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Synthesis of 1,2,3,4-tetrahydroisoquinolines and 2,3,4,5-tetrahydro-1*H*-2-benzazepines combining sequential palladium-catalysed *ortho* alkylation/vinylation with aza-Michael addition reactions

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Abstract—1-Substituted 1,2,3,4-tetrahydroisoquinolines and 2,3,4,5-tetrahydro-1*H*-2-benzazepines were synthesised from *o*-iodoalkylbenzene, *N*-Cbz-bromoalkylamine and an electron-poor olefin through a one-pot palladium-catalysed sequence involving *ortho* alkylation, alkenylation and intramolecular aza-Michael reaction.

The 1-substituted 1,2,3,4-tetrahydroisoquinoline and 2,3,4,5-tetrahydro-1*H*-2-benzazepine nuclei are the basic structure of pharmacologically interesting compounds. Tetrahydroisoquinolines are present in many alkaloids,[1a] and 1-substituted tetrahydro-1*H*-2-benzazepines are active as anticonvulsants and inhibitors of platelet function.[2] Synthetic routes used to build up these molecules are mainly based on Bischler–Napieralsky or Pictet–Spengler type cyclisation of activated 2-phenylethylamine[1b,3] and 3-phenylpropylamine[4] derivatives, under acidic catalysis. However, in the absence of electron-donating substituents (OH, OMe) in the phenyl group the electrophilic ring closure is less selective and more drastic conditions are required.[1b,3a]

Our continuing interest in the palladium-catalysed synthesis of bioactive molecules,[5] led us to consider a new synthetic strategy for the construction of these nuclei. The recently developed palladium-catalysed alkylation/alkenylation of iodobenzene with an alkyl iodide and an olefin proved to be a powerful synthetic tool allowing regioselective aromatic substitution through a multistep sequential process.[6] This methodology was successfully extended to the synthesis of fused carbo-, and oxacycles.[7]

In this communication we report a new synthetic route to compounds **5** based on the combination of the palladium-catalysed alkylation/alkenylation with an aza-Michael addition reaction.[1c] Accordingly, the synthesis of **5** requires the *o*-substituted iodobenzene **1**, an electron-poor olefin **3** and a bromoalkyl derivative **2** bearing a nitrogen functionality, which can be trapped by a Michael acceptor (Scheme 1).

The reaction of **1** (R_1 = Me), **2** (*n* = 1),[8] **3** (R_2 = CO_2Me) leads to compound **5** in 65% yield (on **1**), using $Pd(OAc)_2$/tri-2-furylphosphine as catalyst, norbornene, Cs_2CO_3 as a base in DMF at 80 °C (Scheme 1, Table 1, entry 1).[9] The first formed compound (*E*)-**4** in situ undergoes base-catalysed intramolecular aza-Michael addition affording **5**. Formation of **4** takes place according to the mechanism previously proposed for palladium-catalysed alkylation/alkenylation of iodobenzene (Scheme 2).[6] The aromatic iodide **1** oxidatively adds to palladium(0) affording **6**. Norbornene insertion and subsequent ring closure through C–H activation[10] give palladacycle **8**. The aliphatic bromide **2** then reacts with **8** giving the palladium(IV) metallacycle **9**. Reductive elimination forms **10**, which readily undergoes norbornene

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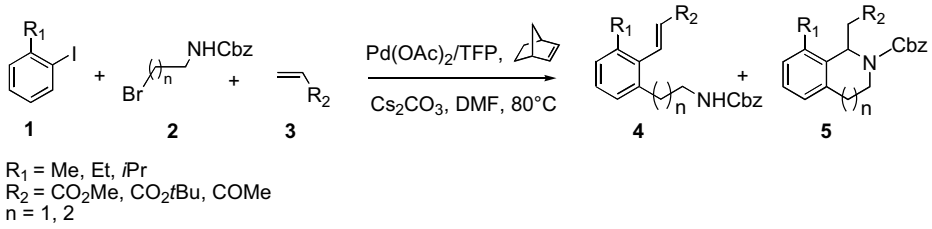
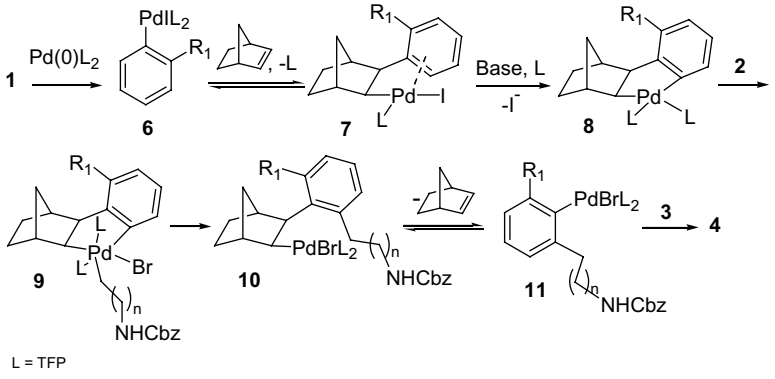


Scheme 1.

Table 1. Reaction of **1**, **2**, **3** in the presence of norbornene, $Pd(OAc)_2$ as catalysts, tri-2-furylphosphine as ligand, Cs_2CO_3 as a base[a]

Entry	*n*	R_1	R_2	Time (h)	Molar ratio[b] **5/4**	Yield (%)[c]	
						5	**4**
1	1	Me	CO_2Me	20	1/0	65	—
2	1	Me	CO_2Me	3	1/9	5	68
3	1	Et	CO_2Me	20	1/0	40	—
4	1	*i*-Pr	CO_2Me	20	1/0	62	—
5	1	Me	CO_2t-Bu	20	1/0	68	—
6	1	Me	COMe	4	1/0	60[d]	—
7	2	Me	CO_2Me	20	0/1	—	70
8	2	Me	CO_2t-Bu	20	0/1	—	65
9	2	Me	CO_2Me	3.5[e]	7/3	34	16
10	2	Me	CO_2t-Bu	4[e]	7.5/2.5	43	11

[a] Unless otherwise reported, the reactions were run using **1** (1 molequiv), **2** (2 molequiv), **3** (2 molequiv), norbornene (2 molequiv), $Pd(OAc)_2$ (10 mol%), tri-2-furylphosphine (TFP) (20 mol%), Cs_2CO_3 (2 molequiv) in DMF at 80 °C, [**1**] = 0.05 M.
[b] Determined by ^{1}H NMR analysis of the crude.
[c] Isolated yield based on **1**.
[d] The reaction was run at 60 °C.
[e] The reaction was run for 2 h at 80 °C, then, after addition of 1 equiv of *t*-BuOK and dilution with DMF, for further 1.5–2 h at rt, [**1**] = 0.03 M.



Scheme 2.

expulsion because of the steric hindrance of the two *ortho* alkyl substituents. At this point methyl acrylate insertion completes the catalytic cycle with formation of **4** (Scheme 2).

Evidence for the intermediacy of **4** was gained by carrying out the reaction for a shorter time (3 h). In this case a mixture of **4**[11] and **5** in a 9/1 molar ratio was obtained (Table 1, entry 2). Treatment of **4** with Cs_2CO_3 in DMF at 80 °C gave **5**. The reaction of *o*-iodotoluene, **2** and other olefins **3** ($R_2 = CO_2t$-Bu, COMe) afforded **5** in satisfactory yields (Scheme 1, Table 1, entries 5 and 6).

Attempts to apply this procedure to the synthesis of new 1-substituted tetrahydro-2-benzazepines **5** (R_1 = Me, $R_2 = CO_2Me$, CO_2t-Bu) starting from **1**, **2** ($n = 2$)[8] and **3** (Scheme 1) led only to compounds (*E*)-**4**, which were isolated in 70–65% yields (Table 1, entries 7 and 8).[12,13] However, treatment of **4** ($n = 2$, $R_2 = CO_2t$-Bu) with *t*-BuOK in DMF (0.03 M) at room temperature for 2 h led to a mixture of **5** and **4** (70/30 molar ratio, ^{1}H NMR analysis of the crude).[14] Thus, seven-membered ring cyclisation could be performed in a one-pot sequence from **1**, **2**, **3** by adding *t*-BuOK (1 equiv) when the formation of **4** was complete (2 h, TLC analysis). Work-up of the reaction and flash chromatography of

Table 2. Variation of solvent, ligand, palladium catalyst and base in the reaction of *o*-iodotoluene with *N*-Cbz-2-bromoethylamine and methyl acrylate[a]

Entry	Solvent	Ligand	Base	Catalyst	Yield of **5** (%)[b]
1	DMF	TFP	Cs_2CO_3	$Pd(OAc)_2$	65
2	MeCN	TFP	Cs_2CO_3	$Pd(OAc)_2$	55
3	DMF	TPP	Cs_2CO_3	$Pd(OAc)_2$	13
4	DMF	TFP	Cs_2CO_3	$Pd_2(dba)_3{\cdot}CHCl_3$	22
5	DMF	TFP	K_2CO_3	$Pd(OAc)_2$	34[c]

[a] The reactions were run using **1** (1 mol equiv), **2** (2 mol equiv), **3** (2 mol equiv), norbornene (2 mol equiv), Pd-catalyst (10 mol%), ligand (20 mol%), base (2 mol equiv) at 80 °C for 20 h, [**1**] = 0.05 M.
[b] Isolated yield based on **1**.
[c] K_2CO_3 (3 mol equiv); 80 °C for 20 h; then 100 °C for 6 h.

the crude, gave compounds **5**, isolated in 34% and 43% overall yields (Table 1, entries 9 and 10).[9]

The presence of an *ortho* substituent in the iodobenzene derivative **1** is needed to block further alkylation.[6,7] Increasing the size of R_1 afforded the expected isoquinolines **5** in 40% and 62% yields starting from *o*-iodoethyl- and *o*-iodoisopropylbenzene, respectively[15] (Scheme 1, Table 1, entries 3 and 4).[9] With other *o*-substituents such as $R_1 = CF_3$ and Cl the reaction failed, while *o*-iodoanisole gave **5** in less than 15% yield. Complex mixtures of side-products were obtained at complete conversion of **1** and **2**.

Reaction conditions can significantly influence selectivity as observed in preliminary experiments with **1** (R_1 = Me), **2** (n = 1) and **3** ($R_2 = CO_2Me$) varying solvent, base, catalyst and ligand. As can be seen from the results reported in Table 2, entries 1, 2, 3, 4, the $Pd(OAc)_2$/tri-2-furylphosphine catalyst combination in DMF turned out to be the most effective. However, the base also plays a role in the reaction sequence. In the presence of K_2CO_3 (3 mol equiv) the reaction gave mainly **4** after 20 h at 80 °C with only traces of **5** (TLC analysis). Conversion was completed by further heating at 100 °C for 6 h and the yield was 34% (entry 5) to be compared with 65% obtained with Cs_2CO_3 (entry 1).

In conclusion, 1-substituted 1,2,3,4-tetrahydroisoquinolines and 2,3,4,5-tetrahydro-1*H*-2-benzazepines **5** were synthesised directly from commercially available and easily accessible molecular components **1**, **2**, **3** under mild conditions. The heterocyclic rings were assembled through the formation of three bonds in a one-pot sequence, combining palladium-catalysed alkylation/alkenylation with aza-Michael reactions.

Acknowledgements

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9. General procedure for the synthesis of **5** (n = 1, 2): a Schlenk-type flask was charged under nitrogen with Cs_2CO_3 (126 mg, 0.39 mmol), $Pd(OAc)_2$ (4.3 mg, 0.019 mmol), tri-2-furylphosphine (9.0 mg, 0.039 mmol), a solution of norbornene (36.5 mg, 0.39 mmol) in anhydrous DMF (1.5 mL). To the stirred mixture, **1** (0.194 mmol), **3** (0.39 mmol) and an anhydrous DMF solution (2.4 mL) of **2** (n = 1) (100 mg, 0.39 mmol) were then added. The reaction mixture was heated under stirring at 80 °C for the time reported (Table 1), then cooled to rt. After addition of a cooled (0 °C) saturated aqueous n-Bu_4NCl (70 mL) and extraction with EtOAc (2 × 15 mL), the combined organic phases were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc 8/2).
The reaction of **1** (0.194 mmol), **2** (n = 2) (0.39 mmol) and **3** (0.39 mmol) norbornene (0.39 mmol) Cs_2CO_3 (0.39 mmol), $Pd(OAc)_2$ (0.019 mmol), tri-2-furylphosphine (0.039 mmol) in DMF (3.9 mL) was carried out according to the above procedure for the time reported (Table 1,

entries 9 and 10). After cooling to rt *t*-BuOK (21.8 mg, 0.194 mmol) and DMF (2.6 mL) were added and the resulting mixture was kept under stirring for an additional 1.5–2 h at rt. Work-up as above gave a crude residue, which was purified by flash chromatography (eluent: hexane/EtOAc 8.5/1.5).

The ^{1}H NMR spectra of **5** ($n = 1$, 2) in DMSO-d_6 were recorded at 85 and/or 100 °C, a complex mixture of *syn*/*anti* rotamers being present at room temperature.

(*R*,*S*) Benzyl 1-(2-methoxy-2-oxoethyl)-8-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate **5** ($n = 1$, R_1 = Me, R_2 = CO_2Me): ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 2.3 (3H, Me), 2.62 (dd, J = 14.4, 4.1 Hz, 1H, A part of an ABX system), 2.76 (dd, J = 14.4, 9.4 Hz, 1H, B part of an ABX system), 2.87–2.92 (m, 2H), 3.54 (s, 3H), 3.54–3.63 (m, 1H), 3.82–3.91 (m, 1H), 5.10 (d, J = 12.6 Hz, 1H, A part of an AB system), 5.15 (d, J = 12.6 Hz, 1H, B part of an AB system), 5.73 (dd, J = 9.4, 4.1 Hz, 1H, X part of an ABX system), 7.00–7.14 (m, 3H), 7.29–7.39 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.6, 27.4, 27.9, 37.7,38.5, 39.1, 50.0, 51.8, 66.7, 127.0, 127.2, 127.4, 127.7, 127.8, 128.2, 128.7, 128.8, 133.9, 134.0, 134.4, 135.1, 137.3, 154.7, 155.2, 170.9. IR (Nujol) 3031, 2951, 1741, 1703 cm^{-1}. HRMS calcd for $C_{21}H_{23}NO_4$ 353.1627; found 353.1647.

(*R*,*S*) Benzyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate **5** ($n = 1$, R_1 = Me, R_2 = CO_2t-Bu): ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.37 (s, 9H), 2.32 (s, 3H), 2.50–2.56 (m, overlapped with the solvent signal, 1H), 2.63–2.71 (m, 1H), 2.89 (ps t, J = 6.7 Hz, 2H), 3.53–3.62 (m, 1H), 3.89–3.98 (m, 1H), 5.09 (d, J = 12.7 Hz, 1H, A part of an AB system), 5.15 (d, J = 12.7 Hz, 1H, B part of an AB system), 5.75 (dd, J = 9.6, 4.3 Hz, 1H), 6.98–7.13 (m, 3H), 7.29–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 26.3, 26.9, 37.0, 37.5, 40.1, 49.0, 65.8, 79.3, 126.7, 126.8, 127.1, 127.4, 127.7, 128.2, 133.3, 133.5, 133.8, 134.9, 136.8, 153.7, 154.1, 168.7. IR (neat) 3032, 2975, 2928, 1703 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{29}NO_4Na$ 418.19887; found 418.19783.

(*R*,*S*) Benzyl 8-ethyl-1-(2-methoxy-2-oxoethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate **5** ($n = 1$, R_1 = Et, R_2 = CO_2Me): ^{1}H NMR (300 MHz, DMSO-d_6, 85 °C) δ 1.2 (t, J = 7.5 Hz, 3H), 2.54–2.94 (m, 6H), 3.54 (s, 3H), 3.56–3.65 (m, 1H), 3.78–3.87 (m, 1H), 5.09 (d, J = 12.7, 1H, A part of an AB system), 5.15 (d, J = 12.7 Hz, 1H, B part of an AB system), 5.81 (dd, J = 9.7, 4.2 Hz, 1H), 7.01 (br d, J = 7.3 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.17 (t, J = 7.48 Hz, 1H), 7.32–7.37 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.2, 23.8, 26.8, 27.3, 37.5, 38.3, 39.7, 49.0, 51.4, 66.3, 66.4, 126.5, 126.7, 127.2, 127.7, 128.3, 134.1, 136.8, 139.4, 154.2, 154.9, 170.4. IR (neat): 3032, 2953, 2879, 1740, 1699 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{25}NO_4Na$ 390.16813; found 390.16683.

(*R*,*S*) Benzyl 8-isopropyl-1-(2-methoxy-2-oxoethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate **5** ($n = 1$, R_1 = *i*-Pr, R_2 = CO_2Me): ^{1}H NMR (300 MHz, DMSO-d_6, 85 °C) δ 1.14 (d, J = 6.7 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H), 2.50–2.57 (m, overlapped with solvent signal, 1H), 2.79–2.87 (m, Hz, 1H), 2.9–2.96 (m, 2H), 3.18 (septet, J = 6.8 Hz, 1H), 3.55 (s, 3H), 3.56–3.65 (m, 1H), 3.77–3.89 (m, 1H), 5.08 (d, J = 12.7 Hz, 1H), 5.16 (d, J = 12.7 Hz, 1H), 5.89 (dd, J = 9.8, 4 Hz, 1H), 6.98–7.01 (m, 1H), 7.18–7.2 (m, 2H), 7.32–7.37 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.9, 23.1, 25.4, 27.3, 27.9, 37.9, 38.6, 40.5, 49.2, 51.9, 66.7, 66.9, 123.8, 123.9, 126.9, 127.1, 127.7, 127.8, 128.2, 128.7, 133.7, 134.3, 134.4, 137.1, 137.3, 144.5, 144.7, 154.7, 155.3, 170.8. IR (neat): 3031, 2871, 2960, 1739, 1699 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{27}NO_4Na$ 404.18378; found: 404.18210.

(*R*,*S*) Benzyl 8-methyl-1-(2-oxopropyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate **5** ($n = 1$, R_1 = Me, R_2 = COMe): ^{1}H NMR (300 MHz, DMSO-d_6, 85 °C) δ 2.1 (s, 3H), 2.3 (s, 3H), 2.67–2.73 (m, 1H), 2.83–2.91 (m, 3H), 3.52–3.62 (m, 1H), 3.82–3.91 (m, 1H), 5.11 (s, 2H), 5.76 (dd, J = 9.4, 4.0 Hz, 1H), 7.00–7.13 (m, 3H), 7.25–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 27.8, 28.1, 38.1, 38.7, 48.4, 48.7, 49.3, 49.6, 67.3, 126.6, 127.0, 127.7, 127.9, 128.4, 128.8, 133.8, 134.0, 135.3, 136.6, 155.0, 155.7, 205.4, 206.2. IR (neat): 3031, 2952, 1698 cm^{-1}. MS (EI, *m*/*z*, %): 337 (5), 280 (67), 246 (37), 236 (90), 202 (17), 144 (20), 91 (100). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. found: C, 74.39; H, 7.15; N, 4.28.

(*R*,*S*) Benzyl 1-(2-methoxy-2-oxoethyl)-9-methyl-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate **5** ($n = 2$, R_1 = Me, R_2 = CO_2Me): ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.50–1.65 (m, 1H), 1.8–2.0 (m, 1H), 2.37 (s, 3H), 2.74–2.84 (m, 2H), 3.1–3.27 (m, 2H), 3.35–3.44 (m, 1H), 3.61 (s, 3H), 4.16 (dt, J = 14.6, 4.5 Hz, 1H), 5.07 (s, 2H), 6.10 (dd, J = 10.2, 5.6 Hz, 1H), 6.95–7.04 (m, 3H), 7.24–7.35 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.4, 19.8, 27.5, 28.3, 34.7, 34.8, 42.7, 42.8, 51.2, 52.0, 52.2, 66.3, 66.4, 127.0, 127.2, 127.3, 127.7, 128.2, 128.3, 128.6, 129.2, 129.3, 135.1, 135.7, 136.7, 136.8, 139.0, 140.6, 154.8, 155.1, 170.6. IR (neat) 3032, 2950.9, 2926.8, 2851.5, 1739.1, 1694.8 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{25}NO_4Na$ 390.16813; found 390.16652. (*R*,*S*) Benzyl 1-(2-*tert*-butoxy-2-oxoethyl)-9-methyl-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate **5** ($n = 2$, R_1 = Me, R_2 = CO_2t-Bu): ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.37 (s, 9H),1.54–1.68 (m, 1H), 1.87–1.97 (m, 1H), 2.38 (br s, 3H), 2.59–2.66 (m, 1H), 2.76–2.84 (m, 1H), 3.04–3.18 (m, 2H), 3.38–3.47 (m, 1H), 4.19 (dt, J = 14.6, 4.2 Hz, 1H), 5.06 (s, 2H), 6.08 (dd, J = 10.9, 5.3 Hz, 1H), 6.96–7.01 (m, 3H), 7.25–7.32 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.2, 19.7, 27.4, 28.3, 34.8, 34.9, 36.2, 36.4, 42.6, 52.5, 52.7, 66.2, 66.6, 80.0, 80.1, 126.9, 127.3, 127.5, 127.7, 128.2, 128.5, 129.1, 129.2, 135.0, 135.5, 136.5, 136.8, 138.9, 140.6, 140.7, 154.8, 155.1, 169.4. IR (neat) 2927, 2853, 1729, 1698 cm^{-1}. HRMS calcd for $C_{25}H_{31}NO_4$ 409.2253; found 409.2254.

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11. Methyl (2*E*)-3-[2-(2-{[(benzyloxy)carbonyl]amino}ethyl)-6-methylphenyl]acrylate **4** ($n = 1$, R_1 = Me, R_2 = CO_2Me): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.89 (t, J = 7.1 Hz, 2H), 3.38–3.45 (m, 2H), 3.84 (s, 3H), 4.73 (br s, 1H), 5.11 (s, 2H), 6.07 (d, J = 16.4 Hz, 1H), 7.07–7.22 (m, 3H), 7.3–7.4 (m, 5H), 7.86 (d, J = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 33.7, 41.5, 51.7, 66.6, 124.4, 127.4, 128.0, 128.4, 128.9, 134.3, 136.5, 136.9, 142.7, 156.1, 166.7. IR (neat): 3352.8, 2950.7, 1718.8, 1639.9, 1528.0 cm^{-1}. HRMS calcd for $C_{21}H_{23}NO_4$ 353.1627; found 353.1590.

12. Methyl (2*E*)-3-[2-(3-{[(benzyloxy)carbonyl]amino}propyl)-6-methylphenyl]acrylate **4** ($n = 2$, R_1 = Me, R_2 = CO_2Me): Mp 84–85 °C (hexane/AcOEt 9/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (quintet, J = 7.6 Hz, 2H) 2.34 (s, 3H), 2.67–2.73 (pseudo triplet, J = 7.8 Hz, 2H), 3.23 (br quartet, J = 6.5 Hz, 2H), 3.82 (s, 3H), 4.75 (br s, 1H), 5.12

(s, 2H), 6.07 (d, J = 16.4 Hz, 1H), 7.06–7.20 (m, 3H), 7.3–7.4 (m, 5H), 7.86 (d, J = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 30.8, 31.0, 40.6, 51.6, 66.6, 124.0, 127.0, 128.0, 128.3, 128.4, 128.5, 133.7, 136.4, 136.6, 139.8, 143.4, 156.3, 166.8. IR (Nujol) 3310, 1722, 1688, 1642 cm^{-1}. MS (EI, m/z, %) 367 (M^+, 10), 335 (12), 279 (25), 248 (20), 200 (25), 165 (30), 149 (20), 108 (60), 91 (100). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91 H, 6.86 N, 3.81. Found: C, 72.29; H, 7.10; N, 3.81.

13. *t*-Butyl (2*E*)-3-[2-(3-{[(benzyloxy)carbonyl]amino}propyl)-6-methylphenyl]acrylate **4** (n = 2, R_1 = Me, R_2 = CO_2t-Me): Mp 51 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.76 (quintet, J = 7.6 Hz, 2H), 2.32 (s, 3H), 2.65–2.70 (pseudo triplet, J = 7.6 Hz, 2H), 3.18–3.24 (br quartet, J = 6.6 Hz, 2H), 4.75 (br s, 1H), 5.10 (s, 2H), 5.95 (d, J = 16.3 Hz, 1H), 7.03–7.17 (m, 3H), 7.28–7.38 (m, 5H), 7.73 (d, J = 16.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 28.2, 30.8, 31.0, 40.7, 66.5, 80.7, 126.1, 126.9, 128.0, 128.1, 128.4, 133.9, 136.4, 136.6, 139.8, 141.9, 156.3, 165.8. IR (Nujol): 3361, 1699, 1685, 1632 cm^{-1}. MS (EI, m/z, %) 335 ($M^+ - t$-BuOH, 27), 200 (46), 91 (100), 57 (34). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.02; H, 7.71; N, 3.20.
14. Further dilution, prolonged reaction time as well as higher temperature (85 °C) did not improve conversion. No cyclisation occurred by treatment of **4** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1 equiv), while a complex mixture was obtained using NaH (1 equiv).
15. Brown, H. C.; Brady, J. D.; Bonner, W. H. *J. Am. Chem. Soc.* **1957**, *79*, 1897–1903.