126 (11), 111 (32), 73 (34), 64 (39).

Desethyl-15-thiono-20,21-didehydro-16α-carbomethoxycleavamine Methiodide (51). A solution of 103 mg (0.300 mmol) of the thionocleavamine **45b** and 5 mL of methyl iodide in 10 mL of dichloromethane and 10 mL of benzene was stirred for 2 h, resulting in precipitation of a red methiodide and complete reaction of the thione (TLC). Concentration, trituration with ether, and drying for 30 min at 0.1 mm provided 145 mg (99%) of the unstable product, mp 170–175 °C: TLC (SiO_2, methanol–triethylamine) R_f 0.2 yellow, CAS, green; UV (ethanol) λ_{max} 228, 285, 293 nm; 270-MHz NMR ($CDCl_3$) δ 9.30 (br d, J = 3 Hz, 1 H), 9.05 (br s, 1 H), 7.50–7.40 (2d, J = 6 Hz, 2 H), 7.20 (t, J = 6 Hz, 1 H), 7.15 (t, J = 6 Hz, 1 H), 6.55 (d, J = 3 Hz, 1 H), 4.70 (m, 1 H), 3.90 (d, J = 8 Hz, 1 H), 3.80 (m, 1 H), 3.70 (s, 3 H), 3.45 (m, 1 H), 3.25–3.10 (m, 1 H), 3.70 (s, 3 H), 3.45 (m, 1 H), 3.25–3.10 (m, 3 H), 2.60 (s, 3 H), 2.50 (m, 3 H); direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 354 (M^+ – HI, 9), 322 (5), 309 (13), 228 (4), 142 (100), 127 (65).

Desethyl-15-methoxycatharanthine (49b). A solution of desethyl-15-thiono-20,21-didehydro-16α-carbomethoxycleavamine methiodide (**51**, 20 mg, 0.04 mmol) and 0.5 mL of diisopropylethylamine in 4 mL of dry methanol was heated at reflux for 40 min. Cooling, concentration under vacuum, and preparative TLC on silica gel with ethyl acetate provided 9 mg of the enol ether **49b** (70%) (R_f 0.2) and 1.5 mg (10%) of the thioenol ether **49a**, R_f 0.3. For **49b**: UV (ethanol) λ_{max} 230, 285, 293 nm; 270-MHz NMR ($CDCl_3$) δ 7.70 (s, 1 H), 7.50 (d, J = 6 Hz, 1 H), 7.25 (d, J = 6 Hz, 1 H), 7.12 (t, J = 6 Hz, 1 H), 7.10 (t, J = 6 Hz, 1 H), 5.25 (dd, J = 6, 2 Hz, 1 H), 4.45 (br d, J = 6 Hz, 1 H), 3.85 (s, 3 H), 3.55 (s, 3 H), 3.40–2.80 (m, 7 H), 2.65 (br s, 1 H), 1.85 (dd, J = 11, 2 Hz, 1 H); direct insertion probe mass spectrum, m/z (relative intensity) 338 (M^+, 60), 214 (9), 168 (21), 154 (18), 137 (100), 123 (37), 109 (55), 95 (16), 83 (23). For **49a**, see below.

Desethyl-15-*S*-methylcatharanthine (49a), Desethyl-15-ethoxycatharanthine (49c), and Desethyl-15,20-didehydro-15-*S*-methylcleavamine (52). Repetition of the preceding reaction with 35 mg (0.073 mmol) of the methiodide in 8 mL of absolute ethanol and centrifugal chromatography of the product on silica gel with ethyl acetate provided 17 mg (66%) of the thioenol ether **49a** [TLC R_f 0.2 (CAS, blue-green)] and small amounts of the ethoxy compound **49c** [R_f 0.1 (CAS, violet)] and the reduction product **52** [R_f 0.6 (CAS pink)]. For **49a**: UV (ethanol) λ_{max} 230, 285, 293 nm; IR (film) ν_{max} 3383, 3364, 2945, 2919, 2877, 2847, 1728, 1494, 1460, 1434, 1343, 1272, 1255, 1229, 1086, 744 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 7.80 (s, 1 H), 7.40 (d, J = 6 Hz, 1 H), 7.15 (d, J = 6 Hz, 1 H), 7.10 (t, J = 6 Hz, 1 H), 7.05 (t, J = 6 Hz, 1 H), 6.00 (dd, J = 5, 1 Hz, 1 H), 4.42 (br d, $J \simeq$ 5 Hz, 1 H), 3.75 (s, 3 H), 3.65–2.80 (m, 7 H), 2.65 (br s, 1 H), 2.20 (s, 3 H), 1.85 (dd, J = 10, 1 Hz, 1 H); direct inlet probe mass spectrum, m/z (relative intensity) 354 (M^+, 38), 167 (12), 153 (30), 149 (25), 139 (17), 125 (33), 111 (15), 86 (49), 84 (96), 69 (73), 57 (89), 55 (100). The enol ether **49c** structure could be tentatively assigned by comparison of the NMR spectrum with that of the corresponding methoxy compound **49b** (above). A reduction product structure **52** was tentatively assigned to the third product on the basis of one olefin and one (C-16) NMR proton signal at δ 5.65 and 5.25[23] and a mass spectrum with m/z 357 (M^+ + 1, 100%) and 355 (M^+ – 1, 80%).

Desethylcatharanthine (50). Under argon, 300 mg of Raney nickel (50% in water at pH 10–11) was washed with 5 × 10 mL of distilled water and with 4 × 10 mL of acetone and then heated at reflux for 2 h with 15 mL of acetone. The liquid phase was withdrawn and the solid catalyst washed with 5 × 10 mL of methanol and then suspended in 10 mL of methanol. Addition of 10 mg of the thioenol ether **49a** in 1 mL of methanol and heating at reflux for 30 min resulted in complete conversion to desethylcatharanthine (**50**). A longer reaction time produced the corresponding dihydro product desethylcoronaridine (mass spectrum, NMR). For desethylcatharanthine (**50**): no real mp could be observed under a microscope for a sample crystallized from ethyl acetate. Decomposition started around 160 °C (see note under *dl*-catharanthine). Reported mp 155–160 °C.[33] TLC (SiO_2, diethyl ether–triethylamine) R_f 0.30; for the thioenol ether **49a** R_f 0.35; for desethylcoronaridine R_f 0.47. Direct insertion probe mass spectrum, m/z (relative intensity) 308 (M^+, 49), 229 (12), 214 (15), 170 (8), 168 (13), 167 (9), 154 (18), 124 (8), 108 (11), 107 (100), 94 (36), 93 (28), 85 (21), 79 (23), 77 (7), 67 (20), 65 (7), 59 (8), 57 (7), 55 (10). The product gave a 270-MHz NMR spectrum which matched a 90-MHz spectrum provided by Prof. R. J. Sundberg. It had the same TLC R_f value as a comparison sample from Virginia.[33]

Acknowledgment. This work was supported by Grant R01-12010 from the National Cancer Institute of the National Institutes of Health. We thank Timothy Spitzer, Patricia Matson, and Bruce Pitner of our group for mass spectra. A valuable comparison sample of desethylcatharanthine was kindly provided by Professor R. J. Sundberg.

Synthesis of the Disaccharide Moiety of Bleomycin. 2-*O*-(3-*O*-Carbamoyl-α-D-mannopyranosyl)-L-gulopyranose Derivatives

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Received January 14, 1986

The synthesis of the carbohydrate moiety of bleomycin [2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose] is described. A key parameter in defining a successful strategy was the lability of the carbamoyl group. Several approaches were investigated; the most successful involved the coupling of 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-β-L-gulopyranose (**19**) and 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl chloride (**17**) via the agency of silver trifluoromethanesulfonate and tetramethylurea. Also reported is the synthesis of 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-gulopyranose (**16**), a dissacharide useful for the synthetic elaboration of decarbamoyl bleomycin.

Our continuing interest in the synthesis of bleomycin group antibiotics[1] necessitated the synthesis of the carbohydrate moiety of bleomycin [2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (**1**)] on a preparative scale and in a form suitable for further elaboration. The successful synthesis of **1**[1b] required access to suitably blocked derivatives of L-gulose[2] and to activated 3-*O*-

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(1) (a) Minster, D. K.; Hecht, S. M. *J. Org. Chem.* **1978**, *43*, 3987. (b) Pozsgay, V.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 3761. (c) Aoyagi, Y.; Katano, K.; Suguna, H.; Primeau, J. L.; Chang, L.-H.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5537.

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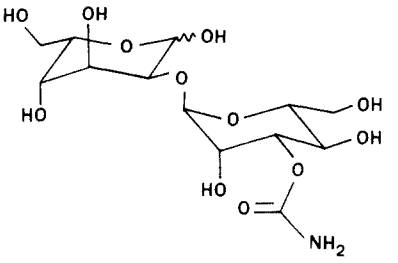


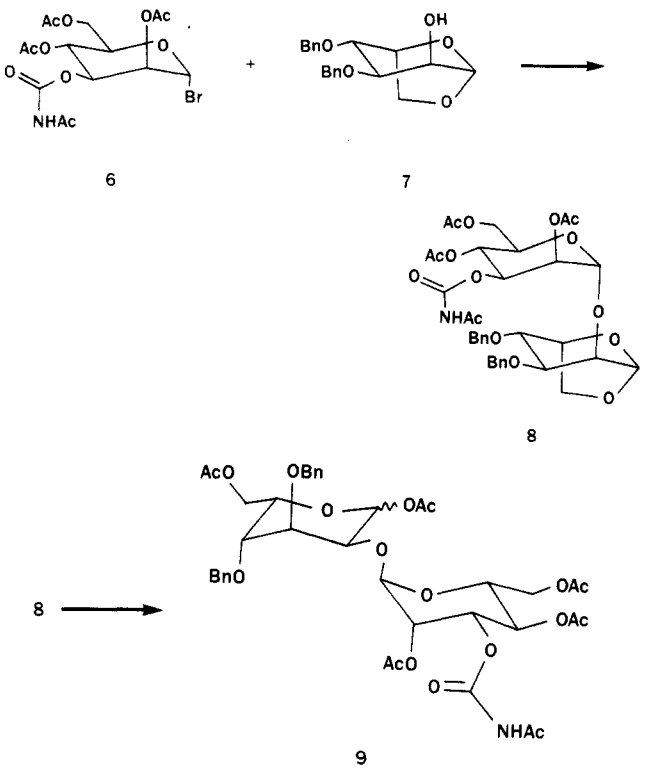
1

carbamoyl-D-mannose derivatives,[3] the preparations of which have been reported. Herein we describe the synthesis of the disaccharide moiety of bleomycin as well as several protected derivatives potentially useful for further elaboration to bleomycin and bleomycin congeners that can help to define the mechanism of action of this group of antibiotics.

Results and Discussion

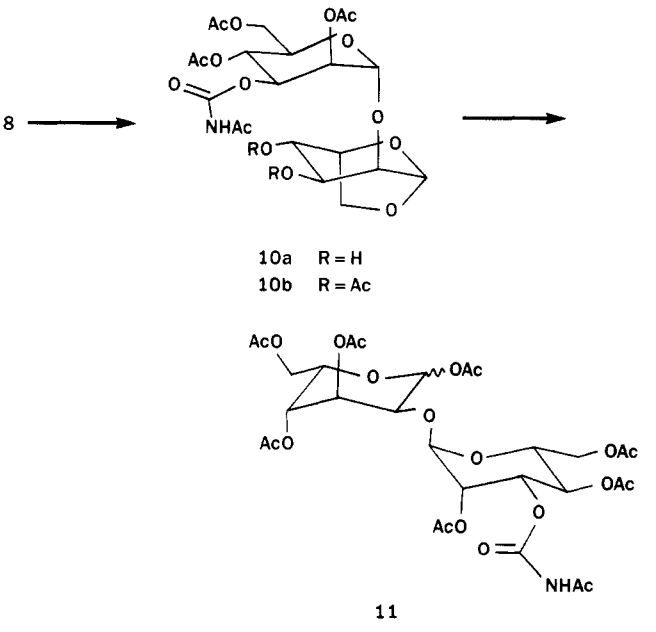
Incorporation of the dissaccharide moiety into the bleomycin molecule involves the regio- and stereospecific incorporation of L-erythro-β-hydroxyhistidine at O-1 of the L-gulose moiety. The configuration required at O-1 is α, i.e., involving 1,2-cis glycosylation.[4] Because a nonparticipating protecting group would logically be required at O-2 to permit access to the requisite configuration at O-1, either of two synthetic strategies seemed possible. The first of these (Scheme I, route a) would provide an L-gulose derivative, e.g., **2**,[1] containing a nonparticipating alkyl group on O-2. Thus glycosylation with an appropriately blocked β-hydroxyhistidine derivative would be expected to give a 1,2-cis glycoside (**3**); deprotection at O-2 and condensation with an appropriate mannopyranosyl halide[3] could then be expected to provide **5**. Alternatively (route b), initial deprotection at O-2 and condensation with the mannosyl halide would provide a disaccharide (**4**) containing a mannose group at O-2 of L-gulose. Glycosylation of the disaccharide at O-1 of the L-gulose moiety would again be expected to provide the requisite 1,2-cis glycoside (**5**). Initial investigation of these two routes quickly established that route b was preferred.[5]

Coupling of the readily available (acetylcarbamoyl)-mannosyl bromide **6** with anhydro-L-gulose derivative **7** (AgOTf, $(CH_3)_2NCON(CH_3)_2$)[6] gave disaccharide **8** in 68% yield. That the mannose glycosyl bond had the α-configuration was indicated by the magnitude of the coupling constant observed for the anomeric proton of mannose (δ 4.89, $J_{1,2}$ ~1 Hz). While further synthetic elaboration of the disaccharide clearly required solvolysis of the 1,6-anhydro linkage, no difficulty was envisaged in view of the relatively mild procedures available for such transformations.[2,7] In fact, treatment of disaccharide **8** with Ac_2O/HOAc (0 °C, catalytic H_2SO_4) provided **9** in 98% yield as a 1:5 mixture of α and β anomers, respectively.



6 7 8 9

Alternatively, hydrogenation of **8** over 10% palladium on carbon provided debenzylated disaccharide **10a**. Peracetylated disaccharide **11** was then obtained via acetylation (**10a** → **10b**) and acetolysis of the 1,6-anhydro linkage. The ratio of α:β anomers was ~1:5, as indicated by ^{1}H NMR (δ 5.88, $J_{1,2}$ = 8.4 Hz, β anomer; δ 6.28, $J_{1,2}$ = 4.4 Hz, α anomer).



10a R = H
10b R = Ac

11

Alternatively, coupling[6] of benzyl 3,4,6-tri-*O*-benzyl-β-L-gulopyranoside (**12**) with **6** provided the expected disaccharide **13** in 82% yield after chromatographic purification. The structure of **13**, including the assignment of anomeric configuration of the mannose and gulose moieties, was confirmed by ^{1}H and ^{13}C NMR.[8] Decoupling studies permitted the assignment of all ^{1}H resonances in

(2) Katano, N.; Chang, P.-I.; Millar, A.; Pozsgay, V.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1985**, *50*, 5807.

(3) Millar, A.; Kim, K. H.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1986**, *51*, 189.

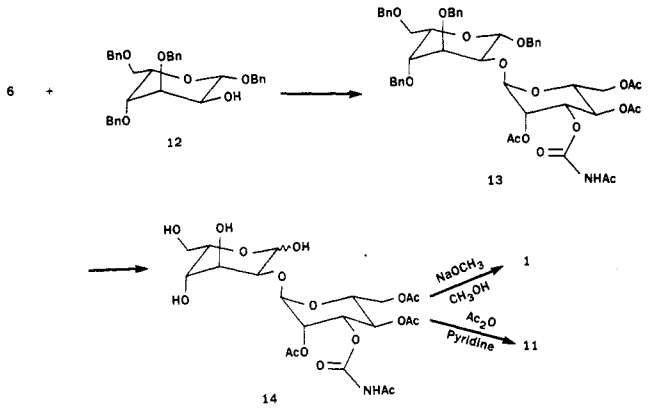
(4) Bochkov, A. F.; Zaikov, G. E. In *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*; Pergamon Press: Oxford, 1979.

(5) Investigation of route a indicated that the conversion **2** → **3** proceeded satisfactorily but that further conversion to **5** did not.

(6) Hanessian, S.; Banoub, J. *Methods Carbohydr. Chem.* **1980**, *8*, 247.

(7) Černaý, M.; Staněk, J. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23 and references therein.

(8) Perlin, A. S. In *MTP International Review of Science, Carbohydrates, Organic Chemistry Series Two*, Vol. 7; Aspinall, G. O., Ed.; Butterworths: London, 1976; pp 1–35.

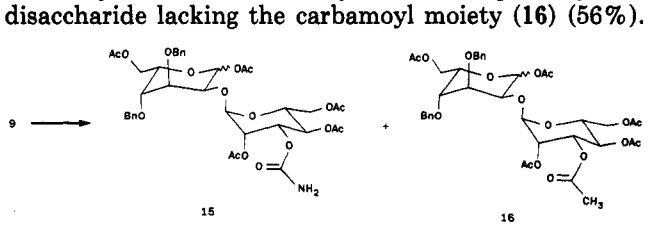


13; the H-1 of mannose (δ 4.70) had $J_{1,2}$ ~1 Hz, while the analogous value for the anomeric proton of gulose (δ 4.94) was $J_{1,2}$ = 8.1 Hz. The anomeric configurations were also confirmed by the ^{13}C resonances: mannose C-1 resonated at δ 93.97 ($J_{C\text{-}1,H\text{-}1}$ = 173.3 Hz), gulose C-1 at δ 98.19 ($J_{C\text{-}1,H\text{-}1}$ = 163.6 Hz). Hydrogenolysis of **13** over 10% palladium-on-carbon provided debenzylated disaccharide **14** in 62% yield.

Although methanolysis of the *N*-acetyl group proved not to be routinely feasible (vide infra), treatment of **14** with catalytic sodium methoxide in CD_3OD resulted (NMR monitoring) in N- and O-deacetylation within 25 min; workup provided deblocked disaccharide **1** in 96% yield. Because **1** was identical with the disaccharide moiety reported for bleomycin, it was instructive to compare the mannose H-3 resonance in **1** (δ 5.13, J = 8.1, 3.6 Hz) with that reported for the natural product (δ 5.20, J = 9, 3 Hz).[9] The agreement between these values provided support for the assigned structure of bleomycin as well as the integrity of the carbamoyl moiety in **1** following deacetylation. Acetylation of **14** provided peracetylated disaccharide **11**, identical in all respects with the sample obtained from **8** (vide supra), with the exception of the anomeric ratio of C-1 of gulose. This finding confirmed the α-D-mannosyl configuration of **8**.

Subsequent investigations using other *N*-acetylcarbamoyl disaccharides[1c] indicated that the carbamoyl moiety was relatively labile,[3] which often resulted in the generation of mixtures of products. Accordingly, the N-deacetylation of the model disaccharide (**9**) was studied in detail.

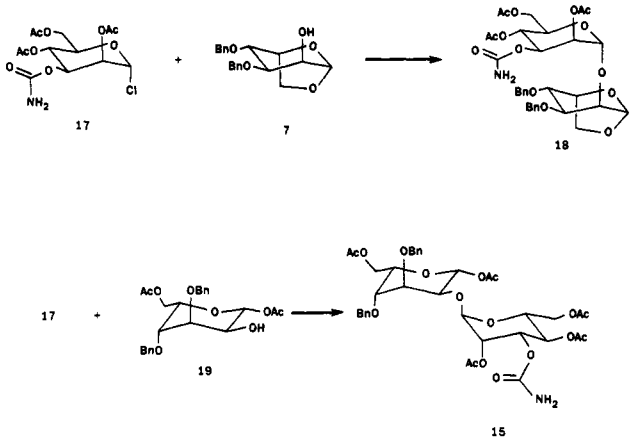
Treatment of **9** with alumina in benzene under conditions found to effect N-deacetylation selectively in a related case[3] resulted in significant material loss but little detectable N-deacetylation. Treatment of **9** with catalytic sodium methoxide in methanol (25 °C, 1 h) followed by O-acetylation (Ac_2O, pyridine) gave two products as indicated by TLC. Following chromatographic purification, these were identified by ^1H NMR as the desired 3-O-carbamoyl derivative **15** (44% yield) and the peracetylated disaccharide lacking the carbamoyl moiety (**16**) (56%).



Interestingly, treatment of **15** with catalytic sodium methoxide in methanol also provided **15** and **16** after subsequent O-acetylation, but the ratio of **15**:**16** was 10:1. This was consistent with the greater reactivity that might be expected for the N-acetylated carbamoyl group.

The lack of selectivity obtained during methanolysis of the disaccharides suggested the need for a modified synthetic strategy. Thus, 3-*O*-carbamoylmannopyranosyl chloride (**17**)[3] was coupled with 1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**7**) using silver trifluoromethanesulfonate and tetramethylurea; the desired disaccharide was obtained as a foam in 54% yield following chromatographic purification. However, solvolysis of the 1,6-anhydro bridge (Ac_2O, H_2SO_4) gave concomitant N-acetylation. Other solvolytic methods[7] employed for related transformations gave mixtures of **18** and N-acetylated product (e.g., Ac_2O–HOAc; Ac_2O–BF_3·Et_2O) or else complex mixtures (e.g., $(CH_3OCH_2)_2$–H_2O–H_2SO_4; $(CH_3OCH_2)_2$–H_2O–$ZnCl_2$; HOAc–H_2O–$Cu(OAc)_2$; CF_3COOH).

The difficulties encountered in the solvolysis of **18** prompted investigation of the obvious alternative, i.e., coupling of **17** with a monocylic gulose derivative (**19**)[2,10] to obviate the need for subsequent solvolysis. The coupling of **17** and **19** was accomplished in 64% yield;[6] with the exception of the anomeric configuration of the gulose moiety, this material was identical with a sample of **15** derived from **9**.



Also investigated was the preparation of a disaccharide that could serve as a precursor for the synthesis of decarbamoyl bleomycin,[12] an analog of interest in defining the metal binding properties of bleomycin. This required the synthesis of a 2-*O*-(α-D-mannopyranosyl)-L-gulopyranose derivative.[13] The specific target molecule of interest, 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-gulopyranose (**16**), was easily accessible on a preparative scale by coupling mannopyranosyl chloride **20**[14] with 1,6-anhydrogulopyranose

(9) Omoto, S.; Takita, T.; Maeda, K.; Umezawa, H.; Umezawa, S. *J. Antibiot. (Tokyo)* **1972**, *25*, 752.

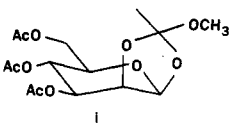
(10) Gulose derivative **19** was prepared[2] from the 1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulose (**7**) by the use of an allyl group to protect O-2. Recently, we have found that the use of a trichloroethoxycarbonate group[11] improved the overall yield of the transformation **7** → **19** from 50% to 78%.

(11) Green, T. W. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1981.

(12) Naganawa, H.; Muraoka, Y.; Takita, T.; Umezawa, H. *J. Antibiot. (Tokyo)* **1977**, *30*, 388.

(13) Tsuchiya, T.; Miyake, T.; Kageyama, S.; Umezawa, S.; Umezawa, H.; Takita, T. *Tetrahedron Lett.* **1981**, *22*, 1413.

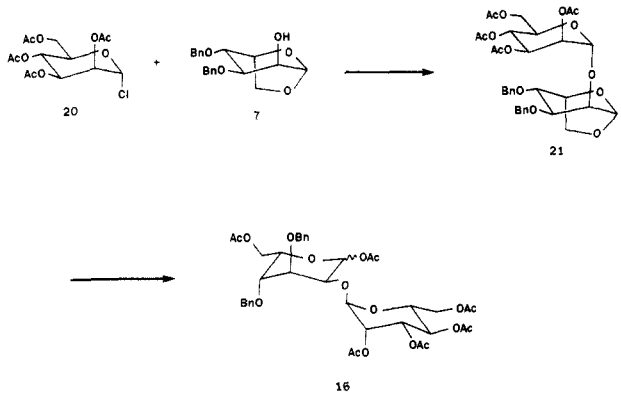
(14) Prepared from the readily available orthoester **i**[15] by treatment with trimethylsilyl chloride.[16]



i

(15) Franks, N. E.; Montgomery, R. *Carbohydr. Res.* **1968**, *6*, 286.

derivative 7. Disaccharide 21 was isolated as colorless



needles in 64% yield and was converted to 16 in 92% yield via the agency of Ac_2O–HOAc–H_2SO_4. The product had the same properties as the sample of 16 obtained from 9. This independent preparation of 16 provided additional support for the structures of the disaccharides reported here, verified the carbamoyl group as the source of difficulty in obtaining selectivity in certain of the transformations discussed, and provided quantities of a key intermediate that facilitated the total synthesis of decarbamoylbleomycin.[17]

Experimental Section

Elemental analyses were carried out by Chemalytics, Inc., or by Atlantic Microlab, Inc. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer. UV spectra were obtained on a Cary Model 15 recording spectrophotometer. Mass spectra were recorded on Perkin-Elmer Hitachi RMU-6, Varian MAT-44 or Finnigan MAT-4500 Series GC/MS mass spectrometers. NMR spectra were determined on Varian T-60, Varian EM-390, or Nicolet NT-360 NMR spectrometers. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter.

1,6-Anhydro-3,4-di-*O*-benzyl-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-β-L-gulopyranose (8). A solution of 1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (0.50 g, 1.46 mmol) (7) in 5 mL of dichloromethane containing 0.48 g (4.18 mmol) of tetramethylurea and 0.75 g (2.92 mmol) of silver trifluoromethanesulfonate was added at 0 °C to a stirred solution containing 1.3 g (2.86 mmol) of 2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl bromide (6) in 5 mL of dichloromethane. The reaction mixture was stirred at 25 °C for 12 h and filtered through Celite. The filtrate was washed with water (3 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on a 60-g silica gel column; elution with 1:1 ethyl acetate–hexane provided 1,6-anhydro-3,4-di-*O*-benzyl-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-β-L-gulopyranose (8) as a colorless syrup, yield 0.71 g (68%): $[\alpha]^{25}_D$ −78.6° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.07 (s, 3), 2.08 (s, 3), 2.11 (s, 3), 2.43 (s, 3), 3.59 (dd, 1, *J* = 7.5, 3.6 Hz, H-6), 3.73 (dd, 1, *J* = 8.5, 3.6 Hz, H-3), 3.81 (m, 1, H-2), 3.92 (dd, 1, *J* = 8.5, 3.5 Hz, H-4), 4.02 (d, 1, *J* = 7.5 Hz, H-6), 4.08–4.28 (m, 3, H-5′,6′), 4.44 (m, 1, H-5), 4.56–4.83 (m, 4), 4.89 (d, 1, *J* = ~1 Hz, H-1′), 5.23 (t, 1, *J* = 9 Hz, H-4′), 5.31 (dd, 1, *J* = 9.0, 3.5 Hz, H-3′), 5.43 (m, 2, H-1,2′), 7.24–7.42 (m, 10).

Anal. Calcd for $C_{35}H_{41}NO_{15}·0.5H_2O$: C, 57.99; H, 5.84. Found: C, 57.92; H, 5.99.

1,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-L-gulopyranose (9). Dibenzyl ether 8 (1.77 g, 2.42 mmol) was dissolved in 20 mL of 3:1 acetic anhydride–acetic acid and treated with 0.2 mL of concentrated sulfuric acid at 0 °C for 1 h with stirring. The solution was poured into an ice–water mixture and extracted with ethyl acetate. The organic phase was washed with water, saturated aqueous $NaHCO_3$, and water, then dried ($MgSO_4$), and concentrated by codistillation with portions of toluene. The resulting colorless syrup was purified by flash chromatography[18] on silica gel (100-g column); elution was with 3:2 ethyl acetate–toluene. Dibenzylated disaccharide 9 was obtained as a colorless foam, yield 1.98 g (98%): ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) (β anomer) δ 2.00 (s, 3), 2.06 (s, 3), 2.08 (s, 3), 2.14 (s, 3), 2.20 (s, 3), 2.43 (s, 3), 3.48 (m, 1, H-4), 3.93 (m, 1, H-3), 3.99 (dd, 1, *J* = 8.3, 2.5 Hz, H-2), 4.06–4.30 (m, 6, H-5′,5,6′,6), 4.34–4.70 (m, 4), 4.77 (d, 1, *J* = 1.5 Hz, H-1′), 5.16–5.34 (m, 3, H-2′,3′,4′), 6.03 (d, 1, *J* = 8.3 Hz, H-1), 7.16–7.45 (m, 10); (α anomer) δ 6.24 (d, 1, *J* = 3.0 Hz, H-1), α:β ~ 1:5.

Anal. Calcd for $C_{39}H_{47}NO_{18}$: C, 57.26; H, 5.79. Found: C, 57.15; H, 5.82.

1,6-Anhydro-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-β-L-gulopyranose (10a). A solution of 0.4 g (0.56 mmol) of dibenzyl ether 8 in 40 mL of ethanol and 1 mL of acetic acid was hydrogenated over 50 mg of 10% palladium-on-carbon (1 atm H_2) for 24 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated. The residue was purified by chromatography on a 10-g silica gel column; elution with 3:1 benzene–CH_3OH provided 1,6-anhydro-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-β-L-gulopyranose (10a) as a colorless foam, yield 0.2 g (67%): ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.06 (s, 3), 2.07 (s, 3), 2.14 (s, 3), 2.37 (s, 3), 2.96 (d, 1, exchangeable with D_2O), 3.16 (br s, 1, exchangeable with D_2O), 3.62 (dd, 1, *J* = 7.6, 4.8 Hz, H-6), 3.65–3.80 (m, 2, H-3,4), 3.86 (m, 1, H-2), 4.01 (d, 1, *J* = 7.8 Hz, H-6), 4.17 (m, 2, H-6′), 4.27 (m, 1, H-5′), 4.45 (m, 1, H-5), 4.94 (d, 1, *J* < 1 Hz, H-1′), 5.18–5.27 (m, 2, H-3′,4′), 5.43 (m, 1, H-2′), 5.59 (d, 1, *J* = 1.7 Hz, H-1), 7.75 (br s, 1, exchangeable with D_2O).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-L-gulopyranose (11). A solution of 0.16 g (0.30 mmol) of 1,6-anhydro-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-β-L-gulopyranose (10a) in 3 mL of pyridine was treated with 3 mL of acetic anhydride at 25 °C for 24 h. The solvent was removed under diminished pressure by codistillation with portions of toluene to provide the peracetate (10b) as a colorless syrup, yield 177 mg (95%): ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.08 (s, 9), 2.13 (s, 3), 2.15 (s, 3), 2.41 (s, 3), 3.72 (m, 2), 4.05–4.31 (m, 4), 4.65 (t, 1), 4.83 (br s, 1, H-1′), 5.08–5.42 (m, 5), 5.55 (d, 1, *J* = 2.0 Hz, H-1), 7.98 (br s, 1, exchangeable with D_2O).

Crude peracetate 10b was treated with 6 mL of acetic anhydride and 0.3 mL of concentrated sulfuric acid at 25 °C for 15 h. The reaction mixture was poured into an ice–water mixture and extracted with ethyl acetate. The organic extract was washed with saturated aqueous $NaHCO_3$ and saturated brine, then dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on a 30-g silica gel column; elution with 1:1 ethyl acetate–hexane provided peracetylated disaccharide 11 as a colorless glass, yield 0.142 g (66%): $[\alpha]^{25}_D$ +13.9° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) (β anomer) δ 2.04 (s, 6), 2.10 (s, 3), 2.12 (s, 6), 2.14 (s, 3), 2.18 (s, 3), 2.38 (s, 3), 3.97 (dd, 1, *J* = 8.4, 2.4 Hz, H-2), 4.04–4.25 (m, 5, H-5′,6′,6), 4.34 (m, 1, H-5), 4.99 (m, 2, H-1′,4), 5.05 (dd, 1, *J* = 10.1, 3.1 Hz, H-3′), 5.13 (dd, *J* = 3.1, 1.7 Hz, H-2′), 5.26 (t, 1, *J* = 10.1 Hz, H-4′), 5.43 (dd, 1, *J* = 3.8, 2.4 Hz, H-3), 5.88 (d, 1, *J* = 8.4 Hz, H-1), 7.28 (br s, 1, exchangeable with D_2O); (α anomer) δ 6.28 (d, 1, *J* = 4.4 Hz, H-1), α:β ~ 1:5.

Anal. Calcd for $C_{29}H_{39}NO_{20}·H_2O$: C, 47.07; H, 5.59. Found: C, 46.96; H, 5.40.

Benzyl 3,4,6-Tri-*O*-benzyl-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-β-L-gulopyranoside (13). A solution containing 0.3 g (0.55 mmol) of benzyl 3,4,6-tri-*O*-benzyl-β-L-gulopyranoside (12) and 1.4 g (3.08 mmol) of 2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl bromide (6) in 20 mL of dichloromethane was treated with 0.51 g (4.43 mmol) of tetramethylurea and 0.75 g (2.92 mmol) of silver trifluoromethanesulfonate at 25 °C for 16 h. The reaction mixture was filtered and the filtrate was washed with 5 mL of 5% aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on a 40-g silica gel column;

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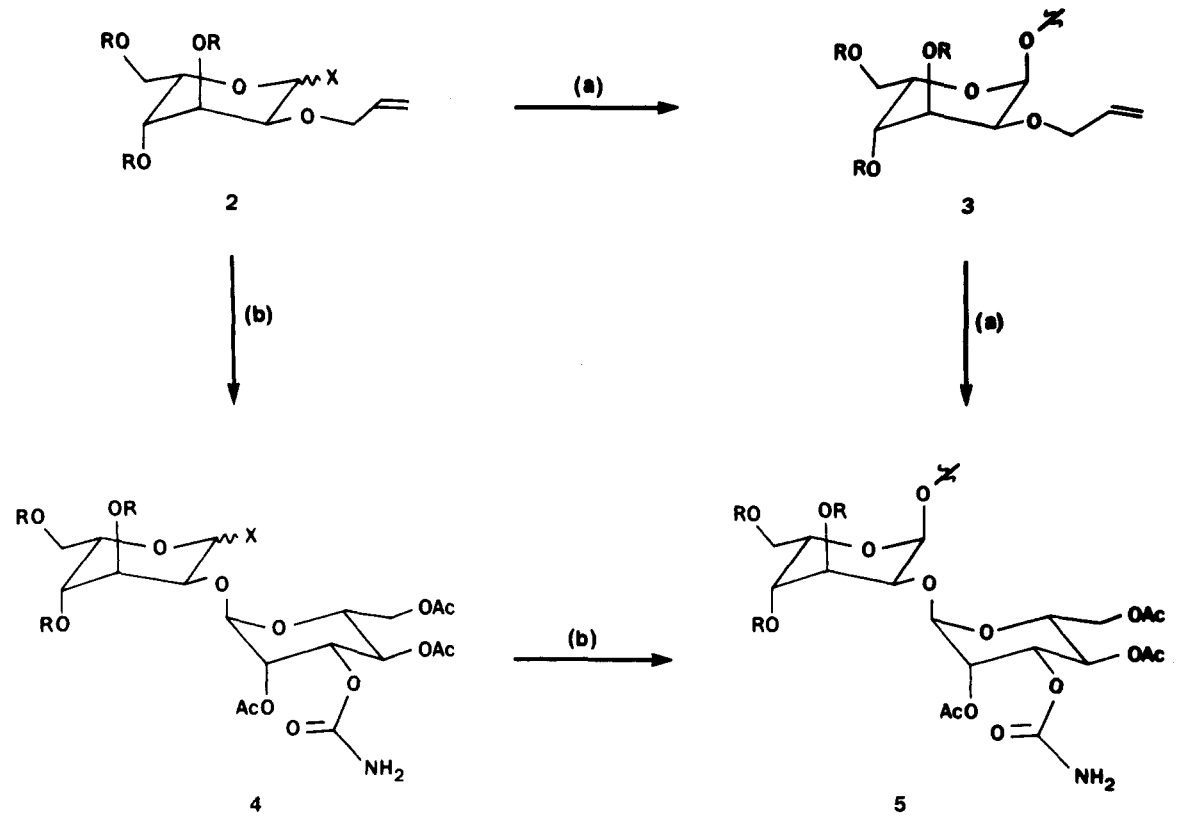
(17) Katano, K.; Hecht, S. M., unpublished results.
(18) Still, W. C.; Kahn, J.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme I



elution with 2:1 hexane–ethyl acetate provided benzyl 3,4,6-tri-*O*-benzyl-2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-β-L-gulopyranoside (**13**) as a colorless syrup, yield 0.41 g (82%): $[\alpha]^{25}_D$ +46.6° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.97 (s, 3), 2.02 (s, 3), 2.17 (s, 3), 2.44 (s, 3), 3.56 (br d, 1, *J* = 3.65 Hz, H-4), 3.60 (dd, 1, *J* = 9.6, 6.9 Hz, H-6), 3.66 (dd, 1, *J* = 9.6, 6.2 Hz, H-6), 3.72–3.78 (m, 2, H-3,6′), 3.89 (dd, 1, *J* = 8.1, 3.1 Hz, H-2), 3.93 (dd, 1, *J* = 12.8, 3.3 Hz, H-6′), 4.16 (m, 1, H-5), 4.28 (m, 1, H-5′), 4.39–4.58 (m, 7), 4.70 (br s, 1, H-1′), 4.93 (d, 1, *J* = 12.3 Hz), 4.94 (d, 1, *J* = 8.1 Hz, H-1), 5.20 (br d, 1, H-2′), 5.22–5.30 (m, 2, H-3′,4′), 7.15–7.38 (m, 20); ^{13}C NMR ($CDCl_3$) δ 20.58, 20.77, 23.88, 61.11, 64.94, 68.00, 68.53, 69.50, 71.01, 71.35, 71.49, 71.74, 71.93, 72.80, 73.29, 73.87, 93.97 ($J_{C\text{-}1',H\text{-}1'}$ = 173.3 Hz), 98.19 ($J_{C\text{-}1,H\text{-}1}$ = 163.6 Hz), 127.55, 127.75, 127.84, 127.94, 128.23, 137.26, 137.45, 137.81, 150.51, 169.54, 169.88, 170.36, 171.57.

Anal. Calcd for $C_{49}H_{55}NO_{16}\cdot 2H_2O$: C, 61.93; H, 6.26. Found: C, 62.20; H, 6.18.

2-*O*-[2,4,6-Tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-L-gulopyranose (14). A solution of 0.3 g (0.33 mmol) of tetrabenzylated disaccharide **13** in 2 mL of ethanol was hydrogenated (1 atm H_2) over 10% palladium-on-carbon for 14 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated. The crude product was purified by chromatography on a 50-g silica gel column; 3:1 benzene–CH_3OH effected elution of 2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-L-gulopyranose (**14**), which was isolated as a colorless amorphous solid following concentration of the appropriate fractions, yield 0.11 g (62%): $[\alpha]^{25}_D$ +48.5° (*c* 0.55, CH_3OH); ^1H NMR (CD_3OD, $(CH_3)_4Si$) δ 2.05 (s, 6), 2.11 (s, 3), 2.19 (s, 3), 3.30 (m, 3), 3.48–4.33 (m, 6), 4.99 (m, 2), 5.35 (m, 3); mass spectrum (FAB), *m/z* 553 (M^+).

Anal. Calcd for $C_{21}H_{31}NO_{16}\cdot 0.5H_2O$: C, 44.82; H, 5.73. Found: C, 44.82; H, 5.93.

2-*O*-(3-*O*-Carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (1). To 30 mg (50 μmol) of tetraacetylated disaccharide **14** in 3.5 mL of CD_3OD was added ~0.5 mg of sodium methoxide. The reaction mixture was placed in an NMR tube and the course of the reaction was monitored by ^1H NMR. After 25 min, the N- and O-acetyl signals had disappeared and the reaction mixture was treated with Dowex 50 (H^+ form), filtered, and concentrated. 2-*O*-(3-*O*-Carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (**1**) was isolated as an amorphous solid, yield 20 mg (96%): $[\alpha]^{25}_D$ +65.8° (*c* 0.5, H_2O); ^1H NMR (D_2O) δ 5.13 (dd, 1, *J* = 8.1, 3.6 Hz, H-3′) (cf. δ 5.20 (dd, 1, *J* = 9, 3 Hz, H-3′)[9]); mass spectrum (FAB), *m/z* 385 (M^+).

Anal. Calcd for $C_{13}H_{23}NO_{12}\cdot 2H_2O$: C, 37.04; H, 6.46. Found: C, 36.77; H, 6.68.

Acetylation of 2-*O*-[2,4,6-Tri-*O*-acetyl-3-*O*-(acetylcarbamoyl)-α-D-mannopyranosyl]-L-gulopyranose (14). Tetraacetate **14** (27 mg, 50 μmol) was dissolved in 1.5 mL of pyridine and treated with 1.5 mL of acetic anhydride. The reaction mixture was maintained at 25 °C for 24 h and then concentrated under diminished pressure. The residue was treated with ice for 1 h, then combined with 5 mL of chloroform, and washed successively with 1 mL each of 5% aqueous H_2SO_4, water, 5% aqueous $NaHCO_3$, and water. The dried (Na_2SO_4) chloroform layer was concentrated to provide peracetylated disaccharide **11** as an amorphous solid, yield 35 mg (99%); with the exception of the anomeric ratio (α:β ~ 1:4), this material was identical in all respects with that obtained from **8**.

Methanolysis and Acetylation of Disaccharide 9. Disaccharide **9** (90 mg, 0.11 mmol) was treated with a catalytic amount of sodium methoxide in methanol (2 mL) at 25 °C for 1 h. The reaction mixture was neutralized with Dowex 50 (H^+ form), then filtered, and concentrated. The residue was treated with 3 mL of acetic anhydride and 5 mL of pyridine at 25 °C for 3 h and then concentrated by codistillation of portions of toluene. The residue was purified by flash chromatography[18] on an 8-g silica gel column; successive elution with 1:1 and then 3:2 ethyl acetate–toluene provided 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-gulopyranose (**16**) as a colorless syrup, yield 49 mg (56%): ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.00 (s, 6), 2.02 (s, 3), 2.05 (s, 3), 2.11 (s, 3), 2.18 (s, 3), 3.48 (m, 1, H-4), 3.82–4.32 (m, 8, H-2,3,5,5′,6,6′), 4.36–4.71 (m, 4), 4.75 (d, 1, *J* = 2 Hz, H-1′), 5.08–5.47 (m, 3, H-2′,3′,4′), 6.02 (d, 0.84, *J* = 8.0 Hz, H-1, β anomer), 6.25 (d, 0.16, *J* = 3.0 Hz, H-1, α anomer), 7.20–7.50 (m, 10).

Anal. Calcd for $C_{38}H_{46}O_{17}\cdot H_2O$: C, 57.55; H, 6.10. Found: C, 57.75; H, 5.99.

Further elution of the column with 3:2 ethyl acetate–toluene gave 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (**15**) as a colorless foam, yield 38 mg (44%): $[\alpha]^{25}_D$ +27.4° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) (β anomer) δ 1.99 (s, 3), 2.07 (s, 3), 2.08 (s, 3),

2.13 (s, 3), 2.20 (s, 3), 3.45 (m, 1, H-4), 3.95 (m, 1, H-3), 3.99 (dd, 1, J = 8.0, 3.0 Hz, H-2), 4.05–4.30 (m, 6, H-5,5′,6,6′), 4.33 (d, 1, J = 12.5 Hz), 4.47 (d, 1, J = 12.5 Hz), 4.54 (d, 1, J = 12.0 Hz), 4.68 (br s, 2, exchangeable with D_2O), 4.73 (d, 1, J = 12.0 Hz), 4.82 (d, 1, J < 1 Hz, H-1′), 5.20–5.30 (m, 3, H-2′,3′,4′), 6.02 (d, 1, J = 8.0 Hz, H-1), 7.2–7.4 (m, 10); (α anomer) δ 6.25 (d, 1, J = 3.0 Hz, H-1), $\alpha:\beta \sim 1:5$.

Anal. Calcd for $C_{37}H_{45}NO_{17}$: C, 57.27; H, 5.85. Found: C, 57.23; H, 5.96.

Methanolysis and Acetylation of Disaccharide 15. Disaccharide **15** (48 mg, 0.06 mmol) was treated with a catalytic amount of sodium methoxide in methanol (1 mL) at 25 °C for 20 min. The reaction mixture was neutralized with Dowex 50 (H^+ form), then filtered, and concentrated. The residue was treated with 1 mL of acetic anhydride and 1 mL of pyridine at 25 °C for 3 h and then concentrated by codistillation of portions of toluene. The residue was purified by flash chromatography[18] on a 5-g silica gel column; elution with 1:1 toluene–ethyl acetate gave 4 mg of compound **16** and 40 mg of **15**. Both compounds were identical with the same materials derived from **9**.

1,6-Anhydro-3,4-di-*O*-benzyl-2-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl)-β-L-gulopyranose (18). 1,6-Anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**7**) (126 mg, 0.37 mmol) and silver trifluoromethanesulfonate (0.19 g, 0.74 mmol) were dried under vacuum and then dissolved in 2 mL of dichloromethane containing 0.16 g (1.4 mmol) of tetramethylurea. The combined solution was cooled to 0 °C under N_2 and then treated with a solution containing 0.27 g (0.74 mmol) of 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl chloride (**17**) in 2 mL of dichloromethane. The reaction mixture was stirred at 25 °C under N_2 for 10 h, diluted with dichloromethane, and filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. Chromatographic purification (silica gel) provided 1,6-anhydro-3,4-di-*O*-benzyl-2-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl)-β-L-gulopyranose (**18**) as a colorless foam, yield 133 mg (54%): $[\alpha]^{25}_D$ +4.8° (*c* 6.6, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.07 (s, 6), 2.13 (s, 3), 3.58 (dd, 1, J = 8.0, 5.0 Hz, H-6), 3.70 (dd, 1, J = 8.5, 3.6 Hz, H-3), 3.77 (m, 1, H-2), 3.94 (dd, 1, J = 8.5, 4.0 Hz, H-4), 4.01 (d, 1, J = 8.0 Hz, H-6), 4.07–4.30 (m, 3, H-5′,6′), 4.44 (m, 1, H-5), 4.55–4.82 (m, 6, 2 H exchangeable with D_2O), 4.87 (d, 1, J < 1 Hz, H-1′), 5.21 (t, 1, J = 9.5 Hz, H-4′), 5.31 (dd, 1, J = 9.5, 3.0 Hz, H-3′), 5.39 (m, 1, H-2′), 5.44 (d, 1, J = 3.0 Hz, H-1), 7.24–7.37 (m, 10).

1,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl)-β-L-gulopyranose (15). 1,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-L-gulopyranose (**19**) (0.67 g, 1.5 mmol) and silver trifluoromethanesulfonate (0.86 g, 3.4 mmol) were dried under vacuum, dissolved in a mixture of 4 mL of dichloromethane and 0.68 g (5.9 mmol) of tetramethylurea, and cooled to 0 °C. This solution was treated dropwise at 0 °C with a solution containing 1.12 g (3.1 mmol) of 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl chloride (**17**) in 10 mL of dichloromethane. The reaction mixture was stirred at 25 °C for 18 h and then filtered through Celite. The filtrate was concentrated and the residue was purified by flash chromatography[18] on silica gel (120-g column); elution with 1:1 toluene–ethyl acetate provided disaccharide **15** as a colorless foam, yield 0.76 g (64%). This material was identical in all respects to putative **15** derived from disaccharide **9**, with the exception of anomeric ratio.

1,6-Anhydro-3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-β-L-gulopyranose (21). 1,6-Anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**7**) (1.58 g, 4.6 mmol) and silver trifluoromethanesulfonate (2.5 g, 9.7 mmol) were dried under vacuum, dissolved in a mixture of 3 mL of dichloromethane and 1.45 g (12.5 mmol) of tetramethylurea, and cooled to 0 °C. This solution was treated dropwise at 0 °C with 3.4 g (9.3 mmol) of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl chloride (**20**) in 6 mL of dichloromethane. The reaction mixture was stirred at 25 °C for 14 h and then filtered through Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel (300-g column); elution with 3:1 toluene–ethyl acetate provided disaccharide **21** as a colorless foam which deposited colorless needles from ether, yield 1.98 g (64%): mp 150–152 °C; $[\alpha]^{25}_D$ +8.6° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.00 (s, 3), 2.05 (s, 3), 2.08 (s, 3), 2.12 (s, 3), 3.59 (dd, 1, J = 7.6, 4.7 Hz, H-6), 3.71 (dd, 1, J = 9.7, 4.3 Hz, H-3), 3.80 (dd, 1, J = 4.3, 2.5 Hz, H-2), 3.94 (dd, 1, J = 9.7, 4.7 Hz, H-4), 4.02 (d, 1, J = 7.6 Hz, H-6), 4.08–4.26 (m, 3, H-5′,6′), 4.44 (m, 1, H-5), 4.56–4.83 (m, 4), 4.85 (d, 1, J = 1.5 Hz, H-1′), 5.23 (t, 1, J = 10.4 Hz, H-4′), 5.37 (dd, 1, J = 3.6, 1.5 Hz, H-2′), 5.41 (dd, 1, J = 10.4, 3.6 Hz, H-3′), 5.44 (d, 1, J = 2.5 Hz, H-1), 7.25–7.35 (m, 10).

Anal. Calcd for $C_{34}H_{10}O_{14}$: C, 60.69; H, 5.99. Found: C, 60.60; H, 5.94.

1,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-gulopyranose (16). 1,6-Anhydro-3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-β-L-gulopyranose (**21**) (1.88 g, 2.8 mmol) in 20 mL of 3:1 acetic anhydride–acetic acid was treated with 0.2 mL of concentrated sulfuric acid at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then poured into an ice–water mixture and extracted with ethyl acetate. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$ and water, then dried ($MgSO_4$), and concentrated. Anomeric acetate **16** was obtained as a colorless foam, yield 1.99 g (92%). This compound was homogeneous on silica gel TLC (development with 2:1 toluene–ethyl acetate gave R_f 0.4) and had the same ^1H NMR as putative **16** derived from **9**.

Acknowledgment. This work was supported by PHS Grant CA27603, awarded by the National Cancer Institute, DHHS.

Stereocontrolled Synthesis of 2-Deoxycrustecdysone and Related Compounds

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Received December 17, 1985

The synthesis of 2-deoxycrustecdysone has been accomplished from pregnenolone. The key reaction is based on successful stereochemical control at C-20 and C-22 involving the stereoselective reduction of lactone **23**, derived from 20-oxosteroid **20** and 2-lithiofuran, to give γ-butyrolactone **25** having a (20*R*,22*R*)-20,22-diol functionality. 5-Epi-2-deoxymakisterone A, 5,24-epi-2-deoxymakisterone A, and 24-epi-2-deoxymakisterone A were also synthesized by application of the same sequence.

Much attention[1] has been paid to the stereocontrolled synthesis of the physiologically active steroids such as ecdysone, antheridiol, brassinolide, and withanolide. Previously, we developed a new transformation of 20-

0022-3263/86/1951-2932$01.50/0