Selective Protection of 1,2- and 1,3-Diols via Acylative Cleavage of Cyclic Formals

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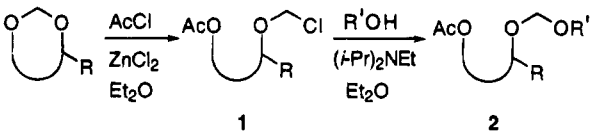
An efficient two-step method for the differential functionalization of 1,2- and 1,3-diols, involving regioselective cleavage of five- and six-membered cyclic formals with acetyl chloride followed by conversion of the resulting chloromethyl ether acetate **1** to an alkoxymethyl ether acetate (**2**), has been developed. When applied to unsymmetrically substituted cyclic formals, the differential functionalization sequence is highly selective and produces an alkoxymethyl ether acetate having the acetate at the less hindered center and the acetal moiety at the more hindered center. Removal of either protecting group affords a selectively monoprotected diol: for the case of an unsymmetrical diol, removal of the acetate gives a product selectively protected with an acetal group at the more hindered hydroxyl.

The development of efficient methodology for the selective, differential protection of diols is a perennial challenge in organic chemistry.[1] A generally useful method should allow for monoprotection of symmetrical diols as well as permit differentiation of the chemically distinct hydroxyl groups of unsymmetrical substrates. While a variety of techniques are available for the monoprotection of symmetrical diols,[1,2] there are few methods that allow for chemoselective functionalization of the more hindered hydroxyl group in an unsymmetrically substituted diol.[1,3] A potentially attractive approach to the differential functionalization of 1,2- and 1,3-diols was suggested by the results of our previous study of the acylative ring-opening of cyclic formals.[4]

As shown below, the acid-catalyzed cleavage of unsymmetrically substituted cyclic formals with acetic anhydride occurs via preferential rupture of the less congested C(2)–O bond to give products having an acetate at the primary site and an acetoxymethyl ether moiety at the secondary position.[4] Such highly selective acylative cleavage, which results from a rate-limiting electrophilic attack that is acutely sensitive to steric effects,[4] was also observed in the Lewis-acid catalyzed reaction of a limited number of cyclic formals with acetyl chloride to afford chloromethyl ether acetates.[4] Herein we report that the regioselectivity of the acylative ring-cleavage of cyclic formals with AcCl,[5] coupled with inherent reactivity of the chloromethyl ether moiety, may be exploited for the selective, differential protection of 1,2- and 1,3-diols.

Scheme 1



Results and Discussion

A representative selection of cyclic formals, prepared from the corresponding diols by the method of Aftalion and co-workers[6] or available via the Prins reaction from an alkene and formaldehyde, were chosen to assess the efficiency of the two-step preparation of differentially protected diols depicted in Scheme 1. Acylative cleavage of the formals was readily accomplished at room temperature by simply stirring an ethereal solution of the acetal and 1.0–1.2 mol equiv of acetyl chloride in the presence of a catalytic quantity of anhydrous zinc chloride. The ring-opening affords chloromethyl ether acetates **1** in virtually quantitative yield with a high degree of selectivity for cleavage of the C(2)–O bond that is remote from the substituent (vide infra). While such products may be isolated by concentration of the reaction mixture, these difunctional materials are potentially toxic and, for this reason, it is prudent to avoid isolation of the chloromethyl ether acetates **1**. To this end, the crude reaction product, containing **1** and residual AcCl, was added to a solution of an excess of an appropriate alcohol (typically 4 mol equiv) and *N,N*-diisopropylethylamine (typically 1.2 mol equiv) in dry diethyl ether. Under these conditions, as shown in Scheme 1, the reactive OCH_2Cl moiety of **1** is converted in high yield to a conventional alkoxymethyl ether protecting group. Pure

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(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991. (b) Wilkinson, S. G. In *Comprehensive Organic Chemistry*; Pergamon Press: New York, 1979; Vol. 1, p 681 ff.

(2) (a) Lenzoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327 and references therein. (b) Babler, J. H.; Coghlan, M. J. *Tetrahedron Lett.* **1979**, 1971. (c) Posner, G. H.; Oda, M. *Tetrahedron Lett.* **1981**, *22*, 5003. (d) Kunieda, T.; Mori, T.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1985**, *26*, 1977. (e) Ogawa, H.; Ichimura, Y.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2481. (f) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388. (g) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947. (h) Nishiguchi, T.; Taya, H. *J. Am. Chem. Soc.* **1989**, *111*, 9102. (i) Nishiguchi, T.; Fujisaki, S.; Ishii, Y.; Yano, Y.; Nishida, A. *J. Org. Chem.* **1994**, *59*, 1191 and references therein.

(3) Most methods that have been used for protection of the more hindered hydroxyl group in an unsymmetrically substituted diol involve selective cleavage of various cyclic species. See, for example: (a) Shanzer, A. *Tetrahedron Lett.* **1980**, *21*, 221. (b) Marx, M. H.; Wiley, R. A. *Tetrahedron Lett.* **1985**, *26*, 1379. (c) Pautard, A. M.; Evans, S. A., Jr. *J. Org. Chem.* **1988**, *53*, 2300. (d) Guindon, Y.; Girard, Y.; Berthiaume, S.; Gorys, V.; Lemieux, R.; Yoakim, C. *Can. J. Chem.* **1990**, *68*, 897. (e) Reginato, G. R.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132. (f) Rychnovsky, S. D.; Kim, J. *Tetrahedron Lett.* **1991**, *32*, 7219. (g) Barton, D. H. R.; Zhu, J. *Tetrahedron Lett.* **1992**, *39*, 8837. (h) Cheng, W.-L.; Yeh, S.-M.; Luh, T.-Y. *J. Org. Chem.* **1993**, *58*, 5576.

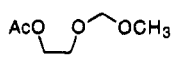
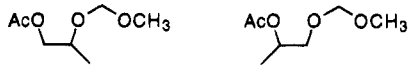
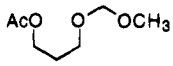
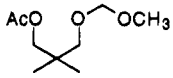
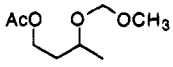
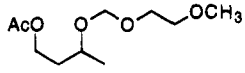
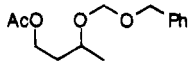
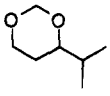
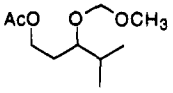
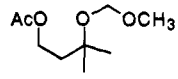
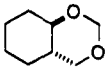
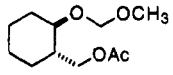
(4) Bailey, W. F.; Rivera, A. D. *J. Org. Chem.* **1984**, *49*, 4958.

(5) The cleavage of 1,3-dioxolane with acetyl chloride to give 1-acetoxy-2-(chloromethoxy)ethane has been reported: Foye, W. O.; Kauffman, J. K.; Kim, Y. H. *J. Heterocycl. Chem.* **1982**, *19*, 497.

(6) Aftalion, F.; Lumbroso, M.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1965**, 1958.

0022-3263/95/1960-2532$09.00/0

Table 1. Selective Protection of Diols (Scheme 1)

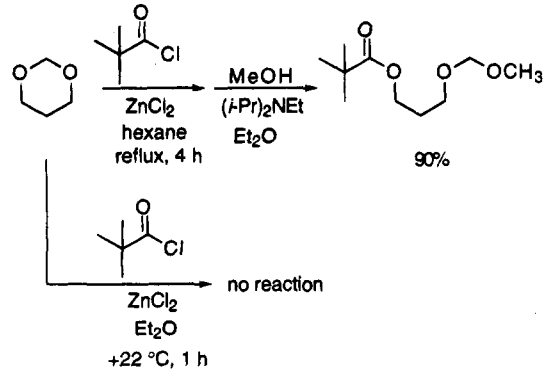
entry	acetal	ROH	product	yield,[a] % (product ratio)
1		MeOH		92
2		MeOH		90 (3.0:1)
3		MeOH		97
4		MeOH		85
5		MeOH		95
6		$MeO(CH_2)_2OH$		88
7		$PhCH_2OH$		75
8		MeOH		95
9		MeOH		89
10		MeOH		90

[a] Isolated yield of chromatographically pure product.

alkoxymethyl ether acetates **2** are easily isolated by pentane elution from a short column of neutral alumina (Table 1).

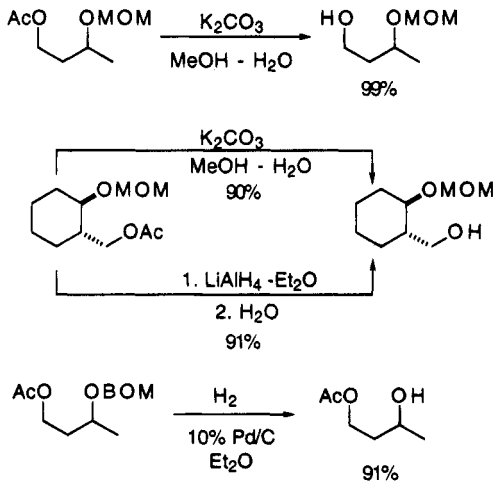
The results summarized in Table 1 demonstrate that the two-step conversion of a cyclic formal to an alkoxymethyl ether acetate (Scheme 1) is efficient and often highly selective. As noted previously,[4] the ring-opening of 4-substituted, 4,4-disubstituted, or 4,5-disubstituted-1,3-dioxanes proceeds with total specificity within the limits of detection by GC analysis of the reaction products. Consequently, a single isomer of the differentially protected diol is afforded by the two-step protocol (Table 1, entries 5–10). The cleavage of five-membered cyclic formals is less selective and a mixture of regioisomeric products results (Table 1, entry 2). In an effort to increase the selectivity of the process for the differential protection of unsymmetrical 1,2-diols, acylative ring-opening of formals using pivaloyl chloride was explored.

Not surprisingly, the reaction of a cyclic formal with the more sterically demanding pivaloyl chloride is much slower than is cleavage with AcCl. Indeed, the ring-opening of formals with pivaloyl chloride in the presence of a catalytic quantity of $ZnCl_2$ is best conducted at elevated temperature in a hydrocarbon solvent rather than in diethyl ether at room temperature. The reactivity of 1,3-dioxane, illustrated below, is representative of the sluggish reaction of cyclic formals with this hindered acid chloride.

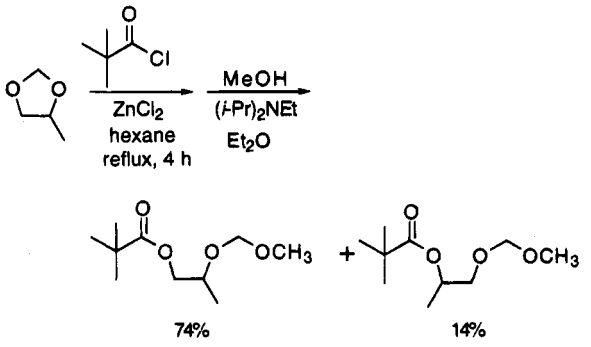


Treatment of 4-methyl-1,3-dioxolane with pivaloyl chloride in hexane at reflux followed by conversion of the resulting chloromethyl ether moiety to the MOM ether afforded an 88% yield of the two regoisomers, depicted below, in a ratio of 5.3:1. Thus, the cleavage of 4-methyl-1,3-dioxolane with pivaloyl chloride is indeed more selective than is the reaction with AcCl (*cf.* Table 1, entry 2).

Scheme 2



Unfortunately, even with this bulky acid chloride, the ring-opening of unsymmetrically substituted 1,3-dioxolanes appears to be inherently less regioselective than the cleavage of analogously substituted 1,3-dioxanes with AcCl. Be that as it may, the acylative cleavage–etherification sequence illustrated in Scheme 1 provides a convenient route to selectively functionalized diols.



The chemistry summarized in Scheme 1 may be easily extended to the preparation of monoprotected diols by selective removal of one of the protecting groups. Since the two-step differential functionalization sequence (Scheme 1) invariably produces, either as the sole product or as the major regioisomer, an alkoxymethyl ether acetate having the acetate at the primary center and an acetal moiety at the more congested carbon (Table 1), removal of the acetate affords a diol that is selectively protected as an alkoxymethyl ether at the more sterically encumbered center. As demonstrated by the representative results summarized in Scheme 2, unmasking the primary hydroxyl group is a trivial matter: lithium aluminum hydride reduction or, more economically, methanolysis affords a diol that is selectively protected as a MOM ether at the more substituted site. The capability to site-selectively protect the more hindered hydroxyl in an unsymmetrical diol is a particularly attractive feature of the methodology since it complements the normal chemoselectivity which favors functionalization of the primary site in the reaction of an unsymmetrical diol with a derivatizing reagent.[1,2]

It might be noted that removal of a MOM or MEM ether protecting group from an alkoxymethyl ether acetate derivative of a 1,2- or 1,3-diol is problematic due to the rapid isomerization of the monoacetate product in the presence of trace amounts of base or acid.[7] However, as illustrated in Scheme 2, the BOM ether group (Table 1, entry 7) is readily removed by hydrogenolysis under neutral conditions to give isomerically pure monoacetate in high yield.

In summary, the two-step preparation of differentially protected 1,2- and 1,3-diols depicted in Scheme 1 provides a convenient, efficient and highly selective route to these useful materials. As a practical matter it should be noted that the methodology, which employs inexpensive, readily available reagents, has been used to prepare differentially protected diols in quantities ranging from 10 mmol to 1.0 mol with little change in protocol.

Experimental Section

General. General spectroscopic and chromatographic procedures as well as methods used for the purification of reagents and solvents have been previously described.[4] NMR spectra were recorded using solutions in $CDCl_3$ unless otherwise noted and all chemical shifts are reported relative to Me_4Si at δ = 0.00.

Acetyl chloride and pivaloyl chloride were freshly distilled at atmospheric pressure in an apparatus protected from moisture; *N,N*-diisopropylethylamine was distilled from powdered NaOH; diethyl ether was freshly distilled from dark-purple solutions of sodium/benzophenone. Literature procedures were followed for the preparation of 4-isopropyl-1,3-dioxane[6] and *trans*-1,3-dioxadecalin;[8] the remaining formals are either commercially available or were prepared as previously described.[4]

General Procedure for the Preparation of Differentially Protected 1,2- or 1,3-Diols (Scheme 1). An appropriately sized flask, fitted with a magnetic stirrer and addition funnel capped with a rubber septum was flame-dried under nitrogen. The flask was charged with 50 mmol of the cyclic formal, 30 mL of anhydrous diethyl ether, and a catalytic quantity of anhydrous zinc chloride (*ca.* 1 crystal or 2 drops of a 1.0 M solution of $ZnCl_2$ in Et_2O). This solution was stirred under a positive pressure of nitrogen, a solution of 60 mmol of freshly distilled acetyl chloride in 30 mL of anhydrous diethyl ether was added dropwise, and the resulting solution was stirred for 1 h at room temperature.[9] A separate dry round-bottomed flask, fitted with a mechanical stirrer and addition funnel, and charged with a solution of 1.2 mol equiv of freshly distilled *N,N*-diisopropylethylamine and 4.0 mol equiv of an anhydrous alcohol in *ca.* 10 mL of anhydrous diethyl ether was immersed in an ice bath. The crude chloromethyl ether acetate reaction mixture was transferred to the addition funnel via a cannula under a positive pressure of nitrogen and the solution was added dropwise to the ice-cold mixture of alcohol and amine. Copious quantities of ammonium salt formed during the addition. After complete addition, the cooling bath was removed, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then concentrated at reduced pressure, pentane was added to the residue, and the flask was cooled to induce crystallization of the ammonium salts. The supernatant was passed through a short column of neutral alumina (*ca.* 30 g for a 50 mmol-scale reaction) using pentane as the eluent. Removal of the solvent by rotary evaporation afforded essentially pure alkoxymethyl ether acetate in the yields given in Table 1.

(7) (a) McClelland, R. A.; Seaman, N. E.; Cramm, D. *J. Am. Chem. Soc.* **1984**, *106*, 4511. (b) Santry, L. J.; Azer, S.; McClelland, R. A. *J. Am. Chem. Soc.* **1988**, *110*, 2909.

(8) Bailey, W. F.; Rivera, A. D.; Zarcone, L. M. J. *Synth. Commun.* **1987**, *17*, 1769.

(9) If desired, the chloromethyl ether acetate product may be isolated in essentially quantitative yield by concentration of the reaction mixture and distillation of the residue. **CAUTION**: these products are potentially toxic. For details see: Rivera, A. D. Ph.D Dissertation, University of Connecticut, Storrs, CT, 1983.

1-Acetoxy-2-(methoxymethoxy)ethane (Table 1, entry 1) is a known compound: bp 168–170 °C (760 mm) [lit.[10] bp 184 °C (760 mm)]. The structures of the remaining products were established on the basis of the data presented below; product yields are given in Table 1.

1-Acetoxy-2-(methoxymethoxy)propane and 2-Acetoxy-1-(methoxymethoxy)propane (Table 1, entry 2). A 3.0:1.0 mixture of the title compounds, bp 95 °C (29 mm), was separated and analytically pure samples were prepared by preparative GC on a 10-ft, 5% TCEP on Chromasorb G (AW-DMCS) column at 139 °C. The major product, which had the longer retention time, was found to be **1-acetoxy-2-(methoxymethoxy)propane** on the basis of the following spectroscopic data: IR (neat) 2950, 2900, 1750, 1450 cm.$^{-1}$; ^{1}H NMR δ 4.69 and 4.68 (AB, J_{AB} = 0.8 Hz, 2H), 4.09–4.05 (m, 2H), 3.98–3.92 (m, 1H), 3.38 (s, 3H), 2.09 (s, 3H), 1.21 (d, J = 6.32 Hz, 3H); ^{13}C NMR δ 170.6, 95.1, 70.7, 67.4, 55.1, 20.6, 17.1. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.69; H, 8.60. The minor isomer was found to be **2-acetoxy-1-(methoxymethoxy)propane** on the basis of the following spectroscopic properties: IR (neat) 2940, 2890, 1740, and 1450 cm^{-1}; ^{1}H NMR δ 5.16–5.01 (m, 1H), 4.64 (apparent s, 2H), 3.57 (d, J = 5.00 Hz, 2H), 3.37 (s, 3H), 2.07 (s, 3H), 1.26 (d, J = 6.50 Hz, 3H); ^{13}C NMR δ 170.5, 96.5, 69.9, 69.4, 55.2, 21.2, 16.6. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.47; H, 8.68.

1-Acetoxy-3-(methoxymethoxy)propane (Table 1, entry 3): bp 94–96 °C (20 mm); IR (neat) 2920, 2870, 1740, 1380, 1360 cm^{-1}; ^{1}H NMR δ 4.61 (s, 2H), 4.18 (t, J = 6.50 Hz, 2H), 3.60 (t, J = 6.21 Hz, 2H), 3.35 (s, 3H), 2.05–1.85 [overlapping patterns, 5H, *i.e.*, 2.05 (s, 3H), 1.92 (apparent pentet, J = 6.32 Hz, 2H)]; ^{13}C NMR δ 170.7, 96.2, 64.0,61.4, 55.0, 28.9, 20.6. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.80; H, 8.78.

1-Acetoxy-2,2-dimethyl-3-(methoxymethoxy)propane (Table 1, entry 4): bp 108–110 °C (15 mm); IR (neat) 2960, 2820, 1740, 1475, 1375 cm^{-1}; ^{1}H NMR δ 4.44 (s, 2H), 3.78 (s, 2H), 3.23 (s, 2H), 3.19 (s, 2H), 1.98 (s, 3H), 0.91 (s, 6H); ^{13}C NMR δ 170.8, 96.6, 73.3, 69.6, 54.9, 35.1, 21.9, 20.8. Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.99; H, 9.80.

1-Acetoxy-3-(methoxymethoxy)butane (Table 1, entry 5): bp 95–98 °C (20 mm); IR (neat) 2970, 1740, 1365, 1245, cm^{-1}; ^{1}H NMR δ 4.70 and 4.60 (AB, J_{AB} = 6.90 Hz, 2H), 4.17 (t, J = 6.63 Hz, 2H), 3.82 (apparent sextet, J = 6.42 Hz, 1H), 3.36 (s, 3H), 2.05 (s, 3H), 1.85–1.76 (m, 2H), 1.20 (d, J = 6.2 5 Hz, 3H); ^{13}C NMR δ 170.7, 95.1, 70.1, 61.4, 55.3, 36.2, 20.8, 20.5. Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.55; H, 9.12.

1-Acetoxy-3-[(methoxyethoxy)methoxy]butane (Table 1, entry 6): bp 113–116 (3.4 mm); IR (neat) 2970, 2930, 2885, 2820, 1740, 1454, 1369 cm^{-1}; ^{1}H NMR δ 4.79 and 4.71 (AB, J_{AB} = 7.14 Hz, 2H), 4.16 (t, J = 6.53 Hz, 2H), 3.91–3.82 (m, 1H), 3.73–3.68 (m, 2H), 3.58–3.53 (m, 2H), 3.40 (s, 3H), 2.05 (s, 3H), 1.85–1.75 (m, 2H), 1.21 (d, J = 6.19 Hz, 3H); ^{13}C NMR δ 170.9, 93.9, 71.8, 70.1, 66.9, 61.3, 58.9, 36.0, 20.8, 20.3. Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.44; H, 9.25.

1-Acetoxy-3-[(benzyloxy)methoxy]butane (Table 1, entry 7): bp 136–138 °C (0.85 mm); IR (neat) 3065, 3035, 2970, 2890, 1740, 1496, 1452 cm^{-1}; ^{1}H NMR δ 7.34–7.26 (m, 5H), 4.86 and 4.73 (AB, J_{AB} = 7.16 Hz, 2H), 4.61 (s, 2H), 4.20 (t, J = 6.48 Hz, 2H), 3.97–3.87 (six lines, J = 6.26 Hz, 1H), 2.02 (s, 3H), 1.87–1.79 (m, 2H), 1.24 (d, J = 6.11 Hz, 3H); ^{13}C NMR δ 170.9, 137.9, 128.4, 127.7, 127.6, 93.0, 70.1, 69.4, 61.3, 36.0, 20.8, 20.3. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.76; H, 8.20.

1-Acetoxy-3-(methoxymethoxy)-4-methylpentane (Table 1, entry 8): bp 97–98 °C (6.8 mm); IR (neat) 2960, 2880, 1740, 1465, 1365 cm^{-1}; ^{1}H NMR δ 4.66 and 4.62 (AB, J_{AB} = 6.90 Hz, 2H), 4.22–4.13 (m, 2H), 3.47–3.38 [overlapping patterns, *i.e.*, 3.47–3.43 (m, 1H), 3.38 (s, 3H)], 2.05 (s, 3H), 1.94–1.72 (m, 3H), 0.92 (d, J = 6.83 Hz, 3H), 0.91 (d, J = 6.83 Hz, 3H); ^{13}C NMR δ 170.7, 96.2, 79.6, 61.6, 55.5, 31.1, 29.6, 20.7, 17.9, 17.3. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.90; H, 9.95.

1-Acetoxy-3-(methoxymethoxy)-3-methylbutane (Table 1, entry 9): bp 59–64 °C (1.6 mm); IR (neat) 2990, 2940, 1750, 1475 cm^{-1}; ^{1}H NMR δ 4.55 (s, 2H), 4.07 (t, J = 7.02 Hz, 2H), 3.25 (s, 3H), 1.98 (s, 3H), 1.80 (t, J = 7.02 Hz, 2H), 1.23 (s, 3H); ^{13}C NMR δ 170.8, 91.0, 74.9, 61.1, 55.1, 40.5, 26.6, 20.9.

***trans*-1-(Acetoxymethyl)-2-(methoxymethoxy)cyclohexane** (Table 1, entry 10): bp 88–89 °C (0.85 mm); IR (neat) 2920, 2850, 1740, 1450, 1370 cm^{-1}; ^{1}H NMR δ 4.73 and 4.56 (AB, J_{AB} = 6.90 Hz, 2H), 4.26–4.04 (m, 2H), 3.43–3.27 [overlapping patterns, *i.e.*, 3.35 (s, 3H), 3.40–3.20 (m, 1H)], 2.05 (s, 3H), 1.84–1.14 (m, 9H); ^{13}C NMR δ 70.9, 95.0, 76.3, 65.6, 55.3, 42.7, 32.0, 28.3, 24.9, 24.4, 20.6. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.96; H, 9.60.

3-(Methoxymethoxy)-1-(trimethylacetoxy)propane. A solution of 0.64 mL (7.5 mmol) of 1,3-dioxane, 1.2 mL (10 mmol) of pivaloyl chloride, and a catalytic amount of anhydrous $ZnCl_2$ in 5.0 mL of dry hexane was stirred for 4 h at reflux. Hexane was removed under a strong stream of nitrogen, the crude chloromethyl ether was diluted with 5 mL of dry diethyl ether, and the ethereal solution was transferred, *via* metal cannula, to a previously flame–dried addition funnel mounted on a two-necked 50-mL round-bottomed flask. The flask was fitted with a magnetic stirring bar, charged with 1.4 mL (8.0 mmol) of *N,N*-diisopropylethylamine, 1.2 mL (30 mmol) of anhydrous methanol, and 5.0 mL of anhydrous diethyl ether, and cooled in an ice-bath. The ethereal solution of chloromethyl ether was added dropwise to the alcohol solution, the ice-bath was then removed, and the solution was allowed to stand at room temperature with stirring for 2 h. The reaction mixture was worked-up as described above, and the residue was distilled to afford 1.32 g (86%) of the title compound: bp 113–116 °C (45 mm). An analytically pure sample was prepared by preparative GC on a 10 ft, 10% FFAP Chromosorb W (NAW 80/100 mesh) column at 160 °C: IR (neat): 2920, 1728, 1475, 1460, 1393 cm^{-1}; ^{1}H NMR δ 4.62 (s, 2H), 4.17 (t, J = 6.34 Hz, 2H), 3.61 (t, J = 6.25 Hz, 2H), 3.36 (s, 3H), 1.93 (apparent pentet, J = 6.30 Hz, 2H), 1.20 (s, 9H); ^{13}C NMR δ 178.4, 96.4, 64.0, 61.3, 55.1, 38.7, 29.0, 27.2. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.70; H, 9.85.

2-(Methoxymethoxy)-1-(trimethylacetoxy)propane and 1-(Methoxymethoxy)-2-(trimethylacetoxy)propane. Following the procedure described immediately above, 0.66 g (7.5 mmol) of 4-methyl-1,3-dioxolane was converted into a 5.3:1 mixture of the title compounds, bp 86–90 °C (13 mm). The isomers were separated and analytically pure samples were prepared by preparative GC on a 10-ft, 10% FFAP on Chromosorb W (NAW, 80/100 mesh) column at 140 °C. The major product, which had the longer retention time, was found to be **2-(methoxymethoxy)-1-(trimethylacetoxy)propane** on the basis of the following spectroscopic data: IR (neat) 2985, 1733, 1481, 1461, 1400, 1368 cm^{-1}; ^{1}H NMR δ 4.70 (apparent s, 2H), 4.05 (d, J = 5.23 Hz, 2H), 3.94 (m, 1H), 3.39 (s, 3H), 1.22 (s, 9H), 1.21 (d, J = 6.29 Hz, 3H); ^{13}C NMR δ 178.3, 95.3, 71.0, 67.5, 55.3, 38.7, 27.2, 17.4. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80 H, 9.87. Found: C, 58.72; H, 10.00. The minor isomer was identified as **1-(methoxymethoxy)-2-(trimethylacetoxy)-propane** on the basis of the following properties: IR (neat) 2977, 2823, 1729, 1480, 1460, 1398 cm^{-1}; ^{1}H NMR δ 5.05 (m, 1H), 4.62 (s, 2H), 3.55 (d, J = 5.93 Hz, 2H), 3.35 (s, 3H), 1.21 (d, J = 6.48 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR δ 178.0, 96.5, 70.0, 69.0, 55.2, 38.7, 27.1, 16.6.

3-(Methoxymethoxy)-1-butanol. A mixture of 2.40 g (13.6 mmol) of 1-acetoxy-3-(methoxymethoxy)butane, 25 mL of methanol, and 68 mL of 0.5 M aqueous potassium carbonate was stirred for 1.5 h at room temperature and then extracted with two 25-mL portions of ether. Solid sodium chloride (*ca.* 6 g) was added to the aqueous layer, and the mixture was extracted with an additional three 25-mL portions of ether. The combined organic extracts were dried (K_2CO_3) and concentrated at reduced pressure to afford an oil that was distilled

(10) Rakhmankulov, I. L.; Kantor, E. A.; Valitov, R. B.; Rakhmankulov, D. L. *Zh. Prikl. Khim.* **1977**, *50*, 220.

to give 1.79 g (99%) of product: bp 60–61 °C (1.9 mm) [lit.[11] bp 67–69 °C (5 mm)]; ^{1}H NMR (DMSO-d_6) δ 4.60 and 4.54 (AB, J_{AB} = 6.78 Hz, 2H), 4.36 (t, J = 4.83, 1H), 3.80–3.68 (m, 1H), 3.47 (apparent q, J = 5.89 Hz, 2H), 3.25 (s, 3H), 1.71–1.44 (m, 2H), 1.10 (d, J = 6.20 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 94.4, 70.1, 57.7, 54.6, 40.0, 20.4.

***trans*-1-(Hydroxymethyl)-2-(methoxymethoxy)cyclohexane.** A mixture of 2.00 g (9.30 mmol) of *trans*-1-(acetoxymethyl)-2-(methoxymethoxy)cyclohexane, 17.0 mL of methanol, and 50 mL of 0.5 M aqueous potassium carbonate was stirred and heated at reflux for 4 h. The reaction mixture was cooled to room temperature, and then extracted with two 25-mL portions of diethyl ether. Solid sodium chloride (*ca.* 10 g) was added to the aqueous layer, and the mixture was extracted with an additional three 25-mL portions of diethyl ether. The combined organic extracts were dried (K_2CO_3) and concentrated at reduced pressure to afford an oil that was distilled to afford 1.45 g (90%) of product: bp 89–92 °C (1.1 mm). An analytically pure sample was prepared by preparative GC on a 9-ft, 10% FFAP on Chromasorb W (NAW, 60/80 mesh) column at 175 °C: IR (neat) 3440, 2930, 2855, 1450, 1380 cm^{-1}; ^{1}H NMR δ 4.80 and 4.61 (AB, J_{AB} = 6.77 Hz, 2H), 3.67–3.61 (m, 2H), 3.41 (s, 3H), 3.54–3.38 (m, 1H), 2.85 (t, J = 5.60 Hz, 1H), 2.13–2.06 (m, 1H), 1.85–1.13 (m, 8H); ^{13}C NMR δ 94.7, 79.5, 65.9, 55.4, 45.4, 31.7, 27.9, 25.0, 24.4. Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.94; H, 10.71.

The title compound was also prepared by reduction of 1.21 g (5.59 mmol) of *trans*-1-(acetoxymethyl)-2-(methoxymethoxy)-cyclohexane with 0.50 g (13.2 mmol) of lithium aluminum hydride in 20 mL of anhydrous diethyl ether to give, following workup, 0.970 g (99%) of the MOM-ether.

4-Acetoxybutan-2-ol. A thick-walled bottle was charged with 2.19 g (8.68 mmol) of 1-acetoxy-3-[(benzyloxy)methoxy]-butane, 50 mL of anhydrous diethyl ether, and 0.70 g of 10% palladium on activated carbon. The mixture was attached to a hydrogenation apparatus and, once evacuated, hydrogen gas was added until the pressure in the bottled reached 30 psi. Agitation of the mixture resulted in a rapid (*ca.* 10 min) pressure drop to 14 psi. Hydrogen gas was again added until the pressure in the bottled reached 25 psi, and agitation was continued for 1 h. The reaction mixture was filtered through a pad of Celite, and solvent was removed to give an oil which was distilled to give 1.04 g (91%) product: bp 94–96 °C (10 mm) [lit.[12] bp 87–89 °C (13 mm)]; IR (neat) 3435, 2970, 2940, 1740, 1372 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.55 (d, J = 4.89 Hz, 1H), 4.05 (t, J = 6.67 Hz, 2H), 3.75–3.61 (m, 1H), 1.98 (s, 3H), 1.64–1.54 (m, 2H), 1.07 (d, J = 6.20 Hz, 3H).

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(11) Safarou, M. G.; Rakhmankulov, D. L.; Safarova, V. G.; Komissarou, V. D. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1976**, *6*, 1393.

(12) Kulpinski, M. S.; Nord, F. F. *J. Org. Chem.* **1943**, *8*, 256.