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ASYMMETRIC SYNTHESIS XX[1].
PREPARATION OF A NOVEL SPIROPIPERIDINE SYSTEM BY THE CN(R,S) METHOD.

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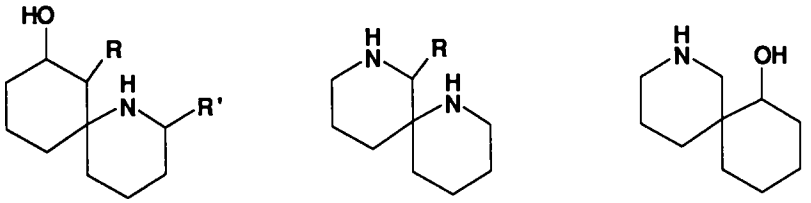
Abstract : A novel spiropiperidine system i.e an aza structural analog of histrionicotoxin has been constructed from 2-cyano-6-phenyloxazolopiperidine synthon 3. The suitable quaternary carbon was created by alkylation at the position α to the nitrile followed by transformation of the nitrile group into a primary amine. Final aminoreductive cyclisation gave the spiro system.

Natural histrionicotoxin and its perhydro congeners possess unique pharmacological activity as neurotoxins[2]. Structure activity relationship studies suggested the importance of the two heteroatoms in the mode of action of these series of alkaloids[3]. It was therefore attractive to synthesize a molecule in which two piperidine rings have a spiro-junction i.e. aza structural analogs 9 of both the hitherto reported spiropiperidine alkaloids histrionicotoxin 1 and nitramine 2[4] (figure).

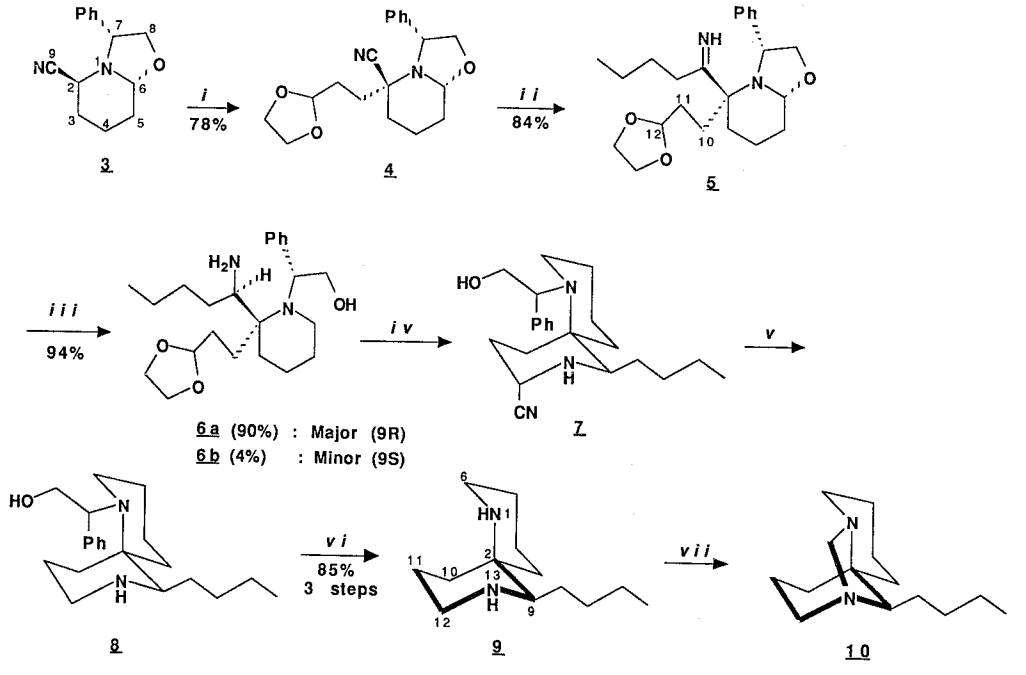


1 9 2

Figure

Our operating strategy was based on our recent finding that 1,2-diamines could be obtained in a stereoselective manner from 2-cyano-6-phenyloxazolopiperidine synthon 3[5]. Indeed reaction of a lithio derivative or a cuprate on the nitrile group of 3 afforded an imine which was subsequently reduced to a primary amine. However our strategy involved the reactivity of a tertiary nitrile whose behaviour was unknown ; in particular elimination could not be excluded[6].

The synthesis started with the alkylation of synthon 3 by the ethylene ketal of bromo-3 propanal (Scheme). The absolute configuration at C-2 is known as R on the basis



SCHEME

i) LDA, THF, - 78°C then 2-(2-Bromoethyl)-1,3-dioxolane ; ii) BuLi, Et_2O, - 78°C → 0°C ; iii) $NaBH_4$, MeOH ; iv) CH_2Cl_2, H_2O, KCN, HCl, pH. 2-4 ; v) $NaBH_4$, MeOH ; vi) H_2, Pd-C, MeOH ; vii) HCHO, CH_3COOH.

of our previous results[7]. Compound 4 was submitted to reaction with BuLi in ether to give the imine 5 (y = 84%) ; the formation of elimination or dialkylation products was not observed. The use of cuprate derivative did not improve the yield as observed in our first report[5]. The concomitant reduction of the imine and amino-ether functions were performed with $NaBH_4$ in MeOH ; the primary amine 6 was obtained as a mixture of two isomers 6a/6b[8] (95/5) in 94% yield. The absolute configuration of the new chiral center C-9 as R in the major product 6a can be explained by a preferred attack on the Re-face, as discussed earlier[5], to minimize steric hindrance. The Si-face attack would imply an approach of the nucleophile with three strong steric interactions (H-4, H-6 and H-7) so the absolute configuration of 6a is 2R,9R.

All attempts to obtain the bicyclic product 9 directly from 6a by a deprotective and amino-reductive sequence failed[9]. The only product isolated resulted from the condensation of the aldehyde with the nitrogen of the piperidine ring[10]. It was thus

necessary to follow a stepwise scheme. The deprotection of the aldehyde function and cyclization were performed in acidic medium. The intermediate iminium was trapped with KCN to furnish the unstable amino-nitrile 7 which was not purified but subjected immediately to reduction ($NaBH_4$, MeOH), leading to the diamino alcohol 8[11]. The hydrogenolysis of the chiral appendage furnished the spirodiamine 9[12] as a single compound (y = 85% from 6). The absolute configuration of the two chiral centers being settled as R, the examination of Dreiding models showed that 9 can adopt the conformation indicated on the scheme in which the C-2..N-1 bond is axial and the butyl chain equatorial. In order to confirm this structure we prepared the tricyclic derivative 10 by condensation of the diamine with formaldehyde in acidic medium. The aminal 10[13] was obtained in good yield showing the proximity of the two nitrogen atoms.

In conclusion, the reaction of synthon 1 with organometallic derivatives is a valuable method for the preparation of 1',2'substituted 1,2-diamines allowing the construction of a new aza-spiro skeleton. The preparation of more functionalized compounds and the study of their pharmacological properties are under investigation and will be reported later.

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8 - Diamine 6. 6a : oil,$[\alpha]_D^{20}$: - 33° ($CHCl_3$, c = 3.0). IR : 3300, 2900, 1460cm^{-1}. MS, m/e (%) : 390 (M^+, 2), 359(5), 304(100). ^1H NMR : 0.90 (t, J = 6.0 Hz, Me),

1.2-1.8 (m, 16H), 2.67 (td, J = 9.2 Hz, J = 2.5 Hz, H-6ax), 3.0-3.2 (m, H-6eq, H-9, OH, NH_2), 3.42 (dd, J = 10.8 Hz, J = 4.9 Hz, H-7 or H-8), 3.70 (m, 4H, $-OCH_2CH_2O-$), 3.86 (t, J = 10.8 Hz, H-7 or H-8), 4.50 (br.s, H-12), 4.61 (dd, J = 10.8 Hz, J = 4.9 Hz, H-7 or H-8), 7.2-7.4 (m, 5H). ^{13}C NMR : 13.9 (Me), 21.1, 22.6, 26.5, 29.1, 29.9, 30.1, 32.0 (8 CH_2), 41.7 (C-9), 57.8 (C-6), 60.4 (C-7), 61.1 (C-2), 62.7 (C-8), 64.6 (OCH_2CH_2O), 104.2 (C-12), 126.8, 127.7, 129.3, 140.2 (ArC).

6b : oil, $[\alpha]_D^{20}$: - 44° ($CHCl_3$, c = 3.0). IR : 3300, 2950cm^{-1}. MS, m/e (%) : 390 (M^+, 2), 359(8), 304(100). ^1H NMR : 0.95 (t, J = 6.0 Hz, Me), 1.2-2.0 (m, 16H), 2.57 (td, J = 9.3 Hz, J = 2.5 Hz, H-6ax), 3.23 (ddd, J = 9.3 Hz, J = 2.0 Hz, J = 1.0 Hz, H-6 eq), 3.46 dd, (J = 10.8 Hz, J = 2.3 Hz, H-7 or H-8), 3.70 (m, 4H, OCH_2CH_2O), 3.72 (m, H-9), 4.01 (t, J = 10.8 Hz, H-7 or H-8), 4.24 (dd, J = 10.8 Hz, J = 2.3 Hz, H-7 or H-8), 7.2-7.4 (m, 5H). ^{13}C NMR : 13.8 (Me), 21.1, 22.6, 25.9, 28.4, 28.7, 28.9, 29.3, 30.7 (8 CH_2), 42.5 (C-9), 57.7 (C-6), 60.4 (C-7), 61.3 (C-8), 62.2 (C-2), 64.9 (OCH_2CH_2O), 103.9 (C-12), 127.6, 128.1, 130.0, 137.9 (Ar.C).

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- Detailed results of this reaction will be reported elsewhere.

- Spiro derivative 8 : IR : 3300, 2950cm^{-1}. MS, m/e (%) : 330 (M^+, 2), 299 (77), 231(62), 230(100), 217(65), 209(67), 124(69). ^1H NMR : 0.90 (t, J = 6.0 Hz, Me), 1.0-1.8 (m, 16H), 1.90 (m, H-12 ax), 2.67 (m, H-9), 2.75 (m, H-6ax), 2.95 (dt, J = 14.5 Hz, J = 3.9 Hz, H-6 eq), 3.28 (ddd, J = 9.5 Hz, J = 1.5 Hz, J = 1.0 Hz, H-12 eq), 3.43 (dd, J = 10.3 Hz, J = 5.0 Hz, H-7 or H-8), 3.91 (t, J = 10.3 Hz, H-7 or H-8), 4.53 (dd, J = 10.3 Hz, J = 5.0 Hz, H-7 or H-8). ^{13}C NMR : 14.3 (Me), 19.5, 22.7, 22.9, 23.3, 25.2, 29.4, 31.1, 31.3 (8 CH_2), 39.2 (C-12 or C-6), 40.2 (C-6 or C-12), 56.1 (C-2), 56.9 (C-9), 59.0 (C-7), 61.7 (C-8).

- 7-butyl 1,8-diazaspiro (5,5)-undecane 9 : $[\alpha]_D^{20}$: + 40° ($CHCl_3$, c = 1.0). IR : 3300, 2950, 1420cm^{-1}. MS : m/e (%) : 210 (M^+, 5), 184(100), 153(10), 96(100). ^1H NMR : 0.90 (t, J = 6.0 Hz, Me), 1.0-2.0 (m, 15H), 2.28 (m, H-9 ax), 2.38 (dt, J = 13.9 Hz, J = 2.5 Hz, H-3 eq or H-10 eq), 2.58 (td, J = 10.2 Hz, J = 4.2 Hz, H-12 ax), 2.77 (m, 2xH-6), 3.00 (dt, J = 11.6 Hz, J = 3.8 Hz, H-12 eq). ^{13}C NMR : 14.2 (Me), 19.9, 22.1, 23.0, 26.9, 28.3, 29.3, 30.2, 33.4 (8 CH_2), 40.2 (C-6), 46.8 (C-12), 52.2 (C-2), 65.2 (C-9).

- Aminal 10 : $[\alpha]_D^{20}$: + 67° ($CHCl_3$, c = 1.5). IR : 2950cm^{-1}. MS : m/e (%) 222 (M^+, 30), 181(100), 165(63), 123(53). ^1H NMR : 0.88 (t, J = 6.5 Hz, Me), 1.1-2.1 (m, 16H), 2.6-2.9 (m, 5H, 2xH-6, 2xH-10, H-9), 3.58 and 3.87 (2d, 2d, $N-C\underline{H}_2-N$). ^{13}C NMR : 14.2 (Me), 19.9, 20.1, 23.1, 25.5, 27.8, 29.8, 30.2, 32.7 (8 CH_2), 44.7 (C-6 or C-12), 56.3 (C-12 or C-6), 59.0 (C-2), 71.9 (C-9), 74.7 ($N-\underline{C}H_2-N$).

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