occurred. Products were isolated by filtration, rinsing with methylene chloride and washing the filtrate with 10% hydrochloric acid to remove the amine. After drying with anhydrous magnesium sulfate the solution was concentrated and the residue was either distilled or recrystallized.

The properties of products prepared and the means of identification employed are listed in Table II which will appear only in the microfilm edition of this journal.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of the research.

Registry No.—*trans*-methyl 2-hexenoate, 13894-63-8; *cis*-methyl 2-hexenoate, 13894-64-9; Pd, 7440-05-3; TE formate, 585-29-5; TB formate, 7204-61-7.

Supplementary Material Available: Table II, listing the properties of the products prepared (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) N. A. Cortese and R. F. Heck, *J. Org. Chem.*, **42**, 3491 (1977).
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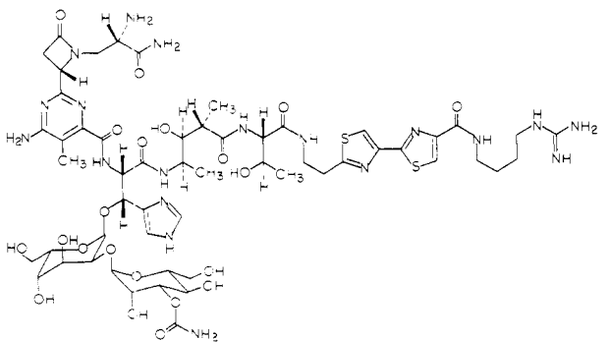
Communications

Synthesis of L-Gulose from D-Glucose via Aldose Interchange

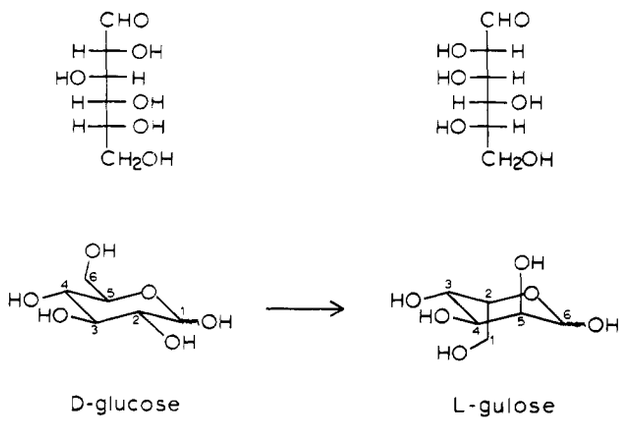
Summary: L-Gulose has been prepared from D-glucose in a form suitable for reconstruction of bleomycin.

Sir: Bleomycin (1) is an antitumor antibiotic possessing clinically useful activity in the treatment of squamous cell carcinomas.[1] Our interest in the total synthesis of bleomycin B_2 (1) has prompted us to consider practical methods for



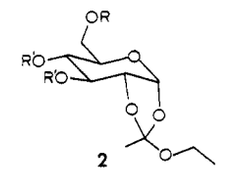
1

preparation of the rare sugar L-gulose in a form suitable for synthetic elaboration of the carbohydrate moiety of bleomycin. Since gulose must be attached stereoselectively to L-*erythro*-β-hydroxyhistidine and 3-*O*-carbamoylmannose via O-1 and O-2, respectively, the sugar must be prepared in a form that permits O-1 and O-2 to be differentiated from each other, and from O-3, O-4, and O-6, in subsequent synthetic transformations. Therefore, while syntheses of L-gulose have been reported,[2] none of these was suitable for our purposes; we report herein an efficient synthesis of an appropriate L-gulose derivative.



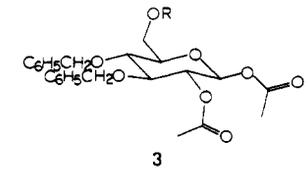
D-glucose L-gulose

Fischer recognized the conceptually simple relationship between the readily available D-glucose and L-gulose, which differ only in oxidation state at C-1 and C-6, and utilized this principle for the preparation of L-gulose from D-glucaric acid in low yield by successive reductions with sodium amalgam.[2a] In the present case, more direct interconversion has been achieved by oxidation of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-D-glucopyranose (**3b**) to the corresponding 6-aldehydo sugar [isolated as the respective *N,N*-dimethylhydrazone (**4**)] and subsequent borohydride reduction of the latent dialdehyde with sodium borohydride, affording the desired 3,4-di-*O*-benzyl-1-(*N,N*-dimethylhydrazino)-L-gulopyranose (**5**) as a clear oil in 42% overall yield from D-glucose. Verification of structure was accomplished by conversion to 1,6-anhydro



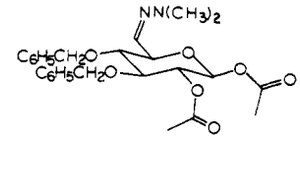
2

a R,R′ = $COCH_3$
b R = $C(C_6H_5)_3$, R′ = H
c R = $C(C_6H_5)_3$, R′ = $CH_2C_6H_5$



3

a R = $C(C_6H_5)_3$
b R = H



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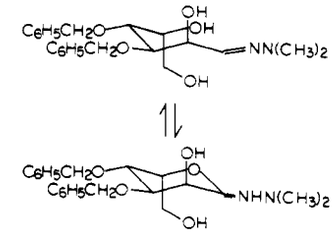

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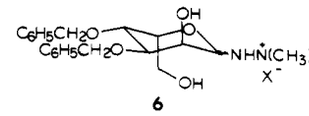

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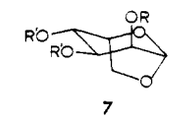

7

a R = H, R′ = $CH_2C_6H_5$
b R, R′ = $COCH_3$
c R, R′ = H

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sugars **7b** and **7c**, the optical antipodes of which are known species.[3]

Glucopyranosyl diacetate **3b**, obtained in 80% overall yield from **2a** (→ **2b** → **2c** → **3a** → **3b**),[4] was chosen as the substrate for terminal functionality interchange to provide a suitably blocked L-gulose derivative. Initial efforts to effect oxidation at C-6 (e.g., with $SO_3 \cdot C_6H_5N$, Me_2SO,[5] or pyridinium chlorochromate[6]) gave unstable products reactive with dinitrophenylhydrazine, in addition to benzaldehyde.[7] Analysis by NMR suggested major structural alterations, including possible epimerization at C-5 as well as loss of the well-defined signals corresponding to the anomeric and acetate methyl protons.[8] To obviate the loss of the acetate moieties, which would render chemically indistingishable the aldehyde groups at C-6 and C-1, a less acidic oxidant was employed. Thus **3b** was treated with *N*-chlorosuccinimide–dimethyl sulfide[9] (4 h, −25 °C) to give a chromatographically homogeneous, albeit unstable product [IR 1710 cm^{-1}; NMR δ 1.93 (s, 3), 2.05 (s, 3), and 9.59 (s, 1)] which was immediately converted to the respective *N,N*-dimethylhydrazone (**4**)[10] [1 equiv of $(CH_3)_2NNH_2$, 2 equiv of $(C_2H_5)_3N$, 25 °C, 18h], isolated as colorless needles in 66% yield (based on **3b**): mp 146–147 °C; $[\alpha]^{25}_D$ +56° (*c* 3.3, $CHCl_3$); NMR [$CDCl_3$, $(CH_3)_4Si$] δ 1.94 (s, 3), 2.07 (s, 3), 2.85 (s, 6), 3.6–4.3 (envelope, 3), 4.75 (m, 4), 4.93–5.30 (m, 1), 5.72 (d, 1), 6.28 (d, 1), and 7.33 (s, 10).

Transformation of diacetate **4** to 2,2-dimethylhydrazinyl 3,4-di-*O*-benzyl-L-gulopyranoside (**5**) may be envisioned via removal of the acetates and reduction of the C-1 aldehyde. Although consideration of the intermediates involved in the conversion **4** → **5** suggests a number of possible competing processes,[11] treatment of **4** with catalytic $NaOCH_3$ (48 h, 25 °C) effected deacetylation without epimerization at C-5 or C-2.[12] The diol thus obtained was reduced with $NaBH_4$ (1 equiv, C_2H_5OH–H_2O) and the product was isolated as a chromatographically homogeneous white foam in quantitative yield (based on **4**) by extractive workup of the residue remaining after concentration of the reaction mixture; the product consisted of a 70:30 equilibrium mixture of hydrazino glycoside–acyclic hydrazone, as judged by NMR:[13] [$CDCl_3$, $(CH_3)_4Si$] δ 2.42 (s, 0.6), 2.49 (s, 3.6), 2.72 (s, 1.8), 3.1–4.1 (envelope, 7), 4.3–5.0 (envelope, 5), 6.73 (d, 0.3, J = 5 Hz), and 7.3 (s, 10).

Confirmation of the D-glucose → L-gulose transformation was obtained by conversion of species **5** (→ **6** → **7a** → **7b** → **7c**)[4] to crystalline 1,6-anhydro gulose derivatives **7b** and **7c**, the optical antipodes of which have been prepared and characterized.[3] The facile preparation of gulose derivatives **5** and **6**[14] provides intermediates of potential utility for elaboration of the carbohydrate moiety of bleomycin and establishes an efficient procedure for (formal) carbohydrate epimerizations by functionalization of nonchiral carbon atoms.

Acknowledgments. We thank Dr. Ki-Hyup Kim and Mr. Daniel Lieberman for assistance with optimization of certain synthetic transformations. This investigation was supported in part by contract NO1-CM 43712 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

Supplementary Material Available: Details of the conversion of **2a** to **3b** and **5** to **7b** and **7c** (3 pages). Ordering information is given on any current masthead page.

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(2) (a) E. Fischer and O. Piloty, *Ber. Dtsch. Chem. Ges.*, **24**, 521 (1891); (b) K. Heyns and M. Beck, *Chem. Ber.*, **91**, 1720 (1958); (c) R. L. Whistler and J. N. BeMiller, *Methods Carbohyd. Chem.*, **1**, 137 (1962); (d) M. E. Evans and F. W. Parrish, *Carbohyd. Res.*, **28**, 359 (1973).
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(5) W. v. E. Doering and J. R. Parikh, *J. Am. Chem. Soc.*, **89**, 5505 (1967). The reagent is reported to be of utility for the oxidation of carbohydrates [G. M. Cree, D. W. Mackie, and A. S. Perlin, *Can. J. Chem.*, **47**, 511 (1969)].
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(8) The latter changes probably occurred as a consequence of the Lewis acid catalyzed conversion of the 1,2-diacetate to an acetoxonium ion.
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(11) E.g., loss of stereochemistry at C-2 via the Lobry de Bruyn-Alberda van Ekenstein transformation (E. F. L. J. Anet in "The Carbohydrates. Chemistry and Biochemistry", Vol. IA, W. Pigman and D. Horton, Eds., Academic Press, New York, N.Y., 1972, pp 175 ff) and at C-5 in analogy with the putative intermediates in the Amadori rearrangement [J. E. Hodge, *Adv. Carbohyd. Chem.*, **10**, 169 (1955)], the latter of which could also result in transformation to an acyclic C-5 keto sugar.
(12) The integrity of these stereochemical centers may be inferred from the lack of significant alteration of the chemical shifts of the methylhydrazinyl (δ 2.78) and C-6 (δ 6.33) hydrogens and of the coupling constant (J = 5 Hz) of the latter, as well as the observed coupling constant (J = 3 Hz) between the equational anomeric hydrogen and the C-2 hydrogen [R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966)].
(13) Assigned by consideration of the chemical shifts of the hydrazino methyl signals and C-1 hydrogen: the singlet at δ 2.72 represented 30% of the integrated intensity corresponding to the methyl hydrogens; the doublet at δ 6.73 (J = 5 Hz) constituted one-sixth of this, suggesting that these signals were attributable to the acyclic hydrazone [G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3923 (1968)]. The remaining integrated intensity appeared as singlets at δ 2.49 and 2.42 (6:1) and was attributed to the hydrazinylglycoside (**5**).
(14) The facile displacement of trimethylhydrazine from **6** suggests the possible utility of this compound (or some suitable O-6-substituted derivative) in the preparation of the carbohydrate moiety of bleomycin.
(15) National Cancer Institute Postdoctoral Trainee, 1975–1977.
(16) National Cancer Institute Career Development Awardee, 1975–1980. Alfred P. Sloan Research Fellow, 1975–1979. John Simon Guggenheim Fellow, 1977–1978.

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