Tetrahedron Letters, Vol. 34, No. 19, pp. 3119-3122, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Enantiospecific Syntheses of Indolizidines 167B and 209D

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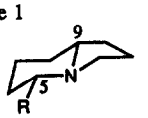
Key words: β-Amino acid, pyrrole, rhodium acetate, catalytic hydrogenation

Abstract: Indolizidine 209D (2) was synthesized in 11 steps from L-aspartic acid (3) in an overall yield of 16%. 3R-pyrrolylnonanoic acid, prepared from 3, was converted into the α-keto diazomethyl derivative, which on $Rh_2(OAc)_4$ catalyzed cyclization and catalytic hydrogenation gave 2. A similar procedure, starting from 3, afforded 3R-pyrrolylhexanoic acid, an intermediate which had previously been converted in 3 steps to indolizidine 167B.

The indolizidine alkaloids, the so-called gephyrotoxins, are constituents of the skin secretions of certain neotropical frogs whose habitat is Central and nearby South America.[1] These exotic substances have attracted attention on account of the ability of some of them to block neuromuscular transmission.[2] Unfortunately, most are obtainable in only infinitesimally small amounts. Indolizidines 167B and 209D (**1** and **2**) are typical (Scheme 1). They were isolated on only one occasion from unidentified dendrobatid frogs found in a single population on the Isla de Colòn, Panamà.[3] Their structures were based on mass spectral evidence whereas their absolute configurations were simply inferred as 5R,9R. Consequently, syntheses have been undertaken to prepare **1** and **2** in greater quantities for further investigation.[4] Three approaches to enantiomerically pure **1** and **2** have been reported. The first relied on the use of a non-recoverable chiral auxiliary.[5] The second exploited the innate chirality of D-norvaline to control the formation of the indolizidine skeleton.[6] The third method also used an α-amino acid, but one already possessing the future pyrrolidine moiety, namely S-pyroglutamic acid.[7] We now describe how homochiral β-amino acids can be conveniently prepared as precursors and wholly fashioned into the indolizidine structure to give **1** and **2** in a practical manner.

Scheme 1

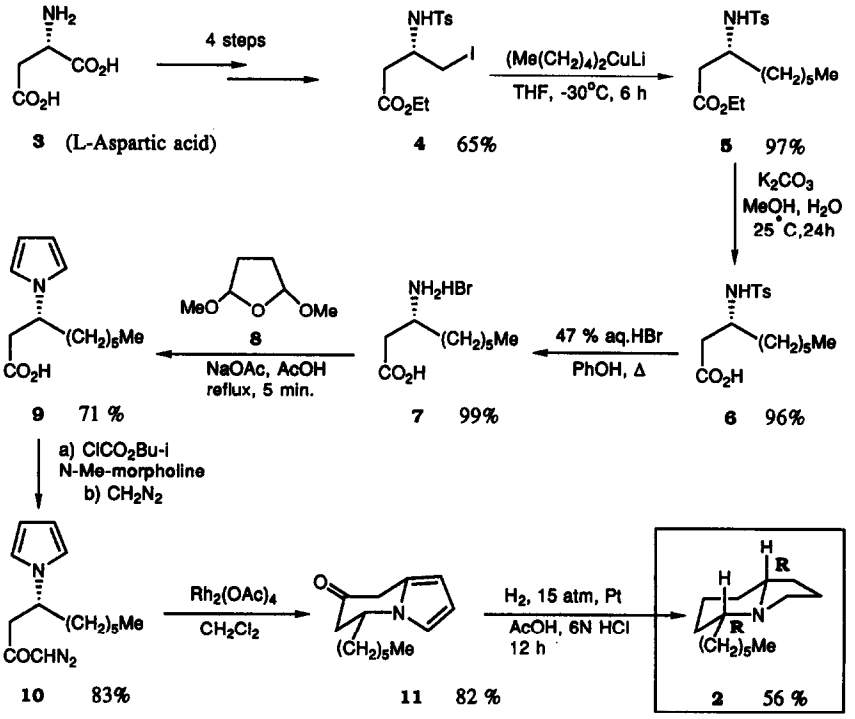


1 R = Pr
2 R = $(CH_2)_5Me$

L-Aspartic acid (**3**) was converted in 4 steps into the key intermediate,[8] the iodo-ester **4** (Scheme 2). Next, treatment of **4** with lithium dipentylcuprate in THF gave the 3-(N-tosylamino)nonanoate ester **5** in 97% yield. Saponification of **5** with base afforded the 3R-(N-tosylamino)-β-amino acid **6** which was further deprotected by heating with 47% aqueous hydrobromic acid and phenol under reflux. The resulting β-amino acid hydrobromide **7** was then treated directly with 2,5-dimethoxytetrahydrofuran (**8**) for 5 minutes in the presence of sodium acetate. The amino acid was transformed into the corresponding pyrrole analogue **9** in 71% yield.[9] The free acid **9** was then derivatized as the mixed carbonate by reaction with *i*-butyl chloroformate and N-methylmorpholine. Quenching with an excess of diazomethane furnished the critical α-diazoketone **10** in 83% yield. Cyclization was smoothly effected in 82% yield by catalysis with $Rh_2(OAc)_4$ at 20°C.[10]

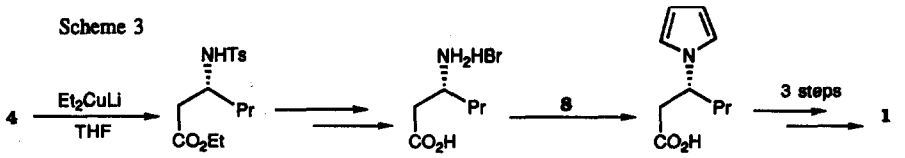
Submission of the resulting bicyclic keto pyrrole **11** to hydrogenation in strong acid medium over Adams catalyst occurred with concomitant reduction of the keto and pyrrole functions. Neutralization with sodium carbonate afforded analytically pure indolizidine 209D (**2**) in 56% yield. It was spectroscopically identical and optically similar to the previously prepared sample.[11] Clearly, hydrogenation of the pyrrole ring in **11** had occurred stereospecifically thanks to the vested chirality at the C5 position to give **2** having the 5R,9R configuration. The complete reduction of the non-conjugated carbonyl group is unusual and may have occurred by a Clemmensen-type deoxygenation.[6,12]

Scheme 2



Indolizidine 167B (**1**) was formally prepared by following the same synthetic sequence (Scheme 3). The iodo-ester **4** was treated with lithium diethylcuprate to give ethyl 3-(N-tosylamino)hexanoate (**12**) in 76% yield. Hydrolysis and deprotection to the β-amino acid hydrobromide **13**, and derivatization with 2,5-methoxytetrahydrofuran (**8**) furnished the crucial pyrrole relay **14** in an overall yield of 37% from **4**. Once again, the configurational integrity initially assured by L-aspartic acid was in no way compromised by the subsequent chemical modifications. The spectral characteristics of **14**, in particular its optical activity,[13] were identical to those of a previously prepared sample which had been converted to indolizidine 167B in 3 steps.[6]

Scheme 3



In conclusion, it is seen that easily accessible homochiral β-amino acids, apart from their intrinsic virtues, are also valuable as intermediates for the preparation of 5-alkylindolizidines of natural origin. Application of the present procedure for preparing other 5-substituted indolizidines, such as the piclavines,[14] and more complex alkaloids, in particular the 3,5 and 5,8-dialkyl derivatives, should be feasible and is under study.

Acknowledgments. We thank the Swiss National Science Foundation (grant No 20-32'166.91) for support of this work.

References and Notes

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3. The structure of indolizidine 167B has been tentatively assigned as 5-propylindolizidine on the basis of the GC-MS electron-impact mass spectrum, the lack of catalytic hydrogenation and the presence of a non-acetylatable nitrogen atom (J.W. Daly, *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205). Further data (NMR spectra, optical rotations, etc.) were not obtained (T.F. Spande and J.W. Daly, personal communication).

4. Racemic indolizidine 167B has been synthesized by using a classical procedure (F. Lions, A.M. Willison, *J. Proc. R. Soc. N.S.W.* **1940**, *73*, 240; *Chem. Abstr.* **1940**, *34*, 584), (T.F. Spande, private communication); and also more recently: E. Zeller, H. Sajus, D.S. Grierson, *Synlett* **1991**, 44; A.L. Smith, S.F. Williams, A.B. Holmes, L.R. Hughes, Z. Lidert, C. Swithenbank, *J. Org. Chem.* **1991**, *56*, 1393.

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8. C.W. Jefford, J.B. Wang, *Tetrahedron Lett.* **1993**, *34*, 1111.

9. The pyrrole derivative (**9**) was prepared by the modified Clauson-Kaas procedure adopted for α-amino acids (C. Kashima, T. Maruyama, K. Harada, S. Hibi, Y. Omote, *J. Chem. Res., Miniprint* **1988**, 601; J. Gloede, K. Poduška, J. Rudinger, *Collect. Czech. Chem. Commun.* **1968**, *33*, 1307)

10. Compounds **5-7** are crystalline solids (m.p.'s **5**, 48-51° (ether:hexane); **6**, 105-106° (ether); **7**, not determined), whereas **9-11** are oils. All were fully characterized. Optical rotations ($[\alpha]_D^{20}$) were determined in $CHCl_3$ and had the following values: **5**, +21.0° (c 1.6); **6**, +21.6° (c 1.0); **7**, -26.8° (c 0.33); **9**, -19.5° (c 1.2); **10**, -128.8° (c 1.08); and **11**, +85.1° (c 1.2). ^{1}H-NMR were determined at 200 MHz and in $CDCl_3$, except where noted: **5**, 0.81 (t, *J* = 6.32 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.05-1.50 (m, 10H), 2.36 (d, *J* = 2.7 Hz, 1H), 2.39 (d, *J* = 2.7 Hz, 1H), 2.40 (s, 3H), 3.48 (m, 1H), 4.04 (qd, *J* = 1.1, 7.1 Hz, 2H), 5.25 (d, *J* = 9.0 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H); **6**, 0.82 (t, *J* = 6.2 Hz, 3H), 1.05-1.52 (m, 10H), 2.40 (s, 3H), 2.47 (d, *J* = 5.0 Hz, 2H), 3.50 (m, 1H), 5.45 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H); **7**, (D_2O) 0.66 (t, *J* = 6.8 Hz, 3H), 1.05-1.28 (m, 8H), 1.43 (m, 2H), 2.21 (dd, *J* = 8.1, 16.6 Hz, 1H), 2.37 (dd, *J* = 4.9, 16.6 Hz, 1H), 3.27 (m, 1H); **9**, (400 Hz) 0.85 (t, *J* = 6.8 Hz, 3H), 1.07-1.29 (m, 8H), 1.74-1.80 (m, 2H), 2.78 (t, *J* = 6.8 Hz, 2H), 4.35 (m, 1H), 6.15 (t, *J* = 2.0 Hz, 2H), 6.68 (t, *J* = 2.0 Hz, 2H); **10**, 0.83 (t, *J* = 6.4 Hz, 3H), 1.16-1.30 (m, 8H), 1.70-1.81 (m, 2H), 2.67 (m, 2H), 4.30-4.42 (m, 1H), 4.93 (s, 1H), 6.12 (t, *J* = 2.1 Hz, 2H), 6.65 (t, *J* = 2.1 Hz, 2H); **11**, 0.86 (t, *J* = 6.7 Hz, 3H), 1.15-1.42 (m, 8H), 1.56-1.81 (m, 2H), 2.62 (dd, *J* = 16.0, 3.9 Hz, 1H), 2.87 (dd, *J* = 16.0, 5.4 Hz, 1H),3.59 (dd, *J* = 21.5, 1.0 Hz, 1H), 3.72 (dd, *J* = 21.5, 0.9 Hz, 1H), 4.27-4.38 (m, 1H), 5.94-5.98 (m, 1H), 6.15 (dd, *J* = 3.4, 2.7 Hz, 1H), 6.67 (dd, *J* = 2.7, 1.6 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) 14,02, 22.53, 26.03, 28.91, 31.60, 36.14, 38.50, 45.02, 54.34, 105.69, 118.83, 124.28, 206.41.

11. Indolizidine 209D (**2**) was obtained as an oil and purified by column chromatography over alkaline Al_2O_3 (pentane:ether, 5:1). $[\alpha]_D^{20}$ = -76.5° (c 0.74, CH_2Cl_2); lit.[5] $[\alpha]_D$ =-80.4° (c 1.0, CH_2Cl_2); IR 2932, 2859, 2788, 1459, 1379, 1113, 808, 756, 690; ^{1}H-NMR (200 MHz, $CDCl_3$) 0.86 (t, *J* = 6.7 Hz, 3H), 1.13-1.95 (m, 22H), 2.00 (q, *J* = 8.4 Hz, 1H), 3.28 (td, *J* = 8.5, 2.1 Hz, 1H), ^{13}C-NMR (50 MHz, $CDCl_3$) 14.04, 20.27, 22.57, 24.52, 25.77, 29.62, 30.33, 30.53, 30.63, 31.77, 34.34, 51.32, 63.91, 65.13; MS 209 (M^+, 4), 208 (11), 125 (12), 124 (100), 96 (13), 83 (7).

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13. 3R-Pyrrolylhexanoic acid (**14**), obtained as an oil, was purified over SiO_2 (EtOAc). $[\alpha]_D^{20}$ = -20.2° (c 0.5, MeOH), lit.[6] $[\alpha]_D^{20}$ = -20.0° (c 0.96, MeOH); ^{1}H-NMR (200 MHz, $CDCl_3$)$_3$ 0.87, (t, *J* = 7.1 Hz, 3H), 1.15-1.30 (m, 2H), 1.68-1.80 (m, 2H), 2.73 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.80 (dd, *J* = 16.0, 7.5 Hz, 1H), 4.26-4.42 (m, 1H), 6.13 (t, *J* = 2.1 Hz, 2H), 6.67 (t, *J* = 2.1 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) 13.62, 19.32, 38.12, 41.56, 55.95, 108.04, 118.87, 176.74. MS 181 (M^+, 36), 158 (10), 149 (17), 139 (32), 122 (23), 106 (21), 94 (100), 80 (31), 67 (58).

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(Received in Germany 1 March 1993)