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A Biomimetic Transformation of Serratinine into Serratezomine A through a Modified Polonovski Reaction

Hiroshi Morita and Jun'ichi Kobayashi*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

jkobay@pharm.hokudai.ac.jp

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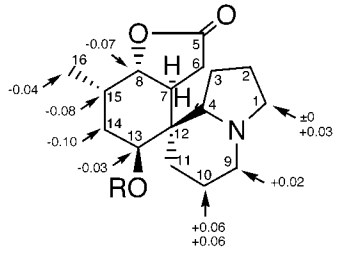
Abstract: Application of a modified Polonovski reaction for serratinine (**1**) resulted in generation of serratezomine A (**2**) with a novel seco-serratinine-type skeleton recently isolated from the club moss *Lycopodium serratum* var. *serratum*. This biomimetic transformation supports a biogenetic pathway proposed for serratezomine A (**2**). The absolute stereochemistry of serratezomine A (**2**) was established by an induced exciton chirality and modified Mosher methods.

Lycopodium alkaloids[1] such as serratinine (**1**) and lycodoline, possessing a common formula of $C_{16}N$, together with lucidines A and B with that of $C_{30}N_3$, are a class of natural products with unique ring systems that have attracted great interest from biogenetic,[1,2] synthetic,[1,3] and biological[4] points of view. In our search for biogenetic intermediates of *Lycopodium* alkaloids,[5,6] we have isolated serratezomines A (**2**) and B (**3**), new alkaloids with seco-serratinine-type and serratinine-type skeletons, respectively, from the club moss *Lycopodium serratum* var. *serratum*[5] and proposed a biogenetic path for serratezomine A (**2**) generated from serratinine (**1**) through Polonovski-type fragmentation[7] as shown in Scheme 1. Although the relative stereochemistry of serratezomine A (**2**) has been elucidated by 2D NMR data and the floating chirality method,[8] the absolute stereochemistry remains unsolved. Recently, the absolute configuration at C-8 of **2** was elucidated on the basis of an induced exciton chirality method,[9] a modified Mosher method,[10] and a biomimetic transformation of **1** into **2**. This paper describes the determination of the absolute stereochemistry of **2** and a biomimetic transformation of **1** into **2** through a modified Polonovski reaction.

Results and Discussion

Absolute Stereochemistry of Serratezomine A (2).[11] To determine the absolute configuration at C-8, **2** was treated with 3-cyanocarbonyl-3′-methoxycarbonyl-2,2′-binaphthalene to yield the 8-*O*-binaphthyl ester (**4**) of **2**, to which an induced exciton chirality method[9] was applied. In the CD spectrum of **4**, a split CD curve having a negative exciton chirality at 256 nm and a positive one at 234 nm was observed (Figure 1). The calculated screw sense of the 2-naphthyl group in a conformer (**4a**)[12] energetically more stable than the other conformer (**4b**) was coincident with that expected from its exciton chirality (Figure 2). Thus, the configuration at C-8 of **2** was assigned as *S*. This assignment was also confirmed by application of a modified Mosher method for compound **5** derived from serratezomine A (**2**) (see below).[13]

A Biomimetic Transformation of Serratinine (1) into Serratezomine A (2). To substantiate the proposal as shown in Scheme 1, a modified Polonovski reaction[8] was applied to serratinine (**1**) as follows (Scheme 2). Sequential treatment of **1** with *m*-chloroperbenzoic acid (*m*-CPBA), trifluoroacetic anhydride (TFAA),[14,15] and sodium cyanotrihydroborate ($NaBH_3CN$) gave two compounds, **2** and **5** (Scheme 2). In this one-pot reaction, compound **2**, which was identified as serratezomine A (**2**) by comparison of spectral data, was predominant at lower temperatures (−50 and −20 °C), while compound **5**,



5a R=(*S*)-MTPA
5b R=(*R*)-MTPA

Δδ values [Δδ (in ppm) = δ_S - δ_R] obtained for (*S*)- and (*R*)-MTPA esters (**5a** and **5b**, respectively).

* To whom correspondence should be addressed. Phone: (011)706-4985. Fax: (011)706-4989.

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(11) The absolute configuration at C-8 of **2** was not defined by using modified Mosher method, since the hydroxyl group at C-8 took an axial orientation and $\Delta\delta_S - \Delta\delta_R$ values obtained from the (*S*)- and (*R*)-2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) esters at C-8 of **2** were all negative.

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(13) To confirm the absolute configuration at C-13, compound **5** was converted into its (*S*)- and (*R*)-MTPA esters (**5a** and **5b**, respectively) at C-13. Δδ values ($\delta_S - \delta_R$) as shown below suggested that C-13 was of the *S*-configuration.

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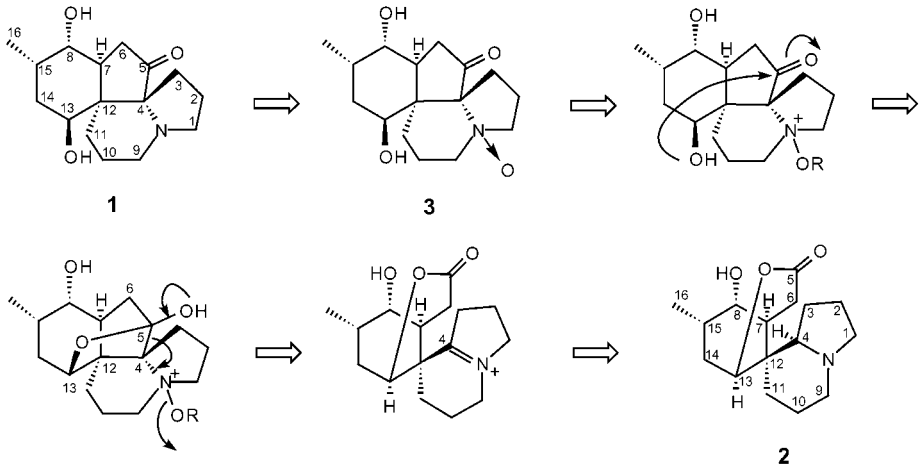
SCHEME 1



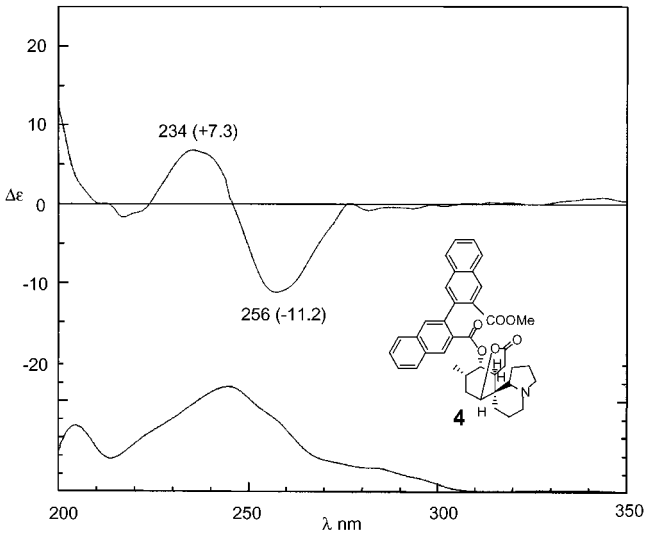


FIGURE 1. CD and UV spectra of 8-*O*-binaphthyl ester (**4**) of serratezomine A (**2**).

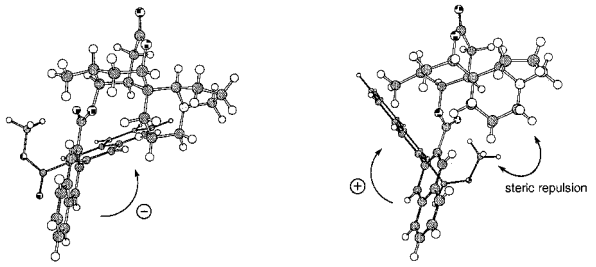


FIGURE 2. Two representative stable conformers (**4a** and **4b**) of the 8-*O*-binaphthyl ester (**4**) of serratezomine A (**2**) analyzed by Monte Carlo simulation followed by minimization and clustering analysis.

which was also obtained by treatment of **2** with *p*-TsOH, increased with increasing temperature (0 and 20 °C) (Table 1). The structure of **5** was elucidated as follows. Compound **5** [*m*/*z* 280.1926, $(M + H)^+$, Δ +1.3 mmu] showed the same molecular formula, $C_{16}H_{25}NO_3$, as that of serratezomine A (**2**). IR absorptions implied the presence of hydroxyl (3370 cm^{-1}) and γ-lactonic carbonyl (1780 cm^{-1}) functionalities. The structure of **5** having a γ-lactone ring (C-5 ∼ C-8 and O-8) was elucidated by analyses of 2D NMR data including $^1H-^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD. The relative stereochemistry of **5** deduced from NOESY correlations and ^3J proton couplings (H-7/H-8, 12 Hz; H-13/Hb-14, 13 Hz) was the same as that of serratezomine A (**2**), as shown in a computer-generated three-dimensional drawing (Figure 3).

A possible mechanism of the one-pot reaction (Scheme 2) is proposed in Scheme 3. Trifluoroacetylation of the *N*-oxide (**3**) of serratinine (**1**) could be followed by attack of the hydroxy group at C-13 to the ketone at C-5 to yield its hemiketal, which was accompanied by cleavage of the C-4−C-5 bond to form a lactone ring (**2**) between C-5 and C-13. Formation of another lactone ring (**5**) might occur through migration of the ester linkage.[16] Compounds **2** and **5** were obtained in CH_2Cl_2, $CHCl_3$, or CH_3CN but not in THF and toluene (Table 1).[17] The increasing amount of **5** with elevating temperature after addition of TFAA (Table 1) indicated acid-catalyzed cleavage of the δ-lactone ring of serratezomine A (**2**) followed by formation of a γ-lactone ring with a hydroxy group at C-8 after conformational change of a cyclohexane ring (C-7 ∼ C-8 and C-12 ∼ C-15). The rigid conformation of serratinine (**1**) consisting of a fused tetracyclic ring system was expected to induce fragmentation through Polonovski reaction, since the bond C(4)−C(5) in the *N*-oxide (**3**) of **1** was synperiplanar to the N−O bond (Figure 4).[18] A molecular model[19] and the X-ray crystal structure[20] of **1** (Figure 5) indicated that in $NaBH_3CN$ reduction of an unstable iminium intermediate, hydride must enter from the α-face of the molecule due to its

(14) Polonovski reaction has been studied well using various conditions and reagents.[8] Among them, trifluoroacetic anhydride has been demonstrated to be the most efficient reagent for effecting the desired transformation.

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(16) The transformation of **2** into **5** may be involved in a more complex mechanism than direct translactonization, although it was not able to be clarified.

(17) The solvent effects observed in the present studies are almost the same as the results reported for other cases of Polonovski reaction.[7]

(18) For Polonovski reaction, the Cα-carbon bond to be broken must be both activated toward cleavage by an adjacent electron-donating center and be oriented antiperiplanar to the N−O bond. To our knowledge, cleavage of the bond that is oriented synperiplanar to the N−O bond is unprecedented.

SCHEME 2

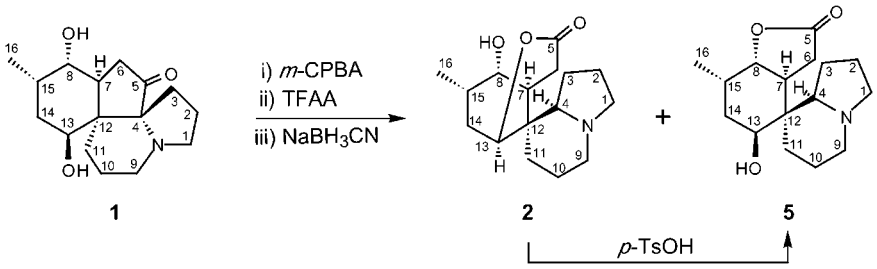


TABLE 1. Effetct of Solvents and Temperature on Generation of Compounds 2 (Serratezomine A) and 5 from Serratinine (1) through a Modified Polonovski Reaction

				yield (%)		recovered (%)
entry	solvent	temp[a]	time	**2**	**5**	**1**
1	CH_2Cl_2	−50	2 h	30	6	
2	CH_2Cl_2	−20	1 h	48	27	
3	CH_2Cl_2	0	1 h	17	38	
4	CH_2Cl_2	20	1 h		65	
5	$CHCl_3$	−20	1 h	27	13	
6	CH_3CN	−20	1 h	17	6	
7	THF	−20	1 h	0	0	66
8	toluene	−20	1 h	0	0	54

[a] Temperature was elevated after addition of TFAA.

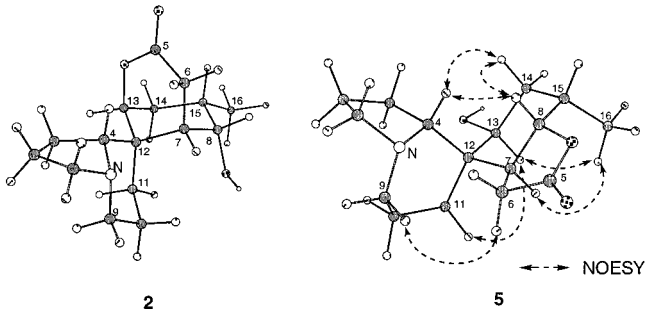


FIGURE 3. Energy-minimized three-dimensional structures of serratezomine A (**2**) and compound **5** and selected NOESY correlations for **5**.

steric hindrance, thereby generating an *R*-configuration at C-4. Compound **5** with an energetically more stable γ-lactone ring seems to be produced from **2** by acid catalysis cleavage of its unstable δ-lactone ring followed by recyclization with a hydroxyl group at C-8.

In the present study, the absolute stereochemistry of serratezomine A (**2**) was established by spectroscopic methods such as an induced exciton chirality and modified Mosher methods. Furthermore, the conversion of serratinine (**1**) into serratezomine A (**2**) through serratezomine B (**3**) was achieved by Polonovski-type fragmentation.[21] This one-pot chemical transformation of **1** into **2** through cleavage of the C-4−C-5 bond after formation of a hemiacetal ring and then a stereospecific reduction of an iminium intermediate might be regarded as a biomimetic reaction.

(19) Inspection of molecular models were obtained by MMFF calculations using MacroModel version 6.0 developed by C. Still, Columbia University: Halgren, T. *J. Am. Chem. Soc.* **1990**, *112*, 4710−4723.

(20) X-ray crystallographic data of **1** have already been cited in our previous paper.[5]

(21) Serratezomine A (**2**) was also obtained by treatment of serratezomine B (**3**) with TFAA and *p*-TsOH followed by $NaBH_3CN$.

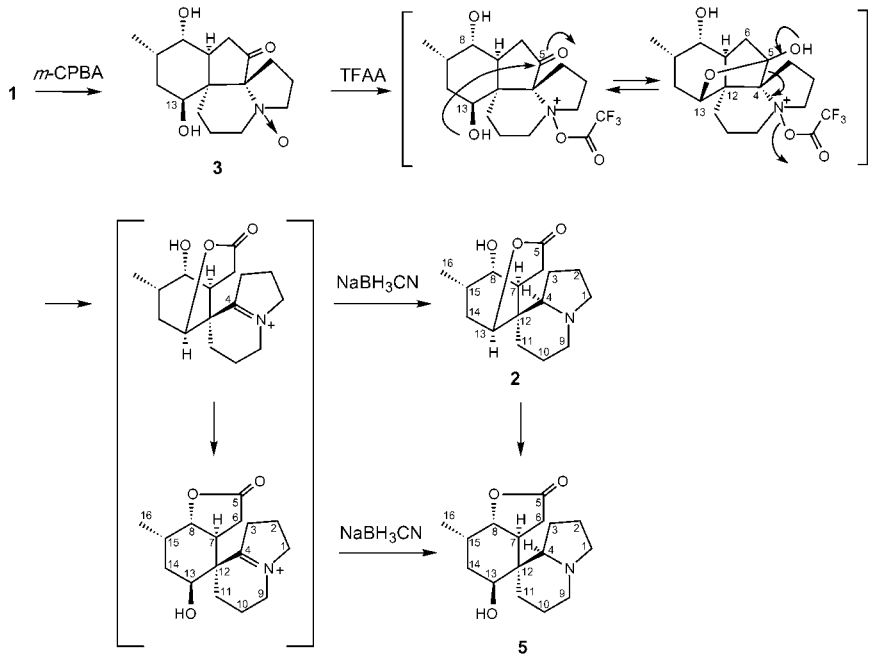
Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded on a 600 MHz spectrometer equipped with an X32 computer and a temperature control unit. 1D NMR spectra were measured at 300 K with 16K data points, which were multiplied by a Gaussian filter and zero filled to 32K data points before Fourier transformation. 2D NMR spectra were measured at 300 K, and NOESY and HOHAHA spectra in the phase-sensitive mode were recorded using the TPPI method. HOHAHA spectra were recorded by a spin-lock field preceded and followed by 2.5 ms trim pulses. NOESY spectra were measured with mixing times of 800 ms. Typically, 256 FIDs of 2K data points and 32 scans each were employed. Chemical shifts were measured using residual CD_3OD (δ_H 3.31 and δ_C 49.00) or $CDCl_3$ (δ_H 7.26 and δ_C 77.03) as an internal standard. Standard pulse sequences were employed for 2D NMR experiments. HMBC spectra were recorded using a 50 ms delay time for long-range C−H coupling with a *Z*-axis PFG. FABMS was measured by using glycerol as a matrix.

Binaphthylation of Serratezomine A (2). To a solution of serratezomine A (**2**, 0.5 mg, 0.0018 mmol) and 3-cyanocarbonyl-3′-methoxycarbonyl-2,2′-binaphthalene (3 mg, 0.0082 mmol) in acetonitrile (100 μL) was added 4-(dimethylamino)pyridine (2 mg, 0.016 mmol), and the mixture was stirred at 50 °C for 12 h. After removal of the solvent in vacuo, C_{18} HPLC (50% CH_3CN/0.1% TFA) of the residue afforded compound **4**, the binaphthyl ester (**4**) of **2** (0.2 mg, 18%): FABMS *m*/*z* 618 $(M + H)^+$; HRFABMS *m*/*z* 618.2831 (M + H; calcd for $C_{39}H_{40}NO_6$, 618.2856); UV (MeOH) λ_{max} 244 (ϵ 76 200) and 340 (ϵ 2300); CD (MeOH) $\Delta\epsilon_{256}$ −11.2 and $\Delta\epsilon_{234}$ +7.3; ^1H NMR ($CDCl_3$) δ 0.87 (3H, d, 7.3, H-16), 3.47 (3H, s, OMe), 4.01 (1H, m, H-13), 5.02 (1H, m, H-8), 7.57−8.30 (12H, m, binaphthyl protons).

A Modified Polonovski Reaction for Serratinine (1). *m*-Chloroperbenzoic acid (8 mg, 0.047 mmol) in 0.1 mL of CH_2Cl_2 was added at 0 °C to a stirred solution of serratinine (**1**, 10 mg, 0.036 mmol) in 0.1 mL of CH_2Cl_2. After 1 h, the reaction mixture was concentrated and then trifluoroacetic anhydride (0.02 mL, 0.14 mmol) was added to a stirred solution of the residue in dry CH_2Cl_2 (0.2 mL) under N_2 at −20 °C. After 1 h, excess solvent and TFAA were immediately distilled off in vacuo at 0 °C. The residue was dissolved in MeOH (0.1 mL), and excess $NaBH_3CN$ was added at 0 °C. After 15 min, the reaction mixture was poured into H_2O (10 mL) and extracted with $CHCl_3$. C_{18} HPLC (15% CH_3CN/0.1% TFA) of the residue afforded compounds **2** (4.8 mg, 48%) and **5** (2.7 mg, 27%). **2**: $[\alpha]_D$ +12° (c 0.6, MeOH), spectral data and $[\alpha]_D$ value were identical with those of serratezomine A (**2**), $[\alpha]_D$ +13° (*c* 0.5, MeOH). **5**: colorless solid; $[\alpha]_D$ +15° (*c* 0.5, MeOH); FABMS *m*/*z* 280 $(M + H)^+$; HRFABMS *m*/*z* 280.1926 (M + H; calcd for $C_{16}H_{26}NO_3$, 280.1939); IR (neat) ν_{max} 3374, 3148, 2928, 1780, 1680, and 1195 cm^{-1}; ^1H NMR (CD_3OD) δ 3.16 (1H, m, H-1a), 3.41 (1H, ddd, 10.1, 10.1, 10.1, H-1b), 2.15 (2H, m, H-2), 2.22 (1H, m, H-3a), 2.38 (1H, m, H-3b), 4.02 (1H, dd, 6.8, 12.3, H-4), 2.53 (1H, m, H-6a), 2.61 (1H, dd, 14.1, 16.5, H-6b), 2.35 (1H, m, H-7), 4.44 (1H, dd, 5.4, 12.4, H-8), 2.96 (1H, dt, 3.6, 13.3, H-9a), 3.14 (1H, m, H-9b), 1.74 (1H, brd, 14.5, H-10a), 2.52 (1H, dd, 7.4, 16.5, H-10b), 1.65 (1H, brd, 13.7, H-11a), 1.88 (1H, dd, 5.0, 14.1, H-11b), 3.95 (1H, dd, 4.8, 11.5, H-13), 1.82 (1H, ddd, 1.9, 4.8, 14.6, H-14a), 2.03 (1H, ddd, 5.3, 11.6, 16.7, H-14b), 2.46 (1H, m, H-15), 1.04 (3H, d, 7.2, H-16); ^{13}C NMR (CD_3OD) δ 54.0 (C-1), 19.7 (C-2), 24.0 (C-3), 63.9

SCHEME 3



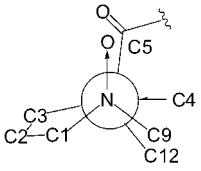


FIGURE 4. Rotation model for the N−C4 bond of serratezomine B (**3**).

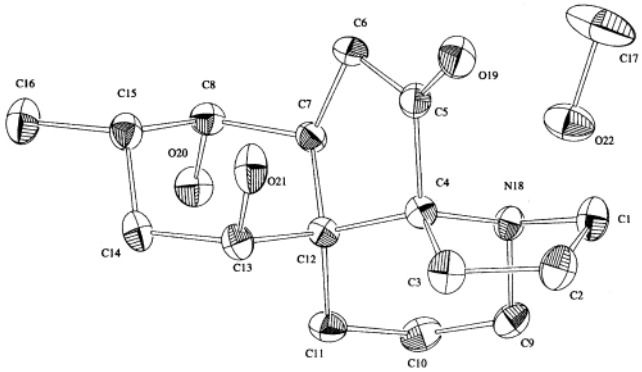


FIGURE 5. Molecular structure of serratinine (**1**) obtained by X-ray analysis (ORTEP drawing; ellipsoids are drawn at the 30% probability level). One molecule of MeOH is contained in the crystal, and hydrogen atoms are omitted for clarity.

(C-4), 177.5 (C-5), 36.8 (C-6), 43.6 (C-7), 80.8 (C-8), 47.8 (C-9), 21.4 (C-10), 30.4 (C-11), 42.2 (C-12), 76.0 (C-13), 32.3 (C-14), 31.3 (C-15), 11.6 (C-16).

***(S)*-MTPA Ester (5a) of Compound 5.** To a solution of **5** (0.2 mg) in methylene chloide (50 μL) were added (*R*)-(−)-MTPACl (2 μL) and *N*,*N*-(dimethylamino)pyridine (50 μg). The mixture was allowed to stand at 20 °C for 12 h. After addition of *N*,*N*-(dimethylamino)-1,3-propandiamine (2 μL) and evaporation of the solvent, the residue was passed through a silica gel column (50:1 $CHCl_3$−MeOH) to afford the (*S*)-MTPA ester (**5a**, 0.2 mg) of **5**. **5a**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.32 and 3.60 (m, H-1), 2.20 (m, H-3), 4.56 (m, H-4), 2.64 and 3.38 (m, H-6), 2.12 (m, H-7), 4.71 (dd, 5.6, 12.2, H-8), 2.96 (m, H-9), 1.62 and 1.75 (m, H-10), 4.91 (dd, 4.2, 10.2, H-13), 1.86 (m, H-14), 2.47 (m, H-15), 1.06 (d, 6.8, H-16); FABMS *m*/*z* 496 $(M + H)^+$; HRFABMS *m*/*z* 496.2284 (M + H; calcd for $C_{26}H_{33}NO_5F_3$, 496.2311).

***(R)*-MTPA Ester (5b) of Compound 5.** Compound **5** (0.2 mg) was treated with (*S*)-(+)-MTPACl (2 μL) by the same procedure described above to afford the (*R*)-MTPA ester (**5b**, 0.2 mg) of **5**. **5b**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.32 and 3.57 (m, H-1), 2.20 (m, H-3), 4.56 (m, H-4), 2.64 and 3.38 (m, H-6), 2.13 (m, H-7), 4.78 (m, H-8), 2.94 (m, H-9), 1.56 and 1.69 (m, H-10), 4.94 (m, H-13), 1.96 (m, H-14), 2.55 (m, H-15), 1.10 (d, 6.8, H-16); FABMS *m*/*z* 496 $(M + H)^+$; HRFABMS *m*/*z* 496.2323 (M + H; calcd for $C_{26}H_{33}NO_5F_3$, 496.2311).

Chemical Conversion of Serratezomine A (2) into Compound 5. A solution of **2** (1 mg) and *p*-toluenesulfonic acid (0.1 mg) in 1:1 $CHCl_3$/MeOH (0.1 mL) was stirred at 50 °C for 3 h and then concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and washed with saturated aqueous NaCl and 1% NH_4OH and then dried over anhydrous Na_2SO_4. Removal of the solvent afforded the residue, which was subjected to a silica gel column (9:1 $CHCl_3$/MeOH) to give compound **5** (0.4 mg).

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Supporting Information Available: 1D and 2D NMR spectra of **2** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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