Enantiotopic-Group Differentiation. Asymmetric Monoesterification of Malonic Acids Using Cinchona Alkaloid Derivatives

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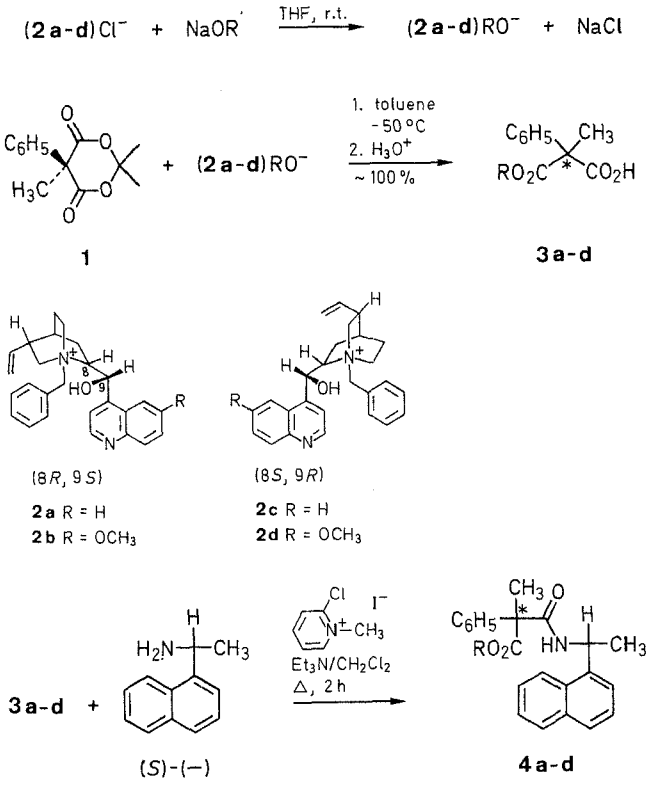
2,2-Dimethyl-5-methyl-5-phenyl-4,6-dioxo-1,3-dioxane (**1**) was cleaved asymmetrically, by nucleophilic attack of primary alkoxide ions, paired with *N*-benzylquaternary ammonium cations, derived from cinchona alkaloids, to give optically active monoalkyl malonates **3** with moderate setereoselectivity. The ester group of **3** was selectively reduced to afford optically active α-methyltropic acid (**5**) in good yield. The relationship between the structure of ammonium cations and the direction of stereoselectivity is described.

Enantioselective monoesterification of prochiral 2,2-disubstituted malonic acid is not only one of the prominent methods of providing versatile chiral building blocks for a number of optically and biologically active compounds,[1-3] but also an attractive method for construction of a quaternary asymmetric carbon center. Chiral monoesters of disubstituted malonic acids have been obtained by utilizing hydrolases such as porcine liver esterase[2,4,5] or microbial lipases.[6,7] Very recently, unsymmetrical propane-1,3-diols were prepared from monosubstituted malonic acids by the use of chiral alcohols.[8] Nevertheless, little has been reported on the construction of quaternary asymmetric carbon center from malonic acids by nonenzymatic method.[9]

We wish to present our results on the differentiation of the enantiotopic carbonyl groups of 2,2-dimethyl-5-methyl-5-phenyl-4,6-dioxo-1,3-dioxane (**1**)[10] by the use of alkoxide anions paired with chiral quaternary ammonium cations derived from cinchona alkaloids. As described in the previous papers,[11,12] one of the principal advantages of this reaction, utilizing cyclic substrate, is that they give only monoester without over-reaction leading to achiral diester. At first, we chose the addition of methoxide anion to **1** as a standard reaction to see the dependence of enantiomeric excess (e.e.) on the reaction conditions and on the structure of chiral ammonium cations. *N*-Benzylquininium methoxide [**(2d)**CH_3O^-] was prepared *in situ* by mixing *N*-benzylquininium chloride [**(2d)**Cl^-] and an equimolar amount of sodium methoxide in dry tetrahydrofuran. The resulting mixture, a slightly cloudy solution, was added as



3, 4	R
a	CH_3
b	C_2H_5
c	*n*-C_3H_7
d	*n*-C_4H_9

Table 1. Asymmetric Monoesterification of **1** with Alkoxide Anions Paired with Various Ammonium Cations **2**[a]

Entry	Alkoxide	Reaction Conditions		Yield[b] (%)	e.e.[c] (%)	Selectivity[d]
		Temp (°C)	Time (h)			
1	**(2a)** CH_3O^-	−50	0.25	88	4	pro-*S*
2	**(2b)** CH_3O^-	−50	0.25	89	27	pro-*S*
3	**(2c)** CH_3O^-	−50	0.25	92	8	pro-*R*
4	**(2d)** CH_3O^-	−50	0.25	73	34	pro-*R*
5	**(2d)** CH_3O^-	−78	0.5[e]	100[f]	37	pro-*R*
6	**(2d)** CH_3O^-	20	5 min	65	23	pro-*R*
7	**(2d)** CH_3O^-	−82	0.25	81	34	pro-*R*
8	**(2a)** $C_2H_5O^-$	−50	2	81	8	pro-*S*
9	**(2b)** $C_2H_5O^-$	−50	2	82	45	pro-*S*
10	**(2b)** $C_2H_5O^-$	−78	2.5[e]	90[f]	45	pro-*S*
11	**(2c)** $C_2H_5O^-$	−50	2	44	20	pro-*R*
12	**(2d)** $C_2H_5O^-$	−50	2	65	43	pro-*R*
13	**(2b)** *n*-$C_3H_7O^-$	−78	3.5[e]	91[f]	51	pro-*S*
14	**(2d)** *n*-$C_3H_7O^-$	−50	2	57	39	pro-*R*
15	**(2d)** *i*-$C_3H_7O^-$	−50	1	–[g]	–	–
16	**(2b)** *n*-$C_4H_9O^-$	−50	2	69	45	pro-*S*
17	**(2d)** *n*-$C_4H_9O^-$	−78	3.5[e]	77[f]	40	pro-*R*

[a] Acylal **1** (0.3 mmol), alkoxide (0.36 mmol), dry toluene (13 mL), dry THF (2 mL).
[b] Overall yield of **4** based on **1**.
[c] Calculated from diastereoisomeric ratios of **4**.
[d] Preferentially attacked carbonyl group of **1**.
[e] Preparative scale reaction (**1**: 1.2–2.1 mmol).
[f] Yield of **3**.
[g] No reaction was observed.

Table 2. ^{1}H-NMR Data of Monoesters **3**

Monoester	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)
3a	1.88 (s, 3H, CH_3); 3.71 (s, 3H, OCH_3); 7.20 (s, 5H, C_6H_5); 9.5 (br s, 1H, CO_2H)
3b	1.25 (t, 3H, *J* = 7.2, CH_3CH_2); 1.87 (s, 3H); 4.20 (q, 2H, *J* = 7.2, CH_3CH_2); 7.23 (s, 5H); 8.3 (br s, 1H, CO_2H)
3c	0.9 (t, 3H, *J* = 7.0, CH_3CH_2); 1.5–1.9 (m, 2H, CH_3CH_2); 1.88 (s, 3H); 4.1 (t, 2H, *J* = 7.0, CO_2CH_2); 7.23 (s, 5H); 8.2 (br s, 1H, CO_2H)
3d	0.8–1.8 (m, 7H, $CH_3CH_2CH_2$); 1.90 (s, 3H); 4.2 (t, 2H, *J* = 6.4, CO_2CH_2); 7.30 (s, 5H); 10.7 (br s, 1H, CO_2H)

such to a cold solution of the acylal **1** under argon atmosphere. The ring-opening reaction proceeded rapidly and quenching the reaction mixture gave the monomethylester **3a** quantitatively (Tables 1, 2). E.e. of **3a** was determined by ^{1}H-NMR or HPLC analysis of the corresponding diastereoisomeric amide-ester **4a** (Table 3), which was prepared from **3a** and (*S*)-1-(1-naphthyl)ethylamine.[7] Racemic **3a** showed 2.4% e.e. by this method, so the e.e. can be determined within an error of ca. ± 2%.

Table 3. Spectral Data of Diastereomeric Amide-esters **4**

Amide-ester	MS (70 eV) *m/z* (%)	^{1}H-NMR (200 MHz, $CDCl_3$/TMS) δ, *J*(Hz)
4a	361 (M^+, 12); 164 (70); 155 (100)	1.6 (2d, 3H, *J* = 6.8, $CHCH_3$); 1.85 (s, 3H, CH_3); 3.58, 3.79 (2s, 3H, CO_2CH_3); 5.94 (m, 1H, CH); 6.8 and 6.9 (2d, br, 1H, NH); 7.2–8.1 (m, $12H_{arom}$)
4b	375 (M^+, 14); 178 (85); 155 (100)	1.0, 1.3 (2t, 3H, *J* = 7.2, CH_2CH_3); 1.6 (2d, 3H, *J* = 6.5, $CHCH_3$); 1.8 (2s, 3H, CH_3); 4.03 (m), 4.26 (q, 2H, *J* = 7.2, CH_2CH_3); 5.9 (m, 1H, CH); 6.85 (br m, 1H, NH); 7.2–8.1 (m, $12H_{arom}$)
4c	389 (M^+, 13); 192 (77); 155 (100)	0.7, 0.9 (2t, 3H, *J* = 7.4, CH_3CH_2); 1.4 (m, 2H, CH_3CH_2); 1.6 (2d, 3H, *J* = 6.5, $CHCH_3$); 1.8 (2s, 3H, CH_3); 3.93 (m), 4.16 (t, 2H, *J* = 6.6, CO_2CH_2); 5.9 (m, 1H, CH); 6.9 (br m, 1H, NH); 7.2–8.1 (m, $12H_{arom}$)
4d	403 (M^+, 10); 206 (62); 155 (100)	0.8–1.4 (m, 5H, CH_2CH_3); 1.55–1.7 (m, 5H, OCH_2CH_2, $CHCH_3$); 1.80 (2s, 3H, CH_3); 3.96 (m), 4.20 (t, 2H, *J* = 6.6, CO_2CH_2); 5.9 (m, 1H, CH); 6.93 (br m, 1H, NH); 7.2–8.1 (m, $12H_{arom}$)

The yield and the extent of stereoselectivity of the reaction were highly affected by the nature of the reaction medium, polarity of the solvent and the solubility of the nucleophile [**(2a–d)** RO^-]. Preliminary experiments revealed that relatively non-polar and aprotic solvent such as toluene, dimethoxyethane, and tetrahydrofuran were found to be preferable solvents from both chemical and optical yields. Therefore the reaction was carried out in a mixture of dry tetrahydrofuran and dry toluene throughout the experiments.

The ring-opening reaction was completed within a few minutes and the conversion was 100% (GC) for all the experiments using methoxide anion as nucleophile. The yield was given as an isolated yield of diastereoisomeric **4a**. The selectivity of the reaction was determined from the absolute configuration of α-methyltropic acid **(5)** prepared from **3a** by selective reduction of the ester group (*vide infra*). When the reaction was conducted at room temperature, decarboxylation accompanied to some extent, resulting in low chemical yield. However, it could completely be avoided by lowering the reaction temperature to −50 °C. Ammonium cations derived from cinchonine and cinchonidine (entry 1 and 3) gave much lower e.e.'s than the case with quininium and quinidinium cations (entry 2 and 4). The observed low selectivity was attributed mainly to the fact that *N*-benzylcinchoninium methoxide [**(2a)**CH_3O^-] and *N*-benzylcinchonidinium methoxide [**(2c)**CH_3O^-] are much less soluble in tetrahydrofuran when they were prepared *in situ*, resulting in preferential ion-pairing of methoxide anion with Na^+ instead of chiral ammonium cations, **2a** or **2c**. It is worth noting that the cations **2a** and **2b**, having the same C-8(*R*)–C-9(*S*) configuration, promoted the preferential attack of CH_3O^- on the pro-*S*-carbonyl group of **1** (entry 1 and 2), whereas the cations **2c** and **2d** having the C-8(*S*)–C-9(*R*)- configuration showed pro-*R*-selectivity (entry 3,4). This type of stereocontrol is observed generally in cinchona alkaloid-mediated asymmetric induction such as 1,4-addition of nucleophile to α,β-unsaturated carbonyl compounds[13,14] and asymmetric methanolysis of cyclic acid anhydrides.[10,11] Primary alkoxide, $C_2H_5O^-$, *n*-$C_3H_7O^-$, and *n*-$C_4H_9O^-$ were also found to react with **1** to give the corresponding monoester in high yields. The reaction for these alkoxides was much slower than for CH_3O^-, and they required 1.5-2 hours for completion at −50 °C. But the optical yields were generally improved to 40–50% e.e. Secondary alkoxide *i*-$C_3H_7O^-$ was unreactive, and **1** was recovered quantitatively.[10] As for the direction of stereoselectivity, the cations **2a** and **2b** promoted pro-*S*-attack and **2c** and **2d**, pro-*R*-attack of alkoxides examined, showing the same stereochemical preferences as found with CH_3O^-.

A preparative scale reaction was effected and selective reduction of the ester group with lithium borohydride[12] afforded optically active 3-hydroxy-2-methyl-2-phenylpropanoic acid [α-methyltropic acid **(5)**] (Table 4). The treatment of **1** with methoxide [**(2d)**CH_3O^-] gave (*S*)-**5** with $[\alpha]_D^{20}$ −10.9° (*c* = 1.0, C_2H_5OH) in an overall yield of 82% from **1**. The optical purity of **5** was calculated to be 38% e.e. based on the reported maximum rotation, $[\alpha]_D^{20}$ +28.7° (C_2H_5OH) for optically pure (*R*)-**5**.[1] The optical purity (38% e.e.) agreed with that of the monoester **3a** (37% e.e.) which was calculated from the diastereoisomeric excess of the corresponding amide-ester **4a**. The same procedure was applied to the reactions of **1** with alkoxides [**(2b)**$C_2H_5O^-$], [**(2b)***n*-$C_3H_7O^-$], and [**(2d)***n*-$C_4H_9O^-$]. In all cases selective reduction of the ester group was well achieved and optically active **5** was obtained in 77–86% yield from **1**. The absolute configuration of **5** thus obtained clarified the direction of asymmetric induction, i.e. pro-*R*- or pro-*S*-attack, for each monoester **3** studied.

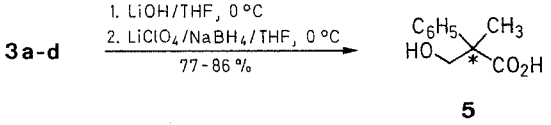


Table 4. Preparation of α-Methyltropic Acid **(5)** from **1**[a]

Entry	Alkoxide Used	Yield[b] (%)	$[\alpha]_D^{20}$ (*c* = 1, EtOH)	Optical Purity[c] (%)	Configuration of **5**
1	**(2d)** CH_3O^-	82	−10.9°	38	*S*
2	**(2b)** $C_2H_5O^-$	86	+11.3°	39	*R*
3	**(2b)** *n*-$C_3H_7O^-$	86	+12.3°	43	*R*
4	**(2d)** *n*-$C_4H_9O^-$	77	−11.0°	38	*S*

[a] Reaction conditions of ring-opening: **1** (1.2–2.1 mmol), alkoxide (1.2 equiv of **1**), dry toluene/THF (40–90 mL), −78 °C, 2–3 h.
[b] Overall yield of **5** based on **1**. The structure and the purity of **5** were ascertained by ^{1}H-NMR, MS, and microanalyses.
[c] Calculated from the reported value $[\alpha]_D^{20}$ +28.7° (C_2H_5OH).[1]

Finally, although the stereoselectivity still remains to be improved, the present study opens a new route to chiral malonic acid derivatives via enantioselective ring-opening of cyclic acylal **1** with alkoxide anion by the use of cinchona alkaloids.

THF was dried by distillation from sodium wire immediately before use. Toluene, EtOH, MeOH, CH_2Cl_2, and 1,2-dimethoxyethane were distilled over CaH_2 and stored over molecular sieves 4 Å. Quaternary ammonium salts of cinchona alkaloids were prepared by a modified procedure reported in refs. 15 and 16. ^{1}H-NMR spectra were measured on a Varian EM 360 (60 MHz) and Varian VXR 200 (200 MHz) instruments. Microanalyses were performed by a Yanaco MT-3. Mass spectra were recorded on a JEOL JMS-DX-300. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. GC-analyses were carried out on Shimadzu GC-4B instrument equipped with a flame ionization detector. HPLC-analyses were performed on a Jasco BIP-1 chromatograph system (column, silica gel NUCLEOSIL 50-5, 25 cm × 4 mm; eluent, hexane/2-propanol; detection, 280 nm). Melting points were determined on a hot plate apparatus and are uncorrected.

Asymmetric Monoesterification of 2,2-Dimethyl-5-methyl-5-phenyl-4,6-dioxo-1,3-dioxane (1); Typical Procedure:

N-Benzylquininium chloride [**(2d)**Cl^-, 162 mg, 0.36 mmol)] is suspended in dry THF (2 mL) and a methanol solution of NaOMe (3.0 mmol/mL, 120 µL, 0.36 mmol) is added to the mixture at room temperature. The suspension immediately becomes opaque. The mixture is stirred for 10 min at room temperature, and then is added dropwise to a solution of **1** (70.3 mg, 0.3 mmol) in dry toluene (13 mL) at −50 °C. The reaction is monitored by GC [5% XE-60, 1 m, 160 °C, carrier gas flow rate 40 mL/min, R_t: 0.52 min (product, detected as methyl 2-phenylpropionate), 6.1 min **(1)**]. The substrate **1** is completely consumed within 5 min. After the mixture is stirred at −50 °C for 15 min, it is quenched by adding 3% citric acid solution (30 mL). The organic layer is separated and the aqueous layer is extracted with ether (3 × 20 mL). The combined organic layer is washed with sat. brine and dried (Na_2SO_4). Evaporation below 50 °C gives quantitatively methyl hydrogen methylphenylmalonate **(3a)** as a colorless oil. In order to determine the e.e. of **3a**, it is reacted with (*S*)-1-(1-naphthyl)ethylamine according to the procedure given below.

Determination of Enantiomeric Excess; Typical Procedure for 4a:

A mixture of (*S*)-1-(1-naphthyl)ethylamine (61.6 mg, 0.36 mmol), 2-chloro-1-methylpyridinium iodide (92.0 mg, 0.36 mmol), Et_3N (72.9 mg, 0.72 mmol), and **3a** (0.3 mmol) in dry CH_2Cl_2 (5 mL) is heated under reflux for 2 h. The mixture is evaporated and the residual oil is passed through a short-pass silica gel column using EtOAc eluent. Diastereomeric mixture of the amide-ester **4a** is obtained as colorless oil; yield: 88.2 mg (81% based on **1**). The e.e. is determined by the integration of the diastereomeric proton peaks (δ = 3.58 and 3.79) or by HPLC (hexane/propan-2-ol, 100:3, flow rate 0.7 mL/min, R_t: 9.7 and 10.5 min).

Selective Reduction of Ester-group; Typical Procedure Starting from 3a:

Powdered anhydrous LiOH (47.7 mg, 1.99 mmol) is dissolved in dry THF (60 mL), and then methyl hydrogen methylphenylmalonate [**3a**; 415 mg, 1.99 mmol, prepared from **1** and **(2d)**CH_3O^-, 37% e.e.] is added to the solution and the mixture is stirred at 0 °C until homogeneous. The temperature should be kept below 0 °C until reducing reagent is added in order to avoid decarboxylation of **3a**. To this slightly cloudy solution are added anhydrous $LiClO_4$ (848 mg, 7.97 mmol) and $NaBH_4$ (302 mg, 7.97 mmol) successively under argon atmosphere at 0 °C. The mixture is stirred for 3 h at 0 °C, then at room temperature for 2.5 h. The solvent is evaporated and the residue is quenched with ice-cold 2 N HCl (40 mL). The aqueous solution is extracted with ether (4 × 30 mL) and the combined extract is washed with sat. brine and dried (Na_2SO_4). Evaporation and distillation gives 3-hydroxy-2-methyl-2-phenylpropanoic acid (α-methyltropic acid, **5**) as colorless syrup which crystallizes upon standing; yield: 294 mg (82% based on **1**); bp 156–159 °C (bath)/0.7 mbar; mp 79–81 °C (Lit.[1] mp 77–79 °C); $[\alpha]_D^{20}$ −10.9° (*c* = 1.0, C_2H_5OH) [Lit.[1] $[\alpha]_D^{20}$ +28.7° (C_2H_5OH) for optically pure (*R*)-**5**].

^{1}H-NMR ($CHCl_3$, 200 MHz): δ = 1.68 (s, 3 H, CH_3); 3.66, 4.10 (2 d, 1 H each, *J* = 11.4 Hz, 2 H, CH_2O) 6.9 (br s, 2 H, OH, CO_2H); 7.3 (m, 5 H, C_6H_5).

$C_{10}H_{12}O_3$	calc.	C 66.65	H 6.71
(180.2)	found	66.90	6.76

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(1) Knabe, J., Junginger, H., Geismar, W. *Arch. Pharm. (Weinheim, Ger.)* **1971**, *304*, 1.
(2) Iriuchijima, S., Hasegawa, K., Tsuchihashi, G. *Agric. Biol. Chem.* **1982**, *46*, 1907.
(3) Foster, R., Ing, H.R. *J. Chem. Soc.* **1956**, 938.
(4) Schneider, M., Engel, N., Boensmann, H. *Angew. Chem.* **1984**, *96*, 54; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 66.
(5) Björkling, F., Boutelje, J., Gatenbeck, S., Hult, K., Norin, T., Szmulik, P. *Tetrahedron* **1985**, *41*, 1347.
(6) Kitazume, T., Sato, T., Ishikawa, N. *Chem. Lett.* **1984**, 1811.
(7) Kitazume, T. Sato, T., Kobayashi, T., Jenq, T.L. *J. Org. Chem.* **1986**, *51*, 1003.
(8) Ihara, M., Takahashi, M., Taniguchi, N., Fukumoto, K., Kametani, T. *J. Chem. Soc. Chem. Commun.* **1987**, 619.
(9) Zhu, X., Wu, Y., Yin, C. *Gaodeng Xuexiao Huaxue Xuebao* **1984**, *5*, 807; *C.A.* **1985**, *102*, 131521.
(10) Scheuer, P.J., Cohen, S.G. *J. Am. Chem. Soc.* **1958**, *80*, 4933.
(11) Hiratake, J., Yamamoto, Y., Oda, J. *J. Chem. Soc. Chem. Commun.* **1985**, 1717.
(12) Hiratake, J., Inagaki, M., Yamamoto, Y., Oda, J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1053.
(13) Hiemstra, H., Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.
(14) Kobayashi, N. *Br. Polym. J.* **1984**, *16*, 205.
(15) Jacobs, W.A., Heidelberger, M. *J. Am. Chem. Soc.* **1919**, *41*, 2090.
(16) Colonna, S., Re, A., Wynberg, H. *J. Chem. Soc. Perkin Trans. 1* **1981**, 547.