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CHEMICAL SIMULATION OF THE BIOGENESIS OF CEDRENE

N. H. Andersen and D. D. Syrdal*

Department of Chemistry, University of Washington, Seattle, Washington 98195

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Recently there has been an increased effort at providing chemical analogies for various stages of purported sesquiterpene biogeneses. Illustrating this with the proposed biogenesis of the tricyclic compounds cedrene[1,2] and zizaene,[2,3]

(alaskadiene) ⟶ cedrene
nerolidol ⟶ monocyclic ⟶ spirane tricyclics
(or farnesol) (bisabolatrienes)
(acoradiene) ⟶ ⟶ zizaene

it is well established that nerolidol and farnesol afford bisabolenes on acid-treatment[4] and that the appropriate spiranes (such as α-alaskene,[2] "α-acoradiene" and "α-acorenol"[5]) afford natural α-cedrene in high yield. Thus the demonstration of an efficient (bisabolene ⟶ spirane)-cyclization would constitute a total synthesis of cedrene that parallels the proposed biogenesis so closely that it could be considered an example of chemical simulation of biogenesis. The recent report of Ohta and Hirose[6] concerning the occurrence of cedrenes in the complex product mixture resulting from BF$_3$ treatment of farnesol prompts us to report a portion of our work in this area. With nerolidol (rather than farnesol) cyclization can be effected with high selectivity under mild conditions resulting in an efficient (25% yield) synthesis of α-cedrene. Using optically active nerolidol, the optical activity (or lack of it) of various products allows us to define the mechanism of the chemical transformation in some detail and to contrast it to the likely in vivo process.

Asymmetric Induction in the Cyclization of (+)-Nerolidol

As shown in the table, we find that (+)-nerolidol and its derivatives cyclize producing predominantly (-)-bisabolenes under a variety of conditions as might be predicted from the analogous monoterpene cyclization.[7,8] A similar concerted process would be expected to produce enantiomers of the natural germacrenes and we therefore propose that (-)-nerolidol is a most attractive precursor for the majority of natural sesquiterpenes (vide infra).[9]

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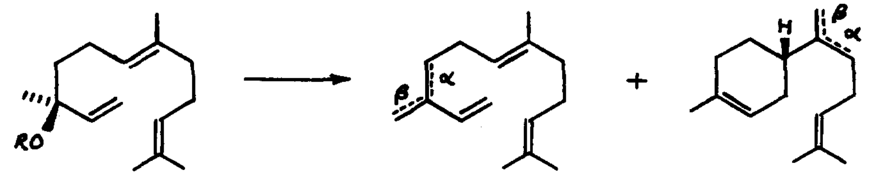
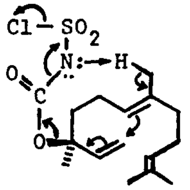
* National Science Foundation Predoctoral Fellow, 1968-1971



(+)-nerolidol (R=H)[8] farnesenes bisabolenes[8]

R	conditions	yield	%-farnesenes	%-bisabolenes	optical purity (-)-β-bisabolene
H	HCO_2H/nC_5H_{12} 25°[10]	>80%	10	35β, 26α	>31%
H	$AlCl_3/Et_2O$ 25°	N.D.	40	25β, 27α	>18%
$CH_3(Cl)CHCO$	200° [10]	N.D.	64	19β, 15α	>22%
CH_3SO_2	C_5H_{12} 25°	>60%	30	25β, 20α	>12%
PO_3H_2	1N H_2SO_4/C_5H_{12}[10]	>85%	< 5	80β, 6α	>11%
Li	$ClSO_2NCO/Et_2O$	>60%	30	29β, 14α	>37%

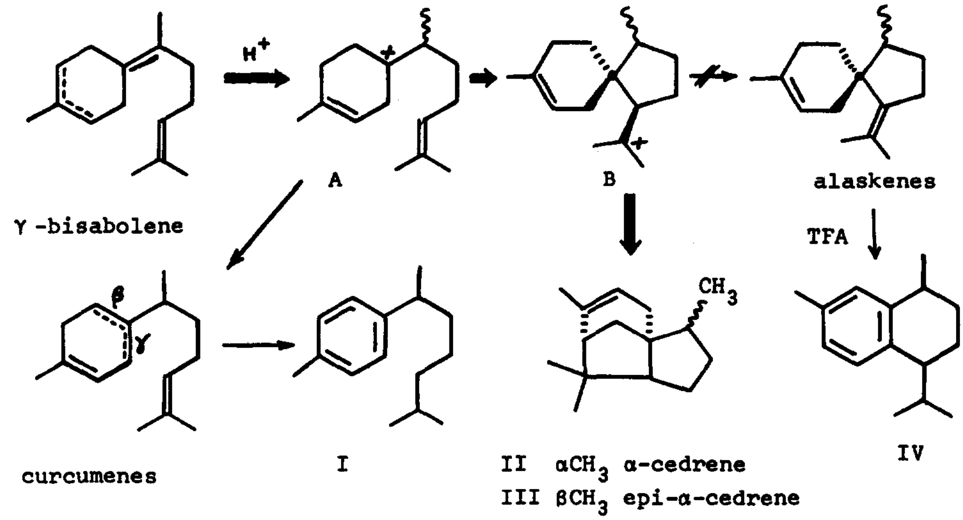
The reaction of the lithium salt of nerolidol with $ClSO_2NCO$ deserves some discussion since it has produced the highest degree of asymmetric induction. The addition product can be isolated and has been demonstrated to decompose according to the stoichiometry below. A concerted process is an attractive rationale for the substantial optical activity observed in the product.



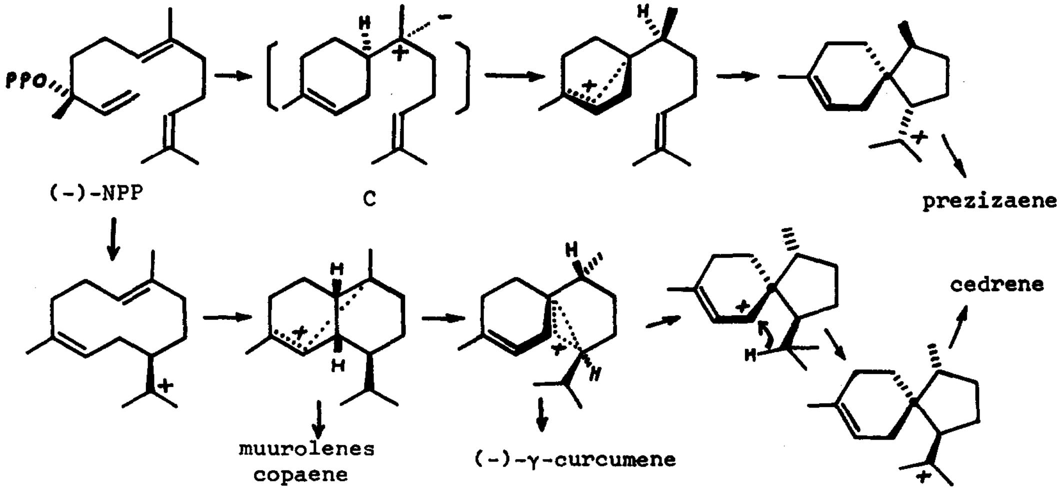
$\longrightarrow$ alkenes + CO_2 + Cl^- + $[SO_2NH \longrightarrow (SO_2NH)_3]$

The Further Cyclization of β-Bisabolene

Since β-bisabolene was available from nerolidol, its reaction under more vigorous conditions was studied. On warming in formic acid or very brief (<20 sec.@ 25°C) exposure to CF_3CO_2H, γ-bisabolene was obtained. Further reaction in formic acid (@ 80°) produced an exceedingly complex mixture of products which could be demonstrated to contain ca 5% each of racemic α-cedrene (II) and epi-α-cedrene (III). A similar mixture is obtained from β-curcumene under these conditions. However when a pentane solution of β-bisabolene is stirred with CF_3CO_2H, the γ-bisabolene produced cyclizes cleanly producing an olefin mixture in nearly quantitative yield. This mixture is composed of I, α-cedrene (II), and epi-α-cedrene (III) - 20, 30, and 25% respectively - and completes a two stage synthesis of cedrene from nerolidol. Furthermore the known behavior of curcumenes (→I) and spiradienes such as the alaskenes (→IV) under these conditions[11] demonstrates that ion A proceeds to the cedrene via ion B without intermediate deprotonation.



A one-pot synthesis of α-cedrene can be accomplished by treating a pentane solution of nerolidol first with formic acid and then CF_3CO_2H. In this way α-cedrene can be produced in 20% yield in less than two hours. This synthesis, as the previous one, produces racemic cedrene and raises the question of the in vivo pathway that produces optically active α-cedrene without producing epi-α-cedrene.[12] A hypothetical pathway which can be tested by feeding studies and hopefully simulated chemically is presented below:



The key feature is that acoranes (and acorane-derived tricyclics such as prezizaene, etc.) and alaskanes (and cedrene) arise via two distinct cyclizations of (-)-NPP, with stereochemical integrity due to assisted hydride shifts. Ion C represents an asymmetrically solvated or bound (+)-bisabolyl ion or bisabalol. The predicted[14] fragmentation of muurolenes to (-)-curcumenes which is incorporated in the scheme has now been chemically confirmed in our laboratory.

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4. C. D. Gutsche, J. R. Maycock and C. T. Chang, *Tetrahedron*, **24**, 859 (1968) and references therein.
5. B. Tomita and Y. Hirose, *Tetrahedron Letters*, 143 (1970).
6. Y. Ohta and Y. Hirose, *Chemistry Letters*, 263 (1972).
7. The cyclization of (-)-R-linaloyl phosphate in aqueous mineral acid produces (+)-α-terpineol of 40% optical purity - see W. Rittersdorf and F. Cramer, *Tetrahedron*, **24**, 43 (1968).
8. The assignment of absolute stereochemistry to all natural substances described herein may be found in the Ph.D. thesis of D.D.S. (University of Washington, 1971).
9. Nerolidol from plant sources is always found to be dextrorotatory (often weakly so), however this would not be the first case of natural accumulation of the non-metabolized enantiomer of an important precursor in plants.
10. Farnesene and β-bisabolene are essentially inert to these reaction conditions.
11. N. H. Andersen, D. D. Syrdal, and C. Graham, *Tetrahedron Letters*, **903** (1972).
12. Epi-α-cedrene has not been reported as a naturally occurring substance and our own search for it in conifer oils has been fruitless. It has however been prepared previously[2,13] and there is no question concerning the structure assignment.
13. E. Demole, P. Enggist and Mlle. C. Borer, *Helv. Chim. Acta.*, **54**, 1845 (1971).
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