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OXIDATIVE SYNTHESIS OF ISOXAZOLINE-*N*-OXIDE FROM OPTICALLY ACTIVE NITRO ALCOHOLS

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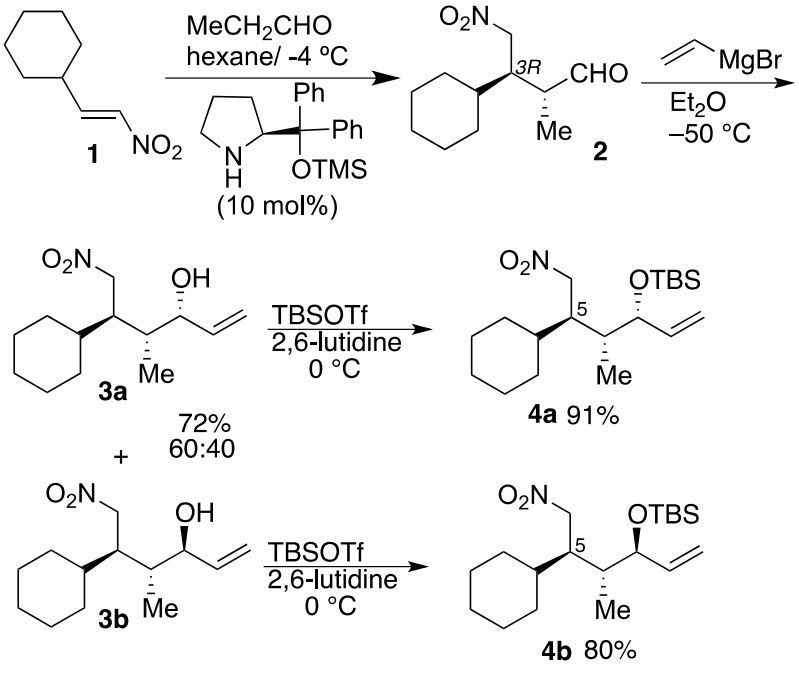
Abstract – Treatment of optically active 6-nitrohex-1-en-3-ols with Ag_2O and iodine under basic conditions resulted in an oxidative intramolecular cyclization reaction to give isoxazoline-*N*-oxide along with bicyclo[3.1.0]hexane. The stereoselectivity and chemoselectivity of the reaction depended on the configuration of the stereogenic center adjacent to the alkenyl group. The structure was determined by X-ray crystallographic analyses as well as coupling constants from NMR data. Stereochemical preferences in the transition structure of the reaction are discussed.

Aliphatic nitro compounds are useful synthetic building blocks because they act as nucleophiles during carbon-carbon bond forming reactions. The nitro group serves as a precursor for an amino group or a carbonyl group.[1] Asymmetric synthesis of nitro compounds has been actively explored in recent years and chiral nitro compounds are readily available.[2] We have recently reported a novel oxidative cyclization reaction of aliphatic nitro compounds that affords bicyclic nitrocyclopropanes.[3] Cyclopropanes are observed among many natural or bioactive products and development of an efficient process for their synthesis has been of interest in organic chemistry.[4] Using our methodology, 5-nitrobicyclo[3.1.0]hexanes and 6-nitrobicyclo[4.1.0]heptanes were prepared in a highly stereoselective manner.[5] This methodology gives isoxazoline-*N*-oxide as a side product, which is selectively formed when a relatively bulky group, such as an isopropyl or a cyclohexyl group, is located at the carbon adjacent to the nitro group. To apply this reaction for the preparation of chiral heterocyclic systems, we employed optically active 7-nitrohept-1-en-4-ols as the precursors, and successfully prepared optically active 6-nitrobicyclo[4.1.0]heptan-3-one in a stereoselective manner.[6] We were also interested in performing the

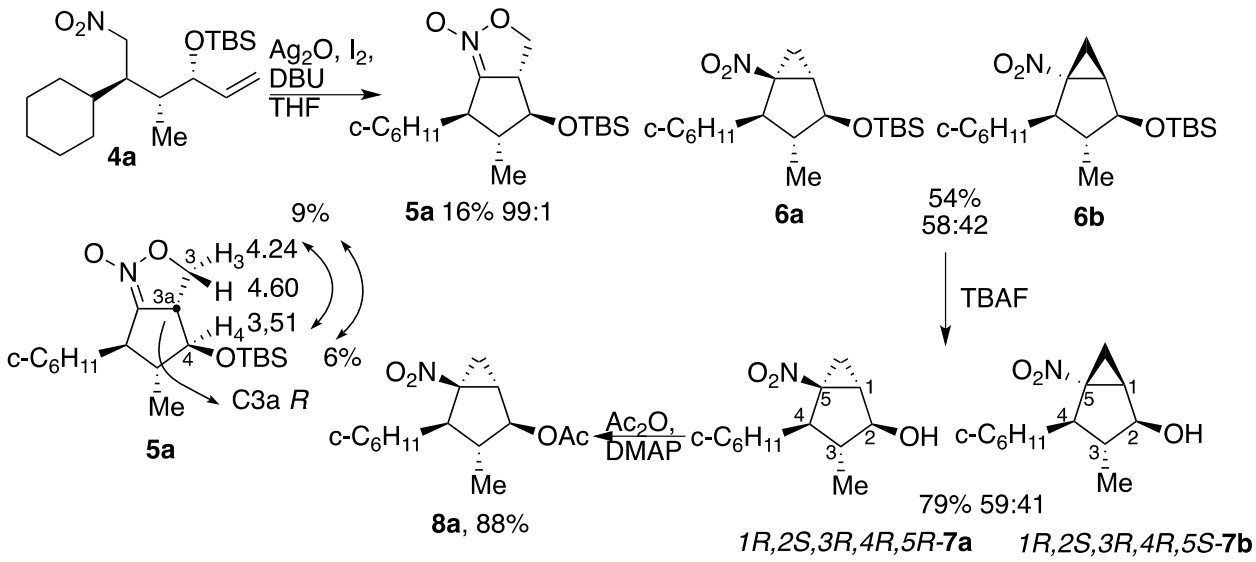
same cyclization reaction using precursors with one less carbon atom. In this paper, we report that the intramolecular oxidative cyclization reaction of chiral 6-nitrohex-1-en-3-ols affords optically active bicyclic isoxazoline-*N*-oxide, along with chiral 5-nitrobicyclo[3.1.0]hexanes. We discuss the stereoselectivity of the reaction.

The precursor of the cyclization reaction was prepared from nitro alkene **1** (Scheme 1). The asymmetric conjugate addition reaction of propionaldehyde with nitro alkene **1**, catalyzed by a L-proline-derived organocatalyst, afforded nitro aldehyde **2** in good yield.[7] Treatment of compound **2** with vinylmagnesium bromide resulted in the formation of two possible diastereomers **3a** and **3b** in 72% yield. NMR spectra revealed that the diastereomeric ratio of the two isomers was approximately 60:40. Compounds **3a** and **3b** were separated easily using routine flash column chromatography. Each of the hydroxyl groups of compound **3** were protected by a TBS group under standard conditions, resulting in **4a** and **4b** in 91% and 80% yields, respectively. These precursors were expected to form isoxazoline-*N*-oxide preferentially because a bulky cyclohexyl group was introduced at the C5 position, the carbon adjacent to the nitro group.



Scheme 1. Preparation of cyclization precursors, **4a** and **4b**

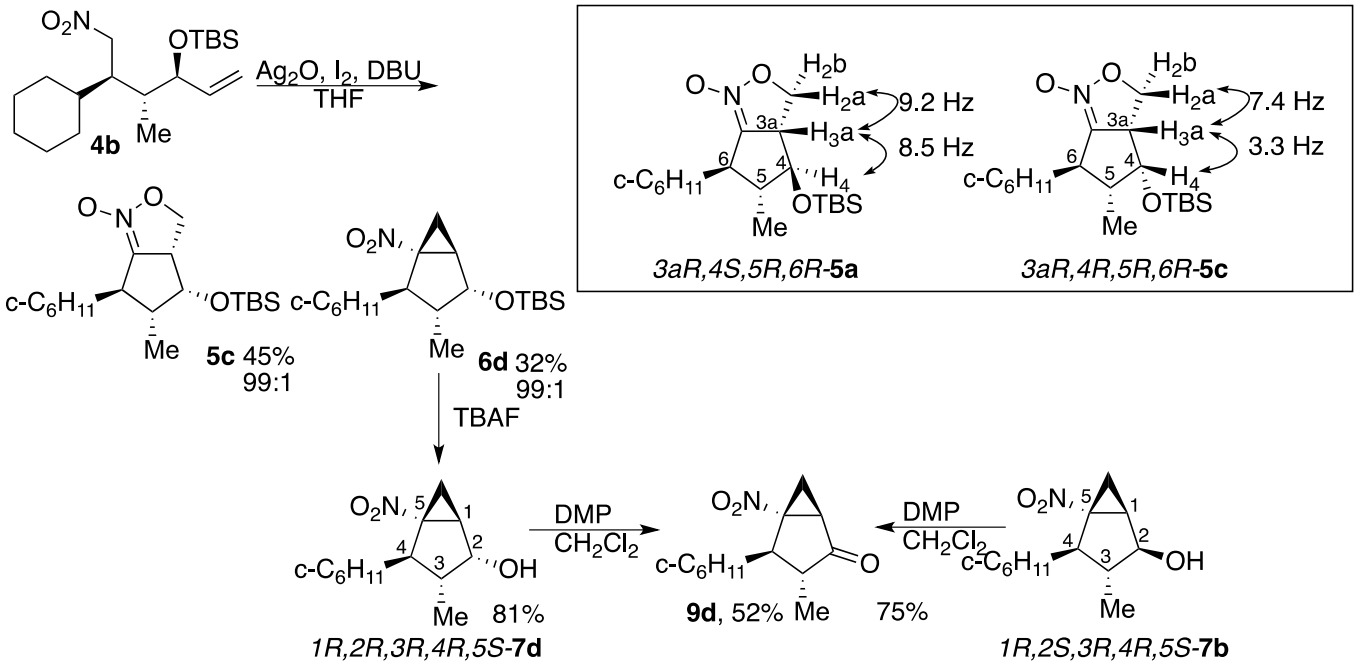
Treatment of precursor **4a** with Ag_2O and iodine in the presence of DBU resulted in the smooth formation of bicyclic isoxazoline-*N*-oxide **5a** and 5-nitrobicyclo[3.1.0]hexane **6**. Compound **5a** was obtained as a single isomer, while compound **6** contained two stereoisomers **6a** and **6b**, in the ratio of 58:42, which were obtained as an inseparable mixture. The configuration of isoxazoline-*N*-oxide **5a** was determined using an NOE experiment, in which H3 and H4 protons were irradiated. Signal enhancements of 9% and 6% were observed, respectively. Thus, it was inferred that the C3a in **5a** is in an *R* configuration.



Scheme 2. Oxidative cyclization reaction of **4a** and stereochemical elucidation of products

To determine the stereochemistry of **6**, the TBS groups of **6a** and **6b** were removed to give the alcohol **7** in 79% yield. The diastereomeric ratio between **7a** and **7b** was 59:41, which was unchanged during the transformation. Fortunately, the two diastereomers were separated by flash chromatography, and the minor isomer **7b** gave a good crystal. X-Ray crystallographic analysis of **7b** unambiguously revealed that compound **7b** had *1R,2S,3R,4R,5S* configuration.[8] In this configuration, the cyclohexyl and cyclopropyl groups are in a *cis*-configuration, which is contrary to previous results.[6] The major isomer **7a** did not give good crystal. We acetylated the hydroxyl group to convert it to **8a** in 88% yield. Compound **8a** afforded good crystals that were suitable for X-ray crystallographic analysis, which show that configuration of **8a** was *1S,2S,3R,4R,5R*,[9] indicating that the cyclohexyl group and the cyclopropane ring are located in *trans* configuration.

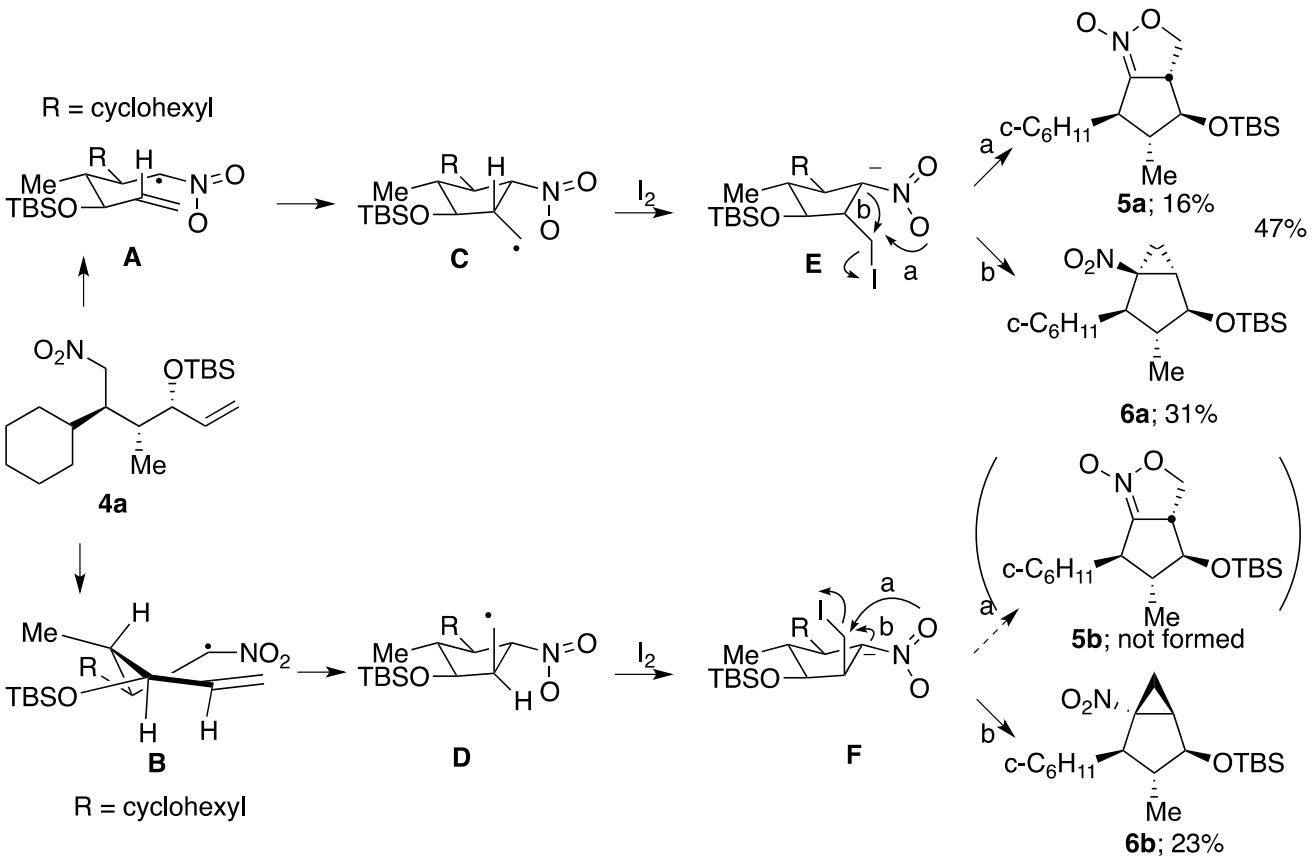
The cyclization reaction from the minor isomer **4b** was examined (Scheme 3). Compound **4b** underwent a similar cyclization reaction to give isoxazoline-*N*-oxide **5c** and compound **6d** in 45 and 32% yields, respectively. Both products contained single isomers, and the reaction progressed in a stereoselective manner. Comparison of the coupling constants between the bridgehead proton H3a and the adjacent protons H2a and H4 afforded useful information towards the determination of the configuration of compound **5c**. For example, compound **5a** showed that ^{1}H NMR coupling constants between H3a and H2a and between H3a and H4 were 9.2 and 8.5 Hz, respectively. On the other hand, the corresponding coupling constants in compound **5c** were 7.4 and 3.3 Hz, respectively. These results clearly suggest that the stereochemical differences between **5a** and **5c** arise from the difference of configuration at the C4 carbon, the carbon adjacent to the TBSO group. Thus, we concluded that the configuration of **5c** should be *3aR,4R,5R,6R*.



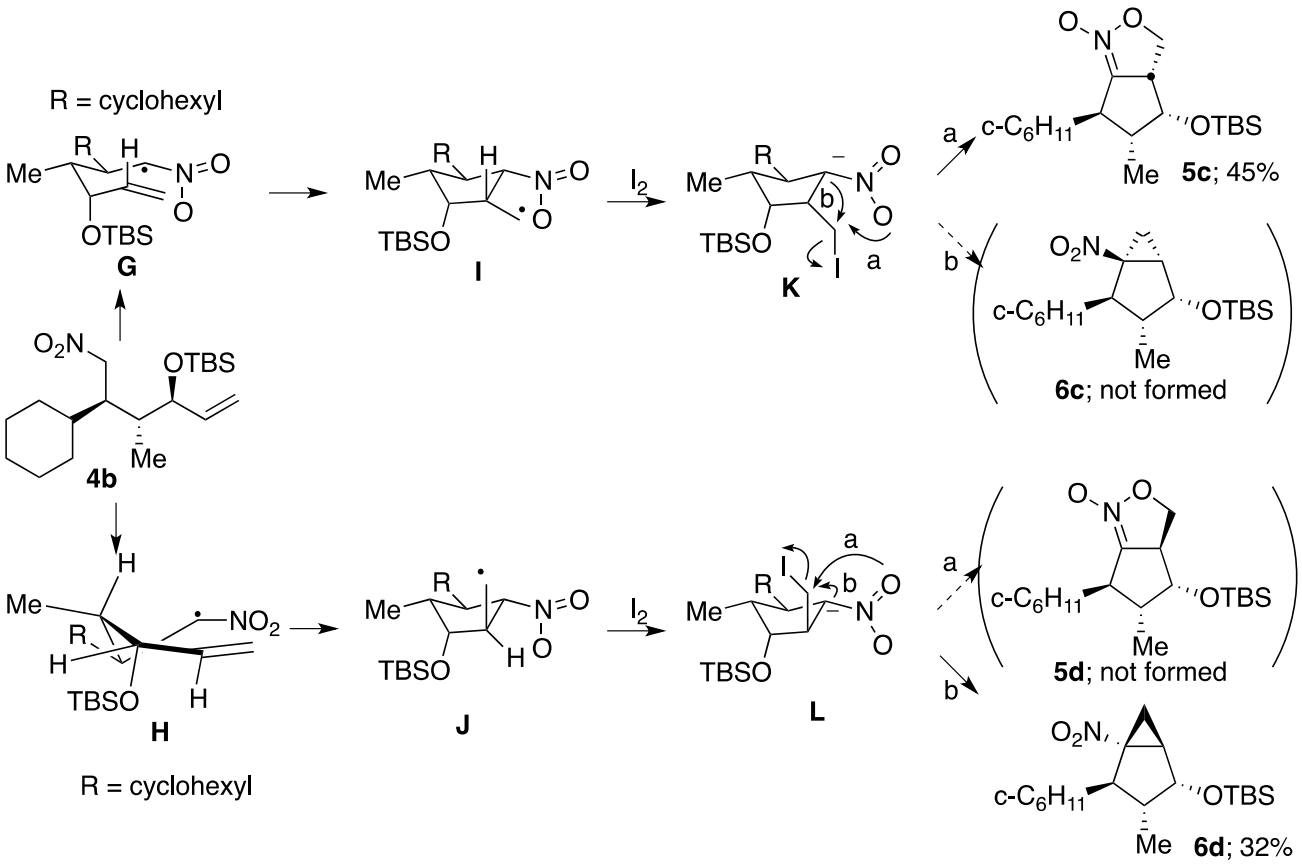
Scheme 3. Oxidative cyclization reaction of **4b** and stereochemical elucidation of products

The stereochemistry of **6d** was determined by chemical conversion. Deprotection of the TBS group followed by oxidation provided the cyclic ketone **9d** in 52% yield as a single isomer. The same conversion from compound **7b** gave **9d** in 75% yield. The NMR spectra for these compounds were identical. Thus, the stereochemical difference between **7d** and **7b** should come from the differences of the configuration at the C2 carbon. We concluded that the configuration of **7d** should be *1R,2R,3R,4R,5S* as shown in Scheme 3. Thus, the cyclohexyl group and the cyclopropane in compound **7d** were *cis* to each other.

Based on the previous results for the formation of isoxazoline-*N*-oxide and bicyclo[3.1.0]hexane,[5] the stereochemical course of the reaction from **4a** and **4b** is assumed to be as shown in the following routes (Scheme 4). Precursor **4a** undergoes radical cyclization through intermediate radical **A**, in which all of substituents occupy equatorial positions. A 5-exo-trig mode cyclization of **A** affords cyclized radical **C** that is trapped by iodine to give iodomethyl intermediate **E**. Subsequent intramolecular cyclization results in the formation of either **5a** (pass a), through an oxygen-centered nucleophile, or **6a** (pass b), through a carbon-centered nucleophile. However, the relatively bulky cyclohexyl group and the TBSO group induce a gauche–gauche interaction that destabilizes the all-equatorial conformation of **A**. As a result, some parts of the reaction progresses through twist-boat conformation **B**, which passes through intermediates **D** and **F** to yield **6b**. Note that pass b dominates in the intramolecular substitution reaction from intermediate **F** and the formation of the isoxazoline-*N*-oxide **5b** was not observed.



Scheme 4. Plausible reaction pathways from **4a**



Scheme 5. Plausible reaction pathways from **4b**

The reaction from **4b** is also realized through an analogous reaction mechanism (Scheme 5). In this case, the conformations of the two initial radicals **G** and **H** determine the formation of products. Thus, isoxazoline-*N*-oxide **5c** is formed through a chair transition structure **G** that gives the intermediates **I** and **K**, while nitrocyclopropane **6d** is formed through the twist-boat transition structure **H** that gives the intermediates **J** and **L**. Note that compounds **6c** and **5d** are not formed through this reaction mechanism and the stereoselectivity of the product is well-controlled by the cyclohexyl and TBSO groups.

In conclusion, we successfully prepared optically active isoxazoline-*N*-oxide along with bicyclo[3.1.0]hexane. These compounds are potential useful intermediates for the further synthesis of heterocyclic compounds, which is being investigated in our laboratory and will be reported in due course.

EXPERIMENTAL

Optically active nitroaldehyde **2** was prepared by the reported method.[7] Vinylmagnesium bromide in THF solution was purchased from Aldrich. All ^{1}H and ^{13}C NMR spectra were recorded on JEOL lamda-500 or JNM-ECA 500 Delta2 (500 MHz for ^{1}H and 126 MHz for ^{13}C) spectrometer. All the reactions in this paper were performed under nitrogen atmosphere unless otherwise mentioned. High-resolution mass spectra (HRMS) were measured by JEOL JMS T-100LP LC-ESI mass spectrometer.

Preparation of (*4R,5R*)-5-cyclohexyl-4-methyl-6-nitrohex-1-en-3-ol (3): Under nitrogen atmosphere, vinylmagnesium bromide (1 M in THF, 6.0 mL, 6.0 mmol) was added to a solution of compound **2** (0.4848 g, 2.27 mmol) in THF (23 mL) at –20 °C. The reaction mixture was stirred at the same temperature for 1 h. Aqueous NH_4Cl (30 mL) was added to the reaction mixture, and THF was removed by rotary evaporator. Aqueous phase was extracted with EtOAc (20 mL × 3). The organic phase was combined and dried over Na_2SO_4. After filtration, solvent was removed by rotary evaporator, and residue was purified by flash chromatography (silica gel/hexane then hexane-EtOAc 32:1 to 7:1 v/v) to give **3a** and **3b** in 72% yield (0.3919 g, 1.62 mmol). Further carful separation by flash chromatography provided diastereomerically pure **3a** and **3b**.

(*3R,4R,5R*)-5-Cyclohexyl-4-methyl-6-nitrohex-1-en-3-ol (3a): Colorless oil; $[\alpha]_D$ +13.8 ($CHCl_3$, c 0.97); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.82 (m, 1H), 5.26 – 5.15 (m, 2H), 4.59 (dd, *J* = 13.1, 5.1 Hz, 1H), 4.43 (dd, *J* = 13.7, 5.6 Hz, 1H), 4.24 (s, 1H), 2.25 (q, *J* = 5.1 Hz, 1H), 1.90 – 1.41 (m, 8H), 1.30 – 1.02 (m, 4H), 0.97 (d, *J* = 5.3 Hz, 3H), 0.96 – 0.85 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.2, 115.2, 76.5, 73.1, 45.7, 39.0, 37.8, 31.7, 29.3, 26.7, 26.5, 26.4, 11.8; HRMS (ESI-TOF): calcd for $C_{13}H_{23}NNaO_3$, 264.1576 [M + Na^+], found 264.1561.

(*3S,4R,5R*)-5-Cyclohexyl-4-methyl-6-nitrohex-1-en-3-ol (3b): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.75 (m, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 4.45 (dd, *J* = 9.0, 2.2 Hz, 1H), 4.44 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.98 (t, *J* = 7.9 Hz, 1H), 2.47 – 2.41 (m, 1H), 1.79 – 1.56 (m, 8H),

1.33 – 0.96 (m, 4H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.89 – 0.79 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 117.3, 76.6, 75.7, 43.8, 39.5, 37.7, 32.7, 29.3, 26.8, 26.6, 26.4, 13.4.

Preparation of (*3R,4R,5R*)-3-*tert*-butyldimethylsilyloxy-5-cyclohexyl-4-methyl-6-nitrohex-1-ene (4a): Under nitrogen atmosphere, TBSOTf (0.90 mL, 3.92 mmol) and 2,6-lutidine (0.48mL, 4.16 mmol) were added to a solution of compound **3a** (0.4532 g, 1.88 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 48 h. Water (20 mL) was added and the organic layer was separated. Water phase was extracted with EtOAc (30 mL × 3). The organic phase was combined and dried over Na_2SO_4. After filtration, solvent was removed by rotary evaporator, and residue was purified by flash chromatography (silica gel/hexane then hexane-EtOAc 50:1 v/v) to give **4a** in 91% yield (0.6064 g, 1.71 mmol). Colorless oil; $[\alpha]_D$ +21.7 ($CHCl_3$, c 0.84); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.78 (m, 1H), 5.17 – 5.09 (m, 2H), 4.64 (dd, *J* = 13.1, 5.7 Hz, 1H), 4.35 (dd, *J* = 13.3, 6.8 Hz, 1H), 4.14 – 4.07 (m, 1H), 2.26 (p, *J* = 6.3 Hz, 1H), 1.64 (t, *J* = 12.7 Hz, 5H), 1.55 – 1.44 (m, 1H), 1.30 – 1.02 (m, 6H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 115.7, 76.6, 76.4, 44.5, 39.9, 38.6, 31.9, 29.0, 26.9, 26.6, 26.4, 26.0 (3C), 18.2, 13.2, -3.8, -4.7; HRMS (ESI-TOF): calcd for $C_{19}H_{37}NNaO_3Si$, 378.2440 [M + Na^+], found 378.2433.

Preparation of (*3S,4R,5R*)-3-*tert*-Butyldimethylsilyloxy-5-cyclohexyl-4-methyl-6-nitrohex-1-ene (4b): Under nitrogen atmosphere, TBSOTf (0.90 mL, 3.92 mmol) and 2,6-lutidine (0.48mL, 4.16 mmol) were added to a solution of compound **3b** (0.1245 g, 0.516 mmol in CH_2Cl_2 (1.5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 48 h. Water (20 mL) was added and the organic layer was separated. Water phase was extracted with EtOAc (30 mL × 3). The organic phase was combined and dried over Na_2SO_4. After filtration, solvent was removed by rotary evaporator, and residue was purified by flash chromatography (silica gel/hexane, then hexane-EtOAc 100:1 v/v) to give **4b** in 80% yield (0.1462 g, 0.411 mmol). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 17.4, 10.3, 6.7 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.41 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.35 (dd, *J* = 12.6, 7.7 Hz, 1H), 4.04 (t, *J* = 6.2 Hz, 1H), 2.42 – 2.36 (m, 1H), 1.78 – 1.62 (m, 4H), 1.30 – 0.95 (m, 7H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.89 – 0.80 (m, 1H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7, 116.3, 76.8, 76.5, 43.3, 40.4, 37.3, 32.8, 29.3, 26.9, 26.6, 26.4, 26.0 (3C), 18.2, 13.1, -3.8, -4.8.

Oxidative cyclopropanation reaction of 4a: Under nitrogen atmosphere, DBU (0.24 mL, 1.6 mmol), Ag_2O (0.6470 g, 2.79 mmol) and iodine (0.6750 g , 2.66 mmol) were added in this order to a solution of **4a** (0.4743 g , 1.33 mmol) in dry THF (20 mL) at room temperature. The reaction mixture was stirred for 4 h at the same temperature, then the precipitate was filtered. The filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (silica gel/hexane-EtOAc 50:1 then 10:1 v/v) to give **5a** in 16% yield (0.0772 g, 0.218 mmol) along with a mixture of **6a** and **6b** in 54% yield (0.2547 g, 0.720 mmol). The Compound **5a** was isolated as diastereomerically pure single isomers and the ratio was >99/1.

The ratio of Compound **6a** and **6b** was 58:42, which cold not be separated by usual chromatographic treatment.

(*3aR,4S,5R,6R*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-cyclohexyl-5-methyl-3a,4,5,6-tetrahydro-3*H*-cyclopenta[*c*]isoxazole-*N*-oxide (5a): White solid; mp 148.0 – 148.8 °C; $[\alpha]_D$ –16.1 ($CHCl_3$, c 0.35); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (ddd, *J* = 9.2, 7.7, 1.1 Hz, 1H), 4.24 (ddd, *J* = 8.8, 7.6, 1.0 Hz, 1H), 3.72 (qd, *J* = 8.7, 2.9 Hz, 1H), 3.51 (t, *J* = 8.6 Hz, 1H), 2.23 – 2.09 (m, 2H), 1.84 – 1.68 (m, 5H), 1.67 – 1.48 (m, 2H), 1.31 – 1.12 (m, 4H), 1.10 (dd, *J* = 6.3, 1.0 Hz, 3H), 0.92 – 0.80 (m, 9H), 0.04 (d, *J* = 1.0 Hz, 3H), -0.02 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.4, 81.5, 70.6, 57.0, 50.1, 48.3, 41.6, 32.0, 31.2, 26.5, 26.4, 26.2, 25.7 (3C), 18.4, 17.9, -4.3, -4.6; HRMS (ESI-TOF): calcd for $C_{19}H_{35}NNaO_3Si$, 376.2284 [M + Na^+], found 376.2287.

(*1S,2S,3R,4R,5R*)-2-*tert*-Butyldimethylsilyloxy-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexane (6a): Colorless oil; $[\alpha]_D$ –59.0 ($CHCl_3$, c 0.30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 1H), 2.61 (t, *J* = 10.7, 5.6 Hz, 1H), 2.21 – 2.10 (m, 2H), 1.79 – 0.99 (m, 13H), 0.96 (d, *J* = 7.8 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 79.1, 73.8, 53.5, 45.5, 37.5, 36.9, 31.2, 27.9, 26.7, 26.7, 26.2, 25.8 (3C), 23.3, 22.2, 18.0, -4.7, -4.7; HRMS (ESI-TOF): calcd for $C_{19}H_{35}NNaO_3Si$, 376.2284 [M + Na^+], found 376.2266.

(*1R,2S,3R,4R,5S*)-2-*tert*-Butyldimethylsilyloxy-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexane (6b): White solid; mp 81.3 – 82.0 °C; $[\alpha]_D$ –77.5 ($CHCl_3$, c 0.26); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 – 3.94 (m, 1H), 2.60 (dd, *J* = 9.9, 4.6 Hz, 1H), 2.24 – 2.20 (m, 2H), 1.82 – 1.47 (m, 8H), 1.41 – 1.30 (m, 1H), 1.29 – 1.13 (m, 4H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.0, 70.2, 49.3, 42.8, 40.5, 36.7, 31.7, 31.2, 26.9, 26.8, 26.4, 25.8 (3C), 18.5, 18.1, 15.8, -4.4, -4.7; HRMS (ESI-TOF): calcd for $C_{19}H_{36}NO_3Si$, 354.2464 [M + H^+], found 354.2476.

Oxidative cyclopropanation reaction of 4b: Under nitrogen atmosphere, DBU (0.10 mL, 0.67 mmol), Ag_2O (0.2138 g, 0.923 mmol) and iodine (0.2329 g, 0.918 mmol) were added in this order to a solution of **4b** (0.1595 g, 0.449 mmol) in dry THF (7.5 mL) at room temperature. The reaction mixture was stirred for 4 h at the same temperature, then filtered. The filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (silica gel/hexane-EtOAc 50:1 then 10:1 v/v) to give **5c** in 45% yield (0.0710 g, 0.201 mmol) in diastereomerically pure form along with single isomer of **6d** in 32% yield (0.0509 g, 0.144 mmol).

(*3aR,4R,5R,6R*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-cyclohexyl-5-methyl-3a,4,5,6-tetrahydro-3*H*-cyclopenta[*c*]isoxazole-*N*-oxide (5c): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (td, *J* = 7.4, 1.8 Hz, 2H), 4.37 (td, *J* = 6.9, 1.6 Hz, 1H), 3.87 (td, *J* = 3.3, 2.9, 0.9 Hz, 2H), 3.81 (tdd, *J* = 8.2, 3.5, 1.6 Hz, 1H), 2.35 – 2.23 (m, 2H), 1.77 – 1.66 (m, 3H), 1.67 – 1.57 (m, 1H), 1.52 – 1.41 (m, 1H), 1.42 – 1.29 (m, 1H), 1.26 – 1.09 (m, 3H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (126

MHz, $CDCl_3$) δ 123.2, 72.4, 65.2, 56.5, 48.2, 47.5, 40.4, 32.7, 30.6, 26.6, 26.5, 26.3, 25.9, 18.2, 15.1, -4.1, -4.5.

(*1R,2R,3R,4R,5S*)-2-*tert*-Butyldimethylsilyloxy-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexane (6d): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (d, *J* = 4.4 Hz, 1H), 2.88 (dd, *J* = 10.6, 4.4 Hz, 1H), 2.29 (dd, *J* = 9.8, 5.8 Hz, 1H), 2.02 (dd, *J* = 10.1, 6.1 Hz, 1H), 1.80 – 1.47 (m, 6H), 1.36 – 1.07 (m, 6H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 74.9, 71.8, 48.7, 40.7, 39.6, 39.5, 32.4, 31.0, 27.1, 27.0, 26.4, 25.8 (3C), 18.2, 18.1, 14.2, -4.6, -4.9.

Conversion of a mixture of 6a and 6b to 7a and 7b: TBAF (1.0 M in THF, 1.1 mL, 1.1 mmol) was added to a solution of mixture of **6a** and **6b** (0.2547 g, 0.720 mmol, 58:42) in THF (2 mL) and the reaction mixture was stirred at room temperature for 48 h. $NaHCO_3$ aq (20 mL) was added and THF was removed in vacuo. Resulting aqueous solution was extracted with EtOAc (3 x 30 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, solvent was removed and the residue was subjected to flash chromatography (silica gel/hexane-EtOAc 15:1 then 7:1 v/v) to give diastereomerically pure **7a** in 57% yield (0.1197 g, 0.417 mmol) and **7b** in 22% yield (0.0660 g, 0.234 mmol), respectively.

(*1S,2S,3R,4R,5R*)-4-Cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexan-2-ol (7a): Colorless oil; $[\alpha]_D$ – 64.7 ($CHCl_3$, c 0.59); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 1H), 2.73 – 2.66 (m, 1H), 2.25 – 2.16 (m, 2H), 1.92 (s, 1H), 1.78 – 1.62 (m, 4H), 1.58 (dd, *J* = 10.6, 6.0 Hz, 0H), 1.49 (d, *J* = 13.0 Hz, 1H), 1.42 – 1.04 (m, 8H), 1.00 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.9, 73.6, 53.7, 44.9, 37.4, 36.7, 31.2, 27.9, 26.6, 26.5, 26.2, 23.5, 22.2; HRMS (ESI-TOF): calcd for $C_{13}H_{21}NNaO_3$, 262.1419 [M + Na^+], found 262.1417.

(*1R,2S,3R,4R,5S*)-4-Cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexan-2-ol (7b): White solid; mp 101.1 – 102.0 °C; $[\alpha]_D$ –92.3 ($CHCl_3$, c 0.393); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (t, *J* = 7.8, 4.8 Hz, 1H), 2.65 (dd, *J* = 9.6, 5.5 Hz, 1H), 2.31 (dt, *J* = 9.9, 5.3 Hz, 1H), 2.25 (dd, *J* = 9.6, 5.9 Hz, 1H), 1.84 – 1.58 (m, 8H), 1.54 (t, *J* = 5.9 Hz, 1H), 1.52 – 1.47 (m, 1H), 1.37 – 1.28 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.25 – 1.07 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 77.7, 70.0, 49.9, 42.5, 40.5, 36.0, 31.7, 31.2, 26.9, 26.8, 26.3, 18.5, 15.5; HRMS (ESI-TOF): calcd for $C_{13}H_{21}NNaO_3$, 262.1419 [M + Na^+], found 262.1410.

Conversion of 6d to 7d: TBAF (1.0 M in THF, 0.25 mL, 0.25 mmol) was added to a solution of **6d** (0.0509 g, 0.144 mmol) in THF (0.2 mL) and the reaction mixture was stirred at room temperature for 48 h. $NaHCO_3$ aq (20 mL) was added and THF was removed in vacuo. Resulting aqueous solution was extracted with EtOAc (3 x 30 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, solvent was removed and the residue was subjected to flash chromatography (silica gel/hexane-EtOAc 15:1 then 10:1 v/v) to give **7d** in 81% yield (0.0277 g, 0.116 mmol).

(*1R,2R,3R,4R,5S*)-4-Cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexan-2-ol (7d): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 – 3.90 (m, 1H), 2.87 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.34 (ddd, *J* = 10.0, 6.8, 1.3 Hz, 1H), 2.19 (t, *J* = 10.0, 6.1 Hz, 1H), 1.85 – 1.50 (m, 8H), 1.28 (t, *J* = 6.3 Hz, 1H), 1.22 – 1.14 (m, 4H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 74.7, 71.9, 48.7, 40.1, 39.6, 38.6, 32.2, 31.1, 27.0, 26.9, 26.4, 17.9, 13.5.

Preparation of (*1S,2S,3R,4R,5R*)-2-aceroxy-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexane (8a): Ac_2O (0.05 mL, 0.529 mmol) and DMAP (0.0204 g, 0.167 mmol) were added to a solution of compound **7a** (0.0710 g, 0.297 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 4 h. Aqueous $NaHCO_3$ (20 mL) was added to the solution and the organic phase was separated. The water phase was extracted with CH_2Cl_2 (20 mL × 2). The organic phase was combined and dried over Na_2SO_4. After filtration, solvent was removed by rotary evaporator. The residue was purified by flash chromatography (silica gel/hexane then hexane-EtOAc 13:1 v/v) to give **8a** in 88% yield (0.0731 g, 0.260 mmol). White solid; mp 84.2 – 84.9; $[\alpha]_D$ –48.4 ($CHCl_3$, c 1.70); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (s, 1H), 2.76 (t, *J* = 10.1, 6.2 Hz, 2H), 2.27 – 2.16 (m, 2H), 2.08 (s, 3H), 1.78 – 1.63 (m, 4H), 1.49 (d, *J* = 12.8 Hz, 1H), 1.43 – 1.09 (m, 6H), 1.09 (d, *J* = 5.8 Hz, 1H), 1.05 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 80.3, 73.3, 53.4, 42.1, 37.5, 33.6, 31.2, 27.5, 26.6, 26.5, 26.3, 23.1, 21.7, 21.3; HRMS (ESI-TOF): calcd for $C_{15}H_{23}NNaO_4$, 304.1525 [M + Na^+], found 304.1530.

Preparation of (*1R,3R,4R,5S*)-4-Cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexan-2-one 9d from 7d: A mixture of **7d** (0.0277 g, 0.116 mmol) and Dess-Martin periodinane (0.1641 g, 0.387 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 24 h. Precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to flash chromatography (silica gel/hexane then hexane-EtOAc 15:1v/v) to give **9d** in 52% yield (0.0143 g, 0.0603 mmol). Colorless oil; $[\alpha]_D$ –79.6 ($CHCl_3$, c 0.08); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (td, *J* = 7.9, 1.7 Hz, 1H), 2.80 (dd, *J* = 10.6, 6.2 Hz, 1H), 2.65 (dd, *J* = 12.0, 5.2 Hz, 1H), 1.98 (p, *J* = 7.4 Hz, 1H), 1.84 – 1.71 (m, 4H), 1.71 – 1.64 (m, 3H), 1.48 (t, *J* = 10.6 Hz, 2H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.21 – 1.11 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.5, 71.5, 49.1, 45.3, 41.9, 39.8, 31.6, 31.1, 26.4, 26.4, 26.1, 19.3, 16.4; HRMS (ESI-TOF): calcd for $C_{13}H_{20}NO_3$, 238.1443 [M + H^+], found 238.1451.

Preparation of (*1R,3R,4R,5S*)-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexan-2-one 9d from 7b: A mixture of **7b** (0.0171 g, 0.0714 mmol) and Dess-Martin periodinane (0.0464 g, 0.109 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 24 h. Precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to flash chromatography (silica gel/hexane then hexane-EtOAc 15:1v/v) to give **9d** in 75% yield (0.0128 g, 0.0539 mmol). ^{1}H NMR and ^{13}C NMR were identical to **9d** from **7d**.

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8. Crystallographic data (excluding structure factors) for the structures **7b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1477201. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
9. Crystallographic data (excluding structure factors) for the structures **8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1477202. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].