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Tetrahedron Letters 45 (2004) 1243–1246
Tetrahedron Letters

A novel and efficient method for inside selective esterification of terminal *vic*-diols

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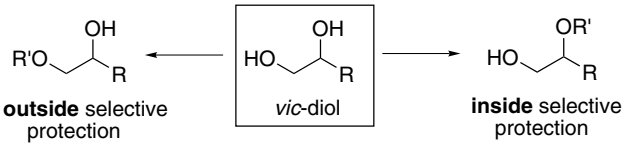
Received 12 September 2003; revised 26 November 2003; accepted 27 November 2003

Abstract—A novel and highly efficient procedure for inside selective esterification of terminal *vic*-diols has been achieved in one-pot via $Yb(OTf)_3$-catalyzed formation and partial hydrolysis of cyclic orthoesters. This method offers several advantages including wide compatibility with acid labile functional groups, and good to high regioselectivity and yields.

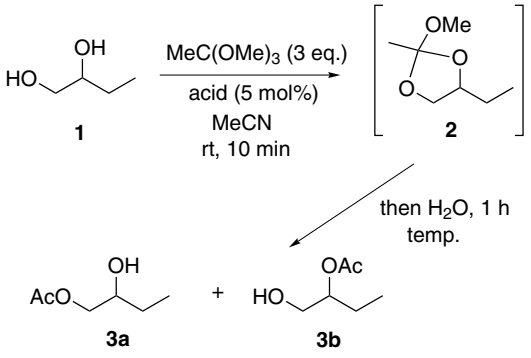
Regioselective transformation of *vic*-diols, which are important structural units or synthetic building blocks for many biologically active compounds, is a significant subject in organic synthesis (Scheme 1).[1] In fact, a variety of techniques has been developed for regioselective protection of a sterically less hindered hydroxy group (outside hydroxy group).[2,3] However, monoprotection of a more hindered one (inside hydroxy group) is considerably difficult, and generally requires multistep transformations;[4] accordingly, the development of a simple and convenient method for regioselective protection of the inside hydroxy group is greatly desirable. For this reason, several methods for inside selective etherification such as benzylation,[5] *tert*-butylation,[6] methoxymethylation,[7] and silylation[8] have been reported. However, in spite of the highly potent synthetic utility of 2-acyloxy-1-alkanols,[9] there have been few studies concerning inside selective esterification of terminal *vic*-diols.[10] As a novel strategy for the regioselective preparation of 2-acyloxy-1-alkanols, we focused on the hydrolytic cleavage of cyclic orthoesters. This is a general method for esterification of polyols, particularly in the field of carbohydrate syntheses,[11] but the generality of this reaction including the regioselectivity for cleavage is not fully established.[12] In particular, to the best of our knowledge, there has been no report about inside selective esterification of terminal *vic*-diols via the cyclic orthoesters. In this paper, we wish



Scheme 1.

to report an effective one-pot procedure for inside selective acetylation and benzoylation of terminal *vic*-diols by hydrolysis of the corresponding cyclic orthoesters.

Under several acidic conditions, at the outset, we investigated the transformation of 1,2-butanediol (**1**) to cyclic orthoacetate **2** and the following hydrolysis by a one-pot operation in order to establish the best reaction conditions (Scheme 2).[13] Some of our results are



Scheme 2.

Keywords: Esterification; Regioselectivity; Lanthanide triflate; Orthoester.

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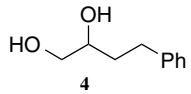
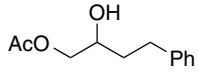
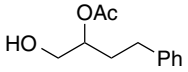
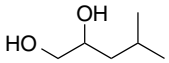
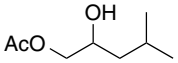
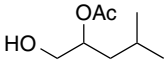
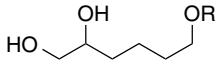
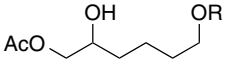
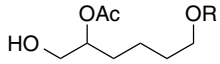
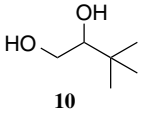
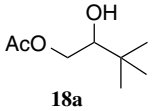
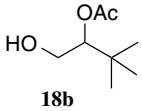
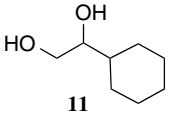
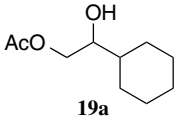
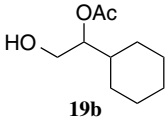
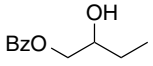
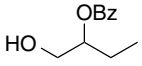
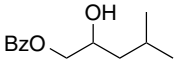
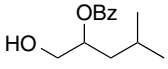
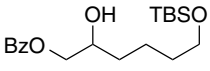
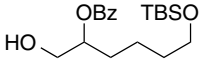
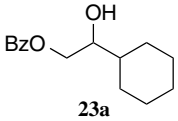
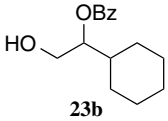
doi:10.1016/j.tetlet.2003.11.128

Table 1. Acetylation of 1,2-butanediol via orthoacetate **2**[a]

Entry	Acid	Temperature (°C)	Ratio (**3a**:**3b**)[b]	Yield (%)[c]
1	CSA	0	47:53	88
2	$Yb(OTf)_3$	0	23:77	84
3	$Yb(OTf)_3$	−40 to 0	18:82	85
4	$Y(OTf)_3$	−40 to 0	25:75	86
5	$Eu(OTf)_3$	−40 to 0	30:70	86
6	$La(OTf)_3$	−40 to 0	41:59	83
7	$Yb(OTf)_3$	−40 to 0	19:81	83

[a] A typical reaction procedure is described in the text. Reaction time for entries 1–6 was 1 h, and that for entry 7 was 5 h (1 h at −40 to 0 °C and then 4 h at 0 °C).
[b] The ratio was determined from ^{1}H NMR spectra.
[c] Total yield of **3a** and **3b**.

Table 2. Inside selective esterification of various *vic*-diols[a]

Entry	*vic*-Diol	Method[b]	Product		Ratio (**a**:**b**)[c]	Yield (%)[d]
1	 **4**	A	 **12a**	 **12b**	17:83	96
2	 **5**	A	 **13a**	 **13b**	11:89	94
		A				
3	**6** : R = MPM	A	**14a**	**14b**	16:84	99
4	**7** : R = MOM	A	**15a**	**15b**	19:81	90
5	**8** : R = TBS	A	**16a**	**16b**	15:85	98
6	**9** : R = Tr	A	**17a**	**17b**	15:85	95
7	 **10**	A	 **18a**	 **18b**	15:85	90
8	 **11**	A	 **19a**	 **19b**	10:90	96
9	**1**	B	 **20a**	 **20b**	14:86	90
10	**5**	B	 **21a**	 **21b**	7:93	94
11	**8**	B	 **22a**	 **22b**	12:88	76
12	**11**	B	 **23a**	 **23b**	5:95	95

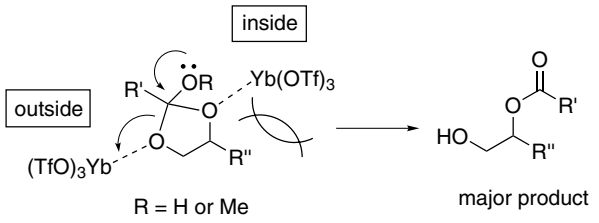
[a] Typical reaction procedures for methods A and B are described in the text.
[b] Method A: 3 equiv of $MeC(OMe)_3$, 5 mol% of $Yb(OTf)_3$, MeCN, room temperature, 10 min, and then H_2O, −40 to 0 °C, 1–2 h. Method B: 3 equiv of $PhC(OMe)_3$, 5 mol% of $Yb(OTf)_3$, MeCN, room temperature, 4–12 h, and then H_2O, −40 to 0 °C, 3–6 h.
[c] The ratio was determined from ^{1}H NMR spectra.
[d] Total yield of **a** and **b**.

summarized in Table 1. Although the desired secondary acetate **3b** was not regioselectively obtained using camphorsulfonic acid (CSA) as a Brønsted acid (entry 1),[14] the use of various lanthanide triflates [i.e., $Yb(OTf)_3$, $Y(OTf)_3$, and $Eu(OTf)_3$] as a Lewis acid gave **3b** in good regioselectivity and high yields (entries 2–5).[15] Unexpectedly, an attempt with $La(OTf)_3$ led to poor regioselectivity (entry 6). Above all, the treatment of $Yb(OTf)_3$ at low temperature (−40 to 0 °C) afforded the best result (entry 3). In addition, acyl migration between two hydroxyl groups under these conditions, was hardly observed even after prolonged treatment (entry 7).

Encouraged by the results described above, we next examined the reaction with various *vic*-diols **4**–**11** under the optimized conditions of entry 3 in Table 1, and the results are summarized at entries 1–8 in Table 2. In all cases, the acetylation proceeded smoothly to give the desired secondary acetates **12**–**19b** in good regioselectivity and high yields. This method was successfully applicable to substrates **7**–**9** containing a variety of acid-sensitive protecting groups such as MOM ether, TBS ether, and Tr ether (entries 4–6). In addition, this system allowed not only acetylation but also benzoylation, which is one of the most popular and useful protecting groups in organic synthesis, by using $PhC(OMe)_3$ instead of $MeC(OMe)_3$ (entries 9–12). In each case, the regioselectivity was rather higher than the corresponding regioselectivity of acetylation (entry 3 in Table 1 vs entry 9 in Table 2, entries 2, 5, and 8 vs entries 10–12).

Although the details, including the relation between the regioselective cleavage and stereochemistry of the cyclic orthoester, are unclear, a possible reaction mechanism is proposed in Scheme 3. It appears that $Yb(OTf)_3$ would coordinate with the outside oxygen more preferably than the inside oxygen because of steric interaction,[16] which would lead to regioselective cleavage of the outside C–O bond.

In conclusion, we have developed a novel and highly efficient procedure using $Yb(OTf)_3$ as a catalyst for inside selective acetylation and benzoylation of terminal *vic*-diols. This method offers several advantages such as a one-pot operation, mild reaction conditions, experimental simplicity, wide compatibility with other functional groups, and good to high regioselectivity and yields.[17] We believe that the present study would be greatly helpful in the transformation of *vic*-diols to 2-acyloxy-1-alkanols, which are commonly employed as building blocks in organic synthesis.[9]



Scheme 3.

Typical experimental procedure for acetylation (method A: entry 2 in Table 2):[18] To a stirred solution of *vic*-diol **5** (100 mg, 0.85 mmol) in anhydrous acetonitrile (2.5 mL) were added $MeC(OMe)_3$ (324 μL, 2.54 mmol) and $Yb(OTf)_3$ (26 mg, 5 mol %) at room temperature. After the starting material disappeared on TLC (ca. 10 min), H_2O (250 μL) was added dropwise to the reaction mixture at under −40 °C, which was gradually warmed to 0 °C for 1 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give an almost pure mixture of acetates **14a** and **14b** (**14a**:**14b** = 11:89, 128 mg, 94%) without further purification.

For benzoylation (method B: entry 11 in Table 2):[18] To a stirred solution of *vic*-diol **5** (56 mg, 0.47 mmol) in anhydrous acetonitrile (1.4 mL) were added $PhC(OMe)_3$ (244 μL, 1.42 mmol) and $Yb(OTf)_3$ (15 mg, 5 mol %) at room temperature. After stirring at room temperature for 12 h, H_2O (280 μL) was added dropwise to the reaction mixture at under −40 °C, which was gradually warmed to 0 °C for 1 h and stirred for 1 h at 0 °C additionally. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (EtOAc/hexane = 1:6 to 1:4) to give a mixture of benzoates **23a** and **23b** (**23a**:**23b** = 7:93, 99 mg, 94%).

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13. Orthoacetate **2** was so unstable that we performed the following hydrolysis without isolation of **2**.
14. Kusumoto and co-workers have reported a similar result with a catalytic amount of TsOH. See: Ref. 12a.
15. Interestingly, Bianco et al. have reported that hydrolysis of cyclic orthoacetates derived from *vic*-diols, in the presence of lanthanide chloride dispersed on silica, afforded primary acetates regioselectively. See: Ref. 12b.
16. It is known that lanthanoid triflates can work as a Lewis acid in aqueous media and can be recovered without loss of activity. See: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.
17. We tried an application of this method to a 1,1-disubstituted 1,2-diol system and 1,3-diol system as well, but, unfortunately, the regioselectivities were none to moderate.
18. Spectra for **3a** and **3b**, see: Ref. 12a. For **12a**, see: Ref. 12b. For **12b**, **13a**, and **13b**, see: Egri, G.; Baitz-Gacs, E.; Poppe, L. *Tetrahedron: Asymmetry* **1996**, *7*, 1437. For **14b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37–1.67 (6H, m), 1.91 (1H, t, $J = 6$ Hz), 2.09 (3H, s), 3.44 (2H, t, $J = 6$ Hz), 3.57–3.75 (2H, m), 3.80 (3H, s), 4.42 (2H, s), 4.90 (1H, m), 6.87 (2H, d, $J = 9$ Hz), 7.25 (2H, d, $J = 9$ Hz). IR ν_{max} (KBr): 3417, 2862, 1734, 1586, 1462 cm^{-1}. For **15b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.38–1.66 (6H, m), 1.94 (3H, br t, $J = 6$ Hz), 2.09 (3H, s), 3.35 (3H, s), 3.52 (2H, t, $J = 6$ Hz), 3.64 (1H, dt, $J = 12$, 6 Hz), 3.72 (1H, ddd, $J = 4$, 6, 12 Hz), 4.61 (2H, s), 4.91 (1H, m). IR ν_{max} (KBr): 3460, 2937, 1738, 1439 cm^{-1}. For **16b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.89 (9H, s), 1.40–1.62 (6H, m), 2.09 (3H, s), 3.60 (2H, t, $J = 6$ Hz), 3.63 (1H, dd, $J = 6$, 12 Hz), 3.72 (1H, dd, $J = 3$, 12 Hz), 4.91 (1H, m). IR ν_{max} (KBr): 3441, 2933, 1738, 1471 cm^{-1}. For **17b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.36–1.68 (6H, m), 1.92 (3H, br t, $J = 5$ Hz), 2.07 (3H, s), 3.05 (2H, t, $J = 6$ Hz), 3.54–3.72 (2H, m), 4.89 (1H, m), 7.19–7.32 (9H, m), 7.40–7.44 (6H, m). IR ν_{max} (KBr): 3458, 3058, 2942, 2868, 1736, 1490, 1448 cm^{-1}. For **18b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (9H, s), 2.13 (3H, s), 3.61 (1H, dd, $J = 8$, 12 Hz), 3.86 (1H, dd, $J = 2$, 12 Hz), 4.71 (1H, dd, $J = 2$, 8 Hz). IR ν_{max} (KBr): 3378, 2966, 1719, 1480 cm^{-1}. For **19b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01–1.28 (5H, m), 1.60–1.77 (6H, m), 1.88 (1H, br t, $J = 6$ Hz), 2.11 (3H, s), 3.70 (1H, dt, $J = 6$, 12 Hz), 3.75 (1H, ddd, $J = 3$, 6, 12 Hz), 4.73 (1H, m). IR ν_{max} (KBr): 3425, 2928, 2854, 1736, 1449 cm^{-1}. For **20a**, see: Ref. 3b. For **20b**, see: Ref. 3c. For **21b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (3H, d, $J = 6$ Hz), 0.98 (3H, d, $J = 8$ Hz), 1.48 (1H, m), 1.70–1.81 (2H, m), 2.07 (1H, br t, $J = 6$ Hz), 3.76 (1H, dt, $J = 12$, 6 Hz), 3.83 (1H, ddd, $J = 4$, 6, 12 Hz), 5.27 (1H, m), 7.42–7.60 (3H, m), 8.04–8.08 (2H, m). IR ν_{max} (KBr): 3421, 2957, 1716, 1602, 1452 cm^{-1}. For **22b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.87 (9H, s), 1.45–1.59 (4H, m), 1.71–1.79 (2H, m), 2.20 (1H, br t, $J = 4$ Hz), 3.61 (2H, t, $J = 6$ Hz), 3.74–3.86 (2H, m), 5.17 (1H, m), 7.41–7.60 (3H, m), 8.03–8.07 (2H, m). IR ν_{max} (KBr): 3438, 2929, 1719, 1602, 1452 cm^{-1}. For **23b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11–1.28 (5H, m), 1.66–1.80 (6H, m), 2.07 (1H, br t, $J = 6$ Hz), 3.82–3.88 (2H, m), 4.99 (1H, m), 7.43–7.60 (3H, m), 8.05–8.08 (2H, m). IR ν_{max} (KBr): 3410, 2926, 2853, 1716, 1602, 1584, 1450 cm^{-1}.