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ASYMMETRIC SYNTHESIS OF 1-ALKYL-2-DEOXYIMINOFURANOSES VIA THE IRIDIUM-CATALYZED INTRAMOLECULAR CYCLIZATION OF AN ALLYLIC CARBONATE†

Yoshihiro Natori,[a] Shunsuke Kikuchi,[a] Yuichi Yoshimura,[a] Atsushi Kato,[b] Isao Adachi,[b] and Hiroki Takahata[a]*

[a]Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, Sendai 981-8558, Japan [b]Department of Hospital Pharmacy, University of Toyama, Toyama 930-0194, Japan

Abstract – An asymmetric synthesis of 1-alkyl-2-deoxyiminofuranoses was achieved in which the Ir-catalyzed intramolecular cyclization was the key step. The diastereoselective cyclization converted an allylic carbonate into pyrrolidine derivatives. The α-glucosidase inhibitory activities of the prepared 2-deoxyiminofuranoses were also investigated.

INTRODUCTION

Sugar mimics are very interesting compounds because of their ability to interact with carbohydrate-processing enzymes, where they act as competitive inhibitors of glycosidases and/or glycosyltransferases.[1] Therefore, sugar mimics have the potential for use as anti-diabetic, antiobesity, antiviral, and therapeutic agents for certain types of genetic disorders. Sugar mimic type drugs, such as acarbose (Glucobay™), voglibose (Basen™), and miglitol (Glyset™) are already in use for the treatment of type 2 diabetes and miglustat (Zavesca™) is used as a therapeutic agent for the treatment of type 1 Gaucher disease (Figure 1).[2]

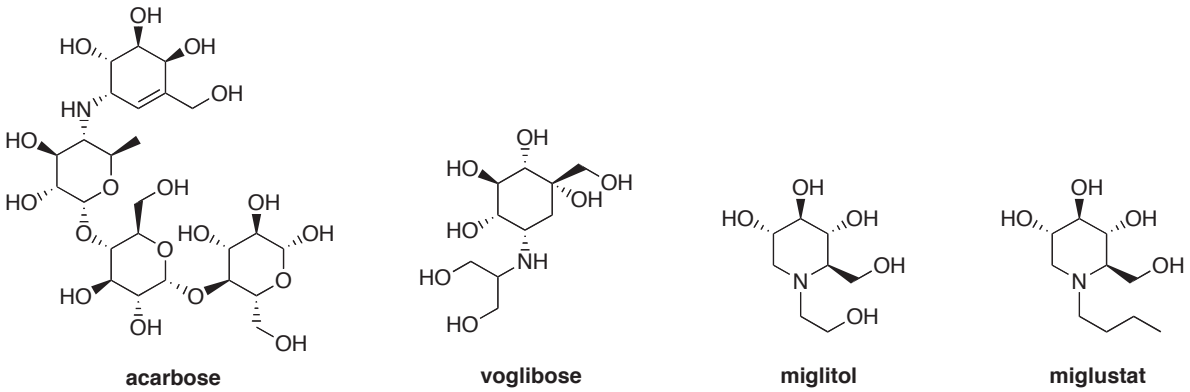


Figure 1. Commercial drugs of sugar mimics

Iminosugars as transition state analogues are of particular interest in terms of the design of inhibitors. Accordingly, in recent years, extensive efforts have been directed to developing methodologies for the asymmetric syntheses of iminosugars.[3] In general, a few systematic studies of the biological properties of the L-enantiomers of iminosugars have been reported. Therefore, our attention was focused on the synthesis and biological evaluation of both enantiomers of several iminosugars.[4] We recently reported on the asymmetric synthesis of both enantiomers of 1-C-alkyl-*arabino*iminofuranose derivatives, and their inhibitory activities with respect to α-glucosidase.[5] Surprisingly, the inhibitory activities of the L-forms showed quite superior and potent inhibitory activities toward rat intestinal maltase and sucrase. Among the compounds investigated, 1-*n*-butyl-L-*aravino*iminofuranose **1c** showed a greater inhibition against rat intestinal sucrase activity relative to the above commercial drugs that are used for the treatment of type 2 diabetes. This prompted us to investigate the structure–activity relationships of 1-alkyl-L-*arabino*iminofuranose. Herein, we wish to report on the synthesis of 2-deoxy type 1-C-alkyl-*arabino*iminofuranoses α and systematic studies of their α-glycosidase inhibitory activities based on an iridium-catalyzed intramolecular allylic amination reaction.

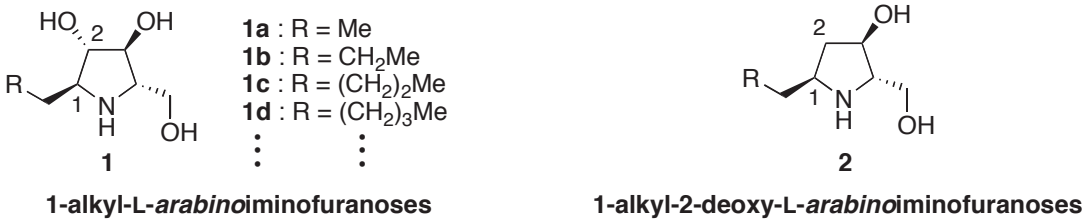
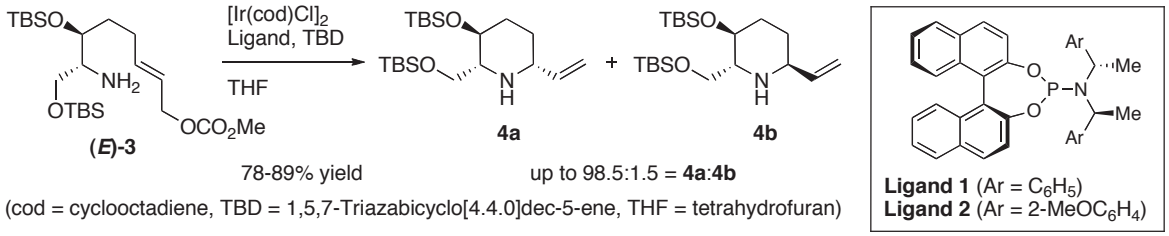


Figure 2. Structures of 1-alkyl-L-*arabino*iminofuranoses and 1-alkyl-2-deoxy-L-*arabino*iminofuranoses

RESULTS AND DISCUSSION

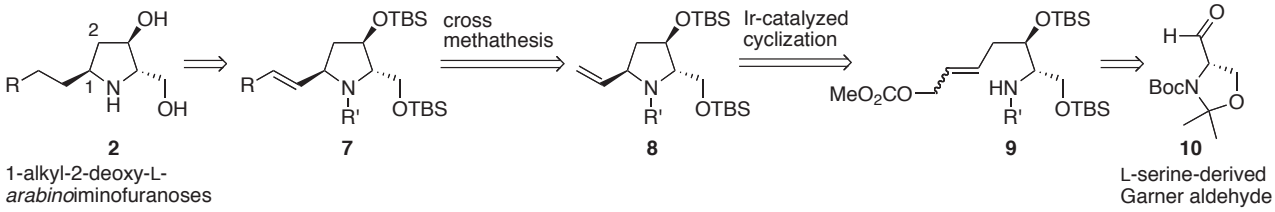
Over the last decade, iridium-catalyzed allylic cyclization has been developed into a powerful tool in the field of organic synthesis, that allows construction of heterocyclic compounds.[6] In 2009, Helmchen and co-workers reported on some Ir-catalyzed allylic cyclizations using chiral ligands to prepare 2,6-disubstituted piperidines, which allow each of the two possible diastereomeric cyclization products to be prepared with a very high degree of diastereoselectivtiy (Scheme 1). The intramolecular cyclizaion of (*E*)-**3** was carried out by using catalytic amount of $[Ir(cod)Cl]_2$, chiral phosphoramidite Ligands and TBD in THF.[7] They reported that piperidine derivatives **4a** and **4b** were produced in good yield with high diastereoselectivity (up to 98.5:1.5). We attempted to apply this concept to the construction of a pyrrolidine ring.



(cod = cyclooctadiene, TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene, THF = tetrahydrofuran)

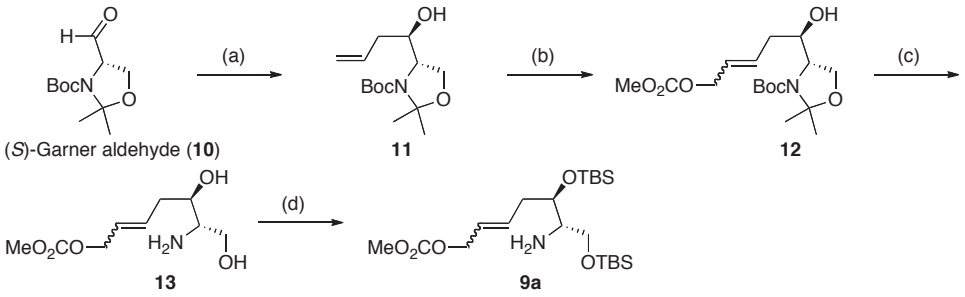
Scheme 1. Intrarmolecular Ir-catalyzed allylic amination

To accomplish this, we used the Ir-catalyzed intramolecular asymmetric allylic amination as a key step for producing 2-deoxy type 1-C-alkyl-L-*arabino*iminofuranoses. Our synthetic plan is shown in Scheme 2. The desired 2-deoxyiminofuranoses **2** can be prepared from **7** through a series of manipulations. The pyrrolidine **7**, with several long side chains at the C1 position, can be obtained by the olefin cross metathesis of a terminal vinyl group of **8**. Pyrrolidine ring of **8** could be constructed by Ir-catalyzed cyclization as a key step from the cyclization precursors **9**, which could be produced from the L-serine-derived Garner aldehyde (**10**).



Scheme 2. Retro synthesis of L-*arabino*-1-alkyl-2-deoxyiminofuranoses

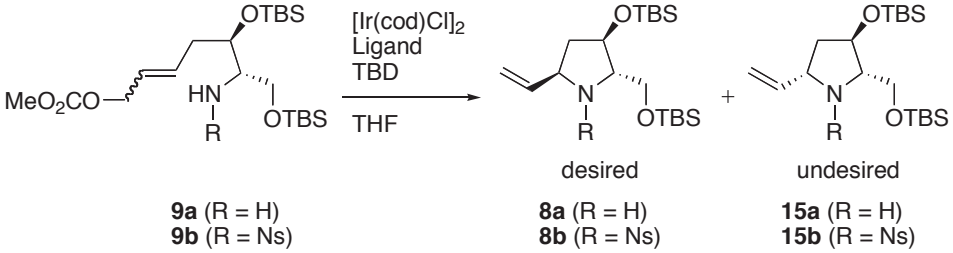
Our synthesis starts from the allylboration of (*S*)-Garner aldehyde (**10**), as shown in Scheme 3. Using know, established procedures, the homoallylic alcohol **11** [$[\alpha]_D^{21}$ –17.9 (*c* 3.4, $CHCl_3$), reported **11** $[\alpha]_D^{20}$ –17.6 (*c* 3.4, $CHCl_3$)] was obtained as a single isomer in good yield.[8] The olefin cross metathesis (Grubbs II catalyst) of **11** and (*Z*)-but-2-ene-1,4-diyl dimethyl dicarbonate (**14**) (5 equiv) afforded the allylic carbonate **12** in 96% yield as a *ca*. 9:1 mixture (^{1}H NMR spectroscopy) of *E* and *Z* isomers. Deprotection of the Boc and hemiaminal groups under acidic conditions gave the diol **13**. Protection of two hydroxy groups of **13** with a TBS group gave the cyclization precursor **9a** in good yield.

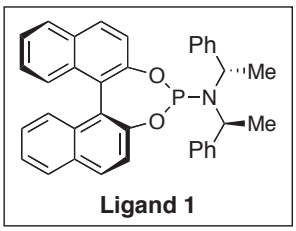


Scheme 3. (a) (+)-B-methoxydiisopinocamphenylborane/allylmagnesium bromide/Et_2O/-80 °C/73%; (b) MeO_2CO—(**14**)—OCO_2Me /Grubbs 2nd catalyst (5 mol%)/CH_2Cl_2/ rt/96%; (c) CF_3CO_2H/CH_2Cl_2/ 0 °C to rt; (d) TBSCl/imidazole/CH_2Cl_2/0 °C to rt/83% (2 steps)

With the cyclization precursors **9a** in hand, the diastereoselective cyclization of allylic carbonate **9a** was examined (Table 1). First, under standard conditions, no reaction occurred and the starting material **9a** was recovered (entry 1). When the reaction was conducted using a larger (two fold) quantity of reagents at 40 °C, pyrrolidine derivatives were produced, but the diastereoselectivity was low (*ca*. 3.5:1 = **8a**:**15a**). (entry 2). When the reaction was carried out at 50 °C, unfortunately, both the yield and diastereoselectivity were lower. (entry 3). Because, the diastereoselectivity of the cyclization of **9a** was unsatisfactory, cyclization of an *N*-protected allylic carbonate such as *N*-nosyl **9b** was performed (entries 4 and 5). When the cyclization of **9b** was attempted under the same conditions at 40 °C, the reaction was incomplete. The cyclization was completed when reagents were added (entry 4). Therefore, we examined the simultaneous use of $[Ir(cod)Cl]_2$ (8 mol %), **Ligand 1** (16 mol %) and TBD (32 mol %) (entry 5). The reaction was carried out at 40 °C, and the desired cyclic compound **8b** was obtained in 88% yield with a high diastereoselectivity (*ca*. 10:1 = **8b**:**15b**).

Table 1. Diastereoselective intramolecular Ir-catalyzed cyclization



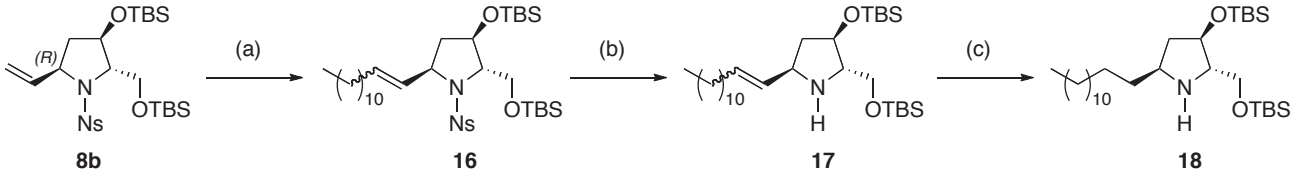


Ligand 1

entry	R	$[Ir(cod)Cl]_2$ (mol %)	Ligand (mol %)	TBD (mol %)	temp. (°C)	time (h)	yield (%)[a] **8**	yield (%)[a] **15**
1	H	2	4	8	rt	48	not detected	not detected
2	H	4	8	16	40	40	62	18
3	H	4	8	16	50	20	49	18
4	Ns	4+4	8+8	16+16	40	15+48	78	8
5	Ns	8	16	32	40	15	88	9

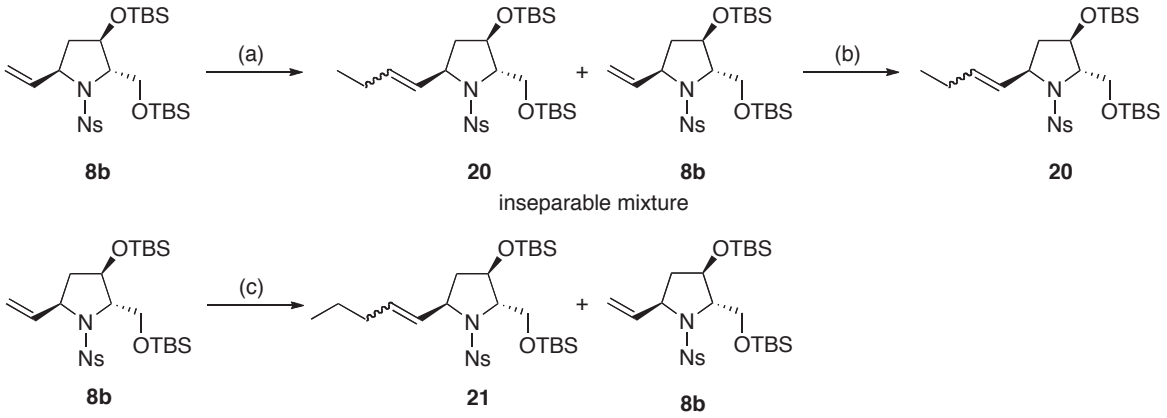
[a] Isolated yield. (cod = cyclooctadiene, TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene, THF = tetrahydrofuran)

The absolute configuration of new tertiary carbon of **8b** was established as *R* by transforming **8b** into the known compound **18** as shown in Scheme 4. An olefin cross metathesis between **8b** and 1-tridecene (**19**) provided alkene **16**. Deprotection of the Ns group was carried out under standard conditions using thiophenol in the presence of K_2CO_3. Hydrogenation of the unsaturated bond unit with H_2 gas and PtO_2 (20 wt%) gave **18** $[[\alpha]_D^{23}$ –12.5 (*c*. 1.06, $CHCl_3)]$, the optical rotation of which was negative, as reported for **18**.[9]



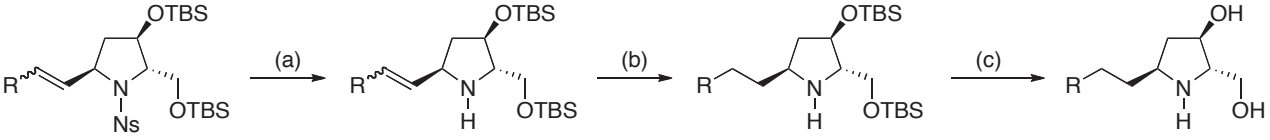
Scheme 4. (a) 1-tridecene (**19**) (10 eq.)/Grubbs 2nd catalyst (20 mol %)/CH_2Cl_2/40 °C/48 h/48%; (b) PhSH (3 eq.)/K_2CO_3 (5 eq.)/MeCN/40 °C/overnight/91%; (c) H_2 (balloon)/PtO_2 (20 wt%)/EtOAc/rt/overnight/51%

Olefin cross metathesis reactions between vinylpyrrolidine derivative **8b** and *Z*-alkenes were carried out using the Grubbs II catalyst to introduce the alkyl chains (Scheme 5). When (*Z*)-hex-3-ene (**22**) was used as the alkene, the reaction product **20** and starting material **8b** were obtained as an inseparable mixture. Therefore, the olefin metathesis reaction of the mixture was extended to finally afford **20**. An olefin cross metathesis reaction using (*Z*)-oct-4-ene (**23**) provided a mixture of the corresponding alkene **21** and **8b**, which were readily separated



Scheme 5. (a) (*Z*)-hex-3-ene (**22**) (10 eq.)/Grubbs 2nd catalyst (20 mol %)/CH_2Cl_2/40 °C/48 h;
(b) (*Z*)-hex-3-ene (**22**) (10 eq.)/Grubbs 2nd catalyst (15 mol %)/CH_2Cl_2/40 °C/48 h/81% (from **8b**);
(c) (*Z*)-oct-4-ene (**23**) (10 eq.)/Grubbs 2nd catalyst (20 mol %)/CH_2Cl_2/40 °C/48 h/**21** (81%) + **8b** (15%)

The three types of prepared alkenylpyrrolidine derivatives **8b**, **20** and **21** were converted into the corresponding 1-alkyl-2-deoxyiminofuranoses **2a-c** (Scheme 6). Deprotection of the Ns group followed by hydrogenation of the alkene unit gave **25a-c** according to a similar method to that shown in Scheme 4. The TBS groups of **25a-c** were deprotected by treatment with 3 N HCl aq. to provide desired iminofuranoses **2a-c** in quantitative yield.

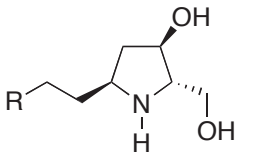


8b (R = H)	99%	**8a** (R = H)	52%	**25a** (R = H)	quant.	**2a** (R = H)
20 (R = CH_2Me)	83%	**24b** (R = CH_2Me)	71%	**25b** (R = CH_2Me)	quant.	**2b** (R = CH_2Me)
21 (R = CH_2CH_2Me)	81%	**24c** (R = CH_2CH_2Me)	63%	**25c** (R = CH_2CH_2Me)	quant.	**2c** (R = CH_2CH_2Me)

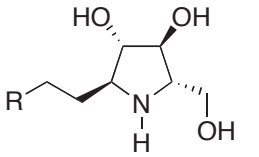
Scheme 6. (a) PhSH (3 eq.)/K_2CO_3 (5 eq.)/MeCN/40 °C/overnight; (b) H_2 (balloon)/PtO_2 (20 wt%)/MeOH/rt/overnight; (c) 3 N HCl aq./100 °C/1 h

Having prepared the 1-alkyl-2-deoxyiminofuranoses **2a-c**, their abilities to serve as inhibitors of rat intestinal α-glucosidase were compared with previous reported data for 1-alkyl L-*arabino*iminofuranoses **1a**, **1c** and **1d** and commercially available drugs such as acarbose, voglibose and miglitol (Table 2).[10] We were disappointed to find that the prepared 1-alkyl-2-deoxyiminofuranoses **2** showed no effective inhibitory activity toward maltase, with a less than 50% inhibition at 1000 μM. On the other hand, the compound was a weak inhibitor of sucrase. Compound **2c,** having *n*-pentyl chain at the C1 position, showed the most potent inhibitory activity among the prepared 2-deoxyiminofuranoses **2**. 1-Alkyl L-*arabino*iminofuranoses have been reported to show inhibitory activities toward α-glucosidases that are as strong as commercially available drugs. The data reported herein indicate that a hydroxy group at the C2 position is necessary for potent inhibitory activity toward α-glucosidase.

Table 2. IC_{50} (μM) values for the rat intestinal α-glucosidases



2a (R = H)
2b (R = CH_2Me)
2c (R = CH_2CH_2Me)



1a (R = H)
1c (R = CH_2Me)
1d (R = CH_2CH_2Me)

substrate	maltase	sucrase
2a	NI	1000
2b	NI	495
2c	NI	259
1a	2.6	0.68
1c	0.2	0.032
1d	0.71	0.19
acarbose	0.16	0.24
voglibose	0.18	0.37
miglitol	0.59	1.0

NI : No Inhibition (less than 50% inhibition at 1000 μM)

In conclusion, we report on the stereoselective synthesis of 1-alkyl-2-deoxyiminofuranoses **2** using Ir-catalyzed allylic cyclization as a key step. The overall yields are 24~30% and the synthesis involves 10 or 11 steps starting from the known compound **11**. Further applications of this Ir-catalyzed intramolecular cyclization for the synthesis of other pyrrolidine alkaloid derivatives is currently in progress.

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 (1H NMR)

spectra were recorded on JEOL JNM-EX 270 (270 MHz) or 300 MHz on a Varian Gemini-300 or JEOL JNM-AL 400 (400 MHz) 500 MHz on a Varian Unity-500 or JNM-LA (600 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) Column chromatography was carried out on Merck Silica Gel 60 (230–400 mesh) or KANTO Silica Gel 60N (40–50 μm) for flash chromatography. Purification of products via ion-exchange resin chromatography was performed with Dowex 1_2 OH_ form, using water as eluent. All non-aqueous reactions were carried out under argon atmosphere. 1-Alkyl-L-arabinoiminofuranoses were available with the reported procedure. Additionally, allylic alcohol **11** was prepared from Garner aldehyde according to known method as a single diastereomer.[8]

(*S*)-*tert*-Butyl 4-[(*R*)-1-hydroxy-5-{(methoxycarbonyl)oxy}pent-3-en-1-yl]-2,2-dimethyloxazolidine-3-carboxylate (12)

To a solution of allylic alcohol **11** (490 mg, 1.81 mmol) and (*Z*)-but-2-ene-1,4-diyl dimethyl dicarbonate (**14**) (1.84 g, 9.03 mmol) in dry CH_2Cl_2 (36 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-yl-idene][benzylidine]ruthenium(IV) dichloride (2nd Grubbs catalyst, 76.7 mg, 90.3 μmol). After the mixture was stirred for 2 h at room temperature, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1 → 3:1) to give **12** (623 mg, 96%) as a brown oil.

$[\alpha]_D^{20}$ –15.7 (*c* 1.71, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer δ 1.49 (9H, s), 1.58 (6H, s), 2.17-2.33 (2H, m), 3.59-4.13 (7H, m), 4.59 (2H, d, *J* = 6.3 Hz), 5.67 (1H, dt, *J* = 6.3, 15.5 Hz), 5.93 (1H, m); *Z* isomer δ 1.49 (9H, s), 1.58 (6H, s), 2.17-2.33 (2H, m), 3.59-4.13 (7H, m), 4.70 (2H, d, *J* = 5.8 Hz), 5.67 (1H, dt, *J* = 6.3, 15.5 Hz), 5.93 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) δ 14.0, 20.8, 24.0, 26.4, 26.5, 28.1, 36.0, 54.5, 60.1, 61.7, 64.2, 64.5, 68.1, 72.1, 80.9, 94.1, 125.7, 132.6, 133.3, 155.4. IR (neat) cm^{-1}: 3483, 2979, 1750, 1698, 1445, 1367, 1268. EI-MS (m/z): 359 (M^+). HRMS Calcd for $C_{17}H_{29}O_7$: 359.1944, Found: 359.1939.

(5*R*,6*S*)-6-Amino-5,7-bis{(*tert*-butyldimethylsilyl)oxy}hept-2-en-1-yl methyl carbonate (9a)

To a solution of **12** (315 mg, 0.876 mmol) in dry CH_2Cl_2 (8 mL) was added TFA (8 mL) at 0 °C. After the mixture was stirred for 2 h at room temperature, the solvents were removed under reduced pressure. Traces of TFA were removed from a mixture by azeotropic distillations with MeOH (2 × 5 mL) and toluene (2 × 5 mL) under reduced pressure at room temperature.

The residue was dissolved in CH_2Cl_2 (8 mL). Imidazole (895 mg, 13.1 mmol) and TBSCl (528 mg, 3.5 mmol) were added to this solution at 0 °C. After the reaction was stirred at room temperature overnight, the reaction was quenched with water (10 mL). The whole was extracted with CH_2Cl_2 (2 × 30 mL) and

the combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1 → 2:1) to give **9a** (324 mg, 83%) as a colorless oil.

$[\alpha]_D^{24}$ –10.7 (*c* 0.95, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer δ 0.05 (12H, s), 0.89 (18H, s), 2.24-2.39 (2H, m), 2.83-2.88 (1H, m), 3.43-3.48 (1H, dd, *J* = 7.2, 9.6 Hz), 3.66-3.73 (2H, m), 3.78 (3H, s), 4.58 (2H, d, *J* = 6.8 Hz), 5.62 (1H, dt, *J* = 6.3, 15.5 Hz), 5.83 (1H, m); *Z* isomer δ 0.05 (12H, s), 0.89 (18H, s), 2.24-2.39 (2H, m), 2.83-2.88 (1H, m), 3.43-3.48 (1H, dd, *J* = 7.2, 9.6 Hz), 3.66-3.73 (2H, m), 3.78 (3H, s), 4.69 (2H, *J* = 6.8 Hz), 5.62 (1H, dt, *J* = 6.3, 15.5 Hz), 5.83 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) δ –5.4, –5.3, –4.7, –4.6, –4.3, 18.0, 18.3, 25.8, 25.9, 26.0, 35.8, 54.7, 56.5, 63.8, 64.8, 65.2, 68.3, 68.4, 73.1, 125.7, 125.8, 131.9, 133.0, 133.3, 155.7. IR (neat) cm^{-1}: 2956, 2858, 1751, 1472, 1259. EI-MS (m/z): 447 (M^+). HRMS Calcd for $C_{21}H_{45}NO_5Si_2$: 447.2836, Found: 447.2845.

(5*R*,6*S*)-5,7-Bis{(*tert*-butyldimethylsilyl)oxy}-6-(2-nitrophenylsulfonamido)hept-2-en-1-yl methyl carbonate (9b)

To a mixture of amine **9a** (2.03 g, 4.52 mmol), Et_3N (1.1 mL, 8.14 mmol) and *N*,*N*-dimethylaminopyridine (133 mg, 1.08 mmol) in dry CH_2Cl_2 (45 mL) was added 2-nitrobenzenesulfonyl chloride (1.20 g, 5.42 mmol) at 0 °C. The mixture was stirred at room temperature overnight. After evaporation, the residue was diluted with EtOAc (50 mL). The whole mixture was transferred to a separatory funnel. The organic layer was washed with brine (15 mL), 5% $KHSO_4$ aq. (15 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10:1 → 8:1) to afford **9b** (5.20 g, 84%) as a pale yellow oil.

$[\alpha]_D^{20}$ +52.7 (*c* 0.88, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer δ –0.17 (3H, s), –0.09 (3H, s), 0.04 (6H, s), 0.78 (9H, s), 0.83 (9H, s), 2.33 (2H, dd, *J* = 6.3, 6.8 Hz), 3.45-3.51 (1H, m), 3.52 (1H, dd, *J* = 4.8, 10.1 Hz), 3.70 (1H, dd, *J* = 4.8, 10.1 Hz), 3.79 (3H, s), 3.98 (1H, m), 4.58 (2H, d, *J* = 6.3 Hz), 5.58 (1H, dt, *J* = 6.3, 15.4 Hz), 5.69 (1H, d, *J* = 7.2 Hz), 5.79 (1H, dt, *J* = 6.8, 15.4 Hz), 7.68 (3H, m), 7.86 (1H, d, *J* = 5.8 Hz), 8.10 (1H, d, *J* = 5.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) δ –5.7, –5.4, –4.4, –4.1, 0.1, 18.2, 18.3, 25.9, 26.0, 36.7, 54.9, 59.8, 61.2, 68.4, 71.7, 125.5, 126.8, 130.6, 131.9, 133.1, 133.4, 135.3, 155.8; IR (neat) cm^{-1}: 3349, 2956, 2858, 1749, 1543, 1443, 1361, 1260. FAB-MS (m/z): 633 $(M+1)^+$. HRMS Calcd for $C_{27}H_{49}N_2O_9SSi_2$: 633.2697, Found: 633.2708.

(2*S*,3*R*,5*R*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-5-vinylpyrrolidine (8a)

(2*S*,3*R*,5*S*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-5-vinylpyrrolidine (15a)

To a solution of $[Ir(cod)Cl]_2$ (3.2 mg, 0.0048 mmol, 4 mol %) and (*S*,*S*,*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-*a*:3,4-*a*']dinaphthalen-4-yl)bis(1-phenylethyl)amine (**Ligand 1**) (5.2 mg, 0.0096 mmol, 8 mol %) in THF (0.3 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (2.7 mg, 0.0192 mmol, 16 mol %). After the mixture was stirred for 1 h at room temperature, a solution of allylic carbonate **9a** (54.0 mg, 0.12 mmol) in THF (0.8 mL) was added to the reaction mixture. After stirring for 40 h at 40 °C, and the mixture was concentrated and the residue purified by silica gel column chromatography (*n*-hexane/EtOAc **=** 10:1) to give **8a** (27.8 mg, 62%) as a pale yellow oil and **15a** (7.9 mg, 18%) as a pale yellow oil.

8a; $[\alpha]_D^{24}$ –14.8 (*c* 1.60, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (12H, s), 0.88 (9H, s), 0.90 (9H, s), 1.56 (1H, dt, *J* = 6.8, 6.8, 13.1 Hz), 2.17 (1H, m), 3.02 (1H, dt, *J* = 4.8, 4.9 Hz), 3.58 (2H, d, *J* = 4.8 Hz), 3.64 (1H, dt, *J* = 7.3, 7.4 Hz), 4.11 (1H, dt, *J* = 5.8, 6.3 Hz), 4.95 (1H, d, *J* = 10.1 Hz), 5.06 (1H, d, *J* = 16.9 Hz), 5.89, (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ –5.48, –5.44, –4.83, –4.60, 17.96, 18.25, 25.78, 25.89, 41.36, 59.17, 62.92, 67.03, 73.57, 113.67, 142.25. IR (neat) cm^{-1}: 3431, 2928, 2856, 1643, 1463, 1256, 1115; EI-MS (m/z): 371 (M^+). HRMS Calcd for $C_{19}H_{41}NO_2Si_2$: 371.2676, Found: 371.2665.

15a; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (12H, s), 0.89 (18H, s), 1.67 (1H, m), 1.87 (1H, m), 3.22 (1H, m), 3.60 (2H, m), 3.86 (1H, q, *J* = 7.7 Hz), 4.37 (1H, m), 4.98 (1H, d, *J* = 9.2 Hz), 5.10 (1H, d, *J* = 16.9 Hz), 5.77 (1H, m).

(2*S*,3*R*,5*R*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-1-{(2-nitrophenyl)sulfonyl}-5-vinylpyrrolidine (8b)

(2*S*,3*R*,5*S*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-1-{(2-nitrophenyl)sulfonyl}-5-vinylpyrrolidine (15b)

To a solution of $[Ir(cod)Cl]_2$ (8.7 mg, 8 mol %) and (*S*,*S*,*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta-[2,1-*a*:3,4-*a*']dinaphthalen-4-yl)bis(1-phenylethyl)amine (**Ligand 1**) (13.9 mg, 16 mol %) in THF (0.45 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (7.2 mg, 0.052 mmol). The mixture was stirred for 1 h at room temperature, a solution of allylic carbonate **9b** (102 mg, 0.161 mmol) in THF (1 mL) was added to the reaction mixture. After stirring for 15 h at 40 °C, and the mixture was concentrated and the residue purified by silica gel column chromatography (*n*-hexane/EtOAc **=** 15:1) to give **8b** as a white solid (78.7 mg, 88%) and **15b** (7.9 mg 9%) as a white solid.

8b; mp 100-102 °C. $[\alpha]_D^{20}$ +142.4 (*c* 1.03, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.05 (6H, s), 0.81 (9H, s), 0.86 (9H, s), 1.65 (1H, d, *J* = 13.5 Hz), 2.47-2.54 (1H, m), 3.45 (1H, dd, *J* = 8.2, 10.1 Hz), 3.92 (1H, dd, *J* = 3.4, 10.0 Hz), 4.04-4.09 (1H, m), 4.40-4.46 (1H, m), 4.75 (1H, d, *J* = 10.1 Hz), 5.01 (1H,

d, *J* = 16.9 Hz), 5.68-5.78 (1H, m), 7.51-7.60 (3H, m), 8.09-8.11 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ –5.5, –5.4, –5.0, –4.9, 17.9, 18.2, 25.7, 25.9, 39.6, 64.0, 64.3, 71.9, 74.7, 117.4, 123.7, 130.5, 131.0, 132.8, 135.8, 138.3. IR (KBr) cm^{-1}: 3097, 2953, 2931, 2886, 2858, 1584, 1546, 1472, 1352. FAB-MS (m/z): 557 $(M+1)^+$. HRMS Calcd for $C_{25}H_{45}N_2O_6SSi_2$: 557.2537, Found: 557.2545.

15b; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (6H,s), 0.07 (6H, s), 0.88 (9H, s), 0.91 (9H, s), 1.29 (1H, d, *J* = 13.5 Hz), 3.49 (1H, m), 3.81 (1H, dd, *J* = 4.8, 10.5 Hz), 3.92 (2H, m), 4.13 (1H, m), 4.26 (1H, m), 4.97 (1H, d, *J* = 10.1 Hz), 5.05 (1H, d, *J* = 16.9 Hz), 5.89 (1H, m), 7.59 (3H, m), 8.08 (1H, m).

(2*S*,3*R*,5*R*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-1-{(2-nitrophenyl)sulfonyl}-5-(tridec-1-en-1-yl)pyrrolidine (16)

To a solution of **8b** (50.9 mg, 0.091 mmol) and 1-tridecene (**19**) (0.22 mL, 0.91 mmol) in dry CH_2Cl_2 (1.0 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]-[benzylidine]ruthenium (IV) dichloride (2nd Grubbs catalyst) (7.8 mg, 0.0091 mmol). After the mixture was stirred for 24 h at 40 °C, 2nd Grubbs catalyst (7.8 mg, 0.0091 mmol) was added to the reaction mixture. After the mixture was stirred for 24 h at 40 °C, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30:1 → 5:1) to give **16** (31.5 mg, 48%) as a colorless oil.

$[\alpha]_D^{24}$ +129.4 (*c* 0.70, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer δ 0.05-0.13 (15H, m), 0.89 (18H, s), 1.25 (18H, m), 1.57 (3H, m), 2.47 (1H, m), 3.45 (1H, dd, *J* = 1.4, 10.1 Hz), 3.98 (1H, dd, *J* = 3.9, 10.2 Hz), 4.08 (1H, m), 4.42 (2H, m), 5.29 (1H, dd, *J* = 10.1, 15.4 Hz), 5.48 (1H, dt, *J* = 6.3, 15.0 Hz), 7.51 (3H, m), 8.13 (1H, d, *J* = 7.7 Hz); *Z* isomer δ 0.05-0.13 (15H, m), 0.89 (18H, s), 1.25 (18H, m), 1.57 (3H, m), 2.47 (1H, m), 3.45 (1H, dd, *J* = 1.4, 10.1 Hz), 3.98 (1H, dd, *J* = 3.9, 10.2 Hz), 4.08 (1H, m), 4.42 (2H, m), 4.83 (1H, m), 5.09 (1H, m), 7.51 (3H, m), 8.13 (1H, d, *J* = 7.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) δ -5.4, -5.3, -4.8, -4.7, 14.3, 18.1, 18.3, 22.8, 25.8, 25.9, 26.0, 28.5, 29.3, 29.5, 29.6, 29.7, 29.8, 30.0, 31.9, 32.1, 39.7, 63.7, 64.4, 72.3, 74.9, 76.8, 123.8, 129.9, 130.5, 130.9, 132.6, 134.6, 136.6, 148.6. IR (neat) cm^{-1}: 3420, 2929, 2857, 1638, 1548, 1471, 1359. FAB-MS (m/z): 711 $(M+1)^+$. HRMS Calcd for $C_{36}H_{67}N_2O_6SSi_2$: 711.4258, Found: 711.4252.

(2*S*,3*R*,5*R*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-5-(tridec-1-en-1-yl)pyrrolidine (17)

To a suspension of **16** (81.5 mg, 0.044 mmol) and K_2CO_3 (30.5 mg, 0.221 mmol) in MeCN (1.1 mL) was added PhSH (13.7 μL, 0.133 mmol). The reaction mixture was stirred overnight at 40 °C. After filtration, the filtrate was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (15 mL). The whole mixture was transferred to a separatory funnel. The organic layer was washed with 10% $Na_2S_2O_3$

aq. (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4.The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc **=** 20:1) to give amine **17** (21.3 mg, 91%) as a colorless oil. $[\alpha]_D^{24}$ –16.8 (*c* 1.24, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer δ 0.05 (12H, s), 0.85 (21H, m), 1.25 (18H, m), 1.50 (1H, m), 1.94 (2H, m), 2.13 (1H, m), 3.01 (1H, dd, *J* = 4.8, 10.1 Hz), 3.55 (3H, m), 4.08 (1H, m), 5.45 (2H, m); *Z* isomer δ 0.05 (12H, s), 0.85 (21H, m), 1.25 (18H, m), 1.50 (1H, m), 1.94 (2H, m), 2.13 (1H, m), 3.01 (1H, dd, *J* = 4.8, 10.1 Hz), 3.55 (3H, m), 4.08 (1H, m), 5.34 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) δ –5.47, –5.42, –4.82, –4.59, 14.10, 17.97, 18.27, 22.67, 25.80, 25.92, 29.19, 29.26, 29.34, 29.50, 29.55, 29.64, 29.68, 31.91, 32.18, 41.79, 58.56, 63.14, 67.09, 73,72, 130.51, 133.92. IR (neat) cm^{-1}: 3422, 2956, 2928, 2857, 1639, 1472, 1464, 1256, 1116. EI-MS (m/z): 525 (M^+). HRMS Calcd for $C_{30}H_{63}NO_2Si_2$: 525.4397, Found: 525.4387.

(2*S*,3*R*,5*S*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-5-tridecyl-pyrrolidine (18)

To a solution of **17** (21.5 mg, 0.0405 mmol) in EtOAc (0.5 mL) was added PtO_2 (4.2 mg, 20 wt%), and the resulting mixture was stirred under hydrogen at atmospheric pressure at room temperature overnight. The reaction mixture was then filtered through a plug of Celite, and the Celite filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc **=** 20:1) to afford **18** (11.8 mg, 63%) as a colorless oil. $[\alpha]_D^{23}$ –12.5 (*c* 1.06, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (12H, s), 0.86 (21H, m), 1.25 (25H, m), 2.10 (2H, m), 2.97 (1H, m), 3.09 (1H, m), 3.60 (2H, d, *J* = 4.3 Hz), 4.09 (1H, ddd, *J* = 5.8, 6.3, 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ –5.31, –5.28, –4.7, –4.4, 14.3, 18.1, 18.4, 22.8, 26.0, 27.2, 29.5, 29.78, 29.8, 32.1, 37.7, 41.4, 56.6, 62.2, 66.7, 73.5. IR (neat) cm^{-1} : 3424, 2956, 2929, 2856, 1638, 1468, 1254, 1081. EI-MS (m/z): 528 (M^+); HRMS Calcd for $C_{30}H_{65}NO_2Si_2$: 527.4554, Found: 527.4556.

(2*S*,3*R*,5*R*)-5-(But-1-en-1-yl)-3-{(*tert*-butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}-methyl]-1-{(2-nitrophenyl)sulfonyl}pyrrolidine (20)

To a solution of **8b** (116 mg, 0.209 mmol) and (*Z*)-hex-3-ene (**22**) (0.26 mL, 2.09 mmol) in dry CH_2Cl_2 (2.1 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-yl-idene][benzylidine]ruthenium (IV) dichloride (2nd Grubbs catalyst) (17.7 mg, 0.0209 mmol). After the mixture was stirred for 24 h at 40 °C, 2nd Grubbs catalyst (17.7 mg, 0.0209 mmol) was added to the reaction mixture. After the mixture was stirred for 24 h at 40 °C, the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (2.1 mL), and 2nd Grubbs catalyst (17.7 mg, 0.0209 mmol) was added to the solution. The mixture was stirred for 24 h at 40 °C, to the reaction mixture was added 2nd Grubbs catalyst (8.9 mg, 0.0105 mmol). After stirring for 24 h at 40 °C, the

solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10:1 → 5:1) to give **20** (99.3 mg, 81%) as a brown oil.

$[\alpha]_D^{24}$ +137.1 (*c* 1.54, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) *E* isomer δ 0.08 (12H, s), 0.62 (3H, t, *J* = 7.3 Hz), 0.87 (18H, s), 1.58 (3H, m), 2.48 (1H, m), 3.46 (1H, m), 3.99 (1H, dd, *J* = 3.4, 6.8 Hz), 4.10 (1H, m), 4.43 (1H, t, *J* = 9.3 Hz), 4.50 (1H, d, *J* = 3.4 Hz), 5.28 (1H, m), 5.48 (1H, m), 7.52 (3H, m), 8.13 (1H, d, *J* = 7.8 Hz); *Z* isomer δ 0.08 (12H, s), 0.71 (3H, t, *J* = 7.3 Hz), 0.87 (18H, s), 1.58 (3H, m), 2.48 (1H, m), 3.46 (1H, m), 3.99 (1H, dd, *J* = 3.4, 6.8 Hz), 4.10 (1H, m), 4.43 (1H, t, *J* = 9.3 Hz), 4.50 (1H, d, *J* = 3.4 Hz) 4.83 (1H, m), 5.09 (1H, m), 7.52 (3H, m), 8.13 (1H, d, *J* = 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) δ –5.5, –5.4, –4.9, –4.9, 12.2, 13.6, 14.0, 17.9, 18.2, 20.1, 21.5, 24.5, 25.7, 25.8, 29.7, 33.8, 39.5, 39.6, 39.9, 57.3, 63.45, 63.5, 64.1, 64.2, 72.0, 72.2, 74.7, 123.6, 123.7, 128.8, 129.1, 130.1, 130.3, 130.4, 130.7, 130.8, 130.9, 132.4, 132.5, 132.6, 134.1, 136.7, 148.4. IR (neat) cm^{-1} 2929.5, 2857.2, 1547.1, 1471.7, 1354.2, 1256.2. FAB-MS (m/z): 585 $(M+1)^+$. HRMS Calcd for $C_{27}H_{49}N_2O_6SSi_2$: 585.2850, Found: 585.2843.

(2*S*,3*R*,5*R*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-1-{(2-nitrophenyl)sulfonyl}-5-(pent-1-en-1-yl)pyrrolidine (21)

To a solution of **8b** (131 mg, 0.236 mmol) and (*Z*)-oct-4-ene (**23**) (0.37 mL, 2.36 mmol) in dry CH_2Cl_2 (4.7 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium (IV) dichloride (2nd Grubbs catalyst) (20.0 mg, 0.0236 mmol). After the mixture was stirred for 24 h at 40 °C, 2nd Grubbs catalyst (20.0 mg, 0.0236 mmol) was added to the reaction mixture. After stirring for 24 h at 40 °C, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 20:1) to give **21** (114.5 mg, 81%) as a brown oil.

$[\alpha]_D^{24}$ +152.6 (*c* 1.07, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer δ 0.08 (12H, s), 0.70 (3H, t, *J* = 7.3 Hz), 0.86 (18H, s), 1.02 (2H, m), 1.60 (3H, m), 2.48 (1H, m), 3.45 (1H, m), 3.98 (1H, dd, *J* = 3.8, 10.6 Hz), 4.08 (1H, dd, *J* = 3.8, 10.4 Hz), 4.42 (1H, t, *J* = 9.2 Hz), 4.50 (1H, d, *J* = 3.9 Hz), 5.30 (1H, dd, *J* = 9.7, 15.4 Hz), 5.46 (1H, m), 7.52 (3H, m), 8.13 (1H, d, *J* = 7.8 Hz). *Z* isomer δ 0.08 (12H, s), 0.70 (3H, t, *J* = 7.3 Hz), 0.86 (18H, s), 1.02 (2H, m), 1.60 (3H, m), 2.48 (1H, m), 3.45 (1H, m), 3.98 (1H, dd, *J* = 3.8, 10.6 Hz), 4.08 (1H, dd, *J* = 3.8, 10.4 Hz), 4.42 (1H, t, *J* = 9.2 Hz), 4.50 (1H, d, *J* = 3.9 Hz), 4.83 (1H, m), 5.09 (1H, m), 7.52 (3H, m), 8.13 (1H, d, *J* = 7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) δ -5.5, -5.4, -5.0, -4.9, 13.6, 17.9, 18.2, 21.5, 25.6, 25.9, 33.8, 39.6, 63.5, 64.2, 72.1, 74.7, 123.6, 130.0, 130.18, 130.22, 130.8, 132.5, 134.1, 136.39, 136.44, 148.39. IR (neat) cm^{-1}: 2930, 2858, 1547, 1472, 1440, 1355, 1256. FAB-MS (m/z): 599 $(M+1)^+$. HRMS Calcd for $C_{28}H_{51}N_2O_6SSi_2$: 599.3006, Found: 599.3002.

(2*S*,3*R*,5*R*)-5-(But-1-en-1-yl)-3-{(*tert*-butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}-methyl]pyrrolidine (24b)

To a suspension of **20** (60.5 mg, 0.103 mmol) and K_2CO_3 (71.5 mg, 0.515 mmol) in MeCN (2.4 mL) was added PhSH (31.9 μL, 0.309 mmol). The reaction mixture was stirred overnight at 40 °C. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc **=** 10:1 → 3:1) to give **24b** (41.2 mg, 99%) as a pale yellow oil. $[\alpha]_D^{26}$ –15.9 (*c* 1.22, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer *δ* 0.05 (12H, s), 0.89 (18H, s), 0.96 (3H, t, *J* = 7.3 Hz), 1.50 (1H, m), 1.64 (1H, d, *J* = 5.4 Hz), 1.97 (1H, m), 2.13 (1H, m), 3.01 (1H, m), 3.55 (3H, m), 4.08 (1H, m), 5.46 (2H, m); *Z* isomer *δ* 0.05 (12H, s), 0.89 (18H, s), 0.96 (3H, t, *J* = 7.3 Hz), 1.50 (1H, m), 1.64 (1H, d, *J* = 5.4 Hz), 1.97 (1H, m), 2.13 (1H, m), 3.01 (1H, m), 3.55 (3H, m), 4.08 (1H, m), 5.33 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *δ* –5.47, –5.42, –4.82, –4.59, 13.46, 13.68, 17.97, 18.27, 22.35, 25.78, 25.91, 34.26, 41.37, 58.56, 62.89, 66.98, 73.58, 132.28, 132.64. IR (neat) cm^{-1}: 3401, 2956, 2930, 2858, 1633, 1588, 1472, 1463, 1256, 1117. EI-MS (m/z): 399 (M^+). HRMS Calcd for $C_{21}H_{45}NO_2Si_2$: 399.2989, Found: 399.2990.

(2*S*,3*R*,5*R*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-5-(pent-1-en-1-yl)pyrrolidine (24c)

To a suspension of **21** (30.9 mg, 0.052 mmol) and K_2CO_3 (35.7 mg, 0.258 mmol) in MeCN (1.2 mL) was added PhSH (15.9 μL, 0.155 mmol). The reaction mixture was stirred overnight at 40 °C. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc **=** 30:1 → 5:1) to give **24c** (17.2 mg, 81%) as a pale yellow oil $[\alpha]_D^{24}$ –20.5 (*c* 1.46, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *E* isomer *δ* 0.05 (12H, s), 0.84 (21H, m), 1.25 (3H,m), 1.48 (1H, m), 1.93 (1H, m), 2.12 (1H, m), 3.01(1H,m), 3.55 (3H, m), 4.09 (1H, m), 5.43 (2H, m); *Z* isomer δ 0.05 (12H, s), 0.84 (21H, m), 1.25 (3H,m), 1.48 (1H, m), 1.93 (1H, m), 2.12 (1H, m), 3.01(1H,m), 3.55 (3H, m), 4.09 (1H, m), 5.29 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of *E*/*Z* isomers) *δ* –5.45, –5.41, –4.80, –4.57, 13.67, 17.99, 18.28, 22.38, 25.81, 25.85, 25.92, 34.27, 41.84, 58.57, 63.17, 67.12, 73.75, 130.25, 134.15. IR (neat) cm^{-1}: 3368, 2957, 2930, 2897, 2858, 1652, 1472, 1464, 1256, 1116. EI-MS (m/z): 413 (M^+). HRMS Calcd for $C_{22}H_{47}NO_2Si_2$: 413.3145, Found: 413.3150.

(2*S*,3*R*,5*S*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-5-ethylpyrrolidine (25a)

To a solution of **8a** (48.3 mg, 0.130 mmol) in MeOH (2.2 mL) was added PtO_2 (9.7 mg, 20 wt%), and the resulting mixture was stirred under hydrogen at atmospheric pressure at room temperature overnight. The

reaction mixture was then filtered through a plug of Celite, and the Celite filter cake was washed with MeOH. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10:1 → 3:1) to afford **25a** (25.2 mg, 52%) as a pale yellow oil.

$[\alpha]_D^{24}$ –24.3 (*c* 1.26, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (12H, s), 0.87 (21H, m), 1.36 (3H, m), 2.10 (1H, m), 2.94 (2H,m), 3.59 (2H, d, *J* = 4.3 Hz), 4.07 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ –5.47, –5.42, –4.80, –4.55, 11.32, 17.99, 18.26, 25.82, 25.91, 30.59, 40.91, 58.01, 62.27, 66.76, 73.47. IR (neat) cm^{-1}: 3429, 2957, 2930, 2858, 2103, 1644, 1471, 1463, 1256, 1114. EI-MS (m/z): 373 (M^+). HRMS Calcd for $C_{19}H_{43}NO_2Si_2$: 373.2832, Found: 373.2823.

(2*S*,3*R*,5*S*)-5-Butyl-3-{(*tert*-butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]pyrrolidine (25b)

To a solution of **24b** (41.2 mg, 0.103 mmol) in MeOH (1.7 mL) was added PtO_2 (8.2 mg, 20 wt%), and the resulting mixture was stirred under hydrogen at atmospheric pressure at room temperature overnight. The reaction mixture was then filtered through a plug of Celite, and the Celite filter cake was washed with MeOH. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography ($CHCl_3$ only → $CHCl_3$/MeOH = 20:1) to afford **25b** (29.6 mg, 72%) as a pale yellow oil.

$[\alpha]_D^{24}$ –22.9 (*c* 0.96, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (12H, s), 0.89 (21H, m), 1.25 (7H, m), 2.10 (1H, m), 2.96 (1H, m), 3.06 (1H, m), 3.60 (2H, d, *J* = 4.3 Hz), 4.08 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ –5.48, –5.43, –4.82, –4.56, 14.06, 17.97, 18.25, 22.77, 25.80, 25.90, 29.26, 37.62, 41.32, 56.36, 62.27, 66.72, 73.47. IR (neat) cm^{-1}: 3401, 2957, 2930, 2859, 1639, 1472, 1256, 1114. EI-MS (m/z): 401 (M^+). HRMS Calcd for $C_{21}H_{47}NO_2Si_2$: 401.3145, Found: 401.3152.

(2*S*,3*R*,5*S*)-3-{(*tert*-Butyldimethylsilyl)oxy}-2-[{(*tert*-butyldimethylsilyl)oxy}methyl]-5-pentylpyrrolidine (25c)

To a solution of **24c** (18.5 mg, 0.045 mmol) in MeOH (1.0 mL) was added PtO_2 (3.7 mg, 20 wt%), and the resulting mixture was stirred under hydrogen at atmospheric pressure at room temperature overnight. The reaction mixture was then filtered through a plug of Celite, and the Celite filter cake was washed with MeOH. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography ($CHCl_3$ only → $CHCl_3$/MeOH = 20:1) to afford **25c** (11.8 mg, 63%) as a pale yellow oil.

$[\alpha]_D^{24}$ –18.2 (*c* 1.45, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (12H, s), 0.86 (21H, m), 1.25 (9H, m), 2.10 (1H, ddd, *J* = 6.8, 6.8, 13.1 Hz), 2.96 (1H, dd, *J* = 4.3, 10.1 Hz), 3.06 (1H, m), 3.60 (2H, d, *J* = 4.3 Hz), 4.08 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ –5.47, –5.44, –4.81, –4.55, 14.04, 17.97, 18.26, 22.61,

25.80, 25.91, 26.70, 31.88, 37.42, 41.17, 56.57, 62.11, 66.64, 73.34. IR (neat) cm^{-1}: 3401, 2956, 2930, 2858, 1639, 1472, 1256, 1116. EI-MS (m/z): 415 (M^+). HRMS Calcd for $C_{22}H_{49}NO_2Si_2$: 415.3302, Found: 415.3311.

(1*S*,3*R*,4*S*)-1-Ethyl-2-deoxy-L-iminofuranose (2a)

Compound **25a** (14.1 mg, 0.038 mmol) was dissolved in 3 N HCl aq. (0.6 mL), and the mixture was stirred for 1 h at 100 °C. The reaction mixture was concentrated *in vacuo*, and the residue was washed with Et_2O (2 × 5 mL) and purified by silica gel column chromatography (CH_2Cl_2 : MeOH : 25% NH_4OH aq.= 50 : 50 : 1 → MeOH : 25% NH_4OH aq. = 100 : 1) to give **2a** (5.5 mg, quant) as a colorless oil.

$[\alpha]_D^{24}$ –16.6 (*c* 0.81, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 0.91 (3H, t, *J* = 7.2 Hz), 1.37 (3H, m), 2.22 (1H, ddd, *J* = 6.6, 6.8, 12.9 Hz), 2.98 (1H, m), 3.51 (1H, dd, *J* = 5.8, 11.1 Hz), 3.58 (1H, dd, *J* = 4.8, 11.0 Hz), 4.02 (1H, m). ^{13}C-NMR (100 MHz, CD_3OD) δ 11.61, 30.37, 41.37, 59.18, 62.81, 67.57, 73.95. IR (neat) cm^{-1}: 3428, 2930, 2127, 1645, 1463, 1422, 1088. EI-MS (m/z): 145 (M^+). HRMS Calcd for $C_7H_{15}NO_2$: 145.1103, Found: 145.1096.

(1*S*,3*R*,4*S*)-1-*n*-Butyl-2-deoxy-L-iminofuranose (2b)

Compound **25b** (22.6 mg, 0.0563 mmol) was dissolved in 3 N HCl aq. (0.9 mL), and the mixture was stirred for 1 h at 100 °C. The reaction mixture was concentrated *in vacuo*, and the residue was washed with Et_2O (2 × 5 mL) and purified by silica gel column chromatography (CH_2Cl_2 : MeOH : 25% NH_4OH aq. = 100 : 50 : 1.5 → MeOH : 25% NH_4OH aq. = 100 : 1) to give **2b** (9.8 mg, quant) as a colorless oil.

$[\alpha]_D^{24}$ –36.7 (*c* 0.16, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 0.86 (3H, t, *J* = 7.3 Hz), 1.19 (7H, m), 2.19 (1H, m), 3.00 (1H, m), 3.12 (1H, m), 3.46 (1H, dd, *J* = 6.3, 11.6 Hz), 3.55 (1H, dd, *J* = 6.8, 11.4 Hz), 4.00 (1H, m). ^{13}C-NMR (100 MHz, CD_3OD) δ 14.33, 23.76, 30.30, 37.11, 41.67, 57.78, 62.62, 67.65, 73.85. IR (neat) cm^{-1}: 3401, 2958, 2928, 2858, 1651, 1463, 1417, 1120, 1089, 1041. EI-MS (m/z): 173 (M^+). HRMS Calcd for $C_9H_{19}NO_2$: 173.1416, Found: 173.1411.

(1*S*,3*R*,4*S*)-2-Deoxy-1-*n*-pentyl-L-iminofuranose (2c)

Compound **25c** (16.1 mg 0.0387 mmol) was dissolved in 3 N HCl aq. (0.6 mL), and the mixture was stirred for 1 h at 100 °C. The reaction mixture was concentrated *in vacuo*, and the residue was washed with Et_2O (2 × 5 mL) and purified by silica gel column chromatography (CH_2Cl_2 : MeOH : 25% NH_4OH = 100 : 50 : 1.5 → MeOH : 25% NH_4OH = 100 : 1) to give **2c** (7.2 mg, quant) as a colorless oil.

$[\alpha]_D^{24}$ –13.0 (*c* 0.61, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 0.90 (3H, m), 1.29 (9H, m), 2.22 (1H, m), 2.97 (1H, m), 3.07 (1H, m), 3.51 (1H, dd, *J* = 5.8, 11.1 Hz), 3.58 (1H, dd, *J* = 5.3, 11.1 Hz), 4.02 (1H, m). ^{13}C-NMR (100 MHz, CD_3OD) δ 14.3, 23.7, 27.8, 33.0, 37.5, 41.7, 57.7, 62.7, 67.6, 72.9. EI-MS

(m/z): 187 (M^+). HRMS Calcd for $C_{10}H_{21}NO_2$: 187.1572, Found: 187.1579.

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REFERENCES (AND NOTES)

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10. Experimental procedure: Male Wistar rats with body weight of 130 g were obtained from Japan SLC, Inc. (Hamamatsu, Japan). Brush border membranes were prepared from the rat small intestine according to the method of Kessler *et al*.,[11] and were assayed at pH 5.8 for rat intestinal maltase, isomaltase, sucrase, cellobiase, and lactase using the appropriate disaccharides as substrates. The reaction mixture contained 25 mM substrate and the appropriate amount of enzyme, and the incubations were performed for 30 min at 37 °C. The reaction was stopped by heating at 100 °C for 3 min. After centrifugation (600 g; 10 min), the resulting reaction mixture were added to 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.
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