JOC Article

Total Synthesis of (−)-Ardeemin

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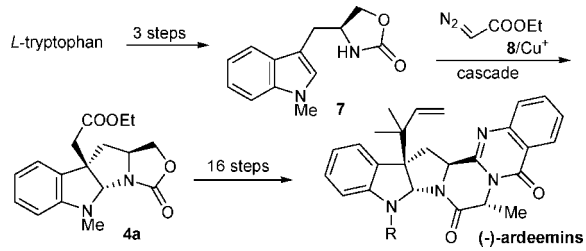
Received October 5, 2008



Total synthesis of potent anti-MDR indole alkaloids (−)-ardeemin and its *N*-acyl analogues has been accomplished from L-tryptophan with about 2% overall yield in 20 steps. The key step depended on the newly developed three-step one-pot cascade reaction of **7** with diazoester **8** via intermolecular cyclopropanation, ring opening, and ring closure to assemble the chiral 3-substituted hexahydropyrrolo[2,3-*b*]indole **4a**.

Introduction

Indole alkaloid ardeemins (Figure 1, **1**−**3**), isolated from the fermentation of a strain of *Aspergillus fischeri* by McAlpine and co-workers in 1993,[1] have demonstrated a potent ability to reverse multi-drug resistance (MDR).[2] For example, combining the use of *N*-acetylardeemin **2** (10 μM) with vinblastine, the cytotoxicity of vinblastine against a drug-resistant KBV-1 tumor cell line was enhanced more than 1000-fold compared with using vinblastine alone. Notably, **2** was 10-fold more effective than a well-known MDR modulator of verapamil[3] in in vitro experiments. The promising MDR reversal activity of ardeemins has attracted the interest of synthetic chemists. Structurally, ardeemins contain a fundamental skeleton of 3-substituted hexahydropyrrolo[2,3-*b*]indole (**4**). Although a variety of methods have been reported for preparing racemic[4] and chiral[5] 3-substituted hexahydropyrrolo[2,3-*b*]indole in the past 2 decades, up to now, only Danishefsky's group accomplished an elegant total synthesis of (−)-ardeemin by using the *N*-phenylselenophthalimide induced selenocyclization of tryptophan as a key step to construct the chiral 3-selenenylated hexahydropyrrolo[2,3-*b*]indole.[6]

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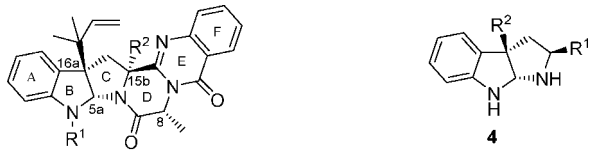
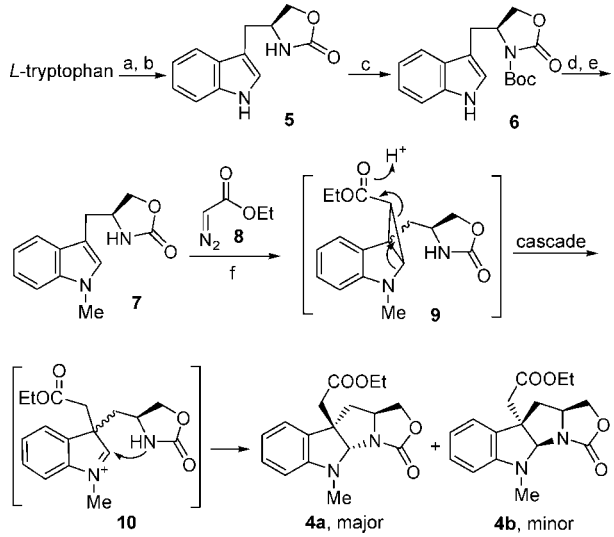
10.1021/jo802216z CCC: $40.75
Published on Web 11/13/2008



Ardeemin (**1**), R^1 = H, R^2 = H;
5-*N*-Acetylardeemin (**2**), R^1 = Ac, R^2 = H;
15b-Hydroxy-5-*N*-acetylardeemin (**3**), R^1 = Ac, R^2 = OH

FIGURE 1. Structures of ardeemins.

SCHEME 1. Intermolecular Cyclopropanation of the Three-Step One-Pot Cascade Reaction[a]



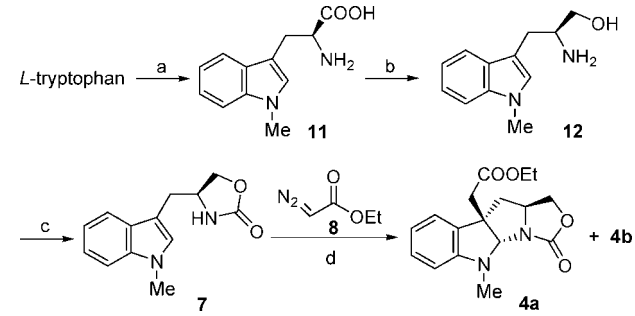
[a] Reagents and conditions: (a) $LiAlH_4$, THF, 90%; (b) triphosgene, aqueous KOH, THF, 84%; (c) Boc_2O, Et_3N, 75%; (d) Cs_2CO_3, Bu_4NHSO_4, MeI, 91%; (e) TFA, 85%; (f) 1 mmol of **7**, 4 equiv of **8**, 5 mol % of $Cu(OTf)_2$, −35 °C in CH_2Cl_2, 30 h, 82% of **4a** and 5% of **4b**.

We have recently reported the total synthesis of the complex polycyclic indole alkaloids (±)-communesin F[7] and (±)-minfiensine[8] by employing an intramolecular cyclopropanation strategy. As a continuation of our methodology development and application, we demonstrated an approach to chiral 3-substituted hexahydropyrrolo[2,3-*b*]indoles **4a** and **4b** from oxazolidinone **7** via a three-step one-pot cascade reaction of intermolecular cyclopropanation, ring opening, and ring closure in a high yield and in a high diastereoselectivity (Scheme 1).[9] Through this approach, three stereocenters of the major isomer **4a** corresponding to the C5a, C15b and C16a of (−)-ardeemins were created. Herein, we wish to report our further efforts on the application of the intermolecular cyclopropanation of a three-step one-pot cascade reaction to the total synthesis of (−)-ardeemin, (−)-*N*-formalardeemin, and (−)-*N*-acetylardeemin.

Results and Discussion

Previously, a preparation of oxazolidinone **7** from L-tryptophan through a five-step reaction resulting in a 44% overall yield was not straightforward and required chromatographic separation and the use of expensive Cs_2CO_3 (Scheme 1).[9] In order to make the procedure more practical, a new synthetic approach to **7** from L-tryptophan was developed via a three-step reaction. As shown in Scheme 2, direct alkylation of L-tryptophan with MeI under a condition of liquid NH_3/Na gave the *N*-methyl-protected **11** in a 92% yield.[10] Reduction of **11** with $LiAlH_4$ gave amino alcohol **12** in high yield. Without purification, compound **12** was treated with triphosgene under an aqueous basic condition in THF, followed by recrystallization from ethyl acetate to afford **7** in a 78% yield in two steps. By this new approach, the overall yield of **7** from L-tryptophan increased by 28% compared to the previously used five-step procedure. The three-step procedure was readily implemented on a 200 g scale without chromatographic separation.

SCHEME 2. Improved Synthesis of Oxazolidinone 7 and 4a[a]



[a] Reagents and conditions: (a) NH_3/Na, MeI, −60 °C, 92%; (b) $LiAlH_4$, THF, rt; (c) triphosgene, 10% aqueous KOH, THF, 78% for two steps; (d) Cu(OTf)−tolulene, toluene, 25 °C, 45% yield of **4a** and 28% yield of **4b**.

For the synthesis of (−)-ardeemin, a large quantity of the key intermediate **4a** was expected to be produced from **7**. Therefore, the efficiency of the three-step one-pot cascade reaction of **7** with diazoester **8** was reevaluated at a larger scale rather than the previous small scale (1 mmol). Unfortunately, although a similar ratio of **4a** to **4b** (20:1) was observed,[9] direct application of the previous condition (4 equiv of diazoester **8**, 0.05 equiv of $Cu(OTf)_2$, −35 °C in CH_2Cl_2) was not successful at a 50 g scale. A low yield of **4a** (22% yield) was obtained as a result of the formation of a large quantity of dark precipitates and rapid non-productive decomposition of diazoester **8**. Because the first step of the cyclopropanation reaction was very sluggish at low temperatures in CH_2Cl_2, to efficiently promote the first step of the cyclopropanation reaction and to avoid the formation of precipitates, the cascade reaction has to be performed at room temperature. To our delight, in the presence of 0.2 equiv of freshly made CuOTf−toluene complex in toluene, the cascade reaction proceeded smoothly for 6 h to give **4a** in a 45 % yield and **4b**[11] in a 28 % yield at a 50 g scale when 4 equiv of **8** was used (Scheme 2).

With easily available pyrroloindole **4a** in hand, our next task was to transfer the ethyl acetate group in **4a** to an isoprenyl group (Scheme 3). Thus, double α-alkylation of the ethyl acetate group with LDA/MeI resulted in dimethylated **13** in a 72% yield. Unfortunately, attempts to directly reduce the ester group in **13** to aldehyde by DIBAL failed due to a lack of functional group selectivity between the ester group and the oxazolidinone group. After screening several reducing reagents, $LiBH_4$ was found to be a good choice for reducing reagent to produce alcohol **14** in a 61% yield. Oxidation of the hydroxyl group in **14** with Dess−Martin reagent, followed by Wittig reaction, furnished olefin **16** in a 93% yield.

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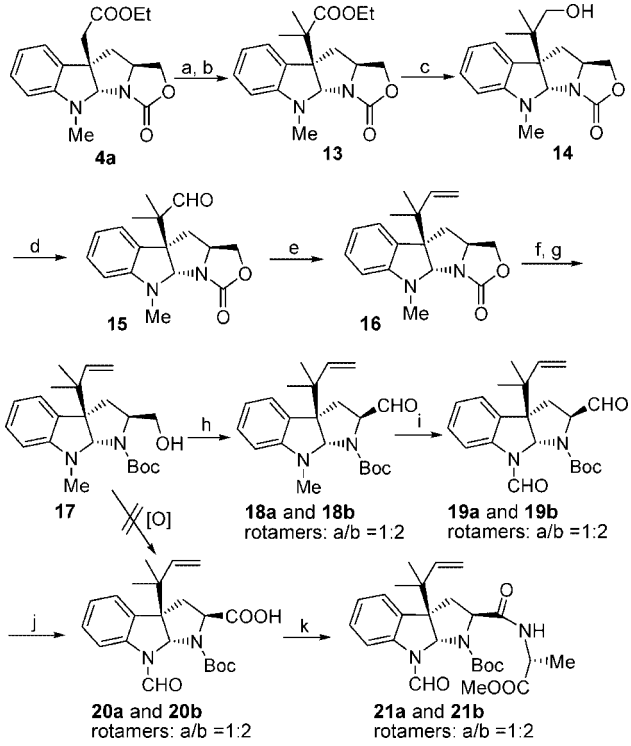
SCHEME 3. Synthesis of Compounds 21a and 21b[a]

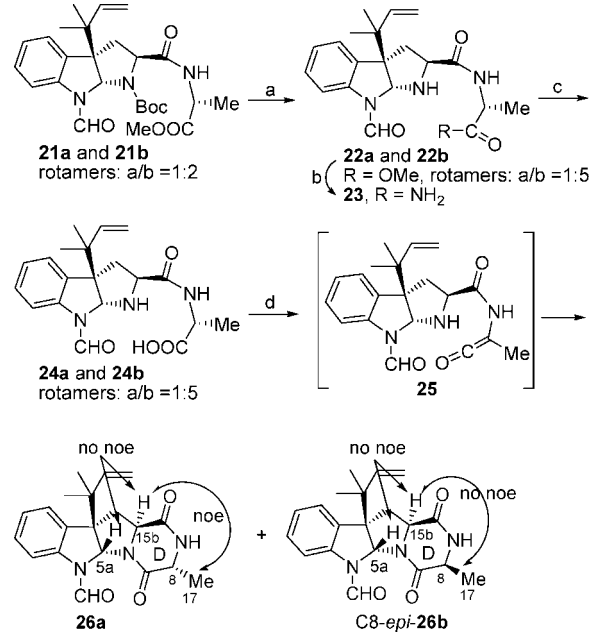


[a] Reagents and conditions: (a) LDA, MeI, THF, −78 °C to rt; (b) LDA, MeI, THF, −78 °C to rt, 72% from **4a**; (c) $LiBH_4$, THF/MeOH, 0 °C, 61%; (d) DMP, CH_2Cl_2, rt, 92%; (e) $Ph_3P^+MeI^-$, LiHMDS, THF, −78 °C to rt, 93%; (f) ^{t}BuOK, aq ^{t}BuOH, rt, quantitative yield; (g) $(Boc)_2O$, CH_2Cl_2, rt, 95%, (h) DMP, CH_2Cl_2, rt, 92%; (i) PCC, CH_2Cl_2, rt, 76%; (j) $NaClO_2$, NaH_2PO_4 buffer, rt, quantitative yield; (k) $ClCOO^iBu$, Et_3N, D-Ala-OMe, CH_2Cl_2, 0 °C, rt, 81%.

Construction of the D-ring by condensation with D-alanine required transformation of oxazolidinone group in **16** to a protected aminocarboxy group (Scheme 3). Opening of the oxazolidinone ring in **16** with ^{t}BuOK and aqueous ^{t}BuOH, followed by protection of the resulting amino group with Boc_2O, resulted in alcohol **17** in an excellent yield for the two steps. Initially, it was planned to oxidize both the hydroxyl group and the methyl group in **17** into an acidic group and a formamido group (**20**) in a single-step reaction. However, a number of oxidation reagents and conditions were tried, but all attempts to realize this direct transformation failed because of the easy formation of an *N*-oxide functionality on the indoline nitrogen under the oxidation conditions tested. Therefore, a stepwise oxidation of **17** had to be conducted. As a result, the hydroxyl group in **17** was first oxidized with Dess−Martin reagent to give a mixture of two rotamers **18a** and **18b** in a 92% yield and a 1:2 ratio. The *N*-methyl group in **18a** and **18b** was then oxidized with PCC to an *N*-formal group to give rotamers **19a** and **19b** in a 76% yield. Treatment of the mixture of **19a** and **19b** with $NaClO_2$ in a NaH_2PO_4 buffer provided a mixture of two rotamers **20a** and **20b** in a quantitative yield. Condensation of **20a** and **20b** with D-alanine methyl ester in the presence of isobutyl chloroformate and triethylamine in CH_2Cl_2 afforded rotamers **21a** and **21b** in an 81% yield.

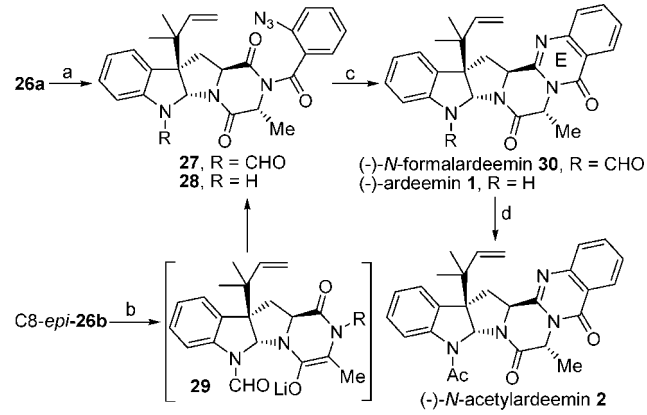
After the Boc group was removed by TMSI,[6a] the ratio of rotamers changed from 1:2 in **21** to 1:5 in **22** because of partial release of the aminal rigidity (Scheme 4). With a congested formal group on the indoline nitrogen of **22**, cyclization of the D-ring by using a solution of saturated methanolic ammonia and a catalytic quantity of DMAP exclusively yielded the amide

SCHEME 4. Synthesis of Compounds 26a and 26b[a]



[a] Reagents and conditions: (a) TMSI, CH_3CN, 0 °C, 98%; (b) MeOH/NH_3, DMAP, 0 °C to rt, 86%; (c) LiOH, aq. MeOH, 95% yield; (d) $ClCOO^iBu$, Et_3N, D-Ala-OMe, CH_2Cl_2, 0 °C to rt, 71% of **23a** and **23b**.

SCHEME 5. Synthesis of Ardeemins[a]



[a] Reagents and conditions: (a) 2 equiv of ^{n}BuLi, *o*-azidobenzoic anhydride, THF, −78 °C, 86% of **27** and **28** in a 1:1 ratio; (b) 2 equiv of ^{n}BuLi, *o*-azidobenzoic anhydride, THF, −78 °C, 33% of **27** and **28** in a 1:1 ratio; (c) ^{n}Bu$_3$P, benzene, rt, 93%; (d) Ac_2O, DIPEA, 60 °C, benzene.[6]

23, only trace amount of **26** was formed. We then turned our efforts of D-ring cyclization to the aid of coupling agents. After hydrolysis of **22** with LiOH in aqueous MeOH, the resulting acid **24** was treated with $ClCOO^iBu/Et_3N$ to afford two separable diketopiperazines **26a** and C8-*epi*-**26b** in a 71% yield and a 1:1 ratio. Rotamerism caused by the formal group in **26** was eliminated after the D-ring was formed. Epimerization at C8 for **26b** probably proceeded through a ketene intermediate **25**. The relative configuration between C8 and C15b in **26a** and **26b** was unambiguously confirmed by noe experiments.

A strategy similar to Danishefsky's E-ring construction was adopted (Scheme 5).[6] Condensation of diketopiperazine **26a** with *o*-azidobenzoic anhydride under a strong basic condition at low temperature provided azido **27** and deformal azido **28** in an 86% yield and 1:1 ratio. Interestingly, although the yield was low (33% yield), the epimerized **26b** also afforded azido **27** and **28** in a 1:1 ratio under the same condensation condition. Obviously,

thermodynamically favorable products **27** and **28** were produced from **26b** via an enolate intermediate **29** after quenching the reaction. Treatment of **27** and **28** with $^{n}Bu_3P$ accomplished the total synthesis of (−)-*N*-formalardeemin **30** and (−)-ardeemin **1**. (−)-*N*-Acetylardeemin **2** was prepared from (−)-ardeemin **1** by using the published procedure.[6b]

Conclusion

In summary, total synthesis of indole alkaloid (−)-ardeemin, (−)-*N*-formalardeemin, and (−)-*N*-acetylardeemin has been accomplished from L-tryptophan with about 2% overall yield in 20 steps. The key step depended on our recently developed three-step one-pot cascade reaction of intermolecular cyclopropanation, ring opening, and ring closure to assemble the chiral 3-substituted hexahydropyrrolo[2,3-*b*]indole with three stereocenters corresponding to (−)-ardeemin. Current synthesis has provided a practicable route to prepare analogues of (−)-ardeemin for further SAR studies of anti-MDR activity.

Experimental Section

Improved Synthesis of Oxazolidinone 7 and 4a. Oxazolidinone 7.[9] Compound **11** (150 g, 0.69 mol) was suspended in anhydrate THF. The resulting mixture was cooled to 0 °C in an ice−water bath, and then $LiAlH_4$ (78.7 g, 2.07 mol) was slowly added within 4 h. After reflux for 2 h, the reaction was cooled to 0 °C and quenched by saturated aqueous Na_2SO_4, filtered, and extracted with EtOAc (500 mL × 6). The combined organic phases were dried over Na_2SO_4 and concentrated to give the red residue.

The above residue was dissolved in THF (200 mL) and a solution of KOH (200 g, 3.6 mol) in H_2O (2,000 mL) was added. At 0 °C, a solution of triphosgene (205 g, 0.69 mol) in THF (500 mL) was slowly added to the above mixture. The reaction was then allowed to warm to room temperature and stirred for 8 h. The mixture was diluted with water (500 mL), extracted with CH_2Cl_2 (500 mL × 3), dried over Na_2SO_4, concentrated, and recrystallized from EtOAc to give oxazolidinone **7** as a white solid (124 g, 78% yield): $[\alpha]^{20}_D = -50°$ (*c* 1.0, $CHC1_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.04−2.97 (m, 2H), 4.22−4.15 (m, 2H), 4.52−4.46 (m, 1H), 5.29 (s, 1H), 6.93 (s, 1H), 7.16−7.12 (m, 1H), 7.27 (td, J = 7.2, 1.2 Hz, 1H), 7.34−7.32 (m, 1H), 7.56−7.54 (m, 1H).

Hexahydropyrroloindoles 4a and 4b.[9] Under N_2, to a solution of **7** (50 g, 0.22 mol) and a freshly made CuOTf−toluene complex (25 g, 0.043 mol)[12] in dry toluene (200 mL) was slowly added a solution of diazo **8** (100 g, 0.88 mol) in dry CH_2Cl_2 (1000 mL) at 25 °C. The reaction mixture was stirred at room temperature for 6 h and then was concentrated. The residue was purified by flash chromatography (17% EtOAc/petroleum) to afford **4a** (31 g, 45% yield) and **4b** (19 g, 28% yield).[9]

4a: $[\alpha]^{20}_D = -175°$ (*c* 1.0, $CHC1_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.6 Hz, 3H), 2.05 (t, J = 6.8 Hz, 1H), 2.56 (dd, J = 12.0, 5.2 Hz, 1H), 2.74 (d, J = 15.6 Hz, 1H), 2.80 (d, J = 16.0 Hz, 1H), 2.92 (s, 3H), 3.77−3.74 (m, 1H), 4.19−4.09 (m, 3H), 4.40 (t, J = 8.0Hz, 1H), 5.38 (s, 1H), 6.42 (d, J = 8.0 Hz, 1H), 6.69 (td, J = 7.6, 0.8 Hz, 1H), 7.08 (dd, J = 7.6, 0.8 Hz, 1H), 7.15 (td, J = 7.6, 1.2 Hz, 1H).

4b: $[\alpha]^{20}_D = +22°$ (*c* 1.0, $CHC1_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 6.8 Hz, 3H), 1.93 (dd, J = 12.4, 9.6 Hz, 1H), 2.50−2.46 (m, 1H), 2.72 (d, J = 16.0 Hz, 1H), 2.78 (d, J = 15.6 Hz, 1H), 3.23 (s, 3H), 3.94 (dd, J = 8.0, 6.8 Hz, 1H), 4.08 (q, J = 7.2Hz, 2H), 4.37−4.31 (m, 1H), 4.43 (t, J = 8.0 Hz, 1H), 5.16 (s, 1H), 6.52 (d, J = 8.0Hz, 1H), 6.71 (t, J = 7.6 Hz, 1H), 7.02−7.00 (m, 1H), 7.16 (td, J = 8.0, 1.2 Hz, 1H).

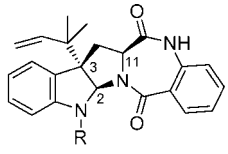
Synthesis of Compounds 21a and 21b. Dimethylated 13. Under N_2, LDA (lithium diisopropylamide, 2.5 M in THF, 19 mL) was slowly dropped to a stirred solution of **4a** (5 g, 15.8 mmol) in THF (100 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h, and then MeI (5.1 mL, 79.1 mmol) was added. After the mixture was stirred for 8 h, and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (17% EtOAc/petroleum) to give a yellowish residue.

Under N_2, the above residue was dissolved in THF (100 mL) at −78 °C. LDA (2.5 M in THF, 19 mL) was slowly dropped to the solution. After the mixture was stirred at −78 °C for 2 h, MeI (5.1 mL, 79.1 mmol) was added, and then the reaction mixture was stirred at −78 °C for another 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and evaporated to give a yellowish residue. Flash chromatography (17% EtOAc/petroleum) of the residue yielded dimethylated **13** as a pale yellow solid (3.91 g, 72% yield), mp 110−111 °C; $[\alpha]^{20}_D = -241°$ (*c* 1.0, $CHC1_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.28 (t, J = 7.2, 3H), 1.30 (s, 3H), 2.21 (dd, J = 22.8, 10.8 Hz, 1H), 2.35 (dd, J = 12.0, 5.6 Hz, 1H), 2.88 (s, 3H), 3.70−3.64 (m, 1H), 4.19−4.12 (m, 3H), 4.36 (dd, J = 8.8, 7.6 Hz, 1H), 5.54 (s, 1H), 6.40 (d, J = 7.6, 1H), 6.67 (td, J = 7.2, 0.8 Hz, 1H), 7.02 (dd, J = 7.6, 1.2 Hz, 1H), 7.15 (td, J = 7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.9, 22.0, 30.8, 40.7, 47.0, 58.6, 61.0, 64.1, 66.9, 85.8, 106.0, 117.2, 124.5, 128.8, 129.3, 151.6, 160.3, 175.7; HRMS-ESI calcd for $C_{19}H_{24}N_2O_4Na$ $(M + Na)^+$ 367.1628, found 367.1630; IR (KBr) 1759, 1603, 1472, 1045 cm^{-1}.

Alcohol 14. To a solution of dimethylated **13** (3.441 g, 10 mmol) in THF (100 mL) and MeOH (0.8 mL, 20 mmol) was added $LiBH_4$ (436 mg, 20 mmol) at 0 °C under N_2. After stirring at 0 °C for 4 h, the reaction was quenched by an ice-cold saturated NH_4Cl solution (100 mL) and extracted with EtOAc (100 mL×3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuum to give a yellow residue. Purification of the residue by column chromatography (67% EtOAc/petroleum) afforded alcohol **14** as a colorless solid (1.844 g, 61% yield), mp 196−198 °C; $[\alpha]^{20}_D = -273°$ (*c* 1.0, $CHC1_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.12 (s, 3H), 2.07 (dd, J = 12.0, 10.8 Hz, 1H), 2.33 (dd, J = 12.0, 5.2 Hz, 1H), 2.60 (s br, 1H), 2.89 (s, 3H), 3.14 (s, 2H), 3.60−3.53 (m, 1H), 4.17 (dd, J = 8.8, 3.2 Hz, 1H), 4.38 (dd, J = 8.8, 8.0 Hz, 1H), 5.43 (s, 1H), 6.54 (d, J = 8.0, 1H), 6.79 (td, J = 7.6, 1.2 Hz, 1H), 7.12 (dd, J = 7.8, 0.8 Hz, 1H), 7.20 (td, J = 7.6, 1.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1, 21.6, 29.7, 31.6, 39.9, 58.4, 64.8, 67.0, 70.4, 85.5, 107.9, 118.8, 124.4, 129.1, 130.7, 151.2, 160.6; HRMS-ESI calcd for $C_{17}H_{22}N_2O_3Na$ $(M + Na)^+$ 325.1523, found 325.1516; IR (KBr) 3471, 1740, 1402, 1246, 1048 cm^{-1}.

Aldehyde 15. To a solution of alcohol **14** (1.512 g, 5 mmol) in CH_2Cl_2 (100 mL) was added Dess−Martin reagent (Dess−Matrin periodinane, 2.544 g, 6 mmol) at room temperature. After stirring

(11) The minor isomer **4b** has the same absolute configurations at C2, C3, and C11 corresponding to natural indole alkaloids epi-aszonalenins A, B and C; see: Rank, C.; Phipps, R. K.; Harris, P.; Frisvad, J. C.; Gotfredsen, C. H.; Larsen, T. O. *Tetrahedron Lett.* **2006**, *47*, 6099.



epi-aszonalenins A, R = COMe
epi-aszonalenins B, R = CHO
epi-aszonalenins C, R = H

(12) CuOTf-toluene was freshly prepared from trifluoromethanesulfonic anhydride and Cu_2O in toluene. Cohen, T.; Ruffner, R. J.; Shull, D. W.; Fogel, E. R.; Falck, J. R. *Org. Synth.* **1979**, *59*, 202.

at room temperature for 1 h, the reaction was quenched by saturated $Na_2S_2O_3$ solution (100 mL). The mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash chromatography (20% EtOAc/petroleum) to give aldehyde **15** (1.382 g, 92% yield), mp 115−116 °C; $[\alpha]^{20}_D$ = −85° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.19 (s, 3H), 2.08 (dd, *J* = 12.0, 10.8 Hz, 1H), 2.34 (dd, *J* = 12.0, 5.2 Hz, 1H), 2.89 (s, 3H), 3.73−3.66 (m, 1H), 4.18 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.39 (dd, *J* = 9.2, 7.6 Hz, 1H), 5.39 (s, 1H), 6.43 (d, *J* = 8.0, 1H), 6.70 (td, *J* = 7.2, 0.8Hz, 1H), 7.05 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.17 (td, *J* = 8.0, 1.2 Hz, 1H), 9.48 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.8, 18.9, 31.0, 39.7, 49.5, 58.5, 62.9, 66.9, 85.1, 106.5, 117.8, 124.5, 128.5, 129.5, 151.4, 160.4, 204.3; HRMS-ESI calcd for $C_{17}H_{20}N_2O_3Na$ $(M + Na)^+$ 323.1366, found 323.1361; IR (KBr) 3441, 1746, 1389, 1190 cm^{-1}.

Olefin 16. To a solution of $Ph_3P^+MeI^-$ (835 mg, 2.07 mmol) in THF (50 mL) at −78 °C was dropped LiHMDS (lithium hexamthyldisilazide, 1 M in THF, 2.3 mL). After stirring at 0 °C for 1 h, the solution was cooled to −78 °C again and was added dropwise a solution of adehyde **15** (400 mg, 1.33 mmol) in THF. The reaction was stirred overnight and allowed to warm to room temperature slowly. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered, and evaporated to give a residue. Flash chromatography (17% EtOAc/petroleum) of the residue yielded olefin **16** as a white solid (368 mg, 93% yield), mp 83−85 °C; $[\alpha]^{20}_D$ = −348° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.09 (s, 3H), 1.99 (dd, *J* = 12.0, 10.8 Hz, 1H), 2.19 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.88 (s, 3H), 3.68−3.61 (m, 1H), 4.18 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.35 (dd, *J* = 8.8, 7.6 Hz, 1H), 5.07 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.13 (dd, *J* = 7.2, 1.2 Hz, 1H), 5.29 (s, 1H), 5.94 (dd, *J* = 17.2, 10.8 Hz, 1H), 6.39 (d, *J* = 8.0, 1H), 6.67 (td, *J* = 7.6, 0.8 Hz, 1H), 7.08 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.15 (td, *J* = 7.6, 1.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 23.3, 30.9, 39.9, 40.7, 58.6, 65.5, 66.8, 85.3, 105.9, 114.3, 117.1, 124.7, 128.9, 129.8, 143.7, 151.7, 160.3; HRMS-ESI calcd for $C_{18}H_{22}N_2O_2Na$ $(M + Na)^+$ 321.1574, found 321.1570; IR (KBr) 1755, 1746, 1604, 1190 cm^{-1}.

Alcohol 17. To a solution of olefin **16** (300 mg, 1.01 mmol) in aqueous ^{t}BuOH (20 mL) was added ^{t}BuOK (452 mg, 4.04 mmol) in one portion at room temperature. After stirring for 4 h, the mixture was diluted with EtOAc (50 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (9% MeOH/CH_2Cl_2) to yield amino alcohol as viscous liquid.

To a solution of the above amino alcohol in CH_2Cl_2 (20 mL) was added Boc_2O (di-*tert*-butyl dicarbonate, 872 mg, 4.00 mmol). After stirring at room temperature overnight, the mixture was concentrated and purified by column chromatography (17% EtOAc/petroleum) to give alcohol **17** (353 mg, 95% yield) as a white solid, mp 88−90 °C; $[\alpha]^{20}_D$ = −232° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.04 (s, 3H), 1.73 (s br, 1H), 1.95−1.89 (m, 2H), 2.97 (s, 3H), 3.46−3.40 (m, 1H), 3.74−3.61 (m, 2H), 5.09 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.09 (dd, *J* = 10.8, 0.8 Hz, 1H), 5.25 (s, 1H), 5.89 (dd, *J* = 17.2, 10.8 Hz, 1H), 6.35 (d, *J* = 7.6, 1H), 6.65 (t, *J* = 7.2, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.11 (td, *J* = 7.6, 0.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 23.0, 28.5, 34.3, 37.5, 40.9, 60.1, 61.9, 63.9, 81.0, 85.6, 106.0, 113.6, 117.1, 124.4, 128.6, 130.8, 144.2, 152.1, 154.9; HRMS-ESI calcd for $C_{22}H_{32}N_2O_3Na$ $(M + Na)^+$ 395.2311, found 395.2305; IR (KBr) 3422, 1680, 1604, 1409, 1075, 750 cm^{-1}.

Aldehydes 18a and 18b. To a solution of alcohol **17** (300 mg, 0.81 mmol) in CH_2Cl_2 (20 mL) was added Dess−Martin reagent (512 mg, 1.21 mmol) at room temperature. After stirring at room temperature for 2 h, the reaction was quenched by saturated $Na_2S_2O_3$ solution (50 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with saturated $NaHCO_4$ solution (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash chromatography (17% EtOAc/petroleum) to give a mixture of two aldehydes **18a** and **18b** (274 mg, 92% yield), $[\alpha]^{20}_D$ = −242° (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) δ 0.94 (rotamer A and B; s, 3H), 1.08 (rotamer A and B; s, 3H), 1.40 (rotamer B; s, 9H), 1.54 (rotamer A; s, 9H), 2.23−2.04 (rotamer A and B; m, 2H), 3.02 (rotamer A; s, 3H), 3.08 (rotamer B; s, 3H), 3.78−3.72 (rotamer A and B; m, 1H), 5.15−5.05 (rotamer A and B; m, 2H), 5.17 (rotamer A; s, 1H), 5.37 (rotamer B; s, 1H), 5.91 (rotamer A and B; dd, *J* = 17.2, 7.2 Hz, 1H), 6.40−6.37 (rotamer A and B; m, 1H), 6.71−6.66 (rotamer A and B; m, 1H), 7.05 (rotamer A and B; d, *J* = 7.6 Hz, 1H), 7.17−7.13 (rotamer A and B; m, 1H), 9.22 (rotamer B; d, *J* = 4.4 Hz, 1H), 9.33 (rotamer A; d, *J* = 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) rotamer B: δ 14.1, 22.6, 22.8, 28.1, 29.6, 33.6, 41.1, 62.0, 64.7, 79.1, 82.0, 109.2, 114.4, 118.4, 124.7, 128.8, 143.6, 149.8, 153.5, 196.5; rotamer A: δ 14.1, 22.6, 22.8, 28.5, 29.3, 33.1, 41.1, 63.4, 64.9, 78.3, 82.0, 109.1, 114.4, 118.9, 123.1, 129.3, 143.1, 149.3, 153.5, 196.5; HRMS-ESI calcd for $C_{22}H_{30}N_2O_3Na$ $(M + Na)^+$ 393.2154, found 393.2149; IR (KBr) 1740, 1696, 1464, 1367, 1260, 803 cm^{-1}.

***N*-Formals 19a and 19b.** To a solution of aldehydes **18a** and **18b** (200 mg, 0.54 mmol) in CH_2Cl_2 (20 mL) was added PCC (pyridinium chlorochromate, 233 mg, 1.08 mmol) at room temperature. After stirring at room temperature for 4 h, the reaction was concentrated and purified by flash chromatography (50% EtOAc/petroleum) to give a mixture of *N*-formals **19a** and **19b** (158 mg, 76% yield), $[\alpha]^{20}_D$ = −72° (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) δ 0.97 (rotamer B; s, 3H), 1.11 (rotamer B; s, 3H), 1.13 (rotamer A; s, 3H), 1.25 (rotamer A; s, 3H), 1.39 (rotamer B; s, 9H), 1.54 (rotamer A; s, 9H), 2.27−2.22 (rotamer A and B; m, 2H), 3.73−3.68 (rotamer A and B; m, 1H), 5.10 (rotamer A and B; d, *J* = 17.2 Hz, 1H), 5.17 (rotamer A and B; d, *J* = 10.8 Hz, 1H), 5.68 (rotamer A; s, 1H), 5.88 (rotamer B; s, 1H), 5.90−5.80 (rotamer A and B; m, 1H), 7.16 (rotamer A and B; q, *J* = 8.0 Hz, 1H), 7.30−7.24 (rotamer A and B; m, 1H), 7.35 (rotamer A and B; t, *J* = 8.0 Hz, 1H), 7.92 (rotamer A; d, *J* = 8.0 Hz, 1H), 8.01 (rotamer B; d, *J* = 8.0 Hz, 1H), 8.68 (rotamer A; s, 1H), 8.93 (rotamer B; s, 1H), 9.26 (rotamer B; d, *J* = 4.4 Hz, 1H), 9.35 (rotamer A; d, *J* = 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) rotamer B: δ 14.1, 22.1, 23.1, 29.3, 29.9, 31.9, 33.3, 41.1, 64.4, 78.7, 83.0, 115.2, 115.7, 116.5, 117.6, 124.7, 129.3, 142.6, 161.8, 196.5; rotamer A: δ 14.1, 22.1, 22.7, 28.0, 28.3, 32.1, 33.3, 41.1, 64.8, 78.2, 83.3, 115.0, 115.7, 117.6, 116.5, 125.1, 129.3, 142.1, 161.1, 196.7; HRMS-ESI calcd for $C_{22}H_{28}N_2O_4Na$ $(M + Na)^+$ 407.1947, found 407.1941; IR (KBr) 1687, 1584, 1439, 1216, 758 cm^{-1}.

Acids 20a and 20b. To a solution of *N*-formals **19a** and **19b** (96 mg, 0.25 mmol) in a mixture of CH_3CN/^{t}BuOH/H_2O (2:2:1, 10 mL) were added $NaH_2PO_4 \cdot 2H_2O$ (117 mg, 0.75 mmol) and $NaClO_2$ (136 mg, 1.5 mmol) sequentially. After stirring at room temperature for 0.5 h, the mixture was diluted with EtOAc (50 mL), washed with saturated $Na_2S_2O_3$ solution (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in a vacuum to give a residue. The residue was purified by column chromatography (9% MeOH/CH_2Cl_2) to yield a mixture of acids **20a** and **20b** (100 mg, 99% yield), $[\alpha]^{20}_D$ = −158° (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) δ 0.97 (rotamer A and B; s, 3H), 1.08 (rotamer B; s, 3H), 1.10 (rotamer A; s, 3H), 1.37 (rotamer B; s, 9H), 1.51 (rotamer A; s, 9H), 2.55−2.31 (rotamer A and B; m, 2H), 3.92 (rotamer A and B; dd, *J* = 9.6, 7.2 Hz, 1H), 5.06 (rotamer A and B; d, *J* = 17.2 Hz, 1H), 5.13 (rotamer A and B; d, *J* = 10.8 Hz, 1H), 5.70 (rotamer A; s, 1H), 5.87−5.77 (rotamer A and B; m, 1H), 5.90 (rotamer B; s, 1H), 7.19−7.13 (rotamer A and B; m, 1H), 7.27−7.24 (rotamer A and B; m, 1H), 7.34 (rotamer A and B; d, *J* = 7.6 Hz, 1H), 7.89 (rotamer A; d, *J*

= 8.0 Hz, 1H), 7.99 (rotamer B; d, J = 8.0 Hz, 1H), 8.65 (rotamer A; s, 1H), 8.91 (rotamer B; s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) rotamer B: δ 22.1, 23.1, 29.6, 31.8, 36.5, 41.0, 59.3, 61.1, 78.8, 82.1, 114.8, 117.7, 124.7, 129.2, 133.3, 140.6, 142.6, 162.1, 152.7, 177.4; rotamer A: 22.1, 23.1, 29.6, 31.8, 34.8, 41.0, 59.3, 62.5, 78.3, 83.1, 114.8, 117.7, 125.1, 129.2, 133.3, 140.2, 142.6, 153.1, 161.3, 177.0; HRMS-ESI calcd for $C_{22}H_{27}N_2O_5$ $(M - H)^-$ 399.1926, found 399.1920; IR (KBr) 3460, 1688, 1596, 1367, 1150, 755 cm^{-1}.

Amides 21a and 21b. To a solution of acids **20a** and **20b** (50 mg, 0.12 mmol) and Et_3N (35 μL, 0.25 mmol) in CH_2Cl_2 (5 mL) was added $ClCOO^tBu$ (33 μL, 0.25 mmol) at 0 °C by using a syringe. After stirring for 15 min, to the mixture was added D-Ala-OMe (methyl D-alaninate, 25.8 mg, 0.25 mmol), and the mixture was allowed to stir for 1 h at 0 °C. The mixture was then quenched by saturated $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography (25% EtOAc/petroleum) to yield a mixture of amides **21a** and **21b** (49 mg, 81% yield), $[\alpha]^{20}_D = -135°$ (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) δ 0.98 (rotamer A and B; s, 3H), 1.01 (rotamer A and B; s, 3H), 1.33 (rotamer B; s br, 9H), 1.45−1.39 (rotamer A and B; m, 3H), 1.50 (rotamer A; s br, 9H), 2.48−2.44 (rotamer A and B; m, 2H), 3.75 (rotamer B; s, 3H), 3.76 (rotamer A; s, 3H), 3.77−3.73 (rotamer A and B; m, 1H), 4.63−4.58 (rotamer A and B; m, 1H), 5.06 (rotamer A and B; d, J = 17.2 Hz, 1H), 5.14 (rotamer A and B; d, J = 10.8 Hz, 1H), 5.70 (rotamer A; s, 1H), 5.86−5.82 (rotamer A and B; m, 1H), 5.90 (rotamer B; s, 1H), 6.24 (rotamer A and B; s br, 1H), 7.16 (rotamer A and B; t, J = 7.2 Hz, 1H), 7.28−7.25 (rotamer A and B; m, 1H), 7.33 (rotamer A and B; t, J = 7.6 Hz, 1H), 7.89 (rotamer A; s br, 1H), 7.97 (rotamer B; d, J = 7.2 Hz, 1H), 8.65 (rotamer A; s, 1H), 8.89 (rotamer B; s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$; a mixture of two rotamers in a 1:2 ratio) rotamer B: δ 18.8, 22.2, 23.0, 28.0, 29.6, 37.3, 40.9, 47.9, 52.5, 61.2, 79.2, 82.2, 114.7, 117.6, 124.7, 129.1, 133.6, 140.9, 142.8, 153.0, 162.0, 170.8, 173.1; rotamer A: δ 18.6, 22.2, 23.0, 28.0, 29.6, 35.5, 40.9, 47.9, 52.5, 60.8, 79.2, 82.2, 114.7, 117.6, 124.5, 129.1, 133.6, 140.9, 142.8, 153.0, 161.5, 170.4, 173.1; HRMS-ESI calcd for $C_{26}H_{35}N_3O_6Na$ $(M + Na)^+$ 508.2418, found 508.2419; IR (KBr) 3322, 1774, 1681, 1460, 1151, 756 cm^{-1}.

Synthesis of Compounds 26a and 26b. Compounds 22a and 22b. A mixture of amides **21a** and **21b** (33 mg, 0.068 mmol) was dissolved in freshly distilled dry MeCN (5 mL), chilled to 0 °C under N_2. To the solution was added TMSI (iodotrimethylsilane, 39 μL, 0.27 mmol) dropwise.[6] After 30 min, the reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (50% EtOAc/petroleum) to give a mixture of **22a** and **22b** (26 mg, 98% yield). $[\alpha]^{20}_D = -47°$ (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of two rotamers in 1:5 ratio) δ 1.03 (rotamer A; s, 3H), 1.07 (rotamer B; s, 6H), 1.10 (rotamer A; s, 3H), 1.40 (rotamer A and B; d, J = 7.2 Hz, 3H), 2.05 (rotamer A and B; s br, 1H), 2.33−2.22 (rotamer A and B; m, 2H), 3.57−3.52 (rotamer A and B; m, 1H), 3.76 (rotamer A and B; s, 3H), 4.61−4.53 (rotamer A and B; m, 1H), 5.06 (rotamer A and B; d, J = 17.6 Hz, 1H), 5.13 (rotamer A and B; d, J = 10.8 Hz, 1H), 5.43 (rotamer A; s, 1H), 5.66 (rotamer B; s, 1H), 5.90 (rotamer A; dd, J = 12.0, 10.8 Hz, 1H), 5.94 (rotamer B; dd, J = 12.0, 10.8 Hz, 1H), 7.14−7.07 (rotamer A and B; m, 2H), 7.30−7.21 (rotamer A and B; m, 1H), 7.35 (rotamer B; d, J = 7.6 Hz, 1H), 8.04 (rotamer A; d, J = 7.6 Hz, 1H), 8.59 (rotamer A; s, 1H), 8.94 (rotamer B; s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$; a mixture of two rotamers in 1:5 ratio) rotamer B: δ 18.2, 22.5, 23.5, 29.7, 40.4, 47.2, 52.4, 60.0, 62.2, 78.3, 108.4, 114.4, 124.6, 126.5, 128.6, 131.1, 134.3, 143.4, 158.6, 172.6, 173.0; rotamer A: δ 19.1, 22.6, 23.3, 29.2, 39.4, 47.5, 52.4, 60.9, 62.2, 80.4, 108.4, 116.2, 124.9, 126.5, 128.8, 131.1, 134.3, 141.0, 159.4, 172.6, 173.0; HRMS-ESI calcd for $C_{21}H_{27}N_3O_4Na$ $(M + Na)^+$ 408.1894, found 408.1899; IR (KBr) 1740, 1696, 1464, 1367, 1260, 803 cm^{-1}.

Amides 23a and 23b. To a mixture of amides **22a** and **22b** (2.5 mg, 0.006 mmol) in MeOH saturated with ammonia (0.5 mL) at 0 °C was added DMAP (4-dimethylaminopyridine, 0.5 mg, 0.004 mmol). The solution was stirred overnight, allowed to warm to room temperature, and concentrated. The residue was purified by flash chromatography (100% EtOAc) to give a mixture of amides **23a** and **23b** (2.0 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of two rotamers in 1:4 ratio) δ 0.98 (rotamer A; s, 3H), 1.02 (rotamer B; s, 3H), 1.07 (rotamer B; s, 3H), 1.10 (rotamer A; s, 3H), 1.40 (rotamer A and B; d, J = 6.8 Hz, 3H), 2.18−2.08 (rotamer A and B; m, 1H), 2.32 (rotamer B; dd, J = 12.4, 5.6 Hz, 1H), 2.40 (rotamer A; dd, J = 12.4, 5.6 Hz, 1H), 2.81 (rotamer A and B; s br, 1H), 3.50 (rotamer A; dd, J = 10.4, 5.6 Hz, 1H), 3.54 (rotamer B; dd, J = 10.4, 5.6 Hz, 1H), 4.44 (rotamer A and B; q, J = 7.2 Hz, 1H), 5.06 (rotamer A and B; d, J = 17.2 Hz, 1H), 5.14 (rotamer A and B; d, J = 10.8 Hz, 1H), 5.29 (rotamer A and B; s br, 1H), 5.41 (rotamer A; s, 1H), 5.65 (rotamer B; s, 1H), 5.90 (rotamer A; dd, J = 17.2, 6.8 Hz, 1H), 5.93 (rotamer B; dd, J = 17.2, 6.8 Hz, 1H), 6.11 (rotamer A and B; s br, 1H), 7.16−7.08 (rotamer A and B; m, 2H), 7.27−7.22 (rotamer A and B; m, 1H), 7.35 (rotamer B; d, J = 8.0 Hz, 1H), 8.04 (rotamer A; d, J = 7.6 Hz, 1H), 8.58 (rotamer A; s, 1H), 8.93 (rotamer B; s, 1H).

Diketopiperazines 26a and 26b. To a solution of **22a** and **22b** (20 mg, 0.052 mmol) in a 10:1 mixture of MeOH/H_2O (5 mL) was added LiOH (11 mg, 0.268 mmol). After stirring for 4 h, the reaction was diluted with CH_2Cl_2 (10 mL), washed with brine (10 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (17% MeOH/CH_2Cl_2) to give a viscous residue.

To a solution of the above residue in CH_2Cl_2 (5 mL) were added Et_3N (14 μL, 0.10 mmol) and $ClCOO^tBu$ (14 μL, 0.10 mmol) at 0 °C. After stirring at 0 °C for 2 h, the mixture was then quenched by saturated $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography (50% EtOAc/petroleum) to yield diketopiperazines **26a** (7.0 mg, 36% yield) and **26b** (6.0 mg, 35% yield).

26a: $[\alpha]^{20}_D = -162°$ (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.12 (s, 3H), 1.43 (d, J = 6.8 Hz, 3H), 2.43 (t, J =12.0 Hz, 1H), 2.65 (dd, J = 12.8, 6.0 Hz, 1H), 3.93 (q, J = 5.6 Hz, 1H), 4.09−4.03 (m, 1H), 5.11 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.8 Hz, 1H), 5.87 (dd, J = 17.2, 10.8 Hz, 1H), 6.13 (s, 1H), 6.26 (s br, 1H), 7.16 (t, J =7.6 Hz, 1H), 7.33 (q, J =7.2 Hz, 2H), 8.06 (d, J = 8.0 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 22.2, 23.0, 37.4, 41.0, 53.3, 57.7, 60.1, 77.6, 115.5, 117.0, 124.9, 129.5, 132.0, 141.4, 142.4, 161.7, 166.3, 167.6; HRMS-ESI calcd for $C_{20}H_{23}N_3O_3Na$ $(M + Na)^+$ 376.1637, found 376.1629; IR (KBr) 3307, 1744, 1674, 1458, 756 cm^{-1}.

26b: $[\alpha]^{20}_D = -199°$ (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.13 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H), 2.47 (t, J =11.2 Hz, 1H), 2.63(dd, J =12.8, 6.0 Hz, 1H), 4.00−3.95 (m, 1H), 4.12 (q, J = 7.2 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.4 Hz, 1H), 5.85 (dd, J = 17.2, 10.8 Hz, 1H), 6.07 (s, 1H), 6.20 (s br, 1H), 7.16 (t, J =7.6 Hz, 1H), 7.35−7.30 (m, 2H), 8.03 (d, J = 7.6 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 22.2, 23.0, 36.5, 40.9, 51.2, 59.0, 60.4, 77.3, 115.3, 117.0, 124.9, 129.4, 132.2, 141.3, 142.4, 161.6, 166.1, 168.8; HRMS-ESI calcd for $C_{20}H_{23}N_3O_3Na$ $(M + Na)^+$ 376.1637, found 376.1632; IR (KBr) 3307, 1682, 1463, 1375, 1160, 757 cm^{-1}.

Compounds 27 and 28 from 26a. To a solution of diketopiperazine **26a** (10.0 mg**,** 0.028 mmol) in THF (3 mL) at −78 °C under N_2 was added ^{n}BuLi (2.5 M in THF, 22 μL, 0.055 mmol). After stirring for 20 min at −78 °C, a solution of *o*-azidobenzoic anhydride (17 mg, 0.056 mmol) in THF (0.1 mL) was added via a syringe. After 10 min, the mixture was poured into a biphasic mixture of saturated $NaHCO_3$ (5 mL) and EtOAc (5 mL). The aqueous layer was separated and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried

over Na_2SO_4, and concentrated. The residue was purified by chromatography (50% EtOAc/petroleum) to give **27** (6.3 mg, 44% yield) and **28** (5.7 mg, 42 % yield).

27: $[\alpha]^{20}_D = -72°$ (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.14 (s, 3H), 1.52 (d, $J = 6.8$ Hz, 3H), 2.67−2.53 (m, 2H), 4.07 (dd, $J = 11.2$, 6.4 Hz, 1H), 5.09 (q, $J = 7.2$ Hz, 1H), 5.15 (d, $J = 17.2$ Hz, 1H), 5.21 (d, $J = 10.4$ Hz, 1H), 5.87 (dd, $J = 17.4$, 3.2 Hz, 1H), 6.17 (s, 1H), 7.20−7.16 (m, 2H), 7.31−7.23 (m, 2H), 7.37 (td, $J = 7.4$, 1.2 Hz, 1H), 7.42 (dd, J =7.8, 1.6 Hz, 1H), 7.52 (td, J =7.8, 1.2 Hz, 1H), 8.09 (d, $J = 7.6$ Hz, 1H), 9.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.4, 22.2, 22.7, 37.3, 41.1, 55.5, 59.0, 60.5, 77.3, 115.7, 117.2, 118.2, 124.9, 125.0, 125.4, 128.3, 129.5, 129.7, 131.8, 132.1, 136.3, 141.3, 142.2, 161.6, 166.3, 167.8, 168.4; HRMS-ESI calcd for $C_{27}H_{26}N_6O_4Na$ $(M + Na)^+$ 521.1908, found 521.1913; IR (KBr) 3342, 2575, 1702, 1430, 1103cm^{-1}.

28:[6a] $[\alpha]^{20}_D = -152°$ (*c* 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.13 (s, 3H), 1.51 (d, $J = 7.6$ Hz, 3H), 2.52 (d, $J = 4.8$ Hz, 1H), 2.54 (d, $J = 2.0$ Hz, 1H), 4.05 (dd, $J = 10.0$, 7.2 Hz, 1H), 5.06 (q, $J = 7.2$ Hz, 1H), 5.08 (s, 1H), 5.11 (dd, $J =$ 16.4, 1.2 Hz, 1H), 5.16 (dd, $J = 10.8$, 0.8 Hz, 1H), 5.62 (s, 1H), 5.98 (dd, $J = 17.2$, 10.8 Hz, 1H), 6.64 (d, $J = 7.6$ Hz, 1H), 6.78 (td, $J = 7.4$, 7.4, 0.8 Hz, 1H), 7.17−7.11 (m, 3H), 7.23 (td, J =7.6, 7.2, 1.2 Hz, 1H), 7.39 (dd, $J = 7.8$, 1.4 Hz, 1H), 7.50 (ddd, $J =$ 8.2, 7.6, 1.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 22.4, 22.9, 36.9, 41.0, 55.5, 59.1, 61.7, 77.5, 109.3, 114.9, 118.2, 119.0, 125.0, 125.2, 128.5, 128.6, 129.2, 131.8, 136.4, 143.3, 149.8, 166.7, 167.9, 169.1.

Compounds 27 and 28 from 26b. To a solution of diketopiperazine **26b** (10.0 mg, 0.028 mmol) in THF (3 mL) at −78 °C under N_2 was added ^{n}BuLi (2.5 M in THF, 22 μL, 0.055 mmol). After 20 min of stirring at −78 °C, a solution of *o*-azidobenzoic anhydride (17.0 mg, 0.056 mmol) in THF (0.1 mL) was added via a syringe. After 10 min, the mixture was poured into a biphasic mixture of saturated $NaHCO_3$ (5 mL) and EtOAc (5 mL). The aqueous layer was separated and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (50% EtOAc/petroleum) to give **27** (2.1 mg, 17% yield) and **28** (1.9 mg, 16 % yield).

Synthesis of Ardeemins. (−)-Ardeemin.[1,6a] Under N_2, tri(*n*-butyl)phosphine (10 μL, 0.04 mmol) was added to a solution of **28** (10 mg, 0.021 mmol) in dry benzene (2 mL). The resulting solution was stirred for overnight under N_2, and concentrated. The residue was purified by chromatography (50% EtOAc/petroleum) to yield (−)-ardeemin (8.0 mg, 93% yield). $[\alpha]^{20}_D = -122°$ (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.18 (s, 3H), 1.49 (d, $J = 7.2$ Hz, 3H), 2.75 (dd, $J = 12.8$, 10.4 Hz, 1H), 2.95 (dd, $J =$ 12.8, 6.0 Hz, 1H), 4.52 (dd, $J = 10.4$, 6.0 Hz, 1H), 5.10 (d, $J =$ 8.4 Hz, 1H), 5.14 (d, $J = 1.6$ Hz, 1H), 5.46 (q, $J = 7.2$ Hz, 1H), 5.60 (s, 1H), 6.03 (dd, $J = 17.2$, 11.2 Hz, 1H), 6.66 (d, $J = 7.6$ Hz, 1H), 6.80 (t, $J = 7.2$ Hz, 1H), 7.14 (t, $J = 7.2$ Hz, 1H), 7.26 (d, $J = 7.5$ Hz, 1H), 7.50 (t, $J = 8.0$, 1H), 7.68 (d, $J = 7.6$Hz, 1H), 7.77 (ddd, $J = 7.0$, 6.6, 1.2 Hz, 1H), 8.27 (dd, $J = 8.0$, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.9, 22.6, 22.9, 38.2, 41.0, 53.2, 58.1, 61.8, 77.8, 109.3, 114.6, 118.9, 120.7, 125.1, 127.0, 127.3, 129.1, 134.7, 143.5, 147.2, 149.8, 150.9, 160.1, 166.6.

(−)-*N*-Formalardeemin. Under N_2, tri(*n*-butyl)phosphine (10 μL, 0.04 mmol) was added to a solution of **27** (10.0 mg, 0.02 mmol) in dry benzene (2 mL). The reaction solution was stirred for overnight under N_2 and concentrated. The residue was purified by chromatography (50% EtOAc/petroleum) to yield (−)-*N*-formalardeemin (7.8 mg, 86% yield), $[\alpha]^{20}_D = -52°$ (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.18 (s, 3H), 1.50 (d, $J =$ 6.8 Hz, 3H), 2.73 (t, J =12.0 Hz, 1H), 3.03 (dd, $J = 13.2$, 6.0 Hz, 1H), 4.57−4.53 (m, 1H), 5.17−5.11 (m, 2H), 5.46 (q, $J = 7.2$ Hz, 1H), 5.89 (dd, $J = 17.2$, 10.8 Hz, 1H), 6.14 (s, 1H), 7.20 (t, $J =$ 7.2 Hz, 1H), 7.37 (t, J =8.0 Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.51 (t, J =7.6 Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 7.78 (t, $J = 7.6$ Hz, 1H), 8.09 (d, $J = 8.0$ Hz, 1H), 8.28 (d, $J = 7.6$ Hz, 1H), 9.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 22.3, 23.0, 38.7, 41.1, 53.2, 58.1, 60.6, 77.3, 115.5, 117.3, 120.5, 124.9, 125.0, 127.0, 127.2, 127.4, 129.6, 132.3, 134.8, 141.1, 142.4, 147.0, 150.1, 159.8, 161.8, 166.2; HRMS-ESI calcd for $C_{27}H_{26}N_4O_3Na$ $(M + Na)^+$ 477.1897, found 477.1893; IR (KBr) 3310, 2895, 1715, 1643, 1410, 1367, 755 cm^{-1}.

(−)-*N*-Acetylardeemin.[1,6a] To a solution of (−)-ardeemin (4 mg, 0.01 mmol) in acetic anhydride (1 mL) was added DIPEA (*N*, *N*-diisoproylethylamine, 5 μL, 0.03 mmol). The reaction mixture was heated to 60 °C for 36 h and then evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (50% EtOAc/petroleum) to give (−)-*N*-acetylardeemin (3.1 mg, 72% yield). $[\alpha]^{20}_D = -49°$ (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ1.02 (s, 3H), 1.21 (s, 3H), 1.42 (d, $J = 7.6$ Hz, 3H), 2.67 (s br, 3H), 2.69−2.68 (m, 1H), 3.02 (dd, $J = 12.8$, 5.7 Hz, 1H), 4.45−4.43 (m, 1H), 5.16−5.12 (m, 2H), 5.37 (q, $J = 7.6$ Hz, 1H), 5.81 (dd, $J = 16.8$, 10.8 Hz, 1H), 6.08 (s br, 1H), 7.24−7.22 (m, 1H), 7.45−7.42 (m, 2H), 7.55−7.52 (m, 1H), 7.73 (d, $J = 8.8$, 1H), 7.80−7.78 (m, 1H), 8.08 (s br, 1H), 8.29 (d, $J = 8.0$, 1H).

Acknowledgment. This research was supported by NSFC (Nos. 20632030, 20772083, and 20825207). We thank the Analytic and Testing Center of Sichuan University for recording spectroscopic data.

Supporting Information Available: NMR spectra of compounds **7**, **4**, **13**−**23**, **26**−**28**, (−)-ardeemin, (−)-*N*-formalardeemin, and (−)-*N*-acetylardeemin and NOEDS spectra of diketopiperazine **26a** and **26b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802216Z