Synthesis and Conformational Studies of β-(1→6)- and β,β-(1→1)-Linked C-Disaccharides†,‡

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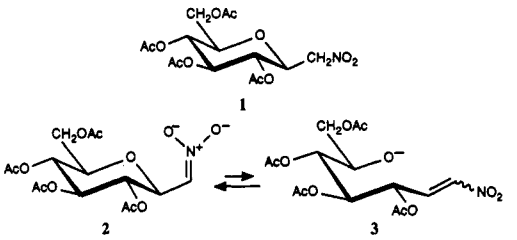
An expeditious methodology for the synthesis of β-(1→6)- and β,β-(1→1)-linked *C*-disaccharides has been developed. The methodology is based on the fluoride ion-mediated coupling of the (base-stable) nitronate anion derived from a glycosylnitromethane (1) and an *aldehydo*-hexodialdose or -hexose derivative. The carba-analogs (methylene-bridged analogs) of β-D-Glc-(1→6)-D-Gal and of β,β-trehalose (β-D-Glc-(1→1)-β-D-Glc) were thus obtained in six steps only from 1 and D-galactose-derived aldehyde 4 or *aldehydo*-D-glucose derivative 12, respectively. The preferred conformation of the (1→1)-linked *C*-disaccharides, including the symmetrical *C*-β,β-trehalose, was established on the basis of the vicinal coupling constants about the interglycosidic C–C linkages. In all the compounds of this series, the β-*C*-glycosidic linkages were found to adopt preferentially the "anti" conformation (C_2–C_1–$C_{7'}$–$C_{1'}$ torsional angle = ~180°). Our studies revealed, in particular, that the solution conformation of *C*-β,β-trehalose, in which no stereoelectronic (exo-anomeric) effects are operating, is the same as the one predicted and determined for β,β-trehalose, thereby demonstrating that steric effects alone are sufficient to cause the greater stability of the preferred conformation of the parent disaccharide.

C-Disaccharides constitute a class of non-natural analogs of disaccharides in which the interglycosidic oxygen atom is replaced by a methylene group. As potential inhibitors of glycosyl hydrolases such as the disaccharidases of the digestive tract,[1] and as probes of the stereoelectronic effects which may control the conformation of oligosaccharides,[2] these pseudodisaccharides are of considerable interest and have started to attract a great deal of attention. The first example of a *C*-disaccharide, methyl *C*-gentiobioside, was reported in 1983 by Sinaÿ and Rouzaud;[3] this compound is also the first of its kind to have been submitted to an X-ray crystal structure analysis.[4] Since then, several other chain-extended[5] and branched-chain[6] *C*-disaccharides have been described; Kishi's extensive contributions in this field have recently culminated with the synthesis of a *C*,*C*-trisaccharide,[7] the bis-carba-analog of a blood group antigenic determinant. With the exception of *C*-sucrose[8] and a few related analogs,[9] no other examples of the challenging carba-analogs of nonreducing disaccharides have been reported. Derivatives of *C*-disaccharides substituted at the methylene bridge[10] have started to appear, and other types of carbon-linked disaccharides[11] have been described.

In preliminary studies,[12] we had shown that silylation of the anion derived from glucosylnitromethane peracetate (1) occurred at the nitronate oxygen atom only, thus indicating that the equilibrium between the cyclic (2) and the open-chain form (3) of this anion[13] was entirely in



favor of the cyclic form. It was expected therefore that nitronate anions of this type could be used as the *C*-nucleophilic species in nitroaldol reactions. Since glycosylnitromethanes are readily accessible from the parent sugars,[14] we have investigated their condensation

† For a preliminary communication of part of this work: Martin, O. R.; Lai, W. *J. Org. Chem.* **1990**, *55*, 5188.

‡ Taken in part from Lai, W. Ph.D. Dissertation, SUNY-Binghamton, 1992.

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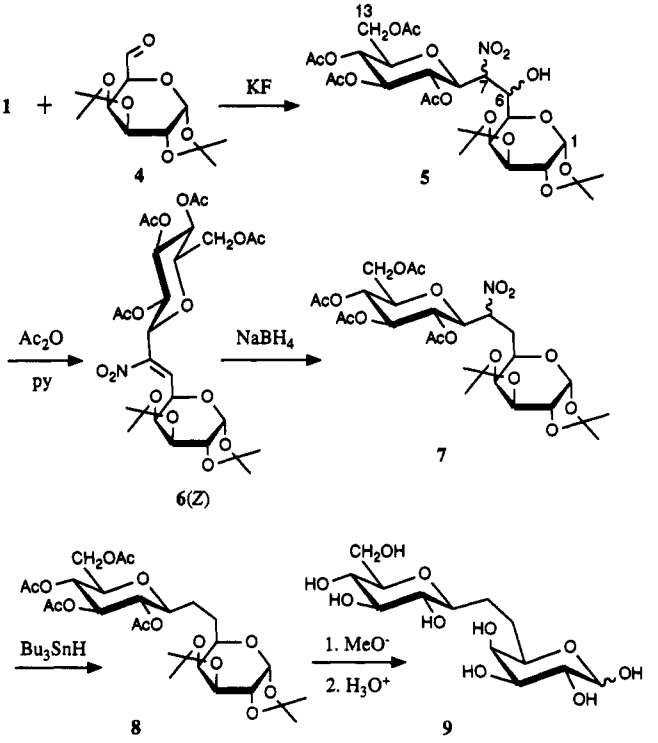
with 6-*aldehydo*-dialdoses and *aldehydo*-hexoses as the key step in a concise approach to (1→6)- and (1→1)-linked *C*-disaccharides. A well-known tool for the chain extension of carbohydrates,[15] the nitroaldol condensation (Henry reaction)[16] has been used previously for the construction of the skeleton of very long chain carbohydrates[17] (e.g., tunicamine) and analogs[11a] but has not been applied to glycosylnitromethane derivatives such as **1**.[18] We report, in this article, the brief and convenient synthesis of β-(1→6)- and β,β-(1→1)-linked *C*-disaccharides, including the symmetrical *C*-β,β-trehalose, by way of this nitroaldol methodology and conformational studies on these pseudo-disaccharides.

Results and Discussion

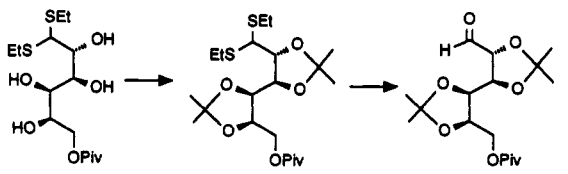
Synthesis. 1. β-(1→6)-Linked System. In the presence of fluoride ion, a reagent that has been used by Suami et al.[17d-f] and others[19] to promote the nitroaldol condensation of base-sensitive substrates, compound **1**[14,20] reacted rapidly with galactose-derived aldehyde **4** to give nitrotridecose derivative **5** in 52% (isolated) yield. Since unreacted **1** was easily recovered by crystallization, the actual yield of the coupling reaction, based on consumed **1**, was greater than 80%. Interestingly, the nitroaldol reaction led to one overwhelmingly predominant stereoisomer (>90%) which exhibited, in its ^{1}H NMR spectrum, the expected series of 13 multiplets corresponding to H-1 to H-13 of the tridecose skeleton. The configuration at C-7 of **5** is probably *R*, as in the case of the major isomer of **7** (see below), but the configuration at C-6 remains uncertain. Compound **5** is only a few straightforward steps away from a (1→6)-linked *C*-disaccharide (Scheme I): dehydration, which was promoted by acetylation of **5** under conventional conditions, leading to nitroalkene **6** (91%, *Z*/*E* ~1:1 initially, slowly isomerizing to *Z* only; assignment based on δ H-6, with δ H-6(*Z*) < δ H-6(*E*)), reduction of the double bond of **6** using $NaBH_4$[17b,21] at 0 °C, to give tridecose derivative **7** (71%, mostly *R* at C-7, see below), radical denitration[22] of **7** using Bu_3SnH which afforded protected *C*-disaccharide **8** (57%, unoptimized), and removal of the protecting groups (89%). This sequence of reactions thus provided **9**, the carba-analog of 6-*O*-β-D-glucopyranosyl-D-galactose,[23] in six steps only from **1**; since glycosylnitromethanes can be obtained from most

Scheme I



free sugars,[12] this expeditious methodology should constitute a general synthesis of β-(1→6)-linked *C*-disaccharides. Compound **9** is a reducing *C*-disaccharide (β/α ratio 2.4:1) exhibiting an optical activity ($[\alpha]^{20}_D$ +11.9° in H_2O) very similar to that observed for the parent *O*-disaccharide (ref 24, $[\alpha]^{18}_D$ +13.9° in H_2O; ref 25, $[\alpha]_D$ +10° in H_2O), which is found as a structural element in certain exocellular polysaccharides.[23]

2. β,β-(1→1)-Linked Systems. Initially, the condensation was attempted between **1** and 5-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-*aldehydo*-D-glucose;[26] with this aldehyde, the ring size of the *C*-glycosidic unit being created would have been controlled. This *aldehydo*-sugar, however, underwent extensive β-elimination under the conditions of the coupling reaction. With O-2 and O-3 incorporated into a cyclic structure, the *aldehydo*-hexose was much more resistant to β-elimination: *aldehydo*-glucose derivative



12, prepared from glucose diethyl dithioacetal by selective pivaloylation,[27] acetalation with dimethoxypropane, and demercaptalation, reacted efficiently with **1** (Scheme II) under the same coupling conditions as **4**. In order to avoid the degradation of the resulting, unstable nitroalditols (**13**, mixture of epimers), the reaction mixture was processed by dilution with ether and filtration through silica

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(16) Baer, H. H.; Urbas, L. In *The Chemistry of the Nitro and Nitroso Groups*; Feuer, H., Ed.; Wiley-Interscience: New York, 1970; Part 2, pp 75–200.

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(18) The reaction of unprotected **1** with formaldehyde was reported shortly before the submission of this paper: Petrus, L.; BeMiller, J. *Carbohydr. Res.* **1992**, *230*, 197.

(19) Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948 and references cited therein.

(20) Sowden, J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1946**, *68*, 1511.

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(22) Ono, N.; Kaji, A. *Synthesis* **1986**, 693.

(23) *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1967; Vol. I, Part F "Carbohydrate Chemistry", p 623.

(24) Freudenberg, K.; Wolf, A.; Knopf, E.; Zaheer, S. H. *Ber.* **1928**, *61*, 1743.

(25) Goldstein, I. J.; Whelan, W. J. *J. Chem. Soc.* **1963**, 4264.

(26) Martin, O. R.; Khamis, F. E.; El-Shenawy, H.; Rao, S. P. *Tetrahedron Lett.* **1989**, *30*, 6139.

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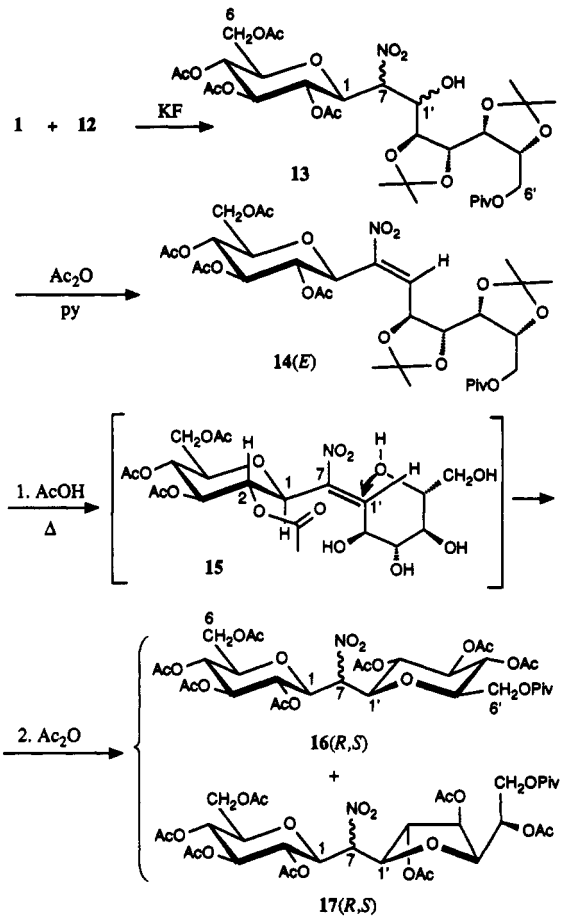
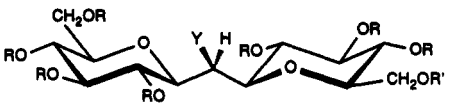
Scheme II



gel, and the products were immediately dehydrated (by acetylation) to afford nitroalkene **14** (mostly *E* isomer) in 44% overall yield from **1** (64% based on **1** consumed). The conversion of **14**(*E*) into bis(glycosyl)nitromethanes required a delicate operation, namely, the cleavage of the isopropylidene groups without affecting the nitroalkene function, followed by the cyclization of the resulting ϵ/ζ-hydroxy-α,β-unsaturated nitro compound **15** by an internal Michael addition. Among the wide variety of conditions investigated, the best results were obtained with 80% AcOH at reflux temperature for 1 h, which promoted both deacetonation and cyclization. The resulting mixture was acetylated and the two major components separated by chromatography:[28] the further elaboration of these components, which exhibited NMR spectra too complex for interpretation, revealed that they were the expected bis(glycosyl)nitromethanes with different ring sizes, pyranose–pyranose derivative **16** (36% from **14**) and pyranose–furanose isomer **17** (25%), both obtained as ~1:1 mixtures of epimers at C-7 and as the "β-anomer" exclusively at C-1′. That **17** was formed with the β-configuration only at C-1′ is remarkable and suggests that the cyclization is not under thermodynamic control:[29] considering that the substrate **15** adopts the sterically most favorable conformation about C-1–C-7 in which the double bond and C-1–H-1 are eclipsed, the "front" (1′-*re*) face of the double bond is considerably more crowded than the "back" face as a result of the presence of the acetoxy group at C-2. We believe, therefore, that both **16** and **17** are formed by an internal nucleophilic attack occurring at the *si* face of the double bond at C-1′ of **15**.

Denitration of the bis(glucopyranosyl)nitromethane derivative **16**(*R,S*) using Bu_3SnH gave a *single* product (**18**, 80%) which was immediately deacylated to afford **19**, *C*-β,β-trehalose or bis(β-D-glucopyranosyl)methane, in 84% yield. Compound **19**, a material extremely hygroscopic in anhydrous form characterized by an optical rotation ($[\alpha]^{22}_D$ −20.4° in H_2O) quite different from that of β,β-trehalose ($[\alpha]_D$ −40°),[30] is the first example of a carba-analog of a symmetrical, (1→1)-linked disaccharide: its peracetate, **20**, exhibits the expected, strikingly simple ^1H NMR spectrum (Figure 1). In both **19** and **20**, the two protons of the methylene bridge are magnetically nonequivalent and appear as a higher-order system which can be simulated (Figure 2), thereby providing useful data for the structural analysis of these symmetrical pseudodisaccharides (see below). Surprisingly, the optical rotation of **20** ($[\alpha]^{22}_D$ −17.2° in $CHCl_3$) is identical with that measured for β,β-trehalose peracetate by E. Fischer in 1909![31]



18 Y=H, R=Ac, R′=Piv
19 Y=R=R′=H
20 Y=H, R=R′=Ac
21 Y=NO_2, R=R′=H
22 Y=NO_2, R=R′=Ac
23 Y=NH_2, R=R′=H
24 Y=NHAc, R=R′=Ac

Deacylation of precursor **16** gave free bis(β-D-glucopyranosyl)nitromethane (**21**)[32] which was reacetylated to provide **22**. In both **21** and **22**, the bridge carbon is *pseudoasymmetric* and the two sugar units are *diastereotopic*, which is quite evident from the ^1H NMR spectrum of **22** (Figure 1).

Reduction of the nitro group in **7** or **21** should give access to aminomethylene-bridged disaccharide analogs; as homologs of potent glycosidase inhibitors (glycosyl-[33] or diglycosylamines[34]), these compounds are of considerable biochemical significance. Catalytic hydrogenation of the nitro group in **21**, under the conditions (H_2–PtO_2) used to reduce the nitro group in glycosylnitromethanes,[35] as well as at elevated pressure and temperature (up to 13 atm and 100 °C), was unsuccessful. A sample of the desired bis(glycosyl)methylamine **23** could be obtained using iron(II) hydroxide as the reducing species, a method described by Petrus and co-workers[36] for the reduction of glycosylnitromethanes; the method, however, gave erratic

(28) It should be noted that while **16** and **17** are fairly well resolved on TLC, the corresponding peracetates are not resolved. Deacylation, after cyclization, followed by reacetylation is therefore not recommended.

(29) The D-glucofuranosylnitromethanes, produced as minor components in the thermodynamically-controlled synthesis of β-D-glucopyranosylnitromethane,[14a] are formed as an α/β (3:2) mixture. See also refs 13 and 14b.

(30) Birch, G. G. *Adv. Carbohydr. Chem.* **1963**, *18*, 201 and references cited therein.

(31) Fischer, E.; Delbrück, K. *Ber.* **1909**, *42*, 2776.

(32) Compound **21** is quite stable under normal deacylation conditions (MeONa in MeOH). No other isomers were formed after 5 days at ambient temperature.

(33) Legler, G. *Pure Appl. Chem.* **1987**, *59*, 1457.

(34) Linek, K.; Alföldi, J.; Defaye, J. *Carbohydr. Res.* **1987**, *164*, 195.

(35) (a) Sowden, J. C.; Bowers, C. H.; Lloyd, K. O. *J. Org. Chem.* **1964**, *29*, 130. (b) Sowden, J. C.; Oftedahl, M. L. *J. Org. Chem.* **1961**, *26*, 1974.

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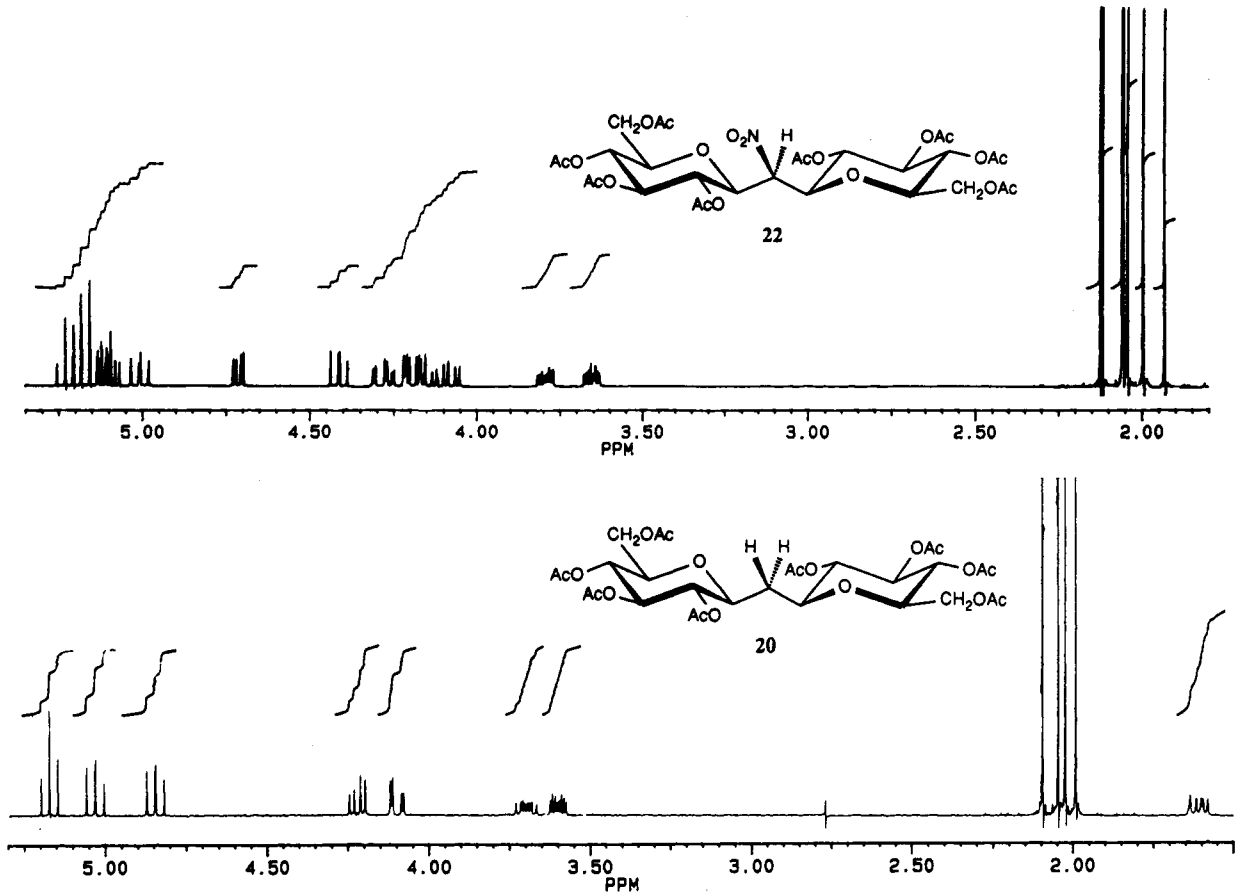


Figure 1. ^{1}H NMR spectra of **20** and **22**.

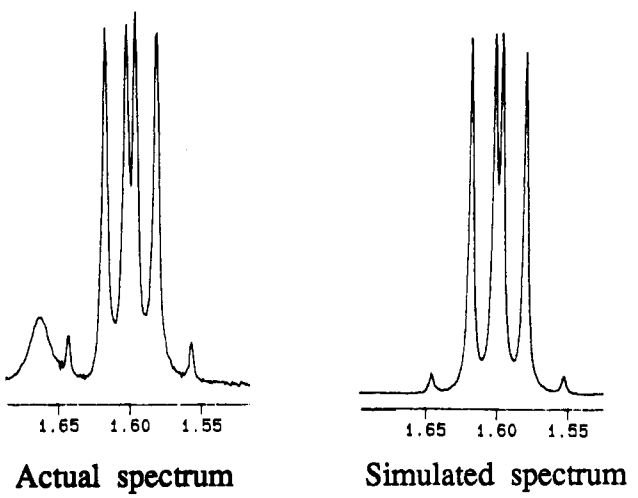
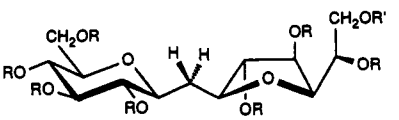


Figure 2. H-7,7′ signal of **20**.



25 R=Ac, R'=Piv
26 R=R'=H
27 R=R'=Ac

results. Steric effects are undoubtedly responsible for the low reactivity of the nitro group in **21**. Compound **23**, characterized as its peracetate **24**, is the first example of an aminomethylene-bridged *C*-disaccharide.

Finally, the pyranose–furanose isomer **17** was denitrated under the same conditions as **16**; this reaction afforded a *single* product, **25**, thereby proving that **17** was constituted of stereoisomers at C-7 only. The β-configuration at C-1′ was established on the basis of the $^3J_{H,H}$ constants in the furanoid unit (see below). Deacylation of **25** gave **26**, an unusual (1→1)-linked *C*-disaccharide (β-D-Glc*p*-*C*-(1→1)-β-D-Glc*f*) containing *C*-β-D-glucosyl units in both pyranoid and furanoid forms. Interestingly, the corresponding *O*-disaccharide, as well as other anomers of D-Glc*p*-(1→1)-D-Glc*f*, are not known.

Conformational Studies. Since oligosaccharides play fundamental biological roles as sensors and markers at the surface of cells, an understanding of the steric and electronic factors governing their three-dimensional structure[37] is essential. In this context, the carba-analogs are particularly useful probes of these factors since the stereoelectronic effects[2] characteristic of the acetal function in glycosides are nonexistent. Kishi's extensive studies on model *C*-glycosides[38] and on *C*-disaccharides[5,39] have led to the controversial conclusion[7] that the conformation of carbohydrates can be predicted solely on the basis of the preference of the glycosidic bond for the "exo-anomeric" conformation (C_2–C_1 and O_1–$C_{aglycon}$ anti) and the consideration of 1,3-diaxial-like interactions.

1. (1→6)-Linked Systems. Because of extensive signal overlap in **8** and the presence of two anomers in **9**, their spectra could not be analyzed and the discussion is restricted to compound **7**. The major stereoisomer of **7**

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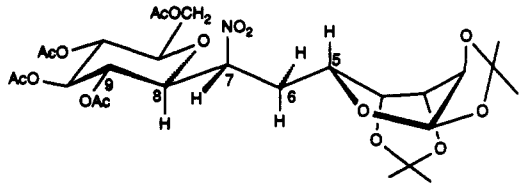
(isomer ratio ~7:1) exhibits coupling constants (Table II) which indicate well-defined anti or gauche relationships between the protons at C-5,6,7, and 8. Of the few combinations of configuration (at C-7) and conformation compatible with this set of coupling constants, one can find only one, **A**, which is devoid of destabilizing interactions (1,3-diaxial-type and gauche).



A (7-*R*)

In structure **A**, six carbon atoms are in a fully extended zig-zag conformation, and the configuration at C-7 is *R*. Since **7** is generated from **6** under conditions of thermodynamic control, it is probable that this structure corresponds to that of the major stereoisomer of **7**, the predominant configuration being favored by conformational effects. This interpretation is consistent with both experimental observations[38] and theoretical calculations[40] which have shown that, in "*β-C*-glycosides", the torsional angle equivalent to C_4–C_5–C_6–C_7 and C_6–C_7–C_8–C_9 in **7** always exhibits a strong preference for the antiperiplanar disposition; the presence of the nitro group at C-7 is unlikely to alter this situation.[41] The measurable coupling constants in **8** (after removal of the nitro group) appear, indeed, to indicate that compound **8** adopts, as one would predict, the same conformation as **7**.

2. (1→1)-Linked Systems. In spite of the equivalence of the two sugar units in **19** and **20**, all of the $^3J_{H,H}$ couplings about the interglycosidic linkages can be determined from the simulation of the signal of the protons at C-7 (Figure 2). The magnitude of these coupling constants (in **19**, $J_{1,7} = J_{1',7'} = 9.6$ Hz; $J_{1,7'} = J_{1',7} = 2.4$ Hz; in **20**, $J_{1,7} = J_{1',7'} = 11.0$ Hz; $J_{1,7'} = J_{1',7} = 3.0$ Hz) indicates unambiguously that each proton at C-7 is anti with respect to one H-1 and gauche with respect to the other H-1. Of the two conformations compatible with these data (**B** and **C**, Figure 3), one of them (**B**, corresponding to standard torsional angles[42] $\phi,\psi = -60°,-60°$) is destabilized by the (1,3-diaxial-type) interactions between the substituent at C-2 and H-1 of the other unit; conformation **C** (which corresponds to $\phi,\psi = +60°,+60°$) is sterically much more favorable and is clearly the preferred solution conformation of the *β,β*-trehalose analogs **19** (in CD_3OD) and **20** (in $CDCl_3$).

In this structure (**C**), both *β-C*-glycosidic linkages adopt the most favorable[38,40] anti conformation, thus forming an extended zig-zag system (comprising seven carbon atoms if the C-3's are included). Most interestingly, *this conformation is essentially the same as the one predicted very recently*[43] *to be the most stable for β,β-trehalose* ($\phi,\psi = +44°,+44°$; MM3 calculations); the conformational analysis of a model compound (*β,β*-form of 2-(tetrahydropyran-2-yloxy)tetrahydropyran) had led previously to similar results.[44] Furthermore, the limited experimental data available on *β,β*-trehalose had been taken as evidence that the nonreducing disaccharide adopts that same conformation in solution.[45] The conformational behavior of *β,β*-trehalose, as determined by theoretical and experimental methods, has been interpreted *as a direct manifestation of the exo-anomeric effect.* Since the methylene-bridged analog **19**, in which there is no exo-anomeric effect, adopts the same conformation, our results show that *steric effects alone are sufficient to cause the higher stability of the +60°,+60° conformation of the parent disaccharide.* Whether or not additional stabilization is provided by the exo-anomeric effect, however, cannot be concluded from the comparison with **19**.[46]

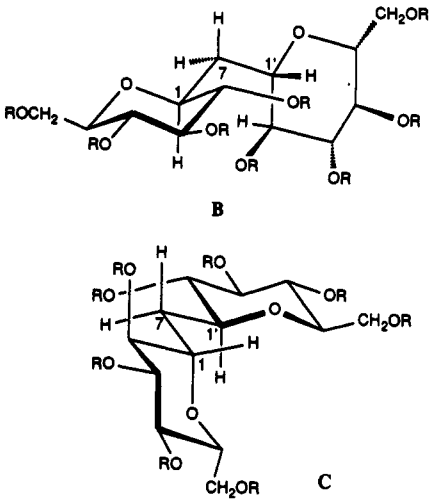
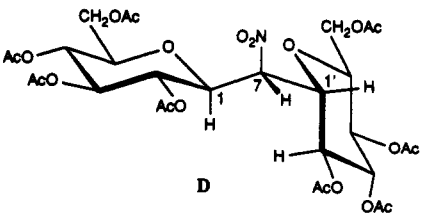


Figure 3. Conformations of **19** (R = H) and **20** (R = Ac).

The replacement of *either* hydrogen of the methylene bridge in **19** or **20** by a substituent (NO_2 or NHAc) introduces a strain between this substituent and the substituent at C-2 or -2′ in 1,3-diaxial relation, which results in a decrease of the $J_{1,7\text{-anti}}$ coupling constant to 8.2 Hz (in **22**) and 7.1 Hz (in **24**). These values indicate either a nonnegligible contribution of a (H,H)-gauche conformation about the corresponding C–C linkage (such as conformation **D**, equivalent to the 180°,+60° conformation[47] of *β,β*-trehalose), the (H,H)-anti conformation remaining the major contributing form of **22** and **24**, or a single conformer deviating from the ideal staggered conformation.



In the pyranose–furanose compounds (**17**, **26**, **27**), the anomeric configuration of the furanoid unit can be

(40) Lopez-Herrera, F. J.; Pino-Gonzalez, M. S.; Planas-Ruiz, F. *Tetrahedron: Asymmetry* **1990**, *1*, 465.

(41) The nitro group is characterized by a much smaller conformational free energy (0.8–1.3 kcal/mol) than alkyl groups (1.7–2.6 kcal/mol). See, for example: (a) Trager, W. F.; Huitric, A. C. *J. Org. Chem.* **1965**, *30*, 3257. (b) Franklin, N. C.; Feltkamp, H. *Tetrahedron* **1966**, *22*, 2801.

(42) For a clear definition of the ϕ,ψ angles, see ref 37. In **19** and **20**, ϕ is H_1–C_1–C_7–$C_{1'}$ and ψ C_1–C_7–$C_{1'}$–$H_{1'}$.

(43) Dowd, M. K.; Reilly, P. J.; French, A. D. *J. Comput. Chem.* **1992**, *13*, 102.

(44) Tvaroska, I.; Vaclavik, L. *Carbohydr. Res.* **1987**, *160*, 137.

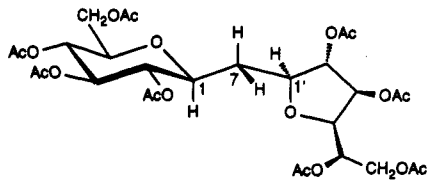
(45) Pavia, A. A.; Ung-Chhun, S. N.; Lacombe, J.-M. *Nouv. J. Chim.* **1981**, *5*, 101.

(46) It is interesting to note that the −60°,−60° (non-exo-anomeric) conformation of *β,β*-trehalose, corresponding to the alternate conformation of **19** (**B**), has been predicted to be more than 9 kcal/mol less stable than the +60°,+60° conformation (**C**) and does not correspond to an energy minimum.[43]

(47) This conformation is only 4 kcal/mol less stable than the +60°,+60° conformation in *β,β*-trehalose.[43]

established conclusively, by contrast with other related systems,[48] from the values of the ring $^3J_{H,H}$ coupling constants. Thus, the fact that the $J_{2',3'}$ coupling is extremely small (0–0.5 Hz) indicates that $\theta_{2',3'}$ is in the order of 80–90°,[49] and, therefore, that the furanoid ring adopts a puckered, $^3T_2$-type conformation, very similar to that of β-D-xylo- and β-D-glucofuranosides;[50] that $J_{1',2'}$ is also very small (1.5–1.9 Hz, $\theta_{1',2'}$ 100–110 °C) is compatible only with the trans relationship of H-1′ and H-2′,[51] thus establishing the β-configuration at C-1′ of **17**, **26**, and **27**. All the ring $^3J_{H,H}$ coupling constants in those systems are remarkably similar to those observed in β-D-xylo- and β-D-glucofuranosides[50] (the additional electronegative substituent at C-1 being responsible for the smaller $J_{1,2}$ in the furanosides).

Finally, the coupling constants observed between the bridge protons and H-1,1′ in **27** (in C_6D_6) establish, again, that the preferred conformation about *both* β-*C*-glycosidic linkages is the anti conformation (both C_2–C_1–C_7–$C_{1'}$ and C_1–C_7–$C_{1'}$–$C_{2'}$ torsional angles ~180°), the C–C linkages forming an extended zig-zag system (**E**); the alternate conformation compatible with the observed *J* is destabilized by 1,3-diaxial-type interactions. A somewhat greater degree of conformational flexibility about the C_7–$C_{1'}$(furanose) linkage is observed in the corresponding free *C*-disaccharide **26**.



E

In conclusion, the carba-analog of β,β-trehalose proved to be a useful probe for the conformational study of a symmetrical disaccharide; the well-defined conformation of this bis(β-*C*-glycoside) provided further evidence for the preferred, anti conformation of the β-*C*-glycosidic linkage. Further investigations on symmetrical *C*-disaccharides are in progress.

Experimental Section

For experimental methods, see ref 52. ^{1}H- and ^{13}C-NMR spectra were recorded at 360 and 90 MHz, respectively, on a Bruker AM-360 spectrometer. Chloroform-*d* was used as the solvent with tetramethylsilane as the internal standard (δ = 0.00 ppm), unless otherwise stated. Chemical shifts and coupling constants were obtained in general from first-order analysis of the spectra; higher-order systems were simulated using the PCPMR program (Serena software). Mass spectra were recorded on a NERMAG R 1010C Model 2000 quadrupole instrument. The following solvent systems were used in chromatographic separations: A, 5:6; B, 1:1; C, 5:8; D, 1:4; E, 2:3, F, 3:2 ethyl acetate–hexanes; G, 3.5:3.5:8:2 chloroform–ethyl acetate–methanol–water; H, 3.5:4:1 chloroform–methanol–water. Elemental analyses were performed by Atlantic Microlab (Norcross, GA).

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol (1). D-Glucose was reacted with nitromethane under the conditions described by Hough and Shute;[53] the resulting, epimeric nitroheptitols were isolated as a crystalline mass in 35–40% yield. The nitroalditols were converted into cyclic products by heating a 0.5–1.0 M aqueous solution under reflux for 30 h.[35a] The technique of Petrus and co-workers[14a] was used to isolate pure **1** [45–50% of recrystallized product, mp 177.0–117.8 °C (MeOH); lit.[14a] mp 175–176 °C; lit.[20] mp 177–177.5 °C]. **Acetylation Procedure.** To a suspension of **1** (5.0 g, 22.4 mmol) in acetic anhydride (60 mL) was added boron trifluoride etherate (1.6 mL); the mixture was stirred for 1 h at room temperature. The resulting solution was added dropwise to crushed ice which promoted the precipitation of **1**; after 15 h at 0 °C, the precipitate was filtered, washed with cold water, and dried. **1**: yield 8.43 g (96%); mp 141.5–142 °C (lit.[20] mp 144–145 °C); $[\alpha]^{23}_D$ +4.6° (*c* 1.3, $CHCl_3$) [lit.[20] $[\alpha]^{22}_D$ +4.2° (*c* 4.2, $CHCl_3$)].

(*Z*)-9,10,11,13-Tetra-*O*-acetyl-8,12-anhydro-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-nitro-α-D-*glycero*-D-*gulo*-D-*galacto*-tridec-6-eno-1,5-pyranose (6(*Z*)). To solution of aldehyde **4**[54] (3.84 g, 14.9 mmol) in CH_3CN (50 mL) were added nitro sugar **1** (4.0 g, 10.2 mmol), KF (0.90 g, 15.6 mmol), and 18-crown-6 (0.50 g). The mixture was stirred for 3 h at room temperature. Water (200 mL) and ethyl acetate (600 mL) were then added; the organic layer was separated, dried (Na_2SO_4), and concentrated, and the residual syrup (7.24 g) was submitted to flash chromatography (solvent A) to give nitro-tridecose derivative **5** as one major (~90%) stereoisomer (3.43 g, 52%) and unreacted **1** (1.44 g, 3.68 mmol). Based on nitro sugar (**1**) consumed, the yield of **5** is 81%. Spectral data for **5**: IR (film) 3500 (OH), 1765 (C=O), 1563 and 1378 cm^{-1} (NO_2); ^{1}H NMR, see Tables I and II; ^{13}C NMR δ 20.50, 20.53 (2 C), 20.62, 24.28, 24.81, 25.61, 25.88 (2 C*Me*$_2$, 4 OCO*Me*), 61.33 (C-13), 67.07, 67.79, 68.82, 69.06, 70.29, 70.38, 70.52, 74.31, 75.14, 76.04, 85.48 (C-2–12), 96.19 (C-1), 109.17, 109.38 (2 *C*Me$_2$), 168.87, 169.22, 170.33, 170.87 (4 *O*COMe). Compound **5** was used without further purification in the next step: to a solution of **5** (3.01 g, 4.64 mmol) in $CHCl_3$ (30 mL) were added, at 0 °C, Ac_2O (2.6 mL) and pyridine (1.5 mL). After 2 d at room temperature, the mixture was extracted with cold aqueous HCl; the organic phase was then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and water (20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (solvent B) of the syrupy residue afforded a homogeneous mixture (2.65 g, 91%) of **6**(*Z*) (R_f 0.70, solvent B) and **6**(*E*) (R_f 0.55); on standing, **6**(*E*) isomerizes slowly to **6**(*Z*). Careful crystallization of the mixture (CH_2Cl_2–hexane) afforded pure **6**(*Z*): mp 200.2–200.3 °C; $[\alpha]^{22}_D$ −75.3° (*c* 1.7, $CHCl_3$); IR (film) 1760 (C=O), 1533 and 1375 cm^{-1} (NO_2); ^{1}H NMR, see Tables I and II; ^{13}C NMR δ 20.39, 20.55 (2 C), 20.71, 24.42, 24.90, 25.91 (2 C), (4 OCO*Me*, 2 C*Me*$_2$), 61.84 (C-13), 65.78, 67.88, 69.96, 70.51, 70.87, 72.76, 74.07, 75.07, 76.47 (C-2–5, C-8–12), 96.23 (C-1), 109.20, 109.87 (2 *C*Me$_2$), 135.83 (C-6), 145.70 (C-7), 169.3, 169.5, 170.2, 170.6 (4 *O*COMe).

Anal. Calcd for $C_{27}H_{37}NO_{16}$ (631.59): C, 51.35; H, 5.90; N, 2.22. Found: C, 51.24; H, 5.92; N, 2.19.

A sample of *E* isomer, **6**(*E*), was isolated by flash chromatography. ^{1}H NMR, see Tables I and II.

9,10,11,13-Tetra-*O*-acetyl-8,12-anhydro-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-nitro-α-D-*erythro*-L-*talo*(or L-*galacto*)-D-*galacto*-trideco-1,5-pyranose (7). To a solution of **6**(*Z*) (256 mg, 0.41 mmol; the mixture of *Z* and *E* isomers can also be used) in a minimum amount of CH_2Cl_2 was added, at 0 °C, a solution of $NaBH_4$ (7.6 mg, 0.2 mmol) in MeOH (5 mL). The mixture was stirred at 0 °C until complete disappearance of the UV-active starting material (~30 min). Ethyl acetate (50 mL) was then added, and the mixture was washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (solvent C) of the residue gave pure **7** (185 mg, 71%), as a 7:1 mixture of stereoisomers at C-7. Flaky crystals of the major stereoisomer were obtained by recrystallization from EtOH: mp 173.2–174.0 °C; R_f 0.65 (solvent B); $[\alpha]^{25}_D$ −35.4° (*c* 0.24, $CHCl_3$, 1-dm cell); IR (film) 1760 (C=O), 1530 and 1370 cm^{-1} (NO_2); ^{1}H

(48) Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698.
(49) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Org. Magn. Reson.* **1981**, *15*, 43. See also: Serianni, A. S.; Barker, R. *J. Org. Chem.* **1984**, *49*, 3292.
(50) Angyal, S. J. *Carbohydr. Res.* **1979**, *77*, 37.
(51) In cis relationship, $\theta_{1',2'}$ would be ≤30° and $J_{1',2'}$ would be at least >3.5 Hz.
(52) Martin, O. R.; Rao, S. P.; El-Shenawy, H. A.; Kurz, K. G.; Cutler, A. B. *J. Org. Chem.* **1988**, *53*, 3287.
(53) Hough, L.; Shute, S. H. *J. Chem. Soc.* **1962**, 4633. The aci-nitroheptitol salts were precipitated using 1-butanol (instead of ether) and $CaSO_4$ was omitted in the reaction mixture.
(54) Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267.

Table I. ^{1}H-NMR Data: Chemical Shifts[a]

	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	H-10	H-11	H-12	H-13A	H-13B	other signals OAc, CMe_2
1[b]							4.41 4.54	4.29	4.94	5.27	5.08	3.76	4.05	4.28	2.02, 2.04, 2.07, 2.08
4A[c]	5.58	4.34	4.62	4.28	[3.73–3.89]										
5	5.44	4.30	4.62	4.43	3.72	4.23	4.86	4.14[d]	[5.14–5.16]		5.07[d]	3.68	4.03	4.26	1.97, 2.01, 2.03, 2.05 1.30, 1.33, 1.42, 1.49 3.21 (OH)
6(*Z*)	5.52	4.35	4.65	4.47	5.00	6.31		4.64	[5.21–5.25]		5.15	3.81	4.14	4.22	1.97, 2.01, 2.05, 2.10 1.31, 1.33, 1.48, 1.50
6(*E*)	5.60	4.39	4.64	4.25	4.80	7.30		4.94	5.52	[5.17, 5.27]		3.75	4.14	4.26	1.94, 1.99, 2.04, 2.10 1.32, 1.38, 1.47, 1.69
7	5.45	4.27	4.58	4.12	3.69	2.05 2.37	4.94	3.92	—[5.07–5.15]—			3.66	[4.13–4.15]		1.98, 2.01, 2.02, 2.06 1.28, 1.33, 1.39, 1.46
8	5.51	4.28	4.58	4.11	3.67	[~1.20–1.85]		3.43	4.88	5.15	5.06	3.60	4.07	4.27	2.00, 2.02, 2.03, 2.09 1.32, 1.35, 1.46, 1.50

[a] δ in ppm, for solutions in $CDCl_3$. [b] For easier comparison, positions 1–7 in 1 have been numbered 7–13 in this table. [c] Data for 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. [d] As a result of the near equivalence of H-9 and H-10, the signals of H-8 and H-11 are complex multiplets.

Table II. ^{1}H-NMR Data: Coupling Constants (in hertz)[a]

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$	$J_{10,11}$	$J_{11,12}$	$J_{12,13}$	$J_{13A,13B}$	other J's
1							2.7 9.0		——[9.5–10]——		10.0	2.2 4.9	12.5	$J_{7A,7B}$ 13.7
4A	5.0	2.4	8.0	1.7	?									
5	4.9	2.4	8.0	1.8	9.2	4.1	4.1		——[~10]——		9.8	4.9 2.4	12.5	
6(*Z*)	5.0	2.6	7.8	2.0	7.5				——[~10]——		9.9	2.2 4.8	12.5	
6(*E*)	5.1	2.6	7.7	1.9	8.2			10.1	—[~10]—		10.0	2.1 4.5	12.6	
7	5.0	2.4	8.0	1.8	11.0[b] 2.1	2.4 11.6	4.0	9.5	——[9.5–10]——			?	?	$J_{6A,6B}$ 15.0
8	5.0	2.3	7.9	1.8	10[b] 2	?	1.9[b] 9.8	9.8	—[9.5–10]—		9.8	2.3 4.7	12.3	

[a] When two values are given, the top value is coupling with H_A, the bottom one with H_B. [b] Order arbitrary.

NMR, see Tables I and II; ^{13}C NMR δ 20.53, 20.54, 20.62, 20.65, 24.22, 24.88, 25.70, 25.90 (4 OCO*Me*, 2 C*Me*$_2$), 29.69 (C-6), 61.61 (C-13), 63.59, 67.80, 68.85, 70.45, 70.88, 72.58, 74.36, 76.23, 77.06, 82.90 (C-2–5, C-7–12), 96.23 (C-1), 108.82, 109.34 (2 *C*Me$_2$), 168.96 (2 C), 170.37, 170.60 (4 *O*COMe); CI-MS 651 (100, $[M + NH_4]^+$).

Anal. Calcd for $C_{27}H_{39}NO_{16}$ (633.60): C, 51.18; H, 6.20; N, 2.21. Found: C, 51.81; H, 6.33; N, 2.10.

9,10,11,13-Tetra-*O*-acetyl-8,12-anhydro-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*gulo*-D-*galacto*-trideco-1,5-pyranose (8). A mixture of 7 (384 mg, 0.61 mmol), Bu_3SnH (0.5 mL, 1.83 mmol), and AIBN (30 mg) was heated under reflux for no more than 30 min. The mixture was then concentrated and the residue submitted to flash chromatography (solvent C), which afforded pure, syrupy 8 (204 mg, 57%): $[\alpha]^{22}_D$ −45.6° (*c* 1.8, $CHCl_3$); R_f 0.65 (solvent B); IR (film) 1760 cm^{-1} (C=O); ^{1}H NMR, see Tables I and II; ^{13}C NMR δ 20.60, 20.65, 20.75, 20.76 (4 OCO*Me*), 24.27, 24.92, 25.96, 26.05, 26.20, 28.08 (2 C*Me*$_2$, C-6,7), 62.28 (C-13), 67.65, 68.63, 70.43, 70.86, 71.93, 73.00, 74.58, 75.65, 77.94 (C-2–5, C-8–12), 96.43 (C-1), 108.32, 108.99 (2 *C*Me$_2$), 169.50, 169.69, 170.45, 170.73 (4 *O*COMe).

Anal. Calcd for $C_{27}H_{40}O_{14}$ (588.60): C, 55.10; H, 6.85. Found: C, 54.92; H, 6.85.

8,12-Anhydro-6,7-dideoxy-D-*glycero*-D-*gulo*-D-*galacto*-tridecose (9). To a solution of 8 (181 mg, 0.31 mmol) in MeOH (15 mL) was added a 0.5 M solution of MeONa in MeOH (1 mL). After 30 min at room temperature, the mixture was neutralized with methanol-washed Amberlite IR-120(H$^+$) resin, the resin was removed by filtration, and the filtrate was concentrated. The residual syrupy product was dissolved in water (10 mL); Amberlite IR-120(H$^+$) ion-exchange resin, previously washed with hot (70 °C) water, was added to the solution and the mixture was heated at 70 °C for 2.5 h. The resin was then removed from the cooled solution by filtration, and the filtrate was concentrated to give pure 9 (94 mg, 89%): $[\alpha]^{22}_D$ +11.9° (*c* 1.4, H_2O); R_f 0.27 (solvent G); ^{1}H NMR (D_2O, ref Me_2CO, δ = 2.12) δ 4.43 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1β), 5.11 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1α), relative intensity β/α 2.4:1; ^{13}C NMR (D_2O, ref Me_2CO, δ = 30.5; some signals overlap) δ 26.12, 27.49 (C-6,7), 61.34 (C-13), 68.59, 69.64, 70.37, 70.90, 72.16, 73.29, 73.77, 75.03, 77.68, 79.43, 79.65, 79.83, 92.47 (C-1α), 96.61 (C-1β).

Anal. Calcd for $C_{13}H_{24}O_{10}\cdot 0.25H_2O$: C, 45.28; H, 7.16. Found: C, 45.14; H, 7.51.

6-*O*-Pivaloyl-D-glucose Diethyl Dithioacetal (10). To a solution of D-glucose diethyl dithioacetal (5.0 g, 17.5 mmol) in pyridine (50 mL) was added, at 0 °C, pivaloyl chloride (2.13 mL, 17.1 mmol), slowly and dropwise. The mixture was stirred at 0 °C for 2 h. Most of the solvent was then removed in vacuo and the residue dissolved in $CHCl_3$ (100 mL); the solution was extracted with cold 0.5 N aqueous HCl, washed with water (20 mL), dried (Na_2SO_4), and concentrated. Crystallization of the residue from CH_2Cl_2–hexanes gave pure 10 (4.27 g, 74%): mp 89.5–90.3 °C; $[\alpha]^{22}_D$ +44.4° (*c* 1.2, $CHCl_3$); R_f 0.30 (solvent A); ^{1}H NMR ($CDCl_3$), before exchange with D_2O, the following OH signals were observed δ 3.40 (d, 1 H, $J_{5,OH}$ = 5.9 Hz, 5-OH), 3.51 (d, 1 H, $J_{3,OH}$ = 8.0 Hz, 3-OH), 3.81 (d, 1 H, $J_{4,OH}$ = 4.1 Hz, 4-OH), 3.90 (d, 1 H, $J_{2,OH}$ = 2.4 Hz, 2-OH); after exchange δ 1.23 (s, 9 H, CMe_3), 1.29 and 1.30 (2 t, 2 × 3 H, 2 SCH_2CH_3), 2.64–2.80 (m, 4 H, 2 $SCH_AH_BCH_3$), 3.66 (dd, 1 H, $J_{1,2}$ = 8.9, $J_{2,3}$ = 2.0 Hz, H-2), 3.72 (dd, 1 H, $J_{3,4}$ = 1.4, $J_{4,5}$ = 7.7 Hz, H-4), 3.97 (ddd, 1 H, $J_{5,6A}$ = 6.0, $J_{5,6B}$ = 3.1 Hz, H-5), 4.11 (d, 1 H, H-1), 4.27 (dd, 1 H, $J_{6A,6B}$ = 11.8 Hz, H-6A), 4.33 (t, 1 H, H-3), 4.40 (dd, 1 H, H-6B); ^{13}C NMR δ 14.43, 14.62, 23.65, 25.97 (2 SCH_2CH_3), 27.21, 38.93 (CMe_3), 55.38 (C-1), 66.13, 67.98, 70.68, 73.63, 75.14 (C-2–6), 179.26 (C=O).

Anal. Calcd for $C_{15}H_{30}O_6S_2$ (370.52): C, 48.62; H, 8.16; S, 17.31. Found: C, 48.57; H, 8.18; S, 17.24.

2,3:4,5-Di-*O*-isopropylidene-6-*O*-pivaloyl-D-glucose Diethyl Dithioacetal (11). To a solution of 10 (5.0 g, 13.5 mmol) in 2,2-dimethoxypropane (sufficient volume to dissolve 10, ~50 mL) was added *p*-TsOH·H_2O (0.99 g). The mixture was stirred for 1 h at room temperature. CH_2Cl_2 (30 mL) was then added, the solution was treated with Amberlite IRA-400(OH$^-$) resin to

Table III. ^{1}H-NMR Data: Chemical Shifts[a]

	H-1	H-2	H-3	H-4	H-5	H-6A H-6B	H-7	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′A H-6′B	other signals
12								9.82	4.405	4.07	4.24	4.44	4.29 4.38	1.22 (Piv) 1.23, 1.37, 1.41, 1.50 (OAc)
14(*E*)	4.91	5.46	[5.21, 5.27]		3.79	4.12 4.33		7.11	5.22	3.78	4.35	4.51	4.33 4.40	1.21 (Piv) 1.445, 1.46, 1.47, 1.63 (CMe_2) 1.96, 1.99, 2.05, 2.06 (OAc)
17[b]	4.2						4.79	4.56	5.39	5.37	4.24		4.05 4.44	
19	3.53	[3.11, 3.32, 3.40]			3.28	3.67 3.90	1.96[c]							
20	3.70	4.85	5.17	5.03	3.60	4.10 4.22	1.60[c]							1.99, 2.025, 2.05, 2.095 (OAc)
22	4.41	5.155	5.23	5.09	3.65	4.07 4.29	4.71	4.19	5.01	5.18	5.105	3.79	4.14 4.23	1.93, 1.99 (6 H), 2.04, 2.05 2.054, 2.115, 2.12 (OAc)
24	3.64[d]	——[4.9–5.2]——			3.57	4.16	4.44	3.86[d]	——[4.9–5.2]——			3.67	4.10 4.18	1.98, 2.00, 2.015, 2.02, 2.038, 2.04 (6 H), 2.10, 2.13, 5.77 (NH)
27	3.62	4.87	5.197	5.085	3.69	4.095 4.24	1.81	4.08	4.995	5.34	4.235	5.187	4.16 4.55	2.005, 2.015, 2.025, 2.045 2.075 (6 H), 2.10, 2.11 (OAc)

[a] δ in ppm, for solution in $CDCl_3$. Compound **19** in CD_3OD. [b] Partial data for major isomer (60% of mixture). [c] For details, see description of **19** and **20**, and discussion. [d] Assignment as 1 or 1′ uncertain.

Table IV. ^{1}H-NMR Data: Coupling Constants (in hertz)

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{1,7}$	$J_{7,1'}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'}$	other J's
12								1.5	7.7	1.6	6.7	6.8 5.7	$J_{6'A,6'B}$ 11.1
14(*E*)	10.0	[9.5–10.0]		9.6	2.0 4.5			10.0	8.8	~1	7.1	7.1 4.9	$J_{6A,6B}$ 12.6 $J_{6'A,6'B}$ 11.5
17[a]	~10					6.8	8.2	1.5	~0	3.2	9.2	6.0 2.8	$J_{6'A,6'B}$ 12.4
19	9.6	——[9–9.5]——			5 2	[4.9, 6.9[b]]							$J_{6A,6B}$ 12
20	10.0	9.3	9.3	10.0	2.4 5.4	[5.3, 7.7[b]]							$J_{6A,6B}$ 12.3
22	9.7	[9–9.5]		9.9	4.75 2.4	8.2	2.9	10.5	8.9	9–9.5	10.0	4.9 2.3	$J_{6A,6B}$ 12.4 $J_{6'A,6'B}$ 12.5
24	9.0	——[9.0–10]——				7.1	2.2	10.1	——[9–10]——		10.1	2.3 5.8	$J_{6'A,6'B}$ 12.3 $J_{7,NH}$ 10.4
27	10.0	9.2	9.5	9.9	2.4 4.2	[7.3, 7.3[c]]		1.9	0.6	3.5	9.2	5.3 2.4	$J_{6A,6B}$ 12.5 $J_{6'A,6'B}$ 12.3

[a] Partial data for major isomer. [b] Apparent J values observed on H-1. For real values, see discussion. [c] These values are the apparent $J_{7A,1'}$ and $J_{7B,1'}$. For spectrum in C_6D_6, see description of **27**.

remove the acid, and the solvents were evaporated in vacuo. Crude **11** thus obtained was purified by flash chromatography (EtOAc–hexanes 1:20); yield 4.41 g (73%); syrup; $[\alpha]^{22}_D$ −55.0° (*c* 1.3, $CHCl_3$); R_f 0.64 (solvent D); IR (film) 1745 (C=O), 1385, 1375 cm^{-1} (CMe_2), no OH absorption; ^{1}H NMR δ 1.23 (s, 9 H, CMe_3), 1.264 and 1.270 (2 t, 6 H, 2 SCH_2CH_3), 1.36 (s, 3 H), 1.42 (s, 6 H), and 1.50 (s, 3 H) (2 CMe_2), 2.7–2.8 (m, 4 H, 2 SCH_2CH_3), 3.91 (d, 1 H, $J_{2,3}$ = 5.4, $J_{3,4}$ = 0 Hz, H-3), 4.13 (d, 1 H, $J_{1,2}$ = 7.9 Hz, H-1), ~4.30 (m, 1 H, H-5), 4.36 (dd, 1 H, H-2), 4.40–4.45 (m, 3 H, H-4, 6A, 6B); ^{13}C NMR δ 14.22, 14.37, 25.29, 25.34, 25.49, 26.74, 26.87, 27.19, 27.30, 38.74, 52.80 (C-1), 63.65, 74.99, 75.28, 77.45, 79.86 (C-2–6), 109.08, 109.98, 178.18.

Anal. Calcd for $C_{21}H_{38}O_6S_2$ (450.65): C, 55.97; H, 8.50; S, 14.23. Found: C, 55.96; H, 8.50; S, 14.26.

2,3:4,5-Di-*O*-isopropylidene-6-*O*-pivaloyl-*aldehydo*-D-glucose (12). To a solution of $HgCl_2$ (13.23 g, 48.3 mmol) in acetone (54 mL) were added $CdCO_3$ (19.21 g, 111 mmol) and water (1.9 mL). The mixture was stirred vigorously for 15 min at room temperature, a solution of dithioacetal **11** (4.4 g, 9.75 mmol) in acetone (35 mL) was then added slowly. After the mixture had been stirred for 10 h, the salts were removed by filtration, the filtrate being received in a flask containing $CdCO_3$ (14.4 g). The solids were washed with acetone (30 mL) and the combined filtrate and washings reduced to a small volume in vacuo in the presence of $CdCO_3$. The residue was extracted with several 20-mL portions of $CHCl_3$, and the resulting solution washed with aqueous KI (5 mL) and then with water until absence of halides in the aqueous phase (test with $AgNO_3$ solution). The organic phase was dried (Na_2SO_4) and concentrated to give a clear and chromatographically homogeneous syrup (3.25 g, 97%): R_f 0.4 (solvent B); IR (film) 1746 cm^{-1} (C=O); ^{1}H NMR see Tables III and IV; ^{13}C NMR δ 25.26, 26.41, 26.66, 27.12 (2 CMe_2), 27.09 (CMe_3), 38.69 (CMe_3) 63.16 (C-6), 74.67, 74.77, 75.09, 81.36 (C-2–5), 109.47, 111.92 (2 CMe_2), 178.05 ($OCOCMe_3$), 201.44 (C-1).

(*E*)-9,10,11,13-Tetra-*O*-acetyl-8,12-anhydro-6,7-dideoxy-2,3:4,5-di-*O*-isopropylidene-7-nitro-1-*O*-pivaloyl-D-*glycero*-D-*gulo*-L-*gulo*-tridec-6-enitol (14(*E*)). To a solution of *aldehydo*-glucose **12** (5.43 g, ~15.8 mmol) in CH_3CN (70 mL) were added nitro sugar **1** (5.50 g, 14.1 mmol), KF (1.27 g, 22 mmol), and 18-crown-6 (100 mg). The mixture was stirred vigorously for 1.5 h at room temperature. Ether (70 mL) was then added, and the mixture was filtered through a short column of silica gel 60 (70–230 mesh) using ether as the eluent. Concentration of the filtrate afforded crude nitroalditols **13** (mixture of stereoisomers) containing some residual starting material. The crude products were immediately dehydrated: to a solution of these nitroalditols in chloroform (70 mL) were added, at 0 °C, acetic anhydride (8.6 mL), pyridine (6.7 mL), and a catalytic amount of DMAP. The mixture was stirred for 25 h at room temperature. The reaction mixture was then extracted with cold dilute aqueous HCl, washed with water (2 × 30 mL), dried (Na_2SO_4), and concentrated. Unreacted nitro sugar **1** (1.73 g, 4.42 mmol) was removed from the mixture by crystallization in ether–hexanes. The mother liquors were concentrated and the residue submitted to flash chromatography (solvent D) which afforded pure nitro enitol **14(*E*)** (4.40 g, 44%; yield based on 1 consumed, 64%): R_f (solvent B) 0.68. A second, UV-active spot (R_f 0.59) detectable in the reaction mixture was assumed to be a trace of the *Z* isomer of **14(*E*)**. Compound **14(*E*)**: foam; $[\alpha]^{22}_D$ −44.6° (*c* 1.6, $CHCl_3$); ^{1}H NMR see Tables III and IV; ^{13}C NMR δ 20.29, 20.45 (2 C),

20.57 (4 OCO*Me*), 24.91, 26.56, 26.62, 26.95 (2 C*Me*$_2$), 27.06 (C*Me*$_3$), 38.67 (*C*Me$_3$), 61.76, 63.21 (C-6,6'), 67.46, 71.45, 71.89, 72.32, 73.19, 73.69, 75.01, 76.35, 78.87 (C-1–5, C-2'–5'), 109.83, 111.10 (2 *C*Me$_2$), 136.68 (C-1'), 150.27 (C-7), 169.26, 169.47, 170.00, 170.41 (4 OCOMe), 178.06 (OCOCMe$_3$).

Anal. Calcd for $C_{32}H_{47}NO_{17}$ (717.72): C, 53.55; H, 6.60; N, 1.95. Found: C, 53.77; H, 6.69; N, 1.64.

Conversion of 14 into Bis(glycosyl)nitromethanes (16(*R,S*) and 17(*R,S*)). A solution of compound 14(*E*) (4.40 g, 6.14 mmol) in 80% acetic acid (250 mL) was heated under reflux for 1 h. The solvent was then removed in vacuo. The residual syrupy mixture was dissolved in Ac_2O (50 mL). $BF_3{\cdot}Et_2O$ (0.43 mL) was added and the solution kept at room temperature for 1 h. The solution was then diluted with CH_2Cl_2 (50 mL), extracted with saturated aqueous $NaHCO_3$ (20 mL), washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated (vacuum pump). Fractionation of the residue by flash chromatography (solvent C) gave the pyranose–furanose isomers 17(*R,S*) (R_f 0.42, solvent B) (1.17 g, 25% from 14(*E*)) and the pyranose–pyranose isomers 16(*R,S*) (R_f 0.35) (1.66 g, 36%). Significant ^{1}H NMR signals: 16(*R,S*), 7*R*:7*S* 1:1, δ 4.685 (dd, J = 2.8 and 7.7 Hz) and 4.665 (dd, J = 2.9 and 7.2 Hz) (H-7 for each isomer); 17(*R,S*), isomer ratio ~3:2, major isomer, see Tables III and IV, minor isomer 4.66 (distorted dd, $J_{7,1'}$ = 9.6, $J_{1',2'(\text{or } 7,1)}$ = 1.4 Hz) and 4.71 (distorted dd, $J_{7,1(\text{or } 1',2')}$ = 2.1 Hz) (H-1' and 7), 5.43 (d, $J_{2',3'}$ <1 Hz, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.28 (dd, $J_{4',5'}$ = 9.4 Hz, H-4'); CI-MS 16(*R,S*), 781 (100, $[M + NH_4]^+$).

2,6:8,12-Dianhydro-7-deoxy-D-*erythro*-L-*galacto*-L-*gulo*-tridecitol (*C*-β,β-Trehalose) (19). To a solution of 16(*R,S*) (700 mg, 0.92 mmol) in toluene (40 mL) were added Bu_3SnH (1.25 mL, 4.58 mmol) and AIBN (77 mg). The mixture was heated under reflux for 30 min. The solvent was evaporated and the residue submitted to flash chromatography (solvent E), which afforded 530 mg (80%) of pure 18 (the 1-*O*-pivaloyl-3,4,5,9,10,11,13-hepta-*O*-acetyl derivative of 19) as a foam: R_f 0.40 (solvent B). Compound 18 was deacylated as follows: to a solution of 18 (424 mg, 0.59 mmol) in MeOH (30 mL) was added 0.5 M sodium methoxide in MeOH (1.9 mL). After 9 h at room temperature, the mixture was neutralized with MeOH-washed Amberlite IR-120(H^+) ion-exchange resin, the resin was removed by filtration, and the filtrate was concentrated. Crude 19 was purified by chromatography on Dowex 50W-X4-400(Ca^{++}) ion-exchange resin using deionized, CO_2-free H_2O as the eluent. This procedure afforded 168 mg (84% from 18) of pure *C*-β,β-trehalose 19. Careful crystallization of this product from absolute ethanol gave a sample of anhydrous 19 as extremely hygroscopic crystals: mp (under N_2) 177.5–177.8 °C; $[\alpha]^{22}_D$ −20.4° (*c* 1.9, H_2O); R_f 0.35 (solvent G); ^{1}H NMR (CD_3OD; ref δ CD_2HOD 3.30 ppm) δ 1.96 (sym m, six lines, relative intensities ~1:20:25:25:20:1, distances from center ±0.9, ±5.9, and ±14.3 Hz, 2 H; J values obtained by simulation $J_{1,7}$ = $J_{1',7'}$ = 9.6, $J_{1,7'}$ = $J_{1',7}$ = 2.4, $J_{7,7'}$ = −14 Hz, H-7,7'), other signals, see Tables III and IV; ^{13}C NMR (CD_3OD; ref δ CD_3OD 49.0 ppm) δ 36.00 (C-7), 63.17 (C-6/6'), 72.07, 75.70, 77.00, 79.81, 81.12 (C-1/1'–5/5'); FAB$^-$-MS (glycerol) 341 (100 $[M + H]^+$); FAB$^-$-MS 339 (100, $[M - H]^-$).

Anal. Calcd for $C_{13}H_{24}O_{10}$ (340.33): C, 45.88; H, 7.11. Found: C, 45.71; H, 7.20.

1,3,4,5,9,10,11,13-Octa-*O*-acetyl-2,6:8,12-dianhydro-7-deoxy-D-*erythro*-L-*galacto*-L-*gulo*-tridecitol (C-β,β-Trehalose Peracetate) (20). A. From 19. Acetylation of 19 under acidic conditions (Ac_2O, $BF_3{\cdot}Et_2O$ catalytic) afforded 20 in 89% yield after purification by flash chromatography.

B. From 22. Compound 22 (31 mg, 0.043 mmol) was denitrated using Bu_3SnH (0.06 mL, 0.22 mmol) and AIBN (catalytic amount) in toluene (10 mL) at reflux temperature for 30 min. The solvent was evaporated and the residue submitted to flash chromatography (solvent A) which afforded pure 20 (22 mg, 76%). Crystalline 20 was obtained from ether–petroleum ether: mp 141.4–142.4 °C; $[\alpha]^{22}_D$ −17.2° (*c* 1.45, $CHCl_3$); R_f 0.44 (solvent F); ^{1}H NMR δ 1.60 (sym m, six lines, relative intensities ~1:12:12:12:12:1, distances from center ±1.1, ±6.5, and ±15.5 Hz, 2 H; J values obtained by simulation $J_{1,7}$ = $J_{1',7'}$ = 11.0, $J_{1,7'}$ = $J_{1',7}$ = 3.0, $J_{7,7'}$ = −16.0 Hz, H-7,7'), other signals, see Tables III and IV; ^{13}C NMR δ 20.54 (2 C), 20.63, 20.67 (OCO*Me*), 33.34 (C-7), 62.53 (C-6/6') 68.92, 71.96, 73.25, 74.38, 76.02 (C-1/1'–5/5'), 169.42, 169.63, 170.22, 170.42 (OCOCH$_3$); CI-MS 694 (100, $[M + NH_4]^+$).

Anal. Calcd for $C_{29}H_{40}O_{10}$ (676.62): C, 51.48; H, 5.96. Found: C, 51.44; H, 5.96.

2,6:8,12-Dianhydro-7-deoxy-7-nitro-D-*arabino*-D-*altro*-L-*gulo*-tridecitol (2,6:8,12-Dianhydro-7-deoxy-7-nitro-D-*arabino*-D-*manno*-L-*gulo*-tridecitol; bis(β-D-glucopyranosyl)nitromethane) (21). To a solution of 16(*R,S*) (600 mg, 0.79 mmol) in MeOH (50 mL) was added 0.5 M sodium methoxide in MeOH (4.2 mL). After having been stirred for 9 h at room temperature, the mixture was neutralized with MeOH-washed Amberlite IR-120(H^+) resin. The resin was removed by filtration and the filtrate concentrated to give essentially pure 21 (300 mg, 98%). Compound 21 was crystallized from a small amount of absolute methanol: mp 206–207 °C; $[\alpha]^{22}_D$ −4.8° (*c* 1.3, H_2O); R_f 0.50 (solvent H); ^{1}H NMR (CD_3OD; ref δ CD_2HOD 3.30 ppm) δ 5.03 (dd, $J_{1,7}$ and $J_{1',7}$ = 2.8 and 6.1 Hz, H-7); ^{13}C NMR (CD_3OD; ref δ CD_3OD 49.0 ppm) δ 62.83, 63.14 (C-6,6'), 71.58, 71.73, 71.85, 74.10, 76.68, 77.18, 79.83, 80.16, 82.32, 82.67 (C-1,1'–5,5'), 87.36 (C-7).

Anal. Calcd for $C_{13}H_{23}NO_{12}$ (385.32): C, 40.52; H, 6.02; N, 3.64. Found: C, 40.32; H, 5.97; N, 3.56.

1,3,4,5,9,10,11,13-Octa-*O*-acetyl-2,6:8,12-dianhydro-7-deoxy-7-nitro-D-*arabino*-D-*altro*-L-*gulo*-tridecitol (Bis(β-D-glucopyranosyl)nitromethane Peracetate) (22). To a suspension of 21 (40 mg, 0.1 mmol) in Ac_2O (15 mL) was added $BF_3{\cdot}Et_2O$ (2 drops). The mixture was stirred for 1 h at room temperature. CH_2Cl_2 (30 mL) was then added, the solution washed with saturated aqueous $NaHCO_3$ and then with water (2 × 10 mL) and dried (Na_2SO_4), and the solvent was evaporated. The residue was submitted to flash chromatography (solvent B) which afforded pure 22 (58 mg, 80%) as a syrup: $[\alpha]^{22}_D$ −5.3° (*c* 1.5, $CHCl_3$); R_f 0.44 (solvent F); ^{1}H NMR see Tables III and IV; ^{13}C NMR δ 20.14, 20.47 (2 C), 20.63 (OCO*Me*'s), 61.65, 61.85 (C-6,6'), 67.83, 68.07, 68.25, 70.77, 73.38, 73.74, 73.88, 74.42, 76.58, 76.91 (C-1,1'–5,5'), 83.34 (C-7), 168.68, 169.12, 169.32, 169.50, 169.67, 170.33, 170.42 (OCOMe's); CI-MS 739 (100, $[M + NH_4]^+$).

7-Acetamido-1,3,4,5,9,10,11,13-octa-*O*-acetyl-2,6:8,12-dianhydro-7-deoxy-D-*arabino*-D-*altro*-L-*gulo*-tridecitol (Bis(β-D-glucopyranosyl)methylamine Peracetate) (24). A solution of 21 (50 mg, 0.13 mmol) in hot water (3 mL) was added to a stirred boiling solution of $FeSO_4{\cdot}7H_2O$ (260 mg) in water (3 mL). Concentrated aqueous NH_3 was then added portionwise to keep the reaction mixture alkaline. After 20 min, the solids were removed by filtration and washed with dilute aqueous NH_3. The filtrate and washings were combined, cooled, and mixed with Amberlite IRA-400(OH^-) ion-exchange resin, and the resulting mixture was concentrated in vacuo to one-third of its original volume. The mixture with the resin was placed in a small column and the column eluted with water. Concentration of the fractions containing 23 gave crude 23 as a syrup. Pure 23 (20 mg, 43%) was obtained by chromatography on Dowex 1-X2-200(OH^-) ion-exchange resin using methanol as the eluent. Compound 23 was characterized as its peracetate, 24: a sample of 23 (5 mg) was acetylated under standard conditions; the resulting peracetate 24 was submitted to flash chromatography (solvent B) which afforded pure 24 (7.7 mg, 75%) as a glassy solid: $[\alpha]^{25}_D$ +6° (*c* 0.2, $CHCl_3$, 1-dm cell); IR (film) 3281 (NH), 2957, 1752 (C=O, esters), 1668 (C=O, amide), 1541 (amide II), 1435, 1372, 1234, 1101, 1036, 909, 736 cm^{-1}; ^{1}H NMR see Tables III and IV; ^{13}C NMR δ 20.58, 20.70, 20.74, 23.11 (*Me*CO's), 47.60 (C-7), 62.34, 62.57 (C-6,6'), 67.50, 68.43, 68.51, 70.60, 74.43, 74.56, 75.56, 76.07, 76.22, ~77.2 (C-1,1'–5,5'), 169.31, 169.36, 169.48, 170.21, 170.30, 170.47 (Me*CO*'s); CI-MS 734 (100, $[M + H]^+$); FAB-HRMS calcd for $[M + H]^+$ 734.25075, found 734.2512; calcd for $[M + Na]^+$ 756.2327, found 756.2371.

2,6:8,11-Dianhydro-7-deoxy-D-*erythro*-L-*galacto*-L-*gulo*-tridecitol (26). Compound 17(*R,S*) (639 mg, 0.84 mmol) was denitrated under the same conditions as 16(*R,S*) (see preparation of 19). Purification of the crude product by flash chromatography (solvent E) gave the 1,3,4,5,9,10,12-hepta-*O*-acetyl 13-*O*-pivaloyl derivative of 26 (compound 25, 452 mg, 75%) as a foam (R_f 0.34, solvent B). Compound 25 (387 mg, 0.54 mmol) was deacylated as described above for the preparation of 19; the crude product was purified by chromatography on Dowex 50W-X4-400(Ca^{++}) resin which afforded pure 26 (153 mg, 83% from 25) as a highly

hygroscopic foam: $[\alpha]^{20}_D$ −31.6° (c 1.9, H_2O); R_f 0.37 (solvent G); ^1H NMR (CD_3OD), significant signals δ 1.62 (ddd, 1 H, $J_{7A,7B}$ = 14.1 Hz, couplings with H-1's 5.9 and 10.2 Hz, H-7A), 2.21 (ddd, 1 H, couplings with H-1's 2.1 and 7.4 Hz, H-7B); ^{13}C NMR (CD_3OD) δ 37.68 (C-7), 63.38, 65.28 (C-6,6'), 71.48, 72.28, 75.88, 78.47, 79.57, 79.78, 81.52, 81.59, 84.21, 84.74 (C-1,1'–5,5').

Anal. Calcd for $C_{13}H_{24}O_{10}·H_2O$ (358.34): C, 43.57; H, 7.31. Found: C, 43.98; H, 7.18.

1,3,4,5,9,10,12,13-Octa-*O*-acetyl-2,6:8,11-dianhydro-7-deoxy-D-*erythro*-L-*galacto*-L-*gulo*-tridecitol (27). Compound **26** (35 mg, 0.1 mmol) was acetylated in Ac_2O (3 mL) containing $BF_3·Et_2O$ (1 drop). After 1 h at room temperature, the mixture was processed as described above (preparation of **22**) and the product purified by flash chromatography (solvent E): yield of **27** 50 mg (72%); syrup; $[\alpha]^{20}_D$ −15.8° (c 1.6, $CHCl_3$); R_f 0.53 (solvent F); ^1H NMR δ 1.81 (higher-order system, 2 H, H-7A,7B), other values, see Tables III and IV; in C_6D_6, H-7A and 7B are separated by 0.11 ppm and the following J's are observed: $J_{1,7A}$ = 10.2, $J_{1,7B}$ = 1.8, $J_{1',7A}$ = 5.4, $J_{1',7B}$ = 9.2, and $J_{7A,7B}$ = 14.3 Hz; ^{13}C NMR δ 20.51, 20.54, 20.59, 20.69, 20.75 (OCO*Me*), 35.27 (C-7), 62.00, 63.26 (C-6,6'), 68.09, 68.46, 71.77, 74.24, 74.27, 75.19, 75.47, 77.74, 80.29, 81.36 (C-1,1'–5,5'), 169.00, 169.41, 169.64, 170.19 (2 C), 170.50 (2 C), 170.53 (*O*COMe); CI-MS 694 (100, $[M + NH_4]^+$).

Anal. Calcd for $C_{29}H_{40}O_{18}$ (676.62): C, 51.48; H, 5.96. Found: C, 51.29; H, 6.01.

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