scheme II



Benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[18] (**15**, Scheme II) with the $NaN_3/HMPT/CO_2$ reagent gave benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (**16**) and benzyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (**17**) in a 1:6 ratio (93%). The diequatorial product (**16**) is formed from **15** by the cleavage of the O–C(3) bond. In the cleavage of **11**, any diequatorial product would have to be formed by cleavage of the O–C(2) bond, subject to the inductive effect of the anomeric center.

Compounds **16** and **17** were reduced by $LiAlH_4$ and subsequently were acetylated to give compounds **22**, **22a** and **23**, **23a**, respectively, prepared previously by independent routes.[17,18]

The methylsulfonyl derivative (**18**) of **16** did not react with NaN_3 in HMPT or Me_2SO. For a convenient large-scale preparation of the diazido sugar **20**, a mixture of the azido hydrins (**16**, **17**) was methylsulfonylated (**18**, **19**). Only the 2-azido-3-*O*-mesyl-α-D-altro derivative **19** reacted with $NaN_3/HMPT$ and gave the α-D-manno diazido sugar **20** along with some benzyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-3-hexenopyranoside (**21**). The major portion of **20** (34% based on **15**) was obtained by recrystallization. Compound **21** (10%), additional **20** (7%), and unreacted **18** (8%) could be recovered by column chromatography from the mother liquor.

Elimination reactions attending azide displacements of carbohydrate sulfonates have been described before,[19,20] especially for a configuration analogous to our compound

(10) Schmidt, E.; Knilling, W. V.; Ascherl, A. *Ber. Dtsch. Chem. Ges. B* **1926**, *59*, 1279.
(11) Winstein, S.; Henderson, R. B. *J. Am. Chem. Soc.* **1943**, *65*, 2196.
(12) Tatsuta, K.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *Carbohydr. Res.* **1977**, *54*, 85.
(13) Bischofsberger, K.; Eitelman, S. T.; Jordaan, A. *Carbohydr. Res.* **1979**, *74*, 145.
(14) Thiem, J.; Elvers, J. *Chem. Ber.* **1979**, *112*, 818.
(15) Thiem, J.; Karl, H. *Chem. Ber.* **1979**, *112*, 1046.
(16) Paulsen, H.; Stoye, D. *Chem. Ber.* **1969**, *102*, 834.
(17) Chan, W. P.; Gross, P. H. *J. Org. Chem.* **1980**, *45*, 1369.
(18) Chiu, T. Doctoral Dissertation, University of the Pacific, Stockton, CA, **1971**.
(19) Al-Radhi, A. K.; Brimacombe, J. S.; Tucker, L. C. N. *Carbohydr. Res.* **1972**, *22*, 103.
(20) Richardson, A. C.; Tarelli, E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 949.

Table I. Influences on the S_N2 Displacement of Methyl Sulfonates (Chair Forms, C_1^4)

parameter	compd 14	18	19
skew (mesyloxy conformation)[a]	S_3^1 (q)	S_5^3 (a)	S_5^1 (q)
O–C–O adjacent	–	–	0
accessibility of skew	–	+	++
parallelism of adjacent O–C–O chair	0	–	0
skew	–	0	0
parallelism of adjacent N_3 chair	–	0	–
skew	–	–	0
reaction noted	no	no	yes

[a] q = quasi and a = (pseudo)axial.

19.[21] Our byproduct **21** was assigned a 3,4-unsaturated configuration because it gave a stable amino derivative **25** after reduction. A vinylic amino group would have been lost. The ^1H NMR spectrum of **25** was assigned by comprehensive decoupling experiments. The allylic azido function in **21** is lost under the conditions of mass spectral analysis [m/e 323 (M – N_3)].

The mass spectrum of compound **19** showed a medium peak at m/e 337 (M – CH_3SO_3H – N_2), which could result from a displacement of axial methanesulfonate by the trans axial azido group. The N_2^+ group of the resulting azidonium ion[22] could be easily lost, along with a proton, to give the observed fragment. However, neither we nor others[9] observed an azidonium mechanism in solution as described by Streitwieser and Pulver.[22] The peak at m/e 337 was absent in the mass spectrum of compound **18**, which has a diequatorial arrangement of methanesulfonate and azido groups. The α-D-manno configuration for compound **20** was proven by reducing it to a crystalline diamino sugar, **24**, which formed cis-fused heterocycles **26** and **27** with *N,N'*-carbonyldiimidazole and diethyl oxalate. TLC of crude **26** and **27** showed no evidence of any of the slow-moving oligomers to be expected[23,24] from a *trans*-2,3-diamino configuration. The mass spectra of **26** and **27** gave the correct molecular weights.

The only methylsulfonyl azido hydrin which reacts with NaN_3/HMPT is compound **19**, with a 3-*O*-mesyl group; compounds **14** and **18**, which have 2-*O*-mesyl groups, are unreactive. For the low reactivity of 2-*O*-mesyl groups, an inductive effect by the anomeric center has been held responsible,[25] but other work[26,27] showed the importance of parallelism of the S_N2 transition state to adjacent dipoles, including also the O–C–O grouping at the anomeric center. β-Aldopyranosides, but not α-aldopyranosides,[28] had S_N2-reactive equatorial and axial 2-*O*-mesyl groups adjacent to an equatorial 3-methoxy group. The inertness of the axial 2-*O*-mesyl group in β-aldopyranoside **14** must then be attributed to the adjacent axial 3-azido group. However, the axial 3-*O*-mesyl group adjacent to an axial 2-azido group in α-aldopyranoside **19** is S_N2 reactive. Therefore, a consistent interpretation of the observed results was obviously impossible on the basis of the only accessible chair form (C_1^4). Boat (B) forms represent conformational energy maxima in the flexible boat–skew cycle for pyranoses[29] but the skew forms S_3^1, S_5^1, and S_5^3, with an intact chair form for the trans-fused 4,6-*O*-benzylidene ring, represent minima (Table I). Inspection of molecular models identified the most reactive skew forms as having "pseudoaxial" or "quasi" methanesulfonate groups and an easy backside access for the azide ion. Significant parallelism of polar groups to the adjacent S_N2 transition state was listed as a negative (–) influence on the proposed displacement. The accessibility of the skews was judged enhanced (+) by the bulky α-benzyl group, shifting from an axial chair position to a "quasi" position in the S_5^3 of **18** and to a pseudoequatorial position in the S_5^1 of **19**. The accessibility of the skew of **14** was judged diminished (–) by the aglycon having to switch from an equatorial chair position to a pseudoaxial posititon in the S_3^1 form of **14**. The skew forms are given in Table I, followed by the conformational assignment of the methanesulfonate nucleofuge.

On consideration of Table I and also the results of Miljkovic et al.,[28] the following hypothesis is proposed: If no adjacent dipoles are parallel to the proposed S_N2 transition state, methanesulfonate groups can be displaced from axial and equatorial chair positions and also from quasi and pseudoaxial positions in easily accessible skew conformations. For methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-mannopyranoside, which may have skew conformation S_3^1(q), without dipolar parallelism to the S_N2 transition state, Miljkovic et al.[28] noted after reaction with NaOBz/DMF many products, which could have arisen from trans elimination[16,19,20,21] or participation by the 1-methoxy group[17] in the C_4^1 chair form. Another compound, which Miljkovic et al.[28] found to be inert, is a configurational analogue of **18**.

Experimental Section

Melting point values reported in this work were determined with a melting point apparatus, Thomas-Hoover 6404H or Büchi SMP-20, and are uncorrected. Optical rotations were measured at the sodium D line with a Rudolph 956 or Perkin-Elmer 141 polarimeter at c = 1 unless stated otherwise. Infrared spectra were recorded on Perkin-Elmer infrared spectrophotometers Model 257 or 337, with KBr pellets by S. Tybussek (Berlin).

The homogeneity of all compounds was checked by thin-layer chromatography on mixtures of Merk silical gel G with silica gel GF_{254}. The compounds were detected on the plates by extinction of the UV fluorescence of a zinc silicate indicator, and also by subsequent spraying with a sulfuric acid/methanol (1:9) mixture, followed by charring at 120 °C for about 10 min. Preparative TLC separations were made on Merck precoated silica gel F_{254} plates (2 mm). The microanalyses were performed by Beller Mikroanalytisches Laboratorium, Göttingen, West Germany (compounds 2–11) or by U. Kampath and G. Witzmann, Mikroanalytisches Laboratorium (Freie Universität Berlin) with a Perkin-Elmer elemental analyzer, Model 240; NMR data (in δ) were obtained on a Varian XL-100 nuclear magnetic resonance spectrophotometer by W. Brauer, G. Dreke, and Dr. K. Roth. The mass spectra were recorded by M. Franke, B. Merten, and Dr. G. Holzmann (Freie Universität Berlin) using a Varian-MAT CH-5-DF (70 EV) spectrometer. Dr. M. Minch (Stockton) recorded and interpreted the NMR spectrum for compound **25** obtained on a 360-MHz pulsed FT Nicolet spectrometer.

Benzyl 3,4,6-Tri-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside (3). In a solution of tri-*O*-acetyl-1,2-dideoxy-D-*arabino*-1-hexenopyranose (1; 35.2 g, 0.13 mol) in benzyl alcohol (140 mL) was dissolved *N*-bromosuccinimide (23.0 g, 0.13 mol) with stirring at 30 °C. The reaction mixture was kept for 8 h at 0 °C. Excess benzyl alcohol (130 mL) was removed in vacuo (0.2 mmHg; bath temp 80 °C). The resulting syrup was dissolved in a minimal amount of diethyl ether. Crystallized succinimide (9.5

(21) Baer, H. H.; Bell, A. J. *Carbohydr. Res.* **1979**, *75*, 175.
(22) Streitwieser, A.; Pulver, S. *J. Am. Chem. Soc.* **1964**, *86*, 1587.
(23) Miyai, K.; Gross, P. H. *J. Org. Chem.* **1969**, *34*, 1638.
(24) Seymour, F. R.; Gross, P. H. *J. Org. Chem.* **1971**, *36*, 1079.
(25) Hough, L.; Richardson, A. C. *Rodd's Chem. Carbon Compd.* (*2nd Ed.*) **1967**, 448.
(26) Jennings, H. J.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 2372.
(27) Ali, Y.; Richardson, A. C. *J. Chem. Soc. C* **1969**, 320.
(28) Miljkovic, M.; Gligorijevic, M.; Glisin, D. *J. Org. Chem.* **1974**, *39*, 3223.
(29) Reeves, R. E. *Annu. Rev. Biochem.* **1958**, *27*, 15.

g, 74%) was filtered off and was washed with diethyl ether. The filtrate was evaporated in vacuo. The remaining syrup was dissolved in a minimal amount of diisopropyl ether. Scratching or seeding produced a precipitate, which was filtered off after 1 h at 5 °C and was washed with diisopropyl ether. (The filtrate and washings were kept for preparation of compound 4.) Recrystallization of the precipitate from ethanol gave 3: 17.1 g (28.6%); mp 112–113 °C; $[\alpha]^{25}$ +25° (pyridine); IR 1747 (C=O), 769, 696 (C_6H_5), 745 cm^{-1} (CBr); ^1H NMR (Me_2SO-d_6) 7.5–7.2 (m, 5 aromatic H), 5.38 (q, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 9 Hz, H^3), 4.98 (d, $J_{1,2}$ = 8.5 Hz, H^1), 4.88 (t, $J_{4,5}$ = 9 Hz, H^4), AB system H_A 4.81, H_B 4.63 (q, $J_{A,B}$ = 12 Hz, $CH_2C_6H_5$), 4.3–3.9 (m, H^5, 2 H^6), 4.02 (m, H^2), 2.02 (s, 2 CH_3CO), 1.97 (s, CH_3CO). Anal. Calcd for $C_{19}H_{23}BrO_8$ (mol wt 459.29): C, 49.69; H, 5.05; Br, 17.41. Found: C, 49.26; H, 5.18; Br, 17.75.

Benzyl 2-Bromo-2-deoxy-α-D-mannopyranoside (4). Benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside (2), obtained as a syrup by evaporation of the mother liquor of 3, was added at 0 °C slowly to a mixture of triethylamine (45.0 mL, 0.324 mol), methanol (200 mL), and water (100 mL). After 8 h at room temperature, the solution was evaporated in vacuo. For removal of AcOH and Et_3N, water was repeatedly added and was evaporated in vacuo from the syrupy residue, which was then crystallized from ethanol by addition of water. Recrystallization from methanol/water gave 11.9 of compound 4. Fractional crystallization in $EtOH/H_2O$ of the residue from the mother liquor gave 13.9 g of compound 4 and 1.1 g of compound 5. Overall, the preparation from 1 gave 25.8 g (60%) of 4: mp 111–113 °C; $[\alpha]^{23}$ +76° (pyridine); IR 3350 (OH), 695, 745 cm^{-1} (C_6H_5); ^1H NMR (Me_2SO-d_6, 60 MHz) 7.5–7.3 (m, 5 aromatic H), 5.4 (d, J = 4 Hz, CHOH), 5.2–5.0 (m, 2 H), 4.8–4.5 (m, 2 H), 4.5–4.3 (m, 1 H), 3.9–3.3 (m, 6 H). Anal. Calcd for $C_{13}H_{17}BrO_5$ (mol wt 333.18): C, 46.86; H, 5.15; Br, 23.99. Found: C, 46.76; H, 5.40; Br, 24.02.

Benzyl 2-Bromo-2-deoxy-β-D-glucopyranoside (5). Benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside (3; 14.0 g, 33 mmol) was dissolved in a stirred mixture of triethylamine (16.8 mL, 0.119 mol), methanol (120 mL), and water (50 mL) and was kept 8 h at room temperature. Evaporation in vacuo left a solid residue, from which water was evaporated repeatedly in vacuo. Crystallization from $EtOH/H_2O$ gave precipitates which were recrystallized from ethanol to give 5: 9.37 g (85.4%); mp 164–165 °C; $[\alpha]^{19}$ −5° (pyridine); IR 3470 (OH), 769, 696 (C_6H_5), 740 cm^{-1} (CBr); ^1H NMR (Me_2SO-d_6) 7.5–7.2 (m, 5 aromatic H), 5.4 (d, J = 5.5 Hz, CHOH), 5.17 (d, J = 5 Hz, CHOH), AB system H_A 4.82, H_B 4.60 (q, $J_{A,B}$ = 12 Hz, $CH_2C_6H_5$), 4.58 (d, $J_{1,2}$ = 8 Hz, H^1), 4.53 (d, J = 11, 5 Hz, CH_2OH), 3.9–3.0 (m, H^{2-5}, 2 H^6). Anal. Calcd for $C_{13}H_{17}BrO_5$: (mol wt, 333.18): C, 46.86; H, 5.15; Br, 23.99. Found: C, 46.62; H, 5.58; Br, 23.93.

Benzyl 4,6-*O*-Benzylidene-2-bromo-2-deoxy-α-D-mannopyranoside (6). Benzyl 2-bromo-2-deoxy-α-D-mannopyranoside (4; 11.9 g, 36 mmol) was dissolved in a solution of fused zinc chloride (15.0 g) in benzaldehyde (100 mL). After 12 h at room temperature, chloroform (200 mL) was added, and the resulting solution was extracted with water. The organic phase was dried over anhydrous $MgSO_4$ and was evaporated in vacuo (20 mmHg.) Excess benzaldehyde (98 mL) was removed in vacuo (0.9 mmHg; bath temperature 60 °C) on a rotary evaporator. The residual syrup, dissolved in diethyl ether (200 mL), was shaken 1 h with 20% aqueous $NaHSO_3$ (100 mL) and 1 h with saturated $KHCO_3$ (100 mL), was washed with water, was dried over anhydrous $MgSO_4$, and was evaporated in vacuo. The residue was dried in vacuo over P_2O_5 for 24 h to give, as a syrup, 14.2 g (95%) of 6. This material was homogeneous on TLC and different from 4. It was further characterized by the preparation of compound 8.

Benzyl 4,6-*O*-Benzylidene-2-bromo-2-deoxy-β-D-glucopyranoside (7). Benzyl 2-bromo-2-deoxy-β-D-glucopyranoside (5; 2.0 g, 6 mmol) was dissolved in a solution of fused zinc chloride (2.0 g) in benzaldehyde (20 mL). After 8 h at room temperature, diisopropyl ether was added until the solution became opaque. The mixture was poured on finely crushed ice with stirring. The precipitate was filtered off and was washed with water and diisopropyl ether. Addition of diisopropyl ether to the organic phase of the filtrate produced more precipitate, which was also filtered off and washed with diisopropyl ether. The combined precipitates, recrystallized from chloroform/methyl cyclohexane, gave 7: 2.3 g (89%); mp 159–160 °C; $[\alpha]^{19}$ −70° (pyridine); IR 3425 (OH), 768, 698 (C_6H_5), 748 cm^{-1} (CBr); ^1H NMR (Me_2SO-d_6) 7.5–7.1 (m; 10 aromatic H), 5.87 (d, J = 6 Hz; CHOH), 5.60 (s, C_6H_5CH), 4.86 (d, $J_{1,2}$ = 8.5 Hz; H^1), AB system H_A 4.79, H_B 4.61 (q, $J_{A,B}$ = 12 Hz, $CH_2C_6H_5$), 4.36–4.11 (m, 1 H), 3.90–3.70 (m, 5 H). Anal. Calcd for $C_{20}H_{21}BrO_5$ (mol wt 421.30): C, 57.01; H, 5.03; Br, 18.97. Found: C, 56.77, H, 5.34; Br, 19.16.

Benzyl 4,6-*O*-Benzylidene-2-bromo-2-deoxy-3-*O*-(methylsulfonyl)-α-D-mannopyranoside (8). Benzyl 4,6-*O*-benzylidene-2-bromo-2-deoxy-α-D-mannopyranoside (6; 14.2 g, 34 mmol) was dissolved in pyridine (30 mL). Methylsulfonyl chloride (5.54 ml, 72 mmol) was added with stirring at −10 °C, over a 30-min period. The mixture was kept 24 h at 0 °C and was poured on finely crushed ice. The mixture was extracted with chloroform (3 × 200 mL). The combined chloroform extracts were washed with water, with saturated aqueous $KHCO_3$, and again with water. After being dried over anhydrous $MgSO_4$, the organic phase was evaporated in vacuo. The resulting syrup, crystallized from chloroform/methyl cyclohexane, gave 8: 12.9 g (77%); mp 133–134 °C; $[\alpha]^{23}$ +16° (pyridine); IR 1360 (S=O), 700, 750 cm^{-1} (C_6H_5). Anal. Calcd for $C_{21}H_{23}BrO_7S$ (mol wt 419.46): C, 50.50; H, 4.65; Br, 16.00; S, 6.42. Found: C, 50.62; H, 4.33; Br, 15.94; S, 6.32.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (10). A mixture of benzyl 4,6-*O*-benzylidene-2-bromo-2-deoxy-3-*O*-(methylsulfonyl)-α-D-mannopyranoside (8; 2.0 g, 4.8 mmol) and anhydrous hydrazine (30 mL) was heated 4 h in a nitrogen atmosphere to 70 °C with stirring. The resulting solution was poured on finely crushed ice (200 g) and was extracted with chloroform (2 × 100 mL). The combined chloroform extracts were washed twice with water, were dried over anhydrous $MgSO_4$, and were evaporated in vacuo. The residual syrup, when treated with diethyl ether, produced a precipitate which was filtered off and was washed with diethyl ether to give the product: 1.5 g; mp 156–157 °C dec. This was presumably compound 9 (89%). Elemental analyses gave values that were too high for N and too low for C. Attempts to free compound 9 from contamination by hydrazine, which presumably caused the deviations, led to erratic analytical results, probably due to decomposition of 9.

Benzyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose hydrazone (9; 0.6 g, 1.7 mmol) was added to dioxane (30 mL), glacial acetic acid (0.2 mL, 3.5 mmol), and benzaldehyde (0.6 mL, 5.9 mmol). The mixture was stirred 2 h at room temperature. The resulting solution was evaporated in vacuo. The residual syrup was chromatographed on a column (inner diameter 1 cm, length 30 cm) of TLC silica gel G. Pure chloroform eluted a light yellow band. The eluate was evaporated to give a syrup which was crystallized from chloroform/methylcyclohexane to give 10: 0.2 g (31%); mp 164–165 °C; $[\alpha]^{23}$ +106° (pyridine); IR 1740 (C=O), 690, 750 cm^{-1} (C_6H_5). Anal. Calcd for $C_{20}H_{20}O_5$ (mol wt 340.36): C, 70.57; H, 5.92. Found: C, 69.94; H, 5.81. The compound proved to be identical by melting and mixture melting point, IR spectrum, and optical rotation with an authentic sample prepared by a different route.[17]

Benzyl 2,3-Anhydro-4,6-*O*-benzylidene-β-D-mannopyranoside (11). A solution of benzyl 4,6-*O*-benzylidene-2-bromo-2-deoxy-β-D-glucopyranoside (7; 6.0 g, 14 mmol) in dioxane (100 mL) was treated, at 20 °C with stirring, with a solution of sodium (0.78 g, 34 mmol) in 2-propanol (20 mL) for 24 h. Iced water was added. The resulting precipitate was filtered off, was washed with water, and was recrystallized from chloroform/methylcyclohexane to give 11: 4.3 g (90%); mp 189–190 °C; $[\alpha]^{19}$ −20° (pyridine); IR 1248, 918, 852 (C–O) 696, 740 cm^{-1} (C_6H_5); ^1H NMR ($CDCl_3$) 7.6–7.2 (m, 10 aromatic H), 5.57 (s, C_6H_5CH), 5.07 (d, $J_{1,2}$ = 1 Hz, H^1), AB system H_A 4.97, H_B 4.71 (q, $J_{A,B}$ = 12 Hz, $CH_2C_6H_5$), 4.4–4.2 (q, 1 H), 3.96–3.68 (m, 2 H), 3.56–3.16 (m, 3 H). Anal. Calcd for $C_{20}H_{20}O_5$ (mol wt 340.36): C, 70.57; H, 5.92. Found: C, 70.54; H, 5.80.

Benzyl 3-Azido-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranoside (12). Procedure A. Benzyl 2,3-anhydro-4,6-*O*-benzylidene-β-D-mannopyranoside (11; 7 g, 21 mmol), sodium azide (13 g, 0.2 mol), and hexamethylphosphoric triamide (HMPT, 75 mL) were stirred for 24 h at 70 °C under carbon dioxide and were poured into stirred ice (150 g). The precipitate was filtered off and was washed with water and cold methanol. Recrystallization from chloroform/methylcyclohexane, followed by recrystallization

from 2-propanol gave **12**: 7.2 g (91%); mp 157–158 °C; $[\alpha]^{23}$ –137° ($CHCl_3$); IR 3520 (OH) 2110, 1270 (N_3) 760, 700 cm^{-1} (C_6H_5); ^1H NMR ($CDCl_3$) 7.6–7.0 (m, 10 aromatic H), 5.56 (s, C_6H_5CH), 4.78 (d, $J_{1,2}$ = 1.5 Hz, H^1), AB system H_A 4.90, H_B 4.61 (q, $J_{A,B}$ = 12 Hz; $CH_2C_6H_5$), 4.45–3.6 (m, 6 H), 2.65 (s, CHOH). Anal. Calcd for $C_{20}H_{21}N_3O_5$ (mol wt 383.4): C, 62.65; H, 5.52; N, 10.96. Found (mass spectrum, *m/e* 383): C, 62.40; H, 5.68; N, 11.09.

Procedure B. Compound **11** (1 g, 3 mmol), sodium azide (0.5 g, 8 mmol) dissolved in water (5 mL), and dioxane (30 mL), were stirred 7 days at 100 °C under carbon dioxide. The mixture was then poured into stirred ice (80 g) and chloroform (20 mL). The phases were separated. The aqueous phase was extracted with chloroform (2 × 10 mL). The combined organic phases were dried over sodium sulfate and were evaporated in vacuo. The oily, yellow residue was dissolved in a small amount of diisopropyl ether. A precipitate of impure **11** forms (tlc; 5:1 (v/v) ethyl acetate/benzene; mp 180–183 °C; 0.4 g, 40%). After evaporation of the mother liquor and recrystallization of the residue as in procedure A, 0.3 g (26%) of **12** was obtained.

Procedure C. Compound **11** (1 g), sodium azide (2 g), and HMPT (15 mL) were stirred 4 days at 70 °C under *nitrogen*. The mixture was poured into stirred ice. The precipitate, after filtration, was washed as described in A. In TLC (chloroform–diisopropyl ether, 2:1 v/v) it showed at least five substances; one of these was **11**, of which 0.8 g could be reclaimed.

Procedure D. Benzyl 4,6-*O*-benzylidene-2-bromo-2-deoxy-β-D-glucopyranoside (**7**; 2.5 g, 6 mmol), sodium azide (3.9 g, 60 mmol), ethyldiisopropylamine (EDPA, 1 mL), and HMPT (7 mL) were stirred 7 days at 100 °C with exclusion of moisture. After addition of EDPA (4 mL), heating was continued for 21 days. The mixture was poured on stirred ice. The gummy precipitate was isolated by centrifugation and was dissolved in isopropyl ether. Seeding with **12** and scratching produced a gummy precipitate which was dissolved in chloroform. The solution was dried with sodium sulfate. Addition of methylcyclohexane crystallized **12**: 0.4 g (17%); mp 157–158 °C (from 2-propanol).

Benzyl 3-Amino-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranoside (13). A solution of benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranoside (**12**; 1.2 g, 3 mmol) in tetrahydrofuran (10 mL) was added slowly to a stirred suspension of $LiAlH_4$ (0.3 g, 8 mmol) in ether (10 mL) at 0 °C. After 6 h at 0 °C, aqueous KOH (40%, 8 mL) was added slowly, with cooling. When the mixture became clear, the phases were separated. The aqueous phase was extracted with tetrahydrofuran/ether (1:1; 2 × 10 mL). The combined organic phases were washed with aqueous 10% KOH, were dried over solid KOH, and were evaporated in vacuo. The residue was dissolved in a minimal amount of diisopropyl ether. At –20 °C, a colorless product crystallized which gave, after recrystallization from 1-butanol and washing with cold diisopropyl ether, **13**: 0.81 g (75%); mp 94–95 °C; $[\alpha]^{23}$ –55° ($CHCl_3$); IR 3360, 3305 (OH, NH) 1610 (NH) 755, 700 cm^{-1} (C_6H_5); ^1H NMR ($CDCl_3$) 7.7–7.2 (m, 10 aromatic H), 5.57 (s, C_6H_5CH), 5.08 (d, $J_{1,2}$ = 1 Hz, H^1), AB system H_A 4.92, H_B 4.62 (q, $J_{A,B}$ = 12 Hz, $CH_2C_6H_5$), 4.5–3.5 (m, 6 H), 2.1–1.4 (OH, NH_2). Anal. Calcd for $C_{20}H_{23}NO_5$ (mol wt 357.4): C, 67.21; H, 6.49; N, 3.92. Found (mass spectrum, *m/e* 357): C, 67.24; H, 6.52; N, 3.80.

Benzyl 3-Azido-4,6-*O*-benzylidene-3-deoxy-2-*O*-(methylsulfonyl)-β-D-altropyranoside (14). Benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranoside (**12**; 5 g, 13 mmol) was dissolved in dry pyridine (20 mL). Methylsulfonyl chloride (2.9 g, 26 mmol) was slowly added at –15 °C. After 12 h at –20 °C and 30 h at 5 °C, the mixture was poured on stirred ice (80 g). Water (100 mL) was added. The precipitate was filtered off, was washed with water and with cold methanol, was recrystallized from 1-butanol, and was washed with diisopropyl ether to give **14**: 4.8 g (80%); mp 177–178 °C; $[\alpha]^{23}$ –96° ($CHCl_3$); IR 2125, 1265 (N_3) 1360, 1177 (SO_2) 765, 700 cm^{-1} (C_6H_5); ^1H NMR ($CDCl_3$) 7.7–7.1 (m, 10 aromatic H), 5.62 (s, C_6H_5CH), 4.92 (d, $J_{1,2}$ = 1 Hz, H^1), AB system H_A 4.92, H_B 4.63 (q, $J_{A,B}$ = 12 Hz, $CH_2C_6H_5$), 4.68 (q, $J_{1,2}$ = 1 Hz, $J_{2,3}$ = 3.5 Hz, H^2), 4.5–3.5 (m, 5 H), 2.98 (s, CH_3). Anal. Calcd for $C_{21}H_{23}N_3O_7S$ (mol wt 461.5): C, 54.66; H, 5.02; N, 9.10; S, 6.95. Found (mass spectrum, *m/e* 462): C, 54.39; H, 5.07; N, 9.04; S, 7.24.

Benzyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (17) and Benzyl 3-Azido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (16). Benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**15**; 6.8 g, 20 mmol), sodium azide (13 g, 0.2 mol), and hexamethylphosphoric triamide (HMPT; 35 mL) were stirred for 5 days at 75 °C in a CO_2 atmosphere. The suspension was diluted with diisopropyl ether (200 mL) and water (100 mL) in a separatory funnel. The organic phase was washed with water (2 × 50 mL). The aqueous phases were again extracted with diisopropyl ether (2 × 80 mL) which was washed with water (2 × 20 mL). The combined diisopropyl ether solutions were dried with anhydrous Na_2SO_4 overnight at –15 °C and were evaporated. The remaining syrup (8 g) was dried by distilling benzene from it and was then directly subjected to chromatographic separation or methylsulfonylation.

Chromatography. The syrup (8 g) was dissolved in dichloromethane (100 mL). Silica gel (Woelm 63–200, for column chromatography; 70 g) and hexane (300 mL) were added. Dichloromethane and part of the hexane were evaporated in vacuo, and the slurry was put on top of a column prepared from a slurry of silica gel (250 g) in hexane after partial evaporation of the hexane in order to deaerate the silica gel. Portions (700 mL) of hexane with increasing amounts of diisopropyl ether (5%, 10%, 25%, 50%, 75%) eluted first compound **17** (6.05 g, 79%; at 25–50% diisopropyl ether) and then compound **16** (1.04 g, 14%; at 75% diisopropyl ether). Both fractions were homogeneous by TLC on silica gel (hexane/diisopropyl ether, 6:1). Compound **17**, faster moving in TLC, was a glass: $[\alpha]^{20}$ +95° ($CHCl_3$); IR 3480 (OH) 2100 (N_3) 750, 698 cm^{-1} (C_6H_5). Anal. Calcd for $C_{20}H_{21}N_3O_5$ (mol wt 383.4): C, 62.65; H, 5.52; N, 10.96. Found (mass spectrum, *m/e* 383): C, 62.98; H, 5.64; N, 10.65. Compound **16**, slower moving in TLC, was recrystallized from methyl cyclohexane: mp 135 °C; $[\alpha]^{20}$ +131° ($CHCl_3$); IR 3450 (OH), 2120 (N_3), 740, 698 cm^{-1} (C_6H_5). Anal. Found (mass spectrum, *m/e* 383): C, 62.65; H, 5.64; N, 10.94.

Benzyl 3-Azido-4,6-*O*-benzylidene-3-deoxy-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (18). Procedure A. Benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (**16**; 0.46 g, 1 mmol) in anhydrous pyridine (2 mL) was treated with distilled methylsulfonyl chloride (0.3 mL) at –10 °C. After 15 h at –10 °C and 40 h at 0 °C, the mixture was poured into a rapidly stirred mixture of ice (30 g), concentrated HCl (1.5 mL), and toluene (30 mL). The aqueous layer was separated, was extracted with toluene (10 mL), and was discarded. The combined toluene extracts were washed with water (2 × 10 mL), were dried over $CaCl_2$, were evaporated to half of their volume, and were placed on a short column of silica gel (1 g). The column was washed with toluene/CH_2Cl_2 (1:1, 20 mL), and the combined colorless effluents were evaporated in vacuo. The residue was freed of toluene by repeatedly distilling methanol from it in vacuo. Crystals were formed in methanol and were filtered off to give **18**: 0.4 g (87%); mp 104–105 °C; $[\alpha]^{22}$ +91° ($CHCl_3$); IR 2120 (N_3), 1360 (SO_3), 735, 695 cm^{-1} (C_6H_5); mass spectrum (120 °C), *m/e* 461 (w) 231, 207 (m) 151, 107, 91 (s). Anal. Calcd for $C_{21}H_{23}N_3O_7S$ (mol wt 461.5): C, 54.7; H, 5.02; N, 9.11. Found: C, 54.32; H, 5.02; N, 8.99.

Procedure B. The column from which compounds **20** and **21** had been eluted was further eluted with benzene containing increasing amounts (10%, 20%, 40%) of CH_2Cl_2. The eluates were analyzed by TLC in two systems: CH_2Cl_2/CCl_4 (1:1) and benzene/methylcyclohexane/CCl_4/diisopropyl ether (3:3:3:1). Fractions containing pure **18** were evaporated, and the residues were treated overnight with a little methanol. Crystals were filtered off, and 3.1 g of **18** (8% based on a 83-mmol total of compounds **16** and **17**) was obtained, identical with **18** obtained as in procedure A.

Benzyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(methylsulfonyl)-α-D-altropyranoside (19). Benzyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (**17**; 2.13 g, 5.5 mmol) in anhydrous pyridine (8 mL) was treated with distilled methylsulfonyl chloride (1.15 g, 12 mmol) at –10 °C overnight. After 40 h at 0 °C, the mixture was poured into a rapidly stirred suspension of ice (100 g), concentrated HCl (7 mL), and distilled toluene (80 mL). The aqueous layer was separated, was extracted with toluene (20 mL), and was discarded. The combined toluene phases were washed with water (2 × 30 mL), were dried over $CaCl_2$ (10 g), were evaporated to half of their volume, and were placed on a short column of silica gel (4 g). The column was washed with

toluene/CH_2Cl_2 (1:1, 100 mL). The combined, colorless effluents were evaporated to leave an oil (2.4 g). The oil was freed of toluene by repeatedly distilling methanol from it in vacuo. The solution of the residual oil in methanol (15 mL) was then poured on crushed ice (80 g). White crystals formed and were rapidly filtered off, together with the remaining ice. As soon as all ice had melted, the crystals were washed with ice–water, were pressed dry, and were transferred to a vial. At 20 °C and 12 mmHg, the crystals soon disintegrated and separated into a glass and water droplets, which were picked up by filter paper. Drying of the vial was then completed, first over $CaCl_2$ and then over P_2O_5, to give 2.2 g (85%) of **19** as a colorless, opaque glass: $[\alpha]^{22}$ +68° ($CHCl_3$); IR 2110 (N_3), 1365 (SO_3), 750, 700 cm^{-1} (C_6H_5); mass spectrum (160 °C), *m/e* 461, 460, 352, 337 (m), 227, 148, 107, 91 (s). Anal. Calcd for $C_{21}H_{23}N_3O_7S$ (mol wt 461.5): C, 54.7; H, 5.03; N, 9.11. Found C, 55.0: H, 5.03; N, 8.94.

Benzyl 2,3-Diazido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranoside (20). The syrupy mixture of compounds **16** and **17** (32 g, 83 mmol; from reaction of 30 g of **15** with NaN_3) was dissolved in anhydrous pyridine (100 mL) and was treated with distilled methylsulfonyl chloride (18 g, 0.16 mol) at −10 °C. The mixture was kept at −20 °C for 3 days and at 0 °C for 1 day. Ice (70 g) was added, and the mixture was shaken for 1 h and was poured into a rapidly stirred suspension of toluene (700 mL), ice (500 g), and concentrated HCl (90 mL). The organic phase was separated, and the aqueous phase was extracted with toluene (2 × 100 mL). The combined toluene solutions were washed neutral with water and were dried with anhydrous Na_2SO_4. After filtration, toluene (300 mL) was evaporated from the solution to remove traces of water, and the residual solution was poured slowly through a column, prepared from a slurry of Woelm silica gel (50 g) in toluene. The column was washed with toluene (1 L) and toluene/CH_2Cl_2(1:1, 1 L). The total eluate was evaporated to give 27 g (59 mmol, 71%) of the methylsulfonyl derivative **19** with a minor amount of **18**, as shown by TLC on silica gel (benzene/methylcyclohexane/CCl_4/diisopropyl ether, 3:3:3:1). The above mixture (**18** and **19**), HMPT (50 mL), and NaN_3 (3 × 7 g; first, fourth, and seventh day) were heated to 70 °C for 12 days with exclusion of moisture. A sample of the solution was diluted with water and was centrifuged. Water was decanted. The residue was washed with water and was dried. Starting material **19** had completely reacted as shown by TLC on silica gel, only **18** was left, and two fast moving spots had appeared. The reaction mixture was partitioned between water (200 mL) and diisopropyl ether (3 × 150 mL). The diisopropyl ether extracts were washed with water, were dried with $CaCl_2$ overnight with stirring, and were evaporated. The solution of the residual oil in hot methanol was decolorized with charcoal and was kept at −5 °C for 2 days. Compound **20** crystallized, the mother liquors were reworked, and a total yield of 12 g (29 mmol, 34% based on compound **15**) of product was obtained after recrystallization from methanol: mp 104 °C; $[\alpha]^{22}$ +93° ($CHCl_3$); IR 2105, 2140 (N_3); 700, 745 cm^{-1} (C_6H_5). Anal. Calcd for $C_{20}H_{20}N_6O_4$ (mol wt 408.4); C, 58.81; H, 4.94; N, 20.58. Found: C, 58.71; H, 5.17; N, 20.85.

Benzyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-3-hexenopyranoside (21). The methanolic mother liquors from the preparation of **20** were evaporated in vacuo. The residue, dried by distilling benzene from it, was disolved in benzene (60 mL). Silica gel (50 g) and heptane (150 ml) were added. The resulting slurry was reduced to half of its volume by evaporation in vacuo and was applied to the top of a column prepared from silica gel (500 g) which had been slurried in petroleum ether and deaerated in vacuo. Mixtures of petroleum ether with 10% benzene and increasing amounts of diisopropyl ether (10%, 20%, and 50%) eluted compound **21** as a colorless oil, which rapidly acquired a yellow tint in light at room temperature. These fractions were followed by fractions containing additional **20** (2.4 g, 7%) as shown by TLC on silica gel with petroleum ether/benzene/diisopropyl ether (7:1:2). Fractions containing pure **21** were dissolved in diethyl ether. The solutions were evaporated in a vial and dried over P_2O_5 in vacuo to give 3.0 g (10%) of **21** as a colorless oil $[\alpha]^{22}$ +331° ($CHCl_3$); IR 2110 (N_3), 1685 (C=C), 750, 700 cm^{-1} (C_6H_5); Mass spectrum *m/e* 323, 216, 197, 149, 107, 91 (s). Anal. Calcd for $C_{20}H_{19}N_3O_4$ (*m/e* 365.4): C, 65.74; H, 5.24; N, 11.50. Found: C, 65.74; H, 5.25; N, 11.39.

Benzyl 3-Amino-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (22) and the *N*-Acetyl Derivative (22a). Compound **16** (0.38 g, 1 mmol), when treated with $LiAlH_4$ as described for compound **13**, gave **22**: 0.3 g (84%); mp 161–162 °C; $[\alpha]^{22}$ +96° ($CHCl_3$); identical by melting point, IR spectroscopy and TLC (CH_2Cl_2/tetrahydrofuran, 4:1) with an authentic sample.[17] The *N*-acetyl derivatives of both samples, prepared with acetic anhydride in methanol, proved to be identical by melting and mixture melting point (237 °C); IR [3400–3290 (OH, NH), 1650, 1550 (HNCO), 740, 700 cm^{-1} (C_6H_5)], and $[\alpha]^{22}$ +83° (dioxane)].

Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (23) and the *N*-Acetyl Derivative (23a). Benzyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (**17**; 0.38 g, 1 mmol) was treated with $LiAlH_4$ as described for compound **13**. After decolorization by charcoal, the residue was recrystallized twice from anhydrous ethanol to give **23**: 0.3 g (84%); mp 158 °C. The sample was identical by melting and mixture melting point, TLC (silica gel; CH_2Cl_2/tetrahydrofuran, 4:1) IR, and optical rotation with an authentic sample prepared by Chiu:[18] $[\alpha]^{22}$ +127° ($CHCl_3$); IR 3500, 3400 (OH, NH_2), 740, 700 cm^{-1} (C_6H_5). A portion of **23** was treated with acetic anhydride in methanol to give the *N*-acetyl derivative **23a**, mp 205 °C (after recrystallization from ethanol). The sample proved to be identical by mixture melting point and IR with an authentic sample prepared by Chiu:[18] IR 3470, 3260 (OH, NH), 1675, 1550 (NHCO), 750, 700 cm^{-1} (C_6H_5).

Benzyl 2,3-Diamino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranoside (24). Benzyl 2,3-diazido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranoside (**20**; 4.08 g, 10 mmol) was reduced with $LiAlH_4$ (1.2 g, 30 mmol) as described for compound **13**. The residue was dissolved in hot benzene. The solution was filtered and was evaporated. The residue was dissolved in a minimal amount of hot benzene/ethanol (1:1), and diisopropyl ether was added to opaqueness. The mixture was rapidly stirred for 20 h and gave an initially gelatinous, later filterable precipitate of **24**: 3.3 g (93%); mp 88–89 °C; $[\alpha]^{22}$ +65° ($CHCl_3$); IR 3355 (NH), 1585 (CN), 745, 700 cm^{-1} (C_6H_5); mass spectrum 356, 265 (m), 248, 190, 149, 120, 108, 107, 105 (s). Anal. Calcd for $C_{20}H_{24}N_2O_4$ (mol wt 356.4): C, 67.39; H, 6.79; N, 7.86. Found: C, 66.83; H, 6.82; N, 7.86.

Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-3-hexenopyranoside (25) and the *N*-Acetyl Derivative (25a). Benzyl 2-azido-4,6-*O*-benzylidene-α-D-*threo*-3-hexenopyranoside (**21**; 2.7 g, 7.4 mmol) was reduced with $LiAlH_4$ (0.8 g) as described for compound **13**. After evaporation of the tetrahydrofuran/ether, the residual oil was chromatographed on silica gel with CH_2Cl_2 containing increasing amounts (1–50%) of 2-propanol. After evaporation in vacuo, the major fractions were obtained as oily residues which were extracted with boiling heptane. From the heptane, on cooling, crystallized **25**: 0.7 g (28%); mp 80 °C; $[\alpha]^{22}$ +181° ($CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) 7.8–7.3 (m, aromatic H), 5.55 (s, C_6H_5CH), 5.42 (d, $J_{3,2}$ = 5 Hz, H^3), 4.82 (s, H^1), AB system H_A 4.81, H_B 4.59 (q, $J_{A,B}$ = 12 Hz, $C_6H_5CH_2$), 4.4 (quintet, $J_{5,6}$ = 7 Hz, H^6), 3.76 (quintet, $J_{6,5}$ = 7 Hz, H^5), 3.36 (d, $J_{2,3}$ = 5 Hz, H^2). Anal. Calcd for $C_{20}H_{21}NO_4$ (mol wt 339.4): C, 70.78; H, 6.25; N, 4.13. Found: C, 70.51; H, 6.19; N, 4.13.

A small amount was dissolved in methanol and was treated with acetic anhydride and pyridine. After 24 h at 5 °C, the product was precipitated with water, which was decanted after centrifuging. Compound **25a** was redissolved in methanol, was precipitated with ice, and was filtered off. The crystals behaved very similarly to those of compound **19**, were similary dried, but gave a melting point of 165 °C and $[\alpha]^{22}$ +174 °C (c 1.5, dioxane). Anal. Calcd for $C_{22}H_{23}NO_5$ (mol wt 381.4): C, 69.27; H, 6.08; N, 3.6. Found: C, 68.88; H, 6.11; N, 3.32.

Benzyl 4,6-*O*-Benzylidene-α-D-mannopyranosido-[2,3:4′,5′]-2′-imidazolinone (26). Compound **24** (0.36 g, 1 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and was treated with *N,N′*-carbonyldiimidazole (0.2 g, 1.3 mmol) at room temperature for 24 hours. Methanol (10 mL) was added, and the mixture was evaporated to dryness in vacuo. Water (20 mL) was added, and the resulting suspension was stirred for 3 h and was filtered. The filter cake was briefly boiled with water, was dried in vacuo over $CaCl_2$, and was recrystallized, first from toluene and then from absolute ethanol, to give **26**: 0.3 g (78%); mp 201–202 °C; $[\alpha]^{22}$ −8° (*c* 1.8, dioxane); mass spectrum (195 °C), *m/e* 382

(w) 291, 207 (s). Anal. Calcd for $C_{21}H_{22}N_2O_5$ (mol wt 382.4): C, 65.96; H, 5.80; N, 7.32. Found: C, 65.88; H, 5.91; N, 7.37.

Benzyl 4,6-*O*-Benzylidene-α-D-mannopyranosido-[2,3:5′,6′]pyrazan-2′,3′-dione (27). Compound **24** (0.74 g, 2 mmol), diethyl oxalate (1.5 mL), and anhydrous ethanol (20 mL) were boiled on reflux for 20 h. Solvents were evaporated in vacuo, and the residue was treated with diisopropyl ether. The resulting crystals were filtered off and were recrystallized from hot dioxane by addition of 1 volume of tetrahydrofuran and 20 volumes of diisopropyl ether. Rapid stirring caused precipitation of an easily filterable form of **27**: 0.7 g (85%); mp 297 °C; $[\alpha]^{22}$ –60° (*c* 1.75, dioxane); mass spectrum (240–280 °C), *m/e* 410, 409 (w), 319 (m), 207, 107, 105, 91 (s). Anal. Calcd for $C_{22}H_{22}N_2O_6$ (mol wt 410.4): C, 64.38; H, 5.40; N, 6.83. Found: C, 63.84; H, 5.56; N, 6.79.

Registry No. **1**, 2873-29-2; **2**, 79698-04-7; **3**, 79698-03-6; **4**, 81625-86-7; **5**, 81625-87-8; **6**, 81625-88-9; **7**, 81625-89-0; **8**, 81625-90-3; **9**, 81625-91-4; **10**, 72869-11-5; **11**, 81625-92-5; **12**, 81625-93-6; **13**, 81625-94-7; **14**, 81625-95-8; **15**, 35905-39-6; **16**, 81625-96-9; **17**, 81625-97-0; **18**, 81625-98-1; **19**, 81625-99-2; **20**, 81626-00-8; **21**, 81626-01-9; **22**, 72869-08-0; **22a**, 81626-02-0; **23**, 72869-09-1; **23a**, 81655-20-1; **24**, 81626-03-1; **25**, 81626-04-2; **25a**, 81626-05-3; **26**, 81626-06-4; **27**, 81655-21-2; NaN_3, 26628-22-8; CO_2, 124-38-9; HMPT, 680-31-9.

Amino-Protecting Reagents: New Promising Reagents for *tert*-Butoxycarbonylation, Benzyloxycarbonylation, and [β-(Trimethylsilyl)ethoxy]carbonylation

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A new method for the preparation of *tert*-butyl- (**1d**), benzyl- (**1e**), and (β-trimethylsilyl)ethyl α-methoxyvinyl carbonates (**1f**) has been devised. The reaction of these reagents with amino compounds proceeds rapidly under mild conditions to give the corresponding *N*-*tert*-butoxycarbonylated (*N*-Boc), *N*-benzyloxycarbonylated (*N*-Z), and *N*-[β-(trimethylsilyl)ethoxy]carbonylated (*N*-Tmseoc) compounds in quantitative yields. Twenty-two examples using amines, amino alcohols, and amino acids were presented.

We have described[1] a preparation of α-methoxyvinyl carbonates (**1a–c**) and their utility for carboalkoxylation and carboaryloxylation of amines. The high reactivity of the reagents under extremely mild conditions (generally performed at 0–20 °C for 1 min–3 h) prompted us to prepare the similar introducing reagents *tert*-butyl- (**1d**), benzyl- (**1e**), and (β-trimethylsilyl)ethyl α-methoxyvinyl carbonate (**1f**) for the *tert*-butoxycarbonylation,[2,3] benzyloxycarbonylation,[2,3w,x,4] and [β-(trimethylsilyl)ethoxy]-carbonylation,[2,5] which are widely employed as useful aminoprotecting methods. However, the previous preparative method involving the reaction of bis[(carbomethoxy)-methyl]mercury with the corresponding chloroformate failed entirely to give the alkyl α-methoxyvinyl carbonates **1d–f** because of instability of the chloroformates.

We report here an efficient preparation of **1d–f** and their potential utility for amino protection.

Preparation of Alkyl α-Methoxyvinyl Carbonates 1d–f. Although direct O-carboalkoxylation of the enolate of methyl acetate with the corresponding chloroformate seems to be a simple route to the reagents **1**, complications were caused by the ambident nature of the enolate as observed in the preparation of isopropenyl carbonates.[1b] Since then, we have succeeded[1a] in the preparation of the α-methoxyvinyl carbonates (**1a–c**) involving the reaction of chlorocarbonate with bis[(carbomethoxy)methyl]mercury[6] as the enolate equivalent of methyl acetate in refluxing toluene (method A, Scheme I). However, this method suffers from many difficulties in the preparation of **1d–f** because of the instability of the chloroformate under the conditions used, the strict control of the reaction conditions needed, and the elaborate purification of the product from the reaction mixture.[7] Success was finally

(1) (a) Kita, Y.; Haruta, J.; Tagawa, H.; Tamura, Y. *J. Org. Chem.* **1980**, *45*, 4519. (b) Tamura, Y.; Haruta, J.; Okuyama, S.; Kita, Y. *Tetrahedron Lett.* **1978**, 3737.

(2) (a) Barton, J. W. In "Protective Groups in Organic Chemistry"; McOmie, J. F. W., Ed.; Plenum Press: London, 1973; Chapter 2. (b) Carpino, L. A. *Acc. Chem. Res.* **1973**, *6*, 191. (c) Shioiri, T. *Yuki Gosei Kagaku Kyokaishi* **1978**, *36*, 740. (d) Hardy, P. M. *Chem. Ind. (London)* **1979**, 617. (e) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981; Chapter 7.

(3) (a) Anderson, G. W.; McGregor, A. C. *J. Am. Chem. Soc.* **1957**, *79*, 6180. (b) Schwyzer, R.; Sieber, P.; Kappeler, H. *Helv. Chim. Acta* **1959**, *42*, 2622. (c) Klee, W.; Brenner, M. *Helv. Chim. Acta* **1961**, *44*, 2151. (d) Carpino, L. A. *J. Org. Chem.* **1964**, *29*, 2820. (e) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. (f) Jones, J. H.; Yound, G. T. *Chem. Ind. (London)* **1966**, 1722. (g) Frankel, M.; Ladkany, D.; Gilon, C.; Wolman, Y. *Tetrahedron Lett.* **1966**, 4765. (h) Broadbent, W.; Morley, J. S.; Stone, B. E. *J. Chem. Soc. C* **1967**, 2632. (i) Gross, H.; Bilk, L. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 570. (j) Fujino, M.; Hatanaka, C. *Chem. Pharm. Bull.* **1967**, *15*, 2015. (k) Schnabel, E.; Herzog, H.; Hoffmann, P.; Klauke, E.; Ugi, I. *Justus Liebigs Ann. Chem.* **1968**, *716*, 175. (l) Guibé-Jample, E.; Bram, G.; Vilkas, M. *Tetrahedron Lett.* **1969**, 3541. (m) Ragnarsson, U.; Karlsson, S. M.; Sandberg, B. E. *Acta Chem. Scand.* **1972**, *26*, 2550. (n) Bram, G. *Tetrahedron Lett.* **1973**, 469. (o) Ragnarsson, U.; Karlsson, S. M.; Sandberg, B. E.; Larsson, L. E. *Org. Synth.* **1973**, *53*, 25. (p) Nagasawa, T.; Kuroiwa, K.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269. (q) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, 4393. (r) Pozdneev, V. F.; *Khim. Prir, Soedin.* **1974**, 764; *Chem. Abstr.* **1975**, *82*, 156690. (s) Moroder, L.; Hallett, A.; Wünsch, E.; Keller, O.; Wersin, G. *Hoppe-Seyler's Z. Physiol. Chem.* **1976**, *357*, 1651. (t) Itoh, M.; Hagiwara, D.; Kamiya, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 718. (u) Paquet, A. *Can. J. Chem.* **1979**, *57*, 2775. (v) Scott, J. W.; Parker, D. *Org. Prep. Proced. Int.* **1980**, *12*, 242. (w) Kunieda, T.; Higuchi, T.; Abe, Y.; Hirobe, M. *Tetrahedron Lett.* **1980**, *21*, 3065. (x) Kunieda, T.; Abe, Y.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1981**, *22*, 1257.

(4) (a) Bergmann, M.; Zervas, L. *Ber.* **1932**, *65*, 1192. (b) Felix, A. M.; Jimenez, M. H.; Meienhofer, J. "Proceedings of the Fifth American Peptide Symposium"; Wiley: New York, 1977; p 532. (c) Paquet, A. *Can. J. Chem.* **1976**, *54*, 733. (d) Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 841.

(5) (a) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711. (b) Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358. (c) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732. (d) Carpino, L. A,; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

(6) Lutsenko, I. F.; Foss, V. L.; Ivanova, N. L. *Dokl. Akad. Nauk SSSR* **1961**, *141*, 1107; *Chem. Abstr.* **1961**, *56*, 12920*d*.

0022-3263/82/1947-2697$01.25/0