5.94 (s, 1 H), 6.18–5.50 (m, 1 H), 5.18–4.83 (m, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.09–1.23 (m, 12 H); mass spectrum, m/e 446 (M^+).

1,4-Dihydro-2,3-bis(methoxycarbonyl)-1-(4-pentenyl)-1,4-epoxynaphthalene (33): colorless oil; R_f 0.20 (hexane/EtOAc = 5/1); IR (neat) 3050, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–6.97 (m, 4 H), 5.91 (s, 1 H), 6.18–5.52 (m, 1 H), 5.22–4.84 (m, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 2.56–1.45 (m, 6 H); mass spectrum, m/e 328 (M^+).

1,4-Dihydro-2,3-bis(methoxycarbonyl)-1-(5-hexenyl)-1,4-epoxynaphthalene (34): colorless oil; R_f 0.27 (hexane/EtOAc = 5/1); IR (neat) 3075, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–6.96 (m, 4 H), 5.91 (s, 1 H), 6.06–5.50 (m, 1 H), 5.18–4.76 (m, 2 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 2.57–1.24 (m, 8 H); mass spectrum, m/e 342 (M^+).

General Procedure for the Competitive Inter- vs. Intramolecular Diels–Alder Reactions of Phthalans 16, 18, 20, and 22 with DMAD. The reaction of **16** is described as an illustrative case. To a mixture of 100 mg (0.274 mmol) of **16** and 34 mL (0.274 mmol) of DMAD in 3 mL of toluene at 110 °C was added a solution of CSA (7 mg, 0.027 mmol) in 1 mL of toluene. After 3 min, solid K_2CO_3 (ca. 50 mg) was added, and the mixture was cooled to room temperature. The reaction mixture was diluted with ether (60 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was chromatographed on silica gel (hexane/EtOAc = 10/1) to give 62 mg (77%) **25** and 1 mg (9%) of **31** in the order of elution.

The results of the similar reactions of **18**, **20**, and **22** are summarized in Table II.

Acknowledgment. We thank Hideyuki Akieda for the fundamentally experimental assistance.

Supplementary Material Available: Experimental details for the preparation of **7–10** and their spectroscopic data (8 pages). Ordering information is given on any current masthead page.

Regioselective and Stereoselective Nucleophilic Addition to Electrophilic Vinylcyclopropanes

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Palladium(0) complexes catalyze ring opening of 1,1-diactivated 2-vinylcyclopropanes **2** with concomitant addition of a carbon nucleophile. The reaction is extremely regioselective and stereoselective in that the alkylation occurs syn to the cyclopropane bond being cleaved in [n.1.0] bicyclic systems (n = 3, 4).

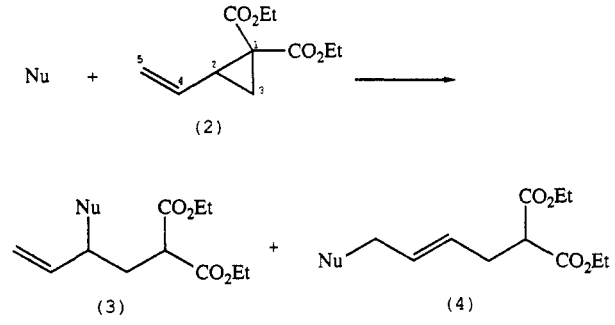
A common tactic in organic synthesis is to cyclopropanate a double bond so that when the strained ring is opened some molecular fragment, or useful functional group, can be introduced. An attractive advantage of this strategy is that one bond of the cyclopropane often may be cleaved selectively due to stereoelectronic control.[1] As a consequence of this, there is considerable interest in new methods for opening cyclopropanes,[2] and subsequently the procedures developed may be applied in total syntheses.[3]

Nucleophilic ring opening of electrophilic vinylcyclopropanes **2** is more difficult to control.[4a] Addition could occur at C^2 or C^5 (using the numbering system shown in Scheme I), and this seems to be governed by the nature of the nucleophile. For instance,[5] thiolate anions (RS^-) preferentially add to C^2 while mercaptyl radicals (RS·) add to C^5.[6] In some cases the selectivity is poor, thus diminishing the utility of this type of reaction; dimethylsodiomalonate, for example, reacts with cyclopropane **2** to give a mixture of the tetraesters **3** and **4** (Scheme I).[4]

This research was undertaken in order to develop mild, selective methods of adding stabilized carbanionic nucleophiles to activated vinylcyclopropanes. Stoichiometric quantities of certain transition-metal complexes react readily with cyclopropanes and vinylcyclopropanes.[7] Catalytic amounts of palladium complexes can cause (i) isomerization of dienylcyclopropanes[8] and dienylaziridines[9] to five-membered ring systems and (ii) addition of amines to vinylcyclopropanes;[10] therefore, palladium catalysis was an obvious starting point for this study.

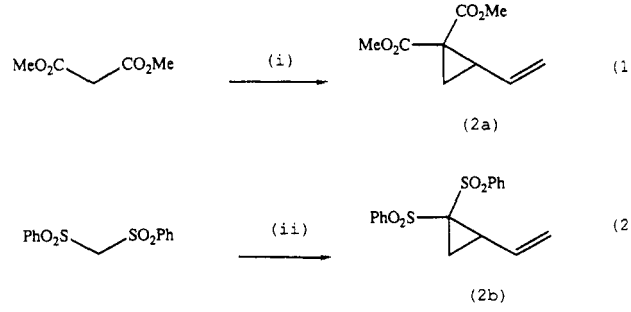
The diesters **2a** and **2b** were conveniently prepared by literature methods[11] or via zerovalent palladium catalysis as described in eq 1, Scheme II. In palladium-catalyzed allylic substitution reactions of the latter type[12] alkoxide ions are formed from the carbonate leaving groups; hence, it is not necessary to add base or to isolate the monosub-

Scheme I[a]



[a] When Nu = $NaCH(CO_2Et)_2$, the ratio of **3** to **4** is 5:1.[4]

Scheme II[a]



[a] Key: (i) MeO_2CO⌒=⌒OCO_2Me, 2 mol % $Pd(PPh_3)_4$, THF, 20 °C, 12 h; (ii) Br⌒=⌒Br, 2.05 $N(n\text{-}Bu)_4OH$(aq), CH_2Cl_2, 20 °C, 4 days.

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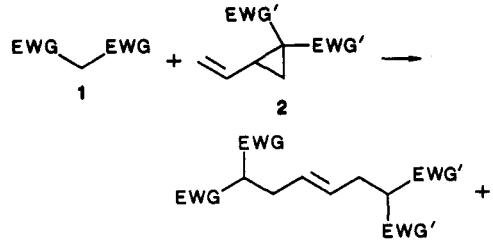
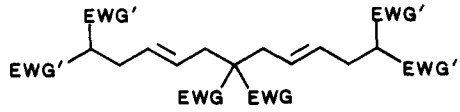
0022-3263/87/1952-2046$01.50/0

Table I. Data for the Ring Opening/Alkylation of the 1,1-Diactivated Vinylcyclopropanes 2



4a: EWG′ = CO_2Me, EWG = MeCO
b: EWG′ = CO_2Me, EWG = SO_2Ph
c: EWG′ = SO_2Ph, EWG = MeCO
d: EWG′ = CO_2Et, EWG = CO_2Me
e: EWG′ = SO_2Ph, EWG = SO_2Ph



5a: EWG′ = CO_2Me, EWG = MeCO
b: EWG′ = CO_2Me, EWG = SO_2Ph
c: EWG′ = SO_2Ph, EWG = MeCO

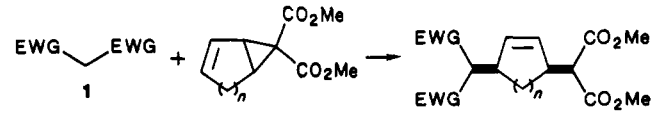
entry[a]	EWG′	EWG	ratio 1 to 2	time, h	isol yields, % 4	5
1	CO_2Me	MeCO	1:1	8.0	30	59
2	CO_2Me	MeCO	2:1	8.0	5	91
3	CO_2Me	MeCO	1:3	8.0	58	30
4[b]	CO_2Me	SO_2Ph	1:1	4.75	94	
5	CO_2Me	SO_2Ph	2:1	3.0		96
6	CO_2Me	SO_2Ph	1:3	4.75	98	
7[c]	SO_2Ph	CO_2Me	1:3	5.5	18	
8	CO_2Et	CO_2Me	1:1	2.0	23	
9	CO_2Et	CO_2Me	1:3	8.0	26	
10	SO_2Ph	MeCO	1:1	5.75	62	32
11[c]	SO_2Ph	MeCO	2:1	5.0	52	
12	SO_2Ph	MeCO	1:3	6.75	76	16
13[b]	SO_2Ph	SO_2Ph	1:3	5.0	61	

[a] 2 mol % of $Pd(Ph_3)_4$, THF, at 20 °C unless otherwise specified. [b] At 65 °C. [c] A complex mixture formed; only the products indicated were isolated.

stituted intermediate formed after one alkylation step.[13] A phase-transfer-catalyzed synthesis of cyclopropanes from 1,2-dibromides[14] was adapted for the preparation of 1,1-bis(phenylsulfonyl)-2-vinylcyclopropane (**2c**), eq 2.

Generally, when substrates **2** were mixed with neutral nucleophile precursor **1** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0), a very clean reaction occurred to give the mono- and bis-alkylated products **4** and **5**, respectively (Table I). The ratio of the two products of this transformation [4:5] is dependent upon the ratio of the two reactants [1:2]. Good yields of the alkylated products were obtained except where EWG′ had a greater or a comparable ability to support an adjacent negative charge relative to the substituent EWG (entries 7–9, EWG = electron-withdrawing group). In the case of entry 5 the second alkylation occurred at the more hindered, sulfone-substituted, methine carbon rather than at the carbon between the two ester groups; presumably this is due to the relative acidities of the active methylene centers.[15] Regioselectivity in these reactions was high; there was no indication of any addition at C^2 in proton NMR spectra of the crude reaction mixtures. All the alkenes isolated were trans as demonstrated by selective irradiation in the ^1H NMR and measurement of coupling constants between the alkene protons. The products of these reactions, **4** and **5**, are functionalized with respect to further alkylation, functional group interconversion of esters, and modification or removal of the phenylsulfonyl fragment.[16]

Table II. Data for Ring Opening/Alkylation of the [*n*.1.0] Bicyclic Systems 6 (*n* = 1) and 7 (*n* = 2)



6: *n* = 1
7: *n* = 2

8a: EWG = COMe, *n* = 1
b: EWG = SO_2Ph, *n* = 1
9a: EWG = COMe, *n* = 2
b: EWG = SO_2Ph, *n* = 2

entry[a]	*n*	EWG	time, h	isol yield, %
1	1	COMe	7.0	89
2	1	SO_2Ph	13.5	66
3	2	COMe	8.0	84
4	2	SO_2Ph	16.5	46[b]

[a] Using a 3:1 ratio of **1** to **6** or **7** in refluxing THF as described in the Experimental Section. [b] Not optimized.

Bicyclic vinylcyclopropanes **6** and **7** (Table II) were also used as substrates in order to elucidate the stereochemistry of this reaction. These compounds, **6** and **7**, were conveniently prepared by rhodium-catalyzed cyclopropanation reactions[17] and were smoothly converted into the mono-

(1) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.
(2) For some recent examples see: (a) Demuth, M.; Raghavan, P. R. *Helv. Chim. Acta* **1979**, *62*, 2338. (b) Demuth, M.; Mikhail, G. *Tetrahedron* **1983**, *39*, 991. (c) Callant, P.; Wilde, H. D.; Vanderwalle, M. *Tetrahedron* **1981**, *37*, 2085. (e) Yates, P.; Stevens, K. E. *Can. J. Chem.* **1982**, *60*, 825. (f) Callant, P.; D'Haenens, L.; Vanderwalle, M. *Synth. Commun.* **1984**, *14*, 155. (g) Mioskowski, C.; Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1983**, *24*, 5521. (h) Keith D. D. *Tetrahedron Lett.* **1985**, *26*, 5907. (i) Taber, D. F.; Krewson, K. R.; Raman, K.; Rheingold, A. L. *Tetrahedron Lett.* **1984**, *25*, 5283. (j) Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579.
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(4) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.
(5) (a) Stewart, J. M.; Olsen, D. R. *J. Org. Chem.* **1968**, *33*, 4534. (b) Schultz, A. G.; Godfrey, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 2414.
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(8) (a) Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 2871. (b) *Isr. J. Chem.* **1984**, *24*, 149.
(9) Fugami, K.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 857.
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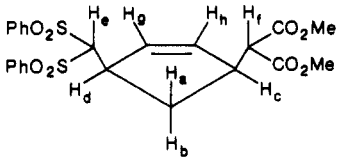
(11) Kierstead, R. K.; Linstead, R. P.; Weedon, B. C. L. *J. Chem. Soc.* **1952**, 3610, 3616. (b) Stewart, J. M.; Pagenkopf, G. K. *J. Org. Chem.* **1969**, *34*, 7.
(12) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809.
(13) Unlike the previous palladium-catalyzed syntheses of vinylcyclopropanes: (a) Genet, J. P.; Piau, F.; Ficini, J. *Tetrahedron Lett.* **1980**, *21*, 3183. (b) Genet, J. P.; Balabane, M.; Charbonnier, F. *Tetrahedron Lett.* **1982**, *23*, 5027.
(14) Blankenship, C.; Paquette, L. A. *Synth. Commun.* **1984**, *14*, 983.
(15) pK_a values for bis(phenylsulfonyl)methane and dimethyl malonate have been estimated as 10 and 14, respectively. Trost, B. M.; Cossy, J.; Burks, J. *J. Am. Chem. Soc.* **1983**, *105*, 1052.
(16) (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. (b) Hwu, J. R. *J. Org. Chem.* **1983**, *48*, 4433. (c) Trost, B. M.; Shimizu, M.; *J. Am. Chem. Soc.* **1983**, *105*, 6757.
(17) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie, P. *Synthesis* **1976**, 600.

Table III. ^{1}H NMR Chemical Shift and Coupling Constant Data for Cyclopentene 8b

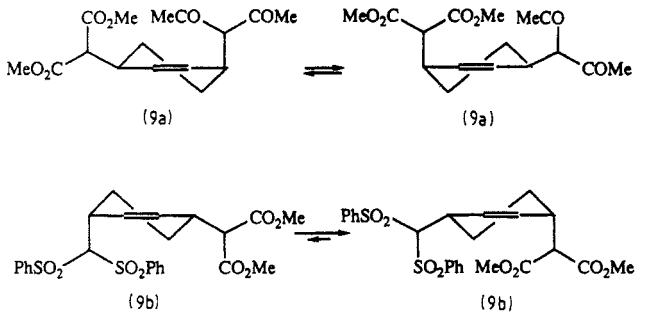


8b

	δ^a	H_a	H_b	H_c	H_d	H_e	H_f	H_g	H_h
H_a	2.03		13.0	7.6	7.7				
H_b	2.40	13.0		7.8	7.7				
H_c	3.34	7.6	7.8				10.0	0.5	1.9
H_d	2.37	7.7	7.7			2.9		2.7	1.7
H_e	4.73				2.9				
H_f	3.43			10.0					
H_g	5.69			0.5	2.7				5.8
H_h	5.54			1.9	1.7			5.8	

[a] At 250 MHz in $CDCl_3$ with chemical shifts reported in δ downfield from $SiMe_4$ and coupling constants in hertz.

Scheme III



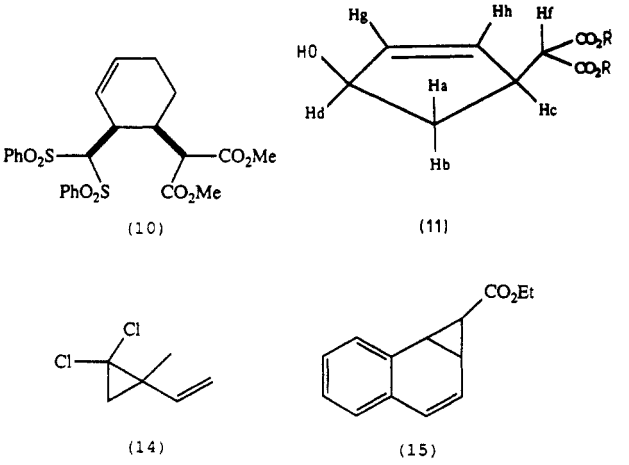


Figure 1.

alkylated products 8 and 9. In one case, entry 2 (Table II), a 7% yield of product **10** was isolated; this corresponds to alkylation at C^2 of vinylcyclopropane **6**. Assignment of cis stereochemistries to the products of these transformations was problematic; the evidence that indicates these molecules are indeed of *Z* configuration is now described in detail.

Some 4-substituted cyclopentenols **11** have been assigned cis stereochemistries on the basis of ^{1}H NMR coupling constants;[18] J_{ac} and J_{ad} are both smaller than J_{bc} and J_{bd}, indicative of a *Z* relationship between H_b, H_c, and H_d.[19] Coupling constants for the 3,5-dialkylcyclopentenes **8** were measured in a series of ^{1}H NMR homonuclear decoupling experiments, and illustrative data are given in Table III. However, since J_{ac}, J_{ad}, J_{bc}, and J_{bd} are of similar magnitude, they cannot be used to deduce the stereochemistry of these molecules.

Attention was then turned to a difference NOE approach since, for *cis*-3,5-dialkylcyclopentenes **8**, irradiation of proton H_b should cause an appreciable NOE enhancement of the allylic protons H_c and H_d. In practice the relevant signals in the ^{1}H NMR spectrum (250 MHz) of compound **8b** are too close together for measurement of NOE enhancements by routine irradiation; consequently, a program facilitating saturation of a particular resonance at relatively low decoupling power was used.[20] Irradiation of the signal at ca. 2.04 ppm, later assigned to H_a, caused a significant enhancement of the resonances due to H_b (17%), H_e (4%), and H_f (5%) *only*; conversely, irradiation of the signal at 2.44 ppm (H_b) gave enhanced signals for both H_c (5%) and H_d (ca. 5%).[21] These data indicate that compound **8b** is a cis isomer.

Another piece of proton NMR data indicates that compound **9b** also has cis stereochemistry. (*Z*)-Cyclohexenones **9** in solution rapidly interconvert between their alternative half-chair conformations (Scheme III); thus, the coupling constants between protons in these molecules are governed by a weighted time average effect. In the case of (*Z*)-**9b**, the bis(phenylsulfonyl)methine group is much larger than the bis(methylcarboxy)methine substituent and it will heavily bias the equilibrium between the half-chair forms toward the conformer with this larger ring substituent in the pseudoequatorial position. One would anticipate, from molecular models of the predominant conformer of **9b**, that the alkene signals would be split by significantly different couplings since the dihedral angle between C_a–H_a and C_b–H_b approaches 90° while for C_c–H_c and C_d–H_d this angle tends toward 0° (Figure 2). An asymmetric pattern for the alkene signals is therefore expected for a cis configuration of **9b**, and this is in fact observed. One resonance is split by relatively large coupling constants [($CDCl_3$) δ 5.58 (ddd, J = 10.4, 4.2, 1.3 Hz, 1 H)] while the other only suffers one measurable coupling, that being the one to the other olefinic proton [δ 5.51 (d, J = 10.4 Hz, 1 H)].[22] A more symmetrical alkene region in the ^{1}H

(18) (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (b) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.

(19) This was deduced by analogy with a series of compounds that were studied previously. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

(20) Kims, M.; Saunders, J. K. M. *J. Magn. Reson.* **1984**, *56*, 518.

(21) If compounds **8** were trans, H_d and H_c could not have both suffered appreciable enhancements as a result of irradiation of Hb.

(22) This effect was simulated with Brucker's PANIC NMR simulation program.

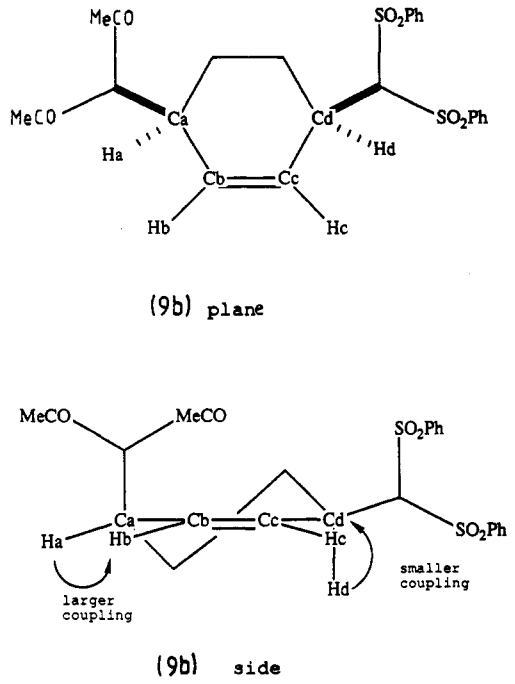


Figure 2.

NMR would be expected for a trans isomer of cyclohexene **9b** because the methine protons that would cause splitting of the alkene hydrogens would both be in pseudoaxial orientations. The alkene ^{1}H NMR signals for either isomer of compound **9a** should give a reasonably symmetrical olefinic proton NMR pattern because the allylic protons with which they couple spend nearly equal amounts of time in pseudoequatorial and pseudoaxial positions.

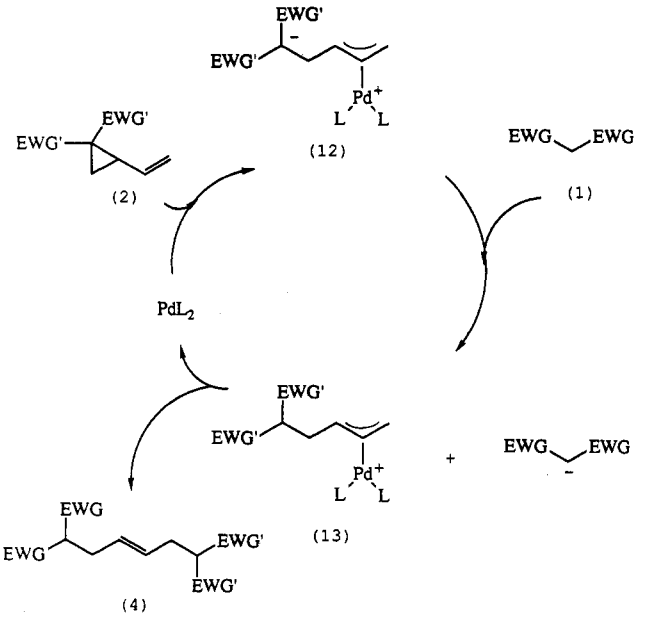
Two substrates, **14** and **15**, would not undergo reaction under the conditions outlined above. Presumably the electron-withdrawing substituents on the cyclopropane rings of these substrates do not provide enough stabilization to allow the ring opening to occur.

Conclusions

A possible mechanism for the palladium-assisted cleavage of 1,1-diactivated vinylcyclopropanes is shown in Scheme IV. Initial coordination of the palladium(0) entity orients the metal in such a way that the organic fragment may easily adjust to a η^3-bonding mode by cleavage of the three-membered ring and formation of a zwitterionic intermediate **12**. Proton transfer from the nucleophile precursor then generates a stabilized carbanion that subsequently adds to the η^3-allyl terminus of **13**. This mechanism is consistent with the *Z* configurations of compounds **8b** and **9b**, deduced by ^{1}H NMR; cis stereochemistries are proposed for products **8a**, **9a**, and **10** by analogy.

The methodology presented here is reminiscent of palladium(0)-catalyzed ring opening of vinylepoxides[18] and underlines the efficacy of such reactions for C–C bond formation under mild, neutral conditions.[23-25]

Scheme IV



Experimental Section

NMR spectra were recorded on a Varian EM390, a Brucker WM250, or a Brucker WH400 spectrometer. IR spectra were recorded on a Perkin-Elmer 983 spectrometer. Mass spectra were taken on a AEI MS30 or an AEI MS902 instrument. Microanalyses were performed by the Microanalysis Department, University Chemical Laboratory, Cambridge.

THF was distilled from sodium/benzophenone ketal immediately prior to use. The R_f values given in the following section were measured with use of Merck silica gel 60 F_{254} (0.25-mm) plates. 1,1-Dicarbomethoxy-2-vinylcyclopropane (**2a**) and the diethyl analogue **2b** were prepared by a literature procedure[11] or by the method described below.

Preparation of 1,1-Dicarbomethoxy-2-vinylcyclopropane (2a). Alternative Procedure. A solution of 0.132 g (1 mmol) of dimethyl malonate and 0.204 g (1 mmol) of (*Z*)-dicarbomethoxybut-2-ene-1,4-diol (**3**)[26] in 10 mL of THF was prepared under dinitrogen in a Schlenk tube capped with a rubber septum. The solution was frozen in a liquid dinitrogen bath, the septum was removed, 0.023 g (2 mol %) of tetrakis(triphenylphosphine)-palladium(0) was introduced quickly against a moderate flow of dinitrogen, and the septum was rapidly replaced. The mixture was freeze/thaw degassed three times and then stirred at 20 °C for 12 h. The solvent was then removed in vacuo, and the residue was flash chromatographed[27] with 5–10% ethyl acetate in hexane as eluant. A fraction at R_f 0.6 (10% ethyl acetate in hexane) was collected: 0.058 g (31%);[28] ^{1}H NMR ($CDCl_3$) δ 5.45–5.25 (m, 2 H), 5.14 (dd, J = 8 Hz, 7 Hz, 1 H), 3.74 (s, 6 H), 2.60 (dd, J = 14 Hz, 12 Hz, 1 H), 1.72 (dd, J = 8 Hz, 7 Hz, 7 H), 1.60 (dd, J = 8 Hz, 7 Hz, 1 H); mass spectrum using chemical ionization (NH_3), m/e 185, 100% (M + 1).

Preparation of 1,1-Bis(phenylsulfonyl)-2-vinylcyclopropane (2c). A 20-mL round-bottom flask equipped with a magnetic stir bar, 5.92 g (20 mmol) of bis(phenylsulfonyl)-methane,[29] and 4.28 g (20 mmol) of 1,4-dibromobut-2-ene[30] was capped with a rubber septum and flushed with dinitrogen. The solids were dissolved by addition of 100 mL of dichloromethane and stirring. Stirring was continued at 20 °C while 13.7 mL of a 40% by weight solution of tetra-*n*-butylammonium hydroxide[30] (21 mmol) was added all at once. The dichloromethane layer

(23) Another example being reactions in which trimethylenemethane is thought to be generated in situ. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

(24) A preliminary communication of this work has been published: Burgess, K. *Tetrahedron Lett.* **1985**, *26*, 3049.

(25) After the preliminary communication of this work was published, a letter appeared that described a related palladium(0)-catalyzed [2 + 3] cycloaddition reaction of vinylcyclopropanes with α,β-unsaturated esters or ketones: Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825.

(26) Bissinger, W. E.; Fredenburg, R. H.; Kadesch, R. G.; Kung, F.; Langston, J. H.; Strain, F. *J. Am. Chem. Soc.* **1947**, *69*, 2955. Commercially available[30] *cis*-2-butene-1,4-diol was used.

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(28) This yield was not optimized. In a publication that appeared after this work was complete,[25] a very similar reaction was described and higher yields were reported.

(29) Stetter, H.; Riberi, B. *Monatsh. Chem.* **1972**, *103*, 1262.

(30) Aldrich Chemical Co.

turned dark brown almost immediately. After 1.25 h of stirring another 13.7 mL (21 mmol) of the same tetra-*n*-butylammonium hydroxide solution was added, and the stirring was continued for 4 days. The mixture was poured into 250 mL of ethyl acetate and washed with two 250-mL portions of 2 M aqueous hydrochloric acid and 250 mL of water and dried over magnesium sulfate containing a trace of activated charcoal. Removal of the solvent gave an oily residue that was flash chromatographed (20% ethyl acetate in hexane), giving one major band at R_f 0.6 (25% ethyl acetate in hexane), 5.17 g (74%). A sample of this material was recrystallized from 95% aqueous ethanol for analysis. **2c**: mp 107.5–108.0 °C; IR (Nujol mull, cm^{-1}) 2924 (m), 2854 (w), 1582 (w), 1451 (m), 1444 (m), 1337 (w), 1160 (s), 1138 (s), 1090 (m), 1078 (m), 1000 (w), 934 (w), 852 (w), 798 (m), 752 (m), 729 (m), 686 (m), 630 (m); ^1H NMR ($CDCl_3$) ∂ 8.93–8.05 (m, 4 H), 7.71–7.49 (m, 6 H), 6.95–6.10 (m, 1 H), 5.43–5.29 (m, 2 H), 3.23 (dd, J = 18 Hz, 9 Hz, 1 H), 2.35 (dd, J = 8 Hz, 6 Hz, 1 H), 2.13 (dd, J = 10 Hz, 6 Hz, 1 H); mass spectrum, exact mass m/e 348.0483 (2.3%, M^+), calcd for $C_{17}H_{16}O_4S_2$ 348.0492. Anal. Calcd for $C_{17}H_{16}O_4S_2$: C, 58.60; H, 4.63; S, 18.40. Found: C, 58.52; H, 4.72; S, 18.67.

Preparation of 1,1-Dicarbomethoxybicyclo[4.1.0]hept-3-ene (7). A suspension of 0.027 g (0.5 mol %) of rhodium(II) acetate in 6.5 mL of freshly cracked cyclopentadiene was stirred with a magnetic stirrer for 21 h at 20 °C while 2.1 g (13 mmol) of dimethyl diazomalonate was added via a syringe pump. The excess cyclopentadiene was remove in vacuo, and the residue was flash chromatographed (10% ethyl acetate in hexane). The major fraction, mass 2.86 g, had R_f 0.3 (10% ethyl acetate in hexane). This was distilled bulb to bulb at 0.1 mmHg to give 1.50 g of the product as an oil that froze below 0 °C. **7**: ^1H NMR ($CDCl_3$) ∂ 5.80–5.77 (m, 1 H), 5.62–5.60 (m, 1 H), 3.70 (s, 3 H), 3.62 (s, 3 H), 2.82–2.79 (m, 1 H), 2.73–2.68 (m, 2 H), 2.45–2.43 (m, 1 H); ^{13}C NMR ∂ 170.3, 166.4, 132.2, 129.4, 52.5, 52.1, 39.3, 38.6, 34.3, 31.6; mass spectrum, exact mass m/e 164.0485 (M^+ – MeOH, 52%), calcd for $C_9H_8O_3$ 164.0496. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.35; H, 6.31.

General Procedure for the Palladium(0)-Catalyzed Ring Opening of Vinylcyclopropanes with Concomitant Nucleophilic Addition. A Schlenk tube equipped with a magnetic stir bar, the nucleophile (see Tables I and II for the quantities), and the vinylcyclopropane (1 mmol) and capped with a rubber septum was cooled to ca. –190 °C. The septum was removed, 0.023 g (2 mol %) of tetrakis(triphenylphosphine)palladium(0)[31] was added quickly against a moderate flow of argon, and the septum was immediately replaced. Any of the catalyst that had adhered to the inner walls of the Schlenk tube was washed and flushed into the bottom of the vessel (still at ca. –190 °C) when the solvent, 2 mL of THF, was added. The mixture was freeze/thaw degassed three times and then maintained at the reaction temperature for the time indicated in Tables I or II. The solvent was then removed in vacuo, and the residue was flash chromatographed with ethyl acetate in hexane as eluant.

Preparation of Diketone 4a. The general procedure above gave a yellowish oil: R_f 0.3 (25% ethyl acetate hexane); IR (liquid, cm^{-1}) 3457 (br, w), 3006 (w), 2956 (s), 2848 (w), 1831 (vs), 1696 (s), 1436 (s), 1356 (m), 1238 (s), 1197 (m), 1159 (s), 1026 (w), 972 (m); ^1H NMR ($CDCl_3$) ∂[33] 16.6 (s), 5.43–5.26 (m), 3.63 (s), 3.58–3.55 (m), 2.83 (d, J = 5 Hz), 2.54–2.40 (m), 2.06 (s), 1.98 (s); ^{13}C NMR ($CDCl_3$) ∂[33] 203.3, 191.1, 169.0, 168.9, 130.9, 128.9, 128.5, 125.7, 107.4, 72.4, 68.0, 52.2, 51.6, 51.4, 31.4, 30.4, 29.9, 29.0, 22.6; mass spectrum, exact mass m/e 284.1248 (M^+, 2%), calcd for $C_{14}H_{20}O_6$ 284.1259. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.16; H, 7.25.

Preparation of Diketone 5a. The general procedure above gave a yellow oil: R_f 0.1 (25% ethyl acetate in hexane); IR (liquid, cm^{-1}) 3746 (br, w), 2957 (w), 2851 (w), 1737 (s), 1698 (s), 1438 (m), 1357 (m), 1235 (m), 1197 (m), 1156 (m), 1026 (w), 976 (w); ^1H NMR ($CDCl_3$) ∂ 5.60–5.42 (m, 2 H), 5.32–5.15 (m, 2 H), 3.72 (s, 12 H), 3.37 (t, J = 7 Hz, 2 H), 2.57–2.49 (m, 8 H), 2.03 (s, 6 H); ^{13}C NMR ($CDCl_3$) ∂ 205.4, 169.0, 130.3, 130.2, 126.8, 70.2, 52.4, 51.5, 33.5, 31.7, 26.6; mass spectrum, exact mass m/e 437.1802 (M^+ – OMe, 2%), calcd for $C_{22}H_{29}O_9$ 437.1819. Anal. Calcd for $C_{23}H_{32}O_{10}$: C, 58.97; H, 6.88. Found: C, 58.67; H, 7.12.

Preparation of Disulfone 4b. The general method above gave a colorless oil: R_f 0.4 (40% ethyl acetate in hexane); IR (liquid, cm^{-1}) 2954 (w), 1733 (s), 1584 (w), 1448 (m), 1331 (s), 1234 (m), 1155 (s), 1079 (m), 1024 (w), 999 (w), 974 (w); ^1H NMR ($CDCl_3$) ∂ 8.05–7.92 (m, 4 H), 7.76–7.53 (m, 6 H), 5.57–5.36 (m, 2 H), 4.40 (t, J = 6 Hz, 1 H), 3.72 (s, 6 H), 3.39 (t, J = 7 Hz, 1 H), 2.84 (t, J = 6 Hz, 4 H),[32] 2.51 (t, J = 7 Hz, 4 H);[32] ^{13}C NMR ($CDCl_3$) ∂ 169.0, 137.9, 134.5, 130.2, 129.6, 129.0, 127.3, 83.7, 52.5, 51.3, 31.3, 28.6; mass spectrum, exact mass m/e 480.0938 (M^+, 0.3%), calcd for $C_{22}H_{24}O_8S_2$ 480.0913. Anal. Calcd for $C_{22}H_{24}O_8S_2$: C, 54.99; H, 5.03; S, 13.34. Found; C, 55.29; H, 5.05; S, 13.45.

Preparation of Disulfone 5b. A colorless crystalline solid was obtained: mp 93.0–93.5 °C; R_f 0.2 (40% ethyl acetate in hexane); IR ($CHCl_3$, cm^{-1}) 1747 (s), 1730 (s), 1446 (m), 1436 (m), 1331 (m), 1311 (m), 1147 (s), 1077 (w), 971 (s), 909 (m); ^1H NMR ($CDCl_3$) ∂ 8.01–7.98 (m, 4 H), 7.70–7.54 (m, 6 H), 5.74–5.34 (m, 4 H), 3.73 (s, 12 H, 3.44 (t, J = 7 Hz, 2 H), 2.88 (d, J = 6 Hz, 4 H), 2.61 (t, J = 7 Hz, 4);[32] ^{13}C NMR ($CDCl_3$) ∂ 169.0, 137.0, 134.5, 131.5, 131.4, 128.5, 124.7, 90.26, 52.5, 51.3, 32.6, 31.6; mass spectrum, exact mass m/e 664.1647 (M^+, 0.1%), calcd for $C_{31}H_{36}O_{12}S_2$ 664.1648. Anal. Calcd for $C_{31}H_{36}O_{12}S_2$ C, 56.01; H, 5.46; S, 9.64. Found: C, 55.94; H, 5.44; S, 9.90.

Preparation of Diketone 4c. **4c** was isolated as a colorless solid: mp (oxazole derivative formed in hot ethanol with hydroxylamine) 110.0–110.5 °C; R_f 0.5 (50% ethyl acetate in hexane); IR (film, cm^{-1}) 3638 (br w), 3065 (w), 2923 (m), 1724 (m), 1697 (s), 1584 (s), 1478 (m), 1447 (s), 1426 (m), 1330 (s), 1154 (s), 1079 (s), 1023 (s), 998 (m), 972 (m), 914 (m), 844 (w); ^1H NMR ($CDCl_3$) ∂ 16.69 (s), 7.92–7.87 (m), 7.71–7.51 (m), 5.49–5.27 (m), 4.45–4.37 (m), 3.65 (m), 2.92–2.80 (m), 2.42 (m), 2.15 (s), 2.03 (s); ^{13}C NMR ($CDCl_3$) ∂ 203.3, 191.3, 137.9, 134.6, 134.5, 132.4, 130.5, 129.5, 129.3, 129.1, 126.9, 124.1, 83.7, 83.4, 67.7, 30.5, 29.9, 29.2, 28.7, 28.6, 22.9; mass spectrum, exact mass 405.0833 (M^+ – COMe, 2%), calcd for $C_{20}H_{21}O_5S_2$ 405.0801. Anal. Calcd for $C_{22}H_{24}O_6S_2$: C, 58.91; H, 5.39; S, 14.29. Found: C, 58.56; H, 5.36; S, 14.32.

Preparation of Diketone 5c. **5c** was isolated as a colorless crystalline solid: mp 95.0–95.5 °C; R_f 0.3 (50% ethyl acetate in hexane); IR ($CHCl_3$, cm^{-1}) 3695 (br w), 2980 (m), 1698 (s), 1445 (s), 1330 (s), 1312 (s), 1280 (w), 1155 (m), 1075 (m), 970 (w), 895 (w); ^1H NMR ($CDCl_3$) ∂ 7.94–7.89 (m, 8 H), 7.68–7.49 (m, 12 H), 5.76–5.68 (m, 2 H), 5.14–5.08 (m, 2 H), 4.54 (t, J = 6 Hz, 2 H), 3.69 (q, J = 7 Hz, 2 H), 2.82 (t, J = 6 Hz, 4 H), 2.57 (d, J = 7 Hz, 4 H), 2.09 (s, 6 H), 1.22 (t, J = 7 Hz, 3 H);[33] ^{13}C NMR ($CDCl_3$) ∂ 205.6, 137.8, 134.5, 131.4, 129.6, 129.3, 129.1, 128.7, 127.9, 83.2, 70.2, 33.3, 28.7, 27.1; mass spectrum, exact mass 796.1509 (M^+, 1%), calcd for $C_{39}H_{40}O_{10}S_4$ 796.1504. Anal. Calcd for $C_{39}H_{40}O_{10}S_4 \cdot C_2H_5OH$: C, 58.41; H, 5.50. Found: C, 58.24; H, 5.56.

Preparation of Tetraester 4d. **4d** was isolated as a colorless oil: R_f 0.4 (25% ethyl acetate in hexane); IR (liquid, cm^{-1}) 2990 (m), 2970 (w), 1735 (vs), 1465 (m), 1365 (m), 1335 (m), 1270 (m), 1230 (s), 1155 (s), 1030 (m), 970 (m), 855 (w); ^1H NMR ($CDCl_3$) δ 5.46–5.42 (m, 2 H), 4.13 (q, J = 7 Hz, 4 H), 3.67 (s, 6 H), 3.36–3.25 (m, 2 H), 2.53–2.49 (m, 4 H), 1.21 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) ∂ 169.0, 168.6, 129.0, 128.6, 61.2, 52.3, 51.9, 51.6, 31.6, 31.5, 13.9; mass spectrum, exact mass m/e 344.1452 (M^+, 5%), calcd for $C_{16}H_{24}O_8$ 344.1471. Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.80; H, 7.02. Found: C, 56.01; H, 7.14.

Preparation of the Tetrasulfone 4e. **4e** was isolated as a colorless crystalline solid: mp 229–230 °C dec; R_f 0.5 (50% ethyl acetate in hexane); ^1H NMR (CD_3SOCD_3) ∂ 7.89–7.61 (m, 8 H), 5.69–5.64 (t, J = 5 Hz, 2 H), 5.14 (t, J = 3 Hz, 2 H), 3.34 (br s, 4 H); ^{13}C NMR (CD_3SOCD_3) ∂ 138.1, 134.6, 129.2, 129.0, 127.3, 79.9, 28.1; mass spectrum, exact mass 503.0612 (M^+ – SO_2Ph), calcd for $C_{24}H_{23}O_6S_3$ 503.0657. Anal. Calcd for $C_{30}H_{28}O_8S_4$: C, 55.88; H, 4.38; S, 19.89. Found: C, 55.76; H, 4.31; S, 19.94.

Preparation of Diketone 8a. **8a** was isolated as a yellow oil via the general procedure described above: R_f 0.2 (25% ethyl acetate in hexane eluant); ^1H NMR ($CDCl_3$) ∂ 5.69–5.37 (m, 1 H), 5.58–5.54 (m, 1 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.54–3.33 (m, 3 H), 3.24 (d, J = 9 Hz, 1 H), 2.40–2.48 (m, 1 H), 2.16 (s, 3 H), 2.15 (s, 3 H), 1.14–1.02 (m, 1 H); ^{13}C NMR ($CDCl_3$) ∂ 203.0, 202.8, 168.6, 133.4, 133.0, 75.3, 56.5, 52.3, 44.9, 44.7, 32.7, 29.7, 29.4; mass spectrum, exact mass m/e 253.1077 (M^+ – COMe, 17%), calcd

(31) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
(32) Theoretically, this pattern should be interpreted as a doublet of doublets.
(33) This spectrum was complicated by keto–enol tautomerism of the sample.

for $C_{13}H_{17}O_5$ 253.1077. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.58; H, 7.09.

Preparation of Disulfone 8b. A colorless crystalline compound was obtained: mp 114.5–115.0 °C; R_f 0.2 (33% ethyl acetate in hexane); ^{1}H NMR ($CDCl_3$) δ 7.93–7.85 (m, 4 H), 7.69–7.61 (m, 2 H), 7.55–7.48 (m, 4 H), 5.71–5.67 (m, 1 H), 5.56–5.52 (m, 1 H), 4.72 (d, J = 3 Hz, 1 H), 3.75–3.63 (m, 7 H), 3.43 (d, J = 10 Hz, 1 H), 3.35–3.30 (m, 1 H), 2.46–2.41 (m, 1 H), 2.08–1.99 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 139.8, 138.5, 134.5, 134.2, 133.6, 130.4, 129.7, 129.3, 129.0, 128.9, 85.5, 55.9, 52.3, 44.7, 44.0, 32.8; mass spectrum, exact mass m/e 351.0896 ($M^+ - SO_2Ph$, 10%), calcd for $C_{17}H_{19}O_6S$ 351.0993. Anal. Calcd for $C_{23}H_{24}O_8S_2$: C, 56.08; H, 4.91; S, 13.02. Found: C, 55.99; H, 4.92; S, 13.53.

Preparation of Disulfone 10. The general procedure given above also afforded this compound (along with **8b**) as a colorless crystalline compound: mp 180.0–180.5 °C; R_f 0.3 (33% ethyl acetate in hexane); ^{1}H NMR ($CDCl_3$) δ 7.98–7.84 (m, 4 H), 7.67–7.60 (m, 2 H), 7.56–7.46 (m, 4 H), 5.78–5.75 (m, 1 H), 5.48–5.45 (m, 1 H), 5.40 (d, J = 2 Hz, 1 H), 3.68 (s, 3 H), 3.65 (s, 3 H), 3.52 (m, 1 H), 3.43–3.39 (m, 2 H), 2.92–2.82 (m, 1 H), 2.20–2.09 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.9, 139.9, 138.6, 134.5, 134.3, 133.7, 130.4, 129.8, 129.5, 129.1, 128.9, 85.7, 56.0, 52.4, 44.8, 44.1, 33.0; mass spectrum, not informative. Anal. Calcd for $C_{23}H_{24}O_8S_2$: C, 56.08; H, 4.91; S, 13.02. Found: C, 56.06; H, 4.77; S, 12.99.

Preparation of Diketone 9a. A pale yellow oil was obtained by the general procedure describe above: R_f 0.3 (40% ethyl acetate in hexane); IR (film, cm^{-1}) 3404 (br s), 3003 (w), 2954 (m), 2870 (w), 1753 (s), 1733 (vs), 1696 (s), 1433 (m), 1358 (m), 1295 (m), 1270 (m), 1193 (m), 1151 (s), 1023 (w), 951 (w), 876 (w); ^{1}H NMR ($CDCl_3$) δ 5.68–5.62 (m, 1 H), 5.56–5.50 (m, 1 H), 3.73 (s, 6 H), 3.65 (d, J = 11 Hz, 1 H), 3.30 (d, J = 9 Hz, 1 H), 3.01–2.99 (m, 1 H), 2.90–2.86 (m, 1 H), 2.18 (s, 3 H), 2.16 (s, 3 H), 1.74–1.24 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 203.3, 203.0, 168.5, 168.4, 130.1, 129.4, 73.9, 56.0, 52.4, 34.8, 34.6, 30.3, 29.3, 23.9, 23.2; mass spectrum, exact mass m/e 267.1208 (M^+ - COMe, 12%), calcd for $C_{14}H_{19}O_5$ 267.1232. Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.76; H, 7.08.

Preparation of Disulfone 9b. From the general procedure described above **9b** was obtained as a colorless crystalline solid: mp 163.5–164.0 °C; R_f 0.4 (40% ethyl acetate in hexane); IR (film, cm^{-1}) 1750 (vs), 1731 (s), 1585 (w), 1447 (s), 1435 (s), 1332 (s), 1312 (s), 1151 (s), 1078 (m), 1021 (w), 999 (w), 979 (w), 950 (w), 902 (w); ^{1}H NMR ($CDCl_3$) δ 7.94–7.88 (m, 4 H), 7.69–7.61 (m, 2 H), 7.55–7.49 (m, 4 H), 5.68–5.63 (m, 1 H), 5.51 (d, J = 10 Hz, 1 H), 4.54 (d, J = 2 Hz, 1 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.55 (d, J = 11 Hz, 1 H), 3.38–3.32 (m, 1 H), 2.88–2.84 (m, 1 H), 2.21–2.15 (m, 1 H), 1.76–1.67 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.5, 139.8, 138.6, 134.5, 134.3, 129.7, 129.3, 129.0, 127.6, 86.7, 55.3, 52.4, 36.5, 33.0, 25.5, 23.1; mass spectrum exact mass m/e 506.1057 (M^+, 0.2%). Anal. Calcd for $C_{22}H_{26}O_8S_2$: C, 56.20; H, 5.17; S, 12.66. Found: C, 56.39; H, 5.08; S, 12.38.

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Synthesis and Chemical Properties of Tetrazole Peptide Analogues

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Tetrazole dipeptide analogues in which the amide bond is replaced with the tetrazole ring were synthesized from the corresponding Z or Pht protected dipeptide esters via the imidoyl chloride and imidoyl azide intermediates. Of the various imidoyl chloride/imidoyl azide forming reagents that were investigated for this conversion, the best combination was found to consist of PCl_5/HN_3. The success of this reaction was found to be dependent upon the amino protecting group employed and also upon the amino acid sequence of the starting dipeptide. Racemization of the α-carbon of the N-terminal amino acid residue was found to occur during the formation of the tetrazole dipeptide analogue. A hypothetical mechanism involving the formation of a ketene amine intermediate is proposed to account for this racemization. Although racemization of the α-carbon of the C-terminal amino acid residue did not occur during tetrazole formation, it did take place when the tetrazole dipeptide ester was saponified with base, as well as when the tetrazole dipeptide acid was coupled with an amino acid ester by using diphenylphosphoryl azide as the coupling reagent. Racemization of the C-terminal amino acid residue did not take place when the normal mixed anhydride, DCC–HOBt, and *N,N*-bis[2-oxo-3-oxazolidinyl]-phosphorodiamidic chloride coupling methods were employed.

The use of peptide bond surrogates in the design and synthesis of analogues of biologically active peptides has seen extensive use in recent years.[1] One such peptide bond surrogate is the trans olefinic moiety. This group has been successfully employed in a number of different peptides as a mimic of the trans configuration of the peptide bond.[2] Although the corresponding cis olefinic group would serve as the ideal mimic of the cis amide bond, the ease with which the cis β,γ-unsaturated carbonyl system isomerizes to the more stable trans α,β-unsaturated carbonyl system[2b] has precluded the use of this particular peptide bond surrogate in the design of peptide analogues. To get around this problem, the tetrazole ring system has been proposed by Marshall et al.[3] as an alternate means of mimicking the cis configuration of a peptide bond. The use of this particular peptide bond surrogate requires the synthesis of 1,5-disubstituted tetrazoles in which the 1 and

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