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Asymmetric Synthesis. XXII[1]. Formal Synthesis of (-) - Perhydrohistrionicotoxin.

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Abstract The synthesis of (-)-depentylperhydrohistrionicotoxin **2** from the 2-cyano-6-oxazolopiperidine synthon (-) **3** has been achieved. The spiro skeleton was formed by an aldol cyclization of a methyl ketone and an aldehyde function belonging to chains borne at C-2. Since the transformation of (±)-**2** into (±)-perhydrohistrionicotoxin **1** is known, the synthesis of (-)-**2** represents a formal synthesis of (-)-perhydrohistrionicotoxin.

A great deal of interest has been shown in the preparation of piperidines containing a spirocyclohexane substituent. This system occurs in the potent frog toxin histrionicotoxin (HTX)[2] which, along with its equally active perhydroderivative (PHTX)[3] **1**, has been the subject of numerous synthetic efforts. Although more than fifty published papers[4] have been concerned with the syntheses in this series only three of them (HTX[4d], PHTX[3c, 5]) deal with asymmetric synthesis.

In this paper, we report an extension of the CN(*R, S*) method[1,6] using the chiral synthon (-)-**3** for the synthesis of spiropiperidine alkaloids. We reasoned that substitution of the aminonitrile anion followed by nucleophile addition to the nitrile should allow the formation of the spiro skeleton via an intramolecular aldol condensation. The methyl ketone **9** was the key intermediate in this strategy; its synthesis should be possible by hydrolysis of the corresponding imine formed by a chemoselective reaction of MeLi on the CN group as we have shown in recent studies[7].

The condensation of the anion derived from (-)-**3** with 2-(2-bromoethyl)-1,3-dioxolane gave **4**; since the reaction proceeds with retention of stereochemistry[8], the newly created quaternary center has the 2*R* configuration, corresponding to the natural HTX[2] series. Treatment of **4** with MeLi in ether afforded imine **5** which was hydrolysed directly, without purification, in acidic medium at room temperature. However the tricyclic ketal **6**[9] was isolated instead of the expected free ketone. Although it has been impossible to confirm the configuration of the ketal center (C-7), an examination of the Dreiding models indicated that only the structure as depicted for compound **6** is possible.

Depentyl PHTX has been claimed to be as active as PHTX[3c] and its conversion into PHTX has been previously reported[10]. So we decided to completely reduce the ether system of **6** with LAH/ $AlCl_3$. The

epimeric mixture (75/ 25) of alcohols **7** formed quantitatively was treated sequentially with H_2/ Pd-C to remove the chiral appendage, then with benzyl bromide to protect the secondary amine with an unsubstituted protective group in order to prevent side reactions. Swern oxidation (oxalyl chloride, DMSO) of alcohols **8** afforded ketone **9** as a single product. Refluxing **9** in 1.5N HCl gave the enone **10**[11] $[\alpha]^{20}_D$ =+68 (c=1.16, $CHCl_3$) resulting from hydrolysis of the ketal followed by intramolecular aldol condensation.

The next step was the 1, 4-reduction of the conjugated ketone with H_2, Pd/ $BaSO_4$. It is interesting to note that in these conditions the benzyl group was unaffected. Many difficulties were encountered in the introduction of the butyl chain by addition onto the keto group of **11** due to steric hindrance. Neither Grignard nor cerium reagents led to the desired product. Finally the alcohol **12** $[\alpha]^{20}_D$ =+4 (c=0.68, $CHCl_3$)[12] was obtained as a single isomer in 37% yield (82% after recovering starting material) by addition of BuLi in ether[13].

The ^1H NMR spectrum of **12** indicated, by comparison with the results published by Pearson[14], that the C.2-N.1 bond and the butyl chain are in a *cis* relationship in the cyclohexane ring[15] since a very large non-equivalence of the benzylic methylene protons was observed (δ=3.76 and 3.12 ppm).

The endocyclic double bond of **13** was obtained by treatment of a solution of **12** in deoxygenated benzene at reflux with HI[16]; this product has been previously obtained in racemic form [14, 17]. Alternatively, dehydration with $POCl_3$ in pyridine led to a mixture of the endocyclic and exocyclic double bonds ; the isomerisation of the later failed in the various conditions previously reported[18], but we noticed that the treatment of the exocyclic isomer with HI furnished the endocyclic compound in good yield. A hydroboration - oxidation reaction as previously described for the racemic form of **13**[16a] afforded the epimeric alcohols **14a** and **14b** in a 2: 1 ratio. Finally hydrogenolysis of the benzyl group furnished (-)-depentylperhydrohistrionicotoxin **2** $[\alpha]^{20}_D$ = -45 (c=0.54, $CHCl_3$) identical in all respects with already described samples ($[\alpha]_D$, MS, NMR[3c]).

In conclusion, the enantioselective synthesis of (-)-depentylperhydrohistrionicotoxin **2** in 14 steps and 8% overall yield compares favorably with the other syntheses.

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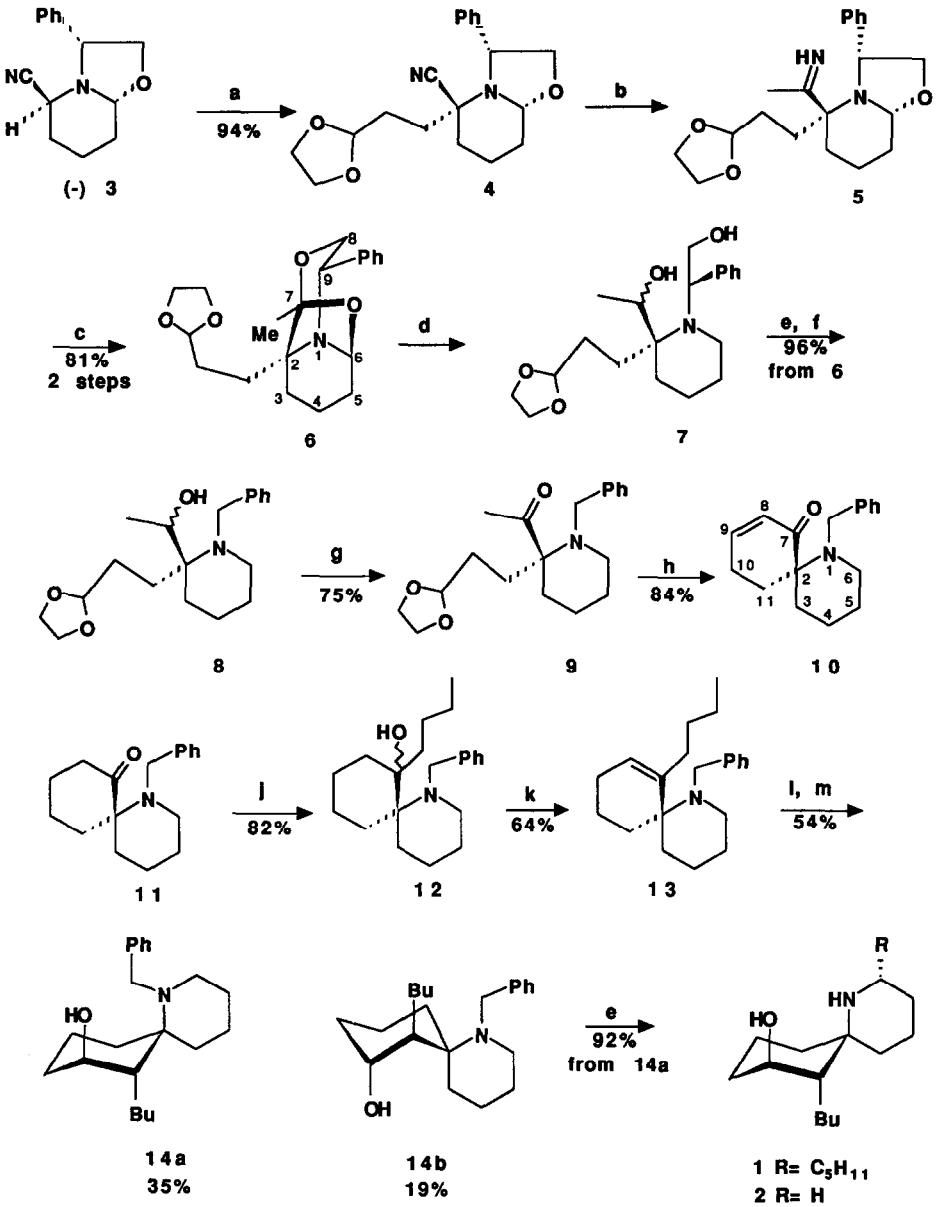
References and Notes

(1) Part 21 : Yue, C.; Royer, J.; Husson, H.-P. *J.Org. Chem.* 1990, **55**, 1140.

(2) Daly, J. W.; Karle, I. L.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* 1971, **68**, 1870.

(3) (a) Daly, J. W. In "Progress in the Chemistry of Organic Natural Products"; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer Verlag: Berlin, 1982; Vol. 41, pp 205-340. Witkop, B.; (b) Gössinger, E. In The Alkaloids; Brossi, A., Ed.; Academic Press : New-York, 1983. pp 139-251. (c) Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta* 1982, **65**, 252.

(4) For a comprehensive review on studies before 1989 see (a) Kotera, M. *Bull. Soc. Chim. Fr.* 1989, 370. For syntheses reported later see (b) Duhamel, P.; Kotera, M.; Monteil, T.; Marabout, B. *J. Org. Chem.* 1989, **54**, 4419. (c) Tanner, D.; Sellén, M.; Bäckvall, J.-E. *J. Org. Chem.* 1989, **54**, 3374. (d) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* 1990, **112**, 5875.



Reagents and conditions: (a) LDA, 2-(2-bromoethyl)-1,3-dioxolane, THF, HMPT, -78°C; (b) MeLi, ether -78°C, 1h then 0°c 2h; (c) Citric acid,H_2O_2- CH_2Cl_2,pH: 2-3; 2 days; (d) LAH/ $AlCl_3$, THF, -40°C; (e) H_2, Pd/C, MeOH; (f) $PhCH_2Br$, DMF, $NaHCO_3$, 80°C, 2h; (g) $(COCl)_2$, DMSO then Et_3N; (h) 1.5 N HCl, reflux; (i) H_2, $Pd/BaSO_4$, AcOEt, 5h; (j) BuLi, ether; (k) HI, benzene, reflux, 13h; (l) $BH_3.Me_2S$, THF reflux, 7h; (m) NaOH, H_2O_2, diglyme, 80°C, 36h.

(5) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* 1989, **111**, 4852.
(6) The generality of this method, allowing a remarkable stereocontrol for the formation of the new R or S asymmetric centers by CN elimination, has led us to call it the CN(R,S) method, in recognition of the Centre National de la Recherche Scientifique which supports this research. For examples of this strategy see ref. (1).
(7) (a) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* 1989, **30**, 5137.
(b) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* 1989, **30**, 6323.
(8) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* 1983, **105**, 7754.
(9) All new compounds have been fully characterized and their spectral data are in accord with the proposed structures. **6** : needles m. p. 118°C (ether-hexane) MS, m/z : 345, 302, 272, 182; $[\alpha]^{20}_D$: -54 (c=1.1, $CHCl_3$), ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) : 1.40-2.50 (m, 10H), 3.78-3.98 (m, 4H), 4.11 (dd, J=11.0 Hz, J=6.7 Hz, H-8eq), 4.20 (dd, J=11.0 Hz, J=10.7 Hz, H-8ax), 4.45 (dd, J=10.7 Hz, J=6.7 Hz, H-9ax), 4.90 (t, J=3.7 Hz, H-6eq), 4.95 (t, J=4.4 Hz, OCHO), 7.15-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.33 MHz) δ (ppm) 16.8 (Me), 17.7, 24.9, 28.1, 29.6, 30.3, 52.7 (C-9), 63.6 (C-8), 65.1 (OCH_2CH_2O), 67.8 (C-2), 90.6 (C-6), 103.8 (C-7), 104.6 (OCHO), 126.9, 127.0, 128.5, 140.0.
(10) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* 1975, **97**, 430.
(11) **10**, oil, IR ($CHCl_3$) ν_{max} : 1675 cm^{-1}, MS, m/z : 255, 187, 91; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) : 1.4-2.35 (m, 9H), 2.42-2.58 (m, H-6ax and H-11), 2.91 (m, H-6eq), 3.46-3.60 (AB system, J=14.1 Hz, NCH_2Ph), 5.95 (d, J=10.0 Hz, H-8), 6.81 (br. d, J=10.0 Hz, H-9), 7.15-7.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 50.33 MHz) δ (ppm) : 20.4, 24.5, 25.5, 27.8, 31.3, 47.2 (C-6), 56.2 (C-7), 64.8 (C-2), 126.6, 128.1, 129.6, 129.9 (C-9), 141.0, 147.5 (C-8), 203.3 (C-7).
(12) **12**.: oil, MS, m/z : 315, 272, 258, 200, 187, 91; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) : 0.90 (t, J=7.0 Hz, Me), 1.15-1.90 (m, 20H), 2.09 (td, J=11.3 Hz, J=3.0 Hz, H-6ax), 2.70 (dt, J=11.3Hz, J=4.5Hz, H-6eq), 3.95 et 4.25 (AB system, J=14.9Hz, NCH_2Ph), 7.15-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.33 MHz) δ (ppm) : 14.3 (Me), 19.5, 19.8, 22.2, 23.1, 23.7, 23.8, 25.3, 30.5, 32.2, 34.0, 44.8 (C-6), 53.1 (NCH_2Ph), 62.3 (C-2), 79.1 (C-7), 126.3, 127.9, 128.5, 142.5.
(13) In each cycle, after the addition of 1 equivalent of n-butyllithium and heating at reflux for 10 min., exactly 1 equivalent of methanol was added. In this way a moderate yield of **12** could be obtained directly despite the occurence of proton transfer from **11** to the lithium reagent in competition with carbonyl addition. See Corey, E. J., Balanson, R. D., *J. Amer. Chem. Soc.* 1974, **96**, 6526. Repeating three times this operation yielded the alcohol **12** in 37% yield.
(14) Pearson, A. J.; Ham, P. *J. Chem. Soc. Perkin Trans. I* 1983, 1421.
(15) Examination of molecular models did not allow the determination of the more stable conformation of the intermediate. A MM2 study of the relative stabilities of the four possible conformers is under investigation and will be reported in the full paper.
(16) Snider, B. B.; Real, R. B. *J. Org. Chem.* 1988, **53**, 4508.
(17) (a) Godleski, S. A.; Heacok, D. J.; Meinhart, J. D.; Wallendael, S. V. *J. Org. Chem.* 1983, **48**, 2101.
(b) Carruthers, W.; Cumming, S. A. *J. Chem. Soc. Perkin Trans. I* 1983, 2383.
(18) Holmes, A. B.; Russell; K.; Stern; E. S.; Stubbs; M. E.; Wellard; N. K. *Tetrahedron Lett.* 1984, **25**, 4163.

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