Preparation of a Novel Piperidine Structure Related to Nitrarine: A Biomimetic Model for the Asymmetric Synthesis of *Nitraria* Alkaloids

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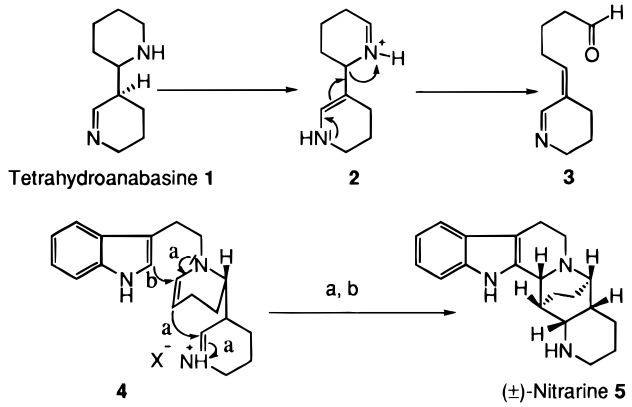
The *Lupinus* and *Nitraria* alkaloids (e.g., ammodendrine, lupinine, and nitrarine) have an obvious structural relationship (piperidine alkaloids), and speculation on their possible common biogenetic origin has led to the suggestion of Δ^1 piperidine as the pivotal intermediate.[1] The experimental evidence is consistent with the intermediacy of tetrahydroanabasine **1**, a dimer of Δ^1 piperidine. Koomen[2] has proposed that *Nitraria* alkaloids might arise from aldehyde **3**, which could be formed from 1 via an oxidized intermediate 2 that undergoes ring opening (Scheme 1). The synthesis of aldehyde **3** remains a challenging problem as far as biomimetic syntheses of *Nitraria* alkaloids and especially nitrarine **5** are concerned. In the case of this alkaloid, combination of **3** with tryptamine would lead initially to intermediate **4**, which would cyclize in a Pictet−Spengler-type reaction. To overcome this unsolved problem, it is obvious that an efficient strategy must take into account the potential of dimer **2** as a precursor of aldehyde **3**. We reasoned that the synthesis of an equivalent or a potential form of **2** could be achieved by cross-condensation of the enamine−iminium system of two dihydropyridine units **6** (Scheme 2). We have postulated this intermediate in the synthesis of 2-cyano-6-phenyloxazolopiperidine (**7**), the building block used for the CN(*R,S*) method[3] in this laboratory. This compound is prepared by condensation of glutaraldehyde, invoked as a C-5 unit in the biogenetic pathway of the title alkaloids, with (*R*)-(−)-phenylglycinol at pH 4 in the presence of KCN.[4]

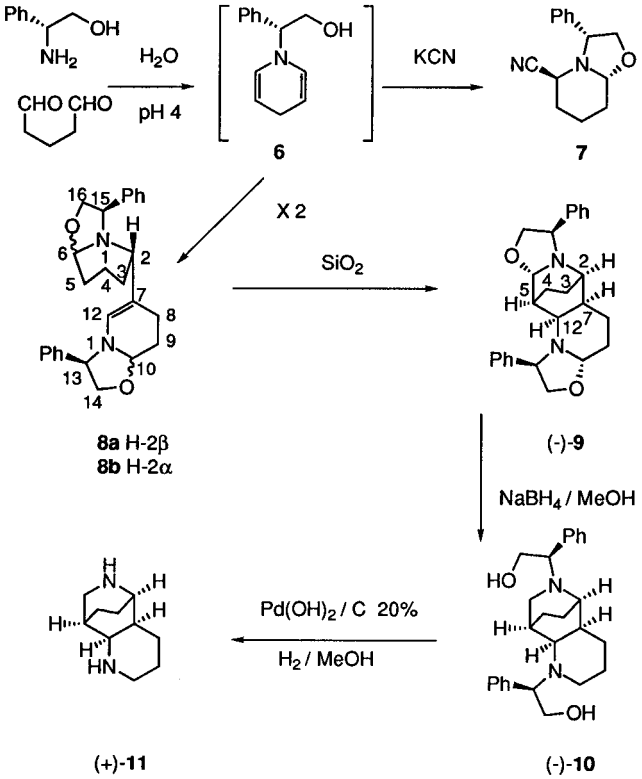
We set out to study the behavior of the intermediate dihydropyridine **6** in self-condensation reactions without trapping with KCN to establish model reactions that could be applied to expeditious biomimetic syntheses of *Nitraria* alkaloids.

Despite the existence of nitrarine **5** as natural racemate, we considered a common enantioselective approach to this group of alkaloids since most of them exist in enantiomerically pure form. As in the CN(*R,S*) method, (*R*)-(−)-phenylglycinol was the chosen chiral starting material, the nitrogen of which is destined to be incorporated into the final product.

Scheme 1



Scheme 2



The equimolecular reaction of (*R*)-(−)-phenylglycinol and glutaraldehyde in water at pH 4 led to a crude mixture of enamines **8a** and **8b**. Flash chromatography on silica gel using CH_2Cl_2 as eluent gave an inseparable 7:3 mixture of pure enamines **8a** and **8b** (yield = 44%). The major isomer was obtained after crystallization from methanol, and its ^1H and ^{13}C NMR spectra showed it to be pure **8a** (mp 97−100 °C; $[\alpha]^{25}_D$ −284 (c = 1, C_6H_{12})).[5] A 10 Hz coupling constant for H-2[6] (δ ppm 2.61) is in agreement with an axial configuration of this proton. Facile thermodynamic equilibration at C-2 was observed in $CDCl_3$ solution in the NMR tube, followed by degradation.

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(2) Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1994**, *59*, 7479−7484. Wanner, M. J.; Koomen, G. J. Stereoselectivity in Synthesis and Biosynthesis of Lupine and Nitraria Alkaloids. In *Studies in Natural Products Chemistry*, *14*, Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994. Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1996**, *61*, 5581−5586 and references therein.

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(4) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth.* **1992**, *70*, 54−59.

(5) New compounds were fully characterized by ^1H and ^{13}C NMR, IR, and MS analysis.

(6) For simplicity, the numbering system adopted throughout this manuscript does not follow official nomenclature rules, with the exception of the X-ray structure of **9** (**9**: 1,8-diphenyldecahydro-6,11-ethano-3a*H*,6*H*-dioxazolo[3,2-a:3′,2′-g][1,6]naphthyridine).

S0022-3263(97)00928-6 CCC: $14.00

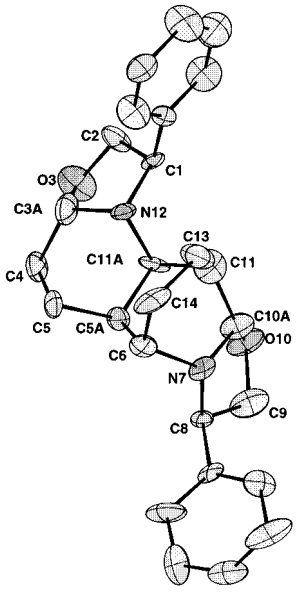

Figure 1. ORTEP diagram of compound (−)-**9**.

The structure of enamines **8a** and **8b** is reminiscent of that of tetrahydroanabasine **1**, a key intermediate in the synthesis of *Lupinus* and *Nitraria* alkaloids. Furthermore, the level of oxidation of this derivative is suitable for further cyclization reactions. Indeed, we observed that the more polar chromatography fractions of the crude **8a** and **8b** reaction mixture contained a product whose structure was determined by X-ray analysis as **9** (Figure 1).

The yield of this compound could be increased by prolonged contact of the crude reaction mixture with silica gel before elution (yield = 23%, one pot reaction). Thus, the expected cross-condensation of the two piperidine−enamine moieties appears to occur at the silica gel surface. This hypothesis was confirmed by a second chromatography of the mixture of pure enamines **8a** and **8b**, which produced more **9** (mp 136−138 °C; $[\alpha]^{25}_D$ −114 (c = 1, $CHCl_3$)).

Only one isomer **9** was found in the reaction mixture, although one could expect the formation of four stereomers (nitrarine and epinitrarine series) if the oxazolidine rings are not taken in account and if trans ring junctions are excluded.

The formation of **9**, controlled by the chiral moiety, can be explained as follows: (*i*) dimerization of **6** into enamines **8a** and **8b** in thermodynamic equilibrium and formation of a new asymmetric center; (*ii*) cross-condensation of the enamine moiety with the Δ^1 piperidinium ion formed by opening of the oxazolopiperidine moiety. The remarkable stereochemical outcome of this reaction is thus the result of a series of equilibrated reactions leading to the more stable stereomer.

Sodium borohydride reduction of (−)-**9** in methanol afforded (−)-**10** ($[\alpha]^{25}_D$ −25 (c = 1, $CHCl_3$)) whose tricyclic system has the relative configuration of the natural (±)-nitrarine **5**.

Removal of the chiral appendage was achieved by hydrogenolysis to give (+)-**11** (mp 69−71 °C; $[\alpha]^{25}_D$ +15 (c = 1, $CHCl_3$)) in good yield.

In summary, the synthesis of the novel tricyclic piperidine (+)-**11** demonstrates an efficient model reaction for the biomimetic preparation of nitrarine **5**.

The simplicity and availability of starting material make this approach interesting for further studies, and other results observed for the *Nitraria* alkaloid series will be reported in due course.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 300 and 75 MHz (Bruker, AMX-300), respectively. Mass spectra were obtained in the chemical ionization mode with NH_3. Starting materials and solvents were purchased from commercial sources. Flash chromatography was carried out on silica gel (35−70 μm). TLC was performed on silica gel plates (Merck 60F-254).

Dioxazolotetrahydroanabasine (8a) and Dimer 9. (*R*)-(−)-phenylglycinol (3.42 g, 25 mmol) was added to a solution of citric acid (4 g) in water (100 mL). The mixture was stirred vigorously until complete dissolution of the phenylglycinol and then cooled to 0−5 °C in an ice−water bath. A solution of 25% aqueous glutaraldehyde (9.4 mL, 25 mmol) was added dropwise over 30 min, and the reaction mixture was stirred for 3 h at room temperature. The aqueous phase was neutralized with a saturated aqueous solution of sodium bicarbonate and extracted (three times) with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated under vacuum to yield 4.8 g of a crude residue. TLC monitoring using cyclohexane/ether (7:3) showed a single spot (R_f = 0.53). The crude residue was dissolved in CH_2Cl_2 and applied to a short flash chromatography column (silica gel, 50 g, 20−45 μm). Elution with CH_2Cl_2 afforded 2.2 g (44%) of an inseparable mixture of enamines **8a** and **8b**. After 12 h, further elution using CH_2Cl_2/MeOH (95:5) yielded the crude dimer **9** (1.18 g, 23%). The unstable enamine mixture was purified by flash chromatography using petroleum ether/ether (8:2) to give 590 mg (12%) of a major component **8a**, which crystallized from MeOH. Dimer **9** crystallized from acetone to yield 670 mg (13%) of white crystals.

8a: mp = 97−100 °C (MeOH); $[\alpha]_D$ = −284 (c = 1, C_6H_6); IR (film) ν cm^{-1} 1660 (C=CN); ^{1}H NMR δ $CDCl_3$ 0.4−0.5 (m, 1), 1.3−1.4 (m, 2), 1.5−1.7 (m, 7), 1.8−1.9 (m, 1), 1.98 (bd, 1, J = 10 Hz, H-8), 2.61 (dd, 1, J = 10, 1.5 Hz, H-2), 3.48 (dd, 1, J = 7, 2 Hz, H-13 or H-15), 3.5−3.7 (m, 3, H-6 or H-10, H-14 and H-16), 3.98 (dd, 1, J = 7, 2 Hz, H-15 or H-13), 4.05−4.15 (m, 2, H-14, H-16), 4.72 (dd, 1, J = 10, 3.5 Hz, H-6 or H-10), 5.73 (bs, 1, H-12), 7.0−7.5 (m, 10, Ar Hs); ^{13}C NMR δ $CDCl_3$: 19.9, 22.3, 24.9, (CH_2), 29.7 (C-8), 30.2 (CH_2), 63.7 (C-13 or C-15), 66.5 (C-2), 66.8 (C-13 or C-15), 73.6 (C-14 or C-16), 74.6 (C-14 or C-16), 89.1 (C-6 or C-10), 96.1 (C-6 or C-10), 113.4 (C-7), 126.5−128.5 (Ar CH), 127.8 (C-12), 138.5 (Ar C), 143.4 (Ar C); MS (CI, NH_3) m/z 403 $(M + 1)^+$; HRMS (EI) m/z M^+ calcd for $C_{26}H_{30}O_2N_2$ 402.2307, found 402.2296. Anal. Calcd for $C_{26}H_{30}O_2N_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 75.67; H, 7.61; N, 6.58.

9: mp = 136−138 °C (acetone); $[\alpha]_D$ = −114 (c = 1, $CHCl_3$); ^{1}H NMR δ $CDCl_3$ 1.05 (m, 1, H-4), 1.35−1.50 (m, 2, Hs-8), 1.50−1.65 (m, 2, H-3 and H-9), 1.7−1.8 (m, 1, H-4), 1.8−1.9 (m, 1, H-3), 2.08 (m, 1, H-5), 2.2−2.3 (m, 1, H-9), 2.4−2.5 (m, 2, H-7, H-2), 3.25−3.40 (m, 2, H-12, H-14 or H-16), 3.44 (dd, 1, J = 8, 7 Hz, H-14 or H-16), 4.05 (t, 1, J = 7 Hz, H-13 or H-15), 4.2−4.4 (m, 3, H-14, H-16, H-13 or H-15), 4.75−4.85 (m, 2, H-6, H-10), 7.2−7.5 (m, 10, Ar Hs); ^{13}C NMR: δ $CDCl_3$: 16.8 (C-4), 20.5 (C-8), 21.5 (C-3), 26.8 (C-9), 32.8 (C-5), 33.8 (C-7), 51.2 (C-12), 53.8 (C-2), 64.2, 66.3 (C-13 and C-15), 72.0, 72.7,

(C-14 and C-16), 93.1, 95.4 (C-10 and C-6), 126.6, 126.9, 128.3 (Ar CH), 142.3, 143.2 (Ar C): MS (CI, NH_3) *m/z* 403 $(M + 1)^+$. Anal. Calcd for $C_{26}H_{30}O_2N_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.53; H, 7.44; N, 6.82.

Synthesis of Diol 10. To a stirred suspension of **9** (614 mg, 1.53 mmol) in MeOH (15 mL) was added $NaBH_4$ (300 mg) at room temperature. When a homogeneous solution had been obtained (15 min), a further 870 mg of $NaBH_4$ was added in small portions. The reaction mixture was stirred for 3 days at room temperature. It was then diluted with water (30 mL) and extracted with CH_2Cl_2. The solvent was evaporated to afford a crude residue that was purified by flash chromatography on silica gel with CH_2Cl_2/MeOH (85:15). The diol **10** (371 mg, 60%) was obtained as a yellow oil: $[\alpha]_D = -25$ (c = 1, $CHCl_3$); IR (film) ν cm^{-1} 3378 (OH); ^1H NMR δ $CDCl_3$ 1.22 (dddd, 1, J = 13, 8, 3, 2 Hz, H-8), 1.3−1.5 (m, 2, H-4, H-9), 1.5−1.9 (m, 5, H-3, H-4, H-8, H-9), 2.0−2.1 (m, 2, H-5, H-7), 2.45−2.55 (m, 2, H-6, H-10), 2.66 (dt, 1, J = 10, 2.5 Hz, H-2), 2.7−2.8 (m, 1, H-10), 2.82 (dd, 1, J = 10, 3 Hz, H-6), 3.05 (dd, 1, J = 9, 3 Hz, H-12), 3.2−4.1 (m, 6, H-13, H-14, H-15, H-16), 7.2−7.5 (m, 10, Ar Hs); ^{13}C NMR δ $CDCl_3$ 18.7 (C-4), 21.1 (C-3), 21.7 (C-8), 22.3 (C-9), 29.5 (C-5 or C-7), 36.5 (C-5 or C-7), 45.1 (C-10), 52.2 (C-2), 52.2 (C-6), 58.0 (C-12), 59.8 (C-14 or C-16), 62.8 (C-13 or C-15), 63.0 (C-14 or C-16), 68.3 (C-13 or C-15), 126.5−128.4 (Ar CH), 140.1 (Ar C), 140.7 (Ar C); MS (CI, NH_3) *m/z* 407 $(M + 1)^+$; HRMS (CI, CH_4) *m/z* $(M + H)^+$ calcd for $C_{26}H_{35}O_2N_2$ 407.2698, found 407.2697.

Synthesis of Diamine 11. A solution of **10** (282 mg, 0.69 mmol) in MeOH (20 mL) was hydrogenated over 20% $Pd(OH)_2$/C at ambient temperature and atmospheric pressure for 40 h. The reaction mixture was filtered through Celite, concentrated in vacuo, and diluted with water. Acidification with HCl 1 N and extraction with $CHCl_3$ afforded 2-phenylethanol. The solution was made alkaline with a saturated aqueous solution of Na_2CO_3 and then extracted with $CHCl_3$. Evaporation of the organic extracts to dryness yielded 150 mg (82%) of diamine **11**, which crystallized from ether: mp = 69−71 °C; $[\alpha]_D$ = +15 (c = 1, $CHCl_3$); IR (film) ν cm^{-1} 3333 (NH); ^1H NMR δ $CDCl_3$ 1.25−1.30 (m, 1, H-8), 1.42−1.50. (m, 3, H-4, H-8, H-9), 1.55−2.0 (m, 6, H-3, H-4, H-5, H-7, H-9), 2.30−2.45 (bs, 2, NH), 2.56 (bs, 1, H-2), 2.75−2.90 (m, 1, H-10), 2.9−3.1 (m, 4, H-6, H-10, H-12); ^{13}C NMR δ $CDCl_3$ 18.4 (C-4), 19.6 (C-8), 21.1 (C-9), 22.6 (C-3), 30.0 (C-5), 39.3 (C-7), 41.6 (C-10), 46.8 (C-6), 47.5 (C-2), 54.1 (C-12); MS (CI/NH_3) *m/z* 167 $(MH)^+$; HRMS (CI, CH_4) *m/z* $(M + H)^+$ calcd for $C_{10}H_{19}N_2$ 167.1548, found 167.1543.

Supporting Information Available: NMR spectra (^1H, ^{13}C, 2D-experiments: $^1H-^1H$, $^1H-^{13}C$) for **8a** and **9**−**11**. X-ray data for (−)-**9** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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