DOI: 10.1002/ejoc.201101296

Concise Total Synthesis of Dihydrocorynanthenol, Protoemetinol, Protoemetine, 3-*epi*-Protoemetinol and Emetine

Shuangzheng Lin,[a,b] Luca Deiana,[a,b] Abrehet Tseggai,[a,b] and Armando Córdova*[a,b,c]

Keywords: Organocatalysis / Asymmetric catalysis / Multicomponent reactions / Total synthesis / Natural products / Alkaloids

A concise asymmetric assembly of secologanine tryptamine and dopamine alkaloids by means of a one-pot three-component cascade reaction methodology is disclosed. This is demonstrated by the expeditious total syntheses of (–)-dihydrocorynanthenol, (–)-protoemetinol, (–)-protoemetine, (–)-3-*epi*-protoemetinol, and emetine (3–6 steps). The biomimetic synthetic strategy involved the following key steps: (i) One-pot three-component highly enantioselective catalytic Michael/Pictet–Spengler/lactamization cascade reactions; (ii) One-pot tandem Swern oxidation/Wittig sequences; (iii) One-pot tandem hydrogenation sequences.

Introduction

Secologanine glucoside **1** is the common biosynthetic precursor for several structurally diverse alkaloids,[1] which exhibit analgesic,[2] antiallergenic,[3] anti-inflammatory,[4] antibacterial[5] and antiviral activities.[6] Among them, secologanine dopamine and tryptamine alkaloids are two different types of natural products (Figure 1).[7] The (*S*)-deacetyl synthase-catalyzed Pictet–Spengler transformation between dopamine **2** and secologanine **1** gives the former class of natural products, whereas the strictodine synthase-catalyzed reaction between tryptamine **3** and **1** gives the latter class of natural products.[8,9] In this context, dihydrocorynanthenol (**4a**),[10] protoemetinol (**5a**),[11] protoemetine (**5c**),[12] and emetine (**5d**)[13] are natural products with biological activity (Figure 1). For example, emetine (**5d**) exhibits antiprotozoic activity[14] and could be useful in the treatment of lymphatic leukemia.[15] In addition, its structural analogue, tubolosine, exhibits antitumor activity.[16] Thus, the secologanine dopamine and tryptamine types of alkaloids have attracted significant interest from the synthetic community. However, most of the approaches that have been developed have delivered the compounds in racemic form, and the asymmetric versions have employed starting materials from the chiral pool.[10–13,17] Traditionally, the total synthesis has also been accomplished on a case-by-case basis. With respect to more general synthetic strategies of secologanine alkaloids, the laboratories of Cook[18] and Martin[19] have disclosed the preparation of (±)-secologanine tryptamine alkaloids. Recently, Williams and English developed a general strategy for the synthesis of both types of dopamine and tryptamine derived alkaloids in racemic form.[20] Tietze have disclosed an elegant combinatorial strategy for the synthesis of secologanine dopamine alkaloids such as emetine **5d** through ruthenium-catalyzed asymmetric hydrogenation.[21] In the realms of organocatalysis, Itoh and co-workers reported the catalytic asymmetric

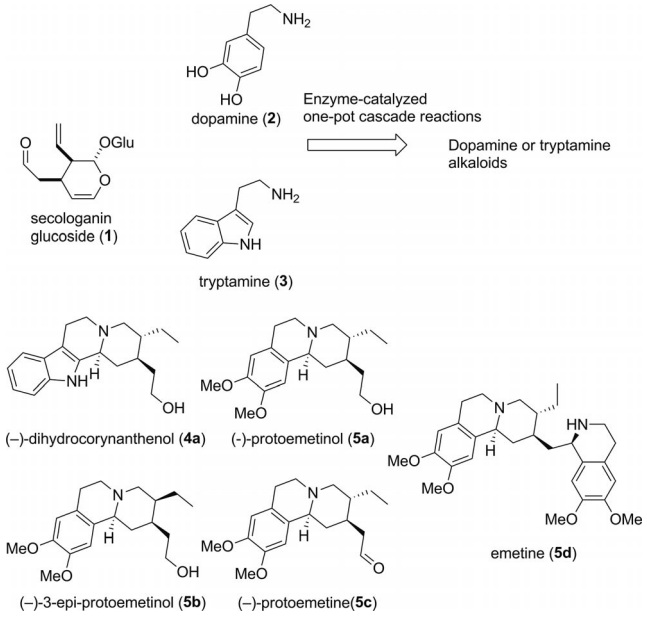


Figure 1. Secologanin tryptamine and dopamine alkaloids.

[a] Department of Organic Chemistry,
The Arrhenius Laboratory, Stockholm University,
106 91 Stockholm, Sweden
[b] The Berzelii Center EXSELENT, Stockholm University,
106 91 Stockholm, Sweden
Fax: +46-8-154-908
E-mail: acordova@organ.su.se
armando.cordova@miun.se
[c] Department of Natural Sciences,
Engineering and Mathematics, Mid Sweden University,
851 70 Sundsvall, Sweden

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101296.

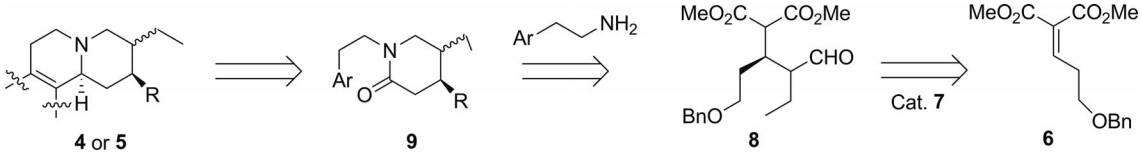
synthesis of *ent*-(+)-dihydrocorynanthenol (**4a**) in four steps using a seven day, proline-catalyzed domino Mannich/Michael transformation as the key step.[22]

Multicomponent and domino reactions that involve the formation of multiple C–C and C–hetero atom bonds and stereocenters in one-pot is an important research field within organic synthesis.[23] They include "green chemistry" parameters such as reduction of synthetic steps, waste, and solvents.[24] However, the development of catalytic asymmetric multicomponent and domino reactions is more challenging.[25] In this context, catalytic construction of quinolizidine core structures through domino sequences were recently disclosed.[26–28] Based on the biological activity of secologanine dopamine and tryptamine alkaloids and on our research interest in the development of multicomponent reactions and asymmetric syntheses,[29] we became interested in developing a general one-pot methodology for the total synthesis of these classes of natural products. Herein, we report the use of a highly enantioselective three-component catalytic asymmetric tandem Michael/Pictet–Spengler/lactamization reaction as the common starting point for the concise total syntheses of (–)-dihydrocorynanthenol, (–)-protoemetinol, (–)-protoemetine, (–)-3-*epi*-protoemetinol, and emetine by one-pot methodologies.

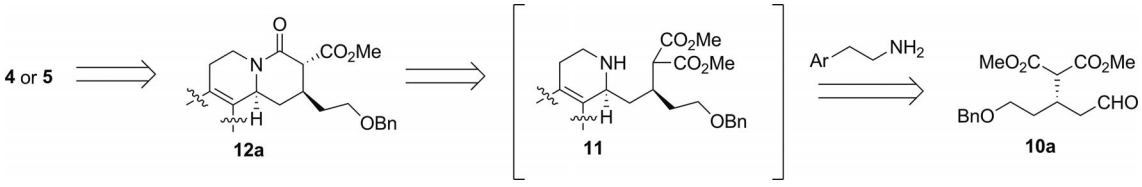
Results and Discussion

Synthetic Plan

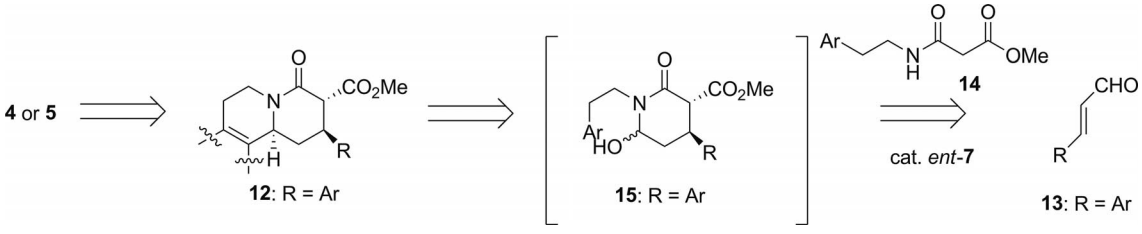
Retrosynthetic analysis suggested several strategies that could be used to generate the alkaloids **4** and **5** [Equations (1–4)]. For example, conjugate addition of butanal to alk-



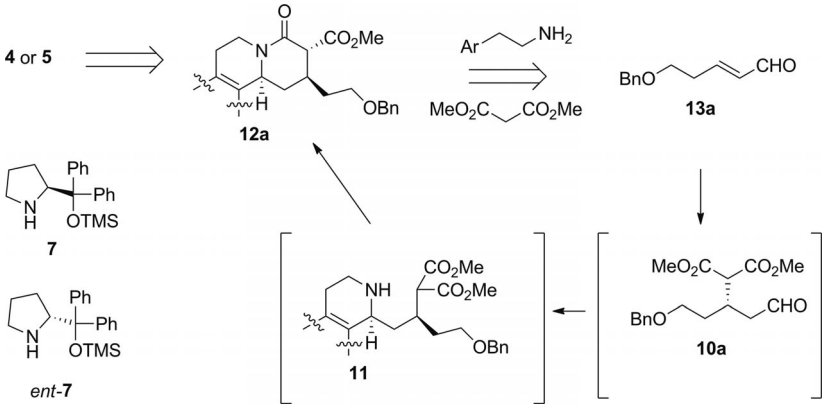
(1)



(2)



(3)



(4)

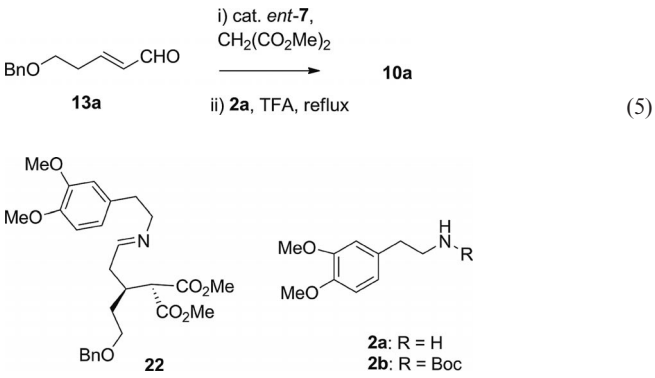
ylidene malonate **6** using chiral amine **7** as the catalyst by our recently disclosed methodology would give aldehyde **8** [Equation (1)].[30] Next, reacting chiral aldehyde **8** with amines **3** or **2** through reductive amination, lactamization, and decarboxylation would give the precursor of the corresponding alkaloid **4** or **5**, compound **9**, respectively. Another alternative would be to use chiral aldehyde **10a** as the starting material and then react it with the amine components **2** or **3** by Wu's recently reported Pictet–Spengler/lactamization cascade sequence to give intermediates **12a** [Equation (2)].[27a] The catalytic construction of the quinolizidine core can also be accomplished by using the procedure developed by Franzén and co-workers [Equation (3)].[28,31] Thus, chiral amine *ent*-**7**-catalyzed Michael reaction between enal **13** and amides **14** followed by one-pot acid-mediated Pictet–Spengler cyclization of aminol **15** was used to give the corresponding intermediates **12**. However, this procedure has only been reported for cinnamic aldehydes **13** as acceptors. According to our retrosynthetic analysis, the shortest route to intermediate **12a** would be a one-pot, three-component catalytic asymmetric Michael/Pictet–Spengler/lactamization cascade sequence employing aliphatic enal **13a**, malonate, and either tryptamine **3** or dopamine **2** derivatives as the substrates and chiral amine *ent*-**7** as the catalyst [Equation (4)]. Next, synthetic precursor **12a** could be readily elaborated to alkaloids **4** or **5**, respectively.

Total Synthesis of (–)-Dihydrocorynanthenol (4a)

We embarked on the total syntheses of alkaloids **4** and **5** by investigating the one-pot, three-component cascade reaction sequence between enal **13a**, malonate, and tryptamine **3**. Thus, first, malonate was added to enal **13a** in the presence of catalyst *ent*-**7** (10 mol-%). After complete conversion of **13a** into aldehyde **10a** (as determined by ^{1}H NMR analysis of the crude reaction mixture), amine **3** and trifluoroacetic acid (TFA) were added and the reaction mixture was heated to reflux for 16 h at 50 °C (Scheme 1).[32] To our delight, the multicomponent cascade reaction gave the corresponding quinolizidine derivative **16a**, which was isolated as a single diastereoisomer in good yield and high enantioselectivity (47% yield, >20:1 *dr*, 92% *ee*). We were also able to isolate other diastereoisomers of **16** in 18% yield. The *dr* was 72:18:9:1 (**16a**/**16b**/**16a′**/**16b′**) as determined by ^{1}H NMR analysis of the crude reaction mixture. The relative stereochemistry of diastereoisomers **16** were determined by NOE NMR experiments. Thus, the one-pot cascade reaction proceeds with a good α/β ratio (81:19) and high *anti*/*syn* ratio (90:10). In addition, the β-diastereomeric precursor **17** was also isolated in 18% yield. By comparison, performing the reaction according to Equation (2),[27a] using TFA as the acid mediator, gave **16a** in lower yield and lower α/β and *anti*/*syn* ratios as well as a slight decrease of the *ee*. The total synthesis was continued by reduction of **16a** with $LiAlH_4$ (LAH) to give the corresponding alcohol **18a** in 70% yield. Oxidation of alcohol **18a** was next performed using Swern's conditions.[33] It is noteworthy that this oxidation step gave quinolizidine aldehyde derivative **19** with a chlorine at the C-6 position (8:1 *dr*) when excess oxalyl chloride was used as the reactant.[34] If desired, alkaloid **19** can serve as a valuable precursor for the generation of chlorinated secologanine tryptamine alkaloids. Thus, we reduced the amount of oxalyl chloride to generate alkaloid **20** in 87% yield. Subsequent Wittig reaction gave the corresponding olefin **21** in more than 99% yield. The final one-pot hydrogenation of **21** completed the total synthesis of (–)-dihydrocorynanthenol (**4a**; 86% yield).[35] Thus, we have achieved a five-step enantioselective synthesis of (–)-dihydrocorynanthenol (**4a**) starting from enal **13a**.

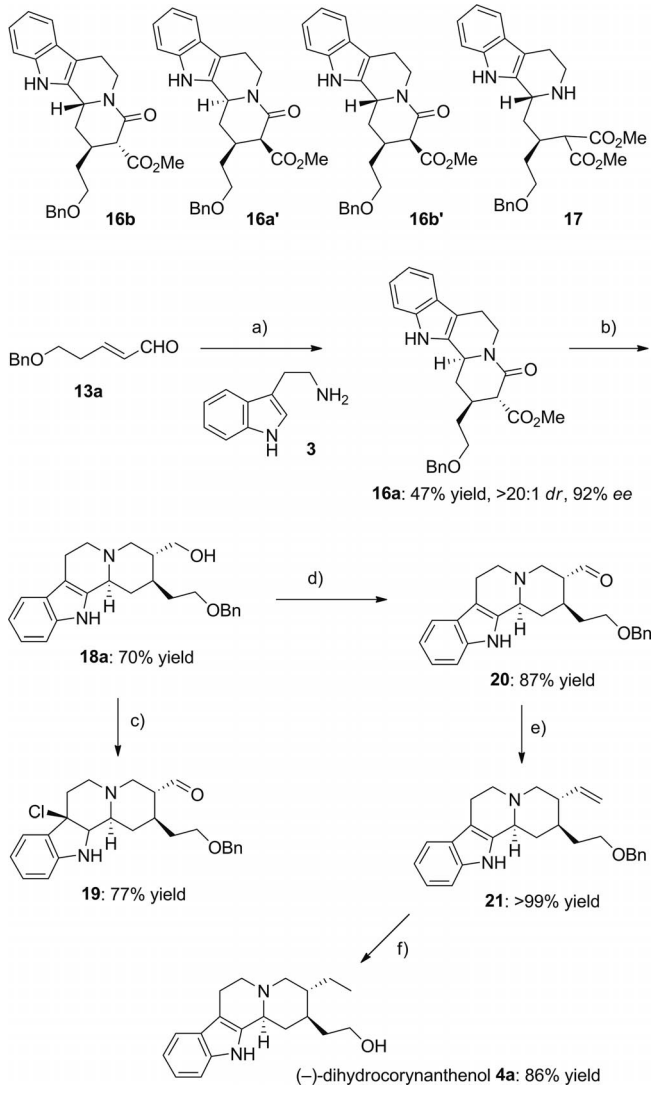
Total Syntheses of Protoemetinol (5a), (–)-Protoemetine (5c), and Emetine (5d)

After completion of the concise assembly of dihydrocorynanthenol (**4a**), we began investigating the total synthesis of protoemetinol (**5a**). Thus, we investigated the one-pot three-component cascade reaction sequence between enal **13a**, malonate, and dopamine derivative **2a**. However, the Pictet–Spengler product was not observed in this case and the Michael adduct **10a** was formed as the predominant product [Equation (5)]. To promote the Pictet–Spengler reaction step, the employment of other acids (e.g., HCl, $BF_3{\cdot}Et_2O$ and formic acid) was investigated; however, no cyclization occurred. Thus, the imine intermediate **22** is not reactive enough under these commonly used Pictet–Spengler conditions.



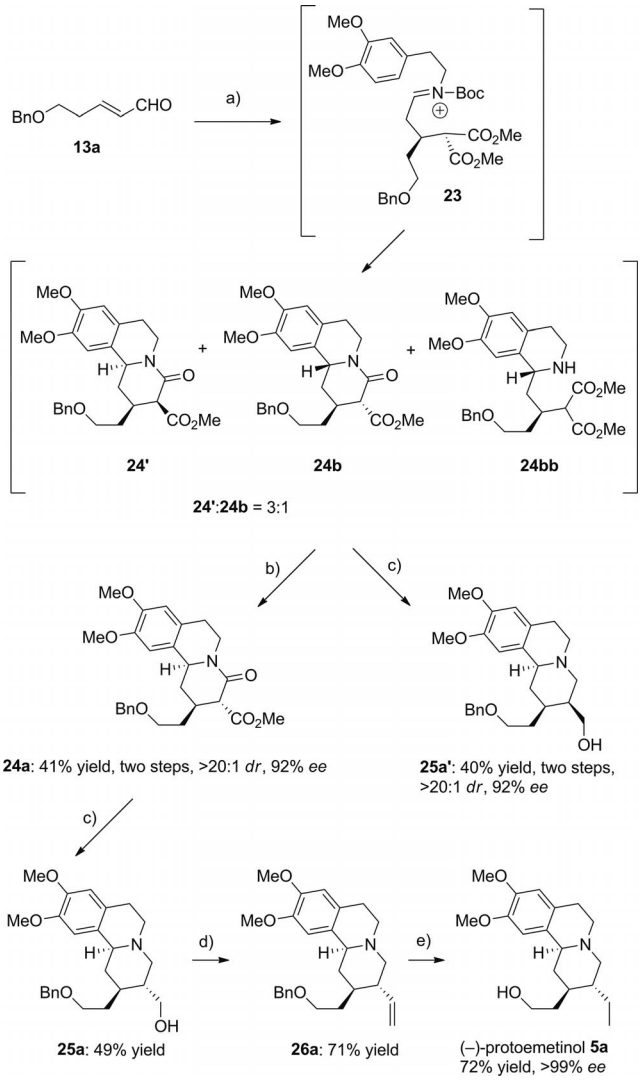
(5)

Because iminium intermediates are more reactive in these types of transformations, we decided to investigate the use of the *N*-Boc protected dopamine derivative **2b** as the amine component (Scheme 2).[36] Thus, we envisioned a one-pot, three-component catalytic asymmetric tandem Michael/Pictet–Spengler/lactamization sequence in which aldehyde **10a**, generated in situ, would condense with amine **2b** to form the reactive iminium intermediate **23** and allow the formation of the desired product **24**. To our delight, the one-pot reaction was successful and the corresponding quinolizidine derivatives **24a′** and **24b** were formed in a 3:1 ratio as the predominant diastereoisomers, together with **24bb**. Isolation by silica gel column chromatography gave



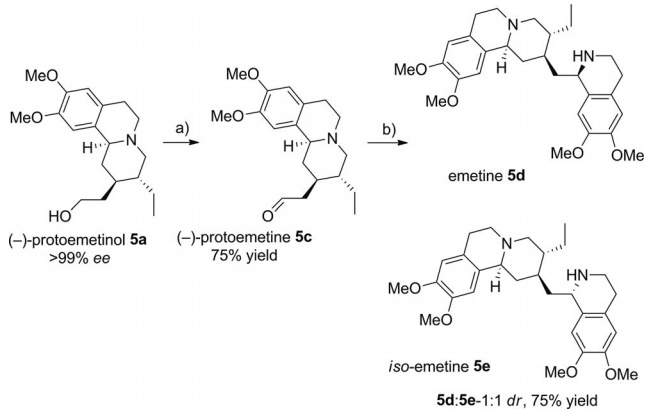
Scheme 1. Reagents and conditions: (a) (i) $CH_2(CO_2Me)_2$, cat. *ent*-**7** (10 mol-%), EtOH, room temp. (ii) **3**, TFA (1 equiv.), CH_2Cl_2, 50 °C. (b) $LiAlH_4$, THF, reflux. (c) $(COCl)_2$ (2 equiv.), DMSO, CH_2Cl_2, TEA, –78 °C. (d) $(COCl)_2$ (0.95 equiv.), DMSO, CH_2Cl_2, TEA, –78 °C. (e) Ph_3PMeBr, BuLi, THF. (f) (i) H_2 (95–115 psi), Pd/C, MeOH. (ii) 3 N HCl, H_2 (95–115 psi), Pd/C, MeOH.

the diastereoisomers **24** in 60% combined yield, and **24bb** in 26% yield with 97% *ee*. To install the same relative stereochemistry as that of alkaloid **5a**, the crude diastereomeric mixture containing α-isomer **24a′** was epimerized using lithium diisopropylamide (LDA) to give **24a** in 41% yield (two steps from **13a**) with more than 20:1 *dr* and 92% *ee*. The other diastereoisomers (**24b**, **24a′**, and **24b′**) were isolated in 16% yield with a respective ratio of 55:28:17. Subsequent, reduction of **24a** with $LiAlH_4$ gave the corresponding alcohol **25a** in 49% yield. The direct reduction of the crude diastereomeric mixture of **24a′** and **24b** (3:1) and **24bb** gave the corresponding alcohol **25a′** in 40% yield (two steps from **13a**) with more than 20:1 *dr* and 92% *ee*. Alcohol **25a** was more resistant to the Swern conditions as compared to alcohol **17**, and we were therefore able to perform a one-pot tandem oxidation/Wittig sequence to give olefin **26a** in 71% yield. The final one-pot hydrogenation of **26a** completed the total synthesis of (–)-protoemetinol (**5a**; 72% yield). Thus, the synthesis of the complex natural product was completed in only four isolation steps. Determination of the *ee* of **5a** showed that it was more than 99%. The optical purification had possibly occurred during the work-up and isolation by recrystallization. We next completed the total synthesis of (–)-protoemetine (**5c**) in 75% yield by using the Swern conditions (Scheme 3). It is noteworthy that protometine **5c** serves as an important precursor for a diverse range of biologically active natural products (e.g., emetine, cephaeline, and tubolosine), which can be prepared by the Pictet–Spengler reaction with dopamine **2** and tryptamine derivatives **3**, respectively. This was exemplified by the one-step synthesis of the ipecacuanha alkaloid emitine **5d** and *iso*-emitine **5e** (**5d**/**5e**, 1:1) in 76%



Scheme 2. Reagents and conditions: (a) (i) $CH_2(CO_2Me)_2$, cat. *ent*-**7** (10 mol-%), EtOH, room temp. (ii) **2b**, HCl (4 N, dioxane), CH_2Cl_2, room temp. (b) LDA, THF, –78 °C. (c) $LiAlH_4$, THF, reflux. (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, –78 °C. (ii) Ph_3PMeBr, BuLi, THF. (e) (i) H_2 (95–115 psi), Pd/C, MeOH. (ii) 3 N HCl, H_2 (95–115 psi), Pd/C, MeOH.

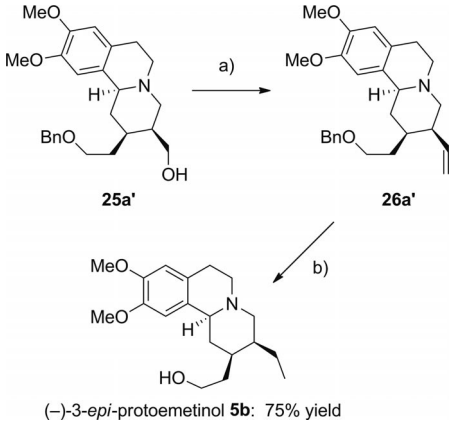
combined yield (Scheme 3). In addition, emitine **5d** can also be prepared stereoselectively in two steps from protometine **5c** using Tietze's procedures.[21]



Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, –78 °C. (b) **2b**, HCl (4N, dioxane), CH_2Cl_2, room temp.

Total Synthesis of (–)-3-*epi*-Protoemetinol (5b)

After completing the total synthesis of secologanine dopamine alkaloids **5a** and **5c**, we finalized the asymmetric synthesis of (–)-3-*epi*-protoemetinol (**5b**; Scheme 4). Thus, performing the one-pot tandem Swern oxidation/Wittig reaction on alcohol **25a′** gave olefin **26a′** in 62% yield. Subsequent one-pot hydrogenation completed the total synthesis of 3-*epi*-protoemetinol (**5b**) in 75% yield.



Scheme 4. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, –78 °C. (ii) Ph_3PMeBr, BuLi, THF. (b) (i) H_2 (95–115 psi), Pd/C, MeOH. (ii) 3 N HCl, H_2 (95–115 psi), Pd/C, MeOH.

Conclusions

We have developed a divergent strategy for the concise total synthesis of secologanine, dopamine, and tryptamine alkaloids through a one-pot, three-component catalytic asymmetric Michael/Pictet–Spengler/lactamization cascade reaction. The total syntheses also included two further one-pot reactions: a tandem Swern oxidation/Wittig and a tandem hydrogenation sequence. The concept of biomimetic synthetic divergent assembly of secologanine natural products was demonstrated by the expeditious total syntheses of (–)-dihydrocorynanthenol (five steps), (–)-protoemetinol (more than 99% *ee*; four steps), (–)-protoemetine (more than 99% *ee*; five steps), (–)-3-*epi*-protoemetinol (three steps), and the total synthesis of emetine (six steps). Studies towards the total synthesis of other natural products, diversity oriented synthesis, and generation of natural-product-like libraries using the disclosed divergent catalytic asymmetric multicomponent approach are ongoing in our laboratories.

Experimental Section

General Methods: Chemicals and solvents were either purchased as puriss P. A. grade from commercial suppliers or purified by standards techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used; compounds were visualized by irradiation with UV light and/or by treatment with a solution of ammonium molybdate (100 g), $Ce(SO_4)_2$ (2 g), and 10% H_2SO_4 (1 L) followed by heating, or by treatment with a solution of potassium permanganate (3 g), K_2CO_3 (20 g), 5% aq. NaOH (5 mL) and water (300 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded with a Bruker AM400 spectrometer. Chemical shifts are given in δ units (ppm) relative to tetramethylsilane (TMS); coupling constants (J) are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature; $CDCl_3$ served as internal standard (δ = 7.26 ppm for ^1H NMR and δ = 77.16 ppm for ^{13}C NMR). Peaks are labeled as: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). HPLC was carried out with a Waters 2690 Millenium fitted with a photodiode array detector. Optical rotations were recorded with a Perkin–Elmer 241 Polarimeter (d = 589 nm, 1 dm cell). High-resolution mass spectra (ESI) were obtained with a Bruker MicroTOF spectrometer.

Typical Experimental Procedure for the Catalytic Asymmetric One-Pot, Three-Component Reaction Between 13a, 3, and Malonate: To a pressure tube containing a solution of enal **13a** (190 mg, 1.0 mmol) in EtOH (2.0 mL), was added catalyst *ent*-**7** (32 mg, 0.1 mmol). After stirring for 2 min, dimethyl malonate (0.34 mL, 3 mmol) was added. The reaction was stirred at room temperature for 64 h to reach full conversion. The solvent was removed under reduced pressure and CH_2Cl_2 (100 mL), tryptamine **3** (240 mg, 1.5 mmol), and trifluoroacetic acid (76 μL, 1.0 mmol) were sequentially added and the sealed tube was heated in an oil bath at 50 °C. After 16 h, the temperature was decreased to room temperature and the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (60 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered and concentrated. The residue was separated with flash chromatography on silica gel (pentane/EtOAc, 2:1 to 2:3) to furnish the product **16a** (204 mg, 47% yield). The other diastereoisomers **16** were also isolated as a mixture of three diastereomers (78 mg, 18% yield; **16b**/**16a′**/**16b′** = 67:26:7). The flash system was then changed to EtOAc/MeOH, 10:1 and **17** (R_f = 0.34; EtOAc/MeOH, 10:1) was isolated (84 mg, 18% yield). Heating **17** in CH_2Cl_2 (20 mL) using a sealed pressure tube gave another crop of product **16b** and **16b′** (**16b**/**16b′** = 84:16, 100 mg).

Methyl (2*R*,3*R*,12b*S*)-2-[2-(Benzyloxy)ethyl]-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (16a): R_f = 0.32 (pentane/EtOAc, 1:1); ^{1}H NMR: δ = 8.33 (br., 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.38–7.30 (m, 6 H), 7.22–7.18 (m, 1 H), 7.15–7.11 (m, 1 H), 5.15–5.10 (m, 1 H), 4.78 (dd, J = 11.2, 3.2 Hz, 1 H), 4.54 (d, J = 12.0 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 3.73 (s, 3 H), 3.63–3.57 (m, 2 H), 3.21 (d, J = 11.6 Hz, 1 H), 2.93–2.75 (m, 3 H), 2.60–2.51 (m, 2 H), 1.83–1.77 (m, 1 H), 1.57–1.50 (m, 1 H), 1.40 (q, J = 12.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 171.2, 165.4, 138.4, 136.4, 132.8, 128.5, 127.9, 127.8, 126.7, 122.2, 119.8, 118.4, 111.1, 108.9, 72. 8, 66.9, 56.5, 53.7, 52.5, 40.3, 33.8, 33.3, 32.3, 21.0 ppm. HRMS (ESI): calcd. for $C_{26}H_{28}N_2O_4Na$ [M + Na]$^+$ 455.1941; found 455.1945. $[a]_D^{25}$ = –53.9 (c = 1.0, $CHCl_3$) for an enantiomerically enriched sample of 92% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (AD column; *i*-hexane/*i*-PrOH, 70:30; 0.5 mL/min; 222 nm); t_r = 22.9 (minor enantiomer), 40.2 (major enantiomer) min.

Methyl (2*R*,3*S*,12b*S*)-2-[2-(Benzyloxy)ethyl]-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (16a′): R_f = 0.17 (pentane/EtOAc, 1:1); ^{1}H NMR: δ = 7.59 (br., 1 H), 7.50 (d, J = 6.0 Hz, 1 H), 7.42–7.31 (m, 6 H), 7.21–7.17 (m, 1 H), 7.14–7.11 (m, 1 H), 5.18–5.12 (m, 1 H), 4.74 (dd, J = 8.8, 4.0 Hz, 1 H), 4.58 (d, J = 9.6 Hz, 1 H), 4.49 (d, J = 9.6 Hz, 1 H), 3.68–3.60 (m, 6 H), 2.90–2.86 (m, 2 H), 2.82–2.77 (m, 1 H), 2.46–2.44 (m, 1 H), 2.18–2.07 (m, 2 H), 1.79–1.74 (m, 1 H), 1.62–1.57 (m, 1 H) ppm. ^{13}C NMR: δ = 170.0, 165.0, 138.5, 136.4, 132.8, 128.7, 128.2, 128.0, 127.0, 122.4, 120.1, 118.6, 111.0, 109.7, 73.2, 67.0, 54.2, 52.7, 52.4, 40.6, 32.4, 31.0, 30.3, 21.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{28}N_2O_4Na$ [M + Na]$^+$ 455.1941; found 455.1943. The relative configuration of compound **16a′** was determined by an epimerization experiment with LDA (**16a**/**16a′** = 4:1).

Methyl (2*R*,3*S*,12b*R*)-2-[2-(Benzyloxy)ethyl]-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (16b′): R_f = 0.17 (pentane/EtOAc, 1:1); ^{1}H NMR: δ = 7.48–7.45 (m, 2 H), 7.39–7.33 (m, 5 H), 7.17–7.09 (m, 3 H), 5.07–5.00 (m, 1 H), 4.97 (br., 1 H), 4.48 (q, J = 9.7 Hz, 2 H), 3.74 (s, 3 H), 3.68–3.63 (m, 1 H), 3.55–3.50 (m, 2 H), 3.00–2.92 (m, 2 H), 2.73–2.67 (m, 1 H), 2.58–2.52 (m, 1 H), 2.25–2.20 (m, 1 H), 2.16–2.13 (m, 1 H), 1.83–1.77 (m, 1 H), 1.75–1.67 (m, 1 H) ppm. ^{13}C NMR: δ = 170.1, 165.4, 138.4, 136.1, 133.2, 128.8, 128.1, 127.9, 127.4, 122.3, 120.0, 118.4, 111.2, 110.8, 73.3, 68.6, 53.5, 53.1, 52.4, 42.5, 31.12, 31.08, 29.0, 21.0 ppm. HRMS (ESI): calcd. for $C_{26}H_{28}N_2O_4Na$ [M + Na]$^+$ 455.1941; found 455.1939.

Methyl (2*R*,3*R*,12b*R*)-2-[2-(Benzyloxy)ethyl]-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (16b): R_f = 0.15 (pentane/EtOAc, 1:1); ^{1}H NMR: δ = 7.47 (d, J = 6.0 Hz, 1 H), 7.43–7.36 (m, 6 H), 7.17–7.15 (m, 2 H), 7.13–7.09 (m, 1 H), 5.09–5.05 (m, 1 H), 4.87–4.84 (m, 1 H), 4.55 (d, J = 9.2 Hz, 1 H), 4.50 (d, J = 9.2 Hz, 1 H), 3.71–3.69 (m, 1 H), 3.68 (s, 3 H), 3.61–3.57 (m, 1 H), 3.35 (d, J = 4.4 Hz, 1 H), 2.95–2.89 (m, 2 H), 2.75–2.72 (m, 1 H), 2.47–2.24 (m, 1 H), 2.20–2.16 (m, 1 H), 1.80–1.75 (m, 2 H) ppm. ^{13}C NMR: δ = 170.8, 165.3, 138.3, 136.2, 132.8, 128.7, 128.0, 127.9, 127.1, 122.1, 119.8, 118.3, 111.2, 109.9, 73.2, 68.3, 54.8, 52.6, 51.7, 41.4, 32.5, 31.6, 30.1, 21.0 ppm. HRMS (ESI): calcd. for $C_{26}H_{28}N_2O_4Na$ [M + Na]$^+$ 455.1941; found 455.1946. $[a]_D^{25}$ = 25.0 (c = 1.0, $CHCl_3$) for an enantiomerically enriched sample of 95% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (AD column; *i*-hexane/*i*-PrOH, 70:30; 0.5 mL/min; 222 nm); t_r = 22.3 (major enantiomer), 29.7 (minor enantiomer) min.

{(2*R*,3*R*,12b*S*)-2-[2-(Benzyloxy)ethyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-3-yl}methanol (18a): Under an N_2 atmosphere, a solution of compound **16a** (392 mg, 0.91 mmol) in dry THF (50 mL) was cooled to 0 °C with an ice-bath. $LiAlH_4$ (138 mg, 3.6 mmol) was added portionwise (over 20 min) to this vigorously stirred solution. The reaction was stirred at this temperature for 30 min and then heated to reflux for 15 h. After decreasing the temperature to 0 °C with an ice-bath, the reaction was carefully quenched with the addition of a small amount of water (added dropwise). The mixture was dried with anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (EtOAc/MeOH, 15:1 to 8:1) to furnish the alcohol product **18a** (248 mg, 70% yield). R_f = 0.24 (EtOAc/MeOH, 10:1); ^{1}H NMR: δ = 7.55 (br., 1 H), 7.47 (d, J = 6.4 Hz, 1 H), 7.42–7.35 (m, 5 H), 7.29 (d, J = 6.4 Hz, 1 H), 7.15–7.12 (m, 1 H), 7.10–7.07 (m, 1 H), 4.61 (d, J = 9.6 Hz, 1 H), 4.47 (d, J = 9.6 Hz, 1 H), 3.74–3.67 (m, 2 H), 3.63–3.55 (m, 2 H), 3.20–3.09 (m, 3 H), 3.03–2.96 (m, 1 H), 2.74–2.71 (m, 1 H), 2.61 (td, J = 9.0, 3.5 Hz, 1 H), 2.37 (t, J = 8.8 Hz, 1 H), 2.07–2.01 (m, 2 H), 1.72 (br., 3 H), 1.47–1.41 (m, 1 H), 1.32 (q, J = 9.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 138.5, 136.1, 134.8, 128.7, 128.3, 128.0, 127.6, 121.5, 119.6, 118.3, 110.8, 108.3, 73.2, 67.8, 63.4, 59.8, 59.1, 53.2, 43.7, 35.5, 34.2, 32.8, 21.8 ppm. HRMS (ESI): calcd. for $C_{25}H_{31}N_2O_2$ [M + H]$^+$ 391.2380; found 391.2389. $[a]_D^{25}$ = 4.9 (c = 1.0, MeOH).

(2*R*,3*R*,12b*S*)-2-[2-(Benzyloxy)ethyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carbaldehyde (20): Under an N_2 atmosphere, to a Schlenk tube containing a solution of oxalyl chloride (12 μL, 0.142 mmol) in dry CH_2Cl_2 (1 mL), was added dropwise a solution of DMSO (21 μL, 0.297 mmol) in CH_2Cl_2 (1 mL) at –78 °C. After stirring for 10 min, a solution of compound **18a** (58 mg, 0.148 mmol) in DMSO/CH_2Cl_2 (2.2 mL, 1:10) was added dropwise over 5 min. The reaction was stirred for 30 min. Next, Et_3N (104 μL, 0.743 mmol) was added dropwise and the mixture was stirred for 15 min. The cold bath was removed and the reaction mixture was stirred for an additional 10 min. Water (2 mL) was added to quench the reaction, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2× 2 mL each). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was separated by flash chromatography on silica gel (pentane/EtOAc, 1:1) to give compound **20** (48 mg, 87% yield). The flash system was changed to EtOAc/MeOH (8:1) and 5 mg of excess compound **18a** could be recovered. R_f = 0.30 (pentane/EtOAc, 1:1); ^{1}H NMR: δ = 9.73 (d, J = 2.8 Hz, 1 H), 7.55 (br., 1 H), 7.47 (d, J = 7.6 Hz, 1 H), 7.42–7.36 (m, 5 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.16 (td, J = 7.1, 1.2 Hz, 1 H), 7.12–7.08 (m, 1 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 3.61–3.57 (m, 2 H), 3.23 (dd, J = 11.4, 1.7 Hz, 1 H), 3.15 (dd, J = 11.3, 4.1 Hz, 1 H), 3.12–3.08 (m, 1 H), 3.02–2.94 (m, 1 H), 2.77–2.72 (m, 1 H), 2.68–2.57 (m, 2 H), 2.43 (t, J = 11.2 Hz, 1 H), 2.17–2.09 (m, 2 H), 1.97–1.92 (m, 1 H), 1.53–1.47 (m, 1 H), 1.29 (q, J = 11.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 203.2, 138.5, 136.1, 134.2, 128.6, 128.2, 127.9, 127.3, 121.5, 119.5, 118.3, 110.8, 108.1, 72.8, 66.9, 59.0, 54.6, 54.4, 52.8, 34.3, 33.7, 33.0, 21.7 ppm. HRMS (ESI): calcd. for $C_{25}H_{29}N_2O_2$ [M + H]$^+$ 389.2224; found 389.2231. $[a]_D^{25}$ = –22.5 (c = 1.0, $CHCl_3$).

(2*R*,3*R*,12b*S*)-2-[2-(Benzyloxy)ethyl]-3-vinyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (21): Under an N_2 atmosphere, methyltriphenylphosphonium bromide (40 mg, 0.113 mmol) was suspended in dry THF (1 mL) in a Schlenk tube at 0 °C. BuLi (2.5 M in hexane, 45 μL, 0.113 mmol) was added dropwise. After stirring for 30 min at this temperature, the mixture was cooled to –78 °C, compound **20** (22 mg, 0.057 mmol) was added dropwise as a solution in THF (1 mL). The reaction was continued at the same temperature for 1 h and then at 0 °C for 30 min. Water (1 mL) was added to quench the reaction and the mixture was extracted with

CH_2Cl_2 (3 × 2 mL). The organic extracts were then combined, dried with anhydrous Na_2SO_4, filtered, concentrated, and purified with by chromatography on silica gel (pentane/EtOAc, 2:1) to give compound **21** (22 mg, >99% yield). R_f = 0.41 (pentane/EtOAc, 2:1); ^{1}H NMR: δ = 7.54 (br., 1 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.44–7.37 (m, 5 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.17–7.13 (m, 1 H), 7.11–7.03 (m, 1 H), 5.66–5.57 (m, 1 H), 5.15–5.09 (m, 2 H), 4.61 (d, J = 12.0 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 3.58 (dd, J = 7.4, 5.3 Hz, 2 H), 3.19 (dd, J = 11.4, 1.6 Hz, 1 H), 3.10–3.06 (m, 1 H), 3.04–2.94 (m, 2 H), 2.75–2.70 (m, 1 H), 2.63–2.56 (m, 1 H), 2.29 (t, J = 11.0 Hz, 1 H), 2.25–2.20 (m, 1 H), 2.08–2.00 (m, 2 H), 1.61–1.56 (m, 1 H), 1.35–1.19 (m, 2 H) ppm. ^{13}C NMR: δ = 139.7, 138.9, 136.1, 134.9, 128.6, 128.2, 127.9, 127.5, 121.4, 119.5, 118.3, 116.9, 110.8, 108.2, 72.8, 67.5, 61.4, 59.7, 53.0, 47.6, 37.2, 34.9, 33.3, 21.9 ppm. HRMS (ESI): calcd. for $C_{26}H_{31}N_2O$ $[M + H]^+$ 387.2431; found 387.2426. $[\alpha]_D^{25}$ = –16.5 (c = 1.0, $CHCl_3$).

(–)-Dihydrocorynanthenol (4a): Compound **21** (18 mg, 0.047 mmol) was stirred in MeOH (1 mL) under H_2 pressure (115 to 95 psi) with Pd/C (10%; 1 mg) overnight (ca. 16 h). HCl (3 M in water, 31 μL, 0.093 mmol) was added and, after stirring for 2 min, Pd/C (10%; 1 mg) was added and the reaction was continued for 24 h under H_2 pressure (115 to 95 psi). The mixture was then filtered through Celite and concentrated on a rotavapor to remove MeOH. The residue was dispersed in saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (2 mL). The phases were separated and the aqueous layers was extracted with CH_2Cl_2 (2 × 2 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography on silica gel (EtOAc/MeOH, 10:1) to furnish the final product **4a** (12 mg, 86% yield). R_f = 0.29 (EtOAc/MeOH, 10:1); ^{1}H NMR: δ = 8.20 (br., 1 H), 7.46 (d, J = 7.2 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.15–7.06 (m, 2 H), 3.75–3.71 (m, 2 H), 3.15–2.97 (m, 4 H), 2.90 (br., 1 H), 2.72 (d, J = 15.0, 4.2 Hz, 1 H), 2.56 (td, J = 11.0, 4.4 Hz, 1 H), 2.22 (d, J = 12.4 Hz, 1 H), 2.06–1.92 (m, 2 H), 1.69–1.60 (m, 1 H), 1.49–1.24 (m, 4 H), 1.17–1.06 (m, 1 H), 0.90 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 136.3, 134.8, 127.5, 121.5, 119.5, 118.3, 111.0, 108.0, 60.44, 60.41, 59.9, 53.1, 41.7, 37.2, 35.6, 35.4, 23.6, 21.7, 11.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{27}N_2O$ $[M + H]^+$ 299.2118; found 299.2113. $[\alpha]_D^{25}$ = –15.1 (c = 1.0, $CHCl_3$).

(2*R*,3*R*,12b*S*)-2-[2-(Benzyloxy)ethyl]-7a-chloro-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-*a*]quinolizine-3-carbaldehyde (19): Under an N_2 atmosphere, to a Schlenk tube containing a solution of oxalyl chloride (8 μL, 0.092 mmol) in dry CH_2Cl_2 (0.5 mL) at –78 °C, was added dropwise a solution of DMSO (14 μL, 0.184 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 10 min, a solution of compound **18a** (18 mg, 0.046 mmol) in DMSO/CH_2Cl_2 (1.1 mL, 1:10) was added dropwise over 5 min. The reaction was stirred for 30 min, then Et_3N (64 μL, 0.46 mmol) was added dropwise. The mixture was stirred for 15 min then the cold bath was removed and the stirring was continued for a further 10 min. Water (2 mL) was added to quench the reaction. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was separated with flash chromatography on silica gel (pentane/EtOAc, 1:1) to give compound **19** (*dr* ca. 8:1, 15 mg, 77% yield). R_f = 0.22 (pentane/EtOAc, 1:1); ^{1}H NMR: δ (major diastereomer) = 9.73 (d, J = 2.0 Hz, 1 H), 7.64 (d, J = 6.2 Hz, 1 H), 7.50–7.48 (m, 1 H), 7.43–7.39 (m, 1 H), 7.34–7.27 (m, 6 H), 4.49 (dd, J = 17.5, 9.5 Hz, 2 H), 3.61 (dd, J = 5.6, 4.4 Hz, 2 H), 3.35 (dd, J = 8.8, 1.7 Hz, 1 H), 3.10–3.08 (m, 1 H), 2.95–2.90 (m, 1 H), 2.84–2.81 (m, 1 H), 2.58 (dt, J = 11.6, 1.9 Hz, 1 H), 2.51–2.43 (m, 2 H), 2.35 (dt, J = 10.8, 1.3 Hz, 1 H), 2.13–2.06 (m, 1 H), 1.97–1.90 (m, 1 H), 1.86–1.80 (m, 1 H), 1.73 (q, J = 9.8 Hz, 1 H), 1.68–1.62 (m, 1 H) ppm. ^{13}C NMR: δ (major diastereomer) = 203.2, 179.5, 152.7, 140.3, 138.4, 130.3, 128.6, 127.9, 127.8, 127.0, 122.8, 121.7, 73.1, 68.8, 67.2, 58.5, 54.9, 54.3, 50.2, 37.6, 34.0, 32.8, 31.6 ppm. HRMS (ESI): calcd. for $C_{25}H_{28}ClN_2O_2$ $[M + H]^+$ 423.1834; found 423.1827. $[\alpha]_D^{25}$ = 35 (c = 0.5, $CHCl_3$).

Typical Experimental Procedure for the Catalytic Asymmetric One-Pot, Three-Component Reaction Between 13a, 2, and Malonate: To a round-bottom flask containing a solution of enal **13a** (190 mg, 1 mmol) in EtOH (2.0 mL), was added catalyst *ent*-**7** (32 mg, 0.1 mmol). After stirring for 2 min, dimethyl malonate (0.34 mL, 3 mmol) was added and the reaction was stirred at room temperature for 64 h to reach full conversion. The solvent was removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (2 mL). After addition of amide **2b** (338 mg, 1.2 mmol), the solution was cooled with an ice-bath and HCl (4.0 M in dioxane, 2 mL, 8 mmol) was slowly added. After complete addition, the temperature was increased to room temperature and the mixture was stirred for 90 min and then poured into water (10 mL). To neutralize the acid, excess solid Na_2CO_3 was carefully added. The resulting mixture was extracted with CH_2Cl_2 (4 × 7 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification using silica gel flash chromatography (EtOAc) gave compounds **24** (272 mg, 60% yield) as a mixture of diastereoisomers (**24a′**/**24b**, 3:1). The mixture was then dissolved in dry THF (15 mL) and the resulting solution was cooled to –78 °C under an N_2 atmosphere, followed by dropwise addition of LDA (2.0 M in THF, 0.55 mL, 1.1 mmol). After stirring this mixture for 3 h at this temperature, the dry ice-acetone bath was replaced with an ice-bath. Water (5 mL) was added to the reaction solution and stirring was continued for 30 min. The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the extracts were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography using silica gel (pentane/EtOAc: 2:3 to 1:4) afforded pure compound **24a** (188 mg, 41% yield based on enal **13a**) and a mixture of the other diastereomers of **24** (72 mg, 16% yield from enal **13a**).

Methyl (2*R*,3*R*,11b*S*)-2-[2-(Benzyloxy)ethyl]-9,10-dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (24a): R_f = 0.60 (EtOAc); ^{1}H NMR: δ = 7.35–7.31 (m, 4 H), 7.30–7.27 (m, 1 H), 6.60 (s, 1 H), 6.55 (s, 1 H), 4.84–4.79 (m, 1 H), 4.67 (dd, J = 11.2, 4.0 Hz, 1 H), 4.54 (d, J = 11.6 Hz, 1 H), 4.46 (d, J = 11.6 Hz, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.65–3.57 (m, 2 H), 3.19 (d, J = 11.2 Hz, 1 H), 2.90–2.80 (m, 2 H), 2.67–2.51 (m, 3 H), 1.82–1.74 (m, 1 H), 1.64–1.58 (m, 1 H), 1.39 (q, J = 12.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 171.4, 165.4, 148.1, 148.0, 138.4, 128.57, 128.53, 127.85, 127.76, 127.11, 111.6, 108.4, 73.1, 67.6, 56.3, 56.2, 56.1, 52.6, 40.0, 36.1, 34.3, 32.9, 28.5 ppm. HRMS (ESI): calcd. for $C_{26}H_{31}NO_6Na$ $[M + Na]^+$ 476.2044; found 476.2046. $[\alpha]_D^{25}$ = –15.1 (c = 1.0, $CHCl_3$) for an enantiomerically enriched sample of 92% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (AS column; *i*-hexane/*i*-PrOH, 70:30; 0.5 mL/min; 210 nm): t_r = 37.4 (minor enantiomer), 49.9 (major enantiomer) min.

{(2*R*,3*R*,11b*S*)-2-[2-(Benzyloxy)ethyl]-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl}methanol (25a): Compound **24a** (421 mg, 0.93 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C with an ice-bath. To this vigorously stirred solution, $LiAlH_4$ (141 mg, 3.72 mmol) was added carefully at this temperature. After stirring for an additional 30 min at this

temperature the resulting reaction mixture was heated to reflux for 16 h. After decreasing the temperature again to 0 °C with an ice-bath, the reaction was carefully quenched with a small amount of water (added dropwise). The mixture was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 10:1 to 6:1) to give the corresponding alcohol product **25a** (188 mg, 49% yield). R_f = 0.25 (EtOAc/MeOH, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.33 (m, 4 H), 7.30–7.28 (m, 1 H), 6.63 (s, 1 H), 6.57 (s, 1 H), 4.54 (dd, J = 14.8, 9.6 Hz, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.73–3.67 (m, 2 H), 3.62–3.58 (m, 2 H), 3.07 (d, J = 9.2 Hz, 3 H), 2.99–2.96 (m, 1 H), 2.64–2.61 (m, 1 H), 2.52–2.47 (m, 1 H), 2.32–2.28 (m, 2 H), 2.08 (s, 1 H), 2.02–1.95 (m, 1 H), 1.69–1.67 (m, 2 H), 1.56–1.51 (m, 1 H), 1.27 (q, J = 9.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 147.2, 138.2, 129.9, 128.6, 127.9, 127.8, 126.8, 111.6, 108.4, 73.3, 68.5, 63.4, 62.6, 59.9, 56.2, 55.9, 52.4, 43.0, 37.5, 34.9, 33.0, 29.2 ppm. HRMS (ESI): calcd. for $C_{25}H_{33}NO_4$ [M + H]$^+$ 412.2482; found 412.2484. $[\alpha]_D^{25}$ = –7.9 (c = 1.0, $CHCl_3$).

(2*R*,3*R*,11b*S*)-2-[2-(Benzyloxy)ethyl]-9,10-dimethoxy-3-vinyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline (26a): Under an N_2 atmosphere, to a solution of oxalyl chloride (46 μL, 0.55 mmol) in dry CH_2Cl_2 (0.5 mL) in a three-neck flask at –78 °C, was added dropwise a solution of DMSO (85 μL, 1.1 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 10 min, a solution of **25a** (188 mg, 0.46 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The reaction was stirred for 30 min and then Et_3N (0.32 mL, 2.3 mmol) was added dropwise. After complete addition at –78 °C, stirring was prolonged for a further 15 min at this temperature. The temperature was increased to room temperature and, after 10 min stirring, water (2 mL) was added to quench the reaction. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2× 5 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde product. This crude product was then dissolved in dry THF (4 mL). Under an N_2 atmosphere, methyltriphenylphosphonium bromide (326 mg, 0.91 mmol) was suspended in dry THF (3 mL) in a Schlenk tube at 0 °C and BuLi (2.5 M in hexane, 0.37 mL, 0.91 mmol) was added dropwise. After stirring for 30 min at this temperature, the mixture was cooled to –78 °C, the above solution of the crude aldehyde was added dropwise. The reaction was continued at the same temperature for 1 h and then at 0 °C for 30 min. Water (2 mL) was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3× 10 mL). The organic extracts were combined, dried with anhydrous Na_2SO_4, filtered, concentrated, and purified by flash chromatography on silica gel (EtOAc) to give compound **26a** (133 mg, 71% yield). R_f = 0.37 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 4 H), 7.29–7.26 (m, 1 H), 6.62 (s, 1 H), 6.57 (s, 1 H), 5.62–5.56 (m, 1 H), 5.14–5.07 (m, 2 H), 4.52 (dd, J = 14.8, 9.6 Hz, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.59–3.57 (m, 2 H), 3.1 (d, J = 10.4 Hz, 2 H), 2.95–2.90 (m, 1 H), 2.90 (dd, J = 6.0, 2.8 Hz, 1 H), 2.62 (d, J = 12.8 Hz, 1 H), 2.51–2.48 (m, 1 H), 2.35 (dt, J = 5.4, 2.6 Hz, 1 H), 2.24 (t, J = 8.9 Hz, 1 H), 2.20–2.14 (m, 1 H), 2.02–1.96 (m, 1 H), 1.61–1.55 (m, 1 H), 1.44–1.37 (m, 1 H), 1.19 (q, J = 9.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 147.3, 140.0, 138.8, 130.2, 128.5, 127.7, 127.7, 126.9, 116.8, 111.6, 108.5, 72.9, 68.2, 62.6, 62.3, 56.3, 56.0, 52.2, 46.9, 38.0, 36.9, 33.7, 29.8, 29.3 ppm. HRMS (ESI): calcd. for $C_{26}H_{33}NO_3$ [M + H]$^+$ 408.2533; found 408.2526. $[\alpha]_D^{25}$ = –2.96 (c = 1.0, $CHCl_3$).

(–)-Protoemetinol (5a): At room temperature, to a solution of compound **26a** (56 mg, 0.14 mmol) in MeOH (3 mL), was added Pd/C (10%; 3 mg), and the mixture was stirred under H_2 pressure (115 to 95 psi) for 20 h. HCl (3 M in water, 93 μL, 0.3 mmol) was added and, after stirring for 2 min, Pd/C (10%; 3 mg) was added. The reaction was continued for 16 h under H_2 pressure (115 to 95 psi). The mixture was then filtered through Celite and concentrated on a rotavapor to remove MeOH. The residue was dispersed in saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2× 5 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 3;1) to furnish the final product **5a** (16 mg, 72% yield). R_f = 0.29 (EtOAc/MeOH, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (s, 1 H), 6.57 (s, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.82–3.75 (m, 2 H), 3.08 (d, J = 8.8 Hz, 3 H), 3.01–2.98 (m, 1 H), 2.63 (d, J = 12.4 Hz, 1 H), 2.52–2.47 (m, 1 H), 2.34 (d, J = 10.4 Hz, 1 H), 2.07 (t, J = 8 Hz, 1 H), 1.98–1.93 (m, 1 H), 1.72–1.65 (m, 1 H), 1.46 (d, J = 4.4 Hz, 3 H), 1.16 (s, 1 H), 1.15–1.11 (m, 1 H), 0.92 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 147.4, 129.9, 126.8, 111.7, 108.5, 62.8, 61.5, 60.8, 56.3, 56.0, 52.5, 41.3, 37.7, 37.3, 36.1, 29.2, 23.6, 11.2 ppm. HRMS (ESI): calcd. for $C_{26}H_{33}NO_3$ [M + H]$^+$ 320.2220; found 320.2227. $[\alpha]_D^{25}$ = –47.4 (c = 0.5, $CHCl_3$).

2-[(2*R*,3*R*,11b*S*)-3-Ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl]ethyl Acetate: To a solution of protometinol **5a** (5 mg, 0.016 mmol) in CH_2Cl_2 (1 mL), was sequentially added DMAP (1 mg), Et_3N (7 μL, 0.05 mmol), and Ac_2O (3 μL, 0.031 mmol). After 16 h stirring at room temperature, the reaction mixture was directly loaded on a silica gel column and purified by chromatography (EtOAc) to give the corresponding acetylated product (5 mg, 88% yield). R_f = 0.20 (EtOAc); ^{1}H NMR: δ = 6.67 (s, 1 H), 6.57 (s, 1 H), 4.19 (dd, J = 7.5, 6.4 Hz, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.15–3.06 (m, 3 H), 3.01–2.96 (m, 1 H), 2.63 (d, J = 15.1 Hz, 1 H), 2.48 (td, J = 11.4, 4.0 Hz, 1 H), 2.32 (dt, J = 12.7, 3.0 Hz, 1 H), 2.06 (s, 3 H), 2.04–2.00 (m, 2 H), 1.72–1.62 (m, 1 H), 1.54–1.38 (m, 3 H), 1.29–1.21 (m, 1 H), 1.18–1.03 (m, 1 H), 0.92 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.3, 147.7, 147.4, 130.0, 126.8, 111.7, 108.4, 62.78, 62.76, 61.4, 56.3, 56.0, 52.5, 41.2, 38.2, 37.3, 31.9, 29.3, 23.6, 21.2, 11.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}NO_4$ [M + H]$^+$ 362.2326; found 362.2316. $[\alpha]_D^{25}$ = –5.6 (c = 0.25, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (AD column; *i*-hexane/*i*-PrOH, 70:30; 0.5 mL/min; 210.5 nm): t_r = 22.8 (major enantiomer) min.

(–)-Protoemetine (5c): Under an N_2 atmosphere, to a Schlenk tube containing a solution of oxalyl chloride (4 μL, 0.045 mmol) in dry CH_2Cl_2 (0.5 mL) at –78 °C, was added dropwise a solution of DMSO (7 μL, 0.09 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 10 min, a solution of protoemetinol **5a** (12 mg, 0.038 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction was stirred for 30 min, then Et_3N (26 μL, 0.19 mmol) was added dropwise. The mixture was stirred for 15 min, then the cold bath was removed and stirring was continued for a further 10 min. Water (2 mL) was added to quench the reaction, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2× 2 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 15:1) to furnish protoemetine **5c** (9 mg, 75% yield). R_f = 0.13 (EtOAc); ^{1}H NMR: δ = 9.87 (dd, J = 1.9, 1.1 Hz, 1 H), 6.63 (s, 1 H), 6.57 (s, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.12–3.06 (m, 3 H), 2.98–2.95 (m, 1 H), 2.72 (ddd, J = 12.6, 3.0, 1.0 Hz, 1 H), 2.64–2.60 (m, 1 H), 2.49 (td, J = 9.3, 6.1 Hz, 1 H), 2.36–2.30 (m, 2 H), 2.07 (t, J = 9.0 Hz, 1 H), 1.98–1.90 (m, 1 H), 1.62–1.54 (m, 1 H), 1.51–1.44 (m, 1 H), 1.27

(dd, J = 19.3, 9.5 Hz, 1 H), 1.17–1.08 (m, 1 H), 0.93 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 202.7, 147.6, 147.3, 129.7, 126.8, 111.6, 108.3, 62.6, 61.3, 56.2, 56.0, 52.6, 48.3, 41.5, 38.4, 36.1, 29.3, 23.9, 11.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{28}NO_3$ [M + H]$^+$ 318.2064; found 318.2067. $[a]_D^{25}$ = –28 (c = 0.1, $CHCl_3$).

Experimental Procedure for the Synthesis of Emetine: To a vial containing a solution of protoemetine **5c** (7 mg, 0.022 mmol) in dry CH_2Cl_2 (0.1 mL), was added amide **2b** (7 mg, 0.026 mmol). The solution was cooled to 0 °C with an ice-bath, and HCl (4.0 M in dioxane, 0.1 mL, 0.4 mmol) was slowly added. After complete addition, the temperature was increased to room temperature and the mixture was stirred for 90 min, then poured into water (2 mL). Excess solid Na_2CO_3 was added carefully to neutralize the acid, and the resulting mixture was extracted with CH_2Cl_2 (4× 2 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, concentrated, and purified with flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_3·H_2O, 9:1:0.1) to give a mixture of emetine and isoemetine (8 mg, 75% yield, 1:1).

Emetine and Isoemetine (Mixture): R_f = 0.53 (CH_2Cl_2/MeOH/NH_3·H_2O, 9:1:0.5); ^{1}H NMR: δ = 6.75 (s, 1 H, emetine), 6.73 (s, 1 H, emetine), 6.66 (s, 1 H, isoemetine), 6.59–6.52 (m, 5 H), 4.10 (br. d, J = 11.0 Hz, 1 H, emetine), 4.06 (t, J = 5.5 Hz, 1 H, isoemetine), 3.87–3.80 (m, 24 H), 3.30–2.95 (m, 12 H), 2.82–2.59 (m, 8 H), 2.53–2.43 (m, 2 H), 2.37 (br. d, J = 13.0 Hz, 1 H, isoemetine), 2.15–2.01 (m, 3 H), 1.80–1.75 (m, 2 H), 1.67–1.58 (m, 3 H), 1.51–1.41 (m, 3 H), 1.23–1.11 (m, 4 H), 0.95 (t, J = 7.4 Hz, 3 H, isoemetine), 0.90 (t, J = 7.4 Hz, 3 H, emetine) ppm. ^{13}C NMR: δ = 147.7, 147.64, 147.55, 147.50, 147.47, 147.4, 147.29, 47.27, 132.5, 132.2, 130.4, 130.2, 127.2, 127.1, 126.8, 112.2, 112.0, 111.7, 111.6, 109.7, 109.4, 108.8, 108.4, 63.0, 62.6, 61.7, 61.6, 56.4, 56.20, 56.16, 56.1, 56.03, 56.00, 55.98, 55.95, 55.5, 52.7, 52.5, 52.0, 43.7, 43.0, 41.9, 41.3, 40.9, 40.3, 39.6, 37.1, 37.0, 29.8, 29.7, 29.54, 29.45, 24.2, 23.8, 11.5, 11.3 ppm. HRMS (ESI): calcd. for $C_{29}H_{41}N_2O_4$ [M + H]$^+$ 481.3061; found 481.3073.

{(2*R*,3*S*,11b*S*)-2-[2-(Benzyloxy)ethyl]-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl}methanol (25a′): To a flask containing a solution of enal **13a** (190 mg, 1 mmol) in EtOH (2 mL), was added catalyst *ent*-**7** (32 mg, 0.1 mmol). After stirring for 2 min, dimethyl malonate (0.34 mL, 3 mmol) was added and the reaction was stirred at room temperature for 64 h to reach full conversion. The solvent was removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (2 mL). After addition of amide **2b** (338 mg, 1.2 mmol), the solution was cooled with an ice-bath and HCl (4.0 M in dioxane, 2 mL, 8 mmol) was slowly added. After complete addition, the temperature was increased to room temperature and the mixture was stirred for 90 min and then poured into water (10 mL). Excess solid Na_2CO_3 was added carefully to neutralize the acid. The resulting mixture was extracted with CH_2Cl_2 (4× 7 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in dry THF (60 mL) and cooled to 0 °C with an ice-bath. To this solution, $LiAlH_4$ (235 mg, 6 mmol) was added carefully with good stirring. The reaction was stirred at this temperature for 30 min, and then heated to reflux for 16 h. After cooling to 0 °C with an ice-bath, the reaction was carefully quenched by the addition of a small amount of water (added dropwise). The mixture was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was separated with flash chromatography on silica gel (EtOAc/MeOH, 20:1 to 10:1) to furnish the alcohol product **25a′** (165 mg, 40% yield). R_f = 0.29 (EtOAc/MeOH, 10:1); ^{1}H NMR: δ = 7.39–7.32 (m, 4 H), 7.30–7.27 (m, 1 H), 6.61 (s, 1 H), 6.54 (s, 1 H), 4.53 (dd, J = 13.2, 9.6 Hz, 2 H), 3.96 (d, J = 8.8 Hz, 1 H), 3.88 (dd, J = 8.8, 2.4 Hz, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.63–3.55 (m, 3 H), 3.19–3.15 (m, 2 H), 3.07–3.01 (m, 1 H), 2.96 (q, J = 4.4 Hz, 1 H), 2.68 (d, J = 8.8 Hz, 1 H), 2.58 (dd, J = 12.4, 2.0 Hz, 1 H), 2.44 (td, J = 11.8, 3.5 Hz, 1 H), 2.20–2.18 (m, 1 H), 2.07–2.03 (m, 1 H), 1.86–1.78 (m, 2 H), 1.69–1.64 (m, 1 H), 1.61–1.59 (m, 1 H) ppm. ^{13}C NMR: δ = 147.6, 147.4, 138.6, 129.8, 128.5, 127.7, 126.6, 114.4, 108.3, 73.0, 68.0, 64.8, 63.1, 62.3, 56.2, 55.9, 52.8, 37.1, 36.2, 35.5, 33.5, 29.5 ppm. HRMS (ESI): calcd. for $C_{25}H_{34}NO_4$ [M + H]$^+$ 412.2482; found 412.2487. $[a]_D^{25}$ = –50.4 (c = 1.0, $CHCl_3$).

(2*R*,3*S*,11b*S*)-2-[2-(Benzyloxy)ethyl]-9,10-dimethoxy-3-vinyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline (26a′): Under an N_2 atmosphere, to a solution of oxalyl chloride (31 μL, 0.36 mmol) in dry CH_2Cl_2 (0.5 mL) in a three-neck flask at –78 °C, was added dropwise a solution of DMSO (56 μL, 0.73 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 10 min, a solution of compound **25a′** (125 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction was stirred for 30 min, then Et_3N (212 μL, 1.5 mmol) was added dropwise. After complete addition, stirring was prolonged for 15 min at this temperature and for 10 min at room temperature. Water (2 mL) was added to quench the reaction, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2× 5 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde product (120 mg). This crude product was then dissolved in dry THF (3 mL).

Under an N_2 atmosphere, methyltriphenylphosphonium bromide (217 mg, 0.61 mmol) was suspended in dry THF (2 mL) in a Schlenk tube at 0 °C, and BuLi (2.5 M in hexane, 243 μL, 0.61 mmol) was added dropwise. After stirring for 30 min at this temperature, the mixture was cooled to –78 °C, and the above solution of the crude aldehyde was added dropwise. The reaction was continued at the same temperature for 1 h and then at 0 °C for 30 min. Water (2 mL) was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3× 7 mL). The organic extracts were then combined, dried with anhydrous Na_2SO_4, filtered, concentrated, and purified with flash chromatography on silica gel (pentane/EtOAc, 2:1) to give **26a′** (77 mg, 62% yield). R_f = 0.35 (pentane/EtOAc, 2:1); ^{1}H NMR: δ = 7.39–7.35 (m, 4 H), 7.31–7.28 (m, 1 H), 6.68 (s, 1 H), 6.59 (s, 1 H), 6.24–6.17 (m, 1 H), 5.07 (br., 1 H), 5.04 (dd, J = 4.8, 1.6 Hz, 1 H), 4.55 (t, J = 10.1 Hz, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.61–3.54 (m, 2 H), 3.11–3.06 (m, 2 H), 2.89 (dd, J = 8.9, 1.8 Hz, 1 H), 2.86–2.82 (m, 1 H), 2.59–2.56 (m, 2 H), 2.46–2.41 (m, 1 H), 2.30 (q, J = 2.5 Hz, 1 H), 2.07 (d, J = 10.0 Hz, 1 H), 2.00–1.93 (m, 1 H), 1.66–1.54 (m, 2 H), 1.36 (dd, J = 19.2, 10.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.4, 147.2, §38.9, 138.7, 130.6, 128.4, 127.7, 127.6, 127.2, 115.9, 111.6, 108.3, 72.9, 67.7, 63.3, 62.7, 56.2, 55.9, 52.9, 43.1, 36.1, 34.3, 34.0, 29.4 ppm. HRMS (ESI): calcd. for $C_{26}H_{34}NO_3$ [M + H]$^+$ 408.2533; found 408.2541. $[a]_D^{25}$ = –65.4 (c = 1.0, $CHCl_3$).

(–)-3-*epi*-Protometinol (5b): To a solution of **26a′** (66 mg, 0.16 mmol) in MeOH (3.2 mL) was added Pd/C (10%; 2 mg) at room temperature, and the mixture was stirred under H_2 pressure (115 to 95 psi) for 20 h. HCl (3 M in water, 108 μL, 0.32 mmol) was added and, after stirring for 2 min, Pd/C (10%; 2 mg) was added and the reaction was continued for 16 h under H_2 pressure (115 to 95 psi). The mixture was then filtered through Celite and concentrated on a rotavapor to remove MeOH. The residue was dispersed in saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL), then the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2× 5 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pres-

sure. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 10:1) to furnish the final product **5b** (39 mg, 75% yield). R_f = 0.37 (EtOAc/MeOH, 10:1); ^{1}H NMR: δ = 6.69 (s, 1 H), 6.57 (s, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.76–3.74 (m, 2 H), 3.10–2.97 (m, 3 H), 2.84 (dd, J = 9.2, 4.8 Hz, 1 H), 2.57 (d, J = 12.4 Hz, 1 H), 2.44 (td, J = 9.3, 3.0 Hz, 1 H), 2.29 (dd, J = 9.2, 2.0 Hz, 1 H), 2.04–2.00 (m, 1 H), 1.94–1.87 (m, 2 H), 1.69–1.55 (m, 3 H), 1.47–1.45 (m, 1 H), 1.35–1.26 (m, 2 H), 0.91 (t, J = 5.8 Hz, 3 H) ppm. ^{13}C NMR: δ = 147.5, 147.2, 130.8, 127.2, 111.7, 108.2, 63.5, 61.0, 59.2, 56.3, 56.0, 53.2, 39.2, 36.8, 36.5, 34.0, 29.5, 17.7, 12.7 ppm. HRMS (ESI): calcd. for $C_{19}H_{30}NO_3$ $[M + H]^+$ 320.2220; found 320.2217. $[\alpha]_D^{25}$ = –88.6 (c = 1.0, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): Complete experimental details, ^{1}H NMR and ^{13}C NMR spectra for all key compounds, HRMS spectra.

Acknowledgments

The authors gratefully acknowledge the Swedish National Research Council (VR) and Wenner-Gren-Foundation for financial support. The Berzelii Center EXSELENT is financially supported by VR and the Swedish Governmental Agency for Innovation Systems (VINNOVA).

[1] a) J. Stöckigt, M. H. Zenk, *J. Chem. Soc., Chem. Commun.* **1977**, 646; b) T. M. Kutchan, *Phytochemistry* **1993**, *32*, 493.
[2] G. Beuchamp, R. Keast, D. Morel, J. Liu, J. Pika, Q. Han, C. Lee, A. B. Smith III, P. A. S. Breslin, *Nature* **2005**, *437*, 45.
[3] M. Yoshikawa, T. Ueda, H. Matsuda, J. Yamahara, N. Murakami, *Chem. Pharm. Bull.* **1994**, *42*, 1691.
[4] a) K. Cimanaga, N. Hermans, S. Aspers, S. V. Miert, H. V. D. Heuvel, M. Claeys, L. Pieters, A. Vlietinick, *J. Nat. Prod.* **2003**, *66*, 97; b) H. K. Ju, T. C. Moon, E. Lee, S. H. Baek, R. B. An, K. Bae, K. H. Son, H. P. Kim, S. S. Kang, S. H. Lee, J. K. Son, H. W. Chang, *Planta Med.* **2003**, *69*, 950; c) K. S. Park, I. M. Chang, *Planta Med.* **2004**, *70*, 778.
[5] Y. Kumarasamy, L. Nahar, P. J. Cox, M. Jaspars, S. D. Sarker, *Phytomedicine* **2003**, *10*, 344.
[6] a) J. L. Chen, P. Blanc, C. A. Stoddart, M. Bogan, E. J. Rozhon, N. Parkinson, Z. Ye, R. Cooper, M. Balick, W. Nanokorn, M. R. Kernan, *J. Nat. Prod.* **1998**, *61*, 1295; b) P. Bermejo, M. J. Abad, A. M. Diaz, L. Fernandez, J. D. Santos, S. Sanches, L. Villaescusa, L. Carrasco, A. Irurzun, *Planta Med.* **2002**, *68*, 106; c) S. Suksmrarn, K. Wongkrajang, K. Kirtikara, A. Suksmrarn, *Planta Med.* **2003**, *69*, 877.
[7] a) T. Fujii, M. Ohba, in: *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1983**, vol. 22, pp. 1–50; b) W. Deeknamkul, A. Ounaroon, T. Tanahashi, T. M. Kutchan, M. H. Zenk, *Phytochemistry* **1997**, *45*, 477.
[8] J. F. Treimer, M. H. Zenk, *Eur. J. Biochem.* **1979**, *101*, 225.
[9] a) G. T. Tan, A. D. Kinghorn, S. H. Hughes, J. M. Pezzuto, *J. Biol. Chem.* **1991**, *266*, 23529; b) H. Takayama, Y. Iimura, M. Kitayama, N. Aimi, K. Konno, H. Inoue, M. Fujiwara, T. Mizuta, T. Yokota, S. Shigeta, K. Tokushida, Y. Hanasaki, K. Katsuura, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3145; c) A. Itoh, T. Kumashiro, M. Yamaguchi, N. Nagakura, Y. Mizushina, T. Nishi, T. Tanahashi, *J. Nat. Prod.* **2005**, *68*, 848.
[10] For isolation, see: a) B. Gilbert, L. D. Autonaccio, C. Djerassi, *J. Org. Chem.* **1962**, *27*, 4702. For selected syntheses, see: b) F. E. Ziegler, J. G. Sweeny, *Tetrahedron Lett.* **1969**, *10*, 1097; c) A. Deiters, S. F. Martin, *Org. Lett.* **2002**, *4*, 3243; d) A. Deiters, M. Pettersson, S. F. Martin, *J. Org. Chem.* **2006**, *71*, 6547; e) P. Nuhant, S. B. Raikar, J.-C. Wypych, B. Delpech, C. Marazano, *J. Org. Chem.* **2009**, *74*, 9413; f) M. J. Palframan, A. F. Parsons, P. Johnson, *Tetrahedron Lett.* **2011**, *52*, 1154.
[11] For isolation, see: a) A. R. Battersby, R. S. Kapil, B. S. Bhakuni, S. P. Popli, J. R. Merchant, S. S. Salgar, *Tetrahedron Lett.* **1966**, *7*, 4965. For selected syntheses, see: b) A. W. Burgstahler, Z. J. Bithos, *J. Am. Chem. Soc.* **1960**, *82*, 5466–5474; c) S. Takano, S. Hatakeyama, K. Ogasawara, *Tetrahedron Lett.* **1978**, *28*, 2519; d) C.-G. Huang, B.-R. Chang, N.-C. Chang, *Tetrahedron Lett.* **2002**, *43*, 2721; e) J.-K. Chang, B.-R. Chang, Y.-H. Chuang, N.-C. Chang, *Tetrahedron* **2008**, *64*, 9685; f) A. W. Burgstahler, Z. J. Bithos, *J. Am. Chem. Soc.* **1960**, *82*, 5466; g) C.-G. Huang, B.-R. Chang, N.-C. Chang, *Tetrahedron Lett.* **2002**, *43*, 2721. See also reference 10e and 10f.
[12] For isolation, see: a) A. R. Battersby, B. J. T. Harper, *J. Chem. Soc.* **1959**, 1748. For selected syntheses: b) S. Takano, Y. Takahashi, S. Hatakeama, K. Ogasawara, *Heterocycles* **1979**, *12*, 765; c) C. Szantay, L. Toke, P. Kolontis, *J. Org. Chem.* **1966**, *31*, 1447.
[13] For isolation, see: a) P.-J. Pelletier, F. Magnedie, *Jour. D Pharm.* **1817**, 145; b) B. H. Paul, A. J. Cownley, *Jahresber. Pharm.* **1894**, 523. For total syntheses see: c) S. Takano, M. Sasaki, H. Kanno, K. Shishido, K. Ogasawara, *J. Org. Chem.* **1978**, *43*, 4169; d) T. Itoh, M. Miyazaki, H. Fukuoka, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1295.
[14] a) M. T. Gonzales-Garza, S. A. Martlin, B. D. Mata-Cardena, S. J. Fernandez, *Pharm. Pharmacol.* **1993**, *45*, 144. For other examples of biological activity of (–)-emitine, see: b) H. H. Miller, R. K. Johnson, J. D. Donahue, W. R. Jondorf, *Biochem. J.* **1970**, *117*, 491.
[15] Y. F. Liou, I. H. Hall, K. H. Lee, *J. Pharm. Sci.* **1982**, *71*, 745.
[16] W. W. Ma, J. E. Andersson, A. T. McKenzie, S. R. Byrn, J. L. Mclaughin, M. S. Hudson, *J. Nat. Prod.* **1990**, *53*, 1009.
[17] a) M. Ihara, K. Yasui, N. Taniguchi, K. Fukumoto, *Tetrahedron Lett.* **1988**, *29*, 4963; b) Y. K. Sawa, H. Matsumura, *Tetrahedron* **1969**, *25*, 5329; c) Y. K. Sawa, H. Matsumura, *Tetrahedron* **1970**, *26*, 2931; d) T. Suzuki, E. Sato, K. Unno, T. Kametani, *Chem. Pharm. Bull.* **1986**, *34*, 1584; e) R. L. Beard, A. I. Meyers, *J. Org. Chem.* **1991**, *56*, 2091; f) T. Fujii, M. Ohba, T. Ohashi, *Tetrahedron* **1993**, *49*, 1879; g) M. Amat, A. Gómez-Esqué, C. Escolano, M. M. M. Santos, E. Molins, J. Bosch, *J. Org. Chem.* **2009**, *74*, 1205; h) Y. Li, T. Kobayashi, S. Katsumura, *Tetrahedron Lett.* **2009**, *50*, 4482.
[18] a) P. Yu, T. Wang, F. Yu, M. J. Cook, *Tetrahedron Lett.* **1997**, *38*, 6819; b) P. Yu, J. M. Cook, *J. Org. Chem.* **1998**, *63*, 9160; c) J. Li, P. Yu, A. Peterson, R. Weber, D. Soerens, D. Grubisha, D. Bennet, J. M. Cook, *J. Am. Chem. Soc.* **1999**, *121*, 6998; d) S. Yu, M. Berner, J. M. Cook, *J. Am. Chem. Soc.* **2000**, *122*, 7827; e) X. Liao, H. Zhou, X. Z. Wearing, J. Ma, J. M. Cook, *Org. Lett.* **2005**, *7*, 3501.
[19] a) A. Deiters, S. F. Martin, *Org. Lett.* **2002**, *4*, 3243; b) A. Deiters, M. Pettersson, S. F. Martin, *J. Org. Chem.* **2006**, *71*, 6547; c) S. F. Martin, B. Benage, J. E. Hunter, *J. Am. Chem. Soc.* **1988**, *110*, 5925; d) S. F. Martin, B. Benage, L. S. Geraci, J. E. Hunter, M. Mortimore, *J. Am. Chem. Soc.* **1991**, *113*, 6161; e) A. Deiters, K. X. Chen, C. T. Eary, S. F. Martin, S. F. Martin, *J. Am. Chem. Soc.* **2003**, *125*, 4541.
[20] a) B. J. English, R. M. Williams, *J. Org. Chem.* **2010**, *75*, 7869–7876.
[21] a) L. F. Tietze, N. Rackelmann, G. Sekar, *Angew. Chem.* **2003**, *115*, 4386; *Angew. Chem. Int. Ed.* **2003**, *42*, 4254; b) L. F. Tietze, N. Rachelmann, I. Müller, *Chem. Eur. J.* **2004**, *10*, 2722.
[22] a) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1533. For the proline catalyzed-domino Mannich/Michael reaction, see: b) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877.
[23] a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis* Wiley-VCH, Weinheim **2006**, p. 672; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; d) H. Guo, J. Ma, *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem. Int. Ed.* **2006**, *45*, 354; e) H. Pellieser, *Tetrahedron* **2006**, *62*, 2143; f) J. Zhu, H. Bienayme, *Multicomponent Reactions*, Wiley-VCH, **2005**.

[24] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice, Oxford University Press, Oxford*, **2000**, p. 135; b) For a review on combining one-pot, step reduction and atom economy in organic chemistry, see: P. A. Clarke, S. Santos, W. H. C. Martin, *Green Chem.* **2007**, *9*, 438; c) B. M. Trost, *Science* **1991**, *254*, 1471.

[25] a) D. J. Ramon, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602; b) L. F. Tietze, A. Dürfert, *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Córdova), Wiley-VCH, **2010**, p 321. For examples in organocatalysis, see: c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; d) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037; e) J. L. Vicario, E. Reyes, D. Badia, L. Carrillo, *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Córdova), Wiley-VCH, **2010**, p. 219; f) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; g) A. N. Alba, X. Companyo, M. Viciano, R. Rios, *Curr. Org. Chem.* **2009**, *13*, 1432.

[26] a) A. W. Pilling, J. Boehmer, D. J. Dixon, *Angew. Chem.* **2007**, *119*, 5524; *Angew. Chem. Int. Ed.* **2007**, *46*, 5428–5430; b) L. S. Santos, R. A. Pilli, V. H. Rawal, *J. Org. Chem.* **2004**, *69*, 1283; c) K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 6212; *Angew. Chem. Int. Ed.* **2005**, *44*, 6058; d) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2006**, *128*, 9646; e) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404; f) D. J. Mergott, S. J. Zuend, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 745; g) C. K. Jana, A. Studer, *Chem. Eur. J.* **2008**, *14*, 6326; h) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796; i) P. Jakubec, M. Helliwell, D. J. Dixon, *Org. Lett.* **2008**, *10*, 4267.

[27] a) H.-H. Fang, X.-Y. Wu, L.-L. Nie, X.-Y. Dai, J. Chen, W.-G. Cao, G. Zhao, *Org. Lett.* **2010**, *12*, 5366; b) X.-Y. Wu, X.-Y. Dai, L.-L. Nie, H.-H. Fang, J. Chen, Z.-J. Ren, W.-G. Cao, G. Zhao, *Chem. Commun.* **2010**, *46*, 2733.

[28] a) J. Franzén, A. Fisher, *Angew. Chem.* **2009**, *121*, 801; *Angew. Chem. Int. Ed.* **2009**, *48*, 787; b) W. Zhang, J. Franzén, *Adv. Synth. Catal.* **2010**, *352*, 499.

[29] a) P. Dziedzic, P. Schyman, M. Kullberg, A. Córdova, *Chem. Eur. J.* **2009**, *15*, 4044–4048; b) G.-L. Zhao, S. Lin, A. Korotvička, L. Deiana, M. Kullberg, A. Córdova, *Adv. Synth. Catal.* **2010**, *352*, 2291–2298; c) L. Deiana, P. Dziedzic, G.-L. Zhao, J. Vesely, I. Ibrahem, R. Rios, J. Sun, A. Córdova, *Chem. Eur. J.* **2011**, *17*, 4904; d) G.-L. Zhao, F. Ullah, L. Deiana, S. Lin, Q. Zhang, J. Sun, I. Ibrahem, P. Dziedzic, A. Córdova, *Chem. Eur. J.* **2010**, *16*, 1585; e) I. Ibrahem, W. Zou, J. Casas, H. Sundén, A. Córdova, *Tetrahedron* **2006**, *62*, 357; f) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343; g) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1957.

[30] a) G.-L. Zhao, J. Vesely, J. Sun, K. E. Christensen, C. Bonneau, A. Córdova, *Adv. Synth. Catal.* **2008**, *350*, 657; after completion of this manuscript, Ma's group reported an elegant asymmetric synthesis using our reaction[30a] as the key step, see: b) X-F. Sun, D.-W. Ma, *Chem. Asian. J.* **2011**, DOI: 10.1002/asia.201100219 .

[31] For the first diaryl prolinol-catalyzed Michael reaction of malonates, see: a) S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305.

[32] The reaction was also investigated at reflux temperature (40 °C). However, lower yield of **14a** was obtained (36%) due to decreased diastereoselectivity.

[33] a) K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651; b) A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480–2482; c) A. J. Mancuso, D. S. Brownfain, D. Swern, *J. Org. Chem.* **1979**, *44*, 4148.

[34] P. López-Alvarado, J. Steinhoff, S. Miranda, C. Avendaño, C. Menéndez, *Synlett* **2007**, 2792.

[35] S. Célanire, I. Salliot-Maire, P. Ribéreau, A. Godard, G. Quéguiner, *Tetrahedron* **1999**, *55*, 9269.

[36] a) L. K. Lukanov, A. P. Venkov, N. M. Mollov, *Synthesis* **1987**, 1031; b) C. Gremmen, M. J. Wanner, G.-J. Koomen, *Tetrahedron Lett.* **2001**, *42*, 8885.

Received: September 5, 2011
Published Online: November 16, 2011

