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Enantioselective Formal Synthesis of Eurylene: Synthesis of the *cis*- and *trans*-THF Fragments Using Oxidative Cyclization

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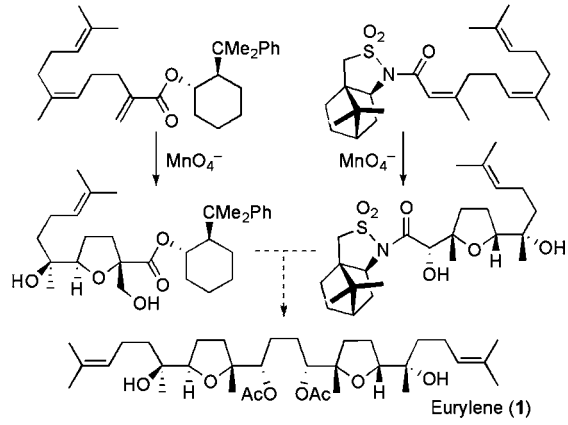
ABSTRACT



A formal synthesis of eurylene is described, where both *cis*- and *trans*-THF-containing fragments were prepared using diastereo- and chemoselective permanganate-mediated oxidative monocyclizations of trienes.

Eurylene (**1**) is a squalenoid natural product isolated from the wood of the tropical Asian shrub *Eurycoma longifolia*, with reported cytotoxicity against lymphocytic leukemia.[1] Structural and partial stereochemical assignments of eurylene were established through analysis of MS and NMR data. Ultimately, X-ray crystallography combined with the analysis of C11 and C14 Mosher ester derivatives allowed the assignment of the relative and absolute stereochemistry to be completed. Thus, it was determined that eurylene contains two nonadjacently linked 2,5-bis-hydroxyalkyltetrahydrofuran (THF diol) systems, with a combined total of eight stereogenic centers. The left segment (C1−C12) contains an acylated *trans*-THF diol, whereas the other acylated THF diol has the *cis* configuration. To date, three total syntheses of eurylene have been reported.[2,3]

Metal−oxo-mediated oxidative cyclization reactions of 1,5-dienes permit direct stereocontrolled entry into *cis*-2,5-

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(1) Itokawa, H.; Kishi, E.; Morita, H.; Takeya, K.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 1803–1804.

(2) For total syntheses of eurylene (**1**), see: (a) Ujihara, K.; Shirahama, H. *Tetrahedron Lett.* **1996**, *37*, 2039–2042. (b) Morimoto, Y.; Muragaki, K.; Iwai, T.; Morishita, Y.; Kinoshita, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4082–4084. (c) Hioki, H.; Yoshio, S.; Motosue, M.; Oshita, Y.; Nakamura, Y.; Mishima, D.; Fukuyama, Y.; Kodama, M.; Ueda, K.; Katsu, T. *Org. Lett.* **2004**, *6*, 961–964. Synthetic studies: (d) Gurjar, M. K.; Saha, U. K. *Tetrahedron Lett.* **1993**, *34*, 1833–1836.

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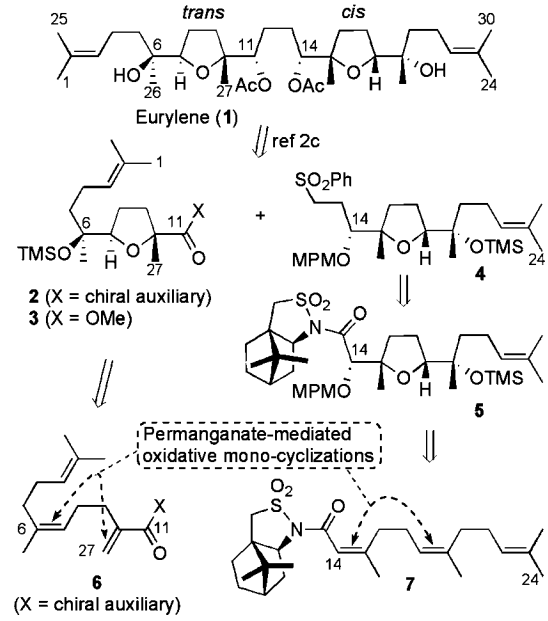
disubstituted THF diol fragments found in numerous natural products including Annonaceous acetogenins and polyethers such as eurylene (**1**).[4−6] However, *trans*-THF diol subunits are also present in many of these natural products, and eurylene contains both *cis*- and *trans*-THF diol motifs. Although *trans*-selective oxidative cyclizations of hydroxyalkenes are known,[8] a stereoselective method for *trans*-selective oxidative cyclization of 1,5-dienes is lacking,[8] leading us to consider a stereospecific method to prepare *trans*-THF diols from *cis*-THF diols.[9] Herein we describe a formal synthesis of eurylene, where stereo- and chemoselective oxidative monocyclizations of trienes are used to generate the *cis*- and *trans*-THF fragments, retaining the electron-rich C2−C3 and C22−C23 trisubstituted alkenes.

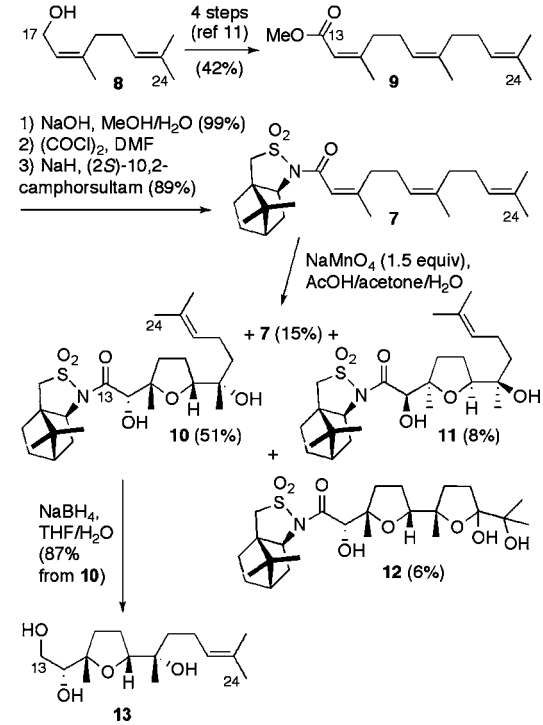
Retrosynthetic analysis of eurylene followed a central disconnection to identify two major THF fragments **2** and **5** (Scheme 1), which could be manipulated to intersect with fragments **3** and **4** employed in Kodama's published route[2c] or serve to explore alternative coupling methodologies. We have reported selective oxidative monocyclizations of trienes and dienynes by exploiting the higher reactivity of permanganate ion toward electron-deficient alkenes and shown how the resulting partially oxidized products can be applied in the synthesis of Annonaceous acetogenins by further oxidative transformations.[10] In the present case, permanganate-mediated oxidative cyclizations of the trienes **6** and **7** would create both THF diol systems, while retaining the C2−C3 and C22−C23 trisubstituted alkenes present in the target. However, for this approach to succeed, we needed to adapt the formally "*cis*-selective" permanganate oxidative cyclization to allow access to the *trans*-THF system (C6−C11) found in eurylene.

Scheme 1. Retrosynthetic Analysis of Eurylene (**1**)



The trieneoate **9**, containing the C13−C24 framework of eurylene, was synthesized by adaptation of reported procedures (Scheme 2).[11] Hydrolysis of methyl ester **9**, activation

Scheme 2. Synthesis of the C13−C24 Portion of Eurylene



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(4) For a review of diene oxidative cyclizations mediated by metal−oxo species, see: Piccialli, V. *Synthesis* **2007**, 2585–2607.

(5) For some additional examples of oxidative cyclization of 1,5-dienes to give *cis*-THF diols: MnO_4^-: (a) Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc.* **1990**, *112*, 5624–5625. (b) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9–39. (c) Cecil, A. R. L.; Hu, Y. L.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368–3374. OsO_4: (d) de Champdore, M.; Lasalvia, M.; Piccialli, V. *Tetrahedron Lett.* **1998**, *39*, 9781–9784. (e) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 948–951. RuO_4: (f) Lygo, B.; Slack, D.; Wilson, C. *Tetrahedron Lett.* **2005**, *46*, 6629–6632. (g) Goksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433–3436.

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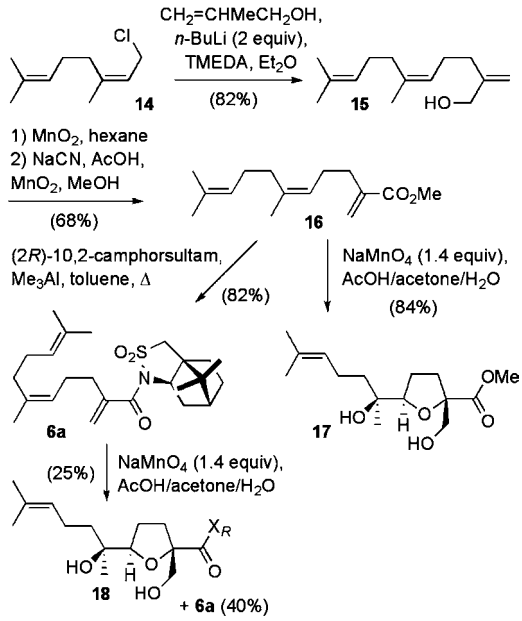
of the resulting acid, and coupling with the (2*S*)-camphor sultam afforded trienoyl sultam **7** in good yield ready for the selective oxidative cyclization. We were delighted to realize the key oxidative monocyclization of triene **7**, which delivered the desired THF diol **10** as the main isolated product. The diastereoisomeric THF diols **10** and **11** were separated by column chromatography to provide the major and minor isomers in 51% and 8% isolated yields, respectively. The overoxidized product **12**, obtained here as a minor component, is the major product when excess permanganate is employed.[11a] Finally, borohydride reduction of the acylsultam **10** afforded the triol **13**, an intermediate used in the Kodama synthesis. Spectroscopic and analytical data for **13** were consistent with those reported by Kodama.[2c]

The C1−C11 fragment containing the *trans*-THF system required a structurally distinct trienoic acid precursor, the synthesis of which commenced by alkylation of methallyl alcohol dianion with neryl chloride (**14**, Scheme 3).[12] A two-

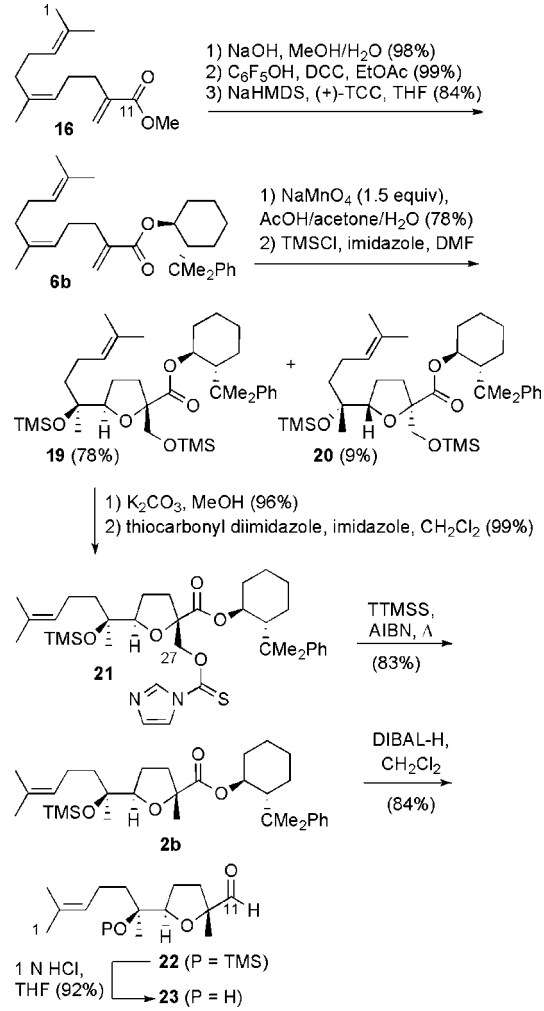
Scheme 3. Synthesis and Oxidative Mono-cyclizations of Trienes **16** and **6a**



step MnO_2-mediated oxidation of the allylic alcohol **15** secured the trienoate **16**,[13] which reacted directly with the (2*R*)-camphor sultam in the presence of $AlMe_3$ to give the oxidative cyclization precursor **6a**.[14] Unfortunately, our initial oxidative cyclization experiments gave mixed results; the desired product **18** was isolated as a single diastereoisomer but in only 25% yield. However, we were strongly encouraged by the observation that the parent methyl trienoate **16** gave the racemic monocyclization product **17** in excellent yield under similar reaction conditions. These contrasting results suggested that the bulk of the camphor sultam was either retarding the rate of oxidation of the enoyl alkene or impeding the subsequent cyclization reaction of the manganese diester intermediate.[15] Thus, in the absence of a relatively rapid oxidative cyclization, a complex mixture of triene oxidation products prevailed.

A number of alternative auxiliaries were investigated, the best of which proved to be bulky cyclohexyl ester system (+)-*trans*-2-(α-cumyl)cyclohexanol ((+)-TCC, Scheme 4).[16,17] Oxidation

Scheme 4. Synthesis of the C1−C11 Fragment



of the 8-phenylmenthol analogue **6b** ultimately afforded the desired oxidative cyclization products in 78% yield, as a mixture of diastereoisomers (dr = 6.7:1) that was not separable by column chromatography on silica gel. However, protection of the THF diol products as their bis-TMS ethers **19** and **20** rendered the diastereoismers chromatographically separable.

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Convertion of the protected *cis*-THF diol **19** to the *trans*-THF motif present in eurylene was achieved through deoxygenation at C27. Selective deprotection of the primary silyl ether and subsequent reaction of the resulting primary alcohol with thiocarbonyldiimidazole gave radical deoxygenation precursor **21**. While inconsistent results were obtained for the deoxygenation of the imidazole thioate **21** mediated by Bu_3SnH, the use of $(Me_3Si)_3SiH$ (TTMSS) yielded the desired product **2b** in 83% yield.[18,19] We note that ester **2b** is an analogue of Kodama's left-hand fragment **3**, which has the potential to be used directly in fragment coupling. However, in order to intersect with Kodama's route, thereby confirming the stereochemistry of the oxidative cyclization product, the ester **2b** was reduced using DIBALH to afford the aldehyde **22**. The formal synthesis was completed by cleavage of the TMS protection from aldehyde **22** to secure the Kodama intermediate **23**. Physical and spectroscopic data for **23** were in agreement with those reported by Kodama, thereby confiming the identity of the major stereoisomer from the oxidative cyclization.

The sense of diastereofacial preference observed in the oxidative cyclization is consistent with approach of the reacting permanganate ion from the front (*Re*) face of the *s-cis* enoate conformer (Figure 1).

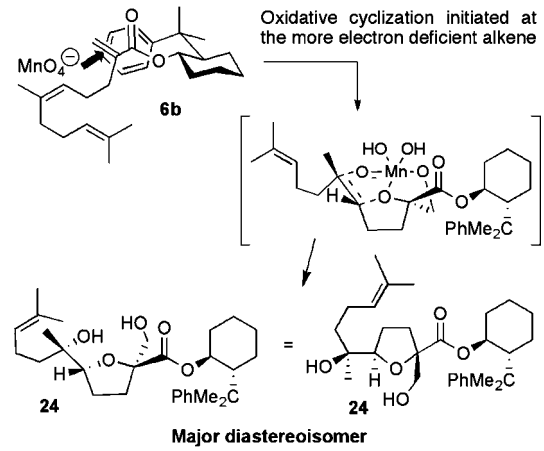

Figure 1. Model for the diastereoselective oxidative cyclization of trieneoate **6b**.

In summary, a formal synthesis of eurylene has been achieved where both *cis*- and *trans*-THF fragments were prepared using diastereo- and chemoselective oxidative monocyclizations of trienes. To the best of our knowledge, this is the first reported case of the application of permanganate-mediated oxidative cyclization to the synthesis of a *trans*-THF.

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Supporting Information Available: Experimental procedures, physical and spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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