Asymmetric Synthesis Based on (2*R*,3*S*)-3,4-Dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione. Synthesis of Highly Optically Active β-Substituted Alkanoic Acids

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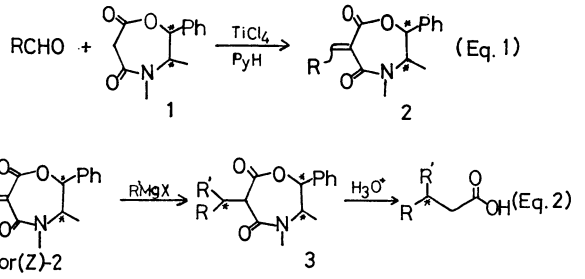
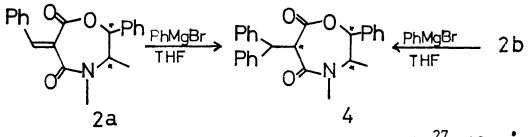
A general method was worked out for the preparation of highly optically pure β-substituted alkanoic acids from aldehydes with use of (2*R*,3*S*)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-diones(**2**) as key intermediates. Oxazepines(**2**) were prepared in high yields by treating aldehydes with (2*R*,3*S*)-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione(**1**) in the presence of titanium tetrachloride. The conjugate addition of Grignard reagents to **2** in the presence of nickel chloride, followed by hydrolysis and decarboxylation afforded highly enantiomerically pure β-substituted alkanoic acids in good yields. The addition of lithium dialkylcuprate to **2** was examined. It was found that (*S*)-(+)-3-phenylheptanoic acid is obtained by the reaction of lithium dibutylcuprate with (*E*)- and (*Z*)-6-benzylidene derivatives of **1**, respectively.

Synthesis of optically active alkanoic acids is important in organic synthesis, and many works have appeared so far. Inouye and Walborsky[1] and Kawana and Emoto[2] reported that partial asymmetric induction is achieved by the addition of Grignard reagents to crotonic or cinnamic esters of (−)-menthol or some sugar derivatives, respectively. Tsuchihashi *et al.* reported that optically active 3-phenylbutanoic acid is obtained by the reaction of optically pure vinyl sulfoxide with diethyl malonate, followed by reduction, hydrolysis, and decarboxylation.[3] Recently, the syntheses of highly optically pure α-and β-substituted alkanoic acids were achieved with the use of optically active oxazoline derivatives.[4]

In a previous paper,[5] a report was given on the preparation of an almost optically pure 3-phenylheptanoic acid in high yield by the conjugate addition of butylmagnesium bromide to (*Z*)-(2*R*,3*S*)-6-benzylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (**2a**) in the presence of a catalytic amount of nickel chloride, followed by hydrolysis and decarboxylation of the adduct (**3**). It was thus shown that the 6-alkylidene derivatives of (2*R*,3*S*)-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione(**1**) are the key intermediates for the preparation of optically active β-substituted alkanoic acids. We have attempted to establish a general route for the synthesis of optically active alkanoic acids starting from aldehydes as in the following.



The first step consists of the condensation of aldehydes with the cyclic compound(**1**)[6] (Eq. 1). The reaction was carried out in the presence of titanium tetrachloride and pyridine using tetrahydrofuran(THF) as a solvent as in the method for the preparation of alkylidene-malonic esters reported by Lehnert.[7] The IR and NMR spectral data of the product(**2b**) obtained from benzaldehyde and **1** do not agree with those of (*Z*)-6-alkylidene derivative(**2a**).[5] In order to determine the configuration of **2b**, **2a** and **2b** were treated with phenylmagnesium bromide (Eq. 3). The NMR and IR spectra of the adducts (**4a** and **b**) were identical, the



value of the specific rotation of **4a** being the same as that of **4b**. Thus, the structure of **2b** was determined to be *E* isomer of **2a**. The configuration of the alkylidene group of **2c—f** was also determined by a comparison of its IR and NMR spectra with those of **2a** and **2b**. It was confirmed that a small amount of *Z*-isomer is produced in the preparation of **2c—f**, almost pure *E* isomer of **2c—f** being obtained by recrystallization of the product. The yields and properties of the products(**2**) are summarized in Table 1.

The conjugate addition of Grignard reagents to **2a** was carried out under various conditions at −78 °C for 3 h (Table 2). Alkanoic acids were obtained by hydrolysis and decarboxylation of the crude adducts(**3**) in 3 M sulfuric acid and acetic acid (Eq. 2). The result shows that the optical purity of the acids depends on the conditions of the addition reaction. The best result was obtained when the reaction was carried out in the presence of a catalytic amount of nickel chloride at low temperature. Though the role of the metal salt in the conjugate addition remains to be resolved,

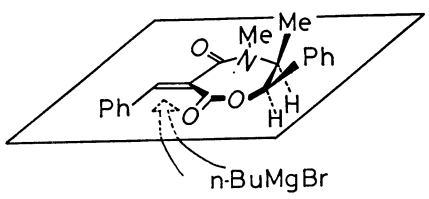


Fig. 1.

Table 1. Yields and properties of (2*R*,3*S*)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-diones(**2**)

	R	Yield (%)	*E* : *Z*[a]	Mp (°C)[b]	$[\alpha]_D^{\circ}$[c] (*t* °C, *c*)	Found (Calcd) (%) C	H	N
2a	(*Z*)Ph-[8]			188—189	−182 (29, 7.59)	74.98 (74.74)	5.89 (5.96)	4.39 (4.36)
2b	(*E*)Ph-	99[d]	100 : 0	195—196	+59.5 (24, 8.45)	74.61 (74.74)	5.79 (5.96)	4.14 (4.36)
2c	(*E*)CH_3-	99[e]		150—151	−150 (27, 1.01)	69.47 (69.48)	6.75 (6.61)	5.44 (5.40)
2d	(*E*)CH_3CH_2-	76	85 : 15	122—124	−146 (26, 1.01)	70.39 (70.31)	7.17 (7.01)	5.13 (5.15)
2e	(*E*)$CH_3(CH_2)_3$-	94	90 : 10	79— 80	−129 (26, 0.776)	71.68 (71.73)	7.90 (7.69)	4.39 (4.65)
2f	(*E*)$(CH_3)_2CH$-	84		123—125	−130 (24, 1.21)	71.27 (71.05)	7.65 (7.37)	4.60 (4.87)

a) Determined by NMR spectrum. b) Melting points uncorrected. c) Measured after recrystallization, dichloromethane being used as a solvent. d) An equimolar amount of aldehyde used. e) Two equimolar amounts of aldehyde used.

Table 2. Effects of added metal salts and/or solvent change in the asymmetric synthesis of 3-substituted alkanoic acids by the reaction of Grignard reagents with **2a**

Entry	RMgX	MX_n	Solvent	Yield (%)	$[\alpha]_D^{\circ}$[a] (*t* °C, *c*)	Optical purity (%)
1	*n*-BuMgBr	—	THF	85	−30.4[b] (24, 8.25)	88[d]
2		—	THF-HMPT[c]	68	−21.2[b] (26, 8.16)	62[d]
3		$NiCl_2$	THF	92	−34.0[b] (24, 8.03)	99[d]
4		$ZnCl_2$	THF	76	−29.3[b] (25, 8.09)	85[d]
5		$FeCl_3$	THF	70	−20.6[b] (26, 8.00)	60[d]
6	$PhCH_2MgCl$	—	THF	75	+ 5.65 (30, 1.93)	9[e]
7		$NiCl_2$	THF	78	+ 4.17 (29, 1.92)	7[e]
8		$ZnCl_2$	THF	85	+ 8.81 (26, 1.93)	15[e]
9		$FeCl_3$	THF	62	+10.6 (30, 1.93)	18[e]
10		—	THF-HMPT[c]	68	−43.7 (24, 1.92)	73[e]
11		$NiCl_2$	THF-HMPT[c]	76	−44.7 (26, 1.94)	75[e]
12		CuI[f]	THF-HMPT[c]	64	−42.4 (27, 1.92)	71[e]
13[g]		CuI[f]	THF-HMPT[c]	55	−44.9 (22, 1.92)	75[e]

a) Benzene used as a solvent. b) $[\alpha]_{578}$. c) A mixture of THF (15 ml) and HMPT (4 ml) used as a solvent for 1.5 mmol of **2a**. d) Based on $[\alpha]_{578}$ −34.4° (*c* 8, benzene) for enantiomerically pure acid.[4c] e) The reported $[\alpha]_D^{28}$ max −60° (*c* 1.92, benzene) determined by resolution method.[2] f) Four mol % amounts of the salt used. g) Addition carried out at −100 °C.

the absolute configuration of (*R*)-(−)-3-phenylheptanoic acid indicates that the Grignard reagent attacks from the opposite side of the phenyl and methyl groups of the oxazepine ring as shown in Fig. 1.

In the same manner, various highly optically active β-substituted alkanoic acids were obtained in high yields utilizing **2a—f** (Table 3).

The relation between the absolute configuration of the alkanoic acid and the configuration of **2** is clearly shown in entries 2 and 5; (*R*)-(−)-3-phenylheptanoic acid was obtained by the reaction of the (*Z*)-6-benzylidene derivative of **1** with butylmagnesium bromide.

TABLE 3. SYNTHESIS OF OPTICALLY ACTIVE ALKANOIC ACIDS BY THE REACTION OF GRIGNARD REAGENTS WITH **2**

Entry	R	R′	Yield (%)	$[\alpha]_D^{\circ}$ a) (t °C, c)	Lit $[\alpha]_D^{\circ}$ a) (c)	Optical purity (%)	Absolute configuration
1	(*Z*)Ph-	CH_3CH_2-	94	−49.2 (25, 7.04)	−49.66[9] (7)	99	*R*
2		$CH_3(CH_2)_3$-	92	−34.0[b] (24, 8.03)	−34.4[b),4c)] (8)	99	*R*
3	(*E*)Ph-	CH_3-	85	+52.6 (26, 9.81)	−57.2[10] (9.80)	92	*S*
4		CH_3CH_2-	94	+49.8 (28, 7.07)		>99	*S*
5		$CH_3(CH_2)_3$-	92	+32.1[b] (24, 8.39)		93	*S*
6	(*E*)CH_3-	$(CH_3)_2CH$-	55	+10.5 (25, neat)	+12.8[11] (neat)	82	*R*
7		$CH_3(CH_2)_3$-	82	− 3.74 (23, neat)	−4.2[12] (neat)	89	*S*
8		Ph-	88	−51.1 (28, 9.84)		89	*R*
9	(*E*)CH_3CH_2-	$CH_3(CH_2)_3$-	78	− 2.91 (23, neat)	+4.69[c),13)] (neat)	62	*S*
10		Ph-	84	−49.5 (28, 7.11)		>99	*R*
11	(*E*)$(CH_3)_2CH$-	CH_3-	73	−11.9 (24, neat)		93	*S*
12	(*E*)$CH_3(CH_2)_3$-	CH_3CH_2-	77	+ 2.70 (24, neat)		58	*R*

a) Benzene used as a solvent. b) $[\alpha]_{578}$. c) Meyers noted that there is some doubt as to the reliability of the reported rotation.[4a)]

TABLE 4. SYNTHESIS OF OPTICALLY ACTIVE ALKANOIC ACIDS BY THE REACTION OF LITHIUM DIALKYLCUPRATE WITH **2**

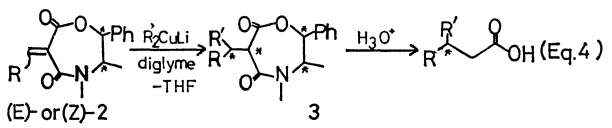
Entry	R	R′	Yield (%)	$[\alpha]_D^{\circ}$ a) (t °C, c)	Optical purity (%)	Absolute configuration
1	(*Z*)Ph-	$CH_3(CH_2)_3$-	76	+34.4[b] (24, 8.12)	>99	*S*
2	(*E*)Ph-	$CH_3(CH_2)_3$-	64	+33.9[b] (25, 7.90)	99	*S*
3	(*E*)CH_3-	$CH_3(CH_2)_3$-	70	−3.78 (25, neat)	90	*S*
4		Ph-	79	−37.6 (20, 9.82)	66	*R*
5	(*E*)CH_3CH_2-	$CH_3(CH_2)_3$-	73	−2.64 (24, neat)	56	*S*
6		Ph-	66	−32.4 (19, 7.29)	65	*R*
7	(*E*)$CH_3(CH_2)_3$-	Ph-	66	−23.2[b] (23, 8.12)	67	*R*

a) Benzene used as a solvent. b) $[\alpha]_{578}$.

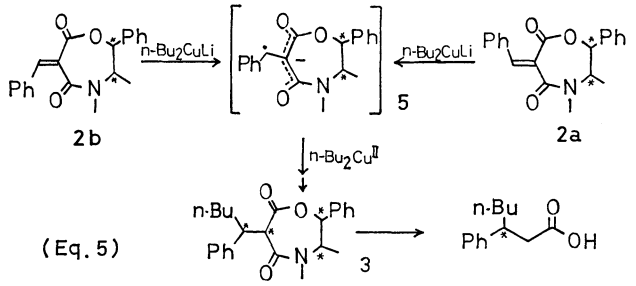
On the other hand, the (*S*)-(+) acid was obtained when the *E* isomer was employed.

It was found that the absolute configuration of the carboxylic acid obtained from **2** possessing the substituent R and Grignard reagent R′MgX differs from that of the carboxylic acid obtained from **2** having the substituent R′ and Grignard reagent RMgX(for example, entries 3 and 8). The results show that the Grignard reagent stereoselectively attacks **2** regardless of the configuration of the alkylidene group or the substituent R of **2**.

Asymmetric addition of lithium dialkylcuprate was also examined. A typical reaction is shown in the following: Lithium dialkylcuprate in diglyme was prepared according to the method for the preparation of the cuprate in ether reported by Whitesides *et al.*[14] The 6-alkylidene derivative of **1** in THF and diglyme was then added at −78 °C. The usual work-up gave the adduct (**3**). The corresponding optically active β-substituted alkanoic acid was obtained in good yield by hydrolysis and decarboxylation of the adduct (**3**) (Eq. 4). The results are summarized in Table 4.



Contrary to the results obtained in the reaction of Grignard reagents, alkanoic acids having the same absolute configuration were produced, regardless of the configuration of the starting 6-alkylidene-1,4-oxazepine(**2**), *viz.*, (*S*)-(+)-3-phenylheptanoic acid was obtained by the reaction of lithium dibutylcuprate with either (*E*)- or (*Z*)-6-benzylidene derivatives of **1**. This can be explained by assuming the existence of the radical anion intermediate(**5**) (Eq. 5).[15]



In conclusion, a general method for the preparation of highly optically pure β-substituted alkanoic acids from aldehydes was established by the use of (2*R*,3*S*)-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione-(**1**).

Experimental

*Reaction of Propionaldehyde with (2*R*,3*S*)-3,4-Dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione(**1**).* Titanium tetrachloride (1.3 ml, 12 mmol) was added to a THF (53 ml) solution of **1**(2.33 g, 10 mmol), propionaldehyde (0.697 g, 12 mmol), and pyridine (2 ml) at −78 °C under an argon atmosphere with vigorous stirring. After being stirred at room temperature overnight, the reaction mixture was poured into a phosphate buffer solution (pH 7). The resulting white precipitate was filtered off through Celite and washed with dichloromethane. The aqueous mixture was extracted with dichloromethane. The combined dichloromethane solution was dried over anhydrous Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2–Et_2O) and (2*R*,3*S*)-3,4-dimethyl-2-phenyl-6-propylideneperhydro-1,4-oxazepine-5,7-dione(**2d**)(2.08 g, 76%) was obtained. Recrystallization (benzene–hexane) gave the pure *E* isomer: IR(KBr) 1725, 1640, 1600 cm^{-1}. NMR($CDCl_3$) δ 1.06 (t, *J*=8 Hz, 3 H), 1.18(d, *J*=7 Hz, 3 H), 2.0—2.7 (m, 2H), 3.05 (s, 3H), 3.67 (q, *J*=7 Hz, 1 H), 5.93 (s, 1 H), 7.28 (t, *J*=8 Hz, 1H), 7.42 (s, 5 H). The oxazepines (**2b—f**) were prepared from **1** and the corresponding aldehydes in a similar manner. The IR and NMR spectra of these compounds were in line with the assigned structures; **2b**;IR(KBr) 1750, 1640, 1600 cm^{-1}. NMR($CDCl_3$)δ 1.23 (d, *J*=7 Hz, 3H), 3.10 (s, 3H), 3.70 (q, *J*=7 Hz, 1 H), 6.20 (s, 1 H), 7.1—7.6(m, 10 H), 7.93 (s, 1 H). **2c**; IR(KBr) 1740, 1642, 1600 cm^{-1}. NMR($CDCl_3$)δ 1.17 (d, *J*=6 Hz, 3 H), 1.96 (d, *J*=7 Hz, 3 H), 3.02 (s, 3 H), 3.62 (q, *J*=6 Hz, 1 H), 5.85 (s, 1 H), 7.4—7.7 (m, 6 H). **2e**; IR(KBr) 1722, 1642, 1605 cm^{-1}. NMR($CDCl_3$)δ 0.6—1.8 (m, 10 H), 2.0—2.7 (m, 2H), 3.05 (s, 3 H), 3.3—3.8 (m, 1 H), 5.89 (s, 1H), 6.8—7.9 (m, 6H). **2f**; IR(KBr) 1725, 1640, 1605 cm^{-1}. NMR($CDCl_3$)δ 0.7—1.5 (m, 9 H), 2.4—2.8 (m, 1 H), 3.01 (s, 3H), 3.2—3.9 (m, 1 H), 5.80 (s, 1 H), 7.01 (d, *J*=10 Hz, 1H), 7.36 (s, 5H).

*Preparation of (S)-(−)-3-Methylheptanoic Acid by the Reaction of (E)-(2R,3S)-6-Ethylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione(**2c**) with Butylmagnesium Bromide.* To a THF (14 ml) solution of **2c** (0.547 g, 2.0 mmol) and nickel chloride (0.013 g, 0.10 mmol) was added a THF solution (3.5 ml) of butylmagnesium bromide (2.45 mmol) at −78 °C under an argon atmosphere. After being stirred for 3 h, the reaction mixture was poured into a phosphate buffer solution (pH 7). The organic layer was extracted with dichloromethane and the extract was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the adduct, which was dissolved in acetic acid (20 ml) and 3M H_2SO_4 (40 ml). The reaction mixture was then refluxed for 6 h. The resulting oily substance was extracted with dichloromethane and the extract was dried over anhydrous Na_2SO_4. After the extract had been condensed under reduced pressure, the residue was distilled according to the Kugel-Rohr method (150—160 °C (bath temperature)/15 mmHg) to give (*S*)-(−)-3-methylheptanoic acid (0.236 g, 82%). The acids (Table 3) were obtained in a similar manner and the structures of the compounds identified by their IR and NMR spectra.

*Preparation of (S)-(+)-3-Phenylheptanoic Acid by the Reaction of (E)-(2R,3S)-6-Benzylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (**2b**) with Lithium Dibutylcuprate.* To a diglyme (10 ml) suspension of cuprous iodide (0.343 g, 1.8 mmol) was added a hexane solution (2.2 ml) of butyllithium (3.43 mmol) at −50 °C under an argon atmosphere. After 2 min, the reaction mixture was cooled to −78 °C. The oxazepine (**2b**) (0.482 g, 1.5 mmol) in THF (5 ml) and diglyme (5 ml) was added dropwise and the mixture was stirred for 2 h. It was then warmed to room temperature and poured into a phosphate buffer solution (pH 7). The resulting insoluble materials were filtered off through Celite and washed with dichloromethane. The aqueous mixture was extracted with dichloromethane. The combined dichloromethane solution was dried over anhydrous Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2–Et_2O) to give a mixture of diastereomers. The adducts were hydrolized and decarboxylated according to the above procedure to give the crude acid which was purified by silica gel chromatography (CH_2Cl_2–Et_2O) to yield 0.193 g (64%) of (*S*)-(+)-3-phenyheptanoic acid. It was then distilled for measurement of specific rotation by the Kugel-Rohr method (180—190 °C (bath temperature)/1.5 mmHg).

The acids (Table 4) were obtained in a similar manner and the structures of the compounds identified by their IR and NMR spectra.

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8) The procedure for the preparation of **2a** was described in Ref. 5. The spectral data are as follows; IR(KBr) 1745, 1640, 1600 cm^{-1}; NMR ($CDCl_3$)δ1.21 (d, J=7 Hz, 3H), 2.85 (s, 3 H), 4.18 (dq, J=2 and 7 Hz, 1 H), 5.73 (d, J= 2 Hz, 1 H), 7.30 (s, 10 H), 7.52 (s, 1 H).

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