Antimalarial Drugs

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Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif**

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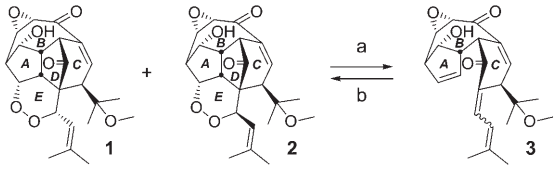
In memory of Udo Gräfe

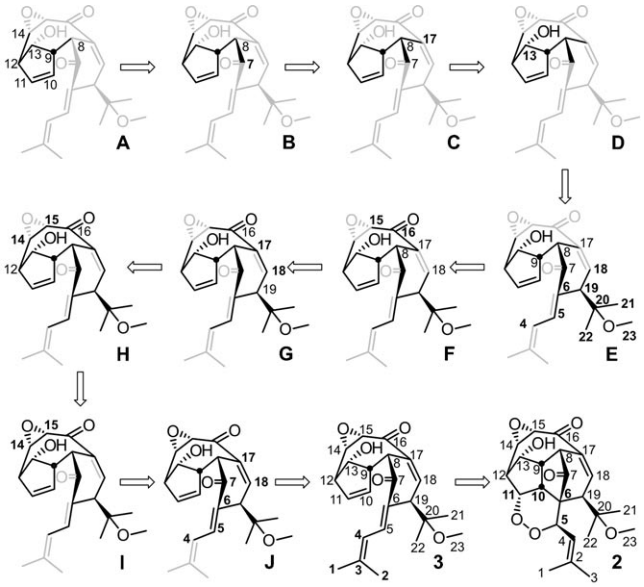
Hexacyclinol (**1**) was isolated by Gräfe and co-workers from the basidiospores collected from *Panus rudis* growing on dead betula woods in Siberia.[1] In 1999, our exploration into German fungal cultures provided a strain of *P. rudis* 99-329 that was not only capable of the biosynthesis of **1** 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) O_2, 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



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

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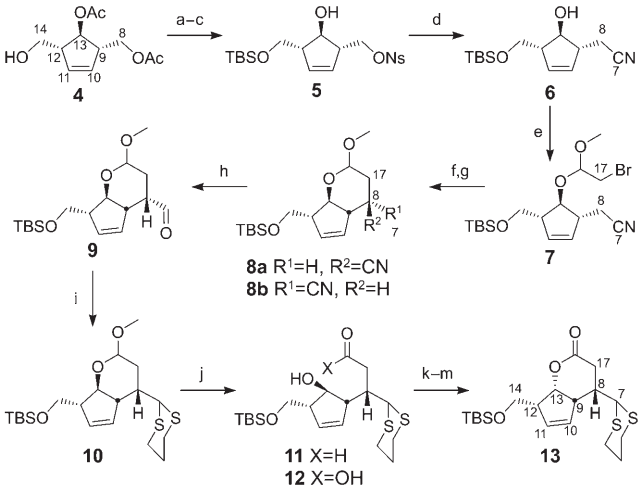
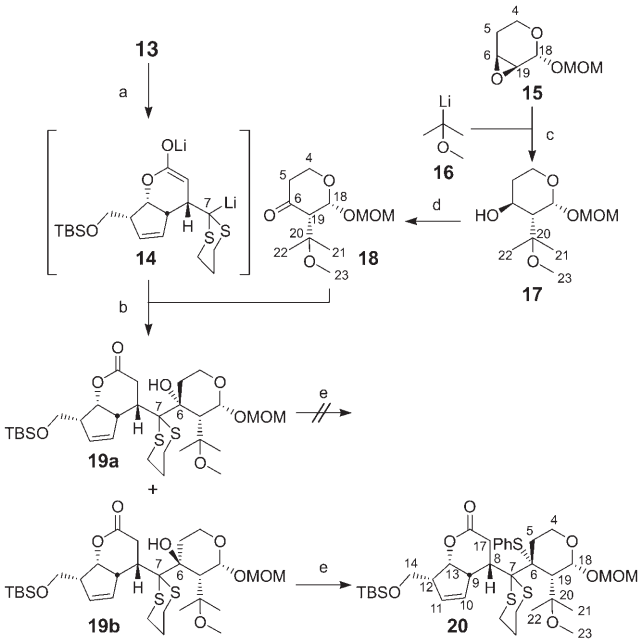


Scheme 3. Access to intermediate **D** through the synthesis of **13**. a) TBSCl, imidazole, DMAP (cat.), CH_2Cl_2; b) NH_3, MeOH, room temperature; c) NsCl, pyridine, 0 °C→RT; d) NaCN (1.5 equiv), DMSO, 85 °C, 32 h, 72% from **4**; e) methylvinyl ether, Br_2; then add to **6**, 2,6-lutidine (2 equiv), CH_2Cl_2, 0 °C→RT, 67%; f) NaHMDS, THF, −78 °C→RT; g) NaHMDS, THF, −78 °C→−40 °C; then Ph_3CO_2H, THF, 67% from **7**; h) DIBAL-H, toluene, −78 °C→RT; i) $(TMSSCH_2)_2CH_2$, $ZnBr_2$, CH_2Cl_2, 59% from **8a**; j) HCl in aq. THF; k) slow addition of Ag_2O in paraffin, CH_2Cl_2, room temperature; l) LiOH, aq. THF; m) PPh_3, DIAD, CH_2Cl_2, room temperature, 16 h, 68% from **10**. TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, 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 *n*BuLi (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 Et_2O to **15** in Et_2O/pentane (8:1 v/v), −78 °C→0 °C, 12 h, 89%; d) TPAP (cat.), NMO, CH_2Cl_2, 92%; e) PhSH, PEt_3, DEAD, CH_2Cl_2, 45 °C, 24 h, 94%. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, MOM = methoxymethyl, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide, DEAD = diethyl azodicarboxylate.

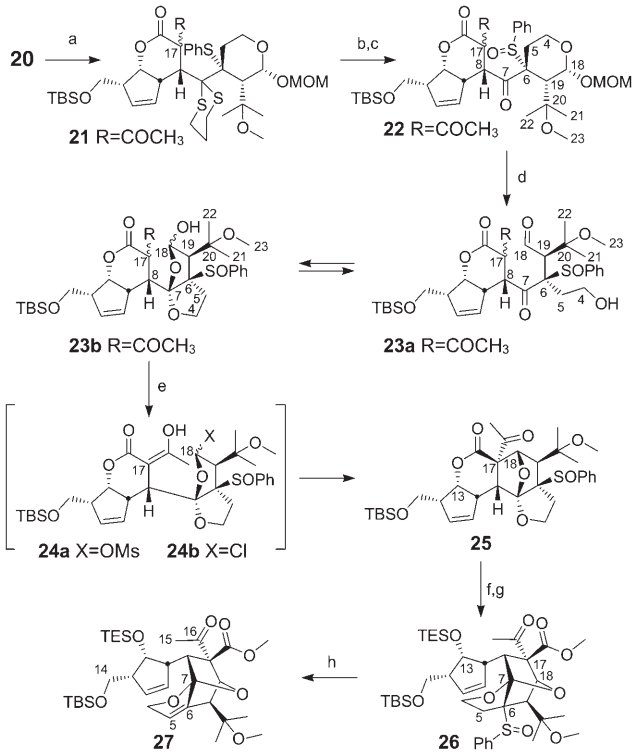
an aldehyde in the presence of a dithiane is a nontrivial operation. For this example, oxidation of **11** to **12** was achieved by delivering Ag_2O in wax (5% Ag_2O in paraffin).[6] Here, slow addition and transfer of Ag_2O to the reaction medium was optimal in favoring aldehyde oxidation. An intramolecular 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 SO_3–pyridine, TPAP—NMO, or Dess–Martin periodinane.

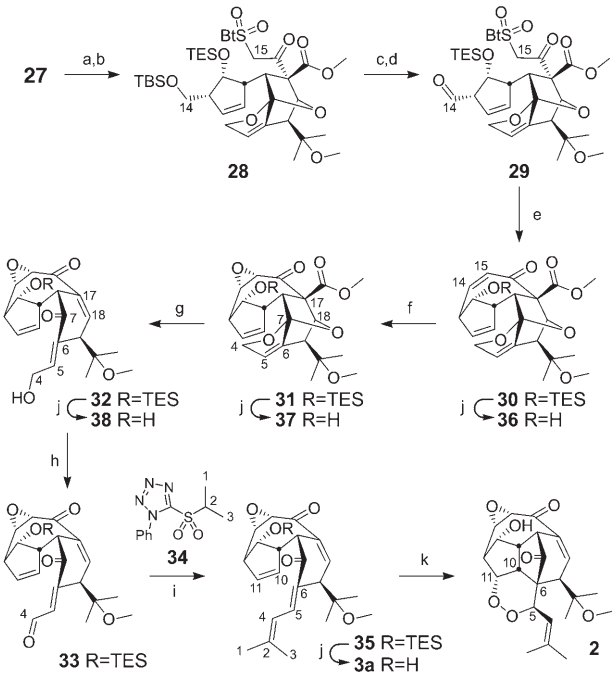
Condensation of **13** with **18** was carried out by generation of dianion **14** by the stepwise addition of LDA and *n*BuLi to **13** (Scheme 4). A chromatographically separable mixture of **19a** and **19b** (1:4.5) was obtained after slow addition of **18** to **14** at −78 °C followed by gradual 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, PBu_3, and acetic acid suggested that the C6-carbinol was too hindered to form the required alkoxyphosphonium intermediate. Completion 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, Et_3N) 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**



Scheme 5. Access to intermediate **G** through the synthesis of **27**. a) LDA (1.1 equiv), THF; −78 °C→−50 °C; then CH_3COCN, −78 °C; then −78 °C→0 °C,12 h, 92%; b) mCPBA (3.0 equiv), CH_2Cl_2; c) CSA (0.2 equiv), room temperature, wet *t*BuOMe, 6 h, 94% from **21**; d) TMSCl (1.2 equiv), H_2O (5.0 equiv), CH_2Cl_2, 0 °C, 97%; e) add MsCl (1 equiv) and Et_3N (1 equiv) in CH_2Cl_2 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, CH_2Cl_2, −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, CH_2Cl_2, 0 °C→RT; e) slow addition of DBU (1.2 equiv), DMAP (cat.), THF, −40 °C→RT, 10 h, 72% from **28**; f) Ph_3COOH, L-(+)-diisopropyltartrate, toluene, CH_2Cl_2 (3:1 v/v), 92%; g) KOTMS, THF, −10 °C→35 °C, 5 h, 69%; h) MnO_2, CH_2Cl_2, 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. H_2SiF_6, CH_3CN/*t*BuOH (9:1 v/v), room temperature, 78% for **3a**; 81% for **36**; 72% for **37**; 84% for **38**; k) O_2, rose bengal, MeOH, *hν*, 0 °C, 82%. Bt = 1-benzothiazole, TBAF = tetra-*n*-butylammonium 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.

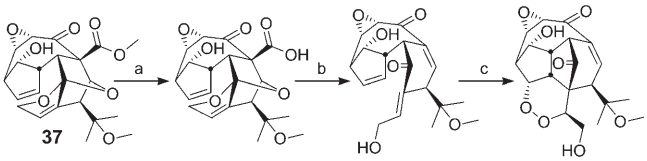
A Julia–Kocienski reaction was selected for this process as the projected enone **30** was envisioned as a suitable precursor to the C14–C15 epoxide (Scheme 6). Sulfone **28** was prepared by α-thiolation of **27** with 2,2′-dithiobis(benzothiazole) followed by oxidation with oxone. Selective deprotection 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 nBu$_3$SnOH[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 nBu$_3$SnOH. At this point, the final carbon atoms C1–C3 were installed through a second Julia–Kocienski reaction (Scheme 6). Allylic oxidation with MnO_2 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** ($[\alpha]_D(4.0\,mg\,mL^{-1}) = +131.5°$) was comparable to that obtained in samples of isolated **1** ($[\alpha]_D(4.0\,mg\,mL^{-1}) = +132.2°$) as well as that reported by Gräfe and co-workers ($[\alpha]_D(4.03\,mg\,mL^{-1}) = +130.5°$),[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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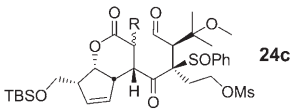

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[17] Physical and spectral properties of **1**: Colorless solid; m.p.: 172–174 °C; $R_f = 0.83$ in CH_3Cl/MeOH (9:1 v/v); IR (film): $\tilde{\nu} = 3417$, 3018, 2985, 2935, 1699, 1625, 1382, 1214, 1009, 1132, 996, 982, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + 1\%$ CD_3OD, 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_3Cl/MeOH (9:1 v/v); IR (film): $\tilde{\nu} = 3418$, 3015, 2980, 2932, 1701, 1626, 1380, 1216, 1005, 1131, 995, 981, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + 1\%$ CD_3OD, 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_3Cl/MeOH (12:1 v/v); IR (film): $\tilde{\nu} = 3417$, 2965, 2955, 1695, 1624, 1422, 1272, 1104, 1002, 992, 972, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + 1\%$ CD_3OD, 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 $CDCl_3$ 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.

