Column chromatography of the semipure 1 on a YMC ODS A60 (40–63 μm) eluting with 22:78 acetonitrile–0.15% phosphate buffer (pH 3.5) followed by adsorption on a column of HP-20 and elution with 80% aqueous acetone (pH 2.5) afforded pure pradimicin A hydrochloride. Zwitterionic pradimicin A was obtained by adjusting the hydrochloride solution to pH 5.5 with NaOH. The resulting precipitate was collected by centrifugation, washed successively with methanol and acetone, and dried at 60 °C under vacuum for at least 24 h. ^{13}C NMR data are shown in Table I. A 40-mg sample of 1 enriched with [1,2-$^{13}C_2$]acetate was dissolved in 0.6 mL of DMSO-d_6 for the 2D INADEQUATE experiment.

Preparation of the ^{13}C-Labeled Aglycon (4). Acid hydrolysis of the two ^{13}C-labeled samples of 1 enriched with [1-^{13}C]- and [2-^{13}C]acetates was conducted as usual (6 N HCl, 110 °C, 12 h), but before reaction, each sample was diluted with unlabeled 1 (three times by weight). In both cases the products were washed with water, adsorbed on a column of HP-20, and eluted with 80% aqueous acetone. For the unlabeled 4: ^{13}C NMR (100.4-MHz, DMSO-d_6, 40 mg/mL, 60 °C) δ 187.2 (C-8), 180.2 (C-13), 174.2 (C-18), 168.1 (C-15), 166.8 (C-14), 165.5 (C-11), 163.7 (C-9), 157.1 (C-1), 145.3 (C-6a), 140.5 (C-4a), 137.9 (C-12a), 136.2 (C-3), 133.3 (C-14a), 131.8 (C-7a), 125.9 (C-2), 118.6 (C-13a), 118.5 (C-14b), 114.9 (C-4), 110.7 (C-7), 110.2 (C-8a), 105.7 (C-12), 103.9 (C-10), 72.4 (C-6), 71.6 (C-5), 55.7 (CH_3O at C-11), 47.8 (C-17), 19.8 (CH_3 at C-3), 17.4 (CH_3 at C-17). For the ^{13}C-labeled 4 derived from [1-^{13}C]-acetate, ^{13}C NMR spectra were identical except for enrichment of the following 12 carbons: C-8, C-15, C-11, C-9, C-1, C-4a, C-12a, C-3, C-14a, C-13a, C-7, and C-6. For the ^{13}C-labeled 4 derived from [2-^{13}C]acetate, ^{13}C NMR spectra were identical except for enrichment of the following 12 carbons: C-13, C-14, C-6a, C-7a, C-2, C-14b, C-4, C-8a, C-12, C-10, C-5, and CH_3 at C-3.

Acknowledgment. We thank Mr. T. Moriyama and Mr. N. Tsunoda for running the ^{13}C NMR spectra.

A Facile, Practical Synthesis of 2,6-Dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol (MDL 25,637)

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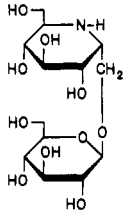
A facile synthetic route useful for large-scale preparation of the α-glucosidase inhibitor, 2,6-dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol (1), is described. The protected heptononitrile **5**, prepared in three steps from the readily available bisulfite adduct of nojirimycin (**2**), was stereospecifically converted to carboxylic acid **6** by acid hydrolysis (90% TFA/$Hg(TFA)_2$) and oxidation (N_2O_4). After reduction, the resultant amino alcohol **7** was N-protected and condensed with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate to provide glucoside **9**. Stepwise deprotection of **9** with transfer hydrogenation and base-catalyzed hydrolysis gave compound 1 in 26% overall yield from **2**.

Inhibitors of α-glycosidases and glycoprotein trimming enzymes[1] have potential therapeutic uses in diabetes mellitus,[2] tumor metastases,[3] and acquired immunodeficiency syndrome.[4] A potent α-glucosidase inhibitor, 2,6-dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol (1), has been identified as a drug candidate for antidiabetic therapy.[5] In the course of preparing quantities of 1, an alternative synthesis was developed to eliminate isomeric separations that were required in the original route.[6] Herein we describe a facile synthetic sequence for the preparation of 1 (Scheme I).



1

The readily available bisulfite adduct of nojirimycin (**2**)[7] was selected as a suitable starting material. The additional hydroxymethyl moiety in 1 was appended in a latent form as a nitrile with expectations of its ready conversion to an alcohol. However, even though nitrile **3** was prepared in

Scheme I

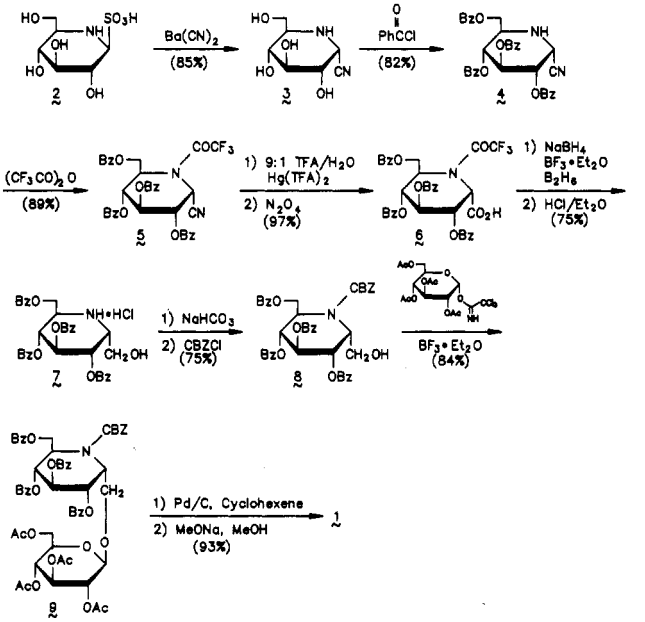


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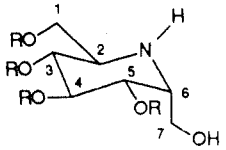
Table I. Chemical Shifts (ppm) of Compounds 10 and 11



	compd 10, R = H		compd 11, R = CH_2Ph	
proton	δ, ppm[a]	J, Hz	δ, ppm[b]	J, Hz
H_1, $H_{1'}$	3.90, 3.56		3.61, 3.32	
H_2	2.86	$J_{2,3}$ = 9.5	2.72	$J_{2,3}$ = 9.7
H_3	3.20	$J_{3,4}$ = 9.4	3.45	$J_{3,4}$ = 10.7
H_4	3.48	$J_{4,5}$ = 10.0	3.74	$J_{4,5}$ = 10.1
H_5	3.74	$J_{5,6}$ = 6.1	3.41	$J_{5,6}$ = 6.1
H_6	3.28		3.09	
H_7, $H_{7'}$	3.78, 3.81		3.67, 3.95	

[a] From deuterated sodium 3-(trimethylsilyl)propionate (D_2O). [b] From TMS (C_6D_6).

good yields by a literature procedure,[8] the subsequent hydrolysis of **3** proved to be surprisingly troublesome. Base-catalyzed hydrolysis of **3** with either sodium hydroxide or potassium hydroxide gave exclusively the undesired carboxylic acid with β-stereochemistry. The two-dimensional *J*-resolved (2-D *J*) ^1H NMR spectrum of the product revealed a doublet centered at δ 3.65 ($J_{2,3}$ = 10.7 Hz) for H-2 indicating an anti relationship between H-2 and H-3. A similar analysis of the α-cyano derivative **3** showed that H-2 resonated at δ 4.42 ($J_{2,3}$ = 5.4 Hz) with H-2 and H-3 existing in a gauche arrangement. Acid-catalyzed hydrolysis (aqueous HCl or H_2SO_4) provided only a 15–20% yield of the desired α-carboxylic acid and other decomposition byproducts. Therefore, we adopted an alternative strategy whereby the transformation of the nitrile was deferred. Benzoylation of **3** with benzoyl chloride/Et_3N gave an 82% yield of the tetrabenzoate **4**. The endocyclic amine was differentially protected by treatment with trifluoroacetic anhydride and Et_3N. The introduction of the strongly electron-withdrawing trifluoroacetyl protecting group proved to be essential for the hydrolysis of the nitrile. While compound **4** would not give clean hydrolytic products under a variety of conditions, the acylamino nitrile **5** underwent smooth hydrolysis in 90% trifluoroacetic acid to the corresponding amide, which was converted to carboxylic acid **6** by subsequent reaction with N_2O_4.[9] The acid hydrolysis of **5**, which could be accelerated by the addition of catalytic amounts of mercuric trifluoroacetate, was stereospecific and gave exclusively the desired α-stereoisomer.

The efficient conversion of *N*-(trifluoroacetyl)amino acid **6** to amino alcohol **7** required considerable experimentation. Treatment of **6** with $NaBH_4$ in ethanol removed the trifluoroacetyl protecting group, but the resultant amino acid was hygroscopic and difficult to isolate. Reduction of **6** with diborane in THF gave poor yields of the corresponding alcohol. The combination of excess $NaBH_4$ and BF_3·Et_2O[10] gave erratic yields of **7** directly; additional diborane was needed to complete the reduction. Best results were obtained by successive treatment of scrupulously dried **6** with diborane, $NaBH_4$, and BF_3·Et_2O. The amino alcohol **7** was isolated as the crystalline hydrochloride.

Deprotection of **7** with methanolic NH_3 gave α-homonojirimycin (compound **10**), which was recently isolated from the leaves of *Omphalea Diandra L.*[11] The high-resolution ^1H NMR spectra of **10** and the known **11**[6] (Table I) are similar. The significantly smaller coupling constant ($J_{5,6}$ = 5.9 Hz) between H-5 and H-6 is indicative of the cis relationship for the two hydrogens. Reaction of amine **7** with benzyl chloroformate gave the primary alcohol **8**, suitably protected for the final glycosidation reaction. Condensation of **8** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of mercuric cyanide provided the β-glucoside in 77% yield. The product, however, was contaminated with detectable amounts (1–2% by ^1H NMR) of the α-glucoside.

Application of Schmidt's glycosidation methodology[12] using 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate produced an 85% yield of the isomerically pure β-glucoside. Stepwise deprotection of **9** with transfer hydrogenolysis, followed by treatment with sodium methoxide in methanol, resulted in a 93% yield of compound **1**, identical in every respect with an authentic sample.[6]

In summary, we have described a facile synthesis of **1** from the nojirimycin–bisulfite adduct (**2**) with an overall yield of 26%. We are presently examining the scope of the Hg(II)-catalyzed hydrolysis of other nitriles in trifluoroacetic acid. Further research in the area of aza sugars is in progress and will be reported in due course.

Experimental Section

All melting points were determined in a Thomas Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1310 grating spectrophotometer. NMR spectra were recorded with a Varian EM 360A spectrometer or a Varian XL-300 spectrometer. Chemical shifts are given as δ values with reference to Me_4Si or deuterated sodium 3-(trimethylsilyl)propionate as internal standards. Low-resolution mass spectra were obtained on a Finnigan 4023 GC/MS/DS instrument operated in the chemical ionization (CI) mode. Analytical TLC was performed on glass plates precoated with Brinkmann silica gel 60-F254 (0.25 μm thickness). Elemental analyses were carried out by the Analytical Department, Merrell Dow Research Institute.

2,6-Dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptononitrile (3). Compound **3** was prepared in 85% yield according to the procedure of Böshagen et al.[8] from nojirimycin bisulfite adduct (**2**), which was purchased from Meiji Seika Kaisha, Ltd., Japan.

2,6-Dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptononitrile 3,4,5,7-Tetrabenzoate (4). To a slurry of compound **3** (50.0 g, 0.266 mol) and triethylamine (158 mL, 1.13 mol) in 1.2 L of ethyl acetate was added dropwise benzoyl chloride (159 g, 1.13 mol)

(1) (a) Elbein, A. D. *Ann. Rev. Biochem.* **1987**, *56*, 497. (b) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744.
(2) Dimitriadis, G. D.; Tessari, P.; Go, V. L. W.; Gerich, J. E. *Metabolism* **1985**, *34*, 261.
(3) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215.
(4) (a) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120. (b) Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206.
(5) (a) Liu, P. S.; Rhinehart, B. L. 191st National Meeting of the American Chemical Society, April 13–18, 1986, New York, NY; Abstract MEDI 72. (b) Rhinehart, B. L.; Robinson, K. M.; Liu, P. S.; Payne, A. J.; Wheatley, M. E.; Wagner, S. R. *J. Pharmacol. Exp. Therap.* **1987**, *241*, 915.
(6) Liu, P. S. *J. Org. Chem.* **1987**, *52*, 4717.
(7) (a) Tsuda, Y.; Okuno, Y.; Kanemitsu, K. *Heterocycles* **1988**, *27*, 63. (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337. (c) Kodama, Y.; Tsuruoka, T.; Niwa, T.; Inouye, S. *J. Antibiot.* **1985**, *38*, 116. (d) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *23*, 2125. (e) Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot.* **1966**, *19*, 288.
(8) Böshagen, H.; Geiger, W.; Junge, B. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 806.
(9) Brenneisen, K.; Tamm, Ch.; Reichstein T. *Helv. Chim. Acta* **1956**, *39*, 1233.
(10) Chauncy, B.; Gellert, E. *Aust. J. Chem.* **1970**, *23*, 2503.
(11) Kite, G. C.; Fellows, L. E.; Fleet, G. W. J.; Liu, P. S.; Scofield, A. M.; Smith, N. G. *Tetrahedron Lett.* **1988**, *29*, 6483.
(12) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

over a period of 40 min. The mixture was stirred under N_2 for 18 h at room temperature. The resulting cream-colored slurry was added to a 1:1 mixture of ethyl acetate and water (2 L), and the phases were separated after mixing thoroughly. The organic layer was washed with brine (500 mL), saturated aqueous Na_2CO_3 solution (500 mL), and brine again (500 mL) and dried over Na_2SO_4. Evaporation of solvents in vacuo from the organic extract gave a viscous oil, which upon trituration with 250 mL of cold methanol provided a white solid. The solid was filtered, washed with cold methanol, and dried in vacuo (at 60 °C) for 5 h to provide 131.2 g (82%) of **4**: mp 179–182 °C; IR (KBr) 3600–3300 (N—H), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.60 (m, 1 H), 3.80 (m, 1 H), 4.35 (dd, 1 H), 4.70 (dd, 1 H), 5.40 (dd, 1 H), 5.55 (t, 1 H), 6.05 (t, 1 H), 7.2–7.6 (m, 12 H, aryl), 7.8–8.1 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 48.8 and 55.0 (2 NCH), 63.3, 70.0, 70.1, and 71.9 (4 OCH), 116.1 (C≡N); MS (CI, C_4H_{10}) 605 (MH^+), 578 (MH^+ – HCN). Anal. Calcd for $C_{35}H_{28}N_2O_8$: C, 69.53; H, 4.67; N, 4.63. Found: C, 69.34; H, 4.65; N, 4.51.

2,6-Dideoxy-2,6-(trifluoroacetimido)-D-*glycero*-D-*ido*-heptononitrile 3,4,5,7-Tetrabenzoate (5). To a stirred solution of compound **4** (75.0 g, 0.124 mol) and triethylamine (17 mL, 0.122 mol) in ethyl acetate (1.25 L) at 0 °C was added trifluoroacetic anhydride (49 mL, 0.345 mol) over a period of 20 min. The resulting solution was stirred at 0 °C for 1 h and at room temperature for 18 h. An additional 7 mL (0.05 mol) of trifluoroacetic anhydride was added to the reaction mixture, and stirring was continued for another 3 h. The mixture was poured into ice–water (1.5 L) and stirred vigorously for 1 h. The phases were separated, and the aqueous layer was extracted with 200 mL of ethyl acetate. The combined extracts were washed with brine (500 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvents in vacuo at <45 °C gave an off-white solid, which was triturated with 100 mL of cold methanol and filtered. The crude product was washed with cold methanol and air-dried to afford 77.5 g (89%) of **5** as a fine white powder: mp 156–159 °C; IR (KBr) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.70 (m, 1 H), 4.90 (m, 2 H), 5.50 (m, 1 H), 5.70 (m, 1 H), 6.0 (m, 2 H) 7.2–7.7 (m, 12 H, aryl), 7.9–8.2 (m, 8 H, aryl); MS (CI, C_4H_{10}) 701 (MH^+), 579 (MH^+ – $PhCO_2H$). Anal. Calcd for $C_{37}H_{27}N_2F_3O_9$: C, 63.43; H, 3.88; N, 4.00. Found: C, 63.60; H, 3.66; N, 4.01.

2,6-Dideoxy-2,6-(trifluoroacetimido)-D-*glycero*-D-*ido*-heptonic Acid 3,4,5,7-Tetrabenzoate (6). A solution of nitrile **5** (76.8 g, 0.110 mol) and mercuric trifluoroacetate (5.1 g, 0.012 mol) in 280 mL of 90% trifluoroacetic acid was stirred at room temperature for 3.5 h. The mixture was cooled to 5 °C, and N_2O_4 was infused vigorously through the solution during 70 min. The reaction mixture was stirred at room temperature for an additional 1.5 h. The yellowish solution was slowly poured into vigorously stirred ice–water (2.5 L). The solid that separated was isolated by filtration and air-dried to give 76.8 g (97%) of **6** as a hygroscopic white powder: mp 103–113 °C; IR (KBr) 3600–2900 (OH), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 4.60 (m, 1 H), 4.90 (m, 2 H), 5.35 (m, 2 H), 5.80 (m, 2 H), 7.3–7.8 (m, 12 H, aryl), 7.9–8.1 (m, 8 H, aryl); MS (CI, C_4H_{10}) 720 (MH^+), 598 (MH^+ – $PhCO_2H$). Anal. Calcd for $C_{37}H_{28}NF_3O_{11}\cdot0.5H_2O$: C, 60.99; H, 4.01; N, 1.92. Found: C, 60.83; H, 3.96; N, 2.03.

2,6-Dideoxy-2,6-imino-D-*glycero*-L-*gulo*-heptitol 1,3,4,5-Tetrabenzoate Hydrochloride (7). To a solution of carboxylic acid **6** (5.8 g, 8 mmol) in 20 mL of THF was added 12 mL of 1 M borane in THF over a period of 10 min. After the mixture was stirred for 0.5 h, $NaBH_4$ (1 g) and $BF_3\cdot Et_2O$ (0.4 mL) were added successively to the mixture, and the resulting solution was kept under N_2 for 16 h at room temperature. The mixture was cooled to 4 °C and, after dropwise addition of methanol (10 mL), stirred for another 0.5 h and then concentrated in vacuo. The dry residue was dissolved in ethyl acetate (70 mL) and washed with 1 N HCl (20 mL), $NaHCO_3$ solution (2 × 20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$) and evaporated to give an oily residue which was redissolved in 50 mL of anhydrous ether. The ethereal solution was added dropwise to a saturated solution of HCl in ether (10 mL), whereby a cream-colored solid precipitated. The resulting slurry was cooled (0 °C) and stirred for 1 h. The hydrochloride **7** was isolated by filtration (4.07 g, 75%): mp 209–211 °C; IR (KBr) 2700–2300 (—NH_2^+), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.15–4.30 (m, 2 H), 4.50 (m, 2 H), 4.90 (m, 2 H), 5.90 (m, 1 H), 6.0 (m, 2 H), 7.2–7.5 (m, 12 H, aryl), 7.9–8.1 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 53.7 and 54.2 (2 NCH), 57.9, 60.0, 66.6, 67.9 and 68.9 (5 OCH); MS (CI, C_4H_{10}) 610 (MH^+), 488 (MH^+ – $PhCO_2H$). Anal. Calcd for $C_{35}H_{32}NClO_9\cdot0.5H_2O$: C, 64.17; H, 5.07; N, 2.14. Found: C, 63.94; H, 4.88; N, 2.16.

2,6-Dideoxy-2,6-[[(phenylmethoxy)carbonyl]imino]-D-*glycero*-L-*gulo*-heptitol 1,3,4,5-Tetrabenzoate (8). A solution of compound **7** (32.2 g, 49.8 mmol) in ethyl acetate (250 mL) was washed with saturated sodium bicarbonate solution (2 × 200 mL), saturated sodium chloride solution (200 mL), and concentrated in vacuo. The residue was dissolved in THF (150 mL), and potassium carbonate (17.8 g, 124 mmol) was added. The slurry was stirred, and benzyl chloroformate (11 mL, 77.0 mmol) was added dropwise. After 30 min, water (30 mL) was added, and the stirred, two-phase mixture was warmed to 50 °C. After 2 h another portion of benzyl chloroformate (5 mL, 35 mmol) was added, and heating was continued for 1 h more. The cooled mixture was diluted with ethyl acetate (150 mL), and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to provide a viscous, pale yellow oil, which was rinsed with hexane and redissolved in a minimum amount of ether. The solid compound **8** precipitating during overnight refrigeration was filtered off to give 17.3 g of a cream-colored powder, and the filtrate was concentrated and applied to a silica gel column. Elution with 3:7 ethyl acetate–hexane gave an additional 11.0 g of **8** as an off-white powder: mp 145–147 °C; IR (KBr) 3600–3200 (OH), 1730 (C=O), 1690 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 3.1 (br m, 1 H, OH), 4.10 (m, 1 H), 4.30 (m, 2 H), 4.65 (dd, 1 H), 5.00 (s, 2 H), 5.05 (m, 1 H), 5.20 (m, 1 H) 5.45 (m, 1 H), 5.55 (m, 1 H), 5.70 (m, 1 H), 7.1–7.6 (m, 17 H, aryl), 7.8–8.1 (m, 8 H, aryl); MS (CI, C_4H_{10}) 744 (MH^+), 726 (MH^+ – H_2O), 622 (MH^+ – $PhCO_2H$). Anal. Calcd for $C_{43}H_{37}NO_{11}$: C, 69.44; H, 5.01; N, 1.88. Found: C, 69.04; H, 5.02; N, 1.79.

2,6-Dideoxy-2,6-[[(phenylmethoxy)carbonyl]imino]-7-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-D-*glycero*-L-*gulo*-heptitol 1,3,4,5-Tetrabenzoate (9). To a cooled solution (−30 °C) of alcohol **8** (185 g, 0.25 mol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate[12] (202 g, 0.37 mol) in 400 mL of CH_2Cl_2 was added 40 mL of $BF_3\cdot Et_2O$ over a period of 5 min. After being stirred for 1.5 h at −20 °C, the mixture was diluted with CH_2Cl_2 (300 mL) and added to aqueous sodium bicarbonate solution (300 mL). The organic phase was separated and washed with saturated $NaHCO_3$ solution (2 × 300 mL), followed by brine (300 mL), and dried ($MgSO_4$). Evaporation of the solvent gave an oily residue, which was redissolved in methanol (740 mL) at 60 °C. Upon cooling overnight, the crude product crystallized as a colorless solid and was collected by filtration and washed successively with cold methanol (500 mL) and ether (500 mL) to provide 226 g (85%) of **9**: mp 141–142 °C; IR (KBr) 1760–1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.9–2.0 (4 s, 12 H, 4 CH_3CO), 3.6–4.2 (m, 4 H), 4.4–5.2 (m, 11 H), 5.4–5.8 (m, 3 H) 7.0–8.1 (m, 25 H, aryl); ^{13}C NMR ($CDCl_3$) δ 52.3 and 55.8 (2 NCH), 99.8 (C_1); MS (CI, C_4H_{10}) 1074 (MH^+), 952 (MH^+ – $PhCO_2H$). Anal. Calcd for $C_{57}H_{55}NO_{20}$: C, 63.74; H, 5.16; N, 1.30. Found: C, 63.65; H, 5.19; N, 1.27.

2,6-Dideoxy-2,6-imino-D-*glycero*-L-*gulo*-heptitol (10). A solution of compound **7** (10.0 g, 15.5 mmol) in ethyl acetate (80 mL) was washed with saturated $NaHCO_3$ solution (2 × 80 mL), followed by saturated NaCl solution (80 mL), and stirred with activated charcoal (5 g) for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to provide a foamy residue. The residue was redissolved in saturated methanolic NH_3 (100 mL) and kept at room temperature for 48 h. The solution was evaporated to dryness, and the resultant residue was dissolved in distilled water (100 mL). The aqueous solution was washed with ethyl acetate (2 × 100 mL), treated with charcoal (0.5 g), and evaporated to provide an oily residue. Trituration of the residue with methanol (50 mL) gave a colorless solid, which was collected and washed with methanol (10 mL) and ether (10 mL) to provide 2.05 g (69%) of **10**: mp 198–199 °C; IR (KBr) 3600–3100 cm^{-1} (OH and NH); ^1H NMR (D_2O) see Table I; MS (CI, CH_4) 194 (MH^+), 176 (MH^+ – H_2O), 162 (MH^+ – CH_3OH), 158 (MH^+ – $2H_2O$); $[\alpha]^{20}_D$ +79.1° (*c* 2.03, H_2O). Anal. Calcd for $C_7H_{15}NO_5\cdot0.2H_2O$: C, 42.72; H, 7.89; N, 7.12. Found: C, 42.88; H, 8.07; N, 7.03.

2,6-Dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol (1). To a stirred slurry of compound **9** (575 g, 0.536 mol) in methanol (3.4 L) and cyclohexene (1.4 L) under argon was added a mixture of 5% Pd/C (58 g) in EtOH (50 mL). The resulting mixture was heated under gentle reflux for 16 h. After cooling, the slurry was filtered through Celite and concentrated to provide a solid, which was redissolved in CH_2Cl_2 (2.4 L) and washed with saturated $NaHCO_3$ solution (1.4 L) and brine (2 × 1.4 L). The organic solution was dried ($MgSO_4$) and concentrated to a foamy residue. To the residue was added methanol (3.8 L) and 25% NaOMe in methanol (10 mL). The mixture was stirred at room temperature for 16 h, and the crystalline solid that separated was collected by filtration, washed with 1:1 methanol–acetone (500 mL), and dried in vacuo to provide **1** as a colorless solid (177 g, 93%): mp 216–219 °C; IR (KBr) 3600–3100 cm^{-1} (OH and NH); ^1H NMR (D_2O) δ 2.89 (ddd, 1 H), 3.23 (dd, 1 H), 3.32 (dd, 1 H), 3.38 (dd, 1 H), 3.4–3.6 (m, 5 H), 3.7 (m, 2 H), 3.9–4.0 (m, 3 H), 4.13 (dd, 1 H), 4.49 (d, 1 H, $H_{1'}$, $J_{1',2'}$ = 7.9 Hz); MS (CI, CH_4) 356 (MH^+), 338 ($MH^+ - H_2O$), 324 ($MH^+ - CH_3OH$); $[\alpha]^{20}_D$ +27.5° (*c* 1.0, H_2O). Anal. Calcd for $C_{13}H_{25}NO_{10}\cdot H_2O$: C, 41.82; H, 7.29; N, 3.75; H_2O, 4.81. Found: C, 41.87; H, 7.44; N, 3.66; H_2O, 4.90 (Karl Fischer).

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Reactions of Benzyl Carbinols with Fluorosulfuric Acid

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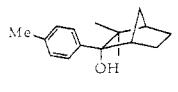
A series of benzyl carbinols have been reacted with HSO_3F at −78 °C, the solutions quenched, and the products isolated and identified. A variety of reaction modes occur including reduction (3-methyl- and 4-methyl-1-benzylcyclohexanol), rearrangement and cyclization (1-benzyl-2-methylcyclohexanol, 6-benzylspiro[4.5]decan-6-ol, 1-benzyl-*trans*-decalin-1-ol, 2-benzylcamphenilol, 2-benzylfenchol, 3-methyl-1-phenylbutan-2-ol, spiro[3-*exo*-benzylbicyclo[2.2.1]heptan-3-*endo*-ol-2,1′-cyclopentane]), and ring expansion (2-benzylnorbornanol). At higher temperatures fluorosulfonation of the product aryl ring can occur. The reaction mechanisms are discussed and that of the benzylnorbornyl ring expansion unambiguously determined by a series of deuterium labeling experiments.

Introduction

The reaction of 2-*p*-tolylcamphenilol (**1**) with HSO_3F to give 11-(fluorosulfonyl)-7,8,12-trimethyltetracyclo-[7.4.0.0^{2,7}0.^{4,8}]trideca-1(9),10,12-triene (**2**)[1] prompted our interest in the use of this super acid as a reagent in organic synthesis. A recent report[2] of the trifluoroacetic acid catalyzed cyclization of 5-aryl-1,1,1-trifluoropentan-2-ols (**3**) to 1-(trifluoromethyl)tetralins **4** requiring temperatures of 140–160 °C shows the difficulty of obtaining carbocation-induced intramolecular cyclization reactions with conventional acids. Reactions with such acids often give



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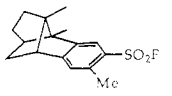

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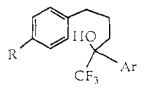

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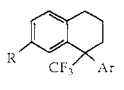

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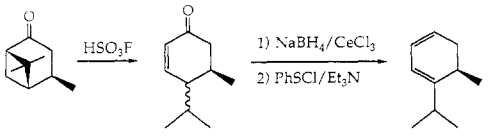
elimination and addition products without skeletal rearrangement. The ability of HSO_3F to generate carbocations in solution at low temperatures in the absence of good nucleophiles gives access to products from rearrangement and intramolecular cyclization not available with acids having counter anions capable of acting as bases and nucleophiles. Despite the fact that superacids have been extensively employed for the spectroscopic study of carbocations,[3] there have been few reports of the use of superacids as reagents in organic synthesis. Since the more complex rearrangements observed with fluorosulfuric acid often lead to synthetically useful structures,[4] we have been examining the use of fluorosulfuric acid as a reagent in organic synthesis. We have previously reported[4a] an application of the use of fluorosulfuric acid in the ring opening of pinanones which included an enantiospecific synthesis of the chiral diene **5** (Scheme I).

Scheme I



5

Carbocations are involved in numerous substitution, elimination, addition, fragmentation, and rearrangement reactions of synthetic, industrial, and biological importance.[5] Rearrangements of carbocations are considered to occur for thermodynamic reasons, wherein an initially

(1) Coxon, J. M.; Pojer, P. M.; Robinson, W. T.; Steel, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, 111.

(2) Bonnet-Delpon, D.; Cambillau, C.; Charpentier-Morize, M.; Jacquot, R.; Mesureur, D.; Ourevitch, M. *J. Org. Chem.* **1988**, *53*, 754.

(3) (a) Olah, G. A.; Prakash, S. G. K.; Sommer, J. *Superacids*; John Wiley & Sons: New York, 1985. (b) Gillespie, R. J. *Acc. Chem. Res.* **1968**, 202. (c) Brown, H. C.; Olah, G. A.; Hogeveen, H.; van Kruchten, E. M. G. A.; Kirmse, W. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1979; Vol 80.

(4) (a) Coxon, J. M.; Hydes, G. J.; Steel, P. J. *Tetrahedron* **1985**, *41*, 5213. (b) Dytnerski, D.; Ranganayakulu, K.; Singh, B. P.; Sorensen, T. S. *J. Org. Chem.* **1983**, *48*, 309.

(5) Olah, G. A.; Schleyer, P. v. R. *Carbonium Ions*; John Wiley & Sons: New York, 1968–1976; Vols. 1–5.

0022-3263/89/1954-2542$01.50/0