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Total Synthesis of 7,11-Cyclobotryococca-5,12,26-triene Using an Oxidative Radical Cyclization as a Key Step

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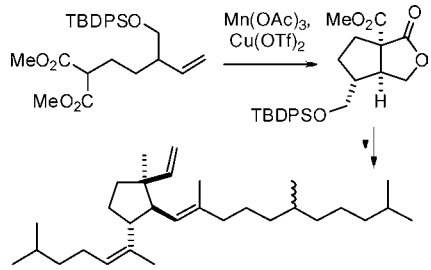
ABSTRACT



7,11-cyclobotryococca-5,12,26-triene

An efficient total synthesis of the novel botryococcene-related hydrocarbon 7,11-cyclobotryococca-5,12,26-triene is reported that uses, as a key step, an oxidative radical cyclization of a 4-pentenyl malonate for the synthesis of a [3.3.0]-bicyclic γ-lactone.

In 2000, Albrecht and co-workers reported the isolation and structure elucidation of a novel botryococcene-related hydrocarbon, 7,11-cyclobotryococca-5,12,26-triene **1** (Figure 1), from the sediments of Lake Cadagno, Switzerland.[1] The structure of **1** was assigned on the basis of NMR spectroscopic and mass spectrometric analysis as well as chemical derivatization. On the basis of a slight splitting in the signal of the C-29 methyl doublet in the ^{1}H NMR spectrum, it was suggested that the natural product was a 9:1 mixture of C-17 diastereomers.[1] The triene **1** represents the first example of a C_{30} botryoccene hydrocarbon with a midchain cyclopentane.[2,3] Synthetically, **1** contains a number of challenging structural motifs including: adjacent tertiary, tertiary, and quaternary stereocenters;[4] two stereodefined trisubstituted alkenes; and no heteroatom-based functionality. A racemic total synthesis of the C-17 diastereomers of **1** would allow confirmation that the natural product is a mixture of diastereomers at this position as well as verify the overall structure of the hydrocarbon. Furthermore, it would provide a platform for the development of an enantioselective

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(1) Behrens, A.; Schaeffer, P.; Bernasconi, S.; Albrecht, P. *Org. Lett.* **2000**, *2*, 1271–1274.

(2) A C_{30} unsaturated hydrocarbon with the same carbon skeleton as 7,11-cyclobotryococca-5,12,26-triene may have previously been isolated. See: ref 1 and Requejo, A. G.; Quinn, J. G. *Geochim. Cosmochim. Acta* **1983**, *47*, 1075–1090.

(3) For discussions concerning the biosynthesis of **1** see ref 1 and Pan, J.-J.; Bugni, T. S.; Poulter, C. D. *J. Org. Chem.* **2009**, *74*, 7562–7565.

(4) For reviews on the asymmetric synthesis of all carbon quaternary stereocenters see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066.

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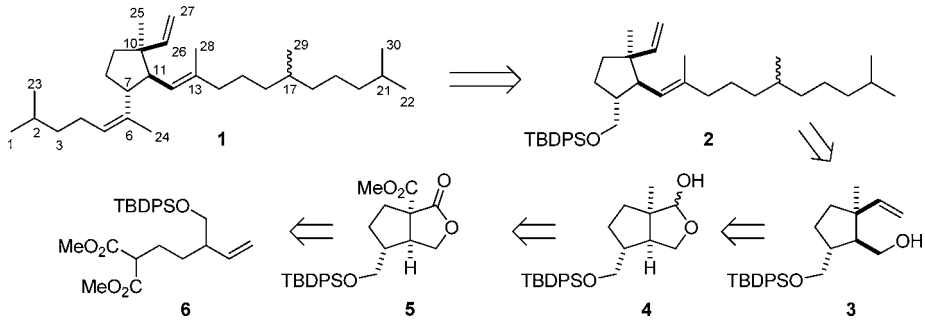


Figure 1. Retrosynthetic analysis of 7,11-cyclobotryococca-5,12,26-triene **1**.

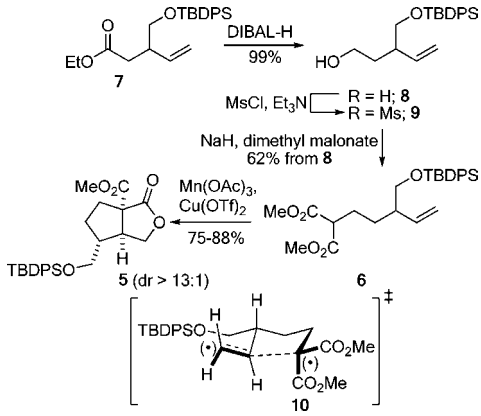
synthesis of the natural product, and related compounds,[5] which would ultimately allow the assignment of the C-17 stereocenter of each diastereomer of **1** relative to the ring stereocenters.

We have recently reported an efficient methodology for the synthesis of [3.3.0]-bicyclic γ-lactones based on the oxidative radical cyclization of 4-pentenyl malonates mediated by manganese(III) acetate.[6,7] Herein we report the application of this methodology to the total synthesis of racemic 7,11-cyclobotryococca-5,12,26-triene **1**.

Retrosynthetic analysis of **1** is shown in Figure 1. The two trisubstituted alkenes were to be installed from the corresponding protected dihydroxymethyl-substituted cyclopentane **3**. The trisubstituted cyclopentane would be synthesized by methylenation of the lactol **4** which would, in turn, be made from the [3.3.0]-bicyclic γ-lactone **5**. The bicyclic γ-lactone **5** was to be prepared by an oxidative radical cyclization of the 4-pentenyl malonate **6** according to our recent report.[6]

The known ester **7** was synthesized in two steps from *cis*-2-butene-1,4-diol using a Johnson−Claisen rearrangement as a key step (Scheme 1).[8] The ester **7** was readily reduced

Scheme 1. Synthesis of the [3.3.0]-Bicyclic γ-Lactone **5**



with DIBAL-H to give the alcohol **8** (99%); $LiAlH_4$ gave nonreproducible results. The alcohol **8** was converted into the cyclization substrate **6**[6] via the corresponding mesylate **9**. Exposure of the 4-pentenyl malonate **6** to manganese(III) acetate and copper(II) triflate[9] in freeze−thaw degassed acetonitrile at reflux delivered the [3.3.0]-bicyclic γ-lactone **5** in good yield.[10] We have conducted this cyclization on scales in excess of 15 g of substrate and always obtained the [3.3.0]-bicyclic γ-lactone **5** in yields in excess of 75% and with good diastereocontrol (>13:1 dr). The mechanism for the formation of the bicyclic γ-lactone **5** most likely involves formation of an electrophilic *C*-centered radical from reaction of the malonate **6** with manganese(III) acetate. The educt radical so formed undergoes 5-*exo*-trig cyclization via the chairlike transition state **10** in accord with the Beckwith−Houk[11,12] model for 5-*exo*-trig radical cyclizations, to deliver an adduct radical which is oxidized by copper(II)[7,13−15] to give the γ-lactone product.

The fused bicyclic γ-lactone **5** was readily decarboxylated under Krapcho conditions to give the γ-lactone **11** as previously demonstrated (Scheme 2).[6,16] Exposure of the γ-lactone **11** to LDA and methyl iodide introduced the

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(7) For reviews of the use of manganese(III) acetate in organic synthesis see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363. (b) Melikyan, G. G. *Org. React.* **1997**, *49*, 427–675. (c) Melikyan, G. G. *Aldrichimica Acta* **1998**, *31*, 50–64. (d) Demir, A. S.; Emrullahoglu, M. *Curr. Org. Synth.* **2007**, *4*, 323–351.

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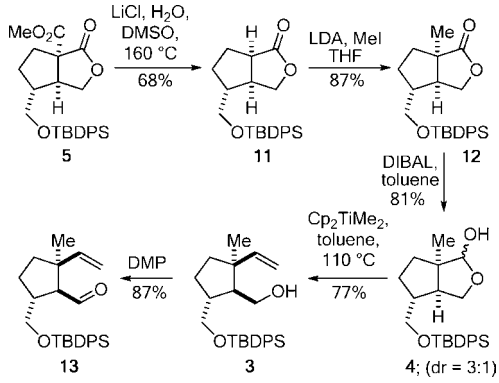
(15) Kochi, J. K. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, pp 594−623.

(16) This reaction was conducted on ca. 1 g scale. On a smaller scale (ca. 300 mg), the yield can be as high as 90%.

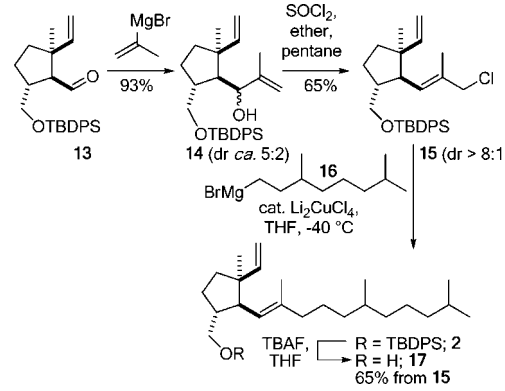
Scheme 2. Elaboration of the [3.3.0]-Bicyclic γ-Lactone **5**



bridgehead methyl group giving **12** with complete stereocontrol. The γ-lactone **12** was readily reduced to the corresponding lactols **4**, and methylenation of the lactols with dimethyltitanocene[17−19] gave the alcohol **3** with the C-10 quaternary stereocenter fully installed; the use of methylene triphenylphosphorane or the Tebbe reagent[20,21] was far less efficient, resulting in protecting group loss or migration. The primary alcohol in **3** was efficiently oxidized to the corresponding aldehyde **13** with the Dess-Martin periodinane[22,23] in readiness for introduction of the C-12 trisubstituted olefin.

The stereoselective formation of trisubstituted double bonds is still a challenge in organic synthesis.[24] We investigated a large number of routes for the introduction of the C-12 olefin including Wittig-type reactions on the aldehyde **13**[25] and hydrometalation/cross-coupling reactions on the methyl-substituted acetylene derived from the aldehyde **13**; however, neither of these approaches proved successful. The aldehyde **13** is sterically quite hindered, and consequently, Wittig reactions were low yielding; additionally, hydrometalation reactions of the acetylene derived from the aldehyde **13** were complicated by the presence of the C-26 terminal alkene.[26] After considerable work, we found that the use of a copper-catalyzed cross-coupling procedure was effective. Thus, iso-propenylmagnesium bromide was added to the aldehyde **13** in excellent yield to give the allylic alcohol **14** which was readily transformed into the allylic chloride **15** with good diastereocontrol (>8:1 C-12 *E*:*Z*) on treatment with thionyl chloride (Scheme 3).[27] After further

Scheme 3. Introduction of the C-11 Side Chain



synthetic effort, we found that addition of a solution of the allylic chloride and Kochi's catalyst (Li_2CuCl_4)[28,29] to a solution of the commercially available racemic Grignard reagent **16** in THF[30] followed by treatment with TBAF allowed isolation of the coupled product **17** as a single olefin diastereomer in excellent yield.[31]

We were attracted to the use of organocopper methodology for the synthesis of the trisubstituted C-5 olefin in the C-7 side chain (Scheme 4). Thus, the primary alcohol **17** was readily oxidized to give the corresponsing aldehyde **18**[22,23] which was converted into the terminal acetylene **19** using the Ohira−Bestmann reaction (89%).[32,33] The terminal acetylene **19** was converted into the corresponding substituted methyl propiolate **20**. Low temperature treatment of the propiolate **20** with the Gilmann reagent, followed by a methanol quench, gave the α,β-unsaturated ester **21** as a single geometric isomer which was reduced to the allylic alcohol **22** on exposure to DIBAL.[34] The allylic alcohol **22** was converted into the natural product by initial chlorination followed by treatment with iso-butylmagnesium chloride and

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(25) For a recent example of difficulty encountered when using a Wittig reaction to form a trisubstituted olefin see: Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744–5745.

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(30) This is the procedure described by Monte and Lindbeck: Monte, W. T.; Lindbeck, A. C. *Org. Process Res. Dev.* **2001**, *5*, 267–269.

(31) The crude ^{1}H NMR of the coupled product **2** did not indicate the presence of any other alkene diastereomers.

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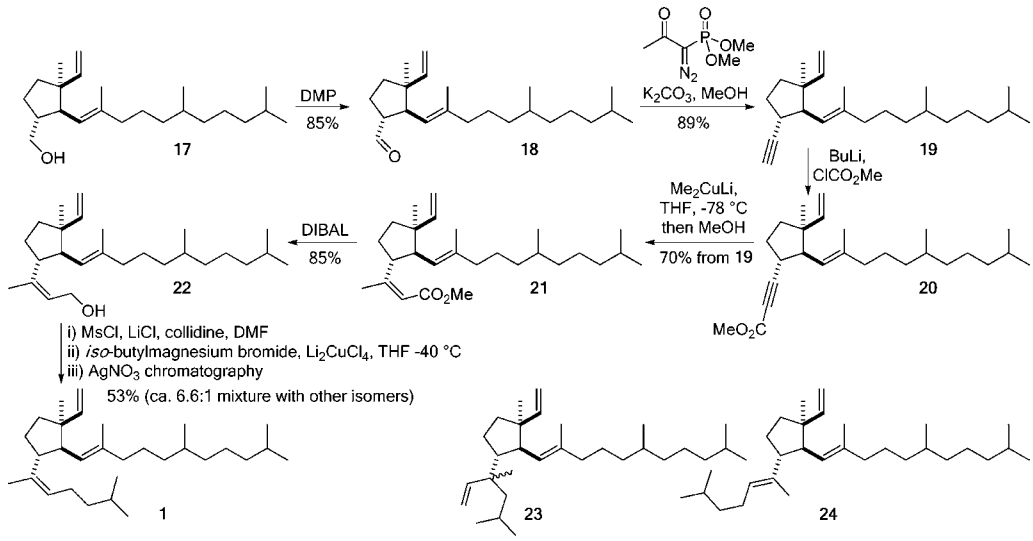
Scheme 4. Completion of the Synthesis of **1**



Kochi's catalyst.[28,29] The crude ^{1}H and ^{13}C NMR indicated the presence of approximately a 1:1 mixture of the natural product **1** with other hydrocarbon byproducts; the structures of the byproducts were tentatively assigned as the isomers **23** and **24**.[35] The natural product could be isolated as the major constituent after argentation chromatography (53% 6:1 mixture with byproducts).[36] The synthetic material is a 1:1 mixture of C-17 diastereomers and had spectroscopic data entirely in accord with the natural material.[37] Furthermore, the synthetic material clearly showed two separate doublets for the C-29 methyl group in the ^{1}H NMR spectrum thus confirming that the natural material is indeed a 9:1 mixture of C-17 diastereomers.

In conclusion, we have developed an efficient synthesis of the hydrocarbon natural product, 7,11-cyclobotryococca-5,12,26-triene **1**, which features an oxidative radical cyclization for the diastereoselective synthesis of a [3.3.0]-bicyclic γ-lactone as a key step, along with copper catalyzed coupling reactions for the stereocontrolled synthesis of the two trisubstituted olefins. Further reports on the use of oxidative radical chemistry in the synthesis of natural products containing all carbon quaternary stereocenters will be forthcoming.

Acknowledgment. We thank Prosidion Limited and the Royal Society (London) for funding this work; Prof. Albrecht for providing copies of the NMR spectra of natural **1**; and Dr Sarah Aves for initial studies.

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

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(34) We followed the procedure of Uguen and co-worker for the preparation of the allylic alcohol **22** from the acetylene **19**: Zoller, T.; Uguen, D.; DeCian, A.; Fischer, J.; Sable, S. *Tetrahedron Lett.* **1997**, *38*, 3409–3412.

(35) The assignment of the structures **23** and **24** is only tentative as isolation of pure compounds was not possible. The formation of **23** and **24** may be due to the formation of isomeric allylic chlorides in the previous step.

(36) Further purification provided pure **1**.

(37) The spectra of the synthetic material completely match the copies of the original spectra kindly supplied by Prof. Albrecht (ref 1). There is a typographical error in the reported ^{13}C NMR data of the natural product (ref 1). The C-15 ^{13}C NMR resonance is quoted at $\delta = 25.79$ ppm, whereas in the original spectra, and the spectra of the synthetic material, C-15 resonates at $\delta = 24.80$ ppm.