The Hexacyclinol Incident

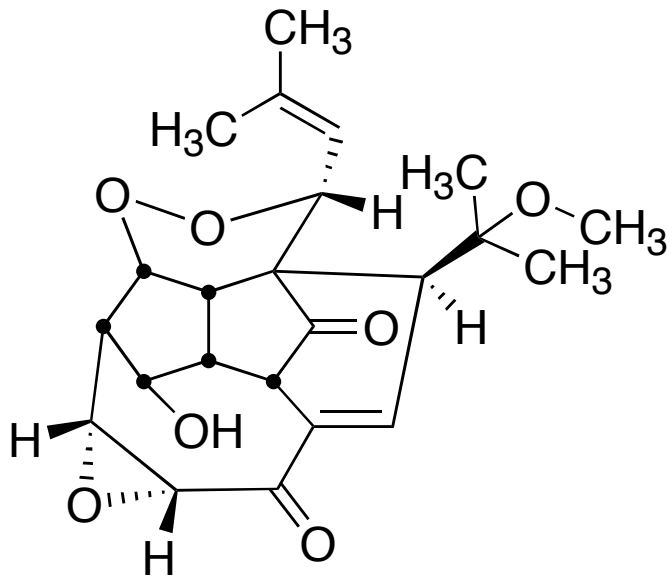
La Clair, J. J., *Angew. Chem. Int. Ed.*, **2006**, *45*, 2769-2773 + supporting info.
Rychnovsky, S. D., *Org. Lett.* **2006**, *8*, 2895-2898
Porco, J. A. Jr.; Su. S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D., *Angew. Chem. Int. Ed.* **2006**, *45*, 5790-5792

Adam Hoye

Current Literature

Sept. 16th, 2006

Hexacyclinol (Gräfe)



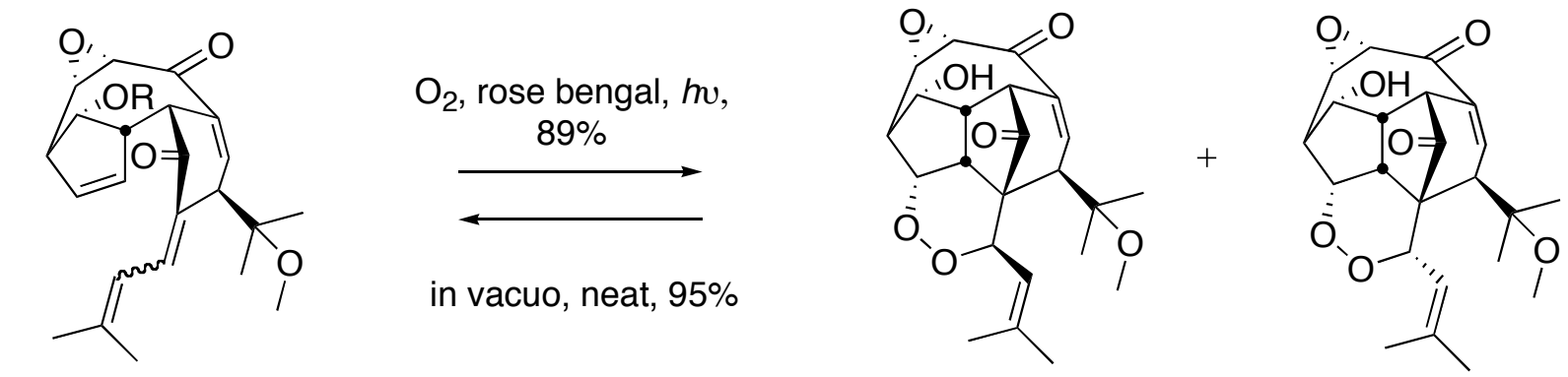
Schlegel, B.; Härtl, A.; Dahse, H-M; Gollmick, F. A.; Gräfe, U.; *J. Antibiot*. **2002**, *55*, 814

Isolated in 2002 as a metabolite from fungal strain *Ranus rudis* HKI 0254 (Antiproliferative activity against L-929 cells and inhibition of respiratory burst activity in PMNL)

Structure determined by mass spectrometry, 1D and 2D NMR spectroscopy (^{1}H, ^{13}C, DEPT, COSY, HMQC, HMBC, NOESY), and IR.

La Clair- Initial Hexacyclinol Observations

La Clair, J. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2769-2773



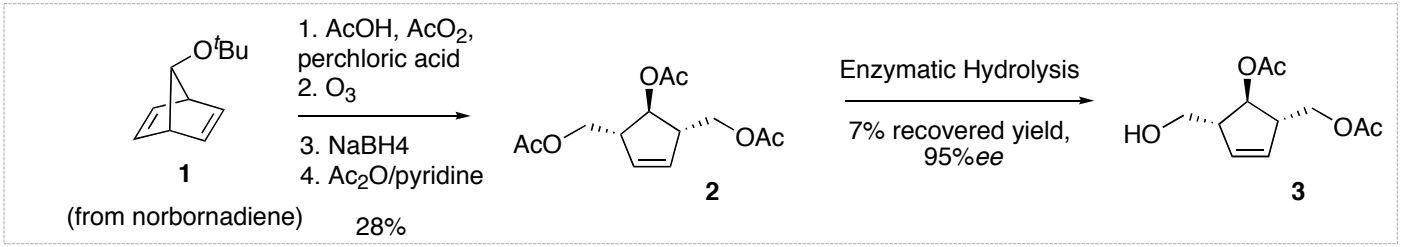
desoxohexacyclinol

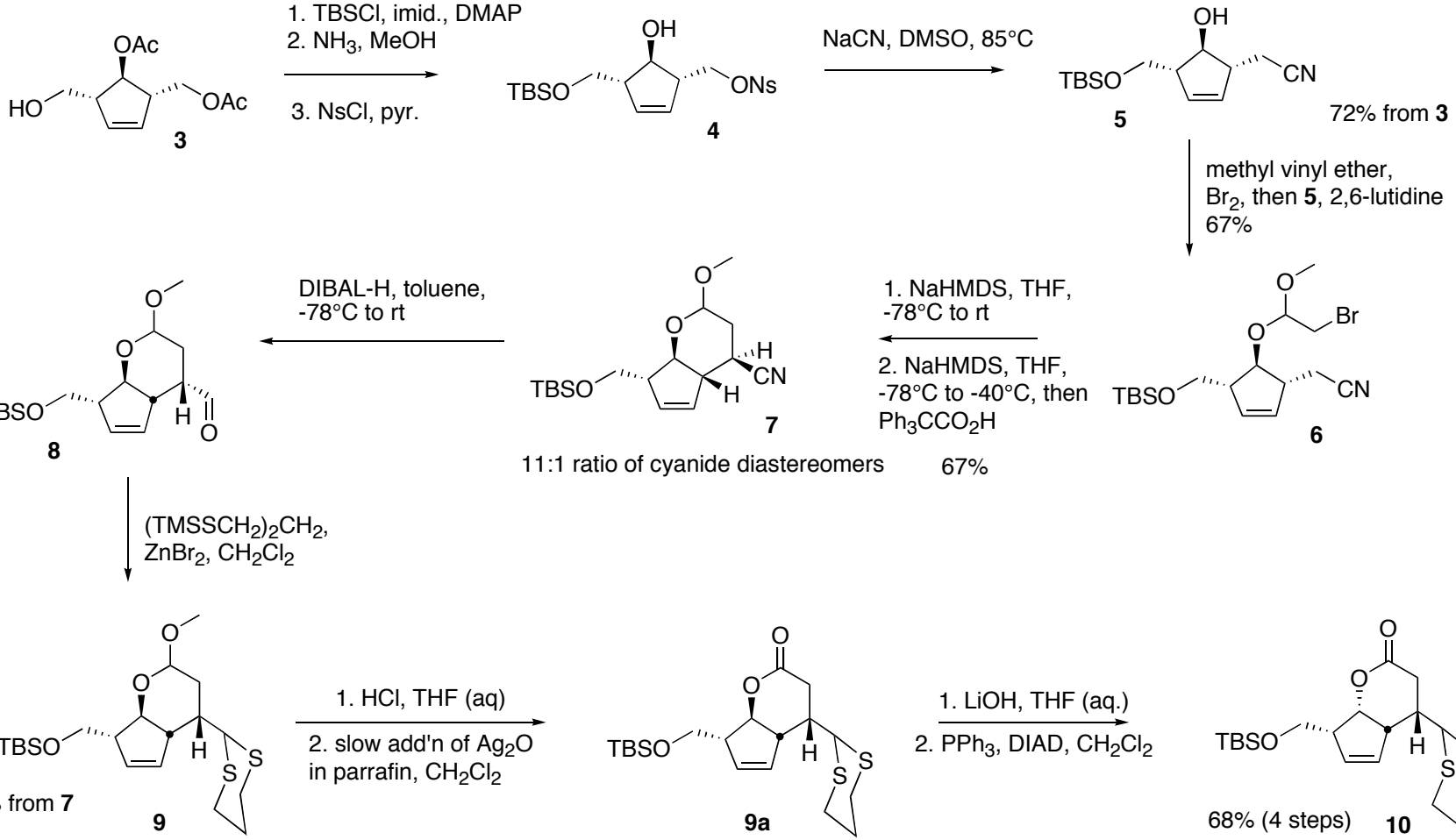
5-*epi*-hexacyclinol

hexacyclinol

J. J. La Clair- previously unpublished results

La Clair's Synthesis

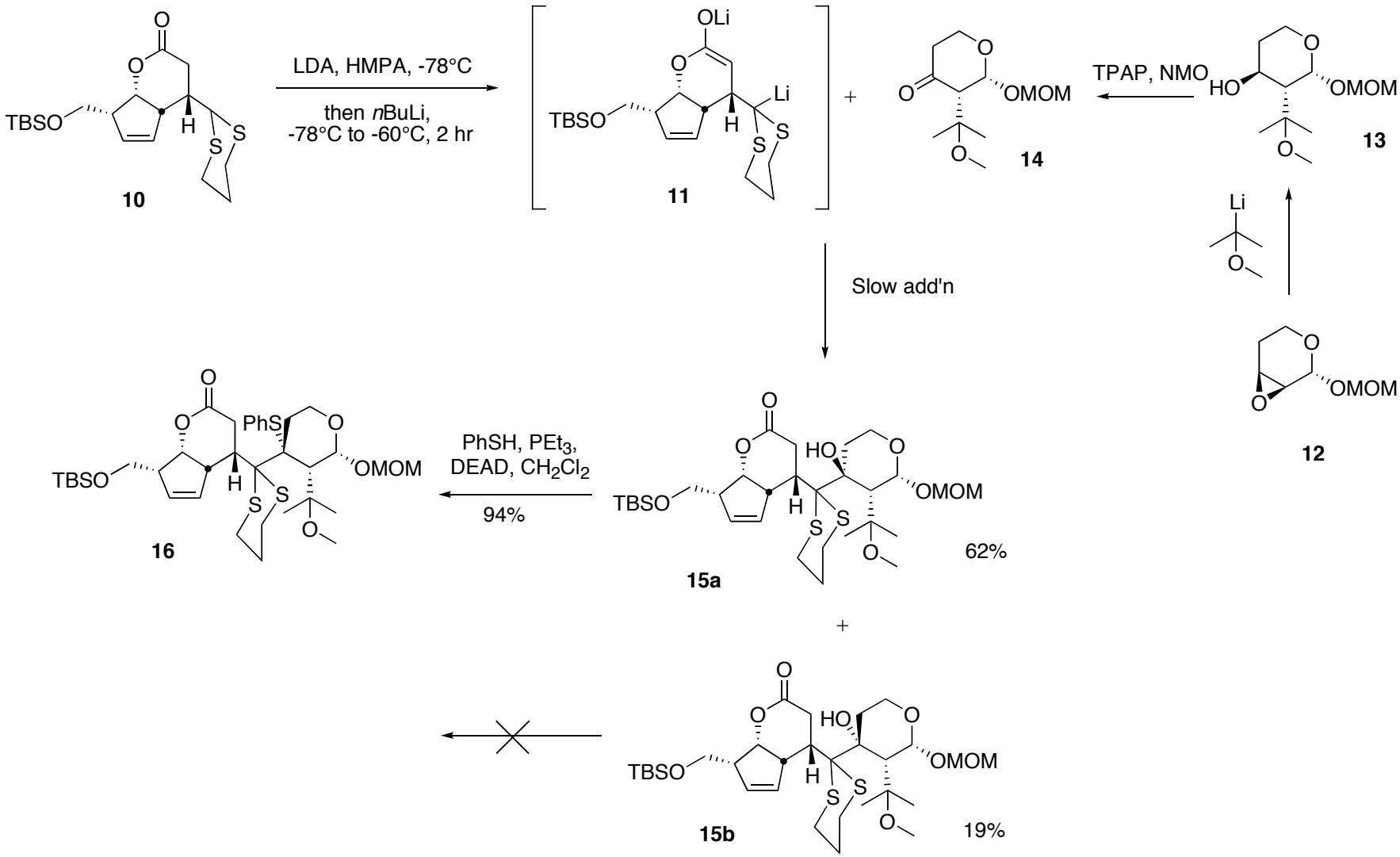




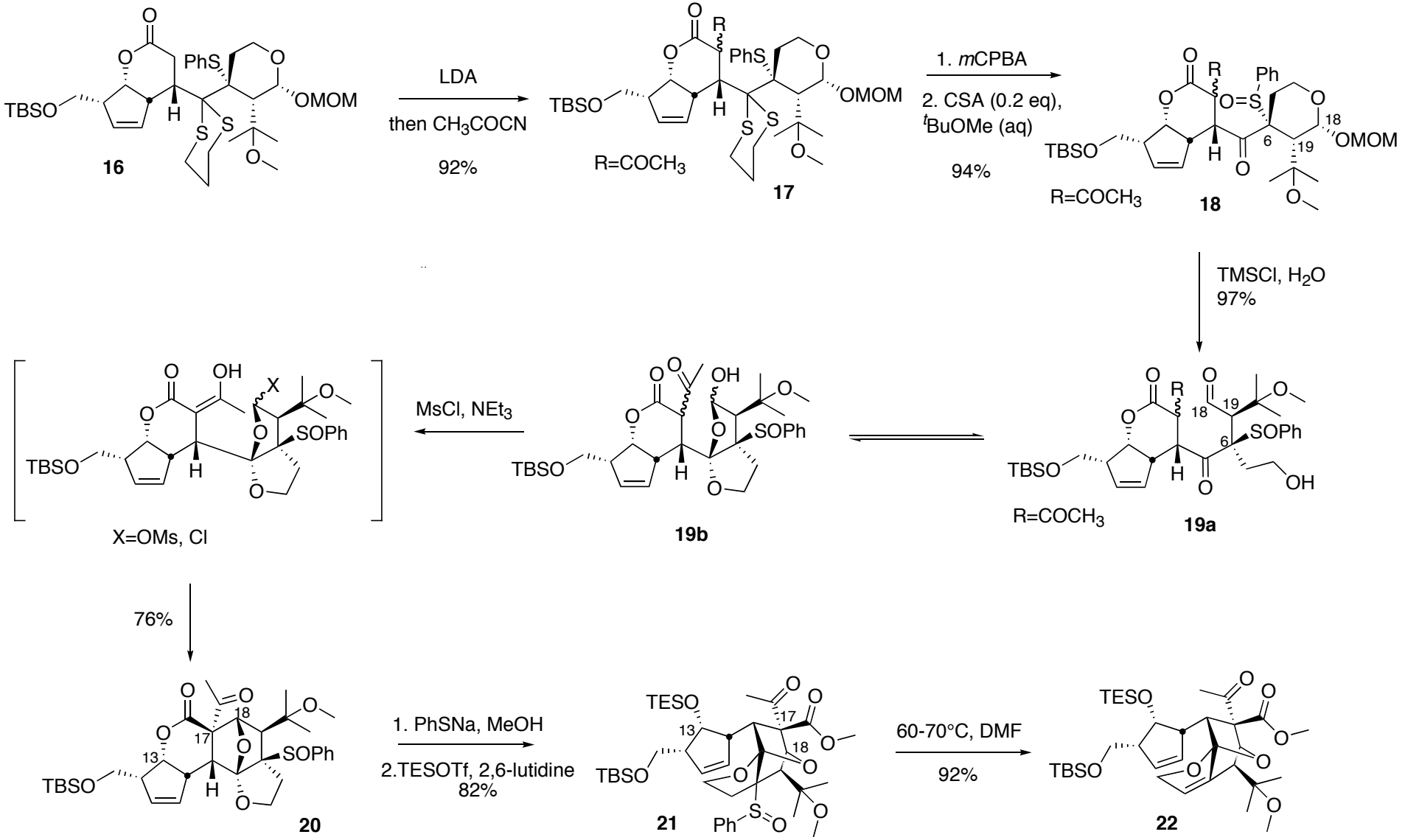
Baumgarten, H. E., *Org Synth*. **1973**, *5*, 151

Tanaka, M.; Norimine, Y.; Fujita, T.; Suemune, H. *J. Org. Chem*. **1996**, *61*, 6952-6957

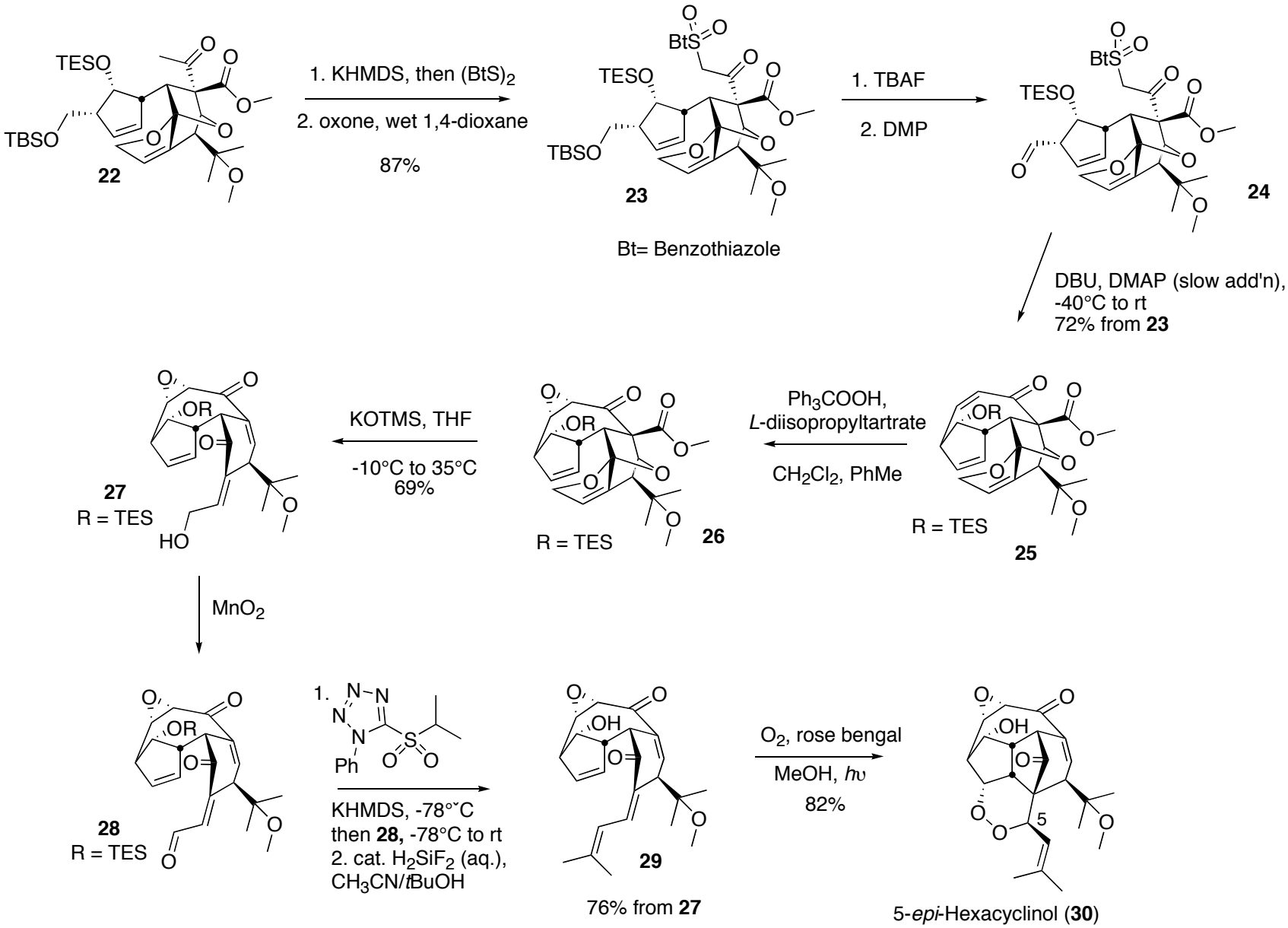
La Clair's Synthesis



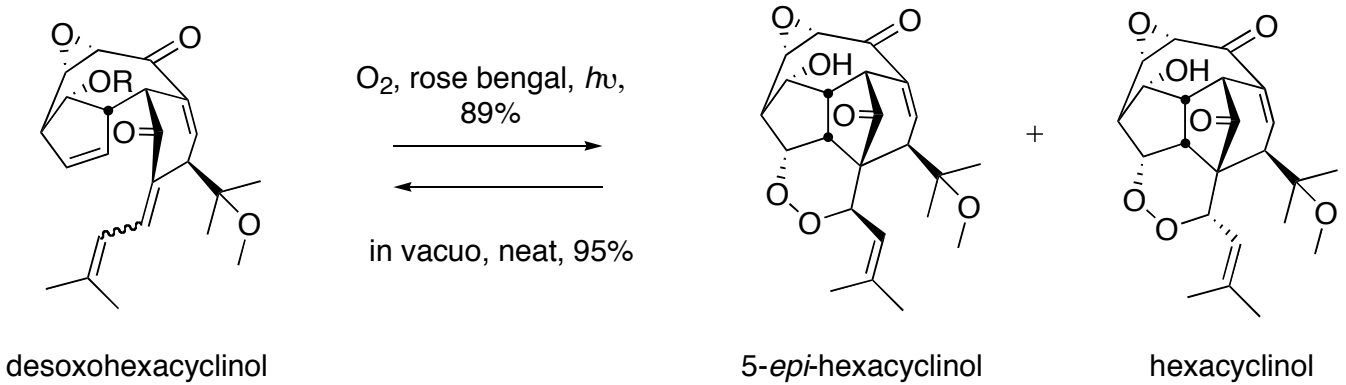
La Clair's Synthesis



La Clair's Synthesis



La Clair's Synthesis



desoxohexacyclinol

5-*epi*-hexacyclinol

hexacyclinol

Overall a 0.8% yielding 39 step synthesis

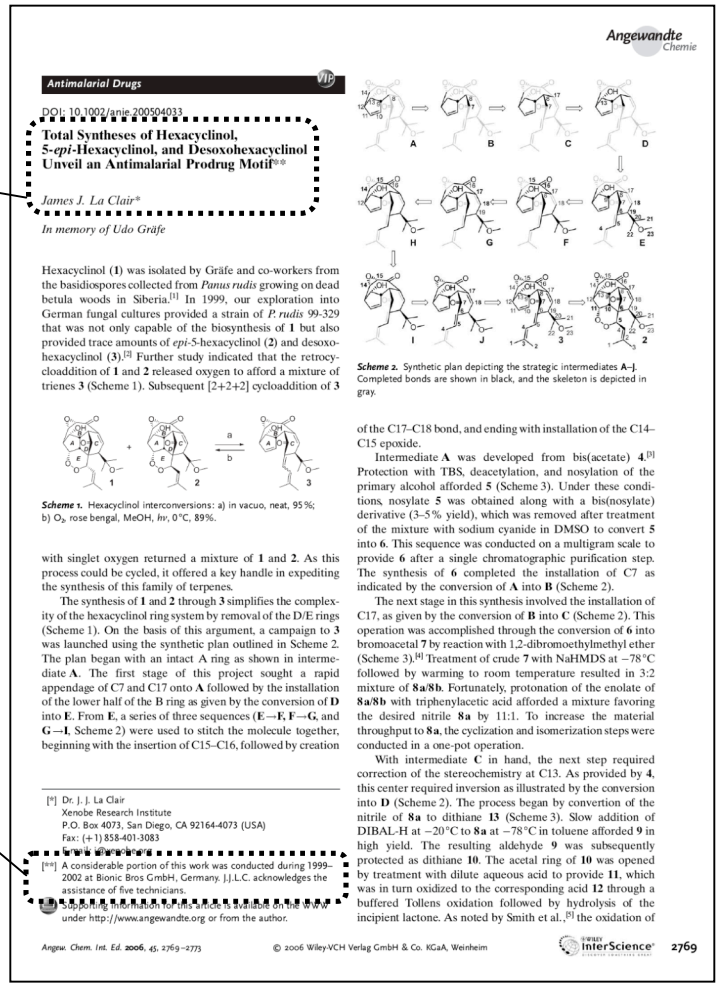
…but several unusual features…

-Authorship:

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

*James J. La Clair**

[**] A considerable portion of this work was conducted during 1999–2002 at Bionic Bros GmbH, Germany. J.J.L.C. acknowledges the assistance of five technicians.



Angewandte Chemie

Antimalarial Drugs

DOI: 10.1002/anie.200504033

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** 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.

Scheme 1. Hexacyclinol interconversions: a) in vacuo, neat, 95%; b) O_2, rose bengal, MeOH, *hν*, 0°C, 89%.

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

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

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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[**] A considerable portion of this work was conducted during 1999–2002 at Bionic Bros GmbH, Germany. J.J.L.C. acknowledges the assistance of five technicians.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

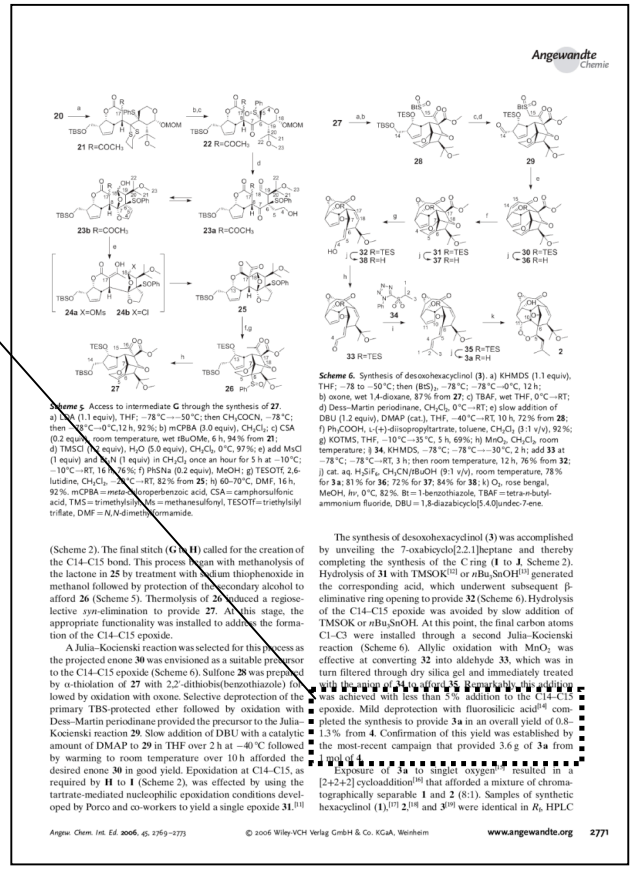
Google search for Bionic Bros. GmbH, Germany yields:
- Recently released a new Role Playing
Game based on the basic elements of life
- Address shares that of a yoga studio in Berlin

…but several unusual features…

Quantities synthesized:

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**.

so to make 3.6 g of final product (9.3 mmol) from 1 mol of diacetate compound, which is synthesized in 1% yield from norbornadiene, which corresponds to 100 moles or 10,700 grams ($0.31/g, so $3,320 for s.m.)



Angewandte Chemie

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 **27**; d) TMSCl (1.0 equiv), H_2O (5.0 equiv), CH_2Cl_2, 0 °C, 97%; e) add MsCl (1 equiv) and DIPEA (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, −78 °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 $(BIS)_2$, −78 °C; −78 °C→0 °C, 12 h; b) ozone, 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_2COOH, 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.

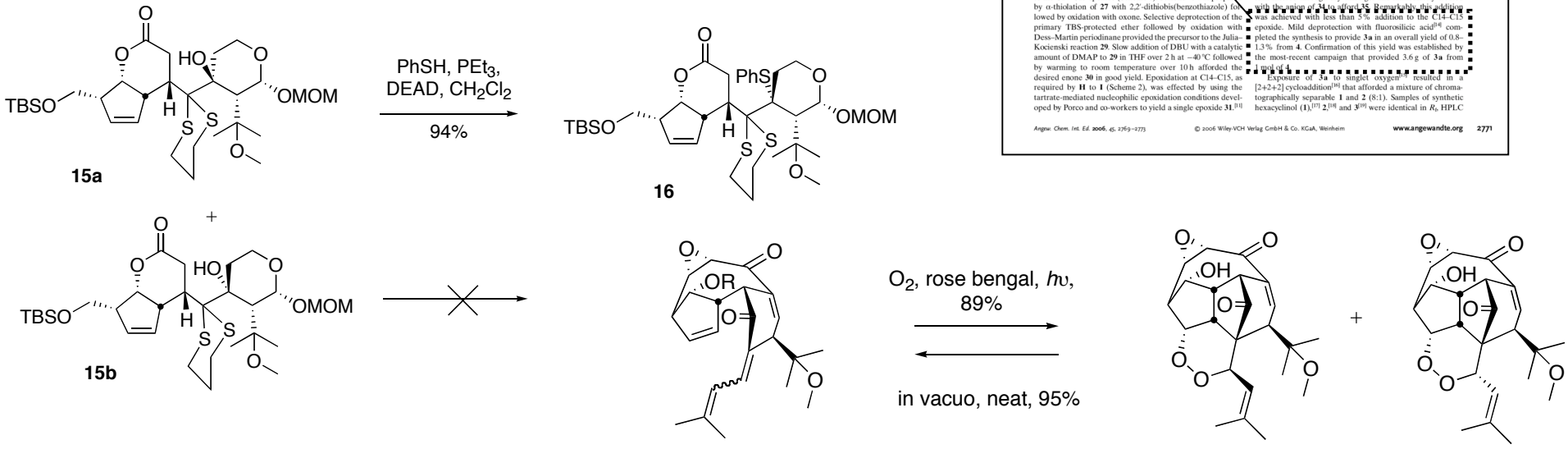
(Scheme 2). The final stitch (**G**→**H**) called for the creation of the C14–C15 bond. This process began with methanolysis of the lactone in **25** by treatment with sodium thiophenoxide in methanol followed by protection of the secondary alcohol to afford **26** (Scheme 5). Thermolysis of **26** induced 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_3SnOH[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_3SnOH. 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, the 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

Questionable Steps:



…but several unusual features…

Supporting information:

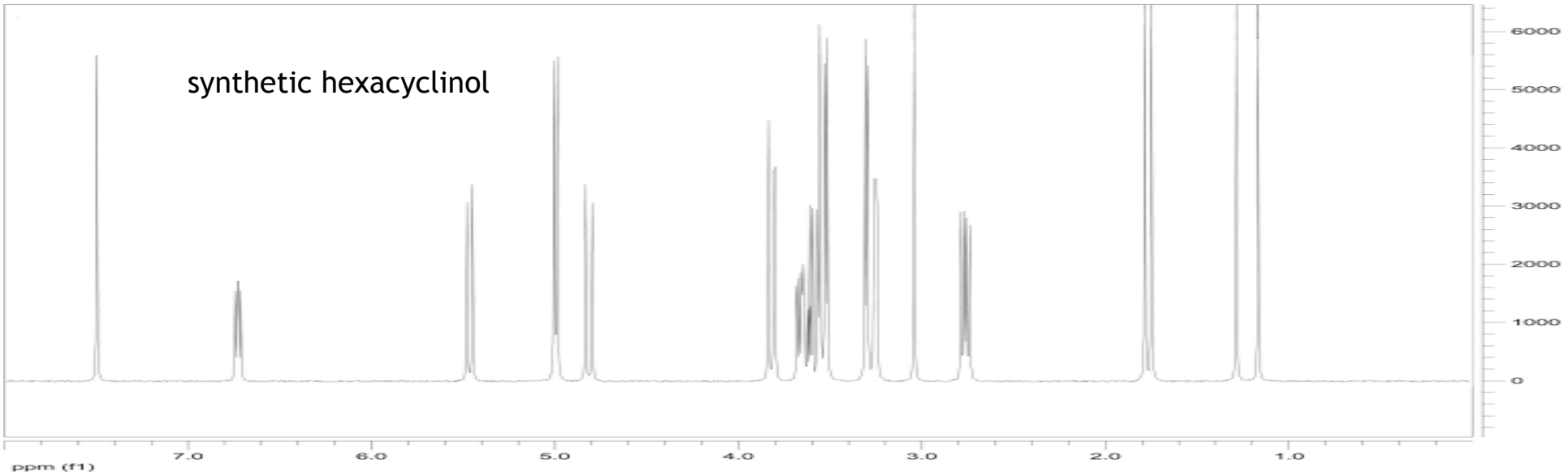
INDEX:

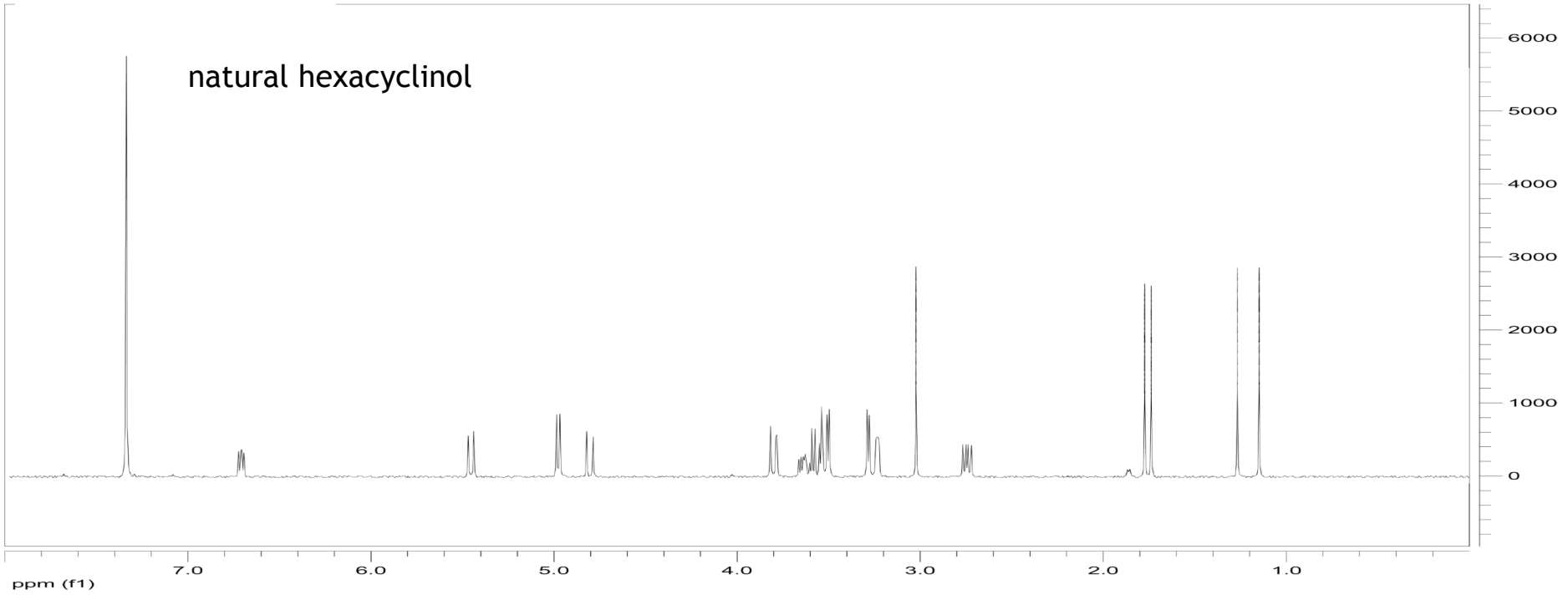
1) NMR data table including couplings as given by ^{1}H-^{1}H COSY
2) NMR spectrum of natural hexacyclinol (**1**)
3) NMR spectrum of synthetic hexacyclinol (**1**)
4) NMR spectrum of natural 5-*epi*-hexacyclinol (**2**) ← not included
5) NMR spectrum of synthetic 5-*epi*-hexacyclinol (**2**)
6) NMR spectrum of natural desoxohexacyclinol (**3**)
7) NMR spectrum of synthetic desoxohexacyclinol (**3**)

[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.

3.6 grams synthesized and no ^{13}C NMR spectrum? Intermediate characterization?

^{1}H NMR Spectra





ORGANIC LETTERS

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Predicting NMR Spectra by Computational Methods: Structure Revision of Hexacyclinol

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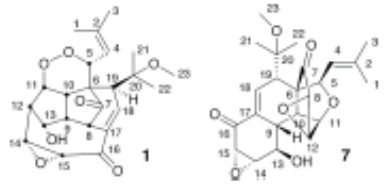
Received May 9, 2006

ABSTRACT



The structure of the natural product hexacyclinol was reassigned from endoperoxide 1 to the diepoxide 7 on the basis of calculated ^{13}C chemical shift data using HF/3-21G geometries and mPW1PW91/6-31G(d,p) GIAO NMR predictions. These predictions correlate very well with experimental data for three other highly oxygenated natural products, elisapterosin B, maoecrystal V, and elisabethin A. Hexacyclinol is proposed to arise from acid-catalyzed rearrangement of panepophenanthrin in the presence of methanol.

Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2895-2898

Rychnovsky's Investigation

Validation of the structure of Hexacyclinol:

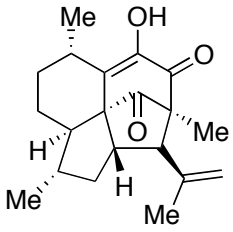
Using ^{13}C NMR data:

-chemical shifts are spread over a wide range
-relatively insensitive to solvent changes
-sensitive to steric and electronic influences in the structure

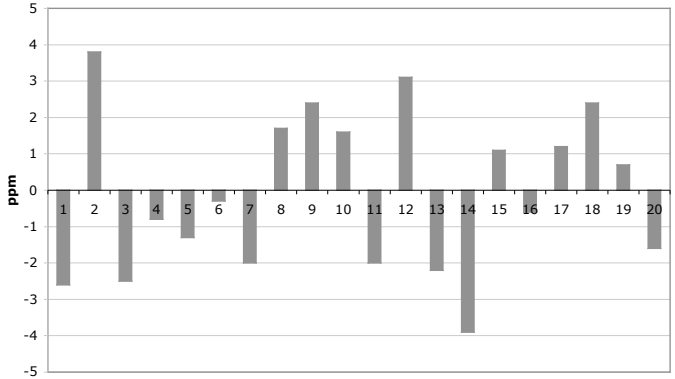
Precedence:

David Forsyth applied MM3 geometry and evaluated NMR shifts using GIAO with the B3LYP method and a specialized basis set to achieve an average **2.3 ppm deviation** from experimental values. Bifulco found that the HF/6-31G(d) method was superior for nonpolar compounds, however highly oxygenated compounds (like hexacyclinol) had not been investigated.

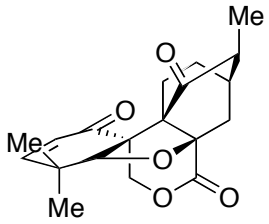
^{13}C NMR calculation data



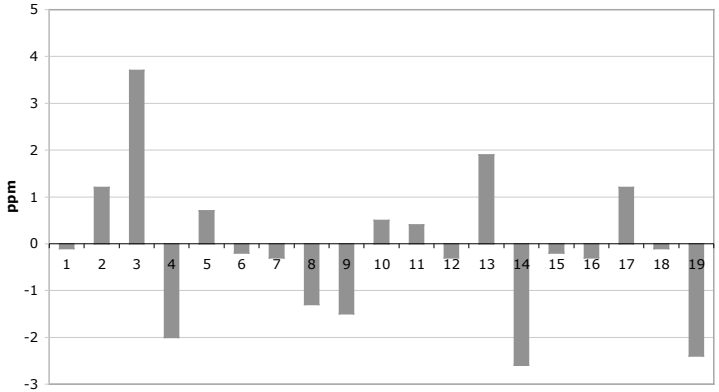
Elisapterosin B



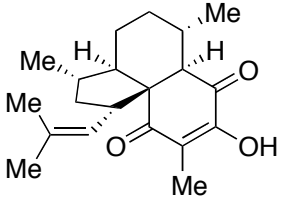
$\Delta\ \delta$= 1.9 ppm (3.8 ppm max)



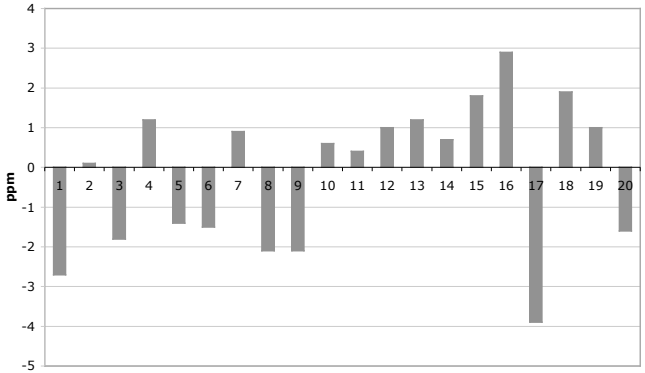
Maoecrystal V



$\Delta\ \delta$= 1.2 ppm (3.7 ppm max)

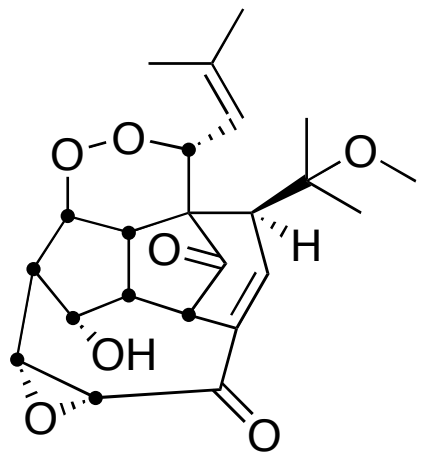


Elisabethin A

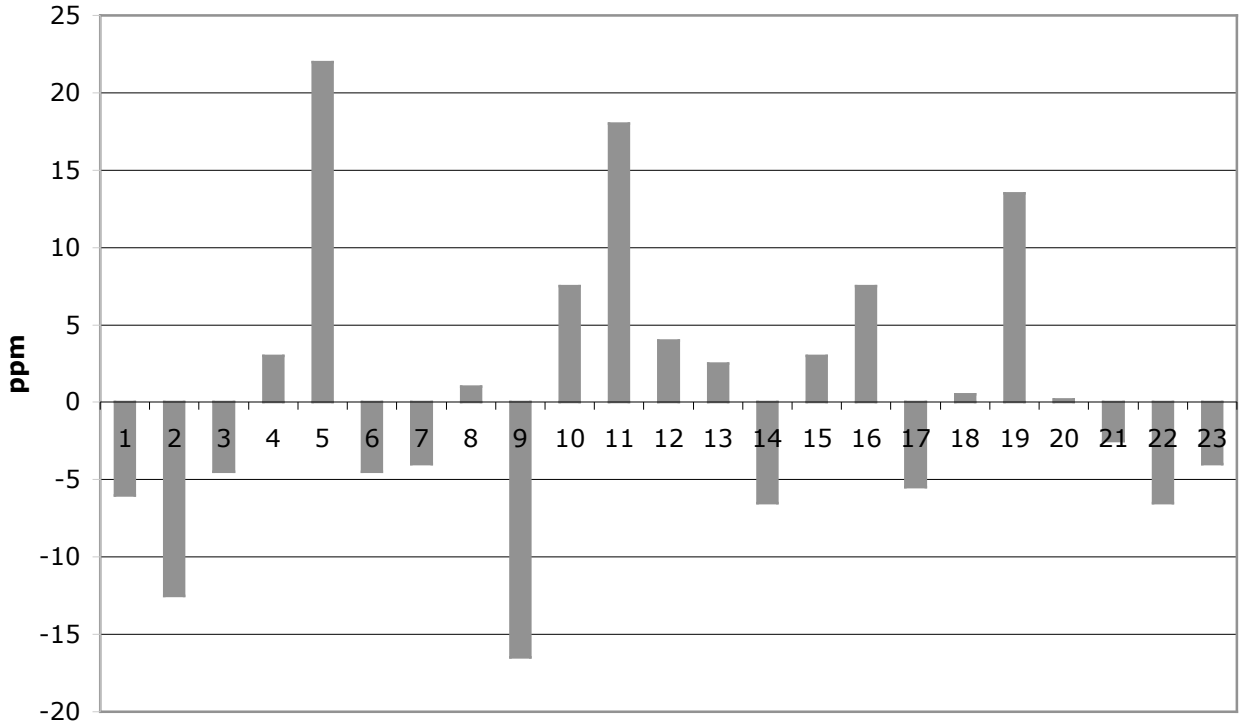


$\Delta\ \delta$= 1.4 ppm (3.8 ppm max)

^{13}C NMR calculation data



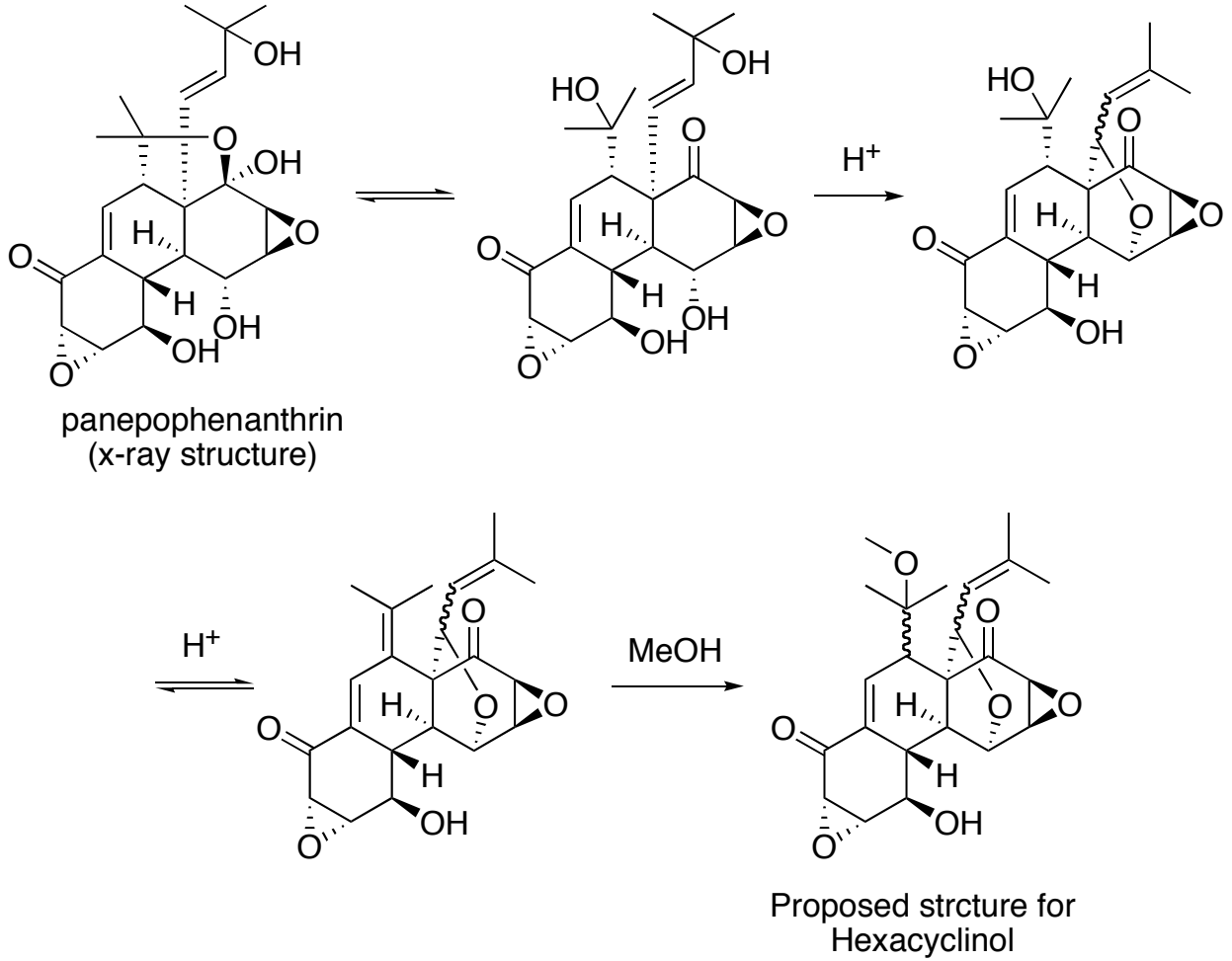
Gräfe Hexacyclinol



$\Delta\ \delta$= 6.8 ppm (22.0 ppm max)

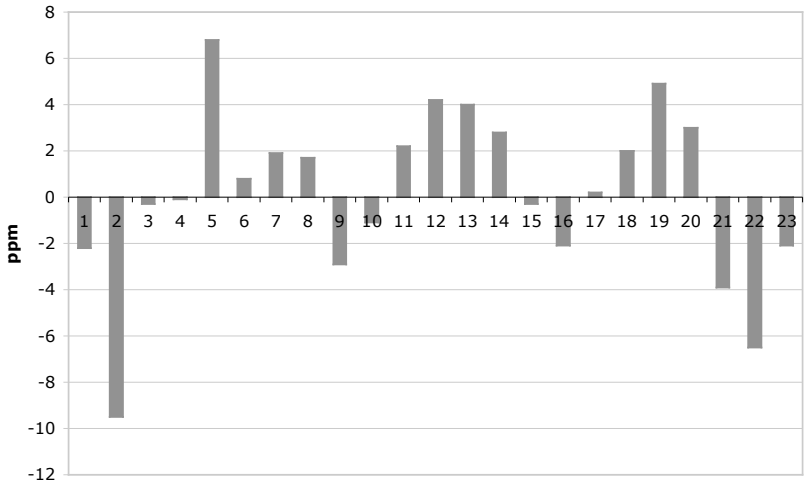
Structure proposal

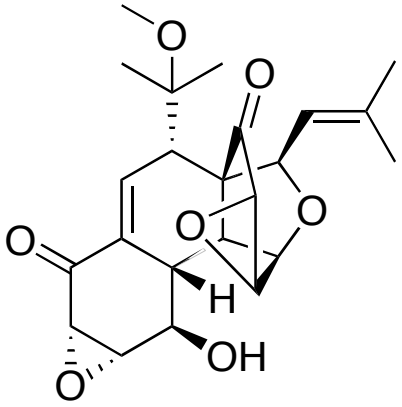
Isolation artifact:



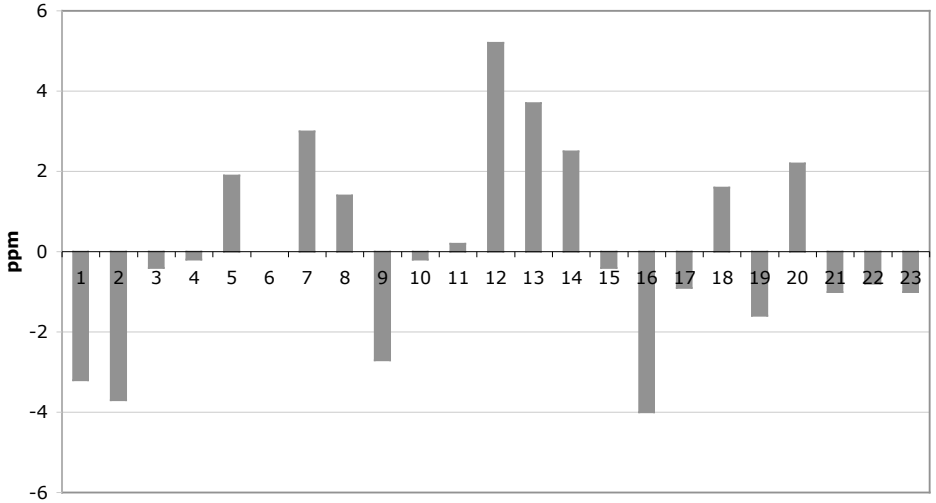
Proposed structure validation

Δ δ= 2.8 ppm (9.5 ppm max)

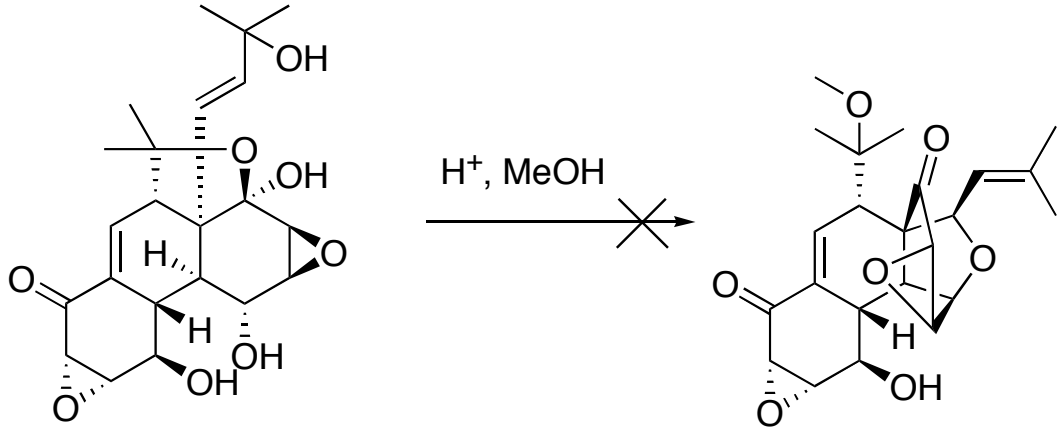




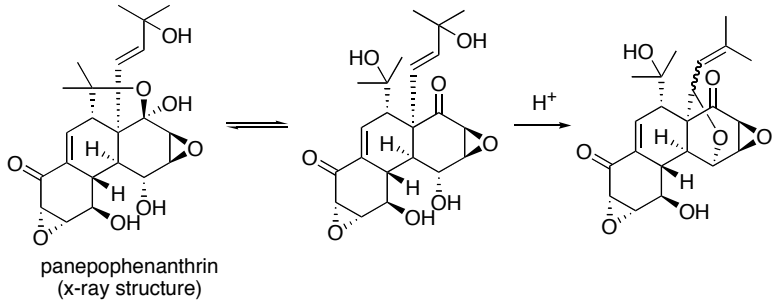
Δ δ= 1.8 ppm (5.2 ppm max)



Porco's Initial Investigation

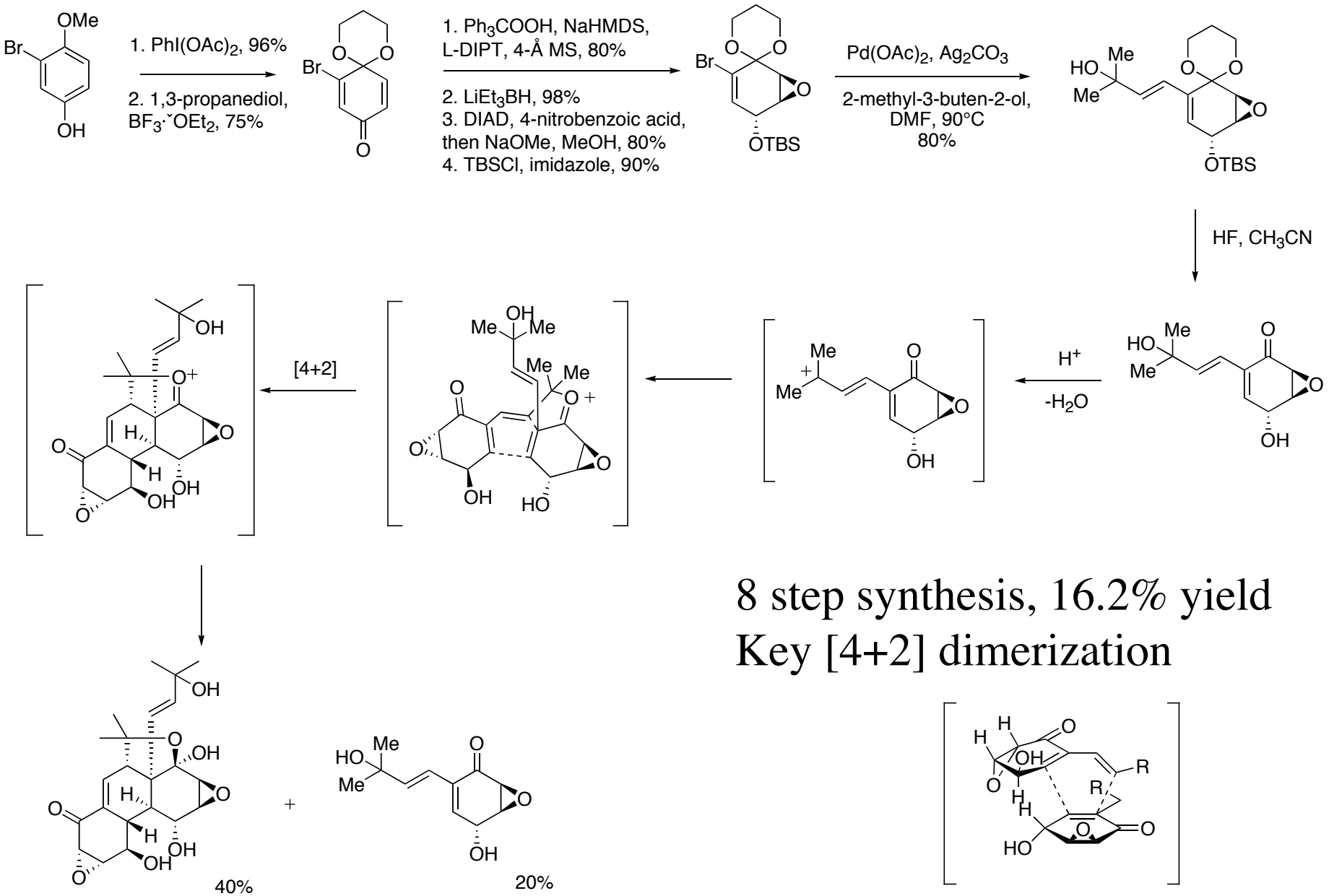


Therefore hexacyclinol not an isolation artifact of panepophenantherin



Porco, J. A. Jr.; Su, X.; Lei, X.; Bardhan, S.; Rychnovsky, S. D.; *Angew. Chem. Int. Ed.* **2006**, *45*, 5790-5792

Porco's Panepophenanthrin

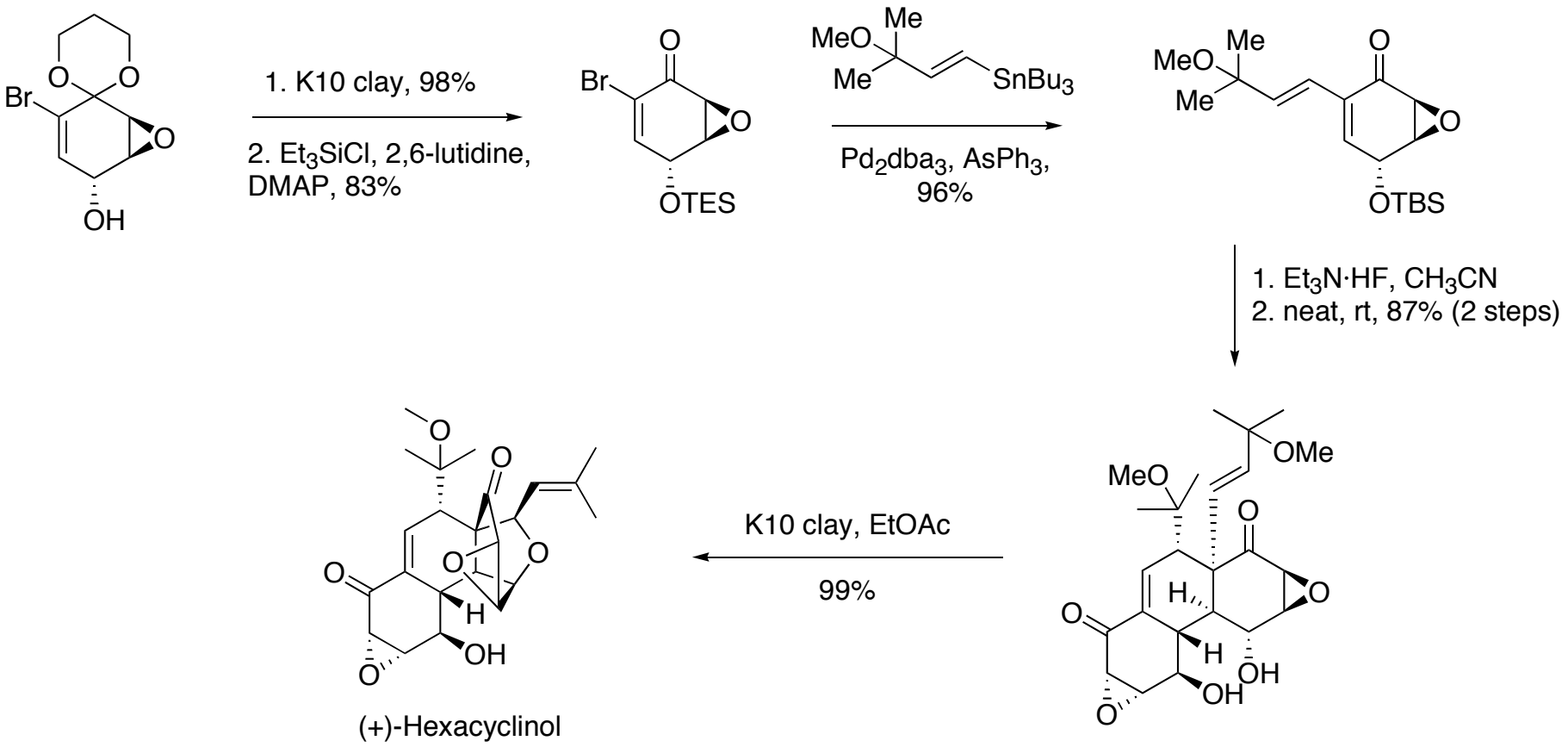


8 step synthesis, 16.2% yield

Key [4+2] dimerization

Lei, X.; Johnson, R. P,; Porco, J. A. Jr. *Angew. Chem. Int. Ed.*, **2003**, *42*, 3913-3917

Porco's Hexacyclinol



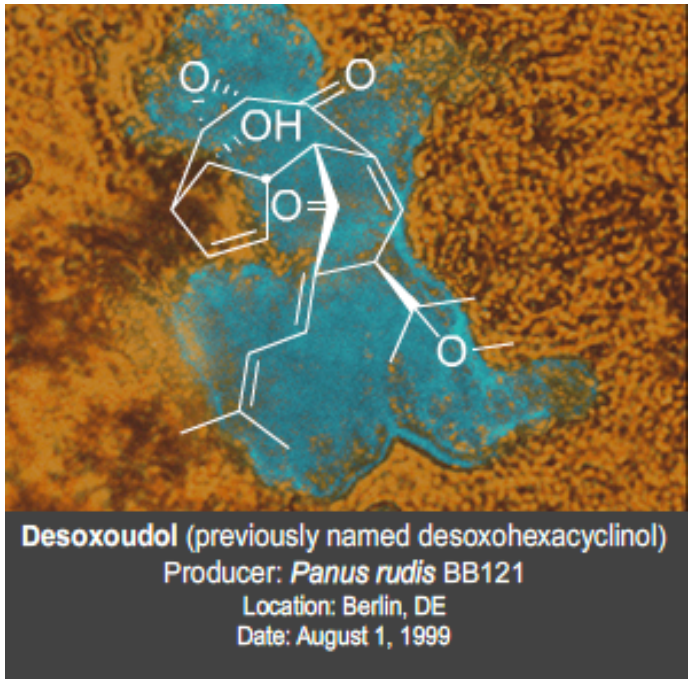
- ^{13}C NMR data matches that of authentic material
- 10 steps, 38% overall yield

Conclusion

- Structure of Hexacyclinol was confirmed by computational methods combined with synthesis- matches (^{13}C NMR) data of authentic material
-Following Porco publication, La Clair re-named 'deoxohexacyclinol' as desoxoudol- claiming the 2 structures gave rise to similar ^{1}H NMR spectra due to similar functionality and connectivity
-La Clair has said a future publication is forthcoming to address voiced concerns of original synthesis (1 year).

"Occasionally, blatantly wrong science is published, and to the credit of synthetic chemistry, the corrections usually come quickly and cleanly," comments Harvard University chemistry professor E. J. Corey

Lessons we can take home from this?



from www.xenobe.org

C & E News, July 31, 2006, p. 11