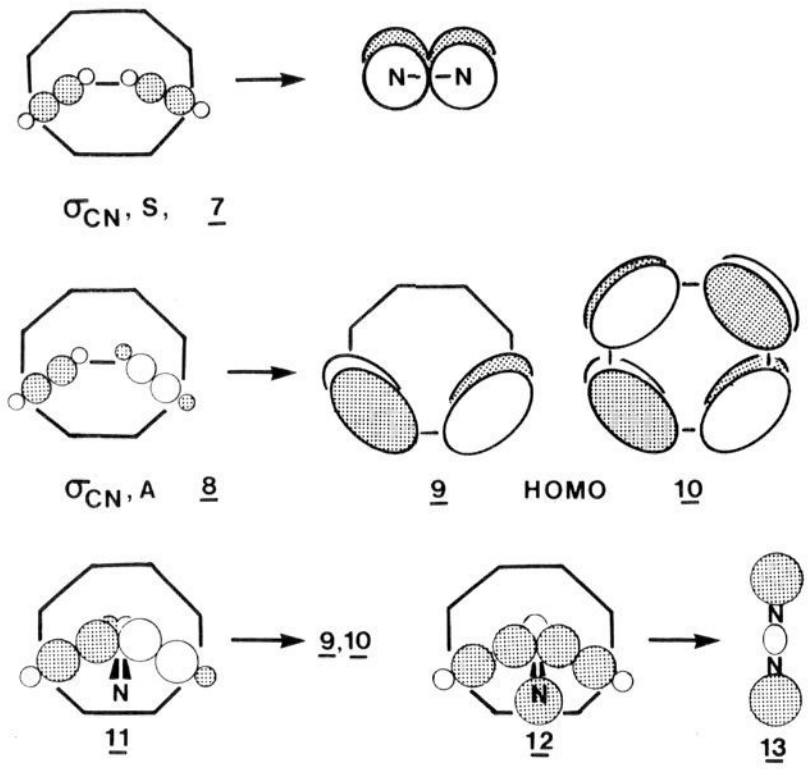

containing upward of ten framework atoms.[19] Nonetheless correlation diagrams constructed from each of the MO schemes reveal a uniform transformation of "σ_{CN}(S)" → π_{N_2} and "σ_{CN}(A)" → π(**10**). Furthermore none of the potential energy surfaces sustain a frontier orbital crossing.

The perspective rendered by the MO correlation predicts the reaction to be "allowed" in the generally accepted sense[2] and circumvents entirely the ambiguous choice between competing (4N) and (4M +2) pericycles. The parallel orbital correlation for linear diazene decomposition of **1a** and **2a** is completely analogous as depicted by **11**–**13**.[20] Interpretations of both the retrocycloadditions and the cheletropic extrusions by means of frontier-orbital theory[21] is equally satisfying and supports the notion that no energy raising factors arise from the primary orbital interactions.

We conclude that, for bis-pericyclic processes of this type, a fragment-by-fragment analysis[6] can be misleading and in general should be avoided in favor of symmetry arguments which accommodate simultaneously all the important orbital components.

Finally we note that the proposed 1,1-diazenes **1a** and **2a** are reported to decompose much less cleanly (71 and 28% COD and COT, respectively) and at higher temperatures (54 vs. −30 °C)[5] than do the 1,2-diazenes **4a** and **5a.** Similarly the ratio of yields for diazene **3a** and azodiene **6** is 0:100% (50–55 °C).[5,15] It is conceivable that 1,1-diazenes **1a**–**3a** are bypassed *in the reduction of precursors* **1b**–**3b,** *they dimerize in part to* tetrazines, or they fragment by a nonpericyclic process.[22] The consequences for drawing conclusions about linear vs. nonlinear cheletropic reactions[5] are obvious.

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Organoselenium-Induced Ring Closures. Sulfur-Containing Prostacyclins. Stereoselective Synthesis of Cyclic α,β-Unsaturated Sulfoxides, Sulfones, and Sulfides and Synthesis of 6,9-Sulfoxa-5(*E*)- and -5(*Z*)-prostacyclin, 6,9-Sulfo-5(*E*)- and -5(*Z*)-prostacyclin, 6,9-Sulfo-6α- and -6β-4(*E*)-isoprostacyclin, and 6,9-Thiaprostacyclin

Sir:

The elegant work of Reich[1] and Sharpless[2] in the early 1970s demonstrated clearly the high potential of organoselenium reagents to organic synthesis. The selenium-based methodology developed since then by the aformentioned authors[3,4] and other workers[5] has already found profound applications to organic synthesis and the construction of complex molecules.[6] As an extension to our previous work on selenium-induced ring closures[7-9] and owing to the increasing importance of sulfur heterocycles in the β-lactam antibiotic[10] and prostacyclin[11] fields, we investigated the reactions of organoselenium reagents with unsaturated sulfur-containing compounds. In this communication we wish to report new, selenium-based methodology leading to the stereoselective synthesis of cyclic α,β-unsaturated sulfoxides and sulfones and its application to the synthesis of a number of novel prostacyclin analogues.

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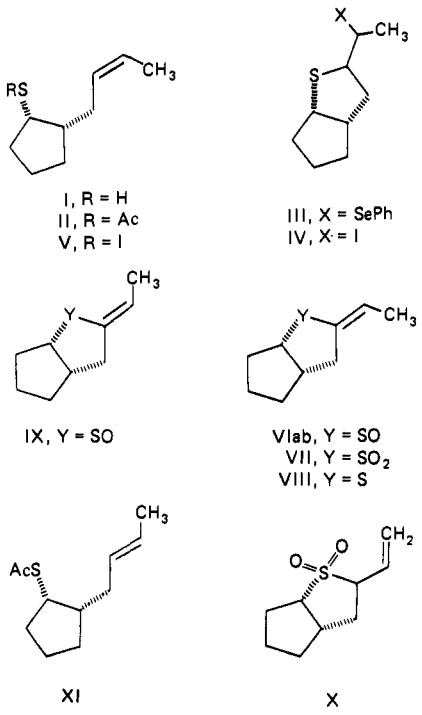
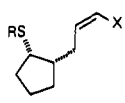
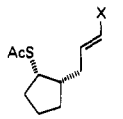
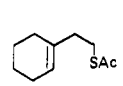
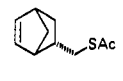
Chart I



Thiol I (Chart I) reacted rapidly with PhSeCl at −78–25 °C in dry methylene chloride[12] to afford the cyclic thioether III[13] in 85% yield.[14] *This ring closure proceeded at least as well when the thioacetate II was used with the same product being formed.* This observation is synthetically important since it allows the cyclization to take place from a stable, protected form of the usually rather labile, unsaturated thiols such as I. When the phenyl seleno thioether III was exposed to excess hydrogen peroxide (8 equiv) in tetrahydrofuran at 25 °C for 24 h (method A), a mixture of (*E*)-sulfone VII and its unconjugated isomer X was obtained in 92% yield (ratio of VII:X, ~3:1 by ^{1}H NMR spectroscopy). Stoichiometric amounts of hydrogen peroxide at 0 °C produced a mixture of sulfoxide VIa,b (major product, mixture of sulfoxide isomers), its unconjugated isomer (mixture of sulfoxide isomers), and sulfones VII and X. However, treatment of the selenide III in methylene chloride with *m*-chloroperbenzoic acid (1.1 equiv at −78 °C followed by another 1.1 equiv at −20 °C and warming to 25 °C) (method B) led selectively to the formation of the (*E*)-sulfoxide VIa,b (mixture of sulfoxide isomers) in 94% yield.[15] Additional *m*-chloroperbenzoic acid (1.1 equiv at 0 °C) (method C) led directly to the (*E*)-sulfone VII in 95% yield. Alternatively, a combination of *m*-chloroperbenzoic acid (2.2 equiv at −78–25 °C) and hydrogen peroxide (4 equiv at 25 °C, 24 h) (method D) can be used for the direct production of the (*E*)-sulfone VII in high yield (95%). The observed sulfoxide → sulfone oxidation with hydrogen peroxide is apparently effected by benzeneperoxyseleninic acid (PhSe(=O)OOH),[16] produced in situ under the reaction conditions. *Thus, it appears that benzeneperoxyseleninic acid would be an excellent reagent for the selective oxidation of sulfur to sulfoxides and sulfones under very mild conditions and in the presence of double bonds* (*vide supra*).

The *E* geometry of the double bond in VIa,b and VII is based on mechanistic considerations, namely the assumed trans addition during the cyclization reaction and the syn nature of the phenyl selenoxide elimination. As expected, the trans unsaturated thioacetate XI, on cyclization with PhSeCl followed by oxidation, led stereoselectively to the (*Z*)-sulfoxide IX (mixture of sulfoxide isomers) in high yield. The *Z* isomer IX was also the product of a similar sequence beginning with the (*Z*)-thiol I and, (a) cyclizing with iodine (1.1 equiv CH_2Cl_2, −78 °C) presumably via the sulfenyl iodide V, undergoing a facile intramolecular addition to the double bond affording IV; (b) oxidizing with hydrogen peroxide (THF, 25 °C); and (c) eliminating with 1,5-diazabicyclo[5.4.0]undec-5-ene (benzene, 0 °C) (70% overall). Thus, by changing the ring-closure initiator, using the proper double-bond isomer, and choosing the correct oxidizing conditions, *the described methodology offers versatile and selective routes to either the E or Z isomers of cyclic α,β-unsaturated sulfoxides and sulfones,* In view of the ease by which sulfoxides are reduced to sulfides, the reported reactions also represent stereoselective syntheses of cyclic α,β-unsaturated sulfides, a rather important class of compounds. For example, VIa,b was smoothly reduced with the recently introduced reagent trimethyliodosilane[17] (CCl_4, 0 °C, pyridine) to the sulfide VIII.

Table I. Organoselenium-Induced Cyclizations of Unsaturated Thioacetates and Thiols

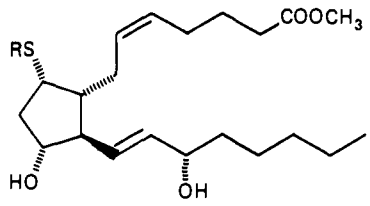
Entry	Substrate	Product	Yield (%)[a]
1	R = H, X = CH_3		80
2	R = Ac, X = CH_3		85[b]
3	R = H, X = $(CH_2)_3COOCH_3$		77
4	R = Ac, X = $(CH_2)_3COOCH_3$		81[b]
5	X = CH_3		88
6	X = $(CH_2)_3COOCH_3$		80
7			77[b]
8			81

[a] Yield of pure product isolated by preparative TLC or column chromatography (silica gel). Reactions were run on 0.1–1 mmol scale in methylene chloride at −78 °C unless otherwise specified. [b] Reaction run in methanol at −78 °C.

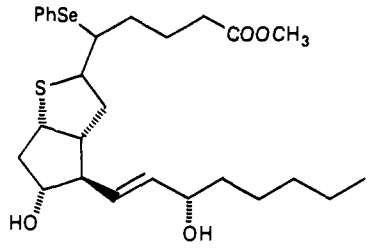
To demonstrate the generality of this ring-forming reaction, a series of unsaturated thioacetates and thiols were prepared and subjected to the PhSeCl-induced cyclization process. The results are shown in Table I.[18]

The selectivity observed with *m*-chloroperbenzoic acid is presumably due to *initial oxidation at sulfur followed by selenoxide formation and syn elimination toward the sulfoxide* group, whereas hydrogen peroxide oxidizes sulfur and selenium at comparable rates leading to some sulfide-selenoxide which eliminates *away from the sulfide* moiety by analogy to the oxygen case.[9]

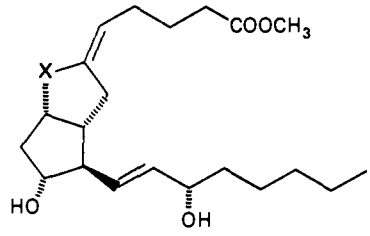
As an excellent application of this new methodology, we report here the synthesis of a series of novel sulfur-containing prostacyclin (PGI_2, XIX) analogues. Exposure of 9-thio-$PGF_{2\alpha}$ methyl ester (XII)[19] (CH_2Cl_2, −78 °C, 80%) or its acetate (XIII) (CH_3OH, −78 °C, 68%, or CH_2Cl_2, −78 °C, 85% based on 50% conversion) to PhSeCl (1.2 equiv) resulted in the formation of the cyclic thioether XIVa.[20] This chromatographically and spectroscopically homogeneous product appears to be a single isomer and is different from XIVb, the isomer obtained from the corresponding 5-*trans*-$PGF_{2\alpha}$[21] precursor (vide supra). Oxidation of the phenyl selenide XIVa according to method B led smoothly to 6,9-sulfoxa-5(*E*)-prostacyclin methyl ester (XVa,b) as a mixture of two sulfoxide isomers separated by preparative layer chromatography (silica gel, 5% methanol in methylene chloride), major isomer XVa



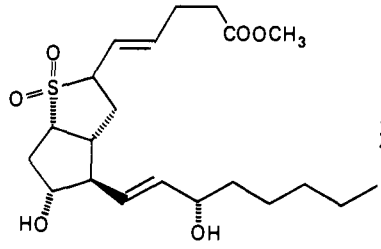
XII, R = H
XIII, R = Ac



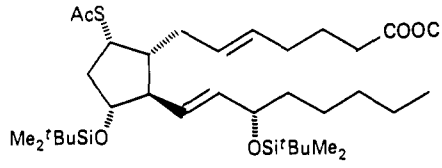
XIVa
XIVb



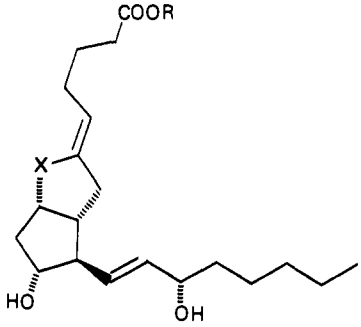
XVab, X = SO
XVI, X = SO_2



XVIIa
XVIIb



XVIII



XIX, X = O
XX, X = S
XXIab, X = SO
XXII, X = SO_2

(R_f 0.06, 51%), minor isomer XVb (R_f 0.04, 27%). The oxidation methods C or D produced selectively 6,9-sulfo-5(*E*)-prostacyclin methyl ester (XVI) (R_f 0.05, silica gel, 2.5% methanol in ether) in 81% yield. Finally, 6,9-sulfo-4(*E*)-isoprostacyclin methyl ester (XVIIa)[20] (R_f 0.05, silica gel, 2.5% methanol in ether) was obtained (29%) by method A together with XVI (50%).

Using similar procedures as described above and starting with the 9-thioacetoxy-5-*trans*-$PGF_{2\alpha}$[21] derivative XVIII we have synthesized the following prostacyclins with the natural 5(*Z*) geometry via the selenide XIVb (single isomer, different from XIVa):[20] 6,9-sulfoxa-5(*Z*)-prostacyclin methyl esters, XXIa (R = CH_3) (major isomer, R_f 0.08, silica gel, 5% methanol in methylene chloride) and XXIb (R = CH_3) (minor isomer, R_f 0.05, silica gel, 5% methanol in methylene chloride), 6,9-sulfo-5(*Z*)-prostacyclin methyl ester XXII (R = CH_3) (R_f 0.09, silica gel, 2.5% methanol in ether), and 6,9-sulfo-4(*E*)-isoprostacyclin methyl ester, XVIIb (R = CH_3) (R_f 0.06, silica gel, 2.5% methanol in ether). Reduction of XXIa,b (R = CH_3) with iodotrimethylsilane (CCl_4, pyridine) leads to 6,9-thiaprostacyclin, XX (R = CH_3), a highly active PGI_2 analogue previously synthesized in these laboratories.[19]

Preliminary investigations with these novel prostacyclins revealed interesting and divergent biological properties including inhibitory activity against human blood platelet aggregation[22] (e.g. XVIIb, R = Na), constricting activity of isolated cat coronary artery,[23] and antagonistic action against PGI_2 (e.g., XXIa, R = Na).[22,24]

Supplementary Material Available: Important spectral data of the prostacyclins (1 page). Ordering information is given on any current masthead page.

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(12) Other solvents such as acetonitrile (−35 °C) or methanol (−78 °C) can also be used. At higher temperatures, however, or in cases where the formation of the ring is not as favorable because of steric reasons, methanol interferes with the reaction; see ref 14a–c.
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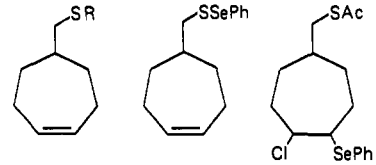
(18) In cases where the geometry of the substrate is not favorable for a ring closure and/or the expected product would be severely hindered, the reaction leads to uncyclized products as illustrated by the formation of iii from i and iv from ii.



i, R = H
ii, R = Ac
iii
iv

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(20) Although the stereochemistry at C-6 in compounds XIVa, XIVb, XVIIa, and XVIIb has not been rigorously established at this point, their chromatographic and ^1H NMR spectral properties point to the 6α (endo) assignment

for XIVa and XVIIa and the 6β (exo) stereochemistry for XIVb and XVIIb (see N. A. Nelson, *J. Am. Chem. Soc.*, **99**, 7362 (1977)).
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(22) Tests on platelet aggregation were carried out by Miss Cherie Ditre and Professors J. B. Smith and M. J. Silver at the Cardeza Foundation, Thomas Jefferson University, Philadelphia, Pa. 19107.
(23) Tests on the isolated cat coronary artery were carried out by Mr. Martin Ogletree and Professor A. M. Lefer, Department of Physiology, Thomas Jefferson Medical College, Philadelphia, Pa. 19107.
(24) This research was supported by The Research Corporation, The University of Pennsylvania, Merck Sharp and Dohme, U.S.A., and Ono Pharmaceutical Co., Japan.

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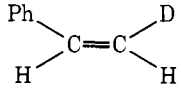
Carbon-14 and Deuterium Isotope Effects during the [2 + 2] Cycloaddition of Diphenylketene to Styrene[1]

Sir:

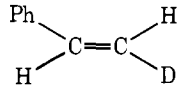
It is well established[2] that concerted [2 + 2] cycloadditions of ketenes to alkenes proceed through crosswise transition states resembling the orientation complex shown in Figure 1. Two orbital symmetry-allowed mechanisms have been proposed[2n] for these reactions: (1) the $[\pi 2_s + \pi 2_a]$ cycloaddition and (2) the $[\pi 2_s + \pi 2_s + \pi 2_s$ (or $\pi 2_s + \pi 2_a + \pi 2_a)]$ mechanism. Both are compatible with the crosswise transition state.

Baldwin and Kapecki[3] were among the first to adduce evidence that styrene and diphenylketene add in a concerted fashion by determining for the reaction the deuterium isotope effects for α- and β-labeled styrenes ($(^Hk/^Dk)_\alpha$ = 1.23; $(^Hk/^Dk)_\beta$ = 0.91 per deuterium, 65 °C). In their measurement of $(^Hk/^Dk)_\beta$, styrene-β,β-d_2 was employed, and $^Hk/^Dk$ per deuterium was calculated therefrom by taking the square root of the observed value. The latter ($(^Hk/^Dk)_\beta$ = 0.91) is inverse, as expected[4] for the $sp^2 \rightarrow sp^3$ hybridization change, but $(^Hk/^Dk)_\alpha$ = 1.23 is unexpected, and has thus far not been explained.[5]

In an attempt to learn more about the reaction of styrene with diphenylketene, we prepared $Ph^{14}CH{=}CH_2$, $PhCH{=}{}^{14}CH_2$, $Ph_2{}^{14}C{=}C{=}O$, and $Ph_2C{=}{}^{14}C{=}O$, and measured[6] $^{12}k/^{14}k$ for all four labeled species during the [2 + 2] addition. In addition we prepared[7] the two forms of β-



cis-β-deuteriostyrene
$^Hk/^Dk$ = 0.889 ± 0.004



trans-β-deuteriostyrene
$^Hk/^Dk$ = 0.879 ± 0.004

deuteriostyrene and, using methods described before,[6] determined the $^Hk/^Dk$ values for these two species as well, for we could deduce no reason—given the crosswide transition state—why $(^Hk/^Dk)_{cis}$ and $(^Hk/^Dk)_{trans}$ should be the same. The results of the four $^{12}k/^{14}k$ determinations are given in Figure 1. Also given (in Figure 1) is the average value for our determination of $(^Hk/^Dk)_{cis}$ and $(^Hk/^Dk)_{trans}$. The individual values for these two deuterium isotope effects are shown in the text under the appropriate structures, and to our surprise are identical within experimental error (they are also very close to the value determined by Baldwin and Kapecki[3]).

Heavy-atom isotope effects are partially understood through use of the Bigeleisen-Mayer expression,[8]

$$k_1/k_2 = \nu^{\ddagger}{}_{1L}/\nu^{\ddagger}{}_{2L}\left[1 + \sum_i^{3n-6} G(u_i)\Delta u_i - \sum_i^{3n'-7} G(u^{\ddagger}{}_i)\Delta u^{\ddagger}{}_i\right] \quad (1)$$

and the relationship to transition-state structure developed by Fry[9] and Sims.[10] In eq 1, subscripts 1 and 2 refer to light and

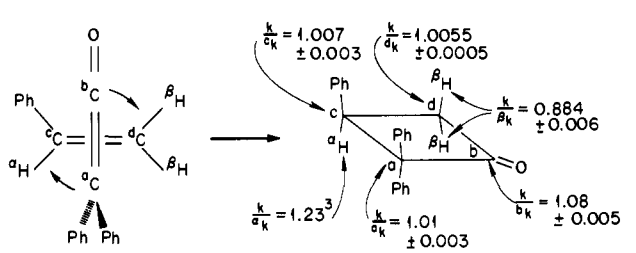


Figure 1.

heavy isotopes, respectively, $\nu^{\ddagger}{}_{1L}/\nu^{\ddagger}{}_{2L}$ is the ratio of the imaginary frequencies at the transition state (always >1). Within the brackets are evaluations of the partition functions for reactant and activated complex. The terms u_i and $u^{\ddagger}{}_i$ are vibrational frequencies, and Δu_i and $\Delta u^{\ddagger}{}_i$ are the frequency shifts caused by isotope substitution. The negative term $\Sigma_i^{3n'-7} G(u^{\ddagger}{}_i)\Delta u_i{}^{\ddagger}$ inside the brackets represents the effect of isotopic substitution on the vibrational frequencies of the transition state, and, the larger it becomes, the smaller the primary heavy-atom isotope effect will be. Equation 1 has been elegantly tested by Kresge and coworkers.[11] The Fry[9]-Sims[10] work relates the structure of the transition state to the magnitude of the heavy-atom isotope effect—a relatively "symmetric" transition state (i.e., one with comparable bond orders for the weakening and forming bonds) corresponds to a larger $k/{}^*k$ than one with substantially unequal bond orders. Applying both the Bigeleisen-Mayer[8] and Fry[9]-Sims[10] relations to our data, the large $^{12}k/^{14}k$ (1.08) for ^bC (Figure 1) is consistent with an activated complex in which there is (a) a highly polarized carbonyl group with a strongly negative[4g] oxygen, (b) a substantial decrease in bonding at ^bC, and (c) a near balancing of old bond breaking and new bond making at ^aC, ^cC, and ^dC. The small carbon-14 isotope effects at ^aC, ^cC, and ^dC would then result from a balance of the weakening of the ^aC-^bC and ^cC-^dC bonds with a corresponding strengthening of the ^aC-^cC and ^bC-^dC bonds. The term $\Sigma_i^{3n'-7} G(u^{\ddagger}{}_i)\Delta u^{\ddagger}{}_i$ must also be small.

The values for the $^Hk/^Dk$'s in the cycloadditions of *cis*- and *trans*-β-deuteriostyrenes to diphenylketene are inverse, as expected, and in accord with the Streitwieser[11] and Wolfberg-Stern[4] treatments for α-deuterium isotope effects (to which these isotope effects in both the α and β positions of styrene belong), in which out-of-plane bending makes the largest contribution to the double differences in zero point energies between ground and transition states. That our values for the two β-deuteriostyrenes are nearly identical is consistent with a transition state in which diphenylketene exerts little compression on cis H or trans H owing to the two phenyls or the carbonyl oxygen. A transition state of the kind indicated in Figure 1 would satisfy this requirement, for the "naked" sp carbon at ^bC must exert negligible steric compression on the trans-β hydrogen (it is, in fact, the sp character of that carbon which makes the concerted [2 + 2] addition possible). The compression of the two phenyls at ^aC against the cis-β hydrogen must also be negligible, particularly when compared with the compression against the α hydrogen (which is flanked by three phenyls). In fact, $^\alpha H$ must be seriously squeezed in the transition state which—presuming the Streitwieser[4] explanation is operating—should make its isotope effect even more negative than that for the β hydrogens. This, of course, works in the wrong direction to explain the large (1.23) value observed[3] for $(^Hk/^Dk)_\alpha$. Thus we conclude that another factor which works in the opposing direction must be called into play, and the special kind of hyperconjugation suggested by Baldwin and Kapecki[3] is the best explanation available at this time.

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