Allylic Alkylation. Palladium-Catalyzed Substitutions of Allylic Carboxylates. Stereo- and Regiochemistry

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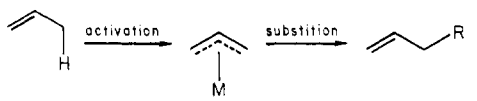
Abstract: The reaction of allyl acetates with the sodium salt of dimethyl malonate or methyl benzenesulfonylacetate in the presence of catalytic quantities of tetrakis(triphenylphosphine)palladium is probed. The reactivity of 1-(1′-acetoxyethyl)cycloalkenes falls in the order $5 \gtrsim 7 \gg 6$. The ability to invert the normal reactivity of two leaving groups is illustrated. With a trisubstituted double bond olefin stereochemistry is completely retained, but with disubstituted double bonds substantial loss of olefin stereochemistry occurs. The displacement of the allyl acetates proceeds with complete retention of stereochemistry at the center suffering displacement except for the anion of bis(benzenesulfonyl)methane, in which case a mixture of stereoisomers results. The loss of stereochemistry in the latter case stems from stereorandomization of the starting allyl acetate competing with the displacement. By use of a lactone, in which stereorandomization of the leaving group cannot occur, complete retention of configuration at the center undergoing substitution is restored. The mechanism of the reaction is discussed.

Chemoselective replacement of an allylic C–H bond by a C–C bond represents a formidable challenge to the synthetic chemist. While some limited methods, such as the Alder ene reaction,[1] exist, a process such as outlined in eq 1 promises to have greater ver-



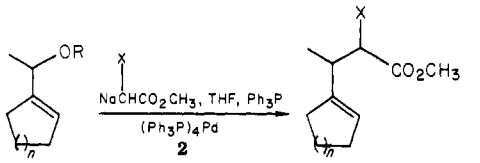
(1)

satility in analogy to carbonyl chemistry where the activation step is enolization and the substitution step involves reactions with electrophiles. The strictly analogous process for olefins, metalation with an organolithium (e.g., *n*-butyllithium–TMEDA) followed by reaction with an electrophile,[2] suffers from the limited types of olefins that successfully react and the incompatibility with virtually all functional groups.

In searching for a mild and chemoselective approach to this problem, we turned to the use of a palladation reaction for the activation step[3-5] and subsequent treatment with a nucleophile for the substitution step.[5a,6,7] Indeed, such an approach has proved to be quite general and, equally important, compatible with most functional groups—including a carbonyl group. In searching to evolve a process of allylic alkylation that would be catalytic in palladium,[8] we turned our attention to the substitution stage since allyl alcohols, allyl phenyl ethers, and allyl carboxylates are reported to react with enamines and active methylene compounds in the presence of catalytic amounts of various palladium species.[9] Hopefully, such a reaction can be combined with a catalytic activation step to have an overall catalytic allylic alkylation. In order to do so, the nature of the catalytic substitution reaction had to be fully defined. Furthermore, such reactions would seem to present advantages over more conventional alkylations and may offer new degrees of selectivity. For example, allyl alcohols and their carboxylates are more readily available in a stereodefined form and more stable in comparison to allyl halides and tosylates, conventional allylating agents. Elimination reactions frequently compete with substitution with these latter groups—especially in cyclic cases like 3-substituted cyclohexenes. The use of palladium to specifically activate otherwise unreactive allyl derivatives points to the possibility of unusual chemoselectivity. In this paper, we wish to report the unusual selectivity that palladium-catalyzed allylic alkylations offer.

Results

Initial investigations were directed toward allyl acetates possessing an endocyclic olefin. Treatment of 1-(1′-acetoxyethyl)-cyclopentene (**1a**) with the sodium enolate of either dimethyl malonate or methyl benzenesulfonylacetate in refluxing tetrahydrofuran in the presence of tetrakis(triphenylphosphine)palladium(0) (**2**) and excess triphenylphosphine led to exclusive alkylation at the exocyclic carbon atom, giving **3a** and **3b** in 79 and 71% yields, respectively.



1, $n = 1$
4, $n = 3$
a, R = $COCH_3$
b, R = H

3, $n = 1$
5, $n = 3$
a, X = CO_2CH_3
b, X = SO_2Ph

The structural assignment was based on ^1H NMR data. In particular, observance of a three-proton doublet ($J = 6.5$ Hz) at

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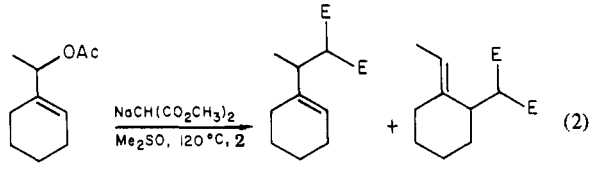
δ 1.08 in **3a** indicated that the methyl group was adjacent to an sp^3-hybridized carbon atom, thus confirming an endocyclic double bond. Diastereomeric methyl groups in **3b** appeared as two doublets (J = 6.5 Hz for each) at δ 1.39 and 1.11.

Similar alkylations of 1-(1′-acetoxyethyl)cycloheptene (**4**) with both nucleophiles proceeded at a somewhat slower rate, giving **5a** and **5b** in 73 and 67% isolated yields (eq 1). Whereas **1a** gave complete reaction after 12–24 h, alkylations with **4** under identical conditions required 38–44 h for total consumption of starting material. The ^{1}H NMR spectra closely resembled those of **3a** and **3b**, with the methyl doublet (J = 7 Hz) occurring at δ 1.03 in **5a** and the diastereomeric methyl group in **5b** appearing as doublets (J = 7 Hz for each) at δ 1.37 and 1.04. Analysis of **5a** by VPC[10a] indicated homogeneity. Attempted alkylations with either **1** or **4** in the absence of palladium resulted in only recovery of starting material.

In contrast to these regiochemical results, 1-(1′-acetoxyethyl)cyclohexene (**6**) was inert toward alkylations under the standard conditions of refluxing tetrahydrofuran. With the more drastic conditions of dimethyl sulfoxide at 120 °C, there was produced an 85:15 mixture of **7a** and **7b** in 50% yield[7] (eq 2).

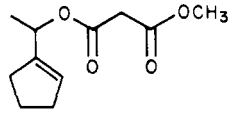


(2)

6 **7a** **7b**

E = CO_2CH_3

Olefin **1b** illustrates the suitability of an allyl alcohol as a substrate for this reaction (eq 1). Although alkylation with dimethyl malonate proceeded at a much slower rate than with the corresponding acetate **1a**, **2a** was formed in 81% yield after 48 h. While formation of π-allyl complexes from allyl alcohols is precedented,[11] initial transesterification to **8**, prior to oxidative addition, cannot be discounted as a mechanistic possibility.



(4)

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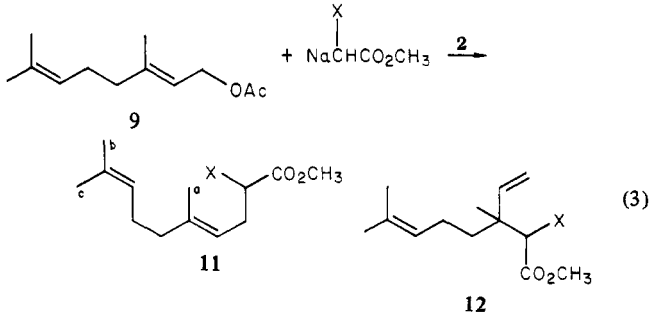
To probe the question of double-bond integrity in these reactions, two isomeric acyclic trisubstituted allyl acetates, geranyl acetate (**9**) and neryl acetate (**10**), were examined (eq 3 and 4).



(3)

9 **11** **12**

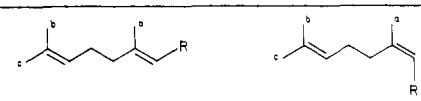
a, X = CO_2CH_3 b, X = $PhSO_2$

(10) (a) 10% DC-710 on Chromosorb W, 60/80 mesh size, 2.44 m × 0.64 cm at 175 °C. (b) 10% XE-60 on Chromosorb W, 60/80 mesh size, 2.44 m × 0.64 cm at 155 °C. (c) Same as (b) except at 110 °C. (d) Same as (a) except at 165 °C. (e) 10% DC-710 on Chromosorb W, 60/80 mesh size, 3.66 m × 0.64 cm at 142 °C. (f) Same as (a) except at 200 °C. (g) Same as (b) except at 95 °C. (h) Same as (b) except at 175 °C. (i) 10% DC-710 on Chromosorb W, 60/80 mesh size, 3.05 × 0.64 cm at 165 °C.

(11) Murahashi, S.; Shimamura, T.; Moritani, I. *J. Chem. Soc., Chem. Commun.* **1974**, 931.

(12) Bohlmann, F.; Zeisberg, R.; Klein, E. *Org. Magn. Reson.* **1975**, *7*, 426.

Table I. ^{13}C NMR Parameters[a] of Model Trisubstituted Olefins[12]



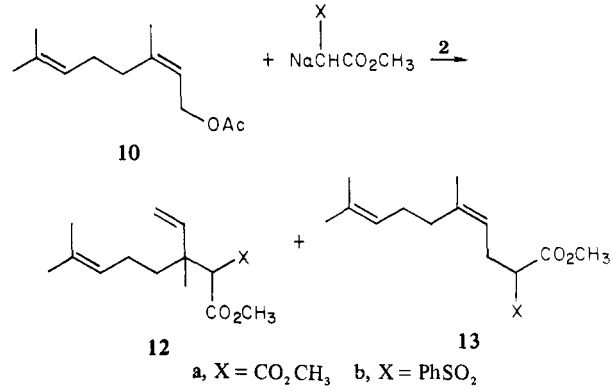
R	entry	a	b	c	entry	a	b	c
CH_2OH	1	16.0	17.4	25.5	4	23.5	17.6	25.5
CH_2OAc	2	16.4	17.7	25.7	5	23.5	17.6	25.7
CHO	3	17.0	17.4	25.3	6	24.4	17.4	25.3

[a] All spectra were recorded in $CDCl_3$ solvent and chemical shifts were measured in parts per million downfield from internal Me_4Si.

Alkylation of **9** with the sodium salt of dimethyl malonate or methyl benzenesulfonylacetate produced a mixture of regioisomers **11** and **12** in 84–92% yields. The regiochemical result exhibited a marked sensitivity to the nature of the nucleophile, with the more sterically encumbered sulfonylacetate giving attack exclusively at the primary carbon atom (<3%, **12b**). In contrast, with dimethyl malonate, **12a** comprised 10% of the product mixture. Isomers **11a** and **12a** were readily separable by VPC[10b] and analyzed by ^{1}H and ^{13}C NMR spectroscopy. The terminal vinyl group of **12a** was identified by three olefinic resonances at δ 5.98 (d of d, J = 17.5, 11 Hz), 5.03 (d, J = 11 Hz), and 4.94 (d, J = 17.5 Hz). For **11a** and **11b**, the one-proton triplets at δ 3.37 (**11a**, J = 8 Hz) and 3.91 (**11b**, J = 7 Hz), assigned to the C(2) methine, indicated that alkylation had occurred at a primary carbon atom. Noteworthy is the fact that the product of substitution at the primary carbon atom had completely retained the olefin geometry. No trace of **13a** (vide infra) was detectable by VPC or NMR (^{1}H or ^{13}C) analysis. Likewise, the ^{1}H and ^{13}C NMR spectra of **11b** provided no evidence for **13b**.

The *E* stereochemistry of **11** was deduced from ^{13}C NMR data, which is known to be an extremely sensitive probe for olefin geometry. In particular, steric compression results in a shielding effect for cis substituents. Comparison of the *E* (entries 1, 2, and 3) and *Z* (entries 4, 5, and 6) isomers compiled in Table I reveals a consistent 7–8-ppm upfield shift for C_a in the *E* isomer. Confirmation of the *E* stereochemistry in **11a** and **11b** was thus accomplished by comparison of C_a (**11a**, δC_a 16.0, δC_b 17.6, δC_c 25.5; **11b**, δC_a 15.8, δC_b 17.4, δC_c 25.4) with the absorptions for this methyl group in the *Z* isomer (vide infra).

Alkylation of neryl acetate (**10**) under the usual conditions gave **13** and **12** in 74–78% isolated yields (eq 4). As in the case of



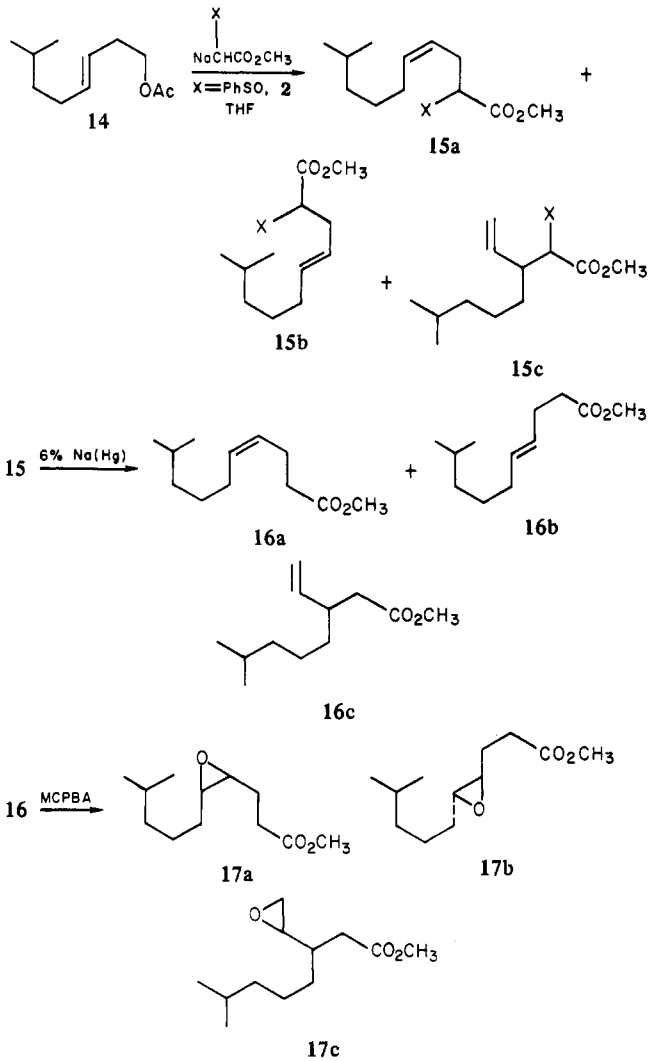
10 **12** **13**

a, X = CO_2CH_3 b, X = $PhSO_2$

9, the product resulting from attack at the primary carbon had completely retained the original olefin geometry, with no trace of **11a** or **11b** detectable by ^{1}H NMR or VPC[10b] analysis. The ^{13}C NMR spectra (**13a**, δC_a 23.3, δC_b 25.5; **13b**, δC_c 23.1, δC_b 17.4, δC_c 25.3) indicated the anticipated downfield shift for C_a in comparison to **11a** and **11b**, confirming the *Z* configuration.

Neryl acetate exhibited a striking sensitivity to the nature of the nucleophile. In contrast to **9**, the major product of alkylation with dimethyl malonate arose from attack at the tertiary carbon atom to give a 35:65 mixture of **13a** and **12a** in overall 74% yield. With methyl benzenesulfonylacetate, reversion to preference for attack at a primary carbon occurred, giving **13b** and **12b** in an 89:11 ratio. Although the regioisomers were chromatographically

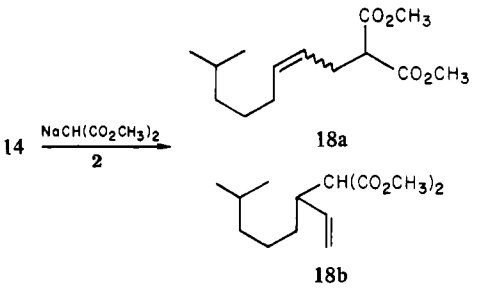
Scheme I. Alkylation of 1-Acetoxy-7-methyl-2-octene (**14**) with Methyl Benzenesulfonylacetate. Derivatization of Alkylated Products



inseparable, the presence of **12b** was indicated by two minor resonances at δ 6.00 and 5.98 (d of d, J = 17, 11 Hz for each) in the ^{1}H NMR spectrum, assigned as a diastereomeric olefinic proton in the terminal vinyl moiety of **12b**.

The acyclic disubstituted olefin 1-acetoxy-7-methyl-2-octene (**14**) (see Scheme I), a 90:10 mixture of Z:E isomers [the composition based on its synthesis[13] from 2-butene-1,4-diol (91% Z, Aldrich Chemical Co.) as well as ^{1}H NMR integration of the two acetoxymethylene protons appearing as doublets (J = 6 Hz for each) at δ 4.58 (Z isomer) and 4.50 (E isomer)], reacted with methyl benzenesulfonylacetate to produce a mixture of regio- and stereoisomers **15a** (32%), **15b** (30%), and **15c** (38%) in 84% yield. This result clearly indicates partial loss of olefin geometry. Unlike alkylations with trisubstituted olefins, **14** reacted at room temperature, although more slowly, producing a 76% yield of alkylated products after 48 h. The decrease in temperature was accompanied by a change in relative product composition (**15a**, 35%; **15b**, 17%; **15c**, 48%), with greater retention of the original olefin geometry observed. Alkylations with the less sterically demanding dimethyl malonate in refluxing tetrahydrofuran exhibited lower selectivity for the primary carbon atom, producing a 35:65 mixture of **18a** and **18b** (eq 5). No attempt to elucidate the ratio of stereoisomers in **18a** was made.

Determination of the isomeric composition of **15** was not possible via direct chromatographic or spectroscopic methods and suitable chemical derivatization was sought. Desulfonylation of



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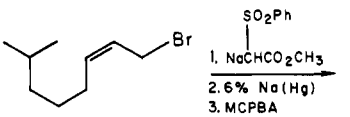
15 (Scheme I) with 6% sodium amalgam in the presence of an acid phosphate buffer[14] allowed subsequent VPC[10c] separation of regioisomer **16c** from stereoisomers **16a** and **16b** and determination of this ratio. The presence of a terminal vinyl group in **16c** was dictated by the characteristic ^{1}H NMR spectrum consisting of resonances at δ 5.62 (d of d of d, J = 17, 10.2, 8.5 Hz), 5.01 (d of d, J = 17, 1 Hz), and 4.99 (d of d, J = 10.2, 1 Hz) for the three olefinic protons. Determination of the relative ratio of **16a** and **16b** by VPC or NMR analysis was unsuccessful. Conversion of this olefin mixture to their epoxides, **17a–c**, facilitated separation and determination of the isomeric ratio by VPC.[10a] Correlation of **17a** and **17b** (VPC, NMR, IR) to independently synthesized material, prepared by alkylation of 1-bromo-7-methyl-2-octene (~85% Z), desulfonylation, and epoxidation (eq 6), confirmed the structural assignment.



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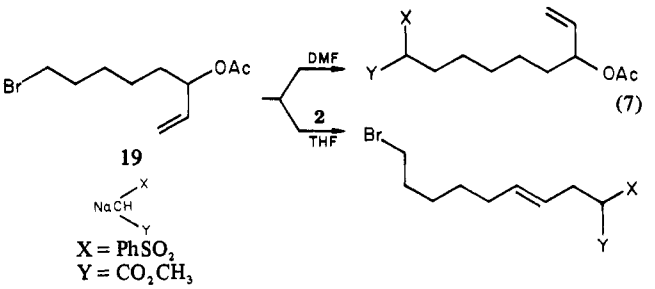
Alkylations conducted with bromoacetate **19** illustrate the unique chemoselectivity afforded by this method (eq 7 and 8).



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(8)

Reaction of **19** with methyl benzenesulfonylacetate in hot dimethylformamide produced **20** as the exclusive product in 75% yield, with the terminal vinyl and acetate methyl protons completely intact. In contrast, treatment of **19** in refluxing THF with the palladium catalyst afforded a 77% yield of **21** and 12% of the dimeric product, **22**. The presence of a two-proton triplet (J = 7 Hz) at δ 3.37 for **21** and a four-proton triplet (J = 7 Hz) at δ 3.38 in **22** confirmed the complete retention of bromine in both products.

To determine the stereochemical course of this reaction, alkylations with the Z (**23**) and E (**24**) isomers of 3-acetoxy-5-carbomethoxy-1-cyclohexene were examined. These substrates

(13) Colonge, J.; Poilane, G. *Bull. Soc. Chim. Fr.* **1955**, 953. Trost, B. M; Taber, D.; Alper, J. *Tetrahedron Lett.* **1976**, 3857.

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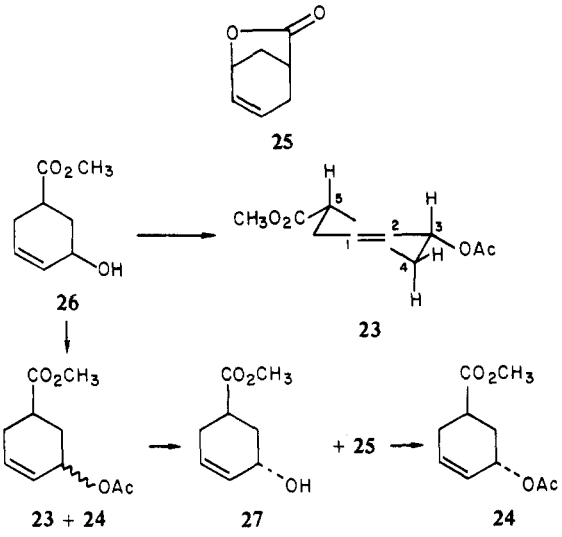
Scheme II. Preparation of (*Z*)- and (*E*)-3-Acetoxy-5-carbomethoxy-1-cyclohexenes



simplify analysis since formation of the π-allyl complex provides a symmetrical structure, thus removing problems arising from differentiation of both stereo- and regioisomers.

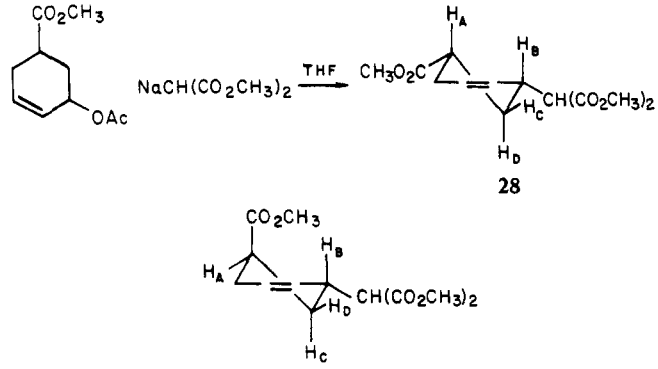
The *Z* isomer **23** was available via methanolysis and acetylation of lactone **25** (see Scheme II). Analysis of this product by VPC[10d] indicated contamination with 2% of the *E* isomer **24** (vide infra), probably arising from ester epimerization during methanolysis. Stereochemical assignment of **23** was based on the unambiguous nature of its synthesis and the ^{1}H NMR spectrum. At 270 MHz, a one-proton resonance at δ 1.76 (t of d, J = 12.5, 9.3 Hz) was assigned as the C-4 axial hydrogen. The large geminal coupling as well as two large vicinal coupling constants clearly indicated that the protons at C-3 and C-5 are pseudoaxial, thus confirming the *Z* configuration.

For the preparation of **24**, an attempted inversion of the hydroxy ester **26** via its mesylate or by activation with diethyl azodicarboxylate and triphenylphosphine proved unsuccessful. Acid-catalyzed isomerization, concomitant with acetylation of **26**, employing traces of perchloric acid in an acetic anhydride–ethyl acetate mixture, provided a 1:3 mixture of **23** and **24**. VPC separation[10d] at this juncture was possible, though tedious. Instead, base-catalyzed hydrolysis of this mixture and selective lactonization of the *Z* component **26** gave **27** contaminated with 7% of **26**. The ^{1}H NMR spectrum indicated the two olefinic protons in each isomer appearing as broad singlets at δ 5.78 (*E*) and 5.66 (*Z*), thus allowing NMR integration to give an accurate ratio of isomers. Acetylation of **27** afforded the trans acetate, contaminated with 7% of **23** as determined by VPC[10d] analysis.

Alkylation of **23** with the sodium salt of dimethyl malonate in the presence of the catalyst **2** and excess triphenylphosphine in refluxing THF produced a 92% isolated yield of **28** (Table II). At 270 MHz, H_C (δ 2.11, d of m, J = 12 Hz) and H_D (δ 1.47, q, J = 12 Hz) were clearly discernible. The requisite coupling constants, $J_{AD} = J_{BD} = J_{CD}$ = 12 Hz, indicate that both H_A and H_B are pseudoaxial. VPC analysis[10b] revealed contamination with approximately 2% of the *E* isomer **29** (vide infra), confirming complete stereospecificity within experimental limits.

Alkylation of **24** under identical conditions provided **29** in 80% yield, which VPC analysis[10b] indicated was contaminated by **28** to the same extent that **24** was contaminated by **23**. Again at 270 MHz, H_C (δ 1.96, d of d of d, J = 13.5, 9.5, 5.5 Hz) and H_D (δ 1.80, d of t, J = 13.5, 4 Hz) were readily observable, with the requisite coupling constants J_{AC} = 5.5, J_{AD} = 4, J_{BC} = 9.5, J_{BD} = 4, and J_{CD} = 13.5 Hz, suggesting that H_A is pseudoequatorial and H_B pseudoaxial. This assignment was further confirmed by the base-catalyzed isomerization of the less stable trans isomer, **29**, with potassium *tert*-butoxide in methanol to give a 75:25 mixture of **28** and **29**. Thus, under the conditions defined, these net S_N2 displacements occur with complete retention of configuration at the carbon undergoing substitution. Further, no evidence of elimination was seen.

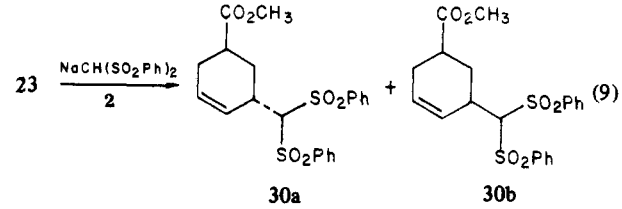
Table II. Alkylations of (*Z*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene with Dimethyl Malonate



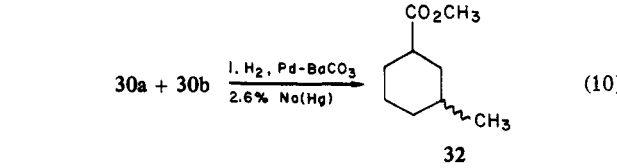
catalyst	ligand added	% yield	**28**:**29**
$Pd(PPh_3)_4$	PPh_3	90	98:2
$Pd(PPh_3)_4$		90	88:12
$Pd(PPh_3)_2C_2H_2$		91	79:21
$Pd(PPh_3)_4$	$(CH_3)_4NOAc$	60	97:3

Variation of the ligand had major effects on the degree of stereospecificity (Table II). Thus, alkylation of **23** under standard conditions with the omission of excess triphenylphosphine produced an 88:12 mixture of **28** and **29**. Decreasing the phosphine ligand concentration further by using ethylenebis(triphenylphosphine)-palladium(0) resulted in a 79:21 mixture of **28** and **29**. In contrast, addition of tetramethylammonium acetate induced a highly stereospecific reaction (**28**:**29**, 97:3).

Variation of the nucleophile also had a marked effect upon alkylation. Whereas reactions of **23** with dimethyl malonate and methyl benzenesulfonylacetate with excess triphenylphosphine were completely stereospecific, use of bis(benzenesulfonyl)methane[15,16] under identical conditions afforded drastically different results. In both tetrahydrofuran and dimethyl sulfoxide solvents, alkylation of **23** occurred in 92 and 74% yields, producing **30a** and **30b** in approximately equal amounts (eq 9). At 270 MHz the observance



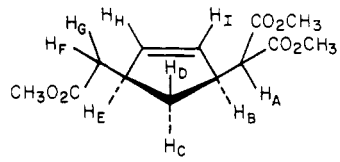
of two methyl ester resonances at δ 3.58 and 3.67 as well as two doublets ($J \simeq$ 2 Hz) at δ 4.57 and 4.54 assigned to the bis-(benzenesulfonyl)methine proton indicated the presence of both **30a** and **30b**. Confirmation of this isomeric relationship was accomplished by hydrogenation of **30a** and **30b**, followed by reductive elimination of the benzenesulfonyl moieties with 6% sodium amalgam to give **32** (eq 10). Comparison of **32** to an authentically



(15) Friedman, A. R.; Graber, D. R. *J. Org. Chem.* **1972**, *37*, 1902. Carpina, L. A. *Ibid.* **1973**, *38*, 2600. Stetter, H.; Steinbeck, K. *Justus Liebigs Ann. Chem.* **1974**, 1315.

(16) For a review of sulfones in synthesis, see: Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.

Table III. ^{1}H NMR Chemical Shift and Coupling Constants for Dimethyl (*Z*)-(3-(Carbomethoxymethyl)-4-cyclopenten-1-yl)malonate (33)[a]

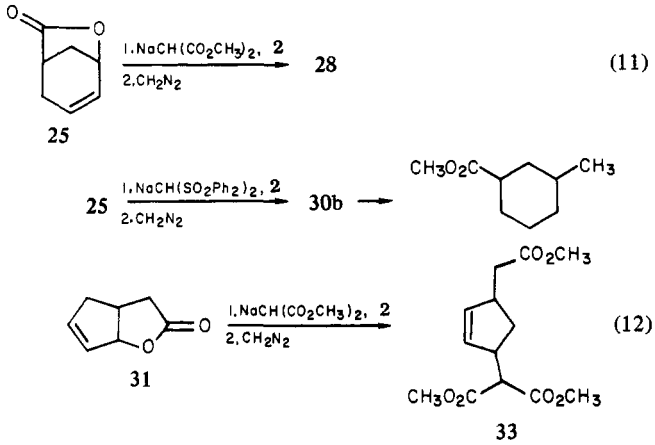


	H_A	H_B	H_C	H_D	H_E	H_F	H_G	H_H	H_I
H_A (δ 3.33)		9							
H_B (δ 3.40)	9		7.8	7.8				2	2
H_C (δ 2.42)		7.8		13.2	8.1				
H_D (δ 1.24)		7.8	13.2		7.8				
H_E (δ 3.03)			8.1	7.8		6.9	8.1	2	2
H_F (δ 2.25)					6.9		15.1		
H_G (δ 2.18)					8.1	15.1			
H_H (δ 5.66)		2			2				5.5
H_I (δ 5.77)		2			2			5.5	

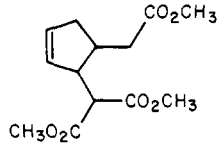
[a] At 270 MHz in C_6D_6 solvent with chemical shifts reported in parts per million downfield from $(CH_3)_4Si$ and coupling constants reported in hertz.

prepared sample[17] (85% *Z*, 15% *E*) by VPC[10e] and ^{1}H NMR revealed a *Z*:*E* ratio of 55:45.

Lactones **25** and **31** proved to be excellent substrates (eq 11 and 12). Thus, palladium-catalyzed alkylation of **25** with di-



methyl sodiomalonate and no excess triphenylphosphine, followed by esterification with diazomethane, produced **28** with an isomeric purity of greater than 99% *Z* (VPC analysis)[10b] in 88% isolated yield. Noteworthy is the high stereospecificity observed even in the absence of excess triphenylphosphine. More remarkably, reaction of **25** with sodium bis(benzenesulfonyl)methane in the presence of **2** and subsequent esterification led exclusively to the product of retention of configuration, **30b**, which was correlated as above with methyl (*Z*)-3-methylcyclohexanecarboxylate. Likewise, reaction of **31** produced a single product, **33**, in 84% yield which was homogeneous by ^{1}H NMR and VPC[10b,f] analysis. The 270-MHz ^{1}H NMR spectrum of **33** allowed assignment of both the regio- and stereochemistry of alkylation. Decoupling experiments provided complete coupling information as summarized in Table III. In particular, irradiation of both olefin protons H_H and H_I had no effect on H_C and H_D, thus negating the possibility of regioisomer **34**. The large chemical-shift difference



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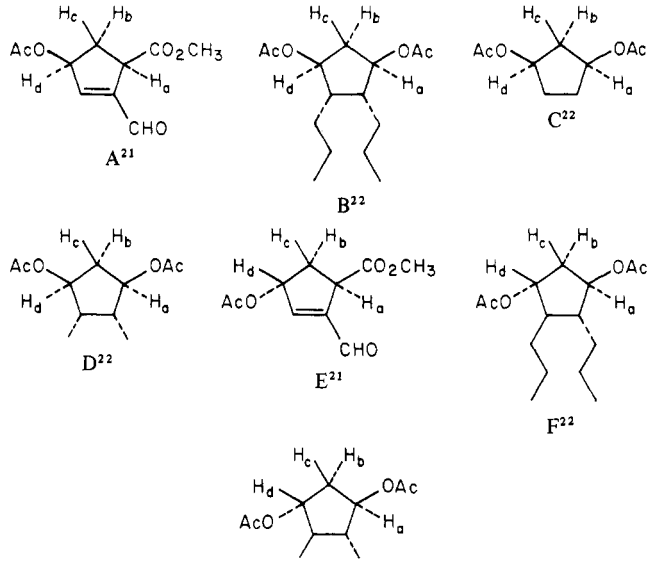
(17) Hussey, A. S. *J. Am. Chem. Soc.* **1951**, *73*, 1364. Goering, H. L.; McCarron, F. H. *Ibid.* **1958**, *80*, 2287. Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 869.

Table IV. ^{1}H NMR Chemical Shift and Coupling Constants for Cyclopentane Model Compounds



	entry						
	A	B	C	D	E	F	G
δH_b	2.86	2.68	2.51	2.66	2.62	2.00	1.97
δH_c	2.08	1.54	1.53	1.50	2.27	2.00	1.97
J_{ba}, Hz	8	7.6	8.8	7.7	8	6.2	7.1
J_{bd}, Hz	8	7.6	6.2	7.7	5	6.2	7.1
J_{ca}, Hz	6	3.3	5.0	4	4	6.2	7.1
J_{cd}, Hz	6	3.3	1.8	4	8	6.2	7.1

between H_C (δ 2.42) and H_D (δ 1.24) reflects a severe difference in their respective magnetic environments. This large difference would only be anticipated for the *Z* isomer, in which the anisotropic effect of both the dimethyl malonyl and methyl acetyl moieties could combine on the same face to create the appreciably different environments experienced by H_C and H_D. The assignment of H_D as the upfield proton is based upon the known shielding effects exerted by the acetyl and malonyl moieties on syn protons in 1-substituted acenaphthenes.[18,19]

Examination of the series of substituted cyclopentene derivatives summarized in Table IV allows final confirmation of the stereochemical assignment. Entries A and B reveal the expected large chemical-shift difference between H_b and H_c in the *Z* isomer in comparison to the *E* analogue. Inspection of the coupling-constant data reveals a potentially useful trend in which the *E* vicinal coupling constants are generally smaller than the *Z* within the same molecule. More generally, though, extreme care must be exercised in promoting configurational assignments in five-membered rings based purely upon the magnitudes of coupling-constant data.[19,20] In the absence of geometrically restraining factors, the conformational flexibility of cyclopentyl-ring systems makes application of the Karplus equation for prediction of vicinal coupling constants not as generally dependable as in conformationally fixed ring systems.

Discussion

The role of palladium in allylic alkylations may be conveniently regarded in terms of a template effect. Specifically, to palladium

(18) Fay, C. K.; Grutzner, J. B.; Johnson, L. F.; Sternhell, S.; Westermann, P. W. *J. Org. Chem.* **1973**, *38*, 3122.

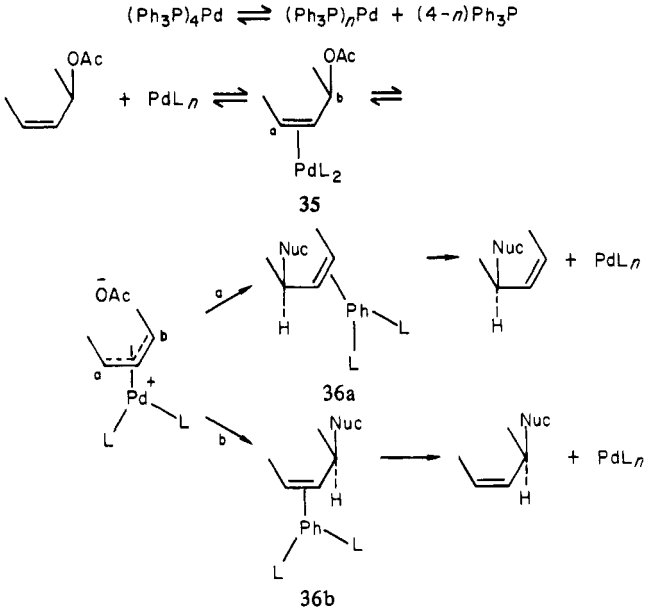
(19) Anteunis, M.; Danniels, D. *Org. Magn. Reson.* **1975**, *7*, 345.

(20) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, 1969; p 287.

(21) DeClerq, P.; Van Haver, D.; Tavernier, D.; Vandervalle, M. *Tetrahedron* **1974**, *30*, 55. Cocu, F. G.; Woczunowicz, G.; Bors, L; Posternak, Th. *Helv. Chim. Acta* **1970**, *53*, 739.

(22) Stanton, J. Ph.D. Thesis, University of Wisconsin—Madison, 1975.

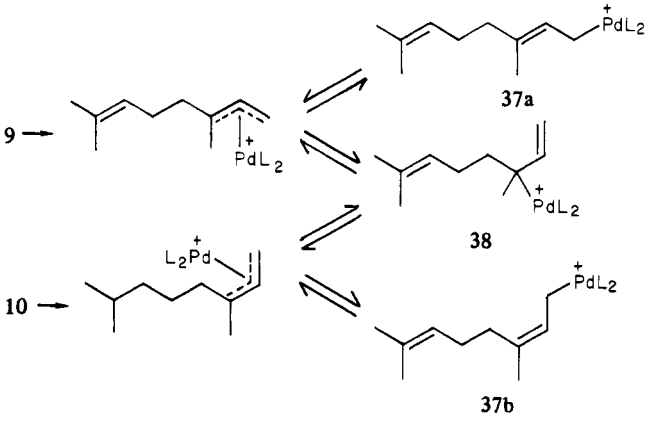
Scheme III. Mechanism of Palladium-Catalyzed Allylic Alkylation



is attributed the ability to orient and activate suitable substrates by coordination, and then to mediate further reactions derived from these activated species. The mechanism of the catalytic alkylation can be depicted as an initial dissociation of tetrakis(triphenylphosphine)palladium(0) into bis- or tris(triphenylphosphine)palladium(0),[23,24] followed by formation of an olefin–palladium π complex[25] (see Scheme III). That the initial dissociation is crucial was confirmed through experiments in which this equilibrium was shifted to the left by addition of a large excess of triphenylphosphine, and a consequent rate deceleration observed. Oxidative addition of the metal to the carbon–oxygen bond with inversion of configuration forms the π-allylpalladium complex.[26-29] Nucleophilic addition with formation of a carbon–carbon bond also with inversion of configuration then effects a net reductive elimination and formation of π-olefin complex **36** with the alkylated product. Dissociation regenerates the catalyst. In essence, palladium(0) behaves as a nucleophile and palladium(2+) serves as a leaving group.

The fact that alkylations with the stoichiometrically prepared π-allyl complexes proceed readily at room temperature,[7] while the catalytic process requires elevated temperatures (refluxing tetrahydrofuran) with similar substrates, suggests that the oxidative addition is the rate-determining step. Consequently, the favorability of initial π complexation of the metal with the allyl acetate should have an important effect on the reaction rate. This importance is clearly reflected in the reactivity trend for the five-, six-, and seven-member-ring olefins (**1**, **5**, and **3**). The reactivity difference of five ≥ seven ≫ six has been demonstrated in palladium-mediated carbonylations[30] and hydroformylations,[31] as well as platinum-catalyzed heterogeneous hydrogenations.[32] In all cases, the five- and seven-member rings react faster and/or in better yields than the six-member-ring analogues, with the rate

Scheme IV. Mechanism for Interconversion of *E* and *Z* Isomers



difference attributed to variation in olefin–metal complexation constants.[25] Four factors appear important: (1) the degree of substitution at the double bond, (2) electronic effects of substituents, (3) the internal strain energy[33] of the olefin, and (4) the steric environment more remote from the olefin.

For olefin **5**, the decreased rate of reaction can be attributed to the 1,3 interactions of palladium with the pseudoaxial hydrogens of the cyclohexene ring in forming the initial π complex. The five- and seven-member rings, not having as great conformational preferences, can minimize such interactions more readily. The observed reactivity difference is probably a combination of both strain and steric factors and suggests a synthetically useful chemoselectivity for alkylations in otherwise indistinguishable systems. It is the unique effect of the transition-metal template which creates this reactivity difference. In particular, nucleophilic additions to an analogous series of allyl halides, in which the reactivity differences should be decided solely by the steric course for approach by the nucleophile, would not be anticipated to exhibit the same degree of selectivity. However, the demonstrated sensitivity of palladium toward the steric environment of the olefin can have a deleterious effect in applications to highly substituted or sterically encumbered olefins.

The regiochemical results observed for olefins **1**, **5**, and **3** can be understood in terms of two competing effects: (1) the steric course for approach by the nucleophile and (2) the stability of the π-olefinic complex **36** (Scheme III) formed upon alkylation. Normally the nucleophile prefers to attack at the least hindered terminus of the π-allyl system.[7] The bulkier a nucleophile, the greater the importance of this factor. Thus, the presence of a tetrahedral sulfone moiety in methyl benzenesulfonylacetate causes an increased regiochemical preference for attack at the least substituted position in comparison to the sterically less demanding dimethyl malonate. However, if palladium bears bulky phosphine ligands, the steric congestion that develops for formation of **36** with highly substituted or conformationally rigid olefins increases the energy of this transition state such that the nucleophile is directed toward the more substituted carbon atom, thus generating the least hindered olefin–palladium π complex. For the five- and seven-member rings, the observance of exclusive attack at the exocyclic position can be understood in terms of least hindered approach as well as the relative stability of the palladium–olefin complex. For the six-member ring, the relatively low preference for complexation with the endocyclic olefin destabilizes the endocyclic olefin–palladium complex and serves to shift a fraction of attack (15%) to the endocyclic position, to form the less hindered exocyclic olefin–palladium complex as the initial alkylated product.

Observance of complete retention of olefin geometry in alkylations of trisubstituted olefins **9** and **10** indicates that nucleophilic attack is faster than syn–anti isomerization. The pathway for isomerization involves π-allyl to σ-allyl interconversion and bond rotation (Scheme IV).[34,35] The rate of isomerization

(23) Otsuka, S.; Nakamure, A.; Yoshida, T.; Naruto, M.; Ataka, K. *J. Am. Chem. Soc.* **1972**, *94*, 2669.
(24) Tolman, C. A.; Seidl, W. C.; Gerlach, D. H. *J. Am. Chem. Soc.* **1972**, *94*, 2669.
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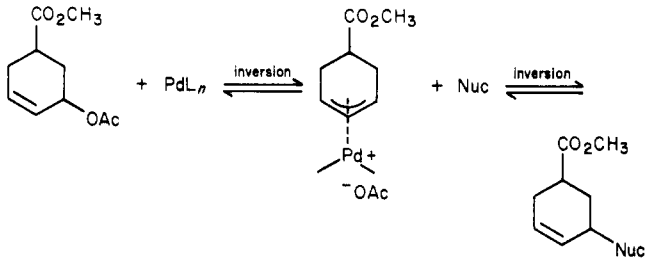
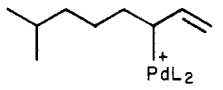
(27) Kudo, K.; Hidai, M.; Uchida, Y. *J. Organomet. Chem.* **1971**, *33*, 393.
(28) Tayim, H. A.; Akl, N. S. *J. Inorg. Nucl. Chem.* **1974**, *36*, 944.
(29) Collman, J. P.; Roper, W. R. *Adv. Inorg. Chem.* **1978**, *7*, 53.
(30) James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810. Heck, R. F. *Ibid.* **1971**, *93*, 6896.
(31) Wender, I.; Metlin, S.; Ergun, E.; Steinberg, H. W.; Greenfield, H. *J. Am. Chem. Soc.* **1956**, *78*, 5401.
(32) Hussey, A. S.; Baker, R. H.; Keulks, G. W. *J. Catal.* **1968**, *10*, 258.
(33) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377.

Scheme V. Stereochemistry of Palladium-Catalyzed Allylic Alkylation



will thus be intimately linked to the stability of σ-allyl intermediate **38**, since intermediates **37a** and **37b** would not lead to interchange of syn and anti substituents. Variable-temperature ^{1}H NMR studies on 1,1-dimethallyl-*1,2,3-h*^{3} complex reveal a coalescence of syn and anti protons before any evidence for exchange of the two methyl groups is observed.[35b] This finding is consistent with a lower energy barrier associated with metal–carbon σ-bond formation at the unsubstituted end of the allyl moiety in comparison to the disubstituted position and is consistent with our results.

The difference in energies between σ-bond formation at an unsubstituted and monosubstituted position is smaller.[35] Interconversion of 1,2-disubstituted olefin isomers via σ-allyl intermediate **39** should therefore become more facile as is demonstrated



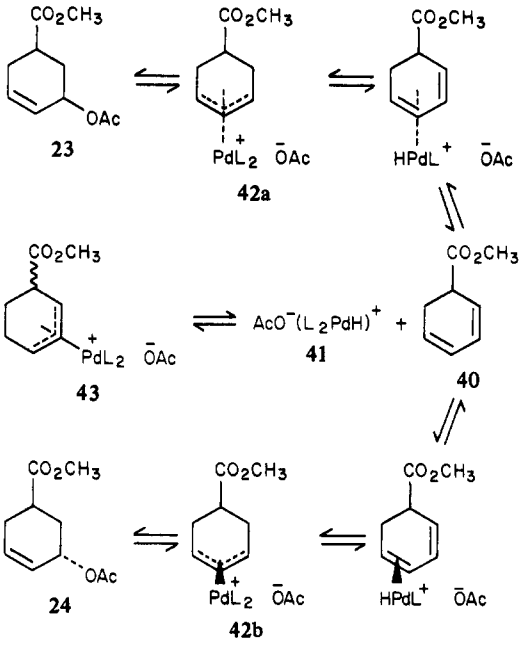
39

with **14**, in which only partial retention of the original olefin geometry is seen.

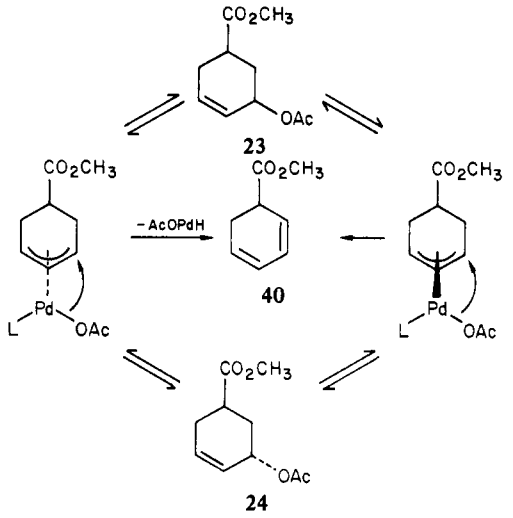
The nearly exclusive nucleophilic attack at the primary carbon with geranyl acetate (**9**) is rationalized in terms of least hindered approach by the nucleophile. This factor is further implicated by considering the increased selectivity for primary attack with methyl benzenesulfonylacetate (>97%) vs. dimethyl malonate (90%). Most remarkable is the high divergence in alkylations with neryl acetate (**10**). While this result may be rationalized, the speculative nature of this rationale leads us to defer further discussion at this time.[36]

The stereochemistry at the carbon undergoing substitution is particularly intriguing with the observance of net retention of configuration. Backside displacement of the acetate from the olefin–palladium complex results in an initial inversion. The oxidative addition of palladium(0) to benzyl halides has been reported to proceed with inversion.[37] Nucleophilic attack must then occur on the face opposite palladium; i.e., the reductive elimination occurs with a second inversion at carbon (Scheme V). Precedent derives from earlier investigations on the stereochemistry of nucleophilic attack on π-allylpalladium complexes with soft carbon nucleophiles.[7,38] Noteworthy is that π-allyl to σ-allyl interconversion in this cyclic system does not jeopardize the stereochemical integrity of the original allyl acetate. This of course would not hold in cases in which the carbon bearing acetate and the olefin were both in an acyclic system. In this situation syn–anti

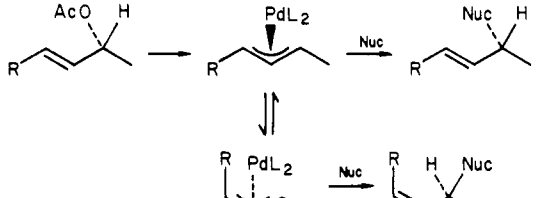
Scheme VI. Interconversion of Cis (**23**) and Trans (**24**) Acetates through Diene Intermediacy



Scheme VII. Interconversion of Cis and Trans Isomers via Internal Transfer



isomerization occurs concomitant with olefin isomerization (eq 13).



(13)

The drop in specificity with decreasing phosphine ligand concentration indicates a competing pathway, leading to isomerization. Considering that alkylation with the same nucleophile on stoichiometrically prepared π-allylpalladium complexes is completely stereospecific[7,38] suggests that isomerization is occurring prior to carbon–carbon bond formation.

One rationale for this interconversion of acetate isomers derives from consideration of the fates of the palladium hydride complex **41** and diene **40**, both produced as a consequence of β-elimination (Scheme VI). Since dissociation and recomplexation of palladium hydride could occur on either face of the cyclohexadiene, hy-

(34) Cotton, F. A.; Fuller, J. W.; Musco, A. *Inorg. Chem.* **1967**, *6*, 179. Co-radinia, P.; Maglio, G.; Musco, G.: Paiaro, G. *Chem. Commun.* **1966**, 618. Chien, J. C. W.; Dehm, H. C. *Chem. Ind. (London)* **1961**, 745. Parker, G.; Werner, H. *Helv. Chim. Acta* **1973**, *56*, 2819. Lefters, J. A.; Aleksanyan, V. T.; Bukalov, S. S.; Rubezhov, A. Z. *Chem. Commun.* **1971**, 265.

(35) (a) Faller, J. W.; Incorvia, M. J.; Thomson, M. E. *J. Am. Chem. Soc.* **1969**, *91*, 518. (b) Faller, J. W.; Thomson, M. E.; Mattina, M. J. *Ibid.* **1971**, *93*, 2542. (c) Faller, J. W.; Mattina, M. J. *Inorg. Chem.* **1972**, *11*, 1296.

(36) The reader is referred to the thesis of T.R.V. for a more complete rationale of this observation: Ph.D. Thesis, University of Wisconsin, 1979.

(37) Law, K. S. Y.; Fries, R. W.; Stille, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 4983. Wong, P. K.; Law, K. S. Y.; Stille, J. K. *Ibid.* **1974**, *96*, 5956. For a mechanistic discussion of the vapor phase reaction with palladium atoms, see: Klabunde, K. J.; Roberts, J. S. *J. Organomet. Chem.* **1977**, *137*, 113.

(38) Jackson, W. R.; Strauss, J. V. G. *Tetrahedron Lett.* **1975**, 2591. Collins, D. J.; Jackson, W. R.; Times, R. N. *Ibid.* **1976**, 495. Jackson, W. R.; Strauss, J. V. *Aust. J. Chem.* **1978**, *31*, 1073.

dropalladation could thus establish the π-allyl complex as a mixture of stereoisomers.[39-41] Nucleophilic attack by acetate would then regenerate an isomeric mixture of allyl acetates.[42]

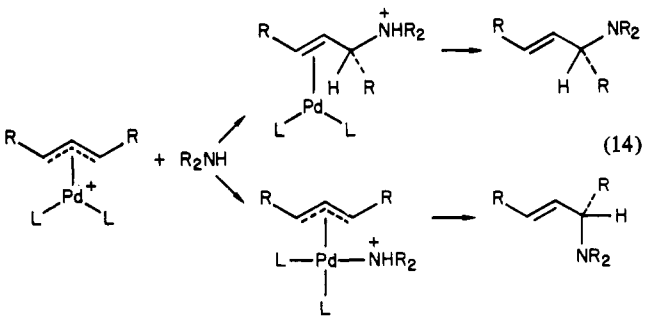
If this mechanism were operative, though, the hydropalladation of diene **40** would reasonably be expected to produce both possible regioisomeric π-allyl complexes **42** and **43**. Consequently, observance of allyl acetates derived from **43** would provide some evidence for the viability of this pathway. Since no products derived from **43** were observed, the intermediacy of diene **40** in this acetate isomerization appears less probable. The slower rate of diene formation compared to cis–trans interconversion is also inconsistent with this proposal.

Postulation of internal delivery of acetate from the same face as palladium could also provide a pathway for acetate isomerization (Scheme VII). Although not strictly proven as an intramolecular reaction, treatment of π-allylpalladium acetate complexes with carbon monoxide does produce allyl acetates in good yields.[42] In light of this possible mechanism, the ability of excess phosphine to increase the stereospecificity in alkylations of **23** is readily rationalized. Phosphine ligands are known to efficiently convert palladium acetate complexes into their cationic derivatives.[43] Thus the carboxylate is removed from the inner coordination sphere of the metal, making internal delivery from the same face as palladium unlikely. The conversion to the cationic complex should also promote the alkylation step by increasing the electron deficiency of the allyl moiety and converting palladium into a better leaving group. Of course, the postulation of internal delivery of acetate from the same face as palladium implies the potential for its microscopic reverse—oxidative addition with retention at the carbon bearing acetate. The facility of this process with respect to the previously described inversion mechanism is not easily assessed.

The ability to establish an equilibrium between an allyl acetate and its π-allylpalladium derivative implies a potentially useful method for acetate isomerization. In fact, inspection of the data for this reaction (see Experimental Section) reveals that, upon establishment of an equilibrium, the amount of the trans isomer **24** exceeds that of the cis isomer **23** by an approximate ratio of 2:1. Whereas this may reflect a rate difference in the β-elimination step, the equilibrium ratio could also indicate a significant rate differential for the oxidative addition. If true, then the ability for selective isomerization of allyl acetates in more sterically biased systems may be possible. The ease with which acetic acid is eliminated under these mild conditions indicates a potentially useful 1,3-diene synthesis. Subsequent to this work, application of this methodology to the synthesis of terminal 1,3-dienes was reported.[9e,44]

Our recent work with nitrogen nucleophiles supports this picture.[45] Competing with the intermolecular attack at carbon on the π-allylpalladium cationic complex appears to be an internal transfer from palladium to carbon after initial intermolecular attack at palladium (eq 14).[46] Thus, with heteroatom nucleophiles, the preference for direct attack at carbon compared to attack at palladium and transfer appears to be significantly less than for carbon nucleophiles.

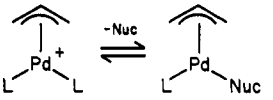
The complete stereospecificity observed in alkylations with lactones **25** and **31** in the absence of excess triphenylphosphine,



as well as in reaction of **23** in the presence of tetramethylammonium acetate, is also readily interpretable by means of the previously postulated isomerization mechanism. With both lactones, internal coordination of the displaced carboxylates to palladium is geometrically impossible and internal return can only occur on the face opposite palladium, to regenerate the original lactones. Likewise, in alkylations of **23**, increasing the soluble acetate ion concentration with tetramethylammonium acetate maximizes the rate of intermolecular acetate return which retains the original configuration of the allyl acetate.

The variance in the degree of stereospecificity observed with bis(benzenesulfonyl)methane illustrates the critical role played by the nucleophile. Two explanations may be proferred. The rate of nucleophilic attack may be anticipated to be slower with the bulkier and more acidic bissulfone (approximately the sme pK_a as acetylacetone[47]) than with the other carbon nucleophiles investigated. The observed low specificity could therefore be a reflection of the increased lifetime of the π-allyl intermediate, allowing for equilibration of *Z* and *E* acetate isomers via the previously described pathway (Scheme VII).

A second rationale focuses on the ambident electrophilic nature of π-allylpalladium complexes. As alluded to previously (for acetate ion), the possibility exists that, kinetically, nucleophilic attack occurs initially at palladium in a reversible process (eq 15).



(15)

Assuming such an equilibrium, the favorability of intramolecular migration of the nucleophile vs. an intermolecular process should depend upon the exothermicity for formation of a C–C bond on a π-olefin complex at the expense of breaking a Pd–nucleophile bond. Highly stabilized anions such as carboxylates or halides appear capable of both modes of transfer.[26,42,48] The migration of acetoacetonate from palladium to carbon upon addition of carbon monoxide to the corresponding complex has been reported,[42,49] although an alternative explanation involving initial dissociation of the nucleophile is also reasonable.[7] Based upon the stereochemical findings of the present investigation (vide supra) and other work,[7,50] stabilized carbanions (dimethyl malonate or methyl benzenesulfonylacetate) appear to prefer intermolecular delivery. With less highly stabilized carbanions, attack at palladium and subsequent migration of the group from palladium to the allyl moiety appear to occur.[48a,51]

Alkylation of lactone **25** with bis(benzenesulfonyl)methane distinguished between these two pathways. Internal return of the carboxylate in **25** could only regenerate the original lactone and

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consequently the lifetime of the π-allyl intermediate would not be the determining factor for the stereochemical outcome. The reaction should be stereospecific regardless of nucleophile as was observed. If intramolecular migration of a complexed bisulfone were a competing process, little difference in the stereochemical result between lactone **25** and acetate **23** would be anticipated, with both substrates producing a mixture of isomers. Thus, although nucleophilic attack at palladium may be kinetically favorable, intramolecular transfer did not occur. Regardless, the ease with which both sulfone moieties can be reductively removed (buffered 6% sodium analgam) accomplishes a facile net incorporation of a methyl group into an allylic position.

Conclusions

The results presented herein demonstrate the modification of palladium-mediated allylic alkylations from the thermodynamically controlled stoichiometric reaction to a kinetically controlled catalytic process. Palladium-catalyzed allylic alkylations permit the use of configurationally stable and easily handled allylic acetates and lactones, overcoming the limitations imposed by the use of more highly activated allyl halides or sulfonate esters. Although substrate dependent, the reaction normally proceeds with net retention of configuration at the carbon undergoing substitution. This provides a useful complement to the normally observed inversion pathway found in other alkylations, and emphasizes the unique role of palladium in modifying normal modes of reactivity.

The mediating effect is further illustrated by its chemoselective nature. Highlighting this is an ability to activate normally unreactive substrates (allyl acetates) toward displacement, even in the presence of the more commonly employed leaving groups (alkyl halides). The high steric sensitivity exhibited by palladium permits its differential reactivity with di- and trisubstituted olefins. More striking are the differences in reaction rates observed for a homologous series of cycloalkanes, which reveal a metal-induced selectivity in an otherwise indistinguishable series.

Thus considering palladium as a template in these catalytic allylic alkylations allows appreciation of the modifying influences that this metal, and transition metals in general, may impose on organic reactions.

Experimental Section

General. All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were determined on a Perkin-Elmer 267 spectrophotometer and are reported in cm^{-1}. ^1H NMR spectra were determined in the indicated solvent on a Jeolco MH-100 (100 MHz) or a Bruker WH270 (270 MHz) instrument. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Coupling constants are reported in hertz. ^{13}C NMR spectra were determined in the indicated solvent on a Jeolco FX-60 (15.1 MHz) instrument with chemical shifts reported downfield relative to tetramethylsilane. Mass spectra were obtained at an ionizing current of 98 mA and an ionizing voltage of 70 eV. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Mich. VPC analyses were obtained with a Varian Aerograph Model 90P. For reactions requiring slow additions, a Sage syringe pump Model 352 was employed. Thin layer or preparative layer plates (1.5 mm) were made of E. Merck AG Darmstadt silica gel PF-254 or Brinkmann silica gel P/UV-254 no. 66 and activated by drying at 120 °C for 2 h. Eluting solvents are indicated in the text, with composition given as volume percent. Removal of the material from silica gel was accomplished by successive washings with ether or ethyl acetate. The term LC is used for high-pressure liquid chromatography and refers to the use of a standard 2.5 (i.d.) × 100 cm column with a precolumn filter of 1.5 (i.d.) × 25 cm dimensions, both of which were packed with 32–63 μm Woelm silica gel and preequilibrated with the indicated solvent mixture. The system utilized a single-stage constant flow pump at an approximate flow rate of 20 mL/min.

For reactions requiring dry solvents, tetrahydrofuran, 1,2-dimethoxyethane, ethyl ether, toluene, and benzene were distilled from sodium benzophenone ketyl. Hexane, pentane, pyridine, dichloromethane, hexamethylphosphorous triamide, diethylamine, cyclohexylisopropylamine, dimethylformamide, and dimethyl sulfoxide were distilled from calcium hydride. Thionyl chloride was purified by distillation from triphenyl phosphite. Sodium hydride was employed as a 55–63% dispersion in mineral oil and weights are recorded for the dispersion. All palladium(0) catalysts were transferred under an inert atmosphere. Glassware for experiments requiring anhydrous conditions was dried by a flame under a stream of nitrogen.

Purity of Products. Unless otherwise stated, the products obtained were checked for purity by chromatographic (TLC and/or VPC) criteria in the solvent and/or column conditions indicated. One spot or one peak was observed. Spectral criteria confirmed the chromatographic analysis.

Preparation of Some Starting Materials. Preparations of methyl benzenesulfonylacetate, 1-(1′-acetoxyethyl)cyclopentene (**1a**), 1-(1′-hydroxyethyl)cyclopentene (**1b**), 1-(1′-acetoxyethyl)cycloheptene (**4**), and (*Z*)-1-acetoxy-7-methyl-2-octene (**14**) were performed by standard methods. Detailed experimental procedures appear as supplementary material.

Alkylation of 1-(1′-Acetoxyethan-1′-yl)cyclopentene (1a) with Dimethyl Malonate. Acetate **1a** (150 mg, 0.974 mmol), triphenylphosphine (25.4 mg, 0.097 mmol), and **2**[54] (7.8 mg, 0.068 mmol) were stirred in 0.75 mL of tetrahydrofuran for 1.5 h. In a separate flask, dimethyl malonate (534 mg, 4.05 mmol) was slowly added to a slurry of pentane-washed sodium hydride (97.2 mg, 4.05 mmol) in 3.5 mL of tetrahydrofuran and stirred for 20 min. The resulting clear solution was added in one portion to the former and the combined mixture heated at reflux for 12 h. The reaction mixture was partitioned between ether and water, the aqueous phase was extracted with ether (3 × 40 mL), and the ether extracts were dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo and purification of the residual oil via preparative TLC (20% ethyl acetate in hexane) gave 173 mg (79%) of methyl 2-carbomethoxy-3-(1′-cyclopenten-1′-yl)butanoate as a clear, colorless oil. NMR (100 MHz, CCl_4): δ 5.35 (m, 1 H), 3.71 (s, 3 H), 3.65 (s, 3 H), 3.33 (d, J = 9 Hz, 1 H), 3.01 (m, 1 H), 2.25 (bt, J = 6.5 Hz, 4 H), 1.80 (m, 2 H), 1.08 (d, J = 6.5 Hz, 3 H). IR (CCl_4): 1765, 1740, 1460, 1440, 1380 cm^{-1}. *Calcd for* $C_{12}H_{18}O_4$: 226.12051. *Found*: 226.12084.

Alkylation of Acetate 1a with Methyl Benzenesulfonylacetate. Acetate **1a** (112 mg, 0.727 mmol), triphenylphosphine (24.3 mg, 0.0927 mmol), and **2** (12 mg, 0.0104 mmol) were stirred in 1 mL of tetrahydrofuran for 15 min. In a separate flask, a solution of methyl benzenesulfonylacetate (512.8 mg, 2.39 mmol) in 1 mL of tetrahydrofuran was slowly added to a slurry of pentane-washed sodium hydride (57.4 mg, 2.39 mmol) in 4 mL of tetrahydrofuran and stirred for 15 min. The resulting clear solution was added in one portion to the former and the combined mixture heated at reflux for 24 h. The thick, yellow reaction mixture was partitioned between ether and water, the aqueous phase was extracted with ether (3 × 30 mL), and the ether extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified via preparative TLC (25% ethyl acetate in hexane) to give 159.4 mg (71%) of methyl 2-benzenesulfonyl-3-(1′-cyclopenten-1′-yl)butanoate as a clear, colorless oil (R_f 0.35). NMR (100 MHz, $CDCl_3$): δ 7.88 (m, 2 H), 2.61 (m, 3 H), 5.41 (m, 1 H), 4.15 and 4.11 (two doublets, J = 9 and 11 Hz, respectively, 1 H), 3.71 and 3.45 (two singlets, 3 H), 3.36 (m, 1 H), 2.2 (m, 4 H), 1.7 (bm, 2 H), 1.39 and 1.11 (two doublets, J = 6 Hz, 3 H). IR (CCl_4): 1745, 1430, 1450, 1335, 1295, 1150, 1095 cm^{-1}. Calcd for $C_{16}H_{20}O_4S$: 308.10823. Found: 308.10807.

Alkylation of 1-(1′-Hydroxyethan-1′-yl)cyclopentene (1b) with Dimethyl Malonate. Alcohol **1b** (142.5 mg, 1.27 mmol), triphenylphosphine (16.9 mg, 0.065 mmol), and **2** (42 mg, 0.0364 mmol) were stirred in 2.5 mL of tetrahydrofuran for 15 min. In a separate flask, dimethyl malonate (473 mg, 3.59 mmol) was added to a slurry of pentane-washed sodium hydride (86 mg, 3.50 mmol) in 8 mL of tetrahydrofuran and stirred for 10 min. The resulting clear solution was added in one portion to the former and the combined mixture heated at reflux for 42 h. The reaction mixture was partitioned between ether and water, the aqueous phase extracted with ether (3 × 30 mL) and dried over anhydrous magnesium sulfate, and the solvent removed in vacuo. The residual oil was purified by preparative TLC (25% ethyl acetate in hexane) to give 251 mg (81%) of methyl 2-carbomethoxy-3-(1′-cyclopenten-1′-yl)butanoate as a clear, colorless oil (R_f 0.4). Analysis by 100-MHz NMR and IR spectroscopy indicated the product to be identical with a sample prepared by the alkylation of 1-(1′-acetoxyethan-1′-yl)cyclopentene with dimethyl malonate.

Alkylation of 1-(1′-Acetoxyethan-1′-yl)cycloheptene (4) with Dimethyl Malonate. Acetate **4** (180 mg, 0.99 mmol), **2** (64.9 mg, 0.056 mmol), and triphenylphosphine (150.7 mg, 0.575 mmol) were reacted with dimethyl sodiomalonate, prepared from dimethyl malonate (594 mg, 4.5 mmol) and pentane-washed sodium hydride (105.6 mg, 4.4 mmol), as for **1a** to give after reflux for 44 h 182.9 mg (73%) of **5a** after purification by preparative TLC (30% ethyl acetate in hexane, R_f 0.68). Analysis

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of the product via VPC[10a] revealed only one peak (retention time = 12.4 min). NMR (100 MHz, $CDCl_3$): δ 5.60 (t, J = 6 Hz, 1 H), 3.70 (s, 3 H), 3.64 (s, 3 H), 3.38 (d, J = 11 Hz, 1 H), 2.86 (d of q, J = 11, 6 Hz, 1 H), 2.08 (bm, 4 H), 2.08–1.2 (bm, 6 H), 1.03 (d, J = 6 Hz, 1 H). IR (CCl_4): 1740, 1452, 1440, 1245 cm^{-1}. Calcd for $C_{14}H_{22}O_4$: 254.151 81. Found: 254.151 24.

Alkylation of Acetate 4 with Methyl Benzenesulfonylacetate. As for **1a** acetate **4** (118 mg, 0.648 mmol), **2** (38.1 mg, 0.033 mmol), and triphenylphosphine (75 mg, 0.286 mmol) were reacted with methyl sodiobenzenesulfonylacetate, prepared from sodium hydride (107 mg, 2.54 mmol) and methyl benzenesulfonylacetate (552 mg, 2.58 mmol), to give, after 38 h and after purification via preparative TLC (40% ethyl acetate in hexane), 144.9 mg (67%) of methyl 2-benzenesulfonyl-3-(1′-cyclohepten-1′-yl)butanoate as a clear, colorless oil (R_f 0.32). Analysis by 100-MHz NMR revealed the product to be a mixture of two diastereomers as evidenced by the presence of two singlets at δ 3.70 and 3.46 assigned as the methyl ester protons. These signals integrated to give a ratio of 45:55, respectively. NMR (100 MHz, $CDCl_3$): δ 7.96 (m, 2 H), 7.69 (m, 3 H), 5.69 (m, 1 H), 4.11 and 4.07 (two doublets, J = 11 Hz, 1 H), 3.70 and 3.46 (two singlets, 3 H), 3.05 (m, 1 H), 2.01–1.0 (bm, 13 H) containing 1.37 and 1.04 (two doublets, J = 8 Hz). IR (CCl_4): 1745, 1445, 1431, 1330 cm^{-1}. Calcd for $C_{18}H_{24}O_4S$: 336.1395. Found: 336.1396.

Preparation of Methyl (*Z*)-2-Benzenesulfonyl-9-methyl-4-decenoate (15a). A solution of methyl benzenesulfonylacetate (574 mg, 2.68 mmol) in 2 mL of tetrahydrofuran was slowly added to a slurry of sodium hydride (146 mg, 3.46 mmol) in 10 mL of tetrahydrofuran to give after 10 min a clear solution. (*Z*)-1-Bromo-7-methyl-2-octene (369.5 mg, 1.935 mmol), which was prepared from (*Z*)-2-butene-1,4-diol (91% cis from Aldrich Chemical Co.) by the method of Colonge and Poilane,[13] was dissolved in 1 mL of tetrahydrofuran and added in one portion. The mixture was maintained at room temperature for 30 min, then at reflux for 6 h. Upon cooling, the mixture was diluted with 20 mL of water, extracted with ether (5 × 30 mL), and dried over anhydrous magnesium sulfate, and the solvent removed in vacuo. The resulting yellow oil was purified by preparative TLC (33% ethyl acetate in hexane) to give 487 mg (75%) of **15a**. NMR (100 MHz, $CDCl_3$): δ 7.80 (m, 2 H), 7.53 (m, 3 H), 5.42 (d of t, J = 11, 7 Hz, 1 H), 5.08 (d of t, J = 11, 7 Hz, 1 H), 3.89 (t, J = 8 Hz, 1 H), 3.56 (s, 3 H), 2.71 (bt, J = 8 Hz, 2 H), 1.94 (m, 2 H), 1.6–1.0 (m, 5 H), 0.86 (d, J = 7 Hz, 6 H).

Preparation of Methyl (*Z*)-9-Methyl-4-decenoate (16a). A mixture of **15a** (487 mg, 1.44 mmol) and anhydrous disodium hydrogen phosphate (949 mg, 5.23 mmol) in 19 mL of methanol was cooled to 0 °C and granulated 6% sodium amalgam (2.53 g) was added. After stirring for 1 h, the mixture was filtered, diluted with ether (100 mL), and washed successively with water (2 × 15 mL), 5% aqueous sodium hydroxide (15 mL), and saturated aqueous sodium chloride (15 mL). The solvent was dried over anhydrous magnesium sulfate and removed in vacuo to give 272.9 mg (96%) of **16a** as a clear, colorless oil. Analysis via VPC[10g] revealed only one peak (retention time = 7.75 min). NMR (100 MHz, $CDCl_3$): δ 5.41 (bm, 2 H), 3.66 (s, 3 H), 2.33 (m, 4 H), 2.05 (m, 2 H), 1.7–1.1 (m, 5 H), 0.87 (d, J = 7 Hz, 6 H). IR (CCl_4): 1745, 1475, 1465, 1445, 1390, 1370 cm^{-1}.

Preparation of Methyl (*Z*)-9-Methyl-4,5-epoxydecanoate (17a). Methyl (*Z*)-9-methyl-4-decenoate (272.9 mg, 1.37 mmol), obtained originally from (*Z*)-1-bromo-7-methyl-4-octene (~90% *Z*), was dissolved in 10 mL of chloroform and cooled to 0 °C. *m*-Chloroperbenzoic acid (85% technical, 458.8 mg, 2.26 mmol) was added in one portion, and the mixture stirred at 0 °C for 20 min. The reaction mixture was diluted with 100 mL of ether, washed with 10% aqueous sodium hydroxide (3 × 30 mL), and dried over anhydrous magnesium sulfate, and the solvent removed in vacuo to give 285 mg (97%) of **17a** as a clear, colorless oil. Analysis of the product via VPC[10d] revealed two peaks, assigned as the *Z* isomer (retention time = 10.8 min) and *E* isomer (retention time = 9.5 min), which integrated in a ratio of 88:12, respectively. NMR (100 MHz, $CDCl_3$): δ 3.69 (s, 3 H), 2.93 (m, 2 H), 2.49 (t, J = 8 Hz, 2 H), 1.85 (m, 1 H), 1.6–1.1 (m, 8 H), 0.87 (d, J = 6 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 171.9, 56.1, 54.7, 50.4, 37.8, 29.9, 27.1, 26.9, 23.5, 22.5, 21.4 with minor resonances at 56.2, 31.3, 26.4, 22.8. IR (CCl_4): 1740, 1460, 1435, 1380, 1365 cm^{-1}.

Alkylation of 1-Acetoxy-7-methyl-2-octene with Methyl Benzenesulfonylacetate. In Refluxing THF. Acetate **14** (*E*:*Z*, 10:90) (199.1 mg, 1.082 mmol), triphenylphosphine (90 mg, 0.343 mmol), and **2** (58.4 mg, 0.051 mmol) were reacted for 2 h as for **1a** with methyl sodiobenzenesulfonylacetate, prepared from methyl benzenesulfonylacetate (793 mg, 3.706 mmol) and sodium hydride (136 mg, 3.23 mmol), to give, after purification via preparative TLC (25% ethyl acetate in hexane), 308.1 mg (84%) of methyl 2-benzenesulfonyl-9-methyl-4-decenoate (*E* and *Z*) and methyl 2-benzenesulfonyl-7-methyl-3-vinyloctanoate as a clear oil (R_f 0.46). Comparison of the 100-MHz NMR and IR spectra of this sample with those of authentic methyl 2-benzenesulfonyl-9-methyl-4-decenoate (88:12, *Z*:*E*) verified its presence. Two singlets at δ 3.53 and 3.42 were assigned as the methyl ester protons of methyl 2-benzenesulfonyl-7-methyl-3-vinyloctanoate. NMR (100 MHz, $CDCl_3$): δ 7.80 (m, 2 H), 7.54 (m, 3 H), 5.74–4.90 (m, >2 H), 4.04–3.83 (m, 1 H), 3.57, 3.56, and 3.44 (three singlets, 3 H), 2,71 (bt, J = 7 Hz, <2 H), 1.91 (bm, <2 H), 1.18 (m, >5 H), 0.84 (bd, J = 7 Hz, 6 H). IR (CCl_4): 1745, 1445, 1435, 1330 cm^{-1}. Calcd for $C_{18}H_{26}O_4S$: 338.1552. Found: 338.1550.

At Room Temperature. In a similar procedure, acetate **14** (*E*:*Z*, 10:90) (197.7 mg, 1.074 mmol), triphenylphosphine (89.8 mg, 0.342 mmol), and **2** (50.7 mg, 0.0439 mmol) were reacted with the sodium salt of methyl benzenesulfonylacetate, prepared from sodium hydride (136 mg, 3.23 mmol) and methyl benzenesulfonylacetate (793 mg, 3.71 mmol) in 9.5 mL of THF. The reaction mixture was stirred at room temperature for 43 h. Workup and purification gave 274.2 mg (76%) of methyl 2-benzenesulfonyl-9-methyl-4-decenoate (*E* and *Z*) and 2-benzenesulfonyl-7-methyl-4-vinyloctanoate as a clear oil. The spectral properties of this sample were similar to those previously reported.

Desulfonylation of Methyl 2-Benzenesulfonyl-9-methyl-4-decenoate and Methyl 2-Benzenesulfonyl-7-methyl-3-vinyloctanoate. A mixture of the title compounds (308.1 mg, 0.912 mmol) (prepared from (*Z*)-1-acetoxy-7-methyl-2-octene in refluxing THF), anhydrous disodium hydrogen phosphate (566.9 mg, 4.0 mmol), and granulated 6% sodium amalgam (1.67 g) gave 175.4 mg (97%) of methyl 9-methyl-4-decenoate and methyl 7-methyl-3-vinyloctanoate as a clear, colorless oil. Separation of the two regioisomers was accomplished by preparative VPC[10c] to give pure methyl 9-methyl-4-decenoate (*E* and *Z*) (retention time = 5.1 min) and methyl 7-methyl-3-vinyloctanoate (retention time = 3.1 min) as clear oils in a ratio of 62:38, respectively. Analysis of methyl 9-methyl-4-decenoate via 270-MHz NMR revealed two singlets at δ 3.68 and 3.67, assigned as the methyl ester protons of the *E* and *Z* isomers. The spectral properties of both isolated products follows. Methyl 9-methyl-4-decenoate: NMR (270 MHz, $CDCl_3$) δ 5.41 (m, 2 H), 3.68 and 3.67 (two singlets, 3 H), 2.35 (m, 4 H), 2.00 (m, 2 H), 1.54 (m, 1 H), 1.33 (m, 2 H), 1.18 (m, 2 H), 0.87 and 0.86 (two doublets, J = 6.3 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 173.0, 131.5, 131.2, 127.5, 126.8, 51.3, 38.5, 38.4, 34.1, 32.6, 27.8, 27.3, 27.2, 22.8, 22.5; IR (CCl_4) 1745, 1475, 1465, 1440, 1390, 1370 cm^{-1}. Calcd for $C_{12}H_{22}O_2$: 198.1620. Found: 198.1616. Methyl 7-methyl-3-vinyloctanoate: NMR (270 MHz, $CDCl_3$) δ 5.62 (d of d of d, J = 17, 10.2, 8.5 Hz, 1 H), 5.01 (d of d, J = 17, 1 Hz, 1 H), 4.99 (d of d, J = 10.2, 1 Hz, 1 H), 3.65 (s, 3 H), 2.51 (bm, 1 H), 2.41 (d of d, J = 15, 6 Hz, 1 H), 2.28 (d of d, J = 15, 8.5 Hz, 1 H), 1.51 (m, 1 H), 1.30 (bm, 4 H), 1.15 (m, 2 H), 0.86 and 0.85 (two doublets, J = 7 Hz, 6 H); IR (CCl_4) 1750, 1445, 1172 cm^{-1}. Calcd for $C_{12}H_{22}O_2$: 198.1620. Found: 198.1623.

In a similar procedure, a mixture of title compounds (274.2 mg, 0.81 mmol) (prepared from (*Z*)-1-acetoxy-7-methyl-2-octene in tetrahydrofuran at room temperature) was desulfonylated with anhydrous disodium hydrogen phosphate (529 mg, 3.73 mmol) and granulated 6% sodium amalgam (1.49 g) in 11 mL of methanol at 0 °C. Workup as described previously afforded 150.8 mg (94%) of methyl 9-methyl-4-decenoate (*E* and *Z*) and methyl 7-methyl-3-vinyloctanoate as a clear, colorless oil. Analysis via VPC as described above gave a ratio of 52:48, respectively.

Preparation of Methyl (7′-Methyl-1′,2′-epoxyoctan-3′-yl)acetate. *m*-Chloroperbenzoic acid (85% technical, 152.5 mg, 0.75 mmol) was added in one portion to a solution of methyl 7-methyl-3-vinyloctanoate (19.1 mg, 0.0965 mmol) in 2.5 mL of chloroform and stirred at room temperature for 2.5 h. After dilution with 30 mL of ether the solvent was washed with 10% aqueous sodium hydroxide (2 × 15 mL) and dried over anhydrous magnesium sulfate and the solvent removed in vacuo to give 18.6 mg (90%) of the title compound as a colorless oil. Analysis of the product via VPC[10d] indicated one peak (retention time = 8.5 min). NMR (100 MHz, $CDCl_3$): δ 3.67 (s, 3 H), 2.78 (m, 2 H), 2.4 (bm, 3 H), 1.7–1.2 (bm, 8 H), 0.88 (d, J = 7 Hz, 6 H). IR (CCl_4): 1740, 1460, 1435, 1380, 1365, 1250 cm^{-1}. Calcd for $C_{12}H_{22}O_3$: 214.1569. Found: 214.1573.

Epoxidation of Methyl 9-Ethyl-4-decenoate and Methyl 7-Ethyl-3-vinyloctanoate. The title compounds (157.5 mg, 0.795 mmol) (originally prepared from (*Z*)-1-acetoxy-7-methyl-2-octene and methyl benzenesulfonylacetate in refluxing tetrahydrofuran) were epoxidized with 291.2 mg (85% technical, 1.43 mmol) of MCPBA as above. Separation of the mixture after workup via preparative VPC[10d] gave methyl (*Z*)-9-methyl-4,5-epoxydecanoate (retention time = 10.8 min), methyl (*E*)-9-methyl-4,5-epoxydecanoate (retention time = 9.5 min), methyl (7′-methyl-1′,2′-epoxyoctan-3′-yl)acetate (retention time = 8.5 min), and methyl 7-methyl-3-vinyloctanoate (retention time = 2.9 min). Methyl 9-methyl-4,5-epoxydecanoate (*Z* and *E*) was identified by direct comparison (VPC and 100-MHz NMR) to an authentic sample prepared in these laboratories. The *Z*:*E* ratio was determined via VPC to be 52:48,

respectively. Methyl (7′-methyl-1′,2′-epoxyoctan-3′-yl)acetate was identified by direct comparison (VPC, 100-MHz NMR) to a sample prepared from pure methyl 7-methyl-3-vinyloctanoate as described previously. Methyl (*Z*)-9-methyl-4,5-epoxydecanoate: NMR (100 MHz, $CDCl_3$) δ 3.70 (s, 3 H), 2.92 (m, 2 H), 2.48 (t, J = 8 Hz, 2 H), 1.85 (m, 1 H), 1.6–1.2 (bm, 8 H), 0.88 (d, J = 7 Hz, 6 H); IR (CCl_4) 1740, 1460, 1435, 1420, 1380, 1365, 1250 cm^{-1}. Calcd for $C_{12}H_{22}O_3$: 214.1569. Found: 214.1570. Methyl (*E*)-9-methyl-4,5-epoxydecanoate: NMR (270 MHz, $CDCl_3$) δ 3.70 (s, 3 H), 2.74 (m, 2 H), 2.46 (t, J = 8 Hz, 2 H), 1.96 (bm, 1 H), 1.77 (m, 1 H), 1.60 (bm, 7 H), 0.88 (d, J = 7 Hz, 6 H); IR (CCl_4) 1740, 1460, 1435, 1380, 1365, 1250, 1200 cm^{-1}. Calcd for $C_{12}H_{22}O_3$: 214.1569. Found: 214.1572.

In a similar procedure, the title compounds (113 mg, 0.57 mmol) (originally prepared from (*Z*)-1-acetoxy-7-methyl-2-octene and methyl benzenesulfonylacetate in tetrahydrofuran at room temperature) were epoxidized with *m*-chloroperbenzoic acid (85% technical, 212.7 mg, 1.05 mmol) in 5 mL of chloroform to give 116 mg (95%) of a clear oil which was analyzed by VPC as described above. The *Z*:*E* ratio of methyl 9-methyl-4,5-epoxydecanoate determined in this manner was 67:33, respectively.

Alkylation of 1-Acetoxy-7-methyl-2-octene (14) with Dimethyl Malonate. Acetate **14** (*E*:*Z*, 10:90) (211.4 mg, 1.15 mmol), triphenylphosphine (95 mg, 0.363 mmol), and **2** (35.2 mg, 0.035 mmol) were treated with dimethyl sodiomalonate, prepared from dimethyl malonate (338 μL, 3.40 mmol) and sodium hydride (140.9 mg, 3.34 mmol), to give after 10 h and after purification by preparative TLC (25% ethyl acetate in hexane) 242.5 mg (82%) of a mixture of alkylated products as a clear, colorless oil. Analysis via VPC[10b] revealed two peaks assigned as **18a** (retention time = 6.6 min) and **18b** (retention time = 4.1 min) in a ratio of 40:60. Analysis of the olefinic region by 270-MHz NMR indicated a broad multiplet extending from δ 5.45 to 5.17 which was assigned as the two olefinic protons of **18a**. Resonances at δ 5.56 (bd of t, J = 17, 10 Hz), 5.02 (bd, J = 17 Hz), and 5.00 (bd, J = 10 Hz) were assigned as the three vinyl protons of **18b**. Integration of this area provided a ratio of these two products of 35:65, respectively. NMR (100 MHz, $CDCl_3$): δ 5.6 (bm, >1 H), [5.02 (bd, J = 17 Hz) and 5.02 (bd, J = 10 Hz), 1 H], 3.72 (s, 6 H), 3.36 (m, 1 H), 2.6 (m, >1 H), 2.00 (m, <2 H), 1.22 (bm, >5 H), 0.86 (bd, J = 6 Hz, 6 H).

Alkylation of Geranyl Acetate with Dimethyl Malonate. Geranyl acetate (228.1 mg, 1.163 mmol), triphenylphosphine (68.5 mg, 0.261 mmol), and **2** (57.8 mg, 0.050 mmol) were reacted as above with dimethyl sodiomalonate, prepared from dimethyl malonate (531 μL, 4.65 mmol) and sodium hydride (183.1 mg, 4.35 mmol), to give, after 36 h and after purification by preparative TLC (40% ethyl acetate in hexane), 289.1 mg (92%) of **11a** and **12a** as a clear, colorless oil. Analysis of the product mixture by 100-MHz NMR revealed a minor resonance at δ 5.98 (d of d, J = 17.5, 11 Hz) assigned as a vinyl proton in **12a**. Analysis via VPC[10b] revealed two peaks corresponding to **11a** (retention time = 7.1 min) and **12a** (retention time = 4.3 min) in a ratio of approximately 87:13, respectively. None of the *Z* isomer was detected by VPC anaylsis. The spectral properties of pure methyl (*E*)-2-carbomethoxy-5,9-dimethyl-4,8-decadienoate, obtained by preparative VPC, follow. NMR (100 MHz, $CDCl_3$): δ 5.06 (m, 2 H), 3.74 (s, 6 H), 3.37 (t, J = 8 Hz, 1 H), 2.60 (bt, J = 7 Hz, 2 H), 2.00 (bs, 4 H), 1.68, 1.64, and 1.59 (three singlets, 9 H). ^{13}C NMR ($CDCl_3$): δ 168.8, 138.1, 130.9, 123.5, 119.0, 52.2, 51.8, 39.5, 27.5, 17.6, 16.0. IR (CCl_4): 1765, 1755, 1440, 1380, 1350, 1270, 1240 cm^{-1}. Calcd for $C_{15}H_{24}O_4$: 268.1675. Found: 268.1675.

Alkylation of Geranyl Acetate with Methyl Benzenesulfonylacetate. Geranyl acetate (229.5 mg, 1.17 mmol), triphenylphosphine (30.4 mg, 0.116 mmol), and tetrakis(triphenylphosphine)palladium(0) (48.3 mg, 0.0418 mmol) in 2 mL of THF were reacted with methyl sodiobenzenesulfonylacetate, prepared from 948 mg (4.42 mmol) of methyl benzenesulfonylacetate and 4.0 mmol of sodium hydride in 7 mL of THF, for 36 h at reflux. Purification of the residue by preparative TLC (30% ethyl acetate in hexane) gave 245.1 mg (84%) of methyl (*E*)-2-benzenesulfonyl-5,9-dimethyl-4,8-decadienoate. Analysis of the product via 100-MHz NMR and ^{13}C NMR gave no evidence (<3%) for the presence of methyl 2-benzenesulfonyl-3,7-dimethyl-3-vinyl-6-octenoate or methyl (*Z*)-2-benzenesulfonyl-5,9-dimethyl-4,8-decadienoate. NMR (100 MHz, $CDCl_3$): δ 7.85 (m, 2 H), 7.57 (m, 3 H), 4.97 (m, 2 H), 3.91 (t, J = 7 Hz, 1 H), 3.61 (s, 3 H), 2.68 (bt, J = 8 Hz, 2 H), 1.95 (bs, 4 H), 1.65 and 1.58 (two broad singlets, 9 H). ^{13}C NMR ($CDCl_3$): δ 165.7, 140.0, 137.3, 131.2, 128.8, 123.5, 117.0, 70.3, 52.4, 39.4, 26.2, 25.4, 17.4, 15.8. IR (CCl_4): 1743, 1448, 1435 cm^{-1}. Calcd for $C_{19}H_{26}O_4S$: 350.1552. Found: 350.1547.

Alkylation of Neryl Acetate with Dimethyl Malonate. Neryl acetate (110.1 mg, 0.562 mmol), triphenylphosphine (40.0 mg, 0.152 mmol), and tetrakis(triphenylphosphine)palladium(0) (39 mg, 0.034 mmol) in 1 mL of THF were reacted with 2.13 mmol of dimethyl sodiomalonate in 4 mL of THF for 22 h at reflux as above. Purification by preparative TLC (40% ethyl acetate in hexane) gave 110.7 mg (74%) of methyl (*Z*)-2-carbomethoxy-5,9-dimethyl-4,8-decadienoate and methyl 2-carbomethoxy-3,7-dimethyl-3-vinyl-6-octenoate. Analysis of the product mixture by VPC[10b] revealed two peaks, corresponding to methyl (*Z*)-2-carbomethoxy-5,9-dimethyl-4,8-decadienoate (retention time = 5.8 min) and methyl 2-carbomethoxy-3,7-dimethyl-3-vinyl-6-octenoate (retention time = 4.3 min) in a ratio of approximately 37:63, respectively. None of the *E* isomer was detected by VPC analysis. The spectral properties of both products obtained by preparative VPC follow. Methyl (*Z*)-2-carbomethoxy-5,9-dimethyl-4,8-decadienoate: NMR (100 MHz, $CDCl_3$) δ 5.04 (m, 2 H), 3.72 (s, 6 H), 3.34 (t, J = 7 Hz, 1 H), 2.59 (bt, J = 7 Hz, 2 H), 2.05 (m, 4 H), 1.68 and 1.60 (two broad singlets, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 138.1, 131.2, 123.5, 119.7, 52.1, 51.9, 31.8, 27.3, 26.3, 25.5, 23.3, 17.5; IR (CCl_4) 1760, 1740, 1435, 1375, 1350, 1270, 1225 cm^{-1}. Calcd for $C_{15}H_{24}O_4$: 268.1675. Found: 268.1673. Methyl 2-carbomethoxy-3,7-dimethyl-3-vinyl-6-octenoate: NMR (100 MHz, $CDCl_3$) δ 5.98 (d of d, J = 17.5, 11 Hz, 1 H), 5.00 (bm, 3 H) containing 5.03 (d, J = 11 Hz) and 4.94 (d, J = 17.5 Hz), 3.71 (s, 6 H), 3.46 (s, 1 H), 1.84–1.40 (bm, 10 H) containing 1.67 and 1.58 (two broad singlets), 1.27 (s, 3 H); IR (CCl_4) 1760, 1740, 1435, 1412, 1375, 1320 cm^{-1}. Calcd for $C_{15}H_{24}O_4$: 268.1675. Found: 268.1684.

Alkylation of Neryl Acetate with Methyl Benzenesulfonylacetate. Neryl acetate (126 mg, 0.643 mmol), triphenylphosphine (18.5 mg, 0.0706 mmol), and tetrakis(triphenylphosphine)palladium(0) (22.5 mg, 0.0195 mmol) in 1 mL of THF were reacted as above with methyl sodiobenzenesulfonylacetate prepared from methyl benzenesulfonylacetate (530.1 mg, 2.48 mmol) in 0.5 mL of THF and sodium hydride (97.5 mg, 2.315 mmol) in 4 mL of THF at reflux for 36 h. Purification via preparative TLC (30% ethyl acetate in hexane) gave 175.3 mg (78%) of methyl (*Z*)-2-benzenesulfonyl-5,9-dimethyl-4,8-decadienoate and methyl 2-benzenesulfonyl-3,7-dimethyl-3-vinyl-6-octenoate. Analysis of the product mixture by 100-MHz NMR revealed two minor signals at δ 6.00 and 5.98 (d of d, J = 17, 11 Hz), assigned as the vinyl proton of methyl 2-benzenesulfonyl-3,7-dimethyl-3-vinyl-6-octenoate (two diastereomers). Integration of the methyl ester resonances for this regioisomer (δ 3.45 and 3.40) and the methyl ester resonance for methyl (*Z*)-2-benzenesulfonyl-5,9-dimethyl-4,8-decadienoate (δ 3.61) indicated a ratio of 11:89, respectively. No evidence for the presence of methyl (*E*)-2-benzenesulfonyl-5,9-dimethyl-4,8-decadienoate was detected via ^1H or ^{13}C NMR analysis. NMR (100 MHz, $CDCl_3$): δ 7.85 (m, 2 H), 7.55 (m, 3 H), 5.00 (bm, 2 H), 3.88 (d of d, J = 9, 6 Hz, 1 H), 3.61 (s, 3 H), 2.68 (m, 2 H), 1.98 (m, 4 H), 1.68, 1.54 (two singlets, 9 H), with minor resonances at 6.0, 5.98 (d of d, J = 17, 11 Hz), 4.04 (s), 3.45 and 3.40 (two singlets), 1.49 and 1.38 (two singlets). ^{13}C NMR ($CDCl_3$): δ 165.7, 140.1, 137.3, 134.0, 131.7, 128.9, 128.8, 123.5, 117.6, 70.6, 52.5, 31.6, 26.0, 24.5, 25.3, 23.1, 17.4. IR (CCl_4): 1750, 1450, 1440, 1350 cm^{-1}. Calcd for $C_{19}H_{26}O_4S$: 350.1552. Found: 350.1553.

Alkylation of 3-Acetoxy-8-bromo-1-octene with Methyl Benzenesulfonylacetate. Tetrakis(triphenylphosphine)palladium(0) (65.5 mg, 0.056 mmol) and 3-acetoxy-8-bromo-1-octene in 1 mL of THF were reacted with methyl sodiobenzenesulfonylacetate, prepared from 350 mg (1.64 mmol) of methyl benzenesulfonylacetate and 61.8 mg (1.54 mmol) of sodium hydride in 3 mL of THF, for 30 min at reflux as above. Purification by preparative TLC (25% ethyl acetate in hexane) gave 290 mg (77%) of monoalkylated product and 36.2 mg (12% based on allylic acetate) of an impure sample of 9-benzenesulfonyl-9-carbomethoxy-1,17-dibromo-6,11-heptadecadiene (**22**). Analysis of the lower R_f fraction (R_f 0.40) by 100-MHz NMR revealed a triplet (J = 7 Hz) at δ 3.37, assigned as the methylene protons α to bromine. This signal integrated for two protons with respect to the five aromatic protons of the benzenesulfonyl moiety. A broad multiplet centered at δ 5.28, assigned as the olefinic protons, integrated for 2.3 protons, indicating the monoalkylated product to be a mixture of methyl 2-benzenesulfonyl-10-bromo-4-decenoate (*E* and *Z*) (**21a**) and methyl 2-benzenesulfonyl-8-bromo-3-vinyloctanoate (**21b**). **22**: NMR (100 MHz, $CDCl_3$) δ 7.82 (bd, J = 7.5 Hz, 2 H), 7.59 (bm, 3 H), 5.47 (m, 4 H), 3.62 and 3.47 (two singlets, 3 H), 3.38 (t, J = 7 Hz, 4 H), 2.79 (m, 4 H), 1.91 (bm, 8 H), 1.39 (m, 8 H); IR (CCl_4) 1745, 1450, 1440, 1325 cm^{-1}; mass spectrum *m*/*e* (%) 453 (0.4), 452 (0.6), 451 (1.3), 450 (1.2), 449 (0.3), 448 (0.6), 353 (1), 232 (2), 278 (2), 277 (5), 263 (26), 262 (16), 261 (28), 260 (12), 231 (6), 203 (7), 181 (8), 179 (11), 177 (10), 158 (31), 149 (16), 143 (12), 141 (26), 137 (10), 126 (12), 125 (24), 123 (10), 121 (12), 112 (35), 110 (20), 108 (17), 98 (22), 95 (23), 94 (40), 85 (23), 83 (20), 82 (25), 81 (42), 79 (24), 77 (100). Lower R_f fraction (R_f 0.40): NMR (100 MHz, $CDCl_3$) δ 7.90 (bd, J = 8 Hz, 2 H), 2.65 (bm, 3 H), 5.28 (bm, 2.3 H), 3.98 (m, 1 H), 3.63 and 3.46 (two singlets, 3 H), 3.37 (t, J = 7 Hz, 2 H), 2.70 (m, <2 H), 1.87 (bm, 4 H), 1.35 (m, 4 H); IR (CCl_4) 1752, 1450, 1438, 1330, 1310 cm^{-1}; mass spectrum *m*/*e* (%) 373 (1), 371 (1), 314 (2), 313 (8), 263 (57), 262 (30), 261 (57), 260 (22), 231 (8), 229

(8), 214 (8), 203 (17), 201 (17), 181 (14), 149 (11), 143 (15), 141 (13), 139 (18), 126 (26), 125 (25), 121 (38), 113 (46), 112 (18), 111 (93), 109 (12), 107 (23), 95 (21), 93 (28), 91 (12), 87 (19), 85 (16), 81 (91), 79 (47), 77 (77), 71 (32), 55 (100). Calcd for $C_{17}H_{23}O_4S^{79}Br$: 402.0500. Found: 402.0494.

Preparation of (*Z*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene (23). Lactone **25**[55] (517 mg, 4.16 mmol) and sodium methoxide (30 mg, 0.56 mmol) were stirred in 25 mL of anhydrous methanol at room temperature for 10 h. The solvent was removed in vacuo and the residue partitioned between ether and 2% aqueous hydrochloric acid. The aqueous phase was extracted with ether and dried over anhydrous magnesium sulfate, and the solvent removed in vacuo to give 537.7 mg (82%) of (*Z*)-3-hydroxy-5-carbomethoxy-1-cyclohexene (**26**). The product, which was homogeneous via TLC (10% ether in chloroform, R_f 0.3) and 100-MHz NMR, was not further purified. All spectral properties (100-MHz NMR, IR) were identical with those previously reported.[55]

Acetyl chloride (5.0 mL, 70.8 mmol) was added over 10 min to a cooled (0 °C) solution of **26** (8.5 g, 54.5 mmol) in 50 mL of dichloromethane and 8 mL of pyridine. The resulting white slurry was stirred for 15 min, neutralized with aqueous sodium bicarbonate, and diluted with 150 mL of ether. The organic phase was washed successively with saturated aqueous sodium bicarbonate (3 × 50 mL), 10% aqueous hydrochloric acid (2 × 50 mL), aqueous sodium bicarbonate (50 mL), and saturated aqueous sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give a yellow liquid which was purified via Kugelrohr distillation (80–90 °C, 0.5 mm) to give 8.27 g (77%) of the title compound as a colorless liquid. Analysis of the product via VPC[10d] revealed an isomer mixture of approximately 98% *Z* (retention time = 11.1 min) and 2% *E* (retention time = 10.4 min). All spectral properties were identical with those reported previously.[22,56] NMR (270 MHz, $CDCl_3$): δ 5.88 (d of t of d, *J* = 10, 3.8, 1.8 Hz, 1 H), 5.64 (d of m, *J* = 10 Hz, 1 H), 5.39 (m, 1 H), 3.70 (s, 3 H), 2.73 (d of t of d, *J* = 12, 7.5, 3 Hz, 1 H), 2.42–2.28 (bm, 3 H), 2.05 (s, 3 H), 1.76 (t of d, *J* = 12.5, 9.3 Hz, 1 H). IR (CCl_4): 3045, 2960, 2855, 1740, 1380, 1250, 1040, 932 cm^{-1}.

Preparation of 3-Acetoxy-5-carbomethoxy-1-cyclohexene (*Z* and *E*). Alcohol **26** (3.09 g, 19.80 mmol) was added to a stirred solution of acetic anhydride (4.8 mL, 50.9 mmol) in 50 mL of ethyl acetate containing 60 μL of 60% aqueous perchloric acid. After stirring at room temperature for 2 h, the reaction mixture was diluted with ethyl acetate (100 mL), washed with saturated aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate and the solvent removed in vacuo to give 3.01 g (77%) of the title compounds. Analysis via VPC[10d] revealed the product to be a mixture of *Z* (retention time = 11.1 min) and *E* (retention time = 10.4 min) isomers in a ratio of approximately 35:65, respectively. Analysis by 270-MHz NMR ($CDCl_3$) revealed two multiplets at δ 5.39 and 5.27 in a ratio of 34:66 assigned as the C-3 methine of the *Z* and *E* isomers.

Preparation of (*E*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene (24). Sodium methoxide (90 mg, 1.68 mmol) was added to a solution of **23** and **24** (*E*:*Z*, 65:35) (8.26 mg, 4.17 mmol) in 40 mL of absolute methanol and stirred at room temperature for 7.5 h. The reaction mixture was concentrated in vacuo and the residue partitioned between ether and 4% aqueous hydrochloric acid. The organic phase was washed with saturated aqueous sodium bicarbonate (20 mL) and dried over anhydrous magnesium sulfate and the solvent removed in vacuo. Purification via preparative TLC (50% ethyl acetate in hexane) gave 453 mg (70%) of **26** and **27**. Analysis of the product mixture by 100-MHz NMR revealed two broad signals at δ 5.78 and 5.66 in a 60:40 ratio assigned as the vinyl protons for the *E* and *Z* isomers, respectively. NMR (100 MHz, CCl_4): δ 5.78 and 5.66 (two broad singlets, 2 H), 4.15 (m, 1 H), 3.68 (s, 3 H), 3.15 (m, 1 H), 2.90–1.10 (bm, 5 H). IR (CCl_4): 3500, 3440, 1742, 1435, 1195 cm^{-1}.

Sodium methoxide (20 mg, 0.37 mmol) and 1.5 g of activated 4-Å molecular sieves were added to a solution of **26** and **27** (*E*:*Z*, 60:40) (112 mg, 0.718 mmol) in 10 mL of benzene. The mixture was heated at reflux for 3 h, cooled, decanted into 2 M aqueous hydrochloric acid, and extracted with ether (4 × 30 mL). The solvent was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC (50% ethyl acetate in hexane) to give lactone **25** and 45 mg (40%) of alcohol **27**. Analysis via 100-MHz NMR revealed two broad singlets at δ 5.78 and 5.66 in a ratio of 93:7 assigned as the olefinic protons for the *E* and *Z* isomers, respectively. NMR (100 MHz, CCl_4): δ 5.78 (bs, 2 H), 4.14 (m, 1 H), 3.68 (s, 3 H), 2.7 (bm, 1 H), 2.2–1.96 (m, 4 H), 1.70 (d of d of d, *J* = 12.5, 11, 4.5 Hz, 1 H).

Alcohol **27** (*E*:*Z*, 93:7) (80.3 mg, 0.515 mmol) was added to a solution of 2 mL of acetic anhydride and 1 mL of pyridine and stirred at room temperature for 9 h. The reaction mixture was poured into 40 mL of water, extracted with ether (4 × 30 mL), and dried over anhydrous magnesium sulfate and the solvent removed in vacuo. Purification of the residue by preparative TLC (50% ethyl acetate in hexane) gave 86.1 mg (85%) of acetate **24**. NMR (CCl_4): δ 5.84 (m, 2 H), 5.16 (m, 1 H), 3.69 (s, 3 H), 2.6 (m, 1 H), 2.28–1.8 (bm, 6 H) containing 2.00 (s), 1.7 (m, 1 H). IR (CCl_4): 1730, 1440, 1435, 1370, 1310, 1240 cm^{-1}. Calcd for $C_{10}H_{14}O_4$: 198.0892. Found: 198.0894.

Alkylation of *cis*-3-Acetoxy-5-carbomethoxy-1-cyclohexene with Dimethyl Malonate. With Triphenylphosphine. As above, triphenylphosphine (74.3 mg, 0.283 mmol), tetrakis(triphenylphosphine)palladium(0) (37.3 mg, 0.0323 mmol), and acetate **23** (cis:trans, 98:2) (189.6 mg, 0.958 mmol) were reacted with dimethyl sodiomalonate, prepared from 3.5 mmol of dimethyl malonate and 2.5 mmol of sodium hydride in 6.6 mL of THF, for 7.5 h at reflux. Purification by preparative TLC (33% ethyl acetate in hexane) gave 231.9 mg (90%) of dimethyl (*Z*)-(5-carbomethoxy-1-cyclohexen-3-yl)malonate (**28**). Analysis by VPC[10b] revealed two peaks in the ratio of 98:2 assigned as the *Z* (retention time = 12.6 min) and *E* (retention time = 10.4 min) isomers. NMR (270 MHz, $CDCl_3$): δ 5.78 (d of d of t, *J* = 10, 5, 2.5 Hz, 1 H), 5.54 (d of m, *J* = 10 Hz, 1 H), 3.75 (s, 6 H), 3.69 (s, 3 H), 3.29 (d, *J* = 8.6 Hz, 1 H), 3.01 (m, 1 H), 2.64 (m, 1 H), 2.34–2.17 (m, 2 H), 2.11 (d of m, *J* = 12 Hz, 1 H), 1.47 (q, *J* = 12 Hz, 1 H). IR (CCl_4): 1760, 1742, 1440 cm^{-1}. Calcd for $C_{13}H_{18}O_6$: 270.110 33. Found: 270.109 75.

Without Added Ligand. As described above, acetate **23** (198.2 mg, 1.00 mmol) and catalyst **2** (40.8 mg, 0.035 mmol) were heated at reflux with dimethyl sodiomalonate, prepared from dimethyl malonate (400 μL, 3.5 mmol) and sodium hydride (100 mg, 2.5 mmol) in 6.6 mL of THF, for 7.5 h at reflux. Purification as previously described gave 245.7 mg (90%) of a clear, colorless oil. Analysis by VPC indicated a *Z*:*E* ratio of 88:12.

With Tetramethylammonium Acetate. As described above, acetate **23** (200.1 mg, 1.011 mmol), catalyst **2** (40.7 mg, 0.0352 mmol), and tetramethylammonium acetate (143.7 mg, 1.080 mmol) were heated at reflux with dimethyl sodiomalonate, prepared from dimethyl malonate (400 μL, 3.5 mmol) and sodium hydride (100 mg, 2.5 mmol) in 6.6 mL of THF, for 2.5–3.0 h at reflux. The reaction mixture was worked up and purified as previously described to give 164.5 mg (60%) of a clear, light yellow oil. Analysis by VPC indicated a *Z*:*E* ratio of 97:3.

With Ethylenebis(triphenylphosphine)palladium(0). As described above, acetate **23** (227 mg, 1.146 mmol) and ethylenebis(triphenylphosphine)palladium(0)[57] (19.2 mg, 0.291 mmol) were heated at reflux with dimethyl sodiomalonate, prepared from dimethyl malonate (360 μL, 3.15 mmol) and sodium hydride (115 mg, 2.88 mmol) in 7 mL of THF, for 30 min at reflux. Workup and purification as previously described afforded 302 mg of a product contaminated with approximately 20 mg of dimethyl malonate for a yield of 91%. Analysis by VPC indicated a *Z*:*E* ratio of 79:21.

Decarbomethoxylation of Dimethyl (*Z*)-(5-Carbomethoxy-1-cyclohexen-3-yl)malonate. Malonate **28** (70 mg, 0.259 mmol) and tetramethylammonium acetate (238 mg, 1.78 mmol) in 2 mL of HMPA were heated at 100 °C for 9 h. The dark reaction mixture was partitioned between ether and water, the aqueous phase was extracted with ether (4 × 30 mL), and the ether extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC (33% ethyl acetate in hexane) to give 41.2 mg (75%) of methyl (*Z*)-(5-carbomethoxy-1-cyclohexen-3-yl)acetate. NMR (CCl_4): δ 5.60 (m, 2 H), 3.70 (s, 6 H), 2.60 (m, 2 H), 2.24 (m, 5 H), 1.25 (bq, *J* = 12 Hz, 1 H). IR (CCl_4): 1750, 1465, 1445, 1425, 1375, 1320, 1300 cm^{-1}. Calcd for $C_{11}H_{16}O_4$: 212.1049. Found: 212.1048.

Alkylation of (*E*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene with Dimethyl Malonate. As usual, acetate **24** (*E*:*Z*, 93:7) (80.1 mg, 0.404 mmol), triphenylphosphine (11.1 mg, 9.6×10^{-3} mmol), and catalyst **2** (11.1 mg, 9.6×10^{-3} mmol) in 1 mL of THF were reacted with dimethyl sodiomalonate, prepared from sodium hydride (50.2 mg, 2.09 mmol) and dimethyl malonate (275 mg, 2.09 mmol) in 6.5 mL of THF, for 24 h at reflux. Purification by preparative TLC (30% ethyl acetate in hexane) gave 87.2 mg (80%) of **29**. Analysis by VPC[10b] revealed two peaks in a ratio of 92:8 assigned to the *E* (retention time = 7.8 min) and *Z* (retention time = 8.6 min) isomers, respectively. NMR (270 MHz, $CDCl_3$): δ 5.80 (d of t of d, *J* = 10.5, 4, 2 Hz, 1 H), 4.61 (d of m, *J* = 10.5 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.69 (s, 3 H), [3.34 (d, *J* = 9.7 Hz) and 3.29 (d, *J* = 8.8 Hz), 1 H], 3.04 (m, 1 H), 2.64 (bq of t,

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Table V

reaction time, h	% Z isomer	% E isomer	% diene
0	98	2	0
0.5	65	28	7
1.0	33	40	27
1.5	20	33	47
2.0	15	35	48
2.5	16	33	51
3.0	14	28	58
3.5	11	23	66
5.0	7	15	78
8.0	3	8	89
23.0	0	0	100

J = 7, 3.5 Hz, 1 H), 2.29 (m, 2 H), 1.96 (d of d of d, J = 13.5, 9.5, 5.5 Hz, 1 H), 1.80 (d of t, J = 13.5, 4 Hz, 1 H). IR (CCl_4): 1760, 1740, 1435 cm^{-1}. Calcd for $C_{13}H_{18}O_6$: 270.1103. Found: 270.1103.

Equilibration of 29. Malonate **29** (*E*:*Z*, 92:8) (25.1 mg, 0.0929 mmol) and potassium *tert*-butoxide (50.1 mg, 0.446 mmol) were combined in 5 mL of dry methanol (freshly distilled from magnesium) and the solution was refluxed for 14 h. Upon cooling, 3 mL of 4% aqueous hydrochloric acid was added and the mixture partitioned between ether and water. The aqueous phase was extracted with ether (3 × 20 mL) and dried over anhydrous magnesium sulfate, and the solvent removed in vacuo. The residue was dissolved in 5 mL of ether, and an ethereal solution of diazomethane added until the reaction mixture remained yellow and effervescence ceased. A few drops of acetic acid were added and the solvent was removed in vacuo to give a yellow oil. Purification via preparative TLC (33% ethyl acetate in hexane) gave 20.1 mg (80%) of dimethyl (5-carbomethoxy-1-cyclohexen-3-yl)malonate. Analysis of 100-MHz NMR revealed a resonance at δ 1.35 (bq, 1 H) assigned as the axial C-4 methine in the *Z* isomer and a resonance at δ 1.84 (m, 2 H) assigned as both C-4 methylene protons in the *E* isomer in ratio of 72:25.

Decarbomethoxylation of *E* Malonate 29. As for **28**, *E* malonate **29** (55.3 mg, 0.205 mmol) and tetramethylammonium acetate (270.2 mg, 2.02 mmol) in 2 mL of hexamethylphosphoric triamide at 95 °C for 20 h gave, after purification by preparative TLC (30% ethyl acetate in hexane), 32.7 mg (75%) of methyl (*E*)-(5-carbomethoxy-1-cyclohexen-3-yl)acetate as a clear, colorless oil. NMR (CCl_4): δ 5.62 (m, 2 H), 3.69 (s, 6 H), 2.6 (bm, 2 H), 2.30–2.12 (bm, 4 H), 1.80 (bm, 2 H). IR (CCl_4): 1740, 1650, 1455, 1440, 1420, 1365, 1350, 1335, 1310 cm^{-1}. Calcd for $C_{11}H_{16}O_4$: 212.1049. Found: 212.1060.

Reaction of (*Z*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene with Tetrakis(triphenylphosphine)palladium(0). A solution of (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene (427 mg, 2.156 mmol) and catalyst **2** (129 mg, 0.112 mmol) in 10 mL of THF was heated at reflux. Aliquots were removed at intervals and analyzed via VPC.[10i] Analysis revealed three components identified as *cis*-3-acetoxy-5-carbomethoxy-1-cyclohexene (retention time = 8.9 min, t = 165 °C), *trans*-3-acetoxy-5-carbomethoxycyclohexene (retention time = 8.1 min, t = 165 °C), and 1-carbomethoxy-2,4-cyclohexadiene (retention time = 1.9 min, t = 165 °C; 4 min, t = 135 °C). The diene component was identified by the 100-MHz NMR spectrum of an isolated sample. 3-Acetoxy-5-carbomethoxy-1-cyclohexene (*Z* and *E*) was identified by coinjection with authentic samples. The results are listed in Table V.

1-Carbomethoxy-2,4-cyclohexadiene: NMR (270 MHz, $CDCl_3$) δ 6.03–5.81 (bm, 4 H), 3.72 (s, 3 H), 3.30 (d of d of t, J = 13.5, 9.5, 2.5 Hz, 1 H), 2.55 (d of d of t, J = 17.5, 13.5, 3 Hz, 1 H), 2.42 (d of d of d of d, J = 17.5, 9.5, 4.5, 1 Hz, 1 H); IR (CCl_4) 3035, 2980, 2940, 2860, 1750, 1435, 1268, 1130, 1032 cm^{-1}.

In a similar procedure, acetate **23** (198.3 mg, 1.00 mmol), tetramethylammonium acetate (135.9 mg, 1.02 mmol), and tetrakis(triphenylphosphine)palladium(0) (66.5 mg, 0.576 mmol) in 1.25 mL of THF were heated at reflux and monitored via VPC. After 3.5 h, approximately 10% of the allylic acetate (*Z* and *E*), and three peaks at low retention times (2.1, 1.8, 1.4 min, t = 165 °C), were observed. These peaks were isolated by preparative VPC (20% SE-30 on Chromosorb W, 60/80 mesh, 3.6 m × 0.64 cm, t = 150 °C) to give 3- and 4-carbomethoxy-1-cyclohexene (retention time = 5.8 min), methyl benzoate (retention time = 6.5 min), and 1-carbomethoxy-1,4-cyclohexadiene (retention time = 8 min). The presence of 1-carbomethoxy-3-cyclohexene and methyl benzoate was determined by coinjection and 100-MHz NMR comparison with authentic samples.

Alkylation of Lactone 25 with Dimethyl Malonate. As usual, lactone **25** (200.7 mg, 1.618 mmol) and catalyst **2** (33 mg, 0.0286 mmol) were reacted with dimethyl sodiomalonate, prepared from 4.73 mmol of dimethyl malonate and 4.55 mmol of sodium hydride in 10 mL of THF, for 6 h at reflux. The reaction mixture was diluted with 10% aqueous hydrochloric acid, extracted with ethyl acetate (75 mL total), and dried over anhydrous magnesium sulfate and the solvent removed in vacuo to give 630 mg of a yellow oil. This was dissolved in 5 mL of ether and an ethereal solution of diazomethane was added until effervescence ceased, and the excess diazomethane was then quenched with acetic acid. Removal of the solvent in vacuo, and purification of the residue by preparative TLC (33% ethyl acetate in hexane), gave 385.2 mg (88%) of dimethyl (*Z*)-(5-carbomethoxycyclohexen-3-yl)malonate, identical with the previously characterized sample (*Z*:*E* > 99:1).

Alkylation of Lactone 31 with Dimethyl Malonate. Dimethyl malonate (700 mg, 5.3 mmol) was slowly added to a slurry of sodium hydride (192 mg, 4.8 mmol) in 10 mL of tetrahydrofuran and stirred at room temperature for 15 min. The resulting clear solution was added in one portion to a mixture of the title compound. As for lactone **25**, lactone **31** (238.7 mg, 1.925 mmol) and catalyst **2** (35 mg, 0.0303 mmol) were reacted with dimethyl sodiomalonate, prepared from 700 mg (5.3 mmol) of dimethyl malonate and 192 mg (4.8 mmol) of sodium hydride in 10 mL of THF, for 6 h at reflux. After the workup outlined, including treatment with diazomethane, purification via preparative TLC (33% ethyl acetate in hexane) gave 437.2 mg (84%) of **33**. Analysis by VPC[10b,f] indicated only one peak with retention times of 12 and 8.1 min on each column, respectively. NMR (270 MHz, $CDCl_3$): δ 5.67 (m, 2 H), 3.67 (s, 6 H), 3.61 (s, 3 H), 3.35 (m, 1 H), 3.26 (d, J = 9 Hz, 1 H), 3.07 (m, 1 H), 2.46–2.22 (bm, 3 H), 1.17 (d of t, J = 13.2, 7.5 Hz, 1 H). NMR (270 MHz, C_6D_6): δ 5.77 (d of t, J = 5.5, 2 Hz, 1 H), 5.66 (d of t, J = 5.5, 2 Hz, 1 H), 3.40 (bs, 10 H), 3.33 (d, J = 9 Hz, 1 H), 3.03 (m, 1 H), 2.42 (d of t, J = 13.2, 8.1 Hz, 1 H), 2.25 (d of d, J = 15.1, 6.9 Hz, 1 H), 2.18 (d of d, J = 15.1, 8.1 Hz, 1 H), 1.24 (d of t, J = 13.2, 7.8 Hz, 1 H). Irradiation (in C_6D_6) at δ 3.03 collapses patterns at δ 5.77 (d of d, J = 5.5, 1.8 Hz), 5.66 (d of d, J = 5.5, 2.2 Hz), 2.42 (d of d, J = 13, 7.8 Hz), 2.25 (d, J = 15 Hz), 2.18 (d, J = 15 Hz), 1.24 (d of d, J = 13, 7.5 Hz). Irradiation (in C_6D_6) at δ 5.77 sharpens resonance at δ 3.03 but has no effect on resonances at δ 2.42 or 1.24. Irradiation (in C_6D_6) at δ 5.66 sharpens resonance at δ 3.03 but has no effect on resonance at δ 2.42 or 1.24. ^{13}C NMR ($CDCl_3$): δ 172.0, 168.1, 135.0, 131.6, 56.5, 51.7, 50.8, 44.9, 41.3, 39.9, 34.3. IR (CCl_4): 1755, 1738, 1434, 1255 cm^{-1}. Calcd for $C_{13}H_{18}O_6$: 270.1103. Found: 270.1097.

Alkylation of Acetate 23 with Bis(benzenesulfonyl)methane. In THF. As usual, catalyst **2** (59.5 mg, 0.0514 mmol), triphenylphosphine (31.5 mg, 0.120 mmol), and the allylic acetate (98% cis) (169 mg, 0.853 mmol) were reacted with bis(benzenesulfonyl)methylsodium, prepared from 290.6 mg (0.982 mmol) of bis(benzenesulfonyl)methane and 40 mg (0.99 mmol) of sodium hydride in 6 mL of THF, for 24 h at reflux. Purification by preparative TLC (33% ethyl acetate in hexane, one elution, and 50% ethyl acetate in hexane, one elution) gave 355 mg (92%) of **30** as a white foam which was contaminated with approximately 6% (via NMR integration) of bis(benzenesulfonyl)methane. Analysis by 270-MHz NMR revealed two singlets at δ 3.67 and 3.65 in a ratio of 1:1 assigned as the methyl ester protons for the cis and trans isomers. NMR (270 MHz, $CDCl_3$): δ 7.93 (m, 4 H), 7.67 (m, 2 H), 7.54 (m, 4 H), 5.68 (m, 1 H), 5.53 (m, 1 H), 4.76 (s, bis(benzenesulfonyl)methane impurity, 6%), 4.56 and 4.55 (two doublets, J = 14 Hz, 1 H), 3.67 and 3.65 (s, 3 H), 3.54 (m, 1 H), 2.89 (m, 0.5 H), 2.59 (m, 0.5 H), 2.43–2.12 (bm, 4 H). IR (CCl_4): 1733, 1450, 1330 cm^{-1}. Calcd for $C_{21}H_{22}O_6S_2$: 434.0858. Found: 434.0845.

In Me_2SO. As usual, triphenylphosphine (60 mg, 0.229 mmol), catalyst **2** (66 mg, 0.057 mmol), and the allylic acetate (98% cis) (200 mg, 1.01 mmol) were reacted with bis(benzenesulfonyl)methylsodium, prepared from 716.8 mg (2.42 mmol) of bis(benzenesulfonyl)methane and 96 mg (2.4 mmol) of sodium hydride in 10 mL of Me_2SO, for 2 h at 65 °C. Initial purification by preparative TLC (25% ethyl acetate in hexane, six elutions) gave only partial separation of the alkylated product and bis(benzenesulfonyl)methane. The impure fraction containing both products was rechromatographed under identical conditions to give 324.1 mg (74%) of alkylated product as a white foam which contained approximately 3% of bis(benzenesulfonyl)methane. Analysis by 270-MHz NMR revealed the product to be identical with that obtained in the previous experiment, with a *Z*:*E* ratio of approximately 1:1.

Hydrogenation and Desulfonylation of 30. Bissulfone **30** (149.3 mg, 0.344 mmol), dissolved in 8 mL of absolute ethanol and 5% palladium on barium carbonate (200 mg), was shaken under 2 atm of hydrogen for 6 h. The reaction mixture was filtered through a pad of Celite and rinsed with ethyl acetate and the combined solvent portions were removed in vacuo. The residual oil was purified by preparative TLC (50% ethyl acetate in hexane) to give 128.6 mg (86%) of bis(benzenesulfonyl)-3-cyclohexane as a white foam contaminated with 6% bis(benzenesulfonyl)methane (NMR integration). NMR (270 MHz, $CDCl_3$): 7.93 (m, 4 H), 7.67 (bt, J = 8 Hz, 2 H), 7.54 (bt, J = 8 Hz, 4 H), 4.422 and 4.417 (two doublets, J = 14 Hz, 1 H), 3.65 and 3.64 (two singlets, 3 H), 2.77 (m, 1 H), 2.48 (bt, J = 12 Hz, 0.5 H), 2.37–1.79 (bm, 4.5 H),

1.70–1.09 (bm, 4 H). IR ($CHCl_3$): 1738, 1452, 1330 cm^{-1}.

The product obtained above (128.6 mg, 0.29 mmol) was dissolved in 7 mL of absolute methanol and cooled to 0 °C. Anhydrous disodium hydrogen phosphate (500 mg, 3.5 mmol) and granulated 6% sodium amalgam (1.5 g) were consecutively added and the mixture was stirred at 0 °C for 1.5 h. The mixture was decanted into 5 mL of pentane, the residue was washed with pentane, and the combined portions were extracted with saturated aqueous ammonium chloride (3 × 30 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by distillation at atmospheric pressure (Vigreux) with the last traces of solvent removed under vacuum for a short time to give 34.7 mg (75%) of 1-carbomethoxy-3-methylcyclohexane as a clear, colorless oil. Analysis of the product by VPC[10c] and coinjection with an authentic sample of (*Z*)- and (*E*)-1-carbomethoxy-3-methylcyclohexane revealed a *Z*:*E* ratio of approximately 55:45.

Alkylation of Lactone 25 with Bis(benzenesulfonyl)methane. As before, lactone **25** (124 mg, 1.0 mmol) and catalyst **2** (69 mg, 0.0598 mmol) were reacted with bis(benzenesulfonyl)methylsodium, prepared from 592 mg (2.0 mmol) of bis(benzenesulfonyl)methane and 76 mg (1.9 mmol) of sodium hydride in 8 mL of THF, for 6 h at reflux. Purification by preparative TLC (50% ethyl acetate in hexane) gave a mixture of alkylated product, bis(benzenesulfonyl)methane, and lactone **25**. The 270-MHz NMR revealed that the alkylated product was a single isomer as evidenced by the appearance of only one singlet at δ 3.67 assigned to the methyl ester protons, and one doublet (J = 1.8 Hz) at δ 4.60 assigned to the bis(benzenesulfonyl)methine proton.

The material prepared above was dissolved in absolute ethanol and hydrogenated over 5% palladium on barium carbonate as described previously. After filtration and removal of the solvent in vacuo, the residue was dissolved in 10 mL of absolute methanol. Anhydrous disodium hydrogen phosphate (700 mg) and granulated 6% sodium amalgam (1.5 g) were added and the mixture was stirred at 0 °C for 30 min. Analysis of the reaction mixture by VPC[10c] and by comparison to an authentic sample of 1-carbomethoxy-3-methylcyclohexane (85% *Z*, 15% *E*) revealed the presence of only the *Z* isomer.

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Supplementary Material Available: Preparation of methyl benzenesulfonylacetate, **1a**, **1b**, **4**, and **14** (4 pages). Ordering information is given on any current masthead page.

Cyclization Catalyzed by Palladium(0). Initial Studies and Macrolide Formation

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Abstract: The intramolecular reaction of stabilized anions with allylic acetates catalyzed by Pd(0) complexes proceeds with high regioselectivity. Four-, five-, and six-membered carbocyclic rings have been observed. Extension to macrolide formation revealed selective formation of 16-, 14-, 12-, and 10-membered rings over the allylically related isomers possessing 14-, 12-, 10-, and 8-membered rings, respectively. Most surprising was the obtention of only nine and eight membered ring lactones rather than the alternative seven and six membered ring systems. Palladium-catalyzed cyclization reactions do not appear to possess any ring size preferences, thus making the reaction an excellent approach to the noncommon rings. The various factors that affect intra- vs. intermolecular reaction and regio- and stereochemistry are discussed. In the course of these studies, total syntheses of the naturally occurring macrolides exaltolide, recifeiolide, phoracantholide I, and phoracantholide J were achieved. In such applications, removal of the carbomethoxy and benzenesulfonyl groups to create a methylene group employed tetramethylammonium acetate in HMPA and 6% sodium amalgam in alcohol solvents buffered with disodium acid phosphate or acetic acid.

Introduction

The structural elucidation of civetone and muscone as large-ring ketones by Ruzika[1] in 1926 earmarks the origin of macrocyclic chemistry. The previous prediction that these ring structures would be planar and thus severely destabilized due to overextension of the internal bond angles from tetrahedral geometry (von Baeyer strain theory) was replaced by the conception of large rings as nonplanar, flexible, and virtually strain-free structures. Although significant synthetic and theoretical advances were realized in the ensuing years,[2] it was with the isolation of the first macrolide antibiotic, pikromycin, in 1950[3] that the biological potential and synthetic challenge of macrocycles were genuinely appreciated.

The term "macrocycle" broadly refers to medium- (8–11 atoms) and large- (12 or more) ring compounds. The term "macrolide", originally reserved as a description of the large-ring lactone antibiotics isolated from *Streptomyces* organisms, has gradually come to denote that subset of macrocycles which incorporates a lactone moiety. Current efforts have focused primarily on macrolide synthesis.

Naturally occurring macrolides may be conveniently classified according to structural type,[4] with the polyoxo (e.g., pikromycin,[7] erythromycin[8]), polyene (e.g., amphoterian B,[9] tetrin[10]), ionophoric (e.g., nonactin,[11] boromycin[12]), and the lactam-containing ansa

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