Stereoselective Michael Addition of the Imines of α-Amino Esters in the Presence of Lithium Bromide/1,8-Diazabicyclo[5.4.0]undec-7-ene

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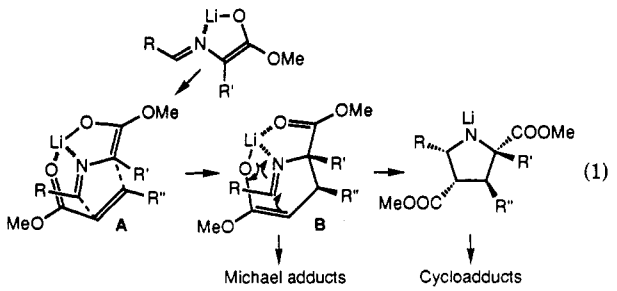
In the presence of lithium bromide/1,8-diazabicyclo[5.4.0]undec-7-ene, methyl [(2,2-dimethylpropylidene)amino]acetate and methyl 2-[(2,2-dimethylpropylidene)amino]propanoate undergo anti- and syn-selective Michael additions with *E* and *Z* isomers of α,β-unsaturated esters and ketones, respectively. The frontier-orbital- and chelation-controlled transition state is responsible for the observed high selectivity. Catalytic reaction effectively suppresses undesired epimerization at the 2-position. Hydrolytic cyclization of the resulting Michael adducts leads to 5-oxopyrrolidine-2-carboxylates and 1-pyrroline-5-carboxylates.

The lithium enolates, or N-lithiated azomethine ylide 1,3-dipoles,[1] generated by lithiation of the imines of α-amino esters by treatment with lithium bromide and triethylamine (or 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) undergo highly stereoselective cycloadditions with α,β-unsaturated esters and ketones.[2,3] Chelation between the lithium and the imine nitrogen and between the lithium and the carbonyl oxygen[2-4] is partially responsible for the high stereoselectivity. Equation 1 represents a typical example of the cycloaddition.



(1)

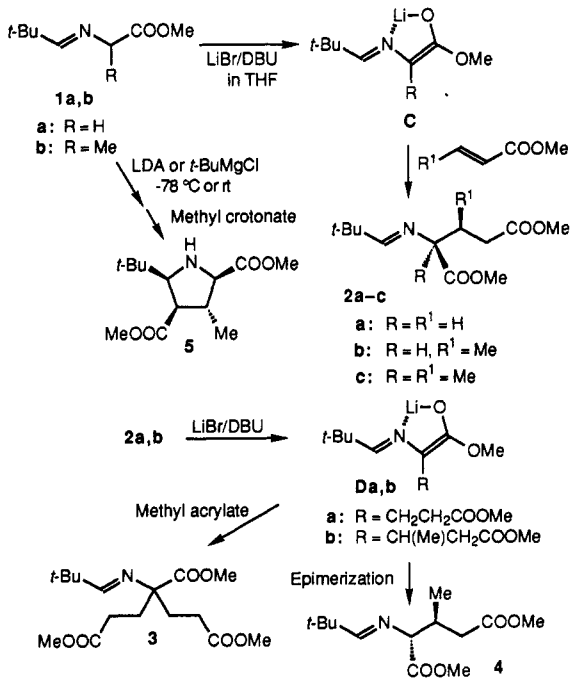
In the course of our work on the reaction of the lithium enolate A (R = Ph, R′ = Me) derived from methyl 2-(benzylideneamino)propanoate with methyl acrylate, a disadvantageous feature of this stereoselective cycloaddition was unveiled: Cycloaddition competes with Michael addition (eq 1),[5] and the product ratio depends on the reaction conditions as well as the metal atom.

A stepwise mechanism via the chelation-stabilized enolates B was proposed for the cycloaddition, indicating the possible utilization of such a frontier-orbital- and chelation-controlled transition state A as a new entry to highly stereoselective Michael addition reactions.

Although Michael reactions using derivatives of α-amino esters have been long examined as a direct method of introducing α-substituents,[6] stereoselective Michael reactions with respect to the newly formed bond are quite rare.[7,8] Some examples of stereoselective Michael additions of ester enolates with α,β-unsaturated esters, which are closely related to the conjugate addition of α-amino ester enolates, have emerged only recently in the literature.[9]

The present paper describes the stereoselective Michael addition of the imines of α-amino esters with α,β-unsaturated esters and ketones. This process offers a useful method for stereoselective alkylation at the α-position of α-amino acids and their derivatives.[10]

Scheme I



(1) N-Lithiated azomethine ylide is another expression of lithium enolate for the reactive species generated by lithiation of the imines of α-amino esters (see ref 5). The enolate nomenclature is used in the present article.

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Table I. Michael Addition of Imines 1 with α,β-Unsaturated Esters and Ketones

entry	imine	Michael acceptor	reactn conditns			product (yield, %)[a]
			meth[b]	temp, °C	time, h	
1	**1a**	methyl acrylate[c]	A	rt[h]	3	**3** (71)
2	**1a**	methyl crotonate	A	rt	10 min	**2b** (77), single
3	**1b**	methyl crotonate	A	rt	24	**2c** (61), single
4	**1a**	(*E*)-3-penten-2-one	A	−5	15 min	**6a** (80), single
5	**1a**	(*E*)-4-phenyl-3-buten-2-one	A	−5	15 min	**6b** (97), single
6	**1a**	(*E*)-5,5-dimethyl-3-hexen-2-one	A	−5	1	**6c** (44),[d] single
7	**1a**	(*E*)-1-phenyl-2-buten-1-one[e]	A	−5	15 min	**6d** (93), 10:1[f]
8	**1a**	(*E,E*)-1,5-diphenyl-2,4-pentadien-1-one	A	−15	30 min	**6e** (93), single
9	**1a**	dimethyl fumarate	A	−15	15 min	**7a** + **7b** (97), 6.7:1
10	**1a**	dimethyl fumarate	B	−15	1.3	**7a** (quant), single
11	**1a**	dimethyl fumarate	B	rt	15	**7a** (94), single
12	**1a**	dimethyl maleate	A	−15	5 min	**7b** + **7a** (91), 2.5:1
13	**1a**	dimethyl maleate	B	−15	1.5	**7b** (quant), single
14	**1b**	dimethyl fumarate	A	rt	17	**7c** + **7d** (88), 6:1
15	**1b**	dimethyl fumarate	A	−10	10 min	**7c** + **7d** (52),[g] 32:1
16	**1b**	dimethyl maleate	A	rt	5	**7d** + **7c** (85), 4:1
17	**1b**	dimethyl maleate	B	rt	20	**7d** + **7c** (64),[g] 12:1

[a] Yield of isolated products. The isomer ratio was determined on the basis of the ^{1}H NMR spectrum. [b] Molar equivalents of imine 1:acceptor:LiBr:DBU = 1:1:1.1:1 (method A) or 1:1:0.1:0.1 (method B). [c] The amount of methyl acrylate employed was 3.3 equiv. [d] The amount of acceptor employed was 1.1 equiv. The yield was based on **1a**. [e] Employed as a 10:1 mixture of *E* and *Z* isomers. [f] A mixture of 2*R**,3*R** and 2*R**,3*S** isomers. [g] Determined by the ^{1}H NMR spectrum of the crude reaction product. Obtained as a mixture with the starting imine and olefin. [h] Room temperature.

Results and Discussion

According to the stepwise reaction mechanism proposed for the stereoselective cycloaddition of lithium enolates of imine esters (shown in eq 1), proper choice of the substituent R would effectively suppress the cycloaddition pathway so that the Michael addition may become the major pathway. Sterically bulky 2,2-dimethylpropanal was the aldehyde of our choice.

Stereoselective Michael Additions. Compared with the ready conversion of methyl (benzylideneamino)acetate into the corresponding lithium enolate by action with lithium bromide/triethylamine in tetrahydrofuran (THF) at room temperature,[2] a stronger base such as DBU was needed to lithiate methyl [(2,2-dimethylpropylidene)-amino]acetate (**1a**) under identical conditions. This indicates that the ease of lithiation depends on the degree of anion stabilization by the aldehyde substituent.

Enolate C (R = H) was successfully generated by treatment of **1a** with lithium bromide/DBU in THF and allowed to react with methyl acrylate to give, after hydrolytic workup, a mixture of 1:1 and 1:2 adducts, **2a** and **3**, in a quantitative combined yield (Scheme I). Separation of either **2a** or **3** through column chromatography on silica gel was unsuccessful because of their ready hydrolytic decomposition, which will be described later. The product ratio changed, depending on the molar equivalents of the acceptor used as well as the reaction conditions. Although the exclusive formation of 1:2 adduct **3** was readily achieved by use of more than 2 equiv of the acrylate (entry 1 of Table I), the 1:1 adduct **2a** was always contaminated by **3** even when <1 equiv of the acrylate was employed at a low temperature.

Formation of 1:2 adduct **3** occurs through the reiterative lithiation of 1:1 adduct **2a** either intramolecularly from the 1:1 adduct anion or intermolecularly from the protonated 1:1 adduct **2a**. The latter pathway seems to be more likely in this case on the basis of the following: (1) The lithiation by lithium bromide/DBU is a reversible process, (2) DBU is a strong enough base to lithiate the imine of methyl-substituted α-amino ester **1b** in the presence of lithium bromide (discussed below), and (3) the dimethyl maleate adduct **7b** undergoes a ready epimerization under similar conditions (discussed below).

The Michael addition of lithium enolate C (R = H) with a 3-substituted 2-alkenoate provides information on diastereoselectivity at the newly formed carbon–carbon bond, which is the central theme in the present work. Trapping enolate C (R = H) with methyl crotonate at room temperature produced a mixture of two diastereomeric Michael adducts **2b** and **4** as labile products, the isomer ratio depending on the reaction time. The ratio decreased with longer reaction times as shown in the following examples: **2b**:**4** = 7:6 after 4 h and 1:1 after 24 h.

It was our delight, however, to notice that a single stereoisomer **2b** was obtained in 77% yield when the reaction mixture was quenched after 10 min at room temperature (entry 2, 66% also as the major stereoisomer after 1 h). Thus, the Michael reaction itself is a kinetically controlled diastereoselective process producing **2b** as a single product, and **2b** undergoes reiterative lithiation at the 2-position under the reaction conditions leading to lithium enolate Db. Since this lithiation is a reversible process, **2b** gradually epimerizes into **4** (pure sample of **2b** epimerized into **4** in THF in the presence of lithium bromide/DBU at room temperature: a 1:1 mixture of **2b** and **4** after 16 h).

It is noteworthy that enolate C produced a stereoselective cycloadduct **5** in 81% yield in the reaction with methyl crotonate when generated from imine **1a** and lithium diisopropylamide (LDA) at −78 °C (Scheme I). Similarly, the magnesium enolate, generated from **1a** and *tert*-butylmagnesium chloride in THF, provided the same product **5** in 88% yield. These results indicate that the Michael addition of **1** is effectively carried out only under the conditions of reversible generation of the intermediate ester enolate C.

Methyl cinnamate was much less reactive toward C (R = H). None of the corresponding Michael adduct was

(8) Exclusive syn selectivity has been observed in the Michael reactions of the lithium enolates of (dibenzylamino)acetates with (*E*)-2-alkenoates (Yamaguchi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377–380).

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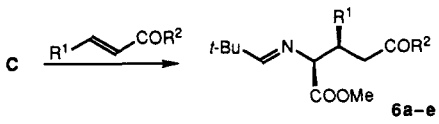
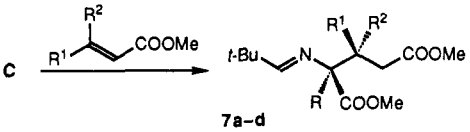
Scheme II



6a–e

a: $R^1 = R^2 = Me$
b: $R^1 = Ph$, $R^2 = Me$
c: $R^1 = t\text{-Bu}$, $R^2 = Me$
d: $R^1 = Me$, $R^2 = Ph$
e: $R^1 = PhCH{=}CH(E)$, $R^2 = Ph$

Scheme III



7a–d

a: $R = R^2 = H$, $R^1 = COOMe$
b: $R = R^1 = H$, $R^2 = COOMe$
c: $R = Me$, $R^1 = COOMe$, $R^2 = H$
d: $R = Me$, $R^1 = H$, $R^2 = COOMe$

formed under the equivalent conditions.

Similarly, the lithiation of methyl 2-[(2,2-dimethylpropylidene)amino]propanoate (**1b**) was performed readily with lithium bromide/DBU in THF at room temperature, and the resulting enolate C (R = Me) was stereoselectively trapped with methyl crotonate to give **2c** again as a single stereoisomer (entry 3). Since no epimerization is possible in this case, careful control of the reaction time was not necessary.

α,β-Unsaturated ketones such as (*E*)-3-penten-2-one, (*E*)-4-phenyl-3-buten-2-one, and (*E,E*)-1,5-diphenyl-2,4-pentadien-1-one reacted with enolate C (R = H). Single stereoisomers **6a,b,e** were produced in all cases, and epimerization at the 2-position was effectively suppressed by a proper choice of reaction conditions (Scheme II and entries 4–8 of Table I). When the β-position of enone is substituted with a bulky group, the Michael addition becomes very sluggish. Thus, the reaction of C (R = H) with 5,5-dimethyl-3-hexen-2-one gave only 44% of adduct **6c** after 1 h of reaction time (entry 6). Use of a 10:1 mixture of *E* and *Z* isomers of 1-phenyl-2-buten-1-one in the reaction with C (R = H) produced a 10:1 mixture of **6d** and its stereoisomer (entry 7), showing that the reactions with both the geometrical isomers are exclusively diastereoselective.

Stereostructures of these Michael adducts were assigned by their conversions into 5-oxo-2-pyrrolidinecarboxylates **8** or 1-pyrroline-5-carboxylates **9**, which will be discussed below.

The reactions of **1a** with dimethyl fumarate and maleate in THF in the presence of lithium bromide/DBU afforded 1:1 adducts **7a** and **7b** as major products, respectively (Scheme III). The minor products are their stereoisomers: **7b** in the fumarate case and **7a** in the maleate case. Compared with the aforementioned reaction of C (R = H) with methyl crotonate, these reactions were completed in shorter reaction times and the stereoselectivities were much lower under equivalent reaction conditions in both cases (**7a**:**7b** = 3:2 and **7b**:**7a** = 1:1 after 15 min at room temperature in the fumarate and maleate cases, respectively).

Accordingly, these Michael reactions have to be quenched in the minimum reaction time to attain a satisfactory isomer ratio, since long reaction times cause undesired epimerization. Our best results are as follows: **7a**:**7b** = 6.7:1 (entry 9) in the reaction with dimethyl fumarate at −15 °C in 15 min; **7b**:**7a** = 2.5:1 (entry 12) with

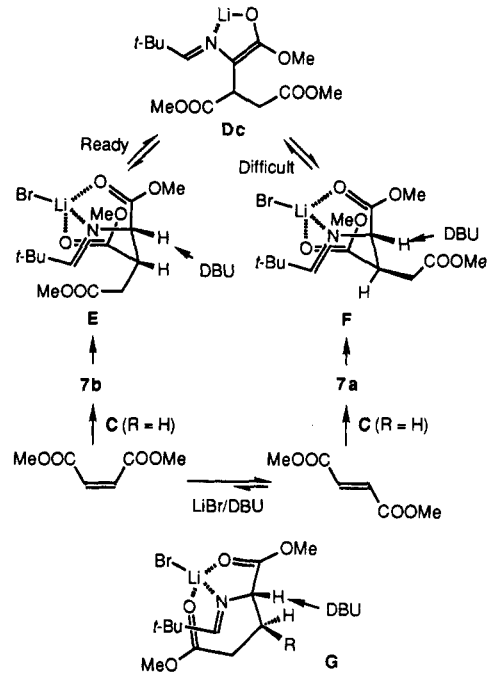


Figure 1. Stereoselectivity in the reactions of ylide C (R = H) with dimethyl fumarate and dimethyl maleate.

dimethyl maleate at −15 °C in 5 min. The selectivity is far from satisfactory.

One reason for the low selectivity in the maleate case is the ready epimerization of maleate adduct **7b**. Lithiation of **7b** with lithium bromide/DBU is probably initiated by the chelate formation of lithium bromide with the ester oxygen and the imine nitrogen, and the α-ester moiety introduced from the acceptor maleate is most likely to join in this chelation, as shown with the chair-like six-membered intermediate E (Figure 1). Although the fumarate adduct **7a** also makes a similar chelate F, the deprotonation with DBU takes place more readily in E than in F from the standpoint of steric hindrance.

A similar steric inhibition of enolization, or epimerization, was observed in the chelate G (R = *t*-Bu) of adduct **6c**, which carries a bulky *tert*-butyl group at the 3-position. Less hindered Michael adducts, such as ones derived from cis-olefinic acceptors or terminal-unsubstituted acceptors, would suffer from such ready epimerization. The acrylate adduct **2a**, or G (R = H), is one example.

In addition, the kinetic stereoselectivity is lower in the reaction with dimethyl maleate than in the case of dimethyl fumarate.[11] For example, enolate C (R = Me) reacted with both dimethyl fumarate and maleate at −10 °C to give **7c** and **7d** as major stereoisomers, with isomer ratios of **7c**:**7d** = 32:1 (entry 15) and **7d**:**7c** = 3.8:1 (15 min), respectively (Scheme III).

An interesting observation is the isomerization of dimethyl maleate into dimethyl fumarate under the reaction conditions, a 4:5 mixture of the maleates and the fumarate being obtained after 4.5 h at room temperature in the presence of lithium bromide/DBU (1.1:1 equiv/equiv).[12] At −15 °C for 10 min, however, only a negligible isomerization ratio as small as 31:1 was observed (^{1}H NMR). When the relative rate of Michael additions with dimethyl fumarate and maleate is taken into account, the low selectivity in the maleate case may be explained. Thus, the

(11) A lowered selectivity with *Z* acceptors has been reported (see ref 9d).

(12) The mechanism for the maleate–fumarate isomerization in the presence of lithium bromide/DBU is not clear so far.

Table II. Hydrolytic Cyclization of the Michael Adducts 2, 3, 6, and 7

entry	Michael adduct	reactn conditns[a] temp	time, h	product	yield of isolated products, % based on the Michael adduct	based on 1
1	3	rt[b]	14	8a	97	69
2	2b	reflux	12	8b	97	75
3	2c	reflux	13	8c	94	57
4	6a	rt	12	9a	48	38
5	6b	rt	3.5	9b	70	68
6	6c	rt	14	9c	63	28
7	6d	rt	3	9d	89	83
8	6e	rt	3	9e	94	87
9	7a	reflux	14	10a	67	65
10	7c	reflux	13	10b	74	65
11	7b	reflux	13	11a	83	78
12	7d	reflux	13.5	11b	79	67

[a] All reactions were carried out in aqueous methanol containing a catalytic amount of acetic acid. [b] Room temperature.

Michael addition of enolate C (R = H) with dimethyl fumarate proceeds more than 15 times faster than that with dimethyl maleate at −15 °C.[13]

As a result, the isomerization of dimethyl maleate into dimethyl fumarate under the conditions of Michael reactions is most responsible for the low stereoselectivity in the maleate case. Epimerization of the Michael adducts also contributes to the lowered selectivity.

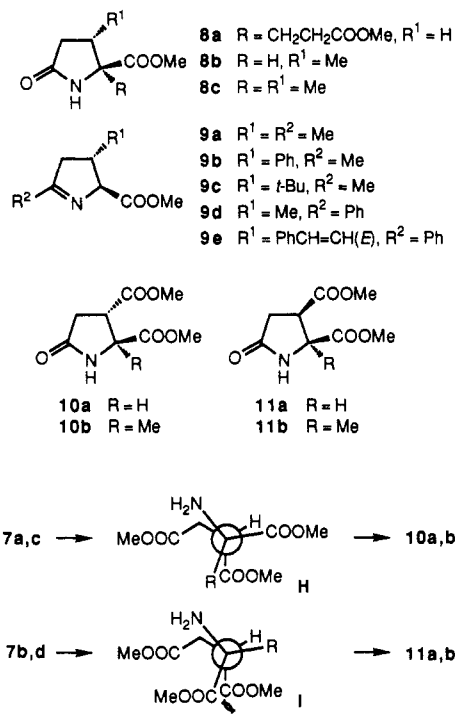
It was found that the maleate–fumarate isomerization could be effectively suppressed by use of a catalytic amount of lithium bromide/DBU, while the moderate reaction rate of Michael addition was maintained. As shown in entries 10, 11, and 13 of Table I, the reactions employing 0.1 equiv each of lithium bromide and DBU (method B) provided single stereoisomers of the corresponding Michael adducts. Even after long reaction times (15 h) at room temperature, no epimerization was observed (entry 11). The catalytic reaction of enolate C (R = Me) with dimethyl maleate offers another advantage (entry 17).

Imine Hydrolysis and Subsequent Cyclization. As described above, the Michael adducts **2–4**, **6**, and **7** are all labile in the presence of moisture. Their attempted purification through silica gel column chromatography was unsuccessful. Treatment of the Michael adducts with acetic acid in aqueous methanol at room temperature (for the ketone adducts **6a–e**) or under reflux (for the ester adducts **2b,c** and **7a–d**) causes smooth hydrolysis of the imine moiety to produce the corresponding cyclized products **8–11** in high yields (Scheme IV and Table II).

2-Aminopentanedioates derived from the imine hydrolysis of the fumarate adducts **7a** and **7c** were found to undergo cyclization more readily than those derived from the maleate adducts **7b** and **7d**. Therefore, the controlled hydrolytic cyclization of the fumarate adducts **7a** and **7c** which are contaminated by the maleate adducts **7b** and **7d**, respectively, affords pure cyclized products **10a** and **10b**, the unreacted amines from the contaminants being recovered. The relatively difficult condensation of the maleate adducts **7b** and **7d** would be due to serious eclipsed repulsion between the two ester moieties as shown in I (Scheme IV).

In conclusion, 2-[(2,2-dimethylpropylidene)amino]alkanoates undergo exclusively anti- and syn-selective Michael additions with *E* and *Z* isomers of α,β-unsaturated carbonyl compounds, respectively, in the presence of lithium bromide/DBU. The catalytic use of lithium bromide/DBU is especially useful for the effective inhibition of epimerization.

Scheme IV



Experimental Section

General. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with JASCO IRA-1 and A-702 spectrometers. ^1H and ^{13}C NMR spectra were recorded on JEOL FX-100 (100 MHz for ^1H NMR and 25.05 MHz for ^{13}C NMR) and GSX-270 (270 MHz for ^1H NMR and 67.94 MHz for ^{13}C NMR) instruments. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra and high-resolution mass spectra (HRMS) were measured with a JEOL-01SG-2 spectrometer at an ionization energy of 70 eV. Elemental analyses were performed on a Hitachi 026 CHN analyzer. For preparative column chromatography, Wakogel C-200 and C-300 (Wako) and silica gel 60 (Merck) were employed. Micro vacuum distillation was carried out on a Sibata GTO-250R Kugelrohr distilling apparatus.

General Procedures for the Michael Additions of Imines 1a,b Leading to 2–4, 6, and 7. The reaction of **1a** with methyl crotonate is described as a typical example. Lithium bromide (0.096 g, 1.1 mmol) was added to a solution of **1a** (0.157 g, 1 mmol) in dry THF (3 mL), and the mixture was stirred at room temperature under nitrogen for a few minutes, during which time all the bromide dissolved. After methyl crotonate (0.1 g, 1 mmol)

(13) The competitive Michael addition was carried out with 1 equiv each of imine **1a**, dimethyl fumarate, and dimethyl maleate in the presence of lithium bromide/DBU (1.1:1 equiv/equiv) in THF at −15 °C for 15 min. The unreacted olefins were measured in the ^1H NMR spectrum of the crude reaction mixture (dimethyl fumarate:dimethyl maleate = 1:15).

in THF (1 mL) and DBU (0.152 g, 1 mmol) were added in this order, the resulting mixture was stirred at room temperature for 10 min. Saturated aqueous ammonium chloride (NH_4Cl, 10 mL) was added, and the organic compounds were extracted with diethyl ether (Et_2O, 30 mL × 3). The combined extracts were dried over magnesium sulfate ($MgSO_4$) and evaporated in vacuo. The residue was almost pure Michael adduct **2b** (0.198 g, 77%) as confirmed by ^1H NMR.

Other reactions were carried out by employing a similar procedure under the reaction conditions shown in Table I, where the results are also listed. All the Michael adducts were too labile to be purified through silica gel column chromatography, serious hydrolytic decomposition having occurred during the attempted purification. Fortunately, the crude product mixtures consisted of single isomers of Michael adducts, in most cases, so that they were submitted to the measurement of spectroscopic data without further purification. Elemental analyses were performed after their conversion into pyrrolidinones or 1-pyrrolines.

Dimethyl (2*R,3*R**)-2-[(2,2-dimethylpropylidene)amino]-3-methylpentanedioate (2b)**: colorless liquid; IR (neat) 3220, 1740, 1700, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J_{Me-3} = 6.6 Hz, 3 H, Me), 1.08 (s, 9 H, *t*-Bu), 2.17 (dd, J_{gem} = 15.7 Hz and J_{4-3} = 8.8 Hz, 1 H, one of H-4), 2.51 (dd, J_{gem} = 15.7 Hz and J_{4-3} = 4.4 Hz, 1 H, the other of H-4), 2.65 (m, 1 H, H-3), 3.63 (d, J_{2-3} = 6.4 Hz, 1 H, H-2), 3.66, 3.72 (each s, each 3 H, COOMe), 7.55 (s, 1 H, N=CH); ^{13}C NMR ($CDCl_3$) δ 20.14 (Me), 26.81 (*t*-Bu), 34.07 (*t*-Bu), 36.90 (C-4), 38.01 (C-3), 51.43, 51.95 (each COOMe), 62.45 (C-2), 172.42, 173.11 (each COOMe), 175.89 (N=CH); MS *m/z* (rel intensity) 257 (M^+, 2), 200 (69), 157 (20), 140 (10), 113 (13), 98 (base peak).

Dimethyl (2*R,3*R**)-2,3-dimethyl-2-[(2,2-dimethylpropylidene)amino]pentanedioate (2c)**: pale yellow liquid; IR (neat) 1740, 1700, 1435, 1245, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J_{Me-3} = 6.6 Hz, 3 H, 3-Me), 1.03 (s, 9 H, *t*-Bu), 1.21 (s, 3 H, 2-Me), 2.12 (dd, J_{gem} = 15.4 Hz and J_{4-3} = 10.3 Hz, 1 H, one of H-4), 2.65 (ddq, J_{3-4} = 10.3 and 3.3 Hz and J_{3-Me} = 6.6 Hz, 1 H, H-3), 2.76 (dd, J_{gem} = 15.4 Hz and J_{4-3} = 3.3 Hz, 1 H, the other of H-4), 3.67, 3.70 (each s, each 3 H, COOMe), 7.41 (s, 1 H, N=CH); ^{13}C NMR ($CDCl_3$) δ 14.99 (3-Me), 18.96 (2-Me), 26.61 (*t*-Bu), 36.60, 36.73, 37.54 (C-3, C-4, and *t*-Bu), 51.43, 51.81 (each COOMe), 70.39 (C-2), 170.29, 173.93 (each COOMe), 174.49 (N=CH).

Dimethyl 4-[(2,2-dimethylpropylidene)amino]-4-(methoxycarbonyl)heptanedioate (3): colorless liquid; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9 H, *t*-Bu), 1.7–2.6 (m, 8 H, CH_2), 3.66 (s, 6 H, COOMe), 3.70 (s, 3 H, COOMe), 7.48 (s, 1 H, N=CH).

Methyl (2*R,3*R**)-2-[(2,2-dimethylpropylidene)amino]-3-methyl-5-oxohexanoate (6a)**: pale yellow liquid; ^1H NMR ($CDCl_3$) δ 0.88 (d, J_{Me-3} = 6.5 Hz, 3 H, Me), 1.09 (s, 9 H, *t*-Bu), 2.13 (s, 3 H, MeCO), 2.2–2.9 (m, 3 H, H-3 and H-4), 3.58 (d, J_{2-3} = 5.6 Hz, 1 H, H-2), 3.71 (s, 3 H, COOMe), 7.50 (s, 1 H, N=CH).

Methyl (2*R,3*S**)-2-[(2,2-dimethylpropylidene)amino]-3-phenyl-5-oxohexanoate (6b)**: colorless liquid; ^1H NMR ($CDCl_3$) δ 1.02 (s, 9 H, *t*-Bu), 2.02 (s, 3 H, MeCO), 2.8–3.0 (m, 2 H, H-4), 3.66 (s, 3 H, COOMe), 3.8–4.0 (m, 2 H, H-2 and H-3), 7.18 (s, 5 H, Ph), 7.27 (s, 1 H, N=CH).

Methyl (2*R,3*S**)-3-*tert*-butyl-2-[(2,2-dimethylpropylidene)amino]-5-oxohexanoate (6c)**: obtained as a mixture with **1a** and (*E*)-5,5-dimethyl-3-hexen-2-one. Purification of **6c** was unsuccessful because of its ready hydrolysis during chromatographic operation. The abstracted ^1H NMR spectrum is as follows: ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, 3-*t*-Bu), 1.07 (s, 9 H, *t*-Bu), 2.37 (dd, J_{gem} = 18.0 Hz and J_{4-3} = 3.7 Hz, 1 H, one of H-4), 2.66 (ddd, J_{3-4} = 7.7 and 3.7 Hz and J_{3-2} = 2.6 Hz, 1 H, H-3), 3.06 (dd, J_{gem} = 18.0 Hz and J_{4-3} = 7.7 Hz, 1 H, the other of H-4), 3.65 (s, 3 H, COOMe), 4.02 (d, J_{2-3} = 2.6 Hz, 1 H, H-2), 7.53 (s, 1 H, N=CH).

Methyl (2*R,3*R**)-2-[(2,2-dimethylpropylidene)amino]-3-methyl-5-phenyl-5-oxopentanoate (6d)**: pale yellow liquid; ^1H NMR ($CDCl_3$) δ 0.96 (d, J_{Me-3} = 6.5 Hz, 3 H, Me), 1.10 (s, 9 H, *t*-Bu), 2.6–3.6 (m, 3 H, H-3 and H-4), 3.70 (s, 3 H, COOMe), 3.71 (overlapping with COOMe, 1 H, H-2), 7.3–7.6 (m, 3 H, Ph), 7.53 (s, 1 H, N=CH), 7.9–8.0 (m, 2 H, Ph).

Methyl (2*R,3*S**)-2-[(2,2-dimethylpropylidene)amino]-3-[(*E*)-2-phenylethenyl]-5-phenyl-5-oxopentanoate (6e)**: yellow solid; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9 H, *t*-Bu), 2.9–3.6 (m, 3 H, H-3 and H-4), 3.62 (s, 3 H, COOMe), 3.98 (d, J_{2-3} = 7.0 Hz, 1 H, H-2), 6.05 (dd, J_{trans} = 16.5 Hz and J_{CH-3} = 9.0 Hz, 1 H, =CH), 6.42 (d, J_{trans} = 16.5 Hz, 1 H, =CH), 7.19 (s, 5 H, Ph), 7.3–7.5 (m, 3 H, Ph), 7.55 (s, 1 H, N=CH), 7.9–8.0 (m, 2 H, Ph).

Dimethyl (2*R,3*R**)-3-(methoxycarbonyl)-2-[(2,2-dimethylpropylidene)amino]pentanedioate (7a)**: colorless liquid; IR (neat) 1730, 1660, 1430, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9 H, *t*-Bu), 2.67 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 4.8 Hz, 1 H, one of H-4), 2.77 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 8.1 Hz, 1 H, the other of H-4), 3.61 (ddd, J_{3-4} = 8.1 and 4.8 Hz and J_{3-2} = 6.6 Hz, 1 H, H-3), 3.66, 3.68, 3.73 (each s, each 3 H, COOMe), 4.19 (d, J_{2-3} = 6.6 Hz, 1 H, H-2), 7.55 (s, 1 H, N=CH); ^{13}C NMR ($CDCl_3$) δ 26.59, 31.76 (each *t*-Bu), 36.73 (C-4), 43.77 (C-2), 51.72, 52.08, 52.38 (each COOMe), 71.77 (C-2), 170.85, 172.10, 172.39 (each COOMe), 177.47 (N=CH); MS *m/z* (rel intensity) 301 (M^+, base peak), 286 (17), 270 (20), 244 (40), 242 (62), 228 (76), 213 (15), 212 (18), 186 (16), 174 (21), 113 (25).

Dimethyl (2*R,3*S**)-3-(methoxycarbonyl)-2-[(2,2-dimethylpropylidene)amino]pentanedioate (7b)**: colorless liquid; IR (neat) 1740, 1665, 1440, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9 H, *t*-Bu), 2.62 (dd, J_{gem} = 13.2 Hz and J_{4-3} = 4.8 Hz, 1 H, one of H-4), 2.82 (dd, J_{gem} = 13.2 Hz and J_{4-3} = 9.5 Hz, 1 H, the other of H-4), 3.49 (m, 1 H, H-3), 3.69 (s, 6 H, COOMe), 3.73 (s, 3 H, COOMe), 4.07 (d, J_{2-3} = 5.9 Hz, 1 H, H-2), 7.59 (s, 1 H, N=CH); ^{13}C NMR ($CDCl_3$) δ 26.62, 32.48 (each *t*-Bu), 36.69 (C-4), 44.62 (C-3), 51.79, 51.98, 52.37 (each COOMe), 72.41 (C-2), 172.13, 172.19 (each COOMe), 177.43 (N=CH); MS *m/z* (rel intensity) 301 (M^+, 69), 286 (23), 270 (28), 244 (24), 243 (14), 242 (base peak), 241 (17), 228 (89), 210 (17), 186 (13), 182 (13), 142 (13).

Dimethyl (2*R,3*R**)-3-(methoxycarbonyl)-2-methyl-2-[(2,2-dimethylpropylidene)amino]pentanedioate (7c)**: pale yellow liquid; ^1H NMR ($CDCl_3$) δ 1.02 (s, 9 H, *t*-Bu), 1.26 (s, 3 H, Me), 2.80 (dd, J_{gem} = 16.9 Hz and J_{4-3} = 9.9 Hz, 1 H, one of H-4), 2.91 (dd, J_{gem} = 16.9 Hz and J_{4-3} = 4.4 Hz, 1 H, the other of H-4), 3.67, 3.69, 3.73 (each s, each 3 H, COOMe), 3.76 (dd, J_{3-4} = 9.9 and 4.4 Hz, 1 H, H-3), 7.40 (s, 1 H, N=CH).

Dimethyl (2*R,3*S**)-3-(methoxycarbonyl)-2-methyl-2-[(2,2-dimethylpropylidene)amino]pentanedioate (7d)**: pale yellow liquid; ^1H NMR ($CDCl_3$) δ 1.02 (s, 9 H, *t*-Bu), 1.42 (s, 3 H, Me), 2.58 (dd, J_{gem} = 13.2 Hz and J_{4-3} = 3.7 Hz, 1 H, one of H-4), 2.82 (dd, J_{gem} = 13.2 Hz and J_{4-3} = 10.3 Hz, 1 H, the other of H-4), 3.54 (dd, J_{3-4} = 10.3 and 3.7 Hz, 1 H, H-3), 3.67, 3.68, 3.72 (each s, each 3 H, COOMe), 7.44 (s, 1 H, N=CH); ^{13}C NMR ($CDCl_3$) δ 21.90 (Me), 26.49, 32.54 (each *t*-Bu), 36.79 (C-4), 49.50 (C-3), 51.92, 52.14 (each COOMe), 68.49 (C-2), 171.44, 172.71, 172.88, 172.92 (COOMe and N=CH); MS *m/z* (rel intensity) 315 M^+, 4), 301 (11), 300 (73), 257 (14), 256 (base peak), 232 (36), 200 (13), 171 (10), 170 (17).

Cycloaddition of Imine 1a with Methyl Crotonate in the Presence of LDA or *tert*-Butylmagnesium Chloride Leading to 5. To a solution of **1a** (0.314 g, 2 mmol) in dry THF (3 mL) was added, under nitrogen at room temperature, *tert*-butylmagnesium chloride (1.1 M solution in THF, 1.82 mL, 2 mmol). After the addition of methyl crotonate (0.32 mL, 3 mmol), the resulting mixture was stirred at room temperature for 19 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with dichloromethane (CH_2Cl_2, 40 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using chloroform ($CHCl_3$) as an eluent to give **5** (0.454 g, 88%): pale yellow viscous liquid; IR (neat) 3440, 1740, 1710, 1430, 1190, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H, *t*-Bu), 2.21 (d, J_{Me-3} = 7.3 Hz, 3 H, 3-Me), 2.5–2.6 (m, 2 H, H-3 and H-4), 2.80 (br s, 1 H, NH), 2.97 (d, J_{5-4} = 5.9 Hz, 1 H, H-5), 3.38 (d, J_{2-3} = 4.8 Hz, 1 H, H-2), 3.63, 3.78 (each s, each 3 H, COOMe); ^{13}C NMR ($CDCl_3$) δ 20.75 (3-Me), 27.43, 32.60 (each *t*-Bu), 44.22 (C-3), 51.47, 52.09 (each COOMe), 53.06 (C-4), 67.76 (C-2), 71.99 (C-5); MS *m/z* (15 eV, rel intensity) 257 (M^+, 1), 201 (11), 200 (base peak); HRMS calcd for $C_{13}H_{23}NO_4$ M 257.1626, found *m/z* 257.1622.

The same compound **5** was also obtained by another route: To a solution of **1a** (0.314 g, 2 mmol) in dry THF (3 mL) was added, at −78 °C, a solution of lithium diisopropylamide in THF (5 mL) freshly prepared from diisopropylamine (0.28 mL, 2 mmol) and butyllithium (1.5 M in hexane, 1.34 mL, 2 mmol). After 10 min, methyl crotonate (0.32 mL, 3 mmol) was added, and stirring was

continued at −78 °C for 18 h. The mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (25 mL × 3). The combined extracts were treated by the method described above, to give **5** (0.415 g, 81%).

General Procedures for the Hydrolytic Cyclization of the Michael Adducts Leading to 8–11. As a typical example, the hydrolytic cyclization of **3** is described as follows. A solution of **3** (0.234 g, 0.71 mmol) in aqueous methanol (methanol, 4 mL; water, 1 mL) containing a few drops of acetic acid was stirred at room temperature for 14 h. All the volatile materials were evaporated in vacuo, and the residue was treated with saturated aqueous sodium hydrogen carbonate (5 mL). After addition of water (5 mL), the products were extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using CH_2Cl_2/ethyl acetate (EtOAc, 1:2 v/v), to give **8a** (0.157 g, 97%).

Other hydrolytic cyclizations were carried out under the reaction conditions listed in Table II, where all the results are summarized.

Methyl 2-[2-(methoxycarbonyl)ethyl]-5-oxo-2-pyrrolidinecarboxylate (8a): colorless prisms [purified by silica gel column chromatography on silica gel with CH_2Cl_2/EtOAc (1:2 v/v) and then crystallization from diethyl ether (Et_2O)]; mp 112–113 °C; IR (KBr) 3200, 1730, 1680, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0–2.5 (m, 8 H, CH_2), 3.68, 3.77 (each s, each 3 H, COOMe), 7.36 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 28.97, 29.72, 30.60, 33.72 (each CH_2), 51.92, 52.84 (each COOMe), 65.02 (C-2), 172.90, 173.62 (each COOMe), 177.43 (C-5); MS *m/z* (rel intensity) 230 (M^+ + 1, 1), 170 (base peak), 138 (14). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.65; H, 6.49; N, 6.00.

Methyl *trans*-3-methyl-5-oxo-2-pyrrolidinecarboxylate (8b): colorless prisms [silica gel column chromatography with $CHCl_3$/EtOAc (1:2 v/v) and then crystallization from Et_2O]; mp 67–68.5 °C; IR (neat) 3300, 1740, 1700, 1440, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, J_{Me-3} = 6.6 Hz, 3 H, 3-Me), 2.02 (dd, J_{gem} = 20.2 Hz and J_{4-3} = 10.3 Hz, 1 H, one of H-4), 2.4–2.7 (m, 2 H, H-3 and the other of H-4), 3.78 (s, 3 H, COOMe), 3.84 (d, J_{2-3} = 5.1 Hz, 1 H, 2-H), 6.91 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 20.11 (3-Me), 34.08 (C-3), 37.98 (C-4), 52.53 (COOMe), 62.58 (C-2), 172.28 (COOMe), 177.39 (C-5); MS *m/z* (rel intensity) 158 (M^+ + 1, 8), 157 (M^+, 19), 98 (base peak), 55 (55), 42 (10). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.47; H, 7.06; N, 8.92. Found: C, 53.21; H, 6.96; N, 8.86.

Methyl *cis*-2,3-dimethyl-5-oxo-2-pyrrolidinecarboxylate (8c): colorless liquid [silica gel column chromatography with $CHCl_3$/EtOAc (1:2 v/v)]; IR (neat) 3230, 1735, 1700, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, J_{Me-3} = 7.0 Hz, 3 H, 3-Me), 1.38 (s, 3 H, 2-Me), 2.06 (dd, J_{gem} = 16.5 Hz and J_{4-3} = 8.8 Hz, 1 H, one of H-4), 2.50 (dd, J_{gem} = 16.5 Hz and J_{4-3} = 8.4 Hz, 1 H, the other of H-4), 2.68 (ddq, J_{3-4} = 8.8 and 8.4 Hz and J_{3-Me} = 7.0 Hz, 1 H, H-3), 3.76 (s, 3 H, COOMe), 6.61 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 15.03 (2-Me), 20.09 (3-Me), 36.46 (C-3), 37.90 (C-4), 52.68 (COOMe), 64.56 (C-2), 174.44 (COOMe), 175.86 (C-5); MS *m/z* (rel intensity) 172 (M^+ + 1, 2), 171 (M^+, 1), 112 (base peak), 69 (22); HRMS calcd for $C_8H_{13}NO_3$ M 171.0896, found *m/z* 171.0893.

Methyl *trans*-2,4-dimethyl-1-pyrroline-5-carboxylate (9a): pale yellow liquid [silica gel column chromatography with $CHCl_3$/EtOAc (2:1 v/v)]; IR (neat) 1735, 1640, 1430, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (d, J_{Me-4} = 7.0 Hz, 3 H, 4-Me), 2.09 (br s, 3 H, 2-Me), 2.19 (br dd, J_{gem} = 17.2 Hz and J_{3-4} = 6.7 Hz, 1 H, one of H-3), 2.56 (m, 1 H, H-4), 2.84 (br dd, J_{gem} = 17.2 Hz and J_{3-4} = 8.8 Hz, 1 H, the other of H-3), 3.76 (s, 3 H, COOMe), 4.21 (m, 1 H, 5-H); ^{13}C NMR ($CDCl_3$) δ 19.76, 20.01 (2- and 4-Me), 36.49 (C-3), 47.43 (C-4), 52.09 (COOMe), 80.93 (C-5), 173.27 (COOMe), 178.22 (C-2); MS *m/z* (rel intensity) 155 (M^+, 19), 140 (20), 113 (39), 96 (base peak), 85 (47), 58 (28); HRMS calcd for $C_8H_{12}NO_2$ M 154.0867, found *m/z* 154.0851.

Methyl *trans*-2-methyl-4-phenyl-1-pyrroline-5-carboxylate (9b): yellow liquid [silica gel column chromatography with $CHCl_3$/EtOAc (2:1 v/v)]; IR (neat) 1740, 1645, 1440, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (d, J_{Me-5} = 1.8 Hz, 3 H, Me), 2.72 (br dd, J_{gem} = 18.0 Hz and J_{3-4} = 7.3 Hz, 1 H, one of H-3), 3.16 (ddd, J_{gem} = 18.0 Hz, J_{3-4} = 9.9 Hz, and J_{3-5} = 1.8 Hz, 1 H, the other of H-3), 3.75 (s, 3 H, COOMe), 3.75 (ddd, J_{4-3} = 9.9 and 7.3 Hz and J_{4-5} = 6.6 Hz, 1 H, H-4), 4.71 (m, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 19.78 (Me), 46.62 (C-3), 48.34 (C-4), 52.30 (COOMe), 126.94, 126.86, 128.84, 143.06 (each Ph), 172.74 (COOMe), 177.45 (C-2); MS *m/z* (rel intensity) 218 (M^+ + 1, 9), 217 (M^+, 41), 159 (13), 158 (base peak), 113 (9); HRMS calcd for $C_{13}H_{15}NO_2$ M 217.1104, found *m/z* 217.1103.

Methyl *trans*-4-*tert*-butyl-2-methyl-1-pyrroline-5-carboxylate (9c): colorless liquid [silica gel column chromatography with $CHCl_3$/EtOAc (2:1 v/v)]; IR (neat) 1740, 1650, 1435, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 9 H, *t*-Bu), 2.06 (d, J_{Me-5} = 1.5 Hz, 3 H, Me), 2.3–2.8 (m, 3 H, H-3 and H-4), 3.75 (s, 3 H, COOMe), 4.4–4.5 (m, 1 H, 5-H); ^1H NMR ($CDCl_3$ + CF_3COOH) δ 0.94 (s, 9 H, *t*-Bu), 2.63 (d, J_{Me-5} = 1.5 Hz, 3 H, Me), 2.71 (ddd, J_{4-3} = 9.5 and 4.4 Hz and J_{4-5} = 4.4 Hz, 1 H, H-4), 3.03 (dd, J_{gem} = 21.5 Hz and J_{3-4} = 4.4 Hz, 1 H, one of H-3), 3.30 (ddd, J_{gem} = 21.5 Hz, J_{3-4} = 9.5 Hz, and J_{3-5} = 2.2 Hz, 1 H, the other of H-3), 3.85 (s, 3 H, COOMe), 4.88 (m, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 19.71 (Me), 27.07, 32.05 (each *t*-Bu), 41.61 (C-3), 51.49 (C-4), 52.22 (COOMe), 76.08 (C-5), 174.05 (COOMe), 178.22 (C-2); MS *m/z* (rel intensity) 198 (M^+ + 1, 4), 197 (M^+, 8), 182 (30), 140 (base peak), 138 (41), 113 (21), 97 (17), 85 (16), 82 (26); HRMS calcd for $C_{11}H_{19}NO_2$ M 197.1415, found *m/z* 197.1410.

Methyl *trans*-2,4-diphenyl-1-pyrroline-5-carboxylate (9d): colorless liquid [silica gel column chromatography with $CHCl_3$/EtOAc (1:1 v/v)]; IR (neat) 1735, 1615, 1445, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J_{Me-4} = 6.6 Hz, 3 H, Me), 2.61 (ddd, J_{gem} = 16.1 Hz, J_{3-4} = 6.6 Hz, and J_{3-5} = 1.8 Hz, 1 H, one of H-3), 2.69 (m, 1 H, H-4), 3.33 (ddd, J_{gem} = 16.1 Hz, J_{3-4} = 8.1 Hz, and J_{3-5} = 1.8 Hz, 1 H, the other of H-3), 3.77 (s, 3 H, COOMe), 4.46 (m, 1 H, H-5), 7.3–7.5 (m, 3 H, Ph), 7.90 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.71 (Me), 36.96 (C-3), 52.98 (COOMe and C-4), 82.16 (C-5), 128.78, 129.25, 131.77, 134.80 (each Ph), 173.93 (COOMe), 176.39 (C-2); MS *m/z* (rel intensity) 218 (M^+ + 1, 5), 217 (M^+, 29), 159 (13), 158 (base peak), 105 (21), 55 (24); HRMS calcd for $C_{13}H_{15}NO_2$ M 217.1104, found *m/z* 217.1108.

Methyl *trans*-2-phenyl-4-[(*E*)-2-phenylethenyl]-1-pyrroline-5-carboxylate (9e): colorless prisms [silica gel column chromatography with $CHCl_3$/EtOAc (1:5 v/v) and crystallization from CH_2Cl_2/hexane]; mp 78.5–79 °C dec; IR (KBr) 1735, 1615, 1450, 1340, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (ddd, J_{gem} = 16.2 Hz, J_{3-4} = 7.0 Hz, and J_{3-5} = 2.6 Hz, 1 H, one of H-3), 3.37 (ddd, J_{gem} = 16.2 Hz, J_{3-4} = 8.8 Hz, and J_{3-5} = 2.2 Hz, 1 H, the other of H-3), 3.45 (m, 1 H, H-4), 3.76 (s, 3 H, COOMe), 4.70 (m, 1 H, H-5), 6.21 (dd, J_{trans} = 15.8 Hz and J_{CH-4} = 8.1 Hz, 1 H, =CH), 6.50 (d, J_{trans} = 15.8 Hz, 1 H, =CH), 7.1–7.5 (m, 8 H, Ph), 7.8–7.9 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ 42.22 (C-3), 44.95 (C-4), 52.25 (COOMe), 79.90 (C-5), 126.22, 127.50, 127.99, 128.46, 128.55, 130.08, 131.10, 131.30, 133.57, 136.76 (Ph and CH=CH), 172.43 (COOMe), 175.06 (2-C). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.65; H, 6.28; N, 4.59. Found: C, 78.69; H, 6.55; N, 4.51.

Dimethyl *trans*-5-oxo-2,3-pyrrolidinedicarboxylate (10a): colorless prisms [silica gel column chromatography with $CHCl_3$/EtOAc (2:1 v/v)]; mp 87.5–88 °C; IR (KBr) 3220, 1735, 1675, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.64 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 7.0 Hz, 1 H, one of H-4), 2.72 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 9.5 Hz, the other of H-4), 3.47 (ddd, J_{3-4} = 9.5 and 7.0 Hz and J_{3-2} = 5.1 Hz, 1 H, H-3), 3.79, 3.80 (each s, each 3 H, COOMe), 4.63 (d, J_{2-3} = 5.1 Hz, 1 H, 2-H), 6.81 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 33.04 (C-4), 42.12 (C-3), 52.89, 53.00 (each COOMe), 57.49 (C-2), 170.94, 172.09 (each COOMe), 174.97 (C-5); MS *m/z* (rel intensity) 202 (M^+ + 1, 4), 201 (M^+, 22), 142 (base peak), 141 (34), 114 (28), 98 (17), 83 (13), 82 (24), 59 (17). Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 48.02; H, 5.49; N, 7.04.

Dimethyl *trans*-2-methyl-5-oxo-2,3-pyrrolidinedicarboxylate (10b): colorless prisms [silica gel column chromatography with $CHCl_3$/EtOAc (2:1 v/v)]; mp 154.5–156.5 °C; IR (KBr) 3280, 1735, 1680, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H, Me), 2.56 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 9.2 Hz, 1 H, one of H-4), 2.79 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 6.6 Hz, 1 H, the other of H-4), 3.69 (dd, J_{3-4} = 9.2 and 6.6 Hz, 1 H, H-3), 3.76, 3.81 (each s, each 3 H, COOMe), 7.45 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 21.24 (Me), 32.92 (C-4), 46.06 (C-3), 52.31, 53.26 (each COOMe), 63.55 (C-2), 171.17, 173.00 (each COOMe), 175.37 (C-5); MS *m/z* (rel intensity) 216 (M^+ + 1, 20), 215 (M^+, 3), 156 (base peak). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.14; H, 6.27; N, 6.61.

Dimethyl *cis*-5-oxo-2,3-pyrrolidinedicarboxylate (11a): colorless prisms [silica gel column chromatography with $CHCl_3$/EtOAc (2:1 v/v)]; mp 74.5–76.5 °C; IR (KBr) 3220, 1740, 1630, 1430, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (dd, J_{gem} = 16.9 Hz and J_{4-3} = 9.2 Hz, 1 H, one of H-4), 2.80 (dd, J_{gem} = 16.9 Hz and J_{4-3} = 8.4 Hz, 1 H, the other of H-4), 3.63 (dt, J_{3-4} = 9.2 and 8.4 Hz and J_{3-2} = 8.4 Hz, H-3), 3.72, 3.74 (each s, each 3 H, COOMe), 4.47 (d, J_{2-3} = 8.4 Hz, 1 H, 2-H), 7.48 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 32.70 (C-4), 42.58 (C-3), 52.50, 52.60 (each COOMe), 57.28 (C-2), 170.61, 171.02 (each COOMe), 176.45 (C-5); MS *m/z* (rel intensity) 202 (M^+ + 1, 12), 201 (M^+, 9), 174 (32), 173 (22), 142 (81), 115 (12), 114 (base peak), 88 (42), 82 (22). Anal. Calcd for $C_8H_{11}NO_5$: C, 47.74; H, 5.51; N, 6.97. Found: C, 47.91; H, 5.53; N, 6.84.

Dimethyl *cis*-2-methyl-5-oxo-2,3-pyrrolidinedicarboxylate (11b): colorless prisms [silica gel column chromatography with $CHCl_3$/EtOAc (2:1 v/v)]; mp 110.5–112 °C; IR (KBr) 3160, 1720, 1690, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (s, 3 H, Me), 2.59 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 9.2 Hz, 1 H, one of H-4), 2.89 (dd, J_{gem} = 17.2 Hz and J_{4-3} = 9.5 Hz, 1 H, the other of H-4), 3.20 (dd, J_{3-4} = 9.5 Hz and 9.2 Hz, 1 H, H-3), 3.72 (s, 6 H, COOMe), 7.53 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 24.66 (2-Me), 33.55 (C-4), 50.15 (C-3), 52.38, 52.80 (each COOMe), 64.22 (C-2), 170.89, 172.29 (each COOMe), 175.66 (C-5); MS *m/z* (rel intensity) 216 (M^+ + 1, 2), 215 (M^+, 1), 157 (8), 156 (base peak). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.42; H, 6.18; N, 6.41.

A Novel Carbon–Carbon Bond-Forming Reaction of Triflates with Copper(I)-Catalyzed Grignard Reagents. A New Concise and Enantiospecific Synthesis of (+)-*exo*-Brevicomin, (5*R*,6*S*)-(−)-6-Acetoxy-5-hexadecanolide, and L-Factor[1]

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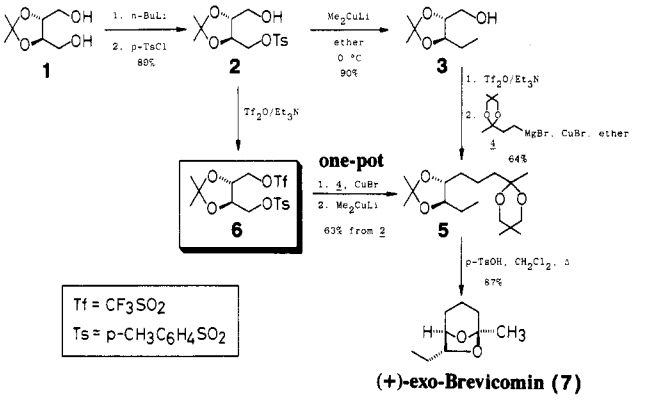
We describe here a full account of a highly concise and enantiospecific synthesis of (+)-*exo*-brevicomin (**7**), (5*R*,6*S*)-(−)-6-acetoxy-5-hexadecanolide (**11**), and L-factor (**16**) originating from D- or L-tartrates as chiral sources. The synthesis employs an efficient carbon–carbon bond-forming reaction of triflates with copper(I)-catalyzed Grignard reagents and, as a consequence, tosyl–triflate derivatives **6** and **15** were found to be a versatile intermediate. This methodology completed the synthetic scheme involving a five-step sequence from **1** to **7**, a 10-step sequence from **2** to **11**, and a seven-step sequence from **12** to **16**. The results present a new rapid means to derive optically active natural products from readily available chiral building blocks.

In recent years, a great deal of success has been achieved in the field of total synthesis of optically active natural products from readily available chiral building blocks.[2] In spite of these enormous advances for amplifying such a convenient chiral source, frequently it becomes a serious problem to elaborate the side chain on the carbon center bearing a β-oxygen functionality.[3,4] However, because of the electron-withdrawing nature of β-oxygen it is generally accepted that alkylation through nucleophilic displacement reaction is not so easy[5] except for the use of highly reactive nucleophiles such as organocuprate reagents.[6,7] To circumvent this difficulty, the usual method consists of alkylation on the epoxide intermediates (eq 1)[8] or oxidation to the corresponding aldehydes followed by Wittig-type olefination (eq 2).[9] More recently, as an alternative ap-

Scheme I



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