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An Asymmetric Synthesis of the Aromatic Fragment of Sespendole

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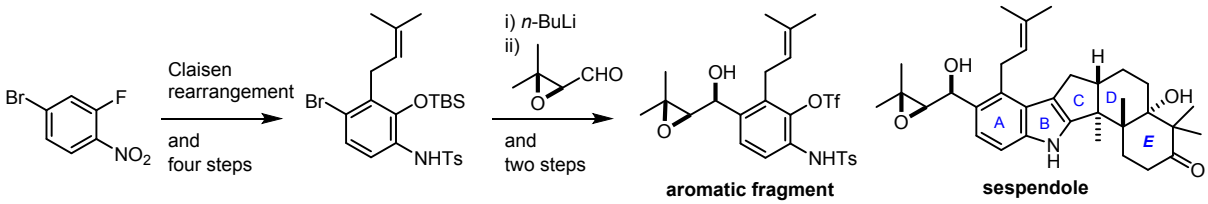
Abstract: Sespendole is an indole sesquiterpene alkaloid bearing two isoprenyl groups, one of which is highly oxidized. Herein, we disclose an eight-step synthesis of the aromatic fragment of sespendole in optically pure form, starting from 4-bromo-2-fluoronitrobenzene. The key steps were a Claisen rearrangement at room temperature for introduction of the prenyl group, and a coupling between the dianion generated from prenylated bromo-*N*-tosylanilide and a chiral epoxy aldehyde.



Key words: natural product synthesis, sespendole, epoxy aldehyde, Claisen rearrangement, isoprenyl group

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INTRODUCTION

Sespendole **1** (**Figure 1**), was isolated by Ōmura and co-workers in 2006 from *Pseudobotrytis terrestris* FKA-25,[1] and determined to contain a sesquiterpene indole core structure bearing two isoprenyl units on the benzene of the indole nucleus, one of which is highly oxygenated.[2] Determination of the relative stereochemistry of the side chain was difficult by spectroscopic methods; we assigned the *syn* relationship by stereoselective synthesis of two possible diastereomers of the indole moiety and comparison of their NMR spectra with those of the natural product.[3] Sespendole was found to be a potent inhibitor of lipid droplet synthesis in macrophages, which leads to arteriosclerosis.[4] However, its mechanism of action was reported to be different from that of terpendole C,[5] a structurally similar diterpene indole, which was reported to inhibit acyl-CoA cholesterol acyltransferase (ACAT) and acyl-CoA synthase (ACS).[4,6] Despite the intriguing nature of its structure and important biological activity, a total synthesis of sespendole has not been reported, although

the syntheses of structurally related terpene indole alkaloids have been extensively investigated.[7] Due to our ongoing interest in the structure and biological activity of these natural products, we have undertaken synthetic studies of sespendole in order to elucidate the importance of the isoprenyl groups of the indole nucleus, and the molecular mechanism of its action.

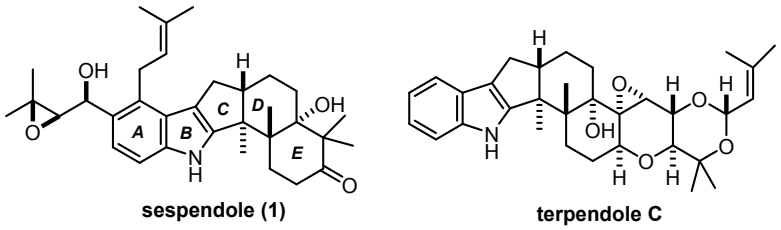
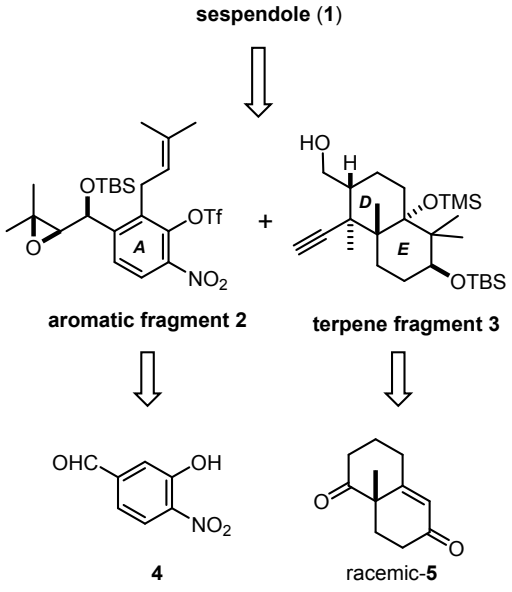


Figure 1. Structures of sependole (**1**) and terpendole C

RESULTS AND DISCUSSION

Our convergent synthetic plan of sespendole is depicted in **Scheme 1**. It relies on our previously reported racemic syntheses of the aromatic fragment **2**[3] and terpene fragment **3**[8] starting from 3-hydroxy-4-nitrobenzaldehyde (**4**) and Wieland Miescher's ketone (**5**), respectively. This paper describes a new synthetic route of the optically active aromatic fragment necessary for total synthesis of sespendole.

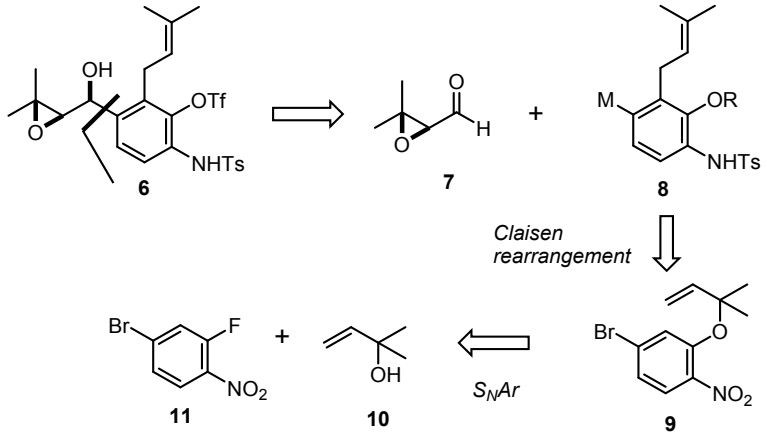


Scheme 1. A synthetic plan for sespendole

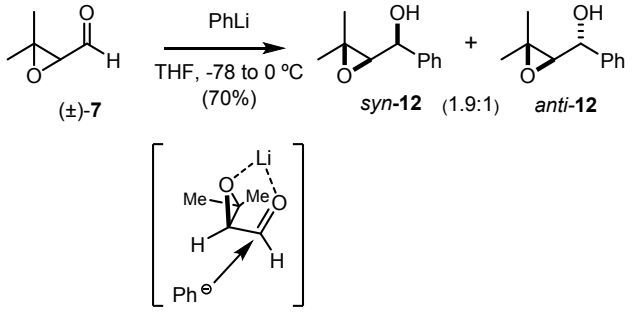
Due to the concise and highly diastereoselective nature of the racemic synthesis of aromatic fragment **2** (10 steps from **4**, a commercially available material), we initially improved the synthetic route, and attempted the asymmetric synthesis of several intermediates used therein.

Unfortunately, all of our attempts to introduce chirality, including kinetic resolution of an allylic alcohol intermediate by either Sharpless asymmetric epoxidation or acylation by various lipases; CBS reduction; or asymmetric epoxidation of an enone intermediate, were unsuccessful (for the details, see SI).

Accordingly, we designed a new synthetic plan, **Scheme 2**: The two contiguous stereogenic centers of a new aromatic fragment **6** would be established by coupling of the known enantiopure (>99% ee) epoxyaldehyde **7**[9] with the functionalized aryl metal **8**. In general, addition of organometallic reagents to epoxy aldehydes gives a diastereomeric mixture of products in moderate *anti*-stereoselectivities, an observation that can be explained by the Felkin-Anh model.[10,11] However, in our preliminary experiments using epoxy aldehyde **7** and phenyllithium, a moderate *syn* stereoselectivity (*syn*-**12**:*anti*-**12** = 1.9:1) was observed,[12] perhaps due to chelation control[13] (**Scheme 3**). We therefore anticipated the same stereopreference in the coupling between **7** and the aryl metal **8**, which we planned to obtain by aromatic nucleophilic displacement (S_NAr mechanism) of 4-bromo-2-fluoronitrobenzene (**11**) with 2-methylbut-3-en-2-ol (**10**) to give **9**, followed by a Claisen rearrangement and metal-halogen exchange.

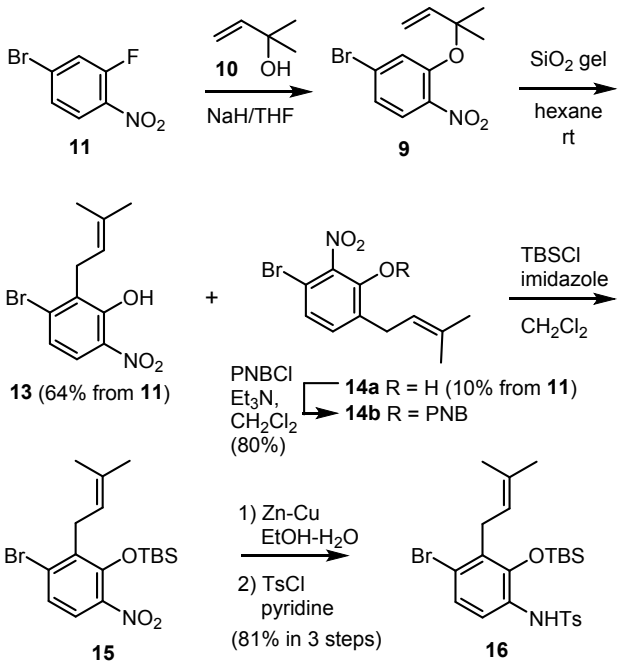


Scheme 2. An alternative plan for the asymmetric synthesis of aromatic fragment **6**

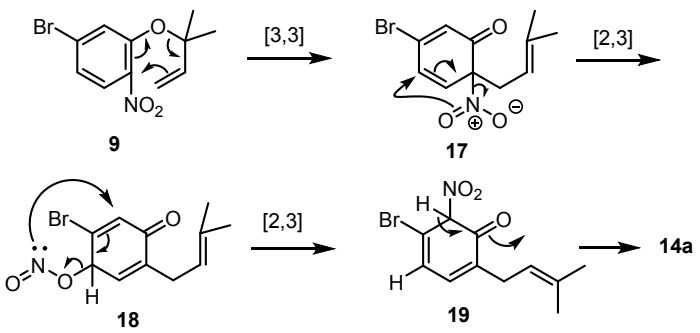


Scheme 3. Model experiments for the construction of the side chain of sespendole

Reaction of 4-bromo-2-fluoronitrobenzene (**11**) with the sodium alkoxide of 2-methylbut-3-en-2-ol (**10**) gave **9** (**Scheme 4**). During silica gel column chromatography of **9**, we unexpectedly found that the rearrangement occurred at room temperature to give the desired product **13** and unusual by-product **14a**. We thus investigated the conditions for the silica gel-mediated Claisen rearrangement, and found that the use of hexane suspended with silica gel was the most efficient, giving **13** and **14a** in 64% and 9% yield from **11** in two steps.[14] The structure of **14a** was initially elucidated by spectroscopic analysis, and later confirmed by X-ray crystallographic analysis of the corresponding *p*-nitrobenzoate **14b**.[15] A possible mechanism from **9** to **14a** is shown in **Scheme 5**. When the Claisen rearrangement occurs at the position substituted with nitro group, the nitro group of the resulting intermediate **17** undergoes a [2,3] sigmatropic rearrangement to give **18**, which undergoes a second [2,3] sigmatropic rearrangement to give **19**, aromatization of which results in by-product **14a**.[16] The desired product **13** of the Claisen rearrangement was transformed to **16** in three steps comprising protection of the phenol with a TBS group, reduction of the nitro group with Zn-Cu couple, and protection of the resulting aniline with a tosyl group.

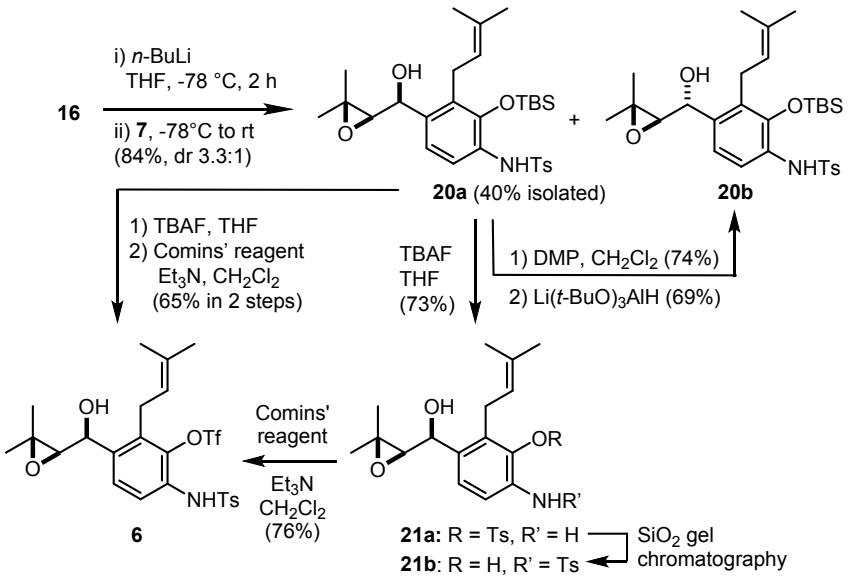


Scheme 4. Synthesis of bromide **16**



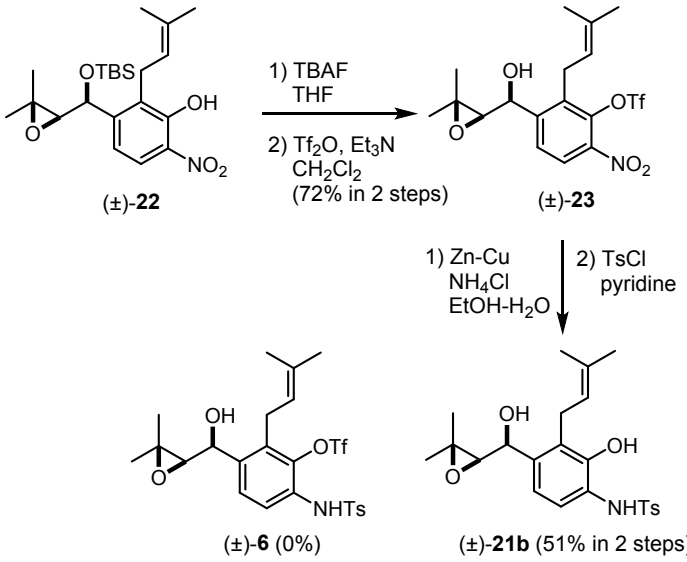
Scheme 5. A proposed mechanism of formation of byproduct **14a** from **9**

The synthesis of aromatic fragment **6** by the coupling of bromide **16** and chiral epoxy aldehyde **7** (>99% ee) was next investigated (**Scheme 6**). Compound **16** was treated with 2.5 equivalents of *n*-BuLi in THF at -78 °C for 2 hours to generate the corresponding dianion, which was reacted with freshly distilled epoxy aldehyde **7**[17] at -78 °C to give a 84% yield of 3.3:1 diastereomeric mixture of **20a** and **20b** as anticipated.[18] The stereoselectivity was slightly higher than that of the model experiment, probably due to the increased steric hindrance of the dianion derived from **16** relative to phenyllithium. Although chromatographic separation of this mixture of stereoisomers was difficult, pure **20a** could be obtained in 40% isolated yield by crystallization from ether. Dess-Martin periodinane (DMP) oxidation of a mixture of **20a** and **20b** followed by reduction of the resulting ketone with Li(*t*-BuO)$_3$AlH gave **20b** as a single product in 69% yield, which may be useful for synthesis of a diastereomeric analogue of sespendole in a future SAR study. Deprotection of the TBS group of the desired diastereomer **20a** with TBAF was followed by triflation with Comins' reagent and Et_3N furnished triflate **6**, an optically active aromatic fragment of sespendole. Careful TLC analysis of a series of the reactions revealed that the first product of the deprotection of the TBS was tosylate **21a**, which readily underwent *O* to *N* migration of the Ts group to provide tosylamide **21b** under the conditions of the next triflation,[19] or silica gel chromatography of **21a**.[20]



Scheme 6. Synthesis of **6**, aromatic fragment, by coupling between **16** and **7**

To confirm the *syn*-configuration of **6**, we initially planned to convert our previously reported *syn* epoxy alcohol (±)-**22** to racemic **6** and compare the spectral data (**Scheme 7**).[21] Deprotection of TBS group of (±)-**22** followed by triflation yielded **23**; however, subsequent reduction of the nitro group with Zn-Cu and tosylation in pyridine[22] did not provide the desired **6**, but instead **21b** was obtained in 51% yield in two steps based on ^{1}H- and ^{19}F-NMR analyses of the crude product.[23] Thus, the *syn*-configuration of the epoxide moiety was confirmed by comparison of NMR spectra of chiral and the racemic **21b**.



Scheme 7. Synthesis of (±)-**21b** from known *syn* epoxy alcohol (±)-**22**

CONCLUSION

In summary, we have developed an eight-step synthesis of the aromatic fragment **6** of

sespendole from **11**, a commercially available starting material, in optically pure form. This new synthesis is strategically different and more concise than the racemic synthesis we previously reported. The key steps are a room temperature Claisen rearrangement and *syn* selective addition reaction of the highly functionalized aryl lithium to epoxy aldehyde **7**. In the course of this synthetic study, an unusual product of the Claisen rearrangement was identified and a mechanism for its formation is proposed. This new route is expected to enable easy access to both sespendole and a variety of its analogs; and studies towards these goals are currently underway.

EXPRIMENTAL SECTION

General Experimental Methods: Melting points (mp) were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra (IR) were recorded on a JASCO FT/IR-4100 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts of all compounds are reported in ppm relative to the residual, undeuterated solvent ($CDCl_3$ as $\delta = 7.26$). ^1H NMR data are reported as follows; chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broadened, m = multiplet), coupling constant, and assignment. Carbon nuclear magnetic resonance ($^{13}C\{^1H\}$ NMR) spectra were recorded on a Bruker Avance-400 (100 MHz) spectrometer. Chemical shifts are reported in ppm relative to the residual undeuterated solvent ($CDCl_3$ as $\delta = 77.0$). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker Avance-400 (376 MHz) spectrometer. Chemical shifts of all compounds are reported in ppm in a scale relative to $C_6H_6CF_3$ as an external standard ($\delta = -63.7$). ^{19}F NMR data are reported as follows; chemical shift, integration, multiplicity (s = singlet). All NMR spectra were measured at 300 K. High-resolution mass spectra (HRMS) were recorded on an Applied Biosystems Mariner ESI-TOF spectrometer for ESI-MS and reported in *m/z*. Elemental analyses were performed by the Analytical Laboratory of Graduate School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin layer chromatography (TLC) on 0.25 mm silica gel coated glass plates $60F_{254}$ (Merck, #1.05715.0001) and visualized with UV light (254 nm) and an appropriate reagent (7% ethanolic phosphomolybdic acid, *p*-anisaldehyde solution in H_2SO_4/AcOH/EtOH, ninhydrin solution in *n*-BuOH/H_2O/H_2SO_4) followed by heating. For open column chromatography, silica gel 60 (particle size 0.063-0.200 mm, Merck, #1.07734.9025) was used. For flash column chromatography, silica gel 60 (spherical, particle size 0.04-0.05 mm, Kanto, #37562-84) was used. Dry THF and CH_2Cl_2 were purchased from Kanto chemical Co.,

Inc. Celite (Hyflo Super-Cel®) was purchased from Nacalai Tesque Co., Inc. All other commercially available reagents were used as received. All moisture sensitive reactions were carried out using flame-dried flask under an argon or nitrogen atmosphere.

***syn*- and *anti*-(3,3-Dimethyloxiran-2-yl)(phenyl)methanol (*syn*-12 and *anti*-12).** Phenyllithium (1.6 M in *n*-Bu_2O, 0.90 mL, 1.4 mmol) was added to a stirred solution of epoxy aldehyde **7** (145 mg, 1.44 mmol) in dry THF (2 mL) at -78 °C over 30 min. The mixture was stirred for 30 min, warmed to 0 °C, stirred for another 30 min, and then diluted with ice-cold sat. NH_4Cl solution. The aqueous layer was separated and extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 5 g, EtOAc/hexane 1:10 to 1:5) to give a 1.9:1 diastereomeric mixture of **12** (180 mg, 70%) as a colorless solid. **12** (*syn: anti* = 1.9:1): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.31 (2H, s), 1.37 (1H, s), 1.45 (2H, s), 1.51 (1H, s), 2.95 (1/3H, d, J = 8.5 Hz), 2.98 (2/3H, d, J = 8.5 Hz), 4.57 (1H, d, J = 8.5 Hz), 7.30-7.47 (5H, m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 18.9, 19.7*, 24.8, 24.9*, 59.7, 60.1*, 66.5, 68.0*, 72.4, 72.6*, 126.0, 126.0*, 128.1, 128.1*, 128.6, 128.7*, 140.1*, 141.5 (signals of the major *syn*-**12** are indicated as *mark.) HR-MS (ESI, positive): calcd. For $C_{11}H_{14}NaO_2$ (M+Na), 201.0886; Found 201.0891. The NMR data were in good agreement with those of literature.[12]

3-Bromo-6-(3-methylbut-2-en-1-yl)-2-nitrophenyl 4-nitrobenzoate (14b). PNBCl (96.4 mg, 0.520 mmol) was added to a solution of **14a** (97.1 mg, 0.339 mmol) and Et_3N (150 μL, 1.02 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under argon at room temperature and stirred. After 10 min, the mixture was diluted with sat. $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in *vacuo.* The residue was purified by column chromatography (silica gel 10 g, CH_2Cl_2/hexane 1:5) to give **14b** (115.7 mg, 80%) as a white solid. **14b:** mp: 79-84 °C. IR (film): ν_{max} (cm^{-1}) 1758, 1542, 1349, 1240, 1056, 1013. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.54 (3H, s), 1.68 (3H, s), 3.25 (2H, d, J = 7.0 Hz), 5.17 (1H, m), 7.33 (1H, d, J = 8.5 Hz), 7.57 (1H, d, J = 8.5 Hz), 8.30 (2H, brd, J = 8.5 Hz), 8.37 (2H, brd, J = 8.5 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 17.8, 25.6, 28.8, 111.2, 119.2, 123.9, 131.5, 131.6, 132.5, 132.8, 135.6, 136.3, 141.2, 145.1, 151.3, 161.6. Anal. Calcd for $C_{18}H_{15}BrN_2O_6$: C, 49.67; H, 3.47; N, 6.44. Found: C, 49.58; H, 3.55; N, 6.21.

3-Bromo-2-(3-methylbut-2-en-1-yl)-6-nitrophenol (13) and 3-bromo-6-(3-methylbut-2-en-1-yl)-2-nitrophenol (14a). 2-Methyl-3-buten-2-ol (**10**) (3.60 mL, 34.1 mmol) was added portion-wise over 10 min to a stirred suspension of 60% NaH (1.86 g, 47.0 mmol) in dry THF (30 mL) at room temperature. The mixture was refluxed for 30 min, cooled to 0 °C, diluted with a solution of 4-bromo-2-fluoronitrobenzene (**11**) (5.01 g, 22.8 mmol) in dry THF (15 mL) (added dropwise), and then stirred for 3 h at room temperature. The mixture was then diluted with ice-cold sat. $NaHCO_3$ solution and NaOH (1 N) solution; the aqueous layer was separated and extracted with EtOAc (100 mL × 5), and the combined organic extracts washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was used for the next reaction without purification. Silica gel (42.3 g, Silica gel 60 (particle size 0.063-0.200 mm, Merck, #1.07734.9025)) was added to a solution of the crude product **9** (6.90 g) in hexane (230 mL). After being stirred vigorously at rt for 12 h, the reaction mixture was filtered through a sintered glass funnel. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 100 g, CH_2Cl_2/hexane 1:10 to 1:5) to give **13** (4.14 g, 64% in 2 steps) as a yellow solid and **14a** (651 mg, 10%) as a yellow oil. **13:** mp: 84-85 °C. IR (film): ν_{max} (cm^{-1}) 2968, 2962, 2361, 1602, 1430, 1268, 1210, 1163, 937. ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.70 (3H, d, J = 1.0 Hz), 1.82 (3H, s), 3.61 (2H, d, J = 7.0 Hz), 5.13 (1H, m), 7.17 (1H, d, J = 9.0 Hz), 7.82 (1H, d, J = 9.0 Hz), 11.16 (1H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 18.2, 25.7, 29.3, 119.1, 122.9, 124.1, 132.7, 132.8, 133.9, 134.2, 153.8. Anal. Calcd for $C_{11}H_{12}BrNO_3$: C, 46.18; H, 4.23; N, 4.90. Found: C, 46.43; H, 4.14; N, 4.74. **14a:** IR (film): ν_{max} (cm^{-1}): 2913, 1590, 1539, 1233, 890. ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.71 (3H, s), 1.76 (3H, s), 3.35 (2H, d, J = 7.5 Hz), 5.26 (1H, m), 7.17 (1H, d, J = 8.0 Hz), 7.21 (1H, d, J = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 17.8, 25.7, 28.3, 113.1, 119.9, 126.2, 131.7, 134.4, 135.2, 135.9, 152.6. HR-MS (ESI, positive): calcd. For $C_{11}H_{13}BrNO_3$ (M+H), 286.0073; Found 286.0079.

***N*-(4-Bromo-2-((*tert*-butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)phenyl)-4-methylbenzenesulfonamide (16).** Imidazole (6.50 g, 36.1 mmol) and TBSCl (4.48 g, 43.2 mmol) were added to a solution of **13** (4.14 g, 14.4 mmol) in CH_2Cl_2 (150 mL) at room temperature and stirred. After 2 h, the mixture was diluted with water (150 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (100 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was used for the next reaction without purification. Zn-Cu (8.69 g) was added to a mixture of crude **15** (10.8 g) and NH_4Cl (36.6 g) in EtOH (400 mL) and water (80 mL) at room temperature. The mixture was

stirred vigorously for 12 h and filtered through a pad of Celite. The filtrate was concentrated to remove EtOH and some of the water. The residue was suspended with EtOAc (500 mL) and filtered through a pad of Celite. The filtrate was washed with brine and evaporated. The residue was used for the next reaction without purification. TsCl (8.32 g, 43.2 mmol) was added to a solution of crude product (5.56 g) in pyridine (140 mL), portion-wise, at room temperature. The mixture was stirred. After 15 h, ice-cold water and then toluene were added, and the mixture concentrated *in vacuo*. The residue was dissolved in water and EtOAc, and then extracted with EtOAc (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 100 g, EtOAc/hexane 1:5) to give **16** (6.12 g, 81% in 3 steps) as a brown oil. **16:** IR (film): ν_{max} (cm^{-1}) 3385, 3118, 2962, 2361, 1951, 1728, 1685, 1608, 1524, 1469. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.21 (6H, s), 1.03 (9H, s), 1.64 (3H, s), 1.66 (3H, s), 2.39 (3H, s), 3.34 (2H, d, J = 6.0 Hz), 4.83 (1H, m), 6.70 (1H, s) 7.11 (1H, d, J = 9.0 Hz), 7.16 (1H, d, J = 9.0 Hz), 7.23 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) -3.6, 18.2, 18.5, 21.5, 25.6, 25.8, 29.9, 117.8, 120.0, 121.0, 126.5, 127.2, 128.3, 129.6, 132.6, 133.0, 136.2, 143.4, 144.0. Anal. Calcd. for $C_{24}H_{34}BrNO_3SSi$: C, 54.95; H, 6.53; N, 2.67. Found: C, 54.95; H, 6.54; N, 2.66.

Preparation of enantiomerically pure epoxy aldehyde 7 in 4 steps as follows (The scheme is given as Scheme S7 in the Supporting Information):

1. Synthesis of (2R)-3,3-dimethyl-2-oxiranemethanol. A flame-dried 500 mL round-bottomed flask fitted with a thermometer was charged with powdered activated molecular sieves 4A (5.04 g) and dry CH_2Cl_2 (300 mL). 3-Methyl-2-buten-1-ol (15.0 ml, 149 mmol) was added to the suspension of *D*-(−)-DIPT (1.80 mL, 8.91 mmol) and Ti(O-*i*-Pr)$_4$ (2.10 mL, 7.43 mmol) at -30 °C and stirred. After 20 min, TBHP (5.05 M toluene solution, 30.0 mL, 152 mmol) was added over 30 min and stirring was continued for 2 h. Bu_3P (7.20 mL, 29.6 mmol) was then added to quench TBHP at -30 °C. Anhydrous citric acid (1.52 g, 14.8 mmol) and Et_2O (200 mL) were added to the reaction mixture at room temperature. The mixture was vigorously stirred for 30 min, then filtered through filter paper under reduce pressure to remove the molecular sieves. The filtrate was evaporated. The same scale synthesis of (2*R*)-3,3-dimethyl-2-oxiranemethanol was conducted three times by the same procedure. These crude products were combined and then purified by column chromatography (silica gel 200 g, EtOAc/ hexane 1:5 to 1:1) to give (2*R*)-3,3-dimethyl-2-oxiranemethanol (28.8 g, 75%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.31 (3H, s), 1.34 (3H, s), 2.04 (1H, brs), 2.97 (1H, dd, J = 6.5, 4.5 Hz), 3.67 (1H, dd, J = 12.0, 6.5 Hz), 3.83 (1H, d, J = 12.0 Hz). This NMR data matches that of the following literature.[9b]

2. p-Nitrobenzoylation of (2R)-3,3-dimethyl-2-oxiranemethanol. **((*R*)-(3,3-dimethyloxiran-2-yl)methyl 4-nitrobenzoate.** PNBCl (58.2 g, 314 mmol) was added portion-wise over 15 min to a solution of (2*R*)-3,3-dimethyl-2-oxiranemethanol (28.8 g, 282 mmol) and Et_3N (120 mL, 861 mmol) in dry CH_2Cl_2 (800 mL) at 0 °C and stirred. After being stirred at the same temperature for 10 min, sat. $NaHCO_3$ solution was poured into the reaction mixture at 0 °C. The mixture was extracted with CH_2Cl_2 (800 mL x 3). The combined extracts were evaporated. EtOAc (200 mL) was added to the residue and the suspension was filtered through a pad of Super-Cel® under reduce pressure to remove insoluble salts. The filtrate was diluted with water and extracted with EtOAc (100 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness in *vacuo.* The residue was dissolved in Et_2O and the solution was cooled at -30 °C to give [(2*R*)-3,3-dimethyloxiran-2-yl]methyl 4-nitrobenzoate (22.9 g, 32%, 99% ee) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis with chiral HPLC column (DAICEL CHIRALCEL, IC, 50% 2-propanol in hexane, 1.0 mL/min). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.39 (6H, s), 3.15 (1H, dd, J = 7.0, 4.0 Hz), 4.30 (1H, dd, J =12.0, 7.0 Hz), 4.66 (1H, dd, J = 12.0, 4.0 Hz), 8.24 (2H, brd, J = 9.0 Hz) 8.30 (2H, d, J = 9.0 Hz). This NMR data matches that of the following literature.[9a]

3. Synthesis of (2R)-3,3-dimethyl-2-oxiranemethanol. Sat. NH_3 in MeOH solution (250 mL) was added to a solution of [(2*R*)-3,3-dimethyloxiran-2-yl]methyl 4-nitrobenzoate (22.9 g, 91.1 mmol) in dry THF (250 mL) at room temperature. After being stirred for 28 h at the same temperature, the reaction mixture was concentrated. The residue was diluted with MeOH. Insoluble material was filtered through filter paper under reduce pressure. The same procedure was repeated twice. The filtrate was purified by column chromatography (silica gel 300 g, EtOAc/hexane 1:5 to 1:1) to give (2*R*)-3,3-dimethyl-2-oxiranemethanol (7.62 g, 82%) as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.30 (3H, s), 1.34 (3H, s), 2.97 (1H, dd, J = 6.0, 4.5 Hz), 3.67 (1H, m), 3.82 (1H, m). This NMR data matches that of the following literature[9b]

4. Oxidation of (2R)-3,3-dimethyl-2-oxiranemethanol. Et_3N (42.0 mL, 297 mmol) and DMSO (21.0 mL, 297 mmol) was added to a solution of (2*R*)-3,3-dimethyl-2-oxiranemethanol (7.62 g, 74.6 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C. After stirring for 10 min, SO_3 pyridine complex (21.5 g, 135 mmol) was added at same temperature. After stirring for 30 min, the reaction was quenched with sat. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (200 mL x 3). The combined organic layer was washed with 3% $CuSO_4$ solution (50 mL x 5) and brine. The mixture was stirred with anhydrous Na_2SO_4 for 1 h, filtered and evaporated. The crude product was distilled under reduced pressure (52 mmHg, 50 °C) to give **7** (1.55 g, 21%). **7:** ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34 (3H, s), 1.37 (3H, s), 3.10 (1H, d, J = 5.0 Hz), 9.36 (1H, d, J = 5.0 Hz). This NMR data matches that of the following literature.[9b]

_N_-(2-((*tert*-butyldimethylsilyl)oxy)-4-((*S*)-((*R*)-3,3-dimethyloxiran-2-yl)(hydroxy)methyl)-3-(3-methylbut-2-en-1-yl)phenyl)-4-methylbenzenesulfonamide (20a) and _N_-(2-((*tert*-butyldimethylsilyl)oxy)-4-((*R*)-((*R*)-3,3-dimethyloxiran-2-yl)(hydroxy)methyl)-3-(3-methylbut-2-en-1-yl)phenyl)-4-methylbenzenesulfonamide (20b). *n*-BuLi (2.60 M in hexane; 5.0 mL, 13.0 mmol) was added to a solution of **16** (2.69 g, 5.11 mmol) in dry THF (50 mL) at -78 °C under positive pressure of argon. The mixture was stirred at -78 °C for 2 h, and then freshly distilled **7** (1.50 mL, 1.55 g, 15.5 mmol) was added. Stirring was continued for 30 min. The reaction mixture was allowed to warm to 0 °C over 30 min; and then left to warm to room temperature, with stirring. After 30 min, the reaction was quenched with sat. NH_4Cl solution and the mixture extracted with EtOAc (200 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 60 g, EtOAc/hexane 0:1 to 1:5 to 1:2) to give a 3.3:1 diastereomeric mixture of **20a** and **20b** (2.34 g, 84%) as a brown solid. The residue was dissolved in Et_2O and the solution was kept at 0 °C for 15 min to give **20a** (1.12 g, 40%) as a white solid. **20a:** mp: 141-143 °C. $[\alpha]_D^{28}$ +7.0 (c 1.05, $CHCl_3$). IR (film): ν_{max} (cm^{-1}) 3385, 2930, 2858, 2360, 1460, 1434, 1385, 1335, 1292, 1263, 1201, 1163, 1091, 1005. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.19 (3H, s), 0.22 (3H, s), 1.03 (9H, s), 1.21 (3H, s), 1.30 (3H, s), 1.62 (6H, s), 2.38 (3H, s), 3.06 (1H, d, J = 6.5 Hz), 3.24 (1H, dd, J = 16.0, 6.0 Hz), 3.39 (1H, dd, J = 16.0, 6.0 Hz), 4.56 (1H, dd, J = 6.5, 3.5 Hz), 4.80 (1H, m), 6.79 (1H, s) 7.04 (1H, d, J = 8.5 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.29 (1H, d, J = 8.5 Hz), 7.70 (2H, d, J = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) -3.6, -3.5, 18.0, 18.6, 19.0, 21.5, 24.7, 25.4, 25.5, 25.9, 59.8, 67.4, 68.7, 116.6, 120.8, 123.1, 127.3, 128.7, 129.6, 131.4, 132.4, 136.0, 136.6, 142.5, 143.9. Anal. Calcd for $C_{29}H_{43}NO_5SSi$: C, 63.82; H, 7.94; N, 2.57. Found: C, 63.83; H, 7.98; N, 2.50.

***Synthesis of pure 20b*.** Dess-Martin Periodinane (98.2 mg, 0.232 mmol) was added to a solution of a diastereomeric mixture (*syn*:*anti* = 1:1) of **20a** and **20b** (98.5 mg, 0.180 mmol) in CH_2Cl_2 (2 mL) at room temperature and the mixture stirred. After 3 h, saturated aqueous $NaHCO_3$ solution was added. The mixture was extracted with EtOAc (30 mL × 3) and the combined extracts washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 5 g, EtOAc/hexane 1:10) to give epoxyketone (72.6 mg, 74%) as a colorless oil. Epoxyketone: $[\alpha]_D^{28}$ -27.0 (c 1.00, $CHCl_3$). IR (film): ν_{max} (cm^{-1}) 2958, 2931, 2859, 2362, 1696, 1590, 1485, 1473, 1438, 1390, 1339, 1305, 1293, 1265, 1243, 1339, 1306, 1293, 1265, 1243, 1163, 1091, 905, 870, 838, 813. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.21 (3H,s), 0.23 (3H, s), 1.05 (9H, s), 1.24 (3H, s), 1.50 (3H, s), 1.55 (3H, s), 1.57 (3H, s), 2.39 (3H, s), 3.44 (1H, dd, J = 15.5, 5.0 Hz), 3.68(1H, dd, J = 15.5, 7.5 Hz), 3.69 (1H, s), 4.84 (1H, m), 7.05 (1H, brs), 7.12 (1H, d, J = 8.5 Hz), 7.26 (2H, d, J = 8.5 Hz), 7.31

(1H, d, J = 8.5 Hz), 7.75 (2H, d, J = 8.5 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) -3.70, -3.60, 18.0, 18.3, 18.5, 21.5, 24.4, 25.4, 25.7, 25.8, 61.6, 65.5, 114.0, 122.6, 123.6, 127.2, 129.8, 132.4, 132.4, 133.0, 134.2, 136.3, 142.4, 144.3, 196.8. HR-MS (ESI, positive); calcd. For $C_{29}H_{41}NNaO_5SSi$ (M+Na), 566.2367; Found 566.2365. $LiAlH(OtBu)_3$ (1.0 M in THF, 300 μL, 0.30 mmol) was added to a solution of epoxyketone (55.5 mg, 0.102 mmol) in THF (2 mL) at -78 °C under a positive pressure of argon and the mixture stirred. After 6 h, saturated aqueous NH_4Cl solution and saturated potassium sodium tartrate solution were added. The mixture was vigorously stirred for 30 min at room temperature and then extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 5 g, EtOAc/hexane 1:10 to 1:5) to give **20b** (38.6 mg, 69%) as a colorless oil. **20b:** $[\alpha]_D^{28}$ +26.3 (c 1.11, $CHCl_3$). IR (film): ν_{max} (cm^{-1}) 3443, 2995, 2960, 2943, 2930, 2359, 1636, 1379, 1333, 1292, 1281, 1261, 1162, 840, 827, 813. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.20 (3H, s), 0.21 (3H, s), 1.03 (9H, s), 1.35 (3H, s), 1.43 (3H, s), 1.64 (6H, s), 1.79 (1H, brs), 2.38 (3H, s), 2.93 (1H, d, J = 7.5 Hz), 3.34 (2H, m, -CH_2), 4.68 (1H, d, J = 7.5 Hz), 4.85 (1H, m), 6.80 (1H, brs), 7.15 (1H, d, J = 8.5 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.32 (1H, d, J = 8.5 Hz), 7.70 (2H, d, J = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) -3.6, -3.5, 18.1, 18.6, 18.8, 21.5, 24.8, 25.4, 25.5, 25.9, 59.7, 66.3, 68.3, 116.5, 120.3, 123.2, 127.2, 128.6, 129.6, 131.5, 132.2, 136.6, 136.6, 142.3, 143.9. HR-MS (ESI, positive); calcd. For $C_{29}H_{43}NNaO_5SSi$ (M+Na), 568.2523; Found 568.2526.

3-((*S*)-((*R*)-3,3-dimethyloxiran-2-yl)(hydroxy)methyl)-2-(3-methylbut-2-en-1-yl)-6-(4-methylphenylsulfonamido)phenyl trifluoromethanesulfonate ((+)-6). TBAF (1.0 M in THF; 0.2 mL, 0.2 mmol) was added to a solution of **20a** (35.5 mg, 0.0650 mmol) in THF (3 mL) at 0 °C under argon. After stirring for 1 h, the mixture was poured into a saturated aqueous solution of NH_4Cl. The aqueous layer was separated and extracted with EtOAc (20 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was used for the next reaction without further purification. The crude product (35.2 mg) was dissolved in CH_2Cl_2 (2 mL) and Et_3N (25 μL, 0.18 mmol) and Comin's reagent (26.2 mg, 0.0667 mmol) was added at rt. The mixture was stirred for 1 h, and then sat. aqueous $NaHCO_3$ solution was added. The aqueous layer was separated and extracted with CH_2Cl_2 (30 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 1 g, EtOAc/hexane 1:5) to give (+)-**6** (23.6 mg, 65% in 2 steps) as a colorless solid. (+)-**6:** mp: 92-96 °C. $[\alpha]_D^{28}$ +6.3 (c 0.82, $CHCl_3$). IR (film): ν_{max} (cm^{-1}) 3385, 2925, 1418, 1339, 1219, 1135. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.31 (3H, s), 1.33 (3H, s),

1.65 (3H, s), 2.40 (3H, s), 3.00 (3H, d, J = 6.5 Hz, 1H), 3.33 (1H, dd, J = 16.0, 5.5 Hz), 3.46 (1H, dd, J = 16.0, 5.5 Hz), 4.67 (1H, dd, J = 6.5, 2.0 Hz), 4.78 (1H, m), 7.00 (1H, brs), 7.24 (2H, d, J = 8.5 Hz), 7.52 (1H, d, J = 8.5 Hz), 7.54 (1H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 18.0, 18.9, 21.6, 24.6, 25.4, 25.6, 60.5, 66.8, 67.6, 118.3 (q, $J_{C\text{-}F}$ = 319 Hz), 120.6, 122.8, 127.4, 127.8, 129.6, 129.7, 133.7, 134.8, 135.9, 138.1, 139.3, 144.4. ^{19}F-NMR (376 MHz, $CDCl_3$) δ (ppm) -74.0 (s). HR-MS (ESI, positive): Calcd. For $C_{24}H_{28}F_3NNaO_7S_2$ (M+Na), 586.1139; Found 586.1151.

***N*-(4-((*S*)-((*R*)-3,3-dimethyloxiran-2-yl)(hydroxy)methyl)-2-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl)-4-methylbenzenesulfonamide ((+)-21b).** TBAF (1.0 M in THF; 0.2 mL, 0.2 mmol) was added to a solution of **20a** (37.0 mg, 0.0678 mmol) in THF (3 mL) at 0 °C under a positive pressure of argon. After stirring for 1 h, the mixture was poured into a saturated aqueous solution of NH_4Cl. The aqueous layer was separated and extracted with EtOAc (20 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 1 g, EtOAc/hexane 1:5) to give (+)-**21b** (21.3 mg, 73% in 2 steps) as a colorless solid. (+)-**21b:** mp: 152 °C. $[\alpha]_D^{28}$ +6.9 (c 0.95, $CHCl_3$). IR (film): ν_{max} (cm^{-1}) 3504, 3359, 2963, 2624, 2854, 2360, 2341, 1731, 1717, 1597, 1493, 1455, 1378, 1331, 1307, 1261, 1238, 1156, 1091, 1021, 1012. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.30 (3H, s), 1.32 (3H, s), 1.71 (3H, s), 1.77 (3H, s), 2.39 (3H, s), 3.04 (1H, d, J = 7.0 Hz), 3.43 (2H, m), 4.64 (1H, d, J = 7.0 Hz), 5.00 (1H, m), 6.17 (1H, brs), 6.68 (1H, brs), 6.87 (1H, d, J = 8.0 Hz), 6.90 (1H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.64 (2H, d, J = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 18.0, 19.1, 21.6, 24.7, 25.6, 25.7, 60.4, 67.1, 69.4, 119.1, 121.5, 121.5, 123.7, 126.8, 127.5, 129.6, 135.2, 135.5, 137.3, 144.1, 148.1. Anal. Calcd for $C_{24}H_{28}F_3NO_7S_2$: C, 51.15; H, 5.01; N, 2.49. Found: C, 51.16; H, 5.11; N, 2.59.

Synthesis of triflate 6 from 21b. Et_3N (150 μL, 0.0993 mmol) and Comin's reagent (16.5 mg, 0.0420 mmol) were added to a solution of the phenol (+)-**21b** (14.3 mg, 0.0331) in CH_2Cl_2 (2 mL) at rt under a positive pressure of argon. After stirring for 1 h, the reaction was quenched with sat. aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2 (30 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc/hexane 1:1) to give (+)-**6** (12.4 mg, 76%) as a colorless solid.

3-((*S)-((*R**)-3,3-Dimethyloxiran-2-yl)(hydroxy)methyl)-2-(3-methylbut-2-en-1-yl)-6-nitrophenyl trifluoromethanesulfonate ((±)-23).** TBAF (1.0 M in THF, 4.9 mL, 4.9 mmol) was added to a solution of (±)-**22**[3] (522 mg, 1.24 mmol) in THF (12 mL) at 50 °C and stirred. After 14.5 h, the mixture was diluted with water. The mixture was extracted with EtOAc (x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was used for the next reaction without purification. Et_3N (800 μL, 5.72 mmol) and Tf_2O (200 μL, 1.25 mmol) were added to a solution of the residue (352 mg) in CH_2Cl_2 (12 mL) at -20 °C and stirred. After 15 min, the mixture was diluted with sat. $NaHCO_3$ solution. The mixture was extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 10 g, EtOAc/hexane 1:1) to give (±)-**23** (394 mg, 72% in 2 steps) as a yellow solid. (±)-**23**: mp: 69-71 °C. IR (film): ν_{max} (cm^{-1}) 3442, 1636, 1539, 1430, 1410, 1353, 1216, 1135, 890, 848, 826. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.35 (3H, s), 1.38 (3H, s), 1.70 (3H, s), 1.75 (3H, s), 2.97 (1H, d, J = 6.0 Hz), 3.08 (1H, brs), 3.51 (1H, dd, J = 16.0, 6.0 Hz), 3.66 (1H, dd, J = 16.0, 6.0 Hz), 4.85 (1H, dd, J = 6.0, 3.0 Hz), 4.96 (1H, m), 7.78 (1H, d, J = 8.5 Hz), 7.95 (1H, d, J = 8.5 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 18.0, 18.9, 24.4, 25.5, 25.8, 61.0, 66.5, 66.9, 116.7, 118.3 (q, J_{C-F} = 315 Hz), 119.7, 120.0, 124.4, 127.3, 135.0, 136.1, 138.2, 142.5, 148.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -73.9 (s). Anal. Calcd for $C_{17}H_{20}F_3NO_7S$: C, 46.47; H, 4.59; N,3.19. Found: C, 46.48; H, 4.57; N, 3.14.

Synthesis of (±)-21b from (±)-23. Zn-Cu (101 mg) was added to a solution of (±)-**23** (65.5 mg, 0.149 mmol) and NH_4Cl (235 mg) in EtOH (3 mL) and water (0.5 mL) at room temperature. After being stirred for 30 min, the reaction mixture was filtered through a pad of Celite. The filtrate was dissolved in water and EtOAc, and then extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 and concentrated. The residue was used for the next reaction without purification. TsCl (45.4 mg, 0.238 mmol) was added to a solution of the crude product (39.3 mg) in pyridine (3 mL) at room temperature. After being stirred at the same temperature for 50 min, an ice-cold water was added. The mixture was dissolved in water and then extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was

purified by column chromatography (silica gel 5 g, EtOAc/hexane 1:5 to 1:2) to give (±)-**21b** (32.7 mg, 39% in 2 steps) as a yellow solid. (±)-**21b:** mp: 156-160 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.30 (3H, s), 1.31 (3H, s), 1.71 (3H, s), 1.77 (3H, s), 2.39 (3H, s), 3.04 (1H, d, J = 7.0 Hz), 3.43 (2H, m), 4.64 (1H, d, J = 7.0 Hz), 5.00 (1H, m), 6.23 (1H, brs), 6.75 (1H, brs), 6.87 (1H, d, J = 8.0 Hz), 6.89 (1H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.64 (2H, d, J = 8.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 18.0, 19.1, 21.6, 24.7, 25.5, 25.7, 60.4, 67.1, 69.4, 119.1, 121.5, 121.6, 123.6, 126.9, 127.5, 129.6, 135.1, 135.5, 137.3, 144.0, 148.2.

Supporting information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXXX.

Attempts for asymmetric synthesis of intermediates in racemic synthesis of aromatic fragment **2**, comparison of ^{13}C{^{1}H}NMR spectra of a mixture of *anti*-**12** and *syn*-**12** of the literature, scheme of asymmetric synthesis of epoxy aldehyde **7**, X-ray crystallographic data for compound **14b**, and spectral data for all new compounds (PDF)

Crystal data for compound **14b** (CIF)

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14. The Claisen rearrangement of **10** proceeded in refluxing toluene to give the desired product **13** and by-product **14a** in yields of 67% and 10%, respectively.
15. CCDC-1878380 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
16. For a similar rearrangement of nitro group of 6-alkyl-6-nitrocyclohexadienone, see: (a) Fischer, A.; Henderson, G. N. IPSO nitration: nitration of 2-alkylphenols in acetic anhydride. Formation of 6-alkyl-6-nitrocyclohexa-2,4-dienones. *Tetrahedron Lett.* **1980**, *21*, 4661-4662. (b) Fischer, A.; Mathivanan. N. Formation of dienones on the reaction of cresols, xylenols, and 2-naphthol with nitrogen dioxide: Observation of keto tautomers of nitrophenols. *Tetrahedron Lett.* **1988**, *29*, 1869-1872.
17. The aldehyde **6** was used within 24 h of distillation, otherwise the yield decreased because of its instability. The aldehyde turned to viscous oil even when kept in a freezer at -30 °C.
18. In order to improve the stereoselectivity, addition of metal salt such as $ZnCl_2$ and $TiCl_4$ was examined. The reaction in addition of $ZnCl_2$ increased the selectivity to 5:1, however, the yield decreased to 36%. The reaction with $TiCl_4$ gave a complex mixture of products.
19. When **21a** was exposed to the conditions of triflation at -20 °C, migration of the Ts group was observed without triflation. When the mixture was then warmed to 0 °C, *O*-triflation of **21b** occurred to **6**. Because of the instability of **21a** and **21b,** compound **6** was synthesized from **20a** without purification of the intermediates.
20. The position of Ts group of **21a** and **21b** was determined by NOESY spectra.
21. X-ray analysis of compound **20a** was unsuccessful because the quality of the crystals was inadequate.
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23. When the triflate of *o*-nitrophenol was exposed to the same reaction conditions, removal of the Tf group was not observed. Thus, removal of the Tf group of **23** might be unusual, and the mechanism is not clear. We greatly appreciate one of the reviewers for his/her comment, which led us to note this unexpected reaction and to investigate the details.