Supporting Information

Biomimetic Organocatalytic Approach to 4-Arylquinolizidine Alkaloids and Application in the Synthesis of (-)-Lasubine II and (+)-Subcosine II

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Experimental Procedures	S2-S12
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General:

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH₂Cl₂ were distilled from CaH₂. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system. HPLC analyses were performed on a Waters chromatographic system using the Breeze software.

Enones 9 and 20 are commercially available and enones 13¹ and 21² were prepared according to the literature procedures. The synthesis of enones 14 and 15 is provided.

Dodecahydro-1H,6H,11H-tripyrido[1,2-a:1',2'-c:1'',2''-e][1,3,5]triazine (10)³

To a solution of *N*-chlorosuccinimide (3.78 g, 27.9 mmol) in diethyl ether (75 mL) was added a solution of distilled piperidine (2.48 mL, 25.2 mmol) in ether (50 mL) over 30 min at room temperature. The reaction mixture was stirred for 3 h at ambient temperature after which it was filtered through a pad of Celite[®] and the residue was washed with ether (1 x 25 mL). The combined filtrates were washed with water (3 x 25 mL), dried over anhydrous Na₂SO₄ and concentrated without heating to give *N*-chloropiperidine.

An ethereal solution of the above *N*-chloropiperidine was added dropwise to ethanolic KOH (prepared by heating 2.1 eq of solid KOH in ethanol (15.0 mL) to 85°C) at room temperature and the reaction was left to stir overnight. The white precipitate of KCl formed was then separated by filtration through a pad of Celite®. The filtrate was concentrated to remove ethanol and the residue was diluted with ethyl acetate. The resulting solution was washed with water (3 x 20 mL) to provide the piperideine **10** (1.45 g, 70% yield over two steps). This is a mixture of monomeric (minor) and trimeric (major) forms (¹H NMR). This material was used as such without purification.

¹H NMR (300 MHz, CDCl₃): Trimer: δ 3.18-3.06 (m, 3H), 2.80 (dd, 3H, J = 7.2, 3.0 Hz), 2.07-1.95 (m, 3H), 1.80-1.61 (m, 9H), 1.60-1.51 (m, 6H), 1.38-1.20 (m, 3H). Visible peaks for the monomer: δ 7.83-7.78 (m, 1H), 3.61-3.53 (m, 1H), 2.21-2.12 (m, 2H), 1.80-1.61 (m, 1H); 13 C NMR (75 MHz, CDCl₃): Trimer δ 82.0, 46.4, 29.2, 25.8, 22.3. Visible peaks for the monomer: δ 163.2, 49.3, 28.8, 18.7; IR (neat): 2924, 2850, 2812, 2775, 2730, 2701, 1446, 1379, 1238, 1131, 1107, 1024, 889, 796 cm⁻¹; HRMS (ESI, pos.): m/z 249.2198 (249.2205 calc. for C₁₅H₂₇N₃ (M⁺)), 250.2275 (250.2283 calc. for C₁₅H₂₈N₃ (M+H)⁺.

Dodecahydrotripyrrolo[1,2-a:1',2'-c:1'',2''-e][1,3,5]triazine (22)⁴

To a stirred mixture of pyrrolidine (2.0 mL, 24.35 mmol), AgNO₃ (21.3 mg, 0.13 mmol) and NaOH (2.0 g, 50 mmol) in water (25 mL) at 0 °C was added dropwise a 25% aqueous solution of sodium peroxodisulfate Na₂S₂O₈ (6.25 g, 26.3 mmol) in water (25 mL). The reaction mixture was stirred at ambient temperature for 2.5 h after which it was extracted with dichloromethane (3 x 10 mL). The organic layer was washed with brine following which it was dried overnight over Na₂SO₄-K₂CO₃ in the refrigerator. The organic layer was then concentrated without heating to provide 22 as a mixture of monomeric (minor) and trimeric (major) forms by ¹H NMR. The crude material was used as such without purification.

IR (neat): 2955, 2871, 2784, 1677, 1613, 1458, 1391, 1337, 1292, 1232, 1194, 1178, 1141, 1065 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): Trimer: δ 3.07-2.95 (m, 6H), 2.37-2.26 (m, 3H), 1.97-1.63 (m, 12H). Visible peaks for the monomer: δ 7.63-7.59 (m, 1H), 3.89-3.80 (m, 2H), 2.58-2.48 (m, 2H), 1.97-1.63 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): Trimer: δ 82.0, 45.9, 27.9, 20.3. Visible peaks for monomer: δ 166.9, 61.2, 36.6, 20.4; HRMS (ESI, pos.): m/z 207.1734 (207.1735 calc. for C₁₂H₂₁N₃ (M⁺)), m/z 208.1816 (208.1814 calc. for C₁₂H₂₂N₃ (M+H)⁺.

General procedure for the synthesis of enones 14 and 15:

To a solution of 1-(triphenylphosphoranylidene)-2-propanone in dichloromethane at 0°C was added a solution of the aldehyde in dichloromethane and the mixture was left to stir overnight at room temperature. After consumption of the aldehyde (TLC), the solvent was removed in vacuo and the crude product was purified using flash column chromatography on silica gel (hexane/EtOAc, 9:1).

(*E*)-4-(3-(Benzyloxy)-4-methoxyphenyl) but-3-en-2-one (14):

Reaction of 3-(benzyloxy)-4-methoxybenzaldehyde (1.3 gm, 5.4 mmol) with 1-(triphenylphosphoranylidene)-2-propanone (2.4 gm, 8.1 mmol) in CH₂Cl₂ for 48 hours according to the general procedure gave, after purification by flash chromatography on silica gel, 818 mg (55%) of **14** as a white solid.

Mp.: 111-113 °C; IR (neat): 3065, 3030, 2933, 2874, 2846, 1660, 1640, 1622, 1595, 1511, 1425, 1363, 1380, 1249, 1220, 1160, 1136, 1009, 980, 807, 739, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.48-7.29 (m, 6H), 7.13 (dd, 1H, J = 8.5, 2.1 Hz), 7.10 (d, 1H, J = 2.1 Hz), 6.90 (d, 1H, J = 8.5 Hz), 6.52 (d, 1H, J = 16.4 Hz), 5.17 (s, 2H), 3.91 (s, 3H), 2.34 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 198.3, 152.1, 148.4, 143.4, 136.6, 128.6, 128.0, 127.3, 127.2, 125.2, 123.3, 112.7, 111.6, 71.1, 56.0, 27.4; HRMS (ESI, pos.): m/z 282.1262 (282.1256 calc. for C₁₈H₁₈O₃ (M⁺)).

(*E*)-4-(2-bromo-4,5-dimethoxyphenyl)but-3-en-2-one (15):

To a solution of veratraldehyde (3.3 g, 20 mmol) in methanol (30 mL), was added bromine (1 mL, 1.05 eq). The reaction was left to stir overnight at room temperature. After consumption of the starting material, the methanol was removed *in vacuuo* and the residue was dissolved with dichloromethane (50 mL). The resulting solution was washed with a saturated aqueous solution of sodium thiosulphate (2 x 50 mL) and then with brine (100 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated to provide 2-bromo-4,5-dimethoxybenzaldehyde (4.5 gm, 92%) as a white solid which was pure by ¹H NMR and was used in the next step without purification.

Reaction of 2-bromo-4,5-dimethoxybenzaldehyde (2.8 gm, 11.4 mmol) with 1-(triphenylphosphoranylidene)-2-propanone (5.1 gm, 17.1 mmol) in CH₂Cl₂ for 48 hours according to the general procedure gave, after purification by flash chromatography on silica gel, 2.27 g (78%) of **15** as a beige solid.

Mp.: 118-119 °C; IR (neat): 2963, 2935, 2919, 2836, 1660, 1637, 1591, 1502, 1435, 1357, 1253, 1210, 1165, 1024, 972 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.83 (d, 1H, J = 16.3 Hz), 7.09 (s, 1H), 7.06 (s, 1H), 6.53 (d, 1H, J = 16.3 Hz), 3.91 (s, 3H), 3.90 (s, 3H), 2.41 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 198.4, 151.6, 148.8, 142.0, 127.9, 126.2, 117.6, 115.6, 109.2, 56.3, 56.1, 26.9; HRMS (ESI, pos.): m/z 284.0037 (284.0048 calc. for C₁₂H₁₃O₃Br (M⁺)), m/z 285.0109 (285.0126 calc. for C₁₂H₁₄O₃Br⁷⁹ (M+H)⁺), m/z 287.0090 (287.0106 calc. for C₁₂H₁₄O₃Br⁸¹ (M+2+H)⁺)

General procedure for the Mannich/aza-Michael reaction:

To the imine trimer **10** or **22** in a vial were added *S*-proline, the enone and DMF at room temperature and the mixture was stirred at ambient temperature for the specified period. Aqueous HCl (1M) was added and the mixture was extracted with EtOAc. The aqueous layer basified to pH 10 with solid NaOH and the basic mixture was extracted with dichloromethane. The combined extracts were dried and concentrated and the residue was purified by flash chromatography on silica gel (CH₂Cl₂/MeOH, 99:1) to provide the required 4-arylquinolizidinone or 5-arylindolizidinone.

(4S,9aS)-4-(3,4-Dimethoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (11):

Synthesis of 11 on >1 mmol scale:

Reaction of (E)-4-(3,4-dimethoxyphenyl)but-3-en-2-one (9, 1.48 g, 7.2 mmol) and (300 mg, 1.2 mmol) in the presence of S-proline (83 mg, 0.12 mmol) in DMF (3.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 624 mg (60%) of $\mathbf{11}$ as a pale yellow foam.

 R_f = 0.36 (EtOAc/MeOH, 80:20); IR (neat): 2927, 2850, 2835, 2796, 1717, 1593, 1508, 1461, 1443, 1256, 1231, 1146, 1076, 1024, 812 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.92 (br s, 1H), 6.87-6.78 (br m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.21 (d, 1H, J = 12.1, 3.3 Hz), 2.84-2.62 (m,

2H), 2.57-2.21 (m, 4H), 1.80-1.18 (m, 7H); 13 C NMR (75 MHz, CDCl₃): δ 207.8, 149.3, 148.3, 135.2, 119.5, 111.1, 109.8, 70.0, 62.5, 56.0, 55.9, 52.8, 50.9, 48.7, 34.3, 25.8, 24.2; HRMS (ESI, pos.): m/z 289.1692 (289.1678 calc. for C₁₇H₂₃NO₃ (M⁺)), m/z 290.1764 (290.1756 calc. for C₁₇H₂₄NO₃ (M+H)⁺); $[\alpha]_D^{20} = -87.2$ (c 0.83, CHCl₃, lit.⁵ $[\alpha]_D = -78.05$ (c 0.30, CHCl₃)); HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), $t_{major} = 6.85$ min., $t_{minor} = 9.82$ min., 98% ee.

(4S,9aS)-4-(3-Hydroxy-4-methoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (1):

Reaction of 10 (200 mg, 0.8 mmol) and (*E*)-4-(3-hydroxy-4-methoxyphenyl)but-3-en-2-one (920 mg, 4.8 mmol) in the presence of *S*-proline (55.2 mg, 0.48 mmol) in DMF (2 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 265 mg (40%) of 1 as a pale yellow foam.

R_f= 0.3 (EtOAc/MeOH, 90:10); IR (neat): 3392, 3010, 2931, 2841, 2795, 1715, 1592, 1441, 1323, 1270, 1218, 1123, 1026, 879, 806, 754 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.97 (br d, 1H, J = 1.4 Hz), 6.82-6.76 (m, 2H), 5.65 (broad s, 1H), 3.88 (s, 3H), 3.17 (dd, 1H, J = 12.1, 3.3 Hz), 2.84-2.75 (m, 1H), 2.71-2.59 (m, 1H), 2.55-2.43 (m, 1H), 2.43-2.20 (m, 3H), 1.78-1.38 (m, 6H), 1.34-1.17 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 208.0, 145.9, 136.0, 118.9, 113.2, 110.6, 69.8, 62.4, 56.0, 52.8, 50.9, 48.8, 34.5, 25.9, 24.2; HRMS (ESI, pos.): m/z 275.1533 (275.1521 calc. for C₁₆H₂₁NO₃ (M⁺)), m/z 276.1606 (276.1600 calc. for C₁₆H₂₂NO₃ (M+H)⁺), 298.1399 (298.1419 calc. for C₁₆H₂₁NO₃Na (M+Na)⁺); [α]_D²⁰ = -67.0 (c 0.56, CHCl₃); HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_{major} = 10.95 min., t_{minor} = 8.72 min., 82% ee.

(4S,9aS)-4-(3-(Benzyloxy)-4-methoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (16):

Reaction of 10 (50 mg, 0.2 mmol) and (*E*)-4-(3-(benzyloxy)-4-methoxyphenyl)but-3-en-2-one (14, 338 mg, 1.2 mmol) in the presence of *S*-proline (13.8 mg, 0.12 mmol) in DMF (1 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 84 mg (40%) of 16 as a pale yellow foam.

R_f= 0.25 (EtOAc/MeOH, 90:10); IR (neat): 2930, 1714, 1521, 1510, 1263, 1248, 1238, 1223, 1163, 1141, 1044, 831 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.46-7.42 (m, 2H), 7.38-7.28 (m, 3H), 6.94 (broad s, 1H), 6.83 (m, 2H), 5.16 (s, 2*H*), 3.87 (s, 3H), 3.15 (dd, 1H, J = 12.0, 3.2 Hz), 2.72-2.18 (m, 6H), 1.75-1.18 (m, 7H); ¹³C NMR (75 MHz, CDCl₃): δ 208.0, 149.2, 148.4, 137.0, 135.2, 128.5, 127.9, 127.5, 120.2, 113.1, 111.8, 71.1, 69.8, 62.4, 56.1, 52.7, 50.9, 48.8, 34.4, 25.9, 24.2; HRMS (ESI, pos.): m/z 365.1998 (365.1991 calc. for C₂₃H₂₇NO₃ (M⁺)), m/z 366.2071 (366.2069 calc. for C₂₃H₂₈NO₃ (M+H)⁺), 388.1889 (388.1889 calc. for C₂₃H₂₇NO₃Na (M+Na)⁺); [α]_D²⁰ = -65.9 (c 0.62, CHCl₃); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 97/3, flow rate 1 mL/min, λ = 254 nm), t_{major} = 17.69 min., t_{minor} = 20.89 min., 95% ee.

(4S,9aS)-4-(2-Bromo-4,5-dimethoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (17):

Reaction of **10** (50 mg, 0.2 mmol) and (*E*)-4-(2-bromo-4,5-dimethoxyphenyl)but-3-en-2-one (**15**, 342 mg, 1.2 mmol) in the presence of *S*-proline (13.8 mg, 0.12 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, unreacted **15** (244 mg) and 45 mg (20%, 35% based on recovered starting material) of **17** as a pale yellow foam.

 R_f = 0.29 (EtOAc/MeOH, 95:5); IR (neat): 2931, 2842, 1720, 1500, 1461, 1439, 1378, 1363, 1343, 1323, 1276, 1246, 1207, 1160, 1119, 1076, 1027 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ

7.14 (s, 1H), 6.96 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.82 (dd, 1H, J = 10.2, 5.2 Hz), 2.83-2.74 (m, 1H), 2.55-2.29 (m, 5H), 1.81-1.66 (m, 3H), 1.62-1.22 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ 207.3, 149.3, 148.6, 133.3, 115.1, 113.2, 110.4, 67.2, 62.0, 56.2, 56.1, 52.3, 48.9, 48.6, 34.4, 25.8, 24.2; HRMS (ESI, pos.): m/z 367.0776 (367.0783 calc. for C₁₇H₂₂BrNO₃ (M⁺)), m/z 368.0848 (368.0861 calc. for C₁₇H₂₃Br⁷⁹NO₃ (M+H)⁺), m/z 370.083 (370.0841 calc. for C₁₇H₂₃Br⁸¹NO₃ (M+H+2)⁺); [α]D²⁰ = -90.7 (c 0.57, CHCl₃); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 97/3, flow rate 1 mL/min, λ = 254 nm), t_{major} = 16.82 min., t_{minor} = 16.12 min., 98% ee. (4S,9aS)-4-(3-(Tert-butyldimethylsilyloxy)-4-methoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (18):

To **1** (54 mg, 0.15 mmol) dissolved in DCM at 0 °C was added TBDMSOTf (52 μL, 0.23 mmol) and pyridine (24.2 μL, 0.30 mmol). The reaction mixture was stirred for 2 hours, after which the solvent was evaporated and the residue was directly purified by flash chromatography on silica gel (CH₂Cl₂/MeOH, 99:1) to provide 45 mg (77%) of **18** as a pale yellow gum. R_f = 0.24 (EtOAc/MeOH, 99:1), IR (neat): 2930, 2856, 2791, 1721, 1507, 1272, 1251, 1225, 1126, 889, 835, 780 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 6.87 (d, 1H, J = 2.1 Hz), 6.84 (dd, 1H, J = 8.3, 2.1 Hz), 6.79 (d, 1H, J = 8.3 Hz), 3.79 (s, 3H), 3.14 (dd, 1H, J = 12.1, 3.2 Hz), 2.80-2.74 (m, 1H), 2.67-2.59 (m, 1H), 2.52-2.45 (m, 1H), 2.39 (dt, 1H, J = 14.0, 2.9 Hz), 2.31 (dt, 1H, J = 14.0, 2.9Hz), 2.29-2.21 (m, 1H), 1.75-1.65 (m, 2H), 1.61 (td, 1H, J = 12.0, 2.6 Hz), 1.57-1.38 (m, 3H), 1.32-1.20 (m, 1H), 0.99 (s, 9H), 0.16 (d, 6H, J = 0.9 Hz); ¹³C NMR (75 MHz, CDCl₃): 208.1, 150.3, 145.2, 135.2, 120.4, 119.7, 112.0, 69.6, 62.4, 55.5, 52.7, 50.9, 48.8, 34.4, 25.9, 25.8, 24.2, 18.5; HRMS (ESI, pos.): m/z 389.2375 (389.2386 calc. for C₂₂H₃₅NO₃Si (M⁺)), m/z 390.2446 (390.2464 calc. for C₂₂H₃₆NO₃Si (M+H)⁺); [α] $_{D}^{20}$ = -64.8 (c 1.56, CHCl₃).

(5S, 8aS)-5-Phenylhexahydroindolizin-7(1H)-one (23):

Reaction of **22** (50 mg, 0.24 mmol) and (E)-4-phenylbut-3-en-2-one (**20**, 204 mg, 1.4 mmol) in the presence of S-proline (16.1 mg, 0.14 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 70 mg (47%) of **23** as a pale yellow gum.

R_f = 0.35 (EtOAc/MeOH, 90:10); IR (neat): 2960, 2819, 2781, 1711, 1371, 1348, 1302, 1290, 1245, 1152, 1029, 765, 701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.40-7.24 (m, 5H), 3.32 (dd, 1H, J = 11.4, 3.6 Hz), 2.86-2.77 (m, 1H), 2.68-2.53 (m, 2H), 2.52-2.36 (m, 3H), 2.05-1.55 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): δ 208.6, 142.2, 128.6, 127.7, 127.1, 66.9, 64.1, 51.5, 49.7, 47.3, 31.1, 21.5; HRMS (ESI, pos.): m/z 215.1304 (215.1310 calc. for C₁4H₁₇NO (M⁺)); [α]_D²⁰ = -100.6 (c 0.76, CHCl₃); HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, $\lambda = 254$ nm), $t_{major} = 5.87$ min., $t_{minor} = 5.10$ min., 94% ee.

(5S, 8aS)-5-(3,4-Dimethoxyphenyl)hexahydroindolizin-7(1H)-one (24):

Reaction of **22** (50 mg, 0.24 mmol) and (E)-4-(3,4-dimethoxyphenyl)but-3-en-2-one (**9**, 288 mg, 1.4 mmol) in the presence of S-proline (16.1 mg, 0.14 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 40 mg (21%) of **24** as a yellow gum.

 R_f = 0.17 (EtOAc/MeOH, 90:10); IR (neat): 2958, 2834, 2796, 1715, 1592, 1511, 1461, 1259, 1234, 1157, 1136, 1025, 728 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.94 (d, 1H, J = 1.9 Hz), 6.8 (dd, 1H, J = 8.2, 1.9 Hz), 6.81 (d, 1H, J = 8.2 Hz), 3.91 (s, 3H), 3.88 (s, 3H), 3.26 (dd, 1H, J = 11.4, 3.5 Hz), 2.87-2.80 (m, 1H), 2.68-2.55 (m, 2H), 2.52-2.34 (m, 3H), 2.07-1.56 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): 208.7, 149.2, 148.4, 134.9, 119.3, 110.9, 109.8, 66.6, 64.1, 56.0, 55.9,

51.5, 49.9, 47.3, 31.1, 21.5; HRMS (ESI, pos.): m/z 275.1526 (275.1521 for C₁₆H₂₁NO₃ (M⁺)), m/z 276.1594 (276.1600 for C₁₆H₂₂NO₃ (M+H⁺)); $[\alpha]_D^{20} = -87.2$ (c 0.83, CHCl₃); HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, $\lambda = 254$ nm), $t_{major} = 8.60$ min., $t_{minor} = 10.62$ min., 90% ee.

(5S, 8aS)-5-(4-Bromophenyl)hexahydroindolizin-7(1H)-one (25):

Reaction of **22** (50 mg, 0.24 mmol) and (E)-4-(4-bromophenyl)but-3-en-2-one (**21**, 315 mg, 1.4 mmol) in the presence of S-proline (16.1 mg, 0.14 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 56 mg (27%) of **25** as a yellow gum.

R_f= 0.23 (EtOAc/MeOH, 90:10); IR (neat): 2948, 2923, 2780, 2702, 1717, 1488, 1365, 1347, 1301, 1282, 1159, 1147, 1070, 1008, 838, 811 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.47(apparent d, 2H, J = 8.5 Hz), 7.26 (apparent d, 2H, J = 8.5 Hz, 2H), 3.29 (dd, 1H, J = 11.2, 3.8 Hz), 2.84-2.75 (m, 1H), 2.63-2.38 (m, 5H), 2.06-1.53 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): δ 208.0, 141.4, 131.8, 128.8, 121.4, 66.2, 64.0, 51.5, 49.6, 47.3, 31.1, 21.5; HRMS (ESI, pos.): m/z 293.0419 (293.0415 for C₁₄H₁₆BrNO (M⁺)), m/z 294.0492 (294.0494 for C₁₄H₁₇Br⁷⁹NO (M+H⁺)), m/z 296.0474 (296.0473 for C₁₄H₁₇Br⁸¹NO (M+2+H⁺)); [α]_D²⁰ = -66.7 (c 0.51, CHCl₃); HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 7.02 min., t_{minor} = 7.60 min., 99% ee.

(-)-Lasubine II (2):

To a solution of **11** (106 mg, 0.37 mmol) in anhydrous THF (1.5 mL) at -78 °C, was added dropwise a solution of L-Selectride (1.0 M in THF, 0.74 mL, 0.74 mmol). The mixture

was stirred at -78 °C for 3 h after which it was warmed to 0 °C and 1N NaOH (2 mL) was added. The resulting mixture was stirred at room temperature for 1 h and the THF was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and the solution was washed with brine (1 x 10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel using gradient elution (EtOAc→EtOAc/MeOH 8:2) to provide 81 mg (76%) of (-)-lasubine (II) as a colourless oil that solidified after storage at -20 °C for several days. Spectroscopic data is in agreement with reported data.⁵

R_f= 0.20 (EtOAc/MeOH, 90:10); Mp: 96-98 °C; IR (neat): 3388 (br), 2924, 1592, 1512, 1462, 1444, 1259, 1228, 1130, 1026 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.91 (br s, 1H), 6.86 (d, 1H, J = 8.2 Hz), 6.79 (d, 1H, J = 8.2 Hz), 4.17-4.12 (br m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.31 (dd, 1H, J = 11.8, 3.3 Hz), 2.72-2.66 (m, 1H), 2.43-2.35 (m, 1H), 1.90-1.83 (m, 1H), 1.83-1.77 (m, 1H), 1.74-1.64 (m, 4H), 1.59-1.23 (m, 6H); ¹³C NMR (75 MHz, CDCl₃: δ 149.0, 147.8, 137.3, 119.7, 111.0, 110.5, 65.1, 63.4, 56.5, 56.0, 55.9, 53.2, 42.9, 40.4, 33.7, 26.2, 24.9; HRMS (ESI, pos.): m/z 291.1830 (291.1834 calc. for C₁₇H₂₅NO₃ (M⁺)), m/z 292.1903 (292.1913 calc. for C₁₇H₂₆NO₃ (M+H)⁺); [α]_D²¹ = -76.5 (c 0.67, CHCl₃), lit.⁶ [α]_D²⁰ = +43.4 (c 1.0, CHCl₃) for (+)-lasubine II.

(+)-Subcosine II (3):

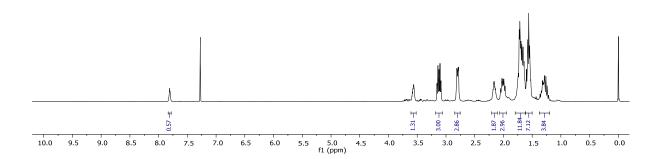
(*E*)-3,4-Dimethoxycinnamic acid (33.3 mg, 0.16 mmol) was added to a solution of crude (-)-lasubine II (48.2 mg, 0.16 mmol) in dichloromethane (2 mL) under nitrogen at ambient temperature. To the resulting solution was added EDCI (36.4 mg, 0.19 mmol) and DMAP (19.5 mg, 0.16 mmol) and the mixture was stirred 19 h at ambient temperature. Water (5 mL) was added and the organic layer was separated, diluted with CH₂Cl₂ (2 mL) and again washed with water (5 mL) and then with brine (5 mL). The organic layer was dried (Na₂SO₄) and concentrated. Purification of the residue by flash chromatography on silica gel (EtOAc) provided 51.3 mg (67%) of **3** as a white foam. Spectroscopic data is in agreement with reported data.⁷

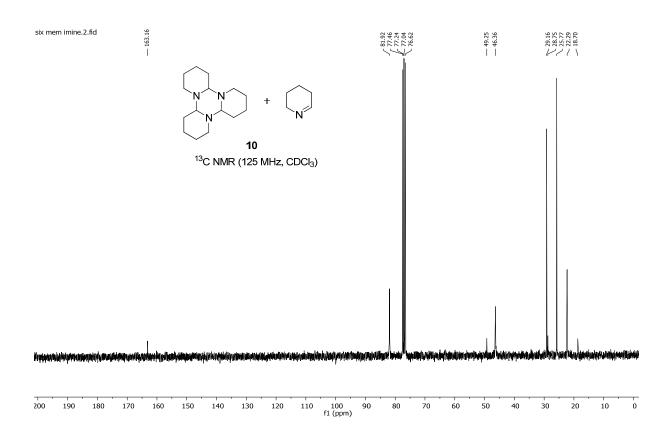
R_f= 0.41 (EtOAc/MeOH, 90:10), $[\alpha]_D^{21} = +89.3$ (c 0.56, MeOH); lit.⁵ $[\alpha]_D^{20} = +85.3$ (c 0.64, MeOH); ¹H NMR (300 MHz, CDCl₃): δ 7.67 (d, 1H, J = 15.9 Hz), 7.16 (dd, 1H, J = 8.2, 2.0 Hz), 7.12 (d, 1H, J = 2.0 Hz), 6.94- 6.83 (m, 2H), 6.90 (d, 1H, J = 8.2 Hz), 6.79 (d, 1H, J = 8.2 Hz), 6.41(d, 1H, J = 15.9 Hz), 5.22-5.18 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.29 (dd, 1H, J = 11.1, 3.8 Hz), 2.77-2.67 (m, 1H), 2.43-2.31 (m, 1H), 2.15-1.81 (m, 3H), 1.79-1.19 (m, 8H); ¹³C NMR (125 MHz, CDCl₃): δ 166.6, 151.2, 149.3, 149.2, 147.9, 144.6, 137.1, 127.5, 122.8, 116.4, 111.1, 109.7, 68.4, 64.2, 57.2, 56.0, 55.9, 53.2, 39.9, 37.5, 33.7, 26.2, 24.9; HRMS (ESI, pos.): m/z 481.2472 (481.2464 calc. for C₂₈H₃₅NO₆ (M⁺)), m/z 482.2544 (482.2543 calc. for C₂₈H₃₆NO₆ (M+H)⁺).

References:

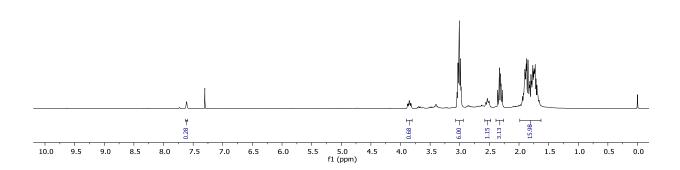
- 1. Chuprajob, T.; Changtam, C.; Chokchaisiri, R.; Chunglok, W.; Sornkaew, N.; Suksamrarn, A. *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 2839.
- 2. Bakos, M.; Dobi, Z.; Fegyverneki, D.; Gyömöre, A.; Fernández, I.; Soós, T. ACS Sustainable Chem. Eng., 2018, 6, 10869.
- 3. Monaco, M. R.; Renzi, P.; Scarpino Schietroma, D. M.; Bella, M. Org. Lett. 2011, 13, 4546.
- 4. 1-Pyrroline was prepared by oxidation of pyrrolidine, see: Nomura, Y.; Ogawa, K.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* **1977**, 693.
 - The crude product was purified by precipitation, see: Baker, J. D.; Heath, R. R.; Millar, J. G. *J. Chem. Ecol.* **1992**, *18*, 1595.
- 5. Trost, B. M.; Hung, C.-I. J. Am. Chem. Soc. 2015, 137, 15940.
- 6. Yu, R. T.; Rovis, T. J. Am. Chem. Soc., 2006, 128, 12370.
- 7. Cui, L.; Li, C.; Zhang, L. Angew. Chem. Int. Ed. 2010, 49, 9178.

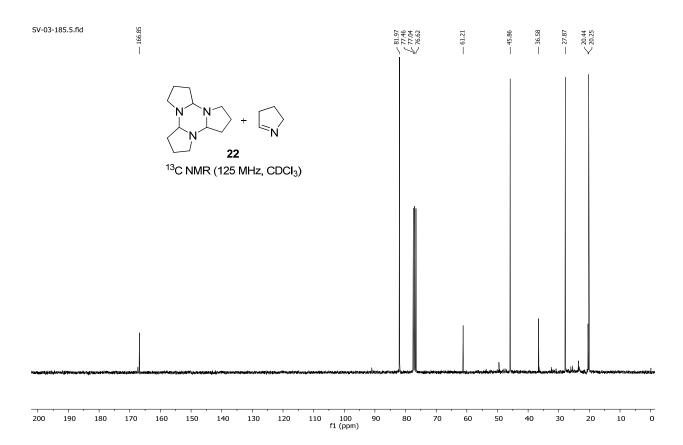
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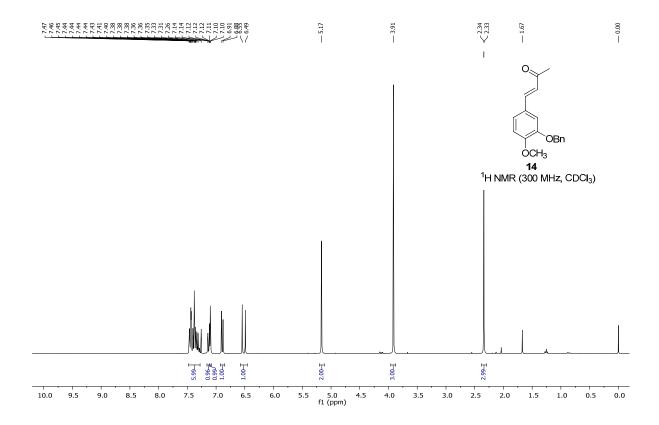


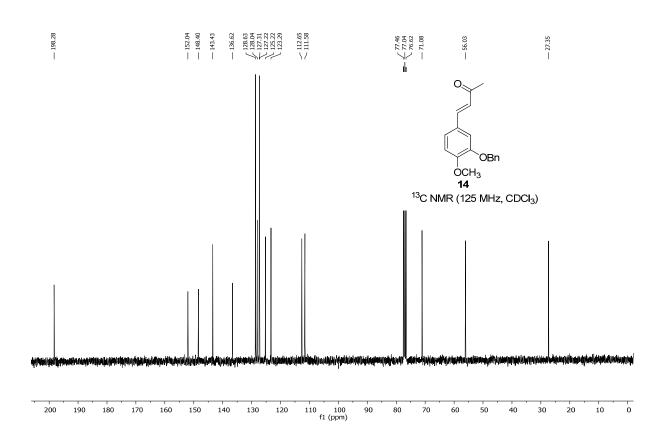


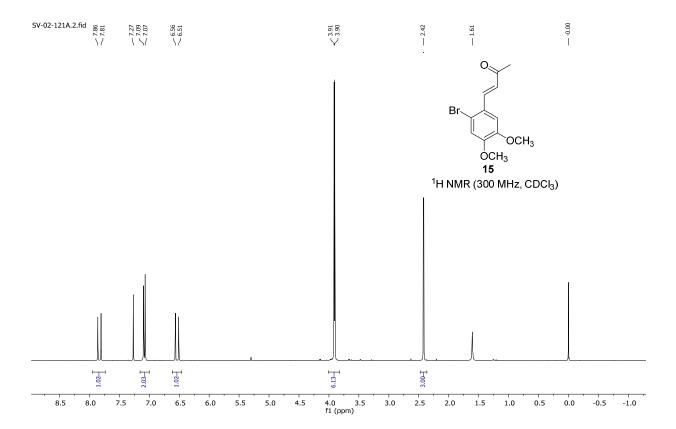
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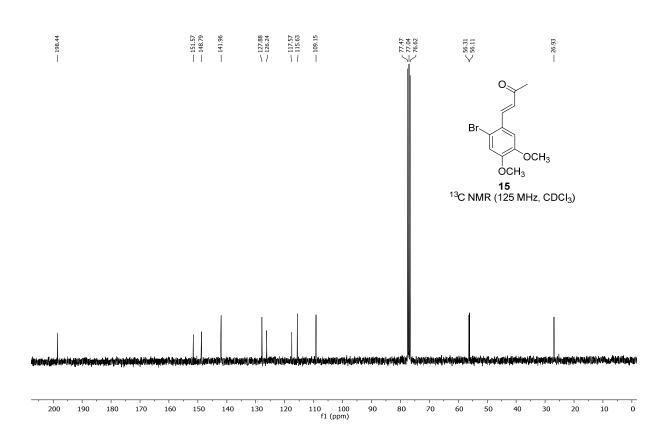


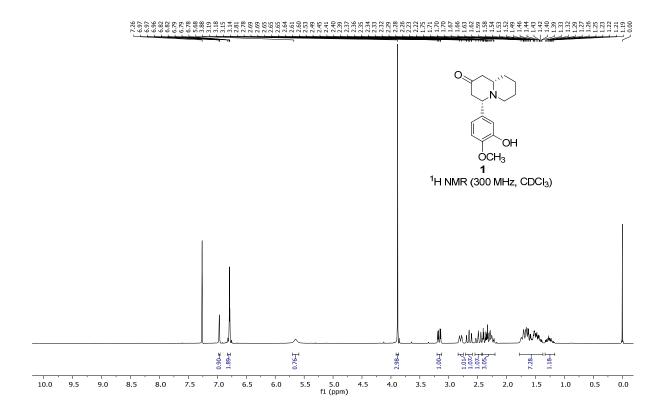


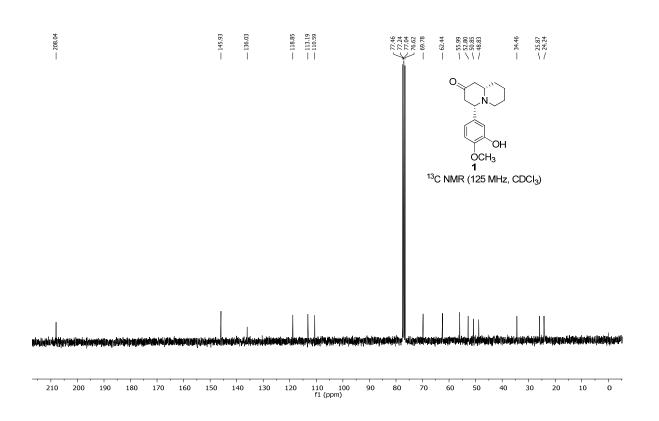


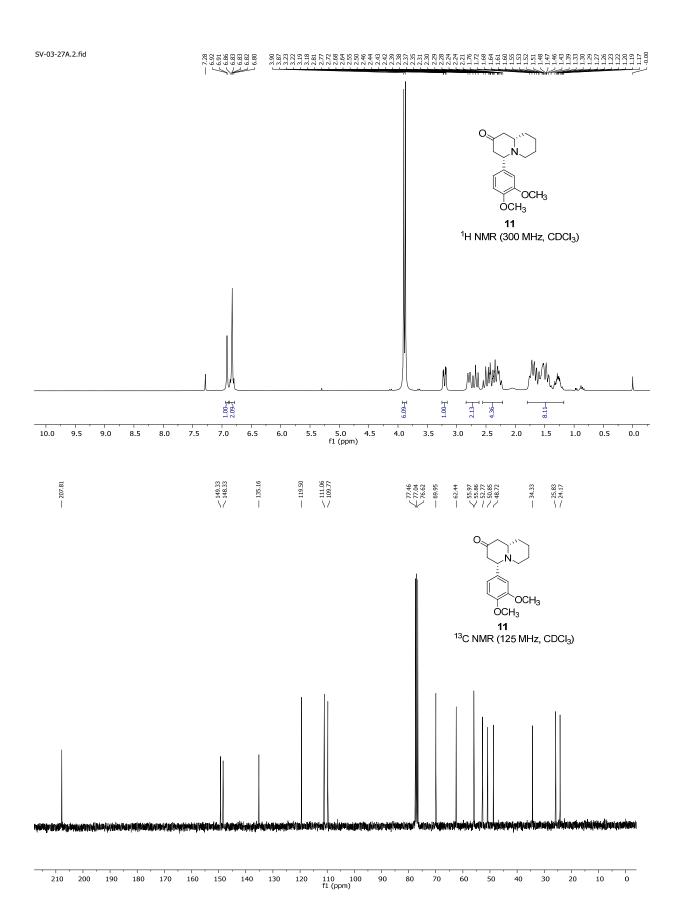


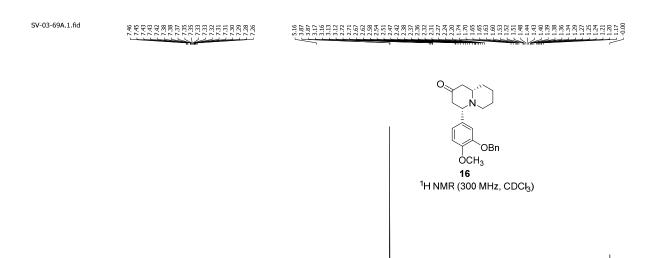












3.094

9.0

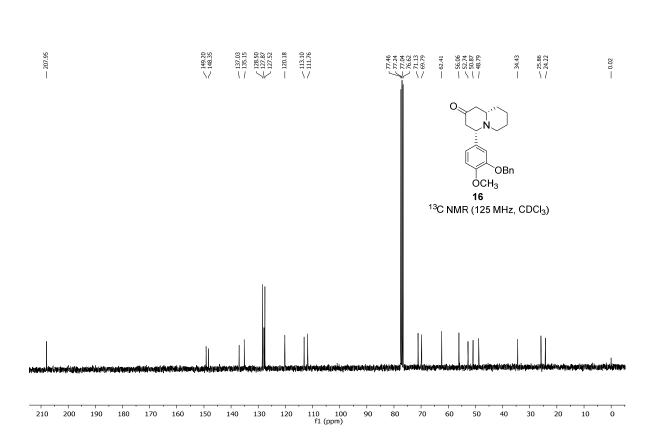
8.5

8.0

7.0

6.5

6.0



5.0 4.5 f1 (ppm) 4.0

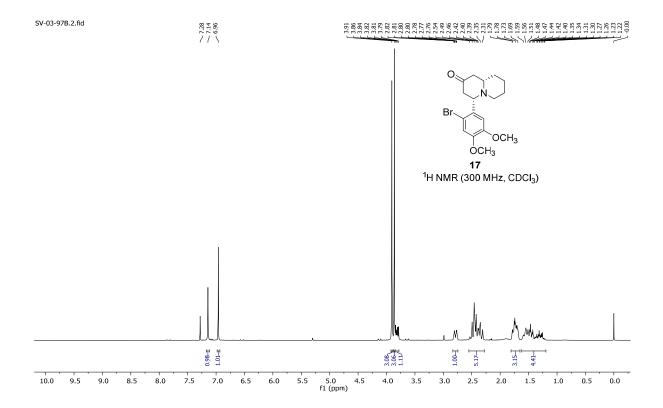
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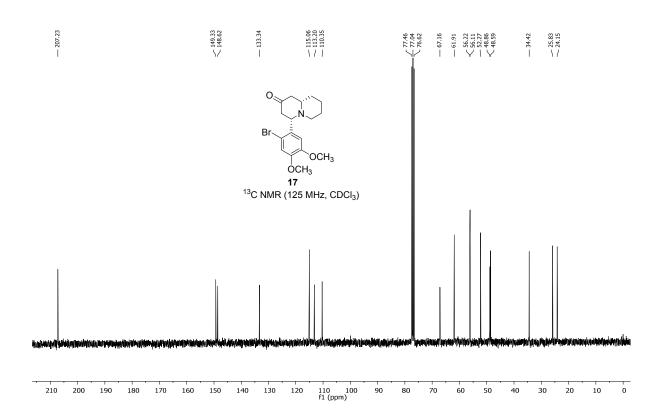
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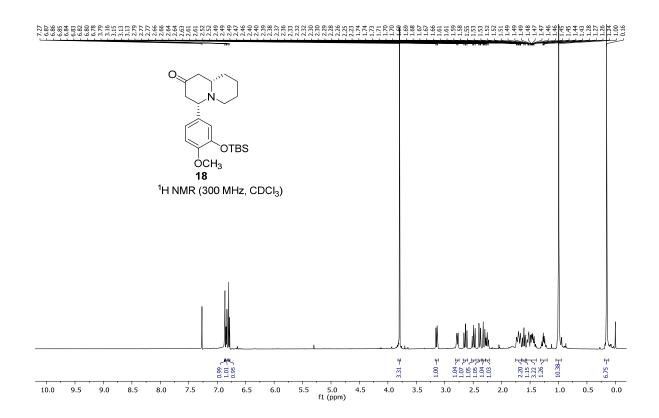
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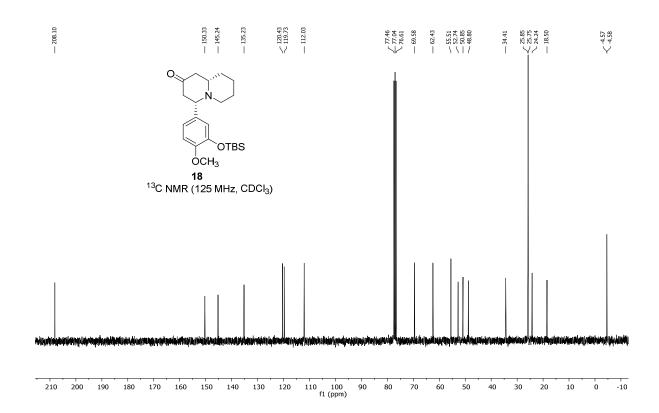
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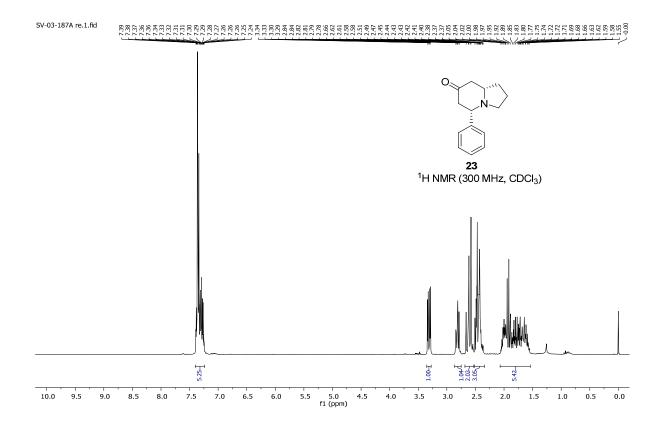
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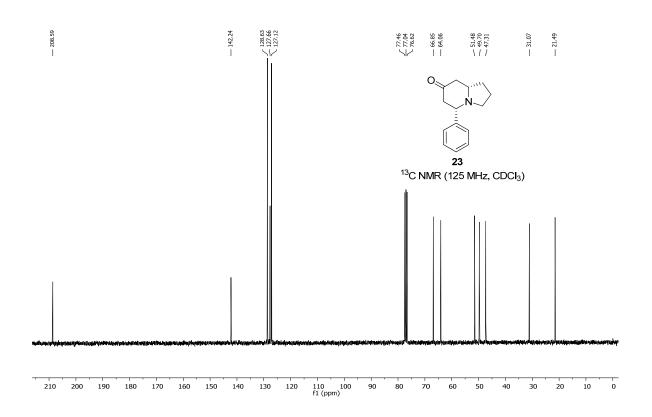


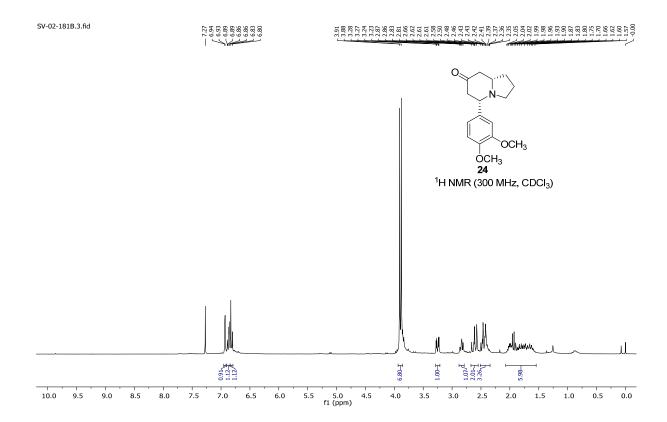


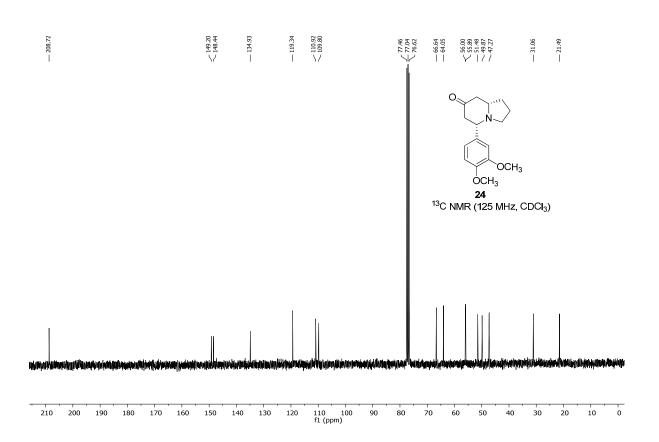


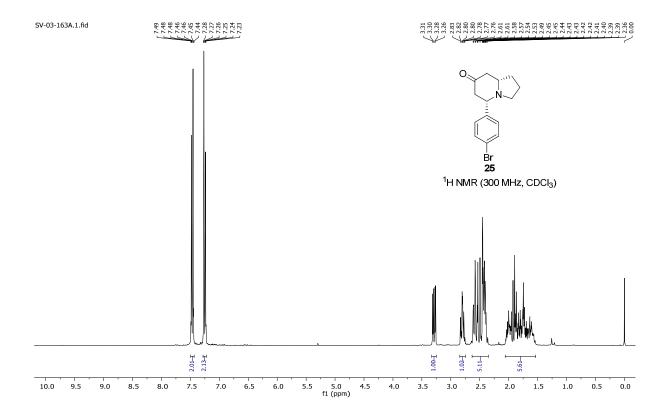


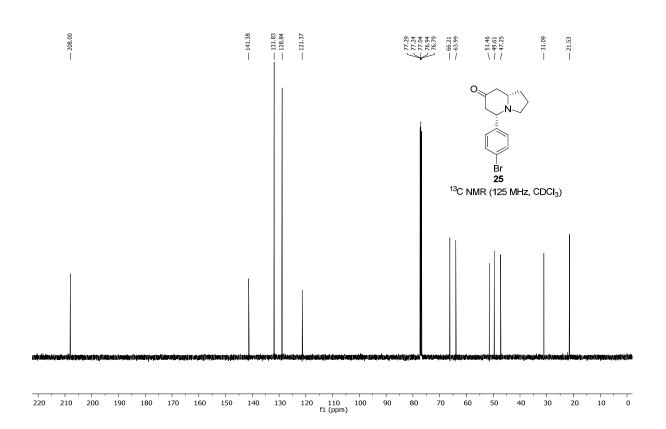


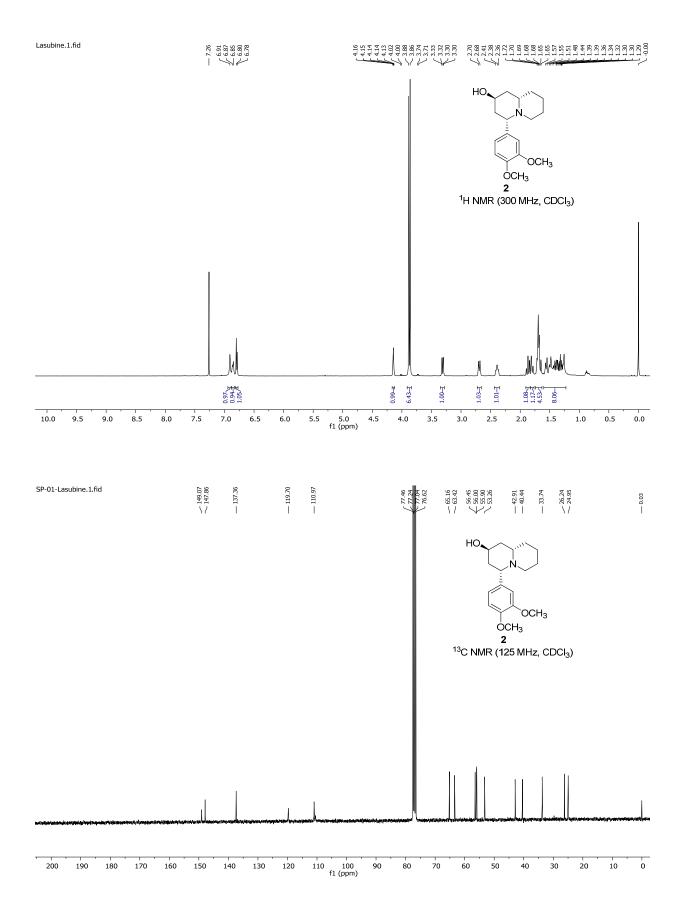


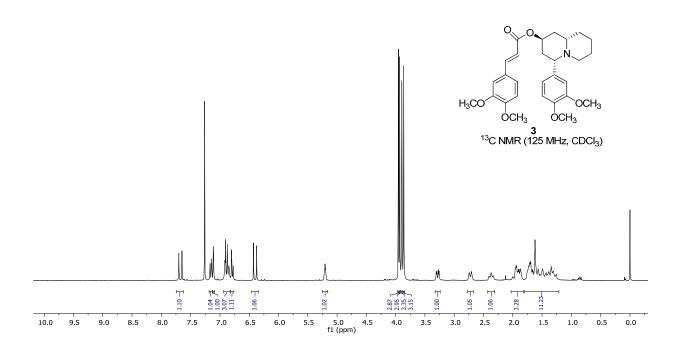


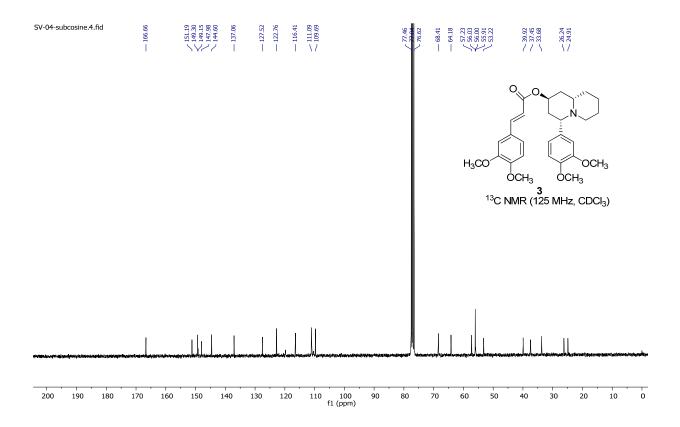












Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-191B Acquired By: Breeze

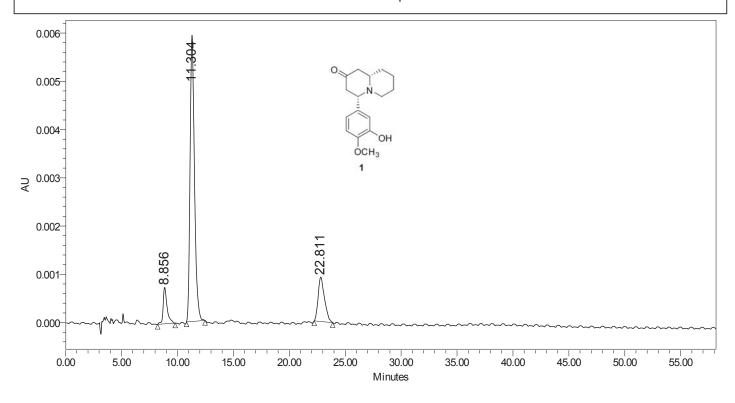
 Sample Type:
 Unknown
 Date Acquired:
 10/04/2018 11:18:23 AM NDT

 Vial:
 1
 Acq. Method:
 OJ_H 80% HEX 20%IPA

 Injection #:
 1
 Date Processed:
 17/04/2018 4:06:21 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 60.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.856	18441	8.51	754	9.92
2	11.304	161824	74.68	5930	78.03
3	22.811	36414	16.81	916	12.06

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:25:48 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-193B Acquired By: Breeze

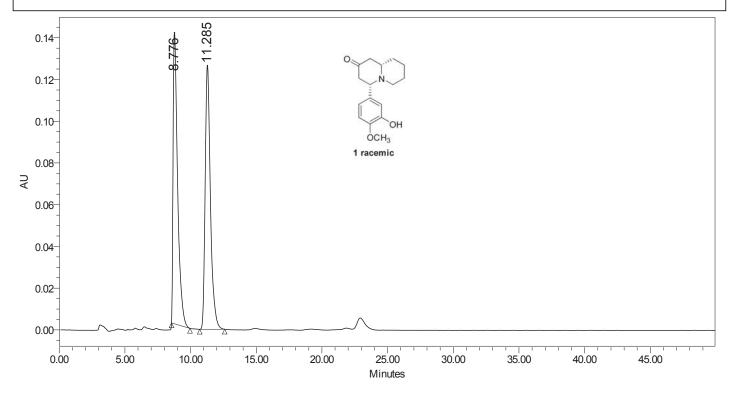
 Sample Type:
 Unknown
 Date Acquired:
 09/04/2018 3:40:38 PM NDT

 Vial:
 1
 Acq. Method:
 OJ_H 80% HEX 20%IPA

 Injection #:
 1
 Date Processed:
 17/04/2018 4:04:51 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 60.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.776	3330788	48.59	139772	52.49
2	11.285	3523655	51.41	126527	47.51

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:26:56 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-03-27A Acquired By: Breeze

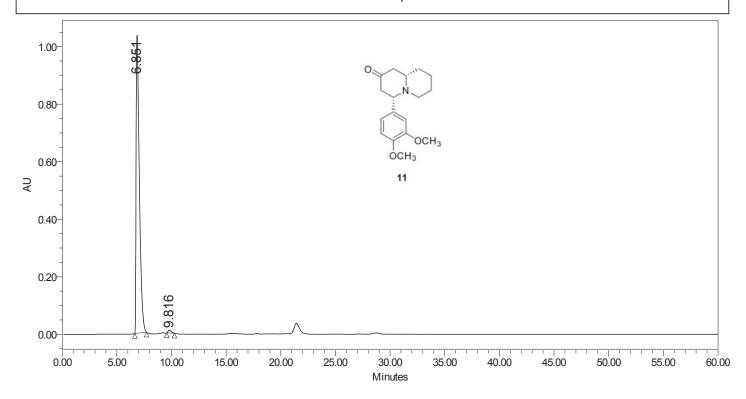
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 Date Acquired:
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 Vial:
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 Acq. Method:
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 Injection #:
 2
 Date Processed:
 23/05/2018 5:01:39 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 60.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	6.851	21382860	99.04	1035780	99.12
2	9.816	207001	0.96	9200	0.88

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:05:04 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-59A Acquired By: Breeze

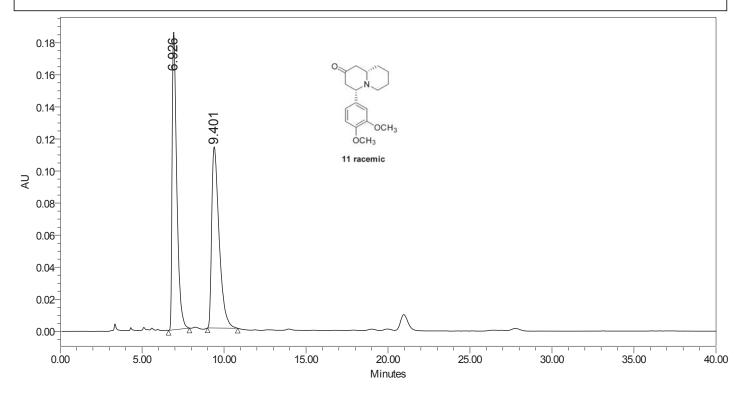
 Sample Type:
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 Date Acquired:
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 Vial:
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 Acq. Method:
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 Injection #:
 1
 Date Processed:
 21/09/2017 3:43:50 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	6.926	3654516	50.67	186275	62.25
2	9.401	3557390	49.33	112948	37.75

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:10:23 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-171C Acquired By: Breeze

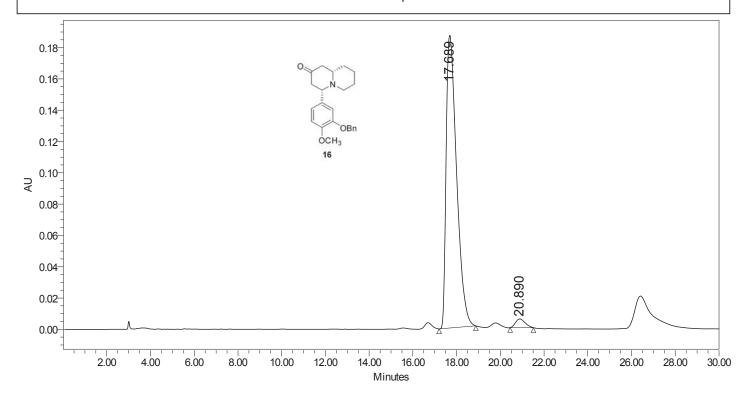
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 Vial:
 1
 Acq. Method:
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 Injection #:
 1
 Date Processed:
 22/08/2018 4:15:53 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 30.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.689	6178862	97.32	187042	97.09
2	20.890	170136	2.68	5605	2.91

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:14:19 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

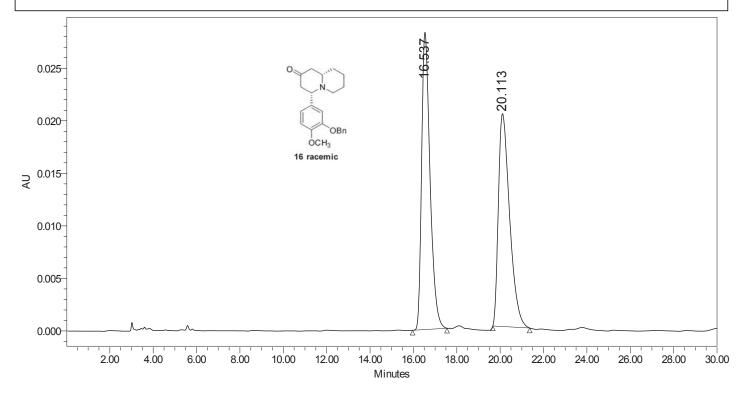
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Sample Type: Unknown Date Acquired: 22/08/2018 4:50:45 PM NDT Vial: 1 Acq. Method: AD_H 97%HEX 3%IPA

Injection #: 1 Date Processed: 19/09/2018 12:59:08 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 30.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.537	760923	51.10	28279	58.27
2	20.113	728147	48.90	20249	41.73

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:15:20 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-147C #14 Acquired By: Breeze

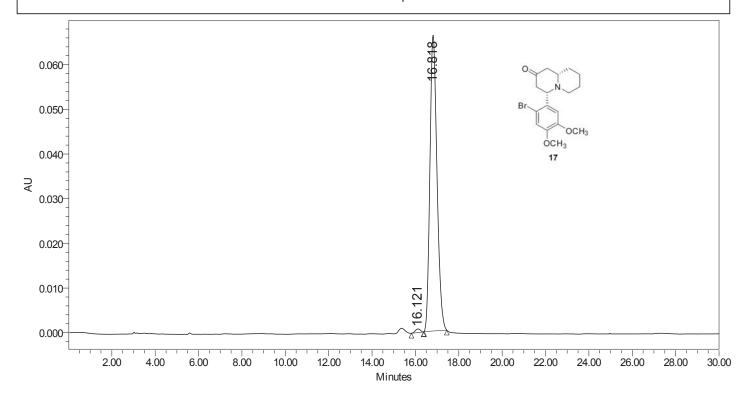
 Sample Type:
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 Date Acquired:
 28/07/2018 2:23:37 PM NDT

 Vial:
 1
 Acq. Method:
 AD_H 97%HEX 3%IPA

 Injection #:
 2
 Date Processed:
 28/07/2018 3:14:23 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 30.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.121	13126	0.87	817	1.22
2	16.818	1494509	99.13	66198	98.78

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:19:17 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-183C Acquired By: Breeze

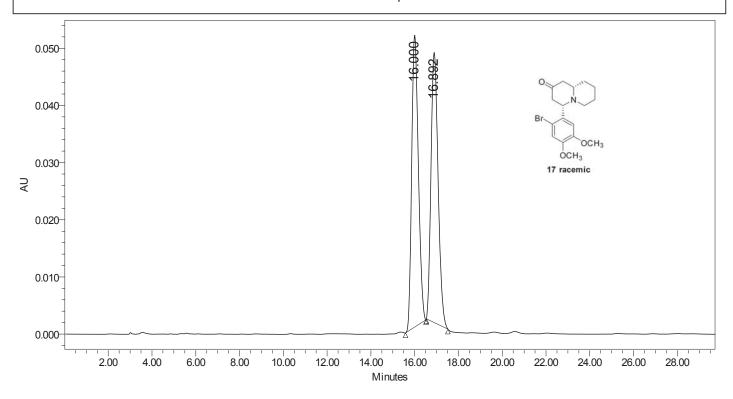
 Sample Type:
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 Date Acquired:
 28/07/2018 1:52:23 PM NDT

 Vial:
 1
 Acq. Method:
 AD_H 97%HEX 3%IPA

 Injection #:
 1
 Date Processed:
 28/07/2018 2:36:24 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.000	1072119	50.26	51025	51.90
2	16.892	1061209	49.74	47280	48.10

Report Method: Untitled Printed: 01/05/2019

Page: 1 of 1 5:18:43 PM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-03-187A re Acquired By: Breeze

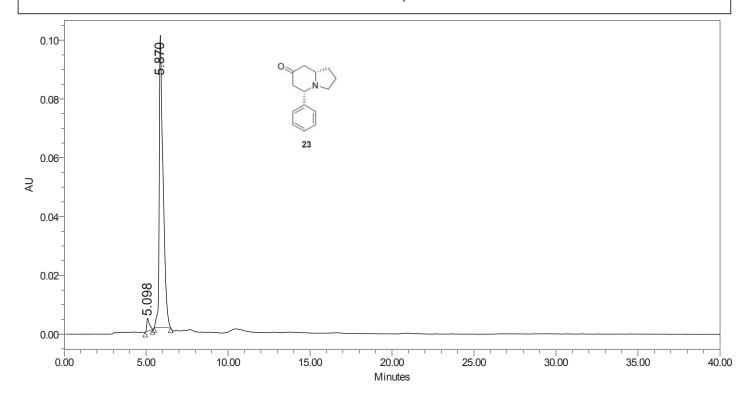
 Sample Type:
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 Date Acquired:
 14/12/2018 11:38:38 AM NST

 Vial:
 1
 Acq. Method:
 OJ_H 80% HEX 20%IPA

 Injection #:
 1
 Date Processed:
 17/12/2018 2:13:02 PM NST

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	5.098	49840	3.01	4359	4.20
2	5.870	1608134	96.99	99479	95.80

Report Method: Untitled Printed: 02/05/2019

Page: 1 of 1 8:53:50 AM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-03-179 A recolumned Acquired By: Breeze

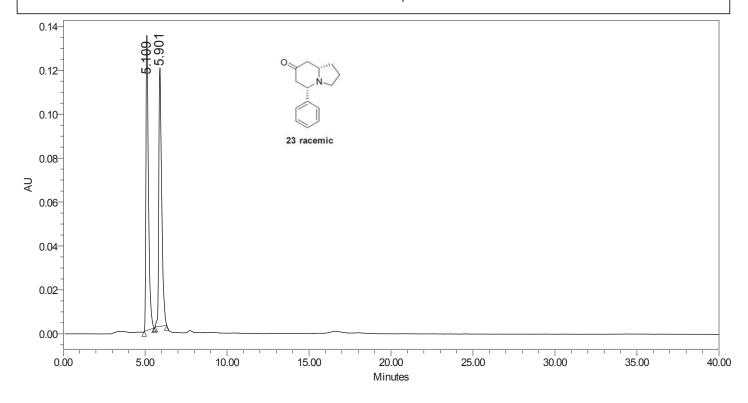
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 Date Acquired:
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 Vial:
 1
 Acq. Method:
 OJ_H 80% HEX 20%IPA

 Injection #:
 1
 Date Processed:
 17/12/2018 2:11:34 PM NST

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	5.109	1444119	50.34	135498	53.52
2	5.901	1424380	49.66	117679	46.48

Report Method: Untitled Printed: 02/05/2019

Page: 1 of 1 8:54:18 AM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-159B Acquired By: Breeze

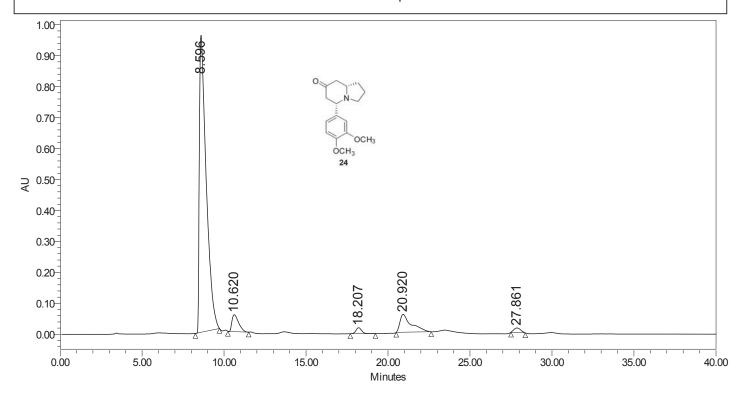
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 Vial:
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 Acq. Method:
 OJ_H 80% HEX 20%IPA

 Injection #:
 4
 Date Processed:
 15/03/2018 4:13:46 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.596	27883394	84.32	959554	86.78
2	10.620	1548895	4.68	54536	4.93
3	18.207	449821	1.36	19255	1.74
4	20.920	2764595	8.36	57662	5.21
5	27.861	422941	1.28	14706	1.33

Report Method: Untitled Printed: 02/05/2019

Page: 1 of 1 8:57:08 AM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-02-181B Racemate Acquired By: Breeze

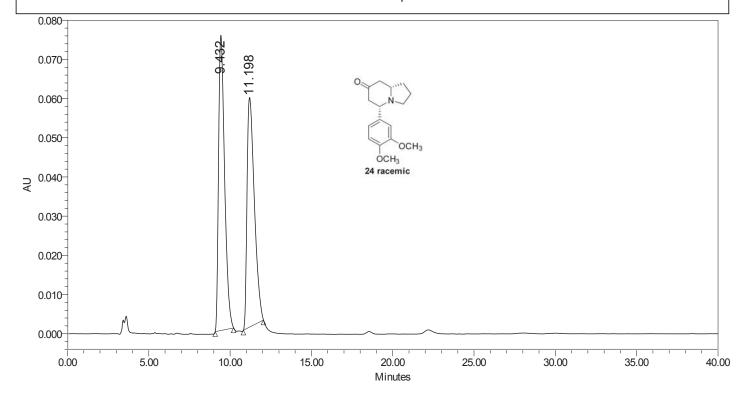
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 Date Acquired:
 22/03/2018 11:49:54 AM NDT

 Vial:
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 Acq. Method:
 OJ_H 80% HEX 20%IPA

 Injection #:
 3
 Date Processed:
 22/03/2018 2:18:05 PM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	9.432	1939280	51.43	75326	56.25
2	11.198	1831356	48.57	58582	43.75

Report Method: Untitled Printed: 02/05/2019

Page: 1 of 1 8:58:23 AM Canada/Newfoundland

Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-03-163A Acquired By: Breeze

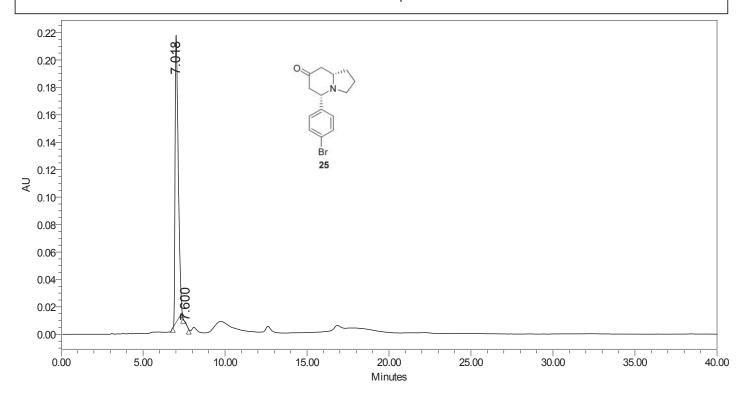
 Sample Type:
 Unknown
 Date Acquired:
 12/10/2018 3:40:37 PM NDT

 Vial:
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 Acq. Method:
 OJ_H 90%HEX 10%IPA

 Injection #:
 1
 Date Processed:
 17/10/2018 9:30:45 AM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.018	2791804	99.80	209214	99.73
2	7.600	5724	0.20	565	0.27

Report Method: Untitled Printed: 02/05/2019

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Project Name SEERAT

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

Sample Name: SV-03-155A recolumn Acquired By: Breeze

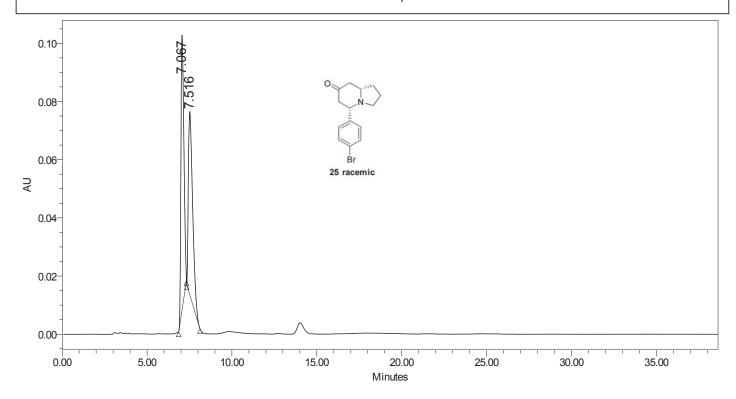
 Sample Type:
 Unknown
 Date Acquired:
 16/10/2018 1:02:10 PM NDT

 Vial:
 1
 Acq. Method:
 OJ_H 90%HEX 10%IPA

 Injection #:
 1
 Date Processed:
 17/10/2018 9:27:44 AM NDT

Injection Volume: 10.00 ul Channel Name: 2487Channel 1

Run Time: 40.00 Minutes Sample Set Name



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.067	1140232	50.88	94126	59.90
2	7.516	1100638	49.12	63000	40.10

Report Method: Untitled Printed: 02/05/2019

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