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STEREODIVERGENT SYNTHESIS OF THE ENOLATES OF A β-AMINO ESTER BY USING LITHIUM N-BENZYLTRIMETHYLSILYLAMIDE[1†]

Naoki Asao, Tadao Uyehara, and Yoshinori Yamamoto*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

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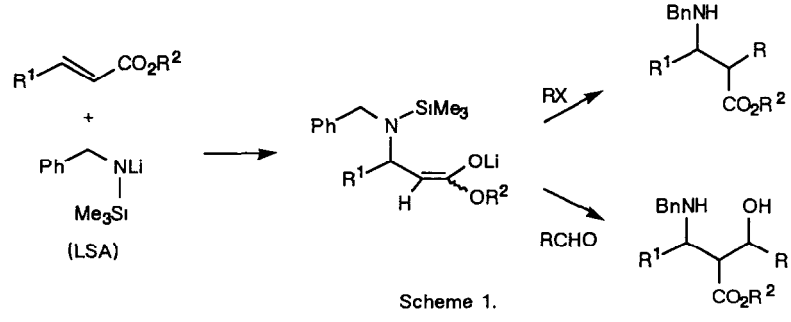
Abstract - Highly stereoselective generation of both Z- and E-enolates (**1** and **3**)[2] is accomplished by the conjugate addition of lithium N-benzyltrimethylsilylamide (LSA) to methyl crotonate. The alkylation with alkyl halides and aldol condensation with aldehydes via **1** and **3** are studied. The alkylation of **3** produces moderate to good syn selectivity, while that of **1** gives no selectivity. The aldol condensation of **1** affords the anti-syn isomer (**11**) predominantly, whereas that of **3** gives the syn-anti isomer (**14**) preferentially.

Lithium amides (R_2NLi) are commonly used as strong bases for deprotonation of organic compounds. However, use of R_2NLi as a nucleophile in organic synthesis has received little attention.[3-5] The major reason is that nucleophilic reactions of R_2NLi are always accompanied by deprotonation reactions; it has been difficult to control the reactivity of R_2NLi. For example, the reaction of α,β-unsaturated esters with ordinary lithium dialkylamides gives a mixture of conjugate adducts (1,4 addition product), deprotonation products at the γ-position, and substitution products at the ester group (1,2 adducts). To overcome this difficulty, we have developed lithium N-benzyltrimethylsilylamide (LSA) as a new nitrogen nucleophile.[1a,c,e,f] LSA reacts with α,β-unsaturated esters selectively in a 1,4-manner to produce the corresponding β-amino ester enolates, which are trapped by electrophiles such as alkyl halides and aldehydes (Scheme 1).



Scheme 1.

The reaction of the enolate with alkyl halides produces synthetically useful β-amino acid esters, which can be converted into β-lactams and trisubstituted enoates.[1e,f] The reaction with aldehydes gives β-amino-β'-hydroxy esters, which are also important building blocks for β-lactam synthesis. In order to accomplish these

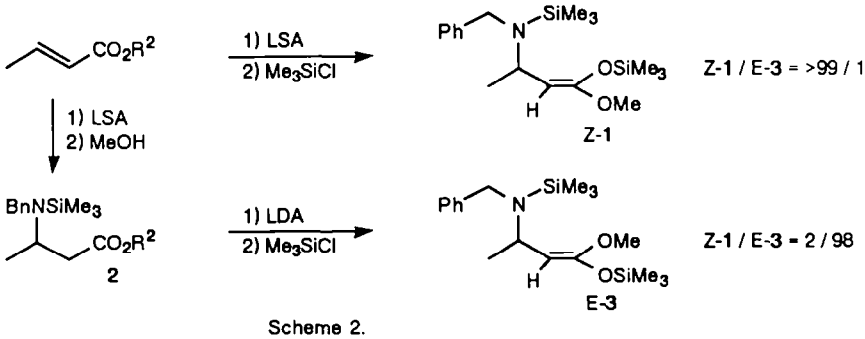
†This paper is warmly dedicated to Professor David Ollis on the occasion of his 65th birthday.

transformations in a stereoselective way, the diastereoselective synthesis of the β-amino ester enolates is required. We now detail highly stereodivergent generation of the Z- and E-enolates of a β-amino ester via conjugate addition to methyl crotonate by using LSA, and report a test of the stereochemistry of aldol reactions of these enolates. It should be worth mentioning that those enolates have been generated mostly in a non-stereoselective way by the deprotonation of β-amino esters.[6]

RESULTS AND DISCUSSION

Stereodivergent Synthesis of the Z- and E-Enolates of a β-Amino Ester. We first tried to isolate the enolate in the silyl ketene acetal form in order to determine the stereochemistry. Fleming reported the stereodivergent synthesis of the β-silyl enolates via silyl cuprate addition to enoates.[7] We examined a similar procedure for lithium amides. LSA was treated with methyl crotonate in THF at -78°C, and then chlorotrimethylsilane was added at this temperature. After additional stirring for several minutes, the solvents were removed in vacuo as soon as the cooling bath was removed. Evaporation was continued until the mixture was warmed to room temperature. Dry hexane was added to the residue, and then lithium chloride precipitated was separated by centrifuge under Ar atmosphere. Removal of hexane under reduced pressure, followed by the Kugelrohr distillation gave colorless oil in an essentially pure form. The 400MHz ^{1}H NMR analysis revealed that the silyl ketene acetal consists of only one stereoisomer. The nuclear Overhauser effect between the olefinic proton and methoxy group was observed (17%), indicating the Z-geometry of the β-amino ketene acetal (1).

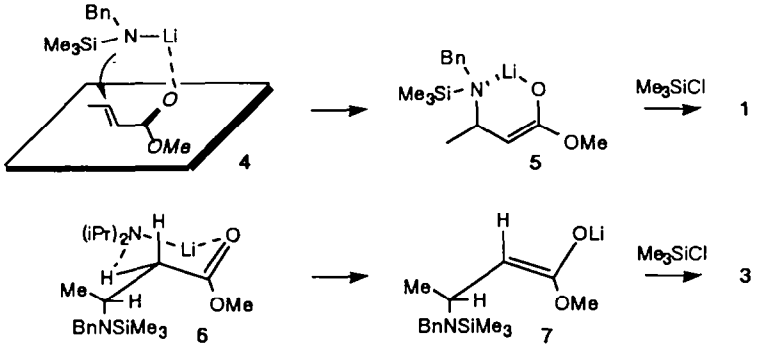
Next, we attempted to generate the E-isomer of the β-amino enolate. The Z-lithium β-amino enolate, derived from LSA and methyl crotonate, was once protonated with methanol to prepare the corresponding β-amino ester (2). Deprotonation of the resulting β-amino ester 2 with lithium diisopropylamide (LDA), subsequent addition of chlorotrimethylsilane, and a similar non-aqueous work-up gave a colorless oil. The ^{1}H NMR analysis indicated the E-form (3), since the nuclear Overhauser effect between the olefinic proton and methoxy group was not observed. Consequently, we are now in a position to prepare both Z- and E- β-amino enolates in a stereodivergent way by merely changing the reagents and conditions (Scheme 2).



Scheme 2.

Very high Z-selective formation of 1 is accounted for by chelation of the lithium to the ester group (Scheme 3). Presumably, the conjugate addition proceeds through the s-cis form (4), resulting in the stereoselective production of the Z-isomer. It is believed that the lithium enolate exists as a chelated species (5). Exclusive formation of the E-enolate via the deprotonation procedure can be explained by the six-membered cyclic transition

state (6), as is proposed in the related system.[8] The sterically bulky substituent takes an equatorial position in 6, resulting in selective formation of the lithium E-enolate (7).



Scheme 3.

Alkylation. Since both geometrical isomers were available for the first time, we examined alkylation reactions in order to clarify their stereoselectivities. The results are summarized in Table 1.[9]

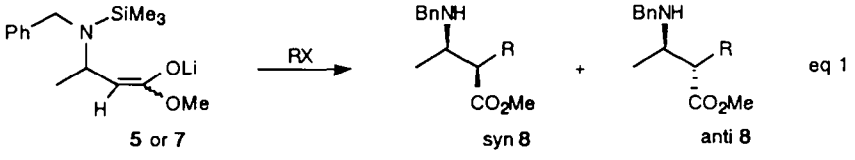
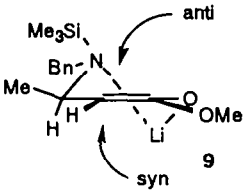


Table 1. Alkylation of 5 and 7.

lithium enolate	RX	syn / anti	yield %
Z-5	MeI	47 / 53	88
Z-5	n-$C_8H_{17}I$	59 / 41	81
E-7	MeI	69 / 31	68
E-7	n-$C_8H_{17}I$	90 / 10	60

The alkylation proceeded in high to good yields (eq 1). The silyl protective group was removed during the work-up process and we obtained finally the benzylamino derivatives. Although essentially no selectivity was observed via the Z-enolate (5), moderate to good syn-selectivity was obtained via the E-enolate (7).[10] In the chelated form (5), the alkyl halides can attack the α-carbon from both faces of the six-membered cyclic structure which can be drawn like **9**. The result suggests that both faces possess almost equivalent sterically and electronically properties. The anti-selectivity via 7 is accounted for by allylic strain concept.[11] The most stabilized conformation of 7 is shown in **10**. The alkylation takes place from the less hindered Me side, giving the syn-selectivity. The relative

stereochemistries of **8** were determined by converting them into the corresponding β-lactams according to the previously reported procedure.[12]



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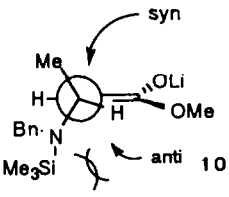
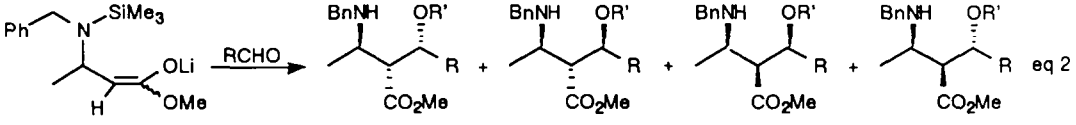


10

Aldol condensation. The reactions of the enolates with benzaldehyde and acetaldehyde are summarized in Table 2. The reaction was normally quenched by water, but in some cases quenched with acetyl chloride to make isolation of products easy. The reaction proceeded in good yields except for the last case of Table 2. The Z-enolate (**5**) gave the anti-syn isomer (**11**) predominantly, while the E-enolate (**7**) produced the syn-anti isomer (**14**) preferentially. As expected, the diastereofacial selectivity was highly dependent upon the geometry of the enolates.



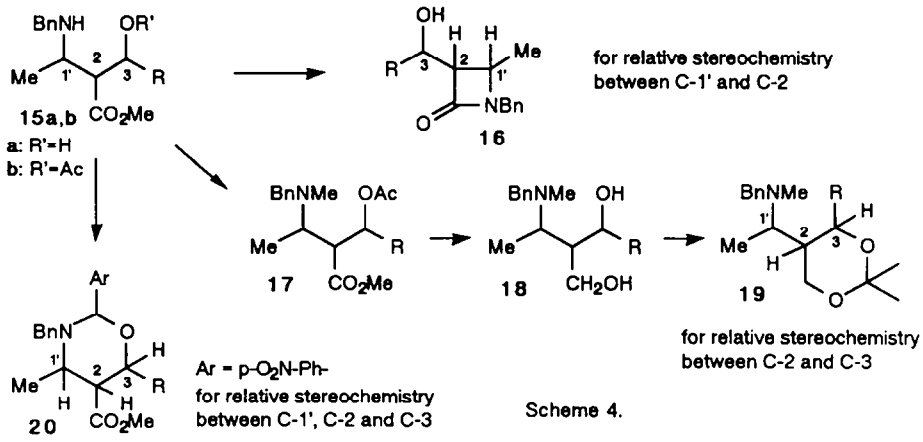
5 or **7** anti-syn **11a,b** anti-anti **12a,b** syn-syn **13a,b** syn-anti **14a,b**

11-14a: R=Ph, R'=H; **11-14b**: R=Me, R'=Ac

Table 2. Aldol condensation of **5** and **7**

lithium enolate	RCHO	yield %	a-s **11** : a-a **12** : s-s **13** : s-a **14**
Z-**5**	PhCHO	72	64 : 11 : 22 : 3
Z-**5**	MeCHO	73	82 : 0 : 18 : 0
E-**7**	PhCHO	64	6 : 1 : 13 : 80
E-**7**	MeCHO	39	0 : 10 : 0 : 90

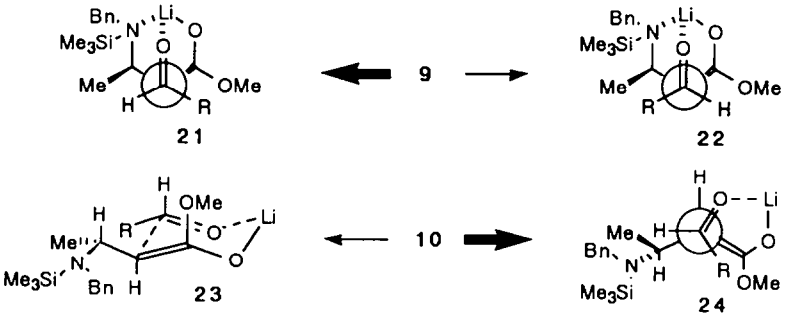
The stereochemistries of the products were determined by three different procedures. (1) The relative stereochemistry between C-1' and C-2 was determined by transforming the adducts (**15a**) into the β-lactams (**16**). Formation of the β-lactams proceeded mostly in satisfactory yields according to the method mentioned above. (2) The adducts (**15b**) were treated with iodomethane in the presence of potassium carbonate in order to protect the amino group, and then the ester group was reduced with $LiAlH_4$. The 1,3-diol derivatives thus obtained were converted to the acetonides (**19**). The stereochemistry between C-2 and C-3 of **15a** was determined by ^1H NMR analysis of the acetonides. (3) Finally the relative stereochemistry between the C-1'&C-2 group and C-2&C-3 group was defined by ^1H NMR analysis of the perhydro-1,3-oxazines (**20**), which were obtained by treating **15a** with *p*-nitrobenzaldehyde.[13]



Scheme 4.

Concerning the diastereofacial selectivity between C-1' and C-2 of **15**, the Z-enolate produces the anti-selectivity predominantly, and the E-enolate gives the syn-selectivity preferentially. As mentioned above, the Z-enolate takes chelation structure (**9**). The aldehyde presumably approaches preferentially from the top-side, since the approach from the bottom-side is unfavorable owing to the presence of the pseudoaxial hydrogen. However, the following question may be raised. Why does the aldehyde attack selectively from the top-side but not the alkyl halides (see Table 1)? The reason is not clear at present, but we assume that coordination of the lithium to the aldehyde oxygen produces the chelated transition state (**21**) and that such a π-π matching is more sensitive to the steric circumstance around the enolate face in comparison with the π-σ (RX) matching. More importantly, the model **21** can explain the syn-selectivity between C-2 and C-3. An alternative model **22**, which produces the anti-selectivity, is destabilized in comparison with **21** owing to the steric repulsion between the R and Me group.

The E-enolate gives predominantly C-1'&C-2 syn- and C-2&C-3 anti-selectivity. The C-1'&C-2 syn-selectivity is in good agreement with the syn-selectivity of alkylation reactions (see Table 1), and can be explained similarly by the model **10**. The C-2&C-3 anti-selectivity can not be explained by the ordinarily proposed chair



transition state model (**23**).[14] The syn-syn isomer should be produced through **23**. Presumably, the distorted six-membered cyclic model (**24**), so-called skewed transition state, is involved in the aldol condensation owing to the presence of the very bulky silylamino group.

Conclusion. Highly stereodivergent generation, with essentially 100% selectivity, of the Z -or E-enolate of a β-amino ester is accomplished by using conjugate addition of LSA to methyl crotonate or by using the LDA mediated deprotonation of the conjugate adduct. This development opens a door to the diastereoselective synthesis of β-amino-β'-hydroxy esters, which are useful precursors of some important β-lactams.

Experimental

^{1}H NMR spectra were recorded with a Varian EM-390, XL-200, JEOL GSX-270, GX-400 or Bruker AM-600 instruments with tetramethylsilane as an internal standard except for 1 and 3, which were referenced to residual solvent resonance (C_6D_6 at 7.15 ppm). Chemical shift values were recorded as parts per million and coupling constants as hertz. IR spectra were recorded with a Hitachi 215 spectrometer. Mass spectra were recorded with a Hitachi M-52, JEOL DX-303 or JMS-HX110 spectrometer. HPLC analysis and separation were performed on a Waters Associates HPLC system with a 10×250 mm LiChrosorb® Si60 (7μm, E.Merck No.860065). Melting points were determined with a Yamato MP-21 capillary melting point apparatus and are uncorrected. N-(Trimethylsilyl)benzylamine was prepared according to the literature procedure.[15] Generation procedure of lithium N-benzyltrimethylsilylamide, its conjugate addition to methyl crotonate and spectra data of 8 and β-lactams derived from 8 were reported earlier.[1e]

Aldol compounds (11-14). Generation procedure of these compounds were reported earlier.[1e] Separation and purification of these compounds were performed by column chromatography on silica gel (hexane / ethyl acetate = 1 / 1 - 5 / 1) and/or HPLC (hexane / ethyl acetate = 2 / 1 - 10 / 1 as eluant).

(2R*,3S*)-Methyl 2-[(R*)-1-benzylaminoethyl]-3-hydroxy-3-phenylpropanoate (11a). ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (10H, m), 5.21 (1H, d, J = 5.0 Hz), 3.82 (1H, d, J = 12.5 Hz), 3.76 (1H, d, J = 12.5 Hz), 3.55 (3H, s), 3.10 (1H, dq, J = 6.2, 6.7 Hz), 2.92 (1H, dd, J = 5.0, 6.2 Hz), 2.02 (1H, s), 1.25 (1H, bq), 1.21 (3H, d, J = 6.7 Hz); IR (CCl_4) 3300, 3040, 2960, 1725, 1455, 1435, 1195, 1165 cm^{-1}; MS calcd for $C_{19}H_{23}NO_3$: m/z 313.1678, Found 313.1669.

The (2R*,3S*,1'S*) isomer of 11a: (13a). ^{1}H NMR ($CDCl_3$) δ 7.41-7.15 (10H, m), 5.14 (1H, d, J = 3.1 Hz), 4.02 (1H, d, J = 12.8 Hz), 3.72 (1H, d, J = 12.8 Hz), 3.42 (3H, s), 3.16 (1H, dq, J = 3.8, 6.3 Hz), 2.71 (1H, dd, J = 3.1, 3.8 Hz), 1.24 (3H, d, J = 6.3 Hz); IR (CCl_4) 3300, 3040, 2960, 1730 cm^{-1}; MS calcd for $C_{19}H_{23}NO_3$: m/z 313.1678, Found 313.1679.

The (2R*,3R*,1'S*) isomer of 11a: (14a). ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (10H, m), 5.35 (1H, d, J = 4.2 Hz), 3.85 (1H, d, J = 12.4 Hz), 3.72 (3H, s), 3.61 (1H, d, J = 12.4 Hz), 2.91 (1H, dq, J = 2.6, 6.5 Hz), 2.75 (1H, dd, J = 2.6, 4.2 Hz), 1.23 (3H, d, J = 7.5 Hz); IR (CCl_4) 3200, 3040, 1740, 1455, 1440, 1195, 1185, 705 cm^{-1}; MS calcd for $C_{19}H_{23}NO_3$: m/z 313.1678, Found 313.1693.

(2R*,3S*)-Methyl 3-acetoxy-2-[(R*)-1-benzylaminoethyl]-3-phenylpropanoate (11a'). Mp 74°C; ^{1}H NMR ($CDCl_3$) δ 7.35-7.12 (10H, m), 6.04 (1H, d, J = 10.0 Hz), 3.75 (1H, d, J = 12.9 Hz), 3.72 (3H, s), 3.59 (1H, d, J = 12.9 Hz), 3.34 (1H, dd, J = 4.6, 10.0 Hz), 2.56 (1H, dq, J = 4.6, 6.5 Hz), 2.38 (1H, bs), 1.96 (3H, s), 1.07 (3H, d, J = 6.5 Hz); IR (KBr) 3430, 1755, 1735, 1240 cm^{-1}; MS calcd for $C_{21}H_{25}NO_4$: m/z 355.1784, Found 355.1786.

The (2R*,3S*,1'S*) isomer of 11a': (13a'). ^{1}H NMR ($CDCl_3$) δ 7.42-7.20 (10H, m), 6.31 (1H, d, J = 10.4 Hz), 3.78 (1H, d, J = 12.9 Hz), 3.73 (3H, s), 3.40 (1H, d, J = 12.9 Hz), 2.98 (1H, dd, J = 4.3, 10.4 Hz), 2.51 (1H, dq, J = 4.3, 6.6 Hz), 1.98 (3H, s), 1.07 (3H, d, J = 6.6 Hz); IR (CCl_4) 3340, 2960, 1745, 1235 cm^{-1}; MS calcd for $C_{21}H_{25}NO_4$: m/z 355.1784, Found 355.1786.

The (2R*,3R*,1'S*) isomer of 11a': (14a'). ^{1}H NMR ($CDCl_3$) δ 7.39-7.20 (10H, m), 6.23 (1H, d, J = 10.2 Hz), 3.96 (1H, d, J = 13.1 Hz), 3.71 (1H, d, J = 13.1 Hz), 3.39 (3H, s), 3.10 (1H, dq, J = 4.0, 6.4 Hz), 3.02 (1H, dd, J = 4.0, 10.2 Hz), 1.85 (3H, s), 1.18 (3H, d, J = 6.4 Hz); IR (CCl_4) 3470, 2970, 1740, 1255, 1245 cm^{-1}; MS calcd for $C_{21}H_{25}NO_4$: m/z 355.1784, Found 355.1783.

(2R*,3R*)-Methyl 3-acetoxy-2-[(R*)-1-benzylaminoethyl]butanoate (11b). ^{1}H NMR ($CDCl_3$) δ 7.39-7.20 (5H, m), 5.31 (1H, dq, J = 6.3, 7.5 Hz), 3.82 (1H, d, J = 13.0 Hz), 3.80 (1H, d, J = 13.0 Hz), 3.71 (3H, s), 2.97 (1H, dq, J = 6.5, 6.5 Hz), 2.79 (1H, dd, J = 6.5, 7.5 Hz), 1.98 (3H, s), 1.23 (3H, d, J = 6.3 Hz), 1.12 (3H, d, J = 6.5 Hz); IR (CCl_4) 3350, 2950, 1740, 1240, cm^{-1}; MS calcd for $C_{16}H_{23}NO_4$: m/z 293.1627, Found 293.1613.

The (2R*,3S*,1'R*) isomer of **11b: (12b).** ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (5H, m), 5.32 (1H, dq, *J* = 6.3, 7.7 Hz), 3.85 (1H, d, *J* = 13.2 Hz), 3.81 (1H, d, *J* = 13.2 Hz), 3.71 (3H, s), 3.00 (1H, dq, *J* = 6.2, 6.2 Hz), 2.793 (1H, dd, *J* = 6.7, 7.7 Hz), 1.96 (3H, s), 1.24 (3H, d, *J* = 6.3 Hz), 1.11 (3H, d, *J* = 6.2 Hz); IR (CCl_4) 3380, 2960, 1740, 1645, 1243, cm^{-1}; MS calcd for $C_{16}H_{23}NO_4$: m/z 293.1627, Found 293.1623.

The (2R*,3R*,1'S*) isomer of **11b: (13b).** ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (5H, m), 5.38 (1H, dq, *J* = 6.2, 7.6 Hz), 3.94 (1H, d, *J* = 12.9 Hz), 3.70 (3H, s), 3.66 (1H, d, *J* = 12.9 Hz), 2.97 (1H, dq, *J* = 6.0, 6.5 Hz), 2.58 (1H, dd, *J* = 6.0, 7.6 Hz), 1.99 (3H, s), 1.21 (3H, d, *J* = 6.2 Hz), 1.18 (3H, d, *J* = 6.5 Hz); IR (CCl_4) 3330, 2960, 1745, 1455, 1375, 1243, cm^{-1}; MS calcd for $C_{16}H_{23}NO_4$: m/z 293.1627, Found 293.1628.

The (2R*,3S*,1'S*) isomer of **11b: (14b).** ^{1}H NMR ($CDCl_3$) δ 7.39-7.19 (5H, m), 5.29 (1H, dq, *J* = 6.2, 8.1 Hz), 3.90 (1H, d, *J* = 12.8 Hz), 3.71 (3H, s), 3.67 (1H, d, *J* = 12.8 Hz), 2.99 (1H, dq, *J* = 6.0, 6.7 Hz), 2.70 (1H, dd, *J* = 6.0, 8.1 Hz), 1.92 (3H, s), 1.24 (3H, d, *J* = 6.2 Hz), 1.17 (3H, d, *J* = 6.7 Hz); IR (CCl_4) 3330, 2970, 1740, 1243, cm^{-1}; MS calcd for $C_{16}H_{23}NO_4$: m/z 293.1627, Found 293.1632.

(2R*,3R*)-Methyl 2-[(R*)-1-benzylaminoethyl]-3-hydroxybutanoate (**11b'**). ^{1}H NMR ($CDCl_3$) δ 7.39-7.20 (5H, m), 4.21 (1H, dq, *J* = 3.6, 6.5 Hz), 3.75 (1H, d, *J* = 12.5 Hz), 3.70 (3H, s), 3.69 (1H, d, *J* = 12.5 Hz), 3.29 (1H, dq, *J* = 6.1, 7.4 Hz), 2.55 (1H, dd, *J* = 3.6, 7.4 Hz), 1.21 (1H, d, *J* = 6.5 Hz), 1.18 (3H, d, *J* = 6.1 Hz); IR (CCl_4) 3270, 2980, 1730, 1440, 1385, 1200, 1175, 730, 700 cm^{-1}; MS calcd for $C_{14}H_{21}NO_3$: m/z 251.1521, Found 251.1519.

The (2R*,3S*,1'S*) isomer of **11b'**: **(14b').** ^{1}H NMR ($CDCl_3$) δ 7.37-7.22 (5H, m), 4.31 (1H, dq, *J* = 6.6, 6.7 Hz), 3.86 (1H, d, *J* = 12.9 Hz), 3.79 (1H, d, *J* = 12.9 Hz), 3.70 (3H, s), 3.23 (1H, dq, *J* = 3.2, 6.3 Hz), 2.52 (1H, dd, *J* = 3.2, 6.7 Hz), 1.28 (1H, d, *J* = 6.6 Hz), 1.18 (3H, d, *J* = 6.3 Hz); IR (CCl_4) 3330, 2980, 1740, 1440, 1175 cm^{-1}; MS calcd for $C_{14}H_{21}NO_3$: m/z 251.1521, Found 251.1518.

O-Silylated ketene acetal.

(Z)-1-Methoxy-1-trimethylsiloxy-3-(N-trimethylsilylbenzylamino)butene (**1**). To a solution of N-(trimethylsilyl)benzylamine (0.22 mL, 1.1 mmol) in THF (2.5 mL) was added a 1.59M hexane solution of BuLi (0.69 mL, 1.1 mmol) at -78 °C. The mixture was stirred at -78°C for 30 min before the addition of methyl crotonate (0.11 mL, 1.0 mmol). After stirring for 30 min at -78°C, chlorotrimethylsilane (0.15 mL, 1.2 mmol) was added. After additional stirring for 2 min, the cooling bath was removed and at the same time, the solvent was removed by vacuo until the mixture was warmed to room temperature. To this residue, dry hexane (5 mL) was added and the white precipitate was separated by centrifuge under Ar atmosphere. Removal of hexane under reduced pressure, followed by the Kugelrohr distillation (153 °C / 0.23 mmHg) afforded pure colorless oil (**1**): ^{1}H NMR (C_6D_6) δ 7.41 (1H, d, *J* = 6.9 Hz), 7.22 (2H, t, *J* = 6.9 Hz), 7.08 (2H, t, *J* = 6.9 Hz), 4.27 (1H, dq, *J* = 6.7 and 8.9 Hz), 4.05 (2H, s), 3.50 (1H, d, *J* = 8.9 Hz), 2.93 (3H, s), 1.25 (3H, d, *J* = 6.7 Hz), 0.24 (9H, s), 0.22 (9H, s); IR (neat) 2970, 1730, 1670, 1255, 1220, 975, 850 cm^{-1}; MS calcd for $C_{18}H_{33}NO_2Si_2$: m/z 351.2050, Found 351.2085.

The E isomer of **1**: (**3**). After conjugate addition of LSA to methyl crotonate described above, methanol (0.045 mL, 1.1 mmol) was added. To this reaction mixture, a solution of LDA prepared by diisopropylamine (0.17 mL, 1.2 mmol) and a 1.59 M hexane solution of BuLi (0.76 mL, 1.2 mmol) was added. The mixture was stirred at -78°C for 30 min before the addition of chlorotrimethylsilane (0.15 mL, 1.2 mmol). After the same non-aqueous work-up, the Kugelrohr distillation (160 °C / 0.09 mmHg) gave pure colorless oil (**3**) (185 mg, 45 %): ^{1}H NMR (C_6D_6) δ 7.41 (1H, d, *J* = 7.2 Hz), 7.22 (2H, t, *J* = 7.2 Hz), 7.09 (2H, t, *J* = 7.2 Hz), 4.26 (1H, dq, *J* = 6.9, 8.5 Hz), 3.90 (1H, d, *J* = 8.5 Hz), 3.29 (3H, s), 1.24 (3H, d, *J* = 6.9 Hz), 0.23 (9H, s), 0.09 (9H, s); IR (neat) 2980, 1750, 1680, 1460, 1265, 1225, 925, 855 cm^{-1}; MS calcd for $C_{18}H_{33}NO_2Si_2$: m/z 351.2050, Found 351.2076.

General Procedures for determination of stereochemistries of **11-14.**

(1) β-lactam synthesis. This procedure was reported earlier.[1e]

(3R*,4R*)-3-[(S*)-1-Hydroxybenzyl]-4-methyl-2-azetidinone (**16a**). Mp 70°C; ^{1}H NMR ($CDCl_3$) δ 7.48-7.23 (10H, m), 4.96 (1H, dd, *J* = 2.3, 7.6 Hz), 4.64 (1H, d, *J* = 15.0 Hz), 4.14 (1H, d, *J* = 15.0 Hz), 3.64 (1H, dq, *J* = 5.6, 6.4 Hz), 3.60 (1H, dd, *J* = 5.6, 7.6 Hz), 3.01 (1H, d, *J* = 2.3 Hz), 1.13 (3H, d, *J* = 6.4 Hz); IR (KBr) 3420, 3040, 1715, 1415, 1025, 740, 695 cm^{-1}; MS calcd for $C_{18}H_{19}NO_2$: m/z 281.1416, Found 281.1419.

The (3R*,4S*,1'R*) isomer of **16a**. Mp 100°C; ^{1}H NMR ($CDCl_3$) δ 7.40-7.18 (10H, m), 5.20 (1H, d, *J* = 3.5 Hz), 4.63 (1H, d, *J* = 15.5 Hz), 4.07 (1H, d, *J* = 15.5 Hz), 3.75 (1H, dq, *J* = 2.0, 6.1 Hz), 3.18 (1H, br),

3.10 (1H, dd, J = 2.0, 3.5 Hz), 0.98 (3H, d, J = 6.1 Hz); IR (KBr) 3380, 3350, 1715, 700 cm^{-1}; MS calcd for $C_{18}H_{19}NO_2$: m/z 281.1416, Found 281.1421.

(3R*,4R*)-3-[(S*)-1-Hydroxyethyl]-4-methyl-2-azetidinone (**16b**). Mp 90°C; ^1H NMR ($CDCl_3$) δ 7.39-7.22 (5H, m), 4.63 (1H, d, J = 15.2 Hz), 4.14 (1H, dq, J = 6.2, 7.6 Hz), 4.12 (1H, d, J = 15.2 Hz), 3.69 (1H, dq, J = 5.4, 6.5 Hz), 3.10 (1H, dd, J = 5.4, 7.6 Hz), 1.64 (1H, br), 1.28 (3H, d, J = 6.2 Hz), 1.22 (3H, d, J = 6.5 Hz); IR (KBr) 3420, 2980, 1722 cm^{-1}; MS calcd for $C_{13}H_{17}NO_2$: m/z 219.1259, Found 219.1258.

The (3R*,4S*,1'R*) isomer of **16b**. ^1H NMR ($CDCl_3$) δ 7.38-7.23 (5H, m), 4.63 (1H, d, J = 15.2 Hz), 4.17 (1H, m), 4.09 (1H, d, J = 15.2 Hz), 3.63 (1H, dq, J = 2.1, 6.2 Hz), 2.78 (1H, dd, J = 2.1, 5.4 Hz), 1.26 (3H, d, J = 6.5 Hz), 1.22 (3H, d, J = 6.2 Hz); IR (CCl_4) 3300, 2975, 1735, 1385 cm^{-1}; MS calcd for $C_{13}H_{17}NO_2$: m/z 219.1259, Found 219.1264.

(2) Acetonide synthesis. Preparation of **19b** is representative. Conversion of **11b** to **17b**. A mixture of **11b** (65 mg, 0.22 mmol), potassium carbonate (0.2 g), and iodomethane (0.14 mL, 2.2 mmol) was stirred at room temperature for overnight. The mixture was then neutralized with 1.4N HCl, extracted with ether, and dried over Na_2SO_4. Evaporation of a solvent and purification of the residue by column chromatography on silica gel (hexane / ethyl acetate = 5 / 1 as eluant) gave (**17b**) (54 mg, 80% yield).

Conversion of **17b** to **18b**. To a solution of **17b** (50 mg, 0.16 mmol) in ether (2 mL) was added excess $LiAlH_4$ at room temperature. After the mixture was stirred for 1 h, it was treated by successive dropwise addition of water (0.12 mL), 15% aqueous NaOH solution (0.12 mL), and water (0.36 mL). A precipitated white solid was filtrated and washed with ether. The combined solvents were removed in vacuo to give the essentially pure crude product, which was directly used in the next step without purification (**18b**) (37 mg, 96% yield).

Conversion of **18b** to **19b**. To a mixture of **18b** (37 mg, 0.16 mmol) and 2,2-dimethoxypropane (2.0 mL) in CH_2Cl_2 was added *p*-toluenesulfonic acid monohydrate (43 mg, 0.23 mmol) at room temperature and the reaction mixture was refluxed. After 3 min, the color of this solution changed to brown. After cooling the reaction mixture, saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2, and dried over Na_2SO_4. Evaporation of solvents gave essentially pure colorless oil (**19b**) (39 mg, 90% yield).

(2R*,3S*)-Methyl 3-acetoxy-2-[(S*)-1-(N-methylbenzylamino)ethyl]-3-phenylpropanoate (**17a**). Mp 109°C; ^1H NMR ($CDCl_3$) δ 7.36-7.15 (10H, m), 6.00 (1H, d, J = 6.9 Hz), 3.58 (3H, s), 3.57 (1H, d, J = 13.1 Hz), 3.38 (1H, d, J = 13.1 Hz), 3.20 (1H, dq, J = 6.7, 10.1 Hz), 3.07 (1H, dd, J = 6.9, 10.1 Hz), 2.06 (3H, s), 2.03 (3H, s), 0.85 (3H, d, J = 6.7 Hz); IR (KBr) 1730, 1245, 1220, 1160, 1030 cm^{-1}; MS calcd for $C_{22}H_{27}NO_4$: m/z 369.1940, Found 369.1940.

(2R*,3R*)-Methyl 3-acetoxy-2-[(R*)-1-(N-methylbenzylamino)ethyl]-butanoate (**17b**). ^1H NMR ($CDCl_3$) δ 7.35-7.19 (5H, m), 5.48 (1H, dq, J = 4.3, 6.5 Hz), 3.71 (3H, s), 3.57 (1H, d, J = 13.2 Hz), 3.51 (1H, d, J = 13.2 Hz), 3.17 (1H, dq, J = 6.6, 10.4 Hz), 2.64 (1H, dd, J = 4.3, 10.4 Hz), 2.05 (3H, s), 1.97 (3H, s), 1.30 (3H, d, J = 6.5 Hz), 0.99 (3H, d, J = 6.6 Hz); IR (CCl_4) 2970, 1740, 1730, 1240 cm^{-1}; MS calcd for $C_{17}H_{25}NO_4$: m/z 307.1784, Found 307.1771.

The (2R*,3R*,1'S*) isomer of **17b**. Mp 62°C; ^1H NMR ($CDCl_3$) δ 7.32-7.17 (5H, m), 5.11 (1H, dq, J = 3.9, 6.3 Hz), 3.73 (3H, s), 3.60 (1H, d, J = 13.2 Hz), 3.42 (1H, d, J = 13.2 Hz), 3.25 (1H, dq, J = 6.5, 11.1 Hz), 2.70 (1H, dd, J = 3.9, 11.1 Hz), 2.06 (3H, s), 2.05 (3H, s), 1.28 (3H, d, J = 6.3 Hz), 1.02 (3H, d, J = 6.5 Hz); IR (CCl_4) 2950, 1735, 1725, 1255, 730, 695 cm^{-1}; MS calcd for $C_{17}H_{25}NO_4$: m/z 307.1784, Found 307.1783.

The (2R*,3S*,1'S*) isomer of **17b**. ^1H NMR ($CDCl_3$) δ 7.32-7.16 (5H, m), 5.07 (1H, dq, J = 5.7, 6.5 Hz), 3.72 (3H, s), 3.62 (1H, d, J = 13.2 Hz), 3.40 (1H, d, J = 13.2 Hz), 3.14 (1H, dq, J = 6.7, 11.4 Hz), 3.01 (1H, dd, J = 5.7, 11.4 Hz), 2.06 (3H, s), 2.02 (3H, s), 1.31 (3H, d, J = 6.5 Hz), 1.04 (3H, d, J = 6.7 Hz); IR (CCl_4) 2980, 2800, 1740, 1455, 1440, 1375, 1245 cm^{-1}; MS calcd for $C_{17}H_{25}NO_4$: m/z 307.1784, Found 307.1789.

(2R*,3R*)-2-[(R*)-1-(N-Methylbenzylamino)ethyl]-1-phenyl-1,3-propanediol (**18a**). ^1H NMR ($CDCl_3$) δ 7.41-7.19 (10H, m), 4.95 (1H, d, J = 2.2 Hz), 3.76 (1H, dd, J = 3.4, 11.2 Hz), 3.70 (1H, d, J = 12.8 Hz), 3.67 (1H, dd, J = 5.0, 11.2 Hz), 3.58 (1H, d, J = 12.8 Hz), 3.40 (1H, dq, J = 6.6, 9.4 Hz), 2.21 (3H, s), 1.78 (1H, dddd, J = 2.2, 3.4, 5.0, 9.4 Hz), 1.27 (3H, d, J = 6.6 Hz); IR (KBr) 3280, 3030, 2900, 1450, 1030, 735, 705 cm^{-1}; MS calcd for $C_{19}H_{25}NO_2$: m/z 299.1885, Found 299.1885.

(2R*,3S*)-2-[(S*)-1-(N-Methylbenzylamino)ethyl]-1,3-butanediol (**18b**). ^1H NMR ($CDCl_3$) δ 7.37-7.21 (5H, m), 4.30 (1H, dq, J = 3.2, 6.7 Hz), 3.87 (1H, dd, J = 3.6, 11.2 Hz), 3.64 (1H, d, J = 12.8 Hz), 3.54 (1H, d, J = 12.8 Hz), 3.53 (1H, dd, J = 4.8, 11.2 Hz), 3.18 (1H, dq, J = 6.6, 10.0 Hz), 2.17 (3H, s), 1.73 (1H,

dddd, J = 3.2, 3.6, 4.8, 10.0 Hz), 1.20 (3H, d, J = 6.7 Hz), 1.10 (3H, d, J = 6.6 Hz); IR (CCl_4) 3350, 2980, 1460, 1380, 1140, 740, 700 cm^{-1}; MS calcd for $C_{14}H_{23}NO_2$: m/z 237.1729, Found 237.1730.

The (2R*,3S*,1'R*) isomer of **18b**. ^1H NMR ($CDCl_3$) δ 7.38-7.21 (5H, m), 4.01 (1H, dd, J = 3.2, 11.2 Hz), 3.98 (1H, dq, J = 2.3, 6.3 Hz), 3.87 (1H, dd, J = 6.5, 11.2 Hz), 3.68 (1H, d, J = 12.7 Hz), 3.54 (1H, d, J = 12.7 Hz), 3.23 (1H, dq, J = 6.8, 9.6 Hz), 2.17 (3H, s), 1.51 (1H, dddd, J = 2.3, 3.2, 6.5, 9.6 Hz), 1.27 (3H, d, J = 6.3 Hz), 1.13 (3H, d, J = 6.8 Hz); IR (CCl_4) 3380, 2980, 1450, 1050 cm^{-1}; MS calcd for $C_{14}H_{23}NO_2$: m/z 237.1729, Found 237.1724.

The (2R*,3R*,1'R*) isomer of **18b**. ^1H NMR ($CDCl_3$) δ 7.38-7.20 (5H, m), 3.99 (1H, dq, J = 4.6, 6.4 Hz), 3.94 (1H, dd, J = 4.3, 10.5 Hz), 3.70 (1H, dd, J = 7.7, 10.5 Hz), 3.69 (1H, d, J = 12.8 Hz), 3.58 (1H, d, J = 12.8 Hz), 2.97 (1H, dq, J = 6.8, 8.1 Hz), 2.19 (3H, s), 1.95 (1H, dddd, J = 4.3, 4.6, 7.7, 8.1 Hz), 1.11 (3H, d, J = 6.4 Hz), 1.08 (3H, d, J = 6.8 Hz); IR (CCl_4) 3370, 2980, 1455, 1375, 1025 cm^{-1}; MS calcd for $C_{14}H_{23}NO_2$: m/z 237.1729, Found 237.1747.

(1R*,2R*)-2-[(R*)-1-(N-Methylbenzylamino)ethyl]-1-phenyl-1,3-O-isopropylidenepropane (**19a**). ^1H NMR ($CDCl_3$) δ 7.40-7.20 (10H, m), 4.72 (1H, d, J= 9.7 Hz), 4.17 (1H, dd, J = 5.1, 11.8 Hz), 4.05 (1H, dd, J = 9.7, 11.8 Hz), 3.53 (1H, d, J = 13.4 Hz), 3.32 (1H, d, J = 13.4 Hz), 2.56 (1H, dq, J = 6.8, 6.8 Hz), 2.11 (1H, dddd, J = 5.1, 6.8, 9.7, 9.7 Hz), 2.02 (3H, s), 1.53 (3H, s), 1.44 (3H, s), 0.52 (3H, d, J = 6.8 Hz); IR (CCl_4) 3000, 1385, 700 cm^{-1}; MS calcd for $C_{22}H_{29}NO_2$: m/z 339.2198, Found 339.2198.

(1R*,2S*)-2-[(R*)-1-(N-Methylbenzylamino)ethyl]-1-methyl-1,3-O-isopropylidenepropane (**19b**). ^1H NMR ($CDCl_3$) δ 7.38-7.19 (5H, m), 3.85 (1H, dd, J = 5.1, 12.0 Hz), 3.81 (1H, dq, J = 6.0, 8.9 Hz), 3.62 (1H, dd, J = 7.9, 12.0 Hz), 3.56 (1H, d, J = 12.9 Hz), 3.54 (1H, d, J = 12.9 Hz), 2.69 (1H, dq, J = 6.9, 6.9 Hz), 2.10 (3H, s), 1.76 (1H, dddd, J = 5.1, 6.9, 7.9, 8.9 Hz), 1.36 (3H, s), 1.33 (3H, s), 1.30 (3H, d, J = 6.0 Hz), 0.99 (3H, d, J = 6.9 Hz); IR (CCl_4) 3000, 1450, 1380, 1230, 1180, 730, 700 cm^{-1}; MS calcd for $C_{17}H_{27}NO_2$: m/z 277.2042, Found 277.2039.

The (1R*,2S*,1'S*) isomer of **19b**. ^1H NMR ($CDCl_3$) δ 7.38-7.18 (5H, m), 3.98 (1H, dd, J = 7.5, 11.5 Hz), 3.89 (1H, dd, J = 5.2, 11.5 Hz), 3.82 (1H, dq, J = 6.1, 8.8 Hz), 3.58 (1H, d, J = 13.3 Hz), 3.43 (1H, d, J = 13.3 Hz), 2.76 (1H, dq, J = 6.9, 6.9 Hz), 2.09 (3H, s), 1.59 (1H, dddd, J = 5.2, 6.9, 7.5, 8.8 Hz), 1.40 (3H, s), 1.37 (3H, s), 1.23 (3H, d, J = 6.1 Hz), 1.04 (3H, d, J = 6.9 Hz); IR (CCl_4) 2990, 1384, 1230, 1180, 730, 700 cm^{-1}; MS calcd for $C_{17}H_{27}NO_2$: m/z 277.2042, Found 277.2047.

The (1R*,2R*,1'R*) isomer of **19b**. ^1H NMR ($CDCl_3$) δ 7.39-7.17 (5H, m), 4.21 (1H, dq, J = 4.0, 6.9 Hz), 4.09 (1H, dd, J = 6.7, 11.8 Hz), 3.98 (1H, dd, J = 4.4, 11.8 Hz), 3.61 (1H, d, J = 13.3 Hz), 3.48 (1H, d, J = 13.3 Hz), 2.87 (1H, dq, J = 6.5, 10.1 Hz), 2.09 (3H, s), 1.80 (1H, dddd, J = 4.0, 4.4, 6.7, 10.1 Hz), 1.41 (3H, s), 1.37 (3H, s), 1.23 (3H, d, J = 6.9 Hz), 1.05 (3H, d, J = 6.5 Hz); IR (CCl_4) 3350, 3000, 1455, 1380, 1190 cm^{-1}; MS calcd for $C_{17}H_{27}NO_2$: m/z 277.2042, Found 277.2043.

(3) 1,3-Oxazine synthesis. Preparation of **20b** is representative. Conversion of **11b** to **11b'**. A mixture of **11b** (100 mg, 0.34 mmol), potassium carbonate (94 mg), and methanol (2.0 mL) was stirred at room temperature for overnight. To the mixture was then added water, extracted with ether, and dried over K_2CO_3. Evaporation of solvents afforded essentially pure colorless oil (**11b'**) (72 mg, 84% yield).

Conversion of **11b'** to **20b**. To a solution of **11b'** (58 mg, 0.23 mmol) in benzene (10 mL) was added *p*-nitro-benzaldehyde (35 mg, 0.23 mmol) at room temperature. The mixture was heated to remove solvents in the presence of molecular shieves 3A. After removal solvents, benzene was injected again and this procedure was repeated many times until the completeness of the reaction. Filtration of molecular shieves, evaporation of solvents, and purification of the residue by column chromatography on silica gel (hexane / ethyl acetate = 15 / 1 as eluant) gave the mixture of stereoisomers (53 mg, 63%). The ratio was determined by NMR (a-s : a-a : s-s = 63 : 5 : 32).

(4R*,5S*,6S*)-3-Benzyl-5-methoxycarbonyl-4-methyl-2-(4-nitrophenyl)-6-phenyltetrahydro-1,3-oxazine (**20a**). Mp 125°C; ^1H NMR ($CDCl_3$) δ 8.21 (2H, d, J = 8.2 Hz), 7.86 (2H, d, J = 8.2 Hz), 7.48-7.14 (10H, m), 5.87 (1H, s), 5.27 (1H, d, J = 3.8 Hz), 3.82 (1H, d, J = 14.5 Hz), 3.68 (1H, dq, J = 1.5, 7.1 Hz), 3.57 (1H, d, J = 14.5 Hz), 3.40 (3H, s), 2.75 (1H, dd, J = 1.5, 3.8 Hz), 1.54 (3H, d, J = 7.1 Hz); IR (KBr) 3450, 3050, 3000, 1740, 1530, 1350, 850 cm^{-1}; MS calcd for $C_{26}H_{26}N_2O_5$: m/z 446.1842, Found 446.1798.

The (4R*,5R*,6S*) isomer of **20a**. Mp 91°C; ^1H NMR ($CDCl_3$) δ 8.16 (2H, d, J= 8.9 Hz), 7.75 (2H, d, J = 8.9 Hz), 7.60-7.20 (10H, m), 5.99 (1H, s), 5.21 (1H, d, J = 10.7 Hz), 3.78 (1H, d, J = 15.0 Hz), 3.66 (1H, d, J = 15.0 Hz), 3.50 (1H, dq, J = 5.3, 6.9 Hz), 3.49 (3H, s), 3.43 (1H, dd, J = 5.3, 10.7 Hz), 1.45 (3H, d, J = 6.9 Hz); IR (CCl_4) 1740, 1530, 1355, 1020 cm^{-1}; MS calcd for $C_{26}H_{26}N_2O_5$: m/z 446.1842, Found 446.1853.

(4R*,5S*,6R*)-3-Benzyl-5-methoxycarbonyl-4,6-dimethyl-2-(4-nitrophenyl)tetrahydro-1,3-oxazine (**20b**). **20b** was contaminated with epimer. The spectra data was based on a 63 : 37 mixture. ^{1}H NMR ($CDCl_3$) δ 8.16 (2H, d, J = 8.5 Hz), 7.75 (2H, d, J = 8.5 Hz), 7.30-7.01 (5H, m), 5.63 (1H, s), 4.25 (1H, dq, J = 3.6, 6.7 Hz), 3.70 (3H, s), 3.68 (1H, d, J = 14.6 Hz), 3.58 (1H, dq, J = 1.9, 7.1 Hz), 3.45 (1H, d, J = 14.6 Hz), 2.28 (1H, dd, J = 1.9, 3.6 Hz), 1.46 (3H, d, J = 6.7 Hz), 1.38 (3H, d, J = 7.1 Hz); IR (CCl_4) 2980, 1745, 1530, 1350, 1010 cm^{-1}; MS calcd for $C_{21}H_{24}N_2O_5$: m/z 384.1685, Found 384.1725.

The (4R*,5R*,6R*) isomer of **20b**. ^{1}H NMR ($CDCl_3$) δ 8.18 (2H, d, J = 8.3 Hz), 7.74 (2H, d, J = 8.3 Hz), 7.35-7.17 (5H, m), 5.77 (1H, s), 4.28 (1H, dq, J = 5.7, 10.7 Hz), 3.64 (3H, s), 3.59 (1H, d, J = 15.1 Hz), 3.51 (1H, d, J = 15.1 Hz), 3.38 (1H, dq, J = 5.6, 7.0 Hz), 2.95 (1H, dd, J = 5.6, 10.7 Hz), 1.40 (3H, d, J = 5.7 Hz), 1.32 (3H, d, J = 7.0 Hz); IR (CCl_4) 1740, 1530, 1350, 1020 cm^{-1}; MS calcd for $C_{21}H_{24}N_2O_5$: m/z 384.1685, Found 384.1684.

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