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(8) (a) Oxidation was carried out by magnetically stirring a solution of the selenide in methylene chloride containing 2 equiv of pyridine with 5 to 10 equiv of 15% aqueous hydrogen peroxide for ~10 min, when oxidation is usually complete (in a few cases the thermal elimination requires somewhat longer reaction times). We have found these conditions for oxidation and elimination to be superior in convenience and purity and yield of products to other methods for any selenide where the olefin product is not attacked rapidly by hydrogen peroxide. (b) Oxidation at room temperature as above gave selenoxide; elimination was completed by refluxing for 5 min in CCl_4 containing 2 equiv of pyridine. This is the only selenoxide among those described here which does not eliminate readily at or below room temperature.

(9) (a) Positional control during synthesis of enones by dehydrobromination of α-halo ketones has been achieved using a similar technique.[9b] (b) P. L. Stotter and K. A. Hill, *J. Org. Chem.*, **38**, 2576 (1973).

(10) Under these conditions ⅔ of the selenium is recovered in the product as Ph_2Se_2; the remainder is removed as $PhSeO_2H$ in the workup.

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(13) J. N. Marx, J. H. Cox, and L. R. Norman [*J. Org. Chem.*, **37**, 4489 (1972)] have dehydrogenated 2-carbomethoxycyclopentanone with SeO_2 in 48% yield. They also were unable to purify their reaction product.

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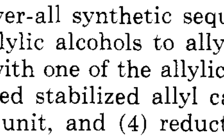
A General 1,5-Diene Synthesis. Application to the Synthesis of Squalene

Summary: A new method for the preparation of geometrically pure 1,5-dienes *via* coupling of allylic sulfones with allylic halides followed by reductive cleavage of the allylated sulfones is described.

Sir: The construction of 1,5-dienes of types I and II involving over-all allyl alcohol coupling with geometrical and positional control has recently received attention as a result of the importance and general utility of such systems for the synthesis of juvenile hormones and cyclic terpenoid or steroidal precursors. In conjunction with another project we required a method for carbon–carbon bond formation with formation of a 1,5-diene unit.[1]



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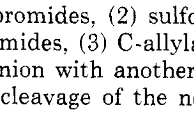
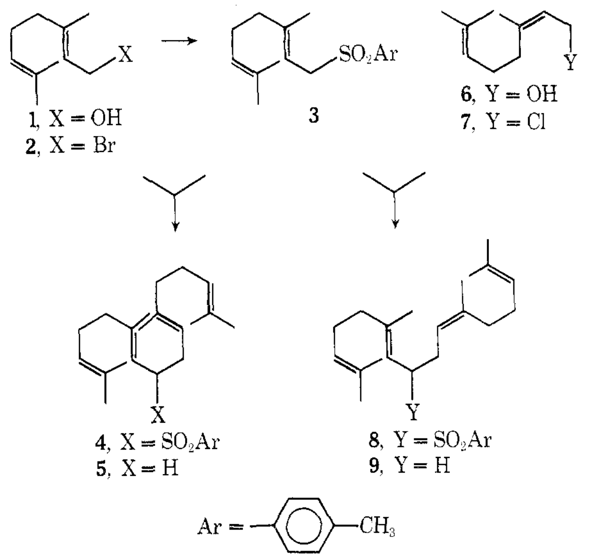


II

We wish to report a new method for the preparation of geometrically pure 1,5-dienes *via* coupling of allylic alcohol units which proceeds in good yields with essentially complete preservation of the geometry and position of the olefinic bonds.

The over-all synthetic sequence involves (1) conversion of the allylic alcohols to allylic bromides, (2) sulfone formation with one of the allylic bromides, (3) C-allylation of the desired stabilized allyl carbanion with another allylic bromide unit, and (4) reductive cleavage of the new sulfone. The complete process can be conveniently carried out in 60–70% yield with <1–2% isomerization, either positional or cis-trans.

Treatment of pure *trans*-geraniol (1) in anhydrous ether with PBr_3 at 0° afforded *trans*-geranyl bromide (2) in near-quantitative yield. Treatment of 2 with sodium *p*-toluenesulfinate in anhydrous DMF at ambient temperature for 18 hr gave *trans*-geranyl *p*-tolyl sulfone 3 in 98% yield. Metalation of sulfone 3 at −20° with *n*-butyllithium in tetrahydrofuran–hexamethylphosphoramide (4:1) followed by cooling to −78° and addition of *trans*-geranyl bromide resulted in formation of pure sulfone 4 (89% yield). Nmr analysis of the coupled sulfone revealed lack of aliphatic methyl resonance, a consequence of coupling at the γ position. In addition the nmr spectrum of 4 revealed no terminal vinyl resonance. Geometrical isomerization was rigorously ruled out by coupling of cis- and trans-allylic isomers and glpc comparison of the respective products derived from reduction cleavage of the sulfone moiety (*vide infra*).

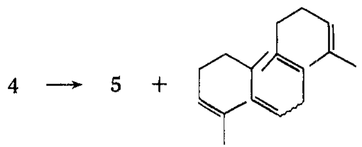


The new sulfone 4 was purified and reduced at 0° with lithium in ethylamine under a nitrogen atmosphere. After stirring for 30 min the reaction mixture was worked up in the standard manner and the product chromatographed on silica gel to yield pure all-trans bisgeranyl 5[2] (77%) [the ratio of cis:trans allylic methyl groups at δ 1.58 and 1.67 was 2.0:1.0 as anticipated for pure trans,trans compound].

Coupling of *trans*-geranyl sulfone 3 with neryl chloride[1d] 7 as described gave sulfone 8 (71%). Reductive cleavage of the sulfone provided an 82% yield of *cis,trans*-nerylgeranyl 9 [nmr ratio of cis:trans allylic methyl groups was 1.0:1.0 as expected for pure cis,trans compounds]. Bisgeranyl 5 and nerylgeranyl 9 are readily separable by glpc and the products of the above couplings indicated <1–2% contamination.

Although the cleavage of the carbon–sulfur bond with lithium in ethylamine proved to be satisfactory, we had initially hoped to be able to perform the required cleavage reaction under milder reaction conditions. Dabby and coworkers[3] have reported that the C–S bond of sulfones can be cleaved with sodium amalgam. To investigate this carbon–sulfur cleavage reaction sulfone 4 was treated with 3% sodium amalgam[4] in ethanol for 1.5 hr. In addition to the expected all-trans tetraene 5 there was obtained the rearranged tetraene 10 in a ratio of 9:4 (90%), making this procedure unattractive from a synthetic viewpoint. Use of hexamethylphosphoramide in ethanol (6:1) resulted in an 11:6 mixture of 5 and 10, respectively. In the case of 8, use of HMPA resulted in a 2:1 mixture of 9 and 11.

In a similar fashion employing the procedures developed above, we have prepared *all-trans*-squalene 16 from pure *trans,trans*-farnesol 12.[5]



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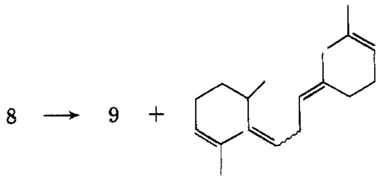

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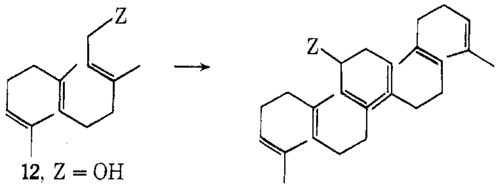

12, Z = OH
13, Z = Br
14, Z = SO_2Ar

15, Z = SO_2Ar
16, Z = H

Treatment of *trans,trans*-farnesol **12** in acetonitrile with carbon tetrabromide and triphenylphosphine[1f] afforded pure *trans,trans*-farnesyl bromide **13** in 90% yield. Reaction of the bromide with sodium *p*-toluenesulfinate in anhydrous dimethylformamide at ambient temperature overnight gave *trans,trans*-farnesyl *p*-tolyl sulfone **14** in 97% yield. Generation of the carbanion from **14** in tetrahydrofuran at −20° with *n*-butyllithium followed by cooling to −78° and addition of 1 equiv of *trans,trans*-farnesyl bromide **13** gave after gradual warming to 0° the pure coupled sulfone **15** in 86% yield after chromatography on silica gel. Nmr analysis of **15** revealed lack of aliphatic methyl resonance.

Cleavage of the carbon–sulfur bond of **15** was conveniently carried out at −78° with lithium in ethylamine. After stirring for 20 min, the reaction mixture was quenched with 1,3-butadiene and the crude product (96%) was chromatographed on silica gel to yield pure (homogeneous by glpc) *all-trans*-squalene **16** (80%), identical with an authentic sample by nmr (ratio of cis:trans allylic methyl groups 3.0:1.0).

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References and Notes

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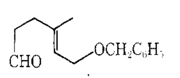
(5) Synthesis of *trans,trans*-farnesol: *trans*-geraniol was protected by O-benzylation[1c] (sodium hydride followed by benzyl bromide in glyme) followed by cleavage (ozone–methanol;[6] dimethyl sulfide[7]) of the isopropylidene terminus resulting in the formation of aldehyde i. The 6,7-trans-trisubstituted double bond was constructed by reaction with isopropenylmagnesium bromide affording allylic alcohol ii which upon Claisen rearrangement[8] with ethyl orthoacetate gave diene ester iii. Lithium aluminum hydride reduction followed by Collins oxidation[9] afforded the aldehyde iv. Reaction of iv with isopropyltriphenylphosphorane gave pure *all-trans*-farnesyl benzyl ether v, which was cleaved by treatment with lithium in ethylamine at −78°.



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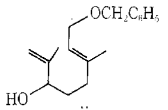

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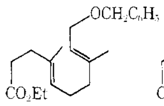

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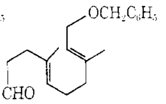

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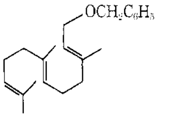

v

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