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Chiral Sulfinylethenes as Efficient Dienophiles for Asymmetric Diels-Alder Reactions

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Chiral Sulfinylethenes as Efficient Dienophiles for Asymmetric Diels-Alder Reactions

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An overview of our recent studies on asymmetric Diels-Alder reactions of chiral vinyl sulfoxides (= sulfinylethenes) is described. For the preparation of sulfinylethenes as Diels-Alder dienophiles, the Andersen method as well as a novel route by diastereoselective oxidation of *exo*-2-hydroxy-10-bornyl vinyl sulfides with 3-chloroperoxybenzoic acid (*m*-CPBA) is presented. The latter methodology has been successfully applied to a facile synthesis of two types of novel sulfoxides, *i.e.*, α-sulfinylmaleate and α-sulfinylmaleimide derivatives. These sulfinyl dienophiles effect Diels-Alder reactions with a high degree of diastereoselectivity. Especially, the chiral α-sulfinylmaleimides readily react with Diels-Alder dienes of rather low reactivity, such as furan, to give the corresponding cycloadducts under conventional conditions. Applications of these asymmetric Diels-Alder reactions to natural product synthesis are also described.

Key words: Chiral vinyl sulfoxides, *exo*-2-hydroxy-10-bornyl group, asymmetric Diels-Alder reaction, chiral auxiliary.

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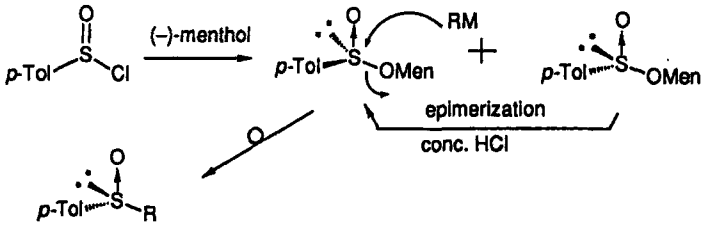
1. INTRODUCTION

Chiral sulfoxides are useful for asymmetric carbon-carbon bond formation.[1] Among a number of C-C bond formation reactions, the Diels-Alder reaction is

the most fascinating strategy which enables the construction of up to four chiral centers in one step. To effect asymmetric Diels-Alder reactions, novel chiral dienophiles and catalysts have been exploited to date.[2] Among the chiral dienophiles those possessing chirality at a sulfur center could serve as useful auxiliaries for highly specific asymmetric induction reactions. The aim of this report is to highlight our recent studies on asymmetric Diels-Alder reactions with chiral sulfinylethenes as efficient dienophiles.

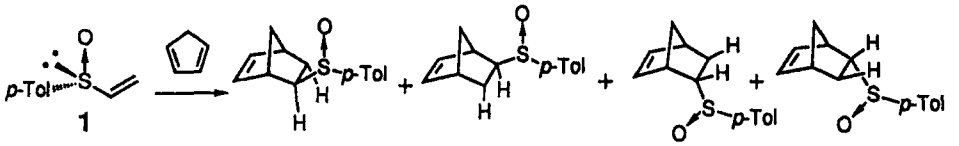
2. DIELS-ALDER REACTIONS OF *p*-TOLYL VINYL SULFOXIDES

For the preparation of optically active vinyl sulfoxides, the Andersen method (= substitution at the sulfur atom of (*S*)-menthyl *p*-toluenesulfinate with an appropriate organometallic reagent) is favored since it has the advantage that the substitution takes place with 100% inversion of configuration (Scheme 1).[3] In addition, (*S*)-menthyl *p*-toluenesulfinate is commercially available.[4]



SCHEME 1

At the outset, the Diels-Alder reaction of (*R*)-*p*-tolyl vinyl sulfoxide (**1**) with cyclopentadiene was envisaged (Scheme 2).[5] Unfortunately, the reactivity of the



90 °C, 19 h[5]	22%	6%	14%	38%
110 °C, 15 h[6]	28%	8%	22%	42%

SCHEME 2

sulfoxide **1** toward cyclopentadiene was poor. Under forced conditions (90 °C, 19 h) cycloaddition takes place to afford a mixture of all four possible adducts in a ratio of 22:6:38:14 in 80% combined yield. Thus, the stereoselectivity (*endo*-sulfinyl vs. *exo*-sulfinyl) is 28:52. Both the *exo*- and the *endo*-diastereoselectivity are low (22:6, 38:14). Similar results have been obtained independently by Maignan.[6]

The poor diastereoselectivity for the cycloaddition of **1** in the *endo* and *exo* modes points to a small difference of the two ground-state conformational energies of the dienophile **1**. Thus, the sulfoxide **1** assumes both the s-*cis* and the s-*trans* conformation (Fig. 1). Cyclopentadiene should thus attack the less hindered lone-pair side in each mode. As a result, the cycloaddition of **1** in the s-*cis* conformation affords an *endo* and an *exo* adduct in 14% and 6% yield, respectively. On the other hand, the cycloaddition of **1** in the s-*trans* conformation gives an *endo* and an *exo* adduct in 38% and 22% yields, respectively.

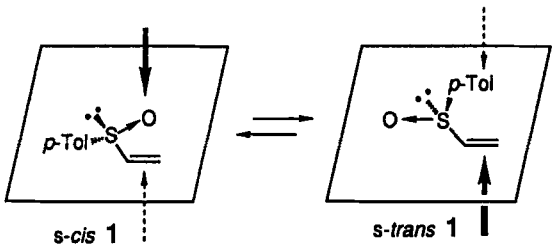


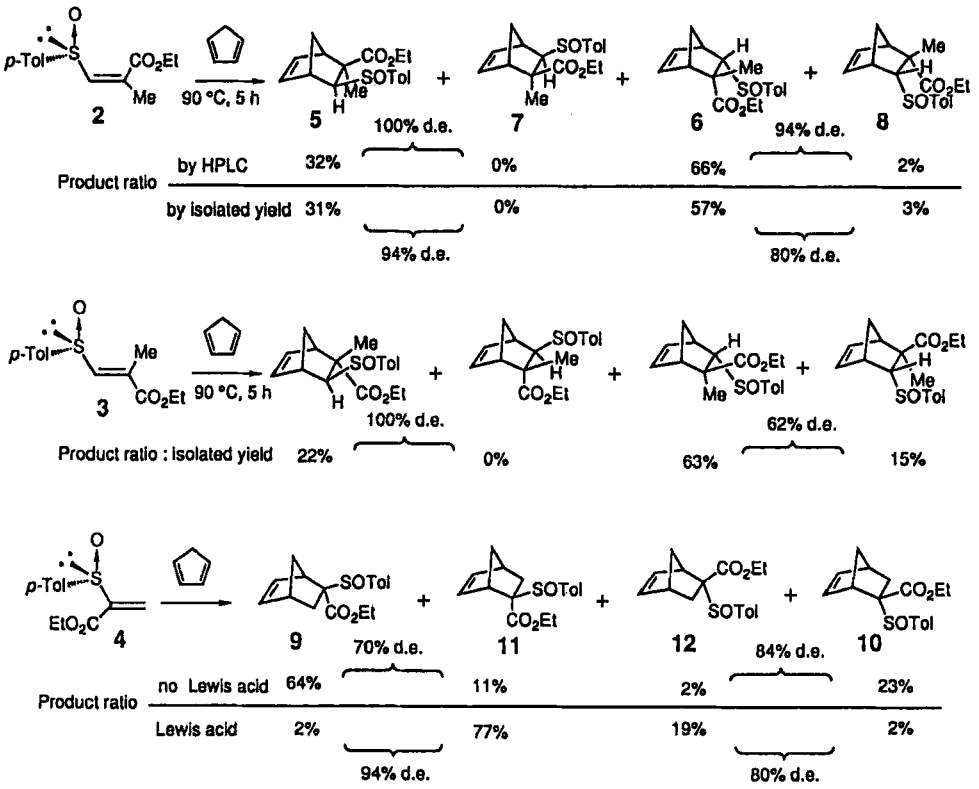
FIG. 1

To enhance both the reactivity and the diastereoselectivity we undertook the preparation of α- and β-alkoxycarbonylvinyl sulfoxides (**2**, **3**, and **4**).[7] It was expected that the dienophilicity would be increased by an additional alkoxycarbonyl group and that the diastereoselectivity might be improved by control of the conformational preference due to the dipole-dipole interaction between the sulfinyl and the alkoxycarbonyl group.

As anticipated, these sulfoxides react with cyclopentadiene under milder conditions. Highly diastereoselective cycloadditions of **2**, **3**, and **4** are observed (Scheme 3). This can be plausibly explained in terms of steric factors by the mechanism shown in Fig. 2.

In the case of **2** conformer **B** must be more stable than conformer **A** with the sulfinyl group remote from the alkoxycarbonyl fragment due to dipole-dipole repulsion. Thus, cyclopentadiene should approach from the less hindered lone-pair side of **B** to give the two major *exo* and *endo* adducts (**5** and **6**). The absolute configuration of **5** was proven by transformation to a known compound. The major *endo* product **6** is employed as a key precursor in the synthesis of (+)-*epi*-β-santalene.[8]

On the other hand, without a Lewis acid, the reaction of **4** and cyclopentadiene afforded the adducts **9** and **10** as the major *exo*- and *endo*-sulfinyl products. This can be reasonably explained by assuming that cyclopentadiene would attack the less hindered face of the more stable conformer **C** of **4**, resulting in the formation of the two major products **9** and **10**. On the other hand, in the presence of a Lewis acid ($ZnCl_2$), the two major adducts **11** and **12** were obtained. The chelation of S→O and C=O with the Lewis acid in the dienophile **4** should freeze the rotation around the bond between C=C and S→O, resulting in the favorable



SCHEME 3

conformer **D**. The *exo*- and *endo*-sulfinyl adducts **11** and **12** are thus obtained as the major products.

To understand the stereochemical outcome of the Diels-Alder reaction of the sulfinyl dienophile, the circular dichroism (CD) spectrum of the vinyl sulfoxide is informative. A negative Cotton effect in the CD spectra of **2** and **3** suggests that in both cases the favored conformation is s-*trans*. On the other hand, the more stable conformation of **4** should be considered to be s-*cis* judged by its positive Cotton effect. The sulfoxides **2**, **3**, and **4** are oils; however, benzyl (*Z*)- and (*E*)-3-(*p*-tolylsulfinyl)propenoate could be obtained as suitable crystalline materials for X-ray analysis. The X-ray crystal structures of benzyl (*Z*)- and (*E*)-3-(*p*-tolylsulfinyl)propenoate show approximate s-*trans* and s-*cis* conformations with respect to the S→O and the C=C bonds, respectively. These X-ray structures also support the preferred conformation of the Diels-Alder transition state proposed by us.

The stereochemical outcome of Diels-Alder reactions of sulfinyl dienophiles has been investigated based upon the computational approach of Hehre and Kahn.[9] However, the theoretical calculations do not lend themselves to rationalizations of all experimental results.[10]

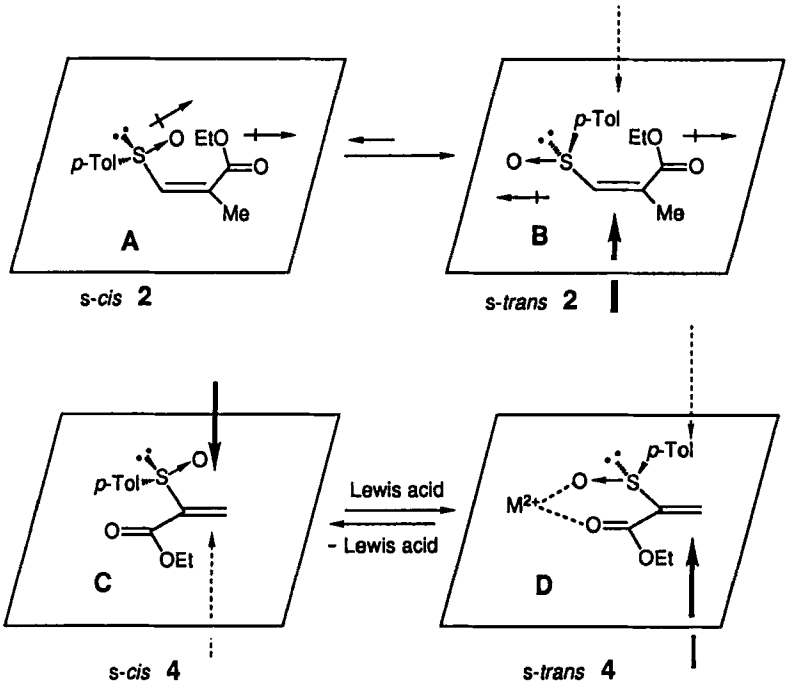


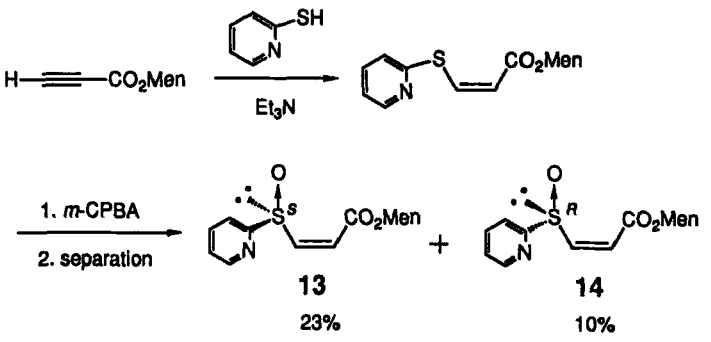
FIG. 2

3. DIELS-ALDER REACTIONS OF 2-PYRIDYL VINYL SULFOXIDES

We have devised the preparation of novel dienophiles by introduction of an alkoxycarbonyl group in the α- or β-position of *p*-tolyl vinyl sulfoxides. It is important to point out here that the alkoxycarbonyl substituent must be introduced in the α-position or the (*Z*)-β-position of the vinyl sulfinyl group to effect a high asymmetric induction.

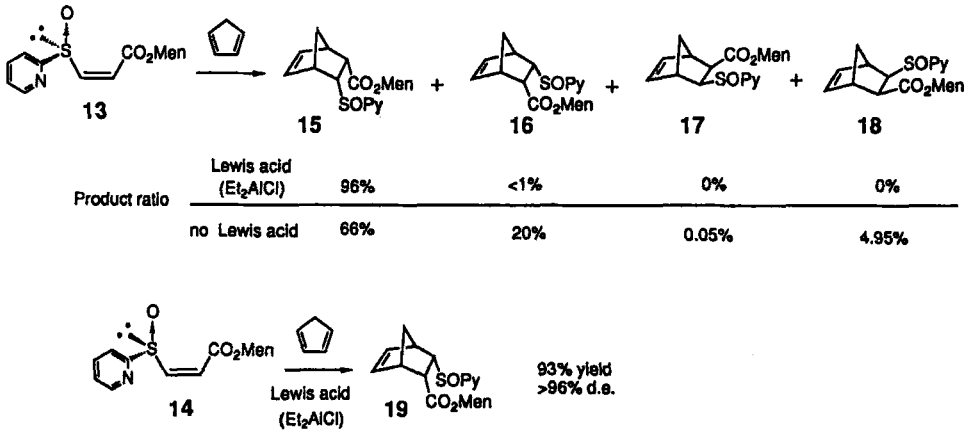
These dienophiles, however, are not sufficiently reactive toward a variety of dienes. For example, the sulfoxide **4** does not react with furan under conventional conditions. This impasse prompted us to seek a highly reactive Diels-Alder dienophile toward unreactive dienes such as furan. In a preliminary study, other arylsulfinylpropenoates such as (2,4-dinitrobenzenesulfinyl)propenoate were shown to effect the Diels-Alder reaction with higher reactivity. Of the arylsulfinyl groups investigated, substituted 2-pyridylsulfinyl groups rather than substituted benzenesulfinyl groups were found to be effective from the point of view of diastereoselectivity. It is easy to understand that a 2-pyridyl group has a good electron-withdrawing inductive effect, and we might expect it to activate the C=C bond.

The menthyl 3-(2-pyridylsulfinyl)propenoates **13** and **14** were envisioned as candidate dienophiles and easily prepared by the reaction sequence shown in Scheme 4.[11]



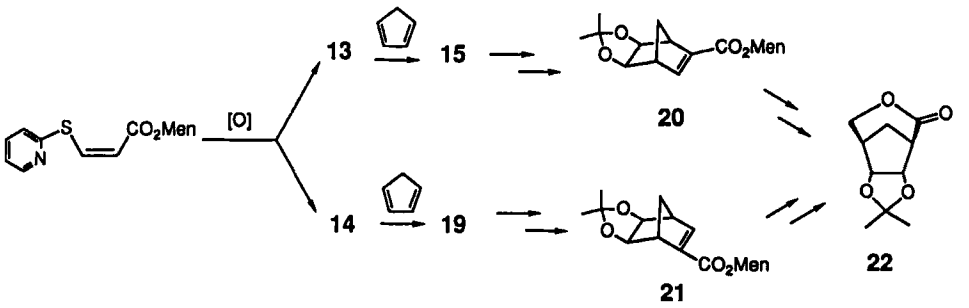
SCHEME 4

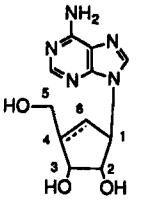
The absolute stereochemistry at the sulfur atom in **13** and **14** was tentatively assigned by comparison of their CD spectra with that of (*Z*)-(*R*$_S$)-(*p*-toluenesulfinyl)propenoate. Although the yields of these diastereoisomeric sulfoxides are low, the reaction of **13** and cyclopentadiene proceeds smoothly in the presence of diethylaluminium chloride at −70 °C to afford a single *endo* diastereoisomer **15**, whereas, in the absence of a Lewis acid, the reaction produces the four adducts **15**, **16**, **17**, and **18** (Scheme 5). For the Lewis acid-promoted Diels-Alder reaction of **14**, the adduct **19** was obtained as essentially a single product.



SCHEME 5

Both **20** and **21**, derived from **15** and **19**, have been transformed to the bicyclic lactone **22** which was utilized in the synthesis of (−)-aristeromycin and (−)-neplanocin A.[12] An enantioconvergent (strictly speaking, diastereoconvergent) synthesis of these carbocyclic nucleosides starting from menthyl 3-(2-pyridylthio)propenoate is achieved (Scheme 6).

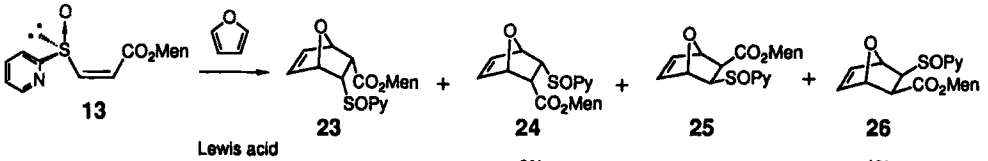




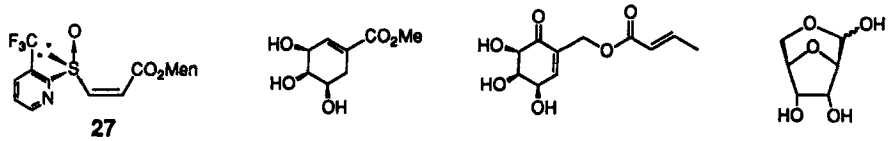
aristeromycin
$\Delta^{4,6}$: neplanocin A

SCHEME 6

Next, we examined the Diels-Alder reaction of **13** with furan which is a poor Diels-Alder diene. The Diels-Alder reaction of **13** with furan proceeds at 50 °C for 6 days to give the cycloadducts **23–26**, albeit with low diastereoselectivity (Scheme 7). Upon addition of a Lewis acid (Et_2AlCl) the cycloaddition takes place in a highly diastereoselective manner. The dienophile **27**, with a trifluoromethyl group in the 3-position of the pyridyl moiety, exhibits high reactivity



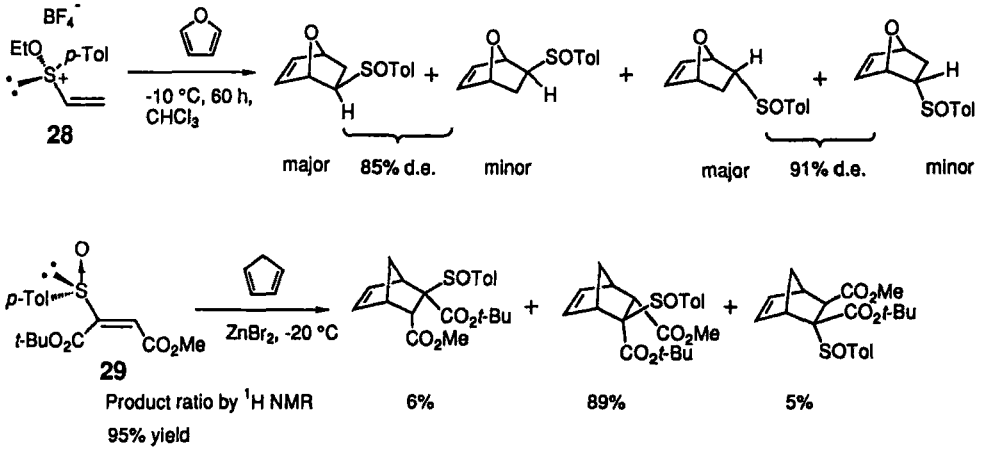
Product ratio	23	24	25	26
Lewis acid (Et_2AlCl, r.t., 7 d)	41%	3%	24%	1%
no Lewis acid (50 °C, 6 d)	27%	22%	12%	1%



SCHEME 7

in this cycloaddition.[13] The successful reactions of **13** and **27** with dienes have been applied to the synthesis of biologically important compounds (glyoxalase I inhibitor,[13] methyl 5-*epi*-shikimate,[14] and D-showdomycin[15]).

Concerning facile Diels-Alder reactions with *p*-tolyl vinyl sulfoxides, Kagan recently reported that *p*-tolyl vinyl sulfoxide is activated for the Diels-Alder reaction by transformation into the corresponding sulfonium salt **28**[16] Also investigated was the *p*-tolylsulfinyl maleate **29** for the Diels-Alder reaction (Scheme 8).[17]

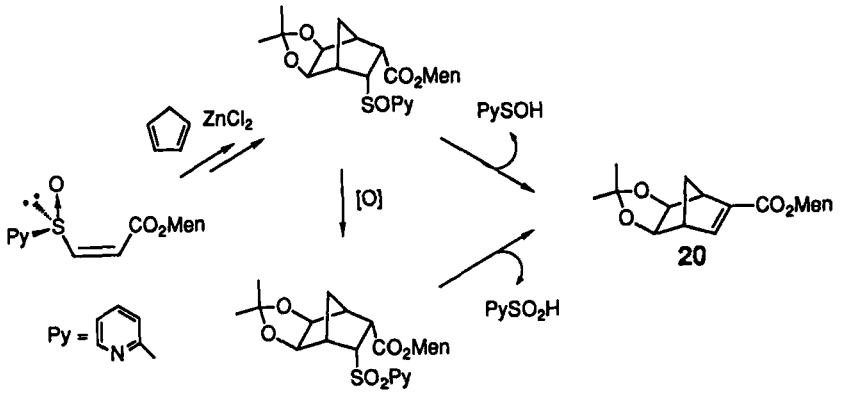


SCHEME 8

We have described the Diels-Alder reaction by the use of the *p*-toluene- and the 2-pyridine-sulfinyl group as a chiral auxiliary; however, from the viewpoint of asymmetric synthesis there are some instrinsic weak points in the chemistry of chiral *p*-tolyl and 2-pyridyl sulfoxides.[18] i) The production of a 1:1-mixture of two diastereoisomeric sulfoxides, *e.g.*, (*R*)- and (*S*)-menthyl sulfoxides such as **13** and **14**, is inappropriate in asymmetric synthesis, ii) the chiral auxiliary, the arenesulfinyl group is lost at a later stage after the asymmetric reaction since the sulfinyl group is removed as an unstable sulfenic acid or a sulfinic acid (Scheme 9), and iii) only a limited range of chiral sulfoxides can be prepared by the Andersen method because their synthesis involves carbanionic species such as Grignard reagents.

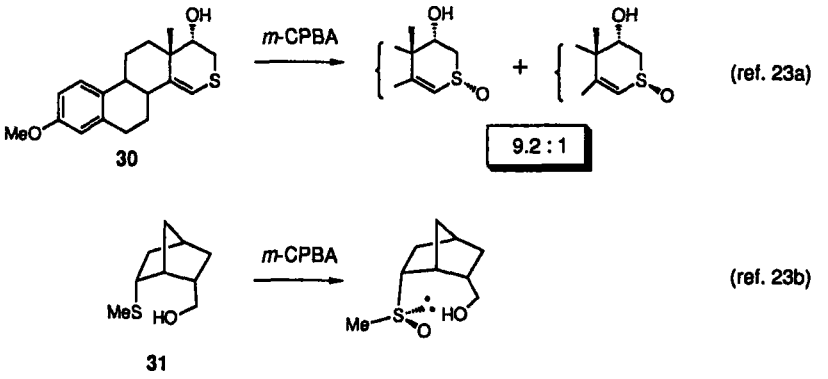
For the preparation of the chiral sulfoxides, other elegant methods through asymmetric oxidation of prochiral sulfides or by separation of diastereoisomeric sulfoxides have been reported.[19] Nevertheless, the optical purity of the sulfoxides obtained is low in some cases and the absolute configuration at the sulfur center appears to be unpredictable except in few cases.[20]

In order to overcome these problems in the chemistry of chiral sulfoxides we focused on 10-mercaptoisoborneol[21] which has been employed as an Eliel's template.[22] It occurred to us that the diastereoselective oxidation of *exo*-2-hydroxy-



SCHEME 9

10-bornyl sulfides could be effected by the directing effect of the hydroxy function in an appropriate position. Furthermore, the use of these sulfoxides would circumvent the three weak points mentioned earlier. The diastereoselective oxidation of the sulfides **30** and **31** with *m*-CPBA has been reported previously (Scheme 10).[23] Moreover, similar approaches based on camphor-derived sulfides have been employed by other groups.[24]



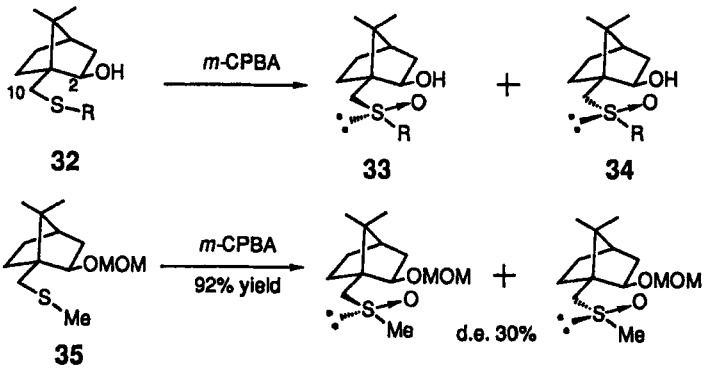
SCHEME 10

4. DIELS-ALDER REACTIONS OF *EXO*-2-HYDROXY-10-BORNYL VINYL SULFOXIDES

4.1. *Diastereoselective Oxidation of* exo-*2-Hydroxy-10-bornyl Sulfides*

The parent sulfides **32** are readily obtained by coupling of 10-mecaptoisoborneol with alkyl halides under basic conditions.[25] The sulfides **32** thus obtained are oxidized with 3-chloroperoxybenzoic acid (*m*-CPBA) under mild conditions to

give the sulfoxides **33** exclusively. The oxidation with *m*-CPBA proceeds with high diastereoselectivity (Scheme 11). In a few cases, the lesser amounts of diastereoisomeric sulfoxides **34** are also obtained in the oxidation.



SCHEME 11

The results are summarized in Table 1. Similar results of diastereoselection in the *m*-CPBA oxidation of some *exo*-2-hydroxybornyl sulfides have been reported by De Lucchi *et al.*, Annunziata *et al.*, T.-K. Yang *et al.*, and Eschler *et al.*[24] The absolute configurations of some sulfoxides thus obtained have been established unequivocally by X-ray analysis; the steric outcome of the oxidation is rationalized by a mechanism in which the secondary hydroxyl group in the bornyl residue would form a hydrogen bond with the carbonyl group in *m*-CPBA and control the stereochemistry of the oxidation.[24a] In the case of the "protected" sulfide **35**, the selectivity of the oxidation is low (d.e. 30%).

TABLE 1 The *m*-CPBA oxidation of the sulfides **32**

32 (R =)	Yield/%	Reaction time/h	Product ratio (**33**:**34**)	d.e./%
Me	95	1	~100:0	~100
Et	95	2	~100:0	~100
*iso*Pr	89	2	~100:0	~100
Allyl	90	1	~100:0	~100
CH_2Ph	91	1	~100:0	~100
CH_2CH_2Ph	68	3	~100:0	~100
CH_2COPh	66	2	57:14	73

It is worth noting that the absolute configuration of the sulfinyl center in the sulfoxide obtained by *m*-CPBA oxidation is predictable. Since the rate of oxidation of sulfides to sulfoxides is generally high, this method would be applicable to the synthesis of chiral sulfoxides with labile groups sensitive to oxidation.

4.2. *Synthesis and Asymmetric Diels-Alder Reactions of α-Sulfinyl Maleate Derivatives*

It is well known that the olefin part in a maleic acid diester is quite reactive toward Diels-Alder dienes.[26] We thought that the application of our synthetic method would make a facile chiral synthesis of α-sulfinylmaleates possible.

It should be emphasized that a high level of stereocontrol in Diels-Alder reactions of vinyl sulfoxides can be achieved only when the additional alkoxycarbonyl substituent is incorporated in the α-position or the (*Z*)-β-position with respect to the sulfinyl group. In the design of a sulfinyl dienophile with two alkoxycarbonyl substituents, the sulfinylmaleate should be preferable to the fumarate congener. That is, the (*Z*)-β-alkoxycarbonyl substituent of the sulfinylfumarate would allow both the s-*cis* and the s-*trans* conformation, whereas the predominant conformer of the sulfinylmaleate would be defined as s-*cis* due to dipole-dipole repulsion (Fig. 3). We thus undertook the synthesis of the sulfinylmaleates.

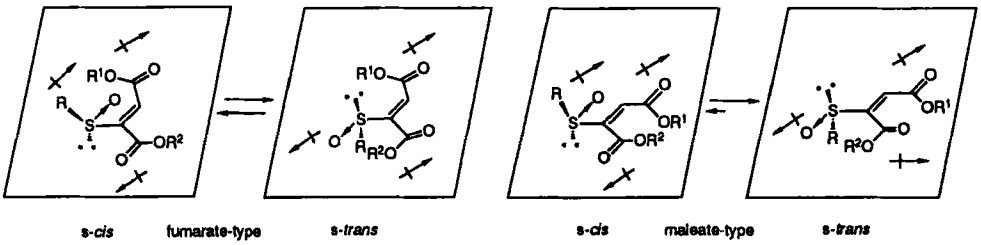
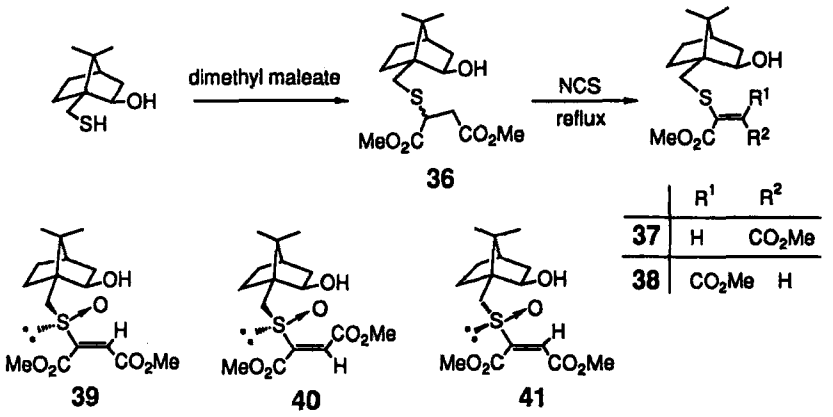


FIG. 3

4.3. *Synthesis of Chiral α-Sulfinyl Maleates*[27]

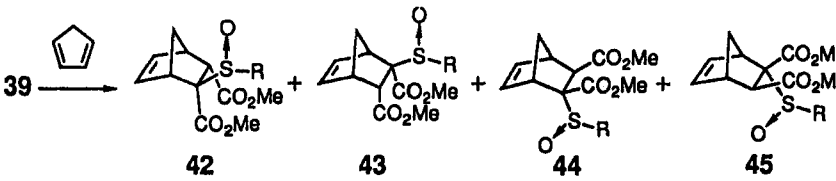
Addition of 10-mercaptoisoborneol to dimethyl maleate gives the sulfide **36** as a diastereoisomeric mixture, which upon heating with *N*-chlorosuccinimide affords the maleate **37** and the fumarate **38** in 35 and 11% yield, respectively (Scheme 12). To optimize the yield of **37**, we sought another route. It was found that the reaction of dimethyl acetylenedicarboxylate with 10-mercaptoisoborneol in the presence of Ph_2PMe produces predominantly **37** (**37**:**38** = 4:1) in 93% yield. These isomers are separable by chromatography. Exposure of **37** to *m*-CPBA affords the sulfinyl maleate **39** as the almost single isomer. Interestingly, the fumarate **38** reacted with *m*-CPBA to give the same product **39** exclusively. The reason for the geometrical isomerization during the oxidation is unclear at present. In both cases, the structure of the minor product (3% yield) was assigned to be **40**, not **41**, from the ^1H NMR spectrum.



SCHEME 12

4.4. *Diels-Alder Reaction of the Sulfoxide 39 with Cyclopentadiene*

Table 2 shows the results of the Diels-Alder reaction of **39** with cyclopentadiene under various conditions. In the presence of a Lewis acid (= chelation-controlled conditions, entries 2–7), the diastereoselectivities (d.e.'s) of the *exo*- and *endo*-sulfinyl adducts are ~100%. In the absence of a Lewis acid the *exo*-sulfinyl adduct **42** is produced predominantly with high diastereoselectivity. Under optimized conditions (entry 4) the stereoselectivity {(**42** + **43**)/(**44** + **45**)} is very high (15.3:1) as is the diastereoselectivity for *endo* addition (**42** vs. **43**).



SCHEME FOR TABLE 2

TABLE 2 Diels-Alder reaction of **39** with cyclopentadiene under various conditions

Entry	Lewis acid	Solvent	Temp./ °C	Product ratio **42:43:44:45**	Yield/%
1	none	CH_2Cl_2	25	11.7:1:0:2.2	87
2	$ZnCl_2$	CH_2Cl_2	0	0:7:1:0	69
3	$ZnCl_2$	toluene	−20	0:8.8:1:0	ND[1]
4	$ZnCl_2$	CH_2Cl_2	−20	0:15.3:1:0	92
5	$ZnCl_2$	CH_2Cl_2	−50	0:8.2:1:0	ND[1]
6	$ZnBr_2$	CH_2Cl_2	−20	0:6.2:1:0	ND[1]
7	Et_2AlCl	CH_2Cl_2	−20	0:3:1:0	ND[1]

[1]ND = not determined

The stereochemistry of the adducts **42–45** was assigned on the basis of the mechanism previously proposed by us (Fig. 4).[28] The structure of the adduct **43** was confirmed by single-crystal X-ray analysis as shown in Fig. 5.

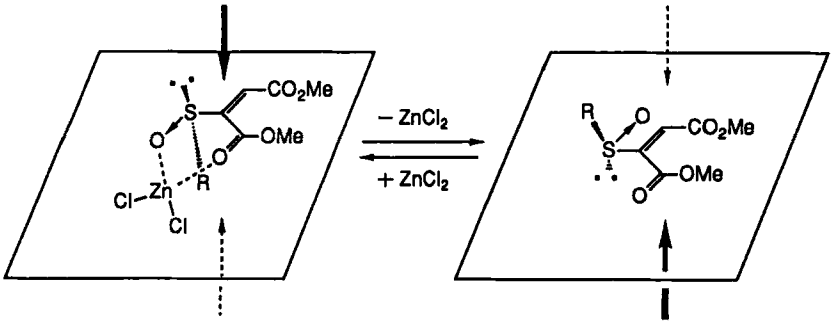


FIG. 4

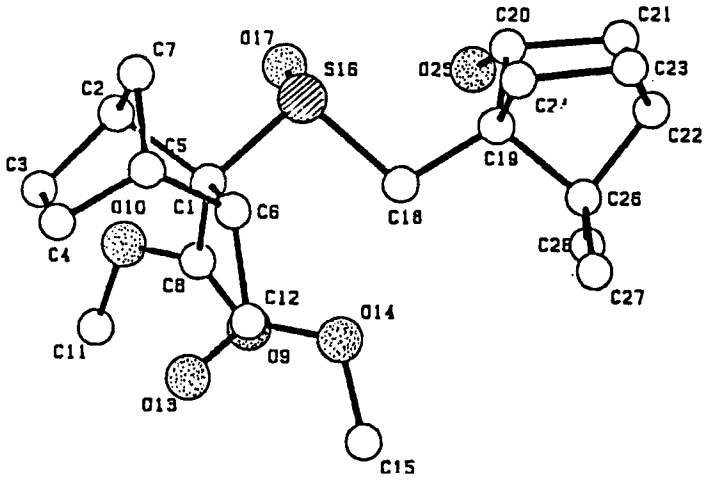
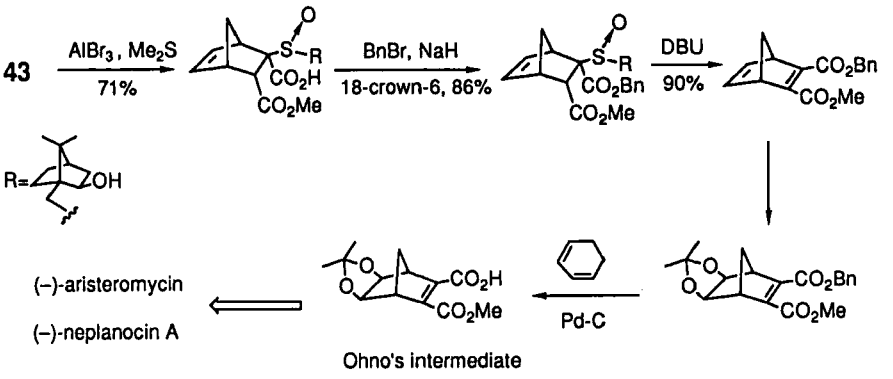


FIG. 5 Molecular structure of the adduct **43**

4.5. *Application to the Enantioselective Synthesis of Natural Products*

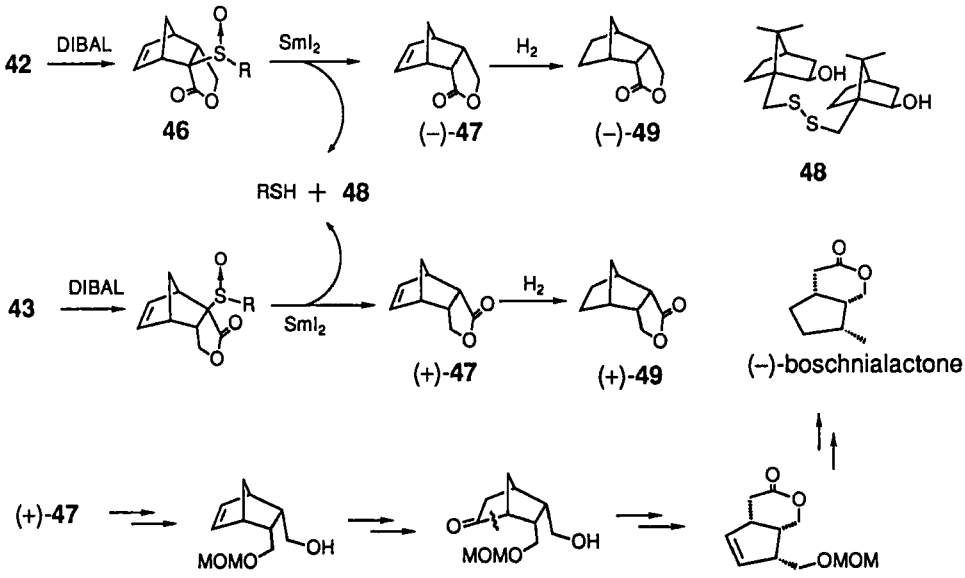
The major Diels-Alder adduct **43** has been converted into the common intermediate of Ohno's synthesis of the carbocyclic nucleosides aristeromycin and neplanocin A (Scheme 13).[29] The reaction sequence in the synthesis involves a selective demethylation of **43** by an $AlBr_3$-Me_2S system.

The adduct **42** is reduced with diisobutylaluminium hydride (DIBAL) to give the lactone **46** in 61% yield (Scheme 14). Attempts to remove the sulfinyl group in **46** with $TiCl_3$ resulted only in recovery of **46**. Deoxygenation with either PBr_3



SCHEME 13

or Zn-AcOH was impractical. Finally, samarium-induced reduction of **46** afforded the lactone (−)-**47** with an efficient recovery of the chiral auxiliary, 10-mercaptoisoborneol, and the disulfide **48**. Without *t*-butyl alcohol as a proton source the sulfide **48** is produced exclusively. In a similar manner, the adduct **43** is transformed into (+)-**47** by these reductions. Hydrogenation of the lactones (+)- and (−)-**47** leads to the saturated lactones (+)- and (−)-**49** one of which have been reported as the key precursor in a synthesis of the natural product.[30] Thus, we achieved an enantiodivergent synthesis of the lactone **47** starting from the dienophile **39**.[31] The lactone (+)-**47** has been transformed into a biologically active terpenoid, (−)-boschnialactone, by us (Scheme 14).[32]



SCHEME 14

4.6. *Synthesis and Diels-Alder Reactions of α-Sulfinyl Maleimide Derivatives*

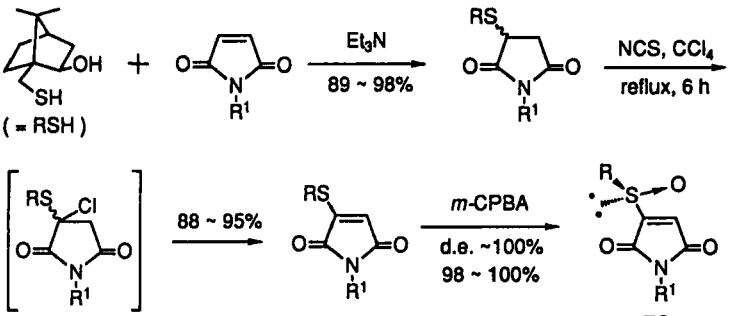
It was found that the dienophile **39** is unreactive toward furan. High-pressure methodology[33] and use of high-pressure effects on cycloadditions in the presence of an inorganic salt[34] could possibly effect the Diels-Alder reaction of **39** with furan.[35] In attempts to carry out the Diels-Alder cycloaddition with furan under conventional conditions, and in a practically useful manner, the use of a sulfinyl maleimide is an obvious choice since the high reactivity[26] of the double bond in maleimides is well known as illustrated in Table 3. In addition, the conformational rigidity of the 5-membered ring and the α-imidocarbonyl group might achieve a high level of stereocontrol.

TABLE 3 Reactivity of dienophiles with cyclopentadiene at 20 °C in dioxane[26]

Dienophile	$10^6 \cdot k_2/[l \cdot mol \cdot sec]$	$\Delta H^{\ddagger}/[kcal \cdot mol]$
N-phenylmaleimide	70500	7.5
maleic anhydride	55600	8.3
N-methylmaleimide	39500	8.6
dimethyl fumarate	742	11.2
dimethyl maleate	6.28	14.1

4.7. *Synthesis of Chiral Maleimide Derivatives*

The chiral α-sulfinyl maleimides **50** can be synthesized in excellent yields from *N*-substituted maleimides and 10-mercaptoisoborneol in a 3-step sequence (Scheme 15).[36] Their oxidation with *m*-CPBA proceeds with high diastereoselectivity (d.e. ≈100%) giving the sulfoxides **50**. Attempts to obtain an *N*-unsubstituted maleimide (**50**, R^1 = H) by the oxidation of the corresponding sulfide were unsuccessful and resulted in polymerization.

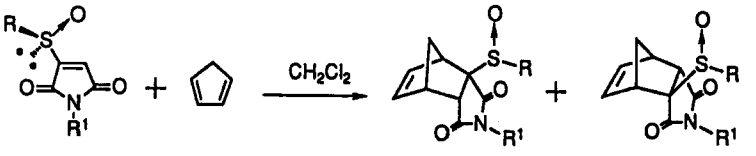


a: R^1 = Me; b: R^1 = Ph; c: R^1 = Bn; d: R^1 = TBDMS;
e: R^1 = *p*-methoxybenzyl; f: R^1 = 3-butynyl

SCHEME 15

4.8. *Diels-Alder Reactions of the Dienophiles* **50**

As anticipated, the maleimides **50** were found to be quite reactive toward Diels-Alder dienes. The results of the Diels-Alder reaction of the *N*-benzyl derivative **50c** with cyclopentadiene at a variety of temperatures are shown in Table 4. In the presence of $ZnCl_2$ the reaction proceeds with high diastereoselectivity (d.s.) to produce the adduct **51c**. In contrast, in the absence of a Lewis acid, the diastereoselectivity is low, and the other adduct **52c** is obtained as the major product. In no case are the *endo*-sulfinyl adducts obtained.



50 **51** **52**

SCHEME FOR TABLE 4

TABLE 4 Diels-Alder reaction of **50c** with cyclopentadiene

	$ZnCl_2$			Without Lewis acid		
Reaction Temp./ °C	Time/ min	Yield/%	d.s. **51c:52c**	Time/ min	Yield/%	d.s. **51c:52c**
40	5	91	94:6	5	~100	31:69
r.t.	20	~100	97:3	60	98	26:74
0	20	~100	97:3	60	97	28:72
−20	20	~100	98:2	60	99	29:71
−78	30	97	97:3	60	~100	36:64

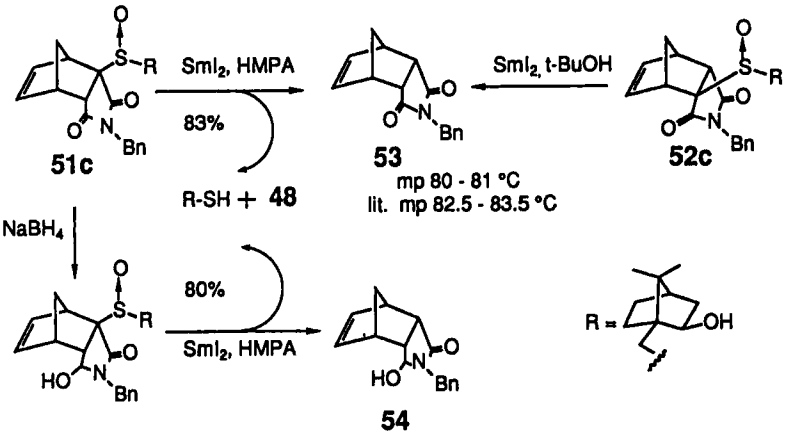
Similar results were observed for the Diels-Alder reaction of the sulfinyl maleimides **50a,b,d** with cyclopentadiene. A couple of examples are shown in Table 5.

TABLE 5 Diels-Alder reaction of **50a,b,d** with cyclopentadiene

Dienophile	Lewis acid	Reaction Temp./°C	Time/h	Product ratio by HPLC	Yield /%
50a	none	0	0.5	**51a:52a** (27:73)	99
50a	$ZnCl_2$	0	0.5	**51a:52a** (94:6)	95
50b	none	0	0.5	**51b:52b** (27:73)	98
50b	$ZnCl_2$	0	0.5	**51b:52b** (90:10)	97
50d	$ZnCl_2$	−80	0.5	**51d:52d** (99:<0.5)	93

The adducts **51c** and **52c** are both transformed to the known *endo*-imidocarbonyl compound **53** by the action of SmI_2, with recovery of the chiral auxiliary

(Scheme 16). The adduct **51c**, whose structure was confirmed by X-ray crystallography (Fig. 6), is likewise transformed to the chiral lactam **54**.



SCHEME 16

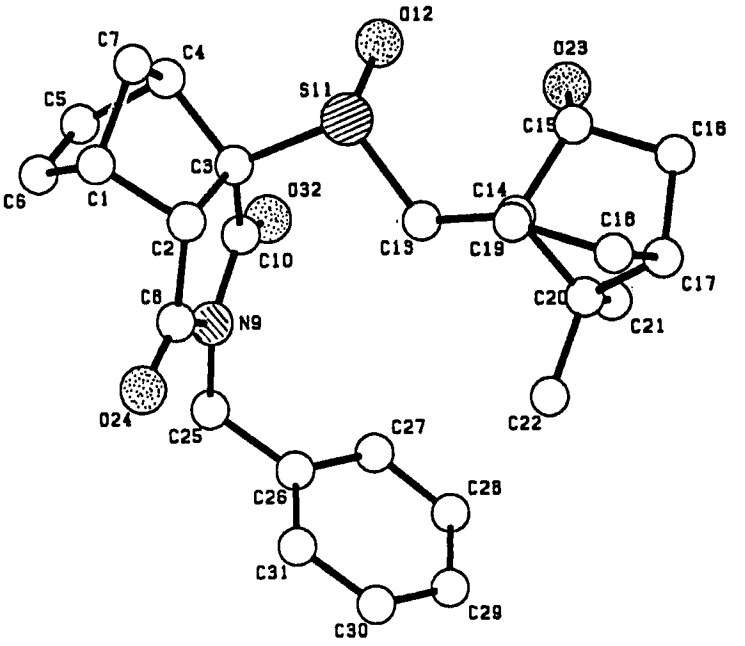
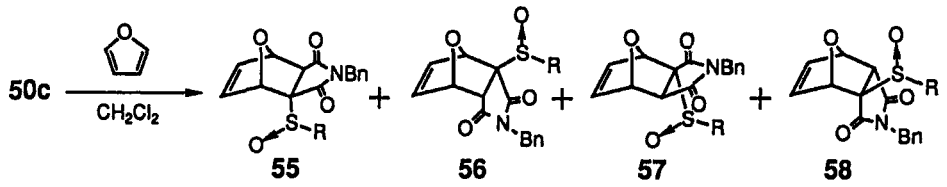


FIG. 6. Molecular Structure of **51c**

The results of the Diels-Alder cycloaddition of **50c** with furan are summarized in Table 6. It was found that the product ratio of the adducts derived from the



SCHEME FOR TABLE 6

TABLE 6 Diels-Alder reaction of **50c** with furan

Entry	Additive (1.5 equiv.)	Temp. /°C	Time/ h	Product (ratio)	Isolated yield/%
1	$ZnCl_2$	−20	62	**55:56:57:58** (49:26:11:15)	60
2	$ZnCl_2$	0	0.5	**55:56** (71:29)	66
3	$ZnCl_2$	0	60	**55:56** (68:32)	72
4	$ZnCl_2$	10	1	**55:56:57:58** (79:9:7:5)	56
5	$ZnCl_2$	10	56	**55:56:57:58** (80:8:4:8)	68
6	$ZnCl_2$	25	20	**55:57** (55:45)	56
7	none	0	24	**55:56:57:58** (29:22:29:20)	56
8	none	25	5	**55:56:57:58** (22:32:24:22)	54

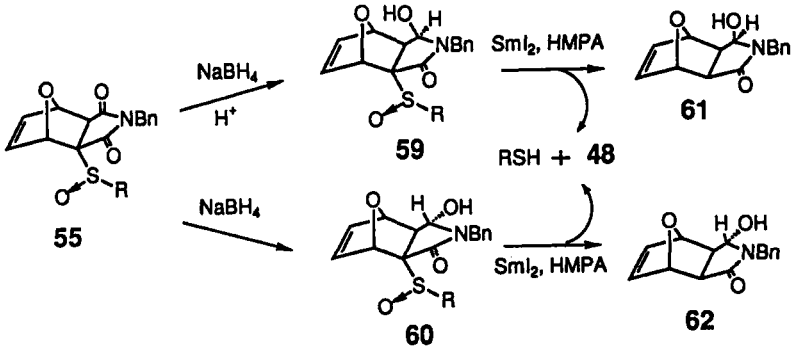
reaction with furan varied depending on the reaction temperature. The reaction conducted at 0 °C (entries 2 and 3) produces a single diastereoisomer each of both the *endo*- and the *exo*-sulfinyl adducts, **55** and **56**. The reaction at room temperature (entry 6) results in exclusive formation of the *endo*-sulfinyl adducts **55** and **57** which reveals that the *exo*-sulfinyl adducts **56** and **58** undergo isomerization to the thermodynamically more stable *endo*-sulfinyl adducts **55** and **57** by dissociation and recombination. It is noteworthy that the reaction conducted at 10 °C (entries 4 and 5) affords the best result with high diastereoselectivity with respect to the *endo*-sulfinyl adducts (**55** vs. **57**) and high exo/endo stereoselectivity {(**55** + **57**) vs. (**56** + **58**)}.

The adduct **55** is converted to **59** by $NaBH_4$ reduction under acidic conditions (Scheme 17). On the other hand, reduction with $NaBH_4$ under basic conditions results in the exclusive formation of **60**. The regioselectivity in the $NaBH_4$ reduction of the imido carbonyl in a rigid tricyclic system such as **55** can be explained by steric factors,[37] in contrast to bicyclic anhydrides and succinimides.[38] The lactams **59** and **60** are desulfinylated with SmI_2 to **61** and **62**, respectively.

It was found that the dienophiles **50** react with butadiene, anthracene, and cyclohexadienes to give the corresponding cycloadducts with high diastereoselectivity.

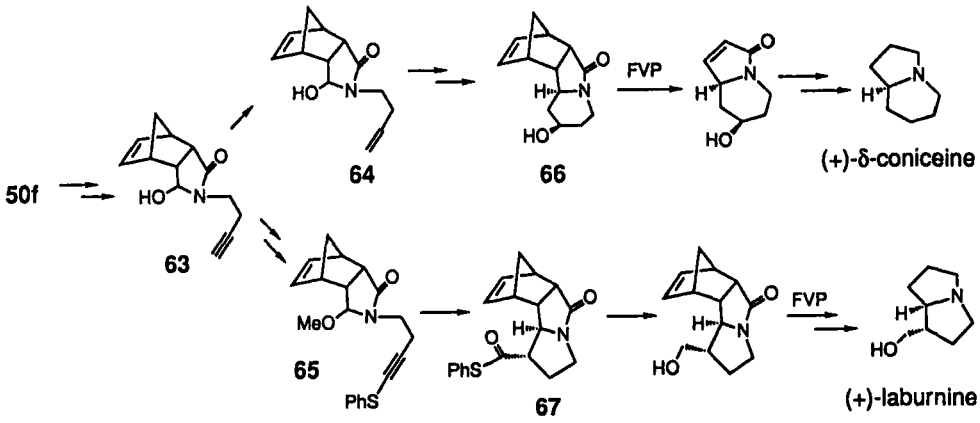
4.9. *Application to Natural Product Synthesis*

The chiral lactams **54**, **61**, and **62** would be useful precursors for the synthesis of nitrogen-containing natural products on the basis of *N*-acyliminocyclization



SCHEME 17

strategy.[39] The application of this methodology has culminated in the enantioselective synthesis of bicyclic alkaloids (Scheme 18). The Diels-Alder reaction of the *N*-butynyl-maleimide **50d** with cyclopentadiene, followed by reduction affords the lactam **63**. The chiral amides **64** and **65**, obtained from **63**, have been further transformed to the tetracyclic amides **66** and **67** by *N*-acyliminocyclization.

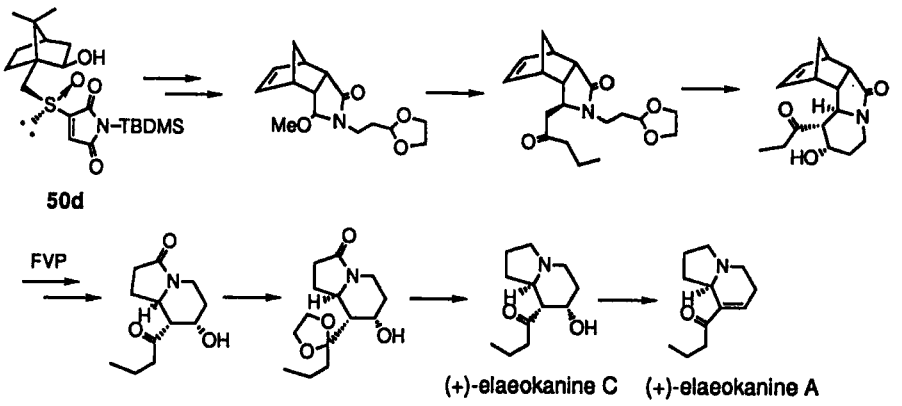


SCHEME 18

Finally, an enantioselective synthesis of (+)-laburnine and (+)-δ-coniceine has been accomplished from **66** and **67** by flash vacuum pyrolysis (FVP).[40]

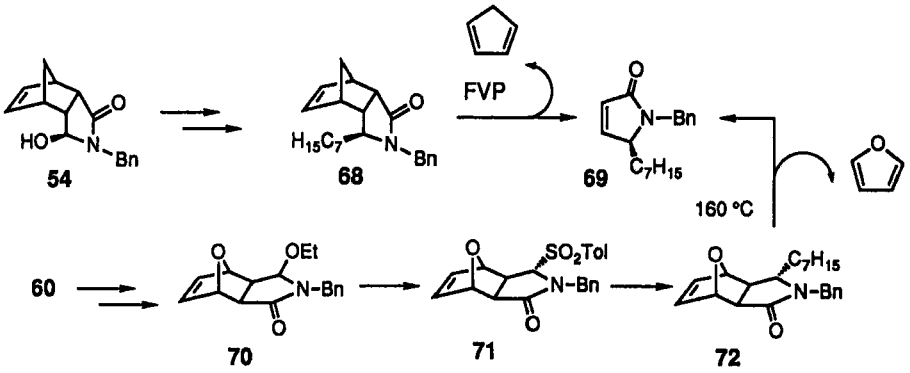
Starting with the adduct **51d** derived from the Lewis acid-promoted Diels-Alder reaction of *N*-TBDMS-maleimide **50d** with cyclopentadiene, we succeeded in the enantioselective synthesis of (+)-elaeokanine A and (+)-elaeokanine C *via* flash vacuum pyrolysis (Scheme 19).[41]

We also attempted the enantioselective synthesis of bicyclic alkaloids on the basis of the strategy involving retro-Diels-Alder cycloreversion by flash vacuum



SCHEME 19

pyrolysis. However, this method was unsuitable for the preparation of chiral monocyclic amides because we observed that the FVP of the tricyclic lactam **68** obtained from **54** led to the pyrrolidinone **69** only with a moderate enantiomeric excess (e.e. 74%). The low e.e. in this reaction must be due to the high reaction temperature (>450 °C) in the FVP. In order to obtain optically pure pyrrolidinones we envisioned the use of the Diels-Alder adduct with furan. As expected, in contrast to Diels-Alder adducts with cyclopentadiene, the use of a Diels-Alder adduct with furan obviated drastic reaction conditions such as FVP in the retro-Diels-Alder cycloreversion. Treatment of **60** with acidic EtOH, followed by desulfinylation (SmI_2), leads to the chiral lactam **70** (Scheme 20).[42] The treatment of **70** with *p*-toluenesulfinic acid in the presence of $CaCl_2$ gives the sulfone **71**.



SCHEME 20

An *N*-acyliminium addition of heptylmagnesium bromide to the sulfone **71** in the presence of $ZnBr_2$ produces the lactam **72** exclusively. The retro-Diels-Alder reaction of **72** by heating in xylene (160 °C, 45 min) proceeds to give **69** of high optical purity (e.e. 93%), which would be a useful precursor for alkaloid

syntheses.[43] The strategy based upon the retro-Diels-Alder reaction of adducts with furan should thus be applied in synthetic approaches to pyrrolidine alkaloids in optically pure form.

5. CONCLUSIONS

We have presented our studies over the past several years of asymmetric Diels-Alder reactions with chiral sulfinyl dienophiles. It has been demonstrated that a high level of stereocontrol in the Diels-Alder reaction can be attained by virtue of the conformational rigidity of a sulfinyl group in the dienophile. It should be emphasized that our conceptual approach to designing efficient dienophiles which combine high asymmetric induction with high reactivity has culminated in the synthesis of two types of novel sulfoxides, the sulfinyl maleates and the sulfinyl maleimides. The methodology of using chiral vinyl sulfoxides will continue to add a useful new features to the usefulness of asymmetric Diels-Alder reactions.

ACKNOWLEDGMENTS

We are indebted to our collaborators, whose names are mentioned in the references. We are thankful to Dr. Motoo Shiro (Shionogi Research Laboratories, now Rigaku Corporation) for his X-ray structure analyses of some sulfoxides.

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35. In a preliminary study, we observed that the Diels-Alder reaction of **39** with furan proceeds to give the *endo*-sulfinyl adduct as a major product under ultrahigh-pressure conditions (10 kbar, 42 °C, CH_2Cl_2, 31 h). The adduct was found to be unstable at ambient temperature, quickly reverting to starting material. We are indebted to Professor H. Kotsuki (Kochi University) for his help in the high-pressure experiment.
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