of the basic tenets of free-radical biology that autoxidation of PUFA in vivo, and particularly lipids in membranes, is responsible for important biological consequences.[34,35] The extent to which cyclic peroxides, endoperoxides, and PG analogues, with either natural (i.e., enzymatically produced) or unnatural structures, may be involved in free-radical biology obviously warrants considerable further research effort. The second hypothesis suggested by our work is that PG-like endoperoxides decompose both thermally and under the mild acid catalysis of the TBA test to produce malonaldehyde, and that endoperoxides are the principal nonvolatile precursor of malonaldehyde under our conditions.

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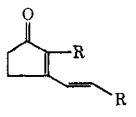

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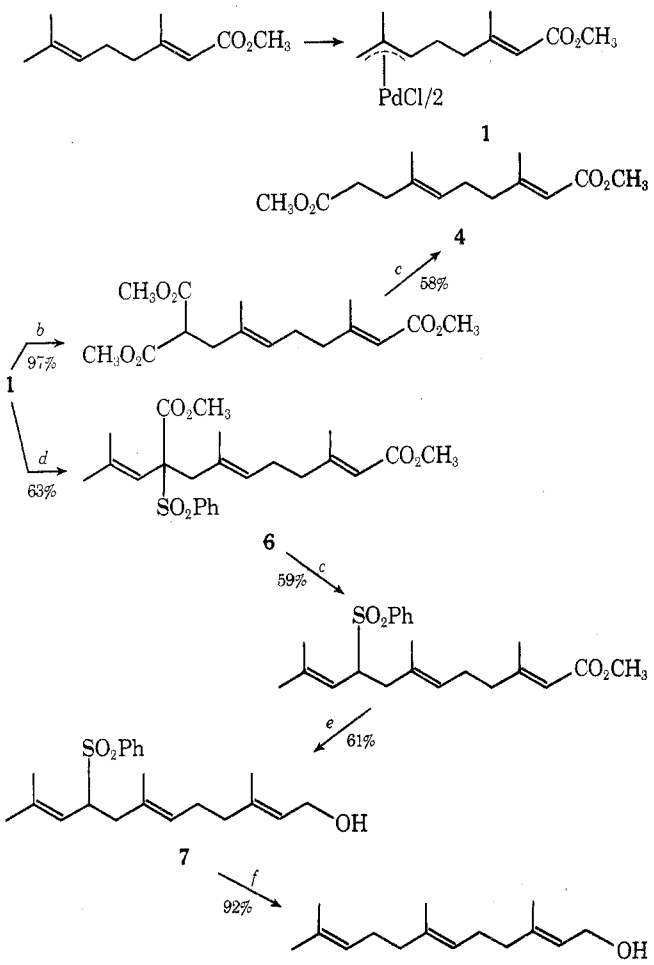
A New Approach for the Stereocontrolled Synthesis of Acyclic Terpenes

Summary: A short stereoselective approach to farnesol, geranylgeraniol, and dimethyl 3,7-dimethyl-(*E*,*E*)-2,6-decadiene-1,10-dioate based upon the regioselectivity and stereospecificity of allylic alkylation via π-allylpalladium complexes is reported.

Sir: The problems of synthesizing trisubstituted double bonds of defined geometry came to the fore in the squalene problem.[1a] Renewed interest developed as a result of the structural elucidation of the juvenile hormone.[1b] The acyclic polyisoprenoids in general represent an important class of natural products because of their myriad of applications as well as their importance as biosynthetic intermediates. We wish to report (1) an unusual chemospecificity in the formation of π-allylpalladium complexes, (2) a stereoselective approach to acyclic terpenoids[2] involving a direct homologation of simpler building blocks, (3) a new approach to prenylation, and (4) the first application of π-allylpalladium complexes in natural products synthesis.[3]

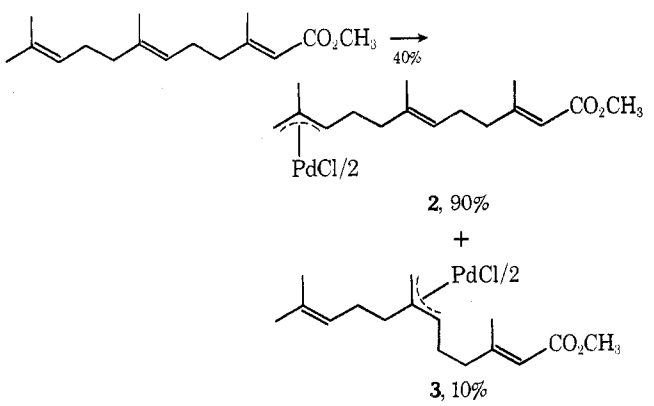
Treatment of methyl geraniate with palladium chloride under standard conditions[4] (PdCl, NaCl, $CuCl_2$, NaOAc, HOAc, 95°, 68%) gave a single π-allylpalladium complex, mp 117–118°, assigned structure **1**[5] (see Scheme I). The NMR spectrum indicated that the *E*-α,β-unsaturated system was intact [δ 5.74 (s, 1 H, 2.18 (s, 3 H)] and the stereochemistry of the π-allyl unit was syn [δ 3.75 (s), 3.50 (t, J = 7 Hz), 2.70 (s), each 1 H]. The preference for the nonconjugated double bond is somewhat surprising in light of the importance of the acidity of the abstracted hydrogen on the rate of formation of π-allyl complexes[6] and by consideration of the usual factors affecting stability of the initial olefin–palladium π complex.[7] Thus, π basicity of the olefin appears to be the predominant factor determining this chemospecificity.

Scheme I
η^3-1-[1′-(3′-Methyl-4′-carbomethoxy-(*E*)-3′-butenyl)]-2-methyl-π-allylpalladium Chloride Dimer as a Synthon[a]



[a] All yields are for compounds purified by chromatography or distillation and are not optimized. [b] $NaCH(CO_2CH_3)_2$, diphos, THF, 25°, 18 hr, [c] LiI, $3H_2O$, NaCN, DMF, 120°, 17 hr. [d] $(CH_3)_2C{-}CH{-}C(SO_2Ph)CO_2CH_3\ Na^+$, diphos, THF, 25°, 24 hr. [e] Dibal, $PhCH_3$–hexane, −40° to 0°. [f] $Li/C_2H_5NH_2$, −78°.

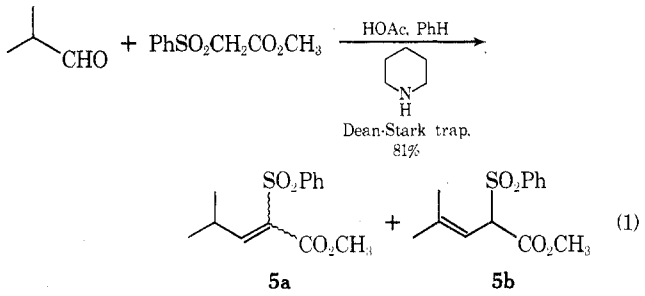
Formation[4] of the π-allyl complexes from methyl farnesoate also involve only the nonconjugated double bonds with a preference for the sterically less crowded terminal olefin (**2:3**, 9:1).[8] The enoate system of **2**[9] [δ 5.63 (1 H, s),



2.15 (3H, s)] and the central trisubstituted double bond [δ 5.12 (1 H, m), 1.61 (3 H, brs)] are unaffected. The π-allyl system is syn [δ 3.69 (s), 3.54 (m), 2.65 (s), each 1 H, 2.06 (3 H, s)].

Activation of complex 1 by adding 1,2-bis(diphenylphosphino)ethane allows smooth condensation with dimethyl malonate with complete regioselectivity and stereospecificity. Decarbomethoxylation[10] completes this short stereoselective synthesis of the dimethyl ester of a pheromone of the Monarch butterfly (**4**).[11]

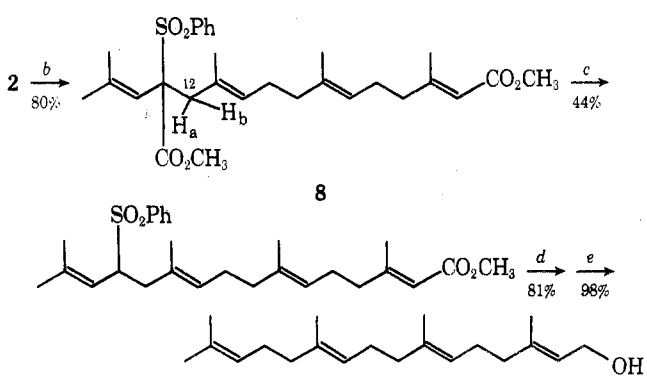
Prenylation was accomplished using the anion derived from the sulfone ester **5**, mp 60–70°, available as shown in eq 1. NMR analysis indicates this material to be a 1.8:1



mixture of the conjugated and unconjugated isomers **5a** [δ 7.18 (d, J = 11 Hz), 3.10 (m), 1.12 (d, J = 7 Hz)] and **5b** [δ 5.12 (d, J = 11 Hz), 4.62 (d, J = 11 Hz), 1.76 (s), 1.58 (s)]. Since both give the same anion, their separation is obviated. Conversion to their anion (NaH, THF, room temperature) and alkylation with **1** produced **6** [δ 5.64 (1 H, s), 5.35 (1 H, s), 5.19 (1 H, m), 3.12 (1 H, d, J = 15 Hz), 2.94 (1 H, d, J = 15 Hz)] as the sole product. The stereochemistry of the 6,7 double bond as *E* was indicated by the NMR spectrum (δ 1.60, 3 H, s) and the subsequent conversion to *all-trans*-farnesol. Decarbomethoxylation and reduction of the ester produced the hydroxy sulfone **7** which was reductively cleaved to *all-trans*-farnesol, identical with an authentic sample.[12] Spectroscopic[13] and chromatographic analysis did not reveal the presence of other geometric isomers.

The utility of this approach is further illustrated by the prenylation of methyl farnesoate to geranylgeraniol (see Scheme II) using the same sequence as above. Alkylation

Scheme II
Synthesis of Geranylgeraniol[a]



[a] All yields are for product after purification by chromatography or distillation and have not been optimized. [b] $(CH_3)_2C{-}CH{-}C(SO_2Ph)CO_2CH_3\ Na^+$, Ph_3P, THF, 25°, 20 hr. [c] LiI, $3H_2O$, NaCN, DMF, 120°, 17 hr. [d] Dibal, $PhCH_3$, −40°. [e] $Li/C_2H_5NH_2$, −78°.

proceeded without any detectable (by NMR) formation of alternative isomers. The alkylation product **8** showed five olefinic methyl groups [δ 2.13 (3 H), 1.76 (3 H), 1.56 (6 H), and 1.44 (3 H)], four vinyl protons [δ 5.58 (s, 1 H), 5.28 (s, 1 H), 5.16 (m, 2 H)], and a clean AB (J = 15 Hz) pattern (δ 3.10 and 2.76) for the C-12 methylene group. The standard methods of decarbomethoxylation and reduction completed the synthesis of geranylgeraniol.

The direct and chemospecific prenylation of simpler terpenes to more complex terpenes should prove to be a useful approach to such compounds. The fact that trisubstituted double bonds can be created with complete stereochemical control enhances the utility of this scheme for such a purpose.

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Reductions with Copper Hydride. New Preparative and Mechanistic Aspects

Summary: Simple copper hydride reagents are described which reduce conjugated carbonyl compounds to the saturated derivatives; a special effect of added *sec*-butyl alcohol allows reduction of acrylates and labeling experiments establish the sources of the added hydrogens.

Sir: Since the first suggestions of unique reduction reactions promoted by complex copper hydrides,[1] related reagents have been shown to be of general utility for conversion of organic halides and sulfonate esters to hydrocarbons,[2–4] and for conversion of α,β-unsaturated ketones into saturated ketones.[4,5] The reagents suggested to be most effective are obtained by generation of CuH at −50°, solubilization with a second ligand, and filtration at low temperature.[4,5] No general procedures for reduction of α,β-unsaturated esters have been reported.

Using the general technique of earlier workers,[1,2] we have developed simple preparations of effective copper-based reagents which provide efficient 1,4 reduction of both conjugated ketones *and* esters, including two examples of acetylenic esters. The reductions show features associated with electron-transfer processes, including a dramatic increase in efficiency in difficult cases with 2-butanol in the medium. In contrast to reduction of halides to hydrocarbons,[2] these reactions involve transfer of a hydrogen atom from the copper hydride to carbon, specifically the β carbon of the unsaturated carbonyl system.

The complex hydrido–metallic species are prepared according to eq 1 and 2. The species involving the lithium cation (eq 1, here referred to as Li complex) and the parallel species with the sodium cation (eq 2, Na complex) are obtained as brown-black suspensions in tetrahydrofuran by simply mixing the reagents at 0° under argon and stirring for 30 min. A series of unsaturated ketones and esters were studied in reaction with both the Li complex and the Na complex; the more efficient conversions are displayed in Table I. Cyclic enones are best reduced with the Li complex, as the Na complex gives lower yields (60–70%). With chalcone and the ester examples, the Na complex gives better results, especially in the presence of excess 2-butanol. In the examples of entries 6, 7, 9, and 10, high molecular weight products were the main products with the Li complex and with the Na complex in the absence of added alcohol.

$$2LiAlH(OCH_3)_3 + CuBr \xrightarrow[THF]{0^\circ} \text{“Li complex”} \quad (1)$$

$$NaAlH_2(OCH_2CH_2OCH_3)_2 + CuBr \xrightarrow[THF]{0^\circ} \text{“Na complex”} \quad (2)$$

The procedure is exemplified by the reduction of methyl 3,4,5-trimethoxycinnamate. Vitride[6] (70% in benzene, 2.24 ml, 16.0 mmol of hydride) was added dropwise to a suspension of cuprous bromide[7] (1.44 g, 8.0 mmol) in 15 ml of THF at 0°. After 30 min, the mixture was cooled to −78° and 2-butanol (1.6 ml, 18.0 mmol) was added, followed by a solution of methyl 3,4,5-trimethoxycinnamate (252 mg, 1.0 mmol) in 4 ml of THF. The mixture was stirred at −20° for 2 hr, quenched with 4 ml of water, and poured into saturated aqueous ammonium chloride. After dilution with ether, the organic layer was washed successively with water and aqueous ammonium chloride solution and concentrated to afford a residue of essentially pure methyl (3,4,5-trimethoxyphenyl)propionate. Short-path distillation [90° (0.01 Torr)] gave a pure sample,[8] 242 mg, 93% yield.

The reductions of 2,2,6,6-tetramethylhept-4-en-3-one and methyl cinnamate were studied in some detail. Both Li complex and Na complex give high yields and selective 1,4 reduction with the ketone. Neither reagent gives high yields of methyl 3-phenylpropionate when allowed to react with methyl cinnamate in THF. In this case, a major product (isolated in 20–28% yield) is dimethyl *meso*-3,4-diphenyladipate (1).[9] The formation of 1, an example of hydrodimerization characteristic of electrolytic reduction,[10] and the tendency to form higher molecular weight products