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Total Synthesis of an Anti-*Helicobacter pylori* Agent, Actinopyrone A

Seijiro Hosokawa,* Kazuya Yokota, Keisuke Imamura, Yasuaki Suzuki, Masataka Kawarasaki, and Kuniaki Tatsuta*[a]

Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

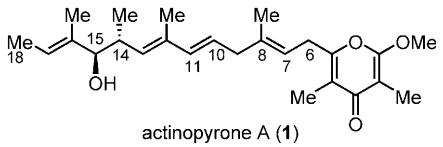
Abstract: Actinopyrone A, an anti-*Helicobacter pylori* agent, was synthesized in nine steps from a silyl dienol ether. A vinylogous *anti*-aldol was stereoselectively synthesized by our developed remote stereoinduction methodology; coupling of this with a sulfone and a phosphonate species led to the construction of a vinylpyrone compound. This was submitted to reductive de-conjugation to give actinopyrone A. The absolute stereochemistry of actinopyrone A was determined to have the configuration 14*R*,15*R*.

Keywords: actinopyrone A · aldol reaction · remote stereoinduction · structural determination · total synthesis

Introduction

Actinopyrone A (**1**) was isolated from a culture broth of *Streptomyces pactum* S12538 as a relatively unstable compound that possesses coronary vasodilating activity and antimicrobial activity.[1] It was later found to exhibit potent activity against *Helicobacter pylori*.[2]

In addition to multi-bioactivity, low toxicity makes actinopyrone A (**1**) a potentially attractive drug candidate for chemotherapy. However, the instability of **1** makes it difficult to promote further research, and its absolute configuration has not yet been disclosed. Therefore, establishment of the synthesis of **1** is important. Herein we present the first total synthesis of actinopyrone A,[3] which is applicable toward a variety of derivatives.[4]



actinopyrone A (**1**)

[a] Prof. Dr. S. Hosokawa, K. Yokota, K. Imamura, Y. Suzuki, M. Kawarasaki, Prof. Dr. K. Tatsuta
Department of Applied Chemistry
Faculty of Science and Engineering
Waseda University, 3-4-1 Ohkubo, Shinjuku-ku
Tokyo 169-8555 (Japan)
Fax: (+81) 3-3200-3203
E-mail: seijiro@waseda.jp
tatsuta@waseda.jp

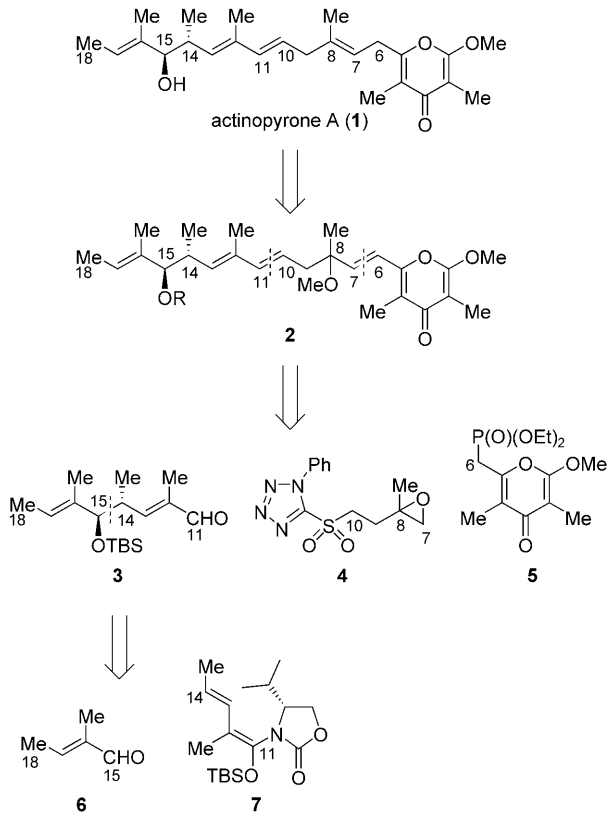
Results and Discussion

Our synthetic plan is shown in Scheme 1. To circumvent the instability of actinopyrone A (**1**), the conjugated pyrone **2** was set up as the precursor. Compound **2** can be subjected to reductive de-conjugation of the conjugated pyrone moiety in the final stage of the synthesis. The conjugated pyrone **2** can be synthesized by connection of compounds **3**–**5**. The chiral centers C14 and C15 of vinylogous *anti*-aldol **3** can be constructed by our developed methodology using the chiral vinylketene *N*,*O*-acetal **7**,[5] which was prepared from D-valine.

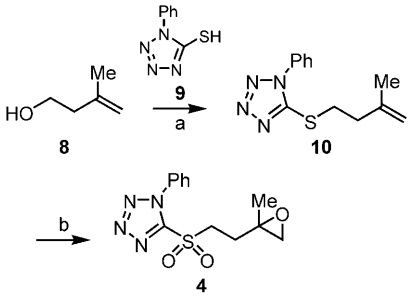
Compound **4** was synthesized from **8** in two steps (Scheme 2). The commercially available compound **8** was converted into tetrazole **10** under Mitsunobu conditions. Both the olefin and sulfide of **10** were oxidized to give epoxysulfone **4** by treatment with *m*CPBA in the presence of $NaHCO_3$.[6]

γ-Pyrone **5** was synthesized as shown in Scheme 3. Treatment of the known α-pyrone **11**[7] with calcium carbonate and dimethyl sulfate in acetone at 50 °C promoted 2-O-methylation to give γ-pyrone **12**[8] as a major product. The regioselectivity of the O-methylation was 2-O-methyl/4-O-methyl = 3:1, and γ-pyrone **12** was isolated in 54% yield. The regioselective chlorination of γ-pyrone **12** to obtain chloromethylpyrone **13** was performed with lithium hexamethyldisilazide and *N*-chlorosuccinimide. Chloromethylpyrone **13** was treated with triethyl phosphite at 140 °C to afford phosphonate **5**.[9]

The next stage was to construct vinylogous *anti*-aldol **3**. Although the vinylogous *anti*-aldol is the structure available



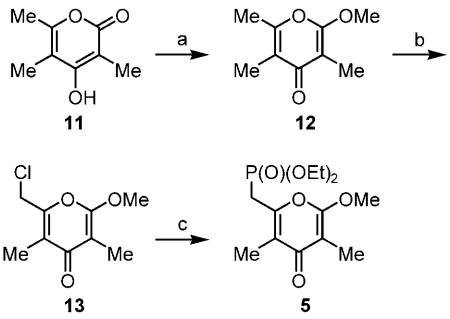
Scheme 1. Retrosynthetic analysis of actinopyrone A (**1**).



Scheme 2. Reagents and conditions: a) DEAD, PPh_3, THF, room temperature, 2 h, 92%; b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, room temperature, 34 days, 85%.

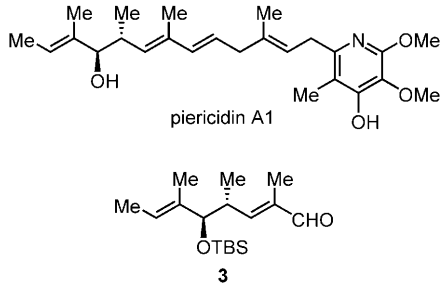
Abstract in Japanese:

強力な抗ピロリ菌活性をもつアクチノピロンAの全合成を達成し、絶対立体配置を決定した。アクチノピロンは断続的な共役系を有する不安定な化合物であるため、合成前駆体として安定なビニルピロン体を設定した。立体化学が不明な14位と15位の不斉炭素を含むC11～C18フラグメントは、我々が開発した遠隔不斉誘導法で一挙に構築した。合成容易な他のユニットを導入してビニルピロン中間体とした後、これに対してヨウ化サマリウムを使った還元的非共役化を行うことによってアリルピロン部を構築し、全合成を完了した。本合成は遠隔不斉誘導反応の基質となるシリルジエノールエーテルより9工程の立体選択的合成法である。本合成法により、アクチノピロンAの両エナンチオマーを合成し、天然物の絶対立体配置を(14*R*, 15*R*)と決定した。



Scheme 3. Reagents and conditions: a) $CaCO_3$, Me_2SO_4, acetone, 50°C, 3 days, 54%; b) LHMDS, NCS, THF, −78°C, 1 h, 67%; c) $P(OEt)_3$, 140°C, 6.5 h, 80%.

through current asymmetric synthesis, stereoselective synthesis of the arrangement requires a long sequence of steps to give the desired product, and the overall yield is low. Boger and co-workers examined some aldol methodologies to construct aldehyde **3** in the total synthesis of piericidin A1,[10] which possesses the same side chain as actinopyrone A (**1**). However, overall yields were 16–27% from propionate possessing chiral auxiliaries, and several steps were necessary to obtain aldehyde **3**.



Recently, we developed highly stereoselective vinylogous Mukaiyama aldol reactions using vinylketene *N*,*O*-acetals possessing the chiral oxazolidone,[5] and have applied these to the total synthesis of natural products. This methodology was used to construct **3**, the C11–C18 unit of **1**. Silyl dienolate **7**,[5c] prepared from 2-methyl-2-pentenoic acid and D-valine-derived oxazolidone in 2 steps, was coupled with tiglic aldehyde (**6**) in the presence of $TiCl_4$ to give the C14–C15 *anti* adduct **14** as a single isomer (Scheme 4). Protection of **14** as the TBS ether afforded crystalline **15**, the stereochemistry of which was determined by X-ray crystallography to be the 14*R*,15*R* isomer, as expected from our previous studies (Figure 1).[5,11] The chiral auxiliary of **15** was removed to give aldehyde **3** by treatment with DIBALH at −78°C.[5c] Thus, the vinylogous *anti*-aldol **3** was provided in three steps from dienol ether **7**. The remote asymmetric induction methodology is an effective and straightforward method to obtain vinylogous *anti*-aldol compounds.

The total synthesis of actinopyrone A (**1**) was accomplished as shown in Scheme 5 and Table 1. The aldehyde **3**

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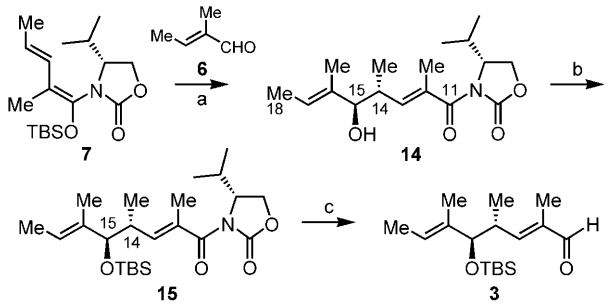


Scheme 4. Reagents and conditions: a) $TiCl_4$, CH_2Cl_2, −60 °C, 4 d, 82 %; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.5 h, 93 %; c) DIBALH, CH_2Cl_2, −78 °C, 2 h, 68 %.

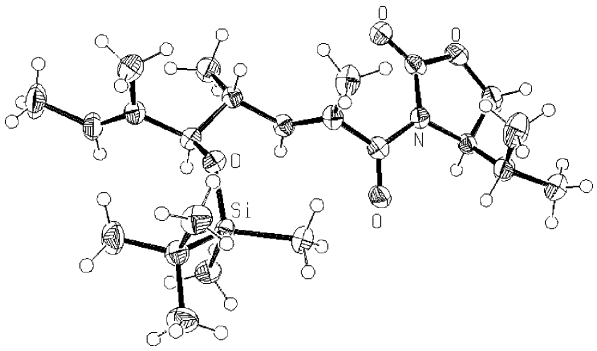
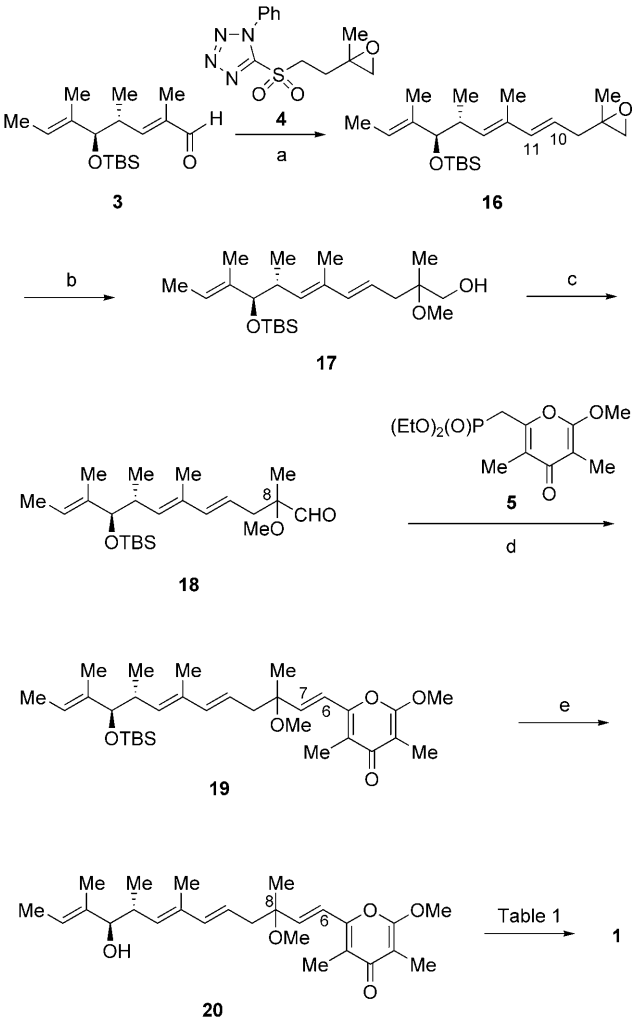


Figure 1. ORTEP drawing of silylether **15**.

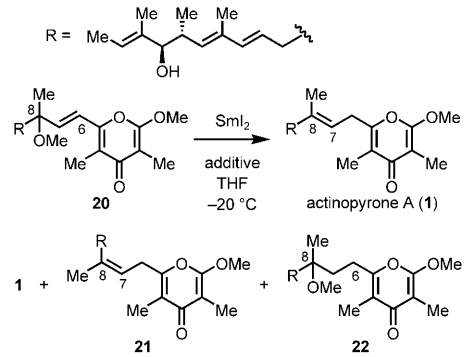
was converted into triene **16** (10,11 *E*/*Z* = 93:7) by Kocieński's method[6] using sulfone **4**. Epoxide **16** was transformed under acidic conditions to primary alcohol **17**, which was separated from the 10,11-*Z* isomer by silica gel column chromatography. Alcohol **17** was submitted to oxidation to afford aldehyde **18**. The pyrone moiety was introduced by Horner–Wadsworth–Emmons reaction of **18** with phosphonate **5** to afford the stable vinylpyrone **19** (**2**: R = TBS). De-O-silylation of **19** under acidic conditions proceeded in good yield to provide **20** (**2**: R = H). The final and key step was settled. Samarium(II)-mediated reductive de-conjugation was examined with vinylpyrone **20** (Table 1).[12]

Addition of hexamethylphosphorous triamide resulted in the production of multiple products, none of which were the target molecule **1** (Table 1, entry 1). Addition of methanol gave actinopyrone A (**1**) along with 7-hydro-8-methoxyactinopyrone A (**22**) (Table 1, entry 2). This result is explained in Scheme 6, which contains intermediate dianion **23**. Compound **1** was obtained by successive elimination of methoxide and protonation at C6 (route a), while **22** was produced by protonation of **23** at C7 followed by protonation of **25** at C6 (route b). Accordingly, the preferred production of **1** should suppress protonation of **23**, thus slowing route b. The best result was obtained by using 2-propanol, with which protonation proceeded slowly enough to complete elimination to give intermediate trienolate **24**, and **22** was not observed at all (Table 1, entry 3). Therefore, actinopyrone A (**1**) was afforded along with the 7,8-*Z* isomer at a ratio of

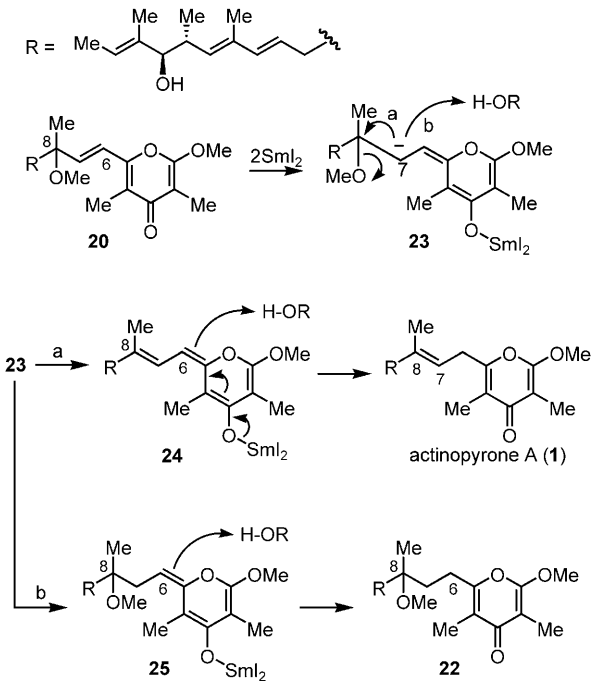


Scheme 5. Reagents and conditions: a) NaHMDS, DME, −60→0 °C, 18 h; b) CSA, MeOH, 0 °C, 1 h, 67 % (2 steps); c) SO_3·Py, DMSO, Et_3N, room temperature, 30 min, 94 %; d) LHMDS, THF, −78→0 °C, 5.5 h, 96 %; e) CSA, MeOH, room temperature, 18 h, 70 %.

Table 1. Reductive de-conjugation of **20** with SmI_2.

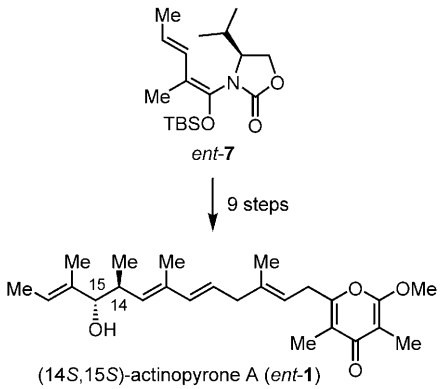


Entry	Additive	Ratio **1**:**21**:**22**
1	HMPA, MeOH	complex mixture
2	MeOH	38:12:50
3	*i*PrOH	88:12:0
4	*t*BuOH	76:16:8



Scheme 6. Production of actinopyrone A (**1**) and 7-hydro-8-methoxyactionpyrone (**22**).

88:12. These isomers were easily separated by silica gel column chromatography to isolate **1** in 70% yield. Synthetic **1** was identical in all respects to the natural product, including optical rotation (synthetic **1**: $[\alpha]_D^{25} = +31.3°$ ($c = 0.43$, CH_2Cl_2), natural **1**: $[\alpha]_D^{26} = +30.8°$ ($c = 0.42$, CH_2Cl_2)). Therefore, the absolute configuration of actinopyrone A (**1**) was determined to be 14*R*,15*R*. We also synthesized the enantiomer of actinopyrone A, showing the opposite optical rotation ($[\alpha]_D^{23} = -31.7°$ ($c = 0.43$, CH_2Cl_2)) by starting from the enantiomer of **7**[5d] derived from L-valine (Scheme 7).



Scheme 7. Synthesis of (14*S*,15*S*)-actinopyrone A (*ent*-**1**) from *ent*-**7**.

Conclusions

The first total synthesis and structural determination of actinopyrone A (**1**) were accomplished by the coupling of four components (compounds **4**, **5**, **6**, and **7**) and reductive deconjugation of the vinylpyrone **20**. The longest linear sequence comprised nine steps and proceeded in 15% overall yield from dienol ether **7**. The stable intermediate **19** made it easy to produce anti-*Helicobacter pylori* drugs. This route is highly convergent for the synthesis of a variety of actinopyrone A analogues to promote drug discovery.

Experimental Section

General methods

^{1}H NMR spectra were recorded at 400 MHz with a JEOL LMN-AL400 instrument. Coupling constants (J) are reported in Hz. ^{13}C NMR spectra were recorded at 100 MHz with a JEOL LMN-AL400 instrument. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Melting point (mp) determinations were performed by using a Yanako MP-S3 instrument. FTIR spectra were recorded with a JEOL JIR-WINSPEC 50 instrument. HRMS and MS data were obtained with a JEOL JMS-SX102A instrument. Optical rotations were measured with a JASCO DIP-370 instrument. X-ray crystallographic analysis was performed with a Rigaku RAXIS-RAPID apparatus. Analytical thin layer chromatography was performed on 0.25-mm E. Merck silica gel plates ($60F_{254}$).

Syntheses

10: A solution of diethyl azodicarboxylate (2.2 M) in toluene (590 μL, 1.30 mmol) was added to a mixture of 3-methyl-3-butene-1-ol (**8**, 131 μL, 1.30 mmol), 1-phenyl-1*H*-tetrazol-5-thiol (**9**, 178 mg, 1.00 mmol) and triphenylphosphine (341 mg, 1.30 mmol) in tetrahydrofuran (THF, 2.7 mL) at 0 °C under argon atmosphere. After stirring at room temperature for 2 h, the reaction mixture was concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to yield thioether **10** (226 mg, 917 μmol, 92%). R_f value: 0.28 (hexane/EtOAc = 6:1). IR (KBr) 3074, 2937, 1648, 1595, 1500, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.77$ (3H, s, Me-8), 2.54 (2H, t, $J = 13.0$ Hz, H-9), 3.54 (2H, t, $J = 13.0$ Hz, H-10), 4.78 (1H, m, H-7), 4.84 (1H, m, H-7′), 7.51–7.64 ppm (5H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 22.0$, 31.4, 36.8, 77.2, 112.4, 123.8, 129.8, 130.1, 133.7, 142.5, 154.3 ppm. HRFAB-MS (m/z): 247.1008 $[M+H]^+$; calcd for $C_{12}H_{15}N_4S_1$: 247.1017.

4: *m*-Chloroperbenzoic acid (*m*CPBA, 6.12 g, 35.5 mmol) in CH_2Cl_2 (75 mL) was added to a mixture of thioether **10** (2.52 g, 10.1 mmol) and sodium bicarbonate (3.04 g, 36.2 mmol) in CH_2Cl_2 (25 mL) at 0 °C under argon atmosphere. After 1 h, sodium bicarbonate (0.85 g, 10.1 mmol) and *m*CPBA (1.75 g, 10.1 mmol) in CH_2Cl_2 (20 mL) was added. The mixture was warmed to room temperature and stirred for 71 h. Dichloromethane (100 mL) was added to the mixture, which was subsequently washed with 1.0 M aqueous sodium thiosulfate (45 mL), 1.0 M aqueous sodium carbonate (45 mL), H_2O (40 mL), and brine (40 mL). The organic layer was concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give epoxide **4** (2.54 g, 8.63 mmol, 85%). R_f value: 0.24 (hexane/EtOAc = 2:1). Prisms recrystallized from isopropanol, mp: 88.3–88.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.40$ (3H, s, Me-8), 2.21 (1H, ddd, $J = 14.4$, 10.8, 5.4 Hz, H-9), 2.32 (1H, ddd, $J = 14.4$, 10.8, 5.6 Hz, H-9′), 2.66 (1H, d, $J = 4.0$ Hz, H-7), 2.71 (1H, d, $J = 4.0$ Hz, H-7′), 3.75 (1H, ddd, $J = 14.8$, 10.8, 5.4 Hz, H-10), 3.83 (1H, ddd, $J = 14.8$, 10.8, 5.6 Hz, H-10′), 7.56–7.64 (3H, m, Ph), 7.65–7.73 ppm (2H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 21.0$, 28.9, 52.1, 53.3, 54.8, 125.1, 129.8, 131.5, 133.0, 153.3 ppm. IR (KBr) $\tilde{\nu} = 2981$, 2927, 1494, 1348, 1324, 1155, 765 cm^{-1}. HRFAB-MS (m/z): 295.0863 $[M+H]^+$; calcd for $C_{12}H_{15}O_3N_4S_1$: 295.0865. Anal. calcd for $C_{12}H_{14}O_3N_4S_1$: C 48.97, H 4.79, N 19.04, found: C 48.92, H 4.78, N 18.91.

12: $CaCO_3$ (298 mg, 2.98 mmol) and dimethyl sulfate (940 mL, 9.93 mmol) were sequentially added to a solution of pyrone **11** (153 mg, 0.99 mmol) in acetone (3.0 mL) at room temperature, and the resulting mixture was stirred at 50 °C under argon atmosphere. After 3 days, the

reaction mixture was filtered, and the residue was washed with acetone. The filtrate was concentrated and separated by silica gel column chromatography ($CHCl_3$/acetone = 8:1) to afford γ-pyrone **12** (89.9 mg, 0.53 mmol, 54%) and α-pyrone (29.2 mg, 0.17 mmol, 18%). γ-pyrone **12** R_f value: 0.33 ($CHCl_3$/acetone = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.83 (3H, s, Me), 1.91 (3H, s, Me), 2.25 (3H, s, Me), 3.93 ppm (3H, s, OMe). IR (KBr) $\tilde{\nu}$ = 2956, 1673, 1594, 1417, 1176 cm^{-1}.

13: A solution of lithium bis(trimethylsilyl)amide (1.06 M) in THF (3.07 mL, 3.25 mmol) was added to a solution of 2-methoxy-γ-pyrone (**12**, 320 mg, 2.50 mmol) in THF (8.4 mL) at −78 °C under argon atmosphere. After 0.5 h, *N*-chlorosuccinimide (0.85 g, 10.1 mmol) in THF (20 mL) was added, and the resulting mixture was stirred for 1 h. The mixture was concentrated, then EtOAc (300 mL) and H_2O (10 mL) were added. The layers were separated, and the aqueous solution was extracted twice with EtOAc. The combined organic extracts were sequentially washed with saturated aqueous sodium bicarbonate (2 × 10 mL) and brine (10 mL). The organic extracts were concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford chloride **13** (338 mg, 1.67 mmol, 67%). R_f value: 0.19 (hexane/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.86 (3H, s, Me), 2.04 (3H, s, Me), 4.01 (3H, s, O*Me*), 4.45 ppm (2H, s, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 7.0, 9.8, 39.4, 55.6, 100.4, 121.4, 151.7, 162.2, 180.2 ppm. IR (KBr) $\tilde{\nu}$ = 3039, 1668, 1602, 1465, 1332 cm^{-1}. FAB-MS (*m*/*z*): 203, 205 $[M+H]^+$. HRFAB-MS (*m*/*z*): 203.0489 $[M+H]^+$; calcd for $C_9H_{12}O_3Cl_1$: 203.0475.

5: Chloride **13** (141 mg, 695 μmol) was dissolved in triethyl phosphite (2.1 mL, 12.2 mmol) under argon atmosphere, and stirred at 140 °C for 6.5 h. The mixture was concentrated to afford the residue, which was purified by silica gel column chromatography (PhMe/acetone = 3:2) to phosphate **5** (169 mg, 555 μmol, 80%). R_f value: 0.19 (PhMe/acetone = 1:1). Prisms recrystallized from *i*Pr$_2$O, mp: 70.0–70.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.32 (6H, t, *J* = 7.1 Hz), 1.85 (3H, s), 1.98 (3H, d, *J* = 3.7 Hz), 3.14 (2H, d, *J* = 22.0 Hz), 3.99 (3H, s), 4.08–4.17 ppm (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 6.9, 10.4 (d, *J* = 3 Hz), 16.5 (d, *J* = 6 Hz), 30.1 (d, *J* = 140 Hz), 55.7, 62.6 (d, *J* = 6 Hz), 99.8, 120.8 (d, *J* = 9 Hz), 149.4 (d, *J* = 12 Hz), 162.3, 180.4 ppm (d, *J* = 3 Hz). IR (KBr) $\tilde{\nu}$ = 2985, 2927, 1672, 1602, 1253, 1020, 977 cm^{-1}. HRFAB-MS (*m*/*z*): 305.1158 $[M+H]^+$; calcd for $C_{13}H_{22}O_6P_1$: 305.1154.

14: $TiCl_4$ (1.78 mL, 16.3 mmol) in CH_2Cl_2 (152 mL) was added to a mixture of oxazolidone **7** (5.26 g, 15.5 mmol) and *trans*-2-methyl-2-butenal (**6**, 2.24 mL, 23.2 mmol) in CH_2Cl_2 (50 mL) at −78 °C under argon atmosphere. The resulting mixture was stirred at −60 °C for 4 days. Pyridine (1.3 mL, 16.1 mmol) was added at 0 °C, and the resulting mixture was poured into saturated aqueous sodium bicarbonate (100 mL). The mixture was filtered through Celite, and the filtrate was separated. The aqueous solution was extracted with $CHCl_3$ (50 mL), and the combined organic extracts were washed with brine (30 mL). The organic extracts were concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to yield *anti* adduct **14** (3.89 g, 12.6 mmol, 82%). R_f value: 0.23 (hexane/EtOAc = 2:1). $[\alpha]_D^{25}$ = + 16.5° (*c* = 1.16, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.82 (3H, d, *J* = 6.6 Hz, Me-14), 0.92 (3H, d, *J* = 7.1 Hz, *i*Pr), 0.93 (3H, d, *J* = 7.1 Hz, *i*Pr), 1.63 (3H, d, *J* = 6.6 Hz, Me-17), 1.66 (3H, d, *J* = 1.2 Hz, Me-16), 1.97 (3H, d, *J* = 1.2 Hz, Me-12), 2.34 (1H, dqq, *J* = 7.1, 7.1, 4.7 Hz, *i*Pr), 2.74 (1H, ddq, *J* = 10.3, 9.3, 6.6 Hz, H-14), 3.31 (1H, d, *J* = 1.7 Hz, OH-15), 3.66 (1H, dd, *J* = 9.3, 1.7 Hz, H-15), 4.18 (1H, dd, *J* = 9.0, 5.6 Hz), 4.34 (1H, dd, *J* = 9.0, 9.0 Hz), 4.57 (1H, ddd, *J* = 9.0, 5.6, 4.7 Hz), 5.47 (1H, q, *J* = 6.6 Hz, H-17), 5.78 ppm (1H, dd, *J* = 10.3, 1.2 Hz, H-13). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.4, 13.1, 14.0, 15.2, 16.1, 17.8, 28.4, 37.8, 58.1, 63.4, 82.2, 123.6, 131.7, 134.8, 142.0, 154.5, 171.5 ppm. IR (KBr) $\tilde{\nu}$ = 3509, 2966, 1772, 1683 cm^{-1}. FAB-MS (*m*/*z*): 308 $[M-H]^+$, 292 $[M-OH]^+$. HRFAB-MS (*m*/*z*): 308.1843 $[M-H]^+$; calcd for $C_{17}H_{26}O_4N_1$: 308.1862.

15: *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 2.23 mL, 12.7 mmol) was added to a mixture of *anti* adduct **14** (3.01 g, 9.78 mmol) and 2,6-lutidine (1.71 mL, 14.7 mmol) in CH_2Cl_2 (60 mL) at 0 °C under argon atmosphere, and the resulting mixture was stirred for 1 h. TBSOTf (171 μL, 977 μmol) was added, and the mixture was stirred for 30 min. H_2O (20 mL) was added to the resulting mixture at 0 °C, and the organic layer was separated. The aqueous solution was extracted with CH_2Cl_2 (20 mL), and the combined organic extracts were washed with brine (20 mL). The organic extracts were concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford silyl ether **15** (3.85 g, 9.12 mmol, 93%). R_f value: 0.55 (hexane/EtOAc = 3:1). $[\alpha]_D^{22}$ = −14.5° (*c* = 1.16, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = −0.06 (3H, s, Si*Me*), 0.01 (3H, s, Si*Me*), 0.84 (9H, s, Si*tBu*), 0.84 (3H, d, *J* = 7.5 Hz, Me-14), 0.89 (3H, d, *J* = 7.5 Hz, *i*Pr), 0.91 (3H, d, *J* = 7.5 Hz, *i*Pr), 1.56 (3H, s, Me-16), 1.59 (3H, d, *J* = 6.7 Hz, Me-17), 1.92 (3H, d, *J* = 1.8 Hz, Me-12), 2.39 (1H, dqq, *J* = 7.5, 7.5, 4.7 Hz, *i*Pr), 2.64 (1H, ddq, *J* = 10.1, 7.5, 7.5 Hz, H-14), 3.76 (1H, d, *J* = 7.5 Hz, H-15), 4.17 (1H, dd, *J* = 9.2, 4.7 Hz), 4.29 (1H, dd, *J* = 9.2, 9.2 Hz), 4.47 (1H, ddd, *J* = 9.2, 4.7, 4.7 Hz), 5.36 (1H, q, *J* = 6.7 Hz, H-17), 5.93 ppm (1H, dd, *J* = 10.1, 1.8 Hz, H-13). ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.1, −4.8, 11.0, 12.9, 14.2, 14.9, 16.5, 17.9, 18.1, 25.8, 28.2, 37.8, 58.4, 63.4, 82.7, 121.7, 130.8, 136.7, 142.3, 153.4, 171.8 ppm. IR (KBr) $\tilde{\nu}$ = 2958, 1783, 1693, 860, 838, 777 cm^{-1}. HRFAB-MS (*m*/*z*): 422.2706 $[M+H]^+$; calcd for $C_{23}H_{40}O_4N_1Si_1$: 422.2727.

3: A solution of diisobutylaluminum hydride (DIBALH, 0.99 M) in toluene (4.09 mL, 4.05 mmol) dissolved in CH_2Cl_2 (123 mL) was added to a solution of silyl ether **15** (1.41 g, 2.70 mmol) in CH_2Cl_2 (23 mL) at −78 °C under argon atmosphere. The resulting mixture was stirred for 2 h. MeOH (3.0 mL) and sodium sulfate decahydrate were added, and the mixture was stirred for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to yield aldehyde **3** (545 mg, 1.84 mmol, 68%). R_f value: 0.44 (hexane/EtOAc = 10:1). $[\alpha]_D^{23}$ = + 9.60° (*c* = 0.50, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = −0.07 (3H, s, Si*Me*), −0.03 (3H, s, Si*Me*), 0.81 (9H, s, Si*tBu*), 0.89 (3H, d, *J* = 6.7 Hz, Me-14), 1.57 (3H, s, Me-16), 1.60 (3H, d, *J* = 6.7 Hz, Me-17), 1.75 (3H, d, *J* = 1.3 Hz, Me-12), 2.85 (1H, ddq, *J* = 10.1, 8.0, 6.7 Hz, H-14), 3.81 (1H, d, *J* = 8.0 Hz, H-15), 5.40 (1H, q, *J* = 6.7 Hz, H-17), 6.36 (1H, dd, *J* = 10.1, 1.3 Hz, H-13), 9.40 ppm (1H, s, H-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.1, −4.7, 9.5, 10.9, 13.0, 16.5, 18.1, 25.7, 38.4, 82.8, 122.3, 136.3, 139.0, 158.8, 195.6 ppm. IR (KBr) $\tilde{\nu}$ = 2929, 1693, 860, 836, 775 cm^{-1}. HRFAB-MS (*m*/*z*): 319.2104 $[M+Na]^+$; calcd for $C_{17}H_{32}O_2Si_1Na_1$: 319.2069.

16: Sodium bis(trimethylsilyl)amide (0.99 M) in THF (273 μL, 270 μmol) was added to a solution of sulfone **4** (83.6 mg, 284 μmol) in dimethoxyethane (420 μL) at −78 °C under argon atmosphere, and the resulting mixture was stirred at −60 °C for 30 min. Aldehyde **3** (42.1 mg, 142 μmol) in dimethoxyethane (600 μL) was added to the mixture, and the stirring mixture was warmed to 0 °C over 18 h. EtOAc (5.0 mL) and H_2O (2.5 mL) were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3.0 mL), and the combined organic extracts were washed with brine (2.5 mL). The organic extracts were concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 25:1) to yield triene **16** (43.1 mg, 118 μmol). R_f value: 0.48 (hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = −0.09 (3H, s, Si*Me*), −0.07 (3H, s, Si*Me*), 0.76 (3H, d, *J* = 6.8 Hz, Me-14), 0.80 (9H, s, Si*tBu*), 1.31 (3H, d, *J* = 2.0 Hz, Me-8), 1.55 (3H, s, Me-12), 1.58 (3H, d, *J* = 6.8 Hz, Me-17), 1.73 (3H, s, Me-16), 2.30 (1H, dd, *J* = 14.4, 7.2 Hz, H-9), 2.41 (1H, dd, *J* = 14.4, 8.0 Hz, H-9′), 2.60 (1H, d, *J* = 4.8 Hz, H-7), 2.62 (1H, dd, *J* = 8.0, 2.0 Hz, H-14), 2.65 (1H, d, *J* = 4.8 Hz, H-7′), 3.63 (1H, d, *J* = 8.0 Hz, H-15), 5.21 (1H, d, *J* = 8.0 Hz, H-13), 5.31 (1H, q, *J* = 6.8 Hz, H-17), 5.45 (1H, ddd, *J* = 14.6, 8.0, 7.2 Hz, H-10), 6.50 ppm (1H, d, *J* = 14.6 Hz, H-11). HRFAB-MS (*m*/*z*): 363.2697 $[M-H]^+$; calcd for $C_{22}H_{39}O_2Si_1$: 363.2719.

17: Camphorsulfonic acid (1.4 mg, 5.9 μmol) was added to a solution of triene **16** (43.1 mg, 118 μmol) in MeOH (800 μL) at 0 °C under argon atmosphere and stirred for 1 h. Triethylamine (5 μL, 36.5 μmol) was added, and the resulting mixture was concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to yield primary alcohol **17** (38.0 mg, 95.8 μmol, 67% in 2 steps). R_f value: 0.09 (hexane/EtOAc = 8:1). $[\alpha]_D^{25}$ = −2.93° (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = −0.09 (3H, s, Si*Me*), −0.07 (3H, s, Si*Me*), 0.75 (3H, d, *J* = 6.7 Hz, Me-14), 0.80 (9H, s, Si*tBu*), 1.12 (3H, s, Me-8), 1.55 (3H, s, Me-12), 1.58 (3H, d, *J* = 6.7 Hz, Me-17), 1.73 (3H, s, Me-16), 1.86 (1H, t, *J* = 6.0 Hz, OH-7), 2.22–2.41 (2H, m, H-9), 2.61 (1H,

ddq, $J=9.6$, 8.0, 6.7 Hz, H-14), 3.26 (3H, s, O*Me*), 3.42 (1H, dd, $J=11.2$, 6.1 Hz, H-7), 3.48 (1H, dd, $J=11.2$, 6.1 Hz, H-7′), 3.62 (1H, d, $J=8.0$ Hz, H-15), 5.19 (1H, d, $J=9.6$ Hz, H-13), 5.32 (1H, q, $J=6.6$ Hz, H-17), 5.46 (1H, dt, $J=15.5$, 7.7 Hz, H-10), 6.09 ppm (1H, d, $J=15.5$ Hz, H-11). The diastereomers at position C8 were not distinguishable by 400 MHz ^{1}H NMR. ^{13}C NMR (100 MHz, $CDCl_3$): (values in brackets are data of the isomer at position C8): $\delta=-5.1$, −4.8, 10.7 [10.8], 12.9, 13.0, 17.5, 18.1, 19.0, 19.1, 25.7, 37.2, 38.5 [38.4], 49.3 [49.3], 66.8 [66.8], 77.3 [77.4], 83.6 [83.6], 121.3 [121.1], 132.8 [132.8], 136.2 [136.1], 137.2, 138.6 ppm [138.6]. IR (KBr) $\tilde{\nu}=3444$, 2927, 860, 835, 773 cm^{-1}. HRFAB-MS (*m*/*z*): 395.2977 $[M-H]^+$; calcd for $C_{23}H_{43}O_3Si_1$: 395.2981.

18: Sulfur trioxide pyridine complex (895 mg, 5.62 mmol) was added to a mixture of primary alcohol **17** (225 mg, 566 μmol) and triethylamine (1.58 mL, 11.3 mmol) in dimethoxyethane (3.9 mL) at room temperature under argon atmosphere, and the resulting mixture was stirred for 30 min. Toluene (12 mL) and H_2O (4.0 mL) were added to the reaction mixture, and the organic layer was separated. The aqueous solution was extracted with toluene (12 mL), and the combined organic extracts were washed twice with brine (2×3.0 mL). The organic extracts were concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc=25:1) to yield aldehyde **18** (211 mg, 535 μmol, 94%). R_f value: 0.48 (hexane/EtOAc=10:1). $[\alpha]_D^{25}=-3.30°$ ($c=1.11$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): (values in brackets are data of the isomer at position C8): $\delta=-0.09$ (3H, s, Si*Me*), −0.07 (3H, s, Si*Me*), 0.75 (3H, d, $J=6.9$ Hz, Me-14), 0.80 (9H, s, Si*tBu*), 1.21 [1.22] (3H, s, Me-8), 1.55 (3H, s, Me-12), 1.58 (3H, d, $J=6.4$ Hz, Me-17), 1.71 (3H, s, Me-16), 2.33–2.52 (2H, m, H-9), 2.59 (1H, ddq, $J=10.1$, 8.0, 6.9 Hz, H-14), 3.32 (3H, s, O*Me*), 3.62 (1H, d, $J=8.0$ Hz, H-15), 5.20 (1H, d, $J=10.1$ Hz, H-13), 5.31 (1H, q, $J=6.4$ Hz, H-17), 5.41 (1H, dt, $J=17.9$, 7.5 Hz, H-10), 6.09 (1H, d, $J=17.9$ Hz, H-11), 9.58 ppm [9.59] (1H, s, H-7). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=-5.1$, −4.8, 10.8 [10.8], 12.9 [13.0], 17.4, 17.5 [17.5], 18.1, 25.7, 37.3, 38.0 [38.2], 51.9 [51.9], 82.4 [82.4], 83.5 [83.6], 118.9, 121.3 [121.3], 132.7, 136.7 [136.7], 137.1, 139.5 [139.6], 205.0 ppm [205.1]. IR (KBr) $\tilde{\nu}=2956$, 2929, 2856, 2701, 1737, 1247, 1079, 1056, 860, 836, 773 cm^{-1}. HRFAB-MS (*m*/*z*): 393.3827 $[M-H]^+$; calcd for $C_{23}H_{41}O_3Si_1$: 393.2825.

19: Lithium bis(trimethylsilyl)amide (1.0 M) in THF (576 μL, 576 μmol) was added to a solution of phosphate **5** (183 mg, 600 μmol) in THF (5.7 mL) at −78 °C under argon atmosphere, and the resulting mixture was stirred at −78 °C for 1 h. Aldehyde **18** (189 mg, 480 μmol) in THF (3.7 mL) was added to the mixture, and the resulting mixture was stirred for 1 h, then warmed to 0 °C over 2.5 h, and stirred at 0 °C for 2 h. Acetic acid was added, and the resulting mixture was concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc=3:1) to give vinylpyrone **19** (250 mg, 459 μmol, 96%). R_f value: 0.10 (hexane/EtOAc=4:1). $[\alpha]_D^{23}=-0.99°$ ($c=1.15$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): (values in brackets are data of the isomer at position C8): $\delta=-0.12$ (3H, s, Si*Me*), −0.10 (3H, s, Si*Me*), 0.75 (3H, d, $J=6.9$ Hz, Me-14), 0.78 [0.79] (9H, s, Si*tBu*), 1.33 [1.34] (3H, s, Me-8), 1.54 (3H, s, Me-12), 1.58 (3H, d, $J=6.7$ Hz, Me-17), 1.71 [1.72] (3H, s, Me-2), 1.87 (3H, s, Me-16), 2.04 (3H, s, Me-4), 2.43 (2H, d, $J=7.1$ Hz, H-9), 2.55–2.67 (1H, m, H-14), 3.24 [3.26] (3H, s, O*Me*-8), 3.62 (1H, d, $J=8.3$ Hz, H-15), 4.00 (3H, s, O*Me*-1), 5.19 (1H, d, $J=10.1$ Hz, H-13), 5.31 (1H, q, $J=6.9$ Hz, H-17), 5.41–5.52 (1H, m, H-10), 6.08 [6.10] (1H, d, $J=15.2$ Hz, H-11), 6.36 (1H, d, $J=16.6$ Hz, H-6), 6.48 ppm [6.49] (1H, d, $J=16.6$, 2.4 Hz, H-7). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=-5.1$, −4.8, 6.9, 9.7, 10.8 [10.8], 12.9 [13.1], 17.5 [18.1], 21.9 [22.3], 25.7, 37.3, 43.4 [43.6], 50.5 [50.6], 55.3 [55.3], 77.2 [77.5], 83.5, 99.6 [99.6], 119.0 [119.0], 119.3 [119.5], 120.7 [120.8], 121.3 [121.3], 132.8 [132.8], 136.3 [136.4], 137.1 [137.1], 138.9 [139.0], 140.3 [140.4], 151.3 [151.3], 161.7, 181.0 ppm. IR (KBr) $\tilde{\nu}=2927$, 1666, 1616, 1253, 860, 835, 773 cm^{-1}. HRFAB-MS (*m*/*z*): 545.3646 $[M+H]^+$; calcd for $C_{32}H_{53}O_5Si_1$: 545.3662.

20: Camphorsulfonic acid (13.3 mg, 57.1 μmol) in MeOH (400 μL) was added to a solution of vinylpyrone **19** (31.1 mg, 57.1 μmol) in MeOH (1.6 mL) at room temperature under argon atmosphere, and left for 18 h. Triethylamine was added to the solution at 0 °C, and the resulting mixture was concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/EtOAc=1:1) to give secondary alcohol **20** (17.2 mg, 39.9 μmol, 70%). R_f value: 0.19 (hexane/EtOAc=1:1). $[\alpha]_D^{25}=+3.64°$ ($c=1.28$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) (values in brackets are data of the isomer at position C8): $\delta=0.81$ (3H, d, $J=6.9$ Hz, Me-14), 1.35 (3H, s, Me-8), 1.63 (3H, d, $J=5.1$ Hz, Me-17), 1.64 (3H, s, Me-12), 1.80 (3H, s, Me-2), 1.87 (3H, s, Me-16), 2.05 (3H, s, Me-4), 2.44 (2H, d, $J=7.2$ Hz, H-9), 2.69 (1H, ddq, $J=9.6$, 9.1, 6.5 Hz, H-14), 3.25 [3.25] (3H, s, O*Me*-8), 3.63 (1H, d, $J=9.1$ Hz, H-15), 4.00 [4.00] (3H, s, O*Me*-1), 5.26 (1H, d, $J=9.6$ Hz, H-13), 5.49 (1H, q, $J=6.2$ Hz, H-17), 5.53–5.63 (1H, m, H-10), 6.13 [6.14] (1H, d, $J=16.3$ Hz, H-11), 6.36 (1H, d, $J=16.3$ Hz, H-6), 6.50 ppm [6.51] (1H, d, $J=16.3$ Hz, H-7). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=6.9$, 9.6, 10.5, 13.1 [13.1], 17.4, 22.2 [22.2], 36.8, 43.5 [43.6], 50.5, 55.3, 77.2 [77.2], 82.8, 99.6, 119.1, 119.5 [119.5], 122.4 [122.5], 123.6, 134.1 [134.1], 135.5 [135.5], 135.6, 138.0 [138.1], 140.0, 151.2, 161.7, 181.0 ppm. IR (KBr) $\tilde{\nu}=3423$, 2971, 2925, 1666, 1602, 1577, 1376, 1336, 968 cm^{-1}. HRFAB-MS (*m*/*z*): 431.2769 $[M+H]^+$; calcd for $C_{26}H_{39}O_5$: 431.2797.

(+)-Actinopyrone A (**1**): Samarium iodide (0.1 M) in THF (438 μL, 43.8 μmol) was added to a mixture of secondary alcohol **20** (6.3 mg, 14.6 μmol) and isopropanol (11 μL, 14.6 μmol) in THF (630 μL) at −78 °C under argon atmosphere, and the resulting mixture was stirred at −20 °C for 30 min. Air was bubbled into the solution. EtOAc (1.0 mL), saturated aqueous sodium bicarbonate (0.5 mL), and H_2O (0.5 mL) were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (0.5 mL), and the combined organic extracts were concentrated to afford the residue, which was purified by silica gel column chromatography (hexane/acetone=4:1) to yield (+)-actinopyrone A (**1**, 4.1 mg, 10.3 μmol, 70%) along with (7,8-*Z*)-actinopyrone (**21**, 0.6 mg, 1.4 μmol, 10%). (+)-actinopyrone A (**1**): R_f value: 0.33 (hexane/acetone=1:1). Synthetic: $[\alpha]_D^{25}=+31.3$ ($c=0.43$, CH_2Cl_2); natural: $[\alpha]_D^{26}=+30.8$ ($c=0.42$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.81$ (3H, d, $J=6.9$ Hz, Me-14), 1.63 (3H, d, $J=6.0$ Hz, Me-17), 1.64 (3H, s, Me-12), 1.67 (1H, br, OH-15), 1.73 (3H, s, Me-16), 1.81 (3H, s, Me-8), 1.84 (3H, s, Me-2), 1.96 (3H, s, Me-4), 2.68 (1H, ddq, $J=9.6$, 9.1, 6.9 Hz, H-14), 2.80 (2H, d, $J=6.9$ Hz, H-9), 3.31 (2H, d, $J=7.3$ Hz, H-6), 3.63 (1H, d, $J=9.1$ Hz, H-15), 3.92 (3H, s, O*Me*-8), 5.24 (1H, d, $J=9.6$ Hz, H-13), 5.26 (1H, t, $J=7.3$ Hz, H-7), 5.49 (1H, q, $J=6.0$ Hz, H-17), 5.56 (1H, dt, $J=15.5$, 6.9 Hz, H-10), 6.10 ppm (1H, d, $J=15.5$ Hz, H-11). The nOe was observed between H-6 and Me-8 (8.2%) and between H-6 and Me-4 (7.5%). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=6.9$, 9.9, 10.5, 13.1, 13.2, 16.6, 17.4, 30.0, 36.9, 42.9, 55.2, 82.8, 99.3, 118.0, 118.1, 123.6, 125.6, 133.8, 135.57, 135.61, 136.4, 138.0, 156.9, 162.1, 181.0 ppm. IR (KBr) $\tilde{\nu}=3407$, 3023, 2958, 2923, 2863, 1666, 1587, 1463, 1378, 1326, 1251, 1164 cm^{-1}. HRFAB-MS (*m*/*z*): 401.2673 $[M+H]^+$; calcd for $C_{25}H_{37}O_4$: 401.2692. (7,8-*Z*)-actinopyrone (**21**): R_f value: 0.34 (hexane/acetone=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.81$ (3H, d, $J=6.7$ Hz, Me-14), 1.63 (3H, d, $J=6.7$ Hz, Me-17), 1.64 (3H, s, Me-8), 1.75 (3H, s, Me), 1.75 (1H, br, OH-15), 1.79 (3H, s, Me), 1.84 (3H, s, Me), 1.96 (3H, s, Me-4), 2.68 (1H, ddq, $J=10.1$, 8.5, 6.7 Hz, H-14), 2.91 (2H, d, $J=6.5$ Hz, H-9), 3.31 (2H, d, $J=7.2$ Hz, H-6), 3.63 (1H, d, $J=8.5$ Hz, H-15), 3.93 (3H, s, O*Me*-8), 5.23 (1H, d, $J=10.1$ Hz, H-13), 5.31 (1H, t, $J=7.2$ Hz, H-7), 5.49 (1H, q, $J=6.7$ Hz, H-17), 5.53 (1H, dt, $J=15.5$, 6.5 Hz, H-10), 6.09 ppm (1H, d, $J=15.5$ Hz, H-11). The nOe was observed between H-6 and Me-4 (3.7%), between H-6 and H-9 (2.0%), and between H-7 and Me-8 (6.7%). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=6.9$, 9.9, 10.5, 13.1, 13.1, 17.4, 23.7, 29.8, 35.3, 36.9, 55.3, 82.8, 99.4, 118.1, 118.5, 123.6, 124.4, 134.0, 135.4, 135.6, 135.9, 137.5, 156.9, 162.1, 181.1 ppm. 7-hydro-8-methoxyactinopyrone (**22**): R_f value: 0.12 (hexane/EtOAc=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (values in brackets are data of the isomer at position C8): $\delta=0.80$ (3H, d, $J=6.9$ Hz, Me-14), 1.25 (3H, s, Me-8), 1.63 (3H, d, $J=6.0$ Hz, Me-17), 1.64 (3H, s, Me-12), 1.71–1.80 (2H, m, H-7), 1.81 (3H, s, Me-16), 1.84 (3H, s, Me-2), 1.94 (3H, s, Me-4), 2.30–2.35 (2H, m, H-6), 2.58–2.73 (3H, m, H-9, H-14), 3.24 (3H, s, OMe-8), 3.63 (1H, d, $J=9.1$ Hz, H-15), 3.93 (3H, s, OMe-1), 5.24 (1H, d, $J=9.9$ Hz, H-13), 5.45–5.61 (2H, m, H-10, H-17), 6.13 ppm [6.14] (1H, d, $J=15.5$ Hz, H-11). IR (KBr) $\tilde{\nu}=3411$, 2958, 2923, 2861, 1668, 1587, 1463, 1378, 1328, 1251, 1168 cm^{-1}. FAB-MS (*m*/*z*): 433 $[M+H]^+$, 415 $[M-OH]^+$, 239 [*M*−(C9–C18 fragment)]$^+$. HRFAB-MS (*m*/*z*): 433.2951 $[M+H]^+$; calcd for $C_{26}H_{41}O_5$: 433.2954.

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