Hexacyclinol

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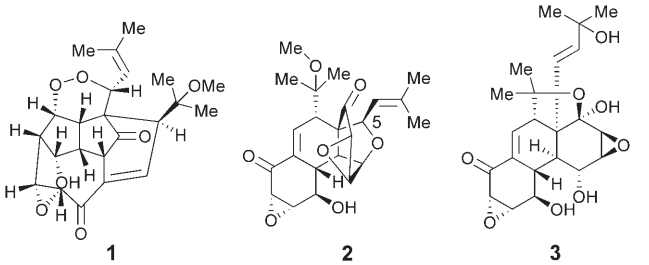
Total Synthesis and Structure Assignment of (+)-Hexacyclinol**

John A. Porco, Jr., Shun Su, Xiaoguang Lei, Sujata Bardhan, and Scott D. Rychnovsky*

The structurally novel antiproliferative metabolite, hexacyclinol (**1**; Scheme 1) was isolated in 2002 by Gräfe and co-workers from *Panus rudis* strain HKI 0254.[1] The proposed

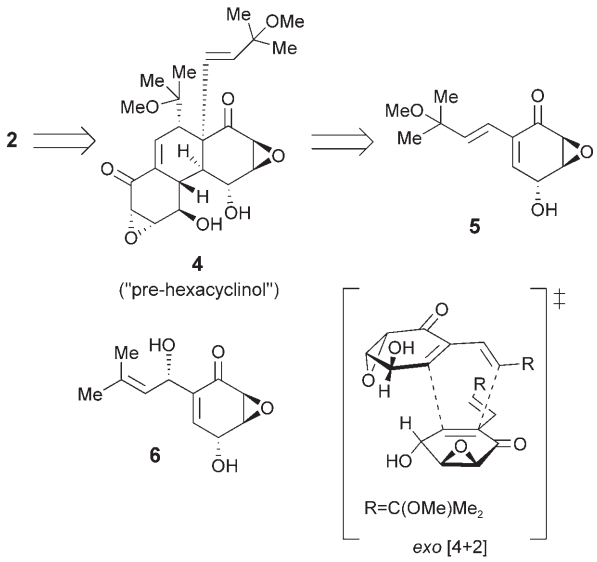


Scheme 1. Structures of hexacyclinol and panepophenanthrin (**3**).

structure contains both reactive epoxyketone and highly strained endoperoxide moieties. A synthesis of the structure proposed by Gräfe and co-workers, as well as preliminary evaluation of non-peroxide-containing precursors as antimalarial agents, was recently reported by La Clair.[2] Recently, one of us[3] proposed an alternative structure of hexacyclinol (**2**; Scheme 1) based on calculated ^{13}C NMR chemical shift correlations. This structure was proposed to arise from acid-catalyzed rearrangement of the ubiquitin-activating enzyme inhibitor, panepophenanthrin (**3**), also isolated from the mushroom strain *Panus rudis* Fr. IFO8994.[4] In light of our prior synthesis of **3** and access to the natural product as well as chiral, nonracemic epoxyquinol monomer precursors,[5] we initiated studies to prepare proposed structure **2**. Herein, we report the total synthesis of the revised (+)-hexacyclinol structure **2** and confirmation of the proposed reassignment of the natural product. The synthesis is designed around the highly stereoselective Diels–Alder dimerization of an epoxyquinol monomer, followed by an intramolecular acid-catalyzed cyclization.

Our initial studies involved treatment of synthetic **3** with methanol under acidic conditions to determine the feasibility of further transformation to **2**. As noted previously,[3] this tactic was based on the proposal that hexacyclinol may arise from panepophenanthrin as an isolation artifact formed by the use of silica gel and methanol during the isolation of the natural product. However, treatment of synthetic (+)-**3** under a variety of acidic conditions (e.g., SiO_2 or K10 clay in MeOH or $CHCl_3$/MeOH mixtures at room temperature) did not lead to observable conversion into **2** or other products. As we have noted earlier,[5] the hemiacetal structure of **3** "locks" the dimeric framework, thus preventing further ring opening to the corresponding hydroxyketone under acidic conditions.

We thus revised our synthetic route as depicted in Scheme 2. Structure **2** may be derived from dimeric precursor



Scheme 2. Revised retrosynthetic analysis for hexacyclinol (**2**).

4 by intramolecular acid-catalyzed demethoxylation.[6] "Pre-hexacyclinol" (**4**) may be derived from highly selective *exo*-Diels–Alder dimerization[5] of epoxyquinol monomer **5**, a rearranged allylic ether formally derived from the natural product panepoxydon (**6**).[7]

The synthesis of epoxyquinol diene monomer **5** was initiated from the readily available *anti*-epoxy alcohol **7**[5] (Scheme 3). For initial studies, we employed (±)-**7** to develop the synthetic route. Ketal deprotection of **7** with Montmorillonite K10 clay in CH_2Cl_2[8] cleanly afforded an intermediate

[*] Prof. Dr. J. A. Porco, Jr., S. Su, X. Lei, S. Bardhan
Department of Chemistry and
Center for Chemical Methodology and Library Development
Boston University
590 Commonwealth Avenue, Boston, MA 02215 (USA)
Fax: (+1) 617-358-2847
E-mail: porco@bu.edu
Prof. Dr. S. D. Rychnovsky
Department of Chemistry
University of California—Irvine
Irvine, CA 92697-2025 (USA)

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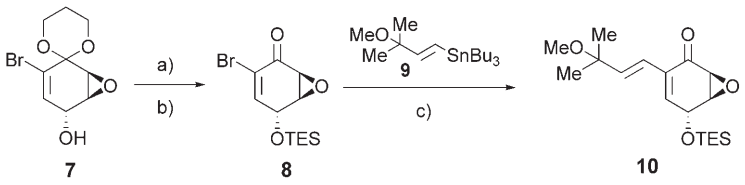
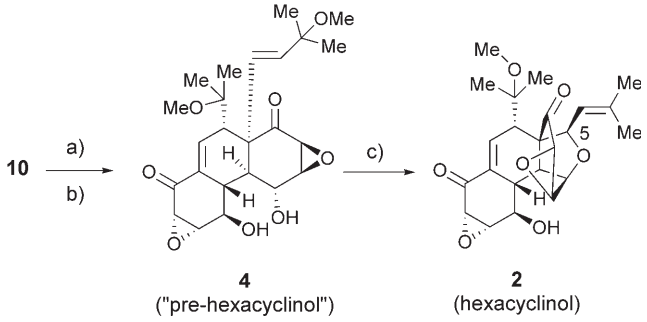


Scheme 3. a) K10 clay, CH_2Cl_2, 6 h, 98%; b) Et_3SiCl, 2,6-lutidine, DMAP (cat.), CH_2Cl_2, 83%; c) [$Pd_2(dba)_3$], $AsPh_3$, toluene, 110°C, 1 h, 96%. dba = dibenzylideneacetone; DMAP = 4-dimethylaminopyridine; TES = triethylsilyl.

epoxyketone (bromoxone),[9] which was protected[10] to afford triethylsilyl ether **8**.[11] In line with a report by Baldwin and coworkers in their synthesis of panepophenanthrin,[10] we elected to utilize Stille coupling for installation of the allylic ether side chain. The requisite vinyl stannane coupling partner **9** was prepared by hydrostannylation of 3-methoxy-3-methyl-1-butyne[12] using Guibé's conditions.[13] Cross-coupling of **8** with **9** was cleanly effected using our previously reported conditions for coupling of related epoxyketone substrates[14] ([$Pd_2(dba)_3$], $AsPh_3$) to afford the silyl-protected monomer **10** (96%).

As anticipated, monomer **10** partially dimerized upon standing without solvent (25°C). Accordingly, after chromatography **10** was immediately deprotected with $Et_3N{\cdot}3HF$ (TREAT-HF)[7b,15] in CH_3CN to give a mixture of monomer **5**



Scheme 4. a) $Et_3N{\cdot}3HF$, CH_3CN, 0°C→RT, 15 min; b) neat, room temperature, 72 h, 87% (two steps); c) K10 clay, EtOAc, room temperature, 99%.

and a trace amount of dimer **4**, which was allowed to further stand at room temperature (neat, 72 h; Scheme 4). Under these conditions, "pre-hexacyclinol" (**4**) was cleanly obtained in 87% yield as a single diastereomer.[5,10] To assess the transformation[7] of panepoxydon (**6**) to monomeric precursor **5**, we treated commercially available[16] **6** with K10 clay in CD_3OD (40°C, 10 h) which afforded epoxyquinol diene monomer **5** (60% conversion according to ^1H NMR spectroscopy).[11]

After considerable experimentation, we found that the final S_N2' substitution/cyclization of **4** to hexacyclinol (**2**) was efficiently mediated by K10 clay[17] (EtOAc, room temperature, 3 min, 99%). Synthetic **2** was confirmed to be identical to spectral data (^1H, ^{13}C NMR) reported by Gräfe and co-workers.[1] X-ray crystal structure analysis fully confirmed the structural framework, including the configuration at the newly created C-5 stereocenter (Figure 1).[11] Interestingly, ±-**2** crystallized as a centrosymmetric racemate ($P\bar{1}$ space group) in a similar fashion to an "open" dimer prepared during our panepophenanthrin synthesis.[5] Examination of the X-ray crystal structure of **2** shows that the S_N2'

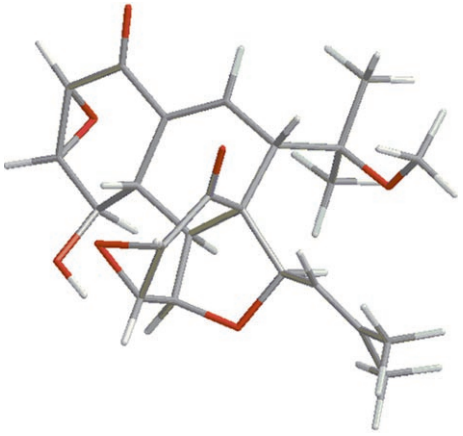


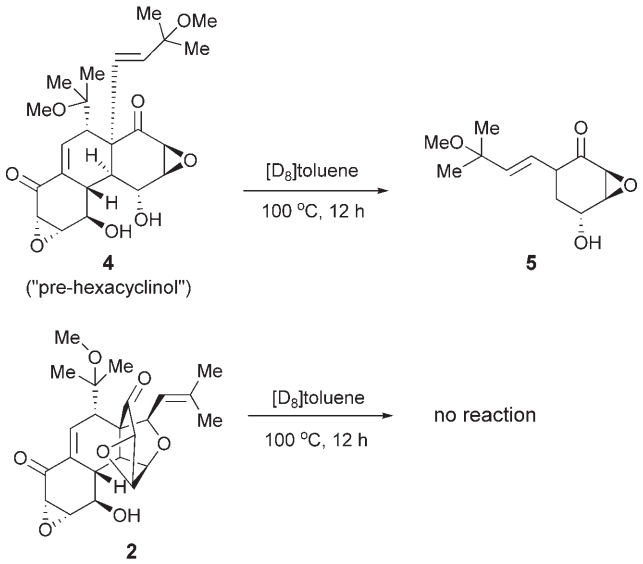
Figure 1. X-ray crystal structure analysis of synthetic **2** (O red, C dark gray, H pale gray).

cyclization places the prenyl substituent at C-5 in a pseudo equatorial orientation, which minimizes steric interactions on the envelope conformation of the tetrahydrofuran ring.

Beginning with chiral, nonracemic (+)-**7** (93% *ee*)[11] we prepared (+)-hexacyclinol (**2**), for which analytical data were confirmed to be identical to those reported for natural (+)-hexacyclinol by ^1H and ^{13}C NMR spectroscopy and optical-rotation studies (synthetic **2**: $[\alpha]_D = +133.3°$, $c = 0.40$, CH_3OH).[11] Our synthesis thus confirms the absolute configuration of (+)-**2** and its relationship to (+)-panepophenanthrin (**3**).

Finally, we performed comparative thermolysis experiments on "pre-hexacyclinol" (**4**) and hexacyclinol (**2**; Scheme 5). Heating of dimer **4** ([D_8]toluene, 100°C, 12 h) led to quantitative production of a solution of monomer **5** (^1H NMR spectroscopy). In contrast, thermolysis of **2** ([D_8]toluene, 100°C, 12 h) led to recovered starting material, indicating that the additional tetrahydrofuran ring of **2** serves to stabilize the pseudodimeric structure towards retro-[4+2] cycloaddition.

In summary, the first enantioselective total synthesis of the reassigned (+)-hexacyclinol structure **2** has been accomplished. Racemic **2** was found to crystallize as a centrosymmetric racemate ($P\bar{1}$ space group), which was crucial for unambiguous structural confirmation of the natural product. Our studies reinforce that hexacyclinol is likely an isolation artifact arising from acid-catalyzed rearrangement of panepoxydon, dimerization, and S_N2' cyclization. Additional synthetic studies related to hexacyclinol, as well as biological



Scheme 5. Comparative thermolysis experiments.

evaluation of **2** and derivatives, are in progress and will be reported in due course.

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