

Acidic, Selective Monoacylation of *vic*-Diols

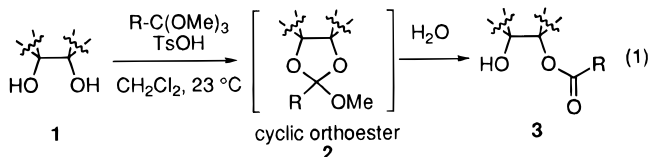
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Selective transformation of diols is an important subject in synthetic chemistry.¹ Several methods have been developed for monoderivatization of polyols, *e.g.*, by means of dibutylstannylene acetals^{2a} or monoalkoxide sodium salt,^{2b} nucleophilic opening of benzylidene-type acetals,^{2c} and transderivatization catalyzed by metallic sulfates or ion-exchange resins.^{2d} Herein we report an effective method for monoacylation of *vic*-diols under acidic conditions.

The present method is outlined in eq 1. At first, a *vic*-diol **1** is converted to the cyclic orthoester **2** by the action of 1.2–1.5 equiv of trimethyl orthoester in the presence of a catalytic amount of TsOH in CH₂Cl₂. The addition

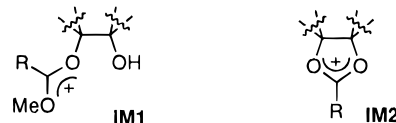


of a stoichiometric amount of water then follows, providing the corresponding monoacetate(s) **3** exclusively in a *one-pot operation*. The yield is moderate to high, and the regioselectivity is often high for unsymmetrical diols.^{3,4}

The results are summarized in Table 1. The disubstituted diols **4** and **6** were selectively converted to the monoacetates **5** and **7**, respectively, by the action of trimethyl orthoacetate (Table 1, entries 1 and 2). It is noteworthy that acetylation of **6** by Ac₂O (1.0 equiv) and pyridine (1.3 equiv) in CH₂Cl₂ (23 °C, 17 h) gave **7** and **8** in 54% and 13% yield, respectively. The total yield is almost the same, but the regioselectivity of the present reaction is better than under conventional reaction conditions. When the trisubstituted diols were subjected to the reaction, the acetyl groups were predominantly introduced to the hydroxyls that are attached to the less substituted carbons (Table 1, entries 3 and 4). The

reaction of less reactive substrates **15** and **18** did not proceed with trimethyl orthoacetate but with trimethyl orthoformate (Table 1, entries 5 and 6). In these cases formylation preferentially occurred at the β-hydroxyls from the ester functionality as in entries 1–3 (Table 1), but the regioselectivities were moderate. As seen in entries 7–9 (Table 1), *tert*-butoxycarbonyl-substituted diol **21** was monoacylated using trimethyl orthoacetate, trimethyl orthobenzoate, or trimethyl ortholaurate⁵ to give the acetate **22**, the benzoate **23**, and the laurate **24**, respectively, without any production of the regioisomers. In the case of a longer acyl group (Table 1, entry 9), however, the yield was poor, and 89% of unreacted **21** was recovered. These high regioselectivities presumably are due to the bulkiness of the *tert*-butyl group though we did not examine the *tert*-butyl ester analog corresponding to the simplest diol **6**. The *tert*-butoxycarbonyl-substituted *erythro*-diol **25** can also be converted regioselectively to the monoacetate **26** in good yield. The present reaction is not simply controlled by the steric interaction alone since equal amounts of **29** and **30** were obtained from 1,2-butanediol **28** (Table 1, entry 11). Other substituents such as phenyl or chloromethyl groups influenced the regioselectivity moderately (Table 1, entries 12 and 13). The method is also applicable to the desymmetrization of symmetrical diols. Thus, ethylene glycol **37** and hydrobenzoin **39** were monoacylated in good yields in entries 14 and 15.

There is no clear relationship between the stereochemistry of cyclic orthoesters, which usually occur as diastereomeric mixtures from unsymmetrical diols (Table 1, entries 1–13), and that of the products. In addition, no significant acyl migration between two hydroxyl groups was observed after the reactions were complete. So the dioxocarbenium ionic species, represented by **IM1** or **IM2**, might be the intermediate for all the reaction entries examined, but there is no evidence to substantiate which of the two predominates. If **IM1** predominates over **IM2**, the regioselectivity of acylation is already controlled during the formation of **IM1** itself. If **IM2** is the real intermediate, the process from **IM2** to the monoacylated product contains the regiodetermining step.⁶ In any case, both the steric interaction and the acidity of the hydroxy groups should be considered to account for the regioselectivity.



As presented herein, monoacylation of diols *via* the orthoester proceeds under mild acidic conditions within a short reaction period to give monoacylates exclusively

(1) For examples in natural product syntheses, see: (a) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653–659. (b) Nicolaou, K. C.; Yue, E. W.; Naniwa, Y.; Riccardis, F. D.; Nadin, A.; Leresche, J. E.; Greca, S. L.; Yang, Z. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2184–2187. (c) Carreira, E. M.; Bois, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 10825–10826. (d) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031. (e) Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239–4243.

(2) (a) Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1373–1374. (b) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390. (c) DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669–672. (d) Nishiguchi, T.; Fujisaki, S.; Ishii, Y.; Yano, Y.; Nishida, A. *J. Org. Chem.* **1994**, *59*, 1191–1195 and references cited therein.

(3) The cleavage of cyclic orthoesters by 80% aqueous AcOH in carbohydrate syntheses is the only example of this type of transformation. See: Hanessian, S.; Roy, R. *Can. J. Chem.* **1985**, *63*, 163–172 and references cited therein.

(4) Quite recently, cleavage of cyclic orthoesters by TsOH/H₂O/CHCl₃ toward the monoacylation of gluco-, ribo-, and xylo-furanoses was reported. See: Bouchra, M.; Calinaud, P.; Gelas, J. *Synthesis* **1995**, 561–565.

(5) Oikawa, M.; Kusumoto, S. *Tetrahedron: Asymmetry* **1995**, *6*, 961–966.

(6) The titanium(IV)-mediated acylation of carbonyl compounds using ethylene glycol-derived orthoesters has been reported by Evans *et al.*⁷ The reaction unequivocally includes **IM2**-type intermediates. From this work it is plausible that the cyclic **IM2**, rather than the opened **IM1**, is also the intermediate in the present acylation of the ethylene glycol-derived orthoester (entry 14 in Table 1).

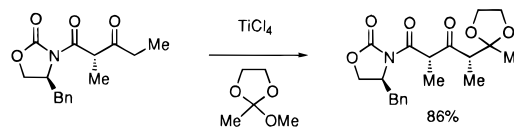


Table 1

entry	vic-diol	conditions	products	yields (%) ^a
1		MeC(OMe) ₃ , TsOH, 2 h then H ₂ O, 18 h		76
2		MeC(OMe) ₃ , TsOH, 1 h then H ₂ O, 21 h	 	62 : 7
3		MeC(OMe) ₃ , TsOH, 2 h then H ₂ O, 21 h	 	84 : <2
4		MeC(OMe) ₃ , TsOH, 1 h then H ₂ O, 30 min	 	<3 : 97
5		HC(OMe) ₃ , TsOH, 90 min then H ₂ O, 16 h	 	31 : 18 ^b
6		HC(OMe) ₃ , TsOH, 1 h then H ₂ O, 12 h	 	38 : 7 ^b
7		MeC(OMe) ₃ , TsOH, 35 min then H ₂ O, 20 min		87
8	21	PhC(OMe) ₃ , TsOH, 1 h then H ₂ O, 30 min		78
9	21	C ₁₁ H ₂₃ C(OMe) ₃ , TsOH, 2 h then H ₂ O, 11 h		9 ^c
10		MeC(OMe) ₃ , TsOH, 90 min then H ₂ O, 30 min	 	90 : <1
11		MeC(OMe) ₃ , TsOH, 140 min then H ₂ O, 19 h	 	36 : 34 ^b
12		MeC(OMe) ₃ , TsOH, 1 h then H ₂ O, 20 h	 	62 : 33 ^b
13		MeC(OMe) ₃ , TsOH, 1 h then H ₂ O, 30 min	 	64 : 25 ^b <i>threo</i> : <i>erythro</i> 4.9 : 1 <i>threo</i> : <i>erythro</i> 5.4 : 1
14		MeC(OMe) ₃ , TsOH, 90 min then H ₂ O, 30 min		80
15		MeC(OMe) ₃ , TsOH, 1 h then H ₂ O, 3 h		100

^a Isolated yields after silica gel chromatography. ^b The product ratio was determined from ¹H-NMR spectra. ^c Yield not optimized.

without any production of byproducts. The operation is simple, and the reaction is often highly regioselective for unsymmetrical diols. Since optically active diols, especially the *threo*-diols from *trans*- α,β -unsaturated esters, can now be obtained by asymmetric dihydroxylation,⁸ we believe the present study has an importance in various situations in synthetic work. Further investigation toward elucidation of the regioselectivities as well as the

differentiation of complicated polyols using the orthoester method is now in progress.

Experimental Section

All reagents and solvents were used as received, and all reactions were carried out at 23 °C under air. The experimental techniques and the characterizing apparatuses used are summarized in our previous paper.⁵

All reactions were carried out on a 100 mg scale. In a typical reaction, *vic*-diol **1** (1 mmol) was converted to the cyclic orthoester **2** by the action of a slight excess of trimethyl orthoester (1.5 mmol) in the presence of a catalytic amount of *p*-toluene-

(7) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547 and references cited therein.

sulfonic acid monohydrate (3.8 mg, 20 μ mol) in CH_2Cl_2 (10 mL) at rt. After the formation of the new orthoester was complete (see Table 1), as monitored by TLC, a stoichiometric amount of water (27 μ L, 1.5 mmol) was added to the mixture. The mixture was then stirred for the period as indicated in Table 1 and concentrated *in vacuo*. Purification of the residue by silica gel flash chromatography gave monoacylated products **3**. The monoacylation products in entries 5, 6, and 11–13 (Table 1) could not be isolated from other isomers by silica gel flash chromatography, so the product data were obtained selectively from the product mixture and the ratio was determined on the basis of $^1\text{H-NMR}$ spectra.

R_f values and $^{13}\text{C-NMR}$ data of the products are summarized in the supporting information.

Data for (\pm)-ethyl 3-acetoxy-2-hydroxy-2-methylpropionate (5): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 4.29–4.25 (m, 3H), 4.13 (d, $J = 11.3$ Hz, 1H), 3.41 (s, 1H), 2.06 (s, 3H), 1.42 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H). Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_5$: C, 50.52; H, 7.42. Found: C, 50.24; H, 7.53.

Data for ethyl (2*R,3*S**)-3-acetoxy-2-hydroxybutanoate (7):** $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 5.25 (dq, $J = 2.5, 6.6$ Hz, 1H), 4.25 (m, 2H), 4.12 (dd, $J = 7.6, 2.5$ Hz, 1H), 2.93 (d, $J = 7.6$ Hz, 1H), 2.02 (s, 3H), 1.37 (d, $J = 6.6$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H). Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_5$: C, 50.52; H, 7.42. Found: C, 50.34; H, 7.55.

Data for ethyl (2*R,3*S**)-3-acetoxy-2-hydroxy-2-methylbutanoate (10):** $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 5.13 (q, $J = 6.4$ Hz, 1H), 4.28–4.15 (m, 2H), 3.26 (s, 1H), 2.01 (s, 3H), 1.35 (s, 3H), 1.28 (d, $J = 6.4$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 1H). Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}_5$: C, 52.93; H, 7.90. Found: C, 52.72; H, 7.98.

Data for (\pm)-ethyl 2-acetoxy-3-hydroxy-3-methylbutanoate (14): $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 4.83 (s, 1H), 4.25 (q, $J = 7.0$ Hz, 2H), 2.63 (s, 1H), 2.18 (s, 3H), 1.33–1.27 (m, 9H). Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}_5$: C, 52.93; H, 7.90. Found: C, 52.92; H, 8.00.

Selected data for (\pm)-ethyl 3-(formyloxy)-2-hydroxy-2,3-dimethylbutanoate (16): $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.05 (s, 1H), 4.28 (dq, $J = 1.6, 7.1$ Hz, 2H), 3.81 (s, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 1.42 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H). Anal. (as the mixture with **17**) Calcd for $\text{C}_9\text{H}_{16}\text{O}_5$: C, 52.93; H, 7.90. Found: C, 53.11; H, 8.06.

Selected data for (\pm)-ethyl 2-(formyloxy)-3-hydroxy-2,3-dimethylbutanoate (17): $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.05 (s, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 2.50 (s, 1H), 1.70 (s, 3H), 1.31 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.29 (s, 3H).

Selected data for ethyl (2*R,3*S**)-3-(formyloxy)-2-hydroxy-3-phenylpropionate (19):** $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 8.11 (s, 1H), 7.43–7.31 (m, 5H), 6.19 (d, $J = 3.0$ Hz, 1H), 4.42 (dd, $J = 7.2, 3.1$ Hz, 1H), 4.24 (m, 2H), 3.07 (d, $J = 7.2$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H). Anal. (as the mixture with **20**) Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5 \cdot 0.1\text{H}_2\text{O}$: C, 60.04; H, 5.96. Found: C, 59.92; H, 5.94.

Selected data for ethyl (2*R,3*S**)-2-(formyloxy)-3-hydroxy-3-phenylpropionate (20):** $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 8.05 (s, 1H), 7.43–7.31 (m, 5H), 5.35 (dd, $J = 4.0, 1.0$ Hz, 1H), 5.25 (dd, $J = 6.1, 4.0$ Hz, 1H), 4.19 (m, 2H), 2.71 (d, $J = 6.1$ Hz, 1H), 1.19 (t, $J = 7.1$ Hz, 3H).

Data for tert-butyl (2*R,3*S**)-3-acetoxy-2-hydroxytetradecanoate (22):** $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 5.17 (dt, $J = 2.3, 6.9$ Hz, 1H), 4.09 (dd, $J = 7.2, 2.3$ Hz, 1H), 2.93 (d, $J = 7.2$ Hz, 1H), 2.02 (s, 3H), 1.77–1.63 (m, 2H), 1.46 (s, 9H), 1.39–1.19 (m, 18H), 0.88 (t, $J = 6.6$ Hz, 3H). Anal. Calcd for $\text{C}_{20}\text{H}_{38}\text{O}_5$: C, 67.00; H, 10.68. Found: C, 67.26; H, 10.60.

Data for tert-butyl (2*R,3*S**)-3-(benzoyloxy)-2-hydroxytetradecanoate (23):** $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 8.00 (dd,

$J = 7.8, \sim 1$ Hz, 2H), 7.55 (tt, $J = 7.8, \sim 1$ Hz, 1H), 7.42 (t, $J = 7.8$ Hz, 2H), 5.40 (dt, $J = 2.1, 7.1$ Hz, 1H), 4.23 (dd, $J = 6.7, 2.1$ Hz, 1H), 3.10 (d, $J = 6.7$ Hz, 1H), 1.88–1.83 (m, 2H), 1.42–1.24 (m, 18H), 1.36 (s, 9H), 0.88 (t, $J = 7.0$ Hz, 3H). Anal. Calcd for $\text{C}_{25}\text{H}_{40}\text{O}_5$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.71.

Data for tert-butyl (2*R,3*S**)-2-hydroxy-3-(dodecanoyloxy)tetradecanoate (24):** $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 5.18 (dt, $J = 2.1, 7.3$ Hz, 1H), 4.08 (dd, $J = 7.1, 2.1$ Hz, 1H), 2.92 (d, $J = 7.1$ Hz, 1H), 2.33 (t, $J = 7.2$ Hz, 2H), 1.73–1.67 (m, 2H), 1.62–1.53 (m, 2H), 1.45 (s, 9H), 1.34–1.22 (m, 34H), 0.88 (m, 6H). Anal. Calcd for $\text{C}_{30}\text{H}_{58}\text{O}_5$: C, 72.24; H, 11.72. Found: C, 72.43; H, 11.83.

Data for tert-butyl (2*R,3*R**)-3-acetoxy-2-hydroxytetradecanoate (26):** $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 5.09 (ddd, $J = 9.4, 4.4, 3.2$ Hz, 1H), 4.20 (dd, $J = 5.7, 3.2$ Hz, 1H), 3.17 (d, $J = 5.7$ Hz, 1H), 2.09 (s, 3H), 1.78–1.69 (m, 1H), 1.52–1.44 (m, 1H), 1.51 (s, 9H), 1.37–1.22 (m, 18H), 0.88 (t, $J = 7.0$ Hz, 3H). Anal. Calcd for $\text{C}_{20}\text{H}_{38}\text{O}_5 \cdot 0.1\text{H}_2\text{O}$: C, 66.67; H, 10.69. Found: C, 66.43; H, 10.63.

Selected data for (\pm)-2-hydroxybutyl acetate (29): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 4.15 (dd, $J = 11.4, 3.0$ Hz, 1H), 3.97 (dd, $J = 11.4, 7.3$ Hz, 1H), 3.77 (m, 1H), 2.10 (s, 3H), 1.52 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H).

Selected data for (\pm)-1-hydroxy-2-butyl acetate (30): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 4.85 (dq, $J = 3.2, 6.4$ Hz, 1H), 3.72 (dd, $J = 12.1, 3.2$ Hz, 1H), 3.64 (dd, $J = 12.1, 6.4$ Hz, 1H), 2.10 (s, 3H), 1.63 (m, 2H), 0.93 (t, $J = 7.6$ Hz, 3H).

Selected data for (\pm)-1-hydroxy-1-phenyl-2-propyl acetate (32): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.38–7.30 (m, 5H), 5.09 (quintet, $J = 6.4$ Hz, 1H), 4.62 (dd, $J = 6.4, 3.6$ Hz, 1H), 2.09 (s, 3H), 1.11 (d, $J = 6.4$ Hz, 3H).

Selected data for (\pm)-2-hydroxy-1-phenylpropyl acetate (33): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.38–7.30 (m, 5H), 5.52 (d, $J = 7.4$ Hz, 1H), 4.06 (m, 1H), 2.12 (s, 3H), 1.08 (d, $J = 6.4$ Hz, 3H).

Data for the Mixture of erythro- and threo-Chlorohydroxybutyl Acetates (35 and 36). Although these four isomers could not be purified by silica gel chromatography, the selectivity was apparently measured by $^1\text{H-NMR}$ (see the supporting information). Anal. Calcd for $\text{C}_6\text{H}_{11}\text{O}_3\text{Cl}$: C, 43.26; H, 6.65. Found: C, 42.99; H, 6.65.

Data for 2-hydroxyethyl acetate (38): $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 4.21 (m, 2H), 3.84 (m, 2H), 2.11 (s, 3H). Anal. Calcd for $\text{C}_4\text{H}_8\text{O}_3 \cdot 0.3\text{H}_2\text{O}$: C, 43.87; H, 7.92. Found: C, 43.91; H, 8.04.

Data for (1*S,2*S**)-2-hydroxy-1,2-diphenylethyl acetate (40):** mp 93–94 $^\circ\text{C}$; $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 7.25–7.17 (m, 6H), 7.15–7.10 (m, 4H), 5.85 (d, $J = 7.3$ Hz, 1H), 4.92 (dd, $J = 7.9, 3.3$ Hz, 1H), 2.58 (d, $J = 3.3$ Hz, 1H), 2.12 (s, 3H). Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$: C, 74.98; H, 6.29. Found: C, 74.62; H, 6.29.

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Supporting Information Available: R_f values and $^{13}\text{C-NMR}$ data of the products and $^1\text{H-NMR}$ spectra of entries 5, 6, and 11–13 in Table 1 (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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