Diastereoselective Synthesis of Chiral 2,2,4-Trisubstituted 1,3-Dioxanes

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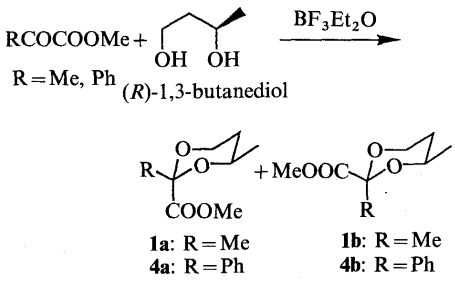
Diastereoselective acetalization of methyl pyruvate and methyl phenylformate with (*R*)-1,3-butanediol afforded predominantly (2*R*,4*R*)-2-methoxycarbonyl-2,4-dimethyl (or 4-methyl-2-phenyl)-1,3-dioxanes (1a, 4a) under thermodynamically controlled conditions. The (2*S*,4*R*)-isomer (1b) was obtained as the major product under kinetically controlled conditions.

Keywords diastereoselective synthesis; acetalization; 2,2,4-trisubstituted 1,3-dioxane; (*R*)-1,3-butanediol

As a part of our studies of asymmetric synthesis using chiral protecting groups,[1] this paper describes diastereoselective acetalization of α-ketoesters with (*R*)-1,3-butanediol. In 1974, Baily and Eliel[2] reported that the acid-catalyzed equilibrium of 2-ethoxycarbonyl-2,4-dimethyl-1,3-dioxanes favored the 2,4-*cis*-dimethyl isomer over the *trans* isomer. Their result prompted us to study the diastereoselectivity of acetalization using chiral (*R*)-1,3-butanediol.[3] Various reaction conditions were examined for acetalization of methyl pyruvate with (*R*)-1,3-butanediol. The use of *p*-toluenesulfonic acid (*p*-TsOH), pyridinium *p*-toluenesulfonate and trimethylsilyl triflate[4] as acid catalysts did not afford satisfactory results. Boron trifluoride (BF_3) etherate was found to be an efficient catalyst. Interestingly, it was found that the diastereoselectivity was affected by reaction temperature and duration (Table I). In entry 1, the 2*S*,4*R*-isomer (**1b**) was obtained as the major product with the diastereoselectivity of 7 to 1. On the contrary, the 2*R*,4*R*-isomer (**1a**) was obtained as a sole product in entry 2. Compounds **1a** and **1b** were easily separable by silica gel column chromatography. Thin layer chromatography (TLC) during the reaction of entry 2 revealed the initial formation of **1b** and subsequent conversion of **1b** to **1a**. Indeed, isolated **1b** could be completely converted to **1a** on treatment with BF_3 etherate, but conversion in the opposite direction was not observed. These results suggest that **1b** is the kinetically controlled product and **1a** is the thermodynamically controlled product.[5] Acetalization of methyl phenylformate did not proceed under the same reaction conditions as entry 1, but in entry 4, the 2*R*,4*R*-isomer (**4a**) was predominantly obtained with the diastereoselectivity of 6.7 to 1.

TABLE I. Acetalization of α-Keto Esters with (*R*)-1,3-Butanediol



1a: R = Me **1b**: R = Me
4a: R = Ph **4b**: R = Ph

Entry	Substrate	Reaction condition	Products and isolated yields (%)	
1	$CH_3COCOOMe$	0 °C 1.5 h	**1a** (4)	**1b** (29)
2	$CH_3COCOOMe$	r.t., 47 h	**1a** (64)	**1b** (0)
3	PhCOCOOMe	r.t., 23 h	**4a** (26)	**4b** (13)
4	PhCOCOOMe	r.t., 47 h	**4a** (47)	**4b** (7)

The stereochemistry of the 1,3-dioxanes (**1a, b** and **4a, b**) was determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectra after conversion into hydroxymethyl compounds (**2** and **5**) and acetoxymethyl compounds (**3** and **6**). In the two-dimensional NOESY (nuclear Overhauser effect spectroscopy) spectrum of **3a**, a cross peak between C_2-CH_2 (δ 4.38) and C_4-H (δ 4.03) was observed. On the other hand, in the spectrum of **2b**, cross peaks between C_2-Me (δ 1.43) and C_4-H (δ 4.07), C_6-H_{ax} (δ 4.01) were observed. In the case of phenyl derivatives, cross peaks between C_2-CH_2 (δ 4.54) and C_4-H (δ 4.30), C_6-H_{ax} (δ 4.11) were observed in **6a**, but no cross peak involving C_2-CH_2 of **6b** was observed. It was confirmed that the methyl group at C_4 in **2**, **3**, **5** and **6** possesses equatorial orientation, as depicted in Chart 1, from the coupling constant of C_4-H ($J_{C_4\text{-}H,C_5\text{-}H_{ax}}$ = 10.2—12.0 Hz, $J_{C_4\text{-}H,C_5\text{-}H_{eq}}$ = 2.5—4.3 Hz).

On acetalization of benzyloxyacetone[6] (*p*-TsOH, ben-

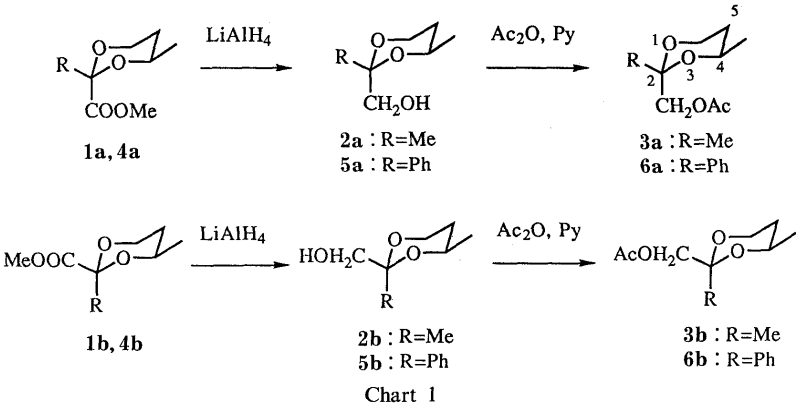
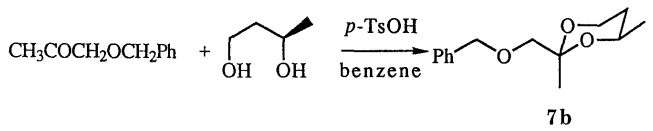


Chart 1



7b

Chart 2

zene, 70 °C) with (*R*)-1,3-butanediol, the 2*S*,4*R*-isomer (**7b**) was obtained as a sole product, whose structure was confirmed by comparison with an authentic sample derived from **2b**.

Asymmetric induction using chiral dioxanes is under investigation in our laboratory.

Experimental

Infrared (IR) spectra were measured on a Jasco A-202 spectrometer, ^{1}H-NMR spectra on a JEOL GX-270 spectrometer, and mass spectra (MS) on a JEOL JMS-D-300 spectrometer. For column chromatography, silica gel 70-230 mesh (Merck, Kieselgel 60) was used. All organic solvent extracts were washed with brine, and dried over anhydrous sodium sulfate.

General Procedure for Acetalization of α-Keto Esters BF_3–Et_2O (0.6 eq) was added to a stirred solution of an α-keto ester (10 eq) and a diol (1 eq) in CH_2Cl_2. The reaction mixture was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ and brine, then dried. After removal of the solvent *in vacuo*, the residue was roughly purified by silica gel column chromatography. The resulting crude mixture of α-keto ester and acetal was submitted to $NaBH_4$ reduction, and usual work-up afforded a residue, which was chromatographed on silica gel.

(2*R*,4*R*)-2-Methoxycarbonyl-2,4-dimethyl-1,3-dioxane (1a) Colorless oil, $[\alpha]_D^{28}$ −9.8° (*c*=1.04, $CHCl_3$). IR (neat): 1745, 1370, 1160, 1015 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, *J*=6.3 Hz, C_4-Me), 1.42 (1H, dddd, *J*=13.2, 2.6, 2.6, 1.6 Hz, C_5-H_{eq}), 1.51 (3H, s, C_2-Me), 1.68 (1H, dddd, *J*=13.2, 11.5, 11.5, 5.6 Hz, C_5-H_{ax}), 3.78—3.88 (2H, m, C_4-H, C_6-H_{ax}), 3.82 (3H, s, COOMe), 3.98 (1H, ddd, *J*=11.9, 5.6, 1.6 Hz, C_6-H_{eq}). MS *m/z*:115 (M^+ −COOMe), 102, 87.

(2*S*,4*R*)-2-Methoxycarbonyl-2,4-dimethyl-1,3-dioxane (1b) Colorless oil, $[\alpha]_D^{28}$ +5.3° (*c*=1.04, $CHCl_3$). IR (neat): 1745, 1370, 1160, 955 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, *J*=5.9 Hz, C_4-Me), 1.65 (3H, s, C_2-Me), 1.60—1.77 (2H, m, C_5-H), 3.82 (3H, s, COOMe), 4.00—4.05 (2H, m, C_6-H), 4.15 (1H, dqd, *J*=10.2, 5.9, 4.3 Hz, C_4-H). MS *m/z*: 159 (M^+ −Me), 115, 102.

(2*R*,4*R*)-2-Methoxycarbonyl-4-methyl-2-phenyl-1,3-dioxane (4a) Colorless solid, $[\alpha]_D^{23}$ +0.51° (*c*=1.15, $CHCl_3$). IR (Nujol): 1743, 1495, 1450, 1245, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, *J*=6.1 Hz, C_4-Me), 1.51 (1H, dddd, *J*=13.2, 2.6, 2.6, 1.6 Hz, C_5-H_{eq}), 1.78 (1H, dddd, *J*=13.2, 11.6, 11.6, 5.3 Hz, C_5-H_{ax}), 3.74 (3H, s, COOMe), 3.97—4.07 (2H, m, C_4-H, C_6-H_{ax}), 4.18 (1H, dddd, *J*=11.6, 5.3, 1.6 Hz, C_6-H_{eq}), 7.32—7.39 (3H, m, Ar-H), 7.64—7.69 (2H, m, Ar-H). MS *m/z*: 177 (M^+-COOMe), 123, 105.

(2*S*,4*R*)-2-Methoxycarbonyl-4-methyl-2-phenyl-1,3-dioxane (4b) Colorless solid, $[\alpha]_D^{24}$ −35.1° (*c*=1.15, $CHCl_3$). IR (Nujol): 1745, 1460, 1245, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, *J*=6.3 Hz, C_4-Me), 1.37 (1H, dddd, *J*=12.5, 4.3, 4.3, 1.6 Hz, C_5-H_{eq}), 1.82 (1H, dddd, *J*=12.5, 11.1, 11.1, 5.1 Hz, C_5-H_{ax}), 3.70 (3H, s, COOMe), 3.85—4.20 (3H, m, $C_{4,6}$-H), 7.33—7.46 (3H, m, Ar-H), 7.56—7.63 (2H, m, Ar-H). MS *m/z*: 177 (M^+ −COOMe), 149, 105.

Reduction of 1a, b and 4a, b A solution of a methyl ester (1 eq) in Et_2O was added dropwise to a stirred suspension of $LiAlH_4$ (1 eq) in Et_2O at 0 °C. The mixture was stirred for 1 h, and usual work-up afforded an oily residue, which was purified by silica gel column chromatography.

(2*R*,4*R*)-2-Hydroxymethyl-2,4-dimethyl-1,3-dioxane (2a) Colorless oil, 79% yield, $[\alpha]_D^{27}$ +3.6° (*c*=1.11, $CHCl_3$). IR (neat): 3450, 1380, 1170, 1110, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, *J*=6.1 Hz, C_4-Me), 1.40 (3H, s, C_2-Me), 1.48 (1H, dddd, *J*=13.2, 3.1, 3.1, 2.1 Hz, C_5-H_{eq}), 1.52 (1H, dddd, *J*=13.2, 11.2, 11.2, 5.8 Hz, C_5-H_{ax}), 1.98 (1H, br, OH), 3.80 (2H, br s, C_2-CH_2), 3.85—4.07 (3H, m, $C_{4,6}$-H). MS *m/z*: 131 (M^+ −Me), 115, 73.

(2*S*,4*R*)-2-Hydroxymethyl-2,4-dimethyl-1,3-dioxane (2b) Colorless oil, 70% yield, $[\alpha]_D^{27}$ +1.8° (*c* 1.02, $CHCl_3$). IR (neat): 3450, 1370, 1170, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, *J*=6.1 Hz, C_4-Me), 1.43 (3H, s, C_2-Me), 1.46 (1H, dddd, *J*=13.2, 3.1, 3.0, 2.0 Hz, C_5-H_{eq}), 1.61 (1H, dddd, *J*=13.2, 12.0, 12.0, 6.1 Hz, C_5-H_{ax}), 2.08, (1H, t, *J*=6.4 Hz, OH), 3.48 (2H, d, *J*=6.4 Hz, C_2-CH_2), 3.89 (1H, ddd, *J*=12.0, 6.1, 2.0 Hz, C_6-H_{eq}), 4.01 (1H, ddd, *J*=12.0, 12.0, 3.0, C_6-H_{ax}), 4.07 (1H, dqd, *J*=12.0, 6.1, 3.1 Hz, C_4-H). MS *m/z*: 131 (M^+ −Me), 115, 55.

(2*R*,4*R*)-2-Hydroxymethyl-4-methyl-2-phenyl-1,3-dioxane (5a) Colorless solid, 75% yield, $[\alpha]_D^{23}$ +23.4° (*c*=1.01, $CHCl_3$). IR (neat): 3400, 1450, 1305, 1160, 1125 cm^{-1}. ^{1}H-NMR (100 MHz) ($CDCl_3$) δ: 1.28 (3H, d, *J*=6.4 Hz, C_4-Me), 1.51—1.86 (3H, m, C_5-H, OH), 3.88 (2H, d, *J*=6.3 Hz, C_2-CH_2), 3.95—4.44 (3H, m, $C_{4,6}$-H). MS *m/z*: 208 (M^+), 177, 105.

(2*S*,4*R*)-2-Hydroxymethyl-4-methyl-2-phenyl-1,3-dioxane (5b) Colorless solid, 74% yield, $[\alpha]_D^{24}$ −29.3° (*c*=1.53, $CHCl_3$). IR (Nujol): 3400, 1460, 1380, 1190, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, *J*=6.1 Hz, C_4-Me), 1.32 (1H, dddd, *J*=13.0, 2.5, 2.5, 1.7 Hz, C_5-H_{eq}), 1.75 (1H, dddd, *J*=13.0, 11.5, 11.5, 5.1 Hz, C_5-H_{ax}), 2.22 (1H, t, *J*=6.4 Hz, OH), 3.51 (2H, d, *J*=6.4 Hz, C_2-CH_2), 3.78—3.99 (3H, m, $C_{4,6}$-H), 7.31—7.46 (5H, m, Ar-H). MS *m/z*: 208 (M^+), 191, 177, 123.

Acetylation of 2a, b and 5a, b Acetylation of the hydroxymethyl compounds (**2**, **5**) in a usual manner afforded the corresponding acetates (**3**, **6**).

(2*R*,4*R*)-2-Acetoxymethyl-2,4-dimethyl-1,3-dioxane (3a) Colorless oil, 80% yield. IR (neat): 1745, 1385, 1250, 1100, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, *J*=6.1 Hz, C_4-Me), 1.40 (3H, s, C_2-Me), 1.48 (1H, dddd, *J*=13.2, 3.0, 3.0, 1.8 Hz, C_5-H_{eq}), 1.60 (1H, dddd, *J*=13.2, 12.0, 12.0, 5.4 Hz, C_5-H_{ax}), 2.11 (3H, s, Ac), 3.86 (1H, ddd, *J*=11.9, 5.4, 1.8 Hz, C_6-H_{eq}), 3.98 (1H, ddd, *J*=12.0, 11.9, 3.0, C_6-H_{ax}), 4.03 (1H, dqd, *J*=12.0, 6.1, 3.0 Hz, C_4-H), 4.34, 4.41 (1H each, d, *J*=11.7 Hz, C_2-CH_2).

(2*S*,4*R*)-2-Acetoxymethyl-2,4-dimethyl-1,3-dioxane (3b) Colorless oil, 85% yield. IR (neat): 1745, 1380, 1250, 1100, 1050 cm^{-1}. ^{1}H-NMR (100 MHz) ($CDCl_3$) δ: 1.18 (3H, d, *J*=6.1 Hz, C_4-Me), 1.46 (3H, s, C_2-Me), 1.52—1.84 (2H, m, C_5-H), 2.11 (3H, s, Ac), 3.81—4.16 (3H, m, $C_{4,6}$-H), 4.02 (2H, s, C_2-CH_2). MS *m/z*: 188 (M^+), 173, 115.

(2*R*,4*R*)-2-Acetoxymethyl-4-methyl-2-phenyl-1,3-dioxane (6a) Colorless oil, 99% yield. IR (neat): 1740, 1370, 1245, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, *J*=6.1 Hz, C_4-Me), 1.61—1.70 (2H, m, C_5-H), 1.98 (3H, s, Ac), 3.95 (1H, ddd, *J*=11.2, 5.1, 4.0 Hz, C_6-H_{eq}), 4.11 (1H, m, C_6-H_{ax}), 4.30 (1H, m, C_4-H). 4.54 (2H, s, C_2-CH_2). MS *m/z*: 235 (M^+ −Me), 177, 105.

(2*S*,4*R*)-2-Acetoxymethyl-4-methyl-2-phenyl-1,3-dioxane (6b) Colorless oil, 91% yield. IR (neat): 1740, 1375, 1245, 1180 cm^{-1}. ^{1}H-NMR (100 MHz) ($CDCl_3$) δ: 1.25 (3H, d, *J*=6.1 Hz, C_4-Me), 1.35—1.85 (2H, m, C_5-H), 1.98 (3H, s, Ac), 3.66—4.00 (3H, m, $C_{4,6}$-H), 4.12 (2H, s, C_2-CH_2). MS *m/z*: 235 (M^+ −Me), 177, 123, 105.

Benzylation of 2a, b An alcohol (**2**, 1.0 eq) was added to a solution of $NaCH_2SOCH_3$ [prepared from NaH (1.5 eq) and dimethylsulfoxide (DMSO)] in DMSO. The mixture was stirred for 30 min at room temperature, then benzyl chloride (1.1 eq) in DMSO was added dropwise, and the whole was stirred for 1 h at room temperature. Usual work-up and silica gel column chromatography afforded **7a, b**.

(2*R*,4*R*)-2-Benzyloxymethyl-2,4-dimethyl-1,3-dioxane (7a) Colorless oil, 98% yield. IR (neat): 1495, 1365, 1165, 1095 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, *J*=6.1 Hz, C_4-Me), 1.41 (1H, m, C_5-H_{eq}), 1.42 (3H, s, C_2-Me), 1.59 (1H, dddd, *J*=13.2, 11.2, 11.2, 6.3 Hz, C_5-H_{ax}), 3.68, 3.73 (1H, each, d, *J*=10.2 Hz, C_2-CH_2), 3.80—4.00 (3H, m, $C_{4,6}$-H), 4.60 (2H, s, CH_2Ph). MS *m/z*: 236 (M^+), 221, 130, 115.

(2*S*,4*R*)-2-Benzyloxymethyl-2,4-dimethyl-1,3-dioxane (7b) Colorless oil, 88% yield. IR (neat): 1500, 1370, 1170, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, *J*=6.1 Hz, C_4-Me), 1.42 (3H, s, C_2-Me), 1.45 (1H, dddd, *J*=13.2, 3.2, 3.2, 1.6 Hz, C_5-H_{eq}), 1.61 (1H, dddd, *J*=13.2, 11.0, 11.0, 5.5 Hz, C_5-H_{ax}), 3.39 (2H, s, C_2-CH_2), 3.86 (1H, ddd, *J*=11.7, 5.5, 1.6 Hz, C_6-H_{eq}), 4.00 (1H, ddd, *J*=11.7, 11.0, 3.2 Hz, C_6-H_{ax}), 4.05 (1H, dqd, *J*=11.0, 6.1, 3.2 Hz, C_4-H), 4.61, 4.64 (1H, each, d, *J*=12.3 Hz, CH_2Ph). MS *m/z*: 236 (M^+), 221, 130, 115.

References and Notes

1) *a*) K. Funakoshi, K. Sakai, T. Hata, and C. Tamura, *Tetrahedron Lett.*, **30**, 4849 (1989); *b*) K. Funakoshi, N. Togo, Y. Taura, and K. Sakai, *Chem. Pharm. Bull.*, **37**, 1776 (1989).
2) W. F. Baily and E. L. Eliel, *J. Am. Chem. Soc.*, **96**, 1798 (1974).
3) D. Seebach and M. Zuger, *Helv. Chim. Acta*, **65**, 495 (1982).
4) T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake, and A. Oku, *J. Am. Chem. Soc.*, **109**, 527 (1987).

5) The result might be rationalized as follows. In the final stage of acetalization, two possible transition state (A, B) may exist (Chart 3). A is considered to be more favorable than B in view of the stereoelectronic and steric factors, resulting in kinetically preferred formation of **1b**. On the other hand, the cyclized **1b** might be more

destabilized than **1a** by an effect similar to the anomeric effect,[7] due to dipole-dipole or electron pair (carbonyl oxygen)-electron pairs (ring oxygens) interactions, which can be represented by the double-headed arrow in C. Thus, **1a** might be thermodynamically preferred to **1b** in the BF_3-catalyzed equilibrium.

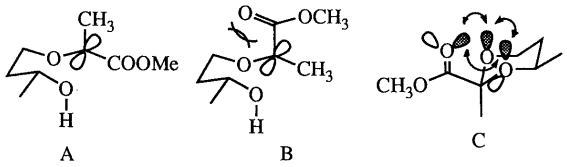
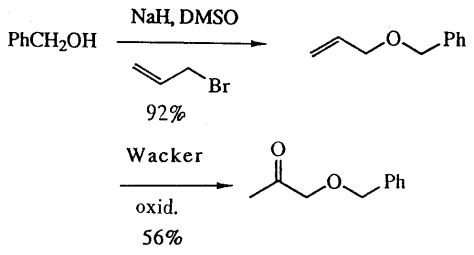


Chart 3

6) Benzyloxyacetone was prepared by conventional methods as follows.



7) P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Pergamon Press, Oxford, 1983, p. 5.