Pergamon

Tetrahedron Letters, Vol. 35, No. 47, pp. 8843-8846, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01903-7

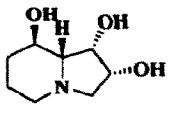
Amino Acids as Precursors to Indolizidine Alkaloids. DPPA-Promoted Decarbonylation of a Bicyclic Amino Acid: An Easy Entry to Hydroxylated Indolizidines.

María J. Martín-López and Francisco Bermejo-González*

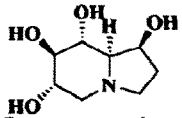
Departamento de Química Orgánica. Facultad de Químicas. Universidad de Salamanca.
Pza de la Merced s.n. 37008 Salamanca. Spain.

Abstract: *The synthesis of 8,8a-trans-8-hydroxy-indolizidine 12 from (D,L)-pipecolinic acid by two alternative routes is described. The stereospecific decarbonylation of the bicyclic carboxyamide 9 promoted by diphenylphosphorazidate (DPPA) is the key step of our strategy. The bicyclic enamide 10 is described as a valuable intermediate in the synthesis of hydroxylated indolizidines.*

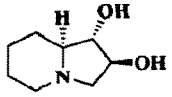
Hydroxylated indolizidines have received considerable attention due to their wide range of biological activity[1]. The importance of (-)-swainsonine[2] and (+)-castanospermine[3] (**1** and **2**, Fig. 1) as specific inhibitors of glucosidases has already been demonstrated. Several analogues of castanospermine have been evaluated as anti-HIV agents and many of this general class of alkaloids also develop other interesting pharmacological activities[4]. Lentiginosine **3**[5] is known as the least hydroxylated glycosidase inhibitor and (8S, 8aR)-6,7-Dehydro-8-hydroxyindolizidine **4**, a potential precursor to several polyhydroxyindolizidines, has been recently prepared from L-proline by a valuable stereocontrolled route[6].



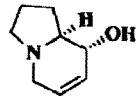
Swainsonine (1)



Castanospermine (2)



Lentiginosine (3)

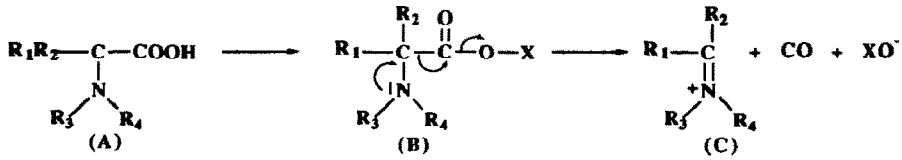


(8S, 8aR)-6,7-Dehydro-8-hydroxyindolizidine (4)

Fig. 1

We recently reported the thermal decarbonylation of the N-Cbz-(D,L)-pipecolinic acid derivative **6b** promoted by diphenylphosphorazidate (DPPA). This fragmentation reaction has been described as the key step of an original route to [4.5]spirolactones and [4.5]spirolactams[7].

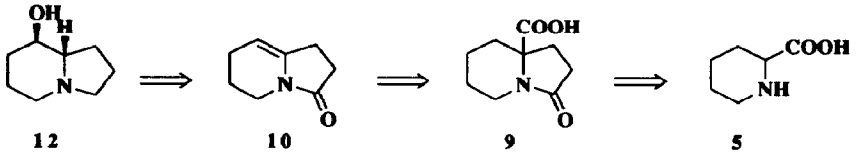
It has been established that α-amino acid derivatives with tertiary nitrogen atoms (A) undergo clean decarbonylation through conveniently activated carboxy functionalities (B). Immonium salts of the type (C) are involved in the thermal fragmentation process[8].



(A) (B) (C)

In this letter we describe the thermal fragmentation of 3-oxo-indolizidine-8a-carboxylic acid **9**, promoted by DPPA. This decarbonylation process has proved to be of general application in the synthesis of hydroxylated indolizidines by the preparation of 8, 8a-*trans*-8-hydroxy-indolizidine **12**, from (D,L)-pipecolinic acid **5**.

Our approach, retrosynthetically depicted in Fig.2, is based on the above-mentioned fragmentation.

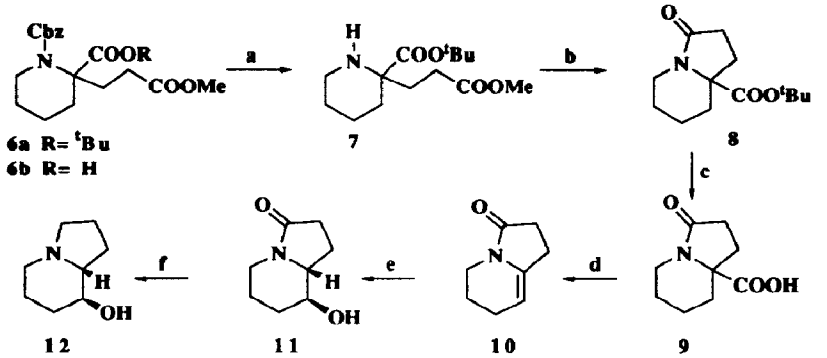


12 **10** **9** **5**

Fig. 2

The ^{t}butyl ester **6a** was prepared from (D,L)-pipecolinic acid as the result of a six-step sequence with 25% overall yield according to a procedure recently reported by our group[7].

Catalytic hydrogenation of **6a** followed by heating in refluxing toluene led quantitatively to the bicyclic amide **8** (Scheme I).



6a R= ^{t}Bu
6b R= H

7 **8**

12 **11** **10** **9**

a: H_2, 10% Pd(C), MeOH, 90%; b: tol, reflux, 100%; c: CF_3COOH, rt, 3h, 100%; d: DPPA, Et_3N, tol, 90°C, 76%; e: $BH_3.SMe_2$, H_2O_2, OH^-, 4.5h, 78%; f: $BH_3.SMe_2$, H_2O_2, 85%.

Scheme I

Removal of the tert-butyl ester of **8** by treatment with trifluoroacetic acid in methylene chloride at room temperature gave quantitatively the acid **9** m.p. 148 °C (hexane) which, by treatment with DPPA and triethylamine in toluene at 90 °C underwent clean decarbonylation to yield the enamide **10** (75%) regiospecifically[8].

Regiospecific formation of the enamide **10** may be certainly explained through a stereolectronically controlled decarbonylation process undergone by the carboxylic acid **9** through the active conformation of its activated acyldiphenylphosphate (Fig. 3).

For the decarbonylation reaction to proceed It seems necessary that the nitrogen lone pair and the carbonyl leaving group should be in trans-position with respect to one another.

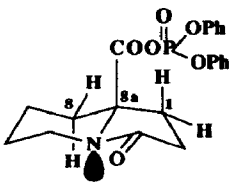
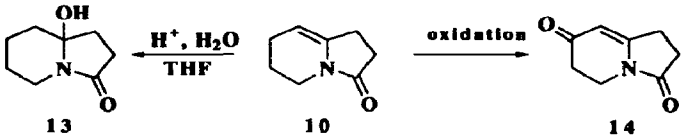


Fig. 3

Under basic conditions, proton abstraction of the axially oriented 8α-H should be favoured against abstraction of the pseudoaxial 1α-H[9].

Attempts made to transform the enamide **10** into carbinolamide **13** never led to completion. The best yields of carbinolamide **13** (45%) were obtained by treatment of **10** with diluted hydrochloric acid in THF. However, the low stability of **13** under standard flash chromatographic conditions made it difficult to reproduce our results[10].

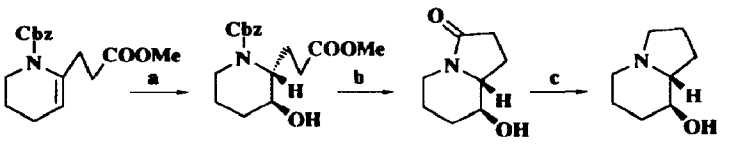
Transformation of **10** into 1,2,5,6-Tetrahydro-3,7-indolizindione **14**[11] by allylic oxidation with CrO_3-3,5-dimethyl pyrazole in methylene chloride (65%) allowed us to confirm unequivocally the structure of the enamide **10**, a valuable intermediate in our synthetic route to hydroxylated indolizidines (Fig. 4).



13 10 14

Fig. 4

Careful hydroboration of the double bond of **10** by treatment of the substrate with $BH_3.SMe_2$ (1.1 eq) in THF at 0ºC followed by treatment with alkaline hydroperoxide led to the bicyclic amide **11** (78 %). Reduction of **11** by reaction with diborane at room temperature allowed us to isolate 8,8a-*trans*-8-hydroxy-indolizidine **12** (85 %)[12].



15 16 11 12

a: $BH_3.SMe_2$, H_2O_2, OH^-, 4.5h, 70%; b:i) H_2, 10% Pd(C), MeOH, 95%; ii): tol, reflux; c: $BH_3.SMe_2$, H_2O_2, 85%.

Scheme II

An alternative structure sequence allowed us to access to **12** and confirm our results. The new route starts from the easily accessible enamine **15**[7] and allowed us to prepare the target molecule through a 4-step sequence with 57 % yield from the enamine **15**. (Scheme II).

Aknowledgement: We thank financial support by the "Dirección General de Investigación Científica y Técnica", Spain. (DGICYT, Grant PB 92-0286).

References and notes.

1) For recent reviews on the chemistry and biological activities of polyhydroxyindolizidine alkaloids, see (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological perspectives*; Pelletier, S. W.; Ed.; Wiley. New York, **1987**; vol 5, chapter 1, pp. 1-54. (b) Michael, J. P. *Natural Products Reports* **1990**, 485-513. (c) Howard, A. S.; Michael, J. P. *Alkaloids* (N. Y.) **1986**, *28*, 183-308.

2) No less than fourteen total syntheses of (-)-swainsonine have been reported to date. For most recent contribution see: Naruse, M.; Aoyagi, S.; Kibayashi C.; *J. Org. Chem.* **1994**, *59*, 1358 and references therein.

3) Castanospermine itself and also structural analogues have been the focus of numerous synthetic efforts. For more recent contributions see; (a) Rapoport, H.; Gerspacher, M. *J. Org. Chem.* **1991**, *56*, 3700. (b) Kibayashi C.; Ina, H. *Tetrahedron. Lett.*, **1991**, *32*, 4147.

4)A review on synthetic approaches to stereoisomers and analogues of castanospermine has appeared: Burgess, K.; Henderson, I. *Tetrahedron*, **1992**, *48*, 4045.

5) Two synthetic contributions to the total synthesis of lentiginosine have recently appeared: (a) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron Asymmetry* **1993**, *4*, 1455. (b) Cordero F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.*, **1994**, *35*, 949.

6) Koskinen Ari M.P., Paul J. M. *Tetrahedron Lett.*, **1992**, *33*, 6853.

7) Martín-López, M. J.; Bermejo-González, F. *Tetrahedron Lett.*, **1994**, *35*, 4235.

8) No traces of other possible isomers were detected by ^{1}Hnmr and ^{13}Cnmr (200 MHz).

9) Maksimov, V. I., *Tetrahedron*, **1965**, *21*, 687.

10) 1N HCl in THF, wet silica in THF and p-toluene sulfonic acid monohydrate in THF were used. All the reactions were performed overnight at room temperature. Variable mixtures of **10** and **13** were obtained in all cases.

11) 1,2,5,6-Tetrahydro-3, 7-indolizindione **14**, has been recently described as the key intermediate in the synthesis of Elaekanin C and Elaecarpin, indolizidine alkaloids isolated from *Elaecarpaceae*: Flitsch, W.; Pandl, K., *Liebigs Ann. Chem.*, **1987**, 649.

12) All new compounds were characterized by spectroscopic methods. Correct microanalytical data have been obtained for **8-16**:

8: IR(film) : ν: 1733, 1699, 1464, 1411, 1368, 1313, 1249, 1154, 1082, 845 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 4.04 (m, 2H); 2.69 (m, 2H); 2.5-1.3(m, 8H); 1.42(s, 9H) ppm. ^{13}CNMR:δ($CDCl_3$): 173.79 (s); 172.01 (s); 81.60 (s); 66.65 (s); 38.43 (t); 34.97 (t); 31.43 (t); 29.13 (t); 27.72(q) ; 23.72(t) and 21.49 (t) ppm.

9: IR(film):ν: 3600-3100 , 3019, 2941, 1723, 1648, 1457, 1420, 1247, 1216, 1160 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 12.01 (s, 1H); 4.05 (m, 2H); 2.85 (m, 2H); 2.6-1.5 (m, 8H) ppm. ^{13}CNMR:δ($CDCl_3$): 175.68 (s); 175.22 (s); 66.90(s); 39.01(t); 35.26(t); 31.71(t); 29.26(t); 23.88(t); 21.59(t) ppm

10: IR(film): ν: 2944, 1689, 1663, 1559, 1507, 1457, 1420, 1364, cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 4.68 (m, 1H); 3.49 (m, 2H); 2.9-1.2 (m, 8H) ppm. ^{13}CNMR:δ($CDCl_3$): 174.23 (s); 138.27 (s); 97.37 (d); 39.02 (t); 29.11 (t); 22.66(t); 21.44 (t); 20.57 (t) ppm.

11: IR(film): ν: 3350-3150, 2996, 2944, 2863, 1667, 1462, 1424, 1358, 1281, 1267, 1179, 1142, 1082, 1022, 978, 889, 831, 760 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 4.03 (m, 1H); 3.97 (m, 1H); 3.45 (m, 1H); 2.52(m, 2H); 2.4-1.2 (m, 7H) ppm. ^{13}CNMR:δ($CDCl_3$): 173.74 (s); 73.16(d); 62.97(d) ; 39.35 (t); 33.48 (t); 30.13(t); 23.39 (t); 22.32 (t) ppm.

12: IR(film): ν: 3350-3150, 2996, 2944, 2863, 1460, 1414, 1350, 1280, 1263, 1100, 1042, 978 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 3.62 (m, 1H); 3.35 (m, 1H); 3.10-2.90 (m, 4H); 2.20-1.10 (m, 8H) ppm. ^{13}CNMR:δ($CDCl_3$): 73.40 (d); 70.35 (d); 54.15 (t); 51.77 (t); 33.87 (t); 28.31(t); 24.36 (t); 20.78 (t) ppm.

13: IR(film): ν: 3600-3200, 3021, 2945, 1703, 1441, 1404, 1373, 1346, 1215, 1159, 1094 cm^{-1}. ^{1}HNMR: δ(CD_3OD): 3.85 (m, 1H); 3.79 (m, 1H); 3.23 (m, 2H); 2.62 (m, 2H); 2.5-1.2(m, 8H) ppm. ^{13}CNMR:δ(CD_3OD): 175.89 (s); 93.53 (s); 38.22 (t); 37.94 (t); 30.62 (t); 28.99 (t); 25.12 (s); 20.60 (t) ppm.

(*Received in UK* 22 *July* 1994; *revised* 16 *September* 1994; *accepted* 23 *September* 1994)