The mass spectrum of the purified product showed the expected molecular ion at m/e 526 ($C_{32}H_{46}O_6$), with major fragments at m/e 466 (M − CH_3COOH), 457 (M − C_5H_9), 434, 397 (M − CH_3COOH, C_5H_9), 227, 219, 214, 205, 191, 177, 119, and 117; infrared $\nu_{max}^{CCl_4}$ 2980, 2955, 2940 (CH), 1745 (acetate), 1728 (methyl ester, α,β-unsaturated), 1712 (six-membered ring ketone), 1375, 1255, 1195, and 1165 cm^{-1}; nmr (100 Mc, CCl_4, TMS as internal reference) 5.80 (doublet, 1 H), 16β proton; 5.00 (multiplet, 1 H), vinyl proton of side chain; 3.55 (singlet, 3 H), OMe of methyl ester; 1.95 (singlet, 3 H), methyl of 16α-acetoxy group; 1.65 (broad doublet, 6 H), methyls of isopropylidene; 1.20 (doublet, 3 H), C-4 methyl; 1.09 (singlet, 3 H), tertiary methyls; 1.05 (singlet, 3 H), tertiary methyls; and 0.94 ppm (singlet, 3 H), tertiary methyls.

Hydrolysis and Isotopic Exchange. The foregoing diketo methyl ester (26 mg) was hydrolyzed by treatment for 15 hr at 25° with 3.1 ml of 1% potassium hydroxide in 95% methanol–water. The solvent was evaporated under nitrogen and the residue was dissolved in water. The solution was washed with ether and acidified with sulfuric acid and the product was extracted into ether, then converted to the methyl ester by treatment with excess diazomethane. The product (19.4 mg) had 351 dpm/mg. Oxidation of this material with an excess of chromic acid in acetone at 10° followed by standard isolation procedure gave a crude product having unchanged specific activity which, however, was not further characterized.

The mass spectrum of the hydrolysis product showed the expected molecular ion at m/e 484 ($C_{30}H_{44}O_5$), with major peaks at m/e 466 (M − H_2O), 452 (M − CH_3OH), 434 (M − H_2O − CH_3OH), 402, 384, 276, 219, 193, 177, and 164; infrared $\nu_{max}^{CCl_4}$ 3500 (broad, OH), 2980, 2960, 2940, 2880 (C–H), 1735, and 1710 cm^{-1}.

The nmr spectrum (100 Mc) was also consistent with the proposed structure, notably in the retention of the singlet methyl of the carbomethoxy group now at 3.75 ppm and the vinyl multiplet at 5.05 ppm (1 H) and the absence of the methyl of the acetoxy group at 1.95 ppm (3 H); the three singlet tertiary methyl groups at 0.95, 1.05, and 1.09 ppm can still be seen, but the methylene envelope is now more complex than in the case of the 16-acetoxy compound.

In the above conversions of fusidic acid methyl ester, tritium is lost in two stages. Based on the specific activity of the starting material (767 dpm/mg), 11% is lost on initial oxidation to the diketone and 54.2% is lost in the subsequent hydrolysis product. The predicted losses in these products are 10.5 and 58.0%, respectively. These values are calculated on the assumption of the proposed pattern of cyclization of squalene oxide and the incorporation of 6 moles of [5-$^3H_2$]mevalonate into each mole of squalene (from which the squalene oxide was synthesized) according to the established biosynthetic sequence.[7] The stereospecific loss of a tritium atom from one farnesyl residue in the course of incorporation into squalene[14] is also taken into account. Thus, only the 11β-^3H should be lost in the initial oxidation whereas the conditions of alkaline hydrolysis should remove further ^3H atoms at C_2 and C_{12} by enolization. The 16α-^3H should also be lost when the 16β-ol is exposed to alkali since epimerization of the OH group is known to occur under these conditions.[11] The observed retention of all radioactivity of the hydrolysis product on chromic acid oxidation supports the assumption that inversion has occurred at C_{16}. The loss of label in the oxidation and the final loss of label after alkaline exchange are in good agreement with the theoretical values and strongly support the identity of the labeled material with fusidic acid.

Nonsaponifiable Products. The examination of the radioactive components of the nonsaponifiable fraction is still in progress. Analysis of these materials by tlc and glpc reveals the presence of a complex mixture of labeled products among which ergosterol and lanosterol have been identified.

These results demonstrate the conversion of squalene 2,3-oxide to fusidic acid in *F. coccineum*, thereby establishing the biological importance of squalene 2,3-oxide as a precursor for the carbon skeleton of this class of antibiotics. The changes in ^3H content of the successive fusidic acid derivatives that are observed in our experiments are evidence for the intact incorporation of the squalene chain into the fusidane skeleton.

Acknowledgment. This research was supported by National Institutes of Health Grants AI 05102 and GM 10421 (to E. E. v. T.) and GM 12493 (to R. B. C.), and a Grant-in-Aid from the American Heart Association (to R. B. C.).

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Received October 17, 1967

(14) J. W. Cornforth, R. H. Cornforth, C. Donninger, G. Popjak, G. Ryback, and G. J. Schroepfer, Jr., *Proc. Roy. Soc.* (London), **B163**, 436 (1966).

A One-Step Synthesis of 1,5-Dienes Involving Reductive Coupling of Allyl Alcohols

Sir:

Preparation of specifically substituted and functionalized 1,5-dienes implies the need for a good method of bonding allyl units.[1] Following an earlier lead from this laboratory,[2] we have now developed a new, useful procedure for the reductive coupling of allyl alcohols, effected without isolation of intermediates through the combined action of titanium trichloride and alkyl- or aryllithium.[3]

In a typical experiment, 3.0 moles of methyllithium and 1.0 mole of titanium trichloride were mixed under nitrogen at −78° in ethylene glycol dimethyl ether. After a few minutes, 2.0 moles of geraniol was added to the solution of reagent maintained at −78°. Warming

(1) For an example of such a need, see E. E. van Tamelen, K. B. Sharpless, R. Hanzlik, R. B. Clayton, A. L. Burlingame, and P. C. Wszolek, *J. Am. Chem. Soc.*, **89**, 7150 (1967).

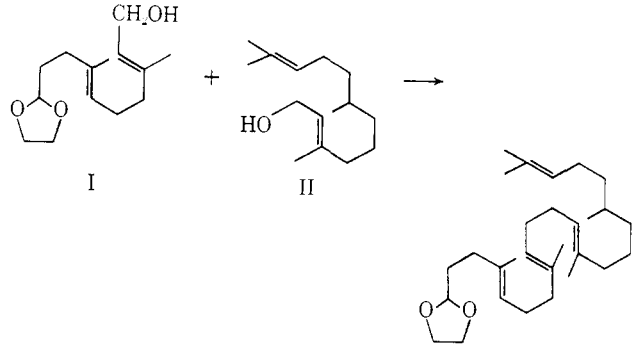
(2) E. E. van Tamelen and M. Schwartz, *ibid.*, **87**, 3277 (1965).

(3) Presentation of the coupling mechanism, a matter of interest in its own right, is deferred until the time of a later publication. Titanium trichloride solvate is reported to react between −50 and −80° with methyllithium in ether to give a dark green solution of unisolated product—presumed to be trimethyltitanium—which decomposes above −20° to gas and "black needles" and reacts with water to yield methane: K. Clauss and C. Beerman, *Angew. Chem.*, **71**, 627 (1959).

to room temperature was permitted during the course of 10 min, and refluxing (80–82°) for 15 min was utilized to ensure completion of the reaction. The hydrocarbon product was isolated by addition of water, petroleum ether (bp 60–80°) extraction, and silica gel chromatography. The entire reaction can be executed within a few hours and provides hydrocarbon consisting of C-1–C-1′:C-1–C-3′ coupled material in the ratio 7:1 (71% yield, 80% yield based on starting material consumed). In various modifications, *n*-butyl-, *t*-butyl-, or phenyllithium could be substituted for methyllithium without disadvantage; however, greater proportions of this reagent substantially lower the yield of coupled product. The success of mixed couplings depends on the molar proportion of the starting allyl alcohols. In a reaction involving equimolar amounts of geraniol and farnesol, a statistical (1:2:1) ratio of products resulted. Nonspecific coupling also was observed with geraniol–crotyl alcohol. However, by using an excess of one of the different allyl alcohols, a good yield of cross product can be realized (see below).

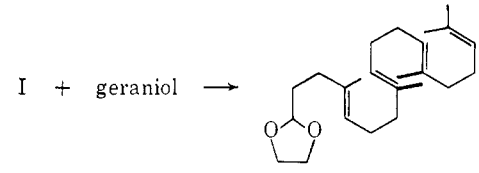
In addition, other related transformations have been carried out. Through the use of the above experimental procedure, *meso*-hydrobenzoin was reduced to *trans*-stilbene in 31% (88%)[4] yield. As expected, benzyl alcohol was transformed into bibenzyl without difficulty and in good yield, *i.e.*, 68% (78%).[4,5]

In order to demonstrate the adaptability of the synthesis scheme, we describe the preparation of 4-^{3}H-labeled *trans,trans,trans*-18,19-dihydrosqualene 2,3-oxide (V), required in this laboratory in a different connection.[1] After synthesis of the two required allyl alcohols I and II by conventional means,[6,7] the unsymmetrical coupling was carried out under conditions described above (70% yield), the dihydrofarnesol being present in ~10 *M* excess. Through isolation–purification by thiourea clathrate formation, followed by chromatography over a silver nitrate column, there was secured the desired all-*trans* acetal III, a colorless oil



I II III

which exhibited one peak on vpc and possessed ir, nmr, and mass spectral properties in agreement with the assigned structure. After hydrolysis (perchloric acid in aqueous tetrahydrofuran) to the corresponding aldehyde, the tritium label was introduced by exchange in acidic tritium oxide–tetrahydrofuran.[8] Production of V, the desired final product, was achieved by treatment of the labeled aldehyde with diphenylsulfonium isopropylide.[8] Similarly, the allyl alcohol I[7] was converted to the cross-coupling product IV by employing geraniol as the second, more abundant alcoholic component.



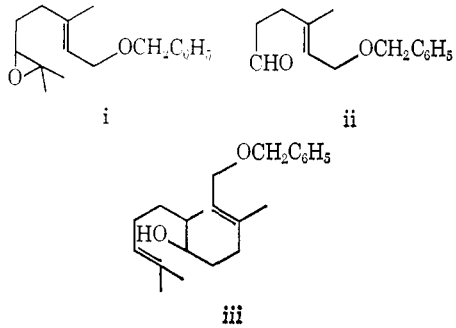
IV

Acknowledgment. The authors are indebted to the National Science Foundation for grant support (NSF GP 5556).

(4) Second yield based on starting material consumed.

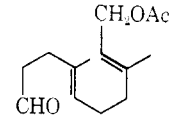
(5) With the metal valence change II → IV in mind,[2] the other direct reductive coupling experiments were carried out. Although vanadium dichloride in refluxing glyme or dioxane served to convert benzyl alcohol to bibenzyl in 25–35% yield, the reaction was found to be erratic and therefore was not pursued. In exploratory experiments, titanium dichloride in refluxing glyme or hexamethylphosphoramide effected conversion of benzyl alcohol to small amounts (≤5%) of bibenzyl.

(6) Synthesis of *trans*-6,7-dihydrofarnesol: *trans*-geraniol was protected by O-benzylation (sodium hydride followed by benzyl chloride, all in glyme), after which the 6,7-oxide i was prepared by successive treatment with N-bromosuccinimide in aqueous *t*-butyl alcohol and base [E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 121 (1962)]; perchloric acid in aqueous tetrahydrofuran effected conversion to glycol, which was cleaved to the aldehyde ii by means of sodium metaperiodate. The carbon chain was then established by reaction with 6-methylhept-5-enyl-2-magnesium chloride; the resulting alcohol iii was tosylated in pyridine in methylene dichloride. Lithium aluminum hydride reduction afforded the dihydrofarnesyl benzyl ether, which was cleaved by treatment with lithium in liquid ammonia.



i ii iii

(7) Synthesis of the ethylene acetal of 10-acetoxy-4,8-dimethyldeca-4,8-dienal: successive treatment of the terminal epoxide of farnesyl acetate [E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963)] with perchloric acid–aqueous tetrahydrofuran and sodium metaperiodate produced the expected aldehyde iv, which was converted to the corresponding ethylene acetal in an oxalic acid catalyzed reaction with ethylene glycol. Saponification was carried out with potassium carbonate in methanol. The structures of all new substances described in this manuscript were consistent with nmr, ir, and/or mass spectral data.



iv

(8) R. Nadeau and R. Hanzlik, *Methods Enzymol.*, in press.

(9) National Institutes of Health Predoctoral Fellow, 1964–1967.

(10) National Science Foundation Fellow, 1966–1967.

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Substituent Effects on Fluorine-19 Chemical Shifts in Saturated Systems[1]

Sir:

Previous work by our group[2] has shown that the effects of substituents on side chains in aromatic sys-

(1) This work was supported by the Air Force Office of Scientific Research through Grant No. AF-AFOSR-1050-67.