Preparation of Monoacetylated Diols via Cyclic Ketene Acetals

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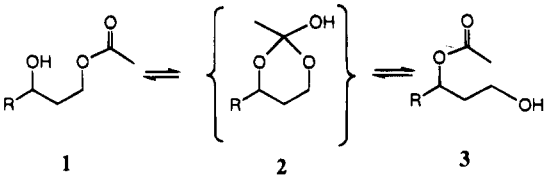
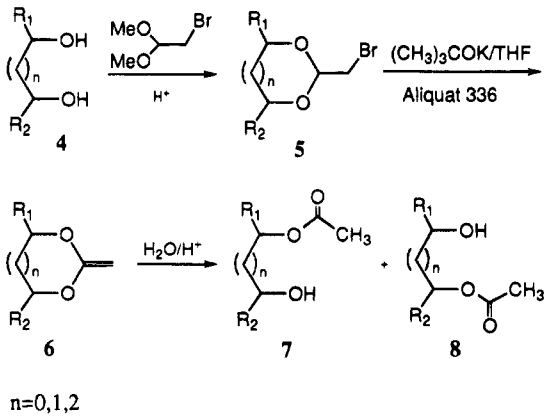
Monoacetylation of diols is an important topic in organic synthesis.[2] Routine acetylation of diols, containing equivalent or similar hydroxyl groups, with 1 equiv of acetic anhydride or 1 equiv of acetyl chloride, will produce a mixture of mono- and diacetylation products as well as unreacted diol. Where one hydroxyl is tertiary and one is primary the selectivity for primary acylation can be high. Selective monoprotection of 1,*n*-diols requires careful control.[3] Despite the numerous attempts made to improve the mono- to diacetylation ratio in solution reactions, selective acetylation of diols with various acylating agents has generally not been successful.[4] Monoacylation via the solid phase technique, where one hydroxyl is bonded to a solid support, can be selective.[5] By cleaving this product from the polymer the protected hydroxyl can be regenerated to give the monoacylated product in high selectivity. However, this method is cumbersome when making large amounts of product. Selective protection in unsymmetrically substituted diols has most often employed the selective cleavage of cyclic species.[6] Ozonolysis of acetals derived from aldehydes gives the corresponding ester and alcohol.[7] Cyclic acetals lead to the corresponding monoacylated diols.[8]

One reason monoacetylation can fail is intramolecular acetyl group equilibration from **1** to **3** via a six-membered cyclic intermediate, **2**, as shown in Scheme 1.[9] The regenerated primary hydroxyl group in **3** will be readily acetylated to form the diacetylation product. Methods which favor monoacetylation, by reacting at a primary hydroxyl more rapidly than at a secondary or tertiary hydroxyl, will often fail for this reason. Therefore, selective synthetic approaches are needed to supplement existing diol monoacetylations.

Scheme 1



Scheme 2



We now report a new approach to selectively monoacetylate diols using cyclic ketene acetals as unisolated intermediates. Cyclic ketene acetals were made from the parent diols via acetal exchange with 2-bromo-1,1-dimethoxyethane, followed by dehydrobromination (Scheme 2). This was performed using an improved dehydrobromination and cyclic ketene acetal isolation procedure recently developed in our labs.[10] Upon acid-catalyzed hydrolytic ring opening of the cyclic ketene acetal only the monoacetylated diols were obtained (100% monoacetylation selectivity).

Selected results on symmetrical diols are shown in Table 1.

Very high regioselectivity was observed during the monoacetylation of the unsymmetrical diols, 2-methyl-2,4-dihydroxypentane (**4f**) and 1,3-dihydroxybutane (**4g**). The least hindered hydroxyl was selectively acetylated. This might be due either to the regioselective hydrolytic ring opening of the corresponding cyclic ketene acetal or to the equilibrium shown in Scheme 1, in cases where the least substituted ester is thermodynamically more stable (Table 2). Subjecting monoester (**7g**) to dilute aqueous acetic acid for 90 s at 27 °C did not lead to the formation of 3-acetoxybutanol, suggesting the regioselectivity originated during ring opening.

The reactive cyclic ketene acetals, **6a-g**, were directly hydrolyzed to monoacetylated diols, **7a-g**, in situ without prior isolation or purification. Rapid cationic polymerization makes many cyclic ketene acetals difficult to purify and store. Therefore, practical procedures were developed for hydrolysis which avoided the isolation of cyclic ketene acetals.

The selective monoacetylation was conducted as follows. Dehydrobromination of **5** produced cyclic ketene acetal (**6**) and KBr as described previously.[1] These products were mixed with the remaining potassium *tert*-butoxide and THF. This mixture was diluted with excess

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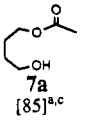
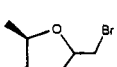
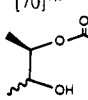
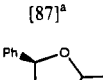
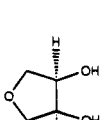
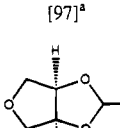
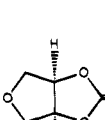
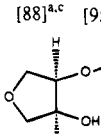
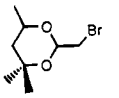
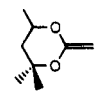
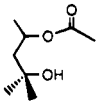
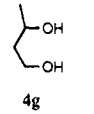
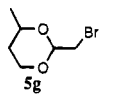
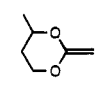
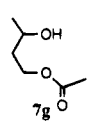
Table 1. Monoacetylation of Symmetrical Diols via Cyclic Ketene Acetals

Parent Diol	Elimination Precursor [Yield, %]	Elimination Time and Temperature	Intermediate Cyclic Ketene Acetal	Monoacetylation Products [Yield, %]
 **4a**	 **5a** [95][a]	90 °C, 4 h	 **6a**	 **7a** [85][a,c]
 **4b**	 **5b** [75][a]	0 °C, 0.5 h	 **6b**	 **7b** [70][b,c]
 **4c**	 **5c** [87][a]	80 °C, 36 h	 **6c**	 **7c** [90][b,c]
 **4d**	 **5d** [97][a]	80 °C, 3 h	 **6d**	 **7d**[d] [88][a,c] [95][b,c]
 **4e**	 **5e** [93][a]	85 °C, 2 h	 **6e**	 **7e** [85][b,c]

[a] Isolated yields. [b] GC yields. [c] No other acetylation products were detected. [d] Racemic.

Table 2. Regioselective Monoacetylation of Unsymmetrical Diols via Cyclic Ketene Acetals

Parent Diol	Elimination Precursor [Yield, %]	Elimination Time and Temperature	Intermediate Cyclic Ketene Acetal	Monoacetylation Products [Yield, %]
 **4f**	 **5f** [92][a]	55 °C, 12 h Reflux, 1 h	 **6f**	 **7f** [85][a,c]
 **4g**	 **5g** [82][a]	85 °C, 4 h	 **6g**	 **7g** [80][b,c]

[a] Isolated yields. [b] GC yields. [c] No other acetylation products were detected.

dry hexane, pentane, or petroleum ether. The solution was removed from the precipitated KBr and potassium *tert*-butoxide by cannula technique and then passed through alumina, held in a connecting adapter, under a small pressure of nitrogen. After most of the solvent was removed from the filtrate, about 2 equiv of water and a small amount of acetic acid were added. Hydrolysis was completed in 2–5 min at room temperature. The crude monoacetylation product was purified by flash chromatography or distillation. The overall yields (isolated or GC yields) starting from the diols ranged from 65% to 95%.

Filtration through alumina removed any remaining potassium *tert*-butoxide. Many cyclic ketene acetals, such as 2-methylene-1,3-dioxolane (**6b**), react rapidly with water in the alumina during the filtration step to give the monoacetylation product. The acidic alumina surfaces contain some water even after drying at 120 °C for 2 h. Even 2-methylene-1,3-dioxepane (**6a**), the most inert cyclic ketene acetal encountered in this series, was converted to 4-acetoxybutanol (**7a**) when passed through alumina.

The rates of cyclic ketene acetal hydrolysis were dependent on their structure.[11] Thus, 2-methylene-4-methyl-1,3-dioxolane and 2-methylene-1,3-dioxepane do not react with water immediately as monitored by GC. A trace of glacial acetic acid (or alumina surface catalysis) was necessary to promote the reaction. This was also observed for **6d** (Table 1).

Experimental Section

All the solvents and reagents were purchased from Aldrich Chemical Co., Inc., except potassium *tert*-butoxide and bromoacetaldehyde dimethyl acetal which were purchased from Lancaster Synthesis, Inc. THF, hexane, pentane, and petroleum ether were freshly distilled over sodium immediately before use. Silica gel (230–400 mesh) was used for column chromatography. Neutral alumina was used for filtration. All the glassware was base-soaked with potassium hydroxide in 2-propanol and then water-rinsed except as otherwise indicated.

Typical Procedure for the Synthesis of 2-(Bromomethyl)-1,3-dioxocyclic Acetals 5a-g. 2-(Bromomethyl)-4,5-dimethyl-1,3-dioxolane, 5c. In a 250-mL flask fitted with a Claisen distillation apparatus were heated 2,3-butanediol (90.12 g, 1.00 mol), bromoacetaldehyde dimethyl acetal (169.03 g, 1.00 mol), and Dowex-x8 (H^+) resin (0.45 g) at 80 °C for 36 h while being stirred. The calculated amount of methanol was continuously removed during the reaction by distillation into a receiver. The reaction progress was followed by gas chromatography (30 M DM-5 column, temperature program: initial temperature of 50 °C for 10 min and final temperature of 300 °C for 2 min at ramp rate of 10 °C/min). The crude product was fractionated at 35 °C (0.15 mmHg) to yield 170 g (87%) of a mixture of the geometrical isomers **5c**. FTIR (neat): 2983.1, 2879.5, 1381.3, 1117.5, 995.0, 665.2 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ for **5c**-*syn* 1.102–1.238 (d, J = 10.8 Hz, 6H, methyls (C-4) and (C-5), since this doublet overlapped with methyl protons of the *anti* isomer, it appeared to be a multiplet), 3.333 (d, 2H, J = 4.3 Hz, $-CH_2Br$), 4.299–4.350 (m, 2H, H(C-4) and H(C-5)), 5.342 (t, 1H, J = 4.1 Hz); δ for **5c**-*anti* 1.102–1.238 (d, 6H, methyls (C-4 and C-5), this doublet was hidden in the methyl proton peaks of δ **5c**-*syn* as can be seen from the 2D-^{13}C–^1H correlation spectrum or area integration of ^1H NMR), 3.381 (d, 2H, J = 4.2 Hz, $-CH_2Br$), 4.176–4.268 (m, 2H, H(C-4) and H(C-5)), 5.062 (t, 1H, J = 4.2 Hz); δ for **5c**-*r-2,cis-4-trans-5* 1.311 (d, 3H, J = 5.7 Hz, methyl (C-4)), 1.256 (d, 3H, J = 5.7 Hz, methyl (C-5), 5.242 (t, 1H, J = 4.0 Hz). ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ for **5c**-*syn* 15.22 (methyls on C-4 and C-5), 32.52 ($-CH_2Br$-6), 75.16 (C-4 and C-5), 100.79 (C-2); δ for **5c**-*anti* 14.12 (methyls on C-4 and C-5), 33.54 ($-CH_2Br$-6), 74.96 (C-4 and C-5), 100.21 (C-2); δ for **5c**-*r-2,cis-4-trans-5* 16.40 (methyl on C-4), 16.60 (methyl on C-5), 33.30 ($-CH_2Br$-6), 80.10 (C-4), 78.70 (C-5), 100.79 (C-2). MS (EI): 193/195 (M-1), 179/181, 121/123, 101, 93/95, 73, 71. HRMS: calcd for $C_6H_{11}O_2Br$ 193.9939/195.9919, found 193.9854/195.9855. Anal. Calcd for $C_6H_{11}O_2Br$: C, 36.95; H, 5.68. Found: C, 36.89; H, 5.63.

The other 2-(bromomethyl)-1,3-dioxocyclic acetals were prepared and fully characterized in a similar manner.[1,12]

Typical Procedure for the Formation of Cyclic Ketene Acetals and Their Acid-Catalyzed Hydrolyses to Monoacetylated Diols. The 2-(bromomethyl)-1,3-dioxocyclic acetals **5a-g**, made by an acid-catalyzed acetal exchange as described above, were subjected to HBr elimination using potassium *tert*-butoxide as a base in THF to afford cyclic ketene acetals. Usually, 1.0–1.5 equiv of the base was needed. The reagents

(11) More rigorous studies are now being undertaken to reveal relative reactivities of different cyclic ketene acetals.

(12) The detailed spctra data for those 2-(bromomethyl)-1,3-dicyclic acetals will be submitted in another paper covering stereochemical studies.

and solvent for the reaction must be moisture free and well protected with dry nitrogen or argon. The reaction temperature varied from 0 to about 90 °C depending on the steric factors in the different starting substrates. The reaction was completed with efficient stirring in reaction times of 30 min to 1 day depending on the temperature employed. GC analysis was used to determine the end point of the eliminations. After a reaction was completed, a large amount of dry pentane or hexane was added portionwise at room temperature (about 100 mL of the solvent for each gram of the cyclic ketene acetal formed). Each time the solvent was added, the reaction solution was stirred for a few minutes and then allowed to stand for about 30 min. KBr and most of the remaining potassium *tert*-butoxide precipitated in the flask. The clear solution was then filtered through 3–4 g of neutral alumina in a connecting adapter held in place by glass wool under nitrogen flow. A flexible needle was used for the transfer. After most of the solvent was removed, 2–4 molar equiv of distilled water (with 1 mol % acetic acid) was added into the filtrate. This mixture was stirred at room temperature for 2–5 min to complete the hydrolysis. For less active cyclic ketene acetals, such as 2-methylene-1,3-dioxepane (**6a**) and 2-methylene-4,5-diphenyl-1,3-dioxolane (**6d**), the use of acetic acid was required. Extra acetic acid was sometimes necessary to neutralize residual base which may be present. However, in most cases, the catalytic amount (about 1 mol %) of acetic acid was enough. The crude monoacetylation product was extracted three times from the acidic water solution with ether and dried with anhydrous sodium sulfate. After the removal of solvent *in vacuo*, the product was purified by flash chromatography or by distillation.

Some of the monoacetylation reactions were analyzed by GC and GC/MS. In these cases, the cyclic ketene acetal hydrolyses also were carried out in *ca.* 5–10 mg scale without isolation of the products. The rest of the procedures were the same as above. The GC-determined yields were equal to or higher than the isolated yields. The molecular ions of monoacetylated diols were not stable enough to be observed using EI MS techniques. Therefore, positive chemical ionization MS was coupled with GC to identify the $(M^+ + 1)$ ion. Methane was used as the chemical ionization gas. The peaks for $(M^+ + 1)$ ions of **7b** (104.8), **7c** (133.1), **7d** (257.0), **7e** (147.0), **7f** (161.0), and **7g** (133.1) were obtained with strong to medium intensity.

4-Acetoxy-2-methylpentan-2-ol (7f). 2-(Bromomethyl)-4,4,6-trimethyl-1,3-dioxane, **5f** (22.3 g, 0.100 mol), Aliquat 336 (0.808 g, 2.00×10^{-3} mol), dry THF (150 mL), and potassium *tert*-butoxide (16.80 g, 0.150 mol) were added to a 250-mL flask fitted with a condenser and protected with nitrogen. After 12 h at 55 °C only 9% of the starting material remained. The mixture was then refluxed for *ca.* 1 h to complete the reaction. Pentane (200 mL × 4) was added. After each addition, the reaction solution was stirred for a few minutes and then allowed to stand for 15 min. The mixture was filtered through 10 g of alumina in a connecting adapter under nitrogen flow. After most of the solvent was removed, the combined concentrated filtrate was treated with distilled water (5.40 g, 0.30 mol) and 4 drops of acetic acid, followed by stirring at room temperature for 3 min. The crude product was extracted from the acidic water solution with ether (20 mL × 3) and dried over anhydrous sodium sulfate. After removal of the solvent at 55 °C and 40 mmHg, the crude product was vacuum distilled to afford monoacetylation product **7f**. GC: single peak (DB-5 column 30 M, initial temperature 50 °C for 10 min and final temperature of 300 °C for 10 min at ramp rate of 10 °C/min.). FTIR (neat): 3466.9 (s), 2988.3, 2920.3, 1723.6 (s), 1459.8, 1365.5, 1252.4, 1139.4, 1045.1, 941.5, 894.4, 819.0 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.223 (s, 3H, methyl), 1.235 (s, 3H, methyl), 1.268 (d, 3H, methyl, J = 6.3 Hz), 1.643 (dd, 1H, one of the $-CH_2-$, J_{vic} = 6.3 Hz, J_{gem} = −15.0 Hz), 1.866 (dd, 1H, another of the $-CH_2-$, J_{vic} = 3.3 Hz, J_{gem} = −14.9 Hz), 2.047 (s, 3 H, methyl), 2.360 (broad, 1H, hydroxyl, disappeared on exchange with D_2O), 5.104–5.185 (m, 1H, >CH−). ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 21.659 (acetoxy methyl), 29.550 and 29.620 (>C*H*CH_3), 48.831 ($-CH_2-$), 68.739 (>CH−), 69.951 (>C<), 170.760 (>C=O). These assignments were confirmed by Hetcore experiments. MS (CI): 161 $(M^+ + 1)$, 145 $(M^+ - CH_3)$, 142 $(M^+ - H_2O)$, 127 (142 − CH_3), 101 $(M^+ - CH_3COO)$, 83 (101 − H_2O). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.09; H, 10.09.

In order to verify the assignments, 4-acetoxy-2-methylpentan-2-ol (**7f**) was also prepared by reaction of 2-methyl-2,4-pentanediol and acetic anhydride using sodium hydride as the base. After workup, compound **7f** was separated from other byproducts by flash chromatography (ethyl acetate:hexane = 99:1). The GC, MS, IR, ^1H NMR, and ^{13}C NMR are identical to **7f** obtained by the above method.

The preparation of **7a-e** and **7g** were carried out as described above. Structural data are given below.

4-Acetoxybutanol (7a). FTIR (neat): 3412.1 (s), 2948.4, 2882.5, 1738.4 (s), 1441.1, 1359.1, 1240, 1046.9, 949.8, 608.6 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.575–1.768 (m, 4H, $-CH_2-CH_2-$), 2.057 (s, 3H, methyl), 2.875 (broad, 1H, hydroxyl, disappeared upon exchange with D_2O), 3.655 (t, 2H, $HOCH_2-$, J = 6.3 Hz), 4.098 (t, 2H, CH_3COOCH_2-, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 20.805 (acetoxy methyl), 24.909 ($HOCH_2-CH_2-$), 28.865 ($CH_3COOCH_2CH_2-$), 61.957 ($HOCH_2-$), 64.239 (CH_3COOCH_2-), 171.296 (CH_3COOCH_2-). Anal. Calcd for $C_6H_{12}O_3$: C, 52.16; H, 9.07. Found: C, 52.16; H, 9.08.

2-Acetoxyethanol (7b). MS (CI): 104.8 $(M^+ + 1)$, 86.9 $(M^+ + 1 - H_2O$, base peak), 97 (115 − H_2O).

3-Acetoxybutan-2-ol (7c). MS (CI): 133.1 $(M^+ + 1)$, 115 $(M^+ + 1 - H_2O)$, 89 $(M^+ - Ac)$, 73 $(M^+ - AcO$, base peak).

2-Acetoxy-1,2-diphenylethanol (7d). Mp 88.0–89.0 °C (5% ethyl acetate in hexane). FTIR (KBr): 3445, 3089, 3064, 3033, 2931, 1955, 1889, 1734, 1496, 1455, 1374, 1240, 1081, 1028, 979, 913, 761, 701, 611, 568, 537 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.967 (s, 3H, methyl), 2.304 (broad, 1H, hydroxyl), 4.949 (d, HOC*H*<, J = 6.0 Hz), 5.881 (d, CH_3COOCH<, J = 6.0 Hz), 7.720–7.312 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 20.904 (methyl), 76.078 (HOCH<), 78.753 (CH_3COOCH<), 126.833, 127.609, 128.087, 136.323, 139.489 (aromatic), 169.741 (acetoxy carbonyl). MS (EI), 256 (M^+), 213 $(M^+ - CH_3CO)$, 196 $(M^+ - CH_3COO, -1)$, 179 $(M^+ - CH_3COO, - H_2O)$, 178 (196 − H_2O), 167 (Ph_2CH^+), 150 (M − PhCHO, rearrangement from M^+), 149 $(M^+ -$ PhCH, − OH), 107 $(M^+ - 149$, base peak), 105 ($PhCO^+$, from 196), 91 ($PhCH^+_2$, from 196), 77 (Ph^+), 43 (CH_3CO^+). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.79; H, 6.32.

1,4-Anhydroerythritol, Monoacetate (7e). MS (CI): 147.0 $(M^+ + 1$, base peak), 129.0 $(M^+ + 1 - H_2O)$.

1-Acetoxy-3-butanol (7g). MS (CI): 133.1 $(M^+ + 1)$, 115 $(M^+ + 1 - H_2O)$, 97 (115 − H_2O). The other isomer, 3-acetoxybutanol, was not formed. The latter was isolated from a monoacetylation resulting from treatment of the diol with acetic anhydride and sodium hydride. A complicated mixture was obtained including the starting material, the diacetylation product, and the two expected monoacetylation products. Each of the monoacetylation products had a totally different MS (CI) fragmentation pattern. **3-Acetoxybutanol.** MS (CI): 133.1 $(M^+ + 1)$, 101 $(M - CH_2OH)$, 73 (M − AcO) and no 115 peak existed.

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