Synthesis of the Carbohydrate Moiety of Bleomycin. 1,3,4,6-Tetra-O-substituted L-Gulose Derivatives

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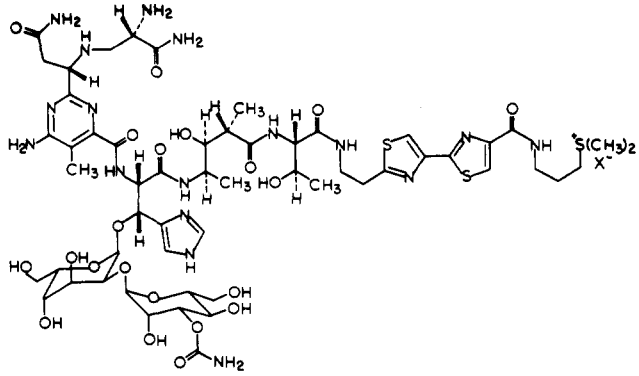
Received May 21, 1985

To facilitate the synthesis of the carbohydrate moiety of bleomycin [2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose] and its subsequent attachment to the remainder of the bleomycin molecule in a regio- and stereoselective fashion, a number of suitably protected gulose derivatives were prepared and their chemistry was studied. Key intermediates included 1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**12**), 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-β-L-gulopyranose (**24**), benzyl 3,4,6-tri-*O*-benzyl-β-L-gulopyranoside (**27**), and 3,4-di-*O*-benzyl-1,6-dideoxy-1,6-(1-hydrazinyl-2-ylidene)-β-D-glucodialdehydo-1,5-pyranose (**28**).

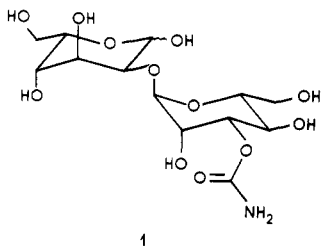
The bleomycins are a family of glycopeptide-derived antitumor antibiotics used for the treatment of certain malignancies; bleomycin A_2 is the major constituent of the clinically used mixture of bleomycins.[1] Ongoing synthetic



bleomycin A_2

studies of bleomycin group antibiotics have permitted verification of the proposed structure, as well as elaboration of bleomycin congeners useful in probing the chemistry and mode of action of this class of molecules.

Structurally, the carbohydrate moiety of bleomycin is composed of 3-*O*-carbamoyl-D-mannose and L-gulose, and the availability of quantities of each is essential for synthetic studies of the bleomycins.[2] Further, the synthesis of the carbohydrate moiety of bleomycin, 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (**1**), requires



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an L-gulose derivative suitably protected for subsequent regio- and stereoselective attachment of L-*erythro*-β-hydroxyhistidine and 3-*O*-carbamoyl-D-mannose to O-1 and O-2, respectively. Herein we describe the requisite L-gulose derivatives and synthetic strategies useful for their preparation.

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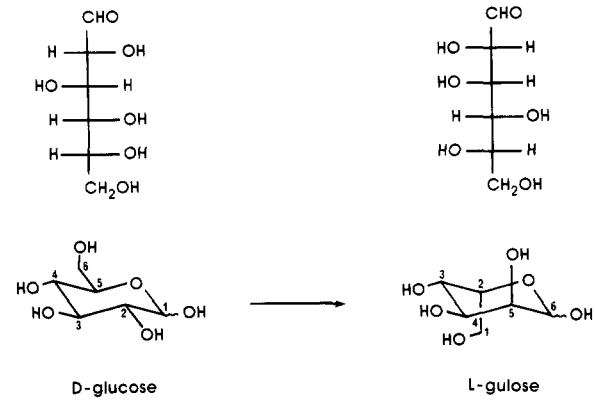
Scheme I. Relationship between D-Glucose and L-Gulose



D-glucose L-gulose

Results and Discussion

Although L-gulose itself has been prepared by a number of different procedures,[3] our protecting group requirements suggested that an alternative route leading directly to an appropriately protected L-gulose derivative might prove of significant advantage for synthesis of the carbohydrate moiety of bleomycin. Our initial route took advantage of the structural relationship between readily available D-glucose and L-gulose (Scheme I).[2a,3a] Clearly, suitable alteration of C-1 and C-6 oxidation states in a di-O-3,4-protected D-glucose derivative could afford the requisite (di-O-3,4-protected) L-gulose derivative efficiently.

Accordingly, D-glucose was converted to the known triacetyl ortho ester derivative **2** (Scheme II).[4] Deacety-

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(4) (a) Lemieux, R. U. *Methods. Carbohydr. Chem.* **1963**, *2*, 221. (b) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**; *43*, 2199.

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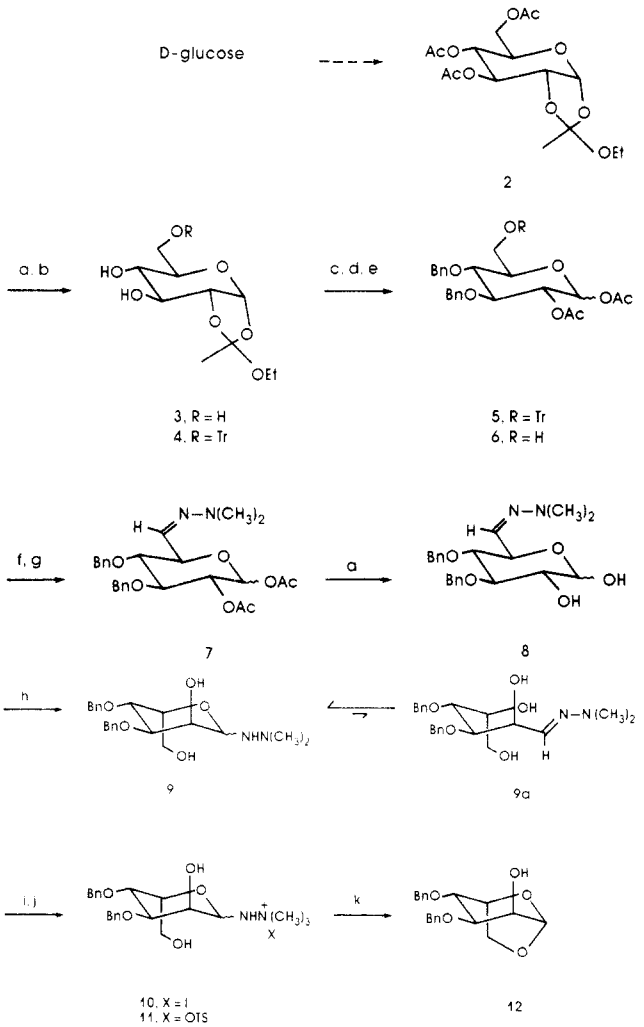
Scheme II[a]



[a] (a) $NaOCH_3$, CH_3OH, 25 °C; (b) $(C_6H_5)_3CCl$, DMF, $(i\text{-}C_3H_7)_2NC_2H_5$, 25 °C; (c) (i) NaH, glyme, 30 min, 0 °C; (ii) $C_6H_5CH_2Br$, 24 h, 0 °C → 25 °C; (d) HOAc, 1.5 h, 25 °C; (e) 80% aqueous HOAc, THF, 5 h, 50 °C; (f) *N*-chlorosuccinimide, $(CH_3)_2S$, Et_3N, toluene, −25 °C → 25 °C; (g) $(CH_3)_2NNH_2$, CH_3OH, 18 h, 25 °C; (h) $NaBH_4$, C_2H_5OH/H_2O, 24 h, 25 °C; (i) CH_3I, THF; (j) $AgOSO_2C_6H_4CH_3$, CH_3OH; (k) $CH_3C_6H_4SO_3H$, glyme, 4.5-h reflux.

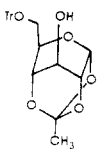
lation of **2** ($NaOCH_3$, CH_3OH) and tritylation of O-6[5] provided ortho ester **4**, which was benzylated (NaH and then $C_6H_5CH_2Br$, 0 → 25 °C) in glyme. The crude 3,4-di-O-benzyl ortho ester was converted directly to the 1,2-di-O-acetate (anhydrous HOAc). The anticipated trans configuration of the acetyl groups in **5** was confirmed by the ^1H NMR spectrum ($J_{1,2}$ = 8 Hz);[6] in addition the same product was obtained when di-O-benzyl **4** was treated with NaOAc–lutidinium perchlorate under conditions known[6d] to give trans diacetates. Selective removal of the trityl group was achieved either by treatment with aqueous acetic acid (83% yield) or by application of a benzene solution of **5** to a dry silica gel column (95% yield).[7]

Oxidation of **6** was attempted by each of several procedures employed routinely in carbohydrate chemistry,[8] but all of these resulted in complex mixtures. The use of pyridinium chlorochromate[8c,e] also gave a complex reaction mixture having the strong, distinctive odor of benzaldehyde.[9] In the belief that the complex mixtures resulted from instability toward the Lewis acids employed for oxidation, conversion of **6** to the respective aldehyde was attempted using *N*-chlorosuccinimide/CH_3SCH_3/Et_3N.[10] This reaction provided the required aldehyde as judged by silica gel TLC; the product (2,4-dinitrophenylhydrazine reactive) resonated at δ 9.65 (^1H NMR spectrum) and absorbed at 1710 and 1765 cm^{-1} in the infrared. Although the aldehyde could be isolated and stored at 4 °C for a few days, it was found to be more convenient to convert it to the corresponding *N*,*N*-dimethylhydrazone derivative **7** prior to further transformation or storage. Compound **7** represented the key intermediate required for the synthesis of a di-O-3,4-protected L-gulose (cf. Scheme I); i.e., it had (i) suitable protecting groups for O-3 and O-4 and (ii) C-1 and C-6 at the same oxidation level, yet chemically differentiable.

Following the successful oxidation and protection of C-6 in glucose derivative **6**, completion of the synthesis of the desired L-gulose derivative required only deacetylation and reduction at C-1. It was noted, however, that deacetylation would afford **8**, a reducing sugar with the potential for scrambling of stereochemistry at C-2 (glucose numbering).[11,12] Accordingly, deacetylation (catalytic $NaOCH_3$ in CH_3OH) was monitored closely by ^1H NMR and silica gel TLC. The ^1H NMR spectrum of **8** indicated that the resonance corresponding to the hydrazone methyl groups was unchanged from hydrazone **7**. Also identical for both compounds was the coupling constant for H-6 (J = 5 Hz), suggesting that the formation of the species identified as **8** involved only the deacetylation of **7**. Crude **8** was dissolved in aqueous ethanol and treated directly with sodium borohydride, providing a compound that was homogeneous on silica gel TLC in several solvent systems. Nonetheless, analysis of the product by ^1H NMR indicated it to be an equilibrium mixture of pyranose (**9**) and acyclic (**9a**) forms of L-gulose derivative **9**, present in a 70:30 ratio, as judged by the intensity and chemical shifts of the methyl resonances, as well as the integrated intensity of a doublet at δ 6.73 (J = 5 Hz) attributed to the hydrazone H in **9a**.[13] The methyl groups of the (major) pyranose form (**9**) were found to appear in the ^1H NMR as two singlets at δ 2.49 and 2.42 in a ratio of 85:15. Presumably, this reflected the ratio of anomers present in the pyranose form of **9**.

Confirmation of Structure of L-Gulose Derivatives.

(5) Tritylation of **3** was carried out in the presence of diisopropylethylamine. The use of pyridine, lutidine, or collidine as the solvent/base resulted in formation of a 1,2,4-ortho ester (i) as the major product.



(6) (a) Dewolfe, R. M. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970; p 339. (b) Lemieux, R. U.; Cipera, J. D. T. *Can. J. Chem.* **1956**, *34*, 906. (c) Lemieux, R. U.; Stevens, J. D. *Can. J. Chem.* **1965**, *43*, 2059. (d) Kochetkov, N. K.; Bochkov, A. F.; Sokolovskaya, T. A.; Snyatkova, V. S. *Carbohydr. Res.* **1971**, *16*, 17.

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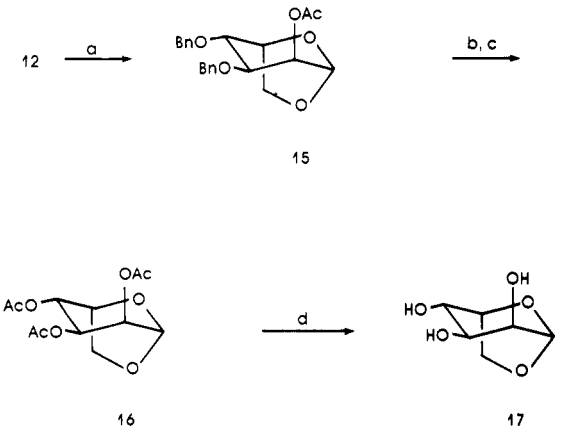
(12) Hodge, J. E. *Adv. Carbohydr. Chem.* **1955**, *10*, 169.

(13) Karabatsos, G. J.; Taller, R. A. *Tetrahedron* **1968**, *24*, 3923.

Scheme III[a]

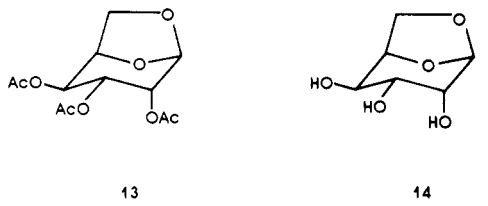


[a] (a) Ac_2O, C_6H_5N, 24 h, 25 °C; (b) $Pd(OH)_2$, H_2 (50 psi), EtOAc, 40 h, 25 °C; (c) Ac_2O, C_6H_5N, 15 min, 100 °C; (d) $NaOCH_3$, CH_3OH.

Having apparently achieved the synthesis of protected L-gulose **9** (⇌**9a**), it was necessary to prove its structure and to effect its conversion to a derivative suitable for coupling with 3-O-carbamoylmannose and L-*erythro*-β-hydroxyhistidine. Both of these objectives were accomplished in a single reaction sequence, as indicated below.

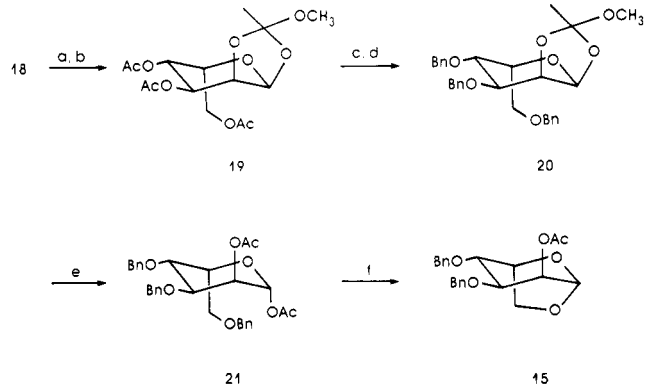
Hydrazone **9** was treated with methyl iodide in THF to form quaternary salt **10**, which was treated with silver *p*-toluenesulfonate in methanol to form tosylate salt **11**. When the tosylate salt was dissolved in glyme and heated at reflux in the presence of *p*-toluenesulfonic acid, 1,6-anhydro-3,4-di-O-benzyl-β-L-gulopyranose (**12**) was formed, as anticipated (75% overall from **7**). The structure of compound **12** was verified by high-field ^1H NMR. Decoupling studies permitted unambiguous assignment of all of the protons and the data agreed with that reported[14] for the D isomer. Especially characteristic was the signal for H-6_{exo}, which appeared at δ 3.62 as a doublet of doublets coupled to H-6_{endo} and H-5, and that for H-6_{endo}, which appeared as a doublet at δ 4.01 that was not coupled to H-5. Also characteristic of the gulo configuration was the large $J_{3,4}$ value of 8.4 Hz, indicative of axial–axial coupling.

Acetylation of compound **12** provided the respective monoacetate **15**, which had the expected ^1H NMR spectral characteristics: there was a new singlet at δ 2.13 corresponding to the acetyl methyl group, and the resonance corresponding to H-2 was shifted downfield by 1.37 ppm. Conversion of 2-O-acetyl-1,6-anhydro-3,4-di-O-benzyl-β-L-gulopyranose (**15**) to **16** and **17** was achieved readily, as outlined in Scheme III. Compound **16** was obtained as colorless needles from chloroform–pentane, mp 114 °C; this compared favorably with the mp of 114–115 °C reported[15] for the D isomer of **16** (**13**). The optical properties of the



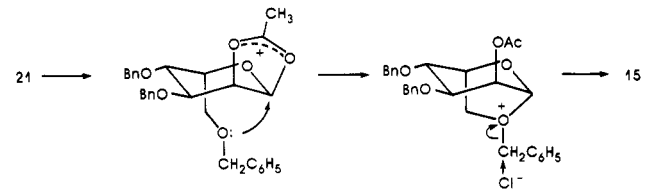
two were also found to correspond ($[\alpha]^{25}_D$ −22.0° for **16**; $[\alpha]^{25}_D$ +22.1° for **13**[15]). Compound **17** was obtained as colorless prisms having the same melting point (153 °C for

Scheme IV[a]



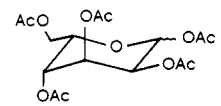
[a] (a) HBr, HOAc; (b) $Et_4N^+Br^-$, CH_3OH, $(i\text{-}Pr)_2NEt$; (c) $NaOCH_3$, CH_3OH; (d) $C_6H_5CH_2Br$, NaH, DMF; (e) (i) glacial HOAc, 1 h, 0 °C, (ii) Ac_2O, C_6H_5N, 2 h, 25 °C; (f) $SnCl_4$, CH_2Cl_2, 15 min, 0 °C.

Scheme V. Possible Mechanism for the Conversion of 21 to 15



17; 154–155 °C for **14**) and magnitude of optical rotation ($[\alpha]^{25}_D$ −50° for **17**; $[\alpha]^{25}_D$ +50.4° for **14**) as authentic 1,6-anhydro-β-D-gulopyranose.[15]

Alternative Synthesis of 1,6-Anhydro-β-L-gulose Derivatives. The synthesis of L-gulose derivatives outlined above proved to be reasonably efficient (25–30% overall yield from **2** to **12**) and provided access to multigram quantities of 1,6-anhydro-β-L-gulose derivatives for further synthetic studies. Ultimately, however, the length of this synthetic route prompted the development of alternate approaches for the preparation of quantities of these compounds. Per-*O*-acetyl-L-gulose (**18**) was chosen



as a suitable starting material for this work and was prepared by acetylation of L-gulose. L-Gulose itself was synthesized either by the method of Evans and Parrish[2b,3g,3i] or by catalytic hydrogenation of L-ascorbic acid[16] and subsequent reduction of L-gulono-1,4-lactone.[17,18]

Per-*O*-acetyl-L-gulopyranose (**18**) was converted to crystalline ortho ester **19** (Scheme IV) by treatment with HBr–HOAc, followed by CH_3OH–*n*-$Bu_4N^+Br^-$–Hünigs base. Tribenzylated ortho ester **20** was obtained by conventional means as colorless microcrystals (94% overall from **19**). Treatment of **20** with glacial acetic acid, followed

(14) Cernay, M.; Stanek, J. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23 and references therein.

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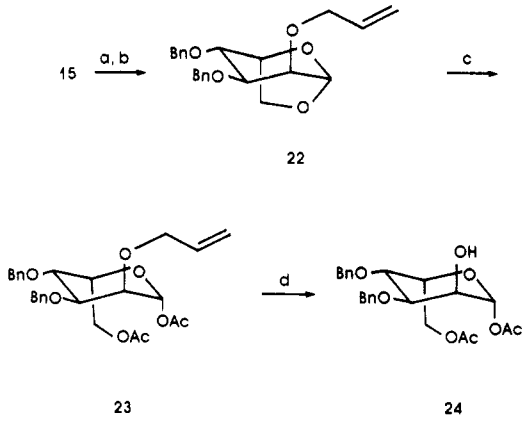
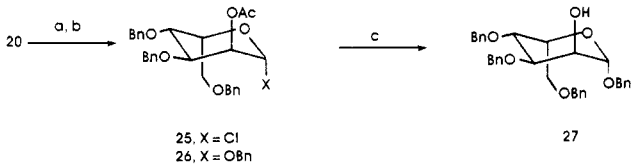
(18) Wolfrom, M. L.; Thompson, A. *Methods Carbohydr. Chem.* **1963**, *2*, 65.

Scheme VI[a]



[a] (a) $NaOCH_3$, CH_3OH; (b) CH_2=$CHCH_2Br$, NaH, DMF; (c) Ac_2O, HOAc, H_2SO_4; (d) 10% Pd/C, 75% HOAc, 24 h, 50 °C.

Scheme VII[a]



[a] (a) $(CH_3)_3SiCl$, CH_2Cl_2, Δ; (b) $C_6H_5CH_2OH$, $AgOSO_2CF_3$, $(CH_3)_2NCON(CH_3)_2$, CH_2Cl_2; (c) $NaOCH_3$, CH_3OH.

by acetic anhydride–pyridine, provided syrupy diacetate **21** (90% yield), which on treatment with $SnCl_4$ at 0 °C for 15 min provided 2-*O*-acetyl-1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulose (**15**) in 95% yield. This compound was identical in all respects with the same compound obtained from D-glucose;[15,19] its formation is envisioned as outlined in Scheme V, i.e., nucleophilic attack by O-6 on an acetoxonium ion derived initially from **21**.[14,20] Consistent with this scheme was the detection of benzyl chloride as a by-product of the reaction.

Preparation of Additional L-Gulose Derivatives. While the 1,6-anhydro-β-L-gulose derivatives were found to be of utility for preparation of the disaccharide moiety of bleomycin,[2b] the availability of alternative building blocks proved to be desirable. In particular, one successful approach to the synthesis of bleomycin required the availability of monocyclic L-gulose derivatives for coupling with 3-*O*-carbamoylmannose.

To provide a gulopyranose derivative suitable for use in the synthesis of the carbohydrate moiety of bleomycin, 1,6-anhydro-β-L-gulose derivative **12** was first protected on O-2 with an allyl group via the agency of NaH–allyl bromide (Scheme VI).[21] The desired compound (**22**) was obtained as a colorless oil in 95% yield. Subsequent treatment with 2% H_2SO_4 in Ac_2O (0 °C, 15 min) provided 1,6-diacetate **23** in 85% yield.[14] Removal of the allyl protecting group provided 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-β-L-gulopyranose (**24**) as an oil in 62% yield (^1H NMR characterization). Compound **24** proved to be suitable for coupling with 3-*O*-carbamoylmannose derivatives.

(19) Treatment of **15**, obtained from per-*O*-acetyl-L-gulose (**18**), with $NaOCH_3$ in methanol provided **12** identical in all respects with that obtained from D-glucose.

(20) Aslani-Shotorbani, G.; Buchanan, J. G.; Edgar, A. R.; Shanks, C. T.; Williams, G. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2267.

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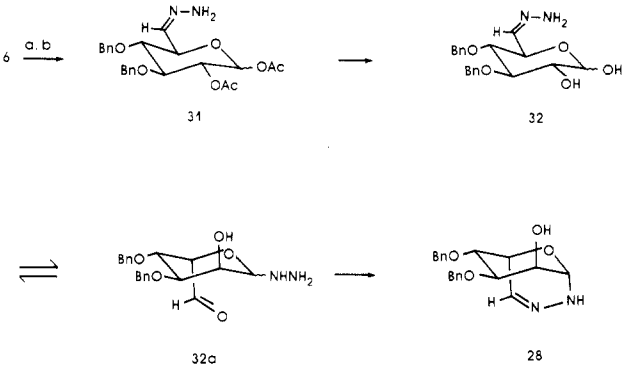
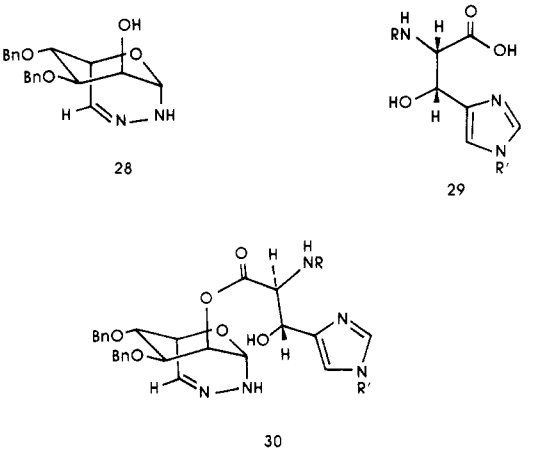
Scheme VIII[a]



[a] (a) *N*-chlorosuccinimide, $(CH_3)_2S$, Et_3N, toluene, −25 °C → 25 °C; (b) $NH_2NH_2 \cdot H_2SO_4$, CH_3OH, 25 °C.

Alternatively, treatment of tribenzyl ortho ester **20** with trimethylsilyl chloride[22] in dichloromethane (reflux, 2 h) provided the respective gulopyranosyl chloride (**25**) as colorless plates (84% yield) (Scheme VII). Compound **25** was converted to 2-*O*-acetyltetra-*O*-benzylgulose derivative **26** by treatment with benzyl alcohol–silver triflate–tetramethylurea. Finally, deacetylation provided key intermediate benzyl 3,4,6-tri-*O*-benzyl-β-L-gulopyranoside (**27**) as colorless plates in 95% yield.

As noted previously,[2a] an essential feature of the L-gulose derivatives chosen for study was the potential of each to facilitate the regio- and stereoselective condensation of appropriate D-mannose and β-hydroxyhistidine derivatives at O-2 and O-1, respectively. In this context, the preparation of 1,6-(1-hydrazinyl-2-ylidene)gulose derivative **28** was of interest, as it was thought that esterification of **28** with a suitable derivative of L-*erythro*-β-hydroxyhistidine (**29**) could provide access to key synthetic intermediate **30**.

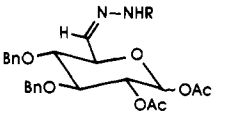


As envisioned, subsequent activation of the hydrazine moiety in **30** (e.g., via dialkylation) would promote its intramolecular displacement by the β-OH group of the β-hydroxyhistidine moiety of **30**, thus establishing the requisite linkage between L-gulose and β-hydroxyhistidine. Saponification of the lactone would then free the 2-OH group in L-gulose for condensation with an appropriate D-mannose derivative.

Synthetically, the most straightforward route to **28** was seen to involve the use of hydrazine, rather than 1,1-dimethylhydrazine, in the derivatization of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose (cf. Schemes II and VIII). Deacetylation of the hydrazone **31** so formed would provide **32**, the latter of which would

(22) Josephson, S.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 297.

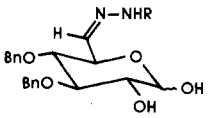
Table I. *N*-Acyl Derivatives of 1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-Hydrazone



compd	R	yield, %	mp,[a] °C	^{1}H NMR,[b] δ	mass spectrum,[c] m/z
31	H	45		1.90 (s, 3), 2.05 (s, 3), 3.53–3.88 (m, 2), 4.21 (dd, 1, *J* = 5.0, 10.0 Hz), 4.47–4.80 (m, 4), 5.10 (m, 1), 5.66 (d, 1, *J* = 8.0 Hz), 7.10–7.35 (m, 10), 7.61 (d, 1, *J* = 4.5 Hz)	397 [(M − 59)$^+$]
33	$COCH_3$	95	186	1.90 (s, 3), 2.08 (s, 3), 2.20 (s, 3), 3.60–3.82 (m, 2), 4.07 (dd, 1, *J* = 6.0, 9.0 Hz), 4.44–4.93 (m, 4), 5.07 (t, 1, *J* = 8.0 Hz), 5.65 (d, 1, *J* = 8.0 Hz), 6.68 (d, 1, *J* = 6.0 Hz), 7.32 (m, 10), 8.73 (br s, 1, exchangeable in D_2O)	499 [(M + 1)$^+$]
34	CHO	50	168	1.92 (s, 3), 2.02 (s, 3), 3.58–3.80 (m, 2), 4.05 (dd, 1, *J* = 6.0, 9.0 Hz), 4.44–4.90 (m, 4), 5.06 (t, 1, *J* = 8.0 Hz), 5.63 (d, 1, *J* = 8.0 Hz), 6.64 (d, 1, *J* = 6.0 Hz), 7.30 (s, 10), 8.55 (d, 1, *J* = 10.5 Hz, collapsed to a singlet on addition of D_2O), 8.99 (d, 1, *J* = 10.5 Hz, exchangeable in D_2O)	
35	$CO_2C(CH_3)_2CCl_3$	70	182–184	1.92 (s, 3), 1.97 (s, 3), 2.00 (s, 3), 2.02 (s, 3), 3.60–3.82 (m, 2), 4.14 (dd, 1, *J* = 6.0, 9.0 Hz), 4.50–4.95 (m, 4), 5.05 (t, 1, *J* = 8.0 Hz), 5.63 (d, 1, *J* = 8.0 Hz), 6.64 (d, 1, *J* = 6.0 Hz), 7.29 (s, 10), 7.68 (br s, 1, exchangeable in D_2O)	661, 559 [(M + 1)$^+$]
36	$CO_2C(CH_3)_3$	41	183–184	1.50 (s, 9), 1.92 (s, 3), 2.02 (s, 3), 3.62–3.82 (m, 2), 4.01 (dd, 1, *J* = 6.0, 10.0 Hz), 4.54–4.90 (m, 4), 5.03 (m, 1), 5.65 (d, 1, *J* = 8.0 Hz), 6.68 (d, 1, *J* = 6.0 Hz), 7.32 (m, 10), 7.87 (br s, 1, exchangeable in D_2O)	

[a] Uncorrected. [b] 90-MHz, $CDCl_3$. [c] Chemical ionization, CH_4.

Table II. *N*-Acyl Derivatives of 3,4-Di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-Hydrazone

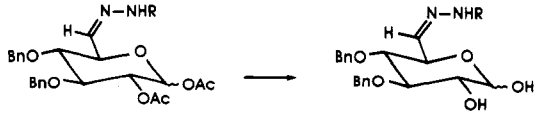


compd	R	yield %	mp,[a] °C	^{1}H NMR,[b] δ	mass spectrum,[c] m/z
37	$COCH_3$	79	166–167 dec	2.13 (s, 3), 3.32–4.10 (m, 3), 4.50–4.90 (m, 4), 4.85 (m, 1), 5.17 (d, 1, *J* = 3.5 Hz), 6.97 (d, 1, *J* = 6.0 Hz), 7.15–7.43 (m, 10)	
38	CHO	89	150–151 dec	3.30–4.15 (m, 3), 4.45–5.00 (m, 5), 5.18 (d, 1, *J* = 3.5 Hz), 7.20–7.40 (m, 11), 8.65 (br s, 1)	
39	$CO_2(CH_3)_2CCl_3$	80	174–175	1.90 (s, 3), 1.94 (s, 3), 3.30–4.05 (m, 3), 4.33–4.95 (m, 5), 5.14 (d, 1, *J* = 3.0 Hz), 6.71 (d, 1, *J* = 6.0 Hz), 7.18–7.40 (m, 10)	577, 575 [(M + 1)$^+$]

[a] Uncorrected. [b] 90-MHz, $CDCl_3$ + Me_2SO-d_6, D_2O. [c] Chemical ionization, CH_4.

be anticipated to exist in equilibrium with the acyclic sugar (cf. 9 ⇌ 9a) and with L-gulose derivative **32a**. Presumably, dehydrative cyclization of **32a** would displace the equilibrium irreversibly toward **28**.

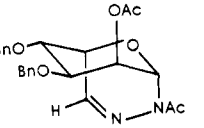
The preparation of hydrazone **31** was carried out as shown in Scheme VIII; although the transformation **6** → **31** was not optimized, the product was obtained as a solid in 45% yield. However, all attempts to effect deacetylation of **31** were unsuccessful, resulting either in O → N acyl migration or else in complex mixtures of products. An alternative approach to **28** involved the initial conversion of **6** to each of four *N*-acylhydrazones (**33–36**), (Table I) three of which could be O-deacetylated without concomitant N-deacetylation by the use of catalytic $NaOCH_3$ in methanol. The crystalline acylhydrazones **37–39** were



33, R = $COCH_3$
34, R = CHO
35, R = $CO_2C(CH_3)_2CCl_3$
36, R = $CO_2C(CH_3)_3$

37, R = $COCH_3$
38, R = CHO
39, R = $CO_2C(CH_3)_2CCl_3$

characterized (Table II) and employed in an effort to prepare **28**. Efforts to effect N-deacylation of **37** and **38** under a variety of conditions ($NaOCH_3$, BF_3·Et_2O, aqueous HBr/THF, CF_3COOH/THF) led either to recovery of starting materials or, where higher temperatures were employed, to extensive decomposition. Compound **28** was prepared successfully from **39**, by treatment with freshly activated zinc dust in phosphate buffer (pH 4.6);[23] the desired product was obtained as a colorless syrup in 25% yield. Characterization of **28** included ^{1}H NMR and mass spectrometry, as well as conversion to the respective diacetate **40**, which was characterized similarly.



40

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 not corrected. UV spectra were obtained on a Cary 15 recording spectrophotometer. Mass spectra were recorded on a Perkin-Elmer Hitachi RMU-6, Varian MAT-44, or Finnigan MAT 4500 Series GC/MS mass spectrom-

(23) Just, G.; Grozinger, K. *Synthesis* **1976**, 457.

eter. NMR spectra were determined on a Varian T-60, Varian EM-390, Hitachi Perkin-Elmer R-22, or Nicolet NT-360 NMR spectrometer.

1,2-*O*-(1-Ethoxyethylidene)-6-*O*-(triphenylmethyl)-α-D-glucopyranose (4). A solution of 1.2 g (3.19 mmol) of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose (**2**)[3] in 10 mL of methanol was treated with 5 mg of sodium methoxide, and the reaction mixture was maintained at 25 °C for 12 h. Concentration of the methanolic solution afforded crude 1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose (**3**): ^{1}H NMR (D_2O) δ 1.18 (t, 3), 1.74 (s, 3), 3.3–3.8 (m, 6), 3.98 (m, 1), 4.40 (br t, 1, J = 5 Hz), 5.81 (d, 1, J = 5 Hz). Crude **3** was dissolved in 8 mL of dimethylformamide containing 2 mL of diisopropylethylamine and stirred under N_2 at 25 °C for 48 h. Trityl chloride (1.8 g, 6.5 mmol) was added, and the reaction mixture was stirred at 25 °C for an additional 24 h. The reaction mixture was diluted with water (125 mL) and extracted with ether (3 × 50 mL). The combined ether extract was washed with brine, dried (Na_2SO_4), and concentrated under diminished pressure to afford an oil. Column chromatography on activated alumina, elution with 1:1 benzene–ethyl acetate and then with a gradient of 10% → 40% methanol in ethyl acetate, gave tritylated glucopyranose **4** as a pale yellow foam: yield 1.26 g (80%); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.18 (t, 3), 1.64 (s, 3), 2.77 (br s, 2, exchangeable in D_2O), 3.2–3.9 (m, 7), 4.20 (br t, 1), 5.67 (d, 1, J = 5 Hz), 7.20 (m, 15); IR ($CHCl_3$) 3560, 1490, 1480, 1450, 1390, 1160, 1040, 905, 675 cm^{-1}.

1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-6-*O*-(triphenylmethyl)-β-D-glucopyranose (5). To a stirred solution of ortho ester **4** (2.5 g, 5.1 mmol) in 100 mL of dry glyme at 0 °C was added 1.25 g (52 mmol) of sodium hydride. This mixture was stirred at 0 °C for 30 min and then treated dropwise with 8.55 g (72 mmol) of benzyl bromide at 0 °C. Stirring was continued at 25 °C for an additional 24 h, after which unreacted sodium hydride was destroyed by slow addition of CH_3OH (5 mL) at 0 °C. The reaction mixture was diluted with ether (200 mL), and the organic phase was washed with water and brine, then dried (Na_2SO_4), and concentrated to provide the crude benzylated ortho ester as a yellow gum: ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.20 (t, 3), 1.67 (s, 3), 3.10–3.95 (m, 5), 4.30–4.80 (m, 7), 5.87 (d, 1, J = 5 Hz), 7.3 (m, 25). The crude ortho ester was treated with dry acetic acid at room temperature for 1.5 h, after which the solution was concentrated under diminished pressure. The residue was dissolved in ether and washed with saturated solutions of $NaHCO_3$ and brine. Concentration of the dried ($MgSO_4$) ether solution afforded a yellow oil, which crystallized from ethanol to give 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-6-*O*-(triphenylmethyl)-β-D-glucopyranose (**5**) as colorless prisms, yield 2.5 g (71%). Recrystallization from ethanol provided an analytically pure sample of **5**: mp 144–145 °C; ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.97 (s, 3), 2.15 (s, 3), 3.1–4.1 (m, 5), 4.4–4.8 (m, 4), 5.19 (t, 1, J = 8 Hz), 5.65 (d, 1, J = 8 Hz), 7.3 (m, 25); IR (CCl_4) 1765 cm^{-1}.

Anal. Calcd for $C_{43}H_{42}O_8$: C, 75.20; H, 6.16. Found: C, 75.49; H, 6.12.

1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranose (6). Method A. Trityl ether **5** (7.4 g, 10.8 mmol) was dissolved in 150 mL of a solution consisting of acetic acid (100 mL), water (25 mL), and THF (25 mL). The reaction mixture was heated at 50 °C for 5 h, and the cooled solution was then concentrated and the residue partitioned between ether and water. The ether layer was washed with saturated solutions of $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a colorless solid. Three recrystallizations from ether–pentane provided 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranose (**6**) as colorless needles: yield 4.0 g (83%); mp 107 °C; $[\alpha]^{25}_D$ +24.2° (*c* 3.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.92 (s, 3), 2.07 (s, 3), 3.3–3.9 (m, 6), 4.73 (m, 4), 5.1 (m, 1), 5.60 (d, 1, J = 8 Hz), 7.30 (s, 10).

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.55; H, 6.35.

Method B. Trityl ether **5** (0.2 g, 0.29 mmol) was dissolved in 5 mL of benzene and applied to the top of a dry silica gel column (Davison Grade 12, 28–200 mesh, 2 × 17 cm, 30 g). The column was washed with benzene (25 mL), maintained at room temperature for 18 h, and then washed with 10% ethyl acetate in benzene (150 mL) followed by 25% methanol in ethyl acetate (200 mL). Concentration of the methanol–ethyl acetate eluate afforded diacetate **6**, which crystallized as colorless needles (yield 124 mg, 95%), identical in all respects with those obtained by method A.

1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehyde-1,5-pyranose 6-Dimethylhydrazone (7). Method A. A stirred solution of 0.93 g (7 mmol) of *N*-chlorosuccinimide in 25 mL of toluene was cooled to 0 °C and treated under N_2 with 1.08 g (17.3 mmol) of dimethyl sulfide. The reaction mixture was cooled to −25 °C and treated dropwise with a solution of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranose (**6**) (2.0 g, 4.5 mmol) in 45 mL of toluene. After the mixture was stirred for 2 h, 1.1 g (9.3 mmol) of triethylamine in 1.5 mL of toluene was added dropwise. The reaction mixture was allowed to warm to room temperature, and then 5 mL of methanol and 0.27 g (4.5 mmol) of 1,1-dimethylhydrazine were added with stirring. Stirring was continued for an additional 18 h, after which the reaction mixture was diluted with 100 mL of ether and washed successively with 2% aqueous sodium hydroxide, water, and saturated brine. Concentration of the dried ($CaSO_4$) organic phase gave a pale yellow solid which crystallized as colorless needles of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-dimethylhydrazone (**7**): yield 1.44 g (66%); mp 146–147 °C; $[\alpha]^{25}_D$ +55.6° (*c* 3.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.94 (s, 3), 2.07 (s, 3), 2.85 (s, 6), 3.6–4.3 (m, 3), 4.75 (m, 4), 5.10 (t, 1), 5.72 (d, 1, J = 8 Hz), 6.28 (d, 1, J = 6 Hz), 7.33 (s, 10); IR (CCl_4) 1765, 1450, 1365, 1235, 1215, 1090, 1060, 695 cm^{-1}.

Anal. Calcd for $C_{26}H_{32}N_2O_7$: C, 64.45; H, 6.66. Found: C, 64.18; H, 6.63.

Method B. A stirred solution of 600 mg (0.45 mmol) of *N*-chlorosuccinimide in 24 mL of dry toluene was cooled to 0 °C and treated dropwise under N_2 with 31 mg (0.5 mmol) of dimethyl sulfide. After 10 min, the reaction mixture was cooled to −20 °C and a solution of 1.2 g (2.7 mmol) of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranose (**6**) in 33 mL of dry toluene was added dropwise. After the mixture was stirred for 4 h, 0.8 g (8.6 mmol) of triethylamine in 2 mL of toluene was added dropwise. The combined solution was allowed to warm to room temperature, was then diluted with 100 mL of dichloromethane, and washed successively with saturated aqueous $NaHCO_3$ (80 mL) and saturated brine (140 mL). The dried (Na_2SO_4) organic phase was concentrated to afford 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose as a colorless syrup: yield 1.17 g (98%); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.95 (s, 3), 2.05 (s, 3), 3.70–3.80 (m, 2), 4.10 (m, 1), 4.70–4.75 (m, 4), 5.01 (m, 1), 5.80 (d, 1, J = 7.5 Hz), 7.25–7.40 (br s, 10), 9.65 (s, 1).

The aldehyde was dissolved in 60 mL of methanol and treated with 0.144 g (2.4 mmol) of 1,1-dimethylhydrazine in 2 mL of methanol. The combined solution was stirred at 25 °C for 18 h and then concentrated to dryness. The residue was dissolved in 125 mL of dichloromethane, washed with saturated brine (4 × 20 mL), and dried (Na_2SO_4). Concentration of the dichloromethane solution afforded a yellow solid. 1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-dimethylhydrazone (**7**) was obtained as colorless needles by crystallization from ether: yield 780 mg (67%); mp 146–147 °C.

1,6-Anhydro-3,4-di-*O*-benzyl-β-L-glucopyranose (12). A solution of 0.55 g (1.12 mmol) of diacetate **7** in 50 mL of methanol was treated with 5 mg of sodium methoxide. The combined solution was maintained at 25 °C for 48 h, then concentrated to provide 3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-dimethylhydrazone (**8**) as a colorless foam. Hydrazone **8** was dissolved in ethanol (25 mL) and water (2 mL) and treated with 43 mg (1.14 mmol) of sodium borohydride at 25 °C for 24 h. The solution was concentrated and then partitioned between chloroform and water. The aqueous phase was extracted with an additional portion of chloform, and the combined organic extract was dried (Na_2SO_4) and concentrated to provide (β,β-dimethylhydrazino)-3,4-di-*O*-benzyl-L-gulopyranoside as a colorless foam, yield 0.4 g (89%). The product was shown to be chromatographically homogeneous on silica gel TLC in several solvent systems, but ^{1}H NMR analysis indicated that it was an equilibrium mixture of the pyranose **9** and acyclic **9a** forms: ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.42 and 2.49 (2 s, 4.2, anomeric $N(CH_3)_2$), 2.72 (s, 1.8, acyclic $N(CH_3)_2$), 3.20–4.10 (m, 7), 4.30–5.00 (m, 5), 6.73 (d, 0.3, J = 5 Hz, acyclic CH=$NN(CH_3)_2$), 7.30 (m, 10).

Hydrazone **9** ⇌ **9a** (0.4 g, 1.0 mmol) was dissolved in 30 mL of tetrahydrofuran and treated with 1.1 mL of methyl iodide at 25 °C for 12 h. Concentration of the reaction mixture provided

crude methiodide **10** as a yellow oil; this oil was dissolved in 30 mL of methanol and treated directly with 500 mg (1.8 mmol) of silver *p*-toluenesulfonate. The reaction mixture was stirred for 30 min, then concentrated to a small volume, and filtered. Dilution of the filtrate with glyme provided an additional precipitate, which was also filtered. The filtrate was concentrated to provide quaternary salt **11** as a white foam. Crude **11** was dissolved in glyme (30 mL) and heated at reflux (N_2) for 5 h in the presence of 150 mg of *p*-toluenesulfonic acid. The cooled reaction mixture was filtered, and the filtrate was concentrated under diminished pressure. The residue was dissolved in ether (50 mL) and washed successively with water and saturated brine. The dried (Na_2SO_4) ether layer was concentrated to give a yellow oil that was purified by chromatography on a silica gel column (15 g; 1.3 × 26 cm); 1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulose (**12**) eluted from the column with 10% ethyl acetate in benzene and was isolated as a colorless oil following concentration of the appropriate fractions, yield 290 mg (75% from **7**): ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.50 (d, 1, J = 3.1 Hz), 3.62 (dd, 1, $J_{6_{exo},6_{endo}}$ = 7.65 Hz, $J_{6_{exo},5}$ = 4.8 Hz), 3.69 (dd, 1, $J_{3,4}$ = 8.4 Hz), $J_{3,2}$ = 4.7 Hz), 3.83 (dd, 1, $J_{4,5}$ = 4.3 Hz, $J_{4,3}$ = 8.4 Hz), 3.91 (m, 1, irradiation at δ 2.50 gave dd, $J_{2,3}$ = 4.6 Hz, $J_{2,1}$ = 2.3 Hz), 4.01 (d, 1, $J_{6_{endo},6_{exo}}$ = 7.65 Hz), 4.43 (dd, 1, $J_{5,6_{exo}}$ = 4.8 Hz, $J_{5,4}$ = 4.3 Hz), 4.68 (s, 2), 4.65 (d, 1, J = 11.8 Hz), 4.75 (d, 1, J = 11.8 Hz), 5.45 (d, 1, $J_{1,2}$ = 2.3 Hz), 7.30 (m, 10); IR (CCl_4) 3570, 1490, 1450, 1210, 1135, 1110, 1035, 925, 695 cm^{-1}.

2-*O*-Acetyl-1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (15). Anhydrogulopyranose **12** (0.53 g, 1.54 mmol) was treated with 4 mL of pyridine and 1.5 mL of acetic anhydride at 25 °C for 12 h. The reaction mixture was poured into an ice–water mixture (50 mL) and extracted with ether. The ether extract was washed successively with 5% aqueous hydrochloric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine. The dried (Na_2SO_4) organic layer was concentrated, and the residue was purified by flash chromatography[24] (30-g column); washing with 30% ethyl acetate in hexane effected elution of 2-*O*-acetyl-1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**15**) as a colorless oil, yield 0.58 g (98%): $[\alpha]^{25}_D$ −33.1° (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.13 (s, 3), 3.63 (dd, 1, $J_{6_{exo},6_{endo}}$ = 7.0 Hz, $J_{6_{exo},5}$ = 4.5 Hz), 3.79 (dd, 1, $J_{3,4}$ = 8.0 Hz, $J_{3,2}$ = 4.5 Hz), 3.86 (dd, 1, $J_{4,3}$ = 8.0 Hz, $J_{4,5}$ = 3.8 Hz), 4.05 (d, 1, $J_{6_{endo},6_{exo}}$ = 7.0 Hz), 4.46 (dd, 1, $J_{5,6_{exo}}$ = 4.5 Hz, $J_{5,4}$ = 3.8 Hz), 4.50–4.83 (m, 4), 5.28 (dd, 1, $J_{2,3}$ = 4.5 Hz, $J_{2,1}$ = 2.0 Hz), 5.40 (d, 1, $J_{1,2}$ = 2.0 Hz), 7.30 (m, 10).

Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.82; H, 6.32.

2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-L-gulopyranose (16).[15] Dibenzylated gulopyranose derivative **15** (0.85 g, 2.21 mmol) was dissolved in 40 mL of ethyl acetate and hydrogenated at 50 psi over $Pd(OH)_2$ (75 mg) for 40 h. The catalyst was filtered through a Celite pad, and the filtrate was concentrated. The residue was dissolved in 5 mL of pyridine and 1.5 mL of acetic anhydride, and the solution was heated briefly on a steam bath. The cooled reaction mixture was poured into 60 mL of an ice–water mixture and extracted with ether. The ether extract was washed successively with 5% aqueous hydrochloric acid, water, saturated $NaHCO_3$, water, and saturated brine. The dried (Na_2SO_4) ether solution was concentrated to give a yellow oil, which deposited colorless needles of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-L-gulopyranose (**16**)[15] from chloroform–pentane, yield 0.25 g (40%): mp 114 °C; $[\alpha]^{25}_D$ −22.0° (*c* 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.00 (s, 3), 2.07 (s, 3), 2.13 (s, 3), 3.69 (dd, 1, J = 8.5 Hz), 4.10 (d, 1, J = 8 Hz), 4.60 (m, 1), 5.23 (m, 3), 5.42 (br s, 1).

Anal. Calcd for $C_{12}H_{16}O_8$: C, 50.00; H, 5.60. Found: C, 49.84; H, 5.73.

1,6-Anhydro-β-L-gulopyranose (17).[15] Triacetylated gulopyranose **16** (150 mg, 0.52 mmol) was dissolved in 25 mL of methanol and treated with a catalytic amount of sodium methoxide. The reaction mixture was maintained at 25 °C for 5 h and then concentrated. The residue crystallized from ethanol as colorless rhombic prisms of 1,6-anhydro-β-L-gulopyranose, yield 59 mg (70%): mp 153 °C; $[\alpha]^{25}_D$ −50° (*c* 2.3, H_2O).

Anal. Calcd for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.21; H, 5.99.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-L-gulopyranose (19). To a solution of per-*O*-acetyl-L-gulose (**18**) (40 g, 0.1 mol) in 90 mL of acetic acid was added 150 mL of 30% HBr in acetic acid. The reaction mixture was maintained at 25 °C for 1.5 h, then diluted with 200 mL of dichloromethane, and washed with ice–water (5 × 200 mL) and saturated aqueous $NaHCO_3$. The dried (Na_2SO_4) organic phase was concentrated to afford a syrup. This syrup was combined with methanol (40 mL), diisopropylethylamine (15 mL), and tetraethylammonium bromide (45 g) in 200 mL of dichloromethane containing 4-Å molecular sieves. The reaction mixture was maintained at 25 °C for 16 h, then filtered, and concentrated under diminished pressure. The residue was partitioned between dichloromethane (200 mL) and water (100 mL), and the organic layer was washed with water (3 × 30 mL) and saturated aqueous $NaHCO_3$ and then dried (Na_2SO_4). Concentration afforded a residue that was purified by chromatography on silica gel (750-g column); 1:1 ethyl acetate-hexane effected elution of the desired compound from the column. Crystallization of the solid product from ethyl acetate–hexane provided 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-L-gulopyranose (**19**) as colorless needles, yield 19.2 g (52%): mp 71–72 °C; $[\alpha]^{25}_D$ −22.1° (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.71 (s, 3), 2.00 (s, 3), 2.05 (s, 3), 2.12 (s, 3), 3.25 (s, 3), 4.1–4.5 (m, 3), 4.60 (dd, 1, J = 6, 3 Hz), 5.16 (dd, 1, J = 7, 3 Hz), 5.50 (m, 1), 5.73 (d, 1, J = 5 Hz); mass spectrum; m/z 363 [$(M + 1)^+$], 331, 289, (chemical ionization) 331.103 (FAB, $C_{14}H_{19}O_9$ requires 331.103).

Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.24; H, 5.68.

3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-α-L-gulopyranose (20). A solution of triacetylated gulopyranose **19** (3.5 g, 9.6 mmol) in 35 mL of methanol was treated with a catalytic amount of sodium methoxide at 25 °C for 30 min. The reaction mixture was concentrated, and the residue was dissolved in 30 mL of DMF and treated with sodium hydride (2 g, 50% dispersion in oil) at 0 °C for 1 h. The reaction mixture was cooled to −20 °C, and 6.5 g (38 mmol) of benzyl bromide was added, after which the combined solution was stirred at 25 °C for 1 h. Methanol (1 mL) was added, and the reaction mixture was stirred for an additional 15 min, poured into 100 mL of an ice–water mixture, and extracted with ethyl acetate. The organic extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (150-g column); washing with 15% ethyl acetate in toluene (containing 1% Et_3N) effected elution of 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-α-L-gulopyranose (**20**) as a syrup, yield 4.6 g (94%). This syrup crystallized on standing and could be recrystallized from ether–hexane as colorless microcrystals: mp 47.5–48.5 °C; $[\alpha]^{25}_D$ +1.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.68 (s, 3), 3.24 (s, 3), 3.77 (m, 4), 4.21 (m, 1), 4.46–4.83 (m, 7), 5.58 (d, 1, J = 5 Hz), 7.24 (m, 15).

Anal. Calcd for $C_{30}H_{34}O_7$: C, 71.12; H, 6.76. Found: C, 70.62; H, 6.71.

1,2-Di-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-L-gulopyranose (21). 3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-α-L-gulopyranose (**20**) (2.0 g, 4.0 mmol) was dissolved in 15 mL of glacial acetic acid; the solution was maintained at 0 °C for 1 h. The reaction mixture was concentrated, and portions of toluene were codistilled to remove traces of acetic acid. The residue was treated with 10 mL of acetic anhydride and 10 mL of pyridine, and the resulting solution was maintained at 25 °C for 2.5 h. The reaction mixture was treated with ice and then concentrated under diminished pressure to provide a yellow oil. Chromatography on silica gel (50-g column), elution with 1:1 ethyl acetate-hexane, provided 1,2-di-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-L-gulopyranose (**21**) as a colorless syrup, yield 2.0 g (90%): ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.93 (s, 3), 2.01 (s, 3), 3.60 (m, 3), 4.00 (t, 1, J = 4 Hz), 4.30 (m, 1), 4.45 (m, 6), 5.15 (dd, 1, J = 9, 4 Hz), 6.10 (d, 1, J = 9 Hz), 7.30 (m, 15); mass spectrum (FAB), m/z 475.214 [$(M - HOAc)^+$] ($C_{29}H_{31}O_6$ requires 475.212).

Anal. Calcd for $C_{31}H_{34}O_8$: C, 69.64; H, 6.41. Found: C, 69.21; H, 6.22.

2-*O*-Acetyl-1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (15). To a solution of diacetate **21** (4.6 g, 8.6 mmol) in 250 mL of dichloromethane was added 1.8 mL (15 mmol) of stannic chloride at 0 °C. The reaction mixture was maintained at 0 °C

for 15 min, then poured onto a mixture of ice–aqueous $NaHCO_3$, and shaken well. Insoluble material was removed by filtration through Celite, and the two phases in the filtrate were separated. The aqueous layer was extracted with dichloromethane, and the combined organic extract was dried ($MgSO_4$) and concentrated. The residue was purified on silica gel (150 g column); the desired product eluted when the column was washed with 25% ethyl acetate in hexane. 2-*O*-Acetyl-1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**15**) was obtained as a colorless oil (3.14 g, 95%), identical in all respects with the same material derived from D-glucose. Treatment of the product with sodium methoxide in methanol provided a compound identical in all respects with authentic 1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**12**).

2-*O*-Allyl-1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (22). A solution containing 2.97 g (8.7 mmol) of 1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**12**) in 40 mL of DMF was treated with 0.5 g of sodium hydride (50% dispersion in oil; 10.4 mmol), and the mixture was maintained at 25 °C for 1 h. The suspension was cooled to −20 °C and treated dropwise with 1.1 g (9.1 mmol) of allyl bromide. The reaction mixture was stirred at 25 °C for 1 h, poured into an ice–water mixture, and extracted with portions of ethyl acetate. The combined ethyl acetate extract was washed with saturated brine, dried ($MgSO_4$), and concentrated to give a syrupy residue. This residue was purified by flash chromatography on silica gel (150 g column); elution with 25% ethyl acetate in hexane provided 2-*O*-allyl-3,4-di-*O*-benzyl-β-L-gulopyranose **22** as a colorless oil, yield 3.16 g (95%): $[\alpha]^{25}_D$ +1.53° (*c* 2.16, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 3.5–4.25 (m, 7), 4.46 (t, 1), 4.56 (d, 1, J = 11 Hz), 4.63 (s, 2), 4.78 (d, 1, J = 11 Hz), 5.1 (br s, 1), 5.22 (q, 1, J = 9, ~1 Hz), 5.35 (d, 1, J = 3 Hz), 5.9 (m, 1), 7.3 (m, 10).

Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.34; H, 6.94.

1,6-Di-*O*-acetyl-2-*O*-allyl-3,4-di-*O*-benzyl-β-L-gulopyranose (23). 2-*O*-Allyl-1,6-anhydro-3,4-di-*O*-benzyl-β-L-gulopyranose (**22**) (2.4 g, 6.28 mmol) was treated with 10 mL of acetic anhydride containing 1% sulfuric acid and 3.3 mL of acetic acid. The reaction mixture was maintained at 0 °C for 15 min and then poured into ice–water and extracted with ethyl acetate. The organic extract was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried ($MgSO_4$), and concentrated. The syrupy residue was purified by flash chromatography on silica gel (80-g column); elution with 25% ethyl acetate in hexane provided 1,6-di-*O*-acetyl-2-*O*-allyl-3,4-di-*O*-benzyl-β-L-gulopyranose (**23**) as a colorless oil, yield 2.61 g (85%): $[\alpha]^{25}_D$ +1.0° (*c* 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.93 (s, 3), 2.05 (s, 3), 3.4 (d, 1, J = 3.5 Hz), 3.63 (dd, 1, J = 9, 3 Hz), 3.87 (t, 1, J = 3 Hz), 3.95–4.8 (m, 9), 5.05–5.35 (m, 2), 5.80 (m, 1), 5.95 (d, 1, J = 9 Hz), 7.3 (m, 10).

Anal. Calcd for $C_{27}H_{32}O_8$: C, 66.92; H, 6.66. Found: C, 66.75; H, 6.71.

1,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-L-gulopyranose (24). A solution of 2.95 g (6.1 mmol) of 2-*O*-allylgulopyranose **23** in 30 mL of acetic acid and 10 mL of water was treated with 1 g of 10% palladium-on-carbon and heated at 50 °C for 24 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated to give a yellow oil. Flash chromatography on silica gel (150-g column) was used for purification of the crude product; the desired material was eluted from the column with 25% ethyl acetate in toluene. 1,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-L-gulopyranose (**24**) was obtained as a colorless oil, yield 1.67 g (62%): $[\alpha]^{25}_D$ +13.2° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.98 (s, 3), 2.13 (s, 3), 2.28 (d, 1), 3.48 (br d, 1, J = 3 Hz), 3.85 (m, 1), 3.90 (t, 1), 4.06–4.25 (m, 3), 4.41–4.60 (m, 4), 5.78 (d, 1, J = 8.5 Hz), 7.30 (m, 10).

Benzyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-L-gulopyranoside (26). A solution of 2.0 g (3.95 mmol) of tribenzyl ortho ester **20** in 30 mL of dichloromethane was treated with 4.3 g (40 mmol) of trimethylsilyl chloride at reflux for 2 h. The cooled solution was concentrated, and the solid residue was crystallized from ether–hexane, providing 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-L-gulopyranosyl chloride (**25**) as colorless plates, yield 1.7 g (84%): mp 79–80 °C; $[\alpha]^{25}_D$ +58.4° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.0 (s, 3), 3.5–3.67 (m, 3), 3.95 (t, 1), 4.22 (m, 1), 4.30–4.50 (m, 6), 5.17 (dd, 1), 5.65 (d, 1), 7.3 (m, 15).

A solution of 1.6 g (3.1 mmol) of gulopyranosyl chloride **25** in 10 mL of dichloromethane was treated at −65 °C with 0.9 g (3.5 mmol) of silver trifluoromethanesulfonate, 2 mL of tetramethylurea, and 1 mL of benzyl alcohol. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 2 h. The reaction mixture was diluted with 20 mL of dichloromethane and filtered through a Celite pad. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (500-g column); elution with 15% ethyl acetate in hexane provided benzyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-L-gulopyranoside as a colorless oil, yield 0.45 g (25%): $[\alpha]^{25}_D$ +27.7° (*c* 1.36, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.17 (s, 3), 3.53 (dd, 1, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz), 3.66 (m, 2), 4.02 (dd, 1, $J_{3,4}$ = 3.5 Hz, $J_{3,2}$ = 2 Hz), 4.16 (td, 1, $J_{5,6}$ = 6.4 Hz, $J_{5,4}$ = 1.4 Hz), 4.40–4.62 (m, 7), 4.90 (d, 1, J = 12 Hz), 4.94 (d, 1, $J_{1,2}$ = 8.3 Hz), 5.09 (dd, 1, $J_{2,1}$ = 8.3 Hz, $J_{2,3}$ = 2 Hz), 7.26 (m, 20).

Anal. Calcd for $C_{36}H_{38}O_7$: C, 74.20; H, 6.57. Found: C, 73.85; H, 6.47.

Benzyl 3,4,6-Tri-*O*-benzyl-β-L-gulopyranoside (27). A solution of 0.5 g (0.86 mmol) of 2-*O*-acetylgulopyranose **26** in 10 mL of methanol was treated with a catalytic amount of sodium methoxide at room temperature for 12 h. The solution was neutralized and concentrated. The residue was partitioned between chloroform and water, and the organic layer was dried (Na_2SO_4) and concentrated to give a solid residue. Crystallization from benzene–hexane gave benzyl 3,4,6-tri-*O*-benzyl-β-L-gulopyranose (**27**) as colorless plates, yield 0.44 g (95%): mp 62.5–63.5 °C; $[\alpha]^{25}_D$ +48.3° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 3.54 (br d, 1), 3.63 (m, 2), 3.82 (m, 1), 3.87 (t, 1), 4.02 (br t, 1), 4.40–4.73 (m, 8), 4.92 (d, 1, J = 8 Hz), 7.27 (m, 20).

Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.79; H, 6.67.

1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-Hydrazone (31). Dimethyl sulfide (56 mg, 0.9 mmol) was added dropwise under N_2 to a cooled (0 °C) solution of *N*-chlorosuccinimide (100 mg, 0.75 mmol) in 4 mL of dry toluene. The reaction mixture was cooled to −20 °C and then treated dropwise over a period of 10 min with a solution of 200 mg (0.45 mmol) of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranose (**6**) in 5.5 mL of toluene. The reaction mixture was stirred at −20 °C for 3 h, then treated dropwise with a solution of 0.2 mL of triethylamine in 0.3 mL of toluene, and allowed to warm to room temperature. Hydrazine sulfate (59 mg, 0.45 mmol) was added as a solid, and the reaction mixture was maintained at 25 °C for 18 h. The reaction mixture was added to 50 mL of dichloromethane and washed successively with saturated aqueous $NaHCO_3$ (20 mL) and saturated brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated to afford a colorless syrup. Purification by preparative silica gel TLC, development with 2% methanol in dichloromethane, provided 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-hydrazone (**31**) as a white solid, yield 93 mg (45%).

General Procedure for Preparation of Di-O-acetylated *N*-Acylhydrazones 33–36. A stirred solution of 200 mg (1.5 mmol) of *N*-chlorosuccinimide in 8 mL of dry toluene was cooled to 0 °C and treated under N_2 with 117 mg (1.88 mmol) of dimethyl sulfide. After 5 min, the reaction mixture was cooled to −20 °C and treated dropwise over a period of 5 min with a solution of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranose (**6**) (0.4 g, 0.9 mmol) in 11 mL of dry toluene. The reaction mixture was stirred at −20 °C for 4 h and then treated dropwise with a solution of 0.4 mL of dry triethylamine in 0.6 mL of toluene. The reaction mixture was allowed to warm to room temperature, diluted with 50 mL of dichloromethane, and washed successively with saturated aqueous $NaHCO_3$ (30 mL) and saturated brine (50 mL). The dried (Na_2SO_4) organic layer was concentrated to provide 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose (**7**) as a heavy, colorless syrup, yield 395 mg (98%): IR (CCl_4) 1765, 1710 cm^{-1}.

The aldehyde was dissolved in 30 mL of methanol and treated with 2 mmol of the appropriate acyl hydrazine.[25] The reaction

(25) The hydrazines used were commercially available with the exception of 1,1-dimethyl-2,2,2-trichloroethyl carbazate, which was prepared by the method of: Sonntag, N. O. *J. Am. Oil Chem. Soc.* **1968**, *45*, 571; *Chem. Abstr.* **1968**, *69*, 76585q.

mixture was stirred at 25 °C for 12–24 h, concentrated under diminished pressure to $^1/_2$ volume, and filtered to provide the requisite 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-acylhydrazone derivative. Concentration of the filtrate provided additional product; purification was achieved by crystallization from methanol–ether.

General Procedure for Preparation of *N*-Acylhydrazones 37–39. A suspension of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-acylhydrazone (0.2 mmol) (**33–35**) in 10 mL of methanol was treated with 20 μL of 1.0 M sodium methoxide in CH_3OH at 25 °C for 1–2 h. The reaction mixture was concentrated and the desired 3,4-di-*O*-benzyl-β-D-glucodialdehydo-1,5-pyranose 6-acylhydrazone was purified by preparative silica gel TLC, development with 5–8% methanol in dichloromethane.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-(1-hydrazinyl-2-ylidene)-β-D-glucodialdehydo-1,5-pyranose (28). Hydrazinoglucodialdehyde derivative **39** (80 mg, 0.14 mmol) in 0.85 mL of THF was treated with 90 mg of freshly activated (HCl washed) Zn dust suspended in 0.17 mL of 0.1 M potassium phosphate buffer, pH 4.6. The reaction mixture was stirred at 25 °C for 48 h, then diluted with ether (20 mL), and filtered. The filtrate was concentrated, and the residue was partitioned between ether (20 mL) and saturated brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 43 mg of a yellow oil, which was purified by preparative silica gel TLC, development with 25% hexane in ethyl acetate. 3,4-Di-*O*-benzyl-1,6-(1-hydrazinyl-2-ylidene)-β-D-glucodialdehydo-1,5-pyranose (**28**) was obtained as a colorless syrup, yield 24 mg (50%): ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.20–2.68 (m, 2), 3.5–3.65 (m, 3), 4.5–4.85 (m, 5), 5.15 (m, 1), 6.7–6.8 (br s, 1), 7.25 (s, 10); mass spectrum (chemical ionization, CH_4), *m/z* 395 [$(M + 41)^+$], 383 [$(M + 29)^+$], 335 [$(M + 1)^+$].

Acetylation (acetic anhydride, pyridine) provided a diacetate that was purified by preparative TLC on silica gel (development with 40% ethyl acetate in hexane) and obtained as a colorless syrup: ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.85 (s, 3), 2.25 (s, 3), 3.60–4.05 (m, 2), 4.4–4.8 (m, 4), 5.00 (m, 1), 5.25 (m, 1), 5.55 (m, 1), 6.75 (br s, 1), 7.25 (m, 10); mass spectrum (chemical ionization, CH_4), *m/z* 438 (M^+), 396.

Acknowledgment. We thank Dr. John Primeau and Dr. Natesan Murugesan, University of Virginia, for investigation of alternate routes leading to L-gulose, and Dr. Steven Carr, Walter Johnson, and Lewis Killmer, Smith, Kline, & French Laboratories, for high-resolution mass spectral data. This work was supported by contract N01-CM-43712 and PHS Grant CA-27603, awarded by the National Cancer Institute, DHHS.

Synthesis of 1,5-Dienes via [2 + 2] Photocycloaddition between 2,5-Dihydrothiophene 1,1-Dioxides (Sulfolenes) and α,β-Unsaturated Cyclic Ketones and Anhydrides. Synthesis of 10-Hydroxygeraniol[1a]

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Received July 22, 1985

Photocycloaddition between 2,5-dihydrothiophene 1,1-dioxide (**1a**) and 2-cyclohexenones **2a,b** afforded cis-anti-cis and cis-trans photoadducts **3a,b** and **4a** in low yield. Photocycloaddition between sulfolene **1a** and 2-cyclopentenones **8a,b** yielded cis-anti-cis photoadducts **9a,b**. The α-methyl derivative **9b** underwent α-cleavage to yield the unsaturated aldehyde **10**. Flash vacuum pyrolysis of photoadduct **3b** yielded the *trans*- and *cis*-2,3-divinylcyclohexanones **11** and **12**, respectively, together with the diunsaturated *trans*-decalin **13**. Photocycloaddition between sulfolenes **1a,b** and the α,β-unsaturated cyclic anhydrides **15a,b** afforded photoadducts **16a,b** in good yields. Esterification of **16a** and **16b** yielded the *cis*-diesters **17** and **23**, respectively. Flash vacuum pyrolysis of **17** gave the disubstituted (*E,Z*)-1,5-diene **18** stereoselectively, whereas **23** afforded the trisubstituted (*E,Z*)-1,5-dienes **25** and **26** less stereoselectively. Flash vacuum pyrolysis of the *trans*-diester **21** yielded the (*E,E*)-1,5-diene **19** stereoselectively, whereas the *trans*-diester **28** yielded both the (*E,E*)- and (*Z,Z*)-1,5-dienes **24a** and **27** as the major products. Reduction of the (*E,E*)-diene **24a** afforded 10-hydroxygeraniol **24b**. The 1,5-dienes were generated by thermal extrusion of sulfur dioxide from the cyclic sulfone diesters followed by a Cope rearrangement of the resulting 1,2-divinyl intermediates.

The [2 + 2] photocycloaddition between substituted cyclobutenes and chiral cyclohexanones has afforded a convenient entry into the stereospecific synthesis of elemane (E), germacrane (G), and cadinane (C) sesquiterpene skeletons,[2] containing a 1,5-diene system (Scheme I). In these reactions the cyclobutene is acting as a 1,2-divinyl synthon. Since cyclobutene and methylcyclobutene are expensive, we sought a cheaper and more readily available 1,2-divinyl synthon. As a solution to this problem, we wish to report the use of 2,5-dihydrothiophene 1,1-dioxides (sulfolenes) as 1,2-divinyl synthons. Secondly, we report the application of this method to the stereoselective synthesis of acyclic 1,5-dienes and have applied it to the synthesis of the monoterpene, 10-hydroxygeraniol.[3]

Results and Discussion

The photocycloaddition reaction between sulfolene **1a** and 2-cyclohexenone **2a** afforded photoadduct **3a** in a low yield (23%) together with the previously reported[4] head-

(1) (a) For the previous paper in this series, see: Williams, J. R.; Callahan, J. F.; Lin, C. *J. Org. Chem.* **1983**, *48*, 3162. (b) Temple University. (c) Smith Kline and French Laboratories.

(2) For 1,2-bis(trimethylsiloxy)cyclobutene, see: (a) Van Audenhove, M.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron Lett.* **1980**, *21*, 1979. (b) Williams, J. R.; Caggiano, T. J. *Synthesis* **1980**, 1024. For 1-methylcyclobutene, see: (c) Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4475. For methyl 1-cyclobutenecarboxylate, see: (d) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267; (e) Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373. (f) Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4479 and references cited therein. For cyclobutenecarboxylic acid, see: (g) Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, 4749. For dimethyl cyclobutene-1,2-dicarboxylate, see: Lange, G. L.; Huggins, M. A.; Neidert, E. *Tetrahedron Lett.* **1976**, 4409.

(3) The preliminary results reported by Williams and Lin (Williams, J. R.; Lin, C. *J. Chem. Soc., Chem. Commun.* **1981**, 752) should be revised in light of the complete experimental data reported herein.

0022-3263/85/1950-5815$01.50/0