Nonstabilized Azomethine Ylides Generated by Decarboxylative Condensation of α-Amino Acids. Structural Variation, Reactivity, and Stereoselectivity

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A variety of aldehydes, containing enolizable aldehydes other than acetaldehyde can be used in the generation method of nonstabilized azomethine ylides by decarboxylative condensation of α-amino acids. Reactivity of the nonstabilized ylides was examined in intermolecular and intramolecular cycloadditions with olefins; stereoselectivity of the intramolecular cycloaddition using nonstabilized ylides was compared with that of ester-stabilized ylides.

Condensation of α-amino esters or related derivatives with carbonyl compounds[1-4] and decarboxylative condensation of α-amino acids[2,4-11] offer a direct and general generation method for carbonyl-stabilized and nonstabilized azomethine ylides, respectively. These two methods can be termed "a deprotonation route" and "a decarboxylation route" for the generation of azomethine ylide 1,3-dipoles.[12]

It was observed in the previous work that two competitive deprotonations took place from the iminium intermediates **A** when an enolizable aldehyde was used in the deprotonation route.[3] One was deprotonation at the α-position (path a in Fig. 1) leading to azomethine ylides **B** and the other at the β′-position leading to enamines **C** (path b). The condensation of ethyl (methylamino)acetate (R=Me) with acetaldehyde exclusively led to enamine **C** (R″=H), and with propanal the **B** : **C** ratio (R″=Me) was 73 : 27.[3]

In the decarboxylation route, the iminium carboxylate betaines **D** must undergo a rapid cyclization into 5-oxazolidinone intermediates, which then lose carbon dioxide to generate nonstabilized azomethine ylides **E**.[2,11] It is therefore expected that a side reaction forming enamine intermediates would be effectively suppressed. However, only limited examples are known for the use of enolizable aldehydes in the decarboxylation route.[5,7,10] In most preceding cases, only aromatic aldehydes and formaldehyde were employed.

Ester-stabilized azomethine ylides, generated from the deprotonation route, have been well studied in terms of ylide structure, reactivity of ylide, and regio- and stereoselectivity of their cycloaddition.[3] However such chemical properties of nonstabilized azomethine ylides, generated by the decarboxylation route, remain unsolved. In most cases, nonstabilized ylides were applied to the reaction with highly activated dipolarophiles such as maleimides and showed a satisfactory reactivity.[5,6,9-11] It is very exceptional that *C*-unsubstituted ylides and its *C*-phenyl derivative reacted with less reactive olefins.[9] In intramolecular versions, however, nonstabilized ylides can be successfully trapped even with nonactivated olefin dipolarophiles.[2,5-7]

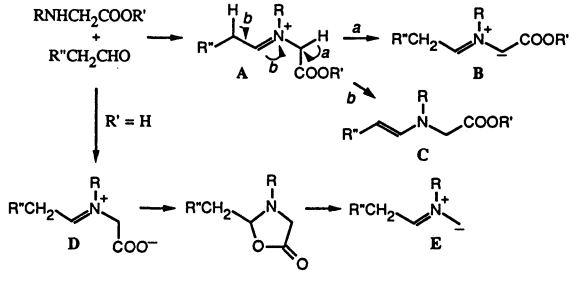


Fig. 1. Generation of azomethine ylides by the deprotonation route and the decarboxylation route.

In the present article, several aldehydes are used in the decarboxylation route of azomethine ylide generation to see the scope and limitation of this method, and the reactivity of the resulting nonstabilized ylides both in inter- and intramolecular cycloadditions. Stereochemical selectivity is also briefly discussed.

Results and Discussion

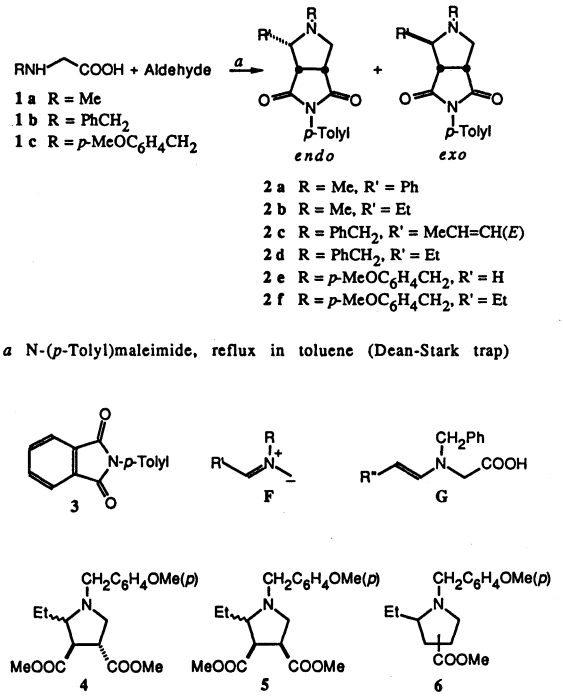
Three *N*-substituted aminoacetic acids, (methylamino)- (**1a**) (benzylamino)- (**1b**), and (*p*-methoxybenzylamino)acetic acid (**1c**), were employed in the decarboxylation route. The benzyl and *p*-methoxybenzyl *N*-protecting groups were selected because they would be readily removed, after cycloaddition by hydrogenation and quinone oxidation, respectively. These α-amino acids were heated with a variety of aldehydes under reflux in toluene and the resulting ylides were trapped with *N*-(*p*-tolyl)maleimide, a highly reactive dipolarophile (Scheme 1 and Table 1).

Though the condensation reaction of (methylamino)acetic acid **1a** with benzaldehyde was previously reported,[9] the result is again listed in Table 1 in order to compare it with other results. Use of crotonaldehyde and paraformaldehyde in the condensation with **1b** and **1c**, respectively, gave no difficulty to generate the corresponding azomethine ylides **F** (R′=MeCH=CH(*E*) and H), while the yield of cycloadduct **2c** from the α,β-unsaturated aldehyde was

Table 1. Decarboxylative Condensation of α-Amino Acids **1a—c** with Aldehydes and Trap of the Resulting Nonstabilized Azomethine Ylides with Olefins

1	Aldehyde	Dipolarophile	Conditions[a]	Product	Yield/%[b]	endo:exo
1a	PhCHO	*N*-(*p*-Tolyl)maleimide	1 h	**2a**	86	5:2[c,d]
1a	EtCHO	*N*-(*p*-Tolyl)maleimide	2 h	**2b**	86	38:48[e]
1b	MeCH=CHCHO(*E*)	*N*-(*p*-Tolyl)maleimide	2 h	**2c**	58	23:35[e]
1b	MeCHO	*N*-(*p*-Tolyl)maleimide	30 min	**2c+3**	72+18	2:3[c,d]
1b	EtCHO	*N*-(*p*-Tolyl)maleimide	2 h	**2d**	84	3:2[c,d]
1c	HCHO	*N*-(*p*-Tolyl)maleimide	10 min	**2e**	100	—
1c	EtCHO	*N*-(*p*-Tolyl)maleimide	50 min	**2f**	74	33:41[e]
1c	EtCHO	Dimethyl fumarate	30 min	**4**	80	52:48[f]
1c	EtCHO	Dimethyl maleate	2 h	**5**	28	20:8[e]
1c	EtCHO	Methyl acrylate	2 h	**6**	39	f,g)

a) Under reflux in dry toluene. b) Yield of isolated products. c) Isomer ratio was determined by ^{1}H NMR. d) Each isomer was separated through column chromatograhy. e) Ratio of isolated isomers. f) Determined by GLC. g) An inseparable mixture of more than three isomers.



Scheme 1.

rather low.

The reaction of α-amino acid **1b** with acetaldehyde, the simplest enolizable aldehyde, under similar conditions resulted in the exclusive formation of enamine intermediate **G** (R″=H), which then underwent further condensation with another molecule of acetaldehyde to generate (1-propenyl)-substituted azomethine ylide **F** (R′=MeCH=CH(*E*)) or dienamine **G** (R″=CH_2=CH). The ylide **F** reacted with *N*-(*p*-tolyl)-maleimide to give cycloadduct **2c** (54%) while the diene **G** underwent a Diels-Alder reaction with the maleimide to afford phthalimide **3** (18%) after deamination and aromatization. A similar Diels-Alder reaction leading to the dihydro derivative of **3** was previously observed in the deprotonation route using acetaldehyde and ethyl (methylamino)acetate.[3]

In contrast with the above disappointing result, a promising feature of the decarboxylation route was unveiled in the reaction of **1a—c** with propanal, the second simplest enolizable aldehyde. The only products **2b, d, f** obtained in better than 80% yields were the cycloadducts of ethyl-substituted azomethine ylide **F** (R′=Et), no enamine intermediate being even detected. This indicates that any alkyl groups except methyl may be directly introduced from aldehyde to nonstabilized azomethine ylides, and this must be a very important synthetic advantage of the decarboxylation route over the deprotonation route.

The maleimide cycloadducts **2a—f** were all mixtures of endo (or 3a,4-cis) and exo (or 3a,4-trans) isomers, however they could be separated from each other by column chromatography over silica gel.

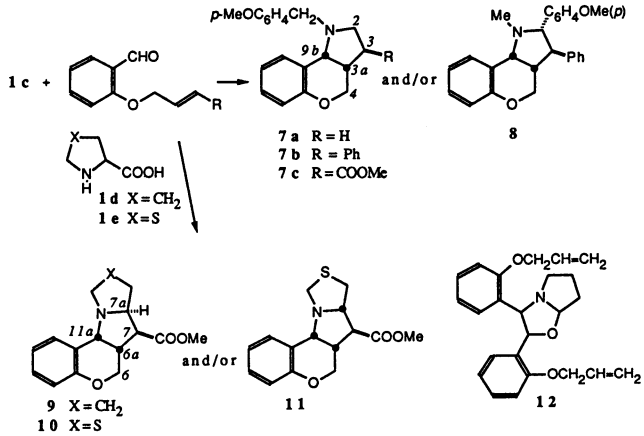
The stereostructures of **2a—f** were determined mainly on the basis of ^{1}H NMR spectra. A stereostructural inspection using molecular models indicates that the substituent at 4-position of both 3a,4-cis and 3a,4-trans isomers of **2** would occupy an equatorial position so that $J_{6\text{-}6a}$ (trans) of the 3a,4-cis isomers becomes zero. It was found that, in addition, difference of the chemical shifts between two nonequivalent hydrogens of *N*-benzyl and *N*-(*p*-methoxybenzyl) moieties was much smaller in the 3a,4-trans isomers (0.28—0.34 ppm) than that in the cis isomers (0.94—0.99 ppm).

Since only a little is known on the reactivity of azomethine ylides bearing an alkyl moiety as the only *C*-substituent,[7,9] ethyl-substituted ylide **F** (R=*p*-$MeOC_6H_4$, R′=Et) was allowed to react with several olefin dipolarophiles (Scheme 1 and Table 1). With highly activated dipolarophiles such as *N*-(*p*-tolyl)-maleimide and dimethyl fumarate, satisfactory yields of cycloadducts **2d** (74%, 41:33) and **4** (80%, 52:48 (by GLC)) were obtained under mild reaction conditions. However, this ylide **F** showed only a poor reactivity toward dimethyl maleate and methyl acrylate; low yields of cycloadduct **5** (28%, 20:8) and **6** (39%, more than three isomers) resulted, respectively. Although

Table 2. Intramolecular Cycloadditions of Azomethine Ylides Generated by the Decarboxylation Route

Amine	Aldehyde	Conditions[a]	Product	Yield/%[b]
1c	*o*-(CH_2=$CHCH_2O$)C_6H_4CHO	4 h	**7a**	53
1c	*o*-(PhCH=$CHCH_2O$)C_6H_4CHO	5 h[c]	**7b**+**8**	33+16[d]
1c	*o*-(MeOOCCH=$CHCH_2O$)C_6H_4CHO	1 h	**7c**	87
1d	*o*-(MeOOCCH=$CHCH_2O$)C_6H_4CHO	4 h	**9**	70
1e	*o*-(MeOOCCH=$CHCH_2O$)C_6H_4CHO	2 h	**10**+**11**	68+22[d]
1d	*o*-(CH_2=$CHCH_2O$)C_6H_4CHO	2 h	**12**	51

a) Under reflux in dry toluene. b) Yield of isolated prducts. c) Under reflux in xylene. d) Yield of separated products.



Scheme 2.

the structure of each isomer was not specified, both regio- and stereoselectivity were very poor in the latter case.

Thus, the reactivity of nonstabilized azomethine ylides and the stereoselectivity of their cycloaddition were not sufficient enough for the decarboxylation route to be utilized effectively in organic synthesis. Therefore, application of these ylides to intramolecular cycloaddition reaction was investigated next.

Three benzaldehydes having an internal olefin dipolarophile were selected as partners of (*p*-methoxybenzylamino)acetic acid (**1c**). It was not surprsing that the ester-activated olefin showed a high reactivity toward an internal nonstabilized ylide to give cycloadduct **7c** in a regio- and stereoselective manner (Scheme 2 and Table 2). Both nonsubstituted and phenyl-substituted olefins were also sufficiently reactive to produce the cis-fused cycloadducts, **7a**, **b** and **8**.[5-7]

2-Pyrrolidine- (**1d**) and 4-thiazolidinecarboxylic acid (**1e**) similarly reacted with methyl (*E*)-4-(2-formylphenoxy)-2-butenoate to produce the cis-fused cycloadducts **9**—**11** in satisfactory yields. However, a nonactivated internal olefin failed to trap the nonstabilized ylide,[5] an aldehyde cycloadduct **12** being obtained instead as a single stereoisomer.

Stereostructures of cycloadducts **7**—**11** were determined on the basis of coupling constants and the rule of stereospecificity of 1,3-dipolar cycloaddition.[12,13] Especially two medium couplings $J_{3a\text{-}4}$ (5.1 and 8.4 Hz for **7c**) and a medium coupling of $J_{3a\text{-}9b}$ (6.0 for **7c**) of **7**—**8** were informative. The 6a,11a-cis structures of **9**—**11** and the 6a,7a-cis structure of **11** were assigned on the basis of $J_{6a\text{-}6}$ (3.7 and 4.8 Hz for **9**) and a magnetic shielding of 10-Hs (δ=3.76 and 3.99 for **11**; 4.27 and 4.46 for **10**) by the fused benzene ring, respectively.

Cycloadduct **8** corresponds to the product of ylide **I**. The initially generated ylide **H** presumably isomerized into the more stabilized ylide **I** by a 1,3-proton migration (Fig. 2). This indicates that nonstabilized azomethine ylides may behave as bases and may abstract a proton from acidic molecules around if no reactive dipolarophile exists.

Although the intramolecular trap of 1,3-dipole with an (*E*)-olefin dipolarophile is not known so far, the exclusive formation of cis-fused cycloadducts **7a**—**c** must have resulted from the sterically least crowded transition state **J**. Similar selectivity was previously observed in the intramolecular cycloadditions using a terminal olefin.[4-7]

Products **9** and **10** are the cis-fused cycloadducts of

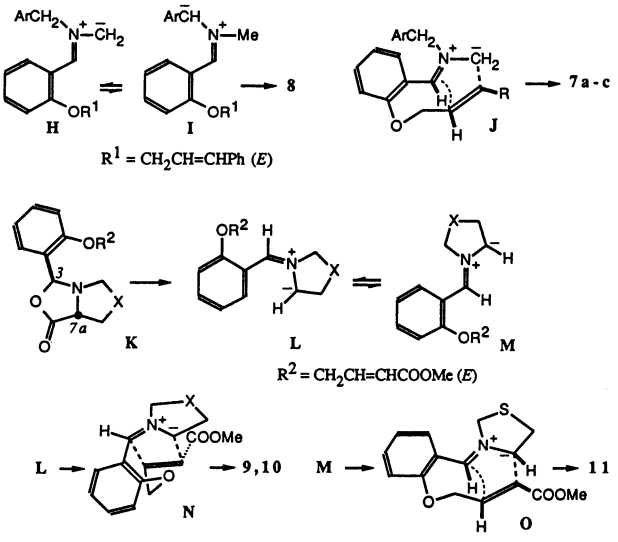


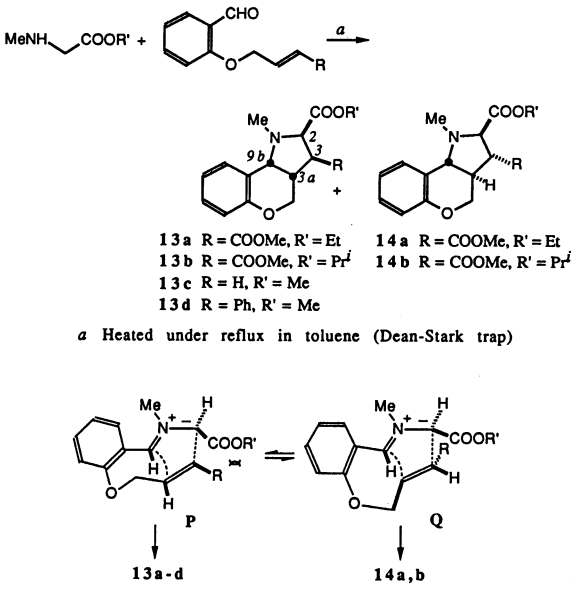
Fig. 2. Stereoselectivity of intramolecular cycloaddition of the nonstabilized azomethine ylides generated by the decarboxylation route.

anti ylides **L** (X=CH_2 and S). Exclusive involvement of **L** (X=CH_2) in the reaction of **1d** was conceivable because of the expected stereospecific extrusion of carbon dioxide from the most favorable 3,7a-trans bicyclic lactone intermediate **K** (X=CH_2).[11] However, there should be a significant steric repulsion between the ester moiety and the five-membered heterocycle in its approach **N** (X=CH_2).

If internal trap of anti ylide **L** is sluggish, **L** equilibrates with syn ylide **M**, which then undergoes a cycloaddition via **O**. The formation of **11**, as a side product, in the reaction of **1e** is the case.[10,11]

Intramolecular cycloadditions of ester-stabilized azomethine ylides were next investigated in order to compare their reactivity and stereoselectivity with those of nonstabilized azomethine ylides. Thus, reaction of ethyl (methylamino)acetate with three benzaldehydes above employed were carried out under similar conditions (Scheme 3). The reactions with unsubstituted and phenyl-substituted internal olefins gave the cis-fused cycloadducts as single isomers, **13c** and **13d**, respectively, of anti forms of ester-stabilized azomethine ylides (Table 3).[4,6]

On the other hand, the reaction with a more reactive ester-activated internal olefin furnished two isomeric cyloadducts **13a** and **14a** in comparable yields.



Scheme 3.

One product **13a** (42%) is cis fused cycloadduct of anti ylide and the other **14a** (44%) trans-fused isomer of anti ylide. A similar result was obtained from the reaction of isopropyl (methylamino)acetate.

These isomeric cycloadducts **13** and **14** were separated from each other by column chromatography over silica gel. The stereostructures of **13a—d** were determined on the basis of two small coupling constants of $J_{3a\text{-}4}$, a magnetic shielding of 2-COOMe by the adjacent phenyl for **13d**, and medium couplings of $J_{2\text{-}3}$ for **13a,b**, and **13d**.

According to a molecular model inspection, 3a-H of isomeric cycloadducts **14a,b** is located antiperiplanar to 3-H, one of 4-Hs, and 9b-H. The observed large couplings among these hydrogens accord with the model structure. A medium coupling of $J_{2\text{-}3}$ confirmed the 2,3-trans stereochemistry.

It was already reported that ester-stabilized azomethine ylides bearing an *N*-substituent participated in cycloadditions in anti forms.[3] In an approach depicted in **P** which leads to the cis-fused cycloadducts **13a—d**, the ester moiety COOR′ derived from α-amino acids and the olefin substituent R close to each other. This approach **P** becomes sterically more favored if R is either small (R=H) or can interact attractively (R=Ph) with the ester moiety. When a steric repulsion exists between COOR′ and R (R=COOMe), the other ring fusion via **Q** competes with **P**.

Formation of trans-fused [5.6] ring systems by intramolecular cycloadditions is quite rare.[14] The competitive participation of such energetically disfavored approach **Q** may be due to a tight structure of the anti forms of ester-stabilized azomethine ylides. This makes a striking contrast with the ready isomerization of nonstabilized ylides, which was shown above in the isomerization example of **N** into **O**.

Thus, it is concluded that (1) the decarboxylation route offers a general preparation method for nonstabilized azomethine ylides, (2) nonstabilized ylides can be effectively trapped intermolecularly by highly activated olefin dipolarophiles such as maleimides and fumarates, (3) nonstabilized ylides can be trapped by nonactivated and phenyl-substituted internal olefins and ester-activated olefins, (4) cis-fused cycloadducts are exclusively produced in intramolecular reaction, (5) the isomerization of nonstabilized ylides can be sufficiently suppressed by the intramolecular cycload-

Table 3. Intramolecular Cycloadditions of Azomethine Ylides Generated by the Deprotonation Route

Amine	Aldehyde	Conditions[a]	Producrt	Yield/%[b]
$MeNHCH_2COOEt$	*o*-(MeOOCCH=$CHCH_2O$)C_6H_4CHO	40 min	**13a+14a**	42+44[c]
$MeNHCH_2COOPr^i$	*o*-(MeOOCCH=$CHCH_2O$)C_6H_4CHO	6 h	**13b+14b**	36+39[c]
$MeNHCH_2COOMe$	*o*-(CH_2=$CHCH_2O$)C_6H_4CHO	1 h	**13c**	53
$MeNHCH_2COOMe$	*o*-(CH_2=$CHCH_2O$)C_6H_4CHO	3 h	**13d**	69

a) Under reflux in dry toluene. b) Yield of isolated products. c) Yield of separated isomers.

ditions using an ester-activated olefin dipolarophile.

Experimental

General. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with a JASCO IRA-1 or a JASCO A-702 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL GSX-270 (270 MHz for ^1H and 67.94 MHz for ^{13}C) and a JEOL FX-100 instrument (100 MHz for ^1H and 25.05 MHz, for ^{13}C). 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 70 eV of ionization energy. Elemental analyses were performed on a Hitachi 026 CHN analyzer. Wakogel C-200, C-300 (Wako), and Silica gel 60 (Merck) were employed for preparative column chromatography. Flash chromatography was carried out on an EYELA EF-10 apparatus using a column (20×180 mm) packed with Silica gel 60 (Merck, size: 0.04—0.063 mm). Gas liquid chromatography (GLC) was accomplished on a Yanaco G-2800 gas chromatograph (Yanagimoto) with an ionization flame detector using a glass column (SE-30, 3×2000 mm) or a glass capillary column (Silicone GE, SE-30, 0.25×50000 mm).

Materials. (Methylamino)acetic acid (**1a**) is commercially available. (Benzylamino)acetic acid (**1b**) and (*p*-methoxybenzylamino)acetic acid (**1c**) were prepared through the condensation of ethyl aminoacetate and aldehydes followed by a reduction with sodium borohydride:[15] The ethyl esters of **1b** and **1c** were first purified by silica-gel chromatography (ethyl acetate-ethanol= 4 : 1 v/v as an eluent) and then hydrolyzed with sodium hydroxide (half an equivalent of the ester used) in aqueous ethanol (75%) at room temperature for 1 h. After 1 M hydrochloric acid (1 M=1 mol dm^{-3}) was added to pH 7, the mixture was evaporated in vacuo and the residue was dried on calcium chloride under vacuum. The resulting α-amino acids **1b** and **1c** containing sodium chloride were used without separation. (3a*R**, 6a*S**)-5-Methyl-4-phenyl-2-(*p*-tolyl)perhydropyrrolo[3,4-*c*]pyrrole-1,3-dione (**2a**)[9] was previously reported.

General Procedure for the Condensations of α-Amino Acids 1a—c with Aldehydes and Trap of the Resulting Azomethine Ylides. A mixture of **1** (2 mmol as a mixture with sodium chloride), an aldehyde (paraformaldehyde and propanal: 5 mmol; crotonaldehyde: 1.5 mmol), and an olefin (1 mmol) was heated under reflux in dry toluene (10—20 ml) with continuous removal of water with the aid of a Dean-Stark trap. Only in the reaction with methyl acrylate, a mixture of **1** (1 mmol), propanal (5 mmol), and methyl acrylate (5 mmol) was employed. After the reaction was complete (checked by TLC), all volatile materials were evaporated in vacuo. The residue was extracted with boiling chloroform (20 ml×2). The chloroform was evaporated and the residue was chromatographed over silica gel by using hexane-ethyl acetate (10 : 1 v/v for **2b,c**; 4 : 1 for **2e, f**; 3 : 1 for **2d**) to give **2a—f** and **3—6**. The reaction conditions and results are summarized in Table 1.

(3a*R,6a*S**)-4-Ethyl-5-methyl-2-(*p*-tolyl)perhydropyrrolo-[3,4-*a*]pyrrole-1,3-dione (2b): 3a,4-*cis*-2b:** Colorless solid; mp 79—81 °C; IR (KBr) 1775, 1700, 1390, and 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.14 (3H, t, *J*=7.0 Hz, Et), 2.4—2.8 (2H, m, Et), 2.21 (1H, m, 4-H), 2.26, 2.37 (each 3H, s, NMe and *p*-Me), 2.40 (1H, dd, J_{gem}=9.5 and J_{6-6a}=7.7 Hz, one of 6-H), 3.22 (1H, dd, J_{3a-4}=8.0 and J_{3a-6a}=7.7 Hz, 3a-H), 3.35 (1H, t, J_{6a-3a}=J_{6a-6}=7.7 Hz, 6a-H), 3.48 (1H, d, J_{gem}=9.5 Hz, the other of 6-H), and 7.1—7.3 (4H, m, Ar); MS *m/z* (rel intensity, %) 272 (M^+, 8), 244 (16), 243 (base peak), and 82 (51). Found: C, 70.57; H, 7.40; N, 10.29%. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.72; H, 7.47; N, 10.19%. **3a,4-*trans*-2b**: Colorless solid; mp 84—86 °C; IR (KBr) 1780, 1705, 1385, and 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.05 (3H, t, *J*=7.5 Hz, Et), 1.48 (1H, ddq, J_{gem}=15.7, *J*= 7.5, and 7.5 Hz, one of Et), 1.84 (1H, ddq, J_{gem}=15.7, *J*=7.5, and 3.2 Hz, the other of Et), 2.34, 2.38 (each 3H, s, NMe and *p*-Me), 2.6—2.7 (2H, m, 3a- and 4-H), 3.15 (1H, dd, J_{gem}=8.6 and J_{6-6a}=5.4 Hz, one of 6-H), 3.38 (1H, t, J_{gem}=J_{6-6a}=8.6 Hz, the other of 6-H), 3.44 (1H, dt, J_{6a-6}=J_{6a-3a}=8.6 and J_{6a-6}=5.4 Hz, 6a-H), 7.15 and 7.27 (each 2H, d, *J*=8.4 Hz, Ar); MS *m/z* (rel intensity, %) 272 (M^+, 7), 243 (base peak), 82 (46), and 57 (59). Found: C, 70.61; H, 7.45; N, 10.38%. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.57; N, 7.40; H, 10.29%.

(3a*R,6a*S**)-5-Benzyl-4-[(*E*)-1-propenyl]-2-(*p*-tolyl)perhydropyrrolo[3,4-*a*]pyrrole-1,3-dione (2c): 3a,4-*cis*-2c:** Pale yellow liquid; IR (neat) 1780 and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.78 (3H, d, *J*=6.5 Hz, MeCH=CH), 2.38 (3H, s, *p*-Me), 3.03 (1H, d, J_{gem}=13.9 Hz, one of $PhCH_2$), 3.13 (1H, dd, J_{gem}=9.2 and J_{6-6a}=8.0 Hz, one of 6-H), 3.22 (1H, dd, J_{3a-6a}=8.0 and J_{3a-4}=7.3Hz, 3a-H), 3.33 (1H, t, J_{6a-3a}=J_{6a-6}=8.0 Hz, 6a-H), 3.42 (1H, d, J_{gem}=9.2 Hz, the other of 6-H), 4.02 (1H, J_{gem}=13.9 Hz, the other of $PhCH_2$), 5.41 (1H, m, =CH), 5.85 (1H, dq, *J*=15.4 and 6.5 Hz, =CH), and 7.0—7.4 (9H, m, Ph and Ar); MS *m/z* (rel intensity, %) 360 (M^+, 4), 91 (45), 86 (50), 84 (68), 59 (22), and 49 (base peak). HRMS Found: *m/z* 360.1839. Calcd for $C_{23}H_{24}N_2O_2$: M, 360.1838. **3a,4-*trans*-2c:** Pale yellow liquid; IR (neat) 1770 and 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.76 (3H, dd, *J*=6.3 and 1.5 Hz, MeCH=CH), 2.38 (3H, s, *p*-Me), 3.01 (1H, dd, J_{gem}=9.7 and J_{6-6a}=3.9 Hz, one of 6-H), 3.16 (1H, dd, J_{gem}=9.7 and J_{6-6a}=8.3 Hz, the other of 6-H), 3.3—3.9 (3H, m, 3a-, 4-, and 6a-H), 3.48 (1H, J_{gem}=13.5 Hz, one of $PhCH_2$), 3.76 (1H, J_{gem}=13.5 Hz, the other of $PhCH_2$), 5.5—5.9, 6.0—6.4 (each 1H, CH=CH), and 7.1—7.4 (9H, m, Ph and Ar); MS *m/z* (rel intensity, %) 360 (M^+, 5), 239 (28), 210 (29), 108 (28), 107 (25), 106 (31), 105 (20), 91 (base peak), 86 (45), 84 (72), 79 (38), and 77 (32). HRMS Found: *m/z* 360.1837. Calcd for $C_{23}H_{24}N_2O_2$: M, 360.1836.

(3a*R,6a*S**)-5-Benzyl-4-ethyl-2-(*p*-tolyl)perhydropyrrolo-[3,4-*a*]pyrrole-1,3-dione (2d): 3a,4-*cis*-2d:** Colorless needles (hexane); mp 98—99 °C; IR (KBr) 1700, 1385, and 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.16 (3H, t, *J*=7.2 Hz, Et), 1.4—2.1 (2H, m, Et), 2.34 (1H, dd, J_{gem}=9.6 and J_{6-6a}=7.5 Hz, one of 6-H), 2.38 (3H, s, *p*-Me), 2.56 (1H, ddd, J_{4-Et}=9.8, 3.2, and J_{4-3a}=7.4 Hz, 4-H), 3.12 (1 H, d, J_{gem}=13.5 Hz, one of $PhCH_2$), 3.19 (1H, dd, J_{3a-6a}=8.0 and J_{3a-4}=7.4 Hz, 3a-H), 3.38 (1H, d, J_{gem}=9.6 Hz, the other of 6-H), 3.39 (1H, dd, J_{6a-3a}=8.0 and J_{6a-6}=7.5 Hz, 6a-H), 4.08 (1H, d, J_{gem}=13.5 Hz, the other of $PhCH_2$), and 7.0—7.4 (9H, m, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ=10.70, 21.17 (each Et), 21.79 (*p*-Me), 42.95 (6a-C), 46.71 (3a-C), 56.24 (6-C), 68.98 (4-C), 126.30, 127.11, 128.30, 129.56, 138.51, 138.80 (each Ph and Ar), 176.00, and 178.45 (each CON); MS *m/z* 348 (M^+, 7), 320 (23), 319 (95), and 91 (base peak). Found: C, 75.93; H, 6.93; N, 8.09%. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.84; H, 6.94; H, 8.04%. **3a,4-*trans*-2d:** Pale yellow prisms (hexane); mp 112—113 °C;

IR (KBr) 1770, 1700, 1370, and 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.04 (3H, t, J=7.2 Hz, Et), 1.3—2.0 (2H, m, Et), 2.38 (3H, s, *p*-Me), 2.84 (1H, dd, J_{gem}=9.7 and $J_{6\text{-}6a}$=4.0 Hz, one of 6-H), 3.0—3.5 (4H, m, 3a-, 4-, 6a-H, and the other of 6-H), 3.50, 3.86 (each 1H, d, J_{gem}=13.3 Hz, $PhCH_2$), and 7.0—7.4 (9H, m, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ=9.69 (q, Et), 21.14 (t, Et), 43.94 (d, 6a-C), 49.19 (d, 3a-C), 53.95 (t, 6-C), 55.28 (t, $PhCH_2$), 67.33 (d, 4-C), 126.22, 127.18, 128.28, 128.39, 129.77 (each d, Ar), 138.40, 138.54 (each s, Ar), 177.79, and 178.12 (each s, CON); MS *m/z* (rel intensity, %) 348 (M^+, 4), 319 (85), and 91 (base peak). Found: C, 75.81; H, 6.92; N, 8.01%. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.84; H, 6.94; H, 8.04%.

(3a*R,6a*S**)-5-(*p*-Methoxybenzyl)-2-(*p*-tolyl)perhydropyrrolo[3,4-*a*]pyrrole-1,3-dione (2e):** Colorless prisms (benzene-hexane); mp 139—140 °C; IR (KBr) 1770, 1695, 1505, 1380, 1240, and 1185 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.39 (3H, s, *p*-Me), 2.44, 2.45 (each 1H, dd, J_{gem}=9.9 and J=6.2 Hz, one of 4-H and one of 6-H), 3.29, 3.33 (each 1H, t, $J_{3a\text{-}6a}$=6.2 and J=6.2 Hz, 3a- and 6a-H), 3.38 (2H, d, J_{gem}=9.9 Hz, the other of 4-H and the other of 6-H), 3.56 (2H, s, $ArCH_2$), 3.79 (3H, *p*-OMe), and 6.8—7.3 (8H, m, Ar); MS *m/z* (rel intensity, %) 350 (M^+, 16), 122 (22), and 121 (base peak). Found: C, 72.06; H, 6.25; N, 7.98%. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99%.

(3a*R,6a*S**)-4-Ethyl-5-(*p*-methoxybenzyl)-2-(*p*-tolyl)-perhydropyrrolo[3,4-*a*]pyrrole-1,3-dione (2f): 3a,4-*cis*-2d:** Pale yellow liquid; IR (neat) 1780, 1715, 1510, 1460, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.18 (3H, t, J=7.5 Hz, Et), 1.4—2.1 (2H, m, Et), 2.2—2.7 (2H, m, 4-H and one of 6-H), 2.40 (3H, s, *p*-Me), 3.10 (1H, d, J_{gem}=13.0 Hz, one of $ArCH_2$), 3.18 (1H, dd, $J_{3a\text{-}4}$=8.0 and $J_{3a\text{-}6a}$=7.5 Hz, 3a-H), 3.37 (1H, d, J_{gem}=9.3 Hz, the other of 6-H), 3.47 (1H, t, $J_{6a\text{-}3a}$=$J_{6a\text{-}6}$=7.5 Hz, 6a-H), 3.78 (3H, s, *p*-MeO), 4.04 (1H, d, J_{gem}=13.0 Hz, the other of $ArCH_2$), and 6.7—7.4 (8H, m, Ar), MS *m/z* (rel intensity, %) 378 (M^+, 6), 349 (10), 121 (base peak), and 109 (13). HRMS Found: *m/z* 378.1949. Calcd for $C_{23}H_{26}N_2O_3$: M, 378.1942. **3a,4-*trans*-2d**: Pale yellow liquid; IR (neat) 1780, 1710, 1510, 1380, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.04 (3H, t, J=7.5 Hz, Et), 1.4—2.0 (2H, m, Et), 2.40 (3H, s, *p*-Me), 2.83 (1H, dd, J_{gem}=9.8 and $J_{6\text{-}6a}$=4.3 Hz, one of 6-H), 3.0—3.5 (4H, m, 3a-, 4-, 6a-H, and the other of 6-H), 3.46 (1H, d, J_{gem}=12.9 Hz, one of $ArCH_2$), 3.78 (3H, s, *p*-MeO), 3.80 (1H, J_{gem}=12.9 Hz, the other of $ArCH_2$), and 6.7—7.6 (8H, m, Ar); MS *m/z* (rel intensity, %) 378 (M^+, 3), 349 (16), and 121 (base peak). HRMS Found: *m/z* 378.1951. Calcd for $C_{23}H_{26}N_2O_3$: M, 378.1942.

Dimethyl (3*R,4*R**)-2-Ethyl-1-(*p*-methoxybenzyl)-3,4-pyrrolidinedicarboxylate (4):** Obtained as an inseparable mixture of two stereoisomers (48:51 by GLC). Pale yellow liquid; IR (neat) 1730, 1615, 1510, 1440, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.91 and 0.95 (each 1/2×3H, t, J=7.3 Hz, Et), 1.2—1.8 (2H, m, Et), 2.4—3.9 (5H, m, 2-, 3-, 4-, and 5-H), 3.14, 3.88 (each 1/2×2H, d, J_{gem}=13.2 Hz, $PhCH_2$), 3.36, 3.86 (each 1/2×2H, d, J_{gem}=12.8 Hz, $PhCH_2$), 3.66, 3.67, 3.71, 3.72 (each 1/2×3H, s, COOMe), 3.79, 3.80 (each 1/2×3H, s, *p*-MeO), and 6.8—7.3 (4H, m, Ar); MS *m/z* (rel intensity, %) 335 (M^+, 9), 306 (31), and 121 (base peak). Found: C, 64.47; H, 7.51; N, 4.18%. Calcd for $C_{18}H_{25}NO_5$: C, 64.62; H, 7.62; N, 4.10%.

Dimethyl (3*R,4*S**)-2-Ethyl-1-(*p*-methoxybenzyl)-3,4-pyrrolidinedicarboxylate (5):** Two stereoisomers were obtained in 20 and 8% yields, but the stereostructures could not be determined. The major isomer: Pale yellow liquid; IR (neat) 1730, 1610, 1430, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.96 (3H, t, J=7.5 Hz, Et), 1.4—1.9 (2H, m, Et), 2.5—3.2 (5H, m, 2-, 3-, 4-, and 5-H), 3.24 (1H, d, J_{gem}=12.5 Hz, one of $ArCH_2$), 3.60, 3.64 (each 3H, s, COOMe), 3.76 (3H, s, *p*-MeO), 3.93 (1H, d, J_{gem}=12.5 Hz, the other of $ArCH_2$), and 6.7—7.4 (4H, m, Ar); MS *m/z* (rel intensity, %) 335 (M^+, 4), 121 (base peak), 78 (21), and 77 (45). HRMS Found: *m/z* 335.1728. Calcd for $C_{18}H_{25}NO_5$: M, 335.1731. The minor isomer: Pale yellow liquid; IR (neat) 1730, 1610, 1510, 1430, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (3H, t, J=7.0 Hz, Et), 1.1—2.0 (2H, m, Et), 2.6—3.5 (5H, m, 2-, 3- 4-, and 5-H), 3.36 (1H, d, J_{gem}=13.5 Hz, one of $ArCH_2$), 3.60, 3.68 (each 3H, s, COOMe), 3.77 (3H, s, *p*-MeO), 3.95 (1H, d, J_{gem}=13.5 Hz, the other of $ArCH_2$), and 6.7—7.3 (4H, m, Ar); MS *m/z* (rel intensity, %) 335 (M^+, 8), 138 (67), 137 (36), 121 (base peak), 109 (42), and 77 (26). HRMS Found: *m/z* 335.1729. Calcd for $C_{18}H_{25}NO_5$: M, 335.1731.

Methyl 2-Ethyl-1-(*p*-methoxybenzyl)-3(or 4)-pyrrolidinecarboxylate (6): An inseparable mixture of more than three isomers was obtained as colorless liquid. Only ^1H NMR and mass spectra were taken. ^1H NMR ($CDCl_3$) δ=0.9—1.0 (3H, m, Et), 1.3—2.0 (2H, m, Et), 2.2—3.0 (6H, m, 2-, 3-, 4-, and 5-H), 3.1—3.2 (1H, m, one of $ArCH_2$), 3.65, 3.68, 3.69 (3H, each s, COOMe), 3.79, 3.81 (3H, each s, *p*-MeO), 3.9—4.1 (1H, m, the other of $ArCH_2$), and 6.8—7.3 (4H, m, Ar); MS *m/z* (rel intensity, %) 277 (M^+, 6), 248 (24), and 121 (base peak).

General Procedure for the Reactions of α-Amino Acids 1c—e with *o*-(2-Alkenyloxy)benzaldehydes. A mixture of **1c** (2 mmol as a mixture with sodium chloride) or **1d, e** (1.2 mmol) and an aldehyde (1 mmol) was heated under reflux in dry toluene or xylene (15 ml) with continuous removal of water with the aid of a Dean-Stark trap. After the completion of reaction (checked by TLC), the solvent was removed. The residue was washed with boiling chloroform (20 ml×2). The chloroform was evaporated in vacuo and the residue was chromatographed over silica gel with hexane-ethyl acetate (15:1 v/v for **7b**; 10:1 for **7a**; 6:1 for **7c**; 3:1 for **9—12**) to give **7a—3c**, **8**, and **9—12**. The reaction conditions and results are summarized in Table 2.

(3a*R,9b*S**)-1-(*p*-Methoxybenzyl)-1,2,3,3a,4,9b-hexahydro-[1]benzopyrano[4,3-*b*]pyrrole (7a):** Pale yellow liquid; IR (neat) 1610, 1580, 1460, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.37, 2.01 (each 1H, m, 3-H), 2.15 (1H, br q, J_{gem}=9.7 and $J_{2\text{-}3}$=9.7 Hz, one of 2-H), 2.42 (1H, m, 3a-H), 2.84 (1H, dt, J_{gem}=9.7, $J_{2\text{-}3}$=9.7, and 2.7 Hz, the other of 2-H), 3.15 (1H, d, J_{gem}=12.1 Hz, $ArCH_2$), 3.22 (1H, d, $J_{9b\text{-}3a}$=5.5 H, 9b-H), 3.77 (3H, s, *p*-MeO), 4.01 (1H, dd, J_{gem}=10.0 and $J_{4\text{-}3a}$=5.5 Hz, one of 4-H), 4.07 (1H, dd, J_{gem}=10.0 and $J_{4\text{-}3a}$=9.9 Hz, the other of 4-H), 4.32 (1H, d, J_{gem}=12.1 Hz, $ArCH_2$), and 6.8—7.3 (8H, m, Ar); MS *m/z* (rel intensity, %) 295 (M^+, 24), 174 (22), 131 (17), 122 (14), and 121 (base peak). Found: C, 77.08; H, 6.96; N, 4.32%. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74%.

(3*R,3a*S**,9b*R**)-1-(*p*-Methoxybenzyl)-3-phenyl-1,2,3,3a,4,9b-hexahydro[1]benzopyrano[4,3-*b*]pyrrole (7b):** Pale yellow liquid; IR (neat) 1600, 1580, and 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.30 (1H, dd, J_{gem}=9.5 and $J_{2\text{-}3}$=9.2 Hz, one of 2-H), 2.55 (1H, dddd, $J_{3a\text{-}4}$=7.6, 5.3, $J_{3a\text{-}9b}$=7.0, and $J_{3a\text{-}3}$=5.4 Hz, 3a-H), 2.93 (1H, ddd, $J_{3\text{-}2}$=9.2, 8.4, and $J_{3\text{-}3a}$=5.4 Hz, 3-H), 3.21 (1H, dd, J_{gem}=9.5 and $J_{2\text{-}3}$=8.4 Hz, the other of 2-H), 3.30 (1H, d, J_{gem}=12.5 Hz, $ArCH_2$), 3.66 (1H, d, $J_{9b\text{-}3a}$=7.0 Hz, 9b-H), 3.72 (3H, s, *p*-MeO), 4.07 (1H, dd J_{gem}=10.6 and

$J_{4\text{-}3a}$=5.3 Hz, one of 4-H), 4.09 (1H, dd, J_{gem}=10.6 and $J_{4\text{-}3a}$=7.6 Hz, the other of 4-H), 4.33 (1H, d, J_{gem}=12.5 Hz, $ArCH_2$), and 6.8—7.4 (13H, m, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ=44.10 (3-C), 44.69 (3a-C), 55.10 ($ArCH_2$), 57.31 (*p*-MeO), 61.14 (2-C), 61.64 (9b-C), 67.07 (4-C), 113.55, 117.16, 120.27, 122.57, 126.52, 127.61, 128.58, 128.69, 129.82, 131.44, 143.34, 155.63, and 158.60 (each Ph and Ar); MS *m/z* (rel intensity, %) 371 (M^+, 4), 370 (14), 267 (26), 238 (34), 150 (25), 131 (38), 121 (base peak), 117 (61), 115 (32), 105 (29), 91 (50), and 76 (36). Found: C, 80.83; H, 6.78; N, 3.77%. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77%.

Methyl (3*R,3a*R**,9b*S**)-1-(*p*-Methoxybenzyl)-1,2,3,3a,4,9b-hexahydrohydro[1]benzopyrano[4,3-*b*]pyrrole-3-carboxylate (7c):** Pale yellow liquid; IR (neat) 1740, 1460, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.46 (1H, dd, J_{gem}=10.0 and $J_{2\text{-}3}$=8.0 Hz, one of 2-H), 2.67 (1H, ddd, $J_{3\text{-}2}$=9.0, 8.0, and $J_{3\text{-}3a}$=4.0 Hz, 3-H), 2.77 (1H, m, 3a-H), 3.06 (1H, dd, J_{gem}=10.0 and $J_{2\text{-}3}$=9.0 Hz, the other of 2-H), 3.27 (1H, d, J_{gem}=12.3 Hz, one of $ArCH_2$), 3.51 (1H, d, $J_{9b\text{-}3a}$=6.0 Hz, 9b-H), 3.69 (3H, s, COOMe), 3.76 (3H, s, *p*-MeO), 4.08 (1H, dd, J_{gem}=10.6 and $J_{4\text{-}3a}$=5.1 Hz, one of 4-H), 4.12 (1H, dd, J_{gem}=10.6 and $J_{4\text{-}3a}$=8.4 Hz, the other of 4-H), 4.24 (1H, d, J_{gem}=12.3 Hz, the other of $ArCH_2$), and 6.8—7.2 (8H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=39.37 (d, 3a-C), 43.20 (d, 3-C), 51.92 (q, *p*-MeO), 52.01 (q, COOMe), 54.43 (t, 2-C), 55.17 (t, $ArCH_2$), 60.70 (d, 9b-C), 66.68 (t, 4-C), 113.59, 117.00, 120.24, 121.46, 128.82, 129.69, 131.26 (each d, Ar), 131.53, 155.42, 158.64 (each s, Ar), and 174.42 (s, COOMe); MS *m/z* (rel intensity, %) 353 (M^+, 35), 232 (28), 131 (54), and 121 (base peak). HRMS *m/z* 353.1648. Calcd for $C_{21}H_{23}NO_4$: M, 353.1620.

(2*R,3*S**,3a*R**,9b*S**)-2-(*p*-Methoxyphenyl)-1-methyl-3-phenyl-1,2,3,3a,4,9b-hexahydro[1]benzopyrano[4,3-*b*]-pyrrole (8):** Colorless prisms (benzene); mp 169—171 °C; IR (KBr) 1605, 1450, 1240, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.33 (3H, s, NMe), 3.26 (1H, dddd, $J_{3a\text{-}9b}$=9.1, $J_{3a\text{-}3}$=8.0, $J_{3a\text{-}4}$=2.9, and 1.1 Hz, 3a-H), 3.70 (3H, s, *p*-MeO), 3.91 (1H, dd, $J_{3\text{-}3a}$=8.0 and $J_{3\text{-}2}$=7.7 Hz, 3-H), 3.97 (1H, dd, J_{gem}=11.4 and $J_{4\text{-}3a}$=2.9 Hz, one of 4-H), 4.08 (1H, dd, J_{gem}=11.4 Hz and $J_{4\text{-}3a}$=1.1 Hz, the other of 4-H), 4.11 (1H, d, $J_{2\text{-}3}$=7.7 Hz, 2-H), 4.59 (1H, d, $J_{9b\text{-}3a}$=9.1 Hz, 9b-H), and 6.6—7.4 (13H, m, Ph and Ar); MS *m/z* (rel intensity, %) 371 (M^+, 47), 254 (36), 222 (61), 148 (37), 131 (base peak), 121 (77), 107 (35), and 91 (27). Found: C, 81.08; H, 6.76; N, 3.88%. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77%.

Methyl (6a*R,7*R**,7a*R**,11a*S**)-6a,7a,8,9,10,11a-Hexahydro-6*H*,7*H*-[1]benzopyrano[4′,3′:2,3]pyrrolo[1,5-*a*]pyrrole-7-carboxylate (9):** Colorless liquid; IR (neat) 1730, 1610, 1590, 1490, and 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.3—1.5, 1.8—2.0, 2.8—3.0 (1H, 3H, and 2H, m, 8-H, 9-H, and 10-H, respectively), 3.25 (1H, t, $J_{7\text{-}6a}$=$J_{7\text{-}7a}$=8.8 Hz, 7-H), 3.38 (1H, dddd, $J_{6a\text{-}7}$=8.8, $J_{6a\text{-}11a}$=7.3, $J_{6a\text{-}6}$=4.8, and 3.7 Hz, 6a-H), 3.71 (3H, s, COOMe), 3.81 (1H, dt, $J_{7a\text{-}7}$=8.8, $J_{7a\text{-}8}$=8.8, and 6.7 Hz, 7a-H), 4.03 (1H, d, $J_{11a\text{-}6a}$=7.3 Hz, 11a-H), 4.15 (1H, dd, J_{gem}=10.0 and $J_{6\text{-}6a}$=3.7 Hz, one of 6-H), 4.20 (1H, dd, J_{gem}=10.0 and $J_{6\text{-}6a}$=4.8 Hz, the other of 6-H), and 6.8—7.4 (4H, m, Ar); MS *m/z* (rel intensity, %) 273 (M^+, 23), 174 (35), 145 (45), 144 (28), 132 (41), 131 (base peak), 115 (43), 91 (32), and 77 (20). HRMS Found: *m/z* 273.1360. Calcd for $C_{16}H_{19}NO_3$: M, 273.1364.

Methyl (6a*R,7*R**,7a*S**,11a*S**)-6a,7a,8,11a-Tetrahydro-6*H*,7*H*,10*H*-[1]benzopyrano[4′,3′:2,3]pyrrolo[1,5-*c*]-thiazole-7-carboxylate (10):** Colorless prisms (diethyl ether-hexane); mp 118—119 °C; IR (KBr) 1730, 1440, 1250, and 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.67 (1H, dd, J_{gem}=10.6 and $J_{8\text{-}7a}$=8.8 Hz, one of 8-H), 3.00 (1H, dd, J_{gem}=10.6 and $J_{8\text{-}7a}$=7.3 Hz, the other of 8-H), 3.09 (1H, dddd, $J_{6a\text{-}7}$=$J_{6a\text{-}11a}$=8.8, $J_{6a\text{-}6}$=4.4, and 4.0 Hz, 6a-H), 3.61 (1H, dd, $J_{7\text{-}6a}$=8.8 and $J_{7\text{-}7a}$=6.6 Hz, 7-H), 3.76 (3H, s, COOMe), 3.84 (1H, ddd, $J_{7a\text{-}8}$=8.8, 7.3, and $J_{7a\text{-}7}$=6.6 Hz, 7a-H), 3.91 (1H, d, $J_{11a\text{-}6a}$=8.8 Hz, 11a-H), 3.99 (1H, dd, J_{gem}=11.4 and $J_{6\text{-}6a}$=4.4 Hz, one of 6-H), 4.15 (1H, dd, J_{gem}=11.4 and $J_{6\text{-}6a}$=4.0 Hz, the other of 6-H), 4.27, 4.46 (each 1H, d, J_{gem}=10.4 Hz, 10-H), and 6.9—7.3 (4H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=33.62 (8-C), 38.92 (6a-C), 47.64 (7-C), 52.14 (COOMe), 56.95 (11a-C), 58.47 (10-C), 67.79 (6-C), 70.08 (7a-C), 117.68, 121.88, 128.84, 129.20, 136.02, 155.91 (each Ar), and 172.03 (COOMe); MS *m/z* (rel intensity, %) 291 (M^+, 31), 232 (39), 186 (35), 145 (20), 132 (76), 131 (base peak), 115 (32), 91 (21), and 77 (24). Found: C, 62.00; H, 6.10; N, 4.74%. Calcd for $C_{15}H_{17}NO_3S$: C, 61.84; H, 5.88; N, 4.81%.

Methyl (6a*R,7*R**,7a*R**,11a*S**)-6a,7a,8,11a-Tetrahydro-6*H*,7*H*,10*H*-[1]benzopyrano[4′,3′:2,3]pyrrolo[1,5-*c*]-thiazole-7-carboxylate (11):** Pale yellow liquid; IR (neat) 1730, 1600, 1580, 1450, and 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.56 (1H, dd, $J_{7\text{-}7a}$=7.7 and $J_{7\text{-}6a}$=5.1 Hz, 7-H), 2.69 (1H, dd, J_{gem}=9.9 and $J_{8\text{-}7a}$=7.7 Hz, one of 8-H), 3.09 (1H, dddd, $J_{6a\text{-}6}$=10.0, 5.0, $J_{6a\text{-}11a}$=7.3, and $J_{6a\text{-}7}$=5.1 Hz, 6a-H), 3.13 (1H, dd, J_{gem}=9.9 and $J_{8\text{-}7a}$=5.1 Hz, the other of 8-H), 3.57 (1H, dt, $J_{7a\text{-}7}$=7.7, $J_{7a\text{-}8}$=7.7, and 5.1 Hz, 7a-H), 3.76 (1H, d, J_{gem}=10.0 Hz, one of 10-H), 3.76 (3H, s, COOMe), 3.92 (1H, dd J_{gem}=10.7 and $J_{6\text{-}6a}$=10.0 Hz, one of 6-H), 3.93 (1H, d, $J_{11a\text{-}6a}$=7.3 Hz, 11a-H), 3.99 (1H, d, J_{gem}=10.0 Hz, the other of 10-H), 4.19 (1H, dd, J_{gem}=10.7 and $J_{6\text{-}6a}$=5.0 Hz, the other of 6-H), and 6.9—7.3 (4H, m, Ar); MS *m/z* (rel intensity, %) 291 (M^+, 28), 245 (26), 132 (74), 131 (base peak), 115 (26), 109 (28), 95 (35), 91 (34), 83 (27), 81 (36), and 77 (30). Found: C, 61.46; H, 5.92; H, 4.34%. Calcd for $C_{15}H_{17}NO_3S$: C, 61.84; H, 5.88; N, 4.81%.

2,3-Bis[*o*-(2-propenyloxy)phenyl]perhydropyrrolo[2,1-*b*]-oxazole (12): Colorless liquid; IR (neat) 1640, 1600, 1585, 1490, 1450, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.7—2.3 (4H, m, 6- and 7-H), 2.8—3.3 (2H, m, 5-H), 4.1—4.3 (4H, m, *O*-allyl), 4.46 (1H, d, $J_{2\text{-}3}$=7.8 Hz, 2-H), 4.9—5.2 (4H, m, *O*-allyl), 5.32 (1H, d, $J_{3\text{-}2}$=7.8 Hz, 3-H), 5.2—5.8 (3H, m, 7a-H and *O*-allyl), 6.4—7.4 (6H, m, Ar), and 7.58 (2H, d, J=8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ=24.33 (6-C), 31.56 (7-C), 56.26 (5-C), 68.96, 69.05 (each *O*-allyl), 71.45 (3-C), 81.23 (2-C), 98.44 (7a-C), 111.80 (*O*-allyl), 116.84, 116.95, 121.03, 127.03, 127.93, 128.39, 128.44, 133.37, 133.63, 156.26, and 156.45 (each Ar and *O*-allyl); MS *m/z* (rel intensity, %) 377 (M^+, 3), 215 (47), 214 (20), 174 (base peak), 146 (23), 145 (23), 132 (28), 131 (38), 91 (24), and 77 (23). HRMS Found: *m/z* 377.1986. Calcd for $C_{24}H_{27}NO_3$: M, 377.1989.

General Procedure for the Reactions of α-Amino Esters with *o*-(2-Alkenyloxy)benzaldehydes. A mixture of the hydrochloride of an ester of (methylamino)acetic acid (1.5—2 mmol), an aldehyde (1 mmol), and triethylamine (1.5—2 mmol) was heated under reflux in dry toluene (10 ml) with continuous removal of water with the aid of a Dean-Stark trap. The solvent was removed in vacuo and the residue was chromatographed over silica gel by using hexane-ethyl acetate (7 : 1 v/v for **13c, d**; 4 : 1 for **13a, b** and **14a, b**) to give **13a—d** and **14a, b**. The reaction conditions and results are summarized in Table 2.

Ethyl (2*R,3*S**,3a*S**,9b*R**)-3-Methoxycarbonyl-1-methyl-1,2,3,3a,4,9b-hexahydro[1]benzopyrano[4,3-*b*]pyrrole-2-car-**

boxylate (13a): Pale yellow liquid; IR (neat) 1730, 1600, 1580, 1450, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30 (3H, t, J=7.5 Hz, Et), 2.40 (3H, s, NMe), 3.38 (1H, dddd, J_{3a-9b}=9.2, J_{3a-3}=9.1, J_{3a-4}=3.7, and 1.3 Hz, 3a-H), 3.47 (1H, dd, J_{3-3a}=9.1 and J_{3-2}=7.0 Hz, 3-H), 3.71 (3H, s, COOMe), 3.87 (1H, dd, J_{gem}=11.4 and J_{4-3a}=3.7 Hz, one of 4-H), 4.01 (1H, d, J_{2-3}=7.0 Hz, 2-H), 4.03 (1H, d, J_{9b-3a}=9.2 Hz, 9b-H), 4.19 (1H, dd, J_{gem}=11.4 and J_{4-3a}=1.3 Hz, the other of 4-H), 4.20 (2H, q, J=7.5 Hz, COOEt), and 6.9—7.3 (4H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=14.43 (Et), 35.58 (NMe), 41.71 (3a-C), 47.70 (3-C), 51.94 (COOMe), 59.84 (2-C), 60.47 (COOEt), 67.66 (9b-C), 69.76 (4-C), 118.02, 121.44, 125.18, 128.62, 129.87, 157.24 (each Ar), 170.98, and 171.77 (COOMe and COOEt); MS m/z (rel intensity, %) 319 (M^+, 6), 246 (base peak), 186 (23), and 131 (21). HRMS Found: m/z 319.1340. Calcd for $C_{17}H_{21}NO_5$: M, 319.1418.

Isopropyl (2*R,3*S**,3a*S**,9b*R**)-3-Methoxycarbonyl-1-methyl-1,2,3,3a,4,9b-hexahydro[1]benzopyrano[4,3-*b*]pyrrole-2-carboxylate (13b):** Colorless liquid; IR (neat) 1730, 1610, 1580, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28, 1.29 (each d, J=6.3 Hz, *i*-Pr), 2.40 (3H, s, NMe), 3.40 (1H, dddd, J_{3a-3}=9.2, J_{3a-9b}=8.8, J_{3a-4}=3.5, and 2.2 Hz, 3a-H), 3.47 (1H, dd, J_{3-3a}=9.2 and J_{3-2}=6.6 Hz, 3-H), 3.71 (3H, s, COOMe), 3.88 (1H, dd, J_{gem}=11.5 and J_{4-3a}=3.5 Hz, one of 4-H), 3.98 (1H, d, J_{2-3}=6.6 Hz, 2-H), 4.00 (1H, d, J_{9b-3a}=8.8 Hz, 9b-H), 4.20 (1H, dd, J_{gem}=11.5 and J_{4-3a}=2.2 Hz, the other of 4-H), 5.10 (1H, m, *i*-Pr), and 6.8—7.4 (4H, m, Ar); MS m/z (rel intensity, %) 333 (M^+, 7), 246 (base peak), 186 (27), 131 (28), 85 (27), and 83 (43). HRMS Found: m/z 333.1575. Calcd for $C_{18}H_{23}NO_5$: M, 333.1575.

Methyl (2*R,3a*S**,9b*R**)-1-Methyl-1,2,3,3a,4,9b-hexahydro-[1]benzopyrano[4,3-*b*]pyrrole-2-carboxylate (13c):** Pale yellow liquid; IR (neat) 1730, 1610, 1590, 1490, and 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.96 (1H, ddd, J_{gem}=13.5, J_{3-2}=8.1, and J_{3-3a}=3.9 Hz, one of 3-H), 2.18 (1H, ddd, J_{gem}=13.5, J_{3-3a}=8.1, and J_{3-2}=3.3 Hz, the other of 3-H), 2.45 (3H, s, NMe), 2.64 (1H, m, 3a-H), 3.72 (3H, s, COOMe), 3.74 (1H, dd, J_{2-3}=8.1 and 3.3 Hz, 2-H), 3.88 (1H, dd, J_{gem}=11.0 and J_{4-3a}=8.4 Hz, one of 4-H), 3.96 (1H, dd, J_{gem}=11.0 and J_{4-3a}=4.7 Hz, the other of 4-H), 3.97 (1H, d, J_{9b-3a}=7.0 Hz, 9b-H), and 6.9—7.2 (4H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=30.40 (3-C), 35.02 (3a-C), 35.54 (NMe), 51.29 (COOMe), 58.72 (2-C), 64.00 (9b-C), 68.10 (4-C), 117.20, 120.21, 121.94, 128.63, 131.30, 155.75 (Ar), and 174.31 (COOMe); MS m/z (rel intensity, %) 274 (M^+, 8), 189 (12), 188 (base peak), and 131 (20). HRMS Found: m/z 247.1209. Calcd for $C_{14}H_{17}NO_3$: M, 247.1207.

Methyl (2*R,3*R**,3a*S**,9b*R**)-1-Methyl-3-phenyl-1,2,3,3a,4,9b-hexahydro[1]benzopyrano[4,3-*b*]pyrrole-2-carboxylate (13d):** Colorless prisms (diethyl ether-hexane); mp 148 °C; IR (KBr) 1710, 1580, 1440, and 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.51 (3H, s, NMe), 3.37 (3H, s, COOMe), 3.38 (1H, dddd, J_{3a-3}=9.9, J_{3a-9b}=9.5, J_{3a-4}=3.6, and 2.2 Hz, 3a-H), 3.86 (1H, dd, J_{gem}=11.4 and J_{4-3}=3.6 Hz, one of 4-H), 3.93 (1H, dd, J_{3-3a}=9.9 and J_{3-2}=7.7 Hz, 3-H), 3.96 (1H, dd, J_{gem}=11.4 and J_{4-3a}=2.2 Hz, the other of 4-H), 4.00 (1H, d, J_{2-3}=7.7 Hz, 2-H), 4.40 (1H, d, J_{9b-3a}=9.5 Hz, 9b-H), and 6.9—7.4 (9H, m, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ=35.98 (NMe), 43.48 (3a-C), 48.58 (3-C), 50.67 (COOMe), 60.11 (9b-C), 68.39 (4-C), 72.37 (2-C), 117.99, 121.42, 125.91, 127.41, 128.39, 128.46, 128.55, 129.77, 137.17, 156.80 (each Ph and Ar), and 172.22 (COOMe); MS m/z (rel intensity, %) 323 (M^+, 3), 265 (20), 264 (base peak), and 132 (11). Found: C, 74.22; H, 6.56; N, 4.45%. Calcd for $C_{20}H_{21}NO_3$: C, 74.29; H, 6.55; N, 4.33%.

Ethyl (2*R,3*R**,3a*R**,9b*R**)-3-Methoxycarbonyl-1-methyl-1,2,3,3a,4,9b-hexahydro[1]benzopyrano[4,3-*b*]pyrrole-2-carboxylate (14a):** Pale yellow liquid; IR (neat) 1730, 1610, 1490, 1460, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.31 (3H, t, J=7.0 Hz, Et), 2.54 (3H, s, NMe), 2.66 (1H, dq, J_{3a-3}=J_{3a-9b}=11.0, J_{3a-4}=11.0, and 4.4 Hz, 3a-H), 3.13 (1H, dd, J_{3-3a}=11.0 and J_{3-2}=6.0 Hz, 3-H), 3.74 (3H, s, COOMe), 3.98 (1H, d, J_{9b-3a}=11.0 Hz, 9b-H), 4.15 (1H, d, J_{2-3}=6.0 Hz, 2-H), 4.18 (1H, dd, J_{gem}=10.3 and J_{4-3a}=11.0 Hz, one of 4-H), 4.24 (2H, q, J=7.0 Hz, COOEt), 4.64 (1H, J_{gem}=10.3 and J_{4-3a}=4.4 Hz, the other of 4-H), and 6.8—7.4 (4H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=14.23 (Et), 38.51 (NMe), 41.45 (3a-C), 48.98 (3-C), 52.50 (COOMe), 61.37 (COOEt), 64.58 (2-C), 69.77 (4-C), 71.70 (9b-C), 116.58, 120.23, 123.29, 125.83, 128.23, 154.12 (each Ar), 172.62, and 172.41 (COOMe and COOEt); MS m/z (rel intensity, %) 319 (M^+, 10), 246 (base peak), and 135 (28). HRMS Found: m/z 319.1418. Calcd for $C_{17}H_{21}NO_5$: M, 319.1418.

Isopropyl (2*R,3*R**,3a*R**,9b*R**)-3-Methoxycarbonyl-1-methyl-1,2,3,3a,4,9b-hexahydro[1]benzopyrano[4,3-*b*]-pyrrole-2-carloxylate (14b):** Pale yellow liquid; IR (neat) 1730, 1610, 1490, and 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28, 1.31 (each 3H, d, J=6.2 Hz, *i*-Pr), 2.56 (3H, s, NMe), 2.66 (1H, dq, J_{3a-2}=J_{3a-9b}=11.4, J_{3a-4}=11.4, and 4.4 Hz, 3a-H), 3.07 (1H, dd, J_{3-3a}=11.4 and J_{3-2}=6.0 Hz, 3-H), 3.75 (3H, s, COOMe), 3.99 (1H, d, J_{9b-3a}=11.4 Hz, 9b-H), 4.12 (1H, d, J_{2-3}=6.0 Hz, 2-H), 4.19 (1H, dd, J_{gem}=9.9 and J_{4-3a}=11.4 Hz, one of 4-H), 4.64 (1H, dd, J_{gem}=9.9 and J_{4-3a}=4.4 Hz, the other of 4-H), 5.08 (1H, m, *i*-Pr), and 6.8—7.4 (4H, m, Ar); MS m/z (rel intenity, %) 333 (M^+, 9), 290 (40), 246 (base peak), 214 (20), 187 (22), 186 (54), 161 (20), 131 (42), and 115 (24). HRMS Found: m/z 333.1573. Calcd for $C_{18}H_{23}NO_5$: M, 333.1575.

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