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STUDIES ON THE MECHANISM OF SESQUITERPENE BIOSYNTHESIS
HUMULENE-GERMACRENE REARRANGEMENT

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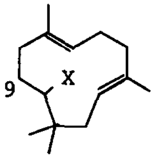
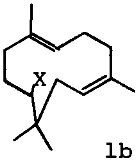
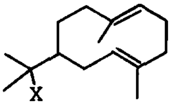
Cations 1a, 1b, 2a, and 2b are presumed to be the key intermediates in the enzymic cyclization of farnesyl pyrophosphate and the starting points for the intricate series of cyclization and rearrangement steps which lead to a variety of polycyclic sesquiterpenes.[1] Despite considerable speculation,[2] there still remains a remarkable lack of knowledge concerning the precise identity of the cyclizing precursors and the intimate nature of their transformations. By comparing enzymic and nonenzymic reactivity of these cations (or their functional equivalents), it becomes possible to identify qualitatively the role of enzymes in directing unusual synthetic behavior. We outline here the first nonenzymic generation of cations 1a and 1b and disclose several unprecedented results.



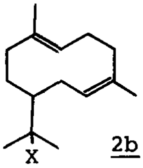
1a



1b



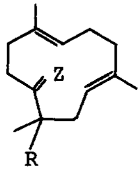
2a

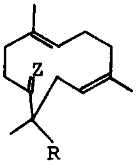


2b

X = + or its functional equivalent

The keto-ester 3a, readily available by a previously reported process,[3] was transformed by lithium aluminum hydride in ether followed by tosyl chloride (1.5 equiv) into the mono-tosylate 4a (90%),[3] and this gave upon reaction with excess lithium aluminum hydride in ether at 0°C for 0.5 h and 25 °C for 1 h the desired alcohol 5a (89%) as colorless needles, mp 88-9 °C.[4,5] Reaction of the alcohol 5a with 10 equiv of methanesulfonyl chloride and 15 equiv of triethylamine in methylene chloride at -20 °C for 15 min[6] afforded the unstable mesylate 6a[7] in quantitative yield after chromatography on silica gel (ether-hexane). The stereoisomeric mesylate 6b was obtained (62% over-all yield) from the *Z*,*E*-isomer 3b by a similar sequence.[8]



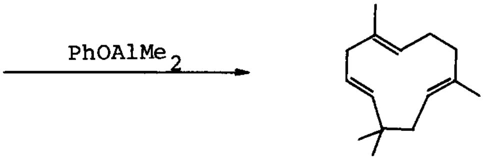


3a, Z = O; R = COOMe
4a, Z = H, OH; R = CH_2OTs
5a, Z = H, OH; R = CH_3
6a, Z = H, OMes; R = CH_3

3b, Z = O; R = COOMe
5b, Z = H, OH; R = CH_3
6b, Z = H, OMes; R = CH_3

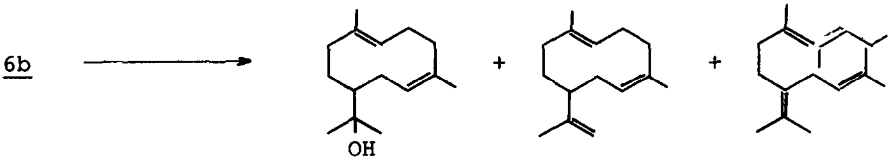
Humulene (7) was formed as a principal product (70%) together with a mixture of several hydrocarbons when the mesylate 6a stood in aqueous acetone at room temperature for several days. More selectively, treatment of 6a in hexane with excess dimethylaluminum phenoxide[9] at -78 °C for 20 min and 25 °C for 18 h produced humulene (7) almost exclusively (> 97% pure, 83% yield). The E configuration of the newly developed olefinic linkage was confirmed by its pmr spectrum ($J_{C(9)H-C(10)H}$= 16 Hz) as well as chromatographic comparison (SiO_2 and SiO_2-$AgNO_3$) with an authentic sample of natural humulene.[3]

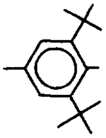
6a



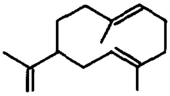
7 (83%)

A total alteration in the course of reaction occurs when a solution of the Z,E-isomer 6b in aqueous acetone stands at room temperature for 4 days. The major product 8 (33% yield)[10] and two minor compounds 9 (14% yield)[11] and 10 (4% yield)[12] were isolated by column chromatography. Subjection of 6b to the action of dimethylaluminum phenoxide[9] in hexane at -78 °C for 20 min and 25 °C for 3.5 h results in formation of the germacrene 9 as the major product (43% yield) and 10 as the minor component (15% yield). It appeared to us that the use of an aluminum reagent of sufficient steric bulk might produce the germacrene 9 as a sole product if the proton abstraction was due to the organic component of the aluminum reagent. Using diisobutylaluminum 2,6-di-tert-butyl-4-methylphenoxide (11),[13] readily prepared from the corresponding phenol and diisobutylaluminum hydride (at -78 °C for 10 min and 25 °C for 30 min), in methylene chloride at -78 °C for 10 min and 0 °C for 5 min, the mesylate 6b was converted into the germacrene 9 almost exclusively (86% yield and > 99% pure).



	8	9	10
aq. acetone	33%	14%	4%
PhOAlMe$_2$	---	43%	15%
 OAlBu$_2$	---	86%	---

As a measure of the efficacy of this bulky reagent in producing the germacrene structure, the mesylate 6a was treated with excess 11 in methylene chloride at -78 °C for 15 min and 0 °C for 15 min to furnish a mixture of hydrocarbons (14% yield).[14] In addition to humulene (7, 63% of this fraction), (±)-germacrene A (12, 37%)[15] was formed and isolated essentially pure by pre-cooled (below 0 °C) column chromatography on silica gel (hexane). This racemic material had spectroscopic properties identical with those reported for the naturally occurring germacrene A.[15]



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These results not only constitute total synthesis of medium ring sesquiterpenes 7 and 12, but also present a number of interesting aspects of the nature of cations 1a and 1b. (1) In regard to formation of the 2E,6E,9E-cycloundecatriene system of humulene (7), it appears that the biochemical elimination from 1a is strongly based on organic chemical foundations and that no uncommon enzymic assistance may be needed to realize stereospecific elimination of a proton at C-9. (2) The facile ring contraction of 6b is noteworthy since the cation 2b provides a reasonable entry into the cadalene group, including cadinene, bulgarene, muurolene, and amorphene.[1f] (3) The function of the enzymes in the synthesis of caryophyllene, which is believed, although by no means proved, to be derived from the cation 1b,[1,3] would appear to be the prevention of the thermodynamically favored ring-contraction and the preservation of its conformation until the final ring-closure.[1b]

References and Notes

(1) For general reviews: (a) G. A. Cordell, Chem. Rev., 76, 425 (1976); (b) T. Money, in "Progress in Organic Chemistry," S. W. Carruthers and J. K. Sutherland ed., Vol. 8, Chapter 2, Butterworth, London, 1973; (c) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compds.," Vol. II,

Academic Press, New York, N.Y., 1972; (d) A. A. Newman ed., "Chemistry of Terpenes and Terpenoids," Academic Press, New York, N. Y., 1972; (e) W. Parker and J. S. Roberts, *Quart. Rev.*, **21**, 331 (1967); (f) D. Arigoni, *Pure and Appl. Chem.*, **41**, 219 (1975).

(2) (a) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959); (b) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," W. A. Benjamine, Inc., New York, N. Y., 1964.

(3) Y. Kitagawa, A. Itoh, S. Hashimoto, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 3865 (1977).

(4) The alcohol **5a** had recently been derived from natural humulene: A. Sattar, J. Forrester, M. Moir, J. S. Roberts and W. Parker, *Tetrahedron Lett.*, 1403 (1976).

(5) Pmr ($CDCl_3$) δ 0.85 (s, 3H), 1.08 (s, 3H), 1.43 (s, 3H), 1.58 (s, 3H), 3.52 (t, *J* = 4 Hz, 1H); ir (nujol) 3290 cm^{-1}; mass *m/e* 222 (M^+).

(6) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

(7) Pmr ($CDCl_3$) δ 0.94 (s, 3H), 1.15 (s, 3H), 1.46 (s, 3H), 1.58 (s, 3H), 3.71 (bt, *J* = 6 Hz, 1H).

(8) **5b**: Pmr ($CDCl_3$) δ 0.82 (s, 3H), 1.05 (s, 3H), 1.61 (s, 3H), 1.66 (s, 3H), 3.37 (dd, *J* = 4.5 and 7 Hz, 1H); ir (liquid film) 3327 cm^{-1}; mass *m/e* 222 (M^+). **6b**: Pmr ($CDCl_3$) δ 0.89 (s, 3H), 1.12 (s, 3H), 1.69 (s, 3H), 1.73 (s, 3H), 4.59 (bt, *J* = 3.5 Hz, 1H).

(9) Y. Kitagawa, S. Hashimoto, S. Iemura, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **98**, 5030 (1976).

(10) Identical in all respects with the reported spectral data: M. Kodama, Y. Matsuki, and S. Ito, *Tetrahedron Lett.*, 1121 (1976).

(11) Pmr ($CDCl_3$) δ 1.69 (bs, 9H, $C=CCH_3$), 4.61 (bs, 2H, $C=CH_2$), 5.05-5.36 (m, 2H); ir (liquid film) 1647, 887, 818 cm^{-1}; mass *m/e* 204 (M^+).

(12) Pmr ($CDCl_3$) δ 1.53 (s, 3H), 1.69 (s, 9H), 2.65 (bd, *J* = 8.5 Hz, 2H, $C=CCH_2C=C$), 5.08-5.43 (m, 2H).

(13) This bulky organoaluminum compound was found to be exceedingly efficient reagent for the transformation of neryl phosphate ester to limonene with high selectivity: unpublished result of A. Itoh, Y. Kitagawa, A. Yasuda, H. Yamamoto, and H. Nozaki.

(14) In this specific case, the major product was a mixture of polar materials which remained still unidentified. The low yield of this process may also be due to the extreme thermal instability of germacrene A in our reaction systems.

(15) A. I. Weinheimer, W. W. Youngblood, P. H. Washecheck, T. K. B. Karns. and L. S. Ciereszko, *Tetrahedron Lett.*, 497 (1970); see also, W. S. Bowers, C. Nishino, M. E. Montgomery, L. R. Nault, and M. W. Nielson, *Science*, **196**, 680 (1977); C. Nishino, W. S. Bowers, M. E. Montgomery, L. R. Nault, and M. W. Nielson, *J. Chem. Ecol.*, **3**, 349 (1977).

(16) We thank Professor S. Ito for the identification of the alcohol **8**.