CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200901843

A Flexible Approach to Grandisine Alkaloids: Total Synthesis of Grandisines B, D, and F

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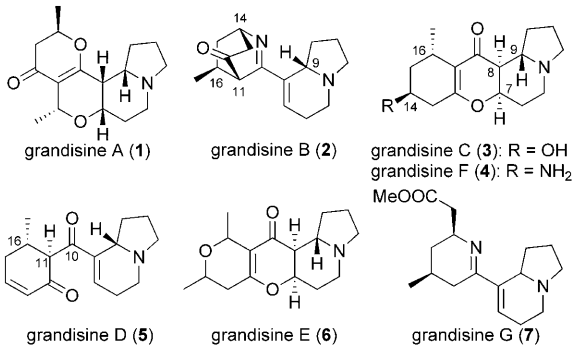
Abstract: This article describes in detail the first total synthesis of grandisine alkaloids, grandisines B, D, and F, which show affinity for the human δ-opioid receptor. The key steps in this synthesis are construction of the isoquinuclidinone moiety of **2** by intramolecular imine formation and the tetracyclic ring system of **4** by stereoselective ring closure of the enolate of amine **8** generated by 1,4-addition of ammonia to **9**. Synthesis of key intermediate **9** featured a highly stereoselective Brønsted acid mediated Morita–Baylis–Hillman (MBH) reaction via the *N*-acyl iminium ion.

Keywords: alkaloids · natural products · nitrogen heterocycles · total synthesis

Introduction

Opioid analgesics, typified by morphine, are widely used to improve the quality of life (QOL) of patients, despite their side effects, which include gastric stasis, respiratory depression, muscle rigidity, dependence, and abuse. Over the years much effort has been directed to finding potent analgesics without these side effects.[1] Multiple opioid receptors (μ, δ, κ) have been identified, and it appears that analgesia mediated through the δ-opioid receptor is not accompanied with respiratory depression, constipation, or other adverse effects.[2] Therefore, selective activation of the δ-opioid receptor is an attractive strategy for the development of new analgesics.

Grandisine alkaloids **1**–**7** isolated from the leaves of the Australian rainforest tree, *Elaeocarpus grandis*, by Carroll and co-workers display an affinity for the human δ-opioid receptor.[3] Although compounds **1**–**7**, containing an indolizidine skeleton, exhibit structural diversity and pharmacological activity, and are attractive target molecules for total synthesis, only grandisine A (**1**) has been synthesized so far.[4] Hence, we were interested in synthesizing other grandisine alkaloids by means of a flexible route that would also be applicable to various grandisine analogues as candidate selective δ-opioid receptor agonists. We focused on three alkaloids, grandisine B (**2**), F (**4**), and D (**5**). Grandisine D (**5**), possessing two α,β-unsaturated ketone units, was proposed to be a biogenetic precursor of grandisines B (**2**) and F (**4**).[3a,b] Grandisine B (**2**) is the only alkaloid isolated to date that contains both an indolizidine moiety and an isoquinuclidinone ring system, which is very rare and has otherwise only been found in the alkaloid mearsine.[5] On the other hand, grandisine F (**4**), which contains a densely functionalized tetracyclic skeleton featuring an aminomethylcyclohexane unit, exhibits the most potent δ-opioid receptor affinity



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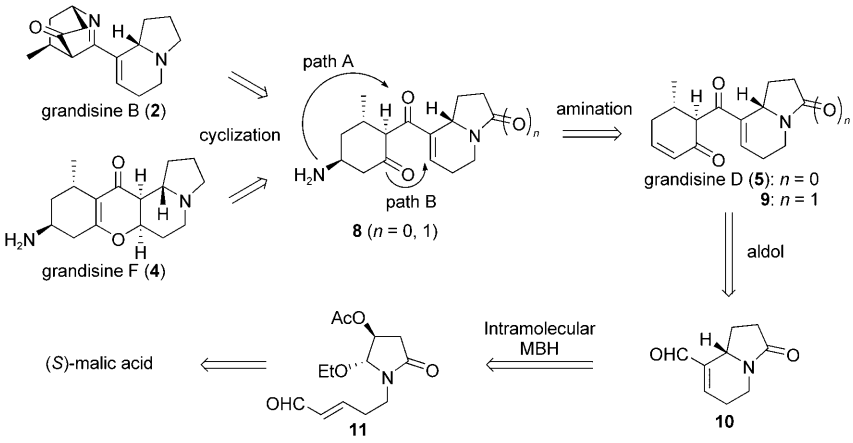
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901843 and contains ^{1}H and ^{13}C NMR spectra for all new compounds.

among the grandisine alkaloids. It features three contiguous stereocenters, of which C-7 and C-8 are *trans* with respect to C-9, in the indolizidine moiety, as do grandisines C (**3**) and E (**6**).[3b]

Inspired by the proposed biogenetic pathway,[3a] we envisaged synthesis of grandisines B (**2**) and F (**4**) via grandisine D (**5**), and describe herein the first total synthesis of **2**, **4**, and **5**[6] from the common key intermediate **9**, which is closely related to **5** (Scheme 1). The synthesis of **9** featured a highly stereoselective Brønsted acid mediated Morita–Baylis–Hillman (MBH) reaction via the *N*-acyl iminium ion.[7–11]

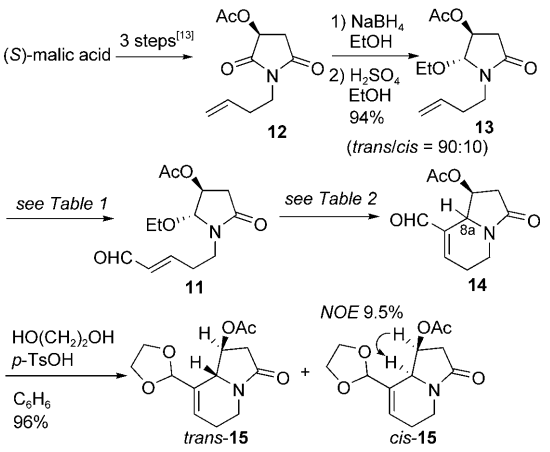
Results and Discussion

Retrosynthetic analysis: Our retrosynthesis is outlined in Scheme 1. We envisaged construction of the isoquinuclidine moiety of **2** or the tetracyclic ring system of **4** by intramolecular imine formation (path A) or stereoselective ring closure of the enolate (path B) of amine **8** that can be generated by the 1,4-addition of ammonia to **5** or **9**. Grandisine D (**5**) would be obtained by an aldol reaction of 8-formylindolizidine (**10**) with (*S*)-5-methylcyclohexenone, readily prepared from (*S*)-pulegone,[12] followed by chemoselective reduction of amide **9**. 8-Formylindolizidine (**10**) would be synthesized by an MBH reaction via the *N*-acyl iminium ion[11] generated from aminal **11**, which can be derived from (*S*)-malic acid.



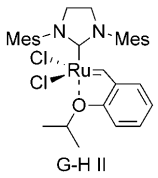
Scheme 1. Retrosynthetic analysis.

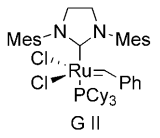
Construction of indolizidine skeleton by using a MBH reaction: We began with the preparation of aminal **11** derived from imide **12**,[13] which was itself obtained from (*S*)-malic acid (Scheme 2). Regioselective reduction of **12** with $NaBH_4$, immediately followed by stereoselective ethanolysis, produced ethoxy lactam **13**.[14] The *trans*/*cis* stereochemistry of compound **13** was tentatively assigned based on the observed vicinal coupling constants ($J_{2H,3H}=0$ for *trans*-**13** and 5.4 Hz for *cis*-**13**).[9]



Scheme 2. Synthesis of indolizidine **15**.

Next, the conditions for the cross-metathesis (CM) reaction of *trans*-**13** with α,β-unsaturated aldehydes were investigated (Table 1).[15] First, one equivalent of *trans*-**13** was treated with three equivalents of acrolein in the presence of 5 mol% of Grubbs–Hoveyda second-generation catalyst (**G–H II**) in CH_2Cl_2 at room temperature for three hours to give α,β-unsaturated aldehyde **11** in moderate yield (entry 1). The use of 10 mol% of **G–H II** was found





to give a high yield of **11** (entry 2). Next we screened different reaction conditions to achieve scalable synthesis. When crotonaldehyde instead of acrolein was used, the yield was slightly improved (entry 3). Replacement of **G–H II** with Grubbs second-generation catalyst (**G II**) furnished the same result (entry 4). Fortunately, when the amount of ruthenium catalyst was decreased even to 2 mol% of **G II**, a comparable result was obtained (entry 5).

We next examined the MBH ring-closure reaction of **11**. Initial investigations were focused on the solvent effect by using trimethylsilyl trifluoromethanesulfonate (TMSOTf) and Me_2S.[11] Although the stereoselectivities were high, the

Table 1. Optimization of the CM reaction.[a]

Entry	Aldehyde	Ru catalyst (amount [mol%])	Yield [%]
1	$OHCCH{=}CH_2$	**G-H II** (5)	53
2	$OHCCH{=}CH_2$	**G-H II** (10)	84
3	(*E*)-$OHCCH{=}CHCH_3$	**G-H II** (5)	72
4	(*E*)-$OHCCH{=}CHCH_3$	**G II** (5)	72
5	(*E*)-$OHCCH{=}CHCH_3$	**G II** (2)	73

[a] Aminal **13** (1 equiv), aldehyde (3 equiv), and CH_2Cl_2 (0.38 M) were used.

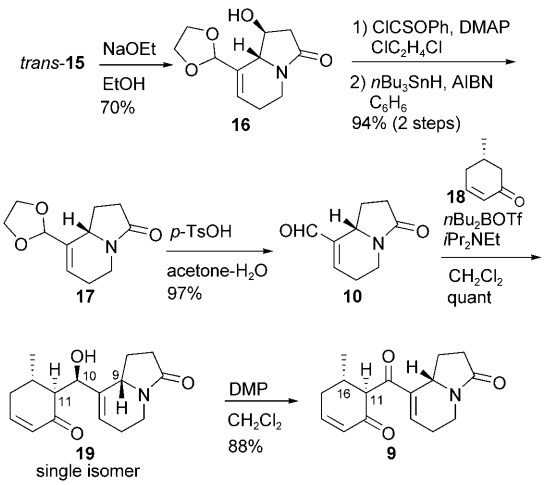
chemical yields were fairly low in CH_2Cl_2, CH_3NO_2, or toluene (Table 2, entries 1–3). Among the solvents, the use of acetonitrile afforded the best yield of the desired indolizidine **14** (entry 4). The *O*-benzoyl derivative of **11** had been expected to give high stereoselectivity due to stronger neighboring-group participation effects,[16] but both the stereoselectivity and the yield were slightly decreased. The effects of Lewis and Brønsted acids were next examined. When $BF_3{\cdot}OEt_2$ instead of TMSOTf was used, the stereoselectivity was slightly lowered (entry 5). After experimentation, the use of a Brønsted acid, such as Tf_2NH or TfOH, was found to give a good yield with high stereoselectivity (entries 6–8). In place of Me_2S, the use of Ph_3P or nBu_3P as a nucleophile was not successful (entries 9–10). Among the conditions examined, the combination of TfOH and Me_2S in acetonitrile was found to be the best for preparative purposes. The *trans*- and *cis*-MBH products **14** were converted into acetals *trans*- and *cis*-**15**, which were readily separated by column chromatography. The stereochemistries at C-8a of *trans*- and *cis*-**15** were confirmed by NOE experiments as depicted in Scheme 2.

Table 2. Morita–Baylis–Hillman reaction of **11**.

	Reagents[a]	Solvent	*T*	Yield [%] (*trans*-**14**/*cis*-**14**)[b]
1	TMSOTf, Me_2S	CH_2Cl_2	−78 °C–RT	32 (96:4)
2	TMSOTf, Me_2S	CH_3NO_2	−15 °C–RT	26 (97:3)
3	TMSOTf, Me_2S	toluene	−60 °C–RT	28 (92:8)
4	TMSOTf, Me_2S	CH_3CN	−35 °C–RT	56 (94:6)
5	$BF_3{\cdot}OEt_2$, Me_2S	CH_3CN	−35 °C–RT	61 (81:19)
6	Tf_2NH, Me_2S	CH_3CN	−35 °C–RT	64 (95:5)
7	TfOH, Me_2S	CH_3CN	−35 °C–RT	67 (96:4)
8	TfOH, tetrahydrothiophene	CH_3CN	−35 °C–RT	65 (94:6)
9	TfOH, Ph_3P	CH_3CN	−35 °C–RT	ND[c]
10	TfOH, nBu_3P	CH_3CN	−35 °C–RT	ND[c]

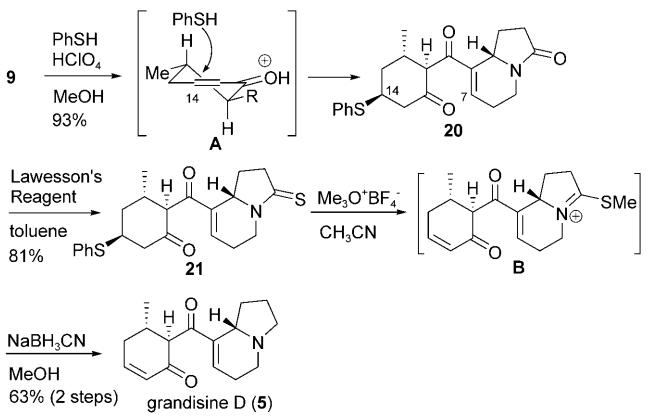
[a] Aminal **11** (1.0 equiv), Lewis acid or Brønsted acid (2.5 equiv) and sulfide or phosphine (1.5 equiv) were used. [b] The ratios of products *trans*- and *cis*-**14** were estimated from the ^1H NMR spectra. [c] Not detected.

Synthesis of key intermediate 9: Removal of the acetoxy group of *trans*-**15** was conducted by deacetylation followed by the Barton–McCombie deoxygenation protocol (Scheme 3).[17] Thus, deacetylation of *trans*-**15** in the presence of a catalytic amount of NaOEt in EtOH led to **16** in 70% yield. Alcohol **16** was converted to the corresponding thionocarbonate, which was removed by a radical-mediated deoxygenation to provide lactam **17** in excellent yield from **16**. Deprotection of the acetal of **17** by acid hydrolysis gave aldehyde **10** in 97% yield. Formation of the C_{10}–C_{11} bond was achieved by an aldol reaction, employing boron enolate methodology, of enone **18**[12] with aldehyde **10** to furnish **19** in quantitative yield as a single isomer.[18] The stereochemistry at the C-10 position of **19** was confirmed by means of the modified Mosher's method (see the Experimental Section).[19] Treatment of alcohol **19** with Dess–Martin periodinane gave **9**, in which the stereochemistry of C-11 was deduced from the large vicinal coupling constant ($J_{H11,H16}$ = 11.2 Hz) in the ^1H NMR spectrum (Figure 1).



Scheme 3. Synthesis of key intermediate **9**.

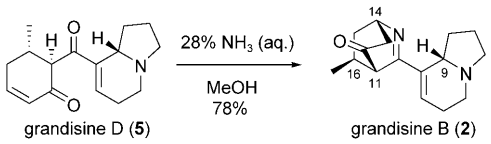
Total synthesis of grandisine D (5): For the synthesis of **5**, chemoselective reduction of the amide carbonyl group of **9** was required (Scheme 4). An attempt at direct conversion of **9** to **5** through a two-step sequence (thioamidation of amide followed by reduction) failed, resulting in significant decomposition. Therefore, the α,β-unsaturated ketone of **9** was protected as the thiophenol adduct **20**.[20] 1,4-Addition



Scheme 4. Total synthesis of grandisine D (**5**).

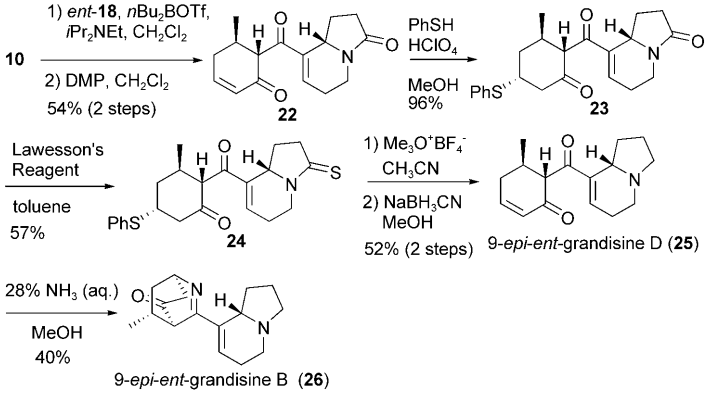
of thiophenol under acidic conditions took place with complete site selectivity at C-14 and *trans* stereoselectivity with respect to the methyl substituent. The top-face attack of thiophenol can be explained in terms of axial attack on the more stable conformation **A** of the cyclohexenone moiety, leading to the chair form of the enol, whereas bottom-face attack should give a twisted form of the enol. Site selectivity of the addition of thiophenol might be due to inefficient conjugation of the double bond in the indolizidine moiety with the carbonyl group in the side chain and/or steric interference of the cyclohexenone moiety with nucleophilic attack at C-7, although the details remain unclear. Amide **20** was converted into the corresponding thioamide **21** by treatment with Lawesson's reagent. Finally, synthesis of **5** was accomplished through a two-step sequence. Thus, thioamide **21** was exposed to Meerwein's salt, which methylated both the thioamide group and phenylthio group, and the resulting dimethylated compound underwent elimination to generate cyclohexenone **B**, which was then treated with $NaBH_3CN$[21] to afford grandisine D (**5**) in 63% yield. Spectral data of synthetic **5** were identical (^1H and ^{13}C NMR spectra and HRMS) with those previously reported, except for the value of optical rotation ($[\alpha]_D^{23}=+65.7$ ($c=0.09$ in MeOH) for synthetic **5**; lit.[3b] $[\alpha]_D^{23}=+34.6$ ($c=0.09$ in MeOH) for a natural sample). The difference between the optical rotation of natural **5** and that of synthetic **5** may be ascribed to a difference in purity. The synthetic product was shown to have a much higher level of purity.

Total synthesis of grandisine B (2): We next examined the synthesis of grandisine B (**2**), which has been proposed to be biosynthesized from grandisine D (**5**) (Scheme 5). Fortunately, grandisine D (**5**), on treatment with ammonia, underwent intermolecular 1,4-addition of ammonia and intramolecular imine formation to afford grandisine B (**2**) as a sole product, the spectral data of which (^1H and ^{13}C NMR spectra) were identical with the literature values.[3a]



Scheme 5. Total synthesis of grandisine B (**2**).

However, the specific optical rotation of synthetic **2** ($[\alpha]_D^{22}=-159$ ($c=0.08$ in CH_2Cl_2)) is quite different from that of the natural product ($[\alpha]_D=+11.0$ ($c=0.1$ in CH_2Cl_2)).[3a] In the literature, although the relative stereochemistry of the isoquinuclidinone moiety of natural **2** was determined by coupling constant analysis, the stereochemistry of C-9 relative to C-11, C-14, and C-16 could not be determined from NMR spectroscopic analysis. The absolute stereochemistry at C-9 and C-16 for **2** was only presumed to be the same as that of the known isoelaeocarpiline.[3a] Therefore, synthesis of 9-*epi*-*ent*-grandisine B (**26**) and comparison of its ^1H and ^{13}C NMR spectra with those of **2** was carried out next. As shown below, the same synthetic sequence of steps starting from **10** and *ent*-**18**, readily prepared from (*R*)-pulegone,[12] led to a final product **26** (Scheme 6). Its



Scheme 6. Synthesis of 9-*epi*-*ent*-grandisine B (**26**).

^{13}C NMR spectrum was similar to that of **2**, but the ^1H NMR spectrum was clearly different (for an ^1H NMR spectral comparison, see Figure 1). Thus, the stereochemistry of grandisine B (**2**) was unambiguously established by total synthesis of grandisine B (**2**) and 9-*epi*-*ent*-grandisine B (**26**). The discrepancy in the specific optical rotation might be due to relatively low purity of the natural product.

Total synthesis of grandisine F (4): An attempt at 1,4-addition of ammonia to grandisine D (**5**) without intramolecular imine formation failed to give grandisine F (**4**). After several experiments, we were delighted to find that lactam **9** was a good starting material for grandisine F (**4**) (Scheme 7). Diketone **9**, on treatment with ammonia solution, underwent intermolecular 1,4-addition of ammonia followed by ring closure of the enolate to afford tetracyclic compound **27** as a single isomer. The relative stereochemistry of the tetracyclic structure **27** was determined by X-ray crystallographic analysis (see ORTEP drawing, Scheme 7)[22] of the corresponding *tert*-butyloxycarbonyl (Boc) derivative **28**, prepared by reaction of amine **27** with Boc_2O. Since the tetracyclic ring system of grandisine F (**4**) was thus assembled with correct stereochemistry, the next task was reduction of the amide carbonyl group. Amide **28** was converted into the corresponding thioamide **29** with Lawesson's reagent, followed by reduction with Raney nickel to afford amine **30** (78% over two steps). Finally, the total synthesis of grandisine F (**4**) was accomplished by removal of the Boc group with trifluoroacetic acid (TFA).

The ^1H[23] and ^{13}C NMR spectra of our synthetic **4** are, however, slightly different from those reported,[3b] and the specific optical rotation of synthetic **4** ($[\alpha]_D^{24}=+140$ ($c=0.09$ in MeOH)) is quite different from that reported for the natural product ($[\alpha]_D^{23}=-22.4$ ($c=0.09$ in MeOH)).[3b] As shown by X-ray crystallographic analysis of the intermediate **28**, synthetic **4** should have the correct (7*R*,8*S*,9*S*,14*S*,16*S*)

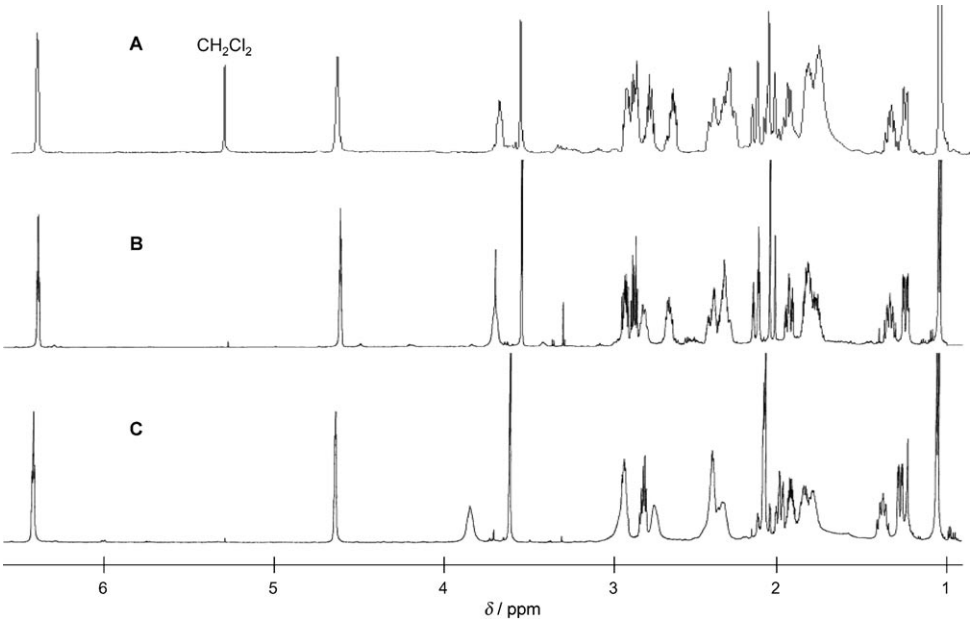
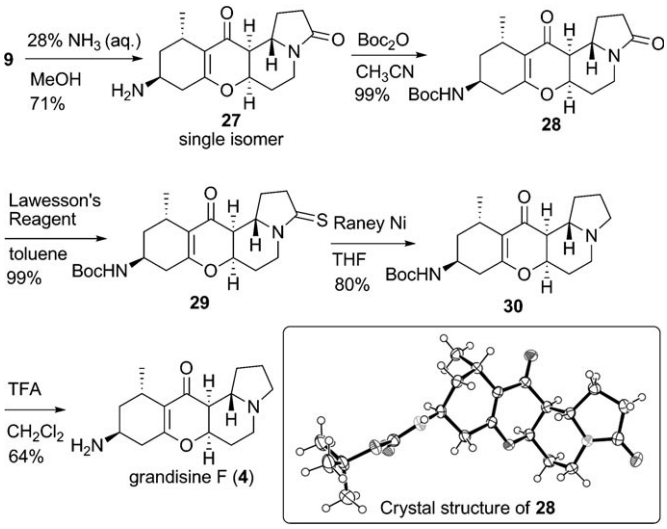


Figure 1. Spectroscopic comparison of natural grandisine B (panel A),[3a] synthetic grandisine B (panel B), and synthetic 9-*epi*-*ent*-grandisine B (panel C) in $CDCl_3$ (600 MHz).



Scheme 7. Total synthesis of grandisine F (**4**).

stereochemistry. Therefore, direct comparison of the ^1H and ^{13}C NMR spectra of synthetic **4** with those of natural grandisine F was carried out. Natural grandisine F was purified by a method similar to that used for synthetic **4**, but the ^1H NMR spectrum of the purified grandisine F was still slightly different from that of synthetic **4**. Fortunately, the ^1H and ^{13}C NMR spectra of a 1:1 mixture of natural grandisine F and synthetic **4** did not show any separated signals, and this experiment demonstrated that synthetic **4** had the expected structure. We speculate that the slight differences in the NMR spectra may be ascribed to partial protonation of the tertiary amine of **4**. Next, the optical purities of natural and synthetic **4** were measured. First the enantiomer of **4** (*ent*-**4**) was synthesized from (*R*)-malic acid and *ent*-**18** through the same sequence of steps as described above. Chiral HPLC analysis (DAICEL CHIRALPAK IA) of natural (purified sample), synthetic **4**, and *ent*-**4** (see the Supporting Information) showed that natural and synthetic **4** are optically pure and the absolute configuration of natural **4** is as shown. Therefore, the discrepancy in the specific optical rotation might have been due to relatively low purity of the natural product.

Conclusion

We have accomplished the first total synthesis of grandisines B (**2**), D (**5**), and F (**4**) from common key intermediate **9** on the basis of a synthetic strategy inspired by the proposed biogenetic pathway. In this synthesis, construction of the indolizidine skeleton features highly stereoselective Brønsted acid mediated MBH reaction of **11**. This flexible strategy should serve as a powerful tool for the synthesis of grandisine analogues as candidate agonists for selective activation of the δ-opioid receptor. Further application of this strategy to the synthesis of other grandisine alkaloids and their analogues, and evaluation of the binding affinity for the human δ-opioid receptor, are in progress in our laboratory.

Experimental Section

General: All reactions that were air- and moisture-sensitive were carried out in flame-dried flasks under argon. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO P-1020 auto digital polarimeter. IR spectra were recorded with Perkin–Elmer Spectrum 100. NMR spectra (^1H and ^{13}C NMR) were recorded on a JEOL JNM-AL300 or a Bruker AV600 spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane ($\delta = 0.00$ ppm) as an internal standard ($CDCl_3$ solution). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Measurements of mass spectra (MS) and high-resolution MS (HRMS) were performed with a JEOL JMS SX-102A or a JEOL JMS-T100LP mass spectrometer. HPLC analyses were conducted by using a JASCO 880-PU with Hitachi 655A UV detection. Column chromatography was carried out on silica gel (silica gel 40–50 μm neutral, (Kanto Chemical) or Chromatorex NH DM2035 200–350 mesh (Fuji Silysia Chemical)). Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) or Fuji Silysia Chemical. TLC Plates (NH) were used for the TLC analysis. After extractive workup, organic layers were dried over anhydrous sodium sulfate or anhydrous magunesium sulfate and the solvent was removed by rotary evaporation under reduced pressure.

(3*S*)-3-Acetoxy-1-(3-buten-1-yl)pyrrolidine-2,5-dione (12): A solution of (*S*)-malic acid (12.2 g, 91.1 mmol) in acetyl chloride (150 mL) was heated at reflux for 2 h. After evaporation of acetyl chloride, the residue was dissolved in CH_2Cl_2 (70 mL). To the resulting solution was added dropwise a mixture of 4-amino-1-butene hydrochloride (22.1 g, 205 mmol) and triethylamine (28.5 mL, 205 mmol) in CH_2Cl_2 (80 mL) at 0 °C and the mixture was stirred at room temperature for 5 h. After evaporation of the solvent, acetyl chloride (150 mL) was added to the residue and the mixture was heated at reflux for 1.5 h. After evaporation of acetyl chloride, the residue was dissolved in a mixture of CH_2Cl_2 (50 mL), water (50 mL), and saturated aqueous $NaHCO_3$ (400 mL). The whole was extracted with CH_2Cl_2 (50 mL × 2), washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/AcOEt, 1:1) to afford imide **12** as a colorless solid (17.4 g, 90 %). M.p. 49.0–50.0 °C (hexane/AcOEt); $[\alpha]_D^{24} = -19.0$ ($c = 0.50$, $CHCl_3$); IR (ATR): $\tilde{\nu} = 2949$, 1743, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.73$ (ddt, $J = 16.5$, 10.8, 6.9 Hz, 1H), 5.43 (dd, $J = 8.8$, 4.8 Hz, 1H), 5.14–5.02 (m, 2H), 3.64 (t, $J = 7.2$ Hz, 2H), 3.15 (dd, $J = 18.3$, 8.6 Hz, 1H), 2.65 (dd, $J = 18.3$, 5.0 Hz, 1H), 2.38 (br q, $J = 7.1$ Hz, 2H), 2.17 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.3$, 173.1, 169.8, 134.0, 117.8, 67.3, 38.2, 35.7, 31.7, 20.5 ppm; MS (CI+): *m/z*: 212 $[M+H]^+$; HRMS (CI+): *m/z*: calcd for $C_{10}H_{14}NO_4$: 212.0923; found: 212.0922 $[M+H]^+$; the optical purity of **12** was measured to be 99.3 % *ee* by chiral HPLC analysis (DAICEL CHIRALPAK IA, 4.6 × 250 mm, measurement of UV260 nm absorbance, hexane/EtOH 6:4, 0.5 mL min^{-1}, $t_R = 35.60$, $t_S = 21.67$ min); the corresponding enantiomer was prepared from (*R*)-malic acid by using the same procedure described above.

(2*R*,3*S*)-1-Butenyl-2-ethoxy-5-oxopyrrolidin-3-yl acetate (*trans*-13) and (2*S*,3*S*)-1-butenyl-2-ethoxy-5-oxopyrrolidin-3-yl acetate (*cis*-13): $NaBH_4$ (8.96 g, 237 mmol) was added to a solution of imide **12** (10.0 g, 47.3 mmol) in EtOH (470 mL) at −15 °C. The mixture was stirred for 15 min at −5 °C and cooled to −52 °C, then a 1 M solution of H_2SO_4 in EtOH (215 mL) was added over 55 min. The mixture was allowed to warm to room temperature, and stirring was continued for 13 h. The mixture was poured into saturated aqueous $NaHCO_3$ (1.5 L), and the whole was extracted with CH_2Cl_2 (200 mL × 4), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/AcOEt 1:1) to afford *trans*-**13** as a colorless oil (9.60 g, 84 %) and *cis*-**13** as a colorless oil (1.11 g, 10 %).

*Product trans-**13***: $[\alpha]_D^{24} = -26.5$ ($c = 0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 2977$, 2934, 1742, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.78$ (ddt, $J = 17.1$, 10.2, 6.9 Hz, 1H), 5.14–5.01 (m, 3H), 4.73 (s, 1H), 3.74 (dq, $J = 9.6$, 7.1 Hz, 1H), 3.67–3.53 (m, 2H), 3.17 (br dt, $J = 13.8$, 7.2 Hz, 1H), 2.88 (ddd, $J = 17.9$, 6.5, 0.8 Hz, 1H), 2.43–2.26 (m, 3H), 2.07 (s, 3H), 1.25 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.5$, 170.3, 135.0, 116.9, 93.0, 70.5, 63.6, 39.7, 35.6, 32.2, 20.9, 15.2 ppm; MS (CI+): *m/z*: 242 $[M+H]^+$; HRMS (CI+): *m/z*: calcd for $C_{12}H_{20}NO_4$: 242.1392; found: 242.1440 $[M+H]^+$.

*Product cis-**13***: $[\alpha]_D^{24} = -57.7$ ($c = 0.49$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 2978$, 2935, 1739, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.76$ (ddt, $J = 17.1$, 10.5, 7.2 Hz, 1H), 5.20–5.04 (m, 4H), 3.72–3.51 (m, 3H), 3.13 (ddd, $J = 14.1$, 7.8, 6.3 Hz, 1H), 2.66 (dd, $J = 16.8$, 7.8 Hz, 1H), 2.60 (dd, $J = 16.8$, 7.8 Hz, 1H), 2.41–2.25 (m, 2H), 2.13 (s, 3H), 1.21 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.9$, 170.7, 134.9, 117.2, 88.2, 67.7, 65.4, 39.9, 34.5, 32.1, 20.7, 15.5 ppm; MS (CI+): *m/z*: 242 $[M+H]^+$; HRMS (CI+): *m/z*: calcd for $C_{12}H_{20}NO_4$: 242.1392; found: 242.1389 $[M+H]^+$.

(2*R*,3*S*)-2-Ethoxy-5-oxo-1-[(3*E*)-5-oxo-3-pentenyl]pyrrolidin-3-yl acetate (11)

Experimental details from Table 1, entry 2: A solution of *trans*-**13** (4.43 g, 18.4 mmol), acrolein (3.68 mL, 55.1 mmol), and Grubbs–Hoveyda second-generation catalyst (1.15 g, 1.84 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 2 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane/AcOEt 1:2) to afford aldehyde **11** as a brown oil (4.14 g, 84 %). $[\alpha]_D^{24} = -24.8$ ($c = 0.47$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 2978$, 1741, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.51$ (d, $J = 7.9$ Hz, 1H), 6.81 (dt, $J = 15.6$, 7.0 Hz, 1H), 6.13 (ddt, $J = 15.6$, 7.9, 1.5 Hz, 1H), 5.07 (d, $J = 6.1$ Hz, 1H), 4.67 (s, 1H), 3.76 (dq, $J = 9.3$, 6.9 Hz, 1H), 3.68–3.54 (m, 2H), 3.44 (br dt, $J = 13.8$, 6.6 Hz, 1H), 2.88 (dd, $J = 17.8$, 6.1 Hz, 1H), 2.75–2.57 (m, 2H), 2.32 (d, $J = 17.8$ Hz, 1H), 2.07 (s, 3H), 1.25 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.6$, 172.7, 170.3, 154.0, 134.6, 93.4, 70.2, 63.7, 39.1, 35.5, 31.4, 20.9, 15.2 ppm; MS (CI+): *m/z*: 270 $[M+H]^+$; HRMS (CI+): *m/z*: calcd for $C_{13}H_{20}NO_5$: 270.1341; found: 270.1364 $[M+H]^+$.

Experimental details from Table 1, entry 5: A solution of *trans*-**13** (300 mg, 1.24 mmol), crotonaldehyde (309 μL, 3.73 mmol), and Grubbs second-generation catalyst (21.1 mg, 0.0248 mmol) in CH_2Cl_2 (3.26 mL) was stirred at room temperature for 2 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane/AcOEt 1:2) to afford aldehyde **11** as a brown oil (245 mg, 73 %).

(1*S*,8a*R*)-8-Formyl-3-oxo-1,2,3,5,6,8a-hexahydroindolizin-1-yl acetate (*trans*-14) and (1*S*,8a*S*)-8-formyl-3-oxo-1,2,3,5,6,8a-hexahydroindolizin-1-yl acetate (*cis*-14): Me_2S (1.64 mL, 22.3 mmol) and TfOH (3.29 mL, 37.1 mmol) were added to a solution of aldehyde **11** (4.00 g, 14.9 mmol) in CH_3CN (75 mL) at −35 °C. The resulting mixture was allowed to warm to room temperature and stirring was continued for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (70 mL). After evaporation of CH_3CN, the whole was extracted with CH_2Cl_2 (30 mL × 3), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (MeOH/AcOEt 1:20) to afford an inseparable mixture of *trans*- and *cis*-**14** as a colorless solid (2.22 g, 67 %, *trans*/*cis* 96:4). IR (ATR): $\tilde{\nu} = 2930$, 2820, 1730, 1675 cm^{-1}; the spectral data of *trans* and *cis*-**14** were measured after deprotection of the acetal of *trans*- and *cis*-**15** obtained below by acid hydrolysis, respectively; MS (CI+): *m/z*: 224 $[M+H]^+$; HRMS (CI+): *m/z*: calcd for $C_{11}H_{14}NO_4$: 224.0923; found: 224.0924 $[M+H]^+$.

*Product trans-**14***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.43$ (s, 1H), 7.00–6.98 (m, 1H), 5.27 (ddd, $J = 10.0$, 5.0, 3.7 Hz, 1H), 4.54–4.51 (m, 1H), 4.39 (br dd, $J = 13.3$, 6.7 Hz, 1H), 2.86 (dd, $J = 17.4$, 8.4 Hz, 1H), 2.88–2.77 (m, 1H), 2.53 (ddd, $J = 17.4$, 6.3, 1.5 Hz, 1H), 2.64–2.35 (m, 2H), 2.16 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 191.3$, 170.4, 170.3, 149.7, 140.2, 69.7, 58.8, 38.3, 35.2, 25.5, 21.0 ppm.

*Product cis-**14***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.45$ (s, 1H), 7.11–7.06 (m, 1H), 5.69 (t, $J = 5.0$ Hz, 1H), 4.64–4.59 (m, 1H), 4.38 (br dd, $J = 12.8$, 5.7 Hz, 1H), 2.92–2.77 (m, 2H), 2.67–2.42 (m, 2H), 2.45 (d, $J = 17.8$ Hz, 1H), 1.91 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 191.0$, 170.7, 169.6, 149.0, 137.5, 68.7, 56.9, 39.3, 35.0, 25.5, 20.8 ppm.

(1*S*,8a*R*)-8-[1,3-Dioxolan-2-yl]-3-oxo-1,2,3,5,6,8a-hexahydroindolizin-1-yl acetate (*trans*-15) and (1*S*,8a*S*)-8-[1,3-dioxolan-2-yl]-3-oxo-1,2,3,5,6,8a-hexahydroindolizin-1-yl acetate (*cis*-15): A solution of indolizidine **14** (350 mg, 1.57 mmol; mixture of *trans*- and *cis*-**14**), ethylene glycol (393 μL, 7.06 mmol), and *p*-toluenesulfonic acid (PTSA) (3 mg, 0.016 mmol) in benzene (20 mL) was heated at reflux for 13 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (150 mL). The whole was extracted with CH_2Cl_2 (200 mL × 4), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (AcOEt) to afford *trans*-**15** as colorless crystals (347 mg, 88 %) and *cis*-**15** as a colorless oil (30.2 mg, 8 %).

*Product trans-**15***: M.p. 90.0–91.0 °C (hexane/AcOEt); $[\alpha]_D^{25} = -88.5$ ($c = 0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 2937$, 2883, 1738, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.15$ (br d, $J = 6.0$ Hz, 1H), 5.46 (br dt, $J = 9.2$, 4.1 Hz, 1H), 5.23 (s, 1H), 4.39–4.37 (m, 1H), 4.27 (br dd, $J = 13.2$, 6.6 Hz, 1H), 4.05–3.84 (m, 4H), 2.92 (dd, $J = 17.6$, 8.2 Hz, 1H), 2.90–2.78 (m, 1H), 2.41 (ddd, $J = 17.6$, 5.5, 1.5 Hz, 1H), 2.37–2.23 (m, 1H), 2.17–2.05 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.6$, 169.9, 132.6, 128.8, 103.8, 70.2, 64.9, 64.8, 60.0, 38.2, 36.0, 23.8, 20.9 ppm; MS (CI+): *m/z*: 268 $[M+H]^+$; HRMS (CI+): *m/z*: calcd for $C_{13}H_{18}NO_5$: 268.1185; found 268.1147 $[M+H]^+$.

*Product cis-**15***: $[\alpha]_D^{25} = +194$ ($c = 0.45$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 2887$, 1735, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.24$ (d, $J = 6.2$ Hz, 1H), 5.49 (t, $J = 4.5$ Hz, 1H), 5.17 (s, 1H), 4.52–4.46 (m, 1H), 4.26 (br dd, $J = 12.9$, 6.0 Hz, 1H), 4.00–3.81 (m, 4H), 2.84–2.71 (m, 2H), 2.38 (d, $J = 17.4$ Hz, 1H), 2.41–2.13 (m, 2H), 1.98 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.8$, 170.4, 130.6, 129.7, 104.4, 69.4, 65.0, 64.9, 57.6, 39.8, 35.7, 24.2, 21.0 ppm; MS (ESI+): *m/z*: 268 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{13}H_{18}NO_5$: 268.1185; found: 268.1187 $[M+H]^+$.

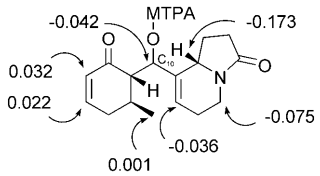
(1*S*,8a*R*)-8-(1,3-Dioxolan-2-yl)-1-hydroxy-1,5,6,8a-tetrahydro-2*H*-indolizin-3-one (16): NaOEt (37.9 mg, 0.557 mmol) in EtOH (6.5 mL) was added to a solution of *trans*-**15** (2.50 g, 9.95 mmol) in EtOH (6.5 mL) at 4 °C, and the mixture was stirred at room temperature. After 1 h, a solution of NaOEt (37.9 mg, 0.557 mmol) in EtOH (2 mL) was added twice every 1 h. The mixture was poured into saturated aqueous NH_4Cl (100 mL), and the whole was extracted with CH_2Cl_2 (40 mL × 2), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (MeOH/AcOEt 1:20) to afford **16** as colorless crystals (1.57 g, 70 %). M.p. 143.5–144.0 °C (hexane/AcOEt); $[\alpha]_D^{25} = -126$ ($c = 0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 3292$, 2864, 1654 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.20$ (d, $J = 5.7$ Hz, 1H), 5.29 (s, 1H), 4.32–3.96 (m, 7H), 3.82 (d, $J = 2.4$ Hz, 1H), 2.77–2.50 (m, 3H), 2.30–2.11 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.3$, 133.1, 128.5, 104.3, 72.3, 65.2, 64.5, 61.8, 39.4, 35.0, 24.6 ppm; MS (EI+): *m/z*: 225 $[M]^+$; HRMS (EI+): *m/z*: calcd for $C_{11}H_{15}NO_4$: 225.1001; found: 225.0972 $[M]^+$.

(1*S*,8a*R*)-8-(1,3-Dioxolan-2-yl)-3-oxo-1,2,3,5,6,8a-hexahydro-indolizin-1-yl phenoxythiocarbonate: A solution of **16** (1.55 g, 6.88 mmol), 4-dimethylaminopyridine (DMAP) (1.26 g, 10.3 mmol), and phenyl chlorothionoformate (1.40 mL, 10.3 mmol) in ClC_2H_4Cl (44 mL) was heated at 60 °C for 12 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane/AcOEt 1:2) to afford the title compound as colorless crystals (2.48 g, quant.). M.p. 144.0–145.0 °C (hexane/AcOEt); $[\alpha]_D^{25} = -30.0$ ($c = 0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 2952$, 2902, 2851, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.39 (m, 2H), 7.36–7.28 (m, 1H), 7.14–7.06 (m, 2H), 6.19 (br d, $J = 6.1$ Hz, 1H), 5.83 (ddd, $J = 8.2$, 5.9, 4.8 Hz, 1H), 5.27 (s, 1H), 4.67–4.61 (m, 1H), 4.32 (br dd, $J = 13.2$, 6.6 Hz, 1H), 4.17–4.04 (m, 2H), 4.02–3.89 (m, 2H), 3.16 (dd, $J = 17.5$, 8.3 Hz, 1H), 2.88 (br td, $J = 11.4$, 4.8 Hz, 1H), 2.62 (ddd, $J = 17.6$, 5.9, 1.4 Hz, 1H), 2.42–2.26 (m, 1H), 2.21–2.08 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.9$, 169.8, 153.3, 132.5, 130.1, 129.6, 126.8, 121.8, 104.8, 79.5, 65.1, 65.0, 58.9, 37.7, 36.0, 24.0 ppm; MS (ESI+): *m/z*: 362 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{18}H_{20}NO_5S$: 362.1062; found: 362.1070 $[M+H]^+$.

(8a*S*)-8-(1,3-Dioxolan-2-yl)-1,5,6,8a-tetrahydro-2*H*-indolizin-3-one (17): A solution of phenoxythiocarbonate derivative prepared above (2.45 g, 6.78 mmol), nBu$_3$SnH (5.39 mL, 20.3 mmol), and 2,2′-azobisisobutyronitrile (AIBN) (55.7 mg, 0.339 mmol) in benzene (34 mL) was heated at reflux for 30 min. After concentration, the crude product was purified by column chromatography on silica gel containing 10 % w/w KF[24] (MeOH/AcOEt 1:20) to afford **17** as colorless crystals (1.33 g, 94 %). M.p. 60.0–61.0 °C (hexane/AcOEt); $[\alpha]_D^{25} = -212$ ($c = 0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 3475$, 2849, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.06$ (br d, $J = 5.7$ Hz, 1H), 5.23 (s, 1H), 4.35–4.18 (m, 1H), 4.23 (dd, $J = 12.6$, 6.0 Hz, 1H), 4.08–3.86 (m, 4H), 2.76 (br td, $J = 11.7$, 4.8 Hz, 1H), 2.52–2.07 (m, 5H), 1.91–1.75 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.2$, 135.3, 126.4, 104.3, 65.1, 64.7, 54.5, 35.8, 31.9, 26.4, 24.4 ppm; MS (EI+): *m/z*: 209 $[M]^+$; HRMS (EI+): *m/z*: calcd for $C_{11}H_{15}NO_3$: 209.1052; found: 209.1061 $[M]^+$.

(8a*S*)-3-Oxo-1,2,3,5,6,8a-hexahydroindolizine-8-carbaldehyde (10): A solution of **17** (1.30 g, 6.21 mmol) and PTSA (1.18 g, 6.21 mmol) in acetone (62 mL) containing H_2O (1.6 mL) was heated at reflux for 15 min. After concentration, the crude product was purified by column chromatography on silica gel (MeOH/AcOEt 1:20) to afford **10** as a colorless oil (997 mg, 97 %). $[\alpha]_D^{25} = -424$ ($c = 0.25$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 3450$, 2935, 2834, 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.44$ (s, 1H), 6.94–6.89 (m, 1H), 4.46–4.29 (m, 2H), 2.85–2.65 (m, 2H), 2.62–2.33 (m, 4H), 1.64–1.49 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 191.7$, 173.3, 147.7, 142.6, 53.6, 35.1, 31.5, 26.0, 25.9 ppm; MS (EI+): *m/z*: 165 $[M]^+$; HRMS (EI+): *m/z*: calcd for $C_9H_{11}NO_2$: 165.0790; found: 165.0777 $[M]^+$.

(8a*S*, 1′*S*, 6′*S*)-8-[(*R*)-Hydroxy(6-methyl-2′-oxo-cyclohex-3′-en-1-yl) methyl]-1,5,6,8a-tetrahydro-2*H*-indolizin-3-one (19): iPr$_2$NEt (791 μL, 6.81 mmol), and nBu$_2$BOTf (1.0 M, 4.54 mL, 6.81 mmol) was successively added dropwise to a solution of (*S*)-5-methylcyclohexenone (**18**)[12] (500 mg, 4.54 mmol) in CH_2Cl_2 (20 mL) at −78 °C. After stirring at the same temperature for 1 h, a solution of aldehyde **10** (500 mg, 3.03 mmol) in CH_2Cl_2 (10 mL) was added slowly at −78 °C. The mixture was allowed to warm to room temperature and stirring was continued for 1 h. The reaction was quenched by addition of MeOH (1.4 mL) and 30 % H_2O_2 (1.4 mL) at 4 °C, and then the mixture was poured into saturated aqueous $NaHCO_3$ (30 mL). The whole was extracted with CH_2Cl_2 (20 mL x 2), washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (MeOH/AcOEt 1:10) to afford **19** as colorless crystals (830 mg, quant.). M.p. 121–123 °C (hexane/EtOH); $[\alpha]_D^{22} = -100$ ($c = 0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 3404$, 2918, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.91$ (dt, $J = 10.1$, 4.1 Hz, 1H), 6.05 (dt, $J = 10.1$, 1.9 Hz, 1H), 5.78 (d, $J = 5.5$ Hz, 1H), 4.37–4.19 (m, 3H), 2.73 (td, $J = 12.1$, 4.7 Hz, 1H), 2.63–2.05 (m, 10H), 1.94–1.80 (m, 1H), 1.14 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 201.1$, 173.1, 148.4, 138.6, 128.6, 123.9, 73.0, 56.1, 55.3, 35.7, 31.9, 31.0, 30.7, 27.3, 24.7, 19.9 ppm; MS (ESI+): *m/z*: 276 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{22}NO_3$: 276.1600; found: 276.1591 $[M+H]^+$; stereochemistry of **19** was determined by modified Mosher's method (Scheme 8). Derivatization of **19** to the corresponding (*R*)- or (*S*)-MTPA esters was conducted according to a usual method, and ^1H NMR spectroscopic data are as follows:



Scheme 8. Modified Mosher's method: Differences of the chemical shifts ($\Delta\delta = (\delta_S - \delta_R)$, $CDCl_3$) between (*R*)- and (*S*)-MTPA esters of **19** (MTPA = a-methoxy-alpha(trifluoromethyl)phenylacetic acid).

*(R)-MTPA ester of **19***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.49$–7.35 (m, 5H), 6.85–6.77 (m, 1H), 6.17 (d, $J = 5.9$ Hz, 1H), 5.97 (dd, $J = 10.3$, 2.9 Hz, 1H), 5.85 (d, $J = 10.6$ Hz, 1H), 4.24 (dd, $J = 13.0$, 6.4 Hz, 1H), 4.16–4.05 (m, 1H), 3.40 (d, $J = 0.7$ Hz, 3H), 2.75–2.55 (m, 3H), 2.43–2.06 (m, 7H), 1.64–1.48 (m, 1H), 1.10 ppm (d, $J = 7.2$ Hz, 3H).

*(S)-MTPA ester of **19***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.29 (m, 5H), 6.88–6.79 (m, 1H), 6.13 (d, $J = 5.5$ Hz, 1H), 6.00 (dd, $J = 10.3$, 2.8 Hz, 1H), 5.81 (d, $J = 11.4$ Hz, 1H), 4.16 (dd, $J = 12.7$, 5.4 Hz, 1H), 3.99–3.88 (m, 1H), 3.58 (d, $J = 1.7$ Hz, 3H), 2.73–2.51 (m, 3H), 2.28–1.83 (m, 7H), 1.10 (d, $J = 7.2$ Hz, 3H), 0.78–0.63 ppm (m, 1H).

(8a*S*,1′*R*,6′*S*)-8-(6′-Methyl-2′-oxo-cyclohex-3′-enecarbonyl)-1,5,6,8a-tetrahydro-2*H*-indolizin-3-one (9): A solution of Dess–Martin periodinane (15 % w/w, 7.76 mL, 3.63 mmol) in CH_2Cl_2 was added to a solution of **19** (500 mg, 1.82 mmol) in CH_2Cl_2 (18 mL) at 4 °C, and then the mixture was allowed to warm to room temperature and stirring was continued for 3 h. The mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and the whole was extracted with CH_2Cl_2 (20 mL × 3), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (MeOH/AcOEt 1:20) to afford **9** as a colorless syrup (436 mg, 88 %). $[\alpha]_D^{24} = -57.6$ ($c = 0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu} = 2906$, 1685, 1671, 1642, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.02$ (ddd, $J = 10.2$, 5.7, 2.7 Hz, 1H), 6.95–6.89 (m, 1H), 6.07 (ddd, $J = 10.1$, 2.7, 1.3 Hz, 1H), 4.62–4.52 (m, 1H), 4.29 (br dd, $J = 12.0$, 6.0 Hz, 1H), 3.81 (d, $J = 11.2$ Hz, 1H), 2.87–2.66 (m, 3H), 2.62–2.30 (m, 5H), 2.17 (ddt, $J = 19.1$, 10.3, 2.8 Hz, 1H), 1.51–1.37 (m, 1H), 0.98 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.7$, 196.3, 173.2, 150.0, 142.8, 140.0, 129.3, 60.5, 54.6, 34.8, 33.2, 33.0, 31.5, 26.7, 25.6, 19.9 ppm; MS (ESI+): *m/z*: 274 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{20}NO_3$: 274.1443; found: 274.1446 $[M+H]^+$.

(8a*S*,1′*R*,2′*S*,4′*S*)-8-(2′-Methyl-6′-oxo-4′-phenylsulfanyl-cyclohexanecarbonyl)-1,5,6,8a-tetrahydro-2*H*-indolizin-3-one (20): 60 % $HClO_4$ (36.8 μL, 0.366 mmol) was added to a solution of **9** (100 mg, 0.366 mmol) and PhSH (112 μL, 1.10 mmol) in MeOH (5 mL) at room temperature, and stirring was continued at the same temperature for 2 h. After concentration in vacuo, the crude product was purified by column chromatography

on silica gel (MeOH/AcOEt 1:20) to afford sulfide **20** as a colorless syrup (132 mg, 94% yield). $[\alpha]_D^{22}=-185$ ($c=0.30$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=2930$, 1709, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.47$–7.39 (m, 2H), 7.37–7.28 (m, 3H), 6.85 (br d, $J=5.3$ Hz, 1H), 4.58–4.48 (m, 1H), 4.29 (dd, $J=13.0$, 6.4 Hz, 1H), 3.82–3.73 (m, 1H), 3.70 (d, $J=8.3$ Hz, 1H), 2.95–2.26 (m, 9H), 2.17 (dt, $J=14.4$, 4.8 Hz, 1H), 1.91 (ddd, $J=14.4$, 9.6, 3.9 Hz, 1H), 1.53–1.37 (m, 1H), 0.96 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.3$, 195.8, 173.5, 141.4, 139.2, 133.1, 132.9, 129.1, 127.8, 63.9, 54.6, 45.9, 43.9, 36.0, 34.9, 32.2, 31.5, 26.6, 25.4, 20.3 ppm; MS (ESI+): *m/z*: 384 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{22}H_{26}NO_3S$: 384.1633; found: 384.1638 $[M+H]^+$.

(8a*S*,2′*R*,3′*S*,5′*S*)-(3-Methyl-5-phenylsulfanyl)-2-(3-thioxo-1,2,3,5,6,8a-hexahydro-indolizine-8-carbonyl)cyclohexanone (21): A mixture of **20** (110 mg, 0.287 mmol) and Lawesson's reagent (63.7 mg, 0.158 mmol) in toluene/CH_2Cl_2 (2:1, 6 mL) was stirred at 65 °C for 15 min. After concentration, the crude product was purified by column chromatography on silica gel (hexane/AcOEt 1:1) to afford thioamide **21** as a colorless syrup (92.6 mg, 81%). $[\alpha]_D^{23}=-263$ ($c=0.30$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=2929$, 1709, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.46$–7.38 (m, 2H), 7.37–7.28 (m, 3H), 6.90 (br d, $J=4.2$ Hz, 1H), 5.07 (dd, $J=12.8$, 5.7 Hz, 1H), 4.81–4.71 (m, 1H), 3.83–3.74 (m, 1H), 3.69 (d, $J=8.8$ Hz, 1H), 3.10–2.43 (m, 9H), 2.22–2.12 (m, 1H), 1.91 (ddd, $J=14.1$, 9.6, 3.9 Hz, 1H), 1.54–1.42 (m, 1H), 0.95 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.1$, 200.0, 195.6, 140.8, 138.9, 133.1, 133.0, 129.1, 127.9, 64.2, 61.9, 45.8, 44.3, 43.9, 39.9, 36.0, 32.1, 28.3, 25.1, 20.3 ppm; MS (ESI+): *m/z*: 400 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{22}H_{26}NO_2S_2$: 400.1405; found: 400.1415 $[M+H]^+$.

Grandisine D trifluoroacetic acid salt (5·TFA): $Me_3O^+BF_4^-$ (55.5 mg, 0.375 mmol) was added to a solution of **21** (50.0 mg, 0.125 mmol) in CH_3CN (1.2 mL) at 4 °C and then the mixture was stirred at room temperature for 1 h. After concentration, the residue (50.0 mg, 0.125 mmol) was dissolved in MeOH (1.2 mL), and $NaBH_3CN$ (15.7 mg, 0.250 mmol) was added to the solution. The mixture was stirred at room temperature for 1 h, and then was poured into saturated aqueous $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (5 mL×3), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) at 4 °C and TFA (12.0 μL, 0.161 mmol) was added to the solution. The resulting mixture was allowed to warm to room temperature, and was then stirred for 1 h. After this time, the mixture was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (AcOEt/MeOH/28% NH_3 50:10:1) to afford **5**·TFA as a colorless oil (20.6 mg, 63% yield). $[\alpha]_D^{23}=+65.7$ ($c=0.09$ in MeOH); IR (ATR): $\tilde{\nu}=2955$, 2926, 2873, 2795, 1675, 1655 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=10.15$ (br s, 1H), 7.34 (apparent t, $J=3.8$ Hz, 1H), 7.19–7.11 (m, 1H), 5.96 (dd, $J=10.0$, 2.1 Hz, 1H), 4.45–4.35 (m, 1H), 4.32 (d, $J=11.6$ Hz, 1H), 3.63–3.47 (m, 1H), 3.40–3.27 (m, 2H), 3.19–3.03 (m, 1H), 2.67–2.56 (m, 2H), 2.53–2.35 (m, 3H), 2.27–2.12 (m, 1H), 2.09–1.92 (m, 2H), 1.72–1.55 (m, 1H), 0.85 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=$ 198.4, 196.8, 151.8, 140.2, 137.3, 128.4, 59.3, 58.0, 53.0, 43.1, 33.0, 32.7, 28.1, 23.0, 20.3, 19.2 ppm; MS (ESI+): *m/z*: 260 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{22}NO_2$: 260.1651; found: 260.1652 $[M+H]^+$.

Grandisine B (2): 28% NH_3 (0.25 mL) was slowly added to a solution of **5**·TFA (5.0 mg, 0.134 mmol) in MeOH (0.50 mL) at 4 °C. The reaction mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was purified by chromatography on NH silica gel (CH_2Cl_2/MeOH/28% NH_3 200:10:1) to give **2** as a colorless oil (2.7 mg, 78%). $[\alpha]_D^{22}=-159$ ($c=0.08$ in CH_2Cl_2); IR (ATR): $\tilde{\nu}=2952$, 1727, 1577 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=6.40$ (td, $J=4.2$, 1.2 Hz, 1H), 4.62–4.60 (m, 1H), 3.71–3.66 (m, 1H), 3.53 (d, $J=3.0$ Hz, 1H), 2.91 (ddd, $J=12.6$, 7.8, 4.8 Hz, 1H), 2.86 (dd, $J=11.4$, 5.4 Hz, 1H), 2.83–2.77 (m, 1H), 2.65 (dt, $J=11.4$, 6.0 Hz, 1H), 2.44–2.27 (m, 3H), 2.14 (dt, $J=19.2$, 3.0 Hz, 1H), 2.04 (dd, $J=18.6$, 1.8 Hz, 1H), 1.97–1.92 (m, 1H), 1.88–1.74 (m, 3H), 1.37–1.31 (m, 1H), 1.25 (ddd, $J=12.6$, 4.8, 1.8 Hz, 1H), 1.04 ppm (d, $J=7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=208.9$, 171.0, 138.4, 130.2, 58.9, 56.4, 55.6, 52.6, 45.2, 40.0, 32.2, 30.0, 29.2, 24.8, 22.3, 21.2 ppm; MS (ESI+): *m/z*: 259 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{23}N_2O$: 259.1810; found: 259.1815 $[M+H]^+$.

(8a*S*,1′*S*,6′*R*)-8-(6′-Methyl-2′-oxo-cyclohex-3′-enecarbonyl)-1,5,6,8a-tetrahydro-2*H*-indolizin-3-one (22): This compound (227 mg, 54% (2 steps), colorless syrup) was obtained from **10** (254 mg, 1.54 mmol) and (*R*)-5-methylcyclohexenone (*ent*-**18**)[12] (254 mg, 2.31 mmol) by using a procedure similar to that for **9** from **10**. $[\alpha]_D^{26}=-214$ ($c=0.33$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=2904$, 1665, 1656, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=$ 7.01 (ddd, $J=10.2$, 5.7, 2.4 Hz, 1H), 6.85 (br d, $J=5.4$ Hz, 1H), 6.02 (ddd, $J=9.9$, 2.7, 1.2 Hz, 1H), 4.61–4.49 (m, 1H), 4.30 (dd, $J=12.6$, 6.0 Hz, 1H), 3.85 (d, $J=11.1$ Hz, 1H), 2.84–2.11 (m, 10H), 1.84–1.74 (m, 1H), 1.01 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=197.9$, 196.4, 173.5, 150.1, 142.8, 138.4, 129.3, 60.0, 54.7, 34.9, 33.2, 31.9, 31.4, 25.8, 25.5, 20.0 ppm; MS (ESI+): *m/z*: 274 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{20}NO_3$: 274.1443; found: 274.1449 $[M+H]^+$.

(8a*S*,1′*S*,2′*R*,4′*R*)-8-(2′-Methyl-6′-oxo-4′-phenylsulfanyl-cyclohexanecarbonyl)-1,5,6,8a-tetrahydro-2*H*-indolizin-3-one (23): This compound (134 mg, 96%, colorless syrup) was obtained from **22** (100 mg, 0.366 mmol) by using a procedure similar to that for **20**. $[\alpha]_D^{26}=-60.4$ ($c=$ 0.20 in $CHCl_3$); IR (ATR): $\tilde{\nu}=2929$, 1708, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.44$–7.40 (m, 2H), 7.36–7.29 (m, 3H), 6.85 (d, $J=$ 5.4 Hz, 1H), 4.59–4.50 (m, 1H), 4.30 (dd, $J=12.9$, 6.3 Hz, 1H), 3.80 (quin., $J=4.5$ Hz, 1H), 3.73 (d, $J=9.3$ Hz, 1H), 2.99–2.84 (m, 1H), 2.79–2.60 (m, 3H), 2.57–2.42 (m, 4H), 2.38–2.26 (m, 1H), 2.17 (br dt, $J=9.6$, 4.5 Hz, 1H), 1.91 (ddd, $J=14.1$, 10.5, 3.9 Hz, 1H), 1.70 (dq, $J=12.6$, 9.9 Hz, 1H), 0.96 ppm (d, $J=6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.7$, 196.1, 174.9, 141.1, 138.0, 133.2, 132.9, 129.2, 127.9, 63.9, 55.7, 46.0, 44.6, 36.3, 35.7, 31.3, 31.1, 25.8, 25.2, 20.4 ppm; MS (ESI+): *m/z*: 384 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{22}H_{26}NO_3S$: 384.1633; found: 384.1633 $[M+H]^+$.

(8a*S*,2′*S*,3′*R*,5′*R*)-(3-Methyl-5-phenylsulfanyl)-2-(3-thioxo-1,2,3,5,6,8a-hexahydro-indolizine-8-carbonyl)cyclohexanone (24): This compound (29.7 mg, 57%, colorless syrup) was obtained from **23** (50.0 mg, 0.130 mmol) by using a procedure similar to that for **21**. $[\alpha]_D^{26}=-132$ ($c=$ 0.37, $CHCl_3$); IR (ATR): $\tilde{\nu}=2928$, 1708, 1666, 1488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.45$–7.40 (m, 2H), 7.36–7.29 (m, 3H), 6.90 (d, $J=$ 5.9 Hz, 1H), 5.08 (dd, $J=13.0$, 6.1 Hz, 1H), 4.82–4.72 (m, 1H), 3.81 (quin., $J=4.5$ Hz, 1H), 3.70 (d, $J=9.5$ Hz, 1H), 3.15–2.86 (m, 4H), 2.78–2.65 (m, 2H), 2.60–2.39 (m, 3H), 2.24–2.14 (m, 1H), 1.91 (ddd, $J=14.4$, 10.5, 3.9 Hz, 1H), 1.72 (dq, $J=12.9$, 9.9 Hz, 1H), 0.97 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.2$, 200.4, 195.9, 141.0, 137.8, 133.3, 133.0, 129.2, 128.0, 64.3, 62.2, 46.0, 44.5, 44.3, 40.1, 36.4, 31.1, 27.6, 25.1, 20.5 ppm; MS (ESI+): *m/z*: 400 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{22}H_{26}NO_2S_2$: 400.1405; found: 400.1406 $[M+H]^+$.

9-*epi*-*ent*-Grandisine D trifluoroacetic acid salt (9-*epi*-*ent*-5·TFA) (25·TFA): This compound (15.8 mg, 56%, colorless oil) was obtained from **24** (30.0 mg, 0.0751 mmol) by using a procedure similar to that for **5**. $[\alpha]_D^{26}=-9.5$ ($c=0.11$ in MeOH); IR (ATR): $\tilde{\nu}=2918$, 1674, 1178, 1129 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=10.20$ (br s, 1H), 7.31 (apparent t, $J=4.0$ Hz, 1H), 7.19–7.10 (m, 1H), 5.93 (dd, $J=10.0$, 2.1 Hz, 1H), 4.48–4.37 (m, 1H), 4.37 (d, $J=11.7$ Hz, 1H), 3.59–3.46 (m, 1H), 3.39–3.26 (m, 2H), 3.20–3.08 (m, 1H), 2.66–2.56 (m, 2H), 2.54–2.31 (m, 3H), 2.29–2.14 (m, 1H), 2.10–1.95 (m, 2H), 1.84–1.69 (m, 1H), 0.86 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=198.4$, 197.0, 151.9, 138.9, 137.3, 128.4, 59.1, 58.1, 52.7, 43.0, 32.7, 32.3, 27.9, 22.4, 20.4, 19.1 ppm; MS (ESI+): *m/z*: 260 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{22}NO_2$: 260.1651; found: 260.1655 $[M+H]^+$.

9-*epi*-*ent*-Grandisine B (26): This compound (1.4 mg, 40%, pale-yellow oil) was obtained from **25**·TFA (5.0 mg, 0.0134 mmol) by using a procedure similar to that for **2**. $[\alpha]_D^{26}=+96.6$ ($c=0.13$ in CH_2Cl_2); IR (ATR): $\tilde{\nu}=2953$, 1728, 1577 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=6.43$ (t, $J=$ 3.6 Hz, 1H), 4.66–4.63 (m, 1H), 3.88–3.81 (m, 1H), 3.61 (d, $J=3.0$ Hz, 1H), 2.98–2.89 (m, 2H), 2.84–2.78 (m, 1H), 2.77–2.70 (m, 1H), 2.48–2.29 (m, 3H), 2.14–2.07 (m, 2H), 2.04–1.98 (m, 1H), 1.97–1.91 (m, 1H), 1.90–1.77 (m, 2H), 1.44–1.35 (m, 1H), 1.29 (ddd, $J=12.6$, 4.2, 1.2 Hz, 1H), 1.06 ppm (d, $J=7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=209.1$, 170.5, 137.5, 129.8, 58.7, 56.3, 55.8, 53.0, 44.8, 39.5, 32.9, 29.7, 29.3, 24.9, 22.3, 21.3 ppm; MS (ESI+): *m/z*: 259 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{23}N_2O$: 259.1810; found: 259.1804 $[M+H]^+$.

(6a*R*,9*S*,11*S*,12a*S*,12b*S*)-9-Amino-11-methyl-1,2,6,6a,8,9,10,11,12a,12b-decahydro-5*H*-chromeno[2,3*g*]indolizine-3,12-dione (27): 28% NH_3 (5 mL) was slowly added to a solution of **9** (130 mg, 4.76 mmol) in MeOH (5 mL) at 4°C. The reaction mixture was stirred for 4 h at room temperature and concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH/28% NH_3 100:10:1) to give **27** as a colorless syrup (97.9 mg, 71%). $[\alpha]_D^{24}=+160$ ($c=0.15$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=3360$, 2925, 1670, 1655, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=4.61$ (q, $J=3.0$ Hz, 1H), 4.09 (ddd, $J=13.5$, 5.8, 1.2 Hz, 1H), 3.59 (ddd, $J=10.8$, 7.5, 6.0 Hz, 1H), 3.35–3.24 (m, 1H), 3.07 (td, $J=13.2$, 2.9 Hz, 1H), 2.90–2.80 (m, 1H), 2.52 (ddd, $J=17.9$, 5.5, 1.2 Hz, 1H), 2.46–2.29 (m, 2H), 2.20–2.02 (m, 5H), 1.76–1.63 (m, 2H), 1.59–1.43 (m, 1H), 1.12 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=191.1$, 173.9, 169.7, 115.8, 74.9, 53.6, 51.8, 42.9, 39.9, 38.6, 34.5, 29.8, 27.9, 25.5, 22.4, 21.8 ppm; MS (ESI+): *m/z*: 291 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{23}N_2O_3$: 291.1709; found: 291.1710 $[M+H]^+$.

(6a*R*,9*S*,11*S*,12a*S*,12b*S*)-(9-Amino-11-methyl-1,2,6,6a,8,9,10,11,12a,12b-decahydro-5*H*-chromeno[2,3*g*]indolizine-3,12-dione-9-yl)carbamic acid *tert*-butyl ester (28): A solution of **27** (85.0 mg, 0.293 mmol) and Boc_2O (83.1 mg, 0.381 mmol) in CH_3CN (3 mL) was stirred at room temperature for 30 min and then concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 20:1) to give the Boc derivative **28** as colorless crystals (113 mg, 99%). M.p. 213–215°C (hexane/AcOEt); $[\alpha]_D^{24}=+92.2$ ($c=0.50$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=3271$, 2965, 1706, 1667, 1606, 1526 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=4.61$ (d, $J=2.8$ Hz, 1H), 4.51 (br s, 1H), 4.09 (dd, $J=13.6$, 4.8 Hz, 1H), 4.01 (br s, 1H), 3.58 (dt, $J=12.7$, 5.5 Hz, 1H), 3.05 (td, $J=18.7$, 6.6 Hz, 1H), 2.91–2.78 (m, 1H), 2.72 (dd, $J=17.8$, 4.2 Hz, 1H), 2.47–2.32 (m, 7H), 1.81–1.65 (m, 4H), 1.46 (s, 9H), 1.16 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=191.0$, 173.9, 169.1, 155.1, 115.7, 79.8, 75.1, 53.5, 51.7, 42.7, 36.0, 35.7, 34.5, 29.8, 28.4, 27.8, 25.0, 22.3, 21.5 ppm; MS (ESI+): *m/z*: 391 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{21}H_{31}N_2O_5$: 391.2233; found: 391.2233 $[M+H]^+$.

(6a*R*,9*S*,11*S*,12a*S*,12b*S*)-(9-Amino-11-methyl-3-thioxo-1,2,3,5,6,6a,8,9,10,11,12a,12b-dodecahydro-12*H*-chromeno-[2,3*g*]indolizine-12-one-9-yl)carbamic acid *tert*-butyl ester (29): A solution of Boc derivative 28 (50.0 mg, 0.128 mmol) with Lawesson's reagent (28.5 mg, 0.0705 mmol) in toluene (1.3 mL) was stirred at 60°C for 15 min and then concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/AcOEt 1:1) to give thioamide **29** as a colorless crystals (51.6 mg, 99%). M.p. 209–210°C (hexane/AcOEt); $[\alpha]_D^{23}=+97.6$ ($c=0.30$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=3329$, 2931, 1691, 1650, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=4.88$ (ddd, $J=13.6$, 5.7, 1.3 Hz, 1H), 4.65–4.61 (m, 1H), 4.50 (br s, 1H), 4.02 (br s, 1H), 3.88 (dt, $J=13.1$, 5.6 Hz, 1H), 3.28 (br t, $J=13.0$ Hz, 1H), 3.15–2.67 (m, 4H), 2.29–2.05 (m, 5H), 1.91–1.78 (m, 1H), 1.75–1.61 (m, 3H), 1.46 (s, 9H), 1.16 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=200.9$, 190.1, 169.3, 155.1, 115.9, 79.8, 74.3, 60.9, 51.6, 43.3, 42.7, 39.6, 35.9, 35.7, 28.4, 27.7, 25.1, 23.9, 21.4 ppm; MS (ESI+): *m/z*: 407 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{21}H_{31}N_2O_4S$: 407.2005; found: 407.1995 $[M+H]^+$.

(6a*R*,9*S*,11*S*,12a*S*,12b*S*)-(9-Amino-11-methyl-1,2,3,5,6,6a,8,9,10,11,12a,12b-decahydro-12*H*-chromeno[2,3*g*]indolizine-12-one-9-yl)carbamic acid *tert*-butyl ester (30): Raney 2800 Nickel (1 g wet weight, suspended in THF; before use, Raney 2800 Nickel was washed extensively with several portions of deionized water (~25 mL total for 1 g wet weight of nickel) and then this process was repeated with THF) was added to a solution of thioamide **29** (40.0 mg, 0.0984) in THF (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min, and then filtered through a pad of Celite, which was washed with CH_2Cl_2/MeOH 5:1. The combined filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH/28% NH_3 200:10:1) to give thioamide **30** as a colorless oil (29.6 mg, 80%). $[\alpha]_D^{24}=+103$ ($c=0.30$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=3330$, 2931, 2801, 1691, 1649, 1602, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=4.51$ (q, $J=2.8$ Hz, 1H), 3.99 (br s, 1H), 3.08 (t, $J=8.0$ Hz, 1H), 2.98 (ddd, $J=11.3$, 5.0, 2.0 Hz, 1H), 2.89–2.75 (m, 1H), 2.67 (dd, $J=17.9$, 4.5 Hz, 1H), 2.41 (dt, $J=16.7$, 6.1 Hz, 1H), 2.23–2.00 (m, 5H), 1.97–1.59 (m, 8H), 1.46 (s, 9H), 1.15 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=192.3$, 168.2, 155.1, 115.5, 79.6, 75.3, 59.6, 53.7, 52.0, 47.1, 42.8, 36.1, 35.7, 29.5, 28.6, 28.4, 25.0, 21.5, 20.5 ppm; MS (ESI+): *m/z*: 377 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{21}H_{33}N_2O_4$: 377.2440; found: 377.2448 $[M+H]^+$.

Grandisine F (4): TFA (0.3 mL) was slowly added to a solution of **30** (18.0 mg, 0.0478 mmol) in CH_2Cl_2 (0.5 mL) at 4°C. The reaction mixture was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH/28% NH_3 50:10:1) to give **4** as a colorless oil (8.5 mg, 64%). $[\alpha]_D^{23}=+140$ ($c=0.09$ in MeOH); IR (ATR): $\tilde{\nu}=3590$, 2964, 2765, 1607, 1563 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2): $\delta=4.48$ (q, $J=3.0$ Hz, 1H), 3.27–3.20 (m, 1H), 3.03 (t, $J=9.0$ Hz, 1H), 2.94 (ddd, $J=11.4$, 5.4, 1.8 Hz, 1H), 2.80–2.74 (m, 1H), 2.42 (dd, $J=18.0$, 5.4 Hz, 1H), 2.38 (dd, $J=11.4$, 3.0 Hz, 1H), 2.13–2.00 (m, 5H), 1.87 (dddd, $J=15.0$, 12.6, 4.8, 2.4 Hz, 1H), 1.76–1.56 (m, 5H), 1.46 (ddd, $J=12.6$, 11.4, 6.0 Hz, 1H), 1.08 ppm (d, $J=7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta=192.5$, 169.2, 115.6, 75.5, 59.9, 54.0, 52.2, 47.4, 43.3, 40.3, 38.9, 29.9, 29.0, 25.9, 21.9, 20.9 ppm; MS (ESI+): *m/z*: 277 $[M+H]^+$; HRMS (ESI+): *m/z*: calcd for $C_{16}H_{25}N_2O_2$: 277.1916; found: 277.1915 $[M+H]^+$; the optical purity of **4** was measured by chiral HPLC analysis (DAICEL CHIRALPAK IA, 4.6×250 mm, measurement of UV 260 nm absorbance, hexane/EtOH/TEA 60:140:1, 0.7 mL min^{-1}, $t_4=6.14$, $t_{ent\text{-}4}=8.13$ min).

Acknowledgements

We are grateful to Dr. T. Ishizaki of Kyorin Pharmaceutical Co., Ltd. for extensive support and Dr. Y. Fukuda of Kyorin Pharmaceutical Co., Ltd., for his encouragement and support of this project. We thank H. Furuta (Kyorin Pharmaceutical Co., Ltd.) for mass spectorometry and IR spectra, Dr. T. Nakane (Showa Pharmaceutical University) for 600 MHz NMR spectra, and Prof. I. Azumaya and Dr. H. Masu (Tokushima Bunri University, Kagawa) for measuring X-ray crystallography. We give thanks to Prof. A. R. Carroll for his generous gift of the natural sample and the ^1H and ^{13}C NMR spectra of grandisine F (**4**).

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Received: July 3, 2009
Published online: October 20, 2009

