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Efficient Synthesis of 1-Azadienes Derived from α-Aminoesters. Regioselective Preparation of α-Dehydroamino Acids, Vinylglycines, and α-Amino Acids

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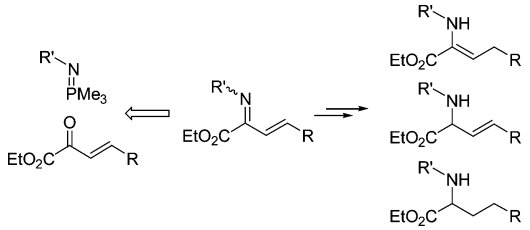

An efficient synthesis of 1-azadienes derived from α-aminoesters is achieved through an aza-Wittig reaction of phosphazenes with β,γ-unsaturated α-ketoesters. Regioselective 1,2-reduction of these functionalized 1-azadienes affords vinylglycine derivatives, while conjugative 1,4-reduction gives α-dehydroamino acid compounds. Reduction of both the carbon−carbon and the imine−carbon−nitrogen double bonds leads to the formation of α-amino acid derivatives.

Introduction

α,β-Unsaturated imines also called 1-azadienes are a versatile family of compounds with a wide range of applications in the field of organic chemistry.[1] Besides the well-known aza-Diels−Alder reaction, 1-azadienes show a very assorted reactivity and have been extensively used in the synthesis of several natural products. Recent examples in which 1-azadiene species are involved in the key step are the synthesis of (+)-abresoline,[2a] piericidin A1 and B1,[2b] ningalin,[2c] phomazarine,[2d] or cystodamine.[2e] Moreover, owing to their ambident electrophilic character, α,β-unsaturated imines can either undergo 1,2[3] or conjugate (1,4)[4] nucleophilic addition processes, although generally, the control on the regioselectivity of the addition process is difficult and the double nucleophilic addition products are frequently obtained.[5]

The simplest method for the synthesis of α,β-unsaturated imines implies condensation of α,β-unsaturated carbonyl compounds with primary amines.[6] This method is often complicated by the Michael addition reaction, especially in the case of α,β-unsaturated ketones, and the olefination reaction of β-phospho-

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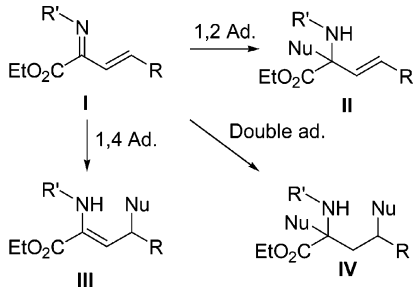
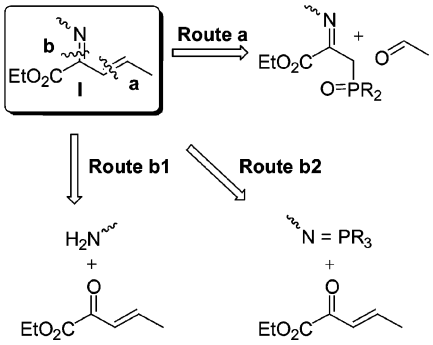
SCHEME 1. Potential Nucleophilic Additions to *β,γ*-Unsaturated α-Iminoesters I



SCHEME 2. Retrosynthesis of *β,γ*-Unsaturated α−Iminoesters I



rated imines or enamines with aldehydes to generate the conjugated C═C bond is usually a good alternative.[7] On the other hand, the aza-Wittig reaction of phosphazenes with carbonyl compounds represents an easy method for the construction of imine carbon−nitrogen double bonds in very mild reaction conditions.[8] Moreover, phosphazenes have proved to be useful building blocks for the synthesis of functionalized imine compounds such as electronically neutral 2-azadienes,[9a] electron-poor 2-azadienes derived from aminophosphorus derivatives,[9b] electron-poor 2-azadienes derived from α-[9c] or *β*-amino acids,[9d] and 3-fluoroalkyl-2-azadienes,[9e] and these azadienes have been used also as key intermediates in the preparation of cyclic compounds.[9] In addition, when a carboxylic substituent is present at the 2 position of the 1-azadiene, the resulting *β,γ*-unsaturated α-iminoesters **I** are α-amino acid derivatives, which could be excellent starting materials for the selective synthesis of vinylglycines **II** (Scheme 1, 1,2-addition), α-dehydro aminoesters **III** (Scheme 1, 1,4-addition), or saturated α-aminoesters **IV**, if the double addition occurs (Scheme 1, 1,2- and 1,4-additions).

The importance of α-amino acids and their derivatives as building blocks of proteins and peptides ensures continued interest in their chemistry.[10] Nonproteogenic α-amino acids are expected to play key roles in improving the original properties and functions of proteins. Among this family are α-dehydroamino acids. They show intriguing biological activities,[11] have been used to modify the conformational properties of peptides,[12] and also represent an important family of compounds in organic synthesis as precursors of α-amino acids, commonly through their enantioselective catalytic hydrogenation.[13] The most common procedure for the preparation of α-dehydroamino acids is the *β*-elimination of α-amino acid derived alcohols or halides,[14a,b] although efficient synthesis of α-dehydroamino acids by ring opening of aziridines[14c] or nucleophilic addition to alkynoates[14d] has also been reported.

Continuing with our interest in the design and the chemical behavior of azadienes, we report here an efficient synthesis of α-alkoxycarbonyl α,*β*-unsaturated imines, as well as the synthetic application of these substrates as intermediates for the preparation of vinylglycine, α-dehydroamino, and α-amino acid derivatives. Retrosynthetically, we envisaged obtaining goal products, *β,γ*-unsaturated α-iminoesters **I** (Scheme 2), through the construction of the carbon−carbon (C═C) double bond by means of the olefination reaction (Wittig−Horner or Wadsworth−Emmons reaction) of imines or tautomeric enamines derived from phosphine oxide (R = C_6H_5, Scheme 2, route a) with carbonyl compounds in a similar way to that previously reported for 1-azadienes.[7] Alternative processes could involve either the formation of the carbon−nitrogen double bond by means of a simple condensation reaction of amines and the α,*β*-unsaturated keto-esters (Scheme 2, route b1) or by the aza-Wittig reaction of phosphazenes with α,*β*-unsaturated keto-esters (Scheme 2, route b2), a strategy widely used for the preparation of 2-azadienes derived from α- and *β*-amino acids.[9]

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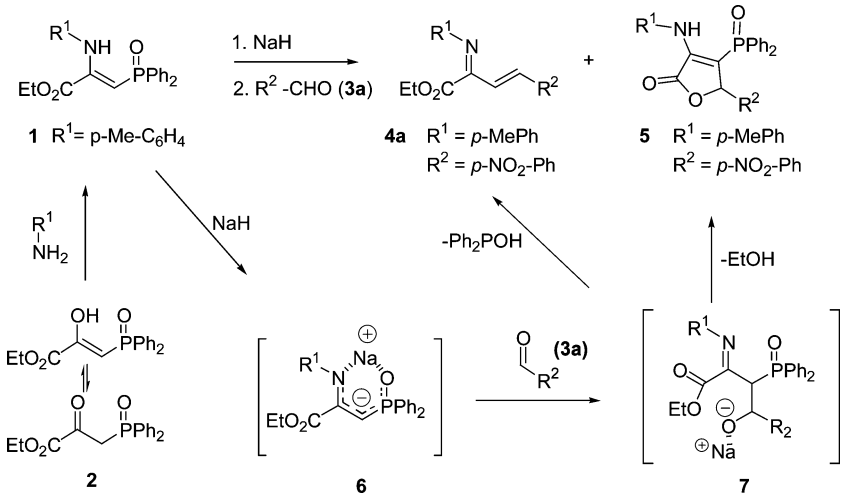
SCHEME 3. Wittig−Horner Reaction of Enamine 1 with *p*-Nitrobenzaldehyde 3a



Results and Discussion

Initially, we explored the preparation of β,γ-unsaturated α-iminoesters **I** through the olefination reaction of imines or tautomeric enamines derived from phosphine oxide (R = C_6H_5, Scheme 2, route a) with carbonyl compounds. Required enamine phosphine oxide **1** was prepared by a condensation reaction of the tautomeric keto/enol mixture of phosphine oxide **2** with *p*-tolylamine (R^1 = *p*-CH_3−C_6H_4, Scheme 3). Only the *Z*-isomer of enamine **1** (R^1 = *p*-CH_3–C_6H_4) was obtained. The coupling constant $^3J_{PC}$ = 17.5 Hz for the carbonyl group of carboxylic ester observed in the ^{13}C NMR spectrum is consistent with a *trans*-configuration of the carboxylic group toward the phosphine oxide group.[7] Then, the Wittig−Horner reaction of enamine-phosphine oxide **1** with aldehyde was studied. Treatment of enamine **1** with NaH in THF and subsequent addition of *p*-nitrobenzaldehyde **3a** (R^2 = *p*-NO_2−C_6H_4) afforded not only the expected functionalized α,β-unsaturated imine **4a** (R^1 = *p*-CH_3−C_6H_4, R^2 = *p*-NO_2−C_6H_4) in low yield (38%) as an *anti/syn*-mixture of imines (60/40), but also cyclic α-dehydroamino acid derivative **5** (R^1 = *p*-CH_3−C_6H_4, R^2 = *p*-NO_2−C_6H_4; 21%) containing a phosphine oxide group (Scheme 3). Imine **4a** and cyclic enamine **5** were fully characterized by ^1H NMR, ^{13}C NMR, MS, and IR spectroscopy. Characteristic coupling constants for the vinyl protons of **4a** in the range of 16 Hz are consistent with an *E* configuration of the double bond. On the other hand, characteristic signals for **5** in the ^1H NMR spectrum are the doublet at δ = 6.65 ppm, with a coupling constant $^3J_{PH}$ = 3.1 Hz, corresponding to the CH proton in the five-membered ring and the singlet δ = 6.84 ppm, which showed interchange with D_2O and was assigned to the NH group. Whereas the ^{13}C NMR spectrum shows a characteristic doublet signal at δ = 81.7 ppm with a coupling constant $^2J_{PH}$ = 3.1 Hz for the CH in the five-membered ring, another doublet at δ = 107.1 with a coupling constant $^1J_{PC}$ = 110.3 Hz and a singlet at δ = 144.1 ppm assigned to the β- and α-enaminic quaternary carbons, respectively, and a doublet at δ = 166.9 with a coupling constant $^3J_{PC}$ = 17.5 Hz for the amide C═O.

Formation of both products could be explained by an initial addition of the carbanion **6** to aldehyde **3a** to give adduct **7**. Olefination reaction with the loss of diphenylphosphine oxide from this intermediate **7** could give functionalized α,β-unsaturated imine **4a**, while intramolecular cyclocondensation of adduct **7** with the loss of ethanol could yield cyclic enamine derived from 2,5-dihydro-furanone **5** (Scheme 3).

The preparative utility of this process for the preparation of imines **4** is limited due to the low yield and the presence of the cyclic enamine **5** with concomitant problems for the separation and purification. For this reason, we explored the preparation of unsaturated imines **4** by formation of carbon−nitrogen double bonds from α,β-unsaturated ketones (Scheme 2, routes b1,2). However, Lewis acid-catalyzed condensation of an amine and β,γ-unsaturated α-ketoester (Scheme 2, route b1) only gave very low yield of the β,γ-unsaturated α-iminoester **4**, because a subsequent conjugate addition of a second molecule of amine to unsaturated derivative took place and 3-amino-2,5-dihydro-1*H*-pyrrolin-2-ones were mainly obtained.[15] For this reason, the preparation of unsaturated imines **4** by construction of the carbon−nitrogen double bonds by aza-Wittig reaction of phosphazenes with β,γ-unsaturated α-ketoesters was explored (Scheme 2, route b2). We have already demonstrated the usefulness of phosphazene species in the selective formation of imine bonds,[9,16] and the increased reactivity of phosphazenes when aromatic substituents at the phosphorus are replaced by alkyl substituents.[17] Therefore, we thought that an efficient selective synthesis of β,γ-unsaturated α-iminoesters **I** could be achieved by aza-Wittig reaction of the very reactive phosphazenes **9** derived from trimethyl phosphine (Scheme 2, route b2, R = Me, vide supra) and β,γ-unsaturated α-ketoesters.

β,γ-Unsaturated α-ketoesters, although not commercially available, can be easily prepared by aldolic or Wittig-type condensation of aldehydes with the corresponding pyruvate-derived reagent, as described in the literature.[15] Phosphazenes were readily prepared in situ by addition of trimethylphosphine to aryl azides **8** and, given the instability of *P*-trialkyl phosphazene species, *N*-aryl trimethylphoshazenes **9** were not isolated[18] and were used without purification for the following purposes. The

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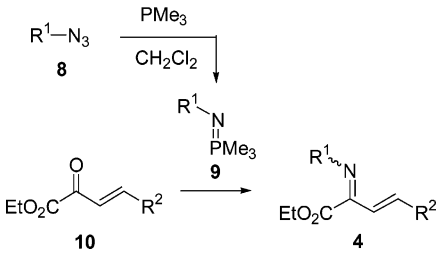
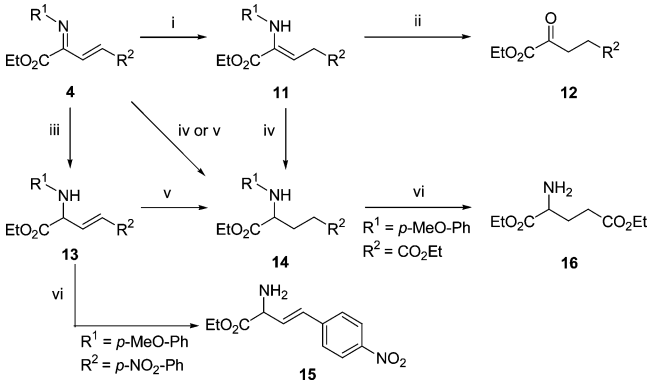
SCHEME 4. Synthesis of 1-Azadienes 4

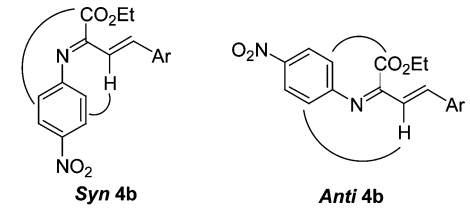


SCHEME 5. Selective Conjugate (1,4) 1,2 or Total Reduction of 1-Azadienes 4[a]



[a] Reagents and conditions: (i) $NaBH_4$, THF, −78 °C; (ii) HCl 3 M, THF; (iii) $NaBH_4$/TFA, CH_3CN, 0 °C; (iv) $NaBH_4$, THF, −30 °C; (v) H_2, Pd−C, MeOH, rt; (vi) CAN, $MeCN/H_2O$.

CHART 1. ^1H and ^{13}C NMR δ Values for *syn*- and *anti*-Imines 4b



subsequent addition of the β,γ-unsaturated α-ketoester **10** afforded the 1-azadienes derived from α-aminoesters **4** (Scheme 4).

1-Azadienes derived from α-aminoesters **4** were obtained as *syn*/*anti*-mixtures. The configuration of the conjugated double bond was retained in all the cases. The assignment of the *syn*- and *anti*-isomers was established on the basis of the "steric compression" observed in the δ values in ^1H and ^{13}C NMR spectra.[19] For 1-azadiene **4b** (Chart 1, vide infra), if the aromatic substituent on the nitrogen has a *cis*-orientation respective of the conjugated double bond (*syn*-isomer), the δ values are smaller in ^1H and ^{13}C NMR than the corresponding δ values when the substituent of the nitrogen has a *trans*-orientation respective of the double bond (*anti*-isomer). The same effect was observed for the α-carboxylic substituent.

TABLE 1. 1-Azadienes 1 Obtained by Aza-Wittig Reaction

entry	compd	R^1	R^2	yield (%)	*syn*/*anti*
1	**4a**	*p*-Me−C_6H_4	*p*-NO_2−C_6H_4	91[a]	41/59
2	**4b**	*p*-NO_2−C_6H_4	*p*-NO_2−C_6H_4	90[a]	38/62
3	**4c**	*p*-MeO−C_6H_4	*p*-NO_2−C_6H_4	91[a]	43/57
4	**4d**	*p*-Me−C_6H_4	*p*-Me−C_6H_4	89[b]	41/59
5	**4e**	*p*-NO_2−C_6H_4	*p*-Me−C_6H_4	82[b]	43/57
6	**4f**	*p*-MeO−C_6H_4	Me	91[b]	36/64
7	**4g**	*p*-MeO−C_6H_4	2-furyl	91[b]	44/66
8	**4h**	*p*-NO_2−C_6H_4	CO_2Et	94[b]	42/68
9	**4i**	*p*-Me−C_6H_4	CO_2Et	94[b]	40/60
10	**4j**	*p*-MeO−C_6H_4	CO_2Et	95[b]	41/59

[a] Isolated yield. [b] Crude yield.

TABLE 2. α-Dehydroamino Esters 11 Obtained by Selective Reduction of 1-Azadienes 4 and β,γ-Unsaturated α-Ketoesters 12

entry	compd	R^1	R^2	yield[a] (%)
1	**11a**	*p*-MeO−C_6H_4	*p*-NO_2−C_6H_4	64
2	**11b**	*p*-NO_2−C_6H_4	CO_2Et	75
3	**11c**	*p*-Me−C_6H_4	CO_2Et	79
4	**11d**	*p*-MeO−C_6H_4	CH_3	71
5	**11e**	*p*-MeO−C_6H_4	2-furyl	69
6	**12a**	*p*-MeO−C_6H_4	*p*-NO_2−C_6H_4	82
7	**12b**	*p*-NO_2−C_6H_4	CO_2Et	85

[a] Isolated yield.

Azadienes **4** showed in general very low stability because they yielded the hydrolysis products when most of the common purification techniques were used. β,γ-Unsaturated α-iminoesters **4a**−**c** (R^2 = *p*-NO_2−C_6H_4; Table 1, entries 1−3) are solids and allowed workup with water and purification by crystallization in diethyl ether; however, only workup with water to get rid of trimethylphosphine oxide was possible for β,γ-unsaturated α-iminoesters **4d**,**e** (R^2 = *p*-Me−C_6H_4; Table 1, entries 4 and 5), **4f** (R^2 = Me; Table 1, entry 6), **4g** (R^2 = 2-furyl; Table 1, entry 7), or **4h**−**j** (R^2 = CO_2Et; Table 1, entries 8−10). Chromatography or distillation of 1-azadienes **4d**−**j** afforded undesirable side products and, therefore, they were used without purification in further steps.

This raised the possibility of the selective reduction of functionalized 1-azadienes **4**. Treatment of 1-azadienes **4** derived from α-amino acids with $NaBH_4$ at −78 °C afforded (*Z*)-α-dehydroaminoesters **11** with good yields (Scheme 5, Table 2, entries 1−5) in a stereoselective fashion. α-Dehydroaminoesters **11** were fully characterized by IR and ^1H and ^{13}C NMR spectroscopy and CIMS and ^1H NMR-NOE experiments were performed to determine the configuration of the enaminic bond. The ^1H NMR spectrum of **11a** (R^1 = *p*-MeO−C_6H_4, R^2 = *p*-NO_2−C_6H_4) showed characteristic doublet at δ = 3.38 ppm and triplet at δ = 6.30 ppm with a coupling constant $^3J_{HH}$ = 7.2 Hz, corresponding to the CH_2 and the olefinic CH, respectively. The doublet for the methylene group showed a NOE effect of 12% with a singlet at δ = 5.68 ppm, which underwent interchange with D_2O and was, therefore, assigned to the NH group, whereas the triplet for the methynic proton showed a NOE effect of 8% with the quadruplet at δ = 4.27 ppm, corresponding to the CH_2 of the ethoxy group. NOE effects are consistent with a *Z* configuration of the double bond.

The scope of the reaction is not restricted to aryl **11a** (R^2 = *p*-NO_2−C_6H_4, Table 2, entry 1) or heterocyclic **11e** (R^2 = 2-furyl, Table 2, entry 5) substituted compounds because

(18) The formation of phosphazene species **9** was evident from the visible nitrogen gas formation during the addition of trimethylphosphine and was monitored by NMR when *p*-nitrophenyl azide was used. The ^{31}P NMR spectrum showed a clear disappearance of the signal corresponding to trimethylphosphine at δ = −61.1 ppm and the appearance of a new signal at δ = 14.7 ppm attributed to the phosphazene **9** (R^1 = *p*-NO_2−C_6H_4).

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TABLE 3. β,γ-Unsaturated α-Aminoesters 13 and Saturated α-Aminoesters 14 Obtained by Selective Reduction of 1-Azadienes 4

entry	compd	R^1	R^2	yield[a] (%)
1	**13a**	*p*-NO_2−C_6H_4	*p*-NO_2−C_6H_4	89
2	**13b**	*p*-Me−C_6H_4	*p*-NO_2−C_6H_4	85
3	**13c**	*p*-MeO−C_6H_4	*p*-NO_2−C_6H_4	83
4	**13d**	*p*-Me−C_6H_4	*p*-Me−C_6H_4	86
5	**13e**	*p*-MeO−C_6H_4	CH_3	81
6	**14a**	*p*-Me−C_6H_4	CO_2Et	88,[b] 82,[c] 78[d]
7	**14b**	*p*-MeO−C_6H_4	CO_2Et	87,[b] 81[c]
8	**14c**	*p*-MeO−C_6H_4	*p*-NO_2−C_6H_4	90,[b] 92[e]
9	**14d**	*p*-MeO−C_6H_4	CH_3	88[b]
10	**14e**	*p*-MeO−C_6H_4	2-furyl	82[b]

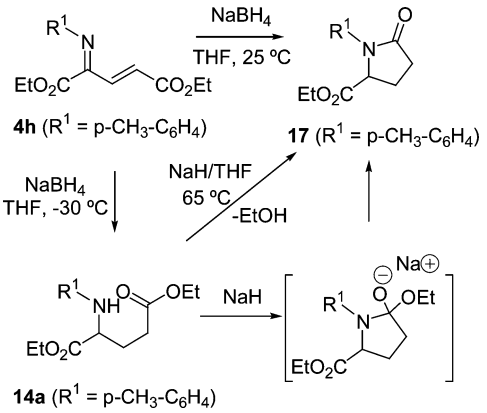
[a] Isolated yield. [b] From 1-azadiene **4** with H_2, Pd−C. [c] From 1-azadiene **4** with $NaBH_4$. [d] From enaminoester **11** with $NaBH_4$. [e] From vinylglycines **13** with H_2, Pd−C.

α-dehydroaminoesters **11b**,**c** derived from glutamic esters (R^2 = CO_2Et, Table 2, entries 2 and 3) or with an alkyl substituent **11d** (R^2 = CH_3, Table 2, entry 4) can be obtained. Saturated α-ketoesters **12a**,**b** were also obtained with very good yields (82−85%) from esters **11a**,**b** by acidic hydrolysis of the enaminic group with HCl.

Different selectivity on the reduction was observed in acidic media, because the treatment of 1-azadienes **4** derived from α-aminoesters with $NaBH_4$ in the presence of trifluoroacetic acid (TFA) at 0 °C yielded the vinylglycines **13** with very good yields (Scheme 5, Table 3, entries 1−5). In the presence of a protic source, the iminium salt is expected to be formed, activating the 1,2-nucleophilic addition of hydride anion. Full characterization of vinylglycines **13** by ^1H and ^{13}C NMR and IR spectroscopy and EIMS was performed. The ^1H NMR spectrum of vinylglycine **13b** shows a double doublet at δ = 6.53 ppm for one of the olefinic protons with a coupling constant $^3J_{HH}$ = 15.9 Hz, characteristic for *E* configuration, with the other olefinic proton at δ = 6.86 ppm and a doublet at δ = 4.75 ppm corresponding to the CHN. The most characteristic signals in the ^{13}C NMR spectrum are those corresponding to the alkene bond at δ = 130.3 and 130.2 ppm and the CHN at δ = 59.1 ppm. When the same acidic conditions were tried with the unstable 1-azadienes derived from glutamate **4h**−**j**, no vinylglycine **13** was obtained, and imine hydrolysis to carbonyl compounds **10** was observed instead.

Among the α-amino acid family, β,γ-unsaturated α-amino acids exhibit important biological activity. The simplest member of this family, α-vinylglycine is a potent inhibitor of several transaminase and decarboxylase enzymes,[20a,b] and nature produces many biologically active molecules bearing substituted α-vinylglycines in their structure. Rhizobitoxin,[20c] radiosumin,[20d] or (*L*)-*trans*-α-methoxyvinylglycine[20e] constitute some examples of natural α-vinylglycines. β,γ-Unsaturated α-amino acid derivatives have been synthesized by deconjugation of dehydro-α-amino acids,[21a,b] three-component reaction of alkenyl boronic acid, amine, and ketoacid,[21c] formation of the vinylic bond by oxidation of the parent γ-functionalized α-amino acids,[21d−g] oxidation of the β-amino alcohol to α-amino acid,[21h] isomerization of β-vinylcyclines,[21c,i] or reduction of the α-iminoester.[21j]

SCHEME 6. Synthesis of Lactam 17



Then the synthesis of the saturated α-aminoesters **14** was explored (Scheme 5, vide supra), and the preparation of these compounds **14** can be achieved by reduction of the α-dehydroamino esters **11** with $NaBH_4$ at −30 °C or by catalytic hydrogenation of the β,γ-unsaturated α-aminoesters **13**. Alternatively, the saturated α-aminoesters **14** can also be prepared directly from the β,γ-unsaturated α-iminoesters **4** either by reduction with $NaBH_4$ at −30 °C or by catalytic hydrogenation (Scheme 4, Table 3, entries 6−10). α-Aminoesters **14** were fully characterized on the basis of their ^1H and ^{13}C NMR, IR, and EIMS.

It is noteworthy that this strategy can also be used for the preparation of vinylglycine derivatives and glutamic ester. Primary vinylglycine **15** and glutamic ester **16** can also be obtained in good yields when *N*-*p*-methoxyphenyl vinylglycine **13c** (R^1 = *p*-MeO−C_6H_4, R^2 = *p*-NO_2−C_6H_4) and glutamic esters **14b** (R^1 = *p*-MeO−C_6H_4, R^2 = CO_2Et) were used. *N*-Deprotection of the *N*-methoxyphenyl vinylglycine **13c** with cerium ammonium nitrate (CAN) in acetonitrile and water (Scheme 5) gave vinylglycine **15** in 62% yield. Similarly, *N*-deprotection of the *N*-methoxyphenyl glutamic ester **14b** with CAN afforded glutamic ester **16** (62%).

A special case is the reduction at 25 °C of β,γ-unsaturated α-aminoester **4h** with two carboxylic substituents. The cyclic lactam **17** derived from glutamic ester was obtained in 73% yield when the β,γ-unsaturated α-aminoester **4h** was treated with $NaBH_4$ in THF at 25 °C (Scheme 6). No lactam **17** was observed when glutamic diester **14a** was heated in THF, but the metalation of the saturated α-amino ester **14a** with NaH in THF and subsequent heating of the anion afforded the cyclic lactam **17**. These results suggest that when the reduction of the β,γ-unsaturated α-aminoester **4h** is carried out, first saturated β,γ-unsaturated α-aminoester **14a** is formed and then the intramolecular attack of the anion to the carbonyl group affords the cyclic product **17** after the loss of ethanol (Scheme 6).

Conclusion

The use of aza-Wittig reaction involving phosphazene species derived from trimethylphosphine constitutes an excellent alter-

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native for the construction of the imine carbon−nitrogen double bond of unsaturated imines derived from α-amino acids, avoiding the usual regioselectivity problems by the condensation of α,*β*-unsaturated carbonylic compounds with amines. A very efficient regioselective synthesis of electron-poor 1-azadienes derived from α-amino acids **4** is described. Regioselective conjugate reduction (1,4-addition) of α,*β*-unsaturated imines derived from α-amino acids **4** gives α-dehydroamino acid derivatives **11**, including α-dehydro glutamic ester, while selective reduction (1,2-addition) of the imine carbon−nitrogen double bond of functionalized α,*β*-unsaturated imines **4** led to the formation of vinylglycine derivatives **13** and **15**. Reduction of both the carbon−carbon and the imine carbon−nitrogen double bonds of α,*β*-unsaturated imines **4** afforded α-amino acid derivatives **14** and **16**, as well as cyclic lactam derived from glutamic ester **17**.

Experimental Section

Representative Example for the Synthesis of 1-Azadienes 4. To a solution of the corresponding azide **8** (5 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added a 1 M solution of trimethylphosphine in toluene (5 mL). The resulting solution was stirred 30 min until N_2 evolution stopped, which indicates the completion of the reaction and the phosphazene **9** formation, and the corresponding neat *β*,*γ*-unsaturated α-ketoester **10** (5 mmol) was then added. The reaction was stirred at rt for 30 min and was then washed with water (3 × 40 mL), dried over $MgSO_4$, and concentrated under reduced pressure. 1-Azadienes **4d**−**i** were used without any further purification in the following steps, and 1-azadienes **4a**−**c** were purified by crystallization from Et_2O.

***syn*- and *anti*-Ethyl 4-(*p*-nitrophenyl)-2-*p*-nitrophenylimino-3-(*E*)-butenoate 4b.** Synthesized according to the general procedure with *p*-nitrophenyl azide (0.82 g, 5 mmol) and ethyl (*E*)-4-*p*-nitrophenyl-2-oxo-3-butenoate (1.25 g, 5 mmol), affording 1.52 g (91%) of **4b** as a yellow solid (*syn*/*anti* = 38/62). Mp 100−101 °C (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.28 and 8.17 (d, $^3J_{HH}$ = 8.5 Hz, d, $^3J_{HH}$ = 8.5 Hz, 2H), 8.23 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.71 and 7.51 (d, $^3J_{HH}$ = 8.5 Hz, d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.60 and 7.36 (d, $^3J_{HH}$ = 16.6 Hz, d, $^3J_{HH}$ = 16.3 Hz, 1H), 7.11 and 6.60 (d, $^3J_{HH}$ = 16.6 Hz, d, $^3J_{HH}$ = 16.3 Hz, 1H), 7.02 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 4.49 and 4.14 (q, $^3J_{HH}$ = 6.9 Hz, q, $^3J_{HH}$ = 7.0 Hz, 2H), 1.48 and 1.02 (t, $^3J_{HH}$ = 6.9 Hz, t, $^3J_{HH}$ = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 163.4 and 162.2, 159.9 and 158.3, 155.3 and 153.9, 148.0, 144.4, 141.5 and 139.6, 140.6, 128.2 and 119.5, 128.0 and 127.8, 124.8 and 124.4, 123.9, 119.7 and 119.3, 65.4 and 62.4, 13.8 and 13.4. FTIR (KBr) ν_{max} (cm^{-1}): 1732, 1600. CIMS *m*/*z* (amu): 370 ($M^+ + 1$, 100). Elem anal. Calcd (%) for $C_{18}H_{15}N_3O_6$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.50; H, 4.11; N, 11.42.

Representative Example for the Selective 1,4-Reduction of 1-Azadienes 4 with $NaBH_4$. Synthesis of (*Z*)-α-Dehydroamino Esters 11: To a suspension of $NaBH_4$ (76 mg, 2 mmol) in THF (3 mL) at −78 °C was added a solution of 1-azadiene **4** (1 mmol) in THF (2 mL). The reaction was stirred at −78 °C for 12 h and was then quenched with a saturated aqueous solution of NH_4Cl (20 mL). The mixture was warmed to rt, extracted with CH_2Cl_2, (3 × 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:3).

Ethyl 2-*p*-Methoxyphenylamino-4-*p*-nitrophenyl-2-(*Z*)-butenoate 11a. Synthesized according to the general procedure with ethyl 2-*p*-methoxyphenylimino-4-*p*-nitrophenyl-(*E*)-3-butenoate **4c** (354 mg, 1 mmol), affording 232 mg (64%) of **11a** as a pale yellow oil. R_f (AcOEt): 0.87. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.13 (d, $^3J_{HH}$ = 9.1 Hz, 2H), 7.28 (d, $^3J_{HH}$ = 9.1 Hz, 2H), 6.82 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 6.76 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 6.30 (t, $^3J_{HH}$ = 7.2 Hz, 1H), 5.68 (s, 1H), 4.27 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 3.78 (s, 3H, CH_3O), 3.38 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.6, 154.4, 147.4, 140.4, 136.9, 131.8, 129.3, 123.7, 120.6, 119.2, 114.5, 61.7, 55.6, 34.5, 14.2. FTIR (film) ν_{max} (cm^{-1}): 3371, 1727. CIMS *m*/*z* (amu): 357 ($M^+ + 1$, 100). Elem anal. Calcd (%) for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.00; H, 5.71; N, 7.82.

Procedure for the Hydrolysis of α-Dehydroamino Esters 11. To a solution of α-dehydroamino ester **11** (0.5 mmol) in THF (1 mL) was added a 3 M aqueous solution of HCl (1 mL), and the resulting mixture was refluxed overnight. The reaction was cooled to rt and neutralized with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL), which was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:3).

Ethyl 4-(4-Nitro-phenyl)-2-oxo-butanoate 12a. Compound **12a** was synthesized according to the general procedure with ethyl (*E*)-2-*p*-methoxyphenylamino-4-*p*-nitrophenyl-3-butenoate **11a** (179 mg, 0.5 mmol), affording 103 mg (82%) of **12a** as a colorless oil. Spectroscopic data are in agreement with literature values.[22]

Representative Example for the Selective 1,2-Reduction of 1-Azadienes 4 with $NaBH_4$ in the Presence of TFA. Synthesis of Vinylglycines 13: $NaBH_4$ (76 mg, 2 mmol) was slowly added to a solution of the corresponding 1-azadiene **4** (1 mmol) and TFA (0.5 mL) in MeCN (3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h and was then quenched with an aqueous saturated solution of $NaHCO_3$ (15 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by crystallization from MeOH.

Ethyl (*E*)-4-*p*-Nitrophenyl-2-*p*-nitrophenylamino-3-butenoate 13a. Compound **13a** was synthesized according to the general procedure with ethyl *p*-nitrophenyl-2-*p*-nitrophenylimino-(*E*)-3-butenoate **4b** (369 mg, 1 mmol), affording 391 mg (89%) of **35a** as a yellow solid. Mp 175−176 °C (Et_2O). ^{1}H NMR (300 MHz, CDCl3): *δ* 8.19 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 8.11 (d, $^3J_{HH}$ = 9.2 Hz, 2H), 7.51 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 6.78 (d, $^3J_{HH}$ = 14.6 Hz, 1H), 6.62 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 6.48 (dd, $^3J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 5.2 Hz, 1H), 5.57 (d, $^3J_{HH}$ = 5.1 Hz, 1H), 4.85 (dd, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 5.2 Hz, 1H), 4.41−4.22 (m, 2H), 1.36 (t, $^3J_{HH}$ = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 169.6, 150.9, 147.4, 141.8, 139.2, 131.2, 128.0, 127.4, 126.3, 124.1, 112.2, 62.9, 57.7, 14.2. FTIR (KBr) ν_{max} (cm^{-1}): 3344, 1728. EIMS *m*/*z* (amu): 371 (M^+, 87), 298 (100). Elem anal. Calcd for $C_{18}H_{17}N_3O_6$: C, 58.22; H, 4.61; N, 11.32. Found: C, 58.17; H, 4.57; N, 11.38.

Representative Examples for the Total Reduction of 1-Azadienes 4. Synthesis of α-Aminoesters 14. Procedure A: catalytic hydrogenation of 1-azadienes **4** or vinylglycines **13**. A solution of 1-azadiene **4** or vinylglycine **13** (1 mmol) in EtOH (5 mL) with Pd−C (10%; 53 mg, 0.05 mmol) was stirred overnight under H_2 atmosphere at 80 psi. The resulting mixture was filtered through Celite and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:3). Procedure B: reduction of 1-azadienes **4** or α-dehydroamino esters **11** with $NaBH_4$. Over a solution of *β*,*γ*-unsaturated 1-azadiene **4** or α-dehydroamino ester **11** (1 mmol) in THF at −30 °C was added $NaBH_4$ (2 mmol). The resulting mixture was stirred at −30 °C for 3 h, quenched with a saturated aqueous solution of NH_4Cl, and extracted with CH_2Cl_2, which was dried over $MgSO_4$. The crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:3).

Diethyl 2-*p*-Tolylaminopentanediate 14a. Compound **14a** was synthesized according to the general procedure A with crude ethyl 4-ethoxycarbonyl-2-*p*-tolylimino-(*E*)-3-butenoate **4i** (289 mg, 1 mmol), affording 258 mg (88%) of **14a** as a colorless oil, synthesized according to the general procedure B with crude ethyl 4-ethoxycarbonyl-2-*p*-tolylimino-(*E*)-3-butenoate **4i** (289 mg, 1 mmol), affording 0.241 mg (82%) of **14a** as a colorless oil, and synthesized according to the general procedure B with ethyl

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4-ethoxycarbonyl-2-*p*-tolylamino-2-(*Z*)-butenoate **11c** (291 mg, 1 mmol), affording 234 mg (78%) of **14a** as a colorless oil. R_f (AcOEt): 0.81. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 6.54 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 4.20−4.09 (m, 5H), 4.07 (dd, $^3J_{HH}$ = 3.2 Hz, $^3J_{HH}$ = 7.5 Hz, 1H) 2.49−2.44 (m, 2H), 2.22 (s, 3H), 2.17−2.03 (m, 2H), 1.24 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.23 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 172.9, 144.5, 129.8, 127.8, 113.8, 61.2, 60.5, 56.5, 30.5, 28.0, 20.4, 14.2, 14.1. FTIR (film) ν_{max} (cm^{-1}): 3355, 1736. EIMS *m*/*z* (amu): 293 (M^+, 100), 220 (90). Elem anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.56; H, 7.86; N, 4.74.

Procedure for the Synthesis of Primary Vinylglycine 15. To a solution of CAN (mg, 1.5 mmol) in water (2 mL) was slowly added vinylglycine **13c** (0.5 mmol) in MeCN (2 mL) at 0 °C. The mixture was stirred for 1 h, and Na_2CO_3 was added until pH became 7. The mixture was filtered through Celite, and the filtrate was extracted with CH_2Cl_2 (3 × 20 mL), which was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 5:1).

Ethyl 2-Amino-4-(4-nitro-phenyl)-but-3-enoate 15. Synthesized according to the general procedure with ethyl (*E*)-2-*p*-methoxyphenylamino-4-*p*-nitrophenyl-3-butenoate **13c** (178 mg, 0.5 mmol), affording 77 mg (62%) of **15** as a yellow oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.11 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 7.24 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 6.76 (d, $^3J_{HH}$ = 15.8 Hz, 1H), 6.03 (dd, $^3J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 4.59 (d, $^3J_{HH}$ = 5.3 Hz, 1H), 4.12−4.00 (m, 2H), 1.12 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 169.7, 142.50, 138.9, 129.2, 127.2, 124.0, 120.5, 60.5, 58.2, 56.4, 13.4. FTIR (KBr) ν_{max} (cm^{-1}): 3365, 1736. CIMS *m*/*z* (amu): 251 ($M^+ + 1$, 100). Elem anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.64; H, 5.61; N, 11.23.

Procedure for the Synthesis of 5-Ethoxycarbonyl-1-*p*-tolyl-pyrrolidin-2-one 17. To a suspension of NaH (24 mg, 1 mmol) in THF (3 mL) at 0 °C was added a solution of diethyl 2-*p*-tolylaminopentanediate **14a** (293 mg, 1 mmol) in THF (2 mL). The reaction was stirred at 0 °C for 1 h and was then refluxed for 12 h. The reaction was cooled and quenched with a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:3), affording 182 mg (73%) of **17** as a pale yellow oil. R_f (AcOEt): 0.48. ^{1}H NMR (300 MHz, CDCl3): δ 7.33 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.11 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 4.64 (dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 6.1 Hz, 1H), 4.18 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 2.69 (m, 1H), 2.48 (m, 2H), 2.26 (s, 3H), 2.15 (m, 1H), 1.21 (t, $^3J_{HH}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 171.8, 135.5, 135.3, 129.5, 122.0, 61.9, 61.5, 30.7, 23.1, 20.8, 13.9. FTIR (film) ν_{max} (cm^{-1}) 1735, 1711. EIMS *m*/*z* (amu): 247 (M^+, 32), 174 (100). Elem anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.01; H, 6.95; N, 5.61. Pyrrolidinone **17** can also be synthesized in a "one pot" reaction from 1-azadiene **4i**: To a suspension of $NaBH_4$ (75 mg, 2 mmol) in THF (3 mL) at 0 °C was added a solution of crude diethyl ethyl 4-ethoxycarbonyl-2-*p*-tolylimino-(*E*)-3-butenoate **4i** (289 mg, 1 mmol) in THF (2 mL). The reaction was stirred at 0 °C for 1 h and was then refluxed for 12 h. The mixture was washed with H_2O, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure, and the crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:3), affording 173 mg (69%) of **17** as a pale yellow oil.

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Supporting Information Available: Full characterization and procedures for the synthesis of enamine **1**, the mixture ketone/enol **2**, furan-2-one **5**, 1-azadienes **4a**,**c**−**i**, α-dehydroamino esters **11b**−**d**, α-ketoester **12b**, vinylglycines **13b**−**d**, and α-aminoesters **14b**−**e** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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