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Diastereoselective rhodium(II)-catalyzed sulfonium ylide formation-[2,3]-sigmatropic rearrangement reaction of chiral non-racemic allylic sulfides

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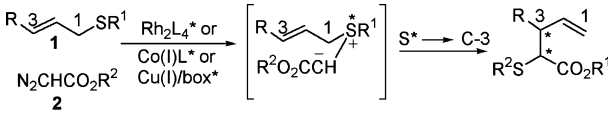
Abstract—The tandem sulfonium ylide formation-[2,3]-sigmatropic rearrangement reaction of chiral non-racemic secondary allylic sulfides, (*E*)-**9** and (*Z*)-**10**, is found to proceed with high diastereocontrol. The C-5 stereocenter bearing the sulfide group is essential for high diastereoselectivity in the reaction. Transition state conformers are proposed to explain the high diastereoselectivity in the formation of the diastereomeric products, **18a** and **18b**. The method is applied to the synthesis of (*R*)-4-(4-chlorophenyl)-2-butyrolactone. Modest enantioselectivity (63% ee) was achieved and this is attributed to partial racemization during the formation of the secondary allylic sulfide **22**.

1. Introduction

The [2,3]-sigmatropic rearrangement[1] of allylic sulfonium ylide intermediates,[2] is an important and widely used carbon–carbon bond forming reaction in organic synthesis. The rearrangement reaction involves a concerted, orbital symmetry-allowed, suprafacial process that generally proceeds with high stereoselectivity.

The use of asymmetric induction[3] to effect enantioselectivity and diastereoselectivity during bond formation in the allylic sulfonium ylide-[2,3]-sigmatropic rearrangement reaction is a topic of ongoing interest[4] and to this end, a number of approaches, including the use of allylic sulfides possessing a chiral auxiliary group on the sulfur atom,[4a–c] the use of sulfonium ylides with a stereochemically defined center either at the sulfonium atom[4d] or at the carbon bearing the sulfide moiety[4e,f] have been devised. Recent investigations[5] have been directed at the chiral metallocarbenoid-mediated tandem sulfonium ylide-[2,3]-sigmatropic rearrangement of allylic sulfides (Eq. (1)). The rearrangement reactions were generally found to proceed with modest to good diastereoselectivity. Enantioselectivity, however, was poor but can be enhanced either via the reaction of allylic sulfides **1** (R^1 = bulky group) and diazoacetates **2** (R^2 = bulky group)[5b,d–f] or via double asymmetric induction strategies involving a chiral catalyst and either **1** (R^1 = chiral auxiliary) or **2** (R^2 = chiral auxiliary).[5b,d] More importantly, the results from the studies of Katsuki, Hashimoto and Wang[5b,e,f] showed that the diastereoselectivity of the reactions of primary allylic sulfides is not catalyst dependent, which strongly suggested that the [2,3]-sigmatropic rearrangement involved a free sulfonium ylide intermediate as opposed to metal-stabilized one.[5c] Enantioselectivity, on the other hand, was determined by the degree of enantiodifferentiation of the two lone pairs of electrons on the sulfur atom in the sulfide moiety during the transfer of the carbene ligand from the chiral metallocarbenoid intermediate to the sulfide unit.



(1)

In connection with our investigations[6] on 1,2-relative induction[3b] during bond formation in Rh(II)–carbenoid mediated transformations, we have investigated the tandem sulfonium ylide formation-[2,3]-sigmatropic rearrangement of chiral non-racemic allylic sulfides typified by **6**, **9** and **10**. The dioxolanyl moiety has been found to be effective in providing good to high diastereocontrol in related sigmatropic rearrangements[7] and it was anticipated that similar levels of diastereocontrol

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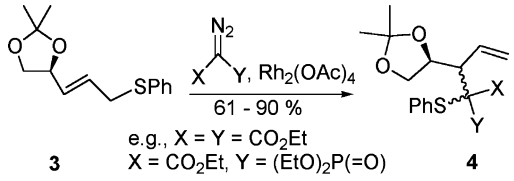
should be possible in the [2,3]-sigmatropic rearrangement in **6**, **9** and **10**. It should be pointed out that the sulfonium ylide-[2,3]-sigmatropic rearrangement reaction of the allylic sulfide **3** with diazo compounds catalyzed by $Rh_2(OAc)_4$ was briefly investigated by Takano and co-workers (Eq. (2)). The rearrangement was found to afford products **4** in modest to good chemical yields; however, the diastereoselectivity of the reaction was not reported.[8]



(2)

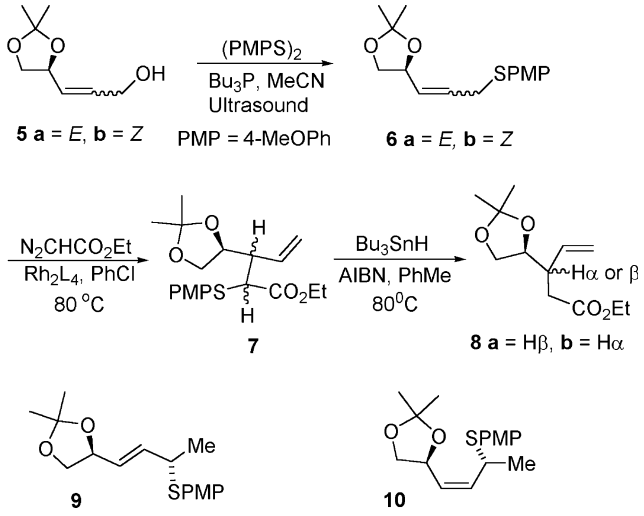
We report herein the details of our investigations into the tandem sulfonium ylide formation-[2,3]-sigmatropic rearrangement of chiral non-racemic allylic sulfides. Excellent diastereoselectivity is possible only with the use of secondary sulfides and the diastereoselectivity is controlled by the C-5 stereocenter that bears the sulfide moiety and not the dioxolanyl moiety of the starting material. The use of chiral Rh(II) catalysts did not result in any enhancement in the diastereoselectivity of the rearrangement reaction.

2. Results and discussion

As described above, the reaction depicted in Eq. (2) has been studied.[8] Interestingly, the same reaction of **3** with ethyl diazoacetate (EDA) was not explored. Our preliminary studies of the reaction of **3** with EDA showed the reaction to be inefficient; poor yields of the rearrangement product **4** (X = CO_2Et, Y = H; 11%) were obtained, and substantial amounts of maleate and fumarate, by-products formed via metallocarbenoid dimerization, were also produced. It was reasoned, in light of Takano's results, that the poor yield of the rearrangement product may be due to the inefficient interception of the Rh(II)–carbenoid intermediate by the sulfur atom of the phenylsulfide moiety because of the decreased electrophilicity of the metallocarbenoid carbon. It was decided to replace the phenylthio unit with a 4-methoxyphenylthio group because the nucleophilicity of the sulfur atom in the latter group should be enhanced due to the electron-donating effect of the 4-methoxy substituent. Therefore, the allylic sulfides **6a**,**b** were prepared and used in our initial studies.

2.1. Preparation of and [2,3]-sigmatropic rearrangement of allylic sulfides (*E*)-6a and (*Z*)-6b

The readily available, known[9] (*E*)- and (*Z*)-allylic alcohols **5a**,**b** were reacted with bis(4-methoxyphenyl)-disulfide[10] and tributylphosphine, under ultrasound irradiation (1.5 h), to afford high yields (86–92%) of the corresponding (*E*)- and (*Z*)-allylic sulfides **6a**,**b**, respectively (Scheme 1). The [2,3]-sigmatropic rearrangement reaction of **6a** catalyzed by $Rh_2(OAc)_4$ (5 mol %) was



Scheme 1.

investigated first. Benzene was initially chosen as the solvent because it is the most commonly used solvent for [2,3]-sigmatropic rearrangements of sulfonium ylides.[2] The reaction gave an improved yield (43%) of the rearrangement products **7**. Maleate and fumarate side-products as well as varying amounts of 1-carboethoxy-2,4,6-cycloheptatriene, which had resulted from the cycloaddition of the Rh(II)–carbenoid to the benzene ring,[11] were also obtained. Neither the cyclopropane product, which could have arisen from metallocarbenoid attack of the double bond nor products that could have formed from decomposition of oxonium ylide intermediates was observed. The use of chlorobenzene as solvent did result in a slight increase in the yield (48–52%) of **7**, but did not completely inhibit cycloheptatriene formation. Therefore, chlorobenzene was used as the solvent in subsequent experiments.

The rearrangement products **7** were obtained as an inseparable mixture of four diastereomers. In the ^1H NMR spectrum of the mixture, the diagnostic H-3 multiplet (ddd) for each of the four diastereomers appeared at δ 2.49, 2.67, 2.69 and 2.85. Due to extensive signal overlap in the ^1H NMR spectrum, no attempts were made to assign the stereochemistry at the newly created C-2 and C-3 stereocenters in each of the four diastereomers nor was it possible to ascertain the ratio of each of the four diastereomers. To facilitate the determination of the diastereoselectivity during the formation of the C-3 stereocenter, the diastereomeric mixture **7** was subjected to reductive desulfurization using Bu_3SnH.[12] This afforded two diastereomers **8a**,**b** having very similar polarity, which were separated by careful column chromatography. The less polar component (R_f = 0.32) was assigned structure **8a** and the more polar component (R_f = 0.25) was assigned structure **8b** on the basis of comparison of their ^1H and ^{13}C NMR data with those reported in the literature.[13] For the determination of the diastereomeric ratio of **8a**:**8b**, the ^1H NMR spectrum of **8a**,**b** was recorded in a 1:1.2 v/v $CDCl_3$:C_6D_6 solvent mixture.[14] This solvent mixture

was conducive for the resolution of some of the overlapping resonances in the spectrum. The integration of the two singlets, each of which were due to one of the methyl groups on the 1,3-dioxolanyl moieties of each of the diastereomers, at δ 1.36 (**8a**) and δ 1.34 (**8b**), gave the ratio of **8a**:**8b**. The results are collected in Table 1.

The $Rh_2(OAc)_4$-catalyzed reaction of (*E*)-**6a** showed no diastereoselectivity during the rearrangement, affording almost equal amounts of **8a** and **8b**. It is also interesting to compare this result to that of the related *ortho* ester Claisen rearrangement ($MeC(OEt)_3$, cat. $MeCH_2CO_2H$)[15] of the (*E*)-allylic alcohol of the type **5**, which was independently studied by Suzuki, Kametani et al.[16] and Mulzer et al.[13b] The former group reported a 3:1 ratio of **8a**:**8b** whereas the latter group obtained a 1:1 ratio of **8a**:**8b**. We therefore studied the reaction of (*Z*)-**6b** because it has been shown[7] in other related reactions that a (*Z*)-double bond generally provides enhanced diastereoselectivity. However, in our case, no diastereoselection was achieved; in fact, the ratio of **8a**:**8b** obtained with (*Z*)-**6b** was very similar to that realized with (*E*)-**6a** (entries 1 and 2).

Due to the poor diastereoselectivity observed with $Rh_2(OAc)_4$, we evaluated the use of the enantiomeric set of $Rh_2(MEPY)_4$ to determine whether the diastereoselectivity of the reaction can be enhanced through double stereoselection. Disappointingly, both chiral Rh(II) catalysts gave **8a** and **8b** in ratios that were very similar to those obtained with $Rh_2(OAc)_4$. More interestingly, the ratio of **8a**:**8b** obtained for the enantiomeric pair of catalysts are also very similar, and show the same preference for the formation of **8a** (entries 3 and 4).

The low diastereoselectivity of the sulfonium ylide-[2,3]-sigmatropic rearrangement involving allylic sulfides of the type **6** suggested that there was minimal 1,2-asymmetric induction from the adjacent dioxolanyl stereocenter during the key [2,3]-sigmatropic rearrangement step. This lack of diastereoselection led us to investigate the sulfonium ylide-[2,3]-sigmatropic rearrangement of chiral non-racemic secondary allylic sulfides **9** and **10** to ascertain whether higher diastereoselectivity can be achieved. It is pertinent to note that two previous studies on the [2,3]-sigmatropic rearrangement of secondary sulfides have been reported.[4e,f] However, in these studies the sulfonium ylides were generated by base-mediated deprotonation of sulfonium salts. The [2,3]-sigmatropic rearrangement of sulfonium ylides generated in situ from the reaction of secondary sulfides with EDA catalyzed by Rh(II) catalysts has not been investigated.

2.2. Preparation of allylic sulfides 9 and 10

The alcohol **12a** has been prepared[13a] by Mulzer and co-workers via reduction (diacetone glucose/9-BBN ate complex) of the enone **11a**. Since we also required alcohol **13a**, we decided to examine the asymmetric reduction of the enones **11a** and **11b**[9a] using the CBS method.[17] It was of concern to us at the outset that the presence of the chiral 1,3-dioxolanyl group in **11a** and **11b** would be detrimental to the diastereoselectivity of the reduction. We were pleased to find that our concerns were unfounded.

Thus, the asymmetric reduction of **11a** was studied first to develop the optimal reaction conditions for the reduction. It was found that the best conditions were (1) a reaction temperature of −20°C, (2) a reaction time of 30 min, and (3) a mole ratio of 1:0.6:0.6 for the **11a**:borane–methyl sulfide complex:(*S*)-2-methyl-CBS-oxazaborolidine (2-MeCBS) catalyst and under these conditions the allylic alcohols **12a** and **12b** were obtained in a combined yield of 90%. Both **12a** and **12b** have very similar polarity and were not readily sepa-

Table 1. Diastereoselectivity of [2,3]-sigmatropic rearrangement of **6a**,**b**, **9** and **10**[a]

Entry	Sulfide	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]	Relative yield (%)	
						8a:**8b**[c]	**20a**:**20b**[d]
1	(*E*)-**6a**	$Rh_2(OAc)_4$	PhCl	80	52	59:41	–
2	(*Z*)-**6b**	$Rh_2(OAc)_4$	PhCl	80	50	62:38	–
3	(*Z*)-**6b**	$Rh_2(5R\text{-MEPY})_4$	PhCl	80	48	56:44	–
4	(*Z*)-**6b**	$Rh_2(5S\text{-MEPY})_4$	PhCl	80	50	63:57	–
5	(*E*)-**9**	$Rh_2(OAc)_4$	PhCl	80	49	–	87:13
6	(*E*)-**9**	$Rh_2(OAc)_4$	PhCl	40	50	–	90:10
7	(*E*)-**9**	$Rh_2(OAc)_4$	PhCl	25	32	–	96:4
8	(*E*)-**9**	$Rh_2(OAc)_4$	CH_2Cl_2	40	54	–	97:3
9	(*E*)-**9**	$Rh_2(OAc)_4$	CH_2Cl_2	25	51	–	98:2
10	(*E*)-**9**	$Rh_2(5R\text{-MEPY})_4$	CH_2Cl_2	25	80	–	95:5
11	(*E*)-**9**	$Rh_2(5S\text{-MEPY})_4$	CH_2Cl_2	25	82	–	94:6
12	(*E*)-**9**	$Rh_2(Cap)_4$	CH_2Cl_2	25	89	–	95:5
13	(*Z*)-**10**	$Rh_2(OAc)_4$	CH_2Cl_2	25	65	–	99:1
14	(*Z*)-**10**	$Rh_2(Cap)_4$	CH_2Cl_2	25	90	–	98:2

[a] 5 mol % Rh(II) catalyst, 3 mol equiv. EDA in the appropriate dry solvent.
[b] Combined yield of diastereomeric products **7** or **18**.
[c] Ratio based on ^{1}H NMR integration of the methyl singlets at δ 1.36 (**8a**) and δ 1.34 (**8b**) of the dioxolanyl moiety in each of the diastereomers in the mixture **8**.
[d] Ratio based on GC analysis of **20**.

rated by column chromatography. Furthermore, the ^{1}H NMR spectrum of the mixture was not useful in that only a single set of signals could be observed. In order to determine the ratio of **12a**:**12b**, the mixture was converted to the benzyl ethers **14**, the ^{1}H NMR spectrum of which revealed two sets of signals. The diastereomeric ratio of **14a**:**14b** was found to be 88:12, based on integration of the H-1 double doublets centered at δ 3.56 (**14a**) and at δ 3.59 ppm (**14b**), which in turn provided the ratio for **12a**:**12b** (Scheme 2).

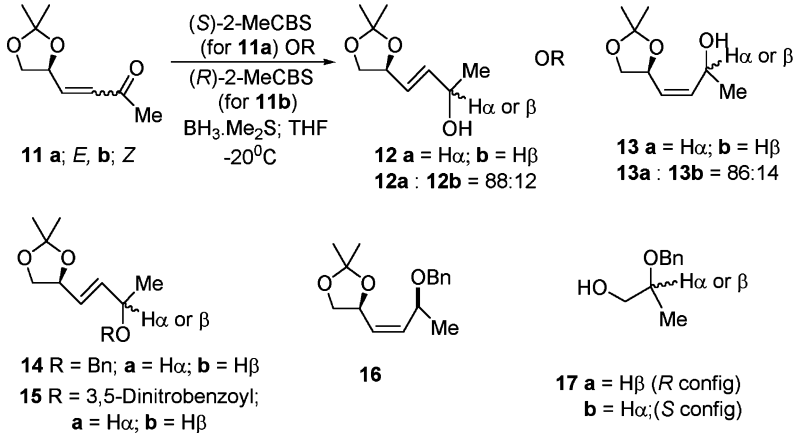
Since the mixture of **12a** and **12b** was very difficult to separate by column chromatography, the mixture was converted to the crystalline 3,5-dinitrobenzoate derivatives **15**. Fractional crystallization of the mixture **15** then gave an 86% yield of the pure diastereomer **15a** and subsequent base hydrolysis of **15a** regenerated the pure **12a** {$[\alpha]_D^{22}$ +24 (*c* 1.8, $CHCl_3$), lit.[18] +28 (*c* 1.4, $CHCl_3$)}. A sample of pure **12a** was converted to the benzyl ether **14a** and the ^{1}H NMR spectrum showed only one set of signals. The absolute configuration at C-5 in alcohol **12a** was confirmed as *R* by degradation to the known[19a] alcohol **17a**, whose specific rotation value {$[\alpha]_D^{22}$ −32 (*c* 0.3, $CHCl_3$), lit.[19a] −47 (*c* 1, $CHCl_3$)} had the same sign and magnitude to that reported in the literature.

For the preparation of the alcohol **13a**, the enone **11b** was reduced ($BH_3{\cdot}Me_2S$) in the presence of the (*R*)-2-MeCBS catalyst under the optimal conditions specified for **11a**. Compounds **13a**,**b** were obtained in a combined yield of 85%. GC analysis of the alcohol mixture showed the ratio of **13a** (t_R = 9.09 min):**13b** (t_R = 9.15 min) was 86:14. The mixture of alcohols **13a**,**b** was amenable to separation by careful column chromatography, which afforded pure diastereomer **13a** (58%). The configuration at C-5 in compound **13a** was confirmed as *S* by its conversion to the known **17b**,[19b] and comparison of its specific rotation value {$[\alpha]_D^{22}$ +44 (*c* 1.3, $CHCl_3$)} with that reported in the literature {$[\alpha]_D^{22}$ +48 (*c* 1.0, $CHCl_3$)}.

With the allylic alcohols **12a** and **13a** in hand, we investigated the preparation of the chiral non-racemic sulfides **9** and **10**. The ultrasound-mediated Mitsunobu reaction that worked very well for the conversion of **5a**,**b**→**6a**,**b** was found to be ineffective for the preparation of **9** from **12a** as substantial amounts of the starting **12a** remained after reaction times of 1.5 and 22 h. Conducting the same reaction at a temperature of 60°C (ultrasound water bath) was also fruitless. After many attempts at varying the reaction conditions (e.g. solvent, phosphine) it was found that a good yield (81%) of **9** was obtained when *freshly prepared* bis(4-methoxyphenyl)disulfide was used with tributylphosphine, and toluene (reflux) was employed as the solvent. Application of the same method to **13a** led to a 90% yield of the sulfide **10**. It is noteworthy that S_N2' reaction products were not detected under these reaction conditions.

2.3. [2,3]-Sigmatropic rearrangement reaction of 9 and 10

The reactions of **9** and **10** with EDA in the presence of Rh(II) catalysts (5 mol%) in chlorobenzene and dichloromethane were studied. Unlike the reaction of the primary allylic sulfides **6a**,**b** the sulfonium ylide-[2,3]-sigmatropic rearrangement reaction of **9** and **10** led to the formation of a mixture of only two diastereomers as evidenced by the presence of the characteristic H-3 resonances, one centered at δ 2.36 (ddd) and the other at δ 2.70 (ddd), of the diastereomers. For characterization purposes, the diastereomeric mixture from the $Rh_2(OAc)_4$-catalyzed rearrangement of **9**, were carefully separated by column chromatography to provide pure **18a** (less polar, R_f = 0.38) and **18b** (more polar, R_f = 0.25). Analysis of the ^{1}H NMR spectra of **18a**,**b** permitted assignment of the H-3 resonance at δ 2.36 to **18a** and the one at δ 2.70 to **18b**. Furthermore, the vicinal coupling constant of the H-2 doublet in **18a** and **18b** was found to be 8.8 and 10.3 Hz, respectively. This suggests that the relative stereochemistry of H-2 and H-3 in **18a** is synclinal (θ = 53°) and in **18b** they have an antiperiplanar (θ = 175°) relationship.[20] Other salient features in the ^{1}H NMR spectra were the resonances due to H-4 and the olefinic hydrogens. In **18a** the H-4 signal was deshielded and occurred at δ 4.72



Scheme 2.

whereas in **18b**, the same proton was shielded and resonated in the region δ 3.91–4.08. The olefinic hydrogens in **18a**,**b** exhibited large coupling constants, $J=14$–15.7 Hz, which indicated that the double bonds in **18a**,**b** had *E*-stereochemistry (Scheme 3).

It is useful to note that with $Rh_2(OAc)_4$ and $Rh_2(Cap)_4$ as catalysts, the rearrangement of **9** resulted in the formation of **18a**:**18b** in a ratio of 1:1.6–2.3. For compound **10**, however, its rearrangement catalyzed by $Rh_2(OAc)_4$ gave **18a** and **18b** in a 1:4 ratio, but this trend was reversed with $Rh_2(Cap)_4$ where the **18a**:**18b** ratio was 2:1. This latter outcome is intriguing and suggests that the diastereoselection at C-2 may be influenced somewhat by the $Rh_2(Cap)_4$ catalyst. Presently, we do not have a satisfactory explanation for this observation.

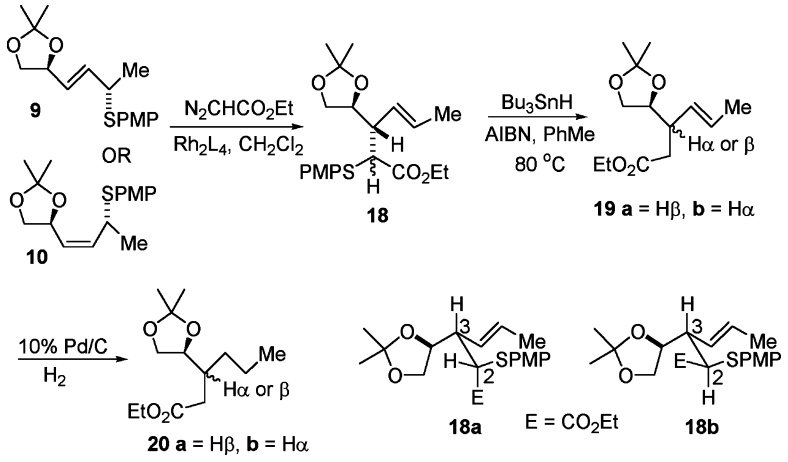
The products **18** were subjected to reductive desulfurization using Bu_3SnH. The ^1H NMR spectrum of the desulfurized product **19** indicated that only one diastereomer was present. The diastereomer was assigned structure **19a** by comparison of its ^1H and ^{13}C NMR data with literature values.[13a] This result also confirmed that the diastereomers **18a**,**b** differed only in the stereochemistry at C-2 and indicated that there was excellent and complete transfer of chirality from the C-5 stereocenter in **9** and **10** to the newly formed C-3 stereocenter in product **18**. The diastereocontrol during the formation of the C-2 stereocenter was modest at best.

To facilitate the determination of the diastereoselectivity of the reaction of **9** and **10**, ester **19a** was hydrogenated to obtain **20a**, which was subjected to GC–MS analysis. The chromatogram showed two well resolved peaks; a major peak at $t_R=17.3$ min was attributed to **20a**, whereas a minor peak at $t_R=17.1$ min was ascribed to **20b** (not detected by ^1H NMR). Each of these compounds showed m/z 229 (M−15) peaks in their mass spectra. All the rearrangement products in subsequent reactions were first transformed to **20a**,**b**, which were then analyzed by GC to ascertain the degree of diastereocontrol during the formation of the new C-3 stereocenter. The results are summarized in Table 1.

From Table 1, it is clear that the reaction of secondary sulfide **9** with EDA, under the optimal reaction conditions (PhCl, 80°C) used for compounds **6**, gave significantly higher diastereoselectivity (entries 1 and 5). However, the combined yield of the rearrangement products **7** and **18** was the same in both cases. It is noteworthy that in chlorobenzene, the cycloheptatriene product that would result from the cycloaddition reaction of the metallocarbenoid with chlorobenzene was not detected. Temperature effects were also evident: At 40°C, an increase in the diastereoselectivity was achieved, but the chemical yield of the products remained the same. On the other hand, the room temperature (25°C) reaction afforded substantially higher diastereoselectivity, but at the expense of chemical yield (entries 6 and 7). The increased diastereoselectivity observed with chlorobenzene at 40°C prompted us to evaluate dichloromethane as a solvent. We were pleased to find that in dichloromethane, the diastereoselectivity of the reaction remained consistently high and was not influenced by reaction temperature (entries 8 and 9).

A similar degree of and the same sense of diastereoselection was realized with the chiral catalysts, Rh_2[(5*R*)-MEPY]$_4$ and Rh_2[(5*S*)-MEPY]$_4$ (entries 10 and 11). These results are in accord with those obtained with **8a** and, collectively, they strongly indicate that the key [2,3]-sigmatropic rearrangement step involved a free sulfonium ylide intermediate.[5b,e,f] This line of reasoning was confirmed with the use of the achiral catalyst $Rh_2(Cap)_4$, which afforded an almost identical ratio of **20a**:**20b** (entries 10, 11 and 12) as well as the same sense of diastereoselection.

It is also interesting to note that the reaction of **9** catalyzed with $Rh_2(OAc)_4$ proceeded with slightly higher diastereoselectivity than those catalyzed using either Rh_2[(5*R*)-MEPY]$_4$, Rh_2[(5*S*)-MEPY]$_4$ or $Rh_2(Cap)_4$; however, the chemical yields of the products obtained with $Rh_2(OAc)_4$ are lower than those with the Rh(II) carboximidates (entries 8–12).



Scheme 3.

The influence of the double bond geometry in the secondary allylic sulfide on the diastereoselectivity of the rearrangement reaction was studied next. Our experience with the rearrangement of the primary sulfides indicated that there was no significant improvement in the diastereoselectivity of the reaction when the (*Z*)-allylic sulfide **6b** (entries 1 and 4) was used. In the case of (*Z*)-**10**, however, we were pleased to find that high diastereoselectivity was achieved with both $Rh_2(OAc)_4$ and $Rh_2(Cap)_4$ (entries 13 and 14).

2.4. Reaction pathway

The overall results suggest that the 1,3-dioxolanyl moiety is ineffective for 1,2-relative induction in the sulfonium ylide rearrangement and furthermore, chiral Rh(II) catalysts have no effect on the diastereoselectivity of the reaction. The C-5 stereocenter bearing the sulfide unit in **9** and **10** was found to be a critical and dominant factor that is essential for high diastereoselectivity during the formation of the new stereocenter at C-3. These findings are important in the context of the synthesis, because the stereochemical information is completely transferred from the C-5 stereocenter of the sulfide to the new C-3 stereocenter in the product, and occurred independently of the dioxolanyl stereocenter located on the carbon directly adjacent to the reacting prochiral C-3 carbon.

The results of the rearrangement reactions of the primary and secondary sulfides, **6**, **9** and **10**, indicate that free sulfonium ylide intermediates were involved. The poor diastereoselectivity of the reaction of the primary sulfides (*E*)-**6a** and (*Z*)-**6b**, suggests that the **6a**-derived sulfonium ylide intermediate underwent sigmatropic rearrangement via all four transition states (**TS**) **A**, **A**′, **B**, **B**′ (R = H, Fig. 1*E*) and the **6b**-derived sulfonium intermediate via **TS-C**, **C**′, **D**, **D**′ (R = H, Fig. 1*Z*). In the case of the secondary sulfides (*E*)-**9** and (*Z*)-**10**, excellent diastereocontrol during the rearrangement was achieved. Furthermore, only two diastereomers were present in the product **18**, which differed only in the stereochemistry at C-2. These results suggest that for (*E*)-**9** and (*Z*)-**10**, only **TS-A** and **A**′ (R = Me, Fig. 1*E*) and **TS-C** and **C**′ (R = Me, Fig. 1*Z*) are involved, respectively. The minor diastereomer **18a** was formed via **TS-A**′ and **C**′ and the major diastereomer **18b** was generated via **TS-A** and **C**. In all these **TS**s, the methyl group occupies the sterically less demanding pseudo-equatorial position in the five-membered envelope[21] **TS**s. The **TS**s **B**, **B**′ and **D**, **D**′ are higher in energy and are not involved; **B** and **B**′ are destabilized by an allylic $A^{1,3}$ strain[22] between the pseudoaxial methyl group and the olefinic hydrogen, and **D** and **D**′ are destabilized by the steric interaction between the pseudoaxial methyl group and the dioxolanyl moiety.

2.5. Synthesis of (*R*)-4-(4-chlorophenyl)-2-butyrolactone

The excellent stereocontrol that is possible during bond formation in the sulfonium ylide rearrangement of the chiral non-racemic secondary allylic sulfide systems encouraged us to apply the method to the synthesis of (*R*)-4-(4-chlorophenyl)-2-butyrolactone **25**, a key intermediate used in the synthesis of the muscle relaxant and $GABA_B$ receptor agonist (*R*)-balcofen.[23]

The known[24] allylic alcohol **21** was prepared from the (*E*)-4-(4-chlorophenyl-3-buten-2-one[25] via reduction with borane-dimethylsulfide catalyzed by (*S*)-2-MeCBS. Under the usual optimized reaction conditions (vide supra), a 78% ee (Chiralpak AD) of the product **21** was realized. However, upon further investigations it was found that if the time of addition of the enone to the borane–catalyst mixture was increased to 1 h, the ee of the alcohol **21** was increased to 92%. A 98% ee was achieved when the addition time was increased to 3.5 h.

Treatment of the alcohol **21** (98% ee) with bis(*p*-methoxyphenyl) disulfide using the above described procedure (e.g. **12a**→**9**) yielded the secondary sulfide **22**[26] (81%). The Rh(II)-catalyzed reaction of **22** with EDA provided a mixture of diastereomers **23** that was not separated, but was subjected to direct reductive desulfurization to give **24** along with a very small amount of an unidentified impurity (^{1}H NMR). Attempts to further purify **24** by repeated chromatography were unsuccessful because the impurity co-eluted with **24**. The double bond in **24** was ozonized and then reduced with sodium borohydride to give the corresponding primary alcohol, which was subjected to lactonization, catalyzed by *p*-toluenesulfonic acid (PTSA), to form the target 2-butyrolactone **25** in 72% yield. Chiral HPLC analysis of **25**, however, indicated an ee of 63%. The low enantioselectivity was unexpected and surprising in light of the fact that the starting alcohol

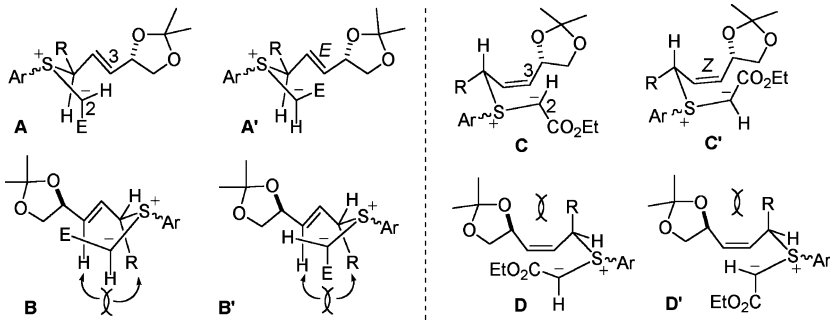
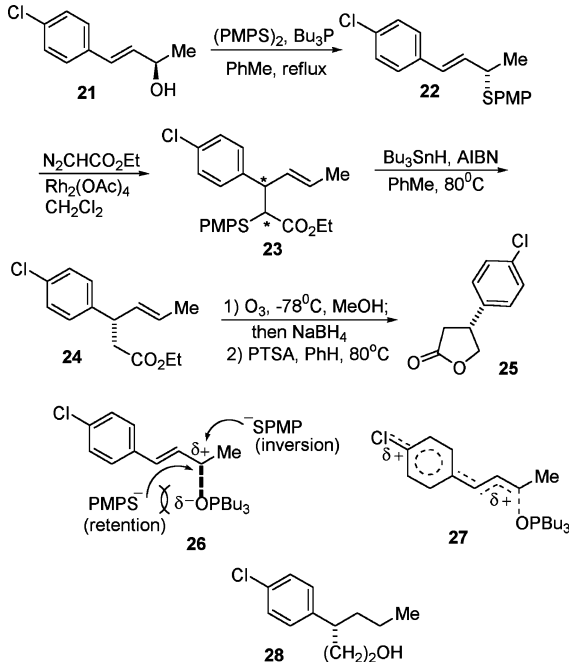


Figure 1.

21 had an ee of 98% and the fact that we have shown that complete transfer of chirality was achieved for the secondary sulfides **9** and **10** (vide supra). We reasoned that partial racemization (~36%) of the C-2 stereocenter must have occurred during the preparation of the sulfide **22** from the alcohol **21**. This may involve the participation of a solvent caged ion pair **26**, under the Mitsonobu reaction conditions, which would lead to the formation of **22** (the product of inversion) as the major product and its enantiomer (the product of retention) as the minor product. The formation of the ion pair is facilitated by resonance stabilization of the carbocation intermediate **27**.[27] We did not detect any S_N2' product resulting from attack at the benzylic position. The primary alcohol **28** was prepared from the desulfurized product **24** and chiral HPLC analysis (Chiralcel OD) showed its ee was 66%. This result further supports the notion that partial loss of stereochemical information at C-2 occurred at the sulfide formation step (Scheme 4).

3. Conclusions

The chiral dioxolanyl moiety that has served well as a diastereocontrol group in other systems was found to be ineffective in the tandem sulfonium ylide-[2,3]-sigmatropic rearrangement of the primary and secondary allylic sulfides **6**, **9** and **10**. The rearrangement reaction was found to involve free sulfonium ylide intermediates and high diastereoselectivity was observed only for the chiral non-racemic secondary sulfides **9** and **10**. In these cases, excellent and complete transfer of chirality (C-5-substrate→C-3-product) was realized. The method was used in the synthesis of (*R*)-4-(4-chlorophenyl)-2-butyrolactone, which was obtained in 63% ee. The modest enantioselectivity was due to partial racemization during the formation of the secondary allylic sulfide **22**. Nevertheless, the method developed here should find application in synthesis. Other methods, which obviate partial racemization during sulfide formation, are currently being investigated. These studies will be reported in the future.



Scheme 4.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot-stage melting point apparatus and were uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1600FT infra-red spectrophotometer and only diagnostic signals are reported. NMR spectra were obtained on a Bruker AC200 QNP spectrometer; chemical shifts are given in parts per million (δ) relative to the appropriate reference signal. ^{1}H NMR spectra were obtained at 200 MHz in $CDCl_3$ using tetramethylsilane ($\delta_H = 0.00$) or $CHCl_3$ ($\delta_H = 7.26$) as reference. Where appropriate, double irradiation experiments were used for proton assignments. ^{13}C NMR spectra were obtained at 50.32 MHz in $CDCl_3$ using $CDCl_3$ ($\delta_C = 77.00$) as reference. Optical rotations were measured on an Optical Activity (AA-5) polarimeter at the sodium D line ($\lambda = 589$ nm). High resolution mass spectra and elemental analyses were performed at the Department of Chemistry, University of Saskatchewan. Gas chromatography (30 m× 0.25 m×0.25 μm SPB™-5 capillary column) was carried out with a Hewlett–Packard Model 5890 Series II Gas Chromatography equipped with a flame ionization detector. GC–MS was carried out with a Hewlett–Packard Model 5890 Gas Chromatography (30 m×0.25 m× 0.25 μm SPB™-5 capillary column) equipped with a Hewlett–Packard 5970A Series Mass Selective Detector (70 eV ionization energy). Reaction progress was monitored by thin-layer chromatography performed on Merck® silica gel 60_{F254} precoated (0.25 mm) on aluminum-backed sheets. Flash chromatography was performed on Merck® silica gel 60 (230–400 mesh). Petroleum ether used is the fraction with bp 35–60°C. Ultrasound-mediated reactions were done in a Sonogen® Automatic Cleaner (Model D-100, Branson Instruments, Inc) with a frequency of 33 kHz and average power output of 100 W. All air and moisture sensitive reactions were carried out under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Acetone was dried by distillation over $KMnO_4$. CH_2Cl_2, $Cl(CH_2)_2Cl$, CH_3CN, toluene, benzene, pyridine and Et_3N were dried by distillation over CaH_2. MeOH was dried by distillation over magnesium methoxide (unless otherwise noted). THF was dried by distillation over sodium using sodium benzophenone ketyl as an indicator. HPLC was performed using a Waters 600 pump equipped with a Waters 2487 UV detector ($\lambda = 254$ nm) and interphased to a Millenium^{32} PC workstation. Allylic alcohols **6a**,**b** were prepared according to literature procedures.[9] $Rh_2(Cap)_4$ [dirhodium(II) tetrakis(caprolactamate)] was prepared according to literature procedures, (*R*)- and (*S*)-

$Rh_2(MEPY)_4$ [dirhodium(II) tetrakis(methyl 2-pyrrolidinone-5-carboxylate)] were purchased from Aldrich.

4.2. (2*S*,3*E*)-1,2-Dihydroxy-1,2-*O*-isopropylidene-5-(4-methoxyphenylthio)-3-pentene, 6a

The alcohol **5a** (78 mg, 0.49 mmol) and freshly made bis(4-methoxyphenyl) disulfide (178.5 mg, 0.64 mmol) were dissolved in dry MeCN (12 mL). Bu_3P (299.3 mg, 1.48 mmol) was added to the above solution and the reaction mixture was immersed in an ultrasound water bath. The reaction mixture was sonicated at rt for 1.5 h. It was then diluted with CH_2Cl_2 (30 mL), washed with 10% aqueous NaOH solution (2×10 mL) then brine (2×10 mL), dried, filtered and evaporated. The residue was subjected to column chromatography (20:1 pet. ether:ether and then 4:1 v/v pet. ether:ether) to yield the sulfide **6a** (118.7 mg, 86%). $[\alpha]_D^{22}$ +40.2 (*c* 3.5, $CHCl_3$). IR ν_{max}: 1592 cm^{-1}. ^1H NMR δ: 1.36 (s, 3H, O-C-Me), 1.37 (s, 3H, O-C-Me), 3.34–3.44 (m, 3H, H-1, 2H-5), 3.80 (s, 3H, OMe), 3.98 (dd, 1H, $J=8.6$, 6.9 Hz, H-1), 4.37–4.50 (m, 1H, H-2), 5.27–5.40 (m, 1H, H-3), 5.71–5.88 (m, 1H, H-4), 6.78–7.37 (m, 4H, ArH). ^{13}C NMR δ: 25.8, 26.6, 38.1, 55.3, 69.3, 76.3, 109.5, 114.4, 129.8, 130.6, 134.5, 159.3. HRMS calcd for $C_{14}H_{18}SO_3$ 280.1133, found 280.1129.

4.3. (2*S*,3*Z*)-1,2-Dihydroxy-1,2-*O*-isopropylidene-5-(4-methoxyphenylthio)-3-pentene, 6b

The sulfide **6b** was prepared, as described for **6a**, starting from **5b** (351.8 mg, 2.22 mmol), freshly made bis(4-methoxyphenyl) disulfide (742.9 mg, 2.67 mmol), Bu_3P (1.13 g, 5.56 mmol) in MeCN (12 mL). Yield of **6b** (20:1 pet. ether:ether and then 4:1 v/v pet. ether:ether) was 576.8 mg, 92%. $[\alpha]_D^{22}$: −86.1 (*c* 0.9, $CHCl_3$). IR ν_{max}: 1591 cm^{-1}. ^1H NMR δ: 1.31 (s, 3H, O-C-Me), 1.36 (s, 3H, O-C-Me), 3.27 ('t', 1H, $J=9.2$ Hz, H-1), 3.37 (ddd, 1H, $J=15.3$, 8.8, 1.5 Hz, H-5), 3.57 (ddd, 1H, $J=15.2$, 10.6, 1.1 Hz, H-5), 3.62 (dd, 1H, $J=9.9$, 8.1 Hz, H-1), 3.80 (s, 3H, OMe), 4.40–4.56 (m, 1H, H-2), 5.27–5.52 (m, 1H, H-3), 5.63–5.80 (m, 1H, H-4), 6.72–7.37 (m, 4H, ArH). ^{13}C NMR δ: 25.9, 26.7, 33.8, 55.4, 69.1, 71.4, 109.2, 114.5, 125.0, 129.8, 129.8, 134.5, 159.6. HRMS calcd for $C_{14}H_{18}SO_3$ 280.1133, found 280.1135.

4.4. (2*S*,3*E*)-1,2-Dihydroxy-1,2-*O*-isopropylidene-3-hexen-5-ol, 12

The enone **11a** (988 mg, 5.80 mmol, dried by azeotropic distillation with dry benzene) in THF (10 mL) was added dropwise via cannula to a solution of BH_3–Me_2S (2.0 M solution in THF, 1.75 mL, 3.48 mmol), (S)-2-methyl-CBS-oxazaborolidine (1 M solution in toluene, 3.50 mL, 3.48 mmol) and THF (60 mL) at −20°C. The reaction was quenched after 30 min with cold dry methanol (10 mL) at −20°C. Saturated aqueous $NaHCO_3$ (20 mL) was added 10 min later and the mixture turned milky white. The mixture was extracted with Et_2O (20 mL×3). The combined organic phases were washed with brine (20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was subjected to flash column chromatography (from 5:1 v/v pet. ether:ether to 1:1 v/v pet. ether:ether) to give the alcohol **12** (896 mg, 90%). IR ν_{max}: 3695–3084 cm^{-1}. ^1H NMR (signals of diastereomers were indistinguishable) δ: 1.24 (d, 3H, $J=6.8$ Hz, H-6), 1.34 (s, 3H, O-C-Me), 1.39 (s, 3H, O-C-Me), 1.61 (s, 1H, -OH), 3.54 (dt, 1H, $J=8.4$, 8.4, 1.0 Hz, H-1), 4.05 (ddd, 1H, $J=8.8$, 6.7, 0.8 Hz, H-1), 4.22–4.39 (m, 1H, H-5), 4.47–4.53 (m, 1H, H-2), 5.61 (dd, 1H, $J=15.4$, 7.4 Hz, H-3), 5.83 (dd, 1H, $J=15.3$, 5.8 Hz, H-4). ^{13}C NMR δ: discernible signals for minor diastereomers in brackets, 23.0, (23.2), (25.7), 25.8, (26.5), 26.6, (66.2), 67.8, 69.3, (68.0), (72.2), 76.4, 112.4, 126.8, (128.3), (136.6), 138.4.

The diastereomeric mixture of **12a**,**b** was converted (NaH, $PhCH_2Br$, cat. Bu_4NI) to the corresponding benzyl ether **14**. The ^1H NMR spectrum of **14a**,**b** showed two sets of signals. Integration of the H-1 double doublets centered at δ 3.56 (**14a**) and at δ 3.59 ppm (**14b**) gave an 88:12 ratio of **14a**:**14b**. Data for benzyl ether **14a**,**b**: IR: 3064, 3031, 1496, 1454, 1372 cm^{-1}. ^1H NMR δ (discernible signals for minor diastereomers in square brackets): 1.20 (d, 3H, $J=6.9$ Hz, H-6), [1.21 (d, $J=6.9$ Hz)], 1.41 (s, 3H, O-C-Me), 1.44 (s, 3H, O-C-Me), 3.56 (dd, 1H, $J=8.0$, 7.4 Hz, H-1), [3.59 (dd, $J=8.6$, 8.1 Hz)], 3.88–4.00 (m, 1H, H-5), 4.02 (dd, 1H, $J=8.6$, 7.1 Hz, H-1), 4.31 (d, 1H, $J=11.9$ Hz, O-CH-Ph), [4.30 (d, $J=12.5$ Hz)], 4.40–4.53 (m, 2H, H-2, O-CH-Ph), 5.49–5.76 (m, 2H, H-3, H-4), 7.13–7.33 (m, 5H, ArH).

4.5. (2*S*,5*S*,3*Z*)-1,2-Dihydroxy-1,2-*O*-isopropylidene-3-hexen-5-ol, 13a

Compound **13** was prepared, following the procedure used for the formation of **12**, from enone **11b** (942 mg, 5.53 mmol), BH_3–Me_2S (2.0 M solution in THF, 1.66 mL, 3.32 mmol) and (*R*)-2-methyl-CBS-oxazaborolidine (1 M solution in toluene, 3.32 mL, 3.32 mmol). Yield of **13** was 801 mg (85%). GC analysis (inlet temperature: 200°C, detector temperature: 300°C, oven temperature: 80°C, 2 min; 80–100°C, 1°C/min ramp) of **13** revealed two well resolved peaks at $t_R=9.09$ min (**13a**) and at $t_R=9.15$ min (**13b**). Integration of the GC peak areas provided the **13a**:**13b** ratio of 86:14. The diastereomeric mixture was carefully separated using flash column chromatography (1:1 v/v pet. ether:ether) to give pure **13a** (552 mg, 58%) as a white solid, mp 49–51°C. $[\alpha]_D^{22}$: +18.6 (*c* 2.6, $CHCl_3$). IR ν_{max}: 3554–3248 cm^{-1}. ^1H NMR δ: 1.21 (d, 3H, $J=6.9$ Hz, H-6), 1.37 (s, 3H, O-C-Me), 1.40 (s, 3H, O-C-Me), 2.50 (s, 1H, -OH), 3.52 (dd, 1H, $J=8.7$, 8.6 Hz, H-1), 4.04 (dd, 1H, $J=9.2$, 7.1 Hz, H-1), 4.57–4.73 (m, 1H, H-5), 4.79–4.93 (m, 1H, H-2), 5.42 (dd, 1H, $J=11.9$, 8.9 Hz, H-3), 5.63 (dd, 1H, $J=12.0$, 9.3 Hz, H-4). ^{13}C NMR δ: 23.5, 25.9, 26.7, 63.7, 69.4, 71.7, 109.4, 127.5, 138.6.

A small sample of **13a** (50 mg, 0.29 mmol) was converted to the benzyl ether **16** (60 mg, 79%). $[\alpha]_D^{22}$: −19.1 (*c* 2.9, $CHCl_3$). IR ν_{max}: 1454, 1370 cm^{-1}. ^1H NMR δ: 1.23 (d, 3H, $J=6.8$ Hz, ME), 1.38 (s, 3H, O-C-Me), 1.43 (s, 3H, O-C-Me), 3.52 (dd, 1H, $J=8.3$, 7.8 Hz, H-1), 3.97 (dd, 1H, $J=8.6$, 7.0 Hz, H-1), 4.27 (ddd, 1H,

$J=7.6$, 7.1, 1.4 Hz, H-5), 4.38 (d, 1H, $J=13.3$ Hz, OCHPh), 4.62 (d, 1H, $J=13.6$ Hz, OCHPh), 4.65–4.79 (m, 1H, H-2), 5.54–5.70 (m, 2H, H-3, H-4), 7.23–7.39 (m, 5H, ArH). ^{13}C NMR δ: 22.0, 25.9, 26.7, 69.3, 69.9, 71.8, 109.4, 127.5, 127.8, 128.3, 129.5, 136.3, 138.5. HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1571.

4.6. Confirmation of absolute configuration of 12a and 13a

Ozone was bubbled into a solution of benzyl ether **14a**,**b** (60 mg, 0.229 mmol) or **16** (52 mg, 0.20 mmol) in methanol (10 mL) at −78°C for 46 s. The reaction mixture was warmed to 0°C and $NaBH_4$ (26 mg, 0.686 mmol) was added. After stirring for 1 h, the reaction mixture was warmed to rt. The reaction was monitored by TLC and when the reaction was complete glacial AcOH (2 drops) was added to destroy excess $NaBH_4$. 50% $NaHCO_3$ aqueous solution was used to neutralize the mixture. After the solvent was evaporated, the residue was subjected to flash column chromatography (1:1 v/v pet. ether:ether) to obtain the product: (*R*)-**17a** (30 mg, 80%) or (*S*)-**17b** (27.5 mg, 85%).

4.6.1. (*R*)-2-Benzyloxy-1-propanol, 17a. $[\alpha]_D^{22}$: −32 (*c* 0.3, $CHCl_3$) {lit.[19a] −47 (*c* 1.0, $CHCl_3$)}. IR ν_{max}: 3601–3143, 3063, 3031, 1453, 1375 cm^{-1}. ^{1}H NMR δ: 1.16 (d, 3H, $J=5.8$ Hz, -Me), 2.20 (s, 1H, -OH), 3.45–3.76 (m, 3H, -CH_2-CH-), 4.50 (d, 1H, $J=11.4$ Hz, -OCHPh), 4.66 (d, 1H, $J=11.4$ Hz, -OCHPh), 7.22–7.40 (m, 5H, ArH). ^{13}C NMR δ: 15.8, 66.3, 70.7, 75.5, 127.7, 127.7, 128.4, 128.4, 138.4. HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0996.

4.6.2. (2*S*)-2-Benzyloxy-1-propanol, 17b. $[\alpha]_D^{22}$: +44 (*c* 1.3, $CHCl_3$) {lit.[19b] +48.0 (*c* 6.4, $CHCl_3$)}. IR ν_{max}: 3601–3143, 3063, 3031, 1453, 1375 cm^{-1}. ^{1}H NMR δ: 1.18 (d, 3H, $J=5.9$ Hz, -Me), 2.41 (bs, 1H, -OH), 3.45–3.77 (m, 3H, -CH_2-CH-), 4.49 (d, 1H, $J=11.5$ Hz, -OCHPh), 4.67 (d, 1H, $J=11.5$ Hz, -OCHPh), 7.20–7.45 (m, 5H, ArH). ^{13}C NMR δ: 15.8, 66.3, 70.7, 75.5, 127.7, 127.7, 128.4, 138.0.

4.7. Obtaining pure (2*S*,5*R*,3*E*)-1,2-dihydroxy-1,2-*O*-isopropylidene-3-hexen-5-ol, 12a

4.7.1. (1) Preparation of 3,5-dinitrobenzoate derivative 15a,b. The alcohol **12a**,**b** (900 mg, 5.23 mmol) and DMAP (63.9 mg, 0.523 mmol) were dissolved in CH_2Cl_2 (20 mL) and were cooled to 0°C. Et_3N (5 mL) was added to the solution and it was stirred for 10 min. 3,5-Dinitrobenzoyl chloride (1.57 g, 6.79 mmol) in CH_2Cl_2 (10 mL) was added via cannula to the above mixture. The solution turned initially orange then brown. The reaction mixture was slowly warmed to rt and then stirred overnight. The reaction mixture was washed with saturated $NaHCO_3$, brine, dried with anhydrous Na_2SO_4, filtered, evaporated and subjected to flash column chromatography (2:1 pet. ether:ether) to give a light yellow solid (1.38 g, 72%). The diastereomeric mixture was subjected to fractional recrystallization (3:1 v/v pet. ether:EtOAc) to obtain the major (5*R*)-**15a** (1.19 g, 86%). mp: 88–89.5°C. $[\alpha]_D^{21}$: −3.5 (*c* 9.9, $CHCl_3$). IR ν_{max}: 3104, 1729, 1629, 1547 cm^{-1}. ^{1}H NMR δ: 1.37 (s, 3H, O-C-Me), 1.42 (s, 3H, O-C-Me), 1.51 (d, 3H, $J=6.4$ Hz, Me), 3.59 (dd, 1H, $J=7.8$, 7.6 Hz, H-1), 4.12 (dd, 1H, $J=8.2$, 6.4 Hz, H-1), 4.52 (m, 1H, H-5), 5.62–6.02 (m, 3H, H-2, H-3, H-4), 9.12 (d, 2H, $J=2.0$ Hz, Ar-H), 9.21 (t, 1H, $J=2.0$ Hz, Ar-H), ^{13}C NMR δ: 19.9, 25.7, 26.5, 29.6, 69.2, 73.0, 75.9, 109.6, 122.3, 129.4, 131.0, 131.6, 134.1, 148.6, 161.6. Anal. calcd for $C_{16}H_{18}N_2O_8$: C, 54.46; H, 4.95; N, 7.65. Found: C, 52.50; H, 5.11; N, 7.57.

4.7.2. (2) Base hydrolysis of derivative 15a. The ester **15a** (300 mg, 0.819 mmol) was dissolved in methanol (10 mL) and powdered K_2CO_3 (170 mg, 1.23 mmol) was added. The pink solution was stirred at rt for 20 h. The solvent was then evaporated and the residue was taken into CH_2Cl_2 (20 mL), washed with brine (2×5 mL), dried, concentrated. Purification by flash column chromatography (1:1 v/v pet. ether:ether) yielded pure alcohol **12a** (140 mg, 100%). $[\alpha]_D^{22}$: +24 (*c* 1.8, $CHCl_3$) {lit.[18] +28 (*c* 1.4)}. IR ν_{max}: 3695–3085 cm^{-1}. ^{1}H NMR δ: 1.24 (d, 3H, $J=6.6$ Hz, Me), 1.35 (s, 3H, O-C-Me), 1.39 (s, 3H, O-C-Me), 1.97 (s, 1H, -OH), 3.55 (dd, 1H, $J=8.1$, 8.0 Hz, H-1), 4.05 (dd, 1H, $J=8.1$, 6.6 Hz, H-1), 4.22–4.37 (m, 1H, H-5), 4.40–4.53 (m, 1H, H-2), 5.61 (dd, 1H, $J=15.4$, 7.8 Hz, H-3), 5.83 (dd, 1H, $J=15.6$, 5.5 Hz, H-4). ^{13}C NMR δ: 23.0, 25.8, 26.6, 67.7, 69.3, 76.4, 109.0, 126.9, 138.4. A small sample of pure **12a** was converted to the benzyl ether **14a** for further characterization. Its NMR data showed only one set of signals. $[\alpha]_D^{22}$: +59.4 (*c* 0.8, $CHCl_3$). IR ν_{max}: 1454, 1370 cm^{-1}. ^{1}H NMR δ: 1.20 (d, 3H, $J=6.8$ Hz, Me), 1.32 (s, 3H, O-C-Me), 1.37 (s, 3H, , O-C-Me), 3.49 ('t', 1H, $J=8.6$ Hz, H-1), 3.82–3.97 (m, 1H, H-5), 4.02 (dd, 1H, $J=9.0$, 6.9 Hz, H-1), 4.31 (d, 1H, $J=13.0$ Hz, OCH-Ph), 4.39–4.53 (m, 2H, H-5, O-CH-Ph), 5.50–5.77 (m, 2H, H-3, H-4), 7.15–7.28 (m, 5H, ArH). ^{13}C NMR δ: 21.4, 25.9, 26.7, 69.5, 70.1, 74.8, 76.5, 109.4, 127.4, 127.5, 127.6, 128.3, 129.3, 136.0, 138.6. HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1559.

4.8. (2*S*,5*S*,3*E*)-1,2-dihydroxy-1,2-O-isopropylidene-5-(4-methoxyphenylthio)-3-hexene, 9

The alcohol **12a** (750 mg, 4.36 mmol) and freshly made bis(4-methoxyphenyl) disulfide (2.43 g, 8.71 mmol) was dissolved in dry toluene (100 mL). Bu_3P (3.53 g, 17.42 mmol) was added and the mixture was heated at reflux for 3 h. Toluene was evaporated and the residue was diluted with CH_2Cl_2 (30 mL) and then washed with 10% NaOH (10 mL×2). The aqueous phase was re-extracted with CH_2Cl_2 (10 mL); the combined CH_2Cl_2 layers were washed with brine (10 mL×2), dried, concentrated and subjected to flash column chromatography (from 20:1 pet. ether:ether to 1:1 v/v pet. ether:ether) to give the sulfide **9** (989 mg, 81%). GC analysis (inlet temperature: 200°C, detector temperature: 300°C, oven temperature: 100°C (2 min), 100–200°C, 10°C/min) showed a single peak at $t_R=18.2$ min. $[\alpha]_D^{21}$: −1.9 (*c* 6.4, $CHCl_3$). IR ν_{max}: 1592, 1494 cm^{-1}. ^{1}H NMR δ: 1.32 (d, 3H, $J=7.5$ Hz, Me), 1.32 (s, 3H, O-C-Me), 1.33 (s, 3H, O-C-Me), 3.19 (dd, 1H, $J=8.2$, 7.7 Hz, H-1), 3.42–3.62 (m, 1H, H-5), 3.76 (s,

3H, -OMe), 3.87 (dd, 1H, $J=7.7$, 6.0 Hz, H-1), 4.28–4.42 (m, 1H, H-2), 5.02 (dd, 1H, $J=15.0$, 7.9 Hz, H-3), 5.60 (dd, 1H, $J=15.0$, 8.8 Hz, H-4), 6.65–7.35 (m, 4H, ArH). ^{13}C NMR δ: 19.9, 25.8, 26.6, 47.0, 55.3, 69.2, 76.6, 109.2, 114.2, 115.0, 124.7, 127.7, 136.3, 136.6. HRMS calcd for $C_{16}H_{22}O_3S$ 294.1290, found 294.1290.

4.9. (2*S*,5*R*,3*Z*)-1,2-dihydroxy-1,2-*O*-isopropylidene-5-(4-methoxyphenylthio)-3-hexene, 10

Compound **10** was prepared in the same way as allylic sulfide **9**, starting from **13a** (390 mg, 2.26 mmol), bis(4-methoxyphenyl) disulfide (1.58 g, 5.66 mmol) and Bu_3P (1.83 g, 9.06 mmol) to give the sulfide **10** (514 mg, 90%). GC analysis (inlet temperature: 200°C, detector temperature: 300°C, oven temperature: 100°C (2 min), 100–200°C, 10°C/min) showed a single peak at $t_R=15.8$ min. $[\alpha]_D^{23}$: −150 (*c* 0.8, CH_3OH) . IR ν_{max}: 1591, 1493 cm^{-1}. ^{1}H NMR δ: 1.33 (d, 3H, $J=7.3$ Hz, Me), 1.28 (s, 3H, O-C-Me), 1.31 (s, 3H, O-C-Me), 3.02 (dd, 1H, $J=9.0$, 8.6 Hz, H-1), 3.19 (dd, 1H, $J=9.0$, 7.1 Hz, H-1), 3.77 (s, 3H, OMe), 3.82–4.00 (m, 1H, H-5), 4.26–4.40 (m, 1H, H-2), 5.26 (dd, 1H, $J=11.4$, 10.0 Hz, H-3), 5.47 (dd, 1H, $J=11.6$, 11.4 Hz, H-4), 6.77–7.39 (m, 4H, ArH). ^{13}C NMR δ: 20.6, 25.8, 42.5, 55.3, 68.8, 71.5, 108.5, 114.3, 124.5, 127.2, 136.5, 137.3, 159.8. HRMS calcd for $C_{16}H_{22}SO_3$ (M^+-1) 294.1290, found 294.1285.

4.10. General procedure for the sulfonium ylide formation-[2,3]-sigmatropic rearrangement reaction of 6a,b, 9 and 10

The primary or secondary allylic sulfide **6a**, **6b**, **9** or **10** (1.0 mmol) was dissolved in dry chlorobenzene or dichloromethane (10 mL) under Ar. The Rh (II) catalyst (5 mol %, predried at 100°C at 0.5 mmHg for 1 h) was added and the mixture was heated at the appropriate temperature (Table 1) or was stirred at rt. A solution of EDA (3.0 mmol) in the same solvent was added via syringe pump over a period of 30 min. After the addition was complete, the mixture was stirred for an additional 30 min. The solvent was then evaporated and the residue was purified by flash column chromatography.

Rearrangement products **7** were separated by careful column chromatography (20:1 v/v pet. ether–ether and then 3:1 v/v pet. ether–ether) into two diastereomerically enriched components: The more polar component consisted of mainly one diastereomer whereas the less polar component consisted of at least three diastereomers. *The less polar component*: IRν_{max}: 1732, 1593 cm^{-1}. ^{1}H NMR δ: [1.16 (t, $J=7.2$ Hz), 1.17 (t, $J=7.5$ Hz), 1.19 (t, $J=7.5$ Hz)] (3H, -CO_2CH_2Me), [1.32 (s), 1.33 (s), 1.37 (s)] (6H, O-C-Me), [2.49 (ddd, $J=10.8$, 10.0, 3.0 Hz), 2.69 (ddd, $J=9.2$, 8.8, 5.0 Hz), 2.85 (ddd, $J=9.4$, 9.0, 6.0 Hz)] (1H, H-3), 3.61–3.83 (m, 2H), 3.80 (s, 3H, OMe), 3.89–4.33 (m, 4H), 5.07–5.98 (m, 3H, -CH=CH_2), 6.71–7.51 (m, 4H, ArH). *The more polar component*: IR: 1730, 1592 cm^{-1}. ^{1}H NMR δ: 1.13 (t, 3H, $J=7.4$ Hz, -CO_2CH_2Me), 1.29 (s, 3H, O-C-CH_3), 1.38 (s, 3H, O-C-Me), 2.67 (ddd, 1H, $J=10.0$, 9.6, 2.8 Hz, H-3), 3.69 (dd, 1H, $J=7.9$, 7.2 Hz, H-5), 3.75 (d, 1H, $J=10.5$ Hz, H-2), 3.80 (s, 3H, OMe), 3.95 (dd, 1H, $J=8.4$, 6.9 Hz, H-5), 3.98–4.26 (m, 3H, H-4, -CO_2CH_2Me), 5.20 (dd, 1H, $J=17.5$, 2.3 Hz, =CH), 5.38 (dd, 1H, $J=10.7$, 2.4 Hz, =CH), 5.67–5.88 (m, 1H, -CH=), 6.77–7.48 (m, 4H, ArH). HRMS (total mixture) calcd for $C_{19}H_{26}SO_5$ 366.1501, found 366.1495.

Rearrangement products **18** were separated into two components by careful column chromatography (20:1 v/v pet. ether:ether to 2:1 v/v pet. ether:ether): The less polar component **18a**, ($R_f=0.38$, 5:1 pet. ether:Et_2O): IR ν_{max}: 1732, 1593, 1495 cm^{-1}. ^{1}H NMR δ: 1.08 (t, 3H, $J=7.3$ Hz, -CO_2CH_2Me), 1.26 (s, 3H, O-C-Me), 1.31 (s, 3H, O-C-Me), 1.62 (dd, 3H, $J=7.2$, 1.6 Hz, =CHMe), 2.36 (ddd, 1H, $J=11.0$, 8.7, 1.8 Hz, H-3), 3.56 (t, 1H, $J=7.5$ Hz, H-5), 3.66 (d, 1H, $J=8.8$ Hz, H-2), 3.73 (s, 3H, OMe), 3.86–4.06 (m, 3H, H-5′, -CO_2CH_2Me), 4.72 (ddd, 1H, $J=7.5$, 7.5, 2.5 Hz, H-4), 5.30 (ddd, 1H, $J=15.7$, 8.8, 1.6 Hz, -CH=), 5.45 (ddd, 1H, $J=15.7$, 6.3, 6.3 Hz, =C*H*Me), 6.75 (d, 2H, $J=8.2$ Hz, ArH), 7.37 (d, 2H, $J=8.0$ Hz, ArH). ^{13}C NMR δ: 14.3, 18.1, 25.2, 26.1, 46.3, 54.9, 55.3, 60.9, 66.9, 73.9, 108.8, 114.4, 124.2, 125.2, 131.4, 135.7, 160.0. The more polar component, **18b** ($R_f=0.25$, 5:1 pet. ether:Et_2O): IR ν_{max}: 1727, 1593, 1494 cm^{-1}. ^{1}H NMR δ: 1.05 (t, 3H, $J=6.5$ Hz, -CO_2CH_2Me), 1.22 (s, 3H, O-C-Me), 1.30 (s, 3H, O-C-Me), 1.71 (dd, 3H, $J=7.0$, 1.2 Hz, =CHMe), 2.70 (ddd, 1H, $J=9.4$, 9.4, 3.0 Hz, H-3), 3.60 (t, 1H, $J=7.5$ Hz, H-5), 3.68 (d, 1H, $J=10.3$ Hz, H-2), 3.72 (s, 3H, OMe), 3.85 (dd, 1H, $J=7.5$, 6.5 Hz, H-5′), 3.91–4.08 (m, 3H, H-4, MeCH_2O), 5.28 (ddd, 1H, $J=14.0$ 9.5, 1.1 Hz, CH=) 5.53 (ddd, 1H, $J=13.7$, 6.3, 6.3 Hz, =C*H*Me), 6.75 (d, 2H, $J=8.2$ Hz, ArH), 7.33 (d, 2H, $J=8.2$ Hz, ArH). ^{13}C NMR δ: 14.0, 18.1, 25.1, 26.0, 46.5, 53.6, 55.3, 60.9, 66.8, 76.1, 109.1, 114.3, 123.3, 125.7, 131.2, 135.5, 136.4, 171.9. Anal. calcd for $C_{20}H_{28}O_5S$ (total mixture): C, 63.13; H, 7.42. Found: C, 63.15; H, 7.35.

4.11. General procedure for the reduction of rearrangement products 7 and 18

Bu_3SnH (0.22 mmol) was syringed to a 25 mL flask under argon. Toluene (5 mL) was added to the above flask and the solution was heated to 80°C. To the above solution was added sulfide **7** or **18** (0.1 mmol) and AIBN (0.02 mmol) in toluene (5 mL) via syringe pump over a period of 1 h. The reaction was kept at 80°C for 2 h. The solvent was evaporated and the residue was added 10% KF aqueous solution (5 mL) and ether (5 mL). The resulting mixture was vigorously stirred at rt for 1 h. The organic phase was collected and the inorganic phase was extracted with ether (2×5 mL). The combined organic phases were evaporated and the residue was purified by flash column chromatography.

4.12. Rearrangement products 8a,b: yield: 66–73%

4.12.1. Less polar diastereomer 8a. ($R_f=0.32$, 5:1 pet. ether:ether): $[\alpha]_D^{22}$: +23.2 (*c* 1.0, $CHCl_3$) {lit.[13b] enantiomer of **8a**: −14.5 (*c* 2.0)}. IRν_{max}: 1735 cm^{-1}. ^{1}H NMR δ: 1.18 (t, 3H, $J=7.3$ Hz, -CO_2CH_2Me), 1.27 (s,

3H, O-C-Me), 1.33 (s, 3H, O-C-Me), 2.27 (dd, 1H, $J=16.0$ 10.5 Hz, H-2), 2.58–2.69 (m, 2H, H-2, H-3), 3.56–3.67 (m, 1H, H-5), 3.83–3.96 (m, 2H, H-4, H-5), 4.07 (q, 2H, $J=7.2$ Hz, -$CO_2\underline{CH_2}$Me), 5.00–5.66 (m, 3H, -CH=CH_2). ^{13}C NMR δ: 14.3, 25.2, 26.2, 35.9, 42.8, 60.5, 66.6, 77.6, 109.1, 117.8, 135.9, 172.1.

4.12.2. More polar diastereomer 8b[13a]. ($R_f=0.25$, 5:1 pet. ether:ether): $[\alpha]_D^{22}$: +15.7 (c 1.6, $CHCl_3$) {lit.[13b] enantiomer of **8b**: −17.2 (c 1.8)}. IR ν_{max}: 1736 cm^{-1}. ^{1}H NMR δ: 1.18 (t, 3H, $J=7.4$ Hz, -$CO_2CH_2\underline{Me}$), 1.27 (s, 3H, O-C-Me), 1.34 (s, 3H, O-C-Me), 2.31 (dd, 1H, $J=15.0$, 8.6 Hz, H-2), 2.46 (dd, 1H, $J=15.2$, 5.6 Hz, H-2), 2.64–2.78 (m, 1H, H-3), 3.59 (dd, 1H, $J=8.0$, 6.7 Hz, H-5), 3.92 (dd, 1H, $J=8.5$, 7.0 Hz, H-5), 4.02–4.11 (m, 1H, H-4), 4.05 (q, 2H, $J=7.2$ Hz, -$CO_2\underline{CH_2}$Me), 5.02–5.77 (m, 3H, -CH=CH_2). ^{13}C NMR δ: 14.2, 25.5, 26.7, 36.6, 44.9, 60.3, 67.9, 77.5, 109.9, 117.8, 136.4, 172.1.

4.13. Rearrangement product 19

Compound **19** (5:1 pet. ether:ether), yield was 76–88%. IR ν_{max}: 1738, 1449 cm^{-1}. ^{1}H NMR δ (only resonances for **19a** observed): 1.21 (t, 3H, $J=7.8$ Hz, -$CO_2CH_2\underline{Me}$), 1.31 (s, 3H, O-C-Me), 1.36 (s, 3H, O-C-Me), 1.64 (dd, 3H, $J=6.2$, 1.1 Hz, Me), 2.29 (dd, 1H, $J=15.1$, 9.2 Hz, H-2), 2.45 (dd, 1H, $J=14.9$, 5.4 Hz, H-2′), 2.66–2.78 (m, 1H, H-3), 3.61 (dd, 1H, $J=8.0$, 7.4 Hz, H-5), 3.92 (dd, 1H, $J=8.0$, 6.3 Hz, H-5′), 4.01–4.15 (m, 3H, H-4, $MeCH_2O$), 5.28 (ddq, $J=15.4$ 8.6, 1.1 Hz, CH=), 5.44–5.67 (m, 1H, =$\underline{CH}$Me). ^{13}C NMR δ: 14.2, 18.0, 25.1, 26.1, 37.1, 41.6, 60.2, 66.5, 77.5, 108.7, 128.5, 172.2. HRMS (**19** from rearrangement of **9**) calcd for $C_{12}H_{19}O_4$ (M^+−15) 227.1283, found 227.1285. HRMS (**20** from rearrangement of **10**) calcd for $C_{12}H_{19}O_4$ (M^+−15) 227.1283, found 227.1279.

4.14. Ethyl (4*S*)-4,5-dihydroxy-4,5-*O*-isopropylidene-3-(propyl)pentanoate, 20

To a Parr flask was added **19** (12.1 mg, 0.05 mmol), 10% palladized charcoal (70% weight by weight of catalyst to substrate) and dry MeOH (15 mL). The flask was then connected to a Parr apparatus. The flask was evacuated and flushed with H_2 gas and this process was repeated three times. The flask was filled with H_2 gas to the pressure of 35 psi. and it was shaken for 1.5 h. Then the flask was evacuated, equilibrated to atmospheric pressure and removed. The reaction mixture was filtered through Celite and the filter cake was washed with CH_2Cl_2 (3×5 mL). The solvent was evaporated and the residue was filtered through a short silica-gel pad to give the hydrogenated compounds (11.5 mg, 94%). GC–MS analysis (inlet temperature: 200°C, detector temperature: 300°C, oven temperature: 100°C (2 min), 100–150°C, 3°C/min) of the mixture provided the ratio of **20a** ($t_R=17.3$ min) and **20b** ($t_R=17.1$ min). IR ν_{max}: 1736 cm^{-1}. ^{1}H NMR δ: 0.90 (t, 3H, $J=6.7$ Hz, -$(CH_2)_2\underline{Me}$), 1.28–1.42 (m, 4H, -CH_2CH_2-), 1.26 (t, 3H, $J=7.2$ Hz, $MeCH_2O$), 1.33 (s, 3H, O-C-Me), 1.39 (s, 3H, O-C-Me), 2.11 (dd, 1H, $J=17.0$, 6.8 Hz, H-2), 2.11–2.18 (m, 1H, H-3), 2.32 (dd, 1H, $J=$ 17.0, 9.0 Hz, H-2), 3.59 (t, 1H, $J=7.8$ Hz, H-5), 3.96 (dd, 1H, $J=7.8$, 6.3 Hz, H-5), 4.12 (q, 2H, $J=7.2$ Hz, -$CO_2\underline{CH_2}$Me), 4.00–4.13 (m, 1H, H-4). ^{13}C NMR δ: 14.1, 14.2, 20.0, 25.2, 26.4, 32.9, 34.9, 37.3, 60.3, 66.4, 77.6, 108.0, 173.0. GC–MS: **20a**, $t_R=10.8$ min, m/z (rel. intensity): 229 (M^+, 68%), 187 (M−MeCH=CH2, 14%), 141 (M−CH_3CO_2Et, 100%), 101 (2,2-dimethyldioxolanyl cation, 93%); **20b**, $t_R=10.7$ min, m/z (rel. intensity): 229 (M^+, 78%), 141 (M−CH_3CO_2Et), 101 (2,2-dimethyldioxolanyl cation, 100%) HRMS: calcd for $C_{12}H_{21}O_4$ (M^+−15) 229.1440, found 229.1444.

4.15. (2*R*,3*E*)-4-(4-Chlorophenyl)-3-buten-2-ol, 21

(3*E*)-4-(4-Chlorophenyl)-3-buten-2-one (336 mg, 1.86 mmol) was dissolved in THF (8 mL) and the solution was added over a period of 3.5 h, via a syringe pump, to a mixture of $BH_3\cdot Me_2S$ (2.0 M in THF, 1.11 mmol, 0.57 mL) and (*S*)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 1.11 mmol, 1.11 mL) in THF (10 mL) at −10 to −15°C. After 40 min, the reaction mixture was quenched with dry cold MeOH (5 mL) at −15°C. Then saturated aqueous $NaHCO_3$ solution (20 mL) was added and after 5 min the mixture turned milky white. The mixture was extracted thoroughly with ether (3×20 mL). The combined organic layer was washed with brine (20 mL), dried, filtered and concentrated. The residue was purified by column chromatography (pet. ether–EtOAc 6:1 v/v) to give the allylic alcohol **21** (321 mg, 95%) as a white solid, mp: 61–61°C. $[\alpha]_D^{22}$: +27.3 (c 0.6, $CHCl_3$), $[\alpha]_D^{20}$ +17.7 (c 1.5, CH_2Cl_2). % ee: 98% (Chiralpack AD, 98:2 v/v hexane:2-propanol, 1.0 mL/min): (*S*)-**21b**; $t_R=14.4$ min, (*R*)-**21b**; $t_R=15.0$ min). IR ν_{max} (neat): 3354, 3050, 1652, cm^{-1}. ^{1}H NMR δ: 1.38 (d, $J=6.38$ Hz, 3H, CH_3), 1.61 (s, 1H, OH), 4.46–4.53 (m, 1H, H-2), 6.24 (dd, $J=6.2$, 15.9 Hz, 1H, H-3), 6.53 (d, $J=15.9$ Hz, 1H, H-4), 7.29–7.34 (m, 4H, Ar-H). ^{13}C NMR δ: 23.4, 68.7, 103.6, 127.7, 127.9, 128.7, 134.2, 135.2.

4.16. (*S*)-4-(4-Chlorophenyl)-2-(4-methoxyphenylthio)-3-butene, 22

The sulfide **22** was prepared, as described for compound **9**, starting from the alcohol **21** (234 mg, 1.28 mmol) and freshly prepared bis(4-methoxyphenyl)-disulfide (714 mg, 2.56 mmol) and Bu_3P (1.04 g, 5.12 mmol) in toluene (25 mL). After the mixture was refluxed (20 h) the solvent was evaporated and the residue was taken into CH_2Cl_2 (10 mL), washed with 10% aqueous NaOH (10 mL), and the aqueous phase was reextracted with CH_2Cl_2 (10 mL), the combined CH_2Cl_2 layers were washed with brine (20 mL), dried, concentrated and purified by column chromatography (pet. ether:ether 15:1v/v) to give the product **22** (316 mg, 81%), mp: 41–42°C, $[\alpha]_D^{22}=+219.0$ (c 1.0, $CHCl_3$). IR ν_{max} (neat): 3002, 1591, 1090 cm^{-1}. ^{1}H NMR δ: 1.43 (d, $J=6.8$ Hz, 3H, CH_3), 3.67–3.75 (m, 1H, H-3), 3.78 (s, 3H, OCH_3), 5.97–6.19 (m, 2H, H-1. H-2), 6.79–6.83 (m, 2H, Ar-H), 7.16–7.39 (m, 6H, Ar-H). ^{13}C NMR δ: 20.2, 47.6, 55.3, 114.1, 127.4, 127.6, 128.5, 128.6, 128.7, 129.2, 132.4, 136.7, 159.7. HRMS calcd for $C_{17}H_{17}ClOS$ 304.0689, found, 304.0693.

4.17. (*R*)-4-(4-Chlorophenyl)-2-butyrolactone, 25

The sulfide **22** (189 mg, 0.62 mmol) and $Rh_2(OAc)_4$ (13.72 mg, 0.031 mmol, 5 mol %, predried at 80°C at 0.5 mmHg for 2 h) were dissolved in CH_2Cl_2 (6 mL). A solution of EDA (1.86 mmol) in 5 mL CH_2Cl_2 was added via syringe pump over a period of 4 h at 45°C. The reaction was conducted at 50°C for 4 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (pet. ether-ether, 30:1 v/v) to obtain **23** as a mixture of diastereomers (184 mg, 76%). IR ν_{max} (neat): 3013, 3036, 1731, 1638, 1592 cm^{-1}. ^1H NMR δ: [1.18 (t, $J=7.0$ Hz] and 1.17 (t, $J=7.0$ Hz) (3H, -$CO_2CH_2\underline{CH_3}$) 1.57–1.61 (m, 3H, H-6), 3.83 (s, 3H, OCH_3), 3.74–3.86 (m, 2H, H-2, H-3), 4.03–4.15 (m, 2H, -O$\underline{CH_2}CH_3$), 5.51–5.63 (m, 2H, -CH=CH-), 6.73–6.86 (m, 2H, Ar-H), 7.08–7.45 (m, 6H, Ar-H). HRMS calcd for $C_{21}H_{23}ClO_3S$ 390.1056, found, 390.1061.

A solution of compound **23** (137 mg, 0.35 mmol) and AIBN (11.49 mg, 0.082 mmol) in 10 mL benzene (10 mL) was added via syringe (syringe pump) over a period of 2 h to a solution of Bu_3SnH (224 mg, 0.77 mmol) in benzene (10 mL) at 80°C. The reaction was kept at 80°C for 2 h and benzene was evaporated. The crude product then dissolved in ether (10 mL) and 10% aqueous KF solution (10 mL) was added. The mixture was vigorously stirred at rt for 1 h and the organic phase was separated. The aqueous phase was reextracted with ether (2×10 mL). The combined organic phases were dried, filtered and evaporated, and the residue was purified by column chromatography (pet. ether–ether, 20:1 v/v). A small amount of an unidentified impurity co-eluted with the ester **24** (48 mg, 54%). IR ν_{max} (neat): 3025, 1732, 1092 cm^{-1}. ^1H NMR δ: 1.17 (t, $J=7.2$ Hz, 3H, -$CO_2CH_2\underline{CH_3}$), 1.67 (dd, $J=1.4$, 4.6 Hz, 3H, H-6), 2.65 (dd, $J=7.5$, 2.2 Hz, 2H, H-2), 3.76–3.84 (m, 1H, H-3), 4.11 (q, $J=7.2$ Hz, 2H), 5.49–5.55 (m, 2H, H-4, H-5), 7.12–7.38 (m, 4H, Ar-H). ^{13}C NMR δ: 14.2, 17.9, 40.8, 44.3, 60.4, 126.0, 127.3, 128.6, 128.8, 132.7, 141.8, 171.7.

The above ester **24** was treated with ozone in dry MeOH (10 mL) at −78°C for 50 s. Excess ozone was then removed and the reaction mixture was warmed to 0°C. Sodium borohydride (1.0 mmol) was added and the mixture was allowed to warm slowly to rt (3 h). Glacial AcOH (10 drops) was then added to destroy excess $NaBH_4$, and the mixture was extracted with CH_2Cl_2, the combined organic phases washed with saturated NaCl solution, and then dried. The filtered solution was evaporated and the crude oil was purified by column chromatography (pet. ether–ether, 3:1 v/v) to furnish the primary alcohol (33 mg, 72%). $[\alpha]_D^{20}=-15.6$ (*c* 1.6, CH_2Cl_2). IR ν_{max} (neat): 3458, 1731 cm^{-1}. ^1H NMR δ: 1.16 (t, $J=7.2$ Hz, 3H, -$CO_2CH_2\underline{CH_3}$), 2.27 (s, 1H, OH), 2.57 (dd, $J=15.7$, 7.9 Hz, 1H, H-2), 2.79 (dd, $J=15.6$, 6.9 Hz, 1H, H-2), 3.26–3.34 (m, 1H, H-3), 3.71 (dd, 2H, $J=6.3$, 3.9 Hz, H-4), 4.05 (q, 2H, $J=7.2$ Hz, -$CO_2\underline{CH_2}CH_3$), 7.13–7.30 (m, 4H, Ar-H). ^{13}C NMR δ: 14.0, 37.1, 43.8, 60.6, 66.4, 128.7, 129.1, 132.7, 139.5, 172.3.

The primary alcohol (30 mg, 0.12 mmol) was dissolved in benzene (5 mL) and PTSA (9.1 mg, 0.05 mmol, 40% mol) was added. The mixture was heated at 80°C for 6 h and then benzene was distilled off over a period of 2 h. Et_3N (1 mL) and CH_2Cl_2 (5 mL) was added to the residue and the mixture was washed with saturated NaCl solution, dried, filtered and the crude product purified by column chromatography (pet. ether–ether, 3:1 v/v) to yield (R)-**25** (24.1 mg, 72%). $[\alpha]_D^{20}=-29.2$ (*c* 1.2, $CHCl_3$) {lit.[19b] $[\alpha]_D^{20}=-48.5$ (*c* 0.5, $CHCl_3$), lit.[23] $[\alpha]_D^{26}$ −50.9 (*c* 0.7, $CHCl_3$)}. %e.e: 63% (Chiralpak AD, 1.0 mL/min, 96:4 v/v hexane:2-propanol): (*R*)-**25**; $t_R=$ 31.0 min, (*S*)-**25**; $t_R=29.5$ min. IR ν_{max} (neat): 3060, 1781, 1023 cm^{-1}. ^1H NMR δ: 2.62 (dd, $J=17.4$ 8.8 Hz, 1H, H-3), 2.93 (dd, $J=17.4$, 8.7 Hz, 1H, H-3), 3.79 (quint., $J=8.2$ Hz, 1H, H-4), 4.23 (dd, $J=8.8$, 7.9 Hz, 1H, H-5), 4.66 (dd, $J=8.8$, 8.0 Hz, 1H, H-5), 7.17 (d, $J=8.4$ Hz, 2H, Ar-H), 7.34 (d, $J=8.4$ Hz, 2H, Ar-H). ^{13}C NMR δ: 35.6, 40.4, 73.7, 128.0, 128.5, 129.2, 137.9, 175.9.

4.18. (*R*)-3-(4-Chlorophenyl)-1-hexanol, 28

Alkene **24** (130 mg, 0.52 mmol) was hydrogenated over 10% palladized charcoal using a Parr hydrogenator to provide ethyl 3-(4-chlorophenyl)hexanoate (94 mg, 78%). This compound was used immediately in the next step.

Ethyl 3-(4-chlorophenyl)hexanoate (88 mg, 0.35 mmol) was dissolved in dry THF (20 mL). $LiAlH_4$ (40 mg, 1.1 mmol) was added to the solution and the reaction mixture was refluxed for 5 h. The reaction mixture was cooled to 0°C, and water (2 mL) was added. The mixture was stirred for 10 min, 10% aqueous NaOH (3 mL) was added and the resulting mixture was stirred for an additional 20 min. The mixture was extracted with ether (2×10 mL) and the combined organic phases were dried, evaporated and the residue was purified by column chromatography to yield **28** (56 mg, 76%). $[\alpha]_D^{22}=-3.3$ (*c* 1.5, $CHCl_3$), % ee: 66% (Chiralcel OD, 1.0 mL/min, 98:2 v/v hexane:2-propanol): (*R*)-**28**; $t_R=11.2$ min, (*S*)-**28**; $t_R=$ 12.7 min. IR ν_{max} (neat): 3342, 3026, 1493, 1042. ^1H NMR δ: 0.86 (t, 3H, $J=7.1$ Hz, CH_3), 1.10–1.27 (m, 2H, H-5), 1.49–1.99 (m, 5H, OH, H-2, H-4), 2.63–2.78 (m, 1H, H-3), 3.44–3.52 (m, 2H, HO$\underline{CH_2}$-), 7.16–7.34 (m, 4H, Ar-H). ^{13}C NMR δ: 14.1, 20.6, 39.2, 39.6, 42.2, 61.2, 126.1, 127.6, 128.4, 145.2.

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