Synthesis of α-Substituted α-Amino Acids via Cationic Intermediates

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A novel synthetic approach to racemic α-substituted α-amino acids is described. The key intermediates of this methodology are highly electrophilic iminium ions, bearing carbonyl substituents at both the iminium carbon and nitrogen atom. The preparation of precursors **8**, **10a–c**, and **12** includes electrochemical oxidation techniques according to literature procedures. When an α-methyl precursor (**8** or **10a**) was used, reactions with allylsilanes and silyl enol ethers led to the desired products, but elimination to dehydroalanine derivatives appeared to be an important side reaction. A major improvement in the yields of the desired products could be effected by using longer reaction times. In this way, efficient syntheses of protected α-methyl-α-amino acids could be developed. The elimination process appeared to be a more serious problem in the α-benzyl (**10b**) and α-allyl (**10c**) cases. On the other hand, the α-phenyl precursor **12** appeared to be highly useful, because the elimination is impossible in this case. High yields of α-phenyl-α-amino acid derivatives were obtained upon reaction of **12** with silicon-activated π-nucleophiles. Deprotection led to various types of free α-substituted α-amino acids.

Introduction

Currently, there is substantial interest in the synthesis of α-amino acids, in particular nonproteinaceous α-amino acids. This is due to the wide utility of such compounds in physical and life sciences. Many synthetic methodologies have already been developed to gain access to a broad spectrum of (optically active) α-amino acids.[3]

In recent years the synthesis of α-substituted α-amino acids has attracted particular attention. The rapidly increasing interest in this class of compounds is caused by their apparent importance as enzyme inhibitors[4] and as conformational modifiers in physiologically active peptides.[5] Many compounds exhibit relevant biological activities, especially in the α-methyl series, but the use of other α-substituents, such as α-CH_2X (X = OR, halogen) and α-aryl, may also lead to interesting amino acids. Several synthetic approaches to α-substituted α-amino acids have been developed, among which the enolate alkylation technique has received most attention.[6–12]

In the last few years, we[13] and others[14] have been engaged in α-amino acid synthesis, using glycine cation equivalents as intermediates. *C,N*-Diacyliminium ion species of type **2**, generated from α-methoxy- or α-haloglycine esters (**1**),[15] were reacted with silicon-stabilized carbon nucleophiles such as allylsilanes[13a] and silyl enol ethers,[13b] leading to new types of (protected) α-amino acids **3** and **4** (Scheme I). Similarly, we recently synthesized α-amino amides **7**, which were enzymatically resolved to give the corresponding optically active α-amino acids.[13c]

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(6) Schöllkopf, U.; Westphalen, K.-O.; Schröder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781, and refs cited therein.

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(8) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276.

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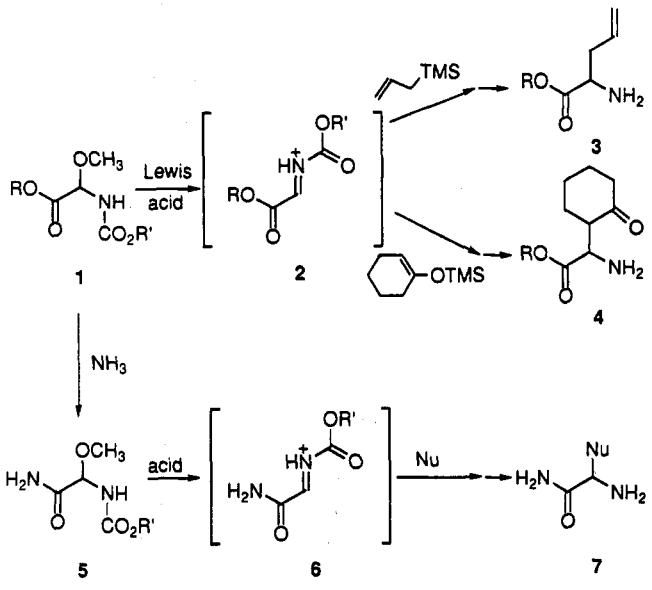
(12) (a) Chaari, M.; Jenhi, A.; Lavergne, J.-P.; Viallefont, P. *Tetrahedron* **1991**, *47*, 4619. (b) O'Donnell, M. J.; Bennett, W. D.; Jacobsen, W. N.; Ma, Y.-a. *Tetrahedron Lett.* **1989**, *30*, 3913. (c) Holladay, M. W.; Nadzan, A. M. *J. Org. Chem.* **1991**, *56*, 3900.

(13) (a) Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1989**, *45*, 4627. (b) Mooiweer, H. H.; Ettema, K. W. A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1990**, *46*, 2991. (c) Roos, E. C.; Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Kamphuis, J. *J. Org. Chem.* **1992**, *57*, 6769. (d) Roos, E. C.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 360. (e) Roos, E. C.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *Synlett* **1992**, 451.

0022-3263/93/1958-3259$04.00/0

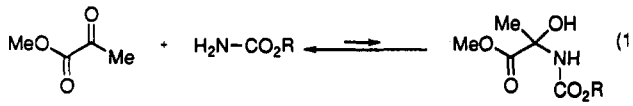
Scheme I



We decided to extend our methodology to the synthesis of α-substituted α-amino acids, using analogous types of cationic intermediates, an area which is relatively unexplored.[16] Several α-substituted precursors were employed to study the generality of this methodology and to establish the reaction mechanism. At the outset we have examined this approach for its efficacy in the racemic series with plans to subsequently develop a stereoselective method for the most promising series of compounds. It will be shown that in the α-methyl and, in particular, the α-phenyl case, a short and efficient synthesis of α-substituted α-amino acids was developed.

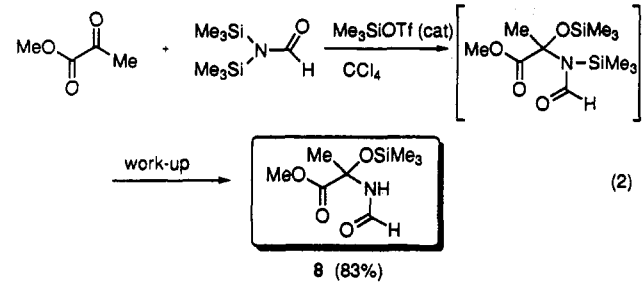
Results and Discussion

Synthesis of Precursors. A. α-Methyl Precursors. In our previous synthetic investigations of α-H α-amino acids, the precursor α-methoxyglycine derivatives were synthesized by condensation of an alkyl carbamate with glyoxylic acid, according to the method described by Ben-Ishai et al.[15a,c] However, when the same type of condensation was attempted in order to synthesize the analogous α-methyl derivative, i.e. reaction of an alkyl carbamate with methyl pyruvate, the reaction turned out to be an unfavorable equilibrium (eq 1).



(1)

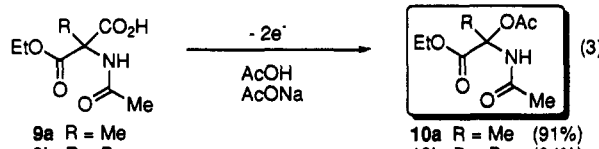
Efforts to favorably influence this equilibrium by varying the temperature, or by using molecular sieves, base, or other additives did not lead to improvement. Our attention was then caught by related work reported by Johnson et al.[17] In their method, methyl pyruvate was reacted with bis(trimethylsilyl)formamide (BSF)[18] in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) (eq 2). Because of its ready availability, we decided to use **8** as precursor for the synthesis of α-methyl-α-amino acids.



(2)

8 (83%)

We also explored other ways to obtain suitable precursors. A second α-methyl precursor was prepared using the method of Matsumoto et al.[19] In this synthesis, the key step is the electrochemical, anodic oxidation of **9a** to **10a** (eq 3; this reaction may be conveniently performed on a 0.1-mol scale). Compound **9a** was obtained by the alkylation of diethyl acetamidomalonate, and subsequent monosaponification. As **10a** contains protective and leaving groups that are different from **8**, both α-methyl precursors were used in the following reactions in order to compare the effect of such variations.



(3)

9a R = Me
9b R = Bn
9c R = allyl

10a R = Me (91%)
10b R = Bn (94%)
10c R = allyl (87%)

B. α-Benzyl and α-Allyl Precursors. Benzyl- or allyl-substituted precursors could be prepared in an

(14) (a) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693. (b) Sinclair, P. J.; Zhai, D.; Reibenspeis, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (c) Yamamoto, Y.; Nishii, S.; Maryuama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778. (d) Allmendinger, T.; Riha, G.; Wetter, H. *Helv. Chim. Acta* **1988**, *71*, 395. (e) Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891. (f) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (g) Ermert, P.; Meyer, L.; Stucki, C.; Schneebell, J.; Obrecht, J. P. *Tetrahedron Lett.* **1988**, *29*, 1265. (h) Bretschneider, T.; Miltz, W.; Münster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403. (i) Manfré, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060. (j) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11. (k) Schöllkopf, U.; Neubauer, H.-J.; Hauptreit, M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1066. (l) Schöllkopf, U.; Grüttner, S.; Anderskewitz, R.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 683. (m) Papadopoulos, A.; Lewall, B.; Steckhan, E.; Ginzel, K.-D.; Knoch, F.; Nieger, M. *Tetrahedron* **1991**, *47*, 563. (n) Agami, C.; Couty, F.; Daran, J.-C.; Prince, B.; Puchot, C. *Tetrahedron Lett.* **1990**, *31*, 2889. (o) Agami, C.; Couty, F.; Prince, B.; Puchot, C. *Tetrahedron* **1991**, *47*, 4343.

(15) (a) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863. (b) Ben-Ishai, D.; Sataty, I.; Bernstein, Z.; *Tetrahedron* **1976**, *32*, 1571. (c) Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881. (d) Ben-Ishai, D.; Moshenberg, R.; Altman, J. *Tetrahedron* **1977**, *33*, 1533. (e) Ben-Ishai, D.; Altman, J.; Peled, N. *Tetrahedron* **1977**, *33*, 2715. (f) Ben-Ishai, D.; Altman, J.; Bernstein, Z.; Peled, N. *Tetrahedron* **1978**, *34*, 467. (g) Review: Zaugg, H. E. *Synthesis* **1985**, 85. (h) Review: Zaugg, H. E. *Synthesis* **1985**, 181. (i) O'Donnell, M. J.; Bennett, W. D.; Polt, R. L. *Tetrahedron Lett.* **1985**, *26*, 695. (j) Ginzel, K.-D.; Brungs, P.; Steckhan, E. *Tetrahedron* **1989**, *45*, 1691. (k) Kohn, H.; Sawhney, K. N.; LeGall, P.; Conley, J. D.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1990**, *33*, 919. (l) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1074–1077.

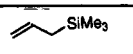
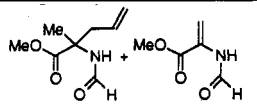
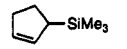
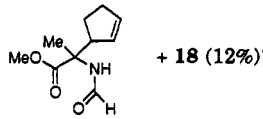
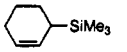
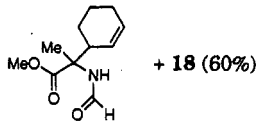
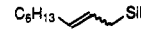
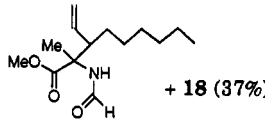
(16) (a) Ozaki, Y.; Iwasaki, T.; Horikawa, H.; Miyoshi, M.; Matsumoto, K. *J. Org. Chem.* **1979**, *44*, 391. (b) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 826. (c) Lipshutz, B. H.; Huff, B.; Vaccaro, W. *Tetrahedron Lett.* **1986**, *27*, 4241. (d) Cativiela, C.; López, M. P.; Mayoral, J. A. *Synlett* **1992**, 121.

(17) Johnson, A. P.; Luke, R. W. A.; Steele, R. W. *J. Chem. Soc., Chem. Commun.* **1986**, 1658.

(18) Unlike the bis(trimethylsilyl)acetamide derivative (*N,O*-disilylated), the formamide derivative has been shown to be *N,N*-disilylated. See, e.g.: Yoder, C. H.; Copenhafer, W. C.; DuBeshter, B. *J. Am. Chem. Soc.* **1974**, *96*, 4283.

(19) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1977**, *42*, 2419.

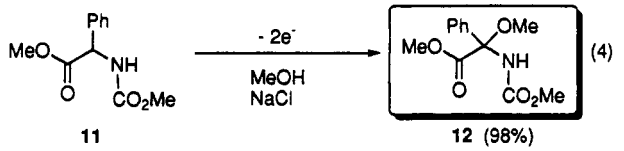
Table I. Me_3SiOTf-Mediated Coupling Reactions of 8

entry	nucleophile (equiv)	reaction time	product (yield, isomer ratio)
1	 **13** (2.0)	3 h	 **17** (27%) **18** (42%)[a]
2	**13** (2.0)	30 h	**17** (72%) + **18** (13%)[a]
3	 **14** (2.0)	4 h	 + **18** (12%)[a] **19** (84%, 70:30)
4	 **15** (2.0)	2 h	 + **18** (60%) **20** (36%, 66:34)
5	**15** (2.0)	5 days	**20** (67%, 66:34) + **18** (32%)
6	 **16** (2.0, Z/E = 18:82)	6 days	 + **18** (37%) **21** (42%, 67:33)

[a] Yields estimated from the ^1H NMR spectrum of the crude product mixture.

analogous manner from the related acetamidomalonate to give **10b** and **10c**.

C. α-Phenyl Precursor. The Matsumoto method described above was initially tried as an approach to an α-phenyl precursor. Introduction of the phenyl substituent in the aminomalonic acid derivative was effected in two steps, involving bromination and Grignard addition.[20] Attempted monosaponification of the diester, however, gave rise to spontaneous decarboxylation of the monoacid, sometimes followed by saponification of the second ester function (if more than 1 equiv of base was present). A more convenient approach turned out to be the direct anodic oxidation of *N*-(methoxycarbonyl)phenylglycine methyl ester (**11**) in methanol, as reported by Shono et al.[21] This furnished the α-phenyl precursor **12** on a 10–20-g scale in very high yield (eq 4).



11 **12** (98%) (4)

Coupling Reactions. A. Synthesis of (Protected) α-Methyl-α-amino Acids. A study was first made on the utility of precursor **8**. This compound was subjected to Lewis acid-mediated reactions with various types of (carbon) nucleophiles. Both boron trifluoride etherate and trimethylsilyl triflate (Me_3SiOTf) were tried as Lewis acids. The latter proved to be superior and was therefore used in the rest of this study. In Table I, some results of the reactions of **8** with allylsilanes are collected.[22] In a typical experiment, Me_3SiOTf (1.5–3.0 equiv) was added at −78 °C to a mixture of **8** (0.2 M) and the nucleophile (2.0 equiv) in CH_2Cl_2. After 15 min of stirring at −78 °C, the reaction mixture was allowed to warm up to room temperature and stirring was continued for the period of time indicated in Table I. Workup began by quenching with aqueous $NaHCO_3$, followed by the usual extractive procedures.

As can be seen from Table I, the coupling reactions with allylsilanes indeed lead to formation of the quaternary carbon center, furnishing protected γ,δ-unsaturated α-methyl-α-amino acids.[23] The yields based on **8** varied from poor to good (e.g. entries 2, 5) and, in one case, excellent (entry 3). In all cases the formation of 2,3-dehydroalanine derivative **18**,[24] a result of proton loss from the cationic intermediate, was an important side reaction. In our first experiments, in which a standard reaction time of 2–4 h was used, the yield of **18** was even discouragingly high. The byproduct was generally formed in a larger amount when more sterically hindered allylsilanes were used. When the standard procedure (vide supra) was carried out in the absence of an allylsilane, **18** was almost the exclusive product.

By taking the reaction with 3-(trimethylsilyl)cyclohexene (entry 4) as an appropriate example, the influence of the amounts of Lewis acid and allylsilane, the type of Lewis acid, the temperature, and reaction time were studied; the ratios of coupling product **20** and elimination product **18** were derived from the ^1H NMR spectrum of the crude product.[25] Most of the variations mentioned had little or no effect on the ratio of the two products, although a slight increase in the ratio in favor of coupling product was realized by using 5 equiv of the allylsilane and increasing the reaction time to 24 h (**20**/**18** 47%:34% isolated yield). A gratifying improvement of the reaction was observed, however, when the amount of allylsilane was kept at 2.0 equiv, but the reaction time was further increased to 5 days. As can be seen from entry 5, **20** was isolated in 67% yield, whereas the yield of **18** was reduced to 32%. In the same manner, yields of other coupling processes could be improved, as is shown in entries 2 and 6.

Compound **10a** was also investigated as a possible precursor for α-methyl-α-amino acids. The reactions, performed from this compound, are outlined in Table II. In the reactions with carbon nucleophiles, $BF_3{\cdot}OEt_2$ (1.5–2.0 equiv) was used as Lewis acid in CH_2Cl_2. The results show the same trend as the reactions shown in Table I; again, longer reaction times give an improved yield of coupling product (cf. entries 1 and 2; the elimination product was not isolated in these cases but the ^1H NMR spectra of the crude material also showed an increased coupling/elimination ratio with longer reaction times). It should be noted that the yields of coupling products are somewhat lower than for similar reactions in Table I.

In contrast with the unsuccessful attempts with precursor **8**, *silyl enol ethers can now be coupled successfully.* The yields are attractive compared to the other reactions in Table II (due to the high reactivity of silyl enol ethers).

B. Synthesis of (Protected) α-Benzyl and α-Allyl-α-amino Acids. In Table III, results from coupling reactions of precursors **10b** and **10c** are collected. The reactions shown in this Table were performed in a similar

(20) Kober, R.; Hammes, W.; Steglich, W. *Angew. Chem. Suppl.* **1982**, 542.
(21) Shono, T.; Matsumara, Y.; Inoue, K. *J. Org. Chem.* **1983**, *48*, 1389.
(22) Related examples may be found in our previous communication (ref 13e).
(23) It should be noted that reactions of **12** with nonactivated alkenes, such as cyclopentene, did not lead to any product formation.
(24) Kolasa, T. *Synthesis* **1983**, 539.
(25) By integration of the *H*CH=C signal of **18** at 6.58 ppm and the C*H*CH=CH signal of **20** at 2.72–2.67 ppm.

Table II. BF_3·OEt_2-Mediated Coupling Reactions of 10a

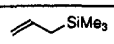
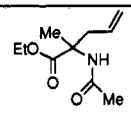
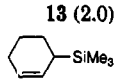
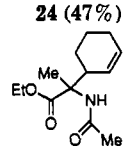
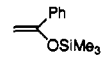
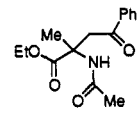
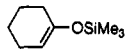
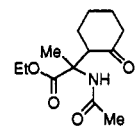
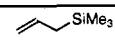
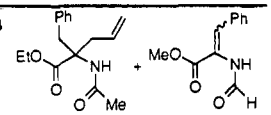
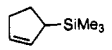
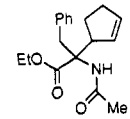
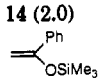
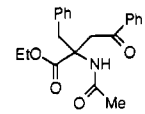
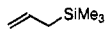
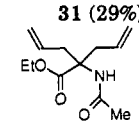
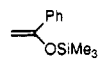
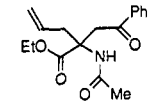
entry	nucleophile (equiv)	reaction time	product (yield, isomer ratio)
1	 **13** (2.0)	3 h	 **24** (22%)
2	**13** (2.0)	2 days	**24** (47%)
3	 **15** (2.0)	2 h	 **25** (28%, 79:21)
4	 **22** (2.1)	3 days	 **26** (71%)
5	 **23** (2.0)	4 days	 **27** (61%, 79:21)

Table III. BF_3·OEt_2-Mediated Coupling Reactions of 10b and 10c[a]

entry	pre-cursor	nucleophile (equiv)	reaction time	product (yield, isomer ratio)
1	**10b**	 **13** (2.0)	2 days	 **28** (37%) **29** (30%)
2	**10b**	**13** (1.9)	6 days	**28** (52%) + **29** (27%)
3	**10b**	 **14** (2.0)	5 days	 + **29** (25%) **30** (25%, 60:40)
4[1]	**10b**	**14** (2.0)	4 days	**30** (47%) + **29** (18%)
5	**10b**	 **22** (2.0)	4 days	 **31** (29%)
6	**10c**	 **13** (2.1)	24 h	 **32** (11%)
7	**10c**	 **22** (2.0)	15 h	 **33** (32%)

[a] In all cases 0.15–0.20 M solutions of the precursor in CH_2Cl_2 were used, except in entry 4 in which the concentration was 0.82 M.

manner as those with **10a**, BF_3·OEt_2 being used as the Lewis acid. Attempts were made to optimize the reaction. Taking the reaction in entry 3 as an example, some variations were made, but except for the slight improvement shown in entry 4, in which a more concentrated solution was used, no major increase in the yield of **30** could be effected (e.g. using MeCN as the solvent furnished 17% of **30** after 5 days, and using $ZnBr_2/Me_3SiCl$ as the Lewis acid[26] **30** was obtained in 28% after 4 days of reaction).

Mechanistic Proposal. From the above studies, the following reaction mechanism is proposed (Scheme II). Because the trimethylsiloxy leaving group is (for steric reasons) not readily accessible and formamide nitrogens are known to be reactive in silylations,[27] the first step is the formation of the *N*-silylated species **34** from **8**. This may rapidly lose Me_3SiOH to give intermediate **35**, which exists as a tautomeric equilibrium. From **35**, the tautomeric *N*-acyliminium intermediate **36** can be formed. Whereas **35** yields the elimination product **18** after workup, intermediate **36** can be attacked by the allylsilane, to give the coupling product after workup. The latter reaction is a slow, rate-determining step, not only because of the difficult formation of the quaternary carbon center (this problem is more serious when sterically more hindered allylsilanes are used), but also because the equilibrium between **35** and **36** strongly favors **35**.

The mechanism was further supported by several additional observations. First, the coupling reaction with allyltrimethylsilane (entry 1) was monitored by ^1H NMR spectroscopy. It could be clearly observed that the ratio of **17** vs **18** (or **35**) gradually increased in time;[28] while this ratio was 1.5:1 after warming up to room temperature, it was increased to 6.5:1 after 1 week and as much as 34:1 after ca. 3 weeks of reaction at room temperature. Second, elimination products of type **18** can, in principle, be used as the starting material in this synthesis, as shown in a recent paper by Cativiela et al.[16d] In our hands, however, this approach has not been successful. Third, we found that the use of silyl enol ethers did not lead to the formation of the expected coupling products at all. This observation can be explained by the fact that the more reactive silyl enol ethers decompose by the Me_3SiOH, present in the acidic medium when **35** and **36** are formed, prior to the coupling reaction.

The differences with **10a** are also accounted for by this mechanism. First, the presence of an acetyl group on the nitrogen instead of a formyl group might render the intermediate **37** somewhat less reactive. Second, with a different Lewis acid (BF_3·OEt_2) mediating the reaction Me_3SiOH is not produced. Subsequent loss of starting silyl enol ether through protodesilylation does not, therefore, occur. It can be concluded that precursors **8** and **10a** show complementary reactivities; while the use of **8** is preferable in the reactions with allylsilanes, **10a** gives good results with silyl enol ethers.

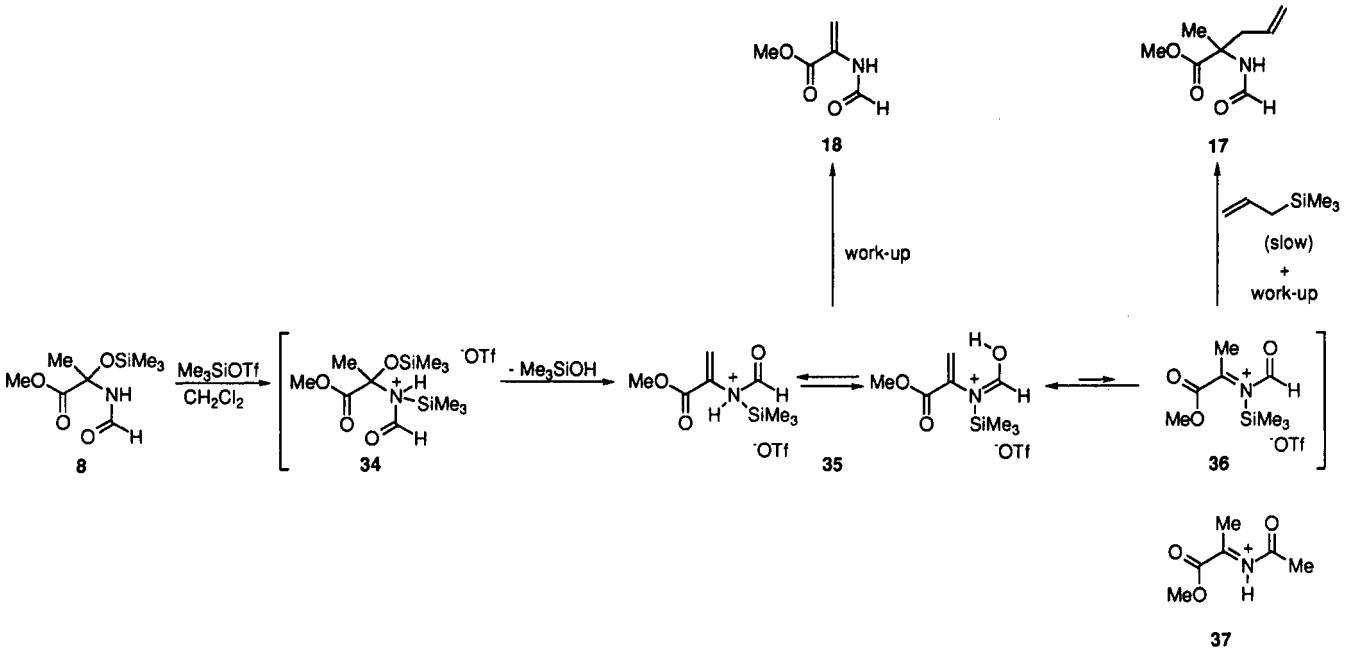
The same mechanistic scheme can be used to explain the results for the benzyl and allyl derivatives. The yields of the products are somewhat lower than for the methyl derivatives, presumably because the coupling reactions outlined here are even more difficult due to increased steric hindrance of the α-substituent and the formation of the

(26) Ohta, T.; Shiokawa, S.; Iwashita, E.; Nozoe, S. *Heterocycles* **1992**, *34*, 895.

(27) Formamides generally show high reactivity towards silylating reagents. See, e.g.: (a) Corriu, R. J. P.; Dabosi, G.; Martineau, M. *J. Organomet. Chem.* **1978**, *150*, 27. In silylations of secondary amides, *N*-silylation is favored over *O*-silylation: (b) Pierce, A. E. *Silylations of Organic Compounds*; Pierce Chemical Co.: Rockford, IL, 1968; p 62–71.

(28) In this case, the ratio was determined by integration of the *H*CH=C signal of (presumably) **35** at 6.54 ppm and the $CH_2CH{=}CH_2$ signal of **17** at 2.74 ppm. Interestingly, the latter signal appeared as a doublet (J = 7.6 Hz) during the reaction in the NMR tube, whereas immediately after quenching, this signal became a double doublet, a pattern that was also found in the isolated product (see Experimental Section).

Scheme II



elimination product[29] should be more facile, because the double bond formed is more highly substituted and conjugated.

C. Synthesis of (Protected) α-Phenyl-α-amino Acids. A study of the use of the α-phenyl substituent was undertaken for several reasons. First, some papers have appeared recently, suggesting (possible) interesting biological activities of α-aryl-α-amino acids.[12b] Second, the proposed mechanism could be further supported using this group. On the basis of that mechanism, we expected to find high yields of coupling products, because the formation of a 2,3-dehydro derivative (similar to **35**) by proton loss from the intermediate is impossible. Furthermore, the intermediate should be more stable due to conjugation with the phenyl group in the α-position. Finally, steric hindrance of this substituent might be somewhat less than in the previous reactions.

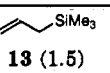
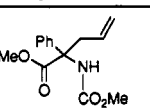
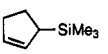
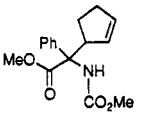
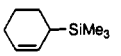
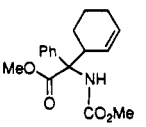
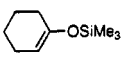
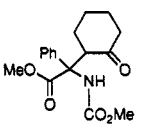
α-Phenyl precursor **12** was investigated in BF_3·OEt_2-mediated reactions with carbon nucleophiles. Results from this study are collected in Table IV. In these reactions, a standard reaction time of 3–6 h was sufficient to accomplish complete conversion. After isolation, protected γ,δ-unsaturated or γ-oxo-α-phenyl-α-amino acids were obtained in excellent yields (ca. 90%). It might be expected that α-amino acids, having other aryl groups as the α-substituent, can be synthesized with the same ease, in which case this method allows easy access to a broad range of α-aryl-α-amino acids.

In several cases throughout this paper mixtures of diastereomers were obtained, one of the two isomers usually being slightly favored. In one case (**41**, Table IV, entry 4) the major diastereomer was obtained in pure form by recrystallization and its X-ray crystal structure determined (Figure 1). The major isomer could thus be assigned the (*S**,*S**)-configuration.

Deprotection. The free α-substituted α-amino acids could be obtained from all of the protected compounds described (Chart I). As examples, compounds **17** and **19** were deprotected in one step using acidic conditions. The

(29) Data of *N*-Boc or *N*-Cbz-dehydrophenylalanine ethyl ester (*E* and *Z*): Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.

Table IV. BF_3·OEt_2-Mediated Coupling Reactions of 12

entry	nucleophile (equiv)	product (yield, isomer ratio)
1	 **13** (1.5)	 **38** (98%)
2	 **14** (2.0)	 **39** (87%, 50:50)
3	 **15** (2.0)	 **40** (90%, 70:30)
4	 **23** (2.0)	 **41** (87%, 72:28)

HCl salts of α-methyl-α-allylglycine (**42**) and α-methyl-α-(2-cyclopentenyl)glycine (**43**) were obtained in almost quantitative yield (70% from methyl pyruvate). Compound **19** was also first hydrogenated (to the cyclopentyl derivative **44**) and then deprotected in the same manner to give the HCl salt of α-methyl-α-cyclopentylglycine (**45**). Cleavage of the carbamate moiety in **41** using Me_3SiI furnished α-amino ester **46** in moderate yield. Subsequent hydrolysis of the ester group then gave the unnatural α-amino acid **47** as the HCl salt (**41** diastereomer ratio 72:28; **47** diastereomer 57:43, 41% overall yield).

Conclusions

The possibility of synthesizing α-substituted α-amino acids via cationic intermediates has been investigated. CC-bond formation can indeed be effected using this approach, but proton loss from the intermediate is an important

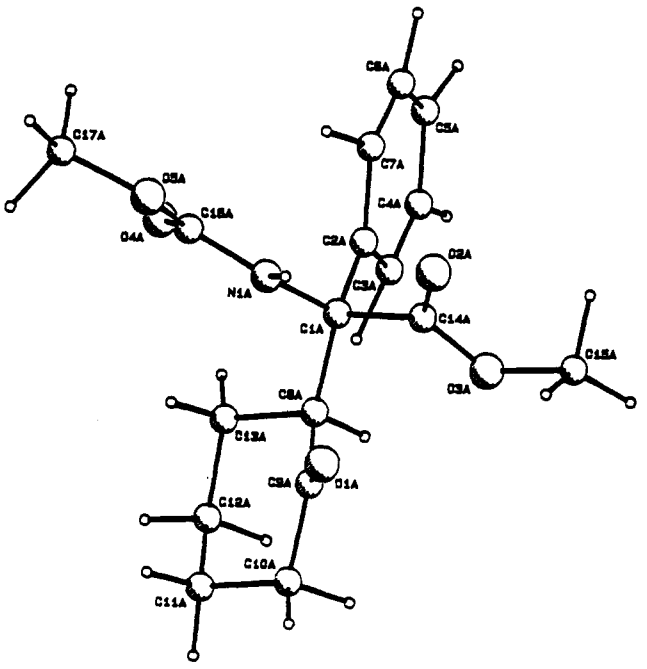
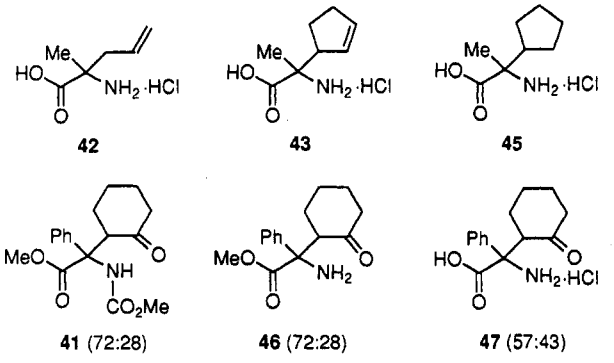


Figure 1. ORTEP diagram of 41.

Chart I



side reaction, particularly with α-allyl and α-benzyl substituents. This problem can be somewhat overcome by using longer reaction times, because this leads to a higher coupling/elimination ratio, which is in accordance with the proposed mechanism. In this way a short synthesis of various types of α-methyl- and α-phenyl-α-amino acids could be achieved. In the case of the α-phenyl substituent, with which proton loss cannot occur, excellent yields of coupling products were obtained. Future goals include the examination of several other α-substituents and the development of an asymmetric version of this synthetic methodology for the α-phenyl-substituted compounds.

Experimental Section

General Information. Experimental techniques and analytical measurements were applied as previously described.[13a] Compounds **8**, **10a–c**, and **12** were prepared according to literature procedures.[17,19,21] While **8** and **12** appear to be stable at 4 °C for several months, **10a–c** are susceptible to decomposition. Therefore, these compounds were used immediately after their preparation, without further purification. IR spectral data are reported in cm^{-1} and NMR chemical shifts in ppm.

General Procedure for the Coupling of 8 with Allylsilanes, Mediated by Me_3SiOTf. The allylsilane (2.0 equiv) was added at room temperature to a 0.2 M solution of **8** in dry CH_2Cl_2. The reaction mixture was cooled to −78 °C. Trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) (1.5–3.0 equiv) was then added slowly to the reaction mixture. After a further 15 min at −78 °C, the reaction mixture was allowed to warm up to room temperature and stirring was continued, usually until the reaction was shown to be complete on TLC. The reaction mixture was then poured out into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed.

Methyl 2-(Formylamino)-2-methyl-4-pentenoate (17) (Table I, entry 1). According to the general procedure, starting from 848 mg (3.87 mmol) of **8**, 1.23 mL (885 mg, 7.75 mmol) of allyltrimethylsilane (**13**), 18.0 mL of CH_2Cl_2, and 2.10 mL (2.58 mg, 11.62 mmol) of Me_3SiOTf and using a reaction time of 3 h there was obtained 176 mg (1.03 mmol, 27%) of **17**, as a colorless oil, after flash chromatography: R_f 0.27 (EtOAc/hexane 1:1.5), as a mixture of amide rotamers (*Z*/*E* = 84:16); IR ($CHCl_3$) 3240, 3390, 1730, 1675, 1490, 1440; ^1H NMR (200 MHz) 8.24 (d, 1 H, *J* = 12.2 Hz, *H*C(O) *E*-rotamer), 8.10 (d, 1 H, *J* = 1.6 Hz, *H*C(O) *Z*-rot.), 6.44 (br s, 1 H, N*H*), 5.71–5.50 (m, 1 H, H_2C=C*H*), 5.21–5.04 (m, 2 H, H_2C=CH), 3.76 (s, 3 H, CH_3O E-rot.), 3.74 (s, 3 H, CH_3O *Z*-rot.), 2.97 (dd, 1 H, *J* = 7.2, 13.9 Hz, H_2CCH=), 2.56 (dd, 1 H, *J* = 7.3, 13.9 Hz, H_2CCH=), 1.62 (s, 3 H, CH_3C *E*-rot.), 1.59 (s, 3 H, CH_3C *Z*-rot.); ^{13}C NMR (50 MHz, most carbons show two peaks because of rotamers) 173.7 (CH_3OC(O)), 160.0 (H*C*(O)), 131.7 and 130.0 (H_2C=*C*H), 120.7 and 119.2 (H_2C=CH), 59.6 (CH_3C), 52.6 and 52.5 (CH_3OC(O)), 44.3 and 40.5 (H_2CCH=), 24.5 and 22.7 (CH_3C); MS (EI) $(M - C_3H_5)^+$ = 130.

Methyl 2-(Formylamino)-2-methyl-4-pentenoate (17) (Table I, entry 2). According to the general procedure, starting from 500 mg (2.28 mmol) of **8**, 0.73 mL (522 mg, 4.57 mmol) of allyltrimethylsilane (**13**), 11.5 mL of CH_2Cl_2, and 1.24 mL (1523 mg, 6.85 mmol) of Me_3SiOTf and using a reaction time of 30 h, there was obtained 282 mg (1.65 mmol, 72%) of **17**, as a colorless oil, after flash chromatography, R_f 0.27 (EtOAc/hexane 1:1.5), as a mixture of amide rotamers (*Z*/*E* = 84:16).

Methyl 2-(2-Cyclopentenyl)-2-(formylamino)propanoate (19). According to the general procedure, starting from 301 mg (1.37 mmol) of **8**, 0.47 mL (385 mg, 2.75 mmol) of 3-trimethylsilylcyclopentene (**14**), 7.0 mL of CH_2Cl_2, and 0.50 mL (611 mg, 2.75 mmol) of Me_3SiOTf and using a reaction time of 4 h there was obtained 227 mg (1.15 mmol, 84%) of **19**, as a white solid, after flash chromatography: R_f 0.36 (EtOAc/hexane 1.4:1), as a mixture of isomers (70:30), as a mixture of amide rotamers (*Z*/*E* = 77:23); mp 39–42 °C; IR ($CHCl_3$) 3420, 3390, 1730, 1675, 1485, 1450, 1435; ^1H NMR (200 MHz) 8.22 (d, 1 H, *J* = 12.1 Hz, *H*C(O) *E*-rot.), 8.11 (br s, 1 H, *H*C(O) *Z*-rot.), 6.06–5.89 (m, 2 H, N*H*, CHC*H*=CH), 5.66–5.38 (m, 1 H, CHCH=C*H*), 3.77 and 3.76 (s, 3 H, CH_3OC(O), minor isomer, *E* and *Z*-rot.), 3.71 (s, 3 H, CH_3-OC(O), major isomer), 3.31–3.23 (m, 1 H, C*H*CH=CH)), 2.33–2.29 (m, 2 H, CH_2CH=CH), 2.09–1.67 (CH_2CH), 1.62 and 1.59 (s, 3 H, CH_3C, major isomer, *E* and *Z*-rot.), 1.56 (s, 3 H, CH_3C, minor isomer); ^{13}C NMR (50 MHz, most carbons show three or four peaks because of isomers and rotamers), 173.7, 173.4 and 173.1 (CH_3OC(O)), 163.3, 162.9, 160.8, and 160.5 (HC(O)), 136.5, 136.0, 134.6, and 134.5 (CHCH=CH), 129.0, 128.2, and 127.5 (CHCH=*C*H), 61.6, 61.5, 61.4, and 61.3 (CH_3C), 54.3, 54.2, 53.4, 53.2, 52.9, 52.7, and 52.3 (CHCH=CH, CH_3OC(O)), 32.0, 31.9, and 31.8 (CH_2CH=CH), 24.4, 24.2, 24.1, and 23.5 (CH_2CH), 22.7, 21.8, and 20.3 (CH_3C); HRMS calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1059. Anal. Calcd for $C_{10}H_{15}NO_3$ (197.11): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.82; H, 7.61; N, 7.07%.

Methyl 2-(2-Cyclohexenyl)-2-(formylamino)propanoate (20) (Table I, entry 4). According to the general procedure, starting from 287 mg (1.31 mmol) of **8**, 0.47 mL (404 mg, 2.62 mmol) of 3-trimethylsilylcyclohexene (**15**), 6.5 mL of CH_2Cl_2, and0.47 mL (583 mg, 2.62 mmol) of Me_3SiOTf and using a reaction time of 2 h there was obtained 102 mg (0.79 mmol, 60%) of **18** and 100 mg (0.47 mmol, 36%) of **20** as a colorless oil, after flash chromatography: R_f 0.36 (EtOAc/hexane 1.5:1), as a mixture of isomers (66:34), as a mixture of amide rotamers (*Z*/*E* = 69:31). Data for **20**: IR ($CHCl_3$) 3420, 3390, 1730, 1680, 1485, 1440; ^1H NMR (200 MHz) 8.23 (d, 1 H, *J* = 12.1 Hz, *H*C(O), major isomer, *E*-rot.), 8.20 (d, 1 H, *J* = 12.1 Hz, *H*C(O), minor isomer, *E*-rot.), 8.12 (d, 1 H, *J* = 1.2 Hz, *H*C(O), major isomer, *Z*-rot.), 8.10 (d, 1 H, *J* = 1.2 Hz, *H*C(O), minor isomer, *Z*-rot.), 6.22–5.85 (m, 2

H, NH, CHCH=CH), 5.59–5.25, (m, 1 H, CHCH=CH), 3.76 (s, 3 H, $CH_3OC(O)$, minor isomer), 3.71 (s, 3 H, $CH_3OC(O)$, major isomer), 2.72–2.67 (m, 1 H, CHCH=CH), 2.01–1.17 (m, 9 H, $(CH_2)_3CH$, CH_3C); ^{13}C NMR (50 MHz) 173.7, 173.2, and 172.8 ($CH_3OC(O)$), 163.4 and 160.6 (HC(O)), 132.8, 132.6, 131.3, and 131.0 (CHCH=CH), 125.0, 124.8, 124.3, and 123.2 (CHCH=CH), 62.0 and 61.9 (CH_3C), 52.6, 52.2, and 52.1 ($CH_3OC(O)$), 43.7, 43.3, 42.6, and 42.4 (CHCH=CH), 24.6, 24.5, 24.1, 24.0, 23.5, 22.7, 22.0, 21.5, and 21.2 ($(CH_2)_3CH$), 21.6, 20.8, 19.9, and 19.4 (CH_3C); HRMS calcd for $C_{11}H_{17}NO_3$ 211.1208, found 211.1210.

Data for **18**: Z/E ratio usually >80:20; R_f 0.60 (EtOAc/hexane 1.5:1); ^1H NMR (200 MHz) 8.51 (d, 1 H, J = 11.2 Hz, HC(O) E-rot.), 8.37 (br s, 1 H, HC(O) Z-rot.), 8.12 (br s, 1 H, NH), 6.58 (s, 1 H, HCH=C Z-rot.), 5.90 (s, 1 H, HCH=C Z-rot.), 5.84 (s, 1 H, HCH=C E-rot.), 5.66 (HCH=C E-rot.), 3.79 (s, 3 H, $CH_3OC(O)$). ^{13}C NMR (50 MHz) 164.0 ($CH_3OC(O)$), 147.9 HC(O)), 130.2 (CH_2=C), 110.3 (CH_2=C), 52.9 ($CH_3OC(O)$); mp 53–56 °C (lit.[24] 53 °C).

Methyl 2-(2-Cyclohexenyl)-2-(formylamino)propanoate (20) (Table I, entry 5). According to the general procedure, starting from 155 mg (0.71 mmol) of **8**, 0.25 mL (218 mg, 1.42 mmol) of 3-trimethylsilylcyclohexene (**15**), 3.6 mL of CH_2Cl_2, and 0.19 mL (236 mg, 1.06 mmol) of Me_3SiOTf and using a reaction time of 5 days there was obtained 25 mg (0.23 mmol, 32%) of **18**, and 101 mg (0.48 mmol, 67%) of **20** as a colorless oil, after flash chromatography: R_f 0.36 (EtOAc/hexane 1.5:1), as a mixture of isomers (66:34), as a mixture of amide rotamers (Z/E = 69:31).

Methyl 2-(Formylamino)-3-hexyl-2-methyl-4-pentenoate (21). According to the general procedure, starting from 200 mg (0.91 mmol) of **8**, 0.45 mL (362 mg, 1.82 mmol) of 1-(trimethylsilyl)-2-nonene (**16**), 4.0 mL of CH_2Cl_2, and 0.25 mL (304 mg, 1.37 mmol) of Me_3SiOTf and using a reaction time of 6 days there was obtained 43 mg (0.33 mmol, 37%) of **18**, and 98 mg (0.38 mmol, 42%) of **21** as a colorless oil, after flash chromatography: R_f 0.36 (EtOAc/hexane 1:1.2), as a mixture of isomers (67:33), as a mixture of amide rotamers (Z/E = 78:22); IR ($CHCl_3$) 3410, 1735, 1680, 1490, 1440; ^1H NMR (200 MHz) 8.14 (d, 1 H, J = 12.2 Hz, HC(O) major isomer, E-rot.), 8.11 (d, 1 H, J = 12.1 Hz, HC(O) minor isomer, E-rot.), 8.04 (d, 1 H, J = 1.6 Hz, HC(O) minor isomer, Z-rot.), 8.01 (d, 1 H, J = 1.5 Hz, HC(O) major isomer, Z-rot.), 6.32–6.28 (m, 1 H, NH), 5.64–5.40 (m, 1 H, H_2C=CH), 5.25–4.99 (m, 2 H, H_2C=CH), 3.80, 3.72, 3.70, and 3.67 (s, 3 H, $CH_3OC(O)$, isomers and rotamers), 2.49–2.30 (m, 1 H, CHCH=), 1.59, 1.52, 1.50, and 1.46 (s, 3 H, CH_3C, isomers and rotamers), 1.36–1.06 (m, 10 H, $(CH_2)_5$), 0.84–0.77 (m, 3 H, CH_3CH_2); ^{13}C NMR (50 MHz) 173.1 and 172.8 ($CH_3OC(O)$), 160.0 and 159.7 (HC(O)), 136.7, 136.5, 136.0, and 135.5 (H_2C=CH), 121.1, 119.9, 119.7, and 119.0 (H_2C=CH), 61.5, 60.8, and 60.0 (CH_3C), 52.6, 52.1, 52.0, and 50.8 ($CH_3OC(O)$, CHCH=), 32.0, 31.3, 28.7, 28.5, 28.3, 28.2, 27.3, 27.0, 26.9, and 22.0 ($(CH_2)_5$), 20.3 and 18.0 (CH_3C), 13.9 and 13.7 (CH_3CH_2); MS (EI) $(M - CH_3C(O))^+$ = 196; $(M - C_9H_{17})^+$ = 130.

General Procedure for the Coupling of 10a–c with Allylsilanes or Silyl Enol Ethers, Mediated by BF_3·OEt_2. The allylsilane or silyl enol ether (2.0 equiv) was added at room temperature to a 0.1–0.2 M solution of **10a**, **10b**, or **10c** in dry CH_2Cl_2. The reaction mixture was cooled to −78 °C. BF_3·OEt_2 (1.5–2.0 equiv) was then added slowly to the reaction mixture. After a further 15 min to 1 h at −78 °C, the reaction mixture was allowed to warm up slowly to room temperature and stirring was continued. The progress of the reaction was monitored by TLC. The reaction was stopped by pouring the reaction mixture out into saturated aqueous $NaHCO_3$ and extraction with CH_2Cl_2 (3×). The combined organic extracts were washed with brine (1×), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed.

Ethyl 2-(Acetylamino)-2-methyl-4-pentenoate (24) (Table II, entry 1). According to the general procedure, starting from 227 mg (1.05 mmol) of **10a**, 0.33 mL (239 mg, 2.09 mmol) of allyltrimethylsilane (**13**), 5.0 mL of CH_2Cl_2, and 0.26 mL (297 mg, 2.09 mmol) of BF_3·OEt_2 and using a reaction time of 3 h there was obtained 45 mg (0.23 mmol, 22%) of **24**, as a colorless oil, after flash chromatography: R_f 0.42 (EtOAc/hexane 1:1); IR ($CHCl_3$) 3420, 1725, 1675, 1500; ^1H NMR (200 MHz) 6.23 (br s, 1 H, NH), 5.69–5.52 (m, 1 H, HC=CH_2), 5.11–5.05 (m, 2 H, HC=CH_2), 4.20 (q, 2 H, J = 7.1 Hz, CH_3CH_2O), 2.96 (AB dd, 1 H, J = 13.8, 7.2 Hz, CH_2CH=), 2.54 (AB dd, 1 H, J = 13.8, 7.4 Hz, CH_2CH=), 1.96 (s, 3 H, $CH_3C(O)N$), 1.58 (s, 3 H, CH_3C), 1.27 (t, 3 H, J = 7.1 Hz, CH_3CH_2); ^{13}C NMR (50 MHz) 173.7 ($CH_3CH_2OC(O)$), 169.3, ($CH_3C(O)N$), 132.3 (H_2C=CH), 119.0 (H_2C=CH), 61.4 and 59.4 ($CH_3CH_2OC(O)$, CH_3C), 40.4 (H_2CCH=), 23.4 and 22.5 (CH_3C, $CH_3C(O)N$), 13.9 ($CH_3CH_2OC(O)$); MS (EI) M^+ = 199; $(M - C_3H_5)^+$ = 158; $(M - CO_2Et)^+$ = 126.

Ethyl 2-(Acetylamino)-2-methyl-4-pentenoate (24) (Table II, entry 2). According to the general procedure, starting from 314 mg (1.45 mmol) of **10a**, 0.46 mL (331 mg, 2.89 mmol) of allyltrimethylsilane (**13**), 5.0 mL of CH_2Cl_2, and 0.36 mL (411 mg, 2.89 mmol) of BF_3·OEt_2 and using a reaction time of 2 days there was obtained 134 mg (0.67 mmol, 47%) of **24**, as a colorless oil, after flash chromatography.

Ethyl 2-(Acetylamino)-2-(2-cyclohexenyl)propanoate (25). According to the general procedure, starting from 225 mg (1.04 mmol) of **10a**, 0.37 mL (320 mg, 2.07 mmol) of 3-(trimethylsilyl)-cyclohexene (**15**), 5 mL of CH_2Cl_2, and 0.26 mL (294 mg, 1.66 mmol) of BF_3·OEt_2 and using a reaction time of 4 days there was obtained 69 mg (0.29 mmol, 28%) of **25**, as a white solid, after flash chromatography: R_f 0.33 (EtOAc/hexane 1:1), as a mixture of isomers (79:21); mp 106–108 °C; IR ($CHCl_3$) 3480–3400, 1725, 1675, 1500; ^1H NMR (200 MHz) 6.05–5.83 (m, 2 H, NH, NCCH=CH), 5.59–5.54 (m, 1 H, HCCH=CH), 4.19 (q, 2 H, J = 7.1 Hz, CH_3CH_2), 2.73–2.68 (m, 1 H, CH_3CH), 1.98 (s, 3 H, $CH_3C(O)N$), 2.07–1.34 (m, 6 H, CH_2), 1.61 (s, 3 H, CH_3CH), 1.26 (t, 3 H, J = 7.1 Hz, CH_3CH_2); ^{13}C NMR (50 MHz, some carbons show two peaks because of diastereomers) 173.1 ($CH_3CH_2OC(O)$), 169.7 ($CH_3C(O)N$), 130.8 and 130.4 (CHCH=CH), 125.4 (CHCH=CH), 62.0 and 61.1 (CH_3C, $CH_3CH_2O(O)$), 42.4 and 42.0 (CHCH=CH), 24.6, 24.1, 23.6, 21.8, and 21.6 ($(CH_2)_3$), 23.5 ($CH_3C(O)N$), 19.5 and 19.1 (CH_3C), 13.9 ($CH_3CH_2OC(O)$); MS (EI): $(M - CO_2Et)^+$ = 166; $(M - C_6H_9)^+$ = 158.

Ethyl 2-(Acetylamino)-2-methyl-4-oxo-4-phenylbutanoate (26). According to the general procedure, starting from 102 mg (0.47 mmol) of **10a**, 0.20 mL (188 mg, 0.98 mmol) of 1-phenyl-1-(trimethylsiloxy)ethene (**22**), 5.0 mL of CH_2Cl_2, and 0.14 mL (166 mg, 1.17 mmol) of BF_3·OEt_2 and using a reaction time of 3 days there was obtained 93 mg (0.34 mmol, 71%) of **26**, as a yellow oil, after flash chromatography: R_f 0.27 (EtOAc/hexane 1:1); IR ($CHCl_3$) 3450, 3410, 1730, 1680, 1660, 1595, 1505; ^1H NMR (200 MHz) 7.93 (m, 2 H, Ph), 7.61–7.28 (m, 3 H, Ph), 6.83 (br s, 1 H, NH), 4.60 (AB d, 1 H, J = 18.0 Hz, $PhC(O)CH_2$), 4.24 (q, 2 H, J = 7.1 Hz, CH_3CH_2), 3.43 (AB d, 1 H, J = 18.0 Hz, $PhC(O)CH_2$), 1.90 (s, 3 H, $CH_3C(O)N$), 1.73 (s, 3 H, CH_3C), 1.26 (t, 3 H, J = 7.1 Hz, CH_3CH_2); ^{13}C NMR (50 MHz) 197.5 ($CH_2C(O)$), 174.3 ($CH_3CH_2OC(O)$), 169.5 ($CH_3C(O)N$), 136.4 (Ph), 133.4, 128.6 and 128.1 (Ph), 61.9 ($CH_3CH_2OC(O)$), 57.5 (CH_3C), 43.8 ($CH_2C(O)$), 24.0 and 23.6 (CH_3C, $CH_3C(O)N$), 13.9 ($CH_3CH_2OC(O)$); HRMS calcd for $C_{15}H_{19}NO_4$ 277.1314, found 277.1363.

Ethyl 2-(Acetylamino)-2-(2-oxocyclohexyl)propanoate (27). According to the general procedure, starting from 227 mg (1.05 mmol) of **10a**, 0.40 mL (356 mg, 2.09 mmol) of 1-(trimethylsiloxy)-cyclohexene (**23**), 5.0 mL of CH_2Cl_2, and 0.26 mL (297 mg, 2.09 mmol) of BF_3·OEt_2 and using a reaction time of 4 days there was obtained 162 mg (0.64 mmol, 61%) of **27**, as a yellow oil, after flash chromatography: R_f 0.16 (EtOAc/hexane 1:1), as a mixture of isomers (79:21); IR ($CHCl_3$) 3420, 1730, 1700, 1670, 1505; ^1H NMR (200 MHz) 6.81 (br s, 1 H, NH minor isomer), 6.62 (br s, 1 N, NH major isomer), 4.18–4.02 (m, 2 H, CH_3CH_2), 3.70 (dd, 1 H, J = 5.6, 12.6 Hz, CHC(O) minor isomer), 2.95 (dd, 1 H, J = 5.2, 12.5 Hz, CHC(O) major isomer), 2.39–1.35 (m, 8 H, $(CH_2)_4$), 1.91 (s, 3 H, $CH_3C(O)N$ major isomer), 1.89 (s, 3 H, $CH_3C(O)N$ minor isomer), 1.57 (s, 3 H, CH_3C major isomer) 1.55 (s, 3 H, CH_3C minor isomer), 1.20 (t, 3 H, J = 7.0 Hz, CH_3CH_2); ^{13}C NMR (50 MHz, most carbons show two peaks because of diastereomers) 211.9 and 210.8 ($CH_2C(O)$), 174.6 and 173.3 ($CH_3CH_2OC(O)$), 169.6 and 169.1 ($CH_3C(O)N$), 61.4 and 61.3 ($CH_3CH_2OC(O)$), 60.5 and 59.3 (CH_3C), 57.1 and 55.3 (CHC(O)), 42.4 and 42.3 ($CH_2C(O)$), 30.3, 28.6, 27.4, 26.9, 25.4 and 24.8 ($CH(CH_2)_3$), 24.2 and 23.9 ($CH_3C(O)N$), 21.0 and 18.9 (CH_3C), 14.0 and 13.9 ($CH_3CH_2OC(O)$); HRMS calcd for $C_{13}H_{21}NO_4$ 255.1471, found 255.1453.

Ethyl 2-(Acetylamino)-2-benzyl-4-pentenoate (28) (Table III, entry 1). According to the general procedure, starting from 200 mg (0.68 mmol) of **10b**, 0.20 mL (155 mg, 1.36 mmol) of

allyltrimethylsilane (**13**), 5.0 mL of CH_2Cl_2, and 0.12 mL (144 mg, 1.02 mmol) of $BF_3{\cdot}OEt_2$ and using a reaction time of 2 days the ^1H NMR showed a mixture of **28** and **29** (1:0.6). After flash chromatography, **28** was isolated as a pale yellow oil (70 mg, 0.25 mmol, 37%), R_f 0.32 (EtOAc/hexane 1:1.5), and **29** as a yellow oil (48 mg, 0.21 mmol, 30%). Data for **28**: IR ($CHCl_3$) 3400, 1725, 1670, 1500 cm^{-1}; ^1H NMR (200 MHz) 7.25–7.01 (m, 5 H, Ph), 6.19 (br s, 1 H, N*H*), 5.68–5.54 (m, 1 H, H_2C=C*H*), 5.14–5.05 (m, 2 H, H_2C=C), 4.31–4.11 (m, 2 H, CH_3CH_2), 3.79 (AB d, 1 H, J = 13.5 Hz, PhCH_2), 3.45 (AB dd, 1 H, J = 13.7, 7.1 Hz, CH_2-CH=), 3.11 (AB d, 1 H, J = 13.4 Hz, PhCH_2), 2.60 (AB dd, 1 H, J = 13.8, 7.5 Hz, CH_2CH=), 1.97 (s, 3 H, H_3CC(O)N), 1.34 (t, 3 H, J = 7.1 Hz, CH_3CH$_2$); ^{13}C NMR (50 MHz) 172.7 (CH_3-CH_2OC(O)), 169.4 (CH_3C(O)N), 136.4 (Ph), 132.3 (H_2C=*C*H), 129.6, 128.1, 126.8 (Ph), 118.9 (H_2C=CH), 65.7 (PhCH_2C), 61.9 (CH_3CH_2OC(O)), 40.2 (*C*H_2CH=CH_2), 39.5 (Ph*C*H_2), 24.2 (*C*H_3C(O)N), 14.2 (*C*H_3CH_2OC(O)); HRMS calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1549.

Data for **29** (cf. ref 29): *E*/*Z* usually between 2:1 and 3:1; ^1H NMR (200 MHz) 7.87 (s, 1 H, PhC*H*=C *E*-isomer), 7.73 (br s, 1 H, N*H* *E*-isomer), 7.45–7.10 (m, 7 H, Ph, PhC*H*=C *Z*-isomer, N*H* *Z*-isomer), 4.29 (q, 2 H, J = 7.1 Hz, CH_3CH_2 *Z*-isomer), 4.11 (q, 2 H, J = 7.1 Hz, CH_3CH_2), 2.13 (s, 3 H, CH_3C(O)N *E*-isomer), 1.98 (s, 3 H, CH_3C(O)N *Z*-isomer), 1.26 (t, 3 H, J = 7.1 Hz, CH_3-CH_2 *Z*-isomer), 1.00 (t, 3 H, J = 7.1 Hz, CH_3CH_2 *E*-isomer).

Ethyl 2-(Acetylamino)-2-benzyl-4-pentenoate (28) (Table III, entry 2). According to the general procedure, starting from 304 mg (1.04 mmol) of **10b**, 0.32 mL (229 mg, 2.00 mmol) of allyltrimethylsilane (**13**), 5.0 mL of CH_2Cl_2, and 0.18 mL (213 mg, 1.50 mmol) of $BF_3{\cdot}OEt_2$ and using a reaction time of 6 days there was obtained 149 mg (0.54 mmol, 52%) of **28** and 66 mg (0.28 mmol, 27%) of **29**, after flash chromatography.

Ethyl 2-(Acetylamino)-2-(2-cyclopentenyl)-3-phenylpropanoate (30) (Table III, entry 3). According to the general procedure, starting from 219 mg (0.75 mmol) of **10b**, 0.25 mL (209 mg, 1.49 mmol) of 3-(trimethylsilyl)cyclopentene (**14**), 5.0 mL of CH_2Cl_2, and 0.14 mL (159 mg, 1.12 mmol) of $BF_3{\cdot}OEt_2$ and using a reaction time of 5 days there was obtained 43 mg (0.18 mmol, 25%) of **29**, and 57 mg (0.19 mmol, 25%) of **30** as a white solid, after flash chromatography: R_f 0.32 (EtOAc/hexane 1:1.5), as a mixture of isomers (40:60); IR ($CHCl_3$) 3400, 1720, 1670, 1500 cm^{-1}; ^1H NMR (200 MHz) 7.29–7.07 (m, 5 H, Ph), 6.23 (br s, 1 H, N*H*), 5.85–5.76 (m, 3 H, HCC*H*=CH two isomers, HCCH=C*H* major isomer), 5.65 (m, 1 H, HCCH=C*H*, minor isomer), 4.23–4.13 (m, 2 H, CH_2CH_3), 4.04–3.94 (m, 1 H, *H*CCH=CH, major isomer), 3.84–3.77 (m, 1 H, *H*CCH=CH minor isomer), 3.82 (AB d, 1 H, J = 13.6 Hz, PhCH_2 minor isomer), 3.80 (AB d, 1 H, J = 13.4 Hz, PhCH_2 major isomer), 3.41 (AB d, 1 H, J = 13.5 Hz, PhCH_2 major isomer), 3.36 (AB d, 1 H, J = 13.5 Hz, PhCH_2 minor isomer), 2.33–1.99 (m, 4 H, H_2CCH=CH, H_2-CCH), 1.96 (s, 3 H, CH_3C(O)N), 1.34–1.25 (m, 3 H, CH_3CH_2); ^{13}C NMR (50 MHz, most of the peaks split into two peaks because of the isomers) 172.3 and 172.0 (CH_3CH_2OC(O)), 169.5 (CH_3C(O)N), 136.9 (Ph), 132.6, 131.7, 130.6, 130.1, 129.9, 129.8, 128.1, 126.6 (Ph, HC*C*H=, H_2CCH=), 67.9 and 67.7 (PhCH_2C), 61.7 (CH_3CH_2OC(O)), 51.6 and 51.3 (H*C*CH=CH), 38.3 and 37.4 (Ph*C*H_2), 32.1 and 31.4 (H_2CCH=CH), 25.0 and 24.5 (*C*H_2CH), 24.4 and 24.3 (*C*H_3C(O)N), 14.1 (*C*H_3CH_2O); HRMS calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1693. An analytical sample was obtained by recrystallization from EtOAc/hexane mp 118–120 °C. Anal. Calcd for $C_{18}H_{23}NO_3$ (301.17): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.68; H, 7.64; N, 4.71%.

Ethyl 2-(Acetylamino)-2-(2-cyclopentenyl)-3-phenylpropanoate (30) (Table III, entry 4). According to the general procedure, starting from 240 mg (0.82 mmol) of **10b**, 0.28 mL (230 mg, 1.64 mmol) of 3-(trimethylsilyl)cyclopentene (**14**), 1.0 mL of CH_2Cl_2, and 0.15 mL (175 mg, 1.23 mmol) of $BF_3{\cdot}OEt_2$ and using a reaction time of 4 days there was obtained 35 mg (0.15 mmol, 18%) of **29** and 116 mg (0.39 mmol, 47%) of **30**, after flash chromatography.

Ethyl 2-(Acetylamino)-2-benzyl-4-oxo-4-phenylbutanoate (31). According to the general procedure, starting from 200 mg (0.68 mmol) of **10b**, 0.28 mL (263 mg, 1.37 mmol) of 1-phenyl-1-(trimethylsiloxy)ethene (**22**), 3.5 mL of CH_2Cl_2, and 0.13 mL (146 mg, 1.03 mmol) of $BF_3{\cdot}OEt_2$ and using a reaction time of 4 days there was obtained 70 mg (0.20 mmol, 29%) of **31** as a yellow oil, after flash chromatography: R_f 0.25 (EtOAc/hexane 1:2.5); IR ($CHCl_3$) 3450, 3405, 1730, 1680, 1660, 1590, 1575, 1500; ^1H NMR (200 MHz) 7.96 (d, 2 H, J = 7.2 Hz) and 7.58–7.42 (m, 3 H) (*Ph*C(O)), 7.25 (m, 3 H) and 7.05 (m, 2 H)(*Ph*CH_2), 6.58 (s, 1 H, N*H*), 4.87 (AB d, 1 H, J = 18.0 Hz, *H*CHC(O)Ph), 4.27–4.17 (m, 2 H, CH_3CH_2), 3.96 AB d, 1 H, J = 13.2 Hz, *H*CHPh), 3.54 (AB d, 1 H, J = 18.0 Hz, HC*H*C(O)Ph), 3.05 (AB d, 1 H, J = 13.3 Hz, HC*H*Ph), 1.90 (s, 3 H, CH_3C(O)N), 1.24 (t, 3 H, J = 7.2 Hz, CH_3CH_2); ^{13}C NMR (50 MHz) 196.0 (CH_2C(O)), 171.0 (CH_3-CH_2OC(O)), 168.7 (CH_3C(O)N), 135.2 and 134.1 (*Ph*C(O) and *Ph*CH_2, quaternary carbons), 132.2, 128.6, 127.4, 126.9, and 125.9 (*Ph*C(O) and *Ph*CH_2), 61.2 and 60.7 (CH_3CH_2OC(O) and CH_3C), 42.8 (CH_2C(O)), 39.6 (Ph*C*H_2), 23.0 (*C*H_3C(O)N), 12.7 (*C*H_3CH_2-OC(O)). HRMS calcd for $C_{21}H_{23}NO_4$ 353.1627, found 353.1663.

Ethyl 2-(Acetylamino)-2-(2-propenyl)-4-pentenoate (32). According to the general procedure, starting from 261 mg (1.07 mmol) of **10c**, 0.35 mL (251 mg, 2.20 mmol) of allyltrimethylsilane (**13**), 5.0 mL of CH_2Cl_2, and 0.20 mL (227 mg, 1.60 mmol) of $BF_3{\cdot}OEt_2$ and using a reaction time of 1 day there was obtained 27 mg (0.12 mmol, 11%) of **32** as a yellow oil, after flash chromatography: R_f 0.29 (EtOAc/hexane 1:1); IR ($CHCl_3$) 3420, 1725, 1670; ^1H NMR (200 MHz) 6.33 (br s, 1 H, N*H*), 5.65–5.48 (m, 2 H, H_2C=C*H*), 5.10–5.03 (m, 4 H, H_2C=CH), 4.22 (q, 2 H, J = 7 Hz, CH_3CH_2), 3.22 (AB dd, 2 H, J = 13.7, 7.2 Hz, CH_2-CH=), 2.49 (AB dd, 2 H, J = 13.8, 7.4 Hz, CH_2CH=), 1.98 (s, 3 H, H_3CC(O)N), 1.28 (t, 3 H, J = 7.1 Hz, CH_3CH_2); ^{13}C NMR (50 MHz) 173.0 (CH_3CH_2OC(O)), 169.2 (CH_3C(O)N), 132.2 (CH_2=CH), 118.9 (CH_2=CH), 64.2 (HN*C*), 61.9 (CH_3CH_2), 39.0 (=C*H*CH_2), 24.0 (CH_3C(O)), 14.2 (*C*H_3CH_2); HRMS calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1391.

Ethyl 2-(Acetylamino) 2-(2-oxo-2-phenylethyl)-4-pentenoate (33). According to the general procedure, starting from 132 mg (0.54 mmol) of **10c**, 0.22 mL (208 mg, 1.08 mmol) of 1-phenyl-1-(trimethylsiloxy)ethene (**22**), 5.0 mL of CH_2Cl_2, and 0.10 mL (115 mg, 0.81 mmol) of $BF_3{\cdot}OEt_2$ and using a reaction time of 15 h there was obtained 53 mg (0.17 mmol, 32%) of **33** as a yellow oil, after flash chromatography: R_f 0.28 (EtOAc/hexane 1:1.5); IR ($CHCl_3$) 3400, 1725, 1675 cm^{-1}; ^1H NMR (200 MHz) 7.92 (d, 2 H, J = 7.3 Hz, Ph), 7.59–7.39 (m, 3 H, Ph), 6.74 (br s, 1 H, N*H*), 5.69–5.51 (m, 1 H, H_2C=C*H*), 5.12–5.04 (m, 2 H, H_2C=CH), 4.67 (AB, d, 1 H, J = 18.0 Hz, CH_2C(O)Ph), 4.22 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 3.41 (AB dd, 1 H, J = 13.6, 7.0 Hz, H_2C=CHCH_2), 3.39 (AB d, 1 H, J = 18.0 Hz, CH_2C(O)Ph), 2.46 (AB, dd, 1 H, J = 13.9, 7.1 Hz, H_2C=CHCH_2), 2.03 (s, 3 H, H_3CC(O)), 1.24 (t, 3 H, J = 7.1 Hz, CH_3CH_2); ^{13}C NMR (50 MHz) 197.1 (Ph*C*(O)R), 172.5 (*C*(O)OEt), 169.4 (CH_3C(O)NH), 136.2 (Ph), 133.2 (H_2C=*C*H), 131.3, 128.4, 127.9 (Ph), 119.1 (H_2C=C), 61.7 (H_2CC(O)Ph), 60.9 (*C*NH), 43.3 (CH_3CH_2), 39.3 (=CH*C*H_2), 23.8 (H_3CC(O)), 13.9 (*C*H_3CH_2); HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1459.

General Procedure for the Coupling of α-Phenyl Precursor 12 with Allylsilanes or Silyl Enol Ethers, Mediated by $BF_3{\cdot}OEt_2$. The allylsilane or silyl enol ether (1.5–2.0 equiv) was added at room temperature to a 0.2 M solution of **12** in dry CH_2Cl_2 under N_2 atmosphere. The reaction mixture was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (2.0 equiv) was then added slowly to the reaction mixture. After further 15 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and the stirring was continued for 3–6 h. The reaction was stopped by pouring it out into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine (1×), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed.

Methyl 2-[(Methoxycarbonyl)amino]-2-phenyl-4-pentenoate (38). According to the general procedure, starting from 280 mg (1.11 mmol) of **12**, 0.26 mL (190 mg, 1.66 mmol) of allyltrimethylsilane (**13**), 6.0 mL of CH_2Cl_2, and 0.72 mL (314 mg, 2.21 mmol) of $BF_3{\cdot}OEt_2$ there was obtained 285 mg (1.08 mmol, 98%) of **38** as a colorless oil, without further purification by flash chromatography: IR ($CHCl_3$) 3420, 3015, 1750–1680, 1505–1490, 1445; ^1H NMR (200 MHz) 7.47–7.26 (m, 5 H, Ph), 6.30 (br s, 1 H, N*H*), 5.77–5.63 (m, 1 H, H_2C=C*H*), 5.21–5.12 (m, 2 H, H_2C=CH), 3.67 (s, 3 H, CH_3OC(O)C), 3.59 (s, 3 H, CH_3-OC(O)N), 3.72–3.52 (m, 1 H, *H*CHCH=), 3.19 (dd, 1 H, J = 7.6, 13.7 Hz, HC*H*CH=); ^{13}C NMR (50 MHz) 172.6 (CH_3OC(O)C), 154.5 (CH_3OC(O)N), 139.6 (Ph), 132.2 (CH_2=*C*H), 128.8, 128.5,

127.8 and 125.9 (Ph), 119.4 (CH_2=CH), 65.0 (CH_2C), 53.1 and 51.9 (2 × CH_3O), 37.7 (CH_2CH=); MS: M^+ = 263; $(M - C_3H_5)^+$ = 222; $(M - CO_2Me)^+$ = 204, HRMS calcd for $C_{14}H_{17}NO_4$ 263.1158, found 263.1131.

Methyl 2-(2-Cyclopentenyl)-2-[(methoxycarbonyl)amino]-2-phenylacetate (39). According to the general procedure, starting from 183 mg (0.72 mmol) of **12**, 0.25 mL (203 mg, 1.45 mmol) of 3-(trimethylsilyl)cyclopentene (**14**), 3.5 mL of CH_2Cl_2, and 0.18 mL (205 mg, 1.45 mmol) of BF_3·OEt_2 there was obtained 182 mg (0.63 mmol, 87%) of **39** as a colorless oil, after flash chromatography: R_f 0.38 (EtOAc/hexane 1:3.5), as a mixture of isomers (50:50); IR ($CHCl_3$) 3410, 1750–1685, 1495, 1445; ^{1}H NMR (200 MHz) 7.49–7.27 (m, 5 H, Ph), 5.91–5.76 (m, 2 H, N*H*, CHC*H*=CH), 5.60–5.50 (m, 1 H, CHCH=C*H*), 4.07–3.92 (br m, 1 H, C*H*CH=CH), 3.73 and 3.72 (2 × s, 3 H, CH_3OC(O)-C, two isomers), 3.63 and 3.59 (2 × s, 3 H, CH_3OC(O)-N, two isomers), 2.31–1.56 (m, 4 H, $(CH_2)_2$); ^{13}C NMR (50 MHz, most carbons show two peaks because of diastereomers) 172.7 and 172.5 (CH_3OC(O)C), 138.9 and 138.8 (Ph), 134.3 (CHCH=CH), 130.4 and 129.8 (CHCH=*C*H), 128.0, 127.5, 127.0, and 126.9 (Ph), 67.8 and 67.7 (CHC), 52.8, 52.6, 52.1, and 52.0 (2 × CH_3O, *C*HCH=CH), 32.2 and 31.6 (CH_2CH=CH), 25.4 and 25.0 (CH_2-CH); the carbamate carbonyl signal (at ca. 155 ppm) was too small to be detectable in this case; MS (EI) $(M - C_5H_7)^+$ = 222.

Methyl 2-(2-Cyclohexenyl)-2-[(methoxycarbonyl)amino]-2-phenylacetate (40). According to the general procedure, starting with 309 mg (1.22 mmol) of **12**, 0.44 mL (376 mg, 2.44 mmol) of 3-(trimethylsilyl)cyclohexene (**15**), 6.0 mL of CH_2Cl_2, and 0.30 mL (347 mg, 2.44 mmol) of BF_3·OEt_2 there was obtained 334 mg (1.10 mmol, 90%) of **40** as a colorless oil, after flash chromatography, as a mixture of isomers (70:30): R_f (major isomer) 0.48, R_f (minor isomer) 0.54 (EtOAc/hexane 1:2); IR ($CHCl_3$) 3430, 1760–1680, 1510–1480, 1445, 1430; ^{1}H NMR (200 MHz) 7.55–7.47 and 7.38–7.24 (m, 5 H, Ph), 5.83–5.76 (m, 1 H, CHC*H*=CH), 5.88–5.38 (m, 2 H, N*H*, CHCH=C*H*), 3.76 (s, 3 H, CH_3OC(O)C, minor isomer), 3.73 (s, 3 H, CH_3OC(O)C, major isomer), 3.64 (s, 3 H, CH_3OC(O)N, major isomer), 3.62 (s, 3 H, CH_3OC(O)N, minor isomer), 3.25 (br m, 1 H, C*H*CH=CH), 1.96–1.45 (m, 6 H, $(CH_2)_3$); ^{13}C NMR (50 MHz, most carbons show two peaks because of diastereomers) 172.6 and 172.0 (CH_3OC(O)C), 155.6 CH_3OC(O)N), 138.0 and 137.7 (Ph), 131.3 (CHCH=CH), 130.0, 128.8, 127.8, 127.2, 127.0 and 126.4 (Ph), 125.3 (CHCH=*C*H), 68.5 and 67.9 (CHC), 52.6, 52.1, and 52.0 (2 × CH_3O), 44.2 (CHCH=CH), 24.9, 24.8, 24.7, 24.4, 21.9, and 21.8 ($(CH_2)_3$); MS (EI) $(M - C_6H_9)^+$ = 222.

Methyl 2-[(Methoxycarbonyl)amino]-2-(2-oxocyclohexyl)-2-phenylacetate (41). According to the general procedure, starting from 324 mg (1.28 mmol) of **12**, 0.49 mL (436 mg, 2.56 mmol) of 1-(trimethylsiloxy)cyclohexene (**23**), 6.5 mL of CH_2Cl_2, and 0.32 mL (364 mg, 2.56 mmol) of BF_3·OEt_2 there was obtained 356 mg (1.12 mmol, 87%) of **41** as a yellow, thick oil, after flash chromatography: R_f 0.36 (EtOAc/hexane 1:2), as a mixture of isomers (72:28); ^{1}H NMR (200 MHz) 7.42–7.26 (m, 5 H, Ph), 6.22 (br s, 1 H, N*H*, major isomer) 6.13 (br s, 1 H, N*H*, minor isomer), 3.71 (s, 3 H, CH_3OC(O)C, minor isomer), 3.62 (s, 3 H, CH_3OC(O)N, minor isomer), 3.60 (s, 3 H, CH_3OC(O)C, major isomer), 3.57 (CH_3OC(O)N, major isomer), 3.76–3.30 (br m, 1 H, CHC(O)), 2.42–1.11 (m, 8 H, $(CH_2)_4$). An amount of the major diastereomer could be obtained in pure form by precipitation from ether/hexane: mp 137–139 °C; IR ($CHCl_3$) 3420, 1750–1710, 1700, 1505, 1495, 1445; ^{1}H NMR (200 MHz) 7.39–7.27 (m, 5 H, Ph), 6.23 (br s, 1 H, N*H*), 3.81–3.60 (m, 1 H, CHC(O)), 3.62 (s, 3 H, CH_3OC(O)C), 3.58 (s, 3 H, CH_3OC(O)N), 2.43–1.55 (m, 8 H, $(CH_2)_4$); ^{13}C NMR (50 MHz) 211.0 (CH_2C(O)), 172.8 (CH_3OC(O)C), 155.3 (CH_3OC(O)N), 135.9 (Ph), 128.3, 127.8 and 126.1 (Ph), 65.2 (CHC), 57.3 (CHC(O)), 53.2 and 51.8 (2 × CH_3O), 42.3 (CH_2C(O)), 29.0, 27.2, and 25.2 ($CH_2CH_2CH_2$); MS M^+ = 319; $(M - CO_2Me)^+$ = 260; HRMS calcd for $C_{17}H_{21}NO_5$ 319.1420, found 319.1447. Anal. Calcd for $C_{17}H_{21}NO_5$ (319.14): C, 63.94; H, 6.63; N, 4.39. Found: C, 63.87; H, 6.68; N, 4.44%. The X-ray crystal structure of this major isomer was determined (see Figure 1 and supplementary material).

2-Amino-2-methyl-4-pentenoic Acid, HCl Salt (42). A solution of **17** (156 mg, 0.91 mmol) in 6 N HCl (4 mL) was stirred at 80 °C for 18 h. The mixture was concentrated in vacuo to give 151 mg (0.91 mmol, 100%) of **42** as a white solid: mp sublimation starts at 197 °C; ^{1}H NMR (200 MHz, D_2O) 5.86–5.65 (m, 1 H, H_2C=C*H*), 5.33–5.25 (m, 2 H, H_2C=CH), 2.79–2.68 (dd, 1 H, J = 6.8, 16.5 Hz, *H*CHCH=), 2.62–2.50 (dd, 1 H, J = 7.9, 16.5 Hz, HC*H*CH=), 1.57 (s, 3 H, CH_3C); ^{13}C NMR (50 MHz, D_2O) 175.7 (HOC(O)), 131.3 (H_2C=CH), 124.2 (H_2C=CH), 61.6 (CH_3C), 42.8 (H_2CCH=), 23.2 (CH_3C); MS (FAB) $(M - Cl^-)^+$ = 130; HRMS $(M - Cl^-)^+$ calcd for $C_6H_{12}NO_2$ 130.0868, found 130.0839.

2-Amino-2-(2-cyclopentenyl)propanoic acid, HCl Salt (43). In a similar fashion as for the deprotection of **17** (vide supra), compound **19** (478 mg, 2.43 mmol) was deprotected to give 453 mg (2.37 mmol, 97%) of **43**, as a brown solid, as a mixture of isomers (50:50): ^{1}H NMR (200 MHz, D_2O) 6.13–6.05 (m, 1 H, CHC*H*=CH), 5.77–5.73 (m, 1 H, CHCH=C*H*, first isomer), 5.59–5.55 (m, 1 H, CHCH=C*H*, second isomer, 3.34 (br m, 1 H, C*H*CH=CH), 2.32–2.44 (m, 2 H, CH_2CH=CH), 2.20–2.04 (m, 1 H, *H*CHCH), 1.78–1.63 (m, 1 H, HC*H*CH), 1.59 (s, 3 H, CH_3C, first isomer), 1.57 (s, 3 H, CH_3C, second isomer); ^{13}C NMR (50 MHz, D_2O, all carbons show two peaks because of diastereomers) 176.0 and 175.9 (HOC(O)), 139.5 and 138.9 (CHCH=CH), 128.8 and 127.9 (CHCH=*C*H), 64.7 and 64.6 (CH_3C), 53.7 and 53.5 (CHCH=CH), 33.6 and 33.5 (CH_2CH=CH), 25.7 and 25.2 (CH_2-CH), 22.1 and 21.7 (CH_3C); MS (FAB) $(M - Cl^-)^+$ = 156.

Methyl 2-Cyclopentyl-2-(formylamino)propanoate (44). To a solution of **19** (534 mg, 2.71 mmol) in ethanol (8.0 mL) was added 5% palladium on charcoal (50 mg). The mixture was hydrogenated at atmospheric pressure for 2.5 h, then filtered through Celite to remove the catalyst, and concentrated in vacuo to give 406 mg (2.04 mmol, 75%) of **44** as a colorless oil, as a mixture of amide rotamers (Z/E 71:29): IR ($CHCl_3$) 3440, 3400, 1725, 1670, 1490, 1445; ^{1}H NMR (200 MHz) 8.17 (d, 1 H, J = 12.1 Hz, *H*C(O) *E*-rot.), 8.04 (s, 1 H, *H*C(O) *Z*-rot.), 6.52 (br s, 1 H, N*H*), 3.71 (s, 3 H, CH_3OC(O) *E*-rot.), 3.67 (s, 3 H, CH_3OC(O) *Z*-rot.), 2.43–2.18 (m, 1 H, C*H*C), 1.66–1.22 (m, 8 H, $(CH_2)_4$), 1.54 (s, 3 H, CH_3C); ^{13}C NMR (50 MHz, most carbons show two peaks because of rotamers) 173.6 (CH_3OC(O)), 163.1 and 160.5 (HC(O)), 61.3 and 61.2 (CH_3C), 52.7 and 52.2 (CH_3OC(O)), 48.4 and 46.9 (CHC), 26.9, 26.8, 26.3, 25.3, 25.2, 25.1, and 25.0 ($(CH_2)_4$), 22.1 and 20.0 (CH_3C); MS (EI) $(M - C_5H_9)^+$ = 140; $(M - CO_2Me)^+$ = 131.

2-Amino-2-cyclopentylpropanoic Acid, HCl Salt (45). In a similar fashion as for the deprotection of **17** and **19** (vide supra), compound **44** (154 mg, 0.77 mmol) was deprotected to give 148 mg (0.76 mmol, 99%) of **45**, as a light brown solid: ^{1}H NMR (200 MHz, D_2O) 2.48–2.31 (m, 1 H, C*H*C), 1.88–1.24 (m, 8 H, $(CH_2)_4$), 1.56 (s, 3 H, CH_3C); ^{13}C NMR (50 MHz, D_2O) 176.1 (HOC(O)), 64.3 (CH_3C), 47.6 (CHC), 28.4 and 28.3 (2 × $CHCH_2$), 26.8 and 26.7 (2 × $CHCH_2CH_2$), 21.7 (CH_3C); MS (FAB) $(M - Cl^-)^+$ = 158.

Methyl 2-Amino-2-(2-oxocyclohexyl)-2-phenylacetate (46). To a solution of **45** (426 mg, 1.34 mmol, 72:28 mixture of isomers) in CH_3CN (7.0 mL) was added at rt Me_3SiI (0.29 mL, 401 mg, 2.00 mmol). After 2 h of stirring at 40 °C, the reaction mixture was poured out into 1 N aqueous $NaHSO_3$. The pH was adjusted to 9 using K_2CO_3, and the mixture was extracted with CH_2Cl_2 (3×). The organic layers were dried (K_2CO_3) and concentrated in vacuo to give 358 mg of a crude product, which was purified using the following acid–base extractive procedure: the crude product was dissolved in 1 N aqueous $NaHSO_4$ and washed with CH_2Cl_2 (2×). The water layer was then made with K_2CO_3 and extracted with CH_2Cl_2 (3×). The organic layers were dried (K_2CO_3) and concentrated in vacuo to give 161 mg (0.62 mmol, 46%) of **46** as a colorless oil which solidified upon standing, as a mixture of isomers (72:28): IR ($CHCl_3$) 3480, 3420, 1725, 1700, 1595; ^{1}H NMR (200 MHz) 7.54–7.19 (m, 5 H, Ph), 3.71 (s, 3 H, CH_3OC(O)C, minor isomer), 3.64 (s, 3 H, CH_3OC(O)C, major isomer), 3.33 (dd, 1 H, J = 5.4, 12.4 Hz, CHC(O), major isomer), 2.98 (dd, 1 H, J = 5.1, 12.9 Hz, CHC(O), minor isomer), 2.39–1.42 (m, 10 H, $(CH_2)_4$, NH_2); ^{13}C NMR (50 MHz, most carbons show two peaks because of diastereomers) 212.7 and 211.4 (CH_2C(O)), 176.4 and 175.1 (CH_3OC(O)C), 141.5 and 140.0 (Ph), 128.6, 128.3, 128.1, 127.8, 127.4, 126.6, 125.9 and 125.2 (Ph), 65.2 and 63.6 (CHC), 60.8 and 58.7 (CHC(O)), 52.3 and 52.0 (CH_3OC(O)C), 42.7 and 42.4 (CH_2C(O)), 30.6, 27.7, 27.6, 27.1, 25.3, and 25.0 ($CH(CH_2)_3$); MS (EI) $(M - CO_2Me)^+$ = 202.

2-Amino-2-(2-oxocyclohexyl)-2-phenylacetic acid, HCl Salt (47). A solution of **46** (89 mg, 0.34 mmol) in 6 N HCl (4 mL)

was stirred at reflux for 30 h. The mixture was concentrated in vacuo to give 87 mg (0.31 mmol, 90%) of **47** as a light yellow solid, as a mixture of isomers (57:43): ^{1}H NMR (200 MHz, D_2O) 7.61–7.40 (m, 5 H, Ph), 4.07 (dd, 1 H, J = 4.8, 14.3 Hz, C*H*C(O) major isomer), 3.70 (dd, 1 H, J = 5.4, 11.7 Hz, C*H*C(O) minor isomer) 2.67–1.43 (m, 8 H, $(CH_2)_4$); ^{13}C NMR (50 MHz, D_2O, some carbons show two peaks because of diastereomers) 216.8 (CH_2C(O)), 174.6 (HO*C*(O)C), 136.0 and 134.8 (Ph), 131.6, 131.5, 131.4, 131.3, 131.1, 130.9, 129.9, and 126.7 (Ph), 67.2 (*C*HC), 57.2 and 56.7 (*C*HC(O)), 43.9 and 43.6 (CH_2C(O)), 32.0, 29.8, 29.4, 28.9, 26.3, and 26.1 (CH(CH_2)$_3$). The product slowly decomposes upon standing in D_2O.

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, i.e. **17**, **19–21**, **24–28**, **30–33**, and **38–47**. Experimental details of the X-ray structure determination of **41**, ORTEP representation of **41**, and tables of fractional atomic coordinates, thermal parameters, and interatomic distances and angles for **41** (57 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.