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An Enantioselective Organocatalytic Approach to Both Enantiomers of Lasubine II

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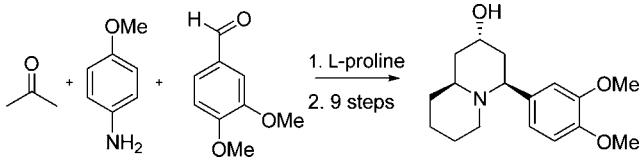
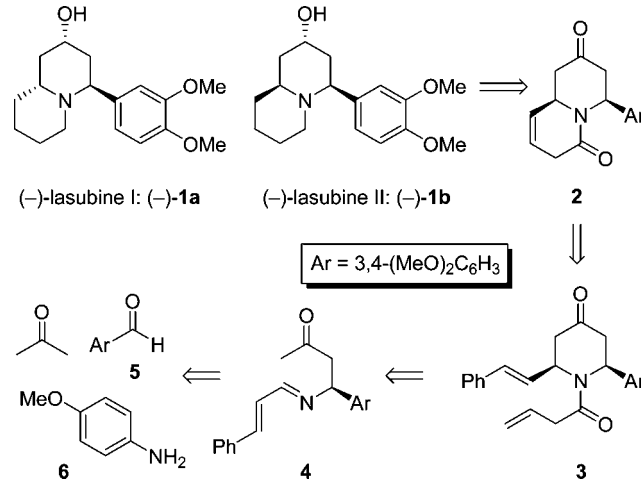
Received January 22, 2009



A concise stereoselective route providing access to both enantiomers of the bioactive quinolizidine alkaloid lasubine II has been developed. The enantioselectivity was introduced by taking advantage of a proline-catalyzed asymmetric Mannich reaction. Next, the bicyclic system was constructed via a diastereoselective Mannich cyclization and subsequent ring-closing metathesis as the key steps.

The quinolizidine skeleton is widely encountered in druglike compounds and natural products, displaying a large array of biological activities.[1] Quinolizidine-based natural products have been mostly isolated from plants, trees, and herbs.[1] Lasubine I (**1a**) and II (**1b**, Scheme 1) represent two of these alkaloids and were isolated from the leaves of the *Lagerstroemia subcostata Koehne* by Fuji et al. in 1978.[2] Synthetic efforts by various groups have resulted in a number of racemic and enantioselective routes to lasubine II.[3] In conjunction with recent work from our group on the total synthesis of quinolizidine-based natural products,[4] and in view of the potentially interesting properties of the lasubines, we set out to develop a new pathway to lasubine II based on the asymmetric proline-catalyzed Mannich reaction. We reasoned that the commercial availability of both the D- and L-forms of the catalyst would provide an entry to both enantiomers of lasubine II.

SCHEME 1. Structures of Lasubine I (1a) and Lasubine II (1b)



Retrosynthetic analysis of lasubine II (**1b**) leads to the bicyclic lactam **2** as a suitable precursor, of which the unsaturated ring can be retrosynthetically cleaved by using ring-closing metathesis, giving rise to piperidinone **3**. We envisioned that the latter compound may be formed via a Mannich cyclization of imine **4**, which in turn would be accessible via an asymmetric proline-catalyzed Mannich reaction involving acetone, veratryl aldehyde (**5**), and *p*-anisidine (**6**).[5]

With this plan in mind, we set out to study the asymmetric three-component Mannich reaction, employing D-proline leading to unnatural (+)-lasubine (Scheme 2). This reaction was studied previously by the group of Hayashi, who were unable to isolate the desired aminoketone with proline as the catalyst.[6] Instead, they used a more expensive protected 4-hydroxyproline derivative. In our hands, careful analysis of the D-proline-catalyzed Mannich reaction (20 mol % D-proline, DMSO, rt) revealed that the product was formed, but accompanied by the formation of enone **9**. We showed that this was formed under the reaction conditions via elimination of *p*-anisidine from the desired product **7**. Gratifyingly, by employing D-proline as the catalyst and careful monitoring of the reaction progress by HPLC and stopping the reaction at ca. 50% conversion, we were able to

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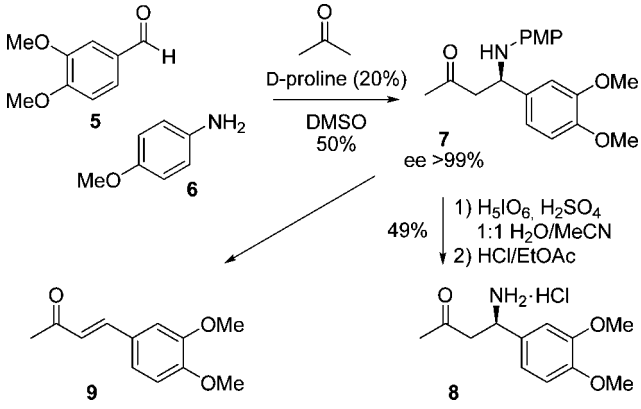
10.1021/jo900141f CCC: $40.75
Published on Web 03/13/2009

SCHEME 2. Formation of 1,3-Aminoketone 8

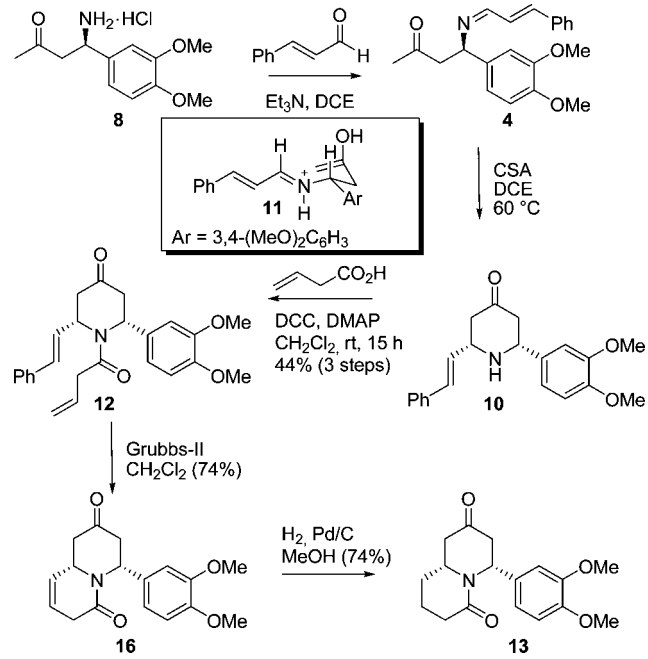


isolate the (*R*)-aminoketone **7** by precipitation from the reaction mixture as a crystalline solid in 50% yield and >99% ee. This crystallization protocol allowed us to scale up the reaction to 10 g scale, furnishing the product in the same yield and selectivity. The (*S*)-enantiomer was also prepared in comparable yield and selectivity by using L-proline as the catalyst.

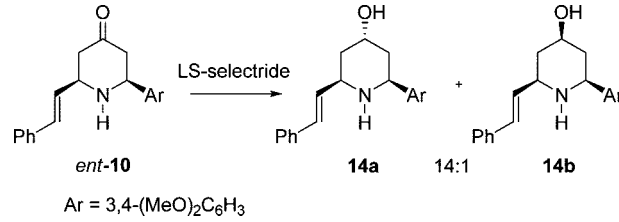
Subsequently, we deprotected *N*-PMP amine **7**, employing H_5IO_6 under acidic conditions.[7] Although cleavage to the free amine by itself proceeded smoothly, isolation of the β-aminoketone appeared problematic due to side reactions (e.g., self-condensation) while concentrating the organic layer after workup. This problem was circumvented by in situ formation of the HCl-salt **8** prior to concentration of the reaction mixture.

Inspired by our own research on iminium ion type cyclizations,[4a,8] we envisioned that conversion of compound **8** into the corresponding imine **4** should lead to a precursor that would be prone to a Mannich cyclization. This idea was underlined by recent work by Davis and co-workers,[9] who carried out similar types of Mannich cyclizations involving furan nucleophiles. The precursor imine **4** was prepared by condensation of **8** with cinnamaldehyde in the presence of triethylamine as a base to liberate the amino group. The condensation was carried out in 1,2-dichloroethane via successive concentration of the reaction mixture under reduced pressure to azeotropically remove water. Because this experiment was conducted in a rotary evaporator, fresh triethylamine and 1,2-dichloroethane were repeatedly added to the residue after each concentration sequence until nearly complete consumption of cinnamaldehyde was observed by HPLC analysis. The Mannich cyclization was then effected by stirring a solution of the crude imine **4** in 1,2-dichloroethane in the presence of an excess of (+)-camphorsulfonic acid (CSA) to yield **10** as a single diastereoisomer. It appeared to be crucial to dry the CSA prior to use and conduct the reaction under exclusion of moisture, since the imine was extremely prone to acidic hydrolysis. To prevent side reactions during workup and purification, the amine of the resulting 2,6-disubstituted piperidinone **10** was directly acylated with vinylacetic acid via standard DCC-coupling, leading to the stable piperidinone **12**. The total yield of **12** after silica gel purification was 44% over the three steps (Scheme 3).

SCHEME 3. Mannich Cyclization



SCHEME 4. LS-Selectride Reduction of Piperidinone *ent*-10



Similar steps were also carried out by using the L-proline route resulting in *ent*-**12** in a comparable yield and complete diastereoselectivity. HPLC analysis and ^{1}H NMR studies (NOESY) on the purified product *ent*-**10** proved that it was formed as a cis-disubstituted diastereoisomer. This outcome can be rationalized by invoking the chairlike cationic intermediate **11** (Scheme 3), in which both the aryl and the stryrenyl substituent will preferentially occupy the least hindered equatorial positions.

Additionally, we tried to alkylate the crude piperidinone *ent*-**10** with 3-bromo-1-butene. Although mass spectrometry of the reaction mixture showed formation of a product with the expected mass, we were unable to isolate the desired product, possibly due to decomposition of the formed product during workup. Anticipating the required conversion of the ketone into the alcohol at a later stage in the synthesis, we reduced product *ent*-**10** with LS-Selectride and observed the formation of products **14a** and **14b** in a 14:1 ratio, favoring the product with the desired stereochemistry (**14a**, Scheme 4). However, alkylation of **14a/b** with 3-bromo-1-butene failed and acylation under the aforementioned conditions only led to poor conversion into the desired amide. The mixture of stereoisomers in combination with the unsuccessful attempts to transform **14a/b** into a suitable ring-closing metathesis precursor led us to return to the earlier described route (Scheme 3).

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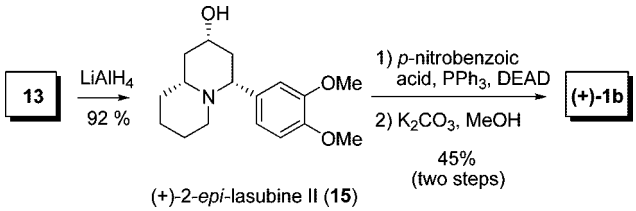
SCHEME 5. Completion of (+)-Lasubine II Synthesis



In the D-proline-based route, we observed that subsequent treatment of piperidinone **12** with the Grubbs second generation catalyst (6 mol %) followed by straightforward hydrogenation of the resulting unsaturated lactam **16** led to the bicyclic structure **13** in good overall yield (Scheme 3).

As the next step, we investigated the stereoselective reduction of the ketone functionality of **13**. Both small and more sterically demanding borohydride reducing agents were evaluated, but all attempts led to the formation of undesired stereochemistry at the C4 carbon. This was proven by subsequent $LiAlH_4$ reduction of the lactam, which provided (+)-2-*epi*-lasubine II (**15**) as the exclusive diastereoisomer in all cases, based on ^{1}H NMR data comparison with literature (Scheme 5). Thus, both carbonyls were reduced in a one-pot procedure by $LiAlH_4$ as the reducing agent. The resulting (+)-2-*epi*-lasubine II (**15**) was transformed into (+)-lasubine II ((+)-**1b**) via a protocol from Zhu et al. (Scheme 5).[3c] In addition, product *ent*-**12** was converted via an identical pathway into natural (−)-lasubine II ((−)-**1b**). NMR spectra, optical rotations, and HPLC chromatograms of both lasubine II enantiomers were in agreement with literature data.[3]

In conclusion, we developed a new stereoselective route to both enantiomers of lasubine II. Key steps include an enantioselective D- or L-proline-catalyzed Mannich reaction employing commercially available starting compounds and a diastereoselective Mannich cyclization. Extension of this methodology to other members of the same class of molecules is currently under investigation in our laboratory.

Experimental Section

(*R*)-4-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenylamino)butan-2-one (7). Under an ambient atmosphere, to a mixture of DMSO (45 mL) and acetone (180 mL) was added 3,4-dimethoxybenzaldehyde (10.5 g, 63.2 mmol), *p*-anisidine (7.75 g, 62.9 mmol), and D-proline (1.52 g, 13.2 mmol). The resulting mixture was stirred for 24 h at rt. The reaction was quenched by the addition of potassium phosphate buffer (0.5 M, pH 7, 100 mL). The resulting mixture was stirred for another 10 min until a precipitate was formed. The precipitate was isolated by filtration and dried in vacuo to afford **7** (10.3 g, 50%) as a white solid. R_f 0.26 (EtOAc/heptane, 1:1). Mp 152−154 °C. $[\alpha]^{20}_D$ −2.7 (*c* 0.93, $CHCl_3$). IR (ATR) 819, 1022, 1139, 1229, 1251, 1506, 1705, 3382 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92−6.87 (m, 2H), 6.83−6.79 (m, 1H), 6.73−6.67 (m, 2H), 6.55−6.49 (m, 2H), 4.69 (t, J = 6.5 Hz, 1H), 4.11 (br s, 1H), 3.85 (s, 6H), 3.70 (s, 3H), 2.89 (d, J = 6.5 Hz, 2H), 2.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.4, 152.4, 149.2, 148.1, 141.0, 135.4, 118.2, 115.4, 114.7, 111.3, 109.5, 55.9, 55.7, 55.2, 51.4, 30.8. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{23}NO_4$ $(M + H)^+$ 330.17053, found 330.17086. HPLC ee >99%, chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, *n*-hexane/2-propanol 80/20, retention times 14.9 min for **7** and 18.4 min for *ent*-**7**.

(*R*)-4-Amino-4-(3,4-dimethoxyphenyl)butan-2-one Hydrochloride (8). Under ambient atmosphere, to a solution of **7** (9.3 g, 28 mmol) in MeCN/H_2O (250 mL, 1:1) was added 1 M aqueous H_2SO_4 (28 mL, 28 mmol) and H_5IO_6 (6.6 g, 29 mmol). The mixture was stirred for 4 h at rt. The mixture was washed with CH_2Cl_2 (3 × 125 mL) and the resulting aqueous phase was diluted with 125 mL of CH_2Cl_2. While stirring the mixture vigorously, the pH of the aqueous layer was brought to 9 via addition of 5 M aqueous KOH. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 × 125 mL). The combined organic layers were dried (Na_2SO_4) and HCl/EtOAc (20 mL) was added. The resulting mixture was concentrated until the product precipitated. The product was isolated by filtration and dried in vacuo to afford the HCl salt **8** (3.6 g, 49%) as a pale yellow solid. R_f 0.38 (MeOH/DCM, 1:1). Mp 158−161 °C. $[\alpha]^{20}_D$ −12 (*c* 0.94, MeOH). IR ν (cm^{-1}) 1022, 1143, 1256, 1515, 1709, 2919, 3399 cm^{-1}. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.06−7.04 (m, 1H), 7.00−6.98 (m, 2H), 4.62 (dd, J = 7.3, 6.3 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.20 (d, J = 7.5 Hz, 1H), 3.20 (d, J = 6.1 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.4, 151.3, 151.0, 130.3, 121.1, 113.1, 112.1, 56.6, 56.5, 52.1, 47.6, 30.0. HRMS (ESI) *m*/*z* calcd for $C_{12}H_{17}NO_3$ $(M + Na)^+$ 246.11061, found 246.10966.

(2*R*,6*S*)-1-But-3-enoyl-2-(3,4-dimethoxyphenyl)-6-styrylpiperidin-4-one (12). To a solution of **8** (3.50 g, 13.5 mmol) in dry 1,2-dichloroethane (200 mL) was added triethylamine (1.45 mL, 10.3 mmol) and *trans*-cinnamaldehyde (1.30 mL, 10.3 mmol). The mixture was concentrated in vacuo. To the residue was added dry 1,2-dichloroethane (150 mL) and triethylamine (1.5 mL, 11 mmol). The mixture was concentrated again in vacuo. Dry 1,2-dichloroethane (150 mL), triethylamine (1.5 mL, 11 mmol), and *trans*-cinnamaldehyde (0.38 mL, 3.0 mmol) were added to the residue. The resulting mixture was concentrated in vacuo. To the residue was added dry 1,2-dichloroethane (125 mL) and triethylamine (1.5 mL, 11 mmol). The resulting mixture was concentrated in vacuo to afford the crude imine **4**. The crude imine was dissolved in dry 1,2-dichloroethane (360 mL) and the resulting mixture was added dropwise to a stirring solution of dry (+)-10-camphorsulfonic acid (20.2 g, 87 mmol) in dry 1,2-dichloroethane (230 mL) at 60 °C. The mixture was stirred for 5 h at 60 °C under an inert atmosphere. The mixture was washed with an aqueous half-saturated sodium bicarbonate solution (3 × 350 mL), dried (Na_2SO_4), and concentrated in vacuo affording the crude piperidinone **10**. Vinylacetic acid (3.8 mL, 45 mmol) and DCC (3.20 g, 15.5 mmol) were dissolved in dry DCM (100 mL) and stirred for 1 h at room temperature. The precipitate was removed by filtration and the solution was diluted with DCM (500 mL). The crude piperidinone **10** and DMAP (2.38 g, 19.5 mmol) were added to this solution. The mixture was stirred for 16 h under an argon atmosphere at room temperature. The mixture was washed with aqueous hydrochloric acid (0.2 M, 500 mL), aqueous sodium bicarbonate (1 M, 500 mL), and brine (500 mL). The mixture was then dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (EtOAc/heptane, 1:2 → 1:1) to afford **12** (2.43 g, 44% over three steps) as a yellow oil. R_f 0.18 (EtOAc/heptane, 1:1). $[\alpha]^{20}_D$ +32 (*c* 0.095, $CHCl_3$). IR (ATR) 1025, 1146, 1254, 1401, 1516, 1642, 1719 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz, T = 323 K) δ 7.37−7.04 (m, 5H), 6.90−6.70 (m, 3H), 6.51−6.33 (m, 1H), 6.11−5.78 (m, 3H), 5.70−5.30 (m, 1H), 5.26−5.05 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 3.35−3.20 (m, 2H), 3.12 (dd, J = 16.4, 5.2 Hz, 1H), 2,80 (dd, J = 16.5 Hz, 6.8 Hz, 1H), 2.74 (d, J = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.6, 171.3, 149.3, 148.4, 135.8, 133.8, 131.6, 131.3, 129.1, 128.4, 128.0, 126.2, 118.7. 118.2, 111.1, 110.0, 55.8, 55.7, 55.0−42.0 (br, 4C), 39.5. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{27}NO_4$ $(M + Na)^+$ 428.18378, found 428.18379. HPLC chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min (*n*-hexane/2-propanol 80/20), retention times 12.4 min for **12** and 11.5 min for *ent*-**12**; dr >19:1 (determined by ^{1}H NMR).

(4*R*,9a*S*)-4-(3,4-Dimethoxyphenyl)-3,4-dihydro-1*H*-quinolizine-2,6(7*H*,9a*H*)-dione (16). To a solution of **12** (2.36 g, 5.82 mmol) in degassed DCM (125 mL) was added Grubbs second generation catalyst (280 mg, 5.7 mol %). The mixture was stirred for 2 h at 40 °C under an inert atmosphere. The mixture was concentrated in vacuo and the residue was purified by column chromatography (MeOH/EtOAc, 0→1%) to afford **16** (1.30 g, 74%)

as an off-white solid. R_f 0.21 (EtOAc/MeOH, 49:1). Mp 148−151 °C. $[\alpha]^{20}_D$ −67 (*c* 0.20, $CHCl_3$). IR (ATR) 1024, 1135, 1255, 1318, 1406, 1515, 1646, 1722, 2359 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.75 (d, $J = 8.2$ Hz, 1H), 6.68−6.60 (m, 2H), 6.03 (ddt, $J = 9.9$, 4.6, 2.7 Hz, 1H), 5.80 (dd, $J = 6.2$, 2.0 Hz, 1H), 5.73 (dt, $J = 9.9$, 1.9 Hz, 1H), 4.85−4.70 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.19 (dt, $J = 21.0$, 4.1 Hz, 1H), 3.18 (dd, $J = 16.5$ Hz, 6.3 Hz, 1H), 3.06 (ddt, $J = 21.5$, 6.3, 2.8 Hz, 1H), 2.92 (dd, $J = 16.4$, 2.3 Hz, 1H), 2.63 (d, $J = 9.0$ Hz, 1H), 2.63 (d, $J = 7.9$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.0, 168.4, 149.2, 148.2, 133.6, 125.7, 124.3, 117.0, 111.2, 109.1, 55.8, 55.7, 52.9, 51.9, 45.3, 45.0, 33.4. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{19}NO_4$ $(M + Na)^+$ 324.12118, found 324.12128. HPLC chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min (*n*-hexane/2-propanol 80/20), retention times 24.5 min for **16** and 34.9 min for ***ent*-16**.

(4*R*,9a*R*)-4-(3,4-Dimethoxyphenyl)tetrahydro-1*H*-quinolizine-2,6(7*H*,8*H*)-dione (13). To a solution of **16** (1.19 g, 3.95 mmol) in MeOH (60 mL) was added 10% Pd/C (459 mg, 11 mol %). A hydrogen atmosphere was applied (balloon) and the mixture was stirred for 16 h at rt. The catalyst was removed by filtration over Celite and the solution was concentrated in vacuo. The residue was purified by column chromatography (MeOH/EtOAc, 0→2%) to afford **13** (885 mg, 74%) as a white solid. R_f 0.54 (DCM/MeOH, 9:1). Mp 181−183 °C. $[\alpha]^{20}_D$ −122 (*c* 0.26, $CHCl_3$). IR (ATR) 1024, 1143, 1255, 1410, 1441, 1511, 1639, 1722, 2941 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.76 (d, $J = 8.3$ Hz, 1H), 6.69 (d, $J = 2.1$ Hz, 1H), 6.65 (ddd, $J = 8.2$, 2.2, 0.9 Hz, 1H), 5.84 (dd, $J = 5.9$, 2.3 Hz, 1H), 4.15−3.98 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.10 (dd, $J = 16.7$, 6.0 Hz, 1H), 2.94 (dd, $J = 16.7$, 2.4 Hz, 1H), 2.67−2.53 (m, 2H), 2.46 (d, $J = 6.8$ Hz, 1H), 2.46 (d, $J = 9.2$ Hz, 1H), 2.10−1.60 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.3, 170.2, 149.1, 148.1, 133.8, 117.0, 111.2, 109.2, 55.8, 55.7, 52.9, 52.2, 45.2, 44.8, 32.1, 30.8, 20.4. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{21}NO_4$ $(M + H)^+$ 304.15488, found 304.15461. HPLC chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min (*n*-hexane/2-propanol 80/20), retention times 23.9 min for **13** and 27.8 min for ***ent*-13**.

(+)-2-*epi*-Lasubine II (15). To a solution of **13** (787 mg, 2.59 mmol) in dry THF (50 mL) was added $LiAlH_4$ (496 mg, 13.1 mmol). The mixture was brought to 60 °C and stirred for 3 h under an inert atmosphere. The reaction was quenched by adding H_2O (644 mg, 1.3 mg/mg $LiAlH_4$), aqueous NaOH (15% in H_2O, 644 mg, 1.3 mg/mg $LiAlH_4$), and H_2O (1.61 g, 3.25 mg/mg $LiAlH_4$). The resulting mixture was stirred vigorously for 10 min and the precipitate was removed by filtration. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (MeOH/EtOAc, 0→7.5%) to afford **15** (698 mg, 92%) as a yellow oil. R_f 0.20 (DCM/MeOH, 9:1). $[\alpha]^{20}_D$ +57 (*c* 0.46, MeOH). IR (ATR) 738, 1030, 1136, 1225, 1259, 1453, 1504, 2354, 2934, 3353 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10−6.60 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81−3.65 (m, 1H), 2.91 (dd, $J = 11.6$, 2.6 Hz, 1H), 2.72−2.63 (m, 1H), 2.05−1.88 (m, 3H), 1.75−1.14 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.9, 136.6, 120.0−119.0 (br, 2C), 111.6−109.0 (br, 2C), 68.4, 68.2, 60.9, 55.9, 55.8, 52.9, 45.1, 42.8, 33.6, 26.0, 24.6. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{25}NO_3$ $(M + H)^+$ 292.19127, found 292.18992. HPLC chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min (*n*-hexane/2-propanol 80/20), retention times 6.8 min for **15** and 8.2 min for ***ent*-15**.

Acknowledgment. This work forms part of the Ultimate Chiral Technology project supported in part with funds provided by SNN (Cooperation Northern Nederlands) and EFRO (European Fund for Regional Development).

Supporting Information Available: NMR spectra, HPLC chromatograms, and characterization data of routes to both enantiomers and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900141F