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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4097–4099

Anodic cyanation of C-4 hydroxylated piperidines: total synthesis of (±)-alkaloid 241D

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Received 12 March 2007; revised 30 March 2007; accepted 3 April 2007
Available online 11 April 2007

Abstract—A stereospecific synthesis of dendrobates (±)-alkaloid 241D is described. Key steps in this approach involved the stepwise electrochemical synthesis of C-4 substituted α-aminonitriles and their alkylation with iodomethane and 1-bromononane, respectively. The *N*-aryl group was removed in the last step through a Birch dearomatization followed by the hydrolysis of the intermediate dienamines.

Alkaloid 241D (**1**) was isolated in minute quantities in 1988 by Edwards and Daly[1] from the methanolic skin extracts of the Panamanian poison frog *Dendrobates speciosus*. The structure of **1** was determined by ^{1}H NMR spectroscopy and was *cis*,*cis*-4-hydroxy-2-methyl-6-nonylpiperidine. This 2,6-dialkyl substitution pattern is found in many animal alkaloids and representative members of this family are drawn in Figure 1.

For example, Solenopsin A (**2**)[2] together with its cis isomer isosolenopsin A (**3**), were isolated from the venom of ants of the genus *Solenopsis*, whereas dihydropinidine (**4**)[3] was extracted as a minor constituent from the Mexican bean beetle *Epilachna varivestis*. From a pharmacological standpoint, racemic alkaloid 241D proved to be a noncompetitive blocker of acetylcholine to ganglionic nicotinic receptor channels.[4] These results were akin to that observed with histrionicotoxin, the most widely used blocker for nicotinic receptors. These interesting biological properties coupled with the impossibility to isolate more than milligram quantities from natural sources, have incited chemists to elaborate new synthetic schemes aimed at the synthesis of **1**. The key step in these methodologies generally involved intramolecular Mannich-type cyclizations,[5] which led to the stereoselective preparation of **1**. In the continuation of our program aimed at the electrochemical preparation of 2,6-dialkylpiperidines[6] we became attracted to the synthesis of **1** as a means to develop new α-aminonitrile chemistry that may be of more general utility. For this, we have applied a strategy delineated in Scheme 1, which is based on the stepwise elaboration of piperidine **5**. The requisite alkyl chains should be introduced via the alkylation of conveniently substituted α-aminonitriles, and we were also curious to investigate what could be the influence of the hydroxyl group (or its protected form) at C(4) concerning the stereochemical outcome of our synthetic plan. Thus, *N*-phenyl-piperidone **6** was selected as the starting material as it is readily accessible from the bimolecular Caubère condensation between bromobenzene and commercially available 4-piperidone ethylene ketal.[7]

The results of our synthesis of (±)-alkaloid 241D are reported in this Letter.

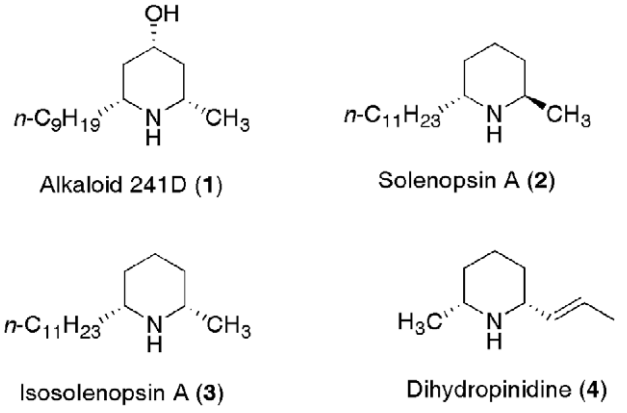

Figure 1. 2,6-Dialkyl-piperidine alkaloids.

Keywords: Alkaloids; Piperidines; Anodic cyanation; Electrochemistry; α-aminonitriles.
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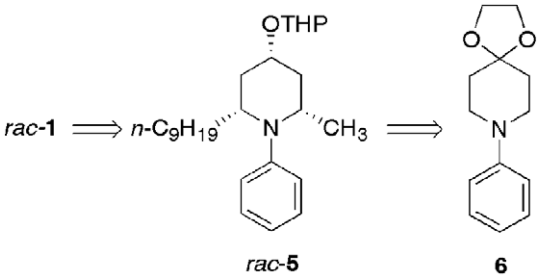
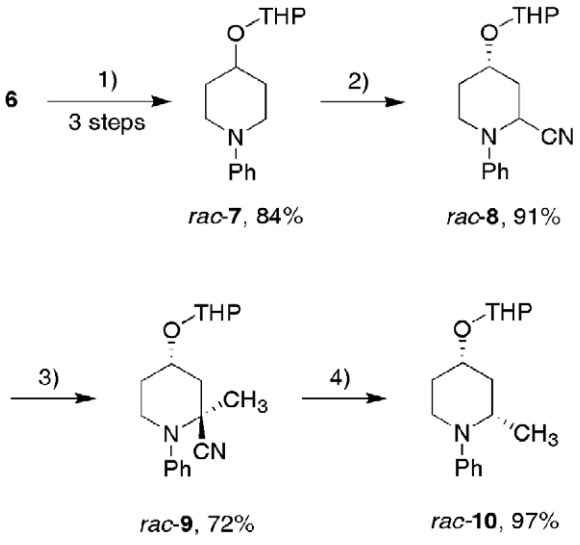
doi:10.1016/j.tetlet.2007.04.010



Scheme 1. Retrosynthetic analysis of alkaloid (±)-241D.

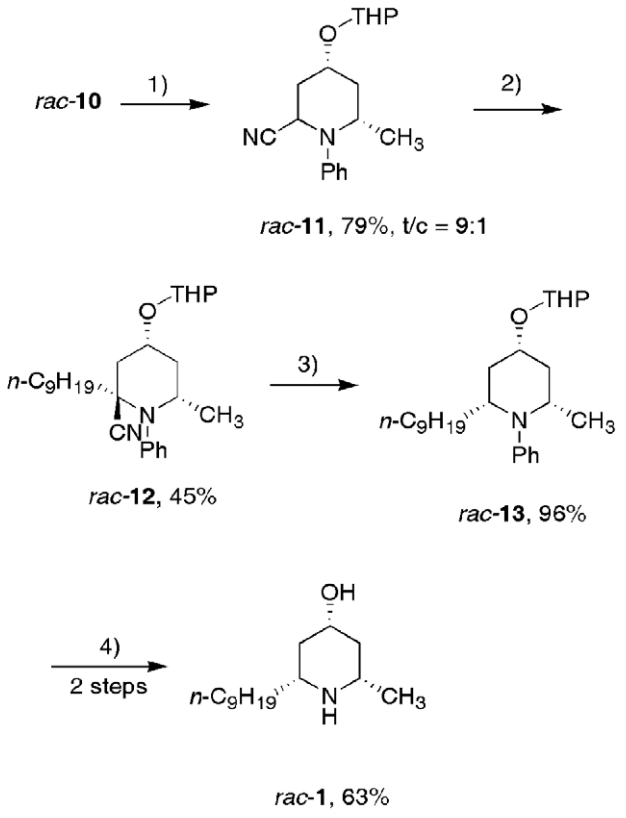
Acid-catalyzed deprotection of piperidone **6** followed by the reduction of the intermediate aminoketone with an excess of $NaBH_4$ in EtOH at 20 °C provided the amino-alcohol, which was protected as the THP derivative **7** (84% yield from **6**).

With the required amine in hand, we decided first to introduce the methyl group at C(2) employing the α-aminonitrile chemistry. Thus, the electrolysis ($E_p = +0.90$ V/SCE, NaCN, 2.3 F/mol) of a methanolic solution of **7** was made in a divided cell equipped with a glassy carbon electrode as anode and a carbon rod as cathode.[8] α-Aminonitrile **8** was obtained as a mixture (4/1) of diastereoisomers[9] which could be separated by column chromatography. On the basis of previous investigations one can assume that the major adduct has a ($2R^*$,$4R^*$) relative configuration in which the cyanide group is axially oriented. Reaction of α-aminonitrile **8** (trans/cis mixture, 4:1) with 1.2 equiv of LDA (prepared from diisopropylamine and *n*-BuLi) at −60 °C, and of the resultant anion with iodomethane at −20 °C, provided adduct **9** (72% yield).[10] The latter was reduced with $NaBH_4$ in EtOH at 20 °C for 12 h, to give the disubstituted piperidine **10** as a single diastereomer (97% yield). At this stage, it was felt that **10** has a ($2R^*$,$4R^*$) relative configuration. The high diastereoselectivity for the reduction of **9** can be understood by the prior formation of an iminium intermediate which is locked in a single conformation according to the presence of the O–THP group at C-4. Axial attack of the hydride anion (under a stereoelectronic control)[11] on this conformer adequately accounts for the formation of **10** as the single product. For the synthesis of (±)-**1**, we were faced with the stereo- and regioselective installation of the nonyl chain at C-6. To this end, the formation of the intermediate α-aminonitrile **11** seemed to us an obvious solution to this problem (see Scheme 2).



Scheme 2. Synthesis of amine *rac*-**10**. Reagents and conditions: (1) (i) THF–HCl 1.5 N (10:1) 65 °C, 24 h; (ii) $NaBH_4$ (4 equiv), EtOH, rt 12 h; (iii) DHP (7 equiv), PTSA (10 mol %), CH_2Cl_2, 40 °C, 12 h; (2) $-2e^-$, $-H^+$, MeOH, NaCN (6 equiv), LiOAc (20 g/L); (3) LDA (1.2 equiv) THF, CH_3I (1.2 equiv), −78 °C to 5 °C, 12 h; (4) $NaBH_4$ (4 equiv) EtOH, rt 12 h.

Indeed, several studies performed in our laboratory[12] and in others[13] have shown that 2-alkyl-piperidine derivatives could be selectively oxidized at C(6) with a high degree of regioselectivity. Accordingly, electrolysis of **10** was made under similar conditions than that for compound **7** providing α-aminonitrile **11** (79% yield) as mixture (9:1) of diastereomers, which could be easily separated by column chromatography. The ^1H NMR spectrum of the major compound showed the methyl group as a doublet ($^3J = 6.0$ Hz) system centered at $\delta = 0.96$ ppm. Likewise, a similar doublet system was found at $\delta = 1.06$ ppm in the ^1H NMR spectrum of the minor diastereomer. Taken together, these observations indicate that oxidation occurred selectively at C(6). The alkylation of **11** (cis/trans mixture = 1:9) with 1-bromononane led to the formation of **12** in a moderate



Scheme 3. Completion of the synthesis of (±)-alkaloid 241D. Reagents and conditions: (1) $-2e^-$, $-H^+$, MeOH, NaCN (7 equiv), LiOAc (20 g/L); 2) LDA (1.2 equiv) THF, *n*-$C_9H_{19}Br$ (1.2 equiv), −78 °C to 5 °C, 12 h; (3) $NaBH_4$ (4 equiv) EtOH, rt 12 h; (4) (i) THF–H_2SO_4 1.5 N (10:1) 65 °C, 6 h; (ii) Li (100 equiv), liq. NH_3–THF–EtOH (20:10:6) −45 °C, 2 h, H_2SO_4–H_2O–EtOH (0.5:4.5:5), 60 °C, 1 h.

45% yield as a single stereoisomer (99% de). Several attempts were made to improve the conversion yield, but all of them remain unsuccessful. Although a single adduct was detected by spectroscopic means (^{1}H and ^{13}C NMR), it was not possible to univocally determine the stereochemistry at this stage. However, one can assume that the substituents were all in a cis configuration as drawn in Scheme 3. Completion of the synthesis of (±)-**1** was made as follows. The acidic cleavage of the tetrahydropyranyl ether resulted in the formation of 2-methyl-6-nonyl-1-phenyl-piperidin-4-ol whose phenyl ring was reduced with Li (100 equiv) in a mixture of THF and liquid ammonia in the presence of EtOH as proton donor (Scheme 3).[14] After work-up, the intermediate crude dienamine mixture was immediately hydrolyzed in aqueous acidic ethanol to produce (±)-**1** (73% yield from **13**) as a white solid which melted at 97 °C. Spectral data of (±)-**1** (^{1}H, ^{13}C NMR, and *m*/*z*) were identical with those reported in the literature.[5b]

In summary, a stereoselective synthesis of (±)-alkaloid 241D has been developed. The alkylation–reduction steps were performed stereoselectively to place the substituents in a cis relative configuration.

Acknowledgement

N.G. thanks the MENRT for a grant.

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9. *Procedure for the synthesis of (2S*,4S*)-1-phenyl-4(tetrahydro-2H-pyran-2-yloxy)piperidine-2-carbonitrile* (**8**). Compound **7** (1.0 g, 3.83 mmol) was dissolved in 100 mL of methanol containing 2 g of lithium acetate dihydrate and 1.07 g (26.8 mmol, 7.0 equiv) of sodium cyanide. The resulting solution was placed in a divided cell and oxidized at a planar vitreous graphite electrode at (+0.9 V/SCE). After the consumption of 870 coulomb (2.35 F/mol), the electrolysis was stopped. The solvent was evaporated in vacuo and the crude material was taken up with water (100 mL) and extracted with ether (100 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified by silica column chromatography (diethyl ether/petroleum ether, 1:1) to afford (2*S**,4*S**)-**8** (0.820 g, 75%, yellow oil) as the major diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.45–1.62 (m, 5H), 1.63–2.08 (m, 4H), 2.10–2.42 (m, 2H), 3.02–3.13 (m, 1H), 3.43–3.58 (m, 1H), 3.84–4.04 (m, 2H), 4.60–4.65 (m, 1H), 4.66–4.70 (m, 1H), 6.95–6.98 (m, 3H), 7.25–7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 19.87, 25.32, 31.05, 31.08, 31.18, 32.94, 34.59, 35.80, 45.07, 45.23, 50.97, 51.02, 62.94, 69.98, 70.64, 97.41, 98.12, 118.25, 122.27, 129.34. HRMS: *m*/*z* calcd for $C_{17}H_{22}N_2O_2$ [M^+]: 286.1681; found, 286.1665.
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14. *Synthesis of alkaloid (±)-241D*. Compound **13** (0.36 g, 1.31 mmol) was dissolved in a THF–H_2SO_4 1.5 N (10:1) mixture and stirred at +65 °C for 6 h. Work-up and purification by column chromatography (diethyl ether/petroleum ether, 1:1) afforded 2-methyl-6-nonyl-1-phenyl-piperidin-4-ol (0.26 g, 96%), which was dissolved in a mixture of liquid ammonia (20 mL) THF (10 mL) and ethanol (6 mL). Then, Li (0.55 g, 80 mmol) was added in small pieces over a 1 h period upon which the solution became blue. Stirring was continued for 2 h and the solution was quenched with an excess of ethanol (5 mL) and ammonia was allowed to evaporate under a well ventilated hood. Water (20 mL) was added and the resulting aqueous mixture was extracted with cyclohexane (50 mL × 2). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to afford a mixture of crude enamines which were dissolved in a H_2SO_4/H_2O/EtOH (0.5:5.0:4.5) mixture. The solution was heated at 60 °C for 1 h and the solvents were evaporated. The sulfate of (±)-**1** was dissolved in water and the solution was made basic by the addition of NaOH pellets. The free amine was extracted with diethyl ether (50 mL × 2) and the combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography with diethyl ether saturated with gaseous ammonia gave (±)-**1** (0.14 g, 76%) as a white solid, mp = 97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (t, $^3J = 7.10$ Hz, 3H), 1.62 (sext, $^3J = 12.5$ Hz, 2H), 1.80 (d, $^3J = 6.5$ Hz, 3H), 2.65–3.20 (s, br, 2H), 1.95–1.42 (m, 16H), 1.83–1.88 (m, 2H), 2.45–2.55 (m, 1H), 2.60–2.64 (m, 1H), 3.57–3.62 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.06$, 22.43, 22.63, 26.02, 29.28, 29.52, 29.54, 29.73, 31.85, 36.77, 41.69, 43.85, 50.17, 54.87, 68.96. HRMS: *m*/*z* calcd for $C_{15}H_{31}NO$ [M^+]: 240.2327; found, 240.2325.