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[14] Crystal structure determination of **2′**$\cdot 4\,CH_3NO_2$: An orange crystal (ca. $0.38 \times 0.32 \times 0.18$ mm) was analyzed with a Bruker SMART CCD-based diffractometer at 200 K with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Monoclinic, space group $P2_1/n$, $a = 14.9174(8)$, $b = 15.4925(8)$, $c = 19.8300(11)$ Å, $\beta = 105.4740(10)^\circ$, $V = 4416.7(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.593$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 1.289$ mm^{-1}, $F(000) = 2156$. ω-scans, 27813 reflections measured ($2\theta_{max} = 55^\circ$), of which 9940 were independent and 7236 were observed [$I > 2\sigma(I)$], 545 refined parameters, $R = 0.0510$, $wR2 = 0.1347$, residual electron density max./min. $1.247/-0.569$ e Å^{-3}, max./min. transmission 0.8014/0.7022. Crystal structure determination of **3**$\cdot 3\,CH_3NO_2$: A black crystal (ca. $0.32 \times 0.28 \times 0.15$ mm) was analyzed with a Bruker SMART CCD-based diffractometer at 193 K with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Monoclinic, space group $P2_1/n$, $a = 14.6914(9)$, $b = 19.0764(11)$, $c = 15.2417(9)$ Å, $\beta = 91.1990(10)^\circ$, $V = 4270.7(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.655$ g cm^3, $\mu(Mo_{K\alpha}) = 1.486$ mm^{-1}, $F(000) = 2164$. ω-scans, 26851 reflections measured ($2\theta_{max} = 55^\circ$), of which 9656 were independent and 5646 were observed [$I > 2\sigma(I)$], 538 refined parameters, $R = 0.0553$, $wR2 = 0.1274$, residual electron density max./min. $0.831/-0.509$ e Å^{-3}, max./min. transmission 0.8621/0.6109. Data reduction for both compounds was performed with the SAINT software, which corrects for Lorentz and polarization factors as well as decay. Absorption corrections were applied with SADABS supplied by G. Sheldrick (Universität Göttingen). The structures were solved by direct methods with the SHELXS-97 program and refined by the least squares method on F^2, (SHELXL-97, incorporated in SHELXTL-PC version 5.10). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated by geometrical methods and refined as a riding model. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-132694 and CCDC-132695. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[18] This result is also supported by the dependence of the magnetization of **2** on the field.

Encoded Helical Self-Organization and Self-Assembly into Helical Fibers of an Oligoheterocyclic Pyridine – Pyridazine Molecular Strand[**]

Louis A. Cuccia, Jean-Marie Lehn,[*]
Jean-Claude Homo, and Marc Schmutz

Helices and superhelices are key structural features of proteins, nucleic acids, and oligosaccharides. It is therefore no surprise that helical structures and superstructures have received increasing attention in biomimetic and synthetic supramolecular systems.[1] Helical organization in synthetic systems has been obtained through covalent conformational restrictions,[2] metal complexation,[3] solvophobic effects,[4] intermolecular interactions,[5] and nonbonding intramolecular interactions.[6] Several approaches to the generation of helical entities have been pursued in our group[7] starting from double-helical metal complexes (helicates),[8] followed by triple helicates,[9] circular helicates,[10] and helically wound, supramolecular liquid crystalline polymers.[11] More recently

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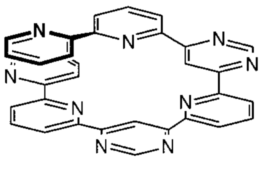
we have introduced a general concept for the strictly enforced generation of helical molecules by intramolecular self-organization of a suitably encoded oligoheterocyclic strand.[12–14] It is based on the design of *helicity codons* that enforce helical winding of the strand due to the *transoid* conformation imposed around the interheterocyclic bonds. Thus, helical induction was achieved by means of extended sequences of "pyridine–pyrimidine" helicity codons, which were shown to generate molecular helices presenting one turn, such as **1**,[12] two turns,[13] and up to four turns,[14] with six heterocycles per turn.



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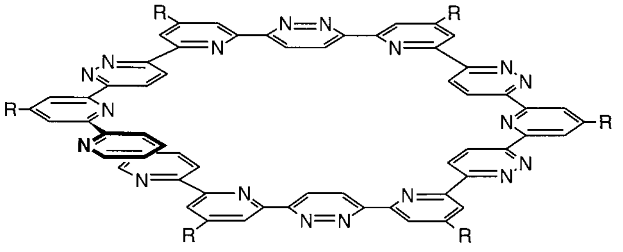
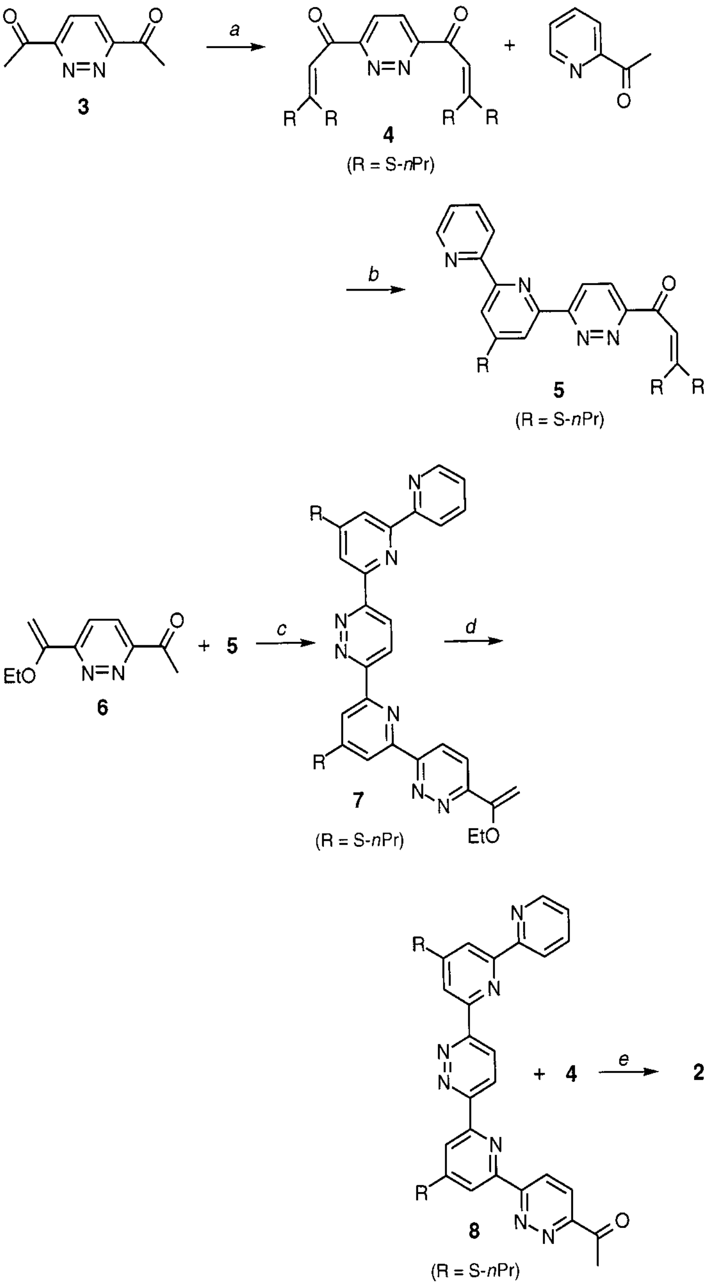
Further steps toward the control of the structural features of molecular and supramolecular helical species involve the design of other suitable codons, the modification of diameter, the number of residues per turn, and the pitch of the helix, as well as the generation of extended multicomponent entities by self-assembly. The work presented here addresses several of these questions. We describe an isomeric, alternating pyridine–pyridazine heterocyclic strand that, a priori, should yield an hexagonal helical structure (**2**) with twelve heterocycles per turn, an outside diameter of about 25 Å, and a central cavity of about 8 Å across.



2 R = S-*n*Pr

Compound **2** was synthesized using the Potts methodology[15] following the sequence of reactions shown in Scheme 1. 3,6-Diacetylpyridazine (**3**) and 3-acetyl-6-(1-ethoxyvinyl)pyridazine (**6**) were synthesized from 3,6-dichloropyridazine using tributyl-(1-ethoxyvinyl)tin, as previously described for their 4,6-substituted pyrimidine counterparts.[13b, 16] The bis-Michael acceptor **4**, prepared from **3**, was treated with one equivalent of 2-acetylpyridine to obtain the mono-addition product **5**. The reaction of Michael acceptor **5** with the unsymmetrically substituted pyridazine **6** gave **7**, which was subsequently hydrolyzed to **8** in aqueous acid. Reaction of two equivalents of **8** with the bis-Michael acceptor **4** gave the desired final product **2**. Compound **2** is soluble in chloroform and insoluble in most other common organic solvents. It is sparingly soluble in dichloromethane and pyridine, and forms viscous, birefringent solutions in these solvents.

The planar *transoid* conformer of 2,2′-bipyridine is calculated to be about 25 kJ mol^{-1} lower in energy than the *cisoid* conformer.[17] This conformational preference may be attributed to: a) weak, favorable interactions between the lone pair of electrons on the nitrogen and the adjacent hydrogen atom on the neighboring heterocycle in the *transoid* conformer, b) favorable antiparallel orientation of the nitrogen dipoles in the *transoid* conformer, and c) unfavorable steric interactions between CH sites in the *cisoid* conformer. A pyridine–pyridazine unit would also be expected to favor the *transoid* conformer in a similar way. Molecular modeling, starting from an extended nonhelical form, confirms that the optimal conformation of compound **2** consists of a helical structure having twelve heterocycles per turn with the two terminal pyridine rings overlapping at approximately 3.4 Å (Figure 1). As a further indication of the generality of intramolecular conformational control based on heterocyclic connectivity,



Scheme 1. a) NaH, CS$_2$, *n*PrI, DMSO, room temperature (66%); b) 1) NaH, THF/DMSO (2/1), room temperature; 2) NH$_4$OAc, AcOH, reflux (24%); c) 1) NaH, THF/DMSO (3/1), room temperature; 2) NH$_4$OAc, AcOH, reflux (33%); d) Acetone/2 N HCl (9/1), room temperature (97%); e) 1) NaH, THF/DMSO (6/1), room temperature; 2) NH$_4$OAc, AcOH, reflux (19%).

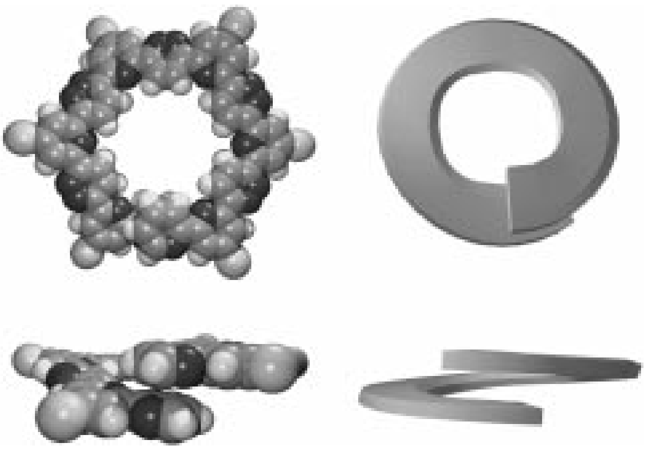


Figure 1. Minimized conformation and schematic representation of compound **2** viewed face on and from the side (propyl groups removed for clarity).

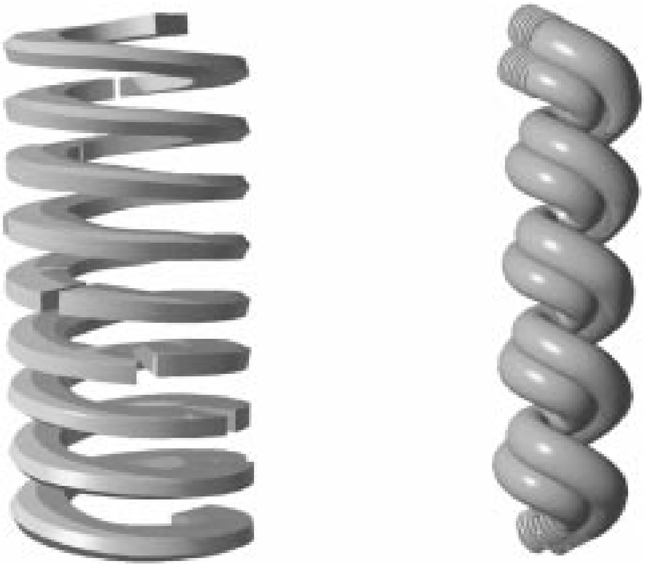


Figure 2. Schematic tentative representations of a self-assembled helical stack of compound **2** (left) and a fiber composed of two coiled-coil self-assembled stacks of compound **2** (right).

2,3-bis-[6-(2,2′-bipyridyl)]pyrazine has also been shown to adopt a curled conformation with four heterocycles per helical turn.[18]

Enforced helix formation of compound **2** in solution was confirmed by significant upfield shifts of the proton resonances at positions C4 and C5[19a] of the terminal pyridine rings ($\delta = 7.06$, 6.53) due to the shielding effects of intramolecular stacking. This marked shielding is diagnostic of helix formation in isomeric pyridine – pyrimidine molecular strands previously studied in our laboratory[12–14] and is also characteristic for the aromatic termini of helicenes and heterohelicenes.[20]

Furthermore, all aromatic proton resonances of compound **2** in chloroform were shifted to higher fields as the concentration was increased. This distinct upfield displacement of 0.6 – 0.8 ppm in a concentration range of 0.1 – 100 mM at 35 °C was attributed to the formation of molecular assemblies, resulting in diamagnetic anisotropy effects between neighboring molecules. Consequently, the observed shift of the protons at positions C4 and C5 of the terminal pyridine rings has both intra- and intermolecular $\pi - \pi$ stacking contributions.[19b] Self-aggregation was confirmed by vapor-pressure osmometry which gave an apparent molecular weight for compound **2** of about 3600 $\mathrm{g\,mol^{-1}}$ (at 36 °C in chloroform over a concentration range of 2 – 18 mM). This value is more than twice the actual value of 1453.92 $\mathrm{g\,mol^{-1}}$. Previous results on the aggregation of phenylacetylene macrocycles have suggested the importance of a preorganized planar geometry to achieve multiple $\pi - \pi$ stacking.[21] Indeed, a pre-organized helical conformation of compound **2** can be envisaged to form self-assembled supramolecular stacks with up to twelve face-to-face $\pi - \pi$ interactions between the aromatic heterocycles of neighboring molecules (Figure 2, left).

Self-aggregation of compound **2** was also observed in dichloromethane and pyridine. Low-molecular-weight gelators for organic solvents generate elongated aggregates which subsequently assemble into fiberlike structures that form an extended entangled network.[22] Gel formation induced by compound **2** prompted an investigation by electron microscopy, that revealed the formation of an extensive fiber network with helical substructures. The freeze-fracture electron micrograph of compound **2** in dichloromethane (1 $\mathrm{mg\,mL^{-1}}$; Figure 3 a) shows uniform fibers with an approximate diameter of 80 Å; these fibres are probably composed of coiled-coil bundles of two or three single supramolecular stacks (Figure 2, right). The chirality observed in the fibers, manifested as helical twisting, could result from favorable

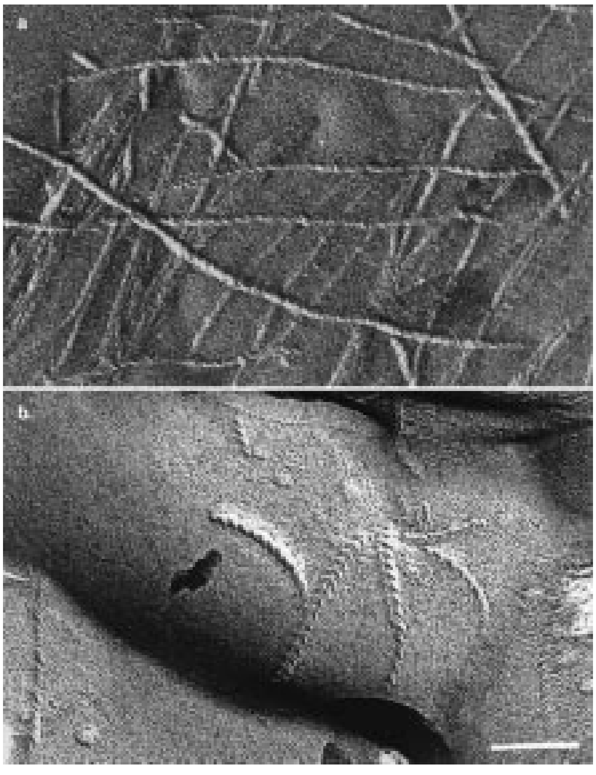


Figure 3. Freeze-fracture electron micrographs of compound **2** in a) dichloromethane and b) pyridine showing fiber network formation with helical textures (scale bar represents 100 nm).

intermolecular π–π stacking interactions from helices of compound **2** of the same helical sense. The molecular helical chirality is consequently translated into supramolecular helicity that is expressed on a nanometer scale. In Figure 3a, a dominance of fibers of same chirality is observed; it may be due to the induction of fiber formation by seeds generated by the breakdown of an initial helical entity caused by the sonication procedure employed. More defined helical structures displaying left- and right-handed helical twists were observed from a birefringent solution of compound **2** in pyridine (2 mg mL^{-1}, Figure 3b), a solvent expected to break intermolecular π–π interactions. The pitch of the helical fibers observed in Figures 3a and 3b is around 115 Å. Networks of fibers of micrometer length subsequently form linear and intertwined macrofibers (Figure 4), yielding a viscous, birefringent organogel in dichloromethane. A solution of compound **2** in pyridine is birefringent but not nearly as viscous as the gel in dichloromethane, and the length of the fibers (and their entanglement) is much greater in dichloromethane than in pyridine. This molecular aggregation into fibers and macrofiber bundles is reminiscent of gels obtained from crown ether substituted phthalocyanins.[23]

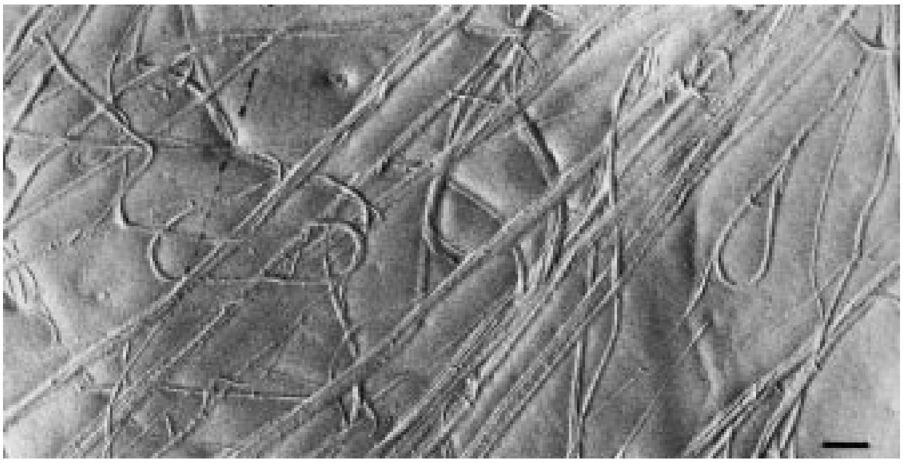


Figure 4. Freeze-fracture electron micrograph showing molecular aggregation of compound **2** into linear and helical fibers and macrofiber bundles in dichloromethane (scale bar represents 200 nm).

Particularly attractive in this self-organizing/self-assembling system is the formation of bundles of extended molecular channels[24] comprising tubular (helical) stacks with hollow cores of finite size (ca. 8 Å diameter), thus opening ways for the design of functional polymolecular materials for multichannel ion-active devices.[25] Further developments towards this end may involve internal functionalization with ion-binding sites.

Analogous to the primary amino acid sequence that encodes the required information for protein folding and assembly, the primary heterocyclic sequence and connectivity encodes for helical self-organization and subsequent self-assembly. Such systems provide access to controlled sequential and hierarchical self-organization processes of well-defined polymolecular architectures at the supramolecular level.

Experimental Section

Physical characterization of compound **2**: m.p. 326.2–329.0 °C (decomp); R_f (alumina, CH_2Cl_2): 0.14; ^{1}H NMR (500.13 MHz, $CDCl_3$ (29 mM), 55 °C): $\delta = 8.17-7.77$ (m, 26H), 7.06 (m, 2H), 6.53 (m, 2H), 3.06 (t, $^3J = 7.1$ Hz, 4H), 3.02 (t, $^3J = 7.1$ Hz, 4H), 2.98 (t, $^3J = 7.1$ Hz, 4H), 1.88–1.70 (m, 12H), 1.21 (t, $^3J = 7.4$ Hz, 6H), 1.17 (t, $^3J = 7.4$ Hz, 6H), 1.10 (t, $^3J = 7.4$ Hz, 6H); ^{13}C NMR (125.77 MHz, $CDCl_3$ (29 mM), 55 °C): $\delta = 157.08$, 156.60, 156.54, 156.53, 156.50, 154.60, 154.09, 153.25, 153.04, 152.16, 151.32, 151.24, 151.16, 151.14, 148.72, 135.72, 123.99, 123.84, 123.79, 123.74, 123.04, 120.14, 118.36, 118.32, 118.15, 118.03, 118.02, 117.36, 33.22, 33.13, 33.00, 21.80, 21.69, 21.68, 13.91, 13.84, 13.65; IR (KBr, cm^{-1}): $\tilde{\nu} = 2960$, 2925, 2870, 1577, 1545, 1458, 1390, 1097, 988, 850, 812; UV/Vis (CH_2Cl_2): $\lambda_{max}(\varepsilon) = 296$ (202000); MS (FAB+): *m*/*z* (%): 1453.5 (100, [M^+]); elemental analysis: $C_{78}H_{72}N_{18}S_6$ (1453.92): calcd: C 64.44, H 4.99, N 17.34; found: C 64.42, H 5.01, N 17.22.

Molecular modeling was carried out with the MacroModel molecular mechanics program (version 5.5) using the Amber* force field and a standard Monte Carlo search for favorable conformations.

Molecular weight determinations were performed with a Knauer twin-thermister hanging-drop vapor-pressure osmometer operated at 36 °C. The molecular weight of compound **2** was measured in HPLC-grade chloroform over a concentration range of 2–18 mM. A calibration curve was generated by using a polystyrene molecular weight standard (MW = 2430, $MN_{VPO} = 2330$, polydispersity = 1.06).

Organogels for freeze–fracture transmission electron microscopy were prepared by dissolving compound **2** (0.5–2.0 mg) in dichloromethane or pyridine with heating and bath sonication. The solutions were aged at room temperature for at least 12 h prior to use. Freeze-fracture experiments were performed in an apparatus developed at IGBMC by J.-C. Homo. Gel solutions were sandwiched between two copper specimen holders and frozen in liquid nitrogen. The frozen samples were transferred to the fracture-replication stage which was kept at a vacuum of 10^{-8} mbar at −178 °C. Replication was performed immediately after fracturing with about 20 Å platinum/carbon at 45° followed by about 200 Å carbon at 90°. The replicas were retrieved and cleaned in chloroform, mounted on carbon coated grids and observed with a Philips CM12 electron microscope operating at 100 keV.

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A New Enantioselective Approach to Total Synthesis of the Securinega Alkaloids: Application to (−)-Norsecurinine and Phyllanthine**

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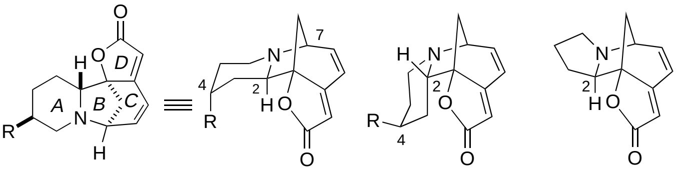
Dedicated to the memory of Professor George Buchi

The securinega alkaloids are a family of approximately 20 tetracyclic compounds produced by several *Securinega* and *Phyllanthus* species of the Euphorbiaceae plant family.[1] The major securinega alkaloid is securinine (**1**), isolated from the leaves of *Securinega suffruticosa*. Its enantiomer, virosecurinine, is also naturally occurring, as are the antipodes of several other alkaloids of this class. Allosecurinine (**3**), which is the C2 epimer of **1**, is also a common alkaloid of this group, as is securitinine (**4**). The enantiomer of **3** (viroallosecurinine) is a natural product as well. Some additional common alkaloids of this group are (−)-norsecurinine (**5**), whose (+)-enantiomer is also naturally occurring, and phyllanthine (**2**).



1 R = H: securinine
2 R = OMe: phyllanthine
3 R = H: allosecurinine
4 R = OMe: securitinine
5: (−)-norsecurinine

These alkaloids are associated with a wide range of biological activity. Securinine causes central nervous system stimulation and clonic–tonic convulsions in laboratory animals. This activity is due to the alkaloid acting as a γ-amino butyric acid (GABA) receptor antagonist.[2] These alkaloids have found a sporadic use clinically for such diseases as poliomyelitis, ALS (amyotrophic lateral sclerosis) and chronic aplastic anemia.[1] Securinine has also been found to be an antimalarial agent[3] and to have antibacterial activity.[4]

To date there has been only limited synthetic work in this area. A nonstereoselective total synthesis of racemic securinine (**1**) was described by Horii et al. in 1966.[5] More recently, Heathcock and coworkers devised a clever route to racemic norsecurinine (**5**).[6] In this synthesis, both the A-ring and the configuration of the C2 atom of **5** were derived from L-proline, although unfortunately optical activity was lost by the racemization of an intermediate. Jacobi et al.[7] have developed an innovative route to both (+)- and (−)-norsecurinine,

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