OXIDATIVE SYNTHESIS OF ISOXAZOLINE-\(N\)-OXIDE FROM OPTICALLY ACTIVE NITRO ALCOHOLS

Takaaki Moriyama,¹ Takuji Kawamoto,¹ Hidemitsu Uno,² and Akio Kamimura*,¹

¹Department of Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University, Ube 755-8611 Japan, and ²Department of Chemistry, Graduate School of Science and Engineering, Ehime University, Matsuyama 790-8577, Japan. ak10@yamafuchi-u.ac.jp

Abstract – Treatment of optically active 6-nitrohex-1-en-3-ols with \(\text{Ag}_2\text{O}\) 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 nitro cyclopropanes.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. 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](image)

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

Treatment of precursor 4a with Ag₂O 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.
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 '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.
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. Vinylmagnesium bromide in THF solution was purchased from Aldrich. All 1H and 13C NMR spectra were recorded on JEOL lamda-500 or JNM-ECA 500 Delta2 (500 MHz for 1H and 126 MHz for 13C) 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 NH4Cl (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 Na2SO4. 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 careful 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; [α]D +13.8 (CHCl3, c 0.97); 1H NMR (500 MHz, CDCl3) 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 – 2.41 (m, 1H), 1.79 – 1.56 (m, 8H), 0.97 (d, J = 5.3 Hz, 3H), 0.96 – 0.85 (m, 1H); 13C NMR (126 MHz, CDCl3) 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 C13H23NNaO3, 264.1576 [M + Na+], found 264.1561.

**(3S,4R,5R)-5-Cyclohexyl-4-methyl-6-nitrohex-1-en-3-ol (3b):** Colorless oil; 1H NMR (500 MHz, CDCl3) 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); 13C NMR (126 MHz, CDCl3) 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 (0.48 mL, 4.16 mmol) were added to a solution of compound 3a (0.4532 g, 1.88 mmol) in CH2Cl2 (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 Na2SO4. 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; [α]D +21.7 (CHCl3, c 0.84); 1H NMR (500 MHz, CDCl3) 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); 13C NMR (126 MHz, CDCl3) δ 139.8, 115.7, 76.8, 76.5, 43.9, 39.8, 31.8, 29.0, 26.9, 26.6, 26.4, 26.0 (3C), 18.2, 13.2, -3.8, -4.7; HRMS (ESI-TOF): calcd for C19H37NNaO3Si, 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 (0.48 mL, 4.16 mmol) were added to a solution of compound 3b (0.1245 g, 0.516 mmol in CH2Cl2 (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 Na2SO4. 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; 1H NMR (500 MHz, CDCl3) 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); 13C NMR (126 MHz, CDCl3) 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), Ag2O (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 could not be separated by usual chromatographic treatment.

\((3aR,4S,5R,6R)-4-\text{((tert-Butyldimethylsilyl)oxy)-6-cyclohexyl-5-methyl-3a,4,5,6-tetrahydro-3H-cyclopenta[c]isoxazole-}\text{N-oxide (5a):}\) White solid; mp 148.0 – 148.8 °C; \([\alpha]_D^{\text{25}}-16.1\) (CHCl₃, c 0.35); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 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, CDCl₃) \(\delta\) 120.4, 81.5, 70.6, 57.0, 50.1, 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 C₁₉H₃₅NNaO₃Si, 376.2284 [M + Na\(^{\text{+}}\)], found 376.2287.

\((1S,2S,3R,4R,5R)-2-\text{tert-Butyldimethylsilyloxy-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexane (6a):}\) Colorless oil; \([\alpha]_D^{\text{25}}-59.0\) (CHCl₃, c 0.30); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 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); \(^{13}\)C NMR (126 MHz, CDCl₃) \(\delta\) 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 C₁₉H₃₅NNaO₃Si, 376.2284 [M + Na\(^{\text{+}}\)], found 376.2266.

\((1R,2S,3R,4R,5S)-2-\text{tert-Butyldimethylsilyloxy-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexane (6b):}\) White solid; mp 81.3 – 82.0 °C; \([\alpha]_D^{\text{25}}-77.5\) (CHCl₃, c 0.26); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 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, CDCl₃) \(\delta\) 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 C₁₉H₃₅NO₃Si, 354.2464 [M + H\(^{\text{+}}\)], found 354.2476.

Oxidative cyclopropanation reaction of 4b: Under nitrogen atmosphere, DBU (0.10 mL, 0.67 mmol), Ag₂O (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).

\((3aR,4S,5R,6R)-4-\text{((tert-Butyldimethylsilyl)oxy)-6-cyclohexyl-5-methyl-3a,4,5,6-tetrahydro-3H-cyclopenta[c]isoxazole-}\text{N-oxide (5c):}\) Colorless oil; \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$SO$_4$. 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; [a]$_D$ – 64.7 (CHCl$_3$, c 0.59); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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): calcld 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; [a]$_D$ –92.3 (CHCl$_3$, c 0.393); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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): calcld 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$_2$SO$_4$. 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\(_3\)) \(\delta 3.95 – 3.90 \) (m, 1H), 2.87 (dd, \(J = 11.5, 4.5 \) Hz, 1H), 2.34 (dd, \(J = 10.0, 6.8, 1.3 \) 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); \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 74.7, 71.9, 48.7, 40.1, 39.6, 38.6, 32.2, 31.1, 27.0, 26.9, 26.4, 17.9, 13.5\).

Preparation of (1S,2S,3R,4R,5R)-2-aceroxy-4-cyclohexyl-3-methyl-5-nitrobicyclo[3.1.0]hexane (8a): Ac\(_2\)O (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\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (20 mL \(\times 2\)). The organic phase was combined and dried over Na\(_2\)SO\(_4\). 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\(_3\)) \(\delta 4.53\) (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); \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 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\(_2\)Cl\(_2\) (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 15:1 v/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\(_3\)) \(\delta 2.96\) (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); \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 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\(_2\)Cl\(_2\) (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 15:1 v/v) to give 9d in 75% yield (0.0128 g, 0.0539 mmol). \(^1\)H NMR and \(^1\)C NMR were identical to 9d from 7d.
ACKNOWLEDGEMENTS

We are grateful to financial aids by the Sasakawa Scientific Research Grant (to T. M.). We are grateful to Drs. Yousuke Oota and Kyouhei Shingai, UBE Scientific Analysis Laboratory Inc., for the NMR analyses of several compounds.

REFERENCES AND NOTES

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].