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CONFORMATIONAL CONTROL OF ENOLATE GEOMETRY: A SHORT SYNTHESIS OF GERMACRENE-D[Φ]

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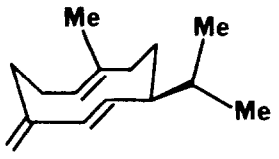
Abstract: A synthesis of (±)-germacrene-D is reported that employs a site- and stereoselective enolization of a conformationally biased ten-membered ring ketone.

Germacrene-D is a ubiquitous plant product[1] that serves as a biogenetic and synthetic precursor to a variety of sesquiterpene families.[2] The recent observation that germacrene-D mimics the action of a sex pheromone of the American cockroach Periplaneta americana[3] has further stimulated interest in this compound and relatives vis-ã-vis structure-activity relationship studies.[4,5] Nevertheless, the synthesis of this material has not heretofore been recorded. In this note a short (seven step) synthesis of racemic



germacrene-D **1**

germacrene-D is described. In conjunction with the previously reported transannular photocyclization reactions of germacrene-D, this method results in eight step syntheses of (±)-β-bourbonene and (±)-mint-sulfide.

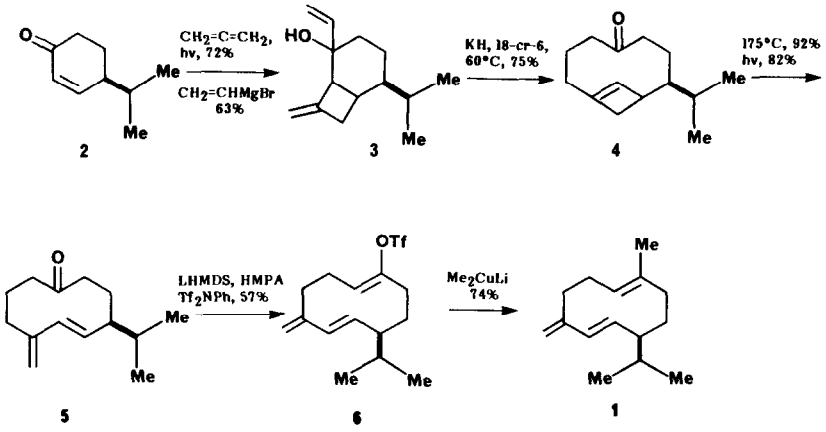
The synthesis of the ten-membered ring ketone **5** from commercially available enone **2** has been reported as part of an investigation that resulted in the synthesis of periplanone-B (Scheme 1).[6] A central feature of that sequence involved the site-selective enolization of **5** and subsequent C-sulfenylative trapping.[7] We have now examined the enolization reaction in greater detail and report conditions that result in trapping of the enolate on oxygen with McMurry's sulfonylating reagent, N-phenyltriflimide.[8]

Our plan to prepare germacrene-D required a site- and stereoselective method to convert the ketone **5** into the E-olefin present in **1**. The positional selectivity we had observed in the enolization-sulfenylation reaction of **5** coupled with the stereospecific nature of organocopper displacement reactions of vinyl triflates[9] encouraged the examination of the McMurry protocol for trisubstituted olefin synthesis.[8,9]

[Φ]Dedicated to our friend and colleague, Professor Harry H. Wasserman, on the occasion of his sixty-fifth birthday.

The results of enolization experiments with **5** and lithium diisopropylamide under a large variety of conditions were uniformly unsatisfactory with regard to the yield of the desired enol triflate. Our earlier studies provided the expectation that lithium hexamethyldisilazide would be required for high positional selectivity in the enolization reaction.[6b] The greater kinetic selectivity observed with this latter reagent is not surprising when the considerable difference in acidity of the corresponding amines is taken into account (iPr_2NH: pKa (THF) = 33.1, $(Me_3Si)_2NH$: pKa (THF) = 24.7).[10] Optimal results for the conversion of **5** into the Z-enol triflate **6** were obtained via the dropwise addition of **5** to a solution of LHMDS (2 eq) in THF at -78°C. The mixture was allowed to stir for thirty minutes whereupon HMPA (3 eq) was added. After ten minutes N-phenyltriflimide (1.5 eq) in THF was added, and stirring was continued for 1 hour. The reaction mixture was quenched with saturated ammonium chloride and subjected to a standard

Scheme 1

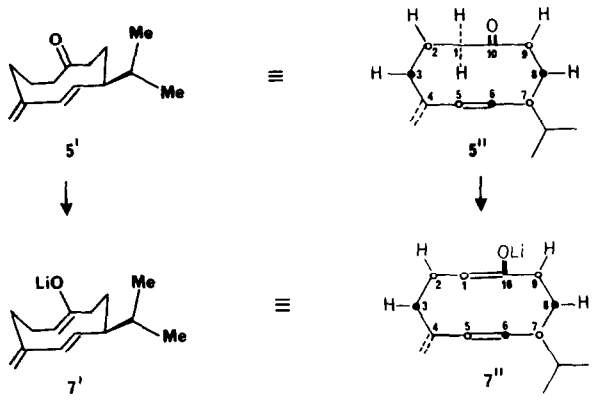


workup procedure. After purification by flash chromatography[11] the labile Z-enol triflate **6** (contaminated with 10% of an isomeric enol triflate) was isolated in 57% yield. These conditions resulted in the exclusive sulfonylation on oxygen; in the absence of HMPA the ratio of oxygen/carbon sulfonylated products was 8/5. In situ trapping of the enolate[12,13] by the addition of **5** to a mixture of LHMDS, HMPA, and N-phenyltriflimide resulted in the isolation of a 10:1 mixture of oxygen/carbon sulfonylated products in comparable yield. The oxygen triflates isolated from this reaction are produced in the same 10:1 ratio (major enol triflate = **6**). The stereochemical assignment of enol triflate **6** was made on the basis of its conversion to germacrene-D upon reaction with lithium dimethylcuprate according to the McMurry procedure.[9] The 10:1 mixture of enol triflates was converted to a 10:1 mixture of germacrene-D and an inseparable isomer. The identity of synthetic germacrene-D was confirmed by comparison of the spectral data (high field ^1H NMR, MS, and IR) of a sample of natural germacrene-D provided by Dr. B. Maurer of Firmenich. Interestingly, the minor component present in our synthetic material appears to be identical with a contaminant present to the same extent (ca. 10%) in the natural material.[14]

The site- and stereoselectivity in the enolization reaction can be rationalized by taking into account the conformational properties of the ketone **5**. The expected boat-chair-chair (BCC) conformation **5'** (**5"**)

depicted in Scheme 2 is in accord with the results of COSY 2D NMR and NOE difference experiments.[15] Enolization of **5** could afford four possible enolate isomers. The formation of enolate **7** with LHMDS can be explained by the peripheral[16] deprotonation of the hydrogen at C_1 (germacrane numbering). Enolization at this carbon results in the formation of a 1,6-cyclodecadiene and is expected to be favored over enolization at the corner carbon, C_9. Consider the dihedral angle of the four carbons that will become the vinylic and allylic carbons of the enolate products. The C_2-C_1-C_{10}-C_9 local conformer contains a dihedral angle of

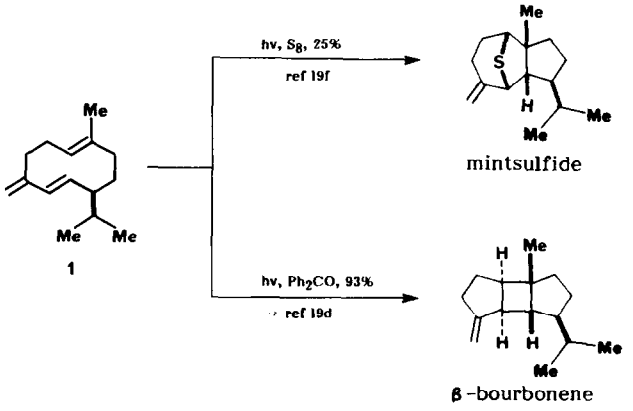
Scheme 2



180° (anti) in both **5** and **7**. The alternative four carbon fragment (C_1-C_{10}-C_9-C_8) in **5** exhibits a dihedral angle of 120° (skew). In the transition state for enolization at C_9, major conformational reorganization must occur with a concommitant increase in strain energy, in order to avoid the formation of a nonplanar enolate.[17,18]

In addition to its role as a biogenetic precursor, germacrene-D has been shown to be a valuable abiological intermediate in the synthesis of a number of classes of sesquiterpenes.[19] Two of these reaction processes were carried out with synthetic germacrene D and are shown in Scheme 3. The irradiation of germacrene-D in the presence of elemental sulfur results in the first total synthesis of racemic mintsulfide,[19f,20] a

Scheme 3



constituent of peppermint oil. Irradiation of **1** in the presence of benzophenone (sensitizer) affords β-bourbonene.[19d,21] These examples illustrate the ability of a single stereocenter on a medium ring to influence the

outcome of transannular cyclization reactions via remote asymmetric induction, and suggest strategies for the synthesis of other important compounds.

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