Title: Total Synthesis of the Cytotoxic Guaipyridine Sesquiterpene Alkaloid (+)-Cananodine
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Experimental, spectroscopic and other physical data for compounds 1, 4–13

(R)-5-Methylhept-6-enenitrile (9)

Into a stirred solution of (R)-(−)-β-citronellene (18.2 mL, 13.8 g, 100 mmol, 1.00 equiv.) in CH2Cl2 (100 mL) was bubbled ozone (105 min), then oxygen (5 min) and finally nitrogen (10 min). The solution was warmed to 0 °C and a solution of NaBH4 (7.98 g, 211 mmol, 2.11 equiv.) in distilled water (35 mL) was added dropwise and the mixture was allowed warm to room temperature over 60 h with stirring. The mixture was added dropwise to aqueous HCl (2 M; 250 mL) at 0 °C, causing vigorous effervescence, and after stirring for 3 h the mixture was filtered to remove a colourless solid and the liquid layers were separated. The aqueous layer was extracted with CH2Cl2 (3 × 50 mL) and the combined organic layers were dried (Na2SO4) and concentrated under reduced pressure to give (R)-4-methylhex-5-en-1-ol (11.9 g, >99%) as a yellow oil with some colourless precipitate. The crude product (identified by 1H NMR) was used directly in the next step without further purification; Rf 0.10 (20% Et2O–petrol); δH (300 MHz) 5.71 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H, CH alkene), 5.01-4.93 (m, 2H, CH2 alkene), 3.65 (t, J = 6.5 Hz, 2H, OCH2), 2.20-2.11 (m, 1H, CH(CH3)), 1.58-1.51 (m, 2H, HOCH2CH3), 1.41-1.33 (m, 2H, HO(CH2)2CH3), 1.02 (d, J = 6.5 Hz, 3H, CH3).

To a stirred solution of crude (R)-4-methylhex-5-en-1-ol prepared as described above (11.9 g, < 100 mmol, 1.00 equiv.) and DMAP (0.122 g, 1.00 mmol, 0.01 equiv.) in anhydrous CH2Cl2 (150 mL) under nitrogen at 0 °C, was added dry triethylamine (15.3 mL, 11.1 g, 110 mmol, 1.10 equiv.). After 10 min, a solution of 4-tolylsulfonyl chloride (17.2 g, 90.0 mmol, 0.90 equiv.) in anhydrous CH2Cl2 (50 mL) was added over 10 min. The solution was allowed to warm to room temperature over 14 h with stirring and was washed with saturated aqueous NH4Cl (200 mL), H2O (200 mL) and brine (200 mL) and dried (Na2SO4). Concentration under reduced pressure and chromatography (5% Et2O–petrol) (R)-4-methylhex-5-enyl tolyl-4-sulfonate (10.2 g, 38% over 2 steps) as a colourless oil; Rf 0.31 (20% Et2O–petrol); δH (300 MHz) 7.81 (d, J = 8.0 Hz, 2H, ortho tolyl), 7.36 (d, J = 8.0 Hz, 2H, meta tolyl), 5.60 (ddd, J = 17.5, 9.5, 8.0 Hz, 1H, CH alkene), 4.95-4.90 (m, 2H, CH(CH3)), 4.03 (t, J = 6.5 Hz, 2H, OCH2), 2.47 (s, 3H, Me tolyl), 2.08-2.02 (m, 1H, CH(CH3)), 1.70-1.61 (m, 2H, OCH2CH2), 1.34-1.29 (m, 2H, O(CH2)2CH2), 0.97 (d, J = 6.5 Hz, 3H, Me); δC (75 MHz) 144.7, 143.4, 133.2, 129.8, 127.9, 113.3, 70.8, 37.3, 32.1, 26.7, 21.6, 20.2.
To a solution of ($R$)-4-methylhex-5-enyl tolyl-4-sulfonate (16.7 g, 62.5 mmol, 1.0 equiv.) in DMSO (1.00 L) was added KCN (4.47 g, 68.7 mmol, 1.1 equiv.) at room temperature with stirring. The mixture was allowed to stir for 18 h, over which time the colourless crystals of potassium cyanide gradually dissolved and the solution became pale yellow in colour. Water (1 L) was added to the solution, causing some heat to evolve, the aqueous layer was extracted with EtOAc (4 × 300 mL) and the combined organic layers washed with H2O (300 mL), dried (Na2SO4) and concentrated under reduced pressure to give the crude product (14.0 g) as a yellow liquid. Quantitative analysis by 1H NMR showed this to be a mixture of the desired product 14 (7.68 g, >99%; 38% over three steps from ($R$)-($-$)-β-citronellene) and DMSO; Rf 0.31 (20% Et2O–petrol); δH (300 MHz) 5.65 (ddd, J = 17.5, 10.0, 8.0 Hz, 1H, CH alkene), 4.99 (dd, J = 17.5, 0.5 Hz, 1H, CH2 alkene), 4.97 (dd, J = 10.0, 0.5 Hz, 1H, CH2 alkene), 2.34 (t, J = 6.0 Hz, 2H, NCCH2), 2.20-2.11 (m, 1H, CH(CH3)), 1.74-1.60 (m, 2H, NC(CH2)2CH2), 1.56-1.43 (m, 2H, NC(CH2)2CH2), 1.02 (d, J = 6.5 Hz, 3H, Me); δC (75 MHz) 143.5, 119.8, 113.6, 37.4, 35.4, 23.2, 20.3, 17.2; in agreement with spectroscopic data previously reported for the racemate.1

(S)-4-Isopropyl-3-((($R$)-5-methylhept-6-enoyl)oxazolidin-2-one (8)

![Chemical Structure](attachment:chemical.png)

To a solution of ($R$)-5-methylhept-6-enenitrile 9 (6.44 g, 52.3 mmol, 1 equiv.) in ethanol (235 mL) was added aqueous NaOH (10%; 60 mL) and the solution was heated to reflux for 16 h. The reaction mixture was allowed to cool and was concentrated under reduced pressure. The crude mixture was partitioned between Et2O (250 mL) and H2O (250 mL) and the organic layer dried (Na2SO4) and concentrated under reduced pressure to give unconsumed nitrile 14 (1.82 g) as a yellow liquid. The aqueous layer was acidified to pH 1 with aqueous HCl (2 M) and extracted with Et2O (4 × 50 mL) and the combined organic layers were dried (Na2SO4) and concentrated under reduced pressure to give ($R$)-5-methyl-6-heptenoic acid (6.18 g, 83%) as a yellow liquid; Rf 0.60 (50% EtOAc–petrol); δH (300 MHz) 5.69 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H, CH alkene), 4.98 (d, J = 17.5 Hz, 1H, CH2 alkene), 4.95 (d, J = 10.0 Hz, 1H, CH2 alkene), 2.36 (t, J = 7.5 Hz, 2H, CO2HCH2), 2.20-2.11 (m, 1H, CH(CH3)), 1.68-1.61 (m, 2H, CO2HCH2CH2), 1.39-1.32 (m, 2H, CO2H(CH2)2CH2), 1.01 (d, J = 6.5 Hz, 3H, Me); δC (75 MHz) 180.2, 144.2, 113.0, 37.6, 35.4, 23.2, 20.3, 17.2; in agreement with spectroscopic data previously reported for the racemate.1
(R)-5-Methyl-6-heptenoic acid (6.59 g, 46.3 mmol, 1 equiv.) was treated with thionyl chloride (8.29 g, 69.7 mmol, 1.5 equiv.), causing the solution to turn orange with heat being evolved. The mixture was heated under reflux (bath temperature 100 °C) for 1 h to give a dark brown liquid, and the remaining thionyl chloride was removed under reduced pressure. Distillation of the liquid residue yielded (R)-5-methyl-6-heptenoyl chloride (6.18 g, 83%) as a colourless oil; bp$_{0.1}$ 116–118 °C.

To a solution of (S)-4-isopropyloxazolidin-2-one (5.46 g, 42.3 mmol, 1.1 equiv.) in THF (100 mL) under nitrogen at −78 °C was added n-BuLi (2.17 M in hexanes; 19.5 mL, 42.3 mmol, 1.1 equiv.) causing a colourless precipitate to form. After stirring for 10 min, a solution of freshly distilled (R)-5-methyl-6-heptenoyl chloride (6.18 g, 38.5 mmol, 1.0 equiv.) in dry THF (20 mL + 2 x 5 mL rinses) under nitrogen at −78 °C was added dropwise. The reaction mixture was allowed to warm to room temperature over 12 h with stirring and the then quenched with saturated aqueous NH$_4$Cl (150 mL). The aqueous layer was extracted with Et$_2$O (3 x 100 mL) and the combined organic layers washed with aqueous NaOH (1 M; 100 mL), H$_2$O (100 mL) and brine (100 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to yield a yellow oil that was purified by chromatography (10%→20% EtOAc–petrol) to give (S)-4-isopropyl-3-((R)-5-methylhept-6-enoyl)oxazolidin-2-one 8 (7.75 g, 78%) as a colourless oil; R$_f$ 0.29 (20% EtOAc–petrol); [α]$_D$$_{24}^{24}$ +73.7 (c 6.0, CHCl$_3$). $\nu_{\text{max}}$ (film) 2954, 2929, 2885, 1734 (br, carbamate and amide carbonyls), 1471, 1464, 1363, 1255, 1178, 1097, 837, 779, 669 cm$^{-1}$; $\delta$$_H$ (400 MHz) 5.68 (ddd, $J$ = 17.5, 10.5, 7.5 Hz, 1H, CH alkene), [4.96 (ddd, $J$ = 17.0, 2.0, 1.0 Hz, 1H), and 4.93 (ddd, $J$ = 11.5, 2.0, 1.0 Hz, 1H), CH$_2$ alkene × 2], 4.43 (dt, $J$ = 8.5, 3.5 Hz, 1H, CHN), [4.26 (dd, $J$ = 9.0, 8.5 Hz, 1H), and 4.20 (dd, $J$ = 9.0, 3.0 Hz, 1H), CH$_2$O × 2], 2.43-2.33 (m, 1H, CH(CH$_3$)$_2$), 2.20-2.11 (m, 3H, COCH$_2$ and CHCH$_3$CH=CH$_2$), [1.67-1.62 (m, 2H) and 1.40-1.32 (m, 2H) COCH$_2$CH$_2$CH$_2$] 1.00 (d, $J$ = 7.0 Hz, 3H, CHCH$_3$CH=CH$_2$), [0.92 (d, $J$ = 7.0 Hz, 3H) and 0.88 (d, $J$ = 7.0 Hz, 3H) Me of isopropyl × 2]; $\delta$$_C$ (75 MHz) 173.3, 154.1, 144.3, 112.9, 63.3, 58.4, 37.7, 35.9, 35.6, 28.4, 22.2, 20.2, 18.0 14.7; $m/z$ (CI) 271 [M+NH$_4$]$^+$, 254 [MH]$^+$, 184, 171, 130, 124, 84, 49 (Found: [MH]$^+$, 254.1750. C$_{14}$H$_{23}$NO$_3$ requires [MH]$^+$, 254.1756).
(2-(Bromomethyl)allyloxy)(tert-butyl)diphenylsilane (12)

\[
\text{OH} \quad \text{OH} \quad \text{TBDPSO} \quad \text{OH} \quad \text{TBDPSO} \quad \text{OMs} \quad \text{TBDPSO} \quad \text{Br}
\]

To NaH (~60% dispersion in mineral oil, 2.28 g, 57.1 mmol, 1.0 equiv.) was added slowly by cannula a solution of 2-methylene-1,3-propanediol (5.03g, 57.1 mmol, 1.0 equiv.) in dry THF (44 mL) at 0 °C. After stirring for 70 min at room temperature under nitrogen, the solution was cooled to 0 °C and TBDPSCl (14.9 g, 14.1 mL, 54.2 mmol, 0.95 equiv.) was added over 2 min, turning the solution cloudy. The reaction mixture was stirred for 16 h at room temperature, the solvent was evaporated and the white pasty residue was dissolved in a mixture of H₂O (50 mL) and Et₂O (50 mL). The aqueous layer was extracted with Et₂O (3 × 50 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a cloudy, colourless oil. Chromatography (10% EtOAc–petrol) gave 2-((tert-butyldiphenylsilyloxy)methyl)prop-2-en-1-ol (15.7 g, 98%) as a colourless oil; Rf 0.28 (20% EtOAc–petrol); νmax (film) 3329, 3072, 3049, 2958, 2931, 2891, 2858, 1892, 1471, 1462, 1427, 1390, 1111, 1070, 908, 825, 741, 702, 615 cm⁻¹; δH (300 MHz), 7.70 (d, J = 7.0 Hz, 4H, ortho phenyl), 7.46-7.38 (m, 6H, meta and para phenyl), [5.18 (app. s, 1H), and 5.14 (app. s, 1H), CH₂ alkene × 2], [4.28 (s, 1H), and 4.20 (s, 1H), CH₂ × 2], 1.80 (br, 1H, OH), 0.93 (s, 9H, Me tBu); δC (75 MHz) 147.3, 135.5, 133.3, 129.8, 127.7, 111.0, 65.0, 64.5, 26.8, 19.2; m/z (CI) 372, 355, 344 [M+NH₄⁺], 327 [MH⁺], 316, 274, 247, 216, 196, 136 (Found: [M+NH₄⁺], 327.1785. C₂₀H₂₆O₂Si requires [MH⁺], 327.1780) (Found: C, 73.67; H, 7.97. C₂₀H₂₆O₂Si requires C, 73.57; H, 8.03%).

To a stirred solution of crude 2-((tert-butyldiphenylsilyloxy)methyl)prop-2-en-1-ol (0.100 g, 0.307 mmol, 1.00 equiv.) and DMAP (4 mg, 0.031 mmol, 0.10 equiv.) in anhydrous CH₂Cl₂ (1 mL) under nitrogen at 0 °C was added dry triethylamine (34 mg, 0.047 mL, 0.338 mmol, 1.10 equiv.). After 5 min, methanesulfonyl chloride (33 mg, 0.023 mL, 0.292 mmol, 0.95 equiv.) was added. The solution was stirred for 2.25 h at room temperature, washed with saturated aqueous NH₄Cl (1 mL) and the aqueous layer was extracted with Et₂O (3 × 1 mL). The combined organic layers were dried (Na₂SO₄), concentrated under reduced pressure and purified by chromatography (20% EtOAc–petrol) to give 2-((tert-butyldiphenylsilyloxy)methyl)allyl methanesulfonate (0.130 g, 100%) as a colourless, crystalline solid; mp 34–36 °C (EtOAc); Rf 0.30 (20% EtOAc–petrol); νmax (film) 3419, 1254, 1198, 1078, 1061 cm⁻¹; δH (300 MHz) 7.68 (d, J = 7.0 Hz, 4H, ortho phenyl), 7.47-7.39 (m, 6H, meta and para phenyl), [5.43 (app. s, 1H), and 5.33 (app. s, 1H), CH₂ alkene × 2], [4.77 (s, 1H), and 4.26 (s, 1H), CH₂ × 2], 2.94 (s, 3H, OSO₂CH₃), 1.09 (s, 9H, Me tBu); δC (75 MHz) 141.1, 135.5, 133.1, 129.9, 127.8, 116.1, 70.0, 64.0, 37.9, 26.8, 19.2; m/z (CI) 422 [M+NH₄⁺], 405 [MH⁺],...
362, 214, 196 (Found: [MH]$^+$, 405.1543. C$_{21}$H$_{28}$O$_4$SSi requires [MH]$^+$, 405.1556) (Found: C, 62.49; H, 7.13. C$_{21}$H$_{28}$O$_4$SSi requires C, 62.34; H, 6.98%).

To a solution of 2-((tert-butyldiphenylsilyloxy)methyl)allyl methanesulfonate (1.67 g, 4.13 mmol, 1 equiv.) in Et$_2$O (20 mL) at room temperature was added LiBr (0.538 g, 6.20 mmol, 1.5 equiv.), turning the solution cloudy. After stirring for 22 h, the colourless emulsion was washed with brine (20 mL) and extracted with Et$_2$O (20 mL). The combined organic layers were dried (Na$_2$SO$_4$), concentrated under reduced pressure and purified by chromatography (20% EtOAc–petrol) to give (2-(bromomethyl)allyloxy)((tert-butyldiphenylsilyloxy)methyl)diphenylsilane 12 (1.52 g, 95%) as a colourless oil; R$_f$ 0.67 (20% EtOAc–petrol); $\nu_{\text{max}}$ (film) 3070, 3049, 2958, 2931, 2856, 1471, 1459, 1427, 1209, 1111, 825, 741, 702 cm$^{-1}$; $\delta_{\text{H}}$ (300 MHz) 7.70 (d, $J = 7.0$ Hz, 4H, ortho phenyl), 7.46-7.39 (m, 6H, meta and para phenyl), 5.33 (app. s, 1H), and 5.31 (app. s, 1H), CH$_2$ alkene × 2), [4.32 (s, 1H), and 4.05 (s, 1H), CH$_2$ × 2, 1.09 (s, 9H, Me tBu); $\delta_{\text{C}}$ (75 MHz) 144.4, 135.5, 133.3, 129.8, 127.8, 115.0, 64.2, 32.8, 26.8, 19.3; m/z (CI) 408 [M+NH$_4$]$^+$, 406 [M+NH$_4$]$^+$, 391 [MH]$^+$, 389 [MH]$^+$, 362, 328, 268, 256, 248, 196, 155, 129, 108, 91 (Found: [MH]$^+$, 391.0926. C$_{20}$H$_{25}$BrOSi requires [MH]$^+$, 391.0912) (Found: C, 61.83; H, 6.48. BrC$_{20}$H$_{25}$BrOSi requires C, 61.69; H, 6.47%).

(S)-3-((2R,5R)-2-((tert-butyldiphenylsilyloxy)methyl)allyl)-5-methylhept-6-enoyl-4-isopropyloxazolidin-2-one (10)

To a solution of oxazolidinone 8 (5.17 g, 20.4 mmol, 1.00 equiv.) in dry THF (100 mL) at –78 °C under nitrogen was slowly added NaHMDS (1 M in THF; 24.5 mL, 24.5 mmol, 1.20 equiv.), turning the solution orange. The solution was stirred at this temperature for 40 min and to this mixture was added dropwise by syringe a solution of bromide 12 (31.4 g, 80.8 mmol, 3.96 equiv.) in dry THF (50 mL + 20 mL rinse) pre-cooled to –78 °C. The reaction mixture was warmed to –50 °C and stirred at this temperature for 16 h. Saturated aqueous NaHCO$_3$ (100 mL) was added and the layers were separated. The aqueous layer was extracted with Et$_2$O (3 × 100 mL) and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a yellow oil which was purified by chromatography (5%→20% EtOAc–petrol) to give unreacted bromide 12 (13.8 g, 44%) and (S)-3-((2R,5R)-2-((tert-butyldiphenylsilyloxy)methyl)allyl)-5-methylhept-6-
(S)-3-((1R,5R)-3-((tert-Butyldiphenylsilyloxy)methyl)-5-methylcyclohept-3-enecarbonyl)-4-isopropyloxazolidin-2-one (11)

To a solution of 1,7-diene 10 (0.100 g, 0.178 mmol, 1.00 equiv.) in dry CH₂Cl₂ (80 mL) under nitrogen was added Grubbs’ catalyst (second generation (IMES); 7.6 mg, 0.0089 mmol, 0.05 equiv.). The solution was stirred under reflux for 3.5 h and the solvent removed under reduced pressure to give a brown oil. Purification by column chromatography (5%→20% EtOAc–petrol) gave (S)-3-((1R,5R)-3-((tert-butyldiphenylsilyloxy)methyl)-5-methylcyclohept-3-enecarbonyl)-4-isopropyloxazolidin-2-one 11 (0.095 g, >99%) as a colourless oil; [α]₂¹D +19.2 (c 3.6, CHCl₃); Rf 0.43 (20% EtOAc–petrol); νmax (film) 2960, 2929, 2856, 1780 (carbamate carbonyl), 1699 (amide carbonyl), 1427, 1387, 1363, 1234, 1203, 1111, 1059, 704 cm⁻¹; δH (400 MHz) 7.69 (d, J = 6.0 Hz, 4H, ortho phenyl), 7.42-7.39 (m, J = 6.0 Hz, 6H, meta and para phenyl), 5.54 (s, 1H, CH alkene), 4.32 (ddd, J = 8.0, 4.0, 3.5 Hz, 1H, NCH), [4.17 (dd, J = 9.0, 8.5 Hz 1H), and 4.10 (dd, J = 9.0, 3.0 Hz, 1H), OCH₂ of oxazolidinone × 2], 4.03 (s, 2H, OCH₂), 3.40 (t, J = 11.0 Hz, 1H, COCH), 2.35-2.22 (m, 2H, CH), [2.13 (d, J = 15.0 Hz, 1H), 2.03-1.98 (m, 1H), 1.75-1.64 (m, 1H), 1.56-1.52 (m, 1H), and 1.23-1.16 (m, 2H), CH₂ × 5], 0.97-0.95 (12H, m, Me and tBu), [0.82 (d, J = 7.0 Hz, 3H),
and 0.76 (d, J = 7.0 Hz, 3H), Me of isopropyl × 2]; δC (75 MHz) 176.7, 153.5, 138.2, 135.5, 134.2, 129.6, 127.6, 68.2, 63.1, 58.4, 41.1, 34.5, 34.2, 33.5, 32.4, 28.4, 26.8, 23.4, 19.2, 18.0, 14.8; m/z (CI) 551 [M+NH4]⁺, 534 [MH]⁺, 476, 419, 391, 311, 302, 283, 274, 224, 216, 196, 147, 130 (Found: [MH]⁺, 534.3050. C32H43NO4Si requires [MH]⁺, 534.3040).

(S)-3-((2R,5R)-2-(2-(Hydroxymethyl)allyl)-5-methylhept-6-enoyl)-4-isopropyloxazolidin-2-one (7)

To a solution of silyl ether 10 (0.500 g, 0.890 mmol, 1 equiv.) in MeOH (32 mL) was added conc. HCl (1.26 mL) dropwise with stirring, causing the solution to turn pale yellow. After stirring for 16 h at room temperature, the solution was neutralised with aqueous NaHCO3 (2 M) and H2O (50 mL). The reaction mixture was extracted with Et2O (3 × 50 mL) and the combined organic layers were dried (Na2SO4) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (25%→33% EtOAc–petrol) gave (S)-3-((2R,5R)-2-(2-(hydroxymethyl)allyl)-5-methylhept-6-enoyl)-4-isopropyloxazolidin-2-one 7 (0.253 g, 88%) as a colourless oil; [α]D 21.0 (c 0.44, CHCl3); Rf 0.43 (33% EtOAc–petrol); νmax (film) 3480 (OH), 2962, 2927, 2871, 1778 (carbamate carbonyl), 1699 (amide carbonyl), 1454, 1387, 1300, 1230, 1201, 1057, 1022, 910 cm⁻¹; δH (300 MHz) 5.66 (ddd, J = 17.5, 9.5, 8.0 Hz, 1H, CH alkene), 4.99 (s, 1H, CH 2 alkene), 4.94-4.91 (m, 3H, CH 2 alkene), 4.49-4.47 (m, 1H, NCH), 4.31-4.21 (m, 2H, OCH 2 of oxazolidinone), 4.18-3.99 (m, 2H, CH 2 alkene), 4.49-4.47 (m, 1H, NCH), 4.31-4.21 (m, 2H, OCH 2 of oxazolidinone), 4.18-3.99 (m, 2H, HOCH 2), 3.68 (s, 1H, COCH 2), 2.61-2.54 (m, 1H), 2.40-2.28 (m, 1H), 2.25-2.18 (m, 1H), 2.12-2.06 (m, 2H), 1.53-1.44 (m, 1H), and 1.29-1.28 (m, 3H, CH2, CH and OH × 9), 0.99 (d, J = 6.5 Hz, 3H, Me), [0.93 (d, J = 7.0 Hz, 3H), and 0.86 (d, J = 7.0 Hz, 3H), Me of isopropyl × 2]; δC (75 MHz) 176.2, 152.9, 146.3, 144.2, 112.9, 112.4, 65.7, 63.2, 58.9, 41.5, 37.9, 36.1, 33.9, 30.4, 28.4, 20.1, 18.0, 14.8; m/z (CI) 341 [M+NH4]⁺, 324 [MH]⁺, 212, 195, 147, 130 (Found: [MH]⁺, 324.2183. C18H29NO4 requires [MH]⁺, 324.2175) (Found: C, 66.79; H, 8.80; N, 4.31. C18H29NO4 requires C, 66.84; H, 9.04; N, 4.33%).
(S)-3-((1R,5R)-3-(Hydroxymethyl)-5-methylcyclohept-3-enecarbonyl)-4-isopropyl-oxazolidin-2-one (6)

To a solution of 1,7-diene 7 (0.248 g, 0.768 mmol, 1 equiv.) in dry CH₂Cl₂ (350 mL) at reflux under nitrogen was added Grubbs’ catalyst (second generation (IMES); 32.6 mg, 0.038 mmol, 0.05 equiv.). The solution was stirred at reflux for 3.5 h and concentrated under reduced pressure to give a brown oil. Purification by column chromatography (20% → 50% EtOAc–petrol) gave (S)-3-((1R,5R)-3-(hydroxymethyl)-5-methylcyclohept-3-enecarbonyl)-4-isopropyl-oxazolidin-2-one 6 (0.236 g, >99%) as a colourless oil; [α]D24 +66.7 (c 0.90, CHCl₃); Rf 0.33 (33% EtOAc–petrol); νmax (film) 3510 (OH), 2960, 2925, 2871, 2852, 1778 (carbamate carbonyl), 1780 (amide carbonyl), 1697 (amide carbonyl), 1560, 1438, 1363, 1300, 1234, 1201, 1093, 1058 cm⁻¹; δH (300 MHz) 5.61 (s, 1H, CH double bond), 4.44-4.42 (m, 1H, NCH), 4.31-4.21 (m, 2H, OCH₂ of oxazolidinone), 4.05 (s, 2H, OCH₂), 3.44 (t, J = 10.5 Hz, 1H, COCH), [2.48-2.25 (m, 4H), 2.09-1.84 (m, 2H), 1.68-1.64 (d, J = 5.0 Hz, 1H), and 1.30-1.26 (m, 2H), CH₂, CH and OH × 9], 1.10-1.07 (m, 3H, Me), 0.95-0.85 (m, 6H, Me of isopropyl); δC (75 MHz) 176.1, 153.9, 139.2, 136.5, 68.5, 63.5, 58.4, 41.1, 34.0, 33.7, 33.6, 33.4, 28.4, 23.2, 18.0, 14.9; m/z (CI) 313 [M+NH₄]⁺, 296 [MH]⁺, 278, 147, 130 (Found: [MH]⁺, 296.1870. C₁₆H₂₃NO₄ requires [MH]⁺, 296.1862) (Found: C, 66.06; H, 8.67; N, 4.38. C₁₆H₂₃NO₄ requires C, 66.21; H, 8.50; N, 4.54%).
To a solution of oxazolidinone 6 (0.148 g, 0.480 mmol, 1.00 equiv.) in dry MeOH (1.85 mL) at 0 °C under nitrogen was added MeONa (oven dried; 28 mg, 0.523 mmol, 1.09 equiv.) with stirring, causing the solution to turn pale yellow. After stirring for 30 min at 0 °C, saturated aqueous NH₄Cl (2 mL) and H₂O (50 mL). The reaction mixture was extracted with CH₂Cl₂ (3 × 5 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (20% EtOAc–petrol) gave (1R,5R)-methyl 3-(hydroxymethyl)-5-methylcyclohept-3-enecarboxylate (0.085 g, 89%) as a colourless oil; [α]D²¹ -30.8 (c 0.39, CHCl₃); Rf 0.46 (50% EtOAc–petrol); ν max (film) 3423 (OH), 2952, 2925, 2870, 2850, 1734 (ester carbonyl), 1454, 1437, 1380, 1323, 1284, 1244, 1223, 1194, 1097, 1022, 985 cm⁻¹; δH (300 MHz) 5.54 (s, 1H, CH alkene), 3.98 (s, 2H, OCH₂), 3.66 (3H, s, OMe), 2.37-2.16 (m, 4H, 2.00 (s, 1H), 1.65-1.60 (m, 1H), and 1.24-1.15 (m, 2H), CH₂, CH and OH × 8], 1.05 (d, J = 7.0 Hz, 3H, Me); δC (75 MHz) 176.7, 138.9, 135.3, 68.2, 51.7, 42.8, 34.1, 33.9, 33.5, 31.9, 30.0; m/z (CI) 216 [M+NH₄]+, 199 [MH]+, 181, 147, 133 (Found: [M+NH₄]+, 216.1600. C₁₁H₁₈O₃ requires [M+NH₄]+, 216.1600).

To a solution of (1R,5R)-methyl 3-(hydroxymethyl)-5-methylcyclohept-3-enecarboxylate (0.270 g, 1.36 mmol, 1.00 equiv.), 4-methyl-2-(4-tolylsulfonyl)-4-pentenoic acid (0.384 g, 1.43 mmol, 1.05 equiv.) and DMAP (~ 4 mg, catalytic) in dry CH₂Cl₂ (8.2 mL) under nitrogen at 0 °C was added dropwise N,N-diisopropylcarbodiimide (0.224 mL, 0.181 g, 1.43 mmol, 1.05 equiv.), causing a colourless precipitate to form. After stirring at 0 °C for 15 min followed by 18 h at room temperature, the solution was filtered, concentrated under reduced pressure and purified by chromatography (10%–25% EtOAc–petrol) to give (1R,5R)-methyl 5-methyl-3-((4-methyl-2-(tolyl-4-sulfonyl)pent-4-enoyloxy)methyl)cyclohept-3-enecarboxylate 5 (0.526 g, 86%) as a colourless oil; Rf 0.72 (50% EtOAc–petrol); ν max (film) 2952, 2927, 2871, 2854, 1738 (ester carbonyl), 1597, 1452, 1439, 1379, 1327, 1290, 1246, 1225, 1196, 1149, 1086, 816 cm⁻¹; δH (300 MHz) 7.76 (d, J = 8.0 Hz, 2H, ortho tolyl), 7.37 (d, J = 8.0 Hz, 2H, meta tolyl), 5.60 (s, 1H, CH alkene), 4.80 (app. s, 1H), and 4.69 (app. s, 1H), CH₂ alkene × 2], 4.47 (d, J = 11.0 Hz, 1H), and
4.36 (d, J = 11.0 Hz, 1H), OCH$_2$ × 2], 4.18-4.13 (m, 1H, TsC), 3.68 (s, 3H, OMe), 2.73-2.65 (m, 2H, TsCHCH$_2$), 2.48 (s, 3H, Me tolyl), [2.37-2.19 (m, 4H), and 1.82-1.78 (m, 1H, CH and CH$_2$ × 5), 1.72 (3H, s, Me allyl), 1.27-1.13 (m, 3H, CH and CH$_2$), 1.07 (d, J = 7.0 Hz, 3H, Me); δ$_C$ (75 MHz) 176.3, 165.6, 145.5, 140.4, 139.8, 133.9, 133.5, 129.9, 129.5, 113.7, 113.4, 71.5, 69.5, 51.7, 42.3, 34.8, 34.7, 34.2, 33.9, 33.6, 32.2, 32.1, 22.9, 21.8, 21.1; m/z (CI) 466 [M+NH$_4^+$], 412, 395, 377, 312, 241, 223, 214, 197, 181, 174, 156, 108 (Found: [M+NH$_4^+$], 466.2257. C$_{24}$H$_{32}$O$_6$S requires [M+NH$_4^+$], 466.2263).

(1R,4S,5R)-Methyl 5-methyl-4-(3-methyl-1-(tolyl-4-sulfonyl)but-3-enyl)-3-methylenecycloheptane carboxylate (4)

To a solution of ester 5 (80.4 mg, 0.179 mmol, 1 equiv.) in dry PhMe (0.9 mL) under nitrogen at room temperature was added KOAc (oven dried; ~4 mg, catalytic) and BSA (0.044 mL, 36.5 mg, 0.179 mmol, 1 equiv.). The colourless reaction mixture was heated to 160 °C for 10 min in a microwave reactor. Concentration under reduced pressure and purification by chromatography (25% Et$_2$O–petrol) gave a mixture of 1-methyl-4-(3-methylbut-3-enylsulfonyl)benzene (6.7 mg, 17%) and (1R,4S,5R)-methyl 5-methyl-4-(3-methyl-1-(tolyl-4-sulfonyl)but-3-enyl)-3-methylenecyclohexane carboxylate 4 (51.3 mg, 71%, 10:14 mixture of diastereoisomers) as a colourless oil; (diastereoisomer a): R$_f$ 0.29 (50% Et$_2$O–petrol); δ$_H$ (300 MHz) 7.74 (d, J = 8.0 Hz, 2H, ortho tolyl), 7.32 (d, J = 8.0 Hz, 2H, meta tolyl), [5.29 (app. s, 1H), and 5.23 (app. s, 1H), CH$_2$ ring-alkene × 2], [4.75 (app. s, 1H), and 4.70 (app. s, 1H), CH$_2$ chain-alkene × 2], 3.68 (s, 3H, OMe), 3.45 (t, J = 5.0 Hz, 1H, TsC), [2.62 (d, J = 13.0 Hz, 1H), and 2.54-2.29 (3H, m), CH$_2$ and CH × 4], 2.45 (s, 3H, Me tolyl), [2.19 (t, J = 12.0 Hz, 1H), 2.05-2.01 (m, 1H), and 1.70-1.09 (m, 5H), CH and CH$_2$ × 7], 1.39 (s, 3H, Me allyl), 1.05 (d, J = 6.5 Hz, 3H, CHCH$_3$); δ$_C$ (75 MHz) 176.3, 145.5, 140.5, 133.5, 129.9, 129.2, 121.3, 114.1, 64.4, 52.1, 50.4, 50.0, 37.3, 36.6, 34.9, 34.5, 33.3; (diastereoisomer b): R$_f$ 0.24 (50% Et$_2$O–petrol); δ$_H$ (300 MHz) 7.76 (d, J = 8.0 Hz, 2H, ortho tolyl), 7.35 (d, J = 8.0 Hz, 2H, meta tolyl), [5.19 (app. s, 1H), and 4.95 (app. s, 1H), CH$_2$ ring-alkene × 2], [4.85 (app. s, 1H), and 4.74 (app. s, 1H), CH$_2$ chain-alkene × 2], 3.68 (s, 3H, OMe), 3.42 (d, J = 11.0 Hz, 1H, TsC), 2.70-2.02 (m, 6H, CH$_2$ and CH), 2.45 (s, 3H, Me tolyl), 1.77-1.61 (m, 3H, CH$_2$ and CH), 1.40 (s, 3H, Me allyl), 1.35-1.22 (m, 2H, CH$_2$ and CH), 1.08 (d, J = 6.5 Hz, 3H, CHCH$_3$); δ$_C$ (75 MHz) 176.2, 144.4, 141.0, 140.3, 137.0, 133.9, 129.8, 9.3, 118.7,
(5R,8R)-Methyl 2,5-dimethyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-8-carboxylate (13)

Through a stirred solution of 1,6-diene 4 (0.090 g, 0.223 mmol, 1 equiv.) in a mixture of CH₂Cl₂ (6 mL) and MeOH (4 mL) at –78 °C was bubbled O₂ (2 min), then O₃/O₂ (25 min) until the solution turned blue, followed by O₂ (10 min). Triphenylphosphine (0.292 g, 1.12 mmol, 5 equiv.) was added and the solution was stirred for 48 h at room temperature. Ethanolic ammonia (2 M; 10 mL) was then added, and the resultant orange-yellow solution was stirred for 18 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography (25% EtOAc–petrol), dissolved in MeOH and purified by ion-exchange chromatography (SCX2 cartridge, resin-bound sulfonic acid; 0.0006 equiv., 1 g) and purified again by chromatography (25% EtOAc–petrol) to give (5R,8R)-methyl 2,5-dimethyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-8-carboxylate 13 (25.1 mg, 48%) as a colourless oil; [α]D²⁰⁻⁴⁴.0 (c 1.09, CHCl₃); Rf 0.51 (50% EtOAc–petrol); νmax (film) 2952, 2925, 2875, 2856, 1734 (ester carbonyl), 1676, 1458, 1437, 1313, 1290, 1252, 1225, 1190, 1165 cm⁻¹; δH (300 MHz) (α = back face and β = front face) 7.39 (d, J = 7.5 Hz, 1H, H-4), 7.00 (d, J = 7.5 Hz, 1H, H-3), 3.67 (s, 3H, OMe), 3.44-3.29 (m, 1H, CH₂-9α), 3.01-2.94 (m, 1H, H-5), 2.67-2.64 (m, 1H, CH₂-9β), 2.51 (s, 3H, C₂ Me), 2.20-2.08 (m, 1H, CH₂-7α), 2.01-1.96 (m, 1H, CH₂-6β), 1.81-1.57 (m, 3H, CH₂-6α, CH₂-7β and H-8), 1.35 (d, J = 7.0 Hz, 3H, C₅ Me); δC (75 MHz) 176.1, 158.8, 154.5, 137.9, 132.6, 121.3, 51.8, 42.1, 40.4, 35.0, 34.8, 33.8, 23.8, 20.4; m/z (CI) 234 [MH]⁺ (Found: [MH]⁺, 234.1497. C₁₄H₁₉NO₂ requires [MH]⁺, 234.1494) (Found: C, 72.20; H, 8.00; N, 6.00. C₁₄H₁₉NO₂ requires C, 72.07; H, 8.21; N, 6.00%).
2-((5R,8R)-2,5-Dimethyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)propan-2-ol (cananodine) (1)

To a stirred, colourless solution of ester 13 (14.5 mg, 0.0622 mmol, 1 equiv.) in dry THF (0.5 mL) at 0 °C under nitrogen was added MeMgBr (3 M in Et₂O; 0.104 mL, 0.311 mmol, 5 equiv.), turning the solution light yellow. The solution was stirred at 0 °C for 2.5 h and quenched by the addition of saturated aqueous NH₄Cl (1 mL). The mixture was extracted with CH₂Cl₂ (5 × 1 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography (5% MeOH–CH₂Cl₂) gave 2-((5R,8R)-2,5-dimethyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)propan-2-ol (cananodine) 1 (14 mg, 97%) as a pale yellow oil; [α]D²¹ +17.9 (c 1.34, CHCl₃); Rf 0.23 (25% EtOAc–petrol); νmax (film) 3384 (OH), 2966, 2924, 2875, 1591, 1577, 1462, 1396, 1377, 1211, 1165, 1142, 820, 808 cm⁻¹; δH (300 MHz) (α = back face and β = front face) 7.34 (d, J = 8.0 Hz, 1H, H-4), 6.93 (d, J = 8.0 Hz, 1H, H-3), 3.23 (dt, J = 13.5, 1.5 Hz, 1H, CH₂-9α), 2.97 (m, J = 7.0 Hz, 1H, H-5), 2.87 (dd, J = 13.5, 10.5 Hz, 1H, CH₂-9β), 2.49 (s, 3H, Me-2), 2.12-2.07 (m, 1H, CH₂-7α), 1.92-1.87 (m, 1H, CH₂-6β), 1.59 (1H, qd, J = 12.0, 3.5 Hz, H-8), 1.31 (d, J = 7.0 Hz, 3H, Me-5), [1.25 (s, 3H), and 1.24 (s, 3H), CH(CH₃)₂OH × 2]; δC (75 MHz) 160.9, 154.2, 138.0, 132.5, 120.7, 73.3, 48.0, 39.4, 36.2, 35.2, 32.8, 27.9, 25.6, 23.7, 20.7; m/z (CI) 234 [MH]+, 212 (Found: [MH]+, 234.1862. C₁₅H₂₃NO requires [MH]+, 234.1858).

Reference for Supporting Information