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# Enantiospecific Synthesis of the Cubitane Skeleton

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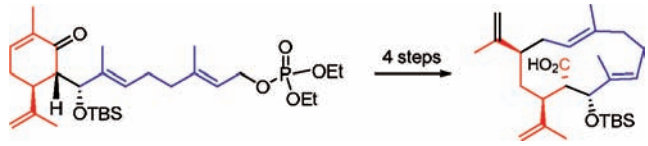
## ABSTRACT




**The fully substituted 12-membered macrocycle of the cubitane-type diterpenoids has been assembled in an enantioselective manner following a novel "bridge-and-cut" strategy. Hydroxyalkylation of (*S*)-carvone afforded a carvonylgeraniol, which underwent transannular cyclization on treatment with samarium diiodide in THF. Fragmentation of one of the shorter bridges of the resulting [8.2.2]bicycle liberated the 12-membered ring with the desired *cis*-arrangement of the isopropenyl side chains.**

Synthesis of monocyclic terpenoid skeletons by fragmentation of rigid bicyclic precursors offers the advantage of excellent stereocontrol. In this communication, we report a novel route to the 12-membered ring system present in irregular diterpenoids of the cubitane type.

Natural products containing the rare cubitane skeleton include (+)-cubitene (**1**, Figure 1) from the East African termite *Cubitermes umbratus*[1] and calyculone F (**2**) from the soft coral *Eunicea calyculata*.[2] Biogenetically, the 12-membered ring appears to be derived from the 14-membered cembrane ring system. Fenical et al. have shown that irradiation of a cembratriene affords a mixture of cubitanoids by ring contracting acyl migration, in addition to cembranoids.[3]

In (+)-cubitene (**1**), the two isopropenyl side chains are *cis*-located. Kodama et al. developed the only enantioselective synthesis of **1** by cyclizing an open-chain α-sulfenyl carbanion (20 steps, 2.8% overall yield).[4] Earlier, Vig et al. had synthesized a mixture of isomeric cubitenes.[5]

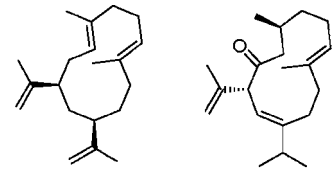



**Figure 1.** Cubitane-type natural products.

Recently, we synthesized carvonylgeraniol **3** by hydroxyalkylation of side-chain hydrogenated (*S*)-carvone.[6] To our surprise, allylphosphate **3** underwent $SmI_2$-induced, transannular cyclization to the hitherto unknown bicyclo[8.2.2] tetradecadienone **4** (Scheme 1). NOESY-based analysis of **4** indicated a *twist boat* conformation of the cyclohexanone ring. On upscaling, we were able to crystallize **4** confirming its three-dimensional structure. The *twist boat* conformation of the cyclohexanone exposes the new α-proton on the opposite side of the 8-membered bridge, whereas the methyl group is situated in the pseudoequatorial position.

(1) (a) Prestwich, G. D.; Wiemer, D. F.; Meinwald, J.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 2560–2561. (b) Wiemer, D. F.; Meinwald, J.; Prestwich, G. D.; Miura, I. *J. Org. Chem.* **1979**, *44*, 3950–3952.
(2) Fenical, W.; Look, S. A. *J. Org. Chem.* **1984**, *49*, 1417–1423.
(3) Fenical, W.; Shin, J. *J. Org. Chem.* **1991**, *56*, 1227–1233.
(4) (a) Kodama, M.; Maeda, H.; Hioki, H. *Chem. Lett.* **1996**, 809–810. (b) Diastereoselective version: Kodama, M.; Takahashi, T.; Kojima, T.; Itô, S. *Tetrahedron Lett.* **1982**, *23*, 3397–3400.

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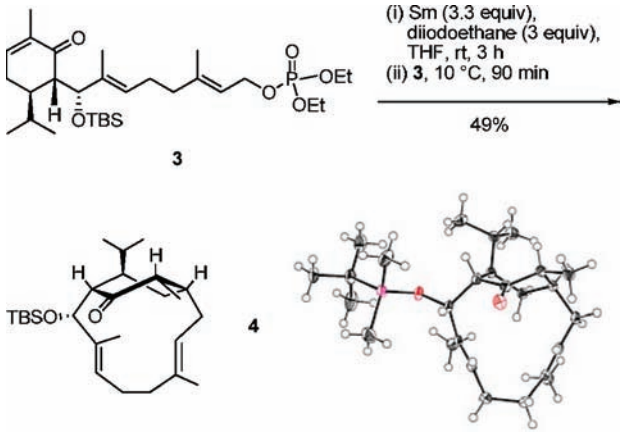
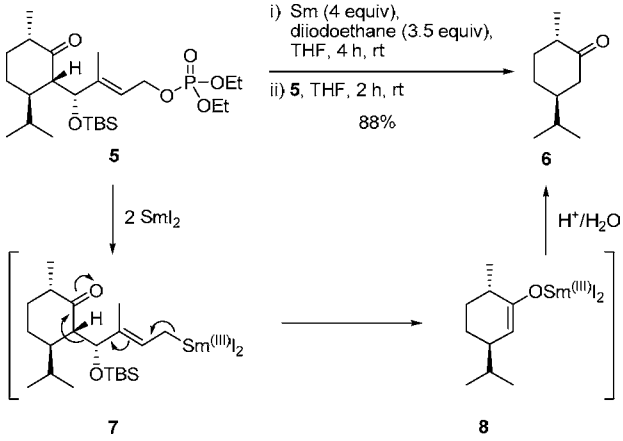
**Scheme 1.** Transannular Cyclization to [8.2.2]Bicycle **4**, Characterized by X-ray Analysis




The mechanism of the cyclization **3** to **4** remains unclear.[7] Butsugan and co-workers had introduced the $SmI_2$-mediated coupling of allylphosphates to saturated aldehydes and ketones.[8] If the allyl phosphate group of **3** behaves like an allyl halogenide, a samarium Barbier reaction will commence with the stepwise reduction of the allylphosphate to an allyl radical and further to an organosamarium species, followed by Michael-type addition to the enone. Organosamarium species prefer 1,2-addition,[9] but steric constraints in intramolecular reactions may also favor 1,4-addition to enones.[10,11]

Formation of an organosamarium intermediate is in agreement with the facile retro aldol fragmentation of the sesquiterpenoid allylphosphate **5** (Scheme 2),[12] where the assumed Sm−C bond is situated in the vinylogous position of the aldol C−C bond. Tetrahydrocarvone (**6**) is formed in 88% yield on reaction of **5** with $SmI_2$/THF, presumably via organosamarium compound **7**.

**Scheme 2.** Retro Aldol Fragmentation of Allyl Phosphate **5** in the Presence of $SmI_2$ in THF




Alternatively, an oxyallyl radical may be formed by one-electron reduction of the cyclohexenone moiety of compound **3**. On attempts to allylate α,β-unsaturated dihydrocarvone with diethyl geranyl phosphate in the presence of $SmI_2$ in THF, we were able to isolate 22% of α,α-homocoupling products as a mixture of diastereomers, together with 38% of geranyl dimers. Butsugan and co-workers[8] and Curran et al.[10] observed that intermolecular couplings of α,β-unsaturated ketones yield complex product mixtures when treated with $SmI_2$ in THF.

Regarding the assembly of 8- up to 11-membered carbocycles, $SmI_2$ has been used to induce Barbier-type cyclizations[13] and ketyl−alkene cyclizations.[14] Molander et al. also reported transannular ketyl−alkene cyclizations employing $SmI_2$.[15] To our knowledge, compound **4** represents the largest transannular ring assembled by a $SmI_2$-mediated reaction.

The highest yields of bicycle **4** were obtained by slowly adding a solution of **3** in THF to a solution of $SmI_2$ (3 equiv) in THF at 5−10 °C. Thus, there is also the possibility that the large excess of $SmI_2$ in the beginning of the reaction generates both the organosamarium species and the oxyallyl radical, which recombine with reliberation of 1 equiv of $SmI_2$.

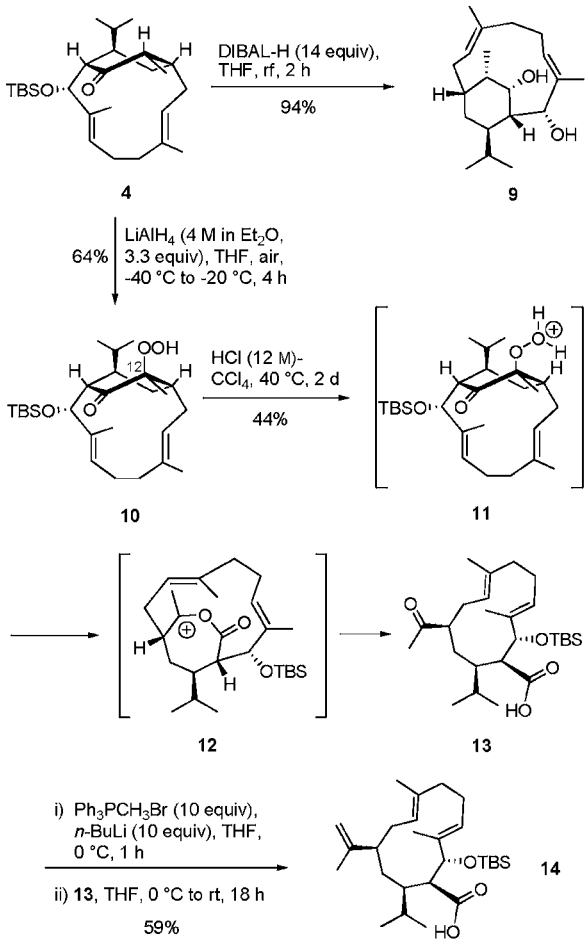
The yield of **4** was 49%, and we wondered whether the clearly defined stereochemistry of **4** could be exploited for a novel stereoselective approach to the 12-membered monocycle of **1** by cutting the oxygenated short bridge. Overall, an effective "bridge-and-cut" strategy would be in place.

Our pathway to the 12-membered cubitane ring was discovered on attempts to reduce the keto group of **4** to the alcohol. The keto group proved to be resistant against attack by $NaBH_4$ in refluxing EtOH. Reduction of ketone **4** only occurred under harsh conditions by refluxing with an excess of DIBAL in THF and afforded the desilylated cyclohexanol **9** in almost quantitative yield (Scheme 3). The NOESY spectrum of **9** indicates that the new hydroxy function points to the 8-membered bridge.

Surprisingly, α-oxygenation was observed on treatment of **4** with $LiAlH_4$ at −40 to −20 °C in the presence of air oxygen affording the hydroperoxide **10** and leaving the keto group intact (Scheme 3). The quaternary α-carbon atom of hydroperoxide **10** exhibited a $^{13}C$ NMR chemical shift of $\delta$


(5) Vig, O. P.; Bari, S. S.; Trehan, I. R.; Vig, R. *Indian J. Chem.* **1980**, *19b*, 446–449.
(6) Schöttner, E.; Jones, P. G.; Lindel, T. *Synthesis* **2009**, 3941–3956.
(7) Recent reviews on the use of $SmI_2$ in organic synthesis: (a) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165. (b) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607–637.
(8) Araki, S.; Hatano, M.; Ito, H.; Butsugan, Y. *J. Organomet. Chem.* **1987**, *333*, 329–335.
(9) (a) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. (b) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773–774.
(10) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317–318.
(11) (a) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418–7429. (b) Molander, G. A.; St. Jean, D. J., Jr. *J. Org. Chem.* **2002**, *67*, 3861–3865.
(12) For synthesis of **5** see the Supporting Information.
(13) (a) Molander, G. A.; Koellner, C. *J. Org. Chem.* **2000**, *65*, 8333–8339, and references cited therein. (b) Tamiya, H.; Goto, K.; Matsuda, F. *Org. Lett.* **2004**, *6*, 545–547, and references cited therein.
(14) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186–3192. (b) Saadi, J.; Lentz, D.; Reissig, H.-D. *Org. Lett.* **2009**, *11*, 3334–3337, and references cited therein.
(15) Molander, G. A.; Czakó, B.; Rheam, M. *J. Org. Chem.* **2007**, *72*, 1755–1764.

**Scheme 3.** Formation and Fragmentation of the Bicyclic α-Hydroperoxyketone **10**



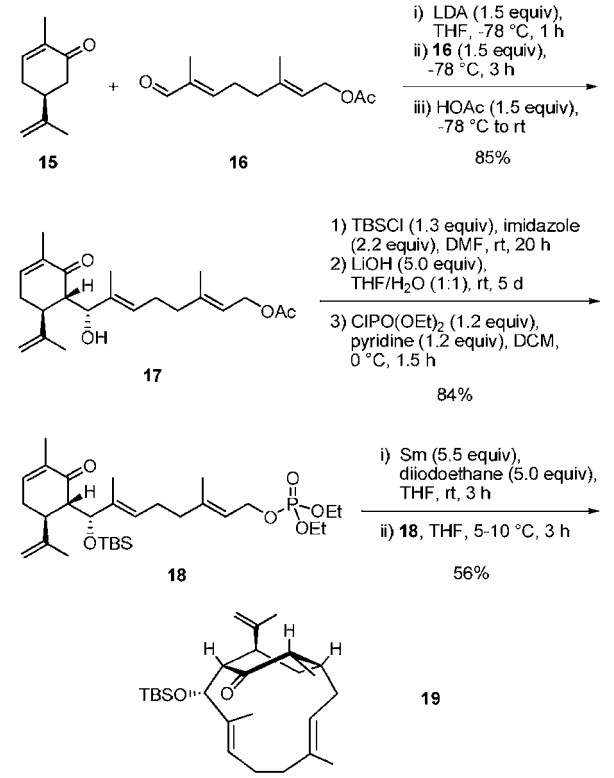

87.8 ppm, whereas the corresponding alcohol, obtained by reduction of **10** with NaI in THF, showed the corresponding signal at $\delta$ 76.2 ppm. To our knowledge, hydroperoxylation of α-positions has never been observed on treatment with $LiAlH_4$/air. Enolates, however, are known to react with molecular oxygen affording the corresponding hydroperoxides, as observed, e.g., by the Reissig[16] and Davies[17] groups.

Apparently, abstraction of the axial proton 12-H becomes faster than the attack of hydride at the keto group. The preferred axial trajectory[18] is blocked by the 8-membered bridge. Prolonged reaction time leads to further reduction of α-hydroperoxide **10** affording the corresponding diol.

When a solution of **10** in $CDCl_3$ was left in the NMR tube for several days, we observed formation of the carboxylic acid **13** as the major product (Scheme 3). It was likely that acid traces were responsible, and we were pleased that on treatment of **10** with HCl−$CCl_4$ complete conversion of **10** afforded **13** in the good yield of 44%. This Hock-type process probably commences with protonation of the hydroxy group (**11**), followed by ring-enlarging acyl migration and loss of water. Carbenium ion **12** would then be attacked by water leading to opening of the 7-membered ring. We also have evidence for the concomitant formation of an ε-lactone by deprotonation of **12**. Ly and Brown observed a similar ring enlargement for cyclohexene-derived allyl hydroperoxides.[19]

Acid **13** contains the 12-membered ring system present in the cubitane-type diterpenoids. Importantly, the isopropyl and acetyl side chains are *cis*-positioned. The acetyl group of **13** was converted to the isopropenyl group by treatment with a 10-fold excess of Wittig reagent affording carboxycubitene derivative **14**.

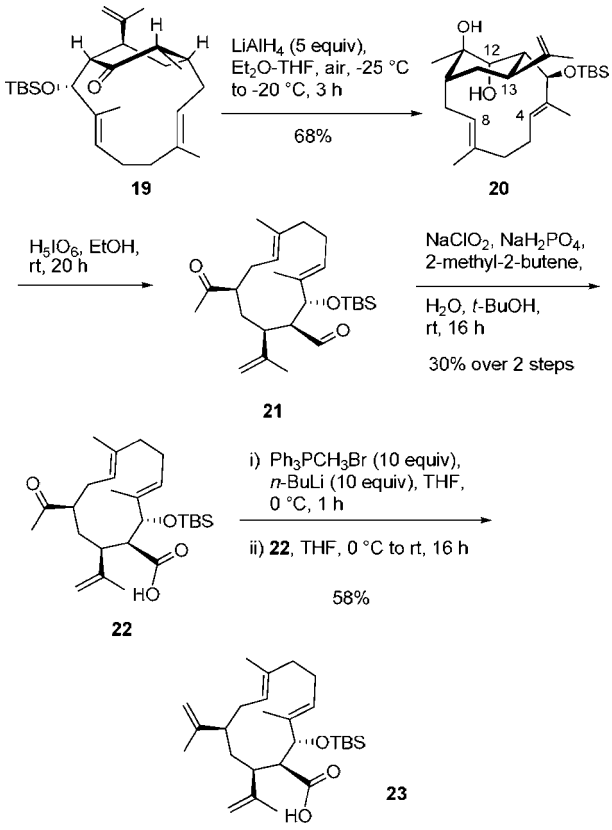
**Scheme 4.** Synthesis of the Isopropenyl-Substituted Bicycle **19**




Toward cubitene (**1**), we had to address the isopropenyl series (Scheme 4). Hydroxyalkylation of (*S*)-carvone with geraniol-derived aldehyde **16**[20] from the sterically less hindered side[21] provided diterpenoid alcohol **17**, which was converted in three steps to the OTBS-protected allyl phosphate **18**. $SmI_2$-induced cyclization afforded [8.2.2]bicycle **19** (40% yield over five steps from carvone). We were able to suppress homodimer formation by slow addition of phosphate **18** to $SmI_2$ at 5 °C.

(16) Reissig, H.-U.; Khan, F. A.; Czerwonka, R.; Dinesh, C. U.; Shaikh, A. L.; Zimmer, R. *Eur. J. Org. Chem.* **2006**, 4419–4428.
(17) Bull, S. D.; Davies, S. G.; Garner, A. C.; O'Shea, M. D.; Savory, E. D.; Snow, E. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2442–2448.
(18) (a) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337–1375. (b) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411–2428.
(19) Sy, L.-K.; Brown, G. D. *Tetrahedron* **2002**, *58*, 897–908.
(20) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.
(21) (a) Chai, Y.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2003**, *5*, 1039–1042. (b) Chai, Y.; McIntosh, M. C. *Tetrahedron Lett.* **2004**, *45*, 3269–3272.

**Scheme 5.** Dihydroxylation and Glycol Cleavage Leading to Carboxycubitene Derivative **23**




On treatment of **19** under conditions identical to **4** with $LiAlH_4$ in the presence of air oxygen, it proved to be more difficult to isolate the hydroperoxide (Scheme 5). Rapid reduction of the hydroperoxide occurred, and the diol **20** became the major product, which could be isolated conveniently. NOESY correlations of the methine proton 13-H with both double bond protons 4-H and 8-H (Scheme 5) indicate that the long bridge is situated below the isopropenyl-substituted small bridge. 12-OH also points toward the long bridge. Analysis of all NOESY correlations (see the Supporting Information) leads to the conclusion that the cyclohexane ring of **20** obtains a chair conformation and that the *trans* diol had been formed.

Since the hydroperoxide could not be isolated, a Hock-type process was not possible. As an alternative, we envisaged glycol cleavage of **20**. We were pleased that treatment of **20** with periodate afforded the rather sensitive aldehyde **21**. To minimize substance loss on chromatography, we immediately oxidized aldehyde **21** to carboxylic acid **22** employing $NaClO_2$/2-methyl-2-butene. Wittig methenylation of the acetyl group afforded carboxycubitene derivative **23** in an enantiospecific manner.

Overall, we have established a highly stereospecific bridge-and-cut approach to the 12-membered ring system of the cubitane diterpenoids. Currently, we are exploring the decarboxylation and deoxygenation of **23**. The carboxyl function will allow further functionalization for studies in chemical biology.

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**Supporting Information Available:** Experimental procedures, characterization data, NMR spectra for all new compounds, and X-ray crystal structure files in the CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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