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Total Syntheses of (−)-Fructigenine A and (−)-5-*N*-Acetylardeemin

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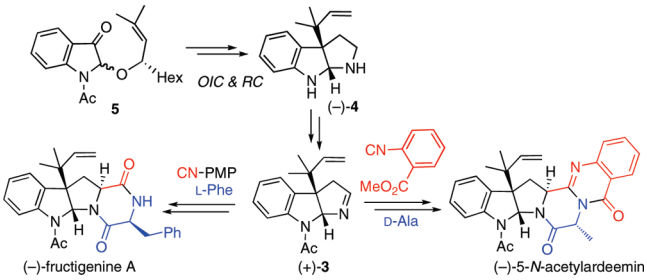

The first total synthesis of (−)-fructigenine A and a novel approach to (−)-5-*N*-acetylardeemin through a common imine intermediate (+)-**3** are described. The key steps include highly enantioselective preparation of (+)-**3** via domino olefination/isomerization/Claisen rearrangement (OIC) of **5**, reductive cyclization (RC), and regioselective oxidation of (−)-**4** and a novel assembly of the pyrazino ring of these alkaloids via Ugi three-component reaction/cyclization of (+)-**3** with the corresponding amino acid and isonitrile.

Introduction

The hexahydropyrazino[2′,1′-5,1]pyrrolo[2,3-*b*]indole ring system bearing a 1,1-dimethylallyl ("reverse-prenyl") group at C10b is a widely distributed structural framework present in a number of biologically active alkaloids such as fructigenine A (**1**),[1] okaramine M,[2] roquefortine D,[3] verrucofortine,[4] brevicompanine B,[5] amauromine,[6] and 5-*N*-acetylardeemin (**2**)[7] (Figure 1). For example, **1** isolated from *Penicillium fructigenium* has growth−inhibitory activity against *Avena coleoptile* and leukemia L-5178Y cells,[1] and the metabolite **2** of the fungus *Aspergillus fischerii* (var. *brasiliensis*) is one of the most potent known inhibitors of multidrug resistance (MDR) to antitumor agents such vinblastine, taxol, and doxorubicin.[7a,8]

The unique structural array and interesting biological activities displayed by this class of compounds make them attractive synthetic targets. Known approaches to these alkaloids started from L-tryptophan derivatives on the basis of proposed biosynthetic pathways. Thus, the total synthesis of amauromine via tryptophan anhydride (1,4-diketopiperazine) including reverse-prenylation/cyclization was performed.[9] Reverse-prenylated *cyclic*-tryptophan (pyrroloindoline-2-carboxylate) derivatives constructed by selenide-mediated cyclization/prenylation of L-tryptophan was applied to synthesize **2**,[10]

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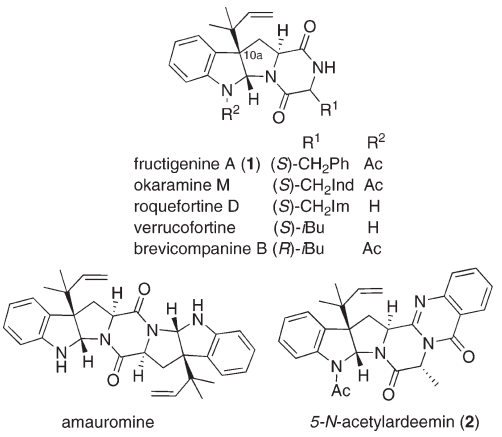


FIGURE 1. Structures of representative pyrazino-pyrroloindole alkaloids: Ind = 3-indolyl, Im = 4-imidazoyl.

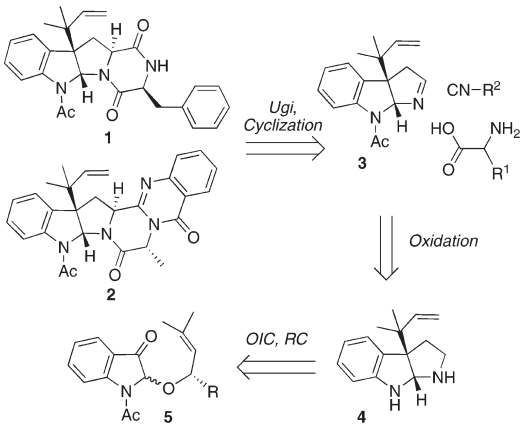
amauromine,[10] roquefortines,[11] and brevicompanine B.[12] Recently, a route to **2** via *cyclic*-tryptophan involving Cu-mediated cyclopropanation of L-tryptophanol has been reported.[13] Some analogues of **2** were also prepared for studies of the anti-MDR activity.[10b,14] In view of the potential of these natural products as lead compounds for new and more biologically active agents, a more effective and a diverse approach to pyrazino-pyrroloindoles is highly desirable.

On our program directed toward the synthesis of these alkaloids and related compounds, we sought an efficient and versatile strategy for the enantioselective assembly of the pyrazino-pyrroloindole skeleton. During the course of our total syntheses of pseudophrynaminol and flustramines, we demonstrated an efficient strategy for construction of the 3a-allylpyrrolo[2,3-*b*]indole architecture by domino olefination/isomerization/Claisen rearrangement (OIC) and reductive cyclization (RC).[15] In a subsequent synthetic investigation, we developed a novel methodology for approach to these pyrazino-pyrroloindole alkaloids (Figure 1), and we describe herein a first total synthesis of (−)-fructigenine A (**1**) together with a new concise total synthesis of (−)-5-*N*-acetylardeemin (**2**).[15e]

Results and Discussion

Our retrosynthetic analysis of **1** and **2** is shown in Scheme 1. A powerful disconnection that has heretofore been unexplored in the synthesis of these alkaloids would involve the Ugi three-component reaction[16] of pyrroloindoline imine **3** with the corresponding amino acid and isonitrile followed by

SCHEME 1. Retrosynthesis of Fructigenine A (1) and (−)-5-*N*-Acetylardeemin (2)



cyclization to assemble the pyrazino ring. The imine **3** could be predicted to serve as an effectively common intermediate to the related alkaloids and obtained by regioselective oxidation of pyrroloindoline **4**. The enantiomerically enriched compound **4** could be readily prepared from **5** by our modified protocol including asymmetric OIC and RC.[15]

To synthesize alkaloids **1** and **2**, we began by preparing the key imine intermediate **3** (Scheme 2). Bromination of 1-acetylindolin-3-one (**6**)[17] at the C2 site followed by substitution with (*S*)-2-methyl-2-decen-4-ol (**7**) (99% ee)[15c] afforded ether **5** in 88% yield. Horner−Wadsworth−Emmons reaction of **5** with diethyl cyanomethylphosphonate in the presence of *t*-BuOK at −78 to 0 °C proceeded smoothly with domino olefination/isomerization/Claisen rearrangement (OIC) to produce an enantiomerically enriched oxindole (−)-**8** in 89% yield and 99% ee.[18,19] For conversion of the alkenyl moiety in **8** to a reverse-prenyl group, a sequence of ozonolysis of (−)-**8** and Wittig olefination with methylidenephosphorane was carried out to provide 3-prenylindolin-2-one (−)-**9** in 65% yield for two steps. The reductive cyclization (RC) of (−)-**9** with $LiAlH_4$ furnished pyrroloindole (−)-**4** in 80% yield. Each procedure in transformation of **6** to (−)-**4** was readily performed on multigram scale in good yield. Successive N^1-Boc-protection of (−)-**4** with Boc_2O and DMAP (90%), acetylation with acetyl chloride in the presence of NaOH and Bu_4NHSO_4 (90%), and removal of the Boc group with TFA (90%) afforded N^8-acetylpyrroloindole (+)-**10**. Oxidation[20] of (+)-**10** with catalytic tetrapropylammonium perruthenate (TPAP) and NMO as a co-oxidant proceeded regioselectively to give imine (+)-**3** with highly enantiomeric purity (99% ee)[17] in 89% yield. The desired key common intermediate (+)-**3** was obtained from **6** in ten steps and 26.5% overall yield.

With easily available key intermediate (+)-**3** in hand, we progressed toward the total synthesis of fructigenine A

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(16) Review: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

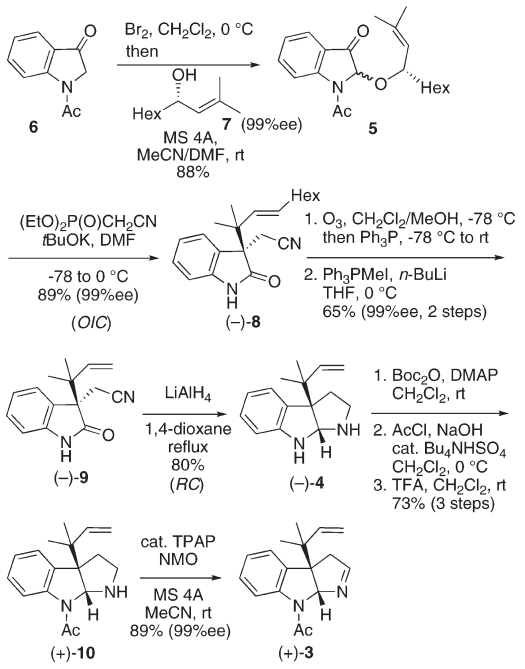
(17) The starting **6** was readily obtained from commercially available 1-acetylindole in 2 steps: Chien, C.-S.; Hasegawa, A.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1986**, *34*, 1493.

(18) The enantiomeric excess was determined by HPLC analysis using stationary phase.

(19) The stereochemistry at the C3 of **8** was tentatively assigned based on comparison with the specific rotation of the 6-bromo derivative of **8**[15c] and ultimately confirmed by NOE experiments following transformation to **12** as shown in Scheme 3.

(20) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

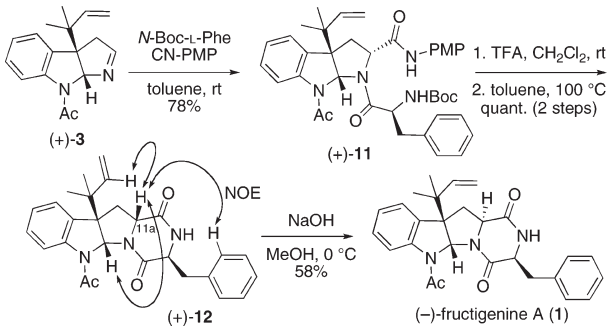
SCHEME 2. Synthesis of Pyrroloindoline Imine (+)-3



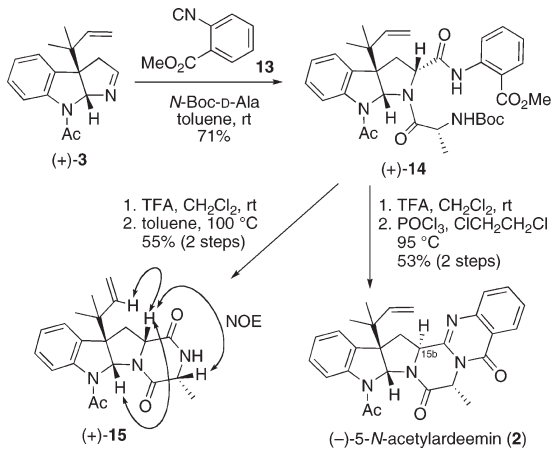
(**1**, Scheme 3). When (+)-**3** was treated with *N*-Boc-L-phenylalanine and *p*-methoxyphenyl (PMP)-isonitrile at room temperature, the stereoselective Ugi three-component reaction[21] proceeded smoothly to afford dipeptide (+)-**11** in 78% yield.[22] On removal of the Boc group from (+)-**11** with TFA and smooth cyclization in heating toluene, diketopiperazine (+)-**12** was obtained in quantitative yield. The stereochemistry of (+)-**12** was confirmed by NOE experiments as shown in Scheme 3. This indicates that the isonitrile attacks predominantly on the side opposite the bulky reverse-prenyl group of imine (+)-**3** in the Ugi reaction. Since (+)-**12** is a C11a-epimer of the natural product **1**, epimerization of (+)-**12** was carried out with NaOH at low temperature to provide (−)-**1**[23] in 58% yield together with a C11a-epimer of **1** (23%). The first total synthesis of fructigenine A (**1**) was achieved in four steps and 45% overall yield from imine **3**.

Next, we performed the synthesis of 5-*N*-acetylardeemin (**2**, Scheme 4). The Ugi reaction of (+)-**3** with *N*-Boc-D-

SCHEME 3. Synthesis of (−)-Fructigenine A (1)



SCHEME 4. Synthesis of (−)-5-*N*-Acetylardeemin (2)



alanine and isonitrile **13**[24,25] provided stereoselectively a 71% yield of tripeptide (+)-**14**.[26] Boc-deprotection of (+)-**14** followed by heating in toluene easily liberated the anthranilic ester to form diketopiperazine (+)-**15**, of which the stereochemistry was determined by NOE experiments on (+)-**15**. For assembling the pyrazino[2,1-*b*]quinazolinone structure[27] of **2**, double-condensation among amino, amide, and ester groups of (+)-**14** was required. In our preliminary exploration of suitable condensing agents, we found the use of phosphorus oxychloride to achieve the desired ring closure. After removal of the Boc group of (+)-**14**, successive heating with phosphorus oxychloride directly constructed the pyrazine and pyrimidine rings together with epimerizion at C15b to give (−)-**2** in 53% yield.[23] The physical and spectral data of the synthetic product (−)-**2** are identical with those of the natural product. The total synthesis of 5-*N*-acetylardeemin (**2**) was accomplished in a 37.6% three-step yield from the common intermediate **3**.

Conclusion

In summary, we have completed the asymmetric total syntheses of two pyrazino-pyrroloindole alkaloids, fructigenine A (**1**) and 5-*N*-acetylardeemin (**2**), via Ugi reaction/cyclization of the common imine intermediate (+)-**3**, which was easily prepared in highly enantiomeric purity, and we demonstrated a novel and concise synthetic methodology for a variety of pyrazino-pyrroloindole compounds. In addition, this first use of isonitrile **13** in Ugi reaction/cyclization inspires a new route to a series of pyrazino[2,1-*b*]-quinazolinone compounds. Further synthetic studies of this

(21) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.

(22) The stereochemistry of **11** was confirmed by NOE experiments on **12** as shown in Scheme 3.

(23) The physical and spectral data of the synthetic product are identical with those of the natural product.

(24) Isonitrile **13** was obtained in quantitative yield from methyl anthranilate via formylation (HCO_2H, toluene, reflux) and dehydration ($POCl_3$, Et_3N, THF, rt): Kobayashi, K.; Nakashima, T.; Mano, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2001**, *30*, 602.

(25) Only a few reactions of isonitrile **13** are known for the preparation of quinolines[24] and pyrazolo[5,1-*b*]quinazoline: Atlan, V.; Buron, C.; Kaïm, L. *Synlett* **2000**, 489.

(26) The stereochemistry of **14** was determined by NOE experiments on **15** as shown in Scheme 4.

(27) This scaffold is contained in a number of bioactive fungal metabolites other than **2**, such as fumiquinazolines, alanttrypinone, and so on: (a) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345. (b) Cledera, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **2000**, *65*, 1743. (c) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892. (d) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545. (e) Liu, J.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339.

class of alkaloids as well as SAR studies of the anti-MDR properties of **2** are now in progress.

Experimental Section

1-Acetyl-2-[(*S*)-2-methyldec-2-en-4-yloxy]indolin-3-one (5). A CH_2Cl_2 solution of Br_2 (1 M, 14.5 mL, 14.5 mmol) was added to a solution of **6** (2.1 g, 12.1 mmol) in CH_2Cl_2 (24 mL) at 0 °C. After being stirred at the same temperature for 1 h, the mixture was concentrated and dissolved in MeCN−DMF (10:1, 25 mL). To the mixture was added MS 4A (powder, 12 g) and (*S*)-2-methyl-2-decen-4-ol (**7**) (4.1 g, 24.3 mmol, 99% ee) at 0 °C. After the mixture was stirred at room temperature for 3 days, excess **7** was acetylated with Ac_2O (2.3 mL, 24.3 mmol), pyridine (30 mL, 36.5 mmol), and DMAP (0.29 g, 2.4 mmol) in CH_2Cl_2 (240 mL) at room temperature for 1 h with stirring. The mixture was washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography with AcOEt/*n*-hexane (1/6) as an eluent to give **5** (3.60 g) in 88% yield as a viscous oil. IR ($CHCl_3$) 2930, 1728, 1682, 1464, 1385 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$, 1:2 diastereomer mixture) δ 0.85 (3H, m), 1.09 (1/3H, s), 1.24 (8H, m), 1.39 (1/3H, s), 1.50 (2/3H, d, J = 0.9 Hz), 1.64 (2/3H, d, J = 0.6 Hz), 2.36 (2/3H, s), 2.44 (1/3H, s), 4.27 (1/3H, br s), 4.76 (2/3H, ddd, J = 6.6, 3.3, 6.6 Hz), 4.99−5.05 (1H, m), 5.12 (2/3H, s), 5.35 (1/3H, s), 7.18 (1H, m), 7.66 (2H, m), 8.46 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 17.5, 18.0, 22.5, 23.7, 24.1, 24.8, 25.1, 25.46, 25.47, 25.61, 25.64, 29.8, 31.7, 35.6, 36.0, 72.1, 74.1, 82.75, 82.79, 85.77, 85.80, 118.1, 118.2, 122.7, 122.8, 123.5, 123.6, 123.9, 124.2, 124.9, 125.4, 135.5, 137.3, 137.8, 139.0, 152.6, 153.1, 169.66, 169.75, 195.2, 196.4; MS (EI) m/z (%) 343 (M^+, 2), 190 (20),175 (11), 153 (26), 149 (17), 148 (100), 132 (19), 97 (18), 83 (13), 69 (45), 43 (13); HRMS (EI) m/z calcd for $C_{21}H_{29}NO_3$ 343.2148, found 343.2148.

(*R*,*E*)-2-[3-(2-Methyldec-3-en-2-yl)-2-oxoindolin-3-yl]acetonitrile [(−)-8]. Under N_2 atmosphere, to a solution of *t*-BuOK (3.7 g, 33 mmol) in DMF (110 mL) was added $(EtO)_2P(O)CH_2CN$ (6.0 mL, d 1.13, 37 mmol) at 0 °C and the mixture was stirred at the same temperature for 2 h. After cooling at −78 °C, to the mixture was added slowly a solution of **5** (3.8 g, 11 mmol) at the same temperature. After consumption of **5** (0.5 h), the stirred reaction mixture was warmed gradually to 0 °C for 7 h, quenched with satd aqueous NH_4Cl, and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/7) to give (−)-**8** (3.2 g, 89%, 99% ee CHIRALCEL AD flow 0.5 mL/min EtOH/*n*-hexane = 4.0/96.0) as a viscous oil. $[\alpha]^{26}_D$ −118 (*c* 0.11, EtOH); IR ($CHCl_3$) 3431, 2928, 1722, 1620, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, t, J = 6.6 Hz), 1.03 (3H, s), 1.16 (3H, s), 1.25−1.43 (8H, m), 2.06 (2H, dd, J = 6.9, 12.9 Hz), 2.84 (1H, d, J = 16.5 Hz), 2.98 (1H, d, J = 16.5 Hz), 5.45 (1H, dt, J = 15.6, 6.6 Hz), 5.62 (1H, d, J = 15.6 Hz), 6.89 (1H, t, J = 7.5 Hz), 7.06 (1H, t, J = 7.5 Hz), 7.25−7.32 (2H, m), 7.56 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 21.7, 22.5, 22.8, 23.0, 29.0, 29.5, 31.8, 32.9, 41.1, 55.7, 109.8, 116.8, 122.1, 125.6, 128.4, 129.0, 131.3, 133.3, 141.2, 178.0; MS (EI) m/z (%) 324 (M^+, 1), 172 (65), 153 (100), 97 (68), 69 (93); HRMS (EI) m/z calcd for $C_{21}H_{28}N_2O$ 324.2202, found 324.2205. Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.70; H, 8.85; N, 8.58.

2-[3-(2-Methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetonitrile [(−)-9]. A solution of (−)-**8** (2.3 g, 7.1 mmol) in CH_2Cl_2/MeOH (14 mL, 10/1) was cooled to −78 °C, and O_3 gas was bubbled into the stirred mixture at −78 °C for 1.5 h. Excess O_3 was purged with N_2 gas at the same temperature for 5 min and PPh_3 (5.6 g, 21.3 mmol) was added to the mixture. The reaction mixture was allowed to warm to room temperature, then stirred for 6 h. The solvent was removed under reduced pressure and the residue was roughly purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/2) to give an aldehyde (1.5 g). Under N_2 atmosphere, to a suspension of Ph_3PCH_3I (8.5 g, 21 mmol) in THF (30 mL) was added *n*-BuLi (10.2 mL, 2.6 M in *n*-hexane, 26.5 mmol) at −78 °C. After being stirred for 10 min, the mixture was added to a solution of the above aldehyde (1.5 g, 6.0 mmol) in THF (30 mL) at the same temperature. After consumption of the aldehyde, the resulting mixture was warmed to 0 °C, quenched with water, and extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 3/7) to give (−)-**9** (1.19 g, 65% from **8**, 99% ee CHIRALCEL AD flow 0.5 mL/min EtOH/*n*-hexane = 13.0/87.0) as colorless crystals. Mp 154−155 °C (AcOEt/*n*-hexane) [lit.[15b] (±)-**9** mp 154−155 °C]; $[\alpha]^{27}_D$ −133.8 (*c* 0.05, EtOH); IR ($CHCl_3$) 3434, 2255, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (3H, s), 1.16 (3H, s), 2.86 (1H, d, J = 16.2 Hz), 3.00 (1H, d, J = 16.5 Hz), 5.10 (1H, dd, J = 17.7, 0.9 Hz), 5.22 (1H, dd, J = 0.6, 10.8 Hz), 6.09 (1H, dd, J = 17.8, 10.8 Hz), 6.93 (1H, br s), 7.07 (1H, ddd, J = 0.9, 0.9, 0.9 Hz), 7.29 (2H, br s), 8.43 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 21.9, 21.9, 41.6, 55.4, 110.1, 115.3, 116.8, 122.3, 125.7, 128.2, 129.3, 141.5, 141.8, 178.4; MS (EI) m/z (%) 240 (M^+, 6), 170 (100), 145 (59), 69 (92), 41 (50); HRMS (EI) m/z calcd for $C_{15}H_{16}N_2O$ 240.1263, found 240.1263. Anal. Calcd for $C_{15}H_{16}N_2O$: C 74.97; H 6.71; N 11.66. Found: C 74.62; H 6.61; N 11.31.

(3a*R*,8a*R*)-3a-(2-Methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole [(−)-4]. To a solution of (−)-**9** (2.5 g, 11 mmol) in 1,4-dioxane (104 mL) was added $LiAlH_4$ (4.2 g, 110 mmol). After heating under reflux for 3 h, the mixture was cooled to 0 °C and quenched with THF/H_2O (5/1). The resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was diluted with AcOEt and then the solution was washed with satd aqueous $NaHCO_3$ and brine. The concentrated residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 5/1) to give (−)-**4** (1.9 g, 80%) as colorless crystals. Mp 57−60 °C (*n*-pentane), [lit.[15b] (±)-**4** mp 57−60 °C]; $[\alpha]^{25}_D$ −115° (*c* 0.88, MeOH); IR ($CHCl_3$) 3425, 1608, 1485, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.13 (3H, s), 1.89 (1H, ddd, J = 11.7, 5.1, 1.2 Hz), 2.10 (1H, dt, J = 11.1, 6.6 Hz), 2.61 (1H, td, J = 11.4, 5.4 Hz), 2.99 (1H, ddd, J = 10.8, 6.3, 1.2 Hz), 4.91 (1H, s), 5.03 (1H, dd, J = 17.1, 1.5 Hz), 5.08 (1H, dd, J = 10.5, 1.5 Hz), 6.03 (1H, dd, J = 17.4, 10.8 Hz), 6.54 (1H, dd, J = 7.5, 0.6 Hz), 6.68 (1H, td, J = 7.5, 1.2 Hz), 7.03 (1H, td, J = 7.8, 1.2 Hz), 7.11−7.14 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 23.3, 37.4, 41.1, 46.5, 65.4, 80.3, 108.3, 113.1, 118.0, 125.4, 127.8, 132.0, 145.0, 151.3; MS (EI) m/z (%) 228 (M^+, 25), 159 (100), 130 (31), 77 (3), 69 (3), 41 (4); HRMS (EI) m/z calcd for $C_{15}H_{20}N_2$ 228.1626, found 228.1629. Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.52; H, 9.18; N, 12.15.

(3a*R*,8a*R*)-8-Acetyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole [(+)-10]. Boc_2O (1.7 mL, 7.4 mmol) was added to a solution of (−)-**4** (1.4 g, 6.1 mmol) in CH_2Cl_2 (61 mL) at room temperature. After being stirred for 4.5 h, 28% aqueous NH_3 (0.7 mL) was added to the mixture in order to quench excess Boc_2O. The mixture was washed with H_2O and the combined water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The concentrated residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/10) to give a *N*-Boc compound (1.8 g, 90%, 99% ee CHIRALCEL AD flow 0.5 mL/min EtOH/*n*-hexane = 5.0/95.0) as a white solid. Mp 115−118 °C (AcOEt); $[\alpha]^{21}_D$ −361 (*c* 0.13, MeOH); IR ($CHCl_3$) 3422, 1678, 1606, 1481, 1466, 1408 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C) δ 0.86 (3H, s), 0.96 (3H, s), 1.36 (9H, s), 1.85 (1H, dd, J = 12.2, 5.9 Hz), 2.14 (1H, td, J = 12.2, 8.3 Hz), 2.64 (1H, td, J = 10.4, 5.9 Hz), 3.47 (1H, dd, J = 10.4, 8.3 Hz),

4.93 (1H, dd, J = 17.6, 1.5 Hz), 4.97 (1H, dd, J = 11.0, 1.5 Hz), 5.60 (1H, s), 5.82 (1H, br s), 5.93 (1H, dd, J = 17.6, 11.0 Hz), 6.47 (1H, d, J = 7.6 Hz), 6.51 (1H, td, J = 7.6, 1.2 Hz), 6.89 (1H, td, J = 7.6, 1.2 Hz), 7.00 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ 22.1, 22.4, 23.4, 26.6, 27.8, 30.9, 31.8, 40.4, 76.6, 78.4, 107.7, 112.5, 116.4, 123.8, 127.3, 144.0, 150.2; MS (EI) m/z (%) 328 (M^+, 17), 272 (4), 203 (100), 159 (21), 130 (16), 77 (1), 69 (3); HRMS (EI) m/z calcd for $C_{20}H_{28}N_2O_2$ 328.2151, found 328.2150. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.23; H, 8.82; N, 8.50.

To a solution of the *N*-Boc compound (65 mg, 0.20 mmol), NaOH (47 mg, 1.2 mmol), and *n*-Bu_4NHSO_4 (1 mg, 2 μmol) in CH_2Cl_2 (2.0 mL) was added AcCl (28 μL, 0.60 mmol). After stirring at room temperature for 10 min, the precipitate was filtered off in the mixture, and the filtrate was washed with brine and dried over anhydrous $MgSO_4$. The concentrated residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/4) to give a *N*-Boc-*N*′-Ac compound (66 mg, 90%) as a viscous oil. $[\alpha]^{20}_D$ −128 (*c* 0.31, MeOH); IR ($CHCl_3$) 1689, 1662, 1477, 1458, 1404 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.12 (3H, s), 1.46 (9H, s), 1.95 (1H, dd, J = 11.8, 5.0 Hz), 2.17 (1H, td, J = 11.8, 7.6 Hz), 2.54 (3H, br s), 2.72 (1H, td, J = 11.8, 5.0 Hz), 3.75 (1H, br s), 5.07 (1H, d, J = 17.1 Hz), 5.08 (1H, d, J = 11.0 Hz), 5.84 (1H, dd, J = 17.1, 11.0 Hz), 5.98 (1H, br s), 7.08 (1H, t, J = 7.6 Hz), 7.22 (1H, d, J = 7.6 Hz), 7.26 (1H, t, J = 7.6 Hz), 8.06 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.6, 24.1 28.4, 32.6, 40.7, 46.5, 63.3, 79.6, 80.4, 113.7, 118.2, 123.6, 124.3, 128.2, 133.0, 143.4, 143.6, 153.8, 170.2; MS (EI) m/z (%) 370 (M^+, 39), 328 (7), 272 (16), 203 (100), 159 (71), 130 (33), 69 (7), 57 (14), 41 (7); HRMS (EI) m/z calcd for $C_{22}H_{30}N_2O_3$ 370.2256, found 370.2255. Anal. Calcd for $C_{22}H_{30}N_2$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.59; H, 8.44; N, 7.33.

TFA (1.8 mL, 24.3 mmol) was added to a suspension of the *N*-Boc *N*-Ac compound (180 mg, 0.49 mmol) in CH_2Cl_2 (9.7 mL) at room temperature. After being stirred for 30 min, the mixture was neutralized with satd aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to give (+)-**10** (117 mg, 90%) as a viscous oil. $[\alpha]^{22}_D$ +21 (*c* 7.26, MeOH); IR ($CHCl_3$) 3362, 1651, 1595, 1481, 1460, 1399 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (2.4H, s), 1.01 (0.6H, s), 1.07 (0.6H, s), 1.12 (2.4H, s), 2.20 (1H, td, J=12.0, 6.8 Hz), 2.16−2.23 (2H, m), 2.33 (2.4H, s), 2.43 (0.6H, s), 2.57 (1H, td, J = 11.0, 5.1 Hz), 3.00 (1H, dd, J = 11.0, 6.8 Hz), 5.06 (1H, d, J = 17.3 Hz), 5.11 (1H, d, J = 10.7 Hz), 5.25 (0.8H, s), 5.62 (0.2H, s), 5.95 (1H, dd, J = 17.3, 10.7 Hz), 7.04 (1H, t, J = 7.4 Hz), 7.21−7.32 (2H, m), 8.18 (1H, d, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 23.0, 23.5, 23.6, 24.1, 25.0, 31.6, 35.9, 36.5, 41.1, 45.2, 46.3, 63.5, 81.1, 82.5, 113.3, 113.6, 116.3, 122.9, 123.2, 124.7, 126.2, 127.7, 128.0, 133.8, 143.5, 144.1, 168.8; MS (EI) m/z (%) 270 (M^+, 23), 201 (35), 159 (100), 130 (24), 77 (2), 69 (2), 41 (2); HRMS (EI) m/z calcd for $C_{17}H_{22}N_2O$ 270.1732, found 270.1732.

(3a*R*,8a*R*)-8-Acetyl-3a-(2-methylbut-3-en-2-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole [(+)-3]. Under N_2 atmosphere, to a solution of (+)-**10** (880 mg, 3.3 mmol) in MeCN (65 mL) was added MS4A (2.5 g), NMO (1.1 g, 9.9 mmol), and TPAP (114 mg, 0.33 mmol) at room temperature. After 15 min of stirring, activated charcoal (4.0 g) was added to the mixture, which was then stirred for 5 min. Then the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to give (+)-**3** (779 mg, 89% 99% ee CHIRALCEL OD flow 0.5 mL/min EtOH/*n*-hexane = 25.0/75.0) as a colorless oil. $[\alpha]^{22}_D$ +88 (*c* 0.26, MeOH); IR ($CHCl_3$) 1663, 1628, 1595, 1479, 1462, 1400 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.10 (3H, s), 2.56 (3H, s), 2.86 (1H, dt, J = 18.3, 1.5 Hz), 3.13 (1H, d, J = 18.3 Hz), 5.09 (1H, dd, J = 17.7, 0.9 Hz), 5.13 (1H, dd, J = 10.8, 0.9 Hz), 5.83 (1H, dd, J = 17.1, 10.8 Hz), 5.96 (1H, d, J = 1.8 Hz), 7.05 (1H, td, J = 7.5, 0.9 Hz), 7.21 (1H, br s), 7.26 (1H, br s), 7.60 (1H, s), 8.20 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 23.5, 24.2, 40.7, 47.3, 58.9, 94.3, 114.2, 117.3, 123.5, 125.0, 128.7, 134.1, 141.6, 143.6, 168.4, 169.0; MS (EI) m/z (%) 268 (M^+, 26), 226 (11), 199 (8), 157 (100), 130 (39), 69 (7), 41 (4); HRMS (EI) calcd for $C_{17}H_{20}N_2O$ 268.1576, found 268.1574.

(2*R*,3a*R*,8a*R*)-8-Acetyl-1-[(*S*)-2-*tert*-butoxycarbonylamino-3-phenylpropanoyl]-2-(4-methoxyphenylcarbamoyl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole [(+)-11]. A solution of (+)-**3** (24 mg, 89 μmol), 4-methoxyphenylisonitrile (18 mg, 0.13 mmol), and *N*-Boc-L-phenylalanine (36 mg, 0.13 mmol) in toluene (0.18 mL) was stirred at room temperature for 1.5 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/5) to give (+)-**11** (60 mg, 78%) as a white solid. Mp 225−227 °C ($CHCl_3$); $[\alpha]^{21}_D$ +159 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3445, 3348, 1699, 1662, 1601, 1537, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (3H, s), 0.84 (3H, s), 1.35 (9H, s), 2.10 (1H, dd, J = 12.4, 9.6 Hz), 2.31 (3H, s), 2.70 (1H, d, J = 12.4 Hz), 2.94 (1H, dd, J = 12.4, 6.8 Hz), 3.06 (1H, dd, J = 12.4, 8.8 Hz), 3.73 (3H, s), 4.72 (1H, d, J = 8.8 Hz), 4.85 (1H, br s), 4.88 (1H, d, J = 17.2 Hz), 4.95 (1H, d, J = 10.8 Hz), 5.43 (1H, dd, J = 16.8, 10.4 Hz), 5.51 (1H, br s), 5.98 (1H, s), 6.61 (2H, d, J = 9.2 Hz), 6.92−7.44 (11H, m), 7.73 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 23.2, 23.6, 28.4, 32.9, 38.6, 40.2, 52.0, 55.4, 61.5, 62.3, 78.5, 79.8, 112.8, 114.1, 117.6, 121.7, 124.7, 127.2, 128.6, 128.8, 129.6, 130.9, 134.6, 135.3, 142.2, 142.8, 155.4, 155.6, 167.9, 170.4, 173.2; MS (EI) m/z (%) 666 (M^+, 65), 566 (31), 548 (4), 497 (12), 475 (11), 447 (20), 419 (10), 378 (11), 334 (37), 332 (34), 308 (27), 269 (100), 201 (31), 159 (40), 120 (84), 69 (28); HRMS (EI) m/z calcd for $C_{39}H_{46}N_4O_6$ 666.3417, found 666.3412.

(3*S*,5a*R*,10b*R*,11a*R*)-6-Acetyl-10b-(2-methylbut-3-en-2-yl)-3-benzyl-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1′,2′:1,2]pyrrolo[4,5-*b*]indole-1,4-dione [(+)-12]. To a solution of (+)-**11** (33 mg, 50 μmol) in CH_2Cl_2 (1.0 mL) was added TFA (180 μL, 2.5 mmol) at room temperature. After being stirred for 1 h, the mixture was neutralized with satd aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was diluted with toluene (1.0 mL) and heated at 100 °C for 23 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/4) to give (+)-**12** (22 mg, quant) as a white solid. Mp 125−128 °C ($CHCl_3$); $[\alpha]^{22}_D$ +56 (*c* 0.52, MeOH); IR ($CHCl_3$) 3397, 1680, 1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, s), 1.01 (3H, s), 2.29 (1H, dd, J = 13.4, 9.6 Hz), 2.48 (1H, dd, J = 13.6, 9.2 Hz), 2.57 (3H, br s), 2.69 (1H, br s), 2.96 (1H, dd, J = 13.2, 3.6 Hz), 3.23 (1H, dd, J = 13.2, 6.0 Hz), 4.09 (1H, br s), 5.06 (1H, d, J = 17.2 Hz), 5.09 (1H, d, J = 10.4 Hz), 5.43 (1H, br s), 5.61 (1H, dd, J = 15.6, 10.4 Hz), 6.02 (1H, s), 7.06 (1H, t, J = 7.6 Hz), 7.15 (1H, d, J = 7.6 Hz), 7.19−7.26 (3H, m), 7.30−7.39 (3H, m), 7.96 (1H, br s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.9, 22.4, 24.4, 34.3, 40.4, 41.1, 55.4, 58.9, 114.7, 118.7, 124.3, 125.5, 125.7, 127.7, 128.4, 128.9, 129.9, 135.4, 141.4, 142.9, 168.6; MS (EI) m/z (%) 443 (M^+, 12), 401 (13), 332 (100), 304 (4), 241 (4), 157 (15), 130 (17), 69 (3), 41 (2); HRMS (EI) m/z calcd for $C_{27}H_{29}N_3O_3$ 443.2209, found 443.2212.

(−)-Fructigenine A [(−)-1]. To a solution of (+)-**12** (13 mg, 29 μmol) in MeOH (0.59 mL) was added NaOH (35 mg, 0.88 mmol) at 0 °C. After being stirred at the same temperature for 30 min, the mixture was neutralized with satd aqueous NH_4Cl and extracted with AcOEt. The extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 3/1) to give (−)-fructigenine A [(−)-**1**, 7.5 mg, 58%] as a white solid. Mp 83−85 °C (CH_2Cl_2); $[\alpha]^{27}_D$ −170 (*c* 0.14, $CHCl_3$) [lit.[1] $[\alpha]_D$ −178 (*c* 0.24, $CHCl_3$)]; IR (KBr) 3347, 1674, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.13 (3H, s), 2.27 (1H, dd, *J* = 12.0, 11.7 Hz), 2.57 (1H, dd, *J* = 12.3, 5.7 Hz), 2.66 (3H, s), 2.80 (1H, dd, *J* = 14.4, 10.5 Hz), 3.55 (1H, dd, *J* = 14.4, 3.3 Hz), 3.80 (1H, dd, *J* = 10.5, 5.5 Hz), 4.23 (1H, dd, *J* = 10.5, 2.4 Hz), 5.11 (1H, d, *J* = 17.4 Hz), 5.13 (1H, d, *J* = 10.5 Hz), 5.62 (1H, s), 5.78 (1H, dd, *J* = 17.1, 10.8 Hz), 6.06 (1H, s), 7.13 (1H, td, *J* = 7.5, 0.9 Hz), 7.16−7.21 (2H, m), 7.24−7.38 (5H, m), 8.00 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.2, 23.6, 36.0, 37.0, 40.4, 56.0, 59.2, 60.9, 79.4, 114.6, 119.2, 124.5, 127.7, 129.1, 129.4, 132.0, 135.3, 143.1, 143.3, 164.9, 168.1, 170.1; MS (EI) *m*/*z* (%) 443 (M^+, 25), 401 (17), 374 (10), 332 (100), 304 (6), 241 (3), 157 (21), 130 (20), 69 (3), 41 (2); HRMS (EI) *m*/*z* calcd for $C_{27}H_{29}N_3O_3$ 443.2209, found 443.2215.

(2*R*,3a*R*,8a*R*)-8-Acetyl-1-[(*R*)-2-*tert*-butyloxycarbonylamino-3-propanoyl]-2-(2-methoxycarbonyl-phenyl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*] indole [(+)-14]. A solution of imine (+)-**3** (8.0 mg, 30 μmol), *o*-methoxycarbonylphenyl isonitrile **13** (7.0 mg, 45 μmol), and *N*-Boc-D-Ala (11.0 mg, 60 μmol) in toluene (0.6 mL) was stirred at room temperature for 45 min. The resulted mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel column with AcOEt/*n*-hexane (1/2) as an eluent to afford (+)-**14** (13.0 mg, 71%) as a viscous oil. $[\alpha]^{18}_D$ +52 (*c* 0.62, MeOH); IR ($CHCl_3$) 3433, 3267, 1701, 1670 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C) δ 0.95 (3H, s), 1.06 (3H, s), 1.10−1.38 (12H, m), 2.42 (3H, br s), 2.53−2.64 (1H, m), 2.71 (1H, d, *J* = 12.8 Hz), 3.85 (3H, s), 4.76 (1H, d, *J* = 8.8 Hz), 5.01 (1H, d, *J* = 17.6 Hz), 5.03 (1H, d, *J* = 10.4 Hz), 5.88 (1H, dd, *J* = 17.2, 10.8 Hz), 6.25−6.82 (1H, br m), 6.68 (1H, t, *J* = 7.6 Hz), 6.78 (1H, t, *J* = 7.6 Hz), 7.04 (1H, dt, *J* = 8.4, 1.2 Hz), 6.97−7.27 (1H, br m), 7.21 (1H, d, *J* = 7.2 Hz), 7.38 (1H, dt, *J* = 8.4, 1.2 Hz), 7.85 (1H, dd, *J* = 8.0, 1.6 Hz), 8.15 (1H, d, *J* = 8.4, Hz), 10.69 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ 16.9, 21.7, 22.7, 23.1, 27.6, 27.8, 40.0, 46.7, 51.7, 61.2, 62.1, 77.7, 78.6, 113.1, 114.4, 116.5, 118.4, 121.7, 123.0, 125.5, 127.3, 129.5, 133.1, 139.3, 142.3, 142.3, 142.9, 154.0, 166.5, 168.1, 168.8, 173.5; MS (FAB) *m*/*z* (%) 619 (M^+ + 1, 23), 201 (13), 190 (10), 185 (80), 159 (10), 134 (22), 130 (10), 93 (100), 75 (24), 57 (16); HRMS (FAB, M^+H) *m*/*z* calcd for $C_{34}H_{43}N_4O_7$ 619.3132, found 619.3128.

(3*R*,5a*R*,10b*R*,11a*R*)-6-Acetyl-10b-(2-methyl-but-3-en-2-yl)-3-methyl-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1′,2′:1,2]pyrrolo[4,5-*b*]indole-1,4-dione [(+)-15]. TFA (170 μL, 2.32 mmol) was added to a solution of (+)-**14** (29 mg, 46 μmol) in CH_2Cl_2 (0.9 mL) at room temperature. The reaction mixture was stirred at the same temperature for 30 min, neutralized with satd aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Then a solution of the residue (22.6 mg) in toluene (870 μL) was heated at 100 °C for 30 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column with AcOEt as an eluent to afford (+)-**15** (15.9 mg, 55%) as a colorless solid. Mp 238−240 °C (CH_2Cl_2); $[\alpha]^{17}_D$ +52 (*c* 0.22, MeOH); IR ($CHCl_3$) 3408, 1688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.14 (3H, s), 1.31 (3H, d, *J* = 6.7 Hz), 2.52 (3H, br s), 2.65 (1H, dd, *J* = 14.1, 10.4 Hz), 2.92 (1H, br s), 3.94 (1H, dd, *J* = 13.4, 6.7 Hz), 4.16 (1H, dd, *J* = 10.4, 4.6 Hz), 5.11 (1H, d, *J* = 18.0 Hz), 5.14 (1H, d, *J* = 11.0 Hz), 5.63 (1H, br d, *J* = 11.3 Hz), 5.77 (1H, br s), 5.82 (1H, dd, *J* = 17.4, 10.7 Hz), 7.09 (1H, t, *J* = 7.6 Hz), 7.25 (1H, t, *J* = 8.0, Hz), 7.29 (1H, d, *J* = 8.2 Hz), 7.92 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 15.4, 22.2, 22.7, 24.0, 30.4, 31.6, 40.9, 51.7, 58.1, 61.1, 80.9, 114.6, 118.8, 124.2, 125.8, 128.8, 133.2, 141.3, 143.2, 169.3; MS (EI) *m*/*z* (%) 367 (M^+, 18), 325 (14), 257 (17), 256 (100), 157 (13), 130 (11); HRMS (EI) *m*/*z* calcd for $C_{21}H_{25}N_3O_3$ 367.1896, found 367.1895.

(−)-5-*N*-Acetylardeemin [(−)-2]. TFA (1.0 mL, 13.7 mmol) was added to a solution of (+)-**14** (170 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. The reaction mixture was stirred at the same temperature for 1 h, neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Then a solution mixture of the residue and phosphorus(V) oxychloride (50 μL, 0.54 mmol) in dichloroethane (6.0 mL) was heated under reflux for 5 h, neutralized with satd aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The residue was purified by silica gel column with AcOEt/*n*-hexane (1/3) as an eluent to afford (−)-*N*-acetylardeemin (**2**) (106 mg, 53%) as white crystals. Mp 211−215 °C (MeOH) [lit.[10b] mp 229−231 °C]; $[\alpha]^{25}_D$ −34 (*c* 0.10, MeOH), $[\alpha]^{18}_D$ −48 (*c* 0.25, $CHCl_3$) [lit. $[\alpha]^{26}_D$ −33 (*c* 0.78, MeOH),[7] $[\alpha]^{20}_D$ −43 (*c* 0.45, $CHCl_3$)[10b]]; IR ($CHCl_3$) 2982, 1684, 1605, 1476, 1460, 1433, 1402, 1389, 1335, 1306, 1287, 1246, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, s), 1.22 (3H, s), 1.44 (3H, d, *J* = 7.2 Hz), 2.62−2.73 (1H, m), 2.67 (3H, br s), 3.02 (1H, dd, *J* = 12.9, 5.7 Hz), 4.41 (1H, dd, *J* = 10.8, 5.7 Hz), 5.08−5.12 (1H, m), 5.13−5.20 (1H, m), 5.41 (1H, q, *J* = 7.2 Hz), 5.85 (1H, dd, *J* = 17.4, 10.5 Hz), 6.06 (1H, br s), 7.18 (1H, dt, *J* = 7.5, 1.2 Hz), 7.30−7.42 (2H, m), 7.50 (1H, ddd, *J* = 8.1, 7.2, 1.2 Hz), 7.66 (1H, br d, *J* = 7.5 Hz), 7.78 (1H, ddd, *J* = 8.4, 7.2, 1.5 Hz), 8.02 (1H, br s), 8.26 (1H, dd, *J* = 7.8, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 22.4, 23.1, 23.4, 37.3, 40.4, 53.4, 58.2, 60.9, 79.4, 114.5, 119.5, 120.4, 124.4, 124.5, 126.8, 127.1, 127.2, 129.1, 132.2, 134.6, 142.9, 143.0, 147.0, 150.3, 159.7, 165.9, 170.0; MS (EI) *m*/*z* (%) 468 (M^+, 21), 426 (17), 358 (24), 357 (100), 355 (12), 130 (13); HRMS (EI) *m*/*z* calcd for $C_{28}H_{28}N_4O_3$ 468.2161, found 468.2160.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1**−**5**, **8**−**12**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.