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A HIGHLY STEREOSELECTIVE SYNTHESIS OF COMPOUNDS RELATED TO (+)-DISPARLURE, THE SEX ATTRACTANT OF THE GYPSY MOTH

By

Barbara Ann Duhl-Emswiler

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ABSTRACT

A HIGHLY STEREOSELECTIVE SYNTHESIS OF COMPOUNDS RELATED TO (+)-DISPARLURE, THE SEX ATTRACTANT OF THE GYPSY MOTH

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Barbara Ann Duhl-Emswiler

A highly stereoselective synthesis of cis,7R,8S-epoxy-2-methyloctadecane, known as (+)-disparlure, and its enantiomer can be carried out in 15-20% overall yield from p-tolyl-ℓ-methylsulfinate. This ester is converted to a t-butylalkyl-sulfoxide via a Grignard reaction followed by an arylalkyl exchange. The α-sulfoxo anion generated from this sulfoxide with n-butyl lithium can be alkylated in a highly stereoselective fashion, employing the chirality of the sulfoxide to induce asymmetry at the alpha carbon. The mixture of diastereomeric β-hydroxysulfoxides thus formed can be separated chromatographically, and the desired compound reduced to the corresponding sulfide. Epoxidation can then be effected by treatment of the β-hydroxysulfide with Meerwein's reagent and subsequent displacement of the sulfonium ion by base.

Variation of the alkyl groups employed in the Grignard reaction and the alkylation produces the two enantiomers of disparlure, and could be used for the production of homologues or analogues.

The episulfide analogues of both (+) and (-)-disparlure can be produced directly from the epoxides, with inversion

of configuration at each center, by treatment with 3-methylbenzothiazole-2-thione and trifluoroacetic acid.

The optical purity of the β-hydroxysulfide precursors to (+) and (-) disparlure were determined by the use of chiral shift reagent in the ^{1}H NMR to be in the range of 95-96% depending on the batch studied.

The entire sequence is amenable to scale-up and if several of the undesired side products along the route are recycled, the synthesis is an economically viable approach to kilogram quantities of disparlure or its analogues.

to John

With All My Love

ACKNOWLEDGMENTS

I would like to thank all of those whose contributions to the gypsy moth project were invaluable, especially Dr. D. G. "Uncle Don" Farnum for his friendship and guidance, Dr. Ring Cardé and the U.S.D.A. for financial support, and my colleagues whose work on the chemistry of the project led to its successful conclusion, including Houston and Elene Brown, Anja Cardé, Ross and Chrysa Muenchausen, Jill Hochlowski, and John Emswiler. I am also grateful for the moral support provided by such friends as the current Farnum group, Jim Larson, Kim Chamberlin, and Larry Klein, In addition, I owe a great debt to the "old" Farnum group for getting me into all of this, particularly Al Hagedorn, Tom Reitz, Chuck Geraci and the late Bill Chambers.

Additional financial support was generously provided to me during my graduate career by Dr. John Boezi of the Department of Biochemistry and Dr. Norman Good of the Department of Plant Pathology.

Finally, I would like to say thanks also to the Fish Monger people (and all of the nice fishes I have known), and to Pepper Cory and the wonderful women of the Calico Cutters, all of whom made my life here a joy.

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INTRODUCTION

Insect behavior has been the subject of considerable research in the last fifteen to twenty years. Many aspects of insect behavior, including aggregation, mating, and trail marking, have been found to be influenced or regulated by chemicals secreted by the insect. One of the most intensely investigated of these behavioral aspects, because of its implications for pest control, is the control of reproduction by sex attractants, called pheromones. These are substances secreted by the adult insect, often the female, for the purpose of attracting a mate of the correct species from a distance. At close range, other compounds, known as excitants, are used by some species to stimulate mating behavior. Because the pheromone system of a given insect is normally species specific, such systems have very real potential for use as population control agents which might augment or replace conventional pesticides in certain cases. Consequently, much attention has been turned toward the isolation, identification, and synthesis of the sex attractants for various insect species, particularly those which are considered economic or environmental pests.

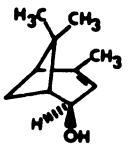
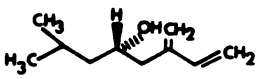
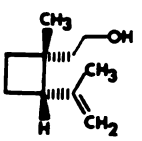
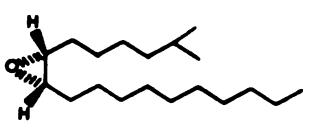
The isolation and identification of the sex attractant

for any particular species of insect poses a challenge due to the minute amounts of material secreted by a single insect. In addition, for some species the active attractant is not a single compound, but is rather a mixture of several components in a precise ratio to one another. A change in that ratio might in fact produce the attractant for another species. With the advent of modern instrumental methods for performing separations and analyses on small quantities of material, the task has become somewhat easier, and the pheromone systems for a number of insects have been identified.[1,2]

Many of the compounds which were first identified as insect pheromones were straight chain olefins or dienes with an alcohol or acetate functionality.[3] These were relatively easy to synthesize for positive verification of their activity by field testing. However, an increasingly large number of attractants are being identified which are more complex molecules, often optically active, and which show much less attractancy in their racemic forms.[2]

Insect species which make use of chiral pheromone components include a number of economically significant pests, such as the bark beetles of the family Scolytidae,[4] the dermestid beetles of the genus Trogoderm (which infest stored grain),[5] the boll weevil,[6] and the gypsy moth.[7] The compounds serving as pheromones for some of these

Table 1. Some Optically Active Insect Pheromone Components.

Structure	Insect	Ref.
	Coleoptera: Scolytidae ips paraconfusus	4
	ips paraconfusus	4
	ips paraconfusus	4
	Coleoptera: Dermestidae Trogoderma inclusum	5
	Trogaderma inclusum	5
	Coleoptera: Curculionidae Anthonomus grandis (Boll weevil)	6
	Lepidoptera Lymantria dispar (Gypsy moth)	16a

species are shown in Table I.

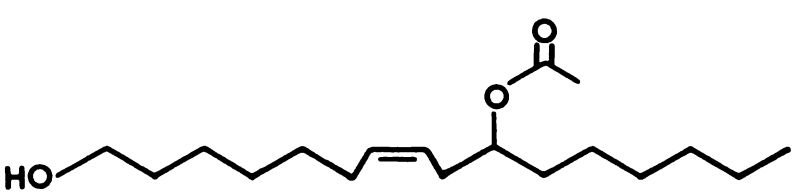
The gypsy moth (Porthetria dispar), in its larval form, is a serious defoliator of shade and forest trees in the northeastern part of the United States.[8] It became established there after being imported from abroad for the purpose of silk production. A steady migration of the gypsy moth is occurring toward the south and west, and it is now considered a serious economic pest. A single caterpillar can consume one square foot of leaf surface per day. In most cases, a hardwood tree cannot survive more than two successive defoliations.[8]

The damage is done entirely by the larvae; the adults do not feed after emergence from pupation. An adult female gypsy moth is incapable of flight, being egg laden, and instead relies upon the release of a pheromone to attract a male for mating, after which she lives only a short time. A male may mate several times, but also enjoys only a brief lifespan as an adult.[8]

Numerous control measures have been used against the gypsy moth, especially since 1958 when the use of DDT was phased out. Several species of predators have been imported to prey upon the insect in its various developmental stages; viral and bacterial diseases have been investigated, and the insecticide Carbaryl (Sevin) can be employed.[8] The use of insecticides against the moth has met with opposition from environmentalists, and at

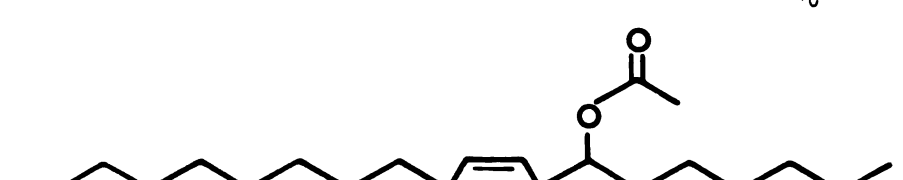
best has only served to minimize damage and slow the spread of the pest. This spread has been accelerated recently by the increasingly large numbers of campers whose vehicles serve as carriers for the egg masses of the gypsy moth. It was hoped that the identification and synthesis of the sex attractant might prove useful in controlling the populations of this pest.

Prior to the identification of the active attractant, crude benzene extracts of the abdominal sections of female moths were used as bait in traps designed to monitor populations. In 1961, Beroza and coworkers reported that they had identified the pheromone as 10-acetoxy-9-hexadecen-1-ol, which they called gyptol,[9] 1. A homologue of gyptol,



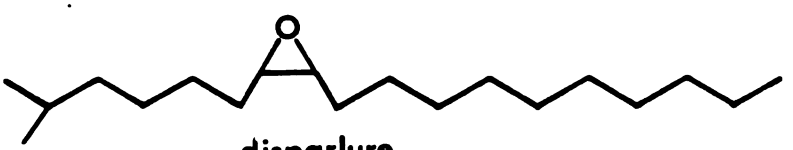
gyptol
1

12-acetoxy-9-octadecen-1-ol, called gyplure, 2, was also



gyplure
2

reported to show activity as an attractant.[10] However, reinvestigation showed that the attractancy stemmed not from either of these compounds, but from contamination by trace amounts of a substance with "extraordinarily high biological activity."[11] Field use of the benzene extracts was resumed until in 1969 the actual pheromone was isolated from 78,000 virgin female moths and identified as cis-7,8-epoxy-2-methyl-octadecane.[7] This compound, christened disparlure, 3, was synthesized in its racemic form by



disparlure
3

epoxidation of the corresponding olefin, (Z)-2-methyl-7-octadecene, 6, as shown in Figure 1, and was found to be

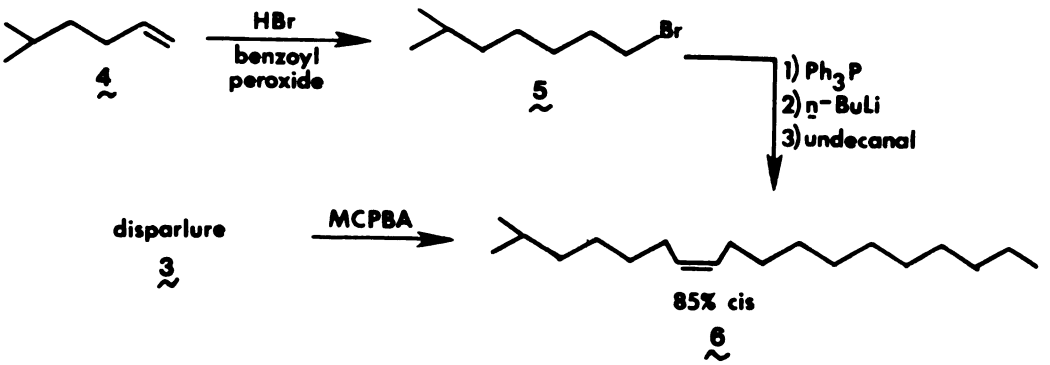
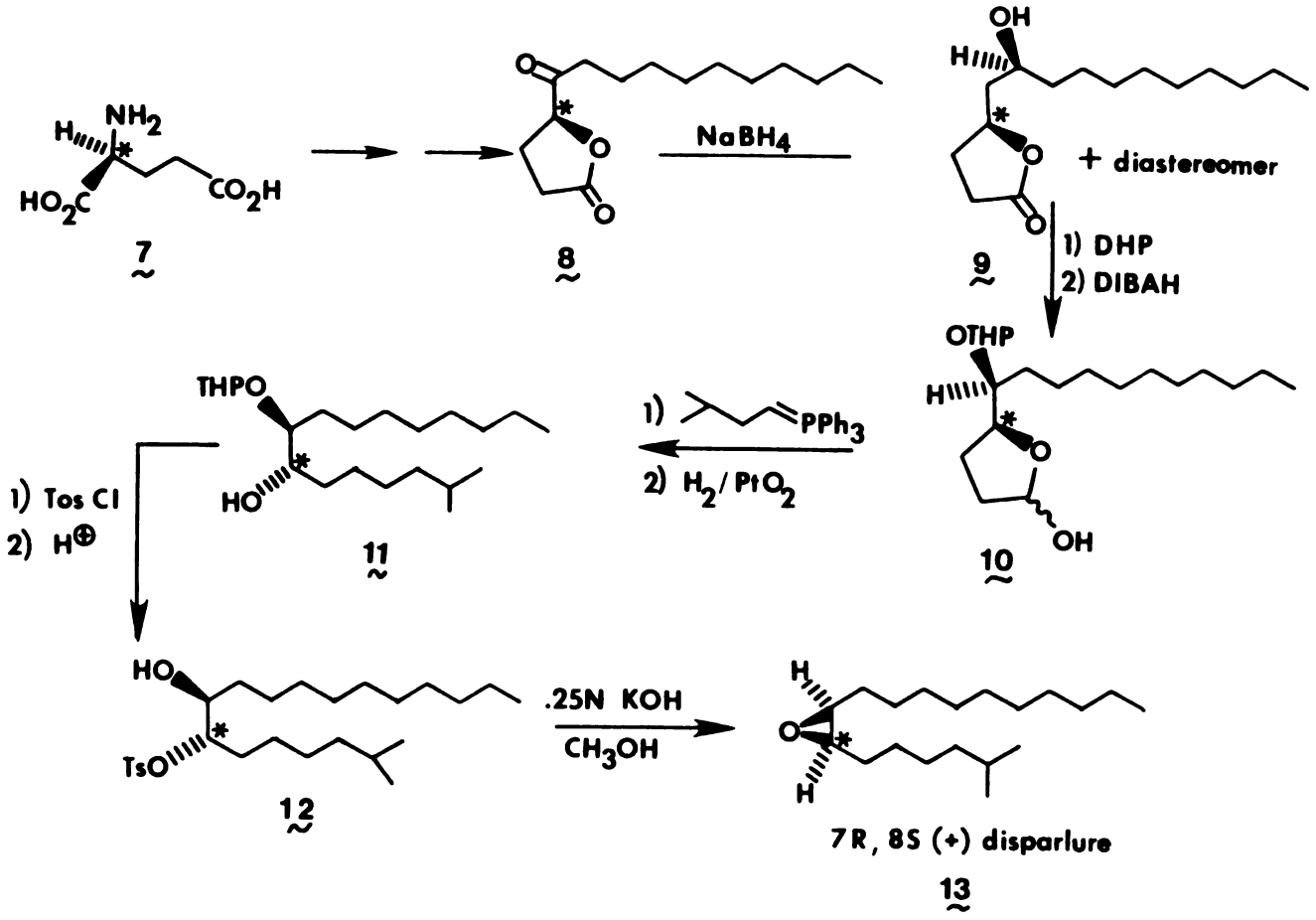


Figure 1. The initial synthesis of racemic disparlure.

attractive to male gypsy moths.[7] Epoxide derived from the trans olefin proved to be inactive in field testing, neither attracting males itself, nor interfering with the attractancy of the cis olefin derived epoxide.[7]

Since then, several other groups have devised syntheses of racemic disparlure.[12-14] The synthetic route of Bestmann and Vostrowsky[12] differed from the original route only in that the 6-methylheptyl bromide, 5, required for the Wittig reaction was prepared by hydrogen bromide treatment of the alcohol formed by the reaction of isoamyl magnesium bromide with oxetane. Other more novel routes have utilized olefin metathesis reactions,[3] double Kolbe electrolysis,[13] and α-silyl alkyl lithium reagents[14] for the synthesis of the olefin precursor to disparlure.

In 1974, Marumo and coworkers published the first synthesis of optically active disparlure.[15] This synthesis, which makes use of S-(+)-glutamic acid, 7, for the control of the stereochemistry at C-7 of disparlure, is shown in Figure 2. This route was not stereospecific, and produced 7R,8S(+)-disparlure, 13, which was contaminated with 5.8% of its enantiomer. However, upon field testing, this material showed more activity than racemic disparlure, whereas 7S,8R-(-)-disparlure (prepared by essentially the same route) showed much less attractancy than racemic material. These results led to the postulation of the existence of a chiral receptor site in the insect, and



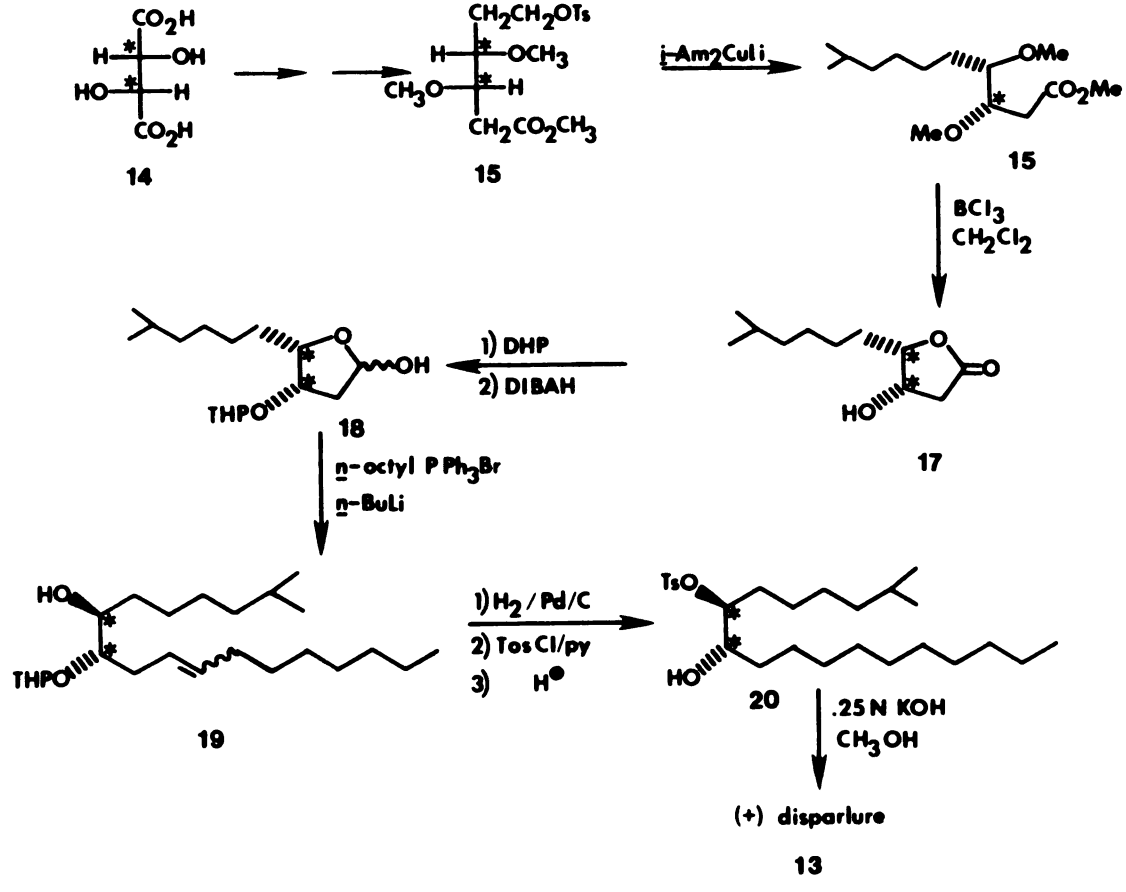
*Denotes asymmetric C from starting material.

Figure 2. The first stereoselective synthesis of (+)-disparlure.

suggested that the natural pheromone is 7R,8S (+)-disparlure. The field tests conducted by Cardé and coworkers[16] supported such a proposal.

Mori and coworkers have also carried out a synthesis of (+)-disparlure.[17] This route, which made use of the asymmetric centers of 2S,3S (+)-tartaric acid, 14, to give the C-7 and C-8 asymmetric centers in (+)-disparlure, is shown in Figure 3. The precursor of the (+)-disparlure produced by this route was shown by proton nmr studies to have an enantiomeric purity in excess of 98%, and the final product also performed well in field tests.[17]

Once the potent attractancy of (+)-disparlure was demonstrated, it was seen that the continued extensive field testing of the pheromone as a possible means of population control would require more than the gram quantities of material readily produced by Mori's synthesis. That route, due to its length and complexity, was not judged amenable to commercial development and scale-up. For this reason, we decided to devise a totally new stereospecific synthesis of (+)-disparlure; one which, with only minor modifications, could be adapted for commercial use. Several ideas were kept in mind during the design and development of our synthesis, including the cost and safety of the reagents employed, the possibilities for recycling of reagents or byproducts, and the adaptability of the route to the production of analogues or homologues which



*Denotes asymmetric C from starting material.

Figure 3. A highly stereoselective synthesis of (+)-disparlure.

might prove to be biologically active. Of particular interest were the preparations of (-)-disparlure, and the episulfide analogues of both (+) and (-)-disparlure.

After the publication of our synthesis of cis-(+)-disparlure,[18] described in the Results and Discussion, Pirkle and coworkers[19] reported a synthesis of (+)-disparlure which was similar to our own in some respects. Since several of the intermediates in that route are the same as those which we employed, this alternative route will be discussed in conjunction with ours. Pirkle's synthesis, while philosophically different from ours, appears to be an alternative, viable route to fairly large quantities of (+)-disparlure, although it has not been used as such yet.

RESULTS AND DISCUSSION

Synthetic Strategy

Two general approaches to the problem of producing an optically active epoxide with very high optical purity were considered by our research group.

The first was the direct asymmetric epoxidation of the corresponding cis olefin, 6. As evidenced by the number of approaches to racemic disparlure which utilize various olefin syntheses, (Z)-2-methyl-7-octadecene was readily available, making such a route very attractive. However, although asymmetric epoxidations have been investigated,[20] the major drawback to the methods devised is the relatively low degree of optical purity obtained, which is generally less than 50% enanthiomeric excess. Furthermore, the best results are obtained in cases where the side chains of the olefin to be epoxidized are markedly different, for example, in cases of allylic alcohols. In the case of the olefinic precursor to disparlure, the great similarity of the alkyl groups would require a highly discriminating chiral epoxidation reagent.

One method which would bear further investigation, however, is based on the work of Panunzi and Paiaro,[21]

and involves the complexation of a chiral platinum (II) reagent to the cis olefin, with subsequent nucleophilic attack by an epoxidizing reagent.

The second approach, and the one to which our group turned its attention, was the nucleophilic displacement of a leaving group to form the epoxide in the last step of a synthetic sequence. This was the method of epoxide formation chosen by both Muramo[15] and Mori,[17] both of whose routes employed α-hydroxy tosylates which were treated with base to yield disparlure.

The consideration of other potential leaving groups for that reaction led us to the work of Johnson and coworkers[22] which provided the real inspiration for our synthesis. In this work, optically active styrene oxide, 25, was produced from a β-hydroxy sulfoxide, 21, as shown in Figure 4. Such a synthesis, making use of the chirality of a sulfoxide to control stereochemistry at the α carbon, followed by reduction to the sulfide and use of the sulfonium ion as the leaving group for the epoxidation, served as an intriguing model for a synthesis of (+)-disparlure. Such a synthesis, diagrammed in Figure 5, would differ from those previously described in that neither of the chiral centers of the epoxide would be present in the starting material, making this a true asymmetric synthesis.

Optically active sulfoxides are readily prepared[23]

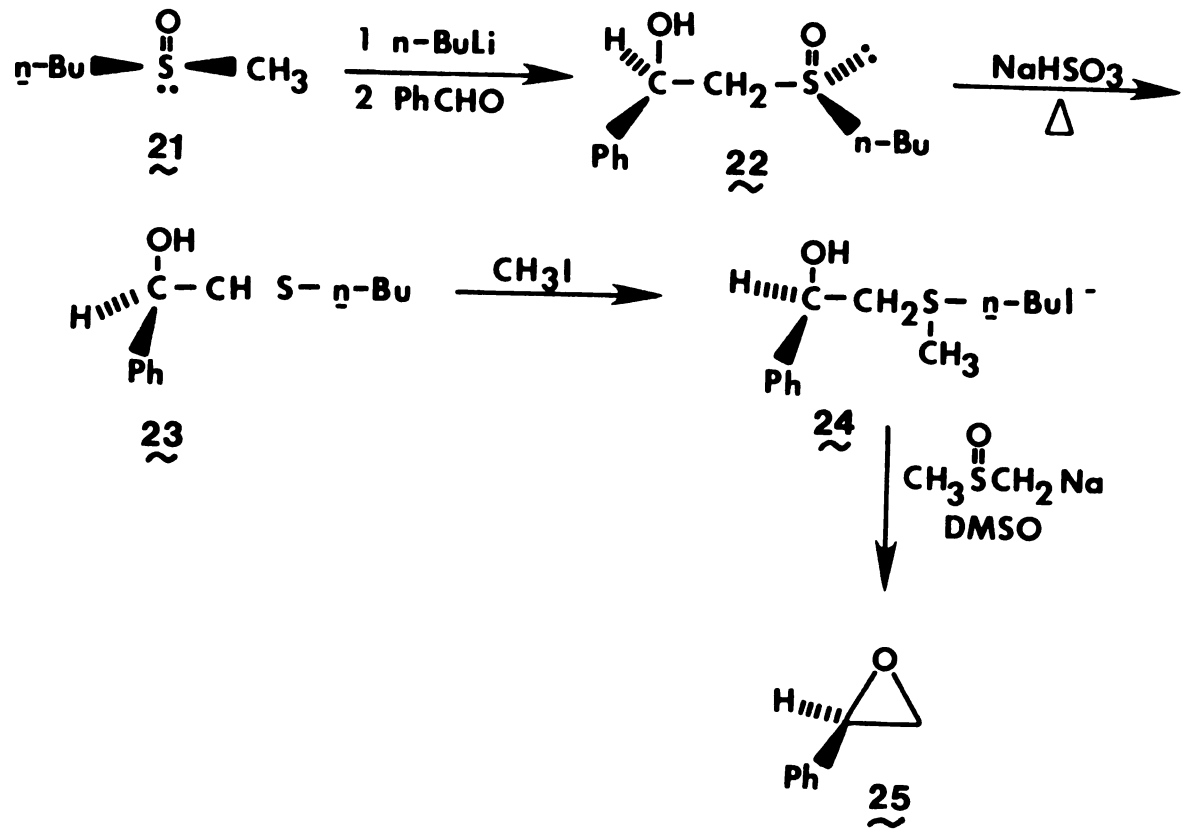


Figure 4. An asymmetric synthesis of an optically active epoxide from an optically active sulfoxide.

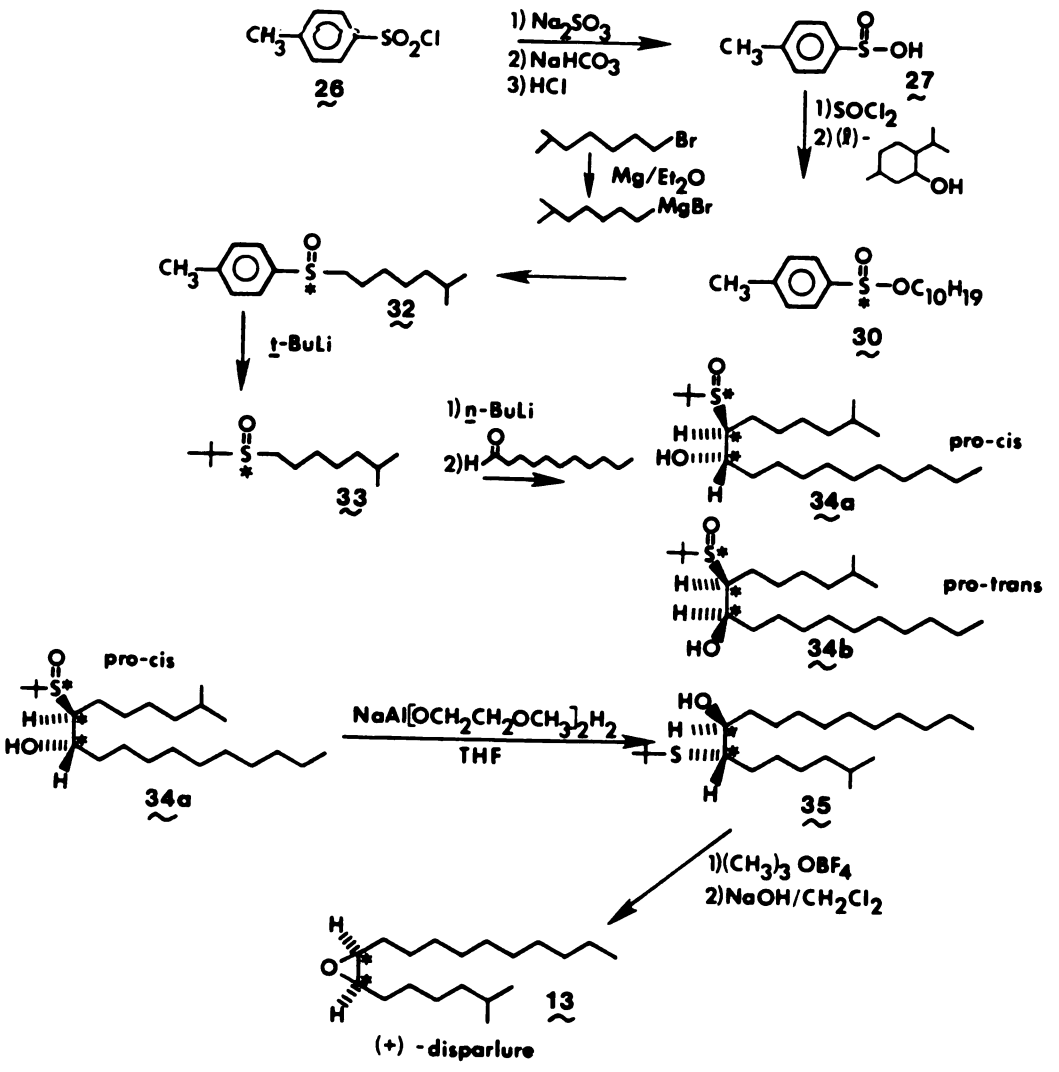


Figure 5. The synthesis of 7R,8S (+)-disparlure as developed by the Farnum group.

by Grignard reactions on l-menthyl-p-toluenesulfinate, 30. In this reaction the l-menthol is recovered, thus recycling the reagent used to generate the optical activity for the entire sequence. The alkyl group of the sulfoxide and the aldehyde used in the condensation could be varied at will, thus enabling the same general reaction sequence to be used for the production of various homologues, and for the production of 7S,8R (-)-disparlure, 41, as shown in Figure 6.

A further opportunity to make this sequence economically efficient is afforded at the β-hydroxysulfoxide stage. After the separation of the diastereomeric hydroxysulfoxides, 34a and 34b, leading to cis and trans epoxide, it was hoped that the pro-trans compound, 34b, could be converted into the more useful pro-cis hydroxysulfoxide, 34a, thus improving the useful yield of this reaction.

The work on the synthesis of (+)-disparlure was done by several members of our research group, whose special contributions are cited in the appropriate sections of the following Discussion. After the viability of the approach was demonstrated, first by model studies conducted by T. Reitz and A. Cardé and then by the initial preparation of a small amount of (+)-disparlure, my work was focused upon several specific aspects of the synthesis. These included the development and scale-up of the synthesis of the early precursors, the proposed interconversion of

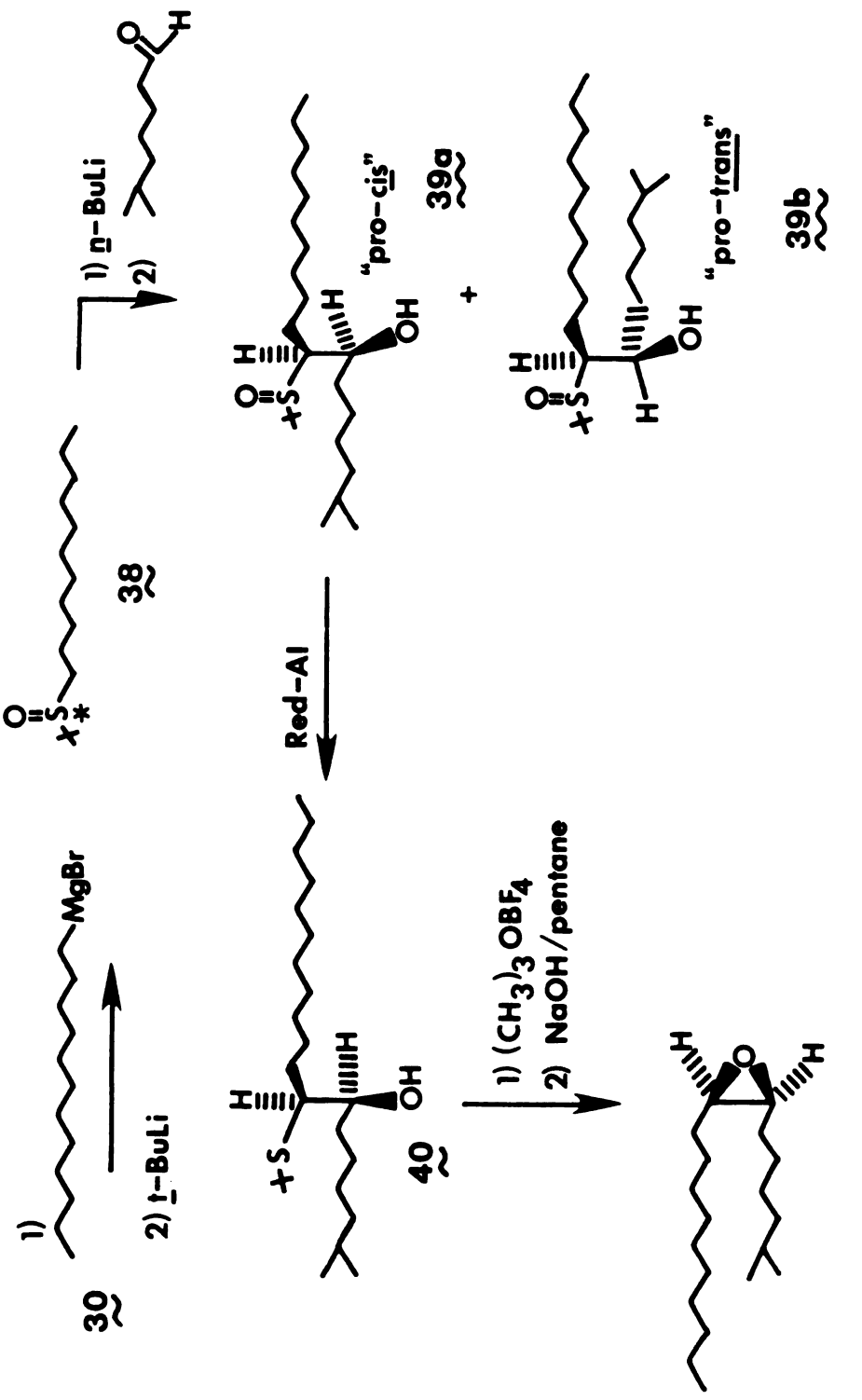


Figure 6. The proposed synthesis of 7S,8R (-)-disparlure.

"pro-cis" and "pro-trans" hydroxysulfoxides mentioned above, and the preparation of analogues, such as the cis-(-)-epoxide and the episulfides previously mentioned.

Synthesis of ℓ-menthyl-p-toluenesulfinate (30)

Since large quantities of ℓ-menthyl-p-toluenesulfinate, 30, would be required for the preparation of significant quantities of (+)-disparlure, or any of its analogues desired, attention was focused upon the optimization of the conditions for its synthesis.

The first reported synthesis of ℓ-menthyl-p-toluenesulfinate was by Phillips,[24] and is shown in Figure 7.

The reduction of p-toluenesulfonyl chloride, 26, was carried out on a large scale as described in Organic Syntheses.[25] The resulting p-toluenesulfinic acid sodium salt was converted to the corresponding acid with hydrochloric acid, then dried under vacuum and with protection from light. Reaction of the acid with thionyl chloride afforded p-toluenesulfinyl chloride, 28, which was used without purification. Attempts to distill the acid chloride gave extensive decomposition.

Initially the menthyl ester was prepared from ethyl-p-toluenesulfinate, 29, as in the Phillips procedure;[24] because it was thought that if the ethyl ester could be purified by distillation, the menthyl ester derived from

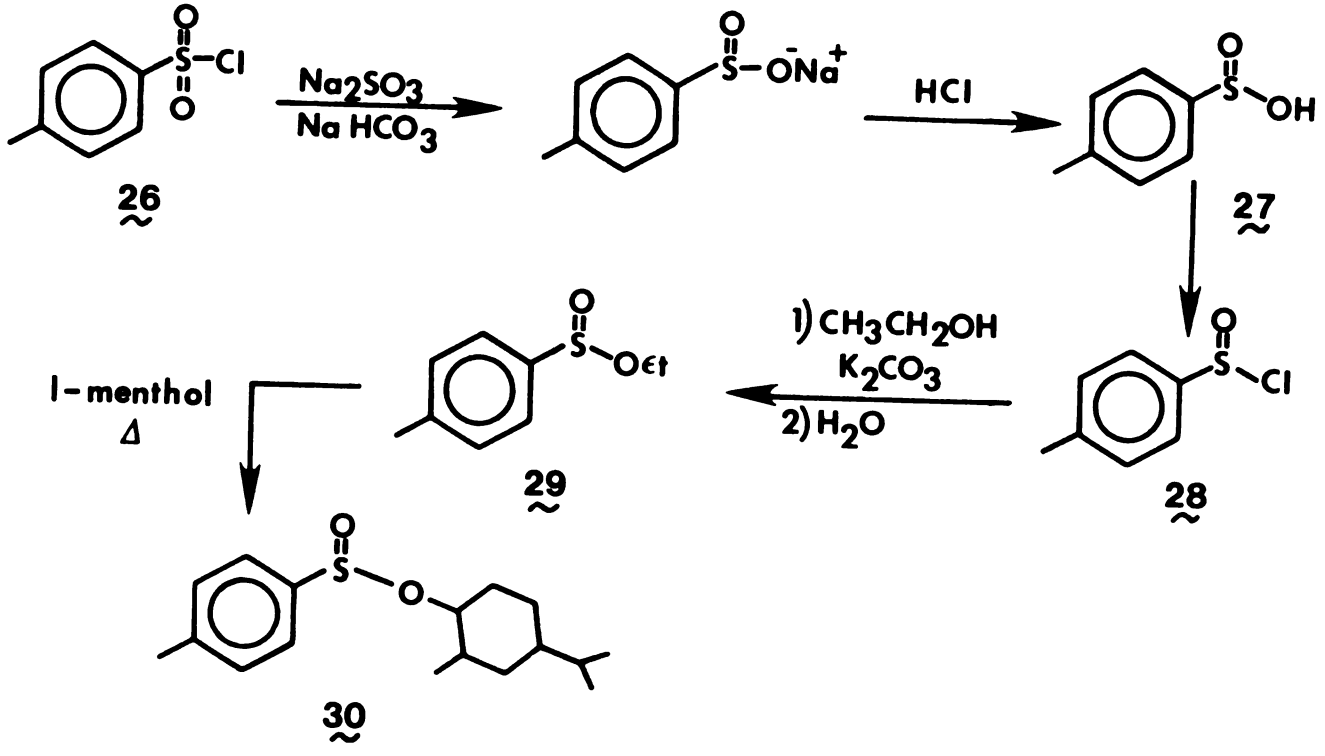


Figure 7. The Phillips synthesis of (ℓ)-menthyl-p-toluenesulfinate.

it would be easier to crystallize. As it happened, this proved unnecessary since direct reaction of ℓ-menthol with freshly prepared p-toluenesulfinyl chloride afforded ℓ-menthyl-p-toluenesulfinate, 30, which crystallized upon standing, or in rare cases, upon scratching or seeding.[26] This material was recrystallized to constant specific rotation, first from acetone; then from an acetone/water mixture. The mother liquor from the first recrystallization could be epimerized to a new equilibrium mixture of diastereomers for further recovery of the crystalline ester by simply allowing it to stand for several weeks. Alternatively, the procedure of Herbrandson and Dickenson[27] could be employed for the epimerization, using tetraethylammonium chloride and hydrogen chloride in nitrobenzene. This was found to be much less convenient than the first method, and gave no better recovery of the desired diastereomer. Without the additional material provided by such epimerization, the overall yield of this sequence was approximately 25% when the ethyl ester was employed, and approximately 45% when the menthyl ester was prepared directly from p-toluenesulfinyl chloride.

Preparation of p-tolyl-undecylsulfoxide (37) and p-tolyl-6-methylheptylsulfoxide (32)

The formation of optically active sulfoxides by Grignard reaction of alkylmagnesium halides on optically active sulfinate esters was first described by Anderson,[23] who observed that the reaction appeared to give inversion of configuration about the sulfur. This was in agreement with the earlier report[28] that sulfinate esters undergo nucleophilic substitution on sulfur with such inversion of configuration. An elegant study by Mislow and co-workers[26b] established the absolute configurations of l-menthyl-p-tolylsulfinate and the sulfoxides derived from it, thereby showing that the Grignard reaction does in fact proceed with inversion of configuration at the sulfur.

By the use of undecyl magnesium bromide, 36, and 6-methylheptyl magnesium bromide, 31, the tolyl sulfoxide precursors for (-) and (+)-disparlure were prepared, as shown in Figure 7. In each case, the menthol by-product was recovered by distillation or sublimation prior to the purification of the sulfoxide. It was established that column chromatography on alumina did not induce racemization of the sulfoxides, and this was the method used for their purification.

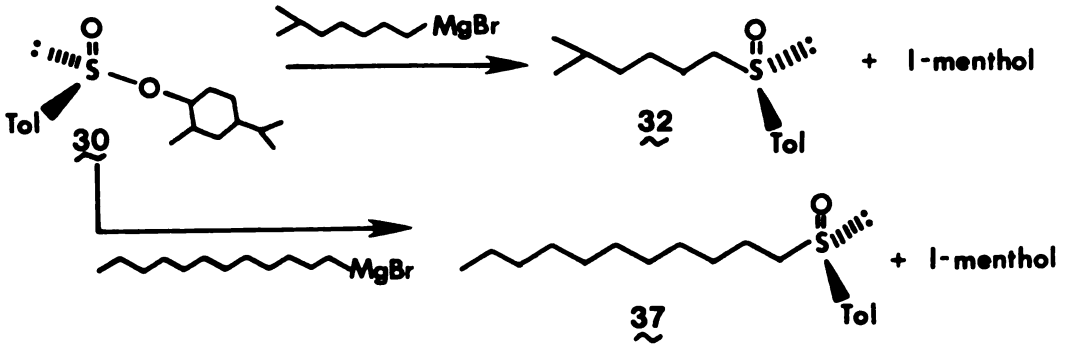
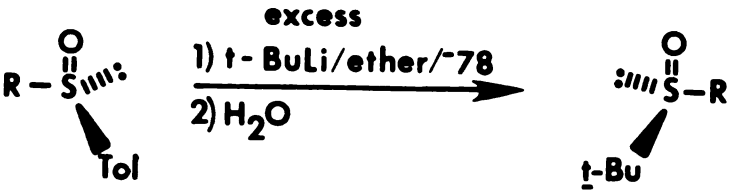


Figure 8. The stereochemistry of the formation of the p-tolylalkylsulfoxide precursors to (+) and (-)-disparlure.



R is undecyl- or 6-methylheptyl

Figure 9. The stereochemical course of the conversion of p-tolylalkylsulfoxides to t-butylalkylsulfoxides.

Preparation of t-butylundecylsulfoxide (38) and t-butyl-6-methylheptylsulfoxide (33)

Since it was observed by Gilman and Webb[29] that the metalation of alkylarylsulfides takes place both α to the sulfide and on the aromatic nucleus, it was thought best to avoid such a side reaction on our sulfoxides by replacing the aryl group by another alkyl substituent. However, it was noted by Johnson and co-workers[30] that, whereas optically active alkyl-arylsulfoxides were readily produced by the method of Anderson,[25] in the case of unsymmetrical dialkylsulfoxides the reaction was much less satisfactory. So it was decided to employ the method described by Johnson[30] for the displacement of aryl groups from diaryl- or alkyl-arylsulfoxides by alkyl lithium reagents. When an excess of t-butyl lithium was added to a solution of p-tolylundecylsulfoxide or p-tolyl-6-methylheptylsulfoxide at -78°C, the corresponding t-butylalkylsulfoxide was formed in excellent yield. This reaction was shown[30] to proceed with inversion of configuration at the sulfoxide, as diagrammed in Figure 8. Purification of these t-butylalkylsulfoxides was attempted, but both distillation and chromatography led to extensive decomposition.

The Preparation of the Diastereomers of 2-methyl-8-hydroxyoctadecan-7-yl-t-butylsulfoxide (34a and b) and 2-methyl-7-hydroxyoctadecan-8-yl-t-butylsulfoxide (39a and b)

The reaction of undecanal[31] with the anion generated by treatment of t-butyl-6-methylheptylsulfoxide, 33, with n-butyl lithium at -78°C resulted, after chromatography (silica gel/ether), in two diastereomeric β-hydroxysulfoxides, 34a and b, as shown in Figure 5. The compound eluting first, 34a, when carried through the remainder of the synthesis, afforded cis-(+)-disparlure. The later material, 34b, when carried through the same sequence, gave the (+)-trans diastereomer of disparlure. These hydroxysulfoxides could be further purified by medium pressure chromatography, removing about 2% other impurities. However, the disparlure produced from this highly purified material was indistinguishable in physical properties and biological activity from disparlure produced from the less pure precursor.[18]

Similarly, treatment of the α-sulfoxo anion of t-butylundecylsulfoxide 38 with 6-methyl-heptanal, 42, gave a mixture of diastereomers, one of which led to cis-(-)-disparlure, 39a, the other, 39b, resulted once again in the production of trans-(+)-7,8-epoxy-2-methyloctadecane.

Since it was by the reaction of the appropriate aldehyde with the anion generated by n-butyl lithium treatment of

the t-butylalkylsulfoxides that the configuration at C-7 of (+)-disparlure or C-8 of (-)-disparlure was established, it is important to consider the stereochemical course of the reaction. That configuration is determined by the conformation of the anion as it reacts with the aldehyde. As the reaction with the electrophile begins to take place, the anion begins to attain a tetrahedral geometry. The possible tetrahedral configurations of the anion are shown in Figure 10, as Newman projections viewed by looking down the C-S bond axis from carbon to sulfur. Conformation 1a of the configuration 1 would be the most stable, since the two bulky alkyl groups are opposite one another and the next largest group, the oxygen of the sulfoxide, is between the hydrogen and the alkyl group. This conformation would probably have the greatest population. If the anion were quenched with D_2O, the D^+ abstraction is rapid, and the product is the one resulting from reaction with the predominant conformation of the anion.[12] In configuration 2, the carbon center has been inverted. Conformation 2a of this configuration is the one which allows the least hindrance to the attack of the anion on a carbonyl or alkyl halide. Since that is the slow, rate determining step in the alkylation of the anion, this most reactive conformation would be the one leading to product. Thus the product from the reaction of the anion with an aldehyde has the opposite configuration from that resulting

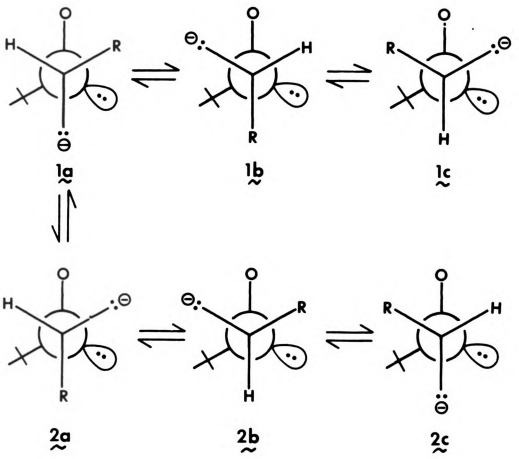


Figure 10. Possible conformations of the two configurations of the α-sulfoxoanion of a t-butylalkylsulfoxide.

from quenching with D_2O.[32]

The reaction, although very stereoselective at carbon α to the sulfoxide, gives a mixture of diastereomers at the β carbon. The 8R and 8S diastereomers are both formed, and must be separated by column chromatography.

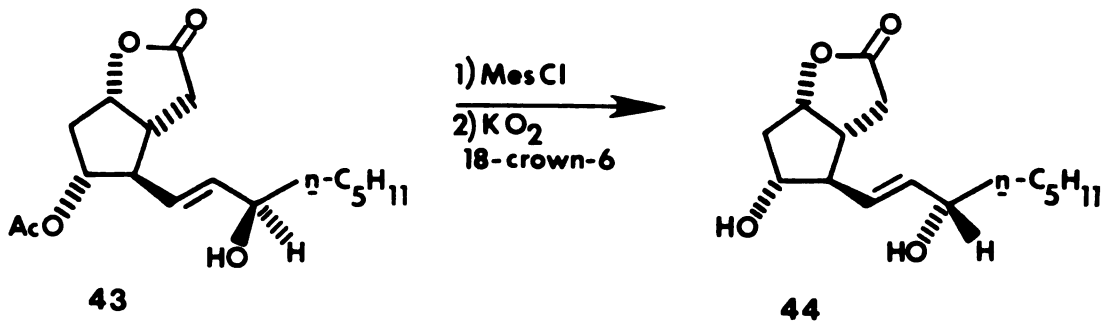
In the early stages of the development of this reaction, 45% pro-*cis* hydroxysulfoxide was produced, as well as 30% pro-*trans*.[18] However, these yields could not be achieved with consistency, and the more usual ratio was actually 35% pro-*cis* : 45% pro-*trans*. This ratio was somewhat sensitive to reaction conditions, especially the temperature at which the reaction was quenched. Work done by H. Brown in our laboratory showed that the addition of aqueous ammonium chloride at -78°C instead of at 0°C did increase the amount of pro-*cis* compound from 30% to 35%. An explanation proposed for this[13] was that during the warming from -78°C to 0°C prior to the quench, a retro-aldol might occur followed by a recondensation whose stereochemical course differed from that of the condensation which had taken place at -78°C.

The production of 45% "pro-*trans*" hydroxysulfoxide in this reaction was discouraging, since the (+)-*trans* diastereomer of disparlure appears to be biologically inactive.[7] Attention was therefore turned toward the possibility of converting the "pro-*trans*" hydroxysulfoxide into the much more important "pro-*cis*" material.

One avenue for this interconversion which was explored was oxidation of the "pro-*trans*" β-hydroxysulfoxide to a β-ketosulfoxide, followed by a stereoselective reduction to give a new mixture of diastereomeric hydroxysulfoxides. Since the approach of a reducing agent from the least hindered side of the keto-sulfoxide would produce the desired hydroxysulfoxide, there seemed to be a good chance of achieving a favorable ratio of "pro-*cis*" : "pro-*trans*". Unfortunately, the alcohol proved very resistant to oxidation under conditions which would not induce recemization of the asymmetric center α to the sulfoxide. Pyridinium chlorochromate[34] treatment of the "pro-*trans*" hydroxysulfoxide did effect some oxidation, but the yields were very poor. Since an alternative approach was available, this approach was shelved.

The method chosen involved the nucleophilic displacement of the mesylate derived from "pro-*trans*" hydroxysulfoxide. Corey, *et al.*[35] developed a procedure whereby the inexpensive, commercially available potassium superoxide (KO_2) could be used as a nucleophilic reagent in organic solvents. By the use of 18-crown-6, the KO_2 could be made soluble enough in such solvents as dimethylsulfoxide, dimethylformamide, or dimethoxyethane to function as a very reactive and effective oxygen nucleophile. It can be used to convert bromides, mesylates and tosylates into the corresponding alcohols in 50-95% yield. For

example, the 15R prostenoid (43) (see Figure 11) was



43 44

Figure 11. The inversion of configuration of a hydroxyl-bearing carbon via nucleophilic displacement by superoxide ion.

epimerized[35] to the 15S prostenoid (44) in 75% yield by treatment of the mesylate of (34b) with four equivalents of KO_2 and 4.5 equivalents of 18-crown-6 in a 1:1:1 mixture of DMSO, DMF, and DME. Previous attempts to carry out this inversion with other nucleophiles had been unsuccessful.

It was noted by Corey[35] that while the use of equimolar amounts of KO_2 and 18-crown-6 gave the shortest reaction times, the reaction could be carried out with catalytic amounts of crown. This seemed imperative in our situation, considering the cost of 18-crown-6 and the fact that a large excess of KO_2 was usually employed. If this were to be a viable method for accomplishing our interconversion, it must be economically, as well as chemically, feasible.

We found that the reaction proceeded successfully

by use of four equivalents of KO_2 and 0.25 equivalent of 18-crown-6. The superoxide was added as a solid, over a period of 10-25 minutes, at 0°C to the "pro-trans" hydroxysulfoxide in a solution of 1:1:1 DMSO, DMF, and DME. The reaction requires more time to go to completion when catalytic amounts of crown are used, so the mixture was allowed to stir at least overnight at room temperature, after the addition of KO_2 was complete. Care must be exercised during the addition, because the reaction is potentially very exothermic. In the case of the reaction with 6-methylheptylbromide in DMSO, there was a short (10 minute) induction period when the reaction was done on a relatively large scale (18 g KO_2), after which the reaction became violent.

Unfortunately, the extremely slow addition of KO_2 (for example one equivalent at a time over a period of several hours), resulted in poor yields of hydroxysulfoxide, even though t.l.c. showed that the starting material had been consumed. This could have been due to the formation of hydroperoxides instead of the desired displacement to form alcohol.

An alternative method for converting the "pro-trans" hydroxysulfoxide into useful material would bear further investigation. This procedure involves formation of the inverted acetate from the hydroxysulfoxide,[36] followed by reduction, which is the usual next step in the synthesis.

The acetate would be reduced along with the sulfoxide, resulting in a mixture of β-hydroxysulfide diastereomers. These could probably be separated during the same chromatography which is required for the purification of the hydroxysulfide.

The Preparation of 7S,8S-2-methyl-8-hydroxyoctadecane-7-yl-t-butylsulfide (35) and 7S,8S-2-methyl-7-hydroxy-8-yl-t-butylsulfide (40)

The reduction of the β-hydroxysulfoxides to β-hydroxysulfides was carried out in the early stages of our work by a procedure developed by Dr. T. Veysoglu.[18] This method involved the treatment of the hydroxysulfoxide with stannous chloride-acetyl chloride[37] at 0°C in a mixture of pyridine, acetonitrile, and dimethylformamide to give the corresponding acetoxysulfide, which was directly cleaved by lithium aluminum hydride to give an 85% yield (after chromatography on silica gel/benzene) of pure hydroxysulfide.

This reaction was carried out on a fairly small scale, and proved unwieldly when the problem of scale-up was attacked by H. Brown.[33] For that reason, a new method was developed, which was a modification of the procedure of Ho and Wang,[38] employing sodium*bis*(methoxyethoxy)aluminum-hydride (Vite, Red-Al). The addition of the reducing agent to the sulfoxide solution at room temperature produced some

elimination product, but this problem was overcome by lowering the temperature during addition to -78°C, followed by warming to 68°C. The result of this change in reagent was a slight decrease in yield (from 86% to 81%), but greatly improved handling of large reaction mixtures.

Other reagents which might also effect this transformation, and should be considered in making future modifications to the synthesis, are sodium cyanoborohydride in conjunction with a catalytic amount of 18-crown-6, as employed by Durst et al.[39] and the bromo- or iodotrimethylsilane reagents developed by Olah et al.[40]

At this point, it seems appropriate to discuss the synthesis of (+)-disparlure by Pirkle and coworkers[19] which was mentioned in the Introduction, since the key intermediate in that synthesis is a β-hydroxysulfide very similar to our own. In this sequence, diagrammed in Figure 12, the hydroxysulfide is prepared in racemic form, and the R-1-(1-naphthyl)ethylisocynate-derived carbamates are used to effect a resolution, by the separation of the diastereomeric carbamates on a high pressure liquid chromatograph.

This is, of course, the basic philosophical difference between the Pirkle synthesis and our own; no asymmetric induction is employed, but rather the racemic material is derivatized and the diastereomers separated. This method leaves the undesired carbamate diastereomer as wasted

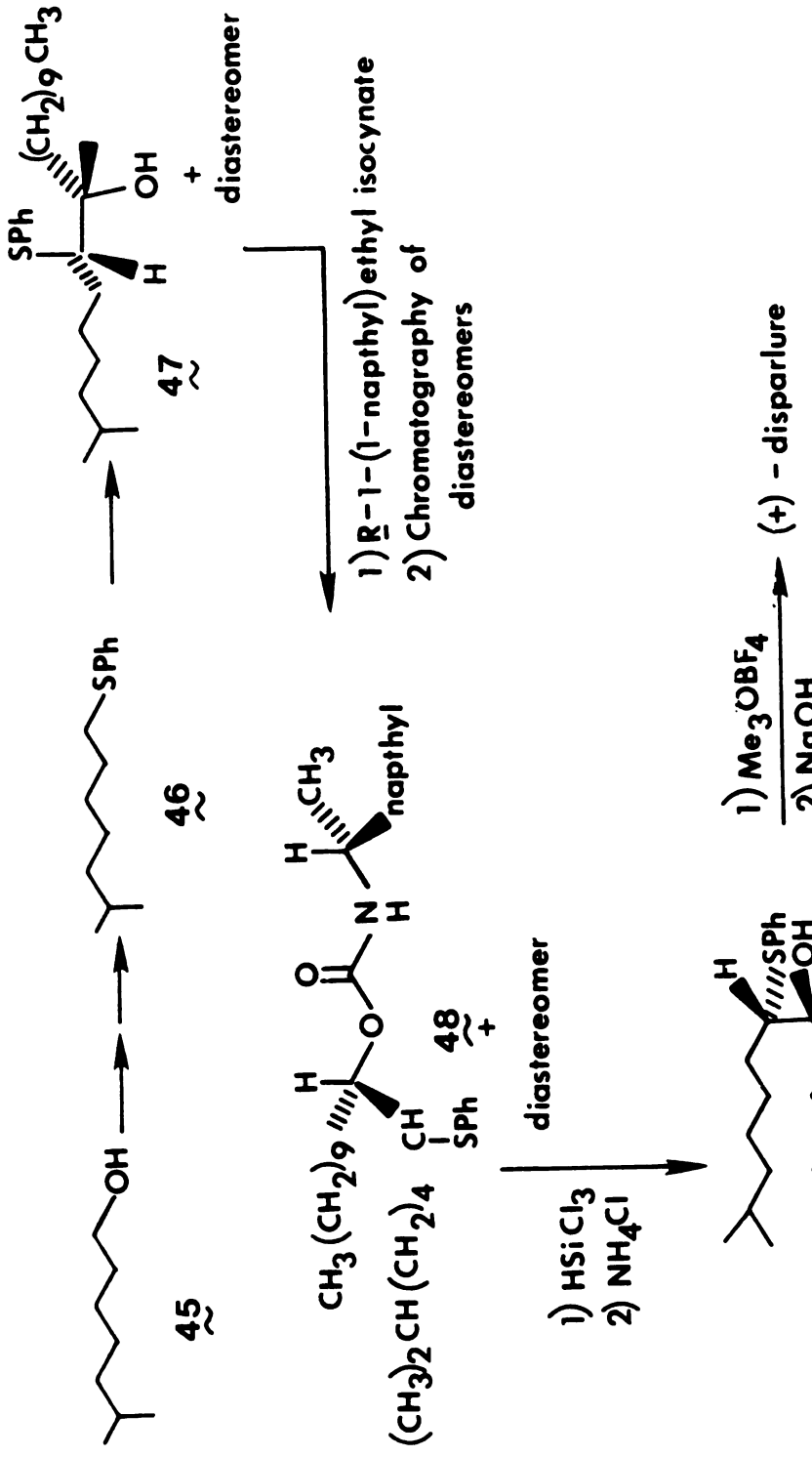


Figure 12. Synthesis of (+) disparlure by Pirkle, et al.

material, which is a problem which would be magnified if the sequence were carried out on a large scale. The expense of the optically active isocyanate might also be prohibitive. However, the procedure could be used to advantage on our hydroxysulfide intermediate, for producing ultra-high purity disparlure in small quantities for testing, or as a standard.

Preparation of 7R,8S (+)-disparlure and 7S,8R (-)-disparlure

The conversion of the β-hydroxysulfide precursors into (+) and (-)-disparlure were originally carried out[18] by a procedure developed by Dr. T. Vesoglu, involving alkylation with trimethyloxoniumfluoborate in CH_2Cl_2/CH_3NO_3 followed by epoxidation with NaOH in CH_2Cl_2/H_2O. The reaction time and temperature for the alkylation were very critical, and the procedure required the rapid removal of solvent under vacuum at 0°C prior to the addition of base. This problem and the fact that the long (10-12 h) reaction time at 0°C for the epoxidation step was both inconvenient and often led to the formation of elimination products, resulted in a reinvestigation of this procedure by H. Brown,[33] R. Muenchausen, and Dr. M. Lipton. After such modifications as the use of 100% CH_2Cl_2 as the solvent for the alkylation, and changing the base from NaOH to NaH were attempted without success, a procedure was

developed by Lipton which resulted in much shorter reaction times and consistently higher yields.

In this method the hydroxysulfide was treated with Meerwein salt at 0°C in CH_2Cl_2, then warmed to room temperature for 1 h, after which time the solvent was removed under vacuum at room temperature. The residual crude sulfonium salt was taken up in pentane, and treated with 0.5 M NaOH, at 0°C. The mixture, after stirring for 4.5 h at 0°C, was warmed to room temperature before work-up. The method gave yields in the range of 45-55% after distillation of the product.

Preparation of 7S,8R,cis-7,8-epithio-2-methyloctadecane and 7R,8S,cis-7,8-epithio-2-methyloctadecane

It was shown by Cardé and coworkers[41] in 1972 that the presence of the olefinic precursor to racemic disparlure, cis-2-methyl-7-octadecane, effectively inhibited the attractancy of disparlure to male moths. The discovery of this inhibitory phenomenon, which had been previously observed with other insect species, led to the synthesis and field testing of a number of compounds related to disparlure to determine whether they might also function as antagonists or attractants.[42] Some of these compounds were found to be somewhat attractive, though none was as good an attractant as racemic disparlure, which seemed to

indicate that the moths' receptors were not entirely specific for disparlure. One of the compounds tested was cis-7,8-epithio-2-methyloctadecane. This compound showed practically no attractancy in its racemic form; however, considering the fact that racemic disparlure is much less attractive than (+)-disparlure, it was thought that perhaps the optically active episulfide of the same configuration as (+)-disparlure might prove attractive. In addition, since (-)-disparlure is rather less attractive than racemic material, perhaps its episulfide analogue, being structurally very similar, might function as an antagonist. Accordingly, we decided to prepare these optically active compounds for electroantennogram and field testing.

Beroza and coworkers[42] prepared the episulfide used in their tests from racemic disparlure by reaction with thiourea.[43] Unfortunately, the reaction gave a yield of only about 5%. Clearly, we could not afford such a low yield if precious (+) and (-)-disparlure were to be used in the episulfide preparations.

The chemistry of thiiranes, including their synthesis from epoxides, has been reviewed by Fokin and Kolomiets.[44] Such a conversion offered an excellent way to produce the episulfides stereospecifically, since the mechanism of the reaction of epoxides with such reagents as potassium thiocyanate or thiourea had been well studied. The mechanism proposed by Ettlinger,[45] which is shown in Figure 13, was

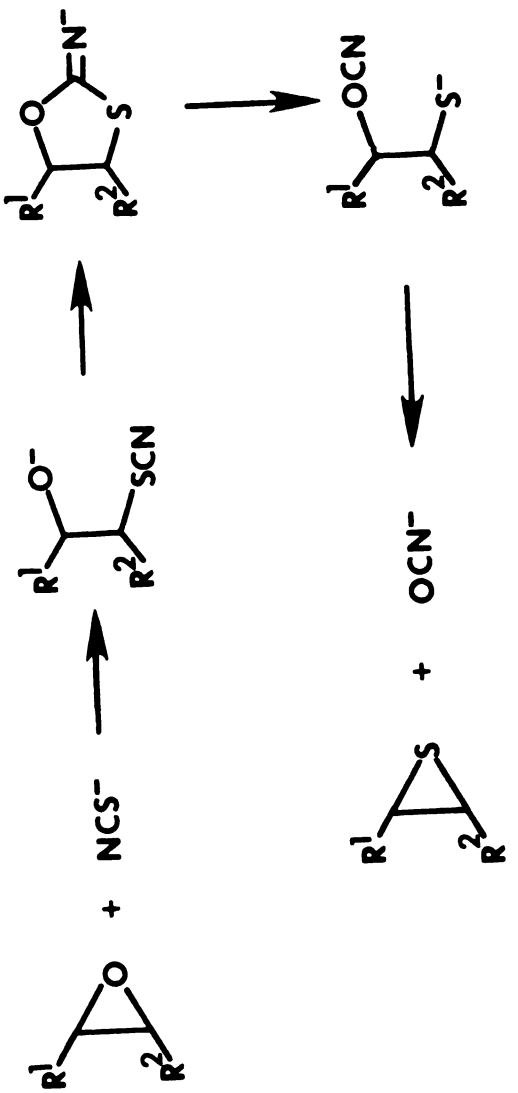


Figure 14. Mechanism for KSCN reaction with epoxides.

rigorously demonstrated by van Tamelen[46] to be correct. The reaction begins with the nucleophilic opening of the epoxide by the thiocyanate anion, followed by the isomerization of the resulting alkoxide anion, via a cyclic intermediate, into a thiolate anion. This is then converted into the thiirane with displacement of the cyanate anion. By this mechanism, inversion should occur at both carbons of the original epoxide ring. A similar mechanism was proposed by Culvenor[47] for the reaction of epoxides with thiourea. These mechanisms were further confirmed by studies of the reactions of KSCN and thiourea with optically active 2-phenyloxirane, 2-methyl-3-phenyloxirane, and 2,3-diphenyloxirane.[48] The conversion of these compounds to the corresponding thiiranes resulted in the inversion of the configuration of the epoxide at both asymmetric centers. This could only be explained by the cyclic intermediate or transition state already proposed.

The conditions for these reactions appeared to be critical in a number of cases, with yields varying from 30-80%, depending upon solvent, pH, and temperature. After trying numerous combinations of those conditions in reactions of racemic disparlure with KSCN or thiourea, it was evident that no significant improvement in yield over that of Beroza[42] would be achieved with these reagents.

An alternative method of carrying out this conversion

was devised by Chan and Finkenbine,[49] which makes use of triphenylphosphine sulfide. This method gave good yields of several thiiranes not readily produced by the KSCN or thiourea procedures. However, the mechanism of this reaction involves a trigonal bipyramidal intermediate or transition state, which could undergo pseudorotation. Thus the stereochemistry of the reaction has not yet been conclusively established.

For this reason, we bypassed that reagent in favor of theprocedure developed by Calo and coworkers[50] in which 3-methylbenzothiazole-2-thione in the presence of trifluoroacetic acid was used to effect the conversion of oxiranes to thiiranes. This procedure was reported to be successful in several cases where the conventional reagents had failed, giving high yields of thiiranes. Of importance to us was the fact that the reaction could be explained mechanistically in a manner similar to that demonstrated to be the case for the thiourea and KSCN reactions. This mechanism is outlined in Figure 1[4], and led us to believe that reaction would probably be stereospecific.

The reaction of racemic disparlure with 3-methylbenzothiazole-2-thione and an equivalent of trifluoroacetic acid gave, after purification by column chromatography and preparative t.l.c. (silica gel, toluene), yields of around 35-40% episulfide. The reaction time was somewhat longer than that reported by Calo,[50] but the progress of the

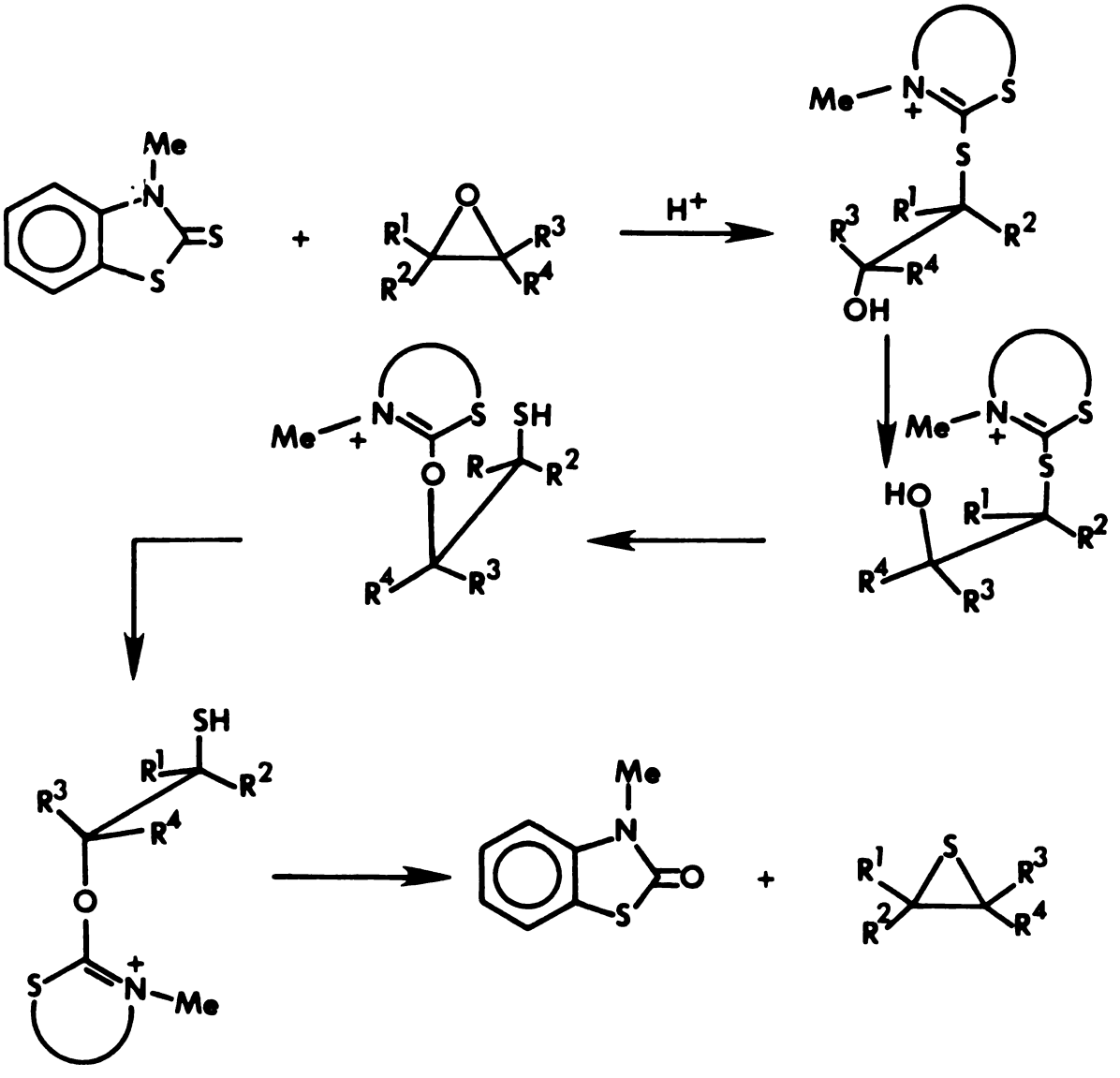


Figure 14. Proposed mechanism for epoxide to episulfide interconversion.

reaction could be followed with t.l.c. The same procedure was used to convert small quantities of (+) and (-)-disparlure to their episulfide analogues for testing, which is incomplete.

Determination of Enantiomeric Purity of Disparlure Precursors

Because the two alkyl chains are very similar, the optical rotation of pure (+)-disparlure is very small: $[\alpha]_D^{25}$ = + 0.48° (CCl_4), $[\alpha]_D^{25}$ = + 0.231° (neat). Thus, optical rotation is not a very accurate means for determination of the enantiomeric purity of disparlure. Our group, as well as every other group which has devised a synthesis of optically active disparlure, was faced with the difficulty of finding a method for making such a determination. Chiral solvating agents such as those extensively studied by Pirkle[51] do not complex with epoxides well enough to produce significant chemical shift differences between enantiotopic protons in the n.m.r. spectrum. Unfortunately, the enantiomers of epoxides equipped with no distinguishing characteristics except two slightly different alkyl side chains are not distinguished by chiral shift reagents either. We ruled out procedures requiring degradation of the epoxide because any method chosen would need to be applied to the naturally occurring material

for comparison, and the difficulty and expense involved in procuring that material in any quantity precludes its use for that purpose.

Thus our group, as did Mori and Pirkle, came to rely upon the determination of the enantiomeric purity of the immediate precursor to the epoxide, in our case the β-hydroxy-t-butylsulfides, 35 and 40. Knowing the optical purity of that precursor, we must rely upon the stereospecific nature of the final epoxidation, which has been demonstrated, and handle the material with sufficient care to prevent accidental racemization during purification.

The t-butyl group proved to be a useful handle for the determination of the enantiomeric purity of the hydroxysulfide by NMR making use of the chiral shift reagent tris(3-heptafluorobutyryl-d-camphorato)europium III, $Eu(hfbc)_3$. The t-butylhydroxysulfoxides could also be studied by this method, but the shifts induced in the sulfides were of greater magnitude, and the sulfide was the immediate precursor to the final epoxide.

In studies conducted by A. Cardé on a Brucker 180 WH instrument, it was found that by the use of approximately 25 mg $Eu(hfbc)_3$ on a 20 mg sample of hydroxysulfide in d_6-benzene, chemical shift differences of approximately 20 Hz between enantiotopic t-butyl protons could be obtained. The hydroxysulfide precursor to (+)-disparlure was found

by this method to be contaminated with 4.5-5.5% of its enantiomer. In the case of the precursor to (-)-disparlure, the hydroxysulfide was found to be 96.6% optically pure.

EXPERIMENTAL

General

All melting points were determined with a Thomas-Hoover apparatus and are uncorrected; boiling points are also uncorrected. Reagents and solvents were reagent grade, and used as received except as noted in individual cases. Routine proton magnetic resonance spectra were obtained on a Varian T-60 instrument. Infrared spectra were measured on a Perkin-Elmer Model 137 Spectrophotometer; liquids were examined as neat films, and solids as Nujol mulls. Gas chromatographic separations were routinely achieved using an F & M Model 700 Laboratory Chromatograph equipped with a thermal conductivity detector. The standard column used was 10 foot 30% SE-30 on Chromasorb W. Other columns and instruments are noted in the individual procedures. Mass spectra were run on an Hitachi RMU-6 instrument with an ionizing voltage of 70 eV.

Preparation of p-toluenesulfinic acid (27)

To a 4 L beaker containing 2.5 L H_2O was added 600 g (4.76 mol.) Na_2SO_3 and 420 g (5.00 mol.) $NaHCO_3$. The mixture was heated with stirring to 70-80°C, and maintained

at this temperature by a regulator on the oil bath or hot plate. To this was added, in 10 g portions over a period of 3 h, 484 g (2.54 mol.) p-toluenesulfonyl chloride. After addition was completed, the mixture was allowed to come to room temperature and stand for a period of 12 h, at which point the beaker was full of white fluffy crystals of the sodium salt of p-toluenesulfinic acid. These crystals were collected and dissolved in hot water, with stirring (70°C). To this solution was added an equivalent of concentrated HCl. After the mixture had cooled enough to handle, the crystals were collected, and the mother liquor evaporated to give additional crops. The combined crops were dried for several days in vacuo over Drierite, followed by P_2O_5, to give a yield of 80-85% for the two steps. This material should be used as quickly as possible after drying is complete, due to its tendency to decompose, especially in the presence of light.

Preparation of p-toluenesulfinyl chloride (28)

Freshly distilled (from triphenyl phosphite) $SOCl_2$ (120 mL, 1.65 mol.) and 120 mL dry ether were placed in a 3 neck flask equipped with mechanical stirring and N_2 flow. Dry p-toluenesulfinic acid, 27, (234 g, 1.5 mol.) was added as a solid, over a period of about 10 minutes. Foaming and gas evolution occurred during the addition and determined the addition rate. Stirring was continued

until no further gas evolution was observed (2-3 h). The system was warmed slightly (30-40°C) toward the end of this period. Excess $SOCl_2$ and ether were then removed under vacuum at room temperature, with care taken to prevent moisture from reaching the acid chloride during this process. The resulting crude p-toluenesulfinyl chloride was not purified further, due to its tendency to decompose during distillation, and the esterification reaction was carried out immediately.

Preparation of ethyl p-toluenesulfinate (29)

Absolute ethanol (86 mL, 1.5 mol.), dry pyridine (133 mL, 1.65 mol.) and 250 mL anhydrous ether were placed in a 1 L, 3 neck flask equipped with mechanical stirring, condenser, addition funnel, and N_2 flow. The mixture was cooled to 0°C, and maintained at that temperature throughout the reaction. The acid chloride, 28, prepared in the previous reaction was added dropwise at a rate which kept the temperature at 0°C. Stirring was continued at 0°C for 1 h after the addition was complete; then the mixture was poured into water and the phases separated. The aqueous phase was extracted twice with ether. The combined ether extracts were washed twice with H_2O, twice with 5% HCl, and once with saturated NaCl solution, then dried over $MgSO_4$. The solvent was removed on the rotary evaporator, and the residue distilled under vacuum. A small forerun

(30-50°C/0.2mm Hg) preceded the ester (95-100°C/0.1 mm Hg). Care had to be taken to assure that the pot temperature did not exceed 120°C, since decomposition was observed at higher temperatures. 160 g of ethyl p-toluenesulfinate, 29, was obtained after distillation, for a yield of 58% over the two steps from the sulfinic acid. ^{1}H NMR ($CDCl_3$): δ0.90 (3H, t, J=3Hz); 2.0 (3H, s) 3.5 (2H, complex m), 7.15 (4H, dd, J=9, J'-4 Hz).

Preparation of ℓ-menthyl-p-toluenesulfinate (30) From (29)

Ethyl-p-toluenesulfinate, 29, (100 g, 0.543 mol.) and ℓ-menthol (84.7 g, 0.543 mole) were stirred together at 60°C under partial vacuum (15 mm Hg) for 48 hr. The mixture was then allowed to cool at atmospheric pressure. The stirring was then stopped and the mixture allowed to stand overnight, after which crystallization had occurred. In other runs, if such spontaneous crystallization did not occur, it could be induced by seeding or scratching. The crystalline mass was taken up in a minimum of acetone and recrystallized to yield menthyl-p-toluenesulfinate (71.8 g, 45%) as white needles, m.p. 106-107°C. This material was then recrystallized 7-8 times from a 17:3 mixture of acetone/H_2O, until a constant specific rotation of $[\alpha]_D^{23}$ = -199.7°±0.3° was obtained in acetone solution. NMR ($CDCl_3$) δ0.70-1.02 (19H, m); 2.40 (3H, s); 7.20-7.75 (4H, m); IR (CCl_4): μ6.25, 8.8, 11.7.

Preparation of 6-methylheptyl-p-tolylsulfoxide (32)

Diastereomerically pure ℓ-menthyl-p-toluenesulfinate, 30, (70.0 g, 0.238 mol.) was dissolved in 625 mL dry ether in a 2 L three-necked round bottom flask equipped with a stirrer, an addition funnel and N_2 inlet-outlet tubes. A solution of 6-methylheptylmagnesium bromide, prepared by refluxing 6-methylheptyl bromide (45.9 g; 0.238 mol.) and magnesium (6.53 g; 0.247 mol.) in dry ether for one hour, was transferred via a cannula to the addition funnel. The Grignard reagent was added dropwise over a period of 50-60 minutes to the stirred reaction mixture. The stirring was continued for an additional three hours. The reaction mixture was then quenched with 300 mL saturated ammonium chloride solution. The layers were separated, and the ethereal layer was washed with water. The aqueous portions were combined and, in turn, extracted with ether. The ethereal portions were combined, dried over Na_2SO_4, and concentrated. The crude product was then subjected to sublimation (50°C at 0.2 mm Hg) until only a very small amount of menthol was detected in the residue by t.l.c. (silica gel/$CHCl_3$). Finally, removal of the unreacted starting material from the residue by column chromatography (Woelm alumina; 1:1 hexane/ether, followed by 100% ether) gave the desired sulfoxide in 65% yield. (Slight contamination with menthol could be tolerated in the next step.)

^{1}H NMR: δ0.80 (6H, d, J=3 Hz) 1.0-1.75, (9H, m); 2.32 (3H, s); 2.65 (2H, t, J=3 Hz); 7.25 (4H, dd, J=8, J'-4 Hz).

Preparation of t-butyl-6-methylheptylsulfoxide (33)

p-Tolyl-6-methylheptylsulfoxide (20.1 g; 0.08 mol.) was dissolved in 2 L of dry ether and added to a flame dried 3 L three-necked flask, equipped with a mechanical stirrer, rubber septum, and N_2 flow. The system was cooled to -78°C, and 177 mL t-butyllithium (1.8 M, 0.32 mol.) was added, slowly at first, to the solution by cannula. The mixture was allowed to stir an additional three hours at -78°C after addition was complete, after which the cold bath was removed and distilled water (300 mL) was added slowly to quench the reaction mixture. Upon warming, the layers were separated, the ether phase extracted with water (150 mL), and the combined aqueous layers extracted with ether (3 x 100 mL). The ether extracts were combined, dried with Na_2SO_4, concentrated, and dried (0.1 mm Hg for 6 h) to give 98-105% crude t-butylsulfoxide, which was used in the next step without further purification, due to its instability.

Preparation of 7S,8S-2-methyl-8-hydroxyoctadecane-7-yl-t-butylsulfoxide (34a, cis Precursor) and its 7S,8R Diastereomer (34b, trans Precursor)

To a flame dried 500 mL three necked flask equipped with a mechanical stirrer, rubber septum, and 125 mL addition funnel with a nitrogen outlet tube, was added crude t-butyl-6-methylheptylsulfoxide (9.47 g; 0.0434 mol.) in 130 mL dry ether. The system was then cooled to -78°C. 23.9 mL n-butyllithium (2.0 M in hexane, 10% excess) was added to the solution. The generated anion (color change from light yellow to dark yellow or light brown) was allowed to stir for 45-60 minutes, after which freshly distilled (54°C, 0.13 mm Hg) undecanal (8.86 g; 0.521 mol.) was added. The reaction mixture was allowed to stir for an additional 45-60 minutes, after which 100 mL cold saturated ammonium chloride solution was added dropwise from the addition funnel. After addition was complete, the ice bath was removed. Upon warming to 0-10°C, the phases were separated, the aqueous phase reextracted with ether (2 x 100 mL), and the combined ether extracts dried with Na_2SO_4. Concentration of the extracts gave 32.3 g crude hydroxysulfoxide. Separation by column chromatography (silica gel/ether) yielded 10.8 g (35%) of "pro-cis" hydroxysulfoxide, 34a, and 13.9 g (45%) of the "pro-trans" diastereomer, 34b. For the 7S,8S pro-cis isomer: ^1H NMR: (CCl_4): δ0.85 (9H, m); 1.1-1.5 (36H, m); 2.6 (1H, m);

3.7 (1H, m); 4.1 (1H, br, s) IR (neat film): μ3.0, 3.5, 5.8 (w), 6.9, 7.4, 8.6, 8.9, 9.3, 10.0. For the 7S,8R, "pro-trans" hydroxysulfoxide: ^{1}H NMR (CCl_4): δ0.85 (9H, m); 1.1-1.8 (36H, m); 3.25 (1H, m); 3.4 (1H, br s); 4.0 (1H, m); IR (neat film): μ2.9, 3.4, 5.75 (w), 6.8, 7.3, 7.6, 8.5, 8.8, 9.9, 13.8.

Preparation of 7S,8S-2-methyl-8-hydroxyoctadecane-7-yl-t-butylsulfide (35)

To a 500 mL round bottom flask, equipped with a West condenser topped by an addition funnel, was added "pro-cis" hydroxysulfoxide (20.0 g; 51.4 mmol.) in 150 mL dry tetrahydrofuran. The system was cooled to -78°C, and sodium bis(methoxyethoxy)aluminum hydride (40.0 mL, 80% solution in benzene) in 100 mL dry THF was added dropwise over a period of two hours. The system was allowed to warm to room temperature over a period of one-half hour, and then warmed to 68°C for at least eight hours. The reaction mixture was allowed to cool, and then slowly added to a mixture of 500 mL 1.0 N HCl and 300 mL benzene in a 2 L separatory funnel. The aqueous layer and resulting salts were extracted with additional benzene (3 x 300 mL), the combined extracts dried with $MgSO_4$, concentrated, and purified by solumn chromatography (silica gel/benzene) to give 15.5 g (81%) of hydroxysulfide which is normally at least 95%

pure by t.l.c. ^{1}H NMR (CCl_4): δ0.8 (m, 9H); 1.0-1.6 (m, 34H); 2.2-2.4 (m, 2H); 3.1-3.2 (m, 2H).

Preparation of (+)-Disparlure (13)

Original procedure: To a 500 mL round bottom flask was added 7S,8S-methyl-8-hydroxyoctadecan-7-yl-t-butyl-sulfide (10.0 g; 28.6 mmol.) and 100 mL of solvent (CH_2Cl_2: CH_3NO_3; 1:1) under nitrogen. After cooling to 0°C, trimethyloxonium tetrafluoroborate (7.94 g; 53.7 mmol.) was added, and the system allowed to stir vigorously for 1 hour and 10 minutes. The solvent was then removed by distillation, with the temperature not rising above 25°C. The total reaction time should not exceed 2 h. CH_2Cl_2 (200 mL) and 0.5 N sodium hydroxide (200 mL) were then added to the reaction flask, and allowed to stir vigorously for 10-12 hours. The reaction mixture was then allowed to separate into layers, the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL), and the combined extracts filtered through a 60 x 20 mm plug of silica gel before concentration. After concentration, the material was chromatographed (silica gel/benzene) to give 4.43 g (58%) of (+)-disparlure. This material was then distilled to remove a yellow impurity (molecular distillation, 110°C, 0.5 mm Hg), and the resulting disparlure determined to be at least 99% pure by t.l.c. and v.p.c. (50' 3% OV-1 on Gaschrom Q microcapillary

column in a Packard gas chromatograph in the lab of Dr. R. Cardé.) ^{1}H NMR (CCl_4): δ0.90 (9H, m); 1.0-1.5 (27H, m); 2.65 (2H, m) IR (neat film): μ3.7, 7.1, 7.5.

Preparation of 1-bromoundecane (36)

To a 300 mL round bottom flask, equipped for reflux and containing 42 mL (0.375 mol.) 48% HBr and 13.2 mL concentrated H_2SO_4, was added 51.6 g (0.30 mol.) undecanol, with cooling. After addition was complete, the mixture was refluxed for a period of 5.5 h., then cooled and poured onto ice. The layers were separated, and the organic phase washed with concentrated H_2SO_4. Again the phases were separated, and CH_2Cl_2 was added to the organic phase prior to washing twice with H_2O, twice with 10% $NaHCO_3$, and once with saturated NaCl. An emulsion tended to form during the aqueous washes, which could be broken by addition on small amounts of additional CH_2Cl_2. The organic phase was dried over $MgSO_4$, solvent removed by rotary evaporator, and the resulting oil distilled (b.p. 95-97°C/1-2 mm) to yield 67.4 g (96%) 1-bromoundecane. Purity was determined by gas chromatography (20 ft x 1/8 in 3% FFAP on Chromasorb W, 178°C). ^{1}H NMR ($CDCl_3$): δ.90 (3H), ∿1.3 (16H), 1.85 (2H), 3.30 (t, J=3 Hz, 2H).

Preparation of Undecyl-p-tolylsulfoxide (37)

Diastereomerically pure ℓ-menthyl-p-toluenesulfinate, 36, (40.0 g; 0.136 mol.) was dissolved in 350 mL anhydrous ether in a 1 L three-necked round bottom flask equipped with stirrer, addition funnel, and N_2 inlet-outlet tubes. A solution of undecylmagnesium bromide, prepared by refluxing 1-bromoundecane, 36, (35 g; 0.149 mol.) and magnesium (3.5 g; 0.149 mol.) in anhydrous ether for 1.5 h, was transferred via a cannula to the addition funnel. This Grignard reagent was added dropwise over a period of 30 minutes to the stirred reaction mixture. The stirring was then continued for an additional 2 h during which time the mixture was maintained at reflux, with external heating when required. The reaction mixture was quenched with 200 mL saturated NH_4Cl solution. The layers were separated, and the ether phase washed with water. The aqueous portions were combined and extracted with ether. The ethereal portions were combined, dried over $MgSO_4$ and concentrated. The menthol was removed from the crude reaction mixture by sublimation (50-70°C/0.2 mm Hg), the process being continued until only traces of menthol were evident by TLC (silica gel, $CHCl_3$). Chromatography of the residue (Woelm Alumina; 1:1 hexane-ether followed by 100% ether) removed residual starting material and afforded the product (37) in approximately 65% yield. The white solid could be recrystallized

with difficulty from a hot mixture of water and acetone, with cooling in an ice bath. This process produced white needles. A second recrystallization gave material with $[\alpha]_D^{23}$ + 127.5°. ^{1}H NMR ($CDCl_3$): δ0.95 (t, 3H, J=3 Hz), 1.15 (18H, m), 2.35 (s, 3H), ∿2.6 (m, 2H), 7.20 (4H, dl, J=7, J'=5 Hz).

Preparation of t-butyl-undecylsulfoxide (38)

To a flame dried 3-neck round bottom flask, equipped with a mechanical stirrer, rubber septum and nitrogen flow, was added p-tolyl-undecylsulfoxide, 37, (14.7 g; 50 mmol.) dissolved in 1.25 L dry ether, and the system was cooled to -78°C. 146 mL t-butyllithium (1.37M, 0.2 mol.) was added, slowly at first, to the solution by cannula. The mixture was allowed to stir for an additional three hours at -78°C after addition was complete, after which the cold bath was removed, and distilled water (200 mL) was added slowly to quench the reaction mixture. Upon warming, the layers were separated, the ether phase extracted with water (100 mL), and the combined aqueous layers extracted with ether (3 x 100 mL). The ether extracts were combined, dried with Na_2SO_4, concentrated and dried (0.1 mm Hg for 6 h) to give 98% crude t-butylsulfoxide, which was used in the next step without further purification. If it became necessary to store this material, it could be kept under N_2 at -40°C,

at which temperature it was a solid. ^{1}H NMR ($CDCl_3$): δ0.85 (3H, s), 1.25 (s) and 1.3-2.0 (m) (together 27H); 3.4 (2H, dd, J=7, J' = 3 Hz) spectrum run on crude material. IR (neat film): μ3.4, 6.8, 7.3, 8.5, 9.6.

Preparation of 6-methylheptyl Tosylate

The silver tosylate used in this reaction was prepared as follows. Anhydrous Ag_2O (6.66 g, 30 mmol.) and p-toluenesulfonic acid (9.50 g, 30 mmol.) were added to 100 mL dry CH_3CN and stirred together, with protection from light, for 0.5 hr. The solution is then filtered and the CH_3CN removed on the rotary evaporator, with protection from light. The resulting white powder was dried in a vacuum oven at 65°C, to constant weight. The silver tosylate thus prepared was used immediately for the preparation of 6-methylheptyl tosylate: 6-methylheptyl bromide (1.93 g; 10 mmol.) was added to a solution of silver tosylate (5.58 g; 20 mmol.) in CH_3CN at 0°C, with stirring, and protection from light. The mixture was stirred at room temperature for 48 hours, after which it was poured into ice water, extracted with ether. The aqueous phaseewas extracted twice with small portions of ether, and the ethereal extracts combined, dried over $MgSO_4$ and concentrated. The crude 6-methyl-heptyltosylate was used without purification for the next reaction. ^{1}H NMR: δ0.80 (6H, d, J=3 Hz); 1.0-1.9 (9H, m); 2.40 (3H, s); 3.80 (2H, t, J=3 Hz); 7.38 (4H, dd, J=13, J'=4 Hz).

Preparation of 1-iodo-6-methylheptane

To a stirred, refluxing solution of sodium iodide (18 g, 120 mmol.) in dry acetone (60 mL) was added 1-bromo-6-methylheptane (10 g, 51.8 mmol.). The mixture is allowed to reflux for 20 h, then poured into H_2O and extracted into ether. After separation, the aqueous phase was washed twice with ether, and the combined ether phases were dried over $MgSO_4$. The ether was removed by rotary evaporator, resulting in 7.9 g, (64%) iodide which was not further purified. ^1H NMR: δ0.85 (6H, d, J=3 Hz); 1.05-2.15 (7H, m); 6.20 (2H, t, J=3 Hz) IR (neat film): μ3.5, 6.9, 7.4, 8.3, 8.6.

Preparation of 6-methylheptan-1-al (42)

In 40 mL anhydrous CH_2Cl_2 was suspended (with vigorous stirring) pyridinium chlorochromate (6.46 g, 30 mmol.) under N_2 flow. 6-methylheptan-1-ol (Chem. Samples, 2.39 g, 18.3 mmol.) was added in one portion to the suspension, which rapidly turned dark. Stirring was continued for 1.5 h, and the progress of the reaction monitored by t.l.c. (silica gel, ether). 40 mL anhydrous ether was then added and the supernatant decanted, leaving a black tar. This residue was washed three times with 40 mL portions of anhydrous ether, and finally became a granular solid. The combined organics were passed quickly through a plug of Florisil on

a sintered glass funnel, with the aid of vacuum. The solvent was removed on the rotary evaporator, and the resulting crude 6-methylheptan-1-al distilled (30-35°C/1 mm Hg) to yield 1.63 g pure material (70%). Alternately, 6-methylheptan-1-al could be produced by addition of either 1-iodo-6-methylheptane or 6-methylheptyltosylate (2.40 g iodide; 10 mmol or 2.84 g tosylate; 10 mmol.) to 50 mL dimethylsulfoxide which had been heated to 150°C, cooled, combined with 7 g $NaHCO_3$, and reheated to 150°C with N_2 bubbling through it. The mixture was stirred at 150° for 4-5 minutes, cooled rapidly and poured into water. The mixture then extracted with ether, and the aqueous phase extracted again with ether. The combined ethereal phases were dried with Na_2SO_3, concentrated and the crude aldehyde distilled as before, to give a 40% yield of pure 6-methylheptanal. ^1H NMR: δ0.85 (6H; d, J=3 Hz), 1.1-1.6 (7H, m); 2.4 (2H, br t, J=3 Hz); 9.3 (1H, br s) IR (neat film): μ3.5, 5.9, 6.9, 7.4, 8.0, 9.4, 12.9.

Preparation of 7S,8S-2-methyl-7-hydroxyoctadecane-8-yl-t-butylsulfoxide (39a, (-)-cis Precursor)

To a flame dried three-necked flask equipped with a mechanical stirrer, rubber septum, and addition funnel with a nitrogen outlet tube, was added crude t-butyl-undecylsulfoxide (6.5 g; 25.0 mmol.) in 75 mL dry ether. The

system was then cooled to -78°C. 18.3 mL n-Butyllithium (1.5 M, 27.5 mmol.) was added to the solution. The generated anion (color change from light yellow to dark yellow or light brown) was allowed to stir for 45-60 minutes, after which freshly distilled 6-methylheptan-1-al (3.18 g; 24.8 mmol.) was added. The reaction mixture was allowed to stir for an additional 45-60 minutes, after which 100 mL cold saturated ammonium chloride solution was added dropwise from the addition funnel. After addition was complete, the ice bath was removed. Upon warming to 0-10°C, the phases were separated, the aqueous phase extracted with ether (2 x 100 mL), and the combined ether phases dried with Na_2SO_4. Concentration of the extracts gave 8.2 g crude hydroxysulfoxide. Separation by column chromatography (silica gel/ether) yielded 2.0 g (21%) pure "pro-cis" hydroxysulfoxide, 39a. Rechromatographing the mixture of diastereomers which overlapped during the initial separation would yield another 0.3-0.5 g of "pro-cis" material, but in the interest of high purity, this was not done in this case. ^1H NMR (CCl_4): δ0.87 (9H, m); 1.2-1.6 (36H, m); 2.7 (1H, m); 3.4 (1H, m); 3.9 (1H, m) IR (neat film): μ3.0, 3.5, 6.9, 7.4, 8.5, 9.0, 9.9, 12.7.

Preparation of 7S,8S-2-methyl-7-hydroxyoctadecane-8-yl-t-butylsulfide (40)

To a 50 mL round bottom flask, equipped with a West condenser topped by an addition funnel and nitrogen flow, was added "pro-cis" hydroxysulfoxide, 39a, (2.0 g; 5.14 mmol.) in 15 mL dry tetrahydrofuran. The system was cooled to -78°C, and sodium bis(methoxyethoxy)aluminum hydride (4.0 mL, 80% solution in benzene) in 10 mL dry THF was added dropwise over a period of an hour. The system was allowed to warm to room temperature over a period of one-half hour, and then warmed to 68°C for at least eight hours. The reaction mixture was allowed to cool, and then slowly added to a mixture of 50 mL 1.0 N HCl and 30 mL benzene. After separation of the phases, the aqueous layer and resulting salts were extracted with benzene (3 x 100 mL). The combined extracts were dried with $MgSO_4$, concentrated, and purified by column chromatography (silica gel/benzene) to give 1.1 g (58%) of hydroxysulfide, 40. ^1H NMR (CCl_4): δ0.85 (9H, m); 1.2-1.6 (36H, m); 2.2-2.4 (2H, br m); 3.2 (1H, m) IR (neat film): μ2.9, 3.5, 6.9, 7.4, 8.6, 9.5 (w), 12.6 (w).

Preparation of 7S,8R (-)-disparlure (41)

Following the procedure developed by M. Lipton, a flame dried 100 mL round bottom flask, equipped with N_2 flow and stirrer, was charged with hydroxysulfide, 40, (1.10 g, 2.96 mmol.) in 12 mL dry CH_2Cl_2. The solution was cooled to 0°C, and trimethyloxonium tetrafluoroborate (0.460 g, 3.1 mmol.) was added in one portion. The cold bath was removed immediately, and the mixture was allowed to stir for 1.0 h. The solvent was carefully removed from the pale yellow mixture at ambient temperature under vacuum, a process which required approximately 30 minutes. The residue, the crude sulfonium salt, was treated with 22 mL pentane and, after 2 minutes, 22 mL 0.5 N NaOH, both of which were prechilled to 0°C. The two phase reaction mixture was allowed to stir at 0°C for 4.5 h. The ice bath was then removed and the mixture warmed to room temperature over a period of 0.5 h. The phases were separated, and the aqueous phase was extracted with four 30 mL portions of pentane. The combined organic extracts were washed once with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give crude (-)-disparlure, 41. This material was purified by preparative t.l.c. (silica gel/ benzene) to yield 0.5 g (60%) (-)disparlure, still somewhat impure. 0.45 g (-) disparlure was obtained after another preparative t.l.c. was done (silica gel/toluene),

with 0.075 g material. Spectra were the same as those reported for (+) disparlure.

Conversion of 7S,8R-2-methyl-8-hydroxyoctadecane-7-yl-t-butylsulfoxide (34b, trans precursor) into 7S,8S-2-methyl-8-hydroxyoctadecane-7-yl-t-butylsulfoxide (34a, cis precursor)

The mesylate of hydroxysulfoxide, 34b, was prepared as follows: To purified (column chromatography, silica gel/ether) 34b (0.374 g, 0.7 mmol.) in 1 mL CH_2Cl_2 and 0.08 mL (1 mmol.) dry pyridine, was added methanesulfonylchloride (0.06 mL, 1 mmol.) at -20°C under N_2 flow. The mixture was stirred for 0.5 h at -20°C, then warmed to room temperature and stirred for another 2 h. At this point, t.l.c. (silica gel, ether) showed only partial conversion to the mesylate, so an additional equivalent of methanesulfonylchloride and pyridine was added and the mixture stirred overnight at room temperature. 10 mL CH_2Cl_2 was added and the mixture was extracted with two 25 mL portions of 5% HCl, two portions of 5% $NaHCO_3$, and once with water. Each of the aqueous phases was back-extracted with CH_2Cl_2. The combined organic phases were dried with anhydrous K_2CO_3, concentrated and dried under vacuum. This material was used in the subsequent reaction without further purification.

The mesylate was dissolved in a 1:1:1 mixture of DMF, DMSO, and DME, all of which had been dried. 18-crown-6 (either 1 equivalent, or a catalytic amount, such as 0.25 equivalent) was added to the mixture, which was kept under N_2 flow. The solution was cooled to 0°C, with stirring, and KO_2 (4 equivalents) was added in small portions over a period of 10 minutes. (Caution: On larger scale reactions, the stirring and cooling must be very efficient, and the addition of superoxide relatively slow, since the reaction can become exothermic.) The mixture was stirred for 1 h at 0° then allowed to slowly warm to room temperature. Stirring was continued until t.l.c. (silica gel/ether) showed disappearance of mesylate. This time period varied with the amount of crown added, from 1 hour when excess crown was used, to 36 hours when only catalytic amounts of crown were employed. After starting material was consumed, the reaction mixture was extracted with 10% Na_2CO_3, and dried over K_2CO_3. Concentration of the organic phase, followed by chromatography (silica gel/ether) gave a 44% yield of 34a "pro-cis" hydroxysulfoxide, whose spectra and retention times on t.l.c. were identical to authentic material. Some 34b, "pro-trans" hydroxysulfoxide was also recovered, due to incomplete mesylate formation.

Preparation of racemic cis-7,8-epithio-2-methyloctadecane

A mixture of racemic disparlure (0.282 g, 1 mmol.) and 3-methyl-benzothiazole-2-thione (0.181 g, 1 mmol.) in approximately 2 mL anhydrous CH_2Cl_2 was cooled, with stirring and under nitrogen, to 0°C. Trifluoroacetic acid (0.114 g, 1 mmol.) was added. Stirring was continued at 0° for 15-20 minutes, until t.l.c. (silica gel/toluene) showed the disappearance of starting epoxide. The mixture was then extracted with H_2O, and the CH_2Cl_2 ohases washed once with 5% $NaHCO_3$ and once with water, then dried with K_2CO_3. Concentration, followed by column chromatography (silica gel/toluene), gave a 45% yield of episulfide, whose purity could be evaluated by g.c., using a 6' column of 3% QF-1 on Chromasorb G at 200°C. ^1H NMR ($CDCl_3$): δ0.82 (9H, m), 1.1-2.0 (27H, m); 2.85 (2H, m) IR (neat film): μ3.75, 7.03, 7.45, 8.10, 10.0, 12.6, 14.1.

The episulfide analogues of (+) and (-) disparlure were prepared in the same manner, on smaller scales. Purification in those cases was by preparative t.l.c. (silica gel/toluene). Spectra were the same as reported for racemic material.

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