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DIASTEREOSELECTIVE α-ALKYLATION OF β-HYDROXY SULFOXIDES AND ITS APPLICATION TO THE SYNTHESIS OF (+)- AND (-)-DISPARLURE

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Summary: *α-Alkylation of the dianions of β-hydroxy sulfoxides proceeds with high 1,2-asymmetric induction to give threo-α-alkyl-β-hydroxy sulfoxides. The utility of the present reaction was demonstrated in the asymmetric synthesis of (+)- and (-)-cis-7,8-epoxy-2-methyloctadecanes (disparlure).*

The chemistry of α-sulfinyl carbanions involving their stereochemistry and reactivity has been intensely investigated from both theoretical and experimental points of view.[1] Recently α-carbanions of chiral sulfoxides have been efficiently utilized for asymmetric carbon-carbon bond forming reactions in terms of easy availability and removal of chiral sulfoxides as chiral auxiliaries.[2] Chiral α-sulfinyl carbanions stabilized with electron withdrawing groups such as ester,[3] amide,[4] dihydroxazole,[5] and sulfenyl groups[6] react with aldehydes to afford the corresponding β-hydroxy sulfoxides with high diastereoselectivity. However, the reaction of non-stabilized α-sulfinyl carbanions proceeds with rather low diastereoselectivity.[7,8] On the other hand, high 1,3-asymmetric induction in the reduction of chiral β-keto sulfoxides with diisobutylaluminum hydride (DIBAL) has been reported to give β-hydroxy sulfoxides, which are useful precursors of optically active secondary alcohols or monosubstituted oxiranes.[9] Herein we wish to describe the diastereoselective α-alkylation[10] of β-hydroxy sulfoxides (**1** and **2**) leading predominantly to *threo*-α-alkyl-β-hydroxy sulfoxides (**3** and **4**) with two asymmetric carbons and its application to the synthesis of (7R,8S)- and (7S,8R)-7,8-epoxy-2-methyloctadecanes, (+)- and (-)-disparlure, the female-produced pheromone of the gypsy moth (*Porthetria dispar*).[11]

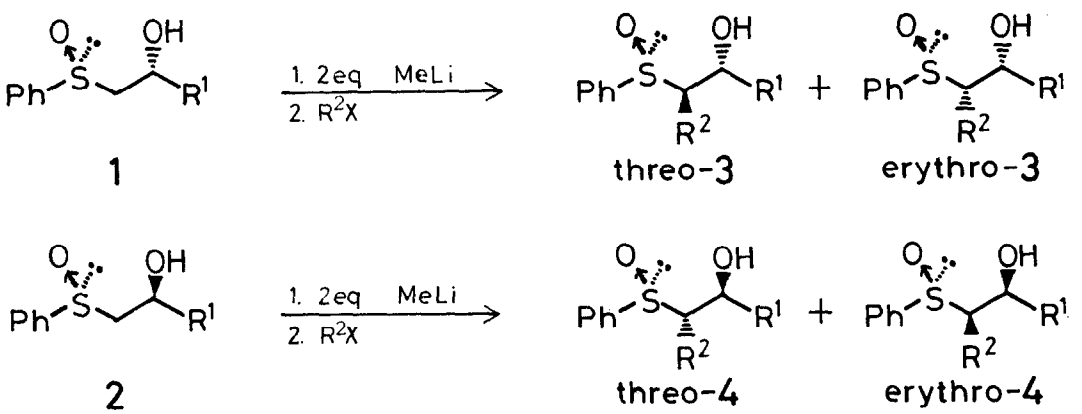


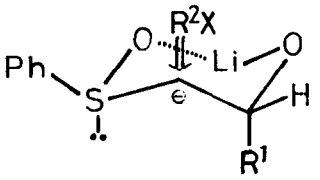
Table 1. α-Alkylation of β-Hydroxy Sulfoxide **1** and **2**.

Entry	β-Hydroxy Sulfoxide **1** or **2**	R^2X[a]	Yield(%) **3** or **4**	Ratio[b] *threo* : *erythro*
1	**1** ($R^1 = CH_3$)	CH_3I	**3** (87)	16 : 1
2	**1** ($R^1 = i\text{-}C_7H_{15}$)	$n\text{-}C_{10}H_{21}I$	**3** (58)	4 : 1[c]
3	**2** ($R^1 = CH_3$)	CH_3I	**4** (76)	11 : 1
4	**2** ($R^1 = CH_3$)	CH_3I	**4** (62)	11 : 1
5	**2** ($R^1 = CH_3$)	$(CH_3O)_3P=O$	**4** (50)	10 : 1
6	**2** ($R^1 = i\text{-}C_7H_{15}$)	$n\text{-}C_{10}H_{21}I$	**4** (75)	20 : 1[c]

[a] The reaction of the dianion of **1** or **2** with alkyl iodide was carried out at -78° to 0 °C (5 - 6h) except entry 5 (-20 °C to r.t., 2h). [b] Determined by HPLC on a JASCO μS-Finepac SIL using $n\text{-}C_6H_{14}$-AcOEt (9 : 1). [c] Based on the isolated yields of the each isomers by TLC.

First, α-alkylation of racemic β-hydroxy sulfoxides was examined *via* the dianions of two diastereomeric sulfoxides (**1** and **2**). β-Hydroxy sulfoxide **1** ($R^1 = CH_3$), prepared by the reduction of 1-(phenylsulfinyl)propan-2-one with DIBAL,[9] was treated with 2.2 equiv of methyllithium in THF at 0 °C for 2 h. To the resulting yellow dianion solution was added methyl iodide (1.3 equiv) at -78 °C and the reaction mixture was allowed to warm to 0 °C over a period of 5 h. Purification of the products on silica gel TLC gave a mixture of *threo*- and *erythro*-**3** ($R^1 = R^2 = CH_3$) in 87% yield with the ratio of 16 to 1 (Table 1, entry 1). The *threo*- and *erythro*-stereochemistry was confirmed by comparison of the ^1H NMR spectra of 3-phenylthio-2-butanol, derived from **3** ($R^1 = R^2 = CH_3$) by the reduction of the sulfinyl group with zinc-chlorotrimethylsilane,[12] with those of *threo*- and *erythro*-authentic samples.[13] The reaction of β-hydroxy sulfoxide **2** ($R^1 = CH_3$), the diastereomer of **1**, obtained by the reduction of 1-(phenylsulfinyl)-propan-2-one with DIBAL-$ZnCl_2$,[9] with methyl iodide gave mainly *threo*-**4** ($R^1 = R^2 = CH_3$) with the *threo* : *erythro* ratio of 11 to 1 (entries 3 and 4). These results indicate that the stereoselectivity of the alkylation reaction is controlled by the stereochemistry of the hydroxyl group, not by that of the sulfinyl group. In contrast to the reported stereochemical reversal in the reaction of α-lithio benzyl methyl sulfoxide with methyl iodide and trimethyl phosphate,[14a] the reaction of **2** ($R^1 = CH_3$) with trimethyl phosphate gave also the *threo*-product (entry 5). In connection with the synthesis of disparlure, introduction of n-decyl group into β-hydroxy sulfoxide **1** ($R^1 = i\text{-}C_7H_{15}$) proceeded with low selectivity (*threo* : *erythro* = 4 : 1), while the diastereomer **2** ($R^1 = i\text{-}C_7H_{15}$) gave *threo*-**4** ($R^1 = i\text{-}C_7H_{15}$, $R^2 = n\text{-}C_{10}H_{21}$) with high diastereoselectivity (*threo* : *erythro* = 20 : 1) (entries 2 and 6).

The above stereoselectivity of *threo*-preference, depending on the stereochemistry of the hydroxyl group, not on that of the sulfinyl group, can be explained by the following transition states **5** and **6** of a six-membered chair ring, produced by the chelation of both oxygens of the hydroxyl and sulfinyl groups to the lithium cation.[5,15] In the case of **1**, the transition state **5** prefers the



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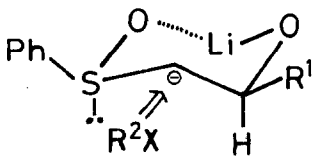

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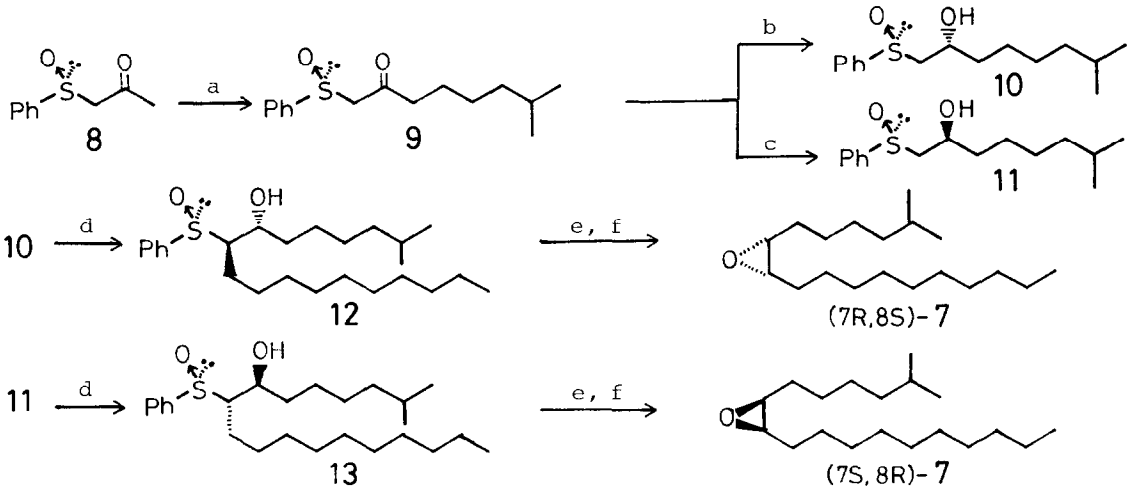
axial attack of R^2X from the upper side by the steric interaction with the axial R^1 group to produce *threo*-**3**. On the other hand, in the case of **2** the equatorial attack in **6** gives thermodynamically stable *threo*-**4**.

threo-α-Alkyl-β-hydroxy sulfoxides (**3** and **4**), obtained by the present reaction, are easily converted into *cis*-epoxides as shown in the following synthesis of both enantiomers of disparlure.[8,16] Alkylation of optically pure (S)-1-(phenylsulfinyl)-propan-2-one (**8**), $[\alpha]_D^{23}$ +256° (c 1, MeOH), prepared easily by the kinetic resolution of racemic **8** with baker's yeast,[17] with isohexyl iodide *via* the dianion of **8**[18] gave β-ketosulfoxide (**9**) in 72% yield. Reduction of **9** with DIBAL gave (Rc,Ss)-β-hydroxy sulfoxide (**10**) in 81% yield accompanied by the diastereomer (**11**) (6%). Pure **10** was subjected to the above alkylation reaction (Table 1, entry 2) and purification on silica gel TLC provided pure **12** in 46% yield. Reduction of β-hydroxy sulfoxide **12** with zinc-chlorotrimethylsilane (89%) and epoxidation[19] by trimethyloxonium fluoroborate-aq NaOH (75%) gave (7R,8S)-(+)-disparlure, $[\alpha]_D^{23}$ +0.6° (c 1.7, CCl_4), lit.[16] $[\alpha]_D^{21}$ +1.1°±0.5° (c 2.3, CCl_4). The enantiomer of natural (+)-disparlure, (7S,8R)-(-)-**7** was synthesized from β-hydroxy sulfoxide **11**, obtained by the reduction of **9** with DIBAL-$ZnCl_2$ (87%, the diastereomeric ratio of **11** : **10** = 33 : 1), in the similar manner in an overall yield of 46% *via* **13**, $[\alpha]_D^{23}$ -0.8° (c 2.2, CCl_4).

Thus, the α-alkylation of the dianions of β-hydroxy sulfoxides diastereoselectively affords *threo*-α-alkyl-β-hydroxy sulfoxides, which are useful precursors of optically active *cis*-epoxides.



(a) NaH-BuLi, then i-$C_6H_{13}I$; (b) DIBAL; (c) DIBAL-$ZnCl_2$; (d) MeLi, then n-$C_{10}H_{21}I$; (e) Zn-Me_3SiCl; (f) Me_3OBF_4, then NaOH aq

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