# Determination of the Absolute Structure of (+)-Akaterpin

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**We describe the total synthesis and structural determination of (+)-akaterpin (1), an inhibitor of phosphatidylinositol-specific phospholipase C (PI-PLC). The key features of the synthetic strategy include the resolution of *β*,*γ*-unsaturated ketone (±)-2a with chiral sulfoximine 6. The absolute stereochemistry was determined by comparison of the specific optical rotation data of (+)-1 and (−)-1 with that of natural akaterpin.**

**Key words** total synthesis; absolute stereochemistry; optical resolution

Umezawa and co-workers originally isolated akaterpin (**1**) from the marine sponge *Callyspongia* sp. as an inhibitor of phosphatidylinositol-specific phospholipase C (PI-PLC).[1)] PI-PLC triggers phosphatidylinositol turnover by hydrolyzing phosphatidylinositol 4,5-bisphosphate ($PIP_2$) into diacylglycerol (DG) and 1,4,5-trisphosphate ($IP_3$). Thus, a specific PI-PLC inhibitor is considered a promising anti-tumor candidate and a valuable tool for the investigation of signal transduction.[2,3)] Until recently the precise structure of akaterpin had not been determined because of difficulties in isolating this compound from the natural source. We have been investigating a synthetic study of akaterpin and recently reported the relative stereochemistry of the compound by synthesizing possible isomers in racemic form and comparing the corresponding spectral data with those of the authentic natural product.[4)] Herein we describe the determination of the absolute stereochemistry of (+)-akaterpin. Our approach was to synthesize optically active akaterpin by resolution of the key intermediate in the racemic synthesis. We reasoned that *β*,*γ*-unsaturated ketone **2a** was suitable for this purpose. Having resolved the key intermediate **2a**, each enantiomer was then separately transformed to akaterpin following the same synthetic procedure as used for the racemate.

In this regard, we previously reported the successful resolution of methyl-protected **2b** by using chiral sulfoximine **6**, which was developed by Johnson.[5,6)] The absolute stereochemistry of both enantiomers of **2b** was then established by X-ray crystallographic analysis of **7b** and **9b**[7)] (Chart 2). We envisaged the resolution of benzyl-protected **2a**, the synthetic intermediate of racemic akaterpin,[8)] would also be possible as **2b**. Thus, both enantiomers of akaterpin could be synthesized

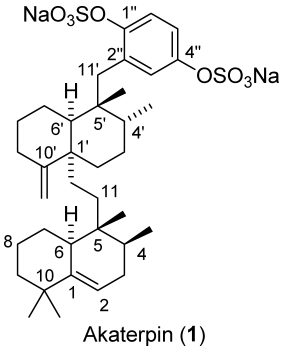


Fig. 1. Relative Stereochemistry of Akaterpin **1**

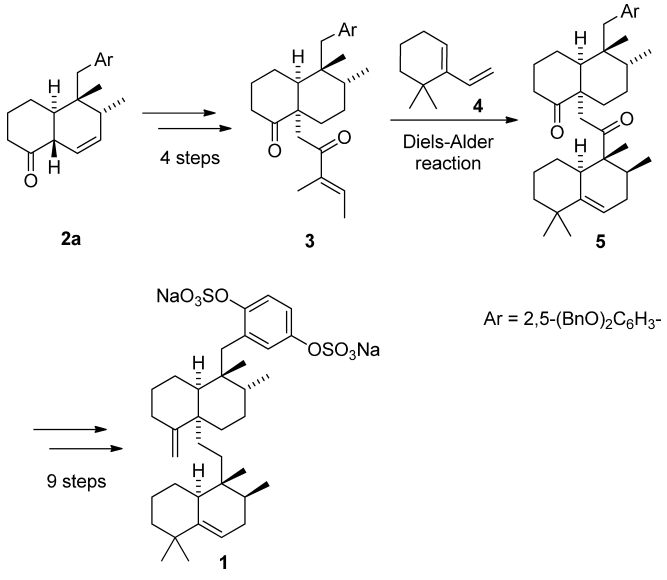


Chart 1. Synthetic Route of Akaterpin **1**

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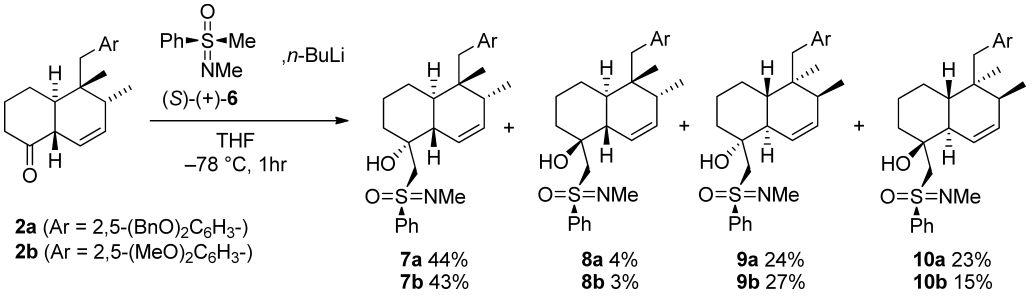


Chart 2. Addition of Chiral Sulfoximine (*S*)-(+)-**6** to *β*,*γ*-Unsaturated Ketone **2**

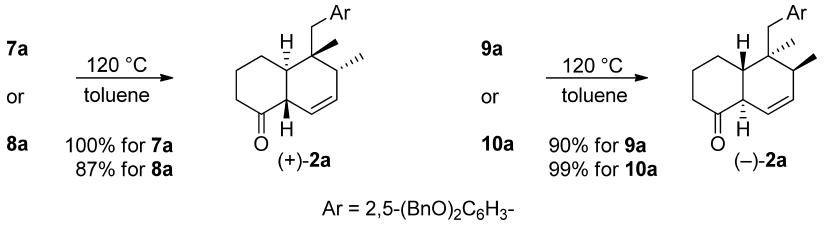


Chart 3. Thermal Elimination of Sulfoximine (*S*)-(+)-**6** Affording (+)-**2a** and (−)-**2a**

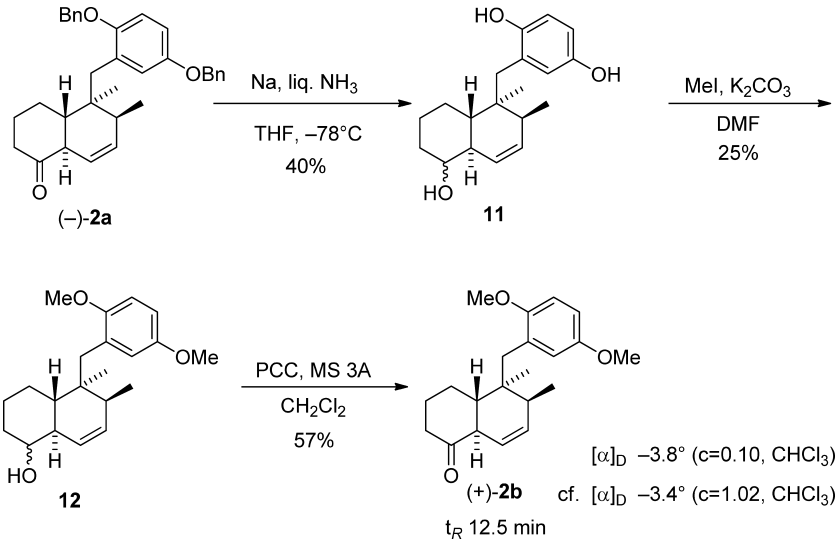


Chart 4. Conversion of (−)-**2a** to Previously Established Enantiomer (+)-**2b**

from **2a** after resolution.

Our synthesis commenced with the addition of the lithio derivative of (*S*)-(+)-**6** to the ketone (±)-**2a**. The resulting four diastereomers **7a**—**10a** were separated by flash column chromatography. The stereochemistry of each isomer was not established because these adducts were unsuitable for X-ray crystallographic analysis. Consequently, the stereochemistry of the four diastereomers **7a**—**10a** was tentatively estimated by comparing the yield and chromatographic behavior (TLC) of **7b**—**10b** whose absolute stereochemistry were unambiguously determined.[7] Then, thermal elimination of each isomer **7a** and **8a** was carried out. As anticipated **7a** and **8a** afforded the same isomer (+)-**2a** upon heating at 120°C in toluene, while **9a** and **10a** gave (−)-**2a** (Chart 3). The absolute stereochemistry of (−)-**2a** was established by converting (−)-**2a** to methyl ether (+)-**2b**. Thus, after removal of the benzyl group of (−)-**2a**, methylation of the hydroxyl group of hydroquinone **11** and subsequent pyridinium chlorochromate (PCC) oxidation of alcohol **12** afforded the known methyl-protected ketone (+)-**2b** for which absolute stereochemistry had already been established (Chart 4). HPLC analysis using a chiral column (DAICEL Chiralpak AD, Hexane/*i*-PrOH=9/1, 254 nm, 0.5 mL/min: $t_R$ of (+)-**2b**, 12.5 min, $t_R$ of (−)-**2b**, 19.9 min) gave results that were consistent with the determined absolute stereochemistry.

After completion of the resolution of key intermediate **2a**, both enantiomers of **2a** were transformed to akaterpin by the same synthetic route as described previously.[4] First, deprotonation of ketone (+)-**2a** with sodium bis(trimethylsilyl) amide (NaHMDS) generated the corresponding dienolate anion, and subsequent attack by iodoacetate from the *α*-face occurred with complete regio- and stereoselectivity to afford *cis*-decalin (−)-**13** as a single isomer (Chart 5). Hydrogenation of (−)-**13** with Crabtree's catalyst[9—11] afforded (−)-**14** in quantitative

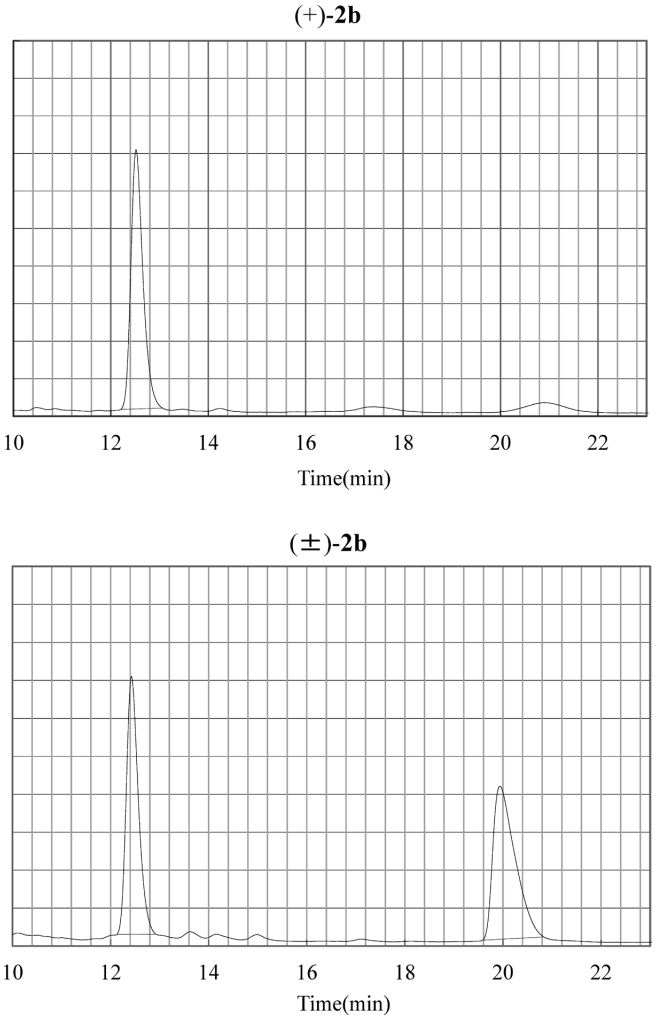


Fig. 2. HPLC Comparison of (±)-**2b** and (+)-**2b**

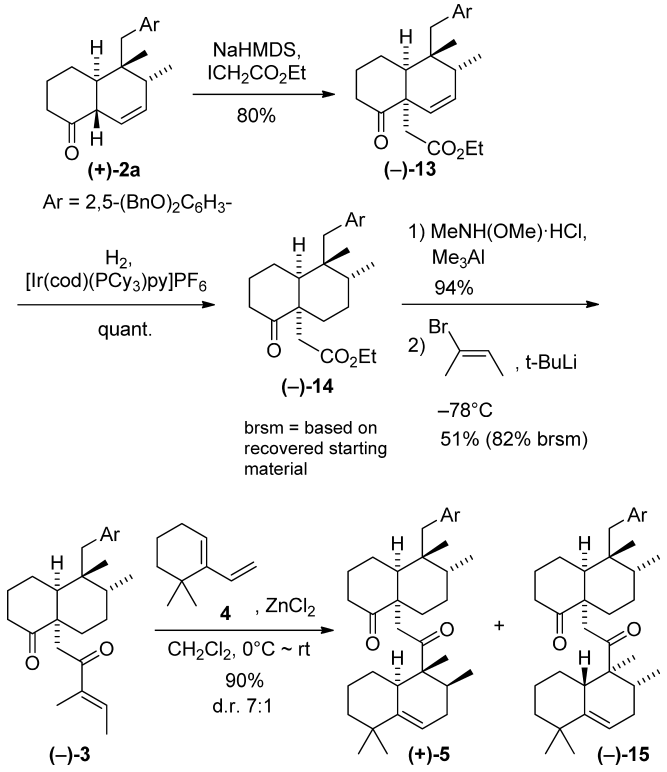


Chart 5. Synthesis of Dienophile (−)-**3** and Intermolecular Diels–Alder Reaction with Diene **4**

yield. After conversion of ester (−)-**14** to Weinreb amide,[12,13] addition of butenyllithium to amide provided the dienophile (−)-**3**. The intermolecular Diels–Alder reaction of enone (−)-**3** and vinylcyclohexene **4**[14,15] proceeded to give *exo*-adducts (+)-**5** and undesired (−)-**15** as a separable mixture.

Next, deoxygenation of the ketone at C11 and *exo*-methylenation at the C10′ were conducted (Chart 6). After the reduction of (+)-**5** with $LiAlH_4$ to obtain the diol as a single isomer, the treatment of the diol with methoxymethyl chloride (MOMCl) selectively afforded mono-MOM ether (+)-**16**. The hydroxyl group of (+)-**16** was then removed by following the Barton–McCombie deoxygenation protocol[16,17] to give MOM ether (+)-**17**. Cleavage of MOM ether by treatment with *B*-bromocatecholborane[18—20] and subsequent tetra-*n*-propylammonium perruthenate (TPAP) oxidation[21] provided ketone (+)-**18**. Introduction of the exomethylene group at the C10′ position was accomplished by using Takai and Utimoto condition[22,23] to give (+)-**19** albeit in a moderate yield. Finally, removal of the benzyl group of (+)-**19** with Li naphthalenide[24,25] and subsequent treatment of the resulting hydroquinone with $SO_3$·Py at 80°C in pyridine[26—28] completed the synthesis of the target compound (+)-**1** ($[\alpha]_D^{23}$ +17.2° (*c*=0.43, MeOH)). Employment of the same synthetic sequence to the ketone (−)-**2a** provided another target compound (−)-**1** ($[\alpha]_D^{23}$ −19.8° (*c*=0.43, MeOH)).

Comparison of the specific optical rotation data for each enantiomer with that of the natural akaterpin ($[\alpha]_D^{24}$ +15° (*c*=0.59, MeOH))[1] unambiguously demonstrates that the absolute structure of akaterpin is (+)-**1**.

In conclusion, we were able to establish the absolute stereochemistry of akaterpin.

## Experimental

All non-aqueous reactions were performed under an atmosphere of dry argon in oven-dried glassware unless otherwise indicated. Solvents were distilled under an atmosphere of argon before use and transferred *via* an oven-dried syringe or cannula. Dichloromethane, toluene, acetonitrile (MeCN), triethylamine, diisopropylethylamine, *N*,*N*-dimethylformamide (DMF), and pyridine were distilled from calcium hydride. Dry tetrahydrofuran (41001-85) and diethyl ether (14547-95) were purchased from KANTO Chemical Industries Ltd. (Japan) in anhydrous Grade.

Flash column chromatography was performed with silica gel (PSQ-100B, Fuji Silysia Co., Ltd., Japan). Solvents for chromatography are listed as volume/volume ratios. Analytical thin layer chromatography was performed using commercial silica gel plates (E. Merck, Silica Gel 60 F254).

Infrared spectra were recorded on a PerkinElmer Spectrum 100 FTIR spectrometer. Absorbance frequencies are recorded in reciprocal centimeters ($cm^{-1}$). High resolution mass spectra (HR-MS) were obtained from Applied Biosystems mass spectrometer (API QSTAR pulsar i) for electrospray ionization (ESI), or from Hitachi M-80B for electroimpact ionization (EI, 70 eV). HR-MS data are reported as *m/z* (relative intensity), with accurate mass reported for the molecular ion $[M+Na]^+$.

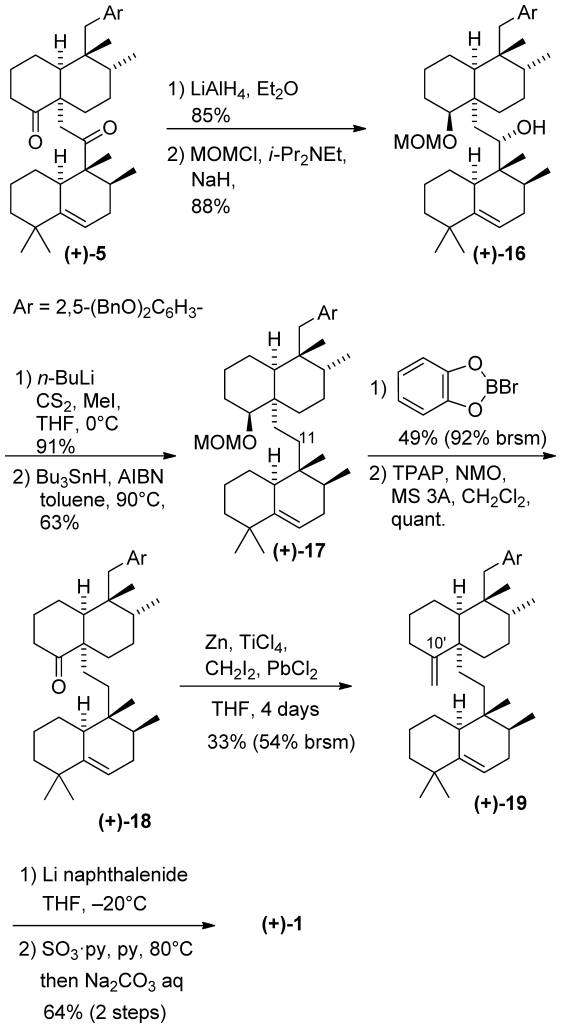


Chart 6. Synthesis of (+)-**1**

Melting points were recorded on Yanaco MP-3S.

$^1$H-NMR spectra were acquired at 400 MHz on a JEOL JNM-LD400 spectrometer or 500 MHz on a JNM-ECP500 spectrometer. Chemical shifts are reported in delta ($\delta$) units in parts per million (ppm) relative to the singlet (7.26 ppm) for chloroform-*d* or the quartet (3.30 ppm) for methanol-$d_4$. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet and br, broad. Coupling constants are recorded in Hertz (Hz). $^{13}$C-NMR spectra were acquired at 100 MHz on a JEOL JNM-LD400 spectrometer or 125 MHz on a JNM-ECP500 spectrometer. Chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for chloroform-*d* or the double quartet at 49.0 ppm for methanol-$d_4$.

**Alcohol 7a—10a** To a solution of (*S*)-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine **6** (244 mg, 1.44 mmol) in tetrahydrofuran (THF) (12.0 mL) was added *n*-BuLi 1.63 M in *n*-hexane (834 $\mu$L, 1.36 mmol) at 0°C. After stirring for 30 min, a solution of ketone (±)-**2a** (198 mg, 0.412 mmol) in THF (9.0 mL) was added at −78°C. After stirring for 1 h at −78°C, the reaction was quenched with a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with $Et_2O$. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=10/1 to 8/1 to 6/1 to 3/1) and PTLC (hexane/AcOEt=3/1) to afford **7a** (119 mg, 44% yield) as a white amorphous, **8a** (11.6 mg, 4% yield) as a white amorphous, **9a** (64.7 mg, 24% yield) as a white amorphous, and **10a** (61.0 mg, 23% yield) as a white amorphous.

**7a**: *Rf* 0.32 (hexane/AcOEt=3/1); $[\alpha]_D^{23}$ +51.6° (*c*=1.39, $CHCl_3$); IR (neat) cm$^{-1}$: 3274, 3028, 2940, 2805, 1736, 1606, 1585, 1494; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.69 (s, 3H), 0.92—1.05 (m, 1H), 1.15 (d, *J*=6.8 Hz, 3H), 1.58—1.92 (m, 5H), 1.98 (d, *J*=12.2 Hz, 1H), 2.08 (t, *J*=12.5 Hz, 1H), 2.39 (d, *J*=13.8 Hz, 1H), 2.60 (s, 3H), 2.78 (d, *J*=13.2 Hz, 1H), 2.89 (d, *J*=13.8 Hz, 1H), 3.20 (d, *J*=13.7 Hz, 1H), 3.75 (d, *J*=13.7 Hz, 1H), 5.00 (s, 2H), 5.01 (s, 2H), 5.36 (d, *J*=10.2 Hz, 1H), 5.67—5.78 (m, 1H), 6.31 (s, 1H), 6.76 (dd, *J*=2.9, 8.8 Hz, 1H), 6.83 (d, *J*=8.8 Hz, 1H), 6.96 (d, *J*=2.9 Hz, 1H), 7.28—7.47 (m, 10H), 7.54—7.66 (m, 3H), 7.88 (d, *J*=6.8 Hz, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 17.5, 17.8, 21.9, 25.4, 28.8, 32.0, 35.6, 36.8, 37.7, 38.8, 49.3, 64.2, 70.5, 70.8, 74.3, 112.1, 112.9, 118.1, 121.6, 127.0, 127.4, 127.6, 127.7, 128.3, 128.4, 128.9, 129.5, 130.2, 133.0, 135.7, 137.3, 137.6, 139.1, 152.0, 152.4; HR-ESI-MS *m*/*z*: 672.3124 (Calcd for $C_{41}H_{47}NO_4NaS$: 672.3118).

**8a**: *Rf* 0.44 (hexane/AcOEt=3/1); $[\alpha]_D^{23}$ +50.4° (*c*=1.80, $CHCl_3$); IR (neat) cm$^{-1}$: 3028, 2932, 2873, 1585, 1496, 1453, 1379, 1217, 1144, 1080, 1026; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.70 (s, 3H), 0.85—0.95 (m, 1H), 1.00 (d, *J*=6.8 Hz, 3H), 1.19—1.37 (m, 2H), 1.47 (d, *J*=14.2 Hz, 1H), 1.59 (s, 1H), 1.73 (d, *J*=12.2 Hz, 1H), 1.81 (t, *J*=6.6 Hz, 1H), 1.94 (d, *J*=11.2 Hz, 1H), 2.19 (d, *J*=13.2 Hz, 1H), 2.25 (d, *J*=13.8 Hz, 1H), 2.76 (s, 3H), 3.07 (d, *J*=13.8 Hz, 1H), 3.29 (d, *J*=14.7 Hz, 1H), 3.51 (d, *J*=14.7 Hz, 1H), 4.97 (s, 2H), 5.00 (s, 2H), 5.66—5.72 (m, 1H), 5.75 (d, *J*=11.2 Hz, 1H), 6.25 (br s, 1H), 6.76 (dd, *J*=2.9, 8.8 Hz, 1H), 6.81 (d, *J*=8.8 Hz, 1H), 6.90 (d, *J*=2.9 Hz, 1H), 7.27—7.45 (m, 10H), 7.54—7.66 (m, 3H), 7.89 (d, *J*=6.8 Hz, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 17.3, 18.0, 22.9, 24.9, 29.3, 32.1, 37.48, 37.53, 37.7, 38.9, 50.9, 58.8, 70.6, 70.8, 72.8, 112.3, 112.9, 118.1, 122.1, 127.1, 127.4, 127.6, 127.8, 128.4, 128.5, 129.0, 129.5, 129.8, 133.0, 135.0, 137.3, 137.6, 139.9, 151.9, 152.4; HR-ESI-MS *m*/*z*: 672.3126 (Calcd for $C_{41}H_{47}NO_4NaS$: 672.3118).

**9a**: *Rf* 0.53 (hexane/AcOEt=3/1); $[\alpha]_D^{23}$ −41.3° (*c*=0.98, $CHCl_3$); IR (neat) cm$^{-1}$: 3270, 3029, 2935, 2872, 2365, 1736, 1497, 1455, 1376, 1217; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.74 (s, 3H), 0.90 (d, *J*=7.1 Hz, 3H), 1.05 (td, *J*=3.3, 12.3 Hz, 1H), 1.17—1.95 (m, 7H), 2.02 (d, *J*=11.0 Hz, 1H), 2.27 (d, *J*=13.9 Hz, 1H), 2.60 (s, 3H), 2.92 (d, *J*=13.0 Hz, 1H), 3.16 (d, *J*=13.9 Hz, 1H), 3.21 (d, *J*=14.2 Hz, 1H), 3.24 (d, *J*=14.2 Hz, 1H), 4.94—5.06 (m, 4H), 5.58—5.68 (m, 1H), 5.78 (d, *J*=10.0 Hz, 1H), 6.75 (dd, *J*=2.9, 8.8 Hz, 1H), 6.82 (d, *J*=8.8 Hz, 1H), 6.89 (d, *J*=2.9 Hz, 1H), 7.27—7.46 (m, 10H), 7.57—7.68 (m, 3H), 7.89 (d, *J*=7.1 Hz, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 17.3, 18.1, 23.7, 25.1, 28.9, 32.1, 37.7, 37.8, 38.0, 38.9, 50.5, 57.7, 70.6, 70.9, 74.7, 112.1, 112.9, 118.1, 112.3, 127.1, 127.4, 127.6, 127.8, 128.4, 128.5, 129.0, 129.6, 129.9, 133.1, 134.6, 137.3, 137.6, 138.9, 152.0, 152.4; HR-ESI-MS *m*/*z*: 672.3112 (Calcd for $C_{41}H_{47}NO_4NaS$: 672.3118).

**10a**: *Rf* 0.15 (hexane/AcOEt=3/1); $[\alpha]_D^{24}$ +10.8° (*c*=1.46, $CHCl_3$); IR (neat) cm$^{-1}$: 3450, 3021, 2960, 2934, 2797, 1604, 1500, 1453, 1385, 1225, 1131; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.69 (s, 3H), 0.82—0.97 (m, 1H), 1.11 (d, *J*=6.8 Hz, 3H), 1.29 (td, *J*=4.6, 13.3 Hz, 1H), 1.57—2.04 (m, 6H), 2.31 (d,

$J$=13.7 Hz, 1H), 2.36 (d, $J$=13.9 Hz, 1H), 2.72 (s, 3H), 3.16 (d, $J$=13.9 Hz, 1H), 3.29 (d, $J$=14.3 Hz, 1H), 3.70 (d, $J$=14.3 Hz, 1H) 4.85 (brs, 1H), 4.98 (s, 2H), 5.01 (s, 2H), 5.50 (d, $J$=10.2 Hz, 1H), 5.71—5.78 (m, 1H), 6.75 (dd, $J$=2.9, 8.8 Hz, 1H), 6.82 (d, $J$=8.8 Hz, 1H), 6.94 (d, $J$=2.9 Hz, 1H), 7.27—7.45 (m, 10H), 7.53—7.64 (m, 3H), 7.86 (d, $J$=6.8 Hz, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 17.5, 17.8, 21.8, 25.2, 29.4, 32.1, 35.9, 37.5, 37.7, 38.8, 48.6, 65.4, 70.5, 70.8, 73.4, 112.2, 112.9, 118.1, 121.5, 127.0, 127.4, 127.6, 127.8, 128.3, 128.5, 128.8, 129.4, 130.1, 132.8, 136.1, 137.3, 137.7, 140.5, 152.0, 152.4; HR-ESI-MS $m/z$: 672.3112 (Calcd for $C_{41}H_{47}NO_4NaS$: 672.3118).

**Ketone (+)-2a** A solution of **7a** (20.9 mg, 0.032 mmol) in deoxygenated toluene (2.1 mL) was heated 120°C in a sealed tube for 5 h, cooled, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=15/1) to afford ketone (+)-**2a** (15.5 mg, 100% yield) as a white solid.

A solution of **8a** (13.8 mg, 0.021 mmol) in deoxygenated toluene (1.4 mL) was heated 120°C in a sealed tube for 5.5 h, cooled, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=15/1) to afford ketone (+)-**2a** (8.9 mg, 87% yield) as a white solid.

(+)-**2a**: $[\alpha]_D^{23}$ +0.7° ($c$=1.63, $CHCl_3$); HPLC condition: (DAICEL Chiralpak AD-H, hexane/$i$-PrOH=9/1, 254 nm, 0.5 mL/min, 99% ee ($t_R$=32.0 min)); the other structural data of (+)-**2a** were described in ref. 4.

**Ketone (−)-2a** A solution of **9a** (15.0 mg, 0.023 mmol) in deoxygenated toluene (1.5 mL) was heated 120°C in a sealed tube for 7.5 h, cooled, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=15/1) to afford ketone (−)-**2a** (10.0 mg, 90% yield) as a white solid.

A solution of **10a** (14.7 mg, 0.023 mmol) in deoxygenated toluene (1.5 mL) was heated 120°C in a sealed tube for 4.5 h, cooled, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=15/1) to afford ketone (−)-**2a** (8.9 mg, 99% yield) as a white solid.

(−)-**2a**: $[\alpha]_D^{23}$ −0.8° ($c$=1.35, $CHCl_3$); HPLC (DAISEL Chiralpak AD-H, hexane/$i$-PrOH=9/1, 254 nm, 0.5 mL/min) 99% ee ($t_R$=23.8 min); the other structural data of (−)-**2a** were described in ref. 4.

**Ketone (+)-2b** To liquid $NH_3$ (28 mL) was added sodium (72 mg, 3.12 mmol) at −78°C. After stirring for 10 min, a solution of a solution of ketone (−)-**2a** (83.9 mg, 0.175 mmol) in THF (4.4 mL) was added at −78°C. After stirring for 1.5 h at −78°C, the reaction was quenched with a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=3/2) to afford debenzyl compound **11** (21.3 mg, 40% yield) as a red oil.

To a solution of debenzyl compound **11** (21.3 mg, 0.070 mmol) in DMF was added methyl iodide (13 $\mu$L, 0.211 mmol) and potassium carbonate (59.9 mg, 0.433 mmol). After stirring for 4 h at room temperature and for 22 h at 40°C, the reaction was extracted with AcOEt. The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=10/1) to afford methyl ether **12** (5.7 mg, 40% yield) as a red oil.

To a suspension of PCC (9.0 mg, 0.042 mmol) and dried MS-3A powder (15.2 mg) in $CH_2Cl_2$ (0.3 mL) was added **12** (5.7 mg, 0.017 mmol) in $CH_2Cl_2$ (0.3 mL). This reaction mixture was stirred for 1 h at room temperature, diluted with the addition of ether, and filtered through a short column of florisil. The residue was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/$Et_2O$=3/1) to afford ketone (+)-**2b** (3.2 mg, 57% yield) as a white solid.

(+)-**2b**: $[\alpha]_D^{23}$ −3.8° ($c$=0.10, $CHCl_3$); the other structural data of (+)-**2b** was described in ref. 7.

**Ketoester (−)-13** To a solution of (+)-**2a** (538 mg, 1.12 mmol) in THF (28 mL) was added $NaN[Si(CH_3)_3]_2$ 1.0 M solution in THF (1.23 mL 1.23 mmol) at 0°C. After stirring for 20 min at 0°C, $ICH_2CO_2Et$ (0.37 mL, 3.14 mmol) was added at −78°C. After stirring overnight at −78°C, the reaction was quenched with $H_2O$. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=15/1) to afford ketoester (−)-**13** (498 mg, 80% yield) as a white solid.

(−)-**13**: $[\alpha]_D^{23}$ −62.3° ($c$=1.55, $CHCl_3$); the other structural data of (−)-**13** were described in ref. 4.

**Reduced Product (−)-14** To a solution of (−)-**13** (85.2 mg, 0.153 mmol) in $CH_2Cl_2$ (6.0 mL) was added [Ir(cod)($PCy_3$)Py] $PF_6$ (2.2 mg, 2.75 $\mu$mol). After stirring for 2 d under $H_2$ at room temperature, the solution was passed through a celite plug, eluting with AcOEt, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=5/1) to afford reduced product (−)-**14** (86.8 mg, quantitative yield) as a white solid.

(−)-**14**: $[\alpha]_D^{23}$ −18.8° ($c$=1.05, $CHCl_3$); the other structural data of (−)-**14** were described in ref. 4.

**Diketone (−)-3** To a solution of *N*,*O*-dimethylhydroxylamine (96.8 mg, 0.993 mmol) in $CH_2Cl_2$ (1.3 mL) was slowly added trimethylaluminum 1.08 M solution in hexane (1.02 mL, 1.10 mmol) at 0°C. After stirring for 30 min at 0°C, a solution of (−)-**14** (86.8 mg, 0.153 mmol) in $CH_2Cl_2$ (1.3 mL) was added dropwise at 0°C. After stirring for 1 h at 0°C, the reaction was quenched with $H_2O$. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=2/1) to afford Weinreb amide (84.3 mg, 94% yield) as a white solid.

To a solution of (*E*)-2-bromobutene (297 mg, 2.20 mmol) in $Et_2O$ (1.0 mL) was slowly dropped *t*-BuLi 1.55 M in *n*-pentane (2.72 mL, 4.22 mmol) at −78°C, then THF (2.0 mL) was added. After stirring for 40 min, a solution of Weinreb amide (214 mg, 0.367 mmol) in THF (1.0 mL) was slowly added dropwise. After 1.5 h, the reaction was quenched with MeOH, then 1 : 1 mixture of THF and a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=8/1 to 6/1 to 3/1) to afford diketone (−)-**3** (107 mg, 51% yield (82% brsm)) as a white solid, along with the recovered Weinreb amide (81 mg, 38%).

(−)-**3**: $[\alpha]_D^{23}$ −41.0° ($c$=1.09, $CHCl_3$); the other structural

data of (−)-**3** were described in ref. 4.

**Cycloadduct (+)-5 and (−)-15** To a suspension of dried $ZnCl_2$ (109 mg, 0.80 mmol) in $CH_2Cl_2$ (4.6 mL) was added vinylcyclohexene **4** (101 mg, 0.743 mmol) and a solution of (−)-**3** (107 mg, 0.186 mmol) in $CH_2Cl_2$ (7.8 mL) was slowly added at 0°C. After stirring overnight at room temperature, the reaction was quenched with a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/diisopropyl ether=20/1 to 15/1 to 10/1) to afford major product (+)-**5** (103 mg, 78% yield) as a white solid and minor product (−)-**15** (15.9 mg, 12% yield) as a white solid.

(+)-**5**: $[\alpha]_D^{23}$ +2.5° (*c*=0.65, $CHCl_3$); (−)-**15**: $[\alpha]_D^{23}$ −25.9° (*c*=1.19, $CHCl_3$); the other structural data of (+)-**5** and (−)-**15** were described in ref. 4.

**MOM Ether (+)-16** To a suspension of lithium aluminum hydride (85.2 mg, 2.25 mmol) in $Et_2O$ (16 mL) was added a solution of (+)-**5** (292 mg, 0.408 mmol) in $Et_2O$ (17 mL) at 0°C. After stirring for 15 min, the reaction was quenched with $H_2O$ and a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=8/1 to 6/1) to afford alcohol (248 mg, 85% yield) as a white amorphous.

To a solution of alcohol (248 mg, 0.345 mmol) in $CH_2Cl_2$ (34.5 mL) were added *i*-$Pr_2NEt$ (2.1 mL, 12.1 mmol), NaH (30.1 mg, 0.690 mmol, 55%), and MOMCl (210 $\mu$L, 2.76 mmol) in order at 0°C. After stirring overnight at room temperature, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with $CH_2Cl_2$. The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=8/1) to afford (+)-**16** (233 mg, 88% yield) as a white amorphous.

(+)-**16**: $[\alpha]_D^{23}$ +18.9° (*c*=0.62, $CHCl_3$); the other structural data of (+)-**16** were described in ref. 4.

**MOM Ether (+)-17** To a solution of (+)-**16** (64.3 mg, 0.0841 mmol) in THF (6.2 mL) was slowly added *n*-butyl lithium 1.42 M solution in hexane (83 $\mu$L, 0.126 mmol) at 0°C. After stirring for 20 min, Carbon disulfide (152 $\mu$L, 2.52 mmol) was added at 0°C. After stirring for 5 min, methyl iodide (79 $\mu$L, 1.26 mmol) was added at 0°C. After stirring for 30 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with $Et_2O$. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=8/1) to afford xanthate (127 mg, 91% yield) as a white amorphous.

To a solution of xanthate (58.3 mg, 0.068 mmol) in toluene (2.4 mL) was added tributyltin hydride (74 $\mu$L, 0.273 mmol) and azobisisobutyronitrile (22.4 mg, 0.137 mmol). After stirring for 30 min at 90°C, the reaction was quenched with $H_2O$. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=15/1) to afford MOM ether (+)-**17** (31.9 mg, 63% yield) as a white amorphous.

(+)-**17**: White amorphous; $[\alpha]_D^{23}$ +31.0° (*c*=0.92, $CHCl_3$); the other structural data of (+)-**17** were described in ref. 4.

**Ketone (+)-18** To a solution of (+)-**17** (25.9 mg, 0.035 mmol) in $CH_2Cl_2$ (8.7 mL) was added bromocatecolborane 0.2 M solution in $CH_2Cl_2$ (226 $\mu$L, 0.045 mmol) dropwise at −78°C. After stirring for 1 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and 0.2 M aqueous solution of NaOH. The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with a 0.2 M aqueous solution of NaOH and $H_2O$, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=40/1 to 30/1) to afford alcohol (11.9 mg, 49% yield (brsm 92%)) as a white amorphous, along with the recovered (+)-**17** (12.2 mg, 47%).

To a solution of alcohol (17.7 mg, 0.025 mmol) in $CH_3CN$ (1.6 mL), dry MS 3A (63.6 mg) was added *N*-methylmorpholine oxide (4.4 mg, 0.038 mmol), and tetra-*n*-propylammonium perruthenate (2.7 mg, 0.008 mmol). After stirring for 6 h at room temperature, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was filtered on florisil and silica gel, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=30/1) to afford ketone (+)-**18** (17.6 mg, quantitative yield) as a white amorphous.

(+)-**18**: $[\alpha]_D^{23}$ +29.8° (*c*=1.48, $CHCl_3$); the other structural data of (+)-**18** were described in ref. 4.

***Exo*-methylene (+)-19** To a suspension of zinc (889 mg, 13.6 mmol) and lead chloride (33.6 mg, 0.120 mmol) in THF (6.9 mL) was added $CH_2I_2$ (610 $\mu$L, 7.57 mmol). After stirring for 30 min, lead chloride (33.6 mg, 0.120 mmol) was add again. After stirring for 30 min, $TiCl_4$ 1.0 M solution in $CH_2Cl_2$ (1.66 mL, 1.66 mmol) was slowly added to the mixture at 0°C. After warming up to room temperature, the resulting mixture was stirred for 1 h to afford a solution of $CH_2I_2$–Zn–$TiCl_4$ reagent.

To a solution of (+)-**18** (29.2 mg, 0.042 mmol) in THF (270 $\mu$L) was added the $CH_2I_2$–Zn–$TiCl_4$ reagent at 0°C. After stirring for 4 d at room temperature, $Et_3N$ (2.6 mL) was added in one portion to the reaction mixture at 0°C and the solution was stirred for 20 min at room temperature. The solution was passed through a celite plug, eluting with AcOEt, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=35/1 to 25/1) and PTLC (hexane/AcOEt=10/1) to afford (+)-**19** (9.7 mg, 33% yield (54% brsm)) as a white amorphous, along with the recovered (+)-**18** (11.2 mg, 38%).

(+)-**19**: $[\alpha]_D^{23}$ +27.2° (*c*=0.64, $CHCl_3$); the other structural data of (+)-**19** were described in ref. 4.

**Disulfate (+)-1** To a solution of naphthalene (513 mg, 4.0 mmol) in THF (10 mL) was added lithium (28 mg, 4.03 mmol) at room temperature. The mixture was stirred at that temperature for 2 h to afford a solution of lithium naphthalenide.

A portion of the solution of lithium naphthalenide (550 $\mu$L, 0.220 mmol, 0.4 M in THF) was added dropwise to a solution of (+)-**19** (9.7 mg, 0.014 mmol) in THF (400 $\mu$L) at −20°C. After stirring for 1 h, the reaction was quenched with a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with $Et_2O$. The combined organic layer was washed with

brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/AcOEt=10/1 to 6/1 to 5/1) to afford debenzyl compound (6.0 mg) as a yellow oil.

To a suspension of debenzyl compound (6.0 mg) in pyridine (260 $\mu$L) was added $SO_3$·Py (18.4 mg, 0.116 mmol) and the reaction mixture was heated to 80°C for 4 h. The reaction mixture was cooled to 0°C, and a saturated aqueous solution of $Na_2CO_3$ (1.5 mL) was added dropwise. After stirring for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$/$CH_3OH$=5/1 to 2/1) to afford disulfate (+)-**1** (6.4 mg, 64% yield for the 2 steps) as a white amorphous.

(+)-**1**: $[\alpha]_D^{23}$ +17.2° ($c$=0.43, MeOH); The other structural data of (+)-**1** were described in ref. 4.

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