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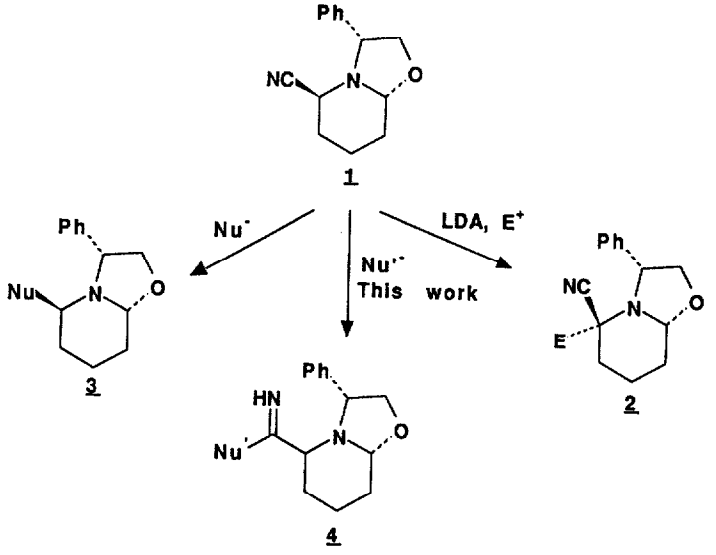
Asymmetric Synthesis XVIII[1].
Preparation of Chiral 1,2-diamines via the CN(R,S) Method. Application to the Synthesis of an Analogue of Tetraponerine.

Jieping ZHU, Jean-Charles QUIRION, Henri-Philippe HUSSON*

Institut de Chimie des Substances Naturelles du C.N.R.S.
91198 Gif-sur-Yvette Cedex, France.

Abstract : The reaction of organo-lithium or cuprate derivatives towards the cyano group of 2-cyano-6-phenyloxazolopiperidine synthon 1 gives an imine which is reduced to a primary amine with a remarkable stereoselectivity. An application of this reaction to the synthesis of an analogue of tetraponerine is presented.

In continuation of our work on the asymmetric synthesis of piperidine alkaloids, we turned our attention to the reactivity of nucleophiles towards the cyano group of synthon 1. In our previous work, the amino-nitrile function had been regarded as a potential iminium ion reacting with nucleophiles or as a masked function leading to an anion for electrophilic substitution[2] (Scheme I).

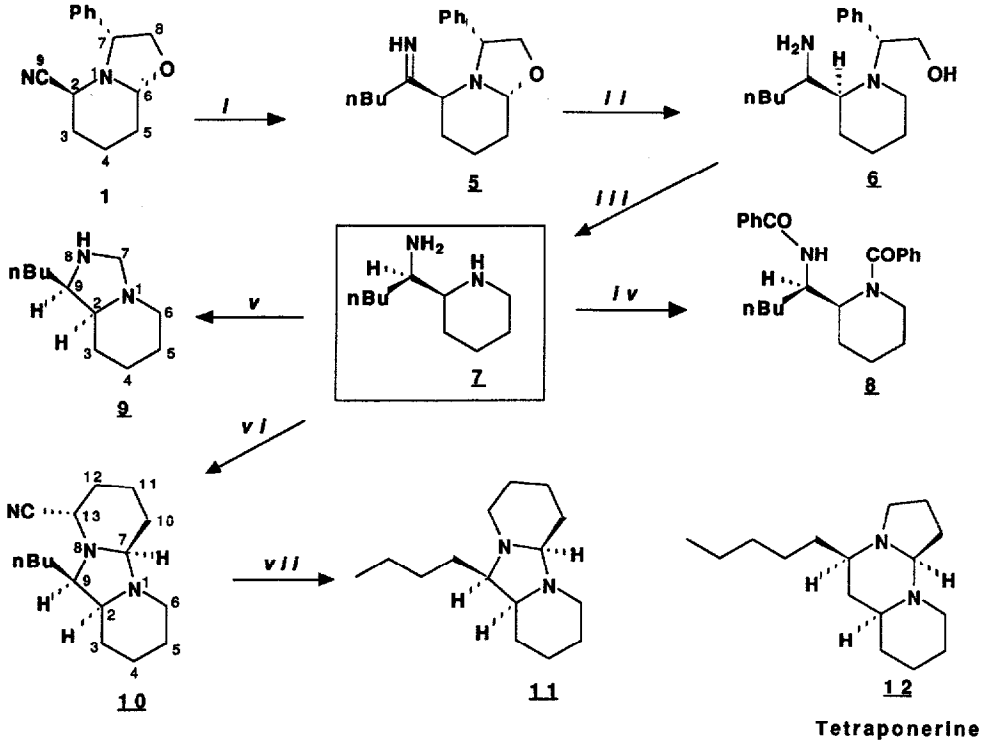


SCHEME I

Recent results obtained in our laboratory[3] and in others[4] have indicated that a lithium derivative can react specifically on an α-amino-nitrile without disrupting the oxazolidine function. We decided to take advantage of these results to prepare some

1,2-diamine derivatives which could be considered as intermediates for the preparation of more sophisticated structures. Here, we present the first applications of this reaction to the preparation of original di and tricyclic diaza compounds.

The reaction of synthon 1 with n-BuLi in ether at 0°C furnished a single imine 5 (IR ; ν_{cm}-1 = 1650) (Scheme II). We observed the same reaction with a cuprate (nBu_2CuLi). This result is rather surprising as cuprates are known to be more reactive towards oxazolidines than amino-nitriles[5]. The complete reduction of 5 with $NaBH_4$ in methanol occured with a remarkable stereoselectivity furnishing the amino-alcohol 6[6].



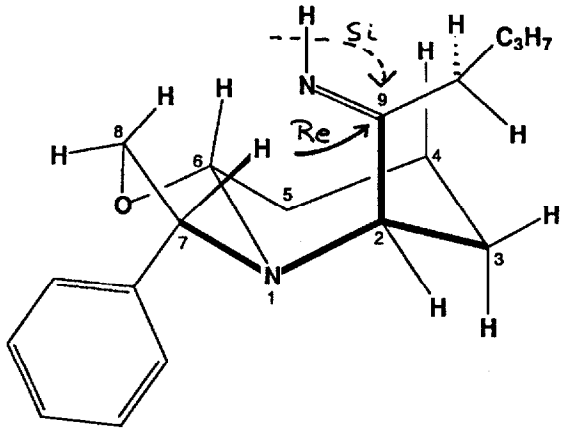
SCHEME II

Reagents : i) nBuLi, Et_2O, 0°C, (87 %) or nBu_2CuLi, Et_2O, - 78° → 0°C (96 %) ; ii) $NaBH_4$, MeOH (91 %, d.e > 95 %) ; iii) H_2, $Pd(OH)_2/C$,MeOH, 5 h ; iv) PhCOCl, pyridine ; v) H_2CO, CH_3CO_2H (68 %, 2 steps) ; vi) Glutaraldehyde, citric acid, KCN (52 %, 2 steps) ; vii) $AgBF_4$, 0°C, then $Zn(BH_4)_2$, -50°C (61 %).

This stereoselectivity can be explained by a preferred attack on the Re-face of the more stable conformation in which the imine group is above the oxazolidine ring to minimize steric hindrance (Figure).

The Si-face attack would imply an approach of the nucleophile with three strong steric interactions (H-6, H-4 and H-7). As the absolute configuration at C-2 of 1 and 5 is

known as S on the basis of our previous results[2] we postulate that the absolute configuration of 6 is 2S, 9R.



FIGURE

Hydrogenolytic cleavage (H_2/Pd(OH)$_2$-C/MeOH, 5 h) furnished the diamine 7 which was very difficult to purify and was caracterized as its diamide derivative 8[7]. The crude product of hydrogenolysis was used for the next steps.

Product 7 was reacted with formaldehyde, thus furnishing the aminal 9[8]. The coupling constant value between H-2 and H-9 (J = 5.3 Hz) is in agreement with the values reported by Crabb[9] and corroborates the configuration described above for the two asymmetric centers.

Our interest in the chemistry and biological properties of ant venom alkaloids prompted us to prepare an analogue of tetraponerine 12 (Scheme II), a natural product previously isolated from Tetraponera sp.[10].

For this purpose, diamine 7 was condensed with glutaraldehyde, in acidic medium. The intermediate iminium was then trapped by KCN to furnish the single compound 10[11]. The stereochemistry of the two new chiral centers was determined after complete attribution of the NMR spectra. Values of the coupling constants of H-13 (J = 3.2 and J = 3.6 Hz) indicated an equatorial position of this proton in agreement with an axial attack of the nitrile on the iminium ion. The ring junction proton H-7 is unambiguously axial (J = 10.3 and J = 1.9 Hz). The preparation of compound 11[12] was performed in THF by generation of the iminium ion ($AgBF_4$) and reduction with Zn(BH_4)$_2$. The use of other reducing agents furnished complex mixtures of products due to the relative instability of the aminal function. Compound 11 appeared to have the same relative configuration as tetraponerine-8 12, and is therefore an analogue differing only by reversal of B and C ring size.

The preparation of other diazapolycyclic compounds is under investigation and will be reported later.

References and Notes

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3 - J.L. Marco, J. Royer, H.-P. Husson, Tetrahedron Lett., 1985, 26, 6345. V. Ratovelomanana, J. Royer, H.-P. Husson unpublished results.

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6 - All new compounds have been fully characterized and their spectral data are in accord with the proposed structures. 6 oil ; MS, m/z : 290 ($M^{+\cdot}$), 204. $[\alpha]_D^{20}$: - 80° ($CHCl_3$, c = 1.0). ^1H NMR ($CDCl_3$, 200 MHz) δ(ppm) : 0.9-1.8 (m, 16H), 2.35 (d.t, J = 10.7 Hz, J = 1.0 Hz, H-2 ax), 2.98 (d.t, J = 11.2 Hz, J = 1.0 Hz, H-6 eq), 3.65 (m, H-7 or H-8 and H-9), 4.10 (t, J = 10.4 Hz, H-7 or H-8), 4.48 (dd, J = 10.4 Hz, J = 4.5 Hz, H-7 or H-8). ^{13}C NMR ($CDCl_3$, 50 MHz) δ : 22.9, 23.8, 24.2, 26.2, 29.2, 34.7, 46.2 (C-6), 49.5 (C-9), 59.8 (C-2), 60.5 (C-7), 60.9 (C-8), 127.4, 128.1, 128.9, 136.4.

7 - 8 : oil, $[\alpha]_D^{20}$: + 48° ($CHCl_3$, c = 1.0), MS, m/z : 378 ($M^{+\cdot}$), 258, 188. ^1H NMR ($CDCl_3$, 200 MHz) δ(ppm) : 3.10 (t.d, J = 12.0 Hz, J = 3.0 Hz, H-6 ax) ; 3.50 (d.t, J = 13.2 Hz, J = 2.0 Hz, H-2 ax), 4.80 (m, H-9), 5.05 (m, H-6 eq).

8 - 9 : oil ; MS, m/z : 182 ($M^{+\cdot}$), 125 ; $[\alpha]_D^{20}$: + 41° ($CHCl_3$, c = 1.0), ^1H NMR ($CDCl_3$, 200 MHz) δ(ppm) : 0.7-1.8 (15 H), 2.03 (t.d, J = 10.5 Hz, J = 3.0 Hz, H-6 ax) 2.11 (d,d.d ; J = 8.0 Hz, J = 5.3 Hz, J = 1.5 Hz, H-2), 3.05 (d, J = 6.3 Hz, H-7) ; 3.08 (d.t, J = 10.5 Hz, J = 1.5 Hz, H-6 eq), 3.25 (d.d.d, J = 6.5 Hz, J = 5.3 Hz, J = 3.1 Hz, H-9), 3.98 (d, J = 6.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 50 MHz) δ(ppm) : 13.7 (CH_3), 22.4, 24.0, 24.4, 25.3, 28.6, 31.2, 49.8 (C-6), 59.7 (C-9), 65.0 (C-2), 68.9 (C-7).

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11 - 10 : oil ; MS, m/z : 267 ($M^{+\cdot}$), 204 ; $[\alpha]_D^{20}$: - 42° ($CHCl_3$, c = 1.1) ; ^1H NMR ($CDCl_3$, 400 MHz) 2.26 (ddd, J = 11.2 Hz, J = 8.7 Hz, J = 2.4 Hz, H-2) ; 2.81 (dd, J = 10.1 Hz, J = 1.9 Hz, H-7), 2.85 (H-9), 3.12 (d.t, J = 10.2 Hz, J = 2.5 Hz, H-6 eq). ^{13}C NMR ($CDCl_3$, 50 MHz), 14.1 (CH_3), 19.9, 23.1, 24.7, 25.7, 28.2, 29.2, 29.3, 32.1, 49.4 (C-6), 50.8 (C-13), 60.9 (C-9), 66.3 (C-2), 80.0 (C-7), 118.2 (CN).

12 - 11 : oil ; MS, m/z 236 ($M^{+\cdot}$), 179 ; $[\alpha]_D^{20}$: + 10° ($CHCl_3$, c = 0.9) ; ^1H NMR ($CDCl_3$, 400 MHz) 0.85 (t, 3 H, J = 6 Hz), 1.2-1.6 (m, 18 H), 1.9-2.5 (m, 5 H, H-2, H-6 ax, H-7, H-9, H-13 ax), 3.08 (m, 2 H, H-6 eq, H-13 eq). ^{13}C NMR ($CDCl_3$, 50 MHz), 14.2 (CH_3), 49.5 (C-6), 51.4 (C-13), 63.2 (C-9), 66.7 (C-2), 84.9 (C-7).

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