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High Enantiocontrol of Michael Additions by Use of 2,2-Dimethyloxazolidine Chiral Auxiliaries. Exclusively *ul,lk*-1,4-Inductive Michael Additions of the Lithium (*Z*)-Enolate of (*S*)-4-Benzyl-2,2,5,5-tetramethyl-3-propanoyl-oxazolidine to α,β-Unsaturated Esters

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Abstract: The lithium (*Z*)-enolate generated from the propanamide of (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine undergoes highly *lk*-1,4/*anti*-selective Michael additions to α,β-unsaturated ester and amide acceptors. However, only poor selectivities result when either the lithium (*Z*)-enolates of an oxazolidine methoxyacetamide derivative or the oxazolidine α,β-unsaturated amide acceptors are used. The observed high chiral inductions in the former cases are based on the facts that *syn*-conformation of the enolate is involved in the transition state where the enolate and oxazolidine planes are coplanar, and that the diastereoface remote from the 4-shielding substituent of the auxiliary is open for the attack of acceptor molecules.

Enantiocontrolled Michael addition reactions using prostereogenic substrates are of special improtance from the viewpoint of straightforward construction of contiguous chiral centers by a simple carbon-carbon bond forming process.[1] Although stereoselective asymmetric Michael additions using either chiral metal enolate donors or chiral α,β-unsaturated carbonyl acceptors belong to this category, only limited examples are known so far. Chiral donor molecules successfully employed in previous works include the lithium enolates derived from 8-phenylmenthyl propanoate,[2] (alkylideneamino)acetates,[3,4] 3-acyloxazolidin-2-ones,[5] imidazolidin-2-ones,[6] and hydrazones.[7] Examples of utilization of chiral acceptor molecules are even more limited. Homochiral α,β-unsaturated sulfoxides[8] and (*E*)-3-(1,3-dioxolan-4-yl)acrylates[9-11] are among them.

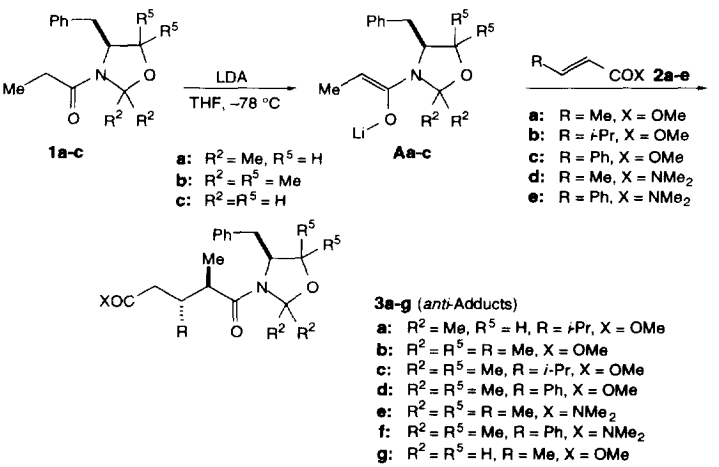
High synthetic potential of 2,2-dialkyloxazolidine chiral auxiliaries has been recently demonstrated, by us and others, in several asymmetric reactions including 1,3-dipolar cycloadditions,[12] conjugate additions of cuprates,[13] and radical additions.[14] In these reactions, the auxiliaries have been incorporated in α,β-unsaturated acceptors. Also useful are alkylations,[15] aldol reactions[16] of the lithium enolates of 2,2-dialkyl-3-[(alkylideneamino)acetyl]oxazolidines, and the imine cycloadditions of their ketene derivatives.[17]

Chirality control by this kind of auxiliary depends upon the restricted rotation of the amide linkage in favor of *syn*-conformation in the transition state, and use of their α,β-unsaturated amide derivatives as acceptor molecules is extremely useful. On the other hand, only rare successful examples of chirality control are known[15,16] when these auxiliaries are incorporated in donor molecules. We have continued to investigate the asymmetric Michael additions of the lithium enolates of 2,2-dialkyloxazolidine amides to α,β-unsaturated carbonyl acceptors. Two major purposes involved herein are (1) to know the synthetic utility of 2,2-dialkyloxazolidine chiral auxiliaries when they are incorporated in donor molecules, and (2) to inspect the chelation transition state structures[18] proposed for Michael addition reactions using metal enolates.

The present work presents exclusively *lk*-1,4/*anti*-selective Michael additions of the lithium (*Z*)-enolates derived from (*S*)-4-benzyl-2,2-dimethyl-3-propanoyloxazolidines to α,β-unsaturated carbonyl acceptors. Similar reactions using *N*-methoxyacetyl derivatives and some other related acceptor molecules are also discussed.

Results and Discussion

(*S*)-4-Benzyl-2,2-dimethyl-3-propanoyloxazolidine (**1a**), used as a chiral substrate in the present work, was readily available in an optically pure form by *N*-acylation of (*S*)-4-benzyl-2,2-dimethyloxazolidine with propanoyl chloride and triethylamine. Amide **1a** was lithiated by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at –78 °C to form the lithium (*Z*)-enolate **Aa**. Michael addition reaction of the resulting enolate **Aa** to methyl (*E*)-4-methyl-2-pentenoate (**2b**) was smoothly completed in a short period at –78 °C (checked by TLC). After quenching the reaction mixture with saturated aqueous ammonium chloride, the corresponding Michael adduct **3a** was obtained in good yield and high diastereomer ratio (98:2, Scheme I and Table 1, entry 1).



Scheme I

Stereoselectivity was disappointingly low when the same reaction was performed in Et_2O - toluene (3:2 v/v) solution, instead of THF, a 69:21:10 mixture of diastereomers being produced in 51% of combined yield. Accordingly, use of THF is important. In addition, a bulky β-substituent such as isopropyl moiety is essential to attain high selectivity since a related reaction of **1a** with methyl crotonate (**2a**), instead of **2b**, was much less stereoselective to give a 69:14:10:7 mixture of four diastereomers. Accordingly, synthetic potential of the (*S*)-4-benzyl-2,2-dimethyloxazolidine chiral auxiliary in asymmetric Michael additions is quite limited.

The chiral lithium (*Z*)-enolate **Ab** derived from propanamide **1b** bears the 4-benzyl-2,2,5,5-tetramethyloxazolidine auxiliary which shows a much more effective shielding ability than the 5-unsubstituted derivative such as **1a**. This enolate **Ab** reacted with a variety of α,β-unsaturated ester and amide acceptors **2a-e** to give *anti*-stereoisomers of Michael adducts **3b-f** as far major products. High synthetic potential of the (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine chiral auxiliary is clear when the Michael addition reactions using two similar enolates **Aa,b** to methyl crotonate (**2a**) are compared (69:14:10:7 vs 96:4). All results are summarized in Table 1 (entries 2 - 6).

Table 1. Asymmetric Michael Additions of the Lithium (*Z*)-Enolates of Oxazolidine Amides **1, 4** to α,β-Unsaturated Esters **2a-e**[a]

Entry	Donor	Acceptor	Time/h	Product	Yield/%[b]	Diastereomer ratio[c]
1	**1a**	**2b**	4	**3a**	72	98:2 (*lk*-1,4/*anti*:*lk*-1,4/*syn*)
2	**1b**	**2a**	5	**3b**	79	96:4 (*lk*-1,4/*anti*:*lk*-1,4/*syn*)[d]
3	**1b**	**2b**	5	**3c**	64	>99:1 (*lk*-1,4/*anti*)
4	**1b**	**2c**	3	**3d**	79	87:13 (*lk*-1,4/*anti*:*lk*-1,4/*syn*)[d]
5	**1b**	**2d**	5	**3e**	88	96:4 (*lk*-1,4/*anti*:*lk*-1,4/*syn*)
6	**1b**	**2e**	5	**3f**	69	92:8 (*lk*-1,4/*anti*:*lk*-1,4/*syn*)
7	**1c**	**2a**	1	**3g**	96	55:26:19[e]
8	**4a**	**2a**	2	**5a**	57	54:24:18:4[e]
9	**4b**	**2a**	4	**5b**	50	62:22:11:5[e]
10	**4c**	**2b**	2	**5c**	64	82:11:7[e]

[a]All reactions were performed in THF at –78 °C. [b]Combined yield of isolated product mixture. [c]Determined by ^{13}C NMR spectrum of the crude reaction mixture. [d]Minor product was tentatively assigned by ^{13}C NMR spectrum. [e]Structures of isomers were not determined.

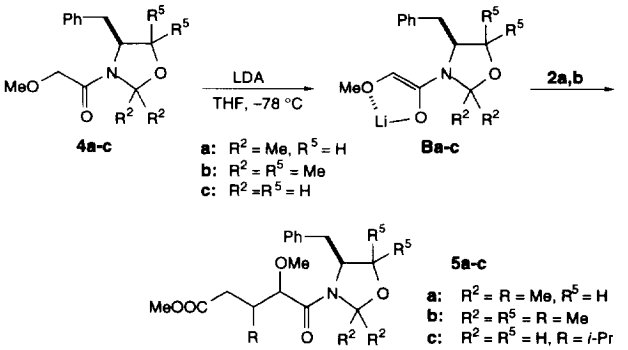
Stereoselectivity of the reaction was estimated on the basis of the ^{13}C NMR spectrum of the crude product mixture, but in some cases, the filtration procedure through a short silica gel column was applied to the crude reaction mixture prior to the estimation of selectivity. Contaminants often consist of the starting amides **1** and the 1,2-addition products. Removal of these contaminants made it much easier to read ^{13}C NMR spectrum.

Structural assignment of the major stereoisomers of Michael adducts **3a-g** was based on the following facts: (1) Absolute configuration of the major diastereomeric Michael adduct **3d** was assigned to be the *lk*-1,4/*anti*-isomer on the basis of X-ray crystallography, which will be discussed later and (2) the fact that Michael additions of amide (*Z*)-enolates generally show high *anti*-selectivities when the amide substituents are bulky.[18] Assignment of minor isomers is only tentative since they were formed in a small quantity and often could not be separated in pure forms. Comparison of the ^{13}C NMR data was useful in the present work. Carbon chemical shifts for the corresponding carbon atoms of *anti*- and *syn*-diastereomers should be significantly different from each other. Especially the carbon atoms directly related with the newly formed stereogenic centers show different values of chemical shifts. On the other hand, diastereofacial isomers which are produced by different chiral induction should show quite similar ^{13}C chemical shifts since local stereochemical relationship around the newly formed stereogenic centers is about the same.

Compared with the high *lk*-1,4-chiral inductions observed in the above reactions using 2,2-dimethyloxazolidine amides **1a,b** (entries 1-6), a similar reaction using the lithium enolate **Ac** derived from 2-unsubstituted oxazolidine amide **1c** was much less stereoselective (entry 7). The enolate intermediate **Ac** involved in the reaction certainly consisted of two conformers, *syn*- and *anti*-conformers with respect to the amide linkage, because the starting amide **1c** existed as a 64:36 conformational mixture in deuteriochloroform at room temperature. Lithium enolate **Ac** is unsubstituted at 2-position and substituted with a benzyl group at 4-position. Accordingly, the *anti*-conformer of enolate **Ac** must be more stable. In such a case, no sufficient chirality control is expected.

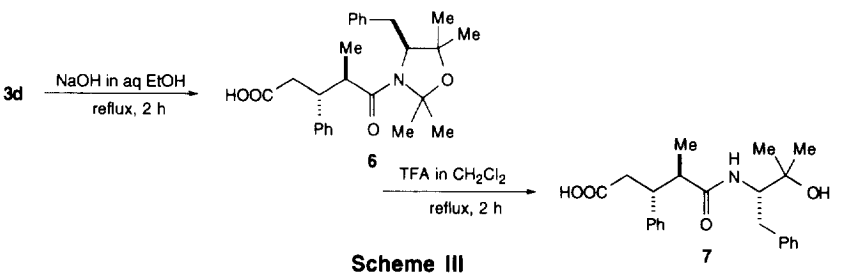
We previously reported that lithiation of *N,N*-disubstituted methoxyacetamides led to the exclusive formation of (*Z*)-enolates and that they underwent highly *syn*-selective Michael additions (the best selectivity: *syn*:*anti* = 99:1) with α,β-unsaturated carbonyl acceptors.[19] Although it is accordingly doubtless that lithiation of methoxyacetamides **4a-c** generates the intramolecularly chelated (*Z*)-enolates **Ba-c** (Scheme II), the Michael addition reaction of **Ba** to methyl crotonate (**2a**) showed only a poor selectivity (entry 8), four stereoisomers of adduct **5a** being formed in a low isomer ratio. Employment of the more effective chiral auxiliary, (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine, did not improve the selectivity (entry 9). However, it

was surprising that the reaction of lithium enolate **Bc** which bears the chiral auxiliary with no substituent at 2-position showed a high selectivity (entry 10).



Scheme II

Above results are summarized as follows: (1) The lithium (*Z*)-enolate **Ab** derived from a chiral propanamide **1b** shows high *anti*-selectivities and *lk*-1,4-chiral inductions to give Michael adducts **3b-f** as far major products (entries 2 - 6). Although Michael addition reactions of amide enolates are usually *anti*-selective, it is known that selectivity depends upon the size of amide moiety.[18] Therefore, not only the excellent chirality inductions but also the high *anti*-selectivities observed in the above reactions should be emphasized. (2) Selectivity is lowered when the 2-position of oxazolidine chiral auxiliary is unsubstituted. (3) The lithium (*Z*)-enolates **Ba-c** derived from chiral methoxyacetamide **4a-c** shows very poor selectivities (entries 8 - 10). (4) Such difference of both chiral induction and simple diastereoselectivity should be due to the difference of transition state structures. However, the transition state structure for the Michael additions of α-heterosubstituted amide or ester enolates remain unsolved.[20] (5) Proposal of an appropriate transition state structure is needed to account for the less effective chiral induction observed in the present reactions of oxazolidine methoxyacetamides **4a-c**. This will be discussed later.



Scheme III

Stereostructure of the major stereoisomers of Michael adducts **3a-g** was assigned on the basis of X-ray crystal structural analysis of the partly hydrolyzed Michael adduct **7**. Thus, adduct **3d** was subjected to alkaline hydrolysis in aqueous ethanol to give carboxylic acid **6** (Scheme III). Subsequent acid hydrolysis of **6** provided fine crystals of **7** after crystallization from 2-propanol, whose configuration was determined to be a 2*R*,3*R*-enantiomer with respect to the glutaric acid moiety. As a result, Michael reactions of the lithium (*Z*)-enolates **A** of propanamides **1** with **2** were concluded to be highly *lk*-1,4/*anti*-selective. Although removal of the oxazolidine chiral auxiliary from **3** can be performed by the $LiAlH_4$ reduction of the ester moiety followed by the acid hydrolysis (12N H_2SO_4), some epimerization takes place in the formation of the corresponding δ-lactones. Removal of the chiral auxiliary without epimerization is now under investigation.

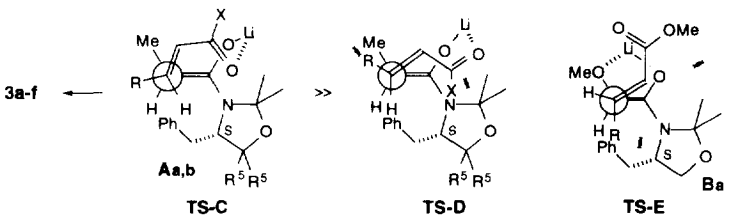


Figure 1. Chelated transition states **TS-C, D, E** which are possible for the Michael additions of the lithium *Z*-enolates derived from oxazolidine amides.

Two chelation transition states, **TS-C** and **TS-D**, are possible for the above highly *lk*-1,4/*anti*-selective asymmetric Michael additions of the lithium (Z)-enolates **A** to α,β-unsaturated carbonyl compounds leading to **3a-f**:[20] *s-cis* conformers of acceptor molecules are involved in **TS-C** and *s-trans* conformers in **TS-D** (Figure 1). Predominant participation of the former transition state **TS-C** is more likely since high levels of *lk*-1,4/*anti*-selectivity have been always observed even when either the β-substituent R or the hetero substituent X of the acceptor molecules becomes bulky as indicated by the reaction examples shown in entries 1, 3, 5, and 6.

The lithium (*Z*)-enolates **Ba-c** derived from methoxyethanamides **4a-c** are certainly stabilized in a form of five-membered intramolecular chelate structure and this chelation-stabilized structure should be maintained in the transition state of their Michael addition reactions to α,β-unsaturated carbonyl acceptors.[21] In addition, Michael reaction is usually accelerated by coordination of the lithium atom of donor enolates to the carbonyl oxygen atom of acceptors. If this happens in the present Michael additions of **Ba-c**, α,β-unsaturated carbonyl acceptors must occupy *s-cis* conformation in the transition state. Accordingly, the chelation-stabilized transition state **TS-E** is only possible. In **TS-E**, the β-*trans* substituent R is extruding toward the bulky oxazolidine auxiliary to cause serious steric repulsion, some other competitive approaches being allowed. This is why low selectivities were observed with respect to both *syn/anti* geometry and enantiomeric selectivity.

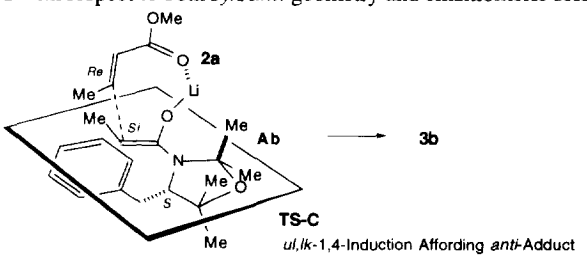
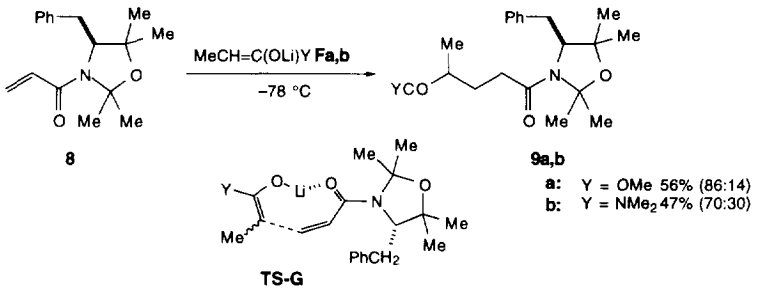


Figure 2. Enolate **Ab** is most reactive when the lonepair axis of the oxazolidine nitrogen atom and the Li-O bond are both perpendicular to the enolate face. Thus, reaction between **Ab** and **2a** shows a high diastereofacial selectivity.

Surprising are these excellent diastereofacial selectivities accomplished by the aid of (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine chiral auxiliary which was incorporated in the donor molecule **Ab**. These results will be explained as follows: A maximum reactivity of the lithium enolate must be provided in the Michael additions of oxazolidine amides **1a,b** when the lithium enolate functionality is in a full conjugation with the oxazolidine nitrogen (Figure 2). This indicates that the enolate double bond and the oxazolidine plane are required to be nearly coplanar in the transition state.[21] In such a case, one of the diastereofaces of the lithium enolates **A**, the one proximate to the shielding substituent at 4-position of the oxazolidine auxiliary, can be effectively shielded from the approach of acceptor molecules. As seen in Figure 2, the enolate **Ab** prefers *syn*-conformation to *anti*-conformation and therefore the *re*-face(Cα) of enolate is effectively hindered from the attack of the

acceptor **2a**, while the *si*-face(Cα) of enolate is almost open. When the 5-position is substituted with two methyl groups, the phenyl plane of the 4-benzyl substituent comes face to face to the enolate plane resulting in the effective diastereofacial selection in Michael additions.



Scheme IV

On the other hand, when a 2,2-dialkyloxazolidine chiral auxiliary was incorporated in the acceptor molecule **8**, only unsatisfactory levels of selectivity were observed. For example, the lithium enolate of methyl propanoate **Fa** or *N,N*-dimethylpropanamide **Fb** reacted with (*S*)-3-acryloyl-4-benzyl-2,2,5,5-tetramethyloxazolidine (**8**) under similar reaction conditions to afford mixtures of adduct isomers in poor diastereofacial selectivities (Scheme IV). Although numbers of Michael addition reactions using some other oxazolidine α,β-unsaturated amides were also examined, selectivities observed were disappointingly low in most cases (details of the results are not described in this report). When the π-system of α,β-unsaturated amides is under an effective conjugation with the amide nitrogen, the electrophilic property of the acceptor molecules must be reduced. Accordingly, the oxazolidine plane of the acceptors should be somehow crossing with the enolate plane (**TS-G**). This can be why Michael addition reactions using the oxazolidine α,β-unsaturated amide **8** were not so effective.

Thus, (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine chiral auxiliary is highly effective for the chirality control in the *anti*-selective Michael additions of lithium (*Z*)-enolates of ordinary amides to α,β-unsaturated carbonyl acceptors when the auxiliary is incorporated in donor molecules. On the other hand, the auxiliary incorporated in acceptor molecules, e.g. use of α,β-unsaturated amide derivatives of the auxiliary, is much less effective. In addition, the same lithium enolate **Ab** shows only poor selectivities in aldol reactions to give mixtures of many stereoisomeric aldols.[22] Difference of transition state structures presumably led to the difference of selectivities; our oxazolidine chiral auxiliaries can not be successfully applied to control the chirality in the six-membered Zimmerman-Traxler transition state of aldol reaction. They fit with the rather flexible eight-membered chelation transition state of Michael addition reaction when incorporated in the donor molecules.

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Experimental

(*S*)-4-Benzyl-2,2-dimethyl-3-propanoyloxazolidine (1a). To a CH_2Cl_2 solution (20 mL) of (*S*)-4-benzyl-2,2-dimethyloxazolidine (1.952 g, 10.2 mmol) and Et_3N (1.11 g, 1.53 mL, 11.0 mmol) was added, slowly by use of a syringe at 0 °C, a CH_2Cl_2 solution (5 mL) of propanoyl chloride (1.02 g, 0.96 mL, 11 mmol). After stirred at 0 °C for 1 h, the mixture was washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The CH_2Cl_2 solution was dried on $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using hexane–AcOEt [6:1 v/v, Rf = 0.35 (hexane–AcOEt = 3:1 v/v)] to give **1a** (1.966 g, 78%) as a colorless liquid. Colorless liquid; $[\alpha]_D^{25} = -73.5°$ (*c* 1.22, $CHCl_3$); IR (neat) 2980, 1640, 1420, 1240, 1080, 840, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.16 (3H, t, $J_{3'\text{-}2'}$ = 7.5 Hz, H-3'), 1.55, 1.73 (each 3H, s, 2-Me), 2.28-2.46 (2H, m, H-2'), 2.86 (1H, dd, J_{gem} = 13.6 and $J_{CH2\text{-}4}$ = 9.9 Hz, one of PhCH_2), 2.97 (1H, dd, J_{gem} = 13.6 and $J_{CH2\text{-}4}$ = 4.0 Hz, the other of PhCH_2), 3.79-4.01 (3H, m, H-4 and H-5), 7.19-7.37 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 9.16 (C-3'), 23.11, 26.95 (each 2-Me), 28.54 (C-2'), 40.36 (PhCH_2), 59.35 (C-4), 66.36 (C-5), 95.37 (C-2), 126.92, 128.88, 129.20, 137.58 (each Ph), 170.32 (CON); mass *m/z* (rel intensity, %) 247 (M^+, 13), 176 (15), 156 (44), 100 (base peak), 57 (15). Anal. Found: C, 72.91; H, 8.51; N, 5.31%. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66%.

(*S*)-4-Benzyl-2,2,5,5-tetramethyl-3-propanoyloxazolidine (1b). Prepared (yield: 72%) from (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine by a method similar to that employed for the preparation of **1a** and purified through a column chromatography on silica gel with hexane–AcOEt [6:1 v/v, Rf = 0.37 (hexane–AcOEt = 3:1 v/v)]. Colorless prisms; mp 63 °C; $[\alpha]_D^{25} = -154.0°$ (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ = 0.84 (3H, t, $J_{3'\text{-}2'}$ = 7.3 Hz, H-3'), 1.29, 1.35 (each 3H, s, 5-Me), 1.40-1.55 (1H, m, one of H-2'), 1.72, 1.75 (each 3H, s, 2-Me), 1.80-1.98 (1H, m, the other of H-2'), 2.85 (1H, dd, J_{gem} = 14.1 and $J_{CH2\text{-}4}$ = 8.2 Hz, one of PhCH_2), 3.00 (1H, dd, J_{gem} = 14.1 and $J_{CH2\text{-}4}$ = 6.1 Hz, the other of PhCH_2), 3.86 (1H, dd, $J_{4\text{-}CH2}$ = 8.2 and 6.1 Hz, H-4), 7.18-7.34 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 9.01 (C-3'), 24.13, 28.06 (each 2-Me), 28.22 (C-2'), 29.01, 29.16 (each 5-Me), 38.52 (PhCH_2), 66.48 (C-4), 80.28 (C-5), 94.25 (C-2), 126.76, 128.85, 129.28, 138.12 (each Ph), 171.60 (CON). Anal. Found: C, 74.11; H, 8.98; N, 5.31%. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09%.

(*S*)-4-Benzyl-3-propanoyloxazolidine (1c). To a toluene solution (30 mL) of (*S*)-3-phenyl-2-propanamido-1-propanol (1.345 g, 6.49 mmol) were added paraformaldehyde (0.78 g) and *p*-toluenesulfonic acid monohydrate (PTSA•H_2O, 0.1 g). After the mixture was refluxed for 2 h, saturated aqueous $NaHCO_3$ was added, and the whole mixture was extracted with Et_2O (40 mL x 3). The combined extracts were dried on $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using hexane–AcOEt (3:1 v/v) to give **1c** (1.16 g, 60%) as a colorless solid which was a 64:36 mixture of rotational isomers (by ^{13}C NMR in $CDCl_3$ solution). Colorless prisms; mp 45-46 °C; $[\alpha]_D^{25} = -37.0°$ (*c* 0.86, $CHCl_3$); IR (KBr) 2900, 1630, 1420, 940, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) major rotamer: δ = 1.20 (3H, t, $J_{3'\text{-}2'}$ = 7.5 Hz, H-3'), 2.22 (2H, q, $J_{2'\text{-}3'}$ = 7.5 Hz, H-2'), 2.67 (1H, dd, J_{gem} = 13.2 and $J_{CH2\text{-}4}$ = 9.9 Hz, one of PhCH_2), 3.25 (1H, dd, J_{gem} = 13.2 and $J_{CH2\text{-}4}$ = 3.3 Hz, the other of PhCH_2), 3.77-3.90 (2H, m, H-5), 4.33-4.41 (1H, m, H-4), 4.87, 4.89 (each 1H, d, J_{gem} = 3.3 Hz, H-2), 7.17-7.36 (5H, m, Ph). minor rotamer (partial): δ = 1.10 (3H, t, $J_{3'\text{-}2'}$ = 7.0 Hz, H-3'), 2.05-2.40 (2H, m, H-2'), 2.82 (1H, dd, J_{gem} = 13.2 and $J_{CH2\text{-}4}$ = 8.8 Hz, one of PhCH_2), 2.96 (1H, dd, J_{gem} = 13.2 and $J_{CH2\text{-}4}$ = 5.5 Hz, the other of PhCH_2), 4.00-4.15 (1H, m, H-4), 5.02, 5.10 (each 1H, d, J_{gem} = 5.1 Hz, H-2); ^{13}C NMR ($CDCl_3$) major rotamer: δ = 8.74 (C-3'), 28.41 (C-2'), 37.56 (PhCH_2), 56.41 (C-4), 70.37 (C-5), 78.73 (C-2), 126.56, 128.55, 129.44, 137.88 (each Ph), 170.16 (CON). minor rotamer: δ = 8.97 (C-3'), 27.43 (C-2'), 39.65 (PhCH_2), 57.28 (C-4), 71.21 (C-5), 79.39 (C-2), 127.01, 128.88, 129.30, 137.10 (each Ph), 171.48 (CON). Anal. Found: C, 71.03; H, 7.85; N, 6.24%. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%.

(*S*)-4-Benzyl-3-methoxyacetyl-2,2-dimethyloxazolidine (4a). Prepared (yield: 80%) from (*S*)-4-benzyl-2,2-dimethyloxazolidine by a method employed for the preparation of **1a** and purified through a column chromatography on silica gel with hexane–AcOEt [5:1 v/v, Rf = 0.43 (hexane–AcOEt = 1:1 v/v)]. Colorless liquid; $[\alpha]_D^{25} = -78.6°$ (*c* 1.1, $CHCl_3$); IR (KBr) 2960, 1650, 1420, 1240, 1200, 1130, 840, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.57, 1.76 (each 3H, s, 2-Me), 2.85 (1H, dd, J_{gem} = 13.4 and J_{CH2-4} = 7.8 Hz, one of PhCH_2), 2.96 (1H, dd, J_{gem} = 13.4 and J_{CH2-4} = 4.9 Hz, the other of PhCH_2), 3.42 (3H, s, MeO), 3.80 (1H, d, J_{gem} = 13.9 Hz, one of H-5), 3.85 (2H, s, H-2'), 4.00 (1H, d, J_{gem} = 13.9, the other of H-5), 4.12-4.18 (1H, m, H-4), 7.19-7.37 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 22.97, 26.87 (each 2-Me), 40.53 (PhCH_2), 58.04 (MeO), 59.02 (C-4), 67.02 (C-5), 72.47 (C-2'), 95.76 (C-2), 126.95, 128.89, 129.28, 137.55 (each Ph), 166.03; mass *m/z* (rel intensity, %) 263 (M^+, 14), 172 (base peak), 112 (16), 91 (20), 83 (26). Found: C, 68.75; H, 8.03; N, 5.24%. Calcd for $C_{15}H_{21}NO_3$: C, 68.40; H, 8.04; N, 5.32%.

(*S*)-4-Benzyl-3-methoxyacetyl-2,2,5,5-tetramethyloxazolidine (4b). Prepared (yield: 71%) from (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine by a method similar to that employed for the preparation of **1a** and purified through a column chromatography on silica gel with hexane–AcOEt [6:1 v/v, Rf = 0.53 (hexane–AcOEt = 1:1 v/v)]. Colorless prisms (hexane); mp 81-81.5 °C; $[\alpha]_D^{25} = -136.4°$ (*c* 1.08, $CHCl_3$); IR (KBr) 2950, 1650, 1420, 1240, 1130, 840, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.33, 1.35 (each 3H, s, 5-Me), 1.72, 1.78 (each 3H, s, 2-Me), 2.83 (1H, dd, J_{gem} = 13.6 and J_{CH2-4} = 9.3 Hz, one of PhCH_2), 2.90 (1H, d, J_{gem} = 13.9 Hz, one of H-2'), 2.97 (1H, dd, J_{gem} = 13.6 and J_{CH2-4} = 5.1 Hz, the other of PhCH_2), 3.16 (3H, s, MeO), 3.23 (1H, d, J_{gem} = 13.9 Hz, the other of H-2'), 4.06 (1H, dd, J_{4-CH2} = 9.3 and 5.1 Hz, H-4), 7.19-7.36 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 24.03, 27.79 (each 2-Me), 28.81, 29.04 (each 5-Me), 38.39 (PhCH_2), 58.75 (MeO), 65.27 (C-4), 72.31 (C-2'), 80.75 (C-5), 94.67 (C-2), 126.92, 129.00, 129.56, 138.14 (each Ph), 167.51 (CON); mass *m/z* (rel intensity, %) 291 (M^+, 2), 200 (base peak), 172 (23), 142 (38), 114 (15), 91 (22), 82 (13). Anal. Found: C, 70.07; H, 8.72; N, 4.82%. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81%.

(*S*)-4-Benzyl-3-(methoxyacetyl)oxazolidine (4c). Prepared (yield: 66%) from (*S*)-2-methoxyacetamido-3-phenyl-1-propanol according to a method similar to that employed for the preparation of **1c** [a 71:29 mixture of rotational isomers (by ^{13}C NMR in $CDCl_3$ solution)] and purified through a column chromatography on silica gel with hexane–AcOEt [2:1 v/v, Rf = 0.6 (hexane–AcOEt = 1:1 v/v)]. Colorless liquid; $[\alpha]_D^{25} = -16.1°$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) major rotamer: δ = 2.70-2.85, 2.90-3.05 (each 1H, br, PhCH_2), 3.42 (3H, s, MeO), 3.83 (2H, s, H-2'), 3.95-4.10 (2H, br, H-5), 4.35-4.50 (1H, br, H-4), 4.91, 4.99 (each 1H, d, J_{gem} = 4.4 Hz, H-2), 7.22-7.31 (5H, m, Ph). minor rotamer (partial): δ = 2.60-2.80 (2H, br, PhCH_2), 3.36 (3H, s, MeO), 3.81 (2H, s, H-2'), 4.20-4.35 (1H, br, H-4), 5.08-5.20 (2H, br, H-2); ^{13}C NMR ($CDCl_3$) major rotamer: δ = 37.32 (PhCH_2), 56.56 (C-4), 58.95 (2'-MeO), 69.76 (C-5), 72.87 (C-2'), 78.50 (C-2), 126.63, 128.56, 129.40, 137.55 (each Ph), 166.68 (CON). minor rotamer (partial): δ = 39.58 (PhCH_2), 71.45 (C-4), 71.85 (C-2'), 79.36 (C-2), 127.01, 128.88, 137.30 (each Ph), 167.12 (CON). Anal. C, 66.07; H, 7.38; N, 5.96%. Calcd for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.29; N, 5.96%.

General Procedure for the Michael additions of the Lithium Enolates Derived from Oxazolidine Amides 1a–c to α,β-Unsaturated Carbonyl Acceptors 2a–e Leading to 3a–g. As a typical example, the reaction of **1a** with **2b** is described as follows: Lithium diisopropylamide (LDA, 1.1 mmol) was freshly prepared form butyllithium (1 M in hexane, 1.1 mL, 1.1 mmol) and diisopropylamine (0.111 g, 1.1 mmol) in THF (2 mL) under dry nitrogen. A THF solution (1 mL) of **1a** (0.247 g, 1 mmole) was slowly added at –78 °C. After stirring for 15 min, a THF solution (1 mL) of **2b** (0.141 g, 1.1 mmol) was added in a period of 5 min by use of a syringe. The reaction was allowed to continue at –78 °C for 4 h, saturated aqueous NH_4Cl was poured and extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue (0.35 g) was filtered through a short silica gel column with hexane–

AcOEt to give the crude product (0.27 g, 72%), the isomer ratio of which was determined by ^1H and/or ^{13}C NMR spectra (a 98:2 mixture of two isomers by ^{13}C NMR). Careful purification of this mixture by a silica gel column chromatography using hexane–AcOEt (8:1 v/v) as an eluent gave the major diastereomer of **3a**.

Other reactions leading to **3b–g** were performed under the reaction conditions listed in Table 1 and all the results are summarized also in the same table. Optical rotations were recorded only for the pure diastereomers and enantiomers.

(*S*)-4-Benzyl-3-[(2*R*,3*S*)-3-(methoxycarbonylmethyl)-2,4-dimethylpentanoyl]-2,2-dimethyloxazolidine (3a). Colorless liquid [Rf = 0.4 with hexane–AcOEt (3:1 v/v)]; $[\alpha]_D^{24}$ = –92.2° (*c* 0.35, $CHCl_3$); IR (neat) 2950, 1730, 1640, 1400, 1230, 1160, 910, 845, 720, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.86 (6H, d, *J* = 7.0 Hz, Me of *i*-Pr), 0.95 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, 2'-Me), 1.49, 1.76 (each 3H, s, 2-Me), 1.56 (1H, m, CH of *i*-Pr), 2.01 (1H, m, H-3'), 2.13 (1H, dd, J_{gem} = 16.7 and $J_{4'\text{-}3'}$ = 6.8 Hz, one of H-4'), 2.60 (1H, m, H-2'), 2.65 (1H, dd, J_{gem} = 16.7 and $J_{4'\text{-}3'}$ = 3.5 Hz, the other of H-4'), 2.89 (1H, dd, J_{gem} = 13.4 and $J_{CH2\text{-}4}$ = 8.6 Hz, one of PhCH_2), 2.96 (1H,dd, J_{gem} = 13.4 and $J_{CH2\text{-}4}$ = 6.1 Hz, the other of PhCH_2), 3.62 (3H, s, COOMe), 3.86 (1H, br d, J_{gem} = 8.8 Hz, one of H-5), 3.93 (1H, dd, J_{gem} = 8.8 and $J_{5\text{-}4}$ = 4.6 Hz, the other of H-5), 4.12 (1H, m, H-4), 7.2-7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 11.76 (2'-Me), 19.99, 21.21 (each Me of *i*-Pr), 22.76, 27.23 (each 2-Me), 30.90 (CH of *i*-Pr), 32.60 (C-4'), 39.44 (C-3'), 41.09 (PhCH_2), 43.09 (C-2'), 51.52 (COO*Me*), 58.85 (C-4), 66.66 (C-5), 95.49 (C-2), 126.97, 128.91, 129.33, 137.52 (each Ph), 173.01 (CON), 174.46 (*C*OOMe); mass *m/z* (rel intensity, %) 375 (M^+, 2), 284 (22), 186 (12), 185 (base peak), 157 (12), 125 (10). Anal. Found: C, 70.37; H, 8.81; N, 3.66%. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73%.

(*S*)-4-Benzyl-3-[(2*R*,3*R*)-4-methoxycarbonyl-2,3-dimethylbutanoyl]-2,2,5,5-tetramethyloxazolidine (3b). Obtained as an inseparable 96:4 mixture (by ^{13}C NMR) and purified through a silica gel column chromatography with hexane–AcOEt (3:1 v/v, Rf = 0.36). Colorless liquid; IR (neat) 2980, 1740, 1640, 1410, 1370, 1260, 1190, 1000, 700 cm^{-1}; ^1H NMR ($CDCl_3$) major (2*R*,3*R*): δ = 0.60 (3H, d, $J_{Me\text{-}2'}$ = 6.2 Hz, 2'-Me), 0.95 (3H, d, $J_{Me\text{-}3'}$ = 6.6 Hz, 3'-Me), 1.26, 1.43 (each 3H, s, 2-Me), 1.71, 1.74 (each 3H, s, 5-Me), 2.07 (1H, dd, J_{gem} = 15.0 and $J_{4'\text{-}3'}$ = 9.2 Hz, one of H-4'), 2.0-2.3 (2H, m, H-2' and H-3'), 2.43 (1H, dd, J_{gem} = 15.0 and $J_{4'\text{-}3'}$ = 3.1 Hz, the other of H-4'), 2.83 (1H, dd, J_{gem} = 14.1 and $J_{CH2\text{-}4}$ = 7.5 Hz, one of PhCH_2), 3.05 (1H, dd, J_{gem} = 14.1 and $J_{CH2\text{-}4}$ = 6.8 Hz, the other of PhCH_2), 3.64 (3H, s, COO*Me*), 4.04 (1H, dd, $J_{4\text{-}CH2}$ = 7.5 and 6.8 Hz, H-4), 7.2-7.4 (5H, m, Ph). minor (2*R*,3*S*, partial): δ = 1.29, 1.35 (each 3H, s, 5-Me), 3.67 (3H, s, COOMe), 3.88 (1H, t, $J_{4\text{-}CH2}$ = 7.0 Hz, H-4); ^{13}C NMR ($CDCl_3$) major (2*R*,3*R*): δ = 11.52 (2'-Me), 18.69 (3'-Me), 24.48, 27.83, 28.96, 29.06 (2-Me and 5-Me), 33.06 (C-4'), 36.36 (C-3'), 39.05 (PhCH_2), 42.58 (C-2'), 51.42 (COO*Me*), 66.09 (C-4), 80.54 (C-5), 94.41 (C-2), 126.77, 128.94, 129.21, 138.02 (each Ph), 173.24, 173.50 (each CO). minor (2*R*,3*S*, partial): δ = 9.20 (2'-Me), 18.43 (3'-Me), 24.23, 29.83 (2-Me and 5-Me), 31.73 (C-4'), 37.19 (C-3'), 38.83 (PhCH_2), 41.71 (C-2'), 66.92 (C-4), 79.46 (C-5), 91.95 (C-2), 126.04, 128.29, 129.59, 138.11 (each Ph), 173.79 (CO); mass *m/z* (rel intensity, %) 375 (M^+, 7), 285 (16), 284 (base peak), 157 (33). Anal. Found: C, 70.49; H, 8.85; N, 3.83%. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73%.

(*S*)-4-Benzyl-3-[(2*R*,3*S*)-3-(methoxycarbonylmethyl)-2,4-dimethylpentanoyl]-2,2,5,5-tetramethyloxazolidine (3c). Obtained as a >99:1 mixture of diastereomers (based on ^{13}C NMR) from which the major isomer, (2*R*,3*S*)-enantiomer, was isolated and purified through a silica gel column chromatography with hexane–AcOEt (3:1 v/v, Rf = 0.48). Colorless needles; mp 88-89 °C; $[\alpha]_D^{24}$ = –111.1° (*c* 0.2, $CHCl_3$); IR (KBr) 2900, 1720, 1620, 1370, 1325, 1245, 1165, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.26 (3H, d, $J_{2'\text{-}Me}$ = 6.6 Hz, 2'-Me), 0.80 (6H, d, *J* = 6.6 Hz, Me of *i*-Pr), 1.30 (1H, m, H-2'), 1.38, 1.55 (each 3H, s, 2-Me), 1.64, 1.79 (each 3H, s, 5-Me), 1.80 (1H, m, CH of *i*-Pr), 1.94 (1H, m, H-3'), 1.95 (1H, dd, J_{gem} = 16.9 and $J_{4'\text{-}3'}$ = 8.4 Hz, one of H-4'), 2.59 (1H, dd, J_{gem} = 16.9 and $J_{4'\text{-}3'}$ = 2.0 Hz, the other of H-4'), 2.86 (1H,

dd, J_{gem} = 13.6 and J_{CH2-4} = 10.3 Hz, one of PhCH_2), 2.98 (1H, dd, J_{gem} = 13.6 and J_{CH2-4} = 4.4 Hz, the other of PhCH_2), 3.59 (3H, s, COOMe), 3.93 (1H, dd, $J_{4\text{-}CH2}$ = 10.3 and 4.4 Hz, H-4), 7.2-7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 9.30 (2'-Me), 20.59, 21.16 (each Me of *i*-Pr), 24.22, 27.40, 28.56, 29.07 (2-Me and 5-Me), 31.34 (CH of *i*-Pr), 32.97 (C-4'), 38.72 (C-3'), 38.77 (PhCH_2), 43.05 (C-2'), 51.33 (COO*Me*), 65.51 (C-4), 80.28 (C-5), 94.41 (C-2), 126.75, 128.82, 129.47, 137.85 (each Ph), 173.99, 174.58 (each CO); mass *m/z* (rel intensity, %) 403 (M^+, 0.5), 312 (12), 204 (11), 186 (11), 185 (base peak), 157 (23), 128 (16), 125 (19), 97 (21), 91 (32), 83 (27), 70 (16). Anal. Found: C, 71.54; H, 9.06; N, 3.61%. Calcd for $C_{24}H_{37}NO_4$: C, 71.43; H, 9.24; N, 3.47%.

(*S*)-4-Benzyl-3-[(2*R*,3*R*)-4-methoxycarbonyl-2-methyl-3-phenylbutanoyl]-2,2,5,5-tetramethyloxazolidine (3d). Obtained as an inseparable 87:13 mixture of diastereomers (based on ^{1}H NMR) by a column chromatography on silica gel with hexane–EtOAc (7:1 v/v). Colorless liquid; ^{1}H NMR ($CDCl_3$) major (2*R*,3*R*): δ = 0.82, 1.08 (each 3H, s, 2-Me), 0.88 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, 2'-Me), 1.47, 1.63 (each 3H, s, 5-Me), 2.6-2.9 (4H, m, H-3', H-4', and one of PhCH_2), 3.04 (1H, dd, J_{gem} = 14.8 and J_{CH2-4} = 8.6 Hz, the other of PhCH_2), 3.4-3.5 (1H, m, H-2'), 3.50 (3H, s, COO*Me*), 3.88 (1H, dd, $J_{4\text{-}CH2}$ = 8.6 and 5.3 Hz, H-4), 7.2-7.3 (10H, m, Ph). minor (partial, 2*R*,3*S*): δ = 1.14, 1.21 (each 3H, s, 2-Me), 1.28, 1.35 (each 3H, s, 5-Me), 3.53 (3H, s, COO*Me*), 4.26 (1H, dd, $J_{4\text{-}CH2}$ = 9.3 and 4.6 Hz, H-4); ^{13}C NMR ($CDCl_3$) major (2*R*,3*R*): δ = 14.24 (2'-Me), 24.55, 27.50 (each 2-Me), 28.68, 28.78 (each 5-Me), 35.90 (C-3'), 39.05 (PhCH_2), 44.48, 44.75 (C-2' and C-4'), 51.43 (COO*Me*), 65.70 (C-4), 80.33 (C-5), 94.17 (C-2), 127.01, 127.73, 128.58, 128.76, 128.88, 137.95, 142.10 (each Ph), 172.28, 172.43 (each CO). minor (partial, 2*R*,3*S*): δ = 15.90 (2'-Me), 24.66, 27.80 (each 2-Me), 28.61, 29.26 (each 5-Me), 37.29 (C-4'), 42.81, 45.84 (C-2' and C-3'), 51.59 (COO*Me*), 65.64 (C-4), 80.65 (C-5), 94.32 (C-2), 126.68, 128.02, 128.12, 128.71, 144.79 (each Ph), 172.35 (CO). Anal. Found: C, 73.88; H, 8.12; N, 3.19%. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20%.

(*S*)-4-Benzyl-3-[(2*R*,3*R*)-2,3-dimethyl-4-(dimethylcarbamoyl)butanoyl]-2,2,5,5-tetramethyloxazolidine (3e). Obtained as a 96:4 mixture of two diastereomers (by ^{13}C NMR) from which the major isomer, (2*R*,3*R*)-enantiomer, was only separated and purified by a column chromatography on silica gel with hexane–AcOEt (1:2 v/v, Rf = 0.31). Colorless prisms; mp 153-154 °C; $[\alpha]_D^{24}$ = –92.9° (*c* 1.3, $CHCl_3$); IR (KBr) 2850, 1650, 1590, 1350, 1240, 1175, 1120, 1100, 990, 930, 840, 740, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.62 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, 2'-Me), 0.96 (3H, d, $J_{Me\text{-}3'}$ = 7.0 Hz, 3'-Me), 1.25, 1.45 (each 3H, s, 2-Me), 1.69, 1.73 (each 3H, s, 5-Me), 2.1-2.5 (4H, m, H-2', H-3', and H-4'), 2.83 (1H, dd, J_{gem} = 14.3 and J_{CH2-4} = 7.3 Hz, one of PhCH_2), 2.93, 2.96 (each 3H, s, NMe_2), 3.05 (1H, dd, J_{gem} = 14.3 and J_{CH2-4} = 7.0 Hz, the other of PhCH_2), 4.08 (1H, dd, $J_{4\text{-}CH2}$ = 7.3 and 7.0 Hz, H-4), 7.2-7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 11.21 (2'-Me), 18.80 (3'-Me), 24.29, 27.63, 28.76, 28.97 (2-Me and 5-Me), 32.38 (C-4'), 34.37 (C-3'), 35.19, 37.11 (each NMe_2), 38.86 (PhCH_2), 42.36 (C-2'), 65.73 (C-4), 80.35 (C-5), 94.05 (C-2), 126.48, 128.67, 129.03, 137.88 (each Ph), 171.77, 173.33 (each CO); mass *m/z* (rel intensity, %) 388 (M^+, 3), 171 (10), 170 (base peak), 142 (16), 91 (11), 72 (28). Anal. Found: C, 71.08; H, 9.34; N, 7.21%. Calcd for $C_{23}H_{36}N_2O_3$: C, 71.26; H, 9.18; N, 7.33%.

(*S*)-4-Benzyl-3-[(2*R*,3*R*)-2-methyl-4-(dimethylcarbamoyl)-3-phenylbutanoyl]-2,2,5,5-tetramethyloxazolidine (3f). Obtained as a 92:8 mixture of diastereomers (based on ^{13}C NMR) from which the major isomer, (2*R*,3*R*)-enantiomer, was only separated and purified through a column chromatography on silica gel with hexane–AcOEt (1:2 v/v, Rf = 0.33). Colorless liquid; $[\alpha]_D^{24}$ = –50.53° (*c* 0.65, $CHCl_3$); IR (neat) 2900, 1650, 1600, 1380, 1250, 1180, 1125, 990, 895, 840, 720, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.86 (3H, d, $J_{Me\text{-}2'}$ = 6.6 Hz, 2'-Me), 1.04, 1.13 (each 3H, s, 2-Me), 1.50, 1.65 (each 3H, s, 5-Me), 2.6-2.9 (4H, m, H-3', H-4', and one of PhCH_2), 2.80, 2.96 (each 3H, s, NMe_2), 3.04 (1H, dd, J_{gem} = 14.5 and J_{CH2-4} = 8.2 Hz, the other of PhCH_2), 3.60 (1H, dd, $J_{2'\text{-}3}$ = 7.0 and $J_{2'\text{-}Me}$ = 6.6 Hz, H-2'), 4.02 (1H, dd,

$J_{4\text{-}CH2}$ = 8.2 and 5.7 Hz, H-4), 7.2-7.3 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.62 (2'-Me), 24.48, 27.43, 28.65, 28.95 (2-Me and 5-Me), 33.59 (C-4'), 35.35, 37.23 (each NMe_2), 39.02 (Ph*C*H_2), 43.93 (C-2'), 44.33 (C-3'), 65.67 (C-4), 80.37 (C-5), 94.08 (C-2), 126.52, 126.57, 127.71, 128.33, 128.73, 128.81, 137.93, 142.89 (each Ph), 171.06, 172.61 (each CO); mass *m/z* (rel intensity, %) 450 (M^+, 2) , 233 (17), 232 (base peak), 204 (14), 131 (11), 91 (23), 72 (53). Anal. Found: C, 73.96; H, 8.54; N, 6.00%. Calcd for $C_{28}H_{38}N_2O_3$: C, 74.63; H 8.50; N, 6.22.

(*S*)-4-Benzyl-3-[(2*R*,3*R*)-4-methoxycarbonyl-2,3-dimethylbutanoyl]oxazolidine (3g). Obtained as a 55:26:19 inseparable mixture of diastereomers (based on ^{13}C NMR) which was purified through a column chromatography on silica gel with hexane–AcOEt (1:1 v/v, Rf = 0.43). Colorless liquid; ^{13}C NMR ($CDCl_3$) major: δ = 15.94 (3'-Me), 15.94 (2'-Me), 32.78 (C-3'), 37.88, 38.70 (C-4' and Ph*C*H_2), 42.63 (C-2'), 51.46 (COO*Me*), 56.44 (C-4), 70.44 (C-5), 78.86 (C-2), 126.58, 128.56, 129.38, 137.82 (each Ph), 172.39, 173.04 (each CO). first minor (partial): δ = 13.85 (3'-Me), 18.20 (2'-Me), 32.68 (C-3'), 37.74, 41.31 (C-4', Ph*C*H_2), 43.61 (C-2'), 56.50 (C-4), 71.36 (C-5), 79.23 (C-2), 126.97, 128.78, 129.44, 137.13 (each Ph), 172.30, 173.17 (each CO). second minor (partial): δ = 13.00 (3'-Me), 14.21 (2'-Me), 33.35 (C-3'), 37.39, 39.83 (C-4', Ph*C*H_2), 42.13 (C-2'), 56.64 (C-4), 71.21 (C-5), 127.05, 128.92, 137.04 (each Ph), 173.43 (CO). Anal. Found: C, 67.58; H, 7.78; N, 4.36%. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39%.

General Procedure for the Michael additions of the Lithium Enolates Derived from Oxazolidine Amides 4a–c to α,β-Unsaturated Esters 2a,b Leading to 5a–c. As a typical example, the reaction of **4a** with **2a** is described as follows: To the freshly prepared LDA (LDA, 1.1 mmol) in THF (2 mL), was added slowly added at –78 °C under dry nitrogen, a THF solution (1 mL) of **4a** (0.263 g, 1 mmole). After stirring for 10 min, a THF solution (1 mL) of **2a** (0.11 g, 1.1 mmol) was added in a period of 5 min by use of a syringe. The reaction was allowed to continue at –78 °C for 2 h, saturated aqueous NH_4Cl was poured and extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue (0.35 g) was filtered through a short silica gel column with hexane–AcOEt to give the crude product (0.207 g, 57%), the isomer ratio of which was determined by ^1H NMR spectrum (a 50:25:17:8 mixture of diastereomers, peak ratios among δ = 3.16, 3.27, 3.33, 3.38). Careful purification of this mixture by a silica gel column chromatography using hexane–AcOEt (6:1 v/v) gave an inseparable mixture of four diastereomers of **5a**.

Other reactions were performed under the reaction conditions listed in Table 1 (entries 8 and 10) and the results are summarized also in the same table. Optical rotations of **5a–c** were not recorded because they are the mixtures of diastereomers.

(*S*)-4-Benzyl-3-[2-methoxy-3-methyl-4-(methoxycarbonyl)butanoyl]-2,2-dimethyloxazolidine (5a). Obtained as a 50:25:17:8 inseparable mixture of diastereomers (based on ^1H NMR, peak ratios among δ = 3.16, 3.27, 3.33, 3.38) which was purified by a column chromatography on silica gel with hexane–AcOEt (3:1 to 6:1 v/v). Pale yellow liquid; IR (neat) 2980, 1730, 1650, 1410, 1360, 1120, 1070, 1045, 850, 790, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) major: δ = 0.99 (3H, d, $J_{Me\text{-}3'}$ = 7.0 Hz, 3'-Me), 1.54, 1.82 (each 3H, s, 2-Me), 2.1-2.8 (3H, m, H-3' and H-4'), 2.8-3.1 (2H, m, PhCH_2), 3.16 (3H, s, MeO), 3.72 (3H, s, COO*Me*), 3.8-4.2 (2H, m, H-5), 3.90 (1H, d, $J_{2'\text{-}3'}$ = 2.6 Hz, H-2'), 4.45 (1H, m, H-4), 7.2-7.5 (5H, m, Ph). first minor (partial): δ = 1.08 (3H, d, $J_{Me\text{-}3'}$ = 6.0 Hz, 3'-Me), 1.59, 1.75 (each 3H, s, 2-Me), 3.38 (3H, s, MeO), 3.65 (3H, s, COO*Me*). second minor (partial): δ = 1.09 (3H, d, $J_{Me\text{-}3'}$ = 6.2 Hz, 3'-Me), 1.56, 1.78 (each 3H, s, 2-Me), 3.33 (3H, s, MeO), 3.67 (3H, s, COO*Me*). third minor (partial): δ = 1.49, 1.76 (each 3H, s, 2-Me) and 3.28 (3H, s, MeO); ^{13}C NMR ($CDCl_3$) major: δ = 14.18 (3'-Me), 22.95, 27.44 (each 2-Me), 32.66 (C-4'), 37.21 (C-3'), 40.95 (Ph*C*H_2), 51.50 (COO*Me*), 57.44 (MeO), 57.54 (C-4), 66.75 (C-5), 80.27 (C-2'), 95.91 (C-2), 126.94, 128.76, 129.64, 137.26 (each Ph), 167.63 (CON),

173.56 (*C*OOMe). first minor (partial): δ = 15.62 (3'-Me), 22.65, 26.91 (each 2-Me), 30.90 (C-4'), 37.44 (C-3'), 40.65 (Ph*C*H$_2$), 51.37 (COO*Me*), 56.17 (MeO), 58.63 (C-4), 66.56 (C-5), 83.71 (C-2'), 95.82 (C-2), 126.89, 128.92, 129.21, 137.84 (each Ph), 167.15 (CON), 172.88 (*C*OOMe). second minor (partial): δ = 16.52 (3'-Me), 22.46, 27.16 (each 2-Me), 33.52 (C-4'), 35.95 (C-3'), 40.78 (Ph*C*H$_2$), 57.38 (MeO), 58.38 (C-4), 66.25 (C-5), 82.75 (C-2'), 96.05 (C-2), 127.08, 128.99, 129.38, 137.99 (each Ph), 167.84 (CON), 173.27 (*C*OOMe); third minor (partial): δ = 15.26 (3'-Me), 22.78, 26.72 (each 2-Me), 40.34 (Ph*C*H$_2$), 56.34 (MeO), 57.62 (C-4), 66.93 (C-5), 83.29 (C-2'), 126.98, 128.65, 137.38 (each Ph), 167.94 (CON); mass *m/z* (rel intensity, %) 363 (M^+, 2), 272 (34), 173 (12), 145 (base peak), 113 (18), 91 (22), 85 (34). Anal. Found: C, 66.03; H, 7.98; N, 4.00%. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85%.

(*S*)-4-Benzyl-3-[2-methoxy-3-methyl-4-(methoxycarbonyl)butanoyl]-2,2,5,5-tetramethyloxazolidine (5b). Obtained as a 62:22:11:5 inseparable mixture of diastereomers (based on ^{13}C NMR) which was purified through a column chromatography on silica gel with hexane–AcOEt (7:1 v/v). Colorless liquid; IR (neat) 2980, 1720, 1650, 1600, 1490, 1430, 1400, 1360, 1300, 1250, 1200, 1140, 1110, 1070, 1000, 900, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) major: δ = 0.90 (3H, d, $J_{Me\text{-}3'}$ = 7.0 Hz, 3'-Me), 1.31, 1.41 (each 3H, s, 5-Me), 1.71, 1.81 (each 3H, s, 2-Me), 2.18 (1H, dd, J_{gem} = 16.5 and $J_{4'\text{-}3'}$ = 3.7 Hz, one of H-4'), 2.28-2.42 (1H, m, H-3'), 2.54 (1H, dd, J_{gem} = 16.5 and $J_{4'\text{-}3'}$ = 9.7 Hz, the other of H-4'), 2.66 (3H, s, MeO), 2.85 (1H, dd, J_{gem} = 13.9 and $J_{CH2\text{-}4}$ = 8.6 Hz, one of Ph*C*H$_2$), 3.07 (1H, dd, J_{gem} = 13.9 and $J_{CH2\text{-}4}$ = 5.9 Hz, the other of Ph*C*H$_2$), 3.33 (1H, d, $J_{2'\text{-}3'}$ = 2.6 Hz, H-2'), 3.75 (3H, s, COO*Me*), 4.43 (1H, dd, $J_{4\text{-}CH2}$ = 8.6 and 5.9 Hz, H-4), 7.17-7.37 (5H, m, Ph). first minor (partial): δ = 1.08 (3H, d, $J_{Me\text{-}3'}$ = 6.6 Hz, 3'-Me), 2.99 (3H, s, MeO), 3.58 (1H, d, $J_{2'\text{-}3'}$ = 4.0 Hz, H-2'), 3.64 (3H, s, COO*Me*), Signals of other diastereomers are hidden in those of the above major isomers; ^{13}C NMR ($CDCl_3$) major: δ = 13.60 (3'-Me), 24.20, 27.60 (each 2-Me), 28.56, 29.33 (each 5-Me), 32.24 (C-4'), 37.30 (C-3'), 38.92 (Ph*C*H$_2$), 51.44 (COO*Me*), 57.26 (MeO), 63.62 (C-4), 79.42 (C-5), 81.19 (C-2'), 94.74 (C-2), 126.67, 128.68, 129.77, 137.83 (each Ph), 168.56 (CON), 173.63 (*C*OOMe). first minor (partial): δ = 17.66 (3'-Me), 24.48, 27.43 (each 2-Me), 28.75, 28.94 (each 5-Me), 33.10 (C-4'), 35.33 (C-3'), 39.22 (Ph*C*H$_2$), 51.36 (COO*Me*), 57.48 (MeO), 64.60 (C-4), 82.59 (C-2'), 94.87 (C-2), 126.79, 128.88, 128.96 (each Ph), 168.21 (CON), 173.48 (*C*OOMe). second minor (partial): δ = 18.56 (3'-Me), 33.19 (C-4'), 39.61 (Ph*C*H$_2$), 57.13 (MeO), 64.98 (C-4), 82.60 (C-2'), 94.60 (C-2), 128.58, 138.58 (each Ph), 172.98 (*C*OOMe); third minor (partial): δ = 17.96 (3'-Me), 58.21 (MeO), 128.26 (Ph); mass *m/z* (rel intensity, %) 391 (M^+, 1), 300 (30), 200 (75), 145 (base peak), 91 (28), 85 (21). Anal. Found: C, 67.17; H, 8.42; N, 4.01%. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.58%.

(*S*)-4-Benzyl-3-[2-methoxy-4-methyl-3-(methoxycarbonylmethyl)pentanoyl]oxazolidine (5c). Obtained as an 82:11:7 inseparable mixture of diastereomers (based on ^{13}C NMR) which was purified by a column chromatography on silica gel with hexane–AcOEt (3:1 v/v, Rf = 0.28). Colorless liquid; IR (neat) 2950, 1730, 1640, 1410, 1260, 1160, 1100, 940, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) major: δ = 0.83, 0.92 (each 3H, d, *J* = 7.0 Hz, Me of *i*-Pr), 2.12 (1H, m, CH of *i*-Pr), 2.2-2.3 (2H, m, H-3' and one of H-4'), 2.44 (1H, dd, J_{gem} = 17.4 and $J_{4'\text{-}3'}$ = 9.3 Hz, the other of H-4'), 2.66 (1H, dd, J_{gem} = 13.2 and $J_{CH2\text{-}4}$ = 9.9 Hz, one of Ph*C*H$_2$), 3.23 (1H, dd, J_{gem} = 13.2 and $J_{CH2\text{-}4}$ = 3.7 Hz, the other of Ph*C*H$_2$), 3.34 (3H, s, OMe), 3.62 (3H, s, COO*Me*), 3.65 (1H, d, $J_{2'\text{-}3'}$ = 4.4 Hz, H-2'), 3.77 (1H, dd, J_{gem} = 8.8 and $J_{5\text{-}4}$ = 4.4 Hz, one of H-5), 3.84 (1H, dd, J_{gem} = 8.8 and $J_{5\text{-}4}$ = 5.9 Hz, the other of H-5), 4.32 (1H, m, H-4), 5.00, 5.24 (each 1H, J_{gem} = 4.8 Hz, H-2), 7.2-7.3 (5H, m, Ph). first and/or second minor(s) (partial): δ = 3.09 (3H, s, MeO), 3.63 (3H, s, COOMe), 4.55 (1H, m, H-4). ^{13}C NMR ($CDCl_3$) major: δ = 16.63, 20.86 (each Me of *i*-Pr), 26.82 (C-4'), 29.68 (CH of *i*-Pr), 37.67 (Ph*C*H$_2$), 40.96 (C-3'), 51.56 (COO*Me*), 57.25, 57.95 (C-4 and MeO), 69.11 (C-5), 78.43 (C-2), 85.09 (C-2'), 126.55, 128.51, 129.38, 137.81 (each Ph), 169.43 (CON), 173.66 (*C*OOMe). first minor (partial): δ = 17.26, 20.86 (each Me of *i*-Pr), 27.13 (C-4'), 30.22

(CH of *i*-Pr), 36.99 (PhCH_2), 41.19 (C-3'), 56.08, 57.77 (C-4 and MeO), 78.18 (C-2), 85.30 (C-2'), 126.91, 138.07 (each Ph), 168.27 (CON), 173.60 (*C*OOMe). second minor (partial): δ = 18.19, 22.17 (each Me of *i*-Pr), 26.94 (C-4'), 29.99 (CH of *i*-Pr), 39.34 (PhCH_2), 42.22 (C-3'), 57.01, 57.65 (C-4 and MeO), 79.25 (C-2), 81.96 (C-2'), 126.25 (Ph), 168.72 (CON), 174.11 (*C*OOMe). mass *m/z* (rel intensity, %) 363 (M^+, 6), 272 (10), 201 (10), 173 (base peak), 141 (19), 113 (31), 91 (19), 71 (17). Anal. Found: C, 66.18; H, 7.96; N, 3.65%. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85%.

(3*R*,4*R*)-4-[(*S*)-(4-Benzyl-2,2,5,5-tetramethyloxazolidin-3-yl)carbonyl]-3-phenylpentanoic Acid (6) and (3*R*,4*R*)-*N*-[(*S*)-1-Benzyl-2-hydroxy-2-methylpropyl]-4-methyl-3-phenylglutaramic Acid (7). A solution of **3d** (0.1 g, 0.23 mmol) and aqueous NaOH (0.15 g in 1 mL) in EtOH (2 mL) was refluxed for 2 h. The mixture was acidified (ca. pH 4) with saturated aqueous solution of citric acid and extracted with Et_2O (40 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue as a colorless liquid was almost pure **6** (0.097g, 100%) which was employed for the following reaction without further purification. To a solution of **6** (0.073 g, 0.2 mmol) in CH_2Cl_2 (2 mL) was added, slowly by use of a syringe at room temperature, CF_3COOH (0.1 mL, 1.3 mmol). The mixture was stirred for 2 h during which time colorless precipitate of **7** was separated out (0.046 g, 60%). Colorless prisms (2-PrOH); mp 215-217 °C; $[\alpha]_D^{24}$ = –61.9° (*c* 0.38, MeOH); IR (KBr) 3280, 2960, 1700, 1650, 1545, 1250, 1150, 750, 700 cm^{-1}; ^1H NMR (CD_3OD) δ = 0.98 (3H, d, $J_{Me\text{-}4}$ = 7.0 Hz, 4-Me), 1.03, 1.08 (each 3H, s, H-3'), 2.42 (1H, dd, J_{gem} = 15.8 and $J_{2\text{-}3}$ = 9.9 Hz, one of H-2), 2.46-2.59 (2H, overlapping, one of PhCH_2 and the other of H-2), 2.62 ($J_{4\text{-}3}$ = 7.7 and $J_{4\text{-}Me}$ = 7.0 Hz, H-4), 3.06 (1H, dd, J_{gem} = 14.3 and $J_{CH2\text{-}1'}$ = 3.3 Hz, the other of PhCH_2), 3.24 (1H, ddd, $J_{3\text{-}2}$ = 9.9, 5.1, and $J_{3\text{-}4}$ = 7.7 Hz, H-3), 3.89 (1H, dd, $J_{1'\text{-}CH2}$ = 10.6 and 3.3 Hz, H-1'), 4.86 (overlapping with OH of CD_3OH, COOH and OH), 7.07-7.21 (10H, m, Ph), 7.56 (1H, br d, CONH). Anal. Found: C, 71.95; H, 7.69; N, 3.62%. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65%.

X Ray Structural Determination of 7. The X-ray diffraction data were collected with graphile-monochronized Cu Ka radiation (l = 1.54184 Å) on an Enraf-Nonius CAD4 computer controlled kappa axis diffractometer. The structure was solved on a VAX computer using MolEN system.[23] A single crystal of **7** grown from 2-propanol had space group $P2_1$, *a* = 10.287 (0), *b* = 12.483 (0), *c* = 9.628 (0) Å, *b* = 117.79 (0)°, *V* = 1093.7 Å, *Z* = 2. The final *R* factor was 0.051 for 1429 observed reflections.[24]

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