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Enantioselective synthesis of (−)-lasubine II

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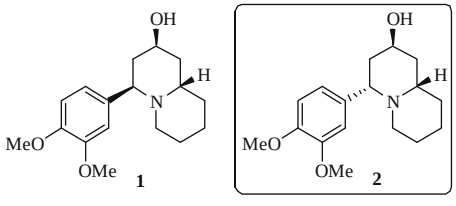
ABSTRACT

A highly enantioselective synthesis of *lythraceae* alkaloid lasubine II has been achieved using organo-catalyzed Mannich reaction, Maruoka allylation, and *aza*-Michael addition as the key steps.

(−)-Lasubine I (**1**) and (−)-lasubine II (**2**, Figure 1) were isolated from the leaves of *Lagerstroemia subcostata koehne* by Fuji et al. in 1978.[1] These *Lythraceae* alkaloids containing the arylquinolizidine ring systems have been found to have a broad range of biological activities.[2] The quinolizidine scaffold of these molecules has attracted great interest from synthetic chemistry point of view and various syntheses have been reported in either racemic form or enantiomerically pure form.[3–6] Herein, we report a new strategy for lasubine II that incorporates organocatalysis and Michael reaction which are our continued interests for synthesis of bio-active natural products.[7,8]

Accordingly our synthesis commenced with the commercially available starting material, 3,4-dimethoxy benzaldehyde **3** and the key steps in the sequence include organo-catalyzed Mannich reaction, Maruoka allylation, and *aza*-Michael addition reactions, which would be generating the asymmetric centers to provide the (−)-lasubine II (Schemes 1 and 2). In the first step, 3,4-dimethoxy benzaldehyde **3** was treated with $BocNH_2$ to generate Boc-imine **4**.[9] The compound **4** was subjected to proline-catalyzed Mannich reaction[10] with acetaldehyde to obtain the β-amino aldehyde **5**, which was immediately subjected to Maruoka allylation[11] using titanium complex (***S,S***)-**I** and allyltributylstannane to furnish the 1,3-amino alcohol **6** in 72% yield with 97% enantiomeric excess (Scheme 1).[12] The enantiomeric excess of Mannich product **5** was confirmed by chiral HPLC method (>98% ee) in its alcohol form.[13] The relative stereochemistry of compound **6** was thoroughly examined at a later stage using intermediate **9**. Thus, **6** was subjected to dihydroxylation (OsO_4/NMO) followed by sodium periodate oxidation and Wittig olefination with ethoxycarbonylmethylene triphenylphosphorane to afford α,β-unsaturated ester **7**. Now, the compound **7** was ready for intramolecular *aza*-Michael addition reaction,[14] which was successfully achieved by the treatment of **7** with 1% HCl in *iso*propanol at 60 °C for 4 h to afford 2,4,6-trisubstituted piperidine **8** in 73% yield. It was gratifying to find that the exclusive product of the reaction was the 2,6-*cis*-isomer, which was confirmed by NOE studies performed on compound **9**.[15] The hydroxyl group of the piperidine that was obtained above was protected as *tert*-butyldimethylsilyl ether using TBSOTf/DIPEA in dichloromethane to get compound **9**. Exposure of compound **9** to DIBAL-H reduction followed by the addition of ethoxycarbonylmethylene triphenylphosphorane provided α,β-unsaturated ester **10** in 54% yield over two steps. Conversion of α,β-unsaturated ester **10** to saturated ester **11** was achieved by $NiCl_2$, $NaBH_4$ reduction and further reduction of ester using DIBAL-H provided the saturated alcohol **12**. Deprotection of TBS group of **12** by TBAF in THF



(-)-Lasubine I (-)-Lasubine II

Figure 1. Structure of (−)-lasubine I (**1**) and (−)-lasubine II (**2**).

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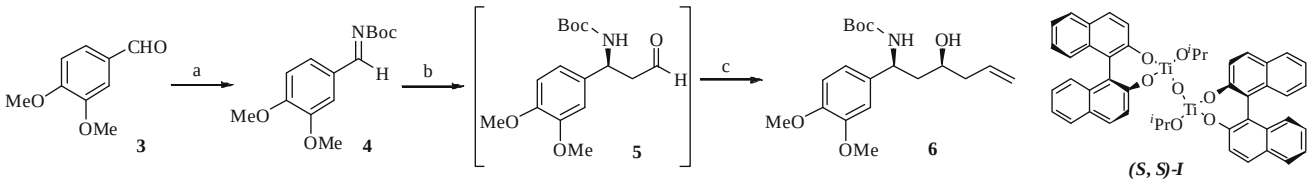
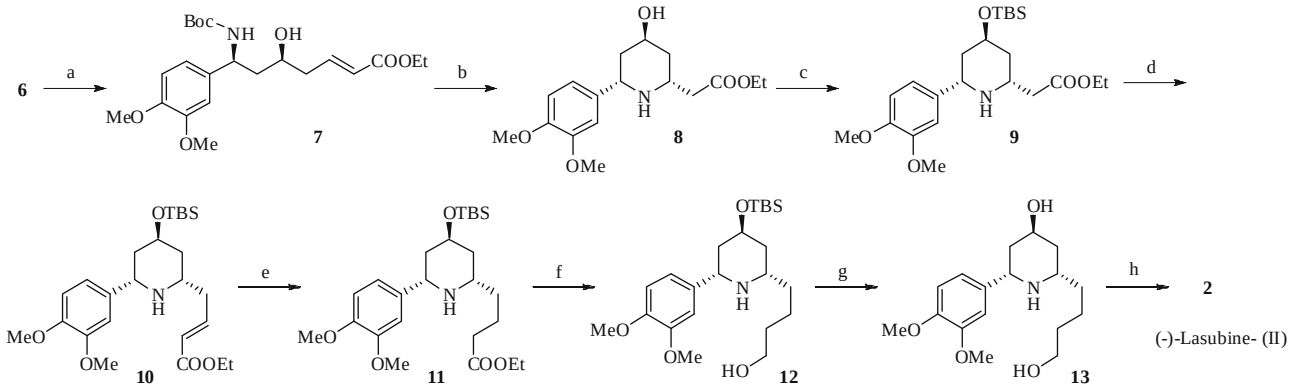


Scheme 1. Reagents and conditions: (a) (i) $BocNH_2$, $PhSO_2Na$, HCOOH, MeOH:H_2O (1:9), rt, 9 h; (ii) K_2CO_3, Na_2SO_4, THF, reflux, 24 h 73% over two steps; (b) CH_3CHO, L-proline (20 mol %), CH_3CN, 0 °C, 3 h, 64%; (c) ***(S, S)-I*** (10 mol %), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15 °C to 0 °C, 24 h, 72%.



Scheme 2. Reagents and conditions: (a) (i) OsO_4, NMO, acetone:H_2O (8:2), rt, 14 h; (ii) $NaIO_4$, CH_2Cl_2:H_2O (8:2), rt, 0.5 h; (iii) $Ph_3P{=}CHCOOEt$, benzene, rt, 4 h, 62% over three steps; (b) 1% HCl in *i*PrOH, 60 °C, 4 h, 73%; (c) TBSOTf , DIPEA, CH_2Cl_2, 0 °C, 1 h, 76%; (d) (i) DIBAL-H, toluene, −78 °C, 2 h, (ii) $Ph_3P{=}CHCOOEt$, benzene, rt, 4 h, 54% over two steps; (e) $NiCl_2$, $NaBH_4$, CH_3OH, 0 °C, 1 h, 67 %; (f) DIBAL-H, CH_2Cl_2, 0 °C, 3 h, 62 %; (g) 1 M TBAF solution in THF, rt, 6 h, 76%; (h) TsCl, pyridine, −20 °C to 0 °C, 8 h, 68%.

gave diol **13**, which upon treatment with TsCl–pyridine conditions gave the target molecule (−)-lasubine II (**2**) in 68% yield (Scheme 2),[16] having spectroscopic data ($[\alpha]_D^{26}$ −41.5, *c* 0.15, MeOH) identical with previously reported data.[1,6]

In conclusion, we have demonstrated an enantioselective total synthesis of *lythraceae* alkaloid, (−)-lasubine II (**2**). Employing organo-catalyzed Mannich reaction, Maruoka allylation, and *aza*-Michael addition reaction, the asymmetric centers were generated. This strategy is currently pursued for the synthesis of other aryl-quinolizidine class of natural products.

Acknowledgments

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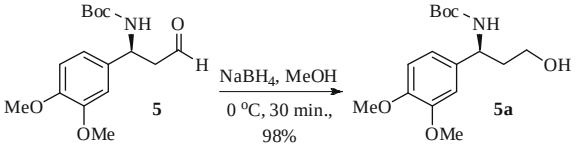
12. Enantiomeric excess of compound **6** was determined by HPLC chiral pak IC (250 × 4.6 mm), flow 1.0 mL/min (15% isopropanol in *n*-hexane), retention time 11.79 (1.17%), 13.57 (98.83%).
13. Compound **5** was reduced to its alcohol using $NaBH_4$ in MeOH at 0 °C as shown below. Enantiomeric excess of this stable alcohol was determined by HPLC chiral pak IC (250 × 4.6 mm), flow rate 1.2 mL/min (12% isopropanol in *n*-hexane), retention time 34.36 (99.06%), 39.61 (0.93%).[16]



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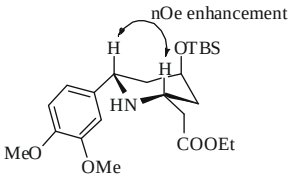
15. NOE experiment has been carried out on TBS-protected compound (**9**) and key NOE enhancements are shown below.



16. Spectral data of selected new compounds: *(S)-tert-butyl 1-(3,4-dimethoxyphenyl)-3-hydroxypropylcarbamate* (**5a**): $[\alpha]_D^{27}$ −27.9 (*c* 0.42, $CHCl_3$); IR (KBr): ν_{max} 3458, 2933, 1644, 1493, 1453, 1366, 1261, 1156, 1028, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.81 (s, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 5.76–5.48 (m, 1H), 4.04 (d, *J* = 5.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.70–3.58 (m, 2H), 2.47 (t, *J* = 5.8 Hz, 1H), 2.12–1.93 (m, 1H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.3, 148.9, 148.0, 132.5, 118.2, 111.1, 109.7, 79.9, 63.1, 58.9, 55.8, 51.3, 39.5, 28.3; ESIMS: m/z 334 $(M+Na)^+$; HRMS calcd for $C_{16}H_{25}NNaO_5$ $(M+Na)^+$: 334.1625, found: 334.1640.

Tert-butyl (1S,3S)-1-(3,4-dimethoxyphenyl)-3-hydroxy hex-5-enylcarbamate (**6**): $[\alpha]_D^{25}$ −23.3 (*c* 0.4, $CHCl_3$); IR (KBr): ν_{max} 3366, 2926, 2853, 1693, 1513, 1259, 1166, 1028, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.80 (s, 2H), 6.78 (d, *J* = 0.9 Hz, 1H), 5.91–5.73 (m, 1H), 5.13–5.01 (m, 3H), 4.84 (t, *J* = 7.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.74–3.63 (m, 1H), 3.55 (br s, 1H), 2.31–2.18 (m, 2H), 1.83–1.75 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.3, 149.4, 148.6, 138.8, 135.1, 118.2, 117.5, 111.6, 111.4, 79.8, 67.3, 55.9, 51.7, 44.4, 41.8, 28.5; ESIMS: *m/z* 374 $(M+Na)^+$; HRMS: calcd for $C_{19}H_{29}NNaO_5$ $(M+Na)^+$: 374.1938, found: 374.1934.

(5S, 7S, E)-ethyl-7-(tert-butoxycarbonylamino)-7-(3,4-dimethoxyphenyl)-5-hydroxyhept-2-enoate (**7**): $[\alpha]_D^{26}$ −57 (*c* 0.4, $CHCl_3$); IR (KBr): ν_{max} 3365, 2925, 1710, 1513, 1262, 1166, 1031, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.03–6.90 (m, 1H), 6.80 (s, 2H), 6.76 (s, 1H), 5.86 (d, *J* = 15.7 Hz, 1H), 4.85 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.10 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83–3.74 (m, 1H), 2.54–2.28 (m, 2H), 1.83–1.72 (m, 2H), 1.45 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.9, 156.6, 149.5, 145.2, 134.6, 123.7, 118.2, 111.7, 110.5, 80.2, 66.7, 60.7, 60.1, 56.0, 51.5, 45.1, 39.9, 28.6, 14.5; ESIMS: *m/z* 446 $(M+Na)^+$; HRMS: calcd for $C_{22}H_{33}NNaO_7$ $(M+Na)^+$: 446.2149, found: 446.2157.

Ethyl-2-((4S,6S)-6-(3,4-dimethoxyphenyl)-4-hydroxy-piperidin-2-yl) acetate (**8**): $[\alpha]_D^{26}$: -31.2 (*c* 0.3, $CHCl_3$); IR (KBr): ν_{max} 3321, 2931, 2847, 1727, 1515, 1264, 1028, 808 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.97 (s, 1H), 6.87 (d, *J* = 6.8 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 4.57–4.52 (m, 2H), 4.19 (s, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.87 (br s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.74–3.61 (m, 1H), 2.44–2.14 (m, 2H), 2.07–1.77 (m, 2H), 1.67–1.51 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz): δ 171.8, 149.2, 148.4, 136.7, 118.9, 111.2, 110.2, 69.3, 60.4, 59.3, 55.9, 55.8, 51.6, 43.8, 41.3, 41.2, 41.0, 14.4; ESIMS: *m/z* 324 $(M+H)^+$; HRMS: calcd for $C_{17}H_{26}NO_5$ $(M+H)^+$: 324.1805, found: 324.1818.

Ethyl-2-((4S,6S)-4-(tert-butyldimethylsilyloxy)-6-(3,4-dimethoxyphenyl)piperidin-2-yl) acetate (**9**): $[\alpha]_D^{26}$ −34.5 (*c* 0.3, $CHCl_3$); IR (KBr): ν_{max} 3448, 2927, 2858, 1729, 1636, 1221, 1101, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.93 (s, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82–3.72 (m, 1H), 3.63 (d, *J* = 11.3 Hz, 1H), 3.18–3.08 (m, 1H), 2.45 (d, *J* = 5.9 Hz, 2H), 1.98–1.90 (m, 2H), 1.87–1.80 (m, 1H), 1.57–1.45 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.3, 148.9, 148.1, 136.9, 118.9, 110.9, 110.0, 69.9, 60.4, 59.3, 55.9, 51.6, 43.8, 41.6, 41.1, 25.8, 18.1, 14.2, −4.6; ESIMS: *m/z* 438 $(M+H)^+$; HRMS: calcd for $C_{23}H_{40}NO_5Si$ $(M+H)^+$: 438.2675, found: 438.2662.

(E)-Ethyl-4-((4S,6S)-4-(tert-butyldimethylsilyloxy)-6-(3,4-dimethoxyphenyl)piperidin-2-yl)but-2-enoate (**10**): $[\alpha]_D^{26}$ −37.9 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 3423, 2928, 2854, 1722, 1514, 1461, 1261, 1099, 840, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.99–6.77 (m, 4H), 5.89 (d, *J* = 15.7 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.82–3.70 (m, 1H), 3.68–3.53 (m, 1H), 2.90–2.77 (m, 1H), 2.51–2.26 (m, 2H), 1.99–1.80 (m, 1H), 1.77–1.67 (s, 2H), 1.59–1.43 (m, 1H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.9, 155.6, 149.9, 148.9, 145.5, 136.8, 123.8, 118.9, 110.9, 110.1, 70.1, 60.3, 59.5, 55.9, 54.0, 51.6, 44.1, 41.8, 39.5, 29.7, 25.8, 14.2, 13.9, −4.5; ESIMS: *m/z* 464 $(M+H)^+$.

4-((4S,6S)-4-(tert-butyldimethylsilyloxy)-6-(3,4-dimethoxyphenyl)piperidin-2-yl)butan-1-ol (**12**): $[\alpha]_D^{26}$ −38.5 (*c* 0.2, $CHCl_3$); IR (KBr): ν_{max} 3384, 2925, 2855, 1642, 1366, 1263, 1105, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz); δ 7.18 (d, *J* = 3.6 Hz, 1H), 6.99 (s, 1H), 6.91 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.82–3.70 (m, 1H), 3.61 (t, *J* = 6.0 Hz, 3H), 2.77–2.66 (m, 1H), 2.00–1.84 (m, 2H), 1.65–1.36 (m, 7H), 1.33–1.19 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.9, 148.2, 136.2, 119.1, 111.0, 110.2, 70.1, 62.6, 59.6, 55.9, 55.4, 43.7, 41.7, 36.2, 32.5, 25.8, 22.1, 18.1, −4.6; ESIMS: *m/z* 424 $(M+H)^+$; HRMS: calcd for $C_{23}H_{42}NO_4Si$ $(M+H)^+$: 424.2878, found: 424.2878.

(2S,4S)-2-(3,4-dimethoxyphenyl)-6-(4-hydroxybutyl) piperidin-4-ol (**13**): $[\alpha]_D^{27}$ −57 (*c* 0.2, MeOH); IR (KBr): ν_{max} 3145, 3045, 1521, 1406, 1264, 1147, 1022 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 7.16 (s, 1H), 7.11–6.98 (m, 2H), 4.28 (d, *J* = 13.8 Hz, 1H), 4.13 (br s, 1H), 4.08–3.92 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.59 (t, *J* = 4.5 Hz, 2H), 2.41–2.19 (m, 2H), 1.99–1.74 (m, 2H), 1.73–1.22 (m, 6H); ^{13}C NMR (CD_3OD, 75 MHz): δ 151.5, 150.8, 135.7, 121.5, 113.1, 112.5, 67.1, 62.4, 60.8, 58.0, 56.6, 46.1, 40.9, 40.3, 38.1, 33.9, 33.2, 30.9, 23.0; ESIMS: *m/z* 310 $(M+H)^+$; HRMS: calcd for $C_{17}H_{28}NO_4$ $(M+H)^+$: 310.2013, found: 310.2011.

(−)-*Lasubine II* (**2**): $[\alpha]_D^{27}$ −41.5 (*c* 0.15, MeOH); IR (KBr): ν_{max} 3356, 2924, 2854, 1736, 1461, 1370, 1266, 1150, 1026, 769 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 7.22–6.78 (m, 3H), 4.02 (br s,1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.69–3.50 (m, 2H), 2.83 (d, *J* = 11.5 Hz, 1H), 2.41–2.21 (m, 1H), 1.95–1.21 (m, 12 H); ^{13}C NMR (CD_3OD, 75 MHz): δ 151.8, 150.6, 137.8, 117.2, 111.8, 111.4, 65.3, 63.1, 56.5, 56.2, 55.5, 42.9, 40.1, 33.2, 26.6, 22.1; ESIMS: m/z 292 $(M+H)^+$; HRMS: calcd for $C_{17}H_{25}NO_3$ $(M+H)^+$: 292.1907, found: 292.1918.