Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Combining Two-Directional Synthesis and Tandem Reactions: A Short Formal Synthesis of Halichlorine

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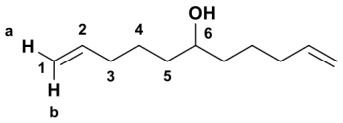
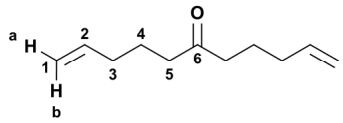
Supplementary Information.

Undeca-1,10-dien-6-ol



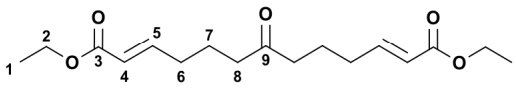
A suspension of magnesium (4.50 g, 185 mmol) in dry tetrahydrofuran (30 mL) was activated by adding iodine crystals. To the resulting yellow solution was added 5-bromo-1-pentene (25.0 g, 168 mmol) dropwise. The reaction mixture was diluted with dry tetrahydrofuran (120 mL) and stirred for 3 h at room temperature. A solution of ethyl formate (6.23 g, 84 mmol) in dry tetrahydrofuran (60 mL) was added dropwise to the Grignard reagent over 2 h via an addition funnel. The reaction mixture was stirred at room temperature for 24 h and then refluxed for 1 h. The reaction mixture was cooled, quenched with saturated aqueous ammonium chloride (200 mL) and extracted with diethyl ether (2×200 mL). The combined organic layers were evaporated *in vacuo* and the resulting residue was dissolved in 15% aqueous solution of potassium hydroxide then refluxed for 6 h. The mixture was separated and the aqueous layer was extracted with diethyl ether (2×100 mL). The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to give undeca-1,10-dien-6-ol **2** (13.3 g, 94%) as a yellow oil: IR ν_{max} (thin film)/cm^{-1} 3465, 3078, 1640, 1242, 998, 916; δ_H (400 MHz, $CDCl_3$) 5.82 (2H, ddt, *J* 16.9, 10.2 and 6.7, 2-H), 5.06 (2H, dd, *J* 16.9 and 1.2, 1-H_b), 4.96 (2H, dd, *J* 10.2 and 1.2, 1-H_a), 3.65-3.55 (1H, m, 6-H), 2.17-2.0 (4H, m, 3-H_2) 1.58-1.38 (8H, m, 4-H_2 and 5-H_2); δ_C (75 MHz, $CDCl_3$) 138.7, 114.6, 71.6, 36.9, 33.7, 24.9; *m/z* (ES) 169 (M+1, 100%), 191 (14); HMRS: found: 191.1410. $C_{11}H_{20}ONa$ (M+Na^+) Requires 191.1406.

Undeca-1,10-dien-6-one 5



To a solution of undeca-1,10-dien-6-ol (13.3 g, 78.8 mmol) in dichloromethane (330 mL) was added silica gel (39.0 g) and PCC (18.7 g, 86.7 mmol). The resulting dark brown solution was stirred at room temperature for 24 h. Silica gel (20.0 g) was added and the reaction mixture was stirred for 30 min. Diethyl ether was added and the reaction mixture was filtered through a pad of silica gel, which was washed with diethyl ether. The filtrate was evaporated *in vacuo* to afford ketodiene **5** (12.5 g, 95%) as a yellow oil: IR ν_{max} (thin film)/cm^{-1} 3079, 1711, 1640, 998, 918; δ_H (300 MHz, $CDCl_3$) 5.77 (2H, ddt, *J* 17.0, 10.2 and 6.7, 2-H), 5.06-4.95 (4H, m, 1-H_2), 2.40 (4H, t, *J* 7.4, 5-H_2), 2.05 (4H, q, *J* 7.4, 3-H_2), 1.67 (4H, quin, *J* 7.4, 4-H_2); δ_C (75 MHz, $CDCl_3$) 210.9, 138.0, 115.2, 41.9, 33.1, 22.8; *m/z* (ES) 184 (M+18, 100%), 167 (25); HMRS: found:184.1694. $C_{11}H_{22}NO$ (M+NH_4^+) Requires 184.1694.

(2*E*,11*E*)-Diethyl-7-oxotrideca-2,11-dienedioate 2

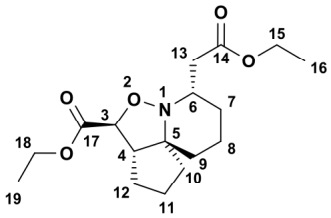


By cross-metathesis:
To a solution of undeca-1,10-dien-6-one **3** (2.0 g, 12.0 mmol) in dichloromethane (150 mL) at room temperature was added ethyl acrylate (10.6 mL, 96.0 mmol), followed by Hoveyda-Grubbs II catalyst (188 mg, 0.30 mmol, 2.5 mol %). The reaction mixture was stirred at room temperature for 3 days, upon which an additional portion of catalyst (188 mg, 0.30 mmol, 2.5 mol %) was added. The reaction was allowed to proceed for a further 2 days. The dark mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluting with 8:2 petroleum ether/ethyl acetate) to give ketodiester **2** (2.95 g, 79%) as a light green oil: IR ν_{max} (thin film)/cm^{-1} 1711, 1654, 979; δ_H (400 MHz, $CDCl_3$) 6.90 (2H, dt, *J* 15.6 and 7.0, 5-H), 5.81 (2H, dt, *J* 15.6 and 1.5, 4-H), 4.17 (4H, q, *J* 7.2, 2-H_2), 2.41 (4H, t, *J* 7.3, 8-H_2), 2.20 (4H, qd, *J* 7.3 and 1.5, 6-H_2), 1.74 (4H, quin, *J* 7.3, 7-H_2), 1.27 (6H, t, *J* 7.2, 1-H_3); δ_C (75 MHz, $CDCl_3$) 209.5, 166.5, 148.0, 122.0, 60.3, 41.8, 31.4, 21.9, 14.3; *m/z* (ES) 333 (M+23, 100%), 311 (12); HMRS: found: 311.1844. $C_{17}H_{27}O_5$ (M+H^+) Requires 311.1853.

By oxidative cleavage and Wittig homologation:
To a solution of undeca-1,10-dien-6-one (10.0g, 60.1 mmol) in THF (750 mL) and water (250 mL), an aqueous solution of 4% osmium tetroxide (3.06 mL , 0.481 mmol) was added. To the resulting brown solution was then charged sodium

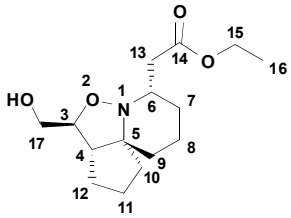
periodate (77.2 g, 360 mmol). The solution then became yellow and a white precipitate slowly appeared. After 15 hours, the solvent was evaporated *in vacuo*. Dichloromethane (500 mL) was added and the slurry was stirred for another hour before filtering off the white precipitate. The remaining solution was concentrated *in vacuo*, giving undeca-1,10-dien-6-one as yellow oil (10.2g, 99%), which was used directly. The undeca-1,10-dien-6-one (10.2 g, 60.2 mmol) was dissolved in dry toluene (750 mL). (Ethoxycarbonylmethylene) triphenylphosphorane (46.1 g, 132 mmol) was then added in one portion. The mixture was heated at reflux for 6 h. The solvent was then removed under reduced pressure. The residue was then purified by silica gel chromatography, eluting with 10:1 petroleum ether/ethyl acetate, affording ketodienoate **2** as an oil (9.47 g, 54%), data as above.

Ethyl [(3a*S,4*S**,7*S**,10a*S**)-4-ethoxycarbonyloctahydrocyclopenta[3,4]-isoxazolo[2,3a]pyridin-7-yl]acetate 3**



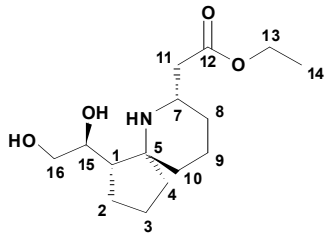
To a stirred solution of dienoate **2** (10.0 g, 32.2 mmol) in anhydrous methanol (400 mL) at room temperature, was added dry hydroxylamine hydrochloride (2.46g, 35.4 mmol) and sodium acetate (6.61g, 80.5 mmol). The reaction mixture was stirred at room temperature for 24 h and was then concentrated *in vacuo*. The white precipitate was then washed with dichloromethane and discarded. The filtrate was concentrated under reduced pressure. The resulting oily residue was solubilized in acetonitrile (200 mL) and refluxed for 2 h and concentrated *in vacuo* again. The brown slurry obtained was heated to reflux in hexane and filtered hot to afford **3** (9.25g, 88%) as pale yellow crystals: m.p. 46-49 °C (Found: C, 62.35; H, 8.31; N, 4.01. $C_{17}H_{27}NO_5$ Requires C, 62.75;, H, 8.36; N, 4.30%); IR ν_{max} (thin film)/cm^{-1} 1732, 1265, 1192; δ_H (400 MHz, $CDCl_3$) 4.27-4.08 (5H, m, 3-H, 15-H_2 and 18-H_2), 3.17 (1H, dd, *J* 15.6 and 3.2, 13-H_a), 3.04 (1H, t, *J* 5.6, 4-H), 2.90 (1H, ddt, *J* 11.2, 9.8 and 3.2, 6-H), 2.30 (1H, dd, *J* 15.6 and 9.8, 13-H_b), 2.11-1.53 (12H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 and 12-H_2), 1.32-1.20 (6H, m, 16-H_3 and 19-H_3); δ_C (75 MHz, $CDCl_3$) 173.0, 172.2, 83.4, 76.6, 61.4, 60.5, 60.1, 51.0, 39.2, 39.1, 33.0, 29.9, 29.2, 21.1, 20.6, 14.3, 14.0; *m/z* (ES) 348 (M+23, 100%), 326 (13), 673 (34); HMRS: found: 348.1775. $C_{17}H_{28}NNaO_5$ (M+Na$^+$) Requires 348.1781.

Ethyl [(3a*S,4*S**,7*S**,10a*S**)-4-hydroxymethyloctahydrocyclopenta[3,4]-isoxazolo[2,3a]pyridin-7-yl]acetate 6**



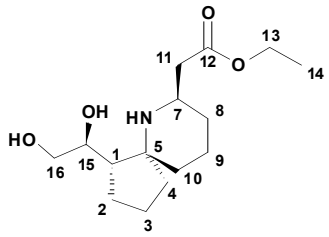
A solution of tricycle **3** (920 mg, 2.83 mmol) in anhydrous ethanol (40 mL) was cooled to 0 ºC and sodium borohydride (332 mg, 8.77 mmol) was added in one portion. The reaction mixture was warmed to room temperature and stirred for 48 h. Acetone (40 mL) was added and the reaction mixture was stirred for another hour before the solvent was evaporated *in vacuo*. The residue was dissolved in water (40 mL) and the aqueous layer was extracted with ethyl acetate (3×40 mL). The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo*. The yellow residue was purified by flash column chromatography on silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford alcohol **6** (488 mg, 61%) as a pale yellow oil: IR ν_{max} (thin film)/cm^{-1} 3445, 1709, 1242, 1172; δ_H (400 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7.2, 15-H_2), 3.80 (1H, dd, *J* 11.3 and 3.7, 17-H_a), 3.74-3.62 (1H, m, 3-H), 3.57 (1H, dd, *J* 11.3 and 3.7 17-H_b), 3.29-3.20 (1H, m, 6-H), 2.74-2.62 (2H, m, 4-H and 13-H_a), 2.27 (1H, dd, *J* 14.9 and 3.8, 13-H_b), 2.11-1.34 (12H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 and 12-H_2), 1.27 (3H, t, *J* 7.2, 16-H_3); δ_C (75 MHz, $CDCl_3$) 175.1, 88.1, 76.6, 62.0, 61.9, 61.0, 45.5, 41.9, 37.7, 31.7, 31.0, 29.3, 26.5, 20.3, 14.0; *m/z* (ES) 306 (M+23, 100%), 284 (39), 589 (16); HMRS: found: 306.1676. $C_{15}H_{26}NNaO_4$ (M+Na$^+$) Requires 306.1676.

Ethyl [(1*S,5*S**,7*S**)-1-[(1*S**)-1',2'-dihydroxyethyl]-6-azaspiro[4.5]dec-7-yl]acetate**



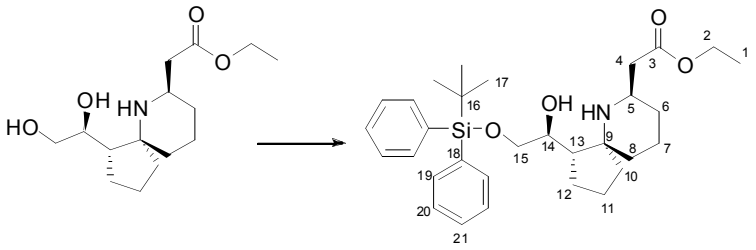
To a solution of alcohol **6** (516 mg, 1.76 mmol) in anhydrous methanol (45 mL) was added palladium on activated carbon (516 mg, 100 wt %). The mixture was hydrogenated at room temperature under atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to afford the product diol (468 mg, 91 %) as a white solid: m.p. 74-80 °C; IR ν_{max} (thin film)/cm^{-1} 3312, 1728, 1294, 1192; δ_H (400 MHz, $CDCl_3$) 4.16 (2H, q, *J* 7.1, 13-H_2), 3.74-3.66 (2H, m, 15-H and 16-H_a), 3.51-3.44 (1H, m, 16-H_b), 3.31-3.19 (1H, m, 7-H), 2.38 (2H, d, *J* 6.0, 11-H_2), 2.18-2.08 (1H, m, 1-H), 1.89-0.98 (15H, m, 2-H_2, 3-H_2, 4-H_2, 8-H_2, 9-H_2, 10-H_2 and 14-H_3); δ_C (100 MHz, $CDCl_3$) 172.2, 74.0, 65.2, 64.6, 60.6, 51.6, 50.0, 40.9, 38.9, 37.0, 31.2, 26.6, 20.1, 19.6, 14.1; *m/z* (ES) 286 (M+1, 100%), 308 (5); HMRS: found: 286.2004. $C_{15}H_{28}NO_4$ (M+H$^+$) Requires 286.2013.

Ethyl [(1*S,5*S**,7*R**)-1-[(1*S**)-1',2'-dihydroxyethyl]-6-azaspiro[4.5]dec-7-yl]acetate 7**



A solution of ethyl [(1*S**,5*S**,7*S**)-1-[(1*S**)-1',2'-dihydroxyethyl]-6-azaspiro[4.5]dec-7-yl]acetate (343 mg, 1.20 mmol) in ethanol (16 mL) was irradiated in the microwave reactor at 120 ºC for 10 h. The reaction mixture was concentrated *in vacuo* to afford diol **7** (343 mg, 100%) as a light brown solid: m.p. 46-49 °C (Found: C, 62.90; H, 9.44; N, 4.56. $C_{15}H_{27}NO_4$ Requires C, 63.13;, H, 9.54; N, 4.91%); IR ν_{max} (thin film)/cm^{-1} 3300, 1721, 1294, 1180; δ_H (300 MHz, $CDCl_3$) 4.15 (2H, q, *J* 7.2, 13-H_2), 3.76-3.68 (2H, m, 15-H and 16-H_a), 3.50 (1H, dd, *J* 11.4 and 6.4, 16-H_b), 3.08 (1H, m, 7-H), 2.42 (1H, dd, *J* 16.6 and 3.4, 11-H_a), 2.29 (1H, dd, *J* 16.6 and 9.0, 11-H_b), 2.03-1.95 (1H, m, 1-H), 1.85-1.38 and 1.29-1.02 (15H, m, 2-H_2, 3-H_2, 4-H_2, 8-H_2, 9-H_2, 10-H_2 and 14-H_3); δ_C (75 MHz, $CDCl_3$) 172.5, 74.1, 65.8, 63.9, 60.5, 51.2, 50.2, 41.4, 38.0, 31.9, 29.1, 24.5, 22.1, 20.4, 14.2; *m/z* (ES) 286 (M+1, 100%), 270 (27); HMRS: found: 286.2025. $C_{15}H_{28}NO_4$ (M+H$^+$) Requires 286.2013.

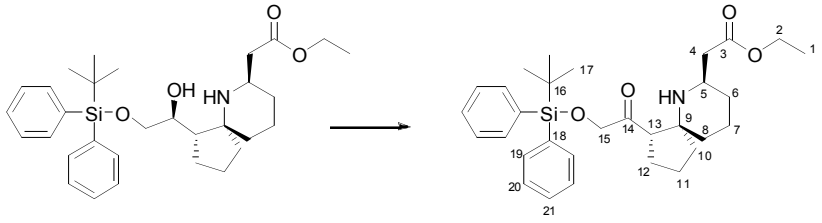
Ethyl 2-[(1*S,5*S**,7*R**)-1-[(1*S**)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-hydroxyethyl]-6-azaspiro[4.5] decan-7-yl]acetate (8)**



To a stirring solution of imidazole (0.36 mmol, 25 mg, 2 eq.) in tetrahydrofuran (1.5 mL) was added *tert*-butyldiphenylchlorosilane (0.18 mmol, 49 mg, 1 eq.) and the resulting solution was stirred for 15 minutes and then cooled to 0 °C. A solution of ethyl 2-[(1*S**,5*S**,7*R**)-1-[(1*S**)-1,2-dihydroxyethyl]-6-azaspiro[4.5]decan-7-yl]acetate (**7**) (0.18 mmol,

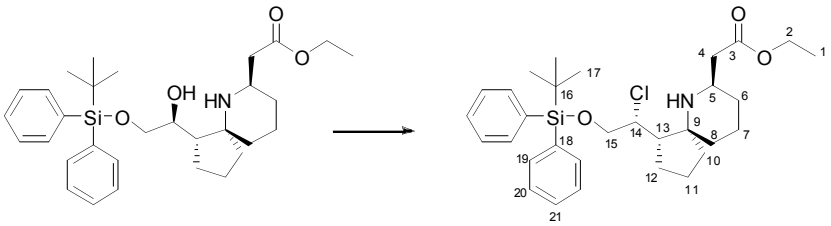
51 mg, 1 eq.) in THF (1.5 mL) was added and the resulting reaction mixture was stirred warming to rt for 96 h. The reaction was quenched with sat. aq. ammonium chloride (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (over silica gel, employing a stepwise gradient elution of pure CH_2Cl_2 to 20:1 CH_2Cl_2/MeOH) gave the product as a clear oil (0.16 mmol, 83 mg, 88%) (Found: C, 71.13; H 8.54; N, 2.75. $C_{31}H_{45}NO_4Si$ requires C, 71.09; H, 8.66; N, 2.67%) R_f 0.17 in 20:1 CH_2Cl_2/MeOH; HRMS calculated for $C_{31}H_{46}NO_5Si$ (M+H) 524.3191, found 524.3172; δ_H (400 MHz; $CDCl_3$) 7.76-7.69 (4H, m, 20-H), 7.46-7.37 (6H, m, 21-H and 22-H), 4.16 (2H, q, *J* 7.0, 2-H_2), 3.82-3.59 (3H, m, 14-H and 15-H_2), 3.13-3.04 (1H, m, 5-H), 2.40 (1H, dd, *J* 16.6 and 3.8, 4-H_a), 2.32 (1H, dd, *J* 16.6 and 9.0, 4-H_b), 2.18-2.06 (1H, m, 13-H), 1.94-1.32 (12H, m, 6-H_2, 7-H_2, 8-H_2, 10-H_2, 11-H_2, and 12-H_2), 1.29 (3H, t, *J* 7.0, 1-H_3), 1.09 (9H, s, 17-H_3); δ_C (100 MHz, $CDCl_3$) 172.7 (C3), 135.7 (C19), 133.9 (C18), 129.6 (C21), 127.7 (C20), 74.8 (C14), 67.7 (C9), 63.9 (C15), 60.5 (C2), 51.5 (C5), 48.5 (C13), 41.6 (C4), 37.9 (C8), 37.4 (C10), 32.2 (C6), 29.4 (C12), 26.9 (C17), 24.5 (C11), 22.4 (C7), 19.4 (C16), 14.3 (C1); IR (thin film, ν/cm^{-1}) 3301, 3072, 1724.

Ethyl 2-[(1*S,5*S**,7*R**)-1-(2-[(*tert*-butyldiphenylsilyl)oxy]acetyl)-6-azaspiro[4.5]decan-7-yl]acetate (9)**



To a stirring mixture of ethyl 2-[(1*S**,5*S**,7*R**)-1-[(1*S**)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-hydroxyethyl]-6-azaspiro[4.5]decan-7-yl]acetate (**8**) (0.145 mmol, 76 mg, 1 eq.) in dimethyl sulfoxide (72.5 mmol, 5.2 mL, 500 eq.) and triethylamine (2.18 mmol, 0.30 mL, 15 eq.) was added pyridine·sulfur trioxide complex (1.02 mmol, 162 mg, 7 eq.) and the resulting solution was stirred for 24 h. Water (10 mL) was added and the resulting slurry was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over potassium carbonate and the solvent was removed *in vacuo*. Purification by column chromatography (over alumina, eluting with 5:1 H/EA) yielded the product as a clear oil (0.102 mmol, 53 mg, 70%) R_f 0.89 in 1:1 H/EA; HRMS calculated for $C_{31}H_{44}NO_4Si$ (M+H) 522.3034, found 522.3052; δ_H (400 MHz; $CDCl_3$) 7.76-7.59 (4H, m, 20-H), 7.47-7-33 (6H, m, 21-H and 22-H), 4.23-3.99 (4H, m, 2-H_2 and 15-H_2), 3.13-2.95 (1H, m, 5-H), 2.70-2.18 (3H, m, 4-H_2 and 13-H), 1.98-1.38 (12H, m, 6-H_2, 7-H_2, 8-H_2, 10-H_2, 11-H_2, and 12-H_2), 1.30-1.21 (3H, m, 1-H_3), 1.07 (9H, s, 17-H_3); δ_C (100 MHz, $CDCl_3$) 210.3 (C14), 172.2 (C3), 135.6 (C19), 132.9 (C18), 129.8 (C21), 127.7 (C20), 70.7 (C15), 65.3 (C9), 60.3 (C2), 57.2 (C13), 49.2 (C5), 42.0 (C4), 36.2 (C8), 35.1 (C10), 32.0 (C6), 29.7 (C12), 26.8 (C17), 23.3 (C11), 21.9 (C7), 19.2 (C16), 14.2 (C1); IR (solution cell, ν/cm^{-1}) 2977, 1726, 1656.

Ethyl 2-[(1*S,5*S**,7*R**)-1-[(1*S**)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-chloroethyl]-6-azaspiro[4.5]decan-7-yl]acetate (12)**



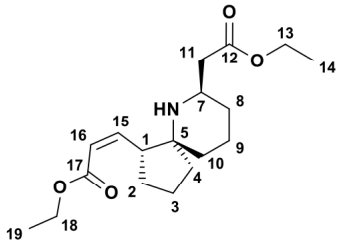
Method I: To a stirring solution of ethyl 2-[(1*S**,5*S**,7*R**)-1-[(1*S**)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-hydroxyethyl]-6-azaspiro[4.5]decan-7-yl]acetate (**8**) (0.907 mmol, 475 mg, 1 eq.) in 1,4-dioxane (20 mL) was added thionyl chloride (1.81 mmol, 0.13 mL, 2 eq.). The solution was stirred for 18 h, whereupon a quench of sat. aq. sodium hydrogen carbonate (30 mL) was added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried over potassium carbonate and sodium sulfate and the solvent was removed *in vacuo* to yield the product as a pale orange oil (0.878 mmol, 476 mg, 97%). R_f 0.75 in 1:1 H/EA; HRMS calculated for $C_{31}H_{45}{}^{35}ClNO_3Si$ (M+H) 542.2852, found 542.2857; δ_H (400 MHz; $CDCl_3$) 7.71-7.65 (4H, m, 20-H), 7.47-7.36 (6H, m, 21-H and 22-H), 4.39

(1H, ddd, *J* 7.2, 5.7 and 3.5, 14-H), 4.13 (2H, q, *J* 7.0, 2-H_2), 3.84 (1H, dd, *J* 10.4 and 5.7, 15-H_a), 3.76 (1H, dd, *J* 10.4 and 7.2, 15-H_b), 3.06 (1H, ddt, *J* 8.9, 4.7 and 2.3, 5-H), 2.34 (1H, dd, *J* 15.7 and 4.7, 4-H_a), 2.26 (1H, dd, *J* 15.7 and 8.9, 4-H_b), 2.12 (1H, td, *J* 8.4 and 3.5, 13-H), 1.93-1.32 (12H, m, 6-H_2, 7-H_2, 8-H_2, 10-H_2, 11-H_2, and 12-H_2), 1.26 (3H, t, *J* 7.0, 1-H_3), 1.07 (9H, s, 17-H_3); δ_C (100 MHz, $CDCl_3$) 172.6 (C3), 135.7 (C19), 133.4 (C18), 129.7 (C21), 127.7 (C20), 66.9 (C9), 63.6 (C15), 63.2 (C14), 60.3 (C2), 50.6 (C5), 48.8 (C13), 42.2 (C4), 36.5 (C8), 36.1 (C10), 32.2 (C6), 26.9 (C17), 26.4 (C12), 22.9 (C11), 22.2 (C7), 19.3 (C16), 14.3 (C1); IR (thin film, ν/cm^{-1}) 2933, 1724.

Ethyl diphenylphosphonacetate

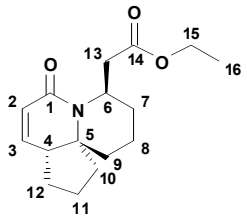
To an anhydrous solution of diphenyl phosphite (2.20 mL, 10 mmol) in dichloromethane (10 mL) cooled to 0 °C, was added ethyl bromoacetate (1.10 mL, 10 mmol), followed by triethylamine (1.95 mL, 14 mmol). The reaction was stirred at 0 °C for 15 min, then warmed to room temperature and stirred for 1 h. The resulting white suspension was quenched with water (25 mL) and the aqueous phase was extracted with a 3:1 mixture of ethyl acetate-hexane (30 mL). The organic phase was washed with water (20 mL), then brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (eluting with 5:1 to 3:1 petroleum ether/ethyl acetate) afforded ethyl diphenylphosphonoacetate (1.59 g, 50 %) as a colourless oil: IR ν_{max} (thin film)/cm^{-1} 3011, 1738, 1593, 1491, 1285, 1188, 952; δ_H (400 MHz, $CDCl_3$) 7.38-7.29 (4H, m, 7-H_4), 7.25-7.16 (6H, m, 6-H_4 and 8-H_2), 4.23 (2H, q, *J* 7.1, 3-H_2), 3.26 (2H, d, *J* 21.6, 1-H_2), 1.27 (3H, t, *J* 7.1, 4-H_3); δ_C (75 MHz, $CDCl_3$) 164.8, 150.0, 129.8, 125.5, 120.6, 62.0, 35.0, 33.2, 14.1; *m/z* (ES) 343 (M+23, 100%), 321 (41); HMRS: found: 321.0892 $C_{16}H_{18}O_5P$ ($M+H^+$) Requires 321.0886.

(2*Z*)-Ethyl--3-[(1*R,5*S**,7*R**)-7-(2-ethoxy-2-oxoethyl)-6-azaspiro[4.5]decan-1-yl]acrylate 14**



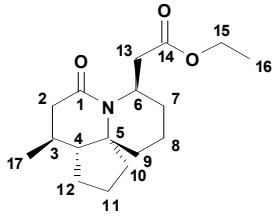
An anhydrous solution of diol **7** (520 mg, 1.82 mmol) in a 7:3 mixture of dichloromethane-water (100 mL) was cooled to 0 °C and then sodium periodate (780 mg, 3.64 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h. The layers were separated and the aqueous phase was extracted with dichloromethane (2×150 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The resulting aldehyde **13** was used directly with no further purification. To a suspension of sodium hydride (60% dispersion in mineral oil, 110 mg, 2.73 mmol) in dry tetrahydrofuran (10 mL), was added at room temperature a solution of ethyl diphenylphosphonoacetate (584 mg, 1.82 mmol) in dry tetrahydrofuran (10 mL). The reaction mixture was stirred for 30 min and then cooled to -78 °C. A solution of the crude aldehyde **13** in tetrahydrofuran (16 mL) was added. The reaction mixture was stirred at -78 °C for 5 h then warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride (20 mL) was added and the aqueous layer was extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over magnesium sulfate and evaporated *in vacuo.* Purification of the residue by flash column chromatography on alumina (eluting with 7:3 petroleum ether/ethyl acetate) afforded the ester **14** (328 mg, 56 %) as a yellow oil: IR ν_{max} (thin film)/cm^{-1} 1715, 1641, 1294, 1191; δ_H (300 MHz, $CDCl_3$) 6.47 (1H, dd, *J* 11.6 and 10.2, 15-H), 5.84 (1H, d, *J* 11.6, 16-H), 4.14 (4H, quin, *J* 7.1, 13-H_2 and 18-H_2), 3.51 (1H, dd, *J* 10.2 and 8.7, 1-H), 3.13-3.02 (1H, m, 7-H), 2.38 (1H, dd, J 15.7 and 4.5, 11-H_a), 2.29 (1H, dd, J 15.7 and 8.4, 11-H_b), 2.17-1.34 and 1.02-0.82 (12H, m, 2-H_2, 3-H_2, 4-H_2, 8-H_2, 9-H_2, and 10-H_2), 1.27 (6H, q, *J* 7.0, 14-H_3 and 19-H_3); δ_C (100 MHz, $CDCl_3$) 172.7, 166.6, 151.0, 120.2, 65.5, 60.3, 59.7, 48.8; 48.4, 41.9, 35.0, 33.3, 32.7, 29.6, 22.5, 21.8, 14.3; *m/z* (ES) 324 (M+1, 100%), 346 (1); HMRS: found: 324.2159. $C_{18}H_{30}NO_4$ ($M+H^+$) Requires 324.2169.

Ethyl 2-[(5*R,8a*S**,8b*R**)-6-oxo-2,3,4,6,8a,9,810,11-octahydro-1*H*-cyclopenta[i]quinolizin-4-yl]acetate 15**



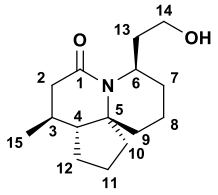
To a solution of conjugated ester **14** (328 mg, 1.01 mmol) in toluene (90 mL) was added acetic acid (87 µL, 1.52 mmol). The reaction mixture was heated to reflux for 12 h. After evaporation *in vacuo*, the residue was purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to afford the conjugated lactam **15** (204 mg, 73%) as yellow crystals: m.p. 88-89 °C (Found: C, 69.03; H, 8.37; N, 4.88. $C_{16}H_{24}NO_3$ Requires C, 69.29; H, 8.36;, N, 5.05%); IR ν_{max} (thin film)/cm^{-1} 1727, 1663, 1601, 1430, 1180; δ_H (300 MHz, $CDCl_3$) 6.21 (1H, dd, *J* 9.9 and 3.0, 3-H), 5.83 (1H, dd, *J* 9.9 and 2.3, 2-H), 4.55-4.52 (1H, m, 6-H), 4.15 (2H, q, *J* 7.1, 15-H_2), 2.96 (1H, dd, *J* 15.3 and 5.2, 13-H_a), 2.60 (1H, dd, *J* 15.3 and 9.3, 13-H_b), 2.48-2.38 (1H, m, 4-H), 2.10-1.50 (12H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 and 12-H_2), 1.26 (3H, t, *J* 7.1, 16-H_3); δ_C (100 MHz, $CDCl_3$) 171.8, 163.4, 142.2, 124.1, 65.5, 60.3, 48.1, 46.9, 39.0, 36.7, 32.8, 30.9, 24.5, 22.6, 16.1, 14.2; *m/z* (ES) 300 (M+23, 100%), 278 (35); HMRS: found: 278.1754. $C_{16}H_{24}NO_3$ (M+H$^+$) Requires 278.1751.

Ethyl 2-[(4*R,8*S**,8a*R**,11a*S**)-8-methyl-6-oxodecahydro-1*H*-cyclopenta[i]quinolizin-4-yl]acetate 16**



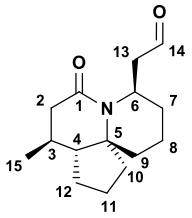
A suspension of copper iodide (358 mg, 1.88 mmol) in dry tetrahydrofuran (13 mL) was cooled to -78 °C. Methyllithium (1.6 M in diethyl ether, 3 mL, 3.76 mmol) was added dropwise. The reaction mixture was warmed to 0 °C, stirred for 30 min then cooled to -78 °C. A solution of conjugated lactam **15** (87 mg, 0.31 mmol), trimethylsilylchloride (0.64 mL, 5.01 mmol) and triethylamine (0.70 mL, 5.01 mmol) in dry tetrahydrofuran (13 mL) was added. The reaction mixture was stirred for 5 h then warmed to room temperature over 1 h by removing the dry ice from the cooling bath. Saturated aqueous ammonium chloride (20 mL) was added and the aqueous layer was extracted with ethyl acetate (2×70 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography over silica gel (eluting with 7:3 to 4:6 petroleum ether/ethyl acetate) afforded methylated lactam **16** (66 mg, 67%) as a pale yellow oil: IR ν_{max} (thin film)/cm^{-1} 1725, 1631, 1180; δ_H (400 MHz, $CDCl_3$) 4.13 (2H, q, *J* 7.1,15-H_2), 3.85-3.72 (1H, m, 6-H), 3.23 (1H, dd, *J* 16.5 and 6.0, 13-H_a), 2.86 (1H, dd, *J* 16.5 and 8.1, 13-H_b), 2.39-2.28 (2H, m, 2-H_a and one H of 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 or 12-H_2), 2.04-1.95 (1H, m, one of 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 or 12-H_2), 1.88 (1H, dd, *J* 17.2 and 11.6, 2-H_b), 1.83-1.52 and 1.50-1.28 (12H, m, 3-H, 4-H and ten of 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 or 12-H_2), 1.22 (3H, t, *J* 7.1, 16-H_3), 0.89 (3H, d, *J* 6.5, 17-H_3); δ_C (100 MHz, $CDCl_3$) 173.9, 172.6, 68.9, 60.2, 53.5, 53.0, 41.4, 39.0, 38.2, 36.0, 31.5, 30.4, 27.7, 23.2, 20.9, 19.2, 14.2; *m/z* (ES) 316 (M+23, 100%), 294 (26); HMRS: found: 316.1883. $C_{17}H_{27}NaNO_3$ (M+Na$^+$) Requires 316.1883

(4*R,8*S**,8a*R**,11a*S**)-4-(2-hydroxyethyl)-8-methyloctahydro-1*H*-cyclopenta[i]quinolizin-6(2*H*)-one 17**



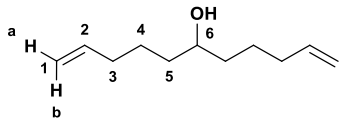
A solution of ester **16** (43 mg, 0.15 mmol) in dry tetrahydrofuran (12 mL) was cooled to 0 ºC and lithium borohydride (2.0 M in tetrahydrofuran, 300 µL, 0.58 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight, upon which acetone (12 mL) was added. The reaction mixture was stirred for 1 h and concentrated *in vacuo*. The residue was dissolved in water (20 mL) and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic phases were dried over magnesium sulfate and evaporated. The yellow oil obtained was purified by flash column chromatography over silica gel (eluting with ethyl acetate) to afford the product (28 mg, 76%) as a colourless oil: IR ν_{max} (thin film)/cm^{-1} 3374, 1610, 1434; δ_H (400 MHz, $CDCl_3$) 4.22-4.03 (1H, m, 6-H), 3.65-3.53 (2H, m, 14-H_2), 2.45 (1H, dd, *J* 16.8 and 4.7, 2-H_a), 2.25-2.15 (1H, m, one of 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2 or 13-H_2), 2.15-1.68 and 1.60-1.40 (16H, m, 2-H_b, 3-H, 4-H, and thirteen of 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2 and 13-H_2), 0.96 (3H, d, *J* 6.8, 15-H_3); δ_C (100 MHz, $CDCl_3$) 172.7, 66.7, 59.8, 52.0, 49.6, 39.1, 38.5, 31.5, 37.8, 34.7, 30.4, 25.9, 22.7, 16.7, 20.1; *m/z* (ES) 274 (M+23, 100%), 252 (10); HMRS: found: 274.1776. $C_{15}H_{25}NNaO_2$ (M+Na$^+$) Requires 274.1778

2-((4*R,8*S**,8a*R**,11a*S**)-8-methyl-6-oxodecahydro-1*H*-cyclopenta[i]quinolizin-4-yl)acetaldehyde 1**



Method A:
To a solution of alcohol **17** (29 mg, 0.11 mmol) in dimethylsulfoxide, were added triethylamine (220 µL, 1.73 mmol) and sulfur trioxide pyridine complex (184 mg, 1.15 mmol). The reaction mixture was stirred at room temperature overnight then quenched with water (5 mL). The aqueous phase was extracted dichloromethane (3×5 mL) then the organic phases were washed with saturated aqueous sodium hydrogen carbonate (2×10 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography over silica gel (eluting with 1:2 petroleum ether/ethyl acetate) afforded aldehyde **1** (11 mg, 38%) as white solid.

Method B:
A solution of ester **16** (13 mg, 0.044 mmol) in dry dichloromethane (4 mL) was cooled to -78 °C and diisobutylaluminium hydride (1.5 M in toluene, 33 µL, 0.049 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 30 minutes then quenched with methanol (2 mL) and saturated aqueous Rochelle's salt solution (5 mL). The aqueous phase was extracted with dichloromethane (3×5 mL) and the organic phases were dried over sodium sulfate. Purification by flash column chromatography over silica gel (eluting with 1:2 petroleum ether/ethyl acetate) gave aldehyde **1** (9 mg, 82%) as a white solid: m.p. 72-80 °C; IR ν_{max} (thin film)/cm^{-1} 1720, 1627; δ_H (300 MHz, $CDCl_3$) 9.73 (1H, s, 14-H), 3.92-3.81 (1H, m, 6-H), 3.45 (1H, ddd, *J* 17.3, 7.2 and 1.1, 13-H_a), 2.84 (1 H, ddd, *J* 17.3, 6.8 and 1.1, 13-H_b), 2.39-2.26 and 2.07-1.22 (16H, m, 2-H_2, 3-H, 4-H, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, and 12-H_2), 0.91 (3H, d, *J* 6.6, 15-H_3); δ_C (75 MHz, $CDCl_3$) 200.3, 173.6, 69.0, 53.5, 51.1, 48.2, 41.3, 38.1, 35.7, 31.1, 30.0, 28.6, 23.0, 20.9, 19.2; *m/z* (ES) 272 (M+23, 100%), 250 (58); HMRS: found: 272.1620. $C_{15}H_{23}NNaO_2$ (M+Na$^+$) Requires 272.1621.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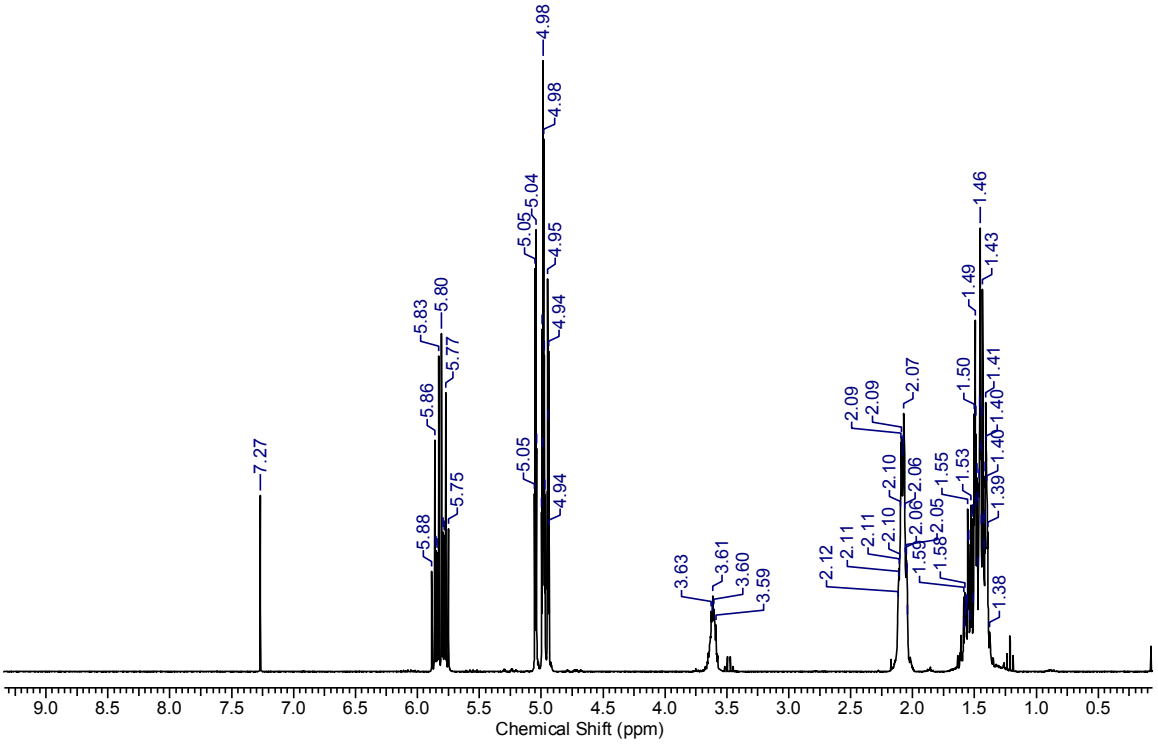
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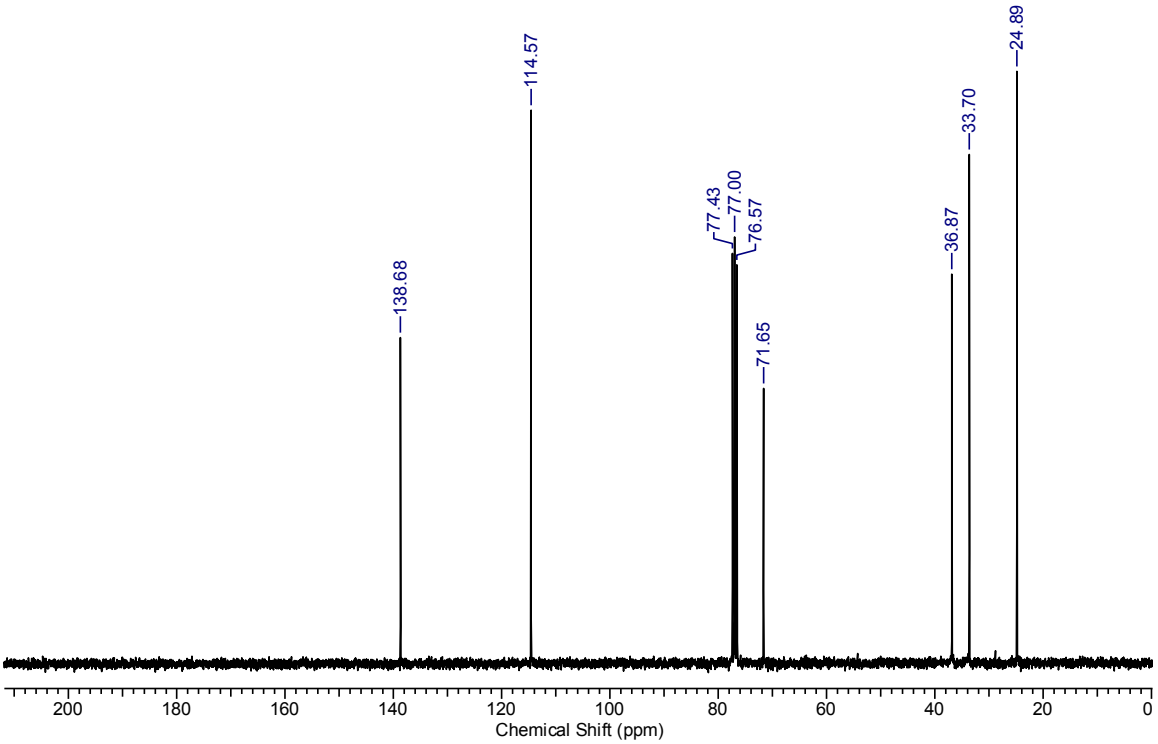
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Chemical Shift (ppm)