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An expedient total synthesis of (±)-caparratriene

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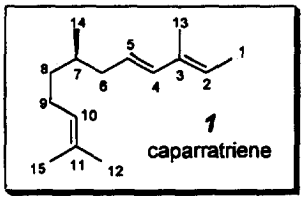
Abstract

(±)-Caparratriene has been synthesized by two succinct routes. The first relies on two Wittig reactions and produces (±)-caparratriene and its 2*Z* isomer as an inseparable 2:1 mixture. The second more efficient synthesis produces only the naturally occurring 2*E* isomer and proceeds in 36% overall yield. The key step in this short synthesis is the Suzuki coupling of *E*-2-bromo-2-butene with the *E*-vinyl borane derived from 4,8-dimethyl-7-nonen-1-yne. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: dienes; Suzuki reactions; terpenes; Wittig reactions.

Caparratriene (**1**) was recently isolated from the oil of *Ocotea caparrapi*, a large tree native to the area surrounding Caparrapi, Colombia.[1] This oil has been used in local remedies to treat a wide variety of ailments, including cancer. Despite its low solubility in aqueous culture media, caparratriene showed remarkable growth inhibition ($IC_{50}=3.0\pm0.5\times10^{-6}$ M) of CEM leukemia cells.[1] Furthermore, the inhibitory activity increased when the cell cultures were exposed to light and air.[1] This observation may suggest that oxidation and/or photochemical processes may be responsible for the observed biological activity. An efficient synthesis of caparratriene (**1**) would allow not only for further study of its anti-leukemia effects but would also facilitate investigation of its oxidation and photochemistry.



1
caparratriene

We sought to devise a concise synthesis of caparratriene (**1**) that was amenable to producing structural analogues in addition to preparing the natural product itself. The first total synthesis of (+)-caparratriene appeared just as we were beginning our study and established that the absolute configuration of the natural product is 7*R*.[2] Thus we chose to continue our work using (±)-citronellal (**2**) as a cost saving measure.

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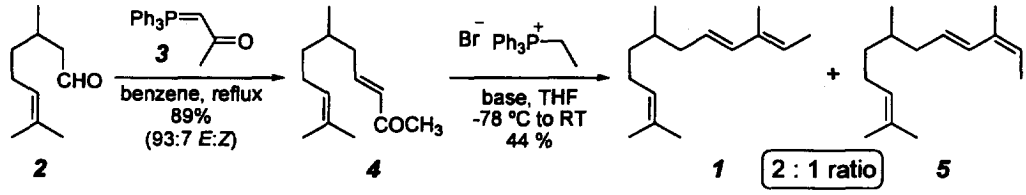
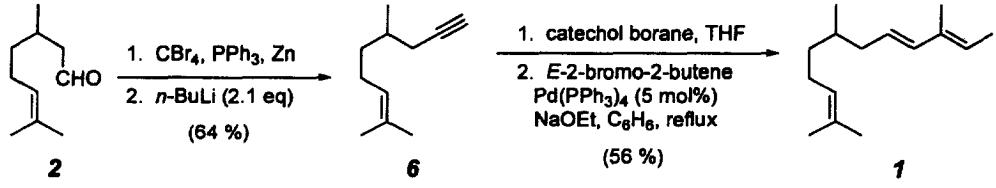
Our first-generation synthesis of caparratriene (**1**) is shown in Scheme 1. A Wittig reaction between citronellal (**2**) and acetylmethylene triphenylphosphorane (**3**) produced *E*-enone **4**[3] in 89% yield. A second Wittig reaction between the ylide formed upon treatment of ethyltriphenylphosphonium bromide with base and enone **4** produced caparratriene (**1**) and its 2*Z* isomer **5** as an inseparable 2:1 mixture in 44% yield. Employing different bases (*n*-BuLi, NaHMDS, KHMDS) in the formation of the ylide did not appreciably change the ratio of **1** and **5** formed in the reaction. Attempts to convert the *Z,E* isomer **5** in the product mixture to the *E,E* isomer **1** via olefin isomerization ($RhCl_3$, I_2) were unsuccessful.[4]



Scheme 1.

Our second-generation synthesis of caparratriene (**1**) produces exclusively the *E,E*-diene and is outlined in Scheme 2. (±)-Citronellal (**2**) was converted to alkyne **6**[5] via Corey–Fuchs homologation in 64% yield for the two steps.[6,7] Treatment of **6** with catecholborane produced the corresponding *E*-vinyl borane in situ. Suzuki coupling of the *E*-vinyl borane with *E*-2-bromo-2-butene produced isomerically pure caparratriene (**1**) in an unoptimized 56% yield after chromatography. The ^1H NMR, ^{13}C NMR, IR and mass spectra of our synthetic caparratriene (**1**) matches that of the natural compound isolated from *Ocotea caparrapi* oil.[8] The synthesis described in Scheme 2 provides gram quantities of caparratriene (**1**) in just three steps and 36% overall yield. The previously published synthesis of (+)-caparratriene (**1**) extends six steps from 3-methyl-2-buten-1-ol in 9% overall yield.



Scheme 2.

In addition to optimizing the synthesis outlined in Scheme 2, current investigations in our laboratory include the preparation of structural analogues of **1** with different substitution patterns on the C2–C3 olefin and the 4*Z* family of isomers using the Suzuki coupling strategy. We are also examining the oxidation and photochemistry of caparratriene and related compounds.

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8. The authors are grateful to Dr. E. Palomino for providing spectra of natural (+)-caparratriene.