

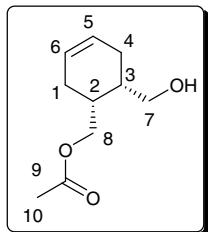
The first synthesis of the ABC-ring system of ‘upenamide

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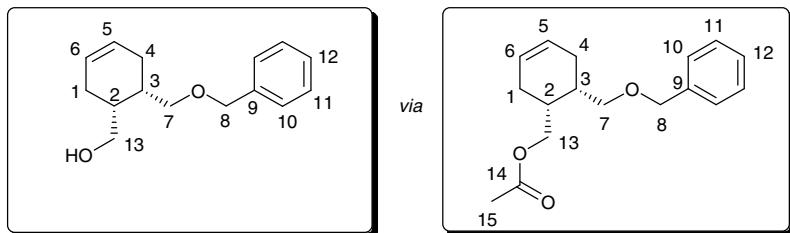
Representative Experimental Procedures and Supplementary Data

Acetic acid (1*R*,6*S*)-6-hydroxymethyl-cyclohex-3-enylmethyl ester (*-*)-5.



To a stirred emulsion of diacetate **7** (21.0 g, 92.8 mmol) in phosphate buffer (200 mL, pH 7) at rt was added *porcine pancreatic lipase* (PPL, Sigma Type II, 100-400 units/mg, 2.00 g). As the reaction proceeded, the pH was kept constant by the addition of NaOH (1 M) from an autoburette (pH set to 7.00). After 24 h, approximately 80 mL of NaOH solution had been added (ca. 80% conversion) and the reaction had stopped. The reaction was then filtered through a pad of Celite® and the solids were washed with Et₂O (200 mL). The filtrate was extracted with Et₂O (3 x 100 mL) and the combined organic layers were dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude oil purified by column chromatography (eluting with 5-80% EtOAc/*iso*-hexane) to furnish alcohol (*-*)-**5** as a colourless oil (13.5 g, 79%); *R*_f 0.16 (30% EtOAc/PE); [α]_D -20.5 (c 2.2, CHCl₃) (Lit.⁴ -19.0 (c 4.0, CHCl₃); δ_H (400 MHz, CDCl₃) 5.68-5.62 (2 H, m, H-5, H-6), 4.20 (1 H, dd, *J* 11.0, 6.0 Hz, H-8_a), 3.96 (1 H, dd, *J*, 11.0, 7.5 Hz, H-8_b), 3.72-3.57 (2 H, m, H-7), 2.29-2.08 (4 H, m, H-1_a, H-2, H-3, H-4_a), 2.07 (3 H, s, H-9), 2.01-1.72 (3 H, m, H-1_b, H-4_b, OH). ¹H-NMR data were consistent with those published.¹

((1*R*,6*S*)-6-Benzylxymethyl-cyclohex-3-enyl)-methanol (+)-9.

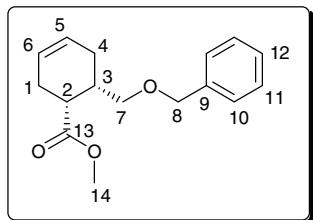


(a) To a stirred solution of alcohol (*-*)-**5** (3.00 g, 16.3 mmol) in α,α,α-trifluorotoluene (40 mL) was added magnesium oxide (1.31 g, 32.6 mmol) and 2-benzylxoy-N-methylpyridinium triflate **8** (16.5 g, 48.9 mmol). The resulting slurry was stirred at 83 °C for 21 h. The reaction was then filtered through Celite® and the solids were washed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure and the crude oil purified by column chromatography (eluting with 2-20% EtOAc/PE) to furnish the intermediate *benzyl ether* as a colourless

oil (4.29 g, 96%); R_f 0.52 (30% EtOAc/PE); $[\alpha]_D +11.1$ (c 1.2, CHCl₃); IR (neat) 3027, 2900, 2847 (C-H_{stretch}), 1739 (C=O_{stretch}); δ_H (400 MHz, CDCl₃) 7.38-7.28 (5 H, m, H-10, H-11, H-12), 5.67-5.60 (2 H, m, H-5, H-6), 4.51 (2 H, s, H-8), 4.11 (1 H, dd, J 11.0, 5.5 Hz, H-7_a), 4.01 (1 H, dd, J 11.0, 8.0 Hz, H-7_b), 3.50 (1 H, dd, J 9.0, 6.5 Hz, H-13_a), 3.41 (1 H, dd, J 9.0, 7.0 Hz, H-13_b), 2.28-1.91 (9 H, m, H-1, H-2, H-3, H-4, H-15); δ_C (100 MHz, CDCl₃) 171.9 (C-14), 138.9 (C-Ar_{quat}), 128.8 (C-Ar), 127.9 (C-Ar), 126.1 (C-5/C-6), 125.4 (C-6/C-5), 73.3 (C-8), 71.3 (C-13), 65.3 (C-7), 34.7 (C-2/C-3), 33.6 (C-3/C-2), 26.63 (C-1/C-4), 26.61 (C-4/C-1), 20.9 (C-15); m/z (Cl) 275 (16), 215 (79) [MH]⁺; HRMS (Cl) calcd. For C₁₇H₂₃O₃, 275.1647. Found: [MH]⁺, 275.1648 (-0.2 ppm error)].

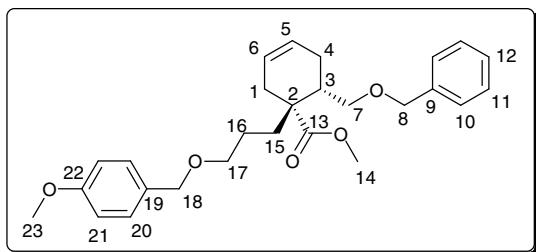
(b) To a stirred solution of the intermediate benzyl ether (3.97 g, 14.5 mmol) in MeOH (60 mL) and water (30 mL) at 0 °C was added lithium hydroxide monohydrate (670 mg, 15.9 mmol). The ice-bath was removed and the reaction mixture was stirred for 45 min. The MeOH was then removed *in vacuo* and the crude aqueous layer partitioned between EtOAc (100 mL) and brine (100 mL). The aqueous phase was extracted using EtOAc (2 x 100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*, to give the alcohol (**+**-9 (3.37 g, 100%) without any further purification; R_f 0.24 (50% Et₂O/PE); $[\alpha]_D +3.3$ (c 1.8, CHCl₃); δ_H (400 MHz, CDCl₃) 7.38-7.27 (5 H, m, H-10, H-11, H-12), 5.64-5.56 (2 H, m, H-5, H-6), 4.55 (1 H, d, J 12.0 Hz, H-8_a), 4.52 (1 H, d, J 12.0 Hz, H-8_b), 3.67-3.53 (3 H, m, H-7_a, H-13), 3.41 (1 H, dd, J 9.5, 4.5 Hz, H-7_b), 3.55 (1 H, br s, OH), 2.27-1.93 (6 H, m, H-1, H-2, H-3, H-4). ¹H-NMR data were consistent with those reported in the literature.⁵

Methyl-(1R,6S)-6-(benzyloxymethyl)cyclohex-3-enecarboxylate (**-**10).



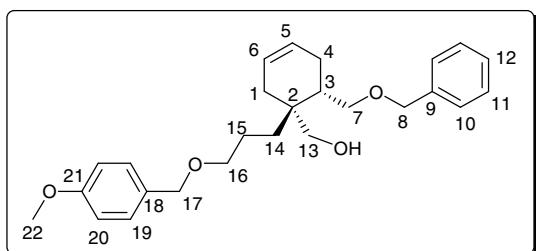
The crude alcohol (**+**-9 (14.0 g, 60.3 mmol) was dissolved in acetone (200 mL) and stirred at 5 °C. To this stirred solution was then added freshly prepared Jones' reagent until a dark red colour persisted for at least 10 min. Stirring was continued for another 30 min before propan-2-ol was added slowly, so as to maintain the internal temperature at or below 10 °C. The reaction was left to warm to rt before the green precipitate was filtered off. The filtrate was concentrated *in vacuo* and the green residue re-dissolved in MeOH (100 mL). To this was added at 0 °C acetyl chloride (2.6 mL, 36.2 mmol). The final solution was subsequently stirred at rt for 14 h. After this time, the MeOH was removed *in vacuo* and the yellow residue dissolved in CH₂Cl₂ (100 mL). The organic solution was washed twice with aqueous NaHCO₃ (sat., 50 mL). The organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure. The crude oil was purified by column chromatography (eluting with 30% Et₂O/PE) to give the *methyl ester* (**-**10 as a colourless oil (11.3 g, 72%); R_f 0.56 (50% Et₂O/PE); $[\alpha]_D -15.5$ (c 1.1, CHCl₃); IR (neat) 3027, 2903, 2851 (C-H_{stretch}), 1734 (C=O_{stretch}); δ_H (400 MHz, CDCl₃) 7.36-7.27 (5 H, m, H-10, H-11, H-12), 5.67-5.60 (2 H, m, H-5, H-6), 4.46 (2 H, s, H-8), 3.59 (3 H, s, H-14), 3.49 (1 H, dd, J 9.0, 5.0 Hz, H-7_a), 3.42 (1 H, dd, J 9.0, 7.0 Hz, H-7_b), 2.82-2.77 (1 H, m, H-2), 2.61-2.53 (1 H, m, H-3), 2.36-2.19 (3 H, m, H-1, H-4_a), 2.11-2.04 (1 H, m, H-4_b); δ_C (100 MHz, CDCl₃) 175.5 (C-13), 138.9 (C-Ar_{quat}), 128.7 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 125.7 (C-5/C-6), 125.3 (C-6/C-5), 73.3 (C-8), 70.7 (C-7), 51.4 (C-14), 39.8 (C-2), 34.5 (C-3), 27.0 (C-4), 24.4 (C-1); m/z (Cl) 261 (100) [MH]⁺; [HRMS (Cl) calcd. For C₁₆H₂₁O₃, 261.1491. Found: [MH]⁺, 261.1492 (-0.6 ppm error)].

*Methyl-(1*R*,6*S*)-6-(benzyloxymethyl)-1-(3-(4-methoxybenzyloxy)propyl)cyclohex-3-enecarboxylate (+)-12.*



To a stirred solution of ester **(+)-10** (700 mg, 2.70 mmol) in THF (7 mL) at -78 °C was added LiHMDS (1 M in THF, 2.83 mL, 2.83 mmol) dropwise. The resulting solution was stirred at that temperature for 2 h before a solution of iodide **11** (1.06 g, 2.96 mmol) in THF (3 mL) was introduced. The final solution was allowed to stir at -78 °C for 15 min after which the cooling-bath was removed and the reaction allowed to warm to rt at which it was stirred for 18 h. The reaction was quenched by the careful addition of water and then partitioned between aqueous NH₄Cl (sat., 25 mL) and EtOAc (25 mL). The aqueous layer was extracted using EtOAc (3 x 25 mL) and the combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. The crude oil was purified by column chromatography (eluting with 20% Et₂O/PE) to give the *title compound* **(+)-12** as a colourless oil (1.04 g, 88%); *R*_f 0.24 (30% Et₂O/PE); [α]_D +31.5 (c 1.3, CHCl₃); IR (neat) 3026, 2929, 2854 (C-H_{stretch}), 1728 (C=O_{stretch}); δ_H (400 MHz, CDCl₃) 7.30-7.17 (7 H, m, H-10, H-11, H-12, H-20), 6.81 (2 H, d, *J* 9.0 Hz, H-21), 5.54-5.48 (2 H, m, H-5, H-6), 4.32 (2 H, s, H-8), 4.34 (2 H, s, H-18), 3.74 (3 H, s, H-23), 3.50 (3 H, s, H-14), 3.35-3.26 (4 H, m, H-7, H-17), 2.33-2.17 (3 H, m, H-1_a, H-3, H-4_a), 2.04-1.97 (2 H, m, H-1_b, H-4_b), 1.61-1.47 (3 H, m, H-15, H-16_a), 1.37-1.26 (1 H, m, H-16_b); δ_C (100 MHz, CDCl₃) 177.3 (C-13), 159.6 (C-22), 138.8 (C-9), 130.9 (C-19), 129.6 (C-Ar), 128.6 (C-Ar), 128.0 (C-Ar), 127.8(C-Ar), 124.8, C-5/C-6), 124.5 (C-6/C-5), 114.0 (C-21), 73.2 (C-8), 72.4 (C-18), 71.3 (C-17), 70.2 (C-7), 55.2 (C-23), 51.4 (C-14), 45.6 (C-2), 39.0 (C-3), 32.0 (C-15), 27.2 (C-4), 24.8 (C-1), 24.2 (C-16); *m/z* (Cl) 439 (6) [MH]⁺; [HRMS (Cl) calcd. For C₂₇H₃₅O₅, 439.2495. Found: [MH]⁺, 439.2488 (-0.7 ppm error)].

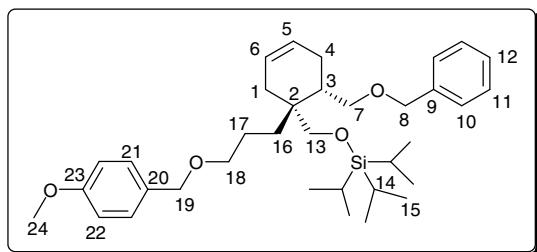
{(1*R*,6*S*)-6-Benzyloxymethyl-1-[3-(4-methoxy-benzyloxy)-propyl]-cyclohex-3-enyl}-methanol **(+)-13**.



To a stirred solution of methyl ester **(+)-12** (10.6 g, 24.2 mmol) in CH₂Cl₂ (100 mL) at -20 °C was added DIBAL-H (1 M in CH₂Cl₂, 50.0 mL, 48.3 mmol). The resulting solution was stirred at -78 °C for 30 min. The reaction was then quenched by the careful addition of EtOAc (10 mL) at -15 °C and the reaction mixture was transferred into a round bottom flask containing Rochelle's salt solution (20% w/w, 500 mL). After stirring vigorously for 3 h, the reaction mixture was partitioned and the aqueous phase extracted with CH₂Cl₂ (3 x 100 mL). The combined organic phases were concentrated *in vacuo* to furnish the *title compound* **(+)-13** as a colourless oil (9.92 g, 100%); *R*_f 0.36 (80% Et₂O/PE); [α]_D +18.8 (c 1.7, CHCl₃); IR (neat) 3431 (O-H_{stretch}), 3023, 2922, 2855 (C-H_{stretch}); δ_H (400 MHz, CDCl₃) 7.29-7.18 (7 H, m, H-10, H-11, H-12, H-19), 6.80 (2 H, d, *J* 9.0 Hz, H-20), 5.52 (1 H, br d, *J* 10.5 Hz, H-5), 5.45 (1 H, br d, *J* 10.5 Hz, H-6), 4.45 (1 H, d, *J* 12.0 Hz, H-8_a), 4.41 (1 H, d, *J* 12.0 Hz, H-8_b), 4.35

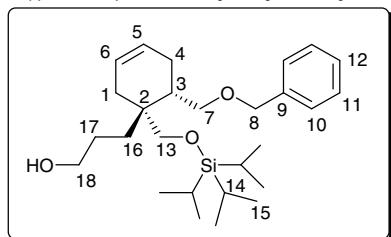
(2 H, s, H-17), 3.71 (3 H, s, H-22), 3.57 (1 H, d, *J* 12.0 Hz, H-13_a), 3.52 (1 H, dd, *J* 9.5, 3.5 Hz, H-7_a), 3.41-3.31 (3 H, m, H-7_b, H-16), 3.14 (1 H, d, *J* 12.0 Hz, H-13_b), 2.20-2.12 (1 H, m, H-4_a), 2.03-1.99 (1 H, m, H-4_b), 1.85-1.77 (2 H, m, H-3, H-15_a), 1.69-1.43 (4 H, m, H-1, H-14_a, H-15_b), 1.30-1.27 (1 H, m, H-1_b); δ_C (100 MHz, CDCl₃) 159.6 (C-21), 137.8 (C-Ar_{quat}), 131.0 (C-18), 129.6 (C-Ar), 128.8 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 125.8 (C-5), 125.1 (C-6), 114.0 (C-20), 73.5 (C-8), 72.5 (C-17), 70.92 (C-16), 70.87 (C-7), 64.8 (C-13), 55.2 (C-22), 39.4 (C-3), 38.5 (C-2), 33.0 (C-15), 31.0 (C-1), 26.4 (C-4), 23.0 (C-14); m/z (CI) 411 (5) [MH]⁺; [HRMS (CI) calcd. For C₂₆H₃₅O₄, 411.2535. Found: [MH]⁺, 411.2532 (0.8 ppm error)].

{(1*R*,6*S*)-6-Benzylloxymethyl-1-[3-(4-methoxy-benzyl oxy)-propyl]-cyclohex-3-enylmethoxy}-triisopropyl-silane (+)-**14**.



To a stirred solution of alcohol (**+/-13**) (9.92 g, 24.2 mmol) in CH₂Cl₂ (200 mL) at 0 °C was added 2,6-lutidine (7.0 mL, 60.5 mmol) followed by triisopropylsilyl trifluoromethane-sulfonate (9.8 mL, 36.3 mmol). The resulting solution was stirred at rt for 5 h. The reaction mixture was then diluted with further CH₂Cl₂ (100 mL) and water (300 mL). The aqueous phase was extracted using CH₂Cl₂ (2 x 100 mL) and the combined organic layers dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude product purified by column chromatography (eluting with 10-50% Et₂O/PE) to furnish the *title compound* (**+/-14**) as a colourless oil (13.3 g, 97%); R_f 0.51 (30% Et₂O/PE); [α]_D +19.2 (c 1.2, CHCl₃); IR (neat) 2941, 2864 (C-H stretch); δ_H (400 MHz, CDCl₃) 7.32 (4 H, d, *J* 4.5 Hz, H-10, H-11), 7.29-7.24 (3 H, m, H-12, H-21), 6.86 (2 H, d, *J* 8.5 Hz, H-22), 5.63 (1 H, br d, *J* 10.0 Hz, H-5), 5.56 (1 H, br d, *J* 10.0 Hz, H-6), 4.51 (1 H, d, *J* 12.0 Hz, H-8_a), 4.43 (1 H, d, *J* 12.0 Hz, H-8_b), 4.42 (2 H, s, H-19), 3.80 (3 H, s, H-24), 3.68 (1 H, d, *J* 10.0 Hz, H-13_a), 3.67 (1 H, dd, *J* 9.0, 3.5 Hz, H-7_a), 3.47-3.39 (4 H, m, H-7_b, H-13_b, H-18), 2.33 (1 H, br d, *J* 16.5 Hz, H-4_a), 2.07-1.96 (2 H, m, H-3, H-4_b), 1.90 (1 H, br d, *J* 18.0 Hz, H-1_a), 1.76 (1 H, br d, *J* 18.0 Hz, H-1_b), 1.63-1.47 (4 H, m, H-16, H-17), 1.02-1.01 (21 H, m, H-14, H-15); δ_C (100 MHz, CDCl₃) 159.6 (C-23), 139.3 (C-Ar_{quat}), 131.3 (C-20), 129.5 (C-Ar), 128.7 (C-Ar), 127.9 (C-Ar), 127.8 (C-Ar), 125.9 (C-5), 125.5 (C-6), 114.0 (C-22), 73.1 (C-8), 72.5 (C-19), 71.4 (C-7), 71.1 (C-16), 66.5 (C-13), 55.3 (C-24), 38.5 (C-3), 31.9 (C-1), 30.8 (C-16), 26.5 (C-4), 23.2 (C-17), 17.9 (C-15), 11.8 (C-14); m/z (FAB) 589 (21) [MNa]⁺; [HRMS (FAB) calcd. For C₃₅H₅₄O₄Si, 589.3684. Found: [MNa]⁺, 589.3686 (0.4 ppm error)].

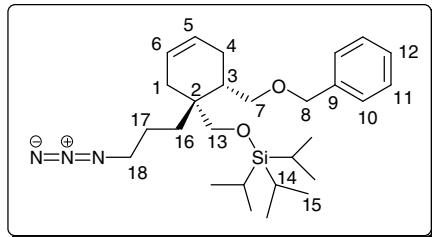
3-((1*R*,6*S*)-6-Benzylloxymethyl-1-(triisopropylsilanyloxy)methyl-cyclohex-3-enyl)-propan-1-ol (+)-**15**.



To a stirred solution of *p*-methoxybenzyl ether (**+/-14**) (13.3 g, 23.5 mmol) in CH₂Cl₂ (160 mL) and water (8 mL) at rt was added 2,3-dichloro-5,6-dicyanobenzoquinone (5.86 g, 25.8 mmol). The final dark green solution was stirred

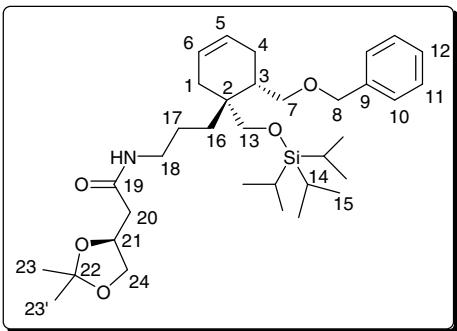
at rt for 15 min (until yellow). The reaction mixture was then diluted with further CH_2Cl_2 (40 mL) and aqueous NaHCO_3 (10%, 150 mL). The aqueous phase was extracted using CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4 . The solvent was removed *in vacuo* and the crude product purified by column chromatography (eluting with 10-100% $\text{Et}_2\text{O}/\text{PE}$) to furnish the *title compound (+)-15* as a colourless oil (9.85 g, 94%); Found C, 72.64%; H, 10.63%. $\text{C}_{27}\text{H}_{46}\text{O}_3\text{Si}$ requires C, 72.59%; H, 10.38%; R_f 0.40 (60% $\text{Et}_2\text{O}/\text{PE}$); $[\alpha]_D$ +24.0 (c 1.0, CHCl_3); IR (neat) 3352 (O-H_{stretch}), 3025, 2941, 2866 (C-H_{stretch}); δ_{H} (400 MHz, CDCl_3) 7.44-7.17 (5 H, m, H-10, H-11, H-12), 5.56 (1 H, br d, J 10.0 Hz, H-5), 5.49 (1 H, br d, J 10.0 Hz, H-6), 4.41 (1 H, d, J 12.0 Hz, H-8_a), 4.39 (1 H, d, J 12.0 Hz, H-8_b), 3.61 (1 H, d, J 10.0 Hz, H-13_a), 3.60 (1 H, dd, J 9.0, 3.5 Hz, H-7_a), 3.54-3.51 (2 H, m, H-18), 3.42 (1 H, d, J 10.0 Hz, H-13_b), 3.36 (1 H, dd, J 9.0, 9.0 Hz, H-7_b), 2.25 (1 H, br d, J , 18.0 Hz, H-4_a), 2.02-1.89 (2 H, m, H-3, H-4_b), 1.83 (1 H, br d, J 18.0 Hz, H-1_a), 1.70 (1 H, br d, J 18.0 Hz, H-1_b), 1.50-1.42 (4 H, m, H-16, H-17), 1.32 (1 H, br s, OH), 1.06-0.99 (21 H, m, H-14, H-15); δ_{C} (100 MHz, CDCl_3) 139.3 (C-Ar_{quat}), 128.7 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 125.9 (C-5), 125.5 (C-6), 73.1 (C-8), 71.3 (C-7), 66.5 (C-13), 64.0 (C-18), 38.42 (C-2), 38.35 (C-3), 31.9 (C-1), 30.4 (C-17), 26.5 (C-4), 26.3 (C-16), 17.9 (C-15), 11.8 (C-14); m/z (Cl) 447 (73) [MH]⁺; [HRMS (Cl) calcd. For $\text{C}_{27}\text{H}_{47}\text{O}_3\text{Si}$, 447.3294. Found: [MH]⁺, 447.3297 (-0.5 ppm error)].

[(1R,6S)-1-(3-Azido-propyl)-6-benzyloxymethyl-cyclohex-3-enylmethoxy]-triiisopropyl-silane (+)-16.



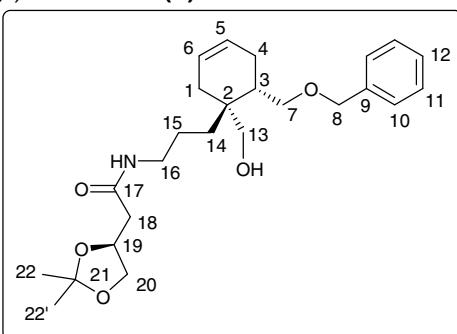
To a stirred solution of triphenylphosphine (6.35 g, 24.2 mmol) in THF (90 mL) at 0 °C was added diisopropyl azodicarboxylate (4.76 mL, 24.2 mmol). The resulting solution was stirred for 15 min until a white precipitate formed. To this was then added a solution of alcohol **(+)-15** (9.00 g, 20.2 mmol) in THF (40 mL) followed by diphenylphosphoryl azide (5.22 mL, 24.2 mmol). The final solution was stirred at rt for 5 h. The solvent was then removed *in vacuo* and the yellow crude oil purified by column chromatography (eluting with 1-3% $\text{Et}_2\text{O}/\text{iso-hexane}$) to furnish *azide (+)-16* as a colourless oil (7.98 g, 83%); R_f 0.32 (5% $\text{Et}_2\text{O}/\text{PE}$); $[\alpha]_D$ +26.2 (c 1.3, CHCl_3); IR (neat) 3025, 2941, 2865 (C-H_{stretch}), 2094 (azide); δ_{H} (400 MHz, CDCl_3) 7.38-7.22 (5 H, m, H-10, H-11, H-12), 5.55 (1 H, br d, J 10.0 Hz, H-5), 5.48 (1 H, br d, J 10.0 Hz, H-6), 4.43 (1 H, d, J 12.0 Hz, H-8_a), 4.37 (1 H, d, J 12.0 Hz, H-8_b), 3.60 (1 H, d, J 10.0 Hz, H-13_a), 3.56 (1 H, dd, J 9.0, 4.0 Hz, H-7_a), 3.48 (1 H, d, J 10.0 Hz, H-13_b), 3.40 (1 H, dd, J 9.0, 9.0 Hz, H-7_b), 3.21 (2 H, t, J 7.0 Hz, H-18), 2.22 (1 H, br d, J 18.0 Hz, H-4_a), 2.12-1.86 (2 H, m, H-3, H-4_b), 1.81 (1 H, br d, J 18.0 Hz, H-1_a), 1.71 (1 H, br d, J 18.0 Hz, H-1_b), 1.67-1.47 (4 H, m, H-16, H-17), 1.08-0.99 (21 H, m, H-14, H-15); δ_{C} (100 MHz, CDCl_3) 139.2 (C-Ar_{quat}), 128.7 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 125.9 (C-5), 125.3 (C-6), 73.2 (C-8), 71.2 (C-7), 66.5 (C-13), 52.4 (C-18), 38.5 (C-2), 38.2 (C-3), 31.9 (C-1), 27.1 (C-17), 26.4 (C-4), 22.7 (C-16), 17.9 (C-15), 11.7 (C-14); m/z (Cl) 472 (55) [MH]⁺, 444 (100) [MH(-N₂)]⁺; [HRMS (Cl) calcd. For $\text{C}_{27}\text{H}_{46}\text{N}_3\text{O}_2\text{Si}$, 472.3359. Found: [MH]⁺, 472.3372 (-2.6 ppm error)].

N-[3-((1R,6S)-6-Benzyloxymethyl-1-triiisopropylsilanyloxymethyl-cyclohex-3-enyl)-propyl]-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-acetamide (+)-18.



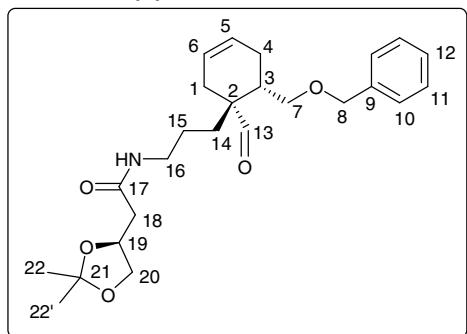
To a stirred solution of azide **(+)-16** (6.84 g, 14.5 mmol) in THF (50 mL) and water (3.3 mL) was added triphenylphosphine (4.18 g, 15.6 mmol). The resulting solution was stirred at reflux for 2 h. TLC analysis showed complete reduction of the azide and formation of a very polar species. The solvent was removed *in vacuo*. The crude solid was then dissolved in CH₂Cl₂ (20 mL) and stirred over Na₂SO₄ (2 g) for 15 min. The solids were then filtered off and washed with further CH₂Cl₂. The filtrate was concentrated to give a white solid which was dissolved in THF (80 mL) and cooled to 0 °C. To this was added acid **(S)-17** (2.79 g, 17.42 mmol) and *N,N*-diisopropylethylamine (5.10 mL, 29.0 mmol) and T3P® (50% w/w in THF, 13.9 g, 21.8 mmol). The final solution was allowed to stir at rt for 16 h. The solvent was removed *in vacuo* and the crude material partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed sequentially with aqueous HCl (10%, 50 mL), aqueous NaHCO₃ (sat., 50 mL) and brine (50 mL), then dried over Na₂SO₄ and concentrated *in vacuo*. The yellow crude oil was purified by column chromatography (eluting with 30% EtOAc/PE) to furnish the amide **(+)-18** as a colourless oil (7.36 g, 86%); *R*_f 0.30 (50% EtOAc/iso-hexane); [α]_D +12.7 (c 1.1, CHCl₃); IR (neat) 3300 (N-H stretch), 3024, 2941, 2865 (C-H stretch), 1646 (C=O stretch); δ_H (400 MHz, CDCl₃) 7.37-7.22 (5 H, m, H-10, H-11, H-12), 5.97 (1 H, br s, NH), 5.61 (1 H, br d, *J* 10.0 Hz, H-5), 5.54 (1 H, br d, *J* 10.0 Hz, H-6), 4.49 (1 H, d, *J* 12.0 Hz, H-8_a), 4.44 (1 H, d, *J* 12.0 Hz, H-8_b), 4.42-4.35 (1 H, m, H-21), 4.12 (1 H, dd, *J* 8.5, 6.0 Hz, H-24_a), 3.71-3.54 (3 H, m, H-7_a, H-13_a, H-24_b), 3.46 (1 H, d, *J* 10.0 Hz, H-13_b), 3.39 (1 H, dd, *J* 9.0, 9.0 Hz, H-7_b), 3.21 (2 H, br s, H-18), 2.47 (1 H, dd, *J* 15.0, 7.5 Hz, H-20_a), 2.40 (1 H, dd, *J* 15.0, 5.0 Hz, H-20_b), 2.28 (1 H, br d, *J* 18.0 Hz, H-4_a), 2.07-1.91 (2 H, m, H-3, H-4_b), 1.87 (1 H, br d, *J* 18.0 Hz, H-1_a), 1.75 (1 H, br d, *J* 18.0 Hz, H-1_b), 1.49 (4 H, br s, H-16, H-17), 1.43 (3 H, s, H-23), 1.36 (3 H, s, H-23'), 1.08-0.96 (21 H, m, H-14, H-15); δ_C (100 MHz, CDCl₃) 169.6 (C-19), 138.7 (C-Ar_{quat}), 128.3 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 125.5 (C-5), 125.0 (C-6), 109.3 (C-22), 73.0 (C-8), 72.5 (C-21), 71.1 (C-7), 69.1 (C-24), 66.5 (C-13), 40.6 (C-20), 40.3 (C-18), 38.5 (C-2), 38.2 (C-3), 31.9 (C-1, C-16/C-17), 26.9 (C-23), 26.5 (C-4), 25.5 (C-23'), 23.1 (C-17/C-16), 18.1 (C-15), 11.9 (C-14); m/z (Cl) 588 (32) [MH]⁺; [HRMS (Cl) calcd. For C₃₄H₅₈NO₅Si, 588.4084. Found: [MH]⁺, 588.4083 (0.1 ppm error)].

N-[3-((1*R*,6*S*)-6-Benzyloxymethyl-1-hydroxymethyl-cyclohex-3-enyl)-propyl]-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-acetamide **(+)-19**.



To a stirred solution of triisopropylsilyl ether (**+**-**18** (7.35 g, 12.5 mmol) in THF (100 mL) was added tetra-*n*-butylammonium fluoride (1 M in THF, 20.0 mL, 20.0 mmol) at 0 °C. The resulting solution was stirred at rt for 5 h. The reaction was quenched by the careful addition of water, then partitioned between CH₂Cl₂ (100 mL) and brine (100 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give a brown oil that was purified by column chromatography (eluting with 50-90% EtOAc/iso-hexane) to furnish the *alcohol* (**+**-**19** as a colourless oil (5.38 g, 100%); *R*_f 0.18 (EtOAc); [α]_D +11.5 (c 1.1, CHCl₃); IR (neat) 3314 (O-H_{stretch}), 2984, 2932 (C-H_{stretch}), 1650 (C=O_{stretch}); δ_H (400 MHz, CDCl₃) 7.44-7.22 (5 H, m, H-10, H-11, H-12), 6.32 (1 H, br s, NH), 5.58 (1 H, br d, *J* 10.0 Hz, H-5), 5.49 (1 H, br d, *J* 10.0 Hz, H-6), 4.52 (1 H, d, *J* 12.0 Hz, H-8_a), 4.48 (1 H, d, *J* 12.0 Hz, H-8_b), 4.42-4.36 (1 H, m, H-19), 4.11 (1 H, dd, *J* 8.5, 6.0 Hz, H-20_a), 3.71-3.55 (3 H, m, H-7_a, H-13_a, H-20_b), 3.51 (1 H, dd, *J* 9.5, 5.0 Hz, H-7_b), 3.40-3.09 (3 H, m, H-13_b, H-16), 2.47 (1 H, dd, *J* 15.0, 7.5 Hz, H-18_a), 2.39 (1 H, dd, *J* 15.0, 5.5 Hz, H-18_b), 2.21 (1 H, ddd, *J* 18.5, 5.5, 3.0 Hz, H-4_a), 2.07 (1 H, br d, *J* 18.5 Hz, H-4_b), 1.87-1.62 (4 H, m, H-1, H-3, H-14_a), 1.51 (1 H, dd, *J* 14.0, 7.0 Hz, H-15_a), 1.48 (1 H, dd, *J* 14.0, 7.0 Hz, H-15_b), 1.43 (3 H, s, H-22), 1.36 (3 H, s, H-22'), 1.26 (2 H, m, H-14_b); δ_C (100 MHz, CDCl₃) 169.9 (C-17), 137.2 (C-Ar_{quat}), 128.5 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 125.5 (C-5), 124.4 (C-6), 109.3 (C-21), 73.6 (C-8), 72.6 (C-19), 70.8 (C-13), 69.1 (C-20), 65.9 (C-7), 40.6 (C-18), 40.2 (C-16), 39.7 (C-3), 38.6 (C-2), 33.1 (C-1), 32.1 (C-14), 26.9 (C-22), 26.6 (C-4), 25.5 (C-22'), 22.9 (C-15); m/z (Cl) 432 (100) [MH]⁺; HRMS (Cl) calcd. For C₂₅H₃₈NO₅, 432.2753. Found: [MH]⁺, 432.2750 (0.7 ppm error)].

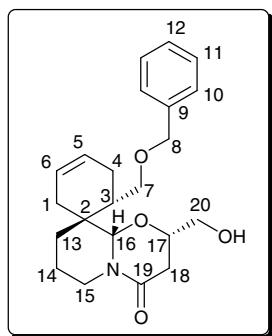
N-[3-((1*R*,6*S*)-6-Benzyloxymethyl-1-formyl-cyclohex-3-enyl)-propyl]-2-(S)-2,2-dimethyl-1,3-dioxolan-4-yl)-acetamide (+**-**20**.**



To a stirred solution of alcohol (**+**-**19** (5.56 g, 12.9 mmol) in CH₂Cl₂ (50 mL) over 4Å molecular sieves was added *N*-methylmorpholine-*N*-oxide (1.81 g, 15.5 mmol) at rt. After stirring for 15 min, tetra-*n*-propylammonium perruthenate (340 mg, 0.97 mmol) was added and the resulting mixture was stirred at rt for 30 min. After evaporating the solvent, the crude product was purified by column chromatography (eluting with 60% EtOAc/iso-hexane) to afford the *aldehyde* (**+**-**20** as a colourless oil (5.48 g, 99%); *R*_f 0.37 (EtOAc); [α]_D +23.3 (c 1.2, CHCl₃); IR (neat) 3304 (N-H_{stretch}), 2961, 2930, 2863 (C-H_{stretch}), 1718 (C=O_{aldehyde}), 1647 (C=O_{amide}); δ_H (400 MHz, CDCl₃) 9.57 (1 H, s, H-13), 7.45-7.18 (5 H, m, H-10, H-11, H-12), 6.07 (1 H, br s, NH), 5.62 (2 H, m, H-5, H-6), 4.44 (1 H, d, *J* 12.0 Hz, H-8_a), 4.39 (1 H, d, *J* 12.0 Hz, H-8_b), 4.39-4.36 (1 H, m, H-19), 4.12 (1 H, dd, *J* 8.5, 6.0 Hz, H-20_a), 3.60 (1 H, dd, *J* 8.5, 7.0 Hz, H-20_b), 3.40 (2 H, m, H-7), 3.20 (2 H, dd, *J* 13.0, 7.0 Hz, H-16), 2.47 (1 H, dd, *J* 15.0, 7.5 Hz, H-18_a), 2.41 (1 H, dd, *J* 15.0, 5.0 Hz, H-18_b), 2.32-2.19 (3 H, m, H-1_a, H-3, H-4_a), 2.08-1.95 (2 H, m, H-1_b, H-4_b), 1.58-1.53 (2 H, m, H-15), 1.50-1.43 (1 H, m, H-14_a), 1.42 (3 H, s, H-22), 1.36 (3 H, s, H-22'), 1.32-1.29 (1 H, m, H-14_b); δ_C (100 MHz, CDCl₃) 205.4 (C-13), 169.9 (C-17), 137.9 (C-Ar_{quat}), 128.4 (C-Ar), 128.3 (C-Ar), 127.62 (C-Ar), 127.59 (C-Ar), 125.0 (C-5), 123.9 (C-6), 109.4 (C-21), 73.2 (C-8), 72.5 (C-19), 70.7 (C-7), 69.1 (C-22').

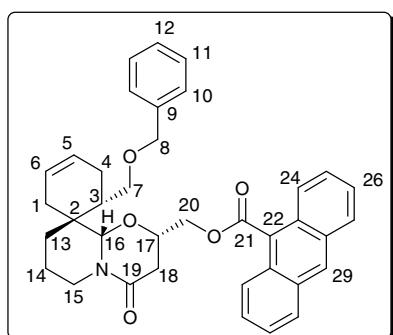
20), 40.6 (C-18), 39.9 (C-2), 39.6 (C-16), 38.3 (C-3), 29.8 (C-14), 26.9 (C-22), 26.4 (C-4), 26.3 (C-1), 25.5 (C-22'), 23.8 (C-15); m/z (Cl) 430 (17) [MH]⁺; HRMS (Cl) calcd. For C₂₅H₃₆NO₄₅, 430.2593. Found: [MH]⁺, 430.2591 (0.5 ppm error)].

(1*R*,2'S,6S,9a'S)-6-(Benzylloxymethyl)-2'-(hydroxymethyl)-6',7',8',9a'-tetrahydro-2'H-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-b][1,3]oxazin]-4'(3'H)-one (**-21**).



To a stirred solution of aldehyde (**+**)-**20** (5.30 g, 12.4 mmol) in CH₂Cl₂ (100 mL) was added tin(II) chloride dihydrate (6.97 g, 30.9 mmol) at rt. The resulting mixture was stirred at rt for 20 h. The reaction mixture was then pre-absorbed onto silica followed by column chromatography (eluting with EtOAc) to afford the spirooxaquinolizidinone (**-21**) as a colourless oil (2.93 g, 78%); R_f 0.11 (EtOAc); [α]_D -102.0 (c 1.0, CHCl₃); IR (neat) 3393 (O-H stretch), 3025, 2933, 2856 (C-H stretch), 1634 (C=O amide); δ_H (400 MHz, CDCl₃) 7.40-7.25 (5 H, m, H-10, H-11, H-12), 5.58-5.54 (2 H, m, H-5, H-6), 4.72 (1 H, s, H-16), 4.69-4.67 (1 H, m, H-15_a), 4.53 (1 H, d, J 12.0 Hz, H-8_a), 4.48 (1 H, d, J 12.0 Hz, H-8_b), 3.93 (1 H, dd, J 10.0, 5.0 Hz, H-7_a), 3.71 (1 H, dddd, J 12.0, 6.0, 3.0, 3.0 Hz, H-17), 3.62 (1 H, br d, J 11.0 Hz, H-20_a), 3.46-3.42 (1 H, m, H-20_b), 3.41 (1 H, dd, J 10.0, 6.5 Hz, H-7_b), 2.51 (1 H, d, J 12.0 Hz, H-18_a), 2.46 (1 H, d, J 12.0 Hz, H-18_b), 2.41-2.32 (2 H, m, H-14_a, H-15_b), 2.26-2.21 (3 H, m, H-4, OH), 1.81-1.71 (3 H, m, H-1_a, H-3, H-14_b), 1.56-1.46 (3 H, m, H-1_b, H-13); δ_C (100 MHz, CDCl₃) 167.6, (C-19), 138.8 (C-Ar_{quat}), 128.8 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 126.1 (C-5), 124.9 (C-6), 91.3 (C-16), 73.0 (C-8), 72.9 (C-17), 71.4 (C-7), 64.4 (C-20), 41.9 (C-3), 40.0 (C-15), 38.7 (C-2), 34.3 (C-1), 33.6 (C-18), 27.8 (C-4), 26.2 (C-14), 19.5 (C-13); m/z (Cl) 372 (100) [MH]⁺; HRMS (Cl) calcd. For C₂₂H₃₀NO₄, 372.2175. Found: [MH]⁺, 371.2173 (0.5 ppm error)].

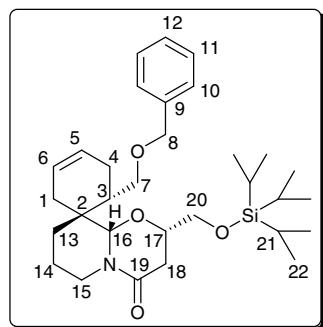
((1*R*,2'S,6S,9a'S)-6-(Benzylloxymethyl)-4'-oxo-3',4',6',7',8',9a'-hexahydro-2'H-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-b][1,3]oxazine]-2'-yl)methyl anthracene-9-carboxylate (**-22**).



To a stirred solution of 9-anthracenecarboxylic acid (90.0 mg, 0.40 mmol) in CH₂Cl₂ at 0 °C was added a drop of DMF followed by oxalyl chloride (71 μL, 0.81 mmol). The solvent was removed *in vacuo* after 30 min and the

resulting yellow solid dried under reduced pressure for 1 h. It was then dissolved in CH₂Cl₂ (1.5 mL) and added to a solution of alcohol (**-21**) (75.0 mg, 0.20 mmol) and pyridine (82 μ L, 1.01 mmol) in CH₂Cl₂ (1.5 mL). The final reaction mixture was stirred at rt for 57 h. The reaction was then partitioned between more CH₂Cl₂ (10 mL) and aqueous NaHCO₃ (sat. 10 mL). The organic layer was subsequently washed with aqueous HCl (10%, 10 mL) and then dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude solid purified by column chromatography (eluting with 30-100% EtOAc/PE) to give the *title compound* (**-22**) as a dark brown solid that was re-crystallised from acetone to give yellow crystals (107 mg, 92%); m.p. 93-95 °C; R_f 0.53 (80% EtOAc/PE); [α]_D -31.4 (c 2.1, CHCl₃); IR (neat) 3025, 2931, 2856 (C-H_{stretch}), 1723 (C=O_{ester}), 1634 (C=O_{amide}); δ_H (400 MHz, CDCl₃) 8.51 (1 H, s, H-29), 8.05 (2 H, d, J 8.5 Hz, H-24), 8.01 (2 H, J 8.5 Hz, H-27), 7.58-7.47 (4 H, m, H-25, H-26), 7.21-7.20 (3 H, H-11, H-12), 7.00-6.94 (2 H, H-10), 5.57 (2 H, br s, H-5, H-6), 4.80 (1 H, dd, J 12.0, 3.0 Hz, H-20_a), 4.74-4.70 (1 H, m, H-15_a), 4.68 (1 H, s, H-16), 4.38 (1 H, dd, J 12.0, 6.5 Hz, H-20_b), 4.18-4.12 (1 H, m, H-17), 3.90 (1 H, d, J 12.0 Hz, H-8_a), 3.87 (1 H, dd, J 9.5, 4.0 Hz, H-7_a), 3.86 (1 H, d, J 12.0 Hz, H-8_b), 3.26 (1 H, dd, J 9.5, 9.5 Hz, H-7_b), 2.57 (1 H, d, J 16.5 Hz, H-18_a), 2.54 (1 H, d, J 16.5 Hz, H-18_b), 2.46-2.38 (2 H, m, H-4_a, H-15_b), 2.30 (1 H, br d, J 18.5 Hz, H-14_a), 2.11-2.04 (1 H, m, H-4_b), 1.93 (1 H, br d, J 13.5 Hz, H-1_a), 1.78-1.69 (2 H, m, H-3, H-14_b), 1.59-1.46 (2 H, m, H-13), 1.36 (1 H, br d, J 13.5 Hz, H-1_b); δ_C (100 MHz, CDCl₃) 169.4 (C-21), 166.3 (C-19), 138.6 (C-Ar_{quat}), 131.0 (C-Ar), 129.9 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.2 (C-Ar), 127.5 (C-Ar), 127.3 (C-Ar), 127.1 (C-Ar), 125.6 (C-Ar), 124.9 (C-Ar), 124.7 (C-5/C-6), 124.5 (C-6/C-5), 92.0 (C-16), 72.6 (C-8), 70.9 (C-17), 70.3 (C-7), 66.4 (C-20), 42.5 (C-3), 40.4 (C-15), 39.0 (C-2), 34.7 (C-18), 33.6 (C-1), 25.7, (C-4), 24.4 (C-14), 19.7 (C-13); m/z (CI) 576 (100) [MH]⁺; HRMS (CI) calcd. For C₃₇H₃₈NO₅, 576.2750. Found: [MH]⁺, 576.2727 (3.9 ppm error)].

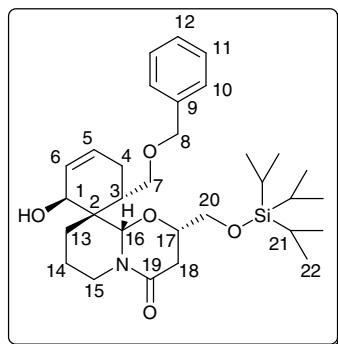
(1R,2'S,6S,9a'S)-6-(Benzylloxymethyl)-2'-(triisopropylsilyloxy)methyl)-6',7',8',9a'-tetrahydro-2'H-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-b][1,3]oxazin]-4'(3'H)-one (**-23**).



To a stirred solution of alcohol (**-21**) (750 mg, 2.02 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added 2,6-lutidine (1.20 mL, 10.1 mmol) followed by triisopropylsilyl trifluoromethanesulfonate (1.36 mL, 5.05 mmol). The resulting solution was stirred at rt for 3 h. The reaction mixture was then diluted with further CH₂Cl₂ (20 mL) and partitioned between water (25 mL). The aqueous phase was extracted using CH₂Cl₂ (3 x 15 mL) and the combined organic layers dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude product purified by column chromatography (eluting with 30-75% EtOAc/PE) to furnish *triisopropylsilyl ether* (**-23**) as a colourless oil (1.04 g, 98%); R_f 0.23 (30% EtOAc/PE); [α]_D -68.2 (c 2.2, CHCl₃); IR (neat) 3024, 2940, 2865 (C-H_{stretch}), 1659 (C=O_{stretch}); δ_H (400 MHz, CDCl₃) 7.36-7.25 (5 H, m, H-10, H-11, H-12), 5.60-5.54 (2 H, m, H-5, H-6), 4.72 (1 H, dddd, J 13.0, 4.5, 2.0, 2.0 Hz, H-15_a), 4.61 (1 H, s, H-16), 4.49 (1 H, d, J 12.0 Hz, H-8_a), 4.46 (1 H, d, J 12.0 Hz, H-8_b), 4.02 (1 H, dd, J 9.5, 4.0 Hz, H-7_a), 3.74-3.68 (2 H, m, H-17, H-20_a), 3.64-3.60 (1 H, m, H-20_b), 3.37 (1 H, dd, J 9.5, 9.5

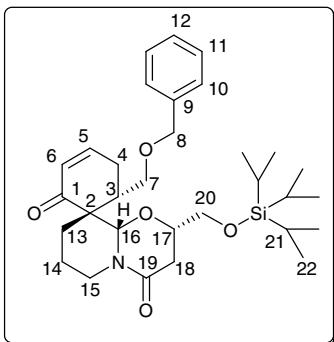
Hz, H-7_b), 2.53-2.34 (4 H, m, H-14_a, H-15_b, H-18), 2.28 (1 H, br d, *J* 18.5 Hz, H-4_a), 2.15 (1 H, br d, *J* 18.5 Hz, H-14_b), 1.92 (1 H, dd, *J* 13.5, 2.0 Hz, H-1_a), 1.83-1.73 (2 H, m, H-3, H-13_a), 1.60-1.49 (2 H, m, H-13_b, H-4_b), 1.40 (1 H, dd, *J* 13.5, 4.5 Hz, H-1_b), 1.07-1.03 (21 H, m, H-21, H-22); δ_C (100 MHz, CDCl₃) 167.7 (C-19), 138.9, (C-Ar_{quat}), 128.5, (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 124.9 (C-5), 124.4 (C-6), 91.9 (C-16), 73.6 (C-17), 73.0 (C-8), 70.8 (C-7), 65.2 (C-20), 42.5 (C-3), 40.3 (C-15), 39.0 (C-2), 34.9 (C-1), 33.9 (C-18), 25.8 (C-14), 24.7 (C-4), 19.8 (C-13), 18.1 (C-22), 12.0 (C-21); m/z (Cl) 528 (100) [MH]⁺; HRMS (Cl) calcd. For C₃₁H₅₀NO₄Si, 528.3509. Found: [MH]⁺, 528.3599 (1.9 ppm error)].

(1*S*,2*S*,2*S*,6*S*,9*a*'S)-6-(Benzylloxymethyl)-2-hydroxy-2'-(triisopropylsilyloxy)methyl)-6',7',8',9*a*'-tetrahydro-2'H-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'H)-one (**-24**).



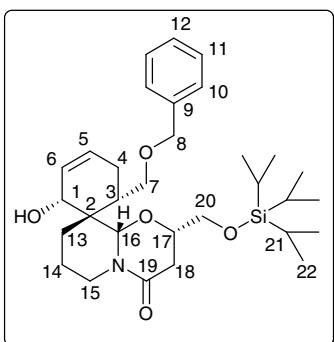
To a stirred solution of cyclohexene (**-23**) (100.0 mg, 0.19 mmol) in EtOH (3 mL) at rt was added selenium(IV) oxide (105.5 mg, 0.95 mmol). The final mixture was stirred at reflux for 17 h. After cooling, a 1:1 mixture of Et₂O/PE was added. The mixture was filtered through Celite®, the solvent was then removed *in vacuo* and the crude residue purified by column chromatography (eluting with 2% MeOH/CH₂Cl₂) to give *alcohol* (**-24**) as a pale yellow oil (80.0 mg, 78%); R_f 0.25 (4% MeOH/CH₂Cl₂); [α]_D -45.3 (c 2.5, CHCl₃); IR (neat) 3405 (OH_{stretch}), 3026, 2942, 2866 (C-H_{stretch}), 1637 (C=O_{stretch}), 1456; δ_H (400 MHz, CD₃OD) 7.33-7.25 (5 H, m, H-10, H-11, H-12), 5.78-5.74 (1 H, m, H-5), 5.72-5.68 (1 H, m, H-6), 4.96 (1 H, s, H-16), 4.66 (1 H, ddd, *J* 13.5, 4.5, 2.0 Hz, H-15_a), 4.51 (1 H, d, *J* 12.0 Hz, H-8_a), 4.48 (1 H, d, *J* 12.0 Hz, H-8_b), 4.12 (1 H, d, *J* 3.5 Hz, H-1), 3.82 (1 H, dd, *J* 9.5, 4.0 Hz, H-7_a), 3.72-3.62 (3 H, m, H-17, H-20), 3.57 (1 H, dd, *J* 9.5, 7.5 Hz, H-7_b), 2.58-2.46 (2 H, m, H-4_a, H-15_b), 2.34 (1 H, dd, *J* 17.0, 11.0 Hz, H-18_a), 2.25 (1 H, dd, *J* 17.0, 3.0 Hz, H-18_b), 2.14 (1 H, ddd, *J* 18.0, 5.0, 5.0 Hz, H-4_b), 2.01 (1 H, dd, *J* 13.5, 2.0 Hz, H-13_a), 1.95-1.89 (1 H, m, H-3), 1.95-1.73 (1 H, m, H-14_a), 1.64 (1 H, ddd, *J*, 13.5, 13.0, 3.5 Hz, H-13_b), 1.53-1.46 (1 H, m, H-14_b), 1.11-1.05 (21 H, m, H-21, H-22); δ_C (100 MHz, CD₃OD) 170.7 (C-19), 140.5 (C-9), 130.1 (C-5/C-6), 130.0 (C-6/C-5), 129.8 (C-Ar), 129.1 (C-Ar), 129.0 (C-Ar), 91.9 (C-16), 75.2 (C-17), 74.2 (C-8), 72.1 (C-7), 66.6 (C-20), 64.9 (C-1), 44.4 (C-2), 41.6 (C-15), 40.4 (C-3), 35.3 (C-18), 31.6 (C-13), 29.6 (C-4), 21.5 (C-14), 18.4 (C-22), 13.0 (C-21); m/z (ESI) 544 (100) [MH]⁺; HRMS (ESI) calcd. For C₃₁H₅₀NO₅Si, 544.3453. Found: [MH]⁺, 544.3445 (1.5 ppm error)].

(1*R*,2*S*,6*S*,9*a*'S)-6-(Benzylloxymethyl)-2'-(triisopropylsilyloxy)methyl)-6',7',8',9*a*'-tetrahydro-2'H-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazine]-2,4'(3'H)-dione (**-25**).



To a stirred solution of alcohol (**-**)-24 (40.0 mg, 0.07 mmol) in CH₂Cl₂ (2 mL) at rt was added manganese(IV) oxide (64.0 mg, 0.73 mmol). The black suspension was stirred at reflux for 4 h. The solids were filtered off and the filtrate purified by column chromatography (eluting with 1-2% MeOH/CH₂Cl₂) to give the enone (**-**)-25 (36.0 mg, 91%) as a colourless oil; *R*_f 0.32 (4% MeOH/CH₂Cl₂); [α]_D -99.6 (c 1.6, CHCl₃); IR (neat) 2941, 2865, (C-H stretch), 1660 (C=O stretch), 1460; δ_H (400 MHz, CDCl₃) 7.32-7.24 (5 H, m, H-10, H-11, H-12), 6.75 (1 H, ddd, *J* 10.0, 5.0, 3.5 Hz, H-5), 5.84 (1 H, ddd, *J* 10.0, 2.0, 2.0 Hz, H-6), 4.75 (1 H, s, H-16), 4.64 (1 H, ddd, *J* 13.0, 4.3, 4.5 Hz, H-15_a), 4.45 (2 H, s, H-8), 3.80 (1 H, dd, *J* 9.5, 4.5 Hz, H-7_a), 3.70-3.64 (1 H, m, H-17), 3.57 (1 H, dd, *J* 10.5, 6.0 Hz, H-20_a), 3.52 (1 H, dd, *J* 9.5, 1.0 Hz, H-7_b), 3.50 (1 H, dd, *J* 10.5, 4.5 Hz, H-20_b), 2.76 (1 H, dddd, *J* 19.0, 8.0, 3.5, 2.0 Hz, H-4_a), 2.45-2.43 (1 H, m, H-4_b), 2.40-2.36 (1 H, m, H-15_b), 2.26-2.25 (2 H, m, H-18), 2.17 (1 H, dddd, *J* 8.0, 8.0, 4.5, 4.5 Hz, H-3), 2.00 (1 H, 2.06-1.96 (1 H, m, H-14_a), 1.91 (1 H, br d, *J* 14.5, Hz, H-13_a), 1.73-1.69 (1 H, m, H-13_b), 1.47-1.40 (1 H, m, H-14_b), 0.98-0.95 (21 H, m, H-21, H-22); δ_C (100 MHz CDCl₃) 199.4 (C-1), 166.7 (C-19), 147.8 (C-5), 138.5 (C-Ar_{quat}), 130.5 (C-6), 128.8 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 88.7 (C-16), 74.1 (C-17), 73.4 (C-8), 70.4 (C-7), 65.3 (C-20), 49.7 (C-2), 44.1 (C-3), 39.7 (C-15), 34.5 (C-18), 32.3 (C-13), 27.4 (C-4), 20.6 (C-14), 17.8 (C-22), 11.6 (C-21); m/z (ESI) 542 (100) [MH]⁺; HRMS (ESI) calcd. For C₃₁H₄₈NO₅Si, 542.3296. Found: [MH]⁺, 542.3291 (1.0 ppm error)].

(1*S*,2*R*,2'S,6*S*,9*a*'S)-6-(Benzylloxymethyl)-2-hydroxy-2'-(triisopropylsilyloxy)methyl)-6',7',8',9*a*'-tetrahydro-2'H-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-b][1,3]oxazin]-4'(3'H)-one (**-**)-2a.

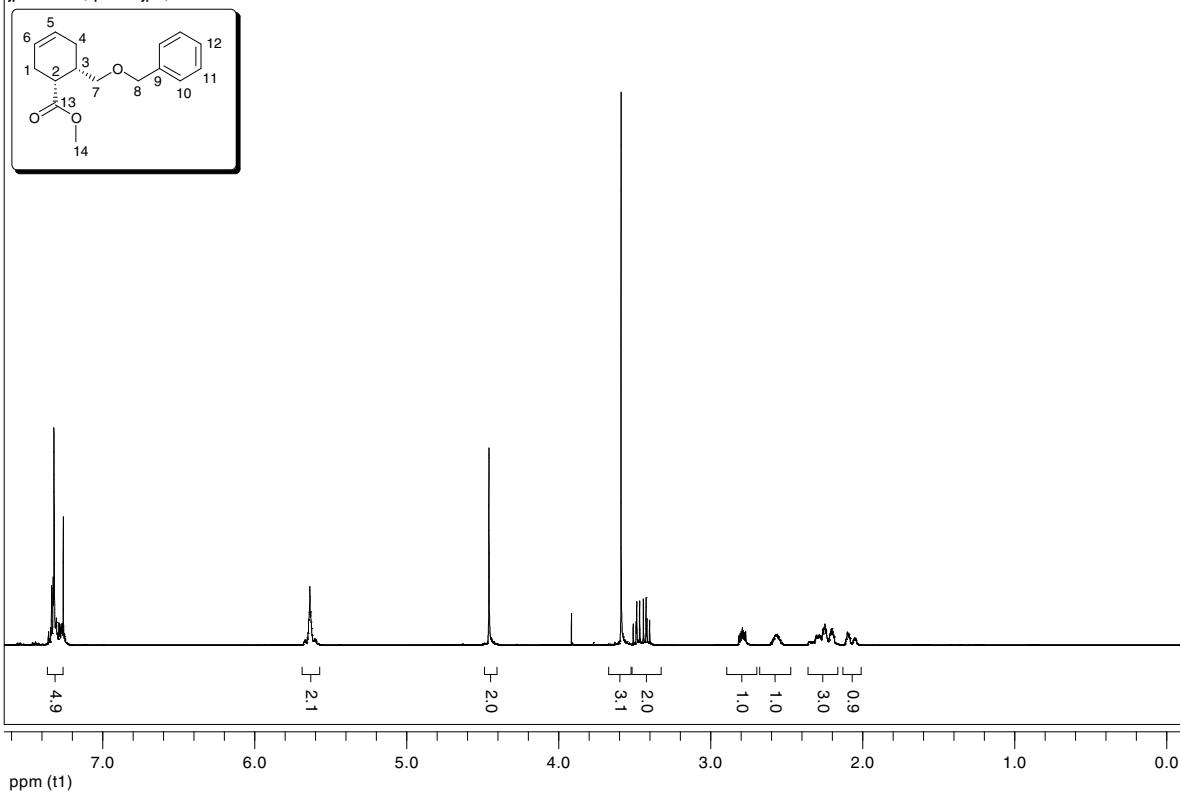


To a stirred solution of enone (**-**)-25 (36.0 mg, 0.07 mmol) in MeOH (2 mL) at rt was added cerium(III) chloride heptahydrate (26.0 mg, 0.07 mmol). The solution was stirred at that temperature for 30 min before it was cooled to 0 °C. To this was then added sodium borohydride (5.0 mg, 0.14 mmol). After stirring at 0 °C for 30 min, the reaction was allowed to warm to rt at which it was stirred for a further 3 h. The excess reducing agent was then quenched by the addition of acetone (0.1 mL). After removal of solvent, the crude residue was purified by column chromatography (eluting with 1-2% MeOH/CH₂Cl₂) to give alcohol (**-**)-2a as a colourless oil (26 mg, 72%); *R*_f 0.34 (4% MeOH/CH₂Cl₂); [α]_D -25.0 (c 0.4, CHCl₃); IR (neat) 3399 (OH stretch), 2941, 2866, (C-H stretch), 1655 (C=O stretch),

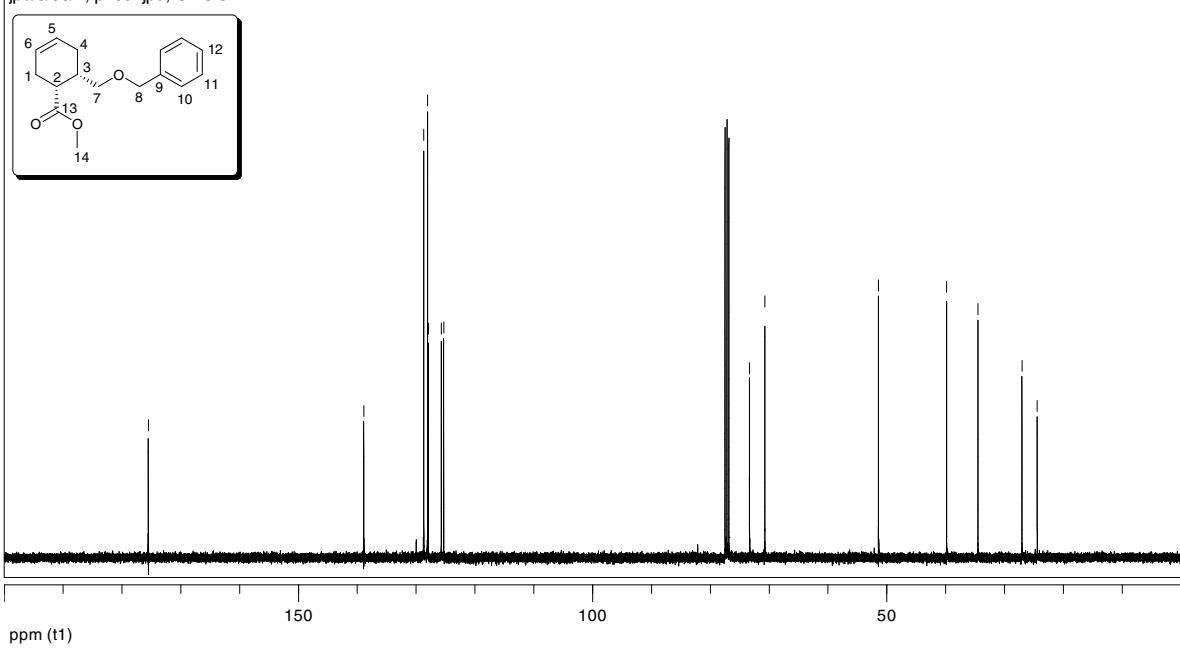
1458; δ_H (400 MHz, CD₃OD) 7.34-7.25 (5 H, m, H-10, H-11, H-12), 5.73-5.66 (2 H, m, H-5, H-6), 5.06 (1 H, s, H-16), 4.58-4.52 (1 H, m, H-15_a), 4.51 (1 H, d, *J* 12.0 Hz, H-8_a), 4.47 (1 H, d, *J* 12.0 Hz, H-8_b), 4.22 (1 H, d, *J* 3.0 Hz, H-1), 4.08 (1 H, dd, *J* 9.5, 3.0 Hz, H-7_a), 3.83 (1 H, ddd, *J* 14.0, 6.0, 2.5 Hz, H-17), 3.78 (1 H, dd, *J* 9.5, 9.0 Hz, H-7_b), 3.70 (1 H, d, *J* 14.0 Hz, H-20_a), 3.65 (1 H, d, *J* 14.0 Hz, H-20_b), 2.73-2.64 (2 H, m, H-15_b, H-18_a), 2.50 (1 H, dd, *J* 18.0, 4.0 Hz H-4_a), 2.28 (1 H, dd, *J* 16.5, 3.0 Hz, H-18_b), 2.25 (1 H, dd, *J* 18.0, 6.5 Hz, H-4_b), 1.92-1.88 (2 H, m, H-3, H-13_a), 1.75-1.66 (1 H, m, H-14_a), 1.61-1.51 (2 H, m, H-13_b, H-14_b), 1.10-1.06 (21 H, m, H-21, H-22); δ_C (100 MHz, CD₃OD) 170.6 (C-19), 140.5 (C-Ar_{quat}), 129.9 (C-Ar), 129.6 (C-Ar), 129.5 (C-Ar), 129.0 (C-5/C-6), 128.7 (C-6/C-5), 93.8 (C-16), 75.7 (C-17), 73.8 (C-8), 72.6 (C-7), 70.1 (C-1), 65.8 (C-20), 43.4 (C-2), 42.9 (C-3), 41.5 (C-15), 34.5 (C-18), 34.2 (C-13), 28.0 (C-4), 20.8 (C-14), 18.3 (C-22), 12.9 (C-21); m/z (ESI) 544 (100) [MH]⁺; HRMS (ESI) calcd. For C₃₁H₅₀NO₅Si, 542.3453. Found: [MH]⁺, 544.3448 (0.9 ppm error)].

- (1) Von Langen, D. J.; Tolman, R. L. *Tetrahedron: Asymmetry* **1997**, *8*, 677.
- (2) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181.
- (3) Jiménez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelley, M. J. *Org. Chem.* **2000**, *65*, 8465.
- (4) Danieli, B.; Leama, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron: Asymmetry* **1990**, *1*, 793.
- (5) O'Brien, P.; Tournayre, J. J. *Tetrahedron* **1997**, *53*, 17527.

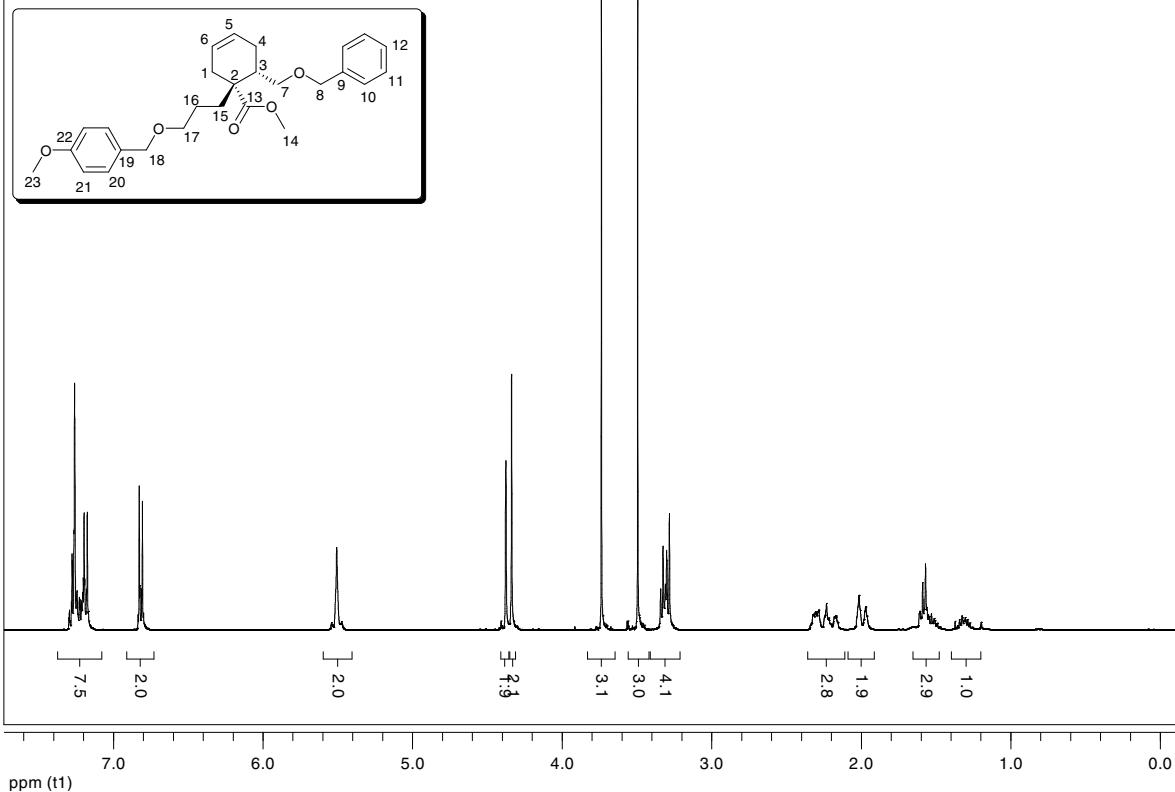
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jps/3/98/1, p2060jps, CDCl_3



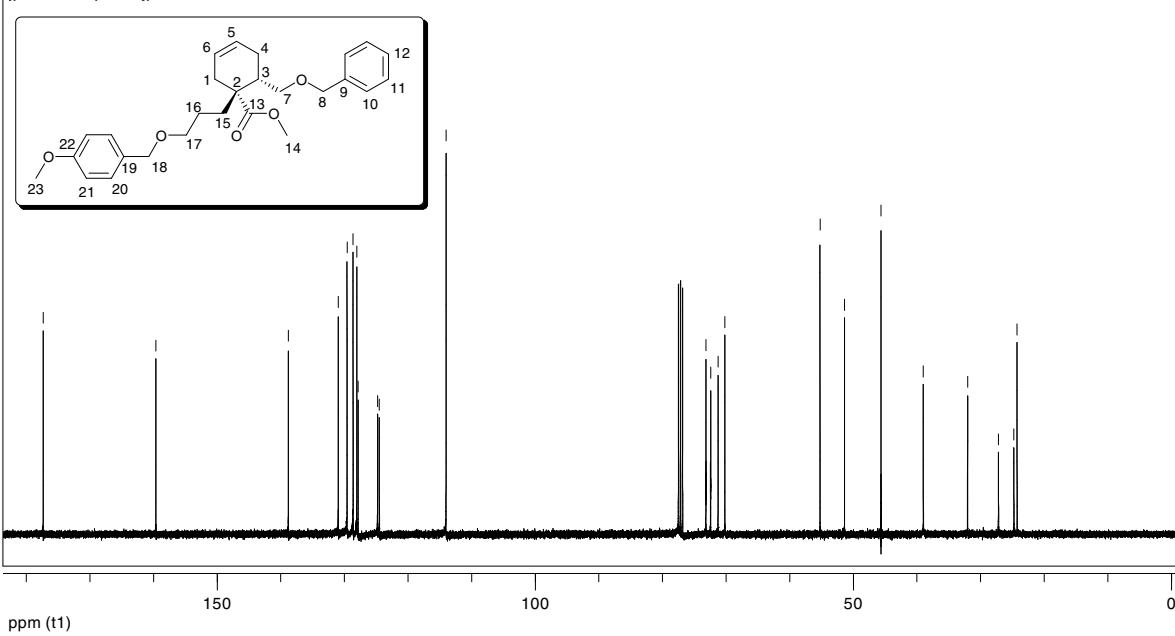
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jps/3/98/1, p2092jps, CDCl_3



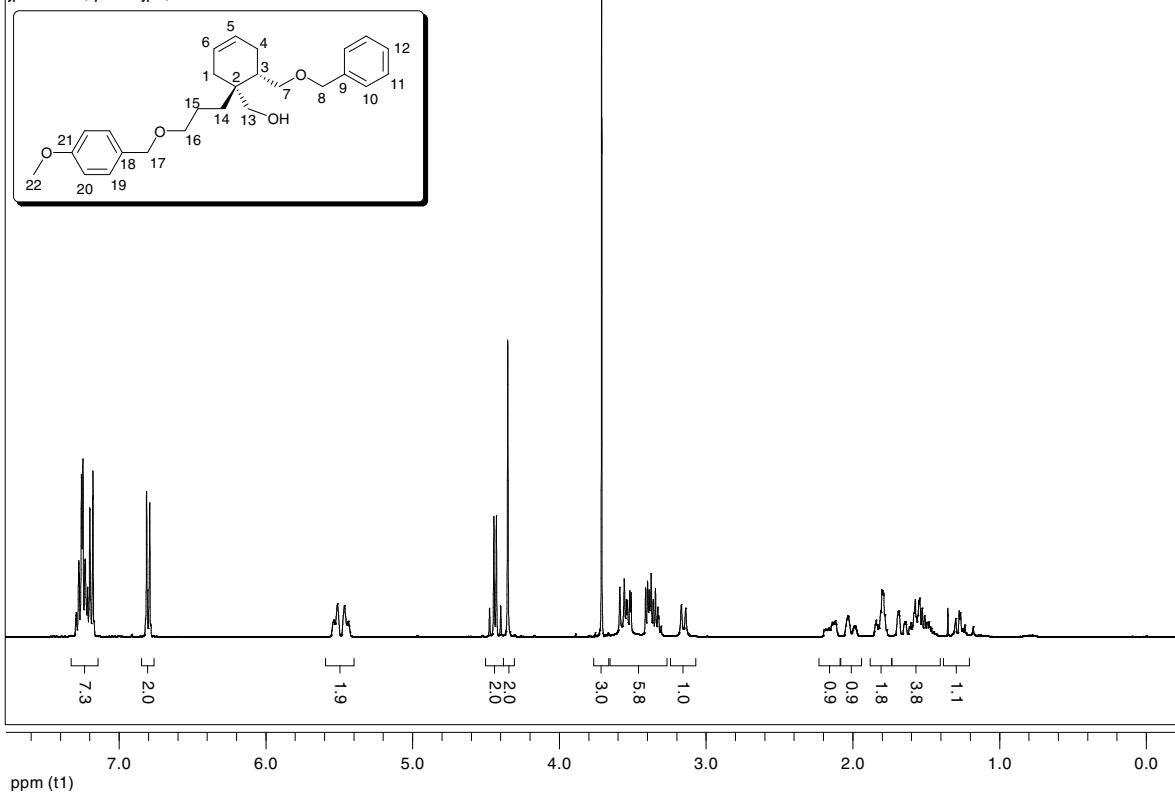
ECX 400 MHz, ¹H-NMR of compound (+)-12
jps/3/94/1, p2625jps, CDCl₃



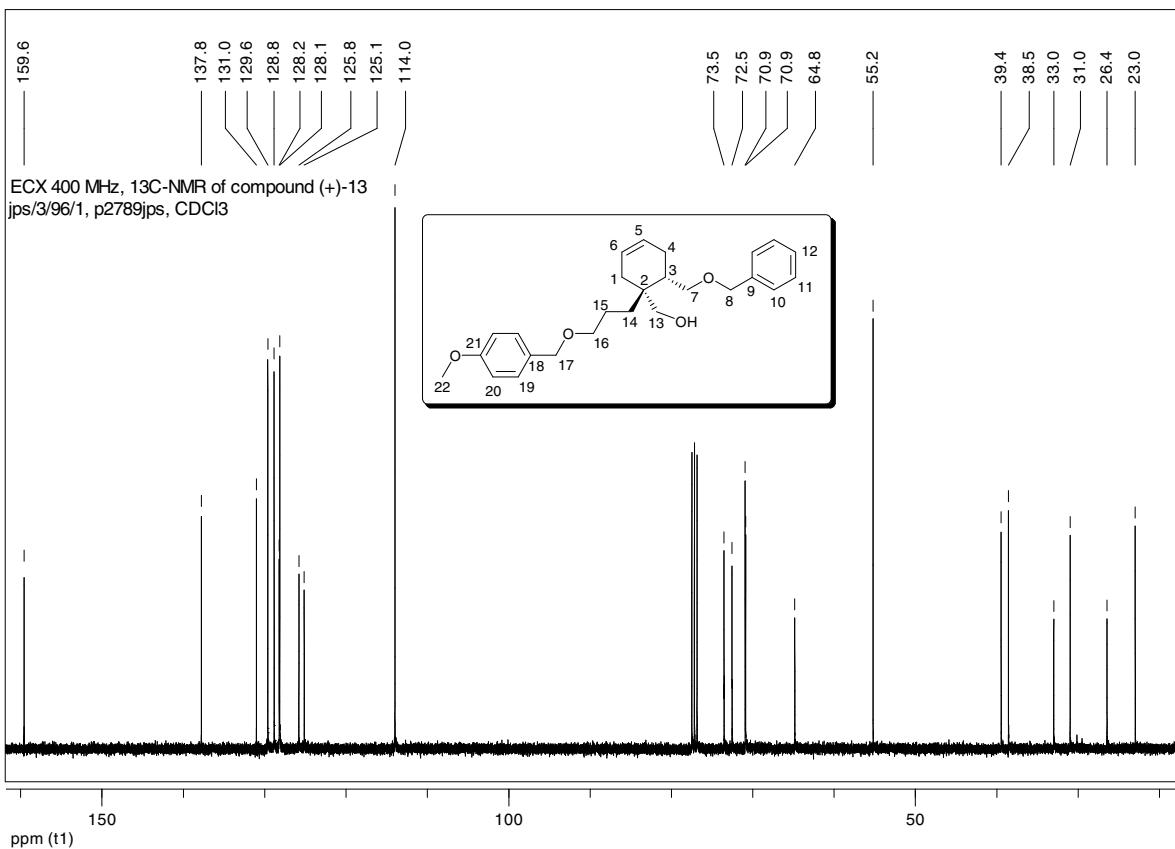
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jps/3/94/1, p2651jps, CDCl₃



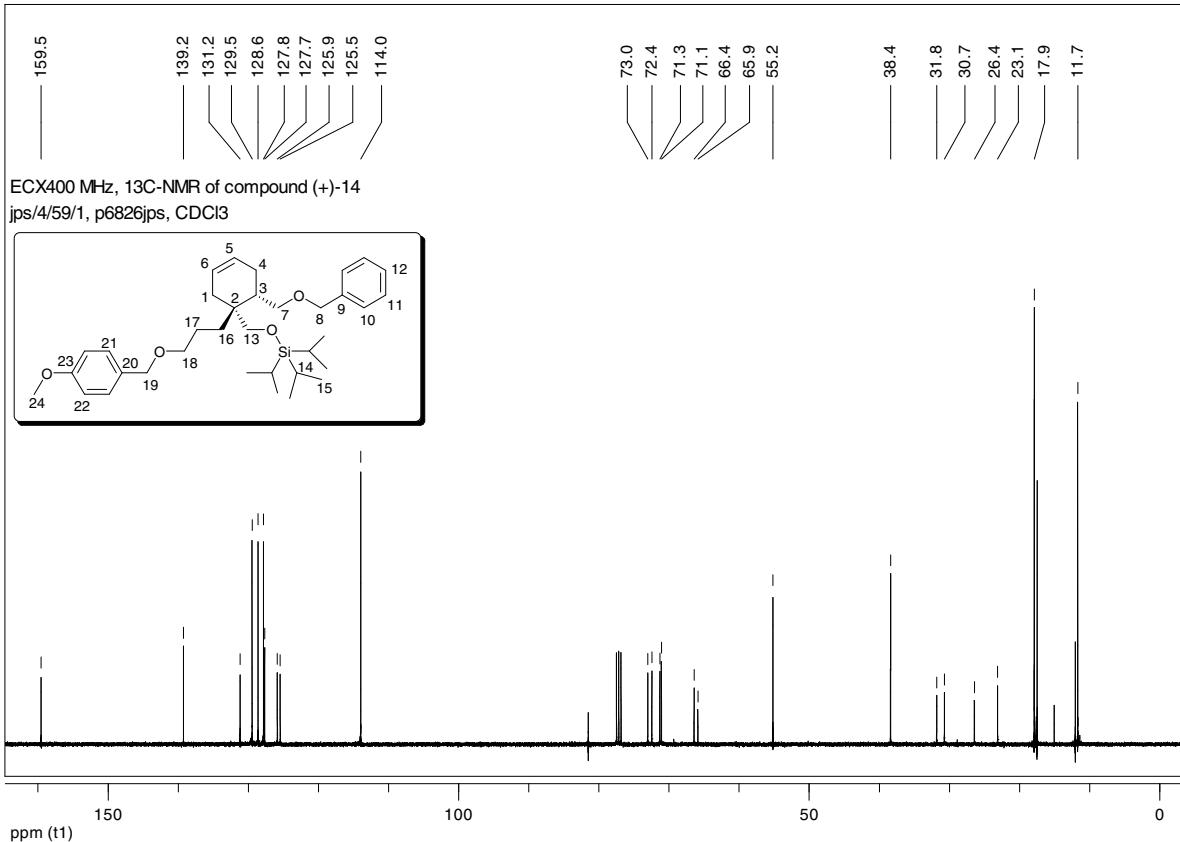
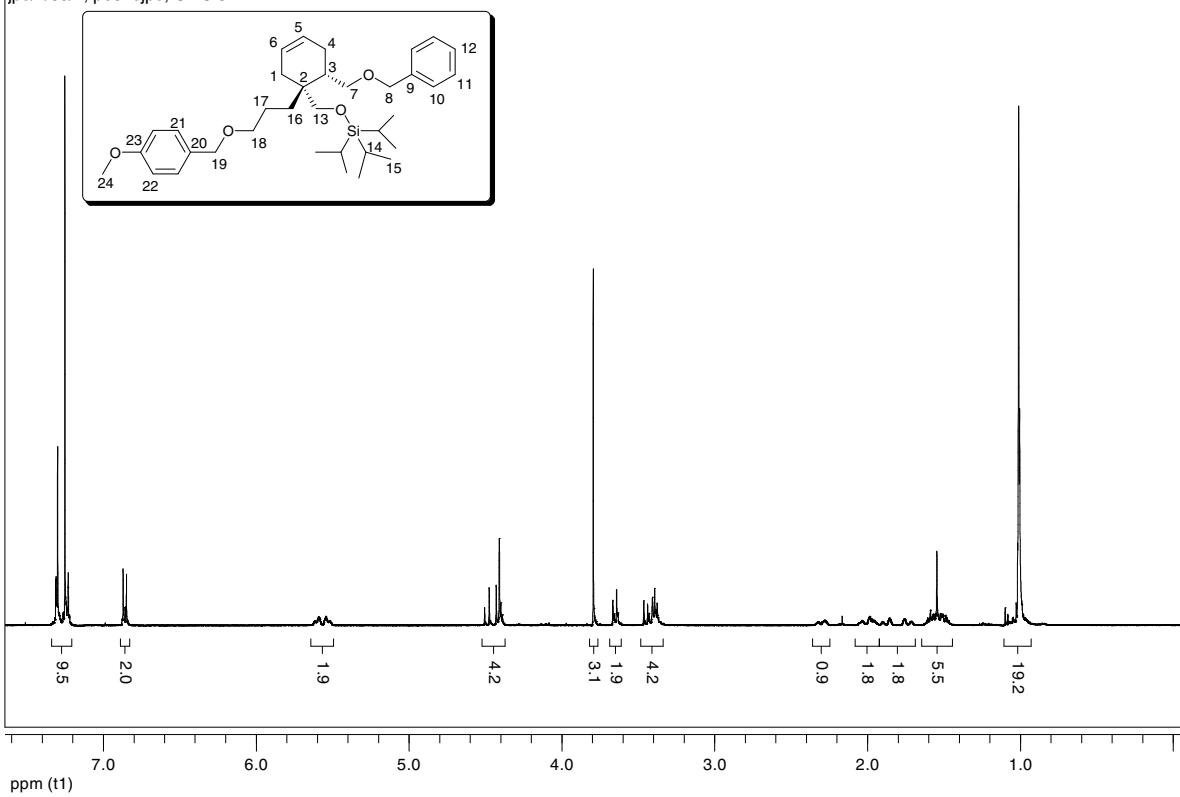
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jps/3/96/1, p2786jps, CDCl₃



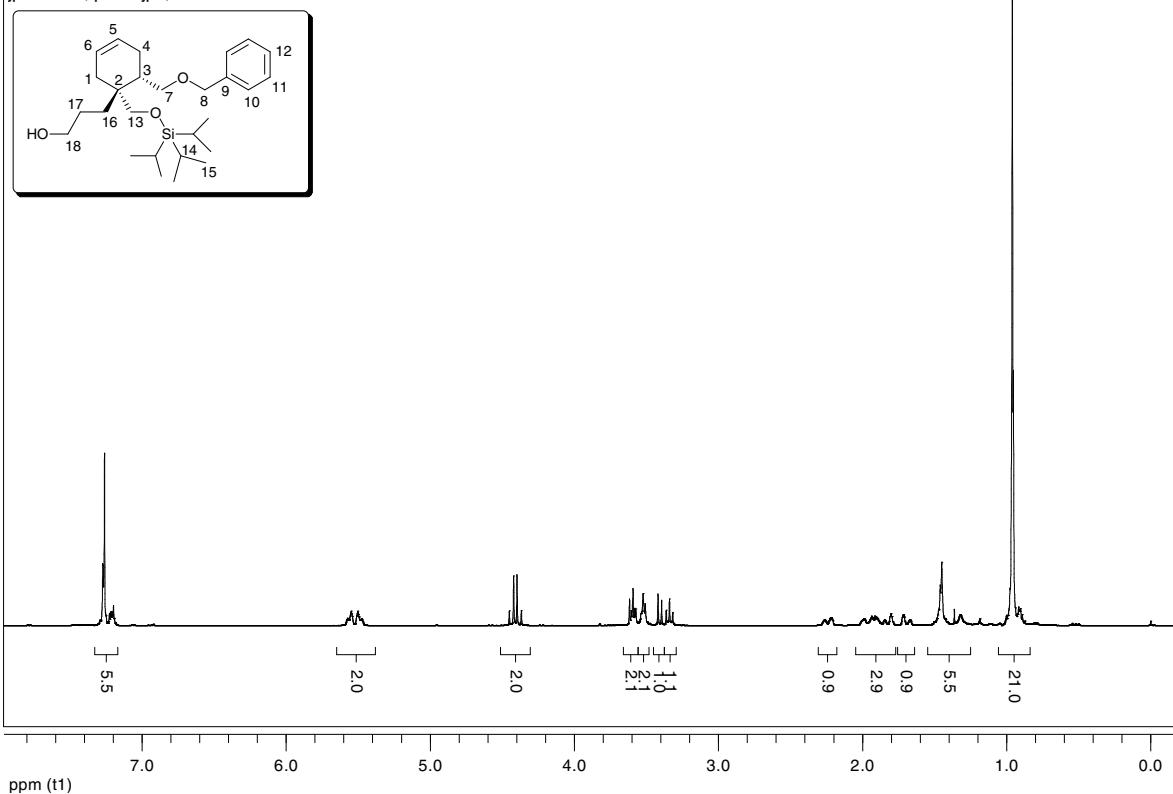
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jps/3/96/1, p2789jps, CDCl₃



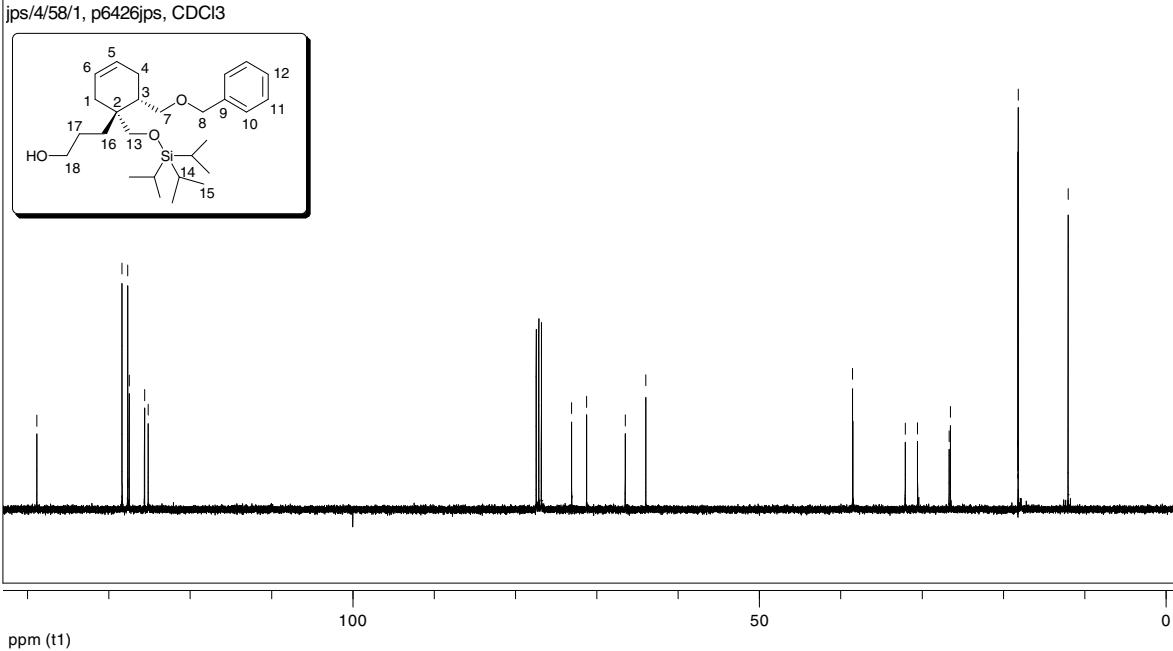
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jps/4/59/1, p6826jps, CDCl₃



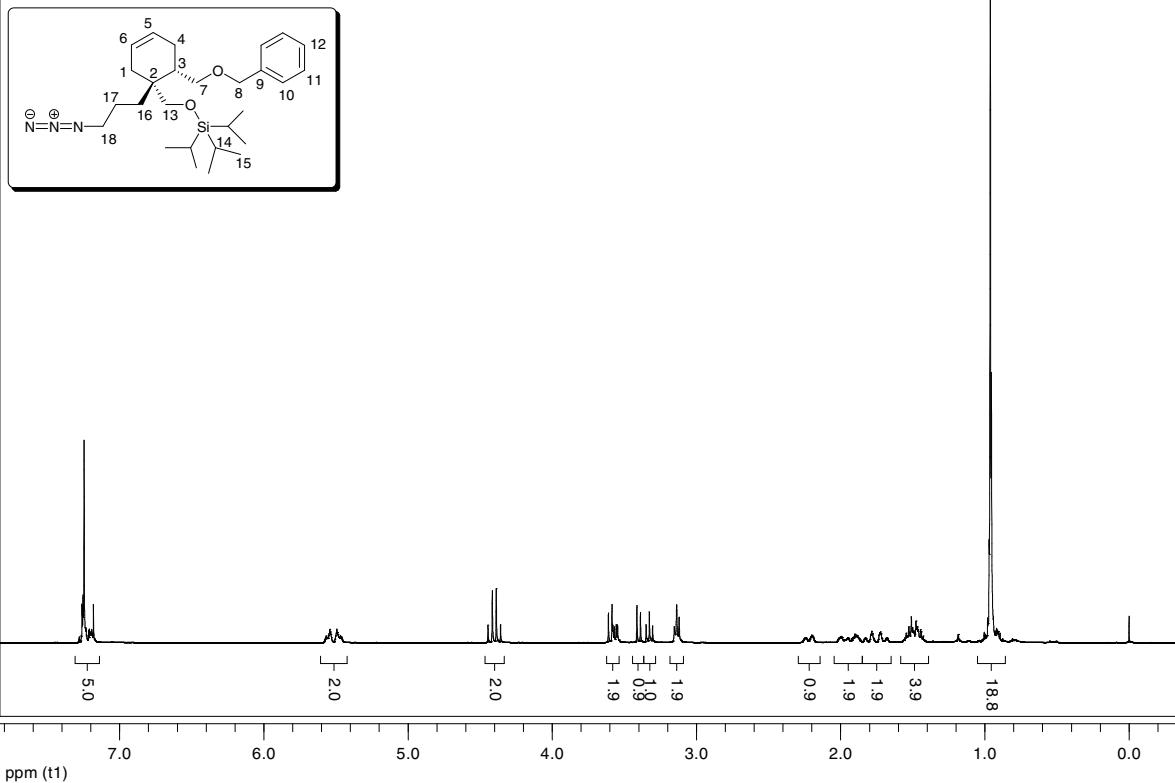
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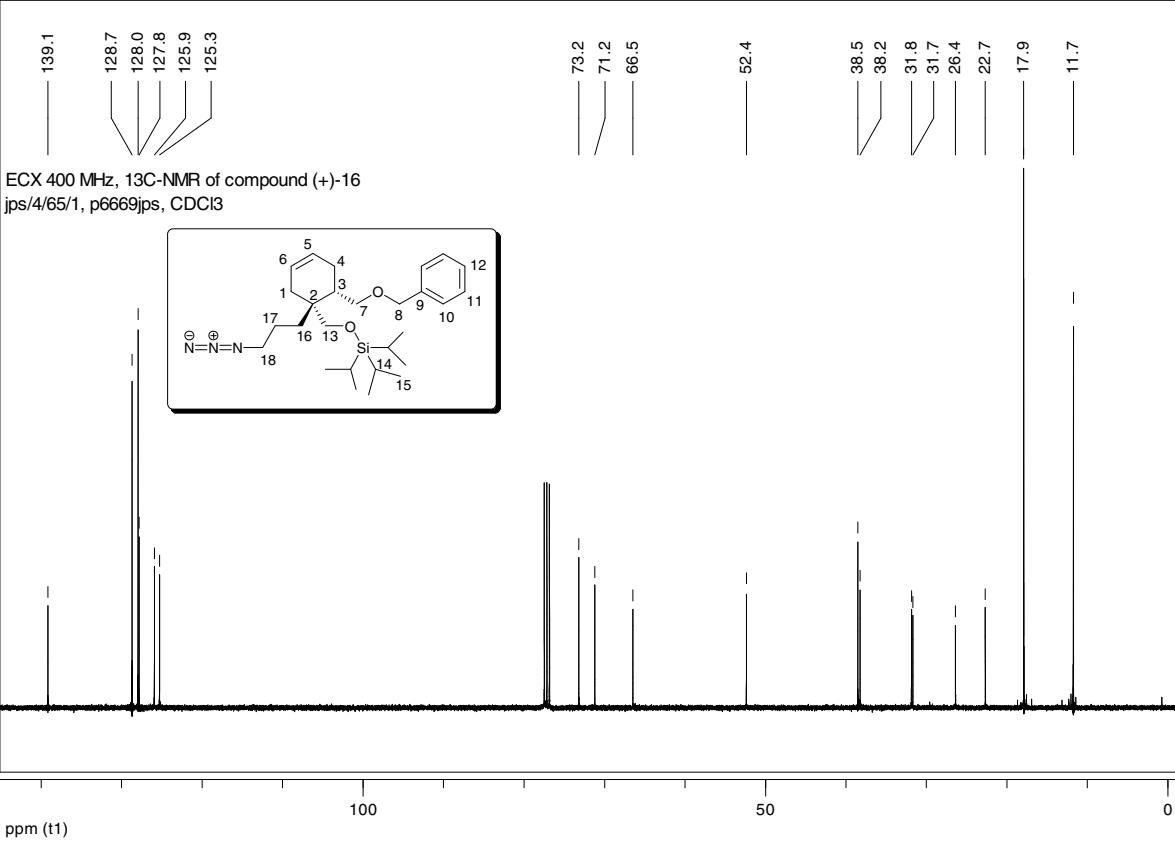
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jps/4/58/1, p6426jps, CDCl_3



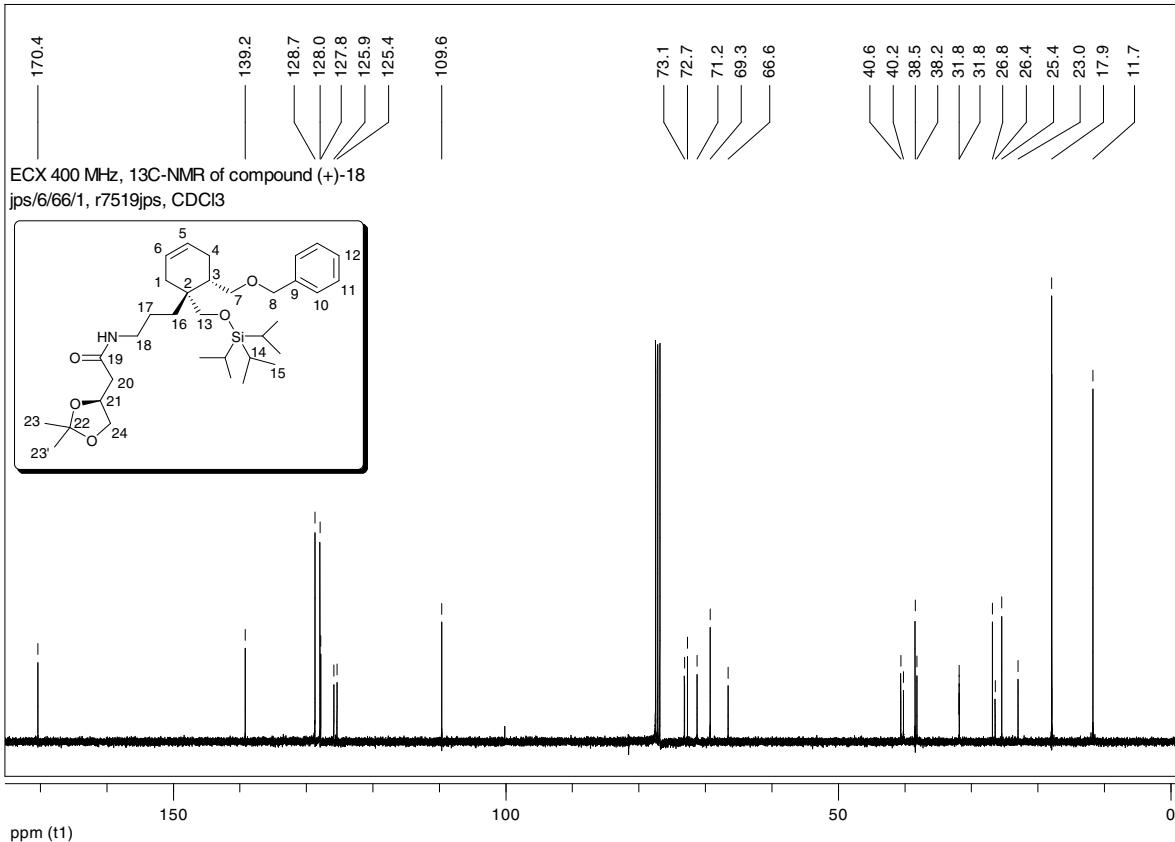
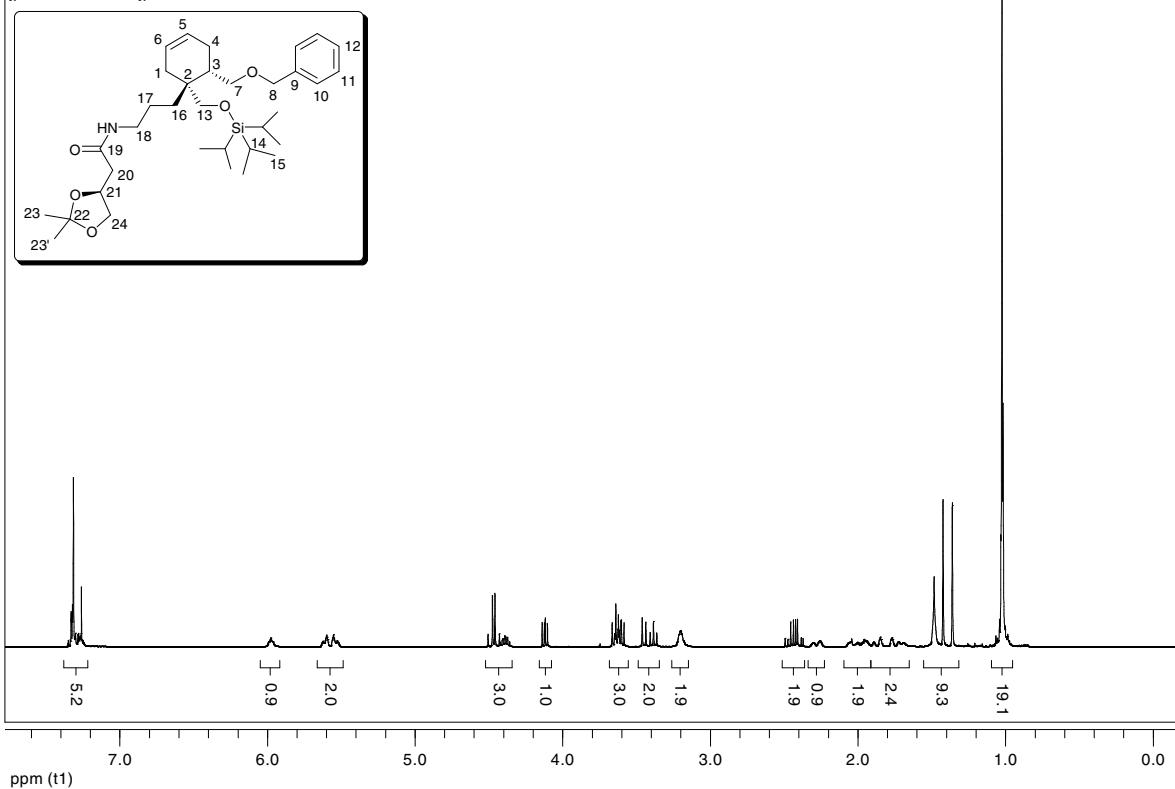
ECX400 MHz, ^1H -NMR of compound (+)-16
jps/4/65/1, p6668jps, CDCl₃

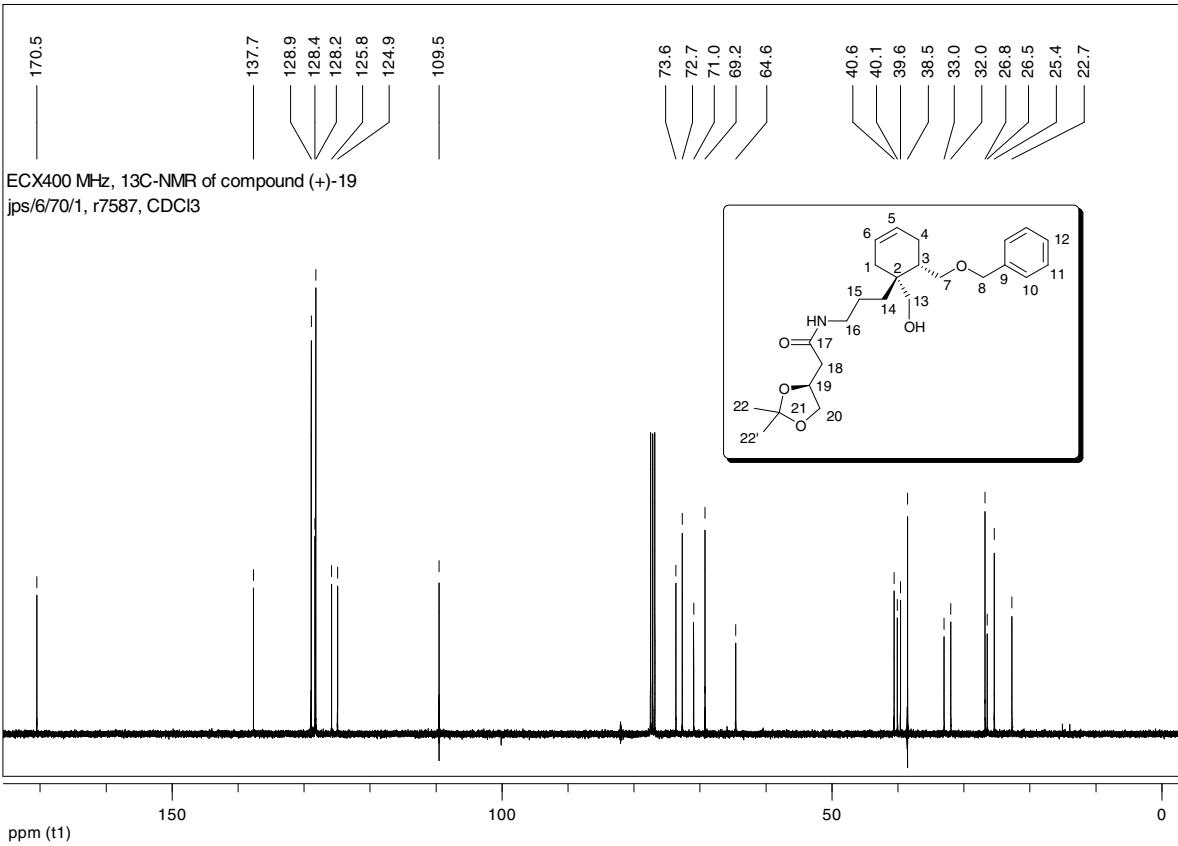
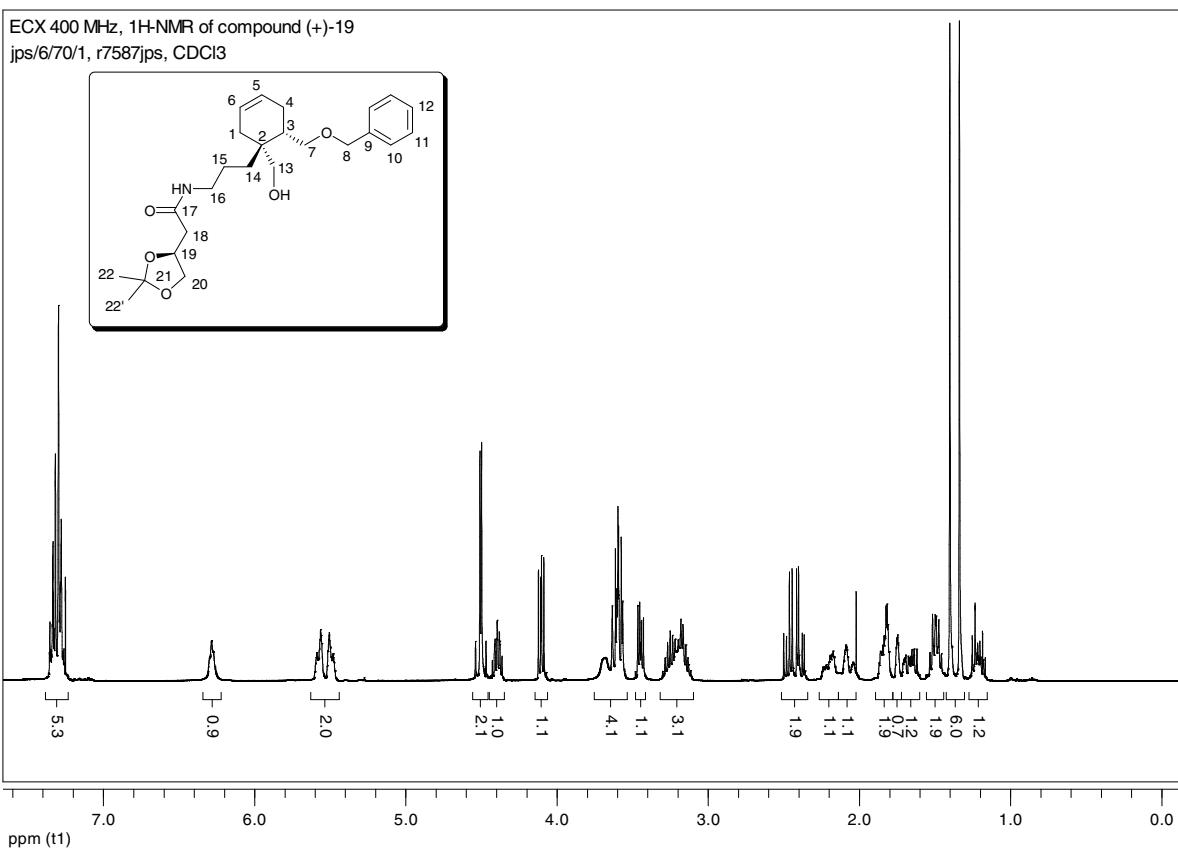


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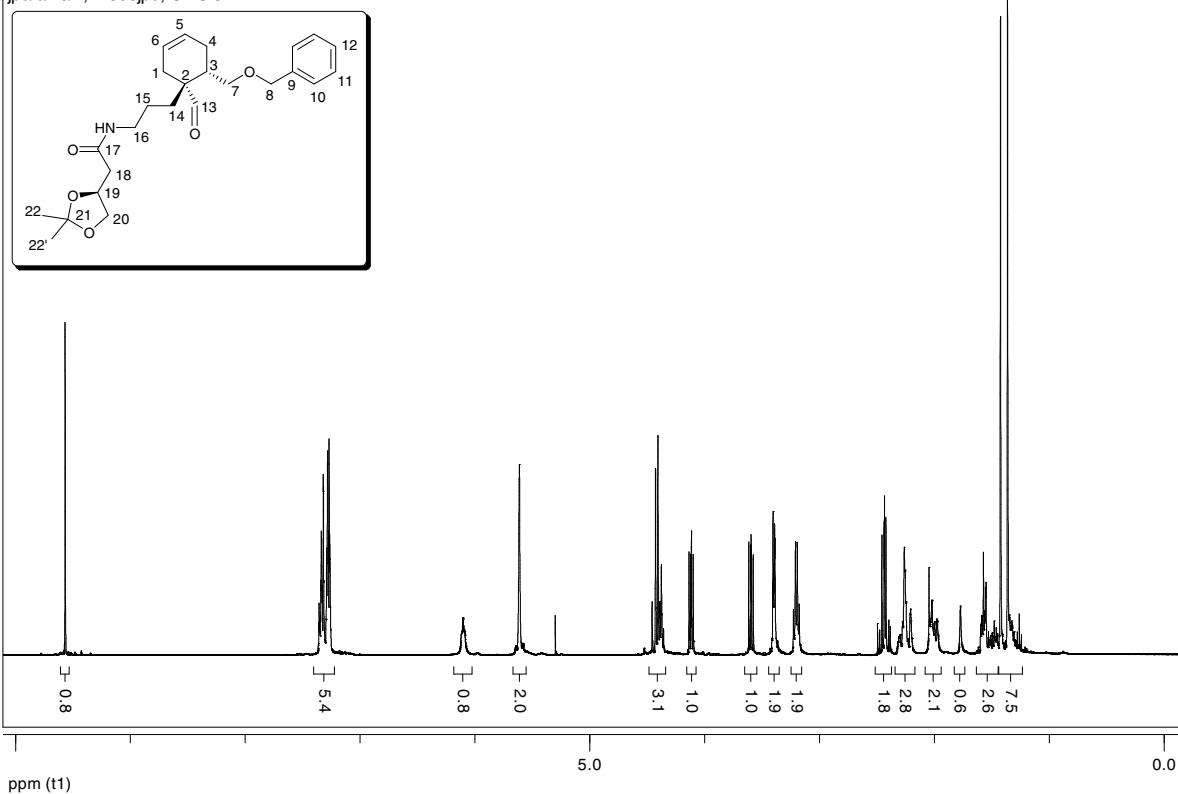


ECX 400 MHz, 1H-NMR of compound (+)-18
jps/6/66/1, r7516jps, CDCl₃

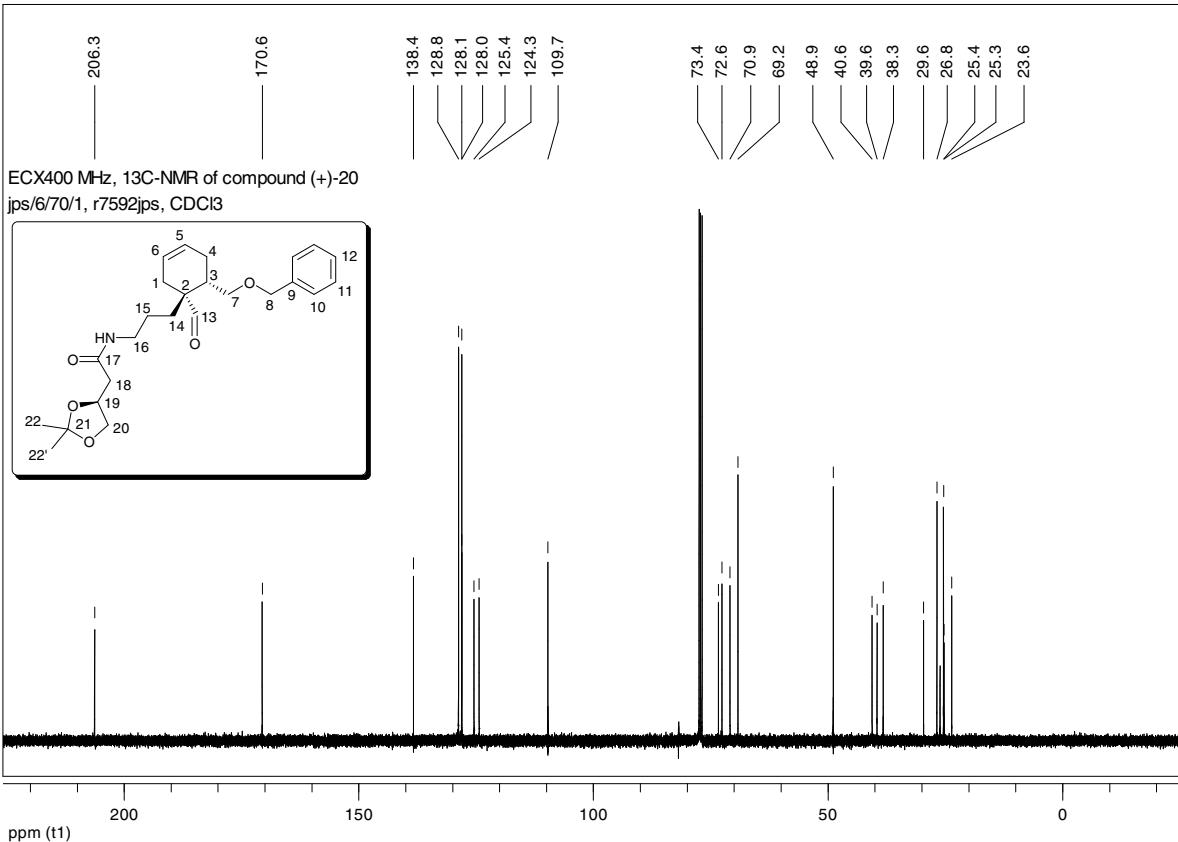




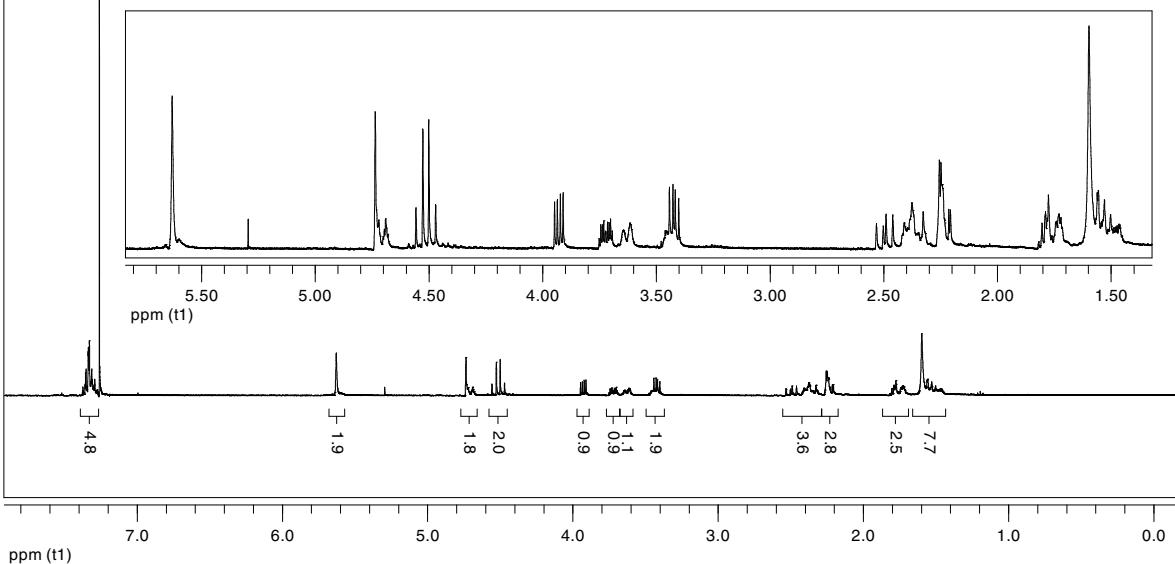
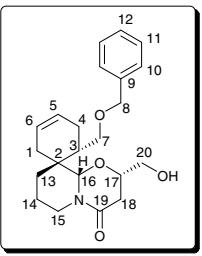
ECX400 MHz, ¹H-NMR of compound (+)-20
jps/6/70/1, r7590jps, CDCl₃



ECX400 MHz, ¹³C-NMR of compound (+)-20
jps/6/70/1, r7592jps, CDCl₃



ECX400 MHz, ^1H -NMR of compound (-)-21
jps/6/51/1, k6069jps, CDCl₃



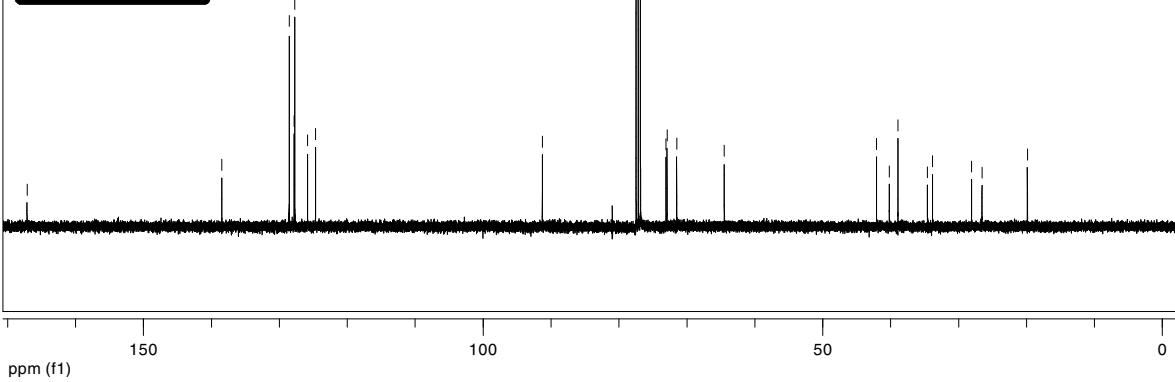
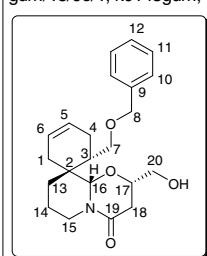
167.1
138.5
128.5
127.8
127.7
125.8
124.7

ECX400 MHz, ^{13}C -NMR of compound (-)-21
gdm/18/96/1, k0143gdm, CDCl₃

91.3

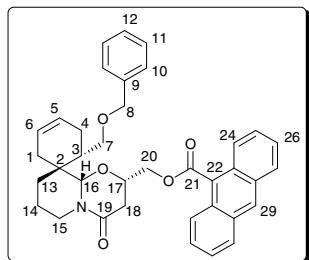
73.1
72.9
71.5
64.5

42.1
40.2
38.9
34.6
33.8
28.1
26.6
19.9

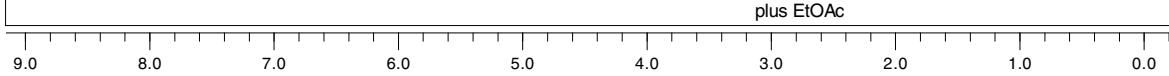


ECX400 MHz, ^1H -NMR of compound (-)-22

jps/6/61/1, r7161jps, CDCl_3

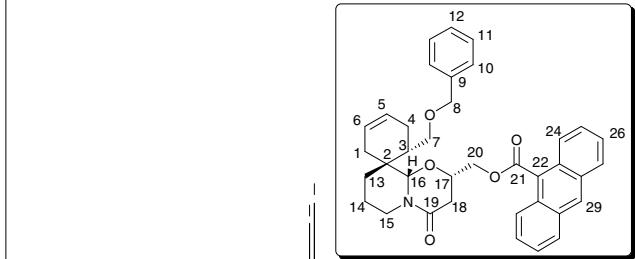


ppm (t1)



ECX400 MHz, ^{13}C -NMR of compound (-)-22

jps/6/61/1, r7161jps, CDCl_3



ppm (t1)



