**A Novel and General α -Regioselective and Highly
Enantioselective Prenylation of Aldehydes**

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Supplementary Material

Supporting Information

General

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification with the following exceptions: Hexane, dichloromethane, ethyl acetate were fractionally distilled. Aldehydes were distilled before used. The aldehydes can be dried over Na_2SO_4 in hexane (for reaction in hexane) before used if they are wet. Hexane for reaction purpose was distilled over CaH_2 .

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. Liquid samples were examined as film between NaCl salt plates.

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker ACF 300 and Bruker Avance DPX 300 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to

the signal of chloroform-d (d 7.264, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). The proportion of diastereomers and geometric isomers was determined from the integration of ¹H NMR and ¹³C NMR spectra. Fluorine nuclear magnetic resonance spectra (¹⁹F NMR) are reported as δ in units of parts per million (ppm) with SR at -1379.128.

Mass spectral analyses were carried out on a VG 7035 micromass mass spectrophotometer at a source temperature of 200 °C and at an ion current of 70 eV. Mass spectral data were reported in units of mass to charge (m/z) and % intensity.

Experimental procedure:

Standard reaction condition:

TfOH (~0.1 equiv) was added into a solution of 3-Phenyl-propionaldehyde (67mg, 0.5mmol, 1 equiv) and 6-Methyl-1-phenyl-hept-5-en-3-ol (172mg, 1.0mmol, 2 equiv) in 20ml hexane, the reaction mixture was stirred for 11 hrs before 15 ml of MeOH was added and stirred for another 3 hrs.

Diluted the reaction mixture with 30ml diethylether, washed with 30ml of mix solution of sat. NaHCO₃ and sat. NaCl (1:1 mixture), and dried over anhydrous MgSO₄.

The solvent was then removed *in vacuo*, purified with silica gel chromatography with mix solvent of hexane and ether at ratio of 20:1. The product was obtained (89mg, 87% yield) as colorless oil.

4-Methyl-1-phenyl-pent-3-en-1-ol

R_f 0.33 (4:1 hexane/ethyl acetate)

¹H NMR (300 MHz, CDCl₃): δ 7.30–7.15 (m, 5H), 5.10 (tq, *J* = 8.0, 1.2, 1H), 4.60 (t, *J* = 6.0, 1H), 2.45–2.31 (m, 2H), 1.65 (s, 3H), 1.53 (s, 1H).

¹³C NMR (75.4 MHz, CDCl₃) δ 144.3, 125.6, 128.3, 127.4, 125.8, 119.8, 74.1, 38.3, 25.9, 17.9.

FTIR (film) 3383, 3087 3063, 3029, 2968, 2914, 2858, 1494, 1453, 1376, 1309 1197, 1108 cm⁻¹.

HRMS Calcd for C₁₂H₁₆O [M⁺]: 176.1201. Found: 176.1199.

[α]_D = +53.3 (c = 0.15 in C₆H₆) (93% e.e.)

[α]_D = +38.7 (c = 0.15 in MeOH) (93% e.e.)

HPLC analysis employing a Daicel Chiracel OD column (Hexane: *i*-propanol 98:2, 2.0 mL/min: *t*₁ = 10.51 for the (*R*) isomer, *t*₂ = 13.52 for the (*S*) isomer).

Note: The absolute configuration was assigned by comparing the optical rotation with that of the known product. literature value: *R* isomer, [α]_D = +50.2 (c = 1.16 in C₆H₆). Ishihara, K.; Mouri, M.; Gao, Q.; Muruyama, T; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490–11495.

1-Benzyloxy-6-methyl-hept-5-en-3-ol

R_f 0.58(1:1 hexane/ethyl acetate)

¹H NMR (300 MHz, CDCl₃): δ 7.35–7.26 (m, 5H), 5.18 (tq, *J* = 7.32, 1.41 Hz, 1H), 4.53 (s, 2H), 3.86–3.60 (m, 3H), 2.80 (broad s, 1H), 2.28–2.13 (m, 2H), 1.80–1.73 (m, 2H), 1.73 (s, 3H), 1.63 (s, 3H).

¹³C NMR (75.4 MHz, CDCl₃) δ 138.0, 134.4, 128.4, 127.7, 127.7, 120.2, 73.3, 71.1, 69.0, 36.2, 35.9, 25.8, 17.9.

FTIR (film) 3435, 1654, 1637, 1617, 669 cm⁻¹.

HRMS Calcd for C₁₃H₁₉O₁ [M⁺ - C₂H₃O]: 191.1436. Found: 191.1438.

[α]_D = -18.2 (c = 0.20 in MeOH) (94% e.e.)

HPLC analysis employing a Daicel Chiracel ODH column (Hexane: *i*-propanol 99:1, 0.3 mL/min: t₁ = 36.33 for the (*R*) isomer, t₂ = 33.22 for the (*S*) isomer).

1-Benzyloxy-7-methyl-oct-6-en-4-ol

R_f 0.63(1:1 hexane/ethyl acetate)

¹H NMR (300 MHz, CDCl₃): δ 7.36–7.26 (m, 5H), 5.19 (broad t, *J* = 7.65, 1H), 4.53 (s, 2H), 3.62 (broad m, 1H), 3.67–3.56 (broad m, 1H), 3.53 (t, *J* = 5.94, 2H), 2.19 (broad t, *J* = 6.9, 2H), 1.75 (s, 3H), 1.65 (s, 3H), 1.82–1.43 (m, 4H).

¹³C NMR (75.4 MHz, CDCl₃) δ 138.3, 134.7, 128.4, 127.7, 127.6, 120.3, 72.94, 71.47, 70.47, 36.2, 33.9, 26.3, 25.9, 17.9.

FTIR (film) 3412, 3063, 3030, 2922, 2857, 1496, 1454, 1362, 1099, 1028, 735, 697 cm^{-1} .

HRMS Calcd for $\text{C}_{11}\text{H}_{15}\text{O}_2$ [$\text{M}^+ - \text{C}_5\text{H}_9$]: 179.1072. Found: 179.1072.

$[\alpha]_{\text{D}} = -13.3$ ($c = 0.30$ in MeOH) (92% e.e.)

HPLC analysis employing a Daicel Chiracel OB column (Hexane: *i*-propanol 98:2, 1.0 mL/min: $t_1 = 8.72$ for the (R) isomer, $t_2 = 11.91$ for the (S) isomer).

9-Benzyloxy-2-methyl-non-2-en-5-ol

R_f 0.65 (1:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 7.35–7.27 (m, 5H), 5.18 (t, $J = 7.32$, 1H), 4.51 (s, 2H), 3.59 (broad m, 1H), 3.49 (t, $J = 6.27$, 2H), 2.19–2.14 (m, 2H), 1.75 (s, 3H), 1.65 (s, 3H), 1.55–1.45 (m, 4H), 1.30–1.23 (m, 2H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 138.6, 134.8, 128.2, 127.5, 127.4, 120.2, 72.8, 71.5, 70.2, 36.5, 36.2, 29.7, 25.8, 22.4, 17.9.

FTIR (film) 3418, 3029, 2934, 2859, 1453, 1100, 1028, 734, 697 cm^{-1} .

HRMS Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2$ [M^+]: 262.1933. Found: 262.1933.

$[\alpha]_{\text{D}} = -27.6$ ($c = 0.25$ in MeOH) (98% e.e.)

HPLC analysis employing a Daicel Chiracel OB column (Hexane: *i*-propanol 99:1, 0.3 mL/min: $t_1 = 38.58$ for the (R) isomer, $t_2 = 33.93$ for the (S) isomer).

6-Methyl-1-phenyl-hept-5-en-3-ol

Rf 0.37 (4:1 hexane/ethyl acetate).

^1H NMR (300 MHz, CDCl_3): δ 7.31–7.16 (m, 5H), 5.16 (tt, J = 7.3, 1.4, 1H), 3.66–3.60 (m, 1H), 2.82 (dt, J = 13.6, 7.7, 1H), 2.68 (dt, J = 13.9, 8.4, 1H), 2.20 (t, J = 6.6, 2H), 1.79 (td, J = 7.6, 6.3, 2H), 1.74 (s, 3H), 1.65 (s, 3H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 142.2, 135.4, 128.5, 128.4, 125.8, 119.9, 119.9, 71.0, 38.5, 36.4, 32.2, 25.9, 18.0.

FTIR (film) 3387, 3084, 3062, 3026, 2913, 2857, 1603, 1496, 1452, 1437, 1375, 1073, 1052, 746, 698 cm^{-1} .

HRMS Calcd for $\text{C}_{14}\text{H}_{20}\text{O}$ $[\text{M}^+]$: 204.1514 Found: 204.1514.

$[\alpha]_{\text{D}} = -38.7$ (c = 0.15 in MeOH) (95% e.e.)

HPLC analysis employing a Daicel Chiracel OD column (Hexane: *i*-propanol 98:2, 2.0 mL/min: t_1 = 12.23 for the (R) isomer, t_2 = 8.12 for the (S) isomer).

2-Methyl-tridec-2-en-5-ol

Rf 0.55 (4:1 hexane/ethyl acetate).

^1H NMR (300 MHz, CDCl_3): δ 5.17 (t, J = 7.0, 1H), 3.60–3.56 (m, 1H), 2.17–2.13 (broad m, 2H), 1.74 (s, 3H), 1.64 (s, 3H), 1.45 (broad s, 2H), 1.28 (broad s, 12H), 0.88 (t, J = 7.0, 3H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 135.1, 120.2, 71.8, 36.9, 36.2, 31.9, 29.7, 29.6, 29.3, 25.9, 25.8, 22.7, 18.0, 14.1.

FTIR (film) 3351, 2956, 2925, 2854, 1465, 1457, 1377, 1126, 1079, 1014 cm^{-1} .

HRMS Calcd for $\text{C}_{14}\text{H}_{28}\text{O}$ $[\text{M}^+]$: 212.2140. Found: 212.2141.

$[\alpha]_{\text{D}} = -33.3$ (c = 0.15 in MeOH) (95% e.e.)

It was protected with *R*(+)- α -Methoxy- β -trifluoromethyl-phenylacetic acid. ^{19}F NMR (282.2 MHz, CDCl_3) 4.05 for *S* isomer, 4.13 for *R* isomer.

7-Hydroxy-10-methyl-undeca-2,9-dienoic acid ethyl ester

Rf 0.63 (4:1 hexane/ethyl acetate).

^1H NMR (300 MHz, CDCl_3): δ 6.93 (dt, $J = 15.7$, 6.99, 1H), 6.79 (d, $J = 15.7$, 1H), 5.13 (t, $J = 7.32$, 1H), 4.15 (q, $J = 7.32$, 2H), 3.58–3.53 (m, 1H), 2.27–2.10 (m 4H), 1.70 (s, 3H), 1.60 (s, 3H), 1.46–1.39 (m, 2H), 1.25 (t, $J = 6.96$, 3H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 166.6, 148.9, 135.0, 121.4, 120.0, 71.2, 60.0, 36.2, 36.1, 32.1, 25.8, 24.2, 17.9, 14.2.

FTIR (film) 3430, 2984, 2915, 2859, 1720, 1651, 1443, 1365, 1310, 1267, 1192, 983, 860 cm^{-1} .

HRMS Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_3$ $[\text{M}^+]$: 240.1725. Found: 240.1731.

$[\alpha]_{\text{D}} = -21.7$ ($c = 0.25$ in MeOH) (98% e.e.)

HPLC analysis employing a Daicel Chiracel OB column (Hexane: *i*-propanol 98:2, 1.0 mL/min: $t_1 = 14.78$ for the (*R*) isomer, $t_2 = 10.48$ for the (*S*) isomer).

4-Methyl-1-naphthalen-2-yl-pent-3-en-1-ol

Rf 0.39 (4:1 hexane/ethyl acetate).

^1H NMR (300 MHz, CDCl_3): δ 7.86–7.82 (m, 4H), 7.52–7.46 (m, 3H), 5.21 (broad t, $J = 7.0$, 1H), 4.85 (dd, $J = 7.3$, 5.6, 1H), 2.65–2.46 (m, 2H), 1.75 (s, 3H), 1.64 (s, 3H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 141.7, 135.7, 133.3, 132.9, 128.0, 127.9, 127.6, 126.0, 125.6, 124.4, 124.1, 119.7, 74.1, 38.1, 25.9, 20.0.

FTIR (film) 3424, 3055, 2938, 2864, 1652, 1635, 1600, 1506, 1449, 1440, 1374, 1121, 1075, 1033, 1022 cm^{-1} .

HRMS Calcd for $\text{C}_{16}\text{H}_{18}\text{O}$ $[\text{M}]^+$: 226.1358. Found: 226.1356.

$[\alpha]_{\text{D}}^{25} = +38.0$ ($c = 0.15$ in MeOH) (87% e.e.)

HPLC analysis employing a Daicel Chiracel OD column (Hexane: *i*-propanol 98:2, 1.0 mL/min: $t_1 = 18.62$ for the (R) isomer, $t_2 = 16.83$ for the (S) isomer).

17-(2-Hydroxy-1,5-dimethyl-hex-4-enyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[a]phenanthren-3-one

^1H NMR (300 MHz, CDCl_3): δ 5.72 (s, 1H), 5.16 (broad t, $J = 8.6$, 1H), 3.64 (dt, $J = 9.4$, 3.7, 1H), 1.74 (s, 3H), 1.65 (s, 3H), 1.18 (s, 3H), 0.96 (d, $J = 6.6$, 3H), 0.74 (s, 1H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 199.7, 171.6, 135.4, 123.8, 121.2, 73.1, 55.5, 53.8, 53.1, 42.8, 41.0, 39.6, 38.6, 35.7, 35.6, 34.0, 32.9, 32.0, 28.9, 27.4, 26.0, 24.3, 21.0, 18.0, 17.4, 12.5, 11.9.

FTIR (film) 3434, 2908, 2851, 1700, 1654, 1626, 1433, 668 cm^{-1} .

HRMS Calcd for $\text{C}_{27}\text{H}_{42}\text{O}_2$ $[\text{M}]^+$: 398.3185. Found: 398.3120.

$[\alpha]_{\text{D}}^{25} = +57.0$ ($c = 0.90$ in MeOH)

17-(2-Hydroxy-1,5-dimethyl-hex-4-enyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[a]phenanthren-3-one

^1H NMR (300 MHz, CDCl_3): δ 5.72 (s, 1H), 5.13 (broad t, J = 7.7, 1H), 3.66 (broad dd, J = 5.2, 3.5, 1H), 1.73 (s, 3H), 1.63 (s, 3H), 1.18 (s, 3H), 0.93 (d, J = 5.9, 3H), 0.71 (s, 1H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 199.7, 171.6, 134.5, 123.8, 120.9, 73.2, 55.7, 53.7, 52.6, 42.3, 39.9, 39.6, 38.6, 35.7, 35.7, 34.2, 34.0, 32.9, 32.0, 27.7, 25.9, 24.1, 21.0, 18.0, 17.4, 11.9, 11.8.

FTIR (film) 3434, 2908, 2851, 1700, 1654, 1626, 1433, 668 cm^{-1} .

HRMS Calcd for $\text{C}_{27}\text{H}_{42}\text{O}_2$ $[\text{M}^+]$: 398.3185. Found: 398.3120.

$[\alpha]_{\text{D}} = +68.2$ (c = 0.60 in MeOH)

Reaction condition:

2, 6,6-Dimethyl-oct-7-ene-1,5-diol

3,4-Dihydro-2H-pyran (DHP) (4.2 g, 50 mmol, 1 equiv) was stirred in a 88 mL co-solvent of 5% HCl, saturated NH_4Cl and THF (5% HCl : NH_4Cl : THF = 8 mL: 40 mL: 40mL) at room temperature for 45 minutes. (Tetrahydro-pyran-2-ol was generated *in situ*.)

The solution was then cooled to 0°C with ice-bath. Zinc powder (6.5 g, 100 mmol, 2 equiv) was added, followed by drop-wise addition of prenyl bromide (8.2 g ,55 mmol, 1.1

equiv). The reaction mixture was allowed to warm up to r.t. and stirred for another 12 h.

The THF in reaction mixture was removed *in vacuo*. The remaining aqueous mixture was added with 80mL Ethyl Acetate, and cool 5% HCl was then added till the solution turn clear. The aqueous was extracted for another 3 times with 60 ml Ethyl Acetate. The organic layer was combined and washed with 50ml sat. NaHCO₃ solution, followed by 50ml of brine, and dried over anhydrous MgSO₄.

After 2 hrs, the Ethyl Acetate was remove *in vacuo*. the mixture was purified with silica gel column chromatography (with co-solvent, hexane : Ethyl Acetate = 4: 1). The product was obtained in 6.45g (75% yield) as colorless oil. Rf 0.33 (1:1 hexane/ethyl acetate).

¹H NMR (300 MHz, CDCl₃): δ 5.80 (dd, *J* = 17.4, 10.80 Hz, 1H), 5.06 (dd, *J* = 7.65, 1.38, 1H), 5.01 (dd, *J* = 12.9, 1.38, 1H), 3.62 (t, *J* = 6.27, 1H), 3.23 (dd, *J* = 10.4, 1.74, 1H), 2.30-2.22 (bm, 2H), 1.63-1.19 (m, 6H), 0.99 (s, 6H).

¹³C NMR (75.4 MHz, CDCl₃) δ 145.5, 113.2, 78.2, 62.5, 41.6, 32.5, 30.8, 23.1, 22.9, 22.2.

FTIR (film) 3351, 3082, 2942 2869, 1726, 1464, 1435, 1415, 1237, 1087, 1062, 1005, 911, 667 cm⁻¹.

Chiral resolution of the **2** was done with (*S*) O-Aceyl mandelic acid.

For the Standard procedure, refer to Whitesell, J. K.; Reynolds, D. J. *Org. Chem.* **1983**, 48, 3548.

(Note: the separation of the (*S*) O-Aceyl mandelic di-ester of **2** was done by silica gel column chromatography with CH₂Cl₂:Hexane = 6:1 as mobile phase)

the enantiomeric excess of both **R-2** and **S-2** are found to be 99% by ^{19}F NMR analysis of thier Mosser derivative.

(*R*)-Mosser acid di-protection ^{19}F NMR (282.2 MHz, CDCl_3) 4.73, 3.89 for **R-2** and 4.84, 3.89 for **S-2**.

The stereo configuration of the two steriodal alcohol are determined by following:

i) TfOH (0.5mg) was added to 10 mg of **3i** in 10 mL CH_2Cl_2 solution at r.t and the reaction was stir for 2 hrs. A single product **4j** was isolated, and ^1H and ^{13}C NMR was taken.

ii) TfOH (0.5mg) was added to 10 mg of **3i** in 10 mL CH_2Cl_2 solution at r.t and the reaction was stir for 2 hrs. A single product **4i** was isolated, and ^1H and ^{13}C NMR was taken.

iii) ^1H and ^{13}C NMR spectra of **4i** and **4j** are compared with the known compound's spectra, which stereochemistry was determined with single X-ray Crystallography. (Loh, T. P.; Hu. Q. Y.; Ma. L. T. *J. Am. Chem. Soc.* **2001**, *123*, 2450-2451.).

iv) **4i** was found to match the known compound.