



Supporting Information

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# Supporting Information

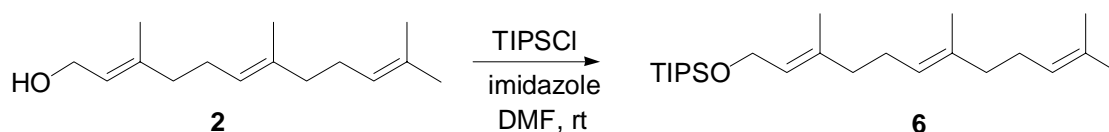
## Enantio- and Diastereoselective Hydrogenation of Farnesol and *O*-Protected Derivatives: Stereocontrol through Adjustment of C=C Bond Configuration

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**General:** Reactions and manipulations of air- and moisture-sensitive compounds were performed in a glovebox under nitrogen or using standard Schlenk techniques, unless otherwise indicated. All chemicals were purchased from Acros Organics, Aldrich, Fluka, Merck and TCI Chemicals, except for (2*E*, 6*E*)-farnesol (**2**) that was a gift from Dr. Thomas Netscher (DSM Nutritional Products). (2*Z*, 6*E*)-farnesol (**12**), (2*E*, 6*Z*)-farnesol (**13**) and (2*Z*, 6*Z*)-farnesol (**14**) were synthesized according to the literature.<sup>1</sup> [Ru{(*R*)-Tol-BINAP}(OAc)<sub>2</sub>] was prepared following the reported procedure.<sup>2</sup>

### Synthesis of (2*E*, 6*E*)-farnesyl triisopropylsilyl ether (**6**)

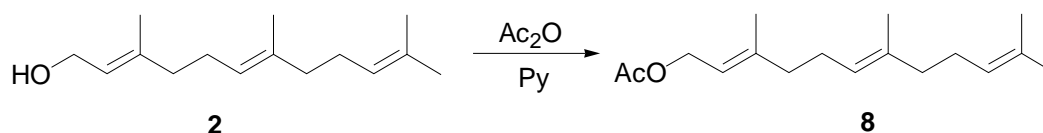


A mixture of (2*E*, 6*E*)-farnesol (0.80 g, 3.6 mmol), triisopropylsilyl chloride (0.96 mL, 4.3 mmol), imidazole (0.62 g, 9.0 mmol) and DMF (4 mL) was stirred at rt for 2.5 d, and then poured into water (50 mL). The resulting mixture was extracted with hexane (3 x 50 mL), and the combined organic phases were washed with water (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The crude product was purified by flash chromatography (silica gel, 3.5 x 15 cm, hexane/ethyl acetate 40:1, R<sub>f</sub> = 0.6), giving (2*E*, 6*E*)-farnesyl triisopropylsilyl ether (1.28 g, 94%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.34 (m, 1H), 5.10 (m, 2H), 4.26 (d, *J* = 6.3 Hz, 2H), 2.14-1.95 (m, 8H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 6H), 1.13-1.04 (m, 21H);

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.7, 135.5, 131.6, 125.2, 124.8, 124.4, 60.9, 40.1, 39.9, 27.2, 26.7, 26.1, 18.4, 18.1, 16.8, 16.4, 12.5;  
MS: (EI,  $m/z$ ) 378 ( $\text{M}^+$ , 1%), 335 (15%), 131 (100%);  
EA: calcd (%) for  $\text{C}_{24}\text{H}_{46}\text{OSi}$  (378.71): C 76.12, H 12.24; found: C 75.88, H 12.10.

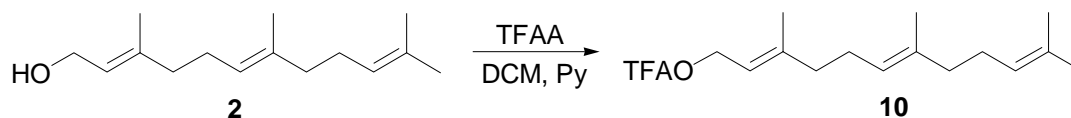
### Synthesis of (2E, 6E)-farnesyl acetate (8)



Acetic anhydride (0.73 mL, 7.6 mmol) was added to a solution of (2E, 6E)-farnesol (1.0 g, 4.4 mmol) in pyridine (0.72 mL, 8.9 mmol). The mixture was stirred at room temperature over night and then diluted with diethylether (100 mL). The organic phase was washed with water (30 mL), 1 M hydrochloric acid (2 x 30 mL), water (30 mL), and brine (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. Flash chromatography (silica gel, 3.5 x 15 cm, hexane/ethyl acetate 9:1,  $R_f = 0.5$ ) provided (2E, 6E)-farnesyl acetate (1.16 g, 98%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.33 (m, 1H), 5.08 (m, 2H), 4.57 (d,  $J = 7.1$  Hz, 2H), 2.10-1.96 (m, 8H), 2.06 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.59 (s, 6H);  
 $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.5, 142.6, 135.8, 131.7, 124.7, 124.0, 118.7, 61.8, 40.1, 39.9, 27.1, 26.6, 26.1, 21.4, 18.1, 16.8, 16.4;  
MS: (EI,  $m/z$ ) 264 ( $\text{M}^+$ , 2%), 69 (100%);  
EA: calcd (%) for  $\text{C}_{17}\text{H}_{28}\text{O}_2$  (264.40): C 77.22, H 10.67; found: C 77.06, H 10.56.

### Synthesis of (2E, 6E)-farnesyl trifluoroacetate (10)



At 0 °C trifluoroacetic anhydride (0.96 mL, 6.8 mmol) was added dropwise to a solution of (2E, 6E)-farnesol (0.88 g, 4.0 mmol) and pyridine (0.66 mL, 8.0 mmol) in dichloromethane (4 mL). The reaction mixture was stirred at 0 °C for 1.5 h, before 50 mL of water was added. The resulting mixture was extracted with diethylether (2 x 50 mL). The combined organic phases were washed successively with 1 M HCl (2 x 20 mL), sat.  $\text{NaHCO}_3$  (20 mL), brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by kugelrohr distillation (110 °C, 1 mbar), yielding (2E,

6*E*)-farnesyl trifluoroacetate (1.12 g, 88%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.39 (m, 1H), 5.08 (m, 2H), 4.85 (d, *J* = 7.6 Hz, 2H), 2.14-1.95 (m, 8H), 1.75 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 157.9 (d, *J* = 42 Hz), 146.2, 136.2, 131.8, 124.6, 123.6, 116.3, 113.6, 65.2, 40.0, 39.9, 27.1, 26.4, 26.1, 18.0, 17.0, 16.4;

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -76.2 (s);

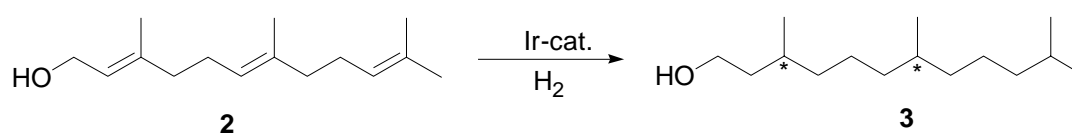
MS: (EI, *m/z*) 318 (M<sup>+</sup>, 3%), 69 (100%);

EA: calcd (%) for C<sub>17</sub>H<sub>25</sub>F<sub>3</sub>O<sub>2</sub> (318.37): C 64.13, H 7.91; found: C 64.10, H 7.84.

### Typical procedure for Ir-catalyzed hydrogenation

Under nitrogen, substrate (0.25 mmol) and catalyst (0.0025 mmol, 1 mol%) were dissolved in dichloromethane (1.25 mL) in a glass vial (2 mL) charged with a magnetic stirrer. The vial was placed in an autoclave and sealed. The autoclave was pressurized to 50 bar with H<sub>2</sub> and the solution was stirred at 700 rpm for 2 hours. Then hydrogen was carefully released and the reaction mixture concentrated under reduced pressure. Hexane (1 mL) was added and the mixture filtered through a 0.2 μm syringe filter. Concentration of the hexane solution gave an oil, which was analyzed by GC and derivatized without further purification.

### Hydrogenation of (2*E*, 6*E*)-farnesol (**2**)



### **3,7,11-Trimethyldodecan-1-ol (hexahydrofarnesol, **3**)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.69 (m, 2H), 1.65-1.47 (m, 3H), 1.39-1.04 (m, 14H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 3H);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 61.9, 40.4, 39.8, 37.9(d), 37.8, 37.7(d), 33.2, 29.9(d), 28.4, 25.2, 24.8, 23.1, 23.0, 20.1, 20.1;

MS: (EI, *m/z*) 228 (M - H<sub>2</sub>O, 5%), 69 (100%);

EA: calcd (%) for C<sub>15</sub>H<sub>26</sub>O (228.41): C 78.88, H 14.12; found: C 78.70, H 13.89.

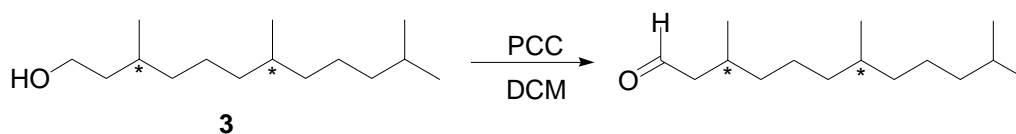
### **GC analysis for conversion determination**

Rtx-1701; 60 kPa He; 240 °C (injector); 270 °C (detector); temperature program: 50 °C (0 min), 10 °C/min, 250 °C (10 min);

*t<sub>R</sub>* = 19.24 min (**3**), 20.59 min (**2**).

### **Determination of the stereoisomeric composition of **3****

For GC analysis, hexahydrofarnesol (**3**) was oxidized to the aldehyde and converted to the corresponding acetals with L- and D-bis-TMS-diisopropyl tartrate, as described by Netscher etc.<sup>3</sup>

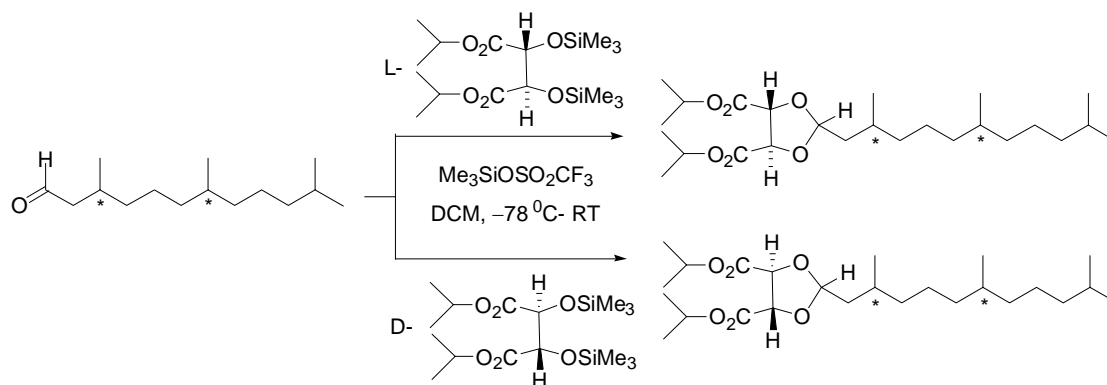


A mixture of 3,7,11-trimethyldodecan-1-ol (0.25 mmol), pyridinium chlorochromate (60 mg, 0.28 mmol) and  $\text{CH}_2\text{Cl}_2$  (1 mL) was stirred at rt for 3 h. Then diethylether (3 mL) was added, the resulting mixture was passed through a short plug of silica gel and washed with a copious amount of diethylether. Concentration of the washings provided 3,7,11-trimethyldodecan-1-carbaldehyde as a colorless oil, which was converted to acetals without further purification.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.75 (s, 1 H), 2.39 (ddd,  $J = 15.9$  Hz,  $J = 5.7$  Hz,  $J = 2.0$  Hz, 1 H), 2.21 (ddd,  $J = 14.8$  Hz,  $J = 7.8$  Hz,  $J = 2.5$  Hz, 1 H), 2.04 (m, 1 H), 1.52 (m, 1 H), 1.37-1.05 (m, 13 H), 0.95 (d,  $J = 6.6$  Hz, 3 H), 0.86 (d,  $J = 6.6$  Hz, 6 H), 0.84 (d,  $J = 6.6$  Hz, 3 H);

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  203.6, 51.6, 39.7, 37.7, 37.6, 37.5, 33.1, 28.6, 28.4, 25.2, 24.8, 23.1, 23.0, 20.1, 20.1;

MS: (EI,  $m/z$ ) 183 (M -  $\text{CH}_2\text{CHO}$ , 1%), 43 (100%).



The obtained 3,7,11-trimethyldodecan-1-carbaldehyde (0.25 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (1.0 mL). To one half of the above solution was added L-bis-TMS-diisopropyltartrate<sup>3</sup> (71 mg, 0.187 mmol), to the other half, D-bis-TMS-diisopropyltartrate (71 mg, 0.187 mmol) was added. Trimethylsilyl triflate (10  $\mu\text{L}$ , 0.05 mmol) was then added at  $-78$  °C to both reaction mixtures. The mixtures were stirred at  $-78$  °C for 30 min and then allowed to warm to rt and stirred for 1.5 h. Triethylamine (0.07 mL, 0.5 mmol) was added to quench the reaction. Concentration under high vacuum yielded an oil, which was passed through a short plug of silica gel and washed with a copious amount of diethylether. Concentration of the washings

provided L- or D-diisopropyl tartrate acetal as a colorless oil, which was dissolved in diethylether (2 mL) for GC analysis

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.29 (t,  $J = 5.0$  Hz, 1H), 5.11(sept,  $J = 6.3$  Hz, 1H); 5.12 (sept,  $J = 6.3$  Hz, 1H), 4.64 (AB,  $J = 4.2$  Hz, 1H); 4.56 (AB,  $J = 4.2$  Hz, 1H); 1.83-1.64 (m, 2H), 1.62-1.43 (m, 2H), 1.28 (d,  $J = 6.3$  Hz, 12H), 1.26-1.10 (m, 12H), 0.94 (dd,  $J = 6.5$  Hz, 3H), 0.85 (d,  $J = 6.6$  Hz, 6H), 0.82 (d,  $J = 6.6$  Hz, 3H);

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.0, 169.2(d), 107.4(d), 77.7(d), 77.6, 70.0 (2C), 41.1 (t), 39.8, 38.0 (t), 37.8 (d), 37.7(t), 33.2, 29.5, 28.4, 25.2(d), 24.6(t), 23.1, 23.0, 22.1 (4C), 20.1, 20.0;

MS: (FAB,  $m/z$ ) 443 ( $M + 1$ , 5%), 43 (100%);

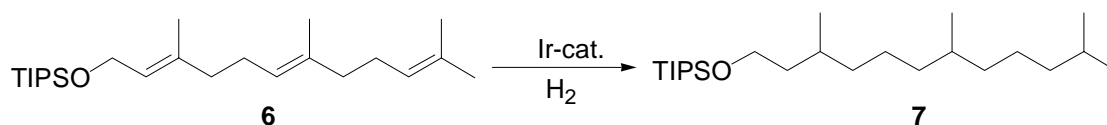
EA: calcd (%) for  $\text{C}_{25}\text{H}_{46}\text{O}_6$  (442.63): C 67.84, H 10.46; found: C 67.82, H 10.48;

GC: CP-sil-88, 90 kPa  $\text{H}_2$ , 250 °C (injector), 250 °C (detector); temperature program: 110 °C (0 min), 0.5 °C/min, 200 °C (0 min);

L-Acetal:  $t_R = 148.16$  min (3*S*, 7*R*), 148.99 min ((3*R*, 7*S*) + (3*S*, 7*S*)), 149.40 min (3*R*, 7*R*);

D-Acetal:  $t_R = 148.16$  min (3*R*, 7*S*), 148.99 min ((3*S*, 7*R*) + (3*R*, 7*R*)) 149.40 min (3*S*, 7*S*).

### Hydrogenation of farnesyl triisopropylsilyl ether (6)



#### **3,7,11-Trimethyldodecanyl triisopropylsilyl ether (7)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.70 (m, 2H), 1.62-1.47 (m, 3H), 1.42-1.04 (m, 35H), 0.87 (d,  $J = 6.6$  Hz, 3H), 0.86 (d,  $J = 6.6$  Hz, 6H), 0.84 (d,  $J = 6.6$  Hz, 3H);

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  62.2, 40.5, 39.8, 37.9, 37.8, 37.7, 33.2, 29.9, 28.4, 25.2, 24.8, 23.1, 23.0, 20.3, 20.1, 18.4, 12.4;

MS: (EI,  $m/z$ ) 384 ( $M^+$ , 0.2%), 341 (100%);

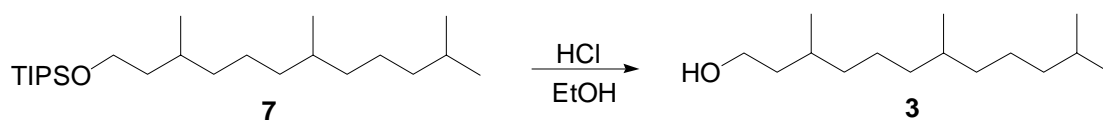
EA: calcd (%) for  $\text{C}_{24}\text{H}_{52}\text{OSi}$  (384.76): C 74.92, H 13.62; found: C 74.94, H 13.46.

#### **GC analysis for conversion determination**

Rtx-1701, 60 kPa He, 240 °C (injector), 270 °C (detector); temperature program: 50 °C (0 min), 10 °C/min, 250 °C (20 min);

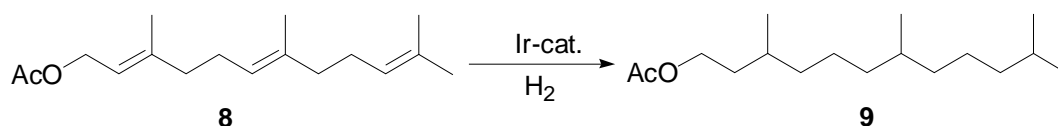
$t_R = 25.89$  min (7), 28.83 min (6).

#### **Hydrolysis of 3,7,11-trimethyldodecanyl triisopropylsilyl ether (7)**



A mixture of 3,7,11-trimethyldodecanyl triisopropylsilyl ether (0.25 mmol) and 1 % HCl solution in ethanol (5 mL) was stirred at rt for 1.5 h. The solvent was evaporated and the residue dissolved in diethylether (20 mL). The organic phase was washed with water (2 x 5 mL), brine (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The crude product was oxidized to the aldehyde without further purification and derivatized for GC analysis as described above.

### Hydrogenation of (2*E*, 6*E*)-farnesyl acetate (8)



#### **3,7,11-trimethyldodecanyl acetate (9)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.07 (m, 2H), 2.04 (s, 3H), 1.71-1.1.61 (m, 1H), 1.57-1.48 (m, 2H), 1.47-1.02 (m, 14H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 3H);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 171.6, 63.6, 39.8, 37.7(3C) 35.9, 33.2, 30.2, 28.4, 25.2, 24.7, 23.1, 23.0, 21.4, 20.1, 20.0;

MS: (FAB, *m/z*) 271 (*M* + 1, 9%), 57 (100%);

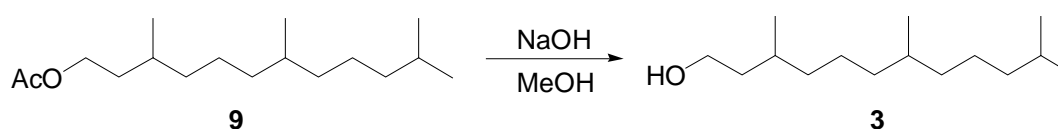
EA: calcd (%) for C<sub>17</sub>H<sub>34</sub>O<sub>2</sub> (270.45): C 75.50, H 12.67; found: C 74.84, H 12.24.

#### **GC analysis for conversion determination:**

Rtx-1701, 60 kPa He, 240 °C (injector), 270 °C (detector); temperature program: 50 °C (0 min), 10 °C/min, 250 °C (10 min);

*t*<sub>R</sub> = 20.21 min (9), 21.75 min (8).

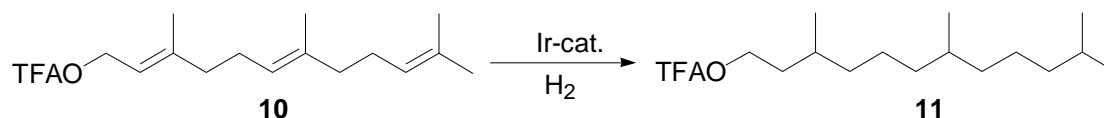
#### **Hydrolysis of 3,7,11-trimethyl-dodecanyl acetate (9)**



To a solution of 3,7,11-trimethyldodecanyl acetate (0.25 mmol) in methanol (4 mL) was added a NaOH solution (3 M, 3 mL) and the mixture was stirred at rt for 1.5 h. After evaporation of methanol diethylether (25 mL) was added. The separated organic phase was washed with water (2 x 5 mL), brine (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The obtained crude product was directly oxidized without further

purification.

### Hydrogenation of (2*E*, 6*E*)-farnesyl trifluoroacetate (**10**)



#### **3,7,11-trimethyldodecanyl trifluoroacetate (**11**)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.39 (m, 2H), 1.79 (m, 1H), 1.54 (m, 2H), 1.41-1.01 (m, 14H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.84 (d, *J* = 7.6 Hz, 3H);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 158.0 (q, *J* = 42 Hz), 115.0 (d, *J* = 287 Hz), 67.2, 39.7, 37.7 (d), 37.6 (d), 37.4 (d), 35.3 (d), 33.1, 30.0 (d), 28.4, 25.2 (d), 24.6, 23.1, 23.0, 20.0 (d), 19.8 (d);

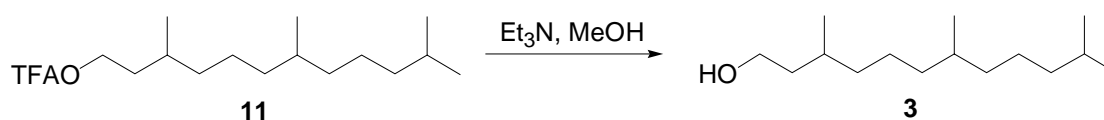
<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -76.3 (s);

MS: (EI, *m/z*) 324 (M<sup>+</sup>, 2.5%), 57 (100%);

EA: calcd (%) for C<sub>17</sub>H<sub>31</sub>F<sub>3</sub>O<sub>2</sub> (324.42): C 62.94, H 9.63; found: C 63.22, H 9.48.

For conversion determination, 3,7,11-trimethyldodecanyl trifluoroacetate (**11**) was hydrolyzed to the free alcohol **3** for GC analysis.

#### **Hydrolysis of 3,7,11-trimethyldodecanyl trifluoroacetate (**11**)**



A mixture of 3,7,11-trimethyldodecanyl trifluoroacetate (0.25 mmol) and triethylamine (0.35 mL, 2.5 mmol) in methanol (5 mL) was stirred at rt for 1 h. Concentration of the reaction mixture under high vacuum provided an oil, which was analyzed by GC for conversion determination and converted to aldehyde without further purification.

#### **GC analysis for conversion determination**

Rtx-1701, 60 kPa He, 240 °C (injector), 270 °C (detector); temperature program: 50 °C (0 min), 10 °C / min, 250 °C (10 min);

*t*<sub>R</sub> = 19.24 min (**3**), 20.59 min (**2**).



### Hydrogenation of (2*Z*, 6*E*)-farnesol (**12**)

#### **GC analysis for conversion determination**

Rtx-1701, 60 kPa He, 240 °C (injector), 270 °C (detector); temperature program: 50 °C (0 min), 10 °C / min, 250 °C (10 min);

$t_R$  = 19.13 min (**3**), 20.16 min (**12**).

### Hydrogenation of (2*E*, 6*Z*)-farnesol (**13**)

#### **GC analysis for conversion determination**

Rtx-1701, 60 kPa He, 240 °C (injector), 270 °C (detector); temperature program: 50 °C (0 min), 10 °C / min, 250 °C (10 min);

$t_R$  = 19.02 min (**3**), 20.08 min (**13**).

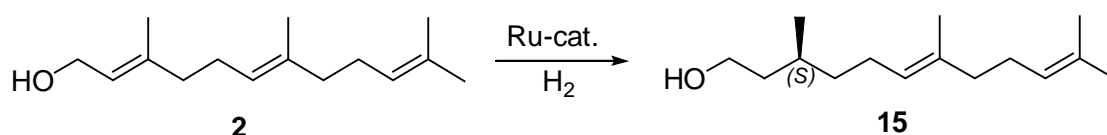
### Hydrogenation of (2*Z*, 6*Z*)-farnesol (**14**)

#### **GC analysis for conversion determination**

Rtx-1701, 60 kPa He, 240 °C (injector), 270 °C (detector); temperature program: 50 °C (0 min), 10 °C / min, 250 °C (10 min);

$t_R$  = 19.01 min (**3**), 19.74 min (**14**).

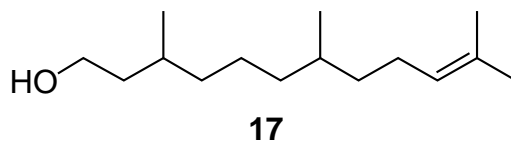
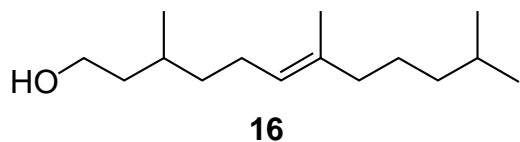
### Ruthenium-catalyzed hydrogenation of (2*E*, 6*E*)-farnesol (**2**)



Under a nitrogen atmosphere, (2*E*, 6*E*)-farnesol (**2**) (55.6 mg, 0.25 mmol) and [Ru{(R)-Tol-BINAP}(OAc)<sub>2</sub>] (4.5 mg, 0.005 mmol) were dissolved in degassed methanol (0.5 mL) in a glass vial (2 mL) charged with a magnetic stirrer. The vial was placed in an autoclave and sealed. The autoclave was pressurized to 50 bar with H<sub>2</sub> and the solution was stirred at 700 rpm for 24 hours. Then hydrogen was carefully released and the reaction mixture concentrated under reduced pressure. The residue was dispersed in hexane/ethyl acetate (1:1) and filtered through a short plug of silica gel eluting with hexane/ethyl acetate (1:1). Concentration of the filtrate gave an oil, which was analyzed by GC and subjected to Ir-catalyzed hydrogenation without further purification.

#### **GC analysis for conversion determination**

Rtx-1701; 60 kPa He; 240 °C (injector); 270 °C (detector); temperature program: 50 °C (0 min), 10 °C/min, 250 °C (10 min);  
 $t_R$  = 19.43 min (**16**, 5%), 19.67 min (**17**, 4%), 20.01 min (**15**, 91%), 20.48 min (**2**, 0%).



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<sup>1</sup> J. S. Yu, T. S. Kleckley, D. F. Wiemer, *Org. Lett.* **2005**, 7, 4803-4806.

<sup>2</sup> M. Kitamura, M. Tokunaga, R. Noyori, *J. Org. Chem.* **1992**, 57, 4053-4054.

<sup>3</sup> A. Knierzinger, W. Walther, B. Weber, R. K. Mueller, T. Netscher, *Helv. Chim. Acta* **1990**, 73, 1087-1107.