Enantioselective Synthesis of Glutarimide Alkaloids Cordiarimides A, B, Crotonimides A, B, and Julocrotine

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Five glutarimide alkaloids cordiarimide A (**5**), cordiarimide B (**6**), crotonimide A (**3**), crotonimide B (**4**), and julocrotine (**2**) have been synthesized starting from Boc-*L*-glutamine (**7**). The benzylic alcohol chiral centre of cordiarimides B (**6**) has been established in 6∶1 diastereoselectivity by catalytic asymmetric hydrogenation using Zhou's catalytic system $Pd(CF_3CO_2)_2$/(*R*,*R*)-Me-DuPhos.

Keywords glutarimides, alkaloids, asymmetric hydrogenation, diastereoselectivity, enantioselective synthesis

Introduction

Glutarimide derivatives are a class of compounds possessing important bioactivities. Racemic thalidomide (**1**) is the most well known glutarimide derivative, as it has been introduced as a sedative drug in the late 1950s (Figure 1). In 1961, it was withdrawn due to teratogenicity and neuropathy. It has been revealed that the *R*-enantiomer is effective against morning sickness but the *S*-enantiomer is teratogenic. There is now a growing clinical interest in thalidomide.[1] It has been discovered that thalidomide was a potent inhibitor of new blood vessel growth (angiogenesis), and is introduced as an immunomodulatory agent used primarily, combined with dexamethasone, to treat multiple myeloma.[2] The FDA has also approved the drug's use in the treatment of erythema nodosum leprosum. There are studies underway to determine the drug's effects on arachnoiditis and several types of cancers.[3] Glutarimide derivatives were reported to be potent aminopeptidase N (APN/CD13) inhibitors.[4] Glutarimide alkaloids were also found in some plants. For example, (3*S*,11*S*)-julocrotine (**2**) was isolated from *Julocroton montevidensis*;[5] *Croton membranaceus*,[6] and other species;[7,9] (*S*)-crotonimides A (**3**) and B (**4**) are found in *Croton pullei* var. *glabrior* Lanj.[9] Recently, (*S*)-cordiarimides A (**5**) and (3*S*,8*S*)-cordiarimides B (**6**) were isolated from the roots of *Cordia globifera* (Boraginaceae), which is native to tropical America, Africa, and Asia (Figure 1).[10] Glutarimide alkaloids isolated from *Croton cuneatus* were reported to exhibit cytotoxic activity.[8] While showed weak cytotoxicity against the MOLT-3 cell line, (*S*)-cordiarimides A (**5**) and (3*S*,8*S*)-cordiarimides B (**6**) inhibited superoxide anion radical formation in the xanthine/xanthine oxidase (XXO) assay, with respective IC_{50} values of 54.1 and 21.7 μmol•L^{-1}, respectively.[10] These radical scavenging activities suggest that both **5** and **6** may have potential for cancer chemoprevention. In connection with our interest in the development of malimides and glutarimides-based synthetic methodologies for the asymmetric synthesis of *N*-containing bioactive compounds,[11] we undertook the synthesis of glutarimide alkaloids **2**—**6**, and the results are reported herein.

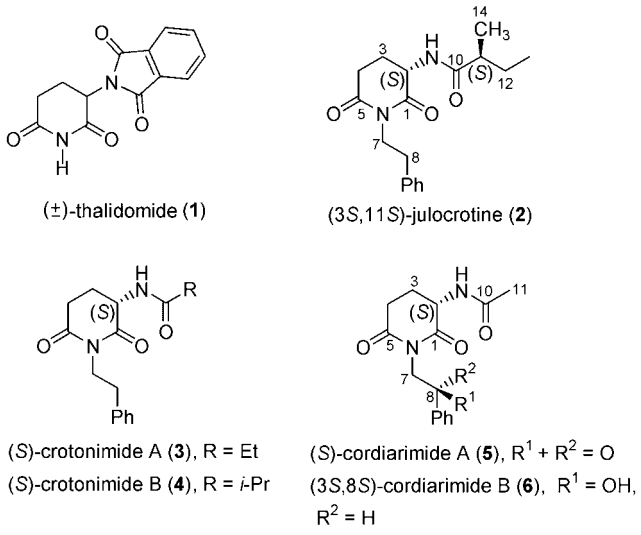

Figure 1 Structures of synthetic and naturally occurring bioactive glutarimide derivatives.

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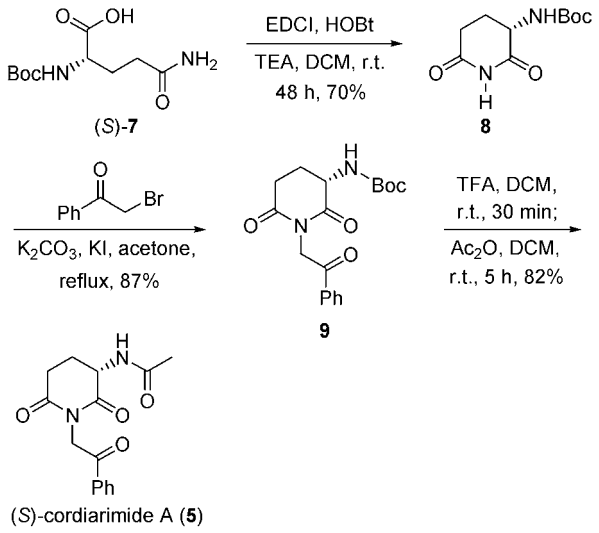
Results and discussion

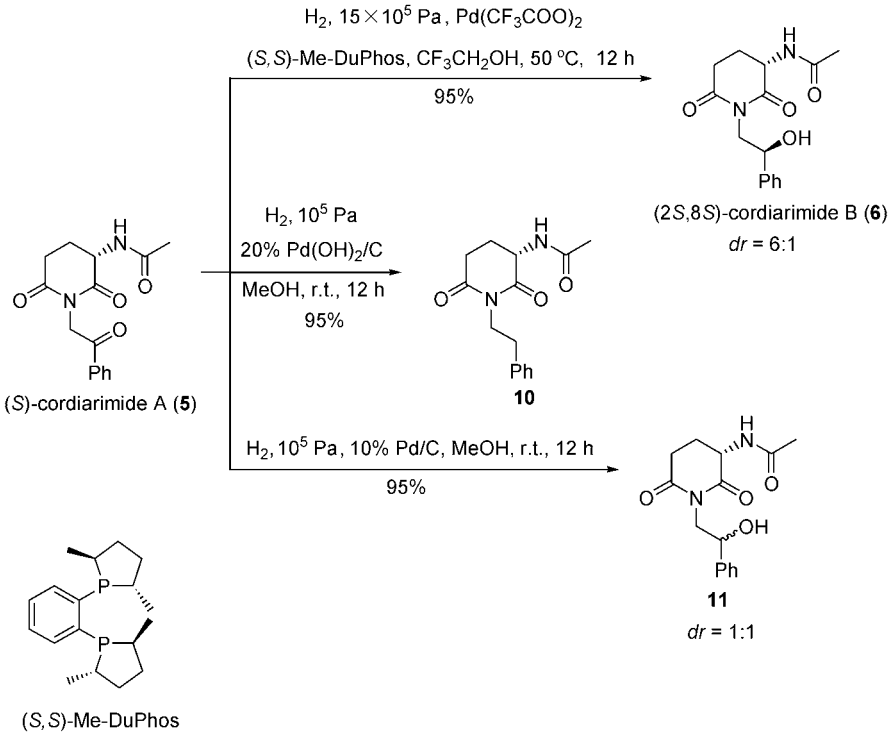
Most methods reported so far for the synthesis of glutarimide derivatives started from glutamic acid,[12] and that started from commercially available Boc-*L*-glutamine appeared to be the most efficient, and was adopted in our study.[4b,4e] Thus, treatment of Boc-*L*-glutamine (**7**) with 1-ethyl-3-(3-dimethylamino-propyl) carbodiimide hydrochloride carbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt) and NEt_3 in dichloromethane gave the desired glutarimide derivative **8** in 70% yield (Scheme 1). Reaction of glutarimide **8** with 2-bromoacetophenone in the presence of K_2CO_3 and a catalytic amount of KI in acetone at reflux for 15 min produced compound **9** in 87% yield. Removal of the Boc group (TFA, 10 equiv., CH_2Cl_2, 0.5 h), followed by acetylation (Ac_2O, CH_2Cl_2, 5 h) gave, in one-pot, (*S*)-cordiarimide A (**5**) in 82% yield. The physical {$[\alpha]_D^{20}$ −32.8 (*c* 0.9, $CHCl_3$), lit.[10] $[\alpha]_D^{20}$ −29 (*c* 0.36, $CHCl_3$)} and spectral data of our synthetic product are in good agreement with those reported,[10] except the resonance at δ 1.96. This resonance corresponds to that appears at δ 1.98 (for compound **5**) in reference 10, in which the interpretation of this peak as a "ddd" with J=4.7, 13.0, 26.2 Hz for H-4 is not convincing. After a detailed NMR study, this peak was interpreted as δ 1.96 (ddt, J=13.0, 5.4, 13.0 Hz, 1H, H-4), and that for the natural product should be revised accordingly.

Scheme 1 Synthesis of (*S*)-cordiarimide A (**5**)



With (*S*)-cordiarimide A (**5**) in hand, we proceeded to investigate its diastereoselective reduction to prepare (3*S*, 8*S*)-cordiarimide B (**6**) (Scheme 2). In an attempt to perform a substrate-controlled reduction, we first tried $Pd(OH)_2$/C-catalyzed hydrogenation in MeOH. However, only deoxygenated product **10** was obtained in 95% yield. Alternatively, Pd/C-catalyzed hydrogenation in MeOH afforded compound **11** as a 1∶1 diastereomeric mixture in 95% combined yield. This result showed that the chiral center in the glutarimide ring had no impact on the diastereoselectivity of the reduction. We then tried the Corey-Bakshi-Shibata (CBS) asymmetric reduction,[15] unfortunately reaction of cordiarimide A with chiral methyl-substituted oxazoborolidine and borane in either DCM or THF did not give the desired product.[15d] The failure may be due to reduction of the carbonyl group of imide by borane.[13]

Scheme 2 Synthesis of (3*S*,8*S*)-cordiarimide B (**6**)



We next called for catalytic asymmetric hydrogenation.[16] In this context, many successful examples of Pd(0)-catalyzed asymmetric hydrogenation methods have been documented in the recent literatures,[14] and Zhou's catalytic system[14a] was adopted. In Zhou's asymmetric catalytic system, ligand (*R*,*R*)-Me-DuPhos was shown to produce *R*-benzylic alcohols. Thus, in the presence of $Pd(CF_3CO_2)_2$ and (*S*,*S*)-Me-DuPhos, cordiarimide A (**5**) was hydrogenised in dry 2,2,2-trifluoroethanol (TFE) under 15×10^5 Pa of hydrogen at 50 ℃ for 12 h to produce the corresponding benzylic alcohol in 6∶1 diastereomeric ratio with 95% combined yield. After decantation, pure major diastereomer was obtained in 75% yield, and was shown to be the desired one (**6**) with a *C*-8 *S* configuration. The physical {$[\alpha]_D^{20}$ +18.8 (*c* 0.71, $CHCl_3$); lit.[10] $[\alpha]_D^{20}$ +20 (*c* 0.53, $CHCl_3$)} and spectral data of the synthetic product were in good agreement with those reported.

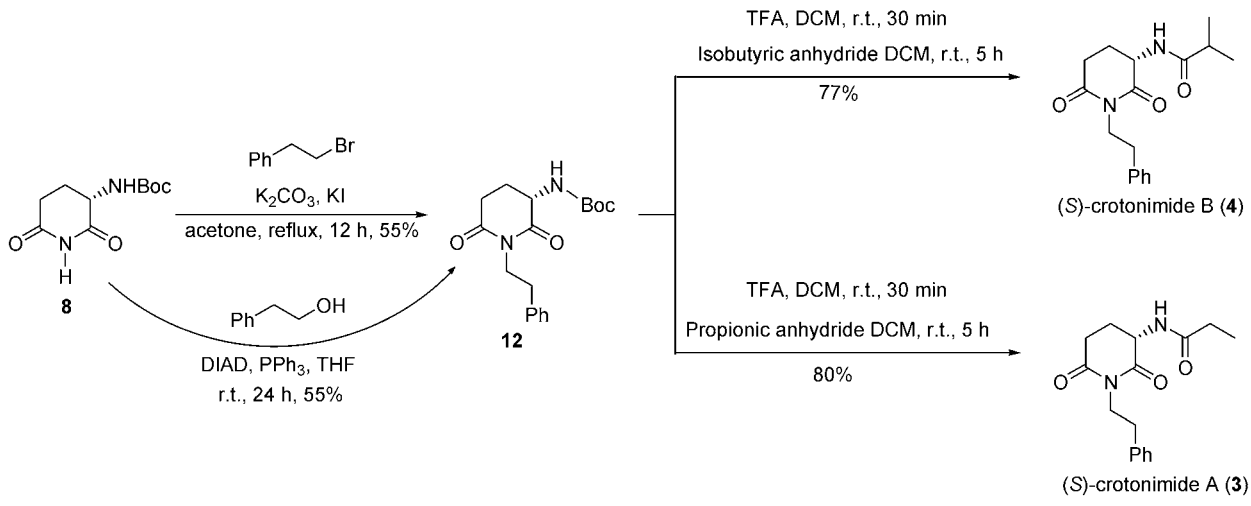
We next turned to the synthesis of (*S*)-crotonimide A (**3**) and (*S*)-crotonimide B (**4**) (Scheme 3). For this purpose, glutarimide **8** was treated with (2-bromoethyl)-benzene in acetone at reflux, which gave the desired alkylated compound **12** in 55% yield. Unfortunately, no optical rotation was observed for compound **12**, which indicated that a total racemization occurred. To avoid the racemization, Mitsunobu reaction[17] was envisioned. Thus, treatment of glutarimide **8** with DIAD, PPh_3, and 2-phenylethanol at r.t. gave the *N*-alkylated product **12** in 55% yield {$[\alpha]_D^{20}$ −15 (*c* 1.0, $CHCl_3$)}. Successive treatment of compound **12** with TFA and propionic anhydride (NEt_3, DMAP (cat.), CH_2Cl_2) provided (*S*)-crotonimide A (**3**) in 80% yield {m.p. 101—102 ℃ (EtOAc/P.E.), lit.[9] m.p. 98.5—99.5 ℃; $[\alpha]_D^{20}$ −10.8 (*c* 0.6, $CHCl_3$), lit.[9] $[\alpha]_D^{20}$ −9.8 (*c* 0.1, $CHCl_3$)}. Similarly, successive treatment of compound **12** with TFA and isobutyric anhydride produced (*S*)-crotonimide B (**4**) in 77% yield {m.p. 126—127 ℃ (EtOAc/P.E.), lit.[9] m.p. 127.5.5—128.5 ℃; $[\alpha]_D^{20}$ −12.8 (*c* 0.42, $CHCl_3$), lit.[9] $[\alpha]_D^{20}$ −12.5 (*c* 0.10, $CHCl_3$)}. The spectral data of our synthetic products are in accordance with that reported.[9]

Alternatively, we also undertook the synthesis of (*S*)-crotonimide A (**3**) from compound **9** by another route (Scheme 4). Treatment of compound **9** with TFA and propionic anhydride provided compound **13** in 75% yield. $Pd(OH)_2$/C-catalyzed hydrogenation of compound **13** in MeOH gave (*S*)-crotonimide A (**3**) in 95% yield. The overall yield by this route increased to 43% comparing with the first one (30%, cf. Scheme 3).

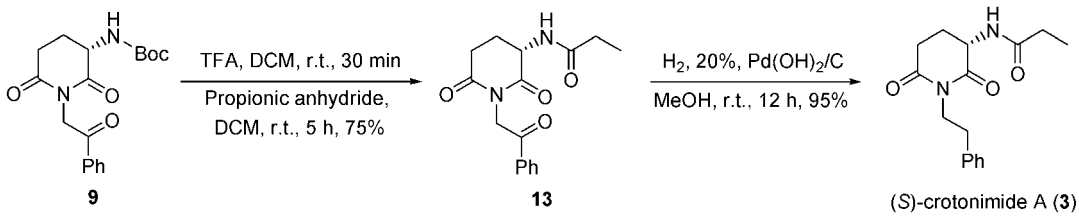
The syntheses of (3*S*, 11*S*)-julocrotine (**2**) were next undertaken (Scheme 5). Successive treatment of compound **12** with TFA and (*S*)-2-methylbutyric anhydride (NEt_3, DMAP (cat.), CH_2Cl_2) produced (3*S*,11*S*)-julocrotine (**2**) {$[\alpha]_D^{20}$ −9.2 (*c* 1.2, $CHCl_3$); lit.[5] $[\alpha]_D^{20}$ −9 (*c* 1.0, $CHCl_3$)} are in good agreement with the reported ones.[7]

In summary, concise and efficient enantioselective syntheses of five glutarimide alkaloids cordiarimides A (**5**), cordiarimides B (**6**), crotonimide A (**3**), crotonimide B (**4**), and julocrotine (**2**) have been achieved for the first time. The benzylic alcohol chiral centre of cordiarimides B (**6**) was established in 6∶1 diastereose-

Scheme 3 Syntheses of (*S*)-crotonimide A (**3**) and (*S*)-crotonimide B (**4**)



Scheme 4 Synthesis of (*S*)-crotonimide A (**3**)



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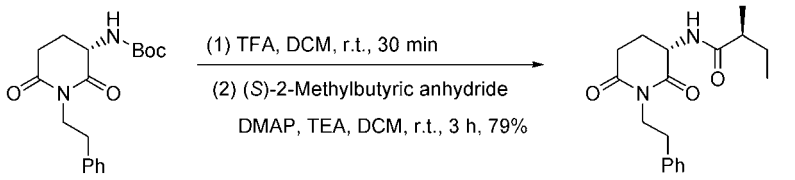
Scheme 5 Synthesis of (3*S*,11*S*)-julocrotine (**2**)



12 (3*S*,11*S*)-julocrotine (**2**)

lectivity by catalytic asymmetric hydrogenation using Zhou's catalytic system $Pd(CF_3CO_2)_2$/(*R*,*R*)-Me-DuPhos. The overall yields from Boc-*L*-glutamine were 49%, 47%, 43%, 29%, and 30%, respectively. The syntheses of these natural products confirmed their structures.

Experimental

General methods

Melting points were determined on a micro melting point apparatus and were uncorrected. Infrared spectra were measured with a FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz and 100 MHz respectively. Chemical shifts (δ) are expressed downfield from TMS. Mass spectra were recorded with a liquid chromatography-mass spectrum apparatus (direct injection). Optical rotations were measured with a polarimeter. Silica gel (300—400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60—90 ℃) mixture. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

***tert*-Butyl (*S*)-2,6-dioxopiperidin-3-ylcarbamate (8)** To a solution of Boc-*L*-glutamine (Boc-*L*-Gln) (*S*)-**7** (284 mg, 1.15 mmol), HOBt (234 mg, 1.70 mmol) and EDCI (332 mg, 1.70 mmol) in dry DCM (15 mL) was added TEA (0.32 mL, 2.5 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 1 h and at room temperature for 48 h. The reaction was quenched with 2 mol•L^{-1} HCl (5 mL). The resulting mixture was washed with sat. aqueous solution of $NaHCO_3$ (5 mL) and brine (5 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc∶PE=1∶1, volume ratio) to afford **8** (185 mg, 70%) as a white solid. m.p. 215—216 ℃ (EtOAc/PE) [lit.[4b] m.p. 212—214 ℃]; $[\alpha]_D^{20}$ −61.0 (*c* 0.95, MeOH) {lit.[4b] $[\alpha]_D^{25}$ −58.2 (*c* 1.05, MeOH)}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.43 (s, 9H), 1.80—2.00 (m, 1H, H-4), 2.45—2.56 (m, 1H, H-4), 2.61—2.82 (m, 2H, H-5), 4.38—4.42 (m, 1H, H-3), 5.37—5.45 (m, 1H, NHBoc), 8.48 (s, 1H, NH)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.4, 28.2, 31.2, 51.9, 80.5, 155.5, 171.6; IR (film) ν_{max}: 3357, 3186, 3086, 2963, 1757, 1736, 1527, 1355 cm^{-1}; MS (ESI) *m*/*z*: 229 (M+H$^+$).

***tert*-Butyl (*S*)-2,6-dioxo-1-(2-oxo-2-phenylethyl)-piperidin-3-ylcarbamate (9)** To a mixture of **8** (315 mg, 1.38 mmol), K_2CO_3 (152 mg, 1.1 mmol) and KI (130 mg, 0.77 mmol) in dry acetone (40 mL) was added 2-bromoacetophenone (272 mg, 1.38 mmol). The reaction mixture was then refluxed for 15 min and filtered. The filtrate was concentrated under reduced pressure to obtain a yellow solid, which was dissolved in 20 mL EtOAc and then washed with water (10 mL) and brine (5 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc∶PE=1∶2, volume ratio) to afford **9** (185 mg, 87%) as a white foam. $[\alpha]_D^{20}$ −36 (*c* 0.6, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.37 (s, 9H), 1.94 (ddt, *J* =13.0, 5.1, 13.0 Hz, 1H, H-4), 2.39—2.44 (m, 1H, H-4), 2.68—2.90 (m , 2H, H-5), 4.36—4.48 (m, 1H, H-3), 5.08 (d, *J*=17.0 Hz, 1H, H-7), 5.15 (d, *J*=17.0 Hz, 1H, H-7), 5.44 (d, *J* =5.1 Hz, 1H, NHBoc), 7.39—7.86 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.5, 28.1, 31.4, 46.3, 52.1, 80.0, 127.8, 128.6, 133.7, 134.4, 155.4, 171.0, 171.6, 191.3; IR (film) ν_{max}: 3381, 2977, 1707, 1512, 1365, 1222, 1156 cm^{-1}; MS (ESI) *m*/*z*: 347 (M+H$^+$). HRMS calcd for $[C_{18}H_{22}N_2O_5+Na]^+$ 370.1460, found 370.1456.

[(*S*)-*N*-(2,6-Dioxo-1-(2-oxo-2-phenylethyl)piperidin-3-yl)acetamide] (*S*)-cordiarimide A (5) To a solution of **9** (107 mg, 0.31 mmol) in DCM (4 mL) was slowly added trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature for 30 min and concentrated under reduced pressure to give a yellow solid, which was dissolved in DCM (4 mL) and then added Ac_2O (0.25 mL, 2.4 mmol). The mixture was stirred at room temperature for 5 h. The solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc ∶ PE = 3 ∶ 1, volume ratio) to afford (*S*)-cordiarimide A (**5**) (73 mg, 82%) as a white foam. $[\alpha]_D^{20}$ −32.8 (*c* 0.9, $CHCl_3$) {lit.[10] amorphous solid, $[\alpha]_D^{26}$ −29 (*c* 0.36, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 1.96 (ddt, *J*=13.0, 5.4, 13.0 Hz, 1H, H-4), 2.05 (s, 3H, CH_3), 2.50—2.58 (ddt, *J*=13.0, 3.0, 5.4 Hz, 1H, H-4), 2.86 (ddd, *J*=13.0, 5.4, 18.0 Hz, 1H, H-5), 2.93 (ddd, *J*=5.4, 3.0, 18.0 Hz, 1H, H-5), 4.74 (ddd, *J*=13.0, 5.4, 5.4 Hz, 1H, H-3), 5.17 (d, *J* =17.0 Hz, 1H, H-7), 5.26 (d, *J*=17.0 Hz, 1H, H-7), 6.57 (d, *J*=5.4 Hz, 1H, NH, D_2O exchangeable), 7.52—8.05 (m, 5H, ArH);

^{13}C NMR ($CDCl_3$, 150 MHz) δ: 23.1, 24.4, 31.5, 46.4, 51.4, 128.0, 128.9, 133.9, 134.6, 170.3, 170.9, 171.8, 191.4; IR (film) ν_{max}: 3288, 3059, 2940, 1685, 1535, 1367, 1237, 1155 cm^{-1}; MS (ESI) *m/z*: 289 (M+H$^+$).

(*S*)-*N*-(2,6-Dioxo-1-phenethylpiperidin-3-yl)acetamide (10) To a mixture of (*S*)-cordiarimide A (**5**) (100 mg, 0.35 mmol) and 20% $Pd(OH)_2$/C (20 mg) was added MeOH (5 mL). The mixture was stirred at room temperature under an atmosphere of H_2 for 12 h, followed by filteration over Celite and concentrated under reduced pressure to afford **10** (100 mg, 95%) as a white solid. m.p. 123.1—124.5 ℃ (EtOAc/PE); $[\alpha]_D^{20}$ −8.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.61 (ddt, *J*=12.9, 4.6, 12.9 Hz, 1H, H-4), 1.98 (s, 3H), 2.45—2.52 (m, 1H, H-4), 2.60—2.80 (m, 4H, H-5, H-8), 3.92—4.08 (m, 2H, H-7), 4.45 (ddd, *J*=12.9, 4.6, 4.6 Hz, 1H, H-3), 6.48—6.52 (m, 1H, NH), 7.12—7.25 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.0, 24.2, 31.5, 33.7, 41.4, 51.2, 126.5, 128.3, 128.8, 137.9, 170.2, 170.8, 171.6; IR (film) ν_{max}: 3292, 3059, 3029, 2957, 1678, 1548, 1367 cm^{-1}; MS (ESI) *m/z*: 275 (M+H$^+$). HRESIMS calcd for $[C_{15}H_{18}N_2O_3 + Na]^+$ 297.1215, found 297.1209.

{*N*-[(*S*)-1-[(*S*)-2-Hydroxy-2-phenylethyl]-2,6-dioxopiperidin-3-yl]acetamide} (3*S*,8*S*)-cordiarimide B (6) To a mixture of (*S*,*S*)-Me-DuPhos (13 mg, 0.04 mmol) and $Pd(CF_3CO_2)_2$ (13 mg, 0.04 mmol) in a dried schlenk tube was added degassed anhydrous acetone (0.5 mL) under nitrogen atmosphere in glove box. The mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure to give the catalyst (pure complex was directly used as the catalyst). This catalyst and the substrate (*S*)-cordiarimide A (**5**) (102 mg, 0.35 mmol) were dissolved in dry 2,2,2-trifluoroethanol (TFE) (1 mL) under nitrogen atmosphere in glove box, and then the mixture was transferred into an autoclave. The reaction mixture in autoclave was stirred under 15×10^5 Pa of hydrogen at 50 ℃. After 12 h, the hydrogen was carefully released. The mixture was filtered over Celite and concentrated under reduced pressure to give the corresponding benzylic alcohol as a foam in 6∶1 diastereomeric ratio (100 mg, 95%). The mixture was purified by decantation with a little of solvent (DCM∶PE=1∶2, volume ratio) several times, and was dried to give the pure diastereomer **6** (75 mg, 75%). $[\alpha]_D^{20}$ +18.8 (*c* 0.7, $CHCl_3$) {lit.[10] amorphous solid, $[\alpha]_D^{26}$ +20 (*c* 0.53, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.73 (m, 1H, H-4), 2.00 (s, 3H), 2.44 (ddt, *J*=13.0, 5.4, 13.0 Hz, 1H, H-4), 2.76—2.93 (m, 2H, H-5), 3.97 (dd, *J*=13.7, 3.3 Hz, 1H, H-7), 4.07 (dd, *J*=13.7, 9.3 Hz, 1H, H-7), 4.48—4.90 (ddd, *J*=13.0, 5.4, 5.4 Hz, 1H, H-3), 4.84 (m, 1H, H-8), 6.32 (d, *J*=5.4 Hz, 1H, NH), 7.20—7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.0, 24.0, 31.6, 47.6, 51.3, 72.1, 125.8, 128.0, 128.5, 141.3, 170.7, 172.0, 172.8; IR (film) ν_{max}: 3343, 1678, 1538, 1370, 1162, 1029 cm^{-1}; MS (ESI) *m/z*: 291 (M+H$^+$).

***tert*-Butyl (*S*)-2,6-dioxo-1-phenethylpiperidin-3-ylcarbamate (12)** To a solution of **8** (448 mg, 1.96 mmol), PPh_3 (562 mg, 2.15 mmol) and diisopropyl azodicarboxylate (DIAD) (0.42 mL, 2.15 mmol) in dry THF (10 mL) was added 2-phenylethanol (0.18 mL, 1.56 mmol). The mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc∶PE=1∶2, volume ratio) to afford **12** (368 mg, 55%) as a white solid. m.p. 127—129 ℃ (EtOAc/PE); $[\alpha]_D^{20}$ −12.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (s, 9H), 1.65 (ddt, *J*=12.6, 5.0, 12.6 Hz, 1H, H-4), 2.32—2.38 (m, 1H, H-4), 2.52—2.64 (m, 1H, H-5), 2.65—2.75 (m, 3H, C^5-H, H-8), 3.84—3.97 (m, 2H, H-7), 4.12—4.20 (m, 1H, H-3), 5.39 (d, *J*=5.0 Hz, 1H, NH), 7.11—7.25 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.6, 28.1, 31.5, 33.7, 41.4, 51.2, 80.1, 126.4, 128.2, 128.8, 138.0, 155.4, 170.9, 171.5; IR (film) ν_{max}: 3347, 2981, 2929, 1702, 1671, 1494, 1367, 1241, 1148 cm^{-1}; MS (ESI) *m/z*: 333 (M+H$^+$). HRIMS calcd for $[C_{18}H_{24}N_2O_4+Na]^+$ 355.1634, found 355.1638.

[(*S*)-*N*-(2,6-Dioxo-1-phenethylpiperidin-3-yl)propionamide] (*S*)-crotonimide A (3) To a solution of **12** (125 mg, 0.37 mmol) in DCM (4 mL) was slowly added trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature for 30 min and concentrated under reduced pressure to give a yellow solid. The solid was dissolved in DCM (4 mL) and then added propionic anhydride (0.48 mL, 3.7 mmol). The mixture was stirred at room temperature for 5 h, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc∶PE=1∶1, volume ratio) to afford (*S*)-crotonimide A (**3**) (85 mg, 80%) as a white solid. m.p. 101—102 ℃ (EtOAc/PE) [lit.[9] colorless solid, m.p. 98.5—99.5 ℃]; $[\alpha]_D^{20}$ −13.8 (*c* 0.4, $CHCl_3$) {lit.[9] $[\alpha]_D$ −9.8 (*c* 0.1, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.11 (t, *J*=7.6 Hz, 1H, CH_3), 1.60 (ddt, *J*=13.0, 5.1, 13.0 Hz, 1H, H-4), 2.35—2.40 (m, 1H, C**H**$_2$CH$_3$), 2.50 (ddt, *J*=13.0, 2.3, 5.1 Hz, 1H, H-4), 2.60—2.65 (m, 1H, H-5), 2.70—2.82 (m, 3H, C^5-H, H-8), 3.93—4.05 (m, 2H, H-7), 4.60 (ddd, *J*=13.0, 5.1, 5.1 Hz, 1H, H-3), 6.36 (d, *J*=5.1 Hz, 1H, NH), 7.18—7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.5, 24.4, 29.5, 31.6, 33.9, 41.6, 57.7, 126.6, 128.4, 128.9, 138.1, 170.9, 171.8, 174.2; IR (film) ν_{max}: 3336, 2957, 2926, 1712, 1675, 1511, 1372, 1148 cm^{-1}; MS (ESI) *m/z*: 289 (M+H$^+$).

(*S*)-*N*-(2,6-Dioxo-1-phenethylpiperidin-3-yl)isobutyramide) (*S*)-crotonimide B (4) To a solution of **12** (100 mg, 0.30 mmol) in DCM (4 mL) was slowly added trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature for 30 min and concentrated under reduced pressure to give a yellow solid. The solid was dissolved in DCM (4 mL) and then added isobutyric anhydride (0.47 mL, 3.0 mmol). The mixture was stirred at room temperature for 5 h, and then con-

centrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc∶PE＝1∶2, volume ratio) to afford (*S*)-crotonimide B (**4**) (69 mg, 77%) as a white solid. m.p. 126.0—127.0 ℃ (EtOAc/PE) [lit.[9] colorless solid, m.p. 127.5—128.5 ℃]; $[\alpha]_D^{20}$ −12.8 (*c* 0.4, $CHCl_3$) {lit.[9] $[\alpha]_D$ −12.5 (*c* 0.10, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.18 (d, *J*＝7.0 Hz, 3H, CH_3), 1.19 (d, *J*＝7.0 Hz, 3H, CH_3), 1.66 (ddt, *J*＝13.0, 5.1, 13.0 Hz, 1H, H-4), 2.38 [m, 1H, C(O)C**H**$(CH_3)_2$], 2.50 (ddt, *J*＝13.0, 2.3, 5.1 Hz, 1H, H-4), 2.60—2.68 (m, 1H, H-5), 2.72—2.81 (m, 3H, H-5, H-8), 3.88—4.07 (m, 2H, H-7), 4.46 (ddd, *J*＝13.0, 5.1, 5.1 Hz, 1H, H-3), 6.35 (d, *J*＝5.1 Hz, 1H, NH), 7.18—7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 19.4, 19.5, 31.7, 33.9, 41.6, 51.3, 126.6, 128.4, 129.0, 138.1, 170.9, 171.8, 177.2; IR (film) ν_{max}: 3347, 2981, 2929, 1702, 1671, 1494, 1367, 1241, 1148 cm^{-1}; MS (ESI) *m/z*: 303 ($M+H^+$).

{(*S*)-*N*-[(*S*)-2,6-Dioxo-1-phenethylpiperidin-3-yl]-2-methylbutanamide} (3*S*,11*S*)-Julocrotine (2) To a solution of **12** (150 mg, 0.43 mmol) in DCM (4 mL) was slowly added trifluoroacetic acid (0.5 mL). The reaction was allowed to stir at room temperature for 30 min, and concentrated under reduced pressure to give a yellow solid. The solid was dissolved in DCM (4 mL) and then added (*S*)-2-methylbutyric anhydride (0.7 mL, 3.44 mmol), Et_3N (0.12 mL, 0.86 mmol) and DMAP (cat.). The mixture was stirred at room temperature for 3 h and the solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc∶PE＝3∶1, volume ratio) to afford (3*S*,11*S*)-julocrotine (**2**) (78 mg, 79%) as a colorless oil. $[\alpha]_D^{20}$ −9.2 (*c* 1.2, $CHCl_3$) {lit.[5a] $[\alpha]_D$ −9 (*c* 1.0, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 0.87 (t, *J*＝7.4 Hz, 3H, $CH_2C\mathbf{H}_3$), 1.09 [d, *J*＝6.9 Hz, 3H, $CH(C\mathbf{H}_3)$], 1.40—1.51 (m, 1H, H-12), 1.60—1.72 (m, 1H, H-12), 1.99 (ddt, *J*＝13.0, 5.3, 13.0 Hz, 1H, H-4), 2.14—2.21 (m, 1H, H-11), 2.44—2.55 (m, 1H, H-4), 2.60—2.82 (m, 4H, H-5, H-8), 3.91—4.07 (m, 2H, H-7), 4.41 (ddd, *J*＝13.0, 5.3, 5.3 Hz, 1H, H-3), 6.23 (d, *J*＝5.3 Hz, 1H, NH), 7.10—7.24 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 11.8, 17.3, 24.4, 27.2, 31.7, 33.9, 41.6, 42.9, 51.1, 126.5, 128.4, 128.9, 138.1, 170.9, 171.8, 176.8; IR (film) ν_{max}: 3309, 2967, 2926, 1675, 1552, 1350, 1145 cm^{-1}; MS (ESI) *m/z*: 317 ($M+H^+$).

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