Structural Feature Relevance of the Chiral Alkyl Residue in the Addition Alkanesulfenic Acids/Enynes. Synthesis and Diels−Alder Reactivity of Enantiopure (*E*)-3-[(1*S*-*exo*)-2-Bornylsulfinyl]-1-methoxybuta-1,3-dienes

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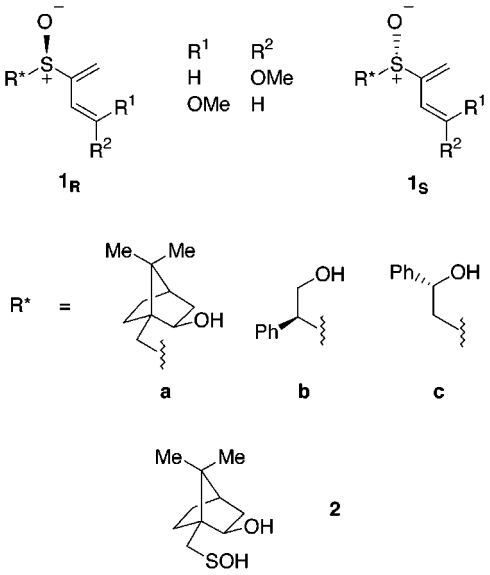

Introduction

The high degree of stereochemical control observed in Diels−Alder (DA) reactions of enantiopure diene sulfoxides holds a large synthetic interest toward this novel class of chiral dienes.[1] Investigations of their reactivity with common dienophiles have shown that cycloadditions generally occur under mild conditions in good yields and very high endo/exo and facial diastereoselectivities.

We have recently described the synthesis of 3-hydroxyalkylsulfinyl-1-methoxybuta-1,3-dienes **1** and their highly stereocontrolled DA reactions with methyl acrylate in the presence of $LiClO_4$.[1e] The synthetic strategy for these 2-sulfinyldienes was based on the sulfenic acid/enyne addition and counted four steps starting from enantiopure hydroxyalkanethiols. The choice of hydroxythiols R*SH (R* = **a**−**c**) was mainly grounded on intramolecular hydrogen bonding between OH and SO functionalities, which sterically characterizes the corresponding sulfenic acids, so enhancing the diastereoselectivity of their reaction with enynes and facilitating the chromatographic separation of the obtained diene epimers. A comparative evaluation of synthetic potential of dienes **1** has confirmed the relevant utility of the camphor skeleton included in the chiral auxiliaries based on sulfoxides.

We now report the synthesis of (*E*)-3-[1*S*-*exo*)-2-bornylsulfinyl]-1-methoxybuta-1,3-dienes **10** (Scheme 1) in which some of the crucial structural features, already present in dienes **1a**, were maintained, such as the highly sterically demanding camphor skeleton and the methoxy group. The directing effect of this last substituent guarantees complete regioselectivity in DA cycloadditions. We designed the new sulfinyldienes **10**, lacking in the hydroxy substituent which is present in **1a**, because of our interest in evaluating the role of the hydroxy function of the alkyl residue in dienes **1a**, and consequently the influence of intramolecular hydrogen bonding in their synthesis and reactivity. Our final purpose was the assessment of structural characteristics required by chiral precursors to be effective in the synthesis of our enantiopure 2-sulfinyldienes to comprise a larger number of terpene derivatives in the pool of suitable starting products.

DA reactions of dienes **10** with *N*-phenylmaleimide (NPM) or methyl acrylate, followed by removal of the sulfinyl auxiliary, afforded highly functionalized and enantiomerically pure cyclohexanones, useful intermediates in the synthesis of pseudosugars and related compounds.[2]

Results and Discussion

The synthesis of (*E*)-3-[1*S*-*exo*)-2-bornylsulfinyl]-1-methoxybuta-1,3-dienes **10** was performed starting from thiol **5** and following the previously described procedure (Scheme 1).[1e] Compound **5** was obtained, in two steps, from the commercially available [(1*S*)-*endo*]-(−)-borneol (**3**) using the Mitsunobu−Rollin reaction,[3] followed by $LiAlH_4$ reduction.[4] Thermolysis of cyanosulfoxides **7** in the presence of (*E*)-1-methoxybut-1-en-3-yne (**9**)[5] was performed in mixed xylenes (140 °C).

Addition of sulfenic acids such as **2** or **8** to enynes opens the way to the synthesis of 2-sulfinyl dienes that are not easily accessible by different routes.[1c,6] However, the most common reaction of sulfenic acids is their self-condensation to thiosulfinates, and this behavior can represent a

(1) (a) Arce, E.; Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421−3426. (b) Gosselin, P.; Bonfand, E.; Hayes, P.; Retoux, R.; Maignan, C. *Tetrahedron: Asymmetry* **1994**, *5*, 781−784. (c) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1339−1367. (d) Carreño, M. C.; Cid, M. B.; García Ruano, J. L.; Santos, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2093−2097. (e) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Jones, D. N. *J. Org. Chem.* **1997**, *62*, 4376−4384.

(2) Aceña, J. L.; Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 6419−6424 and references therein.

(3) Rollin, P. *Tetrahedron Lett.* **1986**, *27*, 4169−4170.

(4) A previously reported procedure (Blanco, J. M.; Caamaño, O.; Eirin, A.; Fernández, F.; Medina, L. *Synthesis* **1990**, 584−586) for the synthesis of thiol **5**, from commercial borneol **3**, was performed in three steps and 59% total yield.

(5) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1971.

(6) Fernández de la Pradilla, R.; Martínez, M. V.; Montero, C.; Viso, A. *Tetrahedron Lett.* **1997**, *38*, 7773−7776.

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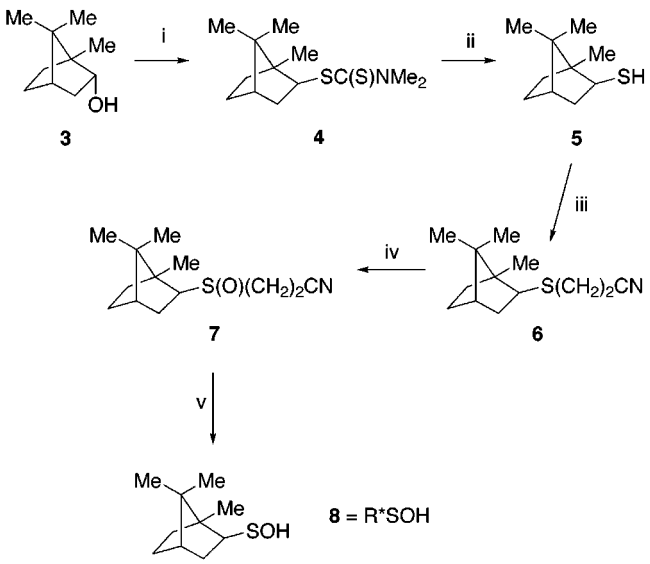
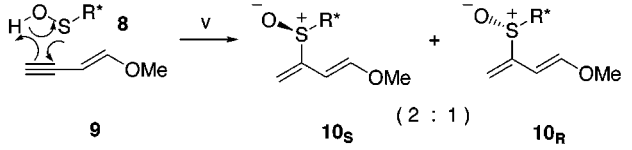
Scheme 1



[a] Reagents: (i) $Zn[SC(S)NMe_2]_2$, DEAD, Ph_3P; (ii) $LiAlH_4$; (iii) CH_2=CHCN, THF, Triton B, −78 up to 0 °C; (iv) *m*-CPBA, CH_2Cl_2, 0 °C; (v) mixed xylenes at reflux.



serious drawback in their synthetic use. Sulfenic acids that form intramolecular hydrogen bonds are in general less reactive in the thiosulfinate formation.[7] Thus, the less prone sulfenic acid is to thiosulfinate formation the higher the yield in diene sulfoxides, when a trapping enyne is added during the sulfenic acid generation by thermolysis. We had these considerations in mind when we chose to synthesize sulfenic acid **2** as the precursor of dienes **1a**, and the results confirmed the expectations.[1e] However, the presence of an intramolecular hydrogen bonding involves the presence of a hydroxy group in a suitable position. This can be a limitation both for the choice of starting products from the chiral pool and for the chemical behavior of the synthesized diene systems, i.e. some unexpected and undesired reactions of the hydroxy function.[8] Thiol **5** represented a suitable precursor for the generation of sulfenic acid **8** with some remarkable structural characteristics, such as the camphor skeleton directly linked to the sulfur function, but having no possibilities of forming intramolecular hydrogen bonds.

Although the concerted addition sulfenic acid **8**/enyne **9** was less diastereoselective, if compared with previous results concerning sulfenic acid **2**,[1e] the epimeric mixture of sulfinyldienes $\mathbf{10_S}$ and $\mathbf{10_R}$ was obtained in high yield (75%). The high steric requirements of camphor residue in **8** played a role similar to the one of intramolecular hydrogen bonding in enhancing the sulfenic acid stability and preventing thiosulfinate formation pro sulfenic acid/enyne addition. The isolation of 9-triptycenesulfenic acid,[9] which can be stabilized only by steric inhibition of thiosulfinate formation, supports our interpretation. The moderate diastereoselectivity observed in the addition of sulfenic acid **8** to enyne **9** is interpretable on the basis of relative stabilities of transition states originated from the approach of enyne to the less hindered side of the sulfenic moiety in **8**. An evaluation of rotamers of (1*S*-*exo*)-2-bornanesulfenic acid (**8**) around the C−S bond suggests that the conformations of **8** depicted in Figure 1 are almost equally populated. The predominance of diene $\mathbf{10_S}$ among the reaction products can be ascribed to the presence of the angular methyl group in **8**, near the reactive site, which causes unfavorable steric interactions in the transition state **A** with respect to **B**, precursor of major diene $\mathbf{10_S}$ (Figure 1). The two epimeric dienes were readily separated by chromatography on silica gel, the minor isomer $\mathbf{10_R}$ being much more mobile than the major isomer $\mathbf{10_S}$ (TLC ΔR_f = 0.25, EtOAc/petroleum ether 70:30).

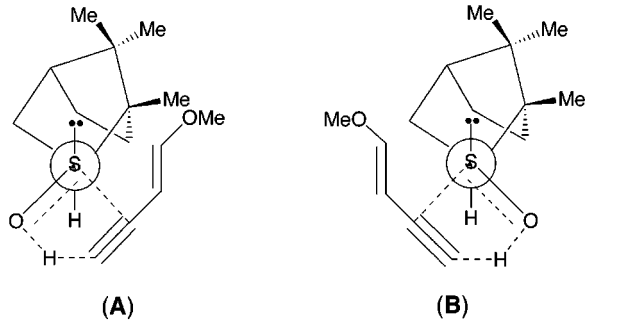


Figure 1. Transition states (A) for the formation of diene $\mathbf{10_R}$ and (B, lower energy) for $\mathbf{10_S}$.

Cycloadditions of epimeric dienes $\mathbf{10_S}$ and $\mathbf{10_R}$ with electron-deficient dienophiles were investigated (Scheme 2). Conditions and catalyst were selected on the basis of preceding experience.[1e] As concerns the diastereomeric composition of the adduct mixtures, endo/exo and facial ratios were established by NMR spectrometry from the relative intensities of well-separated vinyl and methoxycarbonyl proton signals. The obtained results are collected in Table 1.

The choice of dienophiles relapsed into methyl acrylate, for comparing the efficiency of diene systems **10** with the previously investigated **1a**,[1e] and NPM, for its intrinsic ability to produce crystalline cycloadducts with very high endo/exo and facial diastereoselectivities.[10] As a matter of fact, cycloadduct $\mathbf{11_S}$ was obtained as a unique and crystalline product in the cycloaddition of diene $\mathbf{10_S}$ with NPM (entry 1 in Table 1). It was recrystallized from ethyl acetate, and its absolute configuration was established as (1*S*,1′*S*,2*S*,2′*S*,4′*S*,6*S*,S_S) by X-ray crystallographic analysis (Flack parameter = 0.06(9);[11] Figure 2). This result is in line with the configurational control on the newly-formed stereogenic centers exerted by sulfur configuration during the cycloaddition. Moreover, it confirms the absolute configurations tentatively assigned to dienes **10** on the basis of the stereochemical outcome of the sulfenic acid/enyne addition under study.

(7) Davis, F. A.; Jenkins, L. A.; Billmers, R. L. *J. Org. Chem.* **1986**, *51*, 1033−1040.
(8) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Bruno, G.; Giannetto, P.; Nicolò, F. *J. Chem. Soc., Perkin Trans. 2* **1997**, 273−277.
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(11) Rogers, D. *Acta Crystallogr.* **1981**, *A37*, 734−741. Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876−881.

Scheme 2

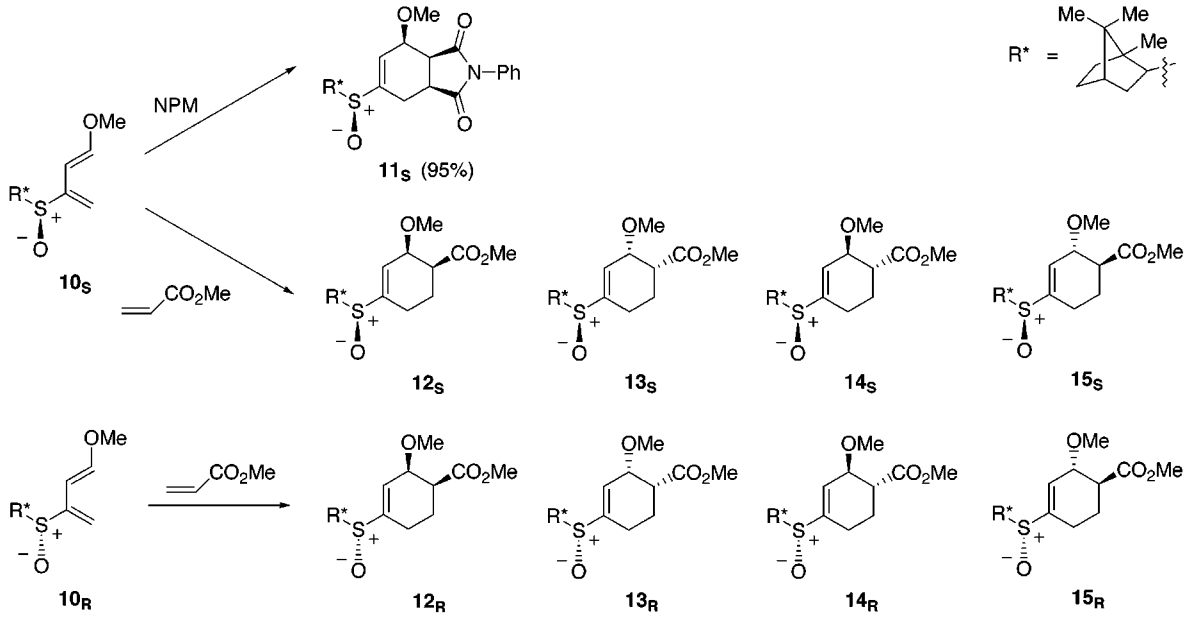


Table 1. Cycloadditions of Sulfinyldienes 10 with Methyl Acrylate and NPM in CH_2Cl_2 at Room Temperature

					adducts		
entry	diene	dienophile	catalyst	time	endo	exo	(ratio)
1	$\mathbf{10_S}$	NPM	none	2.5 h	$\mathbf{11_S}$		100
2	$\mathbf{10_S}$	methyl acrylate	none	20 d	$\mathbf{12_S}$:$\mathbf{13_S}$:	$\mathbf{14_S}$:$\mathbf{15_S}$	38:26:25:11
3	$\mathbf{10_S}$	methyl acrylate	$LiClO_4$	5 h	$\mathbf{12_S}$:$\mathbf{13_S}$:	$\mathbf{14_S}$:$\mathbf{15_S}$	93:7:0:0
4	$\mathbf{10_R}$	methyl acrylate	none	20 d	$\mathbf{13_R}$:$\mathbf{12_R}$:	$\mathbf{15_R}$:$\mathbf{14_R}$	44:34:13:9

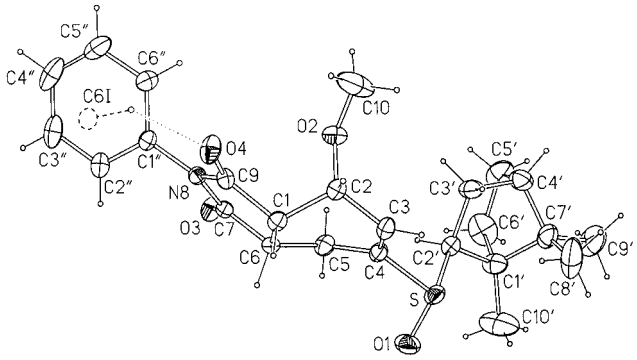
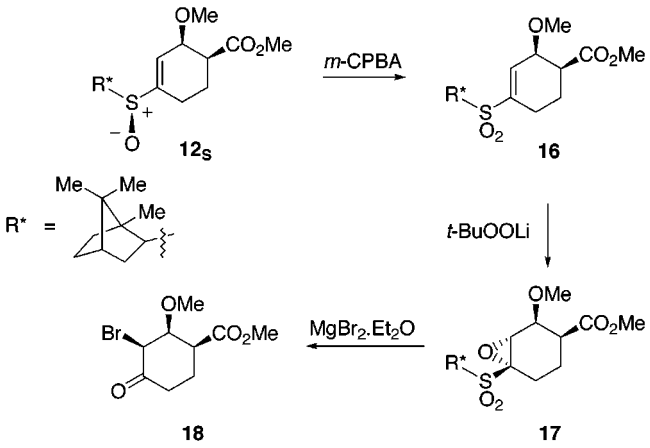


Figure 2. Perspective view (with labeling scheme) of the asymmetric unit represented by one molecule of $\mathbf{11_S}$. Dotted lines denote H interactions with another adjacent molecule (dashed fragment) in the equivalent positions (i) = $1 - x$, $-1/2 + y$, $1 - z$. Thermal ellipsoids are drawn at 20% of probability while hydrogen size is arbitrary.

Reaction of major diene epimer $\mathbf{10_S}$ with methyl acrylate gave rise to moderate facial and endo/exo diastereoselectivities (entry 2 in Table 1), while the same cycloaddition performed with the minor epimer $\mathbf{10_R}$ showed an increased endo/exo diastereoselectivity (entry 4). Energy-minimized models of $\mathbf{10_R}$ and $\mathbf{10_S}$ were compared by overlay of methoxydiene moieties to sulfur atoms:[12] the (1*S*-*exo*)-2-bornane group appears more impending over the reactive diene faces in $\mathbf{10_S}$ than in $\mathbf{10_R}$, and this increased sterical hindrance by the chiral alkyl group in $\mathbf{10_S}$ should disfavor the formation of the endo transition states. Cycloaddition of $\mathbf{10_S}$ with methyl acrylate in the presence of $LiClO_4$ afforded only the two endo cycloadducts $\mathbf{12_S}$ and $\mathbf{13_S}$ in a 93:7 ratio. This stereochemical outcome can be interpreted as previously described.[1e] ^{1}H NMR data of **12**−**15** are in line with their assigned absolute configurations. It is worthy of note that our 3-methoxy-4-methoxycarbonyl cycloadducts, bearing the sulfur functionality at C-1, always show conformational preferences such as the measured $J_{2,3}$ appear indicatively affected by the steric relationship between 3-OMe and 4-CO_2Me ($J_{2,3eq}$ 4.0−4.6 for cis and $J_{2,3ax}$ 1.9 for trans 3,4-disubstitution).

Scheme 3



Cycloadduct $\mathbf{12_S}$ was converted into the polyfunctionalyzed enantiopure cyclohexanone **18** by a sequence of highly stereoselective reactions (Scheme 3). This process[2,13] was exploited after having unsuccessfully tried common desulfurization reactions, such as Raney nickel cleavage of the C−S bond. The cyclic vinyl sulfone **16** was

(12) Molecular Modeling Program: CS Chem3D Pro, version 3.5. Force field: MM2.

obtained in high yield from cycloadduct **12S** by *m*-CPBA oxidation. The reaction of sulfone **16** with lithium *tert*-butylperoxide afforded epoxide **17** as a unique compound, showing a complete diastereoselectivity. Epoxide **17** was used without further purification in the next and final step of the process. Epoxide ring opening and concomitant loss of the alkylsulfonyl group were achieved by means of $MgBr_2 \cdot Et_2O$, and diastereoselection was complete. The stereochemistry depicted in the Scheme 3 for **17** and **18** has been tentatively established on the basis of their ^1H NMR resonances and taking into account previous related results.[10] The proton resonance spectrum of bromo derivative **18** shows H-4 resonating as a double doublet of doublets, characterized by an axial−axial (11.5 Hz) and an axial−equatorial coupling constant (5.5 Hz) with H_2-5. The axial preference of H-4, together with the absolute configuration (3*S*,4*S*) of the cyclohexene **12S**, used as starting material, allows for the assignment of the 2*S*,3*S*,4*S* configuration to the resulting bromocyclohexanone **18** (Scheme 3), if we assume the clear preference of Br substituent for the equatorial position.[2,13d] The stereochemistry assigned to oxirane **17** is anchored to the one of **18** owing to the bromine delivery from the face opposite to the epoxide ring in its cleavage and removal of sulfone moiety. Actually, the vicinal spin−spin coupling constant $J_{2,3eq}$ (4.4 Hz) in **16** is reduced to 1.8 Hz in oxirane **17**.

In conclusion, the structural features of the alkyl residue directly linked to the sulfur function in enantiopure 2-alkylsulfinyldienes play a relevant role in their synthesis on the basis of sulfenic acid/enyne addition. A comparison between previous work[1e] and results described in this paper clearly points out that the presence in the diene precursor of a functionality in the alkyl residue, suitable to form intramolecular hydrogen bond with the sulfoxide oxygen, constitutes an important but not necessary requirement. It certainly enhances the diastereoselectivity observed in the addition of sulfenic acid to enyne causing a sharp preferential formation of one sulfinyldiene epimer. However, the sterical requirements of the alkyl skeleton can be sufficient alone to prevent self-condensation of sulfenic acid to thiosulfinate, so increasing the total yield in dienes. Therefore, a large number of monoterpene systems, some of which already belonging to the chiral pool, can be used as starting products in the synthesis of 2-sulfinyldienes based on sulfenic acid/enyne addition.

The obtainment of epimeric dienes **10** in good yields, and their easy separation by chromatography, represent favorable elements from a synthetic point of view. Starting from [(1*S*)-*endo*]-(−)-borneol, which is the only commercially available enantiomer, we have obtained two epimeric sulfinyldienes, with opposite sulfur configurations, which were reacted separately in a DA manner giving access to enantiopure cycloadducts of opposite stereochemistry after removal of the alkylsulfinyl substituent.

Removal of the chiral auxiliary from our cycloadducts represent an important achievement in this research and opens the way to the use of such enantiopure cyclic derivatives in target-oriented syntheses.

Experimental Section

The general experimental information is similar to that recently described.[1e]

(1*S*-*exo*)-2-Bornyl *N*,*N*-Dimethyldithiocarbamate (4). Compound **4** was obtained as a crystalline compound (71% yield) from (1*S*-*endo*)-borneol (**3**), DEAD, Ph_3P, and zinc dimethyldithiocarbamate (ZIRAM) following the previously reported procedure:[1e] mp 138 °C; $[\alpha]^{25}_D$ −10 (*c* 0.01, $CHCl_3$); ^1H NMR δ 4.38 (dd, 1H), 3.56 (s, 3H), 3.37 (s, 3H), 2.08 (dd, 1H), 1.85 (m, 1H), 1.8−1.2 (m, 5H), 0.95 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 198.8, 58.7, 49.7, 47.6, 45.8, 45.6, 41.4, 39.1, 37.9, 27.2, 20.3, 19.8, 13.4; MS/FAB *m*/*z* 258 (M + 1, 28), 137 (100), 122 (38), 88 (40), 81 (38). Anal. Calcd for $C_{13}H_{23}NS_2$: C 60.65; H, 9.00. Found: C, 60.64; H, 9.00.

(1*S*-*exo*)-2-Bornanethiol (5). Reduction of dimethyldithiocarbamate **4** with $LiAlH_4$ was performed as previously reported,[1e] giving thiol **5** as a low-melting solid not needing purification (92% yield): $[\alpha]^{25}_D$ +47.5 (*c* 5.06, $CHCl_3$) [lit.[4] mp 24−26 °C; $[\alpha]^{25}_D$ +48.3 (*c* 11.8, MeOH)]; IR ($CHCl_3$) 2990, 2954, 2878, 1455, 1389 cm^{-1}; MS/FAB *m*/*z* 137 (M + 1 − H_2S, 100), 138 (25), 136 (85), 107 (14), 81 (62), 77 (15).

(1*S*-*exo*)-2-Bornyl 2-Cyanoethyl Sulfide (6). Bornanethiol **5** was reacted with acrylonitrile in the presence of benzyltrimethylammonium hydroxide (Triton B) following the previously reported procedure.[1e] The sulfide **6** was obtained as an oil, not needing purification (96% yield): $[\alpha]^{25}_D$ +59.9 (*c* 5.09, $CHCl_3$); ^1H NMR δ 2.80 (split ABd, 1H), 2.72 (split ABd, 1H), 2.64 (dd, 1H), 2.59 (split t, 2H), 1.91 (dd, 1H), 1.84 (ddd, 1H), 1.7−1.1 (m, 5H), 0.97 (s, 3H), 0.92 (s, 3H), 0.81 (s, 3H); ^{13}C NMR: δ 118.2, 54.8, 49.2, 47.0, 45.5, 40.7, 38.1, 29.8, 27.0, 20.1, 19.9, 18.8, 13.7; IR (neat oil) 2951, 2876, 2249 (CN), 1455, 1389 cm^{-1}; MS/FAB *m*/*z* 224 (M + 1, 9), 223 (16), 138 (22), 137 (100), 95 (22), 81 (35).

***m*-CPBA Oxidation of Sulfide 6.** This reaction, performed as previously described,[1e] gave (2-cyanoethyl)sulfoxides **7** (91% yield, 1:1 mixture of sulfur epimers) usable for synthesizing sulfinyldienes **10** without purification. The epimeric mixture can be separated by column chromatography, eluting with petrol/EtOAc (75:25). **(1*S*-*exo*)-2-Bornyl 2-cyanoethyl (*S*S)-sulfoxide (7S)**: first eluted solid, mp 79−80 °C; $[\alpha]^{25}_D$ +41.5 (*c* 1.77, $CHCl_3$); ^1H NMR δ 3.0−2.8 (m, 4H), 2.64 (dd, 1H), 2.37 (dddd, 1H), 1.90 (t, 1H), 1.9−1.2 (m, 4H), 1.49 (dd, 1H), 1.04 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 117.5, 69.4, 50.0, 48.2, 47.5, 45.1, 39.0, 28.2, 27.3, 20.0, 19.7, 13.4, 11.7; MS/FAB *m*/*z* 240 (M + 1, 8), 137 (100), 95 (19), 81 (45), 69 (19), 55 (21). **(1*S*-*exo*)-2-bornyl 2-cyanoethyl (*R*S)-sulfoxide (7R)**: oil; $[\alpha]^{25}_D$ +89.4 (*c* 2.69, $CHCl_3$); ^1H NMR δ 3.1−2.6 (m, 5H), 1.8−1.2 (m, 7H), 1.21 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 117.7, 70.7, 50.0, 47.7, 44.8, 39.1, 31.3, 26.9, 20.0, 19.6, 13.7, 10.5; MS/FAB *m*/*z* 240 (M + 1, 14), 138 (22), 137 (100), 81 (23).[14]

Thermolysis of Sulfoxides 7 in the Presence of (*E*)-1-Methoxybut-1-en-3-yne (9). Sulfoxides **7** (1 g, 4.2 mmol) in mixed xylenes (12 mL) containing enyne **9** (1.1 g, 13.5 mmol) were maintained at reflux temperature. When the reaction appeared complete by TLC (20 min), the solution was concentrated under reduced pressure and the obtained reaction mixture was separated by column chromatography. First **(*R*S,*E*)-3-[(1*S*-*exo*)-2-bornylsulfinyl]-1-methoxybuta-1,3-diene (10R)** was eluted with petroleum ether/EtOAc (95:5) as a light yellow oil (271 mg, 1.01 mmol, 24% yield): $[\alpha]^{25}_D$ +48.5 (*c* 1.25, $CHCl_3$); ^1H NMR δ 6.90 (d, 1H), 5.56 (s, 1H), 5.48 (s, 1H), 5.46 (d, 1H), 3.66 (s, 3H), 2.67 (dd, 1H), 2.24 (dddd, 1H), 1.8−1.2 (m, 6H), 1.11 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H); ^{13}C NMR δ 151.3, 112.9, 98.3, 68.8, 56.7, 50.2, 47.1, 45.2, 39.4, 27.4, 26.3, 20.3, 19.6, 13.5;

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(14) The sulfur configurations in **7R** and **7S** are tentatively assigned taking into account the cogent analogies (chromatographic retention times and NMR data) to epimeric dienes **10** whose absolute configurations were allocated for a certainty on the basis of X-ray crystallographic analysis of the adduct of diene **10S** with NPM (Figure 1). Note that the sulfur configuration in **7R** is identical to that in **10S** (and **7S** to **10R**), although they have different designations according to the CIP system.

MS/FAB *m*/*z* 269 (M + 1, 16), 138 (19), 137 (100), 81 (36), 57 (17), 39 (19). The less mobile **(*S*$_S$,*E*)-3-[(1*S*-*exo*)-2-bornylsulfinyl]-1-methoxybuta-1,3-diene (10$_S$)** was eluted with petroleum ether/EtOAc (85:15) as a light yellow oil (542 mg, 2.02 mmol, 48% yield): $[\alpha]^{25}_D$ +10.1 (*c* 1.50, $CHCl_3$); ^{1}H NMR δ 7.08 (d, 1H), 5.64 (d, 1H), 5.55 (s, 1H), 5.41 (s, 1H), 3.68 (s, 3H), 2.68 (dd, 1H), 1.8−1.2 (m, 7H), 1.24 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 151.9, 115.7, 96.5, 96.1, 71.5, 56.7, 49.3, 47.9, 45.0, 39.0, 32.4, 27.1, 20.1, 19.7, 13.6; MS/FAB *m*/*z* 269 (M + 1, 14), 138 (11), 137 (100), 95 (11), 83 (14), 81 (39).

DA Cycloadditions of Dienes 10 with Methyl Acrylate and NPM. Some experimental conditions are reported in Table 1. All the cycloadditions were performed in CH_2Cl_2 (3 mL for 0.6 mmol of diene and 3.6 mmol of dienophile). In the catalyzed cycloaddition, solid $LiClO_4$ was added to the solution of diene and dienophile in a diene/catalyst ratio of 1:0.8. The reaction mixture was stirred until the diene was totally disappeared, as verified by TLC monitoring, and the isolation of adducts was performed by column chromatography. Total yields in cycloadduct mixtures were always higher than 95%.

(1*S*,2*S*,6*S*,*S*$_S$)-4-[(1*S*-*exo*)-2-Bornylsulfinyl]-2-methoxy-8-phenyl-8-azabicyclo[4.3.0]non-3-ene-7,9-dione (11$_S$). Compound **11$_S$** was the only product of the cycloaddition between **10$_S$** and NPM (entry 1 in Table 1). Its isolation was achieved by column chromatography eluting with CH_2Cl_2/EtOAc 80:20: mp 210−211 °C; $[\alpha]^{25}_D$ −170.4 (*c* 0.18, $CHCl_3$); ^{1}H NMR δ 7.5−7.3 (m, 5H), 6.74 (dd, 1H), 4.52 (dd, 1H), 3.46 (ABdd, 1H), 3.36 (ddd, 1H), 3.13 (dd, 1H), 2.72 (t, 1H), 2.26 (ABddd, 1H), 1.6−1.2 (m, 7H), 1.25 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H); MS/FAB *m*/*z* 442 (M + 1, 4), 274 (33), 137 (100), 81 (77), 57 (31), 55 (32).

Cycloadducts from diene 10$_S$ and methyl acrylate (entries 2 and 3 in Table 1) are reported in order of increasing retention times on chromatographic column (eluant petroleum ether/EtOAc 75:25).

(3*R*,4*R*,*S*$_S$)-1-[(1*S*-*exo*)-2-bornylsulfinyl]-3-methoxy-4-methoxycarbonylcyclohexene (13$_S$): mp 193−195 °C; $[\alpha]^{25}_D$ +187.4 (*c* 0.29, $CHCl_3$); ^{1}H NMR δ 6.55 (split d, 1H), 4.15 (dd, 1H), 3.75 (s, 3H), 3.40 (s, 3H), 2.92 (m, 1H), 2.66 (dd, 1H), 2.54 (dt, 1H), 2.1−1.1 (m, 10H), 1.23 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 172.3, 146.1, 130.7, 72.3, 69.9, 57.5, 51.8, 49.2, 47.8, 45.4, 44.9, 38.8, 32.4, 27.1, 20.0, 19.8, 19.1, 18.8, 13.6; MS/FAB *m*/*z* 355 (M + 1, 14), 155 (21), 149 (70), 138 (28), 137 (100).

(3*S*,4*S*,*S*$_S$)-1-[(1*S*-*exo*)-2-Bornylsulfinyl]-3-methoxy-4-methoxycarbonylcyclohexene (12$_S$): mp 105−107 °C; $[\alpha]^{25}_D$ −119.3 (*c* 1.04, $CHCl_3$); ^{1}H NMR δ 6.49 (dt, 1H), 4.15 (t, 1H), 3.73 (s, 3H), 3.40 (s, 3H), 2.81 (dt, 1H), 2.71 (t, 1H), 2.5−1.2 (m, 11H), 1.22 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 172.3, 145.2, 131.8, 73.4, 70.1, 57.6, 51.7, 49.3, 47.8, 45.0, 43.5, 38.9, 32.3, 27.0, 20.0, 19.9, 19.8, 19.2, 13.6; MS/FAB *m*/*z* 355 (M + 1, 10), 187 (14), 138 (12), 137 (100), 95 (12), 81 (43).[15]

(3*R*,4*R*,*R*$_S$)-1-[(1*S*-*exo*)-2-Bornylsulfinyl]-3-methoxy-4-methoxycarbonylcyclohexene (13$_R$). It was the main product of the cycloaddition between **10$_R$** and methyl acrylate (entry 4 in Table 1). Its isolation was achieved by column chromatography eluting with petroleum ether/Et_2O 70:30: mp 114−115 °C; $[\alpha]^{25}_D$ +196.2 (*c* 0.40, $CHCl_3$); ^{1}H NMR δ 6.60 (ddd, 1H), 4.16 (t, 1H), 3.74 (s, 3H), 3.40 (s, 3H), 2.67 (dt, 1H), 2.52 (dd, 1H), 2.3−1.1 (m, 11H), 1.11 (s, 3H), 0.99 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 172.4, 146.9, 126.5, 72.6, 67.8, 57.5, 51.7, 50.1, 47.1, 45.2, 44.8, 39.5, 27.3, 26.9, 22.6, 20.3, 19.6, 19.5, 13.4.[16]

(3*S*,4*S*)-1-[(1*S*-*exo*)-2-Bornylsulfonyl]-3-methoxy-4-methoxycarbonylcyclohexene (16). *m*-CPBA oxidation of the adduct **12$_S$**, performed as previously described,[1e] gave the sulfonylcyclohexene **16** (215 mg, 0.58 mmol, 98% yield), which did not need any purification: mp 95−97 °C; $[\alpha]^{25}_D$ −77.0 (*c* 1.08, $CHCl_3$); ^{1}H NMR δ 6.95 (dt, 1H), 4.19 (t, 1H), 3.74 (s, 3H), 3.43 (s, 3H), 3.05 (t, 1H), 2.69 (dt, 1H), 2.53 (ABdddd, 1H), 2.40 (ABdddd, 1H), 2.2−1.2 (m, 9H), 1.26 (s, 3H), 1.11 (s, 3H), 0.88 (s, 3H); ^{13}C NMR δ 172.0, 142.7, 134.3, 72.7, 67.7, 57.8, 52.1, 51.8, 47.8, 44.8, 43.3, 40.5, 33.2, 26.7, 23.8, 20.7, 20.3, 19.7, 13.2; MS/FAB *m*/*z* 371 (M + 1, 4), 217 (25), 137 (100), 95 (32), 93 (23), 81 (87).

(1*R*,2*R*,3*S*,4*S*)-1-[(1*S*-*exo*)-2-Bornylsulfonyl]-3-methoxy-4-methoxycarbonylcyclohexene Oxide (17). BuLi 1.6 M in hexanes (1.07 mL, 1.71 mmol) was added to a stirred solution of *t*-BuOOH (0.52 mL of 3.3 M toluene solution,[17] 1.71 mmol) in anhydrous THF (6 mL) at −78 °C, under nitrogen atmosphere. After the mixture was stirred for 15 min, the sulfone **16** (210 mg, 0.57 mmol), dissolved in anhydrous THF (3 mL), was added at −78 °C. The reaction mixture was allowed to reach room temperature spontaneously, maintaining the stirring overnight, and then quenched with saturated NaCl aqueous solution (5 mL) and extracted with EtOAc (3 × 25 mL). The collected organic layers were dried over Na_2SO_4, and the solvent was evaporated. The epoxide **17** (200 mg, 0.52 mmol, 91% yield), obtained as a low-melting solid, was used in the next step without further purification: ^{1}H NMR δ 4.13 (m, 1H), 3.97 (d, 1H), 3.73 (s, 3H), 3.47 (s, 3H), 3.21 (t, 1H), 2.8−1.2 (m, 12H), 1.22 (s, 3H), 1.06 (s, 3H), 0.88 (s, 3H); ^{13}C NMR δ 172.3, 74.5, 72.5, 66.9, 59.1, 56.7, 53.0, 51.8, 47.5, 45.2, 40.7, 40.4, 32.9, 26.9, 22.1, 17.2, 20.5, 19.9, 13.7; MS/FAB *m*/*z* 387 (M + 1, 4), 185 (41), 137 (100), 95 (41), 91 (35), 81 (88).

(2*S*,3*S*,4*S*)-2-Bromo-3-methoxy-4-methoxycarbonylcyclohexanone (18). An ethereal solution of $MgBr_2$ was prepared by reacting Mg (126 mg, 5.2 mmol) with a solution of $BrCH_2CH_2Br$ (0.45 mL, 5.2 mmol) in Et_2O (15 mL). The mixture was stirred at room temperature for 30 min, and a solution of epoxide **17** (200 mg, 0.52 mmol) in THF (5 mL) was added. The stirring was continued at room temperature, checking the disappearance of the starting product by TLC (CH_2Cl_2/EtOAc 90:10) and ^{1}H NMR. After completion of the reaction (approximately 72 h), a saturated aqueous solution of NaCl was added. The reaction mixture was extracted with Et_2O, and the organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/CH_2Cl_2 75:25) affording 111 mg (0.42 mmol) of **18** (80% yield) as a low-melting solid: $[\alpha]^{25}_D$ −67.0 (*c* 0.36, $CHCl_3$); ^{1}H NMR δ 4.24 (d, 1H), 4.24 (split dd, 1H), 3.76 (s, 3H), 3.43 (ddd, 1H), 3.41 (s, 3H), 3.04 (ddd, 1H), 2.4−2.2 (m, 3H); ^{13}C NMR δ 202.7, 172.3, 83.0, 58.4, 52.2, 45.6, 40.6, 34.1, 22.0; MS/EI *m*/*z* 234 (15) and 232 (15) (M − MeOH), 207 (5) and 205 (6) (M − CO_2Me), 149 (100).

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Supporting Information Available: General experimental information, X-ray crystallographic data for **11$_S$**, NMR assignments, spin−spin coupling constants, and copies of NMR spectra for compounds **4**−**6**, **7$_R$**, **7$_S$**, **10$_R$**, **10$_S$**−**13$_S$**, **13$_R$**, and **16**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Minor *exo*-adducts **15$_S$** (3*R*,4*S*,*S*S) and **14$_S$** (3*S*,4*R*,*S*S), showing intermediate retention times between **13$_S$** and **12$_S$**, were not isolated but only recognized in the crude adduct mixture by typical ^{1}H NMR resonances such as vinyl multiplets at δ 6.39 and 6.36, respectively.

(16) Major endo adduct **13$_R$** was the less mobile product. Minor *endo*-**12$_R$** [(3*S*,4*S*,*RS*), more mobile adduct] and exo adducts **14$_R$** (3*S*,4*R*,*RS*) and **15$_R$** (3*R*,4*S*,*RS*), showing different retention times, intermediate between the ones of **12$_R$** and **13$_R$**, were not isolated but easily recognized in the chromatographic fractions having different compositions. Typical ^{1}H NMR resonances such as vinyl multiplets and 4-CO_2Me singlets were monitored: **12$_R$** (6.62 and 3.39), **14$_R$** (6.45 and 3.42), **15$_R$** (6.45 and 3.43 ppm).

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