REGIO- AND STEREOSELECTIVE REACTIONS PROMOTED BY NEIGHBORING GROUP PARTICIPATION OF SULFUR ATOM

（硫黄原子の隣接基関与を利用した選択的合成）

KAZUAKI KUDO

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by
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PREFACE

The studies presented in this thesis have been carried out under the direction of Associate Professor Kazuhiko Saigo at the University of Tokyo during 1988-1993. The thesis is concerned with the development of novel selective synthesis promoted by neighboring group participation of a sulfenyl group.

The author express his sincere gratitude to Associate Professor Kazuhiko Saigo for his valuable guidance and encouragement throughout the course of his study. The author wishes to thank Professor Emeritus Masaki Hasegawa for giving him an opportunity for the research.

The author is grateful to Mr. Masao Nohara and Dr. Yukihiko Hashimoto for helpful discussions. He also appreciates the collaboration of Mr. Hitoshi Houchigai and Mr. Katsuyuki Saito. Dr. Hiroki Kimoto, Mr. Makoto Sukegawa, and Mr. Kazushi Kimbara are gratefully acknowledged for their assistance in X-ray crystallographic analysis.

The author extends his thanks to the Japan Scholarship Society and Ono Pharmaceutical Co., Ltd. for the scholarship to him.

Finally, the author wishes to express his hearty thanks to his parents for their affectionate encouragement.

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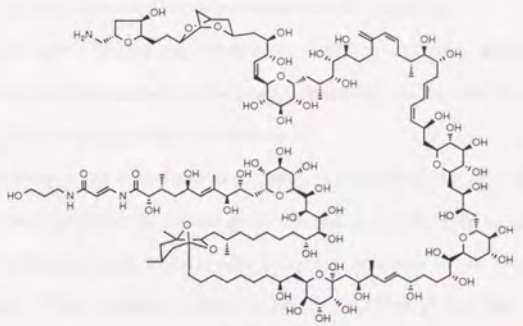
CHAPTER I. GENERAL INTRODUCTION

After Perkin has discovered the first synthetic dye in the middle of the nineteenth century, synthetic organic chemistry, which had been a method only for the identification of natural products until then, has started as an independent field in chemistry. In this century, synthetic organic chemistry has grown explosively and now is playing an important role in the fields of drugs, agricultural chemicals, polymer materials, perfumes, dyes, paints, and so on.

As the organic chemistry is concerned with "organics," the synthesis of natural products has been, and will be, a fascinating theme in organic chemistry. Many natural products exhibit bioactivities, such as a pharmacological activity toward fatal disease for mankind. The researches in biochemical, biological, and medicinal fields, therefore, desire to use such compounds in a large quantity. However, it is difficult to supply them continuously from organisms, because they can be merely obtained in a very small quantity from each of individuals. As a result, synthesis becomes promising to offer such compounds.

The total synthesis of complex natural compounds has been widely explored in the middle of this century mainly with the aid of Woodward's genius. Thereafter, more and more complex compounds were targeted in synthetic organic chemistry with the assistance of the invention of new separation techniques, chromatography, and such analytical methods as nuclear magnetic resonance, mass spectrometry, and X-ray structural determination. Nowadays, highly complex molecules such as palytoxin could be synthesized by the wisdom of mankind at the highest level.[1]



palytoxin

However complex the structure of the target compound is, the synthesis of the target is achieved by the accumulation of simple synthetic reactions. Nevertheless, in almost every case, the total yield of the target is not satisfactory. The reason is clear; the total yield is the mathematical product of the yields of all the steps, and the yield of a reaction is not always 100%. Therefore, it is the mission for synthetic organic chemists to develop an efficient reaction which can be used as a reliable tool in the synthesis of highly complicated molecules.

1. Selectivity in Organic Synthesis

Generally, the development of such a "useful" reaction is accomplished through two steps; 1) the discovery of a novel reaction and 2) the improvement in the selectivity of the reaction.

The discovery of a novel reaction is quite significant because it brings a new concept to synthetic organic chemistry. Such reactions are investigated vigorously in the border of organic and inorganic chemistry; the metal-mediated direct activation of C-C or C-H bond is noteworthy. Also tried is computational methodology for the discovery of new concerted reaction.[2]

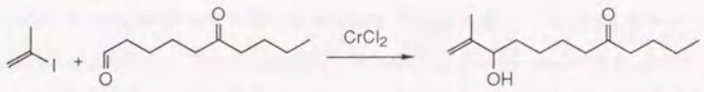
It is rather rare that the reaction found as mentioned above is a "useful" reaction as it is. Improvement of the reaction is needed. The improvement in selectivity of the reaction does not mean a minor-change, but is a truly necessary step.

In a broad sense, the improvement of the yield of a certain reaction is to make the reaction selective. That is to say, the improvement of the yield is achieved when a desired reaction occurs *selectively* compared to other undesired side-reactions.

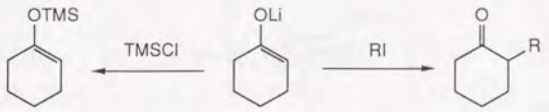
However, the word "selectivity" is usually used for an ability selecting one product among two (or more) possible isomers. Generally, selectivity is divided into three categories; chemoselectivity, regioselectivity, and stereoselectivity.

Chemoselectivity is used for functional group selectivity in the case that the reaction is possible to occur at two (or more) functional groups in one molecule. One elegant example is the Cr(II)-mediated/Ni(II)-catalyzed Barbier-like coupling reaction of an alkenyl iodide with carbonyl compounds.[3] The coupling reaction is selective for formyl function, and consequently keto and alkoxycarbonyl moieties of the substrate remains intact throughout the reaction. The

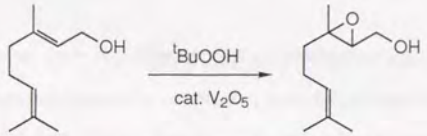
efficiency of this reaction was extensively proved in the total synthesis of many complex natural compounds including palytoxin.[4]



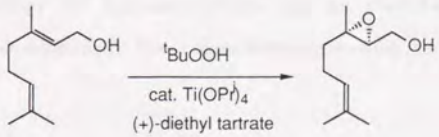
Regioselectivity means a differentiating ability in the reaction point when a certain reaction can occur at two (or more) sites. The reaction of the lithium enolate of a ketone is a case. The enolate anion is a bidentate nucleophile and selectively reacts at the carbon when an alkyl iodide was used. On the other hand, the reaction with a trimethylsilyl chloride gives only *O*-silylated product.



The difference between chemoselectivity and regioselectivity is not strict. For example, the selective epoxidation of geraniol by *tert*-butyl hydroperoxide in the presence of a catalytic amount of vanadium(V) oxide can be expressed as both chemoselective and regioselective reaction.[5]

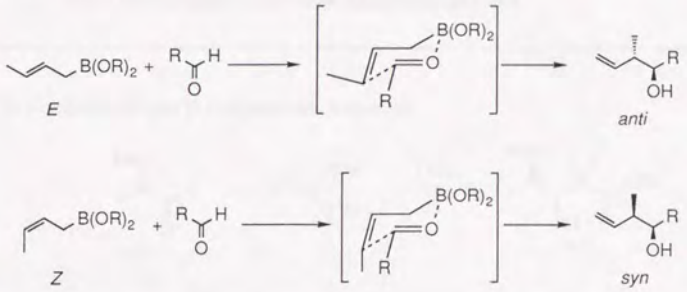


The most important selectivity is stereoselectivity, which means selectivity for isomers when a reaction generates two (or more) stereoisomers. The stereoisomer can be a diastereomer, enantiomer, or *E*/*Z*-isomer. Although examples for this selectivity are too numerous to mention, the stereoselective (enantioselective) version of the above epoxydation can be illustrated.[6] This reaction is also highly reliable, and is used widely in natural products synthesis.

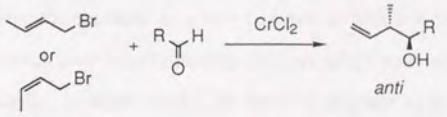


In relation to the stereoselectivity, there is the term of "stereospecificity." The author uses these terms in a sense defined by Zimmerman[7] throughout this thesis: "Stereospecific" means that stereoisomerically different starting materials give rise to the stereoisomerically corresponding products. "Stereoselective," in contrast, simply means that, of two (or more) possible stereoisomeric products in a reaction, one is produced in predominance over all the others. According to the above definition, all stereospecific reactions are necessarily stereoselective, but the converse is not true.

An example of the stereospecific reaction is shown below.[8] The reaction is kinetically-controlled.



On the other hand, there is another type of stereoselective reaction starting from either of stereoisomers; the same stereoisomer is obtained as a product irrespective of the stereochemistry of the starting material. This type of reaction is called "stereoconvergent reaction."[9] The crotylation using Cr(II) and crotyl halide, which is thermodynamically-controlled, is a case.[10]



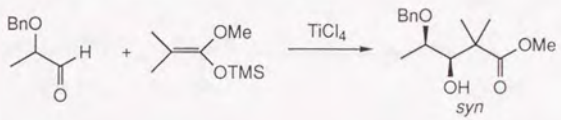
The terminology of stereoselectivity can be classified as shown below (diastereoselectivity is exemplified). Every diastereomer-generating reaction belongs to either A, B, C, or D.

Classification of the reaction which generates stereoisomers

- non-stereoselective reaction (A)
- stereoselective reaction
  - n(reactant) < n(product) (B)
    (no terminology is given for this category)
  - n(reactant) = n(product)
    - stereospecific reaction (C)
    - stereoconvergent reaction (D)

n(x): the number of possible diastereomers of x

The example of type B is asymmetric induction.

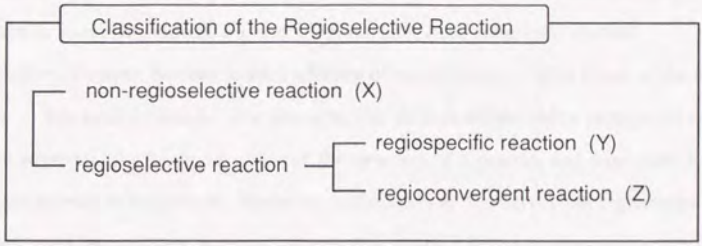


If one of the diastereomers produced is a target compound, the reaction of type B or D could be employed without any problem. Whereas, if we use a reaction type C, we have to *selectively* prepare an appropriate diastereomer for the reactant. In the case that only type A reaction can be applied, troublesome separation step would be required and the yield never exceeds 50%.

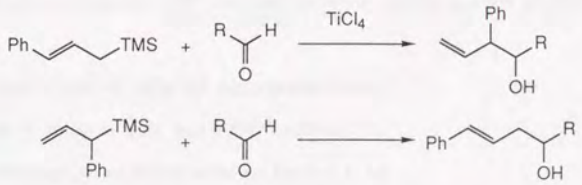
In order to achieve the synthesis of a very complex molecule which has m stereogenic centers (m = 71 for palytoxin), we must synthesize only one of 2^m possible stereoisomers ($2^{71} \approx 2.4 \times 10^{21}$ for palytoxin!). In other words, we have to generate m information about the stereochemistry during the synthesis. In a type B reaction, the generation of the information does occur, whereas it does not in a type D reaction.

Taking into account the above facts, the categories appeared here can be lined up according to the significance in organic synthesis, in the order B > D > C > A.

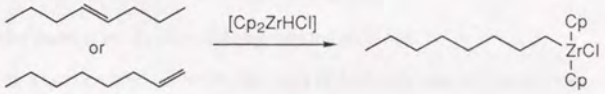
Regioselective reaction is devided into several types as well. However, the types Y and Z can not be easily ranked in order of significance, because the regioisomerically pure compounds are generally more readily available compared to the stereoisomerically pure ones.



Type Y:



Type Z:



Selectivity is a word which can be also used for quantitative meaning; when a certain reaction preferentially gives isomer P1 of two possible isomers P1 and P2, the value

$$S = \frac{\mathrm{P1}}{\mathrm{P1+P2}} \times 100\ (\%)$$

represents the degree of selectivity. In the above discussion, the selectivity was postulated perfect (S = 100), although there are not so many reactions in which S is 100. It is well known that the S values of biochemical processes are always near 100. However, a major drawback of such processes as synthetic reactions is that they are highly substrate-dependent. Therefore, one of the aim of the synthetic organic chemistry today is to find a selective and universal reaction.

2. Sulfur in Organic Chemistry

In order to achieve selectivity in a reaction, hetero-atom-assisted methods have been investigated since 1950's. Including excellent reactions developed by the Nobel-prize-winners, Wittig and Brown for phosphorous and boron, respectively, reactions utilizing many hetero-atoms such as aluminum, silicon, tin, and selenium, have been intensively studied.

Sulfur, of course, belongs to such a family of hetero-atoms. Sulfur is one of the essential elements in bioorganic system. For example, the thiol-disulfide redox process of cysteine-cystine is important for the preservation of the structure of a protein, and coenzyme A plays a very important role in bioprocess. Moreover, sulfanylamide derivatives and cephalosporin-class antibiotics have been widely accepted as effective drugs. Sulfur is also used in the field of materials. Organic conductor TTF and heat-resisting polymers such as PPS and PES are representative.

The characteristics of sulfur are summarized below.

1) The lone pair on sulfur is "soft" and highly nucleophilic.

2) Sulfur can have various oxidation numbers from -2 to +6.

3) Sulfur functions to stabilize both α-anion and α-cation.

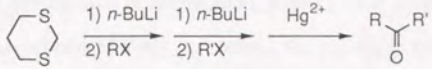
4) Carbon-sulfur bond is easily cleavable by various methods.

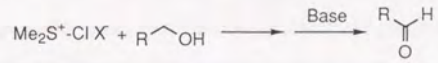
5) Sulfur can be a stable chiral center in the cases of sulfoxide and sulfonium ion.

6) Sulfur-sulfur bond is stable compared to oxygen-oxygen bond.

Sulfur has drawn the attention of synthetic organic chemists; sulfur-mediated reactions are performed in a key step of the total synthesis of natural products such as vitamin B_{12},[11] rifamycin S,[12] and methynolide.[13]

Sulfur-containing reagents have been also developed extensively. Dithiane is an "umpoled synthon"[14] of carbonyl group.[15] Oxidation of alcohols using chlorodimethylsulfonium and related sulfonium salts is one of the most reliable method.[16] Additionally, carbonyl olefination using sulfones is *trans*-selective alternative for Wittig reaction.[17]

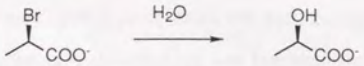




Although there are many other methods using sulfur in organic synthesis, the greater part of them is based on the α-anion stabilizing ability of a sulfur functional group. The application of sulfur in cationic chemistry still wants to be uncovered. The neighboring group participation of a sulfenyl group is one of the unique phenomenon in cationic chemistry of sulfur.

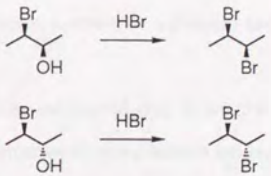
3. Neighboring Group Participation

Neighboring group participation was first observed in the hydrolysis of α-bromopropionic acid by Cowdrey and co-workers in 1930's, where the reaction preceeded with the retention of the configuration around the reaction center.[18]



>90% retention of configuration

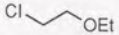
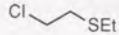
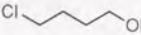
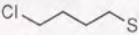
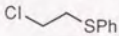
The stereochemical study concerning neighboring group participation was explored by Winstein's group. The stereospecific reaction of 3-bromo-2-butanol is a very famous example.[19] The presence of a "bridged" bromonium ion intermediate was proved by the reaction of chiral bromohydrin.[20]



Then, the participation of chloro, iodo, acetoxyl, and methoxyl groups was successively found by the stereochemical study concerning the solvolytic reactions. The acetoxyl group participates in a rather different manner, namely, *via* a five-membered 1,3-dioxolanilium ion.[21]

The neighboring group participation of a sulfenyl group was first found by Böhme and co-workers for the acceleration of the hydrolysis of alkyl chlorides.[22]

Table I-1. First Order Rate Constants for the Hydrolysis of Several Alkyl Chlorides in Water-Dioxane at 100°C.[22]

Substrate	$k \times 10^{-5}/s^{-1}$	Substrate	$k \times 10^{-5}/s^{-1}$
	6.2		4.8
	1.1		6.3
	17000		5.2
	0.56		110
	550		

According to their study, the participation of a β- or δ-sulfenyl group is distinct, and that of γ-sulfenyl group is almost negligible. No acceleration is observed in the reactions of sulfinyl- or sulfonyl-analogs. Although the reaction of a δ-sulfenylalkyl chloride has to be correctly expressed as a "remoted" group participated reaction, the acceleration of the reaction is easily explicable by considering a thiolanylium ion intermediate like the case of acetoxyl group participation. It is well known that an intramolecular substitution reaction proceeds smoothly when a three- or five-membered ring can be generated under kinetically controlled conditions.

The reasons for outstanding acceleration of solvolysis by a β-sulfenyl group, but not by a β-alkoxyl group, might be following:[23]

1) 3*p* orbital is diffuse compared to 2*p* orbital, hence the attack toward the β-cation easily occurs.

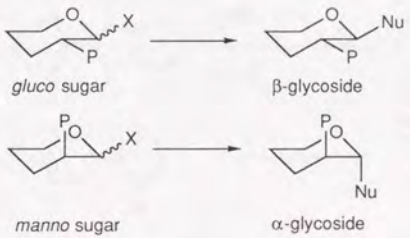
2) Sulfur of sulfide function is resistant to solvation such as hydrogen bonding compared to oxygen in ether function.

3) The strain energy of three-membered ring is smaller for thiirane than for oxirane by 3.0 kcal/mol. Therefore, the formation of episulfonium ion is considered to occur easily.

4) Since the electronegativity of sulfur is smaller than that of oxygen, electron-withdrawing inductive effect, which works as cation destabilizing effect, is weaker for sulfide.

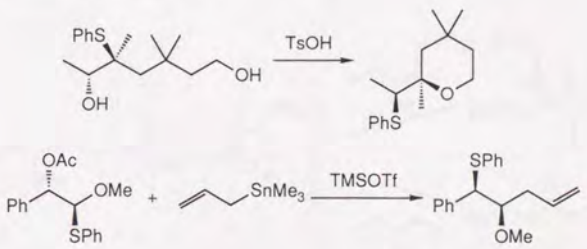
As to other chalcogen group element, β-selenenyl group is known to participate toward the cationic center. However, kinetic data for solvolytic reaction are not available because the elimination of selenenium ion from an intermediate seleniranium ion competes the solvolytic displacement.

The application of neighboring group participation was first carried out in the field of sugar chemistry. The 1,2-*trans* glycosidation of a 2-acyl sugar is often employed as a promising method.[24] 2-Halo-,[25] 2-thio-,[26] 2-seleno-,[27] or 2-*N*-formylamino-[28] derivatives of 2-deoxysugars undergo glycosidation in a similar manner.



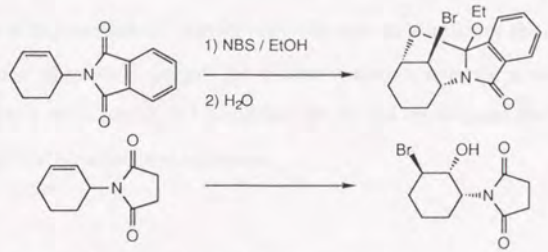
There are several reports on the selective synthesis using neighboring group participation of a β-sulfenyl group.[29-35] The common strategy for the reactions is the nucleophillic displacement of a leaving group with the retention of the configuration. Although the reactions themselves are synthetically interesting, the pattern of the reactions is essentially identical with Weinstein's pioneering work on bromohydrin.

Recently, Warren's group[36-39] and Otera's group[40] independently reported the sulfenyl-group-migrating version of the above reaction. The migration phenomenon is closely related to the Wagner-Meerwein rearrangement.

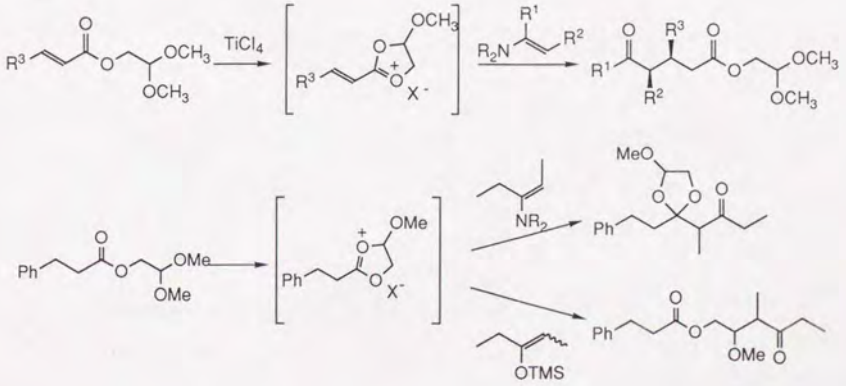


Almost every application for the selective synthesis mentioned above is classified to the category of *stereospecific* reaction. Therefore, in order to extend the synthetic field based on neighboring group participation, it is desired to find a novel selective reaction other than stereospecific reaction.

Concerning this matter, an interesting *regioselective* reaction of *N*-2-cyclohexenyl imides was reported by Sammes and co-workers; upon treatment with NBS in ethanol, followed by aqueous work-up, phthalimide gives a 2-bromo adduct whereas succinimide gives a 3-bromo adduct.[41]



Recently, the C-C bond forming reaction of 2,2-dimethoxyethyl ester, which is a simplified acyclic analog of 2-acyl sugars, has been intensively studied in our laboratory. The study reveals that the esters of α,β-unsaturated acids react with enamines in a *stereoselective* manner to give *syn* isomers,[42] whereas the esters of saturated or aromatic acids *regioselectively* react at different position of an intermediate 1,3-dioxolanylium ion depending on the kind of nucleophiles.[43,44]



4. The Object of This Thesis

As mentioned in the previous section, it was proved that the neighboring group participation could be successfully applied to the selective synthesis. However, there are only these three examples for such kind of selective synthesis.

It is known that the neighboring group participation of an acyloxy group retards a substitution reaction whereas that of a β-iodo, β-/δ-sulfenyl, or δ-methoxyl group accelerates the reaction. Then, the reaction assisted by the latter groups is considered to be worth investigating from the viewpoint of the selectivity; β-sulfenyl group might be a promising candidate because of the facility of the synthesis of starting materials and the stability of the compound. In this thesis, the author intended to explore the hitherto unknown selective synthesis based on the neighboring group participation of a β-sulfenyl group, and investigated the reaction of several vicinally oxygen-sulfur substituted substrates.

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CHAPTER II. REGIOSELECTIVE PINACOL REARRANGEMENT OF SULFENYLMETHYLATED GLYCOLS

Summary: Pinacol rearrangement of glycols having a sulfenylmethyl group smoothly proceeded with high regioselectivity to give ketones which were derived by the elimination of the β hydroxyl group to the sulfur atom. This selectivity is due to the neighboring group participation of the sulfenyl group.

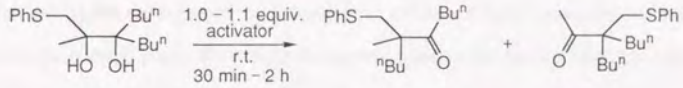
1. Introduction

Pinacol rearrangement of tetrasubstituted glycols offers a unique way to make α-trisubstituted ketones including spiro systems.[1] However, with unsymmetrically tetraalkyl-substituted glycols, this rearrangement has a disadvantage that a mixture of isomeric products was produced due to non-selective nature about the elimination of the hydroxyl groups.[2] Concerning this matter, Nybergh reported a regioselective pinacol rearrangement of 3-ethyl-2-methyl-2,3-pentanediol (Et migration/Me migration = 20/1).[3] The observed selectivity owes both to the cation-stabilizing ability of methyl group by hyperconjugation and to greater migratory aptitude of ethyl group; the direction of the rearrangement is substrate-dependent and the Me-migrated isomer can not be obtained selectively. Therefore, a more general regioselective pinacol rearrangement is wanted to be discovered.

Considering the acceleration of hydrolysis by a β-sulfenyl group but not by a γ-sulfenyl group as mentioned in Chapter I, the author intended to apply the difference of the rate of hydrolysis to a regiocontrolled pinacol rearrangement, and designed a sulfenylmethylated glycol **II-1**.

2. Results and Discussion

The reaction of **II-1** was carried out under various conditions (Table II-1). As expected, the major product was **II-2**, which was formed by the abstraction of the β hydroxyl group to the sulfenyl group. In some cases, the selectivity of the reaction exceeds that of the Nybergh's result.



II-1 **II-2** **II-3**

Table II-1. The Reaction of **II-1** under Various Conditions

Run	Activator	Solvent	Yield/%	**II-2**:**II-3**
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	52	89:11
2	TfOH		38	93:7
3	$MeAlCl_2$		0	–
4	$SbCl_5$		41	68:32
5	TMSOTf		68 (63)[a]	94:6 (94:6)[a]
6		CH_3CN	30	67:33
7		Et_2O	23	90:10
8		Toluene	53 (72)[a]	95:5 (97:3)[a]
9		CCl_4	(23)[a]	(98:2)[a]
10		Hexane	(34)[a]	(95:5)[a]

[a] The values in parentheses are those obtained at 0°C.

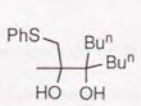
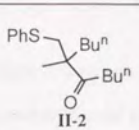
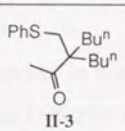
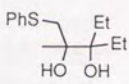
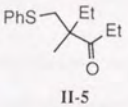
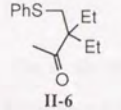
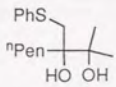
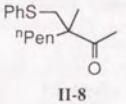
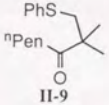
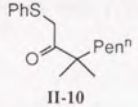
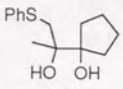
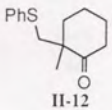
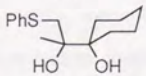
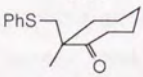
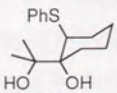
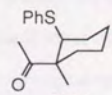
Among the activators examined, trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave the best result in the yield and selectivity (Runs 1-5). Moreover, the solvent effect was apparent; with decreasing the polarity of the solvent, the selectivity was improved (Runs 5-10). This solvent effect may be explained by the terms that the coordination of the solvent toward the cationic center reduces the selectivity. The temperature somewhat affected the reaction; in toluene, both yield and selectivity were better at 0°C than at room tempereture (Run 8). However, the reaction proceeded very slowly below 0°C; only low conversion was observed by TLC analysis even after 48 h when the reaction was performed at -23°C.

The reaction of **II-1** with TMSOTf in the presence of dehydrating agent MS5A was carried out with the expectation that the yield or the selectivity might be improved, but the result was almost identical with that of the reaction in the absence of the dehydrating agent.

Next, rearrangement of several substrates was carried out under the optimized conditions (Table II-2). In general, very high selectivity was attained. Especially when a substrate has a ring structure, only one rearranged ketone was detected (Runs 4-6). It is noteworthy that

substrates having the same carbon framework gave entirely different products depending on the position of the sulfenyl group (Runs 5,6); the present reaction can be expressed as "regiospecific" reaction according to the definition in Chapter I.

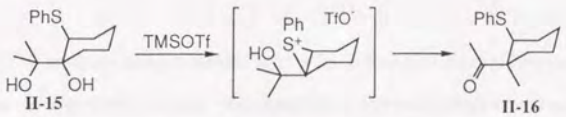
Table II-2. Pinacol Rearrangement of Various Sulfenylmethylated Glycols[a]

Run	Substrate	Product	Yield / %
1	 **II-1**	 **II-2** 97 :  **II-3** 3	72
2	 **II-4**	 **II-5** 97 :  **II-6** 3	62
3	 **II-7**	 **II-8**  **II-9**  **II-10** 92 : 4 : 4	65[b]
4	 **II-11**	 **II-12**	40
5	 **II-13**	 **II-14**	37[c]
6	 **II-15**	 **II-16**	71

[a] The reaction was performed in toluene in the presence of 1.1 equiv. TMSOTf at 0 °C.
[b] TBSOTf was used as an activator.
[c] At room temperature.

Pinacol rearrangement is known to proceed through a concerted mechanism; the configuration at the carbon bearing the leaving hydroxyl group is inverted. In contrast, the

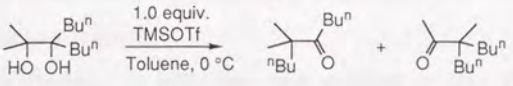
pinacol rearrangement of the sulfenylmethylated glycols characteristically proceeded with complete retention of the configuration (Run 6). This result supports the intervention of an episulfonium-ion-like species.



II-15 **II-16**

The reaction of bis(trimethylsilyl) ether of **II-7** was tried in order to investigate whether the present rearrangement proceed with catalytic amount of TMSOTf. However, only low yield was attained even with 1.1 equiv. of TMSOTf; TMS_2O is poorer leaving group compared to TMSOH.

A control experiment was carried out for **II-17**. The result indicates that the sulfenyl group is not only effective for high selectivity but also for preventing side reactions. In addition, when the sulfenyl group was absent, obtained isomeric ketones were chromatographically inseparable.

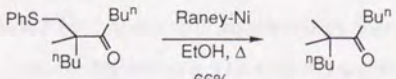


II-17 34% **II-18** : **II-19**

66 : 34

Generally, unsymmetrically tetrasubstituted glycols are synthesized by means of inefficient reductive coupling of different ketones, which make it difficult to apply pinacol rearrangement for such type of glycols. In contrast, starting materials for the present reaction were easily prepared through three steps; (1) the Barbier reaction of alkenyl halides and ketones, (2) epoxydation of the allylic alcohols, and (3) ring opening of the epoxides by a thiolate anion.

Moreover, it was revealed that the rearranged β-sulfenylketone could be easily desulfenylated by usual procedure.



II-2 **II-18**

In conclusion, the present method provides an equivalent to hydroxyl group differentiating pinacol rearrangement.

3. Experimental

General. A GC analysis was performed with a 25 m fused-silica capillary column using cyanopropyl silicone as a stationary phase. The melting points were determined using a metal block apparatus and an open capillary tube, and were uncorrected. NMR spectra were measured on a FT spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C, or on a continuous-wave instrument (60 MHz for ^1H). For ^1H NMR, the δ values are given in ppm with TMS as an internal standard, and the coupling constants are recorded in Hz. For ^{13}C NMR, the chemical shifts are reported in ppm relative to TMS or $CDCl_3$ (δ 77.0). The unit for the values of IR spectra is cm^{-1}. The mass spectra were recorded with the EI method (70 eV); the relative intensity is given in parenthesis after the corresponding *m/z* value. Silica gel was used for column chromatography (particle size: 63-200 μm) and preparative TLC (<46 μm). All solvents were distilled before use and stored over sodium wire or molecular sieves. The compounds are oil unless the melting point is given.

X-ray Measurement. Intensity data were measured on Mac-Science four-circle diffractometer (MXC-18) with graphite monochromated Cu-Kα radiation. Accurate cell dimensions were obtained by a least-squares refinement of 20 reflections in the range of $40° < 2\theta < 60°$. Data were collected with three check reflections. The observed reflections with $|F_O| > 3\sigma(|F_O|)$ were used in the solutions and refinements; no absorption correction was made. The structures were solved by a direct method with the MULTAN 78[4] program and refined by full-matrix least-squares method with the SHELXS 76[5] program.

3-Butyl-2-methyl-1-phenylthio-2,3-heptanediol (II-1): To a solution of thioanisole (10.0 g, 80.5 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (8.1 ml, 81 mmol) in THF (100 ml) was added *n*-BuLi (1.61 M hexane solution, 54 ml, 86 mmol) at -78°C. The resulting solution was stirred for 1 h and then transferred by means of cannula to a flask containing ethyl piruvate (25.0 ml, 226 mmol) in THF (100 ml) at -78°C. The cooling bath was removed and the mixture was stirred for 2 h. After the addition of saturated aqueous NH_4Cl

solution (170 ml) to the reaction mixture, organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml). Combined organic layers were dried over Na_2SO_4 and the solvent was removed by a rotary evaporator. Column chromatography (eluent: hexane/EtOAc = 7/1) of the residue afforded 12.34 g (51 mmol, 64% yield) of Ethyl 2-hydroxy-2-methyl-3-(phenylthio)propionate. ^{1}H NMR (CCl_4, 400MHz) 1.1 (t, 3H, J = 7), 1.4 (s, 3H), 3.2 (ABq, 2H, J = 14), 3.5 (s, 1H), 4.0 (qm, 2H, J = 7), 7.1–7.6 (m, 5H); IR (neat) 3500 (br), 1740, 1200, 745, 695.

To a solution of the above hydroxyester (3.05 g, 12.7 mmol) in THF (30 ml) was added *n*-BuLi (1.65 M hexane solution, 24.0 ml, 39.6 mmol) at 0°C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by a successive addition of ethanol (2 ml) and saturated aqueous NH_4Cl (30 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). After drying the combined organic layers, solvent was stripped off. Purification by column chromatography (eluent: hexane/EtOAc = 19/1) gave the title compound (1.34 g, 4.3 mmol, 34% yield). ^{1}H NMR ($CDCl_3$, 400MHz) 0.92 (t, 6H, J = 7), 1.26 (s, 3H), 1.3–1.7 (m, 12H), 2.45 (br s, 1H), 2.84 (br s, 1H), 3.16 (d, 1H, J = 13), 3.45 (d, 1H, J = 13), 7.2–7.4 (m, 5H); IR (neat) 3480 (br), 1580, 1480, 1470, 1440, 1380, 740, 690.

3-Ethyl-2-methyl-1-phenylthio-2,3-pentanediol (II-4): This compound was synthesized in a similar manner from the above intermediate hydroxyester (EtMgBr was used instead of *n*-BuLi). 43% yield; ^{1}H NMR (CCl_4, 60MHz) 1.0 (t, 6H, J = 8), 1.2 (s, 3H), 1.6 (m, 4H), 2.2 (s, 1H), 2.7 (s, 1H), 3.1 (d, 1H, J = 14), 3.4 (d, 1H, J = 14), 7.3–7.5 (m, 5H).

1-[1-Hydroxy-1-methyl-2-(phenylthio)ethyl]-1-cyclopentanol (II-11): 1-(2-propenyl)-1-cyclopentanol (1.20 g, 9.5 mmol), which was obtained by a ultrasound-promoted Barbier-type coupling reaction[6] of 2-bromopropene and cyclopentanone in 24% yield, was oxidized by using *t*-BuOOH/cat.$VO(acac)_2$ according to a method in the literature[7] to give 0.72 g (53% yield) of the corresponding epoxide. ^{1}H NMR (CCl_4, 60MHz) 1.4 (s, 3H), 1.4_2.0 (m, 9H), 2.5 (d, 1H, J = 5), 2.9 (d, 1H, J = 5).

To a solution of EtONa (30 mmol) in ethanol was successively added PhSH (0.58 ml, 5.6 mmol) and an EtOH (5 ml) solution of the above epoxide (0.72 g, 5.1 mmol). The resulting

mixture was heated to reflux and stirred for 40 min. After cooling to an ambient temperature, each 30 ml of water and CH_2Cl_2 were added. The organic materials were extracted with 10 ml of CH_2Cl_2 and combined organic layers were dried over Na_2SO_4. Purification by column chromatography (eluent: hexane/EtOAc = 19/1) afforded the title compound (0.33 g, 1.3 mmol, 26% yield). ^{1}H NMR (CCl_4, 60MHz) 1.2 (s, 3H), 1.3–2.0 (m, 8H), 2.4 (s, 1H), 2.8 (s, 1H), 3.2 (d, 1H, J = 14), 3.4 (d, 1H, J = 14), 7.2–7.4 (m, 5H). IR (neat) : 3460 (br), 1580, 1480, 1440, 1010, 740, 690.

2-Methyl-3-(phenylthio)methyl-2,3-octanediol (II-7), 1-[1-hydroxy-1-methyl-2-(phenylthio)ethyl]-1-cyclohexanol (II-13), and (1*R, 2*S**)-1-(1-hydroxy-1-methylethyl)-2-phenylthio-1-cyclohexanol (II-15):** These compounds were synthesized by the same procedure as above. The yields given are total yield for three steps (Barbier-type coupling, epoxidation, epoxy opening).

II-7: 25% yield; ^{1}H NMR (CCl_4, 60MHz) 0.9–1.0 (m, 3H), 1.2 (s, 3H), 1.3 (s, 3H), 1.1–1.6 (m, 8H), 2.3 (s, 1H), 2.8 (s, 1H), 3.2 (d, 1H, J = 14), 3.3 (d, 1H, J = 14), 7.1–7.5 (m, 5H). IR (neat) : 3460 (br), 1590, 1480, 1440, 1030, 960, 740, 690.

II-13: 8% yield (low yield was due to the instability of the intermediate epoxide); ^{1}H NMR (CCl_4, 60MHz) 1.2 (s, 3H), 1.3–1.9 (m, 10H), 2.1 (s, 1H), 2.8 (s, 1H), 3.2 (d, 1H, J = 14), 3.4 (d, 1H, J = 14), 7.2–7.4 (m, 5H).

II-15: 25% yield; colorless prisms, mp 76.0–76.5°C (hexane); ^{1}H NMR (CCl_4, 60MHz) 1.3 (s, 3H), 1.5 (s, 3H), 1.6–2.0 (m, 8H), 2.3 (s, 1H), 2.6 (s, 1H), 3.4 (m, 1H), 7.4–7.6 (m, 5H); ^{1}H NMR ($CDCl_3$, 400MHz) 3.39 (br s, 1H, PhSC*H*).

3-Butyl-2-methyl-2,3-heptanediol (II-17): To an EtOH (10 ml) solution of **II-1** (0.86 g, 2.77 mmol) was added an EtOH suspension of Raney Ni W-2 (ca. 5 g), and the mixture was heated to reflux for 2 h. Filtration, followed by evaporation and separation by column chromatography (eluent: hexane/EtOAc = 24/1), gave 237 mg (42% yield) of the title compound. ^{1}H NMR (60 MHz, CCl_4) 1.2 (s, 6H), 0.8–1.6 (m, 18H), 1.8–2.0 (br, 2H, O*H*).

General procedure for the pinacol rearrangement: To a solution of diol (0.5 mmol) in toluene (3 ml) was added a toluene solution (0.87 M) of TMSOTf (0.5 mmol) at -78°C under an argon atmosphere. Then the cooling bath was changed to an ice-water bath, and the solution

was stirred for 1.5 h at 0°C. After the addition of saturated aqueous $NaHCO_3$ (5 ml), the organic materials were extracted with CH_2Cl_2 (4 × 5 ml). Combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. Separation by preparative TLC (eluent: hexane/EtOAc = 7/1) gave rearranged ketones.

6-Methyl-6-(phenylthio)methyl-5-decanone (II-2): ^{1}H NMR (60 MHz, CCl_4) 0.9 (t, 3H, J = 5), 0.9 (t, 3H, J = 6), 1.2 (s, 3H), 1.2–1.7 (m, 10H), 2.4 (t, 2H, J = 8), 3.1 (s, 2H), 7.2–7.4 (m, 5H); IR (neat) 1700; MS 292 (M^+, 22), 207 (17), 183 (89), 123 (67), 110 (14), 85 (100), 57 (50); HRMS, found: 292.1877. Calcd for $C_{10}H_{28}OS$ (M^+): 292.1861. Anal., found: C, 73.70; H, 9.56%. Calcd for $C_{10}H_{28}OS$: C 73.92, H 9.65%.

3-Butyl-3-(phenylthio)methyl-2-heptanone (II-3): ^{1}H NMR (400 MHz, $CDCl_3$) 0.84 (t, 6H, J = 7.3), 1.22–1.78 (m, 12H), 2.12 (s, 3H), 3.18 (s, 2H), 7.2–7.4 (m, 5H).

4-Methyl-4-(phenylthio)methyl-3-hexanone (II-5): ^{1}H NMR (60 MHz, CCl_4) 0.8 (t, 3H, J = 7), 1.0 (t, 3H, J = 7), 1.2 (s, 3H), 1.6 (m, 2H), 2.4 (q, 2H, J = 7), 3.1 (s, 2H), 7.2–7.5 (m, 5H); MS m/z (relative intensity) 236 (M^+, 19), 179 (7), 127 (70), 123 (80), 110 (30), 109 (18), 57 (100); HRMS found: 236.1244. Calcd for $C_{14}H_{20}OS$ (M^+): 236.1235.

3-Ethyl-3-(phenylthio)methyl-2-pentanone (II-6): ^{1}H NMR (400 MHz, $CDCl_3$) 0.75 (t, 6H, J = 8), 1.7–1.8 (m, 4H), 2.13 (s, 3H), 3.17 (s, 2H), 7.2–7.4 (m, 5H).

3-Methyl-3-(phenylthio)methyl-2-octanone (II-8): ^{1}H NMR (60 MHz, CCl_4) 0.9 (t, 3H, J = 5), 1.2 (s, 3H), 1.2–1.8 (m, 8H) , 2.1 (s, 3H), 3.1 (s, 2H), 7.2–7.4 (m, 5H); MS 264 (M^+, 32), 221 (9), 155 (88), 123 (100), 110 (50), 85 (24); HRMS found: 264.1555. Calcd for $C_{16}H_{24}OS$ (M^+): 264.1548.

2-Methyl-2-(phenylthio)methyl-3-octanone (II-9) and 3,3-dimethyl-1-phenylthio-2-octanone (II-10): Chromatographically inseparable 1:1 mixture, ^{1}H NMR (400 MHz, $CDCl_3$) 0.86 (t, 3H, J = 6), 0.88 (t, 3H, J = 6), 1.16 (s, 6H), 1.25 (s, 6H), 1.3 –1.6 (m, 14H), 2.47 (t, 2H for **II-7**, J = 7), 3.16 (s, 2H for **II-7**), 3.92 (s, 2H for **II-8**), 7.2–7.5 (m, 5H).

2-Methyl-2-(phenylthio)methylcyclohexanone (II-12): ^{1}H NMR (60 MHz, CCl_4) 1.2 (s, 3H), 1.7–1.9 (m, 8H) , 2.3 (m, 2H), 3.1 (s, 2H), 7.2–7.4 (m, 5H); MS 234 (M^+, 100), 125 (94), 123 (94), 110 (22), 109 (13), 55 (44); HRMS found: 234.1104. Calcd for $C_{14}H_{18}OS$ (M^+): 234.1079.

2-Methyl-2-(phenylthio)methylcycloheptanone (II-14): ^{1}H NMR (60 MHz, CCl_4) 1.2 (s, 3H), 1.6 (m, 8H) , 2.5 (m, 2H), 3.0 (d, 1H, J = 13), 3.2 (d, 1H, J = 13), 7.2–7.4 (m, 5H); MS 248 (M^+, 75), 139 (100), 123 (100), 110 (35), 109 (18), 55 (52); HRMS found: 248.1262. Calcd for $C_{15}H_{20}OS$ (M^+): 248.1235.

(1*R,2*R**)-1-Acetyl-1-methyl-2-(phenylthio)cyclohexane (II-16):** ^{1}H NMR (60 MHz, CCl_4) 1.3 (s, 3H), 1.5–2.0 (m, 8H), 2.1 (s, 3H), 3.1 (br t, 1H, J = 5), 7.2–7.4 (m, 5H); (400 MHz, $CDCl_3$); 3.10 (dd, 1H, J = 5, 6); IR (neat) 1710; MS 248 (M^+, 64), 139 (77), 123 (74), 121 (33), 110(25), 109 (13); HRMS found: 248.1259. Calcd for $C_{15}H_{20}OS$ (M^+): 248.1235.

6,6-Dimethyl-5-decanone (II-18) and 3-butyl-3-methyl-2-heptanone (II-19): Chromatographically inseparable mixture; 66/34 by GLC analysis. ^{1}H NMR (60 MHz, CCl_4) 0.9 (s, 3H), 1.0 (s, 6H), 0.7–1.8 (m, 8H), 2.0 (s, 3H for **II-19**), 2.4 (br t, 2H for **II-18**, J = 6). From the area ratio of two marker peaks (2/3 for δ = 2.0/2.4), it was concluded that the major product was **II-18**.

Desulfurization of II-2. To an EtOH (10 ml) solution of **II-2** (125.9 mg, 0.43 mmol) was added an EtOH suspension of Raney Ni W-2 (ca. 2 g), and the mixture was heated to reflux for 1 h. Filtration, followed by evaporation and separation using preparative TLC, gave 52.5 mg of desulfurized product **II-18**. ^{1}H NMR (60 MHz, CCl_4) 1.0 (s, 6H), 0.7–1.8 (m, 8H), 2.4 (br t, 2H, J = 6).

(1*R,2*R**)-1-Acetyl-2-benzenesulfonyl-1-methylcyclohexane (II-20): II-16** (79.8 mg, 0.32 mmol) was treated with OXONE® according to the method in the literature[8] to give sulfone **II-20** (52.7 mg, 59% yield), of which the relative configuration was analyzed by single crystal X-ray structural determination. Colorless prisms, mp 108°C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) 1.5–2.2 (m, 8H), 1.54 (m, 3H), 2.26 (s, 3H), 3.27 (dd, 1H, J = 5, 10), 7.5–7.7 (m, 3H), 7.8 - 7.9 (m, 2H); IR (neat) 1700, 1450, 1305, 1150.

Details for the X-ray structural analysis of II-20

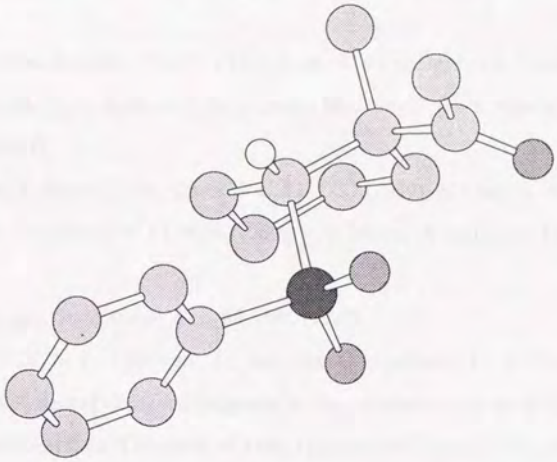
Molecular formula	$C_{15}H_{20}O_3S$
Formula weight	280.4
Crystal size/mm^3	$0.3 \times 0.25 \times 0.25$
a/Å	11.798 (2)
b/Å	11.312 (2)
c/Å	11.340 (2)
β/degrees	108.38 (1)
Volume of unit cell /$Å^3$	1436.4 (4)
Crystal system	Monoclinic
Space group	$P2_1/a$
Z value	4
D_{calc}/g cm^{-3}	1.29
Reflections used	1978
No. of variables	252
R;R_w	0.061; 0.074
Good of fitness	0.75
Maximum shift/e. s. d. in final cycle	0.10
Max. negative peak in final diff. map/e $Å^{-3}$	-0.61
Max. positive peak in final diff. map/e $Å^{-3}$	0.26

Details for the X-ray structural analysis of II-20

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
S 1	0.21933 (7)	0.24800 (7)	0.08262 (7)	3.64 (3)
O 2	0.3074 (2)	0.1327 (2)	0.4031 (2)	4.48 (7)
O 3	0.3384 (2)	0.2930 (3)	0.1051 (2)	5.10 (8)
O 4	0.2051 (3)	0.1236 (2)	0.1021 (2)	5.79 (9)
C 5	0.1926 (3)	0.3026 (3)	0.3140 (3)	3.12 (7)
C 6	0.1789 (3)	0.3594 (3)	-0.1399 (3)	3.72 (8)
C 7	0.1405 (3)	0.3283 (3)	0.1715 (3)	3.26 (8)
C 8	0.1360 (3)	0.2796 (3)	-0.0734 (3)	3.14 (8)
C 9	-0.0340 (4)	0.2438 (3)	-0.2508 (4)	4.4 (1)
C 10	0.3089 (3)	0.3704 (3)	0.3725 (3)	3.74 (9)
C 11	0.1364 (3)	0.4603 (3)	0.1433 (3)	4.1 (1)
C 12	0.0290 (3)	0.2210 (3)	-0.1274 (4)	4.02 (9)
C 13	0.2106 (3)	0.1698 (3)	0.3432 (3)	3.69 (8)
C 14	0.1154 (4)	0.3813 (3)	-0.2631 (3)	4.4 (1)
C 15	0.2527 (4)	0.5256 (3)	0.2053 (4)	5.0 (1)
C 16	0.3000 (4)	0.5014 (3)	0.3445 (4)	4.6 (1)
C 17	0.1051 (4)	0.0885 (4)	0.3052 (5)	5.6 (1)
C 18	0.0963 (3)	0.3426 (4)	0.3722 (3)	4.3 (1)
C 19	0.0107 (4)	0.3226 (3)	-0.3180 (3)	4.4 (1)
H 6	0.245 (3)	0.398 (4)	-0.101 (4)	3.8 (8)
H 7	0.068 (4)	0.291 (4)	0.136 (5)	6 (1)
H 9	-0.108 (4)	0.203 (4)	-0.286 (4)	6 (1)
H 10A	0.372 (3)	0.338 (3)	0.338 (4)	4.1 (8)
H 10B	0.326 (4)	0.361 (4)	0.462 (5)	6 (1)
H 11A	0.119 (3)	0.472 (4)	0.054 (4)	4.4 (8)
H 11B	0.078 (3)	0.492 (3)	0.173 (4)	3.8 (8)
H 12	-0.006 (4)	0.173 (4)	-0.080 (4)	4.7 (9)
H 14	0.144 (4)	0.442 (4)	-0.316 (4)	6 (1)
H 15A	0.241 (5)	0.611 (5)	0.199 (5)	7 (1)
H 15B	0.316 (4)	0.506 (4)	0.162 (4)	5 (1)
H 16A	0.245 (4)	0.532 (4)	0.378 (4)	4.9 (9)
H 16B	0.378 (3)	0.542 (3)	0.378 (4)	3.9 (8)
H 17A	0.138 (6)	0.005 (6)	0.291 (6)	10 (2)
H 17B	0.039 (5)	0.119 (4)	0.236 (5)	6 (1)
H 17C	0.082 (5)	0.091 (5)	0.374 (5)	7 (1)
H 18A	0.115 (4)	0.318 (4)	0.457 (4)	4.8 (9)
H 18B	0.010 (5)	0.313 (4)	0.337 (5)	7 (1)
H 18C	0.091 (4)	0.430 (4)	0.382 (4)	5.2 (9)
H 19	-0.038 (4)	0.336 (4)	-0.392 (5)	5 (1)

Details for the X-ray structural analysis of II-20



Intramolecular Distances (Å) with e.s.d. in parentheses

atom atom	distance	atom atom	distance
S 1 --O 4	1.443 (3)	C 7 --C 11	1.525 (5)
S 1 --C 8	1.769 (3)	C 8 --C 12	1.385 (5)
S 1 --C 7	1.816 (4)	C 9 --C 19	1.382 (6)
O 2 --C 13	1.206 (4)	C 9 --C 12	1.386 (5)
C 5 --C 10	1.528 (4)	C 10 --C 16	1.512 (5)
C 5 --C 13	1.538 (5)	C 11 --C 15	1.521 (5)
C 5 --C 18	1.550 (6)	C 13 --C 17	1.498 (6)
C 5 --C 7	1.564 (4)	C 14 --C 19	1.366 (5)
C 6 --C 8	1.371 (5)	C 15 --C 16	1.524 (6)

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom atom atom	angle	atom atom atom	angle
O 3 --S 1 --O 4	118.1 (2)	C 5 --C 7 --S 1	112.2 (2)
O 3 --S 1 --C 8	108.0 (2)	C 6 --C 8 --C 12	121.0 (3)
O 3 --S 1 --C 7	111.5 (2)	C 6 --C 8 --S 1	119.8 (2)
O 4 --S 1 --C 8	107.2 (1)	C 12 --C 8 --S 1	119.1 (3)
O 4 --S 1 --C 7	107.4 (2)	C 19 --C 9 --C 12	120.0 (3)
C 8 --S 1 --C 7	103.5 (1)	C 16 --C 10 --C 5	114.0 (3)
C 10 --C 5 --C 13	110.6 (2)	C 15 --C 11 --C 7	114.5 (3)
C 10 --C 5 --C 18	110.3 (3)	C 8 --C 12 --C 9	118.7 (4)
C 10 --C 5 --C 7	111.2 (3)	O 2 --C 13 --C 17	120.1 (3)
C 13 --C 5 --C 18	105.2 (3)	O 2 --C 13 --C 5	120.2 (3)
C 13 --C 5 --C 7	112.7 (2)	C 17 --C 13 --C 5	119.5 (3)
C 18 --C 5 --C 7	106.5 (2)	C 19 --C 14 --C 6	119.8 (4)
C 8 --C 6 --C 14	119.7 (3)	C 11 --C 15 --C 16	112.0 (4)
C 11 --C 7 --C 5	112.0 (2)	C 10 --C 16 --C 15	111.8 (3)
C 11 --C 7 --S 1	111.2 (3)	C 14 --C 19 --C 9	120.6 (3)

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CHAPTER III. REGIOSELECTIVE REACTION OF ALLYLIC ACETATES DIRECTED BY A SULFENYL GROUP

Summary: α-(Sulfenylmethyl)allyl acetates reacted with silylated carbon nucleophiles in the presence of a catalytic amount of TMSOTf to give products substituted at the α-position of the sulfenylmethyl group in moderate to good yields with high regioselectivity. The theoretical calculation on an intermediate cationic species indicated that an episulfonium ion was a stable form; the observed regioselectivity was rationalized qualitatively on the basis of the coefficients of LUMO of the cation. Some transformations of the products were also demonstrated.

1. Introduction

Allylic electrophiles are valuable building blocks in organic synthesis because of their high reactivity and synthetic versatility. However, the reaction of such substrates accompanies the problem of the regiochemistry, namely, the reaction can take place in S_N and S_N' fashions. Concerning the regiochemistry, the reaction of allylic electrophiles through organometallics is well studied. For example, the palladium-catalyzed reactions of allylic acetates take place at less hindered site,[1] while tungsten complexes are used to make C-C bond at more hindered site;[2] in general, the regiochemistry of the reaction of allylic electrophiles via η^3 allyl complexes does not depend on the position of the leaving group but on the metal, ligand, substituent on the substrate, and nucleophile.[3] On the other hand, the reaction of allylic electrophiles with copper reagents takes place in S_N2/S_N2' fashion. In this case, the position of the leaving group is as an important factor for the regiochemistry as other reaction conditions.[4]

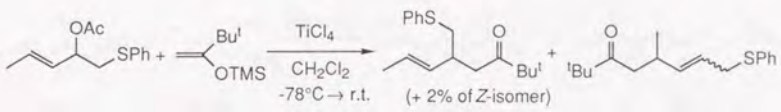
In contrast to the above reactions, the study concerning the acid-catalyzed reaction of allylic electrophiles has not been thoroughly explored in the viewpoint of the regiochemistry. It is known that the acid-catalyzed reaction involves a cationic intermediate, and that the regiochemical course of the reaction is affected by a steric factor; the nucleophile attacks preferentially at less substituted site of the allylic system.[5] Hence, when both allylic sites are secondary, the reaction takes place randomly to give a mixture of regioisomers. To the best of the author's knowledge, an intramolecular reaction of allylic acetates having a silyl enol ether

moiety is a unique example for distinction of two secondary allylic termini.[6] In this case, however, the regiochemical course of the reaction depends on the structure of the allylic acetate moiety.

The non-selectivity for the intermolecular allylation is considered to be due to both steric and electronic equivalence of two termini of the allyl cation. Therefore, if the electronic equivalence is broken, the discrimination of the two termini would be possible. Then, the author thought that such an event would be realized by a neighboring group participation toward one end of the allyl cation, and tried the reaction of α-(sulfenylmethyl)allyl acetate.

2. Results and Discussion

At first, the reaction of allylic acetate **III-1a** with silyl enol ether **III-2a** was attempted in the presence of titanium(IV) chloride. Substrate **III-1a** was easily obtained in one pot by the reaction of lithiated thioanisole and crotonaldehyde, followed by treatment with acetyl chloride. A CH_2Cl_2 solution of titanium(IV) chloride (1.1 equiv.) was added to a mixture of **III-1a** (1.0 equiv.) and **III-2a** (1.2 equiv.) in CH_2Cl_2 at -78°C. The reaction was very slow at -78°C, but completed within 30 min at room temperature. The substitution product **III-3** was obtained in 70% yield as a mixture of chromatographically inseparable isomers, which was found to consist of three isomers in a ratio of 96:2:2 by means of glc analysis. Then, the regiochemistry of the product was determined on the basis of ^1H NMR of the mixture; the main isomer and one of the minor isomers showed double-doublet signals of methyl groups adjacent to an olefin at around 1.7 ppm, whereas the other minor isomer showed a doublet methyl signal at 1.0 ppm. Moreover, the stereochemistry of double bond of main isomer was proved to be *trans* (J = 15 Hz for the olefinic protons), whereas the stereochemistry of the other isomers could not be determined because their olefinic signals were overlapped with those of the main isomer. From the above information, the main isomer was concluded to be an (*E*)-α-substituted product and the two minor isomers were a (*Z*)-α-substituted product and a γ-substituted product. As already described, the reaction of an allylic electrophile under acidic conditions is usually affected by a steric hindrance. The present reaction, however, occurred preferentially at the α-position of the sulfenylmethyl group in spite of steric disadvantage.

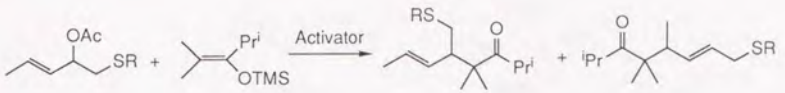


III-1a **III-2a** 70% α–III-3 : γ–III-3

98 : 2

In the next stage, some reaction conditions were examined by using more sterically demanding silyl enol ether **III-2b** as a nucleophile (Table III-1). As anticipated, the regioselectivity for the reaction of **III-1a** with **III-2b** was slightly lower than that with **III-2a**. The metal halide-promoted reactions gave better selectivity, whereas the yield was higher when TMSOTf was used as a promoter even in a catalytic amount (Runs 1–4). Upon lowering the reaction temperature, the selectivity was slightly improved. However, it took very long time in order to complete the reaction (Runs 5, 6). The solvent effect indicates the formation of a cationic intermediate; in less polar toluene, which could not solvate the ionic intermediate, the reaction did not proceed (Run 9).

The reaction of **III-1b**, a methylthio-analog of **III-1a**, was also investigated. With a catalytic amount of TMSOTf, the reaction of **III-1b** did not give **III-5** but a small amount of unidentified very polar products, and most of **III-1b** remained unchanged. When 1.1 equiv. of TMSOTf was used, substrate **III-1b** was completely consumed; **III-5** was obtained in almost the same degree of selectivity as the case of **III-4** (Run 10). However, the yield was a little low due to the formation of very polar by-products. Upon using excess **III-1b**, the yield was improved to some extent (Run 11). These observations can be reasonably explained by assuming that another substrate **III-1b** molecule quenches the intermediate cationic species to give a stable sulfonium salt, a very polar compound, and that the rate for this reaction is comparable to "normal" reaction with nucleophile **III-2b**. As the sulfur of a phenylthio group is less nucleophilic than that of an alkylthio group,[7] a phenylthio group would be better than a methylthio group for the sulfenyl moiety of the substrate in order to prevent side reactions and to achieve better yield. Finally, the author deduced that the optimum reaction conditions were those used in Run 4 in Table III-1.



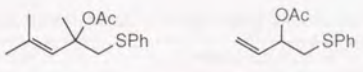
III-1a (**III-1b**) **III-2b** α–**III-4** (α–**III-5**) γ–**III-4** (γ–**III-5**)

Table III-1. Reaction of Allylic Acetate **III-1a** or **III-1b** with Silyl Enol Ether **III-2b** under Various Conditions[a]

Run	Substrate	R	Lewis acid	Solvent	Temp./°C	Product	Yield/%	α^b/γ
1	**III-1a**	Ph	$TiCl_4$	CH_2Cl_2	-78 to r.t.	**III-4**	61	93/7
2			$SnCl_4$				67	93/7
3			TMSOTf				79	89/11
4			TMSOTf[c]				82	89/11
5					-23[d]		61	92/8
6					0[d]		75	89/11
7					r.t.		77	86/14
8				MeCN	-78 to r.t.		79	86/14
9				Toluene			0	—
10	**III-1b**	Me	TMSOTf	CH_2Cl_2		**III-5**	58	88/12
11[e]							70	87/13

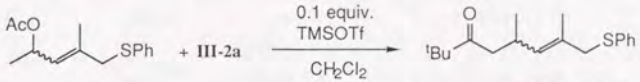
[a] The reaction was carried out for 1 h by using 1.2 equiv. of **III-2b** in the presence of 1.1 equiv. of a Lewis acid. [b] *E*/*Z* = 98/2. [c] A catalytic amount (0.1 eqiuv.) of the Lewis acid was used. [d] The reaction was performed for 15 h. [e] Substrate/nucleophile/Lewis acid = 2.0/1.0/1.0.

The influence of terminal substitution mode of an allylic cation was also investigated. Substrate **III-1c**, which is considered to give an allyl cation with two tertiary ends, was tried to be synthesized, but was too labile to be isolated; the author abandoned the reaction of **III-1c**. Instead, the reaction of the corresponding alcohol of **III-1c** with **III-2a** was tried in the presence of 1.1 equiv. of TMSOTf; the reaction gave no substituted product but a very polar product which was not identified. On the other hand, when the reaction of **III-1d** with **III-2a** was carried out in the presence of TMSOTf, no abstraction of the acetoxyl group occurred even with a stoichiometric amount of the activator. Moreover, when $TiCl_4$ was used instead of TMSOTf for the reaction of **III-1d** with **III-2a**, only a complex mixture was obtained. The presence of a primary allylic terminus might be disadvantageous for the formation of an intermediate cation having an appropriate stability.



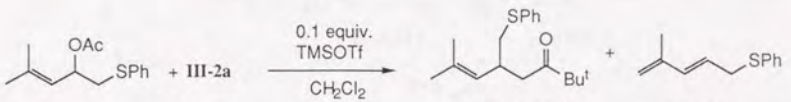
III-1c **III-1d**

Since the sulfenylmethylated tertiary allylic acetate was labile as described above, the author used secondary acetate **III-1e** for the reaction of an allylic cation bearing one secondary and one sulfenylmethylated tertiary ends. Although the reaction of **III-1e** with **III-2a** also showed complexity, the corresponding γ-substituted product could be isolated in 19% yield; the attack occurred only at the γ position, sterically more favorable site. This result demonstrates that the steric factor is more important for determining the regiochemical course of the reaction.



III-1e γ-**III-6** (19%)

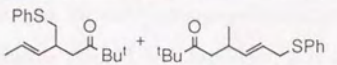
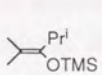
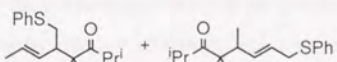
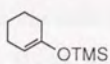
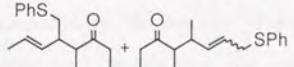
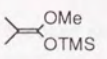
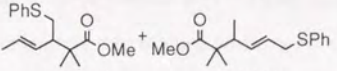
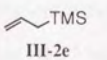
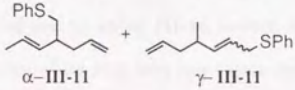
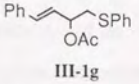
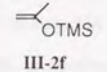
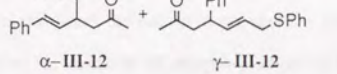
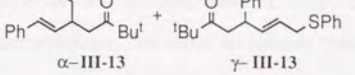
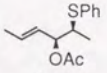
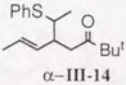
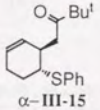
Substrate **III-1f** was expected to give exclusively an α-substituted product from viewpoints of steric requirement and directing effect of the sulfenyl group. Actually, only α-**III-7** was obtained as a substituted product by the reaction of **III-1f** with **III-2a**. The yield was, however, a little lower compared to that of **III-3** from **III-1a**, due to the competing elimination reaction of acetic acid from **III-1f** to give diene **III-8**.



III-1f α-**III-7** (49%) **III-8** (32%)

On the basis of the above observations, it is concluded that the present allylation reaction is useful when both ends of allylic cations are mono-substituted; side reactions are diminished and the corresponding α-substituted products are obtained in good yields. The present reaction is the first example for the discrimination of two secondary ends of an allylic cation in an intermolecular reaction with the aid of the electronic effect of a sulfenyl group.

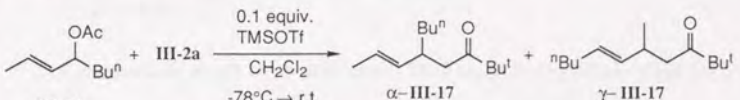
Table III-2. Reaction of α-(Sulfenylmethyl)allyl Acetates with Various Nucleophiles[a]

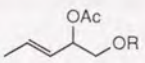
Run	Substrate	Nucleophile	Product(s)	Yield/%	α^b/γ
1	 **III-1a**	 **III-2a**	 α–**III-3** γ–**III-3**	68	94/6
2[c]				70	98/2
3		 **III-2b**	 α–**III-4** γ–**III-4**	82	89/11
4		 **III-2c**	 α–**III-9** γ–**III-9**	84	91[d]/9[d]
5		 **III-2d**	 α–**III-10** γ–**III-10**	78	91/9
6		 **III-2e**	 α–**III-11** γ–**III-11**	59	91/9
7	 **III-1g**	 **III-2f**	 α–**III-12** γ–**III-12**	92	93/7
8		**III-2a**	 α–**III-13** γ–**III-13**	80	92/8
9	 **III-1h**		 α–**III-14**	49	100[d]/0
10	 **III-1i**		 α–**III-15**	76	100/0

[a] The reaction was carried out in CH_2Cl_2 in the presence of 0.1 equiv. TMSOTf at -78°C to room temperature for 2 h. [b] *E*/*Z* = 98/2 except for **III-15**. [c] $TiCl_4$ (1.1 equiv.) was used as an activator. [d] A 1:1 mixture of diastereomers.

The generality of this reaction for the discrimination of two secondary termini of an allylic cation is demonstrated in Table III-2. In every case, the reaction proceeded with good to excellent α-selectivity. As far as using an identical substrate, the selectivity was almost the same degree, regardless of the nucleophile (Runs 1–8). This result is in contrast to the trityl perchlorate-mediated reaction of allyl methyl ethers, in which the regiochemistry was largely affected by the kind of nucleophile;[5a] the synthetic usefulness of the present reaction should be emphasized. The possibility of stereoselective allylation was also tested by using β-monosubstituted nucleophile **III-2c**, but the result was completely disappointing (Run 4). Moreover, in order to elucidate stereospecificity, the reaction of diastereomerically pure substrate **III-1h** with **III-2a** was carried out. In this case, the reaction proceeded non-stereospecifically to give a 1:1 mixture of diastereomers with complete α-selectivity (Run 9), whereas only one diastereomer (*trans* isomer) was attained when cyclic substrate **III-1i** was employed (Run 10).

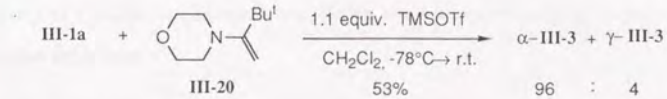
A control experiment was carried out by using **III-16** having no sulfenyl group; the reaction with **III-2a** gave **III-17** only in low yield with very low selectivity. This result strongly supports the idea that in the present reaction the sulfur function not only controls the regiochemistry of the reaction, but also stabilizes the cation to prevent the decomposition of the intermediate. Moreover, the author tried the reaction of oxygen-analogs of **III-1a**, namely **III-18** and **III-19**. However, both of the substrates gave only complex mixtures under the reaction conditions due to instability of the intermediates; this result also shows that a sulfenyl group is advantageous for neighboring-group-participated reactions.





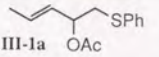
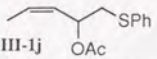
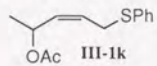
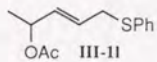
III-18 : R = Ph
III-19 : R = Bn

It is noteworthy that not only silylated carbon nucleophiles but also enamine **III-20** reacted with **III-1a** in the presence of 1.1 equiv. of TMSOTf with high α-selectivity.



In order to look into the mechanism, the reaction of various precursors of 1-methyl-3-(phenylthiomethyl)allyl cation with **III-2b** or **III-2d** was carried out (Table III-3). There observed apparent difference in reaction rate between the reactions with **III-2b**; relative rate was in the order **III-1a** > **III-1j** > **III-1k** ≈ **III-1l**. Nevertheless, in every case, the α/γ and *E*/*Z* ratios of the products were almost identical; the present reaction can be expressed as "regio- and stereoconvergent" reaction according to the definition in Chapter I. These results can be explained by assuming that the reaction proceeds *via* a unique intermediate.

Table III-3. Reaction of Various Precursors for 1-Methyl-3-(phenylthiomethyl) allyl Cation[a]

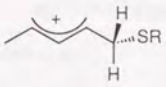
Run	Substrate	Nucleophile	Product	Yield/%	α^b/γ
1	 **III-1a**	**III-2b**	**III-4**	82	89/11
2	 **III-1j**			85	88[c]/12
3	 **III-1k**			54	90/10
4	 **III-1l**			65	92/8
5		**III-2d**	**III-10**	82	92/8

[a] The reaction was carried out in CH_2Cl_2 in the presence of 0.1 equiv. TMSOTf at -78°C to room temperature for 2 h. [b] *E*/*Z* = 98/2 unless otherwise noted. [c] *E*/*Z* = 90/10.

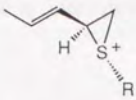
The intermediate might be an allyl cation **III-21a**, an *E*-episulfonium ion **III-22a**, or a five-membered sulfonium ion **III-23a**. To clarify which is most probable, a semiempirical MO calculation was performed for model cations of each species, **III-21b**, **III-22b**, and **III-23b**, using PM3 Hamiltonian.

In the calculation of **III-21b**, the geometry converged to the structure like **III-22b**, which indicates that there are no energy minima around the isolated allyl cation **III-21b**; the

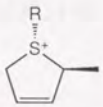
intermediacy of **III-21b** can be ruled out. Other two species successfully converged to the structures like initial ones.



III-21a : R = Ph
III-21b : R = Me

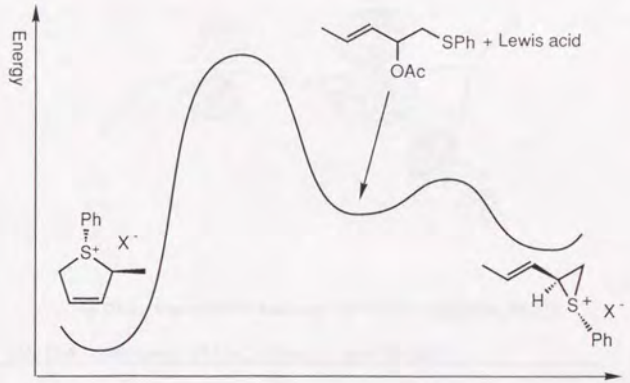


III-22a : R = Ph
III-22b : R = Me



III-23a : R = Ph
III-23b : R = Me

The heat of formation for **III-23b** was about 20 kcal/mol lesser than that for **III-22b**, which might be due to the difference in strain energy of the ring. However, the formation of **III-23a** from **III-1a** or **III-1j** belongs to 5-endo-trig mode of cyclization, which is forbidden by the Baldwin's rule.[8] In contrast, the formation of **III-22a** from **III-1a** is 3-exo-tet mode and allowed by the same rule. These facts can be visualized by the energy diagram shown below.



In the next stage, the author investigated whether the selectivity could be rationalized in terms of charge or orbital of the intermediate cation.

For the cation **III-22b**, charge distribution of the two competing reaction points, C2 and C4, are both very small (Fig. III-1). However, the coefficients of LUMO can be responsible for the observed selectivity. Fig. III-1 clearly shows that LUMO of **III-22b** consists of two localized orbitals; LUMO of the simple allylic cation system C2-C3-C4 and the σ^* orbital of C4-

S7 bond. As the absolute values of the coefficients on C4 are larger than those on C2, C4 is considered to be the most probable reaction site (Table III-4). This result is in good agreement with the α-selectivity. The calculations by other methods (MNDO, AM1, MINDO/3) gave essentially the same result.

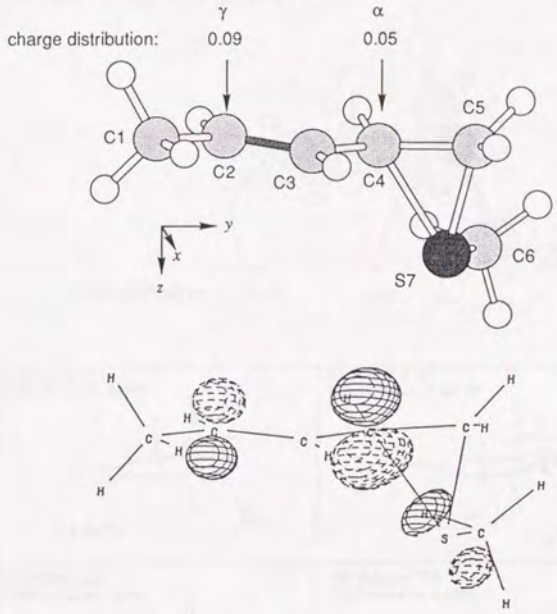


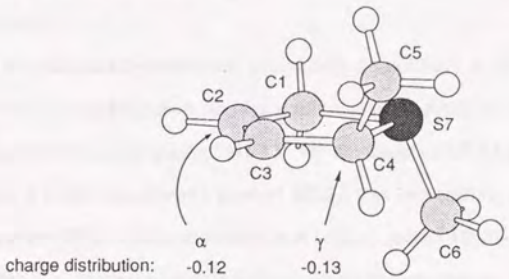
Fig. III-1. Optimized structure and LUMO of model cation **III-22b**

Table III-4. Coefficients of LUMO of Model Cation **III-22b**[a]

	$2s$	$2p_x$	$2p_y$	$2p_z$
C1	0.006	0.003	0.012	0.041
C2	-0.009	0.003	-0.024	-0.398
C3	0.032	0.023	0.045	0.009
C4	-0.218	-0.025	-0.148	0.618
C5	-0.003	-0.007	-0.026	0.031
C6	-0.091	0.147	0.133	-0.054
S7	0.158	0.312	-0.245	0.349

[a] The absolute values of the coefficients of hydrogens were less than 0.083.

On the other hand, neither charge nor orbital can rationalize the α-selectivity when the intermediacy of **III-23b** is assumed (Fig. III-2). In addition, as all five atoms of the ring are almost on the same plane in an optimized structure, the possibility for the S_N2' type reaction at double bond (to give α-substituted product) is suppressed due to little overlap of π orbital of C2-C3 double bond and σ^* orbital of S7-C4 bond.



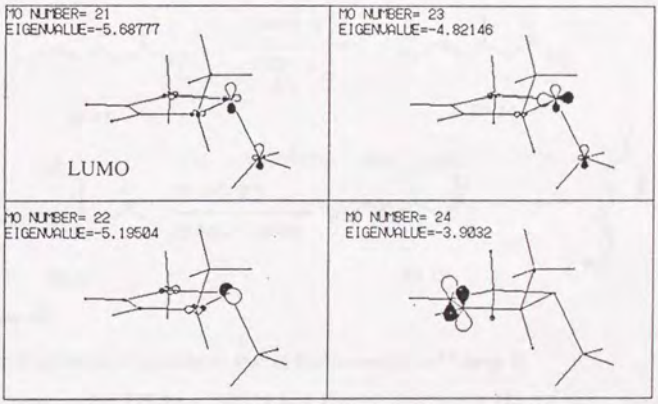
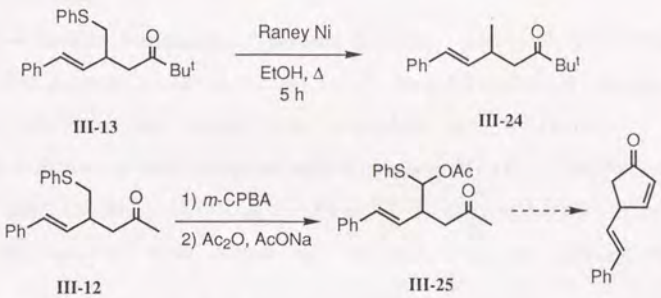


Fig. III-2 Optimized structure and lowest four UMOs of model cation **III-23b**

On the basis of the above results of theoretical calculation, the intermediate of the present allylation is concluded to be the *E*-episulfonium ion **III-22a**. As mentioned, the formation of such a species can take place directly from **III-1a** by a neighboring group participation. Moreover, substrate **III-1j** also ionizes easily to give a *Z*-episulfonium ion, and it isomerizes

very quickly to **III-21a**. In contrast, substrates **III-1k** and **III-1l** are more difficult to ionize because of the lack of the above anchimeric assistance. A cation like **III-21a** is considered to epimerize rapidly, resulting in the loss of the stereochemical information in the reaction of **III-1h**. The reaction of **III-1i**, however, undergoes through the formation of an episulfonium ion having an annelated 6/3 ring system, which can exist only in cis-fused form, and then gives the trans product exclusively.

Since most of synthetically interesting compounds do not have a sulfur function, the removal of such function is an important step for a sulfur-assisted reaction. Then, the author tried the desulfurization reaction of product **III-13**. By treatment of **III-13** with Raney Ni in refluxing ethanol for 4 h, the desulfurized product **III-24** was successfully obtained in 77% yield. Moreover, product **III-12** could be converted to acetoxy sulfide **III-25** by the Pummerer rearrangement,[9] which is a potential precursor for 4-alkenyl-2-cyclopentenone.



3. Experimental

General information is same as that of Experimental in Chapter II.

Silyl enol ethers **III-2a-c**, **III-2f** and ketene silyl acetal **III-2d** were synthesized according to a method in the literature.[10] Enamine **III-20**,[11] and Raney Ni[12] were prepared by a known procedure, respectively.

(*E*)-4-Acetoxy-5-phenylthio-2-pentene (III-1a). To a stirred solution of thioanisole (2.99 g, 24.1 mmol) and TMEDA (2.82 g, 24.3 mmol) in THF (120 ml) was slowly added a hexane solution of *n*-BuLi (1.62 M, 15 ml, 24.3 mmol) at -78°C. The resulting mixture was allowed to warm up to 0°C and stirred for 30 min at that temperature. Then, crotonaldehyde

(1.84 g, 26.3 mmol) in THF (15 ml) was added to the mixture at -78°C, and the stirring was continued for 1 h at that temperature and then for 1 h at room temperature. To the mixture was slowly added acetyl chloride (2.12 g, 27.0 mmol) in THF (15 ml) at -78°C. After stirring for 1 h, the reaction mixture was poured into ice-water (100 ml). The organic layer was washed twice with 1 M NaOH solution (50 ml) and once with brine (50 ml). The organic layer was dried over Na_2SO_4, and the solvent was stripped by using a rotary evaporator. Purification by column chromatography (eluent: ethyl acetate/hexane = 1/20) gave 3.19 g (56% yield) of **III-1a**. ^1H NMR (CCl_4, 60 MHz) 1.8 (3H, d, J = 6), 2.0 (3H, s), 3.2 (2H, d, J = 6), 5.2–6.0 (3H, m), 7.4 (5H, m); IR (neat) 1745, 1240, 965. Found: C, 66.09; H, 6.75%. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82%.

In a similar manner, **III-1b**, **III-1f**, and **III-1g** were obtained. Allylic acetate **III-16** was also prepared by the same procedure (*n*-BuLi was used instead of lithiated thioanisole in the absence of TMEDA).

(*E*)-4-Acetoxy-5-methylthio-2-pentene (III-1b). 61% yield; ^1H NMR (CCl_4, 60 MHz) 1.8 (3H, d, J = 6), 2.1 (3H, s), 2.2 (3H, s), 2.8 (2H, d, J = 6), 5.2–6.0 (3H, m); IR (neat) 1740, 1240, 965. Found: *m/z* 114.0504. Calcd for $C_6H_{10}S$: M-AcOH, 114.0503.

(*E*)-4-Acetoxy-2-methyl-5-phenylthio-2-pentene (III-1f). 81% yield; ^1H NMR (CCl_4, 60 MHz) 1.6 (3H, s), 1.7 (3H, s), 1.9 (3H, s), 3.0–3.2 (2H, m), 5.0–5.9 (2H, m), 7.2–7.6 (5H, m); IR (neat) 1740, 1240. Found: *m/z* 190.0816. Calcd for $C_{12}H_{14}S$: M-AcOH, 190.0816.

(*E*)-3-Acetoxy-1-phenyl-4-phenylthio-1-butene (III-1g). 57% yield; ^1H NMR (CCl_4, 60 MHz) 2.0 (3H, s), 3.2 (2H, d, J = 7), 5.6 (1H, q, J = 7), 6.2 (1H, dd, J = 7, 15), 6.7 (1H, d, J = 15), 7.2–7.6 (10H, m); IR (neat) 1745, 1240, 965. Found: C, 72.54; H, 6.13%. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08%.

(*E*)-4-Acetoxy-2-octene (III-16). NMR (CCl_4, 60 MHz) 1.0 (3H, m), 1.1–1.7 (6H, m), 1.7 (3H, d, J = 6), 2.0 (3H, s), 5.2–5.9 (3H, m); IR (neat) 1740, 1240, 965. Found: *m/z* 170.1319. Calcd for $C_{10}H_{18}O_2$: M, 170.1307.

(*E*)-*rel*-(4*R*, 5*R*)-4-Acetoxy-5-phenylthio-2-hexene (III-1h). (*E*)-2-Trimethylsiloxy-3-pentenenitrile[13] was deprotonated by LDA and allowed to react with 1-chloro-1-

(phenylthio)ethane[14] according to a method in the literature.[15] Purification by column chromatography (eluent: ethyl acetate/hexane = 1/20) gave (*E*)-2-phenylthio-4-hexen-3-one (30% yield). ^{1}H NMR (CCl_4, 60 MHz) 1.4 (3H, d, J = 7), 1.9 (3H, d, J = 6), 3.8 (1H, q, J = 7), 6.5 (1H, dm, J = 16), 6.7–7.1 (1H, m), 7.3 (5H, s).

The above ketone was treated with lithium tri-*sec*-butylborohydride according to a method in the literature,[16] and acetylated with Ac_2O/pyridine. Purification by column chromatography (eluent: ethyl acetate/hexane = 1/20) gave the title compound (48% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 1.26 (3H, d, J = 7), 1.72 (3H, dd, J = 1, 6), 1.99 (3H, s), 3.41 (1H, dq, J = 7, 6), 5.30 (1H, dd, J = 6, 7), 5.52 (1H, ddq, J = 8, 15, 1), 5.78 (1H, dq, J = 6, 15), 7.2–7.5 (5H, m); IR (neat) 1745, 1240, 965. Found: C, 67.06; H, 7.25%. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25%.

***rel*-(3*R*, 4*R*)-3-Acetoxy-4-phenylthio-1-cyclohexene (III-1i).** Allylic acetate **III-1i** was prepared through acetylation of the corresponding alcohol which was prepared according to a procedure in the literature.[17] ^{1}H NMR (CCl_4, 60 MHz) 1.5–2.4 (4H, m), 2.0 (3H, s), 3.4 (1H, m), 5.2–6.2 (3H, m), 7.4 (5H, m); IR (neat) 1735, 1235; MS 248 (M^+, 60), 188 (100), 136 (36), 135 (20), 110 (40), 109 (36). Found: *m/z* 248.0839. Calcd for $C_{14}H_{16}O_2S$: M, 248.0871.

(Z)-4-Acetoxy-5-phenylthio-2-pentene (III-1j). To a stirred solution of thioanisole (12.4 g, 100 mmol) and TMEDA (10 ml, *ca.* 100 mmol) in THF (200 ml) was slowly added a hexane solution of *n*-BuLi (1.62 mol l^{-1}, 62 ml, 100 mmol) at -78°C. The resulting mixture was allowed to warm up to 0°C and stirred for 30 min at that temperature. Then, a THF (10 ml) solution of 2-butynal, which was prepared from 2-butyn-1-ol (5 g, 70 mmol) and MnO_2 (64 g, 0.7 mol) according to a method in the literature,[18] was added to the mixture at -78°C. After removal of the cooling bath, the mixture was stirred overnight at room temperature and then poured into crushed ice. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 ml). The organic layers were combined and dried over sodium sulfate, and then the solvent was evaporated. After most of unreacted thioanisole was distilled off under reduced pressure, the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1/10) to give 1-phenylthio-3-pentyn-2-ol (1.8 g, 13% yield). ^{1}H NMR (CCl_4, 60 MHz) 1.8 (3H, d, J = 2), 2.5 (1H, br s), 3.1 (2H, d, J = 6), 4.2–4.6 (1H, m), 7.1–7.6 (5H, m).

The above alcohol was acetylated by a usual procedure (Ac_2O/pyridine, catalytic DMAP). Purification by column chromatography (eluent: ethyl acetate/hexane = 1/20) gave the corresponding acetate in quantitative yield. ^1H NMR (CCl_4, 60 MHz) 1.8 (3H, d, J = 2), 2.0 (3H, s), 3.2 (2H, d, J = 7), 5.3–5.6 (1H, m), 7.1–7.5 (5H, m).

A stirred mixture of the acetate (2.00 g, 8.5 mmol) and Lindlar catalyst (100 mg) in EtOH (50 ml) was exposed to hydrogen gas at 9.7 atm for 3 days. Filtration of the mixture, followed by evaporation of the solvent, gave the crude oil. Purification by means of column chromatography (ether/hexane = 1/20) afforded **III-1j** (0.67 g, 33% yield). ^1H NMR ($CDCl_3$, 400 MHz) 1.65 (3H, dd, J = 2, 7), 1.97 (3H, s), 3.01 (1H, dd, J = 6, 14), 3.22 (1H, dd, J = 7, 14), 5.39 (1H, ddt J = 9, 11, 2), 5.6–5.8 (2H, m), 7.2–7.4 (5H, m); IR (neat) 1740, 1240. Found: C, 66.07; H, 6.90%. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82%.

(*Z*)-4-Acetoxy-1-phenylthio-2-pentene (III-1k). To a solution of phenyl propargyl sulfide (2.00 g, 13.5 mmol) and TMEDA (1.5 ml, 15 mmol) in THF (25 ml) was added a hexane solution of *n*-BuLi (1.62 mol l^{-1}, 10.0 ml, 16.2 mmol) at -78°C. The resulting dark brown solution was stirred for 15 min at that temperature, then a THF (3 ml) solution of acetaldehyde (0.62 g, 14.1 mmol) was added to the solution. After being stirred for 15 min, a THF (3 ml) solution of acetyl chloride (1.44 g, 18.3 mmol) was added, and the mixture was stirred overnight at room temperature. Usual aqueous workup, followed by column chromatography (eluent: ethyl acetate/hexane = 1/20), gave 4-acetoxy-1-phenylthio-2-pentyne (1.80 g, 57% yield). ^1H NMR (CCl_4, 60 MHz) 1.4 (3H, d, J = 7), 2.0 (3H, s), 3.6 (2H, broad s), 5.4 (1H, broad q), 7.2–7.6 (5H, m).

A stirred mixture of the above alkyne (2.00 g, 8.5 mmol) and Lindlar catalyst (100 mg) in 70 ml of EtOH was exposed to hydrogen gas at 9.7 atm for 5 days. Filtration of the mixture, followed by evaporation of the solvent, gave the crude oil. Purification by means of column chromatography (ether/hexane = 1/20) afforded **III-1k** (0.87 g, 43% yield). ^1H NMR ($CDCl_3$, 400 MHz) 1.10 (3H, d, J = 6), 2.00 (3H, s), 3.55 (1H, ddd, J = 1, 7, 13), 3.76 (1H, ddd, J = 1, 9, 13), 5.43 (1H, ddt J = 9, 10, 1), 5.49 (1H, dq, J = 9, 6), 5.62 (1H, ddd, J = 7, 9, 10), 7.1–7.4 (5H, m); IR (neat) 1735, 1250. Found: C, 66.13; H, 6.72%. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82%.

(*E*)-4-Acetoxy-1-phenylthio-2-pentene (III-1l). An ethereal solution of MeLi (1.06 mol l^{-1}, 9.0 ml, 9.5 mmol) was diluted with 10 ml of THF, and the solution was cooled to 0°C. Then, a THF (5 ml) solution of 4-(phenylthio)crotonaldehyde[19] (1.60 g, 9.0 mmol) was added to the above partially-solidified solution. The reaction mixture was allowed to warm up to room temperature, stirred for 10 min, and poured into ice-water (100 ml). The organic layer was washed successively with saturated aqueous NH_4Cl, water, and brine. After the organic layer was dried over Na_2SO_4, the solvent was evaporated. Column chromatography (eluent: ethyl acetate/hexane = 1/5) was performed to remove less polar by-products. Then, the crude product obtained upon concentration of the fractions containing the main product was acetylated according to a usual procedure (Ac_2O/pyridine, catalytic DMAP) to give 1.27 g (60% yield) of **III-1l** after purification by column chromatography (eluent: ethyl acetate/hexane = 1/20). ^1H NMR ($CDCl_3$, 400 MHz) 1.19 (3H, d, J = 6), 2.00 (3H, s), 3.49 (2H, d, J = 7), 5.26 (1H, dq J = 6, 6), 5.48 (1H, ddt, J = 6, 15, 1), 5.73 (1H, ddt, J = 1, 15, 7), 7.1–7.4 (5H, m); IR (neat) 1740, 1240, 955. Found: *m/z* 236.0845. Calcd for $C_{13}H_{16}O_2S$: M, 236.0871.

Allylic acetate **III-1e** was synthesized in a similar manner.

4-Acetoxy-2-methyl-1-phenylthio-2-pentene (III-1e). 55% yield (ca. 1:1 mixture of diastereomers); ^1H NMR (CCl_4, 60 MHz) 1.1 (3H, d, J = 6), 1.8 (3H, s), 1.9 (3H, s), 3.4 (2H, s), 5.0–5.6 (2H, m), 7.1–7.5 (5H, m); IR (neat) 1735, 1245. Found: *m/z* 250.1041. Calcd for $C_{14}H_{18}O_2S$: M, 250.1027.

(*E*)-2,2-Dimethyl-5-phenylthiomethyl-6-octen-3-one (α-III-3) and 2,2,5-Trimethyl-8-phenylthio-6-octen-3-one (γ-III-3). To a solution of **III-1a** (0.41 mmol) and **III-2a** (0.50 mmol) in CH_2Cl_2 (4 ml) was added a CH_2Cl_2 solution of TMSOTf (1.0 mol l^{-1}, 0.05 ml, 0.05 mmol) at -78°C. Then, the cooling bath was removed, and the mixture was stirred for 2 h. After addition of saturated aqueous $NaHCO_3$ (8 ml), the organic materials were extracted with CH_2Cl_2 (3 × 5 ml). The extracts were combined and then dried over Na_2SO_4, and the solvent was evaporated. Purification by preparative TLC gave **III-3** as an inseparable mixture of regioisomers. IR (neat) 1700, 1475, 960, 735, and 690. Found: C, 73.88; H, 8.78%. Calcd for $C_{17}H_{24}OS$: C, 73.86; H, 8.75%. ^1H NMR ($CDCl_3$, 400 MHz) for α-**III-3** 1.18 (9H, s), 1.71 (3H, dd, J = 2,6), 2.69 (1H, dd, J = 7, 17), 2.81 (1H, dd, J = 6, 17), 3.0 (1H, m), 3.04 (2H, d, J =

7), 5.40 (1H, ddq, J = 8, 15, 2), 5.56 (1H, dq, J = 6, 15), 7.1–7.4 (5H, m); for γ-**III-3** (only distinguishable peaks were recorded) 0.97 (3H, d, J = 7), 1.16 (9H, s), 2.42 (1H, d, J = 7), 3.55 (2H, d, J = 6).

In a similar manner, other products **III-4–15** and **III-17** were obtained. The ratio of regioisomers was determined by means of glc or ^{1}H NMR.

(*E*)-2,4,4-Trimethyl-5-phenylthiomethyl-6-octen-3-one (α-III-4) and (*E*)-2,4,4,5-Tetramethyl-8-phenylthio-6-octen-3-one (γ-III-4). IR (neat) 1690, 1460, 725, 680. Found: *m/z* 290.1665. Calcd for $C_{18}H_{26}OS$: M, 290.1704. ^{1}H NMR ($CDCl_3$, 400 MHz) for α-**III-4** 0.99 (3H, d, J = 7), 1.01 (3H, d, J = 7), 1.09 (3H, s), 1.10 (3H, s), 1.70 (3H, dd, J = 2, 7), 2.57 (1H, ddd, J = 3, 10, 11), 2.76 (1H, dd, J = 11, 12), 2.82 (1H, dd, J = 3, 12), 3.04 (1H, quintet, J = 7), 5.18 (1H, ddq, J = 9, 15, 2), 5.53 (1H, ddq, J = 1, 15, 7), 7.1–7.3 (5H, m); for γ-**III-4** 0.78 (3H, d, J = 7), 0.90 (3H, s), 0.92 (3H, s), 2.48 (1H, dq, J = 7, 7), 3.51 (2H, dq like, J = 7, 1), 5.36 (1H, ddt, J = 8, 15, 1).

(*E*)-2,4,4-Trimethyl-5-methylthiomethyl-6-octen-3-one (α-III-5) and 2,4,4,5-Tetramethyl-8-methylthio-6-octen-3-one (γ-III-5). IR (neat) 1705, 970. Found: *m/z* 228.1563. Calcd for $C_{13}H_{24}OS$: M, 228.1548. ^{1}H NMR ($CDCl_3$, 400 MHz) for α-**III-5** 1.03 (3H, d, J = 7), 1.05 (3H, d, J = 7), 1.07 (3H, s), 1.09 (3H, s), 1.72 (3H, dd, J = 1, 6), 2.05 (3H, s), 2.33 (2H, d, J = 7), 2.56 (1H, dt, J = 9, 7), 3.09 (1H, dq, J = 7, 7), 5.18 (1H, ddq, J = 9, 15, 1), 5.56 (1H, ddq, J = 1, 15, 6); for γ-**III-5** 0.90 (3H, d, J = 7), 2.04 (3H, s).

2,2,5,7-Tetramethyl-8-phenylthio-6-octen-3-one (γ-III-6). 1:1 mixture of diastereomers; ^{1}H NMR (CCl_4, 60 MHz) 0.8 (3H, two doublets, J = 7), 1.1 (9H, s), 1.8 (3H, s), 2.2 (2H, d, J = 7), 2.3 (1H, m), 3.4–3.7 (2H, m), 4.8–5.1 (1H, m), 7.1–7.5 (5H, m); IR (neat) 1710, 740, 690. Found: *m/z* 290.1717. Calcd for $C_{18}H_{26}OS$: M, 290.1705.

2,2,7-Trimethyl-5-phenylthiomethyl-6-octen-3-one (α-III-7). ^{1}H NMR (CCl_4, 60 MHz) 1.1 (9H, s), 1.6 (3H, s), 1.7 (3H, s), 2.4–3.2 (5H, m), 4.8–5.1 (1H, m), 7.1–7.5 (5H, m); IR (neat) 1710, 1480, 735, 690. Found: *m/z* 290.1703. Calcd for $C_{18}H_{26}OS$: M, 290.1705.

(*E*)-2-Methyl-5-phenylthio-1,3-pentadiene (III-8). ^{1}H NMR (CCl_4, 60 MHz) 1.8 (3H, s), 3.6 (2H, d, J = 7), 4.9 (2H, broad s), 5.4–5.9 (1H, m), 6.2 (1H, d, J = 16), 7.1–7.5 (5H,

m); IR (neat) 1480, 1440, 965, 740, 690. Found: *m/z* 190.0780. Calcd for $C_{12}H_{14}S$: M, 190.0816.

(*E*)-2-(1-Phenylthiomethyl-2-butenyl)cyclohexanone (α-III-9) and 2-(2-Methyl-4-phenylthio-2-butenyl)cyclohexanone (γ-III-9). IR (neat) 1710, 970, 740, 695. Found: C, 74.11; H, 8.02%. Calcd for $C_{17}H_{22}OS$: C, 74.40; H, 8.08%. ^{1}H NMR ($CDCl_3$, 400 MHz) for **α-III-9** (a mixture of two diastereomers which are tentatively named as αA and αB, and the assignment of every separated peak for each diastereomer is arbitrary) 1.65 (3H for αA, dd, *J* = 1, another *J* value is missing because of the overlapping of the signal), 1.66 (3H for αB, dd, *J* = 2, another *J* value is missing because of the overlapping of the signal), 1.4–2.0 (6H, m), 2.2–2.8 (4H, m), 2.96 (1H for αA, dd, *J* = 7, 13), 2.99 (1H for αB, dd, *J* = 8, 13), 3.02 (1H for αA, dd, *J* = 6, 13), 3.22 (1H for αB, dd, *J* = 6, 13), 5.24 (1H for αA, ddq, *J* = 8, 15, 2), 5.4–5.6 (1H for αA and 2H for αB, m), 7.1–7.4 (5H, m); for **γ-III-9** (γA and γB, tentatively) 0.89 (3H for γA, d, *J* = 7), 0.90 (3H for γB, d, *J* = 7), 3.48 (2H for γA, d, *J* = 6), 3.50 (2H for γB, d, *J* = 5).

Methyl (*E*)-2,2-dimethyl-3-phenylthiomethyl-4-hexenoate (α-III-10) and Methyl (*E*)-2,2,3-trimethyl-6-phenylthio-4-hexenoate (γ-III-10). IR (neat) 1730, 1480, 970, 760, 690. Found: C, 68.99; H, 7.96%. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.96%. ^{1}H NMR ($CDCl_3$, 400 MHz) for **α-III-10** 1.12 (3H, s), 1.13 (3H, s), 1.70 (3H, dd, *J* = 2, 6), 2.51 (1H, ddd, *J* = 3, 11, 11), 2.76 (1H, dd, *J* = 11, 12), 2.96 (1H, dd, *J* = 3, 12), 3.61 (3H, s), 5.17 (1H, ddq, *J* = 8, 15, 2), 5.52 (1H, dd, *J* = 15, 7), 7.1–7.3 (5H, m); for **γ-III-10** 0.84 (3H, d, *J* = 7), 0.97 (3H, s), 0.97 (3H, s), 2.42 (1H, dq, *J* = 7, 7), 3.50 (2H, d, *J* = 7), 3.65 (3H, s), 5.38 (1H, ddt, *J* = 9, 15, 1).

(*E*)-4-Phenylthiomethyl-1,5-heptadiene (α-III-11) and 4-Methyl-7-phenylthio-1,5-heptadiene (γ-III-11). IR (neat) 1640, 1485, 965, 915, 740, 690. Found: *m/z* 218.1146. Calcd for $C_{14}H_{18}S$: M, 218.1129. ^{1}H NMR ($CDCl_3$, 400 MHz) for **α-III-11** 1.66 (3H, dd, *J* = 2, 6), 2.1–2.4 (3H, m), 2.88 (1H, dd, *J* = 7, 13), 2.94 (1H, dd, *J* = 6, 13), 4.9–5.1 (2H, m), 5.30 (1H, ddq, *J* = 8, 15, 2), 5.47 (1H, ddq, *J* = 1, 15, 6), 5.7–5.8 (1H, m), 7.1–7.4 (5H, m); for **γ-III-11** 0.91 (3H, d, *J* = 7), 3.57 (2H, d, *J* = 7).

(*E*)-6-Phenyl-4-phenylthiomethyl-5-hexen-2-one (α-III-12) and (*E*)-4-Phenyl-7-phenylthio-5-hepten-2-one (γ-III-12). IR (neat) 1715, 1360, 965, 745, 690. Found: *m/z* 296.1255. Calcd for $C_{19}H_{20}OS$: M, 296.1275. ^{1}H NMR ($CDCl_3$, 400 MHz) for **α-III-12** 2.08

(3H, s), 2.61 (1H, dd, J = 7, 17), 2.84 (1H, dd, J = 5, 17), 3.0–3.1 (3H, m), 6.09 (1H, dd, J = 7, 16), 6.41 (1H, d, J = 16), 7.1–7.4 (10H, m); for γ-**III-12** 2.00 (3H, s), 2.71 (2H, d, J = 7), 3.46 (2H, d like, J = 7), 3.83 (1H, q like, J = 7), 5.46 (1H, dt, J = 15, 7), 5.61 (1H, dd, J = 7, 15).

(*E*)-2,2-Dimethyl-7-phenyl-5-phenylthiomethyl-6-hepten-3-one (α-13) and (*E*)-2,2-Dimethyl--5-phenyl-8-phenylthio-6-octen-3-one (γ-III-13). IR (neat) 1710, 1480, 970, 750, 695. Found: *m/z* 338.1683. Calcd for $C_{22}H_{26}OS$: M, 338.1704. ^1H NMR ($CDCl_3$, 400 MHz) for α-**III-13** 1.21 (9H, s), 2.84 (1H, dd, J = 7, 18), 2.95 (1H, dd, J = 5, 18), 3.2 (3H, m), 6.20 (1H, dd, J = 8, 16), 6.50 (1H, d, J = 16), 7.2–7.4 (10H, m); for γ-**III-13** 1.10 (9H, s), 3.58 (2H, d, J = 7), 4.02 (1H, qm, J = 7), 5.58 (1H, ddt, J = 1, 7, 15), 5.74 (1H, ddt, J = 1, 7, 15); MS for α-**III-13** 228 (M-PhSH$^+$, 15), 171 (11), 142 (15), 129 (29), 128 (49), 123 ($PhSCH_2^+$, 15), 85 (23), 57 (100), for γ-**III-13** 229 (M-PhS$^+$, 27), 228 (10), 129 (42), 128 (25), 85 (52), 57 (100).

(*E*)-2,2-Dimethyl-5-[1-(phenylthio)ethyl]-6-octen-3-one (α-III-14). ^1H NMR (CCl_4, 60 MHz) 1.1 (9H, s), 1.0–1.5 (3H, m), 1.7 (3H, m), 2.5–3.5 (4H, m), 5.3–5.5 (2H, m), 7.1–7.5 (5H, m); ($CDCl_3$, 400 MHz) 1.09 (9H, s), 1.12 (9H, s), 1.63 (3H, dd, J = 2, 6), 1.66 (3H, dd, J = 2, 6); IR (neat) 1710, 1480, 970, 750, 695; MS (identical for both diastereomers) 290 (M$^+$, 2), 190 (7), 137 (M-$PhSCHCH_3^+$, 100), 57 (78). Found: C, 74.70; H, 9.07%. Calcd for $C_{18}H_{26}OS$: C, 74.43; H, 9.02%.

3,3-Dimethyl-1-[(1*R, 6*R**)-6-phenylthio-2-cyclohexenyl]-2-butanone (α-III-15).** ^1H NMR ($CDCl_3$, 400 MHz) 1.14 (9H, s), 1.7 (1H, m), 2.0–2.2 (3H, m), 2.55 (1H, dd, J = 9, 18), 2.7 (1H, m), 3.00 (1H, dd, J = 4, 18), 3.02 (1H, ddd, J = 3, 9, 10, PhSC*H*), 5.45 (1H, dm, J = 10), 5.7 (1H, m), 7.3 (3H, m), 7.4 (2H, m); IR (neat) 1715, 1485, 1375, 745, 700. Found: *m/z* 288.1564. Calcd for $C_{18}H_{24}OS$: M, 288.1548.

(*E*)-5-Butyl-2,2-dimethyl-6-octen-3-one (α-III-17) and (*E*)-2,2,5-Trimethyl-6-undecen-3-one (γ-III-17). IR (neat) 1715, 975. Found: *m/z* 210.1996. Calcd for $C_{14}H_{26}O$: M, 210.1983. ^1H NMR ($CDCl_3$, 400 MHz) for α-**III-17** 0.8–0.9 (3H, m), 1.10 (9H, s), 1.2–1.3 (6H, m), 1.62 (3H, dd, J = 2, 7), 2.3–2.5 (2H, m), 2.5–2.6 (1H, m), 5.17 (1H, ddq, J = 9, 15, 2), 5.4 (1H, m); for γ-**III-17** 0.95 (3H, d, J = 7), 1.11 (9H, s), 1.9–2.0 (2H, m), 2.7–2.8 (1H, m), 5.30 (1H, dd, J = 7, 15).

Desulfurization of III-13. To an EtOH (10 ml) solution of **III-13** (258 mg, 0.76 mmol; $\alpha/\gamma = 92/8$) was added an EtOH suspension of Raney Ni W-2 (ca. 5 g), and the mixture was heated to reflux for 4 h. Filtration, followed by evaporation and separation by preparative TLC, gave 135 mg (77% yield) of desulfurized product **III-24** as a 92/8 mixture of regioisomers. IR (neat) 1710, 970, 750, 690. Found: *m/z* 230.1679. Calcd for $C_{16}H_{22}O$: M, 230.1670. ^1H NMR ($CDCl_3$, 400 MHz) for major isomer 1.08 (3H, d, $J = 7$), 1.12 (9H, s), 2.50 (1H, dd, $J = 7$, 17), 2.60 (1H, dd, $J = 6$, 17), 2.9–3.0 (1H, m), 6.13 (1H, dd, $J = 7$, 16), 6.37 (1H, d, $J = 17$), 7.2–7.4 (5H, m); for minor isomer 1.72 (3H, d, $J = 7$), 5.4–5.6 (2H, m); MS for major isomer *m/z* (rel intensity) 230 (M^+, 5), 173 (11), 131 (43), 91 (18), 85 (12), 57 (100), for minor isomer *m/z* (rel intensity) 173 (20), 131 (72), 91 (21), 57 (100).

(*E*)-4-[Acetoxy(phenylthio)methyl]-6-phenyl-5-hexen-2-one (III-25). To a CH_2Cl_2 (4 ml) solution of **III-12** (495 mg, 1.55 mmol; $\alpha/\gamma = 93/7$) was added a CH_2Cl_2 (6 ml) solution of *m*-chloroperbenzoic acid (*m*-CPBA) (83% purity, 326 mg, 1.57 mmol) at -78°C. The mixture was allowed to warm up gradually to room temperature and stirred for 1 h. Then, saturated aqueous $NaHCO_3$ (5 ml) and Na_2SO_3 (2 ml) were added, and the organic materials were extracted with 5 ml of CH_2Cl_2. The extracts were dried over Na_2SO_4. After evaporation of the solvent, the crude oil was purified by means of column chromatography (eluent: ethyl acetate/hexane = 2/1) to afford 474 mg (91% yield) of the intermediate sulfoxide. ^1H NMR (CCl_4, 60 MHz) 2.1 (3 × 0.5H, s), 2.2 (3 × 0.5H, s), 2.6–3.6 (5H, m), 6.3–6.6 (2H, m), 7.2–7.8 (10H, m); IR (neat) 1715, 1360, 1040, 965, 750, 690.

The above sulfoxide (474 mg, 1.52 mmol) was dissolved in Ac_2O (10 ml), and anhydrous NaOAc (0.47 g, 5.73 mmol) was added to the solution. The mixture was refluxed for 5 h. Evaporation of the solvent, followed by column chromatography (eluent: ethyl acetate/hexane = 1/10), gave **III-25** (108 mg, 20% yield) as a mixture of diastereomers. ^1H NMR (CCl_4, 60 MHz) 2.0 (3 × 0.5H, s), 2.1 (3 × 0.5H, s), 2.1 (3 × 0.5H, s), 2.2 (3 × 0.5H, s), 2.5–2.9 (2H, m), 3.1–3.5 (1H, m), 5.8–6.8 (3H, m), 7.1–7.6 (10H, m); IR (neat) 1745, 1720, 1220, 1020, 965, 750, 690. Found: *m/z* 294.1056. Calcd for $C_{19}H_{18}OS$: M-AcOH, 294.1078.

Theoretical calculations. Molecular orbital calculations were performed on HITAC M-880 by using MOPAC Ver. 6.01 with complete geometry optimization.[20]

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CHAPTER IV. ANTI-SELECTIVE REACTION OF α-SULFENYL ACETALS WITH SILYLATED CARBON NUCLEOPHILES

Summary: In the presence of a Lewis acid, α-sulfenyl acetals **IV-1** reacted with various silylated carbon nucleophiles **IV-2** to give anti adducts (*anti*-**IV-3**) with high diastereoselectivity. The stereochemistry was only slightly affected by the reaction conditions, such as temperature, solvent, and Lewis acid. However, the structure of substrate **IV-1** and the kind of nucleophile **IV-2** had considerable effect on the stereochemical course of the reaction. Almost exclusive anti selectivity was attained when 1,1-dimethoxy-2-(*tert*-butylthio)propane (**IV-1b**) was used as a substrate, or when ketene silyl acetal **IV-2c** was employed as a nucleophile. The mechanism of this reaction is essentially S_N2, although the S_N1 process participates to a various extent, depending on the structure of substrate **IV-1**. The usefulness of this anti-selective reaction was exemplified by the easy transformation of *anti*-**IV-3o** to synthetically valuable allylic alcohol *anti*-**IV-6** without any loss of stereochemical information. The reaction of α-benzyloxy acetal **IV-4** with **IV-2** was also investigated. It gave a syn-rich mixture of diastereomers with lower selectivity.

1. Introduction

The Lewis acid-promoted reaction of acetals with nucleophiles is now one of the most common strategies for C-C bond formation; it has been widely investigated by using various types of nucleophiles and activators.[1] Concerning the stereochemical aspect, the reaction of acyclic acetals with silyl enol ethers proceeds syn-selectively, irrespective of the nucleophile geometry. This selectivity is rationalized by assuming an antiperiplanar orientation of the nucleophile and an intermediate oxocarbenium ion.[2] For such an aldol-type reaction there is another interest regarding acyclic stereoselection, i. e., asymmetric induction. From this point of view, the reaction of α-chiral *aldehydes* has been intensively studied both experimentally[3] and theoretically.[4] In contrast, the corresponding *acetals* have not been much explored. Regarding this matter, Heathcock and co-workers elegantly pointed out that the Cram-selectivity of the reaction of α-chiral thioacetals

increases proportionally with increasing the steric bulkiness of the alkylthio group.[5] More recently, they systematically investigated the stereochemical course of the reaction of α-chiral oxoacetals, and arrived at the same conclusion concerning the size of the alkoxy group.[6]

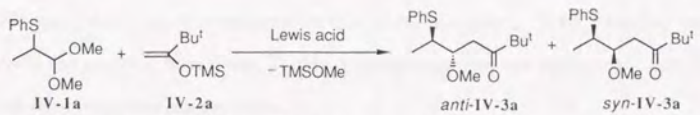
On the other hand, for the reaction of aldehydes, it is well-known that a heteroatom attached to the α-chiral position affects the stereochemistry of the product (chelation/non-chelation control), and that in many cases the selectivity is very high.[7] Taking into account the above-mentioned fact, the reaction of α-heteroatom-substituted α-chiral acetals is of great interest. Although there have been several studies concerning the reaction of such a substrate, only a few refer to the stereochemical course of the reaction. The reactions of 1,1-dimethoxy-2-siloxypropane with a silyl enol ether[8] or a lithium allylborate[9] have been reported by two groups; in both cases, 1/1 mixtures of diastereomers are obtained. The reaction of α-(Boc-amino)acetals with allylsilane gives the corresponding adducts with very low selectivity (anti/syn ≈ 2/1); when the acetal moiety is changed to a chiral one, the template effect of the chiral acetal moiety overrides the 1,2-asymmetric induction, indicating that the 1,2-asymmetric induction is scarcely realized in the reaction.[10] In contrast, excellent stereoselectivity is attained in the reaction of α-(siloxy)diselenoacetals. However, the substrate acts as a nucleophilic species in this case; this reaction proceeds through a lithium-selenium exchange and subsequent C-C bond formation.[11]

Thus, there is no example of highly efficient 1,2-asymmetric induction for the nucleophilic displacement of α-heteroatom-substituted α-chiral acetals. Concerning this matter, the author considered that if the neighboring group participation occurs toward the oxocarbenium ion, the selectivity might increase due to the steric demand of the intermediate episulfonium ion. Therefore, the reaction of α-sulfenyl acetal was attempted.

2. Results and Discussion

At first, the reaction of **IV-1a** with pinacolone-derived silyl enol ether **IV-2a** was carried out in dichloromethane at -78°C in the presence of tin(IV) chloride. The adduct was obtained in 87% yield with a ratio of anti/syn = 87/13; good anti selectivity was observed. Encouraged by this

finding, the author optimized the reaction conditions by using **IV-1a** and **IV-2a**. The results are given in Table IV-1.



IV-1a **IV-2a** *anti*-**IV-3a** *syn*-**IV-3a**

Table IV-1. Reaction of **IV-1a** and **IV-2a** under Various Conditions[a]

Entry	Lewis acid	Solvent	Temp/°C	Yield/%	Anti/Syn
1	$SnCl_4$	CH_2Cl_2	-95	84	78/22
2			-78	87	87/13
3			-45	82	85/15
4			-20	82	88/12
5			0	71	86/14
6		Toluene	-78	61	89/11
7		Et_2O	-78 to rt	0	–
8		CH_3CN	-40	87	93/7
9	$TiCl_4$			88	92/8
10	$BF_3{\cdot}OEt_2$			80	92/8
11	TMSOTf[b]			85	91/9
12	cat. TMSOTf[b,c]			92	92/8

[a] 1.1 equiv. Lewis acid was added to a mixture of **IV-1a** (1.0 equiv.) and **IV-2a** (2.0 equiv.).
[b] 1.2 equiv. **IV-2a** was used. [c] 5 mol% TMSOTf was used.

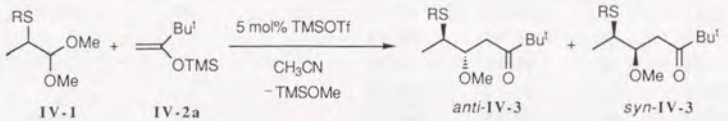
The reaction was carried out at various temperatures (Entries 1-5). The reaction proceeded very smoothly, even at -78°C; a TLC check after 5 min upon the addition of an activator indicated completion of the reaction. The yield was somewhat lower at 0°C because of a partial decomposition of the substrates. An unusual temperature effect for a 1,2-asymmetric induction was observed; the anti selectivity was almost identical between -78°C and 0°C, and slightly lowered at -95°C.

The solvent effect was also subtle (Entries 2, 6-8). The anti selectivity was slightly better in acetonitrile than in the other solvents. When ether was used as a solvent, the reaction did not proceed; the coordination of the solvent might be so strong that the Lewis acid could not activate the substrate.

It is noteworthy that the nature of the Lewis acid (acidity, chelation ability) scarcely affected the stereoselectivity (Entries 8-12).[12] However, among the Lewis acids examined, TMSOTf was practically advantageous for this reaction because: 1) the handling was easy in acetonitrile (no complex formation), 2) only a catalytic amount was sufficient,[2a] and 3) both the yield and selectivity were slightly better.

On the basis of these observations the auther concluded that the optimum reaction conditions were those of Entry 12 in Table IV-1; afterwards the reaction was conducted under such conditions.

The sulfenyl moiety exhibited some influence upon the diastereoselectivity (Table IV-2). A very high anti selectivity was attained for the reaction of substrate **IV-1b** having a *tert*-butylthio group; only one isomer could be detected by GC and ^{1}H NMR. With this substrate, however, an equimolar amount of TMSOTf was required, indicating that α-(*tert*-butylthio)acetal is disadvantageous from the viewpoint of a catalytic reaction.



IV-1 **IV-2a** *anti*-**IV-3** *syn*-**IV-3**

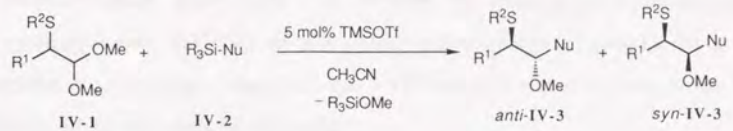
Table IV-2. Effect of Sulfenyl Group

Entry	Substrate	R	Product	Yield/%	Anti/Syn
1	**IV-1a**	Ph	**IV-3a**	92	92/8
2	**IV-1b**	^{t}Bu	**IV-3b**	81[a]	>99/1
3	**IV-1c**	Et	**IV-3c**	88	92/8
4	**IV-1d**	Me	**IV-3d**	83	95/5

[a] 1.1 equiv. TMSOTf was used.

In the next stage, the reactions of several substrates and nucleophiles were carried out in order to elucidate the generality of this reaction (Table IV-3). In most cases, the reaction proceeded with high anti selectivity, although the selectivity was dependent on the kind of nucleophile (Entries 1-4). Nucleophile **IV-2c** showed excellent diastereoselectivity (Entries 3, 9); even with substrate **IV-1h**, which gave very low anti selectivity in the reaction of **IV-2a**, only

one diastereomer was detectable (compare Entries 8 and 9). Moreover, for the reaction of α-(methylthio)acetals, the stereoselectivity was markedly dependent on the carbon framework of the acetals; the reaction of substrates without a branch at the β position proceeded with high anti selectivity (anti/syn ≥ 9/1; Entries 1, 5, 6), whereas the selectivity for substrates having a branch at that position was much lower (anti/syn = 6/4; Entries 7, 8).[13]



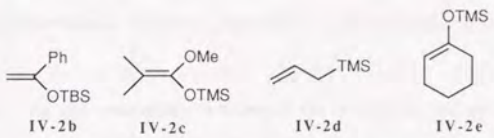


Table IV-3. Reaction of Various α-Sulfenyl Acetals with Silylated Carbon Nucleophiles

Entry	Substrate	R^1	R^2	Nucleophile	Product	Yield/%	Anti/Syn
1	**IV-1d**	Me	Me	**IV-2a**	**IV-3d**	83	95/5
2				**IV-2b**	**IV-3e**	87	94/6
3				**IV-2c**	**IV-3f**	88	>99/1
4				**IV-2d**	**IV-3g**	57	75/25
5	**IV-1e**	Et		**IV-2a**	**IV-3h**	78	98/2
6	**IV-1f**	Bn			**IV-3i**	86	90/10
7	**IV-1g**	Ph			**IV-3j**	80	59/41
8	**IV-1h**	^{i}Pr			**IV-3k**	58	59/41
9				**IV-2c**	**IV-3l**	83	>99/1
10	**IV-1b**	Me	^{t}Bu	**IV-2a**	**IV-3b**	81[a]	>99/1
11				**IV-2d**	**IV-3m**	35[a]	97/3
12	**IV-1i**	Bu	Me		**IV-3n**	66	88/12
13	**IV-1j**	(*E*)-MeCH=CH-	Ph	**IV-2a**	**IV-3o**	89	87/13
14	**IV-1a**	Me	Ph	**IV-2e**	**IV-3p**	93	78/22[b]

[a]1.1 equiv. TMSOTf was used. [b]Four diastereomers were obtained in a ratio of 57:17:21:5. On the basis of the diastereomer ratio, simple diastereoselection was estimated to be syn/anti = 74/26. The main product was (2*R**,1'*R**,2'*S**)-2-(1-methoxy-2-phenylthiopropyl)cyclohexanone.

In order to clarify the effect of the α-sulfenyl group on simple diastereoselection in the aldol reaction of the acetals, the reaction of **IV-1a** with **IV-2e** was carried out (Entry 14 and footnote *b* in Table IV-3). As a result, the simple diastereoselection was 3/1 for syn/anti, which is

much lower than that of the TMSOTf-promoted reaction of 1,1-dimethoxy-2-methylpropane, an α-branched achiral acetal, with **IV-2e** (6/1 for syn/anti).[2a] This result indicates that α-sulfenyl acetals are less favorable for simple diastereoselection than are achiral acetals.

Heathcock's group[6] and Denmark's group[12] have independently reported that when methoxy groups of acetals are changed to bulkier isopropoxy groups, the stereochemical result of the reaction changes dramatically. In contrast, the reaction of 1,1-diisopropoxy-2-(phenylthio)propane (**IV-1k**), an isopropoxy analog of **IV-1a**, with **IV-2a** gave the corresponding adduct with a ratio of anti/syn = 93/7, which is almost the same as that for the reaction of **IV-1a** with **IV-2a** (anti/syn = 92/8).

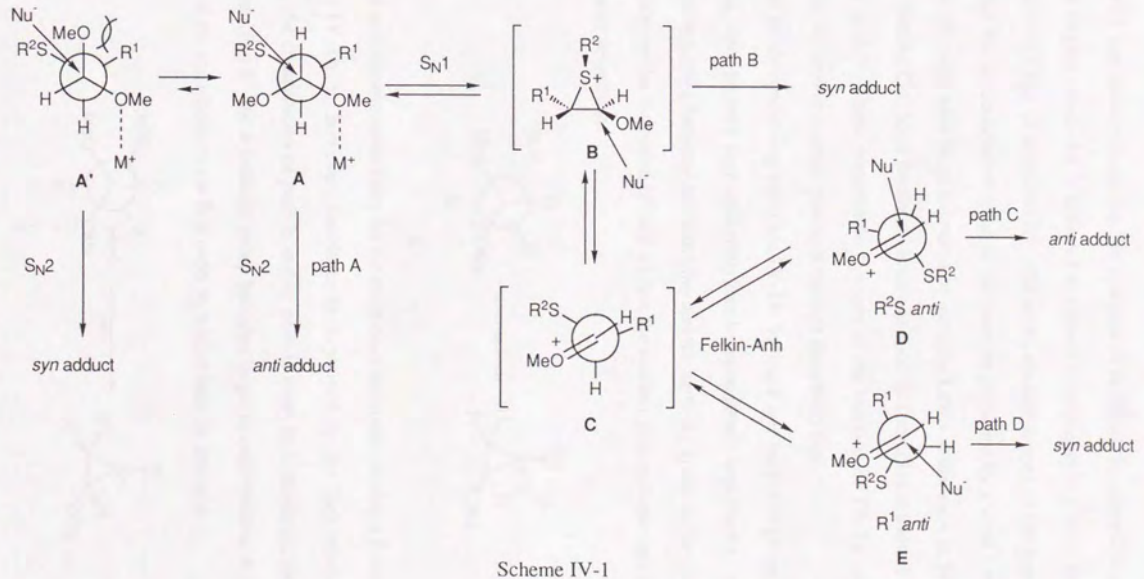
For the present reaction, several reaction paths are considered to be possible, as depicted in Scheme IV-1.

The Lewis acid can coordinate to either of the two alkoxy groups of the acetal moiety. However, the dissociation of C-O bond would take place more easily when the Lewis acid coordinates to the alkoxy group antiperiplanar to the C-S bond, because of the hyperconjugative effect of the C-S bond.[14] Among the conformers of the complex, conformer **A** is more favorable, taking into account the steric repulsion. As a result, the nucleophilic attack occurs toward the acetal center (path A) to lead the preferential formation of the anti isomer.

On the other hand, the episulfonium ion **B** can be formed by a neighboring group participation of the sulfenyl group.[15] When a nucleophilic attack occurs on **B** directly, the syn isomer is obtained (path B). Moreover, oxocarbenium ion **C** can possibly be formed by a further transformation of **B**; the stereochemistry is determined by the Felkin-Anh model of two possible conformers, **D** and **E**, which give the anti and syn adducts, respectively. Due to the electronic effect of the sulfenyl group, conformer **D** is considered to be preferable; the anti isomer becomes the main product (path C).

Thus, the observed anti selectivity would be explained by either path A (S_N2 mechanism) or path C (S_N1 mechanism).

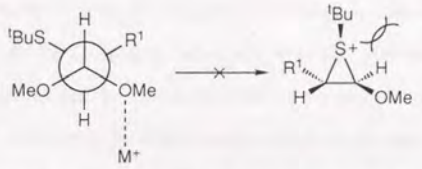
As described above, the stereoselectivity of the reaction of **IV-1a** with **IV-2a** was hardly affected by the reaction conditions such as the temperature and the solvent. This fact is in sharp


Nu⁻
MeO
R²S
R¹
H
OMe
M⁺
A'
A
S_N1
B
path B
syn adduct
S_N2
path A
anti adduct
C
Felkin-Anh
path C
D
R²S anti
path D
E
R¹ anti

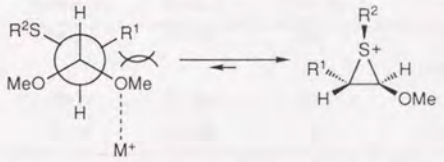
Scheme IV-1

contrast with the result concerning the reaction of α-chiral 1,1-dimethoxy-2-phenylpropane with**IV-2a** (higher selectivity is achieved at a lower temperature in a more polar solvent), which proceeds through S_N1 in acetonitrile.[6] Moreover, another feature of the reaction of **IV-1a** with **IV-2a** is that the stereochemical result of the reaction promoted by a weak Lewis acid, TMSOTf, was almost identical with those promoted by stronger Lewis acids, such as $BF_3{\cdot}OEt_2$ and $SnCl_4$, indicating that the C-C bond formation occurs as soon as a complex is formed between **IV-1a** and the Lewis acid.[16] These remarkable features of the reaction of **IV-1a** with **IV-2a** strongly indicate that the present reaction proceeds through essentially S_N2.

The result concerning substrate **IV-1b**, having a *tert*-butylthio group, supports this S_N2 mechanism, since its very high selectivity can be consistently explained as follows: There is a severe steric repulsion between *tert*-butylthio and the methoxy group in the episulfonium ion **B** to seriously depress the formation of such an ion; the reaction proceeds through only path A to give the anti isomer selectively.



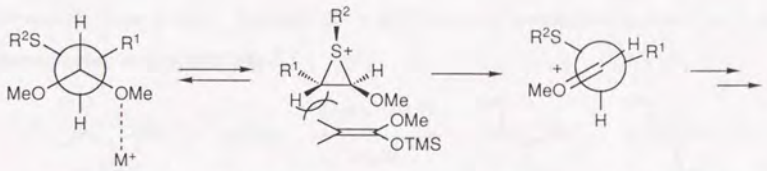
The low diastereoselectivity for the reaction of substrates having a β-branched alkyl group, **IV-1g** and **IV-1h**, is, however, unable to be explained by the S_N2 mechanism. For these substrates, the contribution of path B and/or path D must be considered; the steric interaction between branched R^1 and a methoxy group becomes larger in conformation **A**, thus prompting the formation of the episulfonium ion **B** in order to release such an interaction.



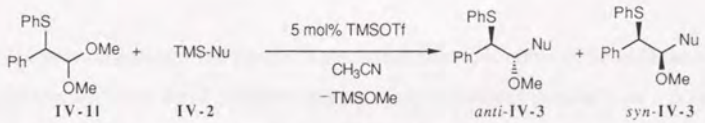
The rather abnormal temperature effect in this reaction can also be consistently explained by this reaction scheme. The intramolecular formation of the episulfonium ion would be faster

than an intermolecular substitution reaction at a lower temperature due to a favorable entropy factor. Since the ionic species reacts more easily than does the non-ionic one, the contribution of path B might become larger at -95°C.

Concerning the quite high anti selectivity observed for the reaction of nucleophile **IV-2c**, even with a β-branched α-sulfenyl acetal, the steric repulsion between the nucleophile and electrophile may play an important role. A molecular model study revealed that there is a substantial repulsive interaction between **IV-2c** and the episulfonium ion **B**; the contribution of path B might be repressed. Subsequently, the reaction occurs via path A and/or path C to give the anti adducts selectively.[17]



Substrate **IV-1l** behaved in an entirely different manner compared to the other substrates (Table IV-4); the reason for the exceptional behavior is not clear. However, in the case of **IV-1l**, the reaction may proceed via path D; the contribution of the path is consistent with the result reported by Otera and co-workers, in which the formation of the same oxocarbenium ion is proposed.[18]



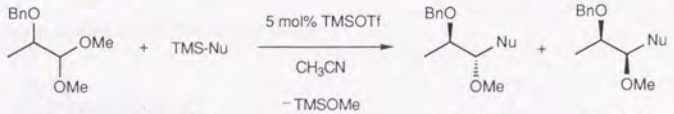
IV-1l **IV-2** *anti*-**IV-3** *syn*-**IV-3**

Table IV-4. Reaction of α-Sulfenyl Acetal **IV-1l** with Silylated Carbon Nucleophiles

Entry	Nucleophile	Product	Yield/%	Anti/Syn
1	**IV-2a**	**IV-3r**	80	21/79
2[a]			93	42/58
3	**IV-2c**	**IV-3s**	92	65/35
4	**IV-2d**	**IV-3t**	83	14/86

[a]The reaction was performed with 1.1 equiv. $TiCl_4$ in CH_2Cl_2 at -78°C.

There have been only a few reports concerning the reaction of acyclic α-oxygenated acetals.[8,9,11] However, the stereocontrol of the vicinal dioxy function is very important in synthetic organic chemistry. From this point of view, the reaction of α-benzyloxy acetal **IV-4** was carried out in order to compare it with that of the α-sulfenyl series (Table IV-5). In this case, a syn preference was observed, irrespective of the kind of nucleophile, though the selectivity was not as satisfactory as in the α-sulfenyl case.[19] In addition, when **IV-4** was allowed to react with **IV-2a** in CH_2Cl_2, a complex mixture was obtained. These facts indicate that the reaction involves a labile ionic intermediate, namely, an oxocarbenium ion. The observed syn preference, however, is quite different from the stereochemical course of the reaction of the corresponding aldehyde under non-chelation control. Although this reaction was not investigated in detail, the counter anion might play an important role.[20]

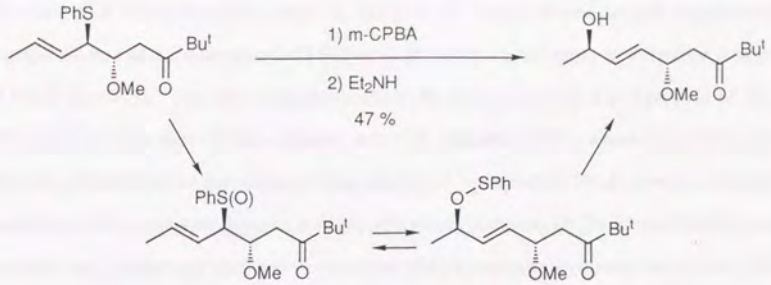


IV-4 **IV-2** *anti*-**IV-5** *syn*-**IV-5**

Table IV-5. Reaction of α-Benzyloxy Acetal **IV-4**

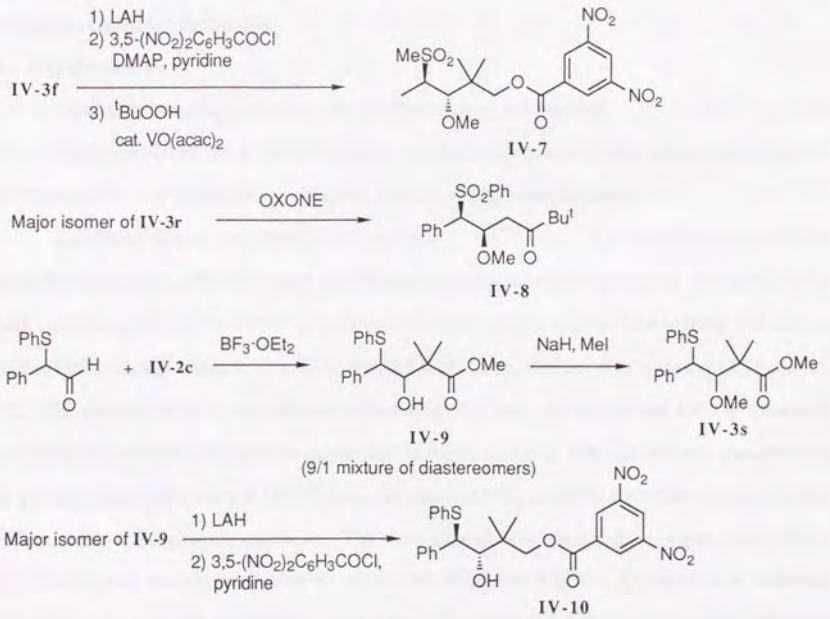
Entry	Nucleophile	Temp/°C	Product	Yield/%	Anti/Syn
1	**IV-2a**	-40 to -15	**IV-5a**	86	23/77
2	**IV-2c**	-40 to rt	**IV-5b**	56	40/60
3	**IV-2d**	-40 to rt	**IV-5c**	55	37/63

The above-mentioned fact manifests the unique electronic effect of the sulfur atom on the stereoselective aldol reaction of α-sulfenyl acetals. From a synthetic point of view it is important to remove the sulfenyl group without any loss of stereochemical information, since most of the synthetically interesting targets do not contain such a functional group. Concerning this matter, *anti*-**IV-3o** was successfully converted via a sulfoxide-sulfenate rearrangement to *anti*-**IV-6**, which should be a valuable precursor for a stereocontrolled, highly oxygenated carbon chain.[21] This example emphasizes the synthetic usefulness of the present diastereoselective reaction of α-sulfenyl acetals.



3. Determination of Relative Stereochemistry of Products

X-ray crystallographic analyses were performed in order to establish the structures of the following compounds: the major isomer of **IV-3o**, the main isomer of **IV-3p**, sulfone **IV-7** derived from **IV-3f**, sulfone **IV-8** derived from major isomer of **IV-3r**, and ester **IV-10** derived from the major isomer of **IV-9** (Scheme IV-2).[17]



Scheme IV-2

Compound **IV-9** was methylated (NaH/MeI) to give **IV-3s** as a 9/1 mixture of diastereomers. The major isomer of the thus-obtained **IV-3s** was proved to be the same as the major isomer of **IV-1l**-derived **IV-3s**. The stereochemistry of **IV-3n** was assured by a comparison of its ^{1}H NMR spectrum with that of the authentic anti-rich mixture (97/3), which was obtained by methylation (NaH/MeI) of the corresponding alcohol.[13] Compounds **IV-5a-c** were analyzed in the same way using authentic syn-rich isomers. To obtain authentic **IV-5a**, a careful methylation procedure was carried out through a reduction (BH_3)-monomethylation-oxidation (PCC) sequence.[6]

Product **IV-3t** is a known compound;[18] its stereochemistry was determined by the ^{1}H NMR spectrum.

The stereochemistries of the other compounds having a sulfenyl group were confirmed on the basis of a correlation of the ^{1}H NMR chemical shifts of selected peaks (*t*-Bu, MeO, MeS); in the case that such a comparison was not available, it was assumed that the reaction proceeded through an analogous mechanism.

4. Experimental

General information is same as that of Experimental in Chapter II.

Nucleophiles **IV-2a-c** and **IV-2e** were synthesized according to a method described in the literature.[22] Allylsilane **IV-2d** was purchased from Shin-etsu Silicone.

1,1-Dimethoxy-2-(phenylthio)propane (IV-1a), 1,1-Dimethoxy-2-(*tert*-butylthio)propane (IV-1b), and 1,1-Dimethoxy-2-(ethylthio)propane (IV-1c). To a flask containing 53.27 g (0.45 mol) of pyruvaldehyde dimethyl acetal (available from Aldrich) in EtOH (200 mL) was added 8.53 g (0.23 mol) of $NaBH_4$ by portions over a period of 15 min at 0°C. The reaction mixture was allowed to warm up to rt and was then stirred for 6 h. Acetone was added by portions until no more exothermic reaction occurred. The mixture was concentrated by a rotary evaporator and a 3 M HCl solution was carefully added to the white syrupy residue until the solution became homogeneous. The water solution was extracted thoroughly with EtOAc (5 × 50 mL), and the combined organic layers were dried over $MgSO_4$. Concentration followed by distillation gave 30.09 g (56%) of 1,1-dimethoxy-2-propanol: bp 64-66°C/35mmHg [lit.[23] 62-67°C/30mmHg]. ^{1}H NMR spectrum was identical with that reported in literature.[23]

The alcohol thus obtained was mesylated according to the method in literature:[24] 91% yield; bp 105-111°C/1mmHg; ^{1}H NMR (CCl_4, 60 MHz) 1.4 (d, 3H, J = 6, CH_3CH), 2.9 (s, 3H, CH_3SO_2), 3.4 (s, 6H, CH_3O), 4.3 (d, 1H, J = 6, $(MeO)_2CH$), 4.3–4.9 (m, 1H, MeCH).

To a stirred solution of sodium thiolate (15 mmol) in EtOH (10 mL) was added an EtOH (2 mL) solution of the mesylate (15 mmol), and the mixture was refluxed for 10 h. Upon progressing the reaction, dense white masses precipitated. To the reaction mixture were added hexane (30 mL) and water (30 mL), and the two layers were separated. The organic layer was washed with 1 M NaOH solution (2 × 10 mL), dried over Na_2SO_4, and concentrated to give the crude material. Purification as described below afforded the α-sulfenyl acetal.

IV-1a: 81% yield; column chromatography (EtOAc/hexane = 1/30); ^{1}H NMR (CCl_4, 60 MHz) 1.2 (d, 3H, J = 7, CH_3CH), 3.2–3.3 (m, 1H, MeCH), 3.3 (s, 3H, CH_3O), 3.4 (s, 3H, CH_3O), 4.6 (d, 1H, J = 6, $(MeO)_2CH$), 7.1–7.6 (m, 5H, phenyl);.^{13}C-NMR ($CDCl_3$-CH_3CN) 15.9, 45.9, 55.1, 55.5, 107.3, 127.0, 129.0, 132.1, 135.0; IR (neat) 1585, 1480, 1440, 1140, 1070, 750, 695; MS 212 (M^+, 48), 181 (17), 149 (37), 137 (11), 109 (26), 75 (100), 47 (23); HRMS calcd for $C_{11}H_{16}O_2S$ 212.0871, found 212.0849.

IV-1b: 40% yield; Kugelrohr distillation; bp 110°C (ot)/1 mmHg; Purity >99% by GC analysis; ^{1}H NMR (CCl_4, 60 MHz) 1.2 (d, 3H, J = 7, CH_3CH), 1.3 (s, 9H, $(CH_3)_3$C), 2.5–3.0 (m, 1H, MeCH), 3.4 (s, 6H, CH_3O), 4.2 (d, 1H, J = 5, $(MeO)_2CH$); HRMS calcd for $C_9H_{20}O_2S$ 192.1184, found 192.1159.

IV-1c: 36% yield; bp 43°C/1 mmHg; Purity >99% by GC analysis; ^{1}H NMR (CCl_4, 60 MHz) 1.2 (t, 6H, J = 7, CH_3CH_2 overlapping CH_3CH), 2.7 (pseudo quintet, 3H, J = 8, $MeCH_2$ overlapping MeCH), 3.3 (s, 3H, CH_3O), 3.4 (s, 3H, CH_3O), 4.2 (d, 1H, J = 6, $(MeO)_2CH$); HRMS calcd for $C_7H_{16}O_2S$ 164.0871, found 164.0864.

1,1-Dimethoxy-2-(methylthio)propane (IV-1d). The α-sulfenyl acetal was prepared under the phase transfer conditions[25] by using the above-mentioned mesylate and commercially available 15% aqueous solution of sodium methanethiolate in the presence of 10 mol% tributylhexadecylphosphonium bromide: 31% yield; bp 46–47°C/6 mmHg; purity >99% by GC analysis; ^{1}H NMR (CCl_4, 60 MHz) 1.2 (d, 3H, J = 7, CH_3CH), 2.1 (s, 3H, CH_3S), 2.7

(quintet, 1H, J = 7, MeC*H*), 3.3 (s, 3H, C*H*$_3$O), 3.4 (s, 3H, C*H*$_3$O), 4.2 (d, 1H, J = 7, (MeO)$_2$C*H*); HRMS calcd for $C_6H_{14}O_2S$ 150.0715, found 150.0697.

1,1-Dimethoxy-2-(methylthio)butane (IV-1e), 1,1-Dimethoxy-3-methyl-2-(methylthio)butane (IV-1h), and 1,1-Dimethoxy-2-(methylthio)hexane (IV-1i). The α-sulfenyl acetals were obtained by the same procedure as that for **IV-1a** by using α-bromoacetals[26] instead of the mesylate. Since it was difficult to isolate the products from unreacted starting materials, the yields were rather low.

IV-1e: 19% yield; bp 57°C/9 mmHg; purity 96% by GC analysis; ^{1}H NMR (CCl_4, 60 MHz) 1.0 (d, 3H, J = 7, C*H*$_3$CH$_2$), 1.2–1.8 (m, 2H, MeC*H*$_2$), 2.1 (s, 3H, C*H*$_3$S), 2.2–2.6 (m, 1H, MeSC*H*), 3.3 (s, 3H, C*H*$_3$O), 3.4 (s, 3H, C*H*$_3$O), 4.3 (d, 1H, J = 6, (MeO)$_2$C*H*).

IV-1h: 6% yield; bp 73–76°C/9 mmHg; purity 99% by GC analysis; ^{1}H NMR (CCl_4, 60 MHz) 0.8 (d, 3H, J = 7, C*H*$_3$CHCH$_3$), 1.0 (d, 3H, J = 7, CH$_3$CHC*H*$_3$), 1.9–2.3 (m, 1H, Me$_2$C*H*), 2.1 (s, 3H, C*H*$_3$S), 2.4 (dd, 1H, J = 3, 8, MeSC*H*), 3.3 (s, 3H, C*H*$_3$O), 3.4 (s, 3H, C*H*$_3$O), 4.3 (d, 1H, J = 8, (MeO)$_2$C*H*); HRMS calcd for $C_8H_{18}O_2S$ 178.1027, found 178.1004.

IV-1i: 38% yield; bp 97°C/3 mmHg; purity >99% by GC analysis; ^{1}H NMR (CCl_4, 60 MHz) 0.7–1.9 (m, 9H, butyl), 2.1 (s, 3H, C*H*$_3$S), 2.3–2.7 (m, 1H, MeSC*H*), 3.4 (s, 3H, C*H*$_3$O), 3.4 (s, 3H, C*H*$_3$O), 4.3 (d, 1H, J = 7, (MeO)$_2$C*H*).

1,1-Dimethoxy-2-methylthio-3-phenylpropane (IV-1f). 2-Methylthio-3-phenylpropanal (2.00 g, 11 mmol)[27] was dissolved in HC(OMe)$_3$ (30 mL). To this solution was added *p*-TsOH (0.5 g, 3.2 mmol), and the mixture was stirred for 2 h at rt. After aqueous alkaline work-up, the crude material was purified by column chromatography (EtOAc/benzene/hexane = 1/1/20): 34% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 2.02 (s, 3H, C*H*$_3$S), 2.74 (dd, 1H, J = 9, 14, PhC*H*H), 2.89 (pseudo quintet, 1H, J = 5, MeSC*H*), 3.13 (dd, 1H, J = 5, 14, PhCH*H*), 3.44 (s, 3H, C*H*$_3$O), 3.47 (s, 3H, C*H*$_3$O), 4.32 (d, 1H, J = 5, (MeO)$_2$C*H*), 7.2–7.3 (m, 5H, phenyl);.^{13}C-NMR ($CDCl_3$) 15.3, 35.9, 51.3, 55.3, 55.8, 107.7, 126.3, 128.2, 129.3, 139.4; HRMS calcd for $C_{12}H_{18}O_2S$ 226.1028, found 226.1028.

1,1-Dimethoxy-2-methylthio-2-phenylethane (IV-1g). To a solution of 1-methoxy-2-phenylethylene[28](1.48 g, 11 mmol), in CH_2Cl_2 (15 mL) was added MeSCl[29] (50 mmol) drop by drop at 0°C. The reaction mixture was allowed to warm up to rt and MeOH (5 mL)

was added to the mixture. After stirring for 8 h, the mixture was concentrated and purified by column chromatography (EtOAc/hexane = 1/20): 54% yield; ^{1}H NMR (CCl_4, 60 MHz) 1.8 (s, 3H, CH_3S), 3.2 (s, 3H, CH_3O), 3.4 (s, 3H, CH_3O), 3.9 (d, 1H, J = 8, MeSC*H*), 4.6 (d, 1H, J = 8, $(MeO)_2CH$), 7.3 (s, 5H, phenyl); ^{13}C-NMR ($CDCl_3$) 14.6, 54.2, 54.4, 54.5, 106.9, 127.3, 128.3, 128.7, 138.3.

(*E*)-1,1-Dimethoxy-2-phenylthio-3-pentene (IV-1j) and 1,1-Dimethoxy-2-phenylthio-2-phenylethane (IV-1l). The α-sulfenyl acetals were synthesized according to the procedure described by Mandai *et al.*[30]

IV-1j: ^{1}H NMR ($CDCl_3$, 400 MHz) 1.60 (dd, 3H, J = 1, 6, CH_3), 3.42 (s, 3H, CH_3O), 3.43 (s, 3H, CH_3O), 3.78 (dd, 1H, J = 5, 9, PhSC*H*), 4.41 (d, 1H, J = 5, $(MeO)_2CH$), 5.3–5.5 (m, 2H, C*H*=C*H*), 7.2–7.3 (m, 3H, phenyl), 7.4 (m, 2H, phenyl); Anal. calcd for $C_{13}H_{18}O_2S$, C 65.51 H 7.61, found C 65.23 H 7.53.

IV-1l: ^{1}H NMR (CCl_4, 60 MHz) 3.2 (s, 3H, CH_3O), 3.4 (s, 3H, CH_3O), 4.3 (d, 1H, J = 6, PhSC*H*), 4.6 (d, 1H, J = 6, $(MeO)_2CH$), 6.8–7.6 (m, 10H, phenyl); ^{13}C-NMR ($CDCl_3$) 54.8, 55.1, 56.5, 106.5, 127.1, 127.3, 128.2, 128.6, 128.9, 132.5, 134.5, 138.4.

1,1-Diisopropoxy-2-(phenylthio)propane (IV-1k). In 2-propanol (30 mL), **IV-1a** (2.53g, 11.9 mmol) was dissolved, and the solution was refluxed for 8 h in the presence of *p*-TsOH (0.1 g). After aqueous alkaline work-up, the reaction mixture was purified by column chromatography (EtOAc/hexanes = 1/50) to give 0.45 g (14% yield) of **IV-1k**: ^{1}H NMR ($CDCl_3$, 400 MHz) 1.14 (d, 3H, J = 6, isopropyl), 1.19 (d, 3H, J = 6, isopropyl), 1.19 (d, 3H, J = 6, isopropyl), 1.22 (d, 3H, J = 6, isopropyl), 1.33 (d, 3H, J = 7, PhSCHCH_3), 3.32 (dq, 1H, J = 4, 7, PhSC*H*CH_3), 3.79 (septet, 1H, J = 6, isopropyl), 3.88 (septet, 1H, J = 6, isopropyl), 4.61 (d, 1H, J = 4, $(i\text{-PrO})_2CH$), 7.2–7.5 (m, 5H, phenyl); ^{13}C-NMR ($CDCl_3$) 15.0, 22.2, 22.6, 23.0, 23.3, 47.5, 69.2, 69.5, 101.0, 126.5, 128.8, 131.2, 136.0; IR (neat) 1380, 1125, 1025, 745, 695; MS 209 (3), 137 (17), 131 (29), 109 (9), 89 (100), 59 (11).

2-Benzyloxy-1,1-dimethoxypropane (IV-4). To a DMF (50 mL) dispersion of NaH (55% in mineral oil; 1.10 g, 25 mmol), which was washed twice with hexane, was added a DMF (6 mL) solution of 1,1-dimethoxy-2-propanol (3.00 g, 25 mmol). After the exothermic reaction ceased, a DMF (6 mL) solution of BnBr (4.24 g, 25 mmol) was added. The mixture was

warmed up to 100°C and stirred for 3 h. Usual aqueous work-up followed by column chromatography (EtOAc/hexane = 1/20 to 1/10) gave 1.82 g (35% yield) of **IV-4**: ^{1}H NMR (CCl_4, 60 MHz) 1.1 (d, 3H, J = 6, CH_3CH), 3.2–3.6 (m, 1H, MeC*H*), 3.4 (s, 6H, CH_3O), 4.1 (d, 1H, J = 6, $(MeO)_2CH$), 4.6 (s, 2H, $PhCH_2$), 7.3 (s, 5H, phenyl); Anal. calcd for $C_{12}H_{18}O_3$, C 68.55 H 8.63, found C 68.41 H 8.53.

General Procedure for the Reaction of the Acetals: To a stirred solution of the acetal (0.5 mmol) and nucleophile (0.6 mmol) in CH_3CN (4 mL) was added TMSOTf (0.1 M solution in CH_3CN , 0.25 mL, 0.025 mmol) at -40°C under an argon atmosphere. The reaction mixture was stirred for 30 min at the temperature and quenched by adding saturated aqueous $NaHCO_3$ solution (3 mL). The organic materials were extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by silica gel column chromatography (ether/hexane = 1/30) or preparative TLC (EtOAc/hexanes = 1/10) to give the corresponding adduct as an inseparable mixture of the diastereomers. The diastereomer ratio was determined by GC or ^{1}H-NMR.

When **IV-2d** was used as a nucleophile, the acetal was added to a mixture of nucleophile and TMSOTf.

5-Methoxy-2,2-dimethyl-6-phenylthio-3-heptanone (IV-3a): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.13 (s, 9 × 0.08H, $(CH_3)_3C$), 1.15 (s, 9 × 0.92H, $(CH_3)_3C$), 1.28 (d, 3 × 0.92H, J = 7, CH_3CH), 1.33 (d, 3 × 0.08H, J = 7, CH_3CH), 2.66 (dd, 1H, J = 4, 17, C*H*HCO), 2.94 (dd, 1H, J = 7, 17, CH*H*CO), 3.19 (td, 1H, J = 4, 7, MeOC*H*), 3.30 (s, 3 × 0.08H, CH_3O), 3.36 (s, 3 × 0.92H, CH_3O), 3.40 (dq, 1H, J = 4, 7, MeC*H*), 7.2–7.3 (m, 3H, phenyl), 7.4–7.5 (m, 2H, phenyl); IR (neat) 1710, 1585, 1480, 1370, 1095, 1070, 750, 695; MS 280 (M^+, 1), 248 (M^+–MeOH, 13), 180 (9), 163 (29), 137 (31), 85 (31), 57 (100), 41 (57); HRMS calcd for $C_{16}H_{24}O_2S$ 280.1497, found 280.1495.

6-*tert*-Butylthio-5-methoxy-2,2-dimethyl-3-heptanone (IV-3b): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.15 (s, 9H, $(CH_3)_3C$), 1.30 (d, 3H, J = 7, CH_3CH), 1.35 (s, 9H, $(CH_3)_3CS$), 2.64 (dd, 1H, J = 4, 17, C*H*HCO), 2.8–2.9 (m, 2H, CH*H*CO overlapping MeC*H*), 3.39 (s, 3H, CH_3O), 3.80 (td , 1H, J = 4, 8, MeOC*H*); IR (neat) 1710, 1365, 1090; MS 228

(M^+–MeOH, 25), 172 (19), 143 (17), 117 (35), 85 (44), 61 (19), 57 (100); HRMS calcd for $C_{13}H_{24}OS$ (M–MeOH) 228.1548, found 228.1540.

6-Ethylthio-5-methoxy-2,2-dimethyl-3-heptanone (IV-3c): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.16 (s, 9 × 0.92H, $(CH_3)_3C$), 1.17 (s, 9 × 0.08H, $(CH_3)_3C$), 1.26 (m, 6H), 2.62 (dd, 1H, J = 4, 17, C*H*HCO), 2.63 (m, 1H), 2.92 (dd, 1H, J = 8, 17, CH*H*CO), 2.99 (dq, 1H, J = 4, 7, MeC*H*), 3.34 (s, 3 × 0.08H, CH_3O), 3.38 (s, 3 × 0.92H, CH_3O), 3.86 (td , 0.92H, J = 4, 8, MeOC*H*), 3.90 (m, 0.08H, MeOC*H*); IR (neat) 1705, 1620, 1480, 1365, 1095; MS 200 (M^+–MeOH, 9), 143 (29), 89 (27), 85 (18), 57 (100); HRMS calcd for $C_{11}H_{20}OS$ (M–MeOH) 200.1235, found 200.1235.

5-Methoxy-2,2-dimethyl-6-methylthio-3-heptanone (IV-3d): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.16 (s, 9 × 0.95H, $(CH_3)_3C$), 1.20 (s, 9 × 0.05H, $(CH_3)_3C$), 1.26 (d, 3 × 0.95H, J = 7, CH_3CH), 1.31(d, 3 × 0.05H, J = 8, CH_3CH), 2.12 (s, 3 × 0.05H, CH_3S), 2.14 (s, 3 × 0.95H, CH_3S), 2.65 (dd, 0.95H, J = 4, 17, C*H*HCO), 2.77 (m, 0.05H, C*H*HCO), 2.86 (m, 0.05H, CH*H*CO), 2.91 (dd, 0.95H, J = 8, 17, CH*H*CO), 3.34 (s, 3 × 0.05H, CH_3O), 3.38 (s, 3 × 0.95H, CH_3O), 3.87 (ddd, 0.95H, J = 4, 7, 8, MeOC*H*), 3.92 (m, 0.05H, MeOC*H*); ^{13}C-NMR ($CDCl_3$) for the anti isomer, 14.1, 16.7, 26.4, 39.2, 44.7, 58.7, 80.4, 213.6; for the syn isomer (identifiable peaks only), 15.7, 37.1, 43.1, 79.0; IR (neat) 1710, 1480, 1460, 1365, 1100; MS 186 (M^+–MeOH, 40), 118 (10), 101 (25), 85 (35), 75 (25), 57 (100), 41 (10); HRMS calcd for $C_{10}H_{18}OS$ (M–MeOH) 186.1078, found 186.1098.

3-Methoxy-4-methylthio-1-phenyl-1-pentanone (IV-3e): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.32 (d, 3 × 0.94H, J = 7, CH_3CH), 1.44(d, 3 × 0.06H, J = 7, CH_3CH), 2.03 (s, 3 × 0.06H, CH_3S), 2.17 (s, 3 × 0.94H, CH_3S), 2.96 (dq, 0.94H, J = 4, 7, MeSC*H*), 3.02 (m, 0.06H, C*H*HCO), 3.16 (dd, 0.94H, J = 4, 17, C*H*HCO), 3.23 (m, 0.06H, MeSC*H*), 3.37 (s, 3 × 0.06H, CH_3O), 3.39 (dd, 1H, J = 7, 17, CH*H*CO), 3.42 (s, 3 × 0.94H, CH_3O), 4.03 (td, 0.94H, J = 4, 7, MeOC*H*), 4.08 (m, 0.06H, MeOC*H*), 7.4–7.6 (m, 3H, phenyl), 7.93 (dm, 2 × 0.06H, phenyl), 7.99 (dm, 2 × 0.94H, phenyl); IR (neat) 1690, 1600, 1455, 1115, 760, 710; MS 206 (M^+–MeOH, 24), 118 (24), 105 (100), 77 (33), 75 (12); HRMS calcd for $C_{12}H_{14}OS$

(M−MeOH) 206.0765, found 206.0764; Anal. calcd for $C_{13}H_{18}O_2S$, C 65.51 H 7.61, found C 65.24 H 7.62.

Methyl 3-Methoxy-2,2-dimethyl-4-(methylthio)pentanoate (IV-3f): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.15 (s, 3H, CH_3CCH_3), 1.22 (s, 3H, CH_3CCH_3), 1.33 (d, 3H, J = 7, CH_3CH), 2.07 (s, 3H, CH_3S), 2.71 (qd, 1H, J = 5, 7, MeC*H*), 3.52 (s, 3H, CH_3O), 3.55 (d, 1H, J = 5, MeOC*H*), 3.67 (s, 3H, $COOCH_3$); IR (neat) 1735, 1270, 1140, 1095, 665; MS 188 (M^+−MeOH, 25), 149 (54), 145 (25), 119 (29), 75 (79), 73 (29), 59 (54), 51 (100); HRMS calcd for $C_9H_{16}O_2S$ (M−MeOH) 188.0872, found 188.0903.

4-Methoxy-5-methylthio-1-hexene (IV-3g): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.27 (d, 3 × 0.25H, J = 7, CH_3CH), 1.28 (d, 3 × 0.75H, J = 7, CH_3CH), 2.13 (s, 3 × 0.75H, CH_3S), 2.14 (s, 3 × 0.25H, CH_3S), 2.2–2.4 (m, 1H, CH_2=CHC*H*H), 2.4–2.5 (m, 1H, CH_2=CHCH*H*), 2.8–2.9 (m, 0.75H, MeSC*H*), 2.9 (m, 0.25H, MeSC*H*), 3.2–3.3 (m, 1H, MeOC*H*), 3.39 (s, 3 × 0.25H, CH_3O), 3.42 (s, 3 × 0.75H, CH_3O), 5.0–5.2 (m, 2H, CH_2=CH), 5.8–5.9 (m, 1H, CH_2=C*H*); IR (neat) 1640, 1455, 1195, 915; MS 160 (M^+, 8), 128 (M^+−MeOH, 40), 119 (53), 85 (100), 75 (20), 71 (15), 55 (27), 41 (16); HRMS calcd for $C_8H_{16}OS$ 160.0922, found 160.0927.

5-Methoxy-2,2-dimethyl-6-methylthio-3-octanone (IV-3h): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.07 (t, 3H, J = 7, CH_3CH_2), 1.16 (s, 9 × 0.98H, $(CH_3)_3C$), 1.17 (s, 9 × 0.02H, $(CH_3)_3C$), 1.43 (qdd, 1H, J = 7, 9, 15, MeC*H*H), 1.65 (dqd, 1H, J = 5, 7, 15, MeCH*H*), 2.11 (s, 3H, CH_3S), 2.59 (td, 1H, J = 5, 9, MeSC*H*), 2.65 (dd, 1H, J = 4, 17, C*H*HCO), 2.95 (dd, 1H, J = 8, 17, CH*H*CO), 3.33 (s, 3 × 0.02H, CH_3O), 3.35 (s, 3 × 0.98H, CH_3O), 3.91 (ddd, 1H, J = 4, 5, 8, MeOC*H*); ^{13}C-NMR ($CDCl_3$) for the anti isomer: 12.3, 14.5, 23.8, 26.3, 39.4, 44.4, 52.7, 58.3, 80.0, 214.1; IR (neat) 1710, 1480, 1465, 1370, 1100; MS 200 (M^+−MeOH, 27), 115 (21), 89 (33), 85 (39), 57 (100), 41 (28); HRMS calcd for $C_{11}H_{20}OS$ (M−MeOH) 200.1235, found 200.1237.

5-Methoxy-2,2-dimethyl-6-methylthio-7-phenyl-3-heptanone (IV-3i): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.13 (s, 9 × 0.1H, $(CH_3)_3C$), 1.15 (s, 9 × 0.9H, $(CH_3)_3C$), 1.96 (s, 3 × 0.1H, CH_3S), 2.00 (s, 3 × 0.9H, CH_3S), 2.6–2.7 (m, 2H, $PhCH_2$), 2.9–3.0 (m, 3H, CH_2CO

and MeSC*H*), 3.34 (s, 3 × 0.1H, CH_3O), 3.34 (s, 3 × 0.9H, CH_3O), 3.78 (td, 0.1H, J = 6, 12, MeOC*H*), 3.97 (td, 0.9H, J = 4, 8, MeOC*H*), 7.2–7.3 (m, 5H, phenyl); IR (neat) 1710, 1480, 1460, 1370, 1110, 1090, 755, 705, 670; MS 262 (M^+–MeOH, 65), 177 (27), 151 (61), 91 (32), 85 (50), 57 (100); HRMS calcd for $C_{16}H_{22}OS$ (M–MeOH) 262.1392, found 262.1422; Anal. calcd for $C_{18}H_{26}O_2S$, C 69.34 H 8.90, found C 69.63 H 8.85.

5-Methoxy-2,2-dimethyl-6-methylthio-6-phenyl-3-hexanone (IV-3j): ^1H NMR ($CDCl_3$, 400 MHz) 1.07 (s, 9 × 0.59H, $(CH_3)_3C$), 1.15 (s, 9 × 0.41H, $(CH_3)_3C$), 1.91 (s, 3 × 0.59H, CH_3S), 1.92 (s, 3 × 0.41H, CH_3S), 2.60 (dd, 0.41H, J = 5, 10, C*H*HCO), 2.65 (dd, 0.41H, J = 5, 10, CH*H*CO), 2.74 (dd, 0.59H, J = 7, 17, C*H*HCO), 2.87 (dd, 0.59H, J = 7, 17, CH*H*CO), 3.25 (s, 3 × 0.41H, CH_3O), 3.39 (s, 3 × 0.59H, CH_3O), 3.89 (m, 1H, MeSC*H*), 4.11 (m, 1H, MeOC*H*), 7.2–7.4 (m, 5H, phenyl); IR (neat) 1710, 1370, 1110, 1090, 705; MS 248 (M^+–MeOH, 11), 163 (13), 137 (22), 115 (33), 57 (100), 41 (35); HRMS calcd for $C_{15}H_{20}OS$ (M–MeOH) 248.1235, found 248.1197; Anal. calcd for $C_{16}H_{24}O_2S$, C 68.53 H 8.63, found C 68.56 H 8.75.

5-Methoxy-2,2,7-trimethyl-6-methylthio-3-octanone (IV-3k): ^1H NMR ($CDCl_3$, 400 MHz) 1.03 (d, 3 × 0.59H, J = 7, CH_3CHCH_3), 1.04 (d, 3 × 0.59H, J = 6, CH_3CHCH_3), 1.08 (d, 3 × 0.41H, J = 7, CH_3CHCH_3), 1.09 (d, 3 × 0.41H, J = 7, CH_3CHCH_3), 1.16 (s, 9 × 0.59H, $(CH_3)_3C$), 1.17 (s, 9 × 0.41H, $(CH_3)_3C$), 1.96 (m, 0.59H, Me_2CH), 2.06(m, 0.41H, Me_2CH), 2.09 (s, 3 × 0.41H, CH_3S), 2.16 (s, 3 × 0.59H, CH_3S), 2.28 (dd, 0.41H, J = 3, 7, MeSC*H*), 2.47 (t, 0.59H, J = 6, MeSC*H*), 2.69 (dd, 0.59H, J = 3, 17, C*H*HCO), 2.89 (dd, 0.41H, J = 8, 17, CH*H*CO), 2.99 (dd, 0.59H, J = 8, 17, CH*H*CO), 3.08 (dd, 0.41H, J = 7, 17, C*H*HCO), 3.31 (s, 3 × 0.41H, CH_3O), 3.34 (s, 3 × 0.59H, CH_3O), 3.98 (ddd, 0.59H, J = 3, 6, 8, MeOC*H*) 4.03 (ddd, 0.41H, J = 3, 7, 8, MeOC*H*); IR (neat) 1710, 1365, 1100; MS 214 (M^+–MeOH, 38), 129 (26), 103 (69), 85 (63), 57 (100), 55 (20); HRMS calcd for $C_{11}H_{22}OS$ (M–MeOH) 214.1391, found 214.1389.

Methyl 3-Methoxy-2,2,5-trimethyl-4-(methylthio)hexanoate (IV-3l): ^1H NMR ($CDCl_3$, 400 MHz) 0.96 (d, 3H, J = 7, CH_3CHCH_3), 1.06 (d, 3H, J = 7, CH_3CHCH_3), 1.15 (s, 3H, CH_3CCH_3), 1.26(s, 3H, CH_3CCH_3), 2.09 (s, 3H, CH_3S), 2.3 (m, 2H, Me_2CH

overlapping MeSC*H*), 3.53 (s, 3H, C*H*$_3$O), 3.60 (d, 1H, *J* = 8, MeOC*H*), 3.65 (s, 3H, COOC*H*$_3$); IR (neat) 1730, 1275, 1140, 1095; MS 248 (M^+, 17), 216 (M^+–MeOH, 15), 149 (76), 145 (73), 138 (54), 103 (24), 75 (59), 55 (100); HRMS calcd for $C_{12}H_{24}O_3S$ 248.1446, found 248.1435.

5-*tert*-Butylthio-4-methoxy-1-hexene (IV-3m): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.32 (d, 3H, *J* = 7, C*H*$_3$CH), 1.33 (s, 9 × 0.97H, (C*H*$_3$)$_3$C), 1.36 (s, 9 × 0.03H, (C*H*$_3$)$_3$C), 2.28 (pseudo td, 1H, *J* = 7, 14, CH_2=CHC*H*H), 2.41(pseudo td, 1H, *J* = 7, 14, CH_2=CHCH*H*), 2.83 (dq, 1H, *J* = 4, 7, MeC*H*), 3.28 (dt, 1H, *J* = 4, 7, MeOC*H*), 3.41 (s, 3 × 0.03H, C*H*$_3$O), 3.43 (s, 3 × 0.97H, C*H*$_3$O), 5.1–5.2 (m, 2H, C*H*$_2$=CH), 5.8–5.9 (m, 1H, CH_2=C*H*); IR (neat) 1640, 1460, 1365, 1090, 915; MS 202 (M^+, 3), 170 (M^+–MeOH, 14), 145 (34), 117 (28), 114 (45), 105 (63), 85 (91), 57 (100); HRMS calcd for $C_{11}H_{22}OS$ 202.1391, found 202.1367.

4-Methoxy-5-methylthio-1-nonene (IV-3n): ^{1}H NMR ($CDCl_3$, 400 MHz) 0.92 (t, 3H, *J* = 7, C*H*$_3$CH$_2$), 1.3–1.7 (m, 6H, -(C*H*$_2$)$_3$-), 2.11 (s, 3 × 0.88H, C*H*$_3$S), 2.12 (s, 3 × 0.12H, C*H*$_3$S), 2.36 (pseudo quintet, 1H, *J* = 7, CH_2=CHC*H*H), 2.50 (pseudo quintet, 1H, *J* = 7, CH_2=CHCH*H*), 2.62 (pseudo quintet, 1H, *J* = 4, MeSC*H*), 3.33 (dt, 1H, *J* = 4, 7, MeOC*H*), 3.38 (s, 3 × 0.12H, C*H*$_3$O), 3.40 (s, 3 × 0.88H, C*H*$_3$O), 5.08 (dm, 1H, *J* = 10, C*H*H=CH), 5.12 (dm, 1H, *J* = 17, CH*H*=CH), 5.86 (tdd, 1H, *J* = 7, 10, 17, CH_2=C*H*); IR (neat) 1640, 1460, 1435, 1095, 910; MS 202 (M^+, 14), 161 (22), 123 (17), 117 (26), 85 (100), 81 (26), 71 (15), 61 (18); HRMS calcd for $C_{11}H_{22}OS$ 202.1392, found 202.1383.

5-Methoxy-2,2-dimethyl-6-phenylthio-7-nonen-3-one (IV-3o): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.13 (s, 9 × 0.87H, (C*H*$_3$)$_3$C), 1.14 (s, 9 × 0.13H, (C*H*$_3$)$_3$C), 1.62 (dd, 3H, *J* = 1, 6, C*H*$_3$CH=CH), 2.64 (dd, 0.87H, *J* = 6, 18, C*H*HCO), 2.82 (dd, 0.13H, *J* = 5, 17, C*H*HCO), 2.88 (dd, 0.13H, *J* = 8, 17, CH*H*CO), 2.89 (dd, 0.87H, *J* = 7, 18, CH*H*CO), 3.35 (s, 3 × 0.13H, C*H*$_3$O), 3.39 (s, 3 × 0.87H, C*H*$_3$O), 3.77 (dd, 0.87H, *J* = 4, 10, PhSC*H*), 3.81 (dd, 0.13H, *J* = 4, 8, PhSC*H*), 3.97 (ddd, 0.13H, *J* = 4, 5, 8, MeOC*H*), 4.00 (ddd, 0.87H, *J* = 4, 6, 7, MeOC*H*), 5.33 (qd, 0.87H, *J* = 6, 15, MeC*H*=CH), 5.4–5.5 (m, 0.87 + 2 × 0.13H, olefin), 7.2–7.5 (m, 5H, phenyl); IR (neat) 1705, 1580, 1480, 1370, 1090, 970, 740, 690.

(5*R,6*S**)-5-Methoxy-2,2-dimethyl-6-phenylthio-7-nonen-3-one (*anti*-IV-3o)**: colorless prisms (EtOH); mp 76°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 1.13 (s, 9H, $(CH_3)_3C$), 1.62 (dd, 3H, J = 1, 6, CH_3CH=CH), 2.64 (dd, 1H, J = 6, 18, C*H*HCO), 2.89 (dd, 1H, J = 7, 18, CH*H*CO), 3.39 (s, 3H, CH_3O), 3.77 (dd, 1H, J = 4, 10, PhSC*H*), 4.00 (ddd, 1H, J = 4, 6, 7, MeOC*H*), 5.33 (qd, 1H, J = 6, 15, MeC*H*=CH), 5.47 (ddd, 1H, J = 1, 10, 15, MeCH=C*H*), 7.2–7.3 (m, 3H, phenyl), 7.4 (m, 2H, phenyl); Anal. calcd for $C_{18}H_{26}O_2S$, C 70.40 H 8.52, found C 70.55 H 8.55.

2-(1-Methoxy-2-phenylthiopropyl)cyclohexanone (IV-3p): The reaction mixture of **IV-1a** (261 mg, 1.23 mmol) and **IV-2e** (245 mg, 1.44 mmol) was purified by preparative TLC (eluent: EtOAc/hexane = 1/10) to give two fractions, A (R_f = 0.5, 237 mg) and B (R_f = 0.4, 81 mg). GC analysis indicated each fraction consists of two components; relative abundance was 77:23 for fraction A, and 81:19 for B. The author assigned the fraction A as 2,3-*syn* isomer and B as 2,3-*anti* isomer on the basis of known chromatographic tendency for 1-methoxyalkyl cyclohexanones.[2a] Anal. calcd for $C_{16}H_{22}O_2S$, C 69.02 H 7.96, found C 68.84 H 7.97 for fraction A; C 69.30 H 8.05 for fraction B.

(2*R,1'*R**,2'*S**)-2-(1-Methoxy-2-phenylthiopropyl)cyclohexanone (2,3-*syn*-3,4-*anti*-IV-3p)**. The major isomer of fraction A, obtained as mentioned above, slowly crystallized upon standing. Then, it was recrystallized from EtOH: colorless hexagonal plates; mp 73°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 1.30 (d, 3H, J = 7, CH_3CH), 1.5–1.7 (m, 3H), 1.8–2.4 (m, 5H), 2.81 (pseudo td, 1H, J = 5, 10, COC*H*), 3.36 (quintet, 1H, J = 7, PhSC*H*), 3.48 (s, 3H, CH_3O), 3.79 (dd, 1H, J = 5, 6, MeOC*H*), 7.2–7.3 (m, 3H, phenyl), 7.4–7.5 (m, 2H, phenyl); IR (KBr) 1705, 1090, 1085, 750; MS 278 (M^+, 2), 246 (M^+–MeOH, 12), 180 (22), 141 (33), 137 (85), 109 (51), 81 (100), 67 (42); HRMS calcd for $C_{16}H_{22}O_2S$ 278.1340, found 278.1362.

Assignable ^{1}H-NMR peaks for other isomers of **IV-3p** ($CDCl_3$, 400 MHz): fraction A(minor) 1.39 (d, J = 6, CH_3), 3.9–4.0 (m, MeOC*H*); fraction B(major) 1.34 (d, J = 7, CH_3), 3.52 (dq, J = 4.9, 7.0, PhSC*H*), 3.55 (s, CH_3O), 3.60 (dd, J = 5, 6, MeOC*H*); fraction B(minor) 1.31 (d, J = 7, CH_3).

5-Isopropoxy-2,2-dimethyl-6-phenylthio-3-heptanone (3q): 63% yield; ^{1}H NMR (CCl_4, 60 MHz) 0.9–1.5 (m, 9H), 1.1 (s, 9H, $(CH_3)_3C$), 2.6–2.9 (m, 2H, CH_2CO), 3.1–4.3 (m, 3H), 7.2–7.6 (m, 5H); MS 308 (M^+, 1), 248 (M^+–*i*-PrOH, 8), 208 (3), 163 (7), 137 (17), 129 (21), 85 (45), 57 (100).

5-Methoxy-2,2-dimethyl-6-phenyl-6-phenylthio-3-hexanone (3r): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.06 (s, 9 × 0.21H, $(CH_3)_3C$), 1.07 (s, 9 × 0.79H, $(CH_3)_3C$), 2.56 (dd, 0.21H, J = 5, 17, C*H*HCO), 2.81 (d, 2 × 0.79H, J = 6, CH_2CO), 2.87 (dd, 0.21H, J = 7, 17, CH*H*CO), 3.31 (s, 3 × 0.21H, CH_3O), 3.31 (s, 3 × 0.79H, CH_3O), 4.1–4.2 (m, 1H, MeOC*H*), 4.37 (d, 0.79H, J = 5, PhSC*H*), 4.42 (d, 0.21H, J = 6, PhSC*H*), 7.1–7.4 (m, 10H, phenyl); IR (neat) 1705, 1480, 1110, 1090, 740, 700; MS 310 (M^+–MeOH, 9), 225 (21), 199 (31), 115 (16), 91 (12), 85 (32), 57 (100); HRMS calcd for $C_{20}H_{22}OS$ (M–MeOH) 310.1392, found 310.1377.

Methyl 3-Methoxy-2,2-dimethyl-4-phenyl-4-(phenylthio)butanoate (3s): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.19 (s, 3 × 0.65H, CH_3CCH_3), 1.20 (s, 3 × 0.35H, CH_3CCH_3), 1.22 (s, 3 × 0.65H, CH_3CCH_3), 1.33 (s, 3 × 0.35H, CH_3CCH_3), 3.20 (s, 3 × 0.65H, CH_3O), 3.39 (s, 3 × 0.35H, CH_3O), 3.64 (s, 3 × 0.35H, CH_3O), 3.74 (s, 3 × 0.65H, CH_3O), 3.96 (d, 1H, J = 7, MeOC*H*), 4.10 (d, 0.65H, J = 7, PhSC*H*), 4.39 (d, 0.35H, J = 7, PhSC*H*), 7.1–7.3 (m, 8H, phenyl), 7.4 (m, 2H, phenyl); IR (neat) 1740, 1270, 1100, 745, 700; MS 344 (M^+, 5), 312 (M^+–MeOH, 44), 235(15), 199 (72), 175 (33), 145 (100), 91 (28), 75 (67); HRMS calcd for $C_{19}H_{20}O_2S$ (M–MeOH) 312.1184, found 312.1162.

6-Benzyloxy-5-methoxy-2,2-dimethyl-3-heptanone (IV-5a): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.12 (s, 9 × 0.77H, $(CH_3)_3C$), 1.13 (s, 9 × 0.23H, $(CH_3)_3C$), 1.16 (d, 3 × 0.23H, J = 6, CH_3(BnO)CH), 1.18 (d, 3 × 0.77H, J = 6, CH_3(BnO)CH), 2.5–2.6 (m, 1H, C*H*HCO), 2.7–2.9 (m, 1H, CH*H*CO), 3.36 (s, 3 × 0.77H, CH_3O), 3.38 (s, 3 × 0.23H, CH_3O), 3.6–3.8 (m, 1H, BnOC*H*), 3.8–3.9 (m, 0.23H, MeOC*H*), 3.90 (pseudo quintet, 0.77H, J = 4, MeOC*H*), 4.48 (d, 1H, J = 12, PhC*H*H), 4.60 (d, 1H, J = 12, PhCH*H*), 7.2–7.4 (m, 5H, phenyl); IR (neat) 1710, 1455, 1365, 1100, 1070, 740, 700, 665; Anal. calcd for $C_{17}H_{26}O_3$, C 73.35 H 9.41, found C 73.19 H 9.22.

Methyl 4-benzyloxy-3-methoxy-2,2-dimethylpentanoate (IV-5b): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.10 (s, 3 × 0.4H, CH_3CCH_3), 1.14 (s, 3 × 0.6H, CH_3CCH_3), 1.16 (d, 3 × 0.6H, J= 6, CH_3CH), 1.21 (s, 3 × 0.4H, CH_3CCH_3), 1.28 (s, 3 × 0.6H, CH_3CCH_3), 1.29 (d, 3 × 0.4H, J= 7, CH_3CH), 3.36 (s, 3 × 0.4H, CH_3O), 3.41 (d, 0.6H, J = 6, MeOC*H*), 3.43 (d, 0.4H, J = 9, MeOC*H*), 3.52 (s, 3 × 0.4H, $COOCH_3$), 3.55 (s, 3 × 0.6H, $COOCH_3$), 3.61 (s, 3 × 0.6H, CH_3O, overlapping m, 1H, MeC*H*), 4.32 (d, 0.4H, J = 11, PhC*H*H), 4.49 (pseudo d, 1H, J = 11, PhCH*H*), 4.58 (d, 0.6H, J = 11, PhC*H*H), 7.2–7.4 (m, 5H, phenyl); IR (neat) 1740, 1145, 1100, 740, 700; Anal. calcd for $C_{16}H_{24}O_4$, C 68.55 H 8.63, found C 68.42 H 8.62.

5-Benzyloxy-4-methoxy-1-hexene (IV-5c): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.17 (d, 3 × 0.63H, J = 6, CH_3CH), 1.21 (d, 3 × 0.37H, J = 6, CH_3CH), 2.2–2.4 (m, 2H, CH_2=CHCH_2), 3.22 (td, 0.63H, J = 5, 8, MeOC*H*), 3.26 (td, 0.37H, J = 5, 7, MeOC*H*), 3.41 (s, 3 × 0.63H, CH_3O), 3.42 (s, 3 × 0.37H, CH_3O), 3.55 (dq, 0.37H, J = 5, 6, BnOC*H*), 3.62 (dq, 0.63H, J = 5, 6, BnOC*H*), 4.50 (d, 0.37H, J = 12, PhC*H*H), 4.51 (d, 0.63H, J = 12, PhC*H*H), 4.60 (d, 0.37H, J = 12, PhCH*H*), 4.62 (d, 0.63H, J = 12, PhCH*H*), 5.0–5.1 (m, 2H, CH_2=CH), 5.8–5.9 (m, 1H, CH_2=C*H*), 7.2–7.4 (m, 5H, phenyl); IR (neat) 1645, 1460, 1100, 920, 740, 700; Anal. calcd for $C_{14}H_{20}O_2$, C 76.33 H 9.15, found C 76.04 H 9.01.

(5*R,8*S**,6*E*)-8-Hydroxy-5-methoxy-2,2-dimethyl-6-nonen-3-one (*anti*-IV-6)**. To a solution of *anti*-**IV-3o** (92.8 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was added drop by drop a CH_2Cl_2 (2 mL) solution of *m*-CPBA (80% purity, 69.6 mg, 0.32 mmol) at 0°C. The mixture was stirred for 15 min at the temperature, and then poured into saturated aqueous $NaHCO_3$ solution (10 mL). The organic materials were extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4. After evaporation, the residue was dissolved in MeOH (5 mL), and Et_2NH (0.2 mL, 1.9 mmol) was added. The mixture was stirred for 12 h and concentrated. Purification by preparative TLC (EtOAc/hexane = 1/3; repeated 3 times) gave 30.5 mg (47% yield) of allyl alcohol *anti*-**IV-6**: ^{1}H NMR ($CDCl_3$, 400 MHz) 1.12 (s, 9H, $(CH_3)_3C$), 1.28 (d, 3H, J = 6, CH_3CHOH), 2.17 (br s, 1H, O*H*), 2.49 (dd, 1H, J = 5, 17, C*H*H), 2.89 (dd, 1H, J = 7, 17, CH*H*), 3.25 (s, 3H, CH_3O), 4.13 (pseudo dt, 1H, J = 5, 7, MeOC*H*), 4.33 (pseudo quintet, J = 6, C*H*OH), 5.54 (ddd, 1H, J = 1, 7, 16, C*H*=CH), 5.79

(dd, 1H, J = 6, 16, CH=C*H*); IR (neat) 3450(br), 1715, 1480, 1370, 1100, 975; MS 196 (23), 149 (53), 121 (23), 115 (27), 97 (40), 81 (48), 69 (92), 67 (35), 57 (100); HRMS calcd for $C_{12}H_{20}O_2$ (M–H_2O) 196.1463, found 196.1460.

(3*R,4*S**)-3-Methoxy-4-methanesulfonyl-2,2-dimethylpentyl 3,5-Dinitrobenzoate (IV-7)**. To a solution of lithium aluminum hydride (0.08 g, 2.10 mmol) in ether (4 mL) was added a solution of ester **IV-3f** (0.39 g, 1.78 mmol) in ether (3 mL). After the exothermic reaction ceased, EtOAc (10 mL) and saturated aqueous NH_4Cl solution (0.5 mL) was successively added to the mixture. Filtration through the celite pad followed by evaporation gave crude oil (0.34 g, 99% yield), which was essentially pure judging from its ^{1}H NMR. The alcohol (0.31 g, 1.61 mmol) and pyridine (0.16 g, 2.05 mmol) were dissolved in benzene (4 mL). To this solution was added a benzene (4 mL) solution of 3,5-dinitrobenzoyl chloride (0.38 g, 1.65 mmol) at 0°C. The reaction mixture was allowed to warm up to rt, and stirred overnight. After aqueous work-up, the organic layer was dried and concentrated to give the crude material, which was in turn dissolved in benzene (10 mL). To the solution was added $VO(acac)_2$ (0.5 g, 1.89 mmol) and *t*-BuOOH (4.36 M solution in isooctane, 0.8 mL, 3.49 mmol), and then the mixture was stirred for 3 h at rt. Usual aqueous work-up followed by recrystallization from EtOH gave 0.38 g (56% overall yield from alcohol) of **IV-7** as yellow needles: mp 142°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 1.10 (s, 3H, C*H*$_3$CCH$_3$), 1.12 (s, 3H, CH$_3$CC*H*$_3$), 1.47 (d, 3H, J = 7, C*H*$_3$(MeSO$_2$)CH), 2.94 (s, 3H, C*H*$_3$SO$_2$), 3.27 (dq, 1H, J = 2, 7, MeC*H*), 3.51 (s, 3H, C*H*$_3$O), 3.91 (d, 1H, J = 2, MeOC*H*), 4.32 (s, 2H, C*H*$_2$), 9.14 (d, 2H, J = 2, phenyl), 9.23 (t, 1H, J = 2, phenyl); IR (KBr) 1737, 1555, 1350, 1310, 1290, 1175, 1140, 960, 725, 500; MS 418 (M^+, 1), 311 (7), 195 (19), 151 (100), 99 (11), 89 (12), 87 (16), 72 (34), 71 (15); HRMS calcd for $C_{16}H_{22}N_2O_9S$ 418.1046, found 418.1085.

(5*R,6*R**)-6-Benzenesulfonyl-5-methoxy-2,2-dimethyl-6-phenyl-3-hexanone (IV-8)**. The major diastereomer of **IV-3r** (17.0 mg, 55 μmol), which was isolated by preparative TLC, was treated with $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ (0.09 g, 145 μmol) according to the method in literature[31] to give 18.0 mg (96% yield) of sulfone **IV-8**: colorless needles (EtOH); mp 133°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 0.97 (s, 9H, (C*H*$_3$)$_3$C), 2.62 (dd, 1H, J = 6, 18,

C*H*HCO), 2.69 (dd, 1H, *J* = 4, 18, CH*H*CO), 3.36 (s, 3H, C*H*$_3$O), 4.53 (d, 1H, *J* = 8, PhSC*H*), 4.73 (ddd, 1H, *J* = 4, 6, 8, MeOC*H*), 7.2–7.3 (m, 5H, phenyl), 7.37 (tm, 2H, *J* = 7, phenyl), 7.49 (tm, 1H, *J* = 7, phenyl), 7.65 (dm, 2H, *J* = 7, phenyl); IR (KBr) 1705, 1315, 1295, 1150, 1105, 770, 700; Anal. calcd for $C_{21}H_{26}O_4S$, C 67.35 H 7.00 S 8.56, found C 67.10 H 6.96 S 8.34.

Methyl 3-Hydroxy-2,2-dimethyl-4-phenyl-4-(phenylthio)butanoate (IV-9). To a mixture of 2-phenyl-2-phenylthioacetaldehyde (0.79 g, 3.5 mmol) and **IV-2c** (0.75 g, 4.3 mmol) in CH_2Cl_2 (8 mL) was added BF_3·OEt_2 (0.98 g, 6.9 mmol) at -78°C. The mixture was stirred for 1 h, and saturated aqueous $NaHCO_3$ (10 mL) was added. The organic materials were extracted by CH_2Cl_2 (2 × 10 mL) and the extracts were dried over Na_2SO_4 and concentrated. Column chromatography (EtOAc/hexane = 1/10) gave 0.91 g (80%) of **IV-9** as a 9/1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) 1.13 (s, 3 × 0.1H, C*H*$_3$CCH$_3$), 1.18 (s, 3 × 0.9H, C*H*$_3$CCH$_3$), 1.23 (s, 3 × 0.9H, CH$_3$CC*H*$_3$), 1.27 (s, 3 × 0.1H, CH$_3$CC*H*$_3$), 3.28 (br, 1H, O*H*), 3.29 (s, 3 × 0.9H, C*H*$_3$O), 3.49 (s, 3 × 0.1H, C*H*$_3$O), 4.07 (dd, 0.9H, *J* = 4, 7, C*H*OH), 4.12 (t, 0.1H, *J* = 6, C*H*OH), 4.22 (d, 0.1H, *J* = 6, PhC*H*), 4.33 (d, 0.9H, *J* = 4, PhC*H*), 7.2–7.4 (m, 10H, phenyl).

(3*R,4*S**)-3-Hydroxy-2,2-dimethyl-4-phenyl-4-(phenylthio)butyl 3,5-Dinitrobenzoate (IV-10).** Ester **IV-9** (109.6 mg, 0.33 mmol) obtained above was treated with lithium aluminum hydride (0.1 g, 2.6 mmol) in ether (5 mL) to give 86.2 mg (86% yield) of 2,2-dimethyl-4-phenyl-4-phenylthio-1,3-butanediol as a 9/1 mixture of the diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) 0.61 (s, 3 × 0.9H, C*H*$_3$CCH$_3$), 0.70 (s, 3 × 0.1H, C*H*$_3$CCH$_3$), 0.91 (s, 3 × 0.9H, CH$_3$CC*H*$_3$), 0.95 (s, 3 × 0.1H, CH$_3$CC*H*$_3$), 2.60 (br, 1H, O*H*), 3.23 (ABq, 2 × 0.9H, *J* = 14, C*H*$_2$OH), 3.40 (br, 1H, O*H*), 3.44 (d, 0.1H, *J* = 11, C*H*HOH), 3.58 (d, 0.1H, *J* = 11, CH*H*OH), 3.91 (d, 0.9H, *J* = 3, C*H*OH), 3.93 (d, 0.1H, *J* = 6, C*H*OH), 4.30 (d 0.1H, *J* = 6, PhC*H*), 4.41 (d, 0.9H, *J* = 3, PhC*H*), 7.2–7.5 (m, 10H, phenyl).

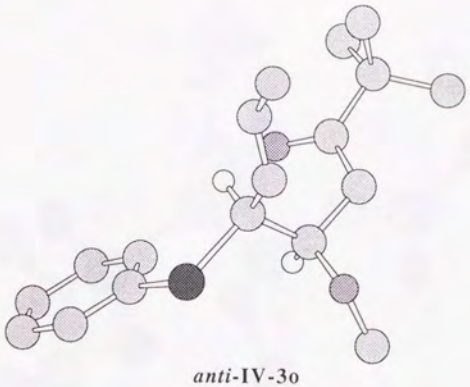
The major isomer of the above diol (5.8 mg, 19 μmol) was dissolved in THF (1 mL), and to this solution were successively added pyridine (10 μL, 124 μmol) and a THF (0.5 mL) solution of 3,5-dinitrobenzoyl chloride (21 mg, 91 μmol) at rt. The mixture was stirred overnight and directly charged onto the preparative TLC (EtOAc/hexane = 1/1). Recrystallization of the main

fraction from EtOH gave 6.6 mg (69% yield) of **IV-10** as pale yellow prisms: mp 133°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 0.74 (s, 3H, CH_3CCH_3), 1.02 (s, 3H, CH_3CCH_3), 1.57 (br s, 1H, O*H*), 3.83 (d, 1H, *J* = 3, PhSC*H*), 4.01 (d, 1H, *J* = 11, C*H*HOCO), 4.33 (d, 1H, *J* = 11, CH*H*OCO), 4.43 (d, 1H, *J* = 3, MeOC*H*), 7.1–7.5 (m, 10H, phenyl), 8.98 (d, 2H, *J* = 2, phenyl), 9.22 (t, 1H, *J* = 2, phenyl); IR (KBr) 3450 (br), 1727, 1545, 1345, 1290, 1175, 720; Anal. calcd for $C_{25}H_{24}N_2O_7S$, C 60.47 H 4.87 N 5.64, found C 60.25 H 5.14 N 5.58.

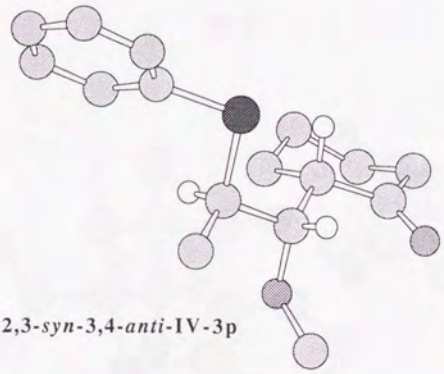
Details for X-ray structural analysis

Compound number	*anti*-**IV-3o**	2,3-*syn*-3,4-*anti*-**IV-3p**	**IV-7**
Molecular formula	$C_{18}H_{26}O_2S$	$C_{16}H_{22}O_2S$	$C_{16}H_{22}N_2O_9S$
Formula weight	306	278	418
Crystal size/mm^3	0.5 × 0.5 × 0.5	0.5 × 0.3 × 0.1	0.3 × 0.2 × 0.2
a/Å	12.465 (4)	10.436 (3)	20.696 (4)
b/Å	15.809 (4)	19.193 (6)	15.158 (3)
c/Å	9.162 (2)	7.528 (2)	6.250 (2)
β/degrees	98.53 (2)	93.80 (2)	96.86 (2)
Volume of unit cell /Å^3	1785.5 (8)	1504.5 (7)	1946.8 (8)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/c$	$P2_1/a$
Z value	4	4	4
D_{calc}/g cm^{-3}	1.14	1.23	1.43
Reflections used	2849	2364	2197
No. of variables	269	239	341
R;R_w	0.050; 0.065	0.056; 0.071	0.083; 0.076
Good of fitness	2.01	1.82	2.22
Maximum shift/e. s. d. in final cycle	0.10	0.08	0.06
Max. negative peak in final diff. map/e Å^{-3}	-0.39	-0.44	-0.62
Max. positive peak in final diff. map/e Å^{-3}	0.22	0.31	0.43

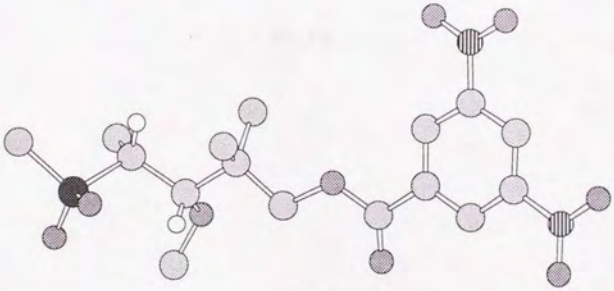
Compound number	**IV-8**	**IV-10**
Molecular formula	$C_{21}H_{26}O_4S$	$C_{25}H_{24}N_2O_7S$
Formula weight	374	496
Crystal size/mm^3	0.3 × 0.3 × 0.3	0.5 × 0.4 × 0.3
a/Å	12.005 (2)	9.667 (2)
b/Å	15.592 (4)	9.733 (9)
c/Å	11.616 (3)	14.158 (4)
α/degrees		107.04 (4)
β/degrees	112.50 (2)	95.63 (2)
γ/degrees		99.23 (4)
Volume of unit cell /Å^3	2009.0 (9)	1242 (1)
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
Z value	4	2
D_{calc}/g cm^{-3}	1.24	1.33
Reflections used	2867	3793
No. of variables	339	412
R;R_w	0.075; 0.089	0.073; 0.089
Good of fitness	0.37	2.55
Maximum shift/e. s. d. in final cycle	0.20	0.14
Max. negative peak in final diff. map/e Å^{-3}	-0.91	-0.39
Max. positive peak in final diff. map/e Å^{-3}	0.38	0.71



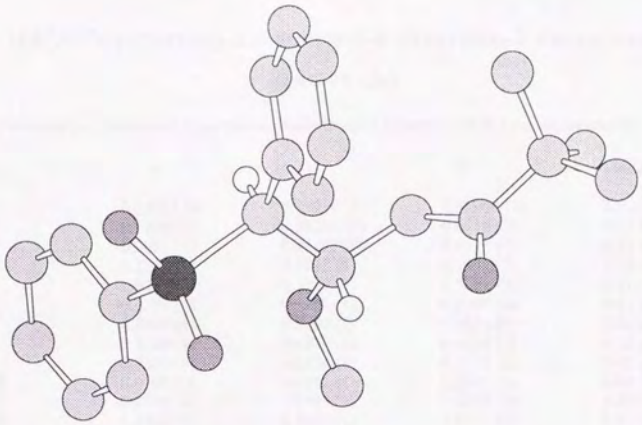
anti-IV-3o



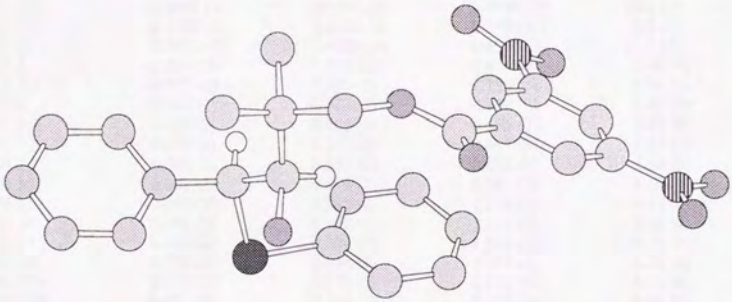
2,3-*syn*-3,4-*anti*-IV-3p



IV-7



IV-8



IV-10

(5*R**,6*S**)-5-Methoxy-2,2-dimethyl-6-phenylthio-7-nonen-3-one

(*anti*-IV-3o)

Positional parameters and equivalentisotropic thermal parameters with e.s.d. inparentheses

atom	x	y	z	B(eq)
S 1	0.07757 (4)	0.25219 (3)	0.92909 (5)	4.82 (2)
O 2	-0.1138 (1)	0.24840 (8)	0.6740 (2)	4.57 (4)
O 3	-0.2081 (1)	0.41147 (9)	0.9915 (1)	4.32 (3)
C 4	-0.1274 (1)	0.3015 (1)	0.7962 (2)	3.53 (4)
C 5	-0.0251 (2)	0.2727 (1)	1.1798 (2)	4.11 (5)
C 6	-0.0157 (1)	0.3369 (1)	0.8566 (2)	3.41 (4)
C 7	-0.2095 (2)	0.3703 (1)	0.7431 (2)	3.87 (4)
C 8	-0.2396 (1)	0.4275 (1)	0.8625 (2)	3.55 (4)
C 9	0.0359 (1)	0.3829 (1)	0.7418 (2)	3.68 (4)
C 10	0.0703 (2)	0.4611 (1)	0.7542 (2)	4.62 (5)
C 11	-0.0303 (2)	0.2583 (1)	1.3274 (2)	4.40 (5)
C 12	0.1386 (2)	0.1932 (1)	1.2016 (2)	4.72 (5)
C 13	0.0480 (2)	0.2115 (1)	1.4126 (2)	4.84 (6)
C 14	0.0599 (2)	0.2403 (1)	1.1158 (2)	3.48 (4)
C 15	0.1321 (2)	0.1792 (2)	1.3483 (2)	5.62 (6)
C 16	-0.3085 (2)	0.5056 (1)	0.8191 (2)	4.69 (5)
C 17	0.1249 (3)	0.5073 (2)	0.6451 (4)	6.50 (8)
C 18	-0.1810 (3)	0.1769 (2)	0.6579 (4)	6.46 (8)
C 19	-0.3493 (4)	0.5409 (3)	0.9549 (5)	10.0 (1)
C 20	-0.2309 (4)	0.5724 (2)	0.7710 (5)	8.8 (1)
C 21	-0.3975 (4)	0.4869 (3)	0.6940 (7)	11.3 (2)
H 4	-0.154 (2)	0.274 (2)	0.871 (3)	3.48 (0)
H 5	-0.075 (2)	0.305 (2)	1.130 (3)	4.06 (0)
H 6	-0.023 (2)	0.374 (2)	0.939 (3)	3.37 (0)
H 7 A	-0.185 (2)	0.402 (2)	0.665 (3)	3.85 (0)
H 7 B	-0.279 (2)	0.343 (2)	0.687 (3)	3.85 (0)
H 9	0.046 (2)	0.354 (2)	0.657 (3)	3.64 (0)
H 10	0.061 (2)	0.493 (2)	0.847 (3)	4.60 (0)
H 11	-0.090 (2)	0.282 (2)	1.370 (3)	4.32 (0)
H 12	0.199 (2)	0.169 (2)	1.157 (3)	4.68 (0)
H 13	0.042 (2)	0.204 (2)	1.514 (3)	4.79 (0)
H 15	0.188 (2)	0.144 (2)	1.404 (3)	5.58 (0)
H 17A	0.123 (3)	0.478 (2)	0.558 (4)	6.44 (0)
H 17B	0.083 (3)	0.554 (2)	0.612 (4)	6.44 (0)
H 17C	0.196 (3)	0.522 (2)	0.683 (4)	6.44 (0)
H 18A	-0.259 (3)	0.189 (2)	0.647 (4)	6.36 (0)
H 18B	-0.169 (3)	0.145 (2)	0.580 (4)	6.36 (0)
H 18C	-0.151 (3)	0.144 (2)	0.749 (4)	6.36 (0)
H 19A	-0.395 (4)	0.593 (3)	0.931 (5)	9.80 (0)
H 19B	-0.363 (4)	0.516 (3)	1.036 (5)	9.80 (0)
H 19C	-0.406 (4)	0.498 (3)	0.923 (5)	9.80 (0)
H 20A	-0.214 (3)	0.548 (3)	0.676 (5)	8.71 (0)
H 20B	-0.283 (3)	0.627 (3)	0.734 (4)	8.71 (0)
H 20C	-0.211 (3)	0.593 (3)	0.870 (5)	8.71 (0)
H 21A	-0.440 (5)	0.534 (4)	0.683 (6)	11.70 (0)
H 21B	-0.444 (4)	0.438 (4)	0.728 (6)	11.70 (0)
H 21C	-0.393 (5)	0.467 (4)	0.632 (6)	11.70 (0)

(5*R**,6*S**)-5-Methoxy-2,2-dimethyl-6-phenylthio-7-nonen-3-one (*anti*-IV-3o)

Intramolecular Distances (Å) with e.s.d. in parentheses

atom	atom	distance	atom	atom	distance
S1	--C 14	1.766 (2)	C 8	--C 16	1.522 (3)
S1	--C 6	1.833 (2)	C 9	--C 10	1.308 (3)
O2	--C 18	1.402 (3)	C 10	--C 17	1.482 (4)
O2	--C 4	1.430 (2)	C 11	--C 13	1.373 (3)
O3	--C 8	1.215 (2)	C 12	--C 15	1.377 (3)
C4	--C 7	1.522 (2)	C 12	--C 14	1.381 (3)
C4	--C 6	1.526 (2)	C 13	--C 15	1.375 (3)
C5	--C 11	1.382 (3)	C 16	--C 21	1.501 (6)
C5	--C 14	1.383 (3)	C 16	--C 19	1.519 (5)
C6	--C 9	1.499 (3)	C 16	--C 20	1.541 (5)
C7	--C 8	1.509 (3)			

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle	atom	atom	atom	angle
C 14	--S 1	--C 6	105.37 (8)	C 9	--C 10	--C 17	125.8 (2)
C 18	--O 2	--C 4	114.7 (2)	C 13	--C 11	--C 5	120.9 (2)
O 2	--C 4	--C 7	108.8 (1)	C 15	--C 12	--C 14	120.2 (2)
O 2	--C 4	--C 6	107.0 (1)	C 11	--C 13	--C 15	118.7 (2)
C 7	--C 4	--C 6	112.8 (1)	C 12	--C 14	--C 5	118.8 (2)
C 11	--C 5	--C 14	120.2 (2)	C 12	--C 14	--S 1	115.4 (2)
C 9	--C 6	--C 4	112.7 (1)	C 5	--C 14	--S 1	125.8 (1)
C 9	--C 6	--S 1	107.1 (1)	C 13	--C 15	--C 12	121.1 (2)
C 4	--C 6	--S 1	111.0 (1)	C 21	--C 16	--C 19	113.5 (3)
C 8	--C 7	--C 4	115.1 (1)	C 21	--C 16	--C 8	111.4 (2)
O 3	--C 8	--C 7	120.0 (2)	C 21	--C 16	--C 20	110.0 (3)
O 3	--C 8	--C 16	120.8 (2)	C 19	--C 16	--C 8	109.2 (2)
C 7	--C 8	--C 16	119.2 (2)	C 19	--C 16	--C 20	106.4 (3)
C 10	--C 9	--C 6	124.5 (2)	C 8	--C 16	--C 20	106.1 (2)

(2*R**,1'*R**,2'*S**)-2-(1-Methoxy-2-phenylthiopropyl)cyclohexanone (2,3-*syn*-3,4-*anti*-IV-3p)

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
S 1	0.91489 (6)	0.18398 (3)	0.36291 (9)	4.27 (2)
O 2	1.1035 (2)	0.09672 (9)	0.7844 (2)	4.45 (5)
O 3	1.3020 (2)	0.2107 (1)	0.7615 (3)	6.96 (7)
C 4	1.1910 (2)	0.1457 (1)	0.5279 (3)	3.19 (5)
C 5	0.6856 (2)	0.1829 (1)	0.1693 (4)	4.54 (7)
C 6	0.9496 (2)	0.1224 (1)	0.5443 (3)	3.28 (5)
C 7	0.6935 (2)	0.0443 (1)	0.0808 (3)	4.41 (7)
C 8	1.2182 (2)	0.0743 (1)	0.4474 (3)	3.68 (6)
C 9	1.3096 (2)	0.1764 (1)	0.6276 (3)	4.01 (6)
C 10	1.4363 (2)	0.1654 (2)	0.5493 (4)	4.55 (7)
C 11	1.0766 (2)	0.1449 (1)	0.6433 (3)	3.33 (5)
C 12	0.5937 (3)	0.0848 (2)	0.0143 (4)	4.78 (7)
C 13	0.8392 (3)	0.1181 (2)	0.6648 (4)	4.95 (8)
C 14	0.7925 (2)	0.0729 (1)	0.1885 (3)	3.88 (6)
C 15	0.7885 (2)	0.1427 (1)	0.2344 (3)	3.37 (5)
C 16	1.3428 (2)	0.0722 (2)	0.3534 (3)	4.18 (7)
C 17	0.5899 (3)	0.1538 (2)	0.0579 (4)	5.04 (8)
C 18	1.0919 (4)	0.1241 (2)	0.9594 (4)	6.6 (1)
C 19	1.4551 (2)	0.0922 (1)	0.4811 (4)	4.34 (7)
H 17	0.518 (4)	0.181 (2)	0.028 (5)	5.08 (0)
H 12	0.529 (3)	0.064 (2)	-0.059 (5)	4.81 (0)
H 7	0.697 (3)	-0.002 (2)	0.045 (5)	4.42 (0)
H 14	0.864 (3)	0.042 (2)	0.224 (4)	3.89 (0)
H 5	0.678 (3)	0.232 (2)	0.207 (5)	4.57 (0)
H 6	0.964 (3)	0.077 (2)	0.486 (4)	3.29 (0)
H 13A	0.858 (4)	0.081 (2)	0.756 (5)	4.95 (0)
H 13B	0.762 (4)	0.108 (2)	0.608 (5)	4.95 (0)
H 13C	0.828 (3)	0.164 (2)	0.724 (5)	4.95 (0)
H 11	1.067 (3)	0.191 (2)	0.697 (4)	3.35 (0)
H 18A	1.008 (4)	0.143 (2)	0.977 (6)	6.58 (0)
H 18B	1.167 (4)	0.156 (2)	0.999 (6)	6.58 (0)
H 4	1.175 (3)	0.177 (1)	0.428 (4)	3.21 (0)
H 8 A	1.221 (3)	0.039 (2)	0.544 (4)	3.68 (0)
H 8 B	1.146 (3)	0.064 (2)	0.359 (4)	3.68 (0)
H 16A	1.338 (3)	0.106 (2)	0.256 (5)	4.19 (0)
H 16B	1.356 (3)	0.025 (2)	0.299 (5)	4.19 (0)
H 19A	1.462 (3)	0.060 (2)	0.590 (5)	4.35 (0)
H 10A	1.499 (3)	0.178 (2)	0.641 (5)	4.58 (0)
H 10B	1.438 (3)	0.198 (2)	0.456 (5)	4.58 (0)
H 18C	1.103 (4)	0.085 (2)	1.028 (6)	6.58 (0)
H 19B	1.537 (3)	0.090 (2)	0.425 (4)	4.35 (0)

(2*R**,1'*R**,2'*S**)-2-(1-Methoxy-2-phenylthiopropyl)cyclohexanone (2,3-*syn*-3,4-*anti*-IV-3p)

Intramolecular Distances (Å) with e.s.d. inparentheses

atom	atom	distance	atom	atom	distance
S 1	--C 15	1.771 (2)	C 6	--C 13	1.516 (4)
S 1	--C 6	1.824 (2)	C 6	--C 11	1.539 (3)
O 2	--C 11	1.422 (3)	C 7	--C 12	1.368 (4)
O 2	--C 18	1.431 (4)	C 7	--C 14	1.384 (3)
O 3	--C 9	1.210 (3)	C 8	--C 16	1.522 (3)
C 4	--C 11	1.522 (3)	C 9	--C 10	1.498 (4)
C 4	--C 9	1.523 (3)	C 10	--C 19	1.512 (4)
C 4	--C 8	1.533 (3)	C 12	--C 17	1.366 (4)
C 5	--C 17	1.379 (4)	C 14	--C 15	1.384 (3)
C 5	--C 15	1.386 (3)	C 16	--C 19	1.515 (4)

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle	atom	atom	atom	angle
\C 15	--S 1	--C 6	102.9 (1)	C 10	--C 9	--C 4	117.4 (2)
C 11	--O 2	--C 18	115.1 (2)	C 9	--C 10	--C 19	113.8 (2)
C 11	--C 4	--C 9	111.4 (2)	O 2	--C 11	--C 4	108.0 (2)
C 11	--C 4	--C 8	112.9 (2)	O 2	--C 11	--C 6	107.4 (2)
C 9	--C 4	--C 8	112.1 (2)	C 4	--C 11	--C 6	114.1 (2)
C 17	--C 5	--C 15	120.1 (2)	C 17	--C 12	--C 7	119.7 (2)
C 13	--C 6	--C 11	113.0 (2)	C 7	--C 14	--C 15	119.7 (2)
C 13	--C 6	--S 1	111.2 (2)	C 14	--C 15	--C 5	119.1 (2)
C 11	--C 6	--S 1	107.6 (1)	C 14	--C 15	--S 1	122.4 (2)
C 12	--C 7	--C 14	120.6 (2)	C 5	--C 15	--S 1	118.4 (2)
C 16	--C 8	--C 4	113.2 (2)	C 19	--C 16	--C 8	110.3 (2)
O 3	--C 9	--C 10	120.9 (2)	C 12	--C 17	--C 5	120.5 (2)
O 3	--C 9	--C 4	121.6 (2)	C 10	--C 19	--C 16	109.8 (2)

(3*R**,4*S**)-3-Methoxy-4-methanesulfonyl-2,2-dimethylpentyl 3,5-Dinitrobenzoate (IV-7)

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
C 2	0.3445 (3)	0.1268 (4)	0.210 (1)	4.0 (2)
S 3	0.30700 (9)	0.0432 (1)	0.3562 (3)	5.23 (5)
O 4	0.3545 (2)	-0.0197 (3)	0.4406 (9)	6.3 (2)
O 5	0.2696 (2)	0.0872 (4)	0.506 (1)	7.6 (2)
C 6	0.2522 (6)	-0.0116 (7)	0.162 (2)	8.8 (4)
C 7	0.3865 (3)	0.1887 (4)	0.370 (1)	3.3 (2)
O 8	0.4536 (2)	0.1784 (2)	0.3558 (7)	4.4 (1)
C 9	0.4840 (4)	0.1088 (6)	0.482 (2)	5.7 (3)
C 10	0.3696 (3)	0.2869 (4)	0.338 (1)	3.5 (2)
C 11	0.2998 (4)	0.3036 (5)	0.381 (2)	5.1 (2)
C 12	0.3796 (4)	0.3185 (5)	0.115 (1)	4.7 (2)
C 13	0.4157 (3)	0.3346 (4)	0.503 (1)	3.8 (2)
O 14	0.3996 (2)	0.4276 (2)	0.5008 (6)	4.4 (1)
C 15	0.4354 (3)	0.4799 (4)	0.637 (1)	3.9 (2)
O 16	0.4798 (2)	0.4548 (3)	0.7624 (8)	5.9 (2)
C 17	0.4142 (3)	0.5733 (4)	0.613 (1)	3.5 (2)
C 18	0.4335 (3)	0.6327 (4)	0.779 (1)	3.8 (2)
C 19	0.4140 (3)	0.7186 (4)	0.754 (1)	3.8 (2)
C 20	0.3770 (3)	0.7506 (4)	0.575 (1)	3.9 (2)
C 21	0.3591 (3)	0.6898 (4)	0.414 (1)	3.7 (2)
C 22	0.3766 (3)	0.6022 (4)	0.431 (1)	3.9 (2)
N 23	0.4333 (3)	0.7812 (4)	0.935 (1)	5.2 (2)
O 24	0.4664 (3)	0.7528 (4)	1.0909 (9)	6.9 (2)
O 25	0.4151 (3)	0.8570 (4)	0.9101 (9)	7.6 (2)
N 26	0.3184 (2)	0.7194 (4)	0.2180 (9)	4.4 (2)
O 27	0.3100 (2)	0.6682 (3)	0.0676 (8)	5.8 (2)
O 28	0.2961 (3)	0.7931 (3)	0.2159 (9)	6.8 (2)
H 1A	0.414 (5)	0.037 (6)	0.08 (1)	10 (3)
H 1B	0.403 (4)	0.129 (6)	-0.05 (2)	11 (3)
H 1C	0.353 (3)	0.064 (5)	-0.04 (1)	6 (2)
H 2	0.307 (3)	0.160 (4)	0.139 (9)	4 (1)
H 6A	0.280 (4)	-0.029 (5)	0.04 (1)	7 (3)
H 6B	0.222 (5)	0.024 (7)	0.10 (2)	11 (3)
H 6C	0.242 (5)	-0.071 (8)	0.21 (2)	13 (4)
H 7	0.377 (2)	0.174 (2)	0.512 (7)	0.6 (8)
H 9A	0.468 (4)	0.056 (5)	0.43 (1)	8 (2)
H 9B	0.469 (3)	0.114 (4)	0.64 (1)	6 (2)
H 9C	0.527 (4)	0.108 (6)	0.47 (1)	9 (3)
H 11A	0.293 (3)	0.285 (4)	0.52 (1)	4 (2)
H 11B	0.266 (4)	0.274 (5)	0.27 (1)	8 (2)
H 11C	0.292 (3)	0.362 (4)	0.370 (9)	4 (1)
H 12A	0.373 (3)	0.385 (4)	0.094 (9)	5 (1)
H 12B	0.353 (3)	0.293 (5)	0.01 (1)	6 (2)
H 12C	0.425 (4)	0.298 (5)	0.08 (1)	7 (2)
H 13A	0.460 (3)	0.330 (4)	0.484 (9)	4 (2)
H 13B	0.416 (3)	0.317 (4)	0.65 (1)	4 (1)
H 18	0.455 (3)	0.615 (4)	0.882 (9)	3 (2)
H 20	0.364 (3)	0.808 (4)	0.553 (9)	4 (1)
H 22	0.363 (3)	0.565 (4)	0.33 (1)	6 (2)

(3*R**,4*S**)-3-Methoxy-4-methanesulfonyl-2,2-dimethylpentyl 3,5-Dinitrobenzoate (IV-7)

Intramolecular Distances (Å) with e.s.d. inparentheses

atom atom	distance	atom atom	distance
C 1 --C 2	1.53 (1)	C 15 --O 16	1.195 (8)
C 2 --C 7	1.558 (8)	C 15 --C 17	1.485 (8)
C 2 --S 3	1.792 (7)	C 17 --C 22	1.374 (8)
S 3 --O 4	1.425 (5)	C 17 --C 18	1.394 (9)
S 3 --O 5	1.449 (6)	C 18 --C 19	1.368 (8)
S 3 --C 6	1.76 (1)	C 19 --C 20	1.367 (9)
C 7 --O 8	1.411 (7)	C 19 --N 23	1.491 (8)
C 7 --C 10	1.537 (8)	C 20 --C 21	1.381 (9)
O 8 --C 9	1.42 (1)	C 21 --C 22	1.378 (9)
C 10 --C 13	1.502 (8)	C 21 --N 26	1.471 (8)
C 10 --C 12	1.51 (1)	N 23 --O 24	1.203 (8)
C 10 --C 11	1.52 (1)	N 23 --O 25	1.214 (8)
C 13 --O 14	1.449 (7)	N 26 --O 28	1.210 (7)
O 14 --C 15	1.323 (7)	N 26 --O 27	1.215 (7)

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom atom atom	angle	atom atom atom	angle
C 1 --C 2 --C 7	113.8 (6)	O 16 --C 15 --O 14	123.9 (5)
C 1 --C 2 --S 3	111.8 (5)	O 16 --C 15 --C 17	124.4 (5)
C 7 --C 2 --S 3	110.0 (4)	O 14 --C 15 --C 17	111.6 (5)
O 4 --S 3 --O 5	117.9 (4)	C 22 --C 17 --C 18	119.6 (6)
O 4 --S 3 --C 6	107.4 (4)	C 22 --C 17 --C 15	121.4 (5)
O 4 --S 3 --C 2	109.9 (3)	C 18 --C 17 --C 15	119.0 (5)
O 5 --S 3 --C 6	108.2 (5)	C 19 --C 18 --C 17	118.4 (6)
O 5 --S 3 --C 2	107.5 (3)	C 20 --C 19 --C 18	124.1 (6)
C 6 --S 3 --C 2	105.2 (5)	C 20 --C 19 --N 23	117.9 (5)
O 8 --C 7 --C 10	108.1 (4)	C 18 --C 19 --N 23	118.0 (5)
O 8 --C 7 --C 2	111.8 (5)	C 19 --C 20 --C 21	115.8 (6)
C 10 --C 7 --C 2	113.5 (5)	C 22 --C 21 --C 20	122.7 (6)
C 7 --O 8 --C 9	115.0 (5)	C 22 --C 21 --N 26	118.5 (5)
C 13 --C 10 --C 12	109.7 (5)	C 20 --C 21 --N 26	118.7 (5)
C 13 --C 10 --C 11	109.6 (6)	C 17 --C 22 --C 21	119.3 (6)
C 13 --C 10 --C 7	105.0 (4)	O 24 --N 23 --O 25	125.5 (6)
C 12 --C 10 --C 11	110.3 (6)	O 24 --N 23 --C 19	117.5 (6)
C 12 --C 10 --C 7	111.8 (5)	O 25 --N 23 --C 19	117.0 (6)
C 11 --C 10 --C 7	110.1 (5)	O 28 --N 26 --O 27	124.1 (6)
O 14 --C 13 --C 10	109.5 (5)	O 28 --N 26 --C 21	118.2 (5)
C 15 --O 14 --C 13	117.7 (4)	O 27 --N 26 --C 21	117.7 (5)

(5R^*,6R^*)-6-Benzenesulfonyl-5-methoxy-2,2-dimethyl-6-phenyl-3-hexanone (IV-8)

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
S 1	0.11123 (6)	0.20978 (5)	0.94742 (7)	4.06 (3)
O 2	0.3096 (2)	0.0775 (2)	0.9969 (2)	5.39 (8)
O 3	0.0513 (2)	0.2881 (2)	0.8962 (3)	5.40 (8)
O 4	0.1056 (2)	0.1781 (2)	1.0616 (2)	5.61 (8)
O 5	0.5131 (2)	0.2034 (2)	1.2990 (2)	6.29 (9)
C 6	0.3033 (2)	0.3165 (2)	1.0188 (3)	3.89 (8)
C 7	0.5542 (3)	0.2069 (2)	1.2187 (3)	3.91 (8)
C 8	0.3293 (3)	0.3752 (2)	0.9458 (4)	5.1 (1)
C 9	0.2703 (3)	0.2256 (2)	0.9754 (3)	3.80 (8)
C 10	0.0534 (3)	0.1304 (2)	0.8308 (3)	4.14 (8)
C 11	0.0268 (3)	0.1511 (2)	0.7090 (3)	4.62 (9)
C 12	0.4823 (3)	0.1703 (2)	1.0901 (3)	4.7 (1)
C 13	0.0342 (3)	0.0482 (2)	0.8647 (3)	5.2 (1)
C 14	0.6780 (3)	0.2430 (2)	1.2439 (3)	4.42 (9)
C 15	0.3050 (3)	0.3421 (2)	1.1358 (3)	5.0 (1)
C 16	0.3482 (3)	0.1564 (2)	1.0598 (3)	4.20 (9)
C 17	-0.0220 (3)	0.0907 (3)	0.6166 (4)	5.6 (1)
C 18	0.7406 (4)	0.2634 (4)	1.3831 (4)	6.4 (1)
C 19	-0.0430 (3)	0.0076 (3)	0.6504 (4)	5.6 (1)
C 20	0.3595 (4)	0.4839 (2)	1.0991 (6)	7.0 (2)
C 21	0.6646 (5)	0.3256 (3)	1.1690 (5)	6.5 (2)
C 22	-0.0147 (4)	-0.0132 (3)	0.7728 (5)	6.6 (1)
C 23	0.3315 (4)	0.4254 (3)	1.1734 (4)	6.4 (1)
C 24	0.7547 (3)	0.1776 (3)	1.2063 (4)	5.6 (1)
C 25	0.3240 (7)	0.0063 (4)	1.0810 (7)	9.1 (2)
C 26	0.3589 (4)	0.4589 (3)	0.9868 (5)	6.8 (2)
H 8	0.337 (2)	0.352 (2)	0.864 (3)	2.7 (5)
H 9	0.277 (2)	0.219 (2)	0.896 (2)	1.4 (4)
H 11	0.036 (4)	0.205 (3)	0.678 (4)	4.8 (8)
H 12A	0.526 (4)	0.115 (3)	1.079 (4)	6 (1)
H 12B	0.493 (4)	0.200 (3)	1.024 (4)	4.7 (8)
H 13	0.074 (5)	0.038 (4)	0.974 (6)	9 (1)
H 15	0.285 (4)	0.306 (3)	1.186 (4)	6 (1)
H 16	0.336 (3)	0.156 (2)	1.142 (3)	3.0 (6)
H 17	-0.044 (4)	0.101 (3)	0.533 (4)	6 (1)
H 18A	0.688 (6)	0.296 (4)	1.406 (5)	7 (1)
H 18B	0.815 (8)	0.306 (5)	1.400 (7)	12 (2)
H 18C	0.752 (4)	0.209 (3)	1.433 (5)	6 (1)
H 19	-0.074 (5)	-0.040 (4)	0.598 (5)	8 (1)
H 20	0.372 (4)	0.542 (3)	1.124 (4)	6.0 (9)
H 21A	0.637 (4)	0.308 (3)	1.082 (4)	5.0 (9)
H 21B	0.627 (6)	0.360 (4)	1.192 (6)	9 (2)
H 21C	0.751 (4)	0.356 (3)	1.191 (3)	5.0 (8)
H 22	-0.042 (6)	-0.065 (4)	0.789 (5)	9 (2)
H 23	0.337 (5)	0.451 (4)	1.254 (5)	7 (1)
H 24A	0.698 (5)	0.161 (4)	1.114 (6)	8 (1)
H 24B	0.759 (4)	0.126 (3)	1.236 (4)	6 (1)
H 24C	0.843 (5)	0.200 (3)	1.233 (4)	7 (1)
H 25A	0.414 (5)	-0.004 (4)	1.131 (5)	8 (1)
H 25B	0.254 (9)	0.019 (7)	1.129 (8)	15 (3)
H 25C	0.297 (6)	-0.036 (6)	1.042 (6)	10 (2)
H 26	0.377 (4)	0.504 (3)	0.944 (4)	6 (1)

(5*R**,6*R**)-6-Benzenesulfonyl-5-methoxy-2,2-dimethyl-6-phenyl-3-hexanone (IV-8)

Intramolecular Distances (Å) with e.s.d. inparentheses

atom	atom	distance	atom	atom	distance
S 1	--O 3	1.426 (2)	C 10	--C 11	1.365 (5)
S 1	--O 4	1.440 (3)	C 10	--C 13	1.386 (5)
S 1	--C 10	1.769 (3)	C 11	--C 17	1.378 (5)
S 1	--C 9	1.827 (3)	C 12	--C 16	1.526 (5)
O 2	--C 16	1.416 (4)	C 13	--C 22	1.386 (6)
O 2	--C 25	1.443 (7)	C 14	--C 21	1.527 (6)
O 5	--C 7	1.212 (5)	C 14	--C 18	1.533 (5)
C 6	--C 8	1.364 (5)	C 14	--C 24	1.544 (6)
C 6	--C 15	1.409 (5)	C 15	--C 23	1.368 (6)
C 6	--C 9	1.506 (4)	C 17	--C 19	1.405 (6)
C 7	--C 14	1.510 (4)	C 19	--C 22	1.369 (7)
C 7	--C 12	1.522 (4)	C 20	--C 26	1.360 (9)
C 8	--C 26	1.387 (5)	C 20	--C 23	1.382 (8)
C 9	--C 16	1.515 (4)			

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle	atom	atom	atom	angle
O 3	--S 1	--O 4	118.9 (2)	C 10	--C 11	--C 17	120.5 (4)
O 3	--S 1	--C 10	107.0 (1)	C 7	--C 12	--C 16	115.5 (3)
O 3	--S 1	--C 9	106.5 (2)	C 22	--C 13	--C 10	119.2 (4)
O 4	--S 1	--C 10	108.8 (2)	C 7	--C 14	--C 21	108.8 (3)
O 4	--S 1	--C 9	107.2 (1)	C 7	--C 14	--C 18	109.3 (3)
C 10	--S 1	--C 9	107.9 (2)	C 7	--C 14	--C 24	110.4 (3)
C 16	--O 2	--C 25	112.9 (3)	C 21	--C 14	--C 18	109.2 (4)
C 8	--C 6	--C 15	119.2 (3)	C 21	--C 14	--C 24	109.9 (4)
C 8	--C 6	--C 9	121.1 (3)	C 18	--C 14	--C 24	109.3 (3)
C 15	--C 6	--C 9	119.7 (3)	C 23	--C 15	--C 6	119.5 (4)
O 5	--C 7	--C 14	121.9 (3)	O 2	--C 16	--C 9	106.5 (2)
O 5	--C 7	--C 12	119.6 (3)	O 2	--C 16	--C 12	110.5 (3)
C 14	--C 7	--C 12	118.4 (3)	C 9	--C 16	--C 12	112.6 (3)
C 6	--C 8	--C 26	120.4 (4)	C 11	--C 17	--C 19	118.8 (4)
C 6	--C 9	--C 16	115.7 (2)	C 22	--C 19	--C 17	120.6 (4)
C 6	--C 9	--S 1	108.0 (2)	C 26	--C 20	--C 23	119.7 (4)
C 16	--C 9	--S 1	111.3 (2)	C 19	--C 22	--C 13	120.0 (4)
C 11	--C 10	--C 13	121.0 (3)	C 15	--C 23	--C 20	120.7 (5)
C 11	--C 10	--S 1	119.8 (2)	C 20	--C 26	--C 8	120.4 (5)
C 13	--C 10	--S 1	119.3 (2)				

(3*R**,4*S**)-3-Hydroxy-2,2-dimethyl-4-phenyl-4-phenylthiobutyl 3,5-Dinitrobenzoate (IV-10)

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
S 1	0.57542 (8)	0.15019 (9)	0.21366 (8)	6.03 (3)
O 2	0.3461 (2)	0.6036 (2)	0.3271 (1)	4.66 (6)
O 3	0.3687 (3)	0.2624 (3)	0.3612 (2)	5.80 (7)
O 4	0.3971 (2)	0.7302 (3)	0.4898 (2)	6.14 (8)
O 5	0.8063 (4)	0.8750 (4)	0.1320 (2)	9.2 (1)
O 6	0.5965 (4)	0.7445 (4)	0.0854 (2)	8.7 (1)
O 7	0.8358 (4)	1.1127 (4)	0.5881 (2)	8.6 (1)
O 8	0.9559 (4)	1.1538 (4)	0.4786 (3)	10.4 (1)
N 9	0.6946 (4)	0.8216 (4)	0.1492 (2)	6.7 (1)
N 10	0.8551 (3)	1.0891 (4)	0.5038 (2)	6.6 (1)
C 11	0.3639 (3)	0.3009 (3)	0.2720 (2)	4.22 (7)
C 12	0.5418 (3)	0.7928 (3)	0.3763 (2)	4.13 (7)
C 13	0.2981 (3)	0.0328 (3)	0.1514 (2)	4.14 (7)
C 14	0.4216 (3)	0.7071 (3)	0.4056 (2)	4.26 (8)
C 15	0.5594 (3)	0.7686 (3)	0.2768 (2)	4.53 (8)
C 16	0.6746 (3)	0.8496 (3)	0.2551 (2)	4.82 (8)
C 17	0.3957 (3)	0.1806 (3)	0.1838 (2)	4.35 (8)
C 18	0.6399 (3)	0.8979 (3)	0.4512 (2)	4.59 (8)
C 19	0.2348 (4)	0.4966 (4)	0.3407 (3)	5.23 (9)
C 20	0.7531 (3)	0.9768 (3)	0.4242 (2)	4.83 (8)
C 21	0.7745 (4)	0.9530 (4)	0.3267 (2)	5.25 (9)
C 22	0.1330 (4)	-0.1542 (4)	0.0226 (3)	6.2 (1)
C 23	0.7044 (5)	0.3745 (5)	0.1516 (4)	6.8 (1)
C 24	0.1924 (4)	-0.1913 (4)	0.1767 (3)	6.0 (1)
C 25	0.2244 (3)	0.3529 (3)	0.2573 (2)	4.49 (8)
C 26	0.0944 (4)	0.2449 (4)	0.2666 (4)	5.8 (1)
C 27	0.2815 (4)	-0.0560 (3)	0.2117 (2)	5.15 (9)
C 28	0.2221 (4)	-0.0201 (4)	0.0548 (2)	5.30 (9)
C 29	0.6813 (3)	0.3234 (4)	0.2302 (3)	5.6 (1)
C 30	0.1163 (4)	-0.2397 (4)	0.0831 (3)	6.2 (1)
C 31	0.2015 (4)	0.3813 (4)	0.1564 (3)	5.5 (1)
C 32	0.7493 (4)	0.4085 (5)	0.3253 (4)	6.8 (1)
C 33	0.7936 (5)	0.5070 (6)	0.1664 (5)	8.4 (2)
C 34	0.8601 (4)	0.5866 (5)	0.2589 (6)	9.0 (2)
C 35	0.8362 (5)	0.5390 (6)	0.3388 (6)	8.2 (2)
H 3	0.434 (6)	0.248 (6)	0.383 (4)	9 (2)
H 11	0.440 (3)	0.386 (3)	0.279 (2)	2.9 (5)
H 15	0.498 (4)	0.704 (4)	0.222 (3)	6.1 (8)
H 17	0.382 (3)	0.211 (3)	0.125 (2)	3.6 (6)
H 18	0.639 (4)	0.913 (4)	0.518 (3)	5.0 (7)
H 19A	0.155 (4)	0.534 (4)	0.345 (3)	6.1 (9)
H 19B	0.267 (4)	0.482 (4)	0.410 (3)	5.9 (8)
H 21	0.836 (6)	1.020 (6)	0.300 (4)	11 (1)
H 22	0.074 (7)	-0.175 (7)	-0.053 (5)	13 (2)
H 23	0.662 (4)	0.322 (5)	0.099 (3)	6 (1)
H 24	0.194 (5)	-0.249 (5)	0.222 (3)	8 (1)
H 26A	0.129 (4)	0.231 (4)	0.324 (3)	6 (1)
H 26B	0.005 (5)	0.283 (5)	0.255 (3)	8 (1)
H 26C	0.083 (4)	0.136 (5)	0.212 (3)	7 (1)
H 27	0.322 (4)	-0.013 (4)	0.284 (3)	5.7 (8)
H 28	0.240 (4)	0.039 (4)	0.018 (2)	5.3 (8)
H 30	0.057 (5)	-0.333 (5)	0.061 (3)	8 (1)
H 31A	0.305 (4)	0.449 (4)	0.144 (3)	6.6 (9)
H 31B	0.200 (3)	0.286 (4)	0.106 (2)	4.7 (7)
H 31C	0.115 (5)	0.435 (5)	0.161 (3)	7.0 (9)
H 32	0.739 (4)	0.374 (5)	0.380 (3)	7 (1)

(3*R**,4*S**)-3-Hydroxy-2,2-dimethyl-4-phenyl-4-phenylthiobutyl 3,5-Dinitrobenzoate (IV-10)

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
H 33	0.780 (6)	0.555 (6)	0.111 (4)	10 (1)
H 34	0.928 (7)	0.675 (7)	0.289 (4)	11 (2)
H 35	0.865 (5)	0.587 (6)	0.394 (4)	7 (1)

Intramolecular Distances (Å) with e.s.d. inparentheses

atom atom	distance	atom atom	distance
S 1 --C 29	1.764 (3)	C 13 --C 17	1.504 (4)
S 1 --C 17	1.838 (3)	C 15 --C 16	1.372 (5)
O 2 --C 14	1.316 (3)	C 16 --C 21	1.368 (4)
O 2 --C 19	1.441 (4)	C 18 --C 20	1.385 (5)
O 3 --C 11	1.418 (4)	C 19 --C 25	1.524 (4)
O 4 --C 14	1.200 (4)	C 20 --C 21	1.374 (5)
O 5 --N 9	1.200 (5)	C 22 --C 30	1.362 (6)
O 6 --N 9	1.218 (4)	C 22 --C 28	1.366 (5)
O 7 --N 10	1.187 (5)	C 23 --C 29	1.368 (8)
O 8 --N 10	1.215 (5)	C 23 --C 33	1.379 (7)
N 9 --C 16	1.482 (4)	C 24 --C 30	1.360 (5)
N 10 --C 20	1.467 (4)	C 24 --C 27	1.376 (4)
C 11 --C 25	1.530 (4)	C 25 --C 31	1.534 (5)
C 11 --C 17	1.535 (4)	C 25 --C 26	1.546 (5)
C 12 --C 18	1.387 (3)	C 29 --C 32	1.389 (5)
C 12 --C 15	1.391 (4)	C 32 --C 35	1.356 (7)
C 12 --C 14	1.485 (4)	C 33 --C 34	1.345 (9)
C 13 --C 27	1.384 (5)	C 34 --C 35	1.37 (1)
C 13 --C 28	1.394 (4)		

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom atom atom	angle	atom atom atom	angle
C 29 --S 1 --C 17	102.2 (2)	C 11 --C 17 --S 1	109.3 (2)
C 14 --O 2 --C 19	119.6 (2)	C 20 --C 18 --C 12	118.6 (3)
O 5 --N 9 --O 6	124.5 (4)	O 2 --C 19 --C 25	107.9 (3)
O 5 --N 9 --C 16	118.0 (3)	C 21 --C 20 --C 18	122.8 (2)
O 6 --N 9 --C 16	117.5 (3)	C 21 --C 20 --N 10	119.0 (3)
O 7 --N 10 --O 8	123.5 (3)	C 18 --C 20 --N 10	118.2 (3)
O 7 --N 10 --C 20	119.4 (3)	C 16 --C 21 --C 20	116.7 (3)
O 8 --N 10 --C 20	117.0 (3)	C 30 --C 22 --C 28	121.3 (3)
O 3 --C 11 --C 25	107.2 (2)	C 29 --C 23 --C 33	120.8 (5)
O 3 --C 11 --C 17	112.5 (3)	C 30 --C 24 --C 27	120.9 (4)
C 25 --C 11 --C 17	117.1 (2)	C 19 --C 25 --C 11	107.2 (2)
C 18 --C 12 --C 15	119.7 (3)	C 19 --C 25 --C 31	108.6 (3)
C 18 --C 12 --C 14	118.4 (2)	C 19 --C 25 --C 26	106.9 (3)
C 15 --C 12 --C 14	121.8 (2)	C 11 --C 25 --C 31	111.2 (3)
C 27 --C 13 --C 28	117.7 (3)	C 11 --C 25 --C 26	112.8 (3)
C 27 --C 13 --C 17	123.6 (2)	C 31 --C 25 --C 26	109.9 (3)
C 28 --C 13 --C 17	118.8 (3)	C 24 --C 27 --C 13	120.6 (3)
O 4 --C 14 --O 2	125.0 (3)	C 22 --C 28 --C 13	120.4 (4)
O 4 --C 14 --C 12	124.1 (2)	C 23 --C 29 --C 32	118.4 (4)
O 2 --C 14 --C 12	110.9 (2)	C 23 --C 29 --S 1	122.2 (3)
C 16 --C 15 --C 12	118.8 (2)	C 32 --C 29 --S 1	119.3 (4)
C 21 --C 16 --C 15	123.3 (3)	C 24 --C 30 --C 22	119.0 (3)
C 21 --C 16 --N 9	117.9 (3)	C 35 --C 32 --C 29	120.2 (6)
C 15 --C 16 --N 9	118.7 (2)	C 34 --C 33 --C 23	119.8 (7)
C 13 --C 17 --C 11	117.8 (2)	C 33 --C 34 --C 35	120.4 (5)
C 13 --C 17 --S 1	106.7 (2)	C 32 --C 35 --C 34	120.4 (5)

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(20) When the reaction of **IV-2a** with **IV-4** was carried out in the presence of 2 equiv. of $EtOSiMe_3$, there was no observed incorporation of an EtO group in the product, and the diastereomer ratio was not changed. This result may rule out the existence of a free oxocarbenium ion intermediate.

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CHAPTER V. STEREOSELECTIVE CATIONIC CYCLIZATION ASSISTED BY A SULFENYL GROUP

Summary: Secondary acetates **V-1** and **V-6** were successfully cyclized upon the successive treatment with Lewis acid and base. An NMR study of the reaction revealed that the intermediate was a five-membered sulfonium ion. In the reaction of **V-6**, thermodynamically less stable cis isomer **V-7** was obtained as the major product due to the conformational restriction of the intermediate.

1. Introduction

An alkylative cyclization toward a cationic center is one of the methods for carbocycle construction and has drawn much attention of synthetic organic chemists. This methodology have been widely applied for terpene synthesis.[1]

Among them, the most simple reaction is a mimic for the biosynthesis of limonene/terpinolene by the cyclization of neryl pyrophosphate. This reaction was originally studied using neryl pyrophosphate itself as a substrate.[2] After that, the leaving group was changed to another one in order to improve its usefulness in a synthetic organic chemistry. Mukaiyama and co-workers showed that 2-halopyridinium salts effectively activate nerol to give the corresponding cyclized product in high yield.[3] Nozaki et al. reported the cyclization-alkylation of diethyl neryl phosphate by organoaluminum species[4] and the halogenative cyclization of nerol by a $TiCl_4$-amine complex.[5] The enantioselective version of the cyclization was also demonstrated by Yamamoto and co-workers by using a chiral leaving group and a suitably designed aluminum reagent.[6]

Thus, the cyclization to give simple cyclohexene system is thoroughly investigated. However, the formation of the corresponding cyclohexane ring has been scarcely reported unless the cation initially formed is tertially or allylic.[7] As easily seen from this fact, one of the drawbacks for this simple cationic cyclization is the dependence on the substrate structure; they must be a precursor for a fairly stable cation. Therefore, the author planned to carry out the

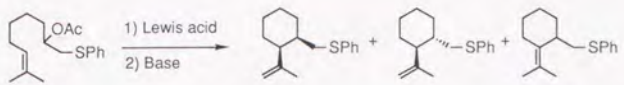
unprecedented cationic cyclization of a secondary acetate, assisted by the neighboring group participation of a sulfenyl group.

In chapter III, the author has described that a cation, to which the neighboring group participation occurs, must have an appropriate stability in order that the reaction occurs cleanly. Otherwise, the reaction became complex, presumably due to a short life-time of the intermediate episulfonium ion. A simple secondary cation belongs to fairly *unstable* cation; therefore the neighboring-group-participated reaction of β-sulfenylated secondary acetate is considered to be hardly successful. In fact, the attempt to alkylate *trans*-1-acetoxy-2-(phenylthio)cyclohexanone with a silyl enol ether resulted in failure. However, such an unstable intermediate might be successfully trapped, if the reaction is designed as an intramolecular one, which is entropically more favorable than an intermolecular counterpart. Therefore, the author tried the reaction of secondary acetate **V-1**.

2. Results and Discussion

When **V-1** was treated with 1.1 equiv. of TMSOTf for one day, the starting material was completely consumed. However, no cyclized product was detected. Instead, a very polar species was formed. The species slowly decomposed upon standing at room temperature to give a much less polar compound, which was identified to a mixture of cyclized products **V-2**, **V-3**, and **V-4**. Then, the reaction conditions were thoroughly examined for the conversion of the polar product into **V-2**, **V-3**, and **V-4**. As a result, it was found that the decomposition was enhanced by treating the polar product with a base. The yield was as high as 85% when triethylamine was used. Thus, the cationic cyclization of the secondary alcohol derivative was proved to be successful with the aid of neighboring group participation. The present reaction is the first example for the formation of 1,2-dialkylcyclohexane by a cationic cyclization. Consequently, the author became further interested in the selectivity of this reaction, and investigated several activators and bases (Table 1).

In a certain case, the formation of exocyclic isomer **V-4** was suppressed (Run 6). However, high stereoselectivity between to diastereomers, **V-2** and **V-3**, was not observed in every case.



V-1 V-2 V-3 V-4

Table V-1. Cyclization of **V-1** under Various Conditions

Run	Lewis acid	Base	Yield/%	V-2:V-3:V-4
1	TMSOTf	none	0	–
2		Et_3N	85	41:54:5
3		proton sponge[a]	74	25:52:23
4		K_2CO_3	33[b]	29:44:27
5	$TiCl_4$	Et_3N	39	40:46:14
6	$SnCl_4$		79	45:55:0

[a] 1,8-Bis(dimethylamino)naphthalene.
[b] TMSOTf was added to the mixture of **V-1** and base.

Then, the author tried to identify what the intermediate polar compound is. The reaction was pursued by using NMR. As shown in Fig. 1, ^1H NMR signal of **V-1** slowly faded and new peaks appeared. The characteristics are:

1) Low field shift of the phenyl protons.

2) Disappearance of two methyne protons around 5 ppm which can be assigned as the olefin proton and the proton on the carbon adjacent to the acetoxy group.

3) Disappearance of the methylene proton on the carbon adjacent to the phenylthio group.

4) Appearance of new signals (at least six kinds) between 3.4 and 4.4 ppm. Three of them are clear double-doublets having a large *J* value which is consistent with that of a geminal coupling.

5) The methyl proton at 1.6 (or 1.7) ppm shifted to higher fields and split into three distinct singlets at 0.9, 1.2, and 1.2 ppm (the area ratio of the three peaks was roughly 1:2:2). The other methyl proton at 1.7 (or 1.6) ppm also split into three different peaks at 1.7, 1.8 and 1.9 ppm (the area ratio was roughly 2:2:1).

The reaction was also monitored by ^{13}C NMR (Fig. 2). The noteworthy are:

6) Disappearance of the signals at 73 (the carbon adjacent to the acetoxy group), 125 (the olefinic carbon), and 127 ppm (the olefinic carbon).

7) Appearance of a set of signals around 45, 80, and 120 ppm.

Fig. V-1. ^{1}H NMR spectra of **V-1**: (a) substrate only; (b) reacted with TMSOTf for 8 h, (c) for 26 h.

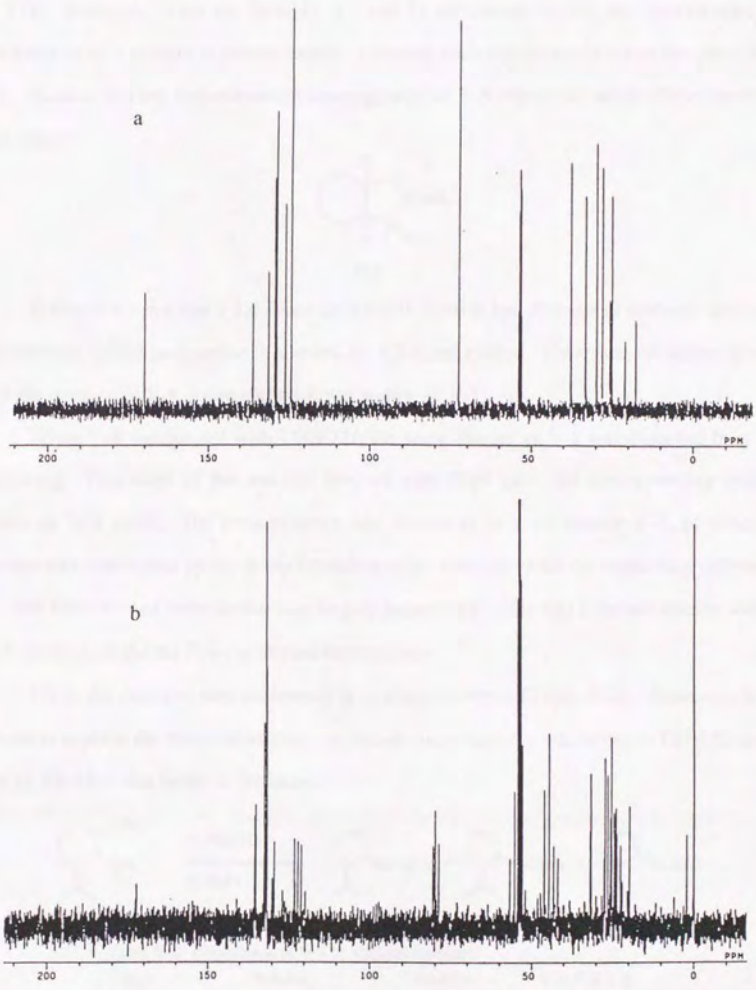
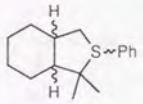


Fig. V-2. ^{13}C NMR spectra of V-1: (a) substrate only; (b) reacted with TMSOTf for 26 h.

Taking into account these observations, it is concluded that the intermediate is sulfonium ion **V-5**. However, from the facts 4), 5), and 7) mentioned above, the intermediate was considered to be a mixture of stereoisomers. Although each signals could not be assigned, it was easily deduced that the stereochemical heterogeneity of **V-5** affects the result of the reaction to some extent.

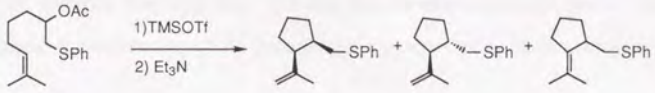


V-5

It is well known that a 5,6-fused carbocyclic system can be exist as both cis- and trans-form whereas only a cis-junction is allowed for 5,5-fused system. Therefore, the author planned to try the reaction of **V-6**, a one-carbon-fewer analog of **V-1**.

When **V-6** was treated with TMSOTf, the same change as **V-1** was observed by a TLC monitoring. Treatment of the reaction mixture with Et_3N gave the corresponding cyclized product in 70% yield. The main product was proved to be a cis isomer **V-7**, of which the structure was determined by the X-ray crystallographic analysis of the corresponding sulfone (**V-10**). The formation of trans isomer was largely suppressed. This fact is in accordance with the above assumption for the five-membered intermediate.

Then, the reaction was performed in various solvents (Table V-2). However, it was difficult to explain the effect of solvent. Although the selectivity was better in CH_3CN than in CH_2Cl_2, the yield was better in the latter.



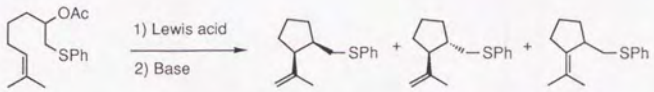
V-6 **V-7** **V-8** **V-9**

Table V-2. Cyclization of **V-6** in Various Solvents

Run	Solvent	Yield/%	**V-7**:**V-8**:**V-9**
1	CH_2Cl_2	70	83:0:17
2	CH_3CN	53	91:0:9
3	CH_3NO_2	64	76:16:18
4	CH_2ClCH_2Cl	79	77:6:17
5	CH_3CH_2CN	62	74:11:15

Therefore, the author next investigated the effect of activator and base when the cyclization was carried out in CH_2Cl_2 (Table V-3).

Trityl perchlorate gave a good result for the selectivity, however, the yield is somewhat problematic (Run 9). The tin(IV) chloride-mediated reaction resulted in a completely different stereochemical course (Run 10).



V-6 **V-7** **V-8** **V-9**

Table V-3. Cyclization of **V-6** by Various Lewis Acids and Bases

Run	Lewis acid	Base	Yield/%	**V-7**:**V-8**:**V-9**
1	TMSOTf	Et_3N	70	83:0:17
2		Et_2NH	68	77:3:20
3		$^{i}BuNH_2$	70	51:4:47
4		DBU	78	58:5:37
5		$^{i}Pr_2NEt$	66	40:3:57
6		EtONa	85	52 :6:42
7		2,6-lutidine	59	13:2:85
8		proton sponge	65	34:4:62
9	$TrClO_4$	Et_3N	47	90:0:10
10	$SnCl_4$		77	32:66:2

The reaction of **V-6** was also monitored by NMR (Figs. V-3 and V-4). In this case, clearer NMR spectrum was obtained. This fact and the stereochemical result of the reaction indicate that the stereochemistry of the intermediate was restricted to cis as anticipated.

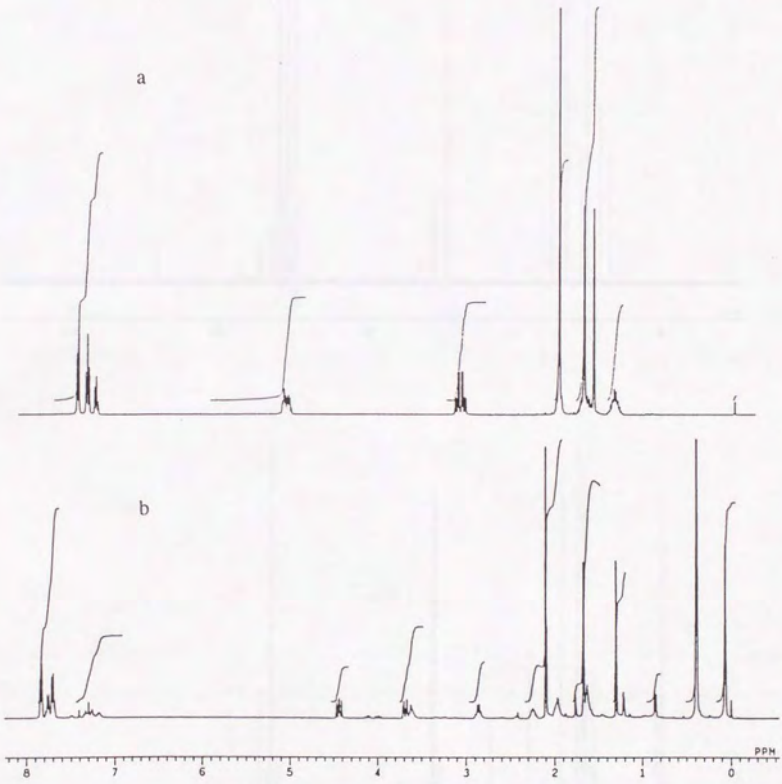


Fig. V-3. ^{1}H NMR spectra of V-6: (a) substrate only; (b) reacted with TMSOTf for 24 h.

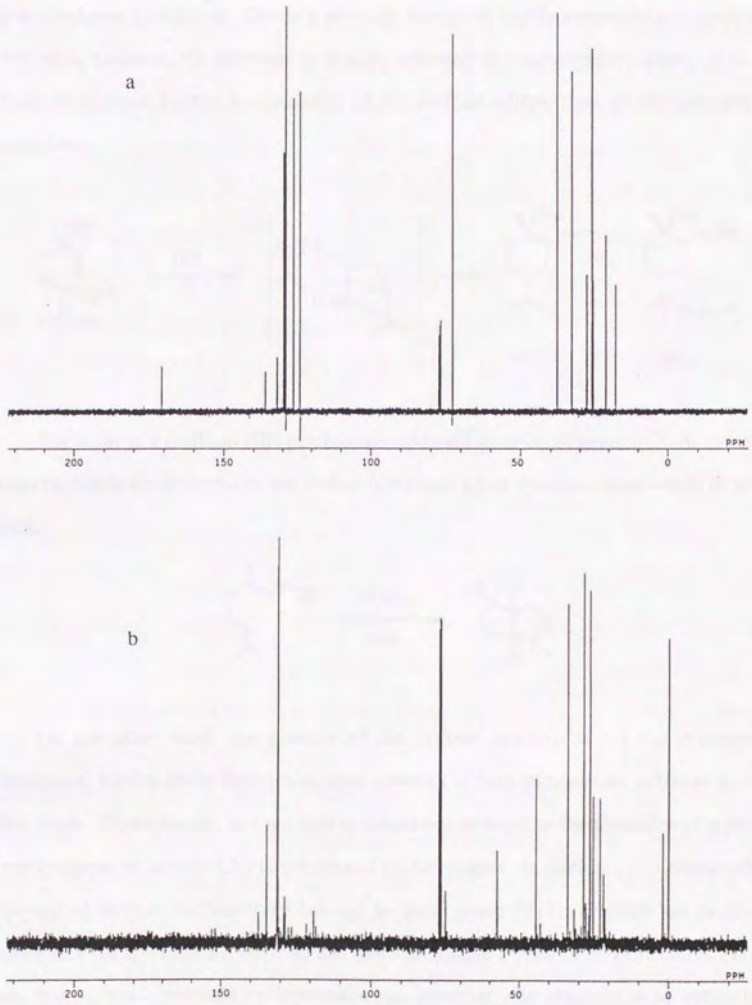
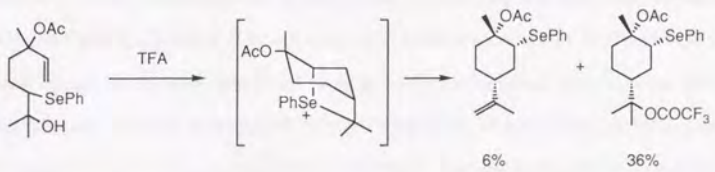
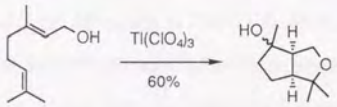


Fig. V-4. ^{13}C NMR spectra of **V-6**: (a) substrate only; (b) reacted with TMSOTf for 24 h.

There are two examples for the formation of a hetero-atom containing five-membered ring in a polyene cyclization. One is a selenium-mediated, highly stereoselective cyclization.[8] In this case, however, the selenium is directly attached to a stereogenic carbon. It is rather difficult to perform further manipulation of the product without loss of the stereochemical information.



The other is a thallium (III) perchlorate-mediated reaction of geraniol.[9] As the product of this reaction is tetrahydrofuran, the further functional group transformation would be severely limited.



On the other hand, the product of the present reaction is *cis*-1,2-disubstituted cyclopentane, having easily functionalizable moieties in both substituents; sulfenyl group and double bond. Consequently, this reaction is considered to result in the formation of a precursor for the synthesis of various 1,2-*cis*-substituted cyclopentanes. In addition, it is noteworthy that the crystal of racemic sulfone **V-10** belongs to space group $P2_12_12_1$, which has no mirror of symmetry; **V-10** is a racemic mixture, and therefore single crystal of **V-10** is chiral. This fact means that 1,2-*cis*-substituted cyclopentanes can potentially be obtained in an optically pure form by using the present five-membered-ring-forming reaction.

3. Experimental

General information is same as that of Experimental in Chapter II.

8-Acetoxy-2-methyl-9-phenylthio-2-nonene (V-1): To a solution of sodium methoxide (0.114 mol) in MeOH (100 ml) was added diethyl malonate (18 ml, 0.118 mol) at room temperature. After being stirred for 10 min, MeOH (20 ml) solution of prenyl bromide (16.31 g, 0.109 mol) was added to the mixture at 0°C. The resulting solution was heated to reflux and stirred for 5 h. Then, the mixture was cooled to room temperature and partitioned between water (100 ml) and CH_2Cl_2 (300 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml) and combined organic layers were dried over $MgSO_4$. After the removal of the solvent, the residue was distilled under reduced pressure (75–80°C/1 mmHg) [lit.[10] 140°C/20 mmHg] to give 16.39 g (66% yield) of diethyl 2-prenylmalonate. ^1H NMR was identical with that reported in the literature.[10]

The above diester was half-hydrolyzed and decarboxylated by DMSO-H_2O-NaCl at 160°C according to the method in the literature.[11] The crude product was essentially pure judging from ^1H NMR, which was identical with that reported in the literature.[12]

To a solution of LAH (2.6g, 68 mmol) in THF (100 ml) was added dropwise the above crude ester (10.5 g, 67 mmol) in THF (20 ml). After the exothermic reaction had ceased, the mixture was stirred for further 15 min. Then the remaining reductant was allowed to react with EtOAc until no more exothermic reaction had occurred. Saturated aqueous Na_2SO_4 (50 ml) was added to the mixture and the resulting precipitates were filtered off using Celite pad. The solid was thoroughly washed with ether. After the most of the solvent was removed, the crude oil was distilled at reduced pressure (98–102°C/40 mmHg) to give 5.45 g (47.8 mmol, 67% yield for two steps) of 5-methyl-4-hexen-1-ol. ^1H NMR was identical with that reported in the literature.[13]

The above alcohol was transformed to the 6-bromo-2-methyl-2-hexene by NBS-PPh_3 according to the method in the literature in 47% yield.[14] ^1H NMR was identical with that reported in the literature.[14]

To a partially-solidified solution of 5-methyl-4-hexenylmagnesium bromide in THF (10 ml), which was prepared from the above bromide (3.61 g, 20.4 mmol), was added 2-

(phenylthio)methyloxirane[15] (2.61 g, 15.7 mmol) in THF (5 ml) at room temperature. Then, CuI (200 mg, 1.0 mmol) was introduced to the mixture. After the induction period (ca. 1 min), the exothermic reaction occurred and the solvent refluxed vigorously, then the reaction was settled in a few minutes. The mixture was stirred for further 30 min, poured into ice-water, and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3 × 30 ml) and the combined organic layers were washed with brine (50 ml). The solution was dried over Na_2SO_4 and concentrated by a rotary evaporator. Purification by column chromatography (eluent: hexane/EtOAc = 10/1) gave 8-methyl-1-phenylthio-7-nonen-2-ol (2.50 g, 60% yield).

The above alcohol was acetylated by Ac_2O-pyridine in the presence of catalytic DMAP to give 2.74 g (95% yield) of the title compound after purification by column chromatography (eluent: hexane/EtOAc = 15/1). ^1H NMR (400 MHz, CD_2Cl_2) 1.2–1.4 (m, 6H), 1.61 (s, 3H), 1.69 (s, 3H), 1.95 (s, 3H), 1.9–2.0 (m, 2H), 3.07 (dd, 1H, J = 5, 14), 3.13 (dd, 1H, J = 6, 14), 4.9–5.0 (m, 1H), 5.0–5.1 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (CD_2Cl_2) 17.7, 21.1, 25.2, 25.8, 28.2, 30.0, 33.5, 38.0, 73.1, 124.8, 126.6, 129.3, 129.9, 131.8, 136.7, 170.7.

7-Acetoxy-2-methyl-8-phenylthio-2-octene (V-6): This material was synthesized in the same method as above using 5-bromo-2-methyl-2-pentene[16] instead of 6-bromo-2-methyl-2-hexene as a source for Grignard reagent. ^1H NMR (400 MHz, $CDCl_3$) 1.2–1.4 (m, 6H), 1.57 (s, 3H), 1.67 (s, 3H), 1.6–1.8 (m, 2H), 1.95 (s, 3H), 3.04 (dd, 1H, J = 6, 14), 3.12 (dd, 1H, J = 6, 14), 5.0–5.1 (m, 2H), 7.2–7.4 (m, 5H) ^{13}C NMR (CD_2Cl_2) 17.7, 21.0, 25.4, 25.7, 27.6, 32.6, 37.7, 72.8, 124.0, 126.3, 128.9, 129.6, 131.9, 136.0, 170.6.

General procedure for cyclization: To a solution of the substrate (0.35 mmol) in CH_2Cl_2 (2 ml) was added CH_2Cl_2 solution of TMSOTf (1.2 M, 0.32 ml, 0.38 mmol) at room temperature, and the resulting mixture was stirred for 24 h. During this period, the solution turned black. Then, triethylamine (0.5 ml, 3.6 mmol) was added to the mixture and the resulting pale-brown solution was stirred for 8 h. The mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 ml) and combine organic layers were dried over Na_2SO_4. After the evaporation of the solvent, the crude material was purified by means of a preparative TLC (eluent: hexane) to give the mixture of cyclized compounds. The identification was carried out by GC-MS and ^1H-NMR.

***cis*-1-(Phenylthio)methyl-2-(2-propenyl)cyclohexane (V-2), *trans*-1-(phenylthio)-methyl-2-(2-propenyl)cyclohexane (V-3), and 1-isopropylidene-2-(phenylthio)methyl-cyclohexane (V-4).** ^{1}H NMR (400 MHz, $CDCl_3$) (only the characteristic peaks were recorded) for **V-2**, 1.62 (s, 3H), 2.77 (dd, 1H, J = 11, 13, PhSC*H*H), 2.89 (ddd, 1H, J = 1, 3, 13, PhSCH*H*), 4.64 (s, 1H), 4.85 (s, 1H), for **V-3**, 1.60 (s, 3H), 1.86 (ddd, 1H, J = 3, 12, 12, $CH_2C(CH_3)CH$), 2.51 (dd, 1H, J = 10, 13, PhSC*H*H), 3.13 (dd, 1H, J = 3, 13, PhSCH*H*), 4.72 (s, 1H), 4.75 (s, 1H), for **V-4**, 1.9–2.0 (m), 2.5–2.6 (m), 3.0–3.1 (m); MS (70 eV); *m/z* (rel intensity) for **V-2**, 246 (M^+, 17), 164 (5), 149 (5), 137 (45), 123 (70), 110 (21), 95 (40), 81 (91), 69 (100), 55 (54), for **V-3**, 246 (M^+, 12), 136 (17), 123 (100), 81 (52), 69 (31), 67 (34), 55 (31), for **V-4**, 246 (M^+, 12), 136 (10), 123 (100), 81 (61), 67 (33), 55 (21).

As the ddd peak at δ = 1.86 ppm ($CH_2C(CH_3)CH$) of **V-3** has one small (3 Hz; H_{eq}-H_{ax} coupling of cyclohexane system) and two large (12 Hz; H_{ax}-H_{ax} coupling) J values, the relative stereochemistry of **V-3** could be easily assigned as trans. On the other hand, the ddd peak at δ = 2.89 ppm (PhSCH*H*) of **V-2** has one very small J value (1 Hz), which indicates there is a W-shape coupling with ring proton. On assuming the cyclohexane has a chair conformation, the only possible case for the W-shape alignment is the one in which (phenylthio)methyl group possesses the axial position. As the *trans*-1,2-carbon-substituted cyclohexane generally prefers 1,2-diequatorial conformation, the stereochemistry of **V-2** could be assigned as *not* trans, but cis.

***cis*-1-(Phenylthio)methyl-2-(2-propenyl)cyclopentane (V-7), *trans*-1-(phenylthio)methyl-2-(2-propenyl)cyclopentane (V-8), and 1-isopropylidene-2-(phenylthio)methylcyclopentane (V-9).** ^{1}H NMR (400 MHz, $CDCl_3$) for **V-7**, 1.5–1.9 (m, 6H), 1.73 (s, 3H), 2.2 -2.3 (m, 1H), 2.43 (t, 1H, J = 12, PhSC*H*H), 2.4–2.5 (m, 1H), 2.86 (dd, 1H, J = 4, 12, PhSCH*H*), 4.74 (s, 1H), 4.87 (s, 1H), 7.1–7.3 (m, 5H), for **V-8** (only the characteristic peaks were recorded) 1.59 (s, 3H), 1.9–2.0 (m, 1H), 2.2 (t, 1H, J = 8), 2.6–2.7 (m, 1H), 2.66 (dd, 1H, J = 9, 12, PhSC*H*H), 3.16 (dd, 1H, J = 3, 12, PhSC*H*H), for **V-9** (only the characteristic peaks were recorded), 2.63 (t, 1H, J = 12, PhSC*H*H), 3.02 (dd, 1H, J = 4, 12, PhSC*H*H); *m/z* (rel intensity) for **V-7**, 232 (M^+, 21), 189 (7), 164 (19), 123 (100), 109 (49), 81 (88), 67 (97), 55 (60), for **V-8**, 232 (M^+, 11), 123 (58), 109 (100), 79 (39), 67 (43), 55 (30), for **V-9**, 232 (M^+, 13), 123 (49), 109 (100), 81 (28), 67 (49), 45 (22).

***cis*-1-(Benzenesulfonyl)methyl-2-(2-propenyl)cyclopentane (V-10):** A mixture of the above cyclopentanes (**V-7**:**V-8**:**V-9** = 83:0:17; 65 mg; 0.28 mmol) was treated with catalytic OsO_4 and excess $NaIO_4$ according to the method in the literature.[17] The starting material was completely consumed within 1 h, and new compound which has smaller R_f value appeared in TLC. After the workup, the reaction mixture was purified by means of preparative TLC (eluent: hexane/EtOAc = 1/1) to give the title compound (40 mg; 0.15 mmol; 54% yield). On the basis of the quantity of the product, **V-10** was assigned as the corresponding sulfone of sulfide **V-7**. The relative configuration of **V-10** was unambiguously determined by means of X-ray structural analysis. Colorless prisms; mp 49-50°C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.4–1.9 (m, 6H), 1.57 (s, 3H), 2.4–2.5 (m, 1H), 2.5–2.6 (m, 1H), 2.75 (dd, 1H, J = 11, 14, $PhSO_2CHH$), 2.94 (dd, 1H, J = 1, 14, $PhSO_2CHH$), 4.64 (s, 1H), 4.83 (s, 1H), 7.5–7.7 (m, 3H), 7.9 (m, 2H).

Details for the X-ray structural analysis of V-10

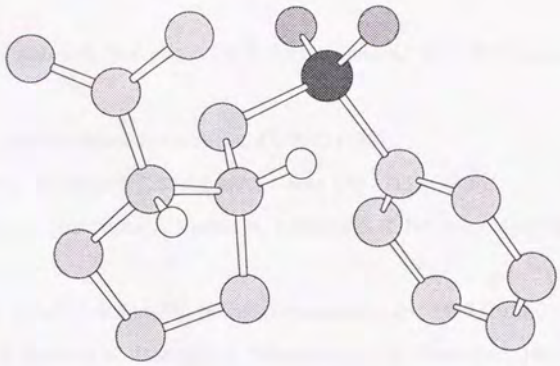
Molecular formula	$C_{15}H_{20}O_2S$
Formula weight	264
Crystal size/mm^3	$0.4 \times 0.3 \times 0.2$
a/Å	10.869 (3)
b/Å	16.352 (4)
c/Å	8.006 (2)
Volume of unit cell /Å^3	1423.0 (6)
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Z value	4
D_{calc}/g cm^{-3}	1.23
Reflections used	1222
No. of variables	243
R;R_w	0.051; 0.055
Good of fitness	0.62
Maximum shift/e. s. d. in final cycle	0.22
Max. negative peak in final diff. map/e Å^{-3}	-0.37
Max. positive peak in final diff. map/e Å^{-3}	0.14

Details for the X-ray structural analysis of V-10

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
S 1	0.2897 (1)	0.27445 (6)	1.0007 (1)	5.13 (3)
O 2	0.3964 (3)	0.3200 (2)	1.0479 (6)	7.2 (1)
O 3	0.2401 (4)	0.2836 (3)	0.8349 (5)	7.7 (1)
C 4	0.1956 (3)	0.2848 (2)	1.3252 (5)	4.12 (8)
C 5	0.4244 (4)	0.1494 (2)	1.1276 (5)	4.61 (9)
C 6	0.1189 (4)	0.3447 (2)	1.4330 (5)	4.24 (9)
C 7	0.1690 (4)	0.2976 (3)	1.1410 (5)	4.6 (1)
C 8	0.0186 (5)	0.2132 (3)	1.4430 (9)	6.1 (1)
C 9	0.2483 (5)	0.1108 (4)	0.9633 (7)	6.1 (1)
C 10	0.4498 (6)	0.0679 (3)	1.1554 (7)	6.2 (1)
C 11	-0.0080 (4)	0.3046 (3)	1.4286 (6)	4.8 (1)
C 12	0.1279 (4)	0.4332 (2)	1.3868 (6)	5.1 (1)
C 13	0.1538 (5)	0.2018 (3)	1.3922 (6)	5.2 (1)
C 14	0.0341 (6)	0.4775 (4)	1.338 (1)	7.4 (2)
C 15	0.3754 (6)	0.0089 (3)	1.0863 (8)	7.0 (2)
C 16	0.2777 (7)	0.0286 (4)	0.9926 (9)	7.4 (2)
C 17	0.2553 (7)	0.4684 (5)	1.399 (1)	8.1 (2)
C 18	0.3236 (4)	0.1695 (2)	1.0340 (5)	4.52 (9)
H 4	0.290 (5)	0.294 (3)	1.331 (7)	6 (1)
H 5	0.468 (4)	0.191 (3)	1.182 (6)	3.8 (8)
H 6	0.155 (5)	0.340 (3)	1.549 (8)	5 (1)
H 7 A	0.160 (4)	0.351 (3)	1.109 (6)	4.3 (9)
H 7 B	0.111 (5)	0.268 (3)	1.104 (6)	4 (1)
H 8 A	-0.041 (5)	0.176 (3)	1.365 (8)	6 (1)
H 8 B	0.009 (6)	0.187 (4)	1.56 (1)	9 (2)
H 9	0.193 (8)	0.133 (4)	0.91 (1)	9 (2)
H 10	0.521 (6)	0.049 (4)	1.23 (1)	8 (2)
H 11A	-0.053 (5)	0.310 (3)	1.328 (7)	5 (1)
H 11B	-0.076 (5)	0.324 (3)	1.526 (8)	6 (1)
H 13A	0.222 (7)	0.196 (5)	1.52 (1)	10 (2)
H 13B	0.167 (6)	0.157 (4)	1.30 (1)	8 (2)
H 14A	0.045 (5)	0.539 (4)	1.301 (9)	7 (2)
H 14B	-0.051 (6)	0.450 (4)	1.33 (1)	9 (2)
H 15	0.392 (5)	0.047 (4)	1.107 (9)	7 (1)
H 16	0.23 (1)	-0.017 (7)	0.98 (2)	12 (3)
H 17A	0.259 (7)	0.522 (6)	1.37 (1)	9 (2)
H 17B	0.312 (5)	0.439 (4)	1.307 (9)	6 (1)
H 17C	0.28 (1)	0.469 (8)	1.50 (2)	15 (3)

Details for the X-ray structural analysis of V-10



Intramolecular Distances (Å) with e.s.d. in parentheses

atom atom	distance	atom atom	distance
S 1 --O 2	1.429 (4)	C 6 --C 11	1.528 (6)
S 1 --O 3	1.441 (4)	C 8 --C 11	1.526 (7)
S 1 --C 7	1.768 (5)	C 8 --C 13	1.536 (7)
S 1 --C 18	1.775 (4)	C 9 --C 18	1.383 (7)
C 4 --C 7	1.518 (6)	C 9 --C 16	1.401 (8)
C 4 --C 13	1.527 (6)	C 10 --C 15	1.375 (8)
C 4 --C 6	1.549 (6)	C 12 --C 14	1.311 (8)
C 5 --C 18	1.367 (6)	C 12 --C 17	1.503 (9)
C 5 --C 10	1.379 (7)	C 15 --C 16	1.34 (1)
C 6 --C 12	1.497 (6)		

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom atom atom	angle	atom atom atom	angle
O 2 --S 1 --O 3	119.5 (3)	C 11 --C 8 --C 13	106.2 (4)
O 2 --S 1 --C 7	108.8 (2)	C 18 --C 9 --C 16	117.5 (5)
O 2 --S 1 --C 18	107.1 (2)	C 15 --C 10 --C 5	119.6 (5)
O 3 --S 1 --C 7	106.6 (2)	C 8 --C 11 --C 6	104.4 (3)
O 3 --S 1 --C 18	108.5 (2)	C 14 --C 12 --C 6	123.9 (4)
C 7 --S 1 --C 18	105.4 (2)	C 14 --C 12 --C 17	121.6 (5)
C 7 --C 4 --C 13	114.0 (4)	C 6 --C 12 --C 17	114.4 (4)
C 7 --C 4 --C 6	110.6 (3)	C 4 --C 13 --C 8	105.7 (4)
C 13 --C 4 --C 6	101.9 (3)	C 16 --C 15 --C 10	121.6 (5)
C 18 --C 5 --C 10	118.8 (4)	C 15 --C 16 --C 9	120.3 (6)
C 12 --C 6 --C 11	117.9 (4)	C 5 --C 18 --C 9	122.1 (4)
C 12 --C 6 --C 4	116.0 (3)	C 5 --C 18 --S 1	118.8 (3)
C 11 --C 6 --C 4	101.6 (3)	C 9 --C 18 --S 1	119.1 (3)
C 4 --C 7 --S 1	116.5 (3)		

4. References

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LIST OF PUBLICATION

1. Original Papers

(1) Highly Regioselective Pinacol Rearrangement of Sulfenylmethylated Glycols

Kazuaki Kudo, Kazuhiko Saigo, Yukihiko Hashimoto, Katsuyuki Saito, Masaki Hasegawa

Chem. Lett. 1449 (1992).

(2) A Highly Regioselective Reaction of Allylic Acetates with Silylated Carbon Nucleophiles Directed by a Sulfenyl Group

Kazuaki Kudo, Kazuhiko Saigo, Yukihiko Hashimoto, Hitoshi Houchigai, Masaki Hasegawa

Tetrahedron Lett. **32**, 4311 (1991).

(3) A Highly Regioselective Reaction of Allylic Acetates with Silylated Carbon Nucleophiles Directed by a Sulfenyl Group. Scope, Limitation, and Mechanistic Aspects

Kazuaki Kudo, Yukihiko Hashimoto, Hitoshi Houchigai, Masaki Hasegawa, Kazuhiko Saigo

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(4) Anti-Cram Selective Reaction of α-Sulfenyl Acetals with Silylated Carbon Nucleophiles

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(5) Anti-Selective Reaction of α-Sulfenyl Acetals with Silylated Carbon Nucleophiles. Scope, Limitation, and Mechanism

Kazuaki Kudo, Yukihiko Hashimoto, Makoto Sukegawa, Masaki Hasegawa, Kazuhiko Saigo

J. Org. Chem. in press.

(6) Stereoselective Cationic Cyclization Assisted by a Sulfenyl Group

Kazuaki Kudo, Yukihiko Hashimoto, Kazuhiko Saigo

J. Am. Chem. Soc., submitted.

2. Related Papers

(1) Stereoselective Synthesis of Ethyl (2*E*,4*E*)-Alkadienoates from Ethyl Sulfolane-2-carboxylate
Kazuhiko Saigo, Kazuaki Kudo, Yukihiko Hashimoto, Nobuhiro Kihara, Masaki Hasegawa
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(2) Facile Synthesis of Selectively Monoprotected Unsymmetrical 1,3-Diketones from 2,2-Dimethoxyethyl Esters
Kazuhiko Saigo, Shigeru Machida, Kazuaki Kudo, Yoshiyuki. Saito, Yukihiko Hashimoto, Masaki Hasegawa
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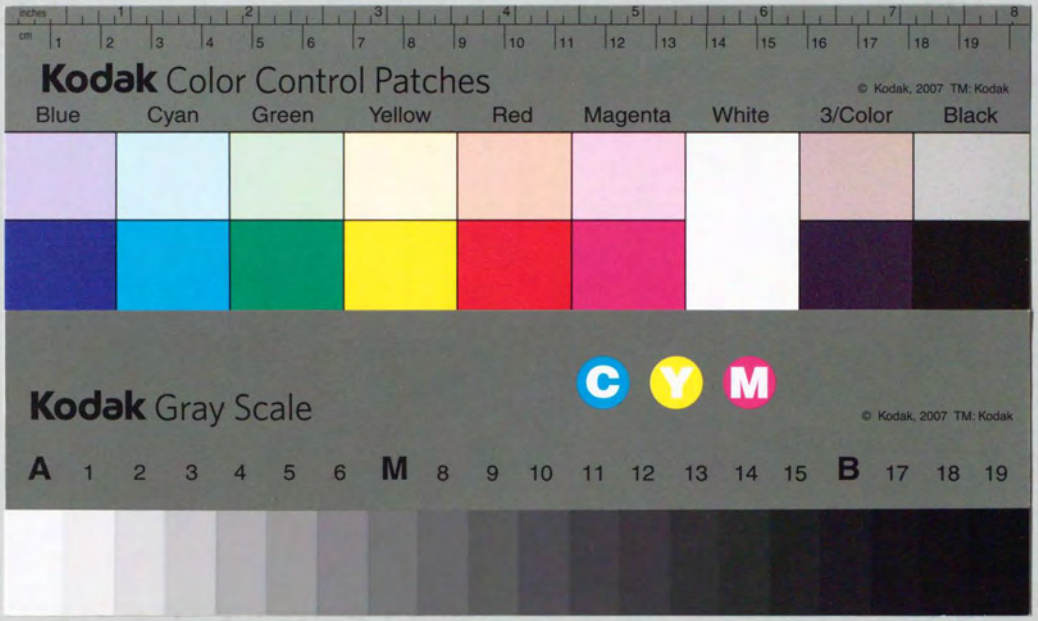
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