# A Stereocontrolled Cyclopentenone Synthesis via Cycloaddition

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**Abstract:** γ-Alkoxy-α,β-unsaturated sulfones are readily available in both racemic and scalemic form, the latter either by asymmetric induction from achiral building blocks or from readily available scalemic starting materials. These electron deficient olefins serve as excellent substrates for [3 + 2] cycloadditions involving the intermediacy of trimethylenemethane–palladium complexes. The highly diastereoselective methylenecyclopentannulation provides a versatile cycloadduct that allows very simple conversion to cyclopentenones and cyclopentadienes and the synthetic equivalent of addition to cycloalkanones and alkynones, two classes of substrate that either frequently give low yields or totally fail in palladium-catalyzed cycloadditions from 2-(acetoxymethyl)-3-(trimethylsilyl)prop-1-ene.

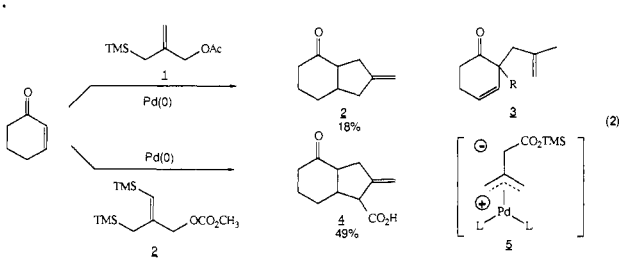
The interest in five-membered ring construction, which developed strongly after the discovery of the prostaglandins, continues to generate many exciting diverse strategies.[1,2] One approach that has had extensive use in synthesis involves ring expansion from three-[3,4] and four-membered rings.[4,5] Cyclizations involving free-radical intermediates have been extraordinarily successful.[6] Transition-metal-based methodology, as exemplified by rhodium-catalyzed diazo insertions[7] and intramolecular carbametalations,[8] has also proven to be particularly fruitful.[9]

Most of the cyclization methodology has involved single bond formation. Multiple bond-forming processes can improve efficiency by increasing molecular complexity more rapidly. Some modest success has come from carbonium ion based methodology.[10] Condensations of various three-carbon fragments including allenyl silanes,[11] allyl stannanes,[12] and other ambiphilic conjunctive reagents[13] with electron-deficient olefins have led to [3 + 2] cycloadditions. A [2 + 2 + 1] strategy using organocobalt reagents has become very popular.[14]

Transition-metal-catalyzed [3 + 2] cycloadditions have great appeal for selective five-membered ring formation. Nickel- and palladium-catalyzed cyclooligomerizations of methylenecyclopropanes hold great promise[15] and appear to be amenable to asymmetric induction.[16] We have explored the cycloadditions of 2-((trimethylsilyl)methyl)allyl carboxylates according to eq 1 as a general route for methylenecyclopentane formation.[17-19]

(1)

In exploring the feasibility of this route as a methylenecyclopentannulation with cyclic enones, the efficiency varied with substrate. Cyclopentenones reacted in good yield,[20] but cyclohexenones require double activation,[21] a type of modification that may be generalized to other ring sizes. The problem of the cycloalkenones appears related to the relative rate of the cycloaddition compared to deprotonation. Thus, alkylation products, like **3**, involving enolate formation compete with the cycloaddition product **2**.[22] Decreasing the basicity of the trimethylenemethane intermediate, as in our carboxylative cyclopentannulation, where the reactive TMM–$PdL_2$ complex is **5**, does substantially improve the cycloaddition with cyclohexenone to form the adduct **4** (eq 2).[23]



(2)

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An alternative strategy envisioned modification of the substrate. We focused on γ-alkoxy-α,β-unsaturated sulfones, such as **6**,

(1) For an overview of prostaglandin syntheses, see: Mitra, A. *The Synthesis of Prostaglandins*; John Wiley & Sons: New York, 1977. Newton, R. F.; Roberts, S. M. *Prostaglandins and Thromboxanes*; Butterworth Scientific: London, 1982. Roberts, S. M.; Schiermann, F. *New Synthetic Routes to Prostaglandins*; Academic Press: London, 1982. *Prostaglandins and Related Substances*; Pace-Asciak, C., Granstrom, E., Ed.; Elsevier: Amsterdam, 1983.

(2) For an overview of five-membered ring syntheses, see: Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. Taber, D. F. *Intramolecular Diels–Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. Ramaiah, M. *Synthesis* **1984**, 529. Paquette, L. A. *Topics Curr. Chem.* **1984**, *119*, 1. Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Berlin, 1987. Krohn, K. *Nachr. Chem. Tech. Lab.* **1987**, *35*, 700.

(3) Trost, B. M. *Topics Curr. Chem.* **1986**, *133*, 3. Salaun, J. R. Y. *Topics Curr. Chem.* **1988**, *144*, 1.

(4) Hudlicky, T.; Kutchan, T. M.; Naqui, S. M. *Org. Reactions* **1985**, *33*, 247. For some recent interesting examples, see: Fleming, A.; Sinai-Zingde, G.; Natchus, M.; Hudlicky, T. *Tetrahedron Lett.* **1987**, *28*, 167. Hudlicky, T.; Radesca-Kwart, L.; Li, L.; Bryant, T. *Tetrahedron Lett.* **1988**, *29*, 3283.

(5) Wong, H. N. C.; Lau, K.; Tam, K. *Topics Curr. Chem.* **1986**, *133*, 83. For some interesting recent examples, see: Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503. Fitzer, L.; Majewski, M.; Kanschif, A.; Egert, E.; Sheldrick, G. M. *Tetrahedron Lett.* **1986**, *27*, 3603. Avasthi, K.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 2557. Greene, A. E.; Charbonnier, F.; Luche, M. J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752. Ue, M.; Kobiro, K.; Kakiuchi, K.; Tobe, Y. *Chem. Lett.* **1987**, 1903. Gadwood, R. C.; Mallick, I. M.; DeWinter, A. J. *J. Org. Chem.* **1987**, *52*, 774. Veenstra, S. J.; deMesmacker, A.; Ernest, B. *Tetrahedron Lett.* **1988**, *29*, 2303.

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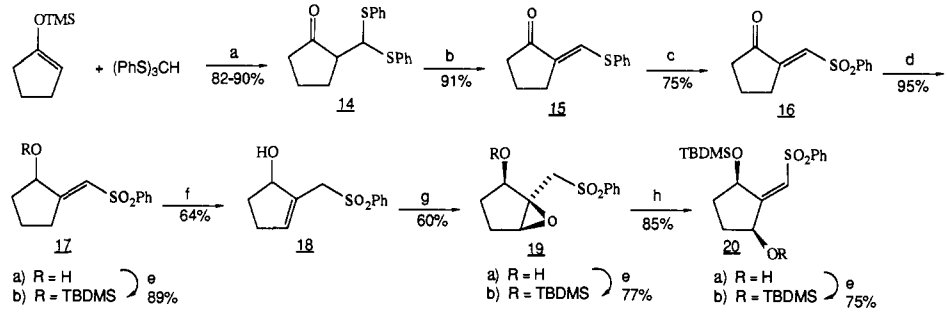
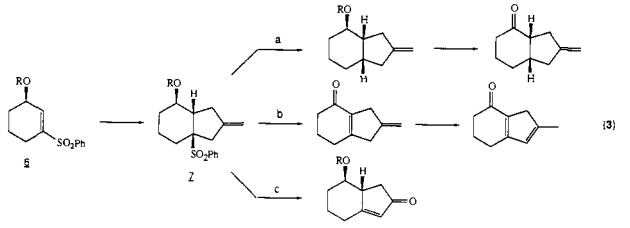
**Scheme I.**[a] Synthesis Utilizing an Enol Silyl Ether As Starting Material




[a] $SnCl_4$, $CH_2Cl_2$, −45 °C; (b) DBU, $CH_2Cl_2$, 0 °C; (c) oxone, borate buffer, $CH_3OH$, $H_2O$, room temperature; (d) $NaBH_4$, $CeCl_3$, $CH_3OH$, room temperature; (e) TBDMS-Cl, $C_3H_4N_2$, DMAP, DMF, room temperature; (f) $t$-$C_4H_9OK$, $t$-$C_4H_9OH$, room temperature; (g) $VO(acac)_2$, $t$-$C_4H_9OOH$, $CH_2Cl_2$, room temperature; (h) LDA, ether, 0 °C.

because of their accessibility[24] and the versatility of their cycloadducts **7**. In this latter regard, reductive desulfonylation and adjustment of the oxidation level of the alcohol provides the full equivalent of the cycloaddition to the cycloalkenone (eq 3a).

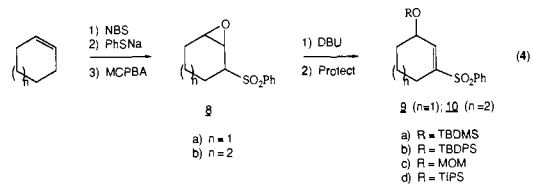



Alternatively, oxidation of the alcohol **7** labilizes the sulfone toward elimination to give the equivalent of a cycloaddition to a cycloalkynone (eq 3b). Isomerization of this initial elimination product may provide a novel cyclopentadiene. A third possibility particularly intrigued us. Oxidative cleavage of the olefin should also labilize the sulfone toward elimination to provide a cyclopentenone annulation (eq 3c).

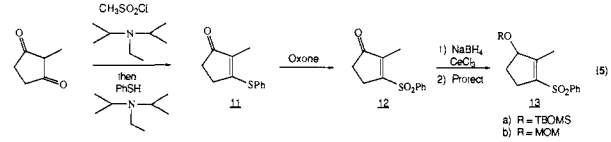
A major advantage of this strategy is the possibility of an asymmetric annulation. The stereochemistry of the bicyclic system depends upon the diastereoselectivity of the methylenecyclopentannulation. To the extent the γ-hydroxy-α,β-unsaturated sulfone is available in enantiomerically pure form, the overall sequence becomes an enantiocontrolled annulation.

In this paper, we explore the suitability of such sulfones as acceptors in our [3 + 2] cycloaddition. In addition, the versatility of their cycloadducts and the possibility of an enantiocontrolled annulation are probed.

**Synthesis of γ-Alkoxy-α,β-Unsaturated Sulfones.** A variety of methods were employed to illustrate the ease and widespread availability of the requisite substrates. Using simple cycloalkenes as starting materials, the six- and seven-membered ring substrates **9** and **10** were prepared by the method of Fuchs according to eq 4.[24] MCPBA was the oxidant of choice to permit simultaneous epoxidation and sulfur oxidation.




Beginning with a 1,3-dicarbonyl compound, a tetrasubstituted substrate was prepared in the five-membered ring series according to eq 5. In a single operation, 2-methylcyclopentane-1,3-dione




was converted to its enol mesylate and in situ substituted with thiopentoxide to give the β-(phenylthio)-α,β-unsaturated ketone **11**. Chemoselective oxidation with oxone to the sulfone **12** proceeded in 78% overall yield from the 1,3-dione.[25] Reduction to the alcohol **13** (R = H) by the method of Luche[26] and protection either as a silyl or MOM ether completes the sequence.

Enol silyl ethers also served as useful starting materials. In a project directed toward the synthesis of the spirocyclic core of ginkgolides,[27] two substrates were prepared as outlined in Scheme

(13) For some examples, see: Knapp, S.; O'Connor, U.; Mobilio, D. *Tetrahedron Lett.* **1980**, *21*, 4557. Danishefsky, S.; Etheridge, S. J. *J. Org. Chem.* **1982**, *47*, 4791. Bucheister, A.; Klemarczyk, P.; Rosenblum, M. *Organometallics* **1982**, *1*, 1679. Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805. Piers, E.; Karunaratre, V. *Chem. Commun.* **1984**, 959. St. Laurent, D. R.; Paquette, L. A. *J. Org. Chem.* **1986**, *51*, 3861. Lee, R. V.; Richardson, K. A. *Tetrahedron Lett.* **1986**, *27*, 5021. Beak, P.; Burg, D. A. *Tetrahedron Lett.* **1986**, *27*, 5911. Lee, T. V.; Richardson, K. A. *Tetrahedron Lett.* **1986**, *27*, 5021. DeLombaert, S.; Nemery, I.; Roekens, B.; Carretero, J. C.; Kinmel, T.; Ghosez, L. *Tetrahedron Lett.* **1986**, *27*, 5099. Beak, P.; Wilson, K. D. *J. Org. Chem.* **1987**, *52*, 218. Bunce, R. A.; Wamsley, E. J.; Pierce, J. D.; Shellhammer, A. J., Jr.; Drumright, E. *J. Org. Chem.* **1987**, *52*, 464. Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 1617.

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(19) For 1,3-diyl reactions, see: Little, R. D. *Chem. Rev.* **1986**, *86*, 875.

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(22) Cf.: Balavoine, G.; Eskenazi, C.; Guillemot, M. *Chem. Commun.* **1979**, 1109.

(23) Trost, B. M.; Mignani, S. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1988**, *110*, 1602.

(24) (a) For imaginative use of these substrates, see: Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4755 and references cited therein. (b) Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118. (c) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 346. (d) Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903.

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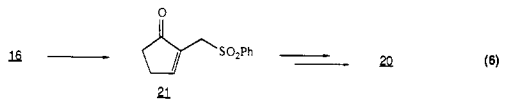
I, starting from 1-(trimethylsiloxy)cyclopentene. A new approach for phenylthiomethylenation of ketones was developed based upon thionium ion chemistry.[28-30] For the condensation with (phenylthio)orthoformate, we examined DMTSF, trityl fluoroborate, trimethyloxonium fluoroborate, and stannic chloride. Only stannic chloride gave satisfactory results. A small amount (~6%) of elimination product **15** accompanied the formation of the simple condensation product **14**. Exposing the latter to DBU most effectively completed the elimination of thiophenol to provide the olefin **15**. The failure of DMTSF to effect this condensation is surprising in light of its effectiveness in the condensation of (phenylthio)orthoformate and phenols.[30] We attribute the failure to an unfavorable competition between the enol silyl ether and the ortho thio ester toward DMTSF because of the lower reactivity of a phenylthio compared to an alkylthio group. While we have not explored the generality of this two-step sequence, we believe it should be a general approach for regioselective phenylthiomethylenation of aldehydes and ketones.

Chemoselective oxidation of **15** proved surprisingly capricious. Using our normal oxone procedure[31] did generate the desired sulfone **16**, but it appeared to suffer further oxidation.[32] Two factors appear to be important to obtain good yields routinely: (1) control of pH and (2) minimizing exposure to the oxidation conditions during reaction and workup. For the former, boric acid proved to be most effective in maintaining an active oxidant at pH 5.5–6.0. The generation of perboric acid as the active oxidant under these conditions cannot be ruled out.[33] The remaining steps for formation of the monoalkoxy sulfone acceptor **17b** were straightforward as outlined in Scheme I.

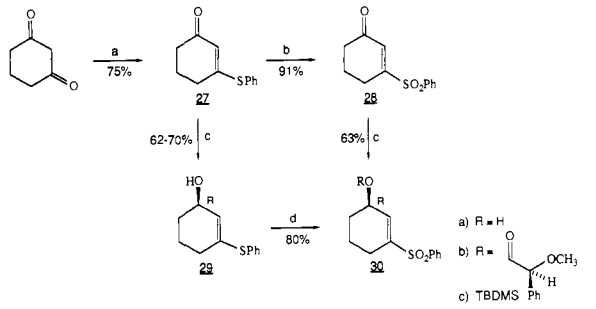
For our studies directed toward the ginkgolides, we were also interested in the dialkoxysulfone **20b**. Our initial approach envisioned double bond isomerization of conjugated sulfone **16** to allyl sulfone **21** (eq 6). A wide variety of bases including po-



(6)

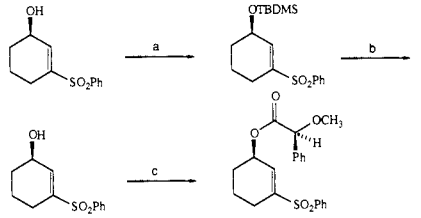
tassium hydroxide, potassium *tert*-butoxide, and lithium diisopropylamide led to rapid destruction of starting material. A 50% yield of enone **21** can be obtained by treating conjugated sulfone **16** with 2 equiv of DBU for 3 min. Longer times led to substantial destruction. The base lability of the system suggested examination of rhodium chloride as a nearly neutral system.[34] At most, 22% of the desired product was obtained.

**Scheme II.**[a] Asymmetric Synthesis of a γ-Alkoxy-α,η-Unsaturated Sulfone




[a] PhSH, TsOH, PhH; (b) oxone, $CH_3OH$, $H_2O$, room temperature; (c) LAH, *N*-methylephedrine, *N*-ethyl-2-aminopyridine, THF, −78 °C; (d) MCPBA, $CH_2Cl_2$, 0 °C.

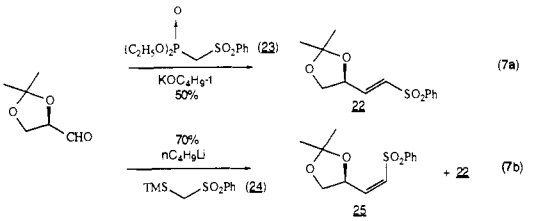
**Scheme III.**[a] Racemization Test for Acceptor




[a] (a) TBDMS-Cl, $C_3H_4N_2$, DMF, room-temperature; (b) TBAF, THF, −78 °C; (c) *S*-*O*-methylmandelic acid, DCC, DMAP, $CH_2Cl_2$, room temperature.

Assessing the difficulty for the olefin isomerization as residing in the high electrophilicity of both **16** and **21**, we turned to the alcohol **17**. This substrate behaved well under very typical conditions for isomerizing vinyl sulfones to allyl sulfones. An advantage of this strategy resides in the ease of diastereoselective epoxidation by utilizing the hydroxyl substituent as a directing group. Elimination of the epoxysulfone proceeded surprisingly slow with alkoxide bases. On the other hand, LDA effected smooth elimination to a single geometric isomer which is tentatively assigned as depicted in **20a** based upon comparison of NMR shifts for the protons α to oxygen. Since silylation to **20b** removed this structural question, the geometry of **20a** was not rigorously established.

The utility of this strategy for the synthesis of enantiomerically pure cyclopentanes first requires the availability of enantiomerically pure γ-alkoxy-α,β-unsaturated sulfones. A simple strategy to such systems draws upon olefination of readily available enantiomerically pure α-alkoxyaldehydes. The acetonide of (*R*)-glyceraldehyde was converted into the pure *E* isomer **22** utilizing




the Emmons–Wadsworth–Horner type reagent **23**.[35] A mixture enriched in the *Z* isomer, **25**, from which the pure *Z* isomer was obtained chromatographically, was produced utilizing the Peterson type of reagent **24**.[36] A glucose derived substrate **26** was also

(28) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719 and earlier references cited therein. Also, see: Dilworth, B. M.; McKewey, M. A. *Tetrahedron* **1986**, *42*, 3731.

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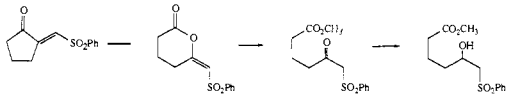
(31) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(32) It appears that the initial keto sulfone undergoes a Baeyer–Villiger type oxidation if the reaction is not carefully controlled based upon the tentative assignment of i for the byproduct after sodium borohydride reduction.




(33) Oxidation of sulfides to sulfones with perborate normally requires basic conditions, see: McKillop, A.; Tarbin, J. A. *Tetrahedron Lett.* **1983**, *24*, 1505.

(34) Cf.: Biellmann, J. F.; Jung, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 1673. Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. I* **1977**, 359.

(35) Shahak, I.; Almog, J. *Synthesis* **1970**, 145.

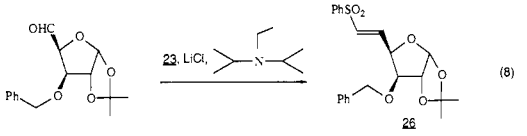
(36) Craig, D.; Ley, S. V.; Simpkins, N. *J. Chem. Soc., Perkin Trans. I* **1985**, 1949.

**Table I.** Effect of Alkoxy-Protecting Group on Diastereofacial Selectivity

| entry | acceptor | n | R | trans/cis[f] ratio | % conversion |
|---|---|---|---|---|---|
| 1 | **9a** | 1 | TBDMS[b] | 9/1 | 53 |
| 2 | **9a** | 1 | TBDMS | 9/1 | 30 |
| 3[a] | **9a** | 1 | TBDMS | 8.5/1 | 36 |
| 4 | **9d** | 1 | TIPS[c] | 5.5/1 | 35 |
| 5 | **9b** | 1 | TBDPS[d] | 5/1 | 40 |
| 6 | **9b** | 1 | TBDPS | 6.3/1 | 72 |
| 7 | **9c** | 1 | MOM[e] | 5.4/1 | 56 |
| 8 | **10a** | 2 | TBDMS | 4.6/1 | 50 |
| 9[a] | **10a** | 2 | TBDMS | 4/1 | 12 |
| 10 | **10b** | 2 | TBDPS | 3/1 | 40 |
| 11 | **10b** | 2 | TBDPS | 3/1 | 50 |
| 12 | **10c** | 2 | MOM | 8/1 | 54 |

[a] Catalyst used was $(Ph_3P)_4Pd$. [b] TBDMS = *tert*-butyldimethylsilyl. [c] TIPS = triisopropylsilyl. [d] TBDPS = *tert*-butyldiphenylsilyl. [e] MOM = methoxymethyl. [f] Facial attack of the TMM–$PdL_2$ with respect to the alkoxy group.

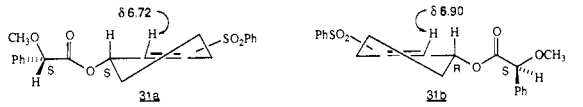
readily available utilizing olefination technology as outlined in eq 8.[37]




(8)

26

An alternative strategy envisions asymmetric introduction of the alkoxy group. A straightforward approach involves an asymmetric carbonyl reduction. Utilizing the procedure of Terashima,[38] which has been claimed to give a high ee in the reduction of cyclohexenone, both the sulfide **27** and the sulfone **28** were reduced to the corresponding alcohols **29** and **30** (R = H), respectively. For determination of the degree of asymmetric induction and of the absolute configuration, the alcohol **30** was converted to its *O*-methylmandelate ester.[39] The *O*-methylmandelate esters **31a** and **b**, derived from the racemic alcohol,

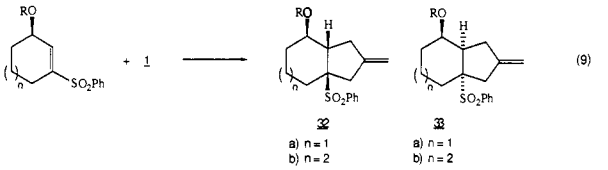



31a 31b

show the vinylic proton to absorb at $\delta$ 6.72 and $\delta$ 6.90, which permits the absolute configuration to be assigned as *S* and *R*, respectively. Comparison of **30b** with the above data reveals the major isomer possesses the *R* configuration. A higher ee was observed in the reduction of **27** (79% ee) than in the reduction of **28** (65% ee). A simple recrystallization of the silyl ether **30c** prepared via the sulfide **29** provides the acceptor **30c** of 93% ee. An attempt to prepare sulfide **29** via asymmetric hydroboration[40] of 1-(phenylthio)cyclohexa-1,3-diene failed.

Since racemization of the acceptor could occur by deprotonation at the activated allylic position during base-catalyzed acylations, silylations, or desilylations, a control sequence was performed as outlined in Scheme III. Beginning with γ-hydroxy-α,β-unsaturated sulfone of 79% ee delivered the final mandelate ester of the same enantiomeric excess. The robustness of the substrates toward racemization enhances their utility for asymmetric synthesis.

**Cycloadditions.** In complete contrast to cyclohexenone and cycloheptenone, the γ-alkoxy-α,β-unsaturated sulfones proved to be excellent substrates for the palladium-catalyzed trimethylenemethane cycloaddition. In an initial screening to probe the effect of the alcohol-protecting group on the diastereoselectivity, 1 equiv of TMM precursor **1**, and 1 equiv of the acceptor **9** or **10** were exposed to a catalyst made by mixing palladium acetate with triisopropyl phosphite, the latter serving as both reducing agent and ligand in toluene at 80 °C (eq 9 and Table I).

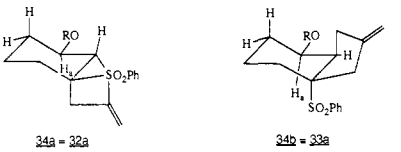



(9)

32 33

a) n = 1 a) n = 1
b) n = 2 b) n = 2

The stereochemistries of **32a** and **33a**, which are depicted conformationally in drawings **34a** and **34b**, respectively, are readily established by NMR spectroscopy. Both the chemical shift and

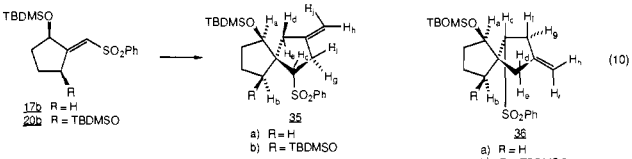



34a = 32a 34b = 33a

coupling constants of $H_a$ are diagnostic. This proton experiences a strong deshielding in the $^1H$ NMR spectrum of **34b** ($\delta$ 4.37) due to its proximity to the phenylsulfonyl group compared to **34a** ($\delta$ 3.19) and exhibits a splitting pattern consistent with only one trans diaxial coupling (dt, $J$ = 9.6, 5.6 Hz) in the spectrum of **34b**, compared to a pattern showing two trans diaxial couplings (td, $J$ = 9.3, 3.8 Hz) in the spectrum of **34a**. The close parallel of the $^1H$ NMR absorptions for the hydroxyl methine proton and for all the protons in the five-membered ring in the $^1H$ NMR spectra between **32b** and **33b** with the corresponding adducts in the six-membered ring series leads us to assign the major isomer as arising from attack anti to the alkoxy group in the seven-membered ring series, as well.

The trends are rather surprising. For example, whereas increasing the size of the silyl group might have been expected to give enhanced selectivity for attack on the face opposite that of the alkoxy group, exactly the opposite occurred (cf. entries 2, 4, and 5 as well as 8 vs 11). Normally, the ratio was independent of the degree of conversion (Table I, entry 1 vs 2 or 10 vs 11). Changing the catalyst ligands had no effect (entries 3 and 9).

The effect of olefin substitution on the diastereoselectivity was also examined. In conjunction with a program directed toward the ginkgolides, the question of the effect of α,β-dialkyl substitution as in substrates **9** and **10** vs β,β-dialkyl substitution as in substrates **17b** and **20b**, in terms of efficacy of cycloaddition as well as diastereoselectivity, becomes of prime importance. Gratifyingly, cycloadditions with both acceptors proceed under our preferred conditions utilizing triisopropyl phosphite as the catalyst ligand, whereas use of triphenylphosphine as ligand does not lead to cycloadducts.




(10)

17b R = H
20b R = TBDMSO

35 36

a) R = H a) R = H
b) R = TBDMSO b) R = TBDMSO

The monosiloxy acceptor **17b** reacts to give two diastereomeric adducts **35a** and **36a** in a 4.2:1 ratio in 61–7% yield at 70–85% conversion. In accord with our earlier observations, the downfield shift of $H_a$ in the minor adduct **36a** ($\delta$ 4.63) compared to the major adduct **35a** ($\delta$ 3.63) suggests the stereochemistry as depicted. NOE studies verify this assignment. Thus, a positive NOE is observed between $H_a$ and $H_d$ ($\delta$ 2.05, d, $J$ = 16 Hz) in the major adduct **35a** but between $H_a$ and $H_c$ ($\delta$ 3.42, m) in the minor adduct **36a**.

The disiloxy acceptor **20b** reacts to give a single detectable stereoisomer in 76% yield at 67% conversion. The close parallel

(37) Cf.: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(38) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* **1984**, 239.
(39) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
(40) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564.

**Table II.** $^1$H NMR Comparisons of Cycloadducts **35** and **36**[a]

| proton | 35a | 35b | 36a |
|---|---|---|---|
| a | 3.63, br d, $J$ = 4.0 Hz | 3.72, dd, $J$ = 7.6, 4.9 Hz | 4.63 t, $J$ = 9.1 Hz |
| b | N.D. | 4.52, t, $J$ = 3.5 Hz | N.D. |
| c | 3.96, dd, $J$ = 9.2, 2.1 Hz | 3.99, dd, $J$ = 7.6, 2.8 Hz | 3.42, m |
| d | 2.05, d, $J$ = 16 Hz | 1.90, d, $J$ = 16 Hz | 2.08, d, $J$ = 15.9 Hz |
| e | 2.65, dd, $J$ = 16.1, 1.8 Hz | 2.73, dq, $J$ = 16, 2.4 Hz | 2.68, d, $J$ = 15.9 Hz |
| f | 2.50, ddd, $J$ = 18.5, 9.2, 2.4 Hz | 2.38, ddq, $J$ = 17.7, 7.6, 2.2 Hz | N.D. |
| g | 2.76, d, $J$ = 18.6 Hz | 2.54, d, $J$ = 17.7 Hz | 2.87 m |
| h[b] | 4.87, br s | 4.87, br s | 4.82, br s |
| i[b] | 4.89, br s | 4.90, br s | 4.87, br s |

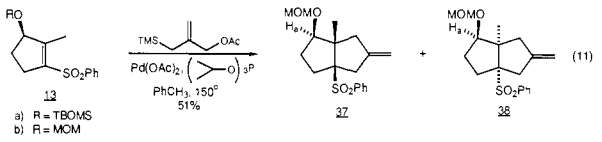
[a] At 400 MHz in $CDCl_3$. [b] These assignments may be reversed.

**Table III.** A Ratio of Cis/Trans Cycloadducts from *Z*-Acceptor **25**

| entry | catalyst | solvent | reaction time, h | reaction temp, °C | cycloadducts % yield | cycloadducts ratio 43:41 |
|---|---|---|---|---|---|---|
| 1 | 14% $(i\text{-}C_3H_7O)_3P$, 2% $Pd(OAc)_2$ | $PhCH_3$ | 10 | 50 | 79 | 1.5 |
| 2 | 14% $(i\text{-}C_3H_7O)_3P$, 2% $Pd(OAc)_2$ | $PhCH_3$ | 6 | 80 | 76 | 1.0 |
| 3 | 10% $(i\text{-}C_3H_7O)_3P$, 2% $(dba)_3Pd_2\cdot CHCl_3$ | $PhCH_3$ | 6 | 80 | 81 | 0.8 |
| 4 | 14% $(i\text{-}C_3H_7O)_3P$, 2% $Pd(OAc)_2$, 4% $n\text{-}C_4H_9Li$ | THF | 6 | 80 | 61 | 0.5 |
| 5 | 14% $(i\text{-}C_3H_7O_3)P$, 2% $Pd(OAc)_2$ | $PhCH_3$ | 24 | 80 | 80 | 0.5 |

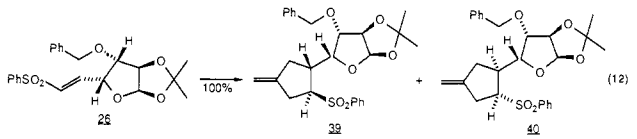
of the $^1$H NMR spectra of this cycloadduct to that of **35a** (see Table II) suggests the same stereochemistry and leads us to assign it to the structure **35b**. These are the first examples of $\beta,\beta$-dialkyl-substituted acceptors undergoing cycloaddition.

An $\alpha,\beta,\beta$-trialkyl-substituted acceptor tests the limits of this cycloaddition. While forcing conditions had to be employed (150 °C, toluene, sealed tube), a 51% yield of two diastereomeric cycloadducts in a 2:1 ratio was obtained for the MOM ether derivative (eq 11). The silyl ether **13a** gave unsatisfactory results.



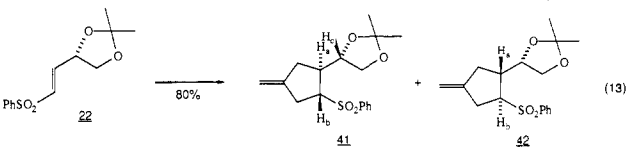

The assignment of stereochemistry was tentatively assigned as depicted in **37** and **38** for the major and minor adducts, respectively, based upon the downfield shift of $H_a$ in **38** ($\delta$ 4.06) compared to **37** ($\delta$ 3.55)—a correlation followed in all the other adducts. Subsequent correlations of these adducts with known compounds verified this assignment (vide infra).

Acyclic sulfones represent a greater challenge for diastereofacial selectivity. The carbohydrate derived (*E*)-sulfone **26** reacts quantitatively to give a 7.5:1 ratio of two cycloadducts (eq 12).



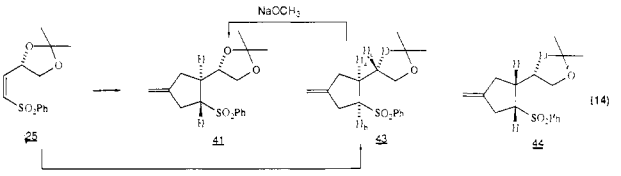

Upon the basis of the analogy to the cycloadduct derived from the substrate identical with **26** except bearing a methoxycarbonyl substituent as the electron-withdrawing group,[41] the major adduct is depicted as **39**.

The dependence of diastereofacial selectivity on the olefin geometry of the acyclic acceptor was examined.[42] The *E* acceptor **22** generated a 2:1 diastereomeric ratio of cycloadducts (eq 13).




The stereochemistry of the major and minor adducts were assigned as **41** and **42**, respectively, by analogy to the cycloaddition to the related acceptor bearing a carbomethoxy group including the observations of $J_{ab}$ = 8.5 and $J_{ac}$ = 4.6 Hz for **41**. The failure of base to interconvert **41** and **42** also indicates they differ in terms of the relative stereochemistry of the ring stereogenic centers compared to the side chain.

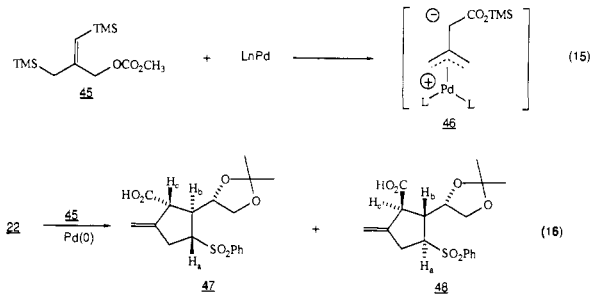
The *Z* acceptor **25** also generates two cycloadducts (eq 14).




One of the cycloadducts was identical with the major cycloadduct from the *E* acceptor, i.e., **41**. The other must be a cis-1,2-disubstituted cyclopentane **43** or **44**. Exposure of this second adduct to methanolic sodium methoxide converts it into diastereomer **41** exclusively in 96% yield. Thus, this adduct can differ from **41** only in the configuration of the carbon bearing the sulfone and, therefore, must be **43** ($J_{ab}$ = 7.95 and $J_{ac}$ = 8.52 Hz). Cycloadducts **41** and **43** arise by attack of the trimethylenemethane unit on the same diastereotopic face of the acceptor. Formation of the trans as well as the cis cycloadducts from the cis acceptor may arise by (1) equilibration of the starting olefin, (2) equilibration of the product, and/or (3) partitioning of an intermediate in the cycloaddition. The first explanation can be ruled out by the fact that the diastereofacial selectivity is markedly different between the *E* and *Z* acceptors. In particular, none of the diastereomer **42** is observed from the *Z* acceptor **25**. An examination of Table III suggests that explanation 2 must be at least partially responsible for the formation of the trans adduct **41**. A contribution from the third possibility, which invokes a rotation in an intermediate in a nonconcerted mechanism, cannot be dismissed.[43] The faithful translation of olefin geometry into the ring geometry of the acceptors related to **22** and **25** but bearing a methoxycarbonyl group as the activating substituent suggests this last possibility is less likely. *Synthetically, Z acceptor* ***25*** *can be converted into the single diastereomeric cycloadduct* ***41*** *in 71% overall yield by simply exposing the cycloaddition mixture of* ***41*** *and* ***43*** *directly to methanolic sodium methoxide*!

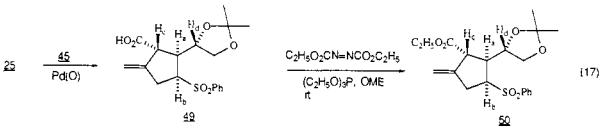
Support for the above interpretation derives from a study of the carboxylative cycloaddition with the *E* and *Z* acceptors **22** and **25**.[23] In this process, the disilyl conjunctive reagent **45** transiently generates the ((trimethylsiloxy)carbonyl)trimethylenemethane–palladium complex **46** (eq 15) in situ. Cycloaddition with the *E* acceptor under our usual conditions in dioxane generated a 3:2 ratio of diastereomeric adducts assigned as depicted in **47** and **48** (eq 16). The 9.0 Hz coupling for both

(41) Trost, B. M.; Lynch, J.; Renaut, P. *Tetrahedron Lett.* **1985**, *26*, 6313.
(42) Trost, B. M.; Mignani, S. M. *Tetrahedron Lett.* **1986**, *27*, 4137.



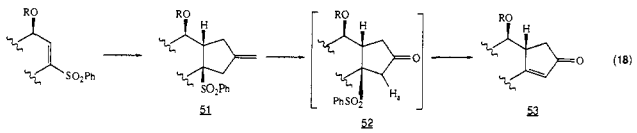
$J_{ab}$ and $J_{bc}$ and analogy to the methoxycarbonyl series suggests the trans,trans ring stereochemistry. As noted previously, the stereochemistry of the carboxylic acid substituent derives from equilibration under the conditions of the reaction and/or during workup. The adducts arise from attack on the two diastereotopic faces of the acceptor. Use of tetrakis(triphenylphosphine)palladium in toluene gave only **47** albeit in 32% yield.

On the other hand, performing a carboxylative methylenecyclopentannulation with the *Z* acceptor **25** produced a single adduct **49**, which also was characterized as its ethyl ester **50** (eq 17). The NMR spectral data (**49**: $J_{ab}$ = 6.5, $J_{ac}$ = 9.6, $J_{ad}$ =



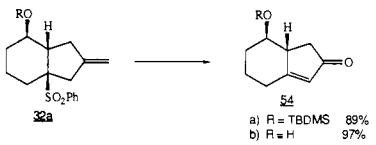
8.8 Hz; **50**: $J_{ab}$ = 7.1, $J_{ac}$ = 8.6, $J_{ad}$ = 8.6 Hz) in comparison to known compounds[17,20,23] indicates the stereochemistry depicted. Thus, complete diastereofacial selectivity is observed with the *Z*-acceptor in contrast to the *E*-acceptor. Furthermore, the reactions of the (siloxycarbonyl)trimethylenemethane–palladium complex are stereospecific, i.e., the olefin geometry of both the *E* and *Z* acceptors completely translates into ring geometry, in direct contrast to the cycloaddition of the parent trimethylenemethane complex with these same acceptors.

**A Cyclopentenone Annulation.** The juxtaposition of functionality in the adducts provides great flexibility. A possible cyclopentenone annulation as outlined in eq 18 provides a striking illustration of



this versatility and simplicity. Oxidative cleavage of the exocyclic methylene group of **51** to generate the ketone **52** simultaneously acidifies $H_a$ of **52** and, thereby, facilitates elimination of the elements of benzenesulfinic acid to give the cyclopentenone in only two operations from the γ-alkoxy-α,β-unsaturated sulfone.

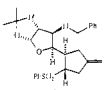
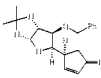
To illustrate, the cycloadducts **32a** (R = TBDMS and R = H) were exposed to ozone in methanol at −78 °C. Addition of dimethyl sulfide followed by triethylamine in the same pot decomposed the ozonide and effected the elimination to form the cyclopentenones **54a** and **54b** in excellent yields. Table IV summarizes our results.



The assignment of stereochemistry of **55** and **56** follows by comparison to the known compounds **61** and **62**.[44] The $^1$H NMR

absorptions for $H_a$ in **61** (δ 4.81, t, *J* = 9 Hz) and **62** (δ 5.02, d, *J* = 5 Hz) are diagnostic of the relative stereochemistry. The

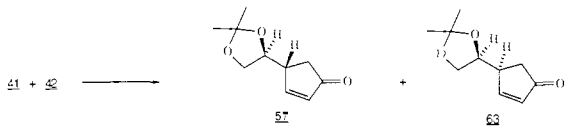
**Table IV.** A Cyclopentenone Synthesis[a]

| entry | cycloadduct | cyclopentenone | % isolated yield |
|---|---|---|---|
| |  |  | |
| 1 | *n* = 1, R = TBDMS | | 89 |
| 2 | *n* = 1, R = H | | 97 |
| 3 | *n* = 2, R = MOM | | 100 |
| 4 | *n* = 2, R = H | | 96 |
| 5 |  |  | 92 |
| 6 |  |  | 93 |
| 7d |  |  | 85 |
| 8 |  |  | 88 |
| 9[b,c] |  |  | 77 |
| 10[b] | **50** |  | 81 |

[a] All reactions were performed with ozone in methanol at −78 °C, followed by sequential addition of dimethyl sulfide and triethylamine unless otherwise noted. [b] Reaction performed in ethanol. [c] Sodium ethoxide (1 eqiv) utilized in lieu of triethylamine. [d] Reaction also performed on a 2:1 mixture of **41** and **42** to give **57** and its 4*S* epimer in 98% yield (both were characterized). Further, a 1:1 mixture of **41** and **43** was converted to **57** in 80% yield.

corresponding absorptions for **55** (δ 3.75, t, *J* = 8.6 Hz) and **56** (δ 3.87, d, *J* = 4.4 Hz) establish the relative stereochemistry as depicted, which, in turn, confirms our tentative assignment of the stereochemistry of the initial cycloadducts.

Ozonolysis of a 2:1 mixture of **41** and **42** (eq 13) produced a 2:1 mixture of the cyclopentenones **57** and **63** (eq 19), which was

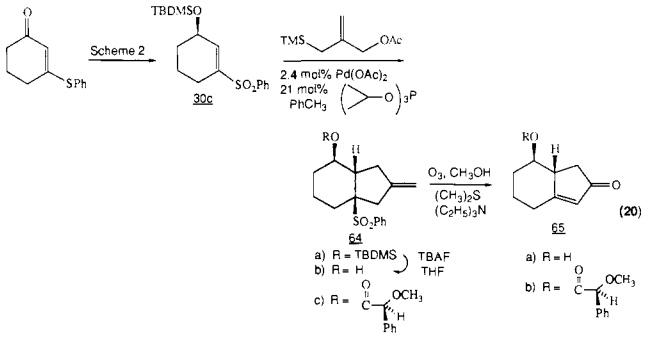


chromatographically separated. The major cyclopentenone was identical with that obtained by ozonolysis of the cycloadduct obtained from the *Z* acceptor after base equilibration (Table IV, entry 7), which provides further verification of the identity of the adducts and, therefore, of the diastereoselectivity of the cycloadditions to the *E* and *Z* acceptors **22** and **25**.

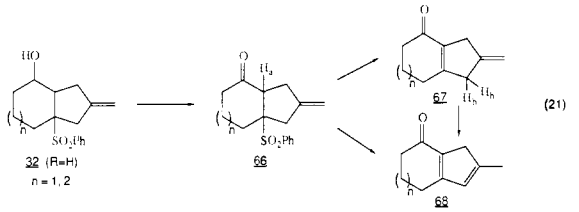
To prevent ester exchange, the ozonolysis of adduct **50** (eq 17) was performed in ethanol. The usual treatment with triethylamine produced the isomerized cyclopentenone **60** exclusively (Table IV, entry 10). Dropwise addition of exactly 1 equiv of sodium ethoxide and immediate workup allowed generation of the kinetic elimination product **59** without complications.

Because the cyclopentenones of entries 7–9 of Table IV derive from enantiomerically pure natural products, the overall sequence corresponds to an asymmetric cyclopentenone annulation. To demonstrate the feasibility of an asymmetric annulation from achiral starting materials, the acceptor **30c** of 93% ee available from achiral 3-(phenylthio)cyclohex-2-enone (Scheme II) was subjected to cycloaddition (70% yield), fluoride ion-promoted desilylation (84%), and olefin oxidative cleavage (85%) as outlined in eq 20. Converting the alcohol of the cycloadduct **64b** as well as the cyclopentenone **65a** into their *O*-methylmandelate esters allows us to assess their enantiomeric excess as identical with that

of the starting material, 93% ee. The availability of the acceptors in scalemic form[45] either from natural products or from asymmetric induction, as in eq 20, translates this route into an enantiocontrolled cyclopentenone annulation.




**γ-Alkoxy-α,β-Unsaturated Sulfones as Ynone Equivalents.** An alternative oxidation elimination sequence provides a different enone system, as outlined in eq 21. Unmasking a carbonyl group



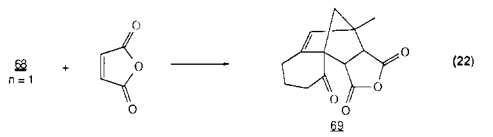

by oxidation of the alcohol labilizes $H_a$ of **66** to facilitate elimination to enone **67**. The latter enone still possesses somewhat acidic hydrogens, $H_b$, which may undergo base-catalyzed tautomerization to form the novel fused cyclopentadiene **68**.

The anticipated lability of the ketone **66** required the use of a mild, nearly neutral oxidizing agent. Chromic acid based oxidants proved marginal, as did the usual Moffatt–Swern conditions. However, when Hunig's base was substituted for triethylamine in the Moffatt–Swern protocol, satisfactory oxidation to the ketones **66** ($n$ = 1 and 2) occurred. Independent experiments revealed the sensitivity of these ketones to triethylamine but their stability toward Hunig's base. To optimize the reaction, reaction times and times of contact of the product with chromatographic absorbents must be minimized. In this way, the keto sulfones **66** $n$ = 1 and $n$ = 2 may be isolated in 68% and 93% yields, respectively.

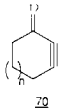
Treatment with bases such as triethylamine, DBU, or magnesium methoxide led to unacceptable mixtures of diene products, whereas milder bases like diisopropylethylamine led to no reaction. On the other hand, neutral alumina suspended in methylene chloride smoothly and cleanly effected elimination to the skipped dienones **67** $n$ = 1 and 2 without competing isomerization of the product. Only prolonged exposure to alumina effected appreciable isomerization of the kinetic elimination product **67**.

The fully conjugated dienone **68** arose upon further base-catalyzed rearrangements of the skipped dienone **67**. A more convenient approach involved direct conversion of ketosulfone **66** by its reaction with triethylamine in the presence of neutral alumina (**68** $n$ = 1, 84% yield) or with DBU in methylene chloride (**68**, $n$ = 2, 70% yield). While each compound in this sequence, including the fully conjugated dienone **68**, is labile towards base, it has been possible to exercise full control so that every intermediate may be isolated.

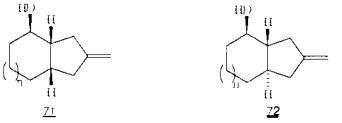
Even though the dienone **68** $n$ = 1 is deactivated, it functioned as a diene toward maleic anhydride to give the cycloadduct **69** without competing tautomerization (eq 22). The sequence of




acceptor **9** being converted into skipped dienone **67** corresponds to the acceptor being a structural synthon for the alkynone **70**.



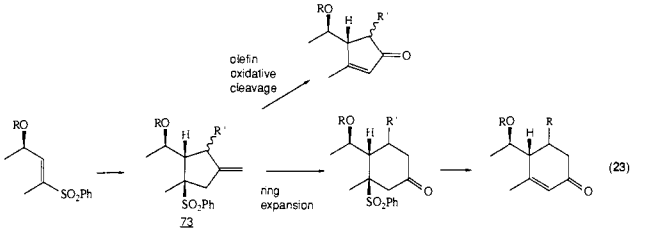

**Reductive Desulfonylation of the Cycloadducts.** To formalize the employment of this strategy as an equivalent of a cycloaddition to an enone, the reductive desulfonylation of the two hydroxysulfones **32** ($n$ = 1, R = H) and **32** ($n$ = 2, R = H) utilizing 6% sodium (amalgam) in buffered methanol was performed. In both cases, desulfonylation proceeded readily (68–81%) even though




the sulfone was bonded to a fully substituted carbon. VPC analysis revealed a 2:1 mixture of **71** and **72** for $n$ = 1 and a 1:1 mixture for $n$ = 2. The major isomer in the former case is tentatively assigned as cis fused on the expectation that protonation should be less hindered from the convex face of the bicyclic nucleus which, incidentally, generates the thermodynamically more stable product.

## Discussion

The continuing development of annulation protocols provides increasingly more powerful and versatile synthetic tools and, subsequently, simplified synthetic strategy to complex molecules.[48] The development of (1) a diastereoselective cyclopentannulation on the equivalent of an enone, (2) a diastereo- and an enantioselective cyclopentenone annulation, and (3) a novel cyclopentadienyl annulation should enhance the accessibility of such five-membered ring compounds. In addition, since methylenecyclopentanes can be ring expanded to six-membered rings by numerous methods based upon pinacol-like rearrangements,[49] we can envision partitioning our cycloadducts **73** to create either a cyclopentenone or a cyclohexenone annulation (eq 23).



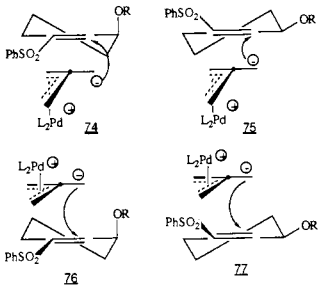

The γ-alkoxy-α,β-unsaturated sulfones qualitatively appear to be exceptionally good acceptors for trimethylenemethane–palladium complexes. The presence of the electronegative γ-alkoxy group presumably enhances the electrophilicity of this class of acceptors.[24] The stereochemistry of addition anti to the alkoxy

(43) Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.
(44) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Am. Chem. Soc.* **1982**, *47*, 2820.
(45) Suggestion of Professor James Brewster to describe an unequal mixture of enantiomers as detailed in the following: Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.
(46) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(47) For use of α-alkoxy-α,β-unsaturated sulfones as an approach to enones by alcohol oxidation and elimination see 24c.
(48) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
(49) For an example, see: Fareasiu, D.; Schleyer, P. R.; Ledlie, D. B. *J. Org. Chem.* **1973**, *38*, 3455. For reviews, see: Gutsche, D. C.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Academic: New York, 1968; Chapter 4. Cowell, G. W.; Ledwith, A. *Quart. Rev.* **1970**, *24*, 119. Pizey, J. S. *Synthetic Reagents*; Ellis Horwood Ltd.: Chichester, U. K., 1974; Vol. 2, pp 102–8. Also see azide based methods: Wohl, R. A. *J. Org. Chem.* **1973**, *38*, 3862. McMurry, J. E.; Coppolino, A. P. *J. Org. Chem.* **1973**, *38*, 2821. McMurry, J. E.; Swenson, R. *Tetrahedron Lett.* **1987**, *28*, 3209.

group is expected based upon analogy to simple organometallics.[24,50] Experimental and theoretical studies support the general notion that a nucleophile should add anti to oxygen as a result of electronic effects.[51] On the other hand, the specific attacking reagent utilized herein is zwitterionic. An attractive interaction between the lone pairs on oxygen and the cationic domain of the attacking reagent could lead to a templating effect depending upon the nature of the oxygen substituent. Indeed, such a templating effect had been noted by Fuchs et al.[24,50] The lower diastereoselectivity for addition trans to the alkoxy group for the silyl ether **9a** compared to the MOM ether **9c** might have been interpreted in this way. The reverse trend in the seven-membered ring, however, undermines such an argument.

On the other hand, analogy to nucleophilic additions for our cycloaddition may not be appropriate. We have debated the question of the mechanism of this methylene cyclopentannulation in terms of an asynchronous concerted vs stepwise process. Our most recent data suggest the latter, in spite of the many similarities of this cycloaddition to the Diels–Alder reaction.[42,43] Even allowing for a stepwise pathway, the geometry of approach of our reactive intermediate may more closely parallel the geometry of an asynchronous cycloaddition than that of simple nucleophilic attack.

If we assume a syn-like geometry of the TMM–$PdL_2$ and acceptor, four diastereomeric transition states **74–77** are possible.



Of the four, the transition state depicted in **76** encounters sufficiently unfavorable steric interactions that it is rather unlikely. Transition states **74** and **75** involve attack anti to the alkoxy group—a stereochemistry that translates into the major cycloadduct. Stereoelectronic considerations in additions to olefins in six-membered rings favor formation of an axial rather than an equatorial bond. For this reason, we favor **74** as depicting the favored transition state leading to our major product.

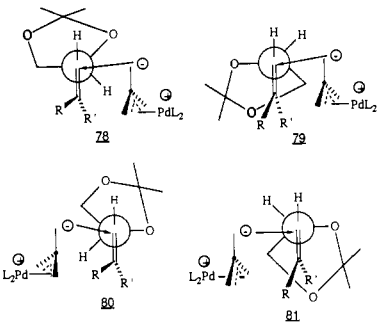
On the other hand, the transition state depicted in **77** also corresponds to the favored axial attack. Further, the syn orientation of the TMM–$PdL_2$ species with respect to the acceptor moves the attacking species away from the alkoxy group and, thereby, minimizes unfavorable steric interactions between the two. Reaction via **77** should then correlate with the preference for the alkoxy group to be equatorial rather than axial.

The conformation possessing the alkoxy group in an axial orientation should be less stable for steric and electronic reasons.[52] Nevertheless, its accessibility in the ground state is suggested by the NMR spectra of **9a–d** ($n$ = 1). The proton ipso to the alkoxy group appears as a multiplet with a half-band width of 13.5 Hz—an observation that indicates a mobile equilibrium between the two half-chair conformations. The energetic accessibility of a conformer having an axial alkoxy group, the minimization of repulsive effects between this substituent and the attacking negative end of the zwitterion, and the favorability of forming an axial bond with the six-membered ring favors reaction via **74** and accounts for our major product.

As the size of the oxygen substituent increases, a transition state requiring the alkoxy group being axial starts to become disfavored relative to one having this substituent equatorial.[53] Of the two transition states having such a stereochemistry, stereoelectronic factors favor **77** over **75**. This effect accounts for the seemingly contradictory observation that the diastereofacial selectivity for attack anti to the oxygen substituent *decreased* as its steric bulk *increased*. For optimum results, we must balance these two opposing effects. Molecular mechanics calculations for the seven-membered ring series reveal that similar arguments may be valid to account for the diastereofacial selectivity observed in this series.

We attribute the low diastereoselectivity in the tetrasubstituted five-membered ring example **13** to the high temperatures required for cycloaddition. The related $\beta,\beta$-disubstituted acceptors **17** and **20** show very good to excellent diastereoselectivity, but both reactions were possible at lower temperatures.

The good to excellent diastereoselectivity observed in the acyclic cases extends the usefulness of this ring-forming reaction substantially. Of particular note is the dependence of the diastereofacial selectivity on olefin geometry.[42,54] Examination of the four most likely rotamers that could lead to cycloaddition reveals conformers **79** and **80** encounter the severest nonbonded interactions between the attacking species and the substrate. Transition states depicted by **78** and **81** lead to opposite diastereofacial selectivity. It becomes apparent that **81** is strongly disfavored when R′ is a bulky substituent, as it is in the $Z$ acceptor but not in the $E$ acceptor. Transition state **78** best minimizes all nonbonded interactions in the cycloaddition with the $Z$ acceptor and accounts for the exclusive formation of a single diastereofacial isomer.



It is interesting to note the comparison between this cycloaddition and a related Diels–Alder reaction. While an early report[55] indicated a high facial selectivity with a related dienophile for both a $Z$ and the corresponding $E$ isomer, a recent report corrects the latter to a facial selectivity of 3–4:1.[56] The very similar facial selectivity in our [3 + 2] cycloaddition may suggest a similar geometric array in accord with the syn array we have proposed.

The synthetic accomplishment of the diastereoselective cyclopentannulation and carboxylative cyclopentannulation with acyclic

(50) Barton, D. L.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.* **1980**, *21*, 1811. Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 915.

(51) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, 1. (b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. (c) Houk also describes the effectiveness of an alkoxy group in withdrawing electron density from a $\pi$-system when the allylic C–O bond is parallel to the $\pi$-system, see: Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Roudan, N. G.; Jager, V.; Schohe, R.; Fronczeck, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (d) For Diels–Alder reactions with acceptors bearing $\gamma$-alkoxy groups, see: Franck, R. W.; John, T. V.; Olejniczak, K.; Blount, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 1106. Schmidlin, T.; Burckhardt, P. E.; Waespe-Sarevic, N.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 450. Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. (e) Contrast: Horton, D.; Machinsmi, T.; Takagi, Y. *Carbohydrate Res.* **1983**, *121*, 135. (f) For nucleophilic additions to such acceptors, see: Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231. Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009. Mulzer, J.; Kappert, M.; Huttner, G.; Jibul, I. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 704.

(52) Lessard, J.; Tan, P. V. M.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015. Lessard, J.; Saunders, J. K.; Viet, M. T. P. *Tetrahedron Lett.* **1982**, *23*, 2059. Zefirov, N. S.; Baranenkov, I. V. *Tetrahedron* **1983**, *39*, 1769.

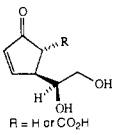
(53) Cf. ref. 51b.

(54) For an example of the dependence of diastereofacial selectivity on olefin geometry in a nucleophilic addition, see: Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525.

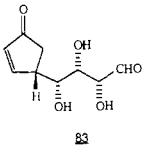
(55) Mulzer, J.; Kappert, M.; Hultner, G.; Jibul, I. *Tetrahedron Lett.* **1985**, *26*, 1631.

(56) Takano, S.; Sugihara, T.; Samizu, K.; Ogasawara, K. *Heterocycles* **1988**, *27*, 2103.

acceptors involves multiplication of the number of stereogenic centers with control. For example, structures such as **82** and **83**




**82**




**83**

may derive from **57** or **59** and **58**, respectively. These advantages for five-membered ring construction speak to the utility of seeking new cycloaddition strategies for ring construction. The expansion of the scope of five-membered ring annulations and the extension of the synthetic benefits to other ring sizes remains a continuing challenge.

## Experimental Section

**Preparation of Acceptors. General Methods.** Substrates **9** and **10** were prepared by the method of Fuchs.[24] The *Z* acceptor **25** from the acetonide of (*R*)-glyceraldehyde was prepared by the method of Ley.[36]

**3-(Methoxymethoxy)-1-(phenylsulfonyl)cycloheptene (10c).** A solution of 2.0 g (7.92 mmol) of 3-(phenylsulfonyl)cycloheptene oxide[24] and 0.15 mL of DBU in 5 mL of DMF was heated at 80 °C until TLC showed disappearance of starting material. After cooling to room temperature, 8.3 mL (48 mmol) of diisopropylethylamine and 2.2 mL (29 mmol) of chloromethyl methyl ether were added. After 15 h, 30 mL of water was added, and the reaction mixture was extracted with ether. The ether extracts were washed with saturated aqueous ammonium chloride (3 times), water, and brine. After drying ($MgSO_4$) and concentration in vacuo, flash chromatography (1:1 hexane/ethyl acetate, $R_f$ 0.57) gave 1.84 g (78%) of the product: IR ($CDCl_3$) 3062, 2938, 2890, 2859, 1445, 1302, 1146, 1122, 1082, 1030 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.8–7.9 (m, 2 H), 7.45–7.65 (m, 3 H), 7.21 (m, 1 H), 4.67 (s, 2 H), 4.38 (m, 1 H), 3.36 (s, 3 H), 2.49 (dd, $J$ = 16.3, 6.4 Hz, 1 H), 2.15 (m, 1 H), 1.8–2.0 (m, 2 H), 1.5–1.7 (m, 3 H), 0.9–1.1 (m, 1 H); calcd for $C_{15}H_{20}O_4S$ 296.1078, found 296.1101.

**3-Alkoxy-2-methyl-1-(phenylsulfonyl)cyclopentene. (a) 2-Methyl-3-(phenylsulfonyl)cyclopent-2-en-1-one (12).** To a suspension of 2-methylcyclopentane-1,3-dione (500 mg, 4.46 mmol) in 5 mL of dry acetonitrile at 0 °C was added diisopropylethylamine (0.633 g, 4.90 mmol) followed by methanesulfonyl chloride (0.561 g, 4.90 mmol). After 15 min at 0 °C, the now homogeneous mixture was treated with an additional 0.633 g (4.90 mmol) of diisopropylethylamine and 0.539 g (4.9 mmol) of thiophenol. When TLC indicated completion of the reaction (~1 h), 25 mL of water was added. After extraction with 2 × 50 mL portions of ether, drying, and evaporation in vacuo, 880 mg of the crude vinyl sulfide **11** was isolated, $R_f$ 0.48 (2:1 hexane/ethyl acetate): $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.5–7.6 (m, 2 H), 7.3–7.45 (m, 3 H), 2.31 (m, 4 H), 1.77 (t, $J$ = 1.65 Hz, 3 H).

Oxone (4.11 g, 3 equiv) was added to a solution of 880 mg of the crude sulfide in 30 mL of methanol and 30 mL of water. After stirring overnight at room temperature, the reaction mixture was extracted with methylene chloride (2 × 50 mL), and the latter was washed with water and with saturated aqueous sodium chloride and dried ($MgSO_4$). Rotary evaporation and flash chromatography (ether) gave 832 mg (78%) of an oil that solidified, mp 54–6 °C: IR ($CDCl_3$) 1720, 1585, 1322, 1308, 1150, 1100 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.9–8.0 (m, 2 H), 7.5–7.75 (m, 3 H), 2.65–2.75 (m, 2 H), 2.45–2.50 (m, 2 H), 2.10 (t, $J$ = 2.3 Hz, 3 H); calcd for $C_{12}H_{12}O_3S$ 236.0507, found 236.0502.

**(b) 2-Methyl-3-(phenylsulfonyl)cyclopent-2-en-1-ol (13, R = H) and Derivatives.** Cerium chloride hydrate (633 mg, 1.7 mmol) and sodium borohydride (64 mg, 1.7 mmol) were added to a solution of 400 mg (1.7 mmol) of ketosulfone **12** in 4 mL of methanol at room temperature. After 15 min, the reaction was diluted with 15 mL of water and extracted with ethyl acetate. The organic phase was washed with water and saturated aqueous sodium chloride and dried ($MgSO_4$). Evaporation in vacuo gave 380 mg (94%) of a colorless oil: IR ($CDCl_3$) 3602, 3488, 1640, 1300, 1142 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.85–7.95 (m, 2 H), 7.5–7.7 (m, 3 H), 4.66 (m, 1 H), 2.2–2.7 (m, 3 H), 2.22 (m, 3 H), 1.85 (br s, 1 H), 1.55–1.75 (m, 1 H); calcd for $C_{12}H_{14}O_3S$ 238.0664, found 238.0667.

The silyl ether was prepared in standard fashion from 96 mg (0.40 mmol) of alcohol, 60 mg (0.88 mmol) of imidazole, and 67 mg (0.44 mmol) of *tert*-butyldimethylsilyl chloride in 1 mL of dry DMF to give 107 mg (82%) of the product **13a** as a solid, mp 64–5 °C, after flash chromatography (2:1 hexane/ethyl acetate): IR ($CDCl_3$) 1645, 1470, 1462, 1448, 1350, 1315, 1300, 1148, 1110 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.85–7.95 (m, 2 H), 7.45–7.65 (m, 3 H), 4.65 (td, $J$ = 7.2, 1.1 Hz, 1 H), 2.1–2.7 (m, 3 H), 2.15 (m, 3 H), 1.5–1.7 (m, 1 H), 0.89 (s, 9 H), 0.084 (s, 3 H), 0.057 (s, 3 H); calcd for $C_{17}H_{25}O_3SSi$ ($M^+$ − 15) 337.1294, found 337.1291.

The MOM ether was prepared in standard fashion from 198 mg (0.83 mmol) of alcohol **13** (R = H) and 335 mg (1.82 mmol) of methoxymethyltriethylammonium chloride in 2 mL of dry acetonitrile at reflux to give 207 mg (88%) of solid, mp 32–3 °C after flash chromatography (2:1 hexane/ethyl acetate): IR ($CDCl_3$) 1498, 1318, 1304, 1149, 1108 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.87 (m, 2 H), 7.5 (m, 3 H), 4.70 (d, $J$ = 6.8 Hz, 1 H), 4.65 (d, $J$ = 6.8 Hz, 1 H), 4.56 (br t, $J$ = 7.2 Hz, 1 H), 3.37 (s, 3 H), 2.39–2.64 (m, 2 H), 2.25 (m, 1 H), 2.21 (td, $J$ = 2.0, 1.2 Hz, 3 H), 1.6–1.85 (m, 1 H); calcd for $C_{14}H_{18}O_4S$ 282.0926, found 282.0912.

**2-((Phenylsulfonyl)methylidene)cyclopentan-1-ol, 2-((Phenylsulfonyl)methylidene)cyclopentan-1,3-diol, and Derivatives (17a and 20). (a) 2-(Bis(Phenylthio)methyl)cyclopentanone (14).** To a cooled solution (−50 °C) of 5.682 g (16.69 mmol) of tris(phenylthio)methane in 55 mL of dry dichloromethane was added a solution of 1.75 mL (3.895 g, 14.95 mmol) of anhydrous stannic chloride in 27 mL of dry dichloromethane. The formed yellow reaction mixture was immediately treated with a solution of 2.37 g (15.17 mmol) of 1-(trimethylsiloxy)cyclopentene in 27 mL of dry dichloromethane, and the mixture was stirred at −50 °C for 35–40 min. The mixture was then poured onto ice water, and, after phase separation, the water phase was extracted with dichloromethane twice. The combined organic layers were washed with water, dried ($Na_2SO_4$), and evaporated to yield 10.57 g of a mixture of the thioacetal **14** and excess tris(phenylthio)methane. Chromatography (6:1 hexane/ethyl acetate) yielded 3.915 g (82%) of pure thioacetal as a colorless solid, mp 40–2 °C (ether–hexane) and a mixed fraction (0.327 g) which contained 25% of **14** and 75% of **15** according to VPC for a calculated total conversion of >90%: IR ($CCl_4$) 1750, 1590, 1485, 1443, 1410 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.51–7.44 (m, 2 H), 7.39–7.34 (m, 2 H), 7.32–7.22 (m, 6 H), 4.95 (d, $J$ = 3.2 Hz, 1 H), 2.63 (td, $J$ = 8.5, 3.2 Hz, 1 H), 2.39–2.32 (m, 2 H), 2.30–2.00 (m, 3 H), 1.74 (m, 1 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 217.26, 134.29, 134.06, 132.65, 132.59, 129.04, 128.92, 127.94, 59.27, 53.30, 39.07, 25.27, 20.40; calcd for $C_{18}H_{18}OS_2$ 314.0800, found 314.0810.

**(b) 2-((Phenylthio)methylidene)cyclopentanone (15).** To a cooled solution (0 °C) of 996.5 mg (3.17 mmol) of thioacetal **14** in 30 mL of dry dichloromethane was added by syringe 511 mg (3.36 mmol) of neat DBU. After stirring for 10 min at 0 °C, the mixture was diluted with dichloromethane and washed successively with water, 1% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried ($Na_2SO_4$), and the solvent was removed in vacuo. The residue was immediately flash chromatographed (6:1 hexane/ethyl acetate) to yield 0.587 g (91%) of an oil, which was crystallized from ethyl acetate, mp 77–78 °C, $R_f$ 0.4 (4:1 hexane/ethyl acetate): IR ($CCl_4$) 1705, 1595, 1585, 1485, 1445, 1288, 1193 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (t, $J$ = 2.5 Hz, 1 H), 7.50–7.44 (m, 2 H), 7.40–7.32 (m, 3 H), 2.64 (td, $J$ = 7.3, 2.5 Hz, 2 H), 2.38 (t, $J$ = 7.8 Hz, 2 H), 2.02 (p(tt), $J$ = ca. 7.6 Hz, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 203.66, 135.72, 133.45, 133.38, 130.65, 129.38, 128.14, 38.43, 28.18, 19.52; calcd for $C_{12}H_{12}OS$ 204.0609, found 204.0607.

**(c) 2-((Phenylsulfonyl)methylidene)cyclopentanone (16).** A buffered oxone solution was prepared by addition of 23 mL of a pH 10 borate buffer to a suspension of 1.81 g (5.89 mmol) of oxone suspended in 4 mL of water to give a final pH of 5.5–6.0. This solution was added, under vigorous stirring, to a solution of 173 mg (0.847 mmol) of sulfide **15** in 20 mL of methanol. After 1.5 h, 200 mg (6.50 mmol) of oxone was added, and the mixture was stirred for another 30 min at room temperature, after which time the conversion was completed. The reaction mixture was diluted with chloroform and water, and the latter layer was extracted again with chloroform. The combined organic layers were washed with brine, and the solvent was evaporated in vacuo to yield 182.7 mg (91%) of crude product, almost pure on TLC. Flash chromatography on florisil (1:1 hexane/ethyl acetate) yielded 150.1 mg (75%) of sulfone **16** as an oil, which was crystallized from ether, mp 61–62 °C, $R_f$ 0.54 (1:1 hexane/ethyl acetate): IR ($CDCl_3$) 1740, 1335, 1317, 1160, 1128, 1092 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.96–7.90 (m, 2 H), 7.70–7.63 (m, 1 H), 7.60–7.54 (m, 2 H), 6.92 (t, $J$ = 3.0 Hz, 1 H), 3.20 (td, $J$ = 7.4, 3.0 Hz, 2 H), 2.40 (t, $J$ = 7.8 Hz, 2 H), 2.05 (p(tt), $J$ = 7.6 Hz, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 205.82, 146.74, 140.14, 134.05, 129.87, 129.41, 127.61, 37.37, 27.80, 19.31; calcd for $C_{12}H_{12}O_3S$ 236.0507, found 236.0504.

**(d) 2-((Phenylsulfonyl)methylidene)cyclopentan-1-ol (17a) and Its Silyl Ether 17b.** Cerium chloride heptahydrate (973.2 mg, 2.612 mmol) and sodium borohydride (98.73 mg, 2.612 mmol) were added sequentially to a solution of ketone **16** (617.2 mg, 2.612 mmol) in 11 mL of dry methanol at room temperature. After 5 min the reaction was quenched by dropwise addition of 1 N aqueous hydrochloric acid until the pH reached 2. The reaction mixture was poured onto saturated aqueous

sodium chloride and extracted twice with methylene chloride. The organic layer was dried ($Na_2SO_4$) and evaporated in vacuo to yield 593.2 mg (95.3%) of allyl alcohol **17a**, pure according to TLC, $R_f$ 0.28 (1:1 hexane/ethyl acetate) and VPC: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93–7.88 (m, 2 H), 7.63–7.58 (m, 1 H), 7.57–7.50 (m, 2 H), 6.47–6.44 (m, 1 H), 4.48 (bt, $J$ = ca. 3.3 Hz, 1 H), 2.97–2.80 (m, 2 H), 2.40–2.15 (m, br, 1 H), 2.13–2.04 (m, 1 H), 1.95–1.85 (m, 1 H), 1.67–1.44 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.28, 141.34, 133.11, 129.01, 126.89, 122.27, 76.09, 33.54, 28.17, 20.45, 17.98, 14.97.

The above material (593.2 mg, 2.489 mmol) was silylated in standard fashion with TBDMS-Cl (1.5 g, 9.957 mmol), imidazole (1.356 g, 19.91 mmol), and DMAP (48 mg, 0.393 mmol) in 4 mL of DMF at room temperature for 40 h to give, after flash chromatography (4:1 hexane/ethyl acetate) 750.9 mg (88.6%) of pure acceptor **17b**, $R_f$ 0.63 (2:1 hexane/ethyl acetate): IR ($CCl_4$) 2950, 2925, 2852, 1641, 1445, 1322, 1255, 1145, 1085, 965 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93–7.88 (m, 2 H), 7.63–7.57 (m, 1 H), 7.56–7.00 (m, 2 H), 6.31–6.28 (m, 1 H), 4.43 (t, br, $J$ = ca. 8 Hz, 1 H), 2.82 (m, 2 H), 1.98 (m, 1 H), 1.84 (m, 1 H), 1.63–1.52 (m, 1 H), 1.51–1.40 (m, 1 H), 0.86 (s, 9 H), 0.055 (s, 3 H), 0.048 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.18, 141.94, 133.05, 129.07, 126.98, 122.16, 76.94, 33.91, 27.54, 25.68, 20.22, 17.95, −3.63, −4.93; calcd for $C_{14}H_{19}O_3SSi$ ($M^+$ − t-$C_4H_9$) 295.0824, found 295.0817.

**(e) 2-((Phenylsulfonyl)methylidene)cyclopentane-*cis*-1,3-diol Silyl Ether 20b.** A solution of alcohol **17a** (429.4 g, 1.802 mmol) in 6 mL of dry *tert*-butyl alcohol, to which was added 160 mg (1.426 mmol) of potassium *tert*-butoxide, was stirred 15 min at room temperature. The reaction was quenched by pouring into water and acidifying to pH 4 by dropwise addition of saturated aqueous sodium bisulfate. The resulting mixture was extracted twice with dichloromethane, and the combined organic layers were washed with brine. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography (1:1 hexane/ethyl acetate plus 4% methanol, $R_f$ 0.32) to yield 276.1 mg (64%) of isomerized allyl alcohol **18**: IR ($CH_2Cl_2$) 3500 (br), 1585, 1475, 1445, 1395, 1305 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90–7.85 (m, 2 H), 7.68–7.62 (m, 1 H), 7.50–7.60 (m, 2 H), 5.747 (br s, 1 H), 4.778 (m, 1 H), 4.08 (d, $J$ = 14 Hz, 1 H), 3.91 (d, $J$ = 14 Hz, 1 H), 2.95–2.50 (m, 1 H), 2.48–2.36 (m, 1 H), 2.35–2.15 (m, 2 H), 1.78–1.70 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.21, 138.09, 133.66, 132.89, 128.89, 128.07, 77.21, 55.54, 33.33, 29.99.

To a solution of the above allyl alcohol (225.4 mg, 0.946 mmol) and vanadyl acetylacetonoate (7.52 mg, 0.028 mmol) was added 0.15 mL of 90% *tert*-butyl hydroperoxide. VPC showed 23% starting material after 40 h at room temperature. Therefore, an additional 2 mg of catalyst and 0.05 mL of peroxide were added, and stirring was continued for an additional 6 h. The reaction was diluted with dichloromethane and the resultant solution washed with 1 M aqueous sodium sulfite and brine. Drying ($Na_2SO_4$) and evaporation in vacuo yielded 221.5 mg of a crude product which was 65% pure epoxy alcohol **19a** by VPC. The crude product mixture was directly carried on.

Standard silylation of the entire sample from above, as described for the preparation of **17b**, gave after flash chromatography (4:1 hexane/ethyl acetate containing 0.5% methanol) 159.5 mg (46% overall) of pure epoxide **19b**: IR ($CCl_4$) 1327, 1254, 1155, 1123, 939, 870, 837 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95–7.85 (m, 2 H), 7.73–7.65 (m, 1 H), 7.65–7.50 (m, 2 H), 4.43 (t, $J$ = 8 Hz, 1 H), 3.942 (d, $J$ = 14.6 Hz, 1 H), 3.347 (s, 1 H), 3.143 (d, $J$ = 14.6 Hz, 1 H), 1.984 (dd, $J$ = 8.2, 14 Hz, 1 H), 1.78–1.68 (m, 1 H), 1.67–1.55 (m, 1 H), 1.36–1.25 (m, 1 H), 0.892 (s, 9 H), 0.114 (s, 3 H), 0.065 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 139.698, 134.02, 129.377, 127.769, 73.813, 61.857, 58.58, 55.484, 26.807, 25.715, 25.563, 24.895, −4.601, −4.908.

An etheral solution (2 mL) of 0.278 mmol of LDA was added to a solution of epoxysulfone **19b** (129 mg, 0.35 mmol) in 2 mL of ether at 0 °C. After 15 min, the reaction mixture was poured into water, the pH was adjusted to 3 by dropwise addition of aqueous sodium bisulfate, and the resultant solution was extracted twice with ether. The combined ether layers were washed with brine, dried ($Na_2SO_4$), and evaporated in vacuo to yield 110.1 mg (85%) of product **20a** which was pure by TLC (4:1 hexane/ethyl acetate containing 0.5% methanol, $R_f$ 0.31) and VPC: IR ($CCl_4$) 3520, 1450, 1324, 1265 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95–7.90 (m, 2 H), 7.70–7.50 (m, 3 H), 6.30 (m, 1 H), 5.05 (d, $J$ = 6.1 Hz, 1 H), 4.39 (m, 1 H), 4.089 (s, 1 H), 2.02–1.83 (m, 3 H), 1.80–1.65 (m, 1 H), 0.843 (s, 9 H), 0.047 (s, 3 H), 0.037 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.035, 140.76, 133.63, 129.38, 127.19, 125.12, 76.36, 68.50, 31.75, 29.67, 25.66, 17.98, −4.36, −4.82.

The above alcohol was silylated as described for the preparation of **17b** to give, after 72 h reaction time and flash chromatography (4:1 hexane/ethyl acetate containing 0.5% methanol, $R_f$ 0.61), 106.7 mg (74%) of pure acceptor **20b**: IR ($CCl_4$) 2950, 2925, 2855, 1470, 1445, 1328, 1308, 1264, 1200, 1151, 1085, 1040, 1003, 923, 875, 837 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97–7.90 (m, 2 H), 7.63–7.45 (m, 3 H), 6.207 (m, 1 H), 5.42 (d, $J$ = 4.5 Hz, 1 H), 4.39 (td, $J$ = 7.6, 2 Hz, 1 H), 1.95–1.85 (m, 3 H), 1.62–1.50 (m, 1 H), 0.904 (s, 9 H), 0.818 (s, 9 H), 0.162 (s, 3 H), 0.128 (s, 3 H), 0.028 (s, 3 H), 0.012 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.065, 141.485, 132.955, 128.861, 127.095, 125.193, 76.116, 68.442, 32.421, 30.995, 25.924, 25.775, 25.647, 18.067, 17.916, −2.993, −4.055, −4.267, −4.544; calcd for $C_{20}H_{33}O_4SSi_2$ ($M^+$ − t-$C_4H_9$) 425.1638, found 425.1644.

**3(*S*),4-Dihydroxy-1-(phenylsulfonyl)-(*E*)-1-butene Acetonide (22).** Diethyl (phenylsulfonyl)methanephosphonate[35] (10.2 g, 35 mmol) in 50 mL of THF was treated with 3.70 g (33 mmol) of potassium *tert*-butoxide at 0 °C. After cooling to −78 °C, the acetonide of *R*-glyceraldehyde (4.0 g, 30 mmol) in 15 mL of THF was added dropwise, and the reaction was stirred 2 h. The reaction was quenched by addition of aqueous sodium bisulfate and warmed to room temperature. Extraction with ether, washing the ether extracts with water and brine, drying the ether extracts ($MgSO_4$), evaporation in vacuo of these extracts, and flash chromatography gave 4.05 g (50%) of *E*-acceptor **22** (*c* 0.0115, $CHCl_3$), $[\alpha]_D^{25}$ + 14.08°: IR ($CDCl_3$) 1449, 1375, 1318, 1308, 1223, 1145, 1085 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.85–7.95 (m, 2 H), 7.48–7.69 (m, 3 H), 6.95 (dd, $J$ = 14.9, 4.4 Hz, 1 H), 6.65 (dd, $J$ = 14.9, 1.5 Hz, 1 H), 4.72 (m, 1 H), 4.21 (dd, $J$ = 8.4, 6.8 Hz, 1 H), 3.70 (dd, $J$ = 8.4, 7.0 Hz, 1 H), 1.41 (s, 3 H), 1.38 (s, 3 H); calcd for $C_{12}H_{13}O_4S$ ($M^+$ − $CH_3$) 253.0534, found 253.0469.

**3-*O*-Benzyl-5,6-dideoxy-(*E*)-5,6-didehydro-1,2-*O*-isopropylidene-α-D-gluco-1,4-furanose 26.** A solution of 5-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-gluco-1,4-furanose (557 mg, 2.0 mmol), diisopropylethylamine (350 μL, 2.0 mmol), lithium chloride (93.2 mg, 2.2 mmol), and diethyl (phenylsulfonyl)methanephosphonate (608 mg, 2.2 mmol) in 10 mL of dry acetonitrile was stirred 18 h. Evaporation in vacuo and recrystallization from ether–hexane gave 270 mg of the (*E*)-sulfone **26**. Evaporation of the mother liquors, flash chromatography (1:1 ether/hexane), and recrystallization gave an additional 255 mg for a total of 525 mg (63%), mp 110–111 °C, $[\alpha_D^{25}$ + 18.0° (*c* 0.01, $CHCl_3$): IR ($CDCl_3$) 1635, 1443, 1371, 1312, 1301, 1143, 1077 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.77–7.90 (m, 2 H), 7.17–7.65 (m, 8 H), 6.98 (dd, $J$ = 15, 3.6 Hz, 1 H), 6.81 (dd, $J$ = 15, 1.7 Hz, 1 H), 5.92 (d, $J$ = 3.6 Hz, 1 H), 4.85 (m, 1 H), 4.61 (d, $J$ = 3.1 Hz, 1 H), 4.60 (d, $J$ = 11.9 Hz, 1 H), 4.44 (d, $J$ = 11.9 Hz, 1 H), 4.01 (d, $J$ = 3.1 Hz, 1 H), 1.44 (s, 3 H), 1.29 (s, 3 H); calcd for $C_{22}H_{24}O_6S$ 416.1294, found 416.1307; calcd for $C_{22}H_{25}O_6S$ ($M^+$ + 1, self CI) 417.1372, found 417.1379.

**Preparation of 3-Hydroxy-1-(phenylsulfonyl)-1-cyclohexene and Analogues 30. (a) 3-(Phenylsulfonyl)cyclohex-2-en-1-one (28).** A solution of oxone (4.6 g, 15 mmol of oxidant) in 25 mL of water was added to a 0 °C solution of 1.02 g (5 mmol) of 3-(phenylthio)cyclohex-2-en-1-one (prepared in 75% yield from cyclohexane-1,3-dione and thiophenol) in 25 mL of methanol. After stirring 4 h at room temperature, 50 mL of water was added, and the mixture was extracted twice with dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.07 g (91%) of a white solid, mp 137–141 °C (dec) after flash chromatography (1:1 hexane/ethyl acetate, $R_f$ 0.51): IR ($CDCl_3$) 1695, 1450, 1320, 1309, 1232, 1154, 1089 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.8–7.95 (m, 2 H), 7.55–7.8 (m, 3 H), 6.68 (t, $J$ = 1.5 Hz, 1 H), 2.55 (td, $J$ = 6.0, 1.5 Hz, 2 H), 2.44 (t, $J$ = 6.2 Hz, 2 H), 2.06 (m, 2 H); calcd for $C_{12}H_{12}O_3S$ 236.0507, found 236.0518.

**(b) 3-(Phenylthio)cyclohex-2-en-1-ol (29).** Racemic: Sodium borohydride (190 mg, 5.0 mmol) was added to a solution of 1.02 g (5.07 mmol) of ketone **27** and 1.90 g (5.10 mmol) of cerium chloride heptahydrate in 12 mL of methanol. The reaction mixture was diluted with 25 mL of water and extracted with ethyl acetate. The oil obtained after drying ($MgSO_4$), and rotary evaporation was chromatographed (2:1 hexane/ethyl acetate, $R_f$ 0.41) to give the racemic title compound as a colorless oil (947 mg, 91%): IR ($CDCl_3$) 3580, 3400, 1622, 1578, 1472, 1435, 1375, 1330, 1250, 1152 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.25–7.45 (m, 5 H), 5.73 (dt, $J$ = 3.8, 1.5 Hz, 1 H), 4.24 (m, 1 H), 2.1 (m, 2 H), 1.93 (m, 2 H), 1.57 (m, 2 H), 1.44 (d, $J$ = 6.4 Hz, 1 H, exchanges with $D_2O$); calcd for $C_{17}H_{14}OS$ 206.0765, found 206.0754.

Optically active: A solution of 5.82 g (32.4 mmol) of 96.2% optically pure (−)-*N*-methylephedrine in 25.5 mL of ether was added dropwise to a suspension of 1.128 g (29.7 mmol) of LAH in 42 mL of ether. After the initial reaction subsided, the mixture was heated at reflux for 1 h and then cooled to 0 °C. 2-(Ethylamino)pyridine (7.92 g, 64.8 mmol) in 25.5 mL of ether was added, and the mixture was brought to reflux for 1 h once more. The green suspension was cooled to −78 °C, and a solution of 1.83 g (8.97 mmol) of enone **27** in 9 mL of ether was added with vigorous stirring. After 3 h, addition of 1.5 mL of methanol quenched the reaction, which was now allowed to warm to room temperature. Following the addition of water (1.5 mL), 15% aqueous potassium hydroxide (6 mL), and water (6 mL), the mixture was thoroughly extracted

with ether. The organic phase was washed with aqueous cupric sulfate, dried ($MgSO_4$), and concentrated in vacuo, and the residue was flash chromatographed (10:1 dichloromethane/ether, $R_f$ 0.35) to give 1.15 g (62% yield) of product, $[\alpha]_D^{25}$ + 59.5° (*c* 0.004, $CHCl_3$), whose spectral properties match those of the racemic compound.

**(c) 3-(Phenylsulfonyl)cyclohex-2-en-1-ol (30a).** Racemic from keto-sulfone **28**: Following the procedure for reduction of keto sulfide, 400 mg (1.7 mmol) of keto sulfone **28**, 633 mg (1.7 mmol) of cerium chloride heptahydrate, and 64 mg (1.7 mmol) of sodium borohydride gave 374 mg (92.5%) of the racemic title compound. IR ($CDCl_3$) 3590, 1448, 1305, 1152, 1090 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.84–7.95 (m, 2 H), 7.47–7.71 (m, 3 H), 6.98 (dt, *J* = 3.0, 1.4 Hz, 1 H), 4.41 (m, 1 H), 2.18 (m, 2 H), 1.78–2.0 (m, 2 H), 1.41–1.75 (m, 2 H); calcd for $C_{12}H_{14}O_3S$ 238.0664, found 238.0669.

Optically active from hydroxy sulfide **29**: A solution of 1.10 g (5.34 mmol) of sulfide **29** and 2.85 g (13.0 mmol) of MCPBA in 50 mL of dichloromethane was stirred at 0 °C for 1 h and at room temperature for 0.5 h. After addition of ether, the solution was washed with aqueous sodium sulfite, water, and brine, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography (ether, $R_f$ 0.39) gave 942 mg (74%) of the title compound as a colorless oil, $[\alpha]_D^{25}$ + 41.1° (*c* 0.01, $CHCl_3$).

The *O*-methylmandelate ester was prepared as described earlier from 18 mg (0.076 mmol) of hydroxy sulfide **29**, 12.5 mg (0.076 mmol) of *S*-*O*-methylmandelic acid, 15.6 mg (0.076 mmol) of DCC, and a few mg of DMAP in 0.5 mL of dichloromethane for 0.5 h. Dilution with ether followed by filtering through a short plug of silica gel gave the product for NMR analysis. The vinyl signals at δ 6.895 for the *R* and 6.724 for the *S* isomer allowed determination of the ee to be 79%.

**(d) (*R*)-3-(*tert*-Butyldimethylsiloxy)-1-(phenylsulfonyl)cyclohexene (30c).** A solution of 900 mg (4.00 mmol) of *R*-alcohol **30a**, 571 mg (4.18 mmol) of *tert*-butyldimethylsilyl chloride, and 0.570 g (8.32 mmol) of imidazole in 3 mL of DMF was stirred 5 h at room temperature. Direct column chromatography (1:1 hexane/ether, $R_f$ 0.8) gave 1.23 g (92%) of silyl ether whose spectral properties were identical with those of the known racemic material. Crystallization from ether–hexane gave 350 mg of 95.5% ee (determined by mandelate analysis) and a second crop of 300 mg of 93% ee for a total of 650 mg, $[\alpha]_D^{25}$ + 51.9° (*c* 0.01, $CHCl_3$).

**Cycloadditions. (a) 2-Methylene-4-(*tert*-butyldimethylsiloxy)-8a-(phenylsulfonyl)octahydroindene (32a and 33a, R = TBDMS) and Corresponding Alcohol (32a, R = H).** In a vigorously deaerated flask, 552 mg (1.64 mmol) of the acceptor **9a** was added to a solution of 11 mg (0.05 mmol) of palladium acetate and 90 μL (0.32 mmol) of triisopropyl phosphite in 2 mL of dry toluene. The solution was immersed into an 80 °C oil bath, and 500 mg (2.68 mmol) of 2-(acetoxymethyl)-3-(trimethylsilyl)-1-propene (**1**) was added. After 40 h at 80 °C, the reaction was concentrated in vacuo, and the resultant oil, which $^1H$ NMR spectroscopy indicated was a 7.5:1 diastereomeric mixture of cycloadducts, chromatographed [4:1 hexane/ethyl acetate, $R_f$ 0.63 (minor) and 0.50 (major)] to give a total of 582 mg (87%) of cycloadducts. The minor isomer was characterized only by IR and $^1H$ NMR spectroscopy: IR ($CDCl_3$) 3090, 2942, 2920, 2850, 1450, 1260, 1135 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.8–7.9 (m, 2 H), 7.45–7.65 (m, 3 H), 4.88 (br s, 1 H), 4.85 (br s, 1 H), 4.37 (dt, *J* = 9.6, 5.6 Hz, 1 H), 3.12 (td, *J* = 9.6, 2.2 Hz, 1 H), 2.93 (fine split d, *J* = 15.0 Hz, 1 H), 2.53 (dd, *J* = 9.1, 2.2 Hz, 2 H), 1.2–2.1 (m, 7 H), 0.87 (s, 9 H), 0.087 (s, 3 H), 0.072 (s, 3 H). The major diastereomer crystallizes as colorless prisms, mp 80–2 °C, from ether–hexane: IR ($CDCl_3$) 3080, 2960, 2950, 2573, 1300, 1260, 1137, 1085 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.82–7.95 (m, 2 H), 7.5–7.7 (m, 3 H), 4.95 (br s, 2 H), 3.19 (td, *J* = 9.3, 3.8 Hz, 1 H), 2.95–3.05 (m, 4 H), 1.4–1.9 (m, 5 H), 1.1–1.3 (m, 2 H), 0.85 (s, 9 H), 0.019 (s, 3 H), –0.003 (s, 3 H); $^{13}C$ NMR (50.1 MHz, $CDCl_3$) δ 147.84, 136.33, 130.43, 128.74, 108.01, 74.66, 72.79, 47.28, 37.23, 36.82, 33.03, 28.82, 25.78, 19.36, 17.90, –3.94. Anal. Calcd for $C_{22}H_{34}O_3SSi$: C, 64.98; H, 8.43; MW, 406.1998. Found: C, 64.99; H, 8.15; MW, 406.1992.

Repeating the reaction with 380 mg (1.13 mmol) of acceptor **9a** of 93% ee, 345 mg (1.70 mmol) of 3-acetoxy-2-((trimethylsilyl)methyl)-1-propene, 6 mg (0.03 mmol) of palladium acetate, 50 μL (0.18 mmol) of triisopropyl phosphite in 1 mL of toluene gave 320 mg (70%) of the major diastereomeric product **32a** of 93% ee, $[\alpha]_D^{25}$ + 26.82° (*c* 0.022, $CHCl_3$).

Desilylation of 897 mg (2.21 mmol) of racemic cycloadduct **32a** (R = TBDMS) proceeded under standard conditions with 30 mL of 1 M TBAF in THF at room temperature. After evaporation in vacuo and partitioning between a 1:1 ether/ethyl acetate and water mixture, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried ($Na_2SO_4$), and concentrated in vacuo. Flash chromatography of the residue (1:1 hexane/ethyl acetate, $R_f$ 0.32) gave 638 mg (quantitative) of the product which was recrystallized from ether to give white needles, mp 116–8 °C: IR ($CDCl_3$) 3479, 2941, 1448, 1295, 1273, 1133, 1081 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.92 (m, 2 H), 7.5–7.8 (m, 3 H), 4.88 (m, 2 H), 3.85 (d, *J* = 12.3 Hz, 1 H), 3.65 (m, 1 H), 2.7–3.1 (m, 3 H), 1.95–2.4 (m, 4 H), 1.65–1.8 (m, 2 H), 1.3–1.6 (m, 2 H); $^{13}C$ NMR (50.1 MHz, $CDCl_3$) δ 145.2 (C), 135.3 (C), 133.9 (CH), 130.3 (CH), 128.9 (CH), 108.8 ($CH_2$), 70.53 (C), 68.1 (CH), 44.6 (CH), 42.9 ($CH_2$), 35.9 ($CH_2$), 28.8 ($CH_2$), 27.6 ($CH_2$), 16.9 ($CH_2$); calcd for $C_{16}H_{21}O_3S$ ($M^+$ + 1, self CI) 293.1211, found 293.1208. Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89. Found: C, 65.60; H, 7.03.

Repeating the above using 300 mg (0.74 mmol) of silyl ether **32a** (R = TBDMS) of 93% ee gave 180 mg (84%) of alcohol **32a** (R = H) $[\alpha]_D^{25}$ –2.3° (*c* 0.01, $CHCl_3$).

**(b) 2-Methylene-4-(methoxymethoxy)-8aβ-(phenylsulfonyl)-3aβ-decahydroazulene (32b, R = MOM) and Its Corresponding Alcohol (32b, R = H).** As described above, a catalyst solution prepared from 15 mg (0.06 mmol) of palladium acetate and 101 mg (0.487 mmol) of triisopropyl phosphite in 2 mL of dry toluene was added to 1.05 g (3.54 mmol) of acceptor **10c** in 2 mL of dry toluene, and then, at 60 °C, 0.95 g (5.3 mmol) of donor **1** were added. After 40 h at 80 °C, concentration in vacuo and flash chromatography (3:1 hexane/ethyl acetate, $R_f$ 0.33) gave 1.15 g (93%) of the pure product. Integration of the absorptions for the exocyclic methylene group at δ 4.66 (major) and 4.75 (minor) gave a 9:1 ratio of diastereomers: IR ($CDCl_3$) 3060, 2935, 1445, 1290, 1138, 1080, 1035 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.87 (m, 2 H), 7.55 (m, 3 H), 4.66 (m, 2 H), 4.42 (d, *J* = 6.84 Hz, 1 H), 4.34 (d, *J* = 6.84 Hz, 1 H), 3.64 (m, 1 H), 3.27 (s, 3 H), 3.10 (m, 2 H), 2.5–2.8 (m, 1 H), 2.0–2.3 (m, 3 H), 1.8–1.95 (m, 3 H), 1.55–1.75 (m, 2 H), 1.3–1.45 (m, 2 H); $^{13}C$ NMR (50.1 MHz, $CDCl_3$) δ 147.7, 136.6, 131.1, 130.4, 128.4, 105.8, 94.2, 77.91, 75.4, 55.3, 46.2, 46.0, 42.5, 38.5, 29.9, 24.7; calcd for $C_{19}H_{27}O_4S$ ($M + 1^+$, self CI) 351.1630, found 351.1619; calcd for $C_{18}H_{23}O_3S$ ($M - OCH_3^+$) 319.1368, found 319.1368.

A solution of bromodimethylborane (4.5 mL of 1.5 M, 6.75 mmol) in dichloromethane was added to 741 mg (2.11 mmol) of the above adduct and 176 μL (1.35 mmol) of triethylamine in 17 mL of dichloromethane at –78 °C. After 3 h, the cold mixture was added to a vigorously stirred mixture of 20 mL of THF and 10 mL of saturated aqueous sodium bicarbonate. Addition of 75 mL of ether, separation of phases, extraction of the aqueous phase with ether, drying ($MgSO_4$) the combined organic phases, evaporation of the solvent in vacuo, and flash chromatography (2:1 hexane/ethyl acetate) of the residue gave 570 mg (88%, 92% based on recovered starting material) of the alcohol, mp 117–8 °C (ether) and 33 mg (4.5%) of recovered starting material: IR ($CDCl_3$) 3605, 3496, 1668, 1588, 1488, 1282 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.8–7.95 (m, 2 H), 7.45–7.7 (m, 3 H), 4.77 (br s, 1 H), 4.68 (br s, 1 H), 4.02 (t, *J* = 6.1 Hz, 1 H), 3.30 (q, *J* = 7.8 Hz, 1 H), 3.04 (d, *J* = 16.7 Hz, 1 H), 2.73 (s, 1 H), 2.59 (dd, *J* = 15.0, 10.0 Hz, 1 H), 2.31 (d, *J* = 16.7 Hz, 1 H), 2.29 (dd, *J* = 15.0, 10.0 Hz, 1 H), 2.3 (m, 1 H), 1.2–2.0 (m, 7 H); $^{13}C$ NMR (50.1 MHz, $CDCl_3$) δ 146.7, 135.9, 133.5, 130.4, 128.7, 106.2, 75.3, 72.2, 47.9, 43.6, 38.3, 34.4, 32.3, 24.7, 23.3. Anal. Calcd for $C_{17}H_{22}O_3S$: C, 66.63; H, 7.24; MW, 306.1289. Found: C, 66.55; H, 7.25; MW, 306.1314.

**(c) 1-(Phenylsulfonyl)-3-methylene-6-(*tert*-butyldimethylsiloxy)spiro[4.4]nonane (35a and 36a).** To a catalyst solution prepared by adding 28 μL of a 1.39 M solution of *n*-butyllithium (39.2 μmol) in hexane to a solution of 4.4 mg (19.6 μmol) of palladium acetate and 24.5 mg (0.118 mmol) of triisopropyl phosphite in 0.2 mL of toluene were added 72.9 mg (0.392 mmol) of donor **1** and a solution of 66.8 mg (0.196 mmol) of acceptor **17b** in 0.3 mL of toluene. After heating at 115–120 °C for 30 h, direct flash chromatography (9:1 hexane/ethyl acetate) of the reaction mixture gave 34.5 mg of the major adduct and 6.6 mg of the minor adduct (total 41.1 mg, 51.6%, 61.0% based upon recovered starting material) in addition to 10.3 mg (15.4%) of recovered starting material. **35a**: $^1H$ NMR (400 MHz, $CDCl_3$) see Table II; calcd for $C_{18}H_{25}O_3SSi$ ($M^+ - t\text{-}C_4H_9$) 349.1294, found 349.1308. Anal. Calcd for $C_{22}H_{34}O_3SSi$: C, 64.98; H, 8.43. Found: C, 65.08; H, 8.78. **36a**: $^1H$ NMR (400 MHz, $CDCl_3$) see Table II. Calcd for $C_{18}H_{25}O_3SSi$ ($M^+ - t\text{-}C_4H_9$) 349.1294, found 349.1304.

**(d) (1-*rS*)-(Phenylsulfonyl)-3-methylene-(6-*rR*,9-*rS*)-bis(*tert*-butyldimethylsiloxy)spiro[4.4]nonane (35b).** As described for cycloaddition to **17b**, 47.3 mg (0.098 mmol) of acceptor **20b** and 36.5 mg (0.196 mmol) of donor **1** using a catalyst derived from 2.2 mg (9.8 μmol) of palladium acetate, 12.2 mg (58.8 μmol) of triisopropyl phosphite, and 14 μL of a 1.39 M solution of *n*-butyllithium in hexane (19.6 μmol) in a total of 4.5 mL of toluene at 115–120 °C for 24 h gave after flash chromatography (4:1 hexane/ethyl acetate containing 0.5% methanol) 26.7 mg (51%, 76% based upon recovered starting material) of a single cycloadduct **35b** and 15.7 mg (33%) of recovered starting material: $^1H$ NMR (400 MHz, $CDCl_3$) see Table II; calcd for $C_{24}H_{39}O_4SSi_2$ ($M^+ - t\text{-}C_4H_9$) 479.2108, found 479.2081. Anal. Calcd for $C_{28}H_{48}O_4SSi_2$: C, 62.64; H, 9.01. Found: C, 63.09; H, 9.58.

**(e) 1-(Phenylsulfonyl)-3-methylene-5-methyl-6-(methoxymethoxy)-*cis*-bicyclo[3.3.0]octane (37 and 38).** To a solution of 280 mg (1.00 mmol) of acceptor **13b**, 11.2 mg (0.050 mmol) of palladium acetate, and 87 μL (0.35 mmol) of triisopropyl phosphite in 1.5 mL of dry toluene in a resealable thick-walled tube was added 360 mg (2.0 mmol) of donor **1**. The sealed tube was immersed into an oil bath preheated to 150 °C and kept there overnight. The reaction mixture was directly chromatographed (2:1 hexane/ethyl acetate) to give 172 mg (51% yield) of the two separable diastereomers **37** (major, $R_f$ 0.52) and **38** (minor, $R_f$ 0.60). **37**: IR ($CDCl_3$) 3032, 2942, 2895, 1660, 1445, 1297, 1140 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.8–7.9 (m, 2 H), 7.45–7.6 (m, 3 H), 4.78 (d, $J$ = 12.9 Hz, 2 H), 4.63 (d, $J$ = 6.8 Hz, 1 H), 4.57 (d, $J$ = 6.8 Hz, 1 H), 3.55 (t, $J$ = 7.0 Hz, 1 H), 3.34 (s, 3 H), 3.22 (d, $J$ = 16.0 Hz, 1 H), 2.5–2.75 (m, 2 H), 2.32 (d, $J$ = 15.2 Hz, 1 H), 1.8–2.05 (m, 3 H), 1.57 (s, 3 H), 1.15–1.35 (m, 1 H); calcd for $C_{18}H_{25}O_4S$ ($M^+$ + 1, self CI) 337.1472, found 337.1478. **38**: IR ($CDCl_3$) 3060, 2950, 2885, 1655, 1448, 1300, 1236, 1190, 1145 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.8–7.9 (m, 2 H), 7.45–7.68 (m, 3 H), 4.80 (br s, 1 H), 4.78 (br s, 1 H), 4.68 (d, $J$ = 7.0 Hz, 1 H), 4.65 (d, $J$ = 7.0 Hz, 1 H), 4.06 (dd, $J$ = 9.7, 6.8 Hz, 1 H), 3.38 (d, $J$ = 16.8 Hz, 1 H), 3.34 (s, 3 H), 2.82 (dd, $J$ = 16.8, 1.5 Hz, 1 H), 2.0–2.4 (m, 4 H), 1.62 (s, 3 H), 1.2–1.6 (m, 2 H); calcd for $C_{18}H_{25}O_4S$ ($M^+$ + 1, self CI) 337.1472, found 337.1448.

**(f) 4-(1-Methylene-4-(phenylsulfonyl)cyclopent-3-yl)-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-threo-1,4-furanose (39).** Using the standard solutions, 208 mg (0.500 mmol) of acceptor **26**, 182 mg (2.00 mmol) of donor **1**, and a catalyst prepared from 6.0 mg (0.048 mmol) of palladium acetate, and 42.0 mg (0.202 mmol) of triisopropyl phosphite in a total of 1 mL of toluene gave, after 18 h at 80–85 °C and purification by flash chromatography (1:1 hexane/ether), 123 mg of the major diastereomer ($[\alpha]_D^{25}$ −4.12° ($c$ 0.076, $CHCl_3$), 104 mg of a mixture, and 8.0 mg of the minor diastereomer for a total of 235 mg (100%): IR ($CHCl_3$) 3000, 2920, 2860, 1442, 1378, 1370, 1298, 1138 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.8–7.95 (m, 2 H), 7.35–7.7 (m, 8 H), 5.86 (d, $J$ = 3.8 Hz, 1 H), 4.79 (dm, $J$ = 21.1 Hz, 2 H), 4.63 (d, $J$ = 11.7 Hz, 1 H), 4.55 (br s, 1 H), 4.53 (d, $J$ = 11.7 Hz, 1 H), 4.35 (app t, $J$ = 3.6 Hz, 1 H), 3.91 (d, $J$ = 3.4 Hz, 1 H), 3.58 (m, 1 H), 3.1 (m, 1 H), 4.35 (app t, $J$ = 3.6 Hz, 1 H), 3.91 (d, $J$ = 3.4 Hz, 1 H), 3.58 (m, 1 H), 3.1 (m, 1 H), 2.6–2.8 (m, 3 H), 2.43 (dd, $J$ = 16.8, 7.0 Hz, 1 H), 1.46 (s, 3 H), 1.30 (s, 3 H); calcd for $C_{25}H_{27}O_6S$ ($M^+$ − $CH_3$) 455.1528, found 455.1440.

**(g) 1-Methylene-3-(2,2-dimethyldioxolan-4*S*-yl)-4-(phenylsulfonyl)-cyclopentane (41 and 43).** From *E* acceptor **22**: A solution of 537 mg (2.0 mmol) of acceptor **22**, 11.2 mg (0.050 mmol) of palladium acetate, 87 μL (0.35 mmol) of triisopropyl phosphite, and 546 mg (3.0 mmol) of donor **1** in 4 mL of dry toluene was immersed into an oil bath and preheated to 80 °C. After 15 h, the reaction was concentrated in vacuo. The residue, dissolved in 3 mL of ethanol, was stirred with 1 mL of ethylenediamine at room temperature for 1 h to facilitate separation of unreacted acceptor. Evaporation in vacuo and flash chromatography (2:1 hexane/ethyl acetate) gave 580 mg (90%) of cycloadducts as a 2:1 mixture of **41** and **42**: IR ($CDCl_3$) 2978, 2930, 1660, 1650, 1445, 1380, 1370, 1300, 1142 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.82–7.94 (m, 2 H), 7.47–7.69 (m, 3 H), 4.87 (br s, 0.66 H), 4.80 (dt, $J$ = 8.1, 1.9 Hz, 1.34 H), 4.30 (ddd, $J$ = 9.14, 4.1, 2.5 Hz, 0.66 H), 3.8–4.15 (m, 1.34 H), 3.45–3.75 (m, 2 H), 2.35–2.95 (m, 4.32 H), 2.04 (d, $J$ = 14.1 Hz, 0.66 H), 1.35 (s, 2 H), 1.26 (s, 2 H), 1.22 (s, 1 H), 1.09 (s, 1 H); calcd for $C_{17}H_{22}O_4S$: 322.1239, found 322.1248.

From *Z* acceptor **25**: As above, 200 mg (0.750 mmol) of *Z* acceptor **25**, 34 mg (0.015 mmol) of palladium acetate, 27 μL (0.105 mmol) of triisopropyl phosphite, and 120 mg (0.75 mmol) of donor **1** in 2 mL of toluene were heated at 80 °C for 6 h. After cooling, the solution was diluted with 20 mL of pH 7 phosphate buffer solution and 20 mL of chloroform. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was flash chromatographed (4:1 hexane/ethyl acetate) to give 180 mg (76%) of a 1:1 mixture of **41** and **43**. Addition of a 1:1 ether/pentane mixture to the oil precipitated 80 mg of pure **43**, mp 120 °C. Concentration of the solvent gave 70 mg of an oil that was mainly the diastereomer **41**. Pure **41** was obtained from both pure **43** and from a 1:1 mixture of **41** and **43**. In the former case, a solution of 15 mg (0.046 mmol) of pure **43** and 3 mg (0.05 mmol) of sodium methoxide in 3 mL of dioxane was heated at 90 °C for 3 h. After cooling, diluting with water, and extracting with chloroform, the obtained organic layer was dried ($MgSO_4$), evaporated in vacuo, and flash chromatographed (3:2 hexane/ethyl acetate) to give 14 mg (96%) of pure **41**. The same procedure starting from 10 mg (0.030 mmol) of a 1:1 mixture of **41** and **43** gave, after flash chromatography, 8.7 mg (87%) of pure **41**. **41**: $[\alpha]_D^{25}$ −27.31° ($c$ 0.465, $CHCl_3$); IR ($CDCl_3$) 1440, 1320, 1300, 1150 $cm^{-1}$; $^1H$ NMR (270 MHz, $C_6D_6$) δ 7.7–7.8 (m, 2 H), 6.8–6.95 (m, 3 H), 4.75 (br s, 1 H), 4.65 (br s, 1 H), 4.35 (dt, $J$ = 5.7, 4.6 Hz, 1 H), 3.59 (dd, $J$ = 5.7, 8.5 Hz, 1 H), 3.46 (q, $J$ = 8.5 Hz, 1 H), 3.26 (dd, $J$ = 8.5, 5.7 Hz, 1 H), 2.6–2.9 (m, 2 H), 2.2–2.5 (m, 2 H), 2.11 (ddq, $J$ = 17.0, 8.5, 1.7 Hz, 1 H), 1.32 (s, 3 H), 1.22 (s, 3 H); calcd for $C_{16}H_{19}O_4S$ ($M^+$ − $CH_3$) 307.1004; found 307.1009. **43**: $[\alpha]_D^{25}$ + 14.83° ($c$ 0.755, $CHCl_3$) IR ($CDCl_3$) 1440, 1365, 1310, 1295, 1140 $cm^{-1}$; $^1H$ NMR (270 MHz, $C_6D_6$) δ 7.6–7.7 (m, 2 H), 6.8–6.9 (m, 3 H), 5.09 (dt, $J$ = 8.5, 5.6 Hz, 1 H), 4.87 (br s, 1 H), 4.72 (br s, 1 H), 4.52 (dd, $J$ = 8.5, 5.4 Hz, 1 H), 3.92 (dd, $J$ = 8.5, 5.7 Hz, 1 H), 3.02 (ddq, $J$ = 17.0, 8.4, 2.8 Hz, 1 H), 2.91 (td, $J$ = 7.9 Hz, 1 H), 2.5–2.65 (m, 2 H), 2.34 (dq, $J$ = 8.5, 7.9 Hz, 1 H), 1.96 (ddq, $J$ = 17.0, 8.4, 2.5 Hz, 1 H), 1.47 (s, 3 H), 1.28 (s, 3 H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ 146.2, 139.3, 133.7, 129.3, 128.3, 109.0, 107.5, 75.7, 69.2, 65.7, 47.3, 35.7, 35.5, 27.0, 25.1; calcd for $C_{17}H_{23}O_4S$ ($M^+$ + 1, self CI) 323.1317, found 323.1309.

**(h) 1-Methylene-2-(hydroxycarbonyl)-3-(2,2-dimethyldioxolan-4*S*-yl)-4-(phenylsulfonyl)cyclopentane (47–49) and Ethyl Ester 50.** From E acceptor **22** in dioxane: In the usual way, 200 mg (0.720 mmol) of E acceptor **22**, 200 mg (0.720 mmol) of donor **45**, and a catalyst prepared from 3.3 mg (0.026 mmol) of palladium acetate and 21.0 mg (0.101 mmol) of triisopropyl phosphite in a total of 2 mL of dioxane at 80 °C for 5 h gave, after flash chromatography on silica gel deactivated with 5% of water (4:1 chloroform/methanol), 110 mg (41%) of a 3:2 mixture of **47** and **48**: $^1H$ NMR (500 MHz, $C_6D_6$) δ 10.0 (s, 1 H, **47** + **48**), 7.55–7.80 (m, 2 H, **47** + **48**), 6.8–7.0 (m, 3 H, **47** + **48**), 4.63 and 5.06 (**47**) and 4.90 and 5.25 (**48**) (all br s, 2 H), 4.50–4.65 (m, **48**) and 4.72 (q, $J$ = 8 Hz, **47**, 1 H), 4.25 (q, $J$ = 8 Hz, **48**) and 4.34 (dd, $J$ = 10.0, 7.0 Hz, **47**, 1 H), 3.95–4.10 (m, 2 H, **47** and **48**), 3.72 (d, $J$ = 9.0 Hz, **47**) and 3.6–3.7 (m, **48**, 1 H), 3.03 (q, $J$ = 9.03 Hz, **47**) and 3.00–3.15 (m, **48**, 1 H), 2.62 (dd, $J$ = 17.5, 7.5 Hz, **47**) and 2.80–2.95 (m, **48**, 1 H), 2.05 (dd, $J$ = 16.2, 6.7 Hz, **48**) and 2.31 (dd, $J$ = 17.5, 7.5 Hz, **47**, 1 H), 1.10 (s, **48**) and 1.25 (s, **47**) and 1.36 (s, **47**, 6 H).

From E acceptor in toluene: Following the usual procedure, 100 mg (0.360 mmol) of E acceptor **22**, 100 mg (0.360 mmol) of donor **45**, and 8.3 mg (0.008 mmol) of tetrakis(triphenylphosphine)palladium in 1 mL of toluene at 80 °C for 48 h gave, after flash chromatography as above, 44 mg (32%) of pure **47**, $[\alpha]_D^{25}$ −0.99° ($c$ 1.61, $CHCl_3$); IR ($CDCl_3$) 3500–2500, 1710, 1440, 1380, 1370, 1305, 1145 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) δ 11.0 (s, 1 H), 7.55–7.80 (m, 2 H), 6.8–7.0 (m, 3 H), 5.06 (br s, 1 H), 4.72 (q, $J$ = 8 Hz, 1 H), 4.63 (br s, 1 H), 4.34 (dd, $J$ = 10.0, 7.0 Hz, 1 H), 4.09 (dd, $J$ = 10.0, 7.0 Hz, 1 H), 4.02 (q, $J$ = 9.0 Hz, 1 H), 3.72 (d, $J$ = 9.0 Hz, 1 H), 3.03 (q, $J$ = 9.0 Hz, 1 H), 2.62 (dd, $J$ = 17.5, 7.5 Hz, 1 H), 2.31 (dd, $J$ = 17.5, 7.5 Hz, 1 H), 1.36 (s, 3 H), 1.25 (s, 3 H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ 181.56, 143.07, 138.58, 133.91, 129.34, 128.39, 111.63, 108.77, 75.54, 69.38, 64.82, 52.83, 46.56, 34.92, 26.34, 25.14; calcd for $C_{18}H_{23}O_6S$ ($M^+$ + H, self CI) 367.1215, found 367.1209.

From Z acceptor: Following the usual procedure, 190 mg (0.70 mmol) of Z acceptor **25**, 200 mg (0.72 mmol) of donor **45**, and a catalyst derived from 3.3 mg (0.026 mmol) of palladium acetate and 21.0 mg (0.101 mmol) of triisopropyl phosphite in a total of 1 mL of toluene at 80 °C for 6 h gave, after flash chromatography as above, 100 mg (64%) of pure **49**, $[\alpha]_D^{25}$ +11.34° ($c$ 1.00, $CH_3OH$), mp 150–2 °C; IR (Nujol) 3500–2500, 1685, 1650, 1280, 1250, 1130 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_3$) δ 12.0 (br s, 1 H), 7.8–7.85 (m, 2 H), 7.7–7.75 (m, 1 H), 7.6–7.65 (m, 2 H), 4.97 (s, 1 H), 4.93 (s, 1 H), 4.62 (ddd, $J$ = 8.8, 3.8, 6.2 Hz, 1 H), 4.12 (td, $J$ = 6.5, 1.7 Hz, 1 H), 3.99 (dd, $J$ = 8.0, 6.2 Hz, 1 H), 3.94 (dd, $J$ = 8.0, 3.8 Hz, 1 H), 3.45 (dd, $J$ = 9.6, 2.3 Hz, 1 H), 3.04 (td, $J$ = 9.6, 6.5 Hz, 1 H), 2.60 (ddq, $J$ = 17.3, 6.5, 1.7 Hz, 1 H), 2.36 (dd, $J$ = 17.3, 1.7 Hz, 1 H), 1.27 (s, 3 H), 1.21 (s, 3 H); $^{13}C$ NMR (125.6 MHz, DMSO-$d_6$) δ 173.71, 146.76, 138.30, 134.10, 129.59, 127.96, 108.71, 108.22, 75.40, 67.75, 63.61, 51.94, 50.07, 35.74, 26.35, 24.99; calcd for $C_{18}H_{22}O_6S$ 366.1137, found 366.1137.

Esterification was performed under Mitsunobu conditions. Triethyl phosphite (23 mg, 0.13 mmol) was added dropwise into a solution of 24 mg (0.13 mmol) of diethyl azodicarboxylate and 50 mg (0.13 mmol) of acid **49** in 2 mL of DME with rigorous stirring at room temperature. After 12 h, the mixture was concentrated under reduced pressure (12.0 mmHg) and flash chromatographed (4:1 hexane/ethyl acetate) to give 39 mg (73%) of ethyl ester, $[\alpha]_D^{25}$ +2.05 ($c$, 0.925, $CHCl_3$): IR ($CHCl_3$) 1725, 1370, 1300, 1140 $cm^{-1}$; $^1H$ NMR (270 MHz, $C_6D_6$) δ 7.0–7.65 (m, 2 H), 6.8–6.9 (m, 3 H), 5.21 (q, $J$ = 2.5 Hz, 1 H), 5.2 (td, $J$ = 8.6, 6.2 Hz, 1 H), 4.85 (q, $J$ = 2.5 Hz, 1 H), 4.40 (dd, $J$ = 8.9, 6.2 Hz, 1 H), 4.15 (dd, $J$ = 8.6, 2.5 Hz, 1 H), 4.02 (dd, $J$ = 6.2, 3.7 Hz, 1 H), 4.00 (q, $J$ = 7.6 Hz, 2 H), 3.55 (dt, $J$ = 8.6, 7.1 Hz, 1 H), 3.2 (td, $J$ = 7.1, 3.7 Hz, 1 H), 2.41 (ddq, $J$ = 17.6, 2.7, 1.4 Hz, 1 H), 2.24 (ddq, $J$ = 17.6, 8.1, 2.7 Hz, 1 H), 1.54 (s, 3 H), 1.25 (s, 3 H), 0.99 (t, $J$ = 7 Hz, 3 H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ 123.21, 145.44, 139.33, 133.88, 129.39, 128.36, 110,19, 109.49, 75.16, 68.97, 65.06, 60.94, 51.59, 50.13, 35.92, 26.48, 24.97, 14.14; calcd for $C_{20}H_{25}O_6S$ ($M^+$ − H) 393.1372, found 393.1356.

**Oxidative Cleavage to Cyclopentenones. (a) 7β-(*tert*-Butyldimethylsiloxy)- and 7β-Hydroxy-1,4,5',6,7,7aβ-hexahydroinden-2-one (54, *n* = 1, R = TBDMS and R = H).** Ozone was bubbled through a solution of

60 mg (0.15 mmol) of methylenecyclopentane **32** ($n$ = 1, R = TBDMS) in 1 mL of methanol at −78 °C until a blue color persisted. The solution was purged of excess ozone by bubbling nitrogen through it, and the ozonide was reduced by addition of a mixture of 1 mL of dimethyl sulfide and 1 mL of methanol at room temperature. After concentration with use of a stream of nitrogen, a solution of 0.5 mL of triethylamine in 2 mL of dichloromethane was added, and the resultant solution was stirred 15 min at room temperature. Concentration in vacuo and flash chromatography (1:1 ether/hexane) gave 35 mg (82%) of the enone **54** ($n$ = 1, R = TBDMS) as a waxy solid: IR ($CDCl_3$) 1693, 1669, 1617, 1401, 1248 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.84 (m, 1 H), 3.27 (td, $J$ = 9.5, 4.5 Hz, 1 H), 1.9–2.25 (m, 4 H), 2.18 (d, $J$ = 17.6 Hz, 1 H), 1.2–1.6 (m, 4 H), 0.86 (s, 9 H), 0.035 (s, 6 H); calcd for $C_{14}H_{23}O_2Si$ ($M^+ - CH_3$) 251.1467, found 251.1458.

A solution of 180 mg (0.616 mmol) of hydroxymethylenecyclopentane **32** ($n$ = 1, R = H) in 2 mL of dry methanol was treated with ozone at −78 °C. After the nitrogen purge and addition of dimethyl sulfide, 1 mL of triethylamine was directly added to the methanol solution, and stirring was continued 15 min. Evaporation in vacuo and flash chromatography (ethyl acetate) gave 91 mg (97%) of the enone **54** ($n$ = 1, R = H): IR ($CDCl_3$) 3600, 1701, 1675, 1622 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.88 (t, $J$ = 1.5 Hz, 1 H), 3.33 (td, $J$ = 9.7, 4.1 Hz, 1 H), 2.55, 2.8 (m, 2 H), 2.62 (dd, $J$ = 21.5, 6.6 Hz, 1 H), 2.29 (dd, $J$ = 21.5, 4.9 Hz, 1 H), 1.85 (m, 4 H), 1.3–1.6 (m, 2 H); calcd for $C_9H_{12}O_2$ 152.0837, found 152.0838.

Repeating the above utilizing 180 mg (0.616 mmol) of alcohol **32** ($n$ = 1, R = H) of 93% ee gave 80 mg (85%) of enone, $[\alpha]_D^{25}$ +16.23° ($c$ 0.0175, $CHCl_3$). Mandelate analysis indicated the enone to be 93% ee. A solution of 25 mg (0.164 mmol) of the hydroxyenone, 27.3 mg (0.164 mmol) of *S*-*O*-methylmandelic acid, 34 mg (0.164 mmol) of DCC, and a few crystals of DMAP in 0.5 mL of dichloromethane was stirred 15 min at room temperature. The mixture was diluted with ether and filtered through a plug of silica gel to give 48 mg (97%) of the mandelate ester. Analysis was most accurate by integrating the absorptions for the vinyl protons at $\delta$ 5.92 and 5.88 for the major and minor diastereomers, respectively.

**(b) 8β-(Methoxymethoxy)- and 8β-Hydroxy-1,2,4,5,6,7,8,8aβ-octahydroazulen-2-one (54, $n$ = 2, R = $CH_2OCH_3$ and R = H).** Following the second procedure above, ozonolysis of 30 mg (0.085 mmol) of the methylenecyclopentane **33** ($n$ = 2, R = $CH_2OCH_3$) in 0.5 mL of dry methanol gave, after flash chromatography (ether), 18 mg (quantitative) of enone **54** ($n$ = 2, R = $CH_2OCH_3$): IR ($CDCl_3$) 1685, 1606, 1445 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.92 (m, 1 H), 4.69 (d, $J$ = 7.0 Hz, 1 H), 4.59 (d, $J$ = 7.0 Hz, 1 H), 3.37 (s, 3 H), 3.3 (m, 1 H), 3.04 (m, 1 H), 2.67 (t, $J$ = 5.5 Hz, 2 H), 2.63 (dd, $J$ = 18.7, 6.2 Hz, 1 H), 2.31 (dd, $J$ = 18.7, 2.6 Hz, 1 H), 1.2–2.0 (m, 6 H); calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1257.

Repeating the above with 58 mg (0.19 mmol) of the hydroxymethylenecyclopentane **32** ($n$ = 2, R = H) in 1 mL of methanol gave 30 mg (96%) of hydroxyenone **54** ($n$ = 2, R = H) after flash chromatography (ethyl acetate): IR ($CDCl_3$) 3605, 1688, 1605 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.94 (m, 1 H), 3.42 (m, 1 H), 2.98 (m, 1 H), 2.77 (m, 2 H), 2.58 (m, 2 H), 1.55–2.1 (m, 6 H), 1.2–1.45 (m, 1 H); calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0986.

**(c) 5β-Methyl-6β-(methoxymethoxy)- and 5α-Methyl-6β-(methoxymethoxy)bicyclo[3.3.0]oct-1-en-3-one (55 and 56).** As above, ozonolysis of 32 mg (0.094 mmol) of methylenecyclopentane **37** in 0.5 mL of dry methanol followed by 0.5 mL of triethylamine gave 17 mg (92%) of enone **55** after chromatography (ether): IR ($CDCl_3$) 1705, 1632, 1380 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.78 (dd, $J$ = 2.2, 1.1 Hz, 1 H), 4.63 (s, 2 H), 3.75 (appt, $J$ = 8.7 Hz, 1 H), 3.35 (s, 3 H), 2.4–2.85 (m, 2 H), 2.35 (d, $J$ = 5.1 Hz, 2 H), 2.0–2.3 (m, 2 H), 1.47 (s, 3 H); calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1098.

Repeating the above using 28 mg (0.082 mmol) of methylenecyclopentane **38** in 0.5 mL of methanol followed by 0.5 mL of triethylamine gave 15 mg (93%) of enone **56** after chromatography (ether): IR ($CDCl_3$) 1705, 1637, 1380 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.81 (t, $J$ = 1.5 Hz, 1 H), 4.65 (d, $J$ = 6.8 Hz, 1 H), 4.51 (d, $J$ = 6.8, 1 H), 2.05–2.14 (m, 2 H), 1.14 (s, 3 H); calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1106.

**(d) 4*R*- and 4*S*-(4*S*-2,2-Dimethyldioxolanyl)cyclopent-2-en-1-one (57 and 63).** From the mixture of **41** and **42**: Following the above procedure, ozonolysis of 270 mg (0.837 mmol) of a 2:1 diastereomeric mixture of **41** and **42** in 1 mL of dry methanol followed by 0.5 mL of triethylamine gave 150 mg (98%) of a 2:1 mixture of **57** and its 4*S* epimer **63**. Preparative TLC [10:1 ether/ethyl acetate, $R_f$ 0.69 (minor) and 0.58 (major)] gave the two pure epimers for characterization. **57**: $[\alpha]_D^{25}$ +146.8° ($c$ 0.790, $CHCl_3$); IR ($CDCl_3$) 1708, 1380, 1370, 1255 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.52 (dd, $J$ = 5.7, 2.5 Hz, 1 H), 6.24 (dd, $J$ = 5.7, 2.1 Hz, 1 H), 4.22 (ddd, $J$ = 6.4, 6.5, 2.1 Hz, 1 H), 4.05 (dd, $J$ = 8.2, 6.5 Hz, 1 H), 3.59 (dd, $J$ = 8.2, 6.4 Hz, 1 H), 3.15 (m, 1 H), 2.43 (dd, $J$ = 18.8, 6.4 Hz, 1 H), 2.21 (dd, $J$ = 18.8, 2.6 Hz, 1 H), 1.38 (s, 3 H), 1.30 (s, 3 H); $^{13}C$ NMR (50.3 MHz), $CDCl_3$) $\delta$ 208.45, 163.19, 136.01, 109.56, 76.36, 66.98, 44.50, 36.50, 26.31, 24.97; calcd for $C_{10}H_{15}O_3$ ($M^+$ + H, self CI) 183.1021, found 183.1020. **63**: IR ($CDCl_3$) 1710, 1380, 1370, $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.73 (dd, $J$ = 5.7, 2.5 Hz, 1 H), 6.26 (dd, $J$ = 5.7, 2.0 Hz, 1 H), 4.03 (m, 2 H), 3.71 (m, 1 H), 3.10 (m, 1 H), 2.48 (dd, $J$ = 19.8, 6.6 Hz, 1 H), 2.00 (dd, $J$ = 19.8, 2.4 Hz, 1 H), 1.42 (s, 3 H), 1.33 (s, 3 H); calcd for $C_9H_{11}O_3$ ($M^+ - CH_3$) 167.0708, found 167.0708.

From the mixture of **41** and **43**: Following the above procedure, ozonolysis of 50 mg (0.15 mmol) of a 1:1 mixture of **41** and **43** in 2 mL of dry methanol followed by 3 mL of triethylamine gave 22 mg (80%) of pure enone **57** after flash chromatography (3:2 hexane/ethyl acetate).

From **41**: Following the above procedure, ozonolysis of 100 mg (0.30 mmol) of pure **41** in 2 mL of dry methanol followed by 3 mL of triethylamine gave 48 mg (85%) of pure enone **57** after flash chromatography.

**(e) 4-(1-Oxocyclopent-2-en-4*S*-yl)-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*threo*-1,4-furanose (58).** Following the above procedure, ozonolysis of 100 mg (0.21 mmol) of methylenecyclopentane **39** in 1.5 mL of methanol followed by 0.5 mL of triethylamine gave 61 mg (88%) of the cyclopentenone **58**, $[\alpha]_D^{25}$ −163.08° ($c$ 0.0195, $CHCl_3$), after flash chromatography (6:1 dichloromethane/ether): IR ($CDCl_3$) 1708, 1448, 1362, 1343 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.35 (m, 5 H), 7.18 (dd, $J$ = 15.7, 2.5 Hz, 1 H), 6.13 (dd, $J$ = 15.7, 2.1 Hz, 1 H), 5.91 (d, $J$ = 3.9 Hz, 1 H), 4.74 (d, $J$ = 11.9 Hz, 1 H), 4.65 (d, $J$ = 3.9 Hz, 1 H), 4.56 (d, $J$ = 11.9 Hz, 1 H), 3.9 (m, 2 H), 3.35 (m, 1 H), 2.54 (dd, $J$ = 6.0, 19.2 Hz, 1 H), 2.38 (dd, $J$ = 19.2, 2.7 Hz, 1 H), 1.44 (s, 3 H), 1.30 (s, 3 H); calcd for $C_{19}H_{22}O_5$ 330.1467, found 330.1457.

**(f) 4*R*-(2,2-Dimethyldioxolan-4*S*-yl)-5(ethoxycarbonyl)cyclopent-2-en-1-one (59).** Ozonolysis of 50 mg (0.13 mmol) of methylenecyclopentane **50** in 2 mL of ethanol at −78 °C followed by quenching with 3.5 mL of dimethyl sulfide was performed as above. Dropwise addition of 1.26 mL (0.126 mmol) of 0.1 M sodium ethoxide in ethanol over 10 min at room temperature was followed by concentration of the reaction in vacuo and flash chromatography (3:2 hexane/ethyl acetate) to give 25 mg (77%) of the titled cyclopentenone **59**, $[\alpha]_D^{25}$ +17.28° ($c$ 0.895, $CHCl_3$): IR ($CHCl_3$) 1730, 1710, 1375 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.57 (dd, $J$ = 5.4, 2.3 Hz, 1 H), 6.20 (dd, $J$ = 5.4, 2.5 Hz, 1 H), 4.29 (dt, $J$ = 6.1, 4.4 Hz, 1 H), 4.20 (q, $J$ = 7.2 Hz, 2 H), 4.08 (dd, $J$ = 8.7, 6.1 Hz, 1 H), 3.65 (dd, $J$ = 8.7, 6.1 Hz, 1 H), 3.55 (ddd, $J$ = 4.4, 3.0, 2.6 Hz, 1 H), 3.29 (d, $J$ = 3.0 Hz, 1 H), 1.37 (s, 3 H), 1.30 (s, 3 H), 1.27 (t, $J$ = 7.2 Hz, 3 H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) $\delta$ 201.27, 168.48, 163.05, 133.62, 109.76, 75.39, 67.07, 61.76, 53.06, 48.68, 26.25, 24.91, 14.14; calcd for $C_{13}H_{17}O_5$ ($M^+$ − H) 253.1076, found 253.1072.

**(g) 3-(2,2-Dimethyldioxolan-4*S*-yl)-2-(ethoxycarbonyl)cyclopent-2-en-1-one (60).** In the normal fashion, ozonolysis of 30 mg (0.076 mmol) of methylenecyclopentane **50** in 5 mL of ethanol followed by 1 mL of triethylamine gave 16 mg (81%) of the titled cyclopentenone **60**, $[\alpha]_D^{25}$ +7.5° ($c$ 0.320, $CHCl_3$), after flash chromatography (3:2 hexane/ethyl acetate): IR ($CHCl_3$) 1755, 1745, 1725, 1710, 1370 $cm^{-1}$; $^1H$ NMR (270 MHz, $C_6D_6$) $\delta$ 4.12 (t, $J$ = 6.5 Hz, 1 H), 3.95 (dd, $J$ = 6.5, 5.7 Hz, 1 H), 3.6–3.8 (AB of $ABX_3$, 2 H), 1.8–1.95 (m, 1 H), 1.5–1.7 (m, 2 H), 1.40 (s, 3 H), 0.95–1.30 (m, 2 H), 1.17 (s, 3 H), 0.90 (t, $J$ = 7.4 Hz, 3 H); calcd for $C_{13}H_{19}O_5$ ($M^+$ + H, self CI) 255.1233, found 255.0857.

**Alcohol Oxidation–Elimination. (a) 2-Methylene-7aβ-(phenylsulfonyl)-3aβ-octahydroinden-4-one (66, $n$ = 1).** To a solution of 67 μL (0.77 mmol) of oxalyl chloride in 3 mL of dry dichloromethane at −78 °C was added a solution of 109 μL (1.54 mmol) of dry DMSO in 2 mL of dichloromethane followed sequentially by 201 mg (0.69 mmol) of alcohol **32** ($n$ = 1) in 2 mL of dichloromethane and, after 1 h, 670 μL (3.85 mmol) of diisopropylethylamine. After 5 min, the mixture was allowed to warm to room temperature and quenched by pouring into a two-phase water–dichloromethane mixture. The organic phase was washed with brine, dried ($Na_2SO_4$), and evaporated in vacuo to give a thick oil that crystallized upon trituration with 2:1 hexane/ethyl acetate to give 138 mg (68%) of the titled compound as colorless crystals, mp 120–1 °C: IR ($CDCl_3$) 1712, 1446, 1320, 1299, 1133 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.85–7.95 (m, 2 H), 7.5–7.75 (m, 3 H), 4.91 (m, 2 H), 3.33 (t, $J$ = 8.7 Hz, 1 H), 2.93 (d, $J$ = 16.6 Hz, 1 H), 2.75 (d, $J$ = 8.1 Hz, 2 H), 2.15–2.5 (m, 5 H), 1.7–1.9 (m, 2 H); (200 MHz, $C_6D_6$) 7.75–7.85 (m, 2 H), 6.85–7.0 (m, 3 H), 4.79 (t, $J$ = 1.0 Hz, 2 H), 3.45 (t, $J$ = 8.2 Hz, 1 H), 2.86 (d, $J$ = 16.8 Hz, 1 H), 2.60 (dt, $J$ = 7.7, 1.0 Hz, 2 H), 1.9–2.15 (m, 5 H), 1.1–1.35 (m, 2 H); calcd for $C_{10}H_{13}O$ ($M^+$ − $PhSO_2$) 149.0966, found 149.1021.

**(b) 2-Methylene-8aβ-(phenylsulfonyl)-3aβ-decahydroazulen-4-one (66, $n$ = 2).** As above, 200 mg (0.65 mmol) of alcohol **32** ($n$ = 2) was oxidized with the Swern–Moffatt reagent prepared from 124 mg (0.98 mmol) of oxalyl chloride and 165 mg (1.96 mmol) of DMSO in a total

of 5 mL of dichloromethane. After addition of 420 mg (3.25 mmol) of diisopropylethylamine and the usual workup, flash chromatography (2:1 hexane/ethyl acetate) gave 184 mg (93%) of an oil that slowly crystallized, mp 118-9 °C: IR ($CDCl_3$) 1709, 1448, 1301, 1140 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.85-7.95 (m, 2 H), 7.45-7.75 (m, 3 H), 4.68 (dt, $J$ = 13.4, 1.9 Hz, 2 H), 4.04 (dd, $J$ = 9.5, 3.5 Hz, 1 H), 2.65-2.95 (m, 3 H), 2.35-2.55 (m, 2 H), 2.20-2.3 (m, 4 H), 1.45-1.75 (m, 3 H); calcd for $C_{17}H_{20}O_3S$ 304.1133, found 304.1101.

**(c) 2-Methylene-1,2,3,4,5,6-hexahydroinden-4-one (67, $n$ = 1).** A suspension of 0.5 g of Woelm alumina in 2 mL of dry dichloromethane containing 69 mg (0.24 mmol) of keto sulfone **66** ($n$ = 1) was stirred until TLC indicated disappearance of starting material (reaction must be promptly stopped since extended contact time promotes isomerization). The alumina was removed by filtration and washed with additional dichloromethane. The combined organic layers were concentrated in vacuo to give 31 mg (88%) of the title compound: IR ($CHCl_3$) 1655, 1630, 1452, 1438, 1408 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.0 (m, 2 H), 3.27 (m, 2 H), 3.21 (m, 2 H), 2.39 (m, 4 H), 2.33 (m, 2 H); calcd for $C_{10}H_{12}O$ 148.0888, found 148.0887.

**(d) 2-Methylene-2,3,5,6,7,8-hexahydroazulen-4-one (67, $n$ = 2).** As above, 56 mg (0.184 mmol) of keto sulfone 66 ($n$ = 2) was treated with 0.5 g of neutral Woelm alumina in 2 mL of dry dichloromethane to give 28 mg (93%) of the enone 67 ($n$ = 2): IR ($CDCl_3$) 1640, 1618, 1450, 1420, 1382 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.94 (m, 2 H), 3.30 (m, 4 H), 2.59 (m, 2 H), 2.42 (m, 2 H), 1.80 (m, 4 H); calcd for $C_{11}H_{14}O$ 162.1045, found 162.1048.

**(e) 2-Methyl-4,5,6,7-tetrahydroinden-7(1*H*)-one (68, $n$ = 1).** A suspension of 1.0 g of neutral Woelm alumina in 2 mL of dry dichloromethane containing 129 mg (0.44 mmol) of keto sulfone 66 and 0.1 mL of triethylamine was stirred 24 h at room temperature. The reaction was filtered, and the alumina was washed with dichloromethane. Concentration of the combined organic layers and flash chromatography (2:1 ether/hexane) gave 55 mg (84%) of conjugated dienone **68** ($n$ = 1): IR ($CDCl_3$) 1636, 1539, 1420, 1407 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 6.13 (q, $J$ = 1.3 Hz, 1 H), 3.15 (td, $J$ = 3.0, 1.1 Hz, 2 H), 2.52 (m, 2 H), 2.38 (t, $J$ = 6.3 Hz, 2 H), 2.11 (d, $J$ = 1.3 Hz, 3 H), 1.95-2.0 (m, 2 H); calcd for $C_{10}H_{12}O$ 148.0888, found 148.0887.

**(f) 2-Methyl-3,4,5,6,7,8-hexahydroazulen-4-one (68, $n$ = 2).** A solution of 106 mg (0.349 mmol) of keto sulfone 66 ($n$ = 2) and 106 mg (0.697 mmol) of DBU in 2 mL of dry dichloromethane was stirred 1 h at room temperature. Removal of solvent in vacuo and flash chromatography (2:1 ether/hexane) gave 40 mg (70%) of conjugated dienone **68** ($n$ = 2): IR ($CDCl_3$) 1618, 1605, 1545, 1395 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 6.02 (m, 1 H), 3.26 (td, $J$ = 3.0, 0.8 Hz, 2 H), 2.64 (m, 4 H), 2.05 (d, $J$ = 1.4 Hz, 3 H), 1.8 (m, 4 H); calcd for $C_{11}H_{14}O$ 162.1045, found 162.1047.

**(g) Diels-Alder Reaction of Dienone (68, $n$ = 1).** A solution of 20 mg (0.13 mmol) of dienone 68, $n$ = 1, and 26 mg (0.27 mmol) of maleic anhydride in 0.5 mL of dry benzene was stirred 24 h at room temperature. Direct flash chromatography (2:1 hexane/ethyl acetate) gave 16 mg (48%) of adduct **69** as a crystalline solid, mp 105-6 °C: IR ($CDCl_3$) 1858, 1775, 1705, 1448, 1228 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.08 (d, $J$ = 1.8 Hz, 1 H), 3.82 (d, $J$ = 8.2 Hz, 1 H), 3.40 (d, $J$ = 8.2 Hz, 1 H), 2.66 (d, $J$ = 4.4 Hz, 1 H), 2.61 (d, $J$ = 4.4 Hz, 1 H), 2.53 (dt, $J$ = 16.3, 3.5 Hz, 1 H), 2.0-2.33 (m, 2 H), 1.90 (d, $J$ = 8.8 Hz, 1 H), 1.6-1.8 (m, 1 H), 1.59 (d, $J$ = 8.8 Hz, 1 H), 1.55 (s, 3 H); calcd for $C_{14}H_{14}O$ 246.0892, found 246.0901.

**Reductive Desulfonylation of Cycloadducts. (a) 2-Methylene-3a$\beta$-octahydroinden-4$\beta$-ol (71 + 72, $n$ = 1).** Powdered sodium amalgam (6%, 690 mg, 1.8 g-atom) was added portionwise to 135 mg (0.459 mmol) of hydroxysulfone (**32**, R = H, $n$ = 1) and 262 mg of disodium acid phosphate in 4 mL of dry methanol at room temperature. After 3 h, additional portions of the acid phosphate (200 mg) and 6% sodium amalgam (400 mg, 1.04 g-atom) were added, and stirring was continued an additional 2 h. Addition of water was followed by pentane extraction. The pentane layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was flash chromatographed (2:1 ether/hexane) to give 48 mg (68%) of the desulfonylated products. VPC analysis showed two peaks at 6.3 min (65%) and 7.1 min (35%): IR ($CDCl_3$) 3605, 1450, 1435 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.87 (m, 2 H), 3.41 (m, 1 H), 0.8-2.8 (m, 13 H); calcd for $C_{10}H_{16}O$ 152.1201, found 152.1189.

**(b) 2-Methylene-3a$\beta$-decahydroazulen-4$\beta$-ol (71 and 72, $n$ = 2).** By using the above procedure, 143 mg (0.464 mmol) of hydroxy sulfone (**32**, R = H, $n$ = 2) was reductively desulfonylated with 6% sodium amalgam (690 mg, 1.8 g-atom and 300 mg, 0.783 g-atom) to give 63 mg (81%) of product. VPC analysis shows equal amounts of two isomers of retention times, 11.5 and 11.8 min: IR ($CDCl_3$) 3605, 1656, 1630, 1449, 1430 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.75 (m, 2 H), 3.25-3.60 (m, 1 H), 2.40-3.15 (m, 3 H), 1.2-2.4 (m, 12 H); calcd for $C_{11}H_{18}O$ 166.1358, found 166.1359.

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# Synthesis of Hydroxylated 1-Azabicyclo[3.1.0]hexane and Prolinol Derivatives by Stereo- and Regiocontrolled Staudinger Aminocyclization. Application to the Nonproteinogenic Amino Acid (2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline (HMP) and Its Enantiomer

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**Abstract:** On treatment with triphenylphosphine the azido epoxides **8/11** form enantio- and diastereomerically pure 1-azabicyclo[3.1.0]hexanes (**9/12**) via a Staudinger type aminocyclization reaction. Benzoic acid anhydride opens the aziridine ring in **9/12** to give prolinol derivatives (**20/23**) exclusively, whereas Boc anhydride shows a strong preference for the formation of hydroxypiperidine derivatives (**21/22**). The bicyclic amines **12** may also be prepared by aminocyclization of the ditosylates **25** and, analogously, prolinols **24** may be obtained from the monomesylates **7**. This novel methodology is applied to the synthesis of the rare amino acid HMP (**4**) and its enantiomer.

1-Azabicyclo[3.1.0]hexanes (**1**) are interesting synthetic intermediates.[1] They are found as an important structural feature in complex natural products (azinomycins) with antitumor activity.[2] On the other hand, proline derivatives such as **2** have

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