α-D-*ribo*-hexopyranoside (6). Compound 3 (1.33 g, 5.0 mmol) and 1.8 mL (15 mmol) of pyridine were dissolved in 30 mL of dichloromethane and cooled to −20 °C. Triflic anhydride (2.0 g, 70 mmol) in 10 mL of dichloromethane was added dropwise to the stirred solution. After addition was complete, the reaction mixture was allowed to warm to room temperature over a period of 1 h, and 1 mL of water was added. Stirring was continued for 14 h, and then the solvent was removed by distillation under reduced pressure. The residue was separated by chromatography into two components. The first of these (R_f 0.35) was a syrup, identified as methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (6; 1.07 g, 4.0 mmol, 80%) on the basis of its NMR spectra and its elemental analysis. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.19; H, 6.99. The second compound (R_f 0.26) was identified as methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (5; 21 mg, .8 mmol, 16%) on the basis of its NMR spectra.

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Total Synthesis of 2,6-Dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol Hydrochloride: A Potent Inhibitor of α-Glucosidases†

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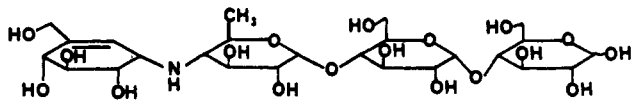
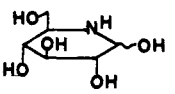
2,6-Dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol hydrochloride (8), a potent inhibitor of α-glucosidases, has been synthesized. Homologation at C1 coupled with amination at C5 of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1) furnished the protected amine 4. A stereospecific intramolecular cyclization of compound 4, catalyzed by mercuric acetate, constituted the key step of the reaction sequence. Glycosylation of the aglycon 6 with acetobromoglucose yielded, after deprotection, the target glucoside 8.

Introduction

The inhibition of intestinal α-glucosidases has recently been demonstrated to be a useful adjunctive therapy for serum glucose control in diabetes mellitus.[1] Several potent α-glucosidase inhibitors had been isolated from bacterial sources,[2] e.g., acarbose (Bayer g 5421) from *Actinoplanes* SE 50 and nojirimycin from *Streptomyces roseochromogenes* R-468.



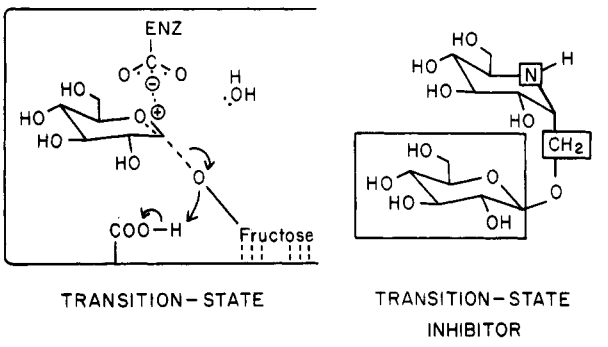
Acarbose



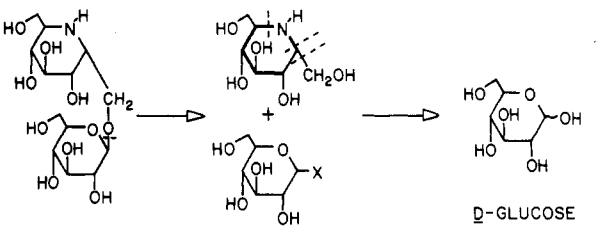
Nojirimycin

The putative mechanism of the enzymatic hydrolysis of disaccharides involves (a) formation of an oxycarbocation, (b) cleavage of the glycosidic linkage, and (c) charge neutralization by water (Scheme I).[3] A carboxylic function at the "active site" of the enzyme is responsible for stabilizing the electron-deficient transition state. We designed, as our prototype transition-state analogue, compound 8, which encompasses the following structural features: (i) replacement of the ring oxygen in glucose by nitrogen as in nojirimycin to facilitate favorable polar–polar interactions with the catalytically important carboxylate at the active site, (ii) insertion of a "methylene" between the two saccharide rings to mimic the lengthening of the severing glycosidic linkage, (iii) a "β"-glycosidic bond to enhance its stability toward enzymatic hydrolysis. The synthesis of this novel α-glucosidase inhibitor utilizing the

Scheme I



Scheme II



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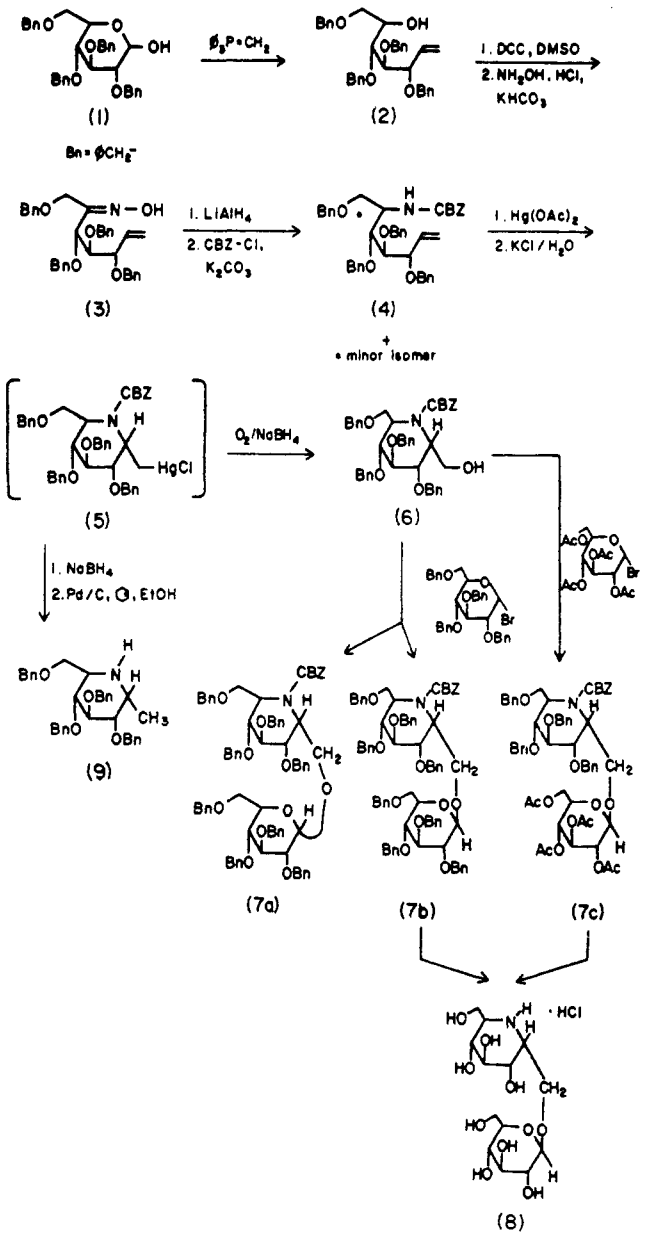
Scheme III



"chiron" approach[4] is the subject of the present paper.

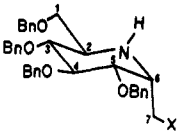
Results and Discussion

Retrosynthetic analysis of our target molecule indicated D-glucose as the suitable chiral starting material (Scheme II). The aglycon was envisaged to be derived from D-glucose via homologation at C1 and replacement of the heteroatom in the pyran ring. Subsequent coupling of the suitably protected aglycon to a glucosyl halide would lead to the desired glucoside.[5]

The synthesis of 8 was accomplished according to the reaction sequence shown in Scheme III. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (1) reacted with methylenetriphenylphosphorane to provide the ene alcohol 2 in 80% yield.[6] Oxidation of 2 using the procedure of Moffatt or Swern[7] gave the corresponding ene ketone, which was immediately converted to the oxime 3 by reaction with hydroxylamine hydrochloride in the presence of potassium bicarbonate.

Reduction of oxime 3 was highly dependent on the reducing agent and solvent. An optimized ratio of 6:1 for the D to L amine (vide infra) was obtained with $LiAlH_4$ in anhydrous ether. The isomeric amines were derivatized as carbamates by reaction with excess benzyl chloroformate and separated by HPLC. Upon treatment with mercuric acetate in THF the D carbamate 4 underwent stereospecific cyclization to give exclusively the α-mercuriomethyl derivative 5 after ligand exchange with aqueous KCl.[8] The assignment of the stereochemistry of the two newly established chiral centers at the ring junctions was based on high-resolution ^1H NMR spectra of 9 and 10. The simple deoxygenated derivative 9 was obtained readily by reduction of 5 with $NaBH_4$ and selective hydrogenolysis of the benzyloxycarbonyl protecting group. The well-resolved, first-order spectrum of 9 (Table I) allowed the determination of pertinent coupling constants $J_{H2,H3}$ (9.7 Hz) and $J_{H5,H6}$ (5.6 Hz), which clearly indicated the trans-diaxial orientation between H2 and H3 as well as the cis relationship between H5 and H6. The 2,6-trans stereochemistry of piperidine 9 was further confirmed by its ^{13}C NMR spectrum, which showed azamethine signals at 48.67 and 52.55 ppm, significantly upfield from representative values in the corresponding cis-disubstituted system.[9] The high stereoselectivity of the cyclization can be accounted for by the chelation effect of mercury with the vicinal α-benzyloxy group, resulting in the preferential addition of the attacking nucleophile (carbamate) from the opposite side of the olefin. It is interesting to note that the stereoselectivity of these mercury-catalyzed reactions is much higher when the nucleophile is alcohol[6] or amide[8] rather than amine.[10,11] The chloromercurial 5 was readily

Table I. Chemical Shifts[a] (δ) from Tetramethylsilane of Compounds 9 and 10



	compound 9, X = H		compound 10, X = OH	
proton	δ	J, Hz	δ	J, Hz
H1	3.66	$J_{1,2}$ = 2.0 $J_{1,1'}$ = 8.7	3.61	$J_{1,2}$ = 3.1 $J_{1,1'}$ = 8.85
H1′	3.61	$J_{1',2}$ = 5.3	3.32	$J_{1',2}$ = 2.4
H2	3.09	$J_{2,3}$ = 9.7	2.72	$J_{2,3}$ = 9.7
H3	3.46	$J_{3,4}$ = 9.1	3.45	$J_{3,4}$ = 10.7
H4	3.82	$J_{4,5}$ = 9.5	3.74	$J_{4,5}$ = 10.1
H5	3.47	$J_{5,6}$ = 5.6	3.41	$J_{5,6}$ = 6.1
H6	3.17	$J_{6,7}$ = 7.0	3.09	$J_{6,7}$ = 9.2 $J_{6,7'}$ = 5.1
H7	1.20		3.67	$J_{7,7'}$ = 10.5
H7′			3.95	

[a] All spectra were recorded in benzene-d_6.

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converted to the pivotal intermediate **6** by reductive oxygenation using $NaBH_4$–DMF–O_2.[10,12] Removal of the carbobenzyloxy group from **6** with transfer hydrogenation gave **10**, whose ^1H NMR spectrum confirmed the structural assignments (Table I).

Coupling of alcohol **6** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide[14] in the presence of mercuric bromide under standard glycosylation conditions[5] furnished both the α- (**7a**) and β-glucosides (**7b**) in 19% and 24% yields, respectively. After HPLC separation, **7b** was deprotected by catalytic hydrogenation to yield the β-glucoside **8** as the final product. The stereochemistry and purity of the anomeric centers were established by ^1H and ^{13}C NMR.[13] ^{13}C NMR spectra of the protected glucosides (**7a** and **7b**) exhibited diagnostic signals for the α- [C1′ δ 97.0 ($J_{^{13}C-^1H}$ = 167.3 Hz)] and β-linkages [C1′ δ 103.5 ($J_{^{13}C-^1H}$ = 157.6 Hz)]. However, when the coupling reaction was performed with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, which contained a participating α-acetoxy group at C2, a single β-glucoside **7c** was obtained in ca. 80% yield. Stepwise deprotection with sodium methoxide in methanol followed by catalytic hydrogenation resulted in a 68% yield of the desired β-glucoside **8**. Again, the ^{13}C NMR spectrum of **7c** showed a signal for the anomeric carbon at δ 100.5 ($J_{^{13}C-^1H}$ = 161.4 Hz) and the ^1H NMR spectrum of **8** exhibited a sharp doublet at δ 4.47 ($J_{1,2}$ = 7.8 Hz) for the axial anomeric proton.

In vitro, compound **8** is a potent competitive inhibitor for intestinal sucrase (rat) with a $K_i = 2 \times 10^{-6}$ M (K_m-(sucrose) = 2×10^{-2} M). It also inhibits maltase, trehalase, glucoamylase, and α-amylase. In mice, when administered simultaneously with sucrose or starch, 2.5 mg/kg of **8** significantly suppresses postprandial hyperglycemia.[15]

Methodologies developed in this study are readily applicable to the synthesis of glycosides of related polyhydroxylated alkaloids, e.g., 4-*O*-β-D-glucopyranosylfagomine,[16] which was recently isolated from *Xanthocercis zambesiaca*. Utilization of the chiral synthon **6** in the preparation of other glycosyl derivatives is in progress and will be reported in a forthcoming paper.

Experimental Section

All melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1310 grating spectrophotometer. NMR spectra were recorded on a Varian EM 360A spectrometer or a Varian XL-300 spectrometer. Chemical shifts are given as δ with reference to Me_4Si or deuteriated 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. Preparative HPLC purifications were performed on a Waters Prep LC/system 500 over Prep Pak 500/silica cartridges. Analytic TLC was performed on Brinkmann, silica gel 60-F254 precoated (0.25-μm thickness) glass plates. Elemental analyses were carried out by the Analytical Department, Merrell Dow Research Institute, or Galbraith Laboratories, Inc., Knoxville, TN.

1,2-Dideoxy-3,4,5,7-tetrakis-*O*-(phenylmethyl)-D-*gluco*-hept-1-enitol (2). Compound **2** was prepared in ca. 80% yield from 2,3,4,6-tetrakis-*O*-(phenylmethyl)-D-glucopyranose (**1**) following the procedure of Pougny et al.[6]

6,7-Dideoxy-1,3,4,5-tetrakis-*O*-(phenylmethyl)-L-*xylo*-hept-6-en-2-ulose Oxime (3). To a stirred solution of 50.0 g (93 mmol) of alcohol **2** in 180 mL of toluene was added 45.0 g (218 mmol) of DDC (dicyclohexylcarbodiimide), 25 mL of DMSO (dimethyl sulfoxide), and 10 mL of pyridine. These were followed by dropwise addition of 10 mL of trifluoroacetic acid. The mixture was stirred at room temperature for 3 h. At the end of the stirring, 50 mL of water was added, followed by 250 mL of ether. The resulting cloudy mixture was filtered through Celite, and the aqueous layer was separated and extracted twice with 100-mL portions of ether. The organic extracts were combined and washed successively with 1 N HCl (2 × 200 mL), saturated $NaHCO_3$ solution (500 mL), and brine (500 mL). The organic layer was dried over anhydrous $MgSO_4$ and then evaporated to dryness in vacuo to provide 46 g (92%) of crude yellow syrupy ketone: IR (neat) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.7–4.7 (m, 13 H), 5.10 (m, 2, CH=CH_2), 5.70 (m, 1, CH=CH$_2$), 7.2 (m, 20, aryl); MS (CI, CH_4) 537 (MH^+), 429 (MH^+ – $PhCH_2OH$). Anal. Calcd for $C_{35}H_{36}O_5 \cdot 0.5H_2O$: C, 77.04; H, 6.84. Found: C, 76.69; H, 6.71.

To a stirred solution of 46.0 g (85 mmol) of the above ketone in 400 mL of MeOH were added 35.0 g of $KHCO_3$ and 25.0 g (362 mmol) of $NH_2OH \cdot HCl$, and the resultant mixture was heated under reflux for 30 min. The reaction mixture was cooled and filtered. The filtrate was evaporated to dryness in vacuo and redissolved in ether. The ethereal extract was washed successively with 1 N HCl, saturated $NaHCO_3$, and NaCl solutions and dried ($MgSO_4$). Evaporation of solvents gave a golden syrup, which was purified by flash chromatography to provide 35 g (75%) of colorless oily oxime **3**: TLC (1:4 ethyl acetate–hexane, silica gel) R_f 0.24; IR (neat) 3500–3100 cm^{-1} (–OH); ^1H NMR ($CDCl_3$) δ 3.6–4.7 (m, 13 H), 5.10 (m, 2, CH=CH_2), 5.70 (m, 1, CH=CH$_2$), 7.2 (m, 20, aryl); MS (CI, CH_4) 552 (MH^+), 444 (MH^+ – $PhCH_2OH$). Anal. Calcd for $C_{35}H_{37}NO_5$: C, 76.20; H, 6.76; N, 2.54. Found: C, 76.05; H, 6.92; N, 2.42.

1,2,6-Trideoxy-6-[[(phenylmethoxy)carbonyl]amino]-3,4,5,7-tetrakis-*O*-(phenylmethyl)-D-*gluco*-hept-1-enitol (4). A solution of oxime **3** (31 g, 56 mmol) in 150 mL of dry ether was added dropwise to a stirred suspension of $LiAlH_4$ (3.8 g, 100 mmol) in 150 mL of ether. The mixture was stirred for another 2 h at room temperature after the addition. Ethyl acetate (90 mL) was added slowly to decompose the excess $LiAlH_4$, followed by 30 mL of 5 N NaOH solution. The resulting cloudy suspension was filtered through a bed of Celite, and the Celite cake was washed thoroughly with ether. The filtrate and washings were combined and shaken with saturated $NaHCO_3$ solution and brine and then dried ($MgSO_4$). Evaporation of solvents from the extracts provided a syrupy amine (25.7 g, 85%). The crude amine was immediately dissolved in 150 mL of THF containing 20 g of anhydrous K_2CO_3, and the slurry was stirred under N_2. A solution of 7 mL of benzyl chloroformate in 20 mL of THF was added to the mixture and stirred at room temperature for 1 h. Water (50 mL) was added and stirring continued for 1 h more. The reaction mixture was poured into water (300 mL), and the resulting emulsion was extracted with ether (500 mL × 2). The ethereal extracts were washed with saturated $NaHCO_3$ solution and brine and dried (Na_2SO_4). Concentration of the extract in vacuo gave a syrup shown to be a 1:6 mixture of two components on TLC (1:4 ethyl acetate–hexane, silica gel): R_f 0.50 and 0.47, respectively. The major component **4** (R_f 0.47) was isolated, after separations on preparative HPLC, as a colorless syrup: 21.4 g, 67%; IR (neat) 3500–3200 cm^{-1} (N—H), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.3–4.8 (m, 15 H), 5.00 (s, 2, COOCH_2Ph), 5.30 (m, 2, CH=CH_2), 5.70 (m, 1, CH=CH$_2$), 7.2 (m, 25, aryl); MS (CI, CH_4) 672 (MH^+), 564 (MH^+ – $PhCH_2OH$), 456 (MH^+ – $2PhCH_2OH$). Anal. Calcd for $C_{43}H_{45}NO_6$: C, 76.87; H, 6.75; N, 2.09. Found: C, 76.85; H, 6.61; N, 2.07.

2,6-Dideoxy-2,6-[[(phenylmethoxy)carbonyl]imino]-1,3,4,5-tetrakis-*O*-(phenylmethyl)-D-*glycero*-L-*gulo*-heptitol (6). To a solution of **4** (21 g, 31 mmol) in 300 mL of dry THF was added mercury(II) acetate (20 g, 62 mmol), and the mixture was stirred under nitrogen at 50 °C overnight. The resulting mixture was evaporated to dryness in vacuo and the residue was redissolved in $CHCl_3$ (500 mL). The chloroform extract was mixed thoroughly with 250 mL of saturated KCl solution. The layers were then separated, and the organic extracts were dried ($MgSO_4$). Evaporation of solvents in vacuo provided a syrup, which was

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dissolved in DMF (100 mL) and added dropwise to a stirred suspension of $NaBH_4$ (2.2 g, 57 mmol) in DMF (80 mL) with continuous infusion of O_2. After addition, the mixture was stirred for 1 h more and then diluted with ether (300 mL). The resulting suspension was filtered through a bed of Celite, and the filtrate was added to H_2O and shaken thoroughly. The layers were separated, and the aqueous portion was extracted with ether again. The combined ethereal extracts were washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). The residue resulting from evaporation of solvents was redissolved in ether (50 mL) and kept overnight at 4 °C. The cooled solution was filtered and concentrated in vacuo to provide a syrupy residue 6: 15.2 g, 71%; IR (neat) 3600–3200 (—OH), 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.4–4.8 (m, 18 H), 5.15 (s, 2, $COOCH_2Ph$), 7.3 (m, 25, aryl); ^{13}C NMR ($CDCl_3$) δ 54.25 (d, NCH), 54.41 (d, NCH); MS (CI, CH_4) 670 ($MH^+ - H_2O$), 580 ($MH^+ - PhCH_2OH$); MS (CI, CH_4) CH_4) monotrimethylsilylated derivative 760 ($M'H^+$). Anal. Calcd for $C_{43}H_{45}NO_7$: C, 75.09; H, 6.59; N, 2.04. Found: C, 74.89; H, 6.57; N, 2.08.

2,6-Dideoxy-2,6-[[(phenylmethoxy)carbonyl]imino]-7-*O*-[2,3,4,6-tetrakis-*O*-(phenylmethyl)-β-D-glucopyranosyl]-1,3,4,5-tetrakis-*O*-(phenylmethyl)-D-*glycero*-L-*gulo*-heptitol (7b) and the α-D-Glucopyranosyl Compound (7a). A slurry of 6.2 g (9.1 mmol) of alcohol **6**, 4.8 g (13.2 mmol) of $HgBr_2$, and 30 g of pulverized 4A molecular sieves in 100 mL of dry CH_2Cl_2 was stirred vigorously at room temperature for 1 h. A solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide[14] in 20 mL of dry CH_2Cl_2 was added slowly to the slurry, and the resulting mixture was stirred overnight at ambient temperatures. The mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of solvents from the extract gave a syrup, which was chromatographed by preparative HPLC (elution solvent, 1:5 ethyl acetate–hexane), and fractions containing material with R_f 0.33 and 0.29 on TLC (elution solvent 1:4 ethyl acetate–hexane, silica gel) were collected. Concentration of the eluates provided 2.68 g (24%) of **7b** (R_f 0.33) and 2.06 g (19%) of **7a** (R_f 0.29) as golden syrups.

7b: IR (neat) 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.2–5.2 (m, 34 H), 7.2 (m, 45, aryl); ^{13}C NMR ($CDCl_3$) δ 53.2 (d, NCH), 55.1 (d, NCH), 103.5 (d, $J_{^{13}C-^1H}$ = 157.6 Hz, C1'), 155.9 (s, C=O); MS (CI, isobutane) 1210 (MH^+). Anal. Calcd for $C_{77}H_{79}NO_{12}$: C, 76.40; H, 6.58. Found: C, 76.74; H, 6.67.

7a: IR (neat) 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.2–5.2 (m, 34 H), 7.2 (m, 45, aryl); ^{13}C NMR ($CDCl_3$) δ 53.3 (d, NCH), 55.5 (d, NCH), 97.0 (d, $J_{^{13}C-^1H}$ = 167.3 Hz, C1'), 155.9 (s, C=O); MS (CI, isobutane) 1210 (MH^+). Anal. Calcd for $C_{77}H_{79}NO_{12}$: C, 76.40; H, 6.58. Found: C, 76.58; H, 6.74.

2,6-Dideoxy-2,6-[[(phenylmethoxy)carbonyl]imino]-7-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,3,4,5-tetrakis-*O*-(phenylmethyl)-D-*glycero*-L-*gulo*-heptitol (7c). To s solution of 24 g (35 mmol) of alcohol **6** in 320 mL of a 1:1 mixture of toluene and nitromethane was added 20 g (48.5 mmol) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, 12.3 g (48.5 mmol) of mercuric cyanide, and 24 g of 4A molecular sieves. The mixture was stirred under N_2 and heated at 60 °C for 3–4 h. The mixture was cooled and diluted with 400 mL of ether, and then 400 mL of saturated aqueous $NaHCO_3$ solution was added. After the resultant mixture was stirred vigorously for 15 min, the layers were separated, and the organic phase was washed successively with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$, and NaCl solutions. The extract was dried over $MgSO_4$ and concentrated to give a syrupy residue of **7c**: 28.2 g, 79%; IR (neat) 1750 (C=O), 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.00 (s, 12, 4 CH_3CO), 3.2–5.1 (m, 26 H), 5.15 (s, 2, $COOCH_2Ph$), 7.3 (m, 25, aryl); ^{13}C NMR ($CDCl_3$) δ 51.8 (d, NCH), 54.5 (d, NCH), 100.5 (d, $J_{^{13}C-^1H}$ = 161.4 Hz, C1, 155.6, 169.0, 169.1, 169.9, 170.3 (5s, 5 C=O); MS (CI, NH_3) 1035 ($M + NH_4^+$), 1018 (MH^+). Anal. Calcd for $C_{57}H_{63}NO_{16}$: C, 67.24; H, 6.24. Found: C, 66.75; H, 6.20.

2,6-Dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol Hydrochloride (8). Method A. The syrupy **7b** (2.20 g, 1.82 mmol) was dissolved in a mixture of 10 mL of $CHCl_3$, 40 mL of EtOH, and 0.6 mL of 5 N HCl. The catalyst (0.5 g of 10% Pd/C) was added, and the mixture was hydrogenated in a Parr apparatus (68 psi) for 3 days. The mixture was filtered, and the filtrate was concentrated in vacuo to provide colorless hygroscopic solid 8: 530 mg, 74%; mp 131–134 °C; IR (KBr) 3600–3200 cm^{-1} (OH); ^1H NMR (D_2O) 3.3–3.6 (m, 6 H), 3.65–3.8 (m, 2 H), 3.9 (m, 5 H), 4.1 (m, 1 H), 4.3 (m, 1 H), 4.47 (d, 1, $J_{1,2}$ = 7.8 Hz, H1); MS (CI, CH_4) 356 (MH^+), 338 ($MH^+ - H_2O$). Anal. Calcd for $C_{13}H_{25}NO_{10}\cdot HCl\cdot H_2O$: C, 38.10; H, 6.89; N, 3.42. Found: C, 38.17; H, 6.74; N, 3.16.

Method B. To a solution of glucoside **7c** (2.53 g, 2.49 mmol) in 5 mL of MeOH was added dropwise a 25% solution of sodium methoxide in methanol (6 equiv, 15 mmol; Aldrich) at room temperature. After being stirred for 1 h, the solution was added to brine (20 mL) and then extracted twice with CH_2Cl_2 (100 mL). The organic extract was washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). Evaporation of solvents from the extracts gave a syrup, which was dissolved in 10 mL of EtOH containing 5 mmol of HCl. After addition of 300 mg of 10% Pd/C, the ethanolic solution was hydrogenated in a Parr apparatus (50 psi) overnight. The catalyst was filtered, and the filtrate was concentrated in vacuo to provide, after cooling and addition of ether, colorless hygroscopic crystals of 8 (660 mg, 68%), in all respects identical with an authentic sample obtained above.

2,6,7-Trideoxy-2,6-imino-1,3,4,5-tetrakis-*O*-(phenylmethyl)-D-*glycero*-L-*gulo*-heptitol (9). To a solution of compound 4 (7 g, 10.3 mmol) in 100 mL of dry THF was added mercury(II) acetate (6.7 g, 21 mmol), and the mixture was stirred under nitrogen at 50 °C overnight. The resulting mixture was evaporated to dryness in vacuo and the residue was redissolved in $CHCl_3$ (200 mL). The chloroform extract was mixed thoroughly with 100 mL of saturated KCl solution. The layers were separated, and the organic extracts were dried ($MgSO_4$). The oily residue obtained after concentrating the extracts was redissolved in DMF (40 mL) and added dropwise to a stirred suspension of $NaBH_4$ (0.73 g, 19 mmol) in DMF (25 mL) under an atmosphere of N_2. After addition, the mixture was stirred for 30 min and diluted with ether (150 mL). The resulting suspension was filtered through a bed of Celite, and the filtrate was added to brine and mixed thoroughly. The layers were separated, and the aqueous portion was extracted again with ether. The combined ethereal extracts were washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). The residue resulting from evaporation of solvents was redissolved in ether (50 mL) and kept overnight at 4 °C. The cooled solution was filtered and concentrated in vacuo to provide a syrupy residue. The residue was taken up in 1:2 cyclohexene–ethanol (75 mL), and 2.0 g of 10% Pd/C was added. The mixture was stirred vigorously under N_2 for 2 days and filtered through Celite. Upon evaporation of solvents and cooling, fine colorless needle-shaped crystals were obtained. Recrystallization of the crude product from ethanol gave long, needle-shaped crystals of **9**: 4.9 g, 89%; mp 94–5 °C; IR (KBr) no absorbance between 1800 and 1600 cm^{-1}; ^1H NMR (benzene-d_6) see Table I; ^{13}C NMR ($CDCl_3$) δ 12.79 (q, CH_3), 48.67 (d, NCH), 52.55 (d, NCH); MS (CI, CH_4) 538 (MH^+), 430 ($MH^+ - PhCH_2OH$). Anal. Calcd for $C_{35}H_{39}NO_4$: C, 78.18; H, 7.31; N, 2.61. Found: C, 78.35; H, 7.19; N, 2.76.

2,6-Dideoxy-2,6-imino-1,3,4,5-tetrakis-*O*-(phenylmethyl)-D-*glycero*-L-*gulo*-heptitol (10). To a solution of compound **6** (1.2 g, 1.75 mmol) in 1:2 cyclohexene–ethanol (15 mL) was added 1.0 g of 10% Pd/C, and the mixture was stirred vigorously under N_2 for 2 days. After the mixture was filtered through Celite, the filtrate was evaporated in vacuo to furnish an oily residue. The residue was taken up in ether, and fluffy colorless crystals appeared upon cooling and with slow solvent evaporation. Recrystallization of the crude product from ether–petroleum ether (1:1) gave fine, needle-shaped crystals of **10**: 800 mg, 83%; mp 76–78 °C; IR (KBr) 3600–3200 cm^{-1} (OH, NH), no absorbance between 1800 and 1600 cm^{-1}; ^1H NMR (benzene-d_6) see Table I; MS (CI, CH_4) 554 (MH^+), 446 ($MH^+ - PhCH_2OH$). Anal. Calcd for $C_{35}H_{39}NO_5$: C, 75.92; H, 7.10; N, 2.53. Found: C, 75.95; H, 7.22; N, 2.51.

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Registry No. 1, 38768-81-9; 2, 79258-18-7; 2 (etone deriv),

110205-68-0; **3**, 110269-17-5; **3** (amine deriv), 110205-69-1; **4**, 104343-30-8; **6**, 104343-31-9; **7a**, 104419-28-5; **7b**, 104343-32-0; **7c**, 104343-35-3; **8**, 104419-80-9; **9**, 110205-70-4; **10**, 110205-71-5; $Ph_3P{=}CH_2$, 3487-44-3; α-glucosidase, 9001-42-7; sucrose, 9001-57-4; maltase, 9001-42-7; trehalase, 9025-52-9; glucoamylase, 9032-08-0; α-amylase, 9000-90-2; 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide, 4196-35-4; 2,3,4,6-tetra-*O*-α-D-glucopyranosyl bromide, 572-09-8.

Conformational Studies by Dynamic NMR. 32.[1] Enantiomerization of Chiral Conformers in Hindered Naphthylamines and Naphthyl Nitroxides

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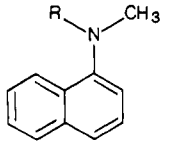
Observation of anisochronous NMR signals in *N*-alkyl-*N*-methyl-1-naphthylamines at low temperature indicates that these molecules adopt a twisted conformation (yielding enantiomeric conformers at the equilibrium) as opposed to the corresponding *N*-alkyl-*N*-methyl-2-naphthylamines which give two planar (thus achiral) conformers. The barriers to enantiomerization in 1-naphthylamines have been measured by line-shape analysis for those amines containing prochiral substituents. The use at low temperature of one of the Pirkle's chiral alcohols as a discriminating agent allowed these barriers to be measured even in absence of prochiral groups. Related alkyl 1-naphthyl nitroxides were also shown to prefer a twisted conformation, but the enantiomerization barriers are too low to be measured by ESR. Examination of a much more hindered nitroxide (2-*tert*-butyl-1-naphthyl ethyl nitroxide) showed that the methylenic hydrogens were anisochronous even at room temperature, indicating that this radical exists as a racemic mixture. The existence of an exponential relationship between the free energies of enantiomerization in the 1-naphthylamines and the nitrogen hyperfine splittings in the analogous nitroxides allowed the barrier for *N*,*N*-dimethyl-1-naphthylamine to be estimated. This barrier could not be measured directly because of the symmetry of the amine.

Introduction

Hindered aromatic amines may adopt a conformation whereby the dynamic plane containing the rapidly inverting nitrogen atom is twisted with respect to the plane of the aromatic ring.[2] In the case of *N*,*N*-diisopropyl-1-naphthylamine,[3] for instance, this arrangement is revealed at low temperature by two different (anisochronous[4]) NMR signals, corresponding to the two methyls within each isopropyl moiety. The anisochrony of these *gem*-methyls is due to the fact that the molecular plane of symmetry is not a plane of symmetry for the sensor group (i.e., the prochiral isopropyl moiety)[4] in a twisted conformation. Accordingly in naphthylamines with two different N-bonded groups, two possible situations may occur. When the molecule is not hindered and a planar conformation is preferred, two conformers in different proportions should be observable: in each of the two conformers the prochiral substituents,[4] if present, would display isochronous geminal groups. On the other hand, in naphthylamines where steric requirements force the molecule into a nonplanar conformation, only one conformer will be observed and prochiral substituents, if present, will display anisochronous geminal groups. In this arrangement the compound is actually a racemic mixture of a pair of enantiomeric conformers that might in principle be detected in a chiral environment. We report here the barriers to enantiomerization for this class of compounds as well as examples of direct detection of their enantiomeric conformers in a chiral medium at low temperature.

Results and Discussion

In the present work the *N*-alkyl-*N*-methyl-1-naphthylamines **1**–**6** were investigated, together with the *N*-isopropyl-*N*-methyl-2-naphthylamine (**7**) by variable-temperature ^1H and ^{13}C NMR spectroscopy.



1, R = Me
2, R = CH_2Me
3, R = CH_2Bu-*t*
4, R = $CHMe_2$
5, R = $CHEt_2$
6, R = *t*-Bu

Dynamic NMR of Naphthylamines. As a typical example the ^{13}C NMR spectrum of **4** displays, at −95 °C, two different methyl signals (ratio 1:1) for the isopropyl moiety and single signals for both NCH and NCH_3. By way of contrast the 2-isomer (**7**) displays (at −148 °C) two lines (ratio 6.5:1) for the NCH carbons and single lines (clearly due to overlapping) for the methyl groups. The less hindered compound **7** thus prefers a quasi-planar

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