choice of initial conditions by examining the data in Figure 4 and comparing the behavior exhibited by the various limiting cases given in Figures 6-8. First, no delay in the decay in the transient absorption signal at 520 nm is observed following photolysis. Thus, models that involve preferential bonding to the terminal alkane region of the solvent will not be able to describe the experimental data. Second, the decay curves exhibit a concave rather than convex curvature. Thus, models that only involve binding to the ends of the solvent will also fail in describing the data. These observations along with the distribution extracted from the ethanol data suggest that a random (or nearly random) solvent coordination model is appropriate.

In Figure 4, the dashed lines are the best fit of a random bonding model (eq 9) requiring that a single rate constant for $k_{C-C}$ be used to fit the entire set of data. The best value found for $k_{C-C}$ was $4 \times 10^9$ s$^{-1}$. The agreement between the calculated and experimental curves for the entire set of data using this rate constant for the migration between carbon atoms strongly supports the conclusion that a unimolecular reaction model can account for the transient absorption dynamics.

We attempted to fit the data using other sets of initial conditions. Small changes from a random distribution have essentially no effect on the quality of the fit. However, as described qualitatively above, models that bias the terminal regions or the center regions of the chain show poor agreement with the data. These observations strongly suggest that photolysis results in random coordination of the metal to all available solvent sites.[15]

In carrying out these simulations, we assumed that the quantum yield for dissociation was solvent independent, thus allowing one to determine relative values of $\epsilon_{OH}$ and $\epsilon_{CH}$ directly from transient absorption measurements. If this assumption is not true, then from eq 7, the simulated curves would be affected. We have examined the effect of the $\epsilon_{OH}$:$\epsilon_{CH}$ ratio on the calculated curves. Changes in this ratio by ±20% had only a small effect on the determination of either $k_{C-O}$ or $k_{C-C}$. In any case, the agreement between the calculated and experimental data is similar to that shown in Figure 4.

In these calculations we have not taken into account the potential role of hydrogen bonding between alcohol molecules. It is possible that in the $Cr(CO)_5(ROH)$ complex the hydroxyl end of the coordinated molecule is hydrogen bonded to a second solvent molecule. In this case, formation of $Cr(CO)_5(HOR)$ would not only involve rupturing of a Cr-alkane bond but also an intermolecular hydrogen bond. Insight into the time scales for this latter process can be obtained from dielectric relaxation studies. The longest Debye relaxation time observed for neat alcohol solutions is commonly associated with the dynamics of intermolecular hydrogen bond breakage.[14a] At 20 °C the Debye relaxation time ranges from 196 ps for ethanol to 1.2 ns for hexanol. These relaxation times are significantly longer than those reflected by the time-resolved absorption data for the relaxation of photogenerated $Cr(CO)_5(ROH)$ to $Cr(CO)_5(HOR)$. From this comparison, we conclude that the rate of breakage of an intermolecular hydrogen bond does not affect the kinetics of the migration process.

**Acknowledgment.** This work is supported by the National Science Foundation. J.D.S. thanks Professor Peter Armentrout for his suggestion of the unimolecular reaction model. We thank Professor Keith Nelson for preprints of his femtosecond work.

**Registry No.** $Cr(CO)_6$, 13007-92-6; *i*-Pro, 67-63-0; cyclohexane, 110-82-7; methanol, 67-56-1; ethanol, 64-17-5; *n*-propanol, 71-23-8; butanol, 71-36-3; pentanol, 71-41-0; octanol, 111-87-5.

# Heteroatom-Directed π-Facial Diastereoselection in Diels–Alder Cycloadditions of Plane-Nonsymmetric Cyclopentadienes

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**Abstract:** The synthesis of a series of pentamethylcyclopentadienes bearing stereogenic C-5 heteroatom substituents and their reactions in [4 + 2] cycloadditions with maleic anhydride and/or *N*-phenylmaleimide are described. Cyclopentadienes (**13**, **14**, **6**, **7**, and **1**) containing the substituents OH, $OCH_3$, $NH_2$, NHAc, and Cl reacted to form syn adducts preferentially. In contrast, with compound **8** (SH) only slight syn discrimination was observed, while the facial selectivity was reversed with other sulfur substituents ($SCH_3$, SPh, $SCH_2Ph$, $SOCH_3$, $SO_2CH_3$) (compounds **9**, **3**, **2**, **10**, and **11**), and anti adducts were the major or exclusive products. This behavior is consistent with the σ donor ability of the C–X versus the C–C bond so that cycloaddition occurs preferentially anti to the best donor due to hyperconjugation of this antiperiplanar σ bond with the developing incipient bond(s).

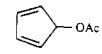
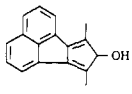
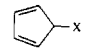
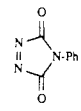
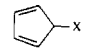
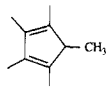
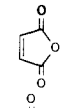
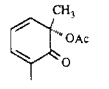
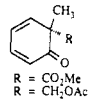
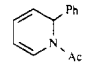
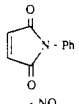
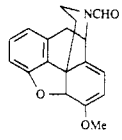
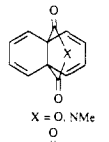
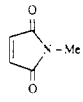
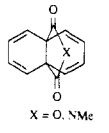
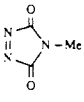
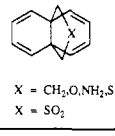
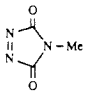
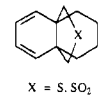
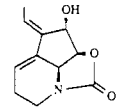
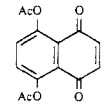
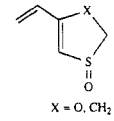
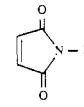
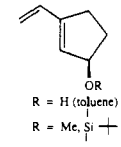
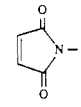
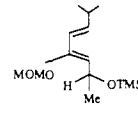
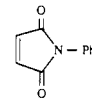
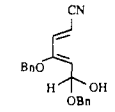
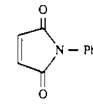
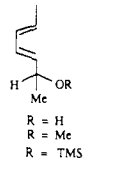
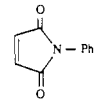
The synthetic utility of the Diels–Alder reaction is well-established.[1] Its continued popularity and study rests, in part, on the ability to generate four new contiguous stereogenic centers in one synthetic step. The regiochemistry may be controlled by the appropriate choice of substituents, and the topography (endo or exo) may be influenced by the electronic nature of the groups attached to the dienophile. A third stereochemical feature, the π-facial diastereoselectivity, which arises when the addends possess two different reactive faces is also important. Frequently the presence of at least one center of chirality imparts sufficient perturbation to influence the diastereofacial selectivity. Alternatively, facial selectivity can be influenced by a chiral auxiliary in which one face of the diene or dienophile is blocked preferentially.[2] Incorporation of a single stereogenic center in an allylic position of either a dienophile or a diene, particularly when a heteroatom is present, is known to exert a directing influence, although the exact factors responsible for the observed facial stereoselection are still imperfectly understood. Nevertheless,

(1) (a) Desimoni, G.; Tacconi, G.; Bario, A.; Pollini, G. P. *Natural Product Syntheses through Pericyclic Reactions*; ACS Monograph 180; American Chemicalla Society: Washington, DC, 1984; Chapter 5.

(2) (a) Helmchen, G.; Karge, R.; Weetman, J. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: New York, 1986; p 261. (b) Paquette, L. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Chapter 7. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, 876.

0002-7863/90/1512-1136$02.50/0 

**Table I.** Diene π-Facial Selectivity: Influence of Allylic Substituents

| entry | diene | dienophile | selectivity (~ratio) | ref |
|---|---|---|---|---|
| 1 |  |  | syn (10:0) | 3 |
| 2 |  |  | syn (10:0) | 4 |
| 3 |  |  | syn (9:1) | 5 |
| 4 |  |  | anti (10:0) | 6 |
| 5 |  |  | anti (1.5:1) (10:0) | 7 |
| 6 |  |  | anti (4:1) | 8 |
| 7 |  |  | syn (10:0) | 9 |
| 8 |  |  | anti (3:1) (0.9:1) | 10 |
| 9 |  |  | syn (3:1) | 11 |
| 10 |  |  | syn (10:0) | 12 |
| 11 |  |  | anti (10:0) | 13 |
| 12 |  |  | syn (10:0) | 14 |
| 13 |  |  | anti (10:0) syn (9.5:0.5) | 14 14 |
| 14 |  |  | syn (10:0) | 14 |
| 15 |  |  | anti(OH) (~9:1) | 15 |
| 16 |  |  | anti (10:0) | 16, 17 |
| 17 |  |  | syn (6.4:3.6) anti (10:0) | 17 |
| 18 |  |  | syn (10:0) | 18 |
| 19 |  |  | syn (10:0) | 19 |
| 20 |  |  | syn (1.7:1) (5:1) (7.3:1) | 20 |
| 21 |  |  | anti (2:1) | 21 |
| 22 |  |  | anti (2.7:1) | 20 |
| 23 |  |  | anti (3:1) | 22 |

considerable progress has been achieved, particularly within the context of asymmetric organic synthesis.[1,2]

Previous studies have examined 1,3-cyclopentadienes,[3-8] 1,3-cyclohexadienes,[9-14] conformationally locked 1(*E*)-substituted 1,3-dienes,[15-17] and acyclic 1,3-dienes containing allylic substitution.[17-22] Space limitations preclude an exhaustive list, but

(3) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183.
(4) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1980**, 739.
(5) (a) Williamson, K. L.; Hsu, Y. L.; Lacko, R.; Young, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 6129. (b) Williamson, K. L.; Hsu, Y. L. *J. Am. Chem. Soc.* **1970**, *92*, 7385. (c) Bianchi, G.; De Micheli, C.; Gamba, A.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 137.
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(11) Krow, G. R.; Carey, J. T.; Zacharias, D. E.; Kraus, E. E. *J. Org. Chem.* **1982**, *47*, 1989.
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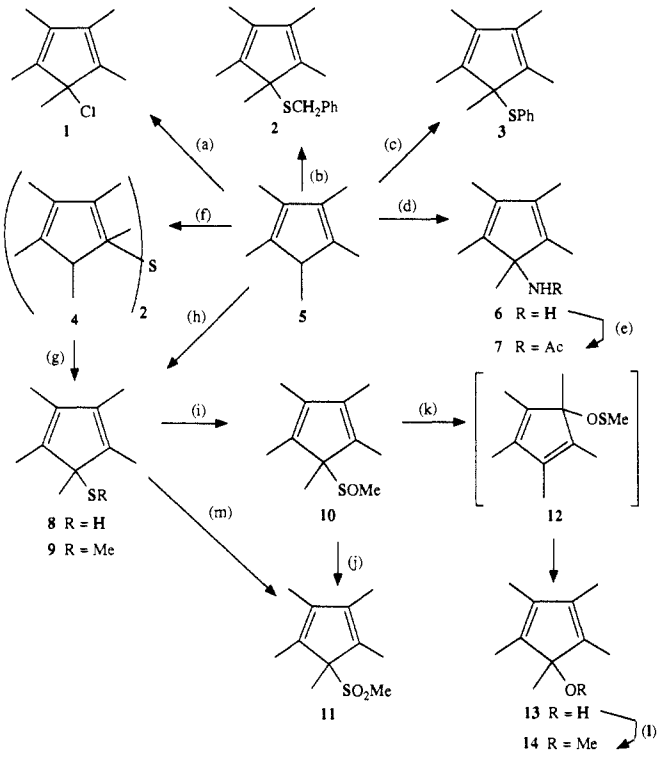
(13) Kaftory, M.; Peled, M.; Ginsburg, D. *Helv. Chim. Acta* **1979**, *62*, 1326.
(14) (a) Gleiter, R.; Ginsburg, D. *Pure Appl. Chem.* **1979**, *51*, 1301. (b) Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095.
(15) Grabby, S.; Kluge, H.; Hoppe, H.-U. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 664.
(16) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

**Scheme I**[a]

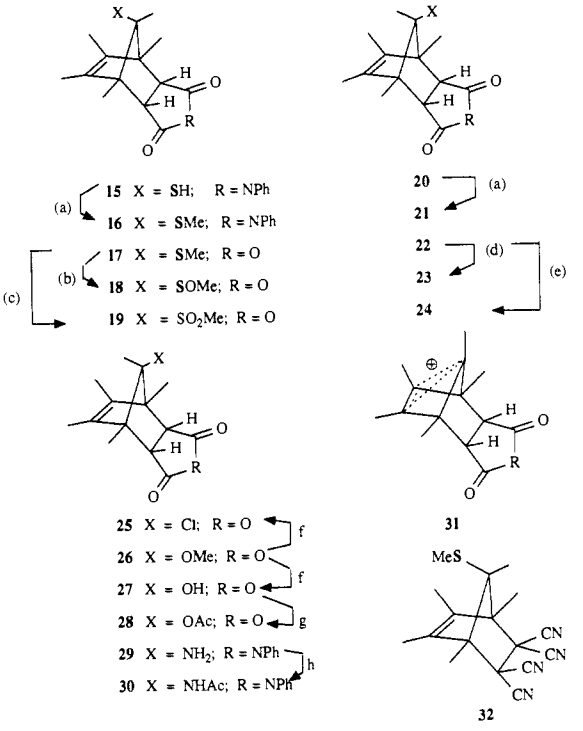



[a] (a) *n*-BuLi, THF, −78 °C, 30 min; NCS, −78 °C to −20 °C, 17 h, 65%; (b) *n*-BuLi, THF, 0 °C, 30 min; $(SCH_2Ph)_2$, 0 °C to 22 °C, overnight, 53%; (c) *n*-BuLi, THF, 0 °C, 30 min; $(SPh)_2$ 0 °C to 22 °C, overnight, 56%; (d) *n*-BuLi, THF, 22 °C, 40 min; $(Ph)_2P(O)ONH_2$, −18 °C to 22 °C, 18 h, 37%; (e) $Ac_2O$, Py, $CH_2Cl_2$, 22 °C, 18 h, 72%; (f) *n*-BuLi, ether, 22 °C, 2 h; $SCl_2$, 0 °C, 34%; (g) Na, $NH_3$, THF, −78 °C, 2 min, 44%; (h) *n*-BuLi, THF, 0 °C, 30 min; $(SMe)_2$, 0 °C to 22 °C, overnight, 68%; (i) *m*-Cl-$C_6H_4CO_3H$, $CH_2Cl_2$, −78 °C, 1.5 h, 93%; (j) *m*-Cl-$C_6H_4CO_3H$, $CH_2Cl_2$, 0 °C, 2 h, 93%; (k) $(MeO)_3P$, MeOH, 22 °C, 22 h, 90%; (l) NaH, THF, 0 °C, 30 min; $CH_3I$, 22 °C, 3.5 days, 90%; (m) oxone, MeOH, $H_2O$, 0 °C, 15 min; 22 °C, 2.5 h, 54%.

examples of all of the important cases are summarized in Table I. In many of these cycloadditions, the dienophile reacts preferentially with the more sterically hindered syn face[23] of the cyclic dienes, when the allylic group contains an electronegative heteroatom. However, the geometric orientation and steric bulk of this functionality with respect to the diene is clearly important. The selectivity is diminished in the acyclic cases, probably as a result of increased nonbonded interactions, although here also, there is a syn preference. In contrast, cycloadditions with many locked dienes, other than hydroxyl-substituted dienes and cyclopentadienes, occurred preferentially from the diene face anti to the allylic substituent. Frequently, the interpretation of these results is complicated by the necessity of determining the relative contribution and reactivity of various conformers in which the heteroatom is aligned "inside" as predicted by electronic factors or "outside" as favored on steric grounds. As described below, cyclic dienes avoid this complication. In addition, examples that are plane-nonsymmetric afford insight into the "addition directing" influence of diverse functional groups.

Clearly, a number of different factors influence the facial selectivity in these cycloadditions, and an all embracing explanation that will account for the examples listed and be of predictive value is not obvious. The important factors that must be considered include steric effects, complexation between the diene and dienophile, secondary orbital interactions including tilting and torsional effects, polarizability, and electrostatic interactions. Prior to the present study, no experimental evidence was available concerning the role of allylic sulfur or nitrogen substituents on cycloadditions in a related series of cyclopentadienes, although a priori they might be expected to resemble their oxygen and chlorine analogues.

**Scheme II**[a]




[a] (a) DBU, $CH_3I$, $C_6H_6$, 22 °C, 2 days, 100%; (b) *m*-Cl-$C_6H_4CO_3H$, $CH_2Cl_2$, −78 °C, 15 min, 83%; (c) *m*-Cl-$C_6H_4CO_3H$, $CH_2Cl_2$, −78 °C, 40 min, 22 °C, 6 h; 40 °C, 16 h, 81%; (d) *m*-Cl-$C_6H_4CO_3H$, $CH_2Cl_2$, −78 °C, 45 min, −78 °C to 22 °C, 91%; (e) *m*-Cl-$C_6H_4CO_3H$, $CH_2Cl_2$, −78 °C, 30 min; 22 °C, 5 h; 40 °C, 16 h; *m*-Cl-$C_6H_4CO_3H$, 22 °C, 4 h, 68%; (f) NaI, $Me_3SiCl$, $CH_3CN$, 22 °C, 4.5 days, 49% **25**, 22% **27**; (g) $Ac_2O$, DMAP, $C_6H_6$, 80 °C, 5.5 days, 52%; (h) $Ac_2O$, Py, $CH_2Cl_2$, 22 °C, 23 h, 100%.

## Results

**Preparation of Cyclopentadienes.** The requisite cyclopentadienes **1–14** were synthesized from 1,2,3,4,5-pentamethylcyclopentadiene (**5**) as outlined in Scheme I. Potential complications from competing [1,5] sigmatropic rearrangements were avoided, since these isomerizations are degenerate and also require more forcing conditions than those anticipated for the room temperature (22 °C) cycloadditions.[24] The amine **6** was prepared as described

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(21) Messager, J. C.; Toupet, L. *Acta Crystallogr., Sect. B: Struct. Sci.* **1986**, *B42*, 371.
(22) (a) Kozikowski, A. P.; Nieduzak, T. R.; Konoike, T.; Springer, J. Pp. *J. Am. Chem. Soc.* **1987**, *109*, 5167. (b) Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1988**, 167.
(23) The nomenclature used to describe the relative stereochemistry of C-7 substituted norbornenes employs the prefix anti when the substituent is on the side of the bridge remote from the double bond. However, this is the adduct which arises from syn attack of the dienophile on a substituted cyclopentadiene. Thus, to avoid confusion the use of the terms syn and anti are restricted to descriptors for the facial approach of the addends so that the syn adducts result from the syn approach of the reactants. This is standard usage; however, an altenative nomenclature is possible such as like and unlike or distal and proximal. On the basis of the Seebach–Prelog convention (Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654) the relative topicities of the approach to the face of an enantiomer are unlike (anti) when the addition occurs on the si face of a double bond possessing an adjacent R allylic center. However for consistency a predetermined priority order must be followed that may differ from the standard sequence rules. Similarly the terms distal and proximal are more useful to describe conformational geometries.
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Table II. Facial Stereoselection of Cycloadditions of C-5 Substituted Cyclopentadienes

| entry | compd | X | reaction time[a] | addition ratio anti | addition ratio syn |
|---|---|---|---|---|---|
| a | **1** | Cl | 30 min | 0 | 10 |
| b | **13** | OH | <30 s | 0 | 10 |
| c | **14** | OMe | <10 min | 0 | 10 |
| d | **6** | $NH_2$ | 3.5 h | 0 | 10[b] |
| e | **7** | NHAc | 3.5 h | 0 | 10 |
| f | **7** | NHAc | 3.5 h | trace | 10[b] |
| g | **8** | SH | 3 h | 4.5[b] | 5.5[b] |
| h | **9** | SMe | 27.5 h | 9 | 1 |
| i | **9** | SMe | 46 h | 9.3[b] | 0.7[b] |
| j | **9** | SMe | <30 s | 10[c] | 0 |
| k | **2** | $SCH_2Ph$ | 48 h | 9 | 1 |
| l | **3** | SPh | 1 h | 9.7 | 0.3 |
| m | **10** | SOMe | 48 h | 10 | 0 |
| n | **11** | $SO_2Me$ | 9 days | 10 | 0 |
| o | **5** | H | <30 s | 2 | 8 |

[a] Approximate time for diene disappearance (TLC); reactions were run at 22 °C; ratios were determined by integration of $^1H$ NMR spectra of the total reaction mixture. [b] *N*-Phenylmaleimide adduct. [c] Tetracyanoethylene adduct.

previously.[25] The parent C-5 alcohol **13** was obtained via the [2,3] sigmatropic rearrangement of the sulfoxide **10** in the presence of a thiophile (trimethyl phosphite) to give **13** directly without the necessity of isolating the intermediate sulfenate ester **12**. Alkylation of **5** (*n*-BuLi, $R_2S_2$) provided the thioethers **2**, **3**, and **9**. The methyl sulfoxide **10** and the sulfone **11** were prepared by oxidation (*m*-$ClC_6H_4CO_3H$) of **9**. Conventional approaches to the mercaptan **8** were unsuccessful. Thus the required material was synthesized from the symmetrical sulfide **4**[26] by sodium/ammonia reduction under carefully controlled conditions. The chloro compound **1** was generated by treating lithium pentamethylcyclopentadiene with *N*-chlorosuccinimide. Unfortunately various attempts to prepare the acetate derivative were unsuccessful since it decomposed rapidly even at low temperature to tetramethylfulvene, and in situ trapping afforded only the fulvene adduct. An authentic sample of the anticipated acetate adduct **28** was prepared independently (Scheme II). Maleic anhydride and/or *N*-phenylmaleimide were employed as the dienophiles on the basis of their reactivity, their established endo selectivity, and their use in previous work, thus facilitating comparisons with earlier studies.

**Cycloadditions.** The results of the room temperature (22 °C) cycloadditions are summarized in Table II. The overwhelming facial preference for syn addition of the chlorine, oxygen, and nitrogen compounds is clearly evident. Of particular significance is the striking reversal of facial selectivity encountered with the sulfur substituents. In addition to being of fundamental interest, these results have potential synthetic utility as do the considerable differences in relative cycloaddition rates within the series.

The structures and stereochemistry of the adducts **15–30** (Scheme II) were established by a combination of X-ray crystallography, spectral analysis, and the chemical correlations summarized in Scheme II. The complete stereostructures of the syn oxygen adducts **26** and **27**, the anti sulfur-substituted adducts **18** and **32**, and the syn chloro adduct were established unambiguously by single-crystal X-ray diffraction. The structural features in all cases are similar, and thus only the drawing for the alcohol product is shown in Figure 1.

Separate samples of the syn and anti mercapto *N*-phenylmaleimide adducts **15** and **20** were methylated with diazabicyclo[5.4.0]undecene (DBU) and methyl iodide to afford products **16** and **21**. These were identical with the adducts obtained from cycloaddition of the thiomethyl diene **9** with *N*-phenylmaleimide. The syn and anti thiomethyl–maleic anhydride adducts were oxidized independently with *m*-chloroperbenzoic acid to the corresponding sulfoxides **23** and **18** and the sulfones **24** and **19**, respectively. The anti compounds were consistent with the structural assignments and indistinguishable from the Diels–Alder adducts. The syn products **23** and **24** were shown to be both different from **18** and **19** and absent from the Diels–Alder reactions of maleic anhydride with **10** and **11**, respectively. Additional structural support was provided by NOE difference (DNOE) measurements on the anti sulfur adducts (X = SMe, SOMe, $SCH_2Ph$, SPh). In these cases the DNOE observed (6–8.5%) between the C-7 methyl group and the exo methine hydrogens established their proximal relationship. In addition, the syn amino acetate–maleic anhydride adduct displayed a 7% DNOE between the exo methine protons and the amine hydrogen. Comparison of the chemical shifts of the exo methine protons in the syn and anti sulfur series **22**, **23**, **24** and **17**, **18**, **19** revealed a consistent downfield shift (~0.5 ppm) in the syn compounds. Furthermore compared to the thioether, the syn sulfoxide **23** deshielded these hydrogens preferentially. They resonated as doublets ($J$ = 8 Hz) at δ 3.57 and 3.95, respectively (anti isomer, 3.17 and 3.20, $J$ = 7.8 Hz).

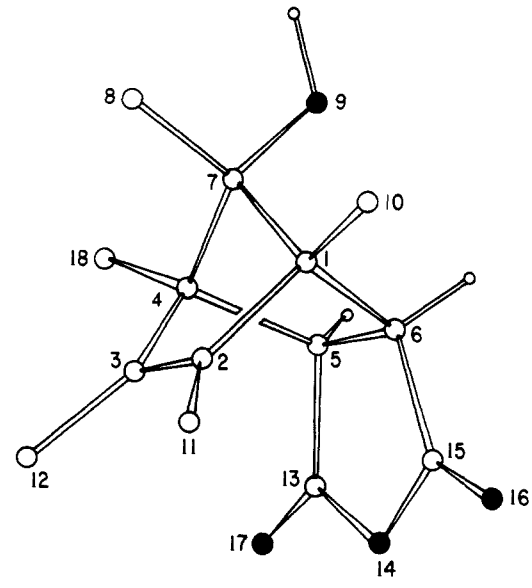


**Figure 1.** A view of 7-hydroxy-1,2,3,4,7-pentamethylbicyclo[2.2.1]-hept-2-ene-5,6-dicarboxylic anhydride (**27**). H-atoms are shown only where they help in visualizing the stereochemistry. C and O atoms are represented by open and solid circles, respectively, and H-atoms by smaller open circles.

In keeping with previous studies of Diels–Alder reactions, it was assumed that the product distributions were kinetic. Experimental confirmation was provided by heating the adducts above the cycloaddition temperature. Samples of the syn and anti thiomethyl adducts **22** and **17** and the syn hydroxy adduct **27** were recovered unchanged after refluxing in benzene for 24 h. A similar result was encountered when these experiments were conducted in refluxing toluene (17.5 h), although in the case of the anti compound **17**, a small amount of isomerization occurred (anti/syn ~10:1).

In the oxygen and nitrogen series the corresponding acetates **28** and **30** were prepared with acetic anhydride, although the alcohol required rather forcing conditions (80 °C, 5.5 days). As anticipated, treatment of the methoxy adduct **26** with chlorotrimethylsilane and sodium iodide in acetonitrile afforded the alcohol **27**, but it was not the major product. Instead the syn chloro adduct **25** was generated, and it became the sole product when sodium iodide was excluded. This unexpected behavior is likely a consequence of the unusual features present in the C-7

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Table III. UV Spectra of Selected Cyclopentadienes

| entry | compd | X | $\lambda_{max}$(hexane) $\epsilon$ |
|---|---|---|---|
| a | **13** | OH | 240 nm (sh) (1080), 279 nm (1040) |
| b | **7** | NHAc | 270 nm (2600) |
| c | **9** | SMe | 253.5 nm (1400), 285.5 nm (1000) |
| d | **10** | SOMe | 262.5 nm (4830) |
| e | **11** | $SO_2Me$ | 274 nm (2410) |

substituted norbornene which allow the formation of the carbonium ion **31** and its capture by chloride.[27] The alkyl iodide may also be formed, but it appears to be very labile and is readily replaced by hydroxide or chloride.

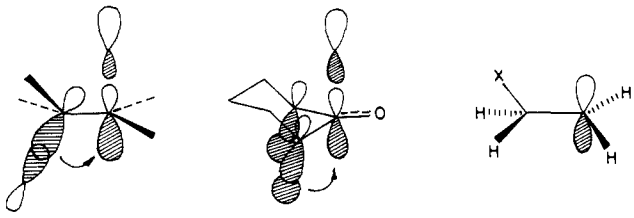
## Discussion

The results of these cycloadditions establish the strong preference for syn addition with chlorine, oxygen, and nitrogen substituents in competition with a methyl group. The reversal of facial selectivity encountered with the sulfur substituents is unexpected but holds promise for interesting synthetic applications. The differences in the relative cycloaddition rates reflect, in part, the extent of the interaction between the reactive diene face and the heteroatom. One measure of this interaction may be reflected in the ultraviolet spectra of the dienes. Table III lists the absorption maxima and extinction coefficients for some of the more stable cyclopentadienes. Compared to cyclopentadiene (238.5 nm, 3400)[28] all the compounds display a bathochromic shift, but there does not appear to be a simple correlation beween these excited-state measurements and the observed cycloaddition behavior.

In the case of the sulfoxide **10** and the sulfone **11**, their large size will cause the dienophile to approach anti, so that addition occurs on the sterically less encumbered methyl face. This is in accord with earlier work which demonstrated that the electronically governed facial selectivity was diminished with a methyl substituent (Table I, entry 0) and was primarily regulated by steric interactions.[8] Thiomethyl and thiol functions are somewhat larger (bulkier) than the corresponding methyl ether and hydroxyl groups, but the relative steric size difference depends in part on the type of parameters and experimental conditions selected.[29] We favor the *n* values[29b] as a measure of steric volume which assigns relative values of 9.5 and 10.3 for the OMe and SMe groups, respectively. Thus the reduced reactivity and the inversion of facial preference for the thiomethyl derivative **9** compared to the methyl ether **14** indicates there is a significant electronic difference in these systems in spite of the fact that the steric bulk is not identical.

For C-5 oxygen-substituted cyclopentadienes, the preferential syn (contrasteric) approach has been rationalized by Fukui and co-workers by orbital mixing between the lone-pair electrons and the diene (HOMO).[30] Alternatively, Anh suggested that a beneficial interaction of the antisymmetric oxygen orbital with the diene LUMO is the dominant influence.[31] In carbocyclic systems such as isodicyclopentadiene, favorable $\sigma/\pi$ interactions are considered responsible for endo attack, and this has been extended to heterocyclic systems.[32] Secondary orbital interactions were considered responsible for the exclusive syn addition of triazolinediones to anhydride and imide-bridged [4.4.3]propellane dienes (Table I, entries 12 and 14)[14] in which the heteroatom bridge is homoallylic. However, this rationalization is not applicable to either *N*-phenylmaleimide or maleic anhydride, and thus the facial selectivity is reversed (entry 11) upon changing the dienophile.[13] In addition, as entries 13 and 14 indicate, the presence of neighboring carbonyl groups and double bonds also influence the selectivity. On the basis of electrostatic interactions Kahn and Hehre concluded that electrophilic dienophiles should add preferentially to the more nucleophilic diene face, syn to "a lone-pair-containing allylic substituent".[33] Clearly this simple electrostatic model cannot be extended in a straightforward manner to sulfur systems. In addition, it was found that, in a propelladiene containing both oxygen and sulfur bridges, cycloaddition was anti to oxygen and syn to sulfur.[14]

Chart I




33 34 35

In the case of 1(*E*)-substituted 1,3-dienes the anti facial selectivity was attributed to destabilizing electronic interactions between the heteroatom and the dienophile in the syn transition state.[17] As illustrated in Table I (entries 18–20, 21–23), it will be noted that acetylene dicarboxylates and tetracyanoethylene exhibit reversed facial selectivity in these acyclic dienes. Thus the thiomethyl diene **9** was treated with tetracyanoethylene (Table II, entry j). A single anti adduct was obtained whose structure **32** was established by X-ray analysis, and no reversal was observed. The planarity and reactivity of the dienophile does influence the facial attack, and it seems likely that in the acyclic cases the predominance of the anti product is a consequence of the preferential trapping of a different rotamer ratio compared to maleic anhydride or *N*-phenylmaleimide. Recent investigations have concluded that nonbonded interactions are of prime importance in these cases as well as for semicyclic dienes.[34] This should allow a measure of facial control by variation of the dienophile that has not been encountered with the cyclopentadienes. However, caution must be exercised in comparing certain dienophiles as recent evidence has indicated that cyanoethylenes and triazolinediones react by an aziridinium imide (1,4-zwitterion) mechanism.[35]

Previous explanations of facial selectivities have tended to focus on the ground-state properties of the substrates which create the $\pi$-facial diastereoselection. An alternative analysis invokes the interaction of the incipient bond with the two nonequivalent faces. This interaction arises due to the differences in the relative stabilities of the diastereomeric transition states.[36] Recently, Cieplak, Tait, and Johnson have expanded upon this concept of transition state stabilization by $\sigma$ electron donation into the vacant $\sigma_+$* orbital associated with the incipient bond.[37] This arises from hyperconjugation of the antiperiplanar $\sigma$ bond with this orbital. This model correctly accounts for the syn approach of a butadiene to 5-fluoroadamantane-2-thione, studied by le Noble and co-workers,[38] where the electrostatic model fails. They demonstrated that for both thermal and photochemical reactions bond formation occurs at the face anti to the most electron-rich $\sigma$ bond. In their study of C-3 substituted cyclohexanones and methylenecyclohexanones Cieplak, Tait, and Johnson[37] found that electronegative cyclohexane substituents and increased electronegativity of a

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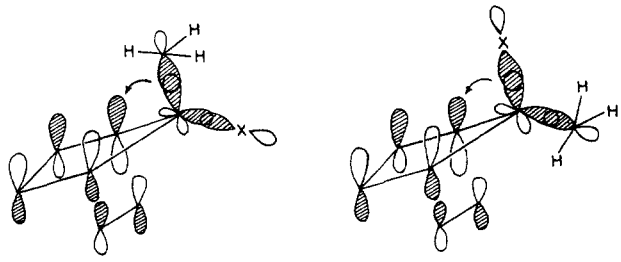
**Chart II**



36 37

substituent in the carbon nucleophile both increased axial attack. Their rationalization of this behavior depends upon the torsional interactions during bond formation, particularly with the neighboring bonds. This is illustrated in general terms (**33**, Chart I) and for the case of cyclohexanone (**34**, Chart I) where hyperconjugative σ assistance favors axial attack because the CH bonds are better σ donors than CC bonds.[37,39]

Applied to cycloadditions such as pentachlorocyclopentadiene (Table I, entry 3), attack syn to chlorine was expected to increase with the addition of electronegative groups to the dienophile as observed by Williamson et al.[5,40] This is consistent with the fact that $\sigma_{CH}$ is a better donor than $\sigma_{CCl}$. The related concept of torsional strain was also considered a major influence by Houk and collaborators[41] in accounting for stereoselection in acyclic systems and cycloadditions of isodicyclopentadienes. Generally, when an electron acceptor bond is suitably aligned with a π system, the energy of both HOMO and LUMO orbitals are lowered so that the electrophilicity of the π system is enhanced and the nucleophilicity decreased.[37]

Computational studies of β-substituted ethyl radicals[42] appear to offer additional insight into the behavior of the cyclopentadienes, since, at one extreme, the Diels–Alder reaction has some characteristics of a free-radical reaction.[43] Consistent with the incipient orbital principle it was found that hyperconjugation was mainly responsible for the conformational preference in substituted radicals. First-row elements prefer an eclipsed conformation with a small rotational barrier (<1 kcal), while secondary-row elements such as sulfur and chlorine adopt an orthogonal geometry (**35**, Chart I) (barrier 2.3–4 kcal) of the type required for cycloaddition irrespective of the substituent atom.[42] However, the nature of the interaction varies. Delocalization of the electron in the SOMO into the antibonding $\sigma_{CCl}$ orbital is the principle contribution with a chlorine substituent, while for sulfur the effect is mainly due to electron delocalization from the bonding $\sigma_{CS}$ orbital into the SOMO, features that are consistent with the relative donor properties of these σ bonds. Our own preliminary calculations support this contention, and the cycloaddition results can therefore be rationalized on the basis of σ donor ability.

## Conclusion

*On the basis of hyperconjugation and the beneficial interaction with the incipient bond one should expect the cycloaddition of the cyclopentadienes to display a preference for anti addition to the antiperiplanar σ bond that is the better donor.*[44] Listed in order of increasing σ donor ability, the common atom combinations are $\sigma_{CO} < \sigma_{CN} < \sigma_{CCl} < \sigma_{CC} < \sigma_{CH} < \sigma_{CS}$.[45] Thus, when the choice is between a carbon–carbon and a carbon–oxygen bond bearing face, one should expect preferential addition anti to the best σ donor (the CC bond) and hence syn to CO as found. Similarly, if the competition is between a CC and CS bond, cycloaddition anti to the CS bond should dominate, as observed. Chart II illustrates this favorable interaction of the antiplanar σ bond with the diene HOMO and the developing incipient bonds with the LUMO of the dienophile. This analysis implies that cycloadditions of thiophene oxides, where the competition is between a lone pair and a sulfoxide oxygen, should be anti to the lone pair. Recently we have confirmed this conclusion experimentally. Addition occurred exclusively in a contrasteric manner syn to oxygen in all cases examined.[46]

A recent study of the conformational preferences in 3-halogenated-1-benzoxepins provides a related example of the importance of intramolecular stereoelectronic σ–σ* orbital interactions.[47] Cyclopentadienes are very reactive dienes and C-5 substituents possess a particularly favorable orbital alignment for these interactions. Thus, in less suitable geometries, one would expect these electronic features to become less important, and steric interactions to play a larger role. Examination of Table I indicates that this is the case. Frank and Tripathy have recently concluded that nonbonding steric interactions dominate the stereocontrol observed in both acyclic and semicyclic dienes.[34]

Thus, from a practical perspective, heteroatom-directed control of π-diastereofacial selectivity by variation of the substituent has considerable synthetic potential. In particular, 1,3-oxathiolane ketals will offer enhanced facial selectivity and provide a chiral environment for cycloadditions applied to the total synthesis of natural products. In addition to the improved understanding of facial preferences of addends generated by the present study, the examination of additional locked dienes will provide further insight into the relative importance of electronic and steric interactions, a key component of all organic transformations.

## Experimental Section

**5-(Methylthio)-1,2,3,4,5-pentamethylcyclopentadiene** (9). *n*-Butyllithium (2.3 M in hexane, 67 mL, 154 mmol, Aldrich) was added to a solution of 1,2,3,4,5-pentamethylcyclopentadiene (20.0 g, 140 mmol, Aldrich) in anhydrous THF (150 mL) at 0 °C. The milky reaction mixture was allowed to warm to room temperature and cooled to 0 °C, and dimethyl sulfide was (19.1 mL, 210 mmol, Aldrich) added. The reaction mixture was allowed to warm to room temperature, stirred overnight, and quenched with saturated ammonium chloride (100 mL). The organic layer was separated, the aqueous layer was extracted with ether (1 × 100 mL), and the combined organic extracts were dried, filtered, and concentrated to give crude material that solidified upon refrigeration. Repeated recrystallization from MeOH afforded 17.25 g (68%) of 9 as a volatile solid: mp 38.5–39 °C; IR ($CHCl_3$) 2918, 1659, 1444, 1378, 1069, 953 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) δ 1.80 (s, 12 H), 1.27 (s, 3 H), 1.10 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 137.6, 134.3, 61.3, 19.4, 10.9, 10.6, 9.4; 253.5 nm (ε 1400); MS calcd for $C_{11}H_{18}S$ 182.1130, found 182.1150.

**5-(Phenylthio)-1,2,3,4,5-pentamethylcyclopentadiene** (3). An analogous procedure (employing diphenyl sulfide) to that described above for 9 was used to afford, after chromatography (petroleum ether), **3** as an oil (56%): IR ($CHCl_3$) 2996, 2963, 2918, 2852, 1659, 1582, 1466, 1444, 1438, 1378, 1135, 1063, 1024 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.2–7.0 (m, 5 H), 1.85 (s, 6 H), 1.48 (s, 6 H), 1.20 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 137.7, 134.6, 134.1, 132.7, 127.6, 127.3, 65.7, 18.8, 10.6, 9.9; MS calcd for $C_{16}H_{20}S$ 244.1286, found 244.1290.

**5-(Benzylthio)-1,2,3,4,5-pentamethylcyclopentadiene** (2). An analogous procedure (employing dibenzyl disulfide) to that described above for 9 was used to afford, after chromatography (petroleum ether), **2** as an oil (53%): IR (film) 3030, 2880, 1665, 1603, 1496, 1450, 1379, 1068, 700 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) δ 7.09 (s, 5 H), 2.83 (s, 2 H), 1.76 (s, 6 H), 1.08 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 138.9, 138.2, 134.4, 128.9,

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(40) This implies that the reaction of styrene with **9** should afford increased syn adduct, but unfortunately styrene was not sufficiently reactive to give any cycloaddition.

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127.9, 126.3, 62.6, 33.1, 19.5, 11.1, 9.5; MS calcd for $C_{17}H_{22}S$ 258.1444, found 258.1439.

**5-(Methylsulfinyl)-1,2,3,4,5-pentamethylcyclopentadiene (10).** *m*-Chloroperbenzoic acid (16.0 g, 76 mmol, 80–85%, Aldrich) was added in portions over 20 min to a solution of **9** (12.55 g, 69 mmol) in $CH_2Cl_2$ (100 mL) at −78 °C. After stirring for 1 h, 5% aqueous (w/v) $NaHCO_3$ (100 mL) was added. The organic layer was separated, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL), and the combined $CH_2Cl_2$ layers were washed with 5% $NaHCO_3$ (1 × 100 mL) and water (1 × 100 mL), dried, filtered, and concentrated. Chromatography afforded the sulfone **11** (vide infra) (1.07 g, 7%) (9:1 petroleum ether/EtOAc) and the sulfoxide **10** (12.65 g, 93%) (1:1 petroleum ether/EtOAc): mp 61–62 °C (hexane); IR ($CHCl_3$) 2918, 1648, 1444, 1383, 1295, 1069, 1019, 947 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.02 (s, 3 H), 1.91 (br s, 3 H), 1.82 (m, 3 H), 1.74 (m, 3 H), 1.67 (br s, 3 H), 1.51 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 139.0, 138.6, 136.1, 132.2, 74.0, 31.7, 15.2, 11.7, 11.2, 10.7, 10.2; MS calcd for $C_{11}H_{18}S$ ($M^+ - O$) 182.1130, found 182.1105.

**5-(Methylsulfonyl)-1,2,3,4,5-pentamethylcyclopentadiene (11).** A solution of oxone (0.811 g, 2.64 mmol of $KHSO_5$, Aldrich) in water (10 mL) was added to a solution of **9** (0.160 g, 0.879 mmol) in MeOH (10 mL) at 0 °C. After stirring for 5 min, the ice–water bath was removed, and stirring was continued for 2.5 h at 22 °C. The reaction mixture was filtered and concentrated. The residue was partitioned between $CHCl_3$ (50 mL) and water (50 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 50 mL), and the combined $CHCl_3$ extracts were washed with water (1 × 50 mL), dried, filtered, and concentrated. Chromatography (8:2 petroleum ether/EtOAc; sample dissolved in $CH_2Cl_2$) yielded **11** (0.101 g, 54%): mp 111.5–112.5 °C (hexane–ether); IR ($CHCl_3$) 2918, 1654, 1295, 1284, 1151, 1129, 1074, 953 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 2.43 (s, 3 H), 1.96 (s, 6 H), 1.84 (s, 6 H), 1.46 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 140.9, 134.2, 78.1, 33.9, 11.5, 10.7; MS calcd for $C_{11}H_{18}SO_2$ 214.1027; found 214.1036.

**5-(Acetylamino)-1,2,3,4,5-pentamethylcyclopentadiene (7).** Pyridine (0.5 mL) and acetic anhydride (0.5 mL) were added to a solution of the aminocyclopentadiene **6**[30] (0.260 g, 1.72 mmol) in $CH_2Cl_2$ (7 mL). The solution was stirred at room temperature for 18 h, then toluene was added, and the reaction mixture was concentrated. The crude product was recrystallized from $CH_2Cl_2$ to afford **7** (0.059 g). A further 0.180 g (total 0.239 g, 72%) was obtained by chromatography (3:2 petroleum ether/EtOAc, then EtOAc; sample dissolved in $CH_2Cl_2$): mp 124–126 °C; IR ($CHCl_3$) 3437, 3393, 2918, 1676, 1654, 1493, 1444, 1378, 1367, 1289, 1091 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) (compound exists as two conformational isomers) $\delta$ 5.51 (br s, 1 H), 5.31 (br s, 1 H), 1.92 (s, 3 H), 1.77 (s, 3 H), 1.76 (s, 3 H), 1.73 (s, 3 H), 1.69 (s, 3 H), 1.48 (s, 3 H), 1.17 (s, 3 H), 1.13 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.7, 168.2, 138.3, 137.4, 134.6, 133.7, 68.0, 67.9, 24.5, 23.7, 22.4, 18.4, 11.1, 11.0, 9.3, 9.1; MS calcd for $C_{12}H_{19}NO$ 193.1467; found 193.1468.

**Cycloaddition of 5-Mercapto-1,2,3,4,5-pentamethylcyclopentadiene (8) with *N*-Phenylmaleimide.** Bis(pentamethylcyclopentadiene)sulfide (**4**)[31] (0.160 g, 0.530 mmol) was dissolved in anhydrous THF (5 mL), and the solution was cooled to −78 °C. Ammonia (~5 mL) was condensed into the flask, and small pieces of sodium were added with stirring until a deep blue color was established. After 2 min the reaction was quenched with solid ammonium chloride. The dry ice bath was removed, and the ammonia was allowed to evaporate under a stream of $N_2$. Water (10 mL) was added, the aqueous layer was extracted with ether (3 × 10 mL), and the combined ether extracts were dried, filtered, and concentrated. Chromatography (petroleum ether; 12 in. height of silica gel) yielded the sulfhydryldiene **8** as an unstable oil (0.039 g, 44%). *N*-phenylmaleimide (0.179 g, 1.00 mmol) was added to a solution of **8** (0.168 g, 1.00 mmol) in anhydrous benzene (1.7 mL). The solution was stirred at room temperature for 16 h and then concentrated. Chromatography (9:1 petroleum ether/EtOAc, sample dissolved in $CH_2Cl_2$) afforded the syn adduct **20** (0.167 g, 49%): mp 168.5–169.5 °C (EtOAc); IR ($CHCl_3$) 2963, 2929, 1769, 1709, 1598, 1499, 1455, 1449, 1378, 1306, 1168, 1135, 1096 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.5–7.3 (m, 3 H), 7.05 (d, 2 H, $J$ = 7.5 Hz), 3.35 (s, 2 H), 1.63 (s, 6 H), 1.42 (s, 6 H), 1.30 (s, 1 H), 1.13 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.4, 135.1, 131.9, 129.1, 128.4, 126.5, 75.3, 61.1, 51.6, 20.5, 11.7; MS calcd for $C_{20}H_{23}NSO_2$ 341.1449, found 341.1438. Further elution (8:2 petroleum ether/EtOAc) gave the anti adduct **15** (0.136 g, 40%): mp 122–123 °C (ether–hexane); IR ($CHCl_3$) 2963, 2929, 1769, 1709, 1598, 1499, 1455, 1378, 1306, 1173, 1168, 1085 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.45–7.35 (m, 3 H), 7.05 (d, $J$ = 7.2 Hz, 2 H), 3.10 (s, 2 H), 1.61 (s, 6 H), 1.49 (s, 6 H), 1.20 (s, 1 H), 1.14 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.0, 137.6, 131.9, 129.2, 128.5, 126.5; MS calcd for $C_{20}H_{23}NSO_2$ 341.1449, found 341.1438.

**Cycloaddition of 5-Hydroxy-1,2,3,4,5-pentamethylcyclopentadiene (13) with Maleic Anhydride.** Anhydrous MeOH (20 mL) was distilled into a flask containing the sulfoxide **10** (1.185 g, 5.98 mmol). Trimethyl phosphite (7.0 mL, 59.8 mmol) (later experiments showed that 1.2 equiv is sufficient) was added, and the solution was stirred for 24 at room temperature (22 °C). Half of the reaction mixture was concentrated to give, after recrystallization from hexane, the alcohol **13** as an unstable white solid $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 1.70 (s, 12 H), 1.46 (br s, 1 H), 1.125 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 139.3, 133.0, 83.9, 21.0, 11.0, 8.8. The other half of the reaction mixture (13.5 mL) was siphoned into a flask containing maleic anhydride (0.293 g, 2.99 mmol) under $N_2$; stirred at room temperature for 3 h, and then concentrated. Chromatography (9:1 benzene/acetone, sample dissolved in acetone) afforded the hydroxy adduct **27** (0.637 g, 85% from **10** based on 2.99 mmol): mp 218–221 °C (EtOAc); IR ($CHCl_3$) 3580, 2929, 1858, 1775, 1455, 1378, 1146, 1080, 914 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 3.34 (s, 2 H), 1.58 (s, 7 H), 1.28 (s, 6 H), 0.96 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 172.5, 135.8, 94.1, 60.5, 52.1, 15.8, 11.1, 10.4; MS calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1214.

**Cycloaddition of 5-Methoxy-1,2,3,4,5-pentamethylcyclopentadiene (14) with Maleic Anhydride.** A solution of the hydroxycyclopentadiene **13** (obtained as described above from sulfoxide **10** (1.00 g, 5.08 mmol) in anhydrous THF (15 mL) was added to a mixture of sodium hydride (0.179 g, 5.59 mmol, 75% oil suspension) and anhydrous THF (5 mL) maintained at 0 °C with an external ice bath. The ice–water bath was removed after gas evolution had ceased, and the reaction mixture was stirred at room temperature for 40 min. Methyl iodide (0.5 mL, 7.95 mmol) was added, and stirring was continued for 24 h. The reaction mixture was quenched with saturated ammonium chloride (20 mL). The organic layer was separated, the aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were dried, filtered, and concentrated. Chromatography (9.8:0.2 petroleum ether/EtOAc, sample dissolved in $CH_2Cl_2$) afforded **14** as a volatile unstable oil (0.761 g, 90% from **10**): $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 2.75 (s, 3 H), 1.74 (s, 6 H), 1.66 (s, 6 H), 1.09 (s, 3 H). Maleic anhydride (0.267 g, 2.73 mmol) in anhydrous benzene (10 mL) was added to a solution of methoxydiene **14** (0.453 g, 2.73 mmol) in anhydrous benzene (10 mL). The reaction mixture was stirred for 2 h at room temperature and then concentrated to yield the crystalline syn adduct **26** (0.660 g, 92%): mp 145.5–147 °C (EtOAc): IR ($CHCl_3$) 2940, 1858, 1775, 1455, 1378, 1372, 1311, 1135, 1080, 914 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 3.33 (s, 2 H), 3.29 (s, 3 H), 1.54 (s, 6 H), 1.32 (s, 6 H), 0.98 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 172.6, 136.0, 98.2, 61.2, 52.6, 11.7, 11.1, 9.2; MS calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1365.

**Cycloaddition of 5-Chloro-1,2,3,4,5-pentamethylcyclopentadiene (1) with Maleic Anhydride.** *n*-Butyllithium (2.3 M in hexane, 3.5 mL, 8.05 mmol) was added to a solution of 1,2,3,4,5-pentamethylcyclopentadiene (1.00 g, 7.34 mmol) in anhydrous THF (30 mL). The reaction mixture was stirred for 30 min at 22 °C and then cooled to −78 °C. *N*-chlorosuccinimide (0.961 g, 7.34 mmol) was added, and stirring was continued for 30 min at −78 °C and then for 16.5 at −20 °C. The reaction mixture was concentrated, the residue was extracted with hexane (3 × 30 mL) at −20 °C, and the combined hexane extracts were concentrated. Distillation (66–67 °C/2.7 mm) afforded the chloride **1** as a pale yellow oil (2.42 g, 65%) of ~90% purity. To a solution of chlorodiene **1** (0.103 g, 0.606 mmol) in anhydrous benzene (1 mL) was added maleic anhydride (0.060 g, 0.606 mmol). Reaction was monitored by TLC, and the diene was consumed within 30 min. Concentration gave the adduct **25** in quantitative yield: mp 191–192 °C (ether–hexane); IR ($CHCl_3$) 2940, 1858, 1775, 1445, 1383, 1311, 1140, 1085, 914 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 3.50 (s, 2 H), 1.64 (s, 6 H), 1.41 (s, 6 H), 1.27 (s. 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.0, 136.4, 92.1, 61.8, 52.6, 18.4, 11.5, 11.0; MS calcd for $C_{14}H_{17}O_3{}^{35}Cl$ 268.0866, found 268.0850.

**Cycloadditions of Sulfur- and Nitrogen-Substituted Dienes 2, 3, 9, 10, 11, 6, and 7. General Procedure.** The dienophile (1 equiv) was added to a solution of the diene (0.13–0.68 M in anhydrous benzene (unless otherwise specified). The reaction mixture was stirred at room temperature (22 °C), monitored by TLC, and then concentrated to give the adducts.

**1. Methylthio Diene 9 with Maleic Anhydride.** Chromatography (9:1 petroleum ether/EtOAc, sample dissolved in $CH_2Cl_2$) afforded the syn adduct **22** (9%): mp 168–170 °C (ether); IR ($CHCl_3$) 2929, 1858, 1775, 1383, 1096, 1080, 914 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 3.55 (s, 2 H), 2.10 (s, 3 H), 1.60 (s, 6 H), 1.35 (s, 6 H), 1.08 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.6, 136.6, 77.2, 62.6, 52.8, 13.8, 12.0, 11.9, 11.6; MS calcd for $C_{15}H_{20}SO_3$ 280.1134, found 280.1126. Further elution (8:2 petroleum ether/EtOAc) gave the anti adduct **17** (82%): mp 142–144 °C (ether); IR ($CHCl_3$) 2929, 1859, 1779, 1445, 1380, 1079, 915 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 3.25 (s, 2 H), 1.95 (s, 3 H), 1.58 (s, 6 H), 1.42 (s, 6 H), 1.05 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.9, 137.9, 77.4, 62.3, 51.7, 14.9, 13.1, 11.8, 11.5; MS calcd for $C_{15}H_{20}SO_3$ 280.1134, found 280.1113.

**2. Methylthio Diene 9 with *N*-Phenylmaleimide.** Chromatography

(9:1 petroleum ether/EtOAc, sample dissolved in $CH_2Cl_2$) afforded the syn adduct **21** (6%): mp 183–184.5 °C (ether); IR ($CHCl_3$) 2929, 1769, 1703, 1598, 1499, 1455, 1378, 1168, 1102 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.5–7.3 (m, 3 H), 7.05 (d, 2 H, $J$ = 7.5 Hz), 3.44 (s, 2 H), 2.13 (s, 3 H), 1.62 (s, 6 H), 1.41 (s, 6 H), 1.11 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 176.8, 135.6, 129.1, 128.4, 126.6, 77.2, 62.0, 51.7, 13.9, 12.8, 12.3, 11.7; MS calcd for $C_{20}H_{22}NO_2$ ($M^+$ – SMe) 308.1650, found 208.1662. Further elution (8:2 petroleum ether/EtOAc) gave the anti adduct **16** (93%): mp 189.5–190.5 °C (ether–$CH_2Cl_2$); IR ($CHCl_3$) 2929, 1769, 1709, 1598, 1499, 1455, 1378, 1306, 1173, 1080 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.5–7.3 (m, 3 H), 7.05 (d, $J$ = 7.0 Hz, 2 H), 3.10 (s, 2 H), 1.96 (s, 3 H), 1.61 (s, 6 H), 1.46 (s, 6 H), 1.11 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 176.1, 136.9, 131.9, 129.1, 128.5, 126.5, 77.3, 61.8, 50.6, 14.7, 13.1, 12.2, 11.6; MS calcd for $C_{20}H_{22}NO_2$ ($M^+$ – SMe) 308.1650, found 308.1624.

**3. Methylthio Diene 9 with Tetracyanoethylene.** Reaction was conducted in anhydrous THF and appeared to be instantaneous (no diene by TLC after 30 s). The adduct **32** was obtained in quantitative yield: mp 178–181 °C (ether–$CH_2Cl_2$): IR ($CHCl_3$) 2985, 2929, 2245, 1659, 1460, 1383, 1096 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) δ 1.99 (s, 3 H), 1.83 (s, 6 H), 1.675 (s, 6 H), 1.47 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 142.8, 111.1, 110.8, 74.0, 69.5, 49.8, 16.2, 13.9, 12.3, 10.2; MS calcd for $C_{11}H_{18}S$ ($M^+$ – tetracyanoethylene) 182.1129, found 182.1138.

**4. Phenylthio Diene 3 with Maleic Anhydride.** Chromatography (9.5:0.5 petroleum ether/EtOAc, sample dissovled in $CH_2Cl_2$) afforded the syn adduct (2%): IR ($CHCl_3$) 2970, 2940, 1858, 1777, 1459, 1442, 1384, 1263, 1100 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 2 H), 7.4–7.25 (m, 3 H), 3.67 (s, 2 H), 1.61 (s, 6 H), 1.42 (s, 6 H), 0.79 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 171.5, 138.0, 137.1, 131.1, 129.2, 128.8, 80.1, 62.3, 52.8, 15.3, 11.8; MS calcd for $C_{14}H_{17}O_3$ ($M^+$ – SPh) 233.1178, found 233.1143. Further elution (9:1 petroleum ether/EtOAc) gave the anti adduct (61%): mp 203–204 °C (EtOAc); IR ($CHCl_3$) 2982, 2943, 1859, 1778, 1461, 1443, 1385, 1312, 1153, 1131 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.45–7.15 (m, 5 H), 3.13 (s, 2 H), 1.59 (s, 6 H), 1.51 (s, 6 H), 0.55 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 171.4, 138.9, 138.6, 133.5, 129.2, 129.0, 82.8, 62.6, 51.9, 16.4, 12.3, 12.0; MS calcd for $C_{16}H_{20}S$ ($M^+$ – maleic anhydride) 244.1286, found 244.1278.

**5. Benzylthio Diene 2 with Maleic Anhydride.** Chromatography (9.5:0.5 to 9:1 petroleum ether/EtOAc, sample dissolved in $CH_2Cl_2$) afforded the syn adduct (6.5%): mp 98–100 °C (ether); IR ($CHCl_3$) 2978, 2943, 1857, 1775, 1499, 1457, 1443, 1385, 1182, 1139, 1099, 1082 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H), 3.80 (s, 2 H), 3.56 (s, 2 H), 1.61 (s, 6 H), 1.38 (s, 6 H), 1.18 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 171.5, 137.4, 136.6, 128.9, 128.7, 127.4, 65.9, 62.5, 52.8, 34.4, 14.6, 12.0, 11.6; MS calcd for $C_{17}H_{22}S$ ($M^+$ – maleic anhydride) 258.1442, found 258.1452. Further elution (8.5:1.5 petroleum ether/EtOAc) gave the anti adduct (52%): mp 183–185 °C (EtOAc–ether); IR ($CHCl_3$) 2980, 2942, 1860, 1780, 1499, 1457, 1383, 1311, 1105, 1082 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5 H), 3.61 (s, 2 H), 3.20 (s, 2 H), 1.56 (s, 6 H), 1.43 (s, 6 H), 1.10 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 170.5, 137.6, 137.5, 128.6, 128.1, 126.7, 79.0, 61.8, 51.2, 34.1, 15.0, 11.5, 11.1; MS calcd for $C_{17}H_{22}S$ ($M^+$ – maleic anhydride) 258.1442, found 258.1479.

**6. Methylsulfinyl Diene 10 with Maleic Anhydride.** The anti adduct **18** was obtained in quantitative yield: mp 158–159 °C ($CH_2Cl_2$–hexane); IR ($CHCl_3$) 2985, 2940, 1858, 1780, 1454, 1383, 1300, 1102, 1080 $cm^{-1}$; $^1H$ NMR (60 MHz, $CD_3COCD_3$) δ 3.62 (d, 1 H, $J$ = 8 Hz), 3.42 (d, 1 H, $J$ = 8 Hz), 2.33 (s, 3 H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 1.23 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 169.9, 169.8, 139.1, 137.1, 88.3, 63.0, 59.4, 52.0, 52.0, 35.6, 13.0, 11.6, 11.5, 6.88; MS calcd for $C_{15}H_{20}O_4$ 296.1083, found 296.1093.

**7. Methylsulfonyl Diene 11 with Maleic Anhydride.** Reaction was conducted in benzene/acetone. The anti adduct **19** was obtained in quantitative yield: mp 187–189 °C ($CHCl_3$); IR ($CHCl_3$) 2940, 1863, 1780, 1455, 1405, 1389, 1300, 1168, 1146, 1124, 1102, 1080, 958, 920 $cm^{-1}$; $^1H$ NMR (60 MHz, $CD_3COCD_3$) δ 3.54 (s, 2 H), 2.71 (s, 3 H), 1.71 (s, 6 H), 1.55 (s, 6 H), 1.33 (s, 3 H); $^{13}C$ NMR ($CD_3COCD_3$) δ 171.5, 138.0, 92.8, 60.2, 53.1, 45.4, 12.5, 11.5, 10.9; MS calcd for $C_{15}H_{20}O_5$ 312.1032, found 312.1032.

**8. Amino Diene 6 with *N*-Phenylmaleimide.** Reaction was conducted in methylene chloride. The syn adduct **29** was obtained in quantitative yield: mp 137–138 °C (EtOAc); IR ($CHCl_3$) 3525, 3448. 2963, 2929, 2874, 1769, 1703, 1598, 1493, 1455, 1378, 1168 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.48–7.3 (m, 3 H), 7.06 (d, 2 H, $J$ = 7.5 Hz), 3.22 (s, 2 H), 1.60 (s, 6 H), 1.30 (s, 6 H), 0.85 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 177.4, 135.1, 132.2, 129.1, 128.3, 126.6, 78.1, 60.3, 51.3, 18.0, 11.4, 10.9; MS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1837.

**9. *N*-Acetylamino Diene 7 with *N*-Phenylmaleimide.** Reaction was conducted in methylene chloride. Chromatography (9.7:0.3 $CHCl_3$/MeOH) gave a very small quantity of the anti adduct: $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.5–7.3 (m, 3 H), 7.05 (d, 2 H, $J$ = 7.2 Hz), 5.2 (br s, 1 H), 3.10 (s, 2 H), 1.91 (s, 3 H), 1.67 (s, 6 H), 1.49 (s, 3 H), 1.42 (s, 6 H). Further elution gave the syn adduct **30** in almost quantitative yield: mp 267–269 °C (EtOAc/MeOH); IR ($CHCl_3$) 3437, 2929, 2874, 1769, 1709, 1598, 1493, 1449, 1378, 1278, 1168, 1151, 1091 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 3 H), 7.05 (d, 2 H, $J$ = 7 Hz), 5.27 (s, 1 H), 3.15 (s, 2 H), 1.98 (s, 3 H), 1.60 (s, 6 H), 1.43 (s, 6 H), 1.28 (s, 3 H); $^{13}C$ NMR ($CD_3COCD_3$) δ 177.2, 170.1, 134.9, 131.9, 129.2, 128.6, 126.5, 80.4, 60.9, 50.8, 24.6, 12.6, 12.0, 11.4; MS calcd for $C_{22}H_{26}N_2O_3$ 366.1942, found 366.1946.

**10. *N*-Acetylamino Diene 7 with Maleic Anhydride.** The syn adduct was obtained in quantitative yield: mp 217–218 °C (EtOAc); IR ($CHCl_3$) 3437, 2940, 1858, 1775, 1692, 1493, 1449, 1383, 1372, 1273, 1151, 1102, 1080, 914 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_3COCD_3$) δ 6.61 (br s, 1 H), 3.69 (s, 2 H), 1.90 (s, 3 H), 1.57 (s, 6 H), 1.39 (s, 6 H), 1.25 (s, 3 H); $^{13}C$ NMR ($CD_3COCD_3$) δ 172.9, 170.7, 136.5, 81.3, 62.0, 52.6, 24.0, 12.4, 12.3, 11.3; MS calcd for $C_{16}H_{21}NO_4$ 291.1470, found 291.1474.

**Cycloaddition of 1,2,3,4-Tetramethylfulvene with Maleic Anhydride.** A solution of alcohol **13** (prepared from sulfoxide **10**, 0.291 g, 1.47 mmol) in anhydrous THF (7 mL) was added to a mixture of sodium hydride (0.070 g, 1.75 mmol, 60% oil dispersion) and anhydrous THF (1 mL) under $N_2$. The solution was stirred for 45 min and then cooled to −78 °C, and acetyl bromide (0.16 mL, 2.16 mmol) was added. The reaction mixture was warmed to ~ −5 °C, stirring was continued for 3 days, then maleic anhydride (0.288 g, 2.94 mmol) was added, and, after an additional 30 min at ~ −5 °C, the solution was allowed to warm to room temperature. After stirring for 19 h, the reaction mixture was concentrated. Chromatography (9.5:0.5 and 8:2 petroleum ether/EtOAc, sample dissolved in $CH_2Cl_2$) afforded the adduct (0.142 g, 42% from **10**): mp 113–114 °C (ether/hexane); IR ($CHCl_3$) 2963, 2929, 2874, 1858, 1775, 1681, 1455, 1438, 1383, 1311, 1107, 1074, 914, 892 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.20 (s, 2 H), 3.19 (s, 2 H), 1.66 (s, 6 H), 1.53 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 170.6, 167.5, 138.5, 87.2, 55.7, 53.1, 12.3, 11.0; MS calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1078.

**Conversion of *anti*-Methylthio Adduct 17 into *anti*-Methylsulfinyl Adduct 18.** *m*-Chloroperbenzoic acid (0.013 g, 0.061 mmol, 80–85%) in $CH_2Cl_2$ (2 mL) was added to a solution of **17** (0.017 g, 0.061 mmol) in $CH_2Cl_2$ (2 mL) at −78 °C. The reaction mixture was stirred for 15 min, then 5% (w/v) aqueous $NaHCO_3$ (5 mL) was added, and the solution was allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined EtOAc layers were washed with 5% $NaHCO_3$ (1 × 5 mL) and $H_2O$ (1 × 5 mL). The $CH_2Cl_2$ layer was washed with $H_2O$ (1 × 5 mL), and the combined organic layers were dried, filtered and concentrated to give the adduct **18** (0.015 g, 83%).

**Preparation of *syn*-Methylsulfinyl Adduct 23.** *m*-Chloroperbenzoic acid (0.020 g, 0.093 mmol, 80–85%) was added to a solution of the syn thiomethyl adduct **22** (0.026 g, 0.093 mmol) in $CH_2Cl_2$ (5 mL) at −78 °C. The reaction mixture was stirred for 45 min, then allowed to warm to room temperature, and 5% $NaHCO_3$ was added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL), and the combined $CH_2Cl_2$ layers were washed with 5% $NaHCO_3$ (1 × 10 mL) and $H_2O$ (1 × 10 mL), then dried, filtered, and concentrated to give **23** (0.025 g, 91%): mp 137–138 °C ($CH_2Cl_2$/hexane); IR ($CHCl_3$) 2940, 1858, 1775, 1455, 1383, 1295, 1096, 1080, 914 $cm^{-1}$; $^1H$ NMR (60 MHz, $CD_3COCD_3$) δ 3.94 (d, 1 H $J$ = 8 Hz), 3.68 (d, 1 H, $J$ = 8 Hz), 2.53 (s, 3 H), 1.61 (s, 6 H), 1.50 (s, 3 H), 1.40 (s, 3 H), 1.09 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 170.3, 139.1, 137.2, 83.6, 62.5, 59.1, 52.8, 51.7, 35.4, 12.9, 12.6, 11.5, 11.4, 6.0; MS calcd for $C_{14}H_{17}O_3$ ($M^+$ – SOMe) 233.1178, found 233.1178.

**Conversion of *anti*-Methylthio Adduct 17 into *anti*-Methylsulfonyl Adduct 19.** *m*-Chloroperbenzoic acid (0.44 g, 0.210 mmol, 80–85%) was added to a solution of **17** (0.028 g, 0.100 mmol) in $CH_2Cl_2$ (5 mL) at −78 °C. The solution was stirred for 40 min and then allowed to warm to room temperature. After 6 h, $CH_2Cl_2$ (5 mL) was added, and the solution was refluxed for 16 h. The reaction mixture was allowed to cool to room temperature, and 5% aqueous $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL), and the combined $CH_2Cl_2$ layers were washed with 5% aqueous $NaHCO_3$ (1 × 10 mL) and $H_2O$ (1 × 10 mL), then dried, filtered, and concentrated to give **19** (0.025 g, 81%).

**Preparation of *syn*-Methylsulfonyl Adduct 24.** *m*-Chloroperbenzoic acid (0.038 g, 0.179 mmol, 80–85%) was added to a solution of the syn thiomethyl adduct **22** (0.025 g, 0.0893 mmol) in $CH_2Cl_2$ (5 mL) at −78 °C. The solution was stirred for 30 min and then allowed to warm to room temperature. After 5 h, $CH_2Cl_2$ (5 mL) was added, and the solution was refluxed for 16 h. The reaction mixture was allowed to cool to room temperature, additional *m*-chloroperbenzoic acid (0.019 g) was added, stirring was continued for 4 h, and 5% aqueous $NaHCO_3$ (5 mL)

was added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL), and combined $CH_2Cl_2$ layers were washed with 5% aqueous $NaHCO_3$ (1 × 10 mL) and $H_2O$ (1 × 10 mL), then dried, filtered, and concentrated. Chromatography (9.9:0.1 $CHCl_3$/MeOH) afforded **24** (0.019 g, 68%): mp 169-171 °C (EtOAc/ether); IR ($CHCl_3$) 2940, 1858, 1775, 1604, 1455, 1383, 1300, 1146, 1096, 1085, 958, 914 $cm^{-1}$; $^1H$ NMR (60 MHz, $CD_3COCD_3$) $\delta$ 3.97 (s, 2 H), 2.95 (s, 3 H), 1.61 (s, 6 H), 1.56 (s, 6 H), 1.37 (s, 3 H); MS calcd for $C_{14}H_{17}O_3$ ($M^+ - SO_2Me$) 233.1178, found 233.1155.

**Procedure for the Conversion of Mercapto Adducts 15 and 20 into Methylthio Adducts 16 and 21, Respectively.** Diazabicyclo[5.4.0]undecene (DBU) (19 $\mu$L, 0.123 mmol) and $CH_3I$ (0.1 mL, 1.6 mmol) were added to a solution of the mercapto adduct (0.021 g, 0.0616 mmol) in anhydrous benzene (10 mL). The reaction mixture was stirred for 2 days, then washed with 1 N HCl (3 × 10 mL) and $H_2O$ (1 × 10 mL), dried, filtered, and concentrated to give the corresponding thiomethyl adduct (0.022 g, quantitative yield).

**Conversion of Amino Adduct 29 into *syn*-*N*-Acetylamino Adduct 30.** Acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added to a solution of **29** (0.023 g, 0.071 mmol) in $CH_2Cl_2$ (7 mL). The solution was stirred for 23 h, then toluene was added, and the solution was concentrated to give **30** (0.026 g, quantitative yield).

**Preparation of *O*-Acetyl Adduct 28.** (Dimethylamino)pyridine (DMAP) (0.025 g, 0.202 mmol) and acetic anhydride (0.2 mL, 2.0 mmol) were added to a solution of the hydroxy adduct **27** (0.046 g, 0.184 mmol) in anhydrous benzene (8 mL). The solution was refluxed for 3.5 days. Additional 4-(dimethylamino)pyridine (0.045 g) and acetic anhydride (0.2 mL) were added, and refluxing was continued for 2 more days. TLC showed that the reaction was still incomplete: however, the solution wsa allowed to cool, diluted to 5 mL with EtOAc, washed with 5% (v/v) HCl (1 × 10 mL) and brine (1 × 10 mL), dried, filtered, and concentrated. Chromatography (8:2 petroleum ether/EtOAc) yielded **28** (0.030 g, 52%): mp 136-138 °C (ether); IR ($CHCl_3$) 2940, 1858, 1775, 1455, 1372, 1317, 1140, 1113, 1080, 1013, 947, 914 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 3.31 (s, 2 H), 2.00 (s, 3 H), 1.56 (s, 6 H), 1.36 (s, 6 H), 1.30 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.4, 169.3, 135.8, 101.6, 60.9, 51.8, 22.0, 12.2, 11.6, 11.2; MS calcd for $C_{16}H_{20}O_5$ 292.1313, found 292.1285.

**Conversion of Methoxy Adduct 26 into Chloro Adduct 25 and Hydroxy Adduct 27.** Anhydrous sodium iodide (0.031 g, 0.205 mmol) and trimethylchlorosilane (27 $\mu$L, 0.205 mmol) were added to a solution of **26** (0.054 g, 0.205 mmol) in anhydrous $CH_3CN$ (2 mL).[48] The stirred reaction mixture was monitored by TLC. After 18 h fresh trimethylchlorosilane (27 $\mu$L) was added, and 26 h later additional sodium iodide (0.031 g) and trimethylchlorosilane (27 $\mu$L) were added. After a total of 3.5 days, further sodium iodide (0.093 g) and trimethylchlorosilane (0.1 mL) were added. Twenty-four hours later the reaction mixture was quenched with $H_2O$ (10 mL). The solution was extracted with ether (3 × 10 mL), and the combined ether extracts were washed with 5% aqueous (w/v) sodium thiosulfate (1 × 10 mL) and brine (1 × 10 mL), then dried, filtered, and concentrated. Chromatography (1:1 petroleum ether/benzene) (sample dissolved in benzene) yielded the chloro adduct **25** (0.027 g, 49%) and hydroxy adduct **27** (0.011 g, 22%) (9:1 benzene/acetone).

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**Supplementary Material Available:** General experimental conditions and details of the X-ray studies and tables of atomic coordinates, interatomic distances, and thermal parameters (6 pages). Ordering information is given on any current masthead page.

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# Synthesis and Selective Molecular Recognition of a Macrotricyclic Receptor Having Crown Ether and Cyclophane Subunits as Binding Sites[1]

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**Abstract:** The synthesis and selective molecular recognition of a new type of cylindrical, macrotricyclic receptor (**1**) having crown ether and cyclophane subunits as binding sites and a large hydrophobic cavity are described. Receptor **1** was synthesized by the stepwise construction of three individually prepared subunits: bis(*p*-toluenesulfonamido)dibenzo-18-crown-6 (**6**); diaminocyclophane (**7**); ethyl 4′-(bromomethyl)biphenyl-4-carboxylate (**8**). The interaction of **1** and various (ω-phenylalkyl)ammonium picrates **2**, for which the number of methylene units varies from 3 to 9, was examined, and they were found to form 1/1 complexes. The selectivity of **1** for **2** was evaluated by comparing the stability constants ($K_s'$) of these complexes. The $K_s'$ values were calculated on the basis of the chemical shift changes of the protons in **2** on varying the **1**/**2** ratio. The $K_s'$ values of the complexes with (5-phenylpentyl)ammonium (**2c**) and (6-phenylhexyl)ammonium picrates (**2d**) were more than 3 times as large as those of the other complexes; i.e., **1** showed selective molecular recognition for **2**. The selectivity could result from a cooperative phenomenon involving the electrostatic and hydrophobic interactions between the crown ether subunit and the ammonium group and between the cyclophane subunit and the phenyl group, respectively.

An understanding of the underlying factors in the selective molecular recognition of organic molecules for organic substrates is very important and has a wide-ranging ramifications, especially in the areas of chemistry and biochemistry. Naturally occurring receptors have a three-dimensional cavity, whose shape plays an important role in determining their binding ability for different substrates, supplementing the effects of the various kinds of nonbonding interactions and leading to stereo- and/or regioselective responses.[2] In the past two decades many types of artificial

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