Supporting Information

Mild Ti^{III}- and Mn/Zr^{IV} Catalytic Reductive Coupling of Allylic Halides: Efficient Synthesis of Symmetric Terpenes

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General Details

Optical rotations were determined using CHCl₃ or CH₂Cl₂ as the solvents. IR spectra were recorded as NaCl plates (films). NMR studies were performed with a 400 (¹H 400 MHz/¹³C 100 MHz) spectrometer. Accurate mass determination was carried out with a mass spectrometer arranged in an EBE geometry and equipped with a FAB (LSIMS) source. The spectrometer was operated at 8 KV accelerating voltage and Cs⁺ were used as primary ions. The low resolution mass spectra were obtained in quadrupolar mass spectrometer equipped with a solids probe for the introduction of the sample. GC/MS analysis was done with a mass spectrometer coupled to a gas chromatograph and equipped with an EI source at 70 eV. The analyses were performed on a capillary column (30 m \times 0.25 mm \times 0.25 µm) inserted directly into the ion source. The temperature program was: 60°C (4 min), 10°C/min to 180°C and 4°C/min to 250°C, then isothermal for 15 min. The carrier gas was helium with a flow rate of 1 mL/min. HPLC with UV detection was used. Semi-preparative HPLC separations were carried out on a column (5 µm Silica, 10 × 250 mm) at a flow rate of 2.0 mL/min. All air- and watersensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. Tetrahydrofuran (THF) was freshly distilled immediately prior to use from sodium/benzophenone. The rest of the solvents used were purified according to standard literature techniques and stored under argon.

General procedure for bromination reaction of allylic alcohols (7, 10, 11, 21, 23, 34): CBr₄ (2.0 mmol) and Ph₃P (2.0 mmol) at 0°C under an Ar atmosphere were added to a stirred solution of allylic alcohol (1.0 mmol) in 7 mL of benzene. The solution was stirred at the same temperature for 2 h (TLC monitoring), and hexane (10 mL) was then added. The reaction mixture was filtered to remove any triphenylphosphine oxide. The filtrate was concentrated under reduced pressure and the resulting crude purified by column chromatography on silica gel to afford the corresponding bromo-derivative. *Geranyl bromide* (6): Commercially available. **Neryl bromide** (7): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 99% of $7.^{1}$

Methyl (2*E*,6*E*)-8-bromo-2,6-dimethyl-2,6-octadienoate (10): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 96% of 10.²

Methyl (2*E*,6*Z*)-8-bromo-2,6-dimethyl-2,6-octadienoate (11): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 90% of 11.²

Allyl bromide (15): Commercially available.

Crotyl bromide (17): Commercially available.

Cinnamyl bromide (19): Commercially available.

(2*E*,6*E*)-8-Bromo-3,7-dimethyl-2,6-octadienyl acetate (21): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 98% of $21.^3$

(-)-**Myrtenyl bromide** (23): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 97% of 23.⁴

(*R*)-Perillyl bromide (34): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 91% of 34. $[\alpha]_D$ + 33.5 (c 1.2, CH₂Cl₂); v (film) 3079, 2923, 2921, 2856, 2838, 1662, 1644, 1434, 1375, 1209, 1164, 890, 816, 649, 601 cm⁻¹; δ_H (400 MHz; CDCl₃) 1.45-1.58 (1H, m), 1.74 (3H, s), 1.85-2.04 (2H, m), 2.10-2.27 (4H, m), 3.96 (2H, s), 4.72 (1H, s), 4.74 (1H, s), 5.91 (1H, bs) ppm; δ_C (100 MHz; CDCl₃) δ 20.8, 26.9, 27.4, 30.9, 39.2, 40.6, 109.0, 127.7, 134.5, 149.4 ppm.

Preparation of 27 and 28

¹ Haibo, X.; Shao, Y.; Becker, J. M.; Naider, F.; Gibbs, R. A. J. Org. Chem. 2000, 65, 8552-8563.

² Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J.; Piedra, M.; Sánchez, E. M. *Org. Lett.* **2005**, *7*, 2301-2304.

³ Oehlschlager, A. C.; Wong, J. W.; Verigin, V. G.; Pierce, H. D. J. Org. Chem. **1983**, 48, 5009-5017.

⁴ a) Hoy, B.; Wei, H. K.; Lecomte, J.; Roger, R. *Bull. Soc. Chim. France* **1946**, 148-150; b) Harwood, L. M.; Julia, M. *Synthesis* **1980**, *6*, 456-457.

Methyl (2*E*,6*E*)-8-chloro-2,6-dimethyl-2,6-octadienoate (27): A mixture of the corresponding hydroxy-ester (245 mg, 1.24 mmol) and triphenylphosphine (455 mg, 1.73 mmol) in CCl₄ (1.24 mL, dried over 4Å sieves) under argon was refluxed for 1 h (TLC monitoring) before being cooled to room temperature. Hexane (20 mL) was added and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and the resulting crude purified by column chromatography on silica gel (hexane/*t*-BuOMe, 5:1) to afford 240 mg (90%) of the corresponding chloro-derivative **27**.⁵

Methyl (2*E*,6*E*)-8-iodo-2,6-dimethyl-2,6-octadienoate (28): The corresponding hydroxy-ester (300 mg, 1.51 mmol) was dissolved in a mixture of acetonitrile (7.5 mL) and toluene (30 mL) under argon. Triphenylphosphine (596 mg, 2.27 mmol), imidazole (154 mg, 2.27 mmol) and iodine (576 mg, 2.27 mmol) were added. The mixture was heated at 60°C for 10 min (TLC monitoring) before being cooled to room temperature. The mixture was diluted with ethyl acetate and washed with an aqueous saturated sodium thiosulfate solution. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was filtered through a short pad of silica gel (hexane/*t*-BuOMe, 2:1) to afford 400 mg (86%) of the corresponding iodo-derivative **28**.

Homocoupling reactions

a. Catalytic Protocol with Ti^{III} (1, 4, 5, 8, 9, 12, 13, 16, 18, 20, 22, 24, 31, 35): A mixture of Cp₂TiCl₂ (190 mg, 0.74 mmol) and Mn dust (1620 mg, 29.44 mmol) in thoroughly deoxygenated THF (50 mL) and under Ar atmosphere was stirred at rt until the red solution turned green. The corresponding allylic halide (3.68 mmol) in strictly deoxygenated THF (1 mL) was then added to the Cp₂TiCl solution. The reaction mixture was stirred for 15 min, quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products.

⁵ Kato, T.; Hirano, T.; Hoshikawa, M.; Uyehara, T. Bull. Chem. Soc. Jpn. 1996, 69, 221-228.

b. Catalytic Protocol with Zr^{IV} (1, 5, 8, 12, 20, 24, 31, 35): A mixture of Cp₂ZrCl₂ (462 mg, 1.58 mmol) and Mn dust (2323 mg, 42.20 mmol) in deoxygenated THF (9 mL) and under Ar atmosphere was stirred at rt. The corresponding allylic bromide (5.28 mmol) in strictly deoxygenated THF (1 mL) was then added, (TLC monitoring). The reaction mixture was quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products.

Compounds 8: After subjecting geranyl bromide (6) to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), the resulting crude was purified by column chromatography (hexane/t-BuOMe, 4:1) on silica gel to afford a yield of 89% ($\alpha\alpha':\alpha\gamma'$ at a 64:36 ratio) and 84% ($\alpha\alpha':\alpha\gamma'$ at a 81:19 ratio), respectively, of a mixture of coupling products. This mixture was subjected to flash column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent and two main fractions being obtained, the first containing the $\alpha\alpha$ coupling products as a mixture of (6E, 10E) and (6Z, 10E) isomers at a 6:1 ratio and the second containing the $\alpha\gamma$ ' coupling products as a mixture of (6E) and (6Z) isomers at a 14:1 ratio when Ti^{III} was used. In the presence of 0.3 equiv of Zr^{IV} the $\alpha\alpha$ ' coupling products are presented as a mixture of (6E, 10E) and (6Z, 10E) isomers at a 50:1 ratio, whilst isomerization $\frac{6E}{6Z}$ in the $\alpha\gamma$ ' coupling products was not observed. The fraction containing $\alpha \alpha$ coupling products was re-subjected to column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent to isolate the (6E,10E)-2,6,11,15tetramethylhexadeca-2,6,10,14-tetraene (8a) isomer in a pure state.⁶ The fraction containing $\alpha \gamma$ ' coupling products was re-subjected to column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent to isolate the 2,6,9,13-tetramethyl-9vinyltetradeca-2,6E,12-triene (8b): v (film) 2966, 2924, 2855, 1637, 1449, 1375, 1105, 1001, 910 cm⁻¹; $\delta_{\rm H}$ (300 MHz; CDCl₃) δ 0.88 (3H, s), 1.20-1.30 (2H, m), 1.51 (6H, s), 1.52 (3H, s), 1.60 (6H, s), 1.78-1.90 (2H, m), 1.92-2.08 (6H, m), 4.86 (1H, dd, J = 1.5, 17.5 Hz), 4.94 (1H, dd, J = 1.5, 10.8 Hz), 5.00-5.14 (3H, m), 5.70 (1H, dd, J = 10.8, 17.5 Hz) ppm; δ_C (75 MHz, CDCl₃) 16.3, 17.7, 17.8, 22.7, 23.0, 25.8, 26.7, 30.0, 39.0, 40.1, 40.4, 111.5, 121.0, 124.5, 125.2, 131.1, 131.3, 136.4, 147.3 ppm; EIMS (70 ev)

⁶ Hoshino, T.; Kumai, Y.; Kudo, I.; Nakano, S.; Ohashi, S. Org. Biomol. Chem. 2004, 2, 2650-2657.

m/z (relative intensity) 274 $[M]^+$ (1), 259 (1), 205 (3), 137 (6), 95 (12), 81 (30), 69 (100).

1,6-diphenyl-1,5-hexadiene (**20a**) and **1,4-diphenyl-1,5-hexadiene** (**20b**): Cinnamyl bromide (**19**) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}) and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 8:1) to afford 85% ($\alpha\alpha':\alpha\gamma':\gamma\gamma'$ at a 45:40:15 ratio) and 82% yield ($\alpha\alpha':\alpha\gamma'$ at a 48:38:14 ratio), respectively, of a mixture of coupling products. The corresponding mixtures were subjected to flash column chromatography on AgNO₃ (20%)-Si gel (hexane/*t*-BuOMe, 97:3), two main fractions being obtained, the first containing the $\alpha\alpha'$ coupling product (1,6-diphenyl-1,5-hexadiene)^{7,8} (**20a**) and the second containing the $\alpha\gamma'$ coupling product (1,4-diphenyl-1,5-hexadiene)⁸ (**20b**).

1,2-bis((**1***S*,**5***R*)-**6,6-dimethylbiciclo**[**3.1.1**]hept-2-en-2-il)ethane (**24**a): Myrtenyl bromide (**23**) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}) and the resulting crude was purified by column chromatography on silica gel (hexano/*t*-BuOMe, 20:1) to afford a 70% yield ($\alpha \alpha', \alpha \gamma' + \gamma \gamma'$ at a 61:39 ratio) and a 65% ($\alpha \alpha', \alpha \gamma' + \gamma \gamma'$ at a 70:30 ratio), respectively, of a mixture of coupling products. The corresponding mixtures were subjected to flash column chromatography on silica gel using hexane as eluent to isolate 1,2-bis((1*S*,5*R*)-6,6-dimethylbiciclo[3.1.1]hept-2-en-2-il)ethane (**24a**).⁹ When the secondary allylic chloride **25**¹⁰ was subjected to the catalytic procedure conditions (Ti^{III}) and the resulting crude was purified by column chromatography on silica gel (hexano/*t*-BuOMe, 40:1), a 90% yield ($\alpha \alpha', \alpha \gamma' + \gamma \gamma'$ at a 61:39 ratio) of a mixture of coupling products **24** was obtained. However when **25** was treated under catalytic procedure conditions (Zr^{IV}) the homocoupling products **24** were not formed and the starting material was recovered unaltered even after prolonged reaction times.

Compounds 35: (*R*)-Perillyl bromide (**34**) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 50:1) to afford a 77% yield ($\alpha \alpha', \alpha \gamma' +$

⁷ Clive, D. L. J.; Anderson, P. C.; Moss, N.; Singh, A. J. Org. Chem. 1982, 47, 1641-1647.

⁸ Orita, A.; Watanabe, A.; Tsuchiya, H.; Otera, J. *Tetrahedron* **1999**, *55*, 2889-2898.

⁹ Filliatre, C.; Villenave, J. J.; Prevot, J. Bull. Soc. Chim. France **1979**, 473-478.

 $^{^{10}}$ Compound **25** was obtained from selective allylic chlorination of β -pinene in a 77% yield in only 5 min.

 $\gamma\gamma'$ at a 54:46 ratio) and a 75% ($\alpha\alpha'$, $\alpha\gamma' + \gamma\gamma'$ at a 63:37 ratio), respectively, of a mixture of coupling products. The corresponding mixtures were subjected to flash column chromatography on AgNO₃ (20%)-Si gel (hexane/*t*-BuOMe, 99:1), and two fractions were obtained, the first containing the $\alpha\alpha'$ coupling product 7,7'-bis((4*R*)-1,8-*p*-menthadiene) (**35a**) and the second containing the $\alpha\gamma'$ coupling product (4*R*)-7-((2*R*,4*R*)-1(7),8-*p*-menthadien-2-il)-1,8-*p*-menthadiene (**35b**). Finally, *t*-BuOMe was added and $\gamma\gamma'$ coupling product (**35c**) could be isolated.

7,7'-bis((**4***R*)-**1,8**-*p*-menthadiene) (**35***a*): $[\alpha]_D$ + 75.9 (c 2.65, CH₂Cl₂); v (film) 3080, 2962, 2921, 2854, 1644, 1455, 1436, 1373, 886 cm⁻¹; δ_H (400 MHz; CDCl₃) 1.48 (2H, ddd, *J* = 5.6, 11.3, 17.1 Hz), 1.75 (6H, s), 1.80-1.85 (2H, m), 1.87-2.15 (10H, m), 2.06 (4H, bs), 4.73 (4H, bs), 5.43 (2H, bs) ppm; δ_C (100 MHz; CDCl₃) 20.9, 28.0, 29.0, 30.9, 36.1, 41.3, 108.5, 120.3, 137.6, 150.3 ppm; EIMS (70 eV) m/z (relative intensity) 270 (15), 227 (35), 187 (22), 159 (18), 145 (32), 134 (25), 119 (55), 105 (61), 93 (95), 91 (100), 79 (73), 67 (42), 44 (45).

(4*R*)-7-((2*R*,4*R*)-1(7),8-*p*-menthadien-2-il)-1,8-*p*-menthadiene (35b): $[\alpha]_D$ + 55 (c 0.85, CH₂Cl₂); v (film) 3069, 2964, 2929, 2854, 1644, 1438, 1374, 1259, 887, 806 cm⁻¹; δ_H (400 MHz; CDCl₃) 1.30 (1H, ddd, *J* = 4.8, 12.3, 17.1 Hz), 1.37-1.50 (2H, m), 1.71 (3H, s), 1.74 (3H, s), 1.75-2.27 (12H, m), 2.55 (1H, m), 4.62 (1H, bs), 4.64 (1H, bs), 4.66-4.76 (4H, m), 5.43 (1H, bs) ppm; δ_C (100 MHz; CDCl₃) 20.9, 21.1, 28.0, 28.7, 30.9, 31.1, 33.1, 35.9, 38.9, 40.9, 41.2, 41.3, 107.6, 108.5, 108.5, 122.4, 135.8, 150.2, 150.3, 152.0 ppm; EIMS (70 eV) m/z (relative intensity) 270 (10), 255 (9), 227 (40), 187 (20), 159 (12), 145 (18), 134 (22), 119 (40), 107 (48), 93 (100), 92 (95), 91 (78), 79 (82), 77 (95), 67 (98), 55 (81).

2,2'-bis((*2R*,*4R*)-1(7),*8-p*-menthadiene) (35c): $[\alpha]_D$ + 39.1 (c 0.9, CH₂Cl₂); v (film) 3068, 2929, 2856, 1645, 1441, 1374, 887 cm⁻¹; δ_H (400 MHz; CDCl₃) 1.28 (2H, ddd, *J* = 4.7, 12.7, 17.2 Hz), 1.44 (2H, dt, *J* = 1.7, 13.0 Hz), 1.72 (6H, s), 1.80-1.90 (2H, m), 1.95 (2H, bd, *J* = 13.5 Hz), 2.10-2.30 (6H, m), 2.69 (2H, bs), 4.55 (2H, bs), 4.63 (2H, bs), 4.70 (4H, s) ppm; δ_C (100 MHz; CDCl₃) 20.9, 31.1, 33.5, 34.0, 38.9, 42.4, 108.3, 108.7, 150.1, 150.5 ppm; EIMS (70 eV) m/z (relative intensity) [M⁺- 43] 227 (3), 159 (8), 145 (9), 134 (25), 105 (32), 93 (48), 91 (100), 79 (78), 67 (93), 55 (48).

7,7'-bis(**1**(*R*),**2**(*R*)-**dihydroxy-8-***p***-mentheno) (36**): 7,7'-bis((4*R*)-1,8-*p*-menthadiene) (**35a**) (285 mg, 1.06 mmol) was added to a solution of AD-mix β (2968 mg) and CH₃SO₂NH₂ (207 mg, 2.11 mmol) in *t*-BuOH:H₂O 1:1 (10 mL) at 0°C and stirred. After 7 h Na₂S₂O₃ (2385 mg) was added to the reaction mixture whilst keeping on stirring for 10 min and 20 min at rt. The *t*-BuOH was removed and extracted with EtOAc. The organic phase was washed with NaOH 6N (3 × 100 mL) and brine, then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, the crude thus obtained being purified by column chromatography on silica gel (*t*-BuOMe) to give **36** (230 mg, 65%). [α]_D + 9.96 (c 0.5, MeOH); v (film) 3399, 3327, 2941, 2916, 2854, 1642, 1441, 1261, 1161, 1062, 880, 749 cm⁻¹; $\delta_{\rm H}$ (400 MHz; DMSO) 1.10-1.65 (16H, m), 1.66 (6H, s), 1.80-1.90 (2H, m), 3.20 (2H, m),¹¹ 4.22 (2H, d, *J* = 6.7 Hz), 4.63 (2H, s), 4.64 (2H, s) ppm; $\delta_{\rm C}$ (100 MHz; DMSO) 20.7, 25.7, 32.3, 33.5, 35.3, 43.2, 71.6, 72.9, 108.4, 149.5 ppm; HRFABMS calcd for C₂₀H₃₄O₄Na [M+Na]⁺ 361.2355, found 361.2354.

β-onoceradiene (1): 11-bromo-8-drimene (29) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 4:1) to afford 87% yield and 73%, respectively, of the homocoupling product $1.^2$

(2*S*,4a*S*,8a*R*)-5,5'-ethylene-bis[2-(*tert*-butyldimethylsilyloxy)-1,1,4a,6-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene] (31): Compound 30 was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1:8) to afford 75% yield and 68%, respectively, of the homocoupling product 31.²

Allylic chlorination of 19-acetoxy-ent-kaur-16-ene (37): PhSeCl (21 mg, 0.10 mmol) was dissolved in DCM (2 mL). To this solution was added 19-acetoxy-ent-kaur-16-ene (70 mg, 0.21 mmol) at rt. To this mixture was added *N*-chlorosuccinimide (31 mg, 0.23 mmol) and stirred for 3 h (TLC monitoring). The solution was concentrated and suspended with diethyl ether. The organic layer was decanted from the solid, washed with H₂O and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced

¹¹ dd (J = 4.6, 11.0 Hz) when the ¹H NMR spectrum was made in DMSO + D₂O

pressure. Then, the resulting crude was dissolved in DCM (5 mL), silica gel was added and heated at reflux for 15 min. The solvent was removed and the crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 18:1) to afford 19-acetoxy-17chloro-*ent*-isokaurene (**38a**) together with 19-acetoxy-15-chloro-*ent*-kaur-16-ene (**38b**) (50 mg, 65%) in variable proportions (from 1:4 to 1:2).

19-acetoxy-15-chloro*ent***-kaur-16-ene** (**38a**): v (film) 2932, 2868, 1738, 1653, 1457, 1390, 1371, 1239, 1032 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 0.96 (3H, s), 1.04 (3H, s), 1.13-1.92 (18H, m), 2.05 (3H, s), 2.80 (1H, bs), 3.88 (1H, d, J = 11.0 Hz), 4.22 (1H, d, J = 11.0 Hz), 4.36 (1H, bs), 5.15 (1H, bs), 5.29 (1H, bs) ppm; $\delta_{\rm C}$ (100 MHz; CDCl₃) 18.2, 18.3, 18.5, 20.1, 21.2, 27.8, 33.0, 35.9, 36.4, 37.2, 38.6, 39.9, 40.6, 42.4, 48.3, 55.5, 56.6, 67.3, 73.9, 111.0, 157.3, 171.6 ppm.

Homocoupling reaction of 38a and 38b

17,17'-bis(19-acetoxy*-ent-***isokaurene) (4)**: A mixture of Cp₂TiCl₂ (37 mg, 0.14 mmol) and Mn dust (53 mg, 0.96 mmol) in strictly deoxygenated THF (1 mL) was stirred at room temperature until the red solution turned green. Then **38a** and **38b** (46 mg, 0.12 mmol) in strictly deoxygenated THF (1 mL) were added to the solution of Cp₂TiCl. The reaction mixture was stirred for 5 min, quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 20:1) to afford a 67% yield of the coupling product **4**. [α]_D - 42.0 (c 1.0, CH₂Cl₂); v (film) 2926, 2865, 1739, 1456, 1371, 1238, 1031 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 0.94 (6H, s), 1.04 (6H, s), 1.20-1.90 (36H, m), 2.04 (6H, s), 2.20 (4H, s), 2.39 (2H, bs), 3.87 (1H, d, *J* = 11.0 Hz), 4.22 (2H, d, *J* = 11.0 Hz), 5.07 (2H, bs) ppm; $\delta_{\rm C}$ (100 MHz; CDCl₃) 18.3, 18.5, 19.1, 19.7, 21.3, 25.8, 27.7, 28.1, 36.6, 37.3, 39.6, 40.2, 40.7, 43.8, 44.0, 49.1, 49.3, 56.8, 67.4, 134.3, 147.0, 171.6 ppm; HR FABMS calcd for C₄₄H₆₆O₄ [M + Na]⁺ 681.4859, found 681.4857.

Squalene (5): *Trans, trans*-farnesyl bromide (**39**) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford a 63% yield $(\alpha \alpha'(EE):\alpha \alpha'(EZ):\alpha \gamma')$ at a 66:22:12 ratio) and 62% ($\alpha \alpha':\alpha \gamma'$) at a 82:18 ratio), respectively, of a mixture of coupling products. The $\alpha \alpha'$ coupling products could be

separated from the $\alpha\gamma'$ coupling products as a mixture of (6*E*, 10*E*, 14*E*, 18*E*) and (6*E*, 10*Z*, 14*E*, 18*E*) by column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent at a 3:1 ratio, whilst the $\alpha\gamma'$ coupling products are presented as a mixture of isomers at a 10:1 ratio when Ti^{III} is used. Fractions enriched with the major isomer were re-subjected to column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent to isolate **5**.¹² In the presence of 0.3 equiv of Zr^{IV} isomerization *E/Z* was not observed.

Procedure for radical cyclization reaction of 10 and 11: A solution of tributyltin hydride (228 mg, 0.76 mmol) and AIBN (7 mg, 0.04 mmol) in dry, degassed benzene (14 mL) was added dropwise (10 mL/h) to a solution of the bromide (10 or 11) (100 mg, 0.38 mmol) in dry, degassed benzene (136 mL) heated to 80°C under an atmosphere of argon. After the addition time plus an additional hour (TLC monitoring), the cooled mixture was evaporated under reduced pressure and the residue dissolved in diethyl ether. An aqueous saturated KF solution (5 mL) was added and the mixture stirred for 2 h at rt. After filtration through celite, the biphasic filtrate was extracted with diethyl ether. The aqueous layer was extracted with diethyl ether after separation. The combined organic extracts were concentrated under reduced pressure and the crude was purified by column chromatography (petroleum ether/diethyl ether, 20:1) on silica gel to afford 50 mg (72%) of the cyclized compound methyl 1-p-menthen-9-oate (14).¹³ $\delta_{\rm H}$ $(400 \text{ MHz}; \text{CDCl}_3)$ 1.12 (3H, d, J = 7.0 Hz), 1.56 (3H, s), 1.50-2.40 (8H, m), 3.65 (3H, s), 5.30-5.40 (1H, m) ppm; (only distintive signals) δ 1.14 (3H, d, J = 7.0 Hz), 3.66 (3H, s) ppm; EIMS (70 eV) m/z (relative intensity) 182 [M⁺] (5), 150 (15), 95 (47), 94 (81), 88 (100), 79 (75), 67 (40); HR EIMS calcd for $C_{11}H_{18}O_2$ [M]⁺ 182.1307, found 182.1311.

¹² He, H.; Cai, Y.; Sun, M.; Corke, H. J. Agric. Food Chem. 2002, 50, 368-372.

¹³ Guth, H. Helv. Chim. Acta **1996**, 79, 1559-1571.































