Construction of Optically Active Isotwistanes and Aminocyclitols Using Chiral Cyclohexadiene as a Common Intermediate

Shinji Harada, a,b Kexin Li, a Ryuto Kino, a Takuya Takeda, a Chia-Hsien Wu, a,c Shiharu Hiraoka, a and Atsushi Nishida*, a,b

*Graduate School of Pharmaceutical Sciences, Chiba University; 1–8–1 Inohana, Chuo-ku, Chiba 260–8675, Japan; a Molecular Chirality Research Center, Chiba University; 1–33 Yayoi-cho, Inage-ku, Chiba 263–8522, Japan; and c Department of Chemistry, National Tsing Hua University; 101, Sec 2, Kuang-Fu Rd., Hsinchu 30013, Taiwan.

Received May 29, 2016; accepted July 9, 2016; advance publication released online July 22, 2016

We have developed a new method for synthesizing chiral isotwistane and homoisotwistane skeletons as well as aminocyclitols in a highly stereoselective manner. These results were achieved through the use of a common intermediate, which was derived from the ytterbium-catalyzed asymmetric Diels–Alder reaction of Danishefsky diene.

Key words isotwistane; homoisotwistane; aminocyclitol; Diels–Alder; asymmetric catalysis; hetero-Diels–Alder

Many biologically active compounds possess a cyclic skeleton with center chirality in their structure. Therefore, the stereoselective synthesis of optically active carbon frameworks is in high demand for synthetic and medicinal chemists. The Diels–Alder reaction has been widely used for this purpose to construct six-membered carbocycles, and the catalytic and enantioselective variant of this reaction has been studied for decades.1) Our group reported the first example of the catalytic and asymmetric Diels–Alder reaction of Danishefsky diene (1)2,3) (Chart 1). Functionalized cyclohexene 3 was obtained in optically pure form, and 3 could be transformed to cyclohexene 4 in quantitative yield. Both functionalized compounds could be potential synthetic intermediates, and we have previously demonstrated the synthetic utility of this reaction.4–7)

In the present study, silyloxy-substituted cyclohexadiene 7 derived from 4 was shown to be a key intermediate for two types of synthetically useful chiral building blocks, i.e., the tricyclo[4.3.1.03,7]decane (isotwistane 8, n=1) and tricyclo[5.3.1.03,8]undecane (homoisotwistane 8, n=2) skeletons via the intramolecular Diels–Alder reaction, and aminocyclitol 10 via the intermolecular hetero-Diels–Alder reaction with nitrosobenzene (Chart 2).

Results and Discussion

Construction of Isotwistane and Homoisotwistane Skeletons

Isotwistane is an all-carbon tricyclic compound, and its structural motif is found in natural products such as pupukeananes,8–12) palhinines,13–15) and seychellene.16–18) These types of compounds with (homo)isotwistane skeleton were attracted by their potential for perfumery, and the difference of scent derived from their chirality could be an important research target. Due to the unique structure of isotwistanes, the total syntheses of biologically active compounds with isotwistane skeletons have been studied by many research groups.19–23) Most of these studies have used the intramolecular Diels–Alder reaction to build the fused structure of isotwistane. Based on these previous studies, we planned the synthesis of a chiral isotwistane skeleton by two Diels–Alder reactions: our asymmetric Diels–Alder reaction and a sequential intramolecular Diels–Alder reaction.

Dienophiles 2a–d with an olefin in the side chain (R) were prepared. We expected that Lewis acidic activation of the dienophile would occur site-specifically only at the acyloxazolidinone moiety, and the Diels–Alder reaction would take place at the adjacent olefin. With the application of our ytterbium catalyst,3) the asymmetric Diels–Alder reaction proceeded chemoselectively. Moreover, no diastereoisomer of 3 was observed (Chart 3). After conversion to cyclic enone 4, the enantioselectivity was determined by chiral HPLC.

The key intermediate 7 was synthesized with the use of tert-butyldimethylsilyl (TBS) triflate and triethylamine. Dienes 7c and d were rather unstable on silica gel, and thus were used for the next reaction after only rough purification. An intramolecular Diels–Alder reaction was performed between the resulting diene moiety and each olefin in the side chain (Chart 4).

Thermal activation of 7 successfully promoted the intramolecular Diels–Alder reaction to give the isotwistane (8, n=1) or homoisotwistane (8, n=2) skeleton in moderate yields. For the reaction using 7c and d, the addition of dibutylhydroxytoluene (BHT) (10mol %) was effective for improving the yield of the product. Partial desilylation was observed in every reaction, and therefore the crude mixture of 8 was directly treated under acidic conditions to give chiral isotwistane and its analogues 11.

Intermolecular Hetero-Diels–Alder Reaction, and the Synthesis of Aminocyclitols

Having successfully obtained the tricyclic carbon frameworks through the intramolecular Diels–Alder reaction, we next extended the application of 7 to the intermolecular Diels–Alder reaction. While we tried several dienophiles, nitrosobenzene24,25) was quite reactive in the Diels–Alder reaction with 7e. The reaction was completed in hexane at 40°C, and afforded the bicyclic compound 12 in 90% yield (major–minor=79:11, Chart 5). The relative stereochemistry of the major product was confirmed by X-ray crystallographic analysis.26)

To evaluate the steric effect of the oxazolidinone group on the diastereoselectivity, the acyl-oxazolidinone unit of 7e...
was converted to a primary alcohol as shown in Chart 6. The intermolecular hetero-Diels–Alder reaction of 13 with nitroso benzene proceeded smoothly at room temperature to give cycloadducts 14 in 82% yield (major–minor=76:9) with opposite π–face selectivity.

The relative stereochemistry of each diastereomer of 14 was
determined as follows: reduction of the acyl-oxazolidinone moiety of 12 major with LiBH₄ afforded 14 minor (Chart 7), both of which had comparable spectral data. In contrast, the reduction of 12 minor gave 14 major. Acyl-oxazolidinone and primary alcohol affected the facial selectivity of the diene compound in the hetero-Diels–Alder reaction. Thus, we realized the stereoselective access to both diastereoisomers of hetero-bicycle 12 and 14. Furthermore, no regioisomer was observed.

The N–O bond of 12 major was then successfully cleaved by hydrogenolysis without loss of the silyl enol ether moiety, and sequential Rubottom oxidation afforded pentasubstituted cyclohexanone 16 (Chart 8). The stereochemistry of the newly bound oxygen functionality was unambiguously confirmed by X-ray crystallographic analysis of compound 17. ²⁷

Chemo- and stereoselective reduction of the carbonyl of 16 afforded hexasubstituted cyclohexane derivative 18 in 86% yield with good diastereoselectivity (Chart 9). The relative...
configuration of 18 major was identified by a n Oe experiment (Fig. 1). Attempted conversion to triol 19 from isolated 18 with 1.5 equiv. of lithium borohydride resulted in messy reaction mixture. Alternatively, triol 19 was obtained by the use of an excess amount of lithium borohydride to 16, although the diastereoselectivity of the reduction of carbonyl was decreased to 3:2. These hexasubstituted chiral cyclohexanes 18 and 19 could be used for the synthesis of chiral aminocyclitols and their derivatives. In addition, no racemization was observed throughout the whole process in Charts 8 and 9.

Conclusion
We have achieved two synthetic applications of our asymmetric Diels–Alder reaction using chiral cyclohexadiene 7 as a common intermediate. The intramolecular Diels–Alder reaction was used to give the isowistane and homoisowistane skeletons. The conversion to aminocyclitols was also accomplished via the intermolecular hetero-Diels–Alder reaction of 7. These results extend the versatility of our ytterbium catalysis.

Experimental
General Information
NMR spectra were recorded at 400 or 600 MHz for 1H-NMR, and at 100 or 150 MHz for 13C-NMR. Chemical shifts for proton are reported in parts per million downfield from tetramethylsilane, and are referenced to residual protium in the NMR solvent (CDCl3 δ: 7.26 ppm). For 13C-NMR, chemical shifts were reported in the scale relative to the NMR solvent (CDCl3 δ: 77.0 ppm) as an internal reference. Infrared spectra were recorded on an attenuated total reflectance (ATR). Optical rotations were measured at 589 nm. Mass spectra were recorded using electrospray ionization (ESI) mode with TOF analyzer. The enantiomeric excess (ee) was determined by HPLC analysis measured at 254 nm. X-Ray crystallographic data were collected at −180°C using filtered Cu-Kα radiation. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise noted. Dry CH2Cl2 for catalyst was purchased from Kanto Chemical Co., Inc. Ytterbium(III) trifluoromethanesulfonate (Yb(OTf)3) was purchased from Aldrich. Other solvents and reagents were purified by usual methods. Flash column chromatography was performed on silica gel, 60 μm particle, unless otherwise noted.

Dienophiles 2a–d were synthesized by following known procedures. Spectral data of synthetic intermediates were also identified with the data in references.

(E)-3-(Hepta-2,6-dienoyl)oxazolidin-2-one (2a) 1H-NMR (400 MHz, CDCl3) δ: 2.25 (2H, dt, J = 6.4, 6.4 Hz), 2.39 (2H, dt, J = 6.8, 6.8 Hz), 4.07 (2H, t, J = 8.4 Hz), 4.42 (2H, d, J = 8.4 Hz), 5.01 (1H, dt, J = 2.0, 10.0 Hz), 5.04 (1H, ddt, J = 2.0, 2.0, 16.8 Hz), 5.81 (1H, dt, J = 6.4, 10.0, 16.4 Hz), 7.16 (1H, d, J = 6.4, 15.2 Hz), 7.26 (1H, dt, J = 1.2, 15.6 Hz); 13C-NMR (100 MHz, CDCl3) δ: 31.9, 32.0, 42.7, 62.0, 115.6, 120.3, 137.0, 150.6, 153.5, 165.2; IR (ATR): v 2924, 1769, 1681, 1633 cm−1; high resolution (HR)-MS (ESI) m/z 477.2199 [M+2+MeOH+Na]+ (Calcd for C22H34N2O8Na: 477.2199).

Methyl (2E,7E)-9-Oxo-9-(2-oxooxazolidin-3-yl)nona-2,7-dienoate (2b) 1H-NMR (400 MHz, CDCl3) δ: 1.65 (2H, tt, J = 8.0, 8.0 Hz), 2.25 (2H, dt, J = 7.2, 7.2 Hz), 2.32 (2H, dt, J = 7.6, 7.6 Hz), 3.73 (3H, s), 4.09 (2H, t, J = 7.61 Hz), 4.43 (2H, t, J = 7.21 Hz), 5.84 (1H, d, J = 15.6 Hz), 6.94 (1H, dt, J = 6.8, 15.6 Hz), 7.13 (1H, dt, J = 6.8, 15.6 Hz), 7.25 (1H, d, J = 15.6 Hz); 13C-NMR (100 MHz, CDCl3) δ: 26.4, 31.5, 31.9, 42.7, 51.4, 62.0, 120.6, 121.6, 148.3, 150.2, 153.3, 165.1, 166.9; IR (ATR): v 2926, 1770, 1717, 1681, 1634 cm−1; HR-MS (ESI) m/z 400.0160 [M+Cs]+ (Calcd for C24H36N2O8Cs: 400.0161).

(E)-3-(7-Methyl-2,7-dienoyl)oxazolidin-2-one (2c) 1H-NMR (600 MHz, CDCl3) δ: 1.65 (2H, t, J = 7.6 Hz), 2.32 (2H, dt, J = 7.8 Hz), 2.88 (2H, dt, J = 7.2, 7.2 Hz), 4.07 (2H, t, J = 7.81 Hz), 4.43 (2H, t, J = 8.41 Hz), 4.69 (1H, s), 4.73 (1H, s), 7.18 (1H, dt, J = 7.2, 15.0 Hz), 7.25 (1H, d, J = 15.0 Hz); 13C-NMR (100 MHz, CDCl3) δ: 22.2, 25.9, 32.1, 37.1, 42.7, 62.0, 110.4, 120.2, 145.0, 151.4, 153.5, 165.3; IR (ATR): v 2932, 1770, 1680, 1633 cm−1; HR-MS (ESI) m/z 246.1113 [M+Na]+ (Calcd for C13H17NO3Na: 246.1106).

Ethyl (7E)-3-Methyl-9-oxo-9-(2-oxooxazolidin-3-yl)nona-2,7-dienoate (2d) (for Major E-Isomer) 1H-NMR (400 MHz, CDCl3) δ: 1.28 (3H, t, J = 7.6 Hz), 1.69 (2H, tt, J = 7.6, 7.6 Hz), 2.15 (3H, d, J = 1.2 Hz), 2.18 (2H, t, J = 7.61 Hz), 2.29 (2H, dt, J = 8.0, 8.0 Hz), 4.08 (2H, t, J = 8.01 Hz), 4.15 (2H, q, J = 7.2 Hz), 4.43 (2H, t, J = 8.01 Hz), 5.67 (1H, s), 7.14 (1H, d, J = 8.8, 15.4 Hz), 7.25 (1H, d, J = 15.4 Hz); 13C-NMR (100 MHz, CDCl3) δ: 14.2, 18.6, 25.9, 31.9, 40.1, 42.7, 59.5, 62.0, 116.1, 120.5, 150.4, 153.5, 158.8, 165.1, 166.7; IR (ATR): v 2916, 1772, 1707, 1681, 1631 cm−1; HR-MS (ESI) m/z 318.1318 [M+Na]+ (Calcd for C15H21NO5Na: 318.1317).

3-((1R,6S)-6-(But-3-en-1-yl)-4-oxy-cyclohex-2-ene-1-carbonyl)oxazolidin-2-one (4a) Yb(OTf)3 (37.2 mg, 60.0 μmol) and (R)-BINUREA (6h) (34.8 mg, 60.0 μmol) taken in a test tube with a stirring bar were heated at 120°C under reduced conditions. 

Chart 9. Synthesis of Aminocyclitols Starting from 4e with 95% Enantiomeric Excess (ee)
pressure (<0.1 mmHg) for 30 min. After being allowed to cool to room temperature, the test tube was charged with dry argon. Dichloromethane (CH₂Cl₂) (2.0 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (18.0 µL, 120.0 µmol) were added successively, and the resulting solution was stirred for 2 h at room temperature. The reaction vessel was cooled to 0°C and a solution of dienophile 2a (117.1 mg, 0.60 mmol) in CH₂Cl₂ (1.0 mL) was added, followed by the addition of Danishefsky diene (1) (300 µL, 1.2 mmol). The mixture was stirred at the same temperature for 3 h, and water (5.0 mL) was then added. Insoluble materials were filtered through a pad of Celite®. The water layer was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the diastereoselectivity (a single diastereomer) was checked by chiral HPLC analysis. 1H-NMR (400 MHz, CDCl₃) of the resulting crude mixture of 3a was dissolved in CH₂Cl₂ (3.0 mL), and BF₃·OEt₂ (188 µL, 1.5 mmol) was added at 0°C and a solution of dienophile 2b (117.1 mg, 0.60 mmol) at 78°C. After being stirred for 10 min at the same temperature, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=5:1) to give 3b (183.4 mg, 91%). The enantiomeric excess was determined by HPLC analysis. 1H-NMR (400 MHz, CDCl₃) of 3b: δ 1.38–1.54 (4H, m), 2.16–2.15 (2H, m), 2.25 (1H, dd, J=10.4, 16.0 Hz), 2.53–2.62 (1H, m), 2.76 (1H, dd, J=4.4, 16.4 Hz), 3.73 (2H, s), 4.10 (2H, ddd, J=4.4, 8.0, 16.0 Hz), 4.50 (2H, dt, J=2.0, 8.0 Hz), 4.62 (1H, dt, J=3.6, 7.2 Hz), 5.81 (1H, ddd, J=2.0, 2.0, 16.4 Hz), 6.13 (1H, dd, J=2.4, 10.0 Hz), 6.72 (1H, dd, J=3.2, 10.0 Hz), 6.90 (1H, ddd, J=7.6, 7.6, 15.6 Hz); 13C-NMR (100 MHz, CDCl₃) of 3b: δ 24.8, 31.8, 33.2, 36.6, 41.0, 42.8, 46.3, 51.4, 62.2, 121.5, 130.7, 144.5, 148.5, 153.3, 167.0, 171.6, 198.0; IR (ATR): ν 2926, 1771, 1677 cm⁻¹; HR-MS (ESI) m/z 358.1272 [M+Na]+ (Calculated for C₁₁H₁₇NO₃Na 358.1267); [α]D₂⁰ +107.2 (c=1.02, CHCl₃); HPLC conditions Daicel CHIRALPAK AS-H, e: Hex–IPA=55:45, f: f=0.8 mL/min, t: 34.7 (minor) and 37.9 (major) min.

3-((1R,6S)-6-(4-Methylpent-4-en-1-yl)-4-oxocyclohex-2-ene-1-carboxyl)oxazolidin-2-one (4c) Yb(OTf)₃ (44.1 mg, 76.0 µmol) and (R)-BINUREA (60 µL, 76.0 µmol) were added successively, and the resulting solution was stirred for 2 h at room temperature. The reaction vessel was cooled to 0°C and a solution of dienophile 2c (170 mg, 0.76 mmol) in CH₂Cl₂ (1.2 mL) was added, followed by the addition of Danishefsky diene (1) (369 µL, 1.52 mmol). The mixture was stirred at the same temperature for 3 h, and water (5.0 mL) was then added. Insoluble materials were filtered through a pad of Celite®. The water layer was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=5:1) to give 4c (142.8 mg, 64%). The enantiomeric excess was determined by chiral HPLC analysis. 1H-NMR (400 MHz, CDCl₃) of 4c: δ 1.22 (1H, d, J=6.0 Hz), 1.35–1.49 (3H, m), 1.68 (3H, s), 1.94–2.01 m.
Enone 4a (123.6 mg, 0.47 mmol) was dissolved in CH₂Cl₂ (0.9 mL). NEt₃ (183 µL, 1.31 mmol) and TBSOTf (129 µL, 0.56 mmol) were added successively to the solution at 0°C. After the solution was stirred for 2 h, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=2:1) to give 7a (158.7 mg, 90%). 1H-NMR (400 MHz, CDCl₃) δ: 0.14 (6H, s), 0.92 (9H, s), 1.48 (1H, ddd, J=6.8, 10.0, 15.6 Hz), 1.55–1.64 (1H, m), 2.05–2.18 (2H, m), 2.84 (1H, ddd, J=5.6, 5.6, 8.4 Hz), 4.01 (2H, ddd, J=7.6, 10.8, 10.8 Hz), 4.21 (1H, ddd, J=2.0, 5.6, 5.6 Hz), 4.42 (2H, t, J=7.6 Hz), 4.92 (1H, ddd, J=2.0, 4.8, 4.95) (1H, dd, J=1.2, 10.0 Hz), 5.01 (1H, ddd, J=2.0, 15.6 Hz), 5.71 (1H, dd, J=5.2, 10.4 Hz), 5.80 (1H, ddt, J=6.4, 10.0, 16.8 Hz), 5.83 (1H, d, J=10.0Hz); 13C-NMR (100 MHz, CDCl₃) δ: −4.5, 18.0, 25.7, 30.8, 33.7, 34.4, 42.9, 43.9, 62.0, 106.4, 114.7, 123.1, 128.5, 138.5, 146.7, 153.2, 172.5; IR (ATR) ν: 2928, 2857, 1774, 1689, 1654 cm⁻¹; HR-MS (ESI) m/z: 378.2984 [M+H]^+ (Calcd for C₂₀H₂₅NO₃Si: 378.2701; [M]^{1}HNO₃Si: +309.4 (c=1.00, CHCl₃).

Methyl (E)-6-(15S,6S)-3-(tert-Butyldimethylsilyloxy)-6-(2-oxoazolidin-3-carbonyl)cyclohexa-2,4-dien-1-yl)hex-2-enoate (7b) Enone 4b (183.4 mg, 0.55 mmol) was dissolved in CH₂Cl₂ (1.1 mL). NEt₃ (213 µL, 1.53 mmol) and TBSOTf (153 µL, 0.66 mmol) were added successively to the solution at 0°C. After the solution was stirred for 2 h, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=2:1) to give 7b (234.6 mg, 95%). 1H-NMR (400 MHz, CDCl₃) δ: 0.14 (6H, s), 0.92 (9H, s), 1.36–1.61 (4H, m), 2.14–2.24 (2H, m), 2.81–2.86 (1H, m), 3.72 (3H, s), 4.01 (2H, ddd, J=8.4, 11.6, 11.6 Hz), 4.19 (1H, ddd, J=2.0, 5.6, 5.6 Hz), 4.43 (2H, dt, J=2.0, 8.4 Hz), 4.89 (1H, dd, J=1.6, 5.2 Hz), 5.70 (1H, dd, J=4.8, 10.0 Hz), 5.81 (1H, d, J=15.6 Hz), 5.83 (1H, dd, J=1.6, 10.0 Hz), 6.94 (1H, dt, J=7.2, 15.6 Hz); 13C-NMR (100 MHz, CDCl₃) δ: −4.5, 18.0, 25.1, 25.6, 32.4, 34.1, 42.9, 43.9, 51.4, 62.0, 106.3, 121.1, 123.2, 128.5, 146.8, 149.2, 153.2, 167.1, 172.4; IR (ATR) ν: 2929, 2857, 1775, 1699, 1653 cm⁻¹; HR-MS (ESI) m/z: 472.2138 [M+Na]^+ (Calcd for C₂₄H₃₃NO₃SiNa: 472.2131; [M]^{25}HNO₃Si: +266.2 (c=1.00, CHCl₃).

3-((15S,6S)-4-((tert-Butyldimethylsilyloxy)-6-(4-methylpent-4-en-1-yl)cyclohexa-2,4-dien-1-carbonyl)oxazolidin-2-one (7e) Enone 4e (119.0 mg, 0.44 mmol) was dissolved in CH₂Cl₂ (8.0 mL). NEt₃ (341 µL, 2.44 mmol) and TBSOTf (281 µL, 1.2 mmol) were added successively to the solution at 0°C. After the solution was stirred for 1 h, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was purified by short-pod column chromatography (SiO₂, hexane–AcOEt=2:1) to give impure 7e (c=143.6 mg, <89%). Compound 7e was rather unstable, thus 7e was used for the next intramolecular
Diels–Alder reaction without further purification.

**Ethyl (E)-6-((tert-Butyldimethylsilyl)oxy)-6-(2-oxooxazoline-3-carbonyl)cyclohexa-2,4-dien-1-yl)-3-methylhex-2-enoate (7d)** Enone 4d (216.9 mg, 0.60 mmol) was dissolved in CH₂Cl₂ (12 mL). NEt₃ (466 µL, 3.35 mmol) and TBSOTf (315 µL, 1.37 mmol) were added successively to the solution at 0°C. After the solution was stirred for 1 h, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was roughly purified by short-path column chromatography (SiO₂, hexane–AcOEt=2:1) to give impure 7d (<263.7 mg, <93%). Compound 7d was used for the next intramolecular Diels–Alder reaction without further purification.

3-((1S,3aS,4R,5R,7aR)-7-Oxocyclooctyl-1H-1,5-methanodine-4-carbonyloxa zdin-2-one (11a) Diene 7a (67.5 mg, 0.22 mmol) was dissolved in toluene (5.0 mL), and was stirred under refluxing condition for 22 h. After the solution was cooled to 0°C, TFA (77 µL, 1.0 mmol) was added to the mixture. After the solution was stirred for 10 min, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with AcOEt, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=3:2) to give 11a (25.7 mg, 49%). ¹H-NMR (400 MHz, CDCl₃) δ: 1.55–1.66 (3H, m), 1.90–2.02 (4H, m), 2.07 (1H, dd, J=2.4, 18.8 Hz), 2.23 (1H, dd, J=4.4, 4.4 Hz), 2.40–2.46 (2H, m), 2.91 (1H, s), 3.61 (1H, s), 3.96–4.10 (2H, m), 4.42 (2H, t, J=8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: 29.0, 32.5, 33.5, 35.0, 35.4, 38.5, 39.2, 42.9, 54.1, 62.0, 153.1, 174.5, 215.4; IR (ATR): ν 2944, 2871, 1766, 1718, 1681 cm⁻¹; HR-MS (ESI) [M+Na⁺]δ 286.1056 (Calcd for C₁₉H₂₁NO₄Na: 286.1055); [α]D²⁺ +26.0 (c=1.00, CHCl₃).

**Methyl (1S,4aR,5S,6R,8aS,9S)-8-Oxo-9-(2-oxooxazolidine-3-carbonyl)decahydro-1,6-methanophthalene-5-carboxylate (11d)** Diene 7d (148.3 mg, 0.31 mmol) was dissolved in toluene (6.0 mL), and BHT (6.8 mg, 31 µmol) was added to the solution. The solution was stirred at 165°C (in a sealed tube) for 45 h. After toluene was evaporated under reduced pressure, CH₂Cl₂ (3.1 mL) and TFA (46 µL, 0.62 mmol) were added to the mixture. After stirred for 5 min, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with AcOEt, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=1:1) to give 11d (67.5 mg, 56% from 4d). ¹H-NMR (400 MHz, CDCl₃) δ: 0.90 (3H, s), 1.16–1.22 (1H, m), 1.27 (3H, t, J=7.2 Hz), 1.43 (1H, dt, J=4.0, 12.8 Hz), 1.52 (1H, d, J=4.4 Hz), 1.64–1.70 (1H, m), 1.80 (2H, d, J=11.2 Hz), 1.86 (1H, d, J=2.8 Hz), 2.00 (1H, dt, J=2.8, 19.6 Hz), 2.73 (1H, t, J=2.0 Hz), 2.82–2.84 (2H, m), 2.94 (1H, d, J=19.6 Hz), 3.74 (1H, s), 3.97–4.09 (2H, m), 4.12 (2H, q, J=7.2 Hz), 4.43 (2H, t, J=8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: 14.2, 17.2, 26.0, 28.0, 29.9, 33.9, 34.0, 34.3, 37.5, 43.0, 44.8, 47.0, 50.9, 59.0, 60.3, 62.0, 153.3, 173.0, 214.0; IR (ATR): ν 2929, 2857, 1771, 1716, 1691 cm⁻¹; HR-MS (ESI) [M+Na⁺]δ 386.1576 (Calcd for C₁₉H₂₁NO₄Na: 386.1580); [α]D²⁻ +29.1 (c=0.99, CHCl₃).

3-((1S,5aS,6R,8aS)-6-Methyloxycyclohexa-2,4-diene-1-carbonyl)oxazolidin-2-one (7e) Enone 4e (R=Me) 995 mg, 4.46 mmol, 96% ee) was dissolved in CH₂Cl₂ (8.9 mL). NEt₃ (3.5 mL, 25 mmol) and TBSOTf (2.4 mL, 10.3 mmol) were added successively to the solution at −10°C. After the solution was stirred for 2 h, the reaction was quenched by the addition of aqueous saturated NaHCO₃. The mixture was extracted three times with CH₂Cl₂, and the combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile materials were removed under re-
duced pressure, the resulting residue was roughly purified by short-path column chromatography (SiO₂, hexane–AcOEt=2:1) to give impure 7e (1.5, g < 99%).

3-((1R,4R,5R,6R)-8-((tert-Butyldimethylsilyloxy)-5-methyl-3-phenyl-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-6-carbonyl)oxazolidin-2-one (12) Major) To a solution of 7e (122.4 mg, 0.36 mmol) in hexane (3.6 mL) was added nitrosobenzene (47 mg, 0.44 mmol). The mixture was stirred for overnight at 40°C. After the volatile material was removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–Et₂O=1:1) to give 12 major (126.4 mg, 79%) as a yellow solid and 12 minor (17.6 mg, 11%) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz) δ: −0.25 (3H, s), −0.01 (3H, s), 0.75 (9H, s), 1.35 (3H, d, J = 6.8 Hz), 2.78–2.80 (1H, m), 3.86 (1H, dd, J = 4.0, 4.0 Hz), 3.91–3.95 (1H, m), 4.00–4.05 (1H, m), 4.06–4.10 (1H, m), 4.43 (2H, t, J = 8.4 Hz), 4.79 (1H, dd, J = 2.4, 6.4 Hz), 5.13–5.15 (1H, m), 6.88 (1H, t, J = 7.6 Hz), 7.00 (2H, d, J = 7.6 Hz), 7.17 (2H, t, J = 4.8 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: −5.6, −4.9, 17.7, 18.0, 25.3, 30.1, 43.0, 50.8, 62.0, 66.7, 72.9, 73.0, 94.8, 117.1, 121.7, 128.2, 152.3, 153.1, 155.0, 170.9; IR (ATR): ν = 1776, 1766, 1703, 1636 cm⁻¹; HR-MS (ESI) m/z 467.968 (M+Na⁺) (Calcd for C₂₃H₂₃NO₅SiNa: 467.197); [α]D²⁶ +111.5 (c = 1.15, CHCl₃).

((1S,4S,5R,6S)-8-((tert-Butyldimethylsilyloxy)-5-methyl-3-phenyl-2-oxa-3-azabicyclo[2.2.2]oct-7-en-6-yl)methanol (14 Minor) ¹H-NMR (CDCl₃, 400 MHz) δ: −0.25 (3H, s), 0.10 (3H, s), 1.00 (3H, s), 1.00 (3H, d, J = 6.8 Hz). 1.00 (2H, brs), 1.01 (2H, brs), 2.47 (2H, t, J = 1.6, 5.2 Hz), 5.70 (1H, dd, J = 4.4, 10.0 Hz), 7.05 (1H, dd, J = 0.98 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: −4.5, 18.0, 20.3, 25.7, 29.3, 43.4, 64.1, 108.2, 126.9, 128.0, 146; IR (ATR): ν = 1711, 1737, 1699, 1637 cm⁻¹; HR-MS (ESI) m/z 277.1585 (M+Na⁺) (Calcd for C₃₄H₃₃NO₅SiNa: 277.1599).

((1R,4S,5R,6S)-8-((tert-Butyldimethylsilyloxy)-5-methyl-3-phenyl-2-oxa-3-azabicyclo[2.2.2]oct-7-en-6-yl)methanol (14 Major) To a solution of 13 (92.7 mg, 0.36 mmol) in hexane (7.2 mL) was added nitrosobenzene (57.8 mg, 0.54 mmol). The mixture was stirred for 1 h at room temperature. After the volatile material was removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–Et₂O=1:1) to give 14 major (98.9 mg, 76%) as a yellow solid and 14 minor (11.7 mg, 9%) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz) δ: −0.29 (3H, s), 0.30 (3H, s), 0.73 (9H, s), 1.02 (3H, d, J = 7.6 Hz), 1.23–1.27 (1H, m), 1.95–2.00 (1H, m), 2.36 (1H, brs), 3.82 (2H, d, J = 6.0 Hz), 3.97 (1H, t, J = 2.8 Hz), 4.76 (1H, d, J = 6.8 Hz), 5.13 (1H, dd, J = 2.4, 6.8 Hz), 6.88 (1H, t, J = 7.2 Hz), 7.02 (2H, d, J = 7.6 Hz), 7.17 (2H, t, J = 7.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: −5.7, −4.9, 13.9, 17.6, 19.7, 25.2, 31.0, 48.3, 63.3, 67.7, 73.0, 98.7, 117.3, 122.0, 128.2, 151.3, 152.0; IR (ATR): ν = 1737, 1364, 1216 cm⁻¹; HR-MS (ESI) m/z 384.1984 [M+Na⁺] (Calcd for C₂₂H₂₃NO₃SiNa: 384.1970); [α]D²⁶ +124.9 (c = 0.87, CHCl₃).
material was removed under reduced pressure. The resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=2:1) to give 16 (67 mg, 58%). ¹H-NMR (CDCl₃, 400 MHz): δ: 0.07 (3H, s), 0.17 (3H, s), 0.94 (9H, s), 1.13 (3H, d, J=7.2 Hz), 2.87–2.91 (1H, m), 2.98 (1H, s), 4.12–4.16 (2H, m), 4.41 (1H, t, J=2.0, 4.4 Hz), 4.46–4.47 (1H, m), 4.7 (2H, t, J=8.0 Hz), 4.59 (1H, br, J=6.5 Hz), 4.72 (1H, br, J=6.4 Hz), 4.88 (1H, d, J=4.8 Hz), 6.52 (2H, d, J=8.0 Hz), 6.70 (1H, t, J=7.6 Hz), 7.15 (1H, t, J=7.6 Hz); ¹³C-NMR (CDCl₃, 150 MHz): δ: −5.4, −4.6, 14.7, 18.4, 25.7, 42.7, 47.1, 59.9, 62.0, 112.9, 117.7, 129.3, 145.9, 152.9, 173.8, 204.9; IR (ATR): ν 1770, 1740, 1685, 1205, 835, 748 cm⁻¹. HR-MS (ESI) m/z 487.2220 [M+Na]⁺ (Calcd for C₈H₁₅NO₅SiNa: 487.2089); [α]D₂⁰ = −12.1 (c=1.78, CHCl₃); HPLC conditions Daicel CHIRALPAK IC: e=Hex–IPA=90:10, f=1.0 mL/min, t: 12.2 (major) and 14.3 (minor) min.

(2S,3S,4S,5R,6R)-2-((tert-Butylidimethylsilyl)-4-(hydroxy methyl)-5-methyl-6-(phenylamino)cyclohexane-1,3-diol) (19) To a solution of 16 (163.5 mg, 0.35 mmol) in THF (15 mL) was added MeOH (0.13 mL, 3.24 mmol) and LiBH₄ (2 M in THF, 97 µL) at 0°C. The mixture was stirred for 1 h at 0°C. H₂O was added to quench the reaction. The water layer was extracted three times with AcOEt. The combined organic layers were washed with brine, and dried over Na₂SO₄. After the volatile material was removed under reduced pressure. The resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=2:1) to give 19 as diastereomixture (101 mg, 76%, dr=3:2 (determined by ¹H-NMR)). The 19 major could be partially isolated by recrystallization from CH₂Cl₂ and hexane. ¹H-NMR (CDCl₃, 600 MHz): δ: −0.14 (3H, s), 0.04 (3H, s), 0.72 (9H, s), 0.79 (3H, d, J=7.2 Hz), 1.53–1.56 (1H, m), 1.76–1.86 (1H, m), 2.80 (1H, brs), 3.05 (1H, brs), 3.36 (1H, br, J=7.2 Hz), 3.56 (1H, brs), 3.64–3.75 (3H, m), 4.07–4.13 (2H, m), 4.65 (1H, brs), 6.61 (1H, t, J=7.2 Hz), 6.62 (2H, d, J=8.4 Hz), 7.09 (2H, t, J=7.6 Hz); ¹³C-NMR (CDCl₃, 150 MHz): δ: −51.0, −5.0, 15.8, 18.3, 25.8, 33.4, 40.0, 61.0, 62.8, 71.5, 73.2, 75.5, 113.6, 117.0, 129.2, 150.9; IR (ATR): ν 1770, 1531, 1213 cm⁻¹; HR-MS (ESI) m/z 404.2222 [M+Na]⁺ (Calced for C₁₉H₂₆NO₅SiNa: 404.2233); [α]D₂⁰ = −9.9 (c=1.09, CHCl₃); HPLC conditions Daicel CHIRALPAK IA: e=Hex–IPA=90:10, f=1.0 mL/min, t: 8.3 (minor) and 10.1 (major) min.

Acknowledgments This work was supported by JSPS KAKENHI (Grant Numbers 22790007, 25460006 (S. Harada), 12J04105 (S. Hiraoka), and 21390002, 25293001 (A. N.) and by JSPS Asian Core Program. C.-H. Wu thanks Financial support by Taiwan ACP program, NSC98-2911-007-001.

Conflict of Interest The authors declare no conflict of interest.

References and Notes
1) Ishihara K., Sakakura A., “Science of Synthesis Stereoselective Synthesis,” Vol. 3, Chap. 2, ed. by De Vries J. G., Molander G. A., Evans P. A., George Thieme, Stuttgart, New York, 2011, pp. 67–123.
2) Sudo Y., Shirasaki D., Harada S., Nishida A., J. Am. Chem. Soc., 130, 12588–12589 (2008).
3) Harada S., Ioudou N., Hiraoka S., Nishida A., Tetrahedron Lett., 50, 5652–5655 (2009).
4) Hiraoka S., Harada S., Nishida A., J. Org. Chem., 75, 3871–3874 (2010).
5) Harada S., Ishii H., Shirasaki D., Nishida A., Heterocycles, 90, 967–977 (2015).
6) Harada S., Morikawa T., Nishida A., Org. Lett., 15, 5334–5337 (2013).
7) Morikawa T., Harada S., Nishida A., J. Org. Chem., 80, 8859–8867 (2015).
8) Burrows B. J., Scheuer P. J., Finer J., Clardy J., J. Am. Chem. Soc., 97, 4763–4764 (1975).
9) Corey E. J., Behfouroz M., Ishiguro M., J. Am. Chem. Soc., 101.
10) Yamamoto H., Sham H. L., *J. Am. Chem. Soc.*, **101**, 1609–1611 (1979).

11) Srikrishna A., Hemamalini P., Veera Raghava Sharma G., *J. Org. Chem.*, **58**, 2509–2516 (1993).

12) Chang N. C., Chang C. K., *J. Org. Chem.*, **61**, 4967–4970 (1996).

13) Zhao F.-W., Sun Q.-Y., Yang F.-M., Hu G.-W., Luo J.-F., Tang G.-H., Wang Y.-H., Long C.-L., *Org. Lett.*, **12**, 3922–3925 (2010).

14) Zhang G.-B., Wang F.-X., Du J.-Y., Qu H., Ma X.-Y., Wei M.-X., Wang C.-T., Li Q., Fan C.-A., *Org. Lett.*, **14**, 3696–3699 (2012).

15) Sizemore N., Rychnovsky S. D., *Org. Lett.*, **16**, 688–691 (2014).

16) Tsuubaki N., Nishimura K., Hirose Y., *Bull. Chem. Soc. Jpn.*, **40**, 597–600 (1967).

17) Wolff G., Ourisson G., *Tetrahedron Lett.*, **9**, 3849–3852 (1968).

18) Srikrishna A., Ravi G., Satyanarayana G., *Tetrahedron Lett.*, **48**, 73–76 (2007).

19) Niwa H., Wakamatu K., Hida T., Niyama K., Kigoshi H., Yamada M., Nagase H., Suzuki M., Yamada K., *J. Am. Chem. Soc.*, **106**, 4547–4552 (1984).

20) Bhamare N. K., Giranger T., John C. R., Yates P., *Tetrahedron Lett.*, **32**, 4439–4442 (1991).

21) Takasu K., Mizutani S., Ihara M., *J. Org. Chem.*, **67**, 2881–2884 (2002).

22) Singh V., Pal S., Mobin S. M., *J. Org. Chem.*, **71**, 3014–3025 (2006).

23) Murphy G. K., Shirahata T., Hama N., Bedermann A., Dong P., McMahon T. C., Twenter B. M., Spiegel D. A., McDonald I. M., Taniguchi N., Inoue M., Wood J. L., *J. Org. Chem.*, **78**, 477–489 (2013).

24) Yamamoto Y., Yamamoto H., *Eur. J. Org. Chem.*, **2006**, 2031–2043 (2006).

25) Caroso S., Miller M. J., *Org. Biomol. Chem.*, **12**, 7445–7468 (2014).

26) CCDC 1476546 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

27) CCDC 1476580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

28) Delgado A., *Eur. J. Org. Chem.*, **2008**, 3893–3906 (2008).

29) Teoh E., Campi E. M., Jackson W. R., Robinson A. J., *New J. Chem.*, **27**, 387–394 (2003).

30) Whittaker M., McArthur C. R., Leznoff C. C., *Can. J. Chem.*, **63**, 2844–2852 (1985).

31) Knol J., Feringa B. L., *Synlett*, **1995**, 1025–1026 (1995).

32) Brown P. M., Kappel N., Murphy P. J., Coles S. J., Hursthouse M. B., *Tetrahedron*, **63**, 1100–1106 (2007).

33) Niwayama S., Cho H., Lin C., *Tetrahedron Lett.*, **49**, 4434–4436 (2008).

34) Ghosh A. K., Nieponski D. R., *Org. Lett.*, **13**, 4328–4331 (2011).

35) Marshall J. A., Andersen M. W., *J. Org. Chem.*, **58**, 3912–3918 (1993).

36) Dias L. C., Melgar G. Z., Jardim L. S. A., *Tetrahedron Lett.*, **46**, 4427–4431 (2005).

37) Nishida A., Kawahara N., Nishida M., Yonemitsu O., *Tetrahedron*, **52**, 9713–9734 (1996).