3.5 Hz, 1 H), 6.89 (br d, J = 8.8 Hz, 2 H), 7.3-7.5 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 55.02, 72.16, 73.10, 75.66, 113.55, 127.24, 127.59, 128.23, 132.41, 137.67, 158.98; IR (KBr) 3500 (m), 3350 (m), 1610 (s), 1515 (s), 1245 (s), 1120 (br s), 1075 (br s), 1025 (br s), 830 (s), 740 (s), 700 (m) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 258 (2, M$^+$), 137 (100), 109 (29), 91 (35), 77 (20); Anal. ($C_{16}H_{18}O_3$) C, H.

Equilibration of [(Benzyloxy)methyl]lithium (43) and 2-Lithio-1,3-dioxane (7). A solution of 185 mg of **44**[2b] (0.485 mmol) in 1 mL of THF was cooled to -78 °C, and n-butyllithium (0.28 mL of a 1.6 M solution in hexanes, 0.44 mmol) was added dropwise. The resulting clear, pale yellow solution was stirred at -78 °C for 20 min, and a solution of **17** (183 mg, 0.485 mmol) in 1 mL of THF was added via a cannula, followed by rinsing with two 1-mL portions of THF. After the mixture was stirred 30 min further, 84 mg of p-anisaldehyde (0.62 mmol, 80 μL) was added dropwise. The resulting solution was stirred for an additional 30 min, and then the reaction was quenched at -78 °C by addition of 2 mL of methanol. Capillary GC analysis revealed that carbinols **19** and **45** were formed in a ratio of 99.3:0.7, corrected for product response factors. Workup as described for the preparation of **45**, followed by flash chromatography using 45% ethyl acetate/hexanes as eluant, gave 92 mg of **19** (93% yield).

Relative Rates of Addition of 43 and 7 to p-Anisaldehyde. A solution of 127 mg (0.31 mmol) of **44** and 116 mg (0.31 mmol) of **17** in 3 mL of THF was cooled to -78 °C, and n-butyllithium (0.39 mL of a 1.6 M solution in hexanes, 0.62 mmol) was added dropwise. The resulting pale yellow solution was stirred for 30 min, and p-anisaldehyde (37 μL, 0.31 mmol) was added all at once. After stirring 30 min further, the reaction was quenched at -78 °C by addition of 2 mL of methanol. Quantitative capillary GC analysis, using octadecane as internal standard, indicated that carbinols **19** and **45** were formed in a ratio of 1.21:1 (52 and 43% yields, respectively). p-Anisyl-n-butylcarbinol (**24**) was also formed in 3% yield.

Acknowledgment. We thank the National Institutes of Health, the American Heart Association, and the Colorado Heart Association for generous financial support.

Registry No. 4, 118418-15-8; **5**, 118418-16-9; **6**, 118418-17-0; **7**, 118418-18-1; **8**, 118418-19-2; **9**, 25604-67-5; **10**, 19798-66-4; **11**, 118418-20-5; **12**, 4544-19-8; **13**, 81381-75-1; **14**, 79411-59-9; **15**, 79411-58-8; **16**, 118418-21-6; **17**, 118418-22-7; **18**, 118418-23-8; **19**, 63457-96-5; **20**, 63458-00-4; **21**, 118418-24-9; **22**, 118418-25-0; **23**, 118418-26-1; **24**, 19523-03-6; **25**, 118418-27-2; **26**, 118418-28-3; **27**, 626-68-6; **28**, 64181-30-2; **29**, 118418-29-4; **30**, 5465-07-6; **31**, 99423-28-6; **35**, 118418-30-7; **36**, 118418-31-8; **43**, 71316-95-5; **44**, 66222-28-4; **45**, 838-66-4; p-anisaldehyde, 123-11-5; 4,4′-di-*tert*-butylbiphenyl, 1625-91-8; ethylene oxide, 75-21-8; trimethylsilyl trifluoromethanesulfonate, 27607-77-8; trimethyl orthoformate, 149-73-5; (phenylthio)-trimethylsilane, 4551-15-9; ethylene glycol, 107-21-1; triethyl orthoformate, 122-51-0; 1,3-propanediol, 504-63-2; galvinoxyl, 2370-18-5; isopropylmagnesium chloride, 1068-55-9; tributyltin hydride, 688-73-3; cyclohexanone, 108-94-1; cyclohexanecarboxaldehyde, 2043-61-0; dimethyl sulfate, 77-78-1; 1-bromo-3-phenylpropane, 637-59-2; cyclopentene oxide, 285-67-6; oxetane, 503-30-0; 2-cyclohexen-1-one, 930-68-7; tetrakis[iodo(tri-n-butylphosphine)copper(I)], 59245-99-7; chloro-tri-n-butylstannane, 1461-22-9.

Redox Glycosidation: A New Strategy for Disaccharide Synthesis‡

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Abstract: A new procedure for the preparation of disaccharides via redox glycosidation is described. The crucial anomeric C-O bond is established by acylation not alkylation as in traditional Koenigs-Knorr chemistry. Tebbe methylenylation followed by cyclization unravels the protected nonreducing or reducing disaccharides. Thus, for example, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) was coupled with 5-[(*tert*-butyldiphenylsilyl)oxy]pentanoyl chloride (**5**). The resultant α-ester **2** was methylenylated with the Tebbe reagent, desilylated, and cyclized with iodine to produce the pyranosylmethyl iodide **4** in good yield. The redox glycosidation protocol was extended to a range of reducing and nonreducing disaccharide systems.

The efficient construction of oligosaccharides in a stereocontrolled manner remains a challenging area for synthetic organic chemistry. Such compounds are of considerable interest in consequence of their diverse, vital roles in many biological processes.[1] Classically, oligosaccharides are assembled with iterative Koenigs-Knorr[2] reactions to sequentially construct the glycosidic bonds. There are now many variations on this theme in which a protected glycosyl halide or related electrophile is condensed with a partially protected second sugar unit.[3] All these existing methods employ an alkylation strategy to elaborate the crucial glycosidic C-O bonds. In oligosaccharide synthesis it is essential that the glycosidation methods used are high yielding. Additionally, the reactions should proceed rapidly and readily control the α versus β diastereoselectivity at each iteration irrespective of ring substituents. However, in spite of extensive studies on variants of Koenigs-Knorr chemistry spanning nearly 100 years, oligosaccharide synthesis cannot yet be considered simple routine.[4]

Herein we describe model studies on a new procedure for the preparation of disaccharides via redox glycosidation. In this process the two units are linked via an ester bond; subsequent reductive unravelling reveals the disaccharide entity. Thus in the process of crucial anomeric C-O bond is established via acylation,

‡ Dedicated to Professor Sir Derek H. R. Barton on the occasion of his 70th birthday.

(1) For examples, see: Kennedy, J. F.; White, C. A. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 5, p 755. Schaner, R. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 131.

(2) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243.

(3) For examples of recent developments in glycosidation chemistry, see: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. Nicolaou, K. C.; Ladduwahetty, J. L. R.; Chuchulowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466. Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189. Nicolaou, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1153.

(4) In contrast to oligosaccharide chemistry, syntheses of oligonucleotides and polypeptides are now highly sophisticated. For examples, see: Letsinger, R. L. Chemical Synthesis of Oligodeoxyribonucleotides: A Simplified Procedure. In *Genetic Engineering: Principles and Methods*; Setlow, J. K., Hollaender, A., Eds.; Plenum Press: New York, 1983; Vol. 5, pp 191-209. Merrifield, B. *Science* **1986**, *232*, 341.

0002-7863/89/1511-1392$01.50/0

Scheme I

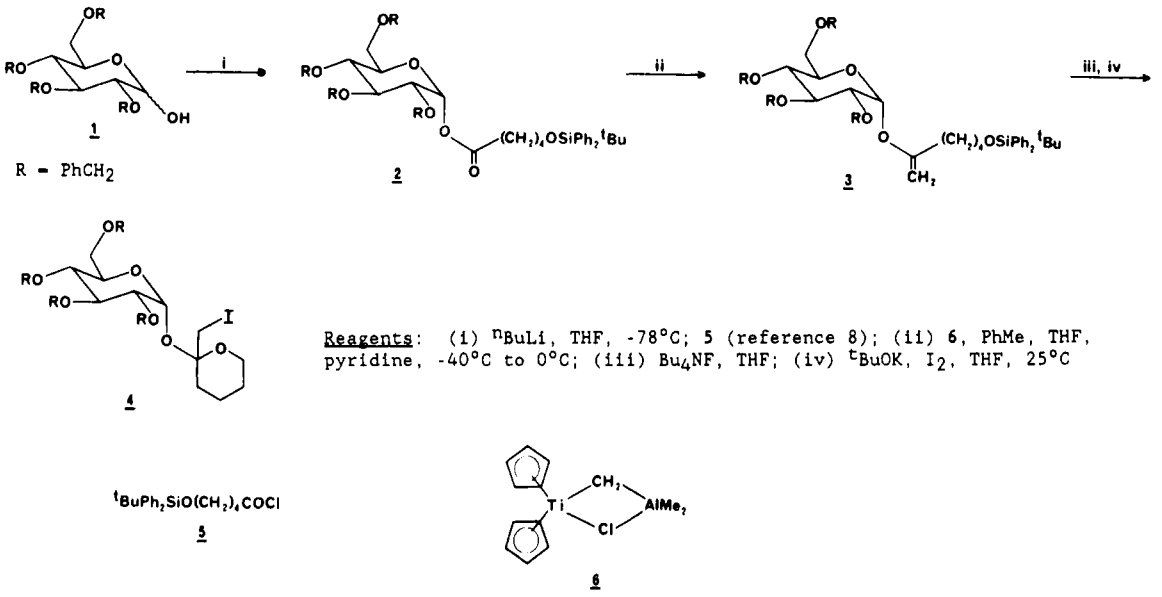

Table I. Tebbe Methylenylation and Iodoetherification of Glycosyl Esters

entry	ester	(method of prepn,[a] % yield, α:β)	vinyl ether	(% yield)	iodo ether	(method of cyclization,[b] % yield, diasteroselectivity)
1	**2**	(A, 50, 13:1)	**3**	(69)	**4**	(A, 72, 1.4:1[c])
2	**7a**	(B, 44, 1:6)	**7b**	(86)	**8**	(A, 63, 1:1[c])
3	**9a**	(C, 52, 1:2)	**9b**	β-isomer (63)[d]	**10**	(B, 79, *e*)
			9b	α-isomer (13)[d]	**11**	(B, 80, 1:1[c])
4	**12a**	(D, 65, 1:11)	**12b**	(67)	**13, 14**	(C, 65, 8:1)
5	**15a**	(E, 80, 7.4:1)	**15b**	(82)	**16, 17**	(C, 59, ≥40:1)
6	**18a**	(D, 71, 1:12)	**18b**	(72)	**19, 20**	(D, 69, 5:1)
7	**21a**	(E, 66, 18:1)	**21b**	(84)	**22, 23**	(D, 65, 2:1)
8	**24a**	(F, 68, *e*)	**24b**	(44)	**25**	(C, 54, 2:1[c])
9	**26a**	(F, 84, *e*)	**26b**	(83)	**27**	(C, 76, 2:1[c])
10	**28a**	(F, 98, *e*)	**28b**	(82)	**29, 30**	(E, 60, 3:1)

[a] Methods for ester preparation from the alcohol by reaction with (A) nBuLi, THF, −78 °C, acyl chloride (ref 8); (B) nBuLi, PhH, 60 °C, acyl chloride (ref 8); (C) iPrN=C=NiPr, 4-(dimethylamino)pyridine, CH_2Cl_2, acid (ref 12); (D) NaH (cat.), CCl_3CN, CH_2Cl_2, 25 °C then acid, CH_2Cl_2 (ref 6); (E) nBuLi, THF, −78 °C, 2-(acylthio)-3-nitropyridine (ref 13); (F) DCC, 4-pyrrolidinopyridine, CH_2Cl_2, acid (ref 12). [b] Methods used for cyclization: (A) Bu_4NF, THF followed by I_2, tBuOK, THF, 0 °C to 25 °C; (B) Bu_4NF, THF followed by I_2, tBuOK, THF, −78 °C to −20 °C; (C) Bu_4NF, silica, I_2, tBuOK, THF; (D) Bu_4NF, THF followed by I_2, tBuOK, THF, −78 °C to −40 °C; (E) Bu_4NF, THF followed by I_2, tBuOK, THF, 0 °C. [c] Structure of major diastereoisomer not assigned. [d] The α- and β-isomers were separated at the vinyl ether stage following desilylation using Bu_4NF in THF. [e] Ratio not determined.

not alkylation. Such a procedure benefits from the fact that acylation reactions are rapid and proceed with moderate to excellent α to β diastereoselectivities.[5,6]

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**1**) was esterified with **5**[7], by using the lithium alkoxide method of Pfeffer[8] to stereoselectively (13:1) produce the α-glucosyl ester **2** (50%). Subsequent methylenylation using the Tebbe reagent **6**[9,10] gave the anomeric vinyl ether **3** (69%). Desilylation and iodoetherification gave the model nonreducing disaccharide **4** (72%) as a mixture of diastereoisomers (1:1.4) (Scheme I). We were delighted that the delicate anomeric C–O bond of **3** was not cleaved at the intermediate iodonium ion stage. The method was extended to a range of disaccharide systems (Table I, Chart I). Four distinct procedures were used for the esterification step:[11] (i) carbodiimide coupling[12] (entries 3, 8–10), (ii) β-selective esterification using trichloroimidate activation[6] (entries 4, 6), (iii) α-selective esterification by reaction of the anomeric alkoxide with the acid chloride[8] (entry 1) or 2-(acylthio)-3-nitropyridine[13,14] (entries 5, 7), and (iv) β-selective esterification by reaction of the anomeric alkoxide with the acid chloride at 60 °C[8] (entry 2). All the esters were smoothly methylenylated, desilylated, and iodocyclized to produce the corresponding protected nonreducing (entries 1–7)

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(9) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1977**, *100*, 3611. Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *Ibid.* **1980**, *102*, 3270. See also: Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733. For an in situ preparation of this reagent: Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386.

(10) For examples of Tebbe methylenylation of carbohydrate systems, see: Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395. RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458.

(11) Carboxylic acids were prepared from the corresponding aldonic acid lactones, see ref 7.

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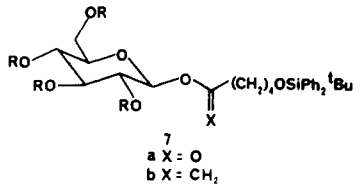
Chart I



7
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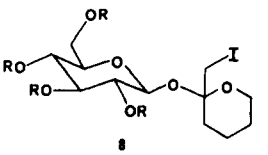

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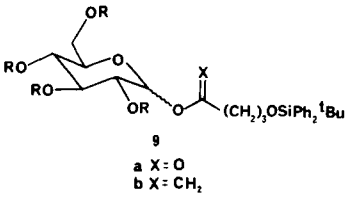

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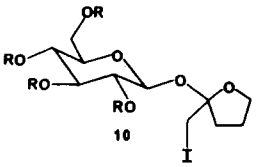

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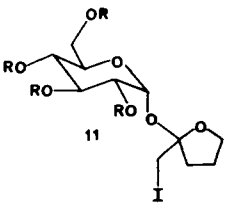
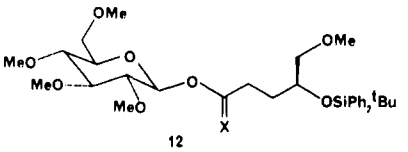


11

R = $PhCH_2$



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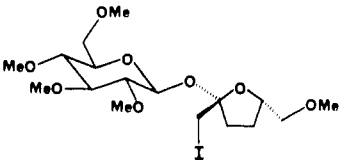

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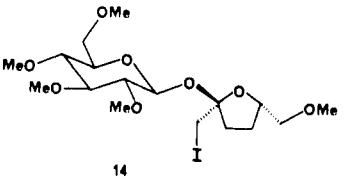

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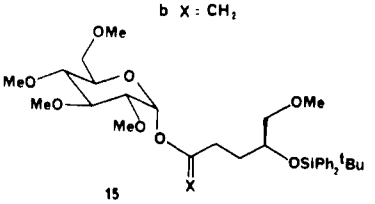

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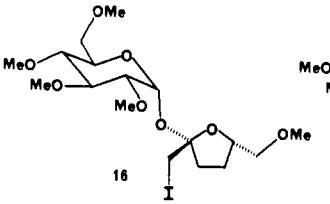

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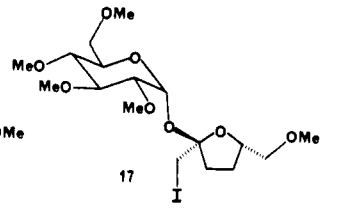

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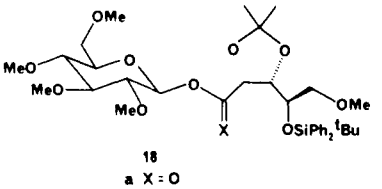

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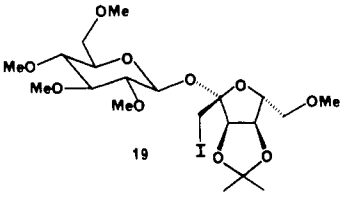

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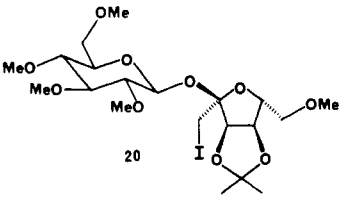

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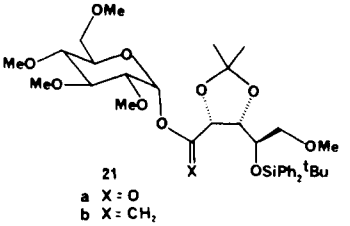

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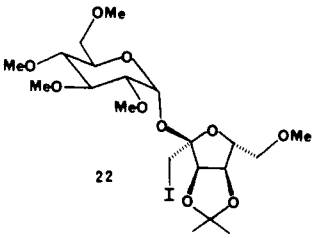

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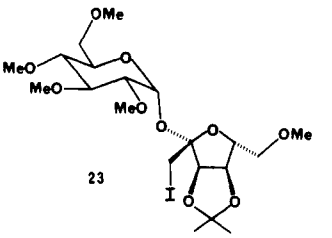

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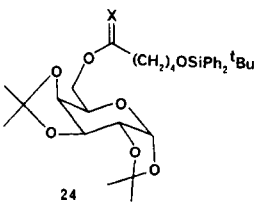

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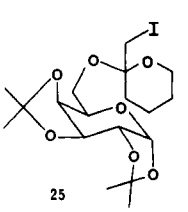

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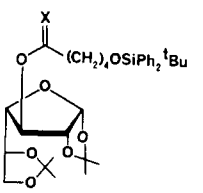

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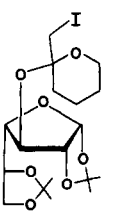

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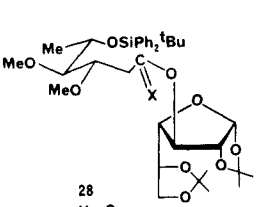
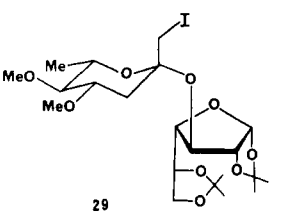
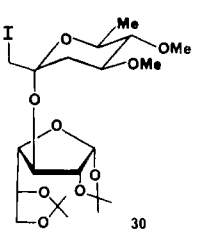


28
a X = O
b X = CH_2



29



30

and reducing (entries 8–10) disaccharides.[15] It is clear from these results that the protocol may be used to introduce either (iodomethyl)pyranosyl or furanosyl groups. It should be noted that the cyclizations which produced pyranosyl methyl iodides were slower than those producing tetrahydrofuran systems.

The stereochemistry of reaction requires comment. The stereochemistries of these iodoetherification reactions are clearly kinetically controlled.[16] Cyclizations of the simple unsubstituted vinyl ethers proceeded without any appreciable stereochemical control by D-glucose (entries 1–3) or D-galactose (entries 8, 9). However, the cyclizations of vinyl ethers bearing side-chain substituents proceeded with modest to excellent diastereoselectivities (2:1 to >40:1). It is particularly interesting to note the variation in the diastereoselectivity in entries 4–7. Presumably stereochemical control by the isopropylidene and the methoxymethyl substituents are mismatched.[17] The redox glycosidation of 2,3:5,6-di-*O*-isopropylidene-α-D-galactofuranose (entry 10) is a favorable auspice for application of this approach in sialic acid chemistry.[18]

In conclusion, it is apparent that the acylation–methylenylation–cyclization protocol provides a novel method for the elaboration of the glycosidic bond. Further studies on this protocol and other redox cosidation technologies are under investigation.

Experimental Section

Representative procedures are given in this section. Full experimental details are provided in the supplementary material.

2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl 2,3-*O*-Isopropylidene-5-*O*-methyl-4-*O*-(*tert*-butyldiphenylsilyl)-D-ribonate (21a). 3,3′-Dinitro-2,2′-dipyridyl disulfide[14] (30 mg) and Ph_3P (26 mg) were added to a solution of 4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-5-*O*-methyl-D-ribonic acid[11] (30 mg) in dry CH_2Cl_2 (1 mL) under N_2 at room temperature, and the slurry was stirred for 4 h. The solids were filtered off, and the resultant thioester was purified by preparative TLC on silica (hexanes/EtOAc 3:1, R_f 0.41). *n*-Butyllithium (0.17 M, 0.4 mL) was added to a solution of 2,3,4,6-tetra-*O*-methyl-D-glucose (19 mg), in dry THF (0.5 mL) at −78 °C under N_2. After 10 min, a solution of the thioester in dry THF (0.5 mL) was added and stirring continued at −78 °C for 32 h. The mixture was quenched by adding it to a saturated aqueous NH_4Cl solution (10 mL), and the ester was extracted with Et_2O. Drying (Na_2SO_4) of the extract followed by evaporation and chromatography on silica (eluant hexanes/EtOAc 3:1) gave the ester (29 mg, 66%) as a 18:1 (**21a**:**18a**) mixture of anomers. The α-anomer **21a** was obtained as a colorless syrup by chromatography on silica (eluant hexanes/Et_2O 3:2): $[\alpha]_D$ +32.8° (*c* = 1.2, $CHCl_3$); TLC R_f 0.2 (silica, hexanes/Et_2O 3:2); IR (neat) 1771, 1757, 1433, 1388, 1150, 1110, 1000, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.68, 7.44–7.32 (2 m, 10 H), 6.29 (d, 1 H, *J* = 3.6 Hz), 4.42 (d, 1 H, *J* = 6.8 Hz), 4.38 (dd, 1 H, *J* = 4.2, 6.8 Hz), 4.22–4.16 (m, 1 H), 3.55–3.20 (m, 8 H), 3.59 (s, 3 H), 3.53 (s, 3 H), 3.37, (s, 3 H), 3.27 (s, 3 H), 3.03 (s, 3 H), 1.59 (s, 3 H), 1.32 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 136.1, 135.9, 134.2, 133.7, 129.6, 129.5, 127.4, 110.4, 90.6, 83.0, 80.9, 79.8, 78.1, 75.5, 73.1, 73.0, 70.4, 70.1, 60.8, 60.5, 59.1, 58.9, 58.2, 27.0, 26.6, 25.3, 19.3; mass spectrum (EI), *m/e* 661 (M^+ − Me), 441, 385, 255, 219, 187, 175, 167, 155, 145, 127, 111, 101, 59. Anal. Calcd for $C_{35}H_{52}O_{11}Si$: C, 62.11; H, 7.74. Found: C, 62.08; H, 7.81.

2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl 2,3-*O*-Isopropylidene-5-*O*-methyl-4-*O*-(*tert*-butyldiphenylsilyl)-D-ribonate (18a). NaH (0.5 mg) was added to a stirred solution of 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (50 mg) in dry CH_2Cl_2 (1 mL) at −40 °C under N_2. After 10 min CCl_3CN (0.5 mL) was added, and the stirring was continued for 1 h, before the solvent and excess CCl_3CN were removed under reduced pressure. Chromatography on silica (eluant hexanes/EtOAc 3:1) gave the corresponding imidate (69 mg). The imidate was dissolved in dry CH_2Cl_2 (1 mL) and 4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-5-*O*-methyl-D-ribonic acid (83 mg) was added. After stirring of the mixture at room temperature under N_2 for 1 h, CH_2Cl_2 (30 mL) and ice were added, and the mixture was washed with 2 M HCl (4 × 20 mL) and saturated aqueous $NaHCO_3$ (1 × 20 mL). Drying ($MgSO_4$), evaporation at reduced pressure, and chromatography on silica (eluant hexanes/Et_2O 3:2) of the CH_2Cl_2 extract gave **21a** and **18a** (87 mg, 71%) as a 1:12 mixture of anomers. Repurification using the same system yielded the pure β-isomer **18a** as a colorless syrup: $[\alpha]_D$ −29.5° (*c* = 2.0, $CHCl_3$); TLC R_f 0.3 (silica, hexanes/Et_2O 3:2); IR (neat) 1763, 1590, 1230, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.68, 7.45–7.30 (2 m, 10 H), 5.39 (d, 1 H, *J* = 8.0 Hz), 4.47 (d, 1 H, *J* = 6.8 Hz), 4.41 (dd, 1 H, *J* = 4.2, 6.8 Hz), 4.32–4.20 (m, 1 H), 3.52–3.05 (m, 8 H), 3.63 (s, 3 H), 3.52 (s, 3 H), 3.41 (s, 3 H), 3.31 (s, 3 H), 2.98 (s, 3 H), 1.57 (s, 3 H), 1.32 (s, 3 H), 1.04 (s, 9 H); ^{13}C NMR (101 MHz $CDCl_3$) δ 168.8, 136.2, 135.9, 134.3, 133.8, 129.5, 129.4, 127.4, 127.3, 110.5, 94.4, 86.8, 82.1, 79.7, 78.6, 75.4, 73.3, 72.9, 70.3, 70.0, 60.7, 60.4, 60.3, 59.2, 58.1, 27.0, 26.5, 25.4, 19.4; mass spectrum (EI), *m/e* 661 (M^+ − Me), 441, 417, 385, 353, 311, 255, 219, 187, 155, 145, 127, 111, 101. Anal. Calcd for $C_{35}H_{52}O_{11}Si$: C, 62.11; H, 7.74. Found: C, 62.30; H, 7.78.

2,2-Dimethyl-5(*R*)-[2-methoxy-1(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-4(*R*)-[1-[(2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosyl)oxy]-ethenyl]-1,3-dioxolane (18b). Tebbe reagent **6** in PhMe (0.50 M, 1 mL) was added dropwise to **18a** in dry PhMe (0.5 mL), dry THF (0.1 mL), and dry pyridine (0.1 mL) at −40 °C. The reaction mixture was stirred at that temperature for 30 min followed by 2 h at 0 °C and 1 h at room temperature. The mixture was cooled to −40 °C and quenched with a 15% NaOH solution (0.5 mL). The reaction mixture was diluted with Et_2O (10 mL) and filtered through Celite. The filtrate was evaporated at reduced pressure, and the crude product was purified by chromatography on silica (eluant hexanes/Et_2O 3:2). Alkene **18b** (40 mg, 72%) was recovered as a cloudy syrup: $[\alpha]_D$ +2.4° (*c* = 1.1, $CHCl_3$); TLC R_f 0.3 (silica, hexanes/Et_2O 3:2); IR (neat) 1650, 1468, 1442, 1387, 1250, 1100, 1000, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.70, 7.45–7.30 (2 m, 10 H), 4.56 (d, 1 H, *J* = 7.6 Hz), 4.46 (d, 1 H, *J* = 7.6 Hz), 4.43 (d, 1 H, *J* = 2.0 Hz), 4.40–4.35 (m, 2 H), 4.27–4.22 (m, 1 H), 3.62 (s, 3 H), 3.53 (s, 3 H), 3.53–3.00 (m, 8 H), 3.38 (s, 3 H), 3.30 (s, 3 H), 2.85 (s, 3 H), 1.49 (s, 3 H), 1.31 (s, 3 H), 1.01 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 135.9, 134.9, 134.8, 129.2, 127.3, 127.1, 108.5, 100.3, 91.2, 86.8, 83.1, 80.5, 79.2, 74.9, 74.0, 71.8, 71.2, 60.7, 60.4, 60.3, 59.3, 57.8, 27.0, 26.1, 24.5, 19.4,; mass spectrum (EI), *m/e* 659 (M^+ − Me), 527, 341, 219, 187, 155, 127, 111. Anal. Calcd for $C_{36}H_{54}O_{10}Si$: C, 64.07; H, 8.06. Found: C, 64.08; H, 8.16.

2,2-Dimethyl-5(*R*)-[2-methoxy-1(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-4(*R*)-[1-[(2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl)oxy]-ethenyl]-1,3-dioxolane (21b). Reaction of **21a** (50 mg) with the Tebbe reagent **6**, as described for **18a**, gave **21b** as a colorless solid (62 mg, 84%). Recrystallization from hexanes gave colorless cubes: mp 103 °C; $[\alpha]_D$ +40.5° (*c* = 1.1, $CHCl_3$); IR (KBr) 1650, 1480, 1440, 1390, 1304, 1230, 1170, 1115, 1102, 1050, 1000, 890, 856, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.65, 7.42–7.29 (2 m, 10 H), 4.93 (d, 1 H, *J* = 4.0 Hz), 4.47 (d, 1 H, *J* = 6.8 Hz), 4.44 (d, 1 H, *J* = 2.0 Hz), 4.34 (dd, 1 H, *J* = 6.6, 6.8 Hz), 4.18 (d, 1 H, *J* = 2.0 Hz), 4.14–4.10 (m, 1 H), 3.52–3.17 (m, 8 H), 3.52 (s, 3 H), 3.48 (s, 3 H), 3.37 (s, 3 H), 3.05 (s, 3 H), 3.01 (s, 3 H), 1.50 (s, 3 H), 1.34 (s, 3 H), 1.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 136.2, 135.9, 134.8, 134.4, 129.4, 129.1, 127.3, 127.1, 108.6, 94.5, 92.0, 83.4, 81.2, 79.5, 78.9, 78.7, 74.1, 70.6, 70.5, 60.6, 60.2, 59.1, 58.6, 58.0, 27.2, 26.8, 25.0, 19.4; mass spectrum (EI), *m/e* 659 (M^+ − Me), 527, 367, 341, 219, 187, 155, 145, 127, 111, 101. Anal. Calcd for $C_{36}H_{54}O_{10}Si$: C, 64.07; H, 8.06. Found: C, 63.96; H, 8.21.

2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl 1-Deoxy-3-*epi*-1-iodo-3,4-*O*-isopropylidene-β-D-fructofuranoside (19) and 2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl 1-Deoxy-3-*epi*-1-iodo-3,4-*O*-isopropylidene-α-D-fructofuranoside (20). The vinyl ether **18b** (50 mg) was dissolved in tetrabutylammonium fluoride in THF (1.0 M; 1.5 mL), and the mixture was stirred at room temperature under N_2 for 24 h. The solvent was removed at reduced pressure and the product alcohol was purified by chromatography on silica (eluant Et_2O, R_f 0.2). To a stirred solution of the alcohol in dry THF (2 mL) under N_2 at room temperature was added ^{t}BuOK (35 mg), and the mixture stirred for 5 min before it was cooled to −78 °C and I_2 (55 mg) was added. After stirring of the mixture for 4 h, the temperature was raised to −40 °C and the stirring was continued for another 18 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (3 mL) and the mixture was extracted with Et_2O (3 × 2 mL). After drying (Na_2SO_4) and evaporation, chromatography on silica (eluant hexanes/Et_2O 2:3) gave **19** and **20** (26 mg, 69%) as a 4.8:1 mixture of isomers: TLC R_f 0.4 (silica, hexanes/Et_2O 2:3). Anal. Calcd for $C_{20}H_{35}IO_{10}$: C, 42.71; H, 6.27. Found: C,

(15) All new compounds were fully authenticated by spectral data and microanalyses or high-resolution mass ion measurement. The stereochemistries of the iodomethyl substituents were confirmed by ^1H and ^{13}C spectral assignments and by extensive NOE experiments (see supplementary material).

(16) For examples of iodoetherification reactions, see: Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R. III *J. Org. Chem.* **1987**, *52*, 4191. Tamamu, Y.; Hojo, M.; Kawanura, S.; Sawada, S.; Yoshida, Z.; *Ibid*, **1987**, *52*, 4062. Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(17) For a discussion of matched and mismatched stereochemical biases, see Masamune, S.; Choy, W. *Aldrichimca Acta* **1982**, *15*, 47.

(18) Vliegenthart, F. G.; Kamerling, J. P. In *Sialic Acids*: *Chemistry, Metabolism and Function*; Schauer, R., Ed.; Springer-Verlag: New York, 1982; p 59–76.

42.50; H, 6.20. The isomers of R_f 0.4 (15 mg) and R_f 0.3 (4 mg) were separated by chromatography on silica (eluant hexanes/Et_2O 1:1). The major isomer **19** (R_f 0.4) was obtained as a colorless syrup: $[\alpha]_D$ -94° (c = 1.15, $CHCl_3$); IR (neat) 1460, 1413, 1390, 1380, 1255, 1216, 1160, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, 1 H, J = 7.6 Hz), 4.68 (d, 1 H, J = 5.6 Hz), 4.57 (dd, 1 H, J = 2.8, 5.6 Hz), 4.43-4.38 (m, 1 H), 3.76 (d, 1 H, J = 10.0 Hz), 3.67-3.41 (m, 5 H), 3.62 (s, 3 H) 3.53 (s, 3 H), 3.52 (s, 3 H), 3.42 (s, 3 H), 3.41 (s, 3 H), 3.29-3.04 (m, 4 H), 1.53 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 113.3, 109.4, 95.4, 87.4, 86.9, 85.8, 83.5, 82.1, 79.4, 74.7, 72.7, 71.5, 60.8, 60.5, 60.4, 59.6, 58.9, 26.9, 25.6, 5.8; mass spectrum (EI), m/e 547 (M^+ - Me), 403, 371, 328, 327, 235, 175, 157, 147, 115, 101. The minor isomer **20** (R_f 0.3) was obtained as a colorless syrup: $[\alpha]_D$ +37° (c = 0.90, $CHCl_3$); IR (CCl_4) 1728, 1691, 1676, 1650, 1555, 1377, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, 1 H, J = 7.2 Hz), 4.68-4.65 (m, 1 H), 4.62 (dd, 1 H, J = 4.0, 7.2 Hz), 4.58 (d, 1 H, J = 8.0 Hz), 3.63 (s, 3 H), 3.58 (s, 3 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 3.63-2.95 (m, 10 H), 1.61 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 116.5, 103.1, 96.3, 87.0, 84.7, 83.5, 82.4, 81.4, 79.6, 74.8, 72.2, 71.5, 61.2, 60.8, 60.3, 59.5, 59.4, 26.4, 26.2, 6.6; mass spectrum (EI), m/e 547 (M^+ - Me), 371, 328, 327, 285, 235, 207, 187, 175, 147.

2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl 1-Deoxy-3-*epi*-1-iodo-3,4-isopropylidene-α-D-fructofuranoside (22) and 2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl 1-Deoxy-3-*epi*-1-iodo-3,4-isopropylidene-β-D-fructofuranoside (23). Treatment of the α-vinyl ether **21b** (50 mg) with Bu_4NF in THF (1.0 M; 1.5 mL) followed by ^{t}BuOK (35 mg) and I_2 (55 mg), as described above for **18b**, gave the disaccharides **22** and **23** (24 mg, 65%) as a 2:1 mixture, after chromatography on silica (eluant hexanes/Et_2O 1:4): $[\alpha]_D$ +86° (c = 1.15, $CHCl_3$); TLC R_f 0.5 (silica, hexanes/Et_2O 1:4): IR (neat) 1460, 1385, 1260, 1220, 1200, 1170, 1110 cm^{-1}; mass spectrum (EI), m/e 547 (M^+ - Me), 371, 343, 327, 285, 235, 207, 187, 175, 157, 147, 115, 101. Anal. Calcd for $C_{20}H_{35}IO_{10}$: C, 42.71; H, 6.27. Found: C, 42.74; H, 6.17. The two anomers respectively showed the following NMR data. α-Anomer **22**: ^1H NMR (400 MHz, C_6D_6) δ 5.45 (d, 1 H, J = 3.6 Hz), 4.69 (d, 1 H, J = 8.0 Hz), 4.62-4.58 (m, 1 H), 4.49 (dd, 1 H, J = 4.8, 8.0 Hz), 4.27-4.22 (m, 1 H), 3.90 (dd, 1 H, J = 9.4 Hz, J = 9.4 Hz), 3.70-3.44 (m, 2 H), 3.65 (s, 3 H), 3.56 (s, 3 H), 3.54 (d, 1 H, J = 11.2 Hz), 3.40 (d, 1 H, J = 11.2 Hz), 3.37-3.08 (m, 4 H), 3.19 (s, 3 H), 3.15 (s, 3 H), 3.04 (s, 3 H), 1.74 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.8, 103.7, 90.1, 85.8, 82.9, 81.9, 81.7, 81.1, 78.8, 72.3, 71.3, 70.7, 60.7, 60.4, 59.6, 59.2, 58.6, 26.7, 26.4, 8.2. β-Anomer **23**: ^1H NMR (400 MHz, C_6D_6) δ 5.46 (d, 1 H, J = 3.6 Hz), 4.98 (d, 1 H, J = 5.6 Hz), 4.93 (dd, 1 H, J = 5.0, 5.6 Hz), 4.36-4.31 (m, 1 H), 4.23-4.18 (m, 1 H), 3.84 (dd, 1 H, J = 9.2 Hz, J = 9.2 Hz), 3.70-3.08 (m, 8 H), 3.63 (s, 3 H), 3.49 (s, 3 H), 3.25 (s, 3 H), 3.16 (s, 3 H), 3.01 (s, 3 H), 1.35 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.6, 108.2, 91.1, 84.6, 83.6, 83.2, 81.7, 81.5, 79.2, 72.6, 71.1, 60.8, 59.2, 58.7, 27.0, 25.4, 5.9.

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Supplementary Material Available: Full experimental details describing the preparation and authentication of all new compounds (40 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis with α,β-Bis[(methoxymethyl)oxy] Ketones. Enantioselective Total Synthesis of Natural (+)-Indolizidine 195B (Bicyclic Gephyrotoxin 195B) and (-)-Pinidine and Their Enantiomers from a Common Chiral Synthon

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Abstract: The first enantioselective total synthesis of naturally occurring (+)-indolizidine 195B (bicyclic gephyrotoxin 195B) and (-)-pinidine and their enantiomers has been achieved starting from 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threitol as a single and common chiral synthon, readily available from L-tartaric acid. This synthesis establishes the absolute stereochemistry of (+)-indolizidine 195B as 3*S*,5*S*,9*S*. The strategy for the synthesis of the alkaloids in both enantiomeric forms is based on the process involving a combination of the creation of new stereogenic centers by 1,2-asymmetric induction and destruction of the original chirality inducing group, i.e., *threo*-bis(methoxymethyl) ether. Actually, these processes consist of highly diastereoselective hydride addition to α,β-bis(methoxymethyl)oxy ketones via chelation or nonchelation control by using a variety of borohydride reagents and stereospecific transformation of *threo*-vicinal diols into both *E* and *Z* olefins.

Stereocontrolled addition of hydride from metal hydride reagents to acyclic ketones has been widely used for the preparation of optically active acyclic secondary alcohols. One of the most widely studied processes for this is the enantioselective hydride addition to prochiral ketones by metal hydride reagents modified with chiral ligands (reagent control).[1] Alternative efforts have been focused on the diastereoselective hydride addition of achiral metal hydride reagents (1,2- or 1,3-asymmetric induction) to ketone substrates having a stereogenic center or linked with a chiral auxiliary (substrate control).[2] Often there is a need for the preparation of molecules in both enantiomeric forms for studies, for example, on their physical or biological properties. In obtaining both enantiomers of a molecule by the methods for asymmetric induction mentioned above, both enantiomers of chiral reagents, chiral building blocks, or chiral auxiliaries are required. In many cases, however, one of the enantiomers of the chiral agents is not readily accessible from commercial sources or may have a high cost (for example, D- vs. L-sugars and L- vs. D-amino acids). To

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