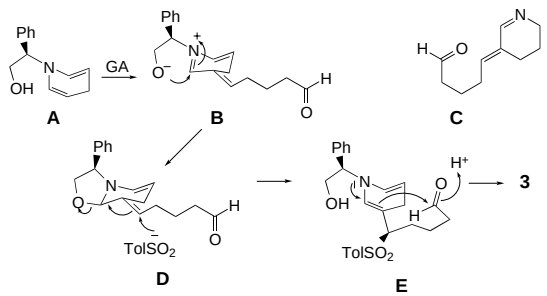
Expeditious Enantioselective Biomimetic Synthesis of the *Nitraria* Alkaloids (+)-Isonitramine and (−)-Sibirine

David François, Marie-Christine Lallemand, Mohamed Selkti, Alain Tomas, Nicole Kunesch,* and Henri-Philippe Husson*

Isonitramine **1** (Scheme 2) is a representative member of the *Nitraria* alkaloid family, for which considerable structural variety is encountered but in which a piperidine ring is an essential feature. We achieved the enantioselective syntheses of the spiropiperidine alkaloids (+)- and (−)-isonitramine,[1] and a number of other racemic[2] and asymmetric syntheses[3] have appeared. Some require numerous steps and have low overall yields. In a continuation of our work on the use of glutaraldehyde for constructing piperidine alkaloids,[4] we report here the most straightforward syntheses of natural sibirine (−)-**2** as well as isonitramines (+)-**1** and (−)-**1** from commercially available starting materials.

Despite the important achievements of Koomen et al.[2] in biomimetic approaches to synthesizing *Nitraria* alkaloids, some desirable objectives have not yet been attained. In particular, generation of a nonracemic chiral biogenetic intermediate with a suitable oxidation level remains an unsolved problem.

We previously showed[1] that the condensation of (*R*)-(−)-phenylglycinol with excess glutaraldehyde gives a tetracyclic compound containing the spiropiperidine skeleton of *Nitraria* alkaloids. However, six and eight additional steps are necessary to transform this precursor into (−)- and (+)-isonitramine, respectively. Such a reaction might form the basis of a biomimetic approach to synthesizing the title alkaloids. Since the first step of the reaction between (*R*)-(−)-phenylglycinol and glutaraldehyde is the formation of the enantiopure intermediate **A** (Scheme 1), we imagined that condensation of a second molecule of glutaraldehyde would afford aldehyde **B**, a chiral derivative of the piperideinoaldehyde **C** postulated by Koomen as a key intermediate in the biosynthesis of *Nitraria* alkaloids.[2]



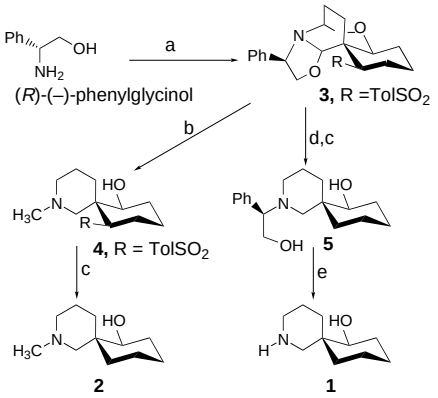
Scheme 1. Mechanism for the formation of spirocompound **3**.

[*] Dr. N. Kunesch, Prof. H.-P. Husson, D. François, Dr. M.-C. Lallemand
URA 1310 associée au CNRS
Faculté des Sciences Pharmaceutiques et Biologiques
Université René-Descartes
4, Avenue de l'Observatoire, F-75270 Paris Cedex 06 (France)
Fax: Int. code + (33) 1-43 29 14 03
e-mail: husson@pharmacie.univ-paris5.fr
Dr. M. Selkti, Prof. A. Tomas
Laboratoire de Biocristallographie, Université René-Descartes

According to this biogenetic hypothesis, the crucial step is the reduction of the conjugated iminium system of **C** to a simple enamine. We reasoned that a stereocontrolled Michael addition of a convenient nucleophile to **B** should a) create a new stereogenic center which would further control the spirocyclization and b) allow elimination of the nucleophile by reductive cleavage.

We chose sodium *p*-toluenesulfinate as the nucleophile in the expectation that 1,4-addition to the α,β-unsaturated oxazolidine system of **D** would generate the desired enamine. Whereas the 1,4-addition of phenylsulfinate ion to α,β-unsaturated ketones is well documented, there are few examples of reaction with iminium salts. As far as conjugated iminium ions are concerned, we observed the only known case for a rearrangement in which a 1,4-addition occurred.[5]

The first step of our synthetic sequence was accomplished by condensation of (*R*)-(−)-phenylglycinol and glutaraldehyde (2.5 equiv) followed by addition of sodium *p*-toluenesulfinate. This resulted in the formation of the spirocompound **3** (51 % yield) as the major diastereomer, which was isolated by simple crystallization (Scheme 2) and characterized by X-ray structure analysis.[6]



Scheme 2. a) Aqueous glutaraldehyde (2.5 equiv), pH 3.5, $NaSO_2Tol$ (2.2 equiv), $ZnBr_2$, 3 h (51 %); b) W-2 Raney Ni, MeOH (reflux), 2 h (91 %); c) Na(Hg), anhydrous MeOH, anhydrous Na_2HPO_4, 24 h, −20 °C (95 %); d) $LiAlH_4$, Et_2O (82 %); e) $H_2/Pd(OH)_2/C$ 20 %, MeOH, 24 h (85 %).

The outcome of this highly efficient reaction suggests that **3** is the most thermodynamically stable compound resulting from a series of equilibration reactions. The possible control elements include a) diastereoselective 1,4-nucleophilic addition of $TolSO_2^-$ to the α,β-unsaturated oxazolidine system of **D**[7] and b) addition of the substituted enamine goup of **E** to the aldehyde group via a chairlike transition state in which the sulfone and the developing secondary alcohol are in a diequatorial arrangement, which provides stereocontrolled spiroaldolization.

Finally, natural sibirine (−)-**2** was obtained in a two-step procedure from **3** by hydrogenolysis/alkylation with Raney nickel in MeOH[8] followed by sulfone elimination (yield 86 %).[9] The synthesis of isonitramine (−)-**1** required reduction with $LiAlH_4$, sulfone elimination, and hydrogenolysis of the chiral N substituent (yield for three steps from **3** 66 %).[10] Natural isonitramine (+)-**1** could be obtained starting from

  1433-7851/98/3701-0104 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 1/2

enantiomeric (*S*)-(+)-phenylglycinol. These results show the crucial role of the chiral phenylglycinol, which serves not only for the transfer of chirality but also for the stabilization of the intermediate iminium.

The nitramine alkaloids (derivatives of 2-azaspiro[5.5]undecan-7-ol) are structurally analogous to the neurotoxic histrionicotoxin alkaloids,[11] compounds which have a 1-azaspiro[5.5]undecan-8-ol skeleton with unsaturated lipophilic side chains. The introduction of such essential side chains on the nitramine skeleton is therefore of particular interest. Intermediate **3** opens the way to a variety of substitutions which can be made a) at the carbon atoms adjacent to the nitrogen of the piperidine ring by selective opening of the oxazolidine and/or 1,3-oxazine in an iminium ion and b) on the cyclohexane ring by the sulfone reactivity.

Experimental Section

All new compounds were characterized by 2D ^{1}H and ^{13}C NMR as well IR spectra, $[\alpha]_D$ values, simple and high-resolution mass spectrometry, or elemental analysis.

(*R*)-(−)-phenylglycinol (6.9 g, 50 mmol) was added to a solution of citric acid (24 g) in distilled water (200 mL). The mixture was stirred vigourously until complete dissolution of the phenylglycinol and then cooled to 0–5 °C in an ice/water bath. A 25% aqueous solution of glutaraldehyde (47 mL, 125 mmol) was added dropwise over 30 min, and then sodium *p*-toluenesulfinate (19.6 g, 110 mmol) was added simultaneously with CH_2Cl_2 (120 mL). The reaction mixture was stirred for 2 h at room temperature. The aqueous phase was neutralized with 5 N aqueous NaOH (80 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were concentrated under vacuum, diluted with MeOH (50 mL), and treated with $ZnBr_2$ (2 g, 8.9 mmol) over 12 h. Evaporation of the solvent gave an oily crude residue which crystallized from MeOH to give 11.19 g (51%) of **3** in two crops.

3: M.p. 222–223 °C; $[\alpha]_D$ −77 (c = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.12 (m, 1H, H-9), 1.50–2.10 (m, 6H, H-5, Hs-8, H-9, Hs-10), 1.95–2.10 (m, 1H, H-5), 2.15–2.35 (m, 2H, Hs-4), 2.44 (s, 3H, CH_3 Tol), 3.28 (dd, 1H, J = 13, 4 Hz, H-7), 3.66 (dd, 1H, J = 9.5, 8.5 Hz, H-13), 3.97 (dd, 1H, J = 11.5, 4.5 Hz, H-11), 4.30 (dd, 1H, J = 3.5, 1.5 Hz, H-6), 4.35 (dd, 1H, J = 8.5, 6.5 Hz, H-13), 4.60 (dd, 1H, J = 9.5, 6.5 Hz, H-12), 5.86 (s, 1H, H-2), 7.20–7.45 (m, 7H, Ar Hs), 7.78 (d, 1H, J = 8 Hz, Tol H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 16.4 (C-4), 21.4 (CH_3 Tol), 21.4 (C-9), 23.6 (C-10), 27.2 (C-5), 28.2 (C-8), 40.7 (C-3), 62.6 (C-7), 63.2 (C-12), 70.4 (C-11), 73.0 (C-13), 78.5 (C-6), 91.3 (C-2), 127.3, 128.2, 129.5 (Ar CH), 136.9 (Ar C), 139.9 (Ar C), 144.3 (Ar C).

4: M.p. 211–213 °C (MeOH); $[\alpha]_D$ −3 (c = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.1–1.2 (m, 1H), 1.3–2.0 (m, 8H), 2.0-2.2 (m, 4H), 2.30 (s, 3H, N-Me), 2.42 (s, 3H, CH_3 Tol), 2.5–2.9 (br m, 2H), 3.5–3.7 (m, 2H), 7.32 (d, 1H, J = 8 Hz, H Tol), 7.72 (d, 1H, J = 8 Hz, H Tol); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.4 (CH_3 Tol), 21.7 (CH_2), 22.3 (CH_2), 23.2 (CH_2), 28.8 (CH_2), 43.0 (C-3), 46.0 (N-Me), 55.3 (C-6), 65.4 (C-2), 68.6 (C-7), 81.9 (C-11), 128.1 (CH Tol), 129.6 (CH Tol), 137.2 (C Tol), 144.3 (C Tol).

5: $[\alpha]_D$ −17 (c = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.7–1.0 (m, 2H), 1.0–1.8 (m, 8H), 1.85 (d, 1H, J = 11 hz, H-2), 2.0–2.1 (m, 2H), 2.25 (td, 1H, J = 10, 3 Hz, H-6), 2.67 (d, 1H, J = 11 Hz, H-2), 2.8–2.9 (m, 1H), 3.5–3.6 (m, 2H), 3.80 (dd, 1H, J = 11, 6 Hz), 4.08 (dd, 1H, J = 11, 8 Hz), 7.0–7.4 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.3 (CH_2), 22.8 (CH_2), 23.8 (CH_2), 28.1 (CH_2), 29.5 (CH_2), 35.9 (C-3), 51.8 (C-6), 62.1 (C-2), 62.7 (C-13), 71.0 (C-12), 79.0 (C-11), 127.8 (Ar CH), 128.4 (Ar CH), 128.6 (Ar CH), 147.5 (Ar C).

Received: July 25, 1997 [Z 10731 IE]
German version: *Angew. Chem.* **1998**, *110*, 112–114

Keywords: alkaloids · asymmetric synthesis · biomimetic synthesis · natural products · spiro compounds

[1] J.-C. Quirion, D. S. Grierson, J. Royer, H.-P. Husson, *Tetrahedron Lett.* **1988**, *29*, 3311–3314.
[2] M. J. Wanner, G.-J. Koomen in *Studies in Natural Products Chemistry: Stereoselectivity in Synthesis and Biosynthesis of Lupine and Nitraria Alkaloids*, *Vol. 14* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1994**, pp. 731–768, and references therein.
[3] a) D. Kim, W. J. Choi, J. Y. Hong, I. Y. Park, Y. B. Kim, *Tetrahedron Lett.* **1996**, *37*, 1433–1434; b) T. Yamane, K. Ogasawara, *Synlett* **1996**, 925–926; c) M. Keppens, N. De Kimpe, *J. Org. Chem.* **1995**, *60*, 3916–3918, and references therein; d) B. Westermann, H. G. Scharmann, I. Kortmann, *Tetrahedron: Asymmetry* **1993**, *4*, 2119–2122; e) T. Imanishi, T. Kurumada, N. Maezaki, K. Sugiyama, C. Iwata, *J. Chem. Soc. Chem. Commun.* **1991**, 1409–1411; f) P. J. McCloskey, A. G. Schultz, *Heterocycles* **1987**, *25*, 437–447.
[4] a) C. Yue, I. Gauthier, J. Royer, H.-P. Husson, *J. Org. Chem.* **1996**, *61*, 4949–4954; b) H.-P. Husson, J. Royer in *Advances in the Use of Synthons in Organic Chemistry: Chemistry of Potential and Reversed Iminium Systems*, *Vol. 2* (Ed.: A. Dondoni), JAI Press, Greenwich, CT, USA, **1995**, pp. 1–68.
[5] D. S. Grierson, J.-L. Bettiol, I. Buck, H.-P. Husson, M. Rubiralta, A. Diez, *J. Org. Chem.* **1992**, *57*, 6414–6421.
[6] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100690. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code + (1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).
[7] a) P. Mangeney, A. Alexakis, J.-F. Normant, *Tetrahedron* **1984**, *40*, 1803–1808; b) M. Huche, J. Aubouet, G. Poncelot, J. Berlan, *Tetrahedron Lett.* **1983**, *24*, 585–586.
[8] a) X.-S. He, A. Brossi, *J. Heterocyclic Chem.* **1991**, *28*, 1741–1746; b) W. Meise, *Methoden Org. Chem. (Houben-Weyl)*, *4th ed. 1980-*, Vol. 4/1c, p. 257.
[9] B. M. Trost, H. C. Arndt, P. E. Strege, T. R. Verhoeven, *Tetrahedron Lett.* **1976**, 3477–3478.
[10] Isonitramine (−)-**1** could be obtained in a single step by treating **3** with Raney nickel at 80 °C and 25 bar in THF; however, the yield was modest (20%, not optimized).
[11] J. W. Daly, H. Martin Garraffo, T. F. Spande in *The Alkaloids: Amphibian Alkaloids*, *Vol. 43* (Ed.: G. A. Cordell), Academic Press, New York, **1993**, pp. 185–288.

Preparation of Lithium Oligosiloxane Aluminates and Acid Strength of Hydroxy Groups in a Molecular Aluminum Oligosiloxane

Michael Veith,* Maria Jarczyk, and Volker Huch

Dedicated to Professor Manfred Weidenbruch on the occasion of his 60th birthday

As we recently reported, the molecular aluminum oligosiloxane **1**, which contains four aluminum atoms that are connected through OH bridges to form a ring, can be readily prepared in a one-step synthesis.[1] We observed that the hydrogen atoms of the OH groups are available for coordination with Lewis bases. Compound **1** can therefore be isolated as an adduct with three molecules of diethyl ether (a fourth is incorporated within the crystal lattice and does not

[*] Prof. Dr. M. Veith, M. Jarczyk, Dr. V. Huch
Institut für Anorganische Chemie der Universität
Postfach 151150, D-66041 Saarbrücken (Germany)
Fax: Int. code + (681) 302-3995
e-mail: veith@rz.uni-sb.de

  1433-7851/98/3701-0105 $ 17.50+.50/0