Hydrazine **36**: ^{1}H NMR δ 1.123 (t, J = 7.1 Hz, 6), 2.771 (q, J = 7.1 Hz, 4), 3.923 (s, 3), 4.620 (m, 1), 7.705 (m, 1), 8.032 (s, 1), 8.167 (s, 1), 8.432 (s, 1); MS 539 (100, M^+), 480 (4); HRMS calcd for $C_{19}H_{18}F_4IN_3O_3$ 539.0323, found 539.0302. Hydrazine **37**: ^{1}H NMR δ 1.125 (t, J = 7.1 Hz, 6), 2.771 (q, J = 7.1 Hz, 4), 3.927 (s, 3), 4.588 (s, 1), 7.461 (t, J = 8.0 Hz, 1), 7.706 (s, 1), 7.849 (d, J = 7.8 Hz, 1), 7.998 (d, J = 8.0 Hz, 1), 8.112 (s, 1); MS, 413 (100, M^+), 398 (25), 382 (6), 296 (20), 263 (12), 163 (3); HRMS calcd for $C_{19}H_{19}F_4N_3O_3$ 413.1357, found 413.1329.

Synthesis of Methyl 3-(4-Amino-2,3,5,6-tetrafluorobenzamido)benzoate (35). A mixture of 452 mg (2.16 mmol) of 4-aminotetrafluorobenzoic acid with 324 mg (2.14 mmol) of methyl 3-aminobenzoate and 447 mg (2.16 mmol) of DCC in $CHCl_3$ (10 mL) was stirred overnight. The mixture was filtered, and the solid was washed by $CHCl_3$ (30 mL). The filtrate was evaporated to leave a solid which was stirred with $CHCl_3$ (10 mL) and filtered, and the solid was dried to leave 267 mg (36%) of **35** as a colorless solid. The ^{1}H NMR spectrum is identical with that for **35** obtained above. The analytical sample of **35** was obtained via recrystallization (THF/hexane) as colorless needles, mp 185–186 °C. Anal. Calcd for $C_{15}H_{10}F_4N_2O_3$: C, 52.64, H, 2.94, N, 8.18. Found: C, 52.95, H, 2.89, N, 8.08.

Acknowledgment. This work was supported by NIH grant GM-27137.

Supplementary Material Available: ^{1}H NMR (300-MHz) spectra of compounds **7**, **8**, **11**, **13–15**, **21**, **25–28**, **30–32**, **34**, **36**, and **37** (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Notes

Synthesis of *C*-Disaccharides through Dimerization of *exo*-Glycals

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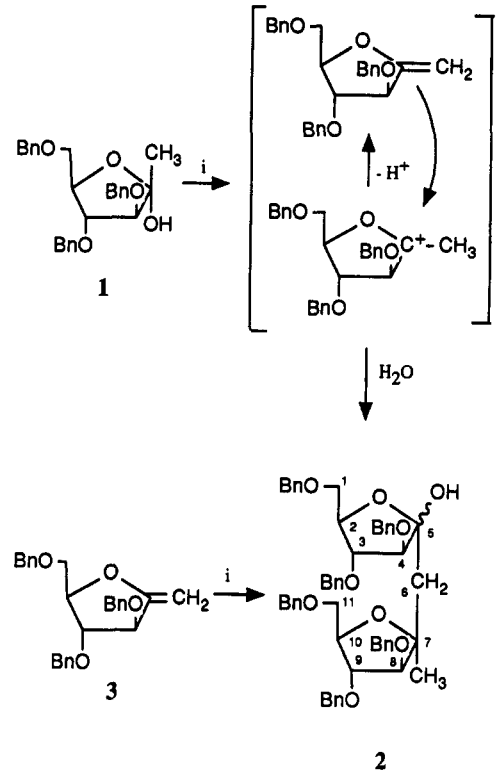
In our studies directed toward the synthesis of potential antimetabolites of natural carbohydrates, we were interested into a convenient method to synthesize *C*-disaccharides, sugars in which two monosaccharides are linked through a carbon atom rather than an oxygen.

The interest in these compounds, documented in the recent literature,[1,2] is supported inter alia by the fact that they can act as inhibitors of glycosidases. Compounds which exhibit this property have shown antiviral,[3] antitumoral,[4] antihyperglycemic,[5] and antiobesity[6] properties.

Scheme I[a]



[a] (i) BF_3·OEt_2, MeCN, 0 °C.

In particular, analogues of sucrose, the sugar of greater commercial relevance, are of interest for the studies of the relation between structure and sweetness and in the search of regulation or modification of enzymatic processes in which sucrose is involved.

Although many examples of synthesis of *C*-disaccharides have been described, to our knowledge only four examples[2] of the synthesis of *C*-disaccharides of nonreducing sugars

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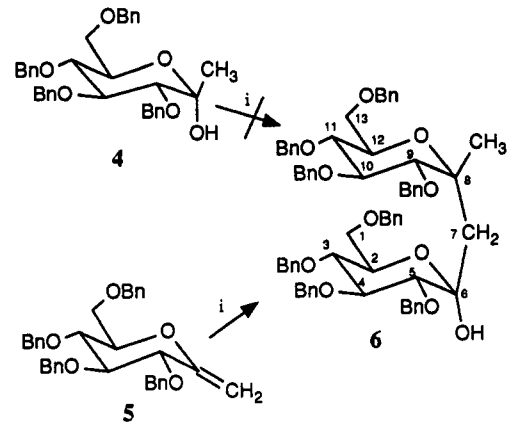
Scheme II[a]



[a] (i) BF_3·OEt_2, MeCN, 0 °C.

have been reported, and in some cases[2a,b] the synthetic approach required the stereoselective build up of the skeleton of one sugar component on a branched chain stereoselectively attached at the anomeric center of the other sugar component. This complicated approach was followed because of the difficulty of joining together, through a carbon atom, the two anomeric carbons with the desired stereochemistry.

To overcome these difficulties, and in light of our recent observations,[2c] we decided to investigate a different approach which consists of the Lewis acid catalyzed reaction of the anomeric center of one sugar with an enol ether function on the other sugar. We observed[2c] that 3,4,6-tri-*O*-benzyl-1-deoxy-D-*arabino*-hexulofuranose (**1**), on treatment with BF_3·OEt_2 in MeCN, affords the *C*-disaccharide **2**, presumably through a process which involves an enol ether intermediate (see Scheme I). However, when we attempted to extend this result to the 3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-heptulopyranose (**4**) no reaction occurred; therefore we decided to synthesize the sugar–enol ethers which are presumably the intermediates in this reaction, and test them.

The enol ethers **3** and **5** were synthesized starting from the corresponding lactones by reaction with Tebbe's reagent.[7] Interestingly they reacted with BF_3·OEt_2 in MeCN to afford the *C*-disaccharide derived from the attack of the enol ether function to the oxonium ion derived from another molecule of enol ether: **3** afforded in 96% yield the same *C*-disaccharide **2** obtained starting from **1**, and **5** afforded in 66% yield the *C*-disaccharide **6** (Scheme II), which was unobtainable starting from **4**. The use of trimethylsilyl triflate instead of BF_3·OEt_2 in the case of **5** did not change the result.

It is interesting to note that the attack of the enol ether on the anomeric oxonium ion occurs with high stereoselectivity from the β-face in the case of **1** (the isomer derived from the α-attack was not detected) and from the α-face in the case of **5** (only **6** was obtained).

The *C*-disaccharide **2** was present as a 1:1 mixture of the α and β anomers at the emiketalic position, which can be separated by chromatography.

The configuration at C-7 of **2** was determined on the separated anomers **2**α and **2**β, on the basis of nuclear Overhauser enhancement (NOE) experiments. In fact, in both anomers, irradiation of the methyl group produced an NOE on H-8 (10% in the higher R_f anomer **2**β, and 27% in the lower R_f anomer **2**α), whereas irradiation of the methylene produced a 6% NOE on the H-4 of **2**β and no NOE in the case of **2**α. The anomeric configurations of **2**α and **2**β were assigned on the basis of the $[\alpha]_D$ values and ^{13}C chemical shifts of the anomeric carbons and of the carbons linked to the anomeric centers. In fact the $[\alpha]_D$ value of **2**β (−32.9°), lower to that of **2**α (+22.8°), follows the Hudson rule[8] which assert that the α-anomer has a higher $[\alpha]_D$ value than the β. Also a comparison of the ^{13}C chemical shift values of the anomeric carbons and of the methylene carbons linked to the anomeric centers in **2**β and **2**α (113.45–116.97 and 49.01–46.14, respectively) is in agreement with the observations that the anomeric carbon of a β-fructofuranoside resonates at higher field then that of the corresponding α-isomer[9] and that a carbon which is cis-related to the adjacent alkoxy substituent resonates at higher field than the corresponding trans-related compound.[2c] The configuration of the *C*-glycosidic center of **6** was inferred from the well-known stereochemical course of the Lewis acid catalyzed attack of enol ethers (and allylsilanes) on D-glucopyranosides, which occurs stereoselectively from the α-face,[10] and was confirmed by NOE experiments (5% NOE between H-2 and CH_2). The attribution of the signals in the ^1H and ^{13}C NMR spectra of **6** was effected through COSY, ^1H–^{13}C heteronuclear shift correlation, and COLOC experiments.

The procedure is at the moment limited to the synthesis of homo-*C*-disaccharides with a methyl group at the *C*-glycosidic center. The high reactivity of the enitols **3** and **5** as electrophiles render the synthesis of etero *C*-disaccharides troublesome. Work is in progress to effect the synthesis of etero *C*-disaccharides circumventing these difficulties.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$; the signals of the aromatic carbons in the ^{13}C NMR spectra are not reported. $[\alpha]_D$ values were measured at 20 °C. Column chromatography was performed with the flash procedure using Merck silica gel 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on Merck silica gel-60 F-254 plates, eluted with hexane–ethyl acetate in the ratio reported in brackets, and visualized with 50% sulfuric acid spray followed by heating at 110 °C for 5 min. All reactions were run under nitrogen in glassware oven-dried overnight at 120 °C and assembled hot. Reagents and dry solvents were added via oven-dried syringes through septa. Usual workup refers to dilution with an organic solvent (CH_2Cl_2), washing with water to neutrality, drying with Na_2SO_4, and evaporating under reduced pressure.

3,4,6-Tri-*O*-benzyl-1-deoxy-D-*arabino*-hexulofuranose (1). To 2,3,5-tri-*O*-benzyl-D-arabinono-1,4-lactone[11] (870 mg, 2.1 mmol) in dry THF (25 mL) was added MeLi (2.8 mL, 1.4 N in Et_2O) at −78 °C. After 5 min (TLC control, 3:1) aqueous NH_4Cl was added. Usual workup and flash chromatography (3:1) afforded **1** (900 mg, quant. yield) as two anomers: ^{13}C NMR δ 21.74 and 25.50 (Me); 70.46, 71.07, 71.92, 72.92, 72.37, 72.63, 73.38, and 73.67 (CH_2O); 80.03, 81.46, 83.07, 83.73, 86.51, 87.50 (CHO); 102.51 and 106.63 (C-2). Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.57; H, 6.89.

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-D-*gluco*-heptulopyranose (4). 2,3,4,6-Tetra-*O*-benzyl-D-glucono-1,5-lactone[12] (540 mg, 1.0

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mmol), treated with MeLi as described in the synthesis of 1, afforded 4 (500 mg, 90% yield): ^{13}C NMR (CD_3COCD_3) δ 26.86 (Me), 70.78, 72.64, 74.19, 75.63, 76.18, 76.35, 80.35, 84.75, 85.50; 98.38 (C-2). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.67; H, 7.08.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-*arabino*-hex-1-enitol (3). The crude reaction mixture formed by the combination of titanocene dichloride (1.25 g, 5 mmol) and Me_3Al (5 mL, 2 M in toluene),[7] was added after 72 h at −60 °C to a stirred solution of 2,3,5-tri-*O*-benzyl-D-arabinono-1,4-lactone[11] (2.0 g, 4.8 mmol) in a mixture of dry THF (3 mL), dry toluene (7 mL), and two drops of dry pyridine. The reaction was monitored by TLC (8:2) and after 2 h warmed to −20 °C, stirred 1.5 more hours, and quenched by slow addition of aqueous NaOH (1 mL, 4 N). Dilution with Et_2O (200 mL), filtration on Celite, and gravity chromatography (8:2) afforded 3 (1.41 g, 71% yield): mp 49–50 °C (from Et_2O–hexane); $[\alpha]_D$ +19.6° (*c* 1.5, $CHCl_3$)(lit.[12] oil, $[\alpha]_D$ +15.9°); ^{1}H NMR δ 3.60 (2 H, m, H-5a and H-5b), 4.05 (1 H, t, *J* = 3 Hz, H-4), 4.17 (2 H, broad s, H-1a and H-1b), 4.37 (1 H, *J* = 3 Hz, H-3), 4.41 (1 H, m, H-5), 4.51 (1 H, d, *J* = 12 Hz, OCHPh), 4.55 (4 H, s, OCH_2Ph), 4.65 (1 H, d, *J* = 13 Hz, OCHPh), 7.3 (15 H, m, PhH); ^{13}C NMR δ 69.93, 71.00, 71.92, and 73.53 (CH_2O); 81.85, 82.39, and 83.67 (C-3, C-4, and C-5); 85.79 (C-1); 160.15 (C-2). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86; H, 6.77. Found: C, 77.72, H, 6.43. FAB MS *m/e* 417.

7,10-Anhydro-6-deoxy-7-*C*-methyl-1,3,4,8,9,11-hexa-*O*-benzyl-D-*gluco*-D-*lyxo*-undec-5-ulofuranose (2). Method A. To a stirred solution of 1 (700 mg, 1.6 mmol) in dry MeCN (25 mL) was added two drops of BF_3·OEt_2 at 0 °C, and the reaction was monitored by TLC (7:3). After 30 min, addition of water (100 mL) and usual workup afforded 2 (637 mg, 93% yield) as a mixture of two anomers.

Method B. To a stirred solution of 3 (580 mg, 1.4 mmol) in dry MeCN (50 mL) was added two drops of BF_3·OEt_2 at 0 °C. The reaction was immediate. Addition of water and usual workup afforded 2 (570 mg, 96% yield) as a 1:1 mixture of two anomers.

The anomers were separated by flash chromatography (8:2).

2β (higher R_f anomer): oil; $[\alpha]_D$ −32.9° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.53 (3 H, s, Me), 2.11 (1 H, d, *J* = 14 Hz, H-6a), 2.99 (1 H, d, *J* = 14 Hz, H-6b), 3.51 (2 H, d, *J* = 6 Hz, H-1 or H-11), 3.58 (2 H, m, H-1 or H-11), 3.92 (1 H, d, *J* = 4 Hz), 4.00 (1 H, d, *J* = 6 Hz, H-4, 6% NOE with H-6b), 4.10 (2 H, m), 4.26 (1 H, d, *J* = 2.5 Hz, H-8, 10% NOE with Me), 4.37 (1 H, d, *J* = 12 Hz, OCHPh), 4.22–4.80 (13 H, m), 7.4 (30 H, m, PhH); ^{13}C NMR δ 23.03 (Me), 49.01 (C-8), 71.20, 71.60, 71.86, 72.36, 72.66, 72.75, 72.12, 73.49 (CH_2O); 80.29, 84.26, 84.58, 84.82, 85.23, 91.00 (CHO); 90.58 (C-7), 113.45 (C-5); EI MS *m/e* 832 (M − H_2O). Anal. Calcd for $C_{54}H_{58}O_9$: C, 76.21; H, 6.87. Found: C, 75.81; H, 7.01.

2α: oil; $[\alpha]_D$ +22.8° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.48 (3 H, s, Me), 2.18 (1 H, d, *J* = 15 Hz, H-6a), 2.40 (1 H, d, *J* = 15 Hz, H-6b), 3.43 (1 H, dd, *J* = 5 and 10.5 Hz, H-1a), 3.51 (1 H, dd, *J* = 5 and 10.5 Hz, H-1b), 3.63 (1 H, dd, *J* = 4.5 and 10 Hz, H-11a), 3.67 (1 H, dd, *J* = 6 and 10 Hz, H-11b), 3.87 (1 H, dd, *J* = 2.5 and 5 Hz, H-3), 3.96 (1 H, d, *J* = 2.5 Hz, H-4), 3.99 (1 H, dd, *J* = 2 and 6 Hz, H-9), 4.10 (1 H, q, *J* = 5 Hz, H-2), 4.19 (1 H, dt, *J* = 4.5, 6 and 6 Hz, H-10), 4.34 (1 H, d, *J* = 2 Hz, H-8, 27% NOE with Me), 4.35–4.75 (12 H, m, OCH_2Ph), 7.4 (30 H, PhH); ^{13}C NMR δ 23.66 (Me), 46.14 (C-6), 70.52, 71.66, 71.79, 72.09, 73.49 (CH_2O); 81.11, 82.49, 82.90, 86.92, 88.37, 94.21 (CHO); 89.04 (C-7), 116.97 (C-5); EI MS *m/e* 832 (M − H_2O). Anal. Found: C, 75.99; H, 6.74.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (5). The crude reaction mixture, formed by the combination of titanocene dichloride (1.25 g, 5 mmol) and Me_3Al (5 mL, 2 M in toluene), was added after 72 h at −60 °C to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[12] (2.6 g, 4.9 mmol) in a mixture of dry THF (3 mL), dry toluene (7 mL), and two drops of dry pyridine. The reaction was monitored by TLC (8:2) and after 2 h warmed to −20 °C, stirred 1.5 more hours, and quenched by slow addition of aqueous NaOH (1 mL, 4 N). Dilution with Et_2O (200 mL), filtration on Celite, and gravity chromatography (8:2) afforded 5 (2.4 g, 92% yield): mp 65–68 °C (lit. mp 65–68 °C);[13] $[\alpha]_D$ +59.5° (*c* 1 $CHCl_3$); ^{1}H NMR, δ 3.66–3.85 (5 H, m), 3.96 (1 H, d, *J* = 9 Hz), 4.40–4.90 (10 H, m), 7.3 (20 H, PhH); ^{13}C NMR δ 68.72, 72.66, 73.40, 74.33, and 74.41 (CH_2O); 77.50, 78.43, 78.91, 84.57 (C-3, C-4, C-5, and C-6); 94.60 (C-1), 156.17 (C-2). Anal. Calcd for $C_{35}H_{36}O_5$: C, 78.33; H, 6.76. Found: C, 78.48; H, 6.55.

8,12-Anhydro-7-deoxy-8-*C*-methyl-1,3,4,5,9,10,11,13-octa-*O*-benzyl-D-*glycero*-D-*ido*-L-*gulo*-tridec-6-ulopyranose (6). 5 (156 mg, 0.28 mmol), treated as described in method B, afforded 6 (101 mg, 66% yield): mp 74–76 °C; $[\alpha]_D$ +49.5° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.51 (3 H, s, Me), 2.20 (1 H, d, *J* = 15 Hz, H-7a), 2.27 (1 H, d, *J* = 15 Hz, H-7b), 3.45–3.63 (3 H, m, H-3, H-9 and H-12), 3.65–3.75 (5 H, m, H-1a, H-1b, H-10, H-11, H-13a, and H-13b), 3.83 (1 H, m, H-2), 3.93 (1 H, d, *J* = 7 Hz, H-5), 4.32 (1 H, dd, *J* = 7 and 8.5 Hz, H-4), 4.47–5.00 (16 H, m, OCH_2Ph), 7.4 (40 H, PhH); ^{13}C NMR δ 29.36 (Me), 39.94 (C-7), 69.94, 70.31 (C-1 and C-13); 73.19 (C-2), 74.38 (C-12), 73.98, 74.19, 74.87, 75.64, 76.28 (OCH_2Ph); 77.32 (C-3), 78.54 (C-11), 82.80 (C-8), 83.63 (C-10), 84.04 (C-4), 85.01 (C-9), 87.77 (C-5), 110.60 (C-6). Anal. Calcd for $C_{70}H_{74}O_{11}$: C, 77.04; H, 6.83. Found: C, 76.89; H, 6.77.

Acknowledgment. We thank the "Progetto finalizzato Chimica Fine II" for the financial support.

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Microbiological Transformations. 22. Microbiologically Mediated Baeyer–Villiger Reactions: A Unique Route to Several Bicyclic γ-Lactones in High Enantiomeric Purity

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Baeyer–Villiger-type oxidation reactions achieved using biocatalysts[1] are a new emerging type of bioconversion allowing for the one-step asymmetric synthesis of chiral lactones. These biocatalysts can be either purified enzymes[2] or whole-cell systems.[3,4] We have recently described a preliminary work showing an unexpected result from such a reaction. Using whole-cell cultures of *Acinetobacter* TD63, we have carried out the preparative-scale transformation of bicyclo[3.2.0]hept-2-en-6-one (**1a**) into the two regioisomeric lactones **2a** and **3a** with enantiomeric excesses (ee's) as high as 95%.[5] This reaction presents two interesting points. First, only a few examples of such high enantioselectivity have been reported for such reactions,[3,6] most substrates leading only to poor (if any) en-

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