A Versatile Intermediate for the Systematic Synthesis of all Regioisomers of *myo*-Inositol Phosphates

Takashi Masuda[a], Kensaku Anraku[b], Mitsuhiro Kimura[a], Kaori Sato[a], Yoshinari Okamoto[a], Masami Otsuka[a]*

[a] Department of Bioorganic Medicinal Chemistry, Faculty of Life Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan E-mail: motsuka@gpo.kumamoto-u.ac.jp

[b] Institute of Health Sciences, Kumamoto Health Science University, 325 Izumi-machi, Kumamoto 861-5598, Japan

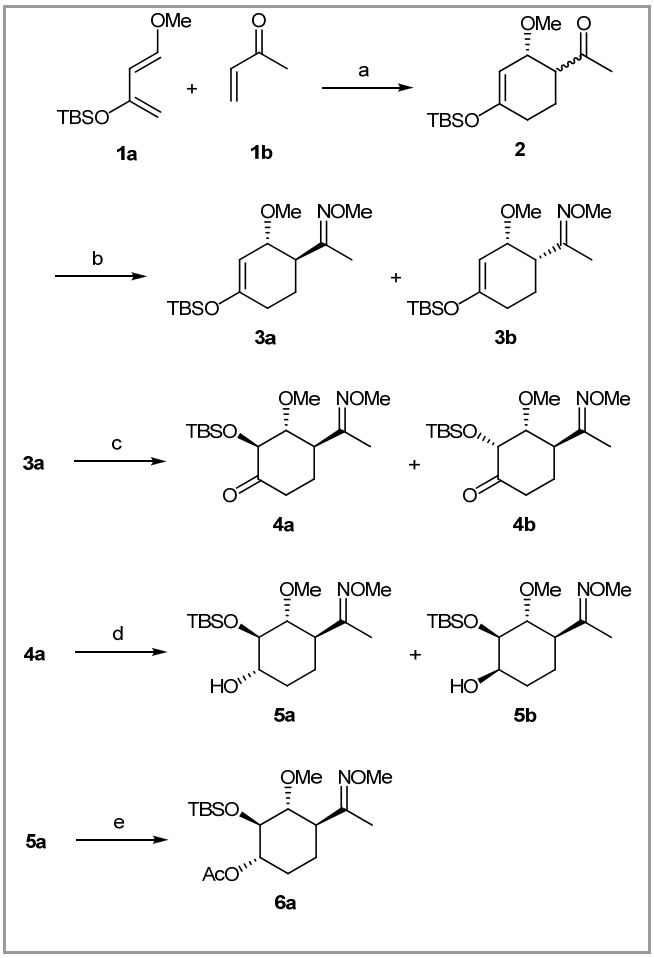
Received: The date will be inserted once the manuscript is accepted.

Abstract: Inositol phosphate derivatives are usually synthesized by repeated protection-deprotection procedures, necessitating development of an independent synthetic route for each inositol derivative. Herein, a synthetic precursor for all regioisomers of inositol phosphate has been prepared. A cycloadduct obtained by the Diels-Alder reaction of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene and methyl vinyl ketone was converted into an inositol derivative by sequential introduction and immediate protection of hydroxyl groups. Thus, the six hydroxyl groups of the obtained inositol derivative are differentiated by different protective groups that are cleavable under independent conditions. This would enable us to prepare all regioisomers of inositol phosphate derivative.

Key words: inositol phosphate, the Diels-Alder reaction, oxidative rearrangement, asymmetric dihydroxylation, monoacylation

There have been many reports on naturally occurring and synthetic inositol phosphates ($InsP_n$)[1,2] ranging from $InsP_1$ to $InsP_6$ that are often closely related to cell function, e. g., D-*myo*-inositol 1,4,5-triphosphate ($Ins(1,4,5)P_3$), a crucial messenger to link the extracellular information to calcium mobilization.[3] We previously reported the synthesis of biotinylated $InsP_n$s for the $InsP_n$-binding study of phospholipase A_2 ,[4] Grp1 Pleckstrin homology domain,[5] and HIV-1 Gag[6] proteins. However, our syntheses of $InsP_n$ derivatives were based on the repeated protection-deprotection of *myo*-inositol and hence we needed to develop an independent synthetic route for each $InsP_n$ derivative[4,5,6] as the other research groups did.[1,7] The present study aimed at a "total synthesis" of an inositol derivative equipped with six different protective groups that are cleavable under independent conditions. Our approach is featured by the Diels-Alder reaction and subsequent sequential introduction of hydroxyl groups.

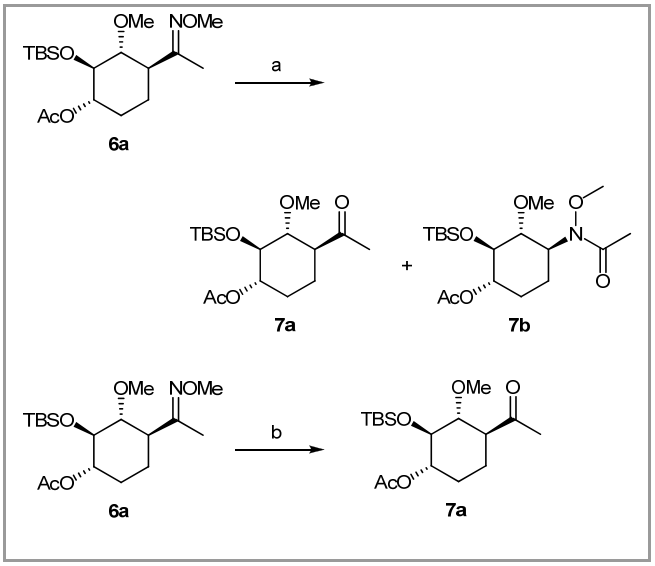
The Diels-Alder reaction of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene affords a six membered ring with oxygen substituents that are convertible into various natural products as pioneered by Danishefsky.[8] We intended to make use of the Danishefsky's diene for the synthesis of inositol derivatives. Thus, siloxy diene **1a** and methyl vinyl ketone **1b** were reacted in the presence of $Eu(fod)_3$ and cycloadduct **2** was obtained as a diastereomeric mixture in 86% yield. The ketone **2** was converted into methoxime **3a** and **3b** which were separated by silicagel chromatography in 62% and 7% yield, respectively.[9] The compound **3a** was then subjected to a modification of the Paquette rearrangement,[10] affording siloxy ketone **4a** (56% yield) and **4b** (1% yield).[11] Ketone **4a** was reduced according to the procedure of Acena[12] using $NaBH_4$ to give alcohol **5a** and **5b** in 72% and 14% yields, respectively.[13] The alcohol **5a** was protected by an acetyl group[14] to give acetate **6a** quantitatively.



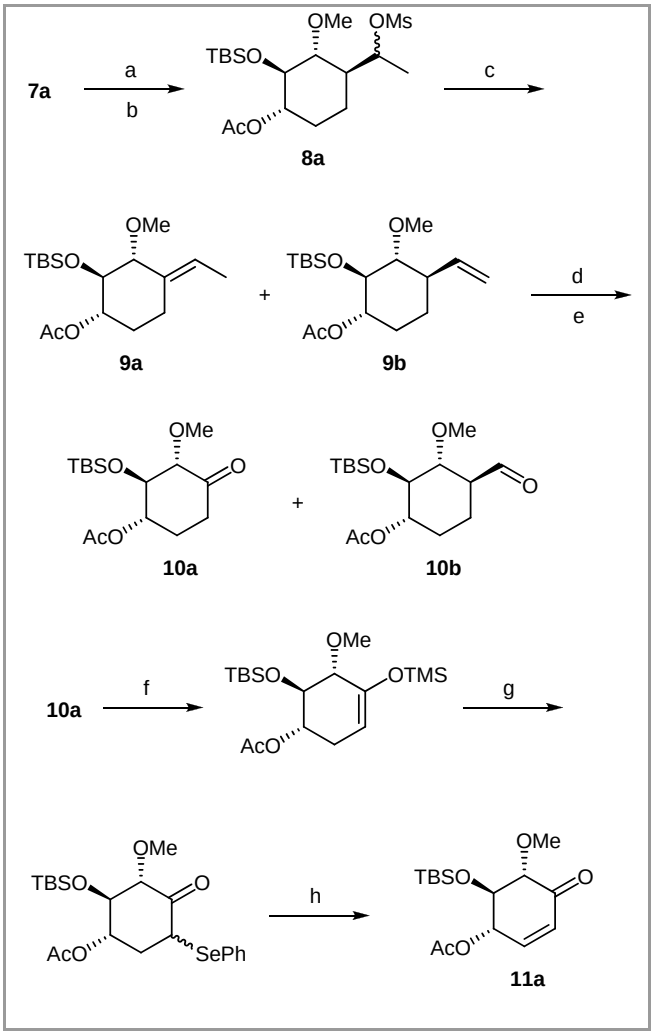
Scheme 1 Synthesis of methoxime **6a**. *Reagents and conditions*: a) $Eu(fod)_3$, CH_2Cl_2, r. t.; b) $NH_2OMe{\cdot}HCl$, MeOH, pyridine; c) mCPBA, CH_2Cl_2, MS4A; d) $NaBH_4$, MeOH; e) pyridine/Ac_2O (2 : 1).

The deprotection of the methoxyimino group of **6a** was not straightforward. The first attempted was use of [hydroxyl(tosyloxy)iodo]benzene (HTIB)[15] and compound **6a** was treated with HTIB in CH_2Cl_2 containing 1% water. Although ketone **7a** was obtained in 30% yield, the major product of this reaction was found to be rearranged product **7b** (50%

yield). The methoxime of **6a** was eventually removed by the Corey's procedure[16] using $TiCl_3$·3THF-DIBAL to give ketone **7a** in 83% yield.



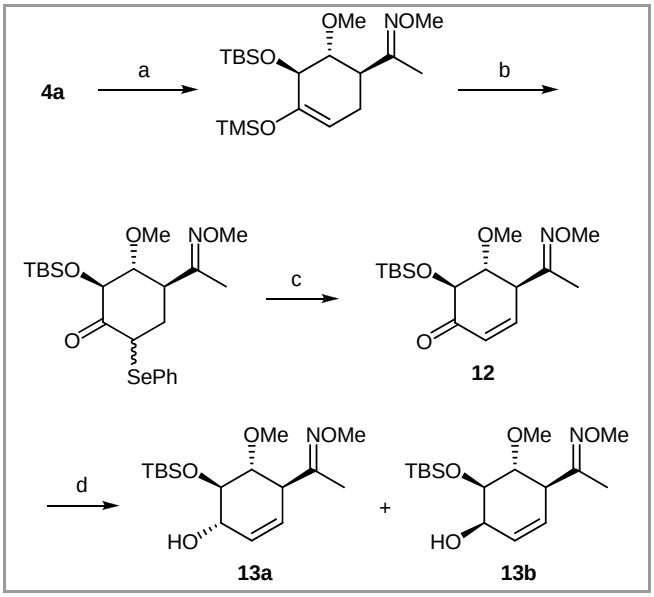
Scheme 2 Synthesis of methyl ketone **7a**. *Reagents and conditions*: a) HTIB, CH_2Cl_2 (1% H_2O); b) $TiCl_3$·3THF-DIBAL, toluene.



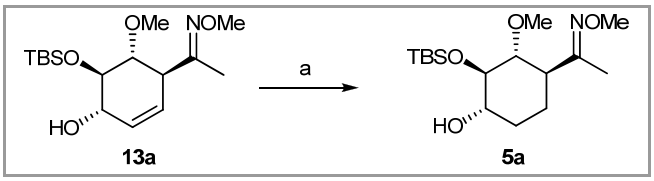
Scheme 3 Synthesis of cyclohexenone **11a**. *Reagents and conditions*: a) $NaBH_4$, MeOH/CH_2Cl_2; b) MsCl, Et_3N, CH_2Cl_2; c) DBU, toluene, Δ; d) O_3, CH_2Cl_2/MeOH; e) Me_2S; f) LiHMDS, TMSCl, THF; g) PhSeCl, CH_2Cl_2; h) $NaHCO_3$, 30% H_2O_2, THF.

As the Baeyer-Villiger oxidation of the methyl ketone **7a** did not work well, the methyl ketone of **7a** was transformed as follows. The ketone **7a** was converted into mesylate **8a** that was treated with DBU to give olefin **9a** and **9b** (**9a** : **9b** = 2 :1). Ozonolysis of the mixture **9a** and **9b** afforded cyclohexanone **10a** and aldehyde **10b** in 25% and 11% overall yield based on **7a**, respectively. Cyclohexanone **10a** was converted into the TMS enolate by treatment with LiHMDS and TMSCl and further transformed to phenylselenyl ketone by PhSeCl treatment. The subsequent oxidative elimination using H_2O_2 gave the desired cyclohexenone **11a** in 18% overall yield based on **10a**. As the acetyl group of **11a** was, unexpectedly, found to be labile, producing a deacetylated byproduct, another synthetic route was explored.

The alternate approach was as follows. Cyclohexanone **4a** was converted into cyclohexenone **12** in 55% overall yield by the treatment with a) LiHMDS then TMSCl, b) PhSeCl, and c) 30% H_2O_2, $NaHCO_3$. The carbonyl group of **12** was reduced with $NaBH_4$ to give allyl alcohol **13a** and **13b** in 84% and 8% yield, respectively. The stereochemistry of compound **13a** and **13b** was determined by converting **13a** into **5a** whose stereochemistry has already been established.

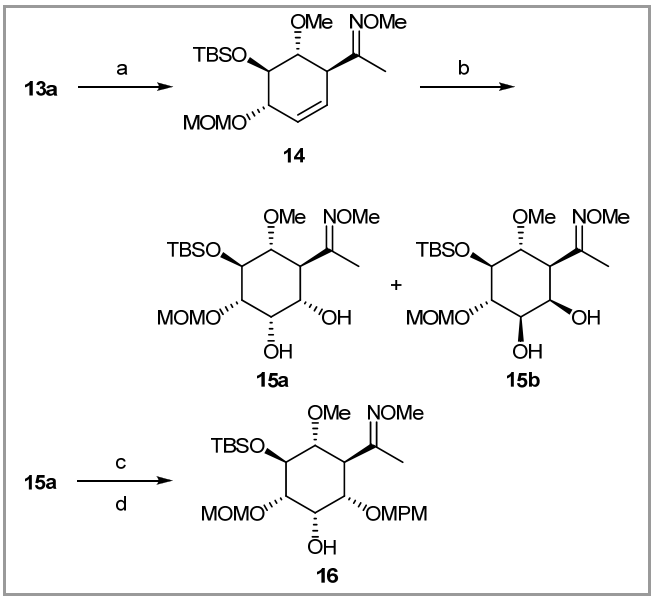


Scheme 4 Synthesis of allyl alcohol **13a**. *Reagents and conditions*: a) LiHMDS, THF then TMSCl; b) PhSeCl, CH_2Cl_2; c) 30% H_2O_2, $NaHCO_3$, THF; d) $NaBH_4$, MeOH.



Scheme 5 Stereochemical assignment of compound **13a**. *Reagents and conditions*: H_2, Pd/C, CH_2Cl_2.

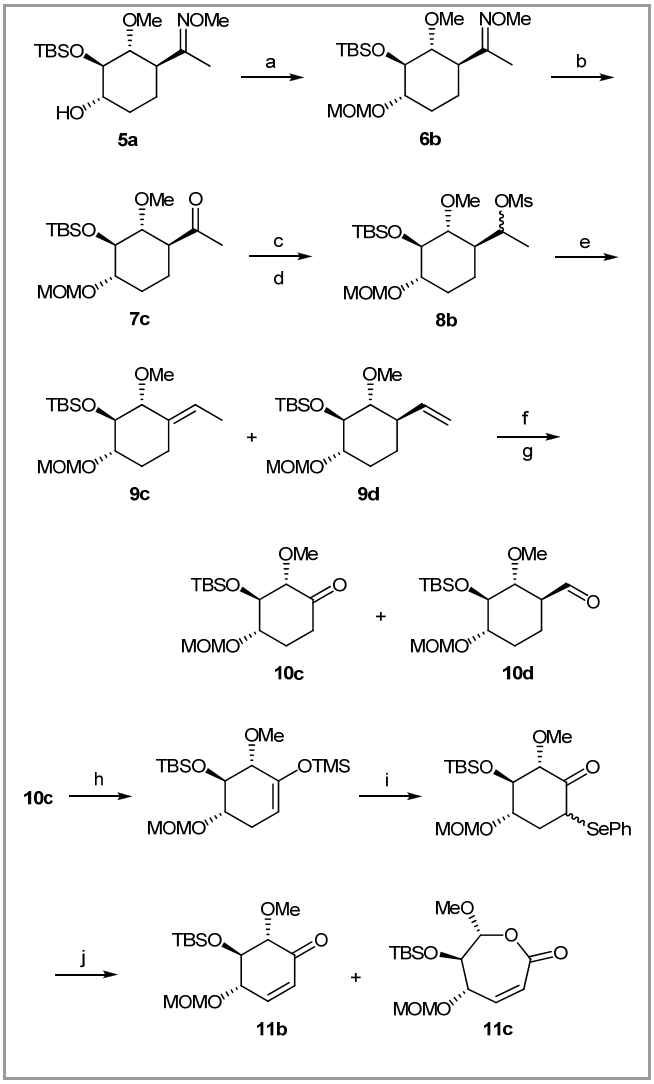
In this approach, the alcohol of **13a** was protected by MOM group (MOMCl, DIPEA) and MOM derivative **14** was obtained in 92% yield. The olefin **14** was converted into *cis* diol **15a** and **15b** in 65% and 29% yield, respectively, by the application of the Armstrong's modification of the Sharpless asymmetric dihydroxylation.[17,18] The diol **15a** was converted into mono-MPM derivative **16** in 52% yield by the Nagashima-Ohno procedure using Bu_2SnO/CsF.[19] Unfortunately, deprotection of the methoxyimino group of compound **16** by the $TiCl_3$·3THF-DIBAL[16] procedure did not work.



Scheme 6 Synthesis of mono-MPM derivative **16**. *Reagents and conditions*: a) MOMCl, DIPEA, CH_2Cl_2; b) AD-mix-β, OsO_4, $(DHQD)_2PHAL$, $MeSO_2NH_2$, *t*-BuOH/H_2O/ CH_2Cl_2; c) Bu_2SnO, toluene; d) CsF, MPMCl, DMF.

Thus, the synthetic route was revised as follows. Cyclohexanol **5a** was protected by a MOM group to give compound **6b** in 92% yield. The methoxyimino goup of **6b** was smoothly removed with $TiCl_3$·3THF-DIBAL[16] to give methyl ketone **7c** in 85% yield. Methyl ketone **7c** was converted into mesylate **8b** by treatment with $NaBH_4$ followed by MsCl. Compound **8b** was further treated with DBU to give olefin **9c** and **9d**. Ozonolysis of the mixture **9c** and **9d** gave cyclohexanone **10c** in 24% yield based on **7c** and aldehyde **10d** (crude).

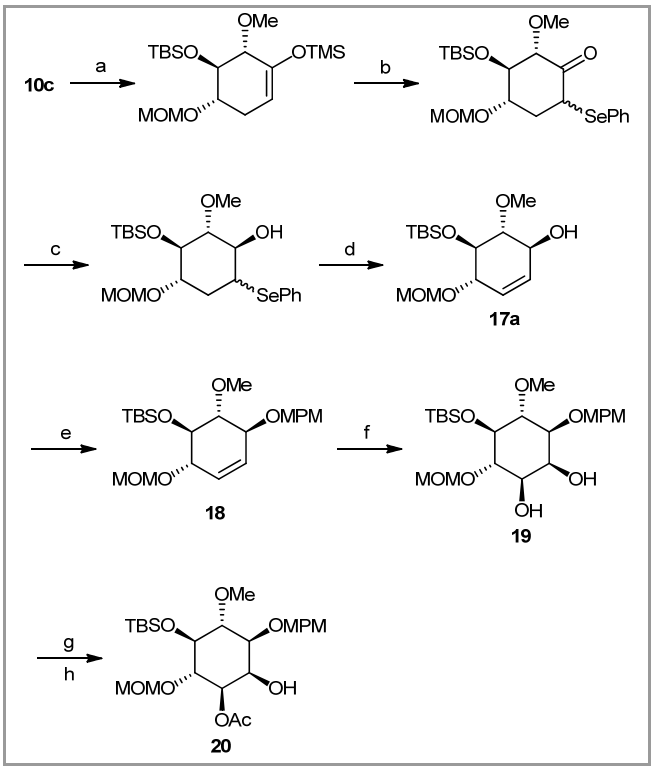
Compound **10c** was converted into cyclohexenone **11b** in 34% yield via the TMS enolate and the phenylselenyl ketone intermediates by the above mentioned procedure. Unexpectedly, H_2O_2 treatment of the phenylselenyl ketone accompanied lactone **11c**, the Baeyer-Villiver product, in 23% yield.



Scheme 7 Synthesis of cyclohexanone **11b**. *Reagents and conditions*: a) MOMCl, DIPEA, CH_2Cl_2; b) $TiCl_3$·3THF-DIBAL, toluene; c) $NaBH_4$, MeOH/CH_2Cl_2; d) MsCl, Et_3N, CH_2Cl_2;e) DBU, toluene, Δ; f) O_3, Et_3N, CH_2Cl_2/MeOH; g) Me_2S; h) LiHMDS, TMSCl, THF; i) PhSeCl, CH_2Cl_2; j) $NaHCO_3$, 30% H_2O_2.

Thus, phenylselenyl ketone obtained from **10c** was converted into the corresponding phenylselenyl alcohol by treatment with $NaBH_4$ and subsequent treatment with 30% H_2O_2/$NaHCO_3$ gave allyl alcohol **17a** in 51% overall yield based on **10c**.[20]

The hydroxyl group of **17a** was protected by MPM group by treatment with NaH/MPMCl/TBAI in the presence of molecular sieves and compound **18** was obtained in 40% yield. Olefin dihydroxylation of compound **18** was achieved by the Armstrong procedure[17] to give *myo*-inositol derivative **19** in 59% yield. Diol **19** was converted into the desired monoacetate **20** in 39% yield by the Nagashima-Ohno procedure.[19]



Scheme 8 Synthesis of protected inositol **20**. *Reagents and conditions*: a) LiHMDS, TMSCl; b) PhSeCl, CH_2Cl_2; c) $NaBH_4$, MeOH; d) $NaHCO_3$, 30% H_2O_2, THF; e) NaH, MPMCl, TBAI, THF, MS4A; f) AD-mix-β, OsO_4, $(DHQD)_2PHAL$, $MeSO_2NH_2$, *t*-BuOH/H_2O/ CH_2Cl_2; g) Bu_2SnO, toluene; h) AcCl, CH_2Cl_2.

In summary, the Diels-Alder product **2** having two oxygen substituents on the cyclohexane ring was subjected to the Paquette's oxidative rearrangement to introduce the third oxygen substituent. Compound **5a** thus obtained was converted into cyclohexanone **10c** where the fourth oxygen group was introduced by ozonolytic cleavage of the carbon appendage. The fifth and sixth hydroxyl groups were constructed and differentiated by the asymmetric dihydroxylation and the subsequent Nagashima-Ohno monoacylation. Thus, the six hydroxyl groups of compound **20** are differentiated by protective groups that are cleavable under independent conditions. This would enable us to prepare not only all $InsP_n$ but also other inositol derivatives.

Reagents and solvents were purified by standard techniques. Thin layer chromatography was performed using Silica gel 60 F_{254} (Merck) visualized by 10% solution of phosphomolybdic acid in EtOH or 0.5% solution of $KMnO_4$ in 1M aqueous NaOH. Column chromatography was carried out with Silica gel 60N (spherical neutral) (Kanto Chemical Co.). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JNM-AL300 with respect to internal standard tetramethylsilane (TMS) and *J* values were given in Hz. Mass spectra [MS (FAB)] and high resolution mass spectra (HRMS) were recorded on JOELJMS-DX303HF MASS spectrometer. IR spectra were recorded on JASCO FT/IR-410. Elemental analyses were performed with Yanaco MT-5S.

(S*)-1-[4-(*tert*-butyldimethylsilyloxy)-2-methoxycyclohex-3-enyl]ethanone (2)

$Eu(fod)_3$ (0.72g, 0.70mmol) and methyl vinyl ketone (2.3mL, 28mmol) were successively dissolved in CH_2Cl_2 (6mL). To the solution *trans*-3-(*tert*-buthyldimethylsiloxy)-1-methoxy-1,3-butadiene (3.0g, 14mmol) was added and the resulting solution was stirred at room temperature for 7 hours. The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 7 : 1) to give yellow oil **2** (3.4g, 86%) as a mixture of diastereomer.

1-[(1S*,2S*)-4-(*tert*-butyldimethylsilyloxy)-2-methoxycyclohex-3-enyl]ethanone *O*-methyl oxime (3a) and 1-[(1R*,2S*)-4-(*tert*-butyldimethylsilyloxy)-2-methoxycyclohex-3-enyl]ethanone *O*-methyl oxime (3b)

NH_2OMe·HCl (3.4g, 40mmol) was dissolved in MeOH (6.1mL) under ice cooling. Pyridine (2.5mL, 31mmol) was added to the solution. The mixture was stirred for 10 minutes and was added to crude **2** (4.1g, crude) under ice cooling. The solution was stirred for 45 minutes under ice cooling then the solution was concentrated in vacuo at room temperature for 45 minutes. The residue was roughly purified by silica gel chromatography (silica gel 10g, Hexane : AcOEt = 20 : 1) and further purified by successive silica gel chromatography (Hexane : AcOEt = 20 : 1) to give colorless oil **3a** (2.8g, 62%) and colorless oil **3b** (0.31g, 7%).

3a

^{1}H-NMR ($CDCl_3$) δ 0.153 (s, 6H, Si-CH_3×2), 0.919 (s, 9H, -CH_3×3), 1.63-1.90 (m, 5H, -CH×2, -CH_3), 1.94-2.05 (ddt, *J*=4.95, 9.89, 17.2Hz, 1H, -CH), 2.09-2.21 (m, 1H, -CH), 2.39-2.46 (ddd, *J*=3.66, 7.88, 11.0Hz, 1H, -CH), 3.25-3.32 (t, *J*=11.9Hz, 3H, -OCH_3), 3.80-3.87 (t, *J*=11.9Hz, 3H, -OCH_3), 4.07-4.13 (m, 1H, -CH), 4.97 (s, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -4.50 (Si-CH_3), -4.41 (Si-CH_3), 12.2 (-CH_3), 18.0 (Si-C), 24.6 (-CH_2), 25.6 (-CH_3), 29.1 (-CH_2), 45.0 (-CH), 54.8 (-OCH_3), 61.2 (=$NOCH_3$), 76.4 (-CH), 104 (=CH), 153 (=C), 158 (-C=N).

IR (film) 1665 cm^{-1}. MS(FAB) *m/z* 314 $(M+H)^+$.

Anal. Calcd for $C_{16}H_{31}NO_3Si$: C,61.30; H,9.97; N,4.47. Found: C,61.03; H,9.97; N,4.52.

3b

^{1}H-NMR ($CDCl_3$) δ 0.150 (s, 3H, Si-CH_3), 0.165 (s, 3H, Si-CH_3), 0.922 (s, 9H, -CH_3×3), 1.72-1.80 (m, 1H, -CH), 1.87 (s, 3H, -CH_3), 1.89-2.12 (m, 3H, -CH×3), 2.39-2.46 (ddd, *J*=3.30, 3.48, 12.1Hz, 1H, -CH), 3.27

(s, 3H, -OCH_3), 3.80-3.88 (m, 4H, -CH, -OCH_3), 5.15-5.17 (d, *J*=3.30Hz, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -4.56 (Si-CH_3), -4.38 (Si-CH_3), 12.9 (-CH_3), 18.0 (Si-C), 20.4 (-CH_2), 25.6 (-CH_3), 30.2 (-CH_2), 44.8 (-CH), 56.0 (-OCH_3), 61.1 (=$NOCH_3$), 75.3 (-CH), 103 (=CH), 156 (=C), 159 (-C=N).

IR (film) 1660 cm^{-1}. MS(FAB) *m/z* 314 $(M+H)^+$.

Anal. Calcd for $C_{16}H_{31}NO_3Si$: C,61.30; H,9.97; N,4.47. Found: C,61.03; H,9.99; N,4.65.

(2S*,3R*,4R*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxy-4-[1-(methoxyimino)ethyl]cyclohexanone (4a) and (2R*,3R*,4R*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxy-4-[1-(methoxyimino)ethyl]cyclohexanone (4b)

Under ice cooling **3a** (0.11g, 0.34mmol) was dissolved in CH_2Cl_2 (12mL) and Molecular sieves 4A was added. After stirring for 10 minutes, a solution of mCPBA in CH_2Cl_2 (2.0mL) was slowly added. The solution was stirred for 3 hours under ice cooling and 24 hours at room temperature. The reaction mixture was roughly purified by chromatography (silica gel 10g, Hexane : AcOEt = 8 : 1) and further purified by successive silica gel chromatography (Hexane : AcOEt = 5 : 1) to give colorless oil **4a** (63mg, 56%) and colorless oil **4b** (1.3mg, 1.0%).

4a

^{1}H-NMR ($CDCl_3$) δ 0.0524 (s, 3H, Si-CH_3), 0.132 (s, 3H, Si-CH_3), 0.945 (s, 9H, -CH_3×3), 1.52-1.65 (ddd, *J*=4.58, 13.6, 26.6Hz, 1H, -CH), 1.84-1.95 (m, 4H, -CH_3, -CH), 2.29-2.40 (m, 1H, -CH), 2.41-2.48 (ddd, *J*=2.93, 4.76, 13.7Hz, 1H, -CH), 2.63-2.72 (ddd, *J*=3.85, 10.6, 12.7 Hz, 1H, -CH), 3.34-3.41 (dd, *J*=9.16, 10.6Hz, 1H, -CH), 3.49 (s, 3H, -OCH_3), 3.87 (s, 3H, =$NOCH_3$), 4.18-4.21 (dd, *J*=0.92, 9.16Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -5.35 (Si-CH_3), -4.75 (Si-CH_3), 12.4 (-CH_3), 18.5 (Si-C), 25.3 (-CH_3), 25.9 (-CH_2), 38.5 (-CH_2), 48.5 (-CH), 60.9 (-OCH_3), 61.4 (=$NOCH_3$), 82.6 (-CH), 85.5 (-CH), 156 (C=N), 206 (C=O).

IR (film) 1732 cm^{-1}.

MS(FAB) *m/z* 330 $(M+H)^{+\cdot}$

Anal. Calcd for $C_{16}H_{31}NO_4Si$: C,58.32; H,9.48; N,4.25. Found: C,58.09; H,9.58; N,4.23.

4b

^{1}H-NMR ($CDCl_3$) δ 0.0816 (s, 3H, Si-CH_3), 0.106 (s, 3H, Si-CH_3), 0.916 (s, 9H, -CH_3×3), 1.56-1.87 (m, 5H, -CH×2, -CH_3), 2.02-2.12 (m, 1H, -CH), 2.56-2.65 (ddd, *J*=5.50, 8.24, 13.7Hz, 1H, -CH), 2.88-2.95 (td, *J*=4.95, 6.96Hz, 1H, -CH), 3.37 (s, 3H, -OCH_3), 3.63-3.66 (dd, *J*=2.93, 6.96Hz, 1H, -CH), 3.85-3.90 (m, 3H, -OCH_3), 4.58-4.59 (dd, *J*=0.92, 2.93Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -5.15 (Si-CH_3), -4.87(Si-CH_3), 13.1 (-CH_3), 18.3 (Si-C), 24.7 (-CH_3), 25.8 (-CH_2), 36.4 (-CH_2), 43.6 (-CH), 58.5 (-OCH_3), 61.5 (=$NOCH_3$), 76.6 (-CH), 84.3 (-CH), 157(C=N), 209 (C=O).

IR (film) 1733 cm^{-1}.

HRMS (FAB) calcd for $C_{16}H_{33}NO_4Si$ $(M+H)^+$: 330.2101. Found: 330.2162.

1-[(1S*,2R*,3R*,4S*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-2-methoxycyclohexyl]ethanone *O*-methyl oxime (5a) and 1-[(1S*,2R*,3R*,4R*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-2-methoxycyclohexyl]ethanone *O*-methyl oxime (5b)

Under ice cooling compound **4a** (0.44g, 1.3mmol) was dissolved in MeOH (5.0mL) and $NaBH_4$ (0.20g, 5.3mmol) was added. The solution was stirred for 30 minutes under ice cooling. The reaction solution was diluted with AcOEt (50mL) and washed with water and brine, and dried with anhydrous Na_2SO_4. The solution was concentrated in vacuo. The solution was purified by silica gel chromatography (Hexane : AcOEt = 3 : 1) to give white crystal **5a** (0.32g, 72%) and colorless oil **5b** (59mg, 14%).

5a

^{1}H-NMR ($CDCl_3$) δ 0.131 (s, 3H, Si-CH_3), 0.146 (s, 3H, Si-CH_3), 0.931 (s, 9H, -CH_3×3), 1.23-1.48 (m, 2H, -CH, -CH), 1.62-1.70 (m, 1H, -CH), 1.84 (s, 3H, -CH_3), 1.91-1.99 (m, 1H, -CH), 2.25-2.33 (m, 4H, -OH, -CH), 3.05-3.11 (dd, *J*=8.61, 10.6Hz, 1H, -CH), 3.28-3.34 (t, *J*=8.61Hz, 1H, -CH), 3.35 (s, 3H, -OCH_3), 3.37-3.48 (m, 1H, -CH), 3.85 (s, 3H, -OCH_3).

^{13}C-NMR ($CDCl_3$) δ -4.61 (Si-CH_3), -4.10 (Si-CH_3), 12.5 (-CH_3), 18.2 (Si-C), 25.2 (-CH_3), 26.0 (-CH_2), 30.1 (-CH_2), 48.9 (-CH), 60.1 (-OCH_3), 61.3 (=$NOCH_3$), 73.8 (-CH), 80.7 (-CH), 83.6 (-CH), 158 (C=N).

mp 56-62 °C.

IR (KBr) 3417, 1639 cm^{-1}.

MS (FAB) *m/z* 332 $(M+H)^+$.

Anal. Calcd for $C_{16}H_{33}NO_4Si$: C,57.97; H,10.03; N,4.22. Found: C,57.72; H,10.04; N,4.14.

5b

^{1}H-NMR($CDCl_3$) δ 0.0994 (s, 3H, Si-CH_3), 0.137 (s, 3H, Si-CH_3), 0.927 (s, 9H, -CH_3×3), 1.39-1.49 (m, 2H, -CH×2), 1.81-1.99 (m, 5H, -CH_3, -CH×2), 2.17-2.26 (ddd, *J*=3.11, 10.6, 12.6 Hz, 1H, -CH), 2.60-2.61 (d, *J*=1.83Hz, 1H, -OH), 3.35-3.41 (dd, *J*=8.61, 10.6Hz, 1H, -CH), 3.39 (s, 3H, -OCH_3), 3.50-3.54 (dd, *J*=3.11, 8.61Hz, 1H, -CH), 3.85 (s, 3H, -OCH_3), 3.89-3.90 (d, *J*=2.75Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.92 (Si-CH_3), -4.63 (Si-CH_3), 11.8 (-CH_3), 17.9 (Si-C), 23.0 (-CH_2), 25.8 (-CH_3), 28.6 (-CH_2), 48.9 (-CH), 60.5 (-OCH_3), 61.2

(=$NOCH_3$), 70.8 (-CH), 77.6 (-CH), 80.8 (-CH), 158 (C=N).

IR (film) 1741 cm^{-1}.

HRMS (FAB) calcd for $C_{16}H_{34}NO_4Si$ $(M+H)^+$: 332.2257. Found: 332.2254.

(1S*,2R*,3R*,4R*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxy-4-[1-(methoxyimino)ethyl]cyclohexyl acetate (6a)

Compound **5a** (1.0g, 3.1mmol) was dissolved in a solution of pyridine and Ac_2O (6.0mL, Pyridine : Ac_2O = 2 : 1). The solution was stirred overnight at 40°C. The reaction solution was concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 3 : 1) to give colorless oil **6a** (1.2g, quant.).

^{1}H-NMR ($CDCl_3$) δ 0.0853 (s, 3H, Si-CH_3), 0.119 (s, 3H, Si-CH_3), 0.878 (s, 9H, -CH_3×3), 1.22-1.35 (m, 1H, -CH), 1.39-1.53 (m, 1H, -CH), 1.61-1.69 (qd, *J*=3.66, 13.4Hz, 1H, -CH), 1.84 (s, 3H, -CH_3), 1.99-2.05 (m, 1H, -CH), 2.05 (s, 3H, -CH_3), 2.23-2.32 (ddd, *J*=3.85, 10.6, 12.5Hz, 1H, -CH), 3.09-3.15 (dd, *J*=8.61, 10.7Hz, 1H, -CH), 3.37 (s, 3H, -OCH_3), 3.51-3.57 (dd, *J*=8.79, 9.16Hz, 1H, -CH), 3.85 (s, 3H, =$NOCH_3$), 4.59-4.68 (ddd, *J*=4.76, 9.34, 11.4Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.63 (Si-CH_3), -4.16 (Si-CH_3), 12.3 (-CH_2), 18.0 (Si-C), 21.4 (-CH_3), 24.9 (-CH_3), 25.8 (-CH_3), 28.7 (-CH_2), 48.7 (-CH), 60.5 (-OCH_3), 61.3 (=$NOCH_3$) 75.6 (-CH), 77.0 (-CH), 84.3 (-CH), 157 (C=N), 170 (O-C=O).

IR (film) 1741 cm^{-1}.

HRMS (FAB) calcd for $C_{18}H_{36}NO_5Si$ $(M+H)^+$: 374.2363. Found: 374.2367.

(1S*,2R*,3R*,4S*)-4-acetyl-2-(*tert*-butyldimethylsilyloxy)-3-methoxycyclohexyl acetate (7a)

Compound **6a** (0.16g, 0.42mmol) was dissolved in toluene (20mL) under argon atmosphere and ice cooling. A 0.25M solution of $TiCl_3$-3THF-DIBAL in toluene (2.1mL, 0.53mmol) was added. The solution was stirred for 20 minutes at room temperature. A solution of $TiCl_3$-3THF-DIBAL in toluene (2.1mL, 0.53mmol) was newly added and the solution was stirred for 20 minutes. Finally a solution of $TiCl_3$-3THF-DIBAL in toluene (2.1mL, 0.53mmol) was newly added and the solution was stirred for 40 minutes at room temperature. The reaction was terminated by addition of aqueous sodium acetate (20mL) and the solution was adjusted to pH 3.0 by aqueous citric acid. The solution was extracted by CH_2Cl_2 (30mL×4) and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 5 : 1) to give white crystal **7a** (0.12g, 83%).

^{1}H-NMR ($CDCl_3$) δ 0.0927 (s, 3H, Si-CH_3), 0.120 (s, 3H, Si-CH_3), 0.881 (s, 9H, -CH_3×3), 1.19-1.32 (m, 1H, -CH), 1.34-1.48 (dq, *J*=3.66, 12.1Hz, 1H, -CH), 1.68-1.76 (qd, *J*=3.66, 13.6Hz, 1H, -CH), 2.01-2.10 (m, 1H, -CH), 2.05 (s, 3H, -CH_3), 2.23 (s, 3H, -CH_3), 2.55-2.64 (ddd, *J*=3.66, 10.3, 12.1Hz, 1H, -CH), 3.28-3.34 (dd, *J*=8.80, 10.3Hz, 1H, -CH), 3.38 (s, 3H, -OCH_3), 3.50-3.56 (dd, *J*=8.80, 9.17Hz, 3H, -CH), 4.57-4.65 (ddd, *J*=4.77, 9.53, 11.0Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.58 (Si-CH_3), -4.18 (Si-CH_3), 18.0 (Si-C), 21.4 (-CH_3), 23.7 (-CH_2), 25.7 (-CH_3), 28.7 (-CH_2), 31.1 (-CH_3), 55.0 (-CH), 61.4 (-OCH_3), 75.3 (-CH), 77.0 (-CH), 84.2 (-CH), 170 (O-C=O), 210 (C=O).

mp 68-70 °C.

IR (KBr) 1737, 1714 cm^{-1}.

HRMS (FAB) calcd for $C_{17}H_{33}O_5Si$ $(M+H)^+$: 345.2097. Found: 345.2102.

(1S*,2R*,3R*,4S*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxy-4-[1-(methylsulfonyloxy)ethyl]cyclohexyl acetate (8a)

Under ice cooling compound **7a** (0.34g, 0.99mmol) was dissolved in a mixed solvent MeOH (3.0mL) and CH_2Cl_2 (2.0mL). $NaBH_4$ (0.19g, 4.9mmol) was added and the resulting solution was stirred for 30 minutes. The reaction solution was diluted with AcOEt (50mL) and washed with water and brine, dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo to give colorless oil.

The obtained crude colorless oil was dissolved in CH_2Cl_2 (19mL) under argon atmosphere and ice cooling. Et_3N (1.4mL, 10mmol) and MsCl (0.56mL, 7.2mmol) was added and the resulting solution was stirred for 1.5 hours. Aqueous $NaHCO_3$ (20mL) was added to the reaction solution. The solution was extracted with CH_2Cl_2 (40mL×3) and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 3 : 1) to give white crystal **8a**.

(1S*,2R*,3R*,E)-2-(*tert*-butyldimethylsilyloxy)-4-ethylidene-3-methoxycyclohexyl acetate (9a) and (1S*,2R*,3R*,4R*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxy-4-vinylcyclohexyl acetate (9b)

Compound **8a** (0.35g, 0.83mmol) was dissolved in toluene (10mL) and DBU (0.93mL, 6.2mmol) was added. The solution was heated at reflux for 48 hours. Saturated aqueous NH_4Cl (15mL) was added to the solution. The solution was extracted withCH_2Cl_2 (20mL×3). The organic layers were combined and washed with brine (45mL) and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 20 : 1) to give colorless oil **9a,b**.

(1S*,2R*,3S*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxy-4-oxocyclohexyl acetate (10a) and (1S*,2R*,3R*,4S*)-2-(*tert*-butyldimethylsilyloxy)-4-formyl-3-methoxycyclohexyl acetate (10b)

Crude compound **9a**,**b** (0.14g) was dissolved in a mixed solvent of CH_2Cl_2 (30mL) and MeOH (6.0mL). Et_3N (0.30mL, 1% v/v) was added and the solution was stirred at -78°C. Ozone was bubbled until the blue color persists. The reaction solution was bubbled with oxygen for 30 minutes at -78°C. Me_2S (0.22mL, 3.1mmol) was added and the resulting solution was stirred for 30 minutes then further stirred at room temperature for 2 hours. The reaction was terminated by addition of aqueous $NaHCO_3$ (50mL). The aqueous layer was extracted with CH_2Cl_2 (30mL×2). The organic layer was washed with brine (100mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 5 : 1) to give white crystal **10a** (79mg, 25% 3steps) and white crystal **10b** (34mg, 11% 3steps).

10a

^{1}H-NMR ($CDCl_3$) δ 0.0756 (s, 3H, Si-CH_3), 0.0976 (s, 3H, Si-CH_3), 0.879 (s, 9H, -CH_3×3), 1.46-1.54 (m, 1H, -CH), 2.08 (s, 3H, -CH_3), 2.18-2.27 (qd, *J*=4.40, 13.2Hz, 1H, -CH), 2.41-2.46 (m, 2H, -CH×2), 3.47 (s, 3H, -OCH_3), 3.61-3.64 (d, *J*=9.16Hz, 1H, -CH), 3.70-3.76 (t, *J*= 8.80Hz, 1H, -CH), 4.97-5.05 (ddd, *J*=4.40, 8.80, 11.0Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.64 (Si-CH_3), -4.42 (Si-CH_3), 18.1 (Si-C), 21.2 (-CH_3), 25.5 (-CH_2), 25.7 (-CH_3), 35.6 (-CH_2), 59.6 (-OCH_3), 74.0 (-CH), 76.3 (-CH), 88.2 (-CH), 170 (O-C=O), 206 (-C=O).

mp 77-81 °C.

IR (KBr) 1753, 1729 cm^{-1}.

HRMS (FAB) calcd for $C_{15}H_{29}O_5Si$ $(M+H)^+$: 317.1784. Found: 317.1782.

10b

^{1}H-NMR ($CDCl_3$) δ 0.106 (s, 3H, Si-CH_3), 0.132 (s, 3H, Si-CH_3), 0.886 (s, 9H, -CH_3×3), 1.26-1.54 (m, 2H, -CH×2), 1.77-1.86 (qd, *J*=4.03, 13.6Hz, 1H, -CH), 2.03-2.12 (m, 4H, -CH×2), 2.41-2.46 (m, 2H, -CH_3, -CH), 2.41-2.52 (m, 1H, -CH), 3.29-3.35 (dd, *J*=8.07, 9.53Hz, 1H, -CH), 3.45 (s, 3H, -OCH_3), 3.62-3.68 (dd, *J*=8.07, 8.43Hz, 1H, -CH), 4.58-4.66 (ddd, *J*=4.03, 8.43, 9.90Hz, 1H, -CH), 9.77-9.78 (d, *J*=2.20Hz, 1H, -CHO).

^{13}C-NMR ($CDCl_3$) δ -4.64 (Si-CH_3), -4.31 (Si-CH_3), 18.0 (Si-C), 20.1 (-CH_2), 21.4 (-CH_3), 25.7 (-CH_3), 27.4 (-CH_2), 54.4 (-CH), 60.7 (-OCH_3), 74.6 (-CH), 75.6 (-CH), 82.7 (-CH), 170 (O-C=O), 202 (-COH).

mp 155-164 °C.

IR (KBr) 1733, 1706 cm^{-1}.

MS(FAB) *m/z* 331 $(M+H)^+$.

(1S*,5S*,6R*)-6-(*tert*-butyldimethylsilyloxy)-5-methoxy-4-oxocyclohex-2-enyl acetate (11a)

Compound **10a** (66mg, 0.21mmol) was dissolved in THF (6.5mL) under argon atmosphere at -78°C. THF solution of LiHMDS (1.6 M, 0.20 mL, 0.32mmol) was added and the solution was stirred for 1 hour at -78°C. TMSCl (51μL, 0.40mmol) was then added and the reaction solution was stirred for 45 minutes at -78°C and for 1 hour at room temperature. The solution was concentrated in vacuo. The residue was dissolved in dry *n*-pentane and the solution was filtered through celite. The filtrate was concentrated in vacuo to give crude product as colorless oil.

The crude colorless oil was dissolved in CH_2Cl_2 (6.0mL) under argon atmosphere at -78°C. A solution of PhSeCl (45mg, 0.23mmol) in CH_2Cl_2 (6.0mL) was added and the solution was stirred for 45 minutes at -78°C and for 15 minutes at room temperature. The reaction solution was concentrated in vacuo to give crude product as yellow oil.

The crude yellow oil was dissolved in THF (6.5mL) under argon atmosphere at ice cooling. $NaHCO_3$ (52mg, 0.62mmol) and 30% H_2O_2 (61μL, 0.63mmol) were successively added and the solution was stirred for 15minutes at the same temperature then for 2 hours at room temperature. Water (30mL) was added to the reaction solution and the mixture was extracted with diethyl ether (40mL×3). The organic layer was washed with brine (60mL) and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 5 : 1) to give white crystal **11a** (12mg, 18% 3steps).

^{1}H-NMR ($CDCl_3$) δ 0.0854 (s, 3H, Si-CH_3), 0.120 (s, 3H, Si-CH_3), 0.888 (s, 9H, -CH_3×3), 2.14 (s, 3H, -CH_3), 3.63-3.67 (d, *J*=10.3Hz, 1H, -CH), 3.64 (s, 3H, -OCH_3), 3.98-4.04 (dd, *J*=8.43, 10.3Hz, 1H, -CH), 5.58-5.62 (td, *J*=2.20, 8.43Hz, 1H, -CH), 6.06-6.10 (dd, *J*=2.20, 10.6Hz, 1H, =CH), 6.63-6.67 (dd, *J*=2.20, 10.6Hz, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -5.09 (Si-CH_3), -4.39 (Si-CH_3), 18.1 (Si-C), 21.0 (-CH_3), 25.6 (-CH_3), 60.9 (-OCH_3), 74.3 (-CH), 75.4 (-CH), 86.2 (-CH), 129 (=CH), 146 (=CH), 170 (O-C=O), 197 (-C=O).

mp 62-68 °C.

IR (KBr) 1744, 1701, 1624 cm^{-1}.

HRMS (FAB) calcd for $C_{15}H_{26}NaO_5Si$ $(M+Na)^+$: 334.1447. Found: 337.1463.

(4R*,5R*,6S*)-6-(*tert*-butyldimethylsilyloxy)-5-methoxy-4-[1-(methoxyimino)ethyl]cyclohex-2-enone (12)

Compound **4a** (1.7g, 5.0mmol) was dissolved in THF (16mL) under argon atmosphere at -78°C. THF solution of LiHMDS (1.6M, 7.5 mL, 12mmol) was

added and the solution was stirred for 1 hour at -78°C. TMSCl (0.95mL, 7.5mmol) was added and the reaction solution was stirred for 45 minutes at -78°C and for 1 hour at room temperature. The solution was concentrated in vacuo. The residue was dissolved in dry n-pentane and the solution was filtered through celite. The filtrate was concentrated in vacuo to give crude product as yellow oil.

The crude yellow oil was dissolved in CH_2Cl_2 (50mL) under argon atmosphere at -78°C. A solution of PhSeCl (1.1g, 5.6mmol) in CH_2Cl_2 (10mL) was added and the solution was stirred for 45 minutes at -78°C and for 15 min at room temperature. The solution was concentrated in vacuo to give crude yellow oil.

The yellow oil was dissolved in THF (40mL) under argon atmosphere and ice cooling. $NaHCO_3$ (1.2g, 15mmol) and 30% H_2O_2 (1.4mL, 15mmol) were successively added and the solution was stirred for 15 minutes at the same temperature then for 2 hours at room temperature. Water (60mL) was added and the mixture was extracted by diethyl ether (80mL×3). The organic layer was washed with brine (120mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 5 : 1) to give **12** (0.91g, 55% 3steps) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.108 (s, 3H, Si-CH_3), 0.199 (s, 3H, Si-CH_3), 0.972 (s, 9H, -CH_3×3), 1.91 (s, 3H, -CH_3), 3.35-3.40 (ddd, *J*=2.20, 3.11, 9.52Hz, 1H, -CH), 3.51 (s, 3H, -OCH_3), 3.56- 3.63 (dd, *J*=9.52, 10.3Hz, 1H, -CH), 4.01 (s, 3H, =$NOCH_3$), 4.19-4.23 (d, *J*=10.3Hz, 1H, -CH), 6.07-6.11 (dd, *J*=3.11, 10.3Hz, 1H, =CH), 6.62-6.66 (dd, *J*=2.20, 10.3Hz, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -5.30 (Si-CH_3), -4.59 (Si-CH_3), 13.3 (-CH_3), 18.6 (Si-C), 25.8 (-CH_3), 50.4 (-CH), 61.0 (-OCH_3), 61.7 (=$NOCH_3$), 80.3 (-CH), 84.1 (-CH), 129 (=CH), 146 (=CH), 155 (C=N), 198 (-C=O).

IR (film) 1702, 1620, 1471, 1443 cm^{-1}.

HRMS (FAB) calcd for $C_{16}H_{30}NO_4Si$ $(M+H)^+$: 328.1944. Found: 328.1921.

1-[(1S*,4S*,5R*,6R*)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-6-methoxycyclohex-2-enyl]ethanone *O*-methyl oxime (13a) and 1-[(1S*,4R*,5R*,6R*)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-6-methoxycyclohex-2-enyl]ethanone *O*-methyl oxime (13b)

Compound **12** (85mg, 0.26mmol) was dissolved in a mixed solvent of MeOH (1.0mL) and CH_2Cl_2 (1.0mL) under ice cooling. $NaBH_4$ (49mg, 1.3mmol) was added and the solution was stirred for 30 minutes. The solution was diluted with AcOEt (50mL), washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 3 : 1) to give colorless oil **13a** (72mg, 84%) and yellow oil **13b** (7.0mg, 8.2%).

13a

^{1}H-NMR ($CDCl_3$) δ 0.141 (s, 6H, Si-CH_3×2), 0.933 (s, 9H, -CH_3×3), 1.81 (s, 3H, -CH_3), 2.06-2.08 (d, *J*=4.40Hz, 1H, -OH), 3.11-3.17 (dq, *J*=2.57, 11.4Hz, 1H, -CH), 3.28-3.34 (d, *J*=9.17Hz, 1H, -CH), 3.41 (s, 3H, -OCH_3), 3.61-3.66 (dd, *J*=7.70, 9.17Hz, 1H, -CH), 3.87 (s, 3H, =$NOCH_3$), 4.17-4.19 (m, 1H, -CH), 5.39-5.44 (dd, *J*=2.57, 10.3Hz, 1H, =CH), 5.68- 5.73 (dd, *J*=2.57, 10.3Hz, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -4.67 (Si-CH_3), -4.21 (Si-CH_3), 12.4 (-CH_3), 18.2 (Si-C), 26.0 (-CH_3), 50.2 (-CH), 60.4 (-OCH_3), 61.4 (=$NOCH_3$), 73.5 (-CH), 78.1 (-CH), 81.2 (-CH), 127 (=CH), 130 (=CH), 157 (C=N).

IR (film) 3444, 1655, 1472 cm^{-1}.

HRMS (FAB) calcd for $C_{16}H_{32}NO_4Si$ $(M+H)^+$: 330.2101. Found: 330.2087.

13b

^{1}H-NMR ($CDCl_3$) δ 0.129 (s, 3H, Si-CH_3), 0.161 (s, 3H, Si-CH_3), 0.939 (s, 9H, -CH_3×3), 1.83 (s, 3H, -CH_3), 2.92 (s, 1H, -OH), 3.02-3.06 (m, 1H, -CH), 3.42 (s, 3H, -OCH_3), 3.44-3.50 (dd, *J*=9.16, 9.53Hz, 1H, -CH), 3.68-3.73 (dd, *J*=4.40, 9.53Hz, 1H, -CH), 3.88 (s, 3H, =$NOCH_3$), 4.11-4.14 (dd, *J*=4.40, 4.77Hz, 1H, -CH), 5.53-5.57 (dd, *J*=2.20, 9.90Hz, 1H, =CH), 5.89-5.95 (ddd, *J*=2.57, 5.13, 9.90Hz, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -5.00 (Si-CH_3), -4.48 (Si-CH_3), 11.9 (-CH_3), 18.0 (Si-C), 25.9 (-CH_3), 50.5 (-CH), 60.7 (-OCH_3), 61.5 (=$NOCH_3$), 67.8 (-CH), 74.6 (-CH), 77.5 (-CH), 128 (=CH), 130 (=CH), 156 (C=N).

IR (film) 3550, 1701, 1471 cm^{-1}.

HRMS (FAB) calcd for $C_{16}H_{31}NNaO_4Si$ $(M+Na)^+$: 352.1920. Found: 352.1919.

Catalytic Hydrogenation of 1-[(1S*,4S*,5R*,6R*)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-6-methoxycyclohex-2-enyl]ethanone *O*-methyl oxime (13a) to 1-[(1S*,2R*,3R*,4S*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-2-methoxycyclohexyl]ethanone *O*-methyl oxime (5a)

To a solution of compound **13a** (55mg, 0.17mmol) in CH_2Cl_2 (10mL) 10% Pd/C (18mg, 17μmol) was added. The mixture was stirred for 2 hours under H_2 atmosphere at room temperature. The solution was filtered to remove the Pd/C which was washed with CH_2Cl_2 and the combined filtrate was concentrated in vacuo to give white crystal **5a** (48mg, 87%). The NMR data of **5a** thus obtained was identical to that of the above described **5a.**

1-[(1S*,4S*,5S*,6R*)-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-4-(methoxymethoxy)cyclohex-2-enyl]ethanone *O*-methyl oxime (14)

Compound **13a** (58mg, 0.18mmol) was dissolved in CH_2Cl_2 (4.0mL) under argon atmosphere with ice cooling. DIPEA (0.74mL, 4.4mmol) was added and the solution was stirred for 15 minutes with ice cooling. MOMCl (0.26mL, 3.4mmol) was added and the solution was stirred for 24 hours at room temperature. The reaction was terminated by addition of aqueous NH_4Cl (2.0mL) and aqueous $NaHCO_3$ (2.0mL). After 10 minutes of hydrolysis, the aqueous layer was extracted by CH_2Cl_2 (4.0mL×2), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 10 : 1) to give colorless oil **14** (61mg, 92%).

^{1}H-NMR ($CDCl_3$) δ 0.0932 (s, 3H, Si-CH_3), 0.121 (s, 3H, Si-CH_3), 0.914 (s, 9H, -CH_3×3), 1.81 (s, 3H, -CH_3), 3.08-3.14 (dddd, *J*=2.20, 3.11, 3.30, 9.16Hz, 1H, -CH), 3.22-3.29 (dd, *J*=9.34, 9.52Hz, 1H, -CH), 3.40 (s, 6H, -OCH_3×2), 3.67-3.74 (dd, *J*=7.69, 9.52Hz, 1H, -CH), 3.87 (s, 3H, =$NOCH_3$), 4.02-4.07 (dddd, *J*=2.02, 2.20, 3.30, 7.69Hz, 1H, -CH), 4.68-4.71 (d, *J*=6.78Hz, 1H, -CH), 4.80-4.82 (d, *J*=6.78Hz, 1H, -CH), 5.35-5.40 (ddd, *J*=2.02, 2.20, 10.3Hz, 1H, =CH), 5.71-5.76 (ddd, *J*=2.20, 2.75, 10.3Hz, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -4.53 (Si-CH_3), -4.26 (Si-CH_3), 12.2 (-CH_3), 18.1 (Si-C), 26.0 (-CH_3), 50.1 (-CH), 55.4 (-OCH_3), 60.7 (-OCH_3), 61.4 (=$NOCH_3$), 76.7 (-CH), 81.6 (-CH), 81.7 (-CH), 98.5 (-OCH_2), 126 (=CH), 130 (=CH), 157 (C=N).

IR (film) 1631 cm^{-1}.

HRMS (FAB) calcd for $C_{18}H_{35}NNaO_5Si$ $(M+Na)^+$: 396.2182. Found: 396.2196.

1-[(1S*,2R*,3S*,4S*,5S*,6S*)-3-(*tert*-butyldimethylsilyloxy)-5,6-dihydroxy-2-methoxy-4-(methoxymethoxy)cyclohexyl]ethanone *O*-methyl oxime (15a) and 1-[(1S*,2R*,3S*,4S*, 5R*,6R*)-3-(*tert*-butyldimethylsilyloxy)-5,6-dihydroxy-2-methoxy-4-(methoxymethoxy)-cyclohexyl]ethanone *O*-methyl oxime (15b)

AD-mix-β (1.3g), OsO_4 (2.3mg, 9.4μmol), $(DHQD)_2$-PHAL (66mg, 84μmol) was dissolved in a mixed solvent of H_2O (5.0mL) and *t*-BuOH (5.0mL) and the solution was stirred for 15 minutes. To this solution, $MeSO_2NH_2$ (89mg, 0.94mmol) and a solution of compound **14** (0.18g, 0.47mmol) in CH_2Cl_2 (10mL) were added and the resulting solution was stirred for a further 2 weeks. After that Na_2SO_3 (0.50g, 0.41mmol) was added and the solution was stirred for 1 hour. The aqueous layer and the organic layer were separated. The aqueous layer was extracted with CH_2Cl_2 (10mL×2). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 1 : 1) to give colorless amorphous **15a** (0.12g, 65%) and white crystal **15b** (55mg, 29%).

15a

^{1}H-NMR ($CDCl_3$) δ 0.0780 (s, 3H, Si-CH_3), 0.112 (s, 3H, Si-CH_3), 0.898 (s, 9H, -CH_3×3), 1.92 (s, 3H, -CH_3), 2.58-2.61 (d, *J*=7.88Hz, 1H, -OH), 2.74-2.81 (dd, *J*=10.6, 11.2Hz, 1H, -CH), 2.75 (s, 1H, -OH), 3.01-3.08 (dd, *J*=8.79, 11.0Hz, 1H, -CH), 3.31-3.35 (dd, *J*=2.75, 9.52Hz, 1H, -CH), 3.35 (s, 3H, -OCH_3), 3.41 (s, 3H, -OCH_3), 3.68-3.75 (ddd, *J*=2.75, 8.06, 11.0Hz, 1H, -CH), 3.83-3.89 (dd, *J*=8.97, 9.16Hz, 1H, -CH), 3.88 (s, 3H, =$NOCH_3$), 4.19-4.21 (m, 1H, -CH), 4.68-4.71 (d, *J*=6.59Hz, 1H, -CH), 4.76-4.80 (d, *J*=6.59Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.38 (Si-CH_3), -4.21 (Si-CH_3), 13.5 (-CH_3), 18.0 (Si-C), 26.0 (-CH_3), 49.6 (-CH), 55.7 (-OCH_3), 60.4 (-OCH_3), 61.5 (=$NOCH_3$), 68.9 (-CH), 72.1 (-CH), 73.9 (-CH), 80.0 (-CH), 82.3 (-CH), 98.0 (-OCH_2), 156 (C=N).

IR (film) 1631, 3200 cm^{-1}.

HRMS (FAB) calcd for $C_{18}H_{38}NO_7Si$ $(M+H)^+$: 408.2418. Found: 408.2410.

15b

^{1}H-NMR ($CDCl_3$) δ 0.0805 (s, 3H, Si-CH_3), 0.122 (s, 3H, Si-CH_3), 0.910 (s, 9H, -CH_3×3), 2.00 (s, 3H, -CH_3), 2.23-2.28 (dd, *J*=1.83, 11.4Hz, 1H, -CH), 3.36-3.40 (ddd, *J*=1.47, 2.93, 8.80Hz, 1H, -CH), 3.41 (s, 3H, -OCH_3), 3.44-3.50 (dd, *J*=8.43, 8.80Hz, 1H, -CH), 3.45 (s, 1H, -OH), 3.45 (s, 3H, -OCH_3), 3.54-3.60 (t, *J*=8.80Hz, 1H, -CH), 3.62-3.68 (dd, *J*=8.43, 11.0Hz, 1H, -CH), 3.88 (s, 3H, =$NOCH_3$), 4.07-4.08 (dd, *J*=2.20, 2.57Hz, 1H, -CH), 4.44 (d, *J*=1.47Hz, 1H, -OH), 4.65-4.67 (d, *J*=6.23Hz, 1H, -CH), 4.73-4.75 (d, *J*=6.60Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.28 (Si-CH_3), -4.20 (Si-CH_3), 15.6 (-CH_3), 18.0 (Si-C), 25.9 (-CH_3), 49.3 (-CH), 55.8 (-OCH_3), 60.9 (-OCH_3), 61.6 (=$NOCH_3$), 70.6 (-CH), 72.7 (-CH), 76.6 (-CH), 81.4 (-CH), 86.5 (-CH), 99.3 (-OCH_2), 158 (C=N).

mp 63-70 °C.

IR (film) 1624, 3450 cm^{-1}.

HRMS (FAB) calcd for $C_{18}H_{38}NO_7Si$ $(M+H)^+$: 408.2418. Found: 408.2417.

1-[(1R*,2R*,3S*,4S*,5S*,6S*)-3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-methoxy-6-(4-methoxybenzyloxy)-4-(methoxymethoxy)cyclohexyl]ethanone *O*-methyl oxime (16)

Compound **15** (0.70g, 0.17mmol) was dissolved in toluene (80mL) and dibutyltin(IV) oxide (0.50g, 2.0mmol) was added. The solution was heated at reflux for 3 hours while the water formed was removed by using the Dean-Stark apparatus. The solvent was removed by evaporation. To the residue CsF (0.30g, 2.0mmol) was added. The resulting material was dried for 1 hour in vacuo and dissolved in DMF (30mL). At -41°C MPMCl (0.27mL, 2.0mmol) was added and the solution was stirred for

24 hours. The solution was concentrated in vacuo and then dried for 24 hours in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 3 : 1) to give colorless oil **16** (0.47g, 52%).

^{1}H-NMR ($CDCl_3$) δ 0.0817 (s, 3H, Si-CH_3), 0.104 (s, 3H, Si-CH_3), 0.889 (s, 9H, -CH_3×3), 1.81 (s, 3H, -CH_3), 2.31 (s, 1H, -OH), 2.78-2.85 (t, *J*=11.2Hz, 1H, -CH), 3.06-3.13 (dd, *J*=8.79, 11.0Hz, 1H, -CH), 3.24-3.28 (dd, *J*=2.57, 9.34Hz, 1H, -CH), 3.35 (s, 3H, -OCH_3), 3.41 (s, 3H, -OCH_3), 3.49-3.53 (dd, *J*=2.56, 11.2Hz, 1H, -CH), 3.80 (s, 3H, -OCH_3), 3.86 (s, 3H, =$NOCH_3$), 3.86-3.92 (dd, *J*=8.97, 9.34Hz, 1H, -CH), 4.22-4.24 (dd, *J*=2.56, 2.56Hz, 1H, -CH), 4.39-4.42 (d, *J*=11.5Hz, 1H, -CH), 4.53-4.56 (d, *J*=11.5Hz, 1H, -CH), 4.70-4.73 (d, *J*=6.78Hz, 1H, -CH), 4.76-4.79 (d, *J*=6.78Hz, 1H, -CH), 6.85-6.88 (d, *J*=8.61Hz, 2H, Bn-H×2), 7.19-7.22 (d, *J*=8.61Hz, 2H, Bn-H×2).

^{13}C-NMR ($CDCl_3$) δ -4.41 (Si-CH_3), -4.16 (Si-CH_3), 15.3 (-CH_3), 18.0 (Si-C), 26.0 (-CH_3), 48.4 (-CH), 55.3 (-OCH_3), 55.6 (-OCH_3), 60.7 (-OCH_3), 61.4 (=$NOCH_3$), 68.9 (-CH), 71.4 (-OCH_2), 73.8 (-CH), 76.9 (-CH), 79.2 (-CH), 83.2 (-CH), 98.0 (-OCH_2), 114 (Bn), 130 (Bn), 130 (Bn), 156 (Bn), 159 (C=N).

IR (film) 1613, 3477 cm^{-1}.

HRMS (FAB) calcd for $C_{26}H_{46}NO_8Si$ $(M+H)^+$: 528.2993. Found: 528.2994.

1-[(1S*,2R*,3R*,4S*)-3-(*tert*-butyldimethylsilyloxy)-2-methoxy-4-(methoxymethoxy)cyclohexyl]ethanone *O*-methyl oxime (6b)

Compound **5a** (1.3g, 3.9mmol) was dissolved in CH_2Cl_2 (120mL) under argon atmosphere and ice cooling. DIPEA (17mL, 98mmol) was added and the solution was stirred for 15 minutes with ice cooling. MOMCl (5.9mL, 78mmol) was added and the solution was stirred for 24 hours at room temperature. The reaction was terminated by addition of aqueous NH_4Cl (60mL) and aqueous $NaHCO_3$ (60mL). After 10 minutes of hydrolysis, the aqueous layer was extracted by CH_2Cl_2 (120mL×2). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 10 : 1) to give colorless oil **6b** (1.4g, 92%).

^{1}H-NMR ($CDCl_3$) δ 0.0762 (s, 3H, Si-CH_3), 0.111 (s, 3H, Si-CH_3), 0.907 (s, 9H, -CH_3×3), 1.33-1.40 (m, 2H, -CH×2), 1.60-1.67 (m, 1H, -CH), 1.83 (s, 3H, -CH_3), 2.03-2.09 (m, 1H, -CH), 2.20-2.29 (ddd, *J*=3.66, 10.6, 12.3Hz, 1H, -CH), 3.04-3.10 (dd, *J*=8.43, 10.6Hz, 1H, -CH), 3.24-3.45 (m, 2H, -CH×2), 3.36 (s, 3H, -OCH_3), 3.38 (s, 3H, -OCH_3), 3.85 (s, 3H, =$NOCH_3$), 4.63-4.66 (d, *J*=6.78Hz, 1H, -CH_2), 4.74-4.76 (d, *J*=6.78Hz, 1H, -CH_2).

^{13}C- NMR ($CDCl_3$) δ -4.33 (Si-CH_3), -4.16 (Si-CH_3), 12.3 (-CH_3), 18.1 (Si-C), 25.2 (-CH_2), 26.0 (-CH_3), 30.5 (-CH_2), 48.7 (-CH), 55.3 (-OCH_3), 60.4 (-OCH_3), 61.3 (=$NOCH_3$), 79.1 (-CH), 80.7 (-CH), 81.0 (-CH), 97.7 (-OCH_2), 158 (C=N).

IR (film) 1613 cm^{-1}.

HRMS (FAB) calcd for $C_{18}H_{38}NO_5Si$ $(M+H)^+$: 376.2519. Found: 376.2536.

1-[(1S*,2R*,3R*,4S*)-3-(*tert*-butyldimethylsilyloxy)-2-methoxy-4-(methoxymethoxy)cyclohexyl]ethanone (7c)

Compound **6b** (1.0g, 2.7mmol) was dissolved in toluene (50mL) under argon atmosphere and ice cooling. A 0.25M solution of $TiCl_3$-3THF- DIBAL in toluene (14mL, 3.5mmol) was added. The solution was stirred for 20 minutes at room temperature. A solution of $TiCl_3$- 3THF-DIBAL in toluene (14mL, 3.5mmol) was newly added and the solution was stirred for 20 minutes. Finally a solution of $TiCl_3$-3THF-DIBAL in toluene (14mL, 3.5mmol) was newly added and the solution was stirred for 40 minutes at room temperature. The reaction was terminated by addition of aqueous sodium acetate (50mL) and the solution was adjusted to pH 3.0 by aqueous citric acid. The solution was extracted by CH_2Cl_2 (75mL×4) and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 5 : 1) to give white crystal **7c** (1.6g, 85%).

^{1}H-NMR ($CDCl_3$) δ 0.0805 (s, 3H, Si-CH_3), 0.110 (s, 3H, Si-CH_3), 0.909 (s, 9H, -CH_3×3), 1.26-1.40 (m, 2H, -CH, -CH), 1.67-1.73 (m, 1H, -CH), 2.06-2.12 (m, 1H, -CH), 2.22 (s, 3H, -CH_3), 2.53-2.62 (ddd, *J*=3.66, 11.7, 13.6Hz, 1H, -CH), 3.22-3.31 (m, 2H, -CH×2), 3.35-3.42 (dd, *J*=6.23, 9.16Hz, 1H, -CH), 3.35 (s, 3H, -OCH_3), 3.38 (s, 3H, -OCH_3), 4.62-4.65 (d, *J*=6.97Hz, 1H, -CH), 4.72-4.75 (d, *J*=6.60Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.38 (Si-CH_3), -4.13 (Si-CH_3), 18.1 (Si-C), 24.0 (-CH_2), 26.0 (-CH_3), 30.6 (-CH_2), 31.2 (-CH_3), 55.1 (-CH), 55.3 (-OCH_3), 61.2 (-OCH_3), 79.1 (-CH), 80.8 (-CH), 84.3 (-CH), 97.7 (-OCH_2), 211 (C=O).

IR (film) 1717 cm^{-1}.

HRMS (FAB) calcd for $C_{17}H_{35}O_5Si$ $(M+H)^+$: 347.2254. Found: 347.2243.

1-[(1S*,2R*,3R*,4S*)-3-(*tert*-butyldimethylsilyloxy)-2-methoxy-4-(methoxymethoxy)cyclohexyl]ethyl methanesulfonate (8b)

Under ice cooling compound **7c** (1.8g, 5.1mmol) was dissolved in a mixed solvent of MeOH (16mL) and CH_2Cl_2 (16mL). $NaBH_4$ (0.58g, 15mmol) was added and the solution was stirred for 30 minutes with ice cooling. The solution was diluted with AcOEt (50mL), washed with water, brine, dried over anhydrous Na_2SO_4 to give colorless oil.

Under argon atmosphere and ice cooling, the crude colorless oil was dissolved in CH_2Cl_2 (32mL), Et_3N (7.1mL, 50mmol) and MsCl (2.9mL, 37mmol) were added and the resulting solution was stirred for 1.5 hours. To the reaction solution was added aqueous $NaHCO_3$ (20mL) and extracted with CH_2Cl_2 (40mL×3). The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to silica gel chromatography (Hexane : AcOEt = 3 : 1) to give **8b** (crude) as white crystal.

tert-butyl[(1R*,2R*,6S*,E)-3-ethylidene-2-methoxy-6-(methoxymethoxy)cyclohexyloxy]dimethylsilane (9c) and _tert_-butyl[(1R*,2R*,3R*,6S*)-2-methoxy-6-(methoxymethoxy)-3-vinylcyclohexyloxy]dimethylsilane (9d)

Compound **8b** (1.7g, crude) was dissolved in toluene (50mL) and DBU (4.4mL, 29mmol) was added. The solution was heated at reflux for 48 hours. To the solution saturated NH_4Cl (75mL) was added. The solution was extracted with CH_2Cl_2 (100mL×3) and the combined organic layers was washed with brine (200mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to silica gel chromatography (Hexane : AcOEt = 20 : 1) to give **9c,d** (crude) as colorless oil.

(2S*,3R*,4S*)-3-(_tert_-butyldimethylsilyloxy)-2-methoxy-4-(methoxymethoxy)cyclohexanone (10c) and (1S*,2R*,3R*,4S*)-3-(_tert_-butyldimethylsilyloxy)-2-methoxy-4-(methoxymethoxy)cyclohexanecarbaldehyde (10d)

Crude compound **9c**,**d** (0.74g) was dissolved in a mixed solvent of CH_2Cl_2 (30mL) and MeOH (6.0mL). Et_3N (0.30mL, 1% v/v) was added and the solution was stirred at -78°C. Ozone was bubbled until the blue color persists. The reaction solution was bubbled with oxygen for 30 minutes at -78°C. Me_2S (1.2mL, 17mmol) was added and the resulting solution was stirred for 30 minutes then further stirred at room temperature for 2 hours. The reaction was terminated by addition of aqueous $NaHCO_3$ (50mL). The aqueous layer was extracted with CH_2Cl_2 (30mL×2). The organic layer was washed with brine (100mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 5 : 1) to give colorless oil **10c** (0.39g, 24% 3steps) and colorless oil **10d** (0.16g, crude).

10c

^{1}H-NMR ($CDCl_3$) δ 0.0762 (s, 3H, Si-CH_3), 0.0945 (s, 3H, Si-CH_3), 0.901 (s, 9H, -CH_3×3), 1.55-1.65 (ddd, *J*=5.49, 10.6, 12.8Hz, 1H, -CH), 2.21-2.30 (m, 1H, -CH), 2.34-2.45 (m, 2H, -CH×2), 3.39 (s, 3H, -OCH_3), 3.46 (s, 3H, -OCH_3), 3.56-3.59 (dd, *J*=0.73, 8.79Hz, 1H, -CH), 3.70-3.76 (dd, *J*=7.33, 8.79Hz, 1H, -CH), 3.68-3.75 (m, 1H, -CH), 4.67-4.70 (d, *J*=6.78Hz, 1H, -CH), 4.81-4.83 (d, *J*=6.78Hz, 1H, -CH).

^{13}C-NMR ($CDCl_3$) δ -4.58 (Si-CH_3 ×2), 18.2 (Si-C), 25.8 (-CH_3), 27.1 (-CH_2), 35.9 (-CH_2), 55.4 (-OCH_3), 59.5 (-OCH_3), 78.2 (-CH), 79.2 (-CH), 88.4 (-CH), 97.5 (-OCH_2), 206 (-C=O).

IR (film) 1731 cm^{-1}.

HRMS (FAB) calcd for $C_{15}H_{30}NaO_5Si$ $(M+Na)^+$: 341.1760. Found: 341.1770.

(1S*,4S*,5R*,6R*)-5-(_tert_-butyldimethylsilyloxy)-6-methoxy-4-(methoxymethoxy)cyclohex-2-enol (17a)

Compound **10c** (61mg, 0.19mmol) was dissolved in THF (1.0mL) under argon atmosphere at -78°C. THF solution of LiHMDS (1.6 M, 0.28mL, 0.45mmol) was added and the solution was stirred for 1 hour at -78°C. TMSCl (36μL, 0.29mmol) was then added and the reaction solution was stirred for 45 minutes at -78°C and for 1 hour at room temperature. The solution was concentrated in vacuo. The residue was dissolved in dry n-pentane and the solution was filtered through celite. The filtrate was concentrated in vacuo to give crude product as colorless oil.

The crude colorless oil was dissolved in CH_2Cl_2 (2.0mL) under argon atmosphere at -78°C. A solution of PhSeCl (40mg, 0.21mmol) in CH_2Cl_2 (1.0mL) was added and the solution was stirred for 45 minutes at -78°C and for 15 minutes at room temperature. The reaction solution was concentrated in vacuo to give crude product as yellow oil.

At -78°C, the crude yellow oil was dissolved in MeOH (2.0mL) and $NaBH_4$ (14mg, 0.38mmol) and the solution was stirred for 30 minutes. The solution was diluted with AcOEt (59mL), washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude yellow oil.

The crude yellow oil was dissolved in THF (3.3mL) under argon atmosphere at ice cooling. $NaHCO_3$ (49mg, 0.58mmol) and 30% H_2O_2 (47μL, 0.49mmol) were successively added and the solution was stirred for 15minutes at the same temperature then for 2 hours at room temperature. Water (30mL) was added to the reaction solution and the mixture was extracted with diethyl ether (40mL×3). The organic layer was washed with brine (60mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 5 : 1) to give colorless oil **17a** (31mg, 51% 4steps).

^{1}H-NMR ($CDCl_3$) δ 0.104 (s, 3H, Si-CH_3), 0.137 (s, 3H, Si-CH_3), 0.920 (s, 9H, -CH_3×3), 2.35-2.37 (d, *J*=5.13Hz, 1H, -OH), 3.12-3.17 (dd, *J*=6.96, 9.16Hz, 1H, -CH), 3.40 (s, 3H, -OCH_3), 3.59 (s, 3H, -OCH_3), 3.72-3.77 (dd, *J*=6.60, 9.16Hz, 1H, -CH), 4.01-4.04 (dd, *J*= 1.83, 6.60Hz, 1H, -CH), 4.15-4.22 (m, 1H, -CH), 4.68-4.70 (d, *J*=6.96Hz, 1H, -CH), 4.77-4.79 (d,

J=6.97Hz, 1H, -CH), 5.66-5.71 (dd, *J*=1.47, 11.0Hz, 1H, =CH), 5.71-5.75 (dd, *J*=1.47, 11.7Hz, 1H, =CH).

^{13}C-NMR ($CDCl_3$) δ -4.64 (Si-CH_3), -4.49 (Si-CH_3), 18.0 (Si-C), 25.9 (-CH_3), 55.5 (-OCH_3), 61.3 (-OCH_3), 71.3 (-CH), 75.0 (-CH), 80.6 (-CH), 85.6 (-CH), 98.0 (-OCH_2), 128 (=CH), 129 (=CH).

IR (film) 3246 cm^{-1}.

HRMS (FAB) calcd for $C_{15}H_{30}NaO_5Si$ $(M+Na)^+$: 341.1760. Found: 341.1767.

tert-butyl[(1R*,2S*,5S*,6R*)-6-methoxy-5-(4-methoxybenzyloxy)-2-(methoxymethoxy)cyclohex-3-enyloxy]dimethylsilane (18)

Under argon atmosphere and ice cooling compound **17a** (55mg, 0.17mmol) was dissolved in THF (3.4mL). NaH (42mg, 1.0mmol) and Molecular Sieves 4A were added and the mixture was warmed to room temperature and stirred for 2 hours at the same temperature. The solution was cooled to 0°C and TBAI (6.4mg, 17μmol) and MPMCl (26μL, 0.19mmol) were added. The solution was warmed to room temperature and stirred for 2 days at the same temperature. To the reaction solution wad added water (5mL) and extracted with AcOEt (5mL×3). The organic layer was washed with brine (15mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 20 : 1) to give **18** (30mg, 40%) colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.0835 (s, 3H, Si-CH_3), 0.124 (s, 3H, Si-CH_3), 0.915 (s, 9H, -CH_3×3), 3.19-3.25 (dd, *J*=7.69, 10.3Hz, 1H, -CH), 3.38 (s, 3H, -OCH_3), 3.58-3.64 (dd, *J*=7.69, 10.3Hz, 1H, -CH), 3.60 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 3.96-4.05 (m, 2H, -CH×2), 4.56-4.60 (d, *J*=11.2Hz, 1H, -CH), 4.62-4.65 (d, *J*=11.0Hz, 1H, -CH), 4.66-4.69 (d, *J*= 6.78Hz, 1H, -CH), 4.77-4.80 (d, *J*=6.78Hz, 1H, -CH), 5.60-5.64 (d, *J*=10.4Hz, 1H, =CH), 5.66-5.70 (d, *J*=10.4Hz, 1H, =CH), 6.86-6.89 (dd, *J*=1.83, 8.61Hz, 2H, Bn-H×2), 7.27- 7.30 (dd, *J*=2.01, 8.61Hz, 2H, Bn-H×2).

^{13}C-NMR ($CDCl_3$) δ -4.58 (Si-CH_3), -4.28 (Si-CH_3), 18.2 (Si-C), 26.0 (-CH_3), 55.3 (-OCH_3), 55.5 (-OCH_3), 61.3 (-OCH_3), 71.9 (-OCH_2), 75.9 (-CH), 80.4 (-CH), 81.6 (-CH), 85.2 (-CH), 98.5 (-OCH_2), 114 (Bn), 127 (=CH), 129 (=CH), 129 (Bn), 131 (Bn), 159 (Bn).

IR (film) 1613 cm^{-1}.

HRMS (FAB) calcd for $C_{23}H_{38}NaO_6Si$ $(M+Na)^+$: 461.2335. Found: 461.2332.

(1S*,2R*,3S*,4S*,5R*,6S*)-4-(_tert_-butyldimethylsilyloxy)-5-methoxy-6-(4-methoxybenzyloxy)-3-(methoxymethoxy)cyclohexane-1,2-diol (19)

AD-mix-β (0.10g), OsO_4 (1.0mg, 4.3μmol), $(DHQD)_2$-PHAL (22mg, 28μmol) was dissolved in a mixed solvent of H_2O (1.5mL) and *t*-BuOH (1.5mL) and the solution was stirred for 15 minutes. To this solution, $MeSO_2NH_2$ (14mg, 0.14mmol) and a solution of compound **18** (31mg, 71μmol) in CH_2Cl_2 (3.0mL) were added and the resulting solution was stirred for a further 2 weeks. After that Na_2SO_3 (76mg, 0.60mmol) was added and the solution was stirred for 1 hour. The aqueous layer and the organic layer were separated. The aqueous layer was extracted with CH_2Cl_2 (3.0mL×2). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 1 : 1) to give colorless oil **19** (20mg, 59%).

^{1}H-NMR ($CDCl_3$) δ 0.0920 (s, 3H, Si-CH_3), 0.142 (s, 3H, Si-CH_3), 0.914 (s, 9H, -CH_3×3), 2.35-2.36 (d, *J*=4.03Hz, 1H, -OH), 2.45 (s, 1H, -OH), 2.92-2.98 (dd, *J*=9.16, 9.34Hz, 1H, -CH), 3.29-3.33 (dd, *J*=2.93, 9.52Hz, 1H, -CH), 3.40 (s, 3H, -OCH_3), 3.45-3.51 (td, *J*=3.30, 9.71Hz, 1H, -CH), 3.60 (s, 3H, -OCH_3), 3.62-3.69 (t, *J*=9.52Hz, 1H, -CH), 3.80 (s, 3H, -OCH_3), 3.84-3.90 (t, *J*=9.16Hz, 1H, -CH), 4.18 (brs, 1H, -CH), 4.63-4.67 (d, *J*=10.8Hz, 1H, -CH), 4.68-4.70 (d, *J*=6.78Hz, 1H, -CH), 4.77-4.79 (d, *J*= 6.78Hz, 1H, -CH), 4.86-4.90 (d, *J*=11.0Hz, 1H, -CH), 6.88-6.91 (dd, *J*=2.02, 8.61Hz, 2H, Bn-H×2), 7.29- 7.33 (dd, *J*=2.93, 8.61Hz, 2H, Bn-H×2).

^{13}C-NMR ($CDCl_3$) δ -4.36 (Si-CH_3), -4.26 (Si-CH_3), 18.1 (Si-C), 26.0 (-CH_3), 55.3 (-OCH_3), 55.7 (-OCH_3), 61.5 (-OCH_3), 71.1 (-CH), 71.5 (-CH), 73.2 (-CH), 75.0 (-OCH_2), 79.9 (-CH), 81.3 (-CH), 85.6 (-CH), 98.0 (-OCH_2), 114 (Bn), 130 (Bn), 131 (Bn), 159 (Bn).

IR (film) 3450 cm^{-1}.

HRMS (FAB) calcd for $C_{23}H_{40}NaO_8Si$ $(M+Na)^+$: 495.2390. Found: 495.2428.

(1R*,2S*,3S*,4R*,5S*,6R*)-3-(_tert_-butyldimethylsilyloxy)-6-hydroxy-4-methoxy-5-(4-methoxybenzyloxy)-2-(methoxymethoxy)cyclohexyl acetate (20)

Compound **19** (20mg, 42μmol) was dissolved in toluene (12mL) and dibutyltin(IV) oxide (13mg, 51μmol) was added. The solution was heated at reflux for 3 hours while the water formed was removed by using the Dean-Stark apparatus. The solvent was removed by evaporation. The mixture was dissolved in CH_2Cl_2 (2.0mL) under argon atmosphere and AcCl (4.6μl, 63μmol) was added at -41°C and the solution was stirred for 24 hours. The solution was concentrated in vacuo and then dried for 24 hours in vacuo. The residue was purified by silica gel chromatography (Hexane : AcOEt = 3:1) to give yellow oil **20** (8.6mg, 39%).

^{1}H-NMR ($CDCl_3$) δ 0.0841 (s, 3H, Si-CH_3), 0.136 (s, 3H, Si-CH_3), 0.910 (s, 9H, -CH_3×3), 2.06 (s, 3H, -CH_3), 2.33 (s, 1H, -OH), 2.98-3.04 (dd, *J*=9.16, 9.34Hz, 1H, -CH), 3.35-3.39 (dd, *J*=2.93, 9.16Hz, 1H, -CH), 3.38 (s, 3H, -OCH_3), 3.57 (s, 3H, -OCH_3), 3.79

(s, 3H, -OCH_3), 3.82-3.87 (dd, *J*=7.51, 9.16Hz, 1H, -CH), 3.87-3.90 (dd, *J*=7.88, 9.52Hz, 1H, -CH), 4.18-4.20 (dd, *J*=2.56, 2.75Hz, 1H, -CH), 4.60-4.63 (d, *J*=11.0Hz, 1H, -CH), 4.67-4.69 (d, *J*=6.78Hz, 1H, -CH), 4.73-4.77 (d, *J*= 10.8Hz, 1H, -CH), 4.76-4.78 (d, *J*=6.59Hz, 1H, -CH), 4.85-4.90 (dd, *J*=2.75, 10.4Hz, 1H, -CH), 6.85-6.88 (dd, *J*=2.75, 8.79Hz, 2H, Bn-H×2), 7.21- 7.24 (dd, *J*=2.75, 8.61Hz, 2H, Bn-H×2).

^{13}C-NMR ($CDCl_3$) δ -4.35 (Si-CH_3), -4.28 (Si-CH_3), 18.1 (Si-C), 21.1(-CH_3), 25.9 (-CH_3), 55.3 (-OCH_3), 55.8 (-OCH_3), 61.7 (-OCH_3), 70.1 (-CH), 72.9 (-CH), 72.9 (-CH), 75.0 (-OCH_2), 79.2 (-CH), 79.9 (-CH), 85.3 (-CH), 98.0 (-OCH_2), 114 (Bn), 129 (Bn), 131 (Bn), 159 (Bn), 170 (O-C=O).

IR (film) 1746, 3391 cm^{-1}.

HRMS (FAB) calcd for $C_{25}H_{42}NaO_9Si$ $(M+Na)^+$: 537.2496. Found: 537.2527.

Acknowledgment

This work is supported in part by a Grant-in-Aid for Scientific Research (B) (23390028) (to M. O.) from Japan Society for promotion of Science, by a Grant-in-Aid for Exploratory Research (19659025) (to M.O.) from the Japan Society for Promotion of Science, and by the aid of a special fellowship (to K. A.) granted by Kumamoto Health Science University for culture, education and science.

References

(1) Prestwich, G. D. *Acc. Chem. Res.* **1996**, *29*, 503.
(2) Potter, B. V. L.; Lampe, D. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1933.
(3) Mikoshiba, K. *Trends Pharmacol. Sci.* **1993**, *14*, 1986.
(4) Anraku, K.; Inoue, T.; Sugimoto K.; Morii, T.; Mori, Y.; Okamoto, Y.; Otsuka, M. *Org. Biomol. Chem.*, **2008**, *6*, 1822.
(5) Anraku, K.; Inoue, T.; Sugimoto, K.; Kudo, K.; Okamoto, Y.; Morii, T.; Mori, Y.; Otsuka M. *Bioorg. Med. Chem.*, **2011**, *19*, 6833.
(6) Anraku, K.; Fukuda, R.; Takamune, N.; Misumi, S.; Okamoto, Y.; Otsuka, M.; Fujita. M. *Biochemistry*, **2010**, *49*, 5109.
(7) (a) Inoue, T.; Kikuchi, K.; Hirose, K.; Iino, M.; Nagano, T. Bioorg. Med. Chem. Lett. 1999, 9, 1697. (b) Han, F.; Hayashi, M.; Watanabe, Y. Tetrahedron. 2003, 59, 7703. (c) Dorman, G.; Chen, J.; Prestwich, G. D. Tetrahedron Lett. 1995, 36, 8719. (d) Thum, O.; Chen, J.; Prestwich, G. D. Tetrahedron Lett. 1996, 37, 9017. (e) Ley, S. V.; Sternfeld, L. Tetrahedron Lett. 1988, 29, 5305. (f) Carless, H. A. J.; Busia, K. Tetrahedron Lett. 1990, 31, 3449-3452.
(8) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. J. Am. Chem. Soc., **1979**, *101* (23), 6996.
(9) The stereochemistry of **3a** and **3b** was assigned by comparing with the closely related known compound whose stereochemistry has already been established by Danishefsky.[8]
(10) (a) Paquette, L. A.; Ho-Shen Lin; Gunn, B. P.; Coghlan, M. *J. J. Am. Chem. Soc.* **1988**, *110*, 5818. (b) Pennanen, S. I. *Tetrahedron Lett.* **1980**, *21*, 657. (c) Rubuttom, G. M.; Gruber, J. M. *Tetrahedron Lett.* **1978**, *19*, 4603. (d) Rubuttom, G. M.; Vazquez, M. A.; Pelegria, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319.
(11) The relative stereochemistry of **4a** and **4b** was assigned based on the NMR coupling constants.
(12) Acena, J. A.; Arjona, O.; Manas, R.; Plumet, J. *J. Org. Chem.* **2000**, *65*, 2580.
(13) The relative stereochemistry of **5a** and **5b** was assigned based on the NMR coupling constants.
(14) Giner, J. L. *J. Org. Chem.* **2005**, *70*, 721.
(15) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.;Naito, T. *J. Org. Chem.* **2000**, *65*, 6922.
(16) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.
(17) Armstrong, A.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020.
(18) The stereochemical assignment of **15a** and **15b** was based on the NMR coupling constants.
(19) Nagashima, N.; Ohno, M. *Chem. Lett.* **1987**, *16*, 141.
(20) Stereochemical assignment of **17a** was tentative at this stage. The stereochemistry was established at later stage of compound **19**.