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Remote stereocontrol by the sulfinyl group: Mukaiyama aldol reactions of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde in the asymmetric synthesis of β-hydroxyacids and 1,3-diols

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Abstract—(*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]acetaldehyde reacts with different *O*-silylated ketenethioacetals in the presence of $Yb(OTf)_3$ yielding β-hydroxythioesters in high yields and diastereoselectivities. The obtained compounds were readily transformed into β-hydroxyacids and their corresponding diols. These Mukaiyama aldol reactions are a direct evidence of the ability of the sulfinyl group to control 1,5- and 1,6-asymmetric induction processes.

1. Introduction

The aldol reaction is a powerful method of forming carbon–carbon bonds in organic synthesis.[1] The control of the absolute configuration at the new stereogenic centers generated in the reaction is an important task and hundreds of papers and a number of excellent comprehensive reviews have appeared covering this topic.[2] Among these processes, the Mukaiyama reaction[3] has enjoyed a noteworthy development in recent years, and it has become the reaction of choice to attain high stereoselectivity, due to the possibility of using chiral enolates,[4] chiral substrates,[5] and especially chiral catalysts.[6] The ability of the sulfinyl group to control the face-selectivity in many different reactions is well-known.[7] Concerning aldol reactions, the role of the sulfinyl group has been investigated in reactions where this chiral auxiliary is present at the nucleophilic enolate[8–11] as well as at the electrophile.[12] The results obtained from all these studies reveal the efficiency of the sulfinyl group in the stereoselectivity control when it is separated by only one or two bonds from the reaction center (1,2- and 1,3-asymmetric induction processes). Less work has been done in the field of aldol reactions involving remote stereofunctionalization (1,*n*-asymmetric induction processes with $n>3$) controlled by sulfoxides. The most important contributions have been achieved with aromatic aldehydes containing an *ortho*-sulfinyl group,[13–15] which include Mukaiyama reactions.[13b,c,16]

Some years ago we initiated a program to investigate the efficiency of the sulfinyl group to control the stereoselectivity of reactions taking place at remote positions. We have mainly studied 1,4-asymmetric induction processes controlled by the sulfinyl group at the nucleophilic moiety,[17] that proceed with an almost complete control of the stereoselectivity. On the other hand, we have reported the hydrocyanation of γ-sulfinyl aromatic aldehydes, with the sulfur function being at the electrophile.[18] In this context, we have also studied the first 1,5-asymmetric induction processes controlled by the sulfinyl group starting from (*S*)-*ortho*-(*p*-tolylsulfinyl)benzyl alkyl (and aryl) ketones and their corresponding aldehydes,[17e] which involve reduction[19a] and hydrocyanation[19b] reactions with aluminum reagents. These reactions occurred with excellent stereoselectivities and afforded diastereomerically enriched carbinols and cyanohydrins respectively, when they were performed in the presence of $Yb(OTf)_3$. We present herein the first results on the stereoselective Mukaiyama reaction of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde (**1**) with thioester *O*-silyl enolates. They would allow to expand the scope of the 1,5-asymmetric induction reactions controlled by the sulfinyl group and would provide interesting synthetic intermediates with a β-hydroxy carbonylic structure.

2. Results and discussion

Initially, we studied the reaction of the aldehyde **1**[17e] with the *O*-silylated ketenethioacetal **2a**[20] at −78 °C in the

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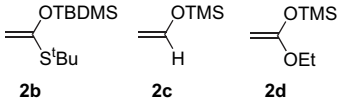
presence of different Lewis acids (1.2 equiv). Mixtures of the two possible diastereoisomeric adducts, epimers at the hydroxylic carbon, were obtained in all cases (Table 1, entries 1–4 and 6). Diastereoselectivity was low with $BF_3{\cdot}OEt_2$, $TiCl_4$, $AlCl_3$, and ZnI_2 (Table 1, entries 1–4). These reactions did not reach completion and a variable amount of starting material was always recovered. No reaction happened under $MgCl_2$ catalysis, even at higher temperatures and longer reaction times (Table 1, entry 5). The best stereoselectivity was achieved under $Yb(OTf)_3$ catalysis (Table 1, entry 6), as it had been also the case in the reactions of other nucleophiles.[19]

Next, we tried to improve the conversion and stereoselectivity of the reactions performed under $Yb(OTf)_3$ catalysis, by changing the temperature, the solvent, the number of equivalents of the reagents, and the reaction time. The best results were obtained by lowering the temperature (Table 1, entries 6–8) and using acetonitrile[21] as the solvent (entries 11–13), which in its turn, also increased the reactivity. The use of THF as the solvent (Table 1, entries 9 and 10) had no positive influence. Under substoichiometric amounts of $Yb(OTf)_3$ a significant decrease in both the reaction rate and the stereoselectivity, was observed, whereas an increase in the amount of the Lewis acid (2 equiv) scarcely modified the reaction rate. Under the optimum conditions, which were those of entry 12 (3 equiv of **2a**, 1.2 equiv of $Yb(OTf)_3$ in acetonitrile at −40 °C), a 94:6 mixture of diastereoisomers **3** and **4** could be isolated in 86% yield. They were easily separated by flash-column chromatography and the major compound **3** (de >98%) could be isolated in 79% yield.

An increase in the size of the silyloxy group had no significant influence on the reactivity or on the selectivity of these reactions. Thus, *tert*-butyldimethylsilyl derivative **2b**[22] (Scheme 1) gave almost identical results to **2a** under similar conditions. Less nucleophilic species, such as trimethylsilyloxy ethylene, **2c**, were not able to react with **1** in the presence of catalysts, even at room temperature. Analogously, the reaction with ketene acetal **2d**[23] (Scheme 1) did not evolve, which was not unexpected because of the low reactivity of this compound toward 2-(arylsulfinyl)-naphthaldehydes, as had been reported by Toru.[13b]

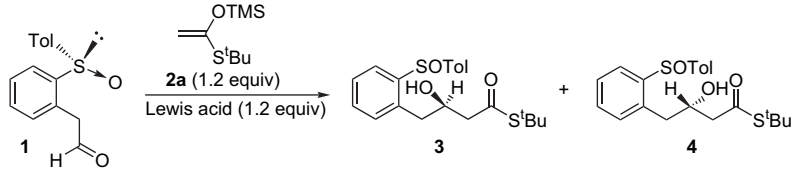


Scheme 1.

Then, we studied the reactions of aldehyde **1** with the substituted *O*-silylated ketenethioacetals (*Z*)-**2e** and (*E*)-**2f**, which would allow the simultaneous formation of two stereogenic centers in one step, providing information about the influence of the remote sulfinyl group in determining the configuration of both centers (1,5- and 1,6-asymmetric induction processes). The reactions were performed under the best conditions of Table 1, acetonitrile being used as the solvent and $Yb(OTf)_3$ as the catalyst. The results are collected in Table 2.

All these reactions afforded only two out of the four possible diastereoisomers. The reactions of sulfinylaldehyde **1** with **2e**[24] in the presence of 1.2 equiv of $Yb(OTf)_3$, were performed at different temperatures (Table 2, entries 1–3), yielding mixtures of *anti* and *syn* α-methyl-β-hydroxythioesters (**5** and **6**), the *anti* isomer **5** being the major one. As expected, the selectivity slightly increased when the temperature became lower and the reaction rate was also diminished. An increase in the number of equivalents of the electrophile had some influence on the reaction rate (shorter reaction times were needed) but not on the stereoselectivity (Table 2, entries 3–5). The use of dichloromethane as the

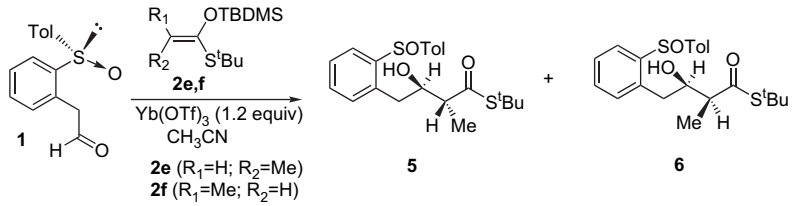
Table 1. Reactions of aldehyde **1** with **2a** catalyzed by Lewis acids



Entry	Solvent	Lewis acid	Temperature (°C)	Time	Conversion (%)[a]	**3**:**4** Ratio[a]
1	CH_2Cl_2	$BF_3{\cdot}OEt_2$[b]	−78	2 h	84	55:45
2	CH_2Cl_2	$TiCl_4$	−78	2 h	87	61:39
3	CH_2Cl_2	$AlCl_3$	−78	2 h	34	66:34
4	CH_2Cl_2	ZnI_2	−78	2 h	72	72:28
5	CH_2Cl_2	$MgCl_2$	rt	5 days	—	—
6	CH_2Cl_2	$Yb(OTf)_3$	−78	2 h	60	88:12
7	CH_2Cl_2	$Yb(OTf)_3$	−40	2 h	83	73:27
8	CH_2Cl_2	$Yb(OTf)_3$	0	2 h	86	61:39
9[c]	THF	$Yb(OTf)_3$	−40	62 h	98	82:18
10	THF	$Yb(OTf)_3$	rt	16 h	98	77:23
11	CH_3CN	$Yb(OTf)_3$	−40	2 h	85	94:6
12[c]	CH_3CN	$Yb(OTf)_3$	−40	1.5 h	100	94:6[d]
13	CH_3CN	$Yb(OTf)_3$	Reflux	2 h	100	83:17

[a] Determined by ^1H NMR spectroscopy.
[b] 2 equiv was used.
[c] 3 equiv of **2a**.
[d] A 77:23 ratio of **3** and **4** was observed by using 0.5 equiv of $Yb(OTf)_3$.

Table 2. Reactions of **1** with *O*-silylated ketenethioacetals **2e** and **2f**



Entry	Enolate (equiv)	Temperature (°C)	Time (h)	Conversion[a] (%)	**5**:**6**[a]
1	**2e** (3)	−40	62	55	78:22
2	**2e** (3)	−10	15	98	74:26
3	**2e** (3)	0	3	100[b]	72:28
4	**2e** (1.5)	0	3	52	72:28
5	**2e** (1.5)	0	6	93	72:28
6[c]	**2e** (1.5)	0	3	—[d]	46:49[e]
7	**2e** (1.5)	rt	3	62	67:33
8	**2f** (3)	0	3	100[f]	83:17
9	**2f** (1.5)	0	7	80	83:17
10	**2f** (3)	−40	120	73	83:17

[a] Determined by ^{1}H NMR spectroscopy.
[b] Combined yield: 71%.
[c] CH_2Cl_2 as the solvent.
[d] Non-evaluated.
[e] A third isomer (5%) was detected.
[f] Combined yield: 73%.

solvent decreased the stereoselectivity, because it afforded nearly equimolar mixtures of *anti*-**5** and *syn*-**6** isomers, along with a third isomer that could be detected by ^{1}H NMR (Table 2, entry 6). The best reaction conditions found for **2e** (Table 2, entries 3 and 5) were also explored with **2f**.[24] In this case the major isomer also was *anti*-**5**, but the stereoselectivity was slightly higher, 83(**5**):17(**6**) at 0 °C (Table 2, entries 8 and 9). When the temperature was lower, the reaction time increased significantly and no change in the stereoselectivity was observed.

Diastereoisomeric mixtures obtained in these reactions could not be separated by column chromatography. However, the major diastereomer **5** could be obtained as a pure compound by crystallization in 40% yield from **2e** and 51% yield from **2e** (Table 2, entries 3 and 8, respectively). All the attempts at −40 °C in THF, in the presence of TBAF as a fluoride source, with the aim of obtaining the *syn* adduct **6** as the major one,[24,25] were unsuccessful.

Configurational assignment of compounds **3**–**6** was carried out as follows:

(1) The configuration of **3** was unequivocally established as [3*R*,(S)*S*] by chemical correlation with alcohol **10** (see later). It allowed us to assign the [3*S*,(S)*S*] configuration for compound **4**.
(2) The oxidation with *m*-CPBA of the 33(**5**):67(**6**) mixture gave two diastereoisomeric sulfones with the same diastereoisomeric ratio as the starting sulfoxides. This result indicated that hydroxysulfoxides **5** and **6** only differed in the configuration of one of the two chiral carbons.
(3) The oxidation with PCC of the above mixture of **5** and **6** afforded two diastereoisomeric ketones, which initially suggested that the starting sulfoxides were epimers at the α-carbon to the thioester group. However, this experience was not conclusive because the composition of the resulting mixture (ca. 1:1) was not identical to that of the starting one (ca. 1:2), thus suggesting partial epimerization of the α-carbon to the thioester group under the reaction conditions. Despite this result, we assumed that both isomers exhibit the same configuration at the hydroxylic carbon because **2e** and **2f** must attack at the same face of the carbonyl group at compound **1**, chelated with $Yb(OTf)_3$, as it was the case of compound **2a**, with a stereoselectivity presumably higher in the former cases due to the bulkier size of the nucleophilic carbon at **2e** and **2f**.
(4) The absolute configuration of the major *anti*-**5** isomer was unequivocally established as [2*R*,3*R*,(S)*S*] by X-ray diffraction studies.[26] Therefore, according to the above considerations we assign the [2*S*,3*R*,(S)*S*] configuration to the minor *syn*-**6**.

Once the configurational assignment of the adducts in the Mukaiyama reactions was unequivocally established, we can conclude that the stereocontrol was very high (from **2a**) or complete (from **2e** and **2f**) at the benzylic carbon (1,5-asymmetric induction process) but only moderate at the α-carbon to the ester group (1,6-asymmetric induction process).

The observed stereoselectivity can be explained by assuming the formation of an eight-membered chelated species between the $Yb(OTf)_3$ and the carbonyl and sulfinyl oxygens at the substrate, as it had been postulated to explain the results obtained in the reduction[19a] and hydrocyanation[19b] of this type of ketosulfoxides. Two conformations can be proposed for this chelated species, **B** (Fig. 1) as the most stable one, because conformation **A** must be strongly unestabilized by steric interactions between the ring and the ligands of the metal. The approach of nucleophile **2a** or **2b** at the pro-*R* face of the carbonyl group in its most stable conformation

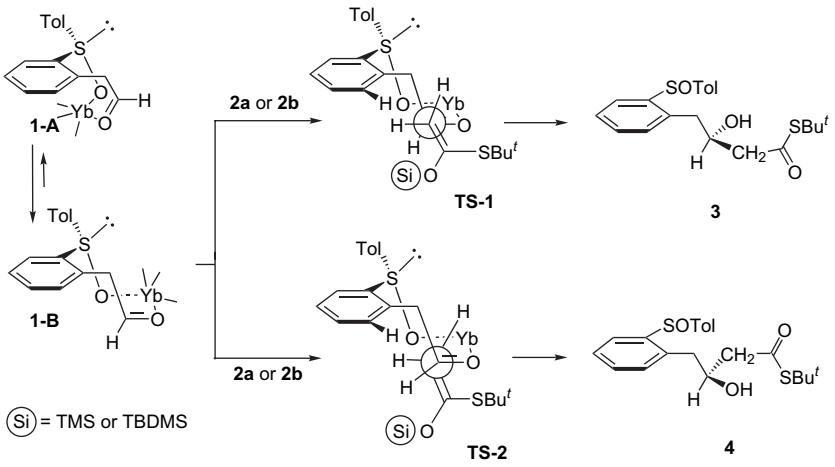


Figure 1. Favored approach of **2a** and **2b** in Mukaiyama aldol reaction of chelated aldehyde **1**.

would yield compound **3** through **TS-1**, whereas the attack at the pro-*S* face would afford **4** through **TS-2**. From Figure 1, it is evident the lower stability of **TS-2**, which would explain the formation of **3** as the major diastereoisomer.

From the above figure it can also be inferred that **TS-2** would be too unstable for substituted enolates, such as **2e** or **2f**, which should evolve in a completely stereoselective manner by attack at the pro-*R* face of the chelated carbonyl through transition states similar to **TS-1**. This fact is in agreement with the complete control of the diastereoselectivity at the hydroxylic center observed for these reactions (Table 2). Different **TS** can be postulated (Fig. 2) differing in the relative arrangement of the C=C and C=O groups. **TS-3** and **TS-5** must be highly unstable due to the strong steric interactions between the ring at **1** and the substituents at **2e** and **2f** adopting an antiperiplanar arrangement with respect to the C=O group. Therefore, the favored transition states are **TS-4** and **TS-4′**, both orientating the H in such an arrangement. As these transition states differ only in the nucleophile face that attacks at the carbonyl group, the obtained products will have the opposite configuration at the attacking nucleophilic carbon. The fact that *anti*-**5** is obtained as the major isomer suggest that the steric interaction of the methylene at the aldehyde with the tetrahedral CH_3 group at the nucleophile, present in **TS-4′**, is stronger than that with the flat olefinic carbon, present in **TS-4**, thus explaining the observed predominance of the *anti*-compounds. From Figure 2 it is easily understood that the *E* or *Z* configuration of the enolates scarcely affects the stereochemical results.[24,27]

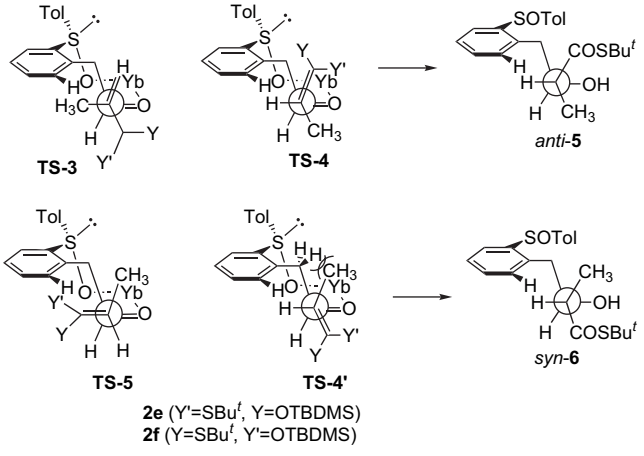
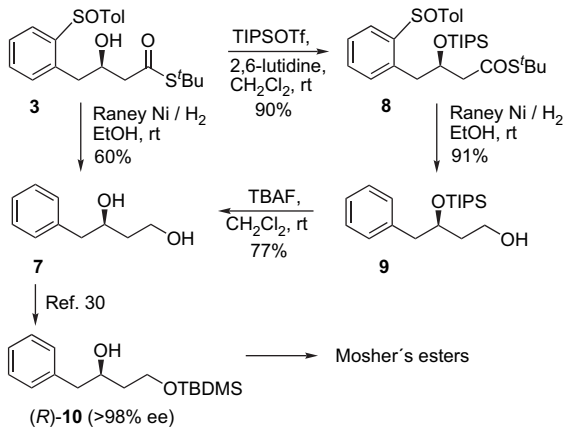


Figure 2. Favored approach of **2e** and **2f** in Mukaiyama aldol reaction of chelated aldehyde **1**.

As the last step of this research we studied the removal of the chiral auxiliary. The reaction of a mixture of **3** and **4** with Raney nickel afforded 4-phenyl-1,3-butanediol (**7**), indicating that the reagent had produced hydrogenolysis of the C–S bond as well as the reduction of the thioester group.[24,28] Reaction of diastereoisomerically pure **3** with Raney nickel under hydrogen atmosphere, yielded compound **7** (60% yield) exhibiting a $[\alpha]_D$ value of +19.0. The protection of the OH group at **3** as a TIPS derivative and further reduction with Raney nickel and desilylation (Scheme 2) also provided compound **7**, but in this case with an $[\alpha]_D$ value of +21.0. This fact suggests that the direct reduction of **3** had taken place with a slight epimerization at the hydroxylic center, as it had been previously reported for other sulfinyl alcohols.[29] Compound **7**, obtained by the indirect way, was transformed into **10**[30] (Scheme 2). The ^{1}H NMR studies on Mosher's esters[31] of compound **10** allowed us to establish the *R* configuration at its hydroxylic carbon as well as its high optical purity (ee >98%). The same configuration must be assigned to its precursor **7**. Therefore, the absolute configuration of **3** was indirectly assigned as [3*R*,(*S*)S], whereas that of [3*S*,(*S*)S] must be assigned to epimer **4**.



Scheme 2.

Desulfinylation and reduction of the thioester moiety with Raney nickel in hydrogen atmosphere were also performed on diastereoisomerically pure **5**, yielding a 83:17 diastereoisomeric mixture of diols **11** and **12** as the result of the partial racemization of the hydroxylic center (Scheme 3). The *anti* stereochemistry of diol **11** was established by comparison of its ^{1}H NMR data with those previously reported for this compound.[32] It can be obtained in its diastereoisomeric pure form by an initial protection of **5** as triisopropylsilyl derivative **13**, reduction with Raney nickel into **14** and final desilylation, as it is indicated in Scheme 3.

Another interesting transformation of hydroxythioester **5** into the corresponding desulfinylated α-methyl-β-hydroxyacid, has been performed (Scheme 4). Hydrolysis of the thioester was readily achieved with lithium hydroxide in THF/H_2O.[33] However, the reaction of the obtained acid **15** with Raney nickel, in order to remove the sulfinyl group, was unsuccessful and the resulting product was unrecoverable. We then protected the sulfinylhydroxyacid **15** as its triisopropylsilyl derivative **16**, which reacted satisfactorily with Raney nickel in very high yield and afforded compound **17**, without apparent racemization at hydroxylic carbon. Desilylation of **17** with HF/pyridine[34] at room temperature afforded the expected hydroxyacid **18** (Scheme 4).

As a conclusion, we have demonstrated that the stereoselectivity of Mukaiyama aldol reactions of aldehydes and *O*-silylated ketenethioacetals can be efficiently controlled by a remote sulfinyl group. The essential role of $Yb(OTf)_3$ as a Lewis catalyst for achieving high level of diastereoselectivity has also been established for these 1,5-asymmetric induction processes. Desulfinylation and further transformation of the resulting isomers provided a new access to interesting carbinols and β-hydroxyacids.

3. Experimental

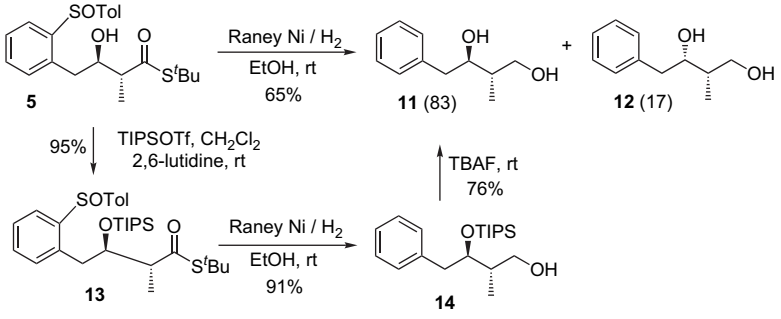
3.1. General methods

NMR spectra were obtained in $CDCl_3$ solutions at 300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively (*J* values are given in hertz). Melting points were measured in open capillary tubes. Mass spectra (MS) were obtained by FAB^+, ES^+ (MeOH+0.1% formic acid) or EI^+ with ionizing voltage of 70 eV. The des were evaluated by integration of well-separated signals of the ^{1}H NMR spectra. All reactions were carried out under an argon atmosphere in anhydrous solvents. THF was distilled from sodium-benzophenone under argon. CH_2Cl_2 was distilled from P_2O_5. Flash-column chromatography was performed using silica gel (230–400 mesh). The silyl thioenolates were synthesized according to the described procedures.

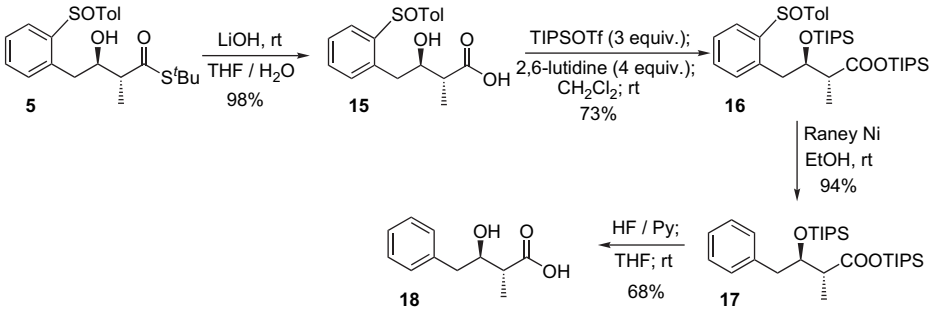
3.2. Mukaiyama aldol reaction. General procedure

A solution of aldehyde **1** (0.39 mmol) and $Yb(OTf)_3$ (0.46 mmol) in CH_3CN (3.4 mL) was stirred at room temperature for 30 min under an argon atmosphere. Then, this solution was cooled to the temperature indicated in each case and the corresponding silyl enol thioester (1.17 mmol) was added. The solution was stirred at the same temperature for the indicated time and then, quenched with an aqueous 1 M solution of HCl. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3.3 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash-column chromatography using the eluent specified for each case.

3.2.1. *S-tert*-Butyl [3*R*,(S)*S*]-3-hydroxy-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (3). Compound **3** was obtained



Scheme 3.



Scheme 4.

from **2a** as a 94:6 mixture of **3** and **4** following the above general procedure at −40 °C for 90 min. Combined yield: 86%. Diastereomerically pure **3** was separated by flash-column chromatography (ethyl acetate–hexane 1:2) as a colorless oil. Yield: 79%; $[\alpha]_D^{20}$ −60.4 (*c* 0.2, $CHCl_3$); IR (film): 3386, 1597, 1216, 704 cm^{-1}; ^1H NMR: δ 7.82 (m, 1H), 7.47 and 7.25 (AA′BB′ system, 4H), 7.46–7.39 (m, 2H), 7.30 (m, 1H), 4.14 (ddt, *J* 7.3, 6.9, and 5.3 Hz, 1H), 2.95 (dd, *J* 14.1 and 6.9 Hz, 1H), 2.89 (dd, *J* 14.1 and 5.7 Hz, 1H), 2.57 (dd, *J* 15.6 and 4.8 Hz, 1H), 2.52 (dd, *J* 15.6 and 7.3 Hz, 1H), 2.37 (s, 3H), 1.45 (s, 9H). ^{13}C NMR: δ 199.9, 143.6, 141.8, 141.1, 136.4, 131.5, 131.2, 130.1, 127.8, 126.1, 125.9, 68.5, 50.0, 48.6, 38.1, 29.7, 21.4; MS (FAB$^+$) *m*/*z* 391 (100) $[M+1]^+$, 373 (12) $[M^+–H_2O]$, 307 (23), 91 (20), 89 (20); HRMS $[M+1]^+$: Calcd for $C_{21}H_{27}O_3S_2$: 391.1401; found, 391.1408.

3.2.2. *S*-*tert*-Butyl [3*S*,(S)*S*]-3-hydroxy-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (4). Compound **4** was obtained as the minor adduct, following the above general procedure, from **2a** at different experimental conditions (see Table 1). It was characterized from a 61:39 mixture of **3** and **4**, obtained by flash-column chromatography (ethyl acetate–hexane 1:2). ^1H NMR: (representative parameters) δ 4.13 (m, 1H), 2.94 (dd, *J* 14.5 and 7.0 Hz, 1H), 2.85 (dd, *J* 14.0 and 5.4 Hz, 1H), 2.65–2.43 (m, 2H); ^{13}C NMR: (representative parameters) δ 199.8, 69.4, 51.0.

3.2.3. *S*-*tert*-Butyl [2*R*,3*R*,(S)*S*]-3-hydroxy-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (5). Compound **5** was obtained from **2e** as a 83:17 mixture of **5** and **6**, following the above general procedure at 0 °C for 3 h. The mixture was purified by flash-column chromatography (ethyl acetate–hexane 1:1). Combined yield: 73%. Crystallization (ethyl acetate–hexane) afforded pure **5** as a white solid. Yield: 51%. Mp: 108–110 °C; $[\alpha]_D^{20}$ −85.5 (*c* 2.5, $CHCl_3$); IR (film): 3372, 2924, 1675, 1455 cm^{-1}; ^1H NMR: δ 7.75 (m, 1H), 7.47 and 7.25 (AA′BB′ system, 4H), 7.42–7.31 (m, 3H), 3.73 (m, 1H), 3.08 (d, *J* 7.7 Hz, 1H), 2.98 (dd, *J* 14.1 and 4.4 Hz, 1H), 2.91 (dd, *J* 14.1 and 8.4 Hz, 1H), 2.67 (m, 1H), 2.37 (s, 3H), 1.43 (s, 9H), 1.24 (d, *J* 6.9 Hz, 3H); ^{13}C NMR: δ 204.5, 143.7, 141.7, 141.1, 137.4, 131.2, 131.1, 130.0, 127.7, 126.2, 125.7, 74.2, 53.3, 48.5, 37.1, 29.7, 21.3, 15.0; MS (FAB$^+$) *m*/*z* 405 (100) $[M+1]^+$, 351 (19), 259 (30), 91(17), 89(9); HRMS $[M+1]^+$: Calcd for $C_{22}H_{29}O_3S_2$: 405.1558; found: 405.1572. Anal. Calcd for $C_{22}H_{28}O_3S_2$: C, 65.32; H, 6.98; S, 15.85. Found: C, 65.27; H, 6.88; S, 15.43.

3.2.4. *S*-*tert*-Butyl [2*S*,3*R*,(S)*S*]-3-hydroxy-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (6). Compound **6** was obtained as the minor adduct from **2e**, following the above general procedure at different experimental conditions (see Table 2). It was characterized from a 37:63 mixture of **5** and **6** obtained by flash-column chromatography (ethyl acetate–hexane 1:1). ^1H NMR: (representative parameters) δ 3.89 (m, 1H), 2.91–2.83 (m, 2H), 2.60 (dq, *J* 6.9 and 4.8 Hz, 1H), 1.45 (s, 9H), 1.23 (d, *J* 6.9 Hz, 3H); ^{13}C NMR: (representative parameters) δ 204.3, 74.1, 53.4, 48.2, 36.4, 29.6, 12.7.

3.2.5. (3*R*)-4-Phenylbutane-1,3-diol[35] (7). A 1 M solution of tetrabutylammonium fluoride in THF (0.59 mL, 0.59 mmol) was added to a solution of monoprotected diol **9** (0.12 mmol) in dichloromethane (1 mL) under an argon atmosphere. The reaction mixture was stirred for 18 h and then, quenched with an aqueous 1 M solution of HCl and extracted with dichloromethane (3×3 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:1). Yield: 77%, colorless oil; $[\alpha]_D^{20}$ +21.0 (*c* 0.6, $CHCl_3$); ^1H NMR: δ 7.35–7.20 (m, 5H), 4.09 (m, 1H), 3.92–3.78 (m, 2H), 2.82 (dd, *J* 13.3 and 5.2 Hz, 1H), 2.76 (dd, *J* 13.3 and 7.7 Hz, 1H), 2.38 (br s, 2H), 1.80–1.72 (m, 2H); ^{13}C NMR: δ 137.9, 129.4, 128.6, 126.6, 73.0, 61.7, 44.3, 37.7.

3.2.6. *S*-*tert*-Butyl [3*R*,(S)*S*]-4-[2-(*p*-tolylsulfinyl)phenyl]-3-(triisopropylsilyloxy)butanethioate (8). Triisopropylsilyl trifluoromethanesulfonate (72.9 μL, 0.27 mmol) was added to a solution of **3** (0.18 mmol) in anhydrous dichloromethane (3 mL) and 2,6-lutidine (41.6 μL, 0.36 mmol) under an argon atmosphere, and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water, extracted with CH_2Cl_2 (3×3 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4) affording pure **8** as a colorless oil. Yield: 90%; $[\alpha]_D^{20}$ −94.0 (*c* 3.9, $CHCl_3$); IR (film): 2961, 2866, 1680, 1462 cm^{-1}; ^1H NMR: δ 7.98 (m, 1H), 7.49 and 7.23 (AA′BB′ system, 4H), 7.45–7.32 (m, 3H), 4.51 (q, *J* 6.0 Hz, 1H), 3.00 (dd, *J* 14.3 and 6.6 Hz, 1H), 2.95 (dd, *J* 14.3 and 6.2 Hz, 1H), 2.48 (dd, *J* 14.9 and 5.6 Hz, 1H), 2.42 (dd, *J* 14.9 and 6.4 Hz, 1H), 2.35 (s, 3H), 1.43 (s, 9H), 0.96 (m, 21H); ^{13}C NMR: δ 197.7, 143.9, 142.0, 141.8, 136.1, 131.2, 130.7, 130.0, 127.7, 126.2, 124.7, 69.6, 51.4, 48.2, 39.1, 29.7, 21.4, 18.0, 12.5; MS (FAB$^+$) *m*/*z* 547 (50) $[M+1]^+$, 503 (100) $[M^+–CH(CH_3)_2]$; HRMS $[M+1]^+$: Calcd for $C_{30}H_{47}O_3S_2Si$: 547.2735; found, 547.2746.

3.2.7. (*R*)-4-Phenyl-3-(triisopropylsilyloxy)butan-1-ol (9). An excess amount of Raney nickel was added, under hydrogen atmosphere, to a solution of silylated alcohol **8** (85 mg, 0.15 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 16 h, and then, filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. Yield: 91%, colorless oil; $[\alpha]_D^{20}$ −15.0 (*c* 0.6, $CHCl_3$); IR (film): 3355, 3063, 2866, 1463 cm^{-1}; ^1H NMR: δ 7.22–7.07 (m, 5H), 4.25 (m, 1H), 3.84 (m, 1H), 3.64 (m, 1H), 2.95 (dd, *J* 13.2 and 4.9 Hz, 1H), 2.77 (dd, *J* 13.2 and 9.4 Hz, 1H), 2.48 (m, 1H, OH), 1.72 (m, 1H), 1.48 (m, 1H), 1.03 (m, 21H); ^{13}C NMR: 138.2, 129.3, 128.4, 126.0, 73.5, 59.9, 43.2, 36.4, 18.1, 12.6; MS (FAB$^+$) *m*/*z* 323 (27) $[M+1]^+$, 279 (20) $[M–CH(CH_3)_2]^+$, 131 (100), 91 (24); HRMS $[M+1]^+$: Calcd for $C_{19}H_{35}O_2Si$: 323.2406; found, 323.2396.

3.2.8. (2*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-phenylbutan-2-ol (10). It was obtained from diol **7**, following the reported procedure[30] $[\alpha]_D^{20}$ +10.6 (*c* 0.6, $CHCl_3$).

3.2.9. *S*-*tert*-Butyl [2*R*,3*R*,(S)*S*]-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]-3-(triisopropylsilyloxy)butanethioate (13). Triisopropylsilyl trifluoromethanesulfonate (66.8 μL, 0.25 mmol) was added to a solution of **5** (0.16 mmol) in

anhydrous dichloromethane (3 mL) and 2,6-lutidine (38.5 μL, 0.33 mmol) under an argon atmosphere, and the mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with water, extracted with CH_2Cl_2 (3×3 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4) affording pure **13** as a colorless oil. Yield: 95%; $[\alpha]_D^{20}$ −110.0 (*c* 4.1, $CHCl_3$); IR (film): 2943, 2866, 1680, 1462 cm^{-1}; ^1H NMR: δ 7.95–7.92 (m, 1H), 7.49 and 7.34 (AA′BB′ system, 4H), 7.42–7.29 (m, 3H), 4.49 (dt, *J* 8.7 and 3.0 Hz, 1H), 2.85–2.29 (m, 2H), 2.76 (dd, *J* 14.3 and 2.6 Hz), 2.34 (s, 3H), 1.46 (s, 9H), 1.23 (d, *J* 7.0 Hz, 3H), 1.04 (m, 7H), 1.89 (m, 14H); ^{13}C NMR: δ 201.6, 144.6, 142.2, 141.4, 137.1, 130.9, 130.5, 129.9, 127.6, 125.9, 124.5, 74.5, 55.0, 48.1, 34.5, 29.8, 21.3, 18.0, 17.9, 17.6, 12.6, 12.3, 9.8. MS (ES^+): 583 (32), 561 (47), 471 (100), 387 (22); HRMS $[M+23]^+$: Calcd for $C_{31}H_{48}O_3NaSiS_2$: 583.2706; found, 583.2704. $[M+1]^+$: Calcd for $C_{31}H_{49}O_3SiS_2$: 561.2886; found, 561.2914.

3.2.10. (2*S*,3*R*)-2-Methyl-4-phenyl-3-(triisopropylsilyloxy)butan-1-ol (14). An excess amount of Raney nickel was added, under hydrogen atmosphere, to a solution of the silylated alcohol **13** (128 mg, 0.23 mmol) in ethanol (4 mL). The reaction mixture was stirred at room temperature for 17 h, and then filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4) affording pure **14** as a colorless oil. Yield: 91%; $[\alpha]_D^{20}$ +11 (*c* 6.4, $CHCl_3$); IR (film): 3384, 3063, 2866, 1463 cm^{-1}; ^1H NMR: δ 7.23–7.07 (m, 5H), 4.15 (ddd, *J* 8.7, 5.5, and 2.4 Hz, 1H), 3.90 (dd, *J* 11.0 and 3.9 Hz, 1H), 3.46 (m, 1H), 2.94 (dd, *J* 13.6 and 5.6 Hz, 1H), 2.85 (dd, *J* 13.6 and 9.1 Hz, 1H), 2.54 (br s, 1H), 1.57 (m, 1H), 1.03 (m, 7H), 0.98 (m, 17H); ^{13}C NMR: δ 138.4, 129.2, 128.4, 126.2, 78.7, 64.4, 41.5, 36.8, 18.2, 18.1, 17.6, 14.8, 12.8, 12.3; HRMS (ES^+) $[M+23]^+$: Calcd for $C_{20}H_{36}O_2NaSi$: 359.2376; found, 359.2369. $[M+1]^+$, Calcd for $C_{20}H_{37}O_2Si$: 337.2557; found, 337.2558.

3.2.11. (2*S*,3*R*)-2-Methyl-4-phenylbutane-1,3-diol (11).[32] A 1 M solution of tetrabutylammonium fluoride in THF (0.95 mL, 0.95 mmol) was added to a solution of monoprotected diol **14** (0.19 mmol) in dichloromethane (2 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 60 h and then filtered through a silica gel pad, which was washed with ethanol, and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:1). Yield: 76%, colorless oil; $[\alpha]_D^{20}$ +49 (*c* 2.3, $CHCl_3$). [Lit.[32] $[\alpha]_D^{25}$ +59 (*c* 0.27, $CHCl_3$)]; ^1H NMR: δ 7.36–7.23 (m, 5H), 3.80–3.74 (m, 2H), 3.67 (dd, *J* 10.9 and 7.1 Hz, 1H), 3.01 (dd, *J* 13.6 and 3.6 Hz, 1H), 2.90 (br s, 71H, OH), 2.66 (dd, *J* 13.6 and 9.5 Hz, 1H), 2.32 (br s, 1H), 1.81 (m, 1H), 1.01 (d, *J* 7 Hz, 3H).

3.2.12. (2*S*,3*R*) and (2*S*,3*S*)-2-Methyl-4-phenylbutane-1,3-diol (11+12).[32] An excess amount of Raney nickel was added, under hydrogen atmosphere, to a solution of the alcohol **5** (85 mg, 0.15 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 18 h, and then filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:1) affording a 83:17 mixture of **11+12**. Yield: 65%, colorless oil; ^1H NMR: (representative parameters of **12**) δ 4.10–4.04 (m, 1H), 2.78 (d, *J* 6.9 Hz, 2H), 1.95–1.87 (m, 1H), 1.04 (d, *J* 6.9 Hz, 3H).

3.2.13. [2*R*,3*R*,(S)*S*]-3-Hydroxy-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]butanoic acid (15). A solution of lithium hydroxide (1.02 mmol) in H_2O (1.5 mL) was added to a solution of **5** (0.17 mmol) in THF (1.5 mL). The reaction mixture was stirred at room temperature for 16 h, and then it was acidified with an aqueous 1 M solution of HCl, and extracted with dichloromethane (3×3 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and the solvent evaporated. Yield: 98%, colorless oil; $[\alpha]_D^{20}$ −28 (*c* 0.5, $CHCl_3$); IR (film): 3356, 2923, 1720, 1594 cm^{-1}; ^1H NMR: δ 7.65 (dd, *J* 8.0 and 1.3 Hz, 1H), 7.44 and 7.23 (AA′BB′ system, 4H), 7.41–7.30 (m, 3H), 3.82 (m, 1H), 3.07 (dd, *J* 14.1 and 8.5 Hz, 1H), 2.98 (dd, *J* 14.1 and 4.1 Hz, 1H), 2.59 (q, *J* 7.0 Hz, 1H), 2.35 (s, 3H), 1.25 (d, *J* 7.2 Hz, 3H); ^{13}C NMR: δ 178.2, 143.1, 141.9, 139.9, 137.6, 131.4, 130.1, 127.8, 126.2, 125.9, 73.5, 44.7, 37.0, 21.4, 14.3; MS (EI^+) *m/z* 315 (75) $[(M+1)-H_2O]^+$, 297 (15), 241 (33), 91 (71); HRMS $[(M+1)-H_2O]^+$: Calcd for $C_{18}H_{19}O_3S$: 315.1055; found: 315.1053.

3.2.14. Triisopropylsilyl [2*R*,3*R*,(S)*S*]-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]-3-(triisopropylsilyloxy)butanoate (16). Triisopropylsilyl trifluoromethanesulfonate (142.0 μL, 0.52 mmol) was added to an anhydrous solution of hydroxyacid **15** (0.17 mmol) and 2,6-lutidine (82 μL, 0.70 mmol) in dichloromethane (3 mL), under an argon atmosphere. The reaction mixture was stirred at room temperature for 16 h, and then, quenched with water and extracted with dichloromethane (3×3 mL). The organic extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4). Yield: 73%, colorless oil; $[\alpha]_D^{20}$ −72.0 (*c* 3.1, $CHCl_3$); IR (film): 2945, 2867, 1715, 1464 cm^{-1}; ^1H NMR: δ 7.80 (m, 1H), 7.45 and 7.20 (AA′BB′ system, 4H), 7.42–7.27 (m, 3H), 4.62 (m, 1H), 3.02–2.87 (m, 2H), 2.54 (m, 1H), 2.33 (s, 3H), 1.33–1.26 (m, 5H), 1.07 (m, 19H), 0.89 (m, 21H); ^{13}C NMR: δ 173.8, 144.8, 142.6, 141.5, 137.0, 130.5, 130.2, 129.9, 127.6, 126.0, 124.2, 74.1, 47.2, 34.7, 21.3, 17.9, 17.8, 12.7, 11.9; MS (FAB^+) *m/z* 645 (27) $[M+1]^+$, 601 (100) $[M-SiCH_3]^+$; HRMS $[M+1]^+$: Calcd for $C_{36}H_{61}O_4SSi_2$: 645.3829; found: 645.3821.

3.2.15. Triisopropylsilyl [2*R*,3*R*]-2-methyl-4-phenyl-3-(triisopropylsilyloxy)butanoate (17). An excess of activated Raney nickel was added to a solution of **16** (0.12 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 14 h under hydrogen atmosphere and then it was filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. Yield: 94%, colorless oil; $[\alpha]_D^{20}$ −6.4 (*c* 1.7, $CHCl_3$); IR (film): 3064, 2893, 1708, 1495 cm^{-1}; ^1H NMR: 7.20–7.07 (m, 5H), 4.43 (dt, *J* 8.7 and 3.4 Hz, 1H), 2.80–2.69 (m, 2H), 2.61 (dd, *J* 13.4 and 8.8 Hz, 1H), 1.32–0.79 (m, 45H); ^{13}C NMR: δ 174.0, 139.4, 129.8, 128.1, 126.1, 75.0, 46.9, 39.9, 18.1, 18.0, 17.9, 12.7, 12.0; MS (FAB^+) *m/z* 507 (8) $[M+1]^+$, 463 (100) $[M-CH(CH_3)_2]^+$, 277 (11),

91 (6); HRMS $[M+1]^+$: Calcd for $C_{29}H_{55}O_3Si_2$: 507.3689; found, 507.3677.

3.2.16. [2*R*,3*R*]-3-Hydroxy-2-methyl-4-phenylbutanoic acid (18).[33] To a solution of **17** (0.04 mmol) in THF (2.1 mL) was dropwise added hydrogen fluoride–pyridine (0.47 mL) at 0 °C. The mixture was stirred at room temperature for 17 h, and then, diluted with ether (1 mL) and cooled at 0 °C before slowly adding a saturated aqueous sodium hydrogencarbonate solution until CO_2 evolution ceased. The organic layer was discarded, and the aqueous one was extracted with ether. The combined organic phases were washed with saturated aqueous $CuSO_4$ solution, water, and brine. The organic layer was separated, dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford the acid as a yellow oil. Yield: 68% (^{1}H NMR); ^{1}H NMR: 7.37–7.21 (m, 5H), 3.93 (m, 1H), 2.95–2.59 (m, 3H), 1.32 (d, *J* 7.0 Hz, 3H).

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