# An Ezomycin Model Glycosylation

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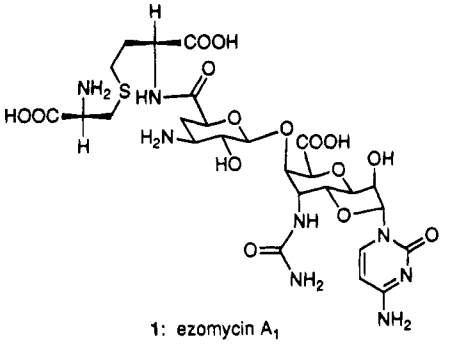
*Received April 19, 1994*®

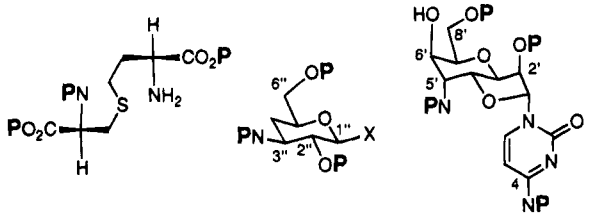
A model glycosylation reaction for application to the synthesis of the ezomycin class of antibiotics is described. The ezoaminuroic thioglycoside donor **13**, with a reduced and protected C-6 position and trifluoroacetamide at C-3, was prepared from the Cerny epoxide **7** by a nine-step procedure. The model D-*gulo*-pyranoside acceptor **20**, which closely resembles an actual acceptor in the vicinity of the reacting axial hydroxyl, was synthesized from methyl β-D-galactopyranoside **14**. Glycosylation with *N*-iodosuccinimide/triflic acid as promoter gave the disaccharide **21** in 90% yield.

Glycosylations with diversely functionalized donor and acceptor components are more challenging than those involving simple hydroxyl-protected glycopyranoside units.[1] As an example, a synthesis of the antifungal antibiotic ezomycin A1 (**1**)[2] would have to address the problem of glycosylation at the hindered C-6′ hydroxyl of the octosyl nucleoside portion (see **4**) with an appropriately protected glycosyl donor corresponding to the ezoaminuroic acid portion (**3**). At the minimum, glycosylation-compatible protecting groups must be identified for the functionality at N-4, C-2′, N-5′, O-8′, O-2″, N-3″, and O-6″. An additional set of protecting group problems is presented by the prospect of adjusting the protection and/or oxidation levels at N-5′, C-8′, and C-6″, attaching the cystathionine portion **2**,[3] and deprotecting.



1: ezomycin $A_1$

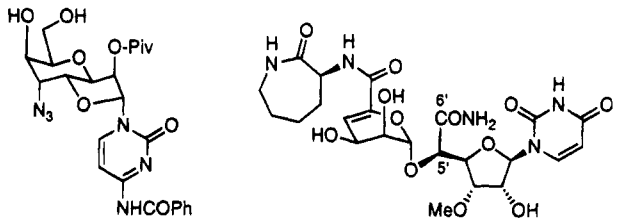
In our studies on the synthesis of some complex nucleoside antibiotics,[4] we have recently synthesized an ezomycin octosyl nucleoside derivative (**5**) that closely resembles glycosylation acceptor **4**.[5,6] We have also completed the synthesis of capuramycin (**6**), an antibiotic that shares certain structural features with **1**.[7] In this paper we describe the synthesis of an ezoaminuroic acid donor of form **3**, and a D-gulopyranoside model for the ezomycin acceptor **4**, and then a successful glycosylation with these components.



**2** (cystathionine) **3** (ezoaminuroic acid) **4** (octosyl nucleoside)

**P** = appropriate protecting group
X = glycosylation activation group

**Synthetic Design.** The synthesis of **6** featured a glycosylation at the C-5′ hydroxyl of an L-talofuranosyl nucleoside acceptor where C-6′ was held as a benzyl-protected carbinol.[7] Attempts to glycosylate O-5′ where



**5** **6**: capuramycin

C-6′ was an ester were unsuccessful, because of the greater electron attraction and/or steric hindrance of the ester group compared with benzyloxy. There are a few precedents in the literature for O-4 glycosylation of

® Abstract published in *Advance ACS Abstracts,* July 15, 1994.

(1) For a recent review and many relevant references on glycosylation, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531.

(2) (a) Sakata, K.; Sakurai, A.; Tamura, S. *Tetrahedron Lett.* **1974**, 1533–1536. (b) *Idem., Ibid.* **1974**, 4327–4330. (c) *Idem., Ibid.* **1975**, 3191–3194. (d) *Idem., Agr. Biol. Chem.* **1975**, *39*, 885–892. (e) *Idem., Ibid.* **1976**, *40*, 1993–1999. (f) Sakata, K.; Uzawa, J. *Ibid.* **1977**, *41*, 413–415.

(3) Snow, M. L.; Dombro, R. S.; Ressler, C. *J. Org. Chem.* **1967**, *32*, 246–248.

(4) (a) Isono, K. *Pharmac. Ther.* **1991**, *52*, 269–286. (b) Garner, P. Synthetic Approaches to Complex Nucleoside Antibiotics. In *Studies in Natural Products Chemistry, Vol. 1, Part A*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988, pp 397–434.

(5) Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nandan, S. R. *J. Org. Chem.* **1994**, *59*, 946–948.

(6) For recent studies on the synthesis of octosyl nucleosides related to **4**, see: (a) Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1057–1062. (b) *Idem., Ibid.* **1986**, *59*, 3523–3528. (c) Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T.; Ishii, T.; Ohba, S.; Saito, Y. *Ibid.* **1986**, *59*, 1753–1759. (d) Hanessian, S.; Dixit, D.; Liak, T. *Pure Appl. Chem.* **1981**, *53*, 129–148. (e) Hanessian, S.; Sato, K.; Liak, T. J.; Dahn, N.; Dixit, D.; Cheney, B. V. *J. Am. Chem. Soc.* **1984**, *106*, 6114–6115. (f) Kim, K. S.; Szarek, W. A. *Carbohydr. Res.* **1982**, *100*, 169–176. (g) *Idem., Can. J. Chem.* **1981**, *59*, 878–887. (h) Bovin, N. V.; Zurabyan, S. E.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25–35. (i) Maier, S.; Preuss, R.; Schmidt, R. R. *Liebigs Ann. Chem.* **1990**, 483–489. (j) Danishefsky, S.; Hungate, R. *J. Am. Chem. Soc.* **1986**, *108*, 2486–2489. (k) Danishefsky, S. J.; Hungate, R.; Schulte, G. *Ibid.* **1988**, *110*, 7434–7440. (l) Hanessian, S.; Kloss, J.; Sugawara, T. *J. Am. Chem. Soc.* **1986**, *108*, 2758–2759.

(7) Knapp, S.; Nandan, S. R. *J. Org. Chem.* **1994**, *59*, 281–283.

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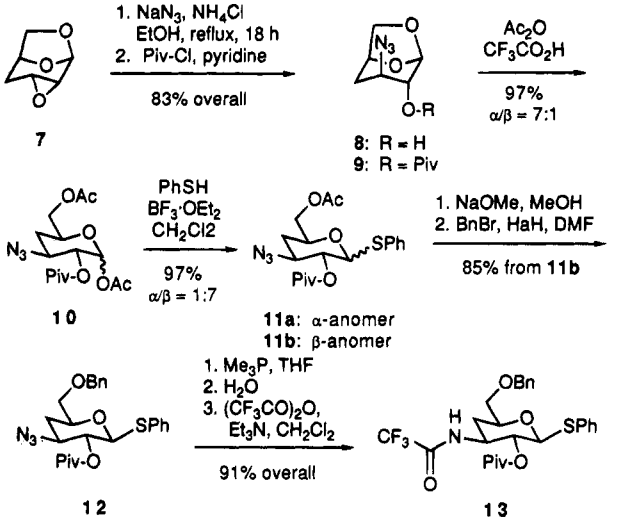
pyranuronic esters,[8] and additional examples where oxidation is postponed until after glycosylation.[9] We initially chose to use the C-8′-reduced form of acceptor **4** for glycosylation at C-6′ to favor the glycosylation and to protect against loss of the C-6′ substituent $\beta$ to a C-8′ ester by an elimination reaction.[2] For simplicity, we also chose to hold C-6″ of the donor **3** as a benzyl-protected carbinol during the glycosylation. Although results with **6** indicate that the ester oxidation state at C-6″ on the glycosyl donor might be compatible,[7] we can also envision deprotection and oxidation at both sites, followed by selective amide formation at the less hindered carboxylic acid. Pivaloyl was designated for O-2″ protection because of its excellent properties as a participating group during glycosylation,[5,7] and phenylthio was selected as the substituent "X" for donor **3** because it is a stable and convenient way to "store" the anomeric center,[10] and because there are now several dependable methods available for its activation.[11-14]

Lewis-basic amino and amide groups are frequently not compatible with efficient glycosylations,[1] and the target **1** has amino- or amide-type functionality at many sites. A major goal of the model study was therefore to identify appropriate protecting or precursor groups for the nitrogen substituents. Azido was chosen for N-5′ of the acceptor **4** because this group is well-known to survive glycosylations[1] and because the C-5′ nitrogen substituent appears first as azido anyway, in the synthesis of **5**.[5] Its transformation to ureido can be carried out under mild conditions.[5] Trifluoroacetamido was chosen for N-3″ of the donor **3** to distinguish it from N-5′. Although less is known about the trifluoroacetamido substituent during glycosylation,[15] it is more weakly Lewis-basic than acetamido and is removable under basic or reductive conditions.[15,16]

The N-4, N-3, and O-2 atoms of the cytosine portion of **4** are Lewis-basic sites that should be protected for efficient glycosylation. In fact, initial glycosylation on the pyrimidine base is known to occur when the glycosyl acceptor is a nucleoside.[7,17] Although an 8-fold excess of the glycosyl donor was used for the successful glycosylation leading to **6**,[7] this is not an attractive option where the donor is more precious, as would be the case for **3**. The interesting question of how to protect pyrimidine bases during glycosylation, however, has been deferred to a separate study. Likewise, the protection of substituents in the cystathionine portion **2**, which would be attached after the glycosylation in any case, is not addressed by the present model study.

**Scheme 1**




**Synthesis of the Ezomycin Glycosyl Donor.** The Cerny epoxide **7** can be prepared in gram quantities from $\beta$-D-galactose pentaacetate;[18] further conversion of **7** to glycosyl donor **13** is displayed in Scheme 1.[19] Transdiaxial opening of the oxirane ring of **7** at C-3″ with azide[20] followed by O-2″ pivaloylation led to 1,6-anhydropyranose **9**, which was cleaved with acetic anhydride and trifluoracetic acid[21] to afford the diacetate **10**. Exchange of the anomeric acetoxy for phenylthio[22] gave the thioglycoside **11**, and replacement of the O-6″ acetyl with benzyl led to **12**. The azido was reduced,[23] and the resulting C-3″ amino was protected as the trifluoroacetamide, to give the glycosyl donor **13**. The synthetic route is well-served by the stability of the anomeric phenylthio substituent during several tranformations elsewhere in the molecule.

**Synthesis of the Model Glycosyl Acceptor.** Scheme 2 shows the preparation of a D-gulopyranoside model **20** for the protected ezomycin octosyl nucleoside **4**. Methyl $\beta$-D-galactopyranoside **14** was converted to its acetonide/methoxyisopropyl derivative,[24] which allowed methylation at O-2. For convenience of isolation, the O-6 protecting group of **15** was hydrolyzed first, the 3,4-acetonide was removed from **16**, and then a 4,6-*O*-

(8) (a) Hirsch, J.; Kova, P.; Kovacik, V. *Carbohydr. Res.* **1977**, *56*, 391–397. (b) Jacquinet, J. C.; Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Torri, G.; Sinay, P. *Carbohydr. Res.* **1984**, *130*, 221–241. (c) Pozsgay, V. In *Carbohydrates—Synthetic Methods and Applications in Medicinal Chemistry*; Ogura, H., Hasegawa, A., Suami, T., Eds.; New York: VCH Publishers; 1992, pp 188–227. (d) Vogel, C.; Steffan, W.; Ott, A. Y.; Betaneli, V. I. *Carbohydr. Res.* **1992**, *237*, 115–129.

(9) (a) Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1988**, *173*, 306–315. (b) Goto, F.; Ogawa, T. *Pure Appl. Chem.* **1993**, *65*, 793–801 (especially Scheme 4 therein).

(10) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189–4192.

(11) See ref 1, pp 1507–1509, for a survey of thioglycoside activation methods.

(12) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580–1581.

(13) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334.

(14) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313–4316.

(15) For trifluoracetamido-compatible glycosylations see: (a) Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. *Chem. Lett.* **1984**, 501–504. (b) Kolar, C.; Kneissl, G. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 809–811. (c) Kolar, C.; Kneissl, G.; Knodler, U.; Dehmal, K. *Carbohydr. Res.* **1991**, *209*, 89–100. (d) Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766–1775.

(16) Knapp, S.; Hale, J. J. *J. Org. Chem.* **1993**, *58*, 2650–2651.

(17) Lichtenthaler, F. W.; Sanemitsu, Y.; Nohara, T. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 772–774.

(18) Knapp, S.; Naughton, A. B. J.; Jaramillo, C.; Pipik, B. *J. Org. Chem.* **1992**, *57*, 7328–7334, and references therein.

(19) For previous syntheses of ezoaminuroic acid derivatives, see: (a) Mieczkowski, J.; Zamojski, A. *Bull. Acad. Pol. Sci.* **1975**, *23*, 581–583. (b) Ogawa, T.; Akatsu, M.; Matsui, M. *Carbohydr. Res.* **1975**, *44*, C22–C24. (c) Knapp, S.; Levorse, A. T.; Potenza, J. A. *J. Org. Chem.* **1988**, *53*, 4773–4779.

(20) (a) Ogawa, T.; Akatsu, M.; Matsui, M. *Carbohydr. Res.* **1975**, *45*, C22–24. (b) Paulsen, H.; Stenzel, W. *Chem. Ber.* **1978**, 2334–2347. (c) *Idem., Ibid.* **1978**, 2348–2357.

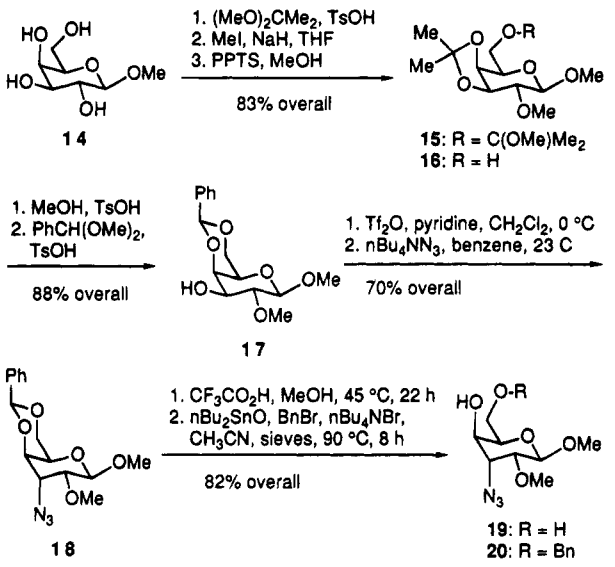
(21) Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102–3114.

(22) Ferrier, R. J.; Furneaux, R. H. *Methods Carbohydr. Chem.* **1980**, *8*, 251–253.

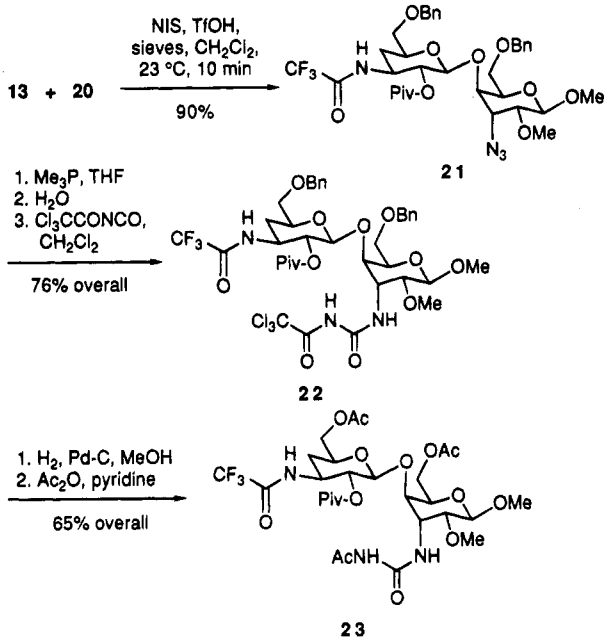
(23) (a) Barrett, A. G.; Sakadarat, S. *J. Org. Chem.* **1990**, *55*, 5110–5117. (b) Murahashi, S.-I., Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292–3303.

(24) (a) Oldham, J. W. H.; Bell, D. J. *J. Am. Chem. Soc.* **1938**, *60*, 323–325. (b) Barili, P. L.; Berti, G.; Catelani, G.; Colonna, F.; Marra, A. *Tetrahedron Lett.* **1986**, *27*, 2307–2310. (c) Catelani, G.; Colonna, F.; Marra, A. *Carbohydr. Res.* **1988**, *182*, 297–300. (d) Barili, P. L.; Berti, G.; Bertozzi, D.; Catelani, G.; Colonna, F.; D'Andrea, F. *Tetrahedron* **1990**, *46*, 5365–5376.

**Scheme 2**




**Scheme 3**




benzylidene protecting group installed to afford **17**, a known β-D-galactopyranoside derivative.[25] Triflation at C-3, followed by azide displacement, gave **18**, and then methanolysis of the benzylidene protecting group and selective benzylation[26] of the primary C-6 hydroxyl furnished the model acceptor substrate **20**. The model **20** resembles an authentic ezomycin glycosylation acceptor with respect to functionality and steric hindrance in the vicinity of the C-4 hydroxyl (compare O-6′ of **4**). The pyranose ring of the model **20** has an approximate $^4C_1$ conformation according to the vicinal H−H coupling constants ($J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = ~1 Hz), which are also similar to those of **4** at the corresponding positions (9.8, 3.4, 3.5, 1.3 Hz, respectively[5]).

**Ezomycin Model Glycosylation.** The model glycosylation (Scheme 3) was carried out by using 1.2 equiv of thioglycoside **13** as the glycosyl donor, 1.0 equiv of azido alcohol **20** as the glycosyl acceptor, and *N*-iodosuccinimide/triflic acid as the promoter according to the procedure of van Boom.[13] The disaccharide **21** was isolated by chromatography in excellent yield, with all the protecting and precursor groups intact. The survival and apparent noninterference of the trifluoracetamido group at C-3″ is noteworthy. $^1$H NMR analysis confirms the formation of the β-linkage ($J_{1',2'}$ = 7.7 Hz).

Some further transformations on the ezomycin model disaccharide **21** are shown in Scheme 3. Reduction of the C-3 azido to amino and then reaction with trichloroacetyl isocyanate,[27] gave the protected urea **22**. For additional characterization, the two benzyl ethers were removed by hydrogenolysis in methanol (the *N*-trichloroacetyl group is also removed under these conditions), and then acetylation gave the triacetate **23**.

In summary, the model study argues for the suitability of azido, trifluoroacetamido, pivaloyloxy, and benzyloxy substituents for glycosylation of an authentic ezomycin octosyl nucleoside acceptor **4**. Additionally, a workable thioglycoside donor (**13**) of form **3** has been identified, and the NIS/TfOH activation method appears to be appropriate for glycosylation at the axial C-6′ hydroxyl of **4**.

## Experimental Section

**Apparatus and Reagents.** Melting points are uncorrected. FT-IR spectra were on thin films (selected absorption maxima are reported in cm$^{-1}$). $^1$H NMR spectra were obtained at 200 MHz on deuteriochloroform solutions unless otherwise specified; all *J* values are in hertz. $^{13}$C NMR spectra were obtained at 50 MHz. Chemical shifts are reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz.

Precoated silica gel plates (Baker Si250F) were used for analytical thin-layer chromatography (TLC). EM Science silica gel 60 (230–400 mesh) was employed for column chromatography. Tetrahydrofuran (THF) was distilled from benzophenone ketyl, and dichloromethane, pyridine, and dimethylformamide (DMF) were distilled from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. Organic solutions were dried over anhydrous magnesium sulfate. All reactions were run under an argon atmosphere.

**1,6-Anhydro-3-azido-3,4-dideoxy-2-*O*-(2,2-dimethylpropionyl)-β-D-glucopyranose (9).** A solution of 1.85 g (14.45 mmol) of Cerny epoxide **7**, 2.75 g (42.30 mmol) of sodium azide, and 1.95 g (36.46 mmol) of ammonium chloride in 75 mL of a 4:1 ethanol/water mixture was heated at 90 °C for 18 h and then cooled and concentrated. Chromatography with 2:1 and then 1:1 petroleum ether/ethyl acetate as the eluant gave 2.08 g (84%) of the azido alcohol **8** as a syrup: $[\alpha]_D$ −12.7° (c = 0.67, MeOH) [lit.[20a] −12.2° (c = 0.63, MeOH)]; IR (cm$^{-1}$) 3433, 2961, 2905, 2108; $^1$H NMR δ 5.41 (s, H-1), 4.52 (t, *J* = 4.6, H-5), 4.13 (d, *J* = 6.9, H-6$_{endo}$), 3.74–3.71 (m, H-6$_{exo}$ and H-3), 3.63 (s, H-2), 3.02 (br s, OH), 2.37 (dt, *J* = 15.1, 4.5, H-4$_{ax}$), 1.66 (d, *J* = 15.1, H-4$_{eq}$); $^{13}$C NMR δ 101.0 (C-1), 71.3, 68.2, 67.0, 57.5 (C-3), 29.5 (C-4).

A solution of 1.96 g (11.46 mmol) of azido alcohol **8** and 1.70 mL (13.80 mmol) of pivaloyl chloride in 15 mL of pyridine was stirred for 4 h. The reaction was quenched by addition of 85 mL of 1 N hydrochloric acid. Extraction with 100 mL of ethyl ether gave a solution that was dried, concentrated, and then chromatographed with 7:1 petroleum ether/ethyl acetate as the eluant to afford 2.90 g (99%) of the pivaloate **9**: mp 42–44 °C, $[\alpha]_D$ +26.5 (c = 0.43, $CHCl_3$); IR (cm$^{-1}$) 2975, 2108, 1731, 1141; $^1$H NMR δ 5.40 (s, H-1), 4.63 (s, H-2), 4.54 (t, *J* = 5.2, H-5), 4.12 (d, *J* = 7.0, H-6$_{endo}$), 3.75–3.70 (m, H-6$_{exo}$ and H-3),

(25) Sorkin, E.; Reichstein, T. *Helv. Chem. Acta* **1945**, *28*, 1–17.
(26) Nagashima, N.; Ohno, M. *Pharm. Chem. Bull.* **1991**, *39*, 1972–1982.
(27) Hecker, S. J.; Minich, M. L.; Lackey, K. *J. Org. Chem.* **1990**, *55*, 4904–4911.

2.32 (dt, $J$ = 15.0, 5.2, H-4$_{ax}$), 1.66 (d, $J$ = 15.0, H-4$_{eq}$), 1.24 (s, C$Me_3$); $^{13}$C NMR $\delta$ 177.4 (C=O), 99.1 (C-1), 70.9, 69.2, 67.1, 55.3 (C-3), 38.7 (*C*Me$_3$), 30.2 (C-4), 27.0 (C*Me*$_3$). Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.48. Found: C, 51.98; H, 6.72; N, 15.96.

**3-Azido-1,6-di-*O*-acetyl-3,4-dideoxy-2-*O*-(2,2-dimethylpropionyl)-α- and -β-D-glucopyranose (10).** A solution of 1.70 g (6.67 mmol) of anhydro sugar **9** and 3 mL (38.2 mmol) of trifluoroacetic acid in 30 mL of acetic anhydride was stirred for 18 h. The reaction was quenched by addition of a solution of 4 mL of triethylamine in 70 mL of water. The reaction mixture was extracted with 100 mL of ethyl ether, and the organic layer was dried, concentrated, and chromatographed with 6:1 and then 5:1 petroleum ether/ethyl acetate as the eluant to provide 2.30 g (97%) of the diacetate **10** as a 7:1 α/B mixture of anomers: mp 54–56 °C, $[\alpha]_D$ +65.5° ($c$ = 1.00, $CHCl_3$); IR (cm$^{-1}$) 2975, 2105, 1745; $^1$H NMR $\delta$ (α-anomer in mixture) 6.59 (d, $J$ = 3.4, H-1), 4.85 (dd, $J$ = 3.4, 10.3, H-2), 4.26–4.09 (m, H-5, H-6a and H-6b), 4.02 (dt, $J$ = 4.8, 11.6, H-3), 2.13 and 2.10 (2 s, OAc), 2.11 (partially obscurred dt, $J$ = 14.4, 4.8, H-4$_{eq}$), 1.62 (q, $J$ = 14.4, H-4$_{ax}$), 1.20 (s, C$Me_3$); $^{13}$C NMR $\delta$ (α-anomer in mixture) 176.8 (Piv C=O), 170.0, 168.4 (two Ac C=O), 89.4 (C-1), 72.4, 68.2, 65.3, 56.5 (C-3), 38.8 (*C*Me$_3$), 32.2 (C-4), 26.9 (C*Me*$_3$), 20.2 (two CO*Me*). Anal. Calcd for $C_{15}H_{23}N_3O_6$: C, 50.42; H, 6.49; N, 11.76. Found: C, 50.35; H, 6.49; N, 11.51.

**Phenyl 6-*O*-Acetyl-3-azido-3,4-dideoxy-2-*O*-(2,2-dimethylpropionyl)-1-thio-β-D-glucopyranoside (11b).** A solution of 1.33 g (3.73 mmol) of the diacetate **10**, 0.5 mL (4.87 mmol) of thiophenol, and 1.5 mL (12.2 mmol) of boron trifluoride etherate in 16 mL of dichloromethane was stirred at 0 °C for 20 h. The reaction was quenched by addition of 3 mL of triethylamine and 100 mL of water. Extraction with 84 mL of dichloromethane gave an organic layer that was dried, concentrated, and then chromatographed with 9:1 and then 5:1 petroleum ether/ethyl acetate as the eluant to give 0.18 g (12%) of the α-thioglucoside **11a** and then 1.30 g (85%) of the β-glucoside **11b**: mp 97–98 °C, $[\alpha]_D$ −14.5° ($c$ = 0.31, $CHCl_3$); IR (cm$^{-1}$) 2974, 2100, 1739, 1726; $^1$H NMR $\delta$ 7.49–7.26 (m, 5 H$_{arom}$), 4.86 (t, $J$ = 9.6, H-2), 4.63 (s, $J$ = 9.6, H-1), 4.17 ($J$ = 5.1, 2 H-6), 3.78 (ddt, $J$ = 12.2, ~1, 5.1, H-5), 3.65 (ddd, $J$ = 12.3, 9.6, 5.0, H-3), 2.09 (s, OAc), 2.06 (ddd, $J$ = 12.6, 5.0, ~1, H-4$_{eq}$), 1.61 (q, $J$ = 12.3, H-4$_{ax}$), 1.29 (s, C$Me_3$); $^{13}$C NMR $\delta$ 176.8 (Piv C=O), 170.0 (Ac C=O), 133.0 (C$_{ipso}$), 132.4, 128.8, 128.0 (C$_{arom}$), 86.9 (C-1), 73.7, 71.2, 65.3, 61.5 (C-3), 38.9 (*C*Me$_3$), 32.7 (C-4), 27.1 (C*Me*$_3$), 20.8 (CO*Me*).

**Phenyl 3-Azido-3,4-dideoxy-2-*O*-(2,2-dimethylpropionyl)-6-*O*-(phenylmethyl)-1-thio-β-D-glucopyranoside (12).** A solution of 0.72 g (1.76 mmol) of thioglycoside **11b** in 20 mL of 1:1 methanol / dichloromethane was treated with 1.76 mL (1.76 mmol) of 1 M sodium methoxide. The mixture was stirred for 30 min, and then neutralized with Amberlyst IR-120 (H+) and concentrated. The residue was triturated with 10 mL of tetrahydrofuran, and the resulting solution was treated with 85 mg (3.54 mmol) of sodium hydride and 0.5 mL (4.20 mmol) of benzyl bromide. After 3 h, the reaction was quenched with 1 mL of methanol, concentrated, and then chromatographed with 12:1 and then 8:1 petroleum ether/ethyl acetate as the eluant to give the 0.68 g (85%) of the benzyl ether **12** as a syrup: IR (cm$^{-1}$) 2972, 2870, 2101, 1739; $^1$H NMR $\delta$ 7.50–7.26 (m, 10 H$_{arom}$), 4.85 (t, $J$ = 9.6, H-2), 4.65 ($J$ = 9.6, H-1), 4.56 (s, PhC$H_2$), 3.77 (m, H-3, H-5, H-6a, H-6b), 2.14 (ddd, $J$ = 12.6, 4.0, ~1, H-4$_{eq}$), 1.59 (q, $J$ = 12.2, H-4$_{ax}$), 1.29 (s, C$Me_3$); $^{13}$C NMR $\delta$ 176.9 (C=O), 137.9, 133.3 (two C$_{ipso}$), 132.2, 128.9, 128.4, 127.8, 127.8, 127.7 (C$_{arom}$), 87.1 (C-1), 75.6, 73.6, 72.0, 71.4, 61.8 (C-3), 38.9 (*C*Me$_3$), 33.2 (C-4), 27.1 (C*Me*$_3$). Anal. Calcd for $C_{24}H_{29}N_3O_4S$: C, 63.30; H, 6.37; N, 9.23. Found: C, 63.06; H, 6.42; N, 8.95.

**Phenyl 3,4-Dideoxy-2-*O*-(2,2-dimethylpropionyl)-6-*O*-(phenylmethyl)-1-thio-3-trifluoroacetamido-β-D-glucopyranoside (13).** A solution of 0.50 g (1.09 mmol) of azide **12** in 9 mL of tetrahydrofuran was treated with 1.75 mL (1.75 mmol) of a 1 M solution of trimethylphosphine in tetrahydrofuran. The reaction was stirred for 1 h, and then 1.75 mL of water was added, and stirring was continued for 2 h. The reaction mixture was concentrated, and the residue was dissolved in 9 mL of dichloromethane and 0.5 mL of triethylamine and then treated with 0.60 mL (4.25 mmol) of trifluoroacetic anhydride. After 30 min, the reaction mixture was concentrated and then chromatographed with 10:1, then 8:1 and then 4:1 petroleum ether/ethyl acetate as the eluant to afford 0.52 g (91%) of the trifluoroacetamide **13**: mp 107 °C, $[\alpha]_D$ −13.8° ($c$ = 0.24, $CHCl_3$); $^1$H NMR $\delta$ 7.50–7.26 (m, 10 H$_{arom}$), 6.71 (d, $J$ = 7.8, NH), 4.77 (d, $J$ = 9.5, H-1), 4.69 (t, $J$ = 9.5, H-2), 4.56 (s, PhC$H_2$), 4.30–4.19 (m, H-3), 3.88–3.76 (m, H-5), 3.69–3.48 (m, 2 H-6), 2.22 (ddd, $J$ = 12.5, 4.3, 1.5, H-4$_{eq}$), 1.59 (q, $J$ = 12.5, H-4$_{ax}$), 1.22 (s, (C$Me_3$); $^{13}$C NMR $\delta$ 178.9 (Piv C=O), 157.0 (q, $J$ = 38, $CF_3CO$), 137.9 (C$_{ipso}$), 133.0, 132.0 (C$_{ipso}$), 128.9, 128.4, 128.2, 127.8, 127.6 (6 C$_{arom}$), 115.5 (q, $J$ = 275, *C*F$_3$CO), 86.2 (C-1), 75.8, 73.5, 71.7, 70.2, 52.1 (C-3), 38.9 (*C*Me$_3$), 33.5 (C-4), 27.0 (C*Me*$_3$). Anal. Calcd for $C_{26}H_{30}F_3NO_5S$: C, 59.43; H, 5.71; N, 2.67. Found: C, 59.37; H, 5.44; N, 2.92.

**Methyl 2-*O*-Methyl-3,4-*O*-(methylethylidene)-β-D-galactopyranoside (16).** A suspension of 1.17 g (6 mmol) of methyl β-D-galactopyranoside (**14**) and 65 mg of $p$-toluenesulfonic acid in 100 mL of 2,2-dimethoxypropane was stirred for 48 h, quenched with 1 mL of triethylamine, and then concentrated to afford the crude acetal/methoxypropyl derivative. The resulting residue was dissolved in 30 mL of tetrahydrofuran and treated with 0.20 g (8.33 mmol) of sodium hydride and 0.5 mL (8.03 mmol) of iodomethane. After 4 h the reaction was quenched by addition of 5 mL of methanol and then concentrated. The residue was partitioned between 50 mL each of water and dichloromethane. The organic phase was dried and concentrated to afford the crude methylated product **15** as a syrup. This material was dissolved in 30 mL of methanol and then treated with 20 mg of pyridinium $p$-toluenesulfonate. After 2 h, 1 mL of triethylamine was added, and the reaction mixture was concentrated and chromatographed with 1:1 and then 1:2 petroleum ether/ethyl acetate as the eluant to give 1.23 g (83%) of acetonide **16**, mp 70–72 °C (lit.[24a] 75–76 °C).

**Methyl 2-*O*-Methyl-4,6-*O*-(phenylmethylene)-β-D-galactopyranoside (17).** A solution of 1.53 g (6.17 mmol) of acetonide **16** in 25 mL of methanol was treated with 0.46 g (2.42 mmol) of $p$-toluenesulfonic acid. The reaction was stirred for 4 h, quenched by the addition of 0.5 mL of triethylamine, and then concentrated. The residue was dissolved in 20 mL of dichloromethane and 2 mL (13.32 mmol) of benzaldehyde dimethyl acetal and stirred for 90 min. Triethylamine (0.5 mL) was added, and the reaction mixture was concentrated and then chromatographed with 1:1 and then 4:1 petroleum ether/ethyl acetate as the eluant to provide 1.60 g (88%) of the benzylidene derivative **17**: mp 159 °C (lit.[25] 164–165 °C); $[\alpha]_D$ −30.0° ($c$ = 0.38, $CHCl_3$) [lit.[25] −35.6°, ($c$ = 1.29, $CHCl_3$)].

**Methyl 3-Azido-3-deoxy-2-*O*-methyl-4,6-*O*-(phenylmethylene)-β-D-gulopyranoside (18).** A solution of 0.39 g (1.15 mmol) of alcohol **17** in 15 mL of dichloromethane and 0.20 (2.47 mmol) of pyridine was treated with 0.30 mL (1.78 mmol) of triflic anhydride at 0 °C. After 20 min at 0 °C, the reaction was diluted with 35 mL of dichloromethane and 50 mL of 1 N hydrochloric acid, and the organic phase was dried and then concentrated. The resulting crude triflate was dissolved in 10 mL of benzene and treated with 1.12 g (3.94 mmol) of tetra-$n$-butylammonium azide. After 24 h, the reaction was diluted with 60 mL each of ether and water, and the organic phase was dried and concentrated. Chromatography with 9:1 petroleum ether / ethyl acetate as the eluant gave 0.30 g (70%) of the azide **18**: mp 79–80 °C, $[\alpha]_D$ −27.4° ($c$ = 1.00, $CHCl_3$); IR (cm$^{-1}$) 2909, 2111; $^1$H NMR $\delta$ 7.52–7.35 (m, 5 H$_{arom}$), 5.51 (s, PhC*H*), 4.65 (d, $J$ = 7.9, H-1), 4.30 (d, $J$ = 12.7, H-6a), 4.17 (t, $J$ = 4.2, 3.2, H-3), 4.00 (dd, $J$ = 12.7, ~1, H-6b), 3.94 (d, $J$ = 4.2, H-4), 3.61–3.54 (m, H-2 and H-5), 3.57 and 3.53 (2 s, OMe's); $^{13}$C NMR $\delta$ 137.3 (C$_{ipso}$), 129.2, 128.2, 126.2 (C$_{arom}$), 101.2 (C-1), 101.2 (Ph*C*H), 77.3, 75.2, 69.1, 65.0, 60.8, 59.0, 56.8. Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.20; H, 5.94; N, 12.90.

**Methyl 3-Azido-3-deoxy-2-*O*-methyl-6-*O*-(phenylmethyl)-β-D-gulopyranoside (20).** A solution of 83 mg (0.26 mmol) of benzylidene derivative **18** in 15 mL of methanol and 0.21 mL (2.72 mmol) of trifluoroacetic acid was heated at 45 °C for

22 h. The reaction mixture was in sequence cooled, quenched with 0.3 mL of triethylamine, concentrated, and chromatographed with 1:2 petroleum ether/ethyl acetate as the eluant to afford 58 mg (97%) of the diol **19** as a syrup: $[\alpha]_D$ −29.7° (*c* = 0.17, $CHCl_3$); IR ($cm^{-1}$) 3358, 2936, 2109; $^1H$ NMR δ 4.62 (d, *J* = 7.8, H-1), 4.12 (br t, *J* = 4.0, H-3), 4.05−3.84 (m, H-4, H-6a, H-6b), 3.73 (t, *J* = 4.5, H-5), 3.58 and 3.55 (2 s, OMe's), 3.54 (dd, *J* = 7.8, 4.0, H-2); $^{13}C$ NMR 102.0 (C-1), 77.5, 71.3, 70.8, 63.7, 61.7, 59.0, 57.1.

A mixture of 52 mg (0.22 mmol) of the diol **19**, 200 mg of activated 3 Å molecular sieves, 59 mg (0.24 mmol) of di-*n*-butyltin oxide, 179 mg (0.56 mmol) of tetra-*n*-butylammonium bromide, 0.18 mL (1.51 mmol) of benzyl bromide, and 5 mL of acetonitrile was heated at 80 °C for 8 h. The reaction mixture was in sequence cooled, diluted with 20 mL of dichloromethane, filtered, and concentrated. Chromatography with 4:1 petroleum ether/ethyl acetate as the eluant afforded 61 mg (85%) of the benzyl ether **20** as a syrup: $[\alpha]_D$ −24.1° (*c* = 0.15, $CHCl_3$); IR ($cm^{-1}$) 3418, 2920, 2109; $^1H$ NMR δ 7.34 (br s, 5 $H_{arom}$), 4.65 and 4.53 (2 d, *J* = 12.1, Ph$CH_2$), 4.56 (d, *J* = 7.8, H-1), 4.12 t, *J* = 3.6, H-3), 3.89 (br t, *J* = 3.6, H-4), 3.85−3.68 (m, H-5, H-6a, H-6b), 3.60−3.50 (m, H-2 and OH), 3.56 and 3.54 (2 s, OMe's); $^{13}C$ NMR 137.2 ($C_{ipso}$), 128.6, 128.0, 127.8 ($C_{arom}$), 102.0 (C-1), 77.5, 73.9, 70.7, 70.4, 70.4, 61.8, 59.0, 65.8. Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.70; H, 6.52; N, 12.52.

**Methyl 3-Azido-3-deoxy-4-[3′,4′-dideoxy-2′-*O*-(2,2-dimethylpropionyl)-6′-*O*-(phenylmethyl)-3′-(trifluoroacetamido)-β-D-glucopyranosyl]-2-*O*-methyl-6-*O*-(phenylmethyl)-β-D-gulopyranoside (21).** A stirred solution of 100 mg (0.19 mmol) of donor **13** and 50 mg (0.16 mmol) of acceptor **20** in 3 mL of dichloromethane was treated sequentially with 500 mg of activated 3 Å molecular sieves, 70 mg (0.31 mmol) of *N*-iodosuccinimide, and 0.75 mL (0.085 mmol) of a 1% dichloromethane solution of triflic acid. After 10 min the reaction was quenched with 0.35 mL of triethylamine and then concentrated. Chromatography of the residue with 5:1 and then 4:1 petroleum ether/ethyl acetate as the eluant produced 103 mg (90%) of the disaccharide **21**: mp 42−44 °C, $[\alpha]_D$ −44.7° (*c* = 0.15, $CHCl_3$); IR ($cm^{-1}$) 2876, 2108, 1728, 1708; $^1H$ NMR δ (400 MHz) 7.37−7.24 (m, 10 $H_{arom}$), 6.81 (d, *J* = 8.7, N*H*-3′), 4.67 (t, *J* = 7.7, H-2′), 4.62 (d, *J* = 7.7, H-1′), 4.57 (d, *J* = 7.7, H-1), 4.57 and 4.49 (2 d, *J* = 12, Ph$CH_2$), 4.45 (s, Ph$CH_2$), 4.15−4.07 (m, H-3′), 4.01 (t, *J* = 4.0, H-3), 3.93−3.38 (m, H-5), 3.85−3.83 (m, H-4), 3.77−3.70 (m, H-5′), 3.70 (dd, *J* = 11.2, 4.8, H-6a), 3.63 (dd, *J* = 11.2, 6.0, H-6b), 3.51 and 3.53 (2 s, OMe's), 3.48 (dd, *J* = 10.6, 5.0, H-6a′), 3.43 (dd, *J* = 10.6, 5.0, H-6b′), 3.37 (dd, *J* = 7.7, 4.0, H-2), 2.21 (ddd, *J* = 12, 4.0, 1.5, H-4′$_{eq}$), 1.55 (q, *J* = 12, H-4′$_{ax}$), 1.20 (s, C*Me*$_3$); $^{13}C$ NMR (*COCF*$_3$ signals not seen) 178.7 (C=O), 139.7 ($C_{ipso}$), 139.5 ($C_{ipso}$), 129.4, 129.3, 128.8, 128.7, 103.2 and 100.8 (C-1 and C-1′), 79.2, 75.1, 74.4, 74.3, 73.7, 73.4, 73.3, 73.0, 71.1, 61.4, 59.7, 57.0, 50.0, 39.9 (*C*Me$_3$), 33.8 (C-4′), 27.7 and 27.6 (*CMe*$_3$ and OMe's). Anal. Calcd for $C_{35}H_{45}F_3N_4O_{10}$: C, 56.91; H, 6.10; N, 7.59. Found: C, 56.58; H, 6.10; N, 7.05.

**Methyl 3-Amino-3-deoxy-4-[3′,4′-dideoxy-2′-*O*-(2,2-dimethylpropionyl)-6′-*O*-(phenylmethyl)-3′-(trifluoroacetamido)-β-D-glucopyranosyl]-2-*O*-methyl-6-*O*-(phenylmethyl)-3-*N*-[(trichloroacetamido)carbonyl]-β-D-gulopyranoside (22).** A solution of 103 mg (0.14 mmol) of disaccharide azide **21** in 3 mL of THF was treated with 0.24 mL (0.24 mmol) of a 1 M tetrahydrofuran solution of trimethylphosphine. After 1.5 h, 0.24 mL of water was added, and the reaction was stirred for 1.5 h, and then concentrated. The residue was dissolved in 3 mL of dichloromethane and treated with 27 μL (0.23 mmol) of trichloroacetyl isocyanate. After 10 min, the reaction mixture was concentrated and then chromatographed with 4:1 and then 2:1 petroleum ether/ethyl acetate as the eluant to give 96 mg (76%) of the (trichloroacetyl)urea **22**: mp 87−88 °C; $[\alpha]_D$ −34.4 (c = 0.25, $CHCl_3$); IR ($cm^{-1}$) 2965, 2935, 2869, 1723, 1706; $^1H$ δ NMR (partial) 8.88 (s, imide NH), 8.24 (d, *J* = 5.0, NH-3), 7.30 (br s, 10 $H_{arom}$), 7.04 (d, *J* = 7.9, NH-3′), 3.57 and 3.45 (2 s, OMe's), 2.21 (ddd, *J* = 12, 4.3, 1.5, H-4′$_{eq}$), 1.60 (q, *J* = 12, H-4′$_{ax}$), 1.20 (s, *CMe*$_3$). Anal. Calcd for $C_{38}H_{47}Cl_3F_3N_3O_{12}$: C, 50.65; H, 5.26; Cl, 11.80; F, 6.32; N, 4.66. Found: C, 50.33; H, 5.21; Cl, 11.87; F, 6.06; N, 4.40.

**Methyl 3-*N*-(Acetamidocarbonyl)-6-*O*-acetyl-3-amino-3-deoxy-4-[6′-*O*-acetyl-3′,4′-dideoxy-2′-*O*-(2,2-dimethylpropionyl)-3′-(trifluoroacetamido)-β-D-glucopyranosyl]-2-*O*-methyl-β-D-gulopyranoside (23).** A solution of 405 mg (0.45 mmol) of the (trichloroacetyl)urea disaccharide **22** in 12 mL of methanol was hydrogenated at room temperature and pressure with 405 mg of 10% palladium-on-carbon as catalyst. After 2 days, the reaction mixture was diluted with 50 mL of methanol, filtered through a pad of Celite, and then chromatographed with 10:1 and then 5:1 dichloromethane/methanol as the eluant to furnish 169 mg (65%) of the diol urea: mp 150−152 °C; IR ($cm^{-1}$) 3341, 2963, 2936, 1715, 1649. A portion of the diol urea was quantitatively acetylated with acetic anhydride in pyridine solution to give the triacetate **23** as a syrup: $^1H$ NMR δ (400 MHz) 8.80 (d, *J* = 5.4, N*H*-3), 8.48 (s, imide NH), 7.09 (d, *J* = 7.8, N*H*-3′), 4.78 (d, *J* = 7.7, H-1′), 4.70 (t, *J* = 7.7, H-2′), 4.38 (d, *J* = 7.7, H-1), 4.30−4.24 (m, H-3), 4.24−4.04 (m, H-3′, H-3, H-4, H-6a, H-6b, H-6a′, H-6b′), 3.94−3.89 (m, H-5), 3.82−3.75 (m, H-5′), 3.51 and 3.39 (2 s, OMe's), 3.37 (dd, *J* = 7.7, 4.0, H-2), 2.16 (ddd, *J* = 12.5, 4.3, 1.5, H-4′$_{eq}$), 2.14, 2.06, 2.03 (3 s, C*H*$_3$CO's), 1.57 (q, *J* = 12.1, H-4′$_{ax}$), 1.17 (s, C*Me*$_3$).

**Acknowledgment.** We are grateful to the Charles and Johanna Busch Memorial Fund, Berlex Corp., and Hoffmann-La Roche for financial support of this work, the Spanish Ministry of Education and Science for a postdoctoral fellowship to C.J., and Dr. Santosh R. Nandan for helpful discussion. S.K. thanks American Cyanamid for a Cyanamid Faculty Award.