oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (64). A solution of the hydroxy tosylate from the previous reaction and triethylamine (50 μL, 0.36 mmol) in tetrahydrofuran (20 mL) was stirred under nitrogen and cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (70 μL, 0.36 mmol) was added by syringe and the reaction mixture was stirred for 20 min. Aqueous saturated sodium bicarbonate was added and the THF layer was separated. The aqueous layer was extracted with ether (3 × 50 mL) and the combined organic layers were then dried over sodium sulfate and concentrated. Flash chromatography on silica gel, eluting with 1:1 ether–hexane, gave 0.052 g (38%) of the title compound: TLC R_f 0.50 (silica, 3:2 ether–hexane, CAS blue); 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.55 (t, J = 7.4 Hz, 3 H), 0.83–0.94 (m, 1 H), 1.05–1.10 (m, 1 H), 1.20 (br s, 1 H), 1.31–1.53 (m, 2 H), 1.60 (d, J = 6.8 Hz, 3 H), 1.90–2.01 (m, 1 H), 2.26–3.30 (m, 1 H), 2.35 (s, 3 H), 2.48–2.64 (m, 3 H), 2.79–2.84 (m, 1 H), 3.03 (s, 1 H), 3.73 (s, 3 H), 3.78 (d, J = 9.6 Hz, 1 H), 3.90 (d, J = 9.5 Hz, 1 H), 4.61–4.63 (m, 1 H), 6.70–6.79 (m, 3 H), 7.02–7.08 (m, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.39–7.47 (m, 3 H), 7.60–7.66 (m, 1 H), 7.73 (d, J = 8.3 Hz, 2 H), 7.78–7.83 (m, 2 H), 8.56 (br s, 1 H), 8.90 (br s, 1 H); mass spectrum, m/z (rel intensity) 752 (M^+, 2), 611 (2), 538 (9), 437 (25), 384 (9), 302 (4), 283 (14), 279 (13), 268 (3), 229 (12), 205 (5), 180 (4), 167 (15), 155 (100), 149 (30), 91 (19).

(7*S*,5*R*)-Methyl 3-[(*S*)-1-(1-Naphthyl)ethyl]-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (65). A solution of 0.040 g (0.059 mmol) of (3a*R*,4*R*)-methyl 3-[(*S*)-1-(1-naphthyl)ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (64) and triethylamine (9.0 μL, 1.1 equiv) in dichloromethane (2 mL) was stirred under nitrogen and brought to 0 °C. *tert*-Butyl hypochlorite (7.7 μL, 1.1 equiv) in dichloromethane (1 mL) was added by syringe, and the mixture was stirred for 5 min, at which time, TLC showed no remaining starting material. The solution was washed with water (5 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give a white foam, which was used directly in the following reaction: TLC R_f 0.50 (silica gel, 3:2 ether–hexane, CAS purple).

To a solution of the chlorination product and vindoline (**3**, 27 mg, 1 equiv) in dry acetone (2 mL) was added tetrafluoroboric acid–diethyl ether complex (19 μL, 2 equiv). The reaction was brought to 0 °C and silver tetrafluoroborate (23 mg, 2 equiv) in acetone (1 mL) was added. The resulting heterogeneous solution was stirred for 10 min, at which time 10% NH_4OH (10 mL) was added. The now homogeneous solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure to give a white foam, which was used directly in the following reaction.

The above material was dissolved in glacial acetic acid (5 mL) and with stirring potassium borohydride (32 mg, 10 equiv) was slowly added. After 15 min the solution was poured onto ice and made strongly basic with concentrated ammonium hydroxide. Extraction with dichloromethane (3 × 10 mL), drying ($MgSO_4$), and concentration gave a white foam, which was used directly in the following reaction: TLC R_f 0.57 (silica gel, ethyl acetate, CAS brown).

To a solution of the above coupled product in tetrahydrofuran (10 mL) at 0 °C was added tetrabutylammonium fluoride (180 μL, 3 equiv, 1 M in THF). The mixture was brought to room temperature and stirred for 15 min, at which time no starting material remained by TLC. The solution was washed with aqueous saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated under vacuum. Flash chromatography on silica gel, eluting with ethyl acetate, gave 0.043 g (72%) of the title compound: TLC R_f 0.46 (silica gel, ethyl acetate, CAS brown). ^{1}H NMR shows mostly broad peaks presumably due to interaction of naphthyl group and remainder of compound. Selected peaks for 270-MHz ^{1}H NMR ($CDCl_3$): δ 0.49 (t, J = 7.3 Hz, 3 H, C18′), 1.01 (t, J = 7.2 Hz, 3 H, C18), 2.11 (s, 3 H, $OCOCH_3$), 3.79 (s, 6 H, 2 × CO_2CH_3); mass spectrum, m/z (rel intensity) 965 (M + 1, 59), 905 (4), 852 (4), 811 (3), 566 (3), 509 (4), 391 (6), 253 (4), 242 (7), 239 (3), 214 (5), 201 (3), 197 (3), 195 (5), 187 (13), 186 (81), 185 (64), 184 (80), 183 (21), 173 (11), 170 (10), 157 (22), 156 (23), 155 (100), 154 (17), 153 (10), 143 (9), 142 (57), 113 (4), 100 (4), 99 (6), 97 (4).

Vinblastine (1). A solution of the epoxide **65** (0.040 g, 0.041 mmol) in methanol (10 mL) was heated at reflux for 40 h, at which time no starting material was present by TLC and a new more polar spot had appeared. The mixture was cooled and 10% palladium on charcoal (5.0 mg) was added. This was then stirred under a hydrogen atmosphere at room temperature for 3 h and filtered, the residue was washed with dichloromethane and methanol, and the filtrates were concentrated under vacuum.

The resulting atropisomer **30** was dissolved in dry toluene (10 mL) and heated at reflux for 8 h, at which time TLC showed no remaining starting material and only the presence of vinblastine in its natural conformation.

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Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **7a**, **7b**, **13**, **14a**, **14b**, **18a**, **19a**, **20a**, **20b**, **21a**, **21b**, the monotosylates of **20a** and **21a**, **22a**, **22b**, **26a**, **27a**, **30**, **31a**, **31b**, **33a**, **33b**, **34**, **35a**, and **35b** (46 pages). Ordering information is given on current masthead page.

Conversion of D-Glucose to L-Glucose: Oxidative Decarboxylation of α-Oxy Carboxylic Acids via Their Diacyl Peroxides

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D-Glucose was converted to an L-glucose derivative. The key step was the oxidative decarboxylation of carboxylic acid **12** via its diacyl peroxide derivative. This synthetic scheme proceeds through C-glycosidic compounds and is applicable to other sugar configurations.

Because L sugars are potentially useful as safe, effective, nonnutritive sweeteners,[1] these less common enantiomers of the carbohydrates have been studied for many years. Chemical syntheses of L-glucose from L-arabinose were reported by Emil Fischer[2] in 1890 and by J. C. Sowden and

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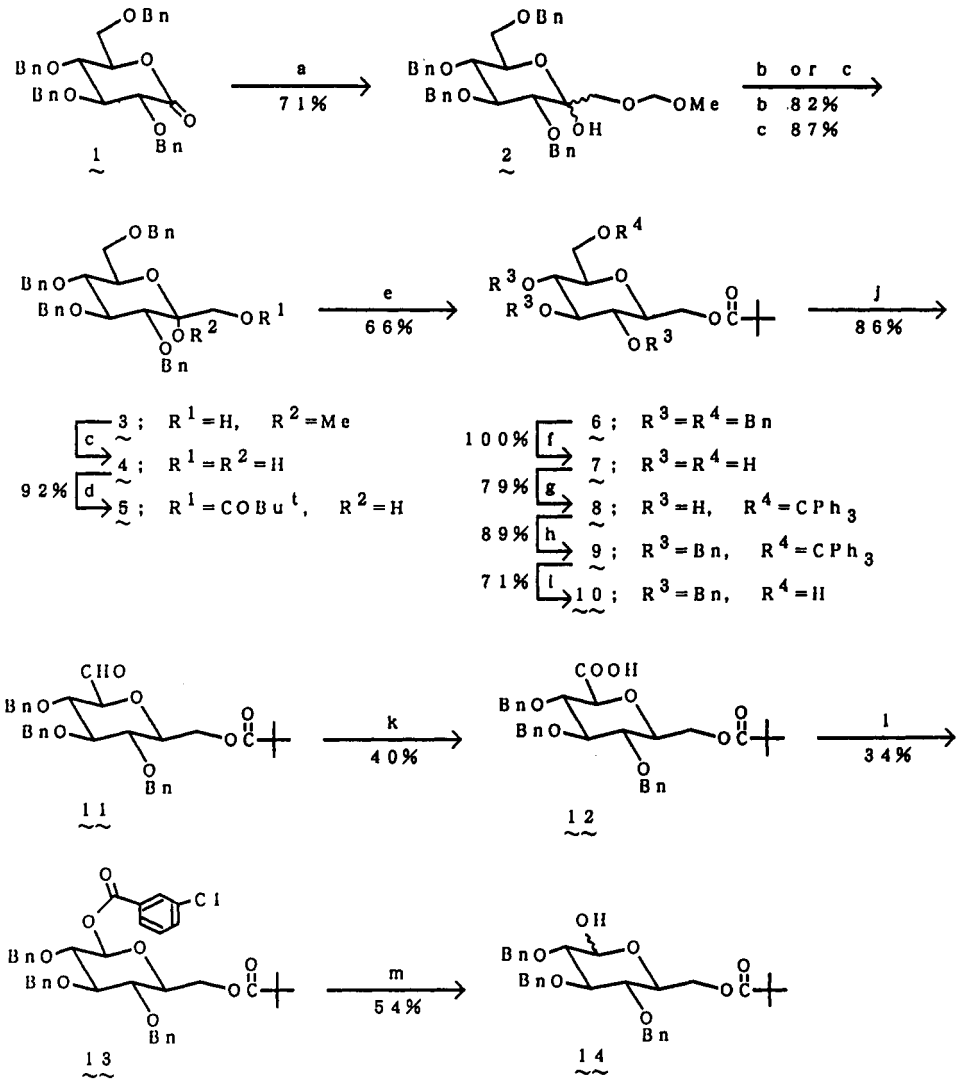
Scheme I[a]



[a] (a) n-$Bu_3SnCH_2OCH_2OMe$, n-BuLi–THF, −78 °C, 71%; (b) MeOH, cat. concentrated HCl, reflux, 82%; (c) THF–6 M HCl (4:7), 60 °C, 87%; (d) PivCl–pyridine, 60 °C, 92%; (e) Et_3SiH, $BF_3{\cdot}OEt_2$–MeCN, room temperature, 66%; (f) H_2, Pd–C–AcOH, 100%; (g) TrCl–pyridine, room temperature, 79%; (h) BnBr, NaH, cat. n-Bu_4NI–THF, room temperature, 89%; (i) 4% H_2SO_4–MeOH, room temperature, 71%; (j) DMSO, $(COCl)_2$, Et_3N–CH_2Cl_2, 86%; (k) $NaIO_4$, cat. $RuO_2{\cdot}xH_2O$/MeCN–CCl_4–H_2O (2:2:3), 40%; (l) 3-ClC_6H_4COOOH, DCC–CH_2Cl_2, 0 °C–room temperature, 34%; (m) 0.1 M NaOH–THF, room temperature, 54%.

H. O. L. Fischer.[3] Conversion of D-glucose into L-glucose has also been reported.[1,4] Our need for an improved method for the synthesis of an L-glucose derivative stimulated the synthesis reported herein, which involves the oxidative decarboxylation of an α-oxy carboxylic acid via its diacyl peroxide as a key step (Scheme I).

The starting material, 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**), was prepared from D-glucose according to a reported method.[5] Treatment of **1** with [(methoxymethoxy)methyl]lithium, $MeOCH_2OCH_2Li$,[6] generated from [(methoxymethoxy)methyl]tributylstannane,[6] gave an anomeric mixture of 1-methoxymethylated heptuloses **2**,[7] which were inseparable chromatographically and partly contained the keto form. Refluxing the mixture **2** in MeOH containing a catalytic amount of concentrated HCl gave only the methyl glycoside **3** (mp 128 °C), whereas treatment of **2** or **3** in THF-6 M HCl (1.3:2.3, v/v) at 60 °C for 1.5 h gave free sugar **4** (mp 118–119 °C, as monohydrate) exclusively. Compound **4** was determined to have the α-anomeric configuration (*S*), because the anomeric hydroxy proton showed a nuclear Overhauser effect for both H-4 and H-6. The primary hydroxy group of **4** was protected with a trimethylacetyl group to give **5**. Dehydroxylation of **5** with triethylsilane–boron trifluoride etherate[7,8] yielded the 2,6-anhydroheptitol derivative **6**. Treatment of **6** with 2.5 equiv of triphenylcarbenium tetrafluoroborate[9] in CH_2Cl_2 gave the selectively monodebenzylated derivative **10** only in low yields (0–23%) with many byproducts. Thus the conditions required for this selective deprotection of OH-7 appeared too subtle, and a stepwise conversion to **10** was therefore pursued. Debenzylation of **6** by catalytic hydrogenation with 10% Pd on carbon gave the tetraol **7**, which was converted into the 7-trityl ether **8** by treatment with triphenylmethyl chloride in pyridine. Benzylation

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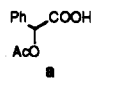
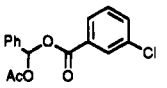
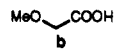
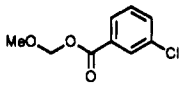
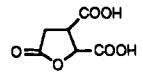
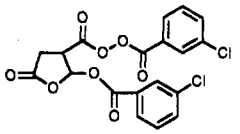
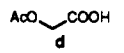
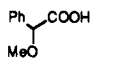
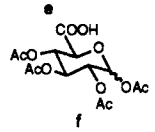
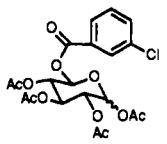
Table I. Oxidative Decarboxylation of α-Oxy Carboxylic Acids with 3-Chloroperbenzoic Acid and DCC

substrate 15	solvent	temp, °C/time, min	product 16	yield, %
 a	CH_2Cl_2	0/15		51
 b	CH_2Cl_2	0/15		56
 c	EtOAc	0/15		15
 d	CH_2Cl_2	0/15	dec	0
 e	EtOAc	rt[a]/45	dec	0
 f	EtOAc	0/15		39

[a] Room temperature.

of **8** to give **9** followed by acid-catalyzed detritylation furnished the primary alcohol **10**. Swern or Moffatt oxidation of **10** with oxalyl chloride–dimethyl sulfoxide–triethylamine or with dimethyl sulfoxide–1,3-dicyclohexylcarbodiimide–cat. phosphoric acid gave the blocked 2,6-anhydro-*aldehydo*-heptose **11**, which was immediately oxidized to the corresponding heptonic acid **12** by using ruthenium(IV) oxide–$NaIO_4$ in CH_3CN–CCl_4–H_2O (2:2:3).[10]

Compound **12** was converted to the L-glucose derivative **13** by oxidative decarboxylation. The oxidative decarboxylation of carboxylic acids via their diacyl peroxides[11] occasionally gave poor results with respect to yield and byproducts for the common carboxylic acids, because diacyl peroxides are often stable enough to withstand thermolysis.[12] It has become obvious that the reaction gives fairly good results with α-acylamino carboxylic acids (especially 2-azetidinone-4-carboxylic acids),[13] and therefore, oxidative decarboxylation of α-oxy carboxylic acids was studied in model experiments (Table I).

α-Oxy carboxylic acids **15a–f**[14] were treated with 1.1 equiv each (for **a**, **b**, and **d–f**) or 2.1 equiv each (for **c**) of 3-chloroperoxybenzoic acid and DCC at room temperature in CH_2Cl_2 or EtOAc to give **16a,b,c,f**, in 51%, 56%, 15%, and 39% yields, respectively. However, **15d** and **15e** underwent degradation. The most typical example was **15c**. The C-5 carboxy function easily rearranged to the acyloxy structure. On the other hand, the C-4 carboxylic acid part yielded only the stable diacyl peroxide, without rearrangement ensuing. Evidently, the α-oxygen of **15c** spurred the oxidative decarboxylation. Application of this reaction to **12** gave a 34% yield of **13**, which was finally saponified to **14**.

The combination of homologation and oxidative decarboxylation may make possible the conversion of other D sugars to L sugars. Parts of this synthetic scheme may be used to link synthetic *C*-glycosides to known sugar configurations.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at 270 MHz with tetramethylsilane as an internal standard. Column chromatography was carried out on a column packed with Merck silica gel 60 (230–400 mesh ASTM), at slightly elevated pressure (1.2 atm) for elution.

[(Methoxymethoxy)methyl]tributylstannane. Anhydrous THF (70 mL) and *i*-Pr_2NH (5.52 mL) were stirred under nitrogen at 0 °C while *n*-BuLi (1.6 M hexane solution, 21.6 mL, 34.5 mmol) was added in drops. The resulting solution was stirred for an additional 5 min, and *n*-Bu_3SnH (10.0 g, 9.11 mL, 34.5 mmol) was added via syringe. After 15 min at 0 °C, this *n*-Bu_3SnLi solution was treated with paraformaldehyde (1.04 g, 34.5 mmol) at room temperature and was stirred for 3 h under nitrogen. To this *n*-Bu_3SnCH_2OLi solution in THF was added $MeOCH_2Cl$ (3.32 g, 3.14 mL, 1.2 equiv). After 1 h the reaction mixture was poured into petroleum ether (300 mL). The solution was washed successively with ice-cold 0.5 M aqueous HCl (100 mL × 2), water, and saturated $NaHCO_3$, then dried over Na_2SO_4, filtered, and concentrated to give an oily mixture, which was chromatographed on a silica gel (100 g) column. Elution with hexane gave *n*-$Bu_3SnCH_2OCH_2OMe$ (7.3 g) in 58% yield as an oil (R_f = 0.345, hexane:EtOAc = 24:1): ^1H NMR ($CDCl_3$) δ 0.86–0.95 (15 H, m), 1.24–1.37 (6 H, m), 1.45–1.58 (6 H, m), 3.33 (3 H, s, OCH_3), 3.74 (1.7 H, s, and 0.3 H, d, J = 16.6 Hz, $SnCH_2O$), 4.51 (2 H, s, OCH_2O). Anal. Calcd for $C_{15}H_{34}O_2Sn$: C, 49.34; H, 9.38. Found: C, 49.57; H, 9.10.

3,4,5,7-Tetra-*O*-benzyl-1-*O*-(methoxymethyl)-α,β-D-*gluco*-2-heptulopyranose (2). To a solution of *n*-$Bu_3SnCH_2OCH_2OMe$ (7.80 g, 21.3 mmol) in THF (35 mL) was added a solution of *n*-BuLi (13.3 mL of a 1.6 M hexane solution,

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(14) Compounds **15a–e** were commercially available. Compound **15f** was prepared from D-glucuronic acid as follows. To a suspension of D-glucuronic acid (20 g) in THF (800 mL)–H_2O (70 mL) was added diphenyldiazomethane (20 g). The mixture was stirred for 10 h and was concentrated to give a residual oil, which was dissolved in pyridine (300 mL) and Ac_2O (450 mL). After 10 h the reaction mixture was concentrated and was chromatographed on a silica gel column to give diphenylmethyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucuronate (36 g; mp 146–148 °C). This benzhydryl ester (0.9 g) was hydrogenolyzed in THF (10 mL) by using 10% Pd on carbon (0.4 g) as a catalyst. The reaction mixture was filtered and was diluted with hexane to deposite an oily residue. The hexane solution was decanted to collect the oily residue. This decantation process was repeated two times to remove diphenylmethane from a mixture of acids **15f** (0.6 g).

21.3 mmol) at −78 °C under nitrogen with stirring. After 10 min, a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**, 7.62 g, 14.16 mmol) in THF (25 mL) was added at −78 °C. After 30 min, the reaction mixture was diluted with ether. The solution was washed with water and brine, then dried over $MgSO_4$, and concentrated to an oily mixture, which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc, 3:1 and then 1:1, gave 6.14 g (71%) of an anomeric mixture of **2** as an oil: IR ν_{max} (neat) 3430, 1730 (w, partly keto form?), 1700 (w, keto form?); ^1H NMR ($CDCl_3$) δ 3.22–3.78 (9 H, m, containing 2 s at δ 3.35 and 3.36, 1.5 H each), 3.97–4.10 (2 H, m), 4.47–4.94 (10 H, m, containing 2 H singlet at δ 4.90, OCH_2OMe), 7.11–7.22 (2 H, m), 7.25–7.44 (18 H, m); MS *m/z* 596 (M − 18), 581, 551. Anal. Calcd for $C_{37}H_{42}O_8 \cdot H_2O$: C, 70.23; H, 7.01. Found: C, 70.39; H, 6.92.

Methyl 3,4,5,7-Tetra-*O*-benzyl-α-D-*gluco*-2-heptulopyranoside (3). A solution of the mixture **2**, (120 mg) in MeOH (4 mL) and concentrated HCl (50 mg) was refluxed for 2 h and was concentrated to give a crude solid, which was purified on a silica gel column to give **3** (94 mg, 82%) as a crystalline solid (**2** and **3** have the same R_f value): mp 127.5–128 °C (from cyclohexane–EtOAc); IR ν_{max} (Nujol) 3525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31 (3 H, s), 3.59–3.74 (7 H, m, H-1,1′,3,5,6,7,7′), 4.10 (1 H, dd, *J* = 8.8, 9.8 Hz, H-4), 4.49–4.61 (3 H, m), 4.72–4.94 (5 H, m), 7.14–7.19 (2 H, m), 7.25–7.36 (18 H, m); MS *m/z* 553 (M^+ − 31). Anal. Calcd for $C_{36}H_{40}O_7$: C, 73.95; H, 6.90. Found: C, 74.10; H, 7.16.

3,4,5,7-Tetra-*O*-benzyl-α-D-*gluco*-2-heptulopyranose (4). A solution of **2** (6.13 g) or **3** in THF (80 mL) and 6 M HCl (140 mL) was heated to 60 °C for 1.5 h and was concentrated to remove THF. A crystalline solid (**4** as its monohydrate, 5.13 g, 87%) precipitated from the remaining aqueous solution: mp 118–119 °C (from H_2O); IR ν_{max} (Nujol) 3500, 3380, 3210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (1 H, dd, *J* = 6.8, 7.1 Hz, OH-1), 3.27 (1 H, d, *J* = 0.7 Hz, OH-2), 3.44 (1 H, dd, *J* = 6.8, 11.5 Hz, H-1), 3.51 (1 H, dd, *J* = 7.1, 11.5 Hz, H-1′), 3.51 (1 H, dd, *J* = 0.7, 9.4 Hz, H-3), 3.64 (1 H, dd, *J* = 9.4, 10.0 Hz, H-5), 3.65 (1 H, dd, *J* = 1.8, 10.8 Hz, H-7), 3.73 (1 H, dd, *J* = 4.2, 10.8 Hz, H-7′), 4.01 (1 H, ddd, *J* = 1.8, 4.2, 10.0 Hz, H-6), 4.05 (1 H, dd, *J* = 9.4, 9.4 Hz, H-4), 4.48–4.92 (8 H, m), 7.15–7.20 (1 H, m), 7.25–7.37 (19 H, m). Anal. Calcd for $C_{35}H_{38}O_7 \cdot H_2O$: C, 71.41; H, 6.85. Found: C, 71.52; H, 6.86.

3,4,5,7-Tetra-*O*-benzyl-1-*O*-(trimethylacetyl)-α-D-*gluco*-2-heptulopyranose (5). A solution of **4**–H_2O (5.09 g) in pyridine (100 mL) and Me_3CCOCl (4.0 g) was heated to 60 °C for 1 h and was concentrated in vacuo to remove pyridine. The residual oil was dissolved in EtOAc, which was washed with dilute HCl, water, aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, and concentrated to give a crude oil. The oil was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (2:1) gave 5.21 g (92%) of **5** as an oil: IR ν_{max} (neat) 3440, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (9 H, s), 3.17 (1 H, s, OH), 3.54–3.80 (5 H, m, H-3,5,6,7,7′), 4.01, 4.20 (2 H, AB q, *J* = 11.2 Hz, H-1,1′), 4.06 (1 H, m, H-4), 4.48–4.66 (4 H, m), 4.83–4.95 (4 H, m), 7.2–7.4 (20 H, m); MS *m/z* 654 (M^+), 636 (M^+ − 18), 563, 545. Anal. Calcd for $C_{40}H_{46}O_8 \cdot H_2O$: C, 71.41; H, 7.19. Found: C, 71.35; H, 7.15.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*O*-(trimethylacetyl)-D-*glycero*-D-*gulo*-heptitol (6). A solution of **5** (5.70 g) in MeCN (150 mL), Et_3SiH (16 mL), and $BF_3 \cdot OEt_2$ (6.5 mL) was stirred for 3 h at room temperature, and the reaction mixture was concentrated in vacuo, was diluted with EtOAc, which was washed with water, aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$, and was concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (4:1) gave 3.68 g (66%) of **6** as an oil that crystallized gradually on standing: mp 47–49 °C (hexane); IR ν_{max} (neat) 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (9 H, s), 3.44–3.77 (7 H, m), 4.22 (1 H, dd, *J* = 4.1, 12.0 Hz, H-1), 4.46 (1 H, dd, *J* = 1.7, 12.0 Hz, H-1′), 4.52–4.65 (5 H, m), 4.82–4.91 (4 H, m), 7.18–7.36 (20 H, m); MS *m/z* 638 (M^+), 637, 547. Anal. Calcd for $C_{40}H_{46}O_7$: C, 75.21; H, 7.26. Found: C, 75.46; H, 7.31.

2,6-Anhydro-1-*O*-(trimethylacetyl)-D-*glycero*-D-*gulo*-heptitol (7). A solution of **6** (1.0 g) in AcOH (50 mL) was hydrogenated for 24 h at room temperature by using 10% Pd/C (1 g), and the reaction mixture was concentrated in vacuo to give 436 mg (quantitatively) of **7** as a powder, which was employed for the next reaction without purification.

2,6-Anhydro-1-*O*-(trimethylacetyl)-7-*O*-(triphenylmethyl)-D-*glycero*-D-*gulo*-heptitol (8). A solution of **7** (436 mg) and Ph_3CCl (524 mg) in pyridine (12 mL) was stirred for 15 h at room temperature, and the reaction mixture was concentrated in vacuo, diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (1:2) gave 643 mg of **8** (79% yield from **6**) as an oil: IR ν_{max} ($CHCl_3$) 3600–3400, 1720, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (9 H, s), 2.60 (1 H, br, OH), 2.83 (1 H, br OH), 3.11 (1 H, br, OH), 3.27–3.46 (5 H, m), 3.50–3.65 (2 H, m), 4.28 (1 H, dd, *J* = 2.0, 12.2 Hz, H-1), 4.54 (1 H, dd, *J* = 3.4, 12.2 Hz, H-1′), 7.20–7.33 (10 H, m), 7.42–7.48 (5 H, m); $[\alpha]^{24}_D$ −14.1° (*c* 1.5, $CHCl_3$); MS *m/z* 520 (M^+), 443; high-resolution mass spectrum calcd for $C_{31}H_{36}O_7$ *m/z* 520.24605, found 520.24445. Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.41; H, 6.80.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-*O*-(trimethylacetyl)-7-*O*-(triphenylmethyl)-D-*glycero*-D-*gulo*-heptitol (9). To a solution of **8** (233 mg) and $PhCH_2Br$ (465 mg) in THF (10 mL) were added *n*-Bu_4NI (40 mg) and NaH (120 mg of a 55% oil dispersion). The mixture was stirred for 15 h at room temperature, diluted with EtOAc, washed with dilute HCl, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (9:1) gave 290 mg of **9** (82% yield) as an oil: IR ν_{max} (neat) 1730, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (9 H, s), 3.19 (1 H, dd, *J* = 2.9, 10.3 Hz, H-7), 3.41 (1 H, dt, *J* = 1.0, 10.3 Hz, H-7′), 3.51–3.77 (4 H, m), 3.94 (1 H, t, *J* = 9.3 Hz, H-4), 4.27 (1 H, dd, *J* = 3.4, 11.5 Hz, H-1), 4.39 (1 H, d, *J* = 11.5 Hz, H-1′), 4.67–5.00 (6 H, m), 6.84–6.88 (2 H, m), 7.16–7.38 (20 H, m), 7.44–7.54 (8 H, m); MS *m/z* 699 (M^+ − Bn), 593, 547 (M^+ − Tr). Anal. Calcd for $C_{52}H_{54}O_7$: C, 78.96; H, 6.88. Found: C, 78.66; H, 7.01.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-*O*-(trimethylacetyl)-D-*glycero*-D-*gulo*-heptitol (10). (a) A suspension of **9** (570 mg) in MeOH (30 mL) containing 4% H_2SO_4 was stirred for 30 min at room temperature. The reaction mixture became a solution, which was diluted with EtOAc, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (4:1) gave 282 mg of **10** (71% yield) as a crystalline solid: mp 90–91 °C (EtOAc–hexane); IR ν_{max} (neat) 3500, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (9 H, s), 3.33–3.40 (1 H, m, H-6), 3.47–3.58 (3 H, m), 3.65 (1 H, dd, *J* = 4.4, 11.7 Hz, H-7), 3.71–3.78 (1 H, m), 3.84 (1 H, dd, *J* = 2.4, 11.7 Hz, H-7′), 4.19 (1 H, dd, *J* = 4.4, 11.7 Hz, H-1), 4.44 (1 H, dd, *J* = 1.5, 11.7 Hz, H-1′), 4.60, 4.67 (2 H, AB q, *J* = 10.7 Hz), 4.74–4.93 (4 H, m), 7.25–7.38 (15 H, m); MS *m/z* 547 (M^+ − 1), 541, 457, 351. Anal. Calcd for $C_{33}H_{40}O_7$: C, 72.24; H, 7.35. Found: C, 71.88; H, 7.19.

(b) To a solution of **6** (64 mg) in CH_2Cl_2 (2 mL) was added $Ph_3C \cdot BF_4$ (83 mg) under nitrogen at room temperature with stirring. After 10 h the reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give a crude oily mixture. This was chromatographed on a silica gel plate. Development with cyclohexane–EtOAc (4:1) gave 13 mg of **10** (R_f = 0.279).

2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-*O*-(trimethylacetyl)-*aldehydo*-L-*glycero*-L-*gulo*-heptose (11). (a) To a solution of **10** (121 mg) in DMSO (3 mL) were added DCC (182 mg) and H_3PO_4 (15 mg). The solution was stirred for 6 h at room temperature. The reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (3:1) gave 92 mg of **11** (76% yield) as an oil, which was employed for the next reaction without further purification.

(b) To a solution of $(COCl)_2$ (0.025 mL) in CH_2Cl_2 (1 mL) was added DMSO (0.045 mL) at −78 °C. After 5 min a solution of **10** (45 mg) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 15 min at −78 °C, and Et_3N (0.2 mL) was added. After 5 min the reaction mixture was allowed to warm to room temperature. Then water (2 mL) was added, and the whole was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated. Column chromatography on silica gel gave 38 mg of **11** (86% yield), which was employed for the next reaction without further pu-

rification: IR ν_{max} (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.59 (1 H, d, J = 0.5 Hz, CHO); MS m/z 546 (M^+); high-resolution mass spectrum calcd for $C_{33}H_{38}O_7$ m/z 546.26174, found 546.26314. Anal. Calcd for $C_{33}H_{38}O_7 \cdot H_2O$: C, 70.19; H, 7.19. Found: C, 70.37; H, 7.53.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-*O*-(trimethylacetyl)-L-*glycero*-L-*gulo*-heptonic Acid (12). To a solution of **11** (92 mg) in MeCN-CCl_4-H_2O (2:2:3, 7 mL) were added $NaIO_4$ (144 mg) and $RuO_2 \cdot xH_2O$ (3 mg). The mixture was stirred for 2 h at room temperature, diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (1:1) and then with EtOAc containing 1% AcOH gave 38 mg (40%) of **12** as an oil: IR ν_{max} (neat) 3600-2500, 1727 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 1.17-1.21 (9 H, m), 3.53-3.82 (3 H, m, H-4,5,6), 4.00 (1 H, m, H-3), 4.21 (1 H, dd, J = 4.9, 12.2 Hz, H-7), 4.45 (1 H, dd, J = 2.0, 12.2 Hz, H-7'), 4.47 (1 H, d, J = 10.2 Hz, H-2), 4.67-4.91 (6 H, m, 3 × CH_2Ph), 7.24-7.34 (15 H, m); MS m/z 561 (M^+ - 1), 471 (M^+ - Bn), 365, 359. Anal. Calcd for $C_{33}H_{38}O_8$: C, 70.44; H, 6.81. Found: C, 70.31; H, 6.71.

2,3,4-Tri-*O*-benzyl-1-*O*-(3-chlorobenzoyl)-6-*O*-(trimethylacetyl)-β-L-glucopyranose (13). To a solution of **12** (24 mg) in CH_2Cl_2 (1 mL) were added 3-chloroperoxybenzoic acid (10.4 mg, 85% purity) and DCC (13 mg) at 0-5 °C with stirring. After 10 min the mixture was warmed to room temperature, stirred for 1 h, and filtered. The filtrate was chromatographed on a silica gel plate. Development with cyclohexane-EtOAc (9:1) gave 10 mg (34%) of **13** (R_f = 0.333) as an oil: $[\alpha]^{25}_D$ +32° (c 0.9, $CHCl_3$); IR ν_{max} (neat) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (9 H, s), 3.60-3.86 (4 H, m, H-2,3,4,5), 4.25 (1 H, dd, J = 4.9, 12.2 Hz, H-6), 4.36 (1 H, dd, J = 2.0, 12.2 Hz, H-6'), 4.57-4.95 (6 H, m), 5.87 (1 H, d, J = 7.8 Hz, H-1), 7.21-7.36 (15 H, m), 7.38 (1 H, t, J = 7.8 Hz), 7.56 (1 H, dq, J = 7.8, 1.0 Hz), 7.90 (1 H, dt, J = 7.8, 1.0-1.5 Hz), 7.97 (1 H, t, J = 2.0 Hz); MS m/z 581 (M^+ - Bn). Anal. Calcd for $C_{39}H_{41}O_8Cl$: C, 69.58; H, 6.14; Cl, 5.27. Found: C, 69.33; H, 6.15; Cl, 5.13.

2,3,4-Tri-*O*-benzyl-6-*O*-(trimethylacetyl)-α,β-L-glucopyranose (14). A solution of **13** (7 mg) in THF (0.5 mL) and 0.1 M NaOH (0.25 mL) was stirred for 4 h at room temperature. The reaction mixture was diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated to give an oily residue, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (3:1) gave 3 mg (54%) of **14** as powder: $[\alpha]^{25}_D$ -26.4° (c 0.32, $CHCl_3$); IR ν_{max} (neat) 3440, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20-1.22 (9 H, m), 3.36-4.52 (6 H, m), 4.56-4.96 (6 H, m), 5.19-5.27 (1 H, m, H-1); MS m/z 517 (M^+ - OH), 443, 425, 337, 319, 282, 253; high-resolution mass spectrum of (M^+ - OH) calcd for $C_{32}H_{37}O_6$ m/z 517.25895, found 517.25885. Anal. Calcd for $C_{32}H_{38}O_7$: C, 71.89; H, 7.16. Found: C, 71.60; H, 7.00.

Acylal Analogues 16a,b,c,f. General Procedure. To a solution of the substrates **15a-f** (1.0 mmol) in a solvent (2-10 mL) cooled in an ice bath were added 3-chloroperoxybenzoic acid (1.1 mmol except for **15c**; 2.1 mmol for **15c**) and then 1,3-dicyclohexylcarbodiimide (1.1 mmol except for **15c**; 2.1 mmol for **15c**) with stirring. After evolution of CO_2 ceased at 0 °C or room temperature, the reaction mixture was filtered and chromatographed on a silica gel column or a silica gel TLC plate.

Physical data are as follows. **16a**: $[\alpha]^{25}_D$ -6.8° (c 2.0, $CHCl_3$); IR ν_{max} (neat) 1762, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (3 H, s), 7.2-7.8 (7 H, m), 7.8-8.1 [3 H, m, containing 1 H singlet at δ 7.92, PhC*H*(OAc)(OAr)]; MS m/z 304 (M^+); high-resolution mass spectrum calcd for $C_{16}H_{13}O_4Cl$ m/z 304.05028, found 304.05088. Anal. Calcd for $C_{16}H_{13}O_4cl$: C, 63.06; H, 4.30; Cl, 11.63. Found: C, 63.00; H, 4.40; Cl, 11.80.

16b: IR (neat) 1725 (neat) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (3 H, s), 5.45 (2 H, s), 7.2-8.1 (4 H, m); MS m/z 200 (M^+, ^{35}Cl); high-resolution mass spectrum calcd for $C_9H_9O_3Cl$ m/z 200.02395, found 200.02315. Anal. Calcd for $C_9H_9O_3Cl$: C, 53.88; H, 4.52; Cl, 17.67. Found: C, 54.02; H, 4.37; Cl, 17.67.

16c: IR ν_{max} (neat) 1810, 1770, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.94 (1 H, dd, J = 9.2, 18.0 Hz), 3.42 (1 H, dd, J = 10.6, 18.0 Hz), 4.02 (1 H, ddd, J = 5.9, 9.2, 10.6 Hz), 7.13 (1 H, d, J = 5.9 Hz), 7.4-8.1 (8 H, m); MS m/z 395 (M^+ - CO_2), 394 (M^+ - CO_2). Anal. Calcd for $C_{19}H_{12}O_8Cl_2$: C, 51.96; H, 2.75; Cl, 16.14. Found: C, 52.45; H, 3.05; Cl, 16.14.

16f: IR ν_{max} (neat) 1750, 1575 cm^{-1}; MS m/z 413 (M^+ - 59), 317 (M^+ - 155). Anal. Calcd for $C_{20}H_{21}O_{11}Cl$: C, 50.80; H, 4.48; Cl, 7.50. Found: C, 50.23; H, 4.54; Cl, 7.48.

Partially OH Depleted Calix[4]arenes

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The partially OH depleted dihydroxy- and trihydroxycalix[4]arenes **2** and **3** were synthesized in order to assess the relative importance of the cyclic hydrogen bond on the conformation of *p-tert*-butylcalix[4]arene. Both compounds were prepared from the same diethyl diphosphate ester precursor under different reductive cleavage conditions. The ring inversion barriers of **2** and **3** are <10 and 11.6 kcal mol^{-1}, respectively. The completely OH depleted calixarene **5** and the MeOH solvate of dihydroxycalixarene **2** exist in the crystal in a 1,2-alternate conformation. Trihydroxycalixarene **3** crystallizes as a 1:2 pyridine solvate in which **3** adopts a cone conformation. One pyridine molecule is hydrogen bonded to one OH group of **3**, while simultaneously being included into the cavity of another molecule of **3**. It is concluded that three phenolic units are sufficient to stabilize the cone conformation.

Introduction

Two systems that have been extensively studied in the last years as host compounds for enzyme mimics are cyclodextrins[1] and calixarenes.[2] Both systems are capable of including small organic molecules into their cavities. However, the cyclodextrins are conformationally rigid whereas the free hydroxyl-containing calixarenes are conformationally flexible on the laboratory timescale. The conformational behavior of calix[4]arenes is normally discussed in terms of four ideal conformations: cone, partial cone, and 1,3- and 1,2-alternate (Figure 1).[3,4] For

(1) For a monograph on cyclodextrins, see: Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978.

(2) For a comprehensive review on calixarenes, see: Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.

(3) Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73.

(4) These conformations are by no means exclusive. For example a "boat" conformation has been recently observed for a sterically crowded calixarene. See: Dahan, E.; Biali, S. E. *J. Org. Chem.* **1989**, *54*, 6003.

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