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DPPA-Promoted Decarbonylation of a N-Cbz-(D,L)-Pipecolinic Acid Derivative: An Easy Entry to [4.5]Spirolactams and [4.5]Spirolactones. Total Synthesis of (±)-δ-coniceine.

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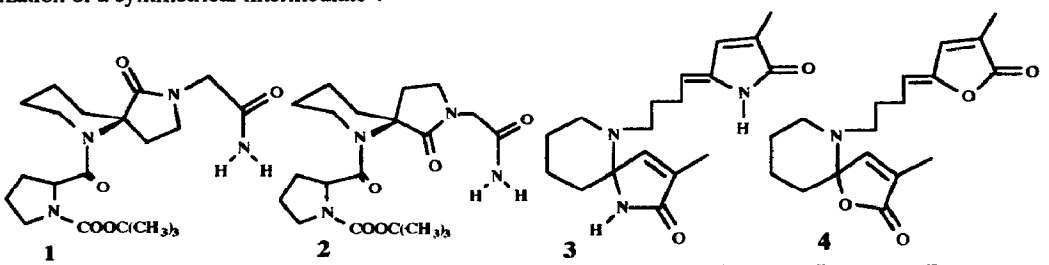
Abstract: *The synthesis of 6-benzyloxycarbonyl-1-oxa-6-azaspiro[4.5]decane-2-one* ***7a*** *and 6-benzyloxycarbonyl-1,6-diazaspiro[4.5]decane-2-one* ***7b*** *from (D,L)-pipecolinic acid is described. The extremely clean decarbonylation of the α-substituted amino acid* ***9d*** *promoted by diphenylphosphorazidate (DPPA) is the key step of our strategy. The total synthesis of (±)-δ-coniceine (**16**) from the enamine ester* ***10a*** *has been successfully achieved.*

Synthetic efforts leading to azaspiro[4.5]decane and azaspiro[5.5]undecane systems are well known[1]. Among them, the diaza[4.5]spirolactams came very recently into the literature because some representatives of this kind of compounds seem to mimic certain secundary structural features of biologically active peptides, namely, the type-IIβ and type-II´β turns[2] (**1** and **2**, Fig. 1). Furthermore, the [4.5]spirolactam and the [4.5]spirolactone moieties are present in some naturally occurring piperidine alkaloids. (±)-Pandamarine (**3**) and (-)-pandamarilactone (**4**) have been isolated from the leaves of *Pandanus amaryllifolius* (Pandanaceae) stem from the Philippines[3]. According to ethnomedical information the leaves and the seeds of this *Pandanus* species induce interesting biological activities[4]. The structure of (+)-pandamarine has been confirmed by X-Ray diffraction and a biosynthetic pathway has been suggested to explain the formation of the racemate based on the cyclization of a symmetrical intermediate[5].



1 **2** **3** **4**

β-Turn mimics **(±)-Pandamarine** **(-)-Pandamarilactone**

Fig. 1

We now wish to report an easy route to the 1-oxo-6-azaspiro[4.5]decane-2-one and 1,6-diazaspiro[4.5]decane-2-one systems based on the clean decarbonylation of the (D,L)-pipecolinic acid derivative **9d** promoted by diphenylphosphorazidate (DPPA).

Our approach, retrosynthetically depicted in Fig **2**, is based on the classical oxidative olefin cyclization of γ,δ–unsaturated acid derivatives. The cyclic enamines **6**, substrates for the cyclization process, were envisaged to be easily accessible from N-Cbz-(D,L)-pipecolinic acid **5**:

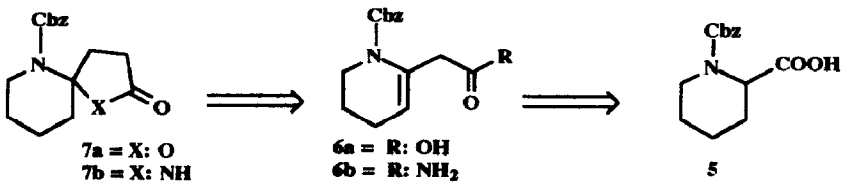
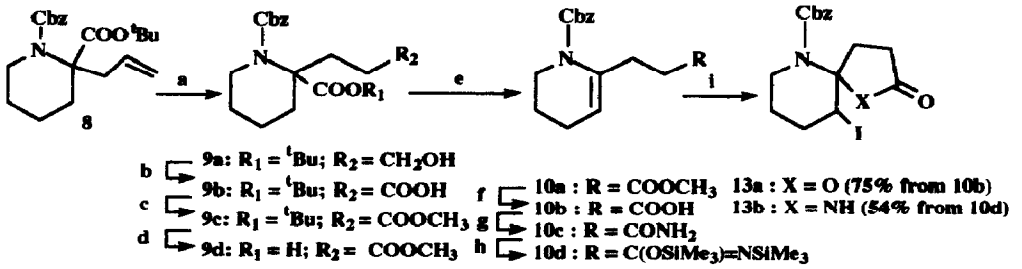


Fig. 2

It has been established that the α-aminoacid derivatives with a tertiary nitrogen atom are capable of undergoing decarbonylation. However, in order to promote the fragmentation reaction the carboxylic moiety of the α-aminoacid derivative needs to be activated (acid chlorides, azides and acylisoureas, etc, are frequently used)[6]. We have made use of the diphenylphosphorazidate (DPPA) to activate the carboxylic moiety of **9d** (Scheme 1) to promote the fragmentation [7].



a: B_2H_6, H_2O_2, OH^-, 4.5 h, 74%; b: PDC, DMF, rt, 22h, 91%; c: CH_2N_2, 90%, d: CF_3COOH, rt, 3h, 100%; e: DPPA, Et_3N, Tol, 90°C, 84%; f: 10N NaOH, CH_3OH, 78%; g: DCC, N-hydroxysuccinimide, NH_4OH, 2.5 h, 52%; h: TMSOTf, Et_3N, pentane; i: NIS, $NaHCO_3$, CH_2Cl_2, rt, 1h.

Scheme 1

The α-allyl derivative **8** was obtained from (D, L)-pipecolinic acid **5** as the result of a three-step sequence with 40% overall yield, according to a procedure reported by Johnson[2].

Hydroboration of the terminal double bond followed by treatment with alkaline hydroperoxide lead to the primary alcohol **9a** (74%) which was further oxidized with PDC in dimethyl formamide to yield the carboxylic acid **9b** (91 %). Treatment of **9b** with an ethereal diazomethane solution lead quantitatively to the methyl ester **9c**.

Removal of the tert-butyl ester in **9c** by treatment with trifluoroacetic acid at room temperature gave the acid **9d** m.p. 104-106°C (hexane) which, by treatment with diphenylphosphorazidate and triethylamine in toluene at 90°C underwent clean decarbonylation to afford the enamine methylester **10a** with 84% yield[8].

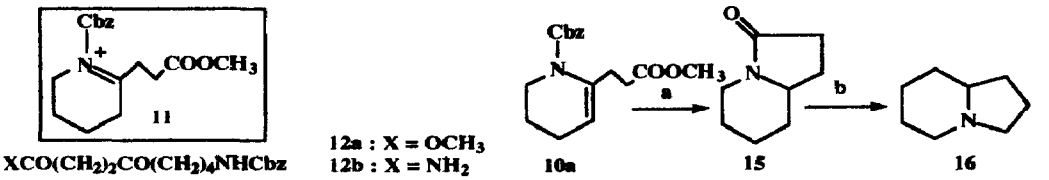
Mechanistically, the reaction takes place in two steps, the first of which is phosphate formation. A balanced equation requires the formation of the triethylamine salt of hydrazoic acid in addition to the phosphate[9]. Then, the decarbonylation takes place (bubbles). Our assumption is that the formation of the enamine **10a** is accomplished through the intermediate immonium salt **11** (Scheme 2) which, finally collapses to the enamine by proton abstraction. The active conformation of the substrate **9d** may have the carboxy group in axial orientation in order to account for the stereoelectronic factor in the fragmentation reaction, which, generally corresponds to the requirements of a synchronous displacement of electron densities from the electron cloud of the free electron pair of the nitrogen to the carbonyl-leaving group[10].

The methyl ester **10a** was hydrolyzed by treatment with methanolic 10N NaOH soln. to the carboxylic acid **10b**. Transformation of **10b** into the amide **10c**, m.p. 64°C (hexane) was succesfully achieved by treatment of the acid with DCC and N-hydroxysuccinimide followed by treatment with an aqueous ammonia solution (52%)[11].

The oxidative cyclization of the γ,δ-unsaturated acid **10b** by treatment with NIS and sodium bicarbonate in dichloromethane at 0°C lead to the iodolactone **13a** (75%)[12] which proved to be unstable under flash chromatographic conditions. An analytical sample was obtained to confirm the structure of the bicyclic iodolactone, and the crude product was inmediately reduced by treatment with tri-n-butyltin hydride and AIBN in THF at 40°C to give 6-benzyloxycarbonyl-1-oxo-6-azaspiro[4.5]decane-2-one **7a** (72%) m.p. 84-86°C (hexane) which was fully characterized by spectroscopic methods.

Analogous transformation of amide **10c** required the generation of the N,O-bis(trimethylsilyl)imidate **10d** as intermediate[13]. Treatment of the unsaturated amide **10c** with trimethylsilyl triflate in pentane and further reaction with NIS in THF lead to the iodolactam **13b** which was further reduced to 6-benzyloxycarbonyl-1,6-diazaspiro[4.5]decane-2-one **7b** (54%) as described above[14].

We have successfully achieved the total synthesis of (±)-δ-coniceine (**16**), the least complex representative of the indolizidine alkaloids, as an ideal model system for investigating a general synthetic strategy for the construction of more complex indolizidine alkaloids.



a: i.H_2, 10% Pd(C), MeOH; ii Tol, reflux, 100% ; b: B_2H_6, THF, r.t., 15 h., 75%.

Scheme 2

Catalytic hydrogenation of enamine ester **10a** followed by heating in refluxing toluene lead quantitatively to the bicyclic amide **15**. Reduction of **15** by treatment with diborane at room temperature for 15 h. allowed us to isolate (±)-δ-coniceine (**16**)[15] in 75% overall yield from **10a**. (Scheme 2)

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6) An ingenious precedent of this fragmentation has been reported by van Tamelen in the synthesis of (+)-Ajmaline: van Tamelen, E. E.; Oliver, L. K., *J. Am. Chem. Soc.*, **1970**, *92*, 2136.

7) The activation of hydroxy groups by using DPPA to convert alcohols into azides has been recently reported as a practical alternative to the Mitsunobu conditions: Thompson, A. S.; Humphrey, G. R.; DeMarco A.M.; Mathre, D. J.; Grabowski, E. J. J., *J. Org. Chem. Soc.*, **1993**, *58*, 5886.

8) Exhaustive elimination of the exccess of trifluoroacetic acid was necessary otherwise yields of the fragmentation reaction were very poor. Obviously the interaction of TFA with the reagents needs to be avoided.

9) We were able to identify the triethylamine salt as the colorless needles crystallized on the water cooler of the reaction system by IR (ν= 3391, 2033 cm-1) and ^{1}HNMR [δ($CDCl_3$): 3.56 (s, 1H); 2.92 (q, J= 7Hz, 2H); 1.28 (t, J= 7Hz, 3H) ppm].

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

11) The enamine derivatives **10a** and **10c** were clearly hydrolyzed by treatment with p-toluenesulphonic acid monohydrate in THF at room temperature to the open ketoderivatives **12a** (colorless oil, 82%) and **12b** m. p. 128-130 °C (80%), respectively.

12) Bartlett, P. A.. "*Olefin Cyclization Processes that form carbon- heteroatom bonds*" in Morrison, J. D., Asymmetric Synthesis Vol. 3, Part B. Academic Press Inc. S. Francisco. (1984).

13) Knapp, S., Levorse, A. T., *J. Org. Chem. Soc.*, **1988**, *53*, 4006.

14) All compounds were completely characterized by spectroscopic methods. For example:

10b: IR(film) ν: 1738, 1709, 1659, 1402, 1344, 1265, 1190, 1051, 737, 700 cm^{-1}.

^{1}HNMR: δ($CDCl_3$): 7.37 (m, 5H); 5.15 (s, 2H); 5.04 (m, 1H); 3.63 (s, 3H); 3.57 (m, 2H); 2.80 (m, 2H); 2.37 (m, 2H); 2.05 (m, 2H); 1.75 (m, 2H) ppm.

^{13}CNMR:δ($CDCl_3$): 173.39 (s); 154.05 (s); 138.27 (s); 136.38 (s); 128.48 (d); 128.08 (d); 128.06 (d); 113.60 (d); 67.35 (t); 51.33 (q); 45.17 (t); 32.89 (t); 30.66 (t); 23.20 (t); 22.85 (t) ppm.

7a: IR(film): 3021, 2957, 1765, 1707, 1408, 1267, 1217, 1171 cm^{-1}.

^{1}HNMR: δ($CDCl_3$): 7.31 (m, 5H); 5.07 (AB system, 2H); 3.68 (m, 1H); 3.48 (m, 1H); 2.79 (t, 2H); 2.47 (m, 2H); 2.0 (m, 2H); 1.69 (m, 2H); 1.21 (m, 2H) ppm.

^{13}CNMR:δ($CDCl_3$): 176.34 (s); 155.58 (s); 135.94 (s); 128.60(d); 128.25 (d); 128.24 (d); 95.75 (s); 67.66 (t); 42.68 (t); 37.84 (t); 34.84 (t); 29.50 (t); 22.53 (t); 17.30 (t) ppm

MS: m/z (%): 289 (2); 234 (5); 216 (10); 190 (5); 155 (15); 110 (15); 91 (100); 65 (10).

7c: IR(film): 3430, 3190, 2929, 2860, 1714, 1684, 1457, 1388, 1332, 1257, 1160 cm^{-1}.

^{1}HNMR: δ($CDCl_3$): 7.60 (s, 1H); 7.34 (m, 5H); 5.09 (AB system, 2H); 3.62 (m, 1H); 3.51 (m, 1H); 2.49 (m, 2H); 2.22 (m, 2H); 1.82 (m, 2H); 1.60 (m, 2H); 1.32 (m, 2H) ppm.

^{13}CNMR:δ($CDCl_3$): 177.12 (s); 156.08 (s); 136.25 (s); 128.52 (d); 128.13 (d); 128.12(d); 75.69 (s); 67.24 (t); 43.19 (t); 37.60 (t); 33.23 (t); 29.92 (t); 23.25 (t); 19.16 (t) ppm.

MS: m/z (%): 288 (10); 200 (1); 181 (10); 153 (10); 136 (25); 91 (100); 65 (10).

15) The spectroscopic properties obtained for **16** were in agreement with those reported for (±)-δ-conoceine: the previous syntheses of this indolizidine alkaloid were reviewed in 1986. Since that time twelve additional syntheses of (±)-δ-coniceine have appeared. For more recent contributions see: Green D.L.C.; Thompson, Ch. M., *Tetrahedron Lett.*, **1991**, *32*, 5051; and Jung, M. E.; Choi Yong Mi, *J. Org. Chem.*, **1991**, *56*, 6729.

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