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Allylic Alkylation: Nature of the Nucleophile and Application to Prenylation

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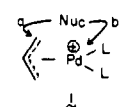
Abstract: Alkylation of π-allylpalladium complexes requires a "soft" nucleophile. Successful alkylating agents include the anions derived from malonate, β-keto sulfones, β-keto sulfoxides, and β-keto sulfides. The regioselectivity as a function of nucleophile is considered. The use of sulfur stabilized anions has proven quite versatile. The sulfone ester can lead to the addition at an allylic position of an acetate by mild desulfonylation or an alkyl group by decarbomethoxylation followed by desulfonylation. The latter has led to a new prenylation sequence which allows direct conversion of lower terpenes into the higher terpenes as illustrated for the conversion of a monoterpene to a sesquiterpene and the latter to a diterpene. The use of β-keto sulfoxides allowed direct alkylation-elimination to a dienoate.

The ability to utilize the olefinic linkage as a point for structural elaboration depends upon carrying out reactions at that site in a specific manner. As shown in the previous two papers in this series, the allylic position of olefins can be selectively activated and alkylated via organopalladium chemistry.[1,2] In this paper, we wish to explore the scope of this process and its application to acyclic terpenes.[3]

Results

The π-allyl cationic complexes are ambident electrophiles. Reaction can be envisioned to occur either at carbon (path a in **1**) or palladium (path b in **1**). With malonate anion, we have shown that reaction occurs via path a;[1] however, the divergency



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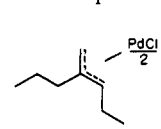
of attack would be expected to be dependent upon the nucleophile. To explore this question, we examined a series of nucleophiles with complex **2** using triphenylphosphine as the



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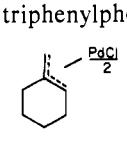

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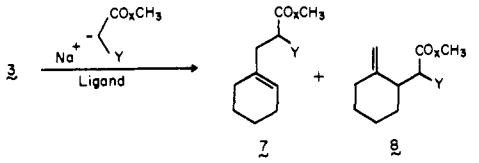
Table I. Range of Nucleophiles



X	Y	Ligand	% yield	7	8
2	CO_2CH_3	HMPT[a]	74	79[c]	21[c]
2	CO_2CH_3	TOT[b]	57	26[c]	74[c]
2	$PhSO_2$	HMPT	73	95	5
2	$PhSO_2$	TOT	78	16	84
2	CH_3SO_2	HMPT	90	100[c]	*c*
2	CH_2SO_2	TOT	90	15[c]	85[c]
2	PhSO	HMPT	71	100	
1	PhS	HMPT	70	90	10
2	PhS	HMPT	*d*	52	43
2	PhS	TOT	15	<1	>99
2	CH_3S	HMPT	*e*		

[a] HMPT, hexamethylphosphorous triamide. [b] TOT, tri-*o*-tolylphosphine. [c] See ref 1b. [d] Not detected. [e] No reaction.

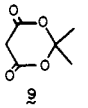
activating ligand. Organometallics like methyllithium, methylmagnesium iodide, and lithium dimethylcuprate and sulfur stabilized anions like dimsylsodium, 2-lithiodithiane, 2-lithiodithiane 1-oxide, 2-lithiodithiane 1,3-dioxide, and 2-lithio-2-trimethylsilyldithiane all failed to give alkylation products. In exploring the sequence **4, 5,** and **6**

$Li^+[CH_3SCH\bar{C}O_2CH_3]$ **4** $Na^+[CH_3S(=O)\bar{C}HCO_2CH_3]$ **5**

$Na^+[CH_3SO_2\bar{C}HCO_2CH_3]$ **6**

neither **4** or **5** reacted with **2** in the presence of triphenylphosphine, whereas **6** did. On the other hand, switching to 1,2-bis(diphenylphosphino)ethane (diphos) allowed alkylation to proceed smoothly with **5.** Thus, proper choice of activating ligand for the given nucleophile is critical for successful alkylation. Table I lists a range of nucleophiles as well as examines the regioselectivity of the reaction. As observed previously, HMPT favors reaction at the exocyclic carbon but TOT favors reactions at the endocyclic carbon.[1b] This selectivity also depends upon nucleophile as well with the anion of methyl phenylsulfonylacetate showing the highest preference for reaction at the exocyclic carbon and that of methyl phenylthioacetate for the endocyclic carbon. Sensitivity of the alkylation to the nucleophile is dramatically illustrated by the fact that, whereas the anion of methyl phenylthioacetate reacts, that of methyl methylthioacetate does not.

The ability to achieve alkylation appears to correlate with the pK_a of the carbon acids, the more acidic the acid, the better the alkylation. A phenylthio group acidifies a carbon acid to a greater extent than a methylthio group (~2–3 pK_a units).[4] Extrapolating from the data of Bordwell et al. and assuming that the pK_a of acetonitrile and methyl acetate are about the same,[5] the pK_a of methyl phenylthioacetate and methyl methylthioacetate are estimated at ~21 and 24, respectively (on the Bordwell scale). An anion that is too stabilized may also



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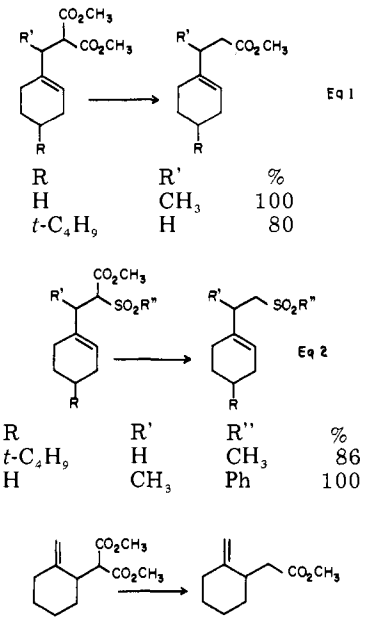
not react as a result of it not being nucleophilic enough. The anion from Meldrum's acid **9** ($pK_a \sim 5$)[6] is much too unreactive.

The alkylation products available with the nucleophiles that react well are very versatile. The malonate and sulfone ester adducts can be decarbomethoxylated using lithium iodide trihydrate and sodium cyanide in DMF at 120 °C[7,8] or tetramethylammonium acetate[9,10] in HMPA at 100 °C as illustrated in the accompanying equations. Of the decarbomethoxylation procedures, subsequent work indicates a strong preference for use of tetramethylammonium acetate. Such conditions are generally preferred to hydrolysis and decarboxylation. For example, alkylated product **10** was hydrolyzed to acid **11.** While **11** could be decarboxylated to the simple sulfone by pyrolyzing its sodium salt, attempts to effect decarboxylation under acid conditions led only to lactone **12.**

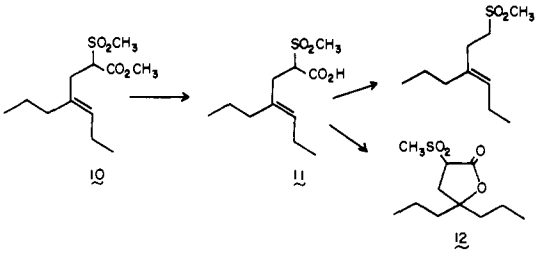


Eq 1

R	R'	%
H	CH_3	100
t-C_4H_9	H	80

Eq 2

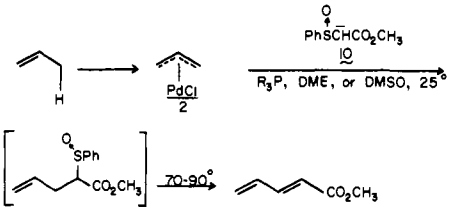
R	R'	R''	%
t-C_4H_9	H	CH_3	86
H	CH_3	Ph	100



10 **11** **12**

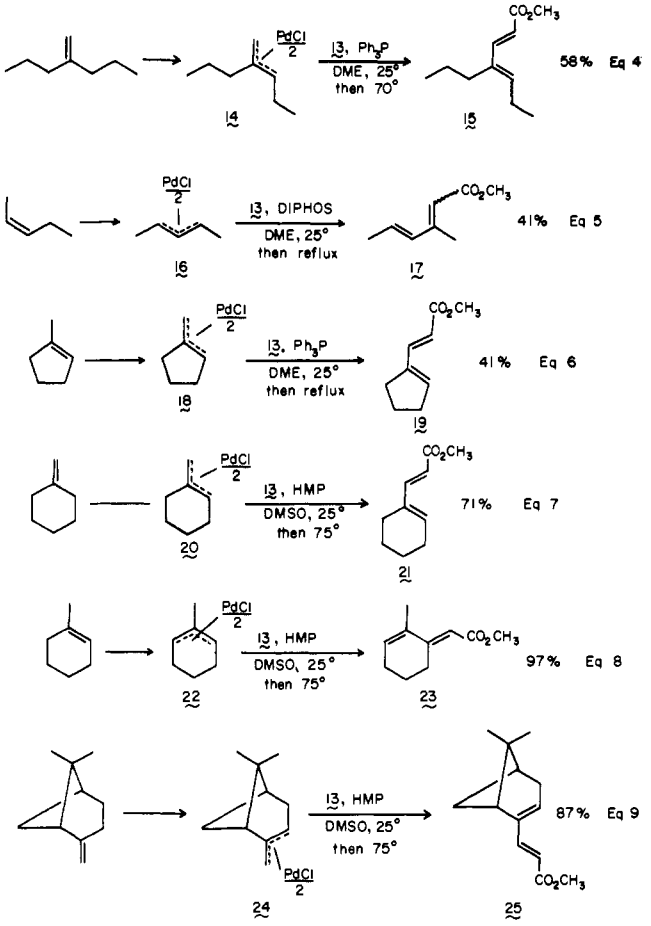
Such a competition is never observed in the direct decarbomethoxylation.

The products from the sulfoxide stabilized anions are most interesting since thermal elimination of sulfenic acid[11] allows direct formation of dienes (eq 3).[3b] This sequence constitutes



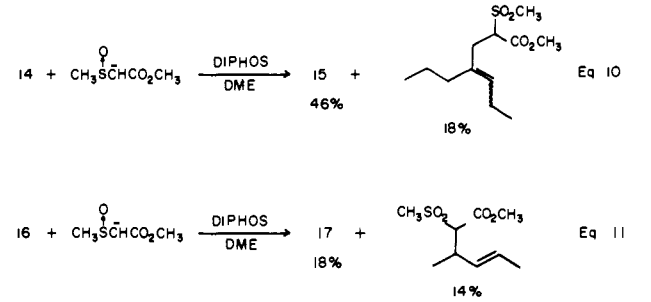
Eq 3

a novel diene synthesis from olefins. Equations 4–9 summarize the specific examples. NMR spectroscopy allows assignment of the stereochemistry as shown. Thus, in the case of **15, 19, 21,** and **25,** the α,β double bond is assigned the *E* configuration by the 16-Hz coupling constant of the vinyl protons. This stereochemistry also follows from the usual observations in the formation of disubstituted olefins via the sulfoxide pyrolysis.[11] In the case of **15,** VPC and NMR analysis indicates a 7:3 *E*:*Z*

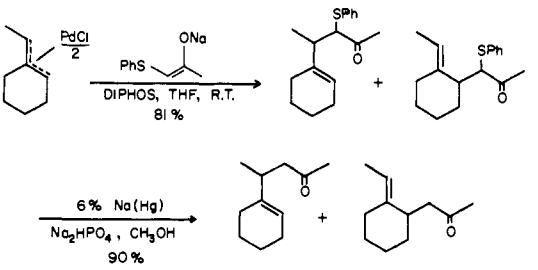


mixture of isomers at the γ,δ double bond. In contrast to eq 4, formation of **17** appears to involve retention of the stereochemistry of the γ,δ unsaturation. This tentative conclusion rests upon the observation of only two isomers by VPC, the appearance of the vinyl methyl region in the NMR spectrum which shows only two singlets for the methyl group at C(3) at δ 2.21 and 1.94 in the ratio of 2:1 for the *E* and *Z* isomers around the 2,3 double bond, and a single doublet (J = 7 Hz) for the terminal methyl group at δ 1.83, and the known tendency for the sulfoxide elimination to produce an *E*,*Z* mixture in the formation of trisubstituted double bonds.[11] Compound **23** is homogeneous as determined by VPC and its spectral properties. The *E* configuration is assigned based upon a $Eu(dpm)_3$ shift study which shows the methyl group shifting only slightly (δ 1.84 → 2.32), whereas the allylic methylene group experiences a huge shift (δ 3.02 → 5.75).

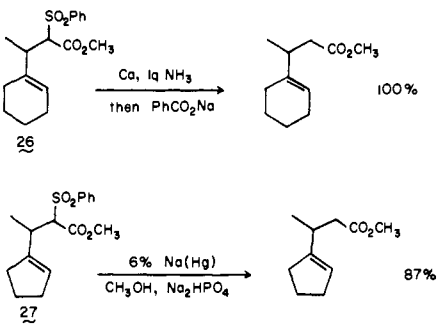
The data in eq 4-9 indicate that the use of HMPT or diphos as the activating ligand and the use of Me_2SO as solvent is best. Presumably improvement in the yields in eq 4-6 would result with such conditions. Use of methyl phenylsulfinylacetate is preferred to use of methyl methylsulfinylacetate because of the temperature of the elimination and because of competing oxidation of the sulfoxide to the sulfone as illustrated in eq 10 and 11.



Scheme I



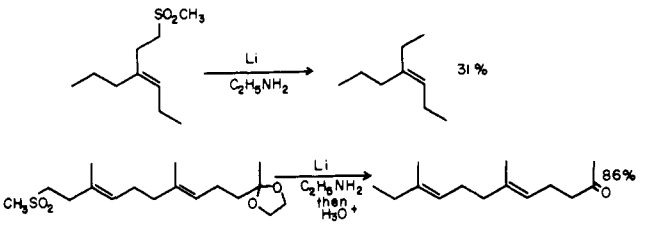
The use of sulfone ester enhances the flexibility of the synthetic sequence since desulfonylation can be easily achieved in high yield at various stages, The sulfone esters **26** and **27** are



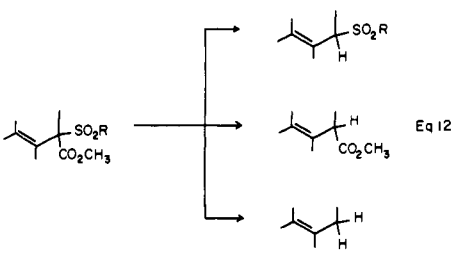
desulfonylated using either calcium in refluxing liquid ammonia or 6% Na(Hg) in buffered methanol.[12] Subsequent work has established the greater generality and utility of the sodium amalgam procedure. The overall achievement is equivalent to alkylation with dimethyl malonate followed by decarboalkoxylation. However, such reactions require strong base, strong acid, and/or high temperatures. The mildness of the desulfonylation procedure, neutral pH at <0 °C, attests to its greater potential in synthesis.

Since enolates do not lead to alkylation, the anions of β-keto sulfides[13] serve as their equivalent as illustrated in Scheme I. Reductive desulfenylation is achievable using the same conditions as employed for desulfonylation.

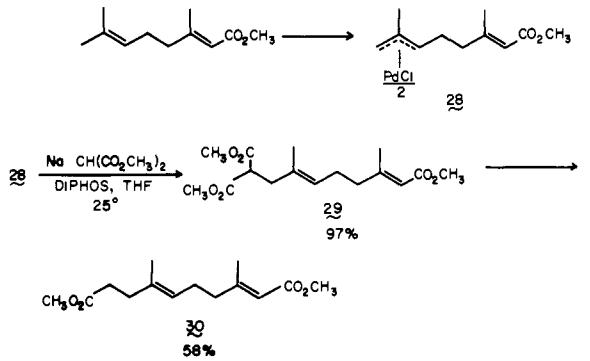
The sulfones obtained by decarbomethoxylation can be desulfonylated either with lithium in ethylamine at −78 °C or 6% sodium amalgum in buffered methanol for the phenyl



sulfones (vide infra).[12] The lower yields in the case of (*Z*)-4-ethyl-3-heptene appear associated with mechanical losses due to volatility as supported by the excellent yield in the isolation of 6,10-dimethyldodeca-5,9-dien-2-one. Thus, the sulfone ester moiety constitutes a quite versatile system.[14a]

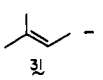


The value of this approach can be illustrated by the direct modification of simple terpenes into more complex ones. Complex **28** is directly available from methyl geraniate[1a] and serves as an intermediate toward a pheromone of the Monarch butterfly and toward the higher terpenoids. In the synthesis of the pheromone, **28** is alkylated with dimethyl sodiomalonate under standard conditions to give a nearly quantitative yield

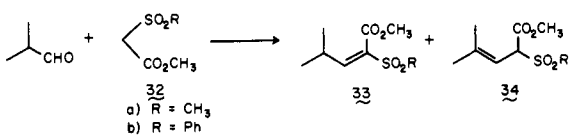


of a single alkylation product. The NMR spectrum shows the two methyl groups as singlets at δ 2.12 and 1.64 and two vinyl protons at δ 5.13 and 5.71 indicating the stereohomogeneity of the compound. To ensure that no signals were hidden, a $Eu(dpm)_3$ study was undertaken and the data are tabulated in Table II. No evidence for a second isomer is seen. The chemical shifts of the methyl groups are evidence for the *E* configuration for both double bonds as drawn. Such is confirmed by the successful completion of the synthesis. From the relative shift data, it is interesting that preferential complexation occurs at the enoate site. Decarbomethoxylation of **29** using lithium iodide trihydrate and sodium cyanide in hot DMF completes the synthesis of the pheromone **30**.[15] It should be noted that some loss of the stereohomogeneity of the double bonds is observed in this decarbomethoxylation which we have subsequently determined can be avoided by using the tetramethylammonium acetate procedure.

To achieve a net prenylation, we required an equivalent of anion **31** which is soft enough to achieve alkylation. Toward



this end, we condensed isobutyraldehyde with methyl methylsulfonylacetate (**32a**) and methyl phenylsulfonylacetate (**32b**) to give a mixture of **33** and **34**[14b] which was not separated since both lead to the same anion. NMR analysis allows easy identification of **33** and **34** and indicates a ratio of 2.5:1 (R =



CH_3) and 1.8:1 (R = Ph). It is interesting to note that only one isomer of **33** is present, but no assignment can be made.

Conversion of **33, 34** (R = CH_3) to the anion **35** and alkylation of **28** using diphos was somewhat erratic. While the desired alkylation product was definitely obtained in some runs, in others the elimination product **37** was obtained. The struc-

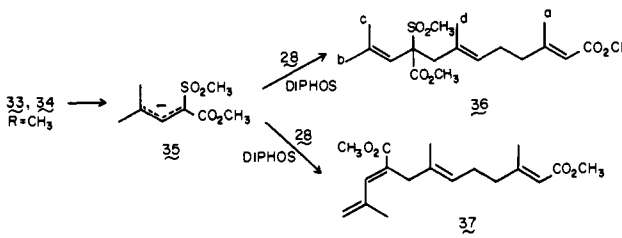
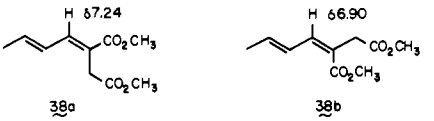


Table II. $Eu(dpm)_3$ Shift Study of **29**

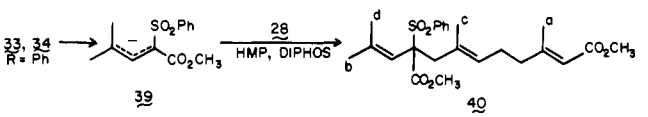
Signal	Assignment	8.4% Eu^{3+}	15.5% Eu^{3+}	ΔHz
1.64	C(7)-CH_3	1.73	1.81	17
2.17	CH_2CH_2-	2.35	2.52	35
2.17	C(3)-CH_3	2.65	3.23	106
2.60[a]	CH_2-CH	2.81	3.06	46
3.59[b]	CH_2CH			
3.72	OCH_3	4.30	4.99	127
3.77	$2OCH_3$	3.92	4.06	29
5.13	=$CHCH_2$	5.37	5.54	41
5.71	=CHCO	6.25	6.88	117

[a] Doublet, J = 8 Hz. [b] Triplet, J = 8 Hz.

ture of **36** follows from its spectra. In particular, the vinyl methyl groups are quite diagnostic indicating not only the regiochemistry but also the stereochemistry. Thus, the methyl groups appear as singlets at δ 2.17 (a), 1.86 (b), and 1.65 (c + d). The low-field position for a and the appearance of two methyl groups on the nonconjugated double bonds at high field confirm the *E,E* configuration. The structure of **37** again follows from its spectra. The UV spectrum shows two maxima—the α,β-unsaturated ester (λ_{max} 220 nm (ϵ 13 330)) and a dienoate (λ_{max} 250 nm (ϵ 8650); calcd 247 nm). The IR and NMR spectra show the absence of the methylsulfonyl group. The NMR spectrum shows only three methyl groups at δ 2.12, 1.90, and 1.65. A singlet at δ 3.09 for a bisallylic methylene group and the CH_2CH_2 unit as a broad absorption at δ 2.14 are the only methylene groups in the compound. Five vinyl protons, four of which are singlets (δ 7.11, 5.55, and 5.08, the last corresponds to 2 H which at 270 MHz are separated into two singlets at δ 5.14 and 5.11) and one a multiplet (δ 4,90), indicate only tri- and 1,1-disubstituted olefins. The presence of a 1,1-disubstituted olefin is confirmed by the 905-cm^{-1} band in the IR spectrum. Thus, the gross structure as shown is confirmed. The chemical shifts of the methyl groups at C(3) (δ 2.12) and C(7) (δ 1.65) suggest the *E,E* configuration for the 2,3 and 6,7 double bonds. The *Z* configuration for the 9,10 double bond is suggested by comparison of the chemical shift of the vinyl proton at C(10) (δ 7.11) with those of **38a** and **38b**[16].

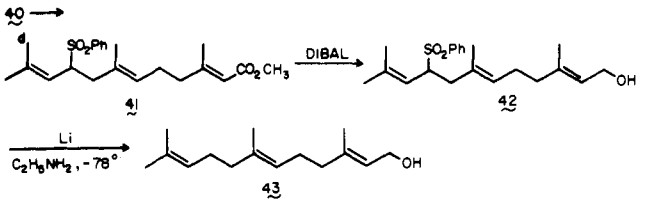


The use of the anion **39** derived from **33, 34** (R = Ph) did not lead to such a complication and led in 63% yield to the desired alkylation product **40** using HMPT as the activating ligand in THF. The regio- and stereochemistry follows from the spectra of **40** and the ultimate success of the prenylation



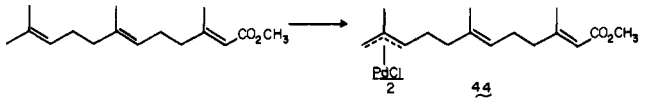
sequence. The appropriate vinyl protons at δ 5.64 (b), 5,35 (b), and 5.19 (m) and an AB pattern with H_A at δ 3.12 and H_B at δ 2.94 (J = 15 Hz) confirms the regiochemistry. The *E* configuration of the 2,3 double bond is confirmed by the δ 2.13 (s) absorption for the C(3) methyl group. The methyl groups on the nonconjugated double bonds appear at δ 1.77, 1.60, and 1.41. The abnormally high-field shift for one methyl group is associated with shielding by the phenylsulfonyl moiety. This conclusion is confirmed by comparison to the spectrum of **36** which shows no abnormalities and **41** which shows one methyl group to be shifted to even higher field. Thus, one methyl group must be held fairly rigidly in the shielding cone of the phen-

ylsulfonyl group which would be most consistent with d in **40**. The remaining two methyl groups absorb quite normally for that expected for b and c in **40**.

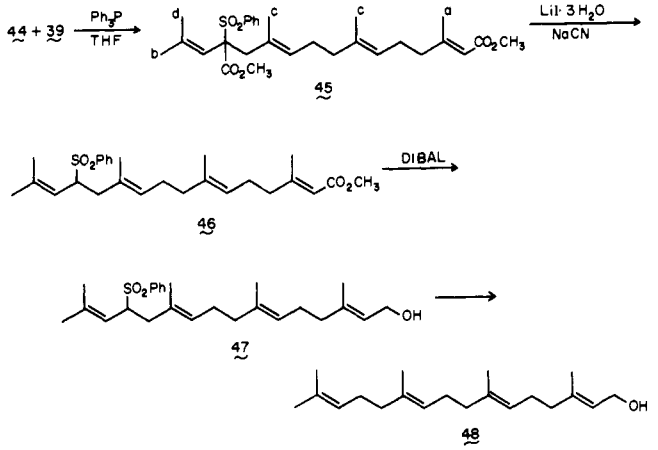


Decarbomethoxylation leads selectively to **41** which shows the methyl groups at δ 2.13, 1.63, 1.53. and 1.14. Note again the extraordinarily high field shift for one of the vinyl methyl groups tentatively assigned d in **41**. The chemoselectivity of this procedure is most pleasing since demethylation of the remaining ester might have been expected to compete. Presumably, the electron-withdrawing effect of the phenylsulfonyl group to the proximal carbomethoxy group makes this particular carboxy group a sufficiently better leaving group that demethylation occurs selectively. DIBAL reduction of **41** produced **42** which was desulfonylated with lithium in ethylamine to give (*E,E*)-farnesol. VPC and NMR analysis shows only the *E,E* isomer to be present. Comparison of spectral and chromatographic properties with those of an authentic sample of *all-trans*-farnesol and an isomeric mixture further confirms the assignment.

The convenience of this prenylation of a monoterpene to a sesquiterpene suggested the prenylation of the sesquiterpene to a diterpene. Complex **44** is available as previously noted[1a]



from (*E,E*)-methyl farnesoate which was obtained by oxidation of *E,E*-farnesol according to the procedure of Corey et al.[17] Alkylation of **44** with **39** using triphenylphosphine in THF led smoothly to a single alkylation product **45** in ~75–79%

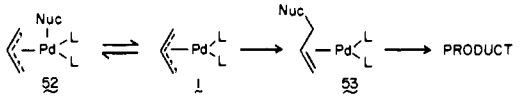


yields. The absorptions for the methyl groups in the NMR spectrum again serve as benchmarks for the regio- and stereochemistry. They appear as four singlets at δ 2.13, 1.76, 1.56 (two methyl groups), and 1.44 for the five methyl groups. As for **40**, one of the methyl groups appears at abnormally high field and is assigned to d in **45**. The appearance of an AB pattern with H_a at δ 3.01 and H_b at δ 2.85 (J = 15 Hz) for the C(12) methylene group further confirms the regiochemistry. This compound could be purified by recrystallization from hexane at −78 °C.

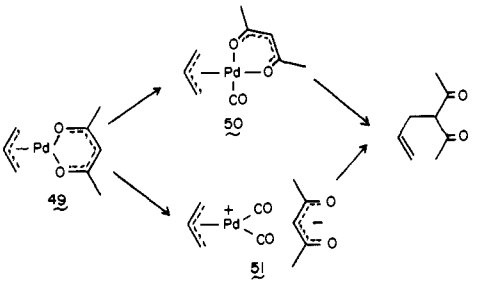
Selective decarbomethoxylation with lithium iodide and sodium cyanide led to **46** (methyl groups absorb at δ 2.12, 1.62, 1.54, 1.48, and 1.14). Our subsequent work suggests that use of tetramethylammonium acetate would be preferred in this step. DIBAL reduction gave **47** (methyl groups absorb at δ 1.66 (two methyl groups), 1.57, 1.53, and 1.16) which was desulfonylated in the usual way. The spectral properties of the *all-trans*-geranylgeraniol agree well with the published data.[18,19]

Discussion

The range of nucleophiles that can react with the intermediate cationic complexes suggests that they must be highly polarizable, soft anions. The reason for this could be severalfold. First, it is possible that kinetically reaction occurs initially at palladium. Subsequent C-alkylation then requires this initial reaction to be reversible. The lower the stability of the anion, the poorer the reversibility. The migration of aceto-



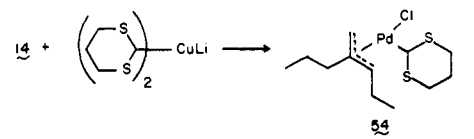
acetonoate from palladium to carbon has been observed in complex **49** upon addition of CO.[20] While this result has been interpreted as intramolecular migration from palladium to carbon through an intermediate such as **50**, an alternative explanation could invoke dissociation to **51** followed by nu-



cleophilic attack as in the alkylations that we observe, The latter interpretation would, of course, support the reasonableness of the reversibility of initial nucleophilic attack.

Alternatively, with an ambident electrophile such as **1**, it is possible that a softer nucleophile prefers to attack at carbon rather than palladium even in a kinetic reaction. The more stable the anion, the greater the importance of the thermodynamic stability of the initial product. It can be argued that formation of a C-C σ bond and an olefin palladium π bond at the expense of a π-allylpalladium bond is more exothermic than formation of a C-Pd σ bond. As the nucleophile becomes harder, charge distribution in **1** becomes more important in determining the regiochemistry. Since more positive charge resides at palladium rather than carbon, attack occurs there—ultimately leading to decomposition.

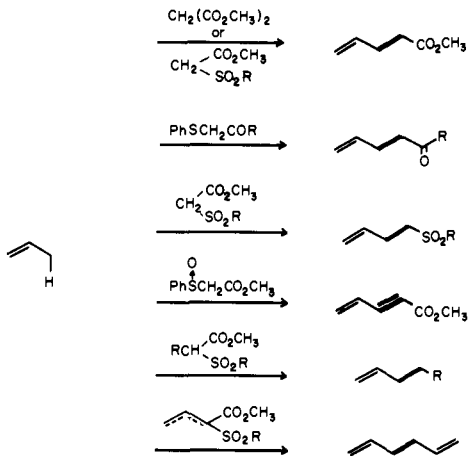
Support for either interpretation derives from the observations to date. Indeed, using the cuprate derived from 2-lithiodithiane a complex was isolated which was tentatively assigned structure **54**. It showed the characteristic multiplet at around



δ 4 for the π-allyl system as well as the typical dithiane absorptions. In addition, the mass spectrum shows a range of peaks at *m/e* 247–254 and one at *m/e* 119 which could arise by cleavage of the palladium–dithiane bond.

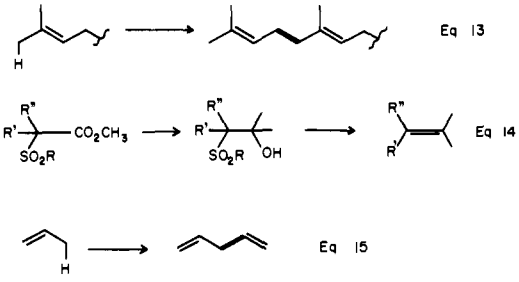
The effect of ligands also supports the above view. An ideal ligand would be a good σ donor to decrease attack at palladium while at the same time be a good π acceptor to delocalize electron density when nucleophilic addition occurs. Indeed, HMPT is the most versatile activating ligand since it allows

Scheme II



the broadest range of nucleophiles to react. Triphenylphosphine, our most commonly explored ligand, is much more limited. For example, with the anions of methyl phenylsulfinylacetate, only poor yields of alkylation product are obtained with triphenylphosphine, better yields with diphos, and best yields with HMPT. The solvent can reinforce the ligand effect. While THF or DME are satisfactory for most anions, when forcing conditions are needed, Me_2SO is preferred. Clearly, much more work must be done before this complex system can be better understood.

At the present time, the synthetic virtues are obvious. With the range of nuclophiles available we can achieve the overall transformations shown in Scheme II with the newly formed bond emboldened. The prenylation sequence (eq 13) is most noteworthy. Since π-allyl complexes are available directly from olefins, simple terpenes can be converted into the higher terpenoids. Considering the ability to use the sulfone ester as a precursor of a β-hydroxy sulfone which can be converted into an olefin (see eq 14),[21] this methodology also allows the overall transformation illustrated in eq 15.



Eq 13

Eq 14

Eq 15

Experimental Section

General. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-8 or Perkin-Elmer 267 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined on a Varian A-60A, Jeolco MH-100, or Brucker 270-MHz spectrometer. Chemical shifts are given in δ units, parts per million relative to tetramethylsilane as internal standard. Splitting patterns are designated s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are given in hertz. Mass spectra were taken on an AEI-MS-902 mass spectrometer at an ionizing current of 98 ms and an ionization energy of 70 eV.

Column chromatography was performed on Grace silica gel, grade 62, mesh size 60–200 (Davidson Chemical). Thick layer chromatography was performed on 200 × 400 1.5 mm layers of Merck silica gel PF-254 (E. Merck AG Darmstadt). Compounds were removed by repeated washings with ethyl ether. Solvent mixture chloroform, ether, 2-propanol is 400:320:8.

Temperatures recorded are external oil-bath temperatures. All reactions were performed under a nitrogen atmosphere. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Alkylation of 3 with Various Anions. With Sodiophenylthioacetone. Di-μ-chlorobis(1,2-tetramethylene-π-allyl)dipalladium(II) (345 mg, 0.728 mmol) and hexamethylphosphorous triamide (475 mg, 2.92 mmol) were stirred for 15 min in 5 mL of dimethyl sulfoxide. In a second flask, sodium hydride (131 mg, 3.0 mmol) was washed with pentane and blown dry with a stream of nitrogen, and 3 mL of dimethyl sulfoxide added. To this was added phenylthioacetone (498 mg, 3.0 mmol) and the solution stirred for 10 min and then added in one portion under a stream of nitrogen to the first solution. After stirring at ambient temperature for 16 h, the solution was poured into water and extracted with ether (2 × 100 mL). The combined ether layers were washed with 10% aqueous hydrochloric acid, water, and saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration and removal of solvent in vacuo gave an oil which was purified by preparative thick layer chromatography (PLC) on silica gel (R_f 0.70, chloroform, ether, 2-propanol) to give 1-(2′-acetylphenylthioethyl)cyclohexene and 2-(acetylphenylthiomethyl)methylenecyclohexane in a 70% (264 mg) yield in a ratio of 90:10 as determined by NMR integration of the peak at 5.48 vs. peaks at 4.6–4.9: NMR ($CDCl_3$) 7.2 (m, 5 H), 5.48 (m) and 4.6–4.9 (m) (1 H), 3.85 (t, J = 7 Hz, 1 H), 2.44 (m, 2 H), 2.20 (s, 3 H), 1.95 (m, 4 H), 1.56 (m, 4 H); IR (CCl_4) 1700, 1580, 1475, 1435, 1350 cm^{-1}; mass spectrum *m/e* (rel %) 360 (5), 218 (6), 217 (37), 166 (20), 152 (10), 151 (100), 150 (11), 149 (9), 135 (18), 133 (30), 123 (63), 121 (14), 110 (25), 109 (23), 108 (11), 107 (66), 95 (17), 93 (15), 91 (26), 83 (10), 81 (18), 79 (59), 78 (13), 77 (24), 67 (20), 66 (12), 65 (17), 55 (15), 53 (19), 51 (11) (calcd for $C_{16}H_{20}OS$, 260.12348; found, 260.12048). The remaining examples are summarized in Table III.

Spectral Properties. 7 (x = 2; Y = $PhSO_2$); NMR ($CDCl_3$) 7.8–8.0 (m, 2 H), 7.4–7.8 (m, 3 H), 5.43 (m, 1 H), 4.13 (dd, J = 9, 7 Hz, 1 H), 3.64 (s, 3 H), 2.64 (m, 2 H), 1.88 (m, 4 H), 1.56 (m, 4 H); IR (CCl_4) 1750, 1649, 1550, 1335, 1135 cm^{-1}; mass spectrum *m/e* (rel %) 308 (1), 168 (5), 167 (49), 166 (100), 151 (11), 138 (12), 135 (46), 134 (20), 125 (10), 107 (31), 105 (12), 95 (14), 94 (30), 93 (16), 92 (17), 91 (34), 81 (13), 79 (53), 78 (20), 77 (60), 67 (19), 65 (12), 59 (13), 57 (16), 55 (29), 53 (16), 51 (26), 45 (48), 44 (83), 43 (28), 42 (25), 41 (40) (calcd for $C_{16}H_{20}O_4S$, 308.1082; found, 308.1083).

8 (x = 2; Y = $PhSO_2$): NMR ($CDCl_3$) 7.4–2.9 (m, 5 H), 4.76, 4.64, and 4.57 (3s, 1 H), 4.37 (d, J = 4 Hz) and 4.07 (d, J = 6 Hz) (1 H, 3.61 and 3.59 (2s, 3 H), 3.0 (m, 1 H), 1.30–2.6 (m, 9 H); IR (CCl_4) 1752, 1695, 1650, 1550, 1430 cm^{-1}; mass spectrum (calcd for $C_{16}H_{20}O_4S$, 308.1082; found, 308.1083).

7 (x = 2; Y = PhS): NMR (CCl_4) 7.40 (m, 5 H), 4.88, 4.74 and 4.71 (3s, 2 H), 3.98 (m, 1 H), 3.59 (s, 3 H), 2.65 (m, 1 H), 1.2–2.6 (m, 8 H); IR (CCl_4) 3070, 2938, 2860, 1740, 1550 cm^{-1}; mass spectrum *m/e* (rel %) 276 (26), 182 (100), 167 (45), 166 (18), 149 (25), 135 (21), 123 (88), 121 (65), 110 (54), 109 (37), 108 (30), 95 (93), 93 (32), 91 (48), 79 (70), 78 (37), 77 (54), 67 (45), 66 (42), 55 (35), 53 (33), 51 (31), 41 (66), 40 (72), 39 (60) (calcd for $C_{16}H_{20}O_2S$, 276.11835; found, 276.11856).

Decarbomethoxylations of 1-(2′-Dicarbomethoxyethyl)-4-*tert*-butylcyclohexene. The diester (83 mg, 0.294 mmol), 225 mg (1.2 mmol) of lithium iodide trihydrate, and 13.3 mg (0.294 mmol) of sodium cyanide in 5 mL of DMF were heated at 120 °C for 12 h. After cooling to room temperature, it was poured into water and extracted (2 × 75 mL) with ether. The combined ether extracts were washed with water, 10% aqueous hydrochloric acid solution, and saturated aqueous sodium chloride solution. After drying and evaporation in vacuo, the crude oil was purified by PLC eluting with chloroform to give 66 mg (100%) of 1-(2′-carbomethoxyethyl)-4-*tert*-butylcyclohexene: NMR ($CDCl_3$) 5.38 (m, 1 H), 3.64 (s, 3 H), 1.0–2.6 (m, 11 H), 0.85 (s, 9 H); IR (CCl_4) 1740 cm^{-1}; mass spectrum *m/e* (rel %) 224 (1), 168 (47), 146 (33), 145 (20), 108 (41), 107 (38), 95 (21), 94 (64), 93 (88), 92 (28), 91 (22), 79 (32), 58 (100) (calcd for $C_{14}H_{24}O_2$, 224.1776; found, 224.1778).

Decarbomethoxylation of 1-(2′-Carbomethoxy-2′-phenylsulfonyl-1′-methylethyl)cyclohexene. The above procedure was repeated using 93 mg (0.29 mmol) of sulfone ester, 271 mg (1.44 mmol) of lithium iodide trihydrate, and 14 mg (0.29 mmol) of sodium cyanide in 5 mL of DMF for 12 h to give 76 mg (100%) of 1-(2′-phenylsulfonyl-1′-methyl)cyclohexene.

Hydrolysis of (*E*)-Methyl 2-Methylsulfonyl-4-propylhept-4-enoate. A solution of 50 mg (0.19 mmol) of **10** in 10 mL of methanol and 1 mL of water containing 90 mg (2.2 mmol) of sodium hydroxide was

Table III. Reaction Details for Alkylations of **3**

Nucleophile (mg, mmol)	Complex, mg, mmol	NaH, mg, mmol	Ligand (mg, mmol)	Product, mg, % yield
$PhSO_2CH_2CO_2CH_3$ (362, 1.69)	200, 0.442	74, 1.69	HMPT (276, 1.69)	200, 73
$PhSO_2CH_2CO_2CH_3$ (296, 1.38)	82, 0.173	60, 1.37	TOT[a] (269, 0.692)	83, 88
$PhSCH_2CO_2CH_3$ (357, 1.96)	116, 0.245	85, 1.96	HMPT (160, 0.98)	*b*
$PhSCH_2CO_2CH_3$ (157, 0.806)	102, 0.215	37.4, 0.86	TOT[a] (262, 0.860)	18, 15

[a] Workup of these reactions involved taking the crude product, adding methanol, cooling to −78 °C, and filtering to remove TOT. [b] Not detected.

stirred for 3 h at 22 °C. After evaporation of the methanol and dilution with water, the resulting aqueous solution was washed with ether and the ether layer discarded. Acidification of the aqueous layer with 2 N hydrochloric acid followed by ether extraction, drying, and evaporation gave 44 mg (93%) of the crystalline acid: mp 75–76 °C (carbon tetrachloride–pentane); NMR ($CDCl_3$) 9.82 (s, 1 H), 5.28 (t, J = 7 Hz, 1 H), 3.95 (dd, J = 10, 6 Hz, 1 H), 3.00 (s, 3 H), 2.65 (m, 2 H, 2.0 (m, 4 H), 1.1–1.7 (m, 2 H), 0.95 (t, J = 7 Hz, 6 H); Ir (CCl_4) 2500–3400 (br), 1720, 1310, 1120 cm^{-1}; mass spectrum *m/e* (rel %) 205 (6), 139 (15), 126 (16), 125 (77), 124 (52), 123 (31), 109 (26), 95 (51), 81 (100), 67 (39), 55 (60), 44 (82), 41 (62). Anal. ($C_{11}H_{20}O_4S$) C, H.

Preparation of 4,4-Dipropyl-2-methylsulfonyl-γ-butyrolactone (13). A suspension of 35 mg (0.14 mmol) of acid **11** in 5 mL of concentrated hydrochloric acid was refluxed for 90 min, cooled, poured into water, and extracted with ether. After drying and evaporation in vacuo, 35 mg (100%) of lactone **13**, mp 78 °C (carbon tetrachloride–pentane), was obtained: NMR (CCl_4) 4.08 (dd, J = 10, 8 Hz), 3.17 (s, 3 H), 2.62 (dd, J = 15, 8 Hz), 2.20 (dd, J = 15, 10 Hz), 1.2–1.9 (m, 8 H), 1.0 (m, 6 H); Ir (CCl_4) 1775, 1330 1145 cm^{-1}; mass spectrum *m/e* (rel %) 205 (12), 125 (100), 119 (24), 118 (72), 117 (74), 83 (16), 82 (18), 71 (10), 55 (20), 43 (42). Anal. ($C_{11}H_{20}O_4S$) C, H, O.

Preparation of (*E*)-1-Methylsulfonyl-3-*n*-propyl-3-hexene (12). A solution of 70 mg (0.28 mmol) of the acid **11** in 0.3 mL of 1.0 N aqueous sodium hydroxide (0.3 mmol) was evaporated to dryness in vacuo. The resulting solid mass was heated at 180–190 °C for 1 h, cooled, diluted with water, and extracted with ether. After drying and evaporation in vacuo, the product was isolated by PLC ($CHCl_3$) to give 43.4 mg (76%) of product as a colorless oil: NMR ($CDCl_3$) 5.21 (t, J = 7 Hz, 1 H), 2.8–3.1 (m, 2 H), 2.80 (s, 3 H), 1.9–2.6 (m, 6 H), 1.2–1.5)m, 2 H), 0.8–1.1 (m, 6 H); IR (CCl_4) 1315 cm^{-1}; mass spectrum *m/e* (rel %) 125 (5), 124 (40), 109 (21), 95 (42), 82 (17), 81 (100), 67 (28), 55 (35), 41 (36); mass spectrum 16 eV 204 (2), 125 (12), 124 (100), 81 (11). Anal. ($C_{10}H_{20}O_2S$) C, H, S.

Alkylative Elimination. Method A. Alkylation of Di-μ-chlorobis(2-methyl-1,3-trimethylene-π-allyl)dipalladium (22) with Methyl Phenylsulfinylacetate. Palladium complex **22** (115 mg, 0.242 mmol) and hexamethylphosphorous triamide (158 mg, 0.968 mmol) were stirred in 5 mL of dimethyl sulfoxide for 5 min. In a second flask, sodium hydride (82.9 mg, 1.94 mmol) was washed with pentane and dried under a stream of nitrogen, and 3 mL of dimethyl sulfoxide added. Methyl phenylsulfinylacetate (383 mg, 1.94 mmol) was added in one portion; the mixture was stirred for 20 min and then added in one portion to the first solution under a stream of nitrogen. After stirring at ambient temperature for 12 h, the solution was heated to 75 °C for 8 h. Upon cooling to room temperature, the solution was poured into water and extracted with ether (2 × 100 mL). The combined ether layers were washed with water and saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration and removal of solvent in vacuo resulted in a dark oil which was purified by preparative thick layer chromatography on silica gel (R_f 0.57, chloroform as eluting solvent) to give 6-carbomethoxymethylene-1-methylcyclohexene (78 mg, 97%) as a colorless oil: NMR ($CDCl_3$) 6.13 (t, J = 4 Hz, 1 H), 5.76 (s, 1 H), 3.73 (s, 3 H), 3.02 (t, J = 7 Hz, 2 H), 2.22 (m, 2 H), 1.84 (s, 3 H), 1.71 (t, J = 6 Hz, 2 H); IR (CCl_4) 1705, 1600 cm^{-1}; mass spectrum *m/e* (rel %) 166 (28), 138 (40), 135 (25), 116 (48), 109 (48), 107 (20), 105 (25), 91 (52), 79 (30), 77 (55), 65 (40), 51 (40) (calcd for $C_{10}H_{14}O_2$, 166.0993; found, 166.0994).

Method B. Alkylation of Di-μ-chlorobis(1,2-trimethylene-π-allyl)dipalladium (18) with Methyl Phenylsulfinylacetate. π-Allyl complex **18** (225 mg, 0.50 mmol) and triphenylphosphine (520 mg, 2.1 mmol) were stirred in 10 mL of dimethoxyethane for 10 min. In a second flask, *n*-butyllithium (1.0 mL, 1.5 M, 1.5 mmol) was added to a solution of diethylamine (200 μl, 2.0 mmol) in 10 mL of dimethoxyethane at 0 °C. After 5 min, methyl phenylsulfinylacetate (300 mg, 1.5 mmol) in 2 mL of dimethoxyethane was added; the resultant mixture was allowed to warm to room temperature and then added in one portion to the first solution, under a stream of nitrogen. The solution was refluxed for 5 h, cooled to room temperature, and poured into ether. The ether solution was washed with water and saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. After filtration and removal of solvent in vacuo the resultant oil was purified by preparative thick layer chromatography on silica gel (chloroform as eluting solvent) to give (*E*)-methyl 3(1′-cyclopentenyl)acrylate (62 mg, 41%). Preparative VPC (8 ft, 10% SE-30, 140 °C) gave a solid: mp 36.5–37.5 °C; NMR ($CDCl_3$) 7.28 (d, J = 16 Hz, 1H), 6.04 (brs, 1 H), 5.56 (d, J = 16 Hz, 1 H), 3.62 (s, 3 H), 2.44 (m, 4 H), 2.0 (m, 2 H); IR (CCl_4) 1720, 1630 cm^{-1}; mass spectrum *m/e* (rel %) 152 (78), 137 (34), 120 (55), 93 (75), 92 (38), 91 (100), 77 (60), 65 (33) (calcd for $C_9H_{12}O_2$, 152.0837; found, 152.0839).

Additional Examples. Alkylative Elimination with 14. Following method B, 250 mg (0.50 mmol) of **14** and 520 mg (2.1 mmol) of triphenylphosphine were reacted with 1.5 mmol of methyl lithiophenylsulfinylacetate in 12 mL of DME for 12 h at room temperature and 2 h at 70 °C to give after PLC (1% ether in chloroform) 105 mg (58%) of methyl 4-*n*-propylhepta-2,4-dienoate (**15**): VPC (10 ft, 20% SE-30, 205 °C) showed two peaks in the ratio of 7:3 (longer:shorter retention time) (using the lithio derivative of methyl methylsulfinylacetate, this ratio was 3.5:1); NMR (CCl_4) 7.48 and 7.05 (2d, J = 16 Hz, 1 H), 5.77 (t, J = 7 Hz, 1 H, 5.66 (d, J = 16 Hz, 1 H), 3.64 and 3.63 (2s, 3 H), 2.19 (m, 4H), 1.4 (m, 2 H), 1.03 and 0.93 (2t, J = 7 Hz, 6 H); IR (CCl_4) 1720, 1630, 980 cm^{-1}; *m/e* mass spectrum (rel %) 182 (14), 152 (43), 139 (50), 113 (100), 111 (60), 97 (47), 81 (43), 79 (35), 59 (38) (calcd for $C_{11}H_{18}O_2$, 182.1306; found, 182.1298).

Alkylative Elimination with 16. Following method B, 210 mg (0.5 mmol) of **16** and 836 mg (2.1 mmol) of diphos were reacted with 1.5 mmol of methyl lithiophenylsulfinylacetate in 15 mL of DME for 22 h at room temperature and 1 h at reflux to give 58 mg (41%) of **17** after PLC (1% ether in chloroform): VPC analysis (10 ft, 20% SE-30 on Chromosorb W, 130 °C) revealed a peak with a shoulder on the front side (thus, the isomer ratio was determined by NMR spectroscopy); NMR (CCl_4) 6.04 and 5.56 (m, 3 H), 3.66 and 3.62 (2s, 3 H), 2.22 and 1.95 (2s, 3 H), 1.85 (d, J = 6 Hz, 3 H); IR (CCl_4) 1720, 1640, 1610, 965 cm^{-1}; mass spectrum *m/e* (rel %) 140 (29), 125 (100), 109 (30), 81 (52), 79 (28), 77 (11), 59 (26) (calcd for $C_8H_{12}O_2$, 140.0837; found, 140.0832).

Alkylative Elimination with 20. Following method a, 131 mg (0.276 mmol) of **20** and 180 mg (1.10 mmol) of HMPT were reacted with 2.2 mmol of methyl sodiophenylsulfinylacetate in 8 mL of Me_2SO for 12 h at room temperature and 6 h at 75 °C to give 65 mg (71% yield) of **21** after PLC (chloroform): NMR ($CDCl_3$) 7.28 (d, J = 16 Hz, 1 H), 6.16 (t, J = 4 Hz, 1 H), 5.76 (d, J = 16 Hz, 1 H), 3.74 (s, 3 H), 2.16 (m, 4 H), 1.66 (m, 4 H); IR (CCl_4) 1730, 1639, 1626, 984 cm^{-1}; mass spectrum *m/e* (rel %) 166 (84), 138 (32), 135 (37), 107 (37), 95 (22), 94 (100), 93 (22), 91 (26), 79 (68), 77 (17), 67 (17), 59 (12) (calcd for $C_{10}H_{14}O_2$, 166.0993; found, 166.0990).

Alkylative Elimination with 24. Following method A, 99 mg (0.178 mmol) of **24** and 116 mg (0.712 mmol) of HMPT were reacted with 1.42 mmol of methyl sodiophenylsulfinylacetate in 8 mL of Me_2SO for 12 h at room temperature and 6 h at 75 °C to give 64 mg (87% yield) of **25** after PLC (chloroform): NMR ($CDCl_3$) 7.24 (d, J = 16 Hz, 1 H), 5.99 (t, J = 4 Hz, 1 H), 5.72 (d, J = 16 Hz, 1 H), 3.72 (s, 3 H), 2.1–2.6 (m, 5 H), 1.33 (s, 3 H), 1.15 (d, J = 7 Hz, 1 H), 0.76 (s, 3 H); IR (CCl_4) 1718, 1632, 980 cm^{-1}; mass spectrum *m/e* (rel

%) 206 (3), 163 (72), 162 (22), 147 (42), 137 (30), 131 (50), 125 (26), 124 (25), 123 (100), 121 (55), 119 (33), 111 (20), 110 (20), 109 (40), 107 (20), 105 (48), 93 (25), 91 (80), 79 (58), 69 (38), 67 (35), 65 (43), 59 (35) (calcd for $C_{13}H_{18}O_2$, 206.1306; found, 206.1319).

Desulfonylation of 26. To a mixture of 140 mg (3.5 mmol) of calcium in 50 mL of liquid ammonia (freshly distilled from sodium) was added 227 mg (0.71 mmol) of **26** in 1 mL of ether. After stirring for 5 min at −78 °C and 10 min at −33 °C and recooling to −78 °C, solid sodium benzoate was added until the blue color discharged. Ammonium chloride and ether were added and the ammonia was allowed to evaporate. The ether layer was washed with water and saturated aqueous sodium chloride solution and then dried ($MgSO_4$). After evaporation in vacuo, PLC (chloroform–ether–2-propanol, 400:320:8) gave 128 mg (100% yield) of methyl 3-(1′-cyclohexenyl)butyrate, identical with a previously characterized sample.

Desulfonylation of 1-(1′-Methyl-2′-carbomethoxy-2′-phenylsulfonylethyl)cyclopentene (27). Sulfone **27** (406 mg, 1.33 mmol), disodium hydrogen phosphate (755 mg, 5.32 mmol), and 6% sodium amalgam (1.5 g) were stirred in 5 mL of methanol at 0 °C for 1 h. After filtration, the solution was poured into saturated aqueous sodium chloride solution and extracted with ether (2 × 75 mL). The combined ether layers were dried over anhydrous magnesium sulfate. Filtration and removal of solvent in vacuo gave an oil which was purified by PLC (R_f 0.65, chloroform) to give methyl 3-(1′-cyclopentenyl)butyrate (190 mg, 87%): NMR ($CDCl_3$) 5.36 (m, 1 H), 3.58 (s, 3 H), 2.76 (m, 1 H), 2.28 (m, 5 H), 1.84 (m, 3 H), 1.06 (d, J = 6 Hz, 3 H); IR (CCl_4) 1730, 1610 cm^{-1}; mass spectrum m/e (rel %) 168 (23), 151 (34), 150 (37), 125 (31), 124 (26), 123 (43), 122 (91), 121 (100), 118 (35), 111 (35), 109 (63), 108 (51), 95 (86), 94 (74), 93 (51), 91 (63), 81 (63), 79 (91), 77 (80), 58 (86) (calcd for $C_{10}H_{16}O_2$, 168.1153; found, 168.1150).

Alkylation of Di-μ-chlorobis(1-methyl-2,3-tetramethylene-π-allyl)dipalladium(II) with Phenylthioacetone. To a solution of the π-allyl complex (293 mg, 0.585 mmol) and 1,2-bis(diphenylphosphino)-ethane (586 mg, 1.18 mmol) in 5 mL of tetrahydrofuran was added a solution of sodiophenylthioacetone prepared from 87 mg of 55% mineral oil dispersion (2.0 mmol) of sodium hydride (washed free of mineral oil with pentane) and 332 mg (2.0 mmol) of phenylthioacetone in 3 mL of THF. After stirring for 16 h at ambient temperature, the solution was poured into water and extracted with ether (2 × 100 mL). The combined ether layers were washed with water and saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration and removal of solvent in vacuo gave an oil which was purified by PLC (R_f 0.70, chloroform–ether–2-propanol) to give 1-(1′-methyl-2′-acetylphenylthioethyl)cyclohexene and 2-(acetylphenylsulfonylmethyl)ethylidenecyclohexane in 81% (256 mg) yield: NMR ($CDCl_3$) 7.2 m, 5 H), 5.1–5.4 (m, 1 H), 3.3–4.1 (m, 1 H), 2.50 (m, 2 H), 2.15 and 2.10 (2s, 3 H), 0.8–2.1 (m, 1 H) (at 270 MHz, the vinyl region shows two unresolved triplets at 5.57 and 5.44 and two quartets at 5.37 and 5.19 in the approximate ratio of 1:1:1:1 as well as four doublets for the methine proton next to sulfur at 4.08, 3.98, 3.67, and 3.65); IR (CCl_4) 1710, 1610, 1510 cm^{-1}; mass spectrum m/e (rel %) 274 (3), 231 (5), 168 (6), 167 (11), 166 (100), 165 (14), 149 (7), 147 (5), 135 (4), 123 (59), 121 (16), 110 (19), 109 (61), 93 (20), 91 (20), 81 (14), 79 (30), 77 (18), 67 (34), 65 (10), 55 (16) (calcd for $C_{17}H_{22}OS$, 274.1391; found, 274.1392).

Desulfurization of 1-(1′-Methyl-2′-acetylphenylthioethyl)cyclohexene and 2-(Acetylphenylthiomethyl)ethylidenecyclohexane. A mixture of 1-(1′-methyl-2′-acetylphenylthioethyl)cyclohexene and 2-(acetylphenylthiomethyl)ethylidenecyclohexane (256 mg, 0.935 mmol), disodium hydrogen phosphate (511 mg, 3.6 mmol), and 6% sodium amalgam (1.5 g) were stirred in 5 mL of methanol at 0 °C for 1 h and then filtered. The filtrate was poured into saturated aqueous sodium chloride solution and extracted with ether (2 × 100 mL), and the combined ether layers were dried over anhydrous magnesium sulfate. Filtration and removal of solvent in vacuo gave an oil which was purified by preparative thick layer chromatography on silica gel (R_f 0.40, chloroform) to give 140 mg (90% yield) of a mixture of 4-(1′-cyclohexenyl)-2-butanone and 2-(acetylmethyl)ethylidenecyclohexane. The compounds were separated by VPC (10-ft DC-710 column at 145 °C). 4-(1′-(Cyclohexenyl)-2-butanone (retention time 10 min): NMR ($CDCl_3$) 5.22 (m, 1 H), 2.16 (m, 3 H), 1.96 (s, 3 H), 1.94 (m, 4 H), 1.60 (m, 4 H), 0.98 (d, J = 6 Hz, 3 H); IR (CCl_4 1720, 1660 cm^{-1}; mass spectrum m/e (rel %) 166 (17), 151 (7), 135 (3), 123 (56), 118 (3), 110 (10), 109 (25), 108 (74), 95 (11), 93 (28), 91 (8), 87 (8), 85 (56), 83 (82), 81 (78), 79 (43), 67 (49), 55 (24), 54 (11), 47 (21), 43 (100) (calcd for $C_{11}H_{18}O$, 166.1358; found, 166.1360).

Desulfonylation of Homoallylic Sulfone. Preparation of 6,10-Dimethyldodeca-5,10-dien-2-one. Into a flask containing 95 mg (0.28 mmol) of 6,10-dimethyl-12-methylsulfonyldodeca-5,9-dien-2-one ethylene ketal was distilled 15 mL of ethylamine from lithium wire. To the resultant solution at 0 °C was added 33 mg (4 mg-atoms) of lithium wire cut into small pieces. The dark blue color persisted for 1.5 h. Slow addition of ammonium chloride quenched the reaction and the excess amine was allowed to evaporate. The gummy residue was partitioned between water and ether and the ether layer was dried ($MgSO_4$) and evaporated in vacuo to give 63 mg of crude ketal: NMR ($CDCl_3$) 5.23 (brt, J = 6 Hz, 2 H), 3.94 (s, 4 H), 1.64 (brs, 6 H), 1.28 (s, 3 H), 1.0 (t, J = 8 Hz, 3 H); mass spectrum m/e (rel %) 252 (21), 150 (100), 115 (55), 107 (92), 101 (70), 82 (64), 81 (61), 67 (80) (calcd for $C_{16}H_{28}O_2$, 252.2088; found, 252.2094).

The ketal (62 mg, 0.26 mmol) dissolved in a mixture of 5 mL of ether, 10 mL of methanol, and 5 mL of 3% aqueous hydrochloric acid was stirred overnight at room temperature. The mixture was poured into saturated aqueous sodium chloride solution and extracted twice with ether. The combined ether layers were dried ($MgSO_4$) and evaporated in vacuo to give 53 mg (86% overall) of ketone which was homogeneous by VPC: NMR ($CDCl_3$) 5.2 (brt, J = 6 Hz, 2 H), 1.8–2.6 (m, 10 H), 2.10 (s, 3 H), 1.64 (brs, 6 H), 0.99 (t, J = 8 Hz, 3 H); IR (CCl_4) 1720, 1650 cm^{-1}; mass spectrum m/e (rel %) 208 (9), 151 (40), 150 (30), 123 (51), 107 (35), 93 (30), 82 (46), 81 (35), 67 (100) (calcd for $C_{14}H_{24}O$, 208.1827; found, 208.1831).

Preparation of (Z)-4-Ethyl-3-heptene. In similar fashion 125 mg (0.613 mmol) of sulfone and 50 mg (7.2 mg-atoms) of lithium in ethylamine gave 24 mg (31%) of olefin: NMR ($CDCl_3$) 5.08 (t, J = 7 Hz, 1 H), 1.96 (m, 8 H), 1.0 (m, 9 H); mass spectrum m/e (rel %) 126 (18), 97 (22), 83 (30), 69 (24), 55 (100), 41 (28) (calcd for C_9H_{18}, 126.1408; found, 126.1404).

Preparation of 29. To a solution of 56.7 mg (0.0878 mmol) of complex **28** and 69.6 mg (0.176 mmol) of diphos in 5 mL of THF, which was heated to 40–50 °C for 45 min and recooled, was added 0.411 mmol of dimethyl sodiomalonate generated in the usual way. The mixture immediately turned red and slowly black. After workup in the usual way and purification by PLC (10% ether in chloroform) 53.1 mg (97%) of **29** was obtained: for NMR, see Table II; IR (CCl_4) 1750, 1731, 1648 cm^{-1}; mass spectrum m/e (rel %) 312 (2), 281 (15), 280 (30), 252 (20), 249 (18), 199 (50), 181)20), 180 (18), 168 (18), 161 (13), 149 (30), 148 (37), 145 (22), 139 (47), 135 (96), 121 (60), 114 (37), 107 (100), 82 (80), 79 (85), 59 (40) (calcd for $C_{16}H_{24}O_6$ 312.1573; found, 312.1579).

Preparation of 30. To a solution of 101 mg (0.326 mmol) of triester **29** in 5 mL of DMF was added 0.498 g (2.64 mmol) of lithium iodide trihydrate and 28.4 mg (0.58 mmol) of sodium cyanide. After heating at 120 °C for 17 h, the cooled mixture was poured into ether and washed with water. After the usual workup, PLC (1% ether in chloroform, two elutions) gave 48 mg (58%) of the desired product which was identical with an authentic sample by comparison of IR, NMR, mass spectrum, and VPC retention time (8 ft × 1/4 in 10% DC 710 on Chrom W column).

Preparation of 33 and 34. Where R = Ph. A mixture of 1.47 g (6.87 mmol) of methyl phenylsulfonylacetate, 0.495 g (7.88 mmol) of isobutyraldehyde, 0.117 g (1.37 mmol) of piperidine, and 0.330 g (5.50 mmol) of acetic acid in 50 mL of benzene was refluxed for 24 h with azeotropic removal of water using a Dean-Stark trap. After cooling to ambient temperature, the mixture was diluted with 30 mL of benzene and washed with water, the water layer was back-extracted with benzene, and the combined benzene layers were dried ($MgSO_4$) and evaporated in vacuo. Distillation of the residue at 130–138 °C (0.1 mm) gave 1.494 g (81%) of product which crystallized upon standing: mp 60–70 °C; NMR (CCl_4) 7.80 (m, 2 H), 7.52 (m, 3 H), 7.18 and 5.12 (2d, J = 11 Hz, 1 H), 4.62 (d, J = 11 Hz) and 3.10 (m, total 1 H), 3.69 (s, 3 H), 1.60 and 1.76 (2s) and 1.12 (d, J = 7 Hz) (total 6 H). IR ($CHCl_3$) 1730, 1617, 1585, 1465, 1319, 1142 cm^{-1}; mass spectrum m/e (rel %) 268 (1), 253 (3), 238 (3), 237 (10), 236 (28), 204 (5), 141 (12), 127 (41), 94 (33), 94 (29), 78 (27), 77 (100), 67 (40), 51 (31) (calcd for $C_{13}H_{16}O_4S$, 268.0769; found, 268.0768). Anal. ($C_{13}H_{16}O_4S$) C, H.

Where R = CH_3. The above procedure using 1.042 g (6.87 mmol) of methyl methylsulfonylacetate, 0.495 g (6.87 mmol) of isobutyraldehyde, 0.117 g (1.37 mmol) of piperidine, and 0.330 g (5.5 mmol) of acetic acid in 13 mL of dry benzene gave after usual workup and purification by column chromatography on silica gel (4:1 hexane–

chloroform) 0.918 g (65%) of product: NMR ($CDCl_3$) 7.15 and 5.14 (2d, J = 10 Hz, 1 H), 4.65 (d, J = 10 Hz) and 2.92–3.32 (m, 1 H), 3.83 and 3.93 (2s, 3 H), 2.98 and 3.19 (2s, 3 H), 1.81 and 1.88 (2s) and 1.14 (d, J = 7 Hz) (total 6 H); Ir ($CHCl_3$) 1730, 1620, 1320, 1134 cm^{-1}; mass spectrum m/e (rel %) 206 (3), 191 (15), 175 (38), 174 (100), 127 (71), 95 (58), 94 (51), 67 (62), 66 (25) (calcd for $C_8H_{14}O_4S$, 206.0613; found, 206.0613).

Preparation of 40. To a solution of 100 mg (0.155 mmol) of complex **28** and 101 mg (0.62 mmol) of HMPT in 5 mL of THF, which was heated for 15 min at 60 °C and then cooled to room temperature, was added a solution of **39** generated by treatment of 213 mg (0.795 mmol) of **33–34** (R = Ph) and 0.795 mmol of sodium hydride washed free of mineral oil. After the mixture was stirred for 16 h at ambient temperature, 123 mg (0.310 mmol) of diphos was added and stirring continued 24 h. After the usual workup and purification by PLC (once using 5:95 hexane–chloroform followed by a second chromatography using 5:95 ether–chloroform) gave 88 mg (63%) of desired product: for NMR, see Results: IR ($CHCl_3$) 1738, 1712, 1647, 1310, 1146 cm^{-1}; mass spectrum m/e (rel %) 256 (2), 167 (4), 156 (10), 150 (11), 141 (25), 127 (10), 95 (14), 94 (21), 77 (100), 69 (24).

Preparation of 41. As described previously 87.2 mg (0.194 mmol) of **40**, 208 mg (1.10 mmol) of lithium iodide trihydrate, and 11.0 mg (0.224 mmol) of sodium cyanide in 3 mL DMF gave after heating for 17 h at 120 °C and the usual workup and purification by PLC (5:95 ether–chloroform) 45 mg (59%) of **41**: NMR ($CDCl_3$) 7.8–8.1 (m, 2 H), 7.5–7.8 (m, 3 H), 5.62 (s, 1 H), 5.10 (m, 1 H), 4.89 (d, J = 11 Hz, 1 H), 3.64 (s, 3 H), 3.64–3.84 (m, 1 H), 2.78–3.12 (m, 2 H), 2.13 (brs, 7 H), 1.63 (s, 3 H, 1.53 (s, 3 H), 1.15 (s, 3 H); IR ($CHCl_3$) 1710, 1642, 1305 1142 cm^{-1}; mass spectrum m/e (rel %) 390 (2), 359 (4), 250 (14), 249 (74), 217 (25), 189 (54), 139 (15), 135 (100), 133 (23), 121 (30), 109 (38), 107 (38), 105 (20), 95 (20), 93 (60), 91 (24), 81 (27) (calcd for $C_{22}H_{30}O_4S$, 390.1865; found, 390.1863).

Preparation of (*E,E*)-Farnesol. To a solution of 44.0 mg (0.113 mmol) of methyl 9-phenylsulfonylfarnesoate in 5 mL of dry toluene at −40 °C was added 1 mL of a 1.40 N (1.4 mmol) solution of DIBAL in hexane. After 2.5 h at −40 °C and 1 h at 0 °C, the solution was cooled to −78 °C and 1 mL of methanol added. After 10 min at −78 °C, 0.5 mL of water was added and the mixture allowed to warm to room temperature. Solid anhydrous sodium sulfate was added and the slurry stirred 2 h. After filtration and washing of the solid with methylene chloride, the combined organic solution was dried again (Na_2SO_4), filtered, and evaporated in vacuo. PLC (15:85 ether–chloroform) gave 25 mg (61%) of alcohol **42**: NMR ($CDCl_3$) 7.7–7.9 (m, 2 H), 7.4–7.6 (m, 3 H), 5.35 (t, J = 8 Hz), 5.10 (m, 1 H), 4.89 (d, J = 11 Hz, 1 H), 4.11 (d, J = 8 Hz, 2 H), 3.83 (td, J = 11, 4 Hz, 1 H), 2.6–3.0 (m, 1 H), 2.2–2.4 (m, 1 H), 1.99 (m, 4 H), 1.63 (s, 6 H), 1.51 (s, 3 H), 1.14 (s, 3 H); IR ($CHCl_3$) 3600, 3500, 1662, 1303, 1141 cm^{-1}; mass spectrum m/e (rel %), no M^+, 221 (4), 220 (5), 147 (23), 136 (13), 135 (68), 133 (18), 121 (33), 119 (28), 109 (48), 107 (60), 105 (35), 95 (38), 93 (100), 79 (43), 78 (37), 77 (50), 69 (88), 67 (36), 55 (67).

To a solution of 24 mg (0.066 mmol) of **42** in 5 mL of dry ethylamine (freshly distilled from lithium) at −78 °C was added 43 mg (6.14 mg-atoms) of lithium wire cut into small pieces. After 1 h at −78 °C, 4.36 g of 1,2-dibromoethane was added and the blue color dissipated. Work-up as outlined in the general procedure for desulfonylations and PLC (5:95 ether–chloroform) gave 13.6 mg (92% yield) of farnesol. Its identity with an authentic sample of (*E,E*)-farnesol (kindly supplied by Professor C. Sih) was established by IR, NMR, and VPC on a column that separates all the isomers.

Preparation of 45. A solution of 268.2 mg (0.343 mmol) of complex **44** and 179.6 mg (0.6856 mmol) of triphenylphosphine in 10 mL of ether was stirred for 10 min and the solvent evaporated in a stream of nitrogen. After drying overnight in vacuo, the oil was dissolved in 5 mL of dry THF and an additional 179.6 mg (0.6856 mmol) of triphenylphosphine added. To this solution, a solution of **39** generated as outlined previously from 367.2 mg (1.37 mmol) of sulfone ester **33–34** and 32.9 mg (60 mg of 55% mineral oil dispersion, 1.37 mmol) in 5 ml of dry THF was added all at once. After the mixture was stirred for 20 h at room temperature, workup and purification by PLC (2:98 ether–chloroform) gave 281.4 mg (80% yield) of desired product **45**: NMR (CCl_4) 7.7–8.0 (m, 2 H), 7.4–7.7 (m, 3 H), 5.58 (s, 1 H), 5.28 (s, 1 H), 5.16 (m, 2 H), 3.62 (s, 6 H), 3.10 (d, J = 15 Hz, 1 H), 2.76 (d, J = 15 Hz, 1 H), 2.13 (br s, 7 H), 1.96 (br s, 4 H), 1.76 (s, 3 H), 1.56 (s, 6 H), 1.44 (s, 3 H); IR ($CHCl_3$) 1728, 1710, 1645, 1585, 1309, 1145 cm^{-1}; mass spectrum m/e (rel %), no M^+, 375 (53), 343 (34), 311 (48), 201 (28), 198 (23), 163 (22), 161 (61), 151 (35), 149 (30), 147 (33), 135 (53), 133 (83), 125 (37), 121 (100), 119 (65), 109 (44), 107 (100), 105 (71), 95 (72), 93 (93), 85 (24), 83 (29), 82 (27), 81 (83), 79 (84), 77 (86), 69 (40). Anal. ($C_{29}H_{40}O_6S$) C, H.

Preparation of (*E,E,E*)-Geranylgeraniol. As outlined for the preparation of **41**, 70.9 mg (0.137 mmol) of **45**, 162.5 mg (0.865 mmol) of lithium iodide trihydrate, and 8.3 mg (0.165 mmol) of sodium cyanide in 3 mL of DMF gave after 20.3 h at 120 °C and PLC (5:95 ether–chloroform) 27.5 mg (44% yield) of **46**: NMR (CCl_4) 7.7–7.9 (m, 2 H), 7.4–7.7 (m, 3 H), 5.58 (s, 1 H), 5.04 (m, 2 H), 4.83 (d, J = 10 Hz, 1 H), 3.68 (td, J = 10, 3 Hz, 1 H), 3.62 (s, 3 H), 2.5–3.0 (m, 2 H), 2.12 (s, 3 H), 1.8–2.1 (m, 8 H), 1.62 (s, 3 H), 1.54 (s, 3 H), 1.48 (s, 3 H), 1.14 (s, 3 H); IR ($CHCl_3$) 1700, 1655, 1585, 1306, 1147 cm^{-1}; mass spectrum m/e (rel %) 458 (<1), 317 (13), 203 (14), 175 (12), 149 (17), 147 (16), 135 (100), 121 (42), 109 (43), 108 (40), 107 (38), 93 (75), 81 (37), 79 (26), 77 (25), 69 (44).

Following the procedure for the preparation of **42**, 27.5 mg (0.060 mmol) of sulfone ester **46** in 4 mL of toluene and 1.0 mL of 1.4 M (1.4 mmol) solution of DIBAL in toluene gave after PLC (16:84 ether–chloroform) 20.8 mg (81%) of alcohol 47: NMR (CCl_4) 7.7–7.9 (m, 2 H), 7.4–7.6 (m, 3 H), 5.38 (m, 1 H), 5.14 (m, 2 H), 4.87 (d, J = 11 Hz, 1 H), 4.08 (d, J = 6 Hz, 2 H), 3.74 (td, J = 11, 3 Hz, 1 H), 2.64–2.84 (m, 3 H), 1.84–2.30 (m, 8 H), 1.66 (s, 6 H), 1.57 (s, 3 H), 1.53 (s, 2 H), 1.16 (s, 3 H); IR ($CHCl_3$) 1665, 1600, 1307, 1146 cm^{-1}; mass spectrum m/e (rel %), no M^+, 412 (0.5), 271 (9), 203 (10), 135 (35), 121 (31), 109 (60), 107 (41), 105 (20), 95 (31), 93 (100), 91 (21), 81 (65), 79 (28), 77 (25), 69 (75), 55 (48) (calcd for $M - H_2O$, $C_{26}H_{36}O_2S$, 412.2436; found, 412.2439).

Following the procedure for the preparation of **43**, 14.1 mg (0.0328 mmol) of sulfone **47** was desulfonylated using 21 mg (3 mg-atoms) of lithium in 20 mL of ethylamine (freshly distilled from lithium) to give, after the usual workup and purification by Kugelrohr distillation at 140–160 °C (0.05 mm) followed by PLC (5:95 ether–chloroform), 9.3 mg (98%) of geranylgeraniol whose NMR and IR spectra agree with published data.[18]

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Stereocontrolled Approach to Steroid Side Chain via Organopalladium Chemistry. Partial Synthesis of 5α-Cholestanone

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Abstract: Stereocontrolled introduction of an acyclic unit onto a cyclic system was accomplished using π-allylpalladium chemistry. Using stoichiometric palladium chemistry, methyl 3-methoxy-19,24-bisnor-20-isocholane-1,3,5(10)-tetraenoate was synthesized from estrone methyl ether. Thus, steroids epimeric at C(20) to the natural series are available from the 17-keto compounds. Alternatively, steroids possessing the natural configuration at C(20) are available from the starting materials via a catalytic palladium reaction. Estrone methyl ether was converted to methyl 3-methoxy-19,24-bisnorcholane-1,3,5(10)-tetraenoate. A partial synthesis of 5α-cholest-24-enone and 5α-cholestanone was achieved from testosterone.

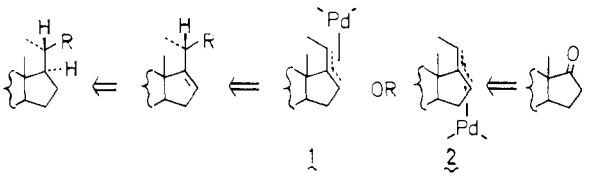
Introduction

The total synthesis of steroids represents one of the great challenges to synthetic chemists and has culminated in several elegant and practical approaches to this ring system,[1,2] One problem in steroid synthesis that has received considerably less attention is the stereocontrolled introduction of the cholesteryl side chain. The importance of this problem is heightened by the interest in ecdysones (insect molting hormones), the metabolites of vitamin D, and other unusual steroids possessing substituted side chains. Biosynthetic and metabolism studies of cholesterol have generated a need for modified side chains. Furthermore, the stereocontrolled attachment of an acyclic side chain onto a ring system constitutes an oftentimes encountered problem. The methodology developed for the steroid system should have broader applicability.

The problem factors down into two major concerns—(1) the ability to add the necessary carbon framework with appropriate substitution for further elaboration and (2) the creation of stereochemistry at C(17) and C(20). To circumvent the latter difficulty, several approaches have used a bisnorcholanic acid derivative in which both these centers already exist in the proper stereochemistry.[3] Indeed, a recent synthesis of a 24,25-dihydroxy system employed this strategy.[4] The center at C(17) is not a major problem since catalytic reduction of Δ^{16} or $\Delta^{17(20)}$ steroids does introduce hydrogen in the 17α configuration.[5] The main difficulty rests in the creation of C(20).

Reduction of $\Delta^{17(20)}$ or $\Delta^{20(22)}$ unsaturated steroids has led to the *R* configuration at C(20) with varying degrees of control.[5,6] Most recently, the formation of the (*E*)-$\Delta^{20(22)}$ unsaturated isomer via a wittig reaction on a 17-acetyl steroid followed by catalytic hydrogenation has been claimed to give only the natural configuration at C(20),[7] although this has been questioned.[7c] Alkylation of the enolate of a 17β-carbomethoxymethyl steroid with 4-methylpentyl bromide is also reported to give a single epimer.[8] A most elegant solution to the problem involved the introduction of the side chain with correct stereochemistry via a Claisen–Johnson rearrangement concomitant with creation of the D ring.[9]

The fact that the reduction of Δ^{16} unsaturated steroids provides the desired configuration at C(17) allows simplification of the problem to one of allylic alkylation with stereochemical control at an acyclic carbon. Using palladium as a template to provide conformational rigidity to direct the stereochemistry appeared to be a reasonable approach to the general problem of stereocontrol in conformationally nonrigid (e.g., acyclic or macrocyclic) systems. Depending upon the stereochemistry of formation of the new C–C bond with the complexed species, either **1** or **2** would be required. The req-



uisite complexes should be available from olefination procedures on a C(17) ketone. Indeed, the ready availability of 17-keto steroids makes them most attractive as starting materials. We, therefore, undertook an investigation of the stereochemistry of alkylation of π-allylpalladium complexes which has resulted in the ability to form either epimer.[10]

Results

Our investigation began with estrone methyl ether (**3**) which was converted to the 17-ethylidene derivative **4** via the Wittig reaction.[11] We find that use of potassium *tert*-butoxide in refluxing THF to be the better conditions (81%) compared with dimsylsodium in Me_2SO (5%) in our hands. The *Z* configuration is assigned in analogy to the literature. A small amount of the *E* isomer is detectable in the NMR spectrum (δ 0.78) of the crude mixture which was removed in the subsequent

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