Pergamon

Tetrahedron Letters 39 (1998) 5189–5192

TETRAHEDRON LETTERS

A New Diastereoselective Route to 5-Substituted-8-methylindolizidines. Synthesis of Indolizidine (-) 209B.

Anita Bardou, Jean-Pierre Célérier, and Gérard Lhommet*

Université Pierre et Marie Curie, Laboratoire de Chimie des Hétérocycles, associé au CNRS.

4 Place Jussieu, 75252 Paris cedex 05, France

Received 8 April 1998; accepted 16 May 1998

Abstract : The highly diastereoselective synthesis of the indolizidine alkaloid (-) **209B** is described via the diastereoselective alkylation of a chiral cyclic β-amino ester prepared from (*R*)-methylbenzylamine.

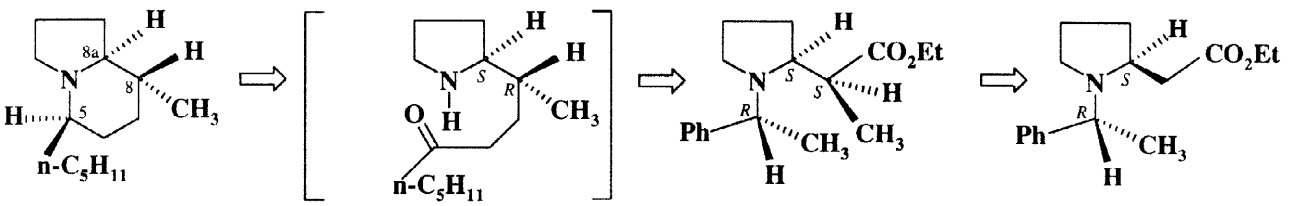
Poison-frogs of the Dendrobatidae family have been a source of numerous alkaloids which present significant biological activity as non-competitive blockers of neuromuscular transmission[1]. Among the bicyclic skeletons, 5-substituted-8-methylindolizidines occur in many alkaloids of this class and substituent is often an alkyl or an alkenyl chain[2]. Six natural compounds of this class have been recently isolated in sufficient quantities to permit their structural elucidation and the determination of their rotation. The indolizidine **209B** has been the most frequently synthesized alkaloid of these series and several diastereoselective or asymmetric syntheses have been reported in the literature[3,4]. As a part of an investigation into the reactivity of chiral cyclic β-enamino esters, we have been engaged in the synthesis of 5,8-disubstituted indolizidines.

Fax : 33 (0)1 44 27 30 56, e-mail : lhommet@ccr.jussieu.fr

0040-4039/98/$19.00
PII: S0040-4039(98)01040-5

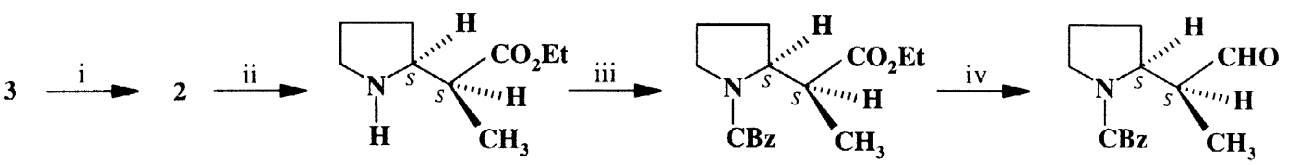
In this paper, we present a new, versatile and highly diastereoselective preparation of (-)-(5*R* ,8*R* ,8a*S*)-8-methyl-5-pentyloctahydroindolizine **1** based on the easy and efficient access to cyclic tetrasubstituted β-amino esters by diastereocontroled alkylation.

In fact, the formation of the third asymmetric center from a δ-amino ketone intermediate is known to be diastereoselective and to lead to the indolizidinic skeleton in which hydrogens H_5 and H_{8a} present a *cis* relative stereochemistry[5]. The key step of this strategy depends, as shown in the retrosynthetic pathway, on the formation of the second stereogenic center during the alkylation of the trisubstituted β-amino ester **3**.



1 **2** **3**

We have previously shown that trisubstituted β-amino esters are diastereoselectively alkylated by halides under kinetic conditions. In fact, condensation of methyl iodide with the lithium enolate of **3** leads to the desired intermediate **2** with a diastereomeric excess up to 98%[6]. Thus, the (*S*,*S*) diastereomer **2** was prepared in five steps from (*R*)-α-methylbenzylamine in 33% overall yield[6,7].

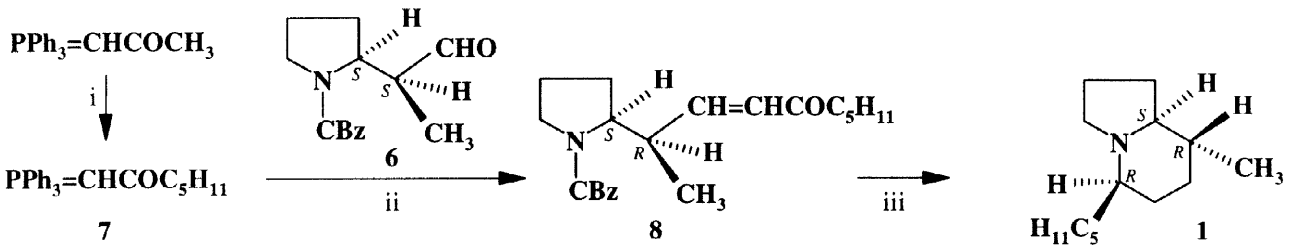


4 **5** **6**

Reaction conditions : i) 1°) LDA, THF, -70 °C, 2°) ICH_3, -70 °C; ii) H_2, Pd/C, EtOH; iii) $ClCO_2CH_2Ph$, K_2CO_3, $CHCl_3$; iv) DIBAH, toluene, -78 °C.

We failed to transform the ester **2** into aldehyde neither by direct reduction nor *via* oxidation of the corresponding alcohol. This could be explained by the presence of the ethylphenyl substituent, which enhances the nitrogen nucleophilic properties. Replacement of the chiral appendage by an protective group permitted to continue the synthesis.

Hydrogenolysis of **2** was achieved with 10% Pd/C to lead to the secondary amine **4** in a good yield (93%). Carbamoylation of **4** afforded the *N*-protected β-amino ester **5** in 74% yield. Finally, the aldehyde **6** could be easily prepared by DIBAH reduction of **5** in 71% yield.



Reaction conditions : i) 1°) BuLi, THF, -78 °C, 2°) C_4H_9I, -78 °C to 0 °C; ii) toluene, 80 °C; iii) H_2, PtO_2, MeOH, 50 °C.

Introduction of the pentyl substituent was realized by a Wittig condensation of **6** with the stabilized ylid **7**, prepared in one step from 1-triphenylphosphoranylidene-2-propanone in 70% yield[8]. Amino enone **8** was then obtained as a mixture of *E/Z* isomers (80/20) in 90% yield.

Hydrogenation of the alkene, nitrogen deprotection, cyclization and finally diastereoselective reduction of the iminium intermediate (de = 90%) were achieved in one step in presence of hydrogen and platinum oxide at 50 °C. After separation, the enantiopure indolizidine (-) **209B** was isolated in 56% yield.

In conclusion, we report herein a highly diastereoselective synthesis of natural indolizidine **209B** in 10 steps and in a 8% overall yield from (*R*)-methylbenzylamine. This new and original strategy is sufficiently versatile to permit its generalization to the synthesis of all natural 5,8-dialkylindolizidines.

References

1. a) Daly, J.W.; Spande, T.F. In *Alkaloids; Chemical and Biological Perspectives*; Pelletier, S.W.; Ed.; Wiley-Interscience: New York, **1986**; Vol. 4, Chapter 1. b) Daly, J.W.; Myers, C.W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023-1095. c) Tokuyama, T.; Tsujita, T.; Shimada, A.; Garrafo, H.M.; Spande, T.F.; Daly, J.W. *Tetrahedron* **1991**, *47*, 5401-5414. d) Daly, J.W.; Nishizawa, Y.; Padgett, W.L.; Tokuyama, T.; Smith, A.L.; Holmes, A.B.; Kibayashi, C.; Aronstam, R.S. *Neurochem. Res.* **1991**, *16*, 1213-1218.

2. Daly, J.W.; Garrafo, H.M.; Spande, T.F. In The Alkaloids, Cordell, G.A., Ed.; Academic Press: New York, **1993**; Vol. 43, pp 185-288.

3. For the syntheses of racemic **209B**, See a) Comins, D.L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889-5892. b) Michael, J.P.; Gravestock, D. *Synlett* **1996**, *10*, 981-982.

4. For enantioselective syntheses of indolizidine **209B**, see a) Holmes, A.B.; Smith, A.L.; Williams, S.F.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393-1405. b) Gnecco, D.; Marazano, C.; Das, B.C. *J. Chem. Soc., Chem. Commun.* **1991**, 625-626. c) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876-2883. d) Satake, A.; Shimizu, I. *Tetrahedron : Asymmetry* **1993**, *4*, 1405-1408. e) Aubé, J.; Rafferty, P.S.; Milligan, G.L. *Heterocycles* **1993**, *35*, 1141-1147. f) Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943-945. g) Åhman, H.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747-9756. h) Michael, J.P.; Gravestock, D. *Pure Appl. Chem.* **1997**, *69*, 583-588.

5. a) Saliou, C.; Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *32*, 3365-3368. b) Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron : Asymmetry* **1992**, *3*, 695-696. c) Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron : Asymmetry* **1993**, *4*, 1429-1430.

6. Bardou, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1997**, *38*, 8507-8510.

7. Nikiforov, T.; Stanchev, S.; Milenkov, B.; Dimitrov, V. *Heterocycles*, **1986**, *24*, 1825-1829.

8. Cooke Jr., M.P. *J. Org. Chem.* **1973**, *38*, 4082-4084.

9. Satisfactory analytical and spectral data were obtained for (-)-(5*R*, 8*R*, 8a*S*)-8-methyl-5-pentyl octahydroindolizine **1**. $[\alpha]^{20}_{D}$ -95 (c=0.585, MeOH); lit [4a]: $[\alpha]^{20}_{D}$ -94 (c=1.85, MeOH). *Anal.* Calcd. for $C_{14}H_{27}N$: C, 80.31; H, 12.99; N, 6.69. Found: C, 80.26; H, 12.99; N, 6.54. IR (neat) ν (cm^{-1})= 2960; 2920; 2860; 2770; 1455; 1375; 1165; 1135. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm)= 0.86 (d, 3H, J= 6.5Hz); 0.88 (t, 3H, J= 6.5Hz); 0.90-1.00 (m, 1H); 1.18-1.52 (m, 11H); 1.58-1.68 (m, 2H); 1.70-1.80 (m, 3H); 1.80-1.87 (m, 1H); 1.87-2.00 (m, 2H); 3.25 (td, 1H, J= 8.8Hz, 1.8Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)=14.1, 19.0, 20.5, 22.7, 25.6, 29.2, 31.4, 32.4, 33.8, 34.7, 36.7, 52.0, 63.7, 71.5.