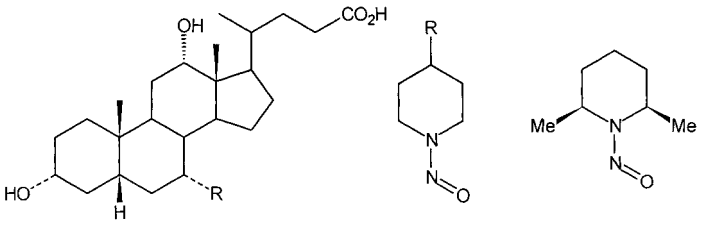
[17] IS was done with the membrane-covered gold electrode as a working electrode against a counter/reference Ag/AgCl electrode in 0.3 M NaCl/20 mM sodium phosphate (pH 7.4). An alternating current voltage (10 mV root mean square amplitude) was applied and the current was recorded with a phase sensitive Lock-In amplifier to measure the complex impedance $Z$, as described elsewhere.[9, 18]
[18] T. Stora, R. Hovius, Z. Dienes, M. Pachoud, H. Vogel *Langmuir* **1997**, *13*, 5211 – 5214.
[19] The T domain consists of the natural N terminus of colicin N (residues 1 – 67), and together with the R domain (68 – 190) forms half (= TR) of the entire colicin N molecule (1 – 387). TR served as a natural mass tag to amplify SPR signals, and did not affect the binding affinity of the isolated R domain to the OmpF receptors in the tethered membranes. The quantities of bound TR at saturation were higher than the expected amounts deduced from the estimation of the incorporated OmpF.[11, 18] This could be a consequence of a favorable orientation of the membrane receptors, which arises from their asymmetric structure or to an underestimation of the receptor content in the layer that results from approximate values of the refractive index of the proteins. TR adsorption on a tethered membrane made of pure lipids was very limited, which leads to a mass adsorption of less than 12 ng cm$^{-2}$.
[20] Since the OmpF single-channel conductivity was reported to be 0.8 nS[11] when 10 mV are applied, a current of 8 pA that passes through a porin corresponds to $10^8$ ions s$^{-1}$.
[21] The calculated capacitance of the layer remained constant within experimental errors. No changes in the conductivity were observed on a pure lipid-tethered membrane upon incubation of the R fragment.
[22] OmpF reconstitution into BLMs were performed as described by R. Benz, *Crit. Rev. Biochem.* **1985**, *19*, 145 – 190. Black lipid membranes were formed by painting a hole of 0.6 mm diameter in a Teflon foil with a solution of 10 mg mL$^{-1}$ soya bean lecithin in decane. OmpF was incorporated afterwards by dilution of 1 μL of OmpF (0.125 mg mL$^{-1}$) in 1% octyl glucoside in the cell and by application of a constant voltage of 250 mV. The current was recorded at a transbilayer potential of 50 mV direct current. Titration was performed in a solution of 0.3 M NaCl/20 mM sodium phosphate (pH 7.4).
[23] R and TR fragments contained hexahistidine sequences on their N termini which served as tags to immobilize the proteins on nitrilotriacetate-covered gold surfaces by following the procedure described in T. A. Keller, C. Duschl, D. Kröger, A.-F. Sévin-Landais, H. Vogel, S. E. Cervigni, P. Dumy, *Supramol. Sci.* **1995**, *2*, 155 – 160. SPR angle shifts of 0.72° and 1.00° (308 and 427 ng cm$^{-2}$) were obtained. Only minor binding of the protein was observed at concentrations up to 100 μM upon addition of detergent-solubilized OmpF (as also used elsewhere[14]) to the bulk phase. A further experiment was performed to reduce the packing of R at the interface in which 15% of the protein at the surface was the TR fragment immobilized through the histidine tag that was located at the random coil T domain.[14] As a result, the R segments of the TR fragments protrude above the densley packed layer of T fragments. In this way we could measure an interaction between OmpF and R domain in detergent.
[24] *Proceedings of the 2nd International Symposium on Miniaturized Total Analysis Systems* (Eds.: H. M. Widmer, E. Verpoorte, S. Barnard), AMI, Basel, **1996**.

# Enantioselective Inclusion Complexation of *N*-Nitrosopiperidines by Steroidal Bile Acids**

Maria Gdaniec,* Maria J. Milewska, and Tadeusz Połoński*

There is currently considerable interest in crystalline inclusion compounds formed by chiral host molecules on account of their application for chiral recognition and optical resolution of racemates.[1] Owing to their ability to accommodate many types of organic guest molecules within their crystal lattices,[2] naturally occuring cholic acid (**CA**) and deoxycholic acid (**DCA**) seem to be very promising hosts for this purpose. However, only very few successful examples of chiral resolution by enclathration with **CA** have been reported,[3] and several attempts to use **DCA** as a resolving agent have failed.[3, 4] On the other hand, we have found recently that the **CA** and **DCA** matrices force conformationally flexible molecules included in the crystals to assume chiral conformations, as indicated by the circular dichroism (CD) spectra.[5]

Here we describe the efficiency of bile acids for chiral recognition of low molecular weight *N*-nitrosamines. The chirality of *N*-nitrosopiperidines **1** – **3** is solely due to hindered rotation of the nitroso group.[6] Because of the partial double bond character of the bond between the two nitrogen atoms in the NNO group, the barrier to rotation about the N–N bond is relatively high (ca. 23 – 25 kcal mol$^{-1}$).[7] Therefore the enantiomers of **2** and **3** are expected to be stable for a short period of time at ambient temperature even after liberation from the crystal host lattices. Obtaining **1** – **3** in the optically active form




**CA**, R = OH
**DCA**, R = H

**1**, R = H
**2**, R = Me

**3**

is challenging from an experimental point of view and would afford very simple models for studying chiroptical spectra of the *N*-nitrosamino chromophore.[8]

[*] Prof. Dr. M. Gdaniec
Faculty of Chemistry
A. Mickiewicz University
PL-60-780 Poznań (Poland)
Fax: (+48) 61-8658-008
E-mail: mg31@krystal.amu.edu.pl
Prof. Dr. T. Połoński, Dr. M. J. Milewska
Department of Chemistry
Technical University of Gdańsk
PL-80-952 Gdańsk (Poland)
Fax: (+48) 58-3472-694
E-mail: tadpol@chem.pg.gda.pl

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The colorless crystals of the 1:1 complexes of **1**–**3** with **CA** were obtained by crystallization of **CA** with the corresponding nitrosamine. The 2:1 **DCA** inclusion compounds were prepared by slow evaporation of a solution of **DCA** and the suitable *N*-nitrosopiperidine in methanol. The X-ray crystallographic analysis of the **CA** complexes[9a–c, f] revealed that the host molecules are assembled through hydrogen bonds into typical corrugated **CA** bilayers. In the case of **1-CA** the guest molecules are accomodated in the $\alpha$-type channels,[2] while in **2-CA** and **3-CA** the channels are of $\beta$-type (Figure 1). The

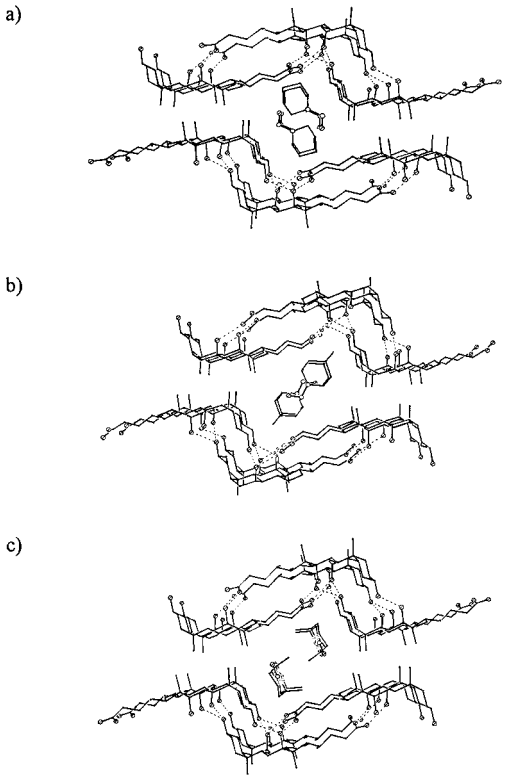


Figure 1. Crystal packing in a) **1-CA** , b) **2-CA**, and c) **3-CA**.

guest molecules are arranged in helicoidal columns propagating through the crystal (Figure 2). Inspection of the data showed that either only one enantiomer is selectively incorporated in the host–guest crystals (**1-CA** and **2-CA**) or a preferential complexation of one enantiomer occurs (**3-CA**, Figure 3). The absolute configuration of the nitrosamine guest molecules can be easily deduced from the X-ray crystal structures of the complexes. In the case of **1-CA** and **2-CA**, the *pR* (planar chirality) and *S* configurations were assigned to the guest molecules **1** and **2**, respectively, whereas for **3-CA** 72% of the nitrosamine molecules assume the *E* configuration (geometric enantiomerism)[10] and the remaining 28% the *Z* configuration. The crystal structure of **3-CA** revealed that the guest nitrosamine **3** adopts a chair conformation with the methyl substituents occupying the axial positions. The diequatorial conformation is destabilized as a consequence of the strong pseudoallylic $A^{(1,3)}$ strain caused by steric interactions between the nitroso group and nearly coplanar methyl substituents.[11] The axial preference of methyl groups in **3** had been already deduced from $^1$H and $^{13}$C NMR measurements

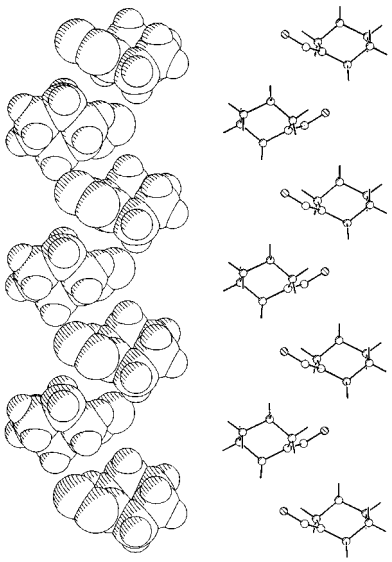

Figure 2. Helicoidal arrangement of the guest molecules in the crystal of **1-CA**.

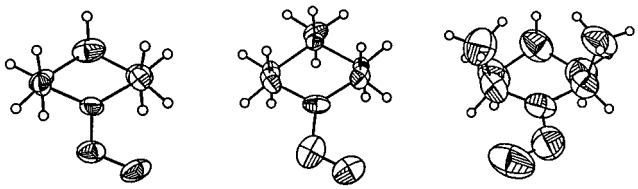

Figure 3. ORTEP drawings of the guest *N*-nitrosamines **1**–**3** (from left to right) in **1-CA**, **2-CA**, and **3-CA** showing the absolute configurations of the nitrosamines.

in solution.[12] The X-ray data for **1-DCA** and **3-DCA** collected at 130 K showed disordered nitrosamine molecules with two enantiomeric molecules occupying the same site in the crystal.[9d–f] Nevertheless, in the case of **3-DCA** the *E*:*Z* ratio of 2:1 indicates the ability of the **DCA** matrices to discriminate between the enantiomers. Unfortunately, no conclusive explanation for the preferably included stereoisomer of **1** in **DCA** could be obtained.

The chirality of the guest *N*-nitrosopiperidines can also be detected with CD spectroscopy (Table 1); the corresponding spectra can be taken for samples in the solid state (KBr disks;[13] Figure 4) as well as in solution (Figure 5). Such

Table 1. Circular dichroism data of the **CA** and **DCA** inclusion compounds.

| Compound | Medium | $\lambda_{max}$ [nm] ($[\theta]$)[a] |
|---|---|---|
| **1-CA** | KBr | 357 (530)[b] |
| **1-DCA** | KBr | 373 (406)[b] |
| **2-CA** | KBr | 371 (320)[b] |
| **2-CA** | MeOH | 350 (−770)[c] |
| **2-DCA** | KBr | 358 (820)[b] |
| **2-DCA** | MeOH | 351 (360)[c] |
| **3-CA** | KBr | 377 (−770)[b] |
| **3-CA** | MeOH | 350 (−)[c,d] |
| **3-DCA** | KBr | 376 (−1200)[b] |
| **3-DCA** | MeOH | 350 (−)[c,d] |

[a] Molecular ellipticity in deg cm$^2$ dmol$^{-1}$. [b] Approximate values, determined by considering the weight concentration (KBr density 2.75 g cm$^{-3}$). [c] Measured immediately after dissolution. [d] Only the CE sign can be determined.

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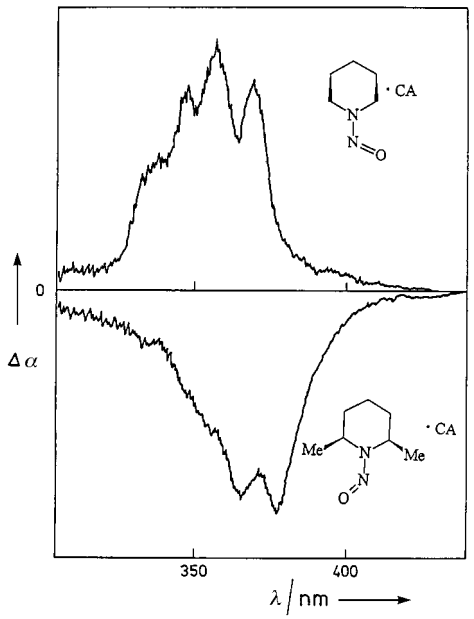


Figure 4. Solid-state CD spectra of **1-CA** and **3-CA** (KBr).

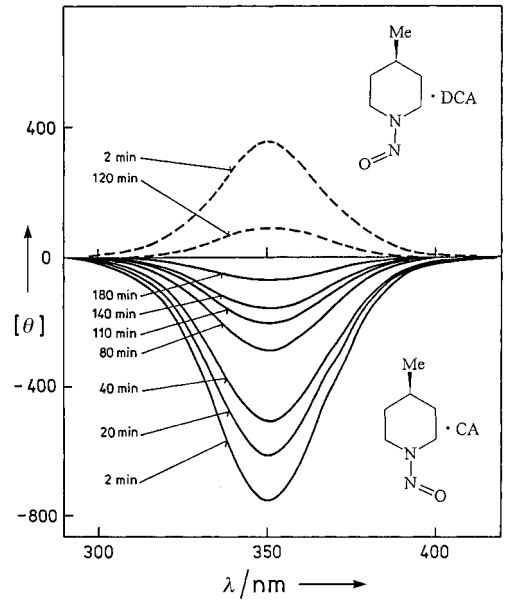


Figure 5. Decay of the CD signal of **2-DCA** (dashed lines) and **2-CA** (solid lines) in methanol at 22 °C.

measurements are possible since the nitrosamine n – π* band near 370 nm remains outside the absorption range of the bile acids. The carboxylic group absorbs at about 210 nm, and therefore the **CA** and **DCA** hosts are transparent at longer wavelengths. The CD spectra of **2-CA** and **2-DCA** in methanol exhibit a moderately strong Cotton effect (CE) near 350 nm, which gradually decreases at room temperature due to the slow N–N rotation and finally vanishes completely after about four hours (Figure 5). The nitrosamine **3** racemizes much faster than **2**, owing to a significantly lower energy barrier to rotation about the N–N bond (18.9 kcal mol$^{-1}$).[7b] Therefore, the CD of **3-CA** and **3-DCA** in solution vanishes within a few minutes after dissolution. Nonetheless, the negative CE sign can be unequivocally detected immediately after dissolution. In the case of **1** the racemization is caused not only by rotation of the nitroso group but also by inversion of the piperidine ring. The energy barrier of the second process is much lower (less than 6 kcal mol$^{-1}$)[14] than that of the first, and for this reason the CD of **1-CA** cannot be observed in solution at room temperature but only in the solid state. The CD spectra of the **CA** and **DCA** complexes with **1** and **2** in KBr exhibit positive CEs near 370 nm, whereas those of **3** (Figure 5) are characterized by negative CEs. At the first glance, it seems surprising that the CD spectra of **2-CA** in solution and in the solid state exhibit n – π* CEs of opposite signs, while **2-DCA**, **3-CA** and **3-DCA** show the same CD signs in the solid state as well as in solution. On the other hand, it is known that the nitrosamine CD is extremely sensitive to any deviations of the chromophore from planarity.[15] An inherent chirality of the twisted NNO group may exert a strong contribution to the CE, which often overweighs the contribution of the dissymmetrically placed substituents and thus governs the sign of the CE.[16] Indeed, the X-ray crystallographic data revealed small distortions of the nitrosamine group from planarity in **1-CA** and **2-CA**, as indicated by the corresponding torsional angles: C(2)-N-N-O 175.6(5)° (**1-CA**), 175.5(4)° (**2-CA**); C(6)-N-N-O −3.2(9)° (**1-CA**), 8.3(7)° (**2-CA**). These deviations are apparently due to the packing forces in the inclusion crystals and may be alleviated in solution. For these reasons configurational assignments based on solid-state CD measurements might be risky. However, the absolute configuration of the guest molecules can be easily predicted from the solution spectra. It is especially important for the **DCA** complexes; the data collected in Table 1 reveal that **DCA** preferentially enclathrates the *R* enantiomer of **2** and the *E* enantiomer of **3**.

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structure was solved by direct methods with SHELXS-86 and refined by the full-matrix least-squares procedure against $F^2$ with SHELXL-93. a) Crystal structure data for **1-CA**: $C_{24}H_{40}O_5 \cdot C_5H_{10}N_2O$, crystal size $0.6 \times 0.3 \times 0.07$ mm, $T = 100$ K, monoclinic, $P2_1$, $a = 13.268(4)$, $b = 7.909(2)$, $c = 13.818(4)$ Å, $\beta = 106.03(2)^\circ$, $V = 1393.6(7)$ Å$^3$, $Z = 2$, $\rho_{calcd} = 1.246$ g cm$^{-3}$, $\mu = 0.086$ mm$^{-1}$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 48^\circ$ ($\theta$-$2\theta$ scans). The structure was refined on 2058 reflections with positive $F^2$ values; 334 refined parameters; $R_1 = 0.044$, $wR_2 = 0.102$, GOF = 1.102 for 1691 reflections with $F > 4\sigma(F)$ ($R_1 = 0.106$, $wR_2 = 0.141$, GOF = 1.281 for all 2376 independent reflections). b) Crystal structure data for **2-CA**: $C_{24}H_{40}O_5 \cdot C_6H_{12}N_2O$, crystal size $0.6 \times 0.2 \times 0.07$ mm, $T = 100$ K, $P2_1$, $a = 12.353(2)$, $b = 7.675(1)$, $c = 16.359(4)$ Å, $\beta = 111.09(2)^\circ$, $V = 1447.1(5)$ Å$^3$, $Z = 2$, $\rho_{calcd} = 1.232$ g cm$^{-3}$, $\mu = 0.085$ mm$^{-1}$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 52^\circ$ ($\theta$-$2\theta$ scans). The structure was refined on 2823 reflections with positive $F^2$ values; 343 refined parameters; $R_1 = 0.043$, $wR_2 = 0.110$, GOF = 1.051 for 2425 reflections with $F > 4\sigma(F)$ ($R_1 = 0.076$, $wR_2 = 0.125$, GOF = 1.084 for all 3066 independent reflections). c) Crystal structure data for **3-CA**: $C_{24}H_{40}O_5 \cdot C_7H_{14}N_2O$, crystal size $0.6 \times 0.2 \times 0.1$, $T = 293$ K, monoclinic, space group $P2_1$, $a = 12.754(3)$, $b = 7.881(2)$, $c = 16.355(3)$ Å, $\beta = 111.97(3)^\circ$, $V = 1524.5(6)$ Å$^3$, $Z = 2$, $\rho_{calcd} = 1.200$ g cm$^{-3}$, $\mu = 0.655$ mm$^{-1}$, $Cu_{K\alpha}$ radiation ($\lambda = 1.54178$ Å). Data were collected up to $2\theta = 140^\circ$ ($\theta$-$2\theta$ scans). The structure was refined on 2534 reflections with positive $F^2$ values; 343 refined parameters; $R_1 = 0.041$, $wR_2 = 0.111$, GOF = 1.077 for 2340 reflections with $F > 4\sigma(F)$ ($R_1 = 0.052$, $wR_2 = 0.122$, GOF = 1.084 for all 2639 independent reflections). The guest *N*-nitroso group is disordered over two positions. Restraints were imposed on 1–2 and 1–3 distances and planarity of the *N*-nitrosamino group during refinement. d) Crystal data for **1-DCA**: $2\,C_{24}H_{40}O_4 \cdot C_5H_{10}N_2O$, crystal size $0.6 \times 0.45 \times 0.2$ mm, $T = 130$ K, orthorhombic, $P2_12_12_1$, $a = 26.730(4)$, $b = 13.228(2)$, $c = 13.971(4)$ Å, $V = 4346(2)$ Å$^3$, $Z = 4$, $\rho_{calcd} = 1.209$ g cm$^{-3}$, $\mu = 0.081$ mm$^{-1}$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 48^\circ$ ($\omega$-$\theta$ scans). The structure was refined on 4345 reflections with the positive $F^2$ values; 530 refined parameters; $R_1 = 0.056$, $wR_2 = 0.132$, GOF = 1.070 for 3459 reflections with $F > 4\sigma(F)$ ($R_1 = 0.080$, $wR_2 = 0.148$, GOF = 1.073 for all 4347 independent reflections). The guest molecule is disordered over three positions. It was refined isotropically as a rigid body with molecular geometry fitted to that of **1** in **1-CA**. Sum of the occupancy factors was refined to 1.00 (0.55(1) for the *pR* isomer and 0.30(1) and 0.15(1) for the *pS* isomer). e) Crystal structure data for **3-DCA**: $2\,C_{24}H_{40}O_4 \cdot C_7H_{14}N_2O$, crystal size $0.4 \times 0.2 \times 0.2$ mm, $T = 130$ K, orthorhombic, $P2_12_12_1$, $a = 26.845(5)$, $b = 13.583(3)$, $c = 14.001(3)$ Å, $V = 5105(2)$ Å$^3$, $Z = 4$, $\rho_{calcd} = 1.206$ g cm$^{-3}$, $\mu = 0.080$ mm$^{-1}$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 48^\circ$ ($\omega$-$\theta$ scans). The structure was refined on 3661 reflections with the positive $F^2$ values; 539 refined parameters; $R_1 = 0.059$, $wR_2 = 0.147$, GOF = 1.013 for 2496 reflections with $F > 4\sigma(F)$ ($R_1 = 0.176$, $wR_2 = 0.200$, GOF = 1.094 for all 4485 independent reflections). The guest molecule was refined anisotropically, but disorder was suspected because of poor molecular geometry, the shape of the elipsoids, and large residual peaks close to the *N*-nitroso atom. Therefore, the geometry of the guest was fitted to that found for **3** in the **3-CA** complex. Subsequently, the guest molecule was refined isotropically as a rigid body. Sum of the two occupancy factors of the guest molecules was kept fixed at 1.0. The occupancy of the higher populated *E* stereoisomer was refined at 0.67(1). f) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101943 – CCDC-101947. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).


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[13] A mixture of the complex (5 mg) and KBr (300 mg) was ground and formed into a disk with a radius of 10 mm. The disk was rotated around the optical axis, and the CD recordings were made for several positions in order to check the reproducibility of the spectra. For details of the experimental procedure, see also a) R. Kuroda, Y. Saito, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 433 – 436; b) K. Rasmussen, N. Ch. P. Hald, *Acta Chem. Scand. Ser. A* **1982**, *36*, 549 – 554.

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## Total Synthesis of (−)-Strychnine via the Wieland – Gumlich Aldehyde**


Daniel Solé, Josep Bonjoch,* Silvina García-Rubio, Emma Peidró, and Joan Bosch*


Strychnine, the most famous of the *Strychnos* alkaloids,[1] is a natural product that has been known for a long time. Its complex heptacyclic structure, which is assembled from only 24 skeletal atoms and contains six contiguous asymmetric carbon atoms (five of which are in the core cyclohexane ring), represents a permanent challenge for synthetic organic chemists.[2] The classical, pioneering total synthesis by Woodward et al.[3] remained the only synthesis of strychnine for nearly 40 years, and five research groups have recently reported new total syntheses of this alkaloid, either via isostrychnine[4] or via the Wieland – Gumlich aldehyde.[5] However, only in one case has the enantioselective total synthesis of the natural enantiomer, (−)-strychnine, been achieved.[5c] The elegant enantioselective synthesis of (−)-strychnine by Overman et al. takes advantage of the tandem cationic aza-Cope rearrangement/Mannich cyclization strategy for the construction of the basic skeleton of the alkaloid and—with almost the same number of reaction steps as the synthesis by Woodward et al.—upped the overall yield by a factor of $10^5$.

As the culmination of our studies on the synthesis of *Strychnos* alkaloids,[6] we present here a new synthesis of (−)-strychnine which proceeds via the Wieland – Gumlich aldehyde and starts with 1,3-cyclohexanedione (the core ring E of strychnine),[7] from which the pyrrolidine, piperidine, and indoline rings are successively built in three well-differenti-


[*] Prof. Dr. J. Bonjoch, Prof. Dr. J. Bosch, Dr. D. Solé, Dr. S. García-Rubio, E. Peidró
Laboratory of Organic Chemistry, Faculty of Pharmacy
University of Barcelona
Av. Joan XXIII s/n, E-08028-Barcelona (Spain)
Fax: (+34) 93-4021896
E-mail: bonjoch@farmacia.far.ub.es



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