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Enzymatic kinetic resolution of α-hydroxysilanes

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ABSTRACT

The enzymatic kinetic resolution of α-hydroxysilanes where the silicon bears a variety of substituents has been explored. Reactions were performed on various α-hydroxysilanes with several commercially available enzymes, solvents, acetylation reagents, and temperatures. The resulting optically active α-hydroxysilanes and their corresponding acetates were obtained in varying yields and ees.

1. Introduction

During our study of the [1,4]-Wittig rearrangement of benzyloxyallylsilanes, we became interested in the synthesis of optically active α-hydroxysilanes (Fig. 1).[1] A literature search revealed asymmetric reduction as the most common approach to such compounds. Specifically, organoborane hydride additions,[2] asymmetric hydrogenations,[3] chiral lithium amide reactions,[4] and biocatalytic transformations[5] of acylsilanes have afforded a variety of α-hydroxysilanes with high levels of enantioselectivity. In many of these examples, the starting acylsilanes are generated by the oxidation of racemic α-hydroxysilanes, which themselves are produced via Brook rearrangement-based processes.

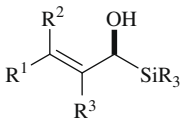

Figure 1. Optically active α-hydroxysilanes.

As the α-hydroxysilanes needed for our [1,4]-Wittig studies were also first made racemic via Brook rearrangements, we also looked into the enzymatic kinetic resolution of α-hydroxysilanes. Enzymatic esterifications or ester hydrolyses would allow us to avoid the oxidation step and provide ready access to both α-hydroxysilane enantiomers.

We only found a few reports of the enzymatic kinetic resolution of a limited number of α-hydroxysilanes. Zong et al. reported Lipase-catalyzed esterifications of 1-trimethylsilylethanol in both organic solvents and ionic liquids.[6,7] Similarly, Uejima et al. resolved 1-trimethylsilylpropanol by a hydrolase-promoted esterification.[8] In contrast, Guintchin and Bienz found that while treatment of (±)-1-[(dimethyl)(phenyl)silyl]but-2-yn-1-ol with a variety of lipases failed to give any acylated material, the corresponding racemic acetate could be partially resolved with *A. niger*.[9]

2. Results and discussion

Owing in part to the limited literature precedent, we decided to conduct our own study on the enzymatic kinetic resolution of α-hydroxysilanes that varied at both the silicon and the organic group flanking the carbinol. Initially, three different enzymes (Amano AK lipase, Amano PS lipase, and Novozym 435) were investigated in the kinetic resolution of (±)-1-hydroxyallyltrimethylsilane *rac*-**1** (Scheme 1). Reactions were run in a sealed tube filled with substrate, enzyme, vinyl acetate, and 3 Å molecular sieves as a mixture in pentane, conditions that had previously been employed during the kinetic resolution of 4-trimethylsilyl-3-butyn-2-ol.[11] The results of these screening experiments are summarized in Table 1. In all cases, (*S*)-**1** reacted faster than (*R*)-**1**, as determined by a Trost-modified Mosher analysis of the unreacted alcohol using *O*-methylmandelate.[12] The sense of enantioselection was similar to that observed by Uejima in the resolution of 1-trimethylsilylpropanol with lipase OF 360 and lipoprotein lipase in water-saturated 2,2,4-trimethylpentane, but opposite[13] to that seen by Zong in the kinetic resolution of 1-trimethylsilylethanol with Novozym 435 in $C_4MIm{\cdot}PF_6$ and with CRL in *n*-hexane.

These experiments also revealed that for the resolution of *rac*-**1**, Novozym 435 was superior to Amano AK Lipase and Amano PS lipase in that it afforded better selectivity and shorter reaction times. As such, the best conditions to emerge out of these first experiments were to place a sealed tube containing a pentane solution of the alcohol, 15 mg Novozym 435/mmol *rac*-**1**, 1.5 equiv of vinyl acetate, and 3 Å molecular sieves under a nitrogen atmosphere into an oil bath heated to 38 °C for 33 h. This protocol afforded (*S*)-acetic acid 1-(trimethylsilyl)-allyl ester (*S*)-**2** in 30% isolated yield with 98%ee as well as unreacted (*R*)-**1**, which was isolated in 33% yield with 73%ee.

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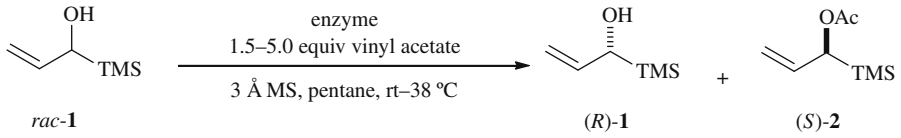


rac-**1** (*R*)-**1** (*S*)-**2**

Scheme 1. Enzymatic resolution of (±)-1-hydroxyallyltrimethylsilane **1**.

Table 1
Kinetic resolution of *rac*-**1** via Scheme 1

130 mg Amano AK Lipase/mmol[a]			130 mg Amano PS Lipase/mmol[b]			15 mg Novozym 435/mmol[c]		
Entry	Time (h)	(*S*)-**2**[c] (%ee)	Entry	Time (h)	(*S*)-**2**[c] (%ee)	Entry	Time (h)	(*S*)-**2**[c] (%ee)
1	23	73	1	22	88	1	8	99
2	96	81	2	24	93	2	13	99
3	120	80	3	48	94	3	22	99
4	168	80	4	96	92	4	27	98
5	192	82	5	169	96	5	33	98

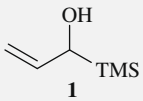
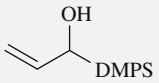
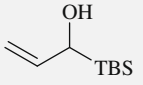
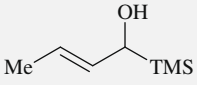
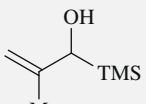
[a] Reactions using Amano AK lipase were performed at rt with 5.0 equiv of vinyl acetate in pentane containing 3 Å molecular sieves.
[b] Reactions using Amano PS lipase and Novozym 435 were performed at 38 °C with 1.5 equiv of vinyl acetate in pentane containing 3 Å molecular sieves.
[c] The absolute configuration was assigned by Mosher analysis and chiral GC analysis determined the %ee.

Additional testing showed that increasing the amount of vinyl acetate (up to 5 equiv) did not improve the selectivity or yield. Likewise, lowering the Novozym 435 loading to 10 mg/mmol *rac*-**1** resulted in longer reaction times, lower yields, and little change in the selectivity.

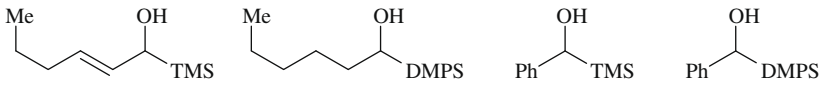
On the basis of the above results, we applied the cited procedure to a series of α-hydroxysilanes. The results from these reactions are summarized in Table 2. Unfortunately, the substrate scope proved narrow. Exchanging the TMS group for a dimethylphenylsilyl (DMPS) group **3** improved the performance of the reaction (entry 2), whereas the *tert*-butyldimethylsilyl (TBS) analogue **5** failed to react (entry 3). Substrates with an additional methyl group at either the α- or β-vinyl positions (entries 4 and 5) did not acylate at 38 °C, even with increased catalyst loadings. As Novozym 435 is stable at 70–80 °C, these substrates were exposed to higher oil bath temperatures.[14] At 78 °C and with increased catalyst loading, (*E*)-1-(trimethylsilyl)-2-buten-1-ol *rac*-**6** did react, albeit slowly and with low yield and poor selectivity (entry 4). Other solvents, including CH_2Cl_2, THF, benzene, toluene, and *t*-amyl alcohol, were examined, but none of which proved superior to pentane.

All other α-hydroxysilanes screened (Fig. 2) failed to react. Even raising the amount of Novozym 435 to 130 mg/mmol of silane, upping the equivalents of vinyl acetate, and/or running the reactions at elevated temperatures did not promote acylation.

Table 2
Results of attempted kinetic resolutions of α-hydroxysilanes with Novozym 435[a]

Entry	Starting α-hydroxysilane	mg/mmol Novozym 435	Time (h)	Temp (°C)	(*R*)-Hydroxysilane %ee[b]	(*R*)-Hydroxysilane % yield	(*S*)-Acetate %ee[b]	(*S*)-Acetate % yield
1	 **1**	15	33	38	73[b]	33% (*R*)-**1**	>98[b]	30% (*S*)-**2**
2	 **3**	15	49	38	>99[b]	43% (*R*)-**3**	>99[b]	37% (*S*)-**4**
3	 **5**	15	24	38	n/a	No reaction	n/a	No reaction
4	 **6**	75	85	78	9[c]	11% (*R*)-**6**	—[d]	12% (*S*)-**7**
5	 **8**	15–75	17	38	n/a	No reaction	n/a	No reaction

[a] Reactions were run in a sealed tube containing substrate, Novozym 435, 1.5 equiv vinyl acetate, 3 Å MS, and pentane.
[b] The absolute stereochemistry was assigned by Mosher analysis and either chiral GC or HPLC analysis determined the %ee.
[c] The absolute stereochemistry and %ee were determined by comparing optical rotations of the unreacted alcohol to the literature $[\alpha]_D$.[10]
[d] All chromatographic and spectroscopic attempts to resolve the enantiomers and thus determine the %ee failed.



9 **10** **11** **12**

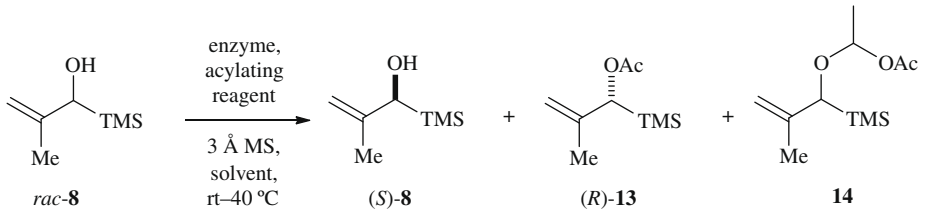
Figure 2. Failed α-hydroxysilanes.

In an attempt to overcome the poor reactivity exhibited by the methylated substrates (Table 2, entries 4 and 5), we turned to several commercially available enzymes that are known to acetylate secondary alcohols. Thus we tested Amano AK lipase, Amano PS-D I lipase, Amano PS-C II lipase, and CRL in the kinetic resolution of 2-methyl-1-(trimethylsilyl)-2-propen-1-ol *rac*-**8** (Scheme 2). These enzymes afforded some level of reactivity (Table 3), with Amano PS-D I lipase giving the best results in terms of enantioselectivity. As shown in entry 6, acetate (*R*)-**13** was obtained in 13% yield with 87%ee, with the alcohol (*S*)-**8** being recovered in 19% yield with 99%ee. The stereochemical preference was opposite to that observed during the resolution of *rac*-**1** with Novozym 435.

The low yields of (*R*)-**13** and (*S*)-**8** were partly due to formation of the acetylated hemiacetal **14** as a main product of the reaction.[15] Again, adjustments in the amount of Amano PS-C I lipase and vinyl acetate and/or solvent did not minimize this acetal formation or improve the resolution results.

To more directly compare the reactivity of Amano PS-D I lipase versus Novozym 435, *rac*-**1** was resolved with Amano PS-D I lipase in the presence of 1.5 equiv of vinyl acetate in toluene at room temperature (Scheme 3). After ~18 h, *rac*-**1** was completely consumed and acetate (*S*)-**2** was formed in 41% yield with 97%ee. This indicates that the observed absolute stereochemistry is highly influenced by relatively small changes to the side chain structure of the α-hydroxysilane.

While the reactions of *rac*-**1** and *rac*-**8** with Amano PS-D I lipase afforded different stereochemical outcomes, they were similar in that both afforded acetal co-products. In the case of *rac*-**1**, acetal



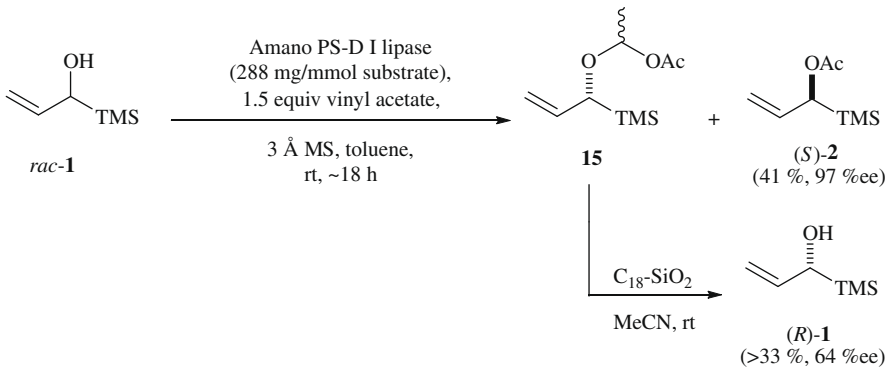
rac-**8** (*S*)-**8** (*R*)-**13** **14**

Scheme 2. Enzymatic resolution of *rac*-**8**.

Table 3
Kinetic resolution of *rac*-**8**[a]

Entry	Lipase (mg/mmol)	Acylation reagent (equiv)	Solvent	Time (h)	Temp (°C)	(*S*)-**8** %ee[b]	(*S*)-**8** % yield[c]	(*R*)-**13** %ee[b]	(*R*)-**13** % yield[c]
1[d]	Amano PS-C II (144)	*p*-ClC_6H_4OAc (1.5)	CH_2Cl_2	209	rt–40	2	14	66	2
2	Amano AK (72)	Vinyl acetate (16.2)	Neat	209	rt	>1[e]	81	21	13
3	CRL (30)	Vinyl acetate (16.0)	Cyclohexane	352	rt	>48[e]	57	9	5
4	Amano PS-D I (144)	Vinyl acetate (1.5)	Toluene	115	40	56	89	74	10
5	Amano PS-D I (144)	Vinyl acetate (1.5)	Toluene	306	10	>99	2	87	5
6	Amano PS-D I (288)	Vinyl acetate (3.0)	Toluene	112	rt	>99	19	87	13
7	Amano PS-D I (432)	Vinyl acetate (1.5)	Toluene	140	rt	90	22	87	16

[a] Reactions were run in a sealed tube containing the substrate, enzyme, acylation reagent, 3 Å MS, and the solvent.
[b] The absolute configuration was determined by Mosher analysis and chiral GC analysis determined the ee.
[c] Yields were determined by GC using decane as an internal standard.
[d] 1.0 equiv triethylamine added.
[e] GC peaks corresponding to (*R*)- and (*S*)-**8** were partially overlapping.

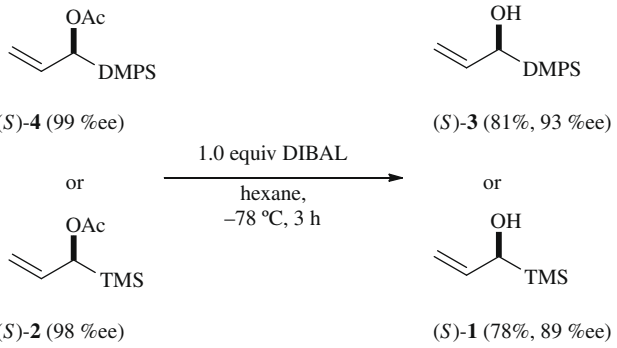


rac-**1** **15** (*S*)-**2** (41 %, 97 %ee) (*R*)-**1** (>33 %, 64 %ee)

Scheme 3. Enzymatic resolution of *rac*-**1** with Amano PS-D I lipase and hydrolysis of **15**.

15 was formed.[16] Compound **15** could not be purified by silica gel column chromatography or fractional distillation. However, we tentatively assigned its structure based on ^{1}H, ^{13}C, HMQC, HMBC, TOCSY, COSY, and IR analyses. Furthermore, we independently prepared **15** by the reduction of *rac*-**2** with DIBAL followed by acylation of the resultant hemiacetal. Interestingly, this newly prepared material had the same impurity profile of **15** made during the resolution. Treatment of the impure acetal[16] with C_{18} silica gel in CH_3CN at room temperature gave (*R*)-**1** with 64%ee in >33% yield (Scheme 3).

Although the substrate scope was not as broad as we had hoped, effective resolutions were realized for **1**, **3**, and **8**. As the advantage of a resolution is the ability to generate both enantiomers, we next investigated the procedures for converting the enantioenriched acetates into their corresponding chiral α-hydroxysilanes. Experimenting on (*S*)-**4**, a variety of reagents were investigated but many of these led to a decrease in the enantiomeric excess. The most efficient results were achieved with DIBAL (Scheme 4). For example, when essentially enantiopure (*S*)-**4** (99%ee) was treated with 1.0 equiv of DIBAL in hexane at −78 °C, the corresponding (*S*)-1-(dimethylphenylsilyl)-2-propen-1-ol (*S*)-**3** was obtained in 81% isolated yield with only modest loss of %ee (>99:1 to 96.5:3.5 er). The same procedure could be applied to (*S*)-**2**, albeit with a slightly greater loss of enantiopurity.



Scheme 4. DIBAL reduction of optically active acetates.

3. Conclusions

In conclusion, we have investigated the scope and limitation of enzymatic kinetic resolution of α-hydroxysilanes in combination with different enzymes, solvents, temperatures, and acetylation reagents. The reactions are sensitive to the structures of both the silyl group and the organic side chain. (±)-1-Hydroxyallyltrimethylsilane and its DMPS analogue respond well to Novozym 435. (±)-2-Methyl-1-(trimethylsilyl)-2-propen-1-ol can be resolved with Amano PS-D I lipase. The addition of the α-methyl group reverses the absolute stereochemistry of the esterification. The optically active acetates so formed can be converted to their enantioenriched α-hydroxysilanes with DIBAL. Unfortunately, the addition of substituents to the β-position of (±)-1-hydroxyallyltrimethylsilane affords substrates that do not resolve under the conditions described herein. We are currently directing efforts to overcome this limitation.

4. Experimental

4.1. General

The NMR spectra were recorded on Varian UnityPlus-500 spectrometer. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. High-resolution mass spectra were acquired at the Michigan State University Mass Spectrometry facility using a Waters QTOF Ultima mass spectrometer equipped with an electrospray ionization (ESI) source. IR spectra were recorded on IR/42 spectrometer by Nicolet at 20 °C. Column chromatography was performed on Siliaflash® P60 by Silicycle. TLC was performed on aluminum-backed TLC plates by Silicycle. The enantiomeric excess (ee) values were determined on an Agilent 1100 series HPLC using a Chiralcel OJ or OD-H columns or on a Varian 3900 GC using a β-dex tm 325 column.

4.2. Preparation of α-hydroxysilanes

4.2.1. 1-Hydroxyallyltrimethylsilane 1

To a cold (−78 °C), stirred solution of allyl alcohol (5.4 mL, 80.0 mmol) in THF (60 mL) under nitrogen conditions was added *n*-BuLi (52.8 mL of a 1.6 M solution in hexane, 84.0 mmol) dropwise via a cannula. Upon complete addition of base, the reaction mixture was stirred for 1 h. Next, TMSCl (10.1 mL, 80.0 mmol (freshly distilled over CaH_2)) was added dropwise via a syringe. Following this addition, the reaction mixture was stirred for 1.5 h and then *t*-BuLi (56.8 mL of a 1.7 M solution in hexane, 97.0 mmol) was added dropwise via a cannula. After stirring for an additional 1.5 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl and then diluted with ether. The phases were separated and the aqueous phase was extracted with ether. The combined organics were washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford 6.4 g of **1** as a colorless oil (61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (ddd, J = 17.2, 10.7, 5.3 Hz, 1H), 5.04 (ddd, J = 17.2, 2.1, 1.6 Hz, 1H), 4.96 (ddd, J = 10.7, 1.9, 1.6 Hz, 1H), 3.99–3.97 (m, 1H), 1.35 (br s, 1H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 109.4, 69.0, −4.3. The spectral data were consistent with the literature values.[17]

4.2.2. 1-(Dimethylphenylsilyl)-2-propen-1-ol 3

The reaction was carried out on allyl alcohol (2.7 mL, 40.0 mmol) as described in the preparation of **1** (Section 4.2.1) except that chlorodimethylphenylsilane (7.0 mL, 42.0 mmol) was used as the silylating agent and that following its addition, the reaction mixture was stirred for 1.25 h and that after the *t*-BuLi addition, it was stirred for an additional 2.0 h. This modified protocol afforded 3.2 g of **3** as a pale yellow oil (42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5–7.54 (m, 2H), 7.39–7.33 (m, 3H), 5.98 (ddd, J = 17.2, 10.7, 5.3 Hz, 1H), 5.07–5.03 (m, 1H), 5.00–4.97 (m, 1H), 4.21 (ddd, J = 5.3, 2.1, 2.1 Hz, 1H), 1.28 (br s, 1H), 0.34 (s, 1H), 0.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 136.0, 134.2, 129.5, 127.8, 110.0, 68.4, −5.8, −6.1; IR (neat) 3420 cm^{-1}; HRMS (EI) (m/z) calcd for $C_{11}H_{16}OSi$ $[M]^+$ 192.0970, found 192.0963. The spectroscopic data were consistent with the literature values.[18]

4.2.3. 1-[(1,1-Dimethylethyl)dimethylsilyl]-2-propen-1-ol 5[19]

To a cold (−78 °C), stirred solution of (1,1-dimethylethyl)dimethyl(2-propen-1-yloxy)silane (8.3 g, 48.6 mmol) in THF (200 mL) under nitrogen condition were added tetramethylethylenediamine (13.1 mL, 88.0 mmol) and then *sec*-BuLi (59.7 mL, 1.4 M in cyclohexane, 84.0 mmol) dropwise. The reaction mixture was warmed up to −40 °C and then stirred for 3.5 h. It was recooled to −78 °C and the reaction was quenched by the addition of AcOH (17.9 mL, 314.0 mmol) in THF (53 mL). The reaction mixture was warmed to room temperature and extracted with ether. Combined organic phases were washed with water and brine and dried over $MgSO_4$. The residue was purified over silica gel column chromatography using EtOAc/hexane (1:30) to afford 0.7 g of **5** as a colorless oil (9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (ddd, J = 17.2, 10.7, 5.3 Hz, 1H), 5.06 (ddd, J = 17.2, 2.1, 1.6 Hz, 1H), 4.97 (ddd,

J = 10.7, 3.5, 1.6 Hz, 1H), 4.16 (ddd, J = 5.3, 2.1, 2.1 Hz, 1H), 0.94 (s, 9H), 0.11 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 109.4, 67.6, 26.0, 17.0, −7.6, −9.2. The spectroscopic data were consistent with the literature values.[20]

4.2.4. (2*E*)-1-(Trimethylsilyl)-2-buten-1-ol 6

The reaction was carried out as described for the preparation of **1** (Section 4.2.1) except that (2*E*)-2-buten-1-ol (5.7 mL, 67.5 mmol) served as the alcohol and reaction times following the addition of TMSCl and *t*-BuLi addition were 2.5 h and 2.0 h, respectively. This modified protocol afforded 5.3 g of **6** as a pale yellow oil (54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61–5.42 (m, 2H), 3.86 (doublet of pentets, J = 6.8, 1.4 Hz, 1H), 1.68 (dt, J = 6.3, 1.4 Hz, 3H), 1.27 (br s, 1H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.4, 122.2, 68.4, 17.8, −4.2; IR (neat) 3416 cm^{-1}; HRMS (EI) (m/z) calcd for $C_7H_{16}OSi$ $[M]^+$ 144.0970, found 144.0970. The spectroscopic data were consistent with the literature values.[21]

4.2.5. 2-Methyl-1-(trimethylsilyl)-2-propen-1-ol 8

The reaction was carried out as described for the preparation of **1** (Section 4.2.1) except that 2-methyl-2-propen-1-ol (6.6 mL, 79.0 mmol) served as the alcohol and that following the addition of TMSCl, the reaction mixture was stirred for 1.0 h, before *t*-BuLi (55.6 mL 1.7 M in hexane, 95.0 mmol) was added dropwise via a cannula. After stirring for an additional 3 h at −33 °C, the cold bath was removed and a solution of acetic acid (5.4 mL, 95.0 mmol) in THF (5 mL) was added. After the reaction mixture was stirred for 30 min, saturated aqueous $NaHCO_3$ (60 mL) and pentane (100 mL) were added. Workup and chromatography as previously described afforded 9.1 g of **8** as a colorless oil (81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (oct, J = 0.8 Hz, 1H), 4.74 (dq, J = 3.0, 1.5 Hz, 1H), 3.86 (s, 1H), 1.69 (t, J = 0.7 Hz, 3H), 1.29 (br d, J = 2.60, 1H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 106.3, 71.6, 20.7, −3.4. The spectroscopic data were consistent with the literature values.[22]

4.2.6. (2*E*)-1-(Trimethylsilyl)-2-hexene-1-ol 9

The reaction was carried out as described for the preparation of **1** (Section 4.2.1) except that (2*E*)-2-hexen-1-ol (2.3 mL, 20.0 mmol) served as the alcohol, *sec*-BuLi (17.1 mL 1.4 M in cyclohexane, 24.0 mmol) was used in the place of *t*-BuLi, and reaction times following the addition of TMSCl and *s*-BuLi addition were 2.5 h and 2.0 h, respectively. This modified protocol afforded 1.9 g of **9** as a pale yellow oil (57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (dddd, J = 1.3, 1.3, 6.6, 15.4 Hz, 1H), 5.47 (dddd, J = 1.5, 6.8, 6.8, 15.1 Hz, 1H), 3.89–3.87 (m, 1H), 2.02–1.97 (m, 2H), 1.37 (sext, J = 7.3 Hz, 2H), 1.27 (br s, 1H), 0.87 (t, J = 7.4 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.4, 127.5, 68.4, 34.6, 22.8, 13.6, −4.2. The spectroscopic data were consistent with the literature values.[23]

4.2.7. 1-(Dimethylphenylsilyl)-1-hexanol 10[24]

Chlorodimethylphenylsilane (9.7 mL, 57.9 mmol) was added to a rapidly stirring mixture of lithium wire (0.9 g, 135.0 mmol (fine cut)) in THF (60 mL) at room temperature. The reaction mixture was stirred for 31 h at room temperature, giving a deep red solution of $PhMe_2SiLi$. This $PhMe_2SiLi$ solution was then added dropwise via a cannula to a cold (−78 °C) stirred solution of hexanal (0.7 mL, 5.8 mmol) in THF (6 mL). The reaction mixture was stirred for 30 min at the same temperature before the reaction being quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was extracted twice with ether. The combined organics were washed with water and brine and then dried over $MgSO_4$. After filtration and evaporation, the residue was purified over silica gel column chromatography using Et_2O/hexane (1:9) to afford 0.6 g of **10** as a pale yellow oil (44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2H), 7.37–7.34 (m, 3H), 3.50–3.47 (m, 1H), 1.55–1.47 (m, 3H), 1.30–1.18 (m, 6H), 0.85 (t, J = 7.04 Hz, 3H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 134.1, 129.2, 127.9, 65.5, 33.4, 31.7, 26.5, 22.6, 14.0, −5.3, −5.7. The spectroscopic data were consistent with the literature values.[25]

4.2.8. α-(Trimethylsilyl)-benzenemethanol 11[26]

At first, DMSO (0.7 mL, 11.0 mmol) was added dropwise by syringe to a stirred cold (−78 °C) solution of oxalyl chloride (0.8 mL, 10.5 mmol) in anhydrous ether under nitrogen. The reaction mixture was warmed to −35 °C and then stirred for 1 h. It was then cooled back down to −78 °C and (trimethylsilyl)methanol (1.2 mL, 10.0 mmol) was added dropwise. The reaction mixture was warmed to −35 °C and stirred for 2 h. It was again cooled to −78 °C and triethylamine (6.9 mL, 50.0 mmol (freshly distilled over CaH_2)) was added dropwise. The reaction mixture was stirred for 2 h at the same temperature and then warmed to 0 °C and stirred for 4 h. It was recooled to −78 °C and bromophenylmagnesium (9.0 mL, 50.0 mmol) was added dropwise. After the reaction mixture was stirred for 2 h at −78 °C, water (20 mL) and ether (90 mL) were added and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with ether. Combined organics were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was purified over silica gel column chromatography using Et_2O/hexane (1:9) to afford 0.8 g of **11** as a colorless oil (47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.18–7.13 (m, 3H), 4.51 (s, 1H), 1.65 (br s, 1H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 128.1, 125.8, 124.9, 70.6, −4.2. The spectroscopic data were consistent with the literature values.[27]

4.2.9. α-(Dimethylphenylsilyl)-benzenemethanol 12

The reaction was carried out as described for the preparation of **10** (Section 4.2.7) except that $PhMe_2SiLi$ was formed over 36 h and benzaldehyde (0.4 mL, 4.3 mmol) served as the aldehyde. This modified protocol afforded 0.4 g of **12** as a colorless oil (40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.39–7.31 (m, 3H), 7.25–7.21 (m, 2H), 7.16–7.12 (m, 1H), 7.08–7.05 (m, 2H), 4.69 (s, 1H), 1.64 (br s, 1H), 0.28 (s, 3H), 0.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 135.9, 134.3, 129.4, 128.0, 127.8, 125.9, 125.1, 70.0, −5.4, −6.3. The spectroscopic data were consistent with the literature values.[23]

4.3. Acylation of α-hydroxysilanes

4.3.1. Acetic acid 1-(trimethylsilyl)-allyl ester 2

To a solution of 1-hydroxyallyltrimethylsilane (0.6 g, 4.81 mmol) and pyridine (0.3 mL, 4.8 mmol) was added acetic anhydride (0.4 mL, 4.8 mmol). The reaction mixture was stirred at room temperature overnight. It was diluted with Et_2O, and then sequentially extracted with 1 M HCl, saturated aqueous $NaHCO_3$, and brine. The ethereal layer was dried over $MgSO_4$, filtered, and evaporated to afford 0.5 g of **2** as a pale yellow oil (67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.0, 10.9, 5.8 Hz, 1H), 5.17 (ddd, J = 5.8, 1.8, 1.8 Hz, 1H), 4.98 (ddd, J = 9.3, 1.7, 1.7 Hz, 1H), 4.96 (m, 1H), 2.07 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 134.9, 111.3, 70.6, 20.9, −4.0; IR 1734 (s) cm^{-1}; HRMS (EI) (m/z) calcd for $C_8H_{16}O_2Si$ $[M]^+$ 172.0920, found 172.0923. The spectroscopic data were consistent with the literature values.[28]

4.3.2. Acetic acid 1-(dimethylphenylsilyl)-prop-2-enyl ester 4

Applying the acylation procedure described for the preparation of **2** to 1-(dimethylphenylsilyl)-2-propen-1-ol (0.4 g, 2.6 mmol) afforded 0.5 g of **4** as a pale yellow oil (85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.40–7.33 (m, 3H), 5.82–5.75 (m, 1H), 5.39 (ddd, J = 5.7, 1.9, 1.9 Hz, 1H), 4.98 (ddd, J = 4.6, 1.6,

1.6 Hz, 1H), 4.95–4.94 (m, 1H), 2.04 (s, 3H), 0.34 (d, J = 0.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 135.5, 134.9, 134.3, 129.8, 128.1, 112.1, 70.2, 21.2, −5.3, −5.4; IR (neat) 1740 cm^{-1}; HRMS (EI) (m/z) calcd for $C_{13}H_{18}O_2Si$ $[M]^+$ 234.1076, found 234.1078. The spectroscopic data were consistent with the literature values.[18a]

4.3.3. Acetic acid 1-(trimethylsilyl)-but-2(*E*)-enyl ester 7

Applying the acylation procedure described for the preparation of **2** to (2*E*)-1-(trimethylsilyl)-2-buten-1-ol (0.7 g, 5.0 mmol) afforded 0.5 g of **7** as a substrate (colorless oil, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49–5.39 (m, 2H), 5.09–5.06 (m, 1H), 2.02 (s, 3H), 1.65 (dd, J = 4.8, 1.1 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 127.5, 124.5, 70.3, 21.0, 17.8, −3.9; IR (neat) 1742 cm^{-1}; HRMS (EI) (m/z) calcd for $C_9H_{18}O_2Si$ $[M]^+$ 186.1076, found 186.1079. The spectroscopic data were consistent with the literature values.[22]

4.3.4. Acetic acid 2-methyl-1-(trimethylsilyl)-allyl ester 13

Applying the acylation procedure described for the preparation of **2** to 2-methyl-1-(trimethylsilyl)-2-propen-1-ol (0.1 g, 0.7 mmol) afforded 0.07 g of **13** as a pale yellow oil (55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.72–4.71 (m, 1H), 4.69–4.67 (m, 1H), 2.06 (s, 3H), 1.71–1.69 (m, 3H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 143.3, 107.9, 72.7, 21.0, 20.7, −3.3; IR (neat) 1770 cm^{-1}; HRMS (EI) (m/z) calcd for $C_9H_{18}O_2Si$ $[M]^+$ 186.1076, found 186.1078. The spectroscopic data were consistent with the literature values.[29]

4.4. Kinetic resolution of α-hydroxysilanes (Table 2)

4.4.1. Resolution of (±)-1-hydroxyallyltrimethylsilane 1 (Table 2, entry 1)

Novozym 435 (30 mg; 15 mg/mmol (*rac*)-alcohol) and vinyl acetate (0.3 mL, 3.0 mmol) were added to a tube containing a mixture of (±)-1-hydroxyallyltrimethylsilane **1** (261 mg, 2.0 mmol) and activated 3 Å molecular sieves in pentane (1.0 mL). The tube was purged with N_2 and sealed. The sealed tube was placed in a 38 °C oil bath and the reaction mixture was stirred with the reaction progress being monitored by GC. After ~50% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite 503, concentrated, and purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford optically active acetate (*S*)-**2** (104 mg, 30%, $[\alpha]_D$ = −17.5 (*c* 1.03, $CHCl_3$, >98%ee)) and unreacted optically active alcohol (*R*)-**1** (86 mg, 33%, $[\alpha]_D$ = −7.1 (*c* 1.05, $CHCl_3$, 73%ee)).

4.4.2. Resolution of (±)-1-(dimethylphenylsilyl)-2-propen-1-ol 3 (Table 2, entry 2)

Applying the kinetic resolution procedure described in Section 4.4.1 to (±)-1-(dimethylphenylsilyl)-2-propen-1-ol **3** (385 mg, 2.0 mmol) afforded after ~49% conversion optically active acetate (*S*)-**4** (174 mg, 37%, $[\alpha]_D$ = −10.1 (*c* 1.26, $CHCl_3$, 99%ee)) and unreacted optically active alcohol (*R*)-**3** (167 mg, 43%, $[\alpha]_D$ = −8.8 (*c* 1.04, $CHCl_3$, 99%ee)).[30]

4.4.3. Resolution of (±)-(2*E*)-1-(trimethylsilyl)-2-buten-1-ol 6 (Table 2, entry 4)

Applying the kinetic resolution procedure described in Section 4.4.1 to (±)-(2*E*)-1-(trimethylsilyl)-2-buten-1-ol **6** (300 mg, 2.1 mmol) at 78 °C afforded after ~46% conversion acetate **7** (46 mg, 12%, (all chromatographic and spectroscopic attempts to resolve the enantiomers and thus determine the %ee failed)) and unreacted optically active alcohol (*R*)-**6** (34 mg, 11%, $[\alpha]_D$ = +4.1 (*c* 1.12, $CHCl_3$, 9%ee)).

4.4.4. PS-D I resolution of *rac*-3 (Table 3, entry 6)

To a sealed tube containing a solution of racemic 2-methyl-1-(trimethylsilyl)-2-propen-1-ol (144 mg, 1.0 mmol) and activated 3 Å molecular sieves in toluene (1 mL) were added PS-D I (288 mg) and vinyl acetate (0.3 mL, 3.0 mmol). The tube was purged with N_2 and sealed. The tube was purged with N_2, sealed, and the reaction mixture was stirred with the reaction progress being monitored by GC. After ~44% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite. Analysis of the filtrate by GC (VF-1ms column) using decane as an internal standard indicated that the optically active acetate (*R*)-**13** was formed in 13% yield (87%ee) and the unreacted optically active alcohol (*S*)-**8** was formed in 19% yield (>99%ee).

4.4.5. Kinetic resolution of *rac*-1 using amino PS-D I lipase (Scheme 3)

At first, PS-D I (288 mg) and vinyl acetate (0.14 mL, 1.5 mmol) were added to a tube containing a mixture of racemic 1-hydroxyallyltrimethylsilane (0.13 g, 1.0 mmol) and activated 3 Å molecular sieves in toluene (1 mL). The tube was purged with N_2, sealed, and the reaction mixture was stirred with the reaction progress being monitored by GC. After ~100% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite 503. Analysis of the filtrate by GC (VF-1ms column) using decane as an internal standard indicated that the optically active (*S*)-**2** was formed in 41% yield (97%ee) as well as presumed **15**[16] and an impurity.

4.5. Preparation and hydrolysis of acetal 15 by C_{18} silica gel (Scheme 3)

At first, PS-D I (2.88 g) and vinyl acetate (1.4 mL, 15.0 mmol) were added to a sealed tube containing a mixture of racemic 1-hydroxyallyltrimethylsilane (1.39 g, 10.6 mmol) and activated 3 Å molecular sieves in toluene (10 mL). The sealed tube was purged with N_2 and the mixture was stirred at room temperature and monitored by GC. The tube was purged with N_2, sealed, and the reaction mixture was stirred with the reaction progress being monitored by GC. After ~100% of the starting material had been consumed, the reaction mixture was filtered through a pad of Celite 503, concentrated, and subjected to silica gel column chromatography using Et_2O/hexane (1:9), which afforded a mixture of (*S*)-**2**, presumed acetal **15**[16], and an unidentified impurity. Compound (*S*)-**2** was removed by rotary evaporation, leaving 117 mg acetal **15** and the impurity. Acetal **15** and the impurity (48 mg) were dissolved in CH_3CN (2 mL) to which C_{18} silica gel (500 mg) was added. The mixture was stirred at room temperature for 20 min, filtered, concentrated, and purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford 10 mg of (*R*)-**1** as a colorless oil (>33%, 64%ee).

4.6. Reductive cleavage of optically active acetates

4.6.1. Reduction of (*S*)-2 (Scheme 4)

A solution of compound (*S*)-**2** (138 mg, 0.8 mmol, >98%ee) in hexane (3 mL) was cooled to −78 °C. To that cold solution, DIBAL (0.8 mL of a 1.0 M solution in hexane, 0.8 mmol) was added dropwise. The reaction mixture was then stirred at the same temperature for 2.5 h. The cold bath was removed, the reaction was quenched with saturated aqueous Rochelle Salt (1.5 mL), and the reaction mixture was diluted with ether. The phases were separated, the aqueous phase was extracted with ether, and the combined organics were dried over Na_2SO_4. After filtration and evaporation, the residual oil was purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford 82 mg of (*S*)-**1** (78%; $[\alpha]_D$ = +8.3 (*c* 1.21, $CHCl_3$, 89%ee[31]).

4.6.2. Reduction of (*S*)-4 (Scheme 4)

Applying the conditions described above (Section 4.6.1) to (*S*)-**4** (73 mg, 0.3 mmol) in hexane (1.5 mL) using 1.1 equiv of DIBAL (0.3 mL of a 1.0 M solution in hexane, 0.3 mmol) afforded 49 mg of (*S*)-**3** (81%; $[\alpha]_D$ = +8.2 (*c* 1.12, $CHCl_3$, 93%ee).

4.7. Chiral GC and HPLC analyses

4.7.1. 1-Hydroxyallyltrimethylsilane 1

GC Column: β-dex tm 325 (30 m × 0.25 mm × 0.25 μm film thickness). Program: 30–150 °C, at 5 °C/min, hold at 150 °C for 2 min. t_r-(*R*) enantiomer (min) = 10.0 min, t_r-(*S*) enantiomer (min) = 9.8 min.

4.7.2. Acetic acid 1-(trimethylsilyl)-allyl ester 2

GC Column: β-dex tm 325 (30 m × 0.25 mm × 0.25 μm film thickness). Program: 30–150 °C, at 5 °C/min, hold at 150 °C for 2 min. Results: t_r-(*R*) enantiomer (min) = 12.9 min, t_r-(*S*) enantiomer (min) = 13.0 min.

4.7.3. 1-(Dimethylphenylsilyl)-2-propen-1-ol 3

HPLC column: Chiralcel OJ. Eluent: IPA/hexane (90:10), 0.18 mL/min. Results: t_r-(*R*) enantiomer (min) = 23.6 min, t_r-(*S*) enantiomer (min) = 30.9 min.

4.7.4. Acetic acid 1-(dimethylphenylsilyl)-prop-2-enyl ester 4

HPLC column: Chiralcel OJ. Eluent: IPA/hexane (90:10), 0.18 mL/min. Results: t_r-(*R*) enantiomer (min) = 31.2 min, t_r-(*S*) enantiomer (min) = 35.4 min.

4.7.5. (2*E*)-1-(Trimethylsilyl)-2-buten-1-ol 6

GC Column: β-dex tm 325 (30 m × 0.25 mm × 0.25 μm film thickness). Program: 30–150 °C, at 1 °C/min, Results: t_r-(*R*) enantiomer (min) = 29.2 min, t_r-(*S*) enantiomer (min) = 29.9 min.

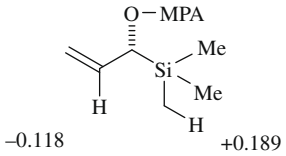
4.7.6. 2-Methyl-1-(trimethylsilyl)-2-propen-1-ol 8

GC Column: β-dex tm 325 (30 m × 0.25 mm × 0.25 μm film thickness). Program: 45 °C for 20 min, 45–150 °C, at 2 °C/min. Results: t_r-(*R*) enantiomer (min) = 27.7 min, t_r-(*S*) enantiomer (min) = 28.1 min.

4.7.7. Acetic acid 2-methyl-1-(trimethylsilyl)-allyl ester 13

GC Column: β-dex tm 325 (30 m × 0.25 mm × 0.25 μm film thickness). Program: 45 °C for 20 min, 45–150 °C, at 2 °C/min. Results: t_r-(*R*) enantiomer (min) = 36.0 min, t_r-(*S*) enantiomer (min) = 35.8 min.

4.8. Mosher's ester analyses[12]

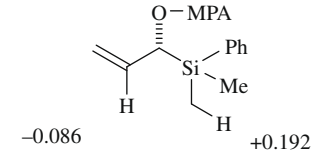


$\delta_{(R)\text{-MPA-}(R)\text{-ester}} - \delta_{(S)\text{-MPA-}(R)\text{-ester}}$

4.8.1. (*R*)-1-Hydroxyallyltrimethylsilane Mosher esters

To a solution of (*R*)-1-hydroxyallyltrimethylsilane (46 mg, 0.35 mmol), (*R*)-(−)-α-methoxyphenylacetic acid (47 mg, 0.28 mmol), and DCC (65 mg, 0.31 mmol) in CH_2Cl_2 (3.5 mL) under nitrogen was added DMAP (4 mg, 0.032 mmol) in a single portion. The reaction mixture was stirred at room temperate for 4 h. The precipitate formed was removed by filtration and the filtrate was washed with cold 1 M HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.75–5.62 (m, 1H), −0.04 (d, *J* = 0.8 Hz, 9H).

Applying the aforementioned procedure to (*R*)-1-hydroxyallyltrimethylsilane (46 mg, 0.35 mmol) and (*S*)-(+)-α-methoxyphenylacetic acid (47 mg, 0.28 mmol) afforded the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.89–5.74 (m, 1H), −0.22 (d, *J* = 0.7 Hz, 9H).

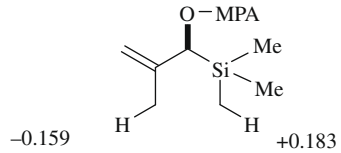


$\delta_{(R)\text{-MPA-}(R)\text{-ester}} - \delta_{(S)\text{-MPA-}(R)\text{-ester}}$

4.8.2. (*R*)-1-(Dimethylphenylsilyl)-2-propen-1-ol Mosher esters

Applying the Section 4.8.1 procedure to (*R*)-1-(dimethylphenylsilyl)-2-propen-1-ol (72 mg, 0.37 mmol) and (*R*)-(−)-α-methoxyphenylacetic acid (50 mg, 0.30 mmol) (7 h reaction time) afforded the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.71–5.58 (m, 1H), −0.27 (d, *J* = 2.8 Hz, 6H).

Applying the Section 4.8.1 procedure to (*R*)-1-(dimethylphenylsilyl)-2-propen-1-ol (72 mg, 0.37 mmol) and (*S*)-(+)-α-methoxyphenylacetic acid (50 mg, 0.30 mmol) (7 h reaction time) afforded the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.79–5.66 (m, 1H), −0.08 (d, *J* = 4.3 Hz, 6H).



$\delta_{(R)\text{-MPA-}(R)\text{-ester}} - \delta_{(R)\text{-MPA-}(S)\text{-ester}}$

4.8.3. (*S*)-2-Methyl-1-(trimethylsilyl)-2-propen-1-ol 8 Mosher esters

Applying the Section 4.8.1 procedure to (*S*)-2-methyl-1-(trimethylsilyl)-2-propen-1-ol (30 mg, 0.21 mmol) and (*R*)-(−)-α-methoxyphenylacetic acid (28 mg, 0.17 mmol) (7 h reaction time) afforded the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 1.67 (s, 3H), −0.19 (s, 9H).

Applying the Section 4.8.1 procedure to (*rac*)-2-methyl-1-(trimethylsilyl)-2-propen-1-ol (100 mg, 0.69 mmol) and (*R*)-(−)-α-methoxyphenylacetic acid (94 mg, 0.56 mmol) (7 h reaction time) afforded the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 1.67 (s, 3H), 1.51 (s, 3H), 0.00 (s, 9H), −0.19 (s, 9H).

4.9. Synthesis of acetal 15[32]

To a cold (−78 °C), stirred solution of (±)-1-trimethylsilylallyl acetate **2** (155 mg, 0.9 mmol) in CH_2Cl_2 (5 mL) under nitrogen conditions was added DIBAL (1.8 mL of a 1.0 M solution in hexane, 1.8 mmol) dropwise. The resulting reaction mixture was then stirred for 45 min, after which pyridine (0.2 mL, 2.7 mmol), a solution of DMAP (221 mg, 1.8 mmol) in CH_2Cl_2 (2 mL), and acetic anhy-

dride (0.5 mL, 5.4 mmol) were added dropwise. After stirring for an additional 29 h, the reaction mixture was warmed to 0 °C and stirred for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and sodium potassium tartrate at 0 °C. The resulting solution was warmed to room temperature, stirred for an additional 0.5 h, and then diluted with CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organics were washed with ice-cooled 1 M sodium bisulfate, saturated aqueous $NaHCO_3$, and brine to afford 61 mg (<31%) of presumed acetal **15**.[16]

Acknowledgments

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16. Acetal **15** proved difficult to purify. GC (VF-1ms column) of the chromatographed material gave three peaks at 2.6, 6.2, and 6.4 min with a ratio of (9:32:59). This mixture provided the following data: major (GC peak at 6.4 min) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (q, J = 5.3 Hz, 1H), 5.92–5.87 (m, overlapped), 5.07–4.96 (m, 2H), 3.83–3.80 (m, 1H), 2.00 (s, 3H), 1.38 (d, J = 5.3 Hz, 3H), 0.03 (s, overlapped); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 137.8, 110.7, 98.1, 78.3, 21.4, 21.1, −4.2; IR (neat) 1740 cm^{-1}; minor (GC peak at 6.2 min) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92–5.87 (m, overlapped), 4.93–4.88 (m, 2H), 3.93–3.89 (m, 1H), 2.06 (s, 3H), 1.40 (d, J = 5.2 Hz, 3H), 0.04 (s, overlapped); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 136.2, 112.6, 96.1, 74.6, 21.2, 20.9, −4.0; IR (neat) 1740 cm^{-1}; HRMS (ESI+) (m/z) calcd for $C_8H_{17}OSi$ $[M+H-CH_3CO_2H]^+$ 157.1049, found 157.1052. These data suggest that the peaks occurring at 6.2 and 6.4 min are diastereomers of **15**. In addition the structure of acetal **15** was consistent with HMQC, HMBC, TOCSY, and COSY data acquired on the mixture. Independent synthesis of **15** (see Section 4.9) afforded material that was spectroscopically similar to that formed during the kinetic resolution. In addition, a GC of the independently synthesized material also gave peaks at 2.6, 6.2, and 6.4 min, albeit in a different ratio (1:59:40).
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30. Woerpel (Ref. 18b) described the preparation of (*S*)-**3** by reduction of 1-(dimethylphenylsilyl)-2-propen-1-one with (+)-DIP-Cl, while Marsden (Ref. 18a) reported the preparation of (*R*)-**3** using (−)-DIP-Cl. Curiously, negative $[\alpha]_D$ values were reported for both the (*R*) and (*S*) enantiomers. To clarify the sign of the $[\alpha]_D$ value, we repeated the previously reported reductions. In our hands, (*R*)-**3** gave a negative $[\alpha]_D$ and (*S*)-**3** gave a positive $[\alpha]_D$. Importantly, HPLC comparison of our enzymatically generated material with both reduction products following the conditions described in Ref. 18b confirmed the absolute configurations assigned in Refs. 18a,b.
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