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Enantioselective total synthesis of the novel antiproliferative metabolite (+)-hexacyclinol

Goverdhan Mehta *, Subhrangsu Roy

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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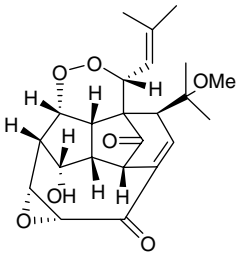
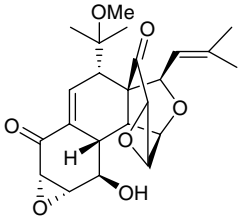
Abstract

An enantioselective total synthesis of the novel bioactive epoxyquinone natural product (+)-hexacyclinol, exhibiting promising growth inhibiting activity against cancer cell lines, has been accomplished from a readily available chiron derived from the Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone.

In 2002, Gräfe and co-workers reported the isolation of a novel antiproliferative metabolite, hexacyclinol, from the fungal species *Panus rudis* strain HKI 0254 collected from dead betula wood in Siberia.[1] The polycyclic structure **1** with an unusual peroxo-bridge was initially proposed for hexacyclinol by these authors on the basis of extensive 1D and 2D NMR studies.[1] The architecturally complex and functionally embellished formulation of **1** with diverse bioactivity attributes ranging from antimalarial (inhibitory activity against *Plasmodium falciparum*) to antiproliferative (inhibition of L-929 and K-562 cells) drew immediate attention. In 2006, a debatable total synthesis of hexacyclinol **1** was claimed by La Clair.[2] Concurrently, Rychnovsky, intrigued by the originally assigned structure of **1**, proposed an alternate epoxyquinone-based formulation **2** for hexacyclinol through some insightful analyses of calculated ^{13}C NMR chemical shift correlations.[3] The key element in this derivation was the recognition of a possible biosynthetic sibling relationship between hexacyclinol **2** and another metabolite panepophenanthrin **3** which has been isolated from another species of *Panus rudis*.[4] Given this backdrop, it is hardly surprising that hexacyclinol **2** constitutes an attractive and challenging target for total synthesis, on account of both its structural complexity and bioactivity profile.



Hexacyclinol structure proposed by Gräfe (**1**)



Hexacyclinol structure revised by Rychnovsky (**2**)

The group of Porco in collaboration with Rychnovsky has recently accomplished an enantioselective total synthesis of the reassigned structure **2** of (+)-hexacyclinol, settling its formulation unambiguously, and also delineated its absolute configuration.[5] As part of our ongoing interest in the total synthesis of epoxyquinol natural products,[6] and particularly in view of our recent accomplishment of the syntheses of both the enantiomers of panepophenanthrin **3**,[7] it was natural for us to be drawn to the reassigned structure of hexacyclinol **2** as a synthetic objective. Herein, we report an enantioselective synthesis of (+)-hexacyclinol **2** by an approach that has in-built flexibility and should be

* Corresponding author. Tel.: +91 8023600367; fax: +91 8023600283.
E-mail address: gm@orgchem.iisc.ernet.in (G. Mehta).

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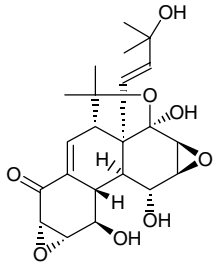
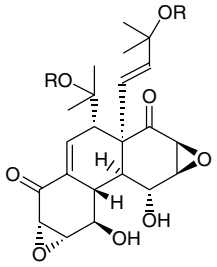
amenable to diversity generation around this novel scaffold.



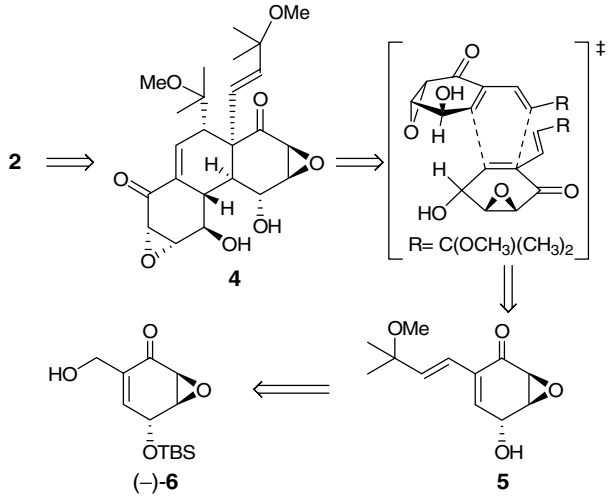
Panepophenanthrin (**3**)



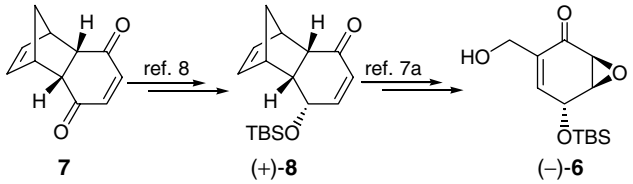
pre-Hexacyclinol (**4**), R = H, Me.

Our synthetic approach to **2** was inspired by its close relationship with panepophenanthrin **3** via pre-hexacyclinol **4** as described by Rychnovsky[3] and their common biosynthetic origin involving the highly stereoselective dimerization of an epoxyquinone monomer **5** through a Diels–Alder reaction (Scheme 1). An acid mediated S_N2' intramolecular cyclization process in pre-hexacyclinol **4** involving the opportunistically positioned hydroxyl group was expected to provide the natural product. Thus, we identified epoxyquinone monomer **5** as an advanced intermediate and sought to access it from the enantiomerically pure precursor **6** following the protocols established during our panepophenanthrin syntheses.[7]

Our synthesis of natural product **2** started from the abundantly available tricyclic Diels–Alder adduct **7** of cyclopentadiene and *p*-benzoquinone, which was readily elaborated to the enantiomerically pure (+)-**8** following a previously reported protocol.[8] Adduct (+)-**8** was further converted to the advanced precursor (−)-**6** following protocols employed by us on a previous occasion (Scheme 2).[7a] DIBAL-H reduction of the carbonyl group in (−)-**6** was stereoselective, possibly through DIBAL-H coordination with the epoxy oxygen and hydride delivery from the β-face, to furnish exclusively the selectively protected triol



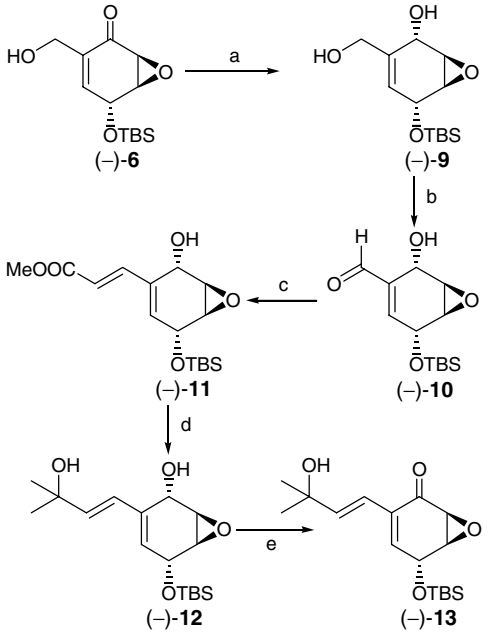
Scheme 1. Retrosynthetic analysis of **2**.



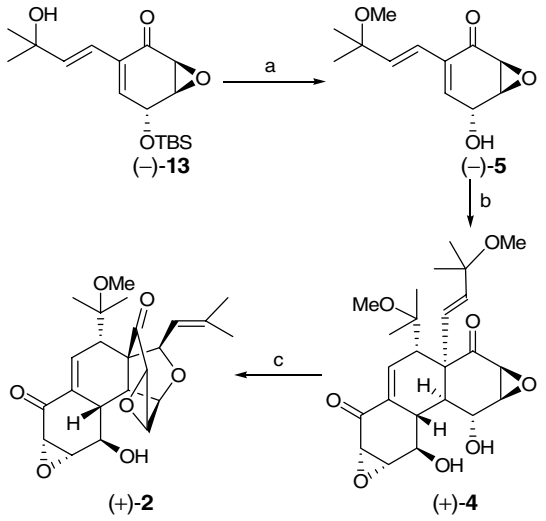
Scheme 2.

(−)-**9**.[9] The primary hydroxyl group in diol (−)-**9** was chemoselectively oxidized to aldehyde **10** using TEMPO–O_2–CuCl.[10] Horner–Wittig olefination of the hydroxy aldehyde (−)-**10** proceeded smoothly and stereospecifically to render (*E*)-α,β-unsaturated ester (−)-**11** in high yield. Addition of an excess of methyl lithium to (−)-**11** at −78 °C followed by gradual warming to −10 °C led to the desired tertiary alcohol **12**. Oxidation of the allylic *sec*-hydroxyl group in (−)-**12** with active MnO_2 furnished dienone (−)-**13** smoothly, Scheme 3.

At this stage, it was necessary to carry out the methylation of the acid sensitive tertiary allylic alcohol in **13** to generate the desired side arm present in **5**. After some experimentation, it was observed that our target, the monomeric precursor **5**, could be obtained directly from **13** on exposure to Dowex-1 resin in methanol through a concomitant methylation and desilylation reaction, Scheme 4.[11] When (−)-**5** was left neat under ambient conditions (~26 °C) for 78 h, it was converted cleanly into a single diastereomer that could be identified spectroscopically as pre-hexacyclinol **4** (R = Me) through the anticipated and desired stereospecific intermolecular Diels–Alder reaction (see Scheme 1).[5]



Scheme 3. Reagents and conditions: (a) DIBAL-H, THF, −78 °C, 88%; (b) TEMPO, CuCl, O_2, DMF, 4 h, 95%; (c) $Ph_3P{=}CHCOOMe$, C_6H_6, 92%; (d) MeLi (1 M in diethyl ether), THF, −78 to −10 °C, 95%; (e) MnO_2, CH_2Cl_2, 72%.



Scheme 4. Reagents and conditions: (a) Dowex-1 × 8, MeOH, 10 h, 55%; (b) neat, rt, 78 h, 99%; (c) Dowex-1 × 8, EtOAc, 8 h, 99%.

Finally, the second exposure to Dowex-1 resin triggered the contemplated S_N2' displacement/cyclization in **4** to furnish exclusively the natural product (+)-**2** in excellent yield (Scheme 4).[11] The identity of our synthetic material was fully established through comparison of ^1H and ^{13}C NMR spectra[1] and the specific rotation $[\alpha]_D^{23}$ +130.9 (*c* 0.42, methanol) with those of the natural product, lit.[1] $[\alpha]_D^{22}$ +130.5 (*c* 0.40, methanol).

In summary, we have accomplished a short, enantioselective total synthesis of the novel antiproliferative metabolite (+)-hexacyclinol **2** from the abundantly available chiral building block (−)-**6**. The successful total synthesis approach to (+)-hexacyclinol **2** delineated here is amenable to enantio- and structural divergence to render access to analogues for biological evaluations.

Acknowledgments

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11. All new compounds were characterized on the basis of IR, ^1H, ^{13}C NMR, and HRMS data. Spectral data for selected compounds: (−)-**5** $[\alpha]_D^{26}$ (−)-170.5 (*c* 0.54, $CHCl_3$); IR (neat) 3390, 2931, 1685, 1252 cm^{-1}, ^1H NMR (400 MHz) ($CDCl_3$) δ 6.61 (dd, $J = 5.2$, 2.4 Hz, 1H), 6.26 (s, 2H), 4.78 (m, 1H), 3.81 (m, 1H), 3.58 (dd, $J = 3.6$, 0.8 Hz, 1H), 3.16 (s, 3H), 2.09 (d, $J = 8.5$ Hz, 1H), 1.30 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 193.13, 140.79, 136.62, 134.0, 121.79, 75.11, 63.66, 57.34, 54.10, 50.59, 25.75, 25.52; HRMS (ES) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{16}O_4Na$, 247.0946; found, 247.0948; (+)-**4** $[\alpha]_D^{23}$ (+)-15.6 (*c* 0.45, $CHCl_3$); IR (neat) 3404, 2933, 1704, 1695 cm^{-1}, ^1H NMR (400 MHz) ($CDCl_3$) δ 6.73 (dd, $J = 4.3$, 2.6 Hz, 1H), 5.80 (1/2ABq, $J = 17.0$ Hz, 1H), 5.44 (1/2ABq, $J = 16.9$ Hz, 1H), 4.46 (br s, 1H), 4.17 (d, $J = 8.4$ Hz, 1H), 3.59 (d, $J = 3.3$ Hz, 1H), 3.57 (d, $J = 3.4$ Hz, 1H), 3.46 (m, 2H), 3.34 (d, $J = 3.2$ Hz, 1H), 3.20 (s, 3H), 3.07 (s, 3H), 3.02 (br s, 1H), 2.76 (br s, 1H), 2.72–2.68 (m, 1H), 2.61 (t, $J = 4.7$ Hz, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 202.62, 194.35, 138.47, 138.35, 133.91, 130.65, 77.32, 75.15, 69.67, 68.03, 61.45, 58.95, 55.19, 53.50, 53.50, 52.91, 50.35, 49.53, 48.51, 46.33, 26.07, 25.12, 24.57, 23.53; HRMS (ES) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{32}O_8Na$, 471.1995; found, 471.1995; (+)-**2** mp = 179–180 °C; $[\alpha]_D^{23}$ (+)-130.9 (*c* 0.42, MeOH); IR (neat) 3436, 2980, 1709, 1627, 1448 cm^{-1}, ^1H NMR (400 MHz) ($CDCl_3$) δ 6.76 (dd, $J = 5.5$, 2.4 Hz, 1H), 5.49 (d, $J = 9.2$ Hz, 1H), 5.02 (dd, $J = 5.0$, 3.7 Hz, 1H), 4.85 (d, $J = 9.2$ Hz, 1H), 3.84 (m, 1H), 3.67 (m, 1H), 3.65–3.60 (m, 2H), 3.54 (d, $J = 3.3$ Hz, 1H), 3.32 (d, $J = 3.2$ Hz, 1H), 3.26 (d, $J = 3.6$ Hz, 1H), 3.05 (s, 3H), 2.77 (dd, $J = 10.2$, 5.2 Hz, 1H), 2.34 (d, $J = 6.8$ Hz, 1H), 1.80 (s, 3H), 1.74 (s, 3H), 1.29 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 202.86, 192.75, 142.21, 139.69, 132.48, 120.70, 77.20, 75.78, 72.67, 71.52, 60.97, 60.45, 54.50, 53.21, 53.11, 49.10, 47.75, 40.88, 40.38, 26.62, 26.23, 24.70, 18.51; HRMS (ES) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{28}O_7Na$, 439.1733; found, 439.1734.