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A BIOMIMETIC CHEMICAL SYNTHESIS OF HUMULENE FROM FARNESOL

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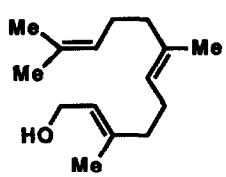
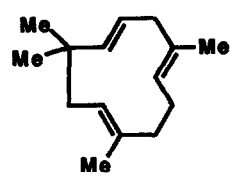
Summary: *The first synthesis of humulene (1) by a biomimetic cation-olefin cyclization route is reported.*

Although several syntheses of the structurally interesting cyclic triene humulene (**1**) have been developed,[1] the direct formation of this sesquiterpene from its biogenetic precursor *E,E*-farnesol has never been reported despite the ready availability of farnesol and the extensive studies of its chemistry. Indeed, it is clear from the literature on farnesyl halides, sulfonates etc. that reactions such as nucleophilic displacement, 1,4-elimination, *E*⇄*Z* isomerization of the 2,3-double bond, and irreversible closure of the 2,3-*Z*-cation to six-membered cyclic products are highly favored pathways relative to closure to 10- or 11-membered cyclic structures. There is obviously an unfavorable entropy factor for the farnesyl cation–humulene closure because of the fact that the former is highly flexible and the latter, or more precisely the transition state leading to the latter, is not. The size of this unfavorable activation entropy factor is not known, but is easy to estimate very roughly. Since there are six rotatable single bonds on the atom path between the allylic cation at one end of the cyclizing molecule and the double bond at the other, the loss in entropy during closure would be R ln 3^6 assuming three-fold barriers for rotation about each single bond, i.e. 6.6 eu, equivalent to *ca.* 4 kcal/mole in free energy at 300 °K. If even greater flexibility is assumed for the farnesyl cation, the entropy factor disfavoring cyclization would be correspondingly greater. Although, at first sight, these entropic factors seem to be of modest size, it must be remembered that the reaction pathways from the farnesyl cation (F^+) which compete with cyclization have very low $\Delta\Delta G^{\neq}$ values. For example ion pair collapse, $F^+ + X^- \rightarrow$ 3° F-X, which forms a



Farnesol



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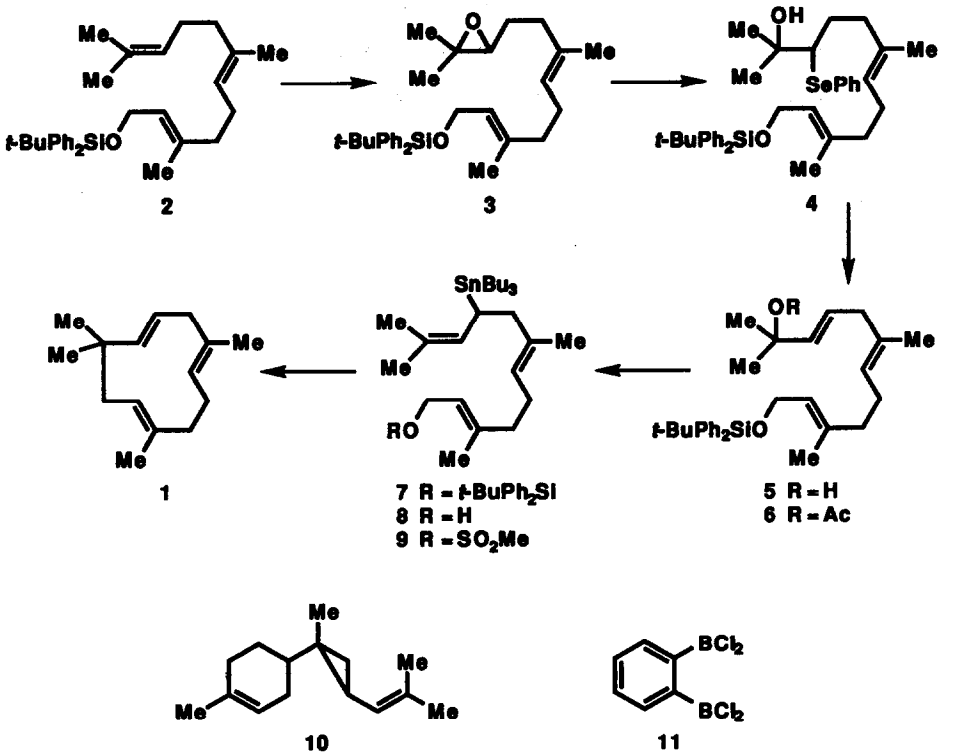
reactive tertiary farnesyl-X derivative with loss of *E*-olefinic geometry, may have a minuscule $\Delta\Delta G^{\neq}$. Therefore, an entropy factor of 6 - 12 eu superimposed on other activation terms for the cation–olefin cyclization to form humulene looms very large indeed. Of course, the ring closure of the *E,E*-farnesyl cation to form humulene is also disfavored enthalpically because of its anti-Markovnikov nature.

The enzyme-catalyzed synthesis of humulene, which probably involves the pyrophosphate of *E,E*-farnesol,[2] is thought to function effectively because the substrate is held by the enzyme in a conformation which brings the pyrophosphate-bearing methylene group in close proximity to the 11,12-double bond at the other end of the molecule. It is not known whether the ring closure occurs via such a correctly folded farnesyl cation which rapidly is channeled to humulene with no entropy problem or via an internal S_N2 pathway with the 11,12-π-bond as the nucleophilic component, but in either case precise enzyme-substrate binding is crucial. The nature of the enzymic binding site which enforces the required conformation on farnesyl pyrophosphate is completely obscure.[2]

This paper addresses the question of whether it is possible to overcome the entropic barrier of the farnesyl → humulene cyclization in a chemical system. There are in principal two different experimental approaches: (1) lower the entropic barrier by the use of a reagent (chemzyme) which both activates the leaving group and enforces the required conformation on the substrate and (2) lower the enthalpic barrier to cyclization sufficiently so that the cyclization reaction to form humulene occurs despite the unfavorable entropy factor. The second strategy was selected for our initial studies. Specifically, the 10,11-double bond of farnesol was activated by the introduction of an allylic tributylstannyl substituent and the hydroxyl group was activated as the mesylate ester. Cyclization to humulene (**1**) could then be effected as summarized below.

The *tert*-butyldiphenylsilyl ether[3] of farnesol (**2**) was converted to the 10,11-epoxide **3** by the sequence: (1) reaction with 1.1 equiv of *N*-bromosuccinimide in 4 : 1 THF–H_2O at 10 °C initially and at 23 °C for 2 h to give after chromatography on silica gel (sg) the 10,11-monobromohydrin (69%) and (2) oxirane ring closure with 2 equiv of K_2CO_3 in CH_3OH at 23 °C for 2 h (84%).[4] Treatment of **3** with a mixture of diphenyldiselenide (0.7 mole equiv) and excess sodium borohydride (to generate $C_6H_5Se^-$) in ethanol at reflux for 2 h gave selenoether **4** (90%, as a colorless oil after sg chromatography) which was converted in 80% yield to the *E,E,E*-allylic alcohol **5** by reaction with excess H_2O_2 and pyridine (2 equiv) in 85 : 15 CH_2Cl_2–THF at 0 °C initially and then at 23 °C for 6 h and subsequent sg chromatography.

Acetylation of alcohol **5** (3 equiv of Ac_2O, and 5 mole % of 4-*N,N*-dimethylaminopyridine in triethylamine at 60 °C for 12 h) gave the corresponding acetate (**6**, 87%) which was treated with a reagent



prepared from 5 equiv of tri-*n*-butyltinlithium (from reaction of tri-*n*-butyltin hydride and lithium diisopropylamide in THF) and 2.5 equiv of cuprous cyanide in dry THF at -78 °C for 8 h to give 90% of the allylic stannane **7**. Conversion of silyl ether **7** to the corresponding alcohol **8** was effected in 97% yield by reaction with tetra-*n*-butylammonium fluoride hydrate (3 equiv, Aldrich Co., 98%) in THF at 23 °C for 1.5 h.

For the cyclization, alcohol **8** was converted to the corresponding mesylate (**9**) by reaction with methanesulfonyl chloride (1.2 equiv) and triethylamine (1.3 equiv) in dry pentane at 0 °C for 35 min, filtration, and rapid concentration *in vacuo* below 0 °C. Since the neat mesylate is quite unstable even at 0 °C, not all of the solvent was removed and the product was immediately cooled to -78 °C diluted with CH_2Cl_2 and used as soon as possible. A solution of mesylate **9** in CH_2Cl_2 at -78 °C was treated dropwise with a solution of dimethylaluminum chloride in toluene (1.1 equiv) and the mixture was stirred at -78 °C for 2 h, quenched with Et_3N followed by sat. aq. $NaHCO_3$ solution, and subjected to extractive isolation (pentane). Sg column chromatography using pentane for elution afforded humulene (37%) which was identified unambiguously by comparison with an authentic sample (IR, MS, 500 MHz ^1H NMR, ^{13}C NMR, and gas chromatography).[5] The major byproducts of the cationic cyclization to form humulene were found to be the *E,E* chloride corresponding

to **8** and a mixture of bisaboline-type products corresponding to **10** which probably arise by loss of 2,3-*E* geometry and subsequent cation-olefin cyclization. Both chloride formation and 2,3-*E* isomerization may result from collapse of the initially formed ion-pair F^+ $Me_2AlClOSO_2Me^-$.

A number of other Lewis acids (LA) were investigated in an attempt to improve the yield of humulene by decreasing the probability of collapse and return from an initial ion pair *E,E* - F^+ $LAOSO_2Me^-$. The Lewis acids $Bu_3SnOSO_2CF_3$ and $LiClO_4$ favored the formation of **10**. Use of $TiCl_4$ or Me_2AlBr in CH_2Cl_2 favored formation of primary halide by mesylate–halide exchange. Liquid SO_2 or CF_2Cl_2 as solvent did not promote cyclization to humulene.

Since ion-pair collapse of the intermediate ion-pair F^+ $LAOSO_2Me^-$ seemed to be the major reason for inefficiency in the cyclization, the use of the known bidentate Lewis acid **11**[6] was investigated. Unfortunately, the major product formed from **11** and mesylate **9** in CH_2Cl_2 at -78 °C was the chloride corresponding to **8**. We were unsuccessful in attempts to prepare the tetrafluoro analog of **11**.

In summary, it has been demonstrated that the activation of the distal bond in farnesyl mesylate by the introduction of an allylic tributyltin substituent lowers the activation energy for the cyclization to form humulene sufficiently to overcome the entropic disadvantage of this cyclization. Also, mesylate is a useful leaving group in conjunction with Lewis-acid acceleration of cation formation. One key to the further improvement in the cyclization **9** → **1** may be the design and synthesis of a Lewis acid which does not allow rapid return or collapse of the initially formed ion pair F^+ $LAOSO_2Me^-$.[7]

References and Notes

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2. See Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089.
3. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975; **1977**, *55*, 562.
4. Satisfactory spectroscopic data were obtained for each compound reported herein.
5. The following spectral data were obtained for synthetic and natural humulene: FTIR (film, cm^{-1}) 2956, 2925, 2866, 2853, 1684, 1446, 1384, 1362, 1210, 1176, 966 and 822; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.57 (dt, *J* = 15.9, 7.4 Hz, 1H), 5.14 (d, *J* = 15.9 Hz, 1H), 4.93 (br t, *J* = 6.3 Hz, 1H), 4.85 (br t, *J* = 7.5 Hz, 1H), 2.49 (d, *J* = 7.4 Hz, 2H), 2.05 - 2.11 (m, 4H), 1.89 (d, *J* = 7.5 Hz, 2H), 1.62 (s, 3H), 1.41 (s, 3H), 1.04 (s, 6H); ^{13}C ($CDCl_3$, 100 MHz) δ 141.0, 139.2, 133.2, 127.7, 125.8, 125.0, 42.0, 40.4, 39.7, 37.3, 23.3, 17.9, 15.1; EIMS: 204 $[M]^+$; HRMS: calcd. for $[C_{15}H_{24}]^+$: 204.1878; found: 204.1880.
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