Oxidation of 9-Hydroxyfluorene and Isolation of Product. To a mixture of bis(quinuclidine)bromine(I) tetrafluoroborate (0.419 g, 1.08 mmol), $AgBF_4$ (0.254 g, 1.30 mmol), and 9-fluorenol (0.200 g, 1.10 mmol) was added 5 mL of CH_2Cl_2 and the mixture allowed to stir for 30 min. After the AgBr was collected, the filtrate was washed with water (5 × 10 mL) and evaporated to leave a yellow solid: mp 75–79 °C (lit. mp 81–83 °C for 9-fluorenone); 0.190 g (96%).

Verification of Products. Cyclopentanone and 2-octanone were verified as products by comparison of the NMR spectrum of the filtrate from the reaction mixture with the spectrum of authentic ketone. For analysis by NMR, the filtrate was washed with water, dried with Na_2SO_4, and concentrated by evaporation. Pentanal was verified as product from the NMR spectrum of the fraction collected around 103 °C in the distillation of the filtrate from the reaction mixture.

Acknowledgment. We thank John Layton, Stanford L. Smith, and the University of Kentucky for assistance and use of the NMR facility. This research was supported by a grant from Research Corporation.

Registry No. 1-BF_4, 85282-86-6; $AgBF_4$, 14104-20-2; 2-pentanol, 6032-29-7; 2-octanol, 123-96-6; 2,4-dimethyl-3-pentanol, 600-36-2; cyclopentanol, 96-41-3; cyclohexanol, 108-93-0; 2-*tert*-butylcyclohexanol, 13491-79-7; 4-*tert*-butylcyclohexanol, 98-52-2; cyclododecanol, 1724-39-6; menthol, 1490-04-6; borneol, 507-70-0; *sec*-phenethylalcohol, 98-85-1; 9-hydroxyfluorene, 1689-64-1; 1-pentanol, 71-41-0; 1-octanol, 111-87-5; neopentyl alcohol, 75-84-3; benzyl alcohol, 100-51-6; 2-pentanone, 107-87-9; 2-octanone, 111-13-7; 2,4-dimethyl-3-pentanone, 565-80-0; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 2-*tert*-butylcyclohexanone, 1728-46-7; 4-*tert*-butylcyclohexanone, 98-53-3; cyclododecanone, 830-13-7; menthone, 10458-14-7; camphor, 76-22-2; acetophenone, 98-86-2; 9-fluorenone, 486-25-9; pentanal, 110-62-3; octanal, 124-13-0; trimethylacetaldehyde, 630-19-3; benzaldehyde, 100-52-7.

Regiospecific Synthesis of 5-Alkyl-1-(phenoxycarbonyl)-1,2-dihydropyridines

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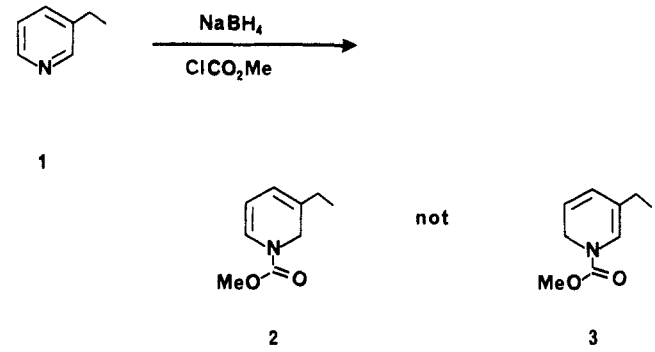
Recently, there has been considerable interest in 1-acyl-1,2-dihydropyridines as intermediates for the synthesis of natural products.[1,2] These relatively stable dihydropyridines are generally prepared by the addition of an organometallic[1,3] or reducing agent[4,5] to a 1-acylpyridinium salt. A substituent at the 5-position of the dihydropyridine intermediate is frequently required in natural product synthesis. Fowler's reduction (pyridine, alkyl chloroformate, $NaBH_4$)[4] is convenient for the synthesis of unsubstituted 1-(alkoxycarbonyl)-1,2-dihydropyridines; however, due to an "ortho" effect,[6] use of this procedure with 3-ethylpyridine (1) and methyl chloroformate leads



1 2 3

to 1-carbomethoxy-3-ethyl-1,2-dihydropyridine (**2**) and not the 5-substituted product **3**.[7] The dihydropyridine **3** is a useful intermediate for the synthesis of the Iboga alkaloid catharanthine[8] and has been prepared from 3-ethylpyridine by Fowler[9] and Raucher.[2h] No regiospecific syntheses of other 1-acyl-5-alkyl-1,2-dihydropyridines have been reported. We report herein a general synthesis of 5-alkyl-1-(phenoxycarbonyl)-1,2-dihydropyridines **8** that does not require a 3-substituted pyridine as an intermediate.

Table I. Synthesis of 5-Alkyl-1-(phenoxycarbonyl)-1,2-dihydropyridines 8

compd[a] 8	R	overall yield of 8,[b] %	compd[a] 8	R	overall yield of 8,[b] %
a	$PhCH_2$	60	**d**	Et	40
b	*n*-Bu	46	**e**	Ph	55
c	Me	46	**f**	C_6H_{11}	42

[a] The reactions were performed on a 2-mmol scale in THF. [b] Yield of purified product obtained from radial preparative-layer chromatography. Yield represents overall yield from **6**. All products were clear oils and gave the expected IR and ^1H NMR spectra. Due to their instability,[4] products **8** were not submitted for elemental analysis.

1-(Phenoxycarbonyl)-1,2-dihydropyridine (**4**) was chosen as starting material; it is a crystalline material that is readily prepared by a modification of Fowler's procedure.[10] Our synthetic plan called for a regiospecific formylation of dihydropyridine **4** at the 5-position (see Scheme I). The 5-position of **4** is electron rich and part of an ene carbamate system, which is susceptible to electrophilic attack. We[11] recently reported a regiospecific Friedel–Crafts β-acylation of 1-acyldihydropyridines, and Shono[12] has described one example of a β-formylation of a 1-acyl-1,4-dihydropyridine.

Formylation of **4** by the Vilsmeier–Haack reaction gave aldehyde **5** in 81% yield. This compound is a crystalline solid that can be stored in a freezer for several months without decomposition. Reduction of **5** with $NaBH_4$/$CeCl_3$[13] gave the alcohol **6** in quantitative yield. Treatment

(1) For a recent review on dihydropyridines, see: Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243.
(2) For leading and recent references, see: (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549–4552. (b) Comins, D. L.; Brown, J. D. *Ibid.* **1986**, *27*, 2219–2222. (c) Comins, D. L.; Abdullah, A. H. *Ibid.* **1985**, *26*, 43–46. (d) Natsume, M.; Utsunomiya, I.; Yamaguchi, K.; Sakai, S. I. *Tetrahedron* **1985**, *41*, 2115–2123 and references therein. (e) Orawa, M.; Natsume, M. *Heterocycles* **1985**, *23*, 831–834. (f) Comins, D. L.; Abdullah, A. H.; Mantlo, N. B. *Tetrahedron Lett.* **1984**, *25*, 4867–4870. (g) Nakazono, Y.; Yamaguchi, R.; Kawanisi, M. *Chem. Lett.* **1984**, 1129–1132. (h) Raucher, S.; Lawrence, R. F. *Tetrahedron Lett.* **1983**, *24*, 2927–2930.
(3) Yamaguchi, R.; Moriyazu, M.; Kawanisi, M. *Tetrahedron Lett.* **1986**, *27*, 211–214. Courtois, G.; Al-arnaout, A.; Miginiac, L. *Ibid.* **1985**, *26*, 1027–1030. Comins, D. L.; Brown, J. D. *Ibid.* **1984**, *25*, 3297–3300. Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315–4319 and references therein.
(4) Fowler, F. *J. Org. Chem.* **1972**, *37*, 1321–1323.
(5) Natsume, M.; Utsunomiya, I. *Chem. Pharm. Bull.* **1984**, *32*, 2477–2479.
(6) For a discussion of the "ortho" effect, see: Abramovitch, R. A.; Singer, G. M. *Pyridine and Its Derivatives*; Abramovitch, R. A., Ed.; Wiley-Interscience: New York, 1974; Vol. 14, Part 1, p 50.
(7) Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677–6682.
(8) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236–3237.
(9) Wyle, M. J.; Fowler, F. W. *J. Org. Chem.* **1984**, *49*, 4025–4029.
(10) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836–4842.
(11) Comins, D. L.; Mantlo, N. B. *Tetrahedron Lett.* **1983**, *24*, 3683–3686.
(12) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.-i.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697–6703.
(13) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

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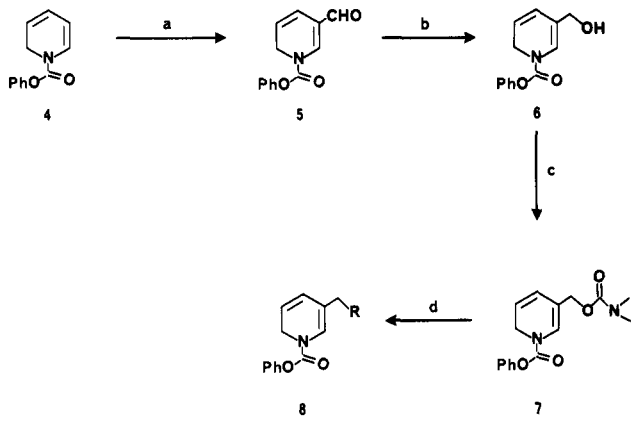
Scheme I[a]



[a] Key: (a) $POCl_3$/DMF, CH_2Cl_2; (b) $NaBH_4/CeCl_3$; (c) Me_2NCOCl, $NaN(Me_3Si)_2$; (d) RMgCl, 10% CuI, THF.

of **6** with dimethylcarbamyl chloride and sodium bis(trimethylsilyl)amide in THF gave the carbamate **7**. Crude **7** was treated with Grignard reagents and cuprous iodide (10%)[14] in THF at −40 °C to give the desired 5-alkyl-1-(phenoxycarbonyl)-1,2-dihydropyridines **8** in good overall yield as shown in Table I.

In addition to allowing for the preparation of crystalline dihydropyridine intermediates **4**, **5**, and **6**, the *N*-phenoxycarbonyl group has advantages over many other *N*-alkoxycarbonyl substituents in that it can be removed with NaOH/EtOH[2f] or transformed into other *N*-acyl groups by reaction with an appropriate nucleophile, i.e. potassium *tert*-butoxide[10,15] or lithium dialkylamide.[11]

Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-300 or a JEOL FX-90-Q spectrometer. Radial preparative-layer chromatography (radial PLC) was carried out by using a Chromatotron (Harrison Associates, Palo Alto, CA). Elemental analyses were carried out by M-H-W laboratories, Phoenix, AZ. Due to their instability,[4] products **8** were not submitted for elemental analysis.

5-Formyl-1-(phenoxycarbonyl)-1,2-dihydropyridine (5). Phosphorus oxychloride (10.2 mL, 0.109 mol) was added slowly to stirred DMF (19.3 mL, 0.25 mol) at 0 °C. The mixture was warmed to room temperature, stirred for 20 min, cooled to 0 °C, and added dropwise via a double-tipped needle to a solution of dihydropyridine **4**[10] (20.0 g, 99.4 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The ice bath was removed, and the orange reaction mixture was heated to reflux for 50 min. After cooling to 0 °C, a solution of KOAc (29.3 g, 0.298 mol) in water (150 mL) was added slowly. The mixture was refluxed for 20 min, cooled to room temperature, and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with 40-mL portions of water, saturated aqueous $NaHCO_3$, and brine. After drying ($MgSO_4$), the solution was concentrated to give 25.0 g of a yellow solid that was recrystallized from MeOH to provide 18.4 g (81%) of **5** as light yellow needles: mp 92–94 °C; IR (KBr) 1750, 1655, 1610, 1415, 1325, 1200, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1 H), 7.68 (s, 1 H), 7.50–7.10 (m, 5 H), 6.47–6.30 (m, 1 H), 5.75–5.61 (m, 1 H), 4.60 (br s, 2 H). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.17; H, 4.82; N, 6.14.

5-(Hydroxymethyl)-1-(phenoxycarbonyl)-1,2-dihydropyridine (6). To a stirred solution of aldehyde **5** (1.15 g, 5 mmol) in THF (5 mL) was added MeOH (15 mL) and $CeCl_3 \cdot 7H_2O$ (1.9 g, 5 mmol). After 30 min, the heterogeneous mixture was cooled to 0 °C and $NaBH_4$ (230 mg, 6 mmol) was added in approximately 10-mg portions over 1 h. Stirring was continued for 2 h at 0 °C, water (25 mL) was added, and the excess MeOH was removed in vacuo at room temperature. The mixture was extracted with ether (2 × 30 mL), and the combined organic layers were washed with 15-mL portions of water and brine. After drying ($MgSO_4$), the solution was concentrated to give 1.15 g (100%) of **6** as a white solid, which was used directly in the next step. A sample was prepared for elemental analysis by recrystallization from CCl_4: mp 61–63 °C; IR (KBr) 3330, 2900, 1705, 1400, 1340, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.11 (m, 5 H), 6.88 and 6.79 (pair of s due to rotamers, 1 H), 5.97 (t, 1 H), 5.70–5.60 (m, 1 H), 4.45 and 4.41 (pair of dd due to rotamers, 2 H, J = 4 Hz and J = 2 Hz), 4.08 (s, 2 H), 2.1 (br s, 1 H). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found: C, 67.29; H, 5.65; N, 6.05.

5-[[(*N*,*N*-Dimethylcarbamyl)oxy]methyl]-1-(phenoxycarbonyl)-1,2-dihydropyridine (7). To a stirred solution of alcohol **6** (1.15 g, 5 mmol) in THF (6 mL) at −78 °C was added dimethylcarbamyl chloride (0.92 mL, 10 mmol). After 5 min, a solution of sodium bis(trimethylsilyl)amide (6 mmol) in THF (6 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h, water (30 mL) was added, and the cooling bath was removed. Extraction with ether (2 × 30 mL), washing the combined organic layers with 15-mL portions of water (4×) and brine, drying ($MgSO_4$), and concentration gave 1.51 g (100%) of crude **7** as a pale yellow oil. This compound was determined to be approximately 80% pure by ^{1}H NMR and is unstable. It was used immediately in the next reaction. A small sample was purified for spectral analysis by radial PLC (SiO_2, EtOAc–hexane) to give a clear oil: IR (neat) 3160, 2970, 1740, 1700, 1595, 1390, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.10 (m, 5 H), 6.98 and 6.89 (pair of s due to rotamers, 1 H), 5.97 (d, 1 H), 5.70–5.57 (m, 1 H), 4.57 (s, 2 H), 4.57 and 4.42 (pair of dd due to rotamers, 2 H, J = 4 Hz and J = 2 Hz), 2.90 (s, 6 H).

5-(2-Phenylethyl)-1-(phenoxycarbonyl)-1,2-dihydropyridine (8a). General Procedure for the Synthesis of 5-Alkyl-1-(phenoxycarbonyl)-1,2-dihydropyridines 8. To a stirred solution of crude **7** (607 mg, 2.01 mmol), CuI (40 mg, 0.20 mmol), and methyl sulfide (0.43 mL, 6.03 mmol) in THF (5 mL) at −23 °C was added a THF solution of benzylmagnesium chloride (2.61 mmol) dropwise. The mixture was stirred at −23 °C for 30 min and then transferred to a freezer (−40 °C). After 48 h, 25 mL of aqueous NH_4Cl–NH_4OH (50:50) and ether (50 mL) were added, and the mixture was warmed to room temperature. After stirring for 20 min, the organic layer was separated, washed with 20-mL portions of water and brine, dried ($MgSO_4$), and concentrated to give 741 mg of a yellow oil. Purification by radial PLC (SiO_2, CH_2Cl_2) gave 369 mg (60%) of **8a** as a clear oil: IR (neat) 3150, 2950, 2875, 1720, 1595, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.10 (m, 10 H), 6.61 and 6.59 (pair of s due to rotamers, 1 H), 5.87 (d, 1 H), 5.71–5.59 (m, 1 H), 4.50 and 4.37 (pair of dd due to rotamers, 2 H, J = 4 Hz and J = 2 Hz), 2.80–2.70 (m, 2 H), 2.36 (t, 2 H).

Spectral Data. 8b: IR (neat) 2940, 1720, 1595, 1373, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.09 (m, 5 H), 6.64 and 6.58 (pair of s due to rotamers, 1 H), 5.86 (d, 1 H), 5.70–5.58 (m, 1 H), 4.51 and 4.38 (pair of dd due to rotamers, 2 H, J = 4 Hz and J = 2 Hz), 2.02 (t, 2 H), 1.50–1.20 (m, 6 H), 0.84–0.96 (m, 3 H).

8c: IR (neat) 3160, 2970, 1725, 1600, 1360, 1210 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.10 (m, 5 H), 6.65 and 6.58 (pair of s due to rotamers, 1 H), 5.86 (d, 1 H), 5.70–5.58 (m, 1 H), 4.50 and 4.38 (pair of dd due to rotamers, 2 H, J = 4 Hz and J = 2 Hz), 2.20–2.05 (t, 2 H), 1.15–1.03 (m, 3 H).

8d: IR (neat) 2950, 1710, 1595, 1400, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.10 (m, 5 H), 6.64 and 6.58 (pair of s due to rotamers, 1 H), 5.86 (d, 1 H), 5.70–5.57 (m, 1 H), 4.51 and 4.38 (pair of dd due to rotamers, 2 H, J = 4 Hz and J = 2 Hz), 2.03 (t, 2 H), 1.52–1.40 (m, 2 H), 0.96–0.82 (m, 3 H).

8e: IR (neat) 3050, 2930, 2850, 1705, 1660, 1600, 1500, 1400, 1200 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.48–7.02 (m, 10 H) 6.75

(14) For a recent paper on the copper(I)-catalyzed cross-coupling of allylic carboxylates with Grignard reagents, see: Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884–2891.

(15) Comins, D. L. *Tetrahedron Lett.* **1983**, *24*, 2807–2810.

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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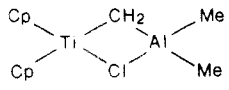
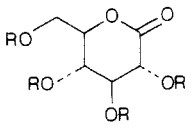
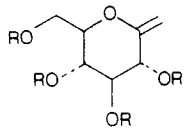
Carbon–carbon bond-forming reactions at the anomeric position of carbohydrates have attracted considerable attention because of the increase interest in the use of simple sugars as chiral synthons[1] for the synthesis of complex natural products including biologically active *C*-glycosides.[2] In a general 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)

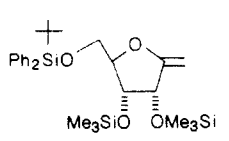


2a, R = CH_2Ph
b, R = $SiMe_3$

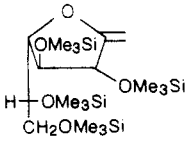


3a, R = CH_2Ph
b, R = $SiMe_3$
c, R = $SiEt_3$
d, R = H

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.



4



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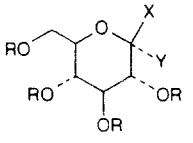

6a, X = H, Y = CH_2OH, R = CH_2Ph
b, X = CH_2OH, Y = H, R = CH_2Ph
c, X = CH_2OCH_2Ph, Y = H, R = CH_2Ph

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.

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