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BIOMIMETIC ENTRY TO ACYCLIC TERPENE SYNTHESIS
A NOVEL REARRANGEMENT OF ALLYL ETHER CATALYZED BY ORGANOALUMINUM REAGENTS

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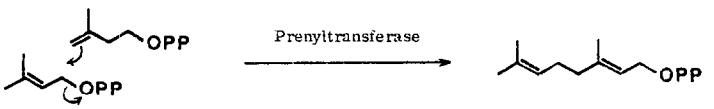
Summary: The intramolecular prenyltransfer reaction is accomplished by the rearrangement of allyl ethers with (2,6-di-tert-butyl-4-methylphenoxy)methylaluminum trifluoromethanesulfonate. The present method provides a simple and highly efficient synthesis of lavandulol.

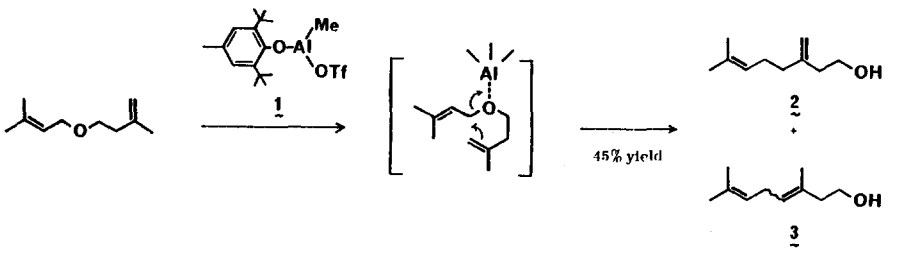
Acyclic terpenes are built in vivo by successive head-to-tail condensation between isopentenyl pyrophosphate and an allylic pyrophosphate catalysed by prenyltransferase.[2] The sequence is envisioned as preceeding by an ionization of the carbon-oxygen bond of the allylic pyrophosphate to create a cationic center which then attacks a molecule of isopentenyl pyrophosphate (eq. 1). Such reaction is typical of the sequential five-carbon polymerizations which constitute the major building steps in terpene metabolism.



(1)

Although much interest has been focused on the search for a mechanistic rationale for this prenyltransfer reaction,[3] little parallel exists in organic chemistry for such processes. Several pertinent chemical analoges have appeared recently for formation of C_{10}, C_{15}, and C_{20} units by the uncontrolled polymerization of isoprene units,[4] but there remains a gap in the development of a biogenetic-type synthesis embodying control of the head-to-tail condensation. Herein we wish to report the intramolecular version of the prenyltransfer reaction catalyzed by organoaluminum reagents to furnish the higher multiple of the basic five-carbon unit.

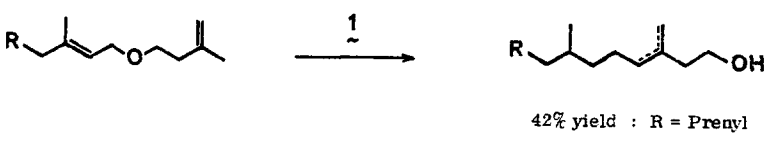
When isopentenyl prenyl ether was treated with (2,6-di-tert-butyl-4-methylphenoxy)methylaluminum trifluoromethanesulfonate (1) in methylene chloride at 25°C, a mixture of the expected C_{10} alcohols was obtained in 45% yield in addition to the only carbon-oxygen bond cleavage product, isopentenyl alcohol. The C_{10} alcohols were separated by preparative GLC and characterized by ^{1}H NMR to be 2 and 3 in a ratio of 1:3. The spectral data (^{1}H NMR, IR, and Mass) of 2 were identical with those of the authentic sample prepared by the literature procedure.[5]



(2)

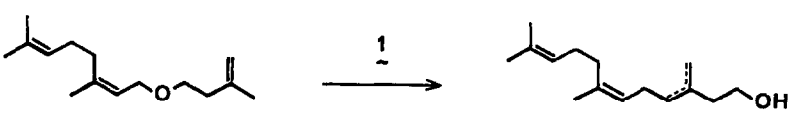
The choice of catalyst is most crucial for the present reaction. For example, the common strong Lewis acids ($TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, etc.) readily attacked both ethereal oxygen and olefins in isopentenyl prenyl ether to furnish a number of side products.[6] Weaker acids would be difficult to cleave the carbon-oxygen bond of isopentenyl prenyl ether. Clearly, a strong oxygenophilic catalyst enough to coordinate ethereal oxygen, but not double bonds was necessary to accomplish a combined carbon-oxygen bond fission-rearrangement process. The organoaluminum reagents would be a better choice to meet the above requirement. Among various modified organoaluminum reagents examined, only the reagent 1 was found to be efficient.[7] At the present stage, the mechanistic features for the intramolecular prenyltransfer reaction has not yet been elucidated, it is likely that the bulky 2,6-di-tert-butyl-4-methylphenoxy group in 1 would play an important role to make a monomeric aluminum species in solution[8] as well as to assist anchimerically the well-directed interaction of the π-electron orbital of the isopentenyl group with a developing empty orbital of the prenyl cation in space via a six-membered transition state as illustrated in eq. 2.

The similar rearrangements of isopentenyl geranyl anf farnesyl ethers were performed equally well to give the C_{15} and C_{20} alcohols[9] in 42% and 33% yields, respectively. However, in case of isopentenyl neryl ether, the cyclization of neryl cation precedes the expected rearrangement, producing the C_{15} alcohols[9] in only 10% yield.



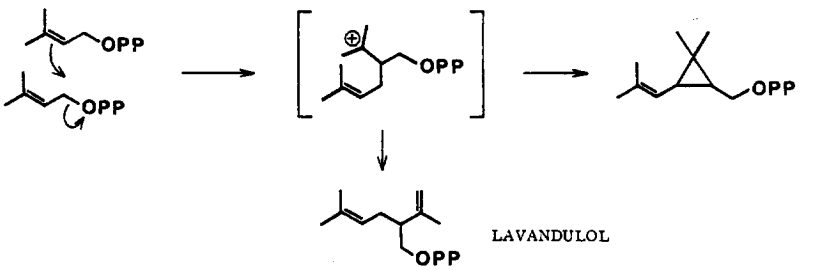
42% yield : R = Prenyl

33% yield : R = Geranyl



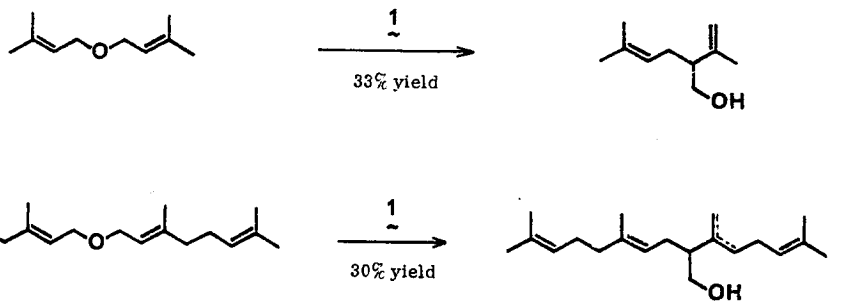
10% yield

Biosynthetically, there has been considerable interest and speculation how presqualene pyrophosphate and a number of irregular monoterpenes including chrysanthemyl pyrophosphate[10] are formed. The various theories have been reviewed[11] and a unified hypothesis has recently been proposed for formation of monoterpenes. According to most of these theories, the initial step always involves the head-to-head dimerization of two molecules of allylic pyrophosphate (eq. 3). Such biogenetic-type head-to-head terpene



(3)

synthesis was also realized by the organoaluminum promoted intramolecular rearrangement of diprenyl ether. Thus, treatment of diprenyl ether with the reagent 1 at 0°C for 1.5 h furnished only lavandulol (33% yield)[12] as a C_{10} alcohol. In a practical sense, this method provides a highly simple route to lavandulol hitherto accessible by multi-step synthesis.[13] In a similar fashion, the C_{20} alcohol 4[9] was obtained from digeranyl ether in 30% yield.



The intramolecular rearrangement of isopentenyl prenyl ether[14] is representative of the general procedure. To a stirred solution of 2,6-di-tert-butyl-4-methylphenol (1.322 g, 6 mmol) in dry methylene chloride (15 mL) was added at -78°C trimethylaluminum (2.5 mL of a 2.36 M hexane solution, 6 mmol) under argon.[8] The resulting mixture was gradually warmed to 0°C and stirred there for 30 min. The clear solution was again cooled to -78°C and treated with trifluoromethanesulfonic acid (0.53 mL, 6 mmol) at -78°C. Upon warming to 0°C, the gas evolution was observed to give the pink solution after further stirring at 0°C for 30 min. Then isopentenyl prenyl ether (616 mg, 4 mmol) in methylene chloride (2 mL) was added dropwise at 0°C. The reaction mixture was stirred at 25°C for 2 h and poured onto iced 5% hydrochloric acid. The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, concentrated, and the crude product purified by column

chromatography on silica gel (ethyl acetate-hexane) to furnish the C_{10} alcohols, 2 and 3 (277 mg, 45% yield) as a colorless oil.

ACKNOWLEDGMENT

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6. Attempted reaction of isopentenyl prenyl ether in methylene chloride with $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, or CF_3SO_3H at -78°C ~ -20°C resulted in formation of many products, and only trace, or no C_{10} alcohols were detected by TLC analysis.

7. The C_{10} alcohols, 2 and 3 were obtained in ~33% yield using bis(diethylaluminum)sulfate under more forcing reaction conditions (n-heptane reflux for several hours). For the preparative method of bis-(diethylaluminum)sulfate, see Matsumura, K.; Atarashi, Y.; Fukumoto, O. J. Organometal. Chem., 1970, 25, 345.

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14. The starting allylic ethers were prepared according to the literature procedure. See Reuter, J. M.; Salomon, R. G. J. Org. Chem., 1977, 42, 3360.

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