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Synthesis of α,α-Disubstituted α-Amino Esters: Nucleophilic Addition to Iminium Salts Generated from Amino Ketene Silyl Acetals

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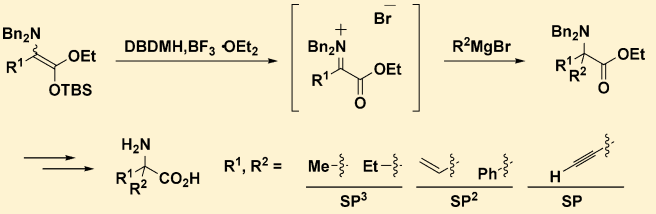
Supporting Information

ABSTRACT: Alkoxycarbonyl iminium species are prepared easily by the oxidation of tetrasubstituted amino ketene silyl acetals, and subsequent nucleophilic addition of Grignard reagents to the iminium salts gives α,α-disubstituted α-amino ester derivatives in moderate to good yields, in which aryl and ethynyl substituents are readily introduced.



INTRODUCTION

α,α-Disubstituted α-amino acids have received considerable attention, because oligopeptides containing them alter the stabilization and the conformation of the secondary structure of the protein.[1] Although various approaches to the synthesis of α,α-disubstituted α-amino acids have been reported,[2] to the best of our knowledge, only a few acceptable methods are known. A practical synthesis of α,α-disubstituted α-amino acids has been achieved using a phase-transfer catalyst.[3] This type of alkylation of the ester enolate has been successfully applied to the synthesis of α-substituted amino acids.[4] However, there are some drawbacks associated with the scope of the reaction. In addition, conventional alkylation approaches are not always applicable to vinylation, arylation, and alkynylation.

Formation of sp^2-sp^3 and $sp-sp^3$ bonds at the position α to carbonyls has recently been resolved by utilizing Pd-catalyzed coupling reactions.[5,6] Although very useful direct α-arylations[6a,b] of ketone,[6c−f] ester,[6g−i] amino ester,[6j−l] and amide[6m] have been reported using palladium catalysts, there still remains a need for a new arylation method for acyclic α,α-disubstituted α-amino esters as well as in the intramolecular cases.[6l]

Consequently, it is of importance to develop methodologies more compatible with the diverse spectra of functional groups. Although more straightforward synthetic approaches involve nucleophilic addition to α-imino esters, they sometimes suffer from lower electrophilicity of the imino moiety as compared with that of α-keto esters, and regio- and chemoselectivity between imino and ester groups is also a critical issue. Except for some reports, the following methods have been used to circumvent the problems: introduction of an electron-withdrawing group at the imino nitrogen moiety, the use of ate complexes as nucleophiles, activation by Lewis acids, and generation of the iminium ions.[4e] For example, iminomalonates, regarded as highly reactive imine derivatives, reacted with organolithium or Grignard reagents to give addition products in moderate yields.[7a,b] In addition, organometallic reagents such as diethylzinc sometimes induced undesirable hydrogenation and N-alkylation as well as C-alkylation of α-imino esters.[7c]

Iminium salts are very reactive and attractive species in organic synthesis. Regarding the synthesis of natural products such as alkaloids, iminium ion mediated cyclization is effective.[8] Reported examples using iminium species involve addition of organometallic reagents for the synthesis of β-amino acids,[9a,b] β-amino ketones, 1,3-amino alcohols,[9c] and so on.[9d−j] Petasis reported the synthesis of α-monosubstituted α-amino acids by the nucleophilic addition of boronates to the iminium ions, which were prepared by the condensation of primary or secondary amines with ethyl glyoxylate in situ.[10] Although the use of iminium ion is a promising procedure, there is much room for the general synthesis of α,α-disubstituted α-amino acids, since only limited examples are available.[10b]

We have recently reported that an alkoxycarbonyl iminium species is generated easily from trisubstituted amino ketene silyl acetal by oxidation, and the subsequent nucleophilic addition of various nucleophiles readily affords the addition products.[11] The applicability of our iminium system would be greatly enhanced with a more convenient synthesis of α,α-disubstituted α-amino acids possessing sp- or sp^2-hybridized carbons: e.g., α,α-diaryl α-amino acids. Therefore, tetrasubstituted amino ketene silyl acetal was chosen as a suitable precursor to the iminium salt. This paper describes a convenient synthesis of α,α-disubstituted α-amino acids, which uses the nucleophilic addition of Grignard reagents to iminum salts generated from amino ketene silyl acetals.

RESULTS AND DISCUSSION

Amino ketene silyl acetals **3a,b** and **4** were prepared from 2-amino esters **1a,b** and **2**. On treatment of ethyl 2-amino propanoates **1a,b** with LDA (Scheme 1, method A) followed by

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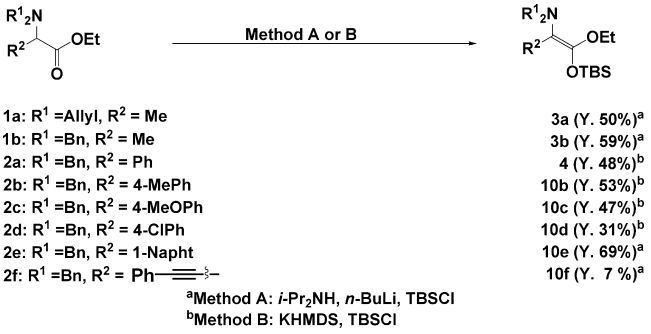
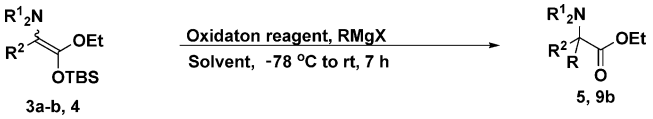
Scheme 1. Preparation of Amino Ketene Silyl Acetals 3, 4, and 10 from 2-Amino Esters



silylation, the desired products **3a,b** were obtained in moderate yields. In the case of ethyl 2-(dibenzylamino)-2-phenylacetate (**2a**), the use of KHMDS as a base gave a better result (method B).

An initial examination was carried out to find a suitable oxidation reagent for the preparation of iminium salt from amino ketene silyl acetals **3a,b** and **4** followed by alkylation with Grignard reagents. Table 1 summarizes the results.

Table 1. Oxidation and Isopropylation or Ethylation of Amino Ketene Silyl Acetals 3a,b and 4



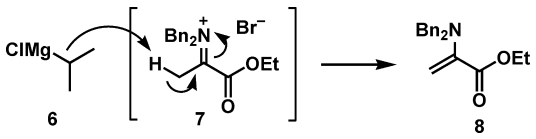
entry	substrate	oxidn reagent	RMgX	solvent	product	yield (%)[a]
1	**3a**	NBS	*i*-PrMgCl	DME	**5a**	0
2	**3a**	NBS	*i*-PrMgCl	THF	**5a**	trace
3	**3a**	NBS	*i*-PrMgCl	Et_2O	**5a**	6
4	**3a**	NBS	*i*-PrMgCl	EtCN	**5a**	22
5	**3a**	$PhI(OAc)_2$	*i*-PrMgCl	EtCN	**5a**	0
6	**3a**	DBDMH	*i*-PrMgCl	EtCN	**5a**	trace
7	**3b**	NBS	*i*-PrMgCl	EtCN	**5b**	7
8	**4**	NBS	*i*-PrMgCl	EtCN	**9d**	53
9	**4**	NBS	*i*-PrMgBr	EtCN	**9d**	64
10	**4**	NBS	EtMgBr	EtCN	**9b**	62
11	**4**	NCS	EtMgBr	EtCN	**9b**	4
12	**4**	NIS	EtMgBr	EtCN	**9b**	56
13	**4**	DCDMH	EtMgBr	EtCN	**9b**	44
14	**4**	DBDMH	EtMgBr	EtCN	**9b**	63
15[b]	**4**	DBDMH	EtMgBr	EtCN	**9b**	73
16	**4**	DIDMH	EtMgBr	EtCN	**9b**	36
17	**4**	$PhI(OAc)_2$	EtMgBr	EtCN	**9b**	0
18	**4**	DDQ	EtMgBr	EtCN	**9b**	10

[a]Reaction conditions: **3a,b** and **4** (0.20 mmol), oxidation reagent (0.20 mmol), RMgX (0.40 mmol), and EtCN (1.0 mL) were used. [b]In the presence of $BF_3{\cdot}OEt_2$ (0.20 mmol).

Although several reaction conditions were investigated (entries 1−7), satisfactory results were not obtained by the oxidation of amino ketene silyl acetal **3** (R^2 = Me) followed by reaction with isopropylmagnesium chloride, presumably due to an undesirable side reaction involving isomerization of the iminium salt **7** into the enamine **8** (Scheme 2).

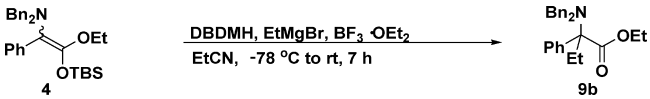
Amino ketene silyl acetal **4** (R^2 = Ph) seemed to be a more suitable substrate because of the ease of oxidation at the benzylic position without a possible isomerization into

Scheme 2. Isomerization of Iminium Salt 7 into Enamine 8



enamine. The reaction of amino ketene silyl acetal **4** with isopropylmagnesium chloride or isopropylmagnesium bromide gave the amino ester **9d** without a side reaction involving isomerization (Table 1, entries 8 and 9). The oxidation reagents were also examined for the preparation of the iminium salt from amino ketene silyl acetal **4** followed by alkylation with ethylmagnesium bromide (entries 10−18). Oxidation with *N*-bromosuccinimide (NBS) or *N,N*-dibromodimethylhydantoin (DBDMH) followed by ethylation gave the amino ester **9b** in moderate yields (entries 10 and 14). In order to improve the yield, the addition of a Lewis acid was investigated next. The presence of $BF_3{\cdot}OEt_2$ was found to be effective to give the desired adduct **9b** in 73% yield (entry 15). The reaction conditions were further investigated regarding the temperature, time, and amounts of reagents and additives (Tables 2 and 3).

Table 2. Examination into Amounts of Reagents



entry	amt of DBDMH (equiv)	amt of EtMgBr (equiv)	amt of $BF_3{\cdot}OEt_2$ (equiv)	yield (%)
1	1.0	1.2	1.0	32
2	1.0	1.5	1.0	59
3	1.0	2.0	1.0	73
4	1.0	2.0	1.5	60
5	1.0	2.0	2.0	62
6	0.5	2.0	1.0	53

The best result was obtained using **4** (0.10 mmol), EtMgBr (0.20 mmol) as a nucleophile, DBDMH (0.055 mmol) as an oxidation reagent, and $BF_3{\cdot}OEt_2$ (0.10 mmol) as an additive in EtCN at 0 °C for 5 min (Table 3, entry 5).

Further studies were carried out to examine the use of alkyl, vinyl, and aryl Grignard reagents. Results of the nucleophilic addition of several Grignard reagents are summarized in Table 4. The reaction of iminium salts derived from amino ketene silyl acetal **4** with Grignard reagents gave the desired product **9** with primary and secondary alkyl, aryl, and vinyl moieties at the α-position in moderate to good yields (entries 1−6 and 8−14). Unfortunately, bulky *tert*-butyl Grignard reagent did not give satisfactory results (entry 7).

The scope of amino ketene silyl acetals was next examined using addition reaction with EtMgBr, and the results are shown in Table 5. The functionalized amino ketene silyl acetals **10** with aryl moieties bearing either electron-withdrawing or electron-donating groups were employed successfully to give the corresponding adducts in moderate to good yields.

The results of the nucleophilic addition of various Grignard reagents with the alkynyl-substituted amino ketene silyl acetal **10f** are shown in Table 6. The alkynyl derivative **10f** was not a suitable substrate for the present oxidative generation of iminium salt followed by nucleophilic addition, and the products were obtained in poor to moderate yields.

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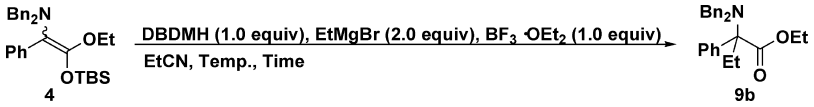
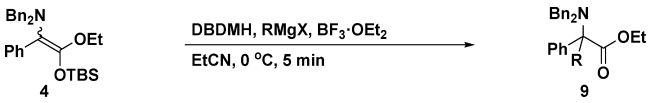
Table 3. Examination into Reaction Temperature and Time



entry	temp and time	yield (%)
1	−78 to −50 °C, 1 h	60
2	−78 °C, 5 min, then room temp, 10 min	71
3	−78 °C, 5 min, then room temp, 30 min	70
4	−78 °C, 5 min, then room temp, 1 h	76
5	0 °C, 5 min	78

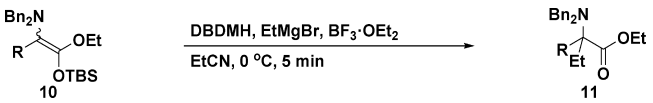
Table 4. Nucleophilic Addition of Grignard Reagents Using 4



entry	RMgX	product	yield (%)
1	MeMgBr	**9a**	83
2	EtMgBr	**9b**	78
3	*n*-PrMgBr	**9c**	80
4	*i*-PrMgBr	**9d**	74
5	c-PrMgBr	**9e**	84[a]
6	c-HexMgBr	**9f**	66
7	*t*-BuMgCl	**9g**	18[b]
8	BnMgCl	**9h**	66
9	(vinyl)MgBr	**9i**	80
10	PhMgBr	**9j**	65
11	4-MeC_6H_4MgBr	**9k**	52
12	4-MeOC_6H_4MgBr	**9l**	56
13	(2-thienyl)MgBr	**9m**	88
14	(ethynyl)MgBr	**9n**	82

[a]The reaction was performed for 30 min. [b]The reaction was performed at −78 °C for 30 min.

Table 5. Nucleophilic Addition of Grignard Reagents Using 10



Entry	R	Product	Yield (%)
1	Ph (**10a**)	**11a**	78
2	4-MePh (**10b**)	**11b**	90
3	4-MeOPh (**10c**)	**11c**	81
4	4-ClPh (**10d**)	**11d**	95
5	1-Napht (**10e**)	**11e**	75
6[a]	Ph—≡—⁝ (**10f**)	**11f**	57

[a]The reaction was performed at −78 °C for 5 min and then at room temperature for 1 h.

A plausible mechanism is shown in Scheme 3. The oxidation of amino ketene silyl acetal **13** gives α-bromo ester **14**, and the subsequent elimination of the bromide ion leads to the formation of iminium salt **15**.[12] It seems that the presence of BF_3·OEt_2 promotes an elimination of the bromide ion or activates the oxidation process as a Lewis acid. Finally, the nucleophilic addition reaction to the iminium salt gives the product **16**.

CONCLUSION

We have studied the generation and reactivity of alkoxycarbonyl iminium salts by the oxidation of amino ketene silyl acetals followed by nucleophilic addition and have found several interesting features. We found that the iminium salts from tetrasubstituted amino ketene silyl acetals, except for the alkynyl-substituted case, were readily prepared using oxidation with *N,N*-dibromodimethylhydantoin and that subsequent nucleophilic addition with several Grignard reagents proceeded in moderate to good yields. Since α,α-disubstituted α-amino acids and oligopeptides containing them have received considerable attention because of their biological interest, for a more systematic study of these useful molecules, this methodology provides us with a straightforward access to them with alkyl, aryl, and vinyl moieties at the α-position, and an easy entry into reactive iminium salts is also shown.

EXPERIMENTAL SECTION

General Considerations. ^{1}H NMR and ^{13}C NMR spectra were recorded on 270, 400, and/or 500 MHz spectrometers using tetramethylsilane as an internal standard. Infrared spectra were determined on an FT-IR spectrometer with the substance as a neat film on a NaCl plate or as a pellet in a mixture with KBr. Mass spectra were recorded on EI, AccuTOFF, and/or CI spectrometers. All solvents were dried and distilled according to standard procedures prior to use. Purification of products was performed by column chromatography on silica gel (silica gel 60 N (spherical, neutral)) and/or preparative TLC on silica gel (Kiesel Gel PF254). All reactions were carried out under an argon atmosphere. KHMDS, *n*-butyllithium, methylmagnesium bromide, vinymagnesium bromide, and ethynylmagnesium bromide were purchased and used as received. Other Grignard reagents were prepared by the usual methods using the appropriate alkyl (aryl) halides and magnesium.

Preparation of 2-Amino Esters 1a,b and 2a−2e. *Typical Procedure for **1a,b**.* Under an argon atmosphere, to a solution of ethyl 2-bromopropionate (20.9 g, 115 mmol) in EtOH (30.0 mL) was added diallylamine (15.6 mL, 127 mmol). After the reaction mixture was refluxed for 19 h, it was concentrated in vacuo, followed by addition of 1 M aqueous NaOH. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (70 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 10/1) to give ethyl 2-(diallylamino)propanoate (**1a**; 65%, 15.0 g).

*Ethyl 2-(Diallylamino)propanoate (**1a**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.3 Hz, 6H), 3.14 (dd, *J* = 6.9, 14.6 Hz, 2H), 3.28 (dd, *J* = 5.5, 14.6 Hz, 2H), 3.58 (q, *J* = 7.3 Hz, 1H), 4.10−4.22 (m, 2H), 5.10 (dd, *J* = 1.9, 10.0 Hz, 2H), 5.19 (dd, *J* = 1.9, 17.4 Hz, 2H), 5.76−7.86 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.3, 14.8, 53.5, 57.3, 60.0, 116.9, 136.5, 173.8. IR (neat): 3081, 2980,

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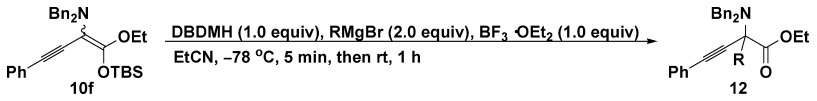
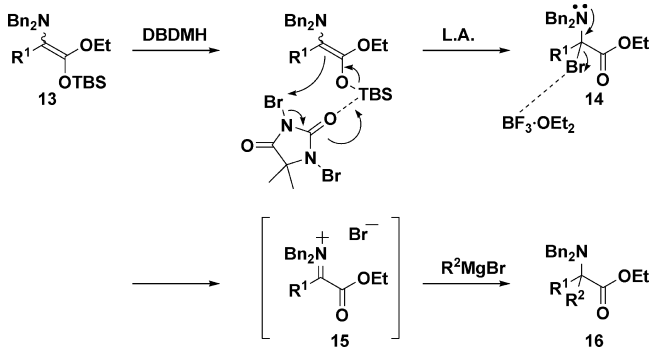
Table 6. Nucleophilic Addition of Grignard Reagents Using 10f



entry	RMgBr	R in **12**	product	yield (%)
1[a]	MeMgBr	Me	**12a**	28
2	EtMgBr	Et	**12b**	57
3	VinylMgBr	Vinyl	**12c**	16
4	PhMgBr	Ph	**12d**	34

[a]DBDMH (1.7 equiv) was used.

Scheme 3. Plausible Reaction Mechanism



2938, 2819, 1732, 1642, 1449, 1378, 1159, 993, 920 cm^{-1}. MS (EI): calcd for $C_{11}H_{19}NO_2$ $(M - C_3H_5O_2)^+$ 124.1126, found 124.1127.

*Ethyl 2-(Dibenzylamino)propanoate (**1b**).*[11b] Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33−1.34 (m, 6H), 3.49 (q, J = 7.3 Hz, 1H), 3.65 (d, J = 14.0 Hz, 2H), 3.83 (d, J = 14.0 Hz, 2H), 4.13−4.27 (m, 2H), 7.20−7.39 (m, 10H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.5, 15.0, 54.4, 56.1, 60.1, 126.9, 128.2, 128.6, 140.0, 173.8.

*Typical Procedure for **2a,d,e**.* Step 1: to a solution of ethyl 2-phenylacetate (8.21 g, 50 mmol) in CCl_4 (50.0 mL) were added successively *N*-bromosuccinimide (10.68 g, 60.0 mmol) and benzoyl peroxide (1.211 g, 5.0 mmol). The reaction mixture was refluxed for 2.5 h. After the whole mixture was stirred for 8 h at ambient temperature, it was filtered through a Celite pad with CCl_4. The whole mixture was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 10/1) to give ethyl 2-bromo-2-phenylacetate (52%, 6.28 g).

Step 2: to a solution of ethyl 2-bromo-2-phenylacetate (4.03 g, 16.6 mmol) in EtOH (50.0 mL) was added dibenzylamine (3.50 mL, 18.2 mmol). The reaction mixture was refluxed for 19 h. After the reaction, the whole mixture was concentrated in vacuo, followed by the addition of 1 M aqueous NaOH. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (70 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 20/1) to give ethyl 2-(dibenzylamino)-2-phenylacetate (**2a**; 83%, 4.95 g).

*Preparation of 2-Amino Esters **2b,c**.* Step 1: to a solution of 2-*p*-tolylacetic acid (10.0 g, 66.6 mmol) in CCl_4 (10.0 mL) was added thionyl chloride (19.4 mL, 266 mmol). The reaction mixture was refluxed for 0.5 h. *N,N*-Dibromodimethylhydantoin (11.4 g, 79.9 mmol), HBr (a few drops), and CCl_4 (50 mL) were added to the reaction mixture. The reaction mixture was heated at 85 °C for 2 h. After cooling, the whole mixture was concentrated in vacuo followed by the addition of EtOH (4.7 mL, 79.9 mmol). The reaction mixture was stirred for a few minutes and concentrated in vacuo. Filtration through a Celite pad with CCl_4 followed by concentration in vacuo gave the 2-bromo ester. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 20/1) to give ethyl 2-bromo-2-*p*-tolylacetate (73%, 11.8 g).

Step 2: to a solution of ethyl 2-bromo-2-*p*-tolylacetate (11.8 g, 48.8 mmol) in EtOH (50.0 mL) was added dibenzylamine (10.3 mL, 53.6 mmol). The reaction mixture was refluxed for 22 h. After the reaction, the whole mixture was concentrated in vacuo followed by the addition of 1 M aqueous NaOH. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (80 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 20/1) to give ethyl 2-(dibenzylamino)-2-*p*-tolylacetate (**2b**; 15%, 2.82 g).

*Ethyl 2-(Dibenzylamino)-2-phenylacetate (**2a**).*[11b] Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, J = 7.3 Hz, 3H), 3.73 (d, J = 14.2 Hz, 2H), 3.75 (d, J = 14.2 Hz, 2H), 4.20−4.34 (m, 2H), 4.60 (s, 1H), 7.19−7.35 (m, 15H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.4, 54.2, 60.4, 65.8, 127.0, 127.7, 128.2, 128.3, 128.8, 136.8, 139.6, 172.1.

*Ethyl 2-(Dibenzylamino)-2-p-tolylacetate (**2b**).*[11b] Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J = 7.3 Hz, 3H), 2.32 (s, 3H), 3.76 (s, 4H), 4.18−4.32 (m, 2H), 4.57 (s, 1H), 7.13−7.34 (m, 15H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.4, 21.1, 54.2, 60.3, 65.7, 126.9, 128.2, 128.7, 128.8, 129.0, 133.7, 137.4, 139.7, 172.3.

*Ethyl 2-(Dibenzylamino)-2-(4-methoxyphenyl)acetate (**2c**).*[11b] Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.28 (t, J = 7.3 Hz, 3H), 3.73 (d, J = 14.0 Hz, 2H), 3.76 (s, 3H), 3.77 (d, J = 14.0 Hz, 2H), 4.14−4.36 (m, 2H), 4.54 (s, 1H), 6.85−6.87 (m, 2H), 7.19−7.35 (m, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.4, 54.1, 55.2, 60.3, 65.2, 113.7, 126.9, 128.2, 128.7, 128.7, 129.9, 139.6, 159.1, 172.3.

*Ethyl 2-(4-Chlorophenyl)-2-(dibenzylamino)acetate (**2d**).*[11b] Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.3 Hz, 3H), 3.71 (d, J = 13.8 Hz, 2H), 3.76 (d, J = 13.8 Hz, 2H), 4.19−4.35 (m, 2H), 4.54 (s, 1H), 7.21−7.34 (m, 14H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.4, 54.2, 60.6, 65.2, 127.1, 128.3, 128.5, 128.8, 130.1, 133.6, 135.4, 139.3, 171.6.

*Ethyl 2-(Dibenzylamino)-2-(naphthalen-1-yl)acetate (**2e**).* Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (t, J = 7.3 Hz, 3H), 3.82 (d, J = 13.4 Hz, 2H), 3.94 (d, J = 13.4 Hz, 2H), 4.23−4.30 (m, 1H), 4.34−4.40 (m, 1H), 5.26 (s, 1H), 7.16−7.27 (m, 10H), 7.34−7.46 (m, 4H), 7.72−7.79 (m, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.4, 54.6, 60.4, 63.3, 124.6, 124.8, 125.7, 125.8, 126.4, 127.0, 128.1, 128.4, 128.9, 129.4, 132.1, 132.5, 134.1, 139.5, 172.7. IR (neat):: 3058, 3028, 2980, 2900, 2845, 1734, 1190, 1026, 752, 699 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{27}NO_2$ $(M - C_3H_7)^+$ 336.1752, found 336.1760.

Preparation of 2-Amino Ester 2f. Ethyl 2-(dibenzylamino)-4-phenylbut-3-ynoate (**2f**) was synthesized according to the literature.[13] Under an argon atmosphere, to a solution of $CuBr_2$ (447 mg, 2.0 mmol) and molecular sieves 4 Å (10 g) in toluene (50.0 mL) were added ethyl glyoxylate (50% in toluene, 4.0 mL, 20 mmol), phenylacetylene (2.2 mL, 20 mmol), and dibenzylamine (10.3 mL, 53.6 mmol). After the reaction mixture was stirred at room temperature for 24 h, it was concentrated in vacuo followed by filtration through a Celite pad with *n*-hexane. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 20/1) followed by recrystallization from EtOH to give ethyl 2-(dibenzylamino)-4-phenylbut-3-ynoate (**2f**; 21%, 1.66 g).

Preparation of Tetrasubstituted Amino Ketene Silyl Acetal. *Scheme 1, Method A, **3a**.* Under an argon atmosphere, to a solution of diisopropylamine (3.08 mL, 22 mmol) in THF (40.0

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mL) was added *n*-butyllithium (1.61 M in *n*-hexane, 13.7 mL, 22 mmol) at 0 °C. Solutions of ethyl 2-(diallylamino)propanoate (3.946 g, 20 mmol) in THF (20.0 mL) and *tert*-butyldimethylchlorosilane (3.316 g, 22 mmol) in THF (20.0 mL) were successively added to a solution of LDA at −78 °C. The reaction mixture was warmed to ambient temperature with stirring for 24 h. The whole mixture was concentrated in vacuo followed by filtration through a Celite pad with *n*-hexane. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 20/1) to give the amino ketene silyl acetal **3a** (50%, 3.154 g, *E*/*Z* = >99/<1). The stereochemistry of amino ketene silyl acetal **3a** was determined in analogously to the amino ketene silyl acetal **10c**.

*N,N-Diallyl-1-(tert-butyldimethylsilyloxy)-1-ethoxyprop-1-en-2-amine (**3a**).* *E*/*Z* = >99/<1. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.84 (s, 9H), 1.15 (t, *J* = 6.7 Hz, 3H), 1.41 (s, 3H), 3.16 (d, *J* = 6.7 Hz, 4H), 3.80 (q, *J* = 6.7 Hz, 2H), 4.91 (dd, *J* = 1.9, 8.6 Hz, 2H), 5.02 (dd, *J* = 1.9, 17.0 Hz, 2H), 5.71−7.59 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ −4.4, 10.8, 15.2, 18.0, 25.7, 56.3, 65.2, 107.7, 115.7, 137.1, 150.8. IR (neat): 3076, 2932, 2859, 1734, 1686, 1468, 1362, 1201, 1127, 836, 782 cm^{-1}. MS (FI): calcd for $C_{17}H_{33}NO_2Si$ (M^+) 311.23, found 311.23.

*Scheme 1, Method A, **3b**.* Under an argon atmosphere, to a solution of diisopropylamine (3.08 mL, 22 mmol) in THF (40.0 mL) was added *n*-butyllithium (1.61 M in *n*-hexane, 13.7 mL, 22 mmol) at 0 °C. A solution of ethyl 2-(dibenzylamino)propanoate (5.95 g, 20 mmol) in THF (20.0 mL) and a solution of *tert*-butyldimethylchlorosilane (3.32 g, 22 mmol) in THF (20.0 mL) were successively added to the preceding solution of LDA at −78 °C. The reaction mixture was warmed to ambient temperature with stirring for 25 h. After the reaction, the whole mixture was concentrated in vacuo, followed by filtration through a Celite pad with *n*-hexane. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt 20/1) to give tetrasubstituted amino ketene silyl acetal **3b** (59%, 4.89 g, *E*/*Z* = >99/<1). The stereochemistry of amino ketene silyl acetal **3b** was determined analogously to the amino ketene silyl acetal **10c**.

*N,N-Dibenzyl-1-(tert-butyldimethylsilyloxy)-1-ethoxyprop-1-en-2-amine (**3b**).* *E*/*Z* = >99/<1. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ −0.00 (s, 6H), 0.97 (s, 9H), 1.36 (t, *J* = 6.7 Hz, 3H), 1.62 (s, 3H), 3.79 (q, *J* = 6.8 Hz, 2H), 3.96 (s, 4H), 7.28−7.42 (m, 6H), 7.47−7.52 (m, 4H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ −4.8, 12.1, 15.1, 17.6, 25.6, 57.1, 64.8, 108.5, 126.5, 127.9, 128.7, 140.4, 150.3. IR (neat): 3062, 3029, 2932, 2858, 1733, 1681, 1495, 1453, 1361, 1254, 1191, 1145, 838, 698 cm^{-1}. MS (CI): calcd for $C_{25}H_{37}NO_2Si$ (M^+) 411.26, found 411.30.

*Typical Procedure: Scheme 1, Method B, **4**.* Under an argon atmosphere, to a solution of KHMDS (0.50 M in toluene 35.4 mL, 17.7 mmol) were added solutions of *tert*-butyldimethylchlorosilane (2.67 g, 17.7 mmol) in THF (20.0 mL) and 2-(dibenzylamino)-2-phenylacetate (5.31 g, 14.7 mmol) in THF (20.0 mL) successively at −78 °C. The reaction mixture was warmed to ambient temperature with stirring for 18 h. The whole mixture was concentrated in vacuo followed by filtration through a Celite pad with *n*-hexane. The crude product was purified by column chromatography on silica gel (*n*-hexane/triethylamine 10/1) to give the amino ketene silyl acetal **4** (48%, 1.67 g, *E*/*Z* = 90/10). The stereochemistry of amino ketene silyl acetal **4** was determined analogously to amino ketene silyl acetal **10c**.

*N,N-Dibenzyl-2-(tert-butyldimethylsilyloxy)-2-ethoxy-1-phenylethenamine (**4**).* *E*/*Z* = 85/15 to 90/10. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.38 (s, 6H), 0.71 (s, 9H), 1.06 (t, *J* = 6.8 Hz, 3H), 3.44 (q, *J* = 6.8 Hz, 2H), 3.94 (s, 4H), 7.17−7.35 (m, 13H), 7.50−7.54 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ −5.3, 14.7, 17.8, 25.5, 55.1, 65.0, 114.0, 125.7, 126.6, 127.3, 127.9, 129.2, 130.4, 138.5, 139.9, 149.2. IR (neat): 3060, 3028, 2930, 2858, 1641, 1484, 1453, 1254, 1204, 1045, 838, 697 cm^{-1}. MS (CI): calcd for $C_{30}H_{39}NO_2Si$ (M^+) 473.28, found 473.30.

*N,N-Dibenzyl-2-(tert-butyldimethylsilyloxy)-2-ethoxy-1-p-tolylethenamine (**10b**).* *E*/*Z* = 92/8. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.38 (s, 6H), 0.72 (s, 9H), 1.05 (t, *J* = 7.3 Hz, 3H), 2.32 (s, 3H), 3.41 (q, *J* = 7.3 Hz, 2H), 3.92 (s, 4H), 7.06−7.09 (m, 2H), 7.17−7.44 (m, 12H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ −5.3, 14.7, 17.8, 21.2, 25.5, 55.9, 65.0, 113.8, 126.5, 127.9, 128.1, 129.2, 130.2, 135.2, 135.4, 140.0, 148.9. IR (neat): 3061, 3027, 2930, 2858, 1641, 1456, 1254, 1203, 1155, 1047, 839, 698 cm^{-1}. MS (CI): calcd for $C_{31}H_{41}NO_2Si$ (M^+) 487.29, found 487.30.

*N,N-Dibenzyl-2-(tert-butyldimethylsilyloxy)-2-ethoxy-1-(4-methoxyphenyl)ethenamine (**10c**).* *E*/*Z* = 95/5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.38 (s, 6H), 0.72 (s, 9H), 1.06 (t, *J* = 7.3 Hz, 3H), 3.41 (q, *J* = 7.3 Hz, 2H), 3.80 (s, 3H), 3.92 (s, 4H), 6.80−6.83 (m, 2H), 7.18−7.23 (m, 2H), 7.27−7.35 (m, 8H), 7.43−7.45 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ −5.3, 14.7, 17.8, 25.5, 55.2, 55.9, 65.1, 112.8, 113.5, 126.5, 127.9, 129.2, 130.8, 131.4, 140.0, 148.5, 157.7. IR (neat): 3062, 3029, 2930, 2857, 1644, 1508, 1244, 1202, 1151, 1040, 840, 699 cm^{-1}. HRMS (EI): calcd for $C_{31}H_{41}NO_3Si$ (M^+) 503.2856, found 503.2857.

*N,N-Dibenzyl-2-(tert-butyldimethylsilyloxy)-2-ethoxy-1-(4-chlorophenyl)-2-ethoxyethenamine (**10d**).* *E*/*Z* = 88/12. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.37 (s, 6H), 0.73 (s, 9H), 1.08 (t, *J* = 7.3 Hz, 3H), 3.45 (q, *J* = 7.3 Hz, 2H), 3.92 (s, 4H), 7.16−7.33 (m, 12H), 7.44−7.47 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ −5.2, 14.7, 17.8, 25.5, 56.1, 65.0, 112.8, 126.7, 127.5, 127.9, 129.1, 129.2, 130.9, 131.4, 137.3, 139.7, 149.7. IR (neat): 3062, 3029, 2931, 2858, 1636, 1489, 1254, 1207, 1156, 1045, 839, 699 cm^{-1}. MS (CI): calcd for $C_{30}H_{38}ClNO_2Si$ (M^+) 507.24, found 507.25.

*N,N-Dibenzyl-2-(tert-butyldimethylsilyloxy)-2-ethoxy-1-(naphthalen-1-yl)ethenamine (**10e**).* *E*/*Z* = >99/<1. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.64 (s, 3H), −0.27 (s, 3H), 0.30 (s, 9H), 1.27 (t, *J* = 7.3 Hz, 3H), 3.66−3.74 (m, 1H), 3.80−3.86 (m, 1H), 3.99 (s, 4H), 7.17−7.49 (m, 12H), 7.69−7.87 (m, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ −5.8, −4.8, 15.0, 17.4, 24.9, 56.3, 65.5, 111.9, 124.8, 124.8, 124.9, 126.6, 127.0, 127.3, 127.8, 127.9, 128.6, 129.2, 132.7, 133.7, 135.6, 140.2, 149.0. IR (neat): 3060, 3031, 2930, 2857, 1652, 1455, 1254, 1216, 1154, 1031, 908, 839, 781, 737, 700 cm^{-1}. MS (CI): calcd for $C_{34}H_{41}NO_2Si$ (M^+) 523.29, found 523.30.

*N,N-Dibenzyl-1-ethoxy-1-(tert-butyldimethylsiloxy)-4-phenylbut-1-en-3-yn-2-amine (**10f**).* *E*/*Z* = >99/<1. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.08 (s, 6H), 0.90 (s, 9H), 1.19 (t, *J* = 7.3 Hz, 3H), 3.79 (q, *J* = 7.3 Hz, 2H), 3.83 (s, 4H), 7.17−7.35 (m, 9H), 7.43−7.47 (m, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ −4.7, 15.1, 18.1, 25.5, 58.8, 65.2, 85.4, 95.0, 97.9, 124.8, 126.6, 127.0, 127.9, 128.2, 129.3, 130.8, 139.7, 158.8. IR (neat): 3061, 3029, 2931, 2858, 2188, 1720, 1633, 1595, 1495, 1453, 1252, 1167, 1106, 1028, 840, 755, 699 cm^{-1}. MS (CI): calcd for $C_{32}H_{39}NO_2Si$ (M^+) 497.28, found 497.30.

Preparation of α,α-Disubstituted Amino Acid Ethyl Esters 5a,b: Typical Procedure (Table 1, Entry 4). Under an argon atmosphere, to *N*-bromosuccinimide (35.6 mg, 0.20 mmol) were successively added a solution of amino ketene silyl acetal **3a** (62.3 mg, 0.20 mmol) in EtCN (1.0 mL) and 0.93 M *i*-PrMgCl in THF (0.43 mL, 0.40 mmol) at −78 °C. The reaction mixture was warmed to ambient temperature with stirring for 7 h. It was quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (developed twice with *n*-hexane/AcOEt 20/1) to give ethyl 2-(diallylamino)-2,3-dimethylbutanoate (**5a**; 22%, 11.1 mg).

*Ethyl 2-(Diallylamino)-2,3-dimethylbutanoate (**5a**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 1.16 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.37 (sept, *J* = 6.7 Hz, 1H), 3.18 (dd, *J* = 6.5, 15.5 Hz, 2H), 3.39 (dd, *J* = 5.0, 15.5 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.00 (dd, *J* = 1.5, 10.1 Hz, 2H), 5.11 (dd, *J* = 1.5, 17.1 Hz, 2H), 5.76−5.84 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.4, 15.4, 16.0, 18.5, 31.0, 51.9, 59.9, 68.4, 115.3, 138.0, 174.9. IR (neat): 2974, 1721, 1236, 1094, 915 cm^{-1}. HRMS (EI): calcd for $C_{11}H_{18}NO_2$ ($M - C_3H_7$)$^+$ 196.1338, found 196.1343.

*Ethyl 2-(Dibenzylamino)-2,3-dimethylbutanoate (**5b**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.14 (s, 3H), 1.32 (t, *J* = 7.3 Hz, 3H), 2.58 (sept, *J* = 6.6 Hz, 1H), 3.71 (d, *J* = 14.9 Hz, 2H), 3.96 (d, *J* = 14.9 Hz, 2H), 4.19

(dq, J = 7.3, 10.9 Hz, 1H), 4.20 (dq, J = 7.3, 10.9 Hz, 1H), 7.05−7.17 (m, 6H), 7.20−7.26 (m, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.6, 16.2, 16.4, 18.9, 30.9, 54.4, 60.0, 70.1, 126.2, 127.7, 128.5, 141.3, 173.7. IR (neat): 2974, 1717, 1495, 1456, 1233, 1127, 1026, 744, 697 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{22}NO_2$ (M − C_3H_7)$^+$ 296.1651, found 296.1654.

Preparation of α,α-Disubstituted Amino Acid Ethyl Esters 9a−n and 11a−f: Typical Procedure (Table 4, Entry 2). Under an argon atmosphere, to *N*,*N*-dibromodimethylhydantoin (57.2 mg, 0.20 mmol) were successively added a solution of amino ketene silyl acetal **4** (94.7 mg, 0.20 mmol) in EtCN (1.0 mL), BF_3·OEt_2 (0.025 mL, 0.20 mmol), and 0.76 M EtMgBr in Et_2O (0.52 mL, 0.40 mmol) at 0 °C. After the mixture was stirred for 5 min at 0 °C and then for 1 h at room temperature, it was quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (developed twice with *n*-hexane/AcOEt 10/1) to give ethyl 2-(dibenzylamino)-2-phenylbutanoate (**9b**; 82%, 64.2 mg).

*Ethyl 2-(Dibenzylamino)-2-phenylpropanoate (**9a**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.3 Hz, 3H), 1.67 (s, 3H), 3.82 (s, 4H), 4.10 (dq, J = 7.3, 11.0 Hz, 1H), 4.20 (dq, J = 7.3, 11.0 Hz, 1H), 7.04−7.15 (m, 6H), 7.18−7.28 (m, 5H), 7.32−7.36 (m, 2H), 7.61−7.64 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.2, 24.2, 55.7, 60.8, 72.2, 126.3, 127.3, 127.4, 127.7, 128.2, 128.6, 140.1, 143.5, 174.2. IR (neat): 2984, 1724, 1493, 1451, 1237, 1137, 1027, 743, 696 cm^{-1}. HRMS (EI): calcd for $C_{22}H_{22}N$ (M − $C_3H_5O_2$)$^+$ 300.1752, found 300.1750.

*Ethyl 2-(Dibenzylamino)-2-phenylbutanoate (**9b**).* White solid. Mp: 55−56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.57 (t, J = 7.3 Hz, 3H), 1.31 (t, J = 7.3 Hz, 3H), 1.79 (dq, J = 7.3, 13.7 Hz, 1H), 2.24 (dq, J = 7.3, 13.7 Hz, 1H), 3.81 (d, J = 15.1 Hz, 2H), 3.90 (d, J = 15.1 Hz, 2H), 4.19 (dq, J = 7.3, 10.5 Hz, 1H), 4.25 (dq, J = 7.3, 10.5 Hz, 1H), 7.08−7.36 (m, 13H), 7.55−7.59 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 9.7, 14.4, 32.6, 55.0, 60.3, 75.9, 126.4, 127.0, 127.1, 127.8, 127.9, 128.0, 128.2, 128.3, 128.6, 128.8, 140.7, 141.3, 172.0. IR (neat): 3086, 3061, 3027, 2978, 2937, 1721, 1602, 1584, 1494, 1454, 1446, 1377, 1366, 1222, 1145, 1099, 1077, 1027, 911, 764, 730, 699 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{24}N$ (M − $C_3H_5O_2$)$^+$ 314.1909, found 314.1908.

*Ethyl 2-(Dibenzylamino)-2-phenylpentanoate (**9c**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62 (t, J = 7.3 Hz, 3H), 0.73−0.86 (m, 1H), 1.03−1.17 (m, 1H), 1.30 (t, J = 7.3 Hz, 3H), 1.76−1.85 (m, 1H), 2.09−2.17 (m, 1H), 3.82 (d, J = 15.1 Hz, 2H), 3.88 (d, J = 15.1 Hz, 2H), 4.16 (qd, J = 7.3, 10.5 Hz, 1H), 4.22 (qd, J = 7.3, 10.5 Hz, 1H), 7.09−7.35 (m, 13H), 7.53−7.56 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.3, 14.4, 18.5, 41.8, 54.9, 60.4, 75.1, 126.4, 127.0, 127.7, 127.8, 127.8, 128.7, 140.5, 141.6, 172.4. IR (neat): 3086, 3027, 2963, 2871, 1721, 1494, 1454, 1217, 1028, 744, 699 cm^{-1}. HRMS (EI): calcd for $C_{24}H_{26}N$ (M − $C_3H_5O_2$)$^+$ 328.2060, found 328.2075.

*Ethyl 2-(Dibenzylamino)-3-methyl-2-phenylbutanoate (**9d**).* White solid. Mp: 72−73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 (d, J = 6.4 Hz, 3H), 0.73 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 7.3 Hz, 3H), 2.93 (sept, J = 6.4 Hz, 1H), 3.83 (d, J = 14.7 Hz, 2H), 3.90 (d, J = 14.7 Hz, 2H), 4.07−4.21 (m, 2H), 7.07−7.31 (m, 11H), 7.50−7.52 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.6, 16.9, 20.2, 31.2, 60.1, 78.3, 126.4, 126.7, 126.9, 127.7, 129.2, 129.4, 137.2, 139.7, 171.4. IR (neat): 3028, 2977, 2931, 2869, 1720, 1602, 1493, 1452, 1384, 1364, 1212, 1140, 1094, 1067, 1030, 942, 911, 739, 699 cm^{-1}. HRMS (EI): calcd for $C_{24}H_{26}N$ (M − $C_3H_5O_2$)$^+$ 328.2060, found 328.2054.

*Ethyl 2-Cyclopropyl-2-(dibenzylamino)-2-phenylacetate (**9e**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.02−0.04 (m, 2H), 0.26−0.30 (m, 1H), 0.35−0.43 (m, 1H), 1.31 (t, J = 7.3 Hz, 3H), 1.49−1.57 (m, 1H), 3.97 (d, J = 15.1 Hz, 2H), 4.02 (d, J = 15.1 Hz, 2H), 4.22 (qd, J = 7.3, 11.0 Hz, 1H), 4.27 (qd, J = 7.3, 11.0 Hz, 1H), 7.03−7.32 (m, 13H), 7.56−7.57 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 2.4, 5.3, 14.4, 19.5, 55.8, 60.5, 76.0, 126.2, 127.3, 127.4, 127.7, 128.5, 128.8, 140.4, 141.2, 172.0. IR (neat): 3084, 3026, 2979, 2852, 1722, 1492, 1451, 1214, 1029, 746, 698 cm^{-1}. HRMS (EI): calcd for $C_{24}H_{24}N$ (M − $C_3H_5O_2$)$^+$ 326.1903, found 326.1906.

*Ethyl 2-Cyclohexyl-2-(dibenzylamino)-2-phenylacetate (**9f**).* White solid. Mp: 103−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.29−0.39 (m, 1H), 0.51−0.61 (m, 1H), 0.75−0.84 (m, 2H), 1.27−1.31 (4H, including triplet at 1.30 ppm (J = 7.1 Hz, 3H)), 1.42−1.48 (m, 2H), 1.56−1.60 (m, 1H), 1.74−1.78 (m, 1H), 1.87−1.91 (m, 1H), 2.40−2.48 (m, 1H), 3.71−3.90 (m, 4H), 4.12−4.29 (m, 2H), 7.07−7.36 (m, 15H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.5, 26.2, 26.6, 26.9, 27.7, 31.1, 60.1, 78.5, 126.4, 126.6, 126.9, 127.8, 129.2, 129.3, 138.2, 139.9, 171.1. IR (neat): 3088, 3028, 2929, 2853, 1719, 1495, 1451, 1215, 1026, 745, 698 cm^{-1}. HRMS (EI): calcd for $C_{27}H_{30}N$ (M − $C_3H_5O_2$)$^+$ 368.2373, found 368.2384.

*Ethyl 2-(Dibenzylamino)-3,3-dimethyl-2-phenylbutanoate (**9g**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H), 4.01−4.10 (3H, including doublet at 4.04 ppm (J = 15.1 Hz, 2H) and quartet of doublets at 4.06 ppm (J = 7.3, 10.5 Hz, 1H)), 4.17−4.26 (3H, including doublet at 4.19 ppm (J = 15.1 Hz, 2H) and quartet of doublets at 4.22 ppm (J = 7.3, 10.5 Hz, 1H)), 6.99−7.08 (m, 10H), 7.19−7.26 (m, 3H), 7.77−7.81 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.1, 30.3, 40.2, 57.3, 60.0, 81.2, 126.0, 127.0, 127.2, 127.5, 128.9, 129.2, 140.4, 141.6, 173.9. IR (neat): 2974, 1720, 1455, 1204, 1031, 748, 700 cm^{-1}. HRMS (EI): calcd for $C_{25}H_{28}N$ (M − $C_3H_5O_2$)$^+$ 342.2216, found 342.2206.

*Ethyl 2-(Dibenzylamino)-2,3-diphenylpropanoate (**9h**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, J = 6.9 Hz, 3H), 2.66 (d, J = 13.3 Hz, 1H), 3.68 (d, J = 13.3 Hz, 1H), 3.83 (d, J = 15.1 Hz, 2H), 4.01 (d, J = 15.1 Hz, 2H), 4.30 (qd, J = 6.9, 10.6 Hz, 1H), 4.37 (qd, J = 6.9, 10.6 Hz, 1H), 6.53−6.55 (m, 2H), 6.91−7.02 (m, 3H), 7.11−7.44 (m, 15H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.6, 46.3, 55.3, 60.5, 77.1, 125.9, 126.6, 127.1, 127.1, 127.3, 128.0, 128.6, 128.8, 130.9, 137.0, 140.7, 140.8, 170.0. IR (neat): 3086, 3028, 2979, 2845, 1718, 1493, 1452, 1214, 1028, 744, 699 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{26}N$ (M − $C_3H_5O_2$)$^+$ 376.2060, found 376.2066.

*Ethyl 2-(Dibenzylamino)-2-phenylbut-3-enoate (**9i**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.4 Hz, 3H), 3.85 (d, J = 14.7 Hz, 2H), 3.91 (d, J = 14.7 Hz, 2H), 4.14 (dq, J = 7.4, 10.5 Hz, 1H), 4.23 (dq, J = 7.4, 10.5 Hz, 1H), 5.33 (dd, J = 0.9, 11.0 Hz, 1H), 5.39 (dd, J = 0.9, 17.4 Hz, 1H), 6.35 (dd, J = 11.0, 17.4 Hz, 1H), 6.99−7.37 (m, 13H), 7.60−7.63 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.2, 56.2, 61.0, 77.2, 117.2, 126.2, 127.5, 128.0, 128.2, 128.6, 128.7, 138.5, 140.3, 140.5, 172.3. IR (neat): 3028, 1728, 1650, 1493, 1452, 1224, 1150, 1029, 928, 743, 695 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{22}N$ (M − $C_3H_5O_2$)$^+$ 312.1747, found 312.1741.

*Ethyl 2-(Dibenzylamino)-2,2-diphenylacetate (**9j**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 7.3 Hz, 3H), 3.66 (s, 4H), 4.18 (q, J = 7.3 Hz, 2H), 6.89−6.97 (m, 6H), 7.11−7.14 (m, 4H), 7.24−7.37 (m, 6H), 7.68−7.71 (m, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 13.9, 58.1, 61.1, 80.7, 126.0, 127.2, 127.2, 127.6, 128.9, 129.4, 139.6, 139.7, 172.1. IR (neat): 3060, 3029, 1728, 1601, 1495, 1449, 1383, 1224, 1100, 1029, 968, 923, 854, 743, 696 cm^{-1}. HRMS (EI): calcd for $C_{27}H_{24}N$ (M − $C_3H_5O_2$)$^+$ 362.1903, found 362.1911.

*Ethyl 2-(Dibenzylamino)-2-phenyl-2-p-tolylacetate (**9k**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 6.8 Hz, 3H), 2.34 (s, 3H), 3.65 (s, 4H), 4.17 (q, J = 6.8 Hz, 2H), 6.88−6.95 (m, 6H), 7.11−7.17 (m, 6H), 7.24−7.36 (m, 3H), 7.55−7.58 (m, 2H), 7.69−7.71 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.0, 21.0, 58.2, 61.1, 80.4, 125.9, 127.1, 127.2, 127.6, 128.4, 129.0, 129.3, 129.4, 136.7, 136.8, 139.7, 139.9, 172.3. IR (neat): 3087, 3027, 2978, 2844, 1733, 1494, 1455, 1221, 1190, 1029, 741, 695 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{26}N$ (M − $C_3H_5O_2$)$^+$ 376.2060, found 376.2066.

*Ethyl 2-(Dibenzylamino)-2-(4-methoxyphenyl)-2-phenylacetate (**9l**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 6.9 Hz, 3H), 3.64 (s, 4H), 3.81 (s, 3H), 4.16 (q, J = 6.9 Hz, 2H), 6.86−6.96 (m, 8H), 7.11−7.12 (m, 4H), 7.25−7.37 (m, 3H), 7.60−7.68 (m, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.0, 55,2, 58.1, 61.1, 80.2, 113.0, 125.9, 127.1, 127.2, 127.6, 129.0, 129.4, 130.7, 131.8, 139.7, 139.7, 158.6, 172.4. IR (neat): 3087, 3028, 2977, 2841, 1730, 1600, 1495, 1454, 1260, 1220, 1056, 1026, 753, 697 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{26}NO$ (M − $C_3H_5O_2$)$^+$ 392.2009, found 392.2010.

*Ethyl 2-(Dibenzylamino)-2-phenyl-2-(thiophen-3-yl)acetate (**9m**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 6.9 Hz, 3H), 3.80 (d, J = 14.6 Hz, 2H), 3.85 (d, J = 14.6 Hz, 2H), 4.01 (qd, J = 6.9, 11.0 Hz, 1H), 4.16 (qd, J = 6.9, 11.0 Hz, 1H), 6.95−7.05 (m, 7H), 7.16−7.31 (m, 9H), 7.67−7.70 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 13.9, 57.0, 61.4, 77.7, 125.7, 125.8, 126.2, 127.4, 127.6, 127.9, 128.4, 128.5, 129.0, 139.5, 141.0, 143.9, 171.9. IR (neat): 3083, 3027, 2979, 2843, 1728, 1492, 1451, 1221, 1026, 749, 698 cm^{-1}. HRMS (EI): calcd for $C_{25}H_{22}NS$ (M − $C_3H_5O_2$)$^+$ 368.1468, found 368.1481.

*Ethyl 2-(Dibenzylamino)-2-phenylbut-3-ynoate (**9n**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (t, J = 7.3 Hz, 3H), 2.90 (s, 1H), 3.68 (s, 4H), 3.76 (qd, J = 7.3, 14.0 Hz, 1H), 3.94 (qd, J = 7.3, 14.0 Hz, 1H), 7.01−7.09 (m, 6H), 7.16−7.31 (m, 7H), 7.99−8.02 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.6, 56.8, 62.1, 74.2, 77.4, 78.5, 126.4, 127.5, 128.0, 128.3, 128.6, 129.1, 137.7, 139.2, 169.8. IR (neat): 3284, 3086, 3028, 2980, 2845, 1740, 1494, 1453, 1227, 1029, 745, 696 cm^{-1}. HRMS (EI): calcd for $C_{26}H_{25}NO_2$ (M)$^+$ 383.1885, found 383.1885.

*Ethyl 2-(Dibenzylamino)-2-p-tolylbutanoate (**11b**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.58 (t, J = 6.9 Hz, 3H), 1.30 (t, J = 7.3 Hz, 3H), 1.78 (dq, J = 6.9, 14.2 Hz, 1H), 2.22 (dq, J = 6.9, 14.2 Hz, 1H), 2.32 (s, 3H), 3.80 (d, J = 15.1 Hz, 2H), 3.90 (d, J = 15.1 Hz, 2H), 4.17 (dq, J = 7.3, 11.0 Hz, 1H), 4.24 (dq, J = 7.3, 11.0 Hz, 1H), 7.08−7.26 (m, 12H), 7.42−7.45 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 9.8, 14.5, 21.0, 32.5, 55.0, 60.3, 75.6, 126.4, 127.8, 127.9, 128.5, 128.6, 136.6, 138.2, 140.7, 172.0. IR (neat): 3085, 3027, 2978, 2854, 1721, 1494, 1453, 1222, 1097, 1026, 747, 698 cm^{-1}. HRMS (EI): calcd for $C_{24}H_{26}N$ (M − $C_3H_5O_2$)$^+$ 328.2060, found 328.2056.

*Ethyl 2-(Dibenzylamino)-2-(4-methoxypheny)butanoate (**11c**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.57 (t, J = 7.3 Hz, 3H), 1.31 (t, J = 7.3 Hz, 3H), 1.75 (dq, J = 7.3, 14.6 Hz, 1H), 2.23 (dq, J = 7.3, 14.6 Hz, 1H), 3.78 (d, J = 15.1 Hz, 2H), 3.79 (s, 3H), 3.90 (d, J = 15.1 Hz, 2H), 4.18 (dq, J = 7.3, 14.1 Hz, 1H), 4.24 (dq, J = 7.3, 14.1 Hz, 1H), 6.85−6.89 (m, 2H), 7.08−7.24 (m, 10H), 7.46−7.51 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 9.8, 14.5, 32.6, 54.9, 55.2, 60.3, 75.3, 113.1, 126.4, 127.8, 128.6, 129.1, 133.3, 140.8, 158.4, 172.2. IR (neat): 3062, 3028, 2979, 2838, 1719, 1612, 1494, 1297, 1250, 1030, 910, 832, 734, 697 cm^{-1}. HRMS (EI): calcd for $C_{24}H_{26}NO$ (M − $C_3H_5O_2$)$^+$ 344.2014, found 344.2007.

*Ethyl 2-(4-Chlorophenyl)-2-(dibenzylamino)butanoate (**11d**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.54 (t, J = 6.9 Hz, 3H), 1.32 (t, J = 7.3 Hz, 3H), 1.70 (dq, J = 6.9, 13.7 Hz, 1H), 2.24 (dq, J = 6.9, 13.7 Hz, 1H), 3.79 (d, J = 15.1 Hz, 2H), 3.86 (d, J = 15.1 Hz, 2H), 4.20 (dq, J = 7.3, 14.2 Hz, 1H), 4.26 (dq, J = 7.3, 14.2 Hz, 1H), 7.10−7.25 (m, 10H), 7.30−7.33 (m, 2H), 7.55−7.59 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 9.7, 14.5, 32.5, 54.9, 60.5, 75.4, 126.6, 127.9, 128.0, 128.6, 129.5, 132.8, 140.0, 140.4, 171.4. IR (neat): 3085, 3028, 2979, 2853, 1721, 1492, 1454, 1224, 1098, 1014, 830, 746, 698 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{23}ClN$ (M − $C_3H_5O_2$)$^+$ 348.1514, found 348.1503.

*Ethyl 2-(Dibenzylamino)-2-(naphthalen-1-yl)butanoate (**11e**).* White solid; mp 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.36 (t, J = 7.3 Hz, 3H), 1.37 (t, J = 6.7 Hz, 3H), 2.38 (q, J = 7.3 Hz, 2H), 3.92 (d, J = 14.7 Hz, 2H), 4.00 (d, J = 14.7 Hz, 2H), 4.33−4.41 (m, 2H), 7.07−7.13 (m, 11H), 7.37−7.52 (m, 4H), 7.76−7.86 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 10.5, 14.5, 30.4, 56.6, 60.4, 77.2, 73.3, 124.4, 125.1, 125.4, 126.4, 126.8, 127.4, 127.8, 128.8, 129.0, 129.2, 131.7, 134.7, 135.9, 140.8, 172.8. IR (neat): 3061, 3026, 2977, 2864, 1720, 1601, 1495, 1454, 1377, 1218, 1107, 1028, 967, 779, 748, 698 cm^{-1}. HRMS (EI): calcd for $C_{27}H_{26}N$ (M − $C_3H_5O_2$)$^+$ 364.2060, found 364.2043.

*Ethyl 2-(Dibenzylamino)-2-ethyl-4-phenylbut-3-ynoate (**11f**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.3 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.88 (dq, J = 7.3, 13.9 Hz, 1H), 1.98 (dq, J = 7.3, 13.9 Hz, 1H), 3.80 (d, J = 14.9 Hz, 2H), 3.97 (d, J = 14.9 Hz, 2H), 4.15 (m, 2H), 7.09−7.22 (m, 6H), 7.30−7.35 (m, 7H), 7.46−7.49 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 9.5, 14.2, 32.1, 55.9, 61.4, 71.5, 86.7, 86.8, 123.0, 126.5, 127.8, 128.2, 128.2, 128.6, 131.9, 140.5, 171.2. IR (neat): 3028, 1734, 1600, 1491, 1455, 1299, 1227, 1131, 1071, 1028, 970, 757, 698 cm^{-1}. HRMS (EI): calcd for $C_{25}H_{24}N$ (M − $C_3H_5O_2$)$^+$ 338.1903, found 338.1898.

Preparation of α,α-Disubstituted Amino Acid Ethyl Esters 12a−d: Typical Procedure (Table 6, Entry 2). Under an argon atmosphere, to *N*,*N*-dibromodimethylhydantoin (63.0 mg, 0.22 mmol) were successively added a solution of amino ketene silyl acetal **10f** (107.8 mg, 0.22 mmol) in EtCN (1.0 mL), BF_3·OEt_2 (0.028 mL, 0.22 mmol), and RMgBr (0.44 mmol) at −78 °C. The reaction mixture was warmed to ambient temperature with stirring for 1 h. It was quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (developed with *n*-hexane/AcOEt 15/1) to give adduct **12**.

*Ethyl 2-(Dibenzylamino)-2-methyl-4-phenylbut-3-ynoate (**12a**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3H), 1.60 (s, 3H), 3.81 (d, J = 14.9 Hz, 2H), 3.94 (d, J = 14.9 Hz, 2H), 4.12−4.21 (m, 2H), 7.10−7.23 (m, 6H), 7.31−7.35 (m, 3H), 7.36−7.40 (m, 4H), 7.45−7.48 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 14.1, 26.9, 55.9, 61.7, 65.8, 85.8, 87.6, 122.9, 126.6, 127.9, 128.2, 128.2, 128.6, 131.9, 140.6, 172.1. IR (neat): 3063, 3025, 2984, 2937, 1739, 1599, 1493, 1455, 1373, 1234, 1118, 1027, 951, 859, 756, 697 cm^{-1}. HRMS (EI): calcd for $C_{24}H_{22}N$ (M − $C_3H_5O_2$)$^+$ 324.1747, found 324.1754.

*Ethyl 2-(Dibenzylamino)-2-(2-phenylethynyl)but-3-enoate (**12c**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 3H), 3.71 (d, J = 14.6 Hz, 2H), 3.83 (dq, J = 7.1, 10.8 Hz, 1H), 3.87 (d, J = 14.6 Hz, 2H), 3.98 (dq, J = 7.1, 10.8 Hz, 1H), 5.28 (dd, J = 1.1, 9.8 Hz, 1H), 5.86 (dd, J = 1.1, 17.2 Hz, 1H), 6.05 (dd, J = 9.8, 17.2 Hz, 1H), 7.09−7.20 (m, 6H), 7.31−7.38 (m, 7H), 7.56−7.59 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 13.9, 55.9, 61.9, 73.2, 83.5, 89.5, 119.0, 122.8, 126.6, 127.7, 128.3, 128.4, 129.1, 132.0, 137.7, 139.6, 169.9. IR (neat): 3062, 3027, 2932, 2843, 1739, 1598, 1491, 1454, 1443, 1225, 1124, 1070, 1029, 990, 935, 757, 744, 696 cm^{-1}. HRMS (EI): calcd for $C_{25}H_{22}N$ (M − $C_3H_5O_2$)$^+$ 336.1747, found 336.1756.

*Ethyl 2-(Dibenzylamino)-2,4-diphenylbut-3-ynoate (**12d**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, J = 7.1 Hz, 3H), 3.77 (s, 4H), 3.83 (dq, J = 7.1, 10.7 Hz, 1H), 3.98 (dq, J = 7.1, 10.7 Hz, 1H), 7.01−7.11 (m, 6H), 7.22−7.34 (m, 7H), 7.37−7.40 (m, 3H), 7.59−7.62 (m, 2H), 8.04−8.07 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 13.7, 56.5, 62.0, 74.4, 84.7, 89.4, 122.9, 126.4, 127.5, 128.1, 128.3, 128.4, 128.5, 129.2, 132.1, 138.4, 139.3, 170.2. IR (neat): 3061, 3028, 1740, 1598, 1490, 1449, 1369, 1220, 1116, 1068, 1048, 1029, 981, 794, 756, 695 cm^{-1}. HRMS (EI): calcd for $C_{29}H_{24}N$ (M − $C_3H_5O_2$)$^+$ 386.1903, found 386.1903.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra of **1a,b**, **2a−e**, **3**, **4**, **10b−f**, **9a−n**, **11b−f**, and **12a−d** and NOESY spectra of **10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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