

Enantiodivergent synthetic entry to the quinolizidine alkaloid lasubine-II

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General experimental methods ----- S2

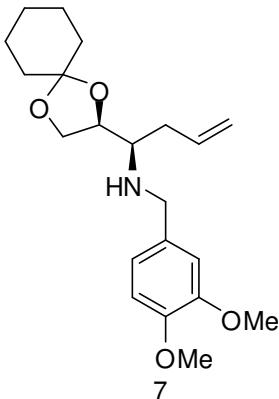
Synthesis of compounds 1-26 -----S3-S21

Reaction sequence and ORTEP diagram of compound 27----- S-22

EXPERIMENTAL

General : Column chromatography was performed on silica gel, Merck grade 230-400 mesh. TLC plates were visualized with UV, in an iodine chamber, or with vaniline solution, unless noted otherwise. Melting points were recorded in open capillaries and are uncorrected. Optical rotations were measured on a Rudolph Autopol-IV polarimeter purchased from a DST grant. IR spectra were recorded on a Perkin-Elmer Spectrum-1 instrument using KBr disks, chloroform solution or as neat. ^1H - NMR and ^{13}C -NMR spectra were recorded on a Bruker Avance 400, operating at 400 and 100 MHz, respectively or on a Bruker 600 spectrometer, purchased in a DST-FIST grant. HRMS were performed in a JEOL-JNM mass spectrometer and obtained from a paid source.

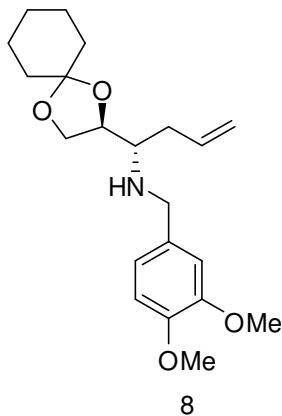
Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF, Toluene, benzene and ether were freshly distilled under argon from a purple solution of sodium benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.



***N*-(3,4-dimethoxybenzyl)-1(*R*)-((*S*)-1,4-dioxaspiro[4,5]decan-2-yl)but-3-en-1-amine (7)**

A stirred solution of the aldehyde **5** (3.0 g, 17.65 mmol) in dry THF (40 mL) was cooled to 5 °C and anhydrous MgSO₄ (8.5 g, 70.6 mmol) was added under argon atmosphere. After stirring for 10 min, a solution of 3,4-dimethoxy-benzylamine (3.24 g, 2.92 mL, 19.41 mmol) in THF (5 mL) was added drop wise over 10 min. The reaction was then allowed to come to room temperature and stirred for 20 h. It was filtered very quickly, the filtrate was concentrated under reduced pressure, and then diluted with dry diethyl ether (30 mL). The solution was cooled to -30 °C and then a solution of allylmagnesium bromide (1M, 18 mL, 18 mmol) was added drop wise to it over 30 min under argon. It was stirred at this temperature for 12 h and then quenched with sat. NH₄Cl solution (10 mL). It was extracted with ethyl acetate (2 × 100 mL) and the combined organic extract was washed with water (1 × 50 mL), brine (1×50 mL) and dried over MgSO₄. It was then filtered and the filtrate was concentrated in vacuum. The crude reaction mixture was analysed by ¹H-NMR to find a *de* of 64% in favour of **7**. The product was purified by flash chromatography over silica gel using 25% ethyl acetate in hexane to give in the order **8** (0.12 g, 2 % in two steps) followed by **7** (4.22 g, 66% over two steps) as oils.

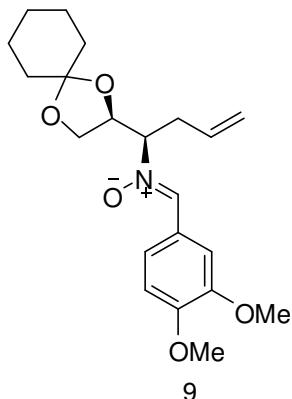
Data for **7**: $[\alpha]_D$ -10.96 (c 0.85, CHCl_3). IR (CHCl_3): 2935, 1515, 1450, 1464, 1264, 1236, 1139, 1161, 1103, 1031 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) : δ = 6.86-6.80 (m, 3 H), 5.84-5.76 (m, 1 H), 5.12-5.07 (m, 2 H), 4.10 (q, J = 6.8 Hz, 1 H), 3.98 (dd, J = 6.4, 8.0 Hz, 1 H), 3.88-3.85 (m, 2 \times OCH_3 + CH, 7H), 3.77-3.73 (m, 2 H), 2.69 (q, J = 6.4 Hz, 1H), 2.31-2.25 (m, 1 H), 1.60-1.57 (m, 11 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 148.9, 147.9, 135.1, 133.3, 120.2, 117.5, 111.3, 110.9, 109.5, 77.8, 66.4, 58.4, 55.9, 55.8, 51.3, 36.4, 35.2, 34.9, 25.2, 24.1, 23.9. HRMS found m/z 362.2327 ($\text{M} + \text{H}$); $\text{C}_{21}\text{H}_{32}\text{NO}_4$ requires 362.2344.



(*N*-(3, 4- dimethoxybenzyl)-1(*S*)-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine (8)

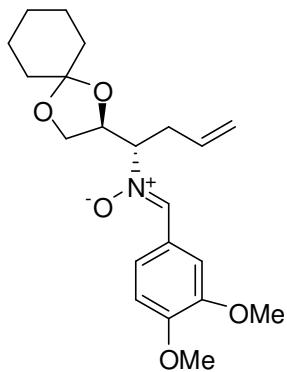
A stirred solution of the aldehyde **5** (3.0 g, 17.65 mmol) in dry THF (40 mL) was cooled to 5-10 °C and anhydrous MgSO_4 (8.5 g, 70.6 mmol) was added under argon atmosphere. After stirring for 10 min, a solution of 3,4-dimethoxy benzylamine (3.24 g, 2.92 mL, 19.41 mmol) in THF (5 mL) was added. The reaction was then allowed to come to room temperature and stirred for 20 h. The reaction mixture was cooled back to 0 °C and a solution of allylzinc bromide [prepared *in situ* by treating allyl bromide (2.33 mL) with Zn dust (1.84 g) in dry THF (15 mL) under sonication] was added drop wise for 15 min. It was then allowed to gradually come to room temperature and stirred for 8 h before being

quenched with water (10 mL). It was then extracted with ethyl acetate (3×100 mL) and the combined extract was washed with water (2×100 mL), brine (1×50 mL) and then dried over anhydrous MgSO_4 . It was then filtered and the filtrate was concentrated under reduced pressure to leave a crude product. The crude reaction mixture was analyzed by $^1\text{H-NMR}$ to find a *de* of 40% in favor of **8**. The crude was purified by flash chromatography over silica gel using a solution of 25% ethyl acetate in hexane to give in the order **8** (4.11 g, 64% over two steps) followed by **7** (0.38 g, 7 % over two steps) as viscous oils. $[\alpha]_D = +24.3$ (*c* 2.08, CHCl_3). IR (CHCl_3): 3332, 2936, 2861, 1516, 1464, 1450, 1265, 1236, 1140, 1031, 928 cm^{-1} . $^1\text{H NMR}$ (CDCl_3 , 400 MHz) : $\delta = 6.87\text{-}6.79$ (m, 3 H), 5.86-5.79 (m, 1 H), 5.14-5.10 (m, 2 H), 4.05-4.01 (m, 2 H), 3.90-3.87 (m, 7 H, 2 \times OMe + CH), 3.79 (d, *J* = 12.8 Hz, 1 H), 3.70 (d, *J* = 12.8 Hz, 1 H), 2.79 (q, *J* = 5.6 Hz, 1 H), 2.31 (2H, t, *J* = 6.0 Hz), 1.61-1.39 (11H, m), $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) $\delta = 148.9, 147.9, 134.9, 133.2, 120.1, 117.8, 111.2, 110.9, 109.3, 77.3, 66.4, 58.0, 55.9, 55.8, 51.5, 36.3, 35.1, 34.8, 25.2, 24.0, 23.8. \text{HRMS}$ found *m/z* 384.2140 (M+Na); $\text{C}_{21}\text{H}_{31}\text{NNaO}_4$ requires 384.2151.



(Z)-N-(3,4-dimethoxybenzylidene)-1(R)-((S)-1,4-dioxaspiro[4.5]decane-2-yl)but-3-en-1-amine oxide (9).

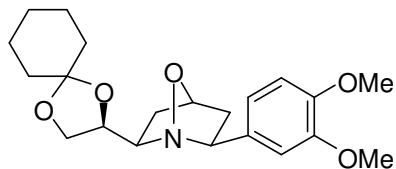
To a stirred solution of the amine **8** (2.0 g, 5.54 m.mol) in acetone+ water (9:1, 25 mL), NaWO₄.7H₂O (74 mg, 4 mol%) followed by H₂O₂ (30% , 2.3 mL, 22.16 mmol) was added slowly over 10 min and the resulting mixture was stirred for 12 h. The solution was then concentrated in vacuum and the residue was extracted with ethyl acetate (2×50 mL). The combined organic extract was washed successively with water (1×50 mL), brine (1×25 mL) and then dried over MgSO₄. It was filtered and the filtrate was concentrated to leave a pale yellow crude product which was purified by flash chromatography over silica gel using 30% ethyl acetate in hexane to give **9** (1.79 g, 86%) as a viscous liquid. $[\alpha]_D = -15.83$ (*c* 0.95, CHCl₃). IR (CHCl₃): 2936, 1595, 1508, 1450, 1273, 1167, 1147, 1024 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 8.41 (d, *J* = 2.0 Hz, 1 H), 7.46 (dd, *J* = 2.0, 8.8 Hz, 1 H), 7.27 (s, 1 H, merged with CHCl₃), 6.90 (d, *J* = 8.4 Hz, 1 H), 5.76-5.72 (m, 1 H), 5.18 (dd, *J* = 1.6, 16.8Hz, 1 H), 5.13 (dd, *J* = 1.2, 11.2 Hz, 1 H), 4.56 (q, *J* = 6.4 Hz, 1 H), 4.15 (dd, *J*= 6.4, 8.8 Hz, 1 H), 3.95 (s, 3 H), 3.93 (s, 3 H), 3.91-3.88 (m, 1 H), 3.79 (ddd, *J* = 3.2, 7.6, 14.4 Hz, 1 H), 2.88 (ddd, *J* = 6.8, 8.4, 15.6 Hz, 1 H), 2.20 (ddd, *J* = 3.2, 7.2, 14.4 Hz, 1 H), 1.64-1.55 (m, 10 H). ¹³C NMR (CDCl₃, 100MHz) : δ = 150.2 (s), 147.9 (s), 134.8 (d), 132.3 (d), 123.0(s), 122.8 (d), 118.3 (t), 110.6(d), 110.0 (d), 109.6(s), 78.2 (d), 74.5 (d), 65.4 (t), 55.4 (q, two signals), 36.1(t), 34.2 (t), 31.8 (t), 24.5 (t), 23.5 (t), 23.2 (t). HRMS found *m/z* 398.1942 (M+ Na); C₂₁H₂₉NNaO₅ requires 398.1943.



(Z)-N-(3,4-dimethoxybenzylidene)-1(S)-((S)-1,4-dioxaspiro[4.5]decane-2-yl)but-3-en-1-amine oxide (13)

Nitrone **13** was prepared following the procedure described for **9**. Yield: 91%.

$[\alpha]_D = +12.02$ (*c* 0.43, CHCl_3). IR (CHCl_3): 2936, 2860, 1597, 1506, 1464, 1273, 1167, 1147, 1025 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.34$ (d, *J* = 1.2 Hz, 1 H), 7.48 (dd, *J* = 1.2, 8.4 Hz, 1 H), 7.30 (s, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 5.85-5.75 (m, 1 H), 5.20 (d, *J* = 16.8 Hz, 1 H), 5.10 (d, *J* = 12.4 Hz, 1 H), 4.58-4.54 (m, 1 H), 4.09 (dd, *J* = 6.0, 8.8 Hz, 1 H), 3.98-3.94 (m, $2 \times \text{OMe} + \text{CH}_2$, 7 H), 3.76 (ddd, *J* = 3.2, 8.0, 10.8 Hz, 1 H), 2.94-2.86 (m, 1 H), 2.66 (ddd, *J* = 2.8, 7.6, 14.4 Hz, 1 H), 1.64-1.41 (m, 10 H). ^{13}C NMR (CDCl_3 , 100 MHz) $\delta = 150.3$ (s), 147.9 (s), 134.8 (d), 132.9 (d), 122.8 (s), 122.7 (d), 118.0 (t), 110.4 (d), 110.1 (d), 109.9 (s), 77.3 (d), 75.2 (d), 65.6 (t), 55.4 (q), 55.3 (q), 36.3 (t), 34.1 (t), 33.0 (t), 24.6 (t), 23.5 (t), 23.2 (t). HRMS found *m/z* 398.1938 ($\text{M} + \text{Na}$); $\text{C}_{21}\text{H}_{29}\text{NNaO}_5$ requires 398.1943.

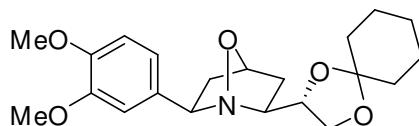


10

(2*S*, 4*R*, 6*R*)-2-(3,4-dimethoxyphenyl)-6-((S)-1,4-dioxaspiro[4.5]decane-2-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (10)

A solution of the nitrone **9** (0.6 g, 1.6 mmol) in dry and degassed toluene (180 mL) was heated to reflux under argon for 30 h. It was then concentrated in vacuum and the pale yellow residue was purified by flash chromatography over silica gel using 15% ethyl acetate in hexane to give the cycloadduct **10** as a colourless solid (486 mg, 81%). The crude reaction mixture was analyzed by ^1H -NMR to find a *de* of 76% in favour of **10**. Mp 72 °C. $[\alpha]_D = -30.15$ (*c* 2.1, MeOH). IR (CHCl_3): 2937,

2860, 1517, 1464, 1268, 1162, 1140, 1105, 1030 cm^{-1} . ^1H NMR(CDCl_3 , 400MHz): δ = 6.97 (d, J = 2.0 Hz, 1 H), 6.88 (dd, J = 2.0, 8.4 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 4.96 (t, J = 4.8 Hz, 1 H), 4.30 (q, J = 6.4 Hz, 1 H), 3.98 (dd, J = 6.4, 8.4 Hz, 1 H), 3.89-3.84 (m, 7 H, 2 \times OMe + CH), 3.75 (dd, J = 6.4, 8.8 Hz, 1 H), 3.22 (dt, J = 4.8, 7.2 Hz, 1 H), 2.13 (dd, J = 8.4, 12.0 Hz, 1 H) , 2.04-1.98 (m, 1 H), 1.77-1.44 (m, 12 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 148.5 (s), 147.5 (s), 136.1 (s), 118.6 (d), 110.4 (d), 109.6 (d), 109.2 (s), 78.1 (d), 76.8 (d), 70.0 (d), 69.2 (d), 64.8 (t), 55.4 (q), 55.3 (q), 42.2 (t), 35.9 (t), 34.1 (t), 24.7 (t), 23.5 (t), 23.2 (t). HRMS found m/z 376.2119 (M+ H); $\text{C}_{21}\text{H}_{30}\text{NO}_5$ requires 376.2124.



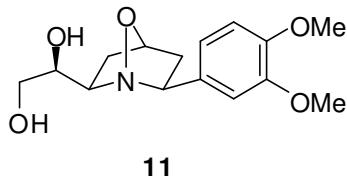
14

(2*R*, 4*R*, 6*S*)-2-(3,4-dimethoxyphenyl)-6-((*S*)-1,4-dioxaspiro[4.5]decane-2yl)-7-oxa-1-azabicyclo[2.2.1]heptane (14)

The cycloadduct **14** was prepared in a manner similar to that described for **10**.

Yield: 78 %. Mp 74 °C. $[\alpha]_D$ = +35.1(c 1.3, CHCl_3). IR (CHCl_3): 2936, 2861, 1516, 1464, 1268, 1162, 1139, 1102, 1029 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ = 6.93 (d, J = 1.6 Hz, 1 H), 6.85 (dd, J = 1.6, 8.0 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 1 H), 5.01 (t, J = 4.8 Hz, 1 H), 4.14 (dd, J = 5.6, 8.8 Hz, 1 H), 4.02 (dd, J = 4.0, 8.4 Hz, 1 H), 3.97-3.92 (m, 1 H), 3.89-3.85 (m, 2xOMe, + CH , 7 H), 2.96 (dt, J = 3.6, 8.4 Hz, 1 H), 2.14 (dd, J = 8.0, 11.2 Hz, 1 H), 2.04-1.99 (m, 2 H), 1.83 (dd, J = 7.6, 11.6 Hz, 1 H), 1.61-1.33 (m, 10 H). ^{13}C NMR (CDCl_3 , 100 MHz), δ = 148.9 (s), 148.0 (s), 136.5 (s), 118.9 (d), 110.9 (d), 110.0 (d), 109.6 (s), 79.4 (d), 78.1 (d), 70.3 (d), 70.0 (d), 68.5 (t), 55.9 (q), 55.8 (q), 42.5 (t), 37.1 (t), 36.7 (t), 34.8 (t),

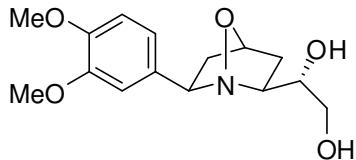
25.1 (t), 24.1 (t), 23.8 (t). HRMS found m/z 398.1980 (M+ Na); $C_{21}H_{29}NNaO_5$ requires 398.1943.



(S)-1-((2R,4R,6S)-6-(3,4-dimethoxyphenyl)-7-oxa-1-azabicyclo [2.2.1]heptan-2-yl)ethane-1,2-diol (11)

A solution of the acetal **10** (1.0 g, 2.67 mmol) in THF (10 mL) was cooled to 0 °C and then HCl (4N, 10 mL) was added to it drop wise while stirring. The resulting mixture was stirred for 3h before being diluted with water (50 mL) and neutralized with NaHCO₃. It was then extracted with chloroform (2×50 mL) and the combined organic extract was washed successively with water (2×50 mL), brine (1×50 mL) and dried over MgSO₄. It was then filtered and the filtrate was concentrated in vacuo to leave a solid mass which was purified by crystallization from ethyl acetate- hexane mixture to provide **11** (661 mg, 84%) as an amorphous powder.

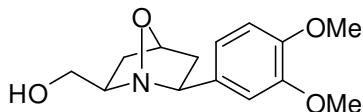
Mp 138-139 °C. $[\alpha]_D = -32.68$ (*c* 3.5, MeOH). IR (CHCl₃): 3283, 2836, 1519, 1255, 1239, 1028 cm⁻¹. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 6.96 (s, 1 H), 6.85 (s, 2 H), 4.91 (t, *J* = 4.8 Hz, 1 H), 4.44 (m, 2 H), 3.95 (dd, *J* = 4.8, 8.4 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.32-3.25 (m, 2 H), 3.21-3.18 (m, 1 H), 2.98-2.96 (m, 1 H), 2.13 (dd, *J* = 8.4, 11.2 Hz, 1 H), 1.80-1.78 (m, 1 H), 1.69 (dd, *J* = 8.0, 11.6 Hz, 1 H), 1.56-1.54 (m, 1 H). ¹³C NMR (CDCl₃, 100 MHz): δ = 149.0, 148.1, 136.2, 118.9, 110.9, 109.9, 79.5, 73.5, 69.8, 69.1, 62.2, 55.9, 55.8, 42.5, 35.2. HRMS found m/z 318.1315 (M+Na); $C_{15}H_{21}NNaO_5$ requires 318.1317.



15

(S)-1-((2S, 4R, 6R)-6-(3,4-dimethoxyphenyl)-7-oxa-1-aza-bicyclo[2.2.1]heptan-2-yl)ethane-1,2-diol (15)

Compound **15** was prepared following the procedure described for **11**. Yield: 88 %. Mp 141-142 °C. $[\alpha]_D = +20.5$ (*c* 0.59, CHCl₃). IR (CHCl₃): 3389, 2927, 1518, 1465, 1255, 1235, 1161, 1140, 1027 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 6.93 (d, *J* = 1.6 Hz, 1H), 6.85 (dd, *J* = 1.6, 8.0 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 5.01 (t, *J* = 4.8 Hz, 1 H), 3.89-3.85 (m, 7 H, 2 \times OMe + CH), 3.71 (s, 2 H), 3.10-3.08 (brs, 1 H), 2.90 (brs, 1 H), 2.16 (dd, *J* = 8.0, 11.6 Hz, 1 H), 2.04-2.00 (m, 2 H), 1.91-1.90 (brs, 2 H), 1.77 (dd, *J* = 8.0, 11.6 Hz, 1 H). ¹³C NMR (CDCl₃, 100 MHz): δ = 149.0 (s), 148.1 (s), 136.2 (s), 118.8 (d), 111.0 (d), 109.9 (d), 79.2 (d), 73.5 (d), 70.1 (d), 69.7 (d), 64.4 (t), 55.9 (q), 55.8 (q), 42.5 (t), 35.0 (t). HRMS found *m/z* 318.1345 (M+Na); C₁₅H₂₁NNaO₅ requires 318.1317.

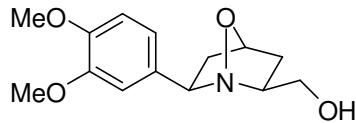


12

((2R, 4S, 6S)-6-(3,4-dimethoxyphenyl)-7-oxa-1-aza-bicyclo[2.2.1]heptan-2-yl)methanol (12)

In a one-necked round bottomed flask equipped with a magnetic stirring bar, diol **11** (100 mg, 0.34 mmol) was placed in acetonitrile /water (3:2, 4 mL) at 5-10 °C, and then NaIO₄ (148 mg, 0.7 mmol) was added during 5 min while stirring for 30 min. It was then filtered and the filter cake was washed with dichloromethane (25

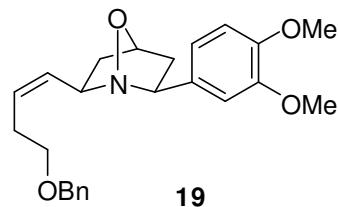
mL). The combined filtrate was washed with water (2×25 mL), brine (1×25 mL) and dried over MgSO_4 . It was then filtered and the filtrate was concentrated in vacuo to leave the crude aldehyde as a pale yellow liquid which was used without purification. It was taken in dry methanol (1 mL) and then NaBH_4 (16 mg, 0.41 mmol) was added while stirring. After 30 min, methanol was evaporated off and the crude product was extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water (2×10 mL), brine (1×10 mL) and then dried over MgSO_4 . It was then filtered and the filtrate was concentrated in vacuo to leave the crude product which was purified by chromatography over silica gel using 50 % ethyl acetate in hexane to give the product **12** as an amorphous solid (81 mg, 90 %). Mp 110-111°C. $[\alpha]_D = -32.1$ (c 1.09, CHCl_3). IR (CHCl_3): 3421, 2953, 2837, 1591, 1516, 1464, 1255, 1161, 1139, 1027 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 6.97 (d, J = 1.6 Hz, 1 H), 6.88 (dd, J = 1.6, 8.0 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 1 H), 4.97 (t, J = 4.8 Hz, 1 H), 3.89-3.86 (m, 2 × OMe, + CH, 7 H) 3.46-3.40 (m, 2 H), 3.18-3.15 (m, 1 H), 2.58 (d, J = 11.2 Hz, 1 H), 2.16 (dd, J = 8.4, 11.2 Hz, 1 H), 2.06-2.02 (m, 1 H), 1.75 (dd, J = 8.0, 11.6 Hz, 1 H), 1.52-1.48 (m, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 149.0 (s), 148.1(s), 136.5 (s), 118.9 (d), 110.9 (d), 110.0 (d), 78.7 (d), 69.6 (d), 69.2 (d), 65.0 (t), 55.9 (q), 55.8 (q), 42.7 (t), 34.7 (t). MS (QTOF MS ES+) found m/z 288 (M+Na); $\text{C}_{14}\text{H}_{19}\text{NNaO}_4$ requires 288.



16

((2S, 4R, 6R)-6-(3,4-dimethoxyphenyl)-7-oxa-1-azabicyclo[2.2.1]heptan-2-yl)methanol (16)

Compound **16** was prepared following the procedure described for **12**. Yield: 87 %. Mp 113⁰C. $[\alpha]_D = +33.2$ (*c* 0.51, CHCl₃). IR (CHCl₃): 3401, 2936, 2837, 1591, 1517, 1464, 1254, 1160, 1139, 1026 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 6.97 (d, *J* = 2.0 Hz, 1 H), 6.88 (dd, *J* = 1.6, 8.4 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 4.97 (t, *J* = 4.8 Hz, 1 H), 3.90-3.86 (m, 2 \times OMe + CH, 7 H), 3.46-3.40 (m, 2 H), 3.19-3.15 (m, 1 H), 2.54 (dd, *J* = 3.2, 9.6 Hz, 1 H), 2.16 (dd, *J* = 8.4, 12.0 Hz, 1 H), 2.05-2.02 (m, 1 H), 1.75 (dd, *J* = 8.0, 11.6 Hz, 1 H), 1.53-1.49 (m, 1 H). ¹³C NMR (CDCl₃, 100 MHz): δ = 149.0 (s), 148.1(s), 136.5 (s), 118.9 (d), 110.9 (d), 109.9 (d), 78.8 (d), 69.7 (d), 69.2 (d), 65.0 (t), 55.9 (q), 55.8 (q), 42.7 (t), 34.7 (t). MS (QTOF MS ES+): found *m/z* 266 (M+H); C₁₄H₂₀NO₄ requires 266.

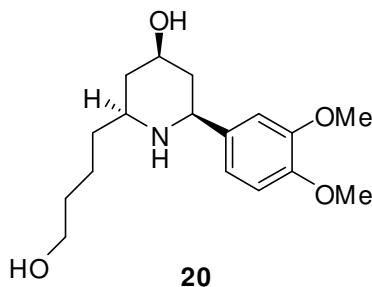


(2R, 4R, 6S)-2-((Z)-(4-(benzyloxy)but-1-enyl)-6-(3,4-dimethoxyphenyl)-7-oxa-1-azabicyclo[2.2.1]heptane (19)

In a one-necked round bottomed flask equipped with a magnetic stirring bar, diol **11**(220 mg, 0.745 mmol) was placed in a mixture of acetonitrile +water (3:2, 10 mL) at 0-5 °C and then NaIO₄ (315 mg, 1.49 mmol) was added portion wise over 5 min while stirring. The reaction mixture was filtered after 30 min and the filter cake was washed with CH₂Cl₂ (25 mL). The combined filtrate was washed with water (1 \times 25 mL), brine (1 \times 25 mL) and then dried (MgSO₄).It was filtered and the filtrate was concentrated in vacuo to leave the crude aldehyde as a pale yellow viscous liquid which was used as such in the next step.

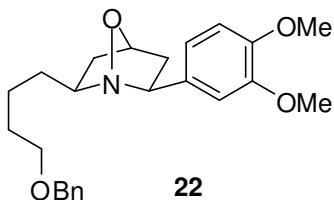
In a 25 mL one-necked round bottomed flask equipped with a magnetic stirring bar, a rubber septum, and argon balloon, was placed the Wittig salt **18**

(556 mg, 1.14 m.mol) in dry THF (10 mL) at -78°C . *n*-BuLi (2M in hexane, 570 μl , 1.14 mmol) was then added drop wise over 5 min and the resulting solution was allowed to come to 0°C over 15 min when the solution turned deep orange-red. It was cooled to -78°C and then a solution of the aldehyde (195 mg, 0.74 mmol assuming pure) in THF (5 mL) was added drop wise over 15 min while stirring. After 30 min it was allowed to come to rt and further stirred for 2.5 h. The reaction mixture was then quenched with aqueous NH_4Cl solution (5 mL) and extracted with ethyl acetate (2×50 mL). The combined organic extract was washed successively with water (1×25 mL) and brine (1×25 mL), and then dried over MgSO_4 . It was then filtered and the filtrate was concentrated in vacuo to leave the crude product which was purified by flash chromatography over silica gel using a mixture of ethyl acetate-hexane (1:4) to give the product **19** (251 mg, 86% over two steps) as a colorless oil. $[\alpha]_D = -79.4$ (*c* 0.4, CHCl_3). IR (CHCl_3): 2951, 1516, 1463, 1267, 1233, 1159, 1139, 1028 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.33$ -7.27 (m, 5 H), 6.98 (d, *J* = 2.0 Hz, 1 H), 6.86 (dd, *J* = 2.0, 8.4 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 5.60 (dd, *J* = 8.8, 10.4 Hz, 1 H), 5.42 (dt, *J* = 10.4, 7.6 Hz, 1 H), 4.99 (t, *J* = 5.2 Hz, 1 H), 4.51 (s, 2 H), 3.90-3.87 (m, 7 H, 2 \times OMe + N-CH), 3.84-3.79 (m, 1 H), 3.52-3.46 (m, 2 H), 2.40 (q, *J* = 7.2 Hz, 2 H), 2.12 (dd, *J* = 8.4, 12.0 Hz, 1 H), 1.99-1.94 (m, 2 H), 1.70-1.66 (m, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) $\delta = 149.0$, 148.1, 138.3, 136.3, 134.4, 128.3, 127.7, 127.6, 125.6, 119.1, 110.9, 110.2, 78.9, 73.0, 69.8, 69.6, 64.7, 55.9, 55.8, 42.7, 41.0, 28.7. HRMS found *m/z* 418.1994 (M+Na); $\text{C}_{24}\text{H}_{29}\text{NNaO}_4$ requires 418.1994.



(2S,4R,6S)-2-(3,4-dimethoxyphenyl)-6-(4-hydroxybutyl)piperidin-4-ol (20).

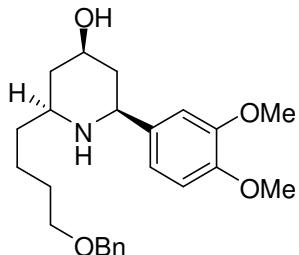
In a one-necked round bottomed flask equipped with a stirring bar and fitted with a hydrogen balloon, olefin **19** (100 mg, 0.25 mmol) was placed in MeOH (3 mL) and acetic acid (300 μ l), and then Pd-C (10%, 20 mg) was added. Hydrogen gas was allowed to pass under atmospheric pressure and the heterogeneous mixture was stirred for 12h. It was filtered through celite and the filter cake was washed with methanol (5 mL). The combined filtrate was concentrated in vacuo to leave the crude product which was purified by column chromatography over silica gel using 20 % methanol in ethyl acetate to give **20** (43mg, 55 %) as a colorless solid. IR (neat) = 3421, 2925, 2854, 1517, 1465, 1266, 1028 cm^{-1} . ^1H NMR (DMSO-d₆, 400 MHz): δ = 7.31 (s, 1 H), 7.03 (d, J = 7.2 Hz, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 5.18 (d, J = 4.0 Hz, 1 H), 4.43 (t, J = 4.8 Hz, 1 H), 4.26-4.00 (br s, 1 H), 3.80-3.76 (m, 7 H, 2 \times OMe + CH), 3.24-3.21 (br s, 1 H), 2.12-1.19 (m, 10 H). ^{13}C NMR (DMSO-d₆, 100 MHz): δ = 149.0, 148.6, 120.2, 111.7, 111.5, 65.2, 60.3, 58.3, 55.8, 55.7, 55.5, 36.5, 32.0, 31.9, 21.3. MS (QTOF MS ES+) found *m/z* 310 (M+H); C₁₇H₂₈NO₄ requires 310.



(2S, 4R, 6S)-2-(4-(benzyloxy)butyl)-6-(3,4-dimethoxyphenyl)-7-oxa-1-azabicyclo[2.2.1]heptane (22)

In a one-necked round bottomed flask equipped with a stirring bar, and fitted with a hydrogen balloon, olefin **19** (200 mg, 0.51 mmol) was placed in MeOH (5 mL), and Pd-C (10%) (20 mg) was added. The heterogeneous mixture was then vigorously stirred under hydrogen atmosphere for 2 h. It was then filtered through

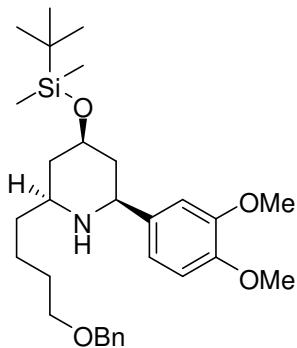
celite, the filter cake was washed with more methanol (10 mL) and the combined filtrate was concentrated under reduced pressure to leave a crude product which on purification by column chromatography over silica gel using 30% ethyl acetate in hexane gave **22** (179 mg, 90%) as an oil. $[\alpha]_D = -27.3$ (*c* 0.43, CHCl_3). IR (CHCl_3): 2939, 2862, 1517, 1464, 1455, 1268, 1104, 1029 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.25\text{-}7.19$ (m, 5 H), 6.91 (d, *J* = 1.6 Hz, 1 H), 6.80 (dd, *J* = 1.6, 8.4 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 4.86 (t, *J* = 4.8 Hz, 1 H), 4.42 (s, 2 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.74 (dd, *J* = 4.8, 8.0 Hz, 1 H), 3.40 (t, *J* = 6.4 Hz, 2 H), 2.82-2.79 (m, 1 H), 2.0 (dd, *J* = 8.4, 11.6 Hz, 1 H), 1.91-1.87 (m, 1 H), 1.72 (dd, *J* = 8.0, 11.6 Hz, 1 H), 1.66-1.21 (m, 7 H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 148.9$, 147.8, 138.6, 137.2, 128.4, 127.7, 127.5, 118.9, 110.8, 109.9, 78.9, 72.9, 70.3, 69.9, 68.0, 55.9, 55.8, 42.5, 39.3, 36.6, 29.7, 23.2. HRMS found *m/z* 420.2123 ($\text{M}+\text{Na}$); $\text{C}_{24}\text{H}_{31}\text{NNaO}_4$ requires 420.2151.



(2S, 4R, 6S)-2-(4-(benzyloxy)butyl)-6-(3,4-dimethoxyphenyl)piperidine-4-ol (23)

In an one-necked round bottomed flask equipped with a small magnetic stirring bar, compound **22** (200 mg, 0.50 m.mol) was placed in a solution of 70% acetic acid in water (1 mL) at 20 °C. Then Zn dust (327 mg, 5.03 mmol) was added portion wise and the resulting heterogeneous mixture was stirred for 10 min by which time the reaction was complete. It was then filtered, diluted with water (10 mL) and then neutralized with solid NaHCO_3 before being extracted with CH_2Cl_2

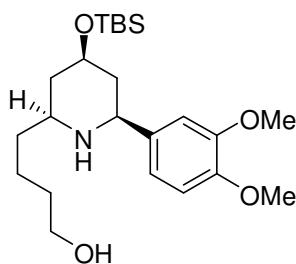
(3×20 mL). The organic extract was washed with water (1×20 mL), and brine (1×20 mL), and then dried over MgSO_4 . It was then filtered and the filtrate was concentrated in vacuo to leave a pale yellow crude product which on purification by chromatography over neutral alumina using 80% ethyl acetate in hexane gave the piperidine derivative **23** (184 mg, 92%) as an oil. $[\alpha]_D = -9.4$ (*c* 2.3, CHCl_3). IR (CHCl_3): 3383, 2927, 2853, 1595, 1518, 1465, 1267, 1026, 772 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 7.35-7.28 (m, 5 H), 6.93 (d, *J* = 1.6 Hz, 1 H), 6.89 (dd, *J* = 1.6, 8.4 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 4.48 (s, 2 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.82-3.75 (m, 1 H), 3.60 (dd, *J* = 2.0, 11.2 Hz, 1 H), 3.46 (t, *J* = 6.4 Hz, 2 H), 2.69 (m, 1 H), 2.10-2.01 (m, 2 H), 1.66-1.58 (m, 6 H), 1.49-1.41 (m, 5 H) 1.14 (q, *J* = 11.2 Hz, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 148.9, 148.2, 138.5, 136.7, 128.4, 127.7, 127.6, 118.8, 111.0, 110.0, 72.9, 70.2, 69.6, 59.5, 55.9 (two signals), 55.3, 43.7, 41.4, 36.4, 29.8, 22.7. HRMS found *m/z* 422.2318 (M+Na); $\text{C}_{24}\text{H}_{33}\text{NNaO}_4$ requires 422.2307.



(2S, 4R, 6S)-2-(4(benzyloxy)butyl)-4-(tert-butyldimethylsilyloxy)-6-(3,4-dimethoxy)piperidine (24)

In a one -necked round bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet, was placed the amino alcohol **23** (200 mg, 0.5 mmol) in dry dichloromethane (5 mL). The solution was cooled to 0 $^{\circ}\text{C}$ and DIEA (130 mg, 175 μl , 1.00 mmol) followed by TBSOTf (160 mg, 140 μl , 0.60 mmol)

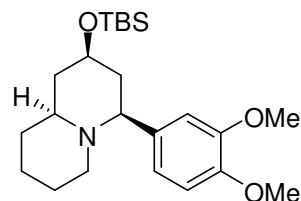
was added drop wise to the stirred solution. Stirring was continued for 40 min at 0 °C and then quenched with dry methanol (1 mL). The reaction mixture was diluted with CH₂Cl₂ (25 mL) and then washed with water (1×25 mL), brine (1×25 mL), and dried over MgSO₄. It was then filtered and the filtrate was concentrated in vacuo to leave a crude product which was purified by flash chromatography over silica gel using 50% ethyl acetate in hexane to give the silyl ether **24** (234 mg, 91%) as a colorless oil. $[\alpha]_D = -2.95$ (*c* 2.0, MeOH). IR (CHCl₃): 3568, 2934, 2856, 1518, 1463, 1259, 1099, 1030, 836 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.35-7.28 (5 H, m), 6.96 (d, *J* = 1.6 Hz, 1 H), 6.91 (dd, *J* = 1.6, 8.4 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 4.51 (s, 2 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.82-3.70 (m, 1 H), 3.59 (dd, *J* = 2.0, 11.6 Hz, 1 H), 3.48 (t, *J* = 6.4 Hz, 2 H), 2.69-2.67 (brs, 1 H), 1.97-1.88 (m, 2 H), 1.66-1.63 (m, 5 H), 1.51-1.46 (m, 4H), 1.23 (q, *J* = 11.2 Hz, 1 H), 0.89 (s, 9 H), 0.1-0.02 (m, 6 H). ¹³C NMR (CDCl₃, 100 MHz): δ = 148.4 (s), 147.7 (s), 138.1 (s), 136.7 (s), 127.9 (d), 127.1 (d), 127.0 (d), 118.4 (d), 110.4 (d), 109.6 (d), 72.4 (t), 69.9 (t), 69.7 (d), 59.2 (d), 55.43 (q), 55.4 (q), 54.8 (d), 43.8 (t), 41.6 (t), 36.1 (t), 29.4 (t), 25.4 (q), 25.2 (q), 22.2 (t), 17.7 (s), -4.98 (q), -5.0 (q). HRMS found *m/z* 536.3194 (M+Na); C₃₀H₄₇NNaO₄Si requires 536.3172.



4-((2*S*, 4*R*, 6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(3,4-dimethoxyphenyl)piperidine-2-yl)butane-1-ol (25)

In a 10 mL one-necked round bottomed flask equipped with a magnetic stirring bar and fitted with hydrogen balloon, the benzyl ether **24** (200 mg, 0.389 m.mol)

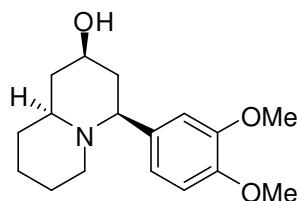
was placed in a mixture of THF and MeOH (1:1, 6 mL) containing 4 drops of TFA. Then $\text{Pd}(\text{OH})_2$ (10 mg) was added, hydrogen gas was let in and the resulting heterogeneous mixture was vigorously stirred at atmospheric pressure for 7 h. It was filtered through celite, the filter cake was washed with methanol (5 mL) and the combined filtrate was concentrated in vacuo. The residue was diluted with ethyl acetate (25 mL) and washed with aqueous NaOH solution (0.1 M, 2 mL), water (1×10 mL) and brine (1×10 mL). It was then dried over MgSO_4 , filtered and the filtrate was concentrated in vacuo. The crude product thus obtained was purified by chromatography over alumina using 10% MeOH in ethyl acetate to give the primary alcohol **25** (137 mg, 83%) as an oil. $[\alpha]_D = -1.2$ (*c* 1.2, MeOH). IR (CHCl_3): 3393, 2932, 2857, 1519, 1464, 1383, 1263, 1142, 1105, 1074, 1029, 838 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.11$ (s, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 4.08-4.03 (m, 10 H), 3.24 (br s, 1 H), 3.05 (br s, 2 H), 2.08-1.98 (m, 3 H), 1.90 (d, *J* = 12.8 Hz, 1 H), 1.55 (q, *J* = 12 Hz, 2 H), 1.32 (br s, 1 H), 1.21-1.14 (m, 3 H), 0.96 (s, 9 H), -0.01-0.07 (overlapping singlets, 6 H, 2 × Me). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 148.9, 148.2, 136.6, 119.0, 110.9, 110.2, 70.2, 62.5, 59.6, 55.9, 55.3, 43.9, 41.9, 36.3, 32.7, 25.9, 22.2, 18.1, -4.5$. HRMS found *m/z* 446.2709 (M+Na); $\text{C}_{23}\text{H}_{41}\text{NNaO}_4\text{Si}$ requires 446.2703.



(2R,4S,9aS)-2-(tert-butyldimethylsilyloxy)-4-(3,4-dimethoxyphenyl)octahydro-1H-quinolizine (26)

In a one-necked round bottomed flask, equipped with stirring bar, a rubber septum, an argon inlet, was placed the amino alcohol **25** (100 mg, 0.24 mmol) in

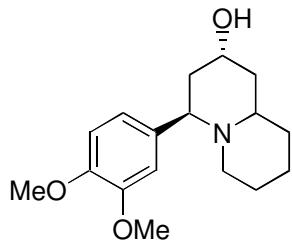
anhydrous THF (12 mL) under argon. The solution was cooled to -5°C and then Ph_3P (124 mg, 0.472 mmol) followed by DEAD (76 mg, 70 μl , 0.472 m.mol) was added drop wise over 5 min to the stirred solution. Stirring was continued for another 3 h at rt. It was then concentrated and the residue was extracted with ethyl acetate (2 \times 25 mL). The combined organic extract was washed with water (1 \times 25 mL), brine (1 \times 25 mL), and then dried over MgSO_4 . It was filtered and the filtrate was concentrated in vacuo to leave a crude mass which was purified by flash chromatography over silica gel using 20 % ethyl acetate in hexane to give the cyclized product **26** (72 mg, 75%) as colorless solid. $[\alpha]_D = -25.0$ (c 1.4, CHCl_3). IR (neat): 2935, 2857, 1514, 1460, 1380, 1261, 1108, 1076, 1035, 843 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 7.28-6.79 (m, 3 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.73-3.67 (m, 1 H), 2.89 (dd, J = 2.4, 11.6 Hz, 1 H), 2.66 (d, J = 11.2 Hz, 1 H), 2.01-1.95 (m, 1 H), 1.92-1.87 (m, 1 H), 1.82-1.77 (m, 1 H), 1.68 (t, J = 12 Hz, 2 H), 1.58-1.55 (m, 2 H), 1.52-1.46 (m, 2 H), 1.45-1.37 (m, 2 H), 1.27-1.20 (m, 1 H), 0.88 (s, 9 H), 0.09-0.07 (overlapping singlets, 6 H, 2 \times Me). ^{13}C NMR (CDCl_3 , 100 MHz) : δ = 147.4 (s), 136.6 (s), 68.6 (d), 67.8 (d), 60.5 (d), 55.4 (q), 55.3 (q), 52.5 (t), 45.1 (t), 42.8 (t), 33.2 (t), 25.6 (t), 25.4 (q), 24.2 (t), 17.7 (s), -3.5 (q). HRMS found m/z 406.2815 ($\text{M}+\text{H}$); $\text{C}_{23}\text{H}_{40}\text{NO}_3\text{Si}$ requires 406.2777.



(2R, 4S, 9aS)-4-(3,4-dimethoxyphenyl)octahydro-1H-quinolizine-2-ol (21)

The quinolizidine derivative **26** (50 mg, 0.123 m.mol) was placed in dry MeOH (1.5 mL) and $\text{Et}_3\text{N}\text{-3HF}$ (100 mg, 100 μl , 0.617 m.mol) was added drop wise at room temperature under argon. The reaction mixture was stirred for 3 h

before being diluted with water (10 mL). The aqueous solution was neutralized with saturated aqueous solution of NaHCO_3 and then extracted with ethyl acetate (2×25 mL). The combined organic extract was washed with water (1×25 mL), brine (1×25 mL), and then dried over MgSO_4 . It was filtered and the filtrate was concentrated under vacuo to leave a crude product which was purified by chromatography over neutral alumina using 10% MeOH in ethyl acetate to give 2-*epi*-lasubine II (**21**) (32 mg, 90%) as a colorless solid. $[\alpha]_D = -66.0$ (*c* 0.5, CHCl_3) [Lit.^{6j} -65.5 (*c* 1.0, CHCl_3) ; -59.1 (*c* 0.6, MeOH) [lit.^{6j} -56.9 (*c* 1.0, MeOH)]. IR (CHCl_3) = 3394, 2928, 2851, 1517, 1459, 1265, 1059, 1027, 769 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 6.99-6.81 (m, 3 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.75 (ddd, *J* = 4.4, 10.8, 15.2 Hz, 1 H), 2.93 (dd, *J* = 2.4, 11.6 Hz, 1 H), 2.69 (d, *J* = 11.6 Hz, 1 H), 2.06-1.96 (m, 3 H), 1.73-1.20 (m, 10 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 147.4 (s), 136.0 (s), 119.2 (d), 110.3 (d), 67.9 (d), 67.8 (d), 60.5 (d), 55.4 (q), 55.3 (q), 52.4 (t), 44.5 (t), 42.2 (t), 33.1 (t), 25.5 (t), 24.1 (t). HRMS found *m/z* 292.1895 ($\text{M}+\text{H}$); $\text{C}_{17}\text{H}_{26}\text{NO}_3$ requires 292.1913.



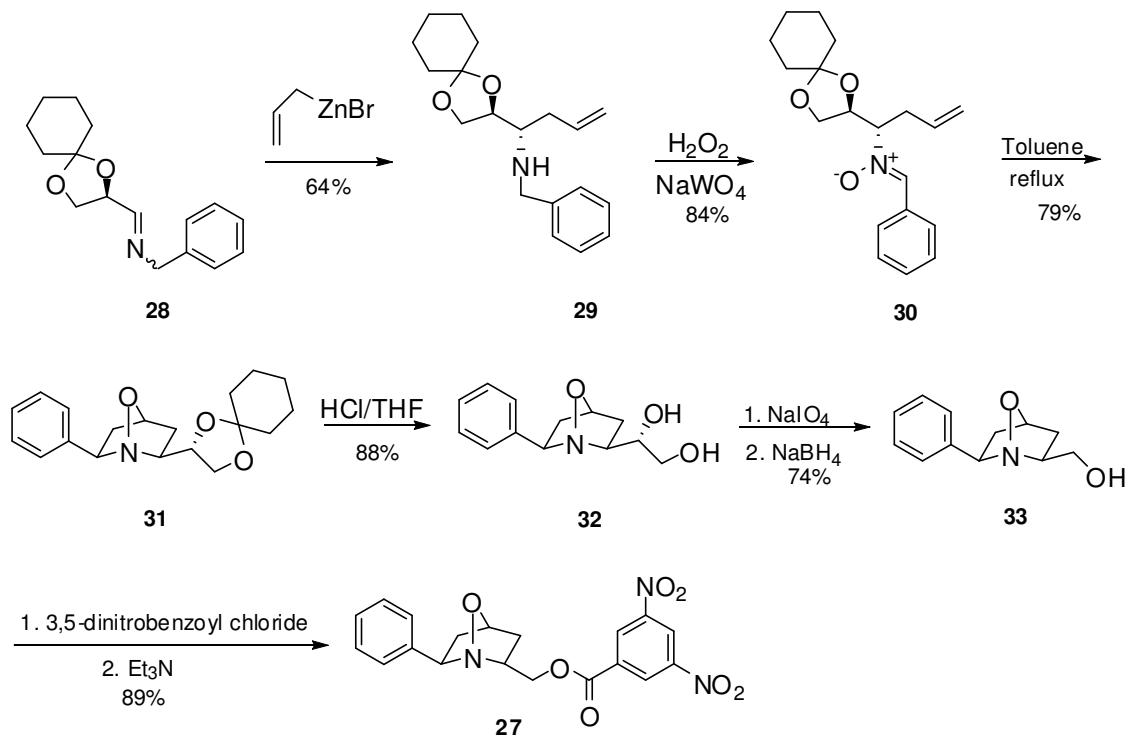
(-) Lasubine II (1)

A solution of 2-*epi*-lasubine II (**21**, 50 mg, 0.17 mmol), Ph_3P (90 mg, 0.34 mmol) and *p*-nitrobenzoic acid (57 mg, 0.34 mmol) in dry toluene (5 mL) was stirred at room temperature under argon for 10 min. Then a solution of DEAD (59 mg, 55 μ l, 0.34 mmol) in dry toluene (1 mL) was added drop wise and stirring was continued for 3 h at room temperature. It was then diluted with ethyl acetate (25 mL) and the combined organic extract was washed successively with saturated aqueous NaHCO_3 (1×25 mL), water (1×25 mL), brine (1×25 mL), and then dried

over MgSO_4 . It was then filtered and the filtrate was concentrated in vacuo to leave a crude residue which was triturated with hexane (10 mL). The precipitated solid was filtered off and the residue was purified by flash chromatography over silica gel using 40% ethyl acetate in hexane. The nitrobenzoate derivative thus obtained was dissolved in MeOH (5 mL) and K_2CO_3 (48 mg, 0.34 m.mol) was added. The solution was stirred for 30 min, and then concentrated in vacuo. The residual mass was diluted with water (10 mL) and then extracted with ethyl acetate (2×20 mL), washed with water (1×25 mL), brine (1×25 mL), and then dried over MgSO_4 . It was filtered and the filtrate was concentrated in vacuo to leave a crude product which was purified by flash chromatography over silica gel using 20% MeOH in ethyl acetate to give (-)-lasubine II (32 mg, 64%) as a colorless oil. $[\alpha]_D$ - 45.7 (*c* 1.2, MeOH) [lit.^{6k} -46 (*c* 2.1, MeOH); lit.^{6l} -47.5 (*c* 3.7, MeOH); lit.¹⁴ -41 (*c* 2.7, MeOH)]. IR (CHCl_3): 3413, 2926, 1628, 1518, 1419, 1265, 1149, 1026 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 6.96 (s, 1 H), 6.88 (br s, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 4.16 (br s, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.35 (br s, 1 H), 2.77 (d, *J* = 10.4 Hz, 1 H), 2.56 (br s, 1 H), 2.07-2.03 (m, 2 H), 1.85-1.81 (m, 2 H), 1.75-1.72 (m, 3 H), 1.61-1.53 (m, 4 H), 1.30 (t, *J* = 4.8 Hz, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 149.0, 147.6, 135.4, 119.5, 110.4, 110.3, 64.3, 63.4, 56.5, 55.5, 55.3, 52.6, 41.5, 39.2, 32.5, 25.1, 24.1. HRMS found *m/z* 292.1907 ($\text{M}+\text{H}$); $\text{C}_{17}\text{H}_{26}\text{NO}_3$ requires 292.1913.

Preparation of the model compound **27 for X-ray analysis:**

The model compound **27** was prepared from the imine **28** following the scheme outlined below:



ORTEP diagram of model compound **27** (CCDC number 835450):

