Conjugate addition of 2-(bromomethyl)- and 2-(2-bromoethyl)-piperidine to alkyl acrylates: application towards the synthesis of 2-(methoxycarbonyl)indolizidine

Matthias D'hooghe, Kourosch Abbaspour Tehrani, Christophe Buyck, and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium
E-mail: norbert.dekimpe@UGent.be

Dedicated to Professor Benito Alcaide on the occasion of his 60th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.309

Abstract
Conjugate addition of 2-(bromomethyl)- and 2-(2-bromoethyl)piperidine hydrobromide to methyl and ethyl acrylate in the presence of triethylamine afforded the corresponding 3-[2-(bromomethyl)piperidin-1-yl]propanoates and 3-[2-(2-bromoethyl)piperidin-1-yl]propanoates for the first time. Furthermore, methyl 3-[2-(bromomethyl)piperidin-1-yl]propanoate was converted into the novel 2-(methoxycarbonyl)indolizidine upon treatment with lithium diisopropylamide in THF. The latter ester was easily reduced by means of lithium aluminium hydride in diethyl ether, affording 2-(hydroxymethyl)indolizidine in high yield.

Keywords: aza-Michael reaction, β-amino esters, piperidines, indolizidines

Introduction

[1]The conjugate addition of amines onto α,β-unsaturated carbonyl compounds, often referred to as the 'aza-Michael reaction', comprises an important methodology in organic synthesis towards the preparation of β-aminocarbonyl derivatives.[1] Furthermore, compounds containing the β-aminocarbonyl motif in their molecular framework are of importance as biologically relevant targets and as intermediates in the synthesis of β-amino ketones, β-amino acids, and β-lactam antibiotics,[2] hence the interest in their preparation. Whereas the 1,4-addition of a variety of

[1] Present address: Vrije Universiteit Brussel, Faculty of Sciences, Department of Applied Biological Sciences, Laboratory for Organic Chemistry, Pleinlaan 2 (WE-ORGC), B-1050 Brussels

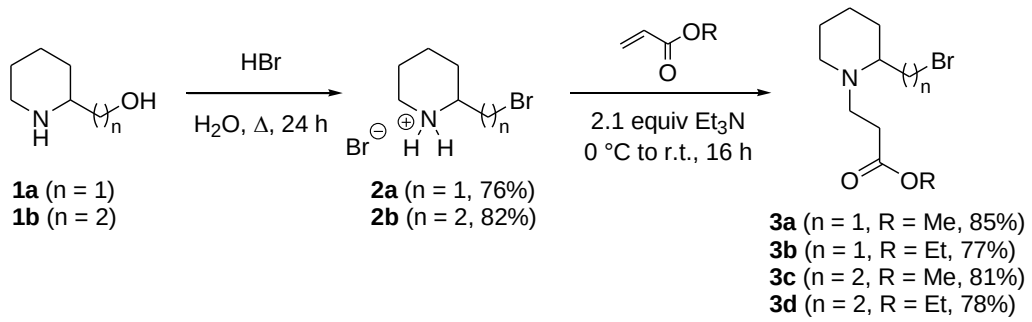
piperidine derivatives onto alkyl acrylates is known in the literature,[3] the aza-Michael reaction of 2-(ω-haloalkyl)piperidines has not been reported so far.

In the present paper, the conjugate addition of 2-(bromomethyl)- and 2-(2-bromoethyl)piperidines across methyl and ethyl acrylate is described. The applicability of the addition products is demonstrated by the synthesis of 2-(methoxycarbonyl)indolizidine for the first time, which was further reduced to 2-(hydroxymethyl)indolizidine.

In the past decades, a whole range of lipophilic skin alkaloids has been isolated from frogs from the Dendrobatidae, Mantellinae, Myobatrachidae and Bufonidae families.[4] Among others, pyrrolizidines, indolizidines and quinolizidines have been characterized. Besides from amphibian skin, interesting alkaloids were also isolated from plants[5] and from micro-organisms.[6] Many of these compounds have caught the attention of the medical world due to their potential biological activities,[7] which explains the interest in new methodologies towards these azaheterocyles.

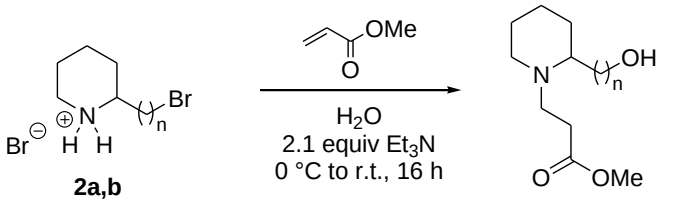
Results and Discussion

2-(Bromomethyl)- and 2-(2-bromoethyl)piperidine hydrobromide salts **2a,b** were prepared from the corresponding alcohols **1a,b** by treatment with hydrogen bromide in water (48%) upon reflux for 24 hours (Scheme 1), in accordance with a literature protocol.[8] Despite their inherent reactivity and synthetic potential, β-bromoamines **2a** and **2b** have only been studied to a limited extend up to now.[9] Subsequently, the conjugate addition of piperidines **2a,b** onto alkyl acrylates was investigated. At first, 2-(bromomethyl)piperidine hydrobromide (**2a**) was treated with 1.05 equiv of an acrylate (methyl, ethyl and *tert*-butyl acrylate) in dichloromethane in the presence of 1.05 equiv of triethylamine at room temperature for 16 hours,[3a] albeit without any success. In all cases, no reaction was observed and the starting compound was recovered. If, however, piperidine hydrobromides **2a,b** were suspended in methyl or ethyl acrylate, followed by the addition of 1.05 equiv of triethylamine at 0 °C, a stirring period of 16 hours at room temperature and then a second addition of 1.05 equiv of triethylamine, the corresponding novel 1-(2-alkoxycarbonylethyl)piperidines **3a-d** were isolated in good yields (Scheme 1).



Scheme 1

It should be noted that the latter addition products **3** are rather unstable in pure form, and thus should be stored in solution (e.g. in diethyl ether) or used immediately for further elaboration. Furthermore, the presence of water has to be avoided during the aza-Michael addition, as nucleophilic displacement of bromide by water takes place smoothly and results in the formation of 2-(hydroxymethyl)- and 2-(2-hydroxyethyl)piperidines **4**. The latter piperidine alcohols were also obtained as the major components upon attempted purification of 3-(piperidin-1-yl)propanoates **3** by means of column chromatography on silica gel. Indeed, if water is added deliberately for the reaction of piperidines **2a,b** with methyl acrylate (H_2O/methyl acrylate 1/1) following the same procedure as described above (i.e. 2.1 equiv Et_3N, 0 °C to r.t., 16 hours), methyl 3-[2-(hydroxymethyl)piperidin-1-yl]propanoate (**4a**) and methyl 3-[2-(2-hydroxyethyl)piperidin-1-yl]propanoate (**4b**) were obtained as the sole reaction products in good yields (Scheme 2).

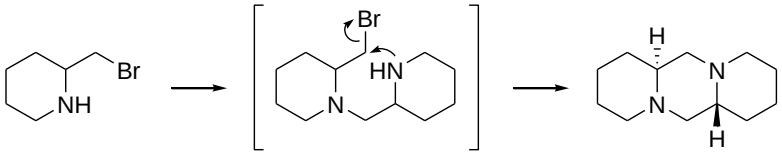


2a,b

4a (n = 1, 64%)
4b (n = 2, 67%)

Scheme 2

Based on detailed GC-analysis of the reaction mixtures obtained after treatment of piperidine hydrobromide **2a** with acrylates in the presence of triethylamine, the presence of a minor constituent was observed in very small quantities (< 5%). This side-product could be isolated in pure form by means of preparative gas chromatography, and was identified as 4a,8a-diazaperhydroanthracene (**6**).[10] The formation of the latter tricyclic compound can be rationalized considering the dimerization of 2-(bromomethyl)piperidine (**2a**) through double nucleophilic substitution via intermediate **5** (Scheme 3).



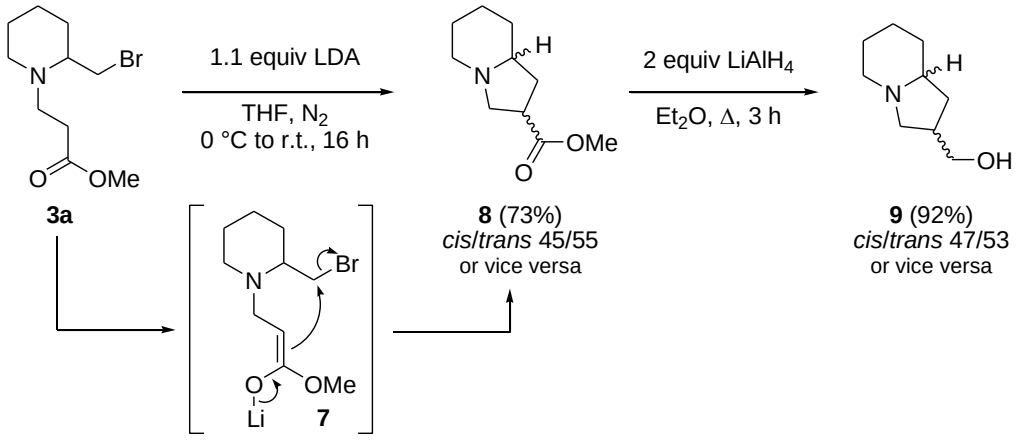
2a **5** **6** (< 5%)

Scheme 3

In the final part, the application of 3-(piperidin-1-yl)propanoates **3** for the construction of a bicyclic framework was investigated. For this purpose, the reaction of methyl 3-[2-

(bromomethyl)piperidin-1-yl]propanoate (**3a**) with lithium diisopropylamide (LDA) was evaluated with the intention to induce ring closure of the intermediate enolate **7**, formed by α-deprotonation by LDA, through nucleophilic displacement of bromide (Scheme 4). Thus, treatment of piperidine **3a** with 1.1 equiv of LDA in THF at 0 °C afforded 2-(methoxycarbonyl)indolizidine (**8**) for the first time after 16 hours at room temperature (Scheme 4). Based on GC-analysis, two diastereomers *cis*-**8** and *trans*-**8** were present in the reaction mixture in a ratio of 45/55 (*cis*/*trans* or *vice versa*). These isomers appeared to be inseparable by means of column chromatography (SiO_2) and preparative gas chromatography. Further derivatization of indolizidine ester **8** was performed using 2 equivalents of lithium aluminium hydride in diethyl ether, affording the corresponding 2-(hydroxymethyl)indolizidine (**9**)[11] in high yield through reduction of the ester moiety (Scheme 4). Again, an inseparable mixture of two diastereomers (47/53 *cis*/*trans* or *vice versa*) was obtained. Extensive efforts towards the separation of the diastereomeric mixture of heterocycles **8** and **9** failed.

The cyclization of 3-[2-(bromomethyl)piperidin-1-yl]propanoates towards the corresponding 2-(alkoxycarbonyl)indolizidines via α-deprotonation constitutes a new synthetic methodology for the construction of the 1-azabicyclo[4.3.0]nonane skeleton. In the light of the broad biological importance of indolizidine alkaloids, the preparation of 2-(methoxycarbonyl)indolizidine (**8**) and 2-(hydroxymethyl)indolizidine (**9**) might also be of relevance from a pharmaceutical point of view.



Scheme 4

In summary, the 'aza-Michael reaction' of 2-(bromomethyl)- and 2-(2-bromoethyl)piperidine hydrobromide onto methyl and ethyl acrylate in the presence of triethylamine was described for the first time, affording the corresponding 3-[2-(bromomethyl)piperidin-1-yl]propanoates and 3-[2-(2-bromoethyl)piperidin-1-yl]propanoates in good yields. Furthermore, methyl 3-[2-(bromomethyl)piperidin-1-yl]propanoate was converted into the novel 2-(methoxycarbonyl)indolizidine as a mixture of diastereomers upon treatment with lithium diisopropylamide in THF, representing a new synthetic approach towards the 1-

azabicyclo[4.3.0]nonane skeleton. Finally, 2-(methoxycarbonyl)indolizidine was easily reduced by means of lithium aluminium hydride in diethyl ether, affording 2-(hydroxymethyl)indolizidine in high yield.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer (VARIAN MAT 112, 70 eV) using a GC-MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). IR spectra were measured with a Perkin Elmer 1310 spectrophotometer or a Spectrum One FT-IR. Elemental analyses were performed with a PerkinElmer Series II CHNS/O Analyzer 2400. Dichloromethane was dried over calcium hydride, while diethyl ether and THF were dried by distillation over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

Synthesis of 3-[2-(bromomethyl)piperidin-1-yl]propanoates 3a,b and 3-[2-(2-bromoethyl)piperidin-1-yl]propanoates 3c,d. General procedure

To an ice-cooled suspension of dry piperidine hydrobromide **2** (5 mmol) in alkyl acrylate (5 mL) was added slowly triethylamine (5.25 mmol). The resulting mixture was stirred for 16 hours at room temperature, after which an additional amount of triethylamine (5.25 mmol) was added. After 10 minutes, the excess of alkyl acrylate and triethylamine was removed in vacuo, and the obtained paste was suspended in diethyl ether (10 mL). After a stirring period of 10 minutes at room temperature, the resulting mixture was filtered under nitrogen atmosphere and the solvent was removed in vacuo, affording alkyl 3-(piperidin-1-yl)propanoate **3**. Due to its lability, the crude alkyl 3-(piperidin-1-yl)propanoate **3** was used immediately as such for further elaboration or dissolved in dry diethyl ether for conservation at -18 °C. Because of the instability of propanoates **3**, no elemental analyses were performed.

Methyl 3-[2-(bromomethyl)piperidin-1-yl]propanoate (3a). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25-1.74 (6H, m); 2.24-2.37 (1H, m); 2.45-2.60 (3H, m); 2.75-2.88 (2H, m); 2.94-3.07 (1H, m); 3.45-3.55 (2H, m); 3.68 (3H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.5, 25.3, 29.6, 31.3, 34.8, 49.1, 50.9, 51.5, 59.8, 172.8. IR (NaCl): ν = 1730 cm^{-1} (C=O). MS (70 eV): m/z (%): 263/5 (1, M^+), 190/2 (14); 184 (12); 170 (100); 110 (15); 96 (61); 59 (10); 56 (10); 55 (26).

Ethyl 3-[2-(bromomethyl)piperidin-1-yl]propanoate (3b). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26 (3H, t, J = 7.2 Hz); 1.25-1.76 (6H, m); 2.26-2.38 (1H, m); 2.43-2.60 (3H, m); 2.75-2.89 (2H, m); 2.93-3.07 (1H, m); 3.45-3.58 (2H, m); 4.14 (2H, q, J = 7.2 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.8, 22.1, 24.9, 29.2, 30.9, 34.4, 48.7, 50.4, 59.2, 59.9, 172.1. IR (NaCl): ν = 1729 cm^{-1} (C=O). MS (70 eV): m/z (%): no M^+; 198 (23); 190/2 (13); 184 (100); 110 (62); 84 (18); 55 (23).

Methyl 3-[2-(2-bromoethyl)piperidin-1-yl]propanoate (3c). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.24-1.78 (6H, m); 1.88-2.05 (1H, m); 2.09-2.24 (1H, m); 2.26-2.36 (1H, m); 2.43-2.57 (3H, m); 2.68-2.87 (2H, m); 2.92-3.04 (1H, m); 3.33-3.57 (2H, m); 3.71 (3H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.5, 22.8, 28.9, 30.7, 31.8, 34.3, 48.6, 50.5, 51.5, 58.1, 173.1. IR (NaCl): ν = 1736 cm^{-1} (C=O). MS (70 eV): m/z (%): 277/9 (1, M^+); 204 (10); 171 (10); 170 (100); 92 (28); 55 (17).

Ethyl 3-[2-(2-bromoethyl)piperidin-1-yl]propanoate (3d). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.27 (3H, t, J = 6.8 Hz); 1.23-1.77 (6H, m); 1.88-2.03 (1H, m); 2.09-2.22 (1H, m); 2.23-2.35 (1H, m); 2.42-2.57 (3H, m); 2.68-2.88 (2H, m); 2.91-3.04 (1H, m); 3.33-3.57 (2H, m); 4.13 (2H, q, J = 6.8 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.8, 22.4, 24.1, 28.6, 30.3, 31.6, 33.9, 48.2, 50.2, 57.7, 59.9, 172.3. IR (NaCl): ν = 1734 cm^{-1} (C=O). MS (70 eV): m/z (%): 292/4 (100, M^++H).

Synthesis of 3-[2-(hydroxymethyl)piperidin-1-yl]propanoate (4a) and 3-[2-(2-hydroxyethyl)piperidin-1-yl]propanoate (4b). General procedure

To an ice-cooled suspension of piperidine hydrobromide **2** (5 mmol) in methyl acrylate (5 mL) and water (5 mL) was added slowly triethylamine (5.25 mmol). The resulting mixture was stirred for 16 hours at room temperature, after which an additional amount of triethylamine (5.25 mmol) was added. After 10 minutes, the excess of methyl acrylate and triethylamine was removed in vacuo, and the obtained paste was suspended in diethyl ether (10 mL). After a stirring period of 10 minutes at room temperature, the resulting mixture was filtered under nitrogen atmosphere and the solvent was removed in vacuo, affording methyl 3-(piperidin-1-yl)propanoate **4**.

Methyl 3-[2-(hydroxymethyl)piperidin-1-yl]propanoate (4a). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.20-1.76 (6H, m); 2.12-2.24 (1H, m); 2.26-2.38 (1H, m); 2.39-2.63 (3H, m); 2.75-3.27 (3H, m); 3.43 (1H, d×d, J = 11.5, 3.9 Hz); 3.69 (3H, s); 3.83 (1H, d×d, J = 11.5, 3.9 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 23.0, 25.3, 29.6, 30.8, 47.6, 50.9, 51.1, 60.9, 62.1, 172.9. IR (NaCl): ν = 3640-3080 cm^{-1} (OH), 1725 cm^{-1} (C=O). MS (70 eV): m/z (%): 202 (100, M^++H). Purity (NMR) > 95%. Anal. Calcd for $C_{10}H_{19}NO_3$: C 59.68, H 9.52, N 6.96. Found: C 59.81, H 9.77, N 6.85.

Methyl 3-[2-(2-hydroxyethyl)piperidin-1-yl]propanoate (4b). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.18-1.76 (6H, m); 1.78-1.94 (1H, m); 2.02-2.17 (1H, m); 2.22-2.37 (1H, m); 2.41-2.60 (3H, m); 2.69-2.89 (2H, m); 2.92-3.05 (1H, m); 3.48-3.65 (1H, m); 3.68 (3H, s); 3.74-3.85 (1H, m); 5.31 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.9, 24.6, 29.2, 31.7, 34.1, 48.6, 50.8, 51.6, 57.1, 60.8, 173.2. IR (NaCl): ν = 3425 cm^{-1} (OH), 1732 cm^{-1} (C=O). MS (70 eV): m/z (%): no M^+; 171 (9); 170 (100); 97 (10); 96 (33); 86 (10); 84 (28); 55 (13). Purity (NMR) > 95%. Anal. Calcd for $C_{11}H_{21}NO_3$: C 61.37, H 9.83, N 6.51. Found: C 61.47, H 10.02, N 6.66.

Synthesis of 2-(methoxycarbonyl)indolizidine (8). To an ice-cooled solution of diisopropylamine (5.5 mmol) in dry tetrahydrofuran (10 mL) under nitrogen atmosphere was added slowly *n*-butyllithium (2.2 mL, 2.5 M in hexane) via a syringe. After 10 minutes, a solution of methyl 3-[2-(bromomethyl)piperidin-1-yl]propanoate (**3a**) (5 mmol) in THF (4 mL) was added, after which the resulting mixture was stirred for 16 hours at room temperature. Afterwards, the reaction mixture was poured into water (20 mL) and extracted with diethyl ether

(3 × 15 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded 2-(methoxycarbonyl)indolizidine (**8**) in 73% yield as a mixture of diastereomers in a 45/55 ratio. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.13-2.19, 2.26-2.38, 2.45-2.59, 2.75-2.90 and 2.98-3.12 (2×14H, 5×m); 3.68 (2×3H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.2, 25.1, 25.3, 30.5, 30.8, 34.4, 34.7, 39.6, 51.7, 51.8, 52.7, 52.7, 56.7, 57.7, 63.6, 64.4, 175.6, 175.7. IR (NaCl): ν = 1740 cm^{-1} (C=O). MS (70 eV): m/z (%): 183 (48, M^+); 182 (81); 168 (97); 154 (28); 152 (39); 124 (66); 123 (10); 122 (28); 97 (100); 96 (55); 94 (20); 83 (29); 82 (23); 81 (14); 80 (17); 69 (44); 68 (51); 67 (14); 56 (11); 55 (39); 54 (15); 53 (12). Purity (NMR) > 95%. Anal. Calcd for $C_{11}H_{21}NO_3$: C 65.54, H 9.35, N 7.64. Found: C 65.37, H 9.63, N 7.49.

Synthesis of 2-(hydroxymethyl)indolizidine (9). To an ice-cooled solution of 2-(methoxycarbonyl)indolizidine (**8**) (2 mmol) in dry diethyl ether (5 mL) was added slowly $LiAlH_4$ (4 mmol). After heating 3 hours under reflux, water (0.5 mL) was added at 0 °C in order to neutralize the excess of $LiAlH_4$. The mixture was stirred for 10 minutes, after which the grey suspension was filtered over K_2CO_3 and celite. The filter cake was then washed thoroughly with dry ether (3 × 5 mL). After removal of the solvent in vacuo, 2-(hydroxymethyl)indolizidine (**9**)[11] was obtained in 92% yield as a mixture of diastereomers in a 47/53 ratio. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.15-2.13, 2.18-2.54 and 2.61-3.15 (2×14H, 3×m); 3.35-3.75 (2×2H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.4, 25.3, 25.4, 25.5, 30.8, 30.9, 34.4, 34.5, 36.8, 37.4, 52.9, 53.1, 58.1, 58.5, 63.4, 64.6, 65.5, 67.0. IR (NaCl): ν = 3380 cm^{-1} (OH).

Acknowledgements

The authors are indebted to the “Fund for Scientific Research - Flanders (Belgium)” (FWO-Vlaanderen) and to Ghent University (GOA) for financial support.

References

1. (a) Perlmutter, P. *Conjugate Addition Reactions*, in: *Organic Synthesis*, Pergamon, New York, **1992**, p. 114. (b) Ambhaikar, N. B.; Shyger, J. P.; Liotta, D. C. *J. Am. Chem. Soc.* **2003**, *125*, 3690. (c) Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2060. (d) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30. (e) Adrian, J. C.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143. (f) Xu, J.-M.; Wu, Q.; Zhang, Q.-Y.; Zhang, F.; Lin, X.-F. *Eur. J. Org. Chem.* **2007**, 1798. (g) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052. (h) Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975. (i) Enders, D.; Muller, S. F.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 879. (j) Varala, R.; Alam, M. M.; Adapa, S. R.; *Synlett* **2003**, 720. (k) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891. (l) Azizi, N.;

Saidi, M. R. *Tetrahedron* **2004**, *60*, 383. (m) Surendra, K.; Krishnaveni, N. S.; Sridhar, R.; Rao, K. R. *Tetrahedron Lett.* **2006**, *47*, 2125. (n) Kumar, R.; Chaudhary, P.; Nimesh, S.; Chandra, R. *Green Chem.* **2006**, *8*, 356. (o) Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045. (p) Kantam, M. L.; Neeraja, V.; Kavita, B.; Neelima, B.; Chaudhuri, M. K.; Hussain, S. *Adv. Synth. Catal.* **2005**, *347*, 763. (q) Yadav, J. S.; Reddy, A. R.; Rao, Y. G.; Narsaiah, A. V.; Reddy, B. V. S. *Synthesis* **2007**, 3447. (r) Hayashi, Y.; Rode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502. (s) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328.

2. (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (b) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramirez de Arellano, M. C.; Fuentes, A. S. *J. Org. Chem.* **2002**, *67*, 4667. (c) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983. (d) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (e) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181.
3. For a few recent examples, see: (a) Le Sann, C.; Huddleston, J.; Mann, J. *Tetrahedron* **2007**, *63*, 12903. (b) Khan, A. T.; Parvin, T.; Gazi, S.; Choudhury, L. H. *Tetrahedron Lett.* **2007**, *48*, 3805. (c) Das, B.; Chowdhury, N. *J. Mol. Catal. A* **2007**, *263*, 212. (d) Hussain, S.; Bharadwaj, S. K.; Chaudhuri, M. K.; Kalita, H. *Eur. J. Org. Chem.* **2007**, 374.
4. (a) Daly, J. W.; Spande, T. F. in *Alkaloids: Chemical and biological perspectives*, Ed. S. W. Pelletier, John Wiley and Sons, New York, **1986**, Vol 4, Chapter 1, pp 1-274. (b) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016. (c) Garraffo, H. M.; Spande, T. F.; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat. Prod.* **1993**, *56*, 357.
5. Rolf, S.; Haverkamp, W.; Borggrefe, M.; Musshoff, U.; Eckhardt, L. Mergenthaler, J.; Snyders, D. J.; Pongs, O.; Speckmann, E.-J., Breithardt, G., Madeja, M. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *362*, 22.
6. He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067.
7. (a) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162. (b) Francke, W.; Schröder, F.; Walter, F. Sinnwell, V.; Baumann, H.; Kaib, M. *Liebigs Ann. Chem.* **1995**, 965. (c) Ritter, F. J.; Rotgans, I.; Talman, E.; Verwiel, P.; Stein, F. *Experientia* **1973**, *29*, 530. (d) Brooke, P.; Harris, D. J.; Longmore, R. B. *J. Agric. Food Chem.* **1996**, *44*, 2129.
8. Schwenkkraus, P.; Otto, H. H. *Arch. Pharm.* **1990**, *323*, 93.
9. (a) Piper, J. R.; Johnston, T. P. *J. Org. Chem.* **1963**, *28*, 981. (b) Wieczorek, J. S.; Plazek, E. *Rec. Trav. Chim. Pays-Bas* **1965**, *84*, 785. (c) Kasuga, S.; Taguchi, T. Chem. *Pharm. Bull.* **1965**, *13*, 233. (d) Searles, S. Jr.; Roelofs, G. E.; Tamres, M.; McDonald, R. N. *J. Org. Chem.* **1965**, *30*, 3443. (e) Taguchi, T.; Kasuga, S. *Chem. Pharm. Bull.* **1965**, *13*, 241. (f) Crabb, T. A.; Newton, R. F. *J. Heterocycl. Chem.* **1969**, *6*, 301. (g) Bromidge, S. M.; Clarke, S. E.; King, F. D.; Lovell, P. J.; Newman, H.; Riley, G.; Routledge, C.; Serafinowska, H. T.; Smith, D. R.; Thomas, D. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1357. (h) Nelson, N. A.;

Tamura, Y. *Can. J. Chem.* **1965**, *43*, 1321. (i) Kourounakis, P. *Pharm.* **1978**, *33*, 655. (j) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. *J. Org. Chem.* **2005**, *70*, 4248.
10. Chastanet, J.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 2910.
11. (a) Buchta, E.; Bayer, W. *Naturwissenschaften* **1959**, *46*, 14. (b) Winterfeld, K.; Küllmar, K. *Arch. Pharm.* **1958**, *291*, 485.