Intramolecular Palladium-Catalyzed Cycloadditions with a Cleavable Tether

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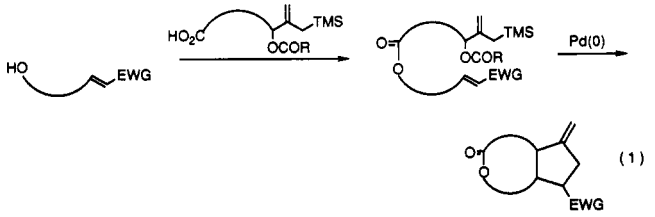
Abstract: A facile synthesis of 2-(acyloxy)-3-methylene-4-(trimethylsilyl)butyric acids evolves from the use of tris(phenylthio)acetaldehyde as a practical glyoxylic ester equivalent. Introduction of the bifunctional donor of a [3 + 2] cycloaddition proceeds simply by esterification of an alcohol possessing TMM-PdL_2 acceptor units. The synthetic flexibility of the sulfone leads to the choice of α,β-unsaturated sulfones as the acceptors. Palladium-catalyzed cycloadditions proceed smoothly at temperatures as low as room temperature. Depending upon the substitution pattern and especially the conformation of the substrate, tethering the ester containing the bifunctional TMM unit at the carbon allylic to the acceptor provides substrates that predominantly to exclusively undergo cycloaddition rather than processes dominated by an alternative Pd(0)-catalyzed ionization. Since the ester linkage is easily cleaved, this sequence serves as a convenient strategy for controlled TMM-PdL_2 cycloadditions. For example, the diastereofacial selectivity of this intramolecular process involves attack syn to the allylic oxygen in a six- or seven-membered-ring acceptor but anti to this oxygen in an intermolecular process. A diastereocontrolled cyclopentenone annulation is developed. Interestingly, the intramolecular cycloaddition of eight- and twelve-membered rings proceeds anti to the allylic oxygen. As an aside, the indefinite shelf life of the crystalline tris(phenylthio)acetaldehyde makes it a convenient glyoxylate synthon.

Extension of the benefits of intramolecular additions to intermolecular processes requires the development of a cleavable tether.[1,2] In evaluating this concept, we focus on an ester linkage as the cleavable functionality since the resultant functional groups are synthetically useful and the substrates should be easily assembled in a convergent manner, as outlined in eq 1. While choice

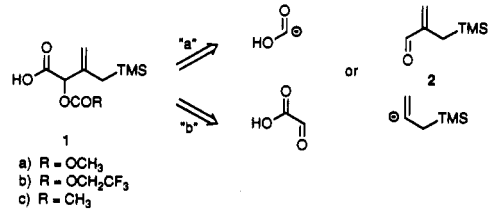


(1)

of the ester group may cause concern considering difficulties experienced in some intramolecular Diels-Alder reactions,[3] its successes[4] and practicality induced us to pursue such an investigation. In this paper, we report our successful development of this concept for palladium-catalyzed [3 + 2] cycloadditions.[5]

Development of Conjunctive Reagents

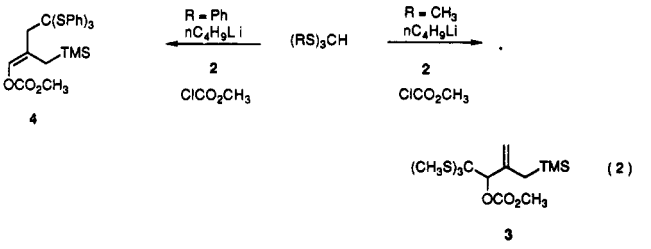
Our demonstration that an acyl group facilitates [3 + 2] cycloadditions led us to select the carboxylic acid **1** as the preferred conjunctive reagent to introduce the bifunctionality necessary for trimethylenemethane (TMM) cycloaddition into a host of acceptors. Our studies initiated with the retrosynthesis "a" because



1
a) R = OCH_3
b) R = OCH_2CF_3
c) R = CH_3

2

of the ready availability of the aldehyde **2**.[6] The anion derived from tris(methylthio)methane[7,8] readily forms the desired adduct **3** (eq 2). Unfortunately, attempts to hydrolyze this ortho thioester



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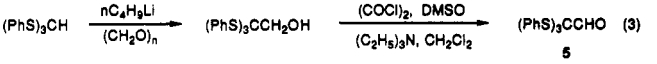
3

failed. Anticipating that the ortho phenyl thioester might be more easily hydrolyzed, we examined the reactions of tris(phenylthio)methyllithium,[7,9] but this anion gave only conjugate addition.[10]

We have previously prepared esters of the acid **1** by the retrosynthetic path "b" using glyoxylates.[11] The problems of oligomerization and hygroscopicity of such glyoxylates made them unattractive as crucial intermediates for a convenient conjunctive reagent. Our success in adding 3-(trimethylsilyl)-2-propenyllithium to ketodithianes[12] suggested that tris(phenylthio)acetaldehyde **5**, readily available in two steps in 75% yield (eq 3), may be a convenient glyoxylate synthon. The fact that aldehyde **5** is a stable crystalline solid that has a long shelf life makes it a very attractive glyoxylate synthon.



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The aldehyde **5** smoothly undergoes carbonyl additions at low temperatures without the complications of either the sulfur analogue of the haloform reaction[13] or desulfenylation.[14] If the

(1) For some relevant references, see: Yoshioka, M.; Nakai, H.; Masaji, O. *J. Am. Chem. Soc.* **1984**, *106*, 1133. White, J. D.; Nolen, E. G., Jr.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150. Shea, K. J.; Fruscella, W. M.; Carr, R. C.; Burke, A. D.; Cooper, D. K. *J. Am. Chem. Soc.* **1987**, *109*, 447. Birtwistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron* **1988**, *44*, 7309. Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885.

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(11) Ochmatowicz, O. Unpublished work in these laboratories.

(12) Trost, B. M.; Grese, T. A. Submitted for publication.

(13) Cf. Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1976**, *41*, 3217. Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.

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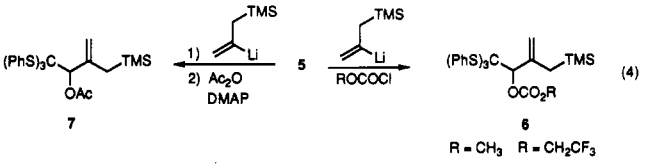
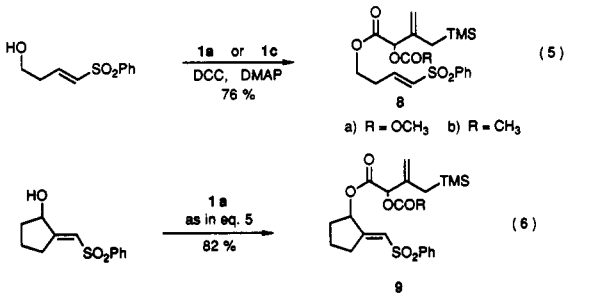
intermediate alkoxide is allowed to warm to 0 °C before quenching, then the conjugate adduct **4** is observed as a contaminant, indicating a haloform-type cleavage followed by conjugate addition at the higher temperatures.



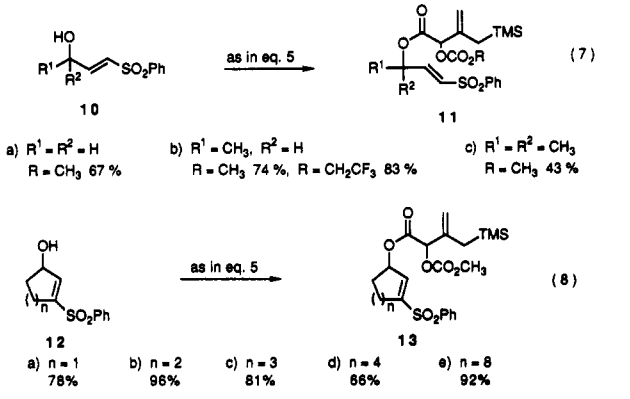
Hydrolysis of the ortho thioester proved remarkably difficult. Mercury and copper reagents led to substantial decomposition of the bifunctionality. However, silver trifluoroacetate[15,16] in refluxing dioxane produced the desired carboxylic acids **1a–c** in 54–67% yields.

Synthesis of Substrates

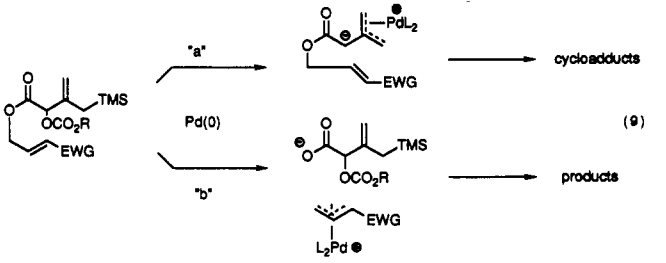
The synthetic versatility of the sulfones, the excellent acceptor properties of vinyl sulfones, and the easy access to hydroxylated unsaturated sulfones focussed our attention on such substrates. DCC in the presence of DMAP-promoted esterification of primary (eq 5) and secondary (eq 6) alcohols with acid **1a**. The ready



availability of γ-hydroxy-α,β-unsaturated sulfones like **10** and **12** from allyl sulfides and sulfones by oxidation to the epoxy sulfone followed by base-catalyzed ring opening[17,18] or from aldehydes by hydroxylative Knoevenagel condensation[19] made such substrates particularly attractive (eqs 7 and 8).

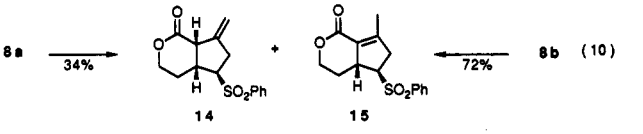


On the other hand, such substrates introduce a major liability. Exposure to Pd(0) can initiate formation of the desired TMM–PdL_2 (eq 9a) but also can promote an alternative ionization mode (eq 9b), which precludes cycloaddition. In fact, the better coordinating ability of an electron-deficient olefin with Pd(0)[20] argues in favor of this nonproductive pathway. Choosing substrates that vary the intrinsic reactivity of the two carboxylate leaving groups and that vary the geometrical accessibility of the nonproductive ionization probes these issues.



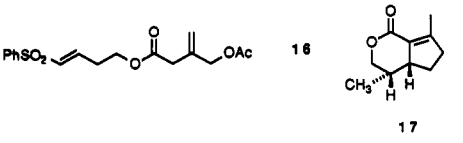
Cycloaddition

In considering the carbonate as the leaving group, we were cognizant of complications that might arise with our substrates. For example, our initial test substrate **8a** can undergo base-catalyzed β-eliminations or transesterifications with the liberated methoxide. Exposing this substrate to our standard conditions of 5 mol % of palladium acetate and 30 mol % of triisopropyl phosphite[21] (henceforth referred to as "the catalyst") in THF at room temperature led to the disappearance of starting material but no cycloadducts. Raising the temperature to 60 °C produced a 1.0:1.2 mixture of **14** and **15** (eq 10). The acetate **8b** under



identical conditions led only to protodesilylation–rearrangement product **16**[22] in addition to recovered starting material. On the other hand, exposing acetate **8b** to the catalyst at 100 °C in dioxane in the presence of BSA gave a 72% yield of a 1.0:7.2 ratio of **14** and **15**. The use of these latter conditions with the carbonate **8a** did not improve its yield of cycloadduct.

The structure of **15** was assigned on the basis of infrared absorbances at 1710 and 1650 cm^{-1} for the unsaturated six-membered ring lactone and an allylic methyl singlet at δ 2.14 in the ^1H NMR spectrum. As with our previous results, the stereochemistry of the starting material was assumed to translate to the product, in accord with literature precedent for *E* acceptors.[23] For **14**, the nonconjugated lactone infrared absorption occurred at 1730 cm^{-1}, and singlets at δ 5.11 and 4.94 in the ^1H NMR spectrum signalled the presence of the *exo*-methylene unit. A 6.9-Hz coupling constant for the bridgehead protons at δ 3.78 and 2.77 (assigned definitively via homonuclear decoupling experiments) indicated the cis ring fusion. The ready accessibility of the cycloadduct **15** suggests that this type of intramolecular cycloaddition should prove to be a valuable strategy to iridoids like neonepatalactone **17**.[24]



(14) Cf. Trost, B. M.; Mao, M. K. T.; Balkovec, J. M.; Bulhmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965.
(15) For thioester hydrolysis, see: Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.
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(17) (a) For a review, see: Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903. Also see: (b) Hardinger, S. A.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 2739. (c) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 3277.
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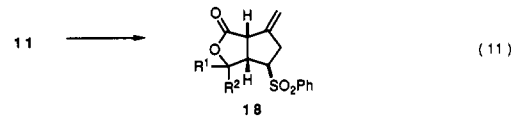
Table I. Equilibria of Methylenecyclopentanes[a]

starting olefin	solvent	exocyclic:endocyclic
19	dioxane	1.0:1.4
21	THF	1.0:2.2
24	dioxane	only[b]
27	THF	5.0:2.0

[a] All reactions were performed at the reflux temperature of the indicated solvent in the presence of triton B. [b] In this case, only unchanged starting material was observed.

At the outset, the chances of achieving cycloaddition of acyclic substrates in which the TMM–carboxylic acid was attached to the allylic carbon of the acceptor seemed remote. The presence of a second allylic carboxylate moiety would likely interfere with the selective ionization of the TMM precursor and lead to substrate decomposition. Furthermore, the electron-deficient vinyl sulfone was expected to be a more attractive coordination site for palladium(0), thus directing ionization away from the TMM precursor. Nevertheless, cycloaddition of **11a** provided 16% of bicyclic lactone **18a**, and **11b** provided a 5.6:1 diastereomeric mixture of lactones **18b** in 20% yield, although dimethyl substrate **11c** gave no cycloaddition product under any conditions (eq 11). The use of higher temperatures (refluxing diglyme) resulted in easier product purification, due to the polymerization of olefin side products, but gave no significant yield enhancements.



(11)

a) $R^1 = R^2 = H$ b) $R^1 = CH_3$ $R^2 = H$ c) $R^1 = R^2 = CH_3$

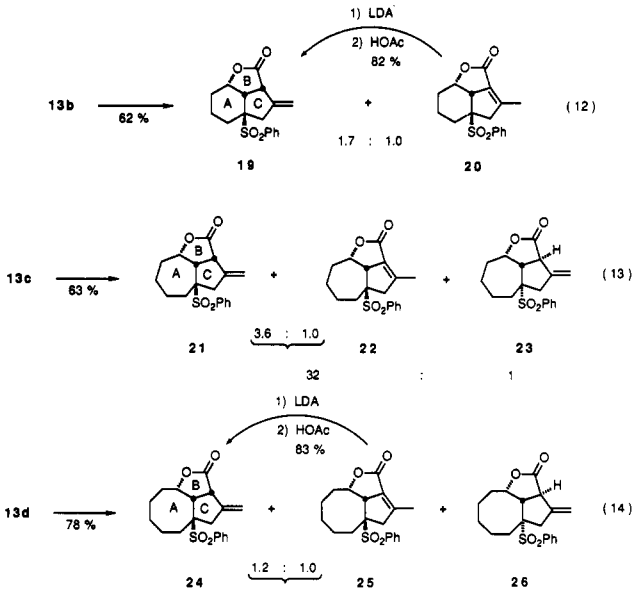
The structure of **18a** was assigned on the basis of the infrared absorbance at 1775 cm^{-1}, characteristic of a butyrolactone, and the *exo*-methylene signals at δ 5.41 and 5.14 in the ^1H NMR spectrum. The stereochemistry was assumed on the basis of precedent and ring strain arguments. Lactone **18b** displays similar characteristics, with the isomeric ratio determined by the relative integration of the *exo*-methylene signals at δ 5.13 (major) and 4.99 (minor) in the ^1H NMR spectrum. The stereochemistry of the major adduct has not been determined; however, it is expected that the sterically more accessible isomer, having the methyl group syn to the sulfone and on the convex face of the bicyclic system, should predominate.

An attempt to improve the leaving-group ability of the carbonate unit by recourse to the trifluoroethyl ester as in **11b** ($R = CH_2CF_3$) failed, apparently due to the inability of trifluoroethoxide ion to effect desilylation of the intermediate. Addition of tetra-*n*-butylammonium acetate as an exogenous silylophile resulted in rapid consumption of the starting material, but no cycloadduct was observed.

Although the yields obtained with these acyclic substrates are not outstanding, the fact that any cycloaddition occurs is indeed remarkable. The results in these simple systems indicate that the rate of ionization of the TMM precursor is competitive with ionization at the tether and imply that structural modification may allow discrimination in the desired direction.

Initial efforts to effect differentiation between tether cleavage and cycloaddition involved cycloalkenyl sulfones as the substrates.[18] The geometrical restrictions leading to a decreased rate of ionization exhibited by cycloalkenyl carboxylates, in comparison with their acyclic counterparts, should minimize the tether cleavage by palladium-catalyzed ionization.[25]

This strategy proved to be extremely successful. As summarized in eqs 12–15, subjecting substrates **13b–13e** to the catalyst provides the structurally interesting tricyclic cycloadducts. The cyclohexenyl, cycloheptenyl, and cyclooctenyl systems required refluxing dioxane, but the cyclododecenyl substrate underwent cycloaddition at room temperature.



In each and every case, the stereoselectivity with respect to the tether was excellent. As expected, the cyclohexenyl substrate gave the syn adducts **19** and **20** exclusively, and the cycloheptenyl one gave the syn adducts **21** and **22** predominantly. Interestingly, the cyclooctenyl and cyclododecenyl systems provide the anti adducts **24** and **25**, and **27** and **28** predominantly to exclusively. Each substrate gave a mixture of exocyclic and endocyclic double bond isomers. *exo*-Methylene products were clearly identifiable by the presence of two one-proton multiplets between δ 4.8 and 5.5 ($J < 3$ Hz) in their ^1H NMR spectra. The endocyclic double bond isomers each exhibited a three-proton resonance between δ 1.63 and 2.01 for the allylic methyl group.

Interconversions establish that the products are of the same stereochemical series and differ only in the position of the double bond. Table I summarizes equilibrations of the exocyclic to endocyclic isomers, which establish that both compounds belong to the same stereochemical series in the case of the six-, seven-, and twelve-membered rings. Since no equilibration was observed under these conditions for the eight-membered ring, this reaction does not permit a correlation.

An alternative correlation involves deconjugation of the endocyclic isomers. While enolization by deprotonation at the γ-methylene group (which would lead to elimination) might have been anticipated to compete with deprotonation of the methyl group, treatment of the endocyclic olefin **20** with LDA followed by quenching with acetic acid smoothly produced the exocyclic isomer **19** in 82% yield. By using this protocol, the eight-membered endocyclic isomer **25** was converted to the exocyclic isomer **24** in 83% yield, allowing the isolation of an exocyclic isomer in good overall yield and providing evidence that both **24** and **25** belong to the same stereochemical series.

The stereochemical assignment of the *exo*-methylene cycloadducts rests upon several arguments. The ring fusion between the two five-membered rings (ring BC) reflects thermodynamic factors. The high strain of a *trans*-bicyclo[3.3.0]octyl system supports the notion that this ring fusion must be cis.[26] The NMR data summarized in Figure 1 supports the remaining stereochemical assignments.

For the six-membered ring **19**, a 2% NOE for H_c and an 8.9% NOE for H_b upon irradiation of H_a supports an all cis arrangement for these protons. The cycloheptenyl system **21** exhibits similar effects, i.e. a 2.7% enhancement of H_c and an 11.1% enhancement

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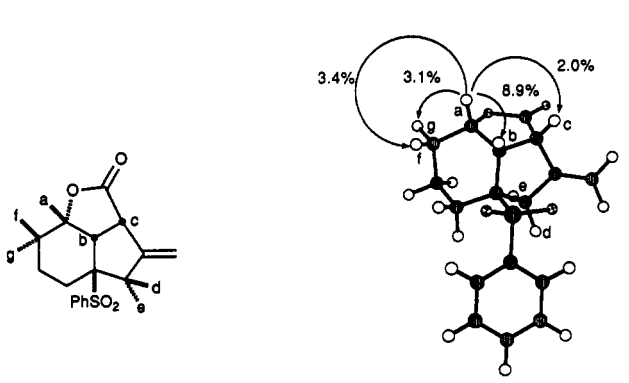
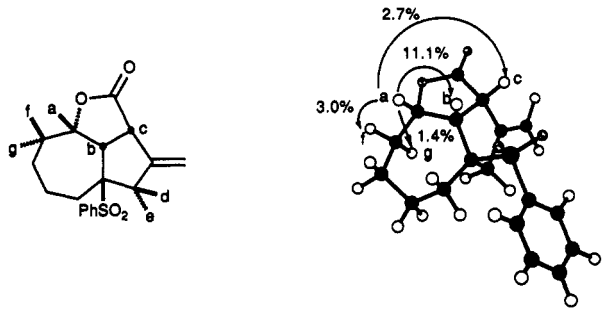
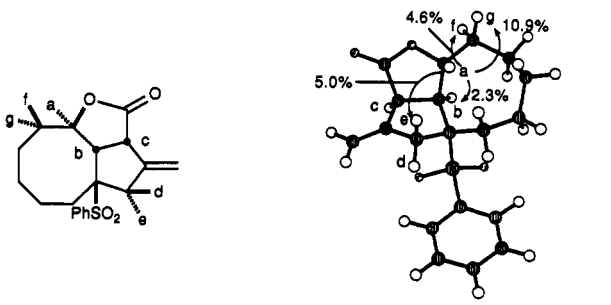


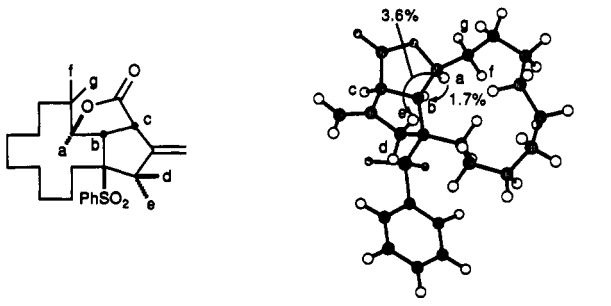
	δ	J	
H_a	4.83		
H_b	3.71		
H_c	3.61	a–b	8.4 Hz
H_d	2.69	a–f	2.9 Hz
H_e	2.47	a–g	2.9 Hz
H_f	2.09	b–c	8.8 Hz
H_g	2.22	d–e	17.6 Hz



	δ	J	
H_a	4.78		
H_b	3.89		
H_c	3.78	a–b	7.9 Hz
H_d	2.26	a–f	small
H_e	2.50	a–g	7.9 Hz
H_f	2.25	b–c	10.2 Hz
H_g	2.10	d–e	16.8 Hz



	δ	J	
H_a	4.24		
H_b	3.62		
H_c	3.69	a–b	8.4 Hz
H_d	3.01	a–f	11.3 Hz
H_e	2.51	a–g	8.2 Hz
H_f	2.30	b–c	8.6 Hz
H_g	1.7	d–e	19.1 Hz



	δ	J	
H_a	4.52		
H_b	3.38		
H_c	3.50	a–b	6.6 Hz
H_d	2.95	a–f	9.5 Hz
H_e	2.52	a–g	1.6 Hz
H_f	obscured	b–c	8.8 Hz
H_g	obscured	d–e	18.6 Hz

Figure 1. NMR data for methylenecyclopentane cycloadducts.

of H_b upon irradiation of H_a, which suggests a similar cis arrangement of these protons.

On the other hand, for the eight-membered ring **24**, the NOE for H_b was considerably smaller (2.3% vs 9–11%) upon irradiation of H_a. Alternatively, a 5.0% NOE was observed for H_e. These observations require H_a to be trans to H_b but cis to the cyclopentyl ring. The twelve-membered ring **27** showed the same behavior and thereby required the same stereochemical deductions.

The stereochemistry of the minor adducts, **23** in the cycloheptenyl system and **26** in the cyclooctenyl system, have not been rigorously determined due to the small amounts obtained. The similarity of their ^1H NMR spectra, however, supports the proposition that they exhibit identical stereochemical relationships (see Figure 2). The most unusual feature of their spectral data is an anomolously large vicinal coupling constant for H_b–H_c (17.1 Hz in **23** and 16.6 Hz in **26**), assigned by decoupling experiments as the bridgehead protons of the B,C ring juncture. A coupling constant of this magnitude can only be explained by an antiperiplanar arrangement of the protons, indicating, therefore, a trans-fused bicyclo[3.3.0]octane. Although several *trans*-bicyclo[3.3.0]octane structures have been reported, none have described a ring-juncture coupling constant of this magnitude.[27] Nevertheless, the rigidity of these systems, imposed by the presence of two sp^2 carbons in the 5,5-system as well as the third ring, forces the dihedral angle between H_b and H_c to be nearly 180°. Interestingly, a natural product, epoxydictymene, has been isolated that demonstrates a similar trans-fused bicyclo[3.3.0]octane

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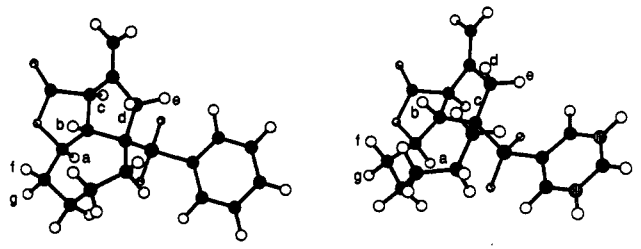


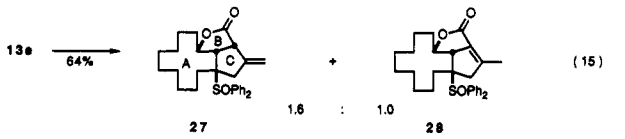
H_a 5.27 ppm	5.26 ppm
H_b 2.81 ppm	2.59 ppm
H_c 4.29 ppm	4.65 ppm
H_d 3.61 ppm	3.52 ppm
H_e 2.64 ppm	2.48 ppm

Figure 2. Chemical shift data from NMR spectra of methylenecyclopentane cycloadducts.

Table II. Calculated and Observed Coupling Constants for Minor Methylenecyclopentanes

	23		26	
J (Hz)	calcd	obsd	obsd	calcd
a–b	10.8	11.1	10.5	10.8
a–f	10.1	7.8	8.0	11.2
a–g	6.1	4.5	4.7	4.9
b–c	13.4	17.1	16.6	13.4
d–e		18.1	18.3	

system, annulated to an eight-membered ring. Unfortunately, the ^1H NMR data for the bridgehead protons have not been published.[28]

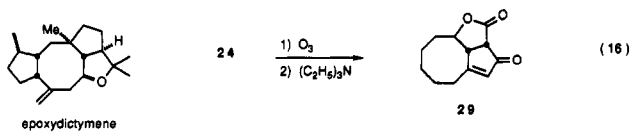


(15)

Molecular modeling[29] suggests a trans fusion of the lactone ring to the seven- and eight-membered rings since the large coupling constants for H_a–H_b (11.1 Hz for **23** and 10.5 Hz in **26**) could only be accommodated by a trans A,B ring fusion (see Table II). The remaining ring-juncture stereochemistry is assigned as trans in order to explain the large downfield shifts observed for H_a and H_c. For the all-trans stereochemistry, both are held rigidly coplanar with the phenyl sulfone and would therefore be expected to experience considerable deshielding.[30] However, it should be noted, that, for the isomers epimeric at the sulfone center, the MM2 estimated coupling constants were approximately the same.

The exocyclic olefin substrate **9**, as well as the cyclopentenyl substrate **13a**, failed to undergo cycloaddition under any conditions. Apparently, the initial cyclization to form the bicyclo[3.3.0]octane system was too energetically unfavorable, and competing processes took precedence. At moderate temperatures, both systems gave slow decomposition, while at elevated temperatures, complex mixtures of products resulted that could not be easily identified.

The type of functionality present in the cycloadducts and its juxtaposition make them quite versatile intermediates. Versatility also dictated the choice of the vinyl sulfone as the acceptor. Reductive desulfonylation[31] is of course possible. Perhaps more useful is the recognition of this sequence as a cyclopentenone annulation.[18] The increasing number of natural products with 5,8-fused ring systems led us to illustrate this point with cycloadduct **24**. Ozonolysis primes the substrate for facile base-



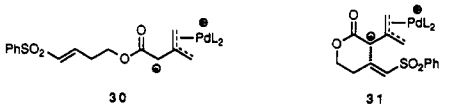
(16)

catalyzed elimination to give the cyclopentenone **29** (eq 16). Performing the reaction in methanol provides the cyclopentenone in 66% yield, but the reaction does not go to completion. Use of methylene chloride–methanol allows the reaction to go to completion but in a slightly lower 60% yield.

Discussion

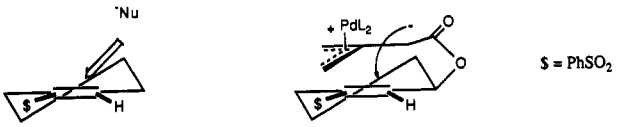
The ester-tethered bifunctional moiety constitutes an excellent substrate for intramolecular palladium-catalyzed cycloadditions. The ability of the [3 + 2] cycloaddition to dominate in substrates having the ester tether at the position allylic to the acceptor vividly demonstrates the efficacy of this cycloaddition. Furthermore, successful cycloadditions of the cyclooctenyl and cyclododecenyl substrates contrasts with the intermolecular versions[18,32] wherein both systems resisted cycloaddition. Indeed, as with other cycloadditions, processes that fail intermolecularly may succeed if converted to an intramolecular reaction.

While the ester linkage has a beneficial effect on the cycloaddition, it appears to be not as activating as a simple ketone.[12] The ester substrate **8a** required a temperature of at least 60 °C to undergo cycloaddition, whereas the corresponding ketone analogue underwent cycloaddition at room temperature. The



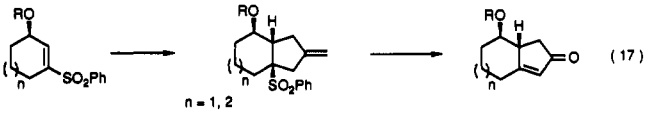
raising of the transition-state energy for the ester cycloaddition may result from destablization associated with the syn ester geometry that **31** required compared to the normally preferred anti conformation of **30**. Apparently, the latter leads to the rearranged protodesilylation product **16** as well as decomposition products from **8b** at 60 °C, whereas at 100 °C, the transition state for cyclization is attainable.

The less satisfactory behavior of the carbonate compared to the acetate in the case of substrate **8** likely derives from base-catalyzed elimination reactions. The fact that the carbonate was effective as the leaving group in the cyclic substrates **13** supports this contention. The stereochemistry observed for the reactions of cyclohexenyl and cycloheptenyl acceptors is consistent with the rationale proposed for intermolecular cycloadditions.[23] For the



intramolecular case, a transition state that places the carbalkoxy group in the pseudoequatorial position allows stereoelectronically favorable axial attack. The rigidity of the cyclohexenyl ring imposes geometrical restrictions that prevent the nucleophile from attaining the proper trajectory for trans attack.[33] Similar results have been described for nucleophilic additions to cyclohexenyl and cycloheptenyl sulfones in which the nucleophile is chelated to an allylic alkoxide.[17]

This stereochemistry complements that which we obtained in the intermolecular cycloadditions.[18] A diastereocontrolled cyclopentenone annulation anti to the γ-hydroxy group was previously developed (eq 17). By tethering the TMM precursor to the γ-hydroxy group, annulation syn to this group is now available.



(17)

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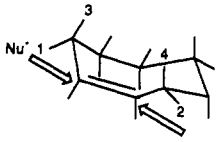
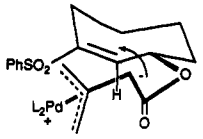
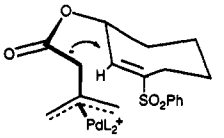
For the more flexible cyclooctenyl and cyclododecenyl systems, the geometric restrictions are relaxed, while steric interactions with the ring become more important. Examination of the preferred conformation for cyclooctene[34] reveals that one face of the olefin is considerably shielded by interaction with transannular hydrogen atoms. A nucleophile tethered at either position 1 or 2 could achieve the proper trajectory for attack on the exposed face, while one tethered at 3 or 4 would undergo considerable geometric strain to do so. For the present case, attachment at either 1 or 2 provides the observed trans-fused isomer. The inversion of stereochemical results that occurs between the cycloheptenyl and cyclooctenyl substrates is consistent with the results of peracid epoxidations and Simmons–Smith cyclopropanations of cyclic allylic alcohols, wherein chelated reagents provide predominantly syn addition to 2-cycloheptenol but anti addition to 2-cyclooctenol.[34a,35] Similar anti additions to other medium- and large-ring allylic alcohols have also been noted.[36]

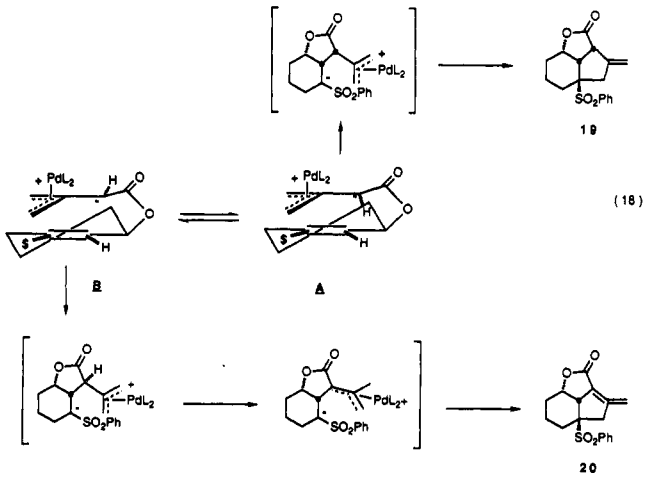






The isolation of mixtures of exocyclic and endocyclic products from each reaction requires further comment. Efforts to induce isomerization of the exocyclic olefin with base sometimes required forcing conditions or failed completely, arguing against the possibility of base-catalyzed isomerization under the cycloaddition conditions. Reexposure of the cycloaddition products to the reaction conditions, as well as extended reaction times, did not change the product ratios. These results imply that isomerization is not taking place after cycloaddition.

Equation 18 offers an explanation to account for this phenomenon for the cyclohexenyl system. If a syn-like geometry of approach is assumed in which the TMM moiety is positioned exo to the ring in order to minimize nonbonded interactions, and nucleophilic attack occurs from the axial orientation as suggested above, two stereochemical alternatives are available. In transition state A, initial bond formation results in cis stereochemistry for the bond that will become the B,C ring juncture, and ring closure provides the observed product **19**. For transition state B, the analogous trans stereochemistry results, and closure to the trans-fused bicyclo[3.3.0]octane system is not possible due to ring strain. Deprotonation–reprotonation of the initial cyclization product therefore takes precedence, and ring closure provides **20**. Similar arguments are valid for the other cycloalkenyl acceptors. For the cyclooctenyl and cycloheptenyl systems, the formation of small amounts of the trans-fused products is indicative that initial cyclization providing that stereochemistry is indeed taking place to some extent. The apparent inversion of stereochemistry at the sulfone center demonstrates that the normal "concerted-like" mechanism for TMM cycloadditions is being derailed to some degree, and that a pathway such as that described above may be intervening.



The intramolecular TMM cycloadditions of compounds containing ester groups in the tether provide access to a variety of bicyclic lactone structures. As a simple extrapolation, cyclic substrates provide rapid access to skeletons with possible applications for iridoids or nepetalactones.[24,37] Substrates containing cycloalkenyl acceptors provide opportunities toward a variety of [5.6], [5.7], or [5.8] ring systems. Further, substrates that may be unreactive in intermolecular reactions may participate in intramolecular ones. Clearly, the range of functionality, rapid assembly, and stereochemical control embodied in these tricyclic frameworks imply a wide range of synthetic applications.

Experimental Section

Preparation of 2,2,2-Tris(phenylthio)ethanol. Formaldehyde, formed by cracking paraformaldehyde (26.5 g, 882 mmol) by heating to 140–150 °C, was carried by a stream of nitrogen into a −78 °C solution of tris(phenylthio)methyllithium formed by adding 116 mL (1.52 M, 176 mmol) of a solution of *n*-butyllithium in hexane to tris(phenylthio)methane[7,9] (50.0 g, 147 mmol) in 750 mL of THF. When the addition was complete, the colorless solution was allowed to warm to room temperature, diluted with 1.5 L of ether, and washed with 1 L of saturated aqueous ammonium chloride. The aqueous layer was extracted with two 500-mL portions of ether, and the combined organic extracts were dried over magnesium sulfate, filtered, and the solvents removed in vacuo. Recrystallization from hexane/ether yielded 43.8 g (80%) of the title compound as a white powder: mp 84–86 °C; IR ($CDCl_3$) 3550, 1580, 1470, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, J = 6.6, 1.7 Hz, 6 H), 7.35 (m, 9 H), 3.50 (d, J = 6.7 Hz, 2 H), 2.40 (t, J = 6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 130.3, 129.8, 76.5, 66.7; exact mass calcd for $C_{20}H_{16}S_3$ $(M - H_2O)^+$ 352.0422, found 352.0418.

Preparation of 2,2,2-Tris(phenylthio)acetaldehyde (5). Oxalyl chloride (18.0 g, 12.4 mL, 142 mmol) was added to a −78 °C solution of DMSO (20.3 g, 18.4 mL, 260 mmol) in 400 mL of methylene chloride. After stirring for 15 min, a solution of the above alcohol (43.8 g, 118 mmol) in 160 mL of methylene chloride at −78 °C was added via cannula. After an additional 30 min at −78 °C, triethylamine (33.4 g, 46.1 mL, 330 mmol) was added and the mixture allowed to warm to room temperature. The cloudy solution was diluted with 2 L of ether and washed with 1.5 L of water, 1 L of saturated aqueous copper(II) sulfate, and 1 L of water, successively. The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed in vacuo, leaving a white solid. Recrystallization from hexane/ether yielded 40.7 g (94%) of the title product as colorless prisms: mp 104 °C; IR ($CDCl_3$) 1710, 1580, 1470, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1 H), 7.54 (d, J = 7.8 Hz, 6 H), 7.2–7.4 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 135.8, 129.6, 129.0, 78.3; exact mass calcd for $C_{14}H_{11}OS_2$ $(M - C_6H_5S)^+$ 259.0251, found 259.0242. Anal. Calcd for $C_{20}H_{16}OS_3$: C, 65.18; H, 4.38. Found: C, 65.22; H, 4.15.

Preparation of 1,1,1-Tris(phenylthio)-2-[(methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butene (6, R = CH_3). 1-(Trimethylsilyl)-1-bromoethene[6,38] (15.8 g, 14.7 mL, 81.6 mmol) dissolved in 625 mL of ether at −78 °C was treated with 81 mL of a 1.79 M solution of *tert*-butyllithium (145 mmol) in pentane. After this solution was stirred for 30 min at −78 °C, a −78 °C solution of aldehyde **5** (25.0 g, 68 mmol)

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in 125 mL of THF was added dropwise via cannula. During the addition, the solution became bright yellow, with the color slowly dissipating over the course of the addition. After an additional 1.5 h at −78 °C methyl chloroformate (27.4 g, 22.4 mL, 290 mmol) was added and stirring continued at −78 °C for 1.5 h. The cloudy solution was poured into 1.5 L of ether and washed with 750 mL of saturated aqueous sodium bicarbonate, and the aqueous layer was washed with two 250-mL portions of ether. The combined organic extracts were dried over magnesium sulfate and filtered, and the solvents were removed in vacuo. Flash chromatography (silica gel, 20:1 hexane/ether) gave a white solid, which was recrystallized from hexane to yield 31.5 g (86%) of the title product as large white pellets: mp 76–78 °C; IR ($CDCl_3$) 1750, 1630, 1580, 1480, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.0, 1.7 Hz, 6 H), 7.2–7.4 (m, 9 H), 5.34 (s, 1 H), 5.22 (s, 1 H), 5.02 (s, 1 H), 3.62 (s, 3 H), 2.01 (d, J = 14.7 Hz, 1 H), 1.85 (d, J = 14.7 Hz, 1 H), −0.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 141.7, 136.1, 132.3, 129.1, 128.5, 117.8, 83.5, 77.2, 54.6, 24.0, −1.5; exact mass calcd for $C_{22}H_{27}O_3S_2Si$ $(M - C_6H_5S)^+$ 431.1171, found 431.1197.

Preparation of 1,1,1-Tris(phenylthio)-2-acetoxy-3-[(trimethylsilyl)-methyl]-3-butene (7). 1-(Trimethylsilyl)-1-bromoethane (1.2 g, 1.12 mL, 6.5 mmol) dissolved in 50 mL of ether at −78 °C was treated with 6.7 mL of a 1.79 M solution of *tert*-butyllithium (12 mmol) in pentane. After 30 min at −78 °C, 1 h at 0 °C, and recooling to −78 °C, a solution of aldehyde **5** (2.0 g, 5.4 mmol) in 10 mL of THF at −78 °C was added dropwise via cannula. During the addition, the solution became bright yellow, with the color slowly dissipating over the course of the addition. After an additional 1.5 h at −78 °C, the mixture was poured into 75 mL of saturated aqueous ammonium chloride and extracted with 150 mL of ether. The aqueous layer was washed with 50 mL of ether, and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo to give 2.87 g (~100%) of the alcohol as a yellow oil. The crude material was not further purified due to instability, decomposing completely in 6 h at room temperature: ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 6 H), 7.30 (m, 9 H), 5.45 (s, 1 H), 5.04 (s, 1 H), 4.06 (d, J = 2.5 Hz, 1 H), 2.95 (d, J = 2.5 Hz, 1 H), 1.89 (d, J = 13.6 Hz, 1 H), 1.65 (d, J = 13.6 Hz, 1 H), −0.10 (s, 9 H).

The crude alcohol (2.87 g, 5.4 mmol) obtained above dissolved in 15 mL of pyridine at 0 °C was treated with acetic anhydride (5.4 g, 5.0 mL, 53 mmol) and DMAP (61 mg, 0.5 mmol). The mixture was allowed to warm to room temperature and stirred for 48 h. The solvent was removed in vacuo and the residue dissolved in 200 mL of hexane and washed with 50 mL of water. Drying over magnesium sulfate, filtration, and concentration in vacuo gave 2.18 g (77%) of the title product as a yellow oil: IR ($CDCl_3$) 1740, 1640, 1580, 1480, 1440, 1420, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.7, 1.7 Hz, 6 H), 7.32 (m, 9 H), 5.42 (s, 1 H), 5.25 (s, 1 H), 5.04 (s, 1 H), 1.98 (d, J = 14.2 Hz, 1 H), 1.89 (d, J = 14.2 Hz, 1 H), 1.69 (s, 3 H), −0.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 142.1, 135.9, 132.8, 129.1, 128.5, 117.0, 79.9, 24.7, 20.2, −1.4; exact mass calcd for $C_{22}H_{27}O_2Si$ $(M - C_6H_5S)^+$ 415.1221; found 415.1226.

Preparation of 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoic Acid (1a). To a solution of ortho thioester **6** (R = CH_3) (10.0 g, 18.5 mmol) in 440 mL of dioxane and 90 mL of water was added silver(I) trifluoroacetate (24.5 g, 111 mmol) in one portion. A large volume of white precipitate was generated immediately, and the resultant slurry was vigorously stirred while warming to reflux. After 6 h at reflux, the gray-brown slurry was filtered through Celite, and the layers were separated. The aqueous layer was washed with three 50-mL portions of chloroform, the combined organic layers were dried over magnesium sulfate and filtered, and the solvents were removed in vacuo. Flash chromatography (silica gel, 4:1 hexane/ethyl acetate, 1% acetic acid), with rechromatography of impure fractions and azeotropic removal of traces of acetic acid by evaporation with carbon tetrachloride, yielded 2.9 g (64%) of the title product as a waxy, white solid: mp 46–47 °C; IR ($CDCl_3$) 3300–2800, 1750, 1730, 1440, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 1 H), 5.17 (s, 1 H), 4.97 (s, 1 H), 3.81 (s, 3 H), 1.69 (d, J = 14.2 Hz, 1 H), 1.60 (d, J = 14.2 Hz, 1 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 155.2, 138.9, 114.9, 78.5, 55.2, 22.4, −1.8; exact mass calcd for $C_8H_{14}O_2Si$ $(M - CH_3OCO_2H)^+$ 170.0763, found 170.0763.

Preparation of 2-Acetoxy-3-[(trimethylsilyl)methyl]-3-butenoic Acid (1c). To a solution of ortho thioester **7** (2.12 g, 4.04 mmol) in 40 mL of acetonitrile containing 10 mL of water was added silver(I) trifluoroacetate (5.34 g, 24.2 mmol) in one portion. A large volume of white precipitate was generated immediately, and the resultant slurry was vigorously stirred while warming to reflux. After 24 h at reflux, the grey-brown slurry was diluted with 500 mL of ether and filtered through Celite. The biphasic mixture was washed with eight 100-mL portions of saturated aqueous sodium bicarbonate, and the combined aqueous layers were carefully brought to pH 2 with solid sodium bisulfate. The mixture was washed with six 100-mL portions of methylene chloride, the combined organic layers were dried over magnesium sulfate and filtered, and the solvents were removed in vacuo to give 502 mg (54%) of the title product, pure by ^1H NMR spectroscopy. A sample was further purified via flash chromatography (silica gel, 1:1 hexane/ethyl acetate, 5% methanol): IR ($CDCl_3$) 3300–2800, 1740, 1730, 1640, 1420, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1 H), 5.12 (s, 1 H), 4.90 (s, 1 H), 2.13 (s, 3 H), 1.68 (d, J = 14.8 Hz, 1 H), 1.59 (d, J = 14.8 Hz, 1 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 170.8, 139.7, 114.2, 76.3, 22.6, 20.4, −1.7; exact mass calcd for $C_{10}H_{18}O_4Si$ (M^+) 230.0974, found 230.0982.

Preparation of (*E*)-4-(Phenylsulfonyl)-3-butenyl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (8a). A solution of acid **1a** (100 mg, 0.41 mmol) in 2 mL of methylene chloride was treated sequentially with (*E*)-1-(phenylsulfonyl)-1-buten-4-ol (87 mg, 0.41 mmol), DMAP (6.1 mg, 0.45 mmol), and *N,N'*-dicyclohexylcarbodiimide (92.8 mg, 0.45 mmol). Dicyclohexylurea precipitated almost immediately, the suspension was stirred at room temperature for 2 h and filtered through Celite, and the solvent was removed in vacuo. Flash chromatography (silica gel, 1:1 hexane/ether) yielded 138 mg (76%) of the title product as a clear, colorless oil: IR ($CDCl_3$) 1740, 1630, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.0, 1.6 Hz, 2 H), 7.61 (tt, J = 7.3, 1.4 Hz, 1 H), 7.52 (t, J = 7.0 Hz, 2 H), 6.92 (dt, J = 15.3, 6.7 Hz, 1 H), 6.40 (dt, J = 15.1, 1.5 Hz, 1 H), 5.09 (s, 1 H), 5.02 (s, 1 H), 4.84 (s, 1 H), 4.27 (t, J = 6.3 Hz, 2 H), 3.80 (s, 3 H), 2.57 (q, J = 6.2 Hz, 2 H), 1.55 (s, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 155.2, 141.7, 140.4, 139.1, 133.6, 133.0, 129.4, 127.8, 114.4, 78.8, 62.5, 55.1, 30.2, 22.4, −1.8; exact mass calcd for $C_{20}H_{28}O_7SSi$ (M^+) 440.1367, found 440.1346. Anal. Calcd for $C_{20}H_{28}O_7SSi$: C, 54.51; H, 6.42. Found: C, 54.55; H, 6.58.

Preparation of (*E*)-4-(Phenylsulfonyl)-3-butenyl 2-Acetoxy-3-[(trimethylsilyl)methyl]-3-butenoate (8b). Ester **8b** was prepared from acid **1c** and (*E*)-1-(phenylsulfonyl)-1-buten-4-ol[39] on a 0.41-mmol scale by the method described above. Flash chromatography (silica gel, 2:1 hexane/ether) yielded 89 mg (54%) of the title product as a clear, colorless oil: IR ($CDCl_3$) 1750, 1740, 1630, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.0, 1.7 Hz, 2 H), 7.61 (m, J = 7.3 Hz, 1 H), 7.52 (t, J = 7.2 Hz, 2 H), 6.92 (dt, J = 15.1, 6.7 Hz, 1 H), 6.40 (dt, J = 15.2, 1.5 Hz, 1 H), 5.14 (s, 1 H), 5.00 (s, 1 H), 4.83 (s, 1 H), 4.24 (t, J = 6.3 Hz, 2 H), 2.56 (q, J = 6.4 Hz, 2 H), 2.11 (s, 3 H), 1.55 (s, 1 H), 1.53 (s, 1 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 168.6, 141.8, 140.4, 139.5, 133.6, 133.0, 129.4, 127.8, 114.2, 76.3, 62.3, 30.2, 22.5, 20.4, −1.7; exact mass calcd for $C_{20}H_{28}O_6SSi$ (M^+) 424.1376, found 424.1361. Anal. Calcd for $C_{20}H_{28}O_6SSi$: C, 56.57; H, 6.66. Found: C, 56.72; H, 6.71.

Preparation of (*E*)-3-(Phenylsulfonyl)-2-propenyl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (11a). The title compound was prepared from acid **1a** on a 0.41-mmol scale by the method described for **8a**. Flash chromatography (silica gel, 2:1 hexane/ether) gave 116 mg (67%) of the product as a clear, colorless oil: IR ($CDCl_3$) 1752, 1639, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.1, 1.6 Hz, 2 H), 7.62 (t, J = 7.3 Hz, 1 H), 7.53 (t, J = 7.4 Hz, 2 H), 6.94 (dt, J = 15.3, 3.8 Hz, 1 H), 6.55 (dt, J = 15.3, 2.0 Hz, 1 H), 5.16 (s, 1 H), 5.08 (s, 1 H), 4.89 (s, 1 H), 4.85 (m, 2 H), 3.74 (s, 3 H), 1.53 (d, J = 4.4 Hz, 2 H), −0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 155.0, 139.8, 138.9, 138.7, 133.6, 131.4, 129.3, 127.7, 114.7, 78.6, 61.9, 55.0, 22.2, −1.9; exact mass calcd for $C_{19}H_{26}O_7SSi$ (M^+) 426.1168, found 426.1197. Anal. Calcd for $C_{19}H_{26}O_7SSi$: C, 53.49; H, 6.16. Found: C, 53.53; H, 6.10.

Preparation of (*E*)-4-(Phenylsulfonyl)-3-buten-2-yl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (11b, R = CH_3). The title compound was prepared from acid **1a** and alcohol **10b**[19] on a 1.22-mmol scale by the method described for **8a**. Flash chromatography (silica gel, 2:1 hexane/ether) gave 399 mg (74%) of the product as a clear, colorless oil, a 1:1 mixture of diastereomers: IR ($CDCl_3$) 1751, 1624, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2 H), 7.62 (m, 1 H), 7.53 (m, 2 H), 6.90 (dd, J = 15.1, 3.9 Hz, 0.5 H), 6.87 (dd, J = 15.1, 4.2 Hz, 0.5 H), 6.57 (dd, J = 15.1, 1.7 Hz, 0.5 H), 6.42 (dd, J = 15.1, 1.7 Hz, 0.5 H), 5.57 (m, 1 H), 5.12 (s, 0.5 H), 5.09 (s, 0.5 H), 5.08 (s, 0.5 H), 5.03 (s, 0.5 H), 4.89 (s, 0.5 H), 4.85 (s, 0.5 H), 3.75 (s, 1.5 H), 3.71 (s, 1.5 H), 1.54 (s, 1 H), 1.46 (s, 1 H), 1.41 (d, J = 6.8 Hz, 1.5 H), 1.37 (d, J = 6.7 Hz, 1.5 H), 0.00 (s, 4.5 H), −0.02 (s, 4.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 167.4, 155.3, 155.2, 143.5, 143.4, 140.0, 139.4, 139.0, 133.8, 133.7, 130.7 (2), 129.5, 129.4, 127.9, 127.7, 114.9, 114.4, 78.8, 78.7, 69.1, 69.0, 55.0, 22.4, 19.0, 18.8, −1.8. Anal.

(39) From 3-(*tert*-butyldimethylsiloxy)propanal (ref 40) and diethyl [(phenylsulfonyl)methyl]phosphonate (ref 41) as described in the appendix.

(40) Harnden, M. R.; Jarvest, R. L. *J. Am. Chem. Soc.* **1988**, *110*, 5995.
(41) Shahak, I.; Almog, J. *Synthesis* **1970**, 145.

Calcd for $C_{20}H_{28}O_7SSi$: C, 54.51; H, 6.42. Found: C, 54.55; H, 6.56.

Preparation of (*E*)-4-(Phenylsulfonyl)-2-methyl-3-buten-2-yl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (11c). The title compound was prepared from acid **1a** and alcohol **10c**[19] on a 0.81-mmol scale by the method described for **8a**. Flash chromatography (silica gel, 3:1 hexane/ether) gave 92 mg of the product as a clear, colorless oil and 82 mg of recovered alcohol (43% yield, based on 55% conversion): IR ($CDCl_3$) 1750, 1607, 1445 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.84 (m, 2 H), 7.56 (m, 3 H), 7.01 (d, J = 15.2 Hz, 1 H), 6.39 (d, J = 15.3 Hz, 1 H), 5.03 (s, 2 H), 4.87 (s, 1 H), 3.72 (s, 3 H), 1.57 (s, 3 H), 1.56 (s, 3 H), 1.53 (s, 2 H), 0.01 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9, 155.2, 148.6, 140.2, 139.3, 133.6, 129.4, 128.7, 127.8, 114.3, 80.3, 76.4, 50.0, 25.7, 22.8, −1.7; exact mass calcd for $C_{21}H_{30}O_7SSi$ (M^+) 454.1481, found 454.1471.

Preparation of 3-(Phenylsulfonyl)-2-cyclohexen-1-yl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (13b). The title compound was prepared from acid **1a** and alcohol **12b**[18] on a 0.5-mmol scale by the method described for **8a**. Flash chromatography (silica gel, 1:1 hexane/ether) gave 224 mg (96%) of the product as a clear, colorless oil, a 1:1 mixture of diastereomers: IR ($CDCl_3$) 1750, 1630, 1480, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2 H), 7.63 (t, J = 7.3 Hz, 1 H), 7.54 (m, 2 H), 6.89 (m, 0.5 H), 6.83 (m, J = 1.7 Hz, 0.5 H), 5.48 (m, 1 H), 5.15 (s, 0.5 H), 5.12 (s, 0.5 H), 5.10 (s, 1 H), 4.93 (s, 0.5 H), 4.91 (s, 0.5 H), 3.80 (s, 1.5 H), 3.79 (s, 1.5 H), 2.1–2.4 (m, 2 H), 1.5–2.0 (m, 6 H), 0.03 (s, 4.5 H), 0.02 (s, 4.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 155.2, 145.3, 145.2, 139.1, 139.0, 138.4, 133.8, 133.5, 133.2, 129.3, 128.3 (2), 114.5, 114.3, 78.7, 68.1, 55.0, 26.5, 26.4, 22.5, 22.4, 18.4, −1.9; exact mass calcd for $C_{22}H_{30}O_7SSi$ (M^+) 466.1481, found 466.1464. Anal. Calcd for $C_{22}H_{30}O_7SSi$: C, 56.62; H, 6.49. Found: C, 56.67; H, 6.37.

Preparation of 3-(Phenylsulfonyl)-2-cyclohepten-1-yl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (13c). The title compound was prepared from acid **1a** and alcohol **12c**[17b] on a 0.4-mmol scale by the method described for **8a**. Flash chromatography (silica gel, 2:1 hexane/ether) gave 147 mg (81%) of the product as a clear, colorless oil, a 1:1 mixture of diastereomers: IR ($CDCl_3$) 1749, 1622, 1446 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2 H), 7.60 (m, 1 H), 7.52 (t, J = 7.6 Hz, 2 H), 7.14 (bs, 0.5 H), 7.03 (bs, 0.5 H), 5.58 (m, 1 H), 5.18 (s, 0.5 H), 5.15 (s, 0.5 H), 5.12 (s, 1 H), 4.94 (s, 0.5 H), 4.93 (s, 0.5 H), 3.81 (s, 3 H), 2.49 (m, 1 H), 1.8–2.0 (m, 2 H), 1.5–1.7 (m, 3 H), 1.61 (s, 1 H), 1.60 (s, 1 H), 1.16 (m, 1 H), 0.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 167.7, 155.3, 155.2, 143.9, 143.7, 142.5, 142.3, 139.3 (2), 139.1, 133.5, 129.3, 128.3, 114.7, 114.4, 79.0, 78.9, 74.1, 74.0, 55.0, 31.2, 31.1, 27.2, 26.3, 25.1, 22.7, 22.6, −1.7; exact mass calcd for $C_{23}H_{32}O_7SSi$ (M^+) 480.1638, found 480.1645. Anal. Calcd for $C_{23}H_{32}O_7SSi$: C, 57.46; H, 6.72. Found: C, 57.20; H, 6.66.

Preparation of 3-(Phenylsulfonyl)-2-cycloocten-1-yl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (13d). The title compound was prepared from acid **1a** and alcohol **12d**[17b] on a 2.4-mmol scale by the method described for **8a**. Flash chromatography (silica gel, 4:1 hexane/ether) gave 798 mg (66%) of the product as a clear, colorless oil, a 1:1 mixture of diastereomers: IR ($CDCl_3$) 1749, 1615, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2 H), 7.60 (t, J = 6.6 Hz, 1 H), 7.51 (m, 2 H), 6.94 (d, J = 7.3 Hz, 0.5 H), 6.82 (d, J = 7.7 Hz, 0.5 H), 5.57 (m, 1 H), 5.17 (s, 0.5 H), 5.15 (s, 0.5 H), 5.12 (s, 1 H), 4.95 (s, 0.5 H), 4.93 (s, 0.5 H), 3.81 (s, 3 H), 2.2–2.5 (m, 2 H), 2.00 (m, 1 H), 1.3–1.8 (m, 7 H), 1.60 (s, 2 H), 0.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 167.7, 155.1, 141.7, 241.6, 139.1, 139.0 (2), 138.8, 133.5, 129.2, 128.2, 128.1, 114.7, 114.3, 78.8, 78.6, 72.9, 72.8, 54.9, 34.1, 34.0, 28.4, 25.3, 25.0, 22.6, 22.4 (2), −1.9; exact mass calcd for $C_{24}H_{34}O_7SSi$ (M^+) 494.1794, found 494.1798. Anal. Calcd for $C_{24}H_{34}O_7SSi$: C, 58.26; H, 6.94. Found: C, 58.23; H, 6.73.

Preparation of 3-(Phenylsulfonyl)-2-cyclododecen-1-yl 2-[(Methoxycarbonyl)oxy]-3-[(trimethylsilyl)methyl]-3-butenoate (13e). The title compound was prepared from acid **1a** and alcohol **12e** on a 0.25-mmol scale by the method described for **8a**. Flash chromatography (silica gel, 4:1 hexane/ether) gave 127 mg (92%) of the product as a clear glass, a 1:1 mixture of diastereomers: IR ($CDCl_3$) 1750, 1740, 1640, 1440, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2 H), 7.4–7.7 (m, 3 H), 6.84 (d, J = 10 Hz, 0.5 H), 6.74 (d, J = 10.1 Hz, 0.5 H), 5.60 (s, 1 H), 5.11 (s, 1 H), 5.06 (s, 0.5 H), 5.01 (s, 0.5 H), 4.90 (s, 0.5 H), 4.89 (s, 0.5 H), 3.80 (s, 1.5 H), 3.78 (s, 1.5 H), 2.72 (m, 1 H), 2.04 (m, 1 H), 0.8–2.0 (m, 18 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 155.2, 155.1, 145.0, 144.6, 139.4, 139.3 (2), 139.2, 138.0, 137.7, 133.5, 133.3, 129.3, 128.1, 114.2, 78.7 (2), 68.6, 55.1, 55.0, 30.5, 30.4, 26.2 (2), 25.8, 25.6, 24.0, 22.8 (2), 22.4, 22.3, 21.8, 21.7, 20.9, −1.8; exact mass calcd for $C_{28}H_{42}O_7SSi$ (M^+) 550.2421, found 550.2434.

Preparation of Standard Catalyst Solution. A standard catalyst solution was prepared on a scale 1–5 times that required for the reaction. Palladium acetate was dissolved in the appropriate solvent (THF, dioxane, or diglyme) to a concentration of 5×10^{-3} M. Six equivalents of triisopropyl phosphite was then added via syringe and the mixture stirred for 10 min. An aliquot of this solution was added via syringe to the substrate, such that the substrate concentration was 0.1 M. The reaction mixture thus produced contained 5 mol % palladium acetate and 30 mol % triisopropyl phosphite relative to the substrate.

Preparation of (6*R,7*R**)-9-Methyl-7-(phenylsulfonyl)-3-oxa-2-oxobicyclo[4.3.0]non-1-ene (15) and (1*S**,6*R**,7*R**)-9-Methylene-7-(phenylsulfonyl)-3-oxa-2-oxobicyclo[4.3.0]nonane (14). Cycloaddition of 8a.** A 1-mL aliquot of the solution prepared above in THF was added to **8a** (5.7 mg, 0.10 mmol) and heated at 60 °C for 2 h. The solvent was removed under a stream of nitrogen and the residue purified via flash chromatrography (silica gel, 4:1 hexane/ethyl acetate, then 1:1 hexane/ethyl acetate) to yield 4.5 mg of **14** and 5.3 mg of **15** (9.8 mg, 34% overall). **14**: white powder, mp 269–273 °C dec (hexane/ether); IR ($CDCl_3$) 1730, 1650, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.56 (t, J = 7.7 Hz, 2 H), 5.11 (s, 1 H), 4.94 (s, 1 H), 4.78 (dt, J = 11.6, 2.9 Hz, 1 H), 3.93 (td, J = 10.2, 8.0 Hz, 1 H), 3.78 (d, J = 6.8 Hz, 1 H), 3.64 (t, J = 11.5 Hz, 1 H), 2.77 (dddd, J = 12.0, 9.4, 7.0, 1.5 Hz, 1 H), 2.63 (dd, J = 17.3, 7.8 Hz, 1 H), 2.53 (dd, J = 17.6, 9.5 Hz, 1 H), 2.33 (d, J = 14.8 Hz, 1 H), 2.03 (dtd, J = 15.4, 12.2, 2.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 145.0, 139.2, 134.1, 129.6, 128.5, 111.4, 66.4, 65.2, 55.6, 43.7, 33.1, 29.3; exact mass calcd for $C_{15}H_{16}O_4S$ (M^+) 292.0769, found 292.0771. **15**: white powder, mp 123 °C (hexane/ether); IR ($CDCl_3$) 1710, 1650, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.1, 1.6 Hz, 2 H), 7.71 (m, J = 7.5 Hz, 1 H), 7.59 (t, J = 7.4 Hz, 2 H), 4.36 (ddd, J = 11.7, 4.8, 2.1 Hz, 1 H), 4.22 (td, J = 12.0, 2.8 Hz, 1 H), 3.54 (q, J = 8.7 Hz, 1 H), 3.50 (m, J = 3.6 Hz, 1 H), 3.00 (ddm, J = 18.0, 9.0 Hz, 1 H), 2.44 (ddm, J = 17.8, 8.6 Hz, 1 H), 2.14 (s, 3 H), 2.00 (dm, J = 13.1 Hz, 1 H), 1.66 (dq, J = 12.4, 4.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 155.4, 138.6, 134.4, 129.8, 128.5, 123.0, 68.8, 67.8, 43.3, 39.5, 30.0, 16.0; exact mass calcd for $C_{15}H_{16}O_4S$ (M^+) 292.0770, found 292.0790.

Cycloaddition of 8b. A 2.1-mL aliquot of the solution prepared above in dioxane and containing BSA (42.7 mg, 51.9 mg, 0.21 mmol) was added to **8b** (90 mg, 0.21 mmol) and heated to 100 °C for 1 h. The solvent was removed in vacuo and the residue purified via flash chromatography (silica gel, 1:1 hexane/ether) to yield 5.4 mg of **14** and 38.7 mg of **15** (44.1 mg, 72% overall).

Cycloaddition of 11a: Preparation of (1*S,5*S**,6*R**)-8-Methylene-6-(phenylsulfonyl)-3-oxa-2-oxobicyclo[3.3.0]octane (18a).** A 3.9-mL aliquot of the solution prepared above in dioxane was added to **11a** (165 mg, 0.39 mmol) and heated to 100 °C for 2 h. The solvent was removed in vacuo and the residue purified via flash chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield 21.9 mg of **18a** (16%) as a white powder: mp 104–106 °C (ether); IR ($CDCl_3$) 1775, 1631, 1448, 1152, 1087, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.3, 1.6 Hz, 2 H), 7.71 (t, J = 7.4 Hz, 1 H), 7.60 (t, J = 7.5 Hz, 2 H), 5.41 (m, 1 H), 5.14 (q, J = 1.9 Hz, 1 H), 4.39 (dd, J = 10.1, 6.4 Hz, 1 H), 4.21 (dd, J = 10.0, 1.9 Hz, 1 H), 3.58 (m, J = 8.8, 2.1 Hz, 2 H), 3.41 (dt, J = 10.0, 7.6 Hz, 1 H), 2.85 (ddt, J = 16.3, 10.0, 2.7 Hz, 1 H), 2.56 (dd, J = 16.5, 7.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 141.0, 138.0, 134.6, 129.8, 128.6, 112.8, 70.2, 67.1, 47.9, 41.4, 35.5; exact mass calcd for C_8H_9O ($M - C_6H_5SO_2$)$^+$ 137.0603, found 137.0617.

Cycloaddition of 11b: Preparation of (1*S,5*S**,6*R**)-8-Methylene-6-(phenylsulfonyl)-4-methyl-3-oxa-2-oxobicyclo[3.3.0]octane (18b).** A 3.0-mL aliquot of the solution prepared above in diglyme was added to **11b** (133.5 mg, 0.30 mmol) and heated at 160 °C for 30 min. The mixture was poured onto a plug of silica gel and eluted with 1:1 hexane/ether. Rechromatography (silica gel, 3:1 hexane/ethyl acetate) yielded 17.2 mg of **18b** (20%) as a clear, colorless oil, a 5.6:1 mixture of diastereomers based on the relative integration of ^1H NMR resonances at δ 5.13 and 4.99, respectively: IR ($CDCl_3$) 1771, 1448, 1151, 1087, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.1, 1.7 Hz, 2 H), 7.70 (t, J = 7.3 Hz, 1 H), 7.60 (t, J = 7.2 Hz, 2 H), 5.39 (q, J = 2.2 Hz, 1 H), 5.13 (q, J = 2.3 Hz, 1 H), 4.43 (qd, J = 6.4, 2.0 Hz, 1 H), 3.64 (d, J = 9.2 Hz, 1 H), 3.42 (dt, J = 9.3, 7.5 Hz, 1 H), 3.19 (ddd, J = 9.3, 7.4, 2.9 Hz, 1 H), 2.86 (m, J = 9.3 Hz, 1 H), 2.58 (ddd, J = 16.6, 7.7, 1.6 Hz, 1 H), 1.33 (d, J = 6.4 Hz, 3 H); minor isomer δ 5.30 (m, 1 H), 4.99 (m, 1 H), 3.81 (d, J = 7.7 Hz, 1 H), 3.12 (m, 1 H), 2.48 (dd, J = 10.0, 8.0 Hz, 1 H), 1.30 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$), major isomer δ 175.1, 141.2, 134.6, 134.5, 129.8, 128.7, 112.6, 79.6, 67.0, 48.1, 48.0, 35.2, 21.1; minor isomer δ 137.9, 134.6, 128.8, 128.5, 77.5, 50.6, 16.8; exact mass calcd for $C_9H_{10}O_2$ ($M - C_6H_5SO_2$)$^+$ 151.0759, found 151.0761.

Cycloaddition of 12b: Preparation of (1*S,4*S**,8*R**,11*S**)-10-Methylene-8-(phenylsulfonyl)-2-oxo-3-oxatricyclo[6.2.1.0^{4,11}]undecane (19) and (4*S**,8*R**,11*S**)-10-Methyl-8-(phenylsulfonyl)-2-oxo-3-oxatricyclo[6.2.1.0^{4,11}]undec-1-ene (20).** A 2.2-mL aliquot of the solution

prepared above in dioxane was added to **13b** (100.6 mg, 0.216 mmol) and heated at 100 °C, inducing vigorous gas evolution. The resulting yellow solution darkened slowly over 1 h and was then concentrated in vacuo. Flash chromatography (silica gel, 1:1 hexane/ether) yielded 15.5 mg of **20** and 26.9 mg of **19** (42.4 mg, 62% overall). **20**: white powder, mp 202–205 °C (hexane/ether); IR ($CDCl_3$) 1750, 1690, 1440, 1140, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.1, 1.4 Hz, 2 H), 7.70 (tm, J = 7.4 Hz, 1 H), 7.59 (tm, J = 7.5 Hz, 2 H), 4.59 (q, J = 8.1 Hz, 1 H), 4.38 (m, 1 H), 3.84 (dq, J = 16.9, 1.6 Hz, 1 H), 2.37 (dd, J = 16.9, 1.2 Hz, 1 H), 2.18 (dd, J = 14.0, 2.8 Hz, 1 H), 2.08 (m, 1 H), 2.01 (d, J = 3.0 Hz, 3 H), 1.45 (m, 2 H), 1.26 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 147.6, 136.3, 135.5, 130.0, 129.7, 126.6, 75.3, 71.5, 54.3, 48.1, 30.1, 29.1, 18.5, 14.7; exact mass calcd for $C_{11}H_{13}O_2$ $(M - C_6H_5SO_2)^+$ 177.0915, found 177.0916. **19**: white powder, mp 136–138 °C (hexane/ether); IR ($CDCl_3$) 1770, 1450, 1140, 1080, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.2, 1.4 Hz, 2 H), 7.69 (t, J = 7.5 Hz, 1 H), 7.55 (t, J = 7.7 Hz, 2 H), 5.07 (dd, J = 1.5, 1.3 Hz, 1 H), 4.89 (t, J = 1.3 Hz, 1 H), 4.83 (dt, J = 7.9, 2.9 Hz, 1 H), 3.71 (t, J = 8.7 Hz, 1 H, 8.9% NOE with irradiation at δ 4.83), 3.61 (dd, J = 9.0, 1.2 Hz, 1 H, 2.0% NOE with irradiation at δ 4.83), 2.69 (d, J = 17.7 Hz, 1 H), 2.47 (dd, J = 17.5, 1.5 Hz, 1 H), 2.22, (d, J = 13.4 Hz, 1 H, 3.1% NOE with irradiation at δ 4.83), 2.09 (m, 1 H, 3.4% NOE with irradiation at δ 4.83), 1.70 (m, 3 H), 1.46 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 142.9, 135.2, 134.5, 130.6, 134.5, 130.6, 129.4, 111.5, 76.3, 71.1, 53.4, 40.0, 27.1, 26.3, 13.5; exact mass calcd for $C_{11}H_{13}O_2$ $(M - C_6H_5SO_2)^+$ 177.0915, found 177.0918.

Cycloaddition of 13c: Preparation of (1*S,4*S**,9*R**,12*S**)-11-Methylene-9-(phenylsulfonyl)-2-oxo-3-oxatricyclo[7.2.1.0^{4,12}]dodecane (21), (4*S**,9*R**,12*S**)-11-Methyl-9-(phenylsulfonyl)-2-oxo-3-oxatricyclo[7.2.1.0^{4,12}]dodec-1-ene (22), and (1*R**,4*R**,9*R**,12*R**)-11-Methylene-9-(phenylsulfonyl)-2-oxo-3-oxatricyclo[7.2.1.0^{4,12}]dodecane (23).** A 1.1-mL aliquot of the solution prepared above in dioxane was added to **13c** (52.2 mg, 0.109 mmol) and heated at 100 °C. The resulting yellow solution slowly became colorless over 1 h and was then concentrated in vacuo. Flash chromatography (silica gel, 1:1 hexane/ether) yielded 17.4 mg of **21**, 4.8 mg of **22**, and a trace (<0.6 mg) of **23**, which could not be fully purified (22.8 mg, 63% overall). **21**: white powder, mp 78–83 °C (pentane/ether); IR ($CDCl_3$) 1770, 1602, 1448, 1145, 1083, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.3, 1.5 Hz, 2 H), 7.69 (t, J = 7.5 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 2 H), 5.48 (q, J = 2.3 Hz, 1 H), 5.11 (q, J = 2.1 Hz, 1 H), 4.78 (t, J = 7.9 Hz, 1 H), 3.89 (dd, J = 10.1, 8.2 Hz, 1 H, 11.1% NOE with irradiation at δ 4.78), 3.78 (dm, J = 10.3, 1.8 Hz, 1 H, 2.7% NOE with irradiation at δ 4.78), 3.26 (dd, J = 17.0, 1.7 Hz, 1 H), 2.50 (m, J = 16.7 Hz, 1 H), 2.25 (dd, J = 12.3, 10.3 Hz, 1 H, 3.0% NOE with irradiation at δ 4.78), 2.10 (m, 1 H, 1.4% NOE with irradiation at δ 4.78), 1.92 (m, 1 H), 1.80 (m, 2 H), 1.65 (dd, J = 14.1, 8.9 Hz, 1 H), 1.50 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 141.8, 135.9, 134.4, 130.5, 129.5, 129.4, 111.3, 81.0, 75.6, 49.5, 48.0,, 32.0, 30.7, 24.5, 23.0; exact mass calcd for $C_{12}H_{15}O_2$ $(M - C_6H_5SO_2)^+$ 191.1072, found 101.1063. **22**: white powder, mp 157–9 °C (pentane/ether); IR ($CDCl_3$) 1753, 1703, 1448, 1435, 1146, 1083, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.1, 1.6 Hz, 2 H), 7.69 (t, J = 7.4 Hz, 1 H), 7.58 (t, J = 7.6 Hz, 2 H), 4.67 (td, J = 8.1, 3.1 Hz, 1 H), 4.56 (dq, J = 8.4, 2.8 Hz, 1 H), 3.79 (dd, J = 17.5, 2.8 Hz, 1 H), 2.44 (d, J = 17.5 Hz, 1 H), 2.00 (bs, 3 H), 1.4–1.9 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 136.3, 134.4, 130.2, 129.5, 127.0, 80.7, 75.5, 52.7, 52.1, 30.2, 28.9, 21.7, 19.4, 14.1; exact mass calcd for $C_{12}H_{15}O_2$ $(M - C_6H_5SO_2)^+$ 191.1071, found 191.1073. **23**: viscous oil; IR ($CDCl_3$) 1783, 1602, 1141, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.1, 1.5 Hz, 2 H), 7.70 (m, 1 H), 7.59 (m, 2 H), 5.41 (q, J = 2.4 Hz, 1 H), 5.27 (ddd, J = 11.1, 7.8, 4.5 Hz, 1 H), 5.05 (q, J = 2.3 Hz, 1 H), 4.29 (dt, J = 17.0, 1.6 Hz, 1 H), 3.61 (ddd, J = 18.1, 2.2, 1.6 Hz, 1 H), 2.81 (dd, J = 17.2, 11.1 Hz, 1 H), 2.64 (dq, J = 18.2, 2.0 Hz, 1 H), 2.30 (m, 1 H), 1.2–1.8 (m, 7 H).

Cycloaddition of 13d: Preparation of (1*S,4*S**,10*R**,13*S**)-12-Methylene-10-(phenylsulfonyl)-2-oxo-3-oxatricyclo[8.2.1.0^{4,13}]tridecane (24), (4*R**,10*R**,13*S**)-12-Methyl-10-(phenylsulfonyl)-2-oxo-3-oxatricyclo[8.2.1.0^{4,13}]tridec-1-ene (25), and (1*R**,4*R**,10*R**,13*R**)-12-Methylene-10-(phenylsulfonyl)-2-oxo-3-oxatricyclo[8.2.1.0^{4,13}]tridecane (26).** A 4.1-mL aliquot of the solution prepared above in dioxane was added to **13d** (203.7 mg, 0.412 mmol) and heated at 100 °C. The resulting yellow solution slowly became colorless over 40 min and was then concentrated in vacuo. Flash chromatography (silica gel, 5:1 hexane/ethyl acetate, then 2:1 hexane/ethyl acetate), with recycling of mixed or impure fractions, yielded 56.5 mg of **24**, 49.1 mg of **25**, and 6.4 mg of **26** (112 mg, 78% overall). **24**: white solid, mp 151–154 °C (ether); IR ($CDCl_3$) 1771, 1445, 1145, 1081, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.1, 1.5 Hz, 2 H), 7.68 (t, J = 7.4 Hz, 1 H), 7.56 (t, J = 7.8 Hz, 2 H), 5.18 (d, J = 2.7 Hz, 1 H), 4.96 (d, J = 1.5 Hz, 1 H), 4.28 (ddd, J = 11.3, 8.2, 3.1 Hz, 1 H), 3.69 (dd, J = 8.6, 2.3 Hz, 1 H), 3.62 (t, J = 8.6 Hz, 1 H, 2.3% NOE with irradiation at δ 4.28), 3.01 (d, J = 19 Hz, 1 H), 2.51 (dq, J = 19.2, 2.9 Hz, 5.0% NOE with irradiation at δ 4.28), 2.30 (m, 2 H, 4.6% NOE with irradiation at δ 4.28), 2.03 (dt, J = 16.2, 4.0 Hz, 1 H), 1.97 (m, 1 H), 1.84 (m, 1 H), 1.6–1.8 (m, 3 H, 10.9% NOE with irradiation at δ 4.28), 1.45 (m, 1 H), 1.30 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 141.8, 136.1, 134.5, 130.4, 129.4, 111.2, 81.1, 75.3, 51.9, 50.4, 42.9, 35.6, 29.3, 25.5, 24.3, 21.4. Anal. Calcd for $C_{19}H_{22}O_4S$: C, 65.86; H, 6.41. Found: C, 65.84; H, 6.45. **25**: white needles, mp 209 °C (ether/trace methylene chloride); IR ($CDCl_3$) 1764, 1698, 1448, 1443, 1081, 1043, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.2, 1.4 Hz, 2 H), 7.64 (t, J = 7.5 Hz, 1 H), 7.53 (t, J = 7.7 Hz, 2 H), 4.24 (ddd, J = 11.3, 9.7, 4.0 Hz, 1 H), 3.95 (dt, J = 9.6, 2.4 Hz, 1 H, 2.4% NOE with irradiation at δ 4.24), 3.48 (d, J = 20.1 Hz, 1 H), 2.48 (ddd, J = 20.0, 2.0, 1.2 Hz, 1 H), 2.30 (dt, J = 15.0, 3.6 Hz, 1 H, ~1.3% NOE with irradiation at δ 4.24), 2.15 (m, 2 H, 3.5% NOE with irradiation at δ 4.24), 2.04 (dtd, J = 15.1, 9.7, 3.7 Hz, 1 H), 1.87 (m, 2 H, 6.1% NOE with irradiation at δ 4.24), 1.75 (m, 1 H), 1.63 (d, J = 2.2 Hz, 3 H), 1.57 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 146.9, 136.7, 134.2, 130.2, 129.7, 129.2, 83.0, 71.5, 57.0, 55.5, 33.3, 32.7, 25.6, 24.7, 20.7, 13.6; exact mass calcd for $C_{13}H_{17}O_2$ $(M - C_6H_5SO_2)^+$ 205.1228, found 205.1227. **26**: white solid, mp 176–178 °C (ether); IR ($CDCl_3$) 1783, 1140, 1081, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.1, 1.4 Hz, 2 H), 7.69 (t, J = 7.2 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 2 H), 5.42 (q, J = 2.5 Hz, 1 H), 5.26 (ddd, J = 10.5, 8.0, 4.7 Hz, 1 H), 5.00 (dt, J = 2.5, 2.1 Hz, 1 H), 4.65 (d, J = 16.6 Hz, 1 H), 3.52 (dd, J = 18.3, 1.2 Hz, 1 H), 2.59 (dd, J = 16.6, 10.5 Hz, 1 H), 2.48 (dq, J = 18.3, 1.9 Hz, 1 H), 2.28 (m, 1 H), 2.05 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 137.1, 136.7, 134.5, 130.1, 129.4, 108.6, 80.2, 67.7, 58.1, 51.7, 49.0, 38.6, 34.4, 30.1, 24.7, 21.8; exact mass calcd for $C_{13}H_{17}O_2$ $(M - C_6H_5SO_2)^+$ 205.1229, found 205.1253; exact mass calcd for $C_{13}H_{16}O_2$ $(M - C_6H_5SO_2H)^+$ 204.1150, found 204.1166.

Cycloaddition of 13e: Preparation of (1*S,4*R**,14*R**,17*S**)-16-Methylene-14-(phenylsulfonyl)-2-oxo-3-oxatricyclo[12.2.1.0^{4,17}]heptadecane (27) and (4*R**,14*R**,17*S**)-16-Methyl-14-(phenylsulfonyl)-2-oxo-3-oxatricyclo[12.2.1.0^{4,17}]heptadec-1-ene (28).** A 1.5-mL aliquot of the solution prepared above in THF was added to **13e** (83.6 mg, 0.15 mmol) and stirred at room temperature. The colorless solution slowly yellowed, eventually became bright yellow, and then slowly returned to colorless over a 4.5-h period. The mixture was concentrated in vacuo and the residue purified via flash chromatography (silica gel, 2:1 hexane/ether, with rechromatography of mixed fractions, 4:1 hexane/ether) to give 23.7 mg of **27** and 14.8 mg of **28** (38.5 mg, 64% overall). **27**: white solid, mp 150–152 °C (hexane/ether); IR ($CDCl_3$) 1766, 1602, 1470, 1448, 1143, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.2, 1.3 Hz, 2 H), 7.68 (t, J = 7.4 Hz, 1 H), 7.55 (t, J = 7.7 Hz, 2 H), 5.10 (d, J = 1.6 Hz, 1 H), 4.90 (s, 1 H), 4.52 (ddd, J = 9.5, 6.4, 1.6 Hz, 1 H), 3.50 (dd, J = 8.9, 2.2 Hz, 1 H), 3.38 (dd, J = 8.8, 6.8 Hz, 1 H, 1.7% NOE with irradiation at δ 4.52), 2.95 (dd, J = 18.6, 1.1 Hz, 1 H), 2.52 (dq, J = 18.6, 2.7 Hz, 1 H, 3.6% NOE with irradiation at δ 4.52 ppm), 1.95 (t, J = 12.2 Hz, 1 H), 1.2–1.9 (m, 17 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 142.8, 136.2, 134.5, 130.4, 129.4, 111.5, 78.3, 77.1, 51.0, 49.5, 40.9, 35.2, 32.2, 27.3, 26.7, 25.4, 24.0, 23.8, 23.1, 22.4; exact mass calcd for $C_{17}H_{25}O_2$ $(M - C_6H_5SO_2H)$ 260.1776, found 260.1770. **28**: white solid, mp 164–166 °C dec (hexane/ether); IR ($CDCl_3$) 1750, 1720, 1700, 1680, 1460, 1440, 1140, 1080, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.5, 1.5 Hz, 2 H), 7.69 (t, J = 7.5 Hz, 1 H), 7.60 (t, J = 7.7 Hz, 1 H), 4.60 (t, J = 9.9 Hz, 1 H), 4.05 (dq, J = 9.5 Hz, 1 H), 3.76 (ddd, J = 17.7, 2.8, 1.5 Hz, 1 H), 2.35 (dd, J = 17.7, 1.4 Hz, 1 H), 2.04 (t, J = 13.3 Hz, 1 H), 1.95 (dd, J = 1.5, 1.3 Hz, 3 H), 1.2–1.9 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 147.2, 136.5, 134.4, 130.1, 129.5, 128.0, 79.8, 75.0, 55.4, 54.0, 33.1, 32.2, 28.5, 27.8, 26.1, 25.1 (2), 23.1, 14.1; exact mass calcd for $C_{17}H_{25}O_2$ $(M - C_6H_5SO_2)$ 261.1854, found 261.1848.

Isomerization of 20 to 19. Cycloadduct **20** (6.5 mg, 0.02 mmol) in 400 μL of THF at −78 °C was treated with 50 μL of a 1.0 M solution of LDA (0.05 mmol) in THF, generating a yellow solution. After 30 min, the reaction was quenched rapidly with acetic acid (30.0 mg, 29.1 μL, 0.5 mmol). The mixture was filtered through a short column of silica gel, eluting with 1:1 hexane/ether, and the solvent was evaporated to give 5.3 mg (82%) of a 7.8:1 mixture of **19**/**20** by integration of ^1H NMR resonances at δ 5.11 and 4.67, respectively.

Isomerization of 25 to 24. Cycloadduct **25** (7.0 mg, 0.02 mmol) in 200 μL of THF at −78 °C was treated with 50 μL of a 1.0 M solution of LDA (0.05 mmol) in THF, generating a yellow solution. After 30 min, the reaction was quenched rapidly with acetic acid (30.0 mg, 20.1 μL, 0.5 mmol). The mixture was filtered through a short column of silica gel, eluting with 2:1 hexane/ether, and the solvent was evaporated to give 5.8 mg (83%) of a ≥20:1 mixture of **24**/**25** by integration of ^1H NMR resonances at δ 3.01 and 3.95, respectively.

Preparation of (1S*,4R*,13R*)-2,12-Dioxo-3-oxatricyclo-[8.2.1.0^{4,13}]tridec-10-ene (29). Ozone was bubbled into a solution of **24** (8.0 mg, 0.023 mmol) in 1.2 mL of methanol at -78 °C until a blue color persisted. Excess ozone was removed by bubbling nitrogen gas through the mixture, and the ozonide was reduced at room temperature by the addition of 0.5 mL of dimethyl sulfide in 0.5 mL of methanol. The solvent was removed under a stream of nitrogen, and the residue was treated with a solution of triethylamine (100 μL) in 500 μL of methylene chloride. After 10 min of stirring at room temperature, the solvent was removed in vacuo and the residue purified via flash chromatography (silica gel, 1:1 hexane/ether) to give 1.1 mg of starting material and 2.7 mg (66%, based on 86% conversion) of **29**, which solidified to a white solid upon trituration with ether: mp 128-130 °C (ether/pentane); IR ($CDCl_3$) 1783, 1712, 1611, 1457, 1429 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1 H), 4.44 (ddd, J = 11.1, 7.1, 3.8 Hz, 1 H), 3.63 (t, J = 7.3 Hz, 1 H), 3.58 (d, J = 7.5 Hz, 1 H), 2.96 (dd, J = 15.0, 7.0 Hz, 1 H), 2.40 (dd, J = 14.7, 10.1 Hz, 1 H), 2.23 (ddt, J = 16.9, 7.7, 3.6 Hz, 1 H), 2.15 (m, 1 H), 1.3-2.0 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 180.7, 168.3, 128.2, 83.9, 54.1, 50.7, 34.7, 32.4, 26.4, 26.3, 25.1; exact mass calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0950.

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Supplementary Material Available: Experimental procedures for **3**, **6** (R = CH_2CF_3), **1b**, (*E*)-1-(phenylsulfonyl)-1-buten-4-ol, **11b** (R = CH_2CF_3), 3-hydroxy-1-(phenylsulfonyl)-1-cyclododecene, **9**, **13a**, and **16**, and equilibrations of **19**, **21**, and **27** (6 pages). Ordering information is given on any current masthead page.

Intramolecular Anodic Olefin Coupling Reactions: A Useful Method for Carbon-Carbon Bond Formation

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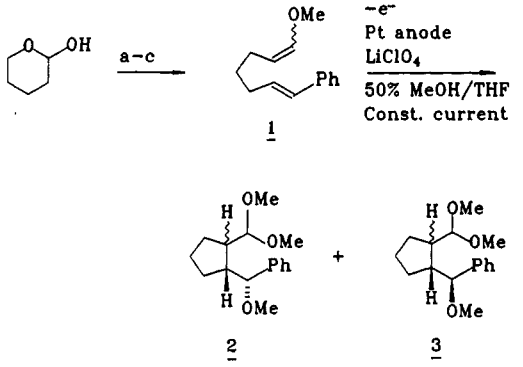
Abstract: The utility of intramolecular anodic olefin coupling reactions for effecting carbon-carbon bond formation has been examined. All of the successful cyclizations studied utilized either an alkyl or silyl enol ether as one of the participating olefins. The enol ethers could be coupled to simple alkyl olefins, styrenes, and allylsilanes in isolated yields ranging from 57 to 84%. The reactions were found to be effective for generating both five- and six-membered rings. The best conditions for cyclization utilized a reticulated vitreous carbon anode, constant-current conditions in an undivided cell, and a lithium perchlorate in either 50% methanol/tetrahydrofuran or 20% methanol/dichloromethane electrolyte solution. The use of an allylsilane as one of the participating olefins allowed for the regiospecific formation of olefinic products. In addition to the olefinic products, these reactions produced a small amount of a cyclized ether product in which the silyl group had not been eliminated. Deuterium-labeling studies showed that at least half of this ether byproduct arose from intramolecular migration of the methoxy group that was initially part of the starting enol ether to the carbon β to the silyl group. Intramolecular migration reactions of this type were found to participate in a number of the reported cyclization reactions.

The discovery of new, useful means for constructing carbon-carbon bonds is essential for the continued growth of synthetic organic chemistry. These reactions are important because they allow not only for the accomplishment of specific transformations within a synthetic sequence but also for the development of entirely new synthetic strategies. One method that appears ideal for initiating new carbon-carbon bond-forming reactions is oxidative organic electrochemistry. Oxidative organic electrochemistry would appear to have the ability to selectively generate highly reactive radical cation intermediates and initiate carbon-carbon bond formation under neutral conditions and at preset potentials.[1] This technique appears particularly attractive when one considers the growing importance of oxidative cyclization reactions.[2,3] It is tempting to suggest that anodic electrochemistry might provide a mild, generally useful method for initiating oxidative cyclization

Scheme I[a]



Yield = 65-73% (Ratio 2/3=5.3)

(a) Ph_3PCHPh, THF, 0 °C-RT. (b) Swern oxidation; styrene isomers were separated by silica gel chromatography. (c) $Ph_3PCHOMe$, THF, 0 °C-RT.

(1) For a general overview, see: (a) Baizer, M. M. *Organic Electrochemistry: An Introduction and a Guide*, 2nd ed.; Baizer, M. M., Lund, H., Eds.; M. Dekker: New York, 1983. For overviews of anodic electrochemistry, see: (b) Torii, S. *Electroorganic Synthesis: Methods and Applications: Part I - Oxidations*; VCH: Deerfield Beach, FL, 1985. (c) Yoshida, K. *Electrooxidation in Organic Chemistry: The Role of Cation Radicals as Synthetic Intermediates*; John Wiley and Sons: New York, 1984. (d) Ross, S. D.; Finkelstein, M.; Rudd, E. J. *Anodic Oxidation*; Academic Press: New York, 1975. (e) Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 911.

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