Asymmetric Construction of All-Carbon Quaternary Stereocenters by Chiral-Auxiliary-Mediated Claisen Rearrangement and Total Synthesis of (+)-Bakuchiol

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Abstract: An asymmetric Claisen rearrangement using Oppolzer’s camphorsultam was developed. Under thermal conditions, a geraniol-derived substrate underwent the rearrangement with good stereoselectivity. The absolute configuration of the newly formed all-carbon quaternary stereocenter was confirmed by the total synthesis of (+)-bakuchiol from the rearrangement product.

Keywords: Claisen rearrangement; chiral auxiliary; camphorsultam; quaternary stereocenter; total synthesis

1. Introduction

The construction of asymmetric quaternary stereocenters remains a challenge in organic synthesis [1–3]. All-carbon quaternary stereocenters are found in a wide range of complex natural products which share such a structural motif, including (+)-hyperforin (1) [4], (+)-perforatumone (2) [5,6], (+)-vibsanin A (3) [7], and (+)-bakuchiol (4) [8–13] (Figure 1). To achieve the total synthesis of these natural products, a practical method for constructing the quaternary stereocenter is necessary. We focused on the Claisen rearrangement as an approach to this challenge. The [3,3]-sigmatropic rearrangement of allyl vinyl ethers, that is, the Claisen rearrangement, is among the most useful tools for forming carbon-carbon bonds and its asymmetric variants have been well studied [14,15]. Herein, we describe a new method for
Oppolzer’s camphorsultam was used as a chiral auxiliary for the asymmetric Claisen rearrangement. We designed a novel substrate, a β-(allyloxy)acrylate derivative bearing the camphorsultam. Accordingly, N-propioloyl camphorsultam 5 was prepared by our previously reported procedure (Scheme 1) [16–18]. The oxy-Michael addition of geraniol to 5 in the presence of a catalytic amount of tributylphosphine gave adduct 6 with complete E-stereoselectivity [19]. A toluene solution of 6 in the presence of butylated hydroxytoluene (BHT) used as a polymerization inhibitor was heated in a sealed tube at 140 °C to provide mainly the (2R,3S)-isomer 7a as the rearrangement product in 72% yield, securing the two contiguous stereocenters including the quaternary carbon. The minor (2S,3R)-isomer 7b (8%) was easily separated from 7a by column chromatography on silica gel [20].

Scheme 1. Claisen rearrangement of geraniol-derived substrate 6.

By using a similar procedure, nerol-derived substrate 8 was prepared from 5 and nerol (Scheme 2). The Claisen rearrangement of 8 afforded (2R,3R)-isomer 7c and (2S,3S)-isomer 7d, accompanied by a
small amount of 7a and 7b, respectively. Compared with the case of 6, however, lower stereoselectivity was observed. Brief exposure of 7a to base caused epimerization at C-2 to produce isomer 7d, indicating that the quaternary stereocenter in nerol-derived rearrangement product 7c has stereochemistry opposite to that in 7a.

Scheme 2. Claisen rearrangement of nerol-derived substrate 8.

The stereochemistry of the newly formed quaternary stereocenter (C-3) in 7a was determined by the total synthesis of (+)-bakuchiol (4), a major component of the Indian medicinal plant *Psoralea corylifolia* Linn [8]. Base hydrolysis of 7a followed by decarboxylation provided enantiomerically pure aldehyde 9, and the chiral auxiliary was recovered (Scheme 3). Treatment of 9 with *p*-MeOC<sub>6</sub>H<sub>4</sub>MgBr afforded alcohol 10, which was subjected to dehydration using phosphoryl chloride to afford bakuchiol methyl ether 11 [21]. By comparing the optical rotation of synthetic 11 \([\alpha]_D^{25} + 28.4 \ (c \ 0.855, \ CHCl_3)\) with that reported for the authentic sample \{lit. \([\alpha]_D^{29} + 31.2 \ (c \ 1.45, \ CHCl_3)\}\ [9], the absolute configuration of the quaternary stereocenter in 7a was assigned as (S). According to a known procedure [22], demethylation of 11 finally provided (+)-bakuchiol (4), which was identical to the natural product in all respects.

Scheme 3. Determination of the stereochemistry at C-3 in 7a and total synthesis of (+)-bakuchiol.
To determine the configuration at C-2, rearrangement product 7a was heated at 160 °C (Scheme 4). The intramolecular carbonyl–ene reaction proceeded to provide cyclized 12a as a mixture of four diastereomers (dr = 3:2:2:1). Similarly, 7c was converted into 12c (dr = 9:8:2:1). Through NOE experiments on the isolated major diastereomers 12aa and 12ca, the stereochemistry at the C-2 in 7a and 7c was assigned as (R). Therefore, the configurations of all stereocenters in the rearrangement products 7a–d were unambiguously assigned.

Scheme 4. Determination of the stereochemistry at C-2 in 7a and 7c.

To expand the scope of this reaction, (E,E)-β-(allyloxy)acrylate substrates 14 and 17 were synthesized by oxy-Michael addition of allylic alcohols 13 and 16 [23] to 5 (Scheme 5). In both cases, the Claisen rearrangements of 14 and 17 afforded (2R,3S)-isomers 15a and 18a preferentially, with good stereoselectivity in more than 70% yield, similarly to the reaction of 6.

Scheme 5. Claisen rearrangements of 14 and 17.
The vicinal stereocenters in 15a and 18a were assigned by chemical transformation (Scheme 6). Chemoselective reduction of 7a, followed by acetylation of the resulting alcohol, provided acetate 19a. The spectroscopic data (1H- and 13C-NMR) of 19a were distinguishable from those of 19b derived from 7b. On the other hand, 15a was converted into acetate 20a. Desilylation of 20a, oxidation of the resulting alcohol to aldehyde, and subsequent Wittig olefination afforded 19a whose NMR spectra matched those of 19a derived from 7a. Compound 18a was also converted into 19a via acetate 21a. Therefore, the configuration of the vicinal stereocenters at the C-2 and C-3 in 15a and 18a coincides with that of 7a.

Scheme 6. Determination of the stereochemistry at C-2 and C-3 in 15a and 18a.

The stereochemical outcomes observed in the reactions of 6, 14, 17, and 8 can be explained by the transition states depicted in Scheme 7.

Scheme 7. Plausible transition states for the Claisen rearrangements of 6, 14, 17, and 8.
In the more favorable conformation of 6, 14, and 17, the carbonyl group is directed anti to the sulfonyl group and adopts an s-cis conformation with respect to the α,β-unsaturated bond [24]. The rearrangement proceeds predominantly from the Ca-Re-face through a six-membered chair-like transition state to avoid the steric repulsion that would be encountered along the Ca-Si-face path. As a result, 7a, 15a, and 18a were obtained as the major isomers. Also nerol-derived substrate 8 rearranges through the same Ca-Re-face path to produce 7c. In this case, the bulky homoprenyl group takes an axial orientation, which causes a decrease of the stereoselectivity.

3. Experimental

General

Melting points are uncorrected. Specific rotations were measured in a 100 mm cell. 1H-NMR spectra were recorded at 500 MHz with tetramethylsilane as an internal standard on a JEOL JNM-ECA500 spectrometer. 13C-NMR spectra were recorded at 125 MHz. All spectra were recorded in CDCl3. High-resolution mass spectra (HRMS) were measured in EI mode (70 eV) on a JEOL JMS-GCMATE spectrometer. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F254 plates. The crude reaction mixtures and extracted materials were purified by column chromatography on Silica gel 60 (Merck) or Wakogel C-300 (Wako). Unless otherwise noted, reactions were carried out at room temperature. Combined organic extracts were dried over anhydrous Na2SO4. Solvents were removed from the reaction mixture and the combined organic extracts by concentration under reduced pressure using an evaporator with bath at 35–45 °C.

(2R)-N-[(E)-3-[(2E)-3,7-Dimethylocta-2,6-dien-1-yl]oxy]acryloyl]bornane-10,2-sultam (6). The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of 5 (302 mg, 1.13 mmol) in CH2Cl2 (11 mL) were added geraniol (218 μL, 1.24 mmol) and n-Bu3P (42 μL, 0.17 mmol). The mixture was stirred at 0 °C for 30 min, diluted with H2O (20 mL), and extracted with CH2Cl2 (10 mL × 3). The combined extracts were washed with saturated brine (20 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 368 mg (77%) of 6 as a colorless oil: TLC Rf 0.54 (EtOAc/hexane, 1:3); [α]D19–59.2 (c 1.19, CHCl3); IR (neat) 2962, 2885, 1678, 1608 cm⁻¹; 1H-NMR (500 MHz): δ 0.97 (s, 3H), 1.18 (s, 3H), 1.34–1.45 (m, 2H), 1.60 (br s, 3H), 1.68 (br s, 3H), 1.71 (br s, 3H), 1.86–1.91 (m, 3H), 2.05–2.17 (m, 6H), 3.43 (d, 1H, J = 13.8 Hz), 3.48 (d, 1H, J = 13.8 Hz), 3.91 (dd, 1H, J = 4.9, 7.7 Hz), 4.45 (d, 2H, J = 6.9 Hz), 5.08 (m, 1H), 5.37 (qt, 1H, J = 1.0, 6.9 Hz), 5.97 (d, 1H, J = 12.1 Hz), 7.70 (d, 1H, J = 12.1 Hz); 13C-NMR (125 MHz) δ16.6, 17.6, 19.9, 20.7, 25.6, 26.1, 26.5, 32.7, 38.5, 39.4, 44.6, 47.7, 48.2, 53.0, 65.0, 68.1, 97.0, 117.5, 123.5, 131.9, 143.4, 163.3, 164.9; HRMS calcd for C23H35NO4S (M⁺) m/z 421.2287, found 421.2286.

(2R)-N-[(2R,3S)-2-Formyl-3,7-dimethyl-3-vinylloct-6-enoyl] bornane-10,2-sultam (7a) and (2R)-N-[(2S,3R)-isomer (7b). A solution of 6 (400 mg, 949 μmol) and BHT (10.5 mg, 47.5 μmol) in toluene (50 mL) was stirred at 140 °C for 65 h in a sealed tube and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 289 mg (72%) of 7a and 30.9 mg (8%) of 7b. Compound 7a was obtained as white crystals: mp 84–87 °C;
TLC Rf 0.49 (EtOAc/hexane, 1:3); [α]D21−77.9 (c 2.55, CHCl3); IR (neat) 2960, 2925, 1730, 1680 cm⁻¹; 
¹H-NMR (500 MHz) δ 0.98 (s, 3H), 1.15 (s, 3H), 1.26 (s, 3H), 1.37−1.46 (m, 3H), 1.56 (br s, 3H), 1.65 (br s, 3H), 1.67 (m, 1H), 1.87−1.96 (m, 5H), 2.06-2.15 (m, 2H), 3.44 (d, 1H, J = 13.8 Hz), 3.51 (d, 1H, J = 13.8 Hz), 3.96 (dd, 1H, J = 5.2, 7.4 Hz), 4.01 (d, 1H, J = 2.3 Hz), 5.02 (m, 1H), 5.07 (d, 1H, J = 17.4 Hz), 5.21 (d, 1H, J = 10.6 Hz), 5.92 (dd, 1H, J = 10.6, 17.4 Hz), 9.61 (d, 1H, J = 2.3 Hz); ¹³C-NMR (125 MHz) δ 17.6, 19.7, 19.9, 20.7, 22.2, 25.6, 26.4, 32.9, 38.5 (2C), 44.8, 45.5, 47.7, 48.1, 53.2, 65.4 (2C), 115.2, 123.7, 131.9, 142.3, 167.5, 197.3; HRMS calcd for C₂₃H₃₅NO₄S (M⁺) m/z 421.2287, found 421.2283. Compound 7b was obtained as white crystals: mp 81−87 °C; TLC Rf 0.61 (EtOAc/hexane, 1:3); [α]D17+38.5 (c 0.965, CHCl3); IR (neat) 2960, 2925, 1730, 1700 cm⁻¹; 
¹H-NMR (500 MHz) δ 0.95 (s, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.34−1.43 (m, 2H), 1.54-1.68 (m, 2H), 1.56 (br s, 3H), 1.65 (br s, 3H), 1.88-1.93 (m, 5H), 2.08 (dd, 1H, J = 7.8, 13.9 Hz), 2.28 (m, 1H), 3.43 (d, 1H, J = 13.7 Hz), 3.48 (d, 1H, J = 13.7 Hz), 3.90 (dd, 1H, J = 4.9, 7.8 Hz), 4.21 (d, 1H, J = 0.9 Hz), 5.04 (m, 1H), 5.12 (dd, 1H, J = 0.6, 17.5 Hz), 5.26 (dd, 1H, J = 0.6, 10.8 Hz), 6.01 (dd, 1H, J = 10.8, 17.5 Hz), 9.60 (d, 1H, J = 0.9 Hz); ¹³C-NMR (125 MHz) δ 17.6, 19.3, 19.9, 20.4, 22.2, 25.7, 26.5, 32.7, 38.2, 38.9, 42.9, 44.5, 47.8, 48.2, 53.1, 65.1, 65.3, 115.1, 124.0, 131.7, 143.5, 166.3, 197.7; HRMS calcd for C₂₃H₃₅NO₄S (M⁺) m/z 421.2287, found 421.2281.

(2R)-N-[(E)-3-[[2(Z),3,7-Dimethylocta-2,6-dien-1-yl]oxy]acryloyl]bornane-10,2-sultam (8). As described for the preparation of 6, compound 5 (210 mg, 785 μmol) and nerol (155 μL, 882 μmol) were treated with n-Bu₃P (32 μL, 0.12 mmol) in CH₂Cl₂ (8 mL) to provide 234 mg (71%) of 8 as white crystals: mp 62−64 °C; TLC Rf 0.52 (EtOAc/hexane, 1:3); [α]D26−71.0 (c 1.22, CHCl₃); IR (neat) 2964, 2884, 1677, 1607 cm⁻¹; ¹H-NMR (500 MHz) δ 0.97 (s, 3H), 1.18 (s, 3H), 1.34−1.45 (m, 2H), 1.60 (br s, 3H), 1.69 (br s, 3H), 1.78 (br s, 3H), 1.87−1.91 (m, 3H), 2.05−2.17 (m, 6H), 3.43 (d, 1H, J = 13.7 Hz), 3.48 (d, 1H, J = 13.7 Hz), 3.91 (dd, 1H, J = 4.9, 7.8 Hz), 4.41 (d, 2H, J = 7.0 Hz), 5.08 (m, 1H), 5.39 (t, 1H, J = 7.0 Hz), 5.96 (d, 1H, J = 12.0 Hz), 7.69 (d, 1H, J = 12.0 Hz); ¹³C-NMR (125 MHz) δ 17.6, 19.9, 20.8, 23.5, 25.7, 26.5 (2C), 32.3, 32.8, 38.6, 44.7, 47.8, 48.2, 53.1, 65.0, 67.9, 79.7, 118.5, 123.3, 132.5, 143.8, 163.4, 165.0; HRMS calcd for C₂₃H₃₅NO₄S (M⁺) m/z 421.2287, found 421.2287.

(2R)-N-[(2Z,3R)-2-Formyl-3,7-dimethyl-3-vinylcyclohex-6-enoyl]bornane-10,2-sultam (7c) and (2R)-N-[(2S,3S)-isomer] (7d). As described for the preparation of 7a and 7b from 6, a solution of 8 (223 mg, 529 μmol) and BHT (5.8 mg, 26 μmol) in toluene (27 mL) was heated at 140 °C for 26 h to provide 147 mg (66%) of a mixture of 7c and 7a (7c/7a = 19:1) and 25.0 mg (11%) of a mixture of 7d and 7b (7d/7b = 10:1), and 27.9 mg (13%) of 8 was recovered. A mixture of 7c and 7a (7c/7a = 19:1) was obtained as a colorless oil: TLC Rf 0.49 (EtOAc/hexane, 1:3); [α]D28−82.4 (c 1.26, CHCl₃); IR (neat) 2965, 2930, 1727, 1684 cm⁻¹; ¹H-NMR (500 MHz) for 7c δ 0.97 (s, 3H), 1.16 (s, 3H), 1.26 (s, 3H), 1.34−1.49 (m, 3H), 1.55 (br s, 3H), 1.65 (br s, 3H), 1.68 (m, 1H), 1.84−1.93 (m, 5H), 2.03−2.09 (m, 2H), 3.43 (d, 1H, J = 13.8 Hz), 3.50 (d, 1H, J = 13.8 Hz), 3.89 (d, 1H, J = 3.5 Hz), 3.92 (dd, 1H, J = 5.5, 7.4 Hz), 5.02 (m, 1H), 5.02 (dd, 1H, J = 1.0, 17.4 Hz), 5.14 (dd, 1H, J = 1.0, 10.9 Hz), 6.02 (dd, 1H, J = 10.9, 17.4 Hz), 9.66 (d, 1H, J = 3.5 Hz); ¹³C-NMR (125 MHz) for 7c δ 17.6, 18.9, 19.9, 20.7, 22.2, 25.6, 26.4, 33.0, 38.2, 39.5, 44.7, 45.8, 47.7, 48.1, 53.3, 65.4, 65.5, 115.2, 123.7, 131.8, 141.7, 167.9, 197.8; HRMS calcd for C₂₃H₃₅NO₄S (M⁺) m/z 421.2287, found 421.2289. A mixture of 7d and 7b (7d/7b = 10:1) was obtained as a colorless oil: TLC Rf 0.61 (EtOAc/hexane, 1:3); [α]D26+2.9
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(c 1.25, CHCl3); IR (neat) 2964, 2924, 1728, 1697 cm−1; 1H-NMR (500 MHz) for 7d δ 0.95 (s, 3H), 1.09 (s, 3H), 1.31–1.42 (m, 2H), 1.34 (s, 3H), 1.57 (m, 1H), 1.57 (br s, 3H), 1.65 (br s, 3H), 1.76 (m, 1H), 1.87–1.95 (m, 5H), 2.07 (dd, 1H, J = 7.9, 14.0 Hz), 2.25 (m, 1H), 3.43 (d, 1H, J = 17.2 Hz), 3.49 (d, 1H, J = 10.9 Hz), 3.90 (dd, 1H, J = 4.9, 7.9 Hz), 4.19 (d, 1H, J = 1.1 Hz), 5.06 (m, 1H), 5.06 (d, 1H, J = 10.9 Hz), 5.17 (d, 1H, J = 17.2 Hz), 5.17 (d, 1H, J = 10.9 Hz), 6.14 (dd, 1H, J = 10.9, 17.2 Hz), 9.68 (d, 1H, J = 1.1 Hz); 13C-NMR (125 MHz) for 7d δ 17.6, 19.9, 20.4, 21.2, 23.4, 25.6, 26.4, 32.7, 38.2, 39.1, 43.3, 44.5, 47.7, 48.2, 53.1, 65.3, 66.2, 114.7, 123.9, 131.7, 142.6, 166.3, 197.0; HRMS calcd for C23H35NO4S (M+) m/z 421.2287, found 421.2288.

Epimerization of 7a. To a stirred solution of 7a (7.9 mg, 19 μmol) in CH2Cl2 (1 mL) was added DBU (3.6 μL, 24 μmol). The mixture was stirred at room temperature for 45 min, diluted with 1 M aqueous HCl (1 mL), and extracted with CH2Cl2 (2 mL × 3). The combined extracts were washed with saturated brine (1 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:25) to provide 1.1 mg (14%) of 7d and 6.7 mg (85%) of 7a was recovered.

(1RS,3R)-1-(4-Methoxyphenyl)-3,7-dimethyl-3-vinyloct-6-enol (10). To a cooled (0 °C) stirred solution of 7a (233 mg, 553 μmol) in THF/H2O (1:1, 5 mL) was added 1.00 M aqueous KOH (1.11 mL, 1.11 mmol). The mixture was stirred at room temperature for 24 h, quenched with saturated aqueous NH4Cl (2 mL), diluted with H2O (2 mL), and extracted with Et2O (5 mL × 3). The combined extracts were washed with saturated brine (15 mL) and dried to provide a solution of aldehyde 9 in Et2O, which was used in the next step without further evaporation and purification.

The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of aldehyde 9 in Et2O obtained above was added 4-methoxyphenylmagnesium bromide (1.50 M solution in Et2O, total 6.27 mL, total 9.41 mmol) in ten times over a period of 2 h. The mixture was quenched with saturated aqueous NH4Cl (30 mL), diluted H2O (10 mL), and extracted with CH2Cl2 (40 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 86.7 mg (55%) of 10 and 114 mg (96%) of camphorsultam. Compound 10 (dr = 1:1) was obtained as a colorless oil: TLC Rf 0.61 (EtOAc/hexane, 1:3); IR (neat) 3442, 2965, 2924, 1728, 1612, 1512 cm−1; 1H-NMR (500 MHz) δ 1.10 (s, 3H × 1/2), 1.11 (s, 3H × 1/2), 1.34 (t, 2H × 1/2, J = 8.5 Hz), 1.40–1.43 (m, 2H × 1/2, 1.57 (br s, 3H × 1/2), 1.59 (br s, 3H × 1/2), 1.66 (br s, 3H × 1/2), 1.67 (br s, 3H × 1/2), 1.80–1.93 (m, 4H), 3.79 (s, 3H), 4.74 (dd, 1H × 1/2, J = 2.6, 8.6 Hz), 4.79 (dd, 1H × 1/2, J = 2.6, 9.3 Hz), 5.02 (dd, 1H × 1/2, J = 1.1, 17.7 Hz), 5.07 (dd, 1H × 1/2, J = 1.1, 10.8 Hz), 5.07 (m, 1H), 5.07 (dd, 1H × 1/2, J = 0.9, 17.7 Hz), 5.14 (dd, 1H × 1/2, J = 0.9, 10.8 Hz), 5.83 (dd, 1H × 1/2, J = 10.8, 17.7 Hz), 5.97 (dd, 1H × 1/2, J = 10.8, 17.7 Hz), 6.86 (d, 2H × 1/2, J = 8.8 Hz), 6.86 (d, 2H × 1/2, J = 8.6 Hz), 7.24 (d, 2H × 1/2, J = 8.8 Hz), 7.25 (d, 2H × 1/2, J = 8.6 Hz); 13C-NMR (125 MHz) δ 17.6, 21.3 (1/2C), 22.5 (1/2C), 22.7 (1/2C), 23.5 (1/2C), 25.7, 39.5, 40.5 (1/2C), 42.5 (1/2C), 50.3 (1/2C), 51.1 (1/2C), 55.3, 71.4 (1/2C), 71.5 (1/2C), 112.2 (1/2C), 112.9 (1/2C), 113.7, 113.8, 124.6 (1/2C), 124.8 (1/2C), 126.9 (2C), 131.2 (1/2C), 131.3 (1/2C), 137.7 (1/2C), 138.3 (1/2C), 147.4 (1/2C), 147.7 (1/2C), 158.8; HRMS calcd for C19H28O2 (M+) m/z 288.2089, found 288.2090.
(1E,3S)-1-(4-Methoxyphenyl)-3,7-dimethyl-3-vinylocta-1,6-diene (11). The following reaction was carried out under Ar. To a stirred solution of 10 (22.5 mg, 78.0 μmol) in pyridine (1 mL) was added POCl3 (8.6 μL, 95 μmol). The mixture was refluxed for 4 h, diluted with EtOAc (15 mL), and washed with H2O (10 mL) and saturated brine (10 mL). The organic layer was dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to provide 18.9 mg (90%) of 11 as a colorless oil: TLC Rf 0.80 (EtOAc/hexane, 1:3); [α]D25 + 28.4 (c 0.855, CHCl3); IR (neat) 2966, 2916, 1609, 1511 cm−1; 1H-NMR (500 MHz) δ 1.20 (s, 3H), 1.48–1.51 (m, 2H), 1.58 (br s, 3H), 1.67 (br s, 3H), 1.93–1.98 (m, 2H), 3.80 (s, 3H), 5.01 (dd, 1H, J = 1.4, 17.5 Hz), 5.03 (dd, 1H, J = 1.4, 10.7 Hz), 5.11 (m, 1H), 5.88 (dd, 1H, J = 10.7, 17.5 Hz), 6.06 (d, 1H, J = 16.4 Hz), 6.26 (d, 1H, J = 16.4 Hz), 6.83 (d, 2H, J = 8.7 Hz), 7.29 (d, 2H, J = 8.7 Hz); 13C-NMR (125 MHz) δ 17.6, 23.2, 23.4, 25.7, 41.3, 42.5, 55.3, 111.8, 113.9 (2C), 124.8, 126.5, 127.1 (2C), 130.7, 131.3, 135.8, 146.0, 158.7; HRMS calcd for C19H26O (M+) m/z 270.1984, found 270.1983.

(+)-Bakuchiol (4). The following reaction was carried out under Ar. To a cooled (0 °C) solution of 11 (30.2 mg, 112 μmol) in Et2O (1 mL) was added MeMgI (0.500 M solution in Et2O, 1.57 mL, 785 μmol). The solvent was removed under reduced pressure. The residue was heated at 180 °C for 15 min and cooled to room temperature. The mixture was quenched with 1 M aqueous HCl (2 mL), diluted with H2O (2 mL), and extracted with CH2Cl2 (5 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:60) to provide 26.1 mg (91%) of 4 as a pale yellow oil: TLC Rf 0.63 (EtOAc/hexane, 1:3); [α]D29 + 25.6 (c 0.795, CHCl3); IR (neat) 3359, 2967, 2924, 1610, 1513 cm−1; 1H-NMR (500 MHz) δ 1.19 (s, 3H), 1.47–1.51 (m, 2H), 1.58 (br s, 3H), 1.67 (br s, 3H), 1.93–1.97 (m, 2H), 4.85 (br, 1H, OH), 5.01 (dd, 1H, J = 1.5, 17.4 Hz), 5.03 (dd, 1H, J = 1.5, 10.8 Hz), 5.11 (m, 1H), 5.88 (dd, 1H, J = 10.8, 17.4 Hz), 6.05 (d, 1H, J = 16.2 Hz), 6.25 (d, 1H, J = 16.2 Hz), 6.76 (d, 2H, J = 8.6 Hz), 7.24 (d, 2H, J = 8.6 Hz); 13C-NMR (125 MHz) δ 17.6, 23.2, 23.3, 25.7, 41.3, 42.5, 55.3, 111.8, 115.3 (2C), 124.8, 126.4, 127.4 (2C), 130.9, 131.3, 135.9, 145.9, 154.6; HRMS calcd for C18H24O (M+) m/z 256.1827, found 256.1829.

(2R)-N-[(1R,2S,5R,6R)-6-Hydroxy-5-isopropenyl-2-methyl-2-vinylcyclohexanecarbonyl]bornane-10,2-sultam (12aa) and its diastereomers. A solution of 7a (22.8 mg, 54.1 μmol) and BHT (a crystal) in toluene (6 mL) was stirred at 160 °C for 50 h in a sealed tube and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:60) to provide 26.1 mg (91%) of 12aa as a pale yellow oil: TLC Rf 0.63 (EtOAc/hexane, 1:3); [α]D25 + 25.6 (c 0.795, CHCl3); IR (neat) 3359, 2967, 2924, 1610, 1513 cm−1; 1H-NMR (500 MHz) δ 1.19 (s, 3H), 1.47-1.51 (m, 2H), 1.58 (br s, 3H), 1.67 (br s, 3H), 1.93–1.97 (m, 2H), 4.85 (br, 1H, OH), 5.01 (dd, 1H, J = 1.5, 17.4 Hz), 5.03 (dd, 1H, J = 1.5, 10.8 Hz), 5.11 (m, 1H), 5.88 (dd, 1H, J = 10.8, 17.4 Hz), 6.05 (d, 1H, J = 16.2 Hz), 6.25 (d, 1H, J = 16.2 Hz), 6.76 (d, 2H, J = 8.6 Hz), 7.24 (d, 2H, J = 8.6 Hz); 13C-NMR (125 MHz) δ 17.6, 23.2, 23.3, 25.7, 41.3, 42.5, 55.3, 111.8, 115.3 (2C), 124.8, 126.4, 127.4 (2C), 130.9, 131.3, 135.9, 145.9, 154.6; HRMS calcd for C18H24O (M+) m/z 256.1827, found 256.1829.
(2R)-N-[(1R,2R,5R,6R)-6-Hydroxy-5-isopropenyl-2-methyl-2-vinylcyclohexanecarboxyl]bornane-10,2-sultam (12ca) and its diastereomers. As described for the preparation of 12aa and its diastereomers from 7a, a solution of 7c (23.5 mg, 55.7 μmol) and BHT (a crystal) in toluene (6 mL) was heated at 160 °C for 40 h to provide 8.7 mg (37%) of 12ca, 9.2 mg (39%) of a mixture of 12cb and 12cc, and 0.9 mg (4%) of 12cd. Compound 12ca was obtained as white crystals: TLC Rf 0.32 (EtOAc/hexane, 1:2); 1H-NMR (500 MHz) δ 0.95 (s, 3H), 1.15 (s, 3H), 1.19 (s, 3H), 1.23–1.41 (m, 3H), 1.50–1.70 (m, 3H), 1.78 (br s, 3H), 1.81–1.96 (m, 3H), 2.02–2.06 (m, 3H), 2.10 (dt, 1H, J = 5.0, 10.6 Hz), 3.00 (d, 1H, J = 10.5 Hz), 3.45 (d, 1H, J = 13.9 Hz), 3.50 (d, 1H, J = 13.9 Hz), 3.95 (dd, 1H, J = 5.2, 7.8 Hz), 4.00 (q, 1H, J = 10.5 Hz), 4.85 (s, 1H), 4.86 (s, 1H), 4.90 (d, 1H, J = 10.6 Hz), 4.98 (d, 1H, J = 17.5 Hz), 6.00 (dd, 1H, J = 10.6, 17.5 Hz).

(2R)-N-[(E)-3-[(2E)-6-(tert-Butyldiphenylsiloxy)-3-methylhex-2-en-1-yl)oxy]acryloyl]bornane-10,2-sultam (14). As described for the preparation of 6, compound 5 (109 mg, 408 μmol) and 13 (165 mg, 448 μmol) were treated with n-Bu3P (15 μL, 61 μmol) in CH2Cl2 (4 mL) to provide 223 mg (86%) of 14 as white crystals: mp 74–77 °C; TLC Rf 0.78 (EtOAc/toluene, 1:4); [α]D26−26 = 45.6 (c 1.02, CHCl3); IR (neat) 2958, 2858, 1678, 1608 cm−1; 1H-NMR (500 MHz) δ 0.97 (s, 3H), 1.05 (s, 9H), 1.17 (s, 3H), 1.36–1.45 (m, 2H), 1.65–1.70 (m, 2H), 1.67 (s, 3H), 1.86–1.91 (m, 3H), 2.08 (dd, 1H, J = 7.8, 13.8 Hz), 2.13 (t, 2H, J = 7.8 Hz), 2.15 (m, 1H), 3.42 (d, 1H, J = 13.8 Hz), 3.48 (d, 1H, J = 13.8 Hz), 3.64 (t, 2H, J = 6.3 Hz), 3.91 (dd, 1H, J = 4.9, 7.8 Hz), 4.41 (d, 2H, J = 7.1 Hz), 5.35 (t, 1H, J = 7.1 Hz), 5.96 (d, 1H, J = 12.0 Hz), 7.36–7.44 (m, 6H), 7.65–7.67 (m, 4H), 7.70 (d, 1H, J = 12.0 Hz); 13C-NMR (125 MHz) δ 16.6, 19.2, 19.9, 20.8, 26.5, 26.9 (3C), 30.5, 32.8, 35.7, 38.6, 44.7, 47.8, 48.2, 53.1, 63.3, 65.0, 68.1, 97.0, 117.6, 127.6 (4C), 129.5 (2C), 134.0 (2C), 135.6 (4C), 143.4, 163.4, 165.0; HRMS calecd for C32H40NO5SSi (M+−t-C4H9) m/z 578.2396, found 578.2398.

(2R)-N-[(2R,3S)-6-(tert-Butyldiphenylsiloxy)-2-formyl-3-methyl-3-vinylhexanoyl]bornane-10,2-sultam (15a) and (2R)-N-[(2S,3R)]-Isomer (15b). As described for the preparation of 7a and 7b from 6, a solution of 14 (209 mg, 329 μmol) and BHT (3.6 mg, 16 μmol) in toluene (17 mL) was heated at 140 °C for 71 h to provide 150 mg (72%) of 15a and 32.1 mg (15%) of 15b. Compound 15a was obtained as a colorless oil: TLC Rf 0.59 (EtOAc/toluene, 1:5); [α]D22−22 = 88.2 (c 1.46, CHCl3); IR (neat) 2961, 2859, 1731, 1688 cm−1; 1H-NMR (500 MHz) δ 0.95 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.23 (s, 3H), 1.35–1.40 (m, 2H), 1.48–1.54 (m, 2H), 1.74 (m, 1H), 1.83–1.91 (m, 4H), 2.07–2.13 (m, 2H), 3.43 (d, 1H, J = 13.8 Hz), 3.50 (d, 1H, J = 13.8 Hz), 3.60 (t, 2H, J = 6.3 Hz), 3.95 (dd, 1H, J = 5.4, 7.5 Hz), 4.01 (d, 1H, J = 2.5 Hz), 5.05 (d, 1H, J = 17.5 Hz), 5.19 (d, 1H, J = 10.9 Hz), 5.88 (dd, 1H, J = 10.9, 17.5 Hz), 7.35–7.43 (m, 6H), 7.63–7.65 (m, 4H), 9.60 (d, 1H, J = 2.5 Hz); 13C-NMR (125 MHz) δ 19.2, 19.8, 19.9, 20.8, 26.4, 26.7, 26.8 (3C), 32.9, 34.5, 38.5, 44.7, 45.3, 47.7, 48.1, 53.2, 63.9, 65.4, 65.5, 115.3, 127.6 (4C), 129.5 (2C), 134.0 (2C), 135.6 (4C), 142.3, 167.4, 197.2; HRMS calecd for C32H40NO5SSi (M+−t-C4H9) m/z 578.2396, found 578.2401. Compound 15b was obtained as a colorless oil: TLC Rf 0.69 (EtOAc/toluene, 1:5); [α]D24+4.6 (c 1.50, CHCl3); IR (neat) 2961, 2859, 1728, 1696 cm−1; 1H-NMR (500 MHz) δ 0.94 (s, 3H), 1.04 (s, 9H), 1.10 (s, 3H), 1.27 (s, 3H), 1.33–1.39 (m, 2H), 1.51 (m, 1H), 1.62 (m, 1H), 1.70 (m, 1H), 1.87–1.91 (m, 4H), 2.06 (dd, 1H, J = 7.8, 14.0 Hz), 2.26 (m, 1H), 3.41 (d, 1H, J = 13.7 Hz), 3.48 (d, 1H, J = 13.7 Hz), 3.61 (t, 2H, J = 6.5 Hz), 3.87 (dd, 1H, J = 4.9, 7.8 Hz), 4.20 (s, 1H), 5.09 (d, 1H, J = 17.5 Hz), 5.23 (d, 1H, J = 10.7 Hz), 5.96 (dd, 1H,
Diluted with H2O (20 mL), and extracted with CH$_2$Cl$_2$ (10 mL × 3). The combined extracts were dried

$J = 10.7, 17.5$ Hz, 7.36–7.43 (m, 6H), 7.64–7.66 (m, 4H), 9.59 (s, 1H); $^{13}$C-NMR (125 MHz) δ 19.2, 19.5, 19.9, 20.4, 26.4, 26.7, 26.9 (3C), 32.8, 34.9, 38.2, 42.7, 44.5, 47.7, 48.2, 53.1, 64.0, 65.2, 65.3, 115.1, 127.6 (4C), 129.5 (2C), 134.0 (2C), 135.6 (4C), 143.4, 166.3, 197.7; HRMS calcd for C$_{32}$H$_{40}$NO$_5$SSSi (M$^+$–t-C$_4$H$_9$) $m/z$ 578.2396, found 578.2389.

(2R)-N-{[(2E)-5-(1,3-Dioxolan-2-yl)-3-methylpent-2-en-1-yl]oxy}acryloyl}bornane-10,2-sultam (17). As described for the preparation of 6, compound 5 (171 mg, 640 μmol) and 16 (121 mg, 703 μmol) were treated with n-Bu$_3$P (24 μL, 97 μmol) in CH$_2$Cl$_2$ (6 mL) to provide 222 mg (79%) of 17 as a colorless oil: TLC $R_f$ 0.67 (EtOAc/toluene, 1:3); [α]$_D$ $^{25}$ $-$59.7 (c 1.16, CHCl$_3$); IR (neat) 2958, 2885, 1677, 1609 cm$^{-1}$; $^1$H-NMR (500 MHz) δ 0.97 (s, 3H), 1.18 (s, 3H), 1.30–1.35 (m, 5H), 1.59–1.65 (m, 2H), 1.67–1.72 (m, 3H), 1.77–1.81 (m, 2H), 1.87–1.91 (m, 3H), 2.07 (dd, 1H, $J = 7.8, 13.9$ Hz), 2.14 (m, 1H), 2.18 (t, 2H, $J = 8.1$ Hz), 3.43 (d, 1H, $J = 13.8$ Hz), 3.48 (d, 1H, $J = 13.8$ Hz), 3.84–3.86 (m, 2H), 3.91 (dd, 1H, $J = 5.0, 7.8$ Hz), 3.95–3.98 (m, 2H), 4.45 (d, 2H, $J = 6.9$ Hz), 4.86 (t, 1H, $J = 4.7$ Hz), 5.41 (t, 1H, $J = 6.9$ Hz), 5.96 (d, 1H, $J = 12.1$ Hz), 7.69 (d, 1H, $J = 12.1$ Hz); $^{13}$C-NMR (125 MHz) δ 16.7, 19.9, 20.8, 26.5, 31.8, 32.7, 33.6, 38.5, 44.6, 47.7, 48.2, 53.0, 64.9 (2C), 65.0, 68.0, 97.0, 104.0, 117.8, 142.7, 163.3, 164.9; HRMS calcd for C$_{22}$H$_{33}$NO$_6$S (M$^+$) $m/z$ 439.2029, found 439.2035.

(2R)-N-{[(2R,3S)-5-(1,3-Dioxolan-2-yl)-2-formyl-3-methyl-3-vinylpentanoyl]bornane-10,2-sultam (18a) and (2R)-N-{[(2S,3R)]-Isomer (18b). As described for the preparation of 7a and 7b from 6, a solution of 17 (219 mg, 498 μmol) and BHT (5.5 mg, 25 μmol) in toluene (25 mL) was heated at 140 °C for 116 h to provide 159 mg (73%) of 18a and 34.0 mg (16%) of 18b. Compound 18a was obtained as white crystals: mp 116–118 °C; TLC $R_f$ 0.67 (EtOAc/toluene, 1:2); [α]$_D$ $^{21}$ $-$119 (c 1.34, CHCl$_3$); IR (neat) 2964, 2886, 1731, 1684 cm$^{-1}$; $^1$H-NMR (500 MHz) δ 0.98 (s, 3H), 1.16 (s, 3H), 1.24 (s, 3H), 1.30–1.43 (m, 3H), 1.50–1.63 (m, 2H), 1.81 (m, 1H), 1.88–1.96 (m, 4H), 2.11–2.12 (m, 2H), 3.44 (d, 1H, $J = 13.7$ Hz), 3.51 (d, 1H, $J = 13.7$ Hz), 3.80–3.83 (m, 2H), 3.91–3.94 (m, 2H), 3.96 (t, 1H, $J = 6.6$ Hz), 4.01 (d, 1H, $J = 2.3$ Hz), 4.81 (t, 1H, $J = 4.2$ Hz), 5.08 (d, 1H, $J = 17.5$ Hz), 5.22 (d, 1H, $J = 10.6$ Hz), 5.89 (dd, 1H, $J = 10.6, 17.5$ Hz), 9.62 (d, 1H, $J = 2.3$ Hz); $^{13}$C-NMR (125 MHz) δ 19.7, 19.9, 20.8, 26.4, 28.0, 32.0, 33.0, 38.5, 44.8, 45.0, 47.7, 48.1, 53.2, 64.9 (2C), 65.4 (2C), 104.3, 115.6, 141.9, 167.4, 197.1; HRMS calcd for C$_{22}$H$_{33}$NO$_5$S (M$^+$) $m/z$ 439.2029, found 439.2036. Compound 18b was obtained as a colorless oil: TLC $R_f$ 0.75 (EtOAc/toluene, 1:2); [α]$_D$ $^{22}$ $+$10.4 (c 1.67, CHCl$_3$); IR (neat) 2962, 2885, 1728, 1697 cm$^{-1}$; $^1$H-NMR (500 MHz) δ 0.94 (s, 3H), 1.10 (s, 3H), 1.29 (s, 3H), 1.30–1.42 (m, 2H), 1.58–1.65 (m, 2H), 1.74 (m, 1H), 1.87–1.94 (m, 4H), 2.07 (dd, 1H, $J = 7.8, 13.8$ Hz), 2.26 (m, 1H), 3.43 (d, 1H, $J = 13.9$ Hz), 3.48 (d, 1H, $J = 13.9$ Hz), 3.81–3.85 (m, 2H), 3.90–3.95 (m, 3H), 4.21 (s, 1H), 4.82 (t, 1H, $J = 4.4$ Hz), 5.12 (d, 1H, $J = 17.5$ Hz), 5.26 (d, 1H, $J = 10.9$ Hz), 5.98 (dd, 1H, $J = 10.9, 17.5$ Hz), 9.61 (s, 1H); $^{13}$C-NMR (125 MHz) δ 19.2, 19.9, 20.4, 26.4, 28.1, 32.6, 32.7, 38.1, 42.5, 44.5, 47.7, 48.2, 53.0, 64.9 (2C), 65.2 (2C), 104.4, 115.5, 143.0, 166.2, 197.5; HRMS calcd for C$_{22}$H$_{33}$NO$_5$S (M$^+$) $m/z$ 439.2029, found 439.2032.

(2R)-N-{[(2R,3S)-2-(Acetoxymethyl)-3,7-dimethyl-3-vinylcyclohex-6-enoyl]bornane-10,2-sultam (19a). To a cooled (0 °C) stirred solution of 7a (158 mg, 375 μmol) in EtOH (4 mL) was added NaBH$_4$ (14.2 mg, 375 μmol). The mixture was stirred at 0 °C for 4 h, quenched with saturated aqueous NH$_4$Cl (1 mL), diluted with H$_2$O (20 mL), and extracted with CH$_2$Cl$_2$ (10 mL × 3). The combined extracts were dried
and concentrated under reduced pressure to provide crude alcohol (152 mg), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude alcohol in CH$_2$Cl$_2$ (4 mL) were added Ac$_2$O (85 μL, 0.90 mmol), Et$_3$N (150 μL, 1.08 mmol), and DMAP (4.4 mg, 36 μmol). The mixture was stirred at room temperature for 2.5 h, diluted with CH$_2$Cl$_2$ (20 mL), and washed with H$_2$O (10 mL × 2). The combined aqueous layers were extracted with CH$_2$Cl$_2$ (30 mL). The combined organic layer and extract were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 137 mg (78% for 2 steps) of 19a as a colorless oil: TLC $R_f$ 0.61 (EtOAc/hexane, 1:2); [α]$_D$+21–38.4 (c 1.46, CHCl$_3$); IR (neat) 2964, 2884, 1745, 1690 cm$^{-1}$; $^1$H-NMR (500 MHz) δ 0.96 (s, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.27–1.47 (m, 3H), 1.55 (br s, 3H), 1.64 (br s, 3H), 1.65 (m, 1H), 1.81–1.92 (m, 5H), 1.99 (s, 3H), 2.09–2.13 (m, 2H), 3.35 (m, 1H), 3.43 (d, 1H, $J$ = 13.7 Hz), 3.50 (d, 1H, $J$ = 13.7 Hz), 3.94 (t, 1H, $J$ = 6.4 Hz), 4.22 (t, 1H, $J$ = 10.6 Hz), 5.01 (m, 1H), 5.01 (d, 1H, $J$ = 17.5 Hz), 5.16 (d, 1H, $J$ = 10.9 Hz), 5.79 (dd, 1H, $J$ = 10.9, 17.5 Hz); $^{13}$C-NMR (125 MHz) δ 17.5, 17.8, 20.0, 20.4, 20.9, 22.3, 25.6, 32.9, 38.6, 38.7, 43.3, 44.5, 47.7 (2C), 52.2, 53.3, 63.0, 65.6, 114.5, 124.1, 131.5, 143.3, 171.0, 172.7; HRMS calcd for C$_{25}$H$_{39}$NO$_5$S (M$^+$) m/z 465.2549, found 465.2556.

(2R)-N-[(2S,3R)-2-(Acetoxymethyl)-3,7-dimethyl-3-vinylloct-6-enoyl]bornane-10,2-sultam (19b). As described for the preparation of 19a from 7a, compound 7b (33.7 mg, 79.9 μmol) was treated with NaBH$_4$ (1.5 mg, 40 μmol) in EtOH (1 mL) to provide crude alcohol (37.0 mg), which was then treated with Ac$_2$O (19 μL, 0.20 mmol), Et$_3$N (33 μL, 0.24 mmol), and DMAP (1.1 mg, 9.0 μmol) in CH$_2$Cl$_2$ (1 mL) to provide 24.2 mg (65% for 2 steps) of 19b as a colorless oil: TLC $R_f$ 0.68 (EtOAc/hexane, 1:2); [α]$_D$+20–54.7 (c 1.06, CHCl$_3$); IR (neat) 2966, 2886, 1742, 1687 cm$^{-1}$; $^1$H-NMR (500 MHz) δ 0.97 (s, 3H), 1.18 (s, 3H), 1.19 (s, 3H), 1.35–1.48 (m, 3H), 1.57 (br s, 3H), 1.61 (m, 1H), 1.65 (br s, 3H), 1.86–1.93 (m, 5H), 1.95 (s, 3H), 2.10 (dd, 1H, $J$ = 7.8, 13.8 Hz), 2.19 (m, 1H), 3.26 (dd, 1H, $J$ = 3.7, 10.6 Hz), 3.47 (d, 1H, $J$ = 13.8 Hz), 3.52 (d, 1H, $J$ = 13.8 Hz), 3.94 (dd, 1H, $J$ = 5.2, 7.8 Hz), 4.06 (t, 1H, $J$ = 10.6 Hz), 4.56 (dd, 1H, $J$ = 3.7, 10.6 Hz), 5.02 (d, 1H, $J$ = 17.4 Hz), 5.06 (m, 1H), 5.16 (d, 1H, $J$ = 11.3 Hz), 5.84 (dd, 1H, $J$ = 11.3, 17.4 Hz); $^{13}$C-NMR (125 MHz) δ 17.6, 18.6, 19.9, 20.8, 21.1, 22.5, 25.7, 26.3, 33.0, 37.9, 38.6, 42.4, 44.6, 47.7, 47.8, 52.0, 53.3, 64.6, 65.8, 114.2, 124.5, 131.2, 143.9, 170.6, 172.6; HRMS calcd for C$_{25}$H$_{39}$NO$_5$S (M$^+$) m/z 465.2549, found 465.2558.

(2R)-N-[(2R,3S)-2-(Acetoxymethyl)-6-(tert-butyldiphenysilyloxy)-3-methyl-3-vinylhexanoyl]bornane-10,2-sultam (20a). As described for the preparation of 19a from 7a, compound 15a (150 mg, 236 μmol) was treated with NaBH$_4$ (4.4 mg, 0.12 mmol) in EtOH (3 mL) to provide crude alcohol (152 mg), which was then treated with Ac$_2$O (56 μL, 0.59 mmol), Et$_3$N (99 μL, 0.71 mmol), and DMAP (3.0 mg, 25 μmol) in CH$_2$Cl$_2$ (3 mL) to provide 151 mg (94% for 2 steps) of 20a as a colorless oil: TLC $R_f$ 0.66 (EtOAc/toluene, 1:5); [α]$_D$+23–28.6 (c 2.01, CHCl$_3$); IR (neat) 2960, 2859, 1744, 1691 cm$^{-1}$; $^1$H-NMR (500 MHz) δ 0.92 (s, 3H), 1.03 (s, 9H), 1.03 (s, 3H), 1.07 (s, 3H), 1.32–1.46 (m, 5H), 1.72 (m, 1H), 1.80 (m, 1H), 1.88–1.90 (m, 2H), 1.98 (s, 3H), 2.06–2.09 (m, 2H), 3.34 (m, 1H), 3.41 (d, 1H, $J$ = 13.8 Hz), 3.47 (d, 1H, $J$ = 13.8 Hz), 3.54–3.60 (m, 2H), 3.92 (t, 1H, $J$ = 6.3 Hz), 4.22 (t, 1H, $J$ = 10.6 Hz), 4.36 (dd, 1H, $J$ = 3.4, 10.6 Hz), 4.99 (d, 1H, $J$ = 17.5 Hz), 5.13 (d, 1H, $J$ = 11.0 Hz), 5.75 (dd, 1H, $J$ = 11.0, 17.5 Hz), 7.35–7.43 (m, 6H), 7.63–7.64 (m, 4H); $^{13}$C-NMR (125 MHz) δ 18.2, 19.1,
19.9, 20.5, 20.9, 26.5, 26.8 (3C), 27.0, 32.9, 34.4, 38.6, 43.0, 44.4, 47.6 (2C), 52.2, 53.3, 63.0, 64.1, 65.6, 114.6, 127.6 (4C), 129.5 (2C), 133.9, 134.0, 135.5 (2C), 135.6 (2C), 143.2, 171.0, 172.6; HRMS calcd for C$_{34}$H$_{44}$NO$_6$SSi (M$^+$–t-C$_4$H$_9$) m/z 622.2659, found 622.2677.

**Synthesis of 19a from 20a.** To a cooled (0 °C) stirred solution of 20a (12.2 mg, 17.9 μmol) in THF (3 mL) was added HF·pyridine (0.2 mL). The mixture was stirred at room temperature for 5 h and quenched with saturated aqueous NaHCO$_3$ (1 mL). This was diluted with H$_2$O (15 mL) and extracted with CH$_2$Cl$_2$ (10 mL × 4). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 8.0 mg (quant.) of alcohol as white crystals: mp 113–115 °C; TLC $R_f$ 0.24 (EtOAc/hexane, 1:2); $[\alpha]_D^{20} –42.7$ (c 1.02, CHCl$_3$); IR (neat) 3529, 2961, 2882, 1741, 1690 cm$^{-1}$; $^1$H-NMR (500 MHz) $\delta$ 0.97 (s, 3H), 1.09 (s, 3H), 1.16 (s, 3H), 1.35–1.58 (m, 5H), 1.67 (m, 1H), 1.88-1.92 (m, 3H), 1.99 (s, 3H), 2.09–2.15 (m, 2H), 3.37 (m, 1H), 3.44 (d, 1H, $J = 13.9$ Hz), 3.50 (d, 1H, $J = 13.9$ Hz), 3.54 (m, 1H), 3.61 (m, 1H), 3.95 (t, 1H, $J = 6.5$ Hz), 4.20 (t, 1H, $J = 10.7$ Hz), 4.40 (dd, 1H, $J = 3.4$, 10.7 Hz), 5.02 (d, 1H, $J = 17.5$ Hz), 5.15 (d, 1H, $J = 11.3$ Hz), 5.80 (dd, 1H, $J = 11.3$, 17.5 Hz); $^{13}$C-NMR (125 MHz) $\delta$ 18.7, 19.9, 20.5, 20.9, 26.5, 27.1, 32.9, 34.4, 38.6, 42.9, 44.5, 47.7 (2C), 51.8, 53.3, 63.0, 63.1, 65.7, 114.5, 143.1, 171.2, 172.6; HRMS calcd for C$_{22}$H$_{35}$NO$_6$S (M$^+$) m/z 441.2185, found 441.2192.

To a cooled (0 °C) stirred solution of alcohol (20.9 mg, 47.3 μmol) in CH$_2$Cl$_2$ (1 mL) was added Dess–Martin periodinane (30.3 mg, 71.4 μmol). The mixture was stirred at room temperature for 2 h and Dess–Martin periodinane (31.1 mg, 73.3 μmol) was added. After being stirred at room temperature for 2.5 h, the mixture was quenched with saturated aqueous Na$_2$S$_2$O$_3$ (3 mL) and saturated aqueous NaHCO$_3$ (3 mL), diluted with H$_2$O (4 mL), and extracted with CH$_2$Cl$_2$ (15 mL × 3). The combined extracts were washed with saturated brine (20 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to provide 20.8 mg (quant.) of aldehyde as a colorless oil, which was immediately used in the next step: TLC $R_f$ 0.33 (EtOAc/hexane, 1:2); $^1$H-NMR (300 MHz) $\delta$ 0.97 (s, 3H), 1.07 (s, 3H), 1.17 (s, 3H), 1.33–1.48 (m, 4H), 1.68 (m, 1H), 1.89–2.04 (m, 2H), 1.99 (s, 3H), 2.11–2.13 (m, 2H), 2.41 (t, 2H, $J = 7.8$ Hz), 3.38 (m, 1H), 3.44 (d, 1H, $J = 13.9$ Hz), 3.52 (d, 1H, $J = 13.9$ Hz), 3.95 (t, 1H, $J = 6.5$ Hz), 4.21 (t, 1H, $J = 10.7$ Hz), 4.37 (dd, 1H, $J = 3.6$, 10.7 Hz), 5.05 (d, 1H, $J = 17.5$ Hz), 5.20 (d, 1H, $J = 10.7$ Hz), 5.78 (dd, 1H, $J = 10.7$, 17.5 Hz), 9.73 (s, 1H).

The following reaction was carried out under Ar. To a cooled (0 °C) stirred suspension of $i$-PrP$^+$Ph$_3$I (21.9 mg, 49.1 μmol) in THF (1 mL) was added $t$-BuLi (1.61 M solution in pentane, 29 μL, 47 μmol). The mixture was stirred at 0 °C for 30 min and a solution of aldehyde (6.9 mg, 16 μmol) in THF (1 mL) was added. After being stirred at 0 °C for 20 min, the mixture was diluted with H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (15 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 3.3 mg (45%) of 19a.

(2R)-N-[(2R,3S)-2-(Acetoxymethyl)-5-(1,3-dioxolan-2-yl)-3-methyl-3-vinylpentanoyl]bornane-10,2-sultam (21a). As described for the preparation of 19a from 7a, compound 18a (154 mg, 350 μmol) was treated with NaBH$_4$ (6.5 mg, 0.17 mmol) in EtOH (3 mL) to provide crude alcohol (158 mg), which was then treated with Ac$_2$O (83 μL, 0.88 mmol), Et$_3$N (146 μL, 1.05 mmol), and DMAP (4.4 mg, 36 μmol)
in CH$_2$Cl$_2$ (4 mL) to provide 150 mg (88% for 2 steps) of 21a as a colorless oil: TLC $R_f$ 0.65 (EtOAc/toluene, 1:2); [$\alpha$]D$^21$–39.5 (c 1.02, CHCl$_3$); IR (neat) 2962, 2884, 1743, 1690 cm$^{-1}$; $^1$H-NMR (500 MHz) $\delta$ 0.97 (s, 3H), 1.08 (s, 3H), 1.16 (s, 3H), 1.36 (m, 1H), 1.43–1.50 (m, 2H), 1.55–1.60 (m, 2H), 1.78 (m, 1H), 1.87–1.91 (m, 3H), 1.99 (s, 3H), 2.11–2.18 (m, 2H), 3.35 (m, 1H), 3.43 (d, 1H, $J = 13.7$ Hz), 3.50 (d, 1H, $J = 13.7$ Hz), 3.78–3.81 (m, 2H), 3.91–3.95 (m, 3H), 4.22 (t, 1H, $J = 10.7$ Hz), 4.38 (dd, 1H, $J = 3.5$, 10.7 Hz), 4.76 (t, 1H, $J = 4.6$ Hz), 5.01 (d, 1H, $J = 17.5$ Hz), 5.17 (d, 1H, $J = 10.7$ Hz), 5.77 (dd, 1H, $J = 10.7$, 17.5 Hz); $^{13}$C-NMR (125 MHz) $\delta$ 18.1, 20.0, 20.5, 20.9, 26.5, 28.3, 32.3, 32.9, 38.6, 42.8, 44.5, 47.7 (2C), 52.2, 53.3, 63.0, 64.7, 64.8, 65.6, 104.5, 114.9, 142.9, 171.0, 172.5; HRMS calcd for C$_{24}$H$_{37}$NO$_7$S (M$^+$) m/z 483.2291, found 483.2291.

Synthesis of 19a from 21a. A solution of 21a (80.5 mg, 166 μmol) in THF (12 mL) and 4 M aqueous HCl (12 mL) was stirred at 0 °C for 15 h, diluted with saturated aqueous NaHCO$_3$ (50 mL), and extracted with CH$_2$Cl$_2$ (60 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to provide 58.2 mg (80%) of aldehyde, which was identical with the aldehyde derived from 20a and converted into 19a as described above.

4. Conclusions

In conclusion, we have developed an asymmetric Claisen rearrangement using Oppolzer’s camphorsultam as a chiral auxiliary. Notably, rearrangement products 7a, 15a, and 18a possess a chiral quaternary carbon with high enantiomeric purity. In addition, this method has been applied to the total synthesis of (+)-bakuchiol (4). Further studies and applications of this work to natural product synthesis are in progress and will be reported in due course.

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*Sample Availability:* Not available.

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