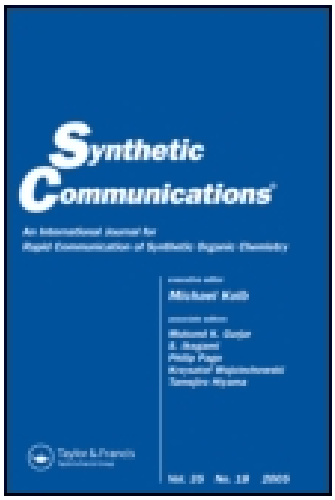


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Vinylogous β-Amino Esters from N-(N,N-Dialkylaminoalkyl)benzotriazoles

José M. Aurrecoechea [a], Alvaro Fernández [a], José M. Gorgojo [a] & Rubén Suero [a]

[a] Departamento de Química Orgánica II, Facultad de Ciencias, Universidad del País Vasco, Bilbao, Spain

Published online: 17 Aug 2006.

To cite this article: José M. Aurrecoechea, Alvaro Fernández, José M. Gorgojo & Rubén Suero (2003) Synthesis of Vinylogous β-Amino Esters from N-(N,N-Dialkylaminoalkyl)benzotriazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:5, 693-702, DOI: 10.1081/SCC-120016308

To link to this article: http://dx.doi.org/10.1081/SCC-120016308

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 5, pp. 693–702, 2003

Synthesis of Vinylogous β-Amino Esters from *N*-(*N*,*N*-Dialkylaminoalkyl)benzotriazoles

José M. Aurrecoechea,* Alvaro Fernández, José M. Gorgojo, and Rubén Suero

Departamento de Química Orgánica II,
Facultad de Ciencias, Universidad del País Vasco,
Bilbao, Spain

ABSTRACT

Treatment of *N*-(*N*,*N*-dialkylaminoalkyl)benzotriazoles with 4-bromocrotonates in the presence of zinc provides a new route to 5-(*N*,*N*-dialkylamino)-2-alkenoate esters. This is formally the result of the γ-addition of zinc dienolate reagents to iminium cations formed in situ by dissociation of the aminoalkylbenzotriazoles. When *N*-allyl protecting groups are incorporated into the benzotriazole substrate,

*Correspondence: José M. Aurrecoechea, Departamento de Química Orgánica II, Facultad de Ciencias, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain; E-mail: gopaufem@lg.ehu.es.

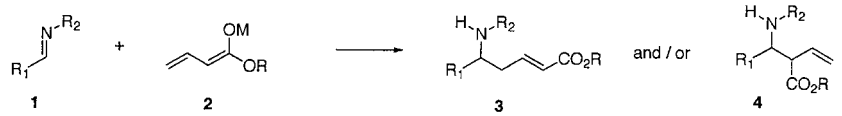
DOI: 10.1081/SCC-120016308 0039-7911 (Print); 1532-2432 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

deallylation of the tertiary allylamine products gives also a ready access to the corresponding secondary amines.

INTRODUCTION

A current research project involving the synthesis of pyrrolidines via radical cyclizations[1] required the synthesis of unsaturated amines of general structure **3** as starting materials. A further requirement in **3** was that the N atom should not contain any aryl- or electron-withdrawing substituents of the carbonyl type.[1] A simple direct route to **3** would involve the γ-addition of an appropriate metallic dienolate **2** to an imine **1** (Sch. 1). While this kind of reaction has been known for some time, significant restrictions do exist. For example, acyclic silyloxy dienes (**2**, $M = SiR_3$) undergo Lewis-acid catalyzed cycloaddition with aldimines leading to the formation of dihydropyridones.[2] Under appropriate conditions, amines **3** are also obtained but the use of either imines derived from aromatic aldehydes[2b,3] or very reactive dienes[2c,2d] is generally required for good yields. The same applies for the similar use of preformed zinc dienolates (2, $M = ZnX$).[4] Exceptions are the Lewis acid-promoted addition of 2-silyloxyfurans to imines that yields γ-addition products in high yields without apparent limitations,[5] and the use of aldonitrones in the presence of TMSOTf, that also leads to products of type **3**.[6] Alternatively, methyl 4-bromocrotonate has been utilized as precursor of in situ-generated chromium-[7] or zinc-[8] dienolates in reactions with imines,[7,8a] *N*-acyl-α-methoxyamines[8b] or α-sulfonyl amides.[8c] Limitations here include the use of less convenient starting materials[8b,8c] and/or predominant formation of α-allylated products **4**.[7,8b] Also effective, in terms of γ-selectivity, is the use of iminium salts, both with silyloxy dienes[9] and with 4-bromocrotonates[10] as starting materials. However, apparently this method has been applied only to additions to benzylic-type positions.

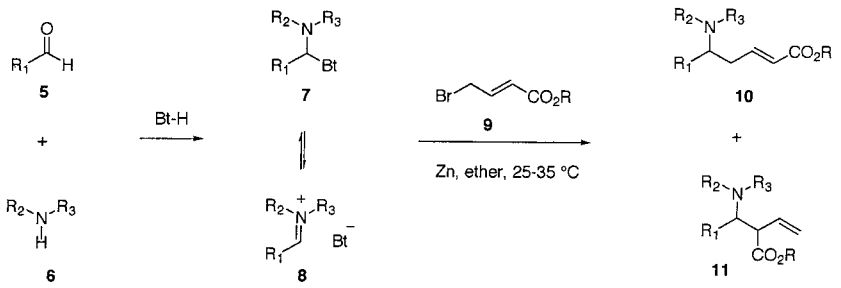


1 2 3 4

Scheme 1.

RESULTS AND DISCUSSION

We have developed a simple procedure that, starting from aldehydes **5** and secondary amines **6**, leads to tertiary amines **10** as a result of selective γ-allylation of an intermediate benzotriazole derivative **7** with an in situ-generated zinc dienolate derived from methyl or ethyl 4-bromocrotonates **9** (Sch. 2). The procedure takes advantage of the ability of *N*-(*N*,*N*-dialkylaminoalkyl)benzotriazoles **7** to dissociate[11] to the corresponding iminium cations **8** and benzotriazolyl anion, and to undergo nucleophilic addition with a large variety of nucleophiles,[12] including Reformatsky reagents,[13] silyl enol ethers,[14] and simple allylic organometallics.[15] We have examined the reactions of some representative substrates **7** with **9** in the presence of Zn and the results are presented in Table 1. γ-Allylation products **10** are obtained preferentially or exclusively in moderate isolated yields, which are given in Table 1 for two steps starting from amines **6**. In some cases, the alternative α-allylation products **11** were also isolated (Entries 1 and 6) as diastereomeric mixtures. Included in Table 1 are examples of reactions of benzotriazole adducts derived from formaldehyde (Entries 1 and 2), an aromatic aldehyde (Entry 6), and aliphatic aldehydes (Entries 3–5), both linear and branched. Therefore, the reaction appears to be of general application for benzotriazole adducts derived from any kind of aldehyde **5**. As for the amine component, both cyclic and acyclic aliphatic amines participate well, and some useful functionality has been incorporated *albeit* with some loss of efficiency (Entries 2, 5, 6). Particularly interesting is the incorporation of benzyl and allyl protecting groups since removal of these would allow the method to be applied also to the synthesis of secondary or even primary amines. As an example, deallylation of **10e** and **10f** with *N*,*N*-dimethylbarbituric acid (NDMBA) and catalytic $Pd(PPh_3)_4$[16] led in good yields to the corresponding secondary amines **12d** and **12f**, respectively (Sch. 3).

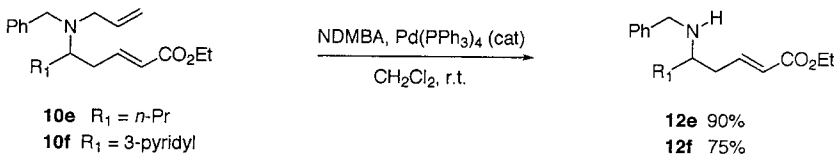


Scheme 2.

Table 1. Preparation of 5-amino-2-alkenoate esters **10** from aldehydes **5** and amines **6**.

Entry	R_1	R_2	R_3	R	t (h)[a]	T (°C)[b]	Yield[c] of **10** (%)
1	H	Bn	Bn	Me	3	25	**10a** (58)[d]
2	H	*n*-Pr	$(CH_2)_2CN$	Me	24	25	**10b** (39)
3	*i*-Pr	Bn	Bn	Me	8	25	**10c** (61)
4	*i*-Pr		$(CH_2)_4$	Et	6	35	**10d** (73)
5	*n*-Pr	Bn	allyl	Et	8	35	**10e** (48)[e]
6	3-pyridyl	Bn	allyl	Et	6	35	**10f** (48)

[a]Time for the reaction between **7** and **9**.
[b]Temperature of the reaction between **7** and **9**.
[c]Two-step yields starting from the corresponding amines **6**.
[d]Alkene **11a** was also isolated in 12% yield.
[e]Alkene **11e** was also isolated in 19% yield.



10e R_1 = *n*-Pr
10f R_1 = 3-pyridyl

12e 90%
12f 75%

Scheme 3.

In summary, the reaction of *N*-(*N*,*N*-dialkylaminoalkyl)benzotriazoles **7** with zinc dienolates results in exclusive or predominant γ-coupling with formation of vinylogous β-amino esters.[17] If the amine **6** precursor of **7** contains an allyl group, deallylation of the tertiary amine product results in a very convenient two-step synthesis of the corresponding secondary amines.

EXPERIMENTAL

All reactions involving air- and moisture-sensitive materials were performed under an atmosphere of dry Ar. THF and diethyl ether were freshly distilled from sodium/benzophenone. CH_2Cl_2 was distilled from CaH_2 previous to use. Flash chromatography[18] was performed on silica gel (230–400 mesh). ^{1}H and ^{13}C-NMR spectra were obtained in $CDCl_3$ at

250 MHz and 62.9 MHz, respectively. IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV. Zn powder was purified according to the literature procedure.[19] Technical methyl- and ethyl 4-bromocrotonate were purified by flash chromatography using 20% EtOAc in Hexanes as eluent. 3-(*N*-Propylamino)propanenitrile was obtained using the literature procedure.[20]

N-Allyl-*N*-benzylamine

Benzyl bromide (2.00 mL, 16.5 mmol) was added dropwise to a stirred mixture of allylamine (6.18 mL, 80.7 mmol) and K_2CO_3 (2.70 g, 19.4 mmol) while keeping the mixture at room temperature. The resulting suspension was stirred for 11 h, filtered over celite, and the solids were washed with CH_2Cl_2 (60 mL). The combined filtrate and washings were evaporated and the residue was chromatographed (10% EtOAc in hexanes and then EtOAc) to yield 1.78 g (74%) of the title compound, identical in spectral characteristics to the reported material.[21]

Preparation of Benzotriazole Adducts (7)

In a typical experiment, a mixture of aldehyde **5** (12.4 mmol), amine **6** (11.4 mmol), benzotriazole (11.5 mmol), and 4 Å molecular sieves (5.7 g) in dry THF (14 mL) was stirred overnight, filtered and evaporated to give the crude adducts **7**, that were used without further purification.

Reactions of Benzotriazoles 7 with Alkyl 4-Bromocrotonates 9

In a typical experiment, a mixture of Zn powder (1.05 g, 16 mmol) and TMSCl (0.4 mL, 3.2 mmol) in dry ether (30 mL) was stirred for 20 min under an Ar atmosphere. A solution of the benzotriazole adduct **7** (0.9 mmol) in dry THF (10 mL) was added and the resulting suspension was refluxed for 5 min and allowed to cool to room temperature. Methyl or ethyl 4-bromocrotonate (0.9 mmol) was added neat via syringe, the mixture was stirred at 25–35°C for 3–24 h (Table 1) and then poured over ice-cold ammonia (10 mL). The mixture was extracted with ether (3×100 mL). The organic extracts were washed successively with water (10 mL), K_2CO_3 (10 mL), and dried (Na_2SO_4).

After filtration and evaporation, the crude product was purified by flash chromatography under the conditions indicated for the individual cases.

Methyl (*E*)-5-(*N*,*N*-dibenzylamino)pent-2-enoate (10a) and methyl 2-[(*N*,*N*-dibenzylamino)]methylbut-3-enoate (11a): Elution with 7% EtOAc in Hexanes yielded first **11a** (12%) and then **10a** (58%) as oils. Data for **10a**: Colorless oil. The analytical sample was obtained after HPLC (μPorasil 10μ, 19 × 1.5 mm, 6% EtOAc in hexanes, 4 mL/min, $t_R = 23$ min). ^{1}H NMR δ 2.41 (t, $J = 7.0$ Hz, 2H, H-4), 2.61 (t, $J = 7.0$ Hz, 2H, H-5), 3.61 (s, 4H, CH_2–Ph), 3.75 (s, 3H, CH_3), 5.82 (d, $J = 15.7$ Hz, 1H, H-2), 6.91 (dt, $J = 15.7$, 7.0 Hz, 1H, H-3), 7.25–7.40 (m, 10H, Ar–H); ^{13}C NMR δ 30.0, 51.3, 51.8, 58.2, 121.6, 126.9, 128.2, 128.7, 139.3, 147.8, 166.85; IR (neat) ν 1740 (C=O), 1670 (C=C) cm^{-1}. Anal. calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.39; H, 7.37; N, 4.64. Data for **11a**: Yellowish oil. The characterized sample was obtained after HPLC (μPorasil 10μ, 19 × 1.5 mm, 6% EtOAc in hexanes, 4 mL/min, $t_R = 15$ min): ^{1}H NMR δ 2.54 (dd, $J = 12.6$, 6.2 Hz, 1H, C-2(CH_2)), 2.92 (dd, $J = 12.7$, 9.3 Hz, 1H, C-2(CH_2)), 3.34–3.48 (m, 3H), 3.46 (d, $J = 13.6$ Hz, 2H, CH_2–Ph, included in m at 3.34–3.48), 3.64 (s, 3H, CH_3), 3.68 (d, $J = 13.6$ Hz, 2H, CH_2–Ph), 5.10 (s, 1H, H-4), 5.15 (d, $J = 6.8$ Hz, 1H, H-4), 5.64–5.78 (m, 1H, H-3), 7.21–7.31 (m, 10H); ^{13}C NMR δ 49.7, 51.7, 56.1, 58.3, 117.8, 127.0, 128.1, 128.9, 134.4, 139.0, 173.3; IR (neat) ν 1740 (C=O), 1650 (C=C) cm^{-1}; HRMS calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1725.

Methyl (*E*)-5-[(*N*-2-cyanoethyl)-*N*-propylamino]pent-2-enoate (10b): Eluted with 30% EtOAc in hexanes. Yellowish oil: ^{1}H NMR δ 0.88 (t, $J = 7.3$ Hz, 3H, CH_3), 1.40–1.49 (m, 2H), 2.30–2.45 (m, 6H), 2.61 (t, $J = 7.3$ Hz, 2H), 2.79 (t, $J = 7.0$ Hz, 2H), 3.71 (s, 3H, CO_2–CH_3), 5.86 (dd, $J = 14.4$, 1.3 Hz, 1H, H-2), 6.93 (dt, $J = 7.0$, 1.3 Hz, 1H, H-3); ^{13}C NMR δ 11.6, 16.4, 20.4, 30.4, 49.6, 51.4, 52.3, 55.5, 118.9, 122.1, 146.9, 166.8; IR (neat) ν 2200 (C≡N), 1700 (C=O), 1635 (C=C) cm^{-1}; HRMS calcd. for $C_{10}H_{18}NO_2$ (M–CH_2CN) 184.1337, found 184.1338.

Methyl (*E*)-5-(*N*,*N*-dibenzylamino)-6-methylhept-2-enoate (10c): Eluted with 2% EtOAc in hexanes. Colorless oil: ^{1}H NMR δ 0.92 (d, $J = 6.6$ Hz, 3H, CH_3–CH), 1.06 (d, $J = 6.6$ Hz, 3H, CH_3–CH), 1.92–2.02 (m, 1H, CH–CH_3), 2.30–2.69 (m, 3H), 3.57 (d, $J = 13.7$ Hz, 2H, CH_2–Ph), 3.82 (d, 13.7 Hz, CH_2–Ph), and 3.80 (s, CO_2CH_3) (total 5H), 5.93 (d, $J = 15.7$ Hz, 1H, H-2), 7.11 (dt, $J = 15.6$, 7.4 Hz, 1H, H-3), 7.25–7.44 (m, 10H, Ar–H); ^{13}C NMR δ 20.5, 21.2, 30.1, 30.4, 51.2, 54.2, 62.8, 121.4, 126.7, 128.1, 128.8, 139.8, 149.7, 166.8; IR (neat) ν 1730 (C=O), 1650 (C=C) cm^{-1}. Anal. calcd. for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.98. Found: C, 78.47; H, 8.27; N, 4.16.

Ethyl (*E*)-6-methyl-5-(pyrrolidin-1-yl)hept-2-enoate (10d): Eluted with 90:8:2 hexanes/EtOAc/Et_3N using silica gel saturated with Et_3N: ^{1}H NMR δ 0.83–0.88 (m, 6H, CH_3), 1.23 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.68 (brs, 4H, CH_2–N), 1.74–1.97 (m, 1H), 2.18 (dd, $J = 9.7$, 4.8 Hz, 1H), 2.29–2.38 (m, 2H), 2.50 (br s, 4H, CH_2–CH_2N), 4.13 (q, $J = 7.1$ Hz, 2H, CO_2CH_2), 5.78 (d, $J = 15.7$ Hz, 1H, H-2), 6.95–7.07 (m, 1H, H-3); ^{13}C NMR δ 14.2, 17.3, 20.2, 23.3, 30.9, 31.6, 51.2, 60.0, 68.0, 121.3, 149.8, 166.6; IR (neat) ν 1735 (C=O), 1650 (C=C) cm^{-1}; HRMS calcd. for $C_{14}H_{25}NO_2$ 239.1885, found 239.1876.

Ethyl (*E*)-5-(*N*-allyl-*N*-benzylamino)oct-2-enoate (10e) and ethyl 2-[1-(*N*-allyl-*N*-benzylamino)butyl]but-3-enoate (11e): Elution with 99:1 hexanes/Et_3N using silica gel saturated with Et_3N yielded first **11e** (19%) and then **10e** (48%) as oils. Data for **10e**: ^{1}H NMR δ 0.85 (t, $J = 7.0$ Hz, 3H, H-8), 1.20–1.56 (m, 7H), 1.30 (t, $J = 7.1$ Hz, OCH_2CH_3, included in m at 1.20–1.56), 2.06–2.18 (m, 1H), 2.42–2.53 (m, 1H), 2.72–2.83 (m, 1H), 3.01 (dd, $J = 14.2$, 6.7 Hz, 1H), 3.12 (dd, $J = 14.2$, 5.7 Hz, 1H), 3.50 (d, $J = 14.0$ Hz, 1H), 3.67 (d, $J = 14.0$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H, OCH_2), 5.05–5.21 (m, 2H), 5.71–5.87 (m, 2H), 6.95 (dt, $J = 15.5$, 7.5 Hz, 1H, H-3), 7.19–7.35 (m, 5H, Ar); ^{13}C NMR δ 13.9, 14.0, 19.8, 32.5, 32.7, 52.0, 53.0, 57.1, 59.8, 116.3, 121.9, 126.5, 127.9, 128.4, 137.1, 140.0, 148.1, 166.1; IR (neat) ν 1725 (C=O), 1650 (C=C) cm^{-1}; HRMS calcd. for $C_{20}H_{29}NO_2$ 315.2198, found 315.2186. Data for **11e** (63:37 diastereomeric mixture): ^{1}H NMR δ 0.84–0.90 (m, 3H, H-6), 1.20–1.64 (m, 7H, OCH_2CH_3, H-4, H-5), 2.98–3.32 (m, 4H, H-2, H-3, $NCH_2CH{=}CH_2$), 3.52 and 3.79 (AB system, $J = 13.9$ Hz, $PhCH_2$, 2H of major isomer), 3.63 and 3.75 (AB system, $J = 14.1$ Hz, $PhCH_2$, 2H of minor isomer), 4.02–4.24 (m, 2H, OCH_2), 5.02–5.21 (m, 4H), 5.65–6.06 (m, 2H), 7.19–7.35 (m, 5H, Ar); ^{13}C NMR δ 13.9, 14.1, 14.2, 20.5, 21.3, 30.5, 31.2, 53.3, 53.5, 53.9, 54.4, 55.9, 60.0, 60.2, 60.3, 116.3, 116.4, 117.2, 118.1, 126.5, 127.8, 127.9, 128.5, 128.7, 135.1, 135.7, 137.3, 137.4, 140.0, 140.3, 173.0; IR (neat) ν 1735 (C=O), 1640 (C=C) cm^{-1}; HRMS calcd. for $C_{20}H_{29}NO_2$ 315.2198, found 315.2185.

Ethyl (*E*)-6-aza-6-benzyl-5-(pyridin-3-yl)non-2,8-dienoate (10f): Eluted with 90:8:2 hexanes/EtOAc/Et_3N using silica gel saturated with Et_3N: ^{1}H NMR δ 1.27 (t, $J = 7.1$ Hz, 3H, CH_3), 2.67 (dt, $J = 14.9$, 6.9 Hz, 1H), 2.77 (dd, $J = 14.3$, 7.3 Hz, 1H), 2.87–2.98 (m, 1H), 3.22 (d, $J = 13.9$ Hz, PhC*H*, overlapped with signal from other proton, total 2H), 3.77 (d, $J = 13.9$ Hz, 1H, PhC*H*), 3.99 (t, $J = 7.6$ Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H, CH_3CH_2), 5.14–5.23 (m, 2H, H-9), 5.82 (d, $J = 15.9$ Hz, H-2, overlapped with signal from H-8, total 2H), 6.92 (dt, $J = 15.7$, 7.1 Hz, 1H, H-3), 7.23–7.32 (m, 6H), 7.56–7.59 (m, 1H), 8.51–8.54 (m, 2H); ^{13}C NMR δ 14.1, 33.2, 52.2, 53.3, 59.2, 60.1, 117.7, 123.0, 123.1,

127.0, 128.3, 128.4, 133.7, 135.6, 136.0, 139.2, 145.8, 148.7, 150.0, 166.1; IR (neat) υ 1725 (C=O), 1660 (C=C) cm^{-1}; HRMS calcd. for $C_{22}H_{26}N_2O_2$ 350.1994, found 350.1994.

Ethyl (*E*)-6-aza-7-phenyl-5-(pyridin-3-yl)hept-2-enoate (12f): A solution of **10f** (1.17 g, 3.35 mmol), $Pd(PPh_3)_4$ (0.039 g, 0.03 mmol), and *N*,*N*-dimethylbarbituric acid (NDMBA) (1.57 g, 10.0 mmol) in dry CH_2Cl_2 (10 mL) was stirred for 24 h under Ar. After removal of the solvent, the residue was redissolved in EtOAc (60 mL) and the solution was washed with sat. K_2CO_3 (3×20 mL) and brine (15 mL), and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, 80:15:5 hexanes/EtOAc/Et_3N and then 65:30:5 hexanes/EtOAc/Et_3N) to afford **12f** (928 mg, 90%) as an oil: ^{1}H NMR δ 1.18 (t, $J = 7.1$ Hz, 3H, CH_3), 1.73 (br s, 1H, NH), 2.48 (t, $J = 7.0$ Hz, 2H), 3.45 and 3.57 (AB system, $J = 13.3$ Hz, 2H, PhCH_2), 3.76 (t, $J = 6.7$ Hz, 1H, H-5), 4.07 (q, $J = 7.1$ Hz, 2H, CH_2O), 5.74 (d, $J = 15.7$ Hz, 1H, H-2), 6.72–6.84 (m, 1H, H-3), 7.12–7.25 (m, 6H), 7.63 (d, $J = 7.7$ Hz, H-4′), 8.45 (dd, $J = 4.8$, 1.4 Hz, 1H, H-6′), 8.50 (d, $J = 1.8$ Hz, 1H, H-2′); ^{13}C NMR δ 13.8, 40.5, 50.9, 58.3, 59.9, 123.2, 123.8, 126.7, 127.7, 128.0, 134.3, 137.8, 139.4, 144.0, 148.6, 148.9, 165.5; IR (neat) ν 3400–3300 (br, N–H), 1725 (C=O), 1660 (C=C) cm^{-1}; HRMS calcd. for $C_{19}H_{23}N_2O_2$ (M + 1) 311.1759, found 311.1767.

Ethyl (*E*)-5-(*N*-Benzylamino)oct-2-enoate (12e): Following the previous procedure, **12e** was obtained from **10e** as an oil in 75% yield after flash chromatography (20% EtOAc in hexanes, then 50% EtOAc in hexanes): ^{1}H NMR δ 0.90 (distorted t, $J \approx 7.0$ Hz, 3H, H-8), 1.29 (t, $J = 7.1$ Hz, OCH_2CH_3 included in m at 1.26–1.48), 1.26–1.48 (m, H-6, H-7, N–H, total 8H), 2.32–2.39 (m, 2H, H-4), 2.69–2.76 (m, 1H, H-5), 3.76 and 3.80 (AB system, $J = 13.0$ Hz, 2H, PhCH_2), 4.19 (q, $J = 7.1$ Hz, 2H, OCH_2), 5.87 (dt, $J = 15.5$, 1.5 Hz, 1H, H-2), 6.97 (dt, $J = 15.6$, 7.5 Hz, 1H, H-3), 7.22–7.32 (m, 5H, Ar); ^{13}C NMR δ 14.1, 14.2, 18.8, 36.3, 36.7, 51.0, 55.7, 60.1, 123.2, 126.8, 128.0, 128.3, 140.4, 146.4, 166.2; IR (neat) ν 3320 (N–H), 1720 (C=O), 1650 (C=C) cm^{-1}; HRMS calcd. for $C_{17}H_{25}NO_2$ 275.1885, found 275.1830.

ACKNOWLEDGMENTS

Financial support was provided by Universidad del País Vasco (UPV 170.310-EC201/94), Ministerio de Ciencia y Tecnología (DGI BQU2000-01354), and Janssen-Cilag. A fellowship to A.F. (Gobierno Vasco) is also gratefully acknowledged.

REFERENCES

1. Aurrecoechea, J.M.; Fernandez, A.; Gorgojo, J.M.; Saornil, C. Tetrahedron **1999**, *55*, 7345–7362.
2. (a) Danishefsky, S.J.; Vogel, C. J. Org. Chem. **1986**, *51*, 3915–3916; (b) Brandmaster, S.M.; Ojima, I. Tetrahedron Lett. **1987**, *28*, 613; (c) Midland, M.M.; McLoughlin, J.I. Tetrahedron Lett. **1988**, *29*, 4653–4656; (d) Waldmann, H.; Braun, M.; Dräger, M. Tetrahedron: Asymmetry **1991**, *2*, 1231–1246.
3. (a) Mladenova, M.; Bellassoued, M. Synth. Commun. **1993**, *23*, 725–736; (b) Bellassoued, M.; Ennigrou, R.; Gil, R.; Lensen, N. Synth. Commun. **1998**, *28*, 3955–3964.
4. Van Maanen, H.L.; Kleijn, H.; Jastrzebski, J.T.B.H.; Lakin, M.T.; Spek, A.L.; van Koten, G. J. Org. Chem. **1994**, *59*, 7839–7848.
5. Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. Synlett **1999**, 1333–1350.
6. Camiletti, C.; Dhavale, D.D.; Donati, F.; Trombini, C. Tetrahedron Lett. **1995**, *36*, 7293–7296.
7. Giammaruco, M.; Taddei, M.; Ulivi, P. Tetrahedron Lett. **1993**, *34*, 3635–3638.
8. (a) El Borgi, A.; Bellassoued, M.; Moreau, J.L. C. R. Acad. Sci. II **1988**, *307*, 1805–1807; (b) Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. Tetrahedron Lett. **1994**, *35*, 1561–1564; (c) Mecozzi, T.; Petrini, M. Tetrahedron Lett. **2000**, *41*, 2709–2712.
9. Martin, S.F.; Chen, K.X.; Eary, C.T. Org. Lett. **1999**, *1*, 79–81, and references cited therein.
10. (a) Shono, T.; Hamaguchi, H.; Sasaki, M.; Fujita, S.; Nagami, K. J. Org. Chem. **1983**, *48*, 1621–1628; (b) Hirai, Y.; Terada, T.; Hagiwara, A.; Yamazaki, T. Chem. Pharm. Bull. **1988**, *36*, 1343–1350.
11. Katritzky, A.R.; Yannakapoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J.M.; Palenik, G.J.; Koziol, A.E.; Szczesniak, M.; Skarjune, R. J. Chem. Soc., Perkin Trans. 1 **1987**, 2673–2679.
12. Recent reviews: (a) Katritzky, A.R.; Lan, X.F.; Yang, J.Z.; Denisko, O.V. Chem. Rev. **1998**, *98*, 409–548; (b) Katritzky, A.R. J. Heterocycl. Chem. **1999**, *36*, 1501–1522; (c) Katritzky, A.R.; Belyakov, S.A. Aldrichim. Acta **1998**, *31*, 35–45.
13. (a) Katritzky, A.R.; Yannakopoulou, K. Synthesis **1989**, 747–751; (b) Katritzky, A.R.; Hong, Q.M.; Yang, Z.J. J. Org. Chem. **1995**, *60*, 3405–3408.
14. Kobayashi, S.; Ishitani, H.; Komiyama, S.; Oniciu, D.C.; Katritzky, A.R. Tetrahedron Lett. **1996**, *37*, 3731–3734.

15. (a) Wang, J.; Zhou, J.; Zhang, Y. Synth. Commun. **1996**, *26*, 3395–3399; (b) Bao, W.; Zhang, Y. Synth. Commun. **1997**, *27*, 615–620; (c) Churlaud, C.; Pornet, J.; Oniciu, D.C.; Katritzky, A.R. Organometallics **1999**, *18*, 4270–4274.
16. Garrohelion, F.; Merzouk, A.; Guibe, F. J. Org. Chem. **1993**, *58*, 6109–6113.
17. A recent paper that highlights the importance of β-amino acids: Ma, D.W.; Sun, H.Y. J. Org. Chem. **2000**, *65*, 6009–6016.
18. Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, *43*, 2923–2925.
19. Perrin, D.D.; Armarego, W.F.L. *Purification of Laboratory Chemicals*, 3rd Ed.; Pergamon Press: Oxford, 1988.
20. Tarbe, D.S.; Shakespeare, N.; Claus, C.J.; Bunnett, J.F. J. Am. Chem. Soc. **1946**, *68*, 1217–1219.
21. Nakanishi, S.; Okamoto, K.; Yamaguchi, H.; Takata, T. Synthesis **1998**, 1735–1741.

Received in the Netherlands February 18, 2002