A highly enantio- and diastereoselective 1,3-dimethylallylation of aldehydes

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Abstract—A highly enantio- and diastereoselective pentenylation of aldehydes is described. The homoallylic alcohol derived from 1,3-dimethylallylation of (–)-menthone undergoes an efficient allyl-transfer reaction with a wide range of aliphatic aldehydes in the presence of an acid catalyst to give rise to the corresponding 4-methyl-2(*E*)-penten-4-yl-5-ol products in good yields with high enantio- and 4,5-*syn*-selectivities.
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1. Introduction

The stereocontrolled synthesis of homoallylic alcohols remains an important subject in organic synthesis due to the wide occurrence of these structural motifs in a number of polyketide natural products. Moreover, homoallylic alcohols can serve as aldol surrogates upon elaboration on the alkene moiety,[1] and as substrates for the Prins reaction that provides tetrahydropyrans (Eq. 1).[2] Accordingly, many methods have been developed for the synthesis of homoallylic alcohols, largely making use of the asymmetric allylation of aldehydes.[3] However, rarely do these protocols allow for access to a disubstituted homoallylic alcohol system (**1**, R_1 and $R_2 \neq H$),[4,5] the precursor for a decorated bispropionate **2** or tetrahydropyran **3**. Thus, the development of an efficient method for the preparation of substituted homoallylic alcohols with reliable control of stereochemistry would be of significant synthetic value.

$$(1)$$
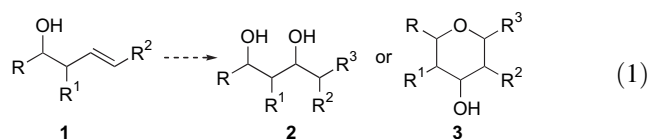
In our investigations aimed at the chemical synthesis of kendomycin,[6] we envisioned that the *C*-aryl glycoside core could be assembled by a Prins reaction with homoallylic alcohol **6** and aromatic aldehyde **7** (Scheme 1).[7] It was anticipated that the requisite intermediate **6** would arise from the asymmetric pentenylation of aldehyde **4**[6] with a reagent such

as Hoffmann's boronic ester **5**.[4] While this plan could indeed be practiced, the high cost for the large-scale preparation and reaction of **5** led us to explore an alternative approach.[8] Noting the allyl-transfer reactions developed by Nokami[9] and Loh,[10] we sought to examine the prospect of extending these methods to the synthesis of **6**. Herein, we report the design, synthesis, and application of a (–)-menthone-derived homoallylic alcohol that accomplishes an allyl-transfer reaction with a range of aldehydes to provide 4-methyl-2-penten-4-yl-5-ol systems with high stereoselectivities.

2. Results and discussion

The design of an allyl-transfer reagent was based on a 2-oxonia-[3,3]-sigmatropic rearrangement mechanism as depicted in Scheme 2. In order to procure **12** (cf. **1**, $R_1 = R_2 = CH_3$) with *E*- and *syn*-selectivities, the condensation of the *Z*-configured **9** with an aldehyde would seem required to achieve transfer of the pentenyl unit through a chair-like transition state adopting the sterically demanding R_L group at an equatorial position. An additional consideration was the utilization of a tertiary alcohol as the pentenyl donor, which should establish a favorable equilibrium for the product formation due to the stability of oxocarbenium ion intermediate **11** vis-à-vis that of **10**. While the feasibility of an allyl-transfer process had never been demonstrated for the preparation of a disubstituted homoallylic alcohol such as **12**,[11] the high levels of enantioselectivities, observed in monosubstituted systems,[9c,9d,10] held promise for an analogous approach to stereospecific pentenyl-transfer processes.
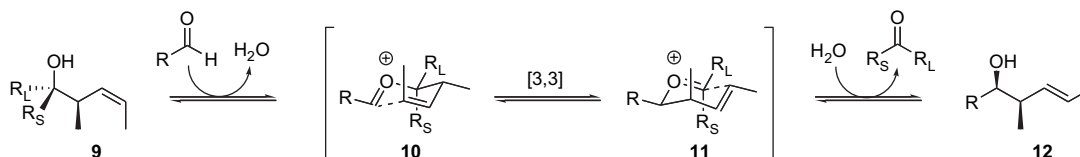
The preparation of an appropriate pentenyl donor of general type **9** was initiated by evaluating 1,3-dimethylallylation of

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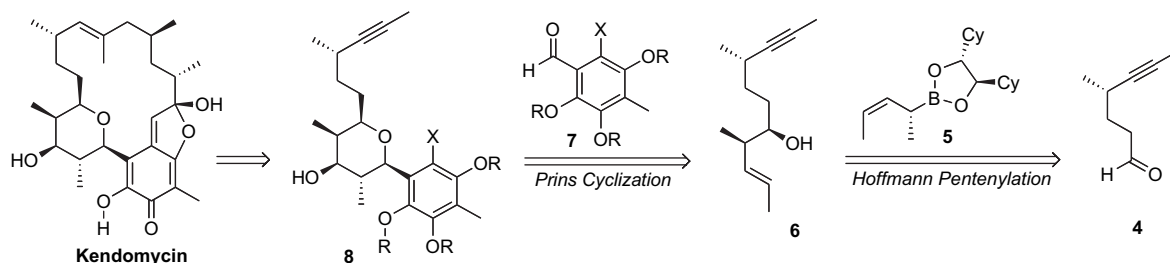
**Scheme 1**. The Prins approach to the total synthesis of kendomycin.

Scheme 2. Strategy for stereospecific pentenylation of aldehydes.

several chiral ketones, among which we focused on menthone due to its ready availability and the well established stereochemical outcome in carbonyl addition processes.[12] In practice, the addition of 1,3-dimethylallyl Grignard reagent **13a** to (–)-menthone gave the desired alcohol **15a** as the major product along with minor diastereomers **15b–d** in a 10:2:1:2 ratio (Scheme 3). With titanium reagent **13b**,[9c,13] the diastereoselectivity was significantly increased to a ratio of 30:4:1:2. Using these two protocols, **15a** could be obtained as a single isomer (>99%) in 30–40% yield after simple chromatographic purification.[14] The major isomer **15a** appears to be derived from transition state **14a**, in which the 1,3-dimethylallyl unit adds to the carbonyl group via the *syn,anti* conformation to minimize the *gauche* interactions of the methyl group with the ligands that are more unfavorable than its $A^{1,3}$ interaction with the hydrogen,[13] thus forming the *Z* geometry in **15a**. It should also be noted that the configuration of the carbinol center of **15a–d** results from the exclusive β-face attack of **13**, as predicted on the basis of the strong facial preference of (–)-menthone.[12]

With homoallylic alcohol **15a** in hand, we then tested its capability to stereospecifically transfer the pentenyl group to aldehydes. As illustrated in Table 1, a range of aldehydes underwent the desired pentenylation process to give rise to the corresponding adducts in good yields with high

stereoselectivities. The major diastereomers were uniformly found to be of *E*-geometry and 4,5-*syn*-stereochemistry, and enantiomerically pure as determined by chiral HPLC or chiral SFC analysis (>99% ee). Typically, the reactions were performed with 2.0 equiv of **15a** and 10 mol % *p*-toluenesulfonic acid monohydrate in CH_2Cl_2 at ambient temperature for 12 h. Lowering the amount of the pentenyl donor **15a** to 1.0 equiv resulted in diminished yields mainly due to the competing Prins process of the product with the starting aldehyde. Both linear and α-branched aldehydes worked well, with the latter requiring longer reaction times (24–48 h, entries 3 and 4). Notably, in addition to aldehyde **16e**, its dimethyl acetal **16f** also proved to be a viable substrate for the reaction without deprotection, thus highlighting an advantage unavailable from the pentenylboronate addition method (entries 5 vs 6).[4] Finally, aldehyde **4**, the intermediate used in our Prins approach to kendomycin, participated well in the reaction providing the desired homoallylic alcohol **6** in 80% yield with 10:1 diastereoselectivity (entry 8).

Although the present reaction could be applied to a range of substrates, it did not fare well with sterically hindered (**16h**), α,β-unsaturated (**16i**), and aromatic (**16j**) aldehydes (Fig. 1). In these cases, no or very low conversion (<15%) occurred over a prolonged reaction time (>48 h).
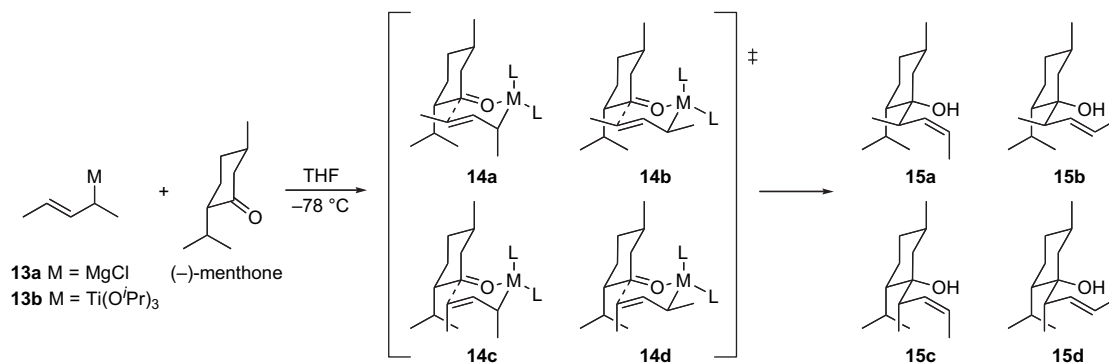
**Scheme 3**. Double stereodifferentiating 1,3-dimethylallyl addition to (–)-menthone.

Table 1. Stereospecific pentenyl-transfer reactions of **15a** with aldehydes **16**

Entry	Aldehyde	Product	Yield (%)[a]	dr[b]	er[c]
1	16a	17a	71	17:1	>99:1
2	16b	17b	57	9:1	>99:1
3	16c	17c	64	5:1	>99:1[f]
4	16d	17d	67 (81)[d]	>20:1[g]	—
5	16e	17e	79[e]	10:1	>99:1
6	16f	17e	66[e]	10:1	>99:1
7	16g	17g	69	11:1	>99:1[f]
8	4	6	80	10:1[g]	—

[a] Isolated yield.
[b] Diastereomeric ratio determined by ¹H NMR.
[c] Enantiomeric ratio determined by chiral HPLC or chiral SFC.
[d] Yield based on the recovered aldehyde.
[e] Combined yield of the mixture of two inseparable diastereomers.
[f] Enantiomeric ratio determined as the corresponding benzoate ester.
[g] Only two diastereomers were detected.

The proposed mechanism of the reaction is shown in Scheme 4, in which the stereospecific 1,3-dimethylallyl-transfer from homoallylic alcohol **15a** to an aldehyde is achieved through a 2-oxonia-[3,3]-sigmatropic rearrangement.[9,10] Under acid catalysis, alcohol **15a** is condensed with the aldehyde to form oxocarbenium ion **18**, which exists in fast equilibrium with **19** via an oxonia-Cope process that involves a chair-like transition state employing the R group at an equatorial position. The more populated cation **19** is then

hydrolyzed to afford the homoallylic alcohol **12** and (−)-menthone.[15] This mechanism explains the E-olefin geometry and syn-stereochemistry observed in the major
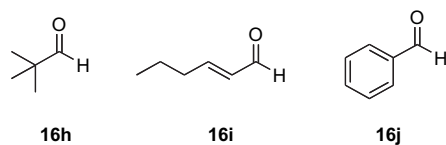
Figure 1. Unreactive aldehydes.
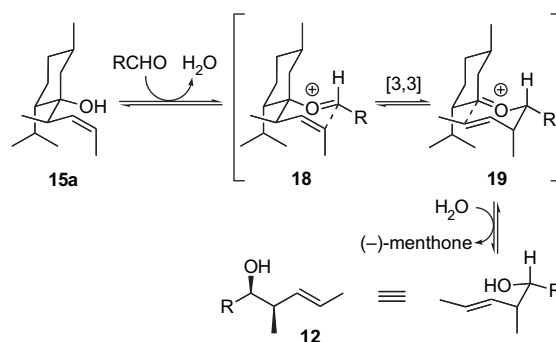
Scheme 4. Proposed mechanism of pentenylation.

diastereomer, and the attenuated reactivity of **15a** toward the aldehydes (cf. Fig. 1) that would have to generate a sterically congested (R=*t*-Bu) or too stable (R=alkenyl, aromatic) oxocarbenium ion **18**.

3. Conclusion

In summary, an efficient and highly stereospecific pentenylation reagent for aldehydes has been developed. The Z-homoallylic alcohol **15a** readily prepared from (–)-menthone reacts smoothly with a range of aliphatic aldehydes under operationally simple and mild acid-catalyzed conditions to provide the corresponding 4-methyl-2-penten-4-yl-5-ol product with high 2*E*- and 4,5-*syn*-selectivities.

4. Experimental

4.1. General method

Unless otherwise noted, commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed using Silicycle silica gel 60 F$_{254}$ plates and visualized using UV light, anisaldehyde, ceric sulfate or potassium permanganate. Flash chromatography was performed on Silicycle silica gel 60 (40–63 μm). ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ on a Varian Inova 400 MHz, 500 MHz or 600 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant in hertz (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift in parts per million from the central peak of CDCl$_3$ (77.23 ppm). Infrared (IR) spectra were recorded on a Nicolet 730 FT-IR spectrometer and reported in frequency of the absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Princeton University Mass Spectrometry Facility. Optical rotations were measured on a Perkin–Elmer 341 polarimeter at 589 nm.

4.2. Synthesis of 15a

4.2.1. Method A: synthesis of 15a by addition of Grignard reagent 13a to (–)-menthone. To a THF suspension of magnesium powder (480 mg, 19.8 mmol) were added a few drops of dibromoethane followed by slow addition of dimethylallyl chloride[16] (1.04 g, 10.0 mmol) at room temperature. Upon completion of the addition, the suspension was cooled to 0 °C, and a THF solution of (–)-menthone (1.54 g, 10 mmol) was added dropwise. After 3 h at 0 °C, the reaction was quenched by the addition of saturated aqueous NH$_4$Cl, and the layers were separated. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated. The ^{1}H NMR analysis of the crude product indicated 70% conversion of (–)-menthone and the diastereomeric ratio to be 10:2:1:2. Separation of the major isomer by flash column chromatography (silica gel, hexanes/toluene=15/1 to 10/1 to 4/1) afforded pure

15a (790 mg, 35% after a single separation; the mixed fractions could be collected and further purified) as a colorless liquid: [α]$_D^{23}$ +6.2 (*c* 2.3, CHCl$_3$); IR (film) 3010, 2953, 2869, 1456, 1378, 1178 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.69 (dq, *J*=10.9, 6.9 Hz, 1H), 5.38 (ddq, *J*=10.9, 10.2, 1.8 Hz, 1H), 3.07 (dq, *J*=10.2, 6.9 Hz, 1H), 2.18 (m, 1H), 1.76 (m, 2H), 1.71 (dd, *J*=6.8, 1.8 Hz, 3H), 1.53 (m, 2H), 1.40 (m, 1H), 1.31 (s, 1H), 1.29 (m, 1H), 1.01 (m, 1H), 0.96 (d, *J*=6.9 Hz, 3H), 0.93 (d, *J*=6.9 Hz, 3H), 0.91 (d, *J*=7.0 Hz, 3H), 0.86 (d, *J*=6.5 Hz, 3H), 0.83 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 132.6, 127.1, 77.25, 46.2, 41.7, 37.6, 35.6, 27.7, 25.5, 23.6, 22.9, 20.7, 18.1, 15.8, 13.6; HRMS-EI (*m/z*): [M]$^+$ calcd for C$_{15}$H$_{28}$O 224.2140, found 224.2141.

4.2.2. Method B: synthesis of 15a by addition of titanium reagent 13b to (–)-menthone. To a THF suspension of magnesium powder (480 mg, 19.8 mmol) were added a few drops of dibromoethane followed by slow addition of dimethylallyl chloride[12] (1.04 g, 10.0 mmol) at room temperature. Upon completion of the addition, the suspension was stirred for 1 h and filtered through a sintered glass funnel under argon. The filtrate was slowly cannulated to a THF solution of ClTi(O^{i}Pr)$_3$ (1.0 M in THF, 10.0 mL, 10.0 mmol) at −78 °C. The resulting solution was stirred at −78 °C for additional 1 h, and a THF solution of (–)-menthone (1.54 g, 10.0 mmol) was added dropwise. The reaction mixture was stirred for an additional 4 h at −78 °C and quenched by aqueous NH$_4$Cl. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated. The ^{1}H NMR analysis of the crude product indicated 55% conversion and the diastereomeric ratio to be 30:4:1:2. Purification of the major isomer by flash column chromatography (silica gel, hexanes/toluene=15/1 to 10/1 to 4/1) afforded analytically pure **15a** (838 mg, 37% after a single separation; the mixed fractions could be collected and further purified) as a colorless liquid.

4.3. General procedure for homoallylic alcohol 17 synthesis (Table 1)

To a 1.0 mL CH$_2$Cl$_2$ solution of **15a** (112 mg, 0.50 mmol) and aldehyde **16** (0.25 mmol) was added TsOH·H$_2$O (4.8 mg, 0.025 mmol) at 25 °C. This solution was stirred for 12–24 h while the progress of the reaction was being monitored by TLC. After complete consumption of aldehyde **16**, the reaction mixture was concentrated, and the crude product was analyzed by ^{1}H NMR for the determination of the diastereomeric ratio (dr). Purification of the crude product by flash column chromatography afforded alcohol **17** in a diastereomerically pure form. The enantiomeric ratio (er) of the major diastereomer was determined by chiral HPLC or chiral SFC.

4.3.1. (*E*)-(3*R*,4*R*)-4-Methyl-1-phenyl-hept-5-en-3-ol (17a). Following the general procedure, the reaction of aldehyde **16a** (34 mg, 0.25 mmol) with **15a** gave alcohol **17a** (36 mg, 71%) as a colorless oil: dr=17:1 by ^{1}H NMR (600 MHz); er>99:1 by chiral HPLC (Chiralpak AD, 10% water in methanol, 1.0 mL/min, 4.40 min (+) isomer, 4.85 min for (−) isomer); [α]$_D^{23}$ +35 (*c* 0.95, CHCl$_3$); IR

(film) 3396, 3026, 2933, 2879, 1496, 1453 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (m, 2H), 7.23 (m, 3H), 5.53 (dqd, J=15.2, 6.6, 0.9 Hz, 1H), 5.37 (ddq, J=15.2, 7.6, 1.5 Hz, 1H), 3.49 (m, 1H), 2.88 (ddd, J=13.8, 10.5, 5.2 Hz, 1H), 2.65 (ddd, J=13.5, 9.8, 5.2 Hz, 1H), 2.27 (m, 1H), 1.83 (m, 1H), 1.70 (dd, J=6.4, 0.6 Hz, 3H), 1.65 (m, 1H), 1.49 (s, 1H), 1.02 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.6, 133.4, 128.7, 128.6, 126.5, 126.0, 74.6, 42.9, 35.9, 32.7, 18.3, 15.3; HRMS-EI (m/z): [M−H$_2$O]$^+$ calcd for C$_{14}$H$_{18}$ 186.1409, found 186.1410.

4.3.2. (E)-(3R,4R)-1-(tert-Butyldiphenylsilanyloxy)-4-methyl-hept-5-en-3-ol (17b). Following the general procedure, the reaction of aldehyde **16b**[17] (78 mg, 0.25 mmol) with **15a** afforded alcohol **17b** (54 mg, 57%) as a colorless oil: dr=9:1 by ^{1}H NMR (500 MHz); er>99:1 by chiral SFC ((R,R) Whelk-01 (25×0.46 cm), 10% isopropanol (0.1% DEA) in CO$_2$ (100 bar), 3.0 mL/min, 3.26 min (−) isomer, 3.57 min for (+) isomer); [α]$_D^{23}$ +6.6 (c 0.70, CHCl$_3$); IR (film) 3510, 2860, 1470, 1430, 1110, 1080 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.67 (m, 4H), 7.42 (m, 6H), 5.46 (dqd, J=15.3, 6.4, 0.7 Hz, 1H), 5.35 (ddq, J=15.3, 7.9, 1.6 Hz, 1H), 3.85 (m, 2H), 3.68 (m, 1H), 3.10 (d, J=3.1 Hz, 1H), 2.21 (m, 1H), 1.71 (m, 1H), 1.66 (d, J=6.2 Hz, 3H), 1.62 (m, 1H), 1.05 (s, 9H), 1.03 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 135.7, 133.8, 133.2, 129.9, 127.9, 125.6, 75.4, 63.8, 43.2, 35.8, 26.9, 19.2, 18.2, 16.0; HRMS-EI (m/z): [M−^{t}Bu]$^+$ calcd for C$_{20}$H$_{25}$O$_2$Si 325.1624, found 325.1606.

4.3.3. (E)-(1R,2R)-1-Cyclohexyl-2-methyl-pent-3-en-1-ol (17c). Following the general procedure, the reaction of aldehyde **16c** (28 mg, 0.25 mmol) with **15a** afforded alcohol **17c** (29 mg, 64%) as a colorless oil: dr=5:1 by ^{1}H NMR (500 MHz); er>99:1 by chiral HPLC (Chiralpak AD, 5% water in methanol, 1.0 mL/min, 5.12 min (−) isomer, 5.71 min for (+) isomer); [α]$_D^{23}$ +26 (c 0.35, CHCl$_3$); IR (film) 3390, 2930, 2850, 1450, 980, 970 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.48 (dqd, J=15.3, 6.1, 1.0 Hz, 1H), 5.40 (ddq, J=15.4, 6.7, 1.5 Hz, 1H), 3.14 (t, J=5.8 Hz, 1H), 2.34 (m, 1H), 1.90 (m, 1H), 1.74 (m, 2H), 1.68 (dd, J=6.1, 1.3 Hz, 3H), 1.64 (m, 1H), 1.58 (m, 1H), 1.46 (s, 1H), 1.40 (m, 1H), 1.29–0.94 (m, 5H), 0.97 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 134.8, 125.3, 79.2, 40.4, 38.9, 29.9, 28.2, 26.7, 26.5, 26.2, 18.3, 13.8; HRMS-EI (m/z): [M]$^+$ calcd for C$_{12}$H$_{22}$O 182.1671, found 182.1674.

4.3.4. (E)-(2S,3S,4R)-2-(tert-Butyldiphenylsilanyloxy)-4-methyl-hept-5-en-3-ol (17d). Following the general procedure, the reaction of aldehyde **16d**[18] (78 mg, 0.25 mmol) with **15a** afforded alcohol **17d** (64 mg, 67%) as a colorless oil: dr>20:1 by ^{1}H NMR (600 MHz); [α]$_D^{23}$ +5.42 (c 1.53, CHCl$_3$); IR (film) 3561, 2961, 2931, 2858, 1427, 1112 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (m, 4H), 7.42 (m, 6H), 5.27 (dq, J=15.3, 6.1 Hz, 1H), 5.19 (ddq, J=15.3, 7.6, 1.5 Hz, 1H), 3.93 (qd, J=6.4, 3.3 Hz, 1H), 3.05 (td, J=7.6, 3.3 Hz, 1H), 2.44 (d, J=7.6 Hz, 1H), 2.28 (m, 1H), 1.56 (d, J=6.1 Hz, 3H), 1.08 (s, 9H), 1.05 (d, J=6.4 Hz, 3H), 1.02 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 136.2, 136.1, 134.5, 134.3, 133.4, 130.0, 129.8, 127.9, 127.6, 125.4, 79.7, 70.4, 40.3, 27.3, 21.2, 19.6, 18.2, 16.5; HRMS-EI (m/z): [M−^{t}Bu]$^+$ calcd for C$_{20}$H$_{25}$O$_2$Si 325.1624, found 325.1626.

4.3.5. (E)-(2R,3R)-3-Methyl-1-phenyl-hex-4-en-2-ol (17e). Following the general procedure, the reaction of aldehyde **16e** (31 mg, 0.25 mmol) with **15a** afforded a mixture of alcohols **17e** and its diastereomer of undetermined stereochemistry (38 mg, 79%) as a colorless oil. The same alcohol **17e** (48 mg, 66%) was obtained from the reaction of dimethyl acetal **16f** (42 mg, 0.25 mmol) with **15a** according to the general procedure: dr=10:1 by ^{1}H NMR (500 MHz); er of the major alcohol **17e**>99:1 by chiral HPLC (Chiralpak AD, 10% water in methanol, 1.0 mL/min, 4.75 min (+) isomer, 6.13 min for (−) isomer); [α]$_D^{23}$ +6.6 (c 0.70, CHCl$_3$); [α]$_D^{23}$ +43 (c 0.83, CHCl$_3$); IR (film) 3441, 3027, 2963, 2917, 2880, 1495, 1453 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (m, 2H), 7.23 (m, 3H), 5.55 (dq, J=15.2, 6.1 Hz, 1H), 5.45 (ddq, J=15.2, 7.3, 1.2 Hz, 1H), 3.67 (m, 1H), 2.89 (dd, J=13.8, 3.7 Hz, 1H), 2.58 (dd, J=13.8, 9.5 Hz, 1H), 2.29 (m, 1H), 1.71 (d, J=6.1 Hz, 3H), 1.52 (d, J=4.0 Hz, 1H), 1.09 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.4, 133.7, 129.5, 128.7, 126.5, 126.3, 76.3, 42.4, 41.0, 18.4, 15.6; HRMS-EI (m/z): [M]$^+$ calcd for C$_{13}$H$_{18}$O 190.1358, found 190.1365.

4.3.6. (E)-(2R,3R)-1-Cyclohexyl-3-methyl-hex-4-en-2-ol (17g). Following the general procedure, the reaction of aldehyde **16g**[19] (26 mg, 0.21 mmol) with **15a** afforded alcohol **17g** (28 mg, 69%) as a colorless oil: dr=11:1 by ^{1}H NMR (500 MHz); er>99:1 (determined as a benzoate ester) by chiral HPLC (Chiralpak AD, 5% water in methanol, 1.0 mL/min, 5.34 min (+) isomer, 6.02 min for (−) isomer); [α]$_D^{23}$ +44 (c 0.42, CHCl$_3$); IR (film) 3370, 2920, 2850, 1450, 990, 970; ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.50 (ddq, J=15.3, 6.4, 0.9 Hz, 1H), 5.37 (ddq, J=15.3, 7.6, 1.5 Hz, 1H), 3.57 (m, 1H), 2.19 (m, 1H), 1.81 (app. d, J=12.8 Hz, 1H), 1.69 (d, J=6.1 Hz, 3H), 1.69–1.63 (m, 4H), 1.45 (m, 1H), 1.33–1.10 (m, 6H), 0.91 (m, 1H), 0.97 (d, J=7.0 Hz, 3H), 0.82 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$); δ 133.5, 126.1, 72.3, 42.9, 41.6, 34.6, 34.2, 32.7, 26.7, 26.5, 26.2, 18.2, 14.8; HRMS-EI (m/z): [M−H$_2$O]$^+$ calcd for C$_{13}$H$_{22}$ 178.1721, found 178.1712.

4.3.7. (E)-(4R,5R,8S)-4,8-Dimethyl-undec-2-en-9-yn-5-ol (6). Following the general procedure, the reaction of aldehyde **4**[6] (99 mg, 0.80 mmol) with **15a** afforded alcohol **6** (125 mg, 80%) as a colorless oil: dr=10:1 by ^{1}H NMR (500 MHz); [α]$_D^{23}$ +51 (c 0.45, CHCl$_3$); IR (film) 3392, 2964, 2931, 2858, 1451, 1429, 1376 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.52 (dqd, J=15.3, 6.1, 0.9 Hz, 1H), 5.39 (ddq, J=15.3, 6.6, 1.5 Hz, 1H), 3.46 (m, 1H), 2.42 (m, 1H), 2.25 (m, 1H), 1.79 (d, J=2.4 Hz, 3H), 1.70 (dd, J=6.1, 1.5 Hz, 3H), 1.38–1.64 (m, 5H), 1.15 (d, J=7.0 Hz, 3H), 1.01 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 133.7, 126.3, 83.8, 76.1, 75.0, 42.8, 33.7, 31.7, 26.0, 21.7, 18.3, 15.1, 3.7; HRMS-EI (m/z): (the corresponding TBS ether) [M−Me]$^+$ calcd for C$_{18}$H$_{33}$OSi 293.2301, found 293.2290.

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