A new entry into 3-hydroxypyrrolidine derivatives from protected α- or β-amino esters

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Abstract
Starting from protected glycine or β-aminopropanoic esters, acyclic 4-alkoxy- or 4-silyloxy-5-aminopent-2-enoate derivatives are conveniently prepared and subjected to condensation with aldehydes, followed by samarium diiodide reduction, to afford substituted pyrrolidine derivatives in good yields and variable stereoselectivity, which was dependent on the type (alkoxy or silyloxy) of substituted-hydroxyl group.

Keywords: Cyclization, 3-hydroxypyrrolidine, radical, amino acid

Introduction

Pyrrolidine derivatives **6** (Scheme 1) are interesting compounds because their 3-hydroxypyrrolidine and γ-hydroxy-γ-aminoacid substructures are found in a number of biologically active products.[1] We have recently described the preparation of compounds **4** from vinylogous Mannich adducts **1** and aldehydes **2** (Scheme 1).[2] Because of the intermediacy of a [3.3.0] bicycle **3**, products **4** were necessarily obtained with a 3,4-*cis*-relationship. The alternative possibility of using previously untested analogous reactions of amines **5** was considered interesting, as it could provide an entry into the corresponding hydroxypyrrolidines **6**, or derivatives thereof, with a 3,4-*trans*-stereochemistry. Radicals may be expected as intermediates[2-4] in the cyclization event leading to **6**, and 3,4-*trans*-relationship is actually predicted by the commonly accepted Beckwith-Houk model[5], which has been successful in a number of cyclizations of densely oxygenated hex-5-enyl radicals.[6] In this paper we report the efficient formation of products **6** prepared, according to Scheme 1, from amines **5** and aldehydes **2**. Products **6** are obtained with variable diastereoselectivity, which is found to be dependent on the hydroxyl protecting group (R^1).
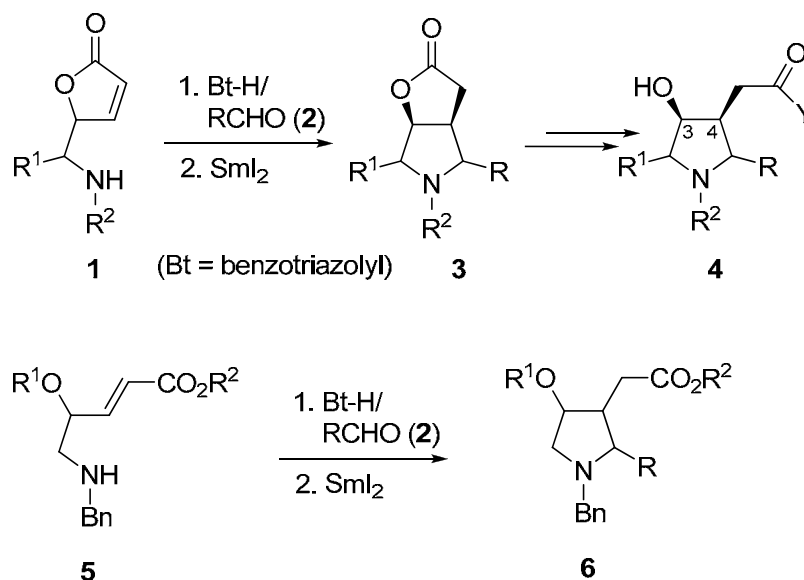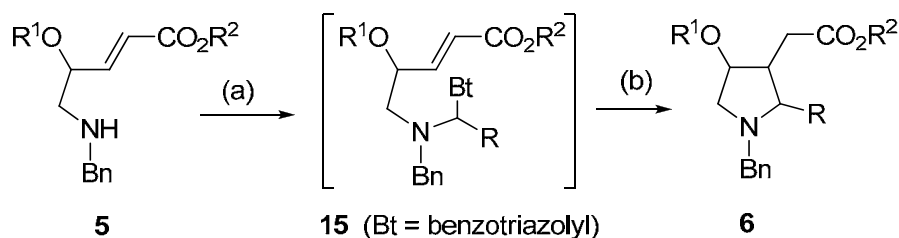
Scheme 1

Results and Discussion

Amines **5a,b** were targeted as suitable model substrates containing representative silyl protecting groups, whereas methoxy derivative **5c** would be a convenient model for the alternative alkyl ether-type protection (Scheme 2). Two routes were devised for the preparation of amines **5** depending on the type of hydroxyl protecting group. Thus, the preparation of silyl-protected derivatives **5a,b** took advantage of the ready availability of aldehyde **7**[7] to perform a piperidine-promoted condensation/[2,3] rearrangement[8] with α -sulfinyl acetate derivative **8** to afford the γ-hydroxy- α ,β -unsaturated ester **9** directly. After hydrolytic removal of the Boc protecting group, the resulting hydroxyamine **10** was silylated with excess TBDMSCl- or TBDPSCl/imidazole to yield after aqueous work-up the desired silyl ethers **5a** and **5b**, respectively. Alternatively, for the preparation of **5c**, protected glycine ester **11**[9] was elaborated into methyl vinyl ether **13** using standard protocols. The double bond was then homologated using an ozonolysis/Wittig sequence, and finally the Boc protecting group was removed under acidic conditions to yield amine **5c**.
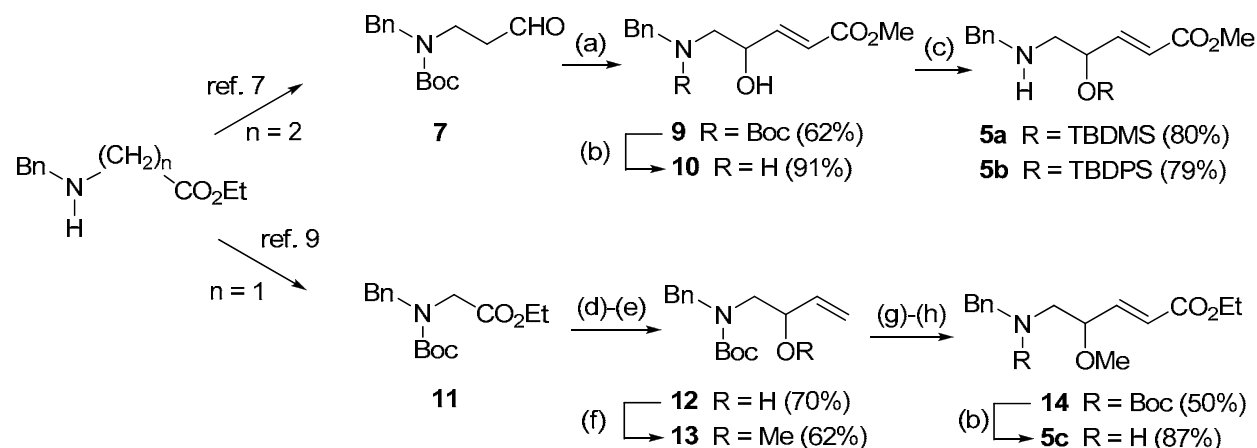
Scheme 2. Reagents and conditions: (a) PhS(O)CH$_2$CO$_2$Me (**8**), piperidine, MeCN, rt. (b) TFA, CH$_2$Cl$_2$, 0 °C → rt. (c) TBDMSCl (**5a**) or TBDPSCl (**5b**), imidazole, DMF, rt. (d) DIBAL-H, CH$_2$Cl$_2$, -78 → -20 °C. (e) vinylmagnesium chloride, THF, -20 → -78 °C. (f) NaH, MeI, 0 °C → rt. (g) (*i*) O$_3$, CH$_2$Cl$_2$, -78 °C; (*ii*) Me$_2$S, rt. (h) Ph$_3$P=CHCO$_2$Et, 0 °C → rt.

Amines **5** were then condensed with hydroxymethylbenzotriazole (BtCH$_2$OH, a surrogate for benzotriazole and formaldehyde) or, alternatively, benzotriazole (Bt-H) and *n*-hexanal, and the resulting adducts of type **15** were treated directly, without purification, with SmI$_2$ to generate the expected pyrrolidines **6**, as mixtures of the corresponding *cis* and *trans* isomers, in good yields for two steps starting from amines **5** (Scheme 3, Table 1). Stereochemical assignments for pyrrolidines **6** were readily made on the basis of the upfield shifts observed in the methine C$_3$ and C$_4$ carbons of the *cis*-isomers relative to the corresponding carbons in the *trans*-isomers, due to the occurrence of eclipsing interactions in the former.[10] Also supportive of the assignments were the downfield shifts observed in the pyrrolidine proton resonances for C*H*OR^1 of the *cis*-isomers when compared to the same resonance in the *trans*-products.[10b,10c]

Scheme 3. Reagents and conditions: (a) BtCH$_2$OH or Bt-H and RCHO, 4 Å MS, benzene (**5a,b**) or THF (**5c**), rt. (b) SmI$_2$, *t*-BuOH, THF, -78 °C → rt.

As seen in Table 1, the choice of alcohol protecting group had an effect on the diastereoselectivity of cyclization. Thus, methoxy derivative **5c** gave a 72:28 *trans/cis* ratio of

pyrrolidines **6d** whereas the corresponding reactions starting from the silyl TBDMSO- and TBDPSO-derivatives **5a** and **5b** proceeded with almost no selectivity (~ 1:1 *trans/cis* for R = H).[11] When compared with the related cyclizations of the rigid lactones **1**, these new reactions from acyclic derivatives **5** are found to proceed with diminished stereoselectivity. Nevertheless, from a practical perspective, it is noticed that the acyclic MeO-substituted substrate **5c** provided a preparatively useful overall isolated yield (~ 60%) of pyrrolidine *trans*-**6c**, whereas going through the related α,β-unsaturated lactones **1** had been shown to result in the exclusive formation of the corresponding *cis*-isomers.[2]

Table 1. Preparation of Pyrrolidines **6** from Amines **5**

Entry	Amine[a]	R[1]	R	Product	Yield (%)	Isomer ratio[b]
1	**5a**	TBDMS	H	**6a**	88	45:55
2	**5b**	TBDMS	*n*-Pent	**6b**	60	[c]
3	**5b**	TBDPS	H	**6c**	73	50:50
4	**5c**	Me	H	**6d**	82	28:72

[a] R^2 = Me (**5a-b**) or R^2 = Et (**5c**). [b] 3,4-*Cis/trans* ratio. [c] Mixture of four diastereoisomers in undetermined ratio.

In summary, the simple synthetic manipulation of readily available protected glycine and β-aminopropanoic esters affords intermediate acyclic 4-alkoxy- and 4-silyloxy-5-aminopent-2-enoate esters which are effective precursors of 3-hydroxypyrrolidine derivatives through sequential aldehyde condensation and SmI_2-promoted cyclization processes. In the case of alkoxy substitution, the resulting 3-hydroxypyrrolidine derivative was obtained with moderate 3,4-*trans*-selectivity, a result that nicely complements the *cis*-selectivity previously observed using α,β-unsaturated-γ-lactone precursors.

Experimental Section

General Procedures. All reactions involving air- and moisture-sensitive materials were performed under an atmosphere of dry Ar. Dichloromethane, benzene, dimethylformamide and acetonitrile were freshly distilled from CaH_2. *t*-Butanol was made anhydrous with Mg-I_2, distilled and stored over molecular sieves. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and, for reactions with SmI_2, it was deoxygenated prior to use. SmI_2 (*ca* 0.1 M in THF) was prepared from Sm and diiodomethane using a literature procedure.[14] Flash column chromatography was performed on silica gel (230-400 mesh). NMR spectra were obtained at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C with $CDCl_3$ as solvent and internal reference (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). The DEPT sequence was routinely used for ^{13}C multiplicity assignment. IR data include only characteristic absorptions. Mass spectra were obtained at

70 eV. GC/MS analysis were performed with a stationary phase of methylphenylsilicone (0.25 μm, 30 m x 0.25 mm) and a 90-180-250 °C (10, 20 °C/min) ramp.

Methyl (*E*)-5-[benzyl(*t*-butoxycarbonyl)amino]-4-hydroxypent-2-enoate (9). To a solution of methyl phenylsulfinyl acetate (**8**) (4.30 g, 21.7 mmol) and piperidine (2.20 mL, 21.7 mmol) in CH$_3$CN (32 mL) was added a solution of **7**[7] (4.77 g, 18.1 mmol) in CH$_3$CN (10 mL) over 2 h with a syringe pump. The reaction mixture was stirred for 18 h at room temperature, and the solvent was evaporated. The crude product was purified by flash chromatography (silica gel, 70:30 hexanes/EtOAc) to yield **9** (3.76 g, 62%) as an oil: ^{1}H NMR δ 1.47 (s, 9H), 3.30-3.43 (m, 2H), 3.73 (s, 3H), 4.35-4.56 (m, 4H), 6.15 (d, *J* = 15.4 Hz, 1H, H-2), 6.84 (dd, *J* = 15.4, 4.4 Hz, 1H, H-3), 7.19-7.37 (m, 5H); ^{13}C NMR δ 28.2 (CH$_3$), 51.6 (CH$_3$), 52.6 (CH$_2$), 71.2 (CH), 81.3 (C), 120.9 (CH), 127.2 (CH), 127.4 (CH), 128.6 (CH), 137.5 (C), 147.7 (CH), 157.9 (C), 166.8 (C); IR (neat) ν 3100-3500 (m, N-H), 1725 (s, C=O), 1700 (s, C=O), 1660 (m, C=C) cm^{-1}; MS (EI) m/z (%) 220 (31), 164 (29), 120 (base), 116 (26), 91 (95); HRMS calculated for C$_{18}$H$_{25}$NO$_5$ 335.1733, found 335.1741.

Methyl (*E*)-5-(benzylamino)-4-hydroxypent-2-enoate (10). Trifluoroacetic acid (2.90 mL, 37.7 mmol) was added dropwise to a solution of **9** (0.744 g, 2.22 mmol) in CH$_2$Cl$_2$ (16 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and then stirred for 3 h. The solvent was evaporated, and the residue was dissolved in EtOAc (25 mL). The solution was washed with saturated K$_2$CO$_3$ (3 x 10 mL) and brine (15 mL), and dried (Na$_2$SO$_4$). Solvent evaporation afforded **10** (469 mg, 91%), as an oil: ^{1}H NMR δ 2.61 (dd, *J* = 12.1, 8.5 Hz, 1H, H-5), 2.78 (dd, *J* = 12.1, 3.8 Hz, 1H, H-5), 3.71-3.85 (m, 7H), 4.35-4.38 (m, 1H, H-4), 6.14 (dd, *J* = 15.6, 1.6 Hz, 1H, H-2), 6.93 (dd, *J* = 15.6, 4.2 Hz, 1H, H-3), 7.20-7.37 (m, 5H); ^{13}C NMR δ 51.6 (CH$_3$), 53.2 (CH$_2$), 68.4 (CH), 120.7 (CH), 127.4 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 138.5 (C), 147.9 (CH), 166.8 (C); IR (neat) ν 3250-3350 (m, NH, OH), 1720 (s, C=O), 1660 (m, C=C) cm^{-1}.

Methyl (*E*)-5-(benzylamino)-4-(*t*-butyldimethylsilyloxy)pent-2-enoate (5a). To a solution of **10** (288.4 mg, 1.23 mmol) in dry DMF (4 mL) was added imidazole (166.9 mg, 2.45 mmol), followed by TBDMSCl (368.1 mg, 2.45 mmol), and the mixture was stirred at room temperature for 24 h. After evaporation of the solvent, the residue was dissolved in diethyl ether (15 mL), and the solution was washed with water (12 mL). The aqueous layer was extracted with diethyl ether (5 x 15 mL), and the combined organic layers were washed with brine (25 mL) and dried (Na$_2$SO$_4$). The residue after evaporation was purified by flash chromatography (silica gel saturated with Et$_3$N, 99:1 hexanes/Et$_3$N) to yield **5a** (345.9 mg, 80%) as an oil: ^{1}H NMR δ 0.04 and 0.06 (2 s, 6H), 0.90 (s, 9H), 1.60 (s, 1H, NH), 2.70 (d, *J* = 5.1 Hz, 2H), 3.74 (s, 3H), 3.81 (s, 2H), 4.43-4.49 (m, 1H), 6.03 (d, *J* = 15.6 Hz, 1H), 6.97 (dd, *J* = 15.6, 4.6 Hz, 1H), 7.25-7.36 (m, 5H); ^{13}C NMR δ -5.1 (CH$_3$), -4.8 (CH$_3$), 17.9 (C), 25.6 (CH$_3$), 51.2 (CH$_3$), 53.4 (CH$_2$), 54.4 (CH$_2$), 71.1 (CH), 120.1 (CH), 126.7 (CH), 127.7 (CH), 128.1 (CH), 139.9 (C), 149.3 (CH), 166.5 (C); IR (neat) ν 3250-3350 (w, N-H), 1725 (s, C=O), 1660 (m, C=C), 840 (s, Si-C) cm^{-1};

MS (EI) m/z (%) 292 (17), 121 (14), 120 (base), 91 (48), 73 (10); HRMS calculated for $C_{19}H_{31}NO_3Si$ 349.2073, found 349.2066.

Methyl (*E*)-5-(benzylamino)-4-(*t*-butyldiphenylsilyloxy)pent-2-enoate (5b). The procedure described above for the preparation of **5a** was followed with TBDPSCl to yield, after flash chromatography (silica gel, 90:10 hexanes/EtOAc and then EtOAc), **5b** (79%) as an oil: ^{1}H NMR δ 1.08 (s, 9H), 2.23 (s, 1H, NH), 2.61 and 2.68 (2 dd, *J* = 12.1, 5.2 Hz, 2H, H-5), 3.60 (s, 2H), 3.72 (s, 3H), 4.48 (qd, *J* = 5.2, 1.5 Hz, 1H, H-4), 5.98 (dd, *J* = 15.6, 1.5 Hz, 1H, H-2), 6.95 (dd, *J* = 15.6, 5.1 Hz, 1H, H-3), 7.15-7.67 (m, 15H); ^{13}C NMR δ 19.3 (C), 27.0 (CH_3), 51.5 (CH_3), 53.4 (CH_2), 54.2 (CH_2), 72.0 (CH), 120.6 (CH), 126.9 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 129.8 (CH), 132.9 (C), 133.5 (C), 135.7 (CH), 135.8 (CH), 139.8 (C), 149.0 (CH), 166.7 (C); IR (neat) ν 3341 (w, N-H), 1725 (s, C=O), 1659 (m, C=C) cm^{-1}; MS (EI) m/z (%) 416 (22), 120 (base), 91 (79); HRMS calculated for $C_{29}H_{36}NO_3Si$ (M + 1) 474.2464, found 474.2475.

Ethyl 2-[benzyl(*t*-butoxycarbonyl)amino]etanoate[9] (11). To a solution of *N*-benzylglycine ethyl ester (4.43 mL, 24.0 mmol) in CH_2Cl_2 (106 mL) at 0 ºC was added dropwise Et_3N (3.68 mL) followed by di-*tert*-butyl dicarbonate (6.07 mL, 26.4 mmol). The reaction mixture was stirred 1.5 h at 0 ºC and 0.5 h at room temperature, and then it was washed with water (75 mL) and 0.5 M HCl (75 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated at reduced pressure, and the resulting oil (7.41 g) was purified by flash chromatography (silica gel, 98:2 hexanes/EtOAc and then 3:1 EtOAc/Et_3N) to give **11** (6.11 g, 87%) as an oil: ^{1}H NMR δ 1.23 and 1.24 (2 t, *J* = 7.1 Hz, 3H), 1.46 and 1.47 (2 s, 9H), 3.76 and 3.91 (2 s, 2H), 4.15 and 4.15 (2 q, *J* = 7.1 Hz, 2H), 4.50 and 4.54 (2 s, 2H), 7.20-7.35 (m, 5H). These data are in agreement with those reported in the literature for the same compound.[9]

***t*-Butyl benzyl(2-hydroxybut-3-enyl)carbamate (12).** To a solution of **11** (6.11 g, 20.84 mmol) in CH_2Cl_2 (15 mL) at -78 °C was added dropwise DIBAL-H (1.0 M in hexanes, 21 mL, 21 mmol) and the solution was stirred for 3 h. The reaction mixture was allowed to reach -20 °C (bath temperature), it was stirred 45 min and then cooled again to -78 °C. Vinylmagnesium chloride (1.6 M in THF, 39 mL, 62.4 mmol) was added dropwise, the bath temperature was raised to 0 °C, and the mixture was stirred further 2.5 h and poured over a saturated solution of NH_4Cl (75 mL). After adding Na_2SO_4 (14 g), the resulting suspension was stirred at room temperature for 14 h and filtered after addition of Celite (5 g). The solid residue was thoroughly washed with CH_2Cl_2, and the washings were added to the filtrate. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (100 mL) and dried (Na_2SO_4). After solvent evaporation at reduced pressure, the crude product was purified by flash chromatography (silica gel saturated with Et_3N, 88:10:2 hexanes/EtOAc/Et_3N) to yield **12** (4.05 g, 70%) as a rotamer mixture: ^{1}H NMR δ 1.46 (s, 9H, CH_3), 2.42 and 3.79 (2 s, 1H, -O*H*), 3.22-3.36 (m, 2H), 4.30-4.57 (m, 3H), 5.13 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.26-5.33 (m, 1H), 5.80 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1H), 7.21-7.36 (m, 5H); ^{13}C NMR δ 28.2 (CH_3), 51.1 (CH_2), 52.2 (CH_2), 53.1 (CH_2), 72.3 (CH), 80.5 (C), 115.5 (CH_2), 127.1 (CH), 127.6 (CH), 128.4 (CH), 138.0 (C), 138.3 (CH), 155.9 (C), 157.3 (C); IR (neat) ν 3420 (m, OH), 1680 (s, C=O) cm^{-1}; MS (EI) m/z 221 (5), 220 (24), 204 (4), 164 (30), 119 (90), 88 (base);

HRMS calculated for $C_{16}H_{24}NO_3$ (M + 1) 278.1756, found 278.1757.

t-Butyl benzyl(2-methoxybut-3-enyl)carbamate (13). To a stirred suspension of NaH (60% in mineral oil, 0.443 g, 11.08 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added dropwise MeI (0.550 mL, 8.87 mmol) followed by a solution of **12** (2.05 g, 7.39 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 2 h, allowed to reach room temperature, and stirred further 24 h. Water (30 mL) was added dropwise, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). After solvent evaporation at reduced pressure, the crude product was purified by flash chromatography (silica gel saturated with Et_3N, 93:5:2 hexanes/EtOAc/Et_3N) to yield **13** (1.33 g, 62%) as a rotamer mixture: ^{1}H NMR δ 1.43 and 1.50 (2 s, 9H), 3.06-3.44 (m, 5H), 3.26 (s, included in m at 3.06-3.44), 3.75-3.90 (m, 1H), 4.43 (d, J = 15.6 Hz, 1H, PhCH), 4.57-4.71 (m, 1H, PhCH), 5.18-5.31 (m, 2H), 5.56-5.72 (m, 1H), 7.21-7.35 (m, 5H); ^{13}C NMR δ 28.4 (CH_3), 50.5 (CH_2), 51.1 (CH_2), 52.2 (CH_2), 56.6 (CH_3), 79.7 (C), 81.7 (CH), 82.4 (CH), 118.2 (CH_2), 118.3 (CH_2), 126.9 (CH), 127.0 (CH), 127.8 (CH), 128.4 (CH), 136.2 (CH), 136.4 (CH), 138.4 (C), 138.8 (C), 155.8 (C); IR (neat) ν 1700 (s, C=O) cm^{-1}; MS (EI) m/z 220 (25), 203 (14), 199 (6), 165 (4), 164 (34), 121 (8), 120 (base), 91 (98); HRMS calculated for $C_{17}H_{25}NO_3$ 291.1834, found 291.1827.

Ethyl 5-[benzyl(t-butoxycarbonyl)amino]-4-methoxypent-2-enoate (14). Ozone (0.4 A, 100 L/h) was bubbled through a solution of **13** (0.58 g, 2.00 mmol) in CH_2Cl_2 (4.0 mL) at -78 °C until a blue solution was obtained. Argon was bubbled until discoloration and then Me_2S (1.47 mL, 20.0 mmol) was added. The solution was allowed to warm to room temperature and stirred for 3 h. Ethoxycarbonylmethylentriphenylphosphorane (0.95 g, 2.74 mmol) was added in portions to the cooled (0 °C) solution. The mixture was stirred 1.5 h at 0 °C and 0.5 h at room temperature. Diethyl ether (10 mL) and water (10 mL) were added and the layers were separated. The organic layer was washed with brine (5 mL) and dried (Na_2SO_4). After solvent evaporation at reduced pressure, the residue was purified by flash chromatography (silica gel saturated with Et_3N, 98:2 hexanes/Et_3N) to afford **(Z)-14** and **(E)-14** (E/Z = 71:29, 50%). Data for **(Z)-14** (rotamer mixture): ^{1}H NMR δ 1.29 (t, J =7.1 Hz, 3H), 1.40 and 1.48 (2 s, 9H), 3.25-3.55 (m, 5H), 3.27 (s, included in m at 3.25-3.55), 4.18 (q, J =7.1 Hz, 2H), 4.41-4.76 (m, 2H, PhCH_2), 5.11 (ddd, J = 12.0, 6.0, 6.0 Hz, 1H, H-4), 5.94 (d, J = 11.7 Hz, H-2), 5.94-6.15 (m, 1H, H-3), 7.20-7.34 (m, 5H); ^{13}C NMR δ 14.2 (CH_3), 28.3 (CH_3), 48.8 (CH_2), 49.1 (CH_2), 50.2 (CH_2), 50.9 (CH_2), 57.2 (CH_3), 60.2 (CH_2), 75.2 (CH), 75.3 (CH), 79.7 (C), 79.8 (C), 122.9 (CH), 123.0 (CH), 127.0 (CH), 127.2 (CH), 127.8 (CH), 128.3 (CH), 138.4 (C), 138.8 (C), 147.9 (CH), 148.3 (CH), 155.8 (C), 155.9 (C), 165.4 (C), 165.7 (C); IR (neat) ν 1720 (s, C=O), 1700 (s, C=O) cm^{-1}; MS (EI) m/z 290 (2), 220 (25), 164 (28), 144 (22), 121 (9), 120 (base), 91 (81); HRMS calculated for $C_{20}H_{29}NO_5$ 363.2046, found 363.2033. Data for **(E)-14** (rotamer mixture): ^{1}H NMR δ 1.28 (t, J = 7.1 Hz, 3H), 1.42 and 1.48 (2 s, 9H), 3.10-3.44 (m, 5H), 3.26 and 3.28 (2 s, included in m at 3.10-3.44), 3.88 and 4.09 (2 q, J = 5.7 Hz, 1H, H-4), 4.18 (q, overlapped with q at 4.09, J = 7.1 Hz, 2H), 4.42-4.65 (m, 2H, PhCH_2), 5.98 (apparent t, J ≈ 16.2 Hz, 1H, H-2), 6.60-6.82 (m, 1H, H-3), 7.17-7.34 (m, 5H); ^{13}C NMR δ 14.1 (CH_3), 28.2 (CH_3), 49.7 (CH_2), 50.3

(CH$_2$), 51.0 (CH$_2$), 52.1 (CH$_2$), 57.4 (CH$_3$), 60.4 (CH$_2$), 79.8 (CH), 79.9 (C), 80.1 (CH), 122.8 (CH), 122.9 (CH), 127.0 (CH), 127.7 (CH), 128.3 (CH), 138.0 (C), 138.3 (C), 145.3 (CH), 145.4 (CH), 155.6 (C), 165.7 (C); IR (neat) ν 1720 (s, C=O), 1690 (s, C=O) cm^{-1}; MS (EI) m/z 290 (3), 264 (4), 262 (4), 220 (33), 178 (6), 164 (40), 144 (35), 120 (base), 115 (15), 91 (93); HRMS calculated for C$_{20}$H$_{29}$NO$_5$ 363.2046, found 363.2037.

Ethyl (*E*)-5-(benzylamino)-4-methoxypent-2-enoate (5c). Trifluoroacetic acid (0.67 mL, 8.67 mmol) was added dropwise to a solution of (*E*)-**14** (0.186 g, 0.51 mmol) in CH$_2$Cl$_2$ (4.0 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 3 h. The solvent was evaporated, and the resulting residue was dissolved in EtOAc (4 mL). The solution was washed with saturated K$_2$CO$_3$ (3 x 2 mL) and brine (2 mL), and it was dried (Na$_2$SO$_4$). Evaporation of the solvent at reduced pressure afforded **5c** (117 mg, 87%): ^{1}H NMR δ 1.29 (t, *J* = 7.1 Hz, 3H), 1.82 (broad s, N-H), 2.68 (dd, *J* = 12.3, 5.5 Hz) and 2.74 (dd, *J* = 12.3, 6.3 Hz) (total 2H, H-5), 3.33 (s, 3H), 3.80 (s, 2H), 3.90-3.98 (m, 1H, H-4), 4.20 (q, *J* = 7.1 Hz, 2H), 6.02 (dd, *J* = 15.8, 1.2 Hz, 1H, H-2), 6.80 (dd, *J* = 15.8, 6.3 Hz, 1H, H-3), 7.20-7.36 (m, 5H); ^{13}C NMR δ 14.2 (CH$_3$), 52.8 (CH$_2$), 53.7 (CH$_2$), 57.3 (CH$_3$), 60.5 (CH$_2$), 80.0 (CH), 122.9 (CH), 127.0 (CH), 128.1 (CH), 128.4 (CH), 139.9 (C), 146.0 (CH), 166.0 (C); IR (neat) ν 3330 (w, N-H), 1710 (s, C=O), 1660 (m, C=C) cm^{-1}; MS (EI) m/z 144 (4), 121 (8), 120 (82), 115 (2), 98 (2), 91 (base), 83 (20); HRMS calculated for C$_{15}$H$_{21}$NO$_3$ 263.1521, found 263.1528.

Procedure for SmI$_2$-mediated cyclizations
In a typical experiment, a mixture of amine **5** (0.59 mmol), *N*-(hydroxymethyl)benzotriazole (89.2 mg, 0.59 mmol) (or alternatively, the corresponding amounts of benzotriazole and *n*-hexanal), and 4 Å molecular sieves (292 mg) in benzene (**5a,b**) or THF (**5c**) (1.5 mL) was stirred overnight at room temperature. The resulting suspension was filtered over Celite, the solid residue was washed with EtOAc (60 mL), and the solution was evaporated to dryness to yield the crude adduct **6**. Without further manipulation, this was dissolved with *t*-BuOH (0.11 mL, 1.15 mmol) in THF (12 mL), and the resulting solution was added dropwise to a solution of SmI$_2$ (*ca* 0.1 M in THF, 18 mL, 1.80 mmol)^{14} at -78 °C. The mixture was stirred at -78 °C for 30 min and allowed to warm to room temperature. After further stirring for 2 h, the reaction mixture was quenched with a 1:1 mixture of saturated K$_2$CO$_3$ solution and water (30 mL). After separation, the aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers were washed with brine (10 mL) and dried (Na$_2$SO$_4$). The residue after evaporation was purified by flash column chromatography in silica gel saturated with Et$_3$N to yield pyrrolidines **6** as oils.

Methyl 2-[1-benzyl-4-(*t*-butyldimethylsilyloxy)pyrrolidin-3-yl]acetate (6a). Prepared from **5a** and *N*-(hydroxymethyl)benzotriazole. Elution with 97:3 hexanes/Et$_3$N yielded ***trans*-6a** (48%) and ***cis*-6a** (40%). Data for ***trans*-6a**: ^{1}H NMR δ 0.01 and 0.03 (2 s, 6H, Si-CH$_3$), 0.86 (s, 9H), 2.30-2.43 (m, 4H), 2.52-2.57 (m, 1H), 2.84-2.92 (m, 2H), 3.55 (d, *J* = 13.1 Hz, 1H, C*H*-Ph), 3.65 (s, OCH$_3$) and 3.66 (d, *J* = 13.1 Hz, C*H*-Ph) (total 4H), 3.94-4.00 (m, 1H, H-4'), 7.21-7.31 (m, 5H); ^{13}C NMR δ -4.9 (CH$_3$), -4.7 (CH$_3$), 17.8 (C), 25.7 (CH$_3$), 37.2 (CH$_2$), 43.4 (CH, C-3'), 51.4 (CH$_3$), 57.6 (CH$_2$), 60.2 (CH$_2$), 61.9 (CH$_2$), 76.5 (CH, C-4'), 126.7 (CH), 128.1 (CH), 128.5

(CH), 138.8 (C), 172.9 (C); IR (neat) ν 1735 (s, C=O), 835 (Si-C) cm^{-1}; MS (EI) m/z (%) 363 (M, 16), 332 (12), 307 (24), 306 (base), 272 (11), 158 (14), 133 (43), 132 (13), 91 (73), 73 (14); HRMS calculated for $C_{20}H_{33}NO_3Si$ 363.2230, found 363.2241. Data for ***cis*-6a**: ^{1}H NMR δ -0.01 and 0.00 (2 s, 6H, Si-CH$_3$), 0.39 (s, 9H), 2.16-2.35 (m, 3H), 2.55-2.62 (m, 2H), 2.92-2.98 (m, 1H), 3.15-3.21 (m, 1H), 3.55-3.69 (m, C*H*$_2$Ph and OCH$_3$, 5H), 4.33-4.39 (m, 1H, H-4'), 7.23-7.31 (m, 5H); ^{13}C NMR δ -5.3 (CH$_3$), -4.7 (CH$_3$), 17.9 (C), 25.7 (CH$_3$), 32.3 (CH$_2$), 39.2 (CH, C-3'), 51.3 (CH$_3$), 58.0 (CH$_2$), 60.7 (CH$_2$), 63.0 (CH$_2$), 71.7 (CH, C-4'), 126.8 (CH), 128.2 (CH), 128.6 (CH), 139.0 (C), 173.6 (C); IR (neat) ν 1740 (s, C=O), 1095 (Si-O-C), 840 (Si-C) cm^{-1}; MS (EI) m/z (%) 363 (M, 14), 332 (14), 307 (23), 307 (23), 306 (base), 272 (13), 158 (17), 133 (47), 132 (15), 91 (66), 73 (17); HRMS calculated for $C_{20}H_{33}NO_3Si$ 363.2230, found 363.2217.

Methyl 2-[1-benzyl-4-(*tert*-butyldimethylsilyloxy)-2-pentylpyrrolidin-3-yl]acetate (6b). Prepared from **5a**, benzotriazole and *n*-hexanal. Elution with 98:2 hexanes/Et$_3$N afforded **6b** (60%) as a mixture of diastereoisomers (1.0:16.3:1.6:9.8 GC/MS ratio). Further chromatographic separation allowed the isolation of a two-isomer fraction (84:16 ratio) for characterization purposes: ^{1}H NMR δ -0.05 and -0.04 (2 s, 6H, Si-CH$_3$), 0.84 (s, 12H), 1.25 (s, 7H), 1.60 (m, 1H), 2.34-2.80 (m, 6H), 3.26 (d, *J* = 13.1 Hz, 1H, minor isomer), 3.35 (d, *J* = 13.5 Hz, 1H, major isomer), 3.67 (s, 3H), 3.98 (d, *J* = 14.9 Hz, 1H, overlapped with 1H of minor isomer), 4.28-4.30 (m, 1H, major isomer), 7.25-7.31 (m, 5H, Ar-H); ^{13}C NMR δ -5.3 (CH$_3$), -4.9 (CH$_3$), 14.1 (CH$_3$), 17.9 (C), 22.6 (CH$_2$, major isomer), 24.4 (CH$_2$, minor isomer), 25.7 (CH$_3$), 26.4 (CH$_2$, major isomer), 29.1 (CH$_2$, major isomer), 30.4 (CH$_2$, major isomer), 31.2 (CH$_2$, minor isomer), 32.2 (CH$_2$, major isomer), 37.2 (CH$_2$, minor isomer), 42.0 (CH), 48.8 (CH$_3$, minor isomer), 51.3 (CH$_3$, major isomer), 51.5 (CH$_2$, minor isomer), 57.7 (CH$_2$, minor isomer), 59.4 (CH$_2$, major isomer), 60.2 (CH$_2$, minor isomer), 60.6 (CH$_2$, major isomer), 64.9 (CH, major isomer), 67.7 (CH, minor isomer), 72.2 (CH, major isomer), 75.3 (CH, major isomer), 126.5 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 139.8 (C, minor isomer), 140.2 (C, major isomer), 172.8 (C=O, minor isomer), 174.2 (C=O, major isomer); MS (EI) m/z (%) 433 (2), 376 (13), 364 (11), 363 (42), 362 (base), 170 (14), 91 (30); HRMS calculated for $C_{25}H_{43}NO_3Si$ 433.3010, found 433.3000.

Methyl 2-[1-benzyl-4-(*t*-butyldiphenylsilyloxy)pyrrolidin-3-yl]acetate (6c). Prepared from **5b** and *N*-(hydroxymethyl)benzotriazole. Elution with 98:2 hexanes/Et$_3$N afforded ***trans*-6c** and ***cis*-6c** (73%, *cis/trans* = 1:1). Data for ***trans*-6c**: ^{1}H NMR δ 1.07 (s, 9H), 2.07-2.10 (m, 2H), 2.27-2.33 (m, 1H), 2.49-2.55 (m, 2H), 2.71-2.91 (m, 2H), 3.49-3.65 (m, C*H*$_2$Ph and OCH$_3$, 5H), 3.95-4.01 (m, 1H, H-4'), 7.21-7.43 (m, 11H), 7.62-7.70 (m, 4H); ^{13}C NMR δ 19.0 (C), 26.9 (CH$_3$), 36.9 (CH$_2$), 44.1 (CH, C-3'), 51.4 (CH$_3$), 57.8 (CH$_2$), 60.0 (CH$_2$), 61.9 (CH$_2$), 77.4 (CH, C-4'), 126.8 (CH), 127.6 (CH), 127.6 (CH), 128.1 (CH), 128.6 (CH), 129.6 (CH), 129.7 (CH), 133.8 (C), 135.7 (CH), 135.7 (CH), 138.7 (C), 172.9 (C); IR (neat) ν 1737 (s, C=O), 1110 (s, Si-O-C) cm^{-1}; HRMS calculated for $C_{30}H_{37}NO_3Si$ 487.2543, found 487.2527. Data for ***cis*-6c**: ^{1}H NMR δ 1.08 (s, 9H), 2.29-2.51 (m, 3H), 2.56-2.81 (m, 3H), 2.91 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.54 (s, 2H, C*H*$_2$Ph), 3.64 (s, 3H), 4.49 (td, *J* = 5.9, 5.1 Hz, 1H, H-4'), 7.21-7.40 (m, 11H), 7.62-7.70 (m, 4H); ^{13}C NMR δ 19.3 (C), 26.9 (CH$_3$), 33.1 (CH$_2$), 39.1 (CH, C-3'), 51.4 (CH$_3$), 57.9 (CH$_2$), 60.3 (CH$_2$), 61.8 (CH$_2$), 73.0 (CH, C-4'), 126.9 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.6

(CH), 129.7 (CH), 133.3 (C), 134.1 (C), 135.7 (CH), 135.8 (CH), 138.6 (C), 173.7 (C); IR (neat) ν 1735 (s, C=O), 1111 (s, Si-O-C) cm^{-1}; HRMS calculated for $C_{30}H_{37}NO_3Si$ 487.2543, found 487.2526.

Ethyl 2-(1-benzyl-4-methoxypyrrolidin-3-yl)acetate (6d). Prepared from **5c** and *N*-(hydroxymethyl)benzotriazole. Elution with 93:5:2 hexanes/EtOAc/Et$_3$N afforded ***trans*-6d** (59%) and ***cis*-6d** (23%). Data for ***trans*-6d**: ^{1}H NMR δ 1.24 (t, *J* = 7.1 Hz, 3H), 2.22 (dd, *J* = 9.3, 5.2 Hz, 1H), 2.34-2.61 (m, 4H), 2.76 (dd, *J* = 10.1, 6.1 Hz, 1H), 2.92 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.28 (s, 3H), 3.53-3.66 (m, 3H), 4.12 (q, *J* = 7.1 Hz, 2H), 7.19-7.37 (m, 5H); ^{13}C NMR δ 14.2 (CH$_3$), 38.1 (CH$_2$), 41.1 (CH, C-3'), 56.9 (CH$_3$), 58.4 (CH$_2$), 59.0 (CH$_2$), 60.1 (CH$_2$), 60.4 (CH$_2$), 85.2 (CH, C-4'), 126.9 (CH), 128.2 (CH), 128.6 (CH), 138.6 (C), 172.4 (C); IR (neat) ν 1730 (s, C=O) cm^{-1}; MS (EI) m/z 277 (M, 14), 276 (8), 246 (7), 245 (11), 232 (28), 186 (26), 158 (36), 133 (31), 91 (base); HRMS calculated for $C_{16}H_{23}NO_3$ 277.1678, found 277.1684. Data for ***cis*-6d**: ^{1}H NMR δ 1.24 (t, *J* = 7.1 Hz, 3H), 2.25-2.37 (m, 2H), 2.46 (dd, *J* = 10.3, 3.8 Hz, 1H), 2.55-2.78 (m, 2H), 2.87 (dd, *J* = 8.7, 7.1 Hz, 1H), 3.02 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.24 (s, 3H), 3.64 (s, 2H, PhC*H*$_2$), 3.86 (ddd, *J* = 6.7, 5.6, 3.9 Hz, 1H, H-4'), 4.11 and 4.12 (2 q, *J* = 7.1 Hz, 2H), 7.22-7.31 (m, 5H); ^{13}C NMR δ 14.2 (CH$_3$), 32.7 (CH$_2$), 38.4 (CH, C-3'), 57.4 (CH$_3$), 58.0 (CH$_2$), 59.2 (CH$_2$), 60.1 (CH$_2$), 60.6 (CH$_2$), 80.5 (CH, C-4'), 126.9 (CH), 128.2 (CH), 128.7 (CH), 138.9 (C), 173.2 (C); IR (neat) ν 1730 (s, C=O) cm^{-1}; MS (EI) m/z 277 (M, 7), 276 (7), 273 (15), 246 (7), 245 (23), 232 (72), 186 (85), 170 (94), 158 (98), 133 (89), 91 (base); HRMS calculated for $C_{16}H_{23}NO_3$ 277.1678, found 277.1676.

Acknowledgements

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