Adducts 26 and 27. Chromatography (EtOAc–hexane, 1:5) gave an oily inseparable mixture of isomeric adducts (175 mg 61%) (ortho endo:exo:meta endo 2.6:2:1): IR (neat) 2203 (CN), 2253 (CN), 1633 (CO) cm^{-1}; ^1H NMR (200 MHz) complex 5.39, 5.45 (d, J = 4.8 Hz ortho endo:exo C_4-H, respectively), 5.51 (s, meta exo C_4-H); HRMS (EI) m/z 287.1159, M^+, 287.1158 calcd for $C_{16}H_{17}O_4N$.

Adducts 28 and 29. Flash chromatography (EtOAc–hexane, 1:4) gave an oily inseparable isomeric mixture of the adducts (190 mg, 63%) (ortho endo:exo:meta endo:exo 7:3.5:2:1): IR (neat) 2203 (br, C≡N), 2255 (br, C≡N), 1746 (br, CO_2Me) cm^{-1}; ^1H NMR (250 MHz) complex δ 5.38, 5.46, 5.31 (d, J = 4.8 Hz, ortho endo:exo:meta endo C_4-H, respectively), 5.59 (s, 1 H, meta exo); HRMS (EI) m/z 303.1101, M^+, 303.1095 calcd for $C_{16}H_{17}O_5N$.

Adducts 30 and 31. Flash chromatography (EtOAc–hexane, 3:7) gave an oily inseparable isomeric mixture of the adducts (178 mg 53%) (ortho endo:exo:meta endo:exo 6:3:1.5:1): IR (neat) 1755 (br CO_2Me) cm^{-1}; ^1H NMR (250 MHz) complex δ 5.34, 3.4, 5.48 (d, J = 4.5 Hz, ortho endo, exo, meta endo C_4-H, respectively), 5.55 (s, meta exo C_4-H); HRMS (EI) m/z 336.1200, M^+, 366.1203 calcd for $C_{17}H_{20}O_7$.

Adducts 32. Flash chromatography (EtOAc–hexane, 1:5) gave an isomeric mixture of adducts **32** (203 mg, 67%) (ortho endo:exo 3:1) which afforded, on crystallization (ether–CH_2Cl_2–hexane), colorless crystals of the ortho endo isomer: mp 163–164 °C; IR (Nujol) 2319 (C≡N), 1746 (br, CO_2Me) cm^{-1}; ^1H NMR (250 MHz) δ 1.98 (dd, 1 H, $J_{H3\alpha-2\beta}$ = 6, $J_{H3\beta-3\alpha}$ = 12 Hz, H3α), 2.47 (ddd, 1 H, $J_{H3\beta-2\beta}$ = 4.5, $J_{H3\beta-H4}$ = 4.8 Hz, $J_{H3\beta-3\alpha}$ = 12 Hz, H3β), 2.93 (dd, 1 H, $J_{H2\beta-3\beta}$ = 4.5, $J_{H2\beta-3\alpha}$ = 6 Hz, H2β), 3.46 (AB q, 2 H, J = 17 Hz, CH_2), 3.83, 3.86, 3.87 (s, 3 H each, OMe), 5.43 (d, 1 H, J = 4.8 Hz, H4), 6.82, 6.85 (s, 1 H each, aromatic H); HRMS (EI) m/z 303.1101, M^+, 303.1107 calcd for $C_{16}H_{17}O_5N$. Anal. Calcd for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.61. Found: C, 63.13; H, 5.69.

Exo isomer (oil): IR (neat) 2241 (C≡N), 1736 (br, CO_2Me) cm^{-1}; ^1H NMR (250 MHz) δ 1.69 (dd, 1 H, $J_{H3\alpha-2\alpha}$ = 10, $J_{H3\alpha-3\beta}$ = 12 Hz, H3α), 2.65 (ddd, 1 H, $J_{H2\alpha-3\beta}$ = 4.5 Hz, $J_{H4-3\beta}$ = 4.7 Hz, $J_{H3\beta-3\alpha}$ = 12 Hz, H3β), 3.43 (dd, 1 H, $J_{H2\alpha-3\beta}$ = 4.5 Hz, $J_{H2\alpha-3\alpha}$ = 10 Hz, $H_{2\alpha}$) 3.32 (AB q, 2 H, J = 17 Hz, CH_2) 3.75, 3.88, 3.91 (s, 3 H each, OMe), 5.42 (d, 1 H, J = 4.7 Hz, H4), 6.87, 6.98 (s, 1 H each, aromatic H); HRMS (EI) m/z 303.1101, M^+, 303.1107 calcd for $C_{16}H_{17}O_5N$.

Adducts 33 and 34. Preparative TLC on silica (EtOAc–hexane, 1:5, triple elution) gave a mixture of endo/exo isomers of ortho and endo isomer of meta (3:1.5:2, respectively) (198 mg, 62%). Meta endo isomer **34** (oil): IR (neat) 1733 (CO_2Me), 1707 ($COCH_3$) cm^{-1}; ^1H NMR (250 MHz) δ 1.87 (dd, 1 H, $J_{H2\alpha-3\alpha}$ = 8.7, $J_{H2\alpha-2\beta}$ = 10.8 Hz, H2α), 2.18 (dd, 1 H, $J_{H2\beta-3\alpha}$ = 4.3, $J_{H2\beta-2\alpha}$ = 10.8 Hz, H2β), 2.29 (s, 3 H, $COCH_3$), 2.65 (dd, 1 H, $J_{H3\alpha-2\beta}$ = 4.31, $J_{H3\alpha-2\alpha}$ = 8.7 Hz, H3α), 3.21, 3.3 (d, 1 H each, J = 15.2 Hz, CH_2), 3.75, 3.86, 3.88 (s, 3 H each, OMe), 5.46 (s, 1 H, H4), 6.86, 6.90 (s, 1 H each, aromatic H); HRMS (EI) m/z 320.1256, M^+, 320.1260 calcd for $C_{17}H_{20}O_6$.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

Diels–Alder Reactions of 1,2-(1,1′-Binaphthalene-2,2′-diyldisulfonyl)ethylene with Symmetrical and Unsymmetrical Dienes[1]

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The C_2-symmetrical chiral reagent 1,2-(1,1′-binaphthalene-2,2′-diyldisulfonyl)ethylene (1) is a reactive dienophile and forms Diels–Alder adducts with symmetrical and unsymmetrical dienes. In the case of unsymmetrical dienes the reaction affords, in most cases, a single diastereomeric adduct whose stereochemistry has been determined by NMR spectroscopy and confirmed by X-ray structure determination of selected adducts. The arylsulfonyl groups can be removed with formation of a double bond, making 1 a chiral synthetic equivalent of acetylene in [4 + 2]-cycloaddition reactions. The binaphthyl auxiliary can be recovered and recycled.

Among the electron-withdrawing groups which most commonly activate the standard Diels–Alder reaction (e.g. COR, COOR, CN, NO_2, SOR, SO_2R) only a few (e.g. COR, CO_2R, SOR, SO_2R) are amenable to the introduction of a chiral auxiliary, and even fewer (e.g. SOR, SO_2R) allow the facile removal of both the activating functionality and the chiral auxiliary. We have developed the sulfonyl activated, C_2-symmetrical chiral dienophile **1**, and we now report its preparation and reactivity, as well as a discussion on the stereochemistry and the factors influencing diastereoselectivity in its [4 + 2]-cycloadditions. Synthetic applications, which are dependent on the availability of quantities of the reagent in optically pure form, will be reported in due course.

Dienophile **1** is structurally similar to (*Z*)- and (*E*)-1,2-bis(phenylsulfonyl)ethylenes ($PhSO_2CH{=}CHSO_2Ph$), thus maintaining the chemical properties associated with these achiral reagents, which have been reported as synthetic equivalents of acetylene in [4 + 2]-cycloaddition reactions.[3-5]

Results and Discussion

Preparation of Dienophile 1. Dienophile **1** is readily available from dithiol **2**[6] by the methodology used for ob-

(1) Presented at the *Second International Conference on Heteroatom Chemistry*: *ICHAC-2* held in Albany, NY, on July 17–22, 1989.

(2) Author to whom inquiries concerning the X-ray crystallographic analysis should be directed.

(3) De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* **1984**, *49*, 596.

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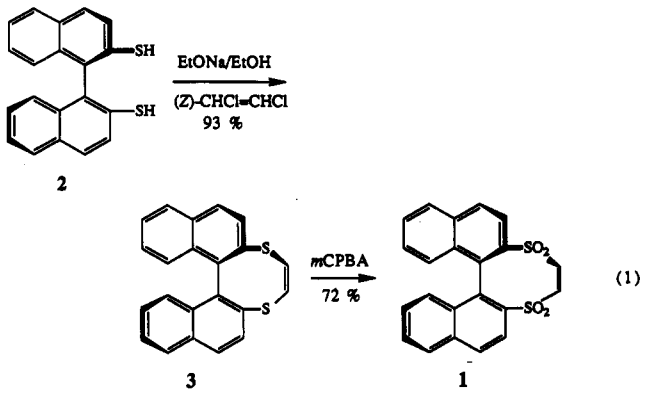
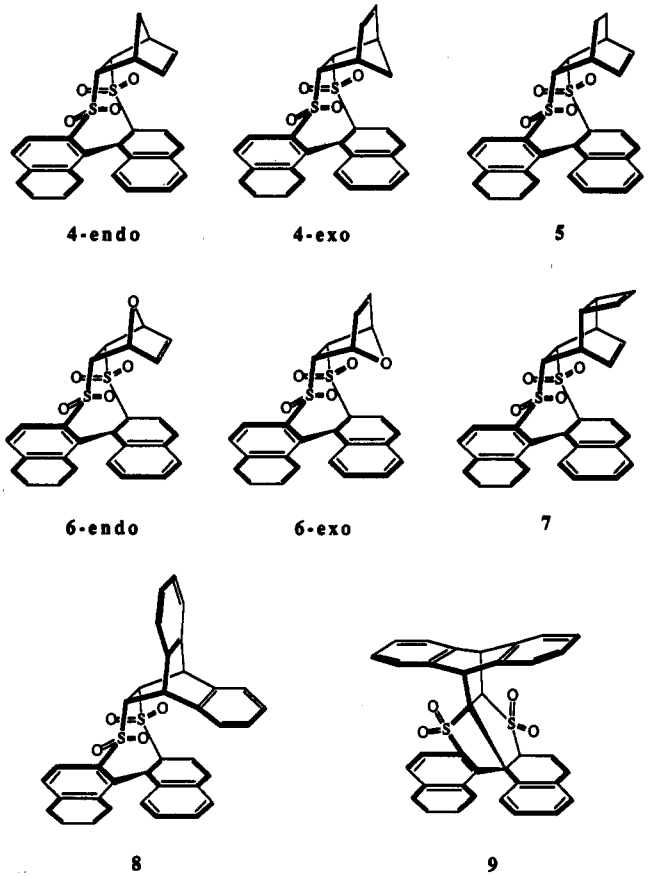
taining (*Z*)-1,2-bis(phenylsulfonyl)ethylene.[3] Treatment of the sodium salt of **2** with (*Z*)-1,2-dichloroethylene afforded a high yield of the dithiocine **3**,[7] which was oxidized with *m*-chloroperbenzoic acid to give **1** (eq 1).



(1)

Cycloaddition of 1 with Symmetrical Dienes. A few reactions with symmetrical dienes were studied in order to test the reactivity of **1** and the stability of the products. Overall, dienophile **1** showed a reactivity comparable to that of the corresponding open chain (*Z*)-1,2-bis(phenylsulfonyl)ethylene.

On adding excess cyclopentadiene to a dichloromethane solution of dienophile **1**, colorless crystals separated after a few seconds. This material was found by ^{1}H NMR to be a mixture of the endo and exo isomers **4** (9:1 ratio) and cyclopentadiene. The signals of cyclopentadiene persisted even after treatment of the crystals under vacuum and were always present in a ca. 2:1 ratio with respect to the adduct to cyclopentadiene. This observation suggests an absorption of the diene between two molecules of the adduct, similar to what has been reported for other molecules.[8] On dissolving the crystals in dichloromethane and evaporating the solvent, or causing precipitation with ethyl ether, the crystalline material which is obtained does not contain cyclopentadiene but rather molecules of solvent, although not in a constant ratio. The characteristic of including small molecules (solvent and/or diene) in the crystal lattice was noticed in all the adducts which have been prepared and caused problems in the determination of the correct elemental analysis.



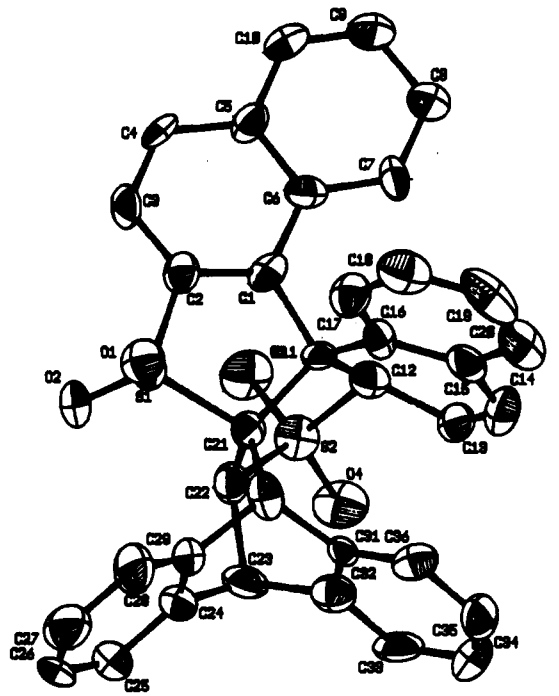


Figure 1. Perspective drawing of structure **9** as determined by the X-ray analysis. Hydrogen atoms are omitted.

Obtaining an endo–exo mixture of adducts was somewhat surprising in view of the fact that (*Z*)-1,2-bis(phenylsulfonyl)ethylene affords only the endo adduct.[3] The endo–exo ratio of adducts **4** did not change on recrystallization, nor on carrying out the reaction at temperatures ranging from −60 to 100 °C, or on changing the solvent. Furthermore, the two pure adducts were recovered unchanged (except for some decomposition) when individually treated as neat materials at 160 °C overnight. These results suggest that the reaction is not reversible, in contrast to the Diels–Alder reaction of other dienophiles with cyclopentadiene.[9]

The cycloaddition of **1** with other symmetrical dienes, as for example 1,3-cyclohexadiene, furan, cyclooctatetraene, and anthracene, proceeded in high yields to produce the expected Diels–Alder adducts **5**–**8**. The anthracene adduct **8** on heating at moderate temperature (ca. 80% °C) or on crystallization from ethanol rearranged to the complex structure **9** which was assigned on the basis of an X-ray analysis (Figure 1).

The mechanism of this transformation is still unclear but it is indicative of the strain of the adduct which ap-

(6) (a) Barber, H. J.; Smiles, S. *J. Chem. Soc.* **1928**, 1141. (b) Armarego, W. L. F.; Turner, E. E. *Ibid.* **1957**, 13. (c) Cram, D. M.; Helgeson, R. C.; Koga, K.; Kyba, E. P.; Madan, K.; Sousa, L. R.; Siegel, M. G.; Moreau, P.; Gokel, G. W.; Timko, J. M.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 2758.

(7) Schroth, W.; Billig, F.; Zschunke, A. *Z. Chem.* **1969**, *9*, 184. Heggelte, H. J.; Bickelhaupt, F.; Loopstra, B. O. *Tetrahedron* **1978**, *34*, 3631.

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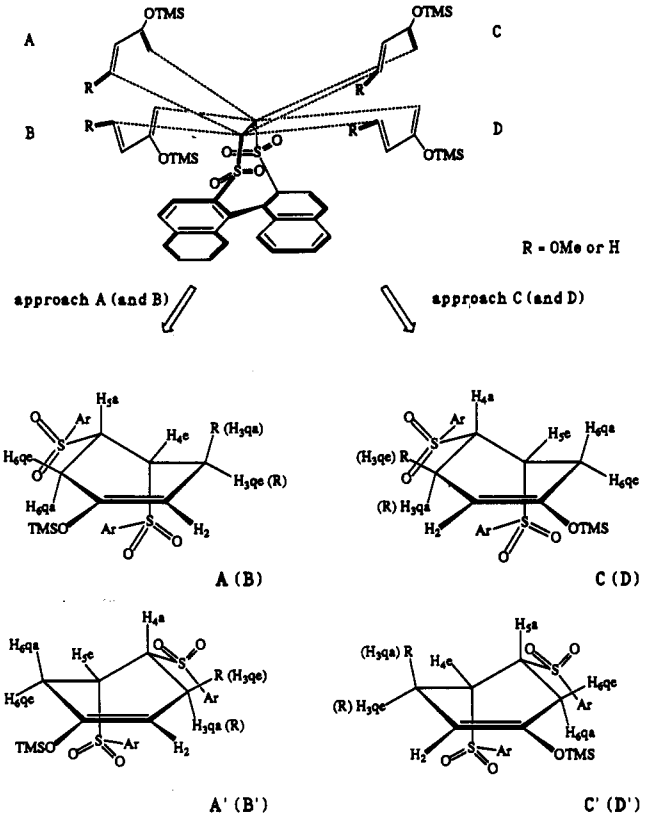
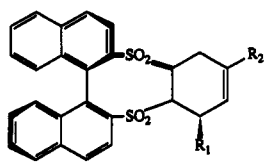
(9) Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121. Karpf, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 414.

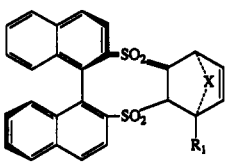
Scheme I



parently suffices to sacrifice the aromaticity of one of the aromatic rings.

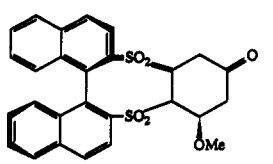
Cycloaddition of 1 to Unsymmetrical Dienes.[10] The ability of dienophile 1 to distinguish between two diastereomeric transition states was seen in the reaction with unsymmetrical dienes. In all the cases so far tested, except in the reaction with isoprene, only the single adducts **10a–h** were formed, showing that the reaction is highly diastereoselective.

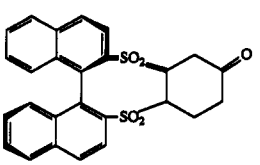




10a R_1 = OMe R_2 = OTMS (mp 185-6 °C)
10b R_1 = OMe R_2 = H (mp 250 °C)
10c R_1 = OTMS R_2 = H (mp 266-8 °C)
10d R_1 = Me R_2 = H (mp 311-3 °C)
10e R_1 = H R_2 = OTMS (mp 230 °C)
10f R_1 = H R_2 = Me (8:2 mixture)

10g R_1 = OMe X = O (mp 180 °C)
10h R_1 = OMe X = $-(CH_2)_2-$ (mp 307 °C)





11 12

The assignment of stereochemistry has primarily been based on ^{1}H NMR analysis. The examples of compounds **10a**, **10d**, **10e**, and **10g**, representative, respectively, of the

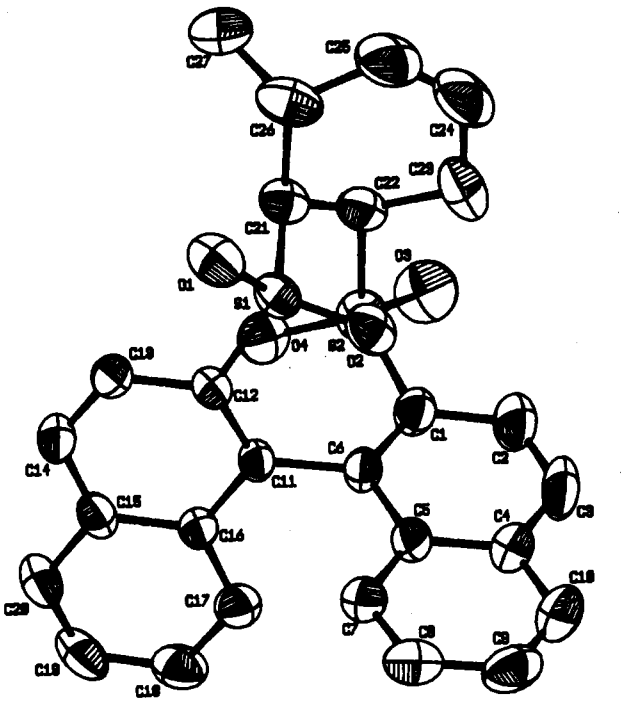


Figure 2. Perspective drawing of structure **10d** as determined by the X-ray analysis. Hydrogen atoms are omitted.

stereochemistry of addition of 1 to a 1,3-substituted, a 1-substituted, a 2-substituted, and a cyclic 1-substituted diene, are discussed below. The other compounds prepared had identical NMR data.

Scheme I (R = OMe) shows the four possible modes of approach of the Danishefsky diene to the dienophile **1**. As can be readily recognized with Dreiding models, each approach leads to a cycloadduct which can exist in two different, very rigid conformations, for a maximum of the eight isomers A/A′, B/B′, C/C′, and D/D′. The two conformations differ in the relative position (axial–equatorial) of the methoxy group with respect to the two sulfonyl groups, which are necessarily cis (i.e. one equatorial and the other axial). The ^{1}H NMR shows a single isomer in a single conformation. Only structures A and C′ (corresponding to approaches A and C) are consistent with all NMR data, including coupling constants and NOE experiments. The choice between these two isomeric molecules results from the inspection of the transition states associated with the two approaches A and C (Scheme I). In approach A the methoxy group would interact with the protons in position 3 of the naphthyl group, while such an interaction would be absent for approach C. On the basis of these considerations, we assign the structure of the observed diastereoisomer to C′ (or as indicated in **10a**). The stereochemistry assigned to this adduct differs from the one expected from cycloadditions of other dienophiles to the Danishefsky diene.[11]

The structure of adduct **10d**, representative of the class of the 1-substituted dienes, has been proven by an X-ray determination (Figure 2). The result is fully in accord with the structures proposed for the other adducts.

Adduct **10e** is representative of the class of 2-substituted dienes. In this case, the endo or the exo approaches are irrelevant to the product stereochemistry (i.e. approaches A and B or C and D in Scheme I (R = H) give identical molecules). It follows that the cycloaddition can give only

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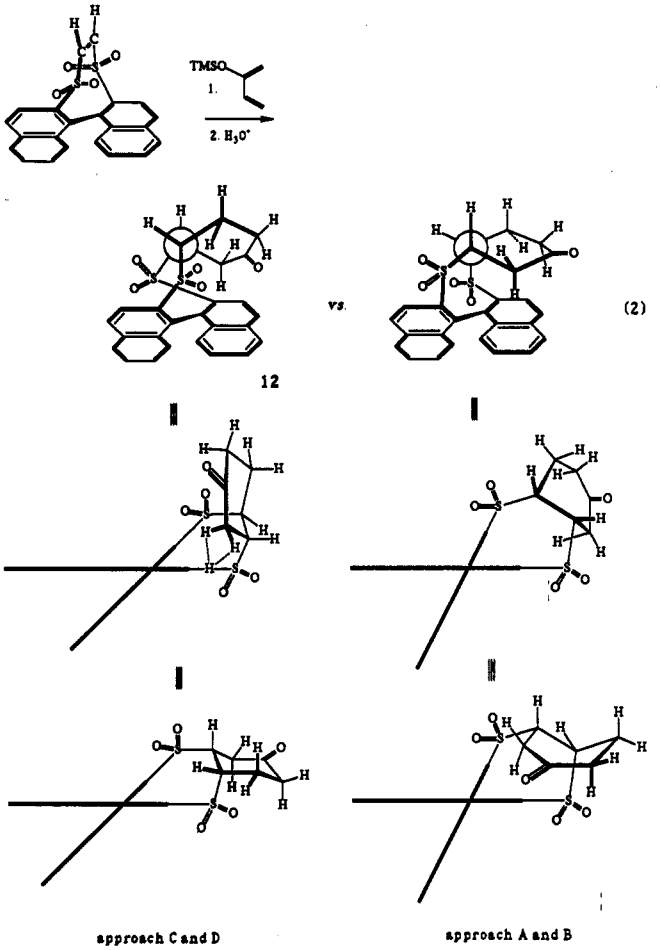
two diastereoisomers which differ in the relative position of the (trimethylsilyl)oxy group with respect to the geometry of the binaphthyl group. Of the two possible diastereoisomers, only one has been obtained. The structure assignment of **10e** is based on ^{1}H NMR data and from the following observations.

On standing in chloroform solution, adduct **10e** slowly converts into the ketone **12** (eq 2) which has the regiochemistry of the primary Diels–Alder adduct (i.e. the keto group is positioned as the same carbon atom originally bearing the (trimethylsilyl)oxy functionality). The ^{1}H



NMR data of the ketone are consistent only with the two conformations shown (see ^{1}H NMR discussion of **10a**), corresponding to the two possible approaches of the type A(B) or C(D) of Scheme I. The ROESY spectrum of **12** shows a polar interaction between both H-3$_{eq}$ and H-3$_{ax}$ and the proton at the naphthyl group. Such observation may account only for the conformer **12**. Consequently, the mode of addition must be via one of the approaches C or D in Scheme I. The position assigned to the trimethylsiloxy group is the same observed in the cycloaddition of the Danishefsky diene suggesting that, in the latter case, the diastereoselection is not only due to the steric interactions of the methoxy group with the naphthyl residue but also to electronic effects of the trimethylsiloxy group.

Final and definite confirmation of the structure of **12** was provided by an X-ray structure determination (Figure 3).

Adduct **10g** is representative of the cycloaddition with cyclic dienes. The size of the coupling constant between H-3 and H-4 (J = 3.8 Hz) is indicative of the exo arrangement of the H-3 proton. The position of the methoxy group with respect to the naphthyl residues was deduced as for the previous examples **10a–d**. Examination of the

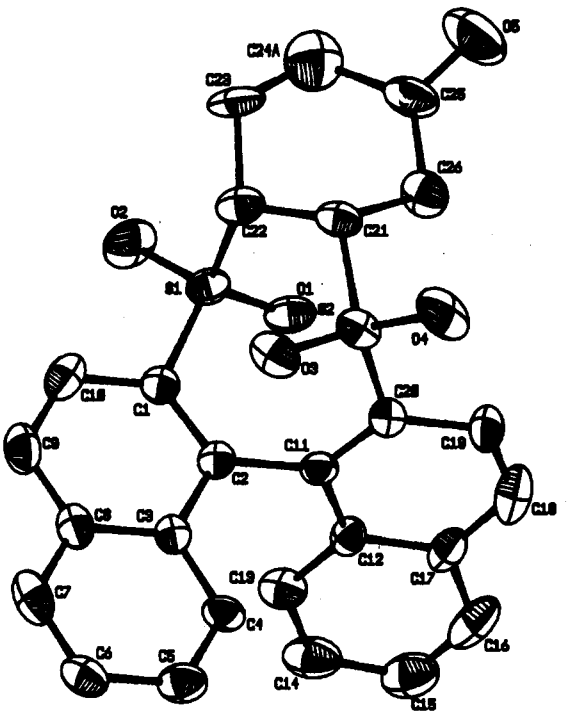
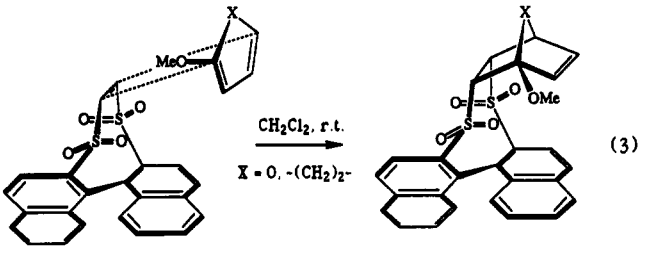
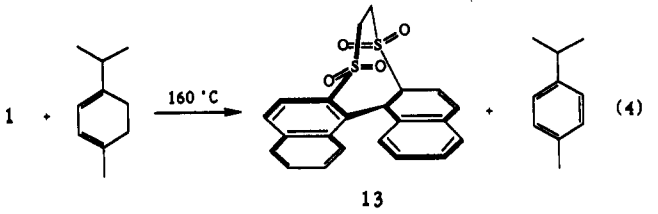


Figure 3. Perspective drawing of structure **12** as determined by X-ray analysis. Hydrogen atoms are omitted.

transition states for the two endo approaches clearly shows that there is less steric interaction between the methoxy group and the protons of the binaphthyl residue when the diene approaches with the methoxy group from the less crowded part of the molecule as indicated (eq 3).



Finally, it is worth mentioning that the cycloaddition with α-terpinene (1-isopropyl-4-methyl-1,3-cyclohexadiene, a 1,4-substituted diene) does not lead to the expected cycloadduct but rather to the formation of the saturated dienophile **13** and to the aromatization of the diene (eq 4). Such a transformation is indicative of electron transfer



from the diene to the dienophile and suggests the greater stability of the saturated adduct with respect to **1**.[12]

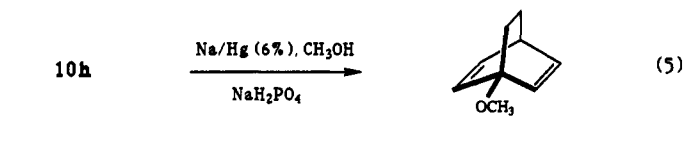
Removal and Recovery of the Chiral Auxiliary. The binaphthylsulfonyl group can be removed from the adducts

(12) It is worth mentioning that the cycloaddition with optically active dienes, such as α-phellandrene and nopadiene, carried out in the aim of kinetically resolving dienophile **1**, did not lead to appreciable optical resolution of the unreacted reagent.

Table I. Crystal Data for Compounds 9, 10d, and 12

	9	10[d]	12
formula	$C_{36}H_{24}O_4S_2$	$C_{27}H_{22}O_4S_2$	$C_{26}H_{20}O_5S_2$
molecular weight	584.71	474.59	476.57
space group	$P2_1/n$ (no. 14)	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)
molecule/unit cell	4	4	4
cell constants:			
a, Å	19.509 (3)	12.077 (2)	11.686 (2)
b, Å	13.319 (2)	15.060 (2)	20.650 (3)
c, Å	10.710 (2)	12.493 (2)	11.724 (2)
β, deg	103.2 (2)	99.9 (2)	118.80 (2)
cell vol. Å^3	2709.4	2238.4	2479.2
D_{calcd}, g/cm^{-3}	1.43	1.41	1.50
crystal dimensions, mm	0.2 × 0.2 × 0.2	0.6 × 0.12 × 0.4	0.24 × 0.3 × 0.6
μ_{calc}, cm^{-1}	1.92	2.23	4.1
scan range, 2θ	4–50	4–56	4–56
unique data	4766	5005	5992
unique data with $F \geq 7\sigma(F)$	1568	2534	3519
variable parameters	379	389	319
R_F	0.0607	0.0384	0.102
R_{WF}	0.0622	0.0508	0.1154
GOF	1.32	1.51	1.55

with formation of a double bond using sodium amalgam in buffered methanol, as for the open chain analogs derived from (*Z*)- and (*E*)-1,2-bis(phenylsulfonyl)ethylenes.[3] For example, diene **14** was obtained from adduct **10h** (eq 5).



(5)

14

Preliminary experiments shows that the chiral auxiliary can be recovered by extraction of the diene **14** with pentane, acidification of the aqueous layer, and further extraction with dichloromethane. Reduction of the crude product with lithium aluminum hydride gives back the starting dithiol **2**.

Experimental Section

X-ray Structure Determinations. Crystallographic details for **9**, **10d**, and **12** are collected in Table I. Atomic coordinates, bond distances, bond angles, and structure factors tables have been deposited as supplementary material (Tables II–XIII). Reflections were collected on a Philips PW 1100 four-circle diffractomer to a $2\theta = 50°$, using Mo Kα monochromatized radiation (λ = 0.71069 Å). The reflections were phased by MULTAN 80 programs. Refinement was performed by block-diagonal least-squares method with anisotropic thermal parameters for all non-hydrogen atoms, unit weights. All calculations were performed with SHELX 76 programs.

Dinaphtho[2,1-*e*:1′,2′-*g*][1,4]dithiocine (3). Sodium (0.45 g, 19.57 mmol) was slowly dissolved in ethanol (50 mL) and (*Z*)-dichloroethylene (1.30 mL, 9.26 mmol) and 1,1′-binaphthalene-2,2′-dithiol (**2**) (2.83 g, 8.88 mmol) were added sequentially. The reaction mixture was stirred for 5 h at 78 °C and cooled to room temperature. Ice and water (ca. 200 mL) was added, and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried over sodium sulfate, and evaporated to afford a colorless solid (2.84 g, 93% yield): mp 220–1 °C (CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, 2 H, J = 9.0 Hz), 7.97 (d, 2 H, J = 9.0 Hz), 7.72 (d, 2 H, J = 9.0 Hz), 7.52 (m, 4 H), 7.30 (m, 2 H), 6.32 (s, 2 H); IR (KBr) 3045, 3006, 1520, 1316, 814, 791, 747, 689, 660 cm^{-1}. Anal. Calcd for $C_{22}H_{14}S_2$: C, 77.18; H, 4.12. Found: C, 77.23; H, 4.15.

Dinaphtho[2,1-*e*:1′,2′-*g*][1,4]dithiocine 1,1,4,4-Tetraoxide (1). A solution of **3** (0.2 g, 0.58 mmol) and *m*-chloroperbenzoic acid (85%, 0.86 g, 4.98 mmol) in chloroform (60 mL) was stirred for 24 h at reflux. Water (100 mL) was added, and the organic layer was separated and washed with a saturated solution of sodium metabisulfite and sodium bicarbonate. The organic solution was dried over magnesium sulfate and rotary evaporated, affording a colorless solid which was purified by flash chromatography (petroleum ether–dichloromethane) to give colorless crystals (0.20 g, 84%): mp 320 °C (CH_2Cl_2–Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23 (s, 4 H), 8.05 (d, J = 7.6 Hz, 2 H), 7.69 (t, J = 7.9 Hz, 2 H), 7.44 (t, J = 7.9 Hz, 2 H), 7.29 (d, J = 7.6 Hz, 2 H), 6.99 (s, 2 H); IR (KBr) 3018, 2982, 1331, 1317, 1146, 1105, 793 cm^{-1}. Anal. Calcd for $C_{22}H_{14}O_4S_2$: C, 65.02; H, 3.47. Found: C, 64.99; H, 3.43.

Cycloaddition of 1 to Cyclopentadiene. Preparation of 4. A solution of **1** (80 mg, 0.20 mmol) and cyclopentadiene (0.1 mL, ca. 1.51 mmol) in dichloromethane (20 mL) was stirred at room temperature for 24 h. The colorless solid that precipitated was collected by filtration, washed several times with ether, and recrystallized from dichloromethane–ether to give 84 mg (90%) of colorless needles consisting in a 9:1 mixture (as determined by NMR) of the 4-endo and 4-exo isomers, which were separated by medium-pressure liquid chromatography on silica gel eluting with dichloromethane. 4-endo: mp >325 °C (CH_2Cl_2–Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32–7.10 (m, 12 H, Ar), 6.25 (dd, J = 5.8, 3.0 Hz, 1 H), 6.17 (dd, J = 5.8, 3.0 Hz, 1 H), 4.20 (dd, J = 9.8, 2.5 Hz, 1 H), 4.02 (dd, J = 9.8, 2.8 Hz, 1 H), 3.72 (br s, 2 H), 1.62 (d, J = 9.5 Hz, 1 H), 1.35 (d, J = 9.5 Hz, 1 H); IR (KBr) 3458, 2922, 1316, 1291, 1270, 1148, 1128, 1106, 877, 816, 751, 704 cm^{-1}. 4-exo: mp >325 °C (CH_2Cl_2–Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.26–7.17 (m, 12 H, Ar), 6.70 (dd, J = 5.5, 3.0 Hz, 1 H), 6.44 (dd, J = 5.5, 3.0 Hz, 1 H), 3.74 (br s, 1 H), 3.66 (br s, 1 H), 3.53 (dd, J = 8.9, 2.1 Hz, 1 H), 3.29 (dd, J = 8.9, 2.1 Hz, 1 H), 1.58 (d, J = 10.0 Hz, 1 H), 1.46 (d, J = 10.0 Hz, 1 H); IR (KBr) 3470, 2962, 2934, 1328, 1310, 1292, 1156, 1129, 1106, 893, 813, 753, 704 cm^{-1}. Anal. Calcd for $C_{27}H_{20}O_4S_2$ (9:1 mixture of isomers) C, 68.62; H, 4.27. Found: C, 68.23; H, 4.47.

Cycloaddition of 1 to 1,3-Cyclohexadiene. Preparation of 5. A solution of **1** (0.1 g, 0.25 mmol) and 1,3-cyclohexadiene (0.1 mL, 1.05 mmol) in dry chloroform (20 mL) was stirred for 2 days at 45 °C. The reaction mixture was concentrated on a rotary evaporator to leave a colorless powder which was recrystallized from dichloromethane–ether (0.11 g, 92%): mp 325 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21–7.15 (m, 12 H, Ar), 6.16 (m, 2 H), 3.96 (dd, J = 9.8, 2.1 Hz, 1 H), 3.74 (br s, 2 H), 3.57 (d, J = 9.8 Hz, 1 H), 1.58 (m, 4 H); IR (KBr) 3443, 3061, 2935, 2866, 1583, 1317, 1170, 1146, 1127, 1108, 817, 748, 703 cm^{-1}. Anal. Calcd for $C_{28}H_{22}O_4S_2$: C, 69.11; H, 4.56. Found: C, 69.04; H, 4.93.

Cycloaddition of 1 to Furan. Preparation of 6. A solution of **1** (80 mg, 0.20 mmol), furan (0.1 mL, 1.37 mmol), and a few crystals of hydroquinone in toluene was stirred at 180 °C for 10 min. The reaction mixture was concentrated to dryness to leave a 6:4 mixture of endo and exo isomers as a colorless solid (90 mg, 96%). These compounds were separated by silica gel flash chromatography eluting with dichloromethane. 6-endo: mp >300 °C (CH_2Cl_2–Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20–7.24 (m, 12 H, Ar), 6.73 (dd, J = 8.2, 1.8 Hz, 1 H), 6.50 (dd, J = 8.2, 1.8 Hz, 1 H), 5.74 (d, J = 1.8 Hz, 1 H), 5.67 (d, J = 1.8 Hz, 1 H), 3.66 (d, J = 8.2 Hz, 1 H), 3.47 (d, J = 8.2 Hz, 1 H). 6-exo: mp >300 °C (CH_2Cl_2–Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27–7.04 (m, 12 H, Ar), 6.64 (dd, J = 5.5, 1.5 Hz, 1 H), 6.51 (dd, J = 5.5, 1.5 Hz, 1 H), 5.52 (s, 1 H), 5.44 (s, 1 H), 4.37 (dd, J = 9.5, 4.0 Hz, 1 H), 4.18 (dd, J = 9.5, 4.0 Hz, 1 H); IR (KBr, 6:4 mixture of endo–exo isomers) 3098, 3070, 2957, 2920, 2857, 1448, 1330, 1308, 1287, 1214, 1172, 1158, 1143, 1130, 1110, 866, 818, 752, 701 cm^{-1}. Anal. Calcd for $C_{26}H_{18}O_5S_2$ (6:4 mixture of endo–exo isomers): C, 65.81; H, 3.82. Found: C, 65.90; H, 3.89.

Cycloaddition of 1 to cyclooctatetraene. Preparation of 7. A solution of **1** (0.1 g, 0.25 mmol), cyclooctatetraene (0.1 mL, 0.89 mmol), and chloroform (15 mL), containing a few crystals of hydroquinone, was placed in a screw-capped Pyrex test tube, purged with nitrogen, sealed, and stirred at 90 °C for 24 h. The reaction mixture was chromatographed on silica gel eluting with dichloromethane, affording a colorless solid which was recrystallized from dichloromethane–petroleum ether (0.116 g, 93%): mp 240–2 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.28–7.14 (m, Ar, 12 H), 5.92–5.82 (m, 4 H), 3.81 (dd, J =9.8, 1.8 Hz, 1 H), 3.72 (m, 2 H), 3.40 (d, J = 9.8 Hz, 1 H), 2.86 (m, 1 H), 2.80 (m, 1 H); IR

(KBr) 3461, 3017, 2922, 1319, 1128, 1108, 876, 818, 748, 706 cm^{-1}. Anal. Calcd for $C_{30}H_{22}O_4S_2$: C, 70.57; H, 4.34. Found: C, 70.41; H, 4.73.

Cycloaddition of 1 to Anthracene. Preparation of 8 and 9. A mixture of anthracene (0.3 g, 1.68 mmol), 1 (0.15 g, 0.37 mmol), and chloroform (20 mL) was placed in a screw-capped Pyrex test tube, purged with nitrogen, sealed, and stirred for 1 h at 200 °C. After being cooled to room temperature, the reaction mixture was chromatographed on silica gel, eluting with dichloromethane, affording 8 as colorless solid which was recrystallized from dichloromethane (192 mg, 89%): mp 310 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.16–6.93 (m, Ar, 20 H), 5.37 (d, J = 1.8 Hz, 1 H), 5.31 (d, J = 1.8 Hz, 1 H), 4.10 (dd, J = 10.4, 1.8 Hz, 1 H), 3.83 (dd, J = 10.4, 1.8 Hz, 1 H); IR (KBr) 3465, 3069, 2945, 1589, 1486, 1457, 1311, 1287, 1268, 1242, 1187, 1167, 1124, 1091, 818, 790, 767 cm^{-1}. Anal. Calcd for $C_{36}H_{24}O_4S_2$: C, 73.95; H, 4.14. Found: C, 74.11; H, 4.21. The adduct in ethanol, heated at the reflux temperature for 15 min, gave after cooling at room temperature 9 as a colorless solid in quantitative yield: mp 289–90 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.04–7.09 (m, 18 H, Ar), 6.65 (t, J = 3.2 Hz, 1 H), 6.05 (d, J = 3.2 Hz, 1 H), 5.93 (dd, J = 4.0, 1.4 Hz, 1 H), 5.26 (dd, J = 4.0, 1.2 Hz, 1 H), 4.96 (d, J = 2.5 Hz, 1 H), 4.74 (d, J = 2.5 Hz, 1 H); IR (KBr) 3548, 3064, 1329, 1172, 1129, 1107, 877, 816, 761, 706 cm^{-1}. Anal. Calcd for $C_{36}H_{24}O_4S_2$ × 1 mol EtOH: C, 72.36; H, 4.79. Found: C, 72.60; H, 5.25.

Figure 1 shows the ORTEP drawing as determined by an X-ray structure determination of 9. X-ray parameters are reported in Table I. Atomic coordinates are collected in Table II, main interatomic distances and bond angles are in Tables III and IV, structure factors in Table V (Tables II–V in Supplementary Material).

Cycloaddition of 1 to 1-Methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene (Danishefsky Diene). Preparation of 10a and 11. A solution of 1 (0.1 g, 0.25 mmol), 1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene (0.1 mL, 0.51 mmol) in dry dichloromethane (10 mL) was stirred at room temperature for 30 min. The reaction mixture was concentrated on a rotary evaporator to leave a colorless solid (0.13 g, 92%): mp 185–6 °C (CH_2Cl_2–Et_2O); ^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (m, 3 H, Ar), 8.01 (dd, J = 3.0, 8.2 Hz, 2 H, Ar), 7.61 (t, J = 7.6 Hz, 2 H, Ar), 7.32 (t, J = 7.6 Hz, 3 H, Ar), 6.99 (t, J = 9.8 Hz, 2 H, Ar), 5.05 (d, J = 5.8 Hz, 1 H, H_1), 4.75 (dd, J = 5.8, 2.1 Hz, 1 H, H_{2eq}), 4.03 (m, 1 H, H_{4ax}), 3.78 (m, 1 H, H_{3eq}), 3.34 (s, 3 H, OMe), 2.56 (dd, J = 5.8, 17.1 Hz, 1 H, H_{5eq}), 2.33 (dd, J = 17.1, 12.2 Hz, 1 H, H_{5ax}). 0.12 (s, 9 H, $SiMe_3$); IR (KBr) 3054, 2957, 2871, 2800, 1666, 1317, 1158, 1127, 1063, 849, 817, 751 cm^{-1}. Anal. Calcd for $C_{30}H_{30}O_6S_2Si$: C, 62.26; H, 5.22. Found: C, 62.23; H, 5.50.

A solution of **10a** (100 mg, 0.2 mmol) and chloroform (5 mL) was heated at reflux for 24 h with stirring. The reaction mixture was purified by flash chromatography, eluting with methylene chloride to give crystalline 11 (96% yield): mp 209–10 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 8.33–6.67 (m, Ar, 12 H), 4.70 (m, 1 H), 3.97 (m, 2 H), 3.37 (s, 3 H), 2.83 (m, 1 H), 2.70 (m, 3 H); IR (KBr) 3462, 3071, 2924, 1723, 1316, 1260, 1158, 1146, 1131, 820, 748, 708 cm^{-1}. Anal. Calcd for $C_{27}H_{22}O_6S_2$: C, 64.02; H, 4.38. Found: C, 64.30; H, 4.50.

Cycloaddition of 1 to (*E*)-1-Methoxy-1,3-butadiene. Preparation of 10b. A solution of 1 (0.1 g, 0.25 mmol) and (*E*)-1-methoxy-1,3-butadiene (0.1 mL, 0.99 mmol) in dichloromethane (15 mL) was stirred for 10 min at room temperature. The reaction mixture was concentrated to dryness on the rotary evaporator, and the colorless residue was recrystallized (0.11 g, 91%): mp 250 °C (CH_2Cl_2–Et_2O); ^1H NMR (200 MHz, $CDCl_3$) δ 8.23–6.96 (m, 12 H, Ar), 5.94 (s, 1 H), 5.92 (s, 1 H), 4.71 (m, 1 H), 3.93 (m, 1 H), 3.85 (m, 1 H), 3.41 (s, 3 H), 2.66 (ddd, J = 17.1, 5.5, 2.1 Hz, 1 H), 2.35 (dd, J = 17.1, 11.3 Hz, 1 H); IR (KBr) 3450, 2954, 1584, 1447, 1428, 1382, 1317, 1146, 1129, 1108, 1035, 875, 847, 819, 751 cm^{-1}. Anal. Calcd for $C_{27}H_{22}O_5S_2$: C, 66.1; H, 4.52. Found: C, 66.31; H, 4.61.

Cycloaddition of 1 to (*E*)-1-((Trimethylsilyl)oxy)-1,3-butadiene. Preparation of 10c. A solution of 1 (0.2 g, 0.49 mmol) and (*E*)-1-((trimethylsilyl)oxy)-1,3-butadiene (0.1 mL, 0.57 mmol) in dichloromethane (10 mL) was stirred for 24 h at room temperature. After the removal of solvent, the residue was flash chromatographed on silica gel with dichloromethane as eluent (0.25 g, 93%): mp 266–8 °C ($CHCl_3$–Et_2O); ^1H NMR (200 MHz, $CDCl_3$) δ 8.21–6.97 (m, 12 H, Ar), 5.83 (m, 2 H), 5.19 (m, 1 H), 4.04 (m, 1 H), 3.68 (m, 1 H), 2.66 (m, 1 H), 2.35 (dd, J = 13.0, 17.0 Hz, 1 H), 0.18 (s, 9 H); IR (KBr) 3450, 3070, 2954, 1713, 1584, 1382, 1317, 1252, 1146, 1129, 1108, 875, 847, 819, 712 cm^{-1}. Anal. Calcd for $C_{29}H_{28}O_5S_2Si$: C, 63.48; H, 5.14. Found: C, 63.66; H, 5.18.

Cycloaddition of 1 to (*E*)-1-Methyl-1,3-butadiene. Preparation of 10d. A solution of 1 (0.20 g, 0.49 mmol) and (*E*)-1-methyl-1,3-butadiene (0.1 mL, 1.01 mmol) in dichloromethane (10 mL) was stirred for 80 h at room temperature. The reaction mixture was chromatographed on silica gel with dichloromethane as eluent to provide a colorless solid (0.22 g, 94%): mp 311 °C (CH_2Cl_2–Et_2O); ^1H NMR (200 MHz, $CDCl_3$) δ 8.18–6.96 (m, 12 H, Ar), 5.63 (m, 2 H), 3.64 (m, 2 H), 3.48 (d, J = 3.7 Hz, 1 H), 2.61 (d, J = 17.0 Hz, 1 H), 2.34 (dd, J = 17.0, 11.5 Hz, 1 H), 1.20 (d, J = 7.3 Hz, 3 H); IR (KBr) 3048, 2931, 1930, 1580, 1315, 1274, 1147, 1125, 1024, 819, 752, 705 cm^{-1}. Anal. Calcd for $C_{27}H_{22}O_4S_2$: C, 68.33; H, 4.67. Found: C, 68.28; H, 5.04.

Figure 2 shows the ORTEP drawing as determined by an X-ray structure determination of **10d**. X-ray parameters are reported in Table I. Atomic coordinates are collected in Table VI, main interatomic distances and bond angles are in Tables VII and VIII, structure factors in Table IX (Tables VI–IX in Supplementary Material).

Cycloaddition of 1 to 2-((Trimethylsilyl)oxy)-1,3-butadiene. Preparation of 10e and 12. A solution of 1 (0.10 g, 0.25 mmol), 2-((trimethylsilyl)oxy)-1,3-butadiene (0.1 mL, 0.57 mmol), and toluene (5 mL), containing a few crystals of hydroquinone, was stirred for 40 h at 110 °C. The reaction mixture was concentrated to dryness and recrystallized (0.13 g, 96%): mp 230 °C (CH_2Cl_2–Et_2O); ^1H NMR (200 MHz, $CDCl_3$) δ 8.18–6.97 (m, 12 H, Ar), 4.79 (dd, J = 5.9, 1.2 Hz, 1 H), 3.71 (m, 2 H), 3.32 (dd, J = 18.0, 6.0 Hz, 1 H), 2.48 (m, 3 H), 0.07 (s, 9 H); IR (KBr) 3075, 2958, 1495, 1315, 1250, 1210, 1145, 1107, 845, 820, 710 cm^{-1}. Anal. Calcd for $C_{29}H_{28}O_5S_2Si$: C, 63.48; H, 5.14. Found: C, 63.09; H, 5.42.

The procedure described for the hydrolysis of **10a** was employed to obtain **12** as a colorless solid (95% yield): mp 199–200 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.25–7.87 (m, Ar, 12 H), 3.77 (m, 1 H), 3.67 (ddd, J = 13.4, 5.2, 4.3 Hz, 1 H), 3.16 (ddt, J = 14.9, 5.8, 2.7 Hz, 1 H), 2.91 (ddt, J = 10.1, 4.9, 1.2 Hz, 1 H), 2.71 (dd, J = 14.9, 13.4 Hz, 1 H), 2.57 (ddt, J = 14.9, 5.8, 1.2 Hz, 1 H), 2.36 (dm, 1 H), 1.90 (dt, J = 14.6, 4.9 Hz, 1 H); IR (KBr) 3408, 3068, 1713, 1583, 1345, 1317, 1228, 1157, 1147, 1128, 815, 756, 745, 729, 703, 676 cm^{-1}. Anal. Calcd for $C_{26}H_{20}O_5S_2$: C, 65.53; H, 4.23. Found: C, 65.72; H, 4.30.

Figure 3 shows the ORTEP drawing as determined by an X-ray structure determination of **12**. X-ray parameters are reported in Table I. Atomic coordinates are collected in Table X, main interatomic distances and bond angles are in Tables XI and XII, structure factors in Table XIII (Tables X–XIII in Supplementary Material).

Cycloaddition of 1 to 2-Methyl-1,3-butadiene. Preparation of 10f. A solution of 1 (0.1 g, 0.25 mmol), 2-methyl-1,3-butadiene (0.1 mL, 1.00 mmol), and a few crystals of hydroquinone was stirred for 2 days at 65 °C. The solution was evaporated to dryness to leave a residue consisting of two isomers in a 8:2 ratio (110 mg, 94%): ^1H NMR (200 MHz, $CDCl_3$) δ 8.17–6.96 (m, Ar, 24 H), 5.37 (s, 2 H), 3.70 (m, 4 H), 3.29 (m, 2 H), 2.50 (m, 6 H), 1.65 (s, 6 H); IR (KBr) 3465, 3069, 2951, 2872, 1303, 1288, 1243, 1230, 1212, 1173, 1157, 1144, 1126, 1105, 821, 754, 703 cm^{-1}. Anal. Calcd for $C_{27}H_{22}O_4S_2$: C, 68.33; H, 4.67. Found: C, 68.21; H, 4.86.

Cycloaddition of 1 to 2-Methoxyfuran. Preparation of 10g. A solution of 1 (0.1 g, 0.25 mmol) and 2-methoxyfuran (0.1 mL, 1.08 mmol) in dichloromethane (10 mL) was stirred at room temperature for 30 min. The reaction mixture was concentrated on a rotary evaporator to leave a colorless solid, which was recrystallized from dichloromethane (0.11 g, 91%): mp 180–1 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.30–7.04 (m, 12 H, Ar), 6.68 (dd, J = 5.8, 2.0 Hz, 1 H), 6.41 (d, J = 5.8 Hz, 1 H), 5.25 (dd, J = 3.8, 2.0 Hz, 1 H), 4.36 (dd, J = 9.6, 3.8 Hz, 1 H), 4.25 (d, J = 9.6 Hz, 1 H), 3.58 (s, 3 H); IR (KBr) 2924, 1741, 1309, 1166, 1126, 820, 775, 752 cm^{-1}. Anal. Calcd for $C_{27}H_{20}O_6S_2$: C, 64.27; H, 4.00. Found: C, 64.40; H, 4.30.

Cycloaddition of 1 to 1-Methoxy-1,3-cyclohexadiene. Preparation of 10h. A solution of 1 (0.2 g, 0.49 mmol) and

1-methoxy-1,3-cyclohexadiene (0.1 mL, 0.84 mmol) in dichloromethane (20 mL) was stirred at room temperature for 3 days. The solvent was removed on a rotary evaporator, and the resulting colorless solid was washed with ether and dried (0.24 g, 94%): mp 307 °C (CH_2Cl_2-Et_2O); ^1H NMR (200 MHz, $CDCl_3$) δ 8.31-7.07 (m, 12 H), 6.07 (m, 2 H), 4.33 (d, J = 9.5 Hz, 1 H), 3.71 (m, 1 H), 3.54 (d, J = 9.5 Hz, 1 H), 3.47 (s, 3 H), 1.87 (m, 2 H), 1.30 (m, 2 H); IR (KBr) 3474, 3056, 2947, 2869, 1616, 1585, 1379, 1313, 1303, 1287, 1162, 1144, 1125, 1107, 892, 815, 751, 742, 717 cm^{-1}. Anal. Calcd for $C_{29}H_{24}O_5S_2$: C, 67.42; H, 4.68. Found: C, 67.27; H, 4.72.

Reaction of 1 with α-Terpinene. A mixture of 1 (0.1 g, 0.25 mmol), α-terpinene (0.1 mL, 0.61 mmol), and a few crystals of hydroquinone, placed into a screw-capped Pyrex test tube, was purged with nitrogen, sealed, and heated with stirring at 160 °C for 2 h. After cooling the mixture to room temperature, **13** was collected as a colorless solid, which was filtered, washed with cold ether, and recrystallized from dichloromethane-ether (0.90 g, 90%): mp 170-1 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.27-6.79 (m, Ar, 12 H), 3.70 (m, 2 H), 3.42 (m, 2 H); IR (KBr) 3057, 2957, 1671, 1584, 1448, 1315, 1128, 1107, 818, 749, 705 cm^{-1}. Anal. Calcd for $C_{22}H_{16}O_4S_2$: C, 64.69; H, 3.95. Found: C, 64.69; H, 3.85.

Reduction of 10h with Sodium Amalgam. Recovery of the Chiral Auxiliary. A mixture of the adduct **10h** (2.0 g, 3.87 mmol) and NaH_2PO_4 (8 g, 66.7 mmol) in dry methanol (25 mL) was purged with nitrogen. Under very efficient stirring, 6% sodium amalgam (8.88 g, ca. 8:1 equivalent ratio sodium to substrate) was added in portions. The reaction mixture was stirred at room temperature and monitored by TLC, eluting with petroleum ether. After 2 h water was added and the reaction mixture was extracted with pentane. The extracts were washed with brine, dried over sodium sulfate, and rotary evaporated to leave essentially pure **14** as a colorless oil (0.39 g, 75%): ^1H NMR (60 MHz, $CDCl_3$) δ 6.42 (d, J = 6.0 Hz, 2 H), 6.27 (t, J = 6.0 Hz, 2 H), 3.67 (br s, 1 H), 3.51 (s, 3 H), 1.32-1.47 (m, 4 H).

The aqueous layer was acidified with dilute HCl and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and rotary evaporated. The residue was refluxed for 1 h in dry THF (50 mL) with a large excess of lithium aluminum hydride (200 mg). Ethyl acetate (50 mL) and HCl (50 mL, 4 N) were added, and the mixture was extracted with dichloromethane. The combined organic solutions were dried (Na_2SO_4) and concentrated to give **2** (0.61 g, 50%) essentially pure by ^1H NMR.

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Supplementary Material Available: Fractional coordinates with equivalent isotropic thermal parameters and selected bond distances and bond angles for compounds **9**, **10d**, and **12** (9 pages); structure factors for **9**, **10d**, and **12** (44 pages). Ordering information is given on any current masthead page.

α-Oximino Amide Trianions in the Stereoselective Synthesis of Isoxazolines and γ-Hydroxy-α-amino Acids

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The trianions **17** and **33**, which were prepared from the corresponding α-oximino amides **7** and **30**, were reacted with 4-methoxybenzaldehyde to stereoselectively provide, on acidification, the corresponding trans-substituted isoxazoline-3-carboxamides **8** and **31/32**, respectively. Additionally, the dianion **24**, which was prepared from the corresponding *O*-silyl oxime **22**, was reacted with 4-methoxybenzaldehyde to stereoselectively give the anti β-hydroxy oxime **23**. Reduction of **8** and **26** stereoselectively gave the 2,3-syn-3,4-anti amino amides **11** and **27**. Amides **11** and **27** were subsequently converted to the γ-hydroxy-α-amino acids **12** and **29** and the corresponding lactones **13** and **28**. Amino acid **29** is the N-terminal amino acid of the antifungal agent nikkomycin B.

Introduction

There are several classes of natural products that contain unusual α-amino acid residues bearing γ-hydroxy groups. Examples include theonellamide F,[1] a marine bicyclic peptide antifungal agent; scytonemin A, a calcium antagonist produced by a blue-green alga;[2] funebrine, a novel pyrrole alkaloid;[3] and the nikkomycins and neopolyoxins,[4,5] which are a group of nucleoside di- and tripeptides noted for their ability to inhibit chitin synthetase. The nikkomycins are exemplified by nikkomycin B (**1**), nikkomycin X (**2**), and nikkomycin J (**3**) (Chart I). These natural products behave as surrogates for uridine diphosphate *N*-acetylglucosamine (**4**), which is the prepolymer converted by a chitin synthetase into chitin. As a result, the nikkomycins are potentially useful as fungicidal or insecticidal agents.

Both König[5,6] and Jäger[7] have reported synthetic methods for the preparation of the N-terminal amino acid

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