Pergamon

Tetrahedron 58 (2002) 6211–6221

TETRAHEDRON

Synthesis of 3-aminopyrrolidines by cyclization of neutral *C*-centered α-aminoalkyl radicals

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

Departamento de Química Orgánica II, Facultad de Ciencias, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain

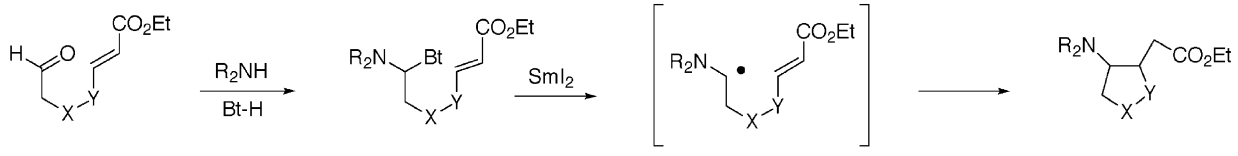
Received 13 March 2002; revised 11 June 2002; accepted 17 June 2002

Abstract—3-Aminopyrrolidines are prepared by SmI_2-promoted cyclization of neutral α-aminoalkyl radicals generated from *N*-(α-benzotriazolyl)alkenylamines. Appropriate manipulation of the two *N*-protecting groups allows further manipulation of the products, which is exemplified with the preparation of a triamide derivative.

1. Introduction

The intramolecular addition of neutral *C*-centered α-aminoalkyl radicals[1] to C–C double bonds has found extensive application in the synthesis of functionalized carbocycles and heterocycles.[2–7] In these and other applications various methods for generation of reactive α-amino radicals have been employed, that include the homolysis of a C–X bond from suitable α-substituted amino derivatives,[8–14] radical addition on enamide derivatives,[15] radical translocation,[2,5,16] decarbonylation of β-amino acyl radicals,[4] photochemically-induced electron transfer from tertiary amines[17–19] and SmI_2-promoted reduction of α-aminoalkyl benzotriazoles.[3,6,7] This last method can be particularly convenient in terms of convergence since cyclization substrates **2** are easily assembled from readily available aldehyde and secondary amine fragments (Scheme 1). Thus, efficient syntheses of cyclopentylamines[3] **4** and 2,3-dialkylpyrrolidines[6,7] have already been reported using this strategy via 5-*exo*-trig radical ring closures. Along these lines, the synthesis of 3-aminopyrrolidines of types **8** and **12** can be easily envisaged through the intermediacy of α-amino radicals **7** and **11**, respectively. These would be derived from aldehydes of general structures **5** or **9**, where a CH_2 group of **1** has been replaced by a conveniently protected amino group. The choice of electron-deficient double bonds as radical traps in these reactions was dictated by previous experience with α-aminoalkyl radicals showing that the use of electron-withdrawing substituents on the alkene moiety results in cyclizations that take place under simpler and milder conditions, as well as with higher yields and stereoselectivities.[3,7,20] While substrates of type **6** contain a double bond with similar electronic and otherwise character as those previously used in α-amino radical cyclizations (Scheme 1), the use of β-aminoacrylate derivatives (e.g. **10**) as radical traps, although known[21–25] had not been investigated to date in reactions of α-aminoalkyl radicals.

The 3-aminopyrrolidine substructure present in products **8** and **12** can be found in a large number of compounds with an extensive range of biological activities,[26–35] and has also seen application in chromatography[36,37] and as chiral auxiliary in synthesis.[38] Earlier to this work, the synthesis of 3-aminopyrrolidines had mainly involved the structural



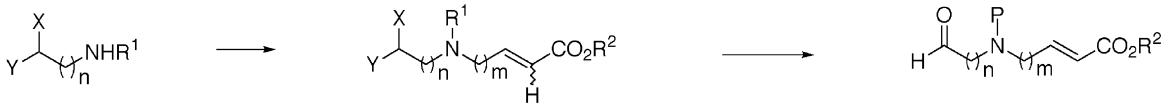
1 X = Y = CH_2	**2**	**3**	**4**
5 X = NP, Y= CH_2	**6**	**7**	**8**
9 X = CH_2, Y = NP	**10**	**11**	**12**

Scheme 1.

Keywords: radical cyclizations; pyrrolidines; samarium.

* Corresponding author. Tel.: +34-946-01-2578; fax: +34-944-64-8500; e-mail: qopaufem@lg.ehu.es

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00621-X



	X	Y	R^1	n	m	R^2
13a	H	OH	Bn	1	1	Et
13b	OMe	OMe	H	1	1	Et
13c	OEt	OEt	H	1	0	Et
13d	OEt	OEt	H	1	0	Me

	P	n	m	R^2
5a	Bn	1	1	Et
5b	Ts	1	1	Et
9a	Cbz	1	0	Et
9b	Bz	1	0	Me
9c	Boc	1	0	Me

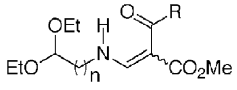
Scheme 2.

modification of preformed pyrrolidine or pyrrolidinone structures to introduce the 3-amino group[31,33,35,38–43] or the cyclization of appropriate diamine and related precursors.[28–30,34,44–47] However, their convergent preparation from acyclic precursors and amine derivatives was much less common.[48–53] Therefore, our radical approach to the convergent synthesis of 3-aminopyrrolidines from readily available aldehyde (**5**, **9**) and amine fragments would be a valuable addition to the synthetic repertoire for formation of these compounds.[54] Additionally, if the amino groups present in products **8** and **12** are orthogonally protected, further manipulation of up to three functionalized sites could lead to substantial structural diversity. This paper reports on the results of our radical cyclization approach to the direct synthesis of 3-aminopyrrolidines and some transformations of these leading to more complex structures.

2. Results and discussion

2.1. Preparation of 3-aminopyrrrolidines

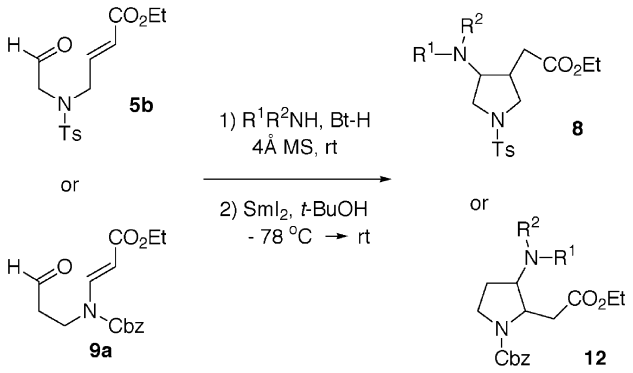
Suitable aldehydes of general structures **5** and **9** were prepared as outlined in Scheme 2. Thus, alkylation of *N*-benzylethanolamine or 2,2-dimethoxyethylamine with ethyl (*E*)-4-bromocrotonate, followed by either alcohol oxidation or tosylation and acetal hydrolysis afforded aldehydes **5a** or **5b**, respectively (Scheme 2). On the other hand, a procedure closely related to that reported for the *N*-Cbz aldehyde **9a**[25a] was followed in the preparation of benzamide **9b** and *N*-Boc aldehyde **9c** (Scheme 2). Thus, secondary amine **13d** was acylated with various reagents and the resulting *N*-protected diethyl acetals were hydrolyzed to yield aldehydes **9b**,**c**. In the base-promoted[25a] benzoylation of **13d**, substantial amounts of the *C*-acylated product **16b** were obtained, besides the desired benzamide (Section 4). Upon attempted *N*-trifluoroacetylation of **13d**, under similar base-promoted conditions,[25a] only the *C*-acylated product **16d** was observed (Section 4).



16b R = Ph
16d R = CF_3

Following our previously reported protocol,[7] aldehydes **5** and **9** were condensed with secondary amines and benzotriazole at room temperature to yield adducts of type **6** or **10**, respectively, that were then treated with SmI_2/*t*-BuOH from −78°C to room temperature to afford the expected pyrrolidine products **8**, **12** (Scheme 3). Results are collected in Table 1. Adducts **6**, **10** were used directly as crude products;[7] therefore, cyclization yields reported in Table 1 are referred in all cases to two steps starting from aldehydes **5** or **9**. No cyclic product was obtained starting with benzylamino aldehyde **5a**. Condensation of this aldehyde with morpholine and benzotriazole gave an unstable adduct **6** that even upon immediate treatment with SmI_2/*t*-BuOH,[7] resulted in extensive degradation with no characterizable product being obtained. On the other hand, under the same reaction conditions, the use of sulfonamido aldehyde **5b** led to the formation of the expected 3-aminopyrrolidines **8a**–**c**, that were isolated in moderate yields (Table 1). A limitation was found in this reaction in that amines containing allyl or benzyl groups, such as dibenzylamine, *N*-methylbenzylamine or diallylamine, did not perform well. The formation of adducts **6** proceeded normally with high conversions but the ensuing cyclizations were messy and the products could not be conveniently purified.[55]

A different regiochemical possibility for synthesis of 3-aminopyrrolidines using this radical approach involves the use of aldehydes of type **9** containing a β-aminoacrylate moiety. In this case, condensation of **9a**[25] with amines and benzotriazole, followed by reduction of the resulting adducts **10**, led in all cases to the expected 3-aminopyrrolidines **12** that were isolated in moderate to high yields



Scheme 3.

Table 1. Preparation of 3-aminopyrrolidines **8**, **12**

Aldehyde	R^1	R^2	Product	Yield (%)[a]	*cis*/*trans*
5b	$(CH_2)_2O(CH_2)_2$		**8a**	61	47:53[b]
5b	$(CH_2)_2N(Ph)(CH_2)_2$		**8b**	58	62:38[b]
5b	$(CH_2)_5$		**8c**	47	55:45[b]
9a	$(CH_2)_2O(CH_2)_2$		**12a**	72	40:60[b]
9a	Me	Bn	**12b**	82	43:57[c]
9a	3,4-Dimethoxyphenethyl	Allyl	**12c**	52	40:60[c]
9a	$(CH_2)_2N(Ph)(CH_2)_2$		**12d**	84	40:60[c]

[a] Two-step yields starting from **5b** or **9a**.
[b] Diastereomeric ratio determined by weight of isolated diastereoisomers after chromatographic separation.
[c] Diastereomeric ratio determined by ^{1}H NMR integration on the purified isomer mixture.

(Table 1). Products **12** were obtained as diastereomeric mixtures from which the individual isomers were readily separated either by chromatographic or chemical means (vide infra). This reaction appears to be more general than that discussed above in that benzyl and allyl groups are well tolerated in the amino moiety and this results in the incorporation into the products of functionality useful for further manipulation (vide infra). The cyclization was totally ineffective starting from benzotriazole adducts derived from *N*-Bz- or *N*-Boc-protected aldehydes **9b**,**c**, as only uncharacterized degradation products were observed upon treatment with SmI_2/*t*-BuOH.

2.2. Stereochemistry of cyclization

The stereochemistry of the 3-aminopyrrolidine products was assigned in all cases from the observation of an upfield shift in the ^{13}C NMR spectrum for the ring C-3 methine carbon (CH–N) of one diastereoisomer (accordingly assigned a *cis* stereochemistry[7,56]) relative to the other isomer (Table 2). This assignment was confirmed chemically in the case of **12c** by spontaneous conversion of the deallylated *cis*-isomer into a bicyclic lactam (vide infra).

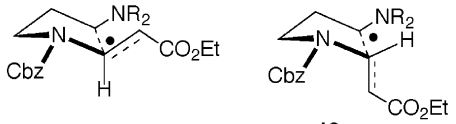
Contrary to other α-aminoalkyl radical cyclizations, the present reactions proceed with poor stereoselectivity. The lack of stereocontrol observed in the formation of pyrrolidines **8** appears surprising. Thus, the all-carbon radical **3** cyclizes with excellent *cis*-selectivity,[3] whereas other *N*-tosyl-1-alkyl-3-aza radicals, structurally related to **7**, have been shown to cyclize with a moderate *cis*-preference.[57–59] The apparently anomalous low selectivity encountered with radical **7** could then be due to the conformational changes associated with the shorter ring C–N bond lengths in this radical compared to the corresponding C–C in **3**. This could in turn lead to a tighter TS where the combined steric demands of dialkylamino and ethoxycarbonylmethyl groups outweigh the stereoelectronic benefits usually associated with a *cis*-TS.[3,60]

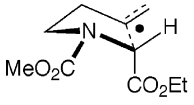
Table 2. ^{13}C NMR resonances for C-3 of pyrrolidines **8**, **12**

8, **12**	C-3[a]	**8**, **12**	C-3[a]
cis-**8a**	65.4	*trans*-**8a**	68.7
cis-**8b**	65.1	*trans*-**8b**	68.6
cis-**8c**	65.8	*trans*-**8c**	69.4
cis-**12a**	66.0	*trans*-**12a**[b]	68.9, 69.8
cis-**12b**[b]	65.9, 66.5	*trans*-**12b**[b]	67.7, 68.6
cis-**12c**[b]	62.4, 63.2	*trans*-**12c**[b]	65.1, 66.1
cis-**12d**[b]	65.7, 66.4	*trans*-**12d**[b]	68.5, 69.5

[a] Determined on the individually isomers from DEPT experiments, except for **12b** where, additionally, the two isomers were identified in the mixture according to signal intensity and by analogy with the other compounds **12**.
[b] Mixture of rotamers.

On the other hand, the low diastereoselectivity observed in the cyclizations of radicals **11** was not completely unexpected, as the normal preference for a chair-like TS **18** leading to *cis*-products[3] is now counterbalanced by the pseudoallylic-1,3-strain that develops between the ethoxycarbonylmethyl group and the *N*-protecting group. This in fact leads to a slight preference for the *trans*-isomer through the alternative boat-like TS **19**. A somewhat related precedent exists in the work of Speckamp where a *trans* preference in pyrrolidine formation was the result of a pseudoaxial disposition of the radical C-1 substituent (e.g. **20**) to avoid interactions with the *N*-substituent in the alternative pseudoequatorial disposition.[61,62]

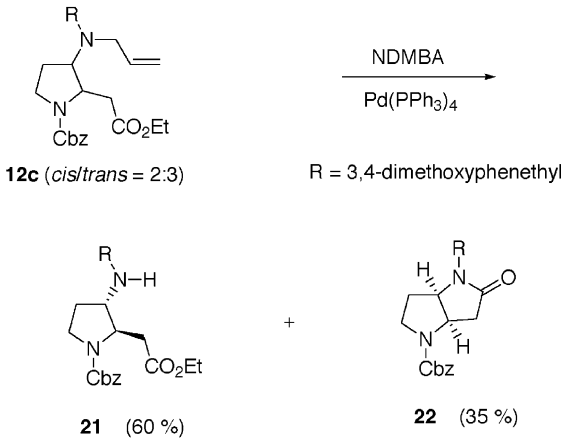




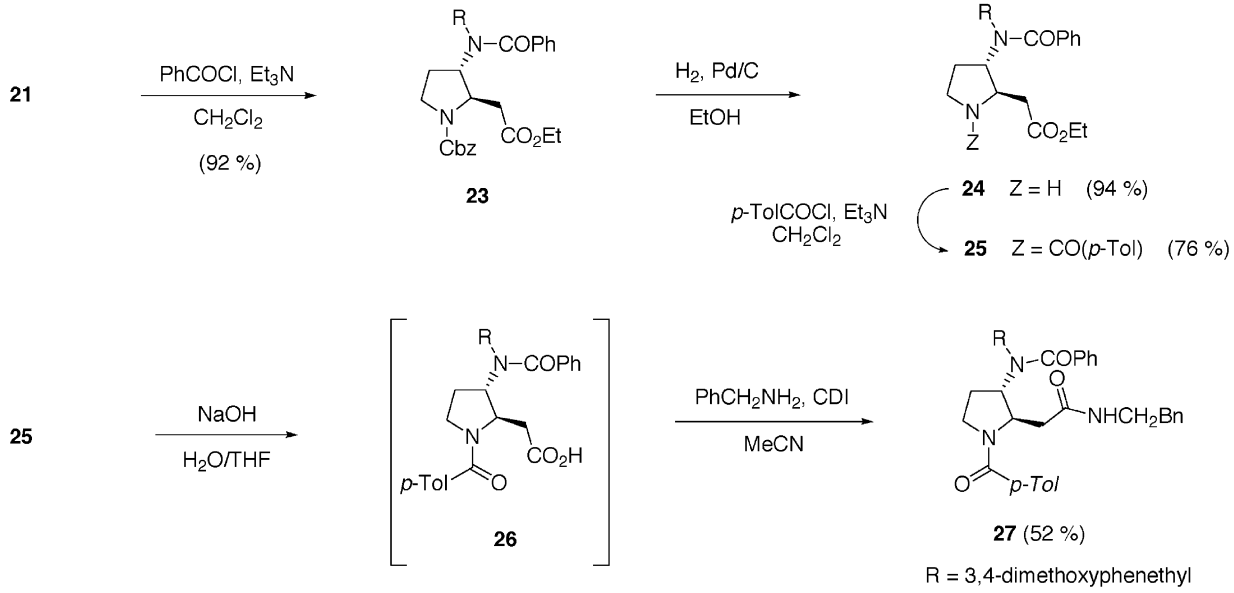
20

2.3. Deprotection-functionalization of 3-aminopyrrolidines

Compounds **8** and **12** contain three reactive sites including protected exocyclic and endocyclic N-atoms, as well as an ethoxycarbonyl group. Therefore, substantial systematic structural diversification is in principle feasible from these compounds if adequate deprotection-functionalization sequences are employed. As an example, selective deprotection of the allylamine moiety of **12c** with $Pd(PPh_3)_4$/NDMBA[63] took place in almost quantitative yield with concomitant cyclization of the deallylated *cis*-isomer to afford an easily separable mixture of *trans*-pyrrolidine **21** and bicyclic lactam **22** (Scheme 4). Gram quantities of



Scheme 4.



Scheme 5.

21 are readily obtained in this manner. Secondary amine **21** was then processed in high yield to benzamide **23** (Scheme 5). Removal of the Cbz-protection of **23** and a second acylation provided diamide **25** in high overall yield. Finally, conversion of the ethoxycarbonyl group of **25** into a secondary amide led to triply functionalized pyrrolidine **27** through the corresponding carboxylic acid **26** (Scheme 5).

3. Conclusions

The intramolecular addition of 1-amino-3- or 4-azahex-5-enyl radicals to suitably positioned C–C double bonds provides an entry into functionalized 3-aminopyrrolidines. With an appropriate selection of *N*-substituents, these products can be manipulated at three different sites, thus providing ample opportunity for structural diversification.

4. Experimental

4.1. General methods

All reactions involving air- and moisture-sensitive materials were performed under an atmosphere of dry Ar. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and, for reactions with SmI_2, it was deoxygenated prior to use. 2-Methylpropan-2-ol and ethanol were distilled from Mg/I_2. CH_2Cl_2 and triethylamine were distilled from CaH_2. *p*-Toluenesulfonyl chloride was purified according to the reported procedure.[64] SmI_2 (ca. 0.1 M in THF) was prepared from Sm and diiodomethane using a literature procedure.[65] Flash chromatography[66] was performed on silica gel (230–400 mesh). HPLC purifications were carried out with a μ-Bondapak column (10 μm, 19 mm×15 cm) using a refraction index detector. Routine ^1H and ^{13}C NMR spectra were obtained at 250 and 62.9 MHz, respectively, using $CDCl_3$ as solvent and internal reference (δ 7.26 for ^1H and δ 77.0 for ^{13}C). IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV.

4.2. Preparation of aldehydes 5, 9

4.2.1. Ethyl (*E*)-4-[*N*-benzyl-*N*-(2-hydroxyethyl)amino]-but-2-enoate (13a). A solution of ethyl (*E*)-4-bromobut-2-enoate (1.00 mL, 7.3 mmol) in THF (5.4 mL) was added dropwise to a mixture of *N*-benzylethanolamine (1.09 mL, 7.3 mmol) and K_2CO_3 (1.33 g, 9.6 mmol) in THF (9.0 mL). The resulting mixture was stirred at room temperature for 12 h and then filtered through Celite. The crude after evaporation was purified by flash chromatography (60:40 hexanes/EtOAc) to yield **13a** (1.22 g, 64%): ^1H NMR δ 1.29 (t, *J*=7.1 Hz, 3H, CH_3), 2.46 (br s, 1H, OH), 2.69 (t, *J*=5.3 Hz, 2H, H-1′), 3.28 (dd, *J*=6.3, 1.6 Hz, 2H, H-4), 3.61 (t, *J*=5.4 Hz, 2H, H-2′), 4.20 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 5.98 (dt, *J*=15.7, 1.6 Hz, 1H, H-2), 6.96 (dt,

J=15.7, 6.3 Hz, 1H, H-3), 7.23–7.37 (m, 5H, Ar); ^{13}C NMR δ 14.0, 54.2, 54.9, 58.0, 58.6, 60.2, 123.2, 127.1, 128.2, 128.6, 138.0, 145.1, 165.8; IR (neat) ν 3440, 1725, 1660 cm^{-1}; LRMS (EI) *m/z* 233 (22), 232 (base), 218 (5), 91 (68); HRMS calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1510.

4.2.2. Ethyl (*E*)-5-aza-5-benzyl-7-oxohept-2-enoate (5a). DMSO (0.16 mL, 2.25 mmol) was added to a solution of oxalyl chloride (0.1 mL, 1.13 mmol) in CH_2Cl_2 (3.3 mL) at −84°C. The solution was stirred for 10 min and then a solution of **13a** (0.293 g, 1.11 mmol) in CH_2Cl_2 (3.3 mL) was added dropwise. The resulting mixture was stirred for 20 min and Et_3N (0.65 mL, 4.66 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. To the resulting suspension were added CH_2Cl_2 (50 mL), H_2O (20 mL) and sat. $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to yield **5a** (0.273 g, 93%) as an orange oil, unstable to chromatography, that was used without purification: ^{1}H NMR δ 1.29 (t, J=6.7 Hz, 3H, OCH_2CH_3), 3.26 (s, 2H, H-6), 3.35 (d, J=4.9 Hz, 2H, H-4), 3.72 (s, 2H, $PhCH_2$), 4.20 (q, J=6.8 Hz, 2H, OCH_2), 6.04 (d, J=15.3 Hz, 1H, H-2), 6.96 (dt, J=15.3, 5.0 Hz, 1H, H-3), 7.26–7.34 (m, 5H, Ar), 9.60 (s, 1H, CHO).

4.2.3. Ethyl (*E*)-5-aza-7,7-dimethoxyhept-2-enoate (13b). To a solution of aminoacetaldehyde dimethyl acetal (4.80 mL, 43.6 mmol) in CH_2Cl_2 (55 mL) was added dropwise ethyl (*E*)-4-bromobut-2-enoate (3.00 mL, 21.8 mmol), the mixture was stirred at room temperature for 5 h and then poured into sat. $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (EtOAc) to yield **13b** (2.63 g, 55%). ^{1}H NMR δ 1.28 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.43 (br s, 1H, NH), 2.74 (d, J=5.4 Hz, 2H, H-6), 3.39 (s, 6H, OCH_3), 3.42 (dd, J=5.5, 1.8 Hz, 2H, H-4), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.45 (t, J=5.5 Hz, 1H, H-7), 5.98 (dt, J=15.8, 1.7 Hz, 1H, H-2), 6.97 (dt, J=15.7, 5.4 Hz, 1H, H-3); ^{13}C NMR δ 13.7, 49.7, 50.1, 53.5, 59.7, 103.3, 121.0, 146.1, 165.7; IR (neat) ν 3320, 1720, 1660 cm^{-1}.

4.2.4. Ethyl (*E*)-5-aza-7,7-dimethoxy-5-tosylhept-2-enoate (14). A solution of *p*-toluenesulfonyl chloride (419 mg, 2.20 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min to **13b** (434 mg, 2.00 mmol) and Et_3N (0.310 mL, 2.22 mmol) in CH_2Cl_2 (5 mL) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for 90 min and evaporated. The residue was dissolved in EtOAc (20 mL), washed with water (20 mL) and brine (20 mL), and dried (Na_2SO_4). The crude product after evaporation was purified by flash chromatography (80:20 hexanes/EtOAc), to yield **14** (704 mg, 95%) as a colorless oil: ^{1}H NMR δ 1.24 (t, J=7.1 Hz, 3H, CH_2CH_3), 2.40 (s, 3H, $ArCH_3$), 3.18 (d, J=5.2 Hz, 2H, H-6), 3.34 (s, 6H, CH_3O), 4.05 (dd, J=5.6, 1.6 Hz, 2H, H-4), 4.13 (q, J=7.1 Hz, 2H, CH_3–CH_2), 4.44 (t, J=5.4 Hz, 1H, H-7), 5.82 (dt, J=15.7, 1.6 Hz, 1H, H-2), 6.65 (dt, J=15.7, 5.8 Hz, 1H, H-3), 7.29 (dd, J=8.5, 0.6 Hz, 2H, Ar), 7.68 (dd, J=6.5, 1.8 Hz, 2H, Ar); ^{13}C NMR δ 14.1, 21.4, 49.4, 49.9, 54.9, 60.4, 104.4, 123.6, 127.1, 129.7, 136.6, 142.4, 143.6, 165.6; IR (neat) ν 1730, 1600 cm^{-1}; LRMS (EI) *m/z* 224 (17), 184 (35), 152 (20), 128 (base), 114 (15), 84 (89); HRMS calcd for $C_{17}H_{25}NO_6S$ (M+1) 372.1481, found 372.1468.

4.2.5. Ethyl (*E*)-5-aza-7-oxo-5-tosylhept-2-enoate (5b). A solution of TFA/H_2O (1:1, 3.5 mL) was added dropwise to **14** (1.86 g, 5.0 mmol) in CH_2Cl_2 (15.0 mL) at 0°C. After vigorously stirring the mixture for 7 days at room temperature, the solvent was removed in vacuo, residue dissolved in EtOAc (20 mL), washed with sat. K_2CO_3 (25 mL), dried (Na_2SO_4) and evaporated, to yield a 9/1 mixture of **5b/14** (1.56 g, 85% estimated yield for **5b** by ^{1}H NMR), as an orange oil, that was used in subsequent reactions. For characterization purposes, a portion of this crude mixture (0.240 g) in CH_2Cl_2 (0.2 mL) was resubmitted to the hydrolysis conditions, with TFA/H_2O (1:1, 40 μL) for 5 days. The solvent was removed in vacuo, the residue dissolved in EtOAc (25 mL) and washed with sat. K_2CO_3 (10 mL). The aqueous layer was back-extracted with EtOAc (3×25 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated to yield pure **5b** (94 mg, 37% from **14**): ^{1}H NMR δ 1.27 (t, J=7.1 Hz, 3H, CH_2CH_3), 2.44 (s, 3H, $ArCH_3$), 3.87 (s, 2H, H-6), 3.98 (dd, J=6.1, 1.3 Hz, 2H, H-4), 4.17 (q, J=7.1 Hz, 2H, CH_2CH_3), 5.90 (dd, J=15.6, 1.3 Hz, 1H, H-2), 6.71 (dd, J=15.6, 6.1 Hz, 1H, H-3), 7.33 (d, J=8.4 Hz, 2H, Ar), 7.69 (d, J=8.4 Hz, 2H, Ar), 9.57 (s, 1H, H-7); ^{13}C NMR δ 14.1, 21.5, 49.8, 56.4, 60.7, 125.0, 127.4, 130.0, 135.2, 140.8, 144.3, 165.2, 197.0; IR (neat) ν 1713, 1648 cm^{-1}; LRMS (EI) *m/z* 322 (2), 297 (16), 296 (base), 96 (35), 91 (74), 88 (51), 73 (39), 70 (70); HRMS calcd for $C_{15}H_{19}NO_5S$ 325.0984, found 325.0971.

4.2.6. Methyl 4-aza-7,7-diethoxyhept-2-enote (13d). The procedure reported for the corresponding ethyl ester[25b] was followed from methyl propiolate (2.47 mL, 27.5 mmol) and 1-amino-3,3-diethoxypropane (4.58 mL, 27.5 mmol) to yield **13d** (6.50 g, 1:2 *E*/*Z*, 100%) as an oil: ^{1}H NMR δ 1.19 (t, J=7.1 Hz, 6H, CH_2CH_3), 1.79–1.90 (m, 2H, H-6), 3.11 (q, J=6.0 Hz, 2H, H-5, *E* isomer), 3.21–3.28 (m, 2H, H-5, *Z* isomer), 3.41–3.54 (m, 2H), 3.57–3.71 (m, 5H), 3.62 and 3.63 (2 s, included in m at 3.57–3.71, CO_2CH_3), 4.44 (d, J=8.3 Hz, 1H, H-2, *Z* isomer), 4.54 (t, J=5.6 Hz, 1H, H-7), 4.68 (d, J=13.1 Hz, 1H, H-2, *E* isomer), 5.09 (br s, 1H, NH, *E* isomer), 6.59 (dd, J=13.1, 7.9 Hz, 1H, H-3, *Z* isomer), 7.43–7.52 (m, 1H, H-3, *E* isomer), 7.82 (br s, 1H, NH, *Z* isomer); ^{13}C NMR δ 15.2, 35.0, 44.6, 50.1, 50.5, 61.5, 62.0, 81.3, 84.8, 100.6, 102.0, 152.3, 170.0, 171.0; IR (neat) ν 3350, 1720, 1616 cm^{-1}; LRMS (EI) *m/z* 231 (M, 32), 186 (17), 185 (24), 126 (22), 114 (base), 85 (26), 82 (84); HRMS calcd for $C_{11}H_{21}NO_4$ 231.1471, found 231.1464.

4.2.7. Methyl (*E*)-4-aza-4-benzoyl-7,7-diethoxyhept-2-enoate (15) and methyl 4-aza-2-benzoyl-7,7-diethoxyhept-2-enoate (16b). *n*-BuLi (1.3 M in hexanes, 24 mL, 30.7 mmol) was added dropwise over 45 min to **13d** (6.88 g, 29.7 mmol) in THF (60 mL) at −78°C under Ar to give a yellow–green solution. After 1 h, benzoyl chloride (3.6 mL, 31.0 mmol) in THF (6 mL) was added over 30 min. The resulting mixture was stirred for 30 min,

allowed to warm to room temperature, stirred further 1 h and quenched with sat. NH_4Cl (75 mL). After separation, the aqueous layer was extracted with EtOAc (3×75 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to afford an oil that was purified by flash chromatography (silica gel saturated with Et_3N, 83:15:2 hexanes/EtOAc/Et_3N) to yield **15** (4.40 g, 44%) and **16b** (2.57 g, 26%). Data for **15**: ^{1}H NMR δ 1.17 (t, J=7.1 Hz, 6H, CH_2CH_3), 1.91–1.99 (m, 2H, H-6), 3.40–3.52 (m, 2H), 3.57–3.69 (m, 5H), 3.62 (s, CO_2CH_3, included in m at 3.57–3.69), 3.85 (t, J=7.4 Hz, 2H, H-5), 4.54 (t, J=5.4 Hz, 1H, H-7), 5.41 (d, J=14.0 Hz, 1H, H-2), 7.33–7.51 (m, 5H, Ar), 7.87 (d, J=14.0 Hz, 1H, H-3); ^{13}C NMR δ 15.1, 30.6, 40.0, 51.2, 61.5, 98.2, 100.8, 128.2, 128.6, 131.2, 133.4, 143.7, 167.6, 171.1; IR (neat) ν 1720, 1685, 1625 cm^{-1}; LRMS *m/z* 335 (M, 3), 291 (4), 290 (10), 276 (20), 129 (30), 105 (base), 85 (21); HRMS calcd for $C_{18}H_{25}NO_5$ 335.1733, found 335.1728. Data for **16b**: ^{1}H NMR δ 1.20–1.26 (m, 6H), 1.90–2.00 (m, 2H, H-6), 3.44–3.58 (m, 7H), 3.51 and 3.53 (2 s, CO_2CH_3, included in m at 3.44–3.58), 3.62–3.74 (m, 2H), 4.57–4.62 (m, 1H, H-7), 7.30–7.58 (m, 5H, Ar), 7.77 (d, J=14.3 Hz) and 8.04 (d, J=13.9 Hz) (total 1H), 9.22 and 10.63 (br s, 1H, NH); ^{13}C NMR δ 15.0, 34.0, 45.6, 45.9, 50.2, 50.5, 61.7, 99.0, 99.3, 100.4, 100.7, 126.8, 127.2, 127.3, 128.0, 129.5, 130.3, 141.2, 142.1, 159.8, 159.9, 167.9, 169.1, 193.2, 195.4; IR (neat) ν 3250, 1720, 1685, 1636 cm^{-1}; LRMS (EI) *m/z* 335 (M, 34), 289 (58), 260 (14), 228 (25), 218 (35), 217 (28), 186 (65), 184 (16), 140 (16), 105 (base); HRMS calcd for $C_{18}H_{25}NO_5$ 335.1733, found 335.1727.

4.2.8. Methyl (*E*)-4-aza-4-*tert*-butoxycarbonyl-7,7-diethoxyhept-2-enoate (17). The procedure described above for **15** was followed using di-*tert*-butildicarbonate instead of benzoyl chloride. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 96:2:2 hexanes/EtOAc/Et_3N) to yield **17** in 92% yield: ^{1}H NMR δ 1.08 (t, J=7.1 Hz, 6H, CH_2CH_3), 1.40 (s, 9H, CCH_3), 1.70–1.78 (m, 2H, H-6), 3.29–3.56 (m, 6H), 3.58 (s, 3H, CO_2CH_3), 4.38 (t, J=5.4 Hz, 1H, H-7), 5.11 (d, J=14.3 Hz, 1H, H-2), 8.05 (d, J=14.3 Hz, 1H, H-3); ^{13}C NMR δ 15.0, 27.7, 30.8, 40.0, 50.8, 61.2, 82.6, 96.3, 100.4, 142.4, 151.6, 168.0; IR (neat) ν 1735, 1630 cm^{-1}; LRMS (EI) *m/z* 331 (M, 3), 275 (11), 230 (54), 202 (18), 186 (32), 156 (26), 141 (54), 126 (53), 114 (55), 85 (base); HRMS calcd for $C_{16}H_{29}NO_6$ 331.1995, found 331.1995.

4.2.9. Methyl 4-aza-7,7-diethoxy-2-trifluoroacetylhept-2-enoate (16d). The foregoing procedure was followed, using in this case trifluoroacetic anhydride. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 92:6:2 hexanes/EtOAc/Et_3N) to yield **16d** in 66% yield as a 3:8 mixture of isomers: ^{1}H NMR δ 1.17 (t, J=7.1 Hz, 6H, CH_2CH_3), 1.87–1.94 (m, 2H, H-6), 3.39–3.71 (m, 9H), 3.68 (s, included in m at 3.39–3.71, CO_2CH_3), 4.51–4.56 (m, 1H, H-7), 7.93 and 8.07 (2 d, J=14.7 Hz, 1H, H-3), 9.81 and 10.66 (br s, 1H, NH); ^{13}C NMR δ 15.0, 33.6, 46.5, 46.6, 51.0, 51.2, 62.3, 95.3, 96.3, 100.9, 101.0, 116.9, 117.2, 160.9, 162.3, 165.5, 167.8, 176.8, 177.9; IR (neat) ν 3240, 1730, 1650, 1600 cm^{-1}; LRMS (EI) *m/z* 327 (M, 24), 281 (63), 212 (18), 210 (60), 184 (61), 178 (base), 140 (59), 85 (50), 72 (92); HRMS calcd for $C_{13}H_{20}NO_5F_3$ 327.1294, found 327.1302.

4.2.10. Methyl (*E*)-4-aza-4-benzoyl-6-formylhex-2-enoate (9b). A solution of **15** (0.55 g, 1.65 mmol) in AcOH/H_2O (2:1, 8 mL) was stirred at room temperature for 24 h, poured into H_2O (20 mL) and basified with solid $NaHCO_3$ to pH=7. The mixture was extracted with EtOAc (3×50 mL), the combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo to afford **9b** (0.35 g, 81%) as an oil unstable to chromatography, that was used without further purification: ^{1}H NMR δ 2.84–2.90 (m, 2H, H-5), 3.68 (s, 3H, CO_2CH_3), 4.14 (t, J=7.2 Hz, 2H, H-6), 5.35 (d, J=14.0 Hz, 1H, H-2), 7.46–7.55 (m, 5H, Ar), 7.88 (d, J=14.0 Hz, 1H, H-3), 9.86 (t, J=1.1 Hz, 1H, C*H*O); ^{13}C NMR δ 37.5, 40.5, 51.4, 98.4, 128.4, 128.7, 131.6, 132.8, 143.2, 167.3, 171.3, 199.4; IR (neat) ν 1714, 1680, 1619 cm^{-1}; LRMS (EI) *m/z* 261 (M, 2), 230 (6), 202 (25), 105 (base), 77 (24); HRMS calcd for $C_{14}H_{15}NO_4$ 261.1001, found 261.0994.

4.2.11. Methyl (*E*)-4-aza-4-*tert*-butoxycarbonyl-7-oxohept-2-enoate (9c). The procedure described above for **9b** was followed from **17** to afford **9c** (0.364 g, 70%) as an oil unstable to chromatography, that was used without further purification: ^{1}H NMR δ 1.42 (s, 9H, CCH_3), 2.64 (t, J=7.1 Hz, 2H), 3.61 (s, 3H, CO_2CH_3), 3.78 (t, J=7.1 Hz, 2H), 5.05 (d, J=14.3 Hz, 1H, H-2), 8.04 (d, J=14.3 Hz, 1H, H-3), 9.69 (s, 1H, C*H*O); ^{13}C NMR δ 27.7, 37.6, 40.8, 51.1, 83.4, 96.6, 141.9, 151.4, 167.7, 199.4.

4.3. Preparation of pyrrolidines 8 and 12

4.3.1. General procedure. In a typical experiment, a mixture of aldehyde **5** or **9** (2.0 mmol), a secondary amine (2.1 mmol), benzotriazole (2.1 mmol) and molecular sieves (4 Å, 1.0 g) in dry THF (12 mL) was stirred overnight at room temperature. The reaction mixture was filtered over Celite and vacuum-dried (0.1 mm Hg) for 2 h to give crude **6** or **10**, which was dissolved with *t*-BuOH (0.38 mL, 4.0 mmol) in THF (40 mL) and added dropwise over 30 min to a solution of SmI_2 (ca. 0.1 M in THF, 62 mL, 6.2 mmol) at −78°C. The mixture was stirred at −78°C for an additional 30 min and allowed to warm to room temperature. After further stirring for 90 min the reaction mixture was quenched with a mixture of sat. K_2CO_3 (50 mL) and water (50 mL). After separation, the aqueous layer was extracted with EtOAc (3×75 mL), the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated to give a crude product that was purified by flash chromatography (silica gel saturated with Et_3N, with mixtures of hexanes/EtOAc/Et_3N as eluent) to give the pure products.

4.3.2. *cis*- and *trans*-4-Ethoxycarbonylmethyl-3-(morpholin-1-yl)-1-tosylpyrrolidine (8a). Prepared from **5b** (9:1 mixture with **14**) and morpholine. Elution with 78:20:2 hexanes/EtOAc/Et_3N, separated the two isomers, that were obtained in 29 and 32% yields, respectively, as oils. Data for *cis*-**8a**: ^{1}H NMR δ 1.18 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.67 (dd, J=17.0, 10.3 Hz, 1H), 2.14–2.58 (m, 10H), 2.38 (s, Ar-CH_3, included in m at 2.14–2.58), 2.94 (t, J=9.5 Hz, 1H), 3.23–3.43 (m, 3H), 3.56 (t, J=4.8 Hz, 4H), 4.03 (q, J=7.1 Hz, 2H, OCH_2CH_3), 7.28 (d, J=7.9 Hz, 2H, Ar), 7.64 (d, J=7.9 Hz, 2H, Ar); ^{13}C NMR δ 14.0, 21.3,

30.8, 35.8, 48.5, 51.9, 52.0, 60.3, 65.4, 66.3, 127.1, 129.6, 133.5, 143.4, 172.4; IR (neat) ν 1735 cm^{-1}; LRMS (EI) *m/z* 351 (18), 241 (base), 212 (79), 126 (7); HRMS calcd for $C_{19}H_{28}N_2O_5S$ 396.1719, found 396.1693. Data for *trans*-**8a**: ^1H NMR δ 1.20 (t, *J*=7.1 Hz, 3H), 2.20 (dd, *J*=17.1, 10.2 Hz, 1H), 2.36–2.50 (m, 10H), 2.39 (s, Ar-CH_3, included in m at 2.36–2.50), 2.67 (dd, *J*=14.1, 6.9 Hz, 1H), 2.86 (dd, *J*=9.9, 6.5 Hz, 1H), 3.02 (dd, *J*=9.9, 6.9 Hz, 1H), 3.28 (dd, *J*=9.8, 7.2 Hz, 1H), 3.41 (dd, *J*=9.9, 7.5 Hz, 1H), 3.54–3.57 (m, 4H), 4.06 (q, *J*=7.1 Hz, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H); ^{13}C NMR δ 14.0, 21.4, 35.8, 37.2, 46.8, 50.0, 51.7, 60.6, 66.8, 68.7, 127.6, 129.6, 132.4, 143.6, 171.6; IR (neat) ν 1730 cm^{-1}; LRMS *m/z* 241 (base), 212 (46), 140 (6), 126 (9); HRMS calcd for $C_{19}H_{28}N_2O_5S$ 396.1719, found 396.1730.

4.3.3. *cis*- and *trans*-4-Ethoxycarbonylmethyl-3-(4-phenylpiperazin-1-yl)-1-tosylpyrrolidine (8b). Prepared from **5b** (9:1 mixture with **14**) and *N*-phenylpiperazine. Elution with 78:20:2 hexanes/EtOAc/Et_3N separated the two isomers, that were obtained in 36 and 23% yields, respectively, as oils. Data for *cis*-**8b**: ^1H NMR δ 1.24 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.76 (dd, *J*=16.9, 10.4 Hz, 1H), 2.37–2.69 (m, 10H), 2.44 (s, ArCH_3, included in m at 2.37–2.69), 3.01–3.13 (m, 5H), 3.32–3.42 (m, 2H), 3.48–3.54 (m, 1H), 4.10 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 6.82–6.90 (m, 3H, Ar), 7.22–7.28 (m, 2H, Ar), 7.34 (d, *J*=8.0 Hz, 2H, Ar), 7.73 (d, *J*=8.0 Hz, 2H, Ar); ^{13}C NMR δ 14.1, 21.4, 31.0, 36.0, 48.6, 48.9, 51.6, 52.0, 60.4, 65.1, 115.8, 119.7, 127.2, 128.9, 129.7, 133.5, 143.5, 150.8, 172.6; IR (neat) ν 1730 cm^{-1}; LRMS (EI) *m/z* 471 (M, 12), 426 (7), 316 (base), 287 (29), 160 (7), 132 (11); HRMS calcd for $C_{25}H_{33}N_3O_4S$ 471.2192, found 471.2185. Data for *trans*-**8b**: the characterized sample was obtained after HPLC (μ-Bondapak-NH_2, 10 μm, 19 mm×15 cm, 72:28 hexanes/EtOAc, 7 mL/min, t_R=11 min); ^1H NMR δ 1.24 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 2.28 (dd, *J*=16.3, 9.4 Hz, 1H), 2.44 (s, 3H, ArCH_3), 2.46–2.62 (m, 6H), 2.77–2.85 (m, 1H), 2.89–2.96 (m, 1H), 3.05–3.12 (m, 5H), 3.34–3.50 (m, 2H), 4.11 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 6.83–6.90 (m, 3H), 7.22–7.29 (m, 2H), 7.34 (d, *J*=8.0 Hz, 2H, Ar), 7.70 (d, *J*=8.3 Hz, 2H, Ar); ^{13}C NMR δ 14.2, 21.5, 36.2, 37.6, 47.2, 49.2, 49.7, 52.0, 60.7, 68.6, 116.1, 120.0, 127.8, 129.1, 129.7, 132.3, 143.8, 151.0, 171.8; IR (neat) ν 1730 cm^{-1}; LRMS (EI) *m/z* 471 (M, 11), 426 (7), 316 (base), 287 (31), 160 (6), 132 (9); HRMS calcd for $C_{25}H_{33}N_3O_4S$ 471.2192, found 471.2195.

4.3.4. *cis*- and *trans*-4-Ethoxycarbonylmethyl-3-(piperidin-1-yl)-1-tosylpyrrolidine (8c). Prepared from **5b** (9:1 mixture with **14**) and piperidine. Elution with 88:10:2 hexanes/EtOAc/Et_3N separated the two isomers, that were obtained in 26 and 21% yields, respectively, as oils. Data for *cis*-**8c**: ^1H NMR δ 1.21 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.34–1.46 (m, 6H), 1.66 (dd, *J*=17.0, 11.1 Hz, 1H), 2.13–2.23 (m, 4H), 2.40 (s, ArCH_3, included in m at 2.40–2.60), 2.40–2.60 (m, 6H), 2.93 (t, *J*=9.5 Hz, 1H), 3.25–3.35 (m, 2H), 3.43 (dd, *J*=9.2, 7.2 Hz, 1H), 4.06 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 7.30 (d, *J*=8.1 Hz, 2H, Ar), 7.67 (d, *J*=8.1 Hz, 2H, Ar); ^{13}C NMR δ 14.1, 21.4, 24.0, 25.5, 30.9, 36.2, 49.2, 51.9, 52.9, 60.3, 65.8, 127.2, 129.6, 133.6, 143.4, 172.8; IR (neat) ν 1735 cm^{-1}; LRMS (EI) *m/z* 394 (M, 1), 349 (15), 239 (base), 210 (63), 198 (7), 124 (8); HRMS calcd for $C_{20}H_{30}N_2O_4S$ 394.1926, found 394.1909. Data for *trans*-**8c**: ^1H NMR δ 1.23 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.37–1.46 (m, 6H), 2.17–2.52 (m, 10H), 2.42 (s, ArCH_3, included in m at 2.17–2.52), 2.66 (dd, *J*=14.7, 7.1 Hz, 1H), 2.86–2.98 (m, 2H), 3.31–3.40 (m, 2H), 4.09 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 7.32 (d, *J*=7.9 Hz, 2H, Ar), 7.67 (d, *J*=7.9 Hz, 2H, Ar); ^{13}C NMR δ 14.1, 21.5, 24.3, 26.0, 36.2, 37.9, 47.6, 52.1, 60.6, 69.4, 127.8, 129.6, 132.3, 143.6, 172.0; IR (neat) ν 1735 cm^{-1}; LRMS (EI) *m/z* 349 (12), 239 (base), 210 (49), 198 (6), 124 (8); HRMS calcd for $C_{20}H_{30}N_2O_4S$ 394.1926, found 394.1910.

4.3.5. *cis*- and *trans*-1-(Benzyloxycarbonyl)-2-ethoxycarbonylmethyl-3-(morpholin-1-yl)pyrrolidine (12a). Prepared from **9b** and morpholine. Elution with 73:25:2 hexanes/EtOAc/Et_3N separated the two isomers, that were obtained in 29 and 43% yields, respectively, as oils. Data for *cis*-**12a** (rotamer mixture): ^1H NMR δ 1.13 and 1.23 (2 t, *J*=7.1 Hz, 3H), 1.60–1.84 (m, 1H), 1.97–2.06 (m, 1H), 2.19 (dd, *J*=15.4, 5.9 Hz) and 2.24–2.32 (m) (total 1H), 2.38–2.55 (m, 4H), 2.62–2.81 (m, 2H), 3.30–3.56 (m, 2H), 3.63 (s, 4H), 3.88 and 4.10 (2 q, *J*=7.1 Hz, 2H), 4.45–4.56 (m, 1H), 5.00–5.17 (m, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR δ 14.0, 25.6, 26.3, 34.7, 35.0, 43.6, 43.8, 52.4, 55.5, 56.0, 60.2, 60.4, 66.0, 66.6, 66.7, 66.8, 127.7, 127.8, 128.3, 136.4, 136.6, 154.5, 171.9; IR (neat) ν 1740, 1710 cm^{-1}; LRMS (EI) *m/z* 376 (M, 35), 331 (26), 303 (16), 288 (19), 281 (15), 241 (base); HRMS calcd for $C_{20}H_{28}N_2O_5$ 376.1998, found 376.2005. Data for *trans*-**12a** (rotamer mixture): The characterized sample was obtained after HPLC (μ-Bondapak-NH_2, 10 μm, 19 mm×15 cm, 75:25 hexanes/EtOAc, 8 mL/min, t_R=7 min); ^1H NMR δ 1.23 and 1.24 (2 t, *J*=7.1 Hz, 3H), 1.95–2.02 (m, 2H), 2.37–2.57 (m, 5H), 2.70 (dd, *J*=15.1, 3.6 Hz) and 2.86 (dd, *J*=15.3, 3.8 Hz) (total 2H), 3.34–3.69 (m, 6H), 4.03–4.16 (m, 2H), 4.23–4.25 (m, 1H), 5.05–5.21 (m, 2H), 7.29–7.37 (m, 5H); ^{13}C NMR δ 14.2, 24.7, 25.2, 37.7, 38.8, 45.0, 45.4, 50.4, 50.5, 56.0, 56.6, 60.5, 66.7, 67.0, 68.9, 69.8, 127.8, 127.9, 128.4, 136.7, 154.4, 170.9, 171.1; IR (neat) ν 1730, 1705 cm^{-1}; LRMS (EI) *m/z* 376 (M, 35), 331 (8), 303 (12), 289 (19), 288 (15), 241 (base); HRMS calcd for $C_{20}H_{28}N_2O_5$ 376.1998, found 376.1999.

4.3.6. 3-(*N*-Benzyl-*N*-methylamino)-1-benzyloxycarbonyl-2-ethoxycarbonylmethylpyrrolidine (12b). Prepared from **9a** and *N*-benzyl-*N*-methylamine. Elution with 88:10:2 hexanes/EtOAc/Et_3N yielded **12b** (82%, 1:1.3 *cis*/*trans* mixture) as an oil. Data for the diastereomeric mixture (mixtures of rotamers): ^1H NMR δ 1.11 and 1.24 (2 t, *J*=7.1 Hz, 3H), 1.71–3.24 (m, 8H), 2.11 and 2.18 (2 s, included in m at 1.71–3.24), 3.36–3.89 (m) and 4.01–4.15 (m) (total 6H), 4.27 (br s) and 4.61–4.65 (m) (total 1H), 5.04–5.23 (m, 2H), 7.27–7.38 (m, 5H); ^{13}C NMR δ 14.0, 23.9, 24.6, 27.0, 27.7, 34.6, 34.9, 37.4, 37.7, 38.6, 40.5, 43.8, 44.0, 45.1, 45.5, 56.2, 56.4, 56.8, 58.8, 60.1, 60.4, 65.9, 66.5, 66.7, 67.7, 68.6, 126.8, 127.6, 127.7, 128.1, 128.2, 128.4, 136.4, 136.7, 138.6, 139.1, 154.3, 154.5, 170.8, 171.0, 172.0, 172.1; IR (neat) ν 1730, 1710 cm^{-1}; LRMS (EI) *m/z* 410 (M, 8), 337 (9), 319 (15), 275 (60), 160 (17), 91 (base); HRMS calcd for $C_{24}H_{30}N_2O_4$ 410.2206, found 410.2193.

4.3.7. 3-[*N*-Allyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]amino]-1-benzyloxycarbonyl-2-ethoxycarbonylmethylpyrrolidine (12c). Prepared from **9a** and 3,4-dimethoxyphenethylamine. Elution with 83:15:2 hexanes/EtOAc/Et_3N yielded **12c** (82%, 2:3 *cis*/*trans* mixture) as an oil. The *cis* isomer was partially separated by HPLC (μ-Bondapak-NH_2, 10 μm, 19 mm×15 cm, 90:10 hexanes/EtOAc, 8 mL/min, t_R=27 min). Data for the diastereomeric mixture (mixtures of rotamers): ^{1}H NMR δ 1.11 (t, *J*=7.1 Hz) and 1.18–1.25 (m) (total 3H), 1.77–2.28 (m, 3H), 2.45–2.85 (m, 6H), 3.09–3.84 (m, 5H), 3.84 and 3.86 (2 s, 6H, OCH_3), 3.91–4.12 (m) and 4.52 (br s) (total 3H), 5.01–5.29 (m, 4H), 5.79–5.93 (m, 1H, CH_2=C*H*), 6.67–6.79 (m, 3H, Ar), 7.26–7.36 (m, 5H, Ar); ^{13}C NMR δ 14.1, 24.3, 24.7, 26.7, 27.4, 31.5, 34.2, 34.6, 34.8, 36.9, 38.1, 43.9, 44.1, 45.2, 45.5, 52.3, 52.7, 53.6, 53.9, 55.7, 55.8, 56.4, 56.6, 56.9, 60.3, 60.4, 62.4, 63.2, 65.1, 66.1, 66.6, 66.8, 111.1, 111.9, 116.8, 117.6, 120.4, 120.5, 127.7, 127.8, 128.4, 132.7, 132.8, 134.4, 134.5, 136.4, 136.8, 147.1, 147.2, 148.6, 148.7, 154.4, 154.6, 154.7, 171.1, 171.3, 172.2, 172.3; IR (neat) ν 1740, 1710, 1650 cm^{-1}. Data for *cis*-**12c** (rotamer mixture): ^{1}H NMR δ 1.11 (t, *J*=7.1 Hz) and 1.20 (distorted t) (total 3H), 1.71–2.28 (m, 3H), 2.60–2.85 (m, 5H), 3.12–3.56 (m, 5H), 3.84 and 3.87 (2 s, overlapped with m from another H, total 7H), 4.12 (q, *J*=7.1 Hz, 1H, CH_3CH_2), 4.49–4.51 (m, 1H), 5.01–5.29 (m, 4H), 5.79–5.95 (m, 1H), 6.66–6.79 (m, 3H), 7.26–7.36 (m, 5H); ^{13}C NMR δ 14.1, 15.2, 26.7, 27.4, 31.5, 34.7, 34.8, 43.9, 44.1, 52.7, 53.5, 55.7, 55.8, 56.4, 57.0, 60.2, 60.4, 62.4, 63.2, 65.8, 66.6, 66.8, 111.0, 111.8, 117.6, 120.4, 127.8, 127.8, 128.3, 132.7, 134.4, 136.5, 136.8, 147.2, 148.7, 154.7, 172.2, 172.3; IR (neat) ν 1740, 1710, 1650 cm^{-1}; LRMS (EI) *m*/*z* 465 (1), 421 (3), 360 (32), 359 (base), 91 (58); HRMS calcd for $C_{29}H_{39}N_2O_6$ (M+1) 511.2808, found 511.2807.

4.3.8. *cis*- and *trans*-1-Benzyloxycarbonyl-2-ethoxycarbonylmethyl-3-(4-phenylpiperazin-1-yl)pyrrolidine (12d). Prepared from **9a** and 4-phenylpiperazine. Elution with 88:10:2 hexanes/EtOAc/Et_3N yielded **12d** (84%, 2:3 *cis*/*trans* mixture) as an oil. Partial separation of the two isomers allowed their individual characterization. Data for *cis*-**12d** (rotamer mixture): ^{1}H NMR δ 1.15 and 1.25 (2 t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.72–1.87 (m, 1H), 2.06 (m, 1H), 2.20–2.37 (m, 1H), 2.62–2.87 (m, 6H), 3.15 (br s, 4H), 3.42–3.61 (m, 2H), 3.92 (q, *J*=7.1 Hz, 1H), 4.12–4.15 (m, 1H), 4.56–4.59 (m, 1H), 5.05–5.22 (m, 2H, PhCH_2), 6.84–6.93 (m, 3H), 7.24–7.36 (m, 7H); ^{13}C NMR δ 14.0, 25.9, 26.7, 34.8, 35.1, 43.7, 43.9, 48.8, 51.9, 55.7, 56.2, 60.2, 60.4, 65.7, 66.4, 66.6, 66.8, 115.8, 119.6, 127.7, 127.8, 128.3, 129.0, 136.4, 136.7, 151.0, 154.5, 171.9; IR (neat) ν 1740–1690, 1600 cm^{-1}; LRMS (EI) *m*/*z* 451 (M, 84), 406 (16), 364 (11), 316 (35), 201 (22), 187 (14), 173 (24), 163 (14), 162 (base); HRMS calcd for $C_{26}H_{33}N_3O_4$ 451.2471, found 451.2472. Data for *trans*-**12d** (rotamer mixture): ^{1}H NMR δ 1.22–1.29 (m, 3H, CH_3), 2.02–2.07 (m, 2H), 2.42–2.94 (m, 6H), 3.02–3.17 (m, 5H), 3.43–3.45 (m, 1H), 3.56–3.71 (m, 1H), 4.05–4.18 (m, 2H, CH_3CH_2), 4.30–4.31 (m, 1H), 5.14–5.24 (m, 2H, PhCH_2), 6.84–6.94 (m, 3H), 7.24–7.38 (m, 7H); ^{13}C NMR δ 14.1, 24.8, 25.2, 37.7, 38.8, 45.0, 45.4, 49.1, 49.7, 49.9, 55.9, 56.6, 60.4, 66.6, 66.8, 68.5, 69.5, 115.9, 119.6, 127.7, 127.8, 128.3, 129.0, 136.5, 136.7, 151.1, 154.3, 170.8, 171.0; IR (neat) ν 1740–1690, 1600 cm^{-1}; LRMS (EI) *m*/*z* 451 (M, 95), 406 (14), 364 (13), 316 (37), 201 (23), 187 (15), 173 (26), 163 (14), 162 (base); HRMS calcd for $C_{26}H_{33}N_3O_4$ 451.2471, found 451.2468.

4.4. Deprotection-functionalization of 3-amino-pyrrolidines

4.4.1. *trans*-3-[*N*-[2-(3,4-Dimethoxyphenyl)ethyl]amino]-1-benzyloxycarbonyl-2-ethoxycarbonylmethylpyrrolidine (21) and *cis*-5-benzyloxycarbonyl-1,5-diaza-1-[2-(3,4-dimethoxyphenyl)ethyl]-2-oxoperhydropentalene (22). A mixture of **12c** (0.510 g, 1.0 mmol, 2:3 *cis*/*trans* mixture), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and *N*,*N*-dimethylbarbituric acid (NDMBA) (0.47 g, 3.0 mmol) in dry degassed CH_2Cl_2 (2 mL), under Ar, was stirred for 24 h at room temperature, the solvent was evaporated and the residue was redissolved in EtOAc (25 mL). The resulting solution was washed with sat. K_2CO_3 (3×10 mL) and brine (10 mL), and dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, 83:15:2 hexanes/EtOAc/Et_3N and then 63:35:2 hexanes/EtOAc/Et_3N) and HPLC (μ-Bondapak-NH_2, 10 μm, 19 mm×15 cm, 40:60 hexanes/EtOAc, 8 mL/min) to yield **21** (279 mg, 60%) and **22** (148 mg, 35%). Data for **21**: t_R=7 min; ^{1}H NMR δ 1.19 (t, *J*=7.1 Hz, 3H, CH_3CH$_2$), 1.59–1.70 (m, 1H), 1.95–2.09 (m, 1H), 2.28 (dd, *J*=15.8, 10.3 Hz, 1H), 2.70–2.96 (m, 5H), 3.14–3.16 (m, 1H), 3.38–3.58 (m, 2H), 3.82 and 3.84 (2 s, 6H, CH_3O), 4.01–4.12 (m, 3H), 5.03–5.19 (m, 2H), 6.70–6.79 (m, 3H), 7.27–7.33 (m, 5H, Ar); ^{13}C NMR δ 14.0, 29.0, 29.8, 35.6, 37.0, 38.1, 44.5, 44.8, 48.8, 55.6, 55.7, 59.5, 60.0, 60.3, 61.7, 62.6, 66.5, 66.6, 111.0, 111.6, 120.4, 127.6, 127.7, 128.3, 132.2, 136.6, 147.2, 148.7, 154.6, 170.9, 171.1; IR (neat) ν 3450, 1745, 1730, 1715, 1700 cm^{-1}; LRMS (EI) *m*/*z* 425 (5), 383 (1), 320 (24), 319 (99), 275 (14), 91 (base); HRMS calcd for $C_{26}H_{34}N_2O_6$ 470.2417, found 470.2417. Data for **22**: t_R=11 min; ^{1}H NMR δ 1.78–2.07 (m, 2H), 2.48–2.95 (m, 4H), 3.12–3.31 (m, 2H), 3.64–3.92 (m, 8H), 3.86 and 3.87 (2 s, included in m at 3.64–3.92, CH_3O), 4.05 (t, *J*=5.1 Hz, 1H), 4.26–4.36 (m, 1H), 5.05–5.20 (m, 2H, PhCH_2), 6.74–6.84 (m, 3H, Ar), 7.27–7.39 (m, 5H, Ar); ^{13}C NMR δ 27.9, 28.4, 33.0, 37.7, 38.6, 42.0, 43.8, 44.2, 54.2, 54.9, 55.8, 55.8, 61.9, 62.8, 66.9, 67.1, 111.1, 111.5, 120.4, 127.9, 128.0, 128.1, 128.4, 128.5, 130.7, 130.8, 136.2, 136.3, 147.6, 148.8, 153.9, 154.1, 173.2, 173.6; IR (neat) ν 1710, 1700 cm^{-1}; LRMS (EI) *m*/*z* 424 (M, 16), 165 (24), 164 (base), 151 (14), 91 (21); HRMS calcd for $C_{24}H_{28}N_2O_5$ 424.1998, found 424.2019.

4.4.2. *trans*-1-Benzyloxycarbonyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]benzoylamino]-2-ethoxycarbonylmethylpyrrolidine (23). To a solution of **21** (0.259 g, 0.55 mmol) and Et_3N (0.140 mL, 1.0 mmol) in CH_2Cl_2 (10 mL) at 0°C was added dropwise over 5 min benzoyl chloride (0.080 mL, 0.66 mmol). The mixture was stirred for 1 h, allowed to warm to room temperature and stirred further 2 h. The reaction mixture was poured into sat. NH_4Cl (15 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 88:10:2 hexanes/EtOAc/Et_3N) to

yield **23** (289 mg, 92%) as an oil: ^{1}H NMR (40°C) δ 1.12–1.18 (m, 3H, CH_2CH_3), 1.97 (br s, $W_{1/2}$=25.5 Hz, 2H), 2.64 (br s, $W_{1/2}$=20.3 Hz, 2H), 2.83 (br s, $W_{1/2}$=20.3 Hz, 2H), 3.26–3.58 (m, 3H), 3.76 and 3.81 (2 s, overlapped with signals from another H, total 7H), 3.98–4.16 (m and br s, 3H), 4.62 (br s, $W_{1/2}$=22.0 Hz, 1H), 5.06–5.16 (m, 2H, $PhCH_2O$), 6.56–6.74 (m, 3H, Ar), 7.27–7.37 (m, 10H).); ^{13}C NMR (40°C) δ 13.9, 28.3, 35.2, 36.5, 44.8, 46.5, 55.8, 55.9, 56.4, 60.2, 61.9, 66.8, 111.7, 112.3, 120.7, 126.4, 127.7, 127.8, 128.3, 128.3, 129.3, 131.2, 136.4, 136.8, 147.8, 149.1, 154.1, 170.2, 172.1; IR (neat) ν 1725, 1695, 1631 cm^{-1}; LRMS (EI) *m/z* 574 (M, 4), 529 (6), 423 (7), 285 (23), 211 (20), 169 (25), 165 (26), 164 (base), 105 (62); HRMS calcd for $C_{33}H_{38}N_2O_7$ 574.2679, found 574.2683.

4.4.3. *trans*-3-[[2-(3,4-Dimethoxyphenyl)ethyl]benzoylamino]-2-ethoxycarbonylmethylpyrrolidine (24). A stirred mixture of **23** (81 mg, 0.14 mmol) and 10% Pd/C (11 mg) in EtOH (1 mL) was treated with H_2 (1 atm)at room temperature for 5 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 18:80:2 hexanes/EtOAc/Et_3N), to yield **24** (58 mg, 94%) as a colorless solid. ^{1}H NMR (40°C) δ 1.24 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.78–2.08 (m, 2H), 2.12–2.30 (m, 1H), 2.52–2.70 (m, 1H), 2.88–3.10 (m, 5H), 3.50–3.56 (m, 3H), 3.82 and 3.84 (2 s, 6H, CH_3O), 3.92–4.04 (m, 1H), 4.12 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 6.65–6.80 (m, 3H, Ar), 7.31–7.41 (m, 5H, Ar); ^{13}C NMR (40°C) δ 14.2, 29.0, 35.2, 38.1, 44.3, 56.0, 56.1, 57.0, 60.6, 63.4, 111.9, 112.6, 120.9, 126.5, 128.6, 129.4, 137.3, 148.0, 149.3, 171.8, 172.5; IR (neat) ν 3435, 1730, 1630 cm^{-1}; LRMS (EI) *m/z* 440 (M, 3), 353 (7), 165 (10), 164 (28), 156 (10), 155 (base), 105 (48); HRMS calcd for $C_{25}H_{32}N_2O_5$ 440.2311, found 440.2295.

4.4.4. *trans*-3-[[2-(3,4-Dimethoxyphenyl)ethyl]benzoylamino]-2-ethoxycarbonylmethyl-1-(*p*-methylbenzoyl)pyrrolidine (25). The procedure described above for **23** was followed form **24** and *p*-methylbenzoyl chloride. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 58:40:2 hexanes/EtOAc/Et_3N) to yield **25** (34 mg, 76%) as an oil: ^{1}H NMR (40°C) δ 1.18 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.89–1.94 (m, 2H), 2.36 (s, 3H, $ArCH_3$), 2.61–2.66 (m, 1H), 2.89 (br s, $W_{1/2}$=19.9 Hz, 3H), 3.27–3.67 (m, 4H), 3.81 and 3.84 (2 s, 6H, CH_3O), 3.99–4.02 (m, 2H, CH_2CH_3), 4.42 (br s, $W_{1/2}$=18.3 Hz, 2H), 4.81 (br s, $W_{1/2}$=25.0 Hz, 2H), 6.62 (br s, $W_{1/2}$=25.2 Hz, 2H), 6.78 (d, *J*=7.9 Hz, 1H), 7.17 (d, *J*=7.9 Hz, 2H), 7.36–7.40 (m, 7H); ^{13}C NMR (40°C) δ 14.1, 21.3, 29.4, 35.1, 35.2, 46.0, 48.3, 55.4, 56.0, 56.1, 60.4, 61.2, 111.9, 112.6, 121.0, 126.6, 127.6, 128.6, 128.9, 129.5, 131.4, 133.1, 137.0, 140.6, 148.1, 149.4, 169.8, 170.6, 172.5; IR (neat) ν 1730, 1680, 1625 cm^{-1}; LRMS (EI) *m/z* 407 (12), 285 (9), 273 (36), 245 (4), 165 (14), 164 (base), 151 (9), 119 (51), 105 (70); HRMS calcd for $C_{33}H_{38}N_2O_6$ 558.2730, found 558.2711.

4.4.5. *trans*-2-Benzylamidomethyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]benzoylamino]-1-(*p*-methylbenzoyl)pyrrolidine (27). To a solution of **25** (50 mg, 0.09 mmol) in THF/H_2O (6:1, 0.7 mL) was added dropwise 1 M NaOH (90 μL, 0.09 mmol) and the mixture was stirred for 20 h at room temperature. After removal of the solvents, the residue was dissolved in H_2O (4 mL) and extracted with CH_2Cl_2 (3×4 mL). The aqueous layer was acidified with 1 M HCl to pH=2 and extracted with CH_2Cl_2 (3×6 mL). The latter organic extracts were dried (Na_2SO_4) and the solvent evaporated to afford **26**. The crude acid **26** and carbonyldiimidazole (CDI) (10 mg, 0.06 mmol) were dissolved in MeCN (0.34 mL) and the mixture was stirred at room temperature for 1.5 h. Benzylamine (100 μL, 0.09 mmol) was added dropwise and the mixture was stirred for 20 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2/H_2O (1:1, 8 mL). After separation, the organic layer was washed with 10% HCl (2 mL) and sat. $NaHCO_3$ (2 mL), and dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, 48:50:2 hexanes/EtOAc/Et_3N) to yield **27** (29 mg, 52%, over two steps) as an oil: ^{1}H NMR (40°C) δ 1.94–2.07 (m, 2H), 2.37 (s, 3H, $ArCH_3$), 2.60 (br s, 1H), 2.84 (br s, 3H), 3.41–3.72 (m, 4H), 3.79 and 3.83 (2 s, 6H, OCH_3), 4.32–4.49 (m, 3H), 4.97 (br s, 1H), 6.42–6.77 (m, 4H), 7.13–7.40 (m, 14H); ^{13}C NMR (40°C) δ 21.3, 28.9, 35.4, 37.2, 43.5, 48.7, 49.6, 56.0, 56.1, 56.5, 61.4, 111.8, 112.4, 120.9, 126.6, 127.3, 127.5, 127.8, 128.6, 129.0, 129.5, 131.2, 133.1, 137.1, 138.4, 140.6, 148.0, 149.3, 169.8, 170.2, 172.8; IR (neat) ν 3295, 1660, 1620 cm^{-1}; LRMS (EI) *m/z* 410 (6), 393 (13), 346 (11), 334 (20), 322 (65), 164 (base), 119 (33), 105 (29); HRMS calcd for $C_{38}H_{42}N_3O_5$ (M+1) 620.3124, found 620.3126.

Acknowledgements

Financial support provided by Janssen-Cilag is gratefully acknowledged.

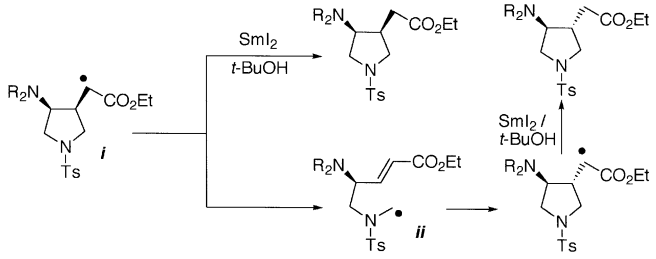
References

1. Renaud, P.; Giraud, L. *Synthesis* **1996**, 913–926.
2. Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825–5828.
3. Aurrecoechea, J. M.; López, B.; Fernández, A.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 1125–1135.
4. (a) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179–180. (b) Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 2323–2328.
5. Ishizaki, M.; Takano, H.; Hoshino, O. *Heterocycles* **1998**, *49*, 305–314.
6. Katritzky, A. R.; Feng, D. M.; Qi, M.; Aurrecoechea, J. M.; Suero, R.; Aurrekoetxea, N. *J. Org. Chem.* **1999**, *64*, 3335–3338.
7. Aurrecoechea, J. M.; Fernandez, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, *55*, 7345–7362.
8. Arya, P.; Wayner, D. M. *Tetrahedron Lett.* **1991**, *32*, 6265–6268.
9. Tsai, Y.-M.; Nieh, H.-C.; Pan, J.-S.; Hsiao, D.-D. *Chem. Commun.* **1996**, 2469–2470.
10. Lesage, M.; Arya, P. *Synlett* **1996**, 237–238.
11. Easton, C. *J. Chem. Rev.* **1997**, *97*, 53–82.
12. Atarashi, S.; Choi, J. K.; Ha, D. C.; Hart, D. J.; Kuzmich, D.; Lee, C. S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226–6241.

13. Clauss, R.; Hunter, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 71–76.
14. Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789–4792.
15. Baker, S. R.; Burton, K. I.; Parsons, A. F.; Pons, J. F.; Wilson, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 427–436.
16. (a) Curran, D. P.; Liu, H. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377–1393. (b) Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles* **2001**, *54*, 747–755.
17. Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **1992**, *25*, 233–240.
18. Santamaria, J. *Pure Appl. Chem.* **1995**, *67*, 141–147.
19. Jonas, M.; Blechert, S.; Steckhan, E. *J. Org. Chem.* **2001**, *66*, 6896–6904 and references cited therein.
20. A review on intramolecular radical conjugate additions: Zhang, W. *Tetrahedron* **2001**, *57*, 7237–7261.
21. Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 417–420.
22. Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445–1446.
23. Lee, E.; Jeong, E. J.; Min, S. J.; Hong, S.; Lim, J.; Kim, S. K.; Kim, H. J.; Choi, B. G.; Koo, K. C. *Org. Lett.* **2000**, *2*, 2169–2171.
24. Lee, E.; Kim, S. K.; Kim, J. Y.; Lim, J. *Tetrahedron Lett.* **2000**, *41*, 5915–5916.
25. (a) Macdonald, S. J. F.; Mills, K.; Spooner, J. E.; Upton, R. J.; Dowle, M. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3931–3936. (b) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445–1446.
26. (a) Yoshida, T.; Yamamoto, Y.; Orita, H.; Kakiuchi, M.; Takahashi, Y.; Itakura, M.; Kado, N.; Yasuda, S.; Kato, H.; Itoh, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1376–1386. (b) Kawakami, K.; Takahashi, H.; Ohki, H.; Kimura, K.; Miyauchi, S.; Miyauchi, R.; Takemura, M. *Chem. Pharm. Bull.* **2000**, *48*, 1667–1672.
27. Rajeev, K. G.; Sanjayan, G. J.; Ganesh, K. N. *J. Org. Chem.* **1997**, *62*, 5169–5173.
28. Macdonald, S. J. F.; Belton, D. J.; Buckley, D. M.; Spooner, J. E.; Anson, M. S.; Harrison, L. A.; Mills, K.; Upton, R. J.; Dowle, M. D.; Smith, R. A.; Molloy, C. R.; Risley, C. *J. Med. Chem.* **1998**, *41*, 3919–3922.
29. Ewing, W. R.; Becker, M. R.; Manetta, V. E.; Davis, R. S.; Pauls, H. W.; Mason, H.; Choi-Sledeski, Y. M.; Green, D.; Cha, D.; Spada, A. P.; Cheney, D. L.; Mason, J. S.; Maignan, S.; Guilloteau, J. P.; Brown, K.; Colussi, D.; Bentley, R.; Bostwick, J.; Kasiewski, C. J.; Morgan, S. R.; Leadley, R. J.; Dunwiddie, C. T.; Perrone, M. H.; Chu, V. *J. Med. Chem.* **1999**, *42*, 3557–3571.
30. Falb, E.; Bechor, Y.; Nudelman, A.; Hassner, A.; Albeck, A.; Gottlieb, H. E. *J. Org. Chem.* **1999**, *64*, 498–506.
31. D'Costa, M.; Kumar, V. A.; Ganesh, K. N. *Org. Lett.* **1999**, *1*, 1513–1516.
32. Cao, B.; Xiao, D.; Joullié, M. M. *Org. Lett.* **1999**, *1*, 1799–1801.
33. Wang, G. T.; Chen, Y.; Wang, S.; Gentles, R.; Sowin, T.; Kati, W.; Muchmore, S.; Giranda, V.; Stewart, K.; Sham, H.; Kempf, D.; Laver, W. G. *J. Med. Chem.* **2001**, *44*, 1192–1201.
34. Bell, I. M.; Gallicchio, S. N.; Abrams, M.; Beshore, D. C.; Buser, C. A.; Culberson, J. C.; Davide, J.; Ellis-Hutchings, M.; Fernandes, C.; Gibbs, J. B.; Graham, S. L.; Hartman, G. D.; Heimbrook, D. C.; Homnick, C. F.; Huff, J. R.; Kassahun, K.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Lynch, J. J.; Miller, P. A.; Omer, C. A.; Rodrigues, A. D.; Walsh, E. S.; Williams, T. M. *J. Med. Chem.* **2001**, *44*, 2933–2949.
35. (a) Nagamani, D.; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 103–106. (b) Kumar, V.; Pallan, P. S.; Meena; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 1269–1272. (c) Vilaivan, T.; Suparpprom, C.; Harnyuttanakorn, P.; Lowe, G. *Tetrahedron Lett.* **2001**, *42*, 5533–5536. (d) D'Costa, M.; Kumar, V.; Ganesh, K. N. *Tetrahedron Lett.* **2002**, *43*, 883–886.
36. Al-Kindy, S.; Santa, T.; Fukushima, T.; Homma, H.; Imai, K. *Biomed. Chromatogr.* **1997**, *11*, 137–142.
37. Zhao, S.; Liu, Y.-M. *Anal. Chim. Acta* **2001**, *426*, 65–70.
38. Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266–8275.
39. Wang, X.; Espinosa, J. F.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 4821–4822.
40. Chan, P. W. H.; Cottrell, I. F.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2997–3006.
41. Lee, H. S.; LePlae, P. R.; Porter, E. A.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 3597–3599.
42. Norton Matos, M. R. P.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron Lett.* **2001**, *42*, 7007–7010.
43. Jean, L.; Baglin, I.; Rouden, J.; Maddaluno, J.; Lasne, M.-C. *Tetrahedron Lett.* **2001**, *42*, 5645–5649.
44. Funaki, I.; Thijs, L.; Zwaneburg, B. *Tetrahedron* **1996**, *52*, 9909–9924.
45. Tomori, H.; Shibutani, K.; Ogura, K. *Heterocycles* **1997**, *44*, 213–225.
46. Moon, S. H.; Lee, S. *Synth. Commun.* **1998**, *28*, 3919–3926.
47. Bell, I. M.; Beshore, D. C.; Gallicchio, S. N.; Williams, T. M. *Tetrahedron Lett.* **2000**, *41*, 1141–1145.
48. Miyata, O.; Muroya, J. K.; Naito, T. *Synlett* **1998**, 271–272.
49. Miyabe, H.; Kanehira, S.; Kume, K.; Kandori, H.; Naito, T. *Tetrahedron* **1998**, *54*, 5883–5892.
50. El Kaim, L.; Gacon, A.; Perroux, A. *Tetrahedron Lett.* **1998**, *39*, 371–374.
51. Naito, T.; Fukumoto, D.; Takebayashi, K.; Kiguchi, T. *Heterocycles* **1999**, *51*, 489–492.
52. Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem* **2000**, 903–912.
53. Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043–5047.
54. For other radical cyclization approaches see Refs. 48–51, 53.
55. Other dialkyl-substituted acyclic amines were not tested. A possible source of complications in these reactions is the β-elimination from radicals **7** to yield a sulfonamidyl radical. See, for example: Parsons, A. F.; Pettifer, R. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 651–660. In the particular case of allyl- or benzyl-substituted amines, an additional undesired possibility that should be taken into account, as suggested by a referee, is 1,5-hydrogen transfer after radical cyclization. Some precedent for this behaviour exists in the related reactions leading to the formation of cyclopentylamines.[3]
56. (a) Yadav, V.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 779–789. (b) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman & Hall: London, 1987.
57. Bertrand, M. P.; Deriggi, I.; Lesueur, C.; Gastaldi, S.; Nouguier, R.; Jaime, C.; Virgili, A. *J. Org. Chem.* **1995**, *60*, 6040–6045.
58. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Wienheim, 1996.
59. Hojo, M.; Yoshizawa, J.; Funahashi, Y.; Okada, R.;

Nakamura, S.; Tateiwa, J.; Hosomi, A. *Heterocycles* **1998**, *49*, 85–88.

60. An alternative explanation that cannot be ruled out would involve a *cis*-selective cyclization of radical **7** followed by competing reduction of the cyclized radical *i* (to terminate the reaction) and ring-opening of *i* to give an α-acylamino radical *ii*. This would then be expected to cyclize with *trans*-selectivity.[58]



61. Esch, P. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 4659–4676.
62. Udding, J. H.; Tuijp, C. J. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 1907–1918.
63. Garrohelion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109–6113.
64. Perrin, D. D.; Armarego, W. F. L. *Purification of Laboratory Chemicals*; 3rd ed; Pergamon: Oxford, 1988; p 291.
65. Molander, G. A. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1994; Vol. 46, pp 211–367.
66. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.