

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

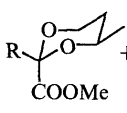
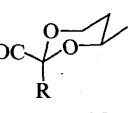
As a part of our studies of asymmetric synthesis using chiral protecting groups,¹⁾ this paper describes diastereoselective acetalization of α -ketoesters with (*R*)-1,3-butanediol. In 1974, Baily and Eliel²⁾ reported that the acid-catalyzed equilibrium of 2-ethoxycarbonyl-2,4-dimethyl-1,3-dioxanes favored 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 triflate⁴⁾ as acid catalysts did not afford satisfactory results. Boron trifluoride (BF₃) etherate was found to be an efficient catalyst. Interestingly, it was found that the diastereoselec-

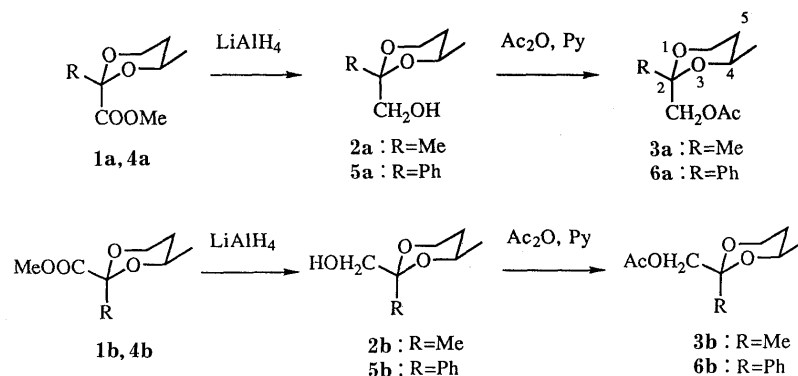
tivity was affected by reaction temperature and duration (Table I). In entry 1, the 2*S*,4*R*-isomer (**1b**) was obtained as the major product with the diastereoselectivity of 7 to 1. On the contrary, the 2*R*,4*R*-isomer (**1a**) was obtained as a sole product in entry 2. Compounds **1a** and **1b** 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 BF₃ 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.

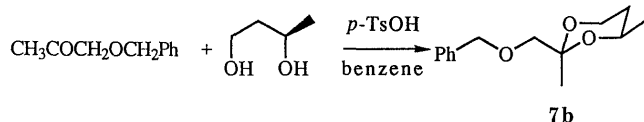
The stereochemistry of the 1,3-dioxanes (**1a**, **b** and **4a**, **b**) was determined from the proton nuclear magnetic resonance (¹H-NMR) spectra after conversion into hydroxymethyl compounds (**2** and **5**) and acetoxymethyl compounds (**3** and **6**). In the two-dimensional NOESY (nuclear Overhauser effect spectroscopy) spectrum of **3a**, a cross peak between C₂-CH₂ (δ 4.38) and C₄-H (δ 4.03) was observed. On the other hand, in the spectrum of **2b**, cross peaks between C₂-Me (δ 1.43) and C₄-H (δ 4.07), C₆-H_{ax} (δ 4.01) were observed. In the case of phenyl derivatives, cross peaks between C₂-CH₂ (δ 4.54) and C₄-H (δ 4.30), C₆-H_{ax} (δ 4.11) were observed in **6a**, but no cross peak involving C₂-CH₂ of **6b** was observed. It was confirmed that the methyl group at C₄ in **2**, **3**, **5** and **6** possesses equatorial orientation, as depicted in Chart 1, from the coupling constant of C₄-H ($J_{C_4-H, C_5-H_{ax}} = 10.2\text{--}12.0\text{ Hz}$, $J_{C_4-H, C_5-H_{eq}} = 2.5\text{--}4.3\text{ Hz}$).

On acetalization of benzyloxyacetone⁶⁾ (*p*-TsOH, ben-

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

$\text{RCOCOOMe} + \begin{array}{c} \text{OH} \quad \text{OH} \\ \quad \\ \text{CH}_2 \quad \text{CH} \\ \quad \\ \text{H} \quad \text{H} \end{array} \xrightarrow{\text{BF}_3 \cdot \text{Et}_2\text{O}}$ R = Me, Ph (R)-1,3-butanediol  1a: R = Me 4a: R = Ph  1b: R = Me 4b: R = Ph				
Entry	Substrate	Reaction condition	Products and isolated yields (%)	
1	CH ₃ COCOOMe	0°C 1.5 h	1a (4)	1b (29)
2	CH ₃ COCOOMe	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)





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, ¹H-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 BF₃·Et₂O (0.6 eq) was added to a stirred solution of an α -keto ester (10 eq) and a diol (1 eq) in CH₂Cl₂. The reaction mixture was diluted with CH₂Cl₂, washed with 5% NaHCO₃ 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 NaBH₄ 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, [α]_D²⁵ −9.8° (*c* = 1.04, CHCl₃). IR (neat): 1745, 1370, 1160, 1015 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.24 (3H, d, *J* = 6.3 Hz, C₄-Me), 1.42 (1H, dddd, *J* = 13.2, 2.6, 2.6, 1.6 Hz, C₅-H_{eq}), 1.51 (3H, s, C₂-Me), 1.68 (1H, dddd, *J* = 13.2, 11.5, 11.5, 5.6 Hz, C₅-H_{ax}), 3.78–3.88 (2H, m, C₄-H, C₆-H_{ax}), 3.82 (3H, s, COOMe), 3.98 (1H, ddd, *J* = 11.9, 5.6, 1.6 Hz, C₆-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, [α]_D²⁵ +5.3° (*c* = 1.04, CHCl₃). IR (neat): 1745, 1370, 1160, 955 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.26 (3H, d, *J* = 5.9 Hz, C₄-Me), 1.65 (3H, s, C₂-Me), 1.60–1.77 (2H, m, C₅-H), 3.82 (3H, s, COOMe), 4.00–4.05 (2H, m, C₆-H), 4.15 (1H, dqd, *J* = 10.2, 5.9, 4.3 Hz, C₄-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, [α]_D²³ +0.51° (*c* = 1.15, CHCl₃). IR (Nujol): 1743, 1495, 1450, 1245, 1110 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.35 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.51 (1H, dddd, *J* = 13.2, 2.6, 2.6, 1.6 Hz, C₅-H_{eq}), 1.78 (1H, dddd, *J* = 13.2, 11.6, 11.6, 5.3 Hz, C₅-H_{ax}), 3.74 (3H, s, COOMe), 3.97–4.07 (2H, m, C₄-H, C₆-H_{ax}), 4.18 (1H, dddd, *J* = 11.6, 5.3, 1.6 Hz, C₆-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, [α]_D²⁴ −35.1° (*c* = 1.15, CHCl₃). IR (Nujol): 1745, 1460, 1245, 1110 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.33 (3H, d, *J* = 6.3 Hz, C₄-Me), 1.37 (1H, dddd, *J* = 12.5, 4.3, 4.3, 1.6 Hz, C₅-H_{eq}), 1.82 (1H, dddd, *J* = 12.5, 11.1, 11.1, 5.1 Hz, C₅-H_{ax}), 3.70 (3H, s, COOMe), 3.85–4.20 (3H, m, C₄-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 Et₂O was added dropwise to a stirred suspension of LiAlH₄ (1 eq) in Et₂O 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, [α]_D²⁷ +3.6° (*c* = 1.11, CHCl₃). IR (neat): 3450, 1380, 1170, 1110, 1055 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.20 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.40 (3H, s, C₂-Me), 1.48 (1H, dddd, *J* = 13.2, 3.1, 3.1, 2.1 Hz, C₅-H_{eq}), 1.52 (1H, dddd, *J* = 13.2, 11.2, 11.2, 5.8 Hz, C₅-H_{ax}), 1.98 (1H, br, OH), 3.80 (2H, br s, C₂-CH₂), 3.85–4.07 (3H, m, C₄-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, [α]_D²⁷ +1.8° (*c* = 1.02, CHCl₃). IR (neat): 3450, 1370, 1170, 1110 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.19 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.43 (3H, s, C₂-Me), 1.46 (1H, dddd, *J* = 13.2, 3.1, 3.0, 2.0 Hz, C₅-H_{eq}), 1.61 (1H, dddd, *J* = 13.2, 12.0, 12.0, 6.1 Hz, C₅-H_{ax}), 2.08, (1H, t, *J* = 6.4 Hz, OH), 3.48 (2H, d, *J* = 6.4 Hz, C₂-CH₂), 3.89 (1H, ddd, *J* = 12.0, 6.1, 2.0 Hz,

C₆-H_{eq}), 4.01 (1H, ddd, *J* = 12.0, 12.0, 3.0, C₆-H_{ax}), 4.07 (1H, dqd, *J* = 12.0, 6.1, 3.1 Hz, C₄-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, [α]_D²³ +23.4° (*c* = 1.01, CHCl₃). IR (neat): 3400, 1450, 1305, 1160, 1125 cm^{−1}. ¹H-NMR (100 MHz) (CDCl₃) δ : 1.28 (3H, d, *J* = 6.4 Hz, C₄-Me), 1.51–1.86 (3H, m, C₅-H, OH), 3.88 (2H, d, *J* = 6.3 Hz, C₂-CH₂), 3.95–4.44 (3H, m, C₄-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, [α]_D²⁴ −29.3° (*c* = 1.53, CHCl₃). IR (Nujol): 3400, 1460, 1380, 1190, 1100 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.26 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.32 (1H, dddd, *J* = 13.0, 2.5, 2.5, 1.7 Hz, C₅-H_{eq}), 1.75 (1H, dddd, *J* = 13.0, 11.5, 11.5, 5.1 Hz, C₅-H_{ax}), 2.22 (1H, t, *J* = 6.4 Hz, OH), 3.51 (2H, d, *J* = 6.4 Hz, C₂-CH₂), 3.78–3.99 (3H, m, C₄-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}. ¹H-NMR (CDCl₃) δ : 1.18 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.40 (3H, s, C₂-Me), 1.48 (1H, dddd, *J* = 13.2, 3.0, 3.0, 1.8 Hz, C₅-H_{eq}), 1.60 (1H, dddd, *J* = 13.2, 12.0, 12.0, 5.4 Hz, C₅-H_{ax}), 2.11 (3H, s, Ac), 3.86 (1H, ddd, *J* = 11.9, 5.4, 1.8 Hz, C₆-H_{eq}), 3.98 (1H, ddd, *J* = 12.0, 11.9, 3.0, C₆-H_{ax}), 4.03 (1H, dqd, *J* = 12.0, 6.1, 3.0 Hz, C₄-H), 4.34, 4.41 (1H each, d, *J* = 11.7 Hz, C₂-CH₂).

(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}. ¹H-NMR (100 MHz) (CDCl₃) δ : 1.18 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.46 (3H, s, C₂-Me), 1.52–1.84 (2H, m, C₅-H), 2.11 (3H, s, Ac), 3.81–4.16 (3H, m, C₄-H), 4.02 (2H, s, C₂-CH₂). 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}. ¹H-NMR (CDCl₃) δ : 1.27 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.61–1.70 (2H, m, C₅-H), 1.98 (3H, s, Ac), 3.95 (1H, ddd, *J* = 11.2, 5.1, 4.0 Hz, C₆-H_{eq}), 4.11 (1H, m, C₆-H_{ax}), 4.30 (1H, m, C₄-H), 4.54 (2H, s, C₂-CH₂). 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}. ¹H-NMR (100 MHz) (CDCl₃) δ : 1.25 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.35–1.85 (2H, m, C₅-H), 1.98 (3H, s, Ac), 3.66–4.00 (3H, m, C₄-H), 4.12 (2H, s, C₂-CH₂). MS *m/z*: 235 (M⁺ − Me), 177, 123, 105.

Benzoylation of 2a, b An alcohol (**2**, 1.0 eq) was added to a solution of NaCH₂SOCH₃ [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**.

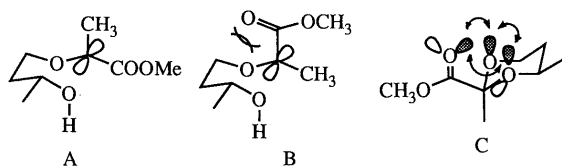
(2*R*,4*R*)-2-Benzoyloxymethyl-2,4-dimethyl-1,3-dioxane (7a) Colorless oil, 98% yield. IR (neat): 1495, 1365, 1165, 1095 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.17 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.41 (1H, m, C₅-H_{eq}), 1.42 (3H, s, C₂-Me), 1.59 (1H, dddd, *J* = 13.2, 11.2, 11.2, 6.3 Hz, C₅-H_{ax}), 3.68, 3.73 (1H, each, d, *J* = 10.2 Hz, C₂-CH₂), 3.80–4.00 (3H, m, C₄-H), 4.60 (2H, s, CH₂Ph). MS *m/z*: 236 (M⁺), 221, 130, 115.

(2*S*,4*R*)-2-Benzoyloxymethyl-2,4-dimethyl-1,3-dioxane (7b) Colorless oil, 88% yield. IR (neat): 1500, 1370, 1170, 1110 cm^{−1}. ¹H-NMR (CDCl₃) δ : 1.17 (3H, d, *J* = 6.1 Hz, C₄-Me), 1.42 (3H, s, C₂-Me), 1.45 (1H, dddd, *J* = 13.2, 3.2, 3.2, 1.6 Hz, C₅-H_{eq}), 1.61 (1H, dddd, *J* = 13.2, 11.0, 11.0, 5.5 Hz, C₅-H_{ax}), 3.39 (2H, s, C₂-CH₂), 3.86 (1H, ddd, *J* = 11.7, 5.5, 1.6 Hz, C₆-H_{eq}), 4.00 (1H, ddd, *J* = 11.7, 11.0, 3.2 Hz, C₆-H_{ax}), 4.05 (1H, dqd, *J* = 11.0, 6.1, 3.2 Hz, C₄-H), 4.61, 4.64 (1H, each, d, *J* = 12.3 Hz, CH₂Ph). MS *m/z*: 236 (M⁺), 221, 130, 115.

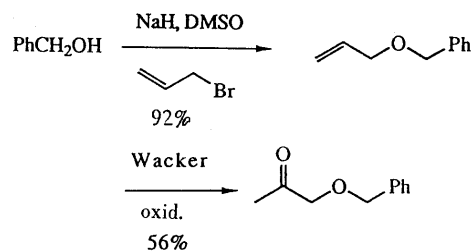
References and Notes

- 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).
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- 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.



- 6) Benzyloxyacetone was prepared by conventional methods as follows.



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