and 6.70 (pair of s due to rotamers, 1 H), 5.85–5.40 (m, 2 H), 4.48 and 4.37 (pair of m due to rotamers, 2 H), 3.35 (s, 2 H).

8f: IR (neat) 2940, 2860, 1720, 1670, 1600, 1390, 1360, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.10 (m, 5 H), 6.60 and 6.54 (pair of s due to rotamers, 1 H), 5.83 (d, 1 H), 5.69–5.52 (m, 1 H), 4.51 and 4.37 (pair of dd due to rotamers, 2 H, J = 4 Hz and J = 2 Hz), 1.92 (d, 2 H), 1.80–1.60 (m, 5 H), 1.45–0.80 (m, 6 H).

Acknowledgment. We thank the National Institutes of Health (Grant GM 34442) for financial support of this research. The 300-MHz NMR spectra were recorded on a Varian XL-300 instrument purchased with funds provided, in part, by the National Science Foundation (Grant CHE-8417529). N.B.M. also thanks the American Chemical Society for a Division of Organic Chemistry Graduate Fellowship sponsored by Pfizer, Inc.

Registry No. **4**, 79328-86-2; **5**, 105335-77-1; **6**, 105335-78-2; **7**, 105335-79-3; **8a**, 105335-80-6; **8b**, 105335-81-7; **8c**, 105371-69-5; **8d**, 105371-70-8; **8e**, 105335-82-8; **8f**, 105335-83-9; $PhCH_2Cl$, 100-44-7; *n*-BuCl, 109-69-3; MeCl, 74-87-3; EtCl, 75-00-3; PhCl, 108-90-7; c-$C_6H_{11}Cl$, 542-18-7.

1-Methylene Sugars as *C*-Glycoside Precursors†

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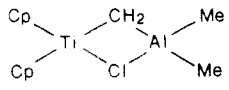
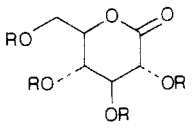
Received August 7, 1986

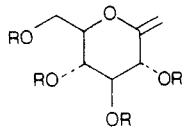
Carbon–carbon bond-forming reactions at the anomeric position of carbohydrates have attracted considerable attention because of the increase interest in the use of simple sugars as chiral synthons[1] for the synthesis of complex natural products including biologically active *C*-glycosides.[2] In a general program directed at the applications of organometallic reagents in carbohydrate chemistry, we have been interested in the reactions of readily available sugar lactones with Tebbe's reagent[3,4] (**1**).



1 (Cp = cyclopentadienyl)

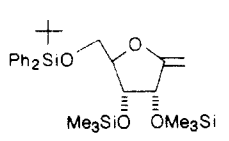


2a, R = CH_2Ph
b, R = $SiMe_3$



3a, R = CH_2Ph
b, R = $SiMe_3$
c, R = $SiEt_3$
d, R = H

For example, 2,3,4,6-tetra-*O*-benzylglucono-1,5-lactone **2a**[5] reacts with **1** at −45 to 0 °C to give the corresponding *exo*-methylene derivative **3a** in 82% yield. Similarly, compounds **3b**, **3c**, **4**, and **5** were prepared in 60–80% yield.



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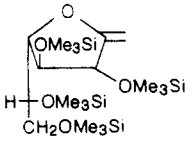

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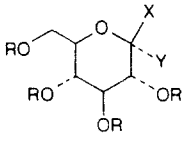


6a, X = H, Y = CH_2OH, R = CH_2Ph
b, X = CH_2OH, Y = H, R = CH_2Ph
c, X = CH_2OCH_2Ph, Y = H, R = CH_2Ph

Since the trimethylsilyl protecting groups are easily removed by fluoride treatment, this scheme constitutes an exceptionally facile method for the synthesis of the corresponding deprotected sugars. For comparison, the reported synthesis of "1-methylene-D-glucose" (**3d**) involves nine steps.[9]

These *exo*-methylene sugars are useful precursors for *C*-glycoside synthesis. For example, hydroboration of **3a** using 9-BBN gives exclusively the β-D-*C*-glucopyranosyl derivative **6b**[10] in 94% yield. However, hydroboration with borane–THF complex yields a 1:1 mixture of α- and β-hydroxymethyl glucosides **6a** and **6b**. The stereochemistry of **6a** (and hence of **6b**) was conclusively established by comparison of physical properties with those of an authentic sample.[11] The structure of **6b** was deduced from the 360-MHz ^1H NMR spectrum of its benzyl ether **6c**. In **6c** only three sets of benzyl protons are observed because of the presence of a plane of symmetry. Also, the signal at δ 3.46 (ddd, J = 9 Hz, 4 Hz, 2 Hz) accounts for 2 H corresponding to H_2 and H_6 (see the Experimental Section). The chemical shifts of H_6 in **6a** and **6b** are also indicative of the anomeric stereochemistry at C_2. In **6a**, it is at δ 4.20 and in **6b** at δ 3.90. The axial hydroxymethyl group induces the downfield shift of H_6 in **6a**.

The lack of reactivity of structurally related enol ethers in hetero Diels–Alder reactions has been well documented.[4b] However, they undergo very facile 1,3-dipolar cycloadditions. For example, **3a** reacts with carbomethoxy nitrile oxide[12] to give stereospecifically the isoxazoline **7**. An important application of this methodology may be in the synthesis of extended sugar derivatives like C-linked polysaccharides. As a model for the synthesis of tunicamycin,[13] we have carried out the stoichiometric dipolar cycloaddition of **3a** with a ribose-derived nitrile oxide[14] **8**. Under the typical Mukaiyama conditions[15] (PhNCO, Et_3N), a single isoxazoline[16] **9** is formed in 78% isolated

† Contribution No. 4088.

(1) (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1983. (b) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161.

(2) See for example: (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Reed, L. A.; Ito, Y.; Masamune, S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 6468 and references cited therein. (c) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622.

(3) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1977**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **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.

(4) (a) While our study was in progress another report appeared in the literature on the use of Tebbe's reagent in carbohydrate chemistry: Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395. (b) For other synthetic applications of methylene sugar derivatives see also: Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303.

(5) Prepared by Swern oxidation (Me_2SO/oxalyl chloride) of the corresponding free sugar.

(6) Lancelin, J.-M.; Pougny, J.-R.; Sinay, P. *Carbohydr. Res.* **1985**, *136*, 369. This paper also discusses another approach to 1-methylene sugars that involves several steps.

(7) Triethylsilyl derivatives are hydrolytically more stable and hence easier to handle.

(8) Horton, D.; Priebe, W. *Carbohydr. Res.* **1981**, *94*, 27.

(9) Hehre, E. J.; Brewer, C. F.; Uchiyama, T.; Schlesselmann, P.; Lehmann, J. *Biochemistry* **1980**, *19*, 3557.

(10) (a) For a more circuitous synthesis of similar compounds, see ref 2b. (b) See also: Vasella, A.; Baumberger, F. *Helv. Chim. Acta* **1983**, *66*, 2210.

(11) Pougny, J.-R.; Nassr, M. A. M.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375.

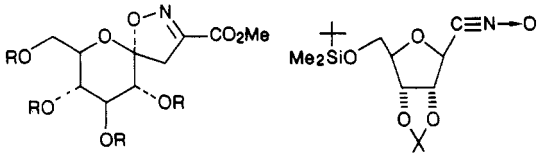
(12) Skinner, G. S. *J. Am. Chem. Soc.* **1924**, *46*, 731.

(13) For a synthesis and leading references see: Suami, T.; Sasai, H.; Matsuno, K.; Suzuki, N.; Fukuda, Y.; Sakanaka, O. *Tetrahedron Lett.* **1984**, *25*, 4533.

(14) Kozikowski, A. P.; Goldstein, S. *J. Org. Chem.* **1983**, *48*, 1139.

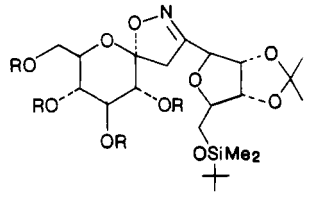
(15) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

0022-3263/86/1951-5458$01.50/0



7, R=CH_2Ph

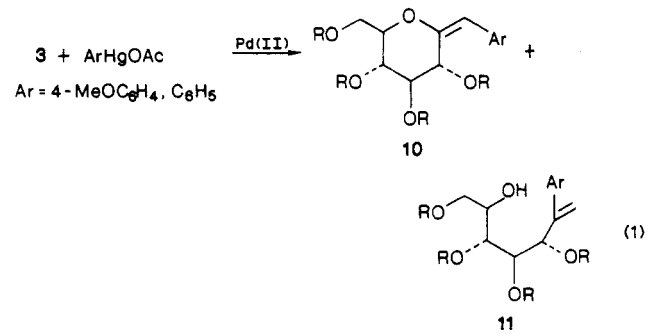
8



9

yield! The remarkably high stereoselectivity is in accord with the steric approach control, in which the rather bulky nitrile oxide attacks the α-face of the methylene sugar. Note that the stereochemical control is similar to the hydroboration (vide supra) of **3a** with bulky 9-BBN to give **6b** exclusively.

A potentially useful reaction for the synthesis of aromatic *C*-glycosides is illustrated by the reaction of **3a** with arylmercuric acetate in the presence of $PdCl_2$[17] (eq 1). The

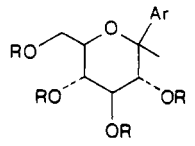


(1)

10

11

intermediate σ-palladium species undergoes β-elimination of hydride (to give **10**)[18] or alkoxide (to give **11**) depending on the regiochemistry of the addition. The acyclic derivative can be cyclized[6] to form an aryl glycoside. For example, treatment of **11** with mercuric trifluoroacetate followed by sodium borohydride gives **12**.[18]



12

Application of 1-methylene sugars for the synthesis of natural and unnatural ketoses, higher sugars, 3-deoxy-2-glyculosonates (KDO, for e.g.), and 2-amino sugars will be the subject of future reports.

Experimental Section

Infrared spectra were determined on a Nicolet Model 7199 FT spectrometer. NMR spectra were obtained on a Varian EM-390, IBM NR 80, or Nicolet 360WB spectrometer and were recorded in $CDCl_3$ with tetramethylsilane as the standard. All reagents were purified prior to use, and the reactions were carried out under nitrogen or argon atmosphere. Tebbe's reagent prepared according to ref 3a was stored in the freezer compartment of a refrigerator and was used as needed as a solution in dry toluene prepared inside a good glovebag. Chromatography on silica gel was performed according to the technique reported by Still et al.[19] All melting points are uncorrected.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (3a). To a solution of 2.023 g (3.755 mmol) of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone in 7 mL of toluene, 3 mL of THF, and 50 μL of pyridine was added 1.175 g (4.13 mmol) of Tebbe's reagent dissolved in 10 mL of dry toluene at −45 °C. The mixture was stirred at −40 to −45 °C for 1 h and then at 0 °C for 30 min. It was then cooled to −10 to −15 °C, and 1.3 mL of 15% sodium hydroxide was added. The cold bath was removed, and the reaction mixture was diluted with 200 mL of ether. Stirring was continued for 10 min, and the inorganic residue was removed by filtration through Celite and anhydrous $MgSO_4$. The filter cake was washed with excess ether, and the product was chromatographed on silica with 40–50% ether/hexane as the solvent: yield 1.654 g (82%); mp (hexane) 68–68.5 °C (lit.[6] mp 65 °C); $[\alpha]_D$ 60.0 ± 0.8° (*c* 1, CH_2Cl_2) [lit. 45.5° (*c* 0.33, $CHCl_3$)]; IR (KBr) 3090, 3030, 2950, 2920, 2870, 1660, 1585, 1500, 1090, 745, 695 cm^{-1}; ^1H NMR (360 MHz) δ 3.66–3.80 (m, 5 H), 3.95 (d, J = 8 Hz, 1 H), 4.48–4.90 (m, 10 H), 7.15 (m, 2 H), 7.30 (m, 18 H). Anal. C, H.

2,3-Bis-*O*-(trimethylsilyl)-5-*O*-(*tert*-butyldiphenylsilyl)-D-ribofurano-1,4-lactone. A flame-dried flask was charged with 1.158 g (3.00 mmol) of 5-*O*-(*tert*-butyldiphenylsilyl)-D-ribono-1,4-lactone in 5 mL of pyridine, 1.33 mL (6.0 mmol) of hexamethyldisilazane, and 0.190 mL (1.50 mmol) of trimethylsilyl chloride. The mixture was stirred for 15 min, and then 100 mL of pentane was added followed by 20 mL of saturated KH_2PO_4 and 10 mL of water. The organic layer was separated, and the aqueous layer was extracted with pentane (100 mL × 3). The combined pentane extract was washed with saturated $NaHCO_3$, dried, and concentrated. The last traces of water were removed by azeotroping with toluene: yield 1.535 g (97%); ^1H NMR (360 MHz) δ 0.11 (s, 9 H), 0.20 (s, 9 H), 1.05 (s, 9 H), 3.75 (dd, J = 11 Hz, 2 Hz, 1 H), 3.87 (dd, J = 11 Hz, 2 Hz, 1 H), 4.30 (m, 2 H), 4.65 (d, J = 5 Hz, 1 H), 7.40 (m, 6 H), 7.63 (m, 4 H). This product was used as such for the subsequent step.

2,5-Anhydro-5-*O*-(*tert*-butyldiphenylsilyl)-1-deoxy-3,4-bis-*O*-(trimethylsilyl)-D-*ribo*-hex-1-enitol (4). A solution of 0.790 g (2.78 mmol) of Tebbe's reagent in 7 mL of dry toluene was prepared inside a glovebag. The reaction flask was charged with 1.476 g (2.78 mmol) of the sugar in 6 mL of dry toluene, 1.5 mL of dry THF, and 40 μL of pyridine. The mixture was cooled to −40 °C, and the Tebbe's reagent solution was added dropwise to the mixture. The reaction was stirred at −40 °C for 30 min and then at 0 °C for 25 min. It was then cooled to −10 to −20 °C, and 0.60 mL of 10% aqueous NaOH was added. The mixture was stirred for 30 min, and 20 mL of water and 100 mL of pentane were added. The organic layer was separated, and the aqueous layer was extracted with pentane (100 mL × 3). The pentane extracts were combined and then washed with 10% KH_2PO_4 and water. It was then dried and concentrated. Flash column chromatography using 10% ether/hexane as solvent yielded 1.033 g (70%) of the product: ^1H NMR (80 MHz) δ 0.08 (2 s, 18 H), 0.90 (s, 9 H), 3.63 (t, J = 2.7 Hz, 2 H), 3.90 (t, J = 1.3 Hz, 1 H), 4.03 (m, 2 H), 4.20 (m, 1 H), 4.37 (m, 1 H), 7.10–7.65 (m, 10 H).

2,6-Anhydro-1-deoxy-3,4,5,7-tetrakis-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol (3b). With 1.471 g of 2,3,4,6-tetrakis-*O*-(trimethylsilyl)D-glucono-1,5-lactone[8] and 0.914 g of Tebbe's reagent and by the above procedure, 0.785 g (54%) of **3b** was prepared: $[\alpha]_D$ 50.80 ± 0.8° (*c* 1, CH_2Cl_2); IR (KBr) 2960, 2900, 1660, 1250, 1090, 840, 750 cm^{-1}; ^1H NMR (360 MHz) δ 0.13 (s, 9 H), 0.16 (s, 9 H), 0.168 (s, 9 H), 0.172 (s, 9 H), 3.44 (m, 2 H), 3.60 (dd, J 10 Hz, 8 Hz, 1 H), 3.70–3.86 (m, 3 H), 4.46 (d, J = 2 Hz, 1 H), 4.59 (d, J = 2 Hz, 1 H); HRMS for $C_{19}H_{44}O_5Si_4$, calcd 464.2265, found 464.2264 (M^+).

2,5-Anhydro-1-deoxy-3,4,6,7-tetrakis-*O*-(trimethylsilyl)-D-*galacto*-hept-1-enitol (5). The title compound was prepared according to the procedure reported in the preious experiment in 67.7% yield: $[\alpha]_D$ −13.6 ± 0.8° (*c* 1, CH_2Cl_2); ^1H NMR (360 MHz) δ 0.09 (s, 9 H), 0.11 (s, 9 H), 0.14 (s, 9 H), 0.17 (s, 9 H), 3.60 (dd, J = 6 Hz, 4 Hz, 2 H), 3.84 (m, 1 H), 3.95 (m, 2 H), 4.13 (t,

(16) The structures of **7** and **9** established by 2D NOE experiments (see the Experimental Section).

(17) For leading references see: Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1983**, *48*, 2870.

(18) The stereochemistry of **10** and **12** has not been established.

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

J = 6 Hz, 1 H), 4.29 (t, J = 2 Hz, 1 H), 4.36 (d, t, J = 2 Hz, 6 Hz, 1 H); HRMS, for $C_{19}H_{44}O_5Si_4$, calcd 464.2286, found 464.2261 (M^+).

2,6-Anhydro-1-deoxy-D-*gluco*-hept-1-enitol (3d). To a solution of 0.35 g (0.75 mmol) of the tetrakis(trimethylsilyl) derivative was added 4.5 mL of a 1 M solution of tetra-*n*-butylammonium fluoride, and the mixture was stirred at room temperature for 3 h. The solvent was stripped on the rotary evaporator and then on the high-vacuum pump. The product was isolated as an oil by chromatography on silica gel using 20% methanol/ethyl acetate as solvent: yield 0.110 g; ^{1}H NMR (360 MHz, D_2O) δ 3.26 (t, J = 9 Hz, 1 H), 3.32 (dt, J = 9 Hz, 3 Hz, 1 H); 3.41 (t, J = 9 Hz, 1 H), 3.62 (dd, J = 13 Hz, 5 Hz, 1 H), 3.79 (m, 2 H), 4.60 (t, J = 2 Hz, 1 H), 4.64 (t, 1 H); ^{13}C NMR (D_2O) δ 60.781, 69.307, 70.605, 76.769, 81.217, 94.193, 158.859.

2,3,4,6-Tetrakis-*O*-(triethylsilyl)-D-glucopyrano-1,5-lactone. A flame-dried flask was charged with 1.78 g (10.0 mmol) of D-glucono-1,5-lactone in 10 mL of pyridine, 10 mL of dry CH_2Cl_2, and 1.74 mL of diisopropylethylamine. To this was added 7.39 mL (44.0 mmol) of distilled triethylsilyl chloride. The mixture was stoppered well and was subsequently stirred for 24 h at room temperature. It was then added to 100 mL of pentane, 30 mL of saturated KH_2PO_4, and 10 mL of water. The product was isolated by repeated extraction into pentane. The combined organic layer was washed with saturated $NaHCO_3$ (~50 mL) and water (~50 mL). It was subsequently dried with anhydrous $MgSO_4$ and then concentrated to give 5.94 g (94%) of the product: ^{1}H NMR (80 MHz) δ 0.35–1.10 (m, 60 H), 3.65–4.20 (m, 5 H), 4.50 (m, 1 H). A fraction of the product was sublimed on the Kugelrohr oven at 160 °C (0.032 mm of mercury pressure). This pure product was used for the subsequent methylenation: HRMS, for $C_{28}H_{61}O_6Si_4$, calcd 605.3545, found 605.3561 ($M^+ - C_2H_5$).

2,6-Anhydro-1-deoxy-3,4,5,7-tetrakis-*O*-(triethylsilyl)-D-*gluco*-hept-1-enitol (3c). A three-necked flask fitted with an addition funnel and thermocouple was thoroughly flame dried and then was charged with 1.818 g (2.80 mmol) of the tetrakis(triethylsilyl) lactone in 2 mL of THF, 6 mL of toluene, and 100 μL of pyridine. The dropping funnel was charged with 0.876 g of Tebbe's reagent in 6 mL of dry toluene. The contents of the flask were cooled to −40 °C, and the reagent was dropped in. The dropping funnel was washed down with 2 mL more of dry toluene, and the mixture was stirred at −40 to −10 °C for 1.5 h. At −10 °C, 2 mL of 10% NaOH solution was added and stirring was continued for 1 min more. To this were added 500 mL of pentane and 50 mL of water. The organic layer was separated, and it was then filtered through a pad of Celite and $MgSO_4$. Concentration and column chromatography on silica gel using 5% ether/hexane yielded 1.561 (86%) of the product: ^{1}H NMR (360 MHz) δ 0.63 (m, 24 H), 0.94 (m, 36 H), 3.65–3.78 (m, 3 H), 3.85 (dd, J = 12 Hz, 1 H), 3.98 (d, J = 4 Hz, 1 H), 4.10 (s br, 1 H), 4.10 (m, 1 H), 4.37 (s br, 1 H).

Hydroboration of 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (6a, 6b). (a) BH_3–THF: To a solution of 0.134 g of **3a** dissolved in 2 mL of THF was added 0.5 mL of a 1 M solution of borane in THF at 0 °C. The mixture was stirred for 2 h at 0 °C → room temperature. To the reaction mixture was added 0.50 mL of 30% aqueous H_2O_2, and stirring was continued for 30 min. Water (10 mL) and ether (20 mL) were added successively, and the product was extracted with ether. The combined ether extracts were washed with saturated NaCl, dried, and concentrated. The product was purified by column chromatography on silica gel using 30% ethyl acetate in hexane as the eluant; yield 0.110 g (79%). It was ascertained as a 1:1 mixture of α- and β-*C*-(hydroxymethyl)-1-deoxy-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides by comparison of TLC and high-field (360-MHz) ^{1}H NMR with those of authentic samples whose preparation is described below.

(b) 9-BBN: To a solution of 0.13 g (0.25 mmol) of **3a** dissolved in 2 mL of anhydrous THF was added 0.55 mL of 1 M 9-BBN solution in THF at 0 °C. The mixture was stirred at 0 °C and warmed to room temperature over a period of 3 h. One milliliter of 30% H_2O_2 was added followed by 0.50 mL of 5% KOH. The product was extracted into ether. The usual workup followed by column chromatography yielded 0.134 g (94%) of *C*-(hydroxymethyl)-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (**6b**): mp 95–95.5 °C (lit.[10b] mp 93–93.5 °C); $[\alpha]^{22}_D$ +16.7 ± 2° (*c* 0.33, MeOH) [lit.[10b] +8.6° (c 1.1, $CHCl_3$)]; IR 3420 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.92 (t, J = 6 Hz, exch D_2O, 1 H), 3.36 (ddd, J = 10 Hz, 5 Hz, 2 Hz, 1 H), 3.49 (ddd, J = 9 Hz, 3 Hz, 2 Hz, 1 H), 3.60–3.82 (m, 6 H), 3.90 (m, 1 H), 4.50–4.92 (4 AB q, 8 H), 7.10–7.35 (m, 20 H). Anal. Calcd: C, 75.77; H, 6.91. Found: C, 75.15; H, 6.95. This compound corresponded to the faster moving component of the diborane reduction. The slower moving compound is identical with an authentic sample of the α-*C*-glycoside (2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-*Glycero*-D-gulol) prepared according to Sinay.[11]

Benzylation of 6b. To a solution of 10 mg of **6b** dissolved in 2 mL of DMF was added 15 mg of mineral oil free sodium hydride. The mixture was cooled to 0 °C, 20 μL of benzyl bromide was added, and the mixture was stirred at 0° → room temperature for 2 h. One milliliter of methanol was added, and the solvent was evaporated on the rotary and then on the pump. The product was isolated by preparative TLC on silica gel plate using 20% ethyl acetate/hexane as the solvent: ^{1}H NMR (360 MHz) δ 3.46 (ddd, J = 9 Hz, 4 Hz, 2 Hz, 2 H, H_2, H_6), 3.61 (t, J = 9 Hz, 2 H, H_3, H_5), 3.65–3.80 (m, 5 H), 4.54–4.85 (3 AB q, 8 H), 4.90 (s, 2 H, C_4-OCH_2Ph), 7.16 (m, 4 H), 7.25–7.37 (m, 21 H).

Addition of Carbomethoxy Nitrile Oxide to 3a. To a solution of 0.27 g (0.50 mmol) of **3a** and 0.14 g (1.00 mmol) of methyl chlorooximinoacetate[12] in 5 mL of dry CH_2Cl_2 at 0 °C was added 0.35 mL (2.50 mmol) of triethylamine dissolved in 5 mL of CH_2Cl_2. The mixture was warmed to room temperature and was subsequently stirred for 18 h. The solvents were removed on the rotary, and the product **7** was isolated by column chromatography on silica; $[\alpha]^{25}_D$ 18.8 ± 0.8 (*c* 0.5, MeOH); IR (KBr) 3080, 3060, 3030, 2900, 2860, 1730, 1590, 1500, 1050, 1100, 750, 695 cm^{-1}; ^{1}H NMR (360 MHz) δ 3.00 (AB q, J_{AB} = 18 Hz, ν_{AB} = 21 Hz, 2 H), 3.56 (dd, J = 11 Hz, 2 Hz, 1 H), 3.68 (d, J = 10 Hz, 1 H), 3.75 (dd, J = 11 Hz, 3 Hz, 1 H), 3.81 (t, J = 9 Hz, 1 H), 3.86 (s, 3 H), 4.04 (d, m, J = 10 Hz, 1 H), 4.11 (t, J = 10 Hz, 1 H), 4.40–5.00 (4 AB q, 8 H); HRMS, calcd 546.2127, found 546.2126 ($M^+ - C_7H_7$).

Addition of β-D-Ribofuranosyl Nitrile Oxide to 3a. To a solution of 0.68 g (1.26 mmol) of **3a** and 0.274 mL of phenyl isocyanate in 1.5 mL of 1,2-dichloroethane was added 0.400 g (1.15 mmol) of 2,5-anhydro-1-deoxy-6-*O*-(dimethylbutylsilyl)-3,4-*O*-isopropylidene-1-nitro-D-allitol[14] and 20 μL of triethylamine dissolved in 1 mL of 1,2-dichloromethane. The syringe was further washed down with 1 mL more of dichloroethane, and the mixture was stirred at room temperature for 3 days. The precipitated diphenylurea was filtered, and the solid was washed with excess methylene chloride. Chromatography on silica gel using 30% ether/hexane as the solvent yielded 0.781 g (78%) of the product (**9**) in addition to 0.073 g of the starting methylene sugar. In the 2D NOE spectrum the lack of any signal enhancements of the pyranose protons upon irradiation of the methylene protons of the oxazoline clearly indicate an *exo*-CH_2 structure for this adduct. This is also consistent with the reagent approach control observed in the hydroboration of the enol ether with a bulky reagent, viz. 9-BBN. The deshielded position of H_{10} (pyranosyl C-5 hydrogen) at δ 4.30 is also indicative of the *exo*-CH_2 structure. The deshielding by the axial oxygen of the isoxazoline is to be expected. (For similar situations see ref 4b and the relative chemical shifts of H_6 in **6a** and **6b**): IR (KBr) 3080, 3060, 3030, 2980, 2950, 2920, 2850, 1600, 1585, 1555, 1250, 835 cm^{-1}; ^{1}H NMR (360 MHz, C_6D_6; hydrogens sequentially numbered starting with the furanosyl C-5 hydrogen as H_1) δ 0.02 (s, 3 H), 0.05 (s, 3 H), 0.96 (s, 9 H), 1.19 (s, 3 H), 1.48 s, 3 H), 3.04 (AB q, J_{AB} = 18 Hz, $\Delta\nu_{AB}$ = 21 Hz, 2 H, H_6's), 3.56 (dd, J = 10 Hz, 2 Hz, 1 H, H_{11}), 3.60 (d, J = 5.0 Hz, 2 H, H_1's) 3.62 (d, J = 10 Hz, 1 H, H_7), 3.75 (dd, J = 11 Hz, 3 Hz, 1 H, H_{11}'s), 4.09 (t, J = 10 Hz, 1 H, H_9), 4.25 (ddd, J = 5 Hz, 5 Hz, 3 Hz, 1 H, H_2), 4.30 (m, 2 H, H_{10}), 4.31 (t, J = 10 Hz, 1 H, H_8), 4.46 (AB q, 2 H, $PhCH_2$), 4.67 (dd, J = 6 Hz, 3 Hz, 1 H, H_3), 4.70–5.00 (3 AB q, 6 H, PhCH_2), 5.14 (dd, J = 6 Hz, 3 Hz, 1 H, H_4), 4.77 (d, J = 3 Hz, 1 H, H_5), 7.00–7.50 (m, 20 H, aromatic); FABMS or EIMS, parent ion not observed.

Addition of Phenylmercuric Acetate to 3a in the Presence of LiCl and Pd(OAc)$_2$. A mixture of 0.27 g (0.50 mmol) of **3a**, 0.135 g (0.40 mmol) of phenylmercuric acetate, 0.034 g (0.80 mmol) of anhydrous lithium chloride, and 0.090 g (0.40 mmol) of Pd(OAc)$_2$ in 3 mL of dry acetonitrile was stirred at room temperature for 4 days. A slow stream of H_2S was passed through the reaction mixture, and the precipitated solid was removed. The solid was

washed with CH_2Cl_2 and the combined organic layers were concentrated. Column chromatography on silica gel using 10% ether/hexane yielded two products identified as 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-phenyl-D-*gluco*-hept-1-enitol (**10**, Ar = Ph) and 3,4,5,7-tetra-*O*-benzyl-2-phenyl-D-*gluco*-hept-1-enitol (**11**, Ar = Ph).

10 (Ar = Ph): ^{1}H NMR (360 MHz) δ 3.75–3.90 (m, 4 H), 4.02 (d br, J = 5 Hz, 1 H), 4.12 (ddd, J = 10 Hz, 5 Hz, 2 Hz, 1 H), 4.50–4.81 (4 AB q, ArCH_2), 5.72 (s, br, 1 H), 7.10–7.40 (m, aromatic H), 7.69 (dm, J = 7 Hz, 2 H).

11 (Ar = Ph): ^{1}H NMR (360 MHz) inter alia δ 5.43 (dd, J = 12 Hz, 4 Hz, 1 H), 6.03 (d, J = 12 Hz, 1 H).

Addition of (4-Methoxyphenyl)mercuric Acetate to 3a. By the procedure described above the corresponding 4-methoxy adducts **10** and **11** were prepared in 13 and 49% yields, respectively.

10 (Ar = 4-OMeC$_6$H$_4$): ^{1}H NMR (360 MHz) δ 3.76 (s, 3 H), 3.75–3.83 (m, 3 H), 3.87 (dd, J = 11 Hz, 2 Hz, 1 H), 4.02 (d br, J = 5 Hz, 1 H), 4.06 (m, 1 H), 4.50–4.82 (m, 8 H), 5.70 (s br, 1 H), 6.76 nd, J = 9 Hz, 2 H), 7.15–7.40 (m, aromatic H), 7.64 (d, J = 9 Hz, 2 H); MS, M$^+$ ion not observed.

11 (Ar = 4-OMeC$_6$H$_4$): ^{1}H NMR (360 MHz) δ 3.00 (d, J = 5 Hz, 1 H), 3.48 (d, AB q, J = 5 Hz, J_{AB} = 10 Hz, 2 H), 3.59 (dd, J = 6 Hz, 3 Hz, 1 H), 3.76 (s, 3 H), 3.77 (m, 1 H), 3.92 (m br, 1 H), 4.19–4.80 (m, 9 H), 5.36 (s br, 1 H), 5.46 (d, J = 2 Hz, 1 H), 6.77 (dm, J = 8 Hz, 2 H), 7.10 (m, 2 H), 7.20–7.40 (m, aromatic); MS, M$^+$ ion not observed.

Addition of (4-Methoxyphenyl)mercuric Acetate to 3c. With **3c** and (4-methoxyphenyl)mercuric acetate the adduct **10** (R = TES, Ar = 4-OMeC$_6$H$_4$) was prepared. Isolation of the open-chain isomer **11** (R = TES, Ar = 4-OMeC$_6$H$_4$) was presumably made difficult because of its hydrolytic instability: ^{1}H NMR (360 MHz) δ 0.65 (m, 24 H), 0.95 (m, 31 H), 3.74 (dd, J = 9 Hz, 2 Hz, 1 H), 3.78–3.87 (m, 2 H), 3.81 (s, 3 H), 3.98 (dd, J = 11 Hz, 2 Hz, 1 H), 4.05 (d, J = 4 Hz, 1 H), 4.32 (ddd, J = 9 Hz, 5 Hz, 2 Hz, 1 H), 5.23 (s, 1 H), 6.81 (d, m, J = 8 Hz, 1 H), 7.60 (dm, J = 8 Hz, 1 H).

Cyclization of 3,4,5,7-Tetra-*O*-benzyl-2-(4-methoxyphenyl)-D-*gluco*-hept-1-enitol (11, R = CH$_2$C$_6$H$_5$, Ar = 4-MeOC$_6$H$_4$). A mixture of 0.123 g of the enitol **11** and 0.090 g of mercuric trifluoroacetate in 3 mL of THF was stirred at 0 °C for 90 min. A check by TLC indicated the reaction to be complete and exceptionally clean. The solution was adjusted to pH 10 with 1 N NaOH, and 0.6 mL of 1 M sodium borohydride in 1 N NaOH was added to the reaction mixture. The solution was stirred for another 1 h at 0 °C, neutralized with 1 M acetic acid, and filtered. The product was extracted into ether. Concentration of the ether extract followed by filtration through a short bed of silica gel yielded the expected product (**12**) with the following characteristic ^{1}H NMR spectrum: ^{1}H NMR (360 MHz) δ 1.62 (s, 3 H), 3.40 (d, J = 10 Hz, 1 H), 3.70–3.90 (m, 5 H), 3.78 (s, 3 H), 4.40–4.95 (m, 8 H), 6.85 (dm, J = 9 Hz, 2 H), 7.07 (m, 2 H), 7.15–7.40 (m, aromatic), 7.52 (d, J = 9 Hz, 1 H).

Carbonyl Reduction by Alcohol Dehydrogenase. A Structure–Activity Study†

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Received June 3, 1986

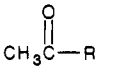
Alcohol dehydrogenase (ADH) catalyzes the oxidation reduction of ethanol as well as many other alcohols and carbonyl compounds:

$$CH_3CH_2OH + NAD \xrightarrow{\text{alcohol dehydrogenase}} CH_3CHO + NADH + H^+ \quad (1)$$

Since the reaction is stereoselective, it has been used to reduce various carbonyl compounds for preparative purposes.[1-3] Although there has been discussion of the structural features that affect the rate of reduction of carbonyl compounds, a large enough data set run under uniform conditions for correlation analysis with substituent constants has not been available. The recent publication by Keinan et al.[3] supplies a good set for analysis.

In undertaking the analysis of their data, we have been guided by our quantitative structure–activity relationships (QSAR) for the inhibition of ADH by a wide variety of inhibitors[4-6] and by a molecular graphics analysis[6] of ADH based on a model constructed from the X-ray crystallographic coordinates of a pyrazole bound to the enzyme.

The active site of ADH is a long narrow cavelike structure with a Zn atom at one end to which electron-rich species may bind. It is to the Zn that the oxygen binds, with the hydrophobic portion of carbonyl compound binding in the long hydrophobic pocket. In the binding of various inhibitors it was found that the hydrophobic and electronic effects of substituents played an important role in the enzyme–ligand interaction. Substituents increasing the electron density on oxygen or nitrogen binding to the Zn increased inhibitor potency. Also an increase in hydrophobicity increased binding. For the present data set in Table I we would also expect steric effects of substituents to play a role in the reduction of the carbonyl group. Hence, one would anticipate having to disentangle electronic, steric, and hydrophobic substituent effects. Normally one likes to have at least five data points/variable in a correlation equation, which would mean 15 for the three variables. In the case of the data in Table I there is so little variation in the electronic effects of the carbon-containing substituents that one could expect a good correlation neglecting electronic effects. A perusal of the results of Keinan et al. reveals that one of the two alkyl groups must be relatively small to obtain reasonable reduction rates. Hence, we have treated only the methyl ketones (I) of which there were, in all, 15. Of these, two



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were inactive [R = CH=C(CH$_3$)$_2$, (CH$_2$)$_3$CH$_3$] and for one [CH$_2$CH$_2$CH=C(CH$_3$)$_2$] the steric parameter E_s is not available. Thus, 12 congeners were suitable for study.

Keinan et al. determined the relative rate of reduction, which is of course composed of two major steps: the formation of the ES complex governed by K_m and the catalytic step (k_{cat}). One would not expect the substituent effect to be the same for these two different enzymic processes, but there is evidence that effects can be additive.[7] In fact we have found that while $1/K_m$ often in-

†This work was supported by NSF Grant DMB-8518169 (C.H.).

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(1) Jones, J. B.; Beckin, J. F. In *Techniques of Chemistry*; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Vol. X, p 248.
(2) Takemura, T.; Jones, J. B. *J. Org. Chem.* **1983**, *48*, 791.
(3) Keinan, E.; Hafeli, E. K.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 162.
(4) Hansch, C.; Schaeffer, J.; Kerley, R. *J. Biol. Chem.* **1972**, *247*, 4703.
(5) Cornell, N. W.; Hansch, C.; Kim, K. H.; Henegar, K. *Arch. Biochem. Biophys.* **1983**, *227*, 81.
(6) Hansch, C.; Klein, T.; McClarin, J.; Langridge, R.; Cornell, N. W. *J. Med. Chem.* **1986**, *29*, 615.
(7) Hansch, C.; Deutsch, E. W.; Smith, R. N. *J. Am. Chem. Soc.* **1965**, *87*, 2738.

0022-3263/86/1951-5461$01.50/0