Regular Article

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

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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 cyclohexenone **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[4.3.1.0^{3,7}]decane (isotwistane **8**, *n*=1) and tricyclo[5.3.1.0^{3,8}]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 intramo-

lecular 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) (10 mol %) 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, nitrosobenzene^{24,25)} 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**

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Chart 1. Enantioselective Diels–Alder Reaction of Danishefsky Diene (1)

Chart 2. Synthetic Applications of Cyclohexadiene 7 via the Diels–Alder Reaction

Chart 3. Catalytic and Asymmetric Diels–Alder Reaction Using Dienophile 2, and Conversion to Siloxy-Substituted Cyclohexadiene 7

was converted to a primary alcohol as shown in Chart 6. The intermolecular hetero-Diels–Alder reaction of **13** with nitrosobenzene 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

Chart 4. Intramolecular Diels-Alder Reaction

Chart 5. Intermolecular Hetero-Diels-Alder Reaction with Nitrosobenzene

Chart 6. Intermolecular Diels-Alder Reaction of **13** with Nitrosobenzene Chart 7. Determination of the Relative Stereochemistry of **14**

determined as follows: reduction of the acyl-oxazolidinone moiety of **12 major** with $LiBH_4$ 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

Chart 8. Transformation to Pentasubstituted Cyclohexanone

Chart 9. Synthesis of Aminocyclitols Starting from **4e** with 95% Enantiomeric Excess (ee)

Fig. 1. Key *n* Oe Correlations of **18 Major**

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 with 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.²⁸⁾ 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 isotwistane and homoisotwistane 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-dienyl)oxazolidin-2-one (2a)^{29–31)} 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, ddt, *J*=2.0, 2.0, 10.0 Hz), 5.04 (1H, ddt, *J*=2.0, 2.0, 16.8 Hz), 5.81 (1H, ddt, *J*=6.4, 10.0, 16.4 Hz), 7.16 (1H, dt, *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): ν 2924, 1769, 1681, 1633 cm^{−1}; high resolution (HR)-MS (ESI) *m/z* 477.2199 [2M+2MeOH+Na]⁺ (Calcd for C₂₂H₃₄N₂O₈Na: 477.2213).

Methyl (2E,7E)-9-Oxo-9-(2-oxooxazolidin-3-yl)nona-2,7-dienoate (2b)^{31–33)} 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*=7.6 Hz), 4.43 (2H, t, *J*=7.2 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, 153.5, 165.1, 166.9; IR (ATR): ν 2926, 1770, 1717, 1681, 1634 cm^{−1}; HR-MS (ESI) *m/z* 400.0160 [M+Cs]⁺ (Calcd for C₁₃H₁₇NO₅Cs: 400.0161).

(E)-3-(7-Methylocta-2,7-dienyl)oxazolidin-2-one (2c)^{34–36)} ¹H-NMR (600 MHz, CDCl₃) δ: 1.64 (2H, tt, *J*=7.2, 7.2 Hz), 1.71 (3H, s), 2.05 (2H, t, *J*=7.8 Hz), 2.28 (2H, dt, *J*=7.2, 7.2 Hz), 4.07 (2H, t, *J*=7.8 Hz), 4.43 (2H, t, *J*=8.4 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): ν 2932, 1770, 1680, 1633 cm^{−1}; HR-MS (ESI) *m/z* 246.1113 [M+Na]⁺ (Calcd for C₁₂H₁₇NO₃Na: 246.1106).

Ethyl (7E)-3-Methyl-9-oxo-9-(2-oxooxazolidin-3-yl)nona-2,7-dienoate (2d) (for Major E-Isomer)^{34,36,37)} 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*=7.6 Hz), 2.29 (2H, dt, *J*=8.0, 8.0 Hz), 4.08 (2H, t, *J*=8.0 Hz), 4.15 (2H, q, *J*=7.2 Hz), 4.43 (2H, t, *J*=8.0 Hz), 5.67 (1H, s), 7.14 (1H, dt, *J*=8.8, 15.4 Hz), 7.25 (1H, d, *J*=15.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: 14.2, 18.6, 25.7, 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): ν 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-oxocyclohex-2-ene-1-carbonyl)oxazolidin-2-one (4a) Yb(OTf)₃ (37.2 mg, 60.0 μmol) and (*R*)-BINUREA (**6**)³⁾ (34.8 mg, 60.0 μmol) taken in a test tube with a stirring bar were heated at 120 °C under reduced

pressure (<0.1 mmHg) for 30 min. After being allowed to cool to room temperature, the test tube was charged with dry argon. Dichloromethane (CH_2Cl_2) (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 CH_2Cl_2 (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 CH_2Cl_2 , and the combined organic layers were washed with brine and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the diastereoselectivity (a single diastereomer) was checked by ^1H -NMR. The crude product could be purified by column chromatography (SiO_2 , hexane–AcOEt=5:1) to give **3a**.

The resulting crude mixture of **3a** was dissolved in CH_2Cl_2 (3.0 mL), and trifluoroacetic acid (TFA) (0.3 mL) was added at 0°C. After being stirred for 10 min at room temperature, the reaction was quenched by the addition of aqueous saturated NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=1:1) to give **4a** (123.6 mg, 78%). The enantiomeric excess was determined by chiral HPLC analysis. ^1H -NMR (400 MHz, CDCl_3) δ : 1.43–1.62 (2H, m), 2.03 (1H, dddd, $J=7.6, 7.6, 7.6, 14.4$ Hz), 2.12–2.21 (1H, m), 2.26 (1H, dd, $J=10.0, 16.4$ Hz), 2.53–2.64 (1H, m), 2.79 (1H, dd, $J=4.4, 16.4$ Hz), 4.10 (2H, dddt, $J=3.6, 3.6, 8.4, 19.6$ Hz), 4.49 (2H, t, $J=8.4$ Hz), 4.63 (1H, dt, $J=3.2, 7.6$ Hz), 4.98 (1H, dd, $J=1.6, 10.0$ Hz), 5.03 (1H, dddd, $J=1.2, 1.2, 16.8$ Hz), 5.75 (1H, dddd, $J=6.8, 6.8, 10.8, 17.2$ Hz), 6.12 (1H, dd, $J=2.8, 10.0$ Hz), 6.73 (1H, dd, $J=3.2, 10.0$ Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ : 30.5, 32.8, 36.4, 40.9, 42.8, 46.4, 62.1, 115.3, 130.7, 137.5, 144.5, 153.2, 171.7, 198.1; IR (ATR): ν 2924, 1769, 1675 cm^{-1} ; HR-MS (ESI) m/z 286.1056 $[\text{M}+\text{Na}]^+$ (Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4\text{Na}$: 286.1055); $[\alpha]_{\text{D}}^{23} +167.4$ ($c=1.02$, CHCl_3); HPLC conditions Daicel CHIRALPAK AS-H, e: Hex–IPA=60:40, $f=0.8$ mL/min, t: 18.3 (major) and 25.0 (minor) min.

Methyl (E)-6-((1S,2R)-5-Oxo-2-(2-oxooxazolidine-3-carbonyl)cyclohex-3-en-1-yl)hex-2-enoate (4b) Yb(OTf)₃ (37.2 mg, 60.0 μmol) and (*R*)-BINUREA (**6**)³ (34.8 mg, 60.0 μmol) taken in a test tube with a stirring bar were heated at 120°C under reduced pressure (<0.1 mmHg) for 30 min. After being allowed to cool to room temperature, the test tube was charged with dry argon. Dichloromethane (CH_2Cl_2) (2.0 mL) and 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 **2b** (160.4 mg, 0.60 mmol) in CH_2Cl_2 (1.0 mL) was added, followed by the addition of Danishefsky diene (**1**) (163 μL , 0.66 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 CH_2Cl_2 , and the combined organic layers were washed with brine and dried over Na_2SO_4 . After the volatile materials were removed

under reduced pressure, the diastereoselectivity (a single diastereomer) was checked by ^1H -NMR. The crude product could be purified by column chromatography (SiO_2 , hexane–AcOEt=5:1) to give **3b**.

The resulting crude mixture **3b** was dissolved in CH_2Cl_2 (3.0 mL), and $\text{BF}_3\cdot\text{OEt}_2$ (188 μL , 1.5 mmol) was added at –78°C. After being stirred for 10 min at the same temperature, the reaction was quenched by the addition of aqueous saturated NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=1:1) to give **4b** (183.4 mg, 91%). The enantiomeric excess was determined by HPLC analysis. ^1H -NMR (400 MHz, CDCl_3) δ : 1.38–1.54 (4H, m), 2.16–1.25 (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, dddt, $J=4.4, 4.4, 8.0, 16.0$ 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); ^{13}C -NMR (100 MHz, CDCl_3) 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 $[\text{M}+\text{Na}]^+$ (Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_6\text{Na}$: 358.1267); $[\alpha]_{\text{D}}^{23} +107.2$ ($c=1.02$, CHCl_3); HPLC conditions Daicel CHIRALCEL OJ-H, e: Hex–IPA=55:45, $f=0.8$ 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-carbonyl)oxazolidin-2-one (4c) Yb(OTf)₃ (47.1 mg, 76.0 μmol) and (*R*)-BINUREA (**6**)³ (44.1 mg, 76.0 μmol) taken in a test tube with a stirring bar were heated at 120°C under reduced pressure (<0.1 mmHg) for 30 min. After being allowed to cool to room temperature, the test tube was charged with dry argon. Dichloromethane (CH_2Cl_2) (2.5 mL) and DBU (22.8 μL , 132.0 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 CH_2Cl_2 (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 CH_2Cl_2 , and the combined organic layers were washed with brine and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the diastereoselectivity (a single diastereomer) was checked by ^1H -NMR. The crude product could be purified by column chromatography (SiO_2 , hexane–AcOEt=5:1) to give **3c**.

The resulting crude mixture of **3c** was dissolved in CH_2Cl_2 (3.0 mL), and TFA (0.3 mL) was added at 0°C. After being stirred for 10 min at room temperature, the reaction was quenched by the addition of aqueous saturated NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=1:1) to give **4c** (142.8 mg, 64%). The enantiomeric excess was determined by chiral HPLC analysis. ^1H -NMR (400 MHz, CDCl_3) δ : 1.22 (1H, d, $J=6.0$ Hz), 1.35–1.49 (3H, m), 1.68 (3H, s), 1.94–2.01

(2H, m), 2.26 (1H, dd, $J=10.0$, 16.0 Hz), 2.53–2.62 (1H, m), 2.78 (1H, dd, $J=4.8$, 16.4 Hz), 4.10 (2H, t, $J=7.6$ Hz), 4.50 (2H, t, $J=8.4$ Hz), 4.62 (1H, ddd, $J=3.2$, 3.2, 7.2 Hz), 4.64 (1H, s), 4.70 (1H, s), 6.12 (1H, dd, $J=2.8$, 10.0 Hz), 6.73 (1H, dd, $J=3.2$, 10.0 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ : 22.3, 24.3, 33.3, 36.9, 37.4, 41.2, 42.8, 46.5, 62.1, 110.2, 130.7, 144.7, 145.3, 153.2, 171.8, 198.3; IR (ATR): ν 2931, 1771, 1676 cm^{-1} ; HR-MS (ESI) m/z 314.1365 $[\text{M}+\text{Na}]^+$ (Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{Na}$: 314.1368); $[\alpha]_{\text{D}}^{24}$ +143.3 ($c=0.99$, CHCl_3); HPLC conditions Daicel CHIRALPAK IA, e: Hex–IPA=80:20, $f=1.0$ mL/min, t: 37.7 (minor) and 39.9 (major) min.

Ethyl 3-Methyl-6-((1*S*,2*R*)-5-oxo-2-(2-oxooxazolidine-3-carbonyl)cyclohex-3-en-1-yl)hex-2-enoate (4d Major) Yb(OTf)₃ (51.5 mg, 83.0 μmol) and (*R*)-BINUREA (**6**)³ (48.1 mg, 83.0 μmol) taken in a test tube with a stirring bar were heated at 120°C under reduced pressure (<0.1 mmHg) for 30 min. After being allowed to cool to room temperature, the test tube was charged with dry argon. Dichloromethane (CH_2Cl_2) (2.8 mL) and DBU (24.9 μL , 166.0 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 **2d** (300.0 mg, 0.83 mmol) in CH_2Cl_2 (1.4 mL) was added, followed by the addition of Danishefsky diene (**1**) (415 μL , 1.66 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 CH_2Cl_2 , and the combined organic layers were washed with brine and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the diastereoselectivity (a single diastereomer) was checked by ^1H -NMR. The crude product could be purified by column chromatography (SiO_2 , hexane–AcOEt=5:1) to give **3d**.

The resulting crude mixture of **3d** was dissolved in CH_2Cl_2 (3.0 mL), and TFA (0.3 mL) was added at 0°C. After being stirred for 10 min at room temperature, the reaction was quenched by the addition of aqueous saturated NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=1:1) to give **4d** (241.5 mg, 80%). The enantiomeric excess was determined by chiral HPLC analysis. ^1H -NMR (400 MHz, CDCl_3) δ : 0.88 (1H, dd, $J=6.8$, 6.8 Hz), 1.24–1.30 (4H, m), 1.38–1.47 (3H, m), 2.09–2.14 (4H, m), 2.26 (1H, dd, $J=11.2$, 16.4 Hz), 2.53–2.59 (1H, m), 2.76 (1H, dd, $J=4.4$, 16.4 Hz), 4.08–4.14 (4H, m), 4.50 (2H, t, $J=8.0$ Hz), 4.61 (1H, dd, $J=3.2$, 3.2 Hz), 5.63 (1H, s), 6.12 (1H, dd, $J=1.2$, 10.0 Hz), 6.72 (1H, dd, $J=3.2$, 10.0 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ : 14.3, 18.5, 24.1, 33.2, 36.8, 40.3, 41.1, 42.8, 46.4, 59.5, 62.2, 116.0, 130.7, 144.5, 153.2, 158.9, 166.7, 171.7, 198.0; IR (ATR): ν 2935, 1772, 1677, 1646 cm^{-1} ; HR-MS (ESI) m/z 386.1572 $[\text{M}+\text{Na}]^+$ (Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_6\text{Na}$: 386.1580); $[\alpha]_{\text{D}}^{23}$ +104.8 ($c=0.99$, CHCl_3); HPLC conditions for **4d major**: Daicel CHIRALCEL OJ-H, e: Hex–IPA=50:50, $f=0.5$ mL/min, t: 49.8 (minor) and 60.4 (major) min. HPLC conditions for **4d minor**: Daicel CHIRALCEL OJ-H, e: Hex–IPA=50:50, $f=0.5$ mL/min, t: 32.2 (major) and 35.8 (minor) min.

3-((1*S*,6*S*)-6-(But-3-en-1-yl)-4-((*tert*-butyldimethylsilyl)-oxy)cyclohexa-2,4-diene-1-carbonyl)oxazolidin-2-one (7a)

Enone **4a** (123.6 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (0.9 mL). NEt_3 (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 NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=2:1) to give **7a** (158.7 mg, 90%). ^1H -NMR (400 MHz, CDCl_3) δ : 0.14 (6H, s), 0.92 (9H, s), 1.48 (1H, dddd, $J=6.8$, 10.0, 10.0, 15.6 Hz), 1.55–1.64 (1H, m), 2.05–2.18 (2H, m), 2.84 (1H, dddd, $J=5.6$, 5.6, 5.6, 8.4 Hz), 4.01 (2H, dddt, $J=7.6$, 10.8, 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, dd, $J=2.0$, 4.8 Hz), 4.95 (1H, dd, $J=1.2$, 10.4 Hz), 5.01 (1H, ddt, $J=2.0$, 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, $J=10.0$ Hz); ^{13}C -NMR (100 MHz, CDCl_3) 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, 1698, 1654 cm^{-1} ; HR-MS (ESI) m/z 378.2094 $[\text{M}+\text{H}]^+$ (Calcd for $\text{C}_{20}\text{H}_{32}\text{NO}_4\text{Si}$: 378.2101); $[\alpha]_{\text{D}}^{25}$ +309.4 ($c=1.00$, CHCl_3).

Methyl (E)-6-((1*S*,6*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-(2-oxooxazolidine-3-carbonyl)cyclohexa-2,4-dien-1-yl)-hex-2-enoate (7b) Enone **4b** (183.4 mg, 0.55 mmol) was dissolved in CH_2Cl_2 (1.1 mL). NEt_3 (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 NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=2:1) to give **7b** (234.6 mg, 95%). ^1H -NMR (400 MHz, CDCl_3) 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, dddt, $J=8.4$, 11.6, 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, ddd, $J=1.6$, 1.6, 10.0 Hz), 6.94 (1H, dt, $J=7.2$, 15.6 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ : -4.5, 18.0, 25.1, 25.6, 32.2, 34.1, 34.7, 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 $[\text{M}+\text{Na}]^+$ (Calcd for $\text{C}_{23}\text{H}_{35}\text{NO}_6\text{SiNa}$: 472.2131); $[\alpha]_{\text{D}}^{25}$ +266.2 ($c=1.00$, CHCl_3).

3-((1*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(4-methylpent-4-en-1-yl)cyclohexa-2,4-diene-1-carbonyl)oxazolidin-2-one (7c) Enone **4c** (119.0 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (8.0 mL). NEt_3 (341 μL , 2.4 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 NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was roughly purified by short-pad column chromatography (SiO_2 , hexane–AcOEt=2:1) to give impure **7c** (<143.6 mg, <89%). Compound **7c** was rather unstable, thus **7c** was used for the next intramolecular

Diels–Alder reaction without further purification.

Ethyl (E)-6-((1S,6S)-3-((tert-Butyldimethylsilyl)oxy)-6-(2-oxooxazolidine-3-carbonyl)cyclohexa-2,4-dien-1-yl)-3-methylhex-2-enoate (7d) Enone **4d** (216.9 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (12 mL). NEt_3 (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 NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was roughly purified by short-pad column chromatography (SiO_2 , hexane–AcOEt=2:1) to give impure **7d** (<263.7 mg, <93%). Compound **7d** was rather unstable, thus **7d** was used for the next intramolecular Diels–Alder reaction without further purification.

3-((1S,3aS,4R,5R,7aR)-7-Oxo-octahydro-1H-1,5-methanoindene-4-carbonyl)oxazolidin-2-one (11a) Diene **7a** (67.5 mg, 0.2 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 NaHCO_3 . The mixture was extracted three times with AcOEt, and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=3:2) to give **11a** (25.7 mg, 49%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.55–1.66 (3H, m), 1.90–2.02 (4H, m), 2.07 (1H, ddd, $J=2.4, 2.4, 18.8$ Hz), 2.23 (1H, dd, $J=4.4, 4.4$ Hz), 2.40–2.46 (2H, m), 2.92 (1H, s), 3.61 (1H, s), 3.96–4.10 (2H, m), 4.42 (2H, t, $J=8.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 29.0, 32.5, 33.5, 35.0, 36.4, 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/z 286.1056 [$\text{M}+\text{Na}$] $^+$ (Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4\text{Na}$: 286.1055); $[\alpha]_{\text{D}}^{26} +26.0$ ($c=1.00$, CHCl_3).

Methyl (1S,4aR,5S,6R,8aS,9S)-8-Oxo-9-(2-oxooxazolidine-3-carbonyl)decahydro-1,6-methanonaphthalene-5-carboxylate (11b) Diene **7b** (89.9 mg, 0.2 mmol) was dissolved in toluene (5.0 mL), and was stirred under refluxing condition for 6 h. After the solution was cooled to -78°C , $\text{BF}_3 \cdot \text{OEt}_2$ (123 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 NaHCO_3 . The mixture was extracted three times with AcOEt, and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=3:2) to give **11b** (49.3 mg, 73%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.42–1.74 (7H, m), 2.05 (1H, d, $J=20.0$ Hz), 2.17–2.22 (2H, m), 2.57 (1H, s), 2.73 (1H, s), 2.77 (1H, s), 2.91 (1H, s), 3.69 (3H, s), 3.91 (1H, s), 3.97–4.12 (2H, m), 4.45 (2H, t, $J=8.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 15.3, 28.2, 28.3, 28.5, 30.3, 33.9, 34.9, 43.0, 44.0, 45.2, 51.4, 52.1, 62.0, 153.3, 173.7, 173.9, 213.3; IR (ATR): ν 2936, 1774, 1719, 1677 cm^{-1} ; HR-MS (ESI) m/z 336.1444 [$\text{M}+\text{H}$] $^+$ (Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_6$: 336.1447); $[\alpha]_{\text{D}}^{26} +29.1$ ($c=1.02$, CHCl_3).

3-((1S,4aS,5R,6R,8aS)-1-Methyl-8-oxodecahydro-1,6-methanonaphthalene-5-carbonyl)oxazolidin-2-one (11c)

Diene **7c** (140.0 mg, 0.35 mmol) was dissolved in toluene (6.9 mL), and BHT (7.6 mg, 34.5 μmol) was added to the solution. The solution was stirred at 165°C (in a sealed tube) for 88 h. After toluene was evaporated under reduced pressure, CH_2Cl_2 (3.3 mL) and TFA (49 μL , 0.66 mmol) were added to the mixture. After stirred for 5 min, the reaction was quenched by the addition of aqueous saturated NaHCO_3 . The mixture was extracted three times with AcOEt, and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=1:1) to give **11c** (60.4 mg, 53% from **4c**). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.90 (3H, s), 1.12 (1H, ddd, $J=4.8, 13.6, 13.6$ Hz), 1.36 (1H, dddd, $J=4.4, 4.4, 14.4, 14.4$ Hz), 1.40 (1H, dd, $J=2.8, 14.0$ Hz), 1.46–1.61 (3H, m), 1.71 (1H, dddd, $J=4.4, 4.4, 13.6, 13.6$ Hz), 1.85 (1H, d, $J=2.8$ Hz), 1.89 (1H, ddd, $J=3.2, 3.2, 13.6$ Hz), 1.93 (1H, dddd, $J=1.2, 1.2, 1.2, 18.0$ Hz), 2.12 (1H, ddd, $J=3.2, 3.2, 19.2$ Hz), 2.53 (1H, dddd, $J=2.8, 2.8, 2.8, 2.8$ Hz), 2.79 (1H, dd, $J=3.6, 3.6$ Hz), 3.78 (1H, dd, $J=2.8, 2.8$ Hz), 3.97–4.10 (2H, m), 4.43 (2H, t, $J=8.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 17.5, 28.4, 30.17, 30.22, 31.98, 32.04, 37.9, 38.1, 38.4, 43.0, 43.5, 57.4, 61.9, 153.3, 174.6, 214.8; IR (ATR): ν 2925, 2867, 1773, 1716, 1691 cm^{-1} ; HR-MS (ESI) m/z 314.1361 [$\text{M}+\text{Na}$] $^+$ (Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{Na}$: 314.1368); $[\alpha]_{\text{D}}^{21} +6.98$ ($c=1.00$, CHCl_3).

Ethyl (1S,4aR,5R,6R,8aS,9S)-4a-Methyl-8-oxo-9-(2-oxooxazolidine-3-carbonyl)decahydro-1,6-methanonaphthalene-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, CH_2Cl_2 (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 NaHCO_3 . The mixture was extracted three times with AcOEt, and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 , hexane–AcOEt=1:1) to give **11d** (67.5 mg, 56% from **4d**). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 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); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 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, 59.0, 60.3, 62.0, 153.3, 173.0, 173.5, 214.0; IR (ATR): ν 2929, 1771, 1719, 1691 cm^{-1} ; HR-MS (ESI) m/z 386.1576 [$\text{M}+\text{Na}$] $^+$ (Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_6\text{Na}$: 386.1580); $[\alpha]_{\text{D}}^{21} +29.1$ ($c=0.99$, CHCl_3).

3-((1S,6S)-4-((tert-Butyldimethylsilyl)oxy)-6-methylcyclohexa-2,4-diene-1-carbonyl)oxazolidin-2-one (7e) Enone **4e** ($\text{R}=\text{Me}$,³⁾ 995 mg, 4.46 mmol, 96% ee) was dissolved in CH_2Cl_2 (8.9 mL). NEt_3 (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 NaHCO_3 . The mixture was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, and dried over Na_2SO_4 . After the volatile materials were removed under re-

duced pressure, the resulting residue was roughly purified by short-pad column chromatography (SiO₂, hexane–AcOEt=2:1) to give impure **7e** (<1.5 g, <99%).

3-((1R,4R,5R,6R)-8-((tert-Butyldimethylsilyl)oxy)-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* 467.1968 [M+Na]⁺ (Calcd for C₂₃H₃₂N₂O₅SiNa: 467.1978); [α]_D²⁶ –17.9 (*c*=1.43, CHCl₃); HPLC conditions Daicel CHIRALPAK AD-H, e: Hex–IPA=95:5, *f*=1.0 mL/min, *t*: 8.5 (minor) and 10.9 (major) min.

3-((1S,4S,5R,6R)-8-((tert-Butyldimethylsilyl)oxy)-5-methyl-3-phenyl-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-6-carbonyl)oxazolidin-2-one (12 Minor) ¹H-NMR (CDCl₃, 400 MHz) δ: –0.30 (3H, s), –0.02 (3H, s), 0.73 (9H, s), 1.04 (3H, d, *J*=7.2 Hz), 3.13 (1H, d, *J*=4.4 Hz), 3.26–3.28 (1H, m), 4.07–4.13 (3H, m), 4.44 (2H, t, *J*=8.4 Hz), 5.03 (1H, d, *J*=6.8 Hz), 5.16–5.17 (1H, m), 6.88 (1H, t, *J*=7.6 Hz), 6.99 (2H, d, *J*=7.6 Hz), 7.16 (2H, t, *J*=7.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: –4.8, 0.0, 14.2, 17.6, 19.8, 25.2, 29.4, 43.1, 52.6, 62.3, 67.2, 73.5, 97.5, 117.3, 122.1, 128.1, 151.8, 152.1, 153.7, 171.4; IR (ATR): ν 1771, 1773, 1699, 1637 cm^{–1}; HR-MS (ESI) *m/z* 467.1985 [M+Na]⁺ (Calcd for C₂₃H₃₂N₂O₅SiNa: 467.1978); [α]_D²⁶ +78.4 (*c*=1.15, CHCl₃).

((1S,6R)-4-((tert-Butyldimethylsilyl)oxy)-6-methylcyclohexa-2,4-dien-1-yl)methanol (13) To a solution of **7e** (139 mg, 0.41 mmol) in tetrahydrofuran (THF) was added lithium borohydride (13.4 mg, 0.61 mmol) and methanol (24.7 μL, 0.61 mmol) at 0°C. The mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of water. 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=2:1) to give **13** (92.7 mg, 89%). ¹H-NMR (CDCl₃, 400 MHz) δ: 0.12 (3H, s), 0.13 (3H, s), 0.92 (9H, s), 1.02 (3H, d, *J*=7.2 Hz), 1.59 (1H, brs), 2.13–2.18 (1H, m), 2.39–2.46 (1H, m), 3.52–3.59 (2H, m), 4.77 (1H, dd, *J*=1.6, 5.2 Hz), 5.70 (1H, dd, *J*=4.4, 10.0 Hz), 5.75 (1H, dd, *J*=0.8, 9.6 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, 146.6; IR (ATR): ν 1771, 1773, 1699, 1637 cm^{–1}; HR-MS (ESI) *m/z* 277.1585 [M+Na]⁺ (Calcd for C₁₄H₂₆O₂SiNa: 277.1599).

((1R,4S,5R,6S)-8-((tert-Butyldimethylsilyl)oxy)-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), 0.0 (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 C₂₀H₃₁NO₃SiNa: 384.1970); [α]_D²⁶ +111.5 (*c*=1.15, CHCl₃).

((1S,4R,5R,6S)-8-((tert-Butyldimethylsilyl)oxy)-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), 0.01 (3H, s), 0.74 (9H, s), 1.38 (3H, d, *J*=6.8 Hz), 1.47–1.53 (1H, m), 1.96–2.01 (1H, m), 3.29 (1H, t, *J*=9.6 Hz), 3.45 (1H, dd, *J*=5.6, 10.8 Hz), 3.93 (1H, s), 4.84 (1H, dd, *J*=3.6, 6.8 Hz), 5.02 (1H, dd, *J*=2.4, 6.8 Hz), 6.86 (1H, t, *J*=7.2 Hz), 7.01 (2H, d, *J*=8.0 Hz), 7.17 (2H, t, *J*=7.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: –5.7, –4.7, 17.7, 18.0, 25.3, 31.9, 48.3, 63.3, 59.2, 65.2, 67.3, 73.5, 96.0, 117.2, 121.7, 128.2, 152.6, 153; IR (ATR): ν 1636, 1488, 1471, 1348 cm^{–1}; HR-MS (ESI) *m/z* 384.1931 [M+Na]⁺ (Calcd for C₂₀H₃₁NO₃SiNa: 384.1970); [α]_D²⁶ –14.29 (*c*=0.87, CHCl₃).

3-((1R,2R,5R,6R)-4-((tert-Butyldimethylsilyl)oxy)-2-hydroxy-6-methyl-5-(phenylamino)cyclohex-3-enecarbonyl)oxazolidin-2-one (15) To a solution of **12 major** (50 mg, 0.11 mmol) in isopropanol (5 mL) was added Pd(OH)₂/C (10% (w/w)). The slurry was stirred for overnight at room temperature under hydrogen atmosphere. The insoluble materials were filtered through a pad of Celite®, and washed with AcOEt. After the volatile material was removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=1:1) to give **15** (51 mg, quant.). ¹H-NMR (CDCl₃, 400 MHz) δ: 0.08 (3H, s), 0.13 (3H, s), 0.76 (9H, s), 0.95 (3H, d, *J*=6.8 Hz), 2.15–2.19 (1H, m), 3.71 (1H, d, *J*=3.2 Hz), 3.94–3.98 (2H, m), 4.0–4.07 (1H, m), 4.32 (2H, t, *J*=8.4 Hz), 4.45–4.47 (1H, d, *J*=9.2 Hz), 4.83 (1H, d, *J*=2.4 Hz), 6.54–6.65 (3H, m), 7.03 (2H, t, *J*=8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: –4.7, –4.5, 14.7, 25.3, 36.3, 42.8, 48.0, 56.6, 61.9, 70.9, 107.6, 113.3, 117.3, 129.0, 149.0, 153.5, 175.1; IR (ATR): ν 1767, 1669, 1651, 1599 cm^{–1}; HR-MS (ESI) *m/z* 469.2102 [M+Na]⁺ (Calcd for C₂₃H₃₄N₂O₅SiNa: 469.2135); [α]_D²⁶ +40.9 (*c*=0.98, CHCl₃); HPLC conditions Daicel CHIRALPAK IA, e: Hex–IPA=75:25, *f*=1.0 mL/min, *t*: 5.3 (minor) and 6.7 (major) min.

3-((1R,2S,3S,5R,6R)-3-((tert-Butyldimethylsilyl)oxy)-2-hydroxy-6-methyl-4-oxo-5-(phenylamino)cyclohexanecarbonyl)oxazolidin-2-one (16) To a solution of **15** (113 mg, 0.25 mmol) in CH₂Cl₂ (10 mL) was added aqueous saturated NaHCO₃ (2.0 mL), then added *m*-chloroperbenzoic acid (*m*CPBA) (max. 77%, 84 mg, 0.38 mmol) at 0°C. The slurry was stirred for 2 h with increasing the reaction temperature from 0°C to room temperature. Aqueous saturated NaHCO₃ was then added, and the water layer was extracted three times with CH₂Cl₂, then 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 **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), 4.47 (2H, t, J =8.0 Hz), 4.59 (1H, brt, J =5.6 Hz), 4.72 (1H, brd, J =6.4 Hz), 4.88 (1H, d, J =4.8 Hz), 6.54 (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, 38.5, 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 485.2089 [M+Na]⁺ (Calcd for C₂₃H₃₄N₂O₆SiNa: 485.2083); [α]_D²⁶ –9.6 (c =0.51, CHCl₃); HPLC conditions Daicel CHIRALPAK AD-H, e: Hex–IPA=70:30, f =0.7 mL/min, t: 16.3 (major) and 26.8 (minor) min.

3-((1R,2S,3S,5R,6R)-2,3-Dihydroxy-6-methyl-4-oxo-5-(phenylamino)cyclohexanecarbonyl)oxazolidin-2-one (17) To a solution of **16** (30.0 mg, 64.8 μ mol) in THF (3.2 mL) was added AcOH (1 M in THF, 65 μ L) and tetrabutylammonium fluoride (TBAF) (1 M in THF, 97 μ L) at –78°C. The resulting mixture was stirred for 3 h with increasing the reaction temperature from –78 to 0°C. Water was then added, and the water layer was extracted three times with AcOEt, then the combined organic layers were dried over Na₂SO₄. After the volatile material was removed under reduced pressure, the resulting residue was purified by column chromatography (SiO₂, hexane–AcOEt=1:1) to give **17** (14.8 mg, 66%). ¹H-NMR (dimethyl sulfoxide (DMSO)-*d*₆, 400 MHz, 55°C) δ : 1.01 (3H, brd, J =6.8 Hz), 2.82 (1H, brt, J =6.8 Hz), 4.01 (2H, t, J =4.8 Hz), 4.12 (1H, brs), 4.40 (3H, brt, J =7.6 Hz), 4.62 (1H, brs), 4.69 (1H, t, J =7.6 Hz), 4.90 (1H, brs), 5.12 (1H, brs), 5.43 (1H, brs), 6.55 (1H, t, J =6.8 Hz), 6.64 (2H, d, J =7.6 Hz), 7.06 (2H, t, J =7.6 Hz); ¹³C-NMR (DMSO-*d*₆, 100 MHz, 55°C) δ : 14.9, 37.6, 42.7, 48.3, 55.7, 59.6, 62.1, 75.4, 75.5, 112.6, 128.7, 146.7, 153.2, 173.1, 175.2, 207.0. IR (ATR): ν 1779, 1735, 1475, 1391, 1365 cm^{–1}; HR-MS (ESI) m/z 371.1204 [M+Na]⁺ (Calcd for C₁₇H₂₀N₂O₆Na: 371.1219); [α]_D²⁶ +1.8 (c =0.43, MeCN); HPLC conditions Daicel CHIRALPAK IC, e: Hex–IPA=40:60, f =0.75 mL/min, t: 27.2 (minor) and 52.0 (major) min.

3-((1R,2S,3S,4R,5R,6R)-3-((tert-Butyldimethylsilyl)-oxy)-2,4-dihydroxy-6-methyl-5-(phenylamino)cyclohexanecarbonyl)oxazolidin-2-one (18) To a solution of **16** (41 mg, 0.09 mmol) in THF (5 mL) was added MeOH (5.3 μ L, 0.13 mmol) and LiBH₄ (2 M in THF, 65 μ L, 0.13 mmol) at 0°C. The mixture was stirred for 20 min 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 **18** (major: 33 mg, 81%; minor: 2.0 mg, 5%). ¹H-NMR (CDCl₃, 600 MHz) δ : 0.20 (6H, s), 0.83 (3H, d, J =7.2 Hz), 1.04 (9H, s), 2.12–2.15 (1H, m), 2.54 (1H, d, J =11.4 Hz), 2.84 (1H, d, J =10.2 Hz), 3.64 (1H, dd, J =3.0, 6.6 Hz), 3.73 (1H, dt, J =1.8, 10.8 Hz), 3.95 (1H, dt, J =4.2, 11.4 Hz), 4.00–4.03 (1H, m), 4.10–4.12 (1H, m), 4.18 (1H, s), 4.32 (1H, t, J =11.4 Hz), 4.35–4.44 (3H, m), 6.66 (1H, t, J =7.8 Hz), 6.68 (2H, d, J =7.8 Hz), 7.14 (2H, t, J =7.8 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ : –4.7, –4.1, 16.0,

18.3, 25.9, 26.0, 37.2, 42.7, 43.9, 57.4, 61.9, 69.0, 73.6, 76.2, 13.2, 117.6, 129.3, 148.9, 154.2, 175.3; IR (ATR): ν 1709, 1359, 1291, 833 cm^{–1}; HR-MS (ESI) m/z 487.2220 [M+Na]⁺ (Calcd for C₂₃H₃₆N₂O₆SiNa: 487.2240); [α]_D²⁶ –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-Butyldimethylsilyl)oxy)-4-(hydroxymethyl)-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, 1.6 mL) 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), 1.07 (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 d, 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 : –5.1, –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 1750, 1351, 1213 cm^{–1}; HR-MS (ESI) m/z 404.2222 [M+Na]⁺ (Calcd for C₂₀H₃₅NO₄SiNa: 404.2233); [α]_D²⁶ –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.

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Conflict of Interest The authors declare no conflict of interest.

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