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Total Synthesis and Repudiation of the Helianane Family

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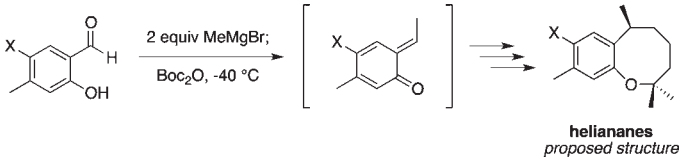
ABSTRACT



Total syntheses of two structures purported as (+)-heliananes were completed in six pots. Spectral comparisons, between the synthetic and natural compounds, revealed a misassignment of the eight-membered ring in the heliananes. The key step in the syntheses of the proposed structures and the confirmation of their actual structures was a diastereoselective inverse-demand Diels–Alder reaction between an optically active enol ether and an *ortho*-quinone methide species, which was generated *in situ* at low temperature by the sequential addition of methylmagnesium bromide and di-*tert*-butyl dicarbonate to a salicylaldehyde.

(+)-Helianane (**1**) was isolated in 1997 from the marine sponge *Haliclona fascigera*.[1a] Some years thereafter, two additional halogenated derivatives **2** and **3** thought to display the same ethereal ring system were reported from *Spirastrella hartmani*.[2] All three metabolites exhibited (+) optical activity. Crews proposed that (*S*)-(+)-curcuphenol (**4**) was the biosynthetic precursor for this family, which appeared to be a very small subset of aromatic bisabolene derived sesquiterpenes exclusively found in marine organisms (Figure 1). The (+)-enantiomer of **4** had been isolated 10 years earlier by Wright from the marine sponge *Didiscus flavus*[3] and then subsequently found in both *Epipolasis*[4] and *Arenochalina sp.*[5] In the latter study, six additional natural products (**5**–**8a**) were also isolated alongside **4**.

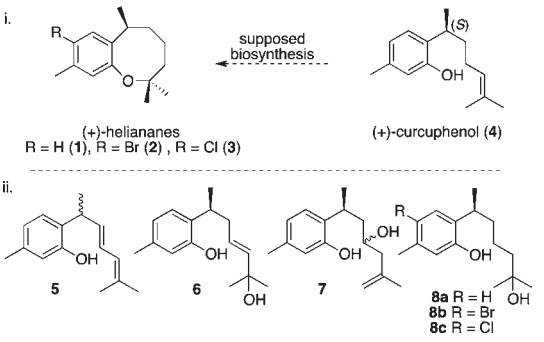


Figure 1. (i) Heliananes' supposed biosynthesis. (ii) Other sponge metabolites (**5**–**8a**) isolated alongside (+)-curcuphenol (**4**).

Conversely, the 12 heliannuols A–L were speculated to comprise a separate albeit larger subset of aromatic bisabolene sequiterpenes that Crews and others proposed to emanate from (*R*)-(−)-curcuquinone (**11**). Members of this family have all been exclusively isolated from terrestrial

(1) Isolation: (a) Harrison, B.; Crews, P. *J. Org. Chem.* **1997**, *62*, 2646–2648. Previous syntheses:(b) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808–2809. (c) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 9653–9655. (d) Sen, P. K.; Biwas, B.; Venkateswaran, R. V. *Tetrahedron Lett.* **2005**, *46*, 8741–8743. (e) Ghosh, S.; Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. *Tetrahedron* **2007**, *53*, 644–651. (f) Bidyut, B.; Sen., P. K.; Venkateswaran, R. V. *Tetrahedron* **2007**, *63*, 12026–12036. (g) Sabui, S.; Ghosh, S.; Sarkar, D.; Venkateswaran, R. V. *Tetrahedron Lett.* **2009**, *50*, 4683–4684. (h) Soga, K.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Synlett* **2011**, *8*, 1171–1173.

(2) Martin, M. J.; Berrue, F.; Amade, P.; Fernandez, R.; Francesch, A.; Reyes, F.; Cuevas, C. *J. Nat. Prod.* **2005**, *68*, 1554–1555.

(3) Wright, A. E.; Pomponi, S. A.; McConnell, O. J.; Kohmoto, S.; McCarthy, P. J. *J. Nat Prod.* **1987**, *50*, 976–978.

(4) Fusetani, N.; Sugano, M.; Matsunaga, S.; Hashimoto, K. *Cell. Mol. Life Sci.* **1987**, *43*, 1234–1235.

(5) Butler, M. S.; Capon, R. J.; Nadeson, R.; Beveridge, A. A. *J. Nat. Prod.* **1991**, *54*, 619–623.

(6) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Chem. Ecol.* **2000**, *26*, 2173–2186.

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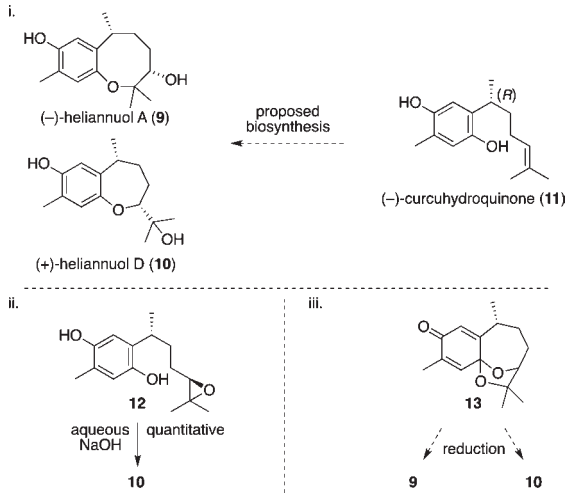


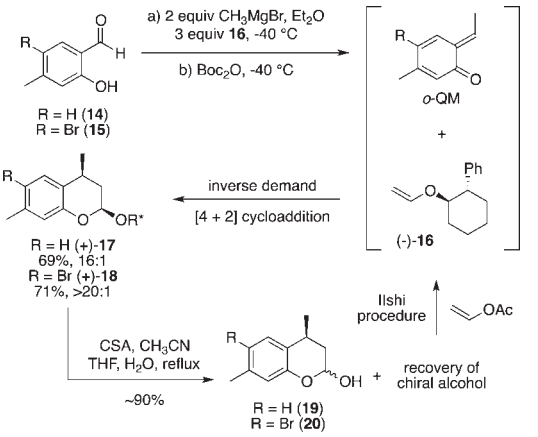
Figure 2. (i) Two (**9**, **10**) of the twelve known helianuols (A–L) and their terrestrial biosynthetic precursor. (ii) Prior synthesis of **10**. (iii) Our proposed divergent biosynthetic pathway to **9** and **10**.

plants, principally the sunflower *Helianthus annuus* that deploys these compounds for phytotoxic alleopathic defenses (Figure 2).[6,7] However, among its members were examples of six-, seven-, and eight-membered etherial ring systems, all of which also displayed an additional phenol and alcohol or alkene residues.

The supposed configurational differences and possible biosynthetic similaries between the marine heliananes and terrestrial heliannuols captured our interest. Macías previously demonstrated a 7-*exo*-tet epoxide opening of **12** to furnish the seven-membered ring present in six of the heliannuols (**B**, **C**, **D**, **F**, **I**, **J**, Figure 2ii).[8] While an 8-*endo*-tet epoxide opening had been proposed for the biosynthesis,[7b] it seemed an unlikely strategy for the five known eight-membered ring containing heliannuols (**A**, **G**, **H**, **K**, **L**). We propose a biosynthetic pathway in which curcuhydroquinone (**11**) undergoes oxidation to a quinone, indiscriminate dihydroxylation of the tethered olefin, and subsequent ketalization to produce the tricyclic quinoid ketals **13**. Reductive aromatization of one diastereomer releases the secondary alcohol to afford heliannuol A (**9**), whereas reduction of the other diastereomer releases the tertiary alcohol to furnish heliannuol D (**10**).

On the other hand, the origin of the eight-membered ring belonging to the heliananes (**1**–**3**) was more of a conundrum for us. The simplest explanation would be a direct conversion of curcuphenol (**4**) to helianane (**1**), as proposed by Crews. We therefore set out to test this hypothesis by treatment of curcuphenol (**4**) to acidic conditions aimed

Scheme 1. Diastereoselective Cycloaddition



at generating a tertiary carbocation that might be trapped by the tethered phenol to provide the cyclic ether. While the idea of constructing an eight-membered ring in this fashion seemed improbable, the mere existence of the natural product gave this unconventional notion some credence. However, to test the transformation we first required an enantioselective construction of the corresponding benzylic stereocenter.

Addition of MeMgBr (2 equiv) to the salicylaldehydes **14** or **15** (1.0 equiv, 0.1 M in Et_2O, −40 °C) resulted in sequential deprotonation of the phenol and addition to the aldehyde (Scheme 1). The respective dianion underwent monocarbonylation upon addition of Boc_2O (1.1 equiv, −40 °C) and β-elimination thereby leading to a short-lived *o*-quinone methide intermediate (*o*-QM) that engaged the nonracemic enol ether (−)-**16**[9] in a diastereoselective inverse-demand Diels–Alder reaction.[10] Thus, three new bonds were formed in a single pot. It appeared that the aryl bromine substituent provided increased diastereocontrol as the chroman ketal **18** formed with > 20:1 selectivity, whereas its hydrido counterpart **17** afforded a 16:1 ratio. Hydrolysis (camphorsulfonic acid, 0.1 equiv) of the ketal provided the respective lactol epimers **19**–**20** in 90% yield and returned the chiral alcohol that was recycled for subsequent preparations of **16**.

After attempting several new processes aimed at converting the masked aldehyde of **19** into the prenyl residue found within **4** in a single pot, a transformation predicated

(7) (a) Macías, F. A.; Varela, R. M.; Torres, A.; Milinillo, J. M. G.; Fronzek, F. R. *Tetrahedron Lett*. **1993**, *34*, 1999–2002. (b) Macías, F. A.; Molinillo, J. M. G.; Varella, R. M.; Torres, A.; Fronzek, F. D. *J. Org. Chem*. **1994**, *59*, 8261–8266. (c) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Tetrahedron Lett*. **1999**, *40*, 4725–4728.

(8) Macías, F. A.; Chinchilla, D.; Molinillo, J. M. G.; Marin, D.; Varela, R. M.; Torres, A. *Tetrahedron* **2003**, *59*, 1679–1683.

(9) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc*. **2002**, *68*, 5225–5227.

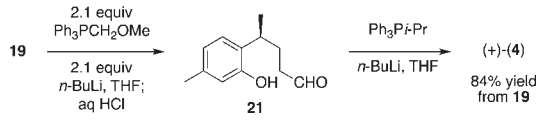
(10) For prior examples of related cycloadditions, see: (a) Van de Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc*. **2000**, *27*, 6502–6503. (b) Jones, R. M.; Van de Water, R. W.; Lindsey, C. C.; Pettus, T. R. R. *J. Org. Chem*. **2001**, *10*, 3435–3341. (c) Selenski, C.; Mejorado, L. H.; Pettus, T. R. R. *Synlett* **2004**, *6*, 1101–1103. (d) Selenski, C.; Pettus, T. R. R. *J. Org. Chem*. **2004**, *26*, 9196–9203.

(11) Fleming, I.; Patterson, I. *Synthesis* **1979**, 446–448.

(12) (a) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem*. **1991**, *56*, 1979–1981. (b) Berard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett*. **2007**, *48*, 8238–8241.

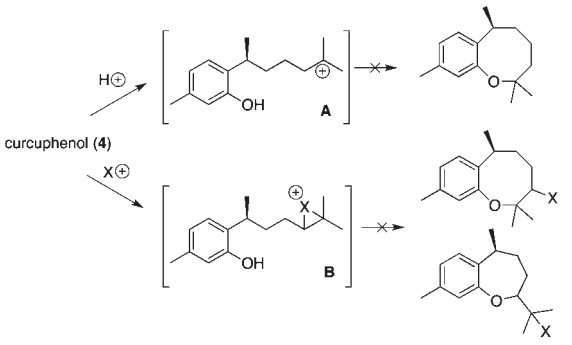
(13) Green, J.; Pettus, T. R. R. *J. Am. Chem. Soc*. **2011**, *133*, 1603–1608.

Scheme 2. Synthesis of (+)-Curcuphenol



upon the homologation of the carbonyl into an allyl silane and subsequent protodesilylation,[11] we chose instead to employ two sequential Wittig reactions with an intervening hydrolysis to the aldehyde **21** (Scheme 2). This sequence provided curcuphenol (+)-**4** in a respectable 84% yield from (+)-**19** over the two pots.

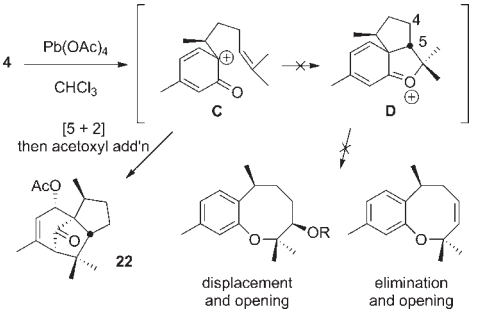
Scheme 3. Attempts for Closing the Eight-Membered Ring[a]



[a] H^+ = F_3CCO_2H, HBr, HCl, H_2SO_4, $MeSO_3H$, *p*-TsOH, camphorsulfonic acid, HCO_2H, AcOH. X^+ = BF_3•Et_2O, $AlCl_3$, I_2, Br_2, PhSeCl, PhSeBr, $SnCl_4$, $ZnCl_2$, $Tl(NO_3)_3$, $Tl(O_2CCF_3)_3$.

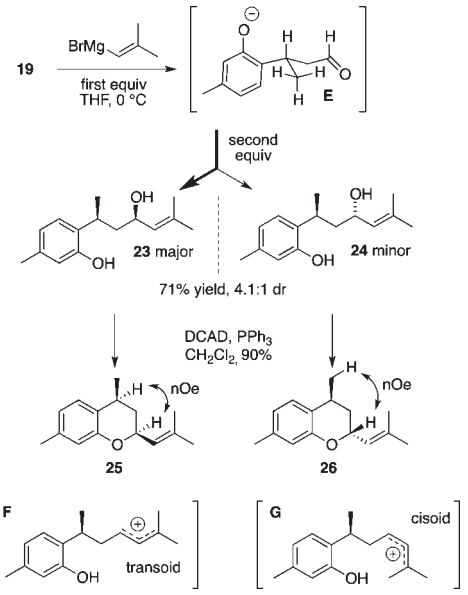
Our first attempts at a biomimetic construction of the etherial ring were guided by the previous investigations of Crews and Macías (Scheme 3). We began by examining a range of nonaqueous Brønsted acids in the hope of forming the tertiary cation intermediate **A**. We also attempted using Lewis acids to form a species resembling **B**, which might undergo cyclization to either the seven- or eight-membered rings. Unfortunately, these efforts all failed to afford any of the desired eight-membered cyclic ether. While we did observe trace amounts of the corresponding seven-membered rings, these experiments mostly led to undesired electrophilic aromatic substitutions or recovered starting material.

Scheme 4. Attempted Intramolecular [3 + 2] Cycloaddition



Our next line of thinking was to explore oxidative formats and perhaps use the dearomatization of **4** and subsequent formation of the phenoxonium **C** to induce an intramolecular [3 + 2] cycloaddition with tethered olefin (Scheme 4). Our initial confidence was bolstered by reports of intermolecular [3 + 2] reactions under oxidative conditions.[12] We reasoned that if **D** were formed in any appreciable amount, then it might restore aromaticity either by displacement from addition at the C5 site or by deprotonation of the C4 site and eliminative opening of the fused five-membered rings. While these notions were not successful in that aspect, they led to the discovery of a novel [5 + 2] cyclization–acetoxylation reaction that provided adduct **22** in 61% yield.[13]

Scheme 5. Syntheses of Benzopyran Natural Products



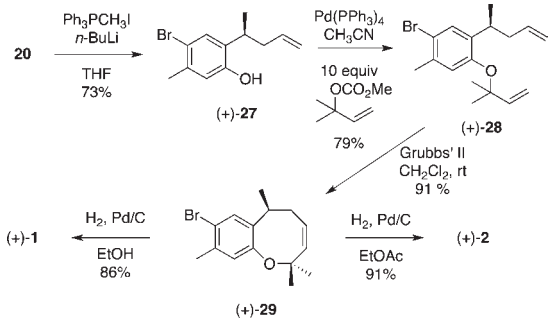
Having exhausted the proposed biomimetic applications emanating from curcuphenol (**4**), our attention turned toward examining the reactivity of the allylic cation that could be generated upon protonation of metabolite **6**. Addition of excess (2-methylprop-1-en-1-yl)-magnesium bromide (2.1 equiv) to the hemiketal **19** afforded an easily separable mixture of the secondary alcohols **23** and **24** in a respective 4.1:1 diastereomeric ratio and 71% combined yield (Scheme 5). This is a surprising stereoselection of special note, as we postulate that a series of A-1,3 steric effects guided the addition to the aldehyde, which emerged from deprotonation of **19**. Whereas treatment of **6** to acidic conditions would generate the transoid allylic cation **F**, we had hoped that protonation of **23** or **24** might afford a fractional amount of the cisoid intermediate **G** and lead to an eight-membered ring. Unfortunately, these attempts afforded only a mixture of benzopyrans **25** and **26**.

(14) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, *8*, 5069–5072.
(15) Isolation:Jakupovic, J.; Warning, U.; Bohlmann, F.; King, R. M. *Rev. Latinoam. Quim.* **1987**, *18*, 75–76.

Individual submission of either **23** or **24** to an intramolecular Mitsunobu reaction afforded the respective ethers in pure form.[14] Remarkably, an inseperable mixture of these two benzopyrans had been partially identified from extracts of the aerial parts of an Argentinian *Baccharis* species.[15] By examination of the various proton−proton relationships apparent from the respective ^{1}H-NOESY spectra for each pure compound, we have confirmed their prior speculative stereochemical assignments. The *cis* diastereomer **25** shows a strong NOE effect between the benzylic and allylic protons, whereas the *trans* diastereomer **26** displays a similar interaction between the benzylic methyl substituent and the allylic proton.

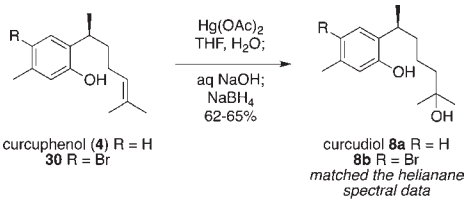
Unable to mimic a plausible biosynthetic reaction, we turned to a metathesis strategy, which had been employed for similar eight-membered rings.[1b,d,f−h] Treatment of (+)-**20** with excess ylide generated from addition of *n*-BuLi (2.05 equiv) to Ph_3PCH_3I (2.1 equiv) resulted in a Wittig olefination and furnished the terminal olefin (+)-**27** (Scheme 6). The phenol of (+)-**27** smoothly underwent reverse O-prenylation upon treatment with methyl (2-methylbut-3-en-2-yl) carbonate (10 equiv) and palladium tetrakis(triphenylphosphine) (0.01 equiv). Ring closing metathesis afforded the expected eight-membered heterocycle (+)-**29.** Palladium-catalyzed hydrogenation in ethanol provided (+)-**1**, whereas solvation with ethyl acetate afforded (+)-**2**.

Scheme 6. Completion of the Eight-Membered Ring



The ^{1}H NMR spectra for our synthetic compound (+)-**1** were identical to those of all seven of the previously reported total syntheses.[1b−h] However, we noted several inconsistencies with the proton resonances of the natural product orignally assigned as (+)-**1**. Contradictions between the ^{13}C NMR spectra for natural and synthetic compounds were more obvious. In the case of the synthetic material, many of the carbon resonances were broad as a consequence of conformational flexibility on the NMR time scale. For the natural material, however, the supposed aliphatic etherial carbon resonance differed by ~10 ppm from the synthetic material. Similar inconsistencies were also apparent for comparisons of synthetic and natural (+)-**2**. Our continued analyses led to the inescapable conclusion that the synthetic and natural compounds had different structures. From our analyses, we speculated that the three compounds previously claimed as the helianes (**1**−**3**) were in fact curcudiol **8a** and its previously unknown halogenated derivatives **8b** and **8c**. Our hypothesis was confirmed by separate oxymercuration and reduction of curcuphenol (**4**)[16] and bromocurcuphenol (**30**),[17] which furnished the synthetic compounds **8a** and **8b** (Scheme 7), the spectra of which were identical to those of the proposed helianes **1** and **2**.

Scheme 7. Syntheses of the Curcudiols



In conclusion, our efforts have led to (1) the enantioselective total syntheses of the two structures previouly assigned as helianes in six pots, (2) the structural revision and repudiation of the helianane family, (3) total syntheses of curcudiol (**8a**) and the previously unrecognized bromocurcudiol (**8b**), (4) the structural confirmation of two additional benzopyran natural products **24** and **25**, (5) the discovery of a new intramolecular [5 + 2] cycloaddition-acetoxylation reaction, and (6) the demonstration of concise applications of our method for construction of benzylic stereocenters.

Acknowledgment. T.R.R.P. is deeply grateful that the National Science Foundation (CHE-0806356) has supported this and other *o*-quinone methide work. J.C.G. would like to thank the Robert H. DeWolfe Fellowship for additional support.

Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Machiko, O.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1995**, *43*, 553–558.

(17) See the Supporting Information for a one-step synthesis of racemic curcuphenol and bromocurcuphenol.