ARTICLE

OBC
www.rsc.org/obc

Diastereoselective preparation of 2,4,6-trisubstituted-2′-cyano-piperidines: application to the construction of the carbon framework of perhydrohistrionicotoxin

Richard Malassene,[a] Enguerran Vanquelef,[a] Loic Toupet,[b] Jean-Pierre Hurvois*[a] and Claude Moinet[a]

[a] *Laboratoire d'Electrochimie, UMR 6509, Institut de Chimie, Université de Rennes I, Campus de Beaulieu, F-35042 Rennes Cedex, France. E-mail: Jean-Pierre.Hurvois@univ-rennes1.fr; Fax: + 33(0) 2 23 23 59 67*

[b] *Groupe Matière Condensée et Matériaux, Université de Rennes I, Campus de Beaulieu, F-35042 Rennes Cedex, France*

Received 26th September 2002, Accepted 25th November 2002
First published as an Advance Article on the web 8th January 2003

The anodic cyanation of methanolic solutions of the 2-alkyl-*N*-phenylpiperidines **6b–d** was performed in a flow cell equipped with a graphite felt anode. The reaction led to the formation of the 2-cyano-6-alkyl-*N*-phenylpiperidines **2b–d** and proceeded with a high degree of regioselectivity. The ^{1}H NMR spectra of the aminonitriles **2b–d** showed an epimeric mixture at C-6. The major isomer has a *trans* configuration in which the cyano group is axial and the alkyl substituent is equatorial. Conversely, electrochemical oxidation of the 4-methyl-6-pentyl-*N*-phenylpiperidine **6e** afforded the trisubstituted aminonitrile **2e** as a single diastereomer (>98% de). The 4-cyanobutyl side chain was incorporated in a two-step procedure to yield dinitrile **4e**. This latter compound was directly converted into spiropiperidine **5e** by using the Thorpe–Ziegler annulation procedure. The overall sequence (4 steps, 43%) allows the construction of the basic carbon framework of perhydrohistrionicotoxin.

Introduction

The histrionicotoxin family encompasses a large number of alkaloids isolated from skin extracts of the Colombian 'poison-arrow' frog *Dendrobates histrionicus*. First isolated by Witkop[1] and co-workers in 1971, histrionicotoxin (HTX) **1** or its saturated congener, perhydrohistrionicotoxin (PHTX) **1a**, are illustrative of this family (Fig. 1). These compounds act as non-competitive blocking agents of the acetylcholine-sensitive conductance system in neuromuscular preparations.[2]

Their unique biological properties coupled with their intriguing molecular frame, the 1-azaspiroundecane ring system, have made these alkaloids popular targets on which to study new synthetic compounds. Indeed, during the last decade, several elegant well-designed total or formal syntheses of (−)-HTX[3] and (±)-PHTX[4] have been completed. Despite these numerous approaches, there is interest in developing new synthetic tools for the construction of the heterocyclic framework of these alkaloids. In a recent report,[5] we have shown that lithiation of the 2-cyano-4-methyl-*N*-phenylpiperidine **2a** (lithium diisopropylamide, tetrahydrofuran, −30 °C) followed by the introduction 1-bromo-4-chlorobutane allowed the diastereoselective synthesis of the bifunctional α-aminonitrile **3a** (R_1 = H, R_2 = CH_3). On further treatment with NaCN in DMSO, substitution of the terminal chlorine atom readily occurred, to afford the dinitrile **4a**. The latter was submitted to a Thorpe–Ziegler condensation[6] (involving the cyano group at C-2 and the terminal nitrile-stabilized carbanion) which allows the construction of the spirocyclic piperidine **5a** through formation of the C-7,8 bond.[7]

Yet, anodic cyanation and alkylation of metallated α-aminonitriles, seemed to be a quite general approach for the formation of new carbon–carbon bonds in the position α relative to the nitrogen atom. Thus, to construct **4d** (R_1 = C_5H_{11}), conditions were needed for the stereoselective preparation of *trans*-**2d**. For the application of this strategy, one should be able to introduce the C-8,11 carbon unit through metallation of **2d**, with retention of configuration at C-2.

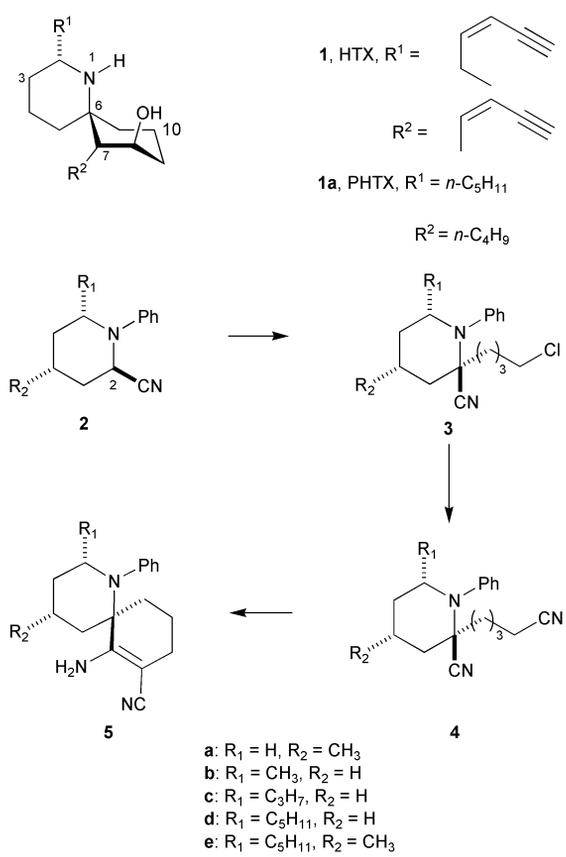
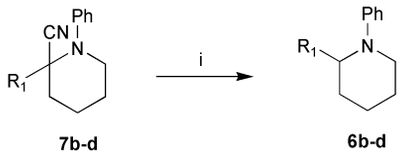


Fig. 1

For this, we focussed on the anodic cyanation[8] of substituted piperidines **6b–d** (Scheme 1), (a) to evaluate the regiochemical course of the oxidation procedure performed on these amines, (b) as an instrument to study the stereochemical course of addition of nucleophiles (H^- or CN^-) onto the

DOI: 10.1039/b209387a



Scheme 1 (i) $NaBH_4$ (4 equiv.), MeOH, 65 °C, 1.5 h.

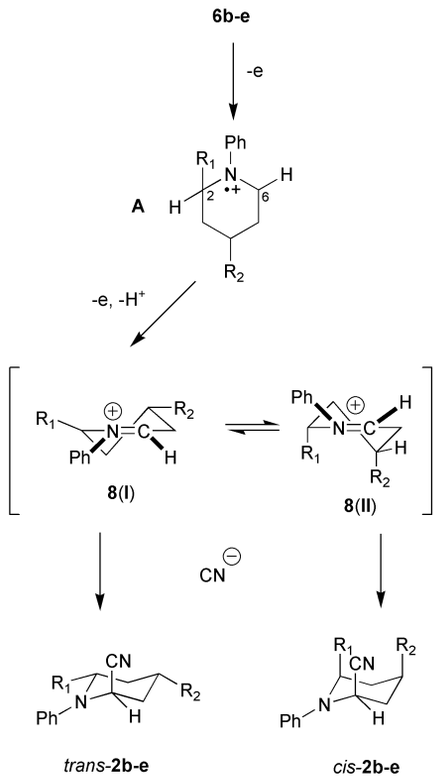
carbon–nitrogen double bond of 3,4,5,6-tetrahydropyridinium species, and (c) to demonstrate that application of the Thorpe–Ziegler annulation procedure could correctly orient the cyanoenamine moiety with respect to the side chain borne at the C-2 position of the piperidine ring. Details concerning the chemical manipulations performed on the resulting aminonitriles **2b–e** as well as the influence of a C-4 methyl substituent on the stereochemical outcome of these transformations are reported in the present paper.

Results and discussion

To demonstrate the generality of our synthetic plan, a series of 2-alkyl-*N*-phenylpiperidines **6b–d** were first synthesized (Scheme 1) by sodium borohydride reduction of *gem*-disubstituted aminonitriles **7b–d**. After extractive work-up and rapid filtration over silica gel, the expected amines were obtained as slightly yellow oils (78–93%).

In the ^{1}H NMR spectra of these amines, characteristic resonance multiplets signals attributed to H-2 were found at δ = 3.8–3.9. We next directly prepared the 2-cyano-6-alkyl-*N*-phenylpiperidines **2b–d**.[9] The electrochemical oxidation of amines **6b–d** (up to 3 g) was effected in a flow cell apparatus (*cf*. experimental section) equipped with graphite felt anode, and a stainless steel cathode. After electrolysis and usual work-up, the expected aminonitriles **2b–d** were obtained as single regioisomers in all cases. On the other hand, the ^{1}H NMR spectra of these aminonitriles revealed two sets of signals, indicating that epimeric mixtures were obtained. The ^{1}H NMR spectra of these mixtures, well resolved, serve to determine the structure of each epimer. For example, in the ^{1}H NMR spectrum of *trans*-**2b**, the H-2 signal appeared as a triplet system (J = 4.5 Hz) at δ = 4.15, whereas H-6 afforded a multiplet signal at δ = 3.30. Also, selective irradiation at δ = 0.91 (6-CH_3) removed a geminal coupling constant (6.0 Hz) from the H-6 signal, which appeared as a doublet of doublet system (J = 10.5 Hz and 4.0 Hz). Collectively, these results indicate that in the major epimer, the cyano group was axial and the methyl group was equatorial. The spectra of aminonitriles **2c** and **2d** closely resemble the spectrum of **2b**, it then appears that epimeric mixtures were also produced during the oxidation of amines **6b–d**. This observation agrees with the prediction that, of the two possible isomers that could be formed from the oxidation of **6b**, the unhindered *trans* adduct **2b** should be the more stable isomer. It was also shown that the *cis*/*trans* stereoselectivity varies with the size of the C-2 substituent. Whereas **6b** gave a 44% de, poor results were obtained with **6c** (26% de) or **6d** (4% de). These results are consistent with the formation of the iminium species **8b–c** in which the phenyl and C-2 substituent are in close proximity causing the so-called $A^{(1,2)}$ allylic effect.[10]

As the C-2 methyl group in **8b** is replaced by larger propyl and pentyl substituents in **8c** and **8d**, respectively, the $A^{(1,2)}$ strain increases significantly in **8b–d** (R_2 = H), shifting the equilibrium from **I** (in which the substituent is in a pseudo equatorial disposition) to the more energetically favoured conformer **II**. Axial attack of the cyanide anion (under a stereoelectronic mode) on each of these two conformers adequately accounts for the formation of either the *cis* and *trans* adducts. The presence of single adducts cyanated at the ring also revealed that favourable interactions should be taken into account between the partially occupied orbital on the nitrogen atom of the



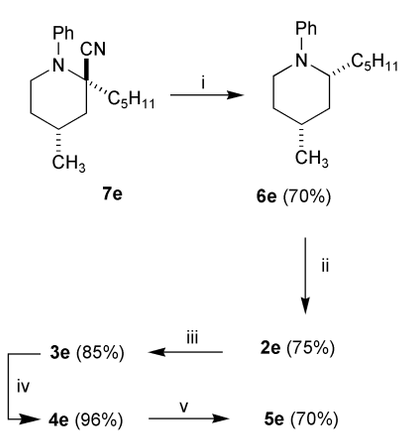
b (75%), *c* / *t*, 28 / 72
c (77%), *c* / *t*, 37 / 63
d (80%), *c* / *t*, 48 / 52
e (75%), *c* / *t*, 1 / 99

Scheme 2

radical cation **A** (Scheme 2) and the vicinal methylene protons at C-6.[11] Note that no detectable amount of the alternative regioisomers (**7b–d**), which could result from a proton loss at C-2 has ever been encountered.

To improve the *trans* selectivity of the reaction we believe that the iminium system **8e** (R_2 = CH_3) should be locked into conformation **I**, in which both the alkyl chains R_1 and R_2 were maintained in a pseudo equatorial position (in the presence of substituents at the C-2 and C-4 ring carbon atoms, conformer **II** should be strongly destabilized by transannular interactions).[12] Note that the all *cis* derivative **2e** should suffer from severe 1,3-diaxial interactions. To apply this strategy, the 2,6-dialkyl-*N*-phenylpiperidine **6e** was prepared from reductive decyanation of **7e**[13] (Scheme 3).

After extractive work-up, the ^{1}H NMR spectrum of the resultant crude reaction mixture revealed **6e** as a single



Scheme 3 (i) $NaBH_4$ (4 equiv.), MeOH, 65 °C, 1.5 h; (ii) −2 e, $-H^+$, NaCN (4 equiv.), AcOLi (20 g l^{-1}), 2.2 F mol^{-1}, MeOH; (iii), LDA, THF (2 M), −80 °C, $Br(CH_2)_4Cl$ (1.1 equiv.); (iv) NaCN (2 equiv.), DMSO, *n*-Bu_4NI (5 mol%), rt, 48 h; (v) LDA, THF, −80 °C to rt, 17 h.

diastereomer (>98% de). The relative stereochemistry of **6e** was not determined at this stage but was presumably the one drawn in Scheme 3. The possibility now exists to create a third stereogenic center at the piperidine ring employing anodic cyanation as the key step. The electrolysis[14] of a methanolic solution of **6e**, performed under conditions similar to those for amines **6b–d**, led predominantly to the expected adduct **2e** (85 : 15 mixture with its regioisomer **7e**). This product distribution reflects differences in the regioselectivity of oxidation between **6b–d** and **6e** and is consistent with a competitive proton loss at both sites α to the nitrogen atom of the ring.

However, the expected trisubstituted aminonitrile **2e** formed during this reaction was obtained as a single stereoisomer as determined from the ^{1}H NMR spectrum of the reaction mixture. Characteristic was the H-2 proton signal of the aminonitrile system which appeared as a doublet of doublet system (J = 4.50 Hz and 2.34 Hz) at δ = 4.24. Since no large coupling constant was observed with its neighbours it was concluded that H-2 was equatorial, hence the cyanide substituent adopted an axial disposition. Subsequent alkylation[15] of **2e** with 1-bromo-4-chlorobutane led to the formation of **3e** as a single diastereomer. The terminal chlorine atom was further displaced by cyanide under standard conditions, this yielded the polar dinitrile **4e** as pure material after chromatographic purification. The ^{13}C NMR spectrum of **4e** contained one set of signals indicating the formation of one geometric isomer. Twenty carbon resonance lines were observed, two of which were due to the C-2 and C-6 carbon atoms found at δ = 62.5 and 58.6, respectively. Also interesting were the two quaternary CN signals found at δ = 119.72 and 121.33. We sought to construct the C-8,7 bond of the azaspiroundecane ring system. To construct new rings in polycyclic systems, the Thorpe–Ziegler annulation[16] is a versatile key reaction for the synthesis of natural products. Accordingly, upon the exposure of a THF solution of **4e** to a stoichiometric amount of LDA at −78 °C and warming the reaction mixture to room temperature over a 17 hour period, the spirocyclic derivative **5e** was obtained (70%) as a slightly brown solid after rapid chromatographic purification. The spectral data of **5e** (^{1}H, ^{13}C NMR and *m/z*) was consistent with the proposed structure and revealed the formation of the cyanoenamine moiety. On the other hand, the relative orientation of the side chain substituent could not be determined from the ^{1}H NMR spectrum. Fortunately, from slow crystallization of a solution of **5e** single crystals were obtained. A further X-ray study[17] performed on one of these crystals indicated that both the pentyl side chain and the C-8,11 carbon unit were in a *cis* configuration (Fig. 2).

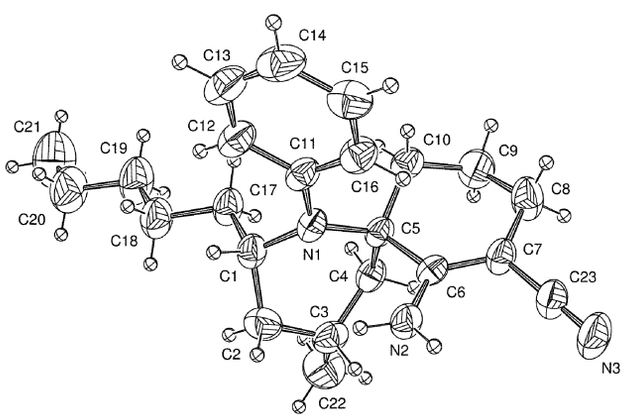


Fig. 2 ORTEP drawing of spiropiperidine **5e**.

Conclusion

In summary, a short and stereoselective route from simple piperidine systems to the heterocyclic core of PHTX has been developed. The presence of a stereodirecting group at C-4 allow the diastereoselective synthesis of the trisubstituted aminonitrile **4e**, an advanced intermediate in the synthesis of new spirocyclic piperidines. The utilization of a removable stereodirecting group is currently under investigation.

Experimental

General

Purification by column chromatography was performed using 70–230 mesh silica gel (Merck). TLC analyses were carried out on alumina sheets precoated with silica gel $60F_{254}$. IR spectra were recorded with a Perkin–Elmer FT-IR 16PC (KBr powder or methylene chloride). NMR spectra were recorded with a Bruker AH 300 FT spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C)] or a Bruker DPI 200 FT [200 MHz (^{1}H) and 50 MHz (^{13}C)]. Chemical shifts are expressed in ppm downfield from TMS where s, d, dd, t, q, m, designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet, respectively, and coupling constants J are given in Hz. High resolution mass spectra were obtained with a Mat 311 double focusing instrument at the CRMPO with a source temperature of 170 °C. An ion accelerating potential of 3 kV and ionizing electrons of 70 eV were used.

Materials

All glassware were oven dried (120 °C) over a 24 h period and cooled under a stream of argon. All reagents were obtained from a commercial source and were distilled prior to use. THF was distilled from sodium benzophenone ketyl and stored under an argon atmosphere. A solution of LDA (2 M) was purchased from Acros and was used without titration.

General procedure for the electrochemical oxidation

Amines **6b–e** (10 mmol), were dissolved in methanol (Carlo Erba RE 99.6%), containing lithium acetate dihydrate (20 g l^{-1}, Aldrich 98%) as the supporting electrolyte and sodium cyanide (4 equiv. per mol of substrate) as the cyanating agent. The solution was filtered over a Millipore (5 μm) system and electrolyzed in a flow cell[18] fitted with a graphite felt anode (diameter = 50 mm, thickness = 12 mm). The flow rate (f) of the solution was regulated by a peristaltic pump at f = 5 mL min^{-1}, and the current ($i_1 + i_2$) calculated according to a bielectronic process (2) is given by the expression : i (ampere) = $2 \times f \times 96500 \times 10^{-3}$ M/60 where M represents the molar concentration of the substrate. The outlet solution was evaporated under reduced pressure, the crude material was taken up in water (100 mL g^{-1} of the starting compound) and extracted with methylene chloride (2 × 100 mL g^{-1} of the starting compound). The organic layer was dried over $MgSO_4$ and concentrated. The α-cyanoamines **2b–e**, were purified by column chromatography on silica gel (eluent: diethyl ether and petroleum ether).

General procedure for the preparation of amines 6b–e

Solutions of cyanoamines **7b–e**[5] (10.0 mmol) in methanol (50 ml), were treated with $NaBH_4$ (40.0 mmol) and stirred at room temperature for 5 min. Then, the solution was warmed to 65 °C for 90 min. After cooling, a solution (30 ml) of ammonia (15%) was added and the solvent was removed under reduced pressure. The crude reaction mixture was extracted (30 ml × 3) with ether. The combined organic phases were dried over $MgSO_4$, and concentrated to give a crude material which was purified by silica gel chromatography using diethyl ether–petroleum ether as the eluent.

2-Methyl-1-phenylpiperidine 6b

R_f = 0.70, diethyl ether–petroleum ether = 1 : 2, colourless oil (1.36 g, 78%). δ_H(200 MHz, $CDCl_3$) 1.01 (3 H, d, J 6.6 Hz), 1.52–1.95 (6 H, m), 2.98 (1 H, td, J = 11.0 and 3.0 Hz), 3.21

(1 H, dm, *J* 12.0 Hz), 3.90 (1 H, m), 6.82 (1 H, t, *J* 7.2 Hz), 6.94 (2 H, d, *J* 8.1 Hz), 7.24 (2 H, m). HRMS calcd. for $C_{12}H_{17}N$ (M^+) 175.1361, found 175.1369.

1-Phenyl-2-propylpiperidine 6c

R_f = 0.75, diethyl ether–petroleum ether = 1 : 2, colourless oil (1.84 g, 91%). Found: C, 83.28; H, 10.35; N, 6.68. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89%. δ_H(300 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 7.1 Hz), 1.12–1.79 (10 H, m), 2.98 (1 H, td, *J* = 11.0 and 3.0 Hz), 3.33 (1 H, dm, *J* 12.0 Hz), 3.78 (1 H, m), 6.74 (1 H, tm, *J* 7.3 Hz), 6.87 (2 H, d, *J* 7.8 Hz), 7.21 (2 H, m). δ_C(75 MHz, $CDCl_3$) 14.2, 19.4, 20.2, 25.6, 27.8, 29.6, 43.7, 55.6, 116.3, 118.1, 129.0, 151.30. HRMS calcd. for $C_{14}H_{21}N$ (M^+) 203.1674, found 203.1684.

2-Pentyl-1-phenylpiperidine 6d

R_f = 0.75, diethyl ether–petroleum ether = 1 : 2, colourless oil (2.14 g, 93%). Found: C, 83.00; H, 10.85; N, 6.03. Calcd. for $C_{16}H_{25}N$: C, 83.06; H, 10.89; H, 6.05%. δ_H(200 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.3 Hz), 1.20–1.90 (14 H, m), 2.97 (1 H, td, *J* 12.6 Hz and 4.2 Hz), 3.32 (1 H, dm, *J* 12.5 Hz), 3.60–3.66 (1 H, m), 6.75 (1 H, t, *J* 7.3 Hz), 6.89 (2 H, d, *J* 7.9 Hz), 7.22 (2 H, m). HRMS calcd. for $C_{16}H_{25}N$ (M^+) 231.1987, found 231.1988.

4-Methyl-2-pentyl-1-phenylpiperidine 6e

R_f = 0.65, diethyl ether–petroleum ether = 1 : 2, colourless oil (1.71 g, 70%). δ_H(300 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 6.4 Hz), 1.03 (3 H, d, *J* 6.1 Hz), 1.1–1.65 (11 H, m), 1.75 (1 H, dm, *J* 10.3 Hz), 1.90 (1 H, dq, *J* 10.2 and 2.9 Hz), 2.77 (1 H, dt, *J* 13.0 and 3.7 Hz), 2.8 (1 H, m), 3.19 (1 H, dt, *J* 13.0 and 4.4 Hz), 7.00–7.11 (3 H, m), 7.20–7.30 (2 H, m). HRMS calcd. for $C_{17}H_{27}N$ (M^+) 245.2143, found 245.2138.

Cyanoamines **2b–d** were obtained as inseparable mixtures of *cis* and *trans* diastereoisomers. The following spectroscopic data refer to these mixtures obtained after chromatographic purification.

6-Methyl-1-phenylpiperidine-2-carbonitrile 2b

R_f = 0.70, diethyl ether–petroleum ether = 1 : 2, slightly amber-coloured oil (1.50 g, 75%). δ_H(200 MHz, $CDCl_3$) 0.90 (d, *J* 6.0 Hz, CH_3, *trans*), 1.15 (d, *J* 6.8 Hz, CH_3, *cis*), 1.25–2.15 (m), 3.22–3.45 (m, H-6, *trans*), 3.90–4.02 (m, H-6, *cis*), 4.15 (t, *J* 3.8 Hz, H-2, *trans*), 4.30 (t, *J* 4.1 Hz, H-2, *cis*), 6.87–7.08 (m), 7.10–7.37 (m). HRMS calcd. for $C_{13}H_{16}N_2$ (M^+) 200.1314, found 200.1316. IR (neat): ν = 2221 cm^{-1} (CN).

6-Propyl-1-phenylpiperidine-2-carbonitrile 2c

R_f = 0.60, diethyl ether–petroleum ether = 1 : 2, slightly amber-coloured oil (1.73 g, 77%). δ_H(300 MHz, $CDCl_3$) 0.75 (t, *J* 7.10 Hz, CH_3, *trans*), 0.85 (t, *J* 7.30 Hz, CH_3, *cis*), 1.05–1.45 (m), 1.50–2.10 (m), 3.19–3.27 (m, H-6, *trans*), 3.85–3.92 (m, H-6, *cis*), 4.15 (t, *J* 3.6 Hz, H-2, *trans*), 4.42 (t, *J* 3.60 Hz, H-2, *cis*), 6.87–7.35 (m). δ_C(75 MHz, $CDCl_3$) 13.9, 14.2, 16.5, 18.1, 20.7, 26.9, 27.3, 29.7, 29.9, 30.8, 31.1, 35.9, 45.5, 54.4, 55.2, 57.5, 116.7, 117.9, 120.5, 120.8, 125.6, 126.0, 129.2, 129.5, 148.3, 149.2. HRMS calcd. for $C_{15}H_{20}N_2$ (M^+) 228.1626, found 228.1626. IR (neat): ν = 2224 cm^{-1} (CN).

6-Pentyl-1-phenylpiperidine-2-carbonitrile 2d

R_f = 0.75, diethyl ether–petroleum ether = 1 : 2, slightly amber-coloured oil (2.15 g, 80%). δ_H(200 MHz, $CDCl_3$) 0.83 (t, *J* 7.4 Hz), 1.05–1.45 (m), 1.50–2.05 (m), 3.19–3.27 (m, H-6, *trans*), 3.75–3.90 (m, H-6, *cis*), 4.14 (t, *J* 3.8 Hz, H-2, *trans*), 4.40 (t, *J* 4.1 Hz, H-2 *cis*), 6.83–6.95 (m), 7.12–7.38 (m). HRMS calcd. for $C_{17}H_{24}N_2$ (M^+) 256.1939, found 256.1944. IR (neat): ν = 2222 cm^{-1} (CN).

4-Methyl-6-pentyl-1-phenylpiperidine-2-carbonitrile 2e

R_f = 0.55, diethyl ether–petroleum ether = 1 : 2, yellow oil (1.99 g, 75%). δ_H(200 MHz, $CDCl_3$) 0.76 (3 H, t, *J* 7.1 Hz), 0.98 (3 H, d, *J* 6.2 Hz), 1.05–1.70 (12 H, m), 1.90 (1 H, dm, *J* 11.9 Hz), 3.12–3.28 (1 H, m), 4.14 (1 H, dd, *J* 4.6 and 2.6 Hz), 7.08–7.28 (5 H, m). δ_C(50 MHz, $CDCl_3$) 14.4, 22.1, 23.0, 24.9, 27.8, 32.4, 34.1, 37.8, 40.1, 54.6, 58.2, 118.5, 126.2, 126.6, 129.7, 149.3. HRMS calcd. for $C_{18}H_{26}N_2$ (M^+) 270.2096, found 270.2066. IR (neat): ν = 2223 cm^{-1} (CN).

2-(4-Chlorobutyl)-4-methyl-6-pentyl-1-phenylpiperidine-2-carbonitrile 3e

A solution (40 ml, THF) of **2e** (1.89 g, 7.00 mmol) was cooled to −80 °C, and treated dropwise with a 2.0 M solution of LDA in THF–*n*-hexane (3.85 ml, 7.70 mmol). The reaction was allowed to warm to −50°C and was maintained at that temperature for 1 h and treated with 1-bromo-4-chlorobutane (0.89 ml, 1.31 g, 7.65 mmol). The solution was warmed to room temperature before being stirred for 3 hours. The reaction mixture was diluted by addition of water (50 ml) and extracted (30 ml × 3) with diethyl ether (50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by silica gel chromatography using diethyl ether–petroleum ether (1 : 2) as the eluent to give **3e** as a colourless oil (2.14 g, 85%). R_f = 0.55. δ_H(200 MHz, $CDCl_3$) 0.85 (3 H, t, *J* 7.3 Hz), 0.95–2.15 (25 H, m), 3.20–3.40 (1 H, m), 3.48 (2 H, t, *J* 6.0 Hz), 7.25–7.40 (5 H, m). HRMS calcd. for $C_{22}H_{33}ClN_2$ (M^+) 360.9636, found 360.9640. IR (neat) ν = 2216 cm^{-1} (CN), 1491 cm^{-1} (Cl).

2-(4-Cyanobutyl)-4-methyl-6-pentyl-1-phenylpiperidine-2-carbonitrile 4e

Chloroamine **3e** (2.0 g, 5.55 mmol) and NaCN (0.55 g, 11.22 mmol) were dissolved in DMSO (10 ml) in the presence of tetrabutylammonium iodide (10 mg). The reaction mixture was stirred for 48 hours then quenched by addition of water (40 ml). The product was extracted by CH_2Cl_2 (20 ml × 3). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography using diethyl ether–petroleum ether (1 : 2) as the eluent to give **4e** (1.87 g, 96%) as a viscous and colourless oil. R_f = 0.27. δ_H(200 MHz, $CDCl_3$) 0.85 (3 H, t, *J* 7.3 Hz), 0.95–2.15 (25 H, m), 2.28 (2 H, t, *J* 6.3 Hz), 3.20–3.35 (1 H, m), 7.25–7.40 (5 H, m). δ_C(50 MHz, $CDCl_3$) 14.4, 17.3, 22.2, 22.8, 23.2, 24.9, 25.7, 28.2, 32.3, 34.9, 39.0, 40.1, 43.8, 58.6, 62.5, 119.7, 121.3, 127.5, 129.3 (2 carbons), 146.3. IR (neat) ν = 2216 cm^{-1} (CN), 2247 cm^{-1} (CN). HRMS calcd. for $C_{23}H_{33}N3$ (M^+) 351.2674, found 351.2670.

7-Amino-4-methyl-2-pentyl-1-phenyl-1-azaspiro[5.5]undec-7-ene-8-carbonitrile 5e

A solution (40 ml, THF) of **4e** (0.520 g, 1.47 mmol) was cooled to −80 °C, and treated dropwise with a 2.0 M solution of LDA in THF–*n*-hexane (0.81 ml, 1.62 mmol). The reaction was allowed to warm to room temperature before being stirred for 17 hours. The reaction mixture was diluted by addition of water (50 ml) and extracted (30 ml × 3) with diethyl ether (50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by silica gel chromatography using diethyl ether–petroleum ether (1 : 2) as the eluent to give **5e** as slightly brown crystals (0.362 g, 70%). R_f = 0.36. δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.8 Hz), 1.08 (3 H, d, *J* 6.1 Hz), 1.20–2.40 (19 H, m), 3.75–3.90 (1 H, m), 4.85 (2 H, broad), 6.80–6.90 (3 H, m), 7.25–7.39 (3 H, m). δ_C(75 MHz, $CDCl_3$) 14.0, 19.0, 22.6, 23.6, 23.8, 24.0, 26.6, 31.9, 35.6, 35.8, 37.0, 46.8, 55.9, 58.9, 72.7, 119.9, 121.1, 128.9 (2 carbons), 146.9, 163.8. HRMS calcd. for $C_{23}H_{33}N_3$ (M^+) 351.2675, found 351.2671. IR (neat) ν = 2182 cm^{-1} (CN), 3364 and 3472 cm^{-1} (NH_2). Mp 116 °C.

Crystal data, X-ray data collection, and refinement results of 5e

$C_{23}H_{33}N_3$, $M = 351.52$, triclinic, space group P-1, $a = 9.413(3)$, $b = 9.609(6)$, $c = 12.855(4)$ Å, $\alpha = 100.19(4)$, $\beta = 95.29(3)$, $\gamma = 109.46(5)°$, $V = 1064.6(8)$ Å^{-3}, $Z = 2$, $D_x = 1.097$ Mg m^{-3}, $\mu = 0.65$ cm^{-1}, λ(MoKα) = 0.71073 Å, $\mu = 0.65$ cm^{-1}, $F(000) = 384$, $T = 293$ K. The sample (0.38 × 0.26 × 0.24 mm) is studied on an automatic diffractometer CAD4 NONIUS with graphite monochromatized MoKα radiation.[19] The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max} = 54°$, scan $\omega/2\theta = 1$, $t_{max} = 60$ s, range HKL : H 0.12, K −12.12, L −16.16) gives 4625 unique reflections from which 2601 with $I > 2.0\sigma(I)$. After Lorenz and polarization corrections[20] the structure was solved with SIR-97[21] which reveals the non hydrogen atoms of the compound. After anisotropic refinement a Fourier Difference reveals all the hydrogens. The whole structure was refined with SHELX97[22] by the full matrix least-square techniques (use of F square magnitude; x, y, r, βij for C and N carbons, x, y, z in riding mode for H atoms, 236 variables and 1084 observations; calc $w = 1/[\sigma^2(Fo^2) + (0.116P)^2]$ where $P = (Fo^2 + 2Fc^2)/3$ with the resulting $R = 0.061$, $Rw = 0.191$, $Sw = 1.095$ (residual $\Delta\rho \leq 0.46$ eÅ^{-3})). Atomic scattering factors are available from International tables for X-ray Crystallography.[23] Ortep views were realized with PLATON98[24] and Ortep-3 for windows.[25]

Acknowledgements

R. M. thanks the MENRT for a grant.

References

1 J. W. Daly, I. Katle, C. W. Myers, T. Tokuyama, J. A. Waters and B. Witkop, *Proc. Natl. Acad. Sci. USA*, 1971, **68**, 1870.

2 (*a*) A. T. Elderfrawi, M. E. Elderfrawi, E. X. Albuquerque, A. C. Oliviera, N. Mansour, M. Alder, J. W. Daly, G. B. Brown, W. Burgermeister and B. Witkop, *Proc. Natl. Acad. Sci. U.S.A*, 1977, **74**, 2172; (*b*) K. Takahashi, B. Witkop, A. Brossi, M. A. Maleque and E. X. Albuquerque, *Helv. Chim. Acta*, 1982, **65**, 252.

3 (*a*) C. J. Smith, A. B. Holmes and N. J. Press, *Chem. Commun.*, 2002, 1214; (*b*) G. Stork and K. Zao, *J. Am. Chem. Soc.*, 1990, **112**, 5875; (*c*) E. C. Davidson, M. E. Fox, A. B. Holmes, S. D. Roughley, C. J. Smith, G. M. Williams, J. E. Davies, P. R. Raithby, J. P. Adams, I. T. Forbes, N. J. Press and M. J. Thompson, *J. Chem. Soc. Perkin Trans. 1*, 2002, **12**, 1494; (*d*) G. M. Williams, S. D. Roughley, J. E. Davies and A. B. Holmes, *J. Am. Chem. Soc.*, 1999, **121**, 4900.

4 (*a*) J. Zhu, J. Royer, J.-C. Quirion and H.-P. Husson, *Tetrahedron Lett.*, 1991, **32**, 2485; (*b*) D. Tanner and L. Hagberg, *Tetrahedron*, 1998, **54**, 7907; (*c*) D. Tanner, L. Hagberg and A. Poulsen, *Tetrahedron*, 1999, **55**, 1427.

5 R. Malassene, L. Toupet, J.-P. Hurvois and C. Moinet, *Synlett*, 2002, 895.

6 B. R. Davis and P. J. Garrat, in *Comprehensive Organic Synthesis*, Vol. 2, ed. C. H. Heathcock, Pergamon, Oxford, 1991, 848.

7 For a general survey of strategies aimed at the construction of the azaspiroundecane ring system see: M. Kotera, *Bull. Soc. Chim. Fr.*, 1989, 370.

8 E. Le Gall, J.-P. Hurvois, T. Renaud, C. Moinet, A. Tallec, P. Uriac, S. Sinbandhit and L. Toupet, *Liebigs Ann. Recl*, 1997, 2089.

9 For a different approach to the 6-alkyl-2-cyanopiperidine system see: (*a*) M. Bonin, J. R. Romero, D. S. Grierson and H.-P. Husson, *J. Org. Chem.*, 1984, **49**, 2392; (*b*) M. Bonin, R. Besselièvre, D. S. Grierson and H.-P. Husson, *Tetrahedron Lett.*, 1983, **24**, 1493; (*c*) M. Bonin, J. R. Romero, D. S. Grierson and H.-P. Husson, *Tetrahedron Lett.*, 1982, **23**, 3369.

10 For synthetic applications of $A^{(1,2)}$ allylic strain on related systems see: H-.P. Husson and J. Royer, *J. Chem. Soc. Rev.*, 1999, **28**, 383.

11 (*a*) E. Steckhan, in *Organic Electrochemistry*, 3rd edn., eds.H. Lund, M. Baizer, Dekker, New York, 1991, 583; (*b*) E. Le Gall, J.-P. Hurvois and S. Sinbandhit, *Eur. J. Org. Chem.*, 1999, 2645.

12 E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 665.

13 For the synthesis and structural determination of compound **7e** see ref. 5.

14 It was anticipated that in view of the previous results, cyanation of **6e** should take place at the unsubstituted C-6 position.

15 It seems likely that deprotonation of **2e** yielded an intermediate lithiated species which was attacked from the equatorial direction by the electrophile to produce **3e** with the stereochemistry indicated in the Fig. 1. For leading references concerning the reactivity of nitrile-stabilized carbanions see: F. F. Fleming and B. C. Shook, *Tetrahedron*, 2002, **58**, 1 and references cited therein.

16 (*a*) A. Toro, P. Nowak and P. Deslongchamps, *J. Am. Chem. Soc.*, 2000, **122**, 4526; (*b*) B. Dansou, C. Pichon, R. Dhal, E. Brown and S. Mille, *Eur. J. Org. Chem.*, 2000, 1527; (*c*) J. T. M Linders, J. L. Flippen-Anderson, C. F. George and K. C. Rice, *Tetrahedron Lett.*, 1999, **40**, 3905; (*d*) M. Luyten and R. Keese, *Tetrahedron*, 1986, **42**, 1687; (*e*) E. Piers, B. F. Abeysekara, D. J. Herbert and I. D. Suckling, *J. Chem. Soc., Chem. Commun.*, 1982, 404.

17 CCDC reference number 195340. See http://www.rsc.org/suppdata/ob/b2/b209387a/ for crystallographic files in .cif or other electronic format.

18 C. Moinet and E. Raoult, *Bull. Soc. Chim. Fr.*, 1991, 214.

19 C. K. Fair, *MolEN, An Interactive Intelligent System for Crystal Structure Analysis*, User manual, Enraf-Nonius, Delft, The Netherlands, 1990.

20 A. L. Spek, *HELENA*, Program for the handling of CAD4-Diffractometer output SHELX(S/L), Utrecht University, Utrecht, The Netherlands, 1997.

21 A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guargliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115.

22 G. M. Sheldrick, SHELX97, Program for the Refinement of Crystal Structures, Univ. of Göttingen, Germany, 1997.

23 International tables for X-ray Crystallography, Vol. C, Kluwer Academic Publishers, Dordrecht, 1992.

24 A. L. Spek, PLATON, A multipurpose crystallographic tool, Utrecht University, Utrecht, The Netherlands, 1998.

25 L. J. Farrugia, *J. Appl. Crystallogr.*, 1998, **30**, 565.