Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1159–1161

A concise synthetic pathway towards 5-substituted indolizidines

Tamás R. Varga,* Péter Nemes, Zoltán Mucsi and Pál Scheiber

Department of Chemistry, Faculty of Veterinary Science, Szent István University, H-1400 Budapest, PO Box 2, Hungary

Received 20 October 2006; revised 5 December 2006; accepted 13 December 2006
Available online 8 January 2007

Abstract—The total synthesis of 5-(2′-hydroxyethyl)indolizidine via 5-thioindolizidinone is described. The key step is the transformation of 5-thioindolizidinone via Eschenmoser's sulfide contraction. The racemic mixture of 5*R*,9*R*- and 5*S*,9*S*-5-(2′-hydroxyethyl)indolizidine was obtained in seven steps in 17% overall yield from 2-allyl cyclopentanone.

1-Azabicyclo[4.3.0]nonane (indolizidine) represents the core of a number of natural products, isolated from both plant and animal sources.[1] A recent review reports more than eight hundred compounds of this type that have been detected in the skin of neotropical poison frogs (family *Dendrobatidae*).[2] Due to their extremely low abundance and strong biological activity, including neuromodulation, enzyme inhibition and antitumor, immunoregulatory and antiviral activity, the simple frog alkylindolizidines are especially attractive targets.[3,4]

We have developed a novel, efficient and concise synthetic strategy to prepare 5-substituted indolizidines of a natural origin (e.g., 167B toxin) or new synthetic products with diverse functionalities on the C-5 side chain (**7**–**11**).

The synthesis of the key intermediate **5** started from cyclopentanone (**1**) (Scheme 1). Stork's enamine protocol[5] was employed to prepare 2-allylcyclopentanone (**2**), which was then converted to 2-(3′-bromopropyl)cyclopentanone (**3a**) via radical, anti-Markovnikov addition of gaseous HBr.[6,7] After bromide–azide exchange, 2-(3′-azidopropyl)cyclopentanone (**3b**) gave 5-indolizidinone **4** via a Schmidt-reaction.[8] Using Lawesson's reagent,[9] lactam **4** was transformed into novel 5-thioindolizidinone **5** in an excellent yield.[10] To attach C-5 side chain **5** was reacted with bromoacetone via Eschenmoser's sulfide contraction sequence.[11] However, the resulting enamino ketone **6** proved unstable. Therefore, it was treated with perchloric acid (*Caution*!) to yield the stable iminium salt **7**, which was subjected to Clemmensen reduction.[12] After chromatographic separation, the products were identified from their mass spectra. The major components were the deoxygenated iminium hydroxide base and the saturated aminoketone, while (±) 5-*n*-propylindolizidine (**8**) was formed in a low yield (10%). The attempted reduction of tosylhydrazone of **6** or **7** with $Na[BH_3CN]$ proved unsuccessful.[13]

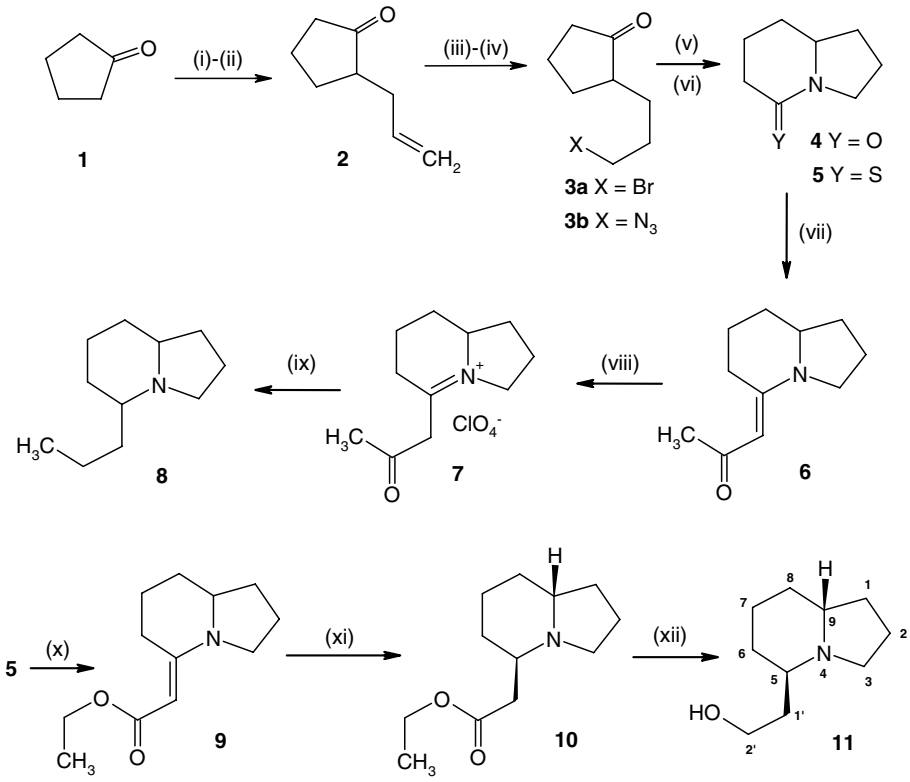
The more stable enamino ester **9** was prepared from **5** with ethyl bromoacetate in a moderate yield. The *E* and *Z* isomers of **9** were characterized by NMR, and isomer *E*:*Z* ratio was found to be 1:3.[14] The catalytic hydrogenation of **9** resulted in β-amino acid ester **10**, quantitatively,[15] which was further reduced smoothly with $LiAlH_4$ to the desired β-amino alcohol **11**.[16]

The ^1H and ^{13}C NMR spectra revealed that hydrogenation of **9** took place with a high diastereoselectivity. The strong Bohlmann bands at 2790 and 2710 cm^{-1} in the infrared spectrum and the absence of an interaction between 5-H/9-H in the selective 1D- and 2D-NOSEY of **10** indicated the axial position of the 2′-hydroxyethyl group on C-5 and consequently 5*R*,9*R*- and 5*S*,9*S*-configurations. A second series of signals in the ^1H NMR spectrum of **10** was assigned to the minor diastereomer, whose yield was 2.3%, as determined by GC–MS.

The overall yield for **11** starting from **2** (seven steps) is 17%. Amino alcohol **11** can also be transformed to **8** from the tosylate of **11** with $(CH_3)_2LiCu$, according to the published procedure.[17]

Keywords: Eschenmoser's sulfide contraction; 5-Thioindolizidinone; 5-Substituted indolizidines; 2-Allyl cyclopentanone.
* Corresponding author. Tel.: +36 1 478 4176; fax: +36 1 478 4268; e-mail: varga.tamas.robert@aotk.szie.hu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.074



Scheme 1. Reagents, conditions and yields: (i) morpholine, cat. HCO_2H, toluene, reflux, 4 h, 50%; (ii) $H_2C{=}CHCH_2Br$, CH_3CN, reflux, 18 h, H_2O, reflux, 1 h, 29%; (iii) HBr gas, cat. $(PhCO)_2O_2$, *n*-pentane, rt, 1 h; (iv) NaN_3, DMF, 35 °C, 48 h; (v) TFA, rt, 1 h, 36% for (iii)–(v); (vi) Lawesson's reagent, THF, rt, 0.5 h, 95%; (vii) $BrCH_2COCH_3$, CH_3CN, rt, 18 h, Ph_3P, *i*-Pr_2NEt, rt, 18 h, 43%; (viii) $HClO_4$ aq, *i*-PrOH/CH_2Cl_2, rt, 5 h, 46%; (ix) Zn(Hg), HCl aq, reflux, 18 h, 10%; (x) $BrCH_2CO_2C_2H_5$, CH_3CN, rt, 18 h, Ph_3P, *i*-Pr_2NEt, CH_3CN, rt, 18 h, 55%; (xi) H_2, 1 MPa, cat. PtO_2, EtOH, rt, 3 h, quant.; (xii) $LiAlH_4$, Et_2O, rt, 0.5 h, 90%.

In conclusion, we have achieved a simple diastereoselective synthesis of 5-substituted indolizidines. The transformations of esters **9** and **10** provide an opportunity to prepare further new derivatives.

Acknowledgements

The research Grant NKB/2006 from Szent István University is greatly acknowledged. The authors are indebted to Ms. Sarolta Gaál for her technical help in the synthesis.

References and notes

1. Gilchrist, T. L. *Heterocyclic Chemistry*; Addison Wesley Longman: UK, 1997; pp 193–207.
2. Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.
3. Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Eur. J. Org. Chem.* **2005**, 505–511.
4. Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, 398–404.
5. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovic, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, 207–222.
6. House, O. H.; Chu, C.; Phillips, W. V.; Sayer, T. S. B.; Yau, C. *J. Org. Chem.* **1977**, *42*, 1709–1717.
7. Crandall, J. K.; Magaha, H. S.; Henderson, M. A.; Widener, R. K.; Tharp, G. A. *J. Org. Chem.* **1982**, *47*, 5372–5380.
8. Aube, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966.
9. Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S. O. *Tetrahedron* **1984**, *40*, 2047–2052.
10. Data for **5**: white crystals; mp 55–56 °C; ν_{max}/cm^{-1} 2938 (C–H), 1520 (C–N), 1109 (C=S); δ_H (250 MHz, $CDCl_3$; Me_4Si) 3.85 (2H, m, 3-H_2), 3.34 (1H, m, 9-H), 2.85 (2H, m, 6-H_2), 1.20–2.25 (8H, br, 1-H_2, 2-H_2, 7-H_2, 8-H_2); δ_C (63 MHz, $CDCl_3$; Me_4Si) 196.12 (C-5), 62.43 (C-9), 53.23 (C-3), 40.38 (C-8), 33.66 (C-6), 29.59 (C-1), 21.92 (C-7), 21.06 (C-2).
11. Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710–734.
12. The preparation of solid **6**·HCl and **6**·HBr failed due to the low basicity of **6**. Organic perchlorates are explosives, therefore one should handle them with great care! Data for **7**: pale yellow crystals; δ_H (400 MHz, CD_3NO_2; Me_4Si) 1.95 (2H, s, CH_2CO), 1.91 (1H, m, 3a-H), 1.70–1.78 (2H, m, 3b-H, 1-H), 0.77 (1H, m, 6a-H), 0.66 (1H, m, 6b-H), 0.22–0.33 (2H, m, 7a-H, 2a-H), 0.16 (3H, s, CH_3), −0.38 to 0.05 (5H, m, 2-H_2, 8-H_2, 2b-H), −0.62 (1H, m, 7b-H); δ_C (100 MHz, CD_3NO_2; Me_4Si) 201.58 (CO), 183.75 (C-5), 66.90 (C-9), 54.87 (C-3), 51.08 (*C*H_2CO), 34.16 (C-6), 32.08 (C-2), 30.63 (CH_3), 26.69 (C-7), 22.31 (C-1), 18.45 (C-8).
13. Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662–3668.
14. Data for **9**: pale yellow oil; *m*/*z* (ESI, HPLC–MS) 210.2 (8.9×10^5, $M+H^+$).
δ_H (400 MHz, $CDCl_3$; Me_4Si) for the *Z*-isomer (minor) 4.37 (1H, br, C=$CHCO_2Et$), 4.17 (2H, q, $J_1 = 7.5$ Hz, CO_2CH_2), 3.20 (3H, m, 3-H_2, 9-H), 2.87 (2H, tt, $J_1 = 3.2$ Hz, $J_2 = 14.8$ Hz, 6-H_2), 1.22 (3H, t, $J_1 =$

7.5 Hz, CH_3), 1.20–1.90 (8H, br m, 1-H_2, 2-H_2, 7-H_2, 8-H_2); δ_C (100 MHz, $CDCl_3$; Me_4Si) 169.70 (CO), 160.52 (C-5), 81.15 (C=*C*HCO$_2$Et), 61.60 (CO_2CH_2), 58.84 (C-9), 47.67 (C-3), 33.59 (C-8), 29.60 (C-1), 25.89 (C-6), 22.47 (C-7), 19.96 (C-2), 14.06 (CH_3); δ_H (400 MHz, $CDCl_3$; Me_4Si) for the *E*-isomer (major) 4.37 (1H, br, C=CHCO$_2$Et), 4.05 (2H, q, $J_1 = 7.5$ Hz, CO_2CH_2), 3.21 (2H, m, 6-H_2), 3.20 (3H, m, 3-H_2, 9-H), 1.22 (3H, t, $J_1 = 7.5$ Hz, CH_3), 1.20–1.90 (8H, br m, 1-H_2, 2-H_2, 7-H_2, 8-H_2); δ_C (100 MHz, $CDCl_3$; Me_4Si) 168.82 (CO), 160.52 (C-5), 81.15 (C=*C*HCO$_2$Et), 57.88 (CO_2CH_2), 58.84 (C-9), 47.67 (C-3), 33.12 (C-8), 29.60 (C-1), 25.89 (C-6), 22.47 (C-7), 19.96 (C-2), 14.71 (CH_3).

15. Data for **10**: pale yellow oil; *m*/*z* (ESI, HPLC–MS) 212.3 (9.7×10^6, M+H$^+$). δ_H (400 MHz, C_6D_6; Me_4Si) 4.08 (2H, q, $J_1 = 7.1$ Hz, CO_2CH_2), 3.19 (1H, dt, $J_1 = 1.6$ Hz, $J_2 = 8.4$ Hz, 3a-H), 2.71 (1H, dd, $J_1 = 5.0$ Hz, $J_2 = 12.3$ Hz, CH_2CO_2Et), 2.60 (1H, m, 5-H), 2.39 (1H, dd, $J_1 = 7.4$ Hz, $J_2 = 14.4$ Hz, CH_2CO_2Et), 2.01 (1H, q, $J_1 = 8.5$ Hz, 3b-H), 1.83 (1H, m, 9-H), 1.68 (4H, br m, 1a-H, 2a-H, 6-H_2), 1.47 (4H, br m, 1b-H, 2b-H, 7a-H, 8a-H), 1.26 (2H, br m, 7b-H, 8b-H); 1.23 (3H, t, $J_1 = 7.1$ Hz, CH_3); δ_C (100 MHz, $CDCl_3$; Me_4Si) 169.51 (CO), 64.19 (C-9), 59.76 (CO_2CH_2), 59.53 (C-5), 51.10 (C-3), 40.60 (CH_2CO_2Et), 31.75 (C-6), 30.66 (C-8), 30.55 (C-1), 24.41 (C-7), 20.40 (C-2), 13.79 (CH_3).

16. Data for **11**: colourless oil; *m*/*z* (ESI, HPLC–MS) 170.4 (5.4×10^5, M+H$^+$).
δ_H (400 MHz, $CDCl_3$; Me_4Si) 3.96 (1H, s, OH), 3.69 (2H, dd, $J_1 = 6.8$ Hz, $J_2 = 7.4$ Hz, CH_2OH), 3.49 (1H, dt, $J_1 = 7.2$ Hz, $J_2 = 5.4$ Hz, 3a-H), 2.53 (1H, m, 5-H), 2.25 (1H, q, $J_1 = 5.6$ Hz, 3b-H,), 2.12 (1H, m, 9-H), 1.20–2.20 (12H, br m, 1-H_2, 2-H_2, 6-H_2, 7-H_2, 8-H_2, CH_2CH$_2$OH); δ_C (100 MHz, $CDCl_3$; Me_4Si) 65.65 (C-9), 61.52 (C-5), 59.41 (CH_2OH), 50.93 (C-3), 34.12 (CH_2CH_2OH), 29.86 (C-6), 29.45 (C-8), 28.51 (C-1), 23.96 (C-7), 19.86 (C-2).

17. Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445–1446.