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Organocatalytic Approach for the Syntheses of Corynantheidol, Dihydrocorynantheol, Protoemetinol, Protoemetine, and Mitragynine

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Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

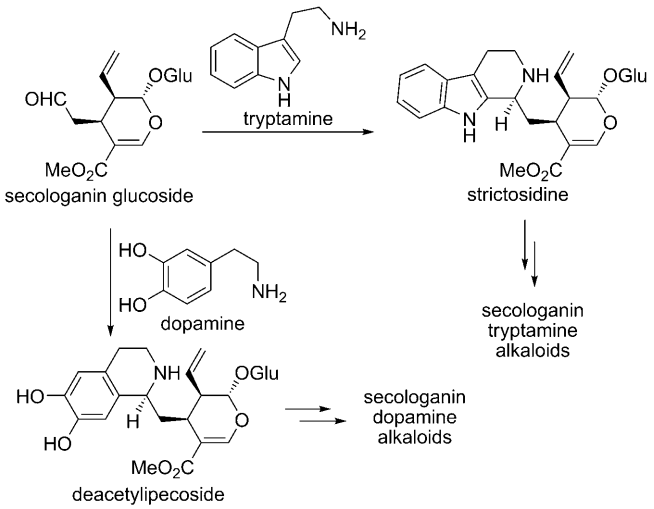
Abstract: *O*-Trimethylsilyl (TMS)-protected diphenylprolinol-catalyzed Michael addition of a functionalized alkylidene malonate and *n*-butanal affords an aldehyde. This adduct can serve as the common intermediate for the assembly of secologanin tryptamine and dopamine alkaloids; this is demonstrated by the total syntheses of corynantheidol, dihydrocorynantheol, protoemetinol, and protoemetine, and the formal synthesis of mitragynine. The key steps include reductive amination of this aldehyde with tryptamine, condensation of this aldehyde with 4-methoxytryptamine, condensation of dimethoxyphenethylamine with a lactone derived from this aldehyde, and subsequent Bischler–Napieralski cyclization and reduction.

Keywords: alkaloids · Michael addition · natural products · organocatalysis · total synthesis

Introduction

In recent years, great progress has been made in the development of organocatalytic Michael addition reactions of aldehydes with electron-deficient olefins. Among the catalysts examined, *O*-trimethylsilyl (TMS)-protected diphenylprolinol has received increasing attention because of its convenient availability and excellent asymmetric induction ability. Owing to relatively poor reactivity of the imine intermediates generated from aldehydes and *O*-TMS-protected diphenylprolinol, the Michael acceptors are limited to those highly reactive electron-deficient olefins, such as nitroolefines,[1] 1,1-bis(benzenesulfonyl)ethylene,[2] maleimides,[3] arylidene malonates,[4] α-keto-α,β-unsaturated esters,[5] and γ-keto-α,β-unsaturated esters.[6] Clearly, this drawback would greatly limit their applications in the syntheses of complex molecules. However, we believe that some simple chiral building blocks can be elaborated in a facile and less expensive manner by using these newly developed Michael addition reactions and will find applications in the synthesis of natural products.

Secologanin tryptamine and dopamine alkaloids are two structurally diverse classes of natural products that share functionalized monoterpene glucoside as the biosynthetic precursor (Scheme 1).[7] These natural products, as well as their derivatives, possess significant analgesic,[8] anti-inflammatory,[9] antiarthritic,[10] antiallergenic,[11] antibacterial,[12]



Scheme 1. Biosynthesis of secologanin-derived alkaloids. Glu = glucosyl.

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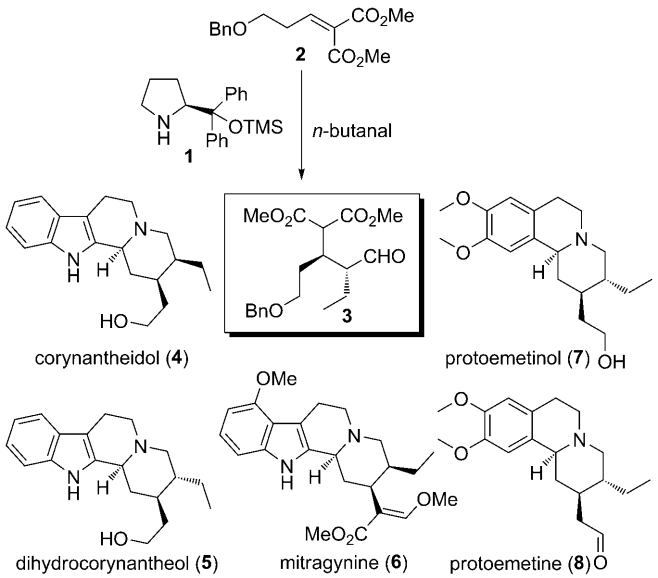
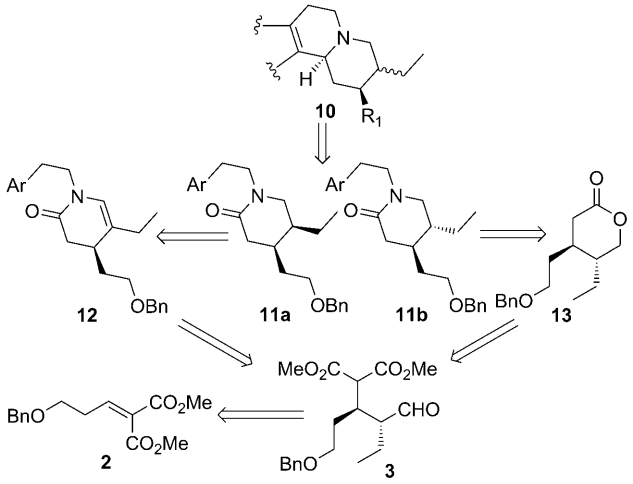
and antiviral[13] activities. More importantly, some of these compounds are therapeutically useful. For instance, mitragynine (**6**; Scheme 2) has been used as a substitute for opioids in the treatment of pain in Thailand.[16f] During recent decades, a considerable number of reports have appeared regarding the total synthesis of these alkaloids. However, most approaches to these alkaloids were investigated on a case-by-case basis. Quite recently, Williams and English developed a general strategy for elaborating both families of alkaloids from a common intermediate, although the synthesis was performed in a racemic manner.[14l] Herein, we wish to demonstrate that diester **3**—a Michael adduct of *n*-butanal with alkylidene malonate **2**—could be utilized for asymmetric syntheses of the tryptamine-derived alkaloids corynantheidol (**4**),[14] dihydrocorynantheol (**5**),[15] and mitragynine (**6**),[16] as well as dopamine-derived alkaloids protoemetinol (**7**)[17] and protoemetine (**8**).[18]



Scheme 2. New strategy for syntheses of tryptamine- and dopamine-derived alkaloids.

Scheme 3 illustrates our detailed retrosynthetic analysis of these alkaloids. We focused our attention on the advanced intermediates **11a** and **11b**, which could be transformed into the corresponding target natural products **10** by Bischler–Napieralski cyclization.[19] We envisioned that **11a** could be obtained by a diastereoselective hydrogenation of unsaturated lactam **12**, whereas **11b** could be assembled from lactone **13**. Both **12** and **13** could be prepared by using aldehyde **3** as a common intermediate.



Scheme 3. Retrosynthetic analysis of secologanin tryptamine and dopamine alkaloids. Bn = benzyl.

Abstract in Chinese:

在本文中我们描述了一个由有机小分子催化的迈克加成产物可以作为一个共用的中间体来合成开联番木鳖苷类色胺生物碱和多巴胺生物碱。这个合成策略通过 5 个生物碱的合成来说明。

Results and Discussion

With this idea in mind, we first explored the Michael reaction of *n*-butanal with alkylidene malonate **2**. The Córdova group[4] has demonstrated that *O*-TMS-protected diphenylprolinol **1** was the best catalyst for promoting the Michael addition of aldehydes to simple arylidene malonates in terms of diastereo- and enantioselectivity.[20] Under their optimized conditions, we found that the desired adduct **3** could be obtained with a slight decrease in the stereochemical outcome (Table 1, entry 1). Changing the reaction media from acetonitrile to water slightly improved the diastereoselectivity without significantly decreasing the efficiency (Table 1, entry 2). However, other solvent systems gave worse results (Table 1, entries 3–7). Unfortunately, we observed that the enantioselectivity dropped to 81.6% *ee* once the reaction was carried out on a 1 mmol scale (Table 1, entry 8), although the reason for this difference was not clear.

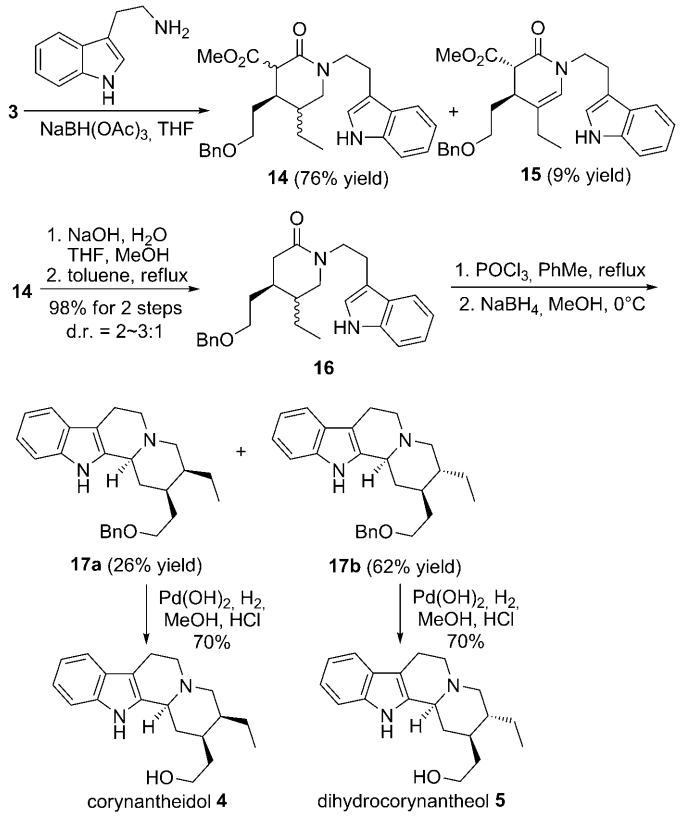
Although the optical purity for our synthesized **3** was not excellent (81.6% *ee*), we continued our synthesis by con-

Table 1. Michael addition of **2** and *n*-butanal under different conditions.[a]

Entry	Solvent	*t* [h]	Conversion[b] [%]	d.r.[b]	*ee*[c] [%]
1	CH_3CN	12	>99	5.4:1	89.5
2	H_2O	10	>95	6.2:1	91.0
3	$CHCl_3$	12	90	4.1:1	91.5
4	$(CH_2Cl)_2$	12	>99	4.3:1	79.3
5	CH_3CN/H_2O (10:1)	12	>99	4.6:1	85.3
6	toluene	12	60	3.5:1	86.2
7	dioxane	12	60	2.9:1	76.5
8	H_2O	10	>95	6.2:1	81.6[d]

[a] Reaction conditions: **2** (0.1 mmol), *n*-butanal (0.5 mmol), **1** (0.02 mmol), solvent (0.2 mL), 0 °C. [b] The diastereomer ratio (d.r.) was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] The enantiomeric excess (*ee*) was determined by chiral-phase HPLC analysis of its derivative **15**. [d] The reaction was carried out on a 1 mmol scale.

necting it with tryptamine. Reductive amination of **3** with tryptamine and subsequent spontaneous lactamization afforded the desired product **14** in 76% yield as an inseparable diastereomeric mixture (Scheme 4). In this case, a side

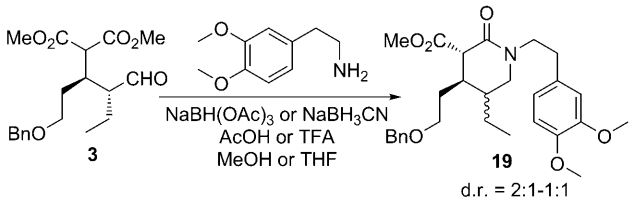


Scheme 4. Total synthesis of **4** and **5**. THF = tetrahydrofuran.

product, **15**, was isolated in 9% yield, which should have resulted from a condensative cyclization/elimination cascade. This observation offered us the chance to tune the geometry of the substituents in the piperidine core (see below). Saponification of **14** and subsequent decarboxylation in toluene at reflux produced lactam **16**. Two diastereomers in a ratio of about 2:1 were detected by ^{1}H NMR spectroscopy. This result indicated that partial epimerization occurred during the transformation steps. Next, Bischler–Napieralski cyclization of lactam **16** followed by reduction with $NaBH_4$ provided separable tetracyclic compounds **17a** and **17b**. Pd/C-catalyzed hydrogenolysis of **17a** and **17b** delivered **4** and **5**, respectively. The analytical data (^{1}H and ^{13}C NMR spectra) of synthetic **4** and **5** were consistent with those previously reported for these two natural products.[14,15] Thus, we achieved a four-step synthesis of **4** and **5** from tryptamine and the Michael adduct **3**.

In the above synthesis, two separable isomers were obtained in a ratio of about 2:1 after decarboxylation, which was acceptable because both of them could be used for synthesizing target alkaloids. Indeed, most secologanin tryptamine alkaloids exist naturally with two diastereomers at the side chains of the right-handed piperidine cycles, and therefore, the aldehyde **3** could be used as a common intermediate for the assembly of these alkaloids. However, for synthesizing secologanin dopamine alkaloids, we have to find a more diastereoselective approach because they usually exist as single diastereomers.

Accordingly, we attempted to improve the diastereoselectivity in the reductive amination/condensative cyclization cascade of **3** and 3,4-dimethoxyphenethylamine (Scheme 5). Unfortunately, low selectivity (1:1 to 2:1) was still observed after changing the reducing agents, additives, and solvents. As the groups of Jørgensen[20a] and Nuhant[17h] have encountered similar problems in their reductive amination operations, we gave up on this improvement.



Scheme 5. Reductive amination/condensative cyclization of **3** and 3,4-dimethoxy-phenethylamine. TFA = trifluoroacetic acid.

We next turned our attention to employing lactone **13** as an intermediate. This compound could be easily assembled from **3** with 68% overall yield by a reduction/lactonization/decarboxylation reaction sequence (Scheme 6). In this case, the diastereomer was isolated in only 9% yield, indicating that no epimerization took place during reduction of the aldehyde moiety. Following the procedure reported by Fukumoto et al.,[17e] we were able to transform **13** into tricyclic intermediate **18** by condensation with 3,4-dimethoxyphenethylamine at 160 °C, treatment of the resulting amide with $POCl_3$, and subsequent reduction with $NaBH_4$. Removal of the benzyl protecting group in **18** produced **7** in 70% yield, which was oxidized with Dess–Martin reagent to deliver **8** in 60% yield.

Our synthetic studies toward **6** are depicted in Scheme 7. As mentioned before, enamine **15** could be isolated as a side product from reductive amination of **3** with tryptamine. We envisioned that the corresponding enamine could be obtained exclusively in the absence of the reducing agent. After some experimentation, we found that reaction of the aldehyde **3** with 4-methoxytryptamine in dichloromethane at room temperature gave the desired enamine **20** in 75% yield as a single diastereomer. Diastereoselective hydrogenation of **20** could be accomplished by catalysis with PtO_2, and the resulting product was subjected to saponification and decarboxylation to deliver lactam **21** in 75% overall yield. Following a similar procedure for converting lactam **16** into **4** and **5**, we obtained alcohol **24**. However, it was difficult to oxidize **24** into the corresponding acid. This problem forced us to perform the oxidation before Bischler–Na-

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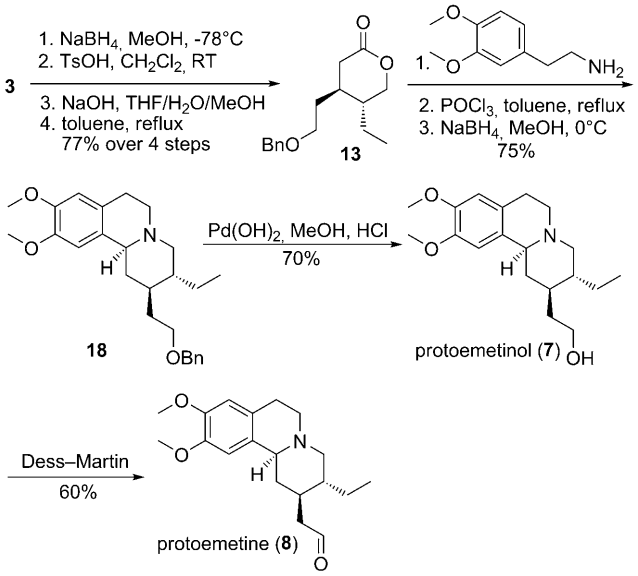
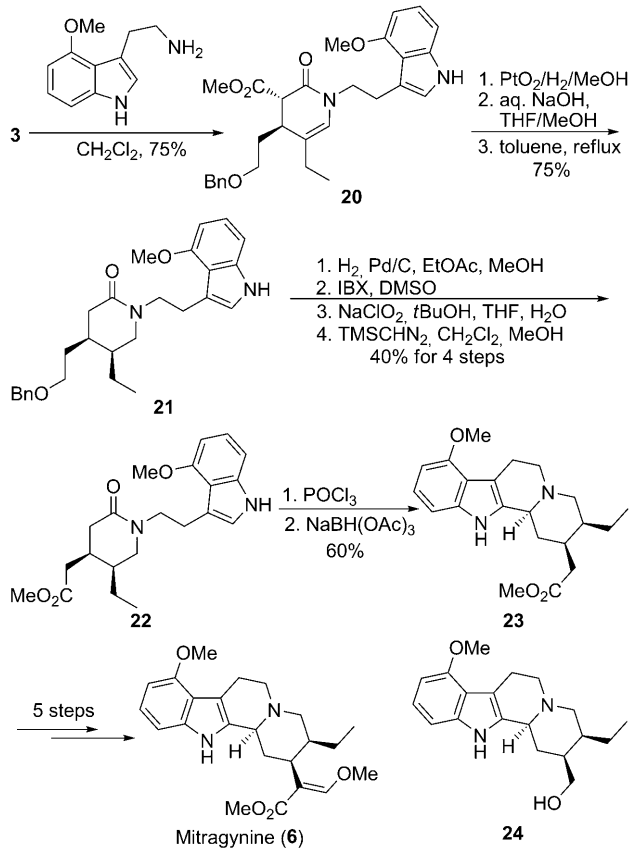


Scheme 6. Total syntheses of **7** and **8**. TsOH = *p*-toluenesulfonic acid.



Scheme 7. Formal synthesis of **6**. DMSO = dimethylsulfoxide, IBX = 2-iodoxybenzoic acid.

pieralski cyclization. Accordingly, debenzylation of **21** through Pd/C-catalyzed hydrogenolysis followed by oxidation of the primary alcohol with IBX produced an aldehyde, which was subjected to Pinnick oxidation and esterification to afford ester **22** in 40% overall yield. Heating a solution of **22** and $POCl_3$ in toluene at reflux followed by reduction with $NaBH(OAc)_3$ in MeOH gave ester **23** in 60% yield, which has been employed by Cook's laboratory for synthesizing **6**.[16f,g] Thus, we were able to achieve the formal synthesis of **6**.

Conclusion

We have developed an organocatalytic approach for the asymmetric synthesis of secologanin tryptamine alkaloids **4**, **5**, and **6**, as well as secologanin dopamine alkaloids **7** and **8**. This protocol is promising for the assembly of other members of the secologanin alkaloids and their analogues. Thus, our results give an additional example to demonstrate the synthetic utility of organocatalytic reactions.

Experimental Section

Michael addition of n-butanal and **2**

A mixture of **1** (6.5 mg, 0.02 mmol), *n*-butanal (45 μL, 0.50 mmol), water (0.2 mL), and **2** (28 mg, 0.10 mmol) was stirred at 0 °C for 10 h. The solution was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$ before it was concentrated under reduced pressure. The residue was purified by chromatography (eluting with 4:1 petroleum ether and ethyl acetate) to give **3** as a colorless oil (30 mg, 85%, d.r. = 8:1). $[\alpha]_D^{21.8} = -26.4$ ($c = 1.08$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.2$ Hz, 3H), 1.31–1.41 (m, 1H), 1.69–1.83 (m, 3H), 2.32–2.34 (m, 1H), 2.95 (dq, $J = 4.0$, 7.2 Hz, 1H), 3.41 (t, $J = 6.0$ Hz, 2H), 3.56 (d, $J = 7.2$ Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 4.41 (s, 2H), 7.32 (m, 5H), 9.65 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.9$, 18.0, 29.2, 35.0, 52.5, 52.6, 54.1, 54.9, 68.0, 72. 8, 127.6, 127.7, 128.4, 138.2, 169.0, 169.1, 203.4 ppm; HRMS: *m*/*z* calcd for $C_{19}H_{26}O_6Na$ $[M+Na]^+$: 373.1622; found: 373.1634.

*Reductive amination of **3** with tryptamine*

Tryptamine (17 mg, 0.11 mmol) and $NaBH(OAc)_3$ (42 mg, 0.20 mmol) were added to a solution of **3** (30 mg, 0.85 mmol) in dry THF (1 mL). The resulting solution was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (eluting with 2:1–1:1 petroleum/ethyl acetate) to give **15** (4 mg, 9%) and **14** (34 mg, 76%).

15: $[\alpha]_D^{23.5} = +40.6$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.2$ Hz, 3H), 1.54–1.62 (m, 1H), 1.64–1.72 (m, 1H), 1.95–2.02 (m, 2H), 2.86 (t, $J = 7.2$ Hz, 3H), 3.00–3.08 (m, 2H), 3.45 (t, $J = 6.0$ Hz, 3H), 3.70 (s, 3H), 3.61–3.74 (m, 1H), 3.96–4.04 (m, 1H), 4.48 (s, 2H), 5.67 (s, 1H), 7.00 (s, 1H), 7.12 (t, $J = 7.2$ Hz, 1H), 7.19 (t, $J = 7.2$ Hz, 1H), 7.33–7.36 (m, 6H), 7.66 (d, $J = 7.6$ Hz, 1H), 8.29 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.6$, 24.2, 25.6, 31.0, 35.6, 46.9, 52.55, 52.63, 67.2, 73.1, 111.3, 112.4, 118.8, 119.4, 122.0, 122.5, 123.4, 124.9, 127.4, 127.7, 127.8, 128.5, 136.4, 138.3, 164.4, 170.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{28}H_{33}N_2O_4$ $[M+H]^+$: 461.2435; found: 461.2437; HPLC (Chiralpak IC, hexane/*i*PrOH = 70:30, flow rate 0.7 mL min^{-1}, $\lambda = 214$ nm), $t_R = 19.43$ (minor), 24.58 (major) min; single; *ee* = 91.0% (*ee* = 80% when the reaction was carried out on 1 mmol scale).

14: $[\alpha]_D^{23.4} = ++21.9$ ($c = 1.07$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): $\delta = 0.69$ (t, $J = 7.2$ Hz, 3H), 1.05–1.17 (m, 1H), 1.34–1.40 (m, 1H), 1.47–1.53 (m, 1H), 1.66–1.85 (m, 2H), 2.14–2.37 (m, 1H), 2.89-2.97 (m, 1H), 3.05–3.17 (m, 3H), 3.32 (d, $J = 8.8$ Hz, 1H), 3.45–3.54 (m, 3H),

3.70–3.81 (m, 4H), 4.46 (s, 2H), 7.03 (s, 1H), 7.11–7.18 (m, 2H), 7.29–7.37 (m, 6H), 7.65 (d, J=8.0 Hz, 1H), 7.90 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ=10.7, 11.7, 23.1 23.8, 31.9, 37.6, 38.5, 48.7, 51.4, 52.3, 54.5, 66.8, 72.9, 111.4, 112.1, 118.5, 119.0, 121.6, 122.4, 127.3, 127.5, 128.3, 136.3, 138.2, 166.4, 171.5 ppm; HRMS (ESI): m/z calcd for $C_{28}H_{35}N_2O_4$ $[M+H]^+$: 463.2591; found: 463.2585.

*Conversion of **14** to **16***

NaOH (51 mg, 1.26 mmol) was added to a solution of **14** (193 mg, 0.42 mmol) in THF/MeOH/H_2O (4/0.8/1.6 mL) at 0 °C. The mixture was stirred at room temperature until the starting material was completely consumed, as monitored by TLC. After 1 N HCl was added to adjust the pH to less than 5, the resulting mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (10 mL) and the solution was heated at reflux for 1 h. The solution was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (petroleum/ethyl acetate=2/1) to give **16** as a colorless oil (165 mg, 98%, d.r.=3:1). $[\alpha]_D^{23.3}$=+32.4 (c=1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): δ=0.75 (t, J=7.2 Hz, 3H), 1.11–1.21 (m, 1H), 1.33–1.40 (m, 2H), 1.46–1.52 (m, 1H), 1.65–1.81 (m, 2H), 2.06 (dd, J=8.0, 17.6 Hz, 1H), 2.53 (dd, J=5.6, 17.6 Hz, 1H), 2.87 (dd, J=8.0, 12.0 Hz, 1H), 3.03 (t, J=7.2 Hz, 2H), 3.16 (dd, J=4.8, 12.0 Hz, 1H), 3.42–3.53 (m, 2H), 3.57–3.75 (m, 2H), 4.48 (s, 2H), 7.04 (s, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.28–7.37 (m, 6H), 7.65 (d, J=7.6 Hz, 1H), 7.98 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ=10.9, 23.2, 23.6, 33.1, 33.4, 36.4, 39.3, 48.2, 51.4, 67.5, 73.1, 111.3, 112.7, 118.7, 119.1, 121.8, 122.2, 127.5, 127.66, 127.68, 128.4, 136.4, 138.3, 169.6 ppm; HRMS (ESI): m/z calcd for $C_{26}H_{32}N_2O_3Na$ $[M+Na]^+$: 427.2356; found: 427.2377.

*Synthesis of **17a** and **17b***

$POCl_3$ (0.5 mL, 4.0 mmol) was added to a solution of **16** (200 mg, 0.50 mmol) in toluene (8 mL). The mixture was heated at reflux (for about 2 h) until the starting material was completely consumed, as monitored by TLC. After being cooled to room temperature, the solution was concentrated under reduced pressure. After the residue was dissolved in MeOH (8 mL), $NaBH_4$ (152 mg, 4.0 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h. The mixture was extracted with ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (MeOH/CH_2Cl_2 1:10) to give **17a** (50 mg, 26%) and **17b** (120 mg, 62%) as colorless oils.

17a: $[\alpha]_D^{23.1}$=−2.4 (c=0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.93 (t, J=7.2 Hz, 3H), 1.27–1.33 (m, 2H), 1.42–1.50 (m, 2H), 1.60–1.78 (m, 4H), 1.81–1.98 (m, 1H), 2.37 (d, J=9.6 Hz, 1H), 2.54–2.61 (m, 1H), 2.69 (d, J=14.4 Hz, 1H), 2.94–3.05 (m, 3H), 3.16 (d, J=10.8 Hz, 1H), 3.59 (t, J=6.4 Hz, 2H), 4.56 (d, J=12.0 Hz, 1H), 4.61 (d, J=12.0 Hz, 1H), 7.10 (t, J=7.2 Hz, 1H), 7.15 (t, J=7.2 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.40–7.43 (m, 5H), 7.48 (d, J=8.0 Hz, 1H), 7.72 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.8, 17.9, 21.9, 32.0, 33.1, 36.8, 39.8, 53.6, 58.1, 60.4, 68.1, 73.0, 108.1, 110.8, 118.2, 119.4, 121.2, 127.6, 127.8, 128.0, 128.6, 135.6, 136.0, 138.7 ppm; HRMS (EI): m/z calcd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2587; found: 389.2594.

17b: $[\alpha]_D^{23.1}$=+12.1 (c=0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.96 (t, J=7.2 Hz, 3H), 1.15–1.30 (m, 2H), 1.37–1.40 (m, 1H), 1.49–1.51 (m, 2H), 1.68–1.76 (m, 1H), 2.02–2.15 (m, 3H), 2.62 (td, J=11.2, 4.8 Hz, 1H), 2.74 (dd, J=15.2, 3.2 Hz, 1H), 3.00–3.14 (m, 4H), 3.62 (t, J=6.4 Hz, 2H), 4.51 (d, J=12.0 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.18 (t, J=7.2 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.39–7.44 (m, 5H), 7.50 (d, J=7.6 Hz, 1H), 7.70 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.2, 21.8, 23.6, 32.5, 37.3, 42.1, 53.2, 53.6, 59.8, 60.5, 67.6, 72.9, 108.0, 110.8, 118.2, 119.4, 121.3, 127.5, 127.8, 128.1, 128.5, 135.0, 136.0, 138.7 ppm; HRMS (EI): m/z calcd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2587; found: 389.2591.

*Corynantheidol (**4**)*

Compound **17a** (50 mg, 0.13 mmol) was dissolved in MeOH (5 mL) before $Pd(OH)_2$ (5 mg, 10%) and concentrated HCl (1 drop) were added. The mixture was stirred under a hydrogen atmosphere for 8 h. The reaction mixture was filtered through a short plug of Celite and then eluted with MeOH/CH_2Cl_2 (1:5). The filtrate was concentrated in vacuo and purified by flash chromatography (methanol/CH_2Cl_2 1:10) to give **4** as a yellow oil (38 mg, 70%). $[\alpha]_D^{22.4}$=−10.4 (c=0.50, $HCCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (t, J=7.2 Hz, 3H), 1.25–1.27 (m, 1H), 1.46–1.59 (m, 5H), 1.88–1.90 (m, 2H), 2.20 (brs, 1H), 2.32 (d, J=11.2 Hz, 1H), 2.50–2.56 (m, 1H), 2.67 (d, J=14.4 Hz, 1H), 2.95–3.03 (m, 3H), 3.16 (d, J=10.0 Hz, 1H), 3.73–3.76 (m, 2H), 7.07 (t, J=7.2 Hz, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.31 (d, J=7.2 Hz, 1H), 7.44 (d, J=8.0 Hz, 1H), 8.14 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.8, 17.9, 21.7, 31.8, 36.0, 36.3, 39.7, 53.5, 57.8, 60.5, 60.8, 107.9, 111.0, 118.2, 119.4, 121.3, 127.5, 135.3, 136.2 ppm; HRMS (MALDI/DHB): m/z calcd for $C_{19}H_{27}N_2O$ $[M+H]^+$ 299.2118; found: 299.2117.

*Dihydrocorynantheol (**5**)*

Compound **17b** (100 mg, 0.26 mmol) was dissolved in MeOH (10 mL) before $Pd(OH)_2$ (10 mg, 10%) and concentrated HCl (1 drop) were added. The mixture was stirred under a hydrogen atmosphere for 8 h. The reaction mixture was filtered through a short plug of Celite and then eluted with MeOH/CH_2Cl_2 (1:5). The filtrate was concentrated in vacuo and purified by flash chromatography (MeOH/CH_2Cl_2 1:10) to give **5** as a yellow solid (77 mg, 70%). $[\alpha]_D^{26.5}$=−8.7 (c=0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.85 (t, J=7.2 Hz, 3H), 1.00–1.07 (m, 1H), 1.17–1.41 (m, 4H), 1.55–1.59 (m, 1H), 1.82–1.87 (m, 2H), 2.13 (d, J=10.4 Hz, 1H), 2.41–2.47 (m, 1H), 2.68 (d, J=10.4 Hz, 1H), 2.88–3.04 (m, 4H), 3.62 (t, J=6.4 Hz, 2H), 7.08 (t, J=7.2 Hz, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.44 (d, J=8.0 Hz, 1H), 8.79 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.1, 21.5, 23.4, 35.0, 35.4, 37.0, 41.4, 53.0, 59.8, 59.9, 60.1, 107.5, 111.2, 118.2, 119.3, 121.3, 127.3, 134.8, 136.3 ppm; HRMS (MALDI/DHB): m/z calcd for $C_{19}H_{27}N_2O$ $[M+H]^+$: 299.2118; found: 299.2116.

*Synthesis of **13***

$NaBH_4$ (74 mg, 2.0 mmol) was added in 3 portions to a cooled solution (−78 °C) of **3** (350 mg, 1.00 mmol) in dry MeOH (5 mL). The mixture was stirred at this temperature for 1 h before 1 N HCl (3 mL) was added to quench the reaction. The solution was warmed to room temperature and then *p*-TsOH (50 mg) was added. The resulting mixture was allowed to stand overnight. The mixture was extracted with ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in THF/MeOH/H_2O (4/1/2 mL) and then NaOH (80 mg, 2.00 mmol) was added at 0 °C. The mixture was stirred at room temperature (overnight) until the starting material was completely consumed, as monitored by TLC. After 1 N HCl was added to adjust the pH to less than 5, the mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (10 mL) and the solution was heated at reflux for 1 h. The cooled solution was concentrated in vacuo. The residue was purified by flash chromatography (petroleum/ethyl acetate=4:1) to give **13** as a colorless oil (200 mg, 77%, d.r.=8:1). $[\alpha]_D^{28.2}$=+15.8 (c=1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.93 (t, J=7.2 Hz, 3H), 1.31–1.38 (m, 1H), 1.45–1.60 (m, 3H), 1.78–1.86 (m, 1H), 1.88–1.97 (m, 1H), 2.25 (dd, J=7.2, 16.0 Hz, 1H), 2.62 (dd, J=6.8, 16.0 Hz, 1H), 3.50 (t, J=6.0 Hz, 2H), 3.99 (dd, J=7.2, 11.2 Hz, 1H), 4.28 (dd, J=4.4, 11.6 Hz, 1H), 4.48 (s, 2H), 7.28–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.3, 24.3, 33.2, 34.2, 35.3, 40.0, 67.2, 70.5, 73.2, 127.7, 127.8, 128.5, 138.2, 172.7 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1461; found: 285.1474.

*Conversion of **13** to **18***

A mixture of **13** (55 mg, 0.20 mmol) and 3,4-dimethoxyphenethylamine (0.24 mL, 1.40 mmol) was heated at 160 °C for 6 h. The cooled solution was diluted with ethyl acetate before it was washed with 1 N HCl, saturat-

ed aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in toluene (2 mL), and then $POCl_3$ (0.1 mL, 0.80 mmol) was added. The mixture was heated at reflux (for about 2 h) until the starting material was completely consumed, as monitored by TLC. After the solution was concentrated under reduced pressure, the residue was dissolved in MeOH (2 mL). $NaBH_4$ (30 mg, 0.8 mmol) was added to this solution at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The mixture was extracted with ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (eluting with 1:1 petroleum/ethyl acetate) to give **18** as a colorless oil (60 mg, 75%). $[\alpha]_D^{27.4} = -11.1$ ($c = 0.98$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.2$ Hz, 3H), 1.11–1.18 (m, 1H), 1.23–1.31 (m, 1H), 1.47–1.48 (m, 3H), 1.64–1.73 (m, 1H), 2.02–2.13 (m, 2H), 2.32 (d, $J = 12.8$ Hz, 1H), 2.54 (td, $J = 11.2$, 4.0 Hz, 1H), 2.66 (d, $J = 15.2$ Hz, 1H), 3.03–3.07 (m, 1H), 3.13 (t, $J = 12.8$ Hz, 3H), 3.60 (t, $J = 6.0$ Hz, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 4.49 (d, $J = 12.0$ Hz, 1H), 4.56 (d, $J = 12.0$ Hz, 1H), 6.57 (s, 1H), 6.61 (s, 1H), 7.28–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.1$, 23.5, 28.9, 32.8, 37.0, 38.1, 40.9, 52.1, 56.0, 56.3, 61.2, 62.6, 68.3, 73.0, 108.7, 111.7, 126.6, 127.7, 128.5, 129.6, 138.7, 147.4, 147.8 ppm; HRMS (ESI): m/z calcd for $C_{26}H_{36}NO_3$ $[M+H]^+$: 410.2690; found: 410.2705.

*Protoemetinol (**7**)*

A mixture of **18** (120 mg, 0.29 mmol), $Pd(OH)_2$ (24 mg, 20%), and concentrated HCl (1 drop) in MeOH (10 mL) was stirred under a hydrogen atmosphere for 8 h. The reaction mixture was filtered through a short plug of Celite and then eluted with MeOH/CH_2Cl_2 (1:5). The filtrate was concentrated in vacuo and purified by flash chromatography (MeOH/CH_2Cl_2 1:10) to give **7** as a yellow oil (66 mg, 70%). $[\alpha]_D^{25.1} = -24.7$ ($c = 1.10$, MeOH); $[\alpha]_D^{26.0} = -40.5$ ($c = 1.20$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.2$ Hz, 3H), 1.07–1.16 (m, 1H), 1.26–1.31 (m, 1H), 1.39–1.45 (m, 3H), 1.62–1.70 (m, 1H), 1.88–1.95 (m, 1H), 2.01 (t, $J = 10.8$ Hz, 1H), 2.33 (d, $J = 12.8$ Hz, 1H), 2.51 (td, $J = 11.6$, 4.4 Hz, 1H), 2.65 (br d, $J = 15.2$ Hz, 1H), 3.00–3.04 (m, 1H), 3.08–3.16 (m, 3H), 3.70–3.75 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 6.57 (s, 1H), 6.58 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.1$, 23.5, 28.9, 35.8, 37.1, 37.6, 41.0, 52.3, 55.9, 56.2, 60.3, 61.3, 62.7, 108.5, 111.6, 126.6, 129.7, 147.3, 147.7 ppm; HRMS (ESI): m/z calcd for $C_{19}H_{30}NO_3$ $[M+H]^+$: 320.2220; found: 320.2225.

*Protoemetine (**8**)*

DMP (33 mg, 0.08 mmol) and $NaHCO_3$ (13 mg, 0.16 mmol) were added to a solution of **7** (9 mg, 0.03 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. The mixture was stirred at this temperature under an argon atmosphere for 1 h before it was extracted with diethyl ether and washed successively with a saturated aqueous solution of $Na_2S_2O_3$, a saturated aqueous solution of $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (eluting with ethyl acetate) to give **8** as a yellow oil (5 mg, 60%). $[\alpha]_D^{28.4} = -28.8$ ($c = 0.40$, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.2$ Hz, 3H), 1.10–1.17 (m, 1H), 1.25–1.34 (m, 2H), 1.49–1.61 (m, 2H), 2.09 (t, $J = 11.2$ Hz, 1H), 2.31–2.36 (m, 2H), 2.49–2.54 (m, 1H), 2.63 (d, $J = 16.0$ Hz, 1H), 2.72 (dd, $J = 3.6$, 17.2 Hz, 1H), 2.97–3.01 (m, 1H), 3.08–3.16 (m, 3H), 3.84 (s, 6H), 6.57 (s, 1H), 6.63 (s, 1H), 9.88 ppm (d, $J = 0.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.2$, 23.9, 29.3, 36.1, 38.3, 41.4, 48.2, 52.6, 56.0, 56.3, 61.2, 62.7, 108.4, 111.7, 126.7, 129.6, 147.5, 147.8, 202.5 ppm; HRMS (ESI): m/z calcd for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064; found: 318.2062.

*Synthesis of **20***

4-Methoxytryptamine (190 mg, 1.0 mmol) was added to a solution of **3** (280 mg, 0.80 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature overnight. The solution was concentrated in vacuo and purified by flash chromatography (eluting with 1:2 petroleum/ethyl acetate) to afford **20** as a brown oil (294 mg, 75%). $[\alpha]_D^{26.9} = +40.4$ ($c = 1.50$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.2$ Hz, 3H), 1.59–1.67 (m, 1H), 1.70–1.78 (m, 1H), 2.01 (q, $J = 7.2$ Hz, 2H), 2.86 (t, $J = 7.2$ Hz, 1H), 3.10 (t, $J = 7.2$ Hz, 2H), 3.43 (s, 1H), 3.48 (t, $J = 6.0$ Hz, 2H), 3.71 (s, 3H), 3.65–3.74 (m, 1H), 3.95 (s, 3H), 3.92–3.97 (m, 1H), 4.50 (s, 2H), 5.73 (s, 1H), 6.49 (d, $J = 8.0$ Hz, 1H), 6.86 (s, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 7.07 (t, $J = 8.0$ Hz, 1H), 7.30–7.37 (m, 5H), 8.32 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.6$, 25.7, 25.9, 31.0, 35.6, 48.2, 52.5, 52.7, 55.1, 67.3, 73.1, 99.3, 104.8, 112.7, 117.3, 121.8, 122.7, 123.7, 124.3, 127.7, 127.8, 128.5, 138.26, 138.31, 154.5, 164.3, 170.2 ppm; HRMS (ESI): m/z calcd for $C_{29}H_{34}N_2O_5Na$ $[M+Na]^+$: 513.2360; found: 513.2369.

*Conversion of **20** into **21***

A mixture of **20** (600 mg, 1.22 mmol) and PtO_2 (60 mg, 10 wt%) in dry MeOH (4 mL) was stirred under a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered through a short plug of Celite and then eluted with ethyl acetate. The filtrate was concentrated in vacuo and dissolved in THF/H_2O/MeOH (12:5:2 mL) before NaOH (98 mg, 2.44 mmol) was added. The mixture was stirred at room temperature (overnight) until the starting material was completely consumed, as monitored by TLC. After 1 N HCl was added to adjust the pH to less than 5, the solution was extracted with ethyl acetate (50 mL) and washed with brine (20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (10 mL) and the solution was heated at reflux for 1 h. The solution was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (eluting with 1:1 petroleum/ethyl acetate) to give **21** as a yellow oil (397 mg, 75%). $[\alpha]_D^{27.5} = +36.1$ ($c = 0.70$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (t, $J = 7.2$ Hz, 3H), 1.17–1.24 (m, 1H), 1.38–1.45 (m, 2H), 1.48–1.53 (m, 1H), 1.78–1.88 (m, 2H), 2.05 (dd, $J = 8.0$, 16.8 Hz, 1H), 2.53 (dd, $J = 5.6$, 16.8 Hz, 1H), 2.93 (dd, $J = 8.0$, 12.4 Hz, 1H), 3.10 (t, $J = 7.2$ Hz, 2H), 3.24 (dd, $J = 4.8$, 12.4 Hz, 1H), 3.45–3.55 (m, 2H), 3.61–3.71 (m, 2H), 3.93 (s, 3H), 4.49 (s, 2H), 6.49 (d, $J = 8.0$ Hz, 1H), 6.90 (s, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 7.07 (t, $J = 8.0$ Hz, 1H), 7.30–7.38 (m, 5H), 8.01 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.2$, 24.0, 24.9, 33.5, 33.7, 36.6, 39.7, 49.2, 51.3, 55.2, 67.8, 73.3, 99.5, 104.7, 113.8, 117.5, 121.4, 122.9, 127.79, 127.84, 128.6, 138.3, 138.5, 154.8, 169.5 ppm; HRMS (ESI): m/z calcd for $C_{27}H_{34}N_2O_3Na$ $[M+Na]^+$: 457.2462; found: 457.2460.

*Ester **22***

A mixture of **21** (245 mg, 0.56 mmol) and Pd/C (25 mg, 10 wt%) in ethyl acetate (3 mL) and MeOH (3 mL) was stirred under a hydrogen atmosphere for 3 h. The reaction mixture was filtered through a short plug of Celite and then eluted with MeOH/CH_2Cl_2 (1:5). The filtrate was concentrated in vacuo and the residue was dissolved in dry DMSO (6 mL) before IBX (157 mg, 0.56 mmol) was added. The mixture was stirred at room temperature for 2 h and then diluted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na2SO_4, filtered, and concentrated in vacuo to afford an aldehyde. The aldehyde was dissolved in THF/H_2O/*t*BuOH (4:4:1 mL) and then NaH_2PO_4 (175 mg, 1.12 mmol), $NaClO_2$ (51 mg, 0.56 mmol), and 2-methylbut-2-ene (2 mL) were added. The mixture was stirred at room temperature for 3 h, extracted with ethyl acetate, and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford an acid. The acid was dissolved in CH_2Cl_2/MeOH (4:4 mL) and $TMSCHN_2$ (0.5 mL) was added at 0 °C. The mixture was stirred at this temperature for 1 h before 1 N HCl (2 mL) was added to quench the reaction. The resulting solution was extracted with ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford **22** as a yellow oil (82 mg, 40% yield for 4 steps, d.r. > 8:1). $[\alpha]_D^{22.5} = +37.8$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.79$ (t, $J = 7.2$ Hz, 3H), 1.16–1.23 (m, 1H), 1.45–1.53 (m, 2H), 1.67–1.73 (m, 1H), 2.12–2.18 (m, 2H), 2.44 (d, $J = 14.4$ Hz, 1H), 2.56 (d, $J = 12.0$ Hz, 1H), 2.95 (dd, $J = 8.0$, 12.8 Hz, 1H), 3.10 (t, $J = 6.4$ Hz, 2H), 3.24 (dd, $J = 4.8$, 12.4 Hz, 1H), 3.61–3.65 (m, 2H), 3.67 (s, 3H), 3.93 (s, 3H), 6.48 (d, $J = 8.0$ Hz, 1H), 6.89 (s, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.06 (t, $J = 8.0$ Hz, 1H), 8.31 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.1$, 23.8, 24.8, 33.9, 36.8, 38.2, 39.1, 49.3, 51.2, 51.8, 55.2, 99.4, 104.8, 113.5, 117.4, 121.5, 122.8,

138.3, 154.7, 168.8, 172.7 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2O_4$ $[M+H]^+$: 373.2122; found: 373.2125.

Synthesis of ***23***

$POCl_3$ (80 μL, 0.64 mmol) was added to a solution **22** (30 mg, 0.08 mmol) in toluene (3 mL). The mixture was heated at reflux (for about 2 h) until the starting material was completely consumed, as monitored by TLC. After being cooled to room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL) and cooled to 0 °C before $NaBH(OAc)_3$ (137 mg, 0.64 mmol) was added to the solution and the resulting mixture was stirred at 0 °C for 1 h. The mixture was extracted with ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (eluting with ethyl acetate) to give **23** as a colorless oil (18 mg, 60 %). $[\alpha]_D^{26.8} = +11.2$ ($c = 0.50$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.2$ Hz, 3H), 1.14–1.21 (m, 1H), 1.33–1.41 (m, 1H), 1.47–1.54 (m, 1H), 1.77–1.83 (m, 1H), 2.05–2.13 (m, 2H), 2.20 (d, $J = 12.4$ Hz, 1H), 2.57 (dt, $J = 4.8$, 12.0 Hz, 1H), 2.70 (dd, $J = 3.2$, 15.2 Hz, 1H), 2.98–3.10 (m, 4H), 3.22 (d, $J = 11.2$ Hz, 1H), 3.72 (s, 3H), 3.87 (s, 3H), 6.46 (d, $J = 7.6$ Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 1H), 7.01 (t, $J = 7.6$ Hz, 1H), 7.75 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.1$, 23.7, 23.9, 36.2, 37.5, 38.2, 41.8, 51.8, 53.6, 55.5, 59.8, 60.3, 100.0, 104.4, 108.2, 117.6, 122.2, 132.8, 137.6, 154.7, 173.8 ppm; HRMS (EI): *m/z* calcd for $C_{21}H_{29}N_2O_3$ $[M+H]^+$: 357.2173; found: 357.2172.

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