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ASYMMETRIC SYNTHESIS OF 2-PROPYLISOFAGOMINE USING ALLYLIC HYDROXY GROUP ACCELERATED RING-CLOSING ENYNE METATHESIS≠

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Abstract – An asymmetric synthesis of 2-propylisofagomine **5** using allylic hydroxy group accelerated ring-closing enyne metathesis (AHA-RCEM) was conducted with high diastereoselectivity in 13% overall yield starting from the commercially available (*E*)-hex-2-ol.

INTRODUCTION

Iminosugars belong to the family of polyhydroxylated alkaloids. Many iminofuranose and iminopyranose analogs are potent α- and β-glycosidase inhibitors[1] and also have antidiabetic, anticancer, and antiviral properties. *N*-Butyl-1-deoxynojirimycin (DNJ) **1** (Zavesca™) is used in the treatment of Gaucher disease. Another iminosugar, Miglitol **2**, which is commercially available in the USA and Canada, is used for the treatment of type II diabetes (GLYSET™). In addition, *Galacto*-DNJ (Migalastat) **3** has been shown to inhibit lysosomal a-galactosidase and is currently in phase III clinical trials for the treatment of Fabry's disease (Figure 1).[2] The chemical and biological properties of iminosugars have been extensively reviewed in past years.[3]

The search for anomer selective β-glycosidase inhibitors has led to the development of a new class of sugar-mimics, 1-*N*-iminosugars with a nitrogen atom at the anomeric position. The first example of such compounds, the 1-*N*-iminosugar isofagomine **4**, was first designed by Bols *et al*.[4] as an apparent transition

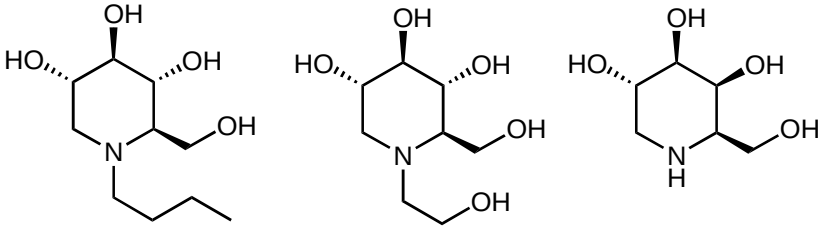


Figure 1. Clinical drugs of iminosugars

state analog that mimics the carbocationic form of the oxycarbenium-like transition state in which the positive charge resides at the anomeric carbon. Isofagomine has been found to be a selective and very strong inhibitor of β-glucosidase [K_i = 0.11 mM, from sweet almonds][4] and isofagomine derivatives have recently received a great deal of attention because they are new candidates for the therapeutic treatment of Gaucher's disease. They are currently in Phase II of clinical development. Gaucher's disease is a lysosomal storage disorder caused by inherited genetic mutations in the GBA gene, which results in deficient activity of glucocerebrosidase (GCase). Deficient GCase activity leads to the progressive accumulation of glucosylceramide (GlcCer). A very promising therapeutic strategy of the treatment of Gaucher's disease involves the use of small molecule pharmacological chaperones, often competitive enzyme inhibitors, to facilitate the proper folding and trafficking of the lysosomal enzymes.[5] In Gaucher's disease, disfunctional lysosomes cause hepatosplenomegaly, anaemia, bone lesions, and, in more severe cases, central nervous system impairment.[6] It has been reported that isofagomine is a more effective pharmacological chaperone for GCase.[7] As a consequence, the development of new stereoselective and versatile procedures for the synthesis of isofagomine-type iminosugars constitutes an area of considerable interest.[8] Recently, the synthesis of 6-alkyl isofagomines and their potent inhibition for Gcase were reported.[9] However, the synthesis of 2-alkyl isofagomines remains unexplored. Here we wish to report a synthesis of 2-propylisofagomine **5** using allylic hydroxy group accelerated ring-closing enyne metathesis (AHA-RCEM) developed by us[10] (Figure 2).

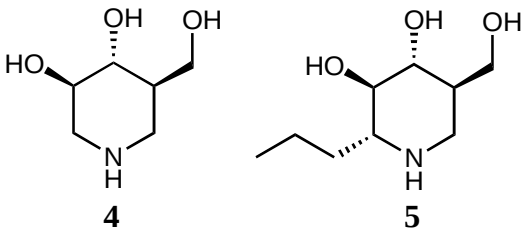
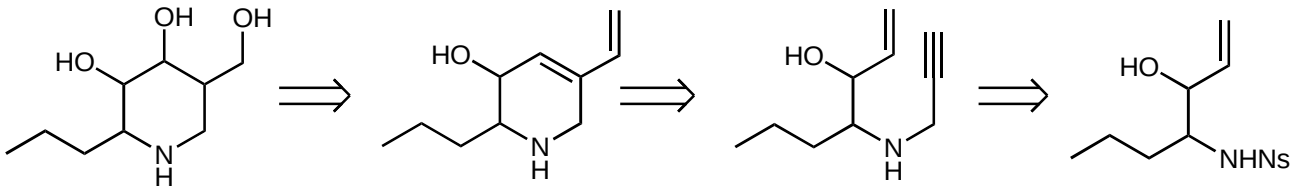


Figure 2. Structures of isofagomine and 2-propylisofagomine

RESULTS AND DISCUSSION

Our strategy for the synthesis of 2-propylisofagomine is outlined in Scheme 1, which shows that the desired iminosugars **A** can be produced from cyclic diene **B** by several operation. The piperidene core could be prepared by the AHA-RCEM of the terminal alkyne **C** as a key step. Therefore, we embarked on a synthesis of the precursor C, which is available from the known chiral *N*-nosyl allylic amine **D**.



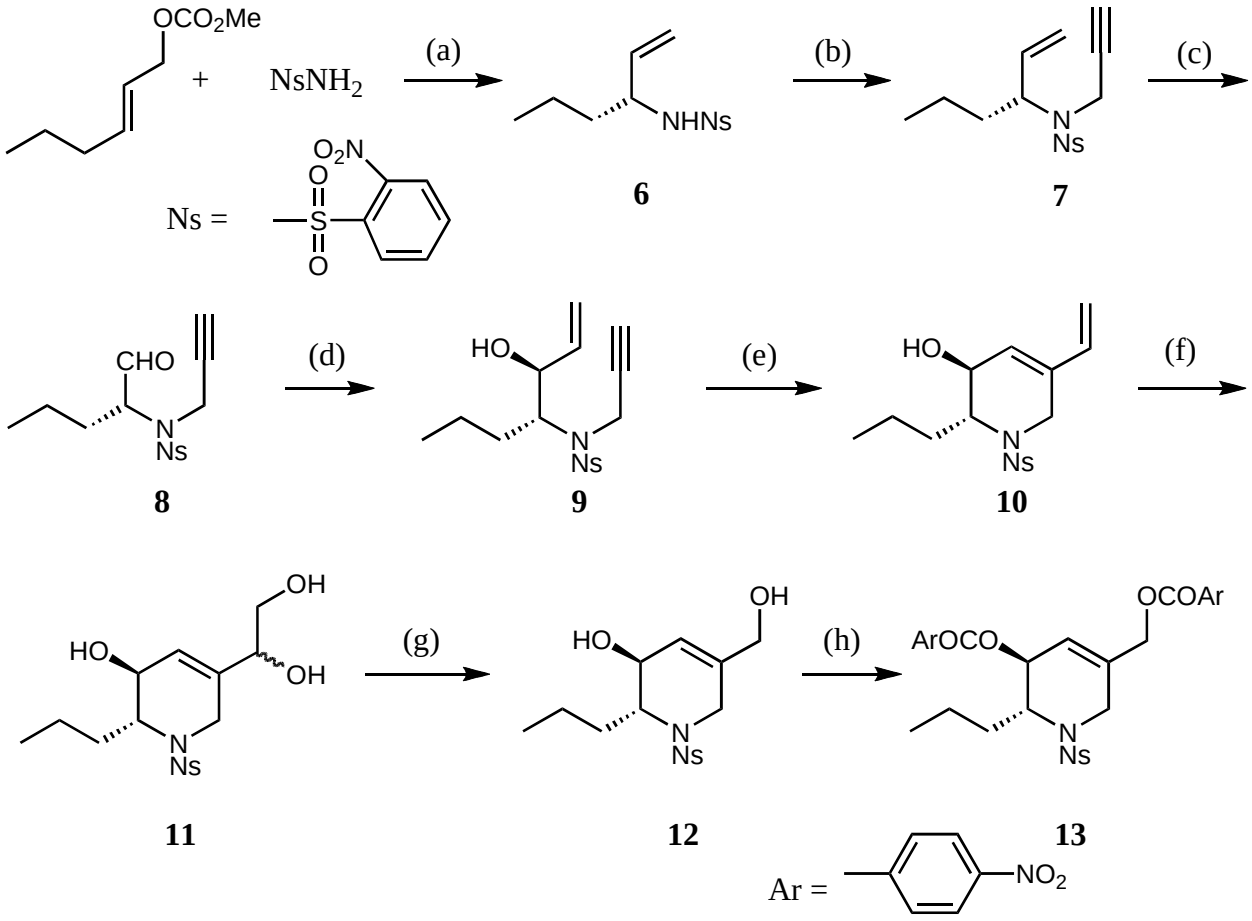
A **B** **C** **D**

Scheme 1. Retrosynthesis of 2-propylisofagomines

In initial experiments, an asymmetric allylic amination between *N*-(*o*-nosyl)amine and carbonate provided the known (*R*)-*N*-hexenylnosylamide **6** in 82% yield with 94% ee using the procedure reported by Weihofen *et al*.[11] The propargylation of **6** with propargyl bromide in the presence of potassium carbonate quantitatively gave the acetylene product **7** in quantitative yield, which, on ozonolysis, afforded the aldehyde **8** in 88% yield.[12] The vinylation of **8** with vinylmagnesium chloide in THF at –78 °C proceeded stereoselectively to give the allyl alcohol **9** as a single diasterteomer in 66% yield. Although the stereochemistry of **9** remains unclear in this stage, we tentatively concluded that it is 3*S*,4*R* in the light of the Felkin-Anh model. Having the precursor **9**, the AHA-RCEM of **9** was carried out using Grubb's I (10 mo%) as a catalyst at room temperature in a short reaction time to afford cyclic diene **10** in 85% yield. Treatment of **10** with AD-mix-β as a bulky oxidant resulted in the highly regioselective dihydroxylation of terminal olefin to provide diol **11** (81%).[13] Oxidative cleavage of the diol **11** with $NaIO_4$, followed by reduction with $NaBH_4$, gave the allyl alcohol **12** (94% over two steps). In this stage, the stereochemistry of **12** was determined by a X-ray crystallographic analysis of **13** obtained by the di-*p*-nitrobenzoate to be 2*R*,3*S* (Figure 3).

With **12** in hand, we attempted to perform a hydroxylation at the 4 position of **12** by hydroboration followed by oxidation. The olefin **12** was treated with BH_3-THF complex (6 equiv.) at room temperature for 13 h, followed by oxidation with 3 M NaOH and 30% H_2O_2 to give a separable mixture of triols **14a** and **14b** in 72% yield.[14] Unfortunately, a ratio of the two diastereomeric triols was about 1:1 with no selectivity. We concluded that **14a** was produced *via* transition state **A** with chelation between the hydroxy group at the 3 position and the borane reagent. Accordingly, the preparation of the desired triol

14b resulted in low selectivity. Therefore, we hypothesized that the hydroboration of a protected silyl ether **15** could preferentially produce the desired isomer *via* transition state **B** due to steric repulsion between boran reagent and bulky *O*-silylated group. In practice, the hydroboration-oxidation of **15** produced the expected product **16** as a single isomer in 60% yield. Removal of the TBDPS group by treatment with TBAF smoothly furnished the triol **17** in 96% yield. Finally, deprotection of Ns group with benzenethiol in the presence of K_2CO_3 gave the desired 2-propylisofagomine **5** in 82% yield. Since a nuclear Overhauser effect (NOE) was observed between axial hydrogens at the 2 and 4 positions and also between axial hydrogenes at 3 and 5 positions as shown in Figure 3, the stereochemistry of **5** was confirmed to be 2*R*,3*R*,4*R*,5*R*. In addition, **14a** was transformed with denosylation into **18** in 90% yield.



Scheme 2. (a) *o*-$NsNH_2$/1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD)/cat. $[Ir(COD)Cl]_2$/(*S*,*S*,*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-3,4-a']dinaphtalen-4-yl)bis(1-phenylethyl)amine/Et_3N/THF/82%, (b) propargyl bromide/ K_2CO_3/MeCN/quant., (c) O_3/ Me_2S/ CH_2Cl_2/88%, (d) vinylmagunesium chloride/THF/66%, (e) cat. Grubbs'1st/CH_2Cl_2/82%, (f) AD-mix-b®/*tert*-BuOH-H_2O/81%, (g) (1) $NaIO_4$/EtOH-H_2O, (2) $NaBH_4$/ EtOH-H_2O/94%, (h) *p*-nitorobenzoyl chloride/ DMAP/ CH_2Cl_2/99%

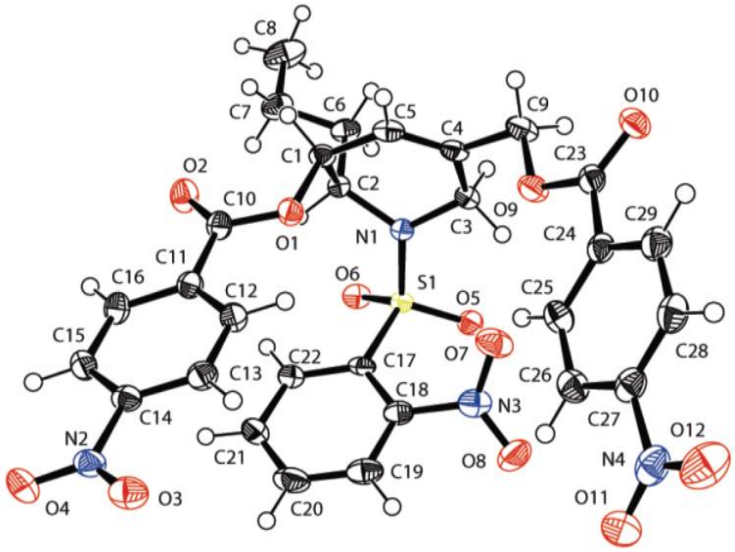


Figure 3. ORTEP diagram of **13**

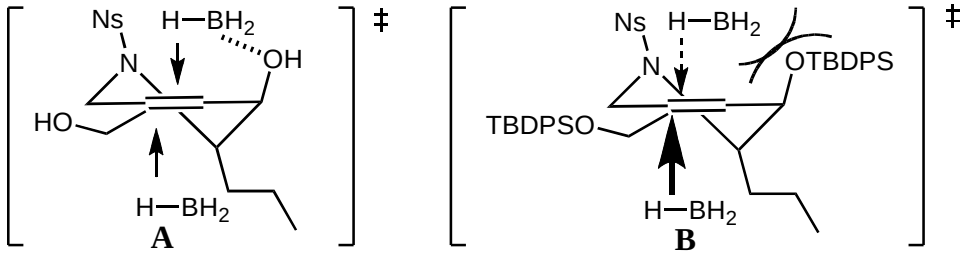
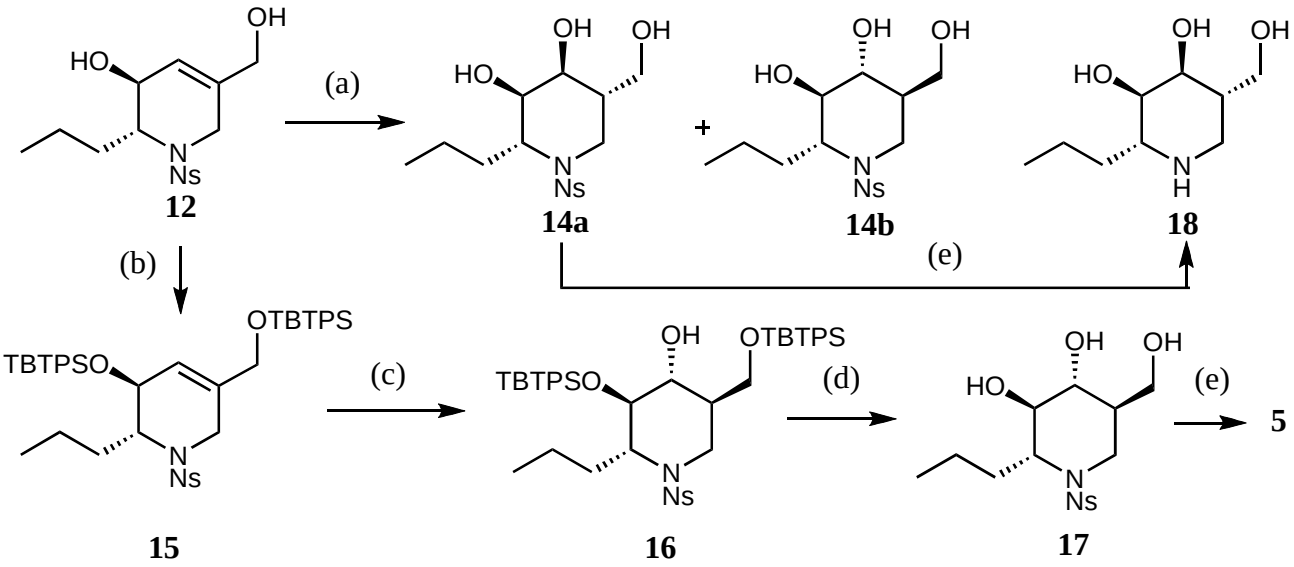
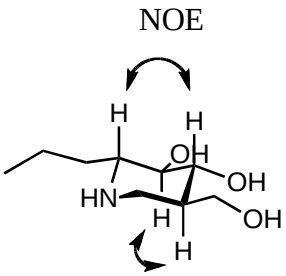


Figure 4. Transition state in the hydroboration of **12** and **15**



Scheme 3. (a) (1)BH_3-THF/THF, (2) 3M NaOH/30% H_2O_2/37% for **14a**/35%, for **14b**, (b) TBDPSCl/imidazole/DMAP/ CH_2Cl_2/93%, (c) BH_3-THF/THF, (2) 3M NaOH/30% H_2O_2/60%, (d) TBAF/THF/96%, (e) benzenethiol/K_2CO_3/MeCN/82%/ for **5**, for 90% for **18**



5

Figure 5. NOE experiment of **5**

Having obtained the 2-propylisofagomines **5** and **18**, their ability to serve as inhibitors of several glucosidases was examined. The results are shown in Table 1. We were disappointed to find that 2-propylisofagimine **5** did not show potent inhibitory activity toward β-glucosidases in less than 50% inhibition at 1000 μM. Since isofagomine has been reported to be a very strong inhibitor of β-glucosidase, this finding was surprising. Although the reason remains unclear, the inhibitory activities would be strongly suppressed by the presence of a 2-propyl substituent. On the other hand, **18** exhibited moderate inhibition towards a-fucosidase (entry 8).

Table 1. Concentration of **5** and **18** for require to achieve 50% inhibition of several glycosidases

entry	enzyme	**5**	**18**
	β-glucosidase		
1	almond	NI	NI
2	bovine liver	NI	NI
3	rat intestinal cellobiase	NI	NI
	α-glucosidase		
4	rice	NI	NI
5	yeast	NI	NI
6	rat intestinal maltase	NI	NI
7	rat intestinal sucrase	NI	NI
	α-fucosidase		
8	bovine epididdymis	NI	253

NI: less than 50% inhibition at 1000 μM.

In summary, 2-propylisofagomine **5** was stereoselectively prepared from the carbonate in 13% overall yield using AHA-RCEM as a key step.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. Microanalyses were performed on a Perkin-Elmer CHN 2400 Elemental Analyzer. Optical rotations were measured with a JASCO DIP-360 or JASCO P-1020 digital polarimeter. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL JNM-AL 400 (400 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was carried out on Merck Silica gel 60 (230-400 mesh) or KANTO Silica Gel 60N (40-50 mm) for flash chromatography.

(*R*)-*N*-(Hex-1-en-3-yl)-2-nitorobenzenesulfonlyamide (6)

A mixture of dried TBD (62.0 mg, 0.45 mmol), $[Ir(COD)Cl]_2$ (68.2 mg, 0.10 mmol), (*S,S,S*)-(+)-(3,5-dioxa-4-phosphacyclohepta [2,1-3,4-a']dinaphtalen-4-yl)bis(1-phenylethyl)amine (111.4 mg, 0.41 mmol) in THF (5 mL) was stirred for 2 h under Ar. To the mixture were successively (*E*)-hex-2-enyl methyl carbonate (791.1 mg, 5.0 mmol)、*o*-nitrobenzenesulfonylamide (1.21 g, 6 mmol), and NEt_3 (0.71 mL, 5.0 mmol) and the whole was stirred at room temperature for 37 h. After evaporation, the residue was purified by silica gel chromatography (*n*-hexane : EtOAc = 15 : 1) to give **6** (1.17 g, 82%, 94% ee) as an oil; Pale yellow oil. $[\alpha]^{27}_D$ +122.7 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.25 Hz), 1.25-1.41 (2H, m), 1.47-1.54 (2H, m), 3.94-4.01 (1H, m), 4.91 (1H, d, *J* = 10.63 Hz), 5.01 (1H, d, *J* = 16.90 Hz), 5.27 (1H, d, *J* = 8.21 Hz), 5.53 (1H, ddd, *J* = 7.25, 9.66, 17.39 Hz), 7.68-7.73 (2H, m), 7.83-7.87 (1H, m), 8.08-8.12 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.6, 18.5, 37.7, 57.4, 116.2, 125.2, 131.0, 132.6, 133.3, 135.1, 137.3, 147.8. IR (neat) cm^{-1} : 3338, 2961, 1645, 1538, 1442, 1415, 1362, 1170. HPLC (Column AD-H): *n*-hexane : *i*-PrOH = 9 : 1, Flow Rate 1.5 mL/min, retention time 44.3 min (major), 48.7 min (minor), 33.9 °C, 254 nm. EI-MS (m/z) 284 (M^+). HRMS Calcd for $C_{12}H_{16}N_2O_4S$: 284.0831 Found 284.0836.

(*R*)-*N*-(Hex-1-en-3-yl)-2-nitro-*N*-(prop-2-ynyl)benzenesulfonlyamine (7)

To a mixture of **6** (1.10 g, 3.87 mmol) in acetonitrile (8.3 mL) was successively addd propargyl bromide (0.6 mL, 7.74 mmol) and K_2CO_3 (1.08 g, 7.74 mmol). The whole was refluxedfor 16 h. After filtration through cotton, the filtrate eas evaporated. The filtrate was purified with chromatography (*n*-hexane : EtOAc = 5 : 1) to yield **7** (1.25 g, quant.).

Pale yellow oil. $[\alpha]^{26}_D$ +59.8 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* = 7.25 Hz), 1.30-1.44 (2H, m), 1.65-1.77 (2H, m), 2.18 (1H, t, *J* = 1.93 Hz), 4.10 (1H, dd, *J* = 2.42, 81.14 Hz), 4.10 (1H, dd, *J* = 2.42, 46.36 Hz), 4.45 (1H, q, *J* = 6.76 Hz), 5.13-5.18 (2H, m), 5.81 (1H, ddd, *J* = 5.8, 11.11, 16.90, Hz), 7.62-7.69 (3H, m), 8.13-8.15 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.7, 19.4, 32.9, 33.8, 60.2, 72.5, 79.6, 118.1, 124.0, 131.3, 131.5, 133.5, 133.8, 135.5. IR (neat) cm^{-1} : 3292, 2961, 2935, 2124,

1642, 1547, 1439, 1425, 1373, 1164. EI-MS (m/z) 322 (M^+). HRMS Calcd for $C_{15}H_{18}N_2O_4S$: 322.0987 Found 322.0986.

(*R*)-2-Nitro-*N*-(1-oxopentan-2-yl)-*N*-(prop-2-ynyl)benzenesulfonamide (8)

A solution of **7** (1.22 g, 3.79 mmol) in CH_2Cl_2 (200 mL) was bubbled with ozone at –78 °C. After passing of excess ozone, Me_2S was slowly added to the solution at the same temperature. The whole was stirred at room temperature for 3 h. After evaporation, the residue was purified by silica gel chromatography (*n*-hexane : EtOAc = 40 : 1) to yield **8** (1.08 g, 88%).

Crystal. mp : 82-83 °C. $[\alpha]^{23}_D$ -61.2 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 7.25 Hz), 1.20-1.30 (1H, m), 1.38-1.47 (1H, m), 1.64-1.74 (1H, m), 1.97-2.06 (1H, m), 2.28 (1H, t, *J* = 2.42 Hz), 4.20 (1H, dd, *J* = 4.35, 10.63), 7.69-7.77 (3H, m), 4.22 (1H, dd, *J* = 2.42, 90.80 Hz), 4.22 (1H, dd, *J* = 2.42, 127.50 Hz), 8.14-8.16 (1H, m), 9.77 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.4, 19.0, 28.2, 34.8, 65.8, 74.5, 78.0, 124.6, 131.5, 132.0, 133.1, 134.1, 147.8, 199.8. IR (KBr) cm^{-1} : 3280, 2968, 2935, 2126, 1590, 1542, 1466, 1435, 1373, 1356, 1165. EI-MS (m/z) 324 (M^+). HRMS Calcd for $C_{14}H_{16}N_2O_5S$: 324.0780 Found 324.0767. Anal. Calcd for $C_{14}H_{16}N_2O_5S$: C, 51.84; H, 4.97; N, 8.64. Found C, 51.87; H, 4.93; N, 8.61.

***N*-(3*S*,4*R*)-3-(Hydroxyhept-1-en-4-yl)-2-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (9)**

Vinylmagunesium chloride (1.86 mL, 2.76 mmol) in THF (1.86 mL) was quickly added to a solution of **8** (300 mg, 0.92 mmol) in THF (9.2 mL) at -78 °C under Ar. Immediately, aq. NH_4Cl was added to the reaction mixture. After evaporation, water and CH_2Cl_2 were added to the residue. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 three tomes. The combined organic solvents were dried with Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (CH_2Cl_2 : Et_2O = 40 : 1) to yield **9** (215.1 mg, 66%). Pale yellow oil. $[\alpha]^{24}_D$ -62.2 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.80 (3H, t, *J* = 7.25 Hz), 1.03-1.09 (1H, m), 1.26-1.33 (1H, m), 1.46-1.52 (1H, m), 1.67-1.75 (1H, m), 2.12 (1H, d, *J* = 4.83 Hz), 2.21 (1H, t, *J* = 2.42 Hz), 3.91 (1H, dt, *J* = 2.89, 10.62 Hz), 4.36 (1H, dd, *J* = 2.42, 124.60 Hz), 4.36 (1H dd, *J* = 2.42, 86.93 Hz), 4.57 (1H, sex, *J* = 2.42 Hz), 5.20 (1H, dt, *J* = 1.45, 10.62 Hz), 5.33 (1H, dt, *J* = 1.45, 15.94 Hz), 5.95 (1H, ddd, *J* = 4.35, 10.62, 17.39 Hz), 7.61-7.63 (1H, m), 7.69 (2H, ddd, *J* = 2.42, 3.86, 6.76), 8.17-8.20 (1 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 19.1, 27.1, 33.6, 61.7, 72.2, 75.1, 80.0, 115.6, 123.8, 131.4, 131.5, 133.2, 133.8, 137.9, 147.8. IR (neat) cm^{-1} : 3546, 3291, 2961, 1544, 1438, 1373, 1347, 1160. EI-MS (m/z) 352 (M^+). HRMS Calcd for $C_{16}H_{20}N_2O_5S$: 352.1093 Found 352.1096.

(2*S*,3*S*)-1-(2-Nitrophenylsulfonyl)-2-propyl-5-vinyl-1, 2, 3, 6-tetrahydropyridin-3-ol (10)

A mixture of **9** (247.4 mg, 0.70 mmol) and Grubbs'1st (57.6 mg, 0.070 mmol) in CH_2Cl_2 (35 mL) was stirred at roomtemperature for 2.5 h under Ar. After evaporation, the residue was purified by silica gel chromatography (CH_2Cl_2 : EtOAc = 40 : 1) to yield **10** (202.3 mg, 82%).

Oil. $[\alpha]^{26}_{D}$ +78.6 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.84 (3H, t, *J* = 7.25 Hz), 1.18-1.50 (4H, m), 2.16 (1H, d, *J* = 9.66 Hz), 3.80 (1H, d, *J* = 17.87), 3.94-4.00 (2H, m), 4.49 (1H, d, *J* = 17.87 Hz), 5.22 (1H, d, *J* = 11.11 Hz), 5.32 (1H, d, *J* = 17.39 Hz), 5.86 (1H, d, *J* = 5.31 Hz), 6.31 (2H, dd, *J* = 11.11, 17.89 Hz), 7.63-7.73 (3H, m), 8.16-8.18 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8, 19.5, 31.4, 40.1, 59.2, 66.2, 115.2, 124.2, 125.2, 131.5, 131.8, 133.5, 133.7, 135.4, 135.7, 147.7. IR (neat) cm^{-1} : 3539, 2961, 2929, 1609, 1543, 1439, 1372, 1345, 1163. EI-MS (m/z) 352 (M^+). HRMS Calcd for $C_{16}H_{20}N_2O_5S$: 352.1093 Found 352.1096.

1-((5*S*,6*R*)-5-Hydroxy-1-(2-nitrophenylsulfonyl)-6-propyl-1,2,5,6-tetrahydropyridin-3-yl)ethane-1,2-diol (11)

A mixture of **10** (56 mg, 0.159 mmol) and AD-mix-β® (513 mg) in *t*-BuOH (0.8 mL) and H_2O (0.8 mL) was stirred at room temperature for 12 h. After addition of Na_2SO_3 (253 mg), Na_2SO_4 was added to the mixture. The whole was filtrated through Celite and the filtrate was evaporated. The residue was purified by silica gel chromatography (CH_2Cl_2 : MeOH = 15 : 1) to yield **11** (49.8 mg, 81%).

Amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83-0.87 (6H, m), 1.23-1.49 (8H, m), 3.64-3.80 (6H, m), 3.89-3.92 (4H, m), 4.20-4.33 (4H, m), 5.93-5.97 (2H, m), 7.65-7.72 (6H, m), 8.16-8.18 (2H, m). EI-MS (m/z) 368 (M^+ -H_2O). HRMS Calcd for $C_{16}H_{20}N_2O_6S$ (-H_2O) : 368.1042 Found 368.1048.

(2*R*,3*R*)-5-(Hydroxymethyl)-1-(2-nitrophenylsulfonyl)-2-propyl-1,2,3,6-tetrahydropyridin-3-ol (12)

A mixture of **11** (141.8 mg, 0.37 mmol) and $NaIO_4$ (119.3 mg, 0.56 mmol) in EtOH (2.6 mL) and H_2O (2.6 mL) was stirred at room temperature for 1.5 h. $NaBH_4$ (22.1 mg, 0.56 mmol) was added to the reaction mixture and the the whole was stirred at room temperature for 0.5 h. After evaporation, water and CH_2CH_2 were added to the residue. The mixture was separated and the aqueous layer was extracted with CH_2CH_2 6 times. The combined organic solvents were dried with Na_2SO_4 and evaporated. The residue was washed with a small amounts of Et_20 and CH_2Cl_2 to yield and dried in vauo to yield **8a** (123.8 mg, 94%). Needle crystal. mp: 180-181 °C. $[\alpha]^{26}_{D}$ +32.2 (*c* 1.0, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, t, *J* = 7.25 Hz), 1.21-1.25 (2H, m), 1.34-1.39 (2H, m), 2.08 (1H, d, *J* = 9.18 Hz), 3.70 (1H, d, *J* = 18.35 Hz), 3.93 (2H, t, *J* = 6.77 Hz), 4.16 (2H, s), 4.31 (1H, d, *J* = 18.35 Hz), 5.90 (1H, d, *J* = 5.80 Hz), 7.63-7.71 (3H, m), 8.16-8.19 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.6, 19.4, 31.3, 40.9, 59.2, 63.1, 65.3, 119.7, 123.9, 131.0, 131.7, 133.4, 135.2, 138.5, 147.8. IR (KBr) cm^{-1} : 3281, 2965, 2935, 1544, 1461, 1435, 1374, 1350, 1161. EI-MS (m/z) 338 (M^+ -H_2O). HRMS Calcd for $C_{15}H_{18}N_2O_5S$ (-H_2O): 338.0936 Found 338.0929. Anal. Calcd for $C_{15}H_{20}N_2O_6S$: C, 50.55; H, 5.66; N, 7.86. Found C, 50.62; H, 5.61; N, 7.83.

((5*S*,6*R*)-5-(4-Nitrobenzoyloxyl)-1-(2-nitrophenylsulfonyl)-6-propyl-1,2,5,6-tetrahydropyridin-3-yl)-methyl 4-nitrobenzenoate (13)

A mixture of 12 (88.4 mg, 0.25 mmol), DMAP (77.1 mg, 0.63 mmol), and *p*-nitorobenzoyl chloride

(118.0 mg, 0.63 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. Aqueous $NaHCO_3$, water, and CH_2Cl_2 were successively added to the mixture and the whole was separated. The aqueous layer was extracted with CH_2Cl_2 twice and the combined organic solvents were dried with Na_2SO_4. After evaporation, the residue was purified by silica gel chromatography (CH_2Cl_2) to yield **13** (161.2 mg, 99%). Crystal. mp: 163-165 °C. $[\alpha]^{28}_D$ +150.7 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J* = 7.25 Hz), 1.32-1.45 (2H, m), 1.56-1.62 (2H, m), 3.84 (1H, d, *J* = 18.35 Hz), 4.30 (1H, t, *J* = 7.25 Hz), 4.56 (1H, d, *J* = 18.35), 4.95 (2H, s), 5.32 (1H, d, *J* = 5.80 Hz), 6.10 (1H, d, *J* = 5.31 Hz), 7.47-7.54 (2H, m), 7.58-7.61 (1H, m), 8.01-8.04 (3H, m), 8.19-8.22 (2H, m), 8.31 (4H, q, *J* = 9.18 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 19.6, 31.6, 41.4, 55.6, 65.7, 68.6, 77.2, 119.4, 123.4, 123.7, 124.4, 131.0, 131.8, 133.4, 134.3, 134.9, 137.6, 150.6, 150.8, 164.2, 164.3. IR (KBr) cm^{-1} : 2962, 1721, 1608, 1528, 1439, 1349, 1162. EI-MS (m/z) 654 (M^+). HRMS Calcd for $C_{29}H_{26}N_4O_{12}S$: 654.1268 Found 654.1293. Anal. Calcd for $C_{29}H_{26}N_4O_{12}S$: C, 53.21; H, 4.00; N, 8.56. Found C, 53.18; H, 3.78; N, 8.48.

Table 2. Crystal data and structure refinement for **13**

Identification code	a0808291kwh	
Empirical formula	C29 H26 N4 O12 S	
Formula weight	654.60	
Temperature	120 K	
Wavelength	0.71073 ≈	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 11.3639(14) ≈	α= 90°.
	b = 11.6881(15) ≈	β= 109.783(1)°.
	c = 12.0016(15) ≈	γ = 90°.
Volume	1500.0(3) ≈^{3}	
Z	2	
Density (calculated)	1.449 Mg/m^3	
Absorption coefficient	0.180 mm^{-1}	
F(000)	680	
Crystal size	0.30 x 0.30 x 0.05 mm^3	
Theta range for data collection	1.80 to 27.27°.	
Index ranges	-13<=h<=14, -8<=k<=14, -15<=l<=14	
Reflections collected	7464	
Independent reflections	4125 [R(int) = 0.0166]	
Completeness to theta = 25.00∞	99.2%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	4125 / 1 / 416
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0270, wR2 = 0.0665
R indices (all data)	R1 = 0.0299, wR2 = 0.0682
Absolute structure parameter	-0.01(6)
Largest diff. peak and hole	0.178 and -0.282 e.$\approx^{-3}$

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for **13**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9178(2)	13038(2)	5470(2)	22(1)
C(2)	8765(2)	11868(2)	4921(2)	21(1)
C(3)	10755(2)	10981(2)	6295(2)	25(1)
C(4)	11236(2)	12178(2)	6575(2)	24(1)
C(5)	10539(2)	13093(2)	6192(2)	24(1)
C(6)	9024(2)	11719(2)	3759(2)	25(1)
C(7)	8030(2)	12298(2)	2724(2)	34(1)
C(8)	8281(3)	12149(3)	1570(2)	49(1)
C(9)	12571(2)	12284(2)	7388(2)	29(1)
C(10)	7371(2)	13719(2)	5850(2)	24(1)
C(11)	6842(2)	14000(2)	6802(2)	23(1)
C(12)	7552(2)	13930(2)	7995(2)	25(1)
C(13)	7030(2)	14228(2)	8848(2)	26(1)
C(14)	5799(2)	14571(2)	8470(2)	24(1)
C(15)	5060(2)	14641(2)	7291(2)	26(1)
C(16)	5599(2)	14351(2)	6448(2)	26(1)
C(17)	7776(2)	10374(2)	6980(2)	21(1)
C(18)	8231(2)	10203(2)	8201(2)	25(1)
C(19)	7502(2)	10422(2)	8896(2)	32(1)
C(20)	6326(2)	10878(2)	8388(2)	40(1)
C(21)	5867(2)	11091(2)	7187(2)	37(1)
C(22)	6578(2)	10811(2)	6480(2)	28(1)
C(23)	13566(2)	12455(2)	9460(2)	25(1)
C(24)	13391(2)	12432(2)	10638(2)	24(1)
C(25)	12275(2)	12046(2)	10752(2)	29(1)
C(26)	12176(2)	11938(2)	11867(2)	31(1)
C(27)	13186(2)	12235(2)	12839(2)	29(1)

C(28)	14281(2)	12674(2)	12751(2)	32(1)
C(29)	14379(2)	12765(2)	11635(2)	31(1)
N(1)	9381(1)	10978(2)	5804(2)	22(1)
N(2)	5244(2)	14901(2)	9375(2)	29(1)
N(3)	9521(2)	9843(2)	8838(2)	31(1)
N(4)	13108(2)	12033(2)	14029(2)	36(1)
O(1)	8546(1)	13322(1)	6313(1)	26(1)
O(2)	6819(1)	13826(2)	4807(1)	34(1)
O(3)	5925(1)	14899(2)	10417(1)	34(1)
O(4)	4134(1)	15153(2)	9038(1)	40(1)
O(5)	9391(1)	9012(1)	6559(1)	25(1)
O(6)	7572(1)	9718(1)	4900(1)	27(1)
O(7)	10363(1)	10365(2)	8628(1)	40(1)
O(8)	9696(2)	9088(2)	9582(2)	50(1)
O(9)	12497(1)	12286(2)	8572(1)	30(1)
O(10)	14565(1)	12599(1)	9327(1)	30(1)
O(11)	12194(2)	11527(2)	14100(2)	45(1)
O(12)	13981(2)	12356(2)	14884(1)	53(1)
S(1)	8560(1)	9919(1)	5994(1)	19(1)

(2*R*,3*R*,4*S*,5*S*)-5-(Hydroxymethyl)-1-(2-nitrophenylsulfonyl)-2-propypiperidine-3,4-diol (14a) and (2*R*,3*R*,4*R*,5*R*)-5-(Hydroxymethyl)-1-(2-nitrophenylsulfonyl)-2-propypiperidine-3,4-diol (14b). BH_3·THF (1.90 mL, 3.42 mmol) was dropwise added to a solution of **12** (204.3 mg, 0.57 mmol) in THF (1.93 mL) at 0 °C. The whole was stirred at room temperature for 13 h. 3M NaOH (1.90 mL, 5.7 mmol) and 30% H_2O_2 (1.90 mL, 57 mmol) were successively added to reaction mixture at 0 °C and thn the whole was stirred at room temperature for 2.5 h. After evaporation, water and CH_2Cl_2 were added to the residue. The mixture separated and the aqueous layer was extracted with CH_2Cl_2 6 times. The combined organic solvents were dried with Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (CH_2Cl_2 : MeOH= 20 : 1) to yield **14a** (79.0 mg, 37%) and **14b** (74.7 mg, 35%). **(14a):** Amorphous. $[\alpha]^{26}_D$ -27.5 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 7.25 Hz), 1.20-1.35 (3H, m), 2.21-2.03 (1H, m), 2.64 (1H, d, *J* = 3.86 Hz), 2.90 (1H, dd, *J* = 12.56, 14.49 Hz), 3.05 (1H, d, *J* = 6.76 Hz), 3.49 (2H, d, *J* = 5.31 Hz), 3.73 (1H, ddd, *J* = 3.86, 6.76, 10.63 Hz), 3.79-3.93 (4H, m), 4.10-4.13 (1H, m), 7.60-7.62 (1H, m), 7.67-7.70 (2H, m), 8.12-8.14 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8, 19.5, 30.8, 39.0, 41.5, 59.6, 63.5, 69.7, 70.0, 123.9, 131.4, 131.6, 133.4, 133.9, 147.8. IR (KBr) cm^{-1} : 3445, 2964, 2938, 1544, 1467, 1439, 1368, 1167. EI-MS (m/z) 374 (M^+). HRMS Calcd for $C_{15}H_{22}N_2O_7S$: 374.1148 Found 374.1161. **(14b):** Amorphous. $[\alpha]^{26}_D$ -126.7 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$)

δ: 0.73 (3H, t, *J* = 7.25 Hz), 0.84-0.92 (1H, m), 1.00-1.14 (2H, m), 1.93 (1H, q, *J* = 5.31), 3.56-3.69 (3H, m), 3.73-3.84 (3H, m), 3.79-3.92 (3H, m), 4.11 (1H, t, *J* = 7.32 Hz), 7.65-7.70 (3H, m), 8.07-8.09 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.6, 19.5, 32.1, 41.1, 42.2, 60.9, 61.9, 71.1, 72.0, 124.0, 130.6, 131.6, 133.4, 134.0, 147.5. IR (KBr) cm^{-1} : 3392, 2936, 1542, 1372, 1168. EI-MS (m/z) 374 (M^+). HRMS Calcd for $C_{15}H_{22}N_2O_7S$: 374.1148 Found 374.1161.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-1-(2-nitrophenyl-sulfonyl)-2-propyl-1,2,3,6-tetrahydropyridine (15) A mixture of **12** (181 mg, 0.51 mmol), imidazole (90.8 mg, 1.32 mmol), DMAP (22.6 mg, 0.18 mol) and TBDPSCl (0.34 mL, 1.27 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 8 h. The mixture was filtrated through celite and the filtrate was washed with brine. The washed solvent was dried with Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (*n*-hexane : EtOAc = 10 : 1) to yield **15** (393.5 mg, 93%). Oil. $[\alpha]^{27}_D$ -1.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.77 (3H, t, *J* = 7.25 Hz), 0.96 (9H, s), 1.01 (9H, s), 1.12-1.26 (4H, m), 3.66 (1H, d, *J* = 18.35 Hz), 3.83 (1H, d, *J* = 18.35 Hz), 3.97 (1H, d, *J* = 5.31 Hz), 4.05 (2H, d, *J* = 13.04 Hz), 4.21 (1H, t, *J* = 7.25 Hz), 5.65 (1H, d, *J* = 4.83 Hz), 7.32-7.46 (13H, m), 7.51-7.72 (10H, m), 8.45 (1H, d, *J* = 7.72). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8, 19.1, 19.2, 19.4, 27.0, 40.1, 59.6, 64.7, 67.9, 120.3, 124.2, 127.7, 127.8, 127.9, 129.8, 129.9, 130.0, 131.8, 132.8, 133.7, 134.3, 135.3, 135.4, 135.7, 135.9, 136.6. IR (KBr) cm^{-1} : 2959, 2932, 1736, 1590, 1546, 1472, 1428, 1346, 1161. EI-MS (m/z) 832 (M^+). HRMS Calcd for $C_{47}H_{56}N_4O_6SSi_2$: 832.3398 Found 832.3381.

(2*R*,3*R*,4*R*,5*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-1-(2-nitrophenyl-sulfonyl)-2-propylpiperidin-4-ol (16). BH_3-THF (4.1 mL, 4.1 mmol) was dropwise added to a solution of **15** (339.1 mg, 0.41 mmol) in THF (1.4 mL) at 0 °C. The whole was stirred at room temperature for 16.5 h. 3M NaOH (1.37 mL, 4.1 mmol) and 30% H_2O_2 (1.37 mL, 12 mmol) were successively added to reaction mixture at 0 °C and thn the whole was stirred at room temperature for 2.5 h. After evaporation, water and CH_2Cl_2 were added to the residue. The mixture separated and the aqueous layer was extracted with CH_2Cl_2 4 times. The combined organic solvents were dried with Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (*n*-hexane : EtOAc = 10 : 1) to yield **16** (208.8 mg, 60%). Amorphous. $[\alpha]^{21}_D$ -32.3 (*c* 0.50, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.79 (3H, t, *J* = 7.25 Hz), 0.93-1.06 (18H, m), 1.27 (2H, t, *J* = 7.25), 1.63-1.73 (2H, m), 1.90 (1H, q, *J* = 5.80), 2.34 (1H, d, *J* = 4.35 Hz), 3.35-3.52 (2H, m), 3.61-3.78 (3H, m), 3.86-3.96 (2H, m), 7.25-7.68 (23H, m), 7.99-8.01 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8, 19.1, 19.2, 19.7, 27.0, 27.1, 32.2, 33.96, 38.52, 40.3, 42.6, 43.3, 60.1, 70.6, 72.3, 123.8, 127.6, 127.7, 127.8,129.7, 130.9, 133.1, 133.4, 133.7, 134.0, 134.2, 136.2. IR (KBr) cm^{-1} : 3567, 2959, 2931, 1546, 1472, 1428, 1373, 1174. EI-MS (m/z) 850 (M^+). HRMS Calcd for $C_{47}H_{58}N_2O_7SSi_2$: 850.3503 Found 850.3499.

(2*R*,3*R*,4*R*,5*R*)-5-(Hydroxymethyl)-2-propylpiperidine-3,4-diol (2-(*n*-propyl)isofagomine) (5). A

solution of **16** (194 mg, 0.049 mmol) and TBAF (0.56 mL, 0.575 mol) in THF (5.6 mL) was stirred at room temperature for 2.5 h. To the reaction solvent was added sat. aq. $NaHCO_3$. After evaporation, water and CH_2CH_2 were added to the residue. The mixture separated and the aqueous layer was extracted with CH_2CH_2 5 times. The combined organic solvents were dried with Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (CH_2Cl_2 : MeOH = 20 : 1) to yield **17** (82.3 mg, 96%). **17** ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.3, 19.3, 31.9, 40.7, 42.2, 60.7, 61.5, 70.6, 71.5, 123.7, 130.3, 131.4, 133.3, 133.6, 147.4. Without further purification, K_2CO_3 (152.1 mg, 1.10 mmol) and PhSH (68.5 mL, 0.66 mmol) were added to a solution of **17** (82.3 mg, 0.219 mmol). The mixture was stirred at room temperature for 16 h. After filtration, the filtrate was evaporated. The residue was purified by silica gel chromatography (MeOH) to yield **5** (33.8 mg, 82%). Viscous solid. $[\alpha]^{23}_D$ +46.6 (*c* 0.65, H_2O) as hydrocloride salt. ^{1}H-NMR (400 MHz, CD_3OD) δ: 0.95 (3H, t, *J* = 7.25 Hz), 1.29-1.1.40 (2H, m), 1.48-1.56 (1H, m), 1.66-1.73 (1H, m), 1.81-1.90 (1H, m), 2.39-2.51 (2H, m), 3.03 (1H, t, *J* = 9.18 Hz), 3.12-3.23 (2H, m), 3.54 (1H, dd, *J* = 6.76, 11.11 Hz), 3.77 (1H, dd, *J* = 3.86, 10.63 Hz). ^{13}C-NMR (100 MHz, CD_3OD) δ: 14.5, 19.7, 35.0, 46.0, 47.8, 61.4, 62.4, 75.7, 77.6. IR (KBr) cm^{-1} : 3369, 2962, 1071. EI-MS (m/z) 189 (M^+). HRMS Calcd for $C_9H_{19}NO_3$: 189.1365 Found 189.1371.

(2*R*,3*R*,4*S*,5*S*)-5-(Hydroxymethyl)-2-propylpiperidine-3,4-diol (18). A mixture of **14a** (31.6 mg, 0.084 mmol), K_2CO_3 (59.7 mg, 0.43 mmol) and PhSH (27 μL, 0.26 mmol) in acetonitrile (2.2 mL) was stirred at room temperature for 18.5 h. After filtration, the filtrate was evaporated. The residue was purified by silica gel chromatography (MeOH : 10% NH_4OH = 40 : 1) to yield **18** (14.3 mg, 90%).

Viscous solid. $[\alpha]^{25}_D$ -15.6 (*c* 0.53, H_2O) as hydrochloride. ^{1}H-NMR (400 MHz, CD_3OD) δ: 0.95 (3H, t, *J* = 7.32 Hz), 1.28-1.1.53 (3H, m), 1.57-1.66 (1H, m), 1.93-2.01 (1H, m), 2.73 (1H, dd, *J* = 7.81, 13.17 Hz), 2.92-3.00 (2H, m), 3.55 (1H, q, *J* = 2.93 Hz), 3.62-3.71 (2H, m), 3.77 (1H, dd, *J* = 2.93, 4.88 Hz). ^{13}C-NMR (100 MHz, CD_3OD) δ: 14.5, 20.5, 32.9, 42.4, 42.9, 58.7, 62.6, 69.3, 71.5. IR (KBr) cm^{-1} : 3402, 2960, 1063. EI-MS (m/z) 189 (M^+). HRMS Calcd for $C_9H_{19}NO_3$: 189.1365 Found 189.1374.

Bioassay of **5** and **18**

The enzymes α-glucosidase (from rice, assayed at pH 5.0), β-glucosidases (from almond, pH 5.0; from bovine liver, pH 6.8), α-L-fucosidase (from bovine epididymis, pH 5.5), were purchased from Sigma–Aldrich Co. Brush border membranes were prepared from the rat small intestine according to the method of Kessler *et al.*,[15] and were assayed at pH 5.8 for rat intestinal maltase, sucrase, and cellobiase, using the appropriate disaccharides as substrates. For rice α-glucosidase and rat intestinal maltase activities, the reaction mixture contained 25 mM maltose and the appropriate amount of enzyme, and the incubations were performed for 10–30 min at 37 °C was stopped by heating at 100 °C (600 g; 10 min), 0.05 mL of the resulting reaction mixture were added to 3 mL of the Glucose CII-test Wako (Wako Pure Chemical Ind., Osaka, Japan). The absorbance at 505 nm was measured to determine the amount of the

released D-glucose. Other glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as substrate at the optimum pH of each enzyme. The reaction mixture contained 2 mM of the substrate and the appropriate amount of enzyme. The reaction was stopped by adding 2 mL of 400 mM Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm.

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REFERENCES AND NOTES

≠Dedicated to Professor AI Padwa, on the occasion of his 75th birthday, in admiration of his many contributions of heterocyclic chemistry.

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12. The use of cat. OsO_4 in the presence of $NaIO_4$ resulted in low yields (20~30%).
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