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ASYMMETRIC SYNTHESIS OF A PHEROMONE FOR *ANDRENA HAEMORRHOA* F FROM A CHIRAL NITRO ALCOHOL OBTAINED BY THE YEAST REDUCTION OF A NITRO KETONE

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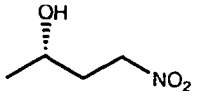
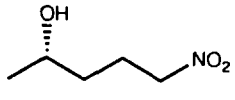
Abstract: The α-position to the nitro group in 4-nitro-2-butanol or 5-nitro-2-pentanol was acylated under DBU-catalysis after the hydroxy group was protected by a *t*-butyl dimethylsilyl group. The present method has been applied to the asymmetric stereoselective synthesis of a pheromone for *Andrena haemorrhoa* F, which has an interesting spiroacetal strucure.

Introduction

Chiral nitro alcohols with a primary nitro group are potentially useful chiral building blocks in organic syntheses because they can be converted into many other useful chiral products *via* a carbon-carbon bond formation at the position α to the nitro group. However, the use of these compounds has scarcely been reported because of the difficulty in their preparation. In the previous paper from our laboratory,[1] we reported that the reduction of nitro ketones, 4-nitro-2-butanone and 5-nitro-2-pentanone, with bakers' yeast afforded the corresponding (*S*)-alcohols (1 and 2) enantioselectively. In order to demonstrate the utility of these nitro alcohols as valuable chiral building blocks in organic syntheses, the Michael addition of an α-nitro carbanion generated from the chiral nitro alcohol was investigated and the method was applied to the total syntheses of (*S*)-sulcatol and (+)-brefeldin A.[2] In this paper, we would like to report another utility of the chiral nitro alcohol: elongation of a carbon chain *via* acylation at α to the nitro substituent. In fact, the acylation of O-protected nitro alcohols with an acylimidazole proceeded smoothly under base-catalysis by 1,8-diazabicyclo-[5.4.0]-7-undecene (DBU).



(*S*)-1



(*S*)-2

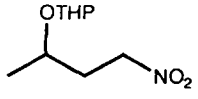
Denitration of the resultant chiral β- and γ-hydroxy α'-keto nitro compounds gave the corresponding chiral γ- and δ-hydroxy ketones, respectively. These substances are useful chiral building blocks for organic syntheses. Using this method, a pheromone for *Andrena haemorrhoa* F (3), which has the 1,8-dioxaspiro[5,6]dodecane spiroacetal structure, has been synthesized in 97% e.e. in five steps starting from (*S*)-1 (e.e. = 97%), the product from the reduction of 4-nitro-2-butanone with bakers' yeast. The pheromone was isolated and its structure was determined by Francke *et al.* as a component of the volatile secretion from the mandibular glands of a bee, *Andrena haemorrhoa* F.[3] The total synthesis of 3 as well as the determination of the stereochemistry of the biologically active isomer were achieved by Mori *et al.*[4] starting from a chiral β-hydroxy ester.

Results and Discussion

The acylation of nitro alcohol derivatives by acylimidazoles was investigated first because this is the key-step for the total synthesis. Acyl chlorides were reacted with imidazole according to the literature procedure[5] to obtain various acylimidazoles quantitatively (Table 1).

Acylation of TBDMS-Substituted 4-Nitro-2-butanol (4) and 5-Nitro-2-pentanol (5). The hydroxy group in the nitro alcohols was protected by a *t*-butyl dimethylsilyl (TBDMS) group and the O-substituted nitro alcohols (4 and 5) were reacted with an acylimidazole in the presence of DBU in tetrahydrofuran (THF). The results are summarized in Table 1. Although the acylation of a nitro compound generally gives a mixture of O-acylated and C-acylated products,[5] fortunately only the C-acylated product was obtained by the present reaction.

Since it was recognized that the structure of the O-substituent, the solvent, and the base to generate an α-nitro carbanion are quite important factors to influence the reaction course, the effects of these factors on the reaction was investigated in detail. In the previous procedure, the lithium nitrorate was prepared, isolated, and was subjected to acylation in dimethyl sulfoxide (DMSO).[5] The isolation of a lithiated carbanion, however, requires specialized techniques and equipment. In addition, removal of the DMSO from such reaction mixtures is usually a troublesome procedure due to low solvent volatility. We, therefore, tried to avoid the use of DMSO, but our attempts to generate the carbanion by lithium-reagents, such as butyllithium and lithium ethoxide, in THF were unsuccessful. At present, we do not know whether the carbanion was not generated or not stable enough to react with an electrophile.



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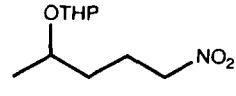

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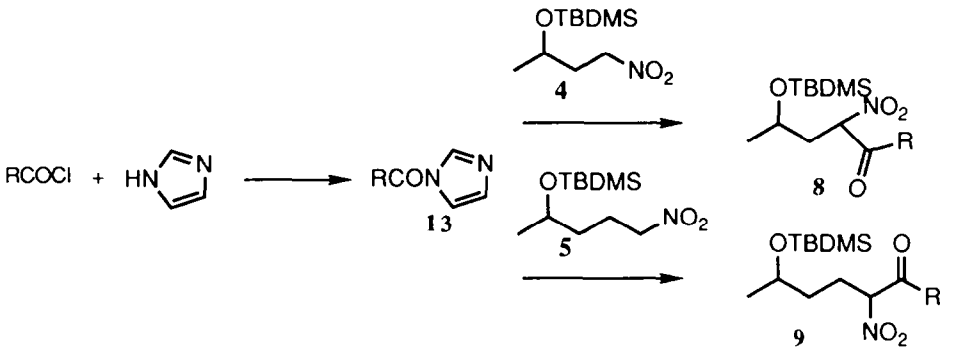
Table 1. The Acylation of the TBDMS-substituted 4-Nitro-2-hydroxybutane (4) and 5-Nitro-2-hydroxypentane (5).[a)]



Acyl Chloride	R	8[b)] Yield (%)	8[b)] d.e.(%)[c)]	9[b)] Yield (%)	9[b)] d.e.(%)[c)]
a	CH_3	60	+31.8	62	0
b	C_2H_5	70	+19.9	58	0
c	C_3H_7	79	+33.3	58	0
d	i-C_3H_7	52	+47.9	51	- 1.3
e	C_4H_9	88	+40.2	56	- 8.6
f	cyclo-C_6H_{11}	68	+37.6	54	+16.0
g	C_6H_5	46	+23.6	70	+ 4.0

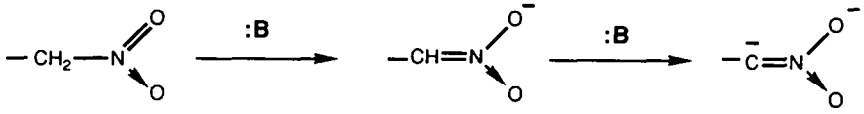
a) The yields of acylimidazoles are 100% in every reaction.
b) The reaction was run in THF for 24 h in the presence of DBU.
c) Predominance of the diastereomer which exibits the signal at lower field in ^{1}H NMR spectrum is designated by +

Therefore, we employed DBU in place of a lithium reagent to generate the carbanion. Sometimes benzene is a good solvent for DBU-catalyzed condensations, especially for alkylation and acylation on an active methylene.[6)] The solubility of acylimidazoles, however, is insufficientin benzene in contrast to THF. We, therefore, finally decided to employ the DBU/THF system in place of the Li/DMSO, which obviates all the above mentioned complexities.

The *t*-butyl dimethylsilyl (TBDMS) group in 4 and 5 was found to be necessary for the acylation reaction. When the TBDMS group was substituted by a tetrahydropyranyl (THP) group (6 and 7), the reaction did not afford the expected product. Instead, the starting material was recovered quantitatively.

In order to test the formation of α-nitro carbanions from 4, 5, 6, and 7,

these compounds were treated with 2 equivalent amounts of DBU in THF, then the reactions were quenched by adding deuterium oxide. Interestingly, both of two methylene protons in 4 and 5 were found to be substituted by deuterons, whereas only one proton in 6 and 7 was substituted. The result reveals that the first molecule of DBU is used to generate the oxyanion instead of a carbanion, then the second molecule of the base reacts with this oxyanion to generate the dianion, in which the anionic charges are localized on the carbon and oxygen atoms.



Probably, the lone-pair electrons on the ring-oxygen atom in the THP moiety prevents the methine-proton in the oxyanion from abstraction by a base due to a proximity effect on the generating carbanionic center. It was also found that no deuteron was incorporated in this position when the hydroxy group of 1 is substituted by an acetyl group. Thus, the acidity of methylene-protons α to the nitro group in these compounds are largely affected by the substituent on the β'-hydroxy-oxygen.

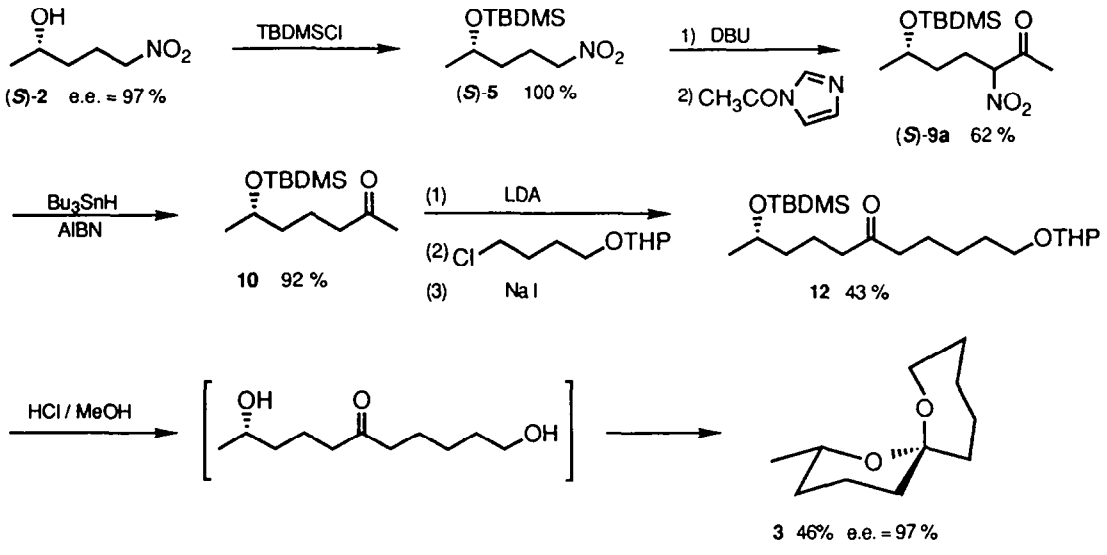
Since the acyl condensation creates a new chiral center, a diastereomeric product is produced and the diastereomeric ratio in the product was measured by ^{1}H NMR analysis. The signals from the methine-protons α to the nitro group in each diastereomers appear at 5.2 and 5.4 ppm. Therefore, the diastereomeric ratio was calculated by comparing the intensities of these two signals. Table 1 lists the diastereomeric excess (d.e.) in the products (8 and 9). The acyl derivatives from 4 gives relatively high d.e. compared to those derived from 5. The bulky TBDMS substituent at the β-position affects the stereochemistry of the reaction of 4, whereas 5 has this substituent on the position one carbon unit further away from the reaction center than that in 4. Consequently, the reaction with the latter compound results in lower stereoselectivity.

The yield of 8 varies from 45% to 90% depending on the structure of the acylating reagent, whereas that of 9 is not affected appreciably by the change in the structure of the acylating reagent. The difference may also be due to the difference in proximity effect of the TBDMS-substituent.

Asymmetric Synthesis of a Pheromone for *Andrena haemorrhoa* F (3). The whole scheme for the total synthesis of 3 is shown in Scheme 1. The starting material, (*S*)-2 (e.e. = 97%), was prepared by the reduction of 5-nitro-2-pentanone with bakers' yeast according to the literature procedure.[1)] Protection of the hydroxy group in (*S*)-2 with TBDMS was achieved by reacting it with *t*-butyl dimethylsilyl chloride at 0 °C in the presence of imidazole in dimethylformamide (DMF). The TBDMS-protected nitro alcohol ((*S*)-5) obtained quantitatively was acetylated by acetylimidazole under the catalysis of DBU in THF. A 1 : 1

diastereomeric mixture of the acetylated compound, (*S*)-9a, was obtained in 62%

Scheme 1



yield. The next step was to eliminate the nitro group from (*S*)-9a. Denitration from nitro compounds by tributyltin hydride has been investigated by Ono *et al.*[7] and Tanner *et al.*[8] It has been reported that the reaction proceeds efficiently from compounds that have an electron-withdrawing group α to the nitro substituent.[9] In fact, the reaction of (*S*)-9a with tributyltin hydride in the presence of catalytic amount of AIBN gave the TBDMS-protected (*S*)-6-hydroxy-2-heptanone (10) in 92% yield. The ω-hydroxybutylation on the methyl group in 6 was achieved by generating the enolate with lithium diisopropylamide (LDA) and reaction with 4-chloro-1-(tetrahydropyranyloxy)butane (11) in the presence of sodium iodide.[4] The product, (*S*)-2,11-dihydroxy-6-undecanone (12) was obtained in 43% yield. Deprotection of 12 with 6 M-hydrochloric acid in methanol gave the desired spiroacetal 3 in 46% yield. More dilute hydrochloric acid did not give a satisfactory result in obtaining the deprotected spirocyclic product, 3.

The optical purity of the product was measured to be 97% by comparing its optical rotation with that reported: $[\alpha]_D^{21}$ -102° (c = 0.50, pentane); lit.[4] $[\alpha]_D^{21}$ -105° (c = 1.1, pentane). Since the starting material had 97% e.e., it is obvious that the stereochemistry at the asymmetric carbon has been kept completely intact throughout the total synthesis.

Experimental

Instruments. ^{1}H NMR spectra were recorded on a Varian VXR-200 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference or in D_2O with sodium 3-(trimethylsilyl)-1-propanesulfonate-1,1,2,2-d_4 (DSS) as an internal reference. IR spectra were recorded on a Hitachi EPI-S2 infrared spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

Materials. Organic reagents were purchased from Nacalai Tesque Co., Tokyo Kasei Co., and Aldrich Chemical Co., respectively, unless otherwise indicated. Acylimidazoles (13) were prepared according to the literature[5] except for acetylimidazole (13a), which was purchased from Tokyo Kasei Co. 4-Chloro-1-(tetrahydropyranyloxy)butane (11) was prepared according to the literature.[4] Elemental analyses of alcohols protected by TBDMS were done after deprotection because the TBDMS group has quite high carbon-content and did not afford satisfactory results.

5-Nitro-2-pentanone. Methyl vinyl ketone (35.1 g, 0.5 mol) was added dropwise to an acetonitrile solution (300 ml) containing nitromethane (152.5 g, 2.5 mol) and tetramethylguanidine (6.26 ml, 0.05 mol) at room temperature. After being stirred for 5 h at the same temperature, the mixture was poured into 100 ml of water. The mixture was acidified with diluted acetic acid to pH 5.0 and the resulted mixture was concentrated *in vacuo* (20 mm Hg) to remove the acetonitrile and nitromethane. The residue was extracted with ethyl acetate (3 x 100 ml) and the combined organic portion was washed with water (2 x 100 ml) and brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was subjected to column chromatography on silica gel with benzene as an eluent to afford 5-nitro-2-pentanone (44.2 g) in 67% yield. ^{1}H NMR ($CDCl_3$) δ = 2.10-2.24 (m, 2H), 2.14 (s, 3 H), 2.58 (t, 2H, J = 6.8 Hz), and 4.40 (t, 2H, J = 6.6 Hz). IR (neat): 1720, 1553, and 1372 cm^{-1}.

Racemic 5-Nitro-2-pentanol (2) 5-Nitro-2-pentanone (70.0 g, 0.60 mol) was reduced with sodium borohydride (12.0 g, 0.33 mol) in ethanol as usual and racemic 5-nitro-2-pentanol (62.5 g) was obtained in 89% yield: bp 73 $^{\circ}$C/0.8 mm Hg. ^{1}H NMR ($CDCl_3$) δ = 1.22 (d, 3H, J = 6.2 Hz), 1.45-1.57 (m, 3 H), 2.03-2.22 (m, 2 H), 3.81-3.90 (m, 1H), and 4.42 (t, 3H, J = 8.0 Hz). IR (neat) 3375, 1550, and 1380 cm^{-1}. Anal. Found: C, 45.08; H,8.48; N,10.37; Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52.

(*S*)-5-Nitro-2-pentanol ((*S*)-2). 5-Nitro-2-pentanone (133 mg) was added to a suspension of bakers' yeast (10 g) and glucose (0.25 g) in 20 ml of water and the whole mixture was incubated at 30 $^{\circ}$C for 7 days. Usual work-up gave a mixture of the starting material and the product, which were separated by column chromatography on silica gel with hexane-ethyl acetate (5 : 1) as an eluant to afford (*S*)-4-nitro-2-pentanol ((*S*)-2) in 40% yield with 97% e.e. $[\alpha]_D^{25}$ +16.9 (c = 1.70, $CHCl_3$). The NMR spectrum of the product was the same with that of racemic 2. The e.e. (97%) was determined by ^{1}H NMR analysis (in $CDCl_3$) of the corresponding (+)-MTPA ester. The signal from the methyl

protons in the (*S*)-enantiomer appears at δ = 1.30 ppm and that of the (*R*)-enantiomer appears at 1.37 ppm.

4-Nitro-2-(*t*-butyldimethylsilyloxy)butane (4). Imidazole (16 g, 0.24 mol) was added dropwise to a stirred solution of dimethylformamide (60 ml) containing 1 (7.0 g, 59 mmol) and *t*-butyl dimethylsilyl chloride (TBDMSCl, 10 g) at 0 °C. The solution was stirred for additional 3 h and the reaction mixture was poured into 100 ml water and the organic materials were extracted with ether (3 x 100 ml). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel using hexane-ethyl acetate (5 : 1) as an eluant giving 4-nitro-2-(*t*-butyl dimethylsilyloxy)butane (4) in a quantitative yield (13.7 g). ^{1}H NMR ($CDCl_3$) δ = 0.03 (s, 6H), 0.86 (s, 9H), 1.16 (d, 3H, J = 7.0 Hz), 1.90-2.27 (m, 2H), 3.85-3.96 (m, 1H), and 4.40-4.50 (m, 2H). IR (neat) 1558 and 1382 cm^{-1}.

5-Nitro-2-(*t*-butyldimethylsilyloxy)pentane (5). This compound was prepared by the same way as described above. Thus, 7.9 g (59 mmol) of 2 gave 14.5 g of 5 in 100% yield. ^{1}H NMR ($CDCl_3$) δ = 0.01 (s, 6H), 0.84 (s, 9H), 1.10 (d, 3H, J = 6.0 Hz), 1.38-1.52 (m, 2H), 1.95-2.20 (m, 2H), 3.65-3.82 (m, 1H), and 4.36 (t, 2H, J = 7.2 Hz). IR (neat) 1555 and 1378 cm^{-1}.

General Procedure for Acylation of 4-Nitro-2-(*t*-butyl dimethylsilyloxy)butane (4). An acylimidazole (1.4 mmol) was added to a mixture of 4 (0.3 g, 1.3 mmol) and DBU (1.4 mmol) in dry THF (2 ml) at room temperature. After being stirred for 24 h, the reaction mixture was poured into 10 ml of water. The resulted mixture was acidified to pH 1.0 with diluted HCl and the organic portion was extracted with ethyl acetate (3 x 30 ml). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography over silica gel with hexane-ethyl acetate (5 : 1) as an eluant to afford the desired acylated product (8).

8a: ^{1}H NMR ($CDCl_3$) δ = 0.0 (s, 6H), 0.89 (s, 9H), 1.20 (d, 3H, J = 6.2 Hz), 1.89-2.08 (m, 2H), 2.30 (s, 3H), 3.75-4.00 (m, 1H), and 5.30 and 5.43 (each dd, total 1H, J= 7.2 and 5.8; 11.2 and 2.4 Hz). IR (neat) 2960, 1740, 1560, and 1380 cm^{-1}. Anal. (deprotected alcohol); Found: C, 44.83; H, 7.04; N, 8.09; Calcd for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69.

8b: ^{1}H NMR ($CDCl_3$) δ = 0.01-0.04 (m, 6H), 0.86-0.89 (m, 9H), 1.07-1.21 (m, 6H), 1.88-2.46 (m, 2H), 2.54-2.68 (m, 2H), 3.75-3.98 (m, 1H), and 5.31 and 5.46 (each dd, total 1H, J = 7.0 and 6.0; 11.2 and 2.6 Hz). IR (neat) 1743, 1565, 1470, 1380, and 1260 cm^{-1}. Anal. (deprotected alcohol); Found: C, 47.90; H, 7.41; N, 7.94 %. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00 %.

8c: ^{1}H NMR ($CDCl_3$) δ = 0.04 (s, 6H), 0.86-0.96 (m, 12H), 1.19 (d, 3H, J = 6.0 Hz), 1.59-1.60 (m, 2H), 1.86-2.45 (m, 2H), 2.53 (dt, 2H, J = 7.0 and 2.8 Hz), 3.75-3.98 (m, 1H), and 5.30 and 5.46 (each dd, total 1H, J = 7.0 and 5.5; 10.8 and 2.5 Hz). IR (neat) 1742, 1565, 1471, 1385, and 1260 cm^{-1}. Anal.

(deprotected alcohol); Found: C, 50.54; H, 7.97; N, 7.40 %. Calcd for $C_8H_{15}NO_4$; C, 50.78; H, 7.99; N, 7.40 %.

8d: ^{1}H NMR ($CDCl_3$) δ = 0.04 (s, 6H), 0.83 (s, 9H), 1.13-1.22 (m, 9H), 2.10-2.47 (m, 1H), 2.75-2.90 (m, 1H), 3.85-4.00 (m, 1H), and 5.50 and 5.66 (each dd, total 1H, J = 7.4 and 5.0; 11.4 and 2.2 Hz). IR (neat) 1740, 1560, 1470, 1380, and 1260 cm^{-1}. Anal. (deprotected alcohol); Found. 50.49; H, 7.93; N, 7.31 %. Calcd $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40 %.

8e: ^{1}H NMR ($CDCl_3$) δ = 0.0-0.05 (m, 6H), 0.86-0.90 (m, 12H) 1.20 (d, 3 H, J = 6.0 Hz), 1.24-1.37 (m, 2H), 1.53-1.67 (m, 12H), 1.86-2.45 (m, 2H), 2.50-2.62 (t, 2H, J = 7.5 Hz), 3.75-3.98 (m, 1H), and 5.31 and 5.45 (each dd, total 1H, J = 7.4 and 5.4; 11.2 and 2.6 Hz). IR (neat) 1741, 1564, 1470, 1380, and 1260 cm^{-1}. Anal. (deprotected alcohol); Found: C, 52.99; H, 8.38; N, 7.07 %. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89 %.

8f: This compound was not isolated. The yield was calculated by ^{1}H MNR analysis of the product. ^{1}H NMR ($CDCl_3$) δ = 0.03 (s, 6H), 0.85 (s, 9H), 1.12-1.26 (m, 9H), 1.55-2.50 (m, 7H), 3.83-3.98 (m, 1H), and 5.48 and 5.61 (each dd, total 1H, J = 7.6 and 4.8; 11.0 and 2.0 Hz).

8g: ^{1}H NMR ($CDCl_3$) δ = 0.04-0.01 (m, 6H), 0.86-0.96 (m, 9H), 1.20-1.23 (dd, 3H, J = 6.2 and 2.0 Hz), 1.94-2.64 (m, 2H), 3.85-4.16 (m, 1H), 6.31 and 6.43 (each dd, total 1H, J = 7.0 and 5.6; 11.2 and 1.0 Hz), and 7.47-8.02 (m, 5H). IR (neat) 1708, 1567, 1470, 1380, and 1260 cm^{-1}. Anal. (deprotected alcohol) Found: C, 59.31 H, 5.88; N, 6.28 %. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28 %.

Acylation of 5-Nitro-2-(*t*-butyldimethylsilyloxy)pentane (5). The acylation of 5 was done by the same method as described above for the acylation of 4 except for the use of hexane-ethyl acetate (1 : 1) as an eluant for the chromatography in place of the hexane-ethyl acetate (5 : 1) mixture.

9a: ^{1}H NMR ($CDCl_3$) δ = 0.04 (s, 6H), 0.87 (s, 9H), 1.13 (d, 3H, J = 6.2 Hz), 1.33-1.52 (m, 2H), 2.03-2.26 (m, 2H), 2.28 (d, 3H, J = 1.8 Hz), 3.78-3.92 (m, 1H), and 5.12 and 5.18 (each dd, total 1H, J = 9.6 and 5.6; 9.0 and 5.0 Hz). IR (neat) 2955, 1739, 1560, and 1380 cm^{-1}. Anal. (deprotected alcohol); Found: C, 47.90; H, 7.37; N, 7.91 %. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00 %.

9b: ^{1}H NMR ($CDCl_3$) δ = 0.05 (s, 6H), 0.86-1.28 (m, 9H), 1.07-1.28 (m, 6H), 1.34-1.48 (m. 2H), 2.03-2.56 (m, 4H), 3.78-3.93 (m, 1H), and 5.15 and 5.20 (each dd, total 1H, J = 8.2 and 6.0; 9.6 and 5.0 Hz). IR (neat) 1740, 1560, 1467, 1380, and 1258 cm^{-1}. Anal. (deprotected alcohol); Found; 50.50; H, 7.98; N, 7.38 %. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40 %.

9c: ^{1}H NMR ($CDCl_3$) δ = 0.04 (s, 6H), 0.85-0.95 (m, 12H), 1.12 (dd, 3H, J = 5.8, and 5.8 Hz), 1.35-1.49 (m, 2H), 1.57-1.70 (m, 2H), 2.02-2.23 (m, 2H), 2.47-2.59 (m, 2H), 3.74-3.89 (m, 1H), and 5.12 and 5.20 (each dd, total 1H, J = 8.2 and 5.8 Hz, 9.6 and 5.0 Hz). IR (neat) 1735, 1555, 1465, 1370 and 1255 cm^{-1}. Anal. (deprotected alcohol); Found: C, 52.91, H, 8.42; N. 7.20 %.

Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89 %.
9d: ^{1}H NMR ($CDCl_3$) δ = 0.04 (s, 6H), 0.87 (s, 9H), 1.13 (d, 3H, J = 6.2 Hz), 1.12-1.18 (m, 6H), 1.34-1.53 (m, 2H), 2.02-2.30 (m, 2H), 2.76-2.91 (ttd, 1H, J = 6.8, 6.8, and 2.4 Hz), 3.77-3.93 (m, 1H), and 5.29 and 5.39 (each dd, total 1H, J = 7.8 and 3.8; 9.4 and 3.0 Hz). IR (neat) 1740, 1565, 1470, 1375, and 1260 cm^{-1}. Anal. (deprotected alcohol); Found: C, 52.96; H, 8.45; N, 7.10 %. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89 %.
9e: ^{1}H NMR ($CDCl_3$) δ = 0.04 (s, 6H), 0.87-0.89 (m, 12H), 1.13 (d, 3H, J = 6.0 Hz), 2.01-2.31 (m, 2H), 2.50-2.59 (m, 2H), 3.78-3.89 (m, 1H), and 5.13 and 5.20 (each dd, total 1H, J = 7.6 and 5.6; 9.6 and 5.0 Hz). IR (neat) 1740, 1560, 1470, 1375, and 1260 cm^{-1}. Anal. (deprotected alcohol); Found: C, 55.31; H, 8.75; N, 6.29 %. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.82; N, 6.45 %.
9f: This compound was not isolated. The yield was calculated by ^{1}H NMR analysis of the product. ^{1}H NMR ($CDCl_3$) δ = 0.04 (s, 6H), 0.87 (s, 9H), 1.10 and 1.30 (each d, total 3H, J = 6.0), 1.23-2.00 (m, 13H), 3.70-3.95 (m, 1H), and 5.27 and 5.36 (each dd, total 1H, J = 8.4 and 5.2; 9.2 and 4.6 Hz).
9g: ^{1}H NMR ($CDCl_3$) δ = 0.06 (s, 6H, 0.81-0.91 (m, 9H), 1.12-1.16 (dd, 3H, J = 6.2 and 2.4 Hz), 1.47-1.60 (m, 2H), 2.26-2.44 (m, 2H), 3.74-4.03 (m, 1H), 6.04 and 6.21 (total 1H, each dd, J = 7.2 and 7.2; 9.2 and 4.6 Hz), and 7.43-8.15 (m, 5H). IR (neat) 1720, 1570, 1465, and 1380 cm^{-1}. Anal. (deprotected alcohol); Found: C, 60.66; H, 6.35; N, 5.91 %. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90 %.

Preparation of 4-Nitro-2-(tetrahydropyranyloxy)butane (6). A dichloromethane solution of 1 (1.5 g, 12.6 mmol), 3,4-dihydro-2H-pyran (1.26 g, 25 mmol), and pyridinium *p*-toluenesulfonate (150 mg) was stirred for 8 h at room temperature. The mixture was washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was distilled to give 6 in 67% yield: bp 105-108 °C/1.8 mm Hg. ^{1}H NMR ($CDCl_3$) δ = 1.15-1.26 (dd, 3 H, J = 6.2 and 22.8 Hz), 1.40-1.80 (m, 6H), 2.00-2.31 (m, 2H), 3.39-3.54 (m, 1H), 3.72-3.94 (m, 2H), and 4.39-4.60 (m, 3H). IR (neat) 1555 and 1380 cm^{-1}. Anal. Found: C, 53.48; H, 8.62; N, 6.63 %. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89%.

Preparation of 5-Nitro-2-(tetrahydropyranyloxy)pentane (7). The same method as described above for the preparation of 6 was employed to obtain 7 in 70% yield: bp 88-92 °C/0.4 mm Hg. ^{1}H NMR ($CDCl_3$) δ = 1.08 and 1.20 (total 3H, each d, J = 6.2 Hz), 1.43-1.77 (m, 8H), 1.94-2.15 (m, 2H), 3.38-3.49 (m, 1H), 3,67-3.85 (m, 2H), 4.32-4.40 (m, 2H), and 4.50-4.60 (m, 1H). IR (neat) 1555 and 1380 cm^{-1}. Anal. Found: C, 55.73 ; H, 8.93 ; N, 6.15 %. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.82; N, 6.45 %.

Reaction of D_2O with the Anion from the Nitro Alcohol Derivatives. Into a THF solution containing 0.5 g of the nitro alcohol derivative, two equivalent amounts of DBU was added dropwise at -40 °C. The resulted mixture was stirred for 2 h at the same temperature, then 1 ml of D_2O was poured into the reaction

mixture and the resulting mixture was stirred for 5 min. Then the organic materials were extracted with ether. After the usual work-up, the products were analyzed by ^{1}H NMR spectroscopy. The signal from the methylene protons adjacent to the nitro group were compared with that from the methine signal. The reactions of 4 and 5 gave the dideuterated products while those of 6 and 7 gave the monodeuterated products. When one equivalent amount of DBU was used in the reaction of 5, a mixture of mono and dideuterated products was obtained.

(*S*)-6-(*t*-Butyldimethylsilyloxy)-2-heptanone (10). A solution containing (*S*)-9a (0.5 g, 1.74 mmol), tributyltin hydride (2.26 mmol), and AIBN (0.3 mmol) in dry benzene (10 ml) was refluxed at 80 °C under argon atmosphere for 4 h. The resulted solution was concentrated *in vacuo* and the residue was chromatographed on silica gel column using hexane-ethyl acetate (5 : 1) as an eluant to give 10 (391 mg, 92.3%). ^{1}H NMR δ = 0.00 (s, 6H), 0.84 (s, 9H), 1.08 (d, 3H), J = 6.0 Hz), 1.33-1.63 (m, 4H), 2.09 (s, 3H), 2.39 (t, 2H, J = 7.0 Hz), and 3.71-3.80 (tq, 1H, J = 6.0 Hz). IR (neat) 2975, 1725, and 1255 cm^{-1}.

4-Chloro-1-(tetrahydropyranyloxy)butane (11). The same method as described above for the preparation of 6 was employed. 4-chloro-1-butanol (10 g) gave 11 (17.4 g, 98%). ^{1}H NMR ($CDCl_3$) δ = 1.49-1.93 (m, 10H), 3.35-3.90 (m, 6H), and 4.57 (t, 1H, J = 2.0 Hz). IR (neat) 2960, 1138, and 1120 cm^{-1}. Anal. Found: C, 55.97; H, 8.96 %. Calcd for $C_9H_{17}O_2Cl$: C, 56.10; H, 8.89 %.

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-11-(tetrahydropyranyloxy)undecan-6-one (12). Under argon atmosphere, 10 (112 mg, 0.46 mmol) was added dropwise to the solution of LDA (0.46 mmol) in THF (5 ml) at -78 °C and the resulted solution was stirred for 5 min. Into the solution, 11 (155 mg, 0.8 mmol) was added dropwise and the mixture was stirred for additional 1 h at the same temperature. Sodium iodide (75 mg, 0.5 mmol) was added to the mixture and the mixture was further stirred for additional 1 h at -78 °C, then the mixture was poured into 20 ml of water and the organic materials were extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with saturated aqueous sodium thiosulfate and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel using hexane-ethyl acetate (10 : 1) as an eluant giving 12 (79 mg, 43.2 %). ^{1}H NMR δ = 0.40 (s, 6H), 0.87 (s, 9H), 1.13 (dd, 3H, J = 6.2, 2.2 Hz), 1.45-1.95 (m, 16H), 2.19-2.43 (m, 6H), 3.36-3.61 (m, 4H), 3.37-3.85 (m, 1H), and 4.52-4.60 (m, 1H). IR (neat) 1725 and 1255 cm^{-1}.

(2*S*,6*R*)-(-)-2-Methyl-1,7-dioxaspiro[5.6]dodecane (3). Hydrochloric acid (6 N, 0.1 ml) was added to a solution containing 12 (47 mg) in methanol (5 ml) and the resulted mixture was stirred for 1.5 h, then refluxed for 30 min. The solution was neutralized with 20 ml saturated aqueous sodium carbonate and the mixture was concentrated *in vacuo* to remove the methanol. The residue was extracted with ether (3 x 20 ml). The organic solution was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was subjected to column chromatography over silica gel using hexane-ethyl acetate

(20 : 1) as an eluant to afford 3 (10 mg, 46% yield) in 97 % optical purity: $[\alpha]_D^{21}$ = -102° (c = 0.5, pentane), lit.[4]; $[\alpha]_D^{21}$ -105° (c = 1.1, pentane). ^{1}H NMR ($CDCl_3$) δ = 1.19 (t, 3H, J = 6.2 Hz), 1.45-1.90 (m, 14H), and 3.70-3.90 (m, 3H). Anal. Found: C, 71.50; H, 11.08 %. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94 %.

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