Total Synthesis of (+)-Eburnamonine

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Abstract: The enantiospecific total synthesis of vinca alkaloid (+)-eburnamonine is accomplished from L-ethyl lactate. Key feature of the synthesis is the construction of the chiral quaternary center involving a Johnson–Claisen rearrangement and assembly of the pentacyclic core by the Pictet–Spengler reaction and ring-closing metathesis.

Key words: eburnamonine, alkaloids, L-ethyl lactate

Indole alkaloids isolated from a number of plant sources have been a subject of synthetic investigation for several decades because of their proven therapeutic significance.[1] Indole alkaloids possess common structural features probably because of their common biogenetic origin. (–)-Eburnamonine (**1**, Figure 1) and structurally related alkaloids vincamine (**2**), eburnamenine (**3**), and eburnamine (**4**) isolated from several plants of *Vinca* species have attracted considerable interest in recent years.

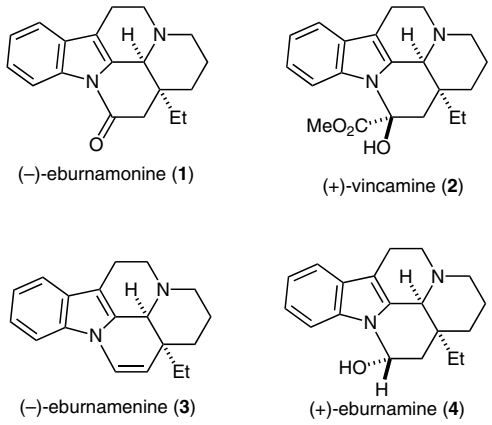
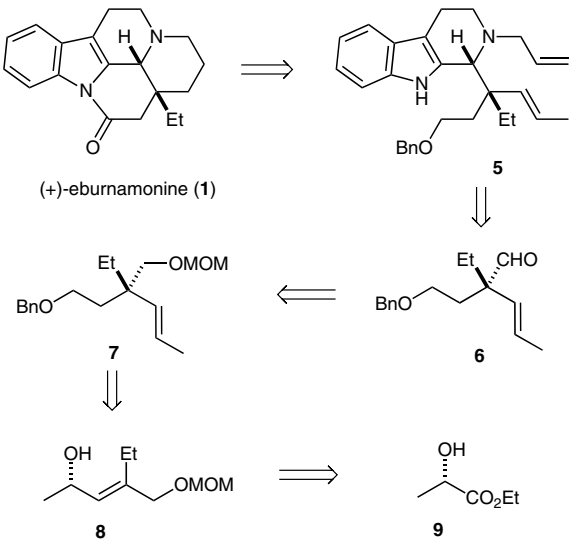


Figure 1 Vinca alkaloids

Although, there has been a plethora of publications over six decades concerning the synthesis of eburnamonine,[2] only a few approaches for the enantioselective synthesis of **1** were reported.[3] Ogasawara's group reported the synthesis of (–)-**1** from L-glutamic acid[3a] while an enantiodivergent synthesis of both enantiomers of eburnamonine was accomplished by Winterfeldt's group using a chiral cyclopropane carboxaldehyde.[3b] Fuji's group disclosed the synthesis of (–)-**1** from a chiral nitro olefin.[3c,d] The asymmetric Birch reduction–alkylation protocol was the main feature in the synthesis of (–)-**1** by Schultz and Pettus[3e] while Rh(II) carbenoid mediated asymmetric insertion of a chiral lactone was the key step in the synthesis reported by Wee and Yu.[3f–g] Very recently, MacMillan's group disclosed the synthesis of a variety of alkaloids based on their organocatalysis strategy in combination with a metal-mediated synthesis.[3h] The Pictet–Spengler or Bischler–Napieralski cyclization is the well-established transformation for the construction of the C2–C3 bond in the pentacyclic framework of eburnamonine. However, the challenging aspect in asymmetric synthesis of the eburnamonine alkaloids is the construction of the chiral quaternary center.

Synthesis of natural products using chiral pool compounds is an attractive method, and we have recently disclosed the synthesis of a number of oxygenated bioactive compounds from tartaric acid.[4] In continuation of our efforts herein, we report the synthesis of the (+)-eburnamonine from L-ethyl lactate. Our approach for the synthesis of (+)-eburnamonine is depicted in Scheme 1. The synthesis of (+)-**1** is envisaged by a ring-closing metathesis (RCM) of the diene in **5** and futher lactamization. Although there have been applications of RCM reaction in alkaloids synthesis,[5] interestingly, the assembly of the eburnamonine alkaloid via RCM is not reported in the literature. Synthesis of **5** is anticipated by the Pictet–Spengler reaction of *N*-allyl tryptamine with aldehyde **6**, the synthesis of which is planned from **7**. Johnson–Claisen rearrangement of the allylic alcohol **8** derived from L-ethyl



Scheme 1 Retrosynthesis for (+)-eburnamonine (**1**)

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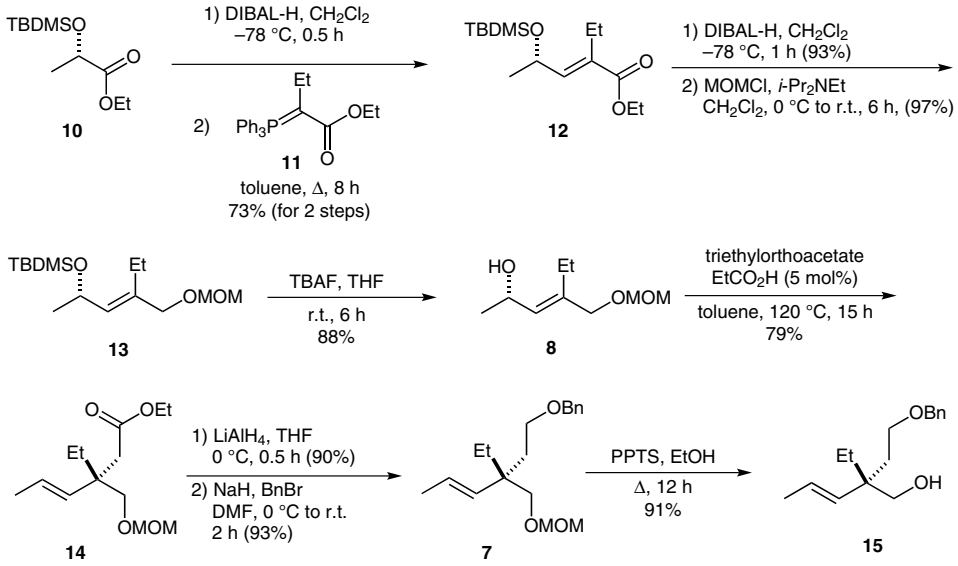
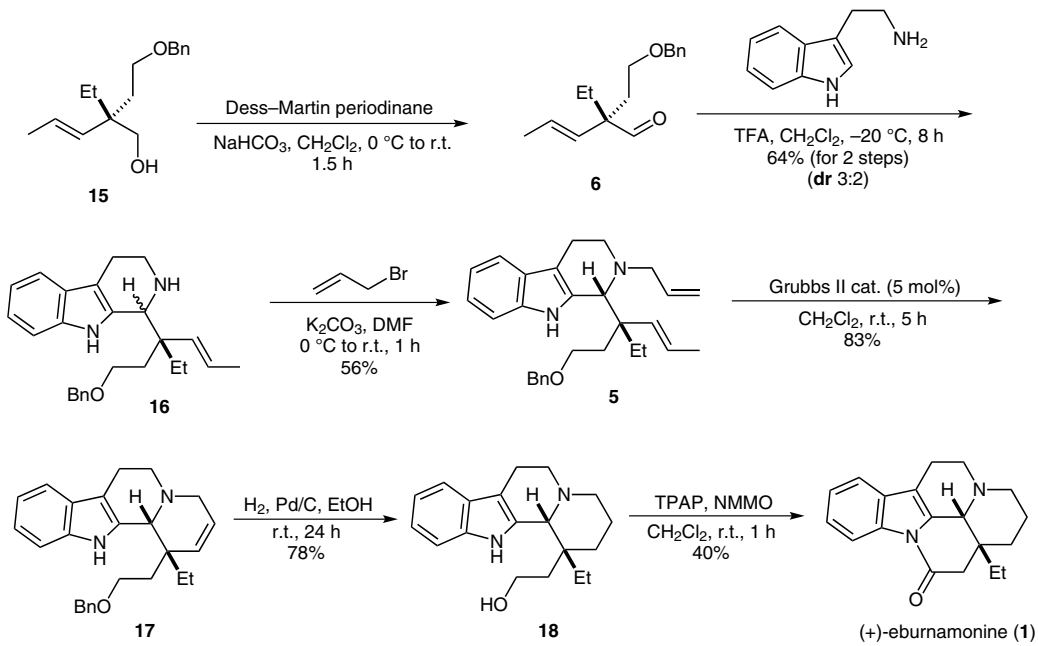
lactate[6] is chosen as the appropriate transformation for the assembly of **7** (Scheme 1).

Accordingly, the synthetic sequence commenced with the homologation of the aldehyde obtained from the ester **10** by Wittig–Horner olefination with the ylide **11**[7] to afford the α,β-unsaturated ester **12** in 73% yield. Reduction of the ester in **12** with DIBAL-H yielded the corresponding alcohol (93% yield), which was protected as the MOM ether **13** in 97% yield. Deprotection of the silyl ether in **13** furnished the alcohol **8** in 88% yield. Treatment of **8** with triethylorthoacetate in the presence of a catalytic amount of propionic acid resulted in the formation of quaternary ester **14** in 79% yield. Reduction of the ester in **14** to the alcohol (90% yield) and further reaction with NaH/BnBr afforded the benzyl ether **7** in 93% yield. Deprotection of the MOM ether in **7** with PPTS in refluxing EtOH afforded the primary alcohol **15** in 91% yield (Scheme 2).

Dess–Martin periodinane[8] oxidation of alcohol **15** produced aldehyde **6**. To our surprise Pictet–Spengler reaction of the aldehyde **6** with *N*-allyl tryptamine did not proceed at all. However, reaction of aldehyde **6** with tryptamine furnished a nonseparable mixture (dr = 3:2) of carbolines **16** in 64% yield. Allylation of **16** yielded a separable mixture of *N*-allyl carbolines in which the major isomer **5** was isolated in 56% yield.[9] Treatment of the diene **5** with the Grubbs second-generation catalyst[10] furnished the product **17** in 83% yield. Hydrogenation of the alkene and deprotection of the benzyl ether in **17** was accomplished by Pd/C-mediated hydrogenation to yield the known alcohol **18** in 78% yield. Using the protocol de-



Scheme 2 Synthesis of the chiral quaternary alcohol from L-ethyl lactate



Scheme 3 Total synthesis of (+)-eburnamonine (**1**)

scribed by Schultz and Pettus, oxidation of **18** with TPAP/NMMO furnished (+)-eburnamonine (**1**) in 40% yield.[11] The spectral and physical data are in complete agreement with that reported in literature (Scheme 3).[3c]

In conclusion, a linear strategy for the synthesis of indole alkaloid (+)-eburnamonine is presented from L-ethyl lactate in 15 steps and 3.2% overall yield. The synthetic sequence showcased the use of the Johnson–Claisen rearrangement for the construction of the chiral quaternary center, Pictet–Spengler reaction and ring-closing metathesis for the completion of the pentacyclic ring. Also, construction of the chiral quaternary center possessing an alkyl, alkenyl, and alcohol functionality makes it a viable building block for the synthesis of other structurally related alkaloids, which is in progress.

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(11) **Preparation of 17**

To a stirred solution of the diene **5** (24 mg, 0.06 mmol) in dry CH_2Cl_2 (6 mL) was added Grubbs II catalyst (2 mg, 5 mol%) under an argon atmosphere, and the reaction mixture was stirred at r.t. for 5 h. After completion of the reaction (TLC), most of the solvent was evaporated off, and the crude residue thus obtained was purified by silica gel column chromatography using PE–EtOAc (7:3) as eluent to afford **17** (18 mg, 83%) as a yellow foam. $[\alpha]_D$ +179.2 (*c* 0.6, $CHCl_3$). IR (neat): ν_{max} = 3371, 2960, 2930, 1458, 1048 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (br s, 1 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.34–7.06 (m, 7 H), 5.87 (dd, J_1 = 10.1 Hz, J_2 = 4.6 Hz, 1 H), 5.44 (d, *J* = 10.1 Hz, 1 H), 4.36 (s, 2 H), 3.64 (s, 1 H), 3.58 (qd, J_1 = 6.0 Hz, J_2 = 2.9 Hz, 1 H), 3.52 (qd, J_1 = 6.0 Hz, J_2 = 3.0 Hz, 1 H), 3.33 (dd, J_1 = 16.4 Hz, J_2 = 4.7 Hz, 1 H), 3.09 (dd, J_1 = 10.9 Hz, J_2 = 4.8 Hz, 1 H), 3.01 (d, *J* = 16.4 Hz, 1 H), 2.98–2.80 (m, 1 H), 2.78 (d, *J* = 16.4 Hz, 1 H), 2.58 (td, J_1 = 8.4 Hz, J_2 = 3.0 Hz, 1 H), 2.02–1.92 (m, 1 H), 1.87 (q, *J* = 7.7 Hz, 2 H), 1.46–1.36 (m, 1 H), 1.10 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 136.2, 133.6, 132.9, 128.2 (2 C), 127.5 (2 C), 127.2, 126.8, 126.1, 121.5, 119.3, 117.9, 111.9, 110.7, 72.7, 68.0, 61.2, 55.1, 52.4, 43.0, 37.4, 32.5, 21.6, 8.9. HRMS: *m/z* calcd for $[C_{26}H_{30}N_2O + H]$: 387.2436; found: 387.2436.

Preparation of 18

To a stirred solution of the alkene **17** (18 mg, 0.05 mmol) in dry EtOH (2 mL) was added preactivated palladium on charcoal (10% w/w, 20 mg) under a nitrogen atmosphere. The reaction mixture was then subjected to hydrogenation under a hydrogen balloon and stirred at r.t. for 24 h. After completion of the reaction (TLC), it was filtered through a short pad of Celite using $CHCl_3$ (20 mL). The solvent was evaporated off, and the crude residue thus obtained was purified by silica gel column chromatography using EtOAc–MeOH (19:1) as eluent to afford **18** (10 mg, 78%) as a white solid. $[\alpha]_D$ +85.8 (*c* 0.4, $CHCl_3$); mp (165–168 °C). IR (KBr): ν_{max} = 3649, 3252, 2922, 1462, 1096 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (br s, 1 H), 7.47 (d, *J* = 7.7 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 7.3 Hz, 1 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 3.75 (td, J_1 = 11.6 Hz, J_2 = 2.4 Hz, 1 H),

3.44 (dt, J_1 = 11.8 Hz, J_2 = 4.4 Hz, 1 H), 3.36 (s, 1 H), 3.09 (d, J = 4.7 Hz, 1 H), 3.08 (s, 1 H), 3.07–2.97 (m, 1 H), 2.72–2.62 (m, 1 H), 2.67 (s, 1 H), 2.45 (td, J_1 = 11.7 Hz, J_2 = 3.0 Hz, 1 H), 2.23–2.00 (m, 1 H), 1.89–1.54 (m, 6 H), 1.37 (d, J = 15.0 Hz, 1 H), 1.26 (s, 1 H), 1.12 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 132.2, 126.7, 121.7, 119.4, 118.2, 111.9, 110.6, 67.1, 58.7, 56.3, 54.0, 40.9, 38.8, 35.7, 32.3, 23.0, 21.3, 8.5. HRMS: *m/z* calcd for [$C_{19}H_{26}N_2O$ + H]: 299.2123; found: 299.2120.

Eburnamonine (+)-1

To a stirred solution of the alcohol **18** (10 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) were added a small amount of 4 Å MS and NMO (7 mg, 0.06 mmol) under a nitrogen atmosphere at r.t., followed by TPAP (1 mg, 10 mol%) after 10 min. The reaction mixture was stirred for 1 h at r.t. After completion of the reaction, it was filtered through a small pad of Celite, which was washed with CH_2Cl_2 (20 mL). The organic layer was washed with sat. Na_2SO_3 (8 mL), brine (5 mL), sat. $CuSO_4$ (5 mL) and dried over anhyd Na_2SO_4. The crude residue obtained after evaporation of the solvent was purified by rapid column chromatography using EtOAc as eluent to afford (+)-**1** (4 mg, 40%) as a white solid. $[\alpha]_D$ + 87.5 (*c* 0.2, $CHCl_3$) {lit[3c] $[\alpha]_D$ –88 (*c* 0.09, $CHCl_3$) for the enantiomer}; mp (171–172 °C) {lit.[3e] mp 173–176 °C)}. IR (KBr): ν_{max} = 2926, 2854, 1696, 1452, 1370 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 7.8 Hz, 1 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.39–7.23 (m, 2 H), 3.99 (s, 1 H), 3.34 (dd, J_1 = 14.0 Hz, J_2 = 6.7 Hz, 1 H), 3.31–3.21 (m, 1 H), 2.98–2.84 (m, 1 H), 2.63 (Abq, $J_1 = J_2$ = 16.7 Hz, 2 H), 2.57–2.45 (m, 1 H), 2.53–2.40 (m, 1 H), 2.40 (dd, J_1 = 11.2 Hz, J_2 = 3.0 Hz, 1 H), 2.13–1.97 (m, 1 H), 1.83–1.58 (m, 4 H), 1.44 (q, J = 13.7 Hz, 2 H), 1.03 (td, J_1 = 13.7 Hz, J_2 = 3.8 Hz, 1 H), 0.93 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 134.2, 132.0, 130.1, 124.3, 123.8, 118.1, 116.3, 112.6, 57.7, 50.7, 44.4, 44.3, 38.5, 28.4, 27.0, 20.7, 16.6, 7.6. HRMS: *m/z* calcd for [$C_{19}H_{22}N_2O$ + H]: 295.1810; found: 295.1811.

