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Mechanistic insight into the cinnamylmetal-thioacetal reaction employing 2-acetoxy-2-phenylacetaldehyde monothioacetal

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Abstract

The reaction of 2-acetoxy-2-phenylacetaldehyde monothioacetal with cinnamylsilane and -tin serves as a model system for disclosing the simple diastereoselectivity of unambiguously assigned S_N1- and S_N2-like reactions between thioacetal and prochiral allylmetals.

Key words: Tin; Silicon; Cinnamylmetal-thioacetal reaction; 2-Acetoxy-2-phenylacetaldehyde monothioacetal

1. Introduction

The last two decades have witnessed the utility of Lewis acid-promoted nucleophilic substitution of acetals in organic synthesis [1]. The stereochemistry of these reactions has received special attention in view of "acyclic stereoselection" and thus elucidation of the reaction mechanism is of central interest today [2]. In general, the reaction consists of coordination of a Lewis acid to an acetal inducing activation of this substrate and subsequent attack by a nucleophile either through an S_N1-like or S_N2-like pathway. The coordination step was studied with cyclic acetals by NMR spectroscopy by Denmark *et al.* [3]. Some information is also available on the S_N1/S_N2 alternative problem. Noyori *et al.* [4] put forth the S_N1 pathway for the trimethylsilyl triflate-promoted reaction. On the other hand, it has generally been recognized that both mechanisms are feasible depending on the conditions [2,5]. Moreover, formation of the S_N1-like solvent separated ion pair or the S_N2-like contact ion-pair has also been suggested [2,5d]. Despite such considerable advances, we have little knowledge about the reaction course beyond this stage which is crucial for elucidating the stereochemistry [6]. This is ascribed to a failure to create reaction systems whose mechanisms are unambiguously assigned.

Reactions employing prochiral silyl [1,7] and tin [8] nucleophiles are particularly important because of their synthetic utility. However, as pointed out by Heathcock *et al.* [5d], mechanistic studies with the acetals suffer from a severe drawback since the diastereotropic alkoxy groups are not easily differentiated especially in an S_N2 reaction. According to the more recent statement by Sammakia *et al.* [2b], "it is difficult to draw any firm conclusions about the mechanism of related acetals". α-Chiral acetals are promising for probing this mechanistic dichotomy. We disclosed earlier that the reaction of 2-acetoxy-2-phenylacetaldehyde monothioacetal (**1**) with allyltins proceeds through an S_N2-like pathway while an S_N1-like mechanism operates in the reaction with allylsilanes [9]. Accordingly, we have been interested in using **1** to elucidate the stereochemistries resulting from unambiguously assigned S_N1-like and S_N2-like reactions.

Another requirement to be satisfied in order to reach reliable conclusions is to employ stereochemically rigid allylmetals. Since crotyltins are very labile to double bond isomerization in the presence of a Lewis acid [10], we chose stereochemically rigid (*E*)-cinnamyltributyltin (**2**) and -trimethylsilane (**3**) [11*].

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* Reference number with asterisk indicates a note in the list of references.

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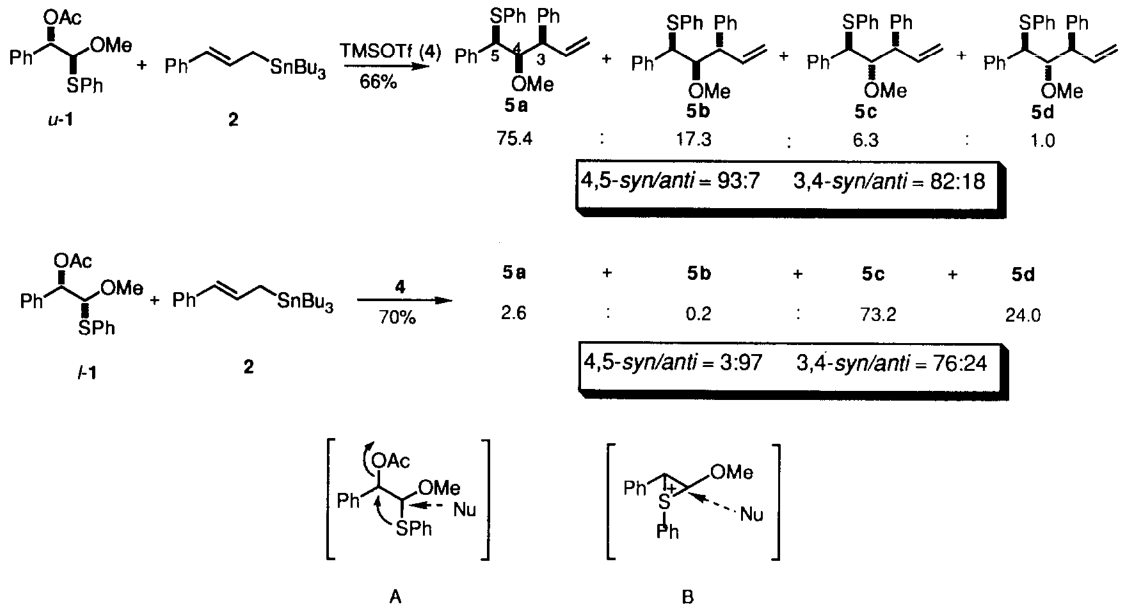
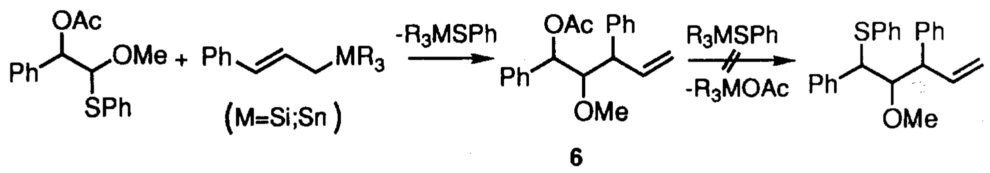
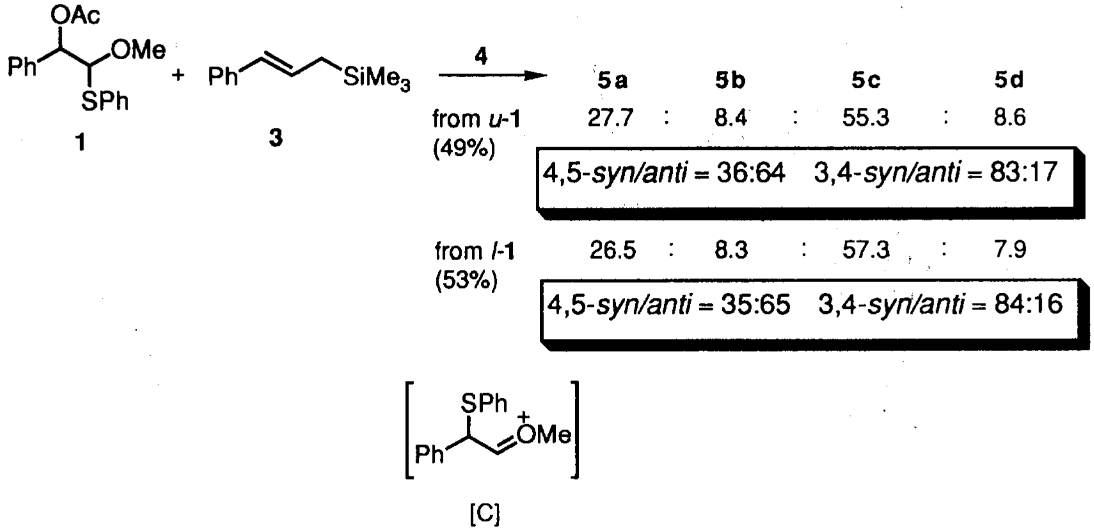


Scheme 1.



Scheme 2.



Scheme 3.

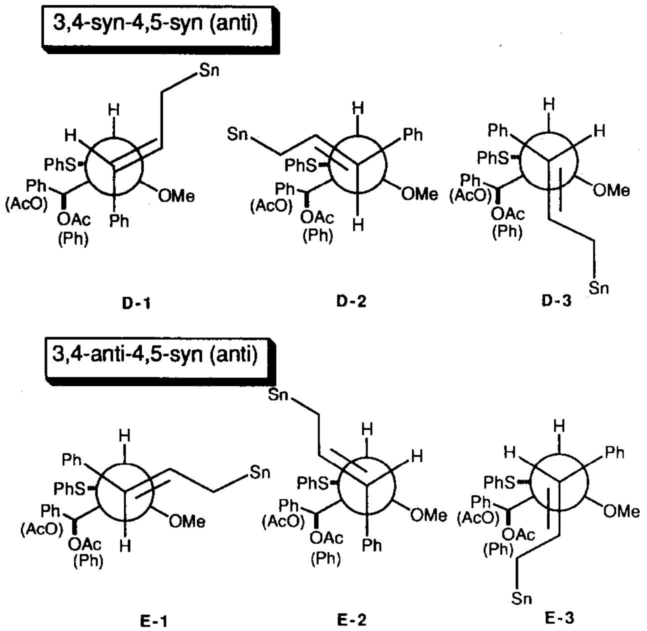
2. Results and discussion

2.1. Reaction of 2-acetoxy-2-phenylacetaldehyde monothioacetal (1) with allylmetals (2,3)

Treatment of the *u*- and *l*-isomers of **1** (1 equiv.) with **2** (1.3 equiv.) in the presence of trimethylsilyl triflate (**4**) (1 equiv.) at $-78°C$ in CH_2Cl_2 afforded after 2H the four diastereomers **5a–5d** in ratios shown in Scheme 1. The stereochemistry of these diastereomers were confirmed by comparison with separately prepared authentic specimens (*vide infra*). The *u*-isomer gave rise to 93:7 4,5-*syn/anti* relation whereas the completely opposite outcome resulted with the *l*-counterpart, providing unequivocal evidence for the S_N2-like reaction. In contrast to the reversal in the 4,5-relation, the 3,4-*syn* preference was observed for both *u*- and *l*-**1**. One may suppose that the reaction is initiated by allylation of the monothioacetal followed by replacement of the acetoxy group with the resulting organometal thiophenoxide (Scheme 2). The invalidity of this mechanism was proved by the following experiments. The putative intermediate **6** which had been separately prepared was exposed to organotin thiophenoxies, however no reaction occurred at all. The reaction is likely to involve attack of cinnamyltin towards the sp^3 carbon of the thioacetal [A] rather than the episulfonium ion [B] as shown in Scheme 1 by analogy to the reaction of allyltins [9,12*].

The reactions with cinnamylsilane **3** were conducted analogously (Scheme 3). In these cases, both isomers of **1** afforded the 4,5-*anti* products predominantly. The S_N1-like mechanism involving an oxocarbenium ion intermediate [C][9] is apparent from these results. The reaction with the less nucleophilic cinnamylsilane has a later transition state. Quite naturally, no reaction occurred between **6** and (phenylthio)trimethylsilane (Scheme 2). It should be noted that no isomerization of the starting material prior to the nucleophilic attack has been confirmed in the previous study by checking the stereochemical purities of the recovered starting materials at low conversions [9]. With regard to the 3,4-relation, the *syn* preference was again observed.

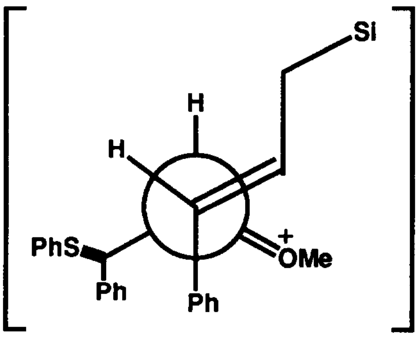
The sense of simple diastereoselection in reactions of acetals with prochiral silyl nucleophiles is usually *syn* [1,2,4,7] except for some special cases where the *anti* preference is observed: the reaction between aromatic acetals and crotylsilanes [13], Denmark's intramolecular allylation [14] and Heathcock's reaction employing a bulky acetal and enol silyl ether [15]. The *syn* selectivity was accounted for in terms of the carbocation intermediacy [4,7,16] the grounds for which are not necessarily explicit, however. The present results sustain that the S_N1-like mechanism can lead to a considerable level of the *syn* preference. Notably, the



Scheme 4.

anti selectivity with bulky acetal and enol silyl ether [15] is likely to emerge from the S_N1-like mechanism since Heathcock came across this idea on the basis of thionium chemistry [16] and proposed the S_N1-like mechanism for the reaction of the same acetal with an achiral enol silyl ether [5d]. The reversal in stereochemistry is attributable to a change in the transition state geometry due to steric demands. On the other hand, there appear to be no precedents for stereochemical studies on reactions which unequivocally proceed by an S_N2-like mechanism. The cinnamyltin reaction described here offers the first such example.

Although it is rather difficult to draw an unambiguous picture of the transition state with the present data alone, we propose, on the basis of steric requirements, a possible explanation as follows. Six transition state geometries are feasible for the 3,4-simple diastereoselection in the S_N2-like mechanism as illustrated in Scheme 4. In the reaction of acetals, the sp^3 carbon to be attacked is concave in striking contrast to the planar sp^2 carbon in carbonyls and, consequently, severe steric interactions arise between the ligands of the acetal carbon and of the nucleophilic carbon of the cinnamyl reagent. Molecular models of **1** tell us that the (acetoxy)phenylmethyl radical is exceedingly larger than methoxyl and hydrogen. Hence, upon nucleophilic attack of cinnamyltin, the largest group of this compound may be aligned so as to occupy the most spacious region that is separated by the methoxyl and hydrogen. Then, let us consider the structure of **2**. The phenyl group and olefinic hydrogens are located within the same plane while the allylic hydrogens deviate up and down from the plane. Accordingly, the allylic metal moiety is likely to work as a more sterically demanding group than the phenyl and hydrogen residues when the C=C face approaches the acetal. It follows from these considerations that the geometries **D-1** and **E-1** are more favored than the others, yet **E-1** suffers from steric hindrance between the allylic hydrogens and the methoxyl. In the event, **D-1** is postulated to be most favored leading to the preferred 3,4-*syn* relative stereochemistry. By similar treatments, the transition state geometry **F** may be proposed for the S_N1-like reaction with cinnamylsilane **3**.



F

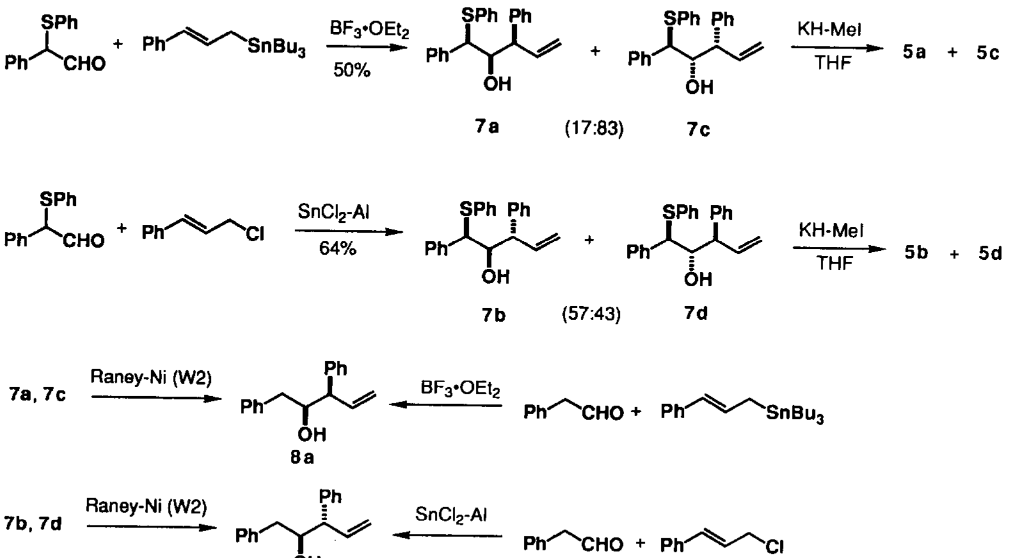
2.2. Preparation of authentic samples and stereochemical assignments

Procedures for authentic **5** are shown in Scheme 5. The 4-hydroxy precursor **7** was obtained by allylation of phenyl(phenylthio)acetaldehyde [17]. A mixture of 3,4-*syn* isomers **7a** and **7c** was prepared by use of cinnamyltributyltin in the presence of $BF_3 \cdot OEt_2$ [18] while 3,4-*anti* products were obtained with cinnamyl chloride in the presence $SnCl_2$–Al [19]. The 4,5-relative stereochemistry of these compounds was determined on the basis of vicinal coupling constants $J_{H4,H5}$; the values for the *syn* isomers (6.59 and 6.96 Hz for **7a** and **7c**, respectively) are larger than that for the *anti* isomers, **7b** and **7d** (4.76 Hz) [20]. The 3,4-relative stereochemistry was determined by reductive desulfurization of **7** to **8**. The stereochemistry of **8** was unambiguously determined by comparison with separately prepared compounds: **8a** was obtained by the reaction of phenylacetaldehyde with cinnamyltributyltin in the presence of $BF_3 \cdot OEt_2$ while **8b** was obtained by reaction of phenylacetaldehyde with cinnamyl chloride in the presence of $SnCl_2$–Al. Finally, *O*-methylation of **7** afforded **5**.

3. Experimental details

3.1. Reaction of (1S,2S*)-1-acetoxy-2-methoxy-1-phenyl-2-(phenylthio)ethane (u-1) and cinnamyltributyltin*

A mixture of *u*-**1** (302 mg, 1 mmol), cinnamyltributyltin (529 mg, 1.3 mmol), TMSOTf (222 mg, 1 mmol) and CH_2Cl_2 (5 ml) was stirred at −78°C for 2H. To this mixture, pyridine (0.3 ml) and aqueous $NaHCO_3$ were added. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. HPLC analysis showed that the crude product consisted of **5a**, **5b**, **5c** and **5d** in a



Scheme 5.

75.4 : 17.3 : 6.3 : 1.0 ratio. Column chromatography (99 : 1 hexane/ethyl acetate) gave the mixture of **5** (251 mg, 70%).

3.2. Reaction of (1S,2R*)-1-acetoxy-2-methoxy-1-phenyl-2-(phenylthio)ethane (l-1) and cinnamyltributyltin in the presence of TMSOTf*

The reaction of *l*-**1** (302 mg, 1 mmol) with cinnamyltributyltin (529 mg, 1.3 mmol) in the presence of TMSOTf (222 mg, 1 mmol) at -78°C for 2H was carried out in a similar manner as described above. Usual work-up and column chromatography afforded **5** (251 mg, 70%); **5a** : **5b** : **5c** : **5d** = 2.6 : 0.2 : 73.2 : 24.0 based on HPLC.

3.3. Reaction of u-1 and cinnamyltrimethylsilane in the presence of TMSOTf

A mixture of *u*-**1** (302 mg, 1 mmol), cinnamyltrimethylsilane (247 mg, 1.3 mmol), TMSOTf (222 mg, 1 mmol) and CH_2Cl_2 (5 ml) was stirred at -78°C for 2H and at -50°C for 1H and then at -20°C for 2H. Usual workup and column chromatography provided **5** (176 mg, 49%); **5a**: **5b**: **5c**: **5d** = 27.7 : 8.4 : 55.3 : 8.6.

3.4. Reaction of l-1 and cinnamyltrimethylsilane

The reaction of *l*-**1** (302 mg, 1 mmol) with cinnamyltrimethylsilane (247 mg, 1.3 mmol) in the presence of TMSOTf (222 mg, 1 mmol) was carried out in a similar manner as described above. Usual workup and column chromatography afforded **5** (191 mg, 53%); **5a** : **5b** : **5c** : **5d** = 26.5 : 8.3 : 57.3 : 7.9 based on HPLC.

3.5. Synthesis of (3S,4R*,5S*)- and (3R*,4S*,5S*)-4-hydroxy-3,5-diphenyl-5-phenylthio-1-pentene (*7a* and *7c*)*

A mixture of phenyl(phenylthio)acetaldehyde (684 mg, 3 mmol), cinnamyltributyltin (1.58 9, 3.9 mmol), $BF_3 \cdot OEt_2$ (426 mg, 3 mmol), and CH_2Cl_2 (13 ml) was stirred at -78°C for 3 h. To this mixture was added aqueous $NaHCO_3$ (3 ml) and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give an oil. Column chromatography (50:50 hexane/benzene) afforded a mixture of **7a** and **7c** (519 mg, 50%); **7a** : **7c** = 17 : 83 based on HPLC. Preparative HPLC provided pure **7a** and **7c**. **7a**: ^{1}H NMR ($CDCl_3$): δ 2.54 (d, J = 2.56 Hz, 1H); 3.55 (dd, J = 6.23, 7.70 Hz, 1H); 4.11 (d, J = 6.59 Hz, 1H); 4.24 (ddd, J = 2.56, 6.23, 6.59 Hz, 1H); 5.08 (dd, J = 1.47, 17.2 Hz, 1H); 5.11 (dd, J = 1.47, 10.2 Hz, 1H); 6.16 (ddd, J = 7.70, 10.2, 17.2 Hz, 1H); 7.1–7.4 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 53.4, 58.6, 76.5, 116.6, 126.9, 127.34, 127.37, 128.35, 128.39, 128.43, 128.6, 129.2, 132.7, 133.6, 139.1, 139.3, 140.3. MS: (m/z) 346 (M^+). HRMS: $C_{23}H_{22}OS$ calcd.: (M^+) 346.1391. Found: 346.1256. IR (CCl_4): 3500, 3600 cm^{-1}. **7c**: ^{1}H NMR ($CDCl_3$): δ 2.01 (d, J = 3.29 Hz, 1H); 3.43 (t, J = 8.06 Hz, 1H); 4.27 (d, J = 4.76 Hz, 1H); 4.29 (ddd, J = 3.29, 4.76, 8.06 Hz, 1H); 5.01 (dd, J = 1.83, 17.2 Hz, 1H); 5.13 (dd, J = 1.83, 10.2 Hz, 1H); 6.01 (ddd, J = 8.06, 10.2, 17.2 Hz, 1H); 7.2–7.4 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 53.4, 56.7, 74.9, 117.1, 126.8, 127.4, 127.5, 128.2, 128.5, 128.6, 128.8, 129.6, 132.4, 134.0, 137.6, 138.2, 140.2. MS: (m/z) 346 (M^+). HRMS: $C_{17}H_{16}O$ calcd.: ($M^+ - C_6H_5SH$) 236.1201. Found: 236.1024. IR (CCl_4): 3680 cm^{-1}.

3.6. Synthesis of (3R,4R*,5S*)- and (3S*,4S*,5S*)-4-hydroxy-3,5-diphenyl-5-phenylthio-1-pentene (7b and 7d)*

To a mixture of $SnCl_2$ (190 mg, 1 mmol), Al (54 mg, 2 mmol), THF (2 ml) and H_2O (1 ml) were added phenyl(phenylthio)acetaldehyde (228 mg, 1 mmol) and cinnamyl chloride (229 mg, 1.5 mmol) at 40°C. The reaction mixture was stirred at the same temperature for 12H. Extraction with ethyl acetate, drying (Na_2SO_4) the organiç layer, and evaporation left an oil. Column chromatography (50 : 50 hexane/benzene) of the residue afforded a mixture of **7b** and **7d** (221 mg, 64%); **7b**:**7d** = 57 : 43 based on HPLC. Preparative HPLC gave pure **7b** and **7d**. **7b**: ^{1}H NMR ($CDCl_3$): δ 2.78 (d, J = 2.57 Hz, 1H); 3.49 (dd, J = 5.50, 9.16 Hz, 1H); 4.08 (d, J = 6.96 Hz, 1H); 4.16 (ddd, J = 2.57, 5.50, 6.96 Hz, 1H); 5.05 (dd, J = 1.83, 17.2 Hz, 1H); 5.22 (dd, J = 1.83, 9.89 Hz, 1H); 6.23 (ddd, J = 9.16, 9.89, 17.2 Hz, 1H); 7.1–7.4 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 53.1, 58.8, 76.7, 118.1, 126.7, 127.2, 127.3, 127.9, 128.1, 128.4, 128.5, 128.6, 132.5, 133.8, 136.5, 140.3, 141.7. MS: (m/z) 346 (M^+). HRMS: $C_{17}H_{16}O$ calcd.: ($M^+ - C_6H_5SH$) 236.1201. Found: 236.1204. IR (CCl_4): 3500, 3570 cm^{-1}. **7d**: ^{1}H NMR ($CDCl_3$): δ 2.33 (d, J = 2.94 Hz, 1H); 3.36 (t, J = 8.06 Hz, 1H); 4.09 (d, J = 4.76 Hz, 1H); 4.22 (ddd, J = 2.94, 4.76, 8.06 Hz, 1H); 5.02 (dd, J = 1.83, 17.2 Hz, 1H); 5.12 (dd, J = 1.83, 10.2 Hz, 1H); 6.08 (ddd, J = 8.06, 10.2, 17.2 Hz, 1H); 7.0–7.4 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 53.5, 56.1, 74.5, 117.4, 126.8, 127.3, 127.6, 128.2, 128.6, 128.8, 129.6, 132.3, 134.0, 137.3, 138.2, 140.7. MS: (m/z) 346 (M^+); HRMS: $C_{23}H_{22}OS$ calcd.: (M^+) 346.1391. Found: 346.1347. IR (CCl_4): 3350, 3630 cm^{-1}.

3.7. Determination of the C-3/C-4 relative stereochemistry of 7

3.7.1. Treatment of 7a and 7c with Raney-Nickel

A mixture of **7a** (30 mg, 0.087 mmol), Raney-Nickel (W2) (300 mg), and EtOH (3 ml) was refluxed for 5 h. The insoluble material was removed by filtration and the filtrate was evaporated to give an oil. Column chromatography of this oil (95:5 hexane/ethyl acetate) afforded (3*S**,4*S**)-4-hydroxy-3,5-diphenyl-1-pentene (**8a**) (14 mg, 68%). ^{1}H and ^{13}C NMR spectra were identical with the authentic sample.

Treatment of **7c** (50 mg, 0.144 mmol) with Raney-Nickel (W2) (500 mg) in EtOH (3 ml) provided **8a** (21 mg, 77%).

*3.7.2. Reaction of **7b** and **7d** with Raney-Nickel*

A mixture of **7b** (45 mg, 0.13 mmol), Raney-Nickel (W2) (500 mg) and EtOH (3 ml) was refluxed for 6 h. Usual workup and column chromatography (95:5 hexane/ethyl acetate) afforded (3*R**,4*S**)-4-hydroxy-3,5-diphenyl-1-pentene (**8b**) (20 mg, 65%). ^{1}H and ^{13}C NMR spectra were identical with the authentic sample.

Treatment of **7d** (30 mg, 0.087 mmol) with Raney-Nickel (400 mg) described above gave **8b** (15 mg, 72%).

3.8. Preparation of authentic 8

3.8.1. (3S,4S*)-4-Hydroxy-3,5-diphenyl-1-pentene (8a)*

A mixture of phenylacetaldehyde (120 mg, 1 mmol), cinnamyltributyltin (528 mg, 1.3 mmol), $BF_3 \cdot OEt_2$ (141 mg, 1 mmol) and CH_2Cl_2 (5 ml) was stirred at -78°C for 3 h. Aqueous $NaHCO_3$ was added to this solution, and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. The crude product proved to consist of (3*S**,4*S**)- and (3*R**,4*S**)-4-hydroxy-3,5-diphenyl-1-pentene (**8a** and **8b**, respectively) in an 83:17 ratio based on HPLC. Column chromatography (50:50 hexane/benzene) gave 4-hydroxy-3,5-diphenyl-1-pentene (119 mg, 50%). Preparative HPLC provided pure **8a**: ^{1}H NMR ($CDCl_3$): δ 1.58 (d, J = 3.66 Hz, 1H); 2.56 (dd, J = 9.53, 13.9 Hz, 1H); 2.97 (dd, J = 2.57, 13.9 Hz, 1H); 3.36 (dd, J = 7.69, 8.79 Hz, 1H); 4.08 (dddd, J = 2.57, 3.66, 7.69, 9.53 Hz, 1H); 5.1–5.2 (m, 2H); 6.15 (m, 1H); 7.1–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 41.0, 56.6, 75.5, 116.9, 126.2, 126.7, 128.3, 128.5, 128.6, 129.3, 138.5, 138.7, 140.6. MS: (m/z) 238 (M^+). HRMS: $C_{17}H_{18}O$ (M^+) 238.1350. Found: 238.1503.

3.8.2. (3R,4S*)-4-hydroxy-3,5-diphenyl-1-pentene (8b)*

To a suspension of $SnCl_2$ (379 mg, 2 mmol) and Al (108 mg, 4 mmol) in THF/H_2O (6 ml, 2:1) were added phenylacetaldehyde (240 mg, 2 mmol) and cinnamyl chloride (458 mg, 3 mmol) at 40°C. The reaction mixture was stirred for 5 h. Extraction with ethyl acetate, drying the organic layer (Na_2SO_4), and evaporation left an oil. Column chromatography (50:50 hexane/benzene) of this oil gave 4-hydroxy-3,5-diphenyl-1-pentene (304 mg, 64%); **8b**:**8a** = 92:8 based on HPLC. Preparative HPLC provided pure **8b**: ^{1}H NMR ($CDCl_3$): δ 1.83 (br, 1H); 2.56 (dd, J = 8.79, 13.9 Hz, 1H); 2.72 (dd, J = 3.66, 13.9 Hz, 1H); 3.31 (dd, J = 7.69, 8.79 Hz, 1H); 4.04 (ddd, J = 3.66, 7.69, 8.79 Hz, 1H); 5.18 (dd, J = 1.47, 17.2 Hz, 1H); 5.23 (dd, J = 1.47,10.2 Hz, 1H); 6.18 (ddd, J = 8.79,10.2,17.2 Hz, 1H); 7.1–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 41.0, 56.4, 75.0, 117.8, 126.2, 126.7, 128.0, 128.3, 128.7, 129.2, 137.9, 138.6, 141.5. MS: (m/z) 238 (M^+). HRMS: $C_{17}H_{16}$ calcd.: ($M^+ - H_2O$) 220.1252. Found: 220.1312.

3.9. Preparation of authentic 4-methoxy-3,5-diphenyl-5-phenylthio-1-pentene (5): methylation of 7 with MeI

To a THF suspension (1 ml) of KH (25% mineral oil suspension, 45 mg, 0.28 mmol) was added **7c** (50 mg, 0.14 mmol) in THF (0.5 ml) at -20°C. After the mixture had been stirred for 10 min, MeI (40 mg, 0.28 mmol) was added. The mixture was stirred at -20°C for 30 min and quenched with aqueous NH_4Cl. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated. Column chromatography (99:1 hexane/ethyl acetate) of the residue afforded (3*R**,4*S**,5*S**)-4-methoxy-3,5-diphenyl-5-phenylthio-1-pentene (**5c**) (47 mg, 93%). ^{1}H NMR ($CDCl_3$): δ 3.03 (s, 3H); 3.48 (dd, J = 7.69, 8.06 Hz, 1H); 3.83 (dd, J = 5.49, 7.69 Hz, 1H); 4.21 (d, J = 5.49 Hz, 1H); 5.03 (dd, J = 1.46, 17.2 Hz, 1H); 5.12 (dd, J = 1.46, 10.2 Hz, 1H); 6.09 (ddd, J = 8.06, 10.2, 17.2 Hz, 1H); 7.1–7.4 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 53.9, 56.6, 61.7, 87.0, 116.8, 126.4, 126.8, 127.1, 127.8, 128.1, 128.6, 128.8, 129.7, 131.7, 134.9, 138.6, 138.9, 140.8. MS: (m/z) 360 (M^+). HRMS: $C_{24}H_{24}OS$ calcd.: (M^+) 360.1548. Found: 360.1545. HPLC (t_R) 18.1 min (Develosil Si 30, 3 μ, 4.6 mm × 250 mm, 99:1 hexane/ethyl acetate, 1 ml min^{-1}).

Reaction of **7a** with MeI described above provided **5a** in 98% yield. ^{1}H NMR ($CDCl_3$): δ 2.99 (s, 3H); 3.72–3.76 (m, 2H); 4.32 (d, J = 3.67 Hz, 1H); 5.12 (dd, J = 1.46,10.2 Hz, 1H); 5.16 (dd, J = 1.46, 17.2 Hz, 1H); 6.18 (m, 1H); 7.0–7.4 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 54.3, 57.4, 61.8, 89.5, 116.9, 126.3, 126.5, 127.1, 128.24, 128.28, 128.4, 128.5, 128.9, 131.2, 135.5, 138.7, 140.7, 141.2. MS: (m/z) 360 (M^+). HRMS: $C_{18}H_{18}O$ calcd.: ($M^+ - C_6H_5SH$) 250.1358. Found: 250.1458. HPLC (t_R) 23.4 min.

Methylation of **7b** gave **5b** in 99% yield. ^{1}H NMR ($CDCl_3$): δ 3.23 (s, 3H); 3.62 (dd, J = 6.23, 8.79 Hz, 1H); 3.74 (dd, J = 5.86, 6.23 Hz, 1H); 4.14 (d, J = 5.86 Hz, 1H); 5.00 (dd, J = 1.83, 16.8 Hz, 1H); 5.18 (dd, J = 1.83, 9.89 Hz, 1H); 6.28 (ddd, J = 8.79, 9.89, 16.8 Hz, 1H); 7.05–7.37 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 53.5, 57.7, 62.1, 89.7, 117.7, 126.3, 126.6, 127.1, 128.1, 128.33, 128.35, 128.4, 128.6, 131.3, 135.3, 136.9, 140.8, 142.0. MS: (m/z) 360 (M^+). HRMS: $C_{18}H_{18}O$ calcd.: ($M^+ - C_6H_5SH$) 250.1358. Found: 250.1377. HPLC (t_R) 28.4 min.

Treatment of **7d** with MeI provided **5d** in 95% yield. ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 3H); 3.55 (dd, $J = 6.59$, 7.33 Hz, 1H); 3.76 (dd, $J = 5.50$, 6.59 Hz, 1H); 4.10 (d, $J = 5.50$ Hz, 1H); 4.98 (dd, $J = 1.83$, 16.8 Hz, 1H); 5.11 (dd, $J = 1.83$, 9.89 Hz, 1H); 6.19 (ddd, $J = 7.33$, 9.89, 16.8 Hz, 1H); 7.1–7.4 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 53.5, 56.1, 61.9, 86.9, 117.2, 126.6, 126.8, 127.2, 127.8, 128.3, 128.5, 128.7, 129.6, 131.7, 134.9, 137.6, 138.8, 141.6. MS: (m/z) 360 (M^+). HRMS: $C_{24}H_{24}OS$ calcd.: (M^+) 360.1548. Found: 360.1459. HPLC (t_R) 24.8 min.

3.10. Preparation of (3R*,4S*,5S*)-5-acetoxy-4-methoxy-3,5-diphenyl-1-pentene

A mixture of methyl mandelate (16.6 g, 100 mmol), t-butyldimethylsilyl chloride (22.6 g, 150 mmol), imidazole (20.4 g, 300 mmol) and DMF (200 ml) was stirred at room temperature for 29 h. Extractive workup and column chromatography on silica gel (97:3 hexane/ethyl acetate) provided methyl (R^*)-(t-butyldimethylsiloxy)phenylethanoate (18.1 g, 65 %). ^{1}H NMR ($CDCl_3$): δ 0.01 (s, 3H); 0.09 (s, 3H); 0.90 (s, 9H); 3.66 (s, 3H); 5.22 (s, 1H); 7.2–7.5 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −5.2, −5.1, 18.2, 25.6, 52.0, 74.3, 126.2, 128.0, 128.2, 139.0, 172.5. MS: (m/z) 280 (M^+). HRMS: $C_{15}H_{23}O_3Si$ calcd.: ($M^+ - H$) 279.1417. Found: 279.1497.

To a solution of methyl (R^*)-(t-butyldimethylsiloxy)-phenylethanoate (8.4 g, 30 mmol) in toluene (60 ml) was added diisobutylaluminum hydride (1.0 M hexane solution, 33 ml, 33 mmol) at −78°C. After stirring at the same temperature for 1 h, the mixture was quenched with saturated aqueous NH_4Cl (5 ml). Extractive workup with ether afforded (S^*)-(t-butyldimethylsiloxy)phenylethanal (8.03 g) which was used in the next step without purification. ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 3H); 0.11 (s, 3H); 0.94 (s, 9H); 5.00 (d, $J = 2.19$ Hz, 1H); 7.2–7.5 (m, 5H); 9.51 (d, $J = 2.19$ Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −4.8, 18.3, 25.7, 79.9, 126.3, 128.3, 128.7, 139.1, 199.4. MS: (m/z) 250 (M^+). HRMS: $C_{13}H_{19}O_2Si$ calcd.: ($M^+ - CH_3$) 235.1154. Found: 235.1252.

A dichloromethane solution of $BF_3 \cdot OEt_2$ (2 M solution, 15 ml, 30 mmol) was added to a mixture of (S^*)-(t-butyldimethylsiloxy)phenylethanal (7.5 g, 30 mmol) described above, cinnamyltributyltin (16.3 g, 40 mmol), and CH_2Cl_2 (100 ml) at −78°C. The mixture was stirred at −78°C for 2 h and then worked up to give an oil. Column chromatography of this oil on silica gel (97:3 hexane/ethyl acetate) gave ($3R^*,4S^*,5S^*$)-5-t-butyldimethylsiloxy-4-hydroxy-3,5-diphenyl-1-pentene (4.82 g, 44%). The 3,4,5-relative stereochemistry of this compound was determined as follows. (1) The C_3-C_4 stereochemistry was tentatively assigned to be *syn* on the basis of the reaction mechanism. (2) A small portion of this compound was treated with Bu_4NF (3.3 equiv.) in THF at room temperature for 5 h to afford ($3R^*,4S^*,5S^*$)-4,5-dihydroxy-3,5-diphenyl-1-pentene in 87% yield. ^{1}H NMR ($CDCl_3$): δ 2.17 (br, 1H); 2.74 (br, 1H); 3.47 (t-like, $J = 7.69$ Hz, 1H); 3.99–4.08 (m, 1H); 4.64 (d, $J = 3.97$ Hz, 1H); 5.09–5.17 (m, 2H); 6.01–6.14 (m, 1H); 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 52.7, 73.5, 77.5, 117.0, 126.5, 126.9, 127.7, 128.4, 128.6, 128.8, 138.6, 140.0, 141.6. The 4,5-*anti* stereochemistry was determined on the basis of $J_{H4,H5} = 3.97$ Hz [21]. IR (CCl_4): 3576 cm^{-1}. 1H NMR ($CDCl_3$): δ 0.06 (s, 3H); 0.13 (s, 3H); 0.90 (s, 9H); 2.90 (d, $J = 4.27$ Hz, 1H); 3.26 (t-like, $J = 7.15$ Hz, 1H); 3.94–4.01 (m, 1H); 4.54 (d, $J = 5.62$ Hz, 1H); 4.97–5.15 (m, 2H); 6.06–6.20 (m, 1H); 7.2–7.7 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −5.1, −4.4, 18.0, 25.7, 52.0, 74.3, 75.6, 78.6, 115.7, 126.2, 126.4, 127.1, 127.7, 128.0, 128.1, 128.2, 129.2, 139.0, 139.9, 140.9, 141.6. MS: (m/z) 368 (M^+).

To a suspension of KH (35% oil dispersion, 1.26 g, 11 mmol) in THF (30 ml) was added ($3R^*,4S^*,5S^*$)-5-t-butyldimethylsiloxy-4-hydroxy-3,5-diphenyl-1-pentene (2.58 g, 7 mmol) in THF (1 ml) at 0°C. After 10 min, MeI (0.92 ml, 14 mmol) was added. The resulting mixture was stirred at room temperature for 17 h and then worked up. Column chromatography on silica gel (99 : 1 hexane/ethyl acetate) provided ($3R^*,4S^*,5S^*$)4-t-butyldimethylsiloxy-5-methoxy-3,5-diphenyl-1-pentene (47 mg, 2%) and ($3R^*,4S^*,5S^*$)-5-t-butyldimethylsiloxy-4-methoxy-3,5-diphenyl-1-pentene (1.14 g, 43%). ($3R^*,4S^*,5S^*$)-4-t-butyldimethylsiloxy-5-methoxy-3,5-diphenyl-1-penten e. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 3H); 0.01 (s, 3H); 0.94 (s, 9H); 2.9–3.05 (m, 1H); 3.02 (s, 3H); 3.79 (d, $J = 7.45$ Hz, 1H); 4.17 (dd, $J =$ 3.66, 7.45 Hz, 1H); 4.78 (d, $J = 17.2$ Hz, 1H); 4.97 (d, $J = 9.89$ Hz, 1H); 6.09–6.13 (m, 1H); 7.0–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.8, −4.1, 18.6, 26.3, 52.7, 56.0, 80.3, 86.1,115.0,126.3,127.8,128.1, 128.3, 130.1, 139.1, 140.5, 141.5. MS: (m/z) 382 (M^+). HRMS: $C_{23}H_{31}O_2Si$ calcd.: ($M^+ - CH_3$) 367.2097. Found: 367.2015. ($3R^*,4S^*,5S^*$)-5-t-butyldimethylsiloxy-4-methoxy-3,5-diphenyl-1-penten e. ^{1}H NMR ($CDCl_3$): δ 0.17 (s, 3H); 0.26 (s, 3H); 1.09 (s, 9H); 3.39–3.45 (m, 1H); 3.49 (s, 3H); 3.74 (t-like, $J = 6.04$ Hz, 1H); 4.83 (d, $J = 6.04$ Hz, 1H); 5.13 (d, $J = 17.1$ Hz, 1H); 5.26 (d, $J = 11.5$ Hz, 1H); 6.30–6.44 (m, 1H); 7.4–7.7 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −5.1, −4.4, 18.0, 25.7, 52.0, 74.3, 75.6, 78.7, 115.8, 126.2, 126.4, 127.1, 127.8, 128.1, 128.7, 129.3, 139.9, 140.6, 141.7. MS: (m/z) 382 (M^+). HRMS: $C_{23}H_{31}O_2Si$ ($M^+ - CH_3O$) 351.2144. Found: 351.2220. A mixture of ($3R^*,4S^*,5S^*$)-5-t-butyldimethylsiloxy-4-methoxy-3,5-diphenyl-1-pentene (1.15 g, 3 mmol), Bu_4NF (1 M THF solution, 6 ml, 6 mmol) and THF (15 ml) was stirred at room temperature for 38 h.

Extractive workup with ethyl acetate and column chromatography on silica gel (90:10 benzene/ethyl acetate) gave (3*R**,4*S**,5*S**)-5-hydroxy-4-methoxy-3,5-diphenyl-1-pentene (430 mg, 53%). IR (CCl_4): 3572 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.82 (br, 1H); 3.02 (s, 3H); 3.45–3.61 (m, 2H); 4.69 (d, $J = 3.42$ Hz, 1H); 5.08–5.18 (m, 2H); 6.10–6.24 (m, 1H); 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 52.4, 61.2, 73.1, 88.9, 116.7, 126.2, 126.3, 127.3, 128.1, 128.7, 138.7, 140.8, 142.2. MS: (m/z) 268 (M^+). HRMS: $C_{18}H_{20}O_2$ calcd.: (M^+) 268.1463. Found: 268.1486.

Reaction of (3*R**,4*S**,5*S**)-5-hydroxy-4-methoxy-3,5-diphenyl-1-pentene (379 mg, 1.5 mmol) with acetic anhydride (1.0 ml, 21.6 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (20 mg) in pyridine (3 ml) at room temperature for 4 h provided **6** (353 mg, 80%). IR (CCl_4): 1746 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.11 (s, 3H); 2.90 (s, 3H); 3.41 (t-like, $J = 7.73$ Hz, 3H); 3.65 (dd, $J = 4.33$, 7.57 Hz, 1H); 4.98–5.14 (m, 2H); 5.76 (d, $J = 4.33$ Hz, 1H); 6.04–6.20 (m, 1H); 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 20.9, 52.8, 61.5, 76.1, 87.4, 116.5, 126.8, 128.1, 128.2, 128.6, 138.1, 140.5, 169.6. MS: (m/z) 310 (M^+). HRMS: $C_{18}H_{17}O$ calcd.: ($M^+ -$ MeCOOH $-$ H) 249.1279. Found: 249.1186.

3.11. Reaction of 6 with $PhSSiMe_3$ or $PhSSnBu_3$ in the presence of TMSOTf

3.11.1. With $PhSSiMe_3$

To a solution of **6** (29.4 mg, 0.1 mmol), $PhSSiMe_3$ (0.5 M CH_2Cl_2 solution, 0.3 ml, 0.15 mmol) in CH_2Cl_2 (1 ml) was added TMSOTf (1 M CH_2Cl_2 solution, 0.2 ml, 0.2 mmol) at -78°C. The resulting mixture was stirred at -78°C for 1 h, -50°C for 1 h, and -20°C for 1 h and then quenched with saturated aqueous $NaHCO_3$ (1 ml). Extractive workup provided an oil (43 mg). TLC, HPLC and ^1H NMR analyses of this oil indicated that no 4-methoxy-3,5-diphenyl-5-phenylthio-1-pentene was formed. Column chromatography on silica gel (90:10 benzene/ethyl acetate) afforded **6** (26 mg) which was identical with an authentic sample.

3.11.2. With $PhSSnBu_3$

Treatment of **6** (29.4 mg, 0.1 mmol) with Bu_3SnSPh (0.5 M CH_2Cl_2 solution, 0.3 ml, 0.15 mmol) and TMSOTf (1 M CH_2Cl_2 solution, 0.2 ml, 0.2 mmol) in CH_2Cl_2 (1 ml) at -78°C for 1 h, -50°C for 1 h, and -20°C for 1 h afforded an oil (78 mg) which was chromatographed on silica gel (90:10 benzene/ethyl acetate) to give **6** (24 mg). No 4-methoxy-3,5-diphenyl-5-phenylthio-1-pentene was produced.

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