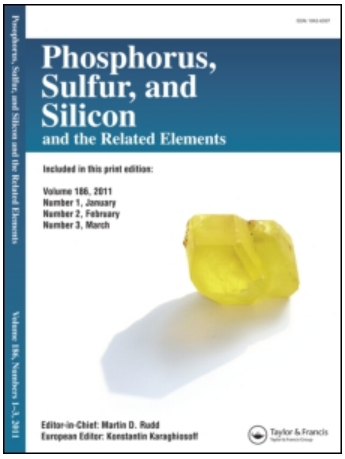

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Sulfinylethenes, Versatile Molecules for the Chiral Synthesis of Bio-Active Compounds

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SULFINYLETHENES, VERSATILE MOLECULES FOR THE CHIRAL SYNTHESIS OF BIO-ACTIVE COMPOUNDS

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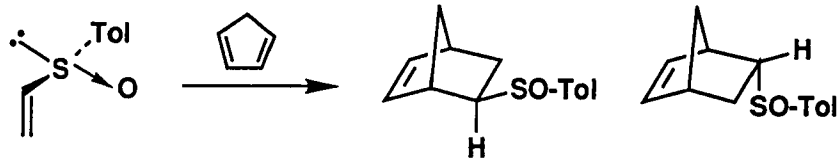
Abstract Molecular design of novel chiral sulfinylethene-type dienphiles which react with low-reactive dienes in highly diastereo- and stereo-selective manner was studied. The application of these dienophiles for the asymmetric synthesis of biologically active compounds was presented.

INTRODUCTION

First of all I would like to review briefly the dienophilic reactivity of some sulfinyl ethenes. p-Tolyl vinyl sulfoxide, the simplest member of sulfinyl ethenes, has been utilized as a good Michael acceptors, but has not been utilized as a dienophile for asymmetric Diels-Alder(D-A) reaction because of its low reactivity. The cycloaddition of p-tolyl vinyl sulfoxide with cyclopentadiene afforded a mixture of four corresponding diastereomers in a ratio shown in SCHEME 1.[1]

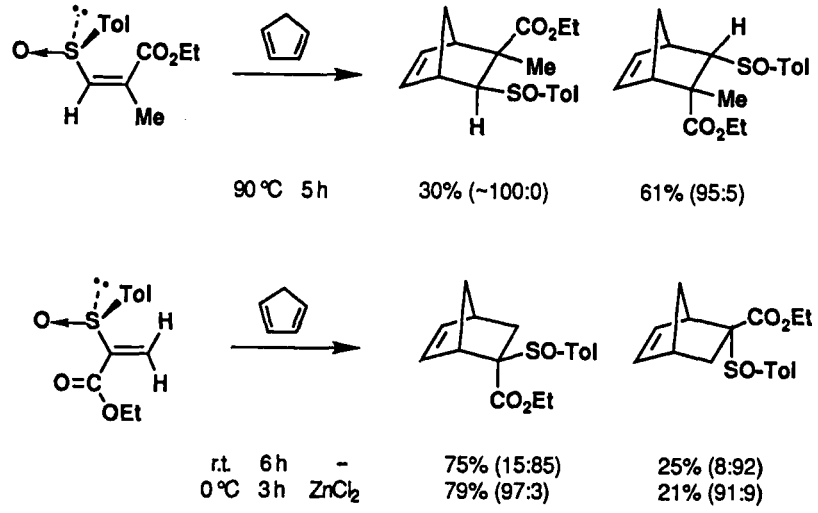


115℃ 15h[a]	36% (28:8)	64% (42:22)
90℃ 19h[b]	28% (22:6)	52% (38:14)

SCHEME 1

The result implies that the vinyl sulfoxide is not reactive enough and does not afford the cycloadducts selectively in terms of stereo- and diastereoselectivity. In this paper, I define the endo/exo products ratio as stereoselectivity, and the ratio of the diastereomers due to the chirality of sulfur as diastereoselectivity.

In order to enhance both reactivity and diastereoselectivity of the vinyl sulfoxides, we considered the introduction of an electron-withdrawing alkoxycarbonyl group at alpha or beta position of vinyl sulfoxides.[2] We expected that the reactivity would be enhanced by increasing the electron deficiency of the double bond and the diastereoselectivity would be improved by controlling the conformational preference due to the dipole-dipole interaction between the sulfinyl function and alkoxycarbonyl function. Our expectation proved to be quite all right as shown in SCHEME 2.

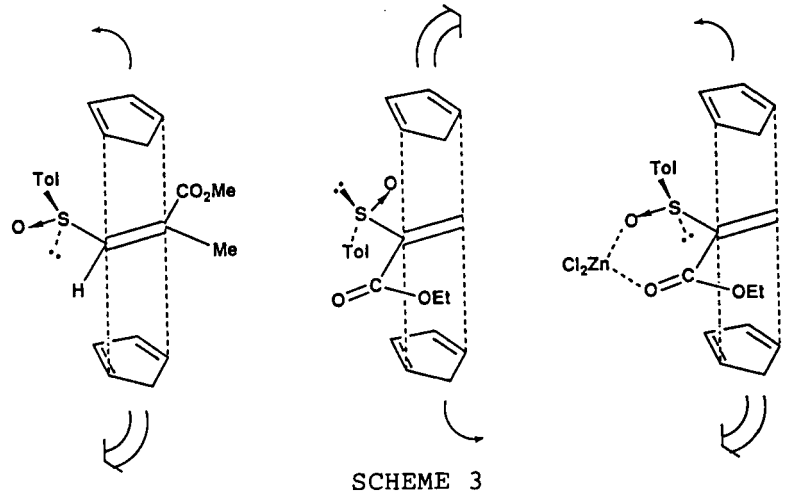


SCHEME 2

Optically active sulfoxides having an ethoxycarbonyl group on beta or alpha position reacted smoothly with 1-2 molar equivalents of cyclopentadiene at low temperature to afford the corresponding cycloadducts in highly diastereoselective manner. The absolute configuration of major diastereomers was determined by the chemical correlation. The results clearly show that the

introduction of ethoxycarbonyl function to alpha or beta position enhanced the reactivity and the selectivity.

Interestingly, in the case of the compound having ethoxycarbonyl group on alpha position,[2b] the major diastereomers obtained were completely different depending on the condition, with or without a Lewis acid catalyst. In the presence of zinc chloride, the major cycloadducts are those two compounds having the absolute configurations depicted in SCHEME 2. On the contrary, without the Lewis acid catalyst, the absolute structures of the major cycloadducts were assigned to be diastereomeric to those shown in the Scheme. The results are reasonably explained in terms of steric factors by the mechanism shown in SCHEME 3. [2,3]



SCHEME 3

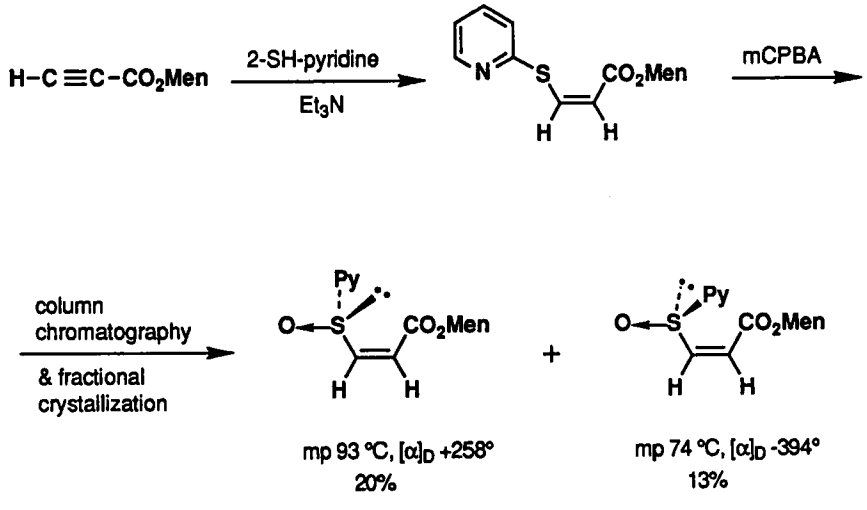
In the case of the dienophile having ethoxycarbonyl function at beta position,[2a-c] the conformation of the dienophile is supposed to be almost in s-trans conformation, probably due to the dipole dipole repulsion between sulfinyl group and carbonyl group. The diene attacks from the less hindered face, namely from the lone pair electron side, to give the endo adduct with the absolute configuration shown in SCHEME 2. In the case of the compound having ethoxycarbonyl function at alpha position,[2b] the most stable conformation is reasonably assigned as s-cis again by the dipole dipole repulsion between the sulfoxide and the carbonyl. The diene approaches from less hindered side to give the corresponding cycloadducts. On the contrary, under the catalytic

condition, the conformation of the dienophile changes to s-trans due to the coordination shown in the SCHEME. The attack of diene from the lone pair side afforded the cycloadducts which are diastereomeric to those obtained in the reaction without Lewis acid catalyst. The results are quite suggestive and useful from the view point of synthetic organic chemistry. It means that one can obtain the cycloadducts having the desired absolute configuration by just controlling the reaction condition, with or without Lewis acid catalyst.

MOLECULAR DESIGN OF NOVEL CHIRAL SULFINYLETHENE-TYPE DIENOPHILES

Optically Active (Pyridylsulfinyl)acrylate

We could devise the good dienophiles by the introduction of carboethoxy group at alpha or beta position of p-tolyl vinyl sulfoxide. Both dienophiles, however, are not reactive enough to various kinds of dienes. For example, the dienophile with alpha-ethoxycarbonyl group does not react with furan. In fact, there have been reported no chiral dienophiles which could react with furan. Then, we turned our attention to the molecular design of a novel dienophile which is highly reactive to give the cycloadducts with low reactive dienes such as furan. Our first approach is to introduce pyridine function in place of p-tolyl

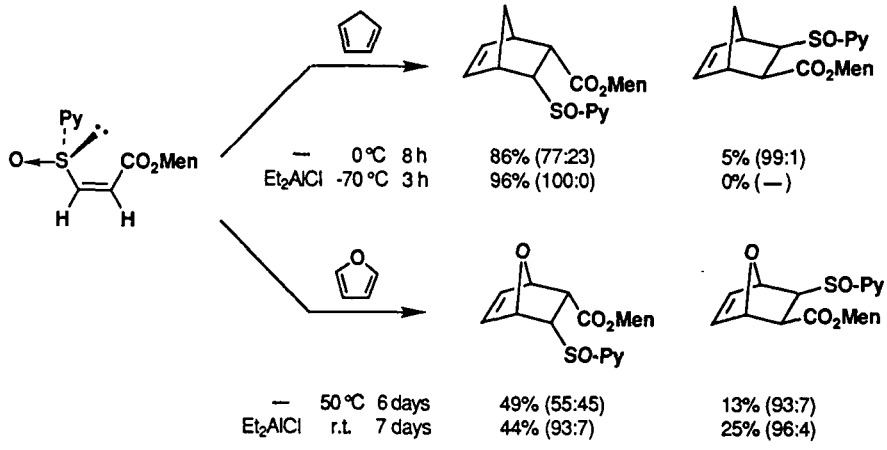


SCHEME 4

group , because pyridine skeleton is well known to be electron withdrawing and we can also expect more electron withdrawing power by using coordination on nitrogen atom.[4]

The objective dienophile, menthyl 2-pyridylsulfinylacrylate, was easily prepared by the reaction sequence shown in SCHEME 4.[4a] The nucleophilic addition of 2-mercaptopyridine to menthyl propiolate in the presence of triethylamine gave the corresponding sulfide with Z configuration. The sulfide was oxidized with mCPBA to give a diastereomeric mixture of sulfoxides both in Z configuration. The optical resolution of sulfoxides was easily accomplished by a combination of column chromatography and fractional crystallization.

The Diels-Alder cycloaddition of the dienophile with S absolute configuration is illustrated in SCHEME 5.

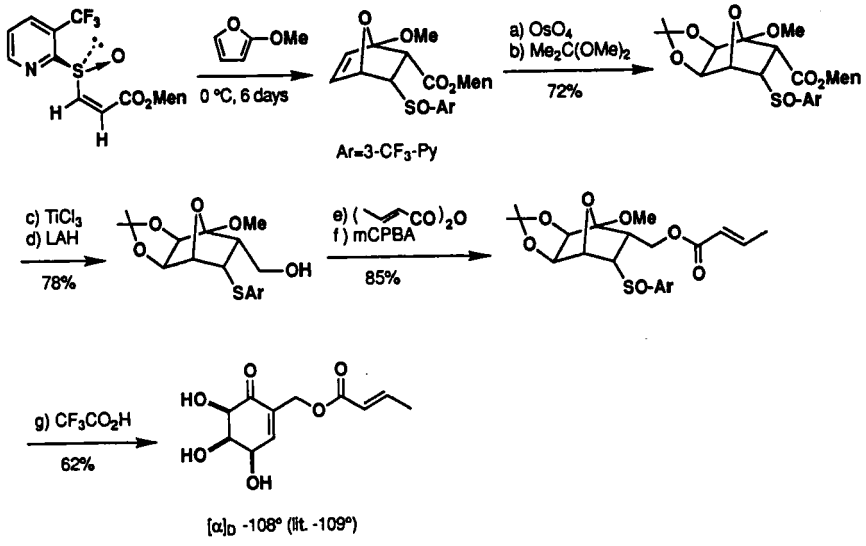


SCHEME 5

The reaction with cyclopentadiene proceeded quite smoothly in the presence of diethylaluminum chloride at -70 °C, to give almost exclusively single endo diastereomer. At 0 °C without the Lewis acid, the selectivity was not so good.

Meanwhile, the cycloaddition with furan did occur without the Lewis acid at 50 °C for 6 days, giving the cycloadducts in low diastereoselectivity. By the addition of the Lewis acid, the cycloaddition took place in highly diastereoselective manner. This is, to the best of our knowledge, the first example of a chiral dienophile which reacts with furan to give optically active cycloadducts.

Having obtained a new chiral dienophile in our hand, we planned to develop the reaction for the preparation of the biologically active and important compounds in optically pure form. Recently we have been successful in the chiral synthesis of glyoxalase I inhibitor.[5] Our approach is shown in SCHEME 6.



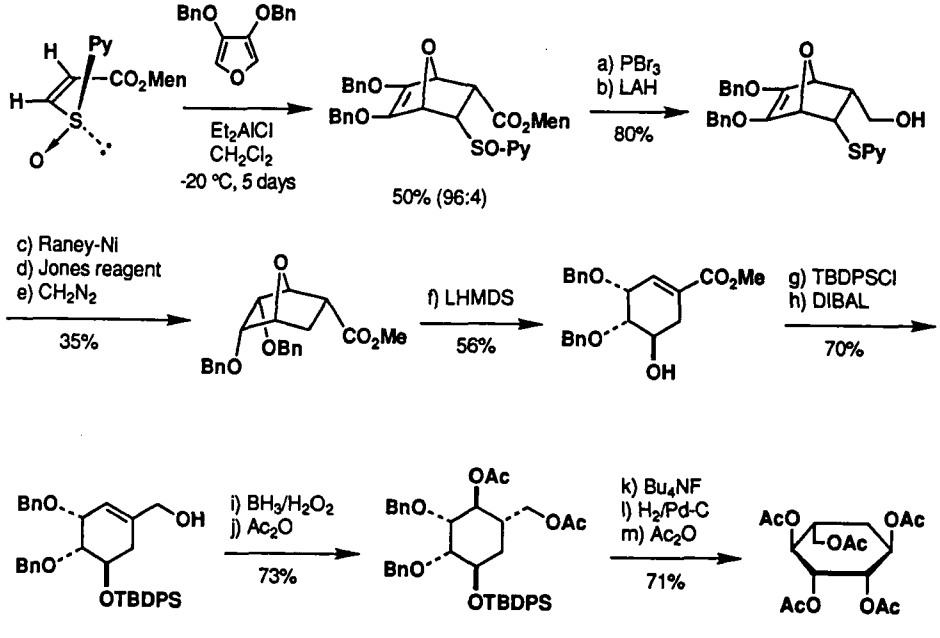
SCHEME 6

Using a chiral dienophile having a trifluoromethyl group at 3-pyridyl position and 2-methoxyfuran, the cycloadduct whose absolute structure is shown in the SCHEME was obtained almost exclusively. The adduct was converted to the objective natural product by the stereoselective introduction of cis diol functionality and the concomitant cleavage of 7-oxabicyclo[2.2.1]heptane ring system and the elimination of the sulfinyl group as key steps.

We are currently investigating the application of the D-A reaction to the chiral synthesis of pseudo-sugars. Pseudo-sugar is a compound in which a ring-oxygen of a pyranoid sugar is replaced by a methylene group.[6] Pseudo-sugar has been expected to be endowed with biological activities because its structure is closely related to that of the parent sugar. The expectation came true when pseudo-α-D-galactopyranose was discovered as a component of natural antibiotic. From these background, much attention has been focussed on the synthesis of enantiomeric pseudo-sugars. Suami and co-workers started their synthesis with

(-)-7-endo-oxabicyclo[2.2.1]hept-5-en-2-carboxylic acid which was obtained by optical resolution of the racemate.[6] Other approaches such as Suami[7] and Kitagawa's[8] relied on the use of natural carbohydrate precursors. There have so far been no report for asymmetric synthesis of pseudo-sugars. We thus designed an access involving asymmetric D-A reaction.

Our approach to the chiral synthesis of pseudo-sugars is based on the strategy using the asymmetric D-A reaction of the pyridylsulfinylacrylate as a key step and using optically active shikimate as a key intermediate.[9] For the stereoselctive introduction of the 3,4-cis diol of shikimic acid to the 7-oxabicyclo[2.2.1]heptene system, we have chosen 3,4-dibenzyloxyfuran as a diene. Because of its bicyclic structure, C=C bond of the cycloadduct is expected to react preferentially onto its exo face, thus ensuring high selectivity. The diol was converted to a shikimate derivative, which was further transformed to pseudo-α-L-mannopyranose derivatives(SCHEME 7).[9c]



SCHEME 7

Preparation of (10-Isoborneolsulfinyl)maleate

As I have mentioned in the first section of this paper, use of pyridyl group in place of p-tolyl group strongly enhances the reactivity of the arylsulfinylacrylate giving the cycloadduct with low reactive diene such as furan. However, there are some drawbacks in this dienophile.

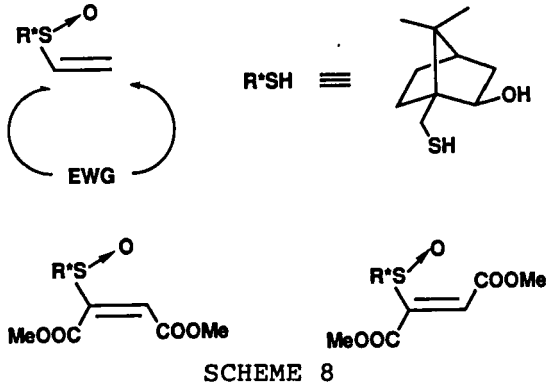
i) Although the dienophile have much higher dienophilic reactivity than the chiral dienophiles so far reported, it took about a week to get the reaction with furan.

ii) Chiral pyridylsulfinylacrylate was obtained by the optical resolution of the corresponding diastereomers, giving two kinds of diastereomers, R and S with respect to sulfur chirality. Furthermore, the chiral auxiliary, pyridylsulfinyl function in this case, is lost during the chemical transformation of the cycloadducts.

iii) D-A reaction of the dienophile did not proceed stereoselectively. In other words, a mixture of exo and endo adducts is obtained from the D-A reaction with furan.

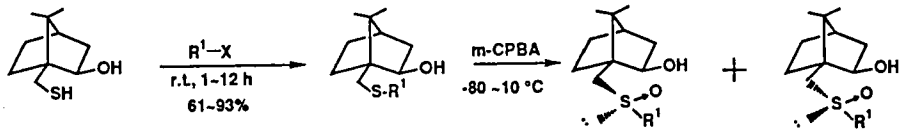
Thus, mostly desired is the development of a novel dienophile which can be prepared as a single diastereomeric sulfoxide , and which reacts with various type of dienes with high stereo- and diastereo-selectivity.

For this purpose we noticed the use of 10-mercaptoisoborneol as a chiral auxiliary because DeLucchi and Modena[10] utilized this thiol effectively for the preparation of some optically active sulfinyl dienophiles. Introduction of this sulfinyl function to fumarate or maleate is expected to afford a new reactive dienophile (SCHEME 8).



SCHEME 8

In order to confirm a generality of using this chiral auxiliary for the preparation of opically active sulfoxides in diastereomerically pure state, we undertook the oxidation of alkyl and vinylic sulfides. As shown in SCHEME 9, the mCPBA oxidation proceeded in a diastereselective manner to give the chiral sulfoxides.[11] The optical purity was approximately 100 % in all cases except the last two cases. The reason for this high selectivity is considered to be due to the hydrogen bonding between the secondary hydroxyl group in the auxiliary and mCPBA.

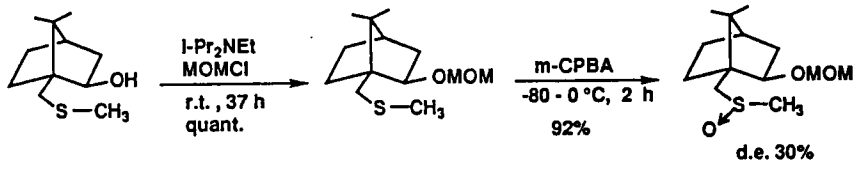


m-CPBA Oxidation of Sulfide

R^1	yield(%)	d.e.(%)	R^1	yield(%)	d.e.(%)
Me	82	~100	CH_2Ph	91	~100
Et	95	~100	CH_2CH_2Ph	68	~100
i-Pr	89	~100	CH_2COMe	76	~100
$CH_2CH{=}CH_2$	90	~100	CH_2COPh	66	73
$CH{=}C{=}CH_2$	74	~100	$CH_2PO(OEt)_2$	71	61

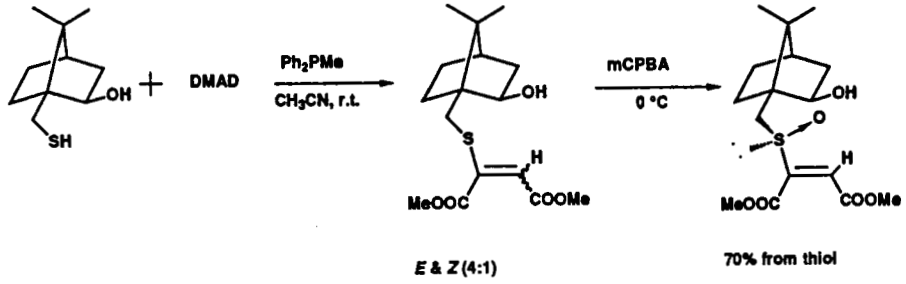
SCHEME 9

The explanation is supported by the experiment using a methyl sulfide in which the secondary hydroxyl group in the chiral auxiliary was protected. The methoxymethylation of the methyl sulfide followed by the mCPBA oxidation afforded 2 to 1 mixture of the corresponding diastereomeric sulfoxides, showing the important role of the secondary hydroxyl function for the observed high diastereoselectivity in the above oxidation(SCHEME 10).



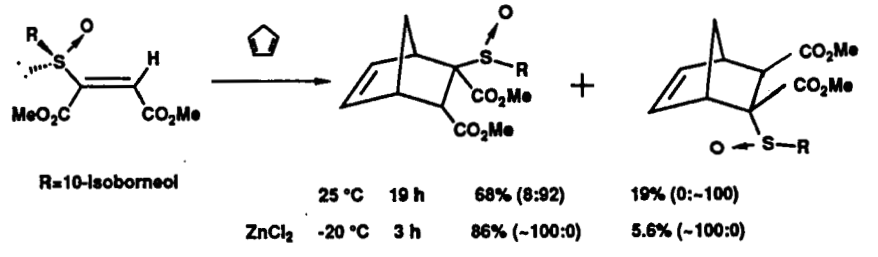
SCHEME 10

Having established that 10-mercaptoisoborneol is a quite useful chiral auxiliary for the exclusive formation of diastereomerically pure sulfinylethenes, we next undertook the preparation of a maleate type dienophile with chiral sulfinyl group on its double bond. The preparation of the chiral dienophile is shown in SCHEME 11.[12]



SCHEME 11

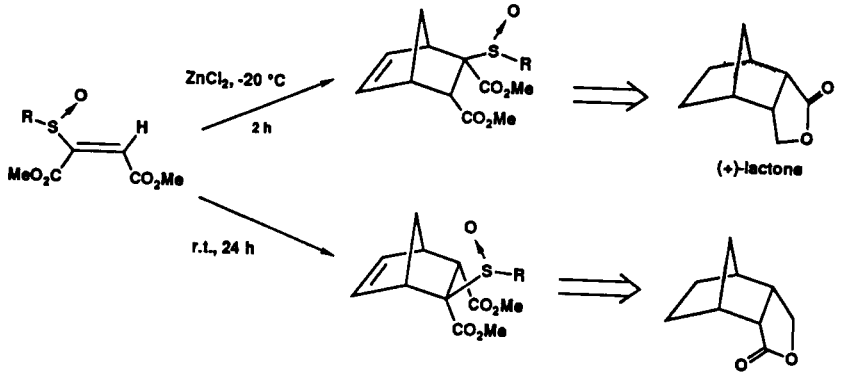
The Michael addition of 10-mercaptoisoboreol to dimethyl acetylenedicarboxylate in the presence of diphenylmethylphosphine afforded a mixture of E and Z stereoisomers in the ratio of 4:1. Fortunately we could use the mixture for the mCPBA oxidation to give almost exclusively a single E-sulfoxide in 70 % overall yield from 10-mercaptoisoborneol. The absolute configuration at sulfur was assigned as R. Thus we could obtain the chiral maleate-type sulfinylethene selectively by using the stereoselective isomerization of Z isomer and also by using the diastereoselective oxidation with mCPBA. The chiral dienophile thus obtained reacted with cyclopentadiene very smoothly and the results are shown in SCHEME 12.



SCHEME 12

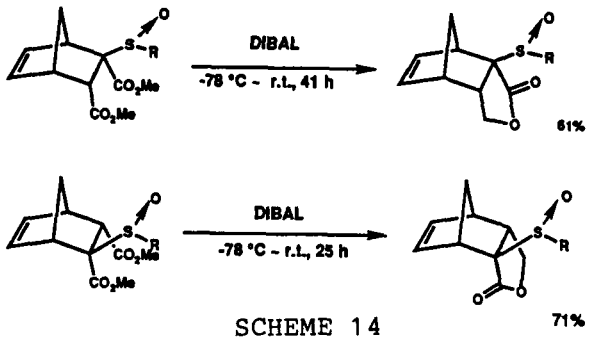
Without Lewis acid, the reaction afforded the exo- and endo-sulfoxides highly diastereoselectively, although the stereoselectivity was not so high. With zinc chloride as a catalyst, the reaction was complete within 3 hrs at -20 °C, to give the adducts diastereo and stereoselectively. A cycloadduct with endo-sulfoxide was obtained only in 5.6 % yield. As is expected, the major diastereomers were completely different depending on the conditions, i.e., in the presence or absence of zinc chloride. The absolute structures of the major exo sulfoxides in both conditions are shown in the SCHEME.

Unfortunately to us, this maleate type chiral dienophile did not have enough reactivity to give cycloadducts with furan. We could utilize, however, the highly stereo- and diastereoselective reaction with cyclopentadiene for the effective and enantiodivergent synthesis of the bicyclo[2.2.1]heptane lactone shown in SCHEME 13.[13] The major cycloadducts with or without zinc chloride as a catalyst could be transformed to the chiral lactones respectively, which are quite useful for the preparation of various chiral biologically important compounds.

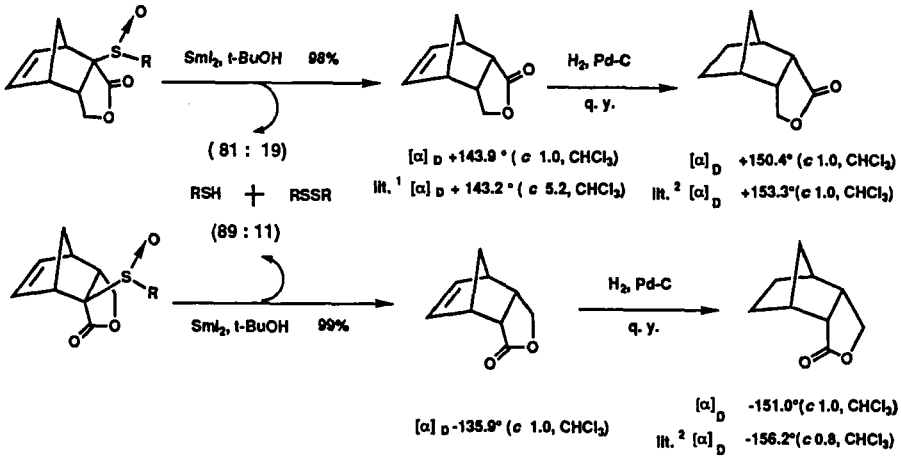


SCHEME 13

The transformation is quite straightforward. The reduction of the cycloadducts with diisobutylaluminum hydride(4 molar equivalents) gave the lactones in fair yield, respectively(Scheme 14). Each of these lactones was treated with samarium iodide to give the desulfurization product quantitatively(SCHEME 15). The bicyclic lactone was hydrogenated to give the dihydro compound.



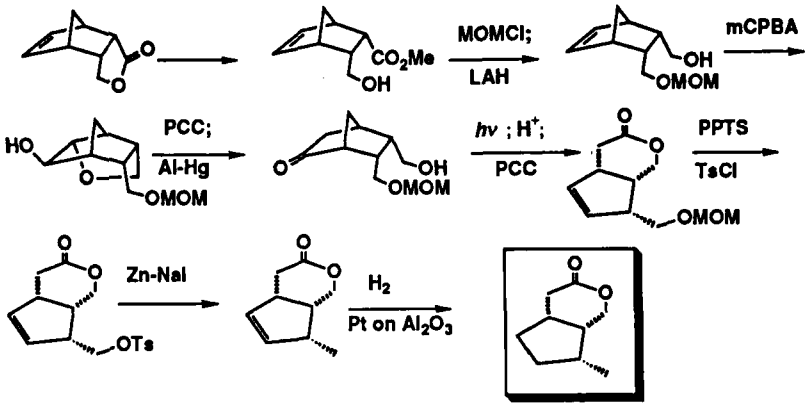
SCHEME 14



[1] J. B. Jones *et al.*, *J. Am. Chem. Soc.*, 1985, 107, 2521.
[2] S. Takano *et al.*, *J. Chem. Soc., Chem. Commun.*, 1987, 1720.

SCHEME 15

Using the unsaturated lactone, we have quite recently achieved the enantioselective synthesis of (-)-boschnialactone(SCHEME 16).[14] Boschnialactone, one of iridoids, was isolated from Boschniakia rossica Hult. Because of its unique biological properties such as cat-attracting effect and insect-repellent, several syntheses of racemic boschnialactone have been reported to date. However, there have been no asymmetric synthesis of this natural product. Saponification of the lactone and the subsequent esterification afforded the ester alcohol, which was protected as the methoxymethyl ether. Careful reduction of the ester yielded the alcohol. Exposure of the alcohol to mCPBA gave



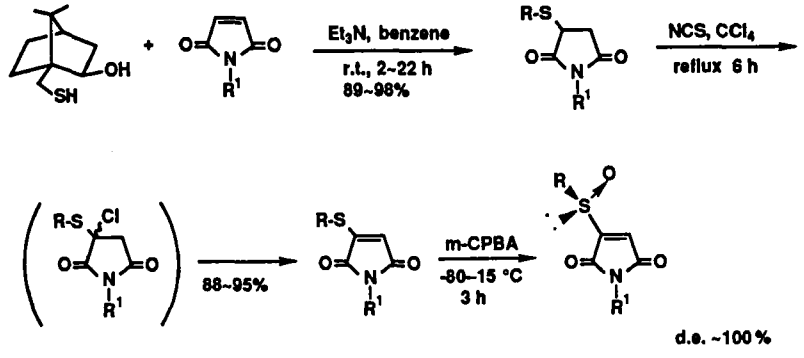
SCHEME 16

the tricyclic ether in 59 % yield. PCC oxidation of the ether followed by reduction with aluminum-amalgam produced the keto alcohol. Photolysis of the ketoalcohol and treatment of a 1:1 mixture of the resulting hemiacetal with PCC gave the lactone in 64 % yield. Removal of the methoxymethyl group, tosylation and reduction afforded dehydroboschnialactone in 80 % yield. Platinum catalyzed hydrogenation furnished (-)-boschnialactone in 85 % yield.

Preparation of chiral (10-isoborneolsulfinyl)maleimides

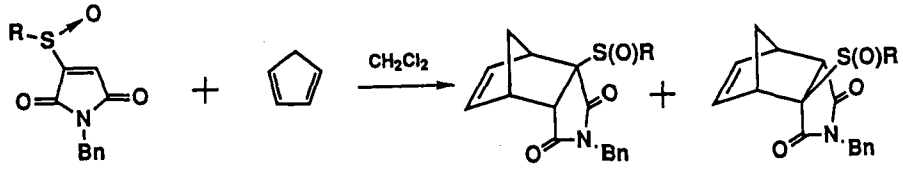
We next undertook the development of a novel dienophile which is more reactive to give the cycloadducts with furan in high diastereoselectivity. According to the literature,[15] the dienophilic reactivity of maleic acid derivatives is known to be in the following order: maleimides and maleic anhydride are much more reactive than dimethyl maleate. Maleic anhydride having chiral sulfinyl group seems to be difficult to handle with. So we focussed our attention to the development of a novel chiral dienophile having chiral sulfinyl group on the double bond of maleimide. For this purpose, again, 10-mercaptoisoborneol seems to be an effective chiral auxiliary, and we designed the following reaction sequences for the preparation of the objective

compounds: an introduction of RS group to maleimide, followed by the diastereoselective oxidation to give a single chiral sulfoxide. The synthetic procedure is shown in SCHEME 17.[16a]



SCHEME 17

Treatment of maleimides with 10-mercaptoisoborneol gave the sulfides, respectively. Chlorination with N-chlorosuccinimide and subsequent elimination of hydrogen chloride afforded the corresponding sulfides. Exposure to mCPBA produced the sulfoxide effectively except in the case of N-unsubstituted simple maleimide. In this case, the oxidation did not yield the corresponding sulfoxide, but caused the decomposition of the starting material. In other cases, the oxidation proceeded with a high degree of diastereoselectivity and the configuration of the sulfinyl center could be assigned as R by the X ray crystallography of the derivative.

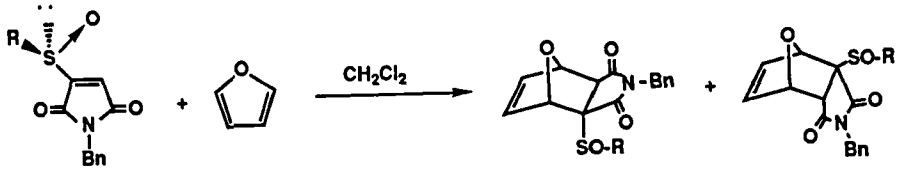


	25 °C	60 min	98% (26:74)
	0 °C	60 min	97% (28:72)
$ZnCl_2$	0 °C	20 min	q.y. (97:3)
	-20 °C	20 min	q.y. (98:2)

SCHEME 18

The D-A reaction of the N-benzylmaleimide with cyclopentadiene proceeded smoothly with high stereoselectivity to give exo-sulfinyl adducts exclusively(SCHEME 18).[16a] Without Lewis acid, the diastereoselectivity was unexpectedly low. However, with zinc chloride as a catalyst, the diatereoselectivity became approximately 100 % irrespective of the reaction temperature. The absolute stereochemistry of the cycloadduct was confirmed by the X ray crystallography.

The reactivity of the dienophile has been enhanced considerably compared to that of the sulfinylmaleate. In fact, the dienophile reacts with furan with or without Lewis acid quite smoothly. The reaction is complete within several hours at room temperature even without Lewis acid catalyst as shown in SCHEME 19.

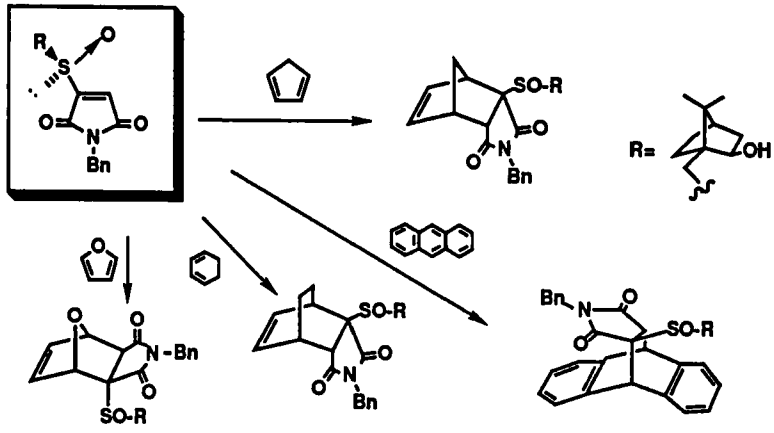


ZnCl2	0 °C	0.5 h	51% (~100:0)	15% (~100:0)
——	25 °C	5 h	25% (49:51)	29% (61:39)

SCHEME 19

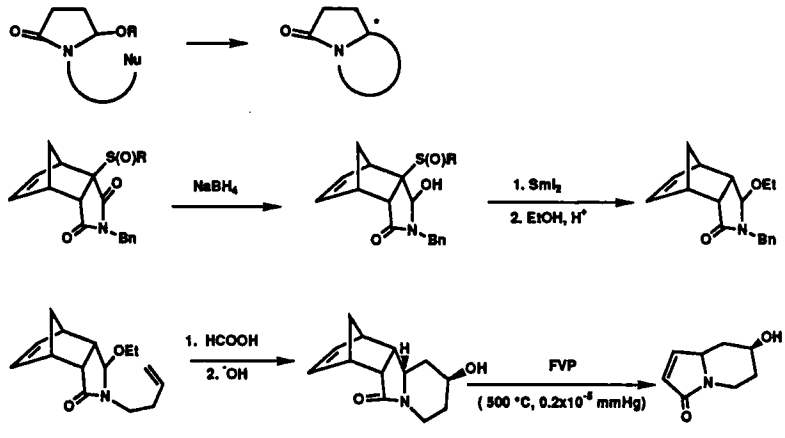
The diastereoselectivity observed was very low. Under the presence of zinc chloride, however, the reaction proceeded much more smoothly (0°C, 0.5 hr), giving the corresponding endo-sulfinyl and exo-sulfinyl adduct in almost 100 % diastereoselectivity. The stereoselectivity for exo sulfinyl to endo sulfinyl was 15:51 under the above conditions.

The dienophile reacts with cyclohexadiene and anthracene respectively to give the corresponding cycloadducts highly selectively in the presence of the Lewis acid catalyst (SCHEME 20). Thus, the sulfinylmaleimide turned out to be a versatile chiral dienophile.



SCHEME 20

In order to demonstrate the synthetic utility of this dienophile, we are currently investigating the preparation of a chiral bicyclic amine, mother skeleton of indolizidine type alkaloid(SCHEME 21).[16b]



SCHEME 21

Although we are in the exploratory stage at the present moment, we have already accomplished the asymmetrization of the cycloadduct using a selective reduction of one of the carbonyl groups with sodium borohydride to get a hemiacetal, which was converted to an aminoacetal after the desulfurization. The alpha-acyliminocyclization of this racemic N-butenyl derivative has been successfully achieved in our group. Thus, the chiral synthesis of the objective indolizidines in an optically pure form will be soon accomplished.

In conclusion, we could design three novel chiral dienophiles, all of which are quite useful in the preparation of synthetic intermediates for the chiral synthesis of biologically active and important compounds.

Finally I would like to express the sincere gratitude to all of my collegues, whose names appeared in the literature for their contribution and devotion to this research and to organic chemistry.

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