ELECTRONIC SUPPORTING INFORMATION

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

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- General Remarks 2
- Synthesis and Characterization data for compounds 7a-7b, 9a-9f. 3
- Synthesis and Characterization data for compounds 10a-f. 9
- Synthesis and Characterization data for compounds 12a-d and macrocyclic Ketones 13-15. 15
- References 21
**General Remarks**

Catalytic reactions were carried out under a N\textsubscript{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.\textsuperscript{i} THF was freshly distilled from sodium/benzophenone under N\textsubscript{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 (\(\delta\)) are given in ppm.
**Synthesis and Characterization data for compounds 7a-7b, 9a-9f.**

![Image of compound 7a](image)

**2,5-Dioxotetrahydro-1H-1-pyrrolyl laurate (7a):** 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. δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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.

![Image of compound 7b](image)

**2,5-Dioxotetrahydro-1H-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 \textit{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.

\[ \delta_H (400 \text{ MHz, CDCl}_3) 1.07 \text{ (d, } 3\text{H, } J = 1.5 \text{ Hz)}, 1.17-1.42 \text{ (m, } 2\text{H)}, 1.60 \text{ (s, } 3\text{H)}, 1.68 \text{ (s, } 3\text{H)}, 2.05-2.08 \text{ (m, } 2\text{H)}, 2.13-2.16 \text{ (m, } 1\text{H)}, 2.44 \text{ (dd, } 1\text{H, } J = 8.7, 1.7 \text{ Hz)}, 2.60 \text{ (dd, } 1\text{H, } J = 8.7, 1.4 \text{ Hz)}, 2.84-2.88 \text{ (m, } 4\text{H)}, 5.09-5.11 \text{ (m, } 1\text{H}); \delta_C (100 \text{ MHz, CDCl}_3) 17.6, 19.3, 25.2, 25.5, 25.6, 36.4, 38.1, 123.8, 131.8, 168.3, 169.1; \text{LRMS (CI) } m/z \text{ (rel.\%) } 285 \text{ (M}^+\text{+NH}_4^+, 100), 170 \text{ (70), 153 (60), 109 (10); HRMS (ESI) } m/z \text{ exact mass calculated for C}_{14}H_{21}N_{1}O_{4} 267.1471, \text{ found: } 267.1468.\]

\begin{center}
\includegraphics[width=0.5\textwidth]{9b}
\end{center}

**Synthesis of 2,4,5-trimethoxybenzeneboronic acid (9b)**: Bromo-2,4,5-trimethoxybenzene\textsuperscript{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.

\[ \delta_H (400 \text{ MHz, CDCl}_3) 3.80 \text{ (s, } 3\text{H)}, 3.85 \text{ (s, } 3\text{H)}, 3.89 \text{ (s, } 3\text{H)}, 6.53 \text{ (s, } 1\text{H)}, 7.03 \text{ (s, } 1\text{H}); \delta_C (100 \text{ MHz, CDCl}_3) 56.1, 56.5, 57.1, 98.7, 100.9, 116.3, 143.7, 149.0, 150.2; \text{LRMS (EI) } m/z \text{ (rel.\%) } 248 \text{ (M}^+, 100), 231 \text{ (60), 203 (40), 188 (20); the data was consistent with that published. 2,4,5-trimethoxybenzeneboronic acid (9a)\textsuperscript{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 1 h and then quenched saturated aqueous NH₄Cl (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, CDCl₃) 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, CDCl₃) 55.9, 56.2, 56.3, 95.9, 118.2, 143.3, 152.4, 159.9; δ_B (87 MHz, CDCl₃) 28.02 (bs, 1B); LRMS (Cl) m/z (rel.%): 213 (M⁺+H⁺, 100), 169 (42); HRMS (Cl) m/z exact mass calculated for C₉H₁₄O₃B+H⁺ 213.0929, found: 213.0928. the data was consistent with that published.

![Diagram](https://via.placeholder.com/150)

**2-Methoxyphenylboronic acid (9a)**: 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 NH₄Cl (20 mL). The phases were separated and extracted with CH₂Cl₂ (30 mL). The organic layers were combined, washed with brine, dried over MgSO₄ 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, CDCl₃) 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, CDCl₃) 55.3, 109.8, 121.1, 132.7, 136.8, 164.4; δ_B (87 MHz, CDCl₃) 28.2; LRMS (EI) m/z (rel.%): 152 (M⁺, 100); Anal. Calcd. for C₇H₉O₃B, C 55.33, H 5.97; Found, C 55.22, H 5.92; the data was consistent with that published.
Synthesis of 4-[1-(tert-buty)-1,1-dimethylsilyl]oxyphenylboronic acid (9c): 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 CHCl₃, 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 CHCl₃. 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 MgSO₄. The solvent was removed by rotary evaporation to yield (7.10 g, 81%) the title compound as colourless oil. δH (400 MHz, CDCl₃) 0.27 (s, 6H), 0.98 (s, 9H), 7.01 (d, 2H, J = 7.9 Hz), 7.81 (d, 2H, J = 7.8 Hz); δC (100 MHz, CDCl₃) -4.5, 18.1, 25.1, 124.7, 131.6, 142.9, 156.9; δSi (54 MHz, CDCl₃) 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): 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 NH₄Cl (10 mL). The phases were separated and extracted with CH₂Cl₂ (20 mL). The organic layers were combined, washed with brine, dried over MgSO₄ 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. $\delta_H$ (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); $\delta_C$ (100 MHz, CDCl$_3$) -4.4, 18.2, 25.6, 119.7, 137.4, 141.8, 159.7; $\delta_{Si}$ (54 MHz, CDCl$_3$) 21.9; $\delta_B$ (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$_3$BSi 252.1353, found: 252.1349; the data was consistent with that published.

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$_2$Cl$_2$. 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. $\delta_H$ (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); $\delta_C$ (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 °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 NH₄Cl (20 mL). The phases were separated and extracted with CH₂Cl₂ (2 X 50 mL). The organic layers were combined, washed with brine, dried over MgSO₄ 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. δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 12.7, 17.9, 124.2, 125.4, 126.5, 128.2, 129.1, 155.7; δB (87 MHz, CDCl₃) 28.1; δSi (54 MHz, CDCl₃) 16.0; LRMS (Cl) m/z (rel.%): 312 (M⁺ + NH₄⁺, 60), 295 (M⁺, 100); HRMS (Cl) m/z exact mass calculated for C₁₅H₂₈O₃BSi+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:**

![Image of compound 10a](image)

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-1H-1-pyrrolyl laurate 7a (0.10 g, 0.37 mmol), Na\(_2\)CO\(_3\) (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 °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\(_2\)O (70:30) to give the title compound 1-(2-methoxyphenyl)-1-dodecanone 10a (0.061 g, 61%) as colourless oil. \(\delta_h\) (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); \(\delta_c\) (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 (Cl) \(m/z\) (rel.%) 291 (M\(^+\)+H\(^+\), 100); HRMS (Cl) \(m/z\) exact mass calculated for C\(_{19}\)H\(_{31}\)O\(_2\)+H\(^+\) 291.2324 found 291.2319.

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Electronic Supplementary Material (ESI) for New Journal of Chemistry
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1-(2-methoxyphenyl)-3,7-dimethyl-6-octen-1-one (10b): 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-1H-1-pyrrolyl 3,7-dimethyl-6-octenoate 7b (0.10 g, 0.37 mmol), Na$_2$CO$_3$ (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 °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$_2$O (75:25) to give the title compound 10b was obtained in good yield (0.088 g, 81%) as colourless oil. $\delta_H$ (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); $\delta_C$ (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.
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-1H-1-pyrrolyl laurate 7a (0.10 g, 0.37 mmol), Na$_2$CO$_3$ (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 °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$_2$O (75:25) to give the title compound in good yield (0.077 g, 59%) as colourless oil. $\delta_H$ (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); $\delta_C$ (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 (Cl) $m/z$ exact mass calculated for C$_{24}$H$_{43}$O$_2$Si+H$^+$ 391.3029 found 391.3027.
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, 0.018 mmol, 5.0 mol%), tricyclohexylphosphine (12.60 mg, 0.045 mmol, 12 mol%), 2,5-dioxotetrahydro-1H-1-pyrrolyl 3,7-dimethyl-6-octenoate 7b (0.10 g, 0.37 mmol), Na$_2$CO$_3$ (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 °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$_2$O (75:25) to give the title compound (0.059 g, 42%) as colourless oil. $\delta$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); $\delta$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.
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\(_2\)CO\(_3\) (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 °C, 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\(_2\)O (75:25) to give the title compound good yield (0.063 g, 69%) as colourless oil. \(\delta_H\) (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); \(\delta_C\) (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 (Cl) \(m/z\) (rel.%) 296 (M\(^+\) + NH\(_4^+\), 10), 279 (M\(^+\), 100); HRMS (Cl) \(m/z\) exact mass calculated for C\(_{18}\)H\(_{27}\)O\(_2\)F+H\(^+\) 279.2146 found 279.2159.
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-1H-1-pyrrolyl 3,7-dimethyl-6-octenoate 7b (0.10 g, 0.37 mmol), 
Na$_2$CO$_3$ (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 °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$_2$O (75:25) to give the title compound (0.072 
g, 71%) as colourless oil. $\delta$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); $\delta$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.

![Chemical structure of 12a](image)

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$_2$CO$_3$ (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 °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. $\delta_H$ (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, 2H, $J = 7.8$ and $J = 1.9$ Hz); $\delta_C$ (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.
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$_2$CO$_3$ (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 °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 $\textit{in vacuo}$. 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. $\delta_H$ (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); $\delta_C$ (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$_3$Si+H$^+$ 407.3016 found 407.2976.
**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$_2$CO$_3$ (0.42 g, 4.0 mmol), and di(Nsuccinimidyl) 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 °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. $\delta_H$ (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); $\delta_C$ (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; $\delta_{Si}$ (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$_3$Si+H$^+$ 449.3491 found 449.3445.
**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 °C. The reaction mixture was stirred vigorously at 0 °C for 0.5 h. An excess of aqueous \(\text{NH}_4\text{Cl}\) (10 mL) was added and organic layer was extracted into \(\text{CH}_2\text{Cl}_2\) (2 \(\times\) 20 mL). The solvent was dried over \(\text{MgSO}_4\) and removed under vacuo. The title compound was obtained by column chromatography of the crude product with 20% \(\text{MeOH/CH}_2\text{Cl}_2\) solvent system as a white solid (0.21 g, 99%). \(\delta_H\) (400 MHz, \(\text{CD}_3\text{OD}\)) 1.25-1.40 (m, 14H), 1.44-1.47 (m, 2H), 1.59-1.61 (m, 2H), 2.85 (t, 2H, \(J = 1.5 \text{ Hz}\)), 3.46 (t, 2H, \(J = 1.8 \text{ Hz}\)), 6.79 (d, 2H, \(J = 8.2 \text{ Hz}\)), 7.82 (d, 2H, \(J = 8.0 \text{ Hz}\)); \(\delta_C\) (100 MHz, \(\text{CD}_3\text{OD}\)) 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 \(\text{C}_{18}\text{H}_{28}\text{O}_3\) \(+\text{H}^+\) 293.2117 found 293.2113; Anal. Calcd. for \(\text{C}_{18}\text{H}_{28}\text{O}_3\) 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 (\(\text{PPh}_3\)) (0.10 g, 0.41 mmol) at 0 °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 \(\text{CH}_2\text{Cl}_2\) (20 mL). The organic phase was separated, dried over \(\text{MgSO}_4\) and concentrated in vacuo. The residue obtained was purified by column
chromatography (Hexane: Et₂O - 70:30) to obtain the title compound (0.020 g, 22%) as colourless oil. δₜₕ (400 MHz, CDCl₃) 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); δₜₖ (100 MHz, CDCl₃) 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 C₁₈H₂₆O₂⁺H⁺ 275.2006; found 275.2008.
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 °C. The reaction mixture was stirred vigorously at 0 °C for 0.5 h. An excess of aqueous NH₄Cl was added and organic layer was extracted into CH₂Cl₂. The solvent was dried over MgSO₄ and removed under vacuo. The title compound was obtained (0.19 g, 99%) by column chromatography of the crude product with 20% MeOH/CH₂Cl₂ solvent system as a white solid. δH (400 MHz, CD₃OD) 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); δC (100 MHz, CD₃OD) 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⁺ + NH₄⁺, 40%), 293 (M⁺+H⁺, 100); HRMS (CI) m/z exact mass calculated for C₁₈H₂₈O₃+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 (PPh₃) (0.10 g, 0.41 mmol) at 0 °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 CH₂Cl₂ (20 mL). The organic phase was separated, dried over MgSO₄ and concentrated in vacuo. The residue obtained was purified by column chromatography (Hexane: Et₂O (70:30)) to obtain the title compound (0.021 g, 23%) yield as
colourless oil. \( \delta_H \) (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); \( \delta_C \) (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.
References


