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Synthesis of 2,4-, 3,4- and 2,3,4-substituted pyrrolidines by cyclization of neutral C-centered α-aminoalkyl radicals

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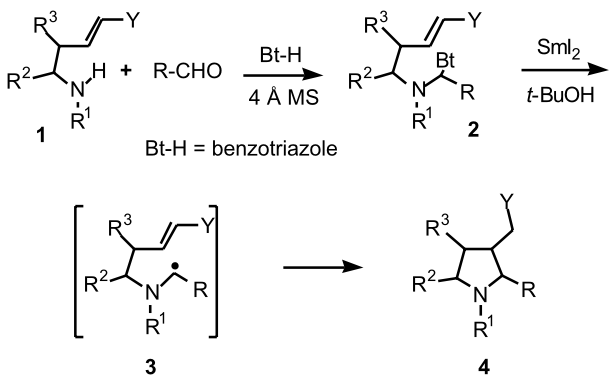
Abstract—The effect of substitution at C-3 or C-4 of the 2-azahex-5-enyl chain has been studied in the SmI_2-promoted cyclizations of neutral α-aminoalkyl radicals generated from *N*-(α-benzotriazolyl)alkenylamines. 2,4-, 3,4- and 2,3,4-substituted pyrrolidines are obtained in this manner in uniformly high yields but with stereoselectivities which depend markedly on the substitution pattern. Thus, a methyl substituent at C-4 (hex-5-enyl numbering) effectively controls the stereochemistry over three contiguous stereogenic centers whereas substituents at C-3 are found to exert a very poor control. Stereochemical results are rationalized according to the existing models for radical ring-closures.

1. Introduction

The pyrrolidine ring system is found in a vast variety of compounds displaying an impressive range of biological activities. Thus, the incorporation of different substitution patterns and motives into the basic heterocyclic structure common to such activities has potential in the discovery of new substances with useful pharmacological properties.[1–5]

Recently, we have reported that a variety of 2,3-disubstituted pyrrolidines **4** (R^2=R^3=H) are available from simple acyclic precursors in a two-step procedure involving condensation of amines **1** with an aldehyde and benzotriazole, followed by SmI_2-promoted reductive cyclization of the so-formed adducts **2** (Scheme 1).[6] This cyclization proceeds through the intermediacy of α-amino radicals[7] **3** generated by reduction of iminium cations formed by in situ dissociation of adducts **2** in solution.[8] It was of interest to extend this methodology to substrates containing substitution at the 3- or 4-positions of the 2-azahex-5-enyl system (R^2, R^3≠H) as this would provide a ready access to pyrrolidines with a wider range of substitution patterns.[9–16] In our previous work it was also noticed that the cyclizations of 1-alkyl-substituted radicals **3** (R=alkyl; R^2=R^3=H; Y=EWG) took place with useful levels of *cis*-selectivity,[6a] in agreement with the Beckwith–Houk model[17] for radical ring-closures. Therefore, the presence of substituents at C-3 or C-4 of **3** would also allow a more complete assessment of the stereochemical impact brought about by the presence of a neutral *N*-alkyl-substituted 2-aza moiety in the cyclizations of substituted hex-5-enyl radicals. This paper describes our results in this area.



Scheme 1.

2. Results and discussion

2.1. Synthesis of 2,4-disubstituted pyrrolidines

Appropriate secondary amine substrates **1a–d** were selected for this study (Schemes 2 and 3). Since we had previously found that electron-deficient alkenes gave best results both in terms of yield and diastereoselectivity of cyclization,[6] amines **1a–d** all contain an electron-withdrawing substituent at the alkene terminus. Amine **1a** was conveniently prepared from *N*-benzylidenebenzylamine (**5**) by addition of a zinc dienolate derived from ethyl 4-bromocrotonate (**6**),[18,19] whereas a similar addition to benzotriazoles **7** provided tertiary allylamines **8b,c** that were easily deallylated[20] to give the desired **1b** and **1c**, as described elsewhere[21] (Scheme 2). Amine **1d**, designed to also exemplify the formation of bicyclic products, was prepared from the

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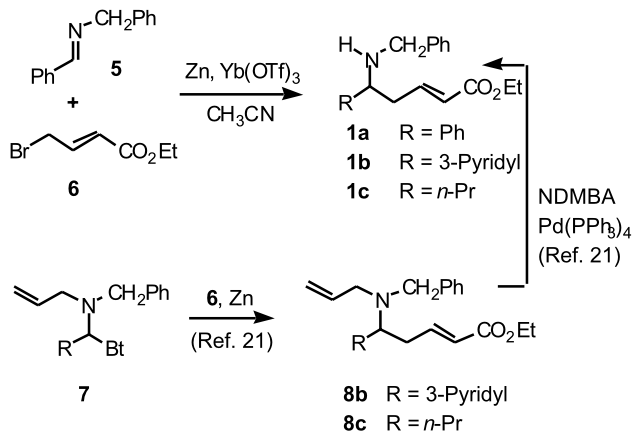
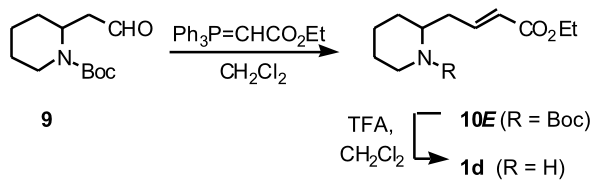


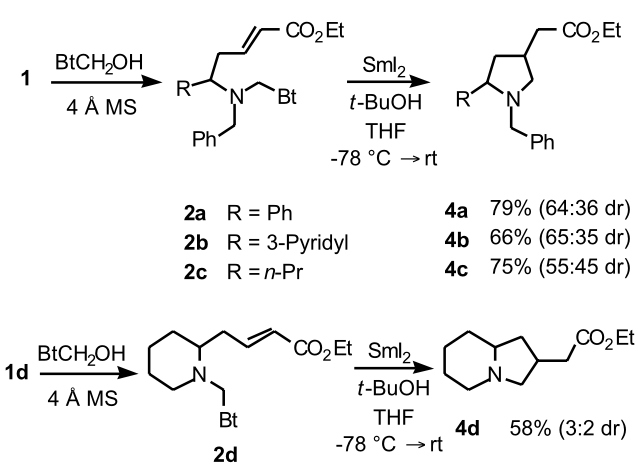
Scheme 2.



Scheme 3.

known aldehyde **9**[22] by Wittig olefination and *N*-deprotection (Scheme 3).

Amines **1a**–**d** were treated with *N*-(hydroxymethyl)benzotriazole (BtCH$_2$OH, the equivalent of formaldehyde and benzotriazole) in the presence of 4 Å molecular sieves to give *N*-(benzotriazolylmethyl)amines **2a**–**d**, that were directly used in the subsequent cyclization reactions in a crude form (Scheme 4). Thus, following our reported procedure,[6a] benzotriazole adducts **2a**–**c** were treated with excess SmI$_2$/*t*-BuOH from −78°C to room temperature to give in all cases high yields (two steps from amines **1a**–**c**) of the expected pyrrolidines **4a**–**c**, that were obtained as diastereomeric mixtures with little selectivity (Scheme 4). The geometrical constraints imposed by the cyclic nature of the substrate **1d** had no effect on the stereochemical outcome of the reaction. Thus, under the same conditions, bicyclic amine **4d** was also obtained with very low

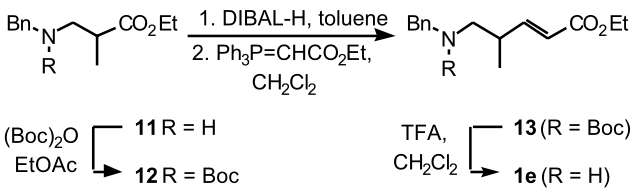


Scheme 4.

stereoselectivity. No attempt was made at the stereochemical elucidation of the individual isomers.

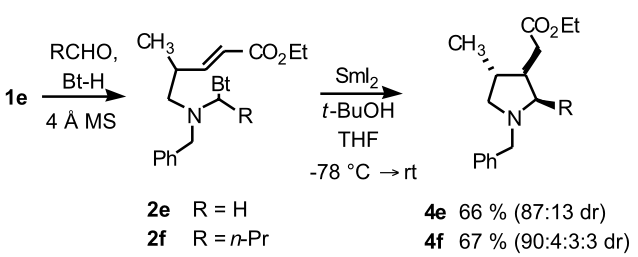
2.2. Synthesis of 3,4- and 2,3,4-substituted pyrrolidines

An appropriate methyl-substituted amine **1e**, bearing an electron-deficient olefin, was prepared from the Michael adduct **11**[23] by DIBAL-H reduction of Boc-protected **12**, followed by Wittig olefination of the resulting aldehyde and *N*-deprotection (Scheme 5).



Scheme 5.

Treatment of the benzotriazole adduct **2e** derived from **1e** and formaldehyde with SmI$_2$ and *t*-BuOH, under the conditions described above, afforded a good yield of the expected 3,4-disubstituted pyrrolidine **4e** (Scheme 6). In contrast to the formation of 2,4-disubstituted pyrrolidines, this time cyclization took place with more useful levels of diastereoselectivity, with the *trans*-isomer being the major one obtained (87:13 dr). This stereochemical assignment was based on the observation of upfield shifts on the carbon resonances of C-3, C-4 and the exocyclic CH$_2$ at C-3,[6,24,25] as well as on the CH$_3$ protons at C-4, for the minor isomer when compared with the major one. Similarly, amine **1e** was condensed with benzotriazole and butyraldehyde to afford an adduct **2f**, which was then treated with SmI$_2$ and *t*-BuOH to give trisubstituted pyrrolidine **4f** in 67% yield with good stereoselectivity. The stereochemistry of the major product was determined with the aid of NOE experiments that showed a ~10% enhancement in the resonances of H-3 upon saturation of H-2, consistent with a 2,3-*cis* relationship. The 3,4-*trans* relationship was established after the observation of small NOE's between H-3 and H-4 (1–3%) and a comparatively greater enhancement (~10%) of the H-3 signal upon saturation of the (C-4)-methyl resonance.



Scheme 6.

2.3. Stereochemistry

The lack of stereoselectivity observed in the formation of 2,4-disubstituted pyrrolidines is in line with that found in cyclizations of related dialkylaminomethyl radicals generated by photoinduced electron transfer (PET).[26,27] Therefore, the introduction of a 2-aza moiety appears to

have an adverse effect on the stereochemical outcome of the otherwise selective 3-alkylhex-5-enyl radical.[17] The aminomethyl radical has been studied in some detail and it is shown to have a delocalized structure with partial double bond character between the N atom and the C atom formally bearing the unpaired electron.[28–30] Calculations[31] performed on a model radical **3** (R=R^3=H, R^1=R^2=CH$_3$, Y=CN) indicate that these structural features are also reflected in the TS for cyclization of the 2-azahex-5-enyl radical. Thus, in the chair- and boat-like transition structures **14a–d** the *N*-methyl substituent occupies a position where it allows some interaction between the unpaired electron and the N lone pair, while the latter is oriented away from the double bond undergoing addition to minimize electron repulsion. The calculated energies are very similar for *cis* and *trans* TS's, in agreement with the observed low isomer ratios.[32a] A gauche-type interaction between the methyl group at C-3 (hex-5-enyl radical numbering) and the *N*-methyl substituent in *cis*-chair **14a** and *trans*-boat **14d**, absent in *cis*-boat **14b** and *trans*-chair **14c**, could be responsible for the lack of a well defined stereopreference in these reactions.

In contrast, similar calculations performed on model radical **3** (R=R^2=H, R^1=R^3=CH$_3$, Y=CN) predict a much better stereoselectivity in the formation of 3,4-substituted pyrrolidines (Fig. 1), as confirmed experimentally.[32b] In both calculations and experiment, the extent and sense of stereoselectivity are in agreement with expectations based on the Beckwith–Houk model,[17] that predicts a preferred *trans*-4,5 relationship (hex-5-enyl radical numbering) through a chair-like transition structure **15c**. Also, the observed diastereomeric ratios are in the range found for the parent 4-methylhex-5-enyl radical.[17d] Therefore, in this radical the introduction of a 2-aza unit appears to have no major consequences on the stereochemistry of cyclization. It is remarkable that upon introduction of an alkyl substituent at C-1 of the 2-aza-4-methylhex-5-enyl chain the cyclization maintained the same high level of stereoselectivity. Thus, in the formation of **4f**, out of four possible isomers one amounts to 90% of the diastereomeric mixture. Interestingly, under the same reaction conditions, the related *cis*-2,3-dialkyl pyrrolidines are formed in diastereomeric ratios in the range 86:14–91:9.[6a] Therefore, the stereochemical effects of the 4-Me and 1-alkyl substitutions (hex-5-enyl radical numbering) appear to reinforce each other, making this reaction a convenient stereoselective entry into 2,3,4-trisubstituted pyrrolidines.

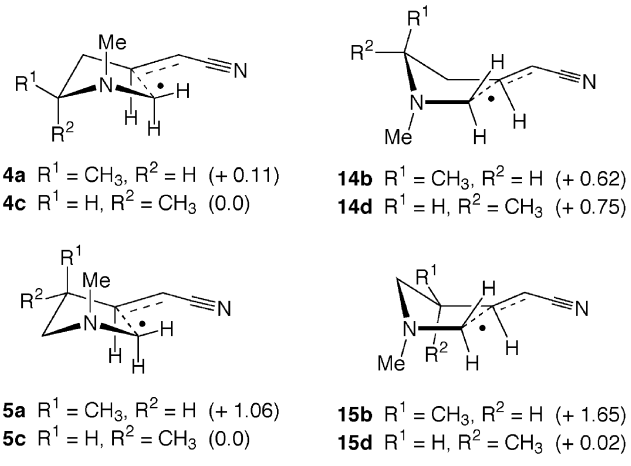


Figure 1. Relative PM3-UHF transition structure energies (kcal/mol) for cyclizations of model radicals **3** (R=H, R^1=Me, Y=CN, R^2 or R^3=Me).

3. Conclusions

The reduction of *N*-(α-benzotriazolyl)alkenylamines provides a useful entry into 2,4-, 3,4- and 2,3,4-substituted pyrrolidines through the intermediacy of 2-azahex-5-enyl radicals. A substituent at C-4 of the 2-azahex-5-enyl chain effectively controls the stereochemistry of cyclization making this a potentially useful method for formation of 2,3,4-trisubstituted pyrrolidines. In contrast, substituents at C-3 afford very poor stereoinduction.

4. Experimental

4.1. General methods

All reactions involving air- and moisture sensitive materials were performed under an atmosphere of dry Ar. Tetrahydrofuran (THF) and toluene were freshly distilled from sodium/benzophenone and, for reactions with SmI_2, THF was deoxygenated prior to use. Acetonitrile and dichloromethane were freshly distilled from CaH_2. SmI_2 (ca. 0.1 M in THF) was prepared from Sm and diiodomethane using a literature procedure.[33] Flash chromatography[34] was performed on silica gel (230–400 mesh). Routine ^{1}H 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 ^{1}H and δ 77.0 for ^{13}C). IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV. GC-MS analysis were performed at 70–280°C (20°C/min) with a stationary phase of methylphenylsilicone (0.25 μm, 30 m×0.25 mm).

4.2. Synthesis of 2,4-disubstituted pyrrolidines

4.2.1. Ethyl (*E*)-6-aza-5,7-diphenylhept-2-enoate (1a). Ethyl (*E*)-4-bromobut-2-enoate (3.85 mL, 28.0 mmol) was added dropwise to a stirred mixture of *N*-benzylidenebenzylamine (2.68 g, 13.8 mmol), Zn (3.66 g, 56.0 mmol), $Yb(OTf)_3$ (1.71 g, 2.76 mmol) and Me_3SiCl (1.78 mL, 14.0 mmol) in acetonitrile (80 mL) at 0°C. The mixture was allowed to warm to room temperature, stirred for 12 h and poured into 32% aq. ammonia (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×200 mL). The combined organic extracts were dried (Na_2SO_4) and filtered over Celite. The crude after evaporation was purified by flash chromatography (85:15 hexanes/EtOAc) to yield **1a** (1.57 g, 37%) as an orange-tinted oil: ^{1}H NMR δ 1.27 (t, *J*=7.1 Hz, 3H, CH_3), 1.66 (br s, 1H, NH), 2.53–2.60 (m, 2H, H-4), 3.54 and 3.67 (AB system, *J*=13.2 Hz, 2H, PhCH_2), 3.79 (t, *J*=6.8 Hz, 1H, H-5), 4.16 (q, *J*=7.1 Hz, 2H, OCH_2), 5.82 (dt, *J*=15.7, 1.4 Hz, 1H, H-2), 6.87 (dt, *J*=15.7, 7.4 Hz, 1H, H-3), 7.21–7.40 (m, 10H, Ar); ^{13}C NMR δ 14.2, 41.1, 51.2, 60.1, 61.1 (C-5), 123.5 (C-2), 126.9, 127.0, 127.3, 128.0, 128.3, 128.5, 140.2, 142.8, 145.4 (C-3), 166.2 (C=O); IR (neat) ν 3320 (N–H), 1720 (C=O), 1650 (C=C) cm^{-1}; LRMS (EI) *m/z*

197 (17), 196 (base), 194 (2), 129 (2), 92 (5), 91 (59); HRMS calcd for $C_{20}H_{23}NO_2$ 309.1729, found 309.1716.

4.2.2. 1-Benzyl-4-(ethoxycarbonylmethyl)-2-phenylpyrrolidine (4a). Representative procedure for formation of adducts 2 and SmI_2-promoted cyclization. A mixture of **1a** (1.17 g, 3.79 mmol), *N*-(hydroxymethyl)benzotriazole (576 mg, 3.79 mmol) and molecular sieves (4 Å, 1.90 g) in benzene (6 mL) was stirred at rt for 12 h. The resulting mixture was filtered over Celite and evaporated to dryness to yield the crude adduct **2a** (1.73 g). The resulting residue and *t*-BuOH (0.72 mL, 7.6 mmol) were dissolved in THF (91 mL) and added dropwise to a solution of SmI_2 (ca. 0.1 M in THF, 114 mL, 11.4 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 2 h the reaction mixture was quenched with a mixture of sat. K_2CO_3 (100 mL) and water (100 mL). After separation, the aqueous layer was extracted with EtOAc (3×200 mL), the combined organic extracts were washed with a mixture of water (100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated to give a crude product that was purified by flash chromatography (silica gel saturated with Et_3N, 99:1 hexanes/Et_3N) to yield **4a** (968 mg, 79%, 64:36 dr) as an oil. Data for the diastereomeric mixture: ^{1}H NMR δ 1.22 and 1.23 (2t, J=7.1 Hz, 3H), 1.39–1.50 and 1.85–2.10 (2m, 2H), 2.37–2.77 (m, 4H), 2.84 (dd, J=9.3, 2.3 Hz) and 3.31 (dd, J=9.1, 7.0 Hz) (total 1H), 3.05 (d, J=13.4 Hz, 1H, PhC*H*), 3.44–3.52 (m, 1H), 3.85 (d, J=13.5 Hz, 1H, PhC*H*), 4.09 and 4.10 (2q, J=7.1 Hz, 2H, OCH_2), 7.19–7.51 (m, 10H, Ar); ^{13}C NMR δ 14.1, 32.2 (C-4), 32.4 (C-4), 39.5, 41.0, 41.3, 42.3, 57.5, 57.8, 58.3, 59.6, 60.1, 60.2, 68.4 (C-2), 69.6 (C-2), 126.6, 126.7, 127.0, 128.4, 128.4, 128.5, 139.2, 139.5, 143.1, 143.5, 172.5 (C=O), 172.9 (C=O); IR (neat) ν 1735 (C=O) cm^{-1}; LRMS (EI) *m/z* 323 (M, 39), 322 (28), 278 (23), 246 (85), 232 (83), 118 (20), 91 (base); HRMS calcd for $C_{21}H_{25}NO_2$ 323.1885, found 323.1879.

4.2.3. 1-Benzyl-4-(ethoxycarbonylmethyl)-2-(pyridin-3-yl)pyrrolidine (4b). Prepared from **1b**[21] using the procedure described above for **4a**. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 90:8:2 hexanes/EtOAc/Et_3N) to yield **4b** (66%, 65:35 dr). Data for the diastereomeric mixture: ^{1}H NMR δ 1.17–1.25 (m, 3H, CH_2CH_3), 1.37–1.48 (m, 1H, isomer A), 1.97–2.01 (m, 1H), 2.36–2.86 (m, 5H), 3.10 (d, J=13.2 Hz, 1H, PhC*H*), 3.27–3.33 (m, 1H, isomer B), 3.48–3.53 (m, 1H), 3.77 (d, J=13.2 Hz, 1H, PhC*H*), 4.08 (m, 2H, CH_3CH_2), 7.26 (br s, $W_{1/2}$=16.7 Hz, 6H), 7.81 (d, J=7.7 Hz, 1H, H-4′), 8.49 (br s, $W_{1/2}$=8.3 Hz, 1H, H-2′), 8.64 (br s, $W_{1/2}$=8.3 Hz, 1H, H-6′); ^{13}C NMR δ 14.1, 32.3, 32.6, 39.1, 40.8, 41.2, 42.2, 57.5, 57.8, 58.3, 59.6, 60.2, 65.8, 67.0, 123.6, 126.8, 126.8, 128.1, 128.2, 128.4, 134.8, 134.9, 138.4, 138.7, 138.9, 139.0, 148.6, 148.7, 149.5, 172.3 (C=O), 172.6 (C=O); IR (neat) ν 1740 (C=O), 1580 cm^{-1}; LRMS (EI) *m/z* 324 (M, 26), 323 (16), 279 (24), 246 (67), 236 (21), 233 (base), 219 (10), 119 (20), 91 (50); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1835.

4.2.4. 1-Benzyl-4-(ethoxycarbonylmethyl)-2-propylpyrrolidine (4c). Prepared from **1c**[21] using the procedure described above for **4a**. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 99:1 hexanes/Et_3N) to yield **4c** (75%, 55:45 dr). Data for the diastereomeric mixture: ^{1}H NMR δ 0.93 (t, J=6.9 Hz, 3H), 1.12–1.85 (m, 9H), 2.14–2.52 (m, 5H), 2.59–2.63 and 3.03–3.16 (2m, 2H), 4.00–4.13 (m, 3H), 7.19–7.31 (m, 5H); ^{13}C NMR δ 14.1, 14.4, 19.2, 19.3, 31.7 (C-4), 32.1 (C-4), 36.1, 36.4, 36.8, 37.5, 39.2, 40.7, 57.7, 58.4, 59.0, 59.9, 60.0, 60.2, 63.3 (C-2), 64.2 (C-2), 126.5, 126.6, 127.9, 128.0, 128.4, 128.7, 139.3, 139.7, 172.5 (C=O), 172.9 (C=O); IR (neat) ν 1740 (C=O) cm^{-1}; LRMS (EI) *m/z* 289 (M, 22), 288 (base), 258 (2), 246 (4), 162 (7), 91 (29); HRMS calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.1989.

4.2.5. Ethyl (*Z*)-4-[*N*-(*tert*-butoxycarbonyl)piperidin-2-yl]prop-2-enoate (10*Z*) and ethyl (*E*)-4-[*N*-(*tert*-butoxycarbonyl)piperidin-2-yl]prop-2-enoate (10*E*). To a solution of **9**[22] (6.81 g, 30.0 mmol) in CH_2Cl_2 (120 mL) at 0°C was added (ethoxycarbonylmethylene)triphenylphosphorane (12.1 g, 33.0 mmol). The mixture was allowed to warm to rt and further stirred for 3.5 h. The solvent was removed in vacuo and the crude product was purified by flash chromatography (86:14 hexanes/EtOAc) to yield in order of elution **10*Z*** (0.519 g, 6%) and **10*E*** (7.68 g, 86%) as oils. Data for **10*Z***: ^{1}H NMR δ 1.23 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.27–1.64 (m, 15H), 1.38 (s, *t*-Bu, included in m at 1.27–1.64), 2.71–2.84 (m, 2H), 3.04–3.18 (m, 1H), 3.87–3.92 (br s, 1H), 4.11 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.28–4.42 (br s, 1H), 5.75 (dt, J=11.5, 1.6 Hz, 1H, H-3′), 6.16 (dt, J=11.5, 7.5 Hz, 1H, H-2′); ^{13}C NMR δ 14.1, 18.9, 25.4, 28.3, 28.5, 29.4, 38.8 (br, C-6), 49.9 (br, C-2), 59.7, 79.1, 120.8 (C-3′), 147.0 (C-2′), 154.9 (NCO), 166.3 (C=O); IR (neat) ν 1725 (C=O), 1695 (C=O), 1.650 (C=C) cm^{-1}; LRMS (EI) *m/z* 224 (29), 198 (13), 184 (75), 152 (40), 129 (39), 128 (base), 114 (16), 84 (18); HRMS calcd for $C_{16}H_{27}NO_4$ 297.1940, found 297.1926. Data for **10*E***: ^{1}H NMR δ 1.25 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.32–1.67 (m, 15H), 1.42 (s, *t*-Bu, included in m at 1.32–1.67), 2.24–2.35 (m, 1H), 2.51–2.78 (m, 2H), 3.96–4.01 (m, 1H), 4.15 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.36 (br s $W_{1/2}$=18.6 Hz, 1H), 5.81 (dt, J=15.5, 1.4 Hz, 1H, H-3′), 6.86 (dt, J=15.5, 7.7 Hz, 1H, H-2′); ^{13}C NMR δ 14.2, 18.8, 25.3, 28.3, 33.0, 38.7 (br, C-6), 49.5 (br, C-2), 60.2, 79.4, 123.1 (C-3′), 145.6 (C-2′), 154.8 (NCO), 166.2 (C=O); IR (neat) ν 1725 (C=O), 1690 (C=O), 1655 (C=C) cm^{-1}; LRMS (EI) *m/z* 224 (26), 198 (11), 184 (43), 152 (28), 129 (30), 128 (86), 114 (21), 84 (base); HRMS calcd for $C_{16}H_{27}NO_4$, 297.1940, found 297.1929.

4.2.6. Ethyl (*E*)-4-(piperidin-2-yl)prop-2-enoate (1d). Trifluoroacetic acid (2.60 mL) was added dropwise to a solution of **10*E*** (594 mg, 2.00 mmol) in CH_2Cl_2 (14.8 mL) at 0°C. The mixture was then stirred at rt for 3 h and evaporated. The residue was dissolved in EtOAc (40 mL), washed with sat. K_2CO_3 (40 mL), dried (Na_2SO_4) and evaporated to dryness, to yield **1d** (382 mg, 97%): ^{1}H NMR δ 1.07–1.48 (m, 6H), 1.26 (t, 7.1H, CH_2CH_3, included in m at 1.07–1.48), 1.56–1.79 (m, 3H), 2.04 (br s, $W_{1/2}$=19.8 Hz, 1H, NH), 2.14–2.34 (m, 2H), 2.55–2.66 (m, 2H), 3.01–3.07 (m, 1H), 4.16 (q, J=7.4 Hz, 2H, CO_2CH_2), 5.86 (dt, J=15.7, 1.4 Hz, 1H, H-3′), 6.83–6.95 (m, 1H, H-2′); ^{13}C NMR δ 14.2, 24.6, 26.0, 32.7, 40.1, 47.0, 55.6 (C-2), 60.3, 123.6 (C-3′), 145.8 (C-2′), 166.4 (C-4′); IR (neat) ν 3400 (N–H), 1720 (C=O), 1655 (C=C) cm^{-1};

LRMS (EI) *m/z* 235 (base), 197 (M, 3), 184 (22), 84 (20); HRMS calcd for $C_{11}H_{19}NO_2$ 197.1416, found 197.1406.

4.2.7. 2-(Ethoxycarbonylmethyl)indolizidine (4d). Prepared from **1d** using the procedure described above for **4a.** The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 92:6:2 hexanes/EtOAc/Et_3N) to yield the two diastereoisomers of **4d** (330 mg and 164 mg, total yield 58%). Data for the less polar isomer: ^{1}H NMR δ 1.00–1.26 (m) and 1.23 (t, J=7.1 Hz, CH_2CH_3) (total 6H), 1.48–1.64 (m, 2H), 1.74–1.85 (m, 3H), 1.92 (td, J=10.9, 4.1 Hz, 1H), 2.02–2.12 (m, 1H), 2.30–2.50 (m, 4H), 2.76 (d, J=8.1 Hz, 1H), 3.00 (dt, J=10.8, 3.1 Hz, 1H), 4.10 (q, J=7.1 Hz, 2H, CH_3CH_2); ^{13}C NMR δ 14.2, 24.2, 25.3, 30.8, 31.0 (C-2), 38.4, 41.2, 52.9, 59.8, 60.0, 64.6 (C-8a), 173.0 (C=O); IR (neat) ν 1740 (C=O) cm^{-1}; LRMS (EI) *m/z* 211 (M, 22), 210 (base), 209 (19), 182 (23), 180 (6), 166 (14), 137 (11), 136 (54), 124 (18); HRMS calcd for $C_{12}H_{21}NO_2$ 211.1572, found 211.1567. Data for the more polar isomer: ^{1}H NMR δ 1.03–1.18 (m, 1H), 1.12 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.35–1.74 (m, 9H), 1.82 (td, J=11.1, 3.5 Hz, 1H), 2.14–2.30 (m, 2H), 2.38–2.56 (m, 1H), 2.89–2.95 (m, 1H), 3.16 (dd, J=9.1, 7.5 Hz, 1H), 3.99 (q, J=7.1 Hz, 2H, CH_3CH_2); ^{13}C NMR δ 14.0, 24.2, 25.1, 30.7, 30.8, 37.0 (C-2), 39.8, 52.7, 60.0, 61.0, 63.0 (C-8a), 172.4 (C=O); IR (neat) ν 1740 (C=O) cm^{-1}; LRMS (EI) *m/z* 211 (M, 39), 210 (base), 209 (17), 182 (61), 180 (25), 166 (27), 138 (27), 136 (28), 124 (50); HRMS calcd for $C_{12}H_{21}NO_2$ 211.1572, found 211.1564.

4.3. Synthesis of 3,4- and 2,3,4-substituted pyrrolidines

4.3.1. Ethyl 4-aza-4-(*tert*-butoxycarbonyl)-5-phenyl-2-methylpentanoate (12). To a solution of benzylamine (1.23 mL, 11.2 mmol) in ethanol (9 mL) was added ethyl methacrylate (7.00 mL, 56.0 mmol) and H_2O (4.00 mL, 224 mmol), and the mixture was stirred for 4 days at rt. The solvent was removed in vacuo and the residue (**11**[23]) was dissolved in EtOAc (5 mL). To this solution at 0°C was added dropwise di*tert*-butyl dicarbonate (2.20 mL, 9.40 mmol) and the mixture was stirred at rt for 16 h. The solution was washed with HCl (1 M, 15 mL), sat. $NaHCO_3$ (15 mL) and brine (15 mL), and dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, 96:4 hexanes/Et_3N) to yield **12** (2.41 g, 80%, rotamer mixture) as an oil: ^{1}H NMR δ 1.11 (d, J=5.6 Hz, 3H, C_2-CH_3), 1.25 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.42 and 1.50 (2s, 9H, *t*-Bu), 2.81–2.91 (m, 1H, H-2), 3.24–3.37 (m, 2H), 4.05–4.15 (m, 2H, OCH_2CH_3), 4.32 (d, J=15.5 Hz, 1H, H-5), 4.51 and 4.62 (2d, J=15.5 Hz, 1H, H-5), 7.21–7.35 (m, 5H, ArH); ^{13}C NMR δ 14.1, 15.0, 28.3, 38.8 (C-2), 39.0 (C-2), 49.4, 49.9, 50.4, 51.5, 60.4, 79.9, 127.0, 127.6, 128.4, 138.0, 138.3, 155.6 (NCO), 155.8 (NCO), 175.2 (CO_2Et), 175.4 (CO_2Et); IR (neat) ν 1740 (C=O), 1700 (C=O) cm^{-1}; LRMS (EI) *m/z* 321 (M, 2), 265 (42), 221 (13), 220 (64), 164 (15), 120 (81), 106 (57), 91 (base); HRMS calcd for $C_{18}H_{27}NO_4$ 321.1940, found 321.1930.

4.3.2. Ethyl 6-aza-6-(*tert*-butoxycarbonyl)-7-phenyl-4-methylhept-2-enoate (13). To a solution of **12** (2.40 g, 7.50 mmol) in toluene (21 mL) at −78°C was added dropwise DIBALH (1.0 M, 9.75 mL, 9.75 mmol). After 15 min a mixture of ethanol–water (1:1, 0.96 mL) was added, followed by solid $Na_2SO_4{\cdot}10H_2O$ (0.63 g). The mixture was allowed to warm to rt, stirred for 3.5 h, filtered over Celite and evaporated. The residue was dissolved in CH_2Cl_2 (31 mL) and (ethoxycarbonylmethylene)triphenylphosphorane (3.20 g, 9.30 mmol) was added. The mixture was stirred at rt for 12 h and evaporated. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 98:2 hexanes/Et_3N) to yield **13** (1.31 g, 64% for two steps from **12**) as an oil: ^{1}H NMR δ 0.95–1.01 (m, 3H, C_4-CH_3), 1.25 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.40 and 1.47 (2s, 9H, *t*-Bu), 2.57–2.70 (m, 1H, H-4), 3.01 (dd, J=14.6, 5.8 Hz) and 3.17–3.26 (m) (total 2H), 4.38–4.44 (m, 2H, OCH_2CH_3), 5.69–5.79 (m, 1H, H-2), 6.76–6.89 (m, 1H, H-3), 7.18–7.32 (m, 5H, Ar-*H*); ^{13}C NMR δ 13.6, 16.4, 27.6, 35.3 (C-4), 35.6 (C-4), 49.5, 50.5, 50.8, 59.3, 79.0, 120.4 (C-2), 126.5, 127.0, 127.8, 137.5, 137.6, 150.7 (C-3), 154.9 (NCO), 165.4 (CO_2Et).

4.3.3. Ethyl 6-aza-7-phenyl-4-methylhept-2-enoate (1e). The procedure described above for **1d** was followed starting from **13** to yield **1e** (100%): ^{1}H NMR δ 1.07 (d, J=6.3 Hz, 3H, C_4-CH_3), 1.28 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.32–1.54 (m, 1H, NH), 2.49–2.63 (m, 3H), 3.77 (s, 2H, H-7), 4.18 (q, J=7.1 Hz, 2H, OCH_2CH_3), 5.85 (dd, J=15.6, 1.0 Hz, 1H, H-2), 6.87 (dd, J=15.6, 7.3 Hz, 1H, H-3), 7.21–7.34 (m, 5H, H-Ar); ^{13}C NMR δ 14.2, 17.4, 36.9 (C-4), 53.8, 54.2, 60.2, 121.0 (C-2), 126.9, 140.0, 152.4 (C-3), 166.6 (CO_2Et); LRMS (EI) *m/z* 121 (8), 120 (90), 106 (6), 92 (8), 91 (base), 65 (5); HRMS calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1578.

4.3.4. *N*-Benzyl-3-(ethoxycarbonylmethyl)-4-methylpyrrolidine (4e). The procedure described above for **4a** was followed starting from **1e**. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, 99:1 hexanes/Et_3N) to yield **4e** (78 mg, 66%, 87:13 *trans*/*cis*) as an oil: ^{1}H NMR δ 0.90 (d, J=7.1 Hz, C_4-CH_3, *cis* isomer) and 1.03 (d, J=6.7 Hz, C_4-CH_3, *trans* isomer) (total 3H), 1.24 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.85 (quint, J=6.9 Hz, *trans* isomer), 1.93–2.19 (m, 2H), 2.23–2.51 (m, 3H), 2.61–2.70 (m, *cis* isomer), 2.73–2.84 (m, *trans* isomer) and 2.94–3.04 (m, *cis* isomer) (total 2H), 3.54 and 3.62 (2d, J=13.1 Hz, 2H, $PhCH_2$), 4.10 (q, J=7.1 Hz, 2H, OCH_2CH_3), 7.19–7.31 (m, 5H, Ar); ^{13}C NMR δ 14.1, 14.7, 18.9, 33.7 (C-3 or C-4, *cis* isomer), 34.6 (C_3-CH_2, *cis* isomer), 36.5 (C-3 or C-4, *cis* isomer), 38.6 (C-3 or C-4, *trans* isomer), 39.1 (C_3-CH_2, *trans* isomer), 42.1 (C-3 or C-4, *trans* isomer), 59.5, 59.8, 60.0, 60.3, 60.5, 61.7, 126.6, 128.0, 128.5, 139.1, 172.8 (C=O); IR (neat) ν 1740 (C=O) cm^{-1}; LRMS (EI) *m/z* 261 (M, 26), 260 (33), 232 (12), 230 (6), 216 (25), 186 (13), 184 (18), 173 (24), 170 (63), 105 (base); HRMS calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1718.

4.3.5. *N*-Benzyl-3-(ethoxycarbonylmethyl)-4-methyl-2-propylpyrrolidine (4f). A mixture of **1e** (114 mg, 0.50 mmol), benzotriazole (60 mg, 0.51 mmol), butyraldehyde (0.04 mL, 0.50 mmol) and molecular sieves (4 Å, 240 mg) in benzene (1.0 mL) was stirred at rt for 18 h. The resulting mixture was filtered over Celite and evaporated to yield **2f** (123 mg). This crude adduct and *t*-BuOH (0.10 mL, 1.0 mmol) were dissolved in THF (12 mL) and added

dropwise to a solution of SmI_2 (ca. 0.1 M in THF, 15 mL, 1.5 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 2 h the reaction mixture was quenched with a mixture of sat. K_2CO_3 (25 mL) and water (25 mL). After separation, the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with a mixture of water (25 mL) and brine (25 mL), dried (Na_2SO_4) and evaporated to give a crude product that was purified by flash chromatography (silica gel saturated with Et_3N, 99:1 hexanes/Et_3N) to yield **4f** (102 mg, 67%), as an oil (a 90:4:3:3 diastereomeric mixture, as determined by ^{13}C NMR). Data for the major isomer: ^1H NMR δ 0.94 (apparent t, J=6.4 Hz, 6H), 1.27 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.33–1.52 (m, 4H), 1.71–1.86 (m, 2H, H-4 and H-5), 2.05–2.16 (m, 1H, H-3), 2.39 (d, J=7.7 Hz, 2H, C_3–CH_2), 2.61–2.69 (m, 1H, H-2), 3.00–3.06 (m, 1H, H-5), 3.19 (d, J=12.9 Hz, 1H, PhC*H*), 4.02 (d, J=12.9 Hz, 1H, PhC*H*), 4.14 (q, J=7.1 Hz, 2H, OCH_2CH_3), 7.20–7.31 (m, 5H, Ar); ^{13}C NMR δ 14.2, 14.6, 18.8, 19.7, 32.4, 34.6, 36.4, 44.6, 59.6, 60.2, 61.8, 65.1 (C-2), 126.6, 128.1, 128.6, 128.7, 140.0, 173.7 (C=O); IR (neat) ν 1740 (C=O) cm^{-1}; GC-MS: t_R=12.8 min, LRMS (EI) *m*/z 260 (M−Pr, 24), 91 (base); t_R=13.1 min, LRMS (EI) *m*/*z* 260 (M−Pr, base), 91 (83), t_R=13.4 min, LRMS (EI) *m*/*z* 260 (M−Pr, 61), 91 (base).

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