## Supporting Information

# Biomimetic Organocatalytic Approach to 4-Arylquinolizidine Alkaloids and 

 Application in the Synthesis of (-)-Lasubine II and (+)-Subcosine IISeerat Virk and Sunil V. Pansare*<br>Department of Chemistry<br>Memorial University<br>St. John's, Newfoundland, Canada A1B 3X7

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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. $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ were distilled from $\mathrm{CaH}_{2}$. 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. ${ }^{1} \mathrm{H}$ NMR and ${ }^{13} \mathrm{C}$ 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 $\mathbf{9}$ and $\mathbf{2 0}$ are commercially available and enones $\mathbf{1 3}^{1}$ and $\mathbf{2 1}^{2}$ 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 ( $3.78 \mathrm{~g}, 27.9 \mathrm{mmol}$ ) in diethyl ether ( 75 mL ) was added a solution of distilled piperidine ( $2.48 \mathrm{~mL}, 25.2 \mathrm{mmol}$ ) 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 ${ }^{\circledR}$ and the residue was washed with ether ( $1 \times 25 \mathrm{~mL}$ ). The combined filtrates were washed with water ( $3 \times 25 \mathrm{~mL}$ ), dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ 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 $(15.0 \mathrm{~mL})$ to $85^{\circ} \mathrm{C}$ ) 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 ${ }^{\circledR}$. The filtrate was concentrated to remove ethanol and the residue was diluted with ethyl acetate. The resulting solution was washed with water ( $3 \times 20 \mathrm{~mL}$ ) to provide the piperideine $\mathbf{1 0}(1.45 \mathrm{~g}, 70 \%$ yield over two steps). This is a mixture of monomeric (minor) and trimeric (major) forms ( ${ }^{1} \mathrm{H}$ NMR). This material was used as such without purification.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): Trimer: $\delta 3.18-3.06(\mathrm{~m}, 3 \mathrm{H}), 2.80(\mathrm{dd}, 3 \mathrm{H}, J=7.2,3.0 \mathrm{~Hz}), 2.07-$ $1.95(\mathrm{~m}, 3 \mathrm{H}), 1.80-1.61(\mathrm{~m}, 9 \mathrm{H}), 1.60-1.51(\mathrm{~m}, 6 \mathrm{H}), 1.38-1.20(\mathrm{~m}, 3 \mathrm{H})$. Visible peaks for the monomer: $\delta 7.83-7.78(\mathrm{~m}, 1 \mathrm{H}), 3.61-3.53(\mathrm{~m}, 1 \mathrm{H}), 2.21-2.12(\mathrm{~m}, 2 \mathrm{H}), 1.80-1.61(\mathrm{~m}, 1 \mathrm{H}) ; \quad{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): Trimer $\delta 82.0,46.4,29.2,25.8,22.3$. Visible peaks for the monomer: $\delta 163.2,49.3,28.8,18.7$; IR (neat): 2924, 2850, 2812, 2775, 2730, 2701, 1446, 1379, 1238, 1131, 1107, 1024, 889, $796 \mathrm{~cm}^{-1}$; HRMS (ESI, pos.): m/z 249.2198 (249.2205 calc. for $\mathrm{C}_{15} \mathrm{H}_{2} 7 \mathrm{~N}_{3}$ $\left(\mathrm{M}^{+}\right)$), $250.2275\left(250.2283\right.$ calc. for $\mathrm{C}_{15} \mathrm{H}_{28} \mathrm{~N}_{3}(\mathrm{M}+\mathrm{H})^{+}$.

## Dodecahydrotripyrrolo[1,2-a:1',2'-c:1',2'-e][1,3,5]triazine (22) ${ }^{4}$



To a stirred mixture of pyrrolidine ( $2.0 \mathrm{~mL}, 24.35 \mathrm{mmol}$ ), $\mathrm{AgNO}_{3}(21.3 \mathrm{mg}, 0.13 \mathrm{mmol})$ and $\mathrm{NaOH}(2.0 \mathrm{~g}, 50 \mathrm{mmol})$ in water $(25 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ was added dropwise a $25 \%$ aqueous solution of sodium peroxodisulfate $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{8}(6.25 \mathrm{~g}, 26.3 \mathrm{mmol})$ in water $(25 \mathrm{~mL})$. The reaction mixture was stirred at ambient temperature for 2.5 h after which it was extracted with dichloromethane ( $3 \times 10 \mathrm{~mL}$ ). The organic layer was washed with brine following which it was dried overnight over $\mathrm{Na}_{2} \mathrm{SO}_{4}-\mathrm{K}_{2} \mathrm{CO}_{3}$ in the refrigerator. The organic layer was then concentrated without heating to provide $\mathbf{2 2}$ as a mixture of monomeric (minor) and trimeric (major) forms by ${ }^{1} \mathrm{H}$ 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 $\mathrm{cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): Trimer: $\delta 3.07-2.95(\mathrm{~m}, 6 \mathrm{H}), 2.37-2.26(\mathrm{~m}, 3 \mathrm{H}), 1.97-1.63$ $(\mathrm{m}, 12 \mathrm{H})$. Visible peaks for the monomer: $\delta 7.63-7.59(\mathrm{~m}, 1 \mathrm{H}), 3.89-3.80(\mathrm{~m}, 2 \mathrm{H}), 2.58-2.48(\mathrm{~m}$, 2H), 1.97-1.63 (m, 2H); ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): Trimer: $\delta 82.0,45.9,27.9,20.3$. Visible peaks for monomer: $\delta 166.9,61.2,36.6,20.4$; HRMS (ESI, pos.): m/z 207.1734 (207.1735 calc. for $\mathrm{C}_{12} \mathrm{H}_{21} \mathrm{~N}_{3}\left(\mathrm{M}^{+}\right)$), m/z 208.1816 (208.1814 calc. for $\mathrm{C}_{12} \mathrm{H}_{22} \mathrm{~N}_{3}(\mathrm{M}+\mathrm{H})^{+}$.

## General procedure for the synthesis of enones 14 and 15:

To a solution of 1-(triphenylphosphoranylidene)-2-propanone in dichloromethane at $0^{\circ} \mathrm{C}$ 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 ( $1.3 \mathrm{gm}, 5.4 \mathrm{mmol})$ with 1 -(triphenylphosphoranylidene)-2-propanone ( $2.4 \mathrm{gm}, 8.1 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ for 48 hours according to the general procedure gave, after purification by flash chromatography on silica gel, $818 \mathrm{mg}(55 \%)$ of $\mathbf{1 4}$ as a white solid.
Mp.: 111-113 ${ }^{\circ} \mathrm{C}$; IR (neat): 3065, 3030, 2933, 2874, 2846, 1660, 1640, 1622, 1595, 1511, 1425, 1363, 1380, 1249, 1220, 1160, 1136, 1009, 980, 807, 739, $698 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 300 MHz , $\left.\mathrm{CDCl}_{3}\right): \delta 7.48-7.29(\mathrm{~m}, 6 \mathrm{H}), 7.13(\mathrm{dd}, 1 \mathrm{H}, J=8.5,2.1 \mathrm{~Hz}), 7.10(\mathrm{~d}, 1 \mathrm{H}, J=2.1 \mathrm{~Hz}), 6.90(\mathrm{~d}$, $1 \mathrm{H}, J=8.5 \mathrm{~Hz}), 6.52(\mathrm{~d}, 1 \mathrm{H}, J=16.4 \mathrm{~Hz}), 5.17(\mathrm{~s}, 2 \mathrm{H}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 2.34(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 75 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 198.3,152.1,148.4,143.4,136.6,128.6,128.0,127.3,127.2,125.2,123.3$, 112.7, 111.6, 71.1, 56.0, 27.4; HRMS (ESI, pos.): m/z 282.1262 (282.1256 calc. for $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{O}_{3}$ $\left(\mathrm{M}^{+}\right)$).

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



To a solution of veratraldehyde ( $3.3 \mathrm{~g}, 20 \mathrm{mmol}$ ) in methanol ( 30 mL ), was added bromine ( $1 \mathrm{~mL}, 1.05 \mathrm{eq}$ ). 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 $(2 \times 50 \mathrm{~mL})$ and then with brine $(100 \mathrm{~mL})$. The organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to provide 2-bromo-4,5dimethoxybenzaldehyde ( $4.5 \mathrm{gm}, 92 \%$ ) as a white solid which was pure by ${ }^{1} \mathrm{H}$ NMR and was used in the next step without purification.

Reaction of 2-bromo-4,5-dimethoxybenzaldehyde ( $2.8 \mathrm{gm}, 11.4 \mathrm{mmol}$ ) with 1-(triphenylphosphoranylidene)-2-propanone ( $5.1 \mathrm{gm}, 17.1 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ for 48 hours according to the general procedure gave, after purification by flash chromatography on silica gel, $2.27 \mathrm{~g}(78 \%)$ of $\mathbf{1 5}$ as a beige solid.

Mp.: 118-119 ${ }^{\circ} \mathrm{C}$; IR (neat): 2963, 2935, 2919, 2836, 1660, 1637, 1591, 1502, 1435, 1357, 1253, $1210,1165,1024,972 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.83(\mathrm{~d}, 1 \mathrm{H}, J=16.3 \mathrm{~Hz}$ ), $7.09(\mathrm{~s}$, $1 \mathrm{H}), 7.06(\mathrm{~s}, 1 \mathrm{H}), 6.53(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}=16.3 \mathrm{~Hz}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 3.90(\mathrm{~s}, 3 \mathrm{H}), 2.41(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 198.4,151.6,148.8,142.0,127.9,126.2,117.6,115.6,109.2,56.3,56.1$, 26.9; HRMS (ESI, pos.): m/z 284.0037 (284.0048 calc. for $\mathrm{C}_{12} \mathrm{H}_{13} \mathrm{O}_{3} \mathrm{Br}\left(\mathrm{M}^{+}\right)$), m/z 285.0109 ( 285.0126 calc. for $\mathrm{C}_{12} \mathrm{H}_{14} \mathrm{O}_{3} \mathrm{Br}^{79}(\mathrm{M}+\mathrm{H})^{+}$), m/z 287.0090 (287.0106 calc. for $\mathrm{C}_{12} \mathrm{H}_{14} \mathrm{O}_{3} \mathrm{Br}^{81}$ $\left.(\mathrm{M}+2+\mathrm{H})^{+}\right)$

## General procedure for the Mannich/aza-Michael reaction:

To the imine trimer $\mathbf{1 0}$ or $\mathbf{2 2}$ 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 $\mathrm{HCl}(1 \mathrm{M})$ 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 $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}, ~ 99: 1\right)$ 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 $>1 \mathrm{mmol}$ scale:

Reaction of (E)-4-(3,4-dimethoxyphenyl)but-3-en-2-one ( $\mathbf{9}, 1.48 \mathrm{~g}, 7.2 \mathrm{mmol}$ ) and $\mathbf{1 0}$ ( $300 \mathrm{mg}, 1.2 \mathrm{mmol}$ ) in the presence of $S$-proline ( $83 \mathrm{mg}, 0.12 \mathrm{mmol}$ ) in DMF ( 3.5 mL ) according to the general procedure gave, after purification by flash chromatography on silica gel, 624 mg (60\%) of $\mathbf{1 1}$ as a pale yellow foam.
$\mathrm{R}_{f}=0.36$ (EtOAc/MeOH, 80:20); IR (neat): 2927, 2850, 2835, 2796, 1717, 1593, 1508, 1461, 1443, 1256, 1231, 1146, 1076, 1024, $812 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 6.92(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 6.87-6.78 (br m, 2H), $3.90(\mathrm{~s}, 3 \mathrm{H}), 3.87(\mathrm{~s}, 3 \mathrm{H}), 3.21(\mathrm{~d}, 1 \mathrm{H}, J=12.1,3.3 \mathrm{~Hz}), 2.84-2.62(\mathrm{~m}$,
$2 \mathrm{H}), 2.57-2.21(\mathrm{~m}, 4 \mathrm{H}), 1.80-1.18(\mathrm{~m}, 7 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 207.8,149.3,148.3$, 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 $\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{NO}_{3}\left(\mathrm{M}^{+}\right)$), $\mathrm{m} / \mathrm{z} 290.1764$ ( 290.1756 calc. for $\left.\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{NO}_{3}(\mathrm{M}+\mathrm{H})^{+}\right) ;[\alpha]_{\mathrm{D}^{20}}=-87.2\left(\mathrm{c} 0.83, \mathrm{CHCl}_{3}\right.$, lit. $^{5}[\alpha]_{\mathrm{D}}=-78.05\left(\mathrm{c} 0.30, \mathrm{CHCl}_{3}\right)$ ); HPLC: Chiralpak OJ-H (hexane $/ i-\mathrm{PrOH}, 80 / 20$, flow rate $1 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}$ ), $t_{\text {major }}=6.85 \mathrm{~min}$., $t_{\text {minor }}=9.82 \mathrm{~min} ., 98 \%$ ee.

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



Reaction of $\mathbf{1 0}(200 \mathrm{mg}, 0.8 \mathrm{mmol})$ and (E)-4-(3-hydroxy-4-methoxyphenyl)but-3-en-2one ( $920 \mathrm{mg}, 4.8 \mathrm{mmol}$ ) in the presence of $S$-proline ( $55.2 \mathrm{mg}, 0.48 \mathrm{mmol}$ ) in DMF ( 2 mL ) according to the general procedure gave, after purification by flash chromatography on silica gel, $265 \mathrm{mg}(40 \%)$ of 1 as a pale yellow foam.
$\mathrm{R}_{f}=0.3$ (EtOAc/MeOH, 90:10); IR (neat): 3392, 3010, 2931, 2841, 2795, 1715, 1592, 1441, 1323, 1270, 1218, 1123, 1026, 879, 806, $754 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 6.97$ (br d, $1 \mathrm{H}, \mathrm{J}=1.4 \mathrm{~Hz}), 6.82-6.76(\mathrm{~m}, 2 \mathrm{H}), 5.65(\operatorname{broad~s}, 1 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 3.17(\mathrm{dd}, 1 \mathrm{H}, J=12.1,3.3$ $\mathrm{Hz}), 2.84-2.75(\mathrm{~m}, 1 \mathrm{H}), 2.71-2.59(\mathrm{~m}, 1 \mathrm{H}), 2.55-2.43(\mathrm{~m}, 1 \mathrm{H}), 2.43-2.20(\mathrm{~m}, 3 \mathrm{H}), 1.78-1.38(\mathrm{~m}$, $6 \mathrm{H}), 1.34-1.17$ (m, 1H); ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 208.0,145.9,136.0,118.9,113.2,110.6$, $69.8,62.4,56.0,52.8,50.9,48.8,34.5,25.9,24.2$; HRMS (ESI, pos.): m/z 275.1533 (275.1521 calc. for $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{NO}_{3}\left(\mathrm{M}^{+}\right)$), $\mathrm{m} / \mathrm{z} 276.1606\left(276.1600\right.$ calc. for $\left.\mathrm{C}_{16} \mathrm{H}_{22} \mathrm{NO}_{3}(\mathrm{M}+\mathrm{H})^{+}\right), 298.1399$ (298.1419 calc. for $\left.\mathrm{C}_{16} \mathrm{H}_{2} \mathrm{NO}_{3} \mathrm{Na}(\mathrm{M}+\mathrm{Na})^{+}\right) ;[\alpha] \mathrm{D}^{20}=-67.0\left(\mathrm{c} 0.56, \mathrm{CHCl}_{3}\right)$; HPLC: Chiralpak OJ-H (hexane $/ \mathrm{i}-\mathrm{PrOH}, 80 / 20$, flow rate $1 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}$ ), $t_{\text {major }}=10.95 \mathrm{~min}$., $t_{\text {minor }}=8.72$ min., $82 \%$ ee.

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



Reaction of $\mathbf{1 0}$ ( $50 \mathrm{mg}, 0.2 \mathrm{mmol}$ ) and ( $E$ )-4-(3-(benzyloxy)-4-methoxyphenyl)but-3-en-2-one $(\mathbf{1 4}, 338 \mathrm{mg}, 1.2 \mathrm{mmol})$ in the presence of $S$-proline $(13.8 \mathrm{mg}, 0.12 \mathrm{mmol})$ in DMF $(1 \mathrm{~mL})$ according to the general procedure gave, after purification by flash chromatography on silica gel, $84 \mathrm{mg}(40 \%)$ of 16 as a pale yellow foam.
$\mathrm{R}_{f}=0.25$ (EtOAc/MeOH, 90:10); IR (neat): 2930, 1714, 1521, 1510, 1263, 1248, 1238, 1223, 1163, 1141, 1044, $831 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.46-7.42$ (m, 2H), 7.38-7.28 (m, $3 \mathrm{H}), 6.94$ (broad s, 1H), $6.83(\mathrm{~m}, 2 \mathrm{H}), 5.16(\mathrm{~s}, 2 \mathrm{H}), 3.87(\mathrm{~s}, 3 \mathrm{H}), 3.15(\mathrm{dd}, 1 \mathrm{H}, J=12.0,3.2 \mathrm{~Hz})$, 2.72-2.18 (m, 6H), 1.75-1.18 (m, 7H); ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 208.0,149.2,148.4,137.0$, 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 $\mathrm{C}_{23} \mathrm{H}_{2} 7 \mathrm{NO}_{3}\left(\mathrm{M}^{+}\right)$), m/z 366.2071 ( 366.2069 calc. for $\mathrm{C}_{23} \mathrm{H}_{28} \mathrm{NO}_{3}(\mathrm{M}+\mathrm{H})^{+}$), 388.1889 ( 388.1889 calc. for $\mathrm{C}_{23} \mathrm{H}_{2} \mathrm{NO}_{3} \mathrm{Na}(\mathrm{M}+\mathrm{Na})^{+}$); $[\alpha]_{\mathrm{D}}{ }^{20}=-65.9\left(\mathrm{c} 0.62, \mathrm{CHCl}_{3}\right)$; HPLC: Chiralpak AD-H (hexane/i-PrOH, $97 / 3$, flow rate 1 $\mathrm{mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}), t_{\text {major }}=17.69 \mathrm{~min} ., t_{\text {minor }}=20.89 \mathrm{~min} ., 95 \%$ ee.
(4S,9aS)-4-(2-Bromo-4,5-dimethoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (17):


Reaction of $\mathbf{1 0}(50 \mathrm{mg}, 0.2 \mathrm{mmol})$ and ( $E$ )-4-(2-bromo-4,5-dimethoxyphenyl)but-3-en2 -one ( $\mathbf{1 5}, 342 \mathrm{mg}, 1.2 \mathrm{mmol}$ ) in the presence of $S$-proline ( $13.8 \mathrm{mg}, 0.12 \mathrm{mmol}$ ) in DMF ( 0.5 mL ) according to the general procedure gave, after purification by flash chromatography on silica gel, unreacted $\mathbf{1 5}(244 \mathrm{mg})$ and $45 \mathrm{mg}(20 \%, 35 \%$ based on recovered starting material) of 17 as a pale yellow foam.
$\mathrm{R}_{f}=0.29$ (EtOAc/MeOH, 95:5); IR (neat): 2931, 2842, 1720, 1500, 1461, 1439, 1378, 1363, 1343, 1323, 1276, 1246, 1207, 1160, 1119, 1076, $1027 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$
$7.14(\mathrm{~s}, 1 \mathrm{H}), 6.96(\mathrm{~s}, 1 \mathrm{H}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}), 3.82(\mathrm{dd}, 1 \mathrm{H}, J=10.2,5.2 \mathrm{~Hz}), 2.83-2.74$ $(\mathrm{m}, 1 \mathrm{H}), 2.55-2.29(\mathrm{~m}, 5 \mathrm{H}), 1.81-1.66(\mathrm{~m}, 3 \mathrm{H}), 1.62-1.22(\mathrm{~m}, 4 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : $\delta 207.3,149.3,148.6,133.3,115.1,113.2,110.4,67.2,62.0,56.2,56.1,52.3,48.9,48.6,34.4$, 25.8, 24.2; HRMS (ESI, pos.): m/z 367.0776 ( 367.0783 calc. for $\mathrm{C}_{17} \mathrm{H}_{22} \mathrm{BrNO}_{3}\left(\mathrm{M}^{+}\right)$), m/z 368.0848 ( 368.0861 calc. for $\left.\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{Br}^{79} \mathrm{NO}_{3}(\mathrm{M}+\mathrm{H})^{+}\right), \mathrm{m} / \mathrm{z} 370.083$ ( 370.0841 calc. for $\left.\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{Br}^{81} \mathrm{NO}_{3}(\mathrm{M}+\mathrm{H}+2)^{+}\right) ;[\alpha]^{20}=-90.7\left(\mathrm{c} 0.57, \mathrm{CHCl}_{3}\right)$; HPLC: Chiralpak AD-H (hexane/i$\operatorname{PrOH}, 97 / 3$, flow rate $1 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}$ ), $t_{\text {major }}=16.82 \mathrm{~min} ., t_{\text {minor }}=16.12 \mathrm{~min} ., 98 \%$ ee. (4S,9aS)-4-(3-(Tert-butyldimethylsilyloxy)-4-methoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (18):


To $1(54 \mathrm{mg}, 0.15 \mathrm{mmol})$ dissolved in DCM at $0{ }^{\circ} \mathrm{C}$ was added TBDMSOTf $(52 \mu \mathrm{~L}, 0.23$ $\mathrm{mmol})$ and pyridine ( $24.2 \mu \mathrm{~L}, 0.30 \mathrm{mmol}$ ). 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 $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}, 99: 1\right)$ to provide $45 \mathrm{mg}(77 \%)$ of $\mathbf{1 8}$ as a pale yellow gum.
$\mathrm{R}_{f}=0.24$ (EtOAc/MeOH, 99:1), IR (neat): 2930, 2856, 2791, 1721, 1507, 1272, 1251, 1225, $1126,889,835,780 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): 6.87 (d, $1 \mathrm{H}, \mathrm{J}=2.1 \mathrm{~Hz}$ ), 6.84 (dd, 1 H , $J=8.3,2.1 \mathrm{~Hz}), 6.79(\mathrm{~d}, 1 \mathrm{H}, J=8.3 \mathrm{~Hz}), 3.79(\mathrm{~s}, 3 \mathrm{H}), 3.14(\mathrm{dd}, 1 \mathrm{H}, J=12.1,3.2 \mathrm{~Hz}), 2.80-2.74$ $(\mathrm{m}, 1 \mathrm{H}), 2.67-2.59(\mathrm{~m}, 1 \mathrm{H}), 2.52-2.45(\mathrm{~m}, 1 \mathrm{H}), 2.39(\mathrm{dt}, 1 \mathrm{H}, J=14.0,2.9 \mathrm{~Hz}), 2.31(\mathrm{dt}, 1 \mathrm{H}, J=$ $14.0,2.9 \mathrm{~Hz}), 2.29-2.21(\mathrm{~m}, 1 \mathrm{H}), 1.75-1.65(\mathrm{~m}, 2 \mathrm{H}), 1.61(\mathrm{td}, 1 \mathrm{H}, J=12.0,2.6 \mathrm{~Hz}), 1.57-1.38$ $(\mathrm{m}, 3 \mathrm{H}), 1.32-1.20(\mathrm{~m}, 1 \mathrm{H}), 0.99(\mathrm{~s}, 9 \mathrm{H}), 0.16(\mathrm{~d}, 6 \mathrm{H}, \mathrm{J}=0.9 \mathrm{~Hz}) ;{ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : 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 $\mathrm{C}_{22} \mathrm{H}_{35} \mathrm{NO}_{3} \mathrm{Si}^{\left(\mathrm{M}^{+}\right) \text {), m/z }}$ $390.2446\left(390.2464\right.$ calc. for $\left.\mathrm{C}_{22} \mathrm{H}_{36} \mathrm{NO}_{3} \mathrm{Si}(\mathrm{M}+\mathrm{H})^{+}\right) ;[\alpha]^{20}=-64.8\left(\mathrm{c} 1.56, \mathrm{CHCl}_{3}\right)$.

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



Reaction of 22 ( $50 \mathrm{mg}, 0.24 \mathrm{mmol}$ ) and ( $E$ )-4-phenylbut-3-en-2-one ( $\mathbf{2 0}, 204 \mathrm{mg}, 1.4$ $\mathrm{mmol})$ in the presence of $S$-proline $(16.1 \mathrm{mg}, 0.14 \mathrm{mmol})$ in DMF $(0.5 \mathrm{~mL})$ according to the general procedure gave, after purification by flash chromatography on silica gel, $70 \mathrm{mg}(47 \%)$ of $\mathbf{2 3}$ as a pale yellow gum.
$\mathrm{R}_{f}=0.35$ (EtOAc/MeOH, 90:10); IR (neat): 2960, 2819, 2781, 1711, 1371, 1348, 1302, 1290, 1245, 1152, 1029, 765, $701 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.40-7.24(\mathrm{~m}, 5 \mathrm{H}), 3.32$ (dd, $1 \mathrm{H}, \mathrm{J}=11.4,3.6 \mathrm{~Hz}$ ), 2.86-2.77 (m, 1H), 2.68-2.53 (m, 2H), 2.52-2.36 (m, 3H), 2.05-1.55 (m, 5 H ); ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 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 $\mathrm{C}_{14} \mathrm{H}_{17} \mathrm{NO}\left(\mathrm{M}^{+}\right)$); $[\alpha]_{\mathrm{D}}{ }^{20}$ $=-100.6$ (c $0.76, \mathrm{CHCl}_{3}$ ); HPLC: Chiralpak OJ-H (hexane $/ \mathrm{i}-\mathrm{PrOH}, 80 / 20$, flow rate $1 \mathrm{~mL} / \mathrm{min}$, $\lambda=254 \mathrm{~nm}), t_{\text {major }}=5.87 \mathrm{~min} ., t_{\text {minor }}=5.10 \mathrm{~min} ., 94 \%$ ee.

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



Reaction of $22(50 \mathrm{mg}, 0.24 \mathrm{mmol})$ and (E)-4-(3,4-dimethoxyphenyl)but-3-en-2-one ( $\mathbf{9}$, $288 \mathrm{mg}, 1.4 \mathrm{mmol})$ in the presence of $S$-proline $(16.1 \mathrm{mg}, 0.14 \mathrm{mmol})$ in DMF ( 0.5 mL ) according to the general procedure gave, after purification by flash chromatography on silica gel, $40 \mathrm{mg}(21 \%)$ of $\mathbf{2 4}$ as a yellow gum.
$\mathrm{R}_{f}=0.17$ (EtOAc/MeOH, 90:10); IR (neat): 2958, 2834, 2796, 1715, 1592, 1511, 1461, 1259, 1234, 1157, 1136, 1025, $728 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 6.94$ (d, $1 \mathrm{H}, J=1.9 \mathrm{~Hz}$ ), 6.8 $(\mathrm{dd}, 1 \mathrm{H}, J=8.2,1.9 \mathrm{~Hz}), 6.81(\mathrm{~d}, 1 \mathrm{H}, J=8.2 \mathrm{~Hz}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 3.26(\mathrm{dd}, 1 \mathrm{H}, J=$ $11.4,3.5 \mathrm{~Hz}), 2.87-2.80(\mathrm{~m}, 1 \mathrm{H}), 2.68-2.55(\mathrm{~m}, 2 \mathrm{H}), 2.52-2.34(\mathrm{~m}, 3 \mathrm{H}), 2.07-1.56(\mathrm{~m}, 5 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): 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 $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{NO}_{3}\left(\mathrm{M}^{+}\right)$), $\mathrm{m} / \mathrm{z} 276.1594\left(276.1600\right.$ for $\mathrm{C}_{16} \mathrm{H}_{22} \mathrm{NO}_{3}\left(\mathrm{M}+\mathrm{H}^{+}\right)$); $[\alpha]_{\mathrm{D}}{ }^{20}=-87.2\left(\mathrm{c} 0.83, \mathrm{CHCl}_{3}\right)$; HPLC: Chiralpak OJ-H (hexane $/ \mathrm{i}-\mathrm{PrOH}, 80 / 20$, flow rate $1 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}$ ), $t_{\text {major }}=8.60 \mathrm{~min}$, $t_{\text {minor }}=10.62 \mathrm{~min}$., $90 \%$ ee.

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



Reaction of 22 ( $50 \mathrm{mg}, 0.24 \mathrm{mmol}$ ) and ( $E$ )-4-(4-bromophenyl)but-3-en-2-one (21, 315 $\mathrm{mg}, 1.4 \mathrm{mmol})$ in the presence of $S$-proline $(16.1 \mathrm{mg}, 0.14 \mathrm{mmol})$ in DMF $(0.5 \mathrm{~mL})$ according to the general procedure gave, after purification by flash chromatography on silica gel, 56 mg (27\%) of 25 as a yellow gum.
$\mathrm{R}_{f}=0.23$ (EtOAc/MeOH, 90:10); IR (neat): 2948, 2923, 2780, 2702, 1717, 1488, 1365, 1347, 1301, 1282, 1159, 1147, 1070, 1008, 838, $811 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 7.47 (apparent d, $2 \mathrm{H}, J=8.5 \mathrm{~Hz}$ ), 7.26 (apparent d, $2 \mathrm{H}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}$ ), $3.29(\mathrm{dd}, 1 \mathrm{H}, J=11.2$, 3.8 Hz ), 2.84-2.75 (m, 1H), 2.63-2.38 (m, 5H), 2.06-1.53 (m, 5H), ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 208.0,141.4,131.8,128.8,121.4,66.2,64.0,51.5,49.6,47.3,31.1,21.5 ;$ HRMS (ESI, pos.): $\mathrm{m} / \mathrm{z} 293.0419$ (293.0415 for $\mathrm{C}_{14} \mathrm{H}_{16} \mathrm{BrNO}\left(\mathrm{M}^{+}\right)$), $\mathrm{m} / \mathrm{z} 294.0492$ (294.0494 for $\mathrm{C}_{14} \mathrm{H}_{17} \mathrm{Br}^{79} \mathrm{NO}$ $\left.\left(\mathrm{M}+\mathrm{H}^{+}\right)\right), \mathrm{m} / \mathrm{z} 296.0474\left(296.0473\right.$ for $\mathrm{C}_{14} \mathrm{H}_{17} \mathrm{Br}^{81} \mathrm{NO}\left(\mathrm{M}+2+\mathrm{H}^{+}\right)$); $[\alpha]_{\mathrm{D}}{ }^{20}=-66.7$ (c 0.51, $\mathrm{CHCl}_{3}$ ); HPLC : Chiralpak OJ-H (hexane $/ \mathrm{i}-\mathrm{PrOH}, 90 / 10$, flow rate $1 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}$ ), $t_{\text {major }}$ $=7.02 \mathrm{~min}$., $t_{\text {minor }}=7.60 \mathrm{~min} ., 99 \%$ ee.

## (-)-Lasubine II (2):



To a solution of $11(106 \mathrm{mg}, 0.37 \mathrm{mmol})$ in anhydrous THF ( 1.5 mL ) at $-78{ }^{\circ} \mathrm{C}$, was added dropwise a solution of L-Selectride ( 1.0 M in THF, $0.74 \mathrm{~mL}, 0.74 \mathrm{mmol}$ ). The mixture
was stirred at $-78^{\circ} \mathrm{C}$ for 3 h after which it was warmed to $0^{\circ} \mathrm{C}$ and $1 \mathrm{~N} \mathrm{NaOH}(2 \mathrm{~mL})$ 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 ( $1 \times 10 \mathrm{~mL}$ ). The organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated. The residue was purified by flash chromatography on silica gel using gradient elution (EtOAc $\rightarrow$ EtOAc $/ \mathrm{MeOH} 8: 2$ ) to provide $81 \mathrm{mg}(76 \%)$ of (-)-lasubine (II) as a colourless oil that solidified after storage at $-20^{\circ} \mathrm{C}$ for several days. Spectroscopic data is in agreement with reported data. ${ }^{5}$
$\mathrm{R}_{f}=0.20$ ( $\mathrm{EtOAc} / \mathrm{MeOH}, 90: 10$ ); Mp: $96-98^{\circ} \mathrm{C}$; IR (neat): 3388 (br), 2924, 1592, 1512, 1462, 1444, 1259, 1228, 1130, $1026 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 6.91$ (br s, 1H), 6.86 (d, 1H, $J=8.2 \mathrm{~Hz}), 6.79(\mathrm{~d}, 1 \mathrm{H}, J=8.2 \mathrm{~Hz}), 4.17-4.12(\mathrm{br} \mathrm{m}, 1 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}), 3.31(\mathrm{dd}$, $1 \mathrm{H}, \mathrm{J}=11.8,3.3 \mathrm{~Hz}), 2.72-2.66(\mathrm{~m}, 1 \mathrm{H}), 2.43-2.35(\mathrm{~m}, 1 \mathrm{H}), 1.90-1.83(\mathrm{~m}, 1 \mathrm{H}), 1.83-1.77(\mathrm{~m}$, $1 \mathrm{H}), 1.74-1.64(\mathrm{~m}, 4 \mathrm{H}), 1.59-1.23(\mathrm{~m}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}: \delta 149.0,147.8,137.3$, 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 $\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{NO}_{3}\left(\mathrm{M}^{+}\right)$), m/z 292.1903 (292.1913 calc. for $\left.\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{NO}_{3}(\mathrm{M}+\mathrm{H})^{+}\right) ;\left[\alpha \mathrm{D}^{21}=-76.5\left(\mathrm{c} 0.67, \mathrm{CHCl}_{3}\right)\right.$, lit. $^{6}[\alpha]_{\mathrm{D}}{ }^{20}=+43.4\left(\mathrm{c} 1.0, \mathrm{CHCl}_{3}\right)$ for $(+)-$ lasubine II.

## (+)-Subcosine II (3):


(E)-3,4-Dimethoxycinnamic acid ( $33.3 \mathrm{mg}, 0.16 \mathrm{mmol}$ ) was added to a solution of crude (-)-lasubine II ( $48.2 \mathrm{mg}, 0.16 \mathrm{mmol}$ ) in dichloromethane ( 2 mL ) under nitrogen at ambient temperature. To the resulting solution was added EDCI ( $36.4 \mathrm{mg}, 0.19 \mathrm{mmol}$ ) and DMAP (19.5 $\mathrm{mg}, 0.16 \mathrm{mmol})$ and the mixture was stirred 19 h at ambient temperature. Water $(5 \mathrm{~mL})$ was added and the organic layer was separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{~mL})$ and again washed with water ( 5 mL ) and then with brine ( 5 mL ). The organic layer was dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated. Purification of the residue by flash chromatography on silica gel (EtOAc) provided $51.3 \mathrm{mg}(67 \%)$ of $\mathbf{3}$ as a white foam. Spectroscopic data is in agreement with reported data. ${ }^{7}$
$\mathrm{R}_{f}=0.41$ (EtOAc/MeOH, 90:10), $[\alpha]_{\mathrm{D}}{ }^{21}=+89.3$ (c 0.56 , MeOH); lit. ${ }^{5}[\alpha] \mathrm{D}^{20}=+85.3$ (c 0.64 , MeOH ); ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.67(\mathrm{~d}, 1 \mathrm{H}, J=15.9 \mathrm{~Hz}$ ), 7.16 (dd, $1 \mathrm{H}, J=8.2,2.0$ $\mathrm{Hz}), 7.12(\mathrm{~d}, 1 \mathrm{H}, J=2.0 \mathrm{~Hz}), 6.94-6.83(\mathrm{~m}, 2 \mathrm{H}), 6.90(\mathrm{~d}, 1 \mathrm{H}, J=8.2 \mathrm{~Hz}), 6.79(\mathrm{~d}, 1 \mathrm{H}, J=8.2$ $\mathrm{Hz}), 6.41(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}=15.9 \mathrm{~Hz})$, 5.22-5.18 (m, 1H), $3.95(\mathrm{~s}, 3 \mathrm{H}), 3.93(\mathrm{~s}, 3 \mathrm{H}), 3.90(\mathrm{~s}, 3 \mathrm{H}), 3.86$ (s, 3H), $3.29(\mathrm{dd}, 1 \mathrm{H}, \mathrm{J}=11.1,3.8 \mathrm{~Hz}$ ), 2.77-2.67 (m, 1H), 2.43-2.31 (m, 1H), 2.15-1.81 (m, $3 \mathrm{H}), 1.79-1.19(\mathrm{~m}, 8 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl} 3$ ): $\delta 166.6,151.2,149.3,149.2,147.9$, $144.6,137.1,127.5,122.8,116.4,111.1,109.7,68.4,64.2,57.2,56.0,55.9,53.2,39.9,37.5$, 33.7, 26.2, 24.9; HRMS (ESI, pos.): m/z 481.2472 (481.2464 calc. for $\mathrm{C}_{28} \mathrm{H}_{35} \mathrm{NO}_{6}\left(\mathrm{M}^{+}\right)$), m/z 482.2544 (482.2543 calc. for $\left.\mathrm{C}_{28} \mathrm{H}_{36} \mathrm{NO}_{6}(\mathrm{M}+\mathrm{H})^{+}\right)$.

## 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.



${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

| 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |



${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$


| 1 | 1 | 1 | 1 |  |  |  | 1 |  |  |  | 1 | 1 | 1 | 1 | 1 | 1 | 1 |  |  | T |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |








$-207.23$

${ }^{13} \mathrm{C}$ NMR $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$





| 210 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 | -10 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  |  |  |  |  |  | f1 (ppm) |  |  |  |  |  |  |  | 20 |  |  |  |










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 Nam¢ |  |



|  | RT <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> 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 |


| 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :--- | :---: | :---: | :---: | :---: | :---: |
| 1 | 8.776 | 3330788 | 48.59 | 139772 | 52.49 |
| 2 | 11.285 | 3523655 | 51.41 | 126527 | 47.51 |

Reported by User: Breeze user (Breeze)

## SAMPLE INFORMATION

| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-03-27A | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 23/05/2018 2:32:06 PM NDT |
| Vial: | 1 | Acq. Method: | OJ_H 80\% HEX 20\%IPA |
| 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \sec )$ | \% Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :--- | ---: | ---: | ---: | ---: | ---: |
| 1 | 6.851 | 21382860 | 99.04 | 1035780 | 99.12 |
| 2 | 9.816 | 207001 | 0.96 | 9200 | 0.88 |


| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-02-59A | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 21/09/2017 3:01:51 PM NDT |
| Vial: | 1 | Acq. Method: | OJ_H 80\% HEX 20\%IPA |
| 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :--- | :---: | :---: | :---: | :---: | :---: |
| 1 | 6.926 | 3654516 | 50.67 | 186275 | 62.25 |
| 2 | 9.401 | 3557390 | 49.33 | 112948 | 37.75 |

Reported by User: Breeze user (Breeze)

| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-02-171C | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 22/08/2018 11:30:10 AM NDT |
| Vial: | 1 | Acq. Method: | AD_H 97\%HEX 3\%IPA |
| 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :--- | :---: | ---: | ---: | ---: | ---: |
| 1 | 17.689 | 6178862 | 97.32 | 187042 | 97.09 |
| 2 | 20.890 | 170136 | 2.68 | 5605 | 2.91 |


| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-02-185A fridge | Acquired By: | Breeze |
| 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V}$ *sec $)$ | \% Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 16.537 | 760923 | 51.10 | 28279 | 58.27 |
| 2 | 20.113 | 728147 | 48.90 | 20249 | 41.73 |


| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-02-147C \#14 | Acquired By: | Breeze |
| Sample Type: | Unknown | 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | $\%$ Area | Height <br> $(\mu \mathrm{V})$ | \% <br> Height |
| :--- | :---: | ---: | ---: | ---: | ---: |
| 1 | 16.121 | 13126 | 0.87 | 817 | 1.22 |
| 2 | 16.818 | 1494509 | 99.13 | 66198 | 98.78 |


|  | S A M P LE | IN F O R M A T I O N |  |
| :--- | :--- | :--- | :--- |
| Sample Name: | SV-02-183C | Acquired By: | Breeze |
| Sample Type: | Unknown | 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 Nam |  |



|  | RT <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | $\%$ Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 16.000 | 1072119 | 50.26 | 51025 | 51.90 |
| 2 | 16.892 | 1061209 | 49.74 | 47280 | 48.10 |


| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-03-187A re | Acquired By: | Breeze |
| Sample Type: | Unknown | 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :--- | :---: | ---: | ---: | ---: | ---: |
| 1 | 5.098 | 49840 | 3.01 | 4359 | 4.20 |
| 2 | 5.870 | 1608134 | 96.99 | 99479 | 95.80 |

Reported by User: Breeze user (Breeze)

| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-03-179 A recolumned | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 17/12/2018 12:53:26 PM NST |
| 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 <br> $(\mathrm{min})$ | Area <br> $(\mu \mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mu \mathrm{V})$ | \% <br> Height |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 5.109 | 1444119 | 50.34 | 135498 | 53.52 |
| 2 | 5.901 | 1424380 | 49.66 | 117679 | 46.48 |

## SAMPLE INFORMATION

| SAMPLE INFORMATION |  |  |  |
| :---: | :---: | :---: | :---: |
| Sample Name: | SV-02-159B | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 15/03/2018 2:29:30 PM NDT |
| Vial: | 1 | 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 Nam |  |



|  | RT <br> $(\mathrm{min})$ | Area <br> $\left(\mu \mathrm{V}^{*} \mathrm{sec}\right)$ | $\%$ Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> 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 |

Reported by User: Breeze user (Breeze)


|  | SAMPLE | IN F O R M A T I O N |  |
| :--- | :--- | :--- | :--- |
| Sample Name: | SV-03-163A | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/10/2018 3:40:37 PM NDT |
| Vial: | 1 | 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 11 |  |
| Run Time: | 40.00 Minutes | Sample Set Nam |  |



|  | RT <br> $(\mathrm{min})$ | Area <br> $\left(\mu \mathrm{V}^{*} \mathrm{sec}\right)$ | $\%$ Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :--- | ---: | ---: | ---: | ---: | ---: |
| 1 | 7.018 | 2791804 | 99.80 | 209214 | 99.73 |
| 2 | 7.600 | 5724 | 0.20 | 565 | 0.27 |

Reported by User: Breeze user (Breeze)

## SAMPLE INFORMATION

| 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 Nam |  |



|  | RT <br> $(\mathrm{min})$ | Area <br> $\left(\mu \mathrm{V}^{*} \mathrm{sec}\right)$ | $\%$ Area | Height <br> $(\mu \mathrm{V})$ | $\%$ <br> Height |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 7.067 | 1140232 | 50.88 | 94126 | 59.90 |
| 2 | 7.516 | 1100638 | 49.12 | 63000 | 40.10 |

