Angewandte
Retraction

The following article from *Angewandte Chemie International Edition*, "Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif" by James J. La Clair, published online on February 9, 2006 in Wiley Online Library (http://onlinelibrary.wiley.com), has been retracted by agreement between the author, the journal Editor in Chief, Peter Gölitz, and Wiley-VCH Verlag GmbH & Co. KGaA. The retraction has been agreed due to lack of sufficient Supporting Information. In particular, the lack of experimental procedures and characterization data for the synthetic intermediates as well as copies of salient NMR spectra prevents validation of the synthetic claims. The author acknowledges this shortcoming and its potential impact on the community.

Antimalarial Drugs

Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif**
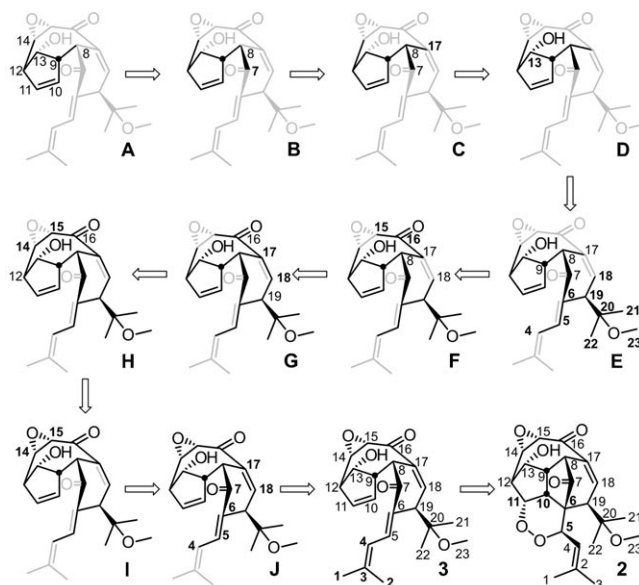
*James J. La Clair**

In memory of Udo Gräfe

Hexacyclinol (**1**) was isolated by Gräfe and co-workers from the basidiospores collected from *Panus rudis* growing on dead betula woods in Siberia.[1] In 1999, our exploration into German fungal cultures provided a strain of *P. rudis* 99-329 that was not only capable of the biosynthesis of **1** but also provided trace amounts of *epi*-5-hexacyclinol (**2**) and desoxohexacyclinol (**3**).[2] Further study indicated that the retrocycloaddition of **1** and **2** released oxygen to afford a mixture of trienes **3** (Scheme 1). Subsequent [2+2+2] cycloaddition of **3**
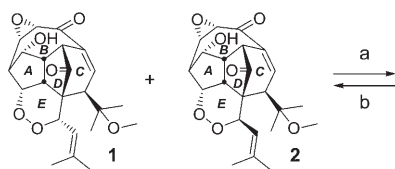
Scheme 1. Hexacyclinol interconversions: a) in vacuo, neat, 95%; b) O₂, rose bengal, MeOH, *hν*, 0°C, 89%.

with singlet oxygen returned a mixture of **1** and **2**. As this process could be cycled, it offered a key handle in expediting the synthesis of this family of terpenes.

The synthesis of **1** and **2** through **3** simplifies the complexity of the hexacyclinol ring system by removal of the D/E rings (Scheme 1). On the basis of this argument, a campaign to **3** was launched using the synthetic plan outlined in Scheme 2. The plan began with an intact A ring as shown in intermediate **A**. The first stage of this project sought a rapid appendage of C7 and C17 onto **A** followed by the installation of the lower half of the B ring as given by the conversion of **D** into **E**. From **E**, a series of three sequences (**E**→**F**, **F**→**G**, and **G**→**I**, Scheme 2) were used to stitch the molecule together, beginning with the insertion of C15–C16, followed by creation

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Scheme 2. Synthetic plan depicting the strategic intermediates **A**–**J**. Completed bonds are shown in black, and the skeleton is depicted in gray.

of the C17–C18 bond, and ending with installation of the C14–C15 epoxide.

Intermediate **A** was developed from bis(acetate) **4**.[3] Protection with TBS, deacetylation, and nosylation of the primary alcohol afforded **5** (Scheme 3). Under these conditions, nosylate **5** was obtained along with a bis(nosylate) derivative (3–5% yield), which was removed after treatment of the mixture with sodium cyanide in DMSO to convert **5** into **6**. This sequence was conducted on a multigram scale to provide **6** after a single chromatographic purification step. The synthesis of **6** completed the installation of C7 as indicated by the conversion of **A** into **B** (Scheme 2).

The next stage in this synthesis involved the installation of C17, as given by the conversion of **B** into **C** (Scheme 2). This operation was accomplished through the conversion of **6** into bromoacetal **7** by reaction with 1,2-dibromoethylmethyl ether (Scheme 3).[4] Treatment of crude **7** with NaHMDS at −78°C followed by warming to room temperature resulted in 3:2 mixture of **8a/8b**. Fortunately, protonation of the enolate of **8a/8b** with triphenylacetic acid afforded a mixture favoring the desired nitrile **8a** by 11:1. To increase the material throughput to **8a**, the cyclization and isomerization steps were conducted in a one-pot operation.

With intermediate **C** in hand, the next step required correction of the stereochemistry at C13. As provided by **4**, this center required inversion as illustrated by the conversion into **D** (Scheme 2). The process began by convertion of the nitrile of **8a** to dithiane **13** (Scheme 3). Slow addition of DIBAL-H at −20°C to **8a** at −78°C in toluene afforded **9** in high yield. The resulting aldehyde **9** was subsequently protected as dithiane **10**. The acetal ring of **10** was opened by treatment with dilute aqueous acid to provide **11**, which was in turn oxidized to the corresponding acid **12** through a buffered Tollens oxidation followed by hydrolysis of the incipient lactone. As noted by Smith et al.,[5] the oxidation of
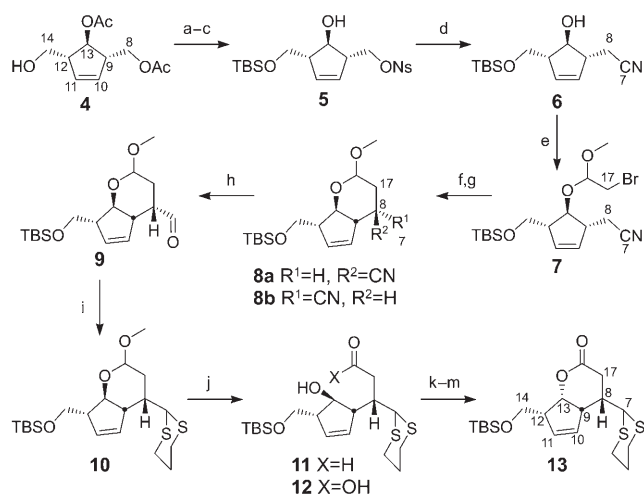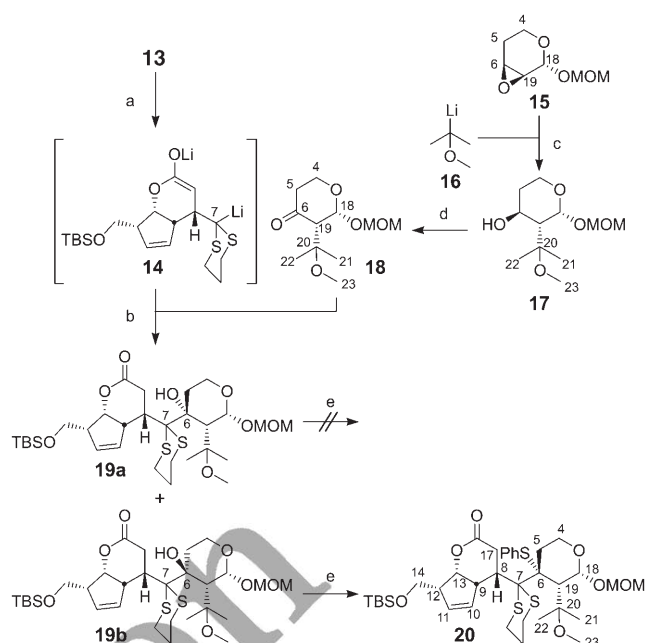
Scheme 3. Access to intermediate **D** through the synthesis of **13**.
a) TBSCl, imidazole, DMAP (cat.), CH₂Cl₂; b) NH₃, MeOH, room temperature; c) NsCl, pyridine, 0°C→RT; d) NaCN (1.5 equiv), DMSO, 85°C, 32 h, 72% from **4**; e) methylvinyl ether, Br₂; then add to **6**, 2,6-lutidine (2 equiv), CH₂Cl₂, 0°C→RT, 67%; f) NaHMDS, THF, −78°C→RT; g) NaHMDS, THF, −78°C→−40°C; then Ph₃CO₂H, THF, 67% from **7**; h) DIBAL-H, toluene, −78°C→RT; i) (TMSSCH₂)₂CH₂, ZnBr₂, CH₂Cl₂, 59% from **8a**; j) HCl in aq. THF; k) slow addition of Ag₂O in paraffin, CH₂Cl₂, room temperature; l) LiOH, aq. THF; m) PPh₃, DIAD, CH₂Cl₂, room temperature, 16 h, 68% from **10**. TBS = tert-butyldimethylsilyl, DMAP = 4-dimethylamino-pyridine, Ns = 4-nitrobenzenesulfonyl, DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane, DIBAL-H = diisobutylaluminum hydride, DIAD = diisopropyl azodicarboxylate.

Scheme 4. Access to intermediate **E** through the synthesis of **20**.
a) LDA (1.1 equiv), HMPA (3 equiv), THF; −78°C then nBuLi (1.1 equiv) at −78°C→−60°C, 2 h; b) slow addition of **18** in THF to **14** in THF, −78°C, 2 h; then −78°C→RT, 62% of **19b** and 15% of **19a**; c) add **16** in Et₂O to **15** in Et₂O/pentane (8:1 v/v), −78°C→0°C, 12 h, 89%; d) TPAP (cat.), NMO, CH₂Cl₂, 92%; e) PhSH, PEt₃, DEAD, CH₂Cl₂, 45°C, 24 h, 94%. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, MOM = methoxymethyl, TPAP = tetrapropylammonium perruthenate, NMO = N-methylmorpho-line-N-oxide, DEAD = diethyl azodicarboxylate.

an aldehyde in the presence of a dithiane is a nontrivial operation. For this example, oxidation of **11** to **12** was achieved by delivering Ag₂O in wax (5% Ag₂O in paraffin).[6] Here, slow addition and transfer of Ag₂O to the reaction medium was optimal in favoring aldehyde oxidation. An intramolecular Mitsunobu inversion of **12** to lactone **13** was used to install the correct stereochemistry at C13.

With **13** in hand, the plan called for the simultaneous appendage of C4–C6 and C18–C23 as indicated by the conversion of **D** into **E** (Scheme 2). Ketone **18** provided an ideal match for the installation of these atoms as it was rapidly prepared from epoxide **15**[7] (Scheme 4). The process was facilitated through anchimeric-assisted addition of corresponding α-lithioether **16**, prepared by the methods of Cohen and Matz,[8] to **15** to yield **17**. Gram quantities of **18** were obtained after oxidation of **17** with either SO₃–pyridine, TPAP—NMO, or Dess–Martin periodinane.

Condensation of **13** with **18** was carried out by generation of dianion **14** by the stepwise addition of LDA and nBuLi to **13** (Scheme 4). A chromatographically separable mixture of **19a** and **19b** (1:4.5) was obtained after slow addition of **18** to **14** at −78°C followed by gradual warming to room temperature. Separation of these diastereomers was enhanced by the selective inversion of **19b** to mercaptan **20**. Under these conditions, the inversion of **19a** was not observed. The fact that **19a** was returned after treatment with DEAD, PBu₃, and acetic acid suggested that the C6-carbinol was too hindered to form the required alkoxyphosphonium intermediate. Com-

pletion of **20** involved the installation of C4–C6 and C18–C23 with the appropriate stereochemistry at C6 and provided functional handles at C17 and C18 for fusion of the B and C rings.

The synthesis continued by a three-stage stitching sequence as depicted by the processing of **E** to **H** (Scheme 2). The operation began with the installation of C15–C16 bond as given by the conversion of **E** into **F**. Experimentally, this was conducted by C-acylation of **20** with pyruvonitrile (Scheme 5).[9] Oxidation of the resulting product **21** with mCPBA followed by treatment with a catalytic amount of CSA in methanol afforded ketosulfoxide **22**. Treatment of **22** with aqueous acid opened the MOM-protected acetal. Analysis of the mixture by NMR spectroscopy indicated that the resulting material existed in a complex equilibrium that contained residues attributable to **23a** and **23b**.
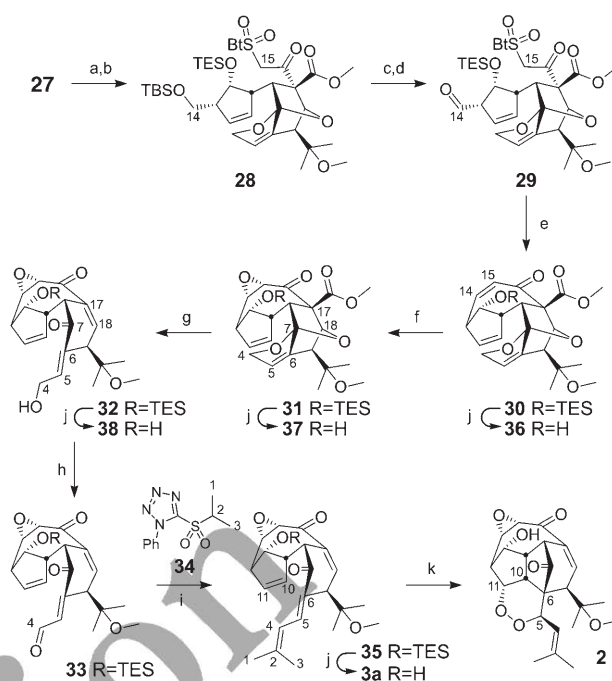
Treatment of this mixture **23a,b** with sulfene (MsCl, Et₃N) led to the formation of a single product **25** (Scheme 5), apparently through incipient generation of mesylate **24a** or chloride **24b**. The reversible nature of mesylation with sulfene was key to this process.[10] After screening conditions, an optimized 74–77% yield of **25** was obtained after adding an equivalent of MsCl and triethylamine once an hour for 5 h. Access to **25** completed the installation of the C17–C18 bond as shown by the conversion of intermediate **F** into **G**

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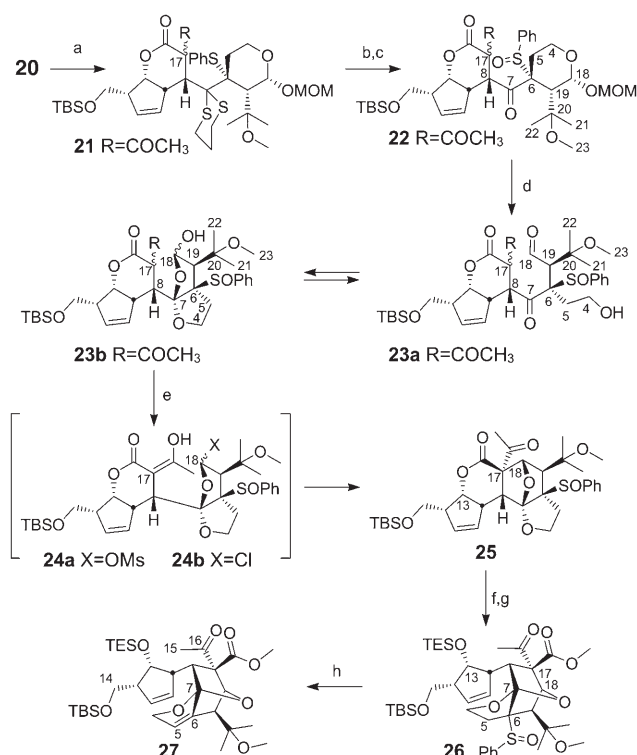
Scheme 5. Access to intermediate **G** through the synthesis of **27**.
a) LDA (1.1 equiv), THF; −78°C→−50°C; then CH₃COCN, −78°C; then −78°C→0°C,12 h, 92%; b) mCPBA (3.0 equiv), CH₂Cl₂; c) CSA (0.2 equiv), room temperature, wet tBuOMe, 6 h, 94% from **21**; d) TMSCl (1.2 equiv), H₂O (5.0 equiv), CH₂Cl₂, 0°C, 97%; e) add MsCl (1 equiv) and Et₃N (1 equiv) in CH₂Cl₂ once an hour for 5 h at −10°C; −10°C→RT, 16 h, 76%; f) PhSNa (0.2 equiv), MeOH; g) TESOTf, 2,6-lutidine, CH₂Cl₂, −20°C→RT, 82% from **25**; h) 60–70°C, DMF, 16 h, 92%. mCPBA = *meta*-chloroperbenzoic acid, CSA = camphorsulfonic acid, TMS = trimethylsilyl, Ms = methanesulfonyl, TESOTf = triethylsilyl triflate, DMF = *N,N*-dimethylformamide.

Scheme 6. Synthesis of desoxohexacyclinol (**3**). a) KHMDS (1.1 equiv), THF; −78 to −50°C; then (BtS)₂, −78°C; −78°C→0°C, 12 h; b) oxone, wet 1,4-dioxane, 87% from **27**; c) TBAF, wet THF, 0°C→RT; d) Dess–Martin periodinane, CH₂Cl₂, 0°C→RT; e) slow addition of DBU (1.2 equiv), DMAP (cat.), THF, −40°C→RT, 10 h, 72% from **28**; f) Ph₃COOH, L-(+)-diisopropyltartrate, toluene, CH₂Cl₂ (3:1 v/v), 92%; g) KOTMS, THF, −10°C→35°C, 5 h, 69%; h) MnO₂, CH₂Cl₂, room temperature; i) **34**, KHMDS, −78°C; −78°C→−30°C, 2 h; add **33** at −78°C; −78°C→RT, 3 h; then room temperature, 12 h, 76% from **32**; j) cat. aq. H₂SiF₆, CH₃CN/tBuOH (9:1 v/v), room temperature, 78% for **3a**; 81% for **36**; 72% for **37**; 84% for **38**; k) O₂, rose bengal, MeOH, *hν*, 0°C, 82%. Bt = 1-benzothiazole, TBAF = tetra-*n*-butyl-ammonium fluoride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

(Scheme 2). The final stitch (**G** to **H**) called for the creation of the C14–C15 bond. This process began with methanolysis of the lactone in **25** by treatment with sodium thiophenoxide in methanol followed by protection of the secondary alcohol to afford **26** (Scheme 5). Thermolysis of **26** induced a regioselective *syn*-elimination to provide **27**. At this stage, the appropriate functionality was installed to address the formation of the C14–C15 epoxide.

A Julia–Kocienski reaction was selected for this process as the projected enone **30** was envisioned as a suitable precursor to the C14–C15 epoxide (Scheme 6). Sulfone **28** was prepared by α-thiolation of **27** with 2,2′-dithiobis(benzothiazole) followed by oxidation with oxone. Selective deprotection of the primary TBS-protected ether followed by oxidation with Dess–Martin periodinane provided the precursor to the Julia–Kocienski reaction **29**. Slow addition of DBU with a catalytic amount of DMAP to **29** in THF over 2 h at −40°C followed by warming to room temperature over 10 h afforded the desired enone **30** in good yield. Epoxidation at C14–C15, as required by **H** to **I** (Scheme 2), was effected by using the tartrate-mediated nucleophilic epoxidation conditions developed by Porco and co-workers to yield a single epoxide **31**.[11]

The synthesis of desoxohexacyclinol (**3**) was accomplished by unveiling the 7-oxabicyclo[2.2.1]heptane and thereby completing the synthesis of the C ring (**I** to **J**, Scheme 2). Hydrolysis of **31** with TMSOK[12] or *n*Bu₃SnOH[13] generated the corresponding acid, which underwent subsequent β-eliminative ring opening to provide **32** (Scheme 6). Hydrolysis of the C14–C15 epoxide was avoided by slow addition of TMSOK or *n*Bu₃SnOH. At this point, the final carbon atoms C1–C3 were installed through a second Julia–Kocienski reaction (Scheme 6). Allylic oxidation with MnO₂ was effective at converting **32** into aldehyde **33**, which was in turn filtered through dry silica gel and immediately treated with the anion of **34** to afford **35**. Remarkably, this addition was achieved with less than 5% addition to the C14–C15 epoxide. Mild deprotection with fluorosilicic acid[14] completed the synthesis to provide **3a** in an overall yield of 0.8–1.3% from **4**. Confirmation of this yield was established by the most-recent campaign that provided 3.6 g of **3a** from 1 mol of **4**.

Exposure of **3a** to singlet oxygen[15] resulted in a [2+2+2] cycloaddition[16] that afforded a mixture of chromatographically separable **1** and **2** (8:1). Samples of synthetic hexacyclinol (**1**),[17] **2**,[18] and **3**[19] were identical in R_f, HPLC

retention, physical properties, and spectral data to authentic samples of **1–3** isolated in our laboratories.[2] The optical rotation of synthetic **1** ($[\alpha]_D(4.0 \text{ mg mL}^{-1}) = +131.5°$) was comparable to that obtained in samples of isolated **1** ($[\alpha]_D(4.0 \text{ mg mL}^{-1}) = +132.2°$) as well as that reported by Gräfe and co-workers ($[\alpha]_D(4.03 \text{ mg mL}^{-1}) = +130.5°$),[1] thereby confirming the absolute stereochemistry of hexacyclinol (**1**).

While the yield and complexity of this synthesis may not be ideal for therapeutic use, the value of this synthetic route became apparent upon screening the activity of the late-stage intermediates. Intermediates **36–38**, prepared by deprotection of the precursors **30–32**, respectively, were analyzed for their inhibition of *Plasmodium berghei*.[2] Remarkably, **36, 37**, and **38** displayed IC_{50} values of 9.3 ± 2.6, 6.1 ± 1.5, and 2.1 ± 0.7 nm, respectively, against a chloroquine-sensitive *P. berghei*. In the same assay, artemisinin displayed an IC_{50} value of 2.5 ± 0.9 nm.[2,20] Comparable activity was also obtained in in vivo antimalarial assays, which indicated that **36, 37**, and **38** displayed ED_{50} values of 8.9, 1.6, and 5.2 mg kg^{-1}, respectively, against chloroquine-sensitive *P. berghei*. This activity was found to be comparable to sodium artesunate, which delivered an ED_{50} value of 4.3 mg kg^{-1} when examined in parallel.[2,21] While the mode of action of these materials has yet to be verified,[2] prior observations on **3** suggest that these materials arise through a three-step prodrug-like motif (Scheme 7). Efforts are now underway to determine the
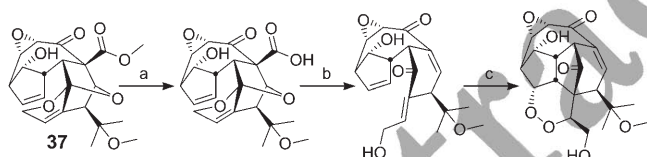
Scheme 7. Suggested mechanism supporting the in vivo activity of **37**. a) Hydrolysis; b) decarboxylative β-elimination; c) [2+2+2] cycloaddition with singlet oxygen.

validity of this mechanism as well as to identify a minimal pharmacophore.[22]

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[6] SmI$_2$ as suggested by Smith et al.[5] also failed. An alternative synthesis using a triethylsilylcyanohydrin was used to alleviate

concerns over the use of a dithiane. Details of this route shall be explained in forthcoming publications.
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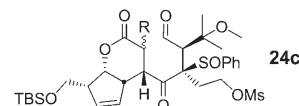
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[17] Physical and spectral properties of **1**: Colorless solid; m.p.: 172–174°C; $R_f = 0.83$ in CH$_2$Cl$_2$/MeOH (9:1 v/v); IR (film): $\tilde{\nu} = 3417$, 3018, 2985, 2935, 1699, 1625, 1382, 1214, 1009, 1132, 996, 982, 910 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$+1% CD$_3$OD, J [Hz]): $\delta = 6.73$ (dd, J = 5.3, 2.4, 1H), 5.46 (d, J = 10.1, 1H), 4.99 (br dd, J = 5.2, 1H), 4.81 (d, J = 10.1, 1H), 3.81 (dd, J = 9.5, 1.6, 1H), 3.64 (m, 1H), 3.59 (d, J = 5.3, 1H), 3.55 (m, 1H), 3.51 (dd, J = 2.8, 0.5, 1H), 3.29 (d, J = 3.0, 1H), 3.24 (d, J = 3.6, 1H), 3.03 (s, 3H), 2.75 (dd, J = 5.2, 7.9, 1H), 1.77 (s, 3H), 1.73 (s, 3H), 1.27 (s, 3H), 1.15 ppm (s, 3H); HR-EIMS: calcd *m/z*: 416.1835; found: 416.1892. See Supporting Information for spectra.
[18] Physical and spectral properties of **2**: Colorless solid; m.p.: 165–169°C; $R_f = 0.79$ in CH$_3$Cl/MeOH (9:1 v/v); IR (film): $\tilde{\nu} = 3418$, 3015, 2980, 2932, 1701, 1626, 1380, 1216, 1005, 1131, 995, 981, 912 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$+1% CD$_3$OD, J [Hz]): $\delta = 6.78$ (dd, J = 5.4, 2.2, 1H), 5.41 (d, J = 10.6, 1H), 5.01 (br dd, J = 5.2, 1H), 4.56 (d, J = 8.2, 1H), 3.76 (dd, J = 9.5, 1.6, 1H), 3.58 (m, 1H), 3.52 (m, 1H), 3.51 (d, J = 5.2, 1H), 3.48 (dd, J = 2.9, 0.5, 1H), 3.32 (d, J = 2.8, 1H), 3.26 (d, J = 3.4, 1H), 3.08 (s, 3H), 2.78 (dd, J = 5.1, 7.8, 1H), 1.81 (s, 3H), 1.72 (s, 3H), 1.28 (s, 3H), 1.17 ppm (s, 3H); HR-EIMS: calcd *m/z*: 416.1835; found: 416.1881. See Supporting Information for spectra.
[19] Physical and spectral properties of **3** as a 1:1 mixture of olefin isomers: Waxy solid; $R_f = 0.68$ in CH$_3$Cl/MeOH (12:1 v/v); IR (film): $\tilde{\nu} = 3417$, 2965, 2955, 1695, 1624, 1422, 1272, 1104, 1002, 992, 972, 912 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$+1% CD$_3$OD, J [Hz]): $\delta = 6.90$ (d, J = 9.2, 1.3, 1H); 6.94 (d, J = 10.5, 0.7, 1H), 5.92 (d, J = 9.3, 1.2, 1H); 5.89 (d, J = 10.5, 0.7, 1H), 5.79 (dd, J = 5.3, 2.4, 1H), 5.56 (dd, J = 9.3, 2.4, 1H), 5.22 (dd, J = 9.3, 1.8, 1H), 3.65 (dd, J = 2.1, 0.8, 1H), 3.51 (dd, J = 2.3, 1.8, 1H), 3.31 (m, 1H), 3.21 (dd, J = 8.4, 1.1, 1H), 3.16 (br d, J = 2.6, 1H), 3.16 (d, J = 2.0, 1H), 3.06 (m, 1H), 2.82 (s, 3H), 1.76 (s, 3H), 1.75 (s, 3H), 1.21 (s, 3H), 1.18 ppm (s, 3H); HR-EIMS: calcd *m/z*: 384.1937; found: 384.1911. See Supporting Information for spectra.

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[22] **Note added in proof**: The ^{1}H NMR spectra for this Communication were determined by contract services. The spectra provided in the Supporting Information were collected by N. Voss (Berlin, Germany). The operator added the peak for CDCl₃ to the spectrum of synthetic hexacyclinol (**1**), however, this was done incorrectly at $\delta \approx 7.5$ ppm and against the request of the author. Additionally, one spectrum was duplicated and a copy of the spectra for natural 5-*epi*-hexacyclinol was not provided.