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Chirality Control by the Aid of 2,2-Dimethyloxazolidine Chiral Auxiliaries. Highly 1,4-Chiral Inductive Asymmetric Alkylations of Amide Enolates

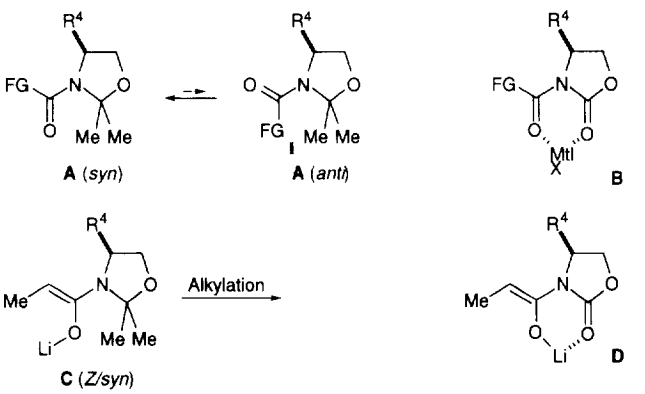
Shuji Kanemasa,* Koichi Ueno,† Kenjiro Onimura,† Takashi Kikukawa,† and Hidetoshi Yamamoto

Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816, Japan

†Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816, Japan

Abstract: The propanamide and methoxyacetamide derivatives of (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine, a new chirality controlling auxiliary based on the restricted rotation around amide bond, generate chiral lithium *Z*-enolates by lithiation. They undergo highly *lk*-1,4- and *ul*-1,4-inductive alkylations with a variety of alkylating reagents, respectively. The diastereotopic face participated in the reactions is that remote from the 4-shielding substituent of oxazolidine in the *syn*-conformations. Coplanarity between the enolate double bond and the oxazolidine plane in the transition state can be a major factor for the observed excellent selectivities.

2,2-Dialkyloxazolidines bearing a chiral center at 4-position have recently been reported by our group[1] and others[2] as new chirality controlling auxiliaries. Conceptual basis of the chirality control by 2,2-dialkyloxazolidine auxiliaries relies on the restricted rotation of the amide linkage. As shown in Scheme 1, the 2,2-dimethyloxazolidine amide **A** prefers to take a form of *syn*-conformer **A** (*syn*) to *anti*-conformer **A** (*anti*) because serious steric hindrance exists in the *anti*-conformer **A** (*anti*) between the functional group (FG) and the 2-methyl groups. Accordingly, the functional group (FG) incorporated in the 3-amide substituent becomes located so closely to the 4-shielding substituent R^4 that effective diastereofacial selection is expected.



Scheme 1.

The related 2-oxazolidinones are well known as Evans' chirality controlling auxiliaries.[3] They have shown highly efficient chiral inductions in asymmetric reactions in the presence of a Lewis acid (MtlX) or a metal ion which works for fixation of the amide conformation in favor of *syn*-conformer **B**. Especially, the

metal enolates of 2-oxazolidinone amides **D** are excellent chiral donor molecules in a variety of asymmetric reactions.

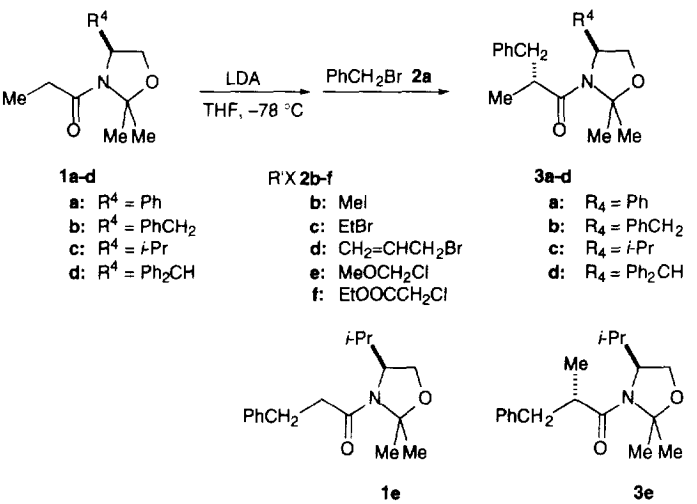
Unlike Evans' 2-oxazolidinones, our 2,2-dialkyloxazolidine auxiliaries do not need the aid of a metal ion. Accordingly, ours are especially useful for the chilarity control of asymmetric reactions which can be performed only in the absence of a metal ion. For example, α,β-unsaturated amide derivatives **A** (FG is CH=CHR) of 2,2-dialkyloxazolidines exist mostly as *syn/s-cis* conformers even at room temperature in chloroform solution,[1a] and the absolute diastereofacial selectivity has been observed in nitrile oxide cycloadditions of the unsaturated amides bearing the 4-shielding substituent appropriately selected (e.g. R^4 is Ph_2CH).[1b] Cuprate conjugate additions were also very effective, while reactions using organolithium or organomagnesium nucleophiles were totally unsuccessful.[4]

Although selectivities change depending upon the structures of substrates and reaction types, the lithium enolates **C** of 2,2-dimethyloxazolidine amides also undergo stereoselective Michael addition reactions with α,β-unsaturated carbonyl acceptors[5] and aldol reactions with bulky aliphatic aldehydes.[6,7] In these two reactions proceeding through chelated transition structures, the stereoselectivities depend sensitively upon the transition state structures. We have learned that reactions through nonchelated transition states would be even more effective in the chirality control by use of the lithium enolates **C**.[7]

The present paper describes the highly diastereoface-selective asymmetric alkylations of the lithium *Z*-enolates of 4-chiral 2,2-dimethyloxazolidine amides.[8] Especially, excellent selectivities are obtained when the 4-benzyl-2,2,5,5-tetramethyloxazolidine chiral auxiliary is employed.

Results and Discussion

Propanamide derivatives **1a-d** of 2,2-dimethyl-3-propanoyloxazolidines bearing a variety of shielding substituents at 4-position were lithiated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C to form the corresponding lithium *Z*-enolates. They were employed in asymmetric alkylations with



Scheme 2.

benzyl bromide in order to examine the efficiency of 1,4-chiral inductions (Scheme 2). Diastereofacial selectivities depended upon the 4-shielding substituents: Phenyl substituent gave the lowest selectivity, but it

was satisfactorily high (86:14, Table 1, entry 1). Benzyl (90:10), isopropyl (95:5), and diphenylmethyl (>99:1) substituents improved the selectivities in this order (entries 2-4), and the exclusive 1,4-chiral induction was attained in the last case.

These results indicate that, in asymmetric alkylations using the lithium *Z*-enolates **C**, one important factor which determines the diastereofacial selectivity is the efficiency of steric shielding by the 4-substituent R^4. The steric shielding can be easily estimated by the magnetic shielding of the acyl moiety at 3-position when the 4-substituent is benzylic, and it is already known that 2,2-dimethyl-4-diphenylmethyloxazolidine and 4-benzyl-2,2,5,5-tetramethyloxazolidine auxiliaries show highly effective magnetic shieldings.[1a] Since the latter chiral auxiliary is readily available in an optical pure form, we decided to employ (*S*)-4-benzyl-2,2,5,5-tetramethyl-3-propanoyloxazolidine (**1f**) in the following asymmetric alkylations.

On the other hand, the lithium *Z*-enolate derived form 3-(3-phenylpropanoyl)oxazolidine **1e** was reacted with methyl iodide as sterically less hindered alkylating reagent in order to examine the steric effect of alkylating agent (Scheme 2). The methylated product **3e**, which is diastereomeric to **3c**, was produced in a lower diastereofacial selectivity (95:5 vs 87:13, entries 3, 5), indicating that a small alkylating reagent is less favored. It was confirmed that the major and minor diastereomers of this reaction were identical to the minor and major diastereomers of the reaction of **1c** with **2a**, respectively.

Table 1. Asymmetric Alkylation of Lithium *Z*-Enolates of 4-Chiral 3-Acyl-2,2-dimethyloxazolidines **1a-f** and **5** Leading to **3a-i** , **4**, and **6a-c**[a]

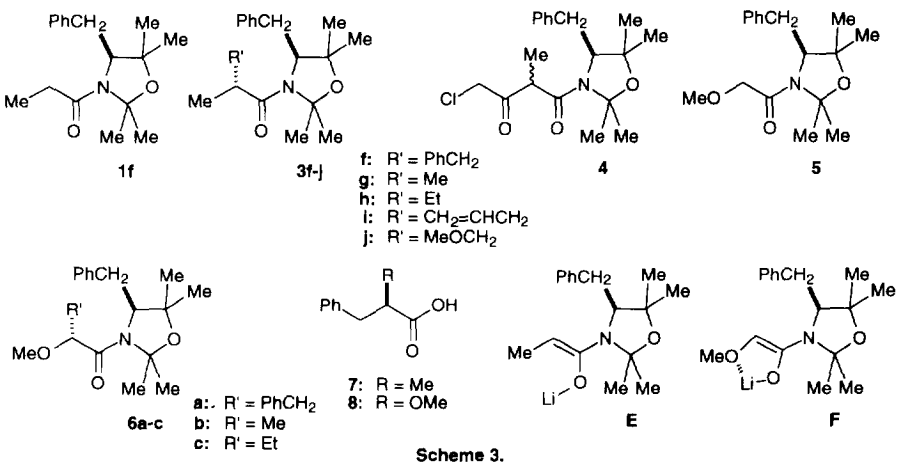
Entry	Amide **1**	R'X **2**	Solvent	Time/h	Product	Yield/%[b,c]	Diatereomer ratio[d,e]
1	**1a**	**2a**	THF	5	**3a**	45 (18)	86:14
2	**1b**	**2a**	THF	5 min	**3b**	91	90:10 (*R*)
3	**1c**	**2a**	THF	5 min	**3c**	88	95:5 (*R*)
4	**1d**[f]	**2a**	THF	5	**3d**	69 (12)	>99:1
5	**1e**	**2b**	THF/HMPA	5 min	**3e**	83 (16)	87:13 (*S*)
6	**1f**[g]	**2a**	THF/HMPA	5 min	**3f**	93	97:3
7	**1f**	**2b**	THF/HMPA	5 min	**3g**	79	-
8	**1f**	**2c**	THF/HMPA	5 min	**3h**	69	95:5
9	**1f**	**2d**	THF/HMPA	5 min	**3i**	57	95:5
10	**1f**	**2e**	THF/HMPA	5 min	**3j**	58 (16)[h]	96:4
11	**1f**	**2f**	THF/HMPA	5 min	**4**	81	96:4
12	**5**	**2a**	THF/HMPA	5 min	**6a**	84	>99:1
13	**5**	**2b**	THF/HMPA	5 min	**6b**	81	97:3
14	**5**	**2c**	THF/HMPA	5 min	**6c**	28	>99:1

[a]A chiral amide **1** or **5** was lithiated with LDA at –78 °C in THF in the presence or absence of HMPA (THF/HMPA = 20:1 v/v). Alkylation was performed at the same temperature for the reaction time listed in Table. [b]Combined yield of isolated products. [c]Recovered amide in parenthesis. [d]Based on ^1H and/or ^{13}C NMR spectrum of the crude reaction mixture. [e]Absolute configuration of the major diastereomer of products in parenthesis. [f]Racemate was used. [g]In the absence of HMPA: 63%, 97:3 (*R*). [h]Product **3j** was inseparable from the starting material **1f**.

Lithiation of (*S*)-4-benzyl-2,2,5,5-tetramethyl-3-propanoyloxazolidine (**1f**) with LDA in THF at –78 °C formed the lithium *Z*-enolate **E**, and its reactions with a variety of alkylating reagents **2a-e** in the presence of hexamethylphosphoric triamide (HMPA, THF/HMPA = 20:1 v/v) gave the alkylated products **3f-j** in excellent diastereofacial selectivities (Scheme 3 and Table 1, entries 6-10). The selectivities were not affect-

ed by the presence of HMPA but instead the yields of alkylated products **3** were improved. For example, in the absence of HMPA, the reaction of entry 6 gave **3f** in 63% yield (ds = 97:3) and that of entry 8 gave **3h** in 49% yield (ds = 95:5).

Alkylation of enolate **E** with chloromethyl methyl ether (**2e**), as highly reactive alkylating reagent, produced the corresponding alkylated product **3j** in 58% yield, but along with some of the unreacted starting amide **1f** (entry 10). Since these two compounds **3j** and **1f** could not be separated from each other, further characterization of **3j** was unsuccessful.



Scheme 3.

When ethyl chloroacetate (**2f**) was used as alkylating reagent under similar conditions (71% in THF at −78 °C), the product isolated was not the alkylated derivative but the Claisen condensation product **4** whose diastereomer ratio was 96:4 (entry 11). Use of HMPA as cosolvent was not effective for the alkylation (**4**: 81% in THF/HMPA 20:1 v/v). A 7:3 mixture of the expected alkylated product and **4** was obtained when ethyl bromoacetate was employed as more reactive alkylating reagent, whose characterization was based only on the ^{1}H NMR analysis of the reaction mixture. Although the attempted epimerization of **4** by the aid of bases was unsuccessful,[9] it is most likely that this selectivity has been thermodynamically controlled.

(*S*)-4-Benzyl-3-methoxyacetyl-2,2,5,5-tetramethyloxazolidine (**5**) was also lithiated with LDA in THF to generate the intramolecularly chelated lithium *Z*-enolate **F** whose alkylations were even much more stereoselective than those using the propanamide enolate **E** (Scheme 3). Thus, alkylated products **6a-c** were produced with diastereofacial selectivities better than 97:3 even when small alkylating reagents such as methyl iodide and ethyl bromide were used (Table 1, entries 12-14). The selectivity of methylation was 97:3 and that of ethylation was >99:1.

Absolute configurations of the alkylated products **3** and **6** were determined by hydrolytic removal of the oxazolidine chiral auxiliary followed by the comparison of optical rotations. Thus, the benzylated product **3c** (ds = 95:5) was transformed to (*R*)-2-methyl-3-phenylpropanoic acid (**7**) which was assigned by comparison of the optical rotation, $[\alpha]_D^{24} = -22.8°$ (90% ee), with that of the authentic sample, ($[\alpha]_D^{24} = -25.4°$).[10] Therefore, the major diastereomer **3e** produced in the reaction of **1e** with methyl iodide (**2b**), which was identical to the minor diasteromer of **3c**, could be assigned to be *S*-configuration at the newly formed chiral center. In addition, a similar hydrolysis of **3b** (ds = 90:10) gave **7** whose optical rotation was $[\alpha]_D^{24} = -20.7°$ (82% ee). These results indicates that no serious racemization takes place in the cleavage step. Similar hydrolytic removal of **6a** gave **8** ($[\alpha]_D^{24} = 6.2°$) in 50% yield.

It was much surprising to us that asymmetric alkylation reactions using the lithium *Z*-enolates **E** and **F** of 2,2-dimethyloxazolidine amides **1** and **5** proceeded with high diastereofacial selectivities. The absolute configuration of the chiral centers newly constructed in the reactions indicates that the *si*-face of enolate **E**, or the *re*-face of enolate **F**, selectively participated in the alkylation reactions. Presumably the lithium *Z*-enolate **E** occupied the *syn*-conformation **G** (*syn*) rather than the *anti*-conformation **G** (*anti*) in the transition state (Figure 1), and the diastereoface remote from the 4-shielding benzyl substituent (*si*-face in the given case) was the place of reaction.

Such excellent diastereofacial selectivities would result only when the enolate plane is nearly coplanar with that of the oxazolidine auxiliary in the transition state **G** (Fig. 1), and this is the case actually happened. We analyze the reaction mechanism as follows: The lithium amide enolates, **E** and **F**, have the maximum nucleophilic reactivity when the enolate moiety is in a full conjugation with the oxazolidine nitrogen atom. Accordingly, the transition state **G** involving the conjugated donor molecule is much more stablized than that involving the deconjugated one, and the *syn*-conformational isomer **G** (*syn*) has predominantly participated in the transition state from the standpoint of steric interaction. As a result, one of the diastereofaces (*Re*-face) is effectively shielded from the attack of alkylating reagent.

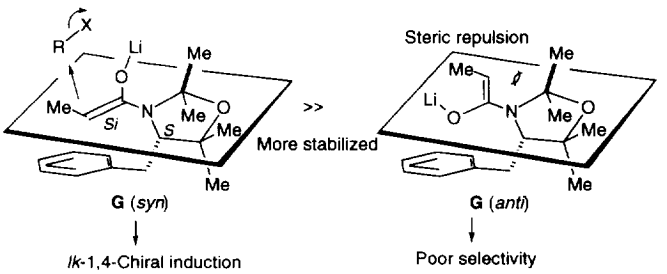


Figure 1. Lithium enolate **G** is most reactive when the enolate moiety is in a full conjugation with the oxazolidine nitrogen so that they are coplanar in the transition state. Thus, alkylation occurs in a preferred *syn*-conformation **G** (*syn*) with a high diastereofacial selectivity.

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Experimental

General Procedure for the Alkylations of Oxazolidine Amides 1. The reaction procedure between (*S*)-4-benzyl-2,2,5,5-tetramethyl-3-propanoyloxazolidine (**1f**) and benzyl bromide is shown as a typical example: To a solution of lithium diisopropylamide (LDA) freshly prepared from diisopropylamine (0.18 mL, 0.81 mmol) and butyllithium (1.6 M in hexane, 0.81 mL, 1.3 mmol) in tetrahydrofuran (THF) was added, at –78 °C under dry nitrogen, a solution of **1f** (0.275 g, 1 mmol) in THF (1 mL). After stirring at this temperature for 1 h, hexamethylphosphoric triamide (HMPA, 0.15 mL) and benzyl bromide (0.13 mL, 1.1 mmol) were added in this order. Stirring was continued at –78 °C for additional 5 h. Saturated NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was submitted to the ^1H and ^{13}C NMR measurement to determine the diastereofacial selectivity (ds = 97:3). The residue was purified by a column chromatography on silica gel using hexane–AcOEt, (4:1 v/v) to give **3f** (0.339 g, 93%).

Other reactions were performed under the reaction conditions listed in Table 1 and all the results are in the same table.

(*S*)-2,2-Dimethyl-3-[(*R*)-2-methyl-3-phenylpropanoyl]-4-phenyloxazolidine (3a): Yield 45 % (ds = 86:14). Colorless prisms (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); mp 124 - 126 °C; major isomer: ^1H NMR ($CDCl_3$) δ = 0.85 (3H, t, $J_{Me\text{-}2'}$ = 6.2 Hz, 2'-Me), 1.46, 1.80 (each 3H, s, 2-Me), 2.52 (1H, m, H-2'), 2.57 (1H, dd, J_{gem} = 12.5 and $J_{3'\text{-}2'}$ = 4.6 Hz, one of H-3'), 2.87 (1H, dd, J_{gem} = 12.5 and $J_{3'\text{-}2'}$ = 10.3 Hz, the other of H-3'), 3.61 (1H, dd, J_{gem} = 8.8 and $J_{5\text{-}4}$ = 1.7 Hz, one of H-5), 3.78 (1H, dd, J_{gem} = 8.8 and $J_{5\text{-}4}$ = 6.6 Hz, the other of H-5), 4.03 (1H, dd, $J_{4\text{-}5}$ = 6.6 and 1.7 Hz, H-4), and 7.12 - 7.36 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.87 (2'-Me), 22.69, 25.40 (each 2-Me), 41.51, 41.95 (C-2' and C-3'), 60.70 (C-5), 70.71 (C-4), 95.85 (C-2), 125.61, 126.42, 127.51, 128.29, 128.70, 128.92, 139.96, 141.81 (each Ph), and 173.87 (CON). minor isomer: ^1H NMR ($CDCl_3$) δ = 1.06 (3H, t, $J_{Me\text{-}2'}$ = 6.2 Hz, 2'-Me), 1.65, 1.83 (each 3H, s, 2-Me), 2.37 (1H, dd, J_{gem} = 12.5 and $J_{3'\text{-}2'}$ = 7.9 Hz, one of H-3'), 2.46 (1H, m, H-2'), 2.71 (1H, dd, J_{gem} = 12.5 and $J_{3'\text{-}2'}$ = 5.5 Hz, the other of H-3'), 3.87 (1H, d, J_{gem} = 9.0 and $J_{5\text{-}4}$ = 2.4 Hz, one of H-5), 4.35 (1H, dd, J_{gem} = 9.0 and $J_{5\text{-}4}$ = 6.4 Hz, the other of H-5), 4.87 (1H, dd, $J_{4\text{-}5}$ = 6.4 and 2.4 Hz, H-4), 6.58 (2H, m, Ph), and 7.02 - 7.32 (8H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.92 (2'-Me), 23.14, 25.38 (each 2-Me), 39.13, 41.12 (C-2' and C-3'), 61.31 (C-5), 71.24 (C-4), 95.98 (C-2), 125.74, 125.78, 127.68, 127.99, 129.02, 129.06, 139.66, 141.87 (each Ph), and 174.23 (CON). Anal. Found: C, 78.20; H, 7.87; N, 4.30%. Calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33%.

(*S*)-4-Benzyl-2,2-dimethyl-3-[(*R*)-2-methyl-3-phenylpropanoyl]oxazolidine (3b): Yield 91 % (ds = 90:10). Colorless plates (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); mp 93 - 94 °C; $[\alpha]_D^{24}$ = –86.8° (*c* 0.96, $CHCl_3$); IR (KBr) 2920, 1640, 1410, 1360, 1305, 1235, 1080, 840, 815, 750, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) major isomer: δ = 1.20 (3H, t, $J_{Me\text{-}2'}$ = 6.2 Hz, 2'-Me), 1.40, 1.66 (each 3H, s, 2-Me), 2.67 - 2.96 (5H, m, H-2', H-3', and PhC<u>H</u>$_2$), 3.14 (1H, ddd, J_{gem} = 9.1, $J_{5\text{-}4}$ = 5.0, and $J_{5\text{-}CH2}$ = 1.1 Hz, one of H-5), 3.34 (1H, quint, $J_{4\text{-}5}$ = $J_{4\text{-}CH2}$ = 4.9 Hz, H-4), 3.50 (1H, d, J_{gem} = 9.1 Hz, the other of H-5), and 7.09 - 7.36 (10H, m, Ph). minor isomer (partial): δ = 1.24, 1.46 (3H, t, $J_{Me\text{-}2'}$ = 6.2 Hz, 2'-Me), and 1.84 (3H, s, 2-Me); ^{13}C NMR ($CDCl_3$) major isomer: δ = 18.38 (2'-Me), 22.73, 26.94 (each 2-Me), 40.49, 41.77, 41.87 (C-2', C-3', and 4-PhC<u>H</u>$_2$), 58.64 (C-5), 65.88 (C-4), 95.34 (C-2), 126.47, 126.80, 128.33, 128.78, 128.94, 128.98, 137.39, 139.73 (each Ph), and 172.50 (CON). minor isomer (partial): δ = 18.57 (2'-Me), 22.57, 28.65 (each 2-Me), 38.01, 40.39, 41.29 (C-2', C-3', and 4-PhC<u>H</u>$_2$), 59.97 (C-5), 65.08 (C-4), 93.04 (C-2), 126.39, 128.47, 129.25, 129.34, 129.38, 138.67, 139.60 (each Ph), and 173.12 (CON). Anal. Found: C, 78.52; H, 8.13; N, 4.01. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15%.

(*S*)-4-Isopropyl-2,2-dimethyl-3-[(*R*)-2-methyl-3-phenylpropanoyl]oxazolidine (3c): Yield 88 % (ds = 95:5). Colorless needles (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); ^1H NMR ($CDCl_3$) δ = 0.86, 0.87 (each 3H, d, *J* = 6.8 Hz, Me of *i*-Pr), 1.23 (3H, d, $J_{Me\text{-}2'}$ = 5.9 Hz, 2'-Me), 1.32, 1.60 (each 3H, s, 2-Me), 1.84 (1H, m, CH of *i*-Pr), 2.69 (1H, dd, J_{gem} = 11.7 and $J_{3'\text{-}2'}$ = 4.0 Hz, one of H-3'), 2.79 (1H, m, H-2'), 2.90 (1H, dd, J_{gem} = 11.7 and $J_{3'\text{-}2'}$ = 9.5 Hz, the other of H-3'), 3.07 (1H, br dd, $J_{4\text{-}5}$ = 5.9 and $J_{4\text{-}CH}$ = 5.7 Hz, H-4), 3.23 (1H, dd, J_{gem} = 9.2 and $J_{5\text{-}4}$ = 5.9 Hz, one of H-5), 3.60 (1H, dd, J_{gem} = 9.2 and $J_{5\text{-}4}$ = 0.7 Hz, the other of H-5), and 7.16 - 7.29 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.25 (2'-Me), 18.46, 19.71 (Me of *i*-Pr), 22.66, 25.97 (each 2-Me), 31.40 (CH of *i*-Pr), 41.44, 41.75 (C-2' and C-3'), 62.11, 63.96

(C-4 and C-5), 95.11 (C-2), 126.37, 128.26, 129.02, 139.72 (each Ph), and 173.47 (CON). Anal. Found: C, 74.82; H, 9.38; N, 4.78%. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84%. The minor diastereomer of **3c** is identical with the major diastereomer of **3e**.

(*RS*)-2,2-Dimethyl-3-[(*SR*)-2-methyl-3-phenylpropanoyl]-4-(diphenylmethyl)oxazolidine (3d): Yield 69 % (reaction solvent: THF, ds = >99:1); Colorless solid (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); mp 170 - 171 °C; ^{1}H NMR ($CDCl_3$) δ = 0.36 (3H, d, $J_{Me\text{-}CH}$ = 6.6 Hz, 2'-Me), 1.47, 1.76 (each 3H, s, 2-Me), 2.36 (1H, m, H-2'), 2.58 (1H, dd, J_{gem} = 13.2 and $J_{3'\text{-}2'}$ = 4.7 Hz, one of H-3'), 2.68 (1H, dd, J_{gem} = 13.2 and $J_{3'\text{-}2'}$ = 10.3 Hz, the other of H-3'), 3.08 (1H, dd, J_{gem} = 9.1 and $J_{5\text{-}4}$ = 4.8 Hz, one of H-5), 3.43 (1H, d, J_{gem} = 9.1 Hz, the other of H-5), 3.96 (1H, dd, $J_{4\text{-}CH}$ = 10.5 and $J_{4\text{-}5}$ = 4.8 Hz, H-4), 4.12 (1H, d, $J_{CH\text{-}4}$ = 10.5 Hz, $Ph_2C\underline{H}$), and 7.06 - 7.35 (15H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.41 (2'-Me), 23.41, 27.30 (each 2-Me), 41.78, 42.32 (C-2' and C-3'), 54.35 ($Ph_2\underline{C}H$), 60.62 (C-5), 67.26 (C-4), 95.95 (C-2), 126.66, 126.86, 126.91, 128.46, 128.61, 128.65, 128.74, 129.12, 129.60, 140.05, 140.87, 141.31 (each Ph), and 174.15 (CON). Anal. Found: C, 81.30; H, 7.59; N, 3.28%. Calcd for $C_{28}H_{31}NO_2$: C, 81.32; H, 7.56; N, 3.39%.

(*S*)-4-Isopropyl-2,2-dimethyl-3-[(*R*)-2-methyl-3-phenylpropanoyl]oxazolidine (3e): Yield 83 % (reaction solvent: HMPA/THF = 1/20 v/v, ds = 87:13). This compound is identical with the minor diasteromer of **3c**: ^{1}H NMR ($CDCl_3$) δ = 0.65, 0.80 (each 3H, d, J = 6.8 Hz, Me of *i*-Pr), 1.13 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, 2'-Me), 1.23 (1H, m, CH of *i*-Pr), 1.50, 1.65 (each 3H, s, 2-Me), 2.55 - 2.72 (2H, m, H-2' and one of H-3'), 3.11 (1H, dd, J_{gem} = 12.3 and $J_{3'\text{-}2'}$ = 6.8 Hz, the other of H-3'), 3.55 (1H, m, H-4), 3.85 (2H, br, H-5), and 7.14 - 7.31 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.66 (2'-Me), 17.94, 19.57 (Me of *i*-Pr), 22.49, 25.80 (each 2-Me), 31.79 (CH of *i*-Pr), 39.62, 41.26 (C-2' and C-3'), 61.90, 63.80 (C-4 and C-5), 95.03 (C-2), 126.08, 128.17, 129.09, 140.02 (each Ph), and 173.64 (CON). Anal. Found: C, 74.69; H, 9.31; N, 4.90%. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84%.

(*S*)-4-Benzyl-2,2,5,5-tetramethyl-3-[(*R*)-2-methyl-3-phenylpropanoyl]oxazolidine (3f): Yield 93 % (reaction solvent: HMPA/THF = 1/20 v/v, ds = 97:3); Colorless solid (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); mp 48 - 49.5 °C; $[\alpha]_D^{24}$ = –71.3° (*c* 1.0, $CHCl_3$); IR (KBr) 2960, 1630, 1410, 1370, 1260, 1190, 1135, 1000, 740, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.74, 1.07, 1.59, 1.67 (each 3H, s, 2-Me and 5-Me), 0.83 (3H, d, $J_{Me\text{-}2'}$ = 6.2 Hz, 2'-Me), 1.11 - 1.34 (1H, m, H-2'), 2.58 - 2.68 (2H, m, H-3'), 2.77 (1H, dd, J_{gem} = 14.8 and $J_{CH2\text{-}4}$ = 5.8 Hz, one of $PhC\underline{H}_2$), 2.89 (1H, m, H-2'), 3.02 (H, dd, J_{gem} = 14.8 and $J_{CH2\text{-}4}$ = 8.4 Hz, the other of $PhC\underline{H}_2$), 3.78 (1H, dd, $J_{4\text{-}CH2}$ = 8.4 and 5.8 Hz, H-4), and 7.15 - 7.35 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.35 (2'-Me), 24.43, 27.69, 28.48, 28.81 (2-Me and 5-Me), 39.03, 41.08, 41.59 (C-2' and C-3'), 65.67 (C-4), 80.24 (C-5), 94.21 (C-2), 126.47, 126.67, 128.52, 128.83, 128.86, 128.94, 137.98, 139.72 (each Ph), and 173.27 (CON). Anal. Found: C, 78.68; H, 8.49; N, 3.95%. Calcd for $C_{24}H_{31}NO_2$: C, 78.87; H, 8.55; N, 3.83%.

(*S*)-4-Benzyl-2,2,5,5-tetramethyl-3-(2-methylpropanoyl)oxazolidine (3g): Yield 79% (reaction solvent: HMPA/THF = 1/20 v/v); Colorless solid (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); mp 97 - 99 °C; $[\alpha]_D^{24}$ = –155.1° (*c* 1.0, $CHCl_3$); IR (KBr) 2960, 1630, 1410, 1360, 1320, 1270, 1190, 1130, 1080, 990, 930, 750, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.53 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, one of Me), 0.98 (3H, d, $J_{Me\text{-}2'}$ = 7.3 Hz, the other of Me), 1.32, 1.39 (each 3H, s, 5-Me), 1.70, 1.78 (each 3H, s, 2-Me), 1.91 (1H, m, H-2'), 2.84 (1H, dd, J_{gem} = 13.9 and $J_{CH2\text{-}4}$ = 9.2 Hz, one of $PhC\underline{H}_2$), 2.99 (1H, dd, J_{gem} = 13.9 and $J_{CH2\text{-}4}$ = 5.3 Hz, the other of $PhC\underline{H}_2$), 3.92 (1H, dd, $J_{4\text{-}CH2}$ = 9.2 and 5.3 Hz, H-4), and 7.17 - 7.35 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.49, 20.01 (each Me), 24.10, 27.95, 29.00, 29.10 (2-Me and 5-Me), 32.96 (C-2'), 38.73 ($PhC\underline{H}_2$), 65.87 (C-4), 80.20 (C-5), 94.21 (C-2), 126.73, 129.21, 129.41, 137.85 (each Ph), and 175.17 (CON). Anal. Found: C, 74.88; H, 9.37; N, 4.61%. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84%.

(*S*)-4-Benzyl-2,2,5,5-tetramethyl-3-[(*R*)-2-methylbutanoyl]oxazolidine (3h): Yield 69% (reaction solvent: HMPA/THF = 1/20 v/v, ds = 95:5); Colorless solid (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); mp 68 - 70.5 °C; $[\alpha]_D^{24}$ = –147.7° (*c* 0.86, $CHCl_3$); IR (KBr) 2920, 1610, 1405, 1360, 1310, 1200, 1190, 1125, 940, 740, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.64 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, 2'-Me), 0.88 (3H, t, $J_{Me\text{-}CH2}$ = 7.3 Hz, H-4'), 1.53 (2H, m, H-3'), 1.26, 1.38 (each 3H, s, 5-Me), 1.71, 1.75 (each 3H, s, 2-Me), 2.04 (1H, m, H-2'), 2.83 (1H, dd, J_{gem} = 14.3 and $J_{CH2\text{-}4}$ = 7.3 Hz, one of $PhC\underline{H}_2$), 3.04 (1H, dd, J_{gem} = 14.3 and $J_{CH2\text{-}4}$ = 7.0 Hz, the other of $PhC\underline{H}_2$), 4.01 (1H, dd, $J_{4\text{-}CH2}$ = 7.3 and 7.0 Hz, H-4),

and 7.18 - 7.35 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 11.56 (C-4'), 15.32 (2'-Me), 24.39, 27.66, 28.01, 29.04, 29.19 (2-Me, 5-Me, and C-3'), 39.03, 39.73 (PhCH$_2$ and C-2'), 65.99 (C-4), 80.40 (C-5), 94.35 (C-2), 126.76, 128.92, 129.23, 138.01 (each Ph), and 174.41 (CON). Anal. Found: C, 75.38; H, 9.62; N, 4.49%. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62%.

(*S*)-4-Benzyl-2,2,5,5-tetramethyl-3-[(*R*)-2-methyl-4-pentenoyl]oxazolidine (3i): Yield 57% (reaction solvent: HMPA/THF = 1/20 v/v, ds = 95:5); Colorless solid (silica gel column chromatography with hexane–AcOEt, 3:1 v/v); mp 46 - 48 °C; $[\alpha]_D^{24} = -115.5°$ (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 0.62 (3H, d, $J_{Me\text{-}2'}$ = 6.2 Hz, 2'-Me), 1.27, 1.39 (each 3H, s, 5-Me), 1.70, 1.75 (each 3H, s, 2-Me), 2.02 - 2.27 (3H, m, H-2' and H-3'), 2.83 (1H, dd, J_{gem} = 14.3 and $J_{CH2\text{-}4}$ = 7.7 Hz, one of PhCH$_2$), 3.04 (1H, dd, J_{gem} = 14.3 and $J_{CH2\text{-}4}$ = 6.6 Hz, the other of PhCH$_2$), 4.01 (1H, dd, $J_{4\text{-}CH2}$ = 7.7 and 6.6 Hz, H-4), 5.00 - 5.07 (2H, m, H-5'), 5.64 - 5.77 (1H, m, H-4'), and 7.18 - 7.33 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 15.68 (2'-Me), 24.38, 27.98, 29.04, 29.19 (2-Me and 5-Me), 38.30, 38.98, 39.14 (PhCH$_2$, C-2', and C-3'), 65.90 (C-4), 80.44 (C-5), 94.40 (C-2), 116.97, 126.79, 128.94, 129.25, 135.49, 137.89 (Ph, C-3', and C-4'), and 173.66 (CON). Anal. Found: C, 76.12; H, 9.29; N, 4.20%. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44%.

(*S*)-4-Benzyl-2,2,5,5-tetramethyl-3-[(*R*)-3-methoxy-2-methylpropanoyl]oxazolidine (3j): Yield 58% (reaction solvent: HMPA/THF = 1/20 v/v, ds = 96:4). Since this product was obtained as inseparable mixture with the starting amide **1f**, partial spectral data are given: ^{1}H NMR ($CDCl_3$) δ = 0.39 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, 2'-Me), 1.29, 1.40 (each 3H, s, 5-Me), 1.72, 1.75 (each 3H, s, 2-Me), 2.39 (1H, m, H-2'), 2.79 (3H, m, H-2' and H-3'), 2.83 (1H, dd, J_{gem} = 13.9 and $J_{CH2\text{-}4}$ = 9.5 Hz, one of PhCH$_2$), 2.98 (1H, dd, J_{gem} = 13.9 and $J_{CH2\text{-}4}$ = 5.5 Hz, the other of PhCH$_2$), 3.16 (1H, dd, J_{gem} = 8.8 and $J_{CH2\text{-}2'}$ = 5.1 Hz, one of MeOCH$_2$), 3.22 (3H, s, MeO), 3.27 (1H, t, J_{gem} = $J_{CH2\text{-}2'}$ = 8.8 Hz, the other of MeOCH$_2$), 4.28 (1H, dd, $J_{4\text{-}CH2}$ = 9.5 and 5.5 Hz, H-4), and 7.17 - 7.34 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 12.56 (2'-Me), 24.08, 27.85, 28.11, 28.85 (2-Me and 5-Me), 38.47, 39.00 (PhCH$_2$ and C-2'), 58.22 (MeO), 65.11 (C-4), 76.52 (C-3'), 80.31 (C-5), 94.09 (C-2), 126.46, 128.59, 128.99, 129.35 (Ph), and 172.75 (CON). MS *m/z* (rel. intensity) 320 (M^+ + 1, 23), 184 (22), and 128 (base peak).

(*S*)-4-Benzyl-[(*R*)-4-chloro-2-methyl-3-oxobutanoyl]-2,2,5,5-tetramethyloxazolidine (4): Yield 81% (reaction solvent: HMPA/THF = 1/20 v/v, ds = 96:4); Colorless solid (silica gel column chromatography with hexane–AcOEt, 3:1 v/v); mp 101 - 103 °C; $[\alpha]_D^{24} = -198.6°$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 0.68 (3H, d, $J_{Me\text{-}2'}$ = 7.0 Hz, 2'-Me), 1.25, 1.27 (each 3H, s, 5-Me), 1.64, 1.72 (each 3H, s, 2-Me), 2.75 (1H, dd, J_{gem} = 13.6 and $J_{CH2\text{-}4}$ = 10.6 Hz, one of PhCH$_2$), 2.91 (1H, q, $J_{2'\text{-}Me}$ = 7.0 Hz, H-2'), 2.91 (1H, dd, J_{gem} = 13.6 and $J_{CH2\text{-}4}$ = 4.4 Hz, the other of PhCH$_2$), 3.89 (1H, dd, $J_{4\text{-}CH2}$ = 10.6 and 4.4 Hz, H-4), 4.07 (2H, s, H-4'), and 7.13 -7.31 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 12.63 (2'-Me), 24.06, 27.54, 28.55, 29.10 (2-Me and 5-Me), 38.42 (PhCH$_2$), 45.37 (C-2'), 51.62 (C-4'), 66.25 (C-4), 80.76 (C-5), 94.87 (C-2), 127.11, 129.20, 129.74, 137.61 (each Ph), 166.36 (CON) and 199.73 (C-3'). Anal. Found: C, 65.60; H, 7.54; N, 4.01%. Calcd for $C_{19}H_{26}NO_3Cl$: C, 64.86; H, 7.45; N, 3.98%.

(*S*)-4-Benzyl-3-[(*R*)-2-methoxy-3-phenylpropanoyl]-2,2,5,5-tetramethyloxazolidine (6a): Yield 84% (reaction solvent: HMPA/THF = 1/20 v/v, ds = >99:1); Colorless solid (silica gel column chromatography with hexane–AcOEt, 4:1 v/v); mp 71.5 - 72.5 °C; $[\alpha]_D^{24} = -37.5°$ (*c* 0.60, $CHCl_3$); IR (KBr) 2960, 1630, 1390, 1360, 1250, 1180, 1110, 990, 720, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.96, 1.08 (each 3H, s, 5-Me), 1.66, 1.70 (each 3H, s, 2-Me), 2.92 (1H, dd, J_{gem} = 15.0 and $J_{CH2\text{-}4}$ = 4.4 Hz, one of PhCH$_2$), 3.03 - 3.14 (3H, m, H-3' and the other of PhCH$_2$), 3.14 (3H, s, MeO), 3.89 (1H, dd, $J_{4\text{-}CH2}$ = 9.2 and 4.4 Hz, H-4), 4.04 (1H, dd, $J_{2'\text{-}3'}$ = 7.2 and 6.9 Hz, H-2'), and 7.15 - 7.35 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 24.54, 27.40, 28.77, 28.85 (2-Me and 5-Me), 39.08, 39.28 (each PhCH$_2$), 57.06 (MeO), 64.75 (C-4), 80.69, 80.95 (C-5 and MeOCH), 94.76 (C-2), 126.76, 126.89, 128.62, 128.65, 128.95, 129.27, 137.23, 137.84 (each Ph), and 168.45 (CON). Anal. Found: C, 74.82; H, 8.17; N, 3.60%. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67%.

(*S*)-4-Benzyl-3-[(*R*)-2-methoxypropanoyl]-2,2,5,5-tetramethyloxazolidine (6b): Yield 81% (reaction solvent: HMPA/THF = 1/20 v/v, ds = 97:3); Colorless solid (silica gel column chromatography with hexane–AcOEt, 1:1 v/v); mp 126.5 - 129 °C; $[\alpha]_D^{24} = -95.4°$ (*c* 1.05, $CHCl_3$); IR (KBr) 2990, 1640, 1450, 1410, 1350, 1260, 1190, 1110, 1080, 930, 830, 750, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.26, 1.37 (each 3H, s, 5-Me), 1.33 (3H, d, $J_{3'\text{-}2'}$ = 6.6 Hz, H-3'), 1.72, 1.77 (each 3H, s, 2-Me), 2.90 (1H, overlapping, one of PhCH$_2$), 2.90 (3H, s, MeO), 3.08 (1H, dd, J_{gem} = 14.3 and $J_{CH2\text{-}4}$ = 7.0 Hz, the other of PhCH$_2$), 3.56 (1H,

q, $J_{2'-3'}$ = 6.6 Hz, H-2'), 3.97 (1H, dd, $J_{4\text{-}CH2}$ = 7.3 and 7.0 Hz, H-4), and 7.19 - 7.37 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 18.14 (C-3'), 24.33, 27.63, 28.91, 29.17 (2-Me and 5-Me), 39.03 (Ph<u>C</u>H$_2$), 56.53 (MeO), 64.87 (C-4), 75.15 (C-2'), 81.05 (C-5), 94.81 (C-2), 126.88, 129.08, 129.21, 137.85 (each Ph), and 170.07 CON). Anal. Found: C, 70.84; H, 8.97; N, 4.53%. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59%.

(*S*)-4-Benzyl-3-[(*R*)-2-methoxybutanoyl]-2,2,5,5-tetramethyloxazolidine (6c): Yield 28% (reaction solvent: HMPA/THF = 1/20 v/v, ds = >99:1); Colorless solid (silica gel column chromatography with hexane–AcOEt, 1:1 v/v); mp 54 - 56 °C; $[\alpha]_D^{24}$ = –85.0 ° (*c* 0.87, $CHCl_3$); IR (KBr) 2980, 1650, 1370, 1260, 1200, 1130, 990, 740, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.00 (3H, t, $J_{4'-3'}$ = 7.3 Hz, H-4'), 1.22, 1.35 (each 3H, s, 5-Me), 1.67 (2H, m, H-3'), 1.72, 1.75 (each 3H, s, 2-Me), 2.90 (1H, dd, J_{gem} = 14.6 and $J_{CH2\text{-}4}$ = 6.2 Hz, one of Ph<u>C</u>H$_2$), 2.99 (3H, s, MeO), 3.11 (1H, dd, J_{gem} = 14.6 and $J_{CH2\text{-}4}$ = 7.7 Hz, the other of Ph<u>C</u>H$_2$) 3.51 (1H, dd, $J_{2'-3'}$ = 6.8 and 5.0 Hz, H-2'), 4.05 (1H, dd, $J_{4\text{-}CH2}$ = 7.7 and 6.2 Hz, H-4), and 7.28 - 7.36 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 9.95 (C-4'), 24.41, 25.69, 27.66, 28.97, 29.10 (2-Me, 5-Me, and C-3'), 39.18 (Ph<u>C</u>H$_2$), 57.06 (MeO), 64.66 (C-4), 80.72, 81.08 (C-5 and C-2'), 94.81 (C-2), 126.84, 129.04, 129.43, 137.92 (each Ph), and 169.21 (CON). Anal. Found: C, 71.29; H, 9.04; N, 4.33%. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38%.

General Procedure for the Removal of the Chiral Auxiliary from 3. Hydrolytic removal of the chiral auxiliary from **3c** is presented as typical example: A solution of **3c** (ds = 95:5, 0.231 g, 0.8 mmol) in acetic acid (4 ml) containing 6*N* sulfuric acid (2 ml) was heated under reflux for 4 h. The mixture was poured into ice water and extracted with diethyl ether (25 ml x 3). The combined extracts were washed with saturated sodium chloride (4 ml) and water (4 ml), dried with anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel with hexane–EtOAc (1:1 v/v) to give (*R*)-2-methyl-3-phenylpropanoic acid (**7**, 0.131 g, 100%) as a pale yellow liquid. Its optical purity was estimated to be 90% ee on the basis of the optical rotation: $[\alpha]_D^{24}$ = –22.8° (*c* 1.32, $CHCl_3$) (lit.[10] $[\alpha]_D^{24}$ = –25.4° (neat)). This acid **7** was then transformed to the methyl ester by treatment with diazomethane in diethyl ether: ^{1}H NMR ($CDCl_3$) δ = 1.06 (3H, d, $J_{Me\text{-}2}$ = 6.6 Hz, 2-Me), 2.62 (2H, m, H-3), 2.94 (1H, m, H-2), 3.54 (3H, s, COOMe) and 7.05 - 7.22 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.66 (2-Me), 39.64, 41.34 (C-2 and C-3), 51.44 (COO<u>Me</u>), 126.23, 128.27, 128.86, 139.26 (each Ph), and 176.42 (<u>C</u>OOMe).

(*R*)-2-Methoxy-3-phenylpropanoic Acid (8): Yield 50%; Yellow liquid; $[\alpha]_D^{24}$ = –6.2 ° (*c* 0.15, $CHCl_3$); IR (neat) 3800-2400, 1725, 1450, 1200, 1150, 1020, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 3.01 (1H, dd, J_{gem} = 14.1 and $J_{3\text{-}2}$ = 7.9 Hz, one of H-3), 3.13 (1H, dd, J_{gem} = 14.1 and $J_{3\text{-}2}$ = 4.2 Hz, the other of H-3), 3.38 (3H, s, MeO), 4.01 (1H, dd, $J_{2\text{-}3}$ = 7.9 and 4.2 Hz, H-2), 7.20 - 7.32 (5H, m, Ph), and 8.95 (1H, br s, COOH); ^{13}C NMR ($CDCl_3$) δ = 38.74 (C-3), 58.61 (MeO), 81.27 (C-2), 126.86, 128.43, 129.38, 136.66 (each Ph), and 176.68 (COOH). Acid **8** was then transformed to the methyl ester (80%) by treatment with diazomethane in diethyl ether: Pale yellow liquid (silica gel column chromatography with hexane–Et_2O, 1:1 v/v); $[\alpha]_D^{24}$ = –26.0 ° (*c* 0.55, $CHCl_3$); IR (neat) 2990, 1745, 1435, 1360, 1270, 1200, 1120, 1025, 745, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.93 - 3.07 (2H, m, H-3), 3.32 (3H, s, MeO), 3.69 (3H, s, COO<u>Me</u>), 3.97 (1H, dd, $J_{2\text{-}3}$ = 7.7 and 5.5 Hz, H-2), and 7.18 - 7.27 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 39.16 (C-3), 51.81 (COO<u>Me</u>), 58.26 (MeO), 81.70 (C-2), 126.69, 128.33, 129.28, 136.94 (each Ph), 172.48 (<u>C</u>OOMe). Anal. Found: C, 67.62; H, 7.23%. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%.

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