ELECTRONIC SUPPORTING INFORMATION

Efficient Synthesis of Macrocyclic Ketones Via Palladium-Catalyzed Activation of Carboxylic Acids

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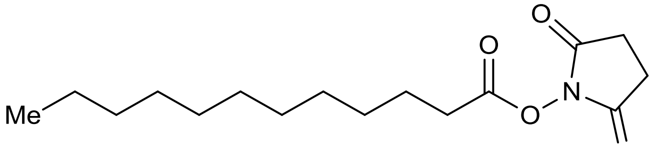
General Remarks

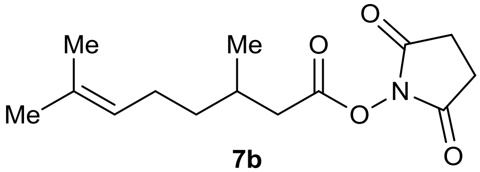
Catalytic reactions were carried out under a N_2 atmosphere using pre-dried glassware. Reagents were obtained from commercial sources, and were used without further purification. 4-Fluorophenyl boronic acid **9d** was prepared according to literature procedure.[i] THF was freshly distilled from sodium/benzophenone under N_2. Yields refer to isolated compounds following chromatography on silica gel, estimated to be >95 % pure as determined by ^{1}H-NMR. Flash chromatography: Macherey-Nagel silica gel 60 (70-230 mesh). NMR: Spectra were recorded on a ECX-400 instrument in the solvent indicated; chemical shifts (δ) are given in ppm.

Synthesis and Characterization data for compounds 7a-7b, 9a-9f.



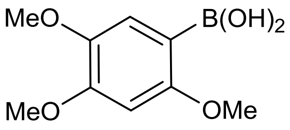
7a

2,5-Dioxotetrahydro-1*H*-1-pyrrolyl laurate (7a)[ii]: To a 250 mL flask was added dodecanoic acid **6a** (5.00 g, 25.0 mmol) in acetonitrile (75 mL). To this was added *N*-hydroxysuccinimide (3.01 g, 26.0 mmol) and dicyclohexylcarbodiimide (DCC) (7.80 g, 37.0 mmol). The resultant mixture was stirred for 4 h at 25 °C. At the end of the reaction the urea formed was filtered. Solvent was removed *in vacuo* to obtain the crude ester in good yield as colourless oil which solidified on standing. Purification of the crude was done by column chromatography using 10% EtOAc/Hexane to obtain (4.72 g, 63%) the title compound as colourless solid. δ_H (400 MHz, $CDCl_3$) 0.85 (t, 3H, *J* = 1.6 Hz), 1.26-1.31 (m, 16H), 1.77 (dt, 2H, *J* = 1.2 and *J* = 0.9 Hz), 2.63 (t, 2H, *J* = 1.6 Hz), 2.84-2.86 (m, 4H); δ_C (100 MHz, $CDCl_3$) 14.0, 22.6, 24.2, 25.5, 28.7, 29.0, 29.3, 29.5, 30.4, 31.8, 168.3, 169.1; LRMS (EI) *m/z* (rel.%) 297 (M^+, 100) ; the data was consistent with that published.



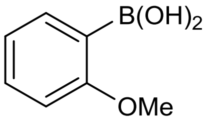
7b

2,5-Dioxotetrahydro-1*H*-1-pyrrolyl 3,7-dimethyl-6-octenoate (7b): To a 250 mL flask was added citronellic acid **6b** (5.00 g, 29.0 mmol) in acetonitrile (75 mL). To this was added *N*-hydroxysuccinimide (3.55 g, 30.0 mmol) and dicyclohexylcarbodiimide (DCC) (8.96 g, 43.0 mmol). The resultant mixture was stirred for 4 h at 25 °C. At the end of the reaction the urea formed was filtered. Solvent was removed *in vacuo* to obtain the crude ester in good yield as colourless oil which solidifies on standing. Purification of the crude was done by column chromatography using 10% EtOAc/Hexane to obtain (6.87 g, 87%) the title compound as a colourless solid. δ_H (400 MHz, $CDCl_3$) 1.07 (d, 3H, *J* = 1.5 Hz), 1.17-1.42 (m, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 2.05-2.08 (m, 2H), 2.13-2.16 (m, 1H), 2.44 (dd, 1H, *J* = 8.7, 1.7 Hz), 2.60 (dd, 1H, *J* = 8.7, 1.4 Hz), 2.84-2.88 (m, 4H), 5.09-5.11 (m, 1H); δ_C (100 MHz, $CDCl_3$) 17.6, 19.3, 25.2, 25.5, 25.6, 36.4, 38.1, 123.8, 131.8, 168.3, 169.1; LRMS (CI) *m/z* (rel.%) 285 (M^++NH_4^+, 100), 170 (70), 153 (60), 109 (10); HRMS (ESI) *m/z* exact mass calculated for $C_{14}H_{21}N_1O_4$ 267.1471, found: 267.1468.



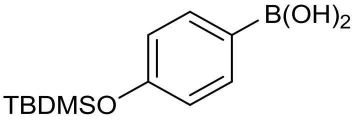
9b

Synthesis of 2,4,5-trimethoxybenzeneboronic acid (9b)[iii]**:** Bromo-2,4,5-trimethoxybenzene**[iii]** : Bromine (1.59 mL, 30.9 mmol) in dichloromethane (50 mL) was added dropwise to a solution of 1,2,4-trimethoxybenzene (4.94 g, 29.4 mmol) in dichloromethane (200 mL) at 0 °C. The resulting mixture was washed with aqueous sodium bisulfite (20 mL), aqueous sodium bicarbonate (50 mL) and water (100 mL). Separation of the organic phase and after removal of the solvent gave (7.00 g, 97%) the title compound as a white solid. δ_H (400 MHz, $CDCl_3$) 3.80 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.53 (s, 1H), 7.03 (s, 1H),; δ_C (100 MHz, $CDCl_3$) 56.1, 56.5, 57.1, 98.7, 100.9, 116.3, 143.7, 149.0, 150.2; LRMS (EI) *m/z* (rel.%) 248 (M^+, 100), 231 (60), 203 (40), 188 (20); the data was consistent with that published. 2,4,5-trimethoxybenzeneboronic acid (**9a**) [iv] : 2,4,5-Trimethoxybromobenzene (5.00 g, 20.0 mmol) was dissolved in THF (40 mL) and cooled to -78 °C. *n*-BuLi (11.0 mL, 21.0 mmol, 2.0 M in hexane) was added via syringe over a period of 10 minutes. The resultant solution is stirred for 30 minutes and trimethyl borate (2.29 g, 22.0 mmol) was added keeping the temperature at -78 °C. The mixture was stirred at -78 °C for 1h and then quenched saturated aqueous NH_4Cl (30 mL). Water (20 mL) was added and the mixture extracted with dichloromethane (2 X 50 mL). On evaporation of the solvent *in vacuo* title compound (2.48 g, 55%) was obtained as a white solid. δ_H (400 MHz, $CDCl_3$) 3.88 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.36 (bs, 2H), 6.51 (s, 1H), 7.32 (s, 1H); δ_C (100 MHz, $CDCl_3$) 55.9, 56.2, 56.3, 95.9, 118.2, 143.3, 152.4, 159.9; δ_B (87 MHz, $CDCl_3$) 28.02 (bs, 1B); LRMS (CI) *m/z* (rel.%): 213 (M^++H^+, 100), 169 (42); HRMS (CI) *m/z* exact mass calculated for $C_9H_{14}O_5B+H^+$ 213.0929, found: 213.0928. the data was consistent with that published.



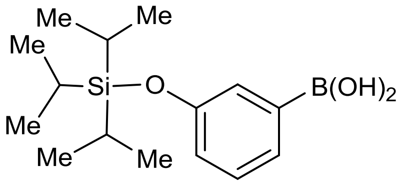
9a

2-Methoxyphenylboronic acid (9a)^{v}: To a solution of 2-bromoanisole (5.0 g, 26.0 mmol) in THF (30 mL) at -78 °C was added dropwise 13.7 mL (29.0 mmol, 1.1 equiv.) of 1.6 M *n*-BuLi solution in hexane. The solution was stirred for 30 minutes and then trimethyl borate (3.0 g, 29.0 mmol, 1.1 equiv.) was added at -78 °C. The reaction mixture was stirred for 3 h and then quenched with NH_4Cl (20 mL). The phases were separated and extracted with CH_2Cl_2 (30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The residue obtained was purified by column chromatography with 40% EtOAc/ Hexane to provide (1.70 g, 42%) the title compound as a white solid. δ_H (400 MHz, $CDCl_3$) 3.94 (s, 3H), 6.86 (s, 2H, OH), 6.92 (d, 1H, *J* = 7.7 Hz), 7.04 (t, 1H, *J* = 7.4 Hz), 7.44 (m, 1H), 7.89 (d, 1H, *J* = 6.9 Hz); δ_C (100 MHz, $CDCl_3$) 55.3, 109.8, 121.1, 132.7, 136.8, 164.4; δ_B (87 MHz, $CDCl_3$) 28.2; LRMS (EI) *m/z* (rel.%): 152 (M^+, 100); Anal. Calcd. for $C_7H_9O_3B$, C 55.33, H 5.97; Found, C 55.22, H 5.92; the data was consistent with that published.



9c

Synthesis of 4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyphenylboronic acid (9c)[vi]**:** (4-bromophenoxy)(*tert*-butyl)dimethylsilane[vi]: To a stirred ice-cold solution of 4-bromophenol (5.0 g, 28.0 mmol) and triethylamine (3.39 g, 33.0 mmol) in 30 mL of CH_2Cl_2, under nitrogen, was added slowly, via syringe, *tert*-butyldimethylsilyl chloride (4.76 g, 31.0 mmol). The reaction mixture was gradually warmed to room temperature, stirred for 18 h, poured into 50 mL of ice-water and extracted with 100 mL of CH_2Cl_2. The organic layer was washed in turn with 100 mL of 1 N HCl, 1 N NaOH, and saturated aqueous bicarbonate solution and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation to yield (7.10 g, 81%) the title compound as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.27 (s, 6H), 0.98 (s, 9H), 7.01 (d, 2H, *J* = 7.9 Hz), 7.81 (d, 2H, *J* = 7.8 Hz); δ_C (100 MHz, $CDCl_3$) -4.5, 18.1, 25.1, 124.7, 131.6, 142.9, 156.9; δ_{Si} (54 MHz, $CDCl_3$) 18.2; LRMS (EI) *m/z* (rel.%): 288 (M^+, 100%); the data was consistent with that published. 4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyphenylboronic acid (**9c**)[vii] : To a solution of (4-bromophenoxy)(*tert*-butyl)dimethylsilane (4.00 g, 14.0 mmol) in THF (25 mL) at -78 °C was added dropwise 7.2 mL (15.3 mmol, 1.1 equiv.) of 1.6 M *n*-BuLi solution in hexane. The solution was stirred for 30 minutes and then trimethyl borate (1.59 g, 15.3 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for 3 h and then quenched with NH_4Cl (10 mL). The phases were separated and extracted with CH_2Cl_2 (20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The residue obtained was purified by column chromatography with 40% EtOAc/ Hexane to provide (3.20 g, 91%) the title compound as white solid. δ_H (400 MHz, $CDCl_3$) 0.24 (s, 6H), 1.04 (s, 9H), 6.95 (d, 2H, *J* = 7.1 Hz), 8.11 (d, 2H, *J* = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) -4.4, 18.2, 25.6, 119.7, 137.4, 141.8, 159.7; δ_{Si} (54 MHz, $CDCl_3$) 21.9; δ_B (87 MHz, $CDCl_3$) 28.0 (bs, 1B); LRMS (EI) *m/z* (rel.%): 252 (M^+, 100%); HRMS (ESI) *m/z* exact mass calculated for $C_{12}H_{21}O_3BSi$ 252.1353, found: 252.1349; the data was consistent with that published.

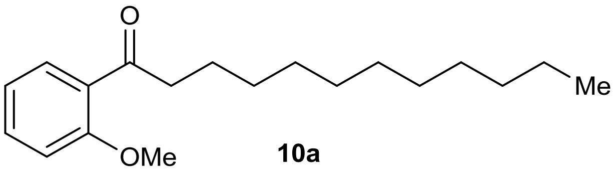


9e

Synthesis of 3-[(1,1,1-triisopropylsilyl)oxy]phenylboronic acid (9e): (3-Bromophenoxy)(triisopropyl)silane: To a stirred ice-cold solution of 3-bromophenol (10.00 g, 57.0 mmol) and triethylamine (6.06 g, 60.0 mmol) in 80 mL of dichloromethane, under nitrogen, was added slowly, via syringe, tri-isopropylsilyl chloride (11.10 g, 58.0 mmol). The reaction mixture was gradually warmed to room temperature, stirred for 18 h, poured into 50 mL of ice-water and extracted with 100 mL of CH_2Cl_2. The organic layer was washed in turn with 100 mL of 1 N HCl, 1 N NaOH, and saturated aqueous bicarbonate solution and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation. Quantitative yield (19.06 g, 99%) of the title compound was obtained as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.97-1.03 (d, 18H), 1.15 (septet, 3H), 6.75-6.77 (m, 1H), 7.01-7.04 (m, 3H); δ_C (100 MHz, $CDCl_3$) 12.5, 17.8, 118.5, 122.4, 123.1, 124.1, 130.3, 156.9; LRMS (EI) *m/z* (rel.%): 329 (M^+, 10%), 287 (100), 259 (50), 243 (15), 231 (75), 215 (50), 201 (25), 155 (10); HRMS (ESI) *m/z* exact mass calculated for $C_{15}H_{25}OBrSi$ 328.0858, found: 328.0854. 3-[(1,1,1-triisopropylsilyl)oxy]phenylboronic acid (**9e**) To a solution of (3-bromophenoxy)(triisopropyl)silane (5.00 g, 15.0 mmol) in THF (40 mL) at -

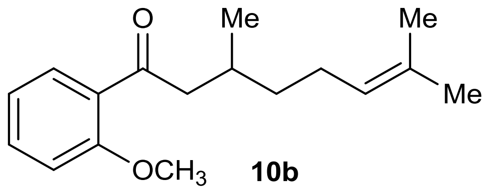
78 ^{o}C was added dropwise 9.7 mL (16.0 mmol, 1.1 equiv.) of 1.6 M *n*-BuLi solution in hexane. The solution was stirred for 30 minutes and then trimethyl borate (4.68 g, 45.0 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 3 h and then quenched with NH_4Cl (20 mL). The phases were separated and extracted with CH_2Cl_2 (2 X 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The residue obtained was purified by column chromatography with 40% EtOAc/ Hexane to provide (3.30 g, 74%) the title compound as a white solid. δ_H (400 MHz, $CDCl_3$) 0.97-1.03 (d, 18H), 1.15 (septet, 3H), 6.98-7.00 (m, 1H), 7.39 (t, 1H, J = 8.5 Hz), 7.72 (d, 1H, J = 8.4 Hz), 7.89 (dd, 1H, J = 8.2 and J = 1.6 Hz); δ_C (100 MHz, $CDCl_3$) 12.7, 17.9, 124.2, 125.4, 126.5, 128.2, 129.1, 155.7; δ_B (87 MHz, $CDCl_3$) 28.1; δ_{Si} (54 MHz, $CDCl_3$) 16.0; LRMS (CI) *m/z* (rel.%): 312 ($M^+ + NH_4^+$, 60), 295 (M^+, 100); HRMS (CI) *m/z* exact mass calculated for $C_{15}H_{28}O_3BSi{+}H^+$ 295.1902, found: 295.1895.

Synthesis and characterization of 10a-f: Representative procedure for palladium-catalyzed cross-coupling of N-alkoxysuccinimides with arylboronic acids:



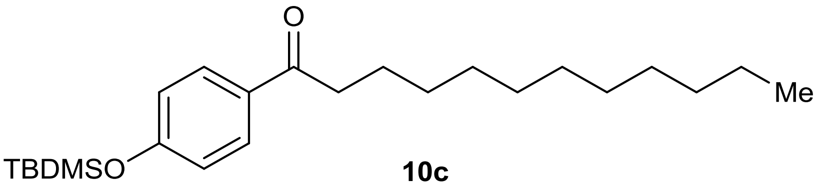
10a

A 10 mL flask was charged with [Pd(OAc)$_2$] (4.00 mg, 0.018 mmol, 5.0 mol%), tricyclohexylphosphine (12.60 mg, 0.045 mmol, 12 mol%), 2,5-dioxotetrahydro-1*H*-1-pyrrolyl laurate **7a** (0.10 g, 0.37 mmol), Na_2CO_3 (0.079 g, 0.74 mmol). The reaction vessel was purged with argon and degassed THF (2 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 2-methoxyphenylboronic acid **9a** (0.065 g, 0.41 mmol) in THF (3 mL) and water (10.0 equiv.) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: Et_2O (70:30) to give the title compound 1-(2-methoxyphenyl)-1-dodecanone **10a** (0.061 g, 61%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.90 (t, 3H, *J* = 1.9 Hz), 1.26-1.43 (m, 16H), 1.63-1.65 (m, 2H), 2.97-2.99 (m, 2H), 3.93 (s, 3H), 6.98 (dt, 2H, *J* = 7.8 Hz), 7.45 (t, 1H, *J* = 7.8 Hz), 7.65 (dd, 1H, *J* = 8.0 and *J* = 2.0 Hz) ; δ_C (100 MHz, $CDCl_3$) 14.0, 22.6, 24.4, 28.7, 29.0, 29.3, 29.5, 31.8, 43.7, 55.4, 111.4, 120.5, 128.4, 130.0, 133.0, 158.2, 198.2; LRMS (CI) *m/z* (rel.%) 291 (M^{+}+H^{+}, 100); HRMS (CI) *m/z* exact mass calculated for $C_{19}H_{31}O_2$+H^{+} 291.2324 found 291.2319.



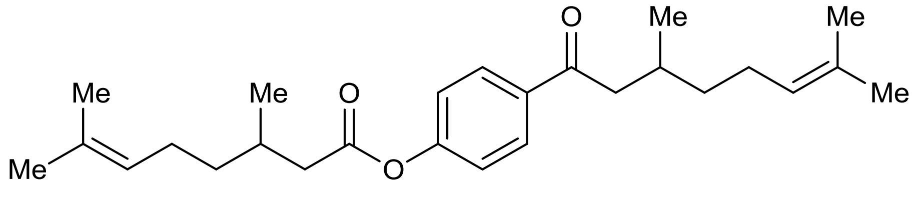
10b

1-(2-methoxyphenyl)-3,7-dimethyl-6-octen-1-one (10b)[viii]**:** A 10 mL flask was charged with [Pd(OAc)$_2$] (4.00 mg, 0.018 mmol, 5.0 mol%), tricyclohexylphosphine (12.60 mg, 0.045 mmol, 12 mol%), 2,5-dioxotetrahydro-1*H*-1-pyrrolyl 3,7-dimethyl-6-octenoate **7b** (0.10 g, 0.37 mmol), Na_2CO_3 (0.079 g, 0.74 mmol). The reaction vessel was purged with argon and degassed THF (2 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 2-methoxyphenylboronic acid **9a** (0.072 g, 0.41 mmol) in THF (3 mL) and water (10.0 equiv.) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: Et_2O (75:25) to give the title compound **10b** was obtained in good yield (0.088 g, 81%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.86 (d, 3H, *J* = 3.1 Hz), 1.17-1.42 (m, 2H), 1.51 (s, 3H), 1.59 (s, 3H), 1.97-1.99 (m, 2H), 2.09-2.11 (m, 1H), 2.68 (dd, 1H, *J* = 8.6, 1.4 Hz), 2.90 (dd, 1H, *J* = 8.8, 1.6 Hz), 3.81 (s, 3H), 5.00-5.02 (m, 1H), 6.91 (dd, 2H, *J* = 8.4 and *J* = 1.2 Hz), 7.38 (t, 1H, *J* = 8.5 Hz), 7.54 (d, 1H, *J* = 7.4 Hz); δ_C (100 MHz, $CDCl_3$) 16.7, 19.0, 24.8, 25.0, 28.7, 36.6, 50.7, 55.1, 111.8, 121.2, 125.2, 130.7, 132.0, 133.7, 159.1, 205.0; LRMS (EI) *m/z* (rel.%) 260 (M^+, 100), 232 (10), 215 (20), 105 (100); HRMS (EI) *m/z* exact mass calculated for $C_{17}H_{24}O_2$ 260.1776 found 260.1775; the data was consistent with that published.



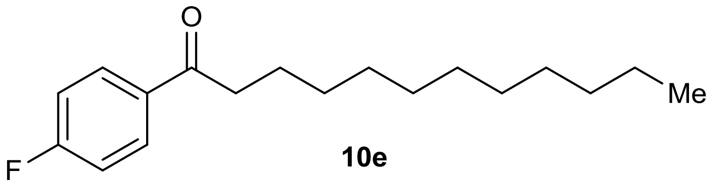
10c

1-(4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyphenyl)-1-dodecanone (10c): A 10 mL flask was charged with [Pd(OAc)$_2$] (4.00 mg, 0.018 mmol, 5.0 mol%), tricyclohexylphosphine (12.60 mg, 0.045 mmol, 12 mol%), 2,5-dioxotetrahydro-1*H*-1-pyrrolyl laurate **7a** (0.10 g, 0.37 mmol), Na_2CO_3 (0.079 g, 0.74 mmol). The reaction vessel was purged with argon and degassed THF (2 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 4-silyloxyphenylboronic acid **9c** (0.095 g, 0.41 mmol) in THF (3 mL) and water (10.0 equiv.) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: Et_2O (75:25) to give the title compound in good yield (0.077 g, 59%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.25 (s, 6H), 0.83 (t, 3H, *J* = 1.7 Hz), 0.98 (s, 9H), 1.26-1.41 (m, 16H), 1.69 (dt, 2H, *J* = 1.9 Hz), 2.91-2.94 (m, 2H), 7.37 (d, 2H, *J* = 7.8 Hz), 7.86 (d, 2H, *J* = 7.8 Hz) ; δ_C (100 MHz, $CDCl_3$) -4.3, 14.1, 18.2, 22.6, 25.4, 28.7, 29.0, 29.3, 29.5, 31.8, 38.5, 119.8, 130.5, 130.7, 160.4, 199.7; LRMS (CI) *m/z* (rel.%) 391 (M^++H^+, 100); HRMS (CI) *m/z* exact mass calculated for $C_{24}H_{43}O_2Si+H^+$ 391.3029 found 391.3027.



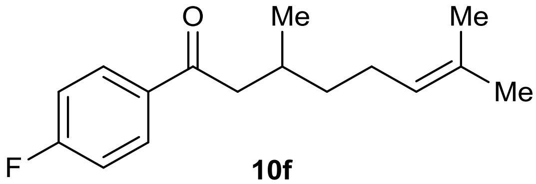
10d

4-(3,7-Dimethyl-6-octenoyl)phenyl 3,7-dimethyl-6-octenoate (10d): A 10 mL flask was charged with [Pd(OAc)$_2$] (4.00 mg g, 0.018 mmol, 5.0 mol%), tricyclohexylphosphine (12.60 mg, 0.045 mmol, 12 mol%), 2,5-dioxotetrahydro-1*H*-1-pyrrolyl 3,7-dimethyl-6-octenoate **7b** (0.10 g, 0.37 mmol), Na_2CO_3 (0.079 g, 0.74 mmol). The reaction vessel was purged with argon and degassed THF (2 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 4-silyloxyphenylboronic acid **9c** (0.10 g, 0.41 mmol) in THF (3 mL) and water (10 equiv.) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: Et_2O (75:25) to give the title compound (0.059 g, 42%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.95 (d, 3H, J = 2.1 Hz), 1.05 (d, 3H, J = 2.2 Hz), 1.20-1.40 (m, 4H), 1.58 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 1.67 (s, 3H), 1.90-2.24 (m, 6H), 2.38 (dd, 1H, J = 8.3, 1.7 Hz), 2.53 (dd, 1H, J = 8.5, 1.7 Hz), 2.61 (dd, 1H, J = 8.9, 1.4 Hz), 2.89 (dd, 1H, J = 8.7, 1.5 Hz), 5.04-5.09 (m, 2H), 7.24 (d, 2H, J = 7.9 Hz), 7.94 (d, 2H, J = 8.1 Hz); δ_C (100 MHz, $CDCl_3$) 17.4, 19.6, 19.8, 25.3, 25.5, 25.7, 29.1, 30.1, 36.8, 37.1, 42.2, 46.4, 121.7, 124.3, 124.5, 129.7, 132.5, 133.1, 137.1, 154.3, 168.1, 199.8; LRMS (EI) *m/z* (rel.%) 399 (M^+, 100); HRMS (EI) *m/z* exact mass calculated for $C_{26}H_{38}O_3$ 398.2821 found 398.2818.



10e

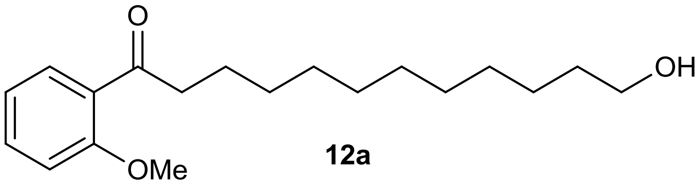
1-(4-Fluorophenyl)-1-dodecanone (10e): A 10 mL flask was charged with [Pd(OAc)$_2$] (4.00 mg, 0.018 mmol, 5.0 mol%), tricyclohexylphosphine (12.60 mg, 0.045 mmol, 12 mol%), 2,5-dioxotetrahydro-1*H*-1-pyrrolyl laurate **7a** (0.10 g, 0.37 mmol), Na_2CO_3 (0.079 g, 0.74 mmol). The reaction vessel was purged with argon and degassed THF (2 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^oC, a solution of 4-fluorophenylboronic acid **9d** (0.054 g, 0.41 mmol) in THF (3 mL) and water (10.0 equiv.) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: Et_2O (75:25) to give the title compound good yield (0.063 g, 69%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.83 (t, 3H, *J* = 1.5 Hz), 1.26-1.31 (m, 16H), 1.65-1.67 (m, 2H), 2.85-2.87 (m, 2H), 7.08 (d, 2H, *J* = 8.4 Hz), 7.92 (d, 2H, *J* = 8.4 Hz) ; δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 24.4, 28.7, 29.0, 29.3, 29.5, 31.8, 38.5, 115.4, 115.7, 130.5, 130.7, 133.9, 165.1, 201.4; LRMS (CI) *m/z* (rel.%) 296 (M^+ + NH_4^+, 10), 279 (M^+, 100); HRMS (CI) *m/z* exact mass calculated for $C_{18}H_{27}OF+H^+$ 279.2146 found 279.2159.



10f

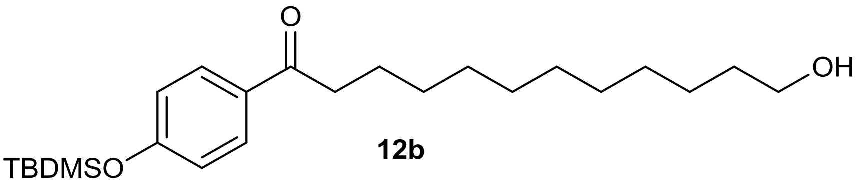
1-(4-fluorophenyl)-3,7-dimethyl-6-octen-1-one (10f): A 10 mL flask was charged with [Pd(OAc)$_2$] (4.00 mg, 0.018 mmol, 5.0 mol%), tricyclohexylphosphine (12.60 mg, 0.045 mmol, 12 mol%), 2,5-dioxotetrahydro-1*H*-1-pyrrolyl 3,7-dimethyl-6-octenoate **7b** (0.10 g, 0.37 mmol), Na_2CO_3 (0.079 g, 0.74 mmol). The reaction vessel was purged with argon and degassed THF (2 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 4-fluorophenylboronic acid **9d** (0.057 g, 0.41 mmol) in THF (3 mL) and water (10.0 equiv.) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: Et_2O (75:25) to give the title compound (0.072 g, 71%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.89 (d, 3H, J = 1.4 Hz), 1.17-1.37 (m, 2H), 1.52 (s, 3H), 1.60 (s, 3H), 1.92-1.94 (m, 2H), 2.03-2.05 (m, 1H), 2.68 (dd, 1H, J = 8.4, 1.3 Hz), 2.84 (dd, 1H, J = 8.3, 1.4 Hz), 5.02-5.03 (m, 1H), 7.05 (t, 2H, J = 7.9 Hz), 7.87 (dd, 2H, J = 7.6 and J = 1.2 Hz); δ_C (100 MHz, $CDCl_3$) 16.7, 19.9, 25.5, 25.7, 29.5, 37.1, 45.8, 115.4, 115.7, 124.3, 130.7, 132.8, 134.7, 160.1, 165.7, 205.0; LRMS (EI) *m/z* (rel.%) 249 (M^+, 100), 191 (10), 123 (20); HRMS (EI) *m/z* exact mass calculated for $C_{16}H_{21}OF$ 248.1576 found 248.1572.

Synthesis and Characterization data for compounds 12a-c and Macrocyclic ketones 13 and 14.



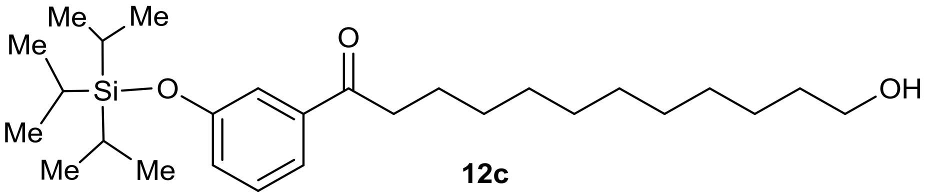
12a

12-hydroxy-1-(2-methoxyphenyl)-1-dodecanone (12a): A 10 mL flask was charged with [Pd(OAc)$_2$] (36.00 mg, 0.1 mmol, 5.0 mol%), tricyclohexylphosphine (66.00 mg, 0.24 mmol, 12 mol%), 12-hydroxydodecanoic acid **11** (0.43 g, 2.0 mmol), Na_2CO_3 (0.42 g, 4.0 mmol), and di(*N*-succinimidyl) carbonate (0.66 g, 2.6 mmol). The reaction vessel was purged with argon and degassed THF (10 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 2-methoxyphenylboronic acid **9a** (0.36 g, 2.4 mmol) in THF (6 mL) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 equiv.) and extracted 3 times with 20 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: EtOAc (60:40) to give the title compound (0.33 g, 54%) as a white solid. δ_H (400 MHz, $CDCl_3$) 1.25-1.40 (m, 14H), 1.54-1.57 (m, 2H), 1.63-1.65 (m, 2H), 2.92 (t, 2H, *J* = 1.2 Hz), 3.61-3.65 (m, 2H), 3.91 (s, 3H), 6.94 (dt, 2H, *J* = 7.8 and *J* = 1.9 Hz), 7.38 (t, 1H, *J* = 7.8 Hz), 7.62 (dd, 1H, *J* = 7.8 and *J* = 1.9 Hz); δ_C (100 MHz, $CDCl_3$) 23.3, 24.6, 28.2, 28.3, 28.4, 28.5, 37.8, 55.7, 62.5, 115.4, 123.4, 126.5, 128.4, 132.7, 161.7, 199.6; LRMS (CI) *m/z* (rel.%): 307 (M^++H^+ , 100%); HRMS (CI) *m/z* exact mass calculated for $C_{19}H_{31}O_3$+H^+ 307.2273 found 307.2269.



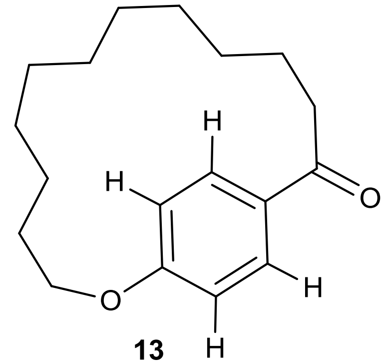
12b

1-(4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyphenyl)-12-hydroxy-1-dodecanone (12b): A 10 mL flask was charged with [Pd(OAc)$_2$] (15.00 mg, 0.05 mmol, 5.0 mol%), tricyclohexylphosphine (33.00 mg, 0.12 mmol, 12 mol%), 12-hydroxydodecanoic acid **11** (0.21 g, 1.0 mmol), Na_2CO_3 (0.21 g, 2.0 mmol), and di(*N*-succinimidyl) carbonate (0.33 g, 1.3 mmol). The reaction vessel was purged with argon and degassed THF (5 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 4-silyloxyphenylboronic acid **9c** (0.30 g, 1.2 mmol) in THF (3 mL) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: EtOAc (60:40) to give the title compound in good yield (0.27 g, 79%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.16 (s, 6H), 0.91 (s, 9H), 1.25-1.40 (m, 14H), 1.49-1.51 (m, 2H), 1.63-1.65 (m, 2H), 2.84 (t, 2H, *J* = 1.5 Hz), 3.56-3.58 (m, 2H), 6.80 (d, 2H, *J* = 7.8 Hz), 7.82 (d, 2H, *J* = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) -4.4, 18.4, 24.5, 25.5, 25.6, 29.3, 29.4, 29.5, 32.7, 38.0, 63.0, 119.8, 130.1, 130.6, 160.0, 199.4; LRMS (CI) *m/z* (rel.%): 407 (M^{+}+H^{+}, 100%), 331 (10); HRMS (CI) *m/z* exact mass calculated for $C_{24}H_{43}O_3Si$+H^{+} 407.3016 found 407.2976.



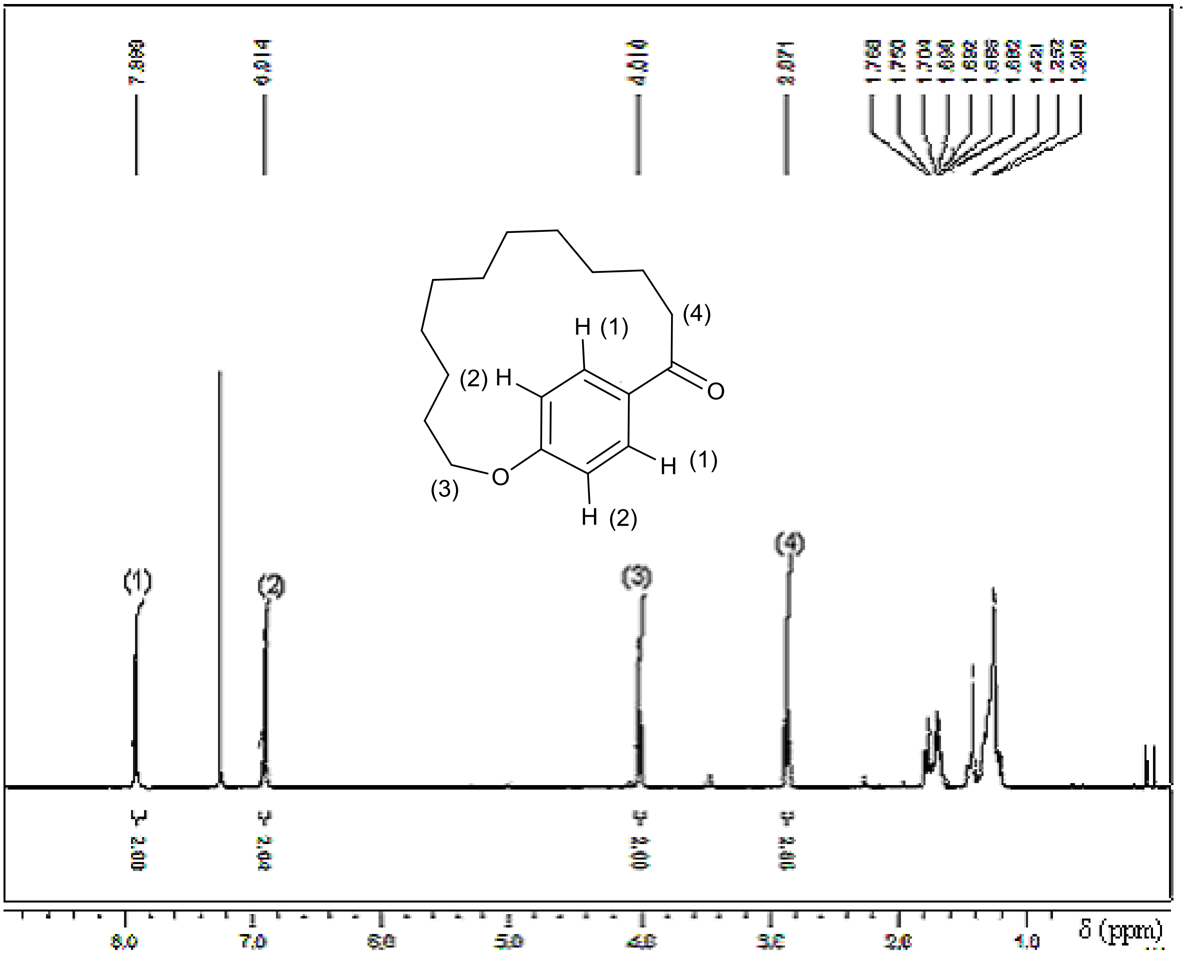
12c

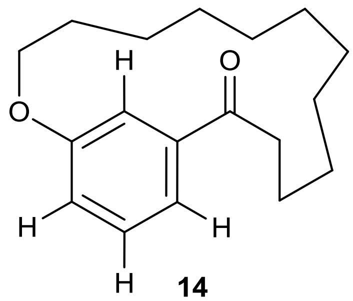
12-hydroxy-1-3-[(1,1,1-triisopropylsilyl)oxy]phenyl-1-dodecanone (12c): A 10 mL flask was charged with [Pd(OAc)$_2$] (36.00 mg, 0.1 mmol, 5.0 mol%), tricyclohexylphosphine (66.00 mg, 0.24 mmol, 12 mol%), 12-hydroxydodecanoic acid **11** (0.43 g, 2.0 mmol), Na_2CO_3 (0.42 g, 4.0 mmol), and di(*N*-succinimidyl) carbonate (0.66 g, 2.6 mmol). The reaction vessel was purged with argon and degassed THF (10 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 ^{o}C, a solution of 3-[(1,1,1-triisopropylsilyl)oxy]phenylboronic acid **9e** (0.70 g, 2.4 mmol) in THF (6 mL) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (20 mL) and extracted 3 times with 20 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with Hexane: EtOAc (60:40) to give the title compound (0.35 g, 40%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 1.05 (d, 18H), 1.16 (m, 3H), 1.25-1.40 (m, 14H), 1.50-1.52 (m, 2H), 1.65-1.68 (m, 2H), 2.84 (t, 2H, *J* = 1.4 Hz), 3.56-3.58 (m, 2H), 7.02 (dd, 1H, *J* = 7.8 and *J* = 1.2 Hz), 7.20 (d, 1H, *J* = 7.8 Hz), 7.39 (d, 1H, *J* = 7.8 Hz), 7.44 (dd, 1H, *J* = 8.0 and *J* = 1.5 Hz); δ_C (100 MHz, $CDCl_3$) 11.3, 16.7, 23.3, 24.6, 28.2, 28.3, 28.4, 28.5, 31.8, 37.8, 62.5, 119.2, 121.1, 124.8, 129.8, 138.9, 157.1, 201.8; δ_{Si} (54 MHz, $CDCl_3$) 16.8; LRMS (CI) *m/z* (rel.%): 466 (M^+ + NH_4^+, 20%), 448 (M^+, 100); HRMS (CI) *m/z* exact mass calculated for $C_{27}H_{49}O_3Si+H^+$ 449.3491 found 449.3445.



13

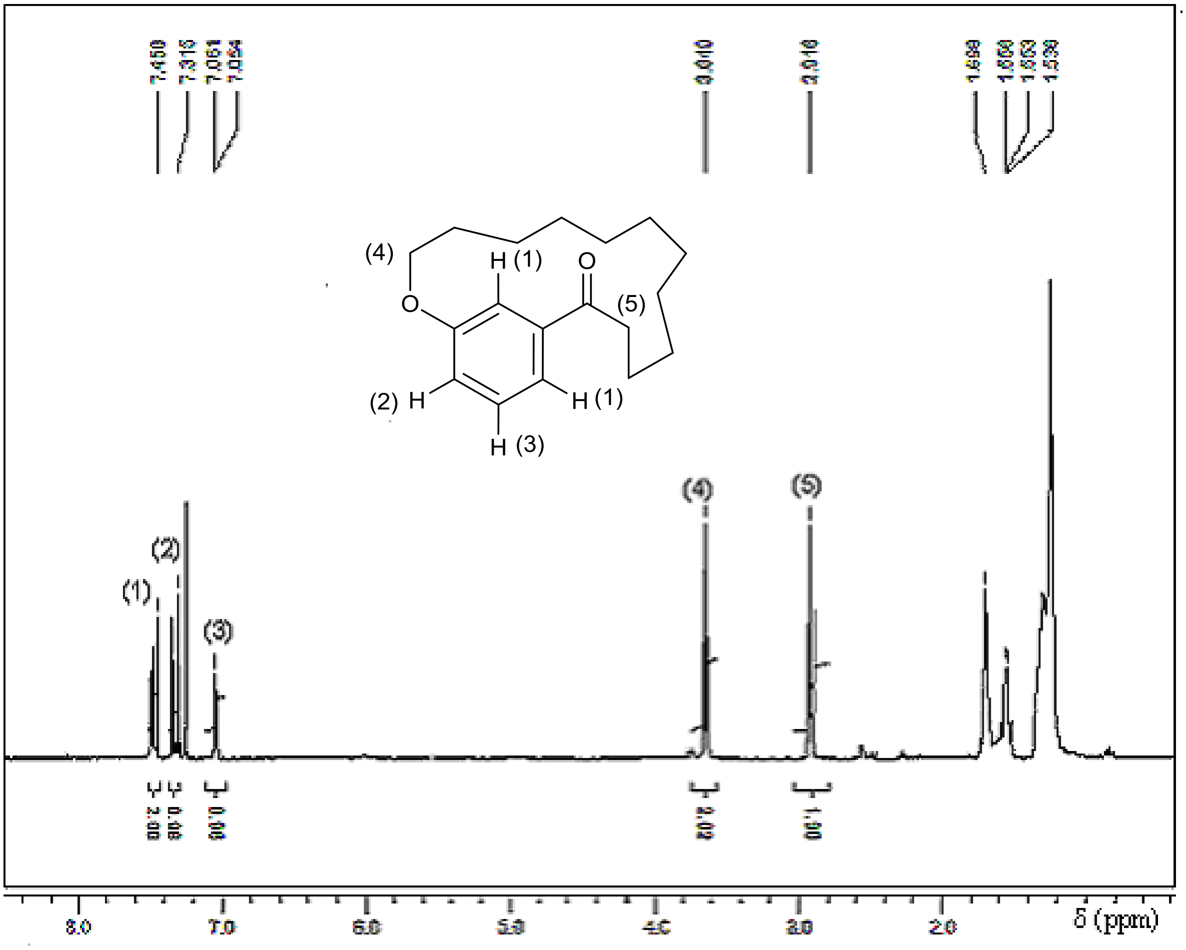
Synthesis of Macroketone 13: 12-hydroxy-1-(4-hydroxyphenyl)-1-dodecanone: To a solution of 1-(4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyphenyl)-12-hydroxy-1-dodecanone **12b** (0.30 g, 0.73 mmol) in THF (10 mL) was added TBAF in THF (1M, 0.81 mL, 0.81 mmol) at 0 ^{o}C. The reaction mixture was stirred vigoruously at 0 ^{o}C for 0.5 h. An excess of aqueous NH_4Cl (10 mL) was added and organic layer was extracted into CH_2Cl_2 (2 X 20 mL). The solvent was dried over $MgSO_4$ and removed under *vacuo*. The title compound was obtained by column chromatography of the crude product with 20% MeOH/CH_2Cl_2 solvent system as a white solid (0.21 g, 99%). δ_H (400 MHz, CD_3OD) 1.25-1.40 (m, 14H), 1.44-1.47 (m, 2H), 1.59-1.61 (m, 2H), 2.85 (t, 2H, *J* = 1.5 Hz), 3.46 (t, 2H, *J* = 1.8 Hz), 6.79 (d, 2H, *J* = 8.2 Hz), 7.82 (d, 2H, *J* = 8.0 Hz); δ_C (100 MHz, CD_3OD) 25.8, 26.7, 30.1, 30.3, 30.4, 30.5, 33.4, 38.8, 63.0, 116.5, 130.3, 132.2, 164.2, 202.7; LRMS (CI) *m/z* (rel.%): 293 (M^++H^+, 100%), 186 (20); HRMS (CI) *m/z* exact mass calculated for $C_{18}H_{28}O_3$+H^+ 293.2117 found 293.2113; Anal. Calcd. for $C_{18}H_{28}O_3$ C 73.93, H 9.63; Found, C 73.91 H 9.61. **Macroketone 13** To a solution of 13-hydroxy-1-(4-hydroxyphenyl)-1-tridecanone (0.10 g, 0.34 mmol) in dry THF (50 mL) was added diisopropylazodicarboxylate (DIAD) (0.082 g, 0.41 mmol) and triphenylphosphine (PPh_3) (0.10 g, 0.41 mmol) at 0 ^{o}C. The reaction mixture was stirred vigorously for 2 days and followed by TLC. Water (30 mL) was added and the solution was extracted with CH_2Cl_2 (20 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated in *vacuo*. The residue obtained was purified by column chromatography (Hexane: Et_2O - 70:30) to obtain the title compound (0.020 g, 22%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 1.19-1.21 (m, 4H), 1.25-1.28 (m, 6H), 1.50-1.68 (m, 8H), 2.81 (t, 2H, J = 1.4 Hz), 3.95-3.98 (m, 2H), 6.63 (d, 2H, J = 8.2 Hz), 7.86 (d, 2H, J = 8.4 Hz); δ_C (100 MHz, $CDCl_3$) 25.7, 26.7, 26.9, 28.4, 28.7, 28.8, 29.5, 29.9, 30.4, 38.4, 68.2, 114.1, 130.1, 130.3, 163.1, 199.6; LRMS (CI) *m/z* (rel.%): 275 (M^++H^+, 100%); HRMS (EI) *m/z* exact mass calculated for $C_{18}H_{26}O_2$+H^+ 275.2006; found 275.2008.





14

Synthesis of Macroketone 14: 12-hydroxy-1-(3-hydroxyphenyl)-1-dodecanone: To a solution of 12-hydroxy-1-3-[(1,1,1-triisopropylsilyl)oxy]phenyl-1-dodecanone **12b** (0.30 g, 0.67 mmol) in THF (10 mL) was added TBAF in THF (1M, 0.75 mL, 0.73 mmol) at 0 ^{o}C. The reaction mixture was stirred vigoruously at 0 ^{o}C for 0.5 h. An excess of aqueous NH_4Cl was added and organic layer was extracted into CH_2Cl_2. The solvent was dried over $MgSO_4$ and removed under *vacuo*. The title compound was obtained (0.19 g. 99%) by column chromatography of the crude product with 20% MeOH/CH_2Cl_2 solvent system as a white solid. δ_H (400 MHz, CD_3OD) 1.25-1.40 (m, 14H), 1.44-1.47 (m, 2H), 1.63-1.65 (m, 2H), 2.88 (t, 2H, *J* = 1.9 Hz), 3.46 (dt, 2H, *J* = 1.6 Hz), 6.98 (dd, 1H, *J* = 7.8 and *J* = 1.2 Hz), 7.22 (d, 1H, *J* = 7.8 Hz), 7.27 (d, 1H, *J* = 7.8 Hz), 7.35 (dd, 1H, *J* = 8.0 and *J* = 1.4 Hz); δ_C (100 MHz, CD_3OD) 25.2, 26.5, 30.0, 30.2, 30.3, 30.4, 33.3, 39.3, 63.1, 101.9, 116.2, 121.3, 122.2, 131.8, 160.5, 205.0; LRMS (CI) *m/z* (rel.%): 315 ($M^+ + NH_4^+$, 40%), 293 (M^++H^+, 100); HRMS (CI) *m/z* exact mass calculated for $C_{18}H_{28}O_3+H^+$ 293.2111 found 293.2105. **Macroketone 14:** To a solution of 13-hydroxy-1-(3-hydroxyphenyl)-1-tridecanone (0.10 g, 0.34 mmol) in dry THF (50 mL) was added diisopropylazodicarboxylate (DIAD) (0.082 g, 0.41 mmol) and triphenylphosphine (PPh_3) (0.10 g, 0.41 mmol) at 0 ^{o}C. The reaction mixture was stirred vigorously for 4 days and followed by TLC. Water (30 mL) was added and the solution was extracted with CH_2Cl_2 (20 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated in *vacuo*. The residue obtained was purified by column chromatography (Hexane: Et_2O (70:30)) to obtain the title compound (0.021 g, 23%) yield as colourless oil. δ_H (400 MHz, $CDCl_3$) 1.17-1.20 (m, 4H), 1.25-1.27 (m, 6H), 1.56-1.58 (m, 4H), 1.70-1.73 (m, 4H), 2.92 (t, 2H, *J* = 1.5 Hz), 3.65-3.69 (m, 2H), 7.06 (d, 1H, *J* = 7.2 Hz), 7.34 (dd, 1H, *J* = 7.4, 1.2 Hz), 7.47 (dt, 2H, *J* = 8.1 Hz); δ_C (100 MHz, $CDCl_3$) 25.7, 26.7, 26.9, 28.4, 28.7, 28.8, 29.5, 29.9, 30.4, 38.4, 63.2, 114.4, 120.4, 120.6, 129.7, 139.3, 163.7, 200.3; LRMS (CI) *m/z* (rel.%): 275 (M^++H^+, 100%); HRMS (CI) *m/z* exact mass calculated for $C_{18}H_{26}O_2$+H^+ 275.2067; found 275.2052.



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