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Decarbonylation of α-Tertiary Amino Acids. Application to the Synthesis of Polyhydroxylated Indolizidines

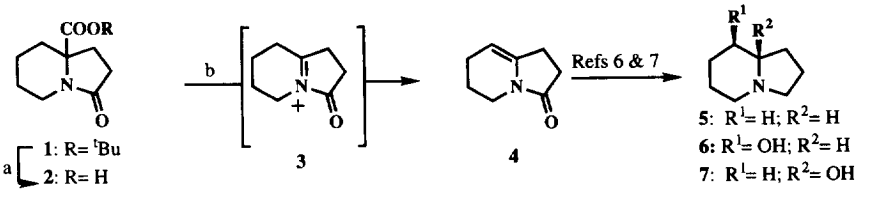
Rosa Rodríguez and Francisco Bermejo*

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

Abstract: The decarbonylation of the bicyclic α-tertiary amino acid **16** easily obtained from D,L-pipecolic acid, is the key step in our strategy to prepare polyhydroxylated indolizidines. Thermal fragmentation of the acyl chloride **17** allowed us access to the enamide **19**, which has been described as a valuable intermediate in the synthesis of (±)-swainsonine. Copyright © 1996 Elsevier Science Ltd

The degradation of α-amino carboxylic acids has proved to be a useful method for the regiospecific preparation of iminium salts.[1] Furthermore, the well known instability of acyl derivatives of α-tertiary amino acids has been widely exploited in synthetic work related to alkaloids such as cephalotaxine,[2] anatoxin,[3] epibatidine,[4] and ferruginine,[5] via decarbonylation/iminium ion cyclization processes.

Based on the instability of activated acyl derivatives of pipecolic acid, we have developed a method to prepare azaspiro[4.5]decane systems[6] and hydroxylated indolizidine alkaloids.[7] The diphenylphosphorazidate (DPPA)-promoted decarbonylation of the readily available bicyclic carboxylic acid **2** led regiospecifically to the enamide **4** via the acyliminium intermediate **3**.[8] The bicyclic enamide **4** has been previously described by our group as a valuable intermediate in the synthesis of indolizidines such as δ-coniceine **5**, 8,8a-trans-8-hydroxyindolizidine **6** and 8a-hydroxyindolizidine **7** (Scheme 1).



a: CF_3COOH, CH_2Cl_2, 0 °C; 100%; **b**: DPPA, Et_3N, toluene, 90 °C, 76%.

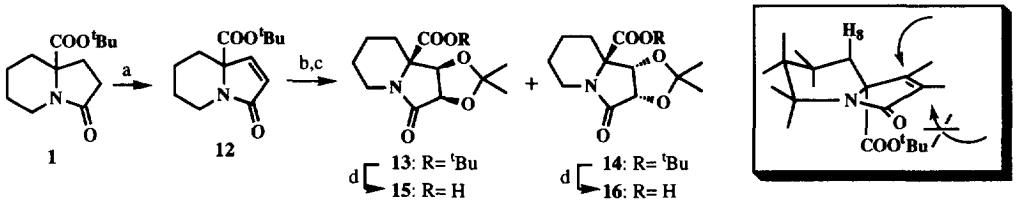
Scheme 1

We now wish to report our results on the synthesis of the trihydroxylated indolizidine alkaloid (±)-swainsonine **22**[9] from D,L-pipecolic acid based on the decarbonylation process carried out on the carboxy acetonides **15** and **16**.

Treatment of the bicyclic lactam **1**[7] with LDA at -78 °C followed by addition of phenylselenyl bromide led to quantitative transformation into a selenide. Deselenoxylation of the resulting product was achieved by reaction

of the crude selenide with 30% hydrogen peroxide in acetic acid to yield the α,β-unsaturated lactam **12** in 70% overall yield. The *syn* dihydroxylation of **12** was achieved by catalytic osmylation with N-methylmorpholine N-oxide (NMO) as cooxidant in aqueous acetone.[10]

The stereoselectivity of the osmylation reaction was determined by ^{1}H NMR analysis of the crude mixture of diols and corroborated after transformation of the mixture of diols into the acetonides **13** (m.p. 70-72 °C)and **14** (m.p. 120-122 °C) by treatment with 2,2-dimethoxypropane and pyridinium p-toluenesulfonate (PPTS) followed by further chromatographic separation on silica gel (**13**:**14** = 1:2). The *trans* stereochemistry of the major isomer **14** was tentatively assigned following a mechanistic rationale[11] and spectroscopic evidence[12] (Scheme 2).

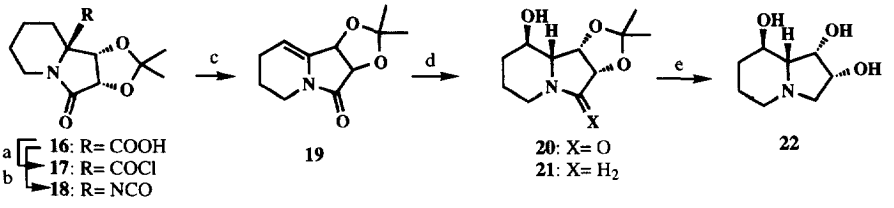


a: i: LDA, THF, -78 °C; ii: PhSeCl; iii: H_2O_2, AcOH; 70%; **b**: OsO_4, NMO, acetone, H_2O, ^{t}BuOH; 70%; c: $CH_3C(OMe)_2CH_3$, PPTS, CH_2Cl_2, 100% ; **d**: CF_3COOH, CH_2Cl_2, 0 °C, 98%.

Scheme 2

Attack of the oxidizing reagent on enamide **12** may preferably take place at the concave face due to two convergent factors: first, the 1,2 interaction with the t-butoxycarbonyl moiety is dominant in comparison with the 1,3 steric interaction with the axial H-8; second, the planarity of the pyrrolinone ring in enamide **12** considerably diminishes the usual preference for attack at the convex face compared to the regular indolizidine arrangement.

Deprotection of the ^{t}butyl esters **13** and **14** by treatment with trifluoroacetic acid (in methylene chloride at 0 °C) led almost quantitatively to the carboxy derivatives **15** and **16**, respectively. However, DPPA-promoted decarbonylation of both isomers under standard conditions[6] led to disappointing results: the minor isomer **15** led to enamide **19** (m.p. 68-70 °C) in only 16% yield and the major carboxy acetonide **16** gave isocyanate **18** (m.p. 70-72 °C), which was isolated in 55% yield after chromatographic purification (hexane:AcOEt = 3:7)[13] (Scheme 3). We assume that the poor yield obtained in the former case may be rationalized in terms of steric hindrance encountered by the reagent (DPPA) to form the intermediate acyldiphenyl phosphate.[6] The formation of **18** in the latter case is clearly explained by a competitive Curtius rearrangement.



a: $(COCl)_2$, 98%; **b**: DPPA, Et_3N, tol, 90 °C, 55%, c: (from 15) 1,2-DCE, xylene, reflux, 15 h, 75%; **d**: B_2H_6, THF, then H_2O_2, NaOH; **e**: i: 6N HCl; ii: Dowex-1X8

Scheme 3

Nevertheless, the decarbonylation was successfully achieved by using a modified version of the previously reported procedure to promote the formation of acyliminium intermediates.[1-5] Treatment of the major

carboxy acetonide **16** with oxalyl chloride allowed us to isolate the rather stable acyl chloride **17** (m.p. 118-120 °C) in quantitative yield. The enamide **19** was obtained in excellent yield upon warming at the end of acid chloride formation by immersion of the solution of **17** in a 1:2 mixture of 1,2-dichloroethane (DCE)/xylene in a preheated bath and stirring overnight under reflux in an Ar atmosphere. We were able to isolate the enamide **19** in 75% yield upon flash chromatography on silica gel (hexane:AcOEt = 1:1).

Treatment of the enamide **19** with diborane[14] in THF followed by reaction with alkaline hydroperoxide led stereospecifically to the racemic swainsonine acetonide **21** (m.p. 90-92 °C) in 85% yield, which was further transformed by acid hydrolysis (6N HCl, THF) to yield (±)-swainsonine (**22**) in 78% yield.[15]

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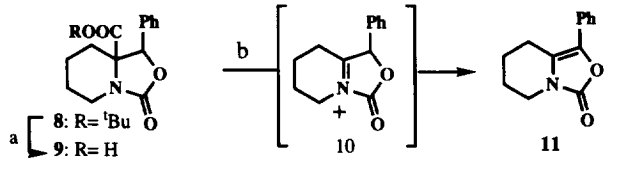
8. In similar cases, however, the double bond formation may take another course; for example, the acyliminium intermediate **10** may be invoked to rationalize the product of the regioselective decarbonylation (DPPA, Et_3N, tol, 90 °C) carried out on the carboxy oxazolidinone **9**. In this case, the regioselectivity of the process is governed by the acidity of the benzylic proton to yield **11** in 85% yield; F. Bermejo and R. Rodríguez, unpublished results.



a: CF_3COOH, CH_2Cl_2, rt, 1h, 98%; **b**: DPPA, Et_3N, toluene, 90 °C, 1h. 85%.

9. For recent reviews on the chemistry and biology of polyhidroxyindolizidine alkaloids, see: Elbein, A. D.; Molyneux, R. J., *Alkaloids: Chemical and Biological perspectives;* Pelletier, S. W.; Ed.; Wiley; New York, **1987**; vol. 5, chapter 1, pp. 1-54. Howard, A. S.; Michael, J. P. *Alkaloids* (N. Y.) **1986**, 28, 183-308. Michael, J. P. *Natural Products Reports* **1990**, 485-513. Rajeswari, S.; Chandrasekharan, S.; Govindachari, R.; *Heterocycles*, **1987**, 25, 659-700.
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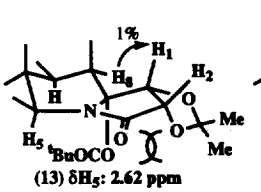
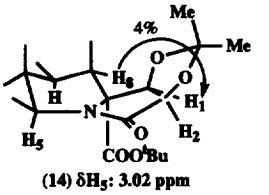
11. For a similar case, see: Oishi T.; Iwakuma T.; Hirama M.; Ito S., *Synlett*, **1995**, 404-406.

12. The downfield shift found for the axial proton H-5 in the major acetonide **14** is only compatible with the *trans* stereochemistry because the strong 1,3-diaxial interactions present in the *cis* isomer **13** would keep the axial proton H-5 far apart from the deshielding carbonyl plane. Furthermore, the minor acetonide **13** exhibited an almost negligible NOE effect (1%) at δ: 4.37 ppm (H-1) when the equatorial H-8 (δ: 2.12 ppm) was irradiated. However, a more pronounced enhancement (4%) of the signal at δ: 4.33 ppm was observed in the ^{1}H NMR spectrum of **14** when the equatorial H-8 (δ: 2.34 ppm) was irradiated.



(13) δH_5: 2.62 ppm



(14) δH_5: 3.02 ppm

13. All new compounds were characterized by spectroscopic methods. Correct microanalytical data have been obtained for **12-22**. For example:

12: IR (film) ν : 1738, 1699, 1452, 1398, 1370, 1248, 1155 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.12-1.29 (m, 1H); 1.45 (s, 9H); 1.68-1.87 (m, 4H); 2.52-2.61 (dt, 1H, J_1= 12.7Hz, J_2= 3.4Hz); 2.95-3.10 (dt, 1H, J_1= 12.8 Hz, J_2= 3.9Hz); 4.19-4.28 (dd, 1H, J_1= 13.3Hz, J_2= 5.0Hz); 6.13 (d, 1H, J= 5.8Hz); 6.99 (d, 1H, J= 5.7Hz) ppm. ^{13}CNMR: δ($CDCl_3$): 20.97(t), 24.68(t), 27.76(q), 33.84(t), 37.65(t), 71.46(s), 82.80(s), 127.36(d), 146.86(d), 167.91(s), 168.78(s) ppm.

13: IR (film) ν : 1715, 1456, 1418, 1371, 1290, 1248, 1154, 1101 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.13-1.23 (m, 1H); 1.30 (s, 3H); 1.33 (s, 3H); 1.38 (s, 9H); 1.58-1.88 (m, 4H); 2.09-2.16 (dt, 1H); 2.59 (dt, 1H, J_1= 12.9Hz, J_2= 3.6Hz); 3.97-4.05 (dd, 1H, J_1= 13.3Hz, J_2= 4.61Hz); 4.37 (d, 1H, J= 5.7Hz); 4.58 (d, 1H, J= 5.8Hz) ppm. ^{13}CNMR: δ($CDCl_3$): 20.69 (t); 23.34 (t); 26.20 (t); 26.05 (q); 26.84 (q); 27.56 (q); 38.47 (t); 68.28 (s); 76.33 (d); 77.22 (d); 82.87 (s); 112.61 (s); 170.00 (s); 170.20 (s) ppm.

14: IR (film) ν : 1738, 1703, 1452, 1371, 1314, 1254, 1215, 1159, 1113 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.10-1.19 (dt, 1H); 1.19 (s, 3H); 1.21 (s, 3H); 1.34 (s, 9H); 1.52-1.59 (m, 4H); 2.29-2.37 (dt, 1H); 2.79-2.94 (dt, 1H, J_1= 13.1 Hz, J_2= 3.7Hz); 3.93-4.01 (dd, 1H, J_1= 13.6Hz, J_2= 4.9Hz); 4.33 (d, 1H, J= 6.64Hz); 4.52 (d, 1H, J= 6.65Hz) ppm. ^{13}CNMR: δ($CDCl_3$): 21.45 (t); 24.02 (t); 25.72 (q); 26.30 (q); 27.82 (q); 33.60 (t); 39.07 (t); 69.54 (s); 77.18 (d); 78.97 (d); 82.29 (s); 113.11 (s); 167.59 (s); 169.20 (s) ppm.

17: IR (film) ν : 1780, 1705, 1422, 1379; 1271, 1213, 1155, 1092, 907cm^{-1}. ^{1}H NMR: δ($CDCl_3$): 1.36 (s, 3H); 1.39 (s, 3H); 1.44-1.91 (m, 4H); 2.74-3.06 (m, 3H); 4.16-4.23 (m, 1H); 4.59 (d, 1H, J= 6.4Hz); 4.73 (d, 1H, J= 6.5Hz) ppm. ^{13}C NMR: δ($CDCl_3$): 21.17 (t); 23.70 (t); 25.59 (q); 26.05 (q); 33.63 (t); 39.34 (t); 56.88 (s); 77.00 (d); 78.59 (d); 114.52 (s); 169.24(s); 174.40(s) ppm.

18: IR (film) ν : 2249, 1705, 1420, 1377, 1215, 1103 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.20-1.40 (m, 1H); 1.43 (s, 3H); 1.52 (s, 3H); 1.62-1.88 (m, 4H); 1.90-2.10 (m, 1H); 2.69-3.04 (dt, 1H, J_1=13.1 Hz, J_2= 3.6 Hz); 4.-07-3.98 (dd, 1H, J_1= 13.3, J_2= 5.0Hz); 4.48 (d, 1H, J= 6.6Hz); 4.70 (d, 1H, J= 7.9Hz).^{13}C NMR: δ($CDCl_3$): 20.19 (t); 24.06 (t); 25.61 (q); 26.24 (q); 37.60 (t); 38.28 (t); 53.32 (s); 77.00 (d); 79.18 (d); 114.99 (s); 126.92 (s); 166.86(s) ppm.

19: IR (film) ν : 1732, 1688, 1410, 1377, 1317, 1252, 1209, 1152, 1096 cm^{-1}. ^{1}H NMR: δ($CDCl_3$): 1.38 (s, 3H); 1.40 (s, 3H); 1.68-1.85 (m, 2H); 2.13-2.21 (m, 2H); 3.30-3.44 (m, 1H); 3.64-3.76 (m, 1H); 4.64 (d, 1H, J= 6.4Hz); 4.93 (d, 1H, J= 6.8Hz); 5.22 (t, 1H, J= 4.1Hz) ppm. ^{13}CNMR: δ($CDCl_3$): 19.52 (t); 20.96 (t); 24.82 (q); 26.07 (q); 38.42 (t); 72.96 (d); 75.69 (d); 103.38 (d); 112.22 (s); 135.42(s); 168.78 (s) ppm.

14. Treatment of the enamide **19** with 9-BBN followed by reaction with alkaline hydroperoxide led selectively to the hydroxycarbamoyl acetonide **20** in 85% yield. Transformation of the amide **20** into **21** was achieved by known methods[9] in quantitative yield.

15. The spectroscopic data obtained for **21** and **22** were identical to those described in the literature for the swainsonine acetonide and the alkaloid, respectively.[9]

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