Self-Induced Diastereoselective Oxidation of Vinyl Sulfides Bearing a Chiral Hydroxy Group as a Way of Preparation of Optically Active Sulfinyl Dienophiles and Their Use in the Asymmetric Diels-Alder Reaction to Cyclopentadiene

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Dienophiles **4**, **5**, **4'**, and **5'** add with excellent diastereoselectivity to cyclopentadiene as a result of the fact that they have assembled most features that are known to govern facial selectivity. Their synthesis entails stereoselective Michael addition of hydroxythiols **1** or **1'** to acetylenes **2a-c** and diastereoselective self-induced oxidation of sulfides **3a-c** to the corresponding sulfoxides **4a-c** and **5a-c**, thus bypassing long and poor-yielding standard procedures. The design of the reaction allows the synthesis of 2-carbomethoxynorbornadiene (**13c**) in high enantiomeric purity in five laboratory steps, virtually without physical separation of the diastereoisomers. The absolute configurations and the preferred conformations in solution of sulfides **3b,c** and of epimeric sulfoxides **4b,c** and **5b,c** were assigned on the basis of NOE experiments. The spectroscopic results were confirmed by X-ray diffractometry on the adduct **7a** and on the sulfones derived from **7c** and **8c**. It was ascertained that the rotational preference of the epimeric sulfoxides drives efficiently and selectively the cyclopentadiene addition to the ene face pointing toward the sulfoxide lone pair. The rotational preference and the subsequent selectivity are to be attributed to hydrogen bonding between sulfoxide and hydroxy groups.

Asymmetric Diels-Alder reactions are recently receiving much attention. Their growing importance in the synthesis of complex products is documented in a monograph[1] and in several reviews.[2-6] Herein we report in full the results[7] obtained with a newly conceived chiral sulfinyl dienophile, whose ready availability and diastereoselective efficiency simplify in many cases the preparation of chiral Diels-Alder adducts.

Design of the Chiral Dienophile. For the design of an efficient chiral dienophile we considered to sum up the greatest number of features that have been shown to direct the diastereofacial selectivity and to include them in its structure, compatibly with the synthetic difficulties. Among the factors that more significantly contribute to the asymmetric induction in Diels-Alder reactions we can cite: (i) highly topologically differentiated *re* and *si* faces (concave and convex faces), as shown by Oppolzer[4] and Helmchen,[8] which are usually obtained from chiral hydrocarbon skeletons derived from terpenes; (ii) conformational rigidity achieved by means of properly located hydrogen bonds[9] or through chelation with metals;[10] (iii) proximity of the chiral centre of the auxiliary moiety to the reactive site, as shown recently by Masamune;[9] (iv) *Z* configuration of the doubly substituted dienophiles, in order to limit the number of potential diastereoisomers.

We thought to utilize the sulfinyl group for the construction of the dienophile, because of the numerous significant applications reported in the field of asymmetric synthesis[11] and because it can be introduced at a single bond distance from the reactive double bond. Indeed the sulfoxide group has long been known to be a moderately activating functionality in Diels-Alder reactions,[12] although the pioneering work of Montanari showed that the chiral sulfoxide is a poor diastereofacially selective agent, as racemic sulfinyl dienophiles add almost indistinctly from the oxygen as well as from the electron pair side and with poor endo selectivity.[13] This finding was recently confirmed by Maignan and Raphael in the cycloaddition of chiral *p*-tolyl vinyl sulfoxides to cyclopentadiene.[14] Good endo stereoselectivity and diastereofacial selectivity have been achieved only with the introduction of an extra activating electronwithdrawing group.[15] However any case reported on the utilization of chiral vinyl sulfoxides in asymmetric Diels-Alder synthesis suffers from practical shortcomings due to the elevated number of reaction steps and the low yields in the preparation of the chiral sulfinyl dienophile. We thought that most of the problems could be bypassed by introducing a chiral auxiliary (for example derived from a terpene) possessing an hydroxy group at a convenient distance. Indeed it has been possible to introduce in a single step the two requirements of steric differentiation and of conformational rigidity, the latter being assured by

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(2) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions", Prentice-Hall: Englewood Cliffs, NJ, 1971.
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(12) See for example: Paquette, L. A.; Moerck, R. E.; Harirchian, B.; Magnus, P. D. *J. Am. Chem. Soc.* **1978**, *100*, 1597 and cited references.
(13) Bertotti, E.; Luciani, G.; Montanari, F. *Gazz. Chim. Ital.* **1959**, *115*, 1564.
(14) Maignan, C.; Raphael, R. A. *Tetrahedron* **1983**, *39*, 3245.
(15) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, *25*, 1727. Koizumi, T.; Hakamada, I.; Yoshii, E. *Ibid.* **1984**, *25*, 87. Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4005. Glass, R. S.; Reineke, K.; Shanklin, M. *Ibid.* **1984**, *49*, 1527.

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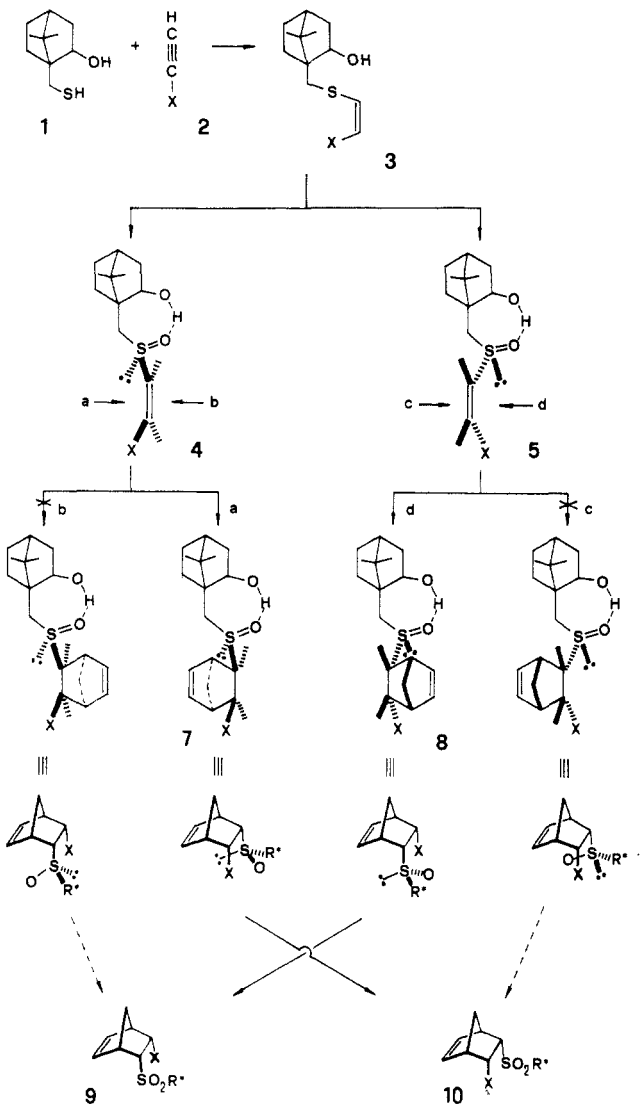
Scheme I[a]



[a] a, X = $PhSO_2$–; b, X = *p*-$ClPhSO_2$–; c, X = MeCOO–.

hydrogen bonding with the sulfoxide group. As the last but not the least relevant point, oxidation of the sulfide occurs with very high diastereoselectivity, likely because of the directing effect of the properly positioned hydroxy group. This point is of particular importance as it allows us to bypass the long procedures for the preparation of optically active vinyl sulfoxides. As described in the following, the preparations of dienophiles with these properties proved to be surprisingly easy and its reactivity satisfactory.

Results and Discussion

The reaction sequence that we have followed is reported in Scheme I for the isobornyl derivative **1**. An analogue reaction sequence was actuated starting from the bornyl derivative **1′**. It has been performed with three different electron-poor acetylenes **2a–c** as starting reagents, while the camphor skeleton was retained. This choice made possible a comparative study of the effect of the two chiral centers: the carbon bearing the hydroxy group and the sulfoxide sulfur.

Preparation of the Chiral Dienophiles. As convenient chiral auxiliaries we choose the hydroxythiols **1** and **1′** derived from (1*S*)-*d*-10-camphorsulfonyl chloride because of their availability in both enantiomeric forms and of their already established preparation. These bornyl

derivatives have been utilized for the asymmetric synthesis of 1,3-oxathianes by Eliel et al.[16] Furthermore both epimeric alcohols are readily obtainable through a one-step reaction from commercially available materials.

Michael addition to the electron-poor acetylenes **2a–c** affords the corresponding adducts in high yields. The *p*-chlorophenylsulfonyl derivatives **2b–5b**, which are crystalline solids, have been prepared for practical reasons, as the unsubstituted derivatives **2a–5a** are oils. The Michael addition occurs strictly in a trans fashion (obtaining *Z* adducts) in the case of the sulfonyl activated acetylenes **2a,b**, but is often nonstereospecific for the propiolic derivatives **2c**, in dependence of the nature of the basic catalyst and of the solvent. This anomalous addition is already known, especially from the work of Montanari and Truce.[17] In our hands the required *Z* adduct was obtained with triethylamine in methanol/water as solvent. When only the *E* isomer **4c** was requested, it was prepared in high yield and essentially uncontaminated by the *Z* isomer using 1,4-diazabicyclo[2,2,2]octane (DABCO) in dry acetonitrile. In our opinion the apparently stereospecific cis addition is attributable to a further addition of DABCO to the already formed *Z* Michael adduct and consequent isomerization to the thermodynamically more stable *E* isomer. The *E* isomer can also be prepared by irradiation at 350 nm of the *Z* form.[18]

It is worth noting that the workup with methyl propiolate **2c** is greatly simplified by the unexpected finding that the *Z* isomer **3c** is a crystalline solid that separates easily from the alcoholic reaction mixture, while the *E* isomer is an oil. It is even possible to utilize the crude mixture yielded from the lithium aluminium hydride reduction of (1*S*)-*d*-10-camphorsulfonyl chloride (ca. 4:1 mixture of isoborneol **1** and borneol **1′**) avoiding the chromatographic separation of the two epimers.

The Michael adducts have been oxidized with a variety of reagents; the most significant ones are reported in Table I. The oxidation is in most cases diastereoselective, as the sulfide sulfur is in a chiral environment induced by the hydrocarbonic skeleton of the bornyl residue and especially by the orientation of the hydroxy group. The best results have been obtained with *m*-chloroperbenzoic acid (mCPBA) in dichloromethane at 0 °C or below. This oxidative procedure is operatively very simple and yields the highest diastereoselectivity (entries 1, 6, 7, 9). Other oxidizing agents (*tert*-butyl hypochlorite, singlet oxygen, *tert*-butyl hydroperoxide/titanium tetrahydropropoxide, DABCO/bromine complex, and iodoso derivatives) give lower diastereoselectivities (entries 4, 5) or complicated mixtures of products (not reported in the table).[19,20]

(16) Eliel, E. L.; Frazee, W. J. *J. Org. Chem.* **1979**, *44*, 3598. Eliel, E. L. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. II, p 125.

(17) Montanari, F. *Tetrahedron Lett.* **1960**, 18. Truce, W. E.; Tichenor, G. J. W. *J. Org. Chem.* **1972**, *37*, 2391. Halphen, P. D.; Owen, T. C. *Ibid.* **1973**, *38*, 3507.

(18) In presence of iodine the cyclized products **12** and **12′** are stereoselectively formed. Work is in progress.

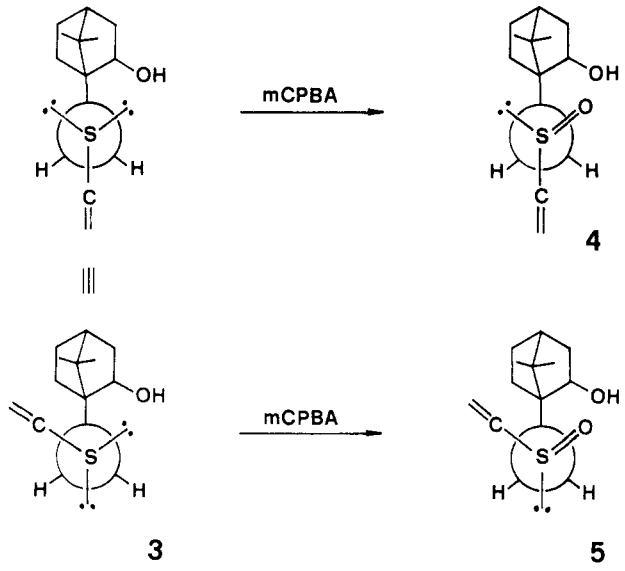
(19) For the oxidation of sulfides to sulfoxides see: Barbieri, G.; Cinquini, M.; Colonna, S.; Montanari, F. *J. Chem. Soc. C* **1968**, 659. Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *196*, 8188. Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325 and cited references. See also ref 2.

Table I. Methods, Diastereoisomeric Ratio, and Yields in the Preparation of the Sulfinyl-Activated Dienophiles 4 and 5

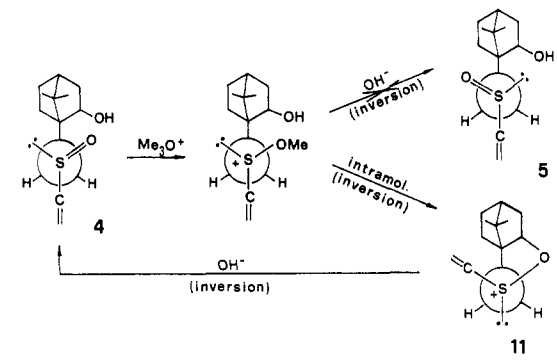
entry	chiral auxiliary[a]	stereo chem	X	sulfide	method	ratio 4:5	yield %
1	A	*Z*	$PhSO_2$–	**3a**	mCPBA/CH_2Cl_2, 0 °C	90:10	74
2				**3a**	mCPBA/MeOH, −20 °C	62:38	80
3				**3a**	mCPBA/Acetone, 0 °C	61:39	70
4				**3a**	*t*-BuOOH/$MoO_2(Acac)_5$ 0 °C	63:37	70
5				**3a**	H_2O_2/CH_3COOOh, room temp.	61:39	80
6	A	*E*	$PhSO_2$–	**3a**	mCPBA/CH_2Cl_2, 0 °C	90:10	75
7	A	*Z*	*p*-$ClPhSO_2$–	**3b**	mCPBA/CH_2Cl_2, 0 °C	91:9	85
8				**3b**	mCPBA/MeOH, −20 °C	63:37	90
9	A	*Z*	MeOOC–	**3c**	mCPBA/CH_2Cl_2, 0 °C	96:4	95
10				**3c**	mCPBA/MeOH, −20 °C	62:38	92
11	A	*E*	MeOOC–	**3c**	mCPBA/CH_2Cl_2, 0 °C	92:8	73
12	B	*Z*	MeOOC–	**3c′**	mCPBA/CH_2Cl_2, −20 °C	85:15	90
13	B	*Z*	MeOOC–	**3c′**	mCPBA/MeOH, −20 °C	62:38	91

[a] A, isoborneol derivatives. B, borneol derivatives.

Scheme II



Scheme III



Obviously it is the presence of the double bond that limits the choice of the oxidant.

The high diastereoselectivity observed in the oxidation with mCPBA in dry dichloromethane is expected on the basis of a recent work by Glass,[21] which has shown that the sulfoxide oxygen is on the same side of the hydroxy group. This specificity was attributed to incipient hydrogen bonding between the substrate hydroxy group and the percarboxylic acid. Actually we have carried out NOE measurements (see below) on sulfides **3b,c** to determine their preferred rotameric conformation in solution and we have found that indeed it is the one which can intuitively be associated with the least steric hindrance (see Scheme II). Under these assumptions one may predict that the major diastereoisomer has the configuration **4** in Scheme II. From the known absolute configuration of the camphor moiety, the absolute configuration of the sulfoxide in **4** can be designed as *R*.

The hypothesis of hydrogen bonding between the substrate and the oxidant is consistent with the observation of a decrease in diastereoselectivity when the mCPBA oxidation is carried out in methanol or acetone (entries 2, 3, 8, 10, 13). It may be presumed that in these cases hydrogen bondings of mCPBA with methanol or of **3** with acetone are competitive with hydrogen bonding between **3** and mCPBA, with the consequence of an indifferentiation of the side of attack. This finding suggests that the oxidation preference is governed by the hydroxy function, while the role played by steric factors seems less relevant.

The oxidation of the adducts derived from the bornyl residue 1′ (entries 12, 13) gives similar results. The somewhat poorer selectivity may be explained by a less favorable geometry of the substrate with a consequent smaller population difference of the two rotamers in Scheme II. Alternatively one can think at a diminished propension of the hydroxy group to hydrogen bond for geometrical reasons.

From a synthetic point of view, the preparation of pure **4** was obtained by purification of the highly enriched mixture yielded in the oxidation with mCPBA in dry dichloromethane. For the preparation of pure **5** we had to resort to the separation of the mixture of epimeric sulfoxides obtained from the oxidation in methanol or acetone. This somewhat synthetically inconvenient procedure was chosen because oxidants that do not hydrogen bond, and hence selectively deliver oxygen on the less hindered side (opposite to the hydroxy group), as for example *tert*-butyl hypochlorite,[20,21] are very inefficient. This unfortunate circumstance prevents the possibility of a simple entry to the two epimeric sulfoxides.

The pyramidal inversion of sulfoxides **4** performed via the alkylation/hydroxide procedure of Johnson,[22] is also unpractical as **4** does not epimerize. This failure may be attributed to the possibility of intramolecular attack of the hydroxy function, to afford the intermediate cyclic oxysulfonium salt **11**, from which the base attack can only lead to the original sulfoxide (Scheme III).

(20) For leading references on the directing effect of the hydroxy group in the oxidation of sulfides see: Hirschon, A. S.; Doi, J. T.; Musker, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 725. Klein, J.; Stollar, H. *Tetrahedron* **1974**, *30*, 2541.

(21) Glass, R. S.; Setzer, W. N.; Prabhu, U. D. G.; Wilson, G. S. *Tetrahedron Lett.* **1982**, *23*, 2335 and cited references.

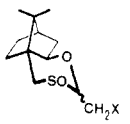
(22) Johnson, C. R. *J. Am. Chem. Soc.* **1963**, *85*, 1020. Johnson, C. R.; McCants, D., Jr. *Ibid.* **1965**, *87*, 5404. Oae, S.; Numata, T.; Yoshimura, T. In "The Chemistry of the Sulphonium Group"; Patai, S., Series Ed., Stirling, C. J. M., Ed.; Wiley: New York, 1981, p 571.

Table II. Diastereoisomeric Ratio in the Cycloaddition of the Sulfinyl Dienophiles 4a–c and 5a–c to Cyclopentadiene

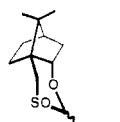
entry	chiral auxiliary[a]	stereo chem	X	Y	solvent	diaster ratio of 4:5	diaster ratio of 7:8
1	A	*Z*	$PhSO_2$–	–SO–	$CDCl_3$	90:10	90:10
2	A	*Z*	$PhSO_2$–	–SO–	CH_2Cl_2	61:39	61:39
3	A	*E*	$PhSO_2$–	–SO–	$CDCl_3$	90:10	mixture
4	A	*Z*	$PhSO_2$–	$-SO_2-$	$CDCl_3$		mixture
5	A	*Z*	*p*-$ClPhSO_2$–	–SO–	$CHCl_3$	91:9	91:9
6	A	*Z*	*p*-$ClPhSO_2$–	–SO–	$CHCl_3$	97:3	97:3
7	A	*Z*	*p*-$ClPhSO_2$–	–SO–	$CHCl_3$	63:37	63:37
8	A	*E*	*p*-$ClPhSO_2$–	–SO–	$CDCl_3$	100:0	mixture
9	A	*Z*	MeOOC–	–SO–	$CDCl_3$	96:4	98:traces
10	A	*Z*	MeOOC–	–SO–	$CDCl_3$	4:96	traces:97
11	A	*Z*	MeOOC–	–SO–	$CDCl_3$	100:0	98:0
12	A	*Z*	MeOOC–	–SO–	MeOH	100:0	98:0
13	A	*Z*	MeOOC–	–SO–	Me_2CO	100:0	98:0
14	A	*Z*	MeOOC–	–SO–	$CHCl_3$	17:83	17:83
15	A	*E*	MeOOC–	–SO–	$CHCl_3$	100:0	mixture
16	A	*Z*	MeOOC–	$-SO_2-$	$CHCl_3$		mixture
17	B	*Z*	MeOOC–	–SO–	$CHCl_3$	100:0	95:0
18	B	*Z*	MeOOC–	–SO–	MeOH	100:0	98:0
19	B	*Z*	MeOOC–	–SO–	CH_2Cl_2	74:26	74:26

[a] A, isoborneol derivatives. B, borneol derivatives.

During the chromatographic separation a small fraction (in dependence of the activation of silica gel and on the time of permanence on it) of the sulfoxide converts into the cyclized products **12** and **12′**. This process, which is



12



12′

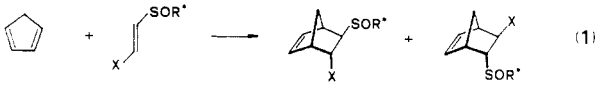
probably an intramolecular Michael addition catalyzed by silica gel, is quite general and highly stereoselective and is currently under investigation.

It has, however, to be pointed out that long chromatographic separations are unnecessary from a synthetic point of view, as the final products, highly enriched in one diastereoisomer, can be readily purified in most cases by crystallization.

Diels–Alder Additions to Cyclopentadiene. Table II lists representative examples of the cycloaddition of dienophiles **4**, **5**, **4′**, and **5′** to cyclopentadiene. For comparative purposes, results obtained with some sulfones[6] and some *E*-isomers have been included. In all cases reported the dienophiles were enough reactive to give rapid and especially stereospecific endo additions at 5 °C, although a somehow higher reactivity has been observed for the carbomethoxy derivatives **4c**, **5c**, **4c′**, and **5c′**. The reactions were carried out in dichloromethane with a 20–30% molar excess of the diene. The ratio between the diastereomeric products was determined from integrated resonances on 200-MHz proton spectra. The interfering signals of excess cyclopentadiene and its dimer were eliminated by rough purification of the reaction mixture by thick layer chromatography, discarding only the firstly eluted hydrocarbon fraction.

As shown in Scheme I, the cycloaddition of each epimer should in principle afford a mixture of two diastereoisomers depending upon the side of approach of the diene. When pure sulfoxides have been used (entries 11–13, 17, 18), we could observe the ^1H NMR pattern of only one diastereoisomer. With regard to the instrumental detection limits, this should mean a purity of at least 98%. When mixtures of sulfoxides **4** and **5** were used, two diastereoisomers (out of the potential four products) were detected in the same ratios of the starting reagents (entries 1–3, 5–7, 9, 10, 14, 19), thus confirming the high diastereoselective degree of the addition. Also when there could be expected a loosening of the conformational rigidity because of hydrogen bonding of the dienophile with solvents such as acetone or methanol (entries 12, 13), no detectable change in product distribution was observed.

On the contrary, the cycloaddition of the *E* isomers affords in all instances a mixture of diastereoisomers deriving from a nonstereospecific reaction (eq 1). A similar



(1)

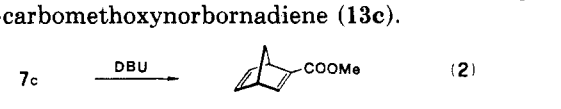
R* = bornyl or isobornyl residue

behavior, which does not seem to depend on the activating functionality, has already been reported.[15]

It is significative that the addition of dienophiles **6a,c** bearing an achiral sulfone group in place of the chiral sulfoxide gives complex diastereomeric mixtures (entries 4 and 16). This finding shows that the diastereospecificity is mostly directed by the sulfoxide chirality and that the sole presence of the chiral hydrocarbon is not sufficient to bias the reaction course. Also the weakening of hydrogen bonding on passing from the sulfoxide to the sulfone functionality may be responsible for the lack of selectivity.

As a final point, the orientation of the hydroxy function does not seem to play a relevant role, as similar diastereomeric adduct ratios have obtained with the sulfoxides **4′** and **5′** derived from borneol (entries 17–19).

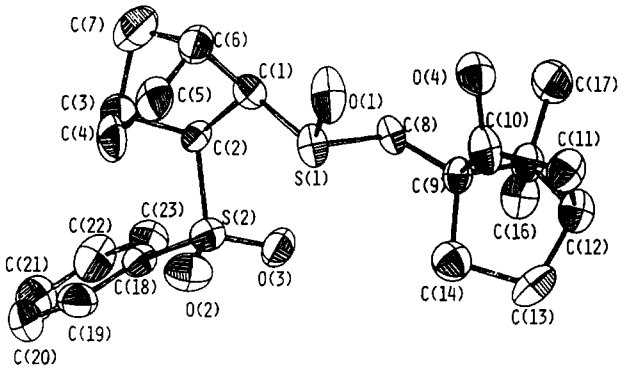
As previously mentioned the pure diastereoisomers could be isolated by fractional crystallization and are amenable to a series of useful manipulations. A review reports many transformations concerning especially the benzenesulfonyl derivatives.[23] Although we were not particularly interested in a further utilization of the adducts prepared in this investigation, we tried some reactions. For example the treatment of the cycloadduct **7c** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) removes the chiral auxiliary to give 2-carbomethoxynorbornadiene (**13c**).



(2)

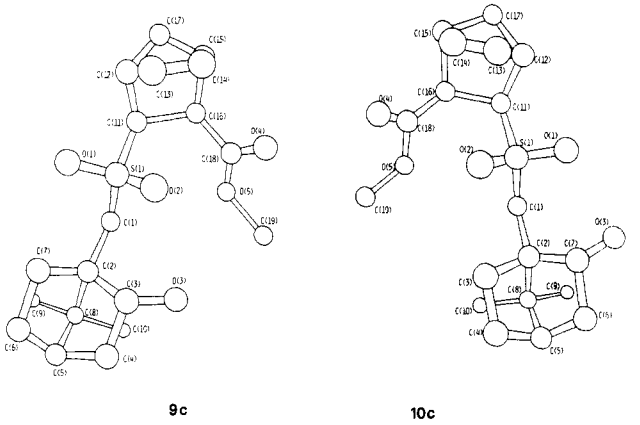
13c

(23) Magnus, P. D. *Tetrahedron* **1977**, *23*, 2019.



7a

Figure 1. ORTEP molecular structure of **7a** showing all non-hydrogen atoms and drawn on the basis of the absolute configuration of C(9) known as *S*.

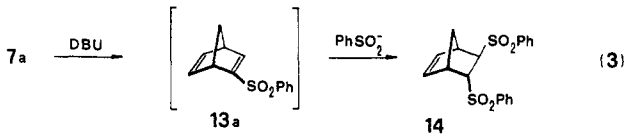


9c 10c

Figure 2. Perspective structure of **9c** and **10c** as determined by X-ray analysis and drawn on the known absolute configuration of C(2) as *S*.

This highly functionalized molecule has been used as a racemic mixture by Corey et al. as starting material for the preparation of biologically active analogues of prostaglandin endoperoxides.[24] It should be pointed out that **13c** is obtained with this method from unexpensive starting materials in high optical purity virtually without necessity of physical separation.

When carried out for **7a**, the same reaction provides a more complex product mixture, from which the bis(benzenesulfonyl) cycloadduct **14** could be isolated in poor



13a 14 (3)

yield. This product was independently synthesized as racemic mixture in the course of another investigation,[25] and derives probably from addition of the benzenesulfinate anion to norbornadiene **12a**. In turn the benzenesulfinate anion may be thought to derive via β-elimination of the precursor **7a**,[26] that may not undergo chemoselective β-elimination. Because the reaction was carried out with enantiomerically pure **7a**, norbornadiene **14** may be of high enantiomeric purity.

As a final remark, although the recovery of the chiral auxiliary seems to be possible, it is unpractical for small scale laboratory preparations because of the low cost of the reagents and of the necessity of further manipulations.

Diffractometric Determination of the Absolute Configurations of Some Adducts to Cyclopentadiene. The crystals of adducts **7c** and **8c**, derived from addition to carbomethoxy derivatives **4c** and **5c**, are not suitable for X-ray analysis, and were therefore oxidized to the corresponding sulfones **9c** and **10c**. The structural investigation was extended to the adduct **7a** of the benzenesulfonyl derivative **4a**.

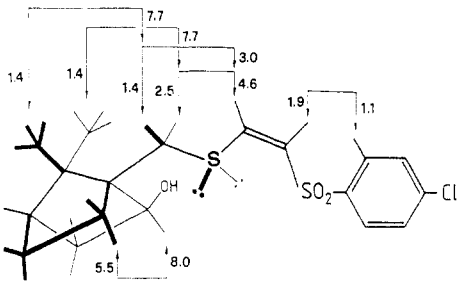
The ORTEP molecular structure of **7a** (Figure 1) was drawn on the basis of *S* absolute configuration around C(9) in the camphor moiety. There follows the *R* configuration for the sulfoxide S(1) center and the *R* and *S* configuration respectively for the two newly introduced chiral centers C(1) and C(2). Hence the cycloaddition to **4a** takes place on the face *re* with respect to the sulfoxide function. From NOE analysis this is the face with minor crowding in the predominant rotamer in solution (see below).

The X-ray structures of the oxidized adducts **9c** and **10c** are shown in Figure 2. The structures of **7a** and **10c** are configurationally identical, confirming that the addition direction is not influenced by the nature of the function (either benzenesulfonyl or carboalkoxy) which activates the addition. At the same time, inspection of the structure **9c** of Figure 2 reveals that the configurations around the two new chiral centers C(11) and C(16) are *S* and *R* respectively, signifying that the addition on **5c** occurred on the face *si* with respect to the sulfoxide group. From NOE observations, this is again the face with minor hindrance in the predominant rotamer.

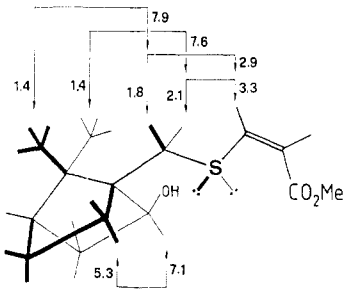
Determination of the Absolute Configuration and of the Rotameric Conformational Preference by NOE Measurements. No suitable crystals of sulfonyl derivatives **3a,b**, **4a,b**, and **5a,b** or of the carbomethoxy derivatives **3c**, **4c**, and **5c** could be isolated for diffractometric analysis. In any case this study could have established the sulfinyl orientation in epimers **4** or **5** (and in fact the *R* configuration at sulfinyl oxygen in **4a** can be deduced from the X-ray structure of the adduct **7a** with cyclopentadiene), but not the preferred rotameric conformation in the reaction environment, i.e., in solution. This knowledge is of paramount importance, as the diastereoselective addition of cyclopentadiene will likely occur on the less crowded side of the dienophilic double bond, and this side is different in different rotamers. Similar considerations hold for the sulfide precursors **3**, where the rotameric preference plays the main role in driving the oxidation direction.

The rotameric preference can be determined from the analysis of NOE measurements[27] by means of NMR differential spectroscopy.[28] The orientation of the sulfinyl oxygen cannot of course be determined by this technique, but we maintain as a firm point that the S–O bond is rigidly constrained toward the side of the hydroxy group by hydrogen bonding, so that the configuration around sulfur and the rotameric preference may be established by checking the spatial proximity of the α-vinyl proton to either proton of the methylenic group. The NOE analysis was limited to the *p*-chlorobenzenesulfonyl **3b–5b** and carbomethoxy **3c–5c** derivatives, but the conclusions may

(24) Corey, E. J.; Shibasaki, M.; Nicolau, K. C.; Malmsten, C. L.; Samuelsson, B. *Tetrahedron Lett.* **1976**, 737.
(25) De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* **1984**, *62*, 2487.
(26) De Lucchi, O.; Pasquato, L. *Gazz. Chim. Ital.* **1984**, *114*, 349. De Lucchi, O.; Lucchini, V.; Zamai, M.; Modena, G. *Can. J. Chem.* **1984**, *62*, 2487.
(27) Noggle, J. H.; Schirmer, R. E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1970.
(28) Sanders, J. K. M.; Mersh, J. D. *Prog. in NMR Spectros.* **1982**, *15*, 353.

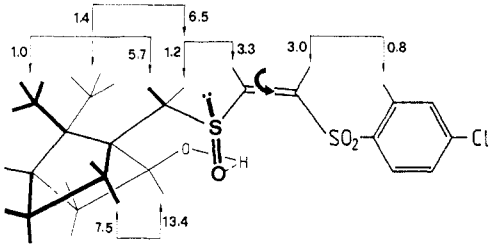


3b

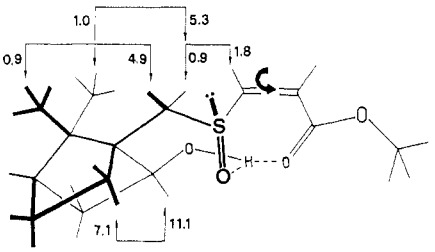


3c

Figure 3. Conformational preference of sulfides **3b,c** as determined by NOE experiments. Numbers give % enhancement upon perturbation of the connected nucleus.



4b

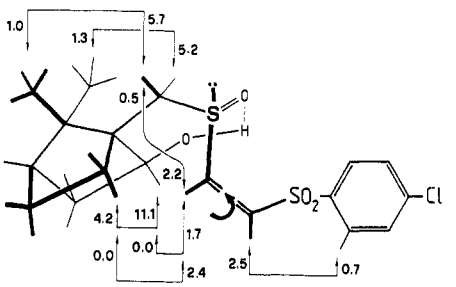


4c

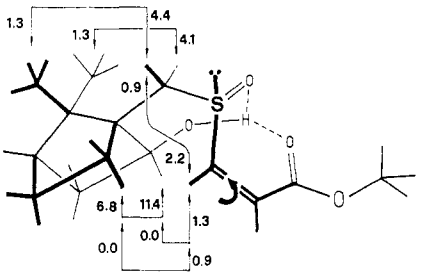
Figure 4. Conformational preference of sulfoxides **4b,c** as determined by NOE experiments. Numbers give % enhancement upon perturbation of the connected nucleus.

be safely extended to the benzenesulfonyl derivatives **3a–5a**. The results are presented in Figures 3–5: numbers give the resonance enhancements of the indicated center upon saturation of the resonance of the connected atom. Cross experiments may give different answers because of efficient dipole–dipole or spin–rotational relaxations associated with some nuclei.[27] Only the results relevant for the present discussion are reported.

In all compounds with exo oriented hydroxy, the NOE enhancements between the low-field methylenic protons



5b



5c

Figure 5. Conformational preference of sulfoxides **5b,c** as determined by NOE experiments. Numbers give % enhancement upon perturbation of the connected nucleus.

and the low-field methyl group in the dimethylmethano bridge are very similar (within experimental uncertainty) to those of the high field counterparts, suggesting that the methylenic moiety and the dimethylmethano bridge are eclipsed. The correct assignment of the low- and high-field resonances to the methyls 7s and 7a respectively syn and anti to the hydroxy group allows the assignment also of the methylenic resonances. The low-field methyl resonance is generally attributed to methyl 7s,[29] but we thought it appropriate to confirm the assignment by means of a lanthanide induced shift (LSI) investigation with $Eu(fod)_3$ on sulfide **3c**. In agreement with a recent report,[30] the LIS is greater for the low-field methyl: LIS (low-field methyl)/LIS (high-field methyl) = 1.72. The same trend is observed for methylenic protons: LIS (low-field protons)/LIS (high-field protons) = 1.51, thus confirming the attribution accomplished with the NOE technique. These considerations may be extended to the other sulfides **3a,b** and to the sulfoxides **4** and **5**, arriving at the general attribution of the low-field doublet to the methylenic proton syn to the hydroxy group.

In all compounds investigated, saturation of the proper methylenic resonance brings about NOE enhancements of the low-field vinylic resonance, therefore attributable to the vicinal vinylic proton. This assignment is confirmed in *p*-chlorobenzenesulfonyl derivatives **3–5b**, where the saturation of the ortho protons causes a discernible enhancement of the high-field vinylic resonance.

In sulfides **3b,c** saturation of either low- or high-field methylenic resonance brings about the same NOE enhancements of the low-field vinylic resonance (Figure 3). The equidistance of the vinylic proton with the two methylenic protons is confirmed by the reverse experiment

(29) Demarco, P. V.; Elzey, T. K.; Lewis, R. B.; Wenkert, E. *J. Am. Chem. Soc.* **1970**, *92*, 5734. Hawkes, G. E.; Leibfritz, D.; Roberts, D. W.; Roberts, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 1659.

(30) Lacombe, L.; Mamlok, L. *J. Chem. Res. Synop.* **1977**, 111.

and suggests that the anti rotameric conformation predominates in solution.

As for sulfoxides **4b,c** obtained as major products from oxidation with mCPBA in dichloromethane, NOE interactions are observed between the low-field vinylic doublet and the low-field methylenic resonance (Figure 4), but not with the high-field resonance. Therefore the dienophilic double bond insists on the side of the hydroxy group, and the *R* configuration is to be attributed to the sulfur atom. In this arrangement the *re* face (with respect to sulfoxide) of the double bond points away from the hydroxy group (toward the viewer in Figure 4). The approach of the dienic reagent on this face (indicated by the curved arrow) is easier than on the *si* face, which is somehow hindered by the presence of the camphor skeleton.

In sulfoxides **5b,c** isolated as minor products from oxidation with mCPBA in methanol or acetone, a NOE interaction of the low-field vinyl resonance is observed with the high-field methylenic resonance only (Figure 5). The spatial proximity of the vicinal vinyl proton and the methylenic proton anti to the hydroxy group is possible when the sulfur atom is in the *S* configuration and the reactive double bond points away from the hydroxy group. Other interactions of the same vinyl resonance are observed with the camphor 2endo proton (which is deshielded by geminal oxygen and resonates consequently in a low-field isolated region) and with a proton resonating under the featureless resonance system of the camphor skeleton. This same proton interacts relevantly with the 2endo proton and is therefore to be identified as the 6endo proton. Actually the Dreiding molecular model reveals that the sulfoxide–hydroxy hydrogen bond compels the vinyl proton to a close proximity with these two camphor protons. In this arrangement the *re* (with respect to sulfoxide) face of the dienophilic double bond is completely hindered by the hydrocarbon skeleton and the approach of the dienic reagent can occur exclusively on the *si* face (as indicated by the curved arrow in Figure 5).

In the case of the carbomethoxy derivatives **4c** and **5c** it may be further presumed that the conformational preferences are reinforced by a second hydrogen bond of the hydroxy proton with the carbonylic oxygen (or, for that matter, with the methoxy oxygen).

The absolute configurations and the rotameric preferences of sulfide **3c′** and sulfoxides **4c′** and **5c′** derived from the borneol 1′ skeleton could not be determined. As a consequence of the endo orientation of the hydroxy group, the resonances of the dimethylmethano bridge on one side and the methylenic resonances on the other are almost or totally isochronous, making their selective saturation impossible.

This spectroscopic investigation allowed the unambiguous identification of the less hindered dienophilic face in the rotameric conformations of epimers **4** or **5** which predominate in solution. This is the *re* face in epimers **4** and the *si* face in epimers **5**. X-ray analyses have actually confirmed that cyclopentadiene adds on these faces with the generally observed endo orientation.

Conclusions

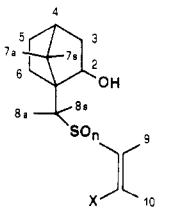
The addition modalities of cyclopentadiene to sulfones **6a,c** demonstrate that the presence of the sole camphor auxiliary is not sufficient for a diastereoselective bias of the reaction. On the other hand, the work of Montanari[13] and of other groups[14,15] has shown that cycloadditions occur indistinctly on both sides of vinyl sulfoxides, when only this latter function is present. The synergism of the two systems is quite evident and the most relevant contribution to diastereoselectivity is likely given by hydrogen bond formation between these units, which assures the necessary molecular rigidity.

The camphor skeleton plays a more determinant role in an earlier stage in reaction Scheme I, when it directs to a good stereoselective degree the oxidation of sulfides **3** and, in case, allows the physical separation of the diastereomeric mixture. Anyway, it suffices to utilize only one chiral auxiliary (either borneol or isoborneol) for the different preparation of both epimeric sulfoxides.

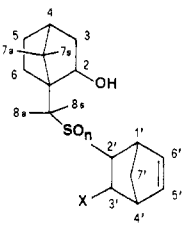
We are currently investigating other new diastereoselective reagents, where the chiral auxiliary can be removed and reutilized more efficiently.

Experimental Section

Melting points are uncorrected. The NMR spectra were recorded on a Bruker WP200SY operating at 200 MHz. Alternatively a Varian EM360A or a Bruker WP60, both operating at 60 MHz, were used. The reported coupling constants are given in Hz and might refer to peak separations measured directly from the instrument in spectra not of first order. The chemical shift of the hydroxy proton was not included in the NMR data. The resonance numbering is given in i and ii. The IR spectra were



i



ii

recorded on a Perkin-Elmer 580B spectrophotometer. Optical rotations were measured on a Perkin-Elmer polarimeter (100 mm, 1-mL cell) in the indicated solvent and concentration (c) in grams of solute per 100 mL of solution. Radial chromatography was performed on a Chromatotron (TC Research) with Merck PF-254 silica gel. Medium-pressure chromatography was conducted on an home-made apparatus on >230 mesh Merck silica gel. Microanalysis were performed in house. Known compounds used in this research were either purchased from standard chemical suppliers or prepared according to literature procedures and purified to match the reported physical and spectral data.

Nuclear Overhauser Effect Measurements.[27] The measurements tubes were freed from oxygen by repeated freeze–thaw cycles and then sealed under vacuum. The usual pulse sequence for differential NOE experiments was adopted;[31] as the only modification, a multiplet was saturated with the least decoupling power by a 8-s cyclic perturbation of all multiplet lines.[32] The % enhancements were obtained from the coefficients of the reference spectrum when brought to exact matching with the perturbed spectrum. Errors are estimated at about 0.5%.

10-Mercaptoisoborneol (1) and 10-Mercaptoborneol (1′). To a mixture of lithium aluminium hydride (4.08 g, 108 mmol) in ca. 100 mL of dry ether a solution of (1*S*)-*d*-10-camphorsulfonyl chloride (13.46 g, 54 mmol) in ca. 100 mL of ether is added at −78 °C under nitrogen in small portions. The mixture is heated first at room temperature and then at reflux overnight. The excess of hydride is cautiously quenched with ethyl acetate and finally with dilute hydrochloric acid (ca. 1–2%). The resulting mixture is filtered through a Celite pad and washed thoroughly with ether, and the filtrate is washed with brine to neutrality. The ether extracts are dried over anhydrous magnesium sulfate and rotoevaporated to dryness. The strongly smelling oily residue (8.20 g, 82% yield) is chromatographed at medium pressure (ca. 20:1 weight ratio adsorbant to substrate) eluting with petrol ether–ethyl acetate 98:2. The first eluted product is (1*S*)-*d*-10-mercaptoisoborneol (1): 6.60 g (67% yield); mp 70 °C (lit.[16] 76–78 °C); $[\alpha]^{24}_{D}$

(31) Hull, W. E. *Aspect 2000 Pulse Programmer*; Bruker Analytische Messtechnik GMBH: Rheinstetten, West Germany, 1981; Program 12.4.
(32) Kinus, M.; Sanders, J. K. M. *J. Magn. Res.* **1984**, *56*, 518.

−57.44° (c 10, $CHCl_3$) (lit.[16] $[\alpha]^{24}_D$ −55.4°); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.83 (s, Me_{7a}), 1.05 (s, Me_{7s}), 0.95–1.80 (7 H, series of m), 1.28 (dd, SH, $J_{8a(8s),SH}$ = 5.5, $J_{8s(8a),SH}$ = 9.5), 2.20 (d, H_2, $J_{2,3(3')}$ = 4.0), 2.56 (dd, H_{8a}, $J_{8a,8s}$ = 12.8), 2.79 (dd, H_{8s}); IR (KBr pellet) ν_{max} (cm^{-1}) 3483, 2959, 1391, 1372, 1311, 1070, 1033.

The second eluted product is (1*S*)-*d*-10-mercaptoborneol (1′): 1.40 g (14% yield); mp 66 °C (lit.[16] 70 °C); $[\alpha]^{25}_D$ −11.76° (c 10, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (Me_{7a} and Me_{7s}), 0.80–2.35 (9 H, series of m), 2.52 (dd, H_{8a}, $J_{8a,8s}$ = 10.1), 2.72 (dd, H_{8s}); IR (KBr pellet) ν_{max} (cm^{-1}) 3444, 2958, 1292, 1267, 1074, 1044.

Preparation of Acetylenes 2a–c. (Phenylsulfonyl)- and ((*p*-chlorophenyl)sulfonyl)acetylenes **2a,b**[33] were prepared by lithium diisopropylamide (LDA) dealkoxylation of the corresponding β-thioacetals[34] followed by mCPBA oxidation of the resulting acetylenic sulfide. Methyl propiolate was commercially available.

(1*S*)-*d*-10-Mercaptoisoborneol Adduct to (Phenylsulfonyl)acetylene (3a). Freshly prepared (phenylsulfonyl)-acetylene (4.32 g, 26 mmol) in 50 mL of acetonitrile is added with stirring at 0 °C to a solution of (1*S*)-*d*-10-mercaptoisoborneol 1 (4.80 g, 26 mmol) in ca. 20 mL of acetonitrile. Two drops of morpholine are added and the reaction mixture is stirred at room temperature for 18 h, poured into water, and extracted with dichloromethane. After washing with brine, the organic layers are anhydrified over sodium sulfate and evaporated. The oily residue (7.8 g, 85% yield) is purified by repeated radial chromatography eluting with petrol ether–ethyl acetate 98:2 to afford a colorless oil (6.6 g; 66% yield): $[\alpha]^{20}_D$ −54.64° (c 2, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.83 (s, Me_{7a}), 1.05 (s, Me_{7s}), 1.48–1.74 (7 H, complex m), 2.70 (d, H_{8a}, $J_{8a,8s}$ = 12.5), 3.20 (d, H_{8s}), 3.82 (broad s, H_{2endo}), 7.21 (d, H_{10}, $J_{9,10}$ = 10.4), 7.35 (d, H_9), 7.42–8.02 (m, Ph); IR (CaF_2 cell, $CHCl_3$), ν_{max} (cm^{-1}) 3526, 3429, 2960, 2896, 1655, 1587, 1592, 1149, 1147, 1087. Anal. Calcd for $C_{18}H_{24}O_3S_2$: C, 61.30; H, 6.86. Found: C, 61.18; H, 6.80.

The *E*-isomer was obtained via direct irradiation at 254 nm (Pyrex filter) of a ca. 0.1 M deuteriochloroform solution of *Z*-**3a**. *E*-**3a**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.87 (s, Me_{7a}), 1.07 (s, Me_{7s}), 0.47–1.90 (8 H, complex m), 2.70 (d, H_{8a}, $J_{8a,8s}$ = 11.3), 3.13 (d, H_{8s}), 6.20 (d, H_{10}, $J_{9,10}$ = 14.7), 7.84 (d, H_9), 7.47–7.93 (m, Ph).

(1*S*)-*d*-10-Mercaptoisoborneol Adduct to ((*p*-Chlorophenyl)sulfonyl)acetylene (3b). It was prepared analogously to **3a**. From 3.75 g (18.7 mmol) of ((*p*-chlorophenyl)sulfonyl)-acetylene **2b** and 3.50 g (18.8 mmol) of (1*S*)-*d*-10-mercaptoisoborneol (1) there was obtained 4.45 g (62% yield) of colorless crystals after crystallization from methanol: mp 130 °C; $[\alpha]^{20}_D$ −71.49°, (c 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85 (s, Me_{7a}), 1.05 (s, Me_{7s}), 0.98–1.98 (7 H, series of m), 2.72 (d, H_{8a}, $J_{8a,8s}$ = 12.5), 3.19 (d, H_{8s}), 3.95 (m, H_{2endo}), 6.18 (d, H_{10}, $J_{9,10}$ = 10.4), 7.31 (d, H_9), 7.51 and 7.92 (2 m, Ph). Anal. Calcd for $C_{18}H_{23}ClO_3S_2$: C, 55.87; H, 5.99. Found: C, 55.67; H, 6.01.

(1*S*)-*d*-Mercaptoisoborneol Adduct to Methyl Propiolate (3c). To a stirred solution of (1*S*)-*d*-10-mercaptoisoborneol (1) (4.00 g; 21.5 mmol) and methyl propiolate (1.80 g, 21.4 mmol) in ca. 50 mL of a 9:1 mixture ethanol–water cooled at 0 °C, a few drops of triethylamine are added. The reaction is allowed to reach room temperature, and after 3 h a white precipitate of the cis adduct *Z*-**3c** forms. The reaction mixture is filtered and the filtrate extracted with dichloromethane, dried, and concentrated to ca. 4–5 mL. Petroleum ether is added and the white crystals are separated. The two crops of crystalline material are combined and recrystallized from dichloromethane–petroleum ether: 4.17 g (72% yield); mp 121 °C; $[\alpha]^{20}_D$ −9.43° (c 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.87 (s, Me_{7a}), 1.98 (s, Me_{7s}), 0.93–1.80 (7 H, complex m), 2.77 (d, H_{8a}, $J_{8a,8s}$ = 11.9), 3.18 (d, H_{8s}), 3.74 (s, OMe), 3.94 (m, H_{2endo}), 5.85 (d, H_{10}, $J_{9,10}$ = 10.1), 7.24 (d, H_9); IR (CaF_2 cell, $CDCl_3$) ν_{max} (cm^{-1}) 3615, 2955, 2885, 2252, 1695, 1574, 1456, 1488, 1366, 1223, 1172, 1072, 1011. Anal. Calcd for $C_{14}H_{22}O_3S$: C, 62.19; H, 8.20. Found: C, 62.01; H, 8.38.

The filtered liquors are evaporated to dryness, and the residue is purified by radial chromatography eluting with petroleum ether–ethyl acetate 98:2 to afford *E*-**3c** as a colorless oil: 1.04 g (18% yield); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.89 (s, Me_{7a}), 1.09 (s, Me_{7s}), 0.84–1.89 (7 H, complex m); 2.73 (d, H_{8a}, $J_{8a,8s}$ = 11.6), 3.17 (d, H_{8s}), 3.70 (s, OMe), 3.84 (m, H_{2endo}); 5.79 (d, H_{10}, $J_{9,10}$ = 15.1), 7.79 (d, H_9).

Z-**3′c**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.94 (s, Me_{7a}), 0.95 (s, Me_{7s}), 0.79–1.11, 1.21–1.48, 1.58–1.92, and 2.07–2.40 (7 H, complex m), 2.92 (dd, H_{8a} and H_{8s}, $J_{8a,8s}$ = 10.3), 3.73 (s, OMe), 4.53 (m, H_{2exo}), 5.86 (d, H_{10}, $J_{9,10}$ = 10.4), 7.09 (d, H_9).

General Procedure for the Oxidation of Sulfides 3 with mCPBA. To a stirred solution of the vinyl sulfide **3** in the appropriate solvent and temperature (see Table I) a solution of 1 equiv mCPBA in the same solvent is added dropwise, and the reaction mixture is monitored by TLC (petroleum ether–ethyl acetate 9:1; UV detection) up to completion. The reaction takes from 8 to 24 h at the temperatures indicated in the Table I. The white suspension is filtered and extracted with dichloromethane. The organic layer is washed with 5% sodium carbonate solution up to neutrality, then with brine. If oxidant is still present at the end of the reaction, the organic extracts are first washed with a reducing solution of sodium sulfite. The organic layer is dried and rotoevaporated to dryness. Diastereomerically pure sulfoxides are obtained after radial chromatography on silica gel, eluting with gradients of petroleum ether–ethyl acetate. Yields and ratios of the sulfoxides are reported in Table I.

Z-**4a**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.91 (s, Me_{7a}), 1.13 (s, Me_{7s}), 1.10–2.00 (7 H, complex m), 3.01 (d, H_{8a}, $J_{8a,8s}$ = 12.5), 3.65 (d, H_{8s}), 4.10 (dd, H_{2endo}), 6.77 (d, H_{10}, $J_{9,10}$ = 10.4), 7.01 (d, H_9), 7.48–8.10 (m, Ph).

Z-**5a**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.89 (s, Me_{7a}), 1.14 (s, Me_{7s}), 1.00–2.00 (7 H, complex m), 3.05 (d, H_{8a}, $J_{8a,8s}$ = 13.6), 3.52 (d, H_{8s}), 4.14 (dd, H_{2endo}), 6.73 (d, H_{10}, $J_{9,10}$ = 10.7), 7.08 (d, H_9), 7.55–8.10 (m, Ph).

Z-**4b**: mp 140 °C (MeOH), $[\alpha]^{22}_D$ +425° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (s, Me_{7a}), 1.12 (s, Me_{7s}), 1.10–1.93 (7 H, complex m), 2.97 (d, H_{8a}, $J_{8a,8s}$ = 12.5), 3.66 (d, H_{8s}), 4.09 (m, H_{2endo}), 6.75 (d, H_{10}, $J_{9,10}$ = 10.4), 7.03 (d, H_9), 7.59 and 7.89 (2 m, Ph). Anal. Calcd for $C_{18}H_{23}ClO_4S_2$: C, 53.65; H, 5.75. Found: C, 53.43; H, 5.72.

Z-**5b**: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.88 (s, Me_{7a}), 1.14 (s, Me_{7s}), 1.09–2.18 (7 H, complex m), 3.04 (d, H_{8a}, $J_{8a,8s}$ = 13.4), 3.49 (d, H_{8s}), 4.17 (m, H_{2endo}), 6.69 (d, H_{10}, $J_{9,10}$ = 10.4), 7.11 (d, H_9), 7.60 and 7.89 (2 m, Ph).

Z-**4c**: oil; $[\alpha]^{20}_D$ 194.40° (c 6, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85 (s, Me_{7a}), 1.10 (s, Me_{7s}), 1.06–1.28 and 1.54–1.95 (7 H, complex m), 2.78 (d, H_{8a}, $J_{8a,8s}$ = 12.8), 3.51 (d, H_{8s}), 3.80 (s, OMe), 4.09 (m, H_{2endo}), 6.34 (d, H_{10}, $J_{9,10}$ = 10.4), 7.13 (d, H_9); IR (CaF_2 cell, $CHCl_3$) ν_{max} (cm^{-1}) 3416, 3056, 2988, 2958, 2885, 2306, 2244, 1716, 1477, 1456, 1390, 1351, 1266, 1225, 1078, 1017, 1004, 1000, 996.

Z-**5c**: oil; $[\alpha]^{20}_D$ −205.87° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.83 (s, Me_{7a}), 1.08 (s, Me_{7s}), 1.05–1.46 and 1.68–1.89 (7 H, complex m), 2.97 (d, H_{8a}, $J_{8a,8s}$ = 13.4), 3.29 (d, H_{8s}), 3.81 (s, OMe), 4.20 (m, H_{2endo}), 6.32 (d, H_{10}, $J_{9,10}$ = 10.4), 7.13 (d, H_9).

E-**4c**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85 (s, Me_{7a}), 1.08 (s, Me_{7s}), 0.80–1.33 and 1.50–1.97 (7 H, complex m), 2.64 (d, H_{8a}, $J_{8a,8s}$ = 13.4), 3.25 (d, H_{8s}), 3.82 (s, OMe), 4.10 (m, H_{2endo}), 6.69 (d, H_{10}, $J_{9,10}$ = 14.9), 7.68 (d, H_9); IR (CaF_2 cell, $CDCl_3$) ν_{max} (cm^{-1}) 3689, 3455, 2957, 2337, 2253, 1726, 1629, 1623, 1455, 1438, 1391, 1302, 1228, 1172, 1078, 1039, 1009, 966.

E-**5c**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.83 (s, Me_{7a}), 1.06 (s, Me_{7s}), 0.80–1.92 (7 H, complex m), 2.94 (d, H_{8a}, $J_{8a,8s}$ = 13.4), 3.52 (d, H_{8s}), 3.85 (s, OMe), 4.12 (m, H_{2endo}), 6.87 (d, H_{10}, $J_{9,10}$ = 14.9), 7.48 (d, H_9).

E-**4a**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.87 (s, Me_{7a}), 1.08 (s, Me_{7s}), 1.00–1.98 (8 H, complex m), 2.64 (d, H_{8a}, $J_{8a,8s}$ = 13.1), 3.31 (d, H_{8s}), 7.20 (d, H_{10}, $J_{9,10}$ = 14.3), 7.75 (d, H_9), 7.48–8.11 (m, Ph).

E-**5a**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85 (s, Me_{7a}), 1.10 (s, Me_{7s}), 1.00–1.98 (8 H, complex m), 2.62 (d, H_{8a}, $J_{8a,8s}$ = 13.2), 3.55 (d, H_{8s}), 7.15 (d, H_{10}, $J_{9,10}$ = 14.4), 7.40 (d, H_9), 7.48–8.11 (m, Ph).

Z-**4′c**: oil; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (s, Me_{7a}, Me_{7s}), 1.00–2.62 (7 H, complex m), 2.98 (d, H_{8a}, $J_{8a,8s}$ = 10.7), 3.00 (d, H_{8s}), 3.81 (s, OMe), 4.26 (m, H_{2exo}), 6.33 (d, H_{10}, $J_{9,10}$ = 10.5), 6.99 (d, H_9).

Oxidation of *Z*-3a with *tert*-Butyl Hydroperoxide/Dioxomolybdenum(VI) Acetylacetonate. To a cooled (0 °C) and stirred solution of *Z*-**3a** (0.1 g, 0.28 mmol) and $MoO_2(Acac)_5$ (2 mg) in 20 mL of dry dichloromethane is added *tert*-butyl hy-

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droperoxide (26 mg, 0.28 mmol), and the solution is stirred at room temperature for 14 h. The reaction mixture is filtered, washed with an aqueous solution (ca. 5%) of sodium sulfite and brine, dried over anhydrous sodium sulfate and rotoevaporated to an oily residue: 104 mg (70% yield).

Oxidation of *Z*-3a with Hydrogen Peroxide in Acetic Acid. To a cooled (0 °C) and stirred solution of *Z*-**3a** (80 mg, 0.23 mmol) in 10 mL of glacial acetic acid, 0.2 mL of 36% hydrogen peroxide is added, and the solution is kept at room temperature 40 h. The reaction mixture is poured into water and extracted with dichloromethane. After the usual workup 67 mg (80% yield) of an oily product is obtained.

General Procedure for the Preparation of Sulfones. The procedure described for the oxidation of the sulfide with mCPBA was used doubling the quality of the oxidant.

Z-**6a**: mp 108 °C (MeOH); $[\alpha]^{25}_D$ −108.90° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.89 (s, Me_{7a}), 1.12 (s, Me_{7s}), 1.18–1.20 and 1.45–1.96 (7 H, complex m), 3.59 and 3.91 (2 d, H_8, ^2J = 13.4), 4.15 (m, H_{2endo}), 6.81 (d, H_{10}, $J_{9,10}$ = 11.6), 6.92 (d, H_9), 7.56–7.78 and 8.05–8.14 (m, Ph); IR (CaF_2 cell, $CHCl_3$) ν_{max} (cm^{-1}) 3564, 2963, 2344, 2257, 1654, 1541, 1304, 1162, 1139. Anal. Calcd for $C_{18}H_{24}O_5S_2$: C, 56.23; H, 6.55. Found: C, 55.86; H, 6.30.

E-**6a**: mp 84 °C (MeOH); $[\alpha]^{25}_D$ −29.85° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.84 (s, Me_{7a}), 1.07 (s, Me_{7s}), 1.03–1.90 (7 H, complex m), 2.95 and 3.55 (2 d, H_8, ^2J = 14.3), 4.80 (dd, H_{2endo}), 7.35 (d, H_{10}, $J_{9,10}$ = 14.6), 7.47 (d, H_9), 7.58–7.98 (m, Ph); IR (CaF_2 cell, $CHCl_3$) ν_{max} (cm^{-1}) 3557, 3053, 2959, 1449, 1392, 1324, 1166, 1153, 1132.

Z-**6c**: mp 61.5 °C (MeOH); $[\alpha]^{20}_D$ −41.98° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85 (s, Me_{7a}), 1.09 (s, Me_{7s}), 1.12–1.23 and 1.46–1.87 (7 H, complex m), 3.19 and 3.69 (2 d, H_8, ^2J = 13.4), 4.14 (m, H_{2endo}), 6.61 (d, H_{10}, $J_{9,10}$ = 11.6), 6.71 (d, H_9); IR (CaF_2 cell, $CDCl_3$) ν_{max} (cm^{-1}) 3556, 2958, 2885, 2352, 2333, 2253, 1738, 1456, 1437, 1232, 1159, 1076. Anal. Calcd for $C_{14}H_{22}O_5S$: C, 55.61; H, 7.33. Found: C, 55.57; H, 7.35.

General Procedure for the Cycloaddition to Cyclopentadiene. Freshly distilled cyclopentadiene (ca. 20–30% excess) is added to a cooled (0 °C) solution of the dienophile in dichloromethane or chloroform (ca. 10^{-2} M), and the reaction mixture is kept in the refrigerator ca. 12 h. The solution is deposited on a TLC plate (silica gel) and eluted with petroleum ether–ethyl acetate 8:2 to eliminate hydrocarbon fractions and analyzed by ^1H NMR. The results are reported in Table II. Yields are over 90%.

7a: mp 70 °C (MeOH); $[\alpha]^{22}_D$ −8.42° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.91 (s, Me_{7a}), 1.15 (s, Me_{7s}), 1.05–1.32 and 1.37–1.93 (7 H, complex m), 1.34 and 1.65 (2 d, $H_{7'}$, ^2J = 9.5), 2.78 and 3.61 (2 br s, $H_{1'}$, and $H_{4'}$), 3.19 and 3.77 (2 d, H_8, ^2J = 12.8), 3.94 and 4.03 (2 d, $H_{2'}$ and $H_{3'}$, $J_{2',3'}$ = 8.9), 4.07 (m, H_{2endo}), 6.39 and 6.63 (2 dd, $H_{5'}$ and $H_{6'}$, $J_{5',6'}$ = 5.5, $J_{1',6'}$ = $J_{4',5'}$ = 2.8), 7.57–7.76 and 7.89–7.97 (m, Ph); IR (CaF_2 cell, $CHCl_3$) ν_{max} (cm^{-1}) 3691, 3025, 3019, 3016, 1456, 1338, 1323, 1152, 1002. Anal. Calcd for $C_{23}H_{30}O_4S_2$: C, 63.50; H, 7.00. Found: C, 63.40; H, 7.10.

7b: mp 240 °C (MeOH); $[\alpha]^{22}_D$ −12.5° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (s, Me_{7a}), 1.14 (s, Me_{7s}), 1.06–1.31 and 1.40–1.89 (7 H, complex m), 1.35 and 1.68 (2 d, $H_{7'}$, ^2J = 9.5), 2.81 and 3.61 (2 br s, $H_{1'}$ and $H_{4'}$), 3.19 and 3.70 (2 d, H_8, ^2J = 12.8), 3.91 and 4.03 (2 d, $H_{2'}$ and $H_{3'}$, $J_{2',3'}$ = 8.8), 4.03 (m, H_{2endo}), 6.38 and 6.63 (2 dd, $H_{5'}$ and $H_{6'}$, $J_{5',6'}$ = 5.8, $J_{1',6'}$ = $J_{4',5'}$ = 2.9), 7.60 and 7.86 (2 m, Ph). Anal. Calcd for $C_{23}H_{29}ClO_4S_2$: C, 58.59; H, 6.23. Found: C, 58.53; H, 6.18.

7c: mp 130 °C (MeOH); $[\alpha]^{20}_D$ 4.44° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.82 (s, Me_{7a}), 1.11 (s, Me_{7s}), 0.88–1.10 and 1.35–1.88 (7 H, complex m), 1.46 and 1.66 (2 d, $H_{7'}$, ^2J = 9.8), 2.94 and 3.05 (2 d, H_8 ^2J = 12.5); 3.30–3.62 (multiplets, $H_{1'}$, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 3.62 (s, OMe), 4.03 (m, H_{2endo}), 6.35 and 6.49 (2 dd, $H_{5'}$ and $H_{6'}$, $J_{5',6'}$ = 5.8, $J_{4',5'}$ = $J_{1',6'}$ = 2.8); IR (CaF_2 cell, $CDCl_3$) ν_{max} (cm^{-1}) 3401, 3057, 2884, 2244, 1730, 1438, 1355, 1248, 1229, 1204, 1009, 1006, 998, 988. Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.00. Found: C, 64.75; H, 7.99.

8c: mp 138 °C (MeOH); $[\alpha]^{20}_D$ −79.79° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85 (s, Me_{7a}), 1.06 (s, Me_{7s}), 0.90–1.42 and 1.70–1.90 (7 H, complex m), 1.46 and 1.66 (2 d, $H_{7'}$, ^2J = 9.8), 2.42 and 3.30 (2 d, H_8, ^2J = 13.1), 3.39–3.69 ($H_{1'}$, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 4.04 (m, H_{2endo}), 6.27 and 6.54 (2 dd, $H_{5'}$ and $H_{6'}$, $J_{5',6'}$ = 5.5, $J_{1',6'}$ = $J_{5',4'}$ = 2.6); IR (CaF_2 cell, $CDCl_3$) ν_{max} (cm^{-1}) 3693, 3550, 2958, 2885, 2237, 1723, 1475, 1440, 1390, 1362, 1338, 1242, 1075, 997. Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.00. Found: C, 64.58; H, 7.93.

7′**c**: oil; $[\alpha]^{20}_D$ −74.68° (*c* 1.5, $CDCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 and 0.93 (2 s, Me_{7a} and Me_{7s}), 1.2–1.82 and 2.16–2.49 (9 H), 2.58 and 3.16 (2 d, H_8, ^2J = 12.5), 3.30–3.69 ($H_{1'}$, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 4.22 (m, H_{2exo}), 6.34 and 6.48 (2 dd, $H_{5'}$, and $H_{6'}$, $J_{5',6'}$ = 6.0, $J_{1',6'}$ = $J_{4',5'}$ = 2.7).

9c: mp 204 °C (MeOH); $[a]^{22}_D$ −53.47° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85 (s, Me_{7a}), 1.09 (s, Me_{7s}), 1.08–1.30 and 1.49–1.85 (7 H, complex m), 1.32 and 1.55 (2 d, $H_{7'}$, ^2J = 9.00), 3.25 and 3.52 (2 br s, $H_{1'}$ and $H_{4'}$), 3.37 and 3.71 (2 d, H_8, ^2J = 13.0), 3.44 and 4.00 (2 dd, $H_{2'}$ and $H_{3'}$, $J_{2',3'}$ = 10.1, $J_{1',2'}$ = $J_{3',4'}$ = 3.4), 4.08 (m, H_{2endo}), 6.29 and 6.55 (2 dd, $H_{5'}$ and $H_{6'}$, $J_{6',5'}$ = 5.8, $J_{6',1'}$ = $J_{4',5'}$ = 3.1); IR (CaF_2 cell, $CDCl_3$) ν_{max} (cm^{-1}) 3523, 2956, 2883, 2367, 2260, 2252, 1747, 1476, 1437, 1353, 1239, 1180, 1014. Anal. Calcd for $C_{19}H_{28}O_5S$: C, 64.93; H, 7.66. Found: C, 64.77; H, 7.63.

10c: mp 148 °C (MeOH); $[\alpha]^{22}_D$ 1.98° (*c* 0.6, $CDCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.84 (s, Me_{7a}), 1.11 (s, Me_{7s}), 1.32 and 1.56 (2 d, $H_{7'}$, ^2J = 9.16), 1.06–1.17 and 1.49–1.86 (7 H), 2.86 and 3.86 (2 d, H_8, ^2J = 13.1), 3.28 and 3.56 (2 br s, $H_{1'}$ and $H_{4'}$), 3.44 and 4.00 (2 dd, $H_{2'}$ and $H_{3'}$, $J_{2',3'}$ = 9.9, $J_{1',2'}$ = $J_{3',4'}$ = 3.2), 3.70 (s, OMe), 4.05 (m, H_{2endo}), 6.32 and 6.52 (2 dd, $H_{5'}$ and $H_{6'}$, $J_{5',6'}$ = 5.8, $J_{1',6'}$ = $J_{4',5'}$ = 3.1); IR (CaF_2 cell, $CDCl_3$) ν_{max} (cm^{-1}) 3694, 3541, 2958, 2884, 2260, 2250, 1746, 1719, 1391, 1340, 1291, 1248, 1077. Anal. Calcd for $C_{19}H_{28}O_5S$: C, 64.93; H, 7.66. Found: C, 64.57; H, 7.73.

Reaction of 7c with 1,8-Diazabicyclo[5.4.0]undec-7-ene. A solution of **7c** (80 mg, 0.23 mmol) in dry toluene (1.5 mL) is swept with argon and 35 mg (0.23 mmol) of DBU is added. The reaction mixture is kept stirring and refluxing 3.5 h, then water is added followed by extraction with dichloromethane. After drying over anhydrous sodium sulfate, the reaction mixture is rotoevaporated and the oily residue is TL chromatographed eluting with petrol ether–ethyl acetate 95:5 to obtain 21 mg (60% yield) on an instable oil whose ^1H NMR spectrum perfectly matches with that of authentic 2-carbomethoxynorbornadiene obtained by addition of methyl propiolate to cyclopentadiene.

13c: $[\alpha]^{22}_D$ −39.22° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 2.13 (m, H_7 and $H_{7'}$), 3.72 and 3.90 (2 br s, H_1 and H_4), 3.73 (s, OMe), 6.73 and 6.92 (2 dd, H_5 and H_6, $J_{5,6}$ = 5.2, $J_{4,5}$ = $J_{1,6}$ = 3.1), 7.61 (d, H_3, $J_{3,4}$ = 3.1).

X-ray Structure Determinations. Crystal data and atomic coordinates for **7a** have been deposited at the Cambridge Crystallographic Data Center[7]. Crystal data for **9c** and **10c** are as follows.

9c: $C_{19}H_{28}O_5S$ crystallizes in the monoclinic system, space group $P2_1$, with a = 14.342 (4) Å, b = 6.721 (3) Å, c = 9.595 (4) Å; β = 98.9 (3)°; V = 913.7 Å^3; Z = 2; F_{000} = 396 e; μ = 1.60 cm^{-1}; D_{calcd} = 1.337 g cm^{-3}; 1844 reflections (1752 unique R = 0.04) were read on a diffractometer Philips PW1100 to a ϑ = 25°, ϑ–2ϑ scan mode, using the Mo Kα monochromatized radiation, λ = 0.7107 Å; SWD was 1.6° and SPE = 0.04. The structure was solved using the same fractional coordinates of its epimer **10c** except the O(3) atom. Refinement was performed with block-diagonal least squares, $W = 1/0.33(\sigma^2(F) + 0.00096F^2)$. All non-hydrogen atoms were anisotropic, while the hydrogen atoms were calculated and not refined. The final conventional R factor for the 1529 considered reflections with $I \geq 3\sigma(I)$ was 0.0536.

10c: $C_{19}H_{28}O_5S$ crystallizes in the monoclinic system; space group $P2_1$ with a = 13.886 (4) Å, b = 6.836 (3) Å, c = 10.180 (4) Å, β = 103.3 (3)°; Z = 2; V = 940.4 Å^3; F_{000} = 396 e; μ = 1.55 cm^{-1}; D_{calcd} = 1.299 g cm^{-3}; 1888 reflections (1799 unique with a R = 0.096) on a Philips PW1100 diffractometer to a ϑ = 25°, ϑ–2ϑ scan mode, using the Mo Kα monochromatized radiation, λ = 0.7107 Å. The reflections were collected with PROFIL program using SWD = 2° with SPE = 0.05. The structure was phased by MULTAN 80 and refined with block-diagonal least squares ($S = 1/\sigma^2(F) + 0.0167F^2$), anisotropically for all non-hydrogen atoms. The hydrogen atoms were calculated and not refined. The final conventional R factor for the 1144 reflections considered with a $I \geq 3\sigma(I)$ was 0.098.

Registry No. 1, 71242-58-5; 1′, 71242-59-6; **2a**, 32501-94-3; **2b**, 32501-91-0; **2c**, 922-67-8; (*Z*)-**3a**, 99894-19-6; (*E*)-**3a**, 100946-58-5; **3b**, 99908-18-6; (*Z*)-**3c**, 99894-20-9; (*E*)-**3c**, 100946-59-6; (*Z*)-**3c**′,

100946-60-9; (Z)-**4a**, 99894-21-0; (E)-**4a**, 101052-88-4; (Z)-**4b**, 99946-18-6; (E)-**4b**, 101052-96-4; (Z)-**4c**, 99946-19-7; (E)-**4c**, 101052-90-8; (Z)-4c', 101052-92-0; (Z)-5a, 99946-17-5; (E)-**5a**, 101052-89-5; (Z)-**5b**, 99894-22-1; (Z)-**5c**, 99894-23-2; (E)-**5c**, 101052-91-9; (Z)-**5c'**, 101052-93-1; (Z)-**6a**, 100946-61-0; (E)-**6a**, 100946-62-1; (Z)-**6c**, 100946-63-2; **7a**, 99894-24-3; **7b**, 99894-25-4; **7c**, 99894-26-5; **7c'**, 101052-94-2; **8a**, 99946-20-0; **8b**, 99946-21-1; **8c**, 99946-22-2; **8c'**, 101052-95-3; **9c**, 100946-64-3; **10c**, 101052-97-5; **13c**, 99946-16-4; (1S)-*d*-10-camphorsulfonyl chloride, 21286-54-4; cyclopentadiene, 542-92-7.

Supplementary Material Available: Tables of crystal data for compounds **9c** and **10c** (6 pages). Ordering information is given on any current masthead page.

Mechanism and Stereochemistry of the Fluorination of Uracil and Cytosine Using Fluorine and Acetyl Hypofluorite

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The products of the reaction of CH_3COOF and F_2 with uracil and cytosine dissolved in acetic acid and water were studied by using ^{18}F as a tracer. Apart from 5-fluorouracil (**2**) and the 5,5-difluoro adducts **5a** and **5b**, the ^1H NMR spectra of the crude reaction mixture showed the presence of two geometric isomers of both 5-fluoro-6-acetoxy-5,6-dihydrouracil (**3a, 4a**) and 5-fluoro-6-hydroxy-5,6-dihydrouracil (**3b, 4b**). In the fluorination of cytosine, corresponding products were observed with the exception of the acetoxy adducts. For both reagents and for both substrates a radical-cation mechanism is proposed. The observed conversions of the acetoxy adducts of uracil are explained by an acylimine (iii) as an intermediary.

In 1957 Wang[1] proposed that in the reaction of N_1-substituted uracils with bromine in aqueous systems, 5-bromo-6-hydroxy-5,6-dihydrouracils were initially formed. Analogous intermediaries were reported for the iodination of N_1-substituted uracils.[2,3] In contrast, uracil itself yields no monohalogenated adduct upon chlorination,[4] bromination,[5] or iodination.[3] Only the 5,5-dihalo-6-hydroxy-5,6-dihydrouracils were found to be stable. Apart from this the 5,6-dihydrocytosine adducts have been reported to be less stable than those of uracil.[6]

This is in accord with our findings that in the synthesis of [^{18}F]-5-fluorocytosine only the 5,5-difluorinated by-product **10a** was found[7] and no monofluorinated adducts as in the fluorination of uracil.[8-10] Interestingly for the monohalogenation with Cl, Br, and I all adducts were found to exist in the trans form,[3,5,11] while for **3a** and **3**, R = CH_3 also only one geometric isomer was obtained but which appeared to have the cis configuration.[9,10,12]

In the reaction of F_2 with uracil, Vine et al.[9] found **3a** to be a stable compound, while Cech et al.[13] obtained **3a** as a very unstable intermediary. The latter author proposed an initial addition of F_2 to uracil and a subsequent displacement of fluorine at C_6 by an acetoxy group.[13] Shiue et al.[14] proposed that the initial step in the reaction of F_2 with uracil in CH_3COOH is the formation of CH_3COOF, followed by a stereospecific syn addition[15] of this compound across the C_5 and C_6 double bond to give **3a**. However, we have recently shown that for reactions with F_2 in CH_3COOH, CH_3COOF is hardly formed.[16]

In view of the above-mentioned conflicting results regarding the reaction of F_2 with uracil and other aspects of interest such as the exclusive cis addition and the different chemical stability of the fluoro adduct **3a** from that of cytosine,[7] we have restudied the addition of F_2 to uracil—using either acetic acid or water as solvent—in comparison to the addition of CH_3COOF. Similar studies were performed with cytosine. Because of the limited solubility of uracil and in order to simplify the detection of the UV-insensitive intermediaries, these experiments were carried out on 5–30 μmol scale using ^{18}F as a tracer.

Results

The products from the reaction of F_2 and CD_3COOF with uracil are given in Figure 1. In order to eliminate a possible HF-catalyzed hydrolysis of the acetate group, gaseous CH_3COOF[17] was also used because in this case F^-

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