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Synthesis of pachastrissamine (jaspine B) and its derivatives by the late-stage introduction of the C-2 alkyl side-chains using olefin cross metathesis

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ABSTRACT

An improved divergent synthesis of the four diastereomers of pachastrissamine from Garner's aldehyde has been reported. The common intermediate was synthesized by an indium-mediated acetoxyallylation reaction. The long alkyl side chain was introduced in the late stage of the synthesis using an olefin cross metathesis reaction. Biological evaluation of the chain modified analogs of the (2*S*,3*S*,4*R*)-isomer demonstrated that biological activity was highly dependent on the chain length.

1. Introduction

Pachastrissamine (Fig. 1, **1a**), a naturally occurring anhydrophytosphingosine derivative, was isolated from the Okinawan marine sponge, *Pachastrissa* sp.[1a] Shortly after this discovery, a French research group isolated the same compound from the Vanuatuan marine sponge, *Jaspis* sp. and named the compound jaspine B.[1b] Pachastrissamine exhibits marked sub-micromolar cytotoxicity against several cancer cell lines. Delgado et al. reported that the potency of cytotoxicity is dependent on the stereochemistry of the tetrahydrofuran moiety.[1c] Salma et al. revealed that pachastrissamine inhibits sphingomyelin synthase to increase the intracellular level of ceramide, inducing apoptotic cell death by a caspase-dependent pathway.[1d] Due to its impressive biological activity, and simple and unique structure, many total syntheses of pachastrissamine,[2,3] and its stereoisomers (Fig. 1, **2a**–**4a**)[3h,j,k,4] have been reported. Previously, we have developed a stereoselective divergent synthesis of four pachastrissamine diastereomers[3h] and identified that all eight isomers of pachastrissamine exhibit moderate to high inhibitory activity against sphingosine kinase (SphK) 1 and 2.[5] This promising biological activity prompted us to establish a more divergent synthetic route to compounds of this structural class. For the structure–activity relationships associated with the C-2 position[1d,6] to be effectively investigated, a variety of alkyl side-chain should be introduced in the late stage of the synthesis. Herein we report an improved stereoselective and divergent strategy developed for the synthesis of four diastereomers of pachastrissamine involving a late-stage olefin cross metathesis reaction.[3a,j,o,p]

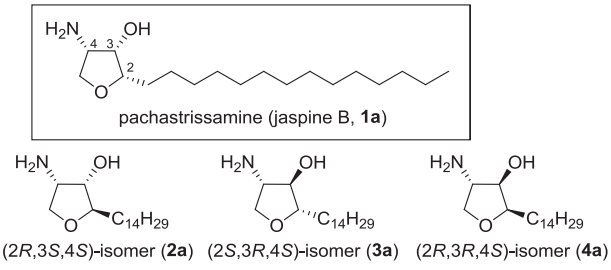

Fig. 1. Structures of pachastrissamine and its diastereomers.

2. Results and discussion

Our strategy for an improved divergent synthesis of pachastrissamine derivatives is outlined in Scheme 1. It was envisaged that the diol **6** could be used as a common intermediate for the synthesis of four isomers. Compound **6** itself could be readily prepared from (*S*)-Garner's aldehyde **5**[7] via an indium-mediated acetoxyallylation.[8] Removal of the acetonide group from **6** would provide the amino triol **7a**. The stereocenter at the C-3 position of

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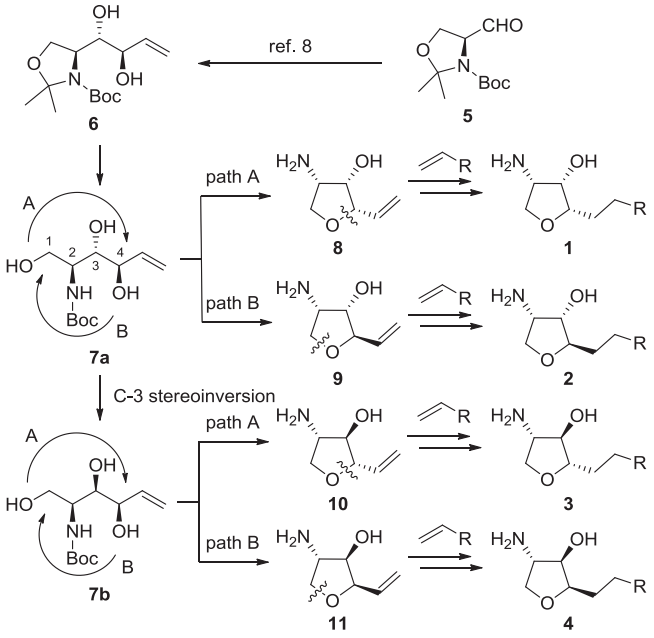
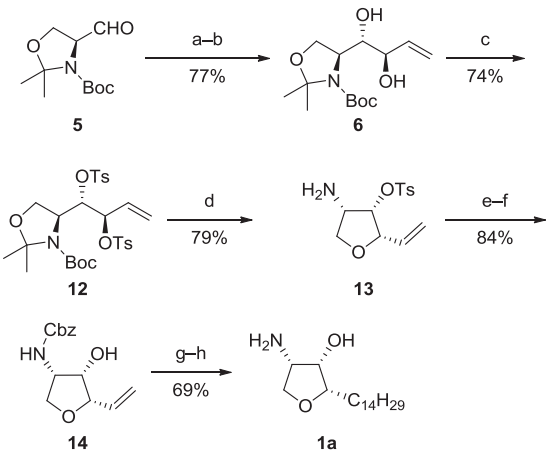


Scheme 1. Strategy for stereoselective divergent synthesis of the four diastereomers of pachastrissamine and their C-2-modified derivatives.

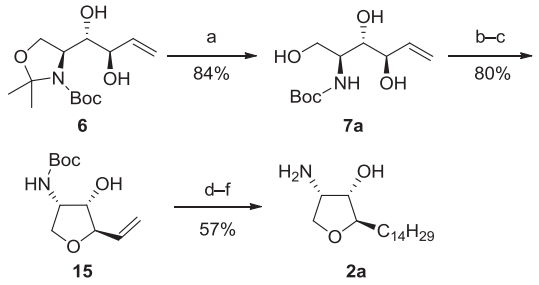
7a could be inverted via a Boc-mediated orthoester ring opening reaction to produce **7b**.[3h] However, this stereoinversion process of **7a** would require fine-tuning of the reaction conditions and/or protecting/activating groups for selective activation of the C-3 position in the presence of the highly active allylic hydroxy group. It was anticipated that the amino triol derivatives **7a** and **7b** would constitute suitable precursors for the tetrahydrofurans **8**–**11**. Thus, the selective activation of the C-4 hydroxy group in **7a** or **7b** would lead to nucleophilic attack by the C-1 hydroxy group to give **8** or **10**, respectively (Scheme 1, path A). In contrast, the conversion of the C-1 hydroxy group in **7a** or **7b** to a suitable leaving group would give **9** or **11**, respectively (Scheme 1, path B). Following the cyclization step, a variety of different alkyl chains could be introduced at the C-2 position using the olefin cross metathesis reaction. Subsequent functional group modification steps would lead to the pachastrissamine derivatives **1**–**4**.

The synthesis started with the acetoxyallylation of (*S*)-Garner's aldehyde **5** (Scheme 2). According to Trombini's protocol,[8] the indium-mediated reductive coupling of **5** with 3-bromoprop-1-enyl acetate followed by solvolysis provided the common intermediate **6** in 77% yield. We initially examined the synthesis of natural pachastrissamine **1a**. The diol **6** was converted to the corresponding bis-tosylate **12** by the treatment with TsCl, Et_3N, and $Me_3N{\cdot}HCl$.[9] The treatment of **12** with $TsOH{\cdot}H_2O$ in MeOH under reflux successfully produced the desired tetrahydrofuran **13** bearing a vinyl group at the C-2-position in 79% yield.[10] Following the cleavage of the tosyl group of **13** with Mg and MeOH, the resulting amino group was protected with the Cbz group.[11] The introduction of the alkyl chain through the olefin cross metathesis reaction with tetradec-1-ene in the presence of the Hoveyda–Grubbs second generation catalyst,[12] followed by concomitant reduction of the double bond and removal of the Cbz group provided pachastrissamine **1a**.



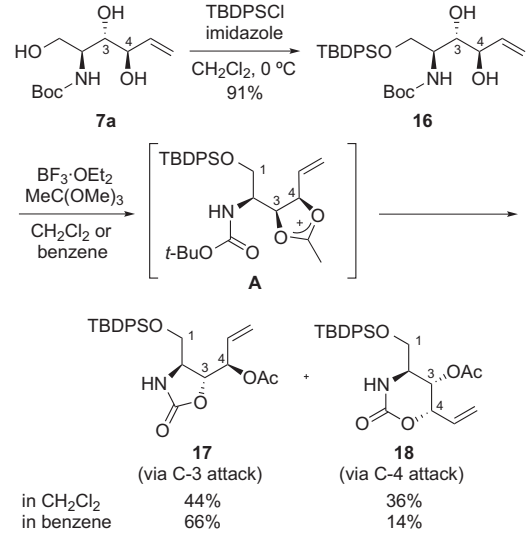
Scheme 2. Synthesis of natural pachastrissamine **1a**. Reagents and conditions: (a) 3-bromoprop-1-enyl acetate, In, DMF, 0 °C; (b) K_2CO_3, $MeOH/H_2O$ (4:1), rt; (c) TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, rt; (d) $TsOH{\cdot}H_2O$, MeOH, reflux; (e) Mg, MeOH, rt; (f) CbzCl, $NaHCO_3$, THF/H_2O (1:1), rt; (g) tetradec-1-ene, Hoveyda–Grubbs II catalyst, CH_2Cl_2, reflux; (h) Pd/C, H_2, EtOH, rt.

The (2*R*,3*S*,4*S*)-isomer **2a** was then prepared in analogy with the reported procedure (Scheme 3).[13] The regioselective tosylation of the primary hydroxy group of **7a**, followed by treatment of the resulting tosylate with K_2CO_3 to give the cyclization product **15**. Following a carbon chain elongation sequence involving the olefin cross metathesis reaction with tetradec-1-ene, followed by hydrogenation, and removal of the Boc group with TFA provided the desired (2*R*,3*S*,4*S*)-isomer **2a**.



Scheme 3. Synthesis of the (2*R*,3*S*,4*S*)-isomer **2a**. Reagents and conditions: (a) $TsOH{\cdot}H_2O$, MeOH, rt; (b) TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, −78 °C; (c) K_2CO_3, MeOH, rt; (d) tetradec-1-ene, Hoveyda–Grubbs II catalyst, CH_2Cl_2, reflux; (e) Pd/C, H_2, EtOH, rt; (f) TFA, CH_2Cl_2, rt.

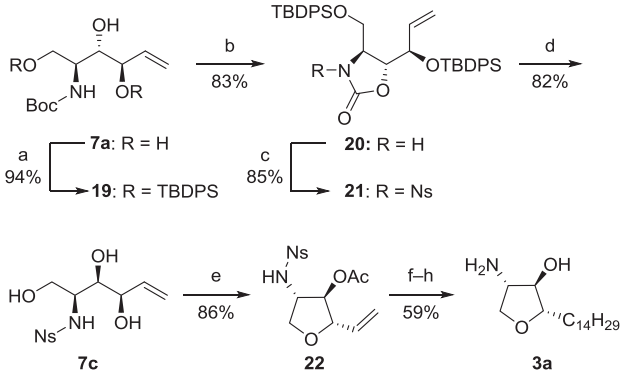
Next, the synthesis of the (2*S*,3*R*,4*S*)-isomer **3a** was attempted, which required the regioselective inversion of the stereogenic center at the C-3 position (Scheme 4). It was envisaged that this transformation could be accomplished via the regio- and stereospecific ring-opening reaction of the orthoester **A** at the C-3



Scheme 4. The stereoinversion of the C-3 position of the **7a** by orthoester formation.

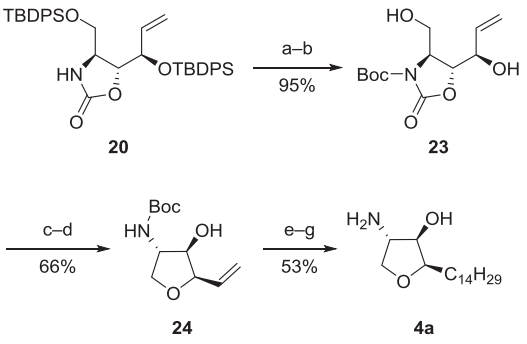
position, based on our previous synthetic strategy.[3h] Thus, the stereoinversion of the C-3 position of **7a** would be achieved through orthoester formation and intramolecular nucleophilic attack of the carbonyl oxygen of the Boc group. Following silyl protection of the primary hydroxy group in **7a**, the resulting silyl ether **16** was subjected to the stereoinversion conditions. The treatment of **16** with $MeC(OMe)_3$ in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 afforded the desired oxazolidinone **17** (44%). Unfortunately, however, the product was also accompanied by a considerable amount of the undesired regioisomer **18** (36%). The low level of regioselectivity observed in this particular case was attributed to the enhanced reactivity at the allylic position toward the nucleophilic attack of the Boc oxygen to promote the formation of the six-membered ring. A series of other reaction conditions were then evaluated with a view to improving the selectivity. When the reaction was conducted in the presence of $BF_3{\cdot}OEt_2$ in benzene, a moderate improvement in the selectivity was observed, with the cyclized products **17** and **18** being obtained in 66% and 14% yields, respectively. In contrast, when the reaction was conducted in the presence of Me_2AlCl or $Zn(OTf)_2$, none of the cyclized product was formed.

With the results of the poor regioselectivity in the stereoinversion process, our work proceeded toward the investigation of an alternative strategy involving the use of thionyl chloride as an activating agent (Scheme 5). The hydroxy groups at the C-1 and C-4 positions were selectively protected with TBDPSCl/imidazole at −20 °C to give the corresponding silyl ether **19** in 94% yield. The desired C-3 stereoinversion product **20** was obtained in 83% yield by the reaction of **19** with thionyl chloride. Subsequent protection of the carbamate nitrogen with a nosyl group followed by cleavage of the silyl ether and cyclic carbamate under strongly basic conditions provided the free triol **7c**. The cyclization of **7c** was then attempted using the hydroxy group at the C-4 position as a leaving group. For this particular transformation, the construction of the tetrahydrofuran ring via the orthoester was attempted according to the conditions reported by Overkleeft et al.[13] in their synthesis of pachastrissamine using an azido-triol. The orthoesterification of **7c** using $MeC(OMe)_3$ in the presence of $BF_3{\cdot}OEt_2$ proceeded smoothly to give the tetrahydrofuran cyclization product **22**. The introduction of the alkyl chain by olefin cross metathesis followed by sequential removal of the Ns and Ac groups and hydrogenation of the alkene provided the (2*S*,3*R*,4*S*)-isomer **3a**.



Scheme 5. Synthesis of the (2*S*,3*R*,4*S*)-isomer **3a**. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, −20 °C; (b) $SOCl_2$, THF, reflux; (c) NsCl, NaH, THF, rt; (d) TBAF, then KOH aq, THF, rt; (e) $MeC(OMe)_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt; (f) tetradec-1-ene, Hoveyda–Grubbs II catalyst, CH_2Cl_2, reflux; (g) PhSH, Cs_2CO_3, then KOH aq, MeCN, rt; (h) Pd/C, H_2, EtOH, rt.

With a successful strategy in hand, the stage was now set for the synthesis of the (2*R*,3*R*,4*S*)-isomer **4a** (Scheme 6). The protection of **20** with Boc_2O, followed by desilylation provided the primary alcohol **23**. Selective monotosylation of the primary hydroxy group, followed by alcoholysis of the oxazolidinone successfully afforded tetrahydrofuran **24**. This compound was subjected to the olefin cross metathesis reaction, followed by sequential hydrogenation and deprotection reactions similar to those used for the other isomers to produce the (2*R*,3*R*,4*S*)-isomer **4a**. The spectroscopic and optical rotation data for the synthetic materials **1a**–**4a** matched those reported previously in all respects.[1–4]



Scheme 6. Synthesis of the (2*R*,3*R*,4*S*)-isomer **4a**. Reagents and conditions: (a) Boc_2O, Et_3N, DMAP, THF, rt; (b) $3HF{\cdot}Et_3N$, THF, reflux; (c) TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, −78 °C; (d) K_2CO_3, MeOH, rt; (e) tetradec-1-ene, Hoveyda–Grubbs II catalyst, CH_2Cl_2, reflux; (f) Pd/C, H_2, EtOH, rt; (g) TFA, CH_2Cl_2, rt.

To conclude this work, the introduction of a variety of different alkyl groups of different chain lengths at the C-2 position was investigated using the established procedures. The protected vinyl congener *ent*-**24**, the precursor of the (2*S*,3*S*,4*R*)-isomer *ent*-**4**, was selected for this particular series of derivatization experiments because it possessed the most potent SphK inhibitory activity of the eight different stereoisomers.[5] The *ent*-**24** was prepared starting from (*R*)-Garner's aldehyde, according to the same procedures used for the synthesis of **24**. Reactions with alkenes of different chain lengths followed by sequential reduction and deprotection afforded the desired products *ent*-**4a**–**l** (Table 1).

ent-**4a**–**e** were then evaluated for their in vitro inhibitory activity of SphK1 and SphK2 using LabChip3000 system (Table 2).[14] For this series of compounds, the *ent*-**4a**, having an alkyl group with the same chain length as natural pachastrissamine, exhibited the most potent inhibitory activity. Side-chain elongated analog *ent*-**4b** was slightly less potent than *ent*-**4a**. Chain truncated derivatives *ent*-**4c**–**e** showed a marked decrease in activity as the alkyl chain length decreased, the similar trend as observed for the inhibition of sphingomyelin synthase.[6b]

3. Conclusions

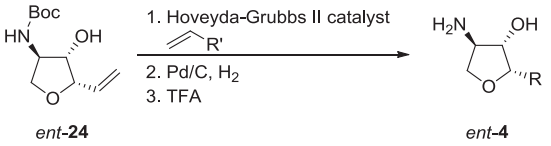
In conclusion, we have developed an improved stereoselective divergent synthesis of four pachastrissamine diastereomers by the late-stage olefin cross metathesis. The regioselectivity issue in the stereoinversion step has been overcome by use of thionyl chloride-mediated cyclization of the appropriately protected triol derivative **19**. This strategy provides an efficient synthetic route to all pachastrissamine stereoisomers and their side-chain derivatives. Biological evaluations of the chain modified analogs of the (2*S*,3*S*,4*R*)-isomer demonstrated that naturally occurring C14 alkyl chain was most appropriate for the potent SphK inhibitory activity.

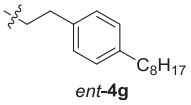
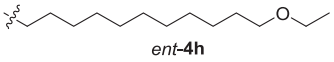
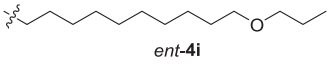
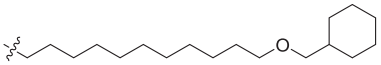
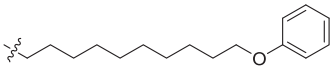
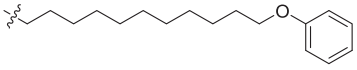
4. Experimental

4.1. General methods

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an argon atmosphere and all

Table 1
Synthesis of the (2*S*,3*S*,4*R*)-isomer (*ent*-**4a**) and its side-chain derivatives (*ent*-**4b**–**l**)



R	Yield (%)
$C_{14}H_{29}$ (*ent*-**4a**)	44
$C_{16}H_{33}$ (*ent*-**4b**)	51
$C_{12}H_{25}$ (*ent*-**4c**)	46
$C_{10}H_{21}$ (*ent*-**4d**)	52
C_8H_{17} (*ent*-**4e**)	44
$CH{=}CH_2$ (*ent*-**4f**)	89[a]
 *ent*-**4g**	20
 *ent*-**4h**	56
 *ent*-**4i**	42
 *ent*-**4j**	53
 *ent*-**4k**	49
 *ent*-**4l**	52

[a] The olefin cross metathesis and reduction were not carried out.

Table 2
SphK inhibitory activity of (2*S*,3*S*,4*R*)-isomer (*ent*-**4a**) and its side-chain derivatives (*ent*-**4b**–**e**)

Compound	IC_{50} (μM)[a]	
	SphK1	SphK2
ent-**4a**	1.0	0.52
ent-**4b**	1.2	2.1
ent-**4c**	8.2	1.9
ent-**4d**	>30	7.7
ent-**4e**	>30	>30

[a] IC_{50} values are the concentrations for 50% inhibition of the sphingosine phosphorylation by SphK1 or SphK2. The data were derived from the dose–response curves generated from duplicate data points.

glassware was dried in an oven for 2 h at 80 °C prior to use. Reactions at −78 °C employed a CO_2–MeOH bath. Melting points were measured by a hot stage melting point apparatus (uncorrected). ^{1}H NMR spectra were recorded at 500 or 400 MHz frequency, and chemical shifts are reported in δ (parts per million) relative to TMS (in $CDCl_3$) as internal standard. ^{13}C NMR spectra were recorded at 125 or 100 MHz frequency and referenced to the residual $CHCl_3$ signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b=broad, s=singlet, d=doublet, t=triplet, q=quartet, br s=broad singlet, m=multiplet), number of protons, and coupling constant(s).

4.2. *tert*-Butyl (*S*)-4-[(1*S*,2*R*)-1,2-dihydroxybut-3-enyl]-2,2-dimethyloxazolidine-3-carboxylate (6)

To a stirred solution of **5** (671 mg, 2.93 mmol) in DMF (15 mL) were added 3-bromoprop-1-enyl acetate (1.06 mL, 8.76 mmol) and indium (1.01 g, 8.80 mmol) at 0 °C. After stirring for 6 h at this temperature, H_2O was added to the mixture, and the whole was extracted with EtOAc. The extract was dried over $MgSO_4$, and the filtrate was concentrated under reduced pressure to give an oily residue, which was dissolved in MeOH/H_2O (15 mL, 4:1). To this solution was added K_2CO_3 (810 mg, 5.86 mmol) at room temperature, and the mixture was stirred for 1 h at this temperature. The mixture was quenched by addition of saturated aqueous NH_4Cl at 0 °C. MeOH was removed under reduced pressure and the aqueous layer was extracted with EtOAc. The extract was dried over $MgSO_4$, and the filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1) to give **6** as a colorless oil (644 mg, 77% yield): $[\alpha]_D^{25}$ +2.2 (*c* 0.97, $CHCl_3$); IR (neat): 3413 (OH), 1690 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.51 (s, 3H), 1.56 (s, 3H), 2.75–3.10 (br s, 1H), 3.66–3.74 (m, 1H), 3.75–3.90 (br s, 1H), 3.94–3.98 (m, 1H), 4.02–4.07 (m, 1H), 4.16–4.18 (m, 1H), 4.26–4.28 (m, 1H), 5.15–5.17 (m, 1H), 5.33–5.37 (m, 1H), 5.96 (ddd, *J*=17.2, 9.2, 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 27.0, 28.4 (3C), 58.8, 65.4, 74.5, 74.9, 81.4, 94.1, 114.9, 136.8, 153.9; HRMS (FAB) calcd for $C_{14}H_{25}NNaO_5$: $[M+Na]^+$, 310.1630; found: 310.1636.

4.3. *tert*-Butyl (*S*)-4-[(1*S*,2*R*)-1,2-bis(tosyloxy)but-3-enyl]-2,2-dimethyloxazolidine-3-carboxylate (12)

To a stirred solution of **6** (77 mg, 0.268 mmol) in CH_2Cl_2 (1.3 mL) were added TsCl (204 mg, 1.07 mmol), Et_3N (300 μL, 2.16 mmol), and $Me_3N{\cdot}HCl$ (26 mg, 0.272 mmol) at room temperature. After stirring for 6 h at this temperature, the mixture was quenched by addition of saturated NH_4Cl at 0 °C, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (7:1) to give **12** as a pale yellow oil (118 mg, 74% yield): $[\alpha]_D^{25}$ −32.6 (*c* 1.90, $CHCl_3$); IR (neat): 1692 (C=O), 1369 (OSO_2), 1178 (OSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32–1.46 (m, 6H), 1.48 (s, 9H), 2.43 (s, 3H), 2.45 (s, 3H), 3.87–3.90 (m, 1H), 3.96–4.10 (m, 2H), 5.17–5.30 (m, 1H), 5.19–5.21 (m, 3H), 5.72 (ddd, *J*=16.0, 10.3, 5.7 Hz, 1H), 7.29 (d, *J*=8.6 Hz, 2H), 7.32 (d, *J*=8.6 Hz, 2H), 7.69 (d, *J*=8.0 Hz, 2H), 7.77 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6 (2C), 24.9, 26.4, 28.3 (3C), 56.2, 63.0, 78.8, 80.9, 81.6, 93.8, 120.6, 127.9 (2C), 128.2 (2C), 129.7 (4C), 129.8, 133.6 (2C), 144.9 (2C), 152.8; HRMS (FAB) calcd for $C_{28}H_{37}NNaO_9S_2$: $[M+Na]^+$, 618.1807; found: 618.1805.

4.4. (2*S*,3*S*,4*S*)-4-Amino-2-vinyltetrahydrofuran-3-yl 4-methyl benzenesulfonate (13)

To a stirred solution of **12** (1.03 g, 1.73 mmol) in MeOH (58 mL) was added $TsOH{\cdot}H_2O$ (330 mg, 1.73 mmol) at room temperature. After stirring for 6 h under reflux, the mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with $CHCl_3$–MeOH–28% NH_4OH (95:4:1) to give **13** as a white solid (386 mg, 79% yield): mp 87–88 °C; $[\alpha]_D^{25}$ +41.2 (*c* 1.01, $CHCl_3$); IR (neat): 3395 (NH), 1367 (OSO_2), 1176 (OSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 2H), 2.46 (s, 3H), 3.51 (dd, *J*=8.3, 8.0 Hz, 1H), 3.75 (ddd, *J*=8.3, 8.3, 4.6 Hz 1H), 4.06 (dd, *J*=8.3, 8.0 Hz, 1H), 4.41 (dd, *J*=5.7, 4.0 Hz, 1H), 4.87 (dd, *J*=4.6, 4.0 Hz, 1H), 4.99–5.01 (m, 1H), 5.17–5.21 (m, 1H), 5.55 (ddd, *J*=17.2, 10.3, 5.7 Hz, 1H), 7.34 (d, *J*=8.0 Hz, 2H), 7.79 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 55.2, 71.6, 81.6, 83.9, 118.4,

127.9 (2C), 129.8 (2C), 132.5, 133.6, 145.1. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 54.89; H, 6.05; N, 4.85.

4.5. Benzyl [(3*S*,4*S*,5*S*)-4-hydroxy-5-vinyltetrahydrofuran-3-yl] carbamate (14)

To a stirred solution of **13** (251 mg, 0.886 mmol) in MeOH (18 mL) was added Mg (215 mg, 8.84 mmol) at room temperature. After stirring for 1 h at this temperature, the mixture was concentrated under reduced pressure followed by rapid filtration through a short pad of silica gel with $CHCl_3$–MeOH–28% NH_4OH (95:4:1) to give a crude amino alcohol, which was used without further purification. To a stirred mixture of the above amino alcohol in THF/H_2O (8.8 mL, 1:1) were added CbzCl (174 μL, 1.23 mmol) and $NaHCO_3$ (104 mg 1.24 mmol), and the mixture was stirred for 30 min at room temperature. THF was removed under reduced pressure, and the residue was extracted with EtOAc and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a white solid, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) to give **14** as a white solid (195 mg, 84% yield): mp 80–81 °C; $[\alpha]_D^{25}$ +17.2 (*c* 0.94, $CHCl_3$); IR (neat): 3337 (NH and OH), 1718 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (br s, 1H), 3.65–3.68 (m, 1H), 4.14–4.16 (m, 2H), 4.45–4.57 (m, 2H), 5.10–5.12 (m, 2H), 5.38–5.40 (m, 2H), 5.46–5.49 (m, 1H), 5.55 (ddd, *J*=17.2, 10.3, 5.2 Hz, 1H), 7.31–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.5, 67.0, 70.3, 71.8, 82.4, 119.1, 128.1, 128.2 (2C), 128.5 (2C), 132.7, 136.2, 156.1. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.71; H, 6.54; N, 5.30.

4.6. (2*S*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (1a)

To a stirred solution of **14** (105 mg, 0.399 mmol) in CH_2Cl_2 (8.0 mL) were added tetradec-1-ene (1.01 mL, 3.99 mmol) and second generation Hoveyda–Grubbs catalyst (25 mg, 0.0399 mmol) at room temperature. After stirring for 10 h under reflux, the mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give the *E*/*Z* mixture of corresponding metathesis product as a white solid. To a stirred solution of the above metathesis product in EtOH (20 mL) was added 10% Pd/C (42 mg, 0.0395 mmol) at room temperature, and the mixture was stirred for 3 h at this temperature under H_2. The mixture was filtrated, and the filtrate was concentrated under reduced pressure to give a white solid, which was purified by column chromatography over silica gel with $CHCl_3$–MeOH–28% NH_4OH (100:3:1) to give **1a** as a white solid (82 mg, 69% yield): mp 94–95 °C; IR (neat): 3344 (NH and OH); $[\alpha]_D^{25}$ +15.6 (*c* 0.49, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.20–1.48 (m, 26H), 1.59–1.73 (m, 2H), 3.51 (dd, *J*=8.6, 6.9 Hz, 1H), 3.64–3.68 (m, 1H), 3.73 (ddd, *J*=7.4, 6.9, 3.7 Hz, 1H), 3.86 (dd, *J*=4.9, 3.7 Hz, 1H), 3.92 (dd, *J*=8.6, 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.3, 29.3, 29.4, 29.6, 29.7 (6C), 29.8, 31.9, 54.3, 71.8, 72.4, 83.2. Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 71.93; H, 12.68; N, 4.61.

4.7. *tert*-Butyl [(2*S*,3*S*,4*R*)-1,3,4-trihydroxyhex-5-en-2-yl] carbamate (7a)

To a stirred solution of **6** (108 mg, 0.376 mmol) in MeOH (7.5 mL) was added TsOH·H_2O (7.2 mg, 0.0379 mmol) at 0 °C, and the mixture was warmed to room temperature. After stirring for 4 h at this temperature, the mixture was quenched by addition of Et_3N (5.3 μL, 0.0379 mmol) at 0 °C, and concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:2) to give **7a** as a white solid (78 mg, 84% yield): mp 88–89 °C; $[\alpha]_D^{25}$ +15.8 (*c* 1.27, $CHCl_3$); IR (neat): 3331 (NH and OH), 1686 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.58–3.59 (m, 2H), 3.67 (d, *J*=5.7 Hz, 1H), 3.71–3.76 (m, 3H), 3.91–3.94 (m, 1H), 4.26–4.27 (m, 1H), 5.26–5.28 (m, 1H), 5.36–5.39 (m, 2H), 6.00 (ddd, *J*=17.2, 10.9, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4 (3C), 52.6, 61.9, 73.9, 74.9, 80.1, 116.8, 136.5, 156.3. Anal. Calcd for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.23; H, 8.37; N, 5.66.

4.8. *tert*-Butyl [(3*S*,4*S*,5*R*)-4-hydroxy-5-vinyltetrahydrofuran-3-yl]carbamate (15)

To a stirred solution of **7a** (69 mg, 0.279 mmol) and Et_3N (773 μL, 5.58 mmol) in CH_2Cl_2 (5.6 mL) were added TsCl (214 mg, 1.12 mmol) and Me_3N·HCl (27 mg, 0.282 mmol) at −78 °C. After stirring for 30 min at this temperature, the mixture was quenched by addition of saturated aqueous NH_4Cl, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a white solid, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give the corresponding tosylate as a white solid. To a stirred solution of the tosylate in MeOH (9.3 mL) was added K_2CO_3 (33 mg, 0.239 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. The mixture was quenched by addition of saturated NH_4Cl, and concentrated under reduced pressure. The residue was extracted with EtOAc and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a white solid, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **15** as a white solid (51 mg, 80% yield): mp 53–54 °C; $[\alpha]_D^{25}$ +28.8 (*c* 0.93, $CHCl_3$); IR (neat): 3438 (NH and OH), 1692 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.79 (br, s, 1H), 3.61–3.64 (m, 1H), 4.02–4.04 (m, 1H), 4.21–4.25 (m, 3H), 5.11 (br, s, 1H), 5.21–5.23 (m, 1H), 5.35–5.38 (m, 1H), 5.84 (ddd, *J*=17.2, 10.3, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (3C), 52.5, 70.6, 74.9, 80.1, 85.4, 116.9, 135.6, 156.0. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.36; H, 8.18; N, 6.08.

4.9. (2*R*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (2a)

To a stirred solution of **15** (109 mg, 0.475 mmol) in CH_2Cl_2 (9.5 mL) were added tetradec-1-ene (1.20 mL, 4.74 mmol) and second generation Hoveyda–Grubbs catalyst (30 mg, 0.0479 mmol) at room temperature. After stirring for 12 h under reflux, the mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give the *E*/*Z* mixture of corresponding metathesis product as a white solid. To a stirred solution of the above metathesis product in EtOH (9.5 mL) was added 10% Pd/C (51 mg, 0.0479 mmol) at room temperature, and the mixture was stirred for 2 h at this temperature under H_2. The mixture was filtrated, and the filtrate was concentrated under reduced pressure to give a white solid, which was dissolved in CH_2Cl_2 (9.5 mL). To this solution was added TFA (9.5 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with $CHCl_3$–MeOH–28% NH_4OH (100:3:1) to give **2a** as a white solid (79 mg, 57% yield): mp 102–103 °C; $[\alpha]_D^{25}$ +14.1 (*c* 0.35, EtOH); IR (neat): 3342 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.22–1.48 (m, 24H), 1.48–1.63 (m, 2H), 1.90–2.37 (br s, 3H), 3.40 (dd, *J*=8.6, 6.9 Hz, 1H), 3.46 (m, 1H), 3.58–3.64 (m, 2H), 4.12 (dd, *J*=8.6, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.8, 29.3, 29.5, 29.6, 29.7 (6C), 31.9, 33.7, 52.6, 73.2, 74.8, 85.2. Anal. Calcd for $C_{18}H_{37}NO_2 \cdot 0.2H_2O$: C, 71.33; H, 12.44; N, 4.62. Found: C, 71.57; H, 12.51, N 4.67.

4.10. *tert*-Butyl [(2*S*,3*S*,4*R*)-1-(*tert*-butyldiphenylsilyloxy)-3,4-dihydroxyhex-5-en-2-yl]carbamate (16)

To a stirred solution of **7a** (2.35 g, 9.50 mmol) in CH_2Cl_2 (95 mL) were added imidazole (1.62 g, 23.8 mmol) and TBDPSCl (3.50 mL, 13.5 mmol) at 0 °C. After stirring for 30 min at this temperature, the mixture was quenched by addition of saturated NH_4Cl, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give **16** as a colorless oil (4.22 g, 91% yield): $[\alpha]_D^{25}$ +16.9 (*c* 1.42, $CHCl_3$); IR (neat): 3442 (NH and OH), 1694 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.43 (s, 9H), 2.79–2.88 (m, 2H), 3.72–3.81 (m, 3H), 4.03 (d, *J*=10.3 Hz, 1H), 4.27–4.29 (m, 1H), 5.07 (d, *J*=8.0 Hz, 1H), 5.20–5.22 (m, 1H), 5.32–5.35 (m, 1H), 6.00 (ddd, *J*=17.8, 10.3, 5.2 Hz, 1H), 7.38–7.46 (m, 6H), 7.64–7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 26.9 (3C), 28.4 (3C), 52.5, 63.8, 74.3, 74.6, 79.9, 115.9, 127.9 (4C), 130.0 (2C), 132.6 (2C), 135.5 (2C), 135.6 (2C), 136.8, 155.9; HRMS (FAB) calcd for $C_{27}H_{40}NO_5Si$: $[M+H]^+$, 486.2670; found: 486.2673.

4.11. (*R*)-1-{(4*S*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2-oxooxazolidin-5-yl}allyl acetate (17) and (4*S*,5*S*,6*S*)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-2-oxo-6-vinyl-1,3-oxazinan-5-yl acetate (18)

To a stirred solution of **16** (56 mg, 0.115 mmol) in CH_2Cl_2 (12 mL) were added $MeC(OMe)_3$ (86 μL, 0.687 mmol) and $BF_3\cdot OEt_2$ (2.8 μL, 0.0227 mmol) at 0 °C, and the mixture was warmed to room temperature. After stirring for 1.5 h at this temperature, the mixture was quenched by addition of MeOH at 0 °C, and concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **17** (23 mg, 44% yield) and **18** (19 mg, 36% yield) both as a colorless oil.

Compound **17**: $[\alpha]_D^{25}$ −33.1 (*c* 0.93, $CHCl_3$); IR (neat): 3262 (NH), 1763 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.05 (s, 3H), 3.60 (d, *J*=5.2 Hz, 2H), 3.68 (dd, *J*=9.5, 5.2 Hz, 1H), 4.40–4.42 (m, 1H), 5.34–5.42 (m, 3H), 5.58 (s, 1H), 6.00 (ddd, *J*=16.6, 10.9, 6.3 Hz, 1H), 7.38–7.42 (m, 4H), 7.43–7.49 (m, 2H), 7.62 (d, *J*=5.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 20.9, 26.7 (3C), 54.9, 65.1, 73.9, 78.0, 121.1, 127.9 (4C), 130.1 (2C), 130.5, 132.5 (2C), 135.5 (4C), 158.2, 169.6; HRMS (FAB) calcd for $C_{25}H_{32}NO_5Si$: $[M+H]^+$, 454.2044; found: 454.2046.

Compound **18**: $[\alpha]_D^{25}$ −40.2 (*c* 1.75, $CHCl_3$); IR (neat): 3249 (NH), 1714 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 2.07 (s, 3H), 3.53–3.57 (m, 1H), 3.65 (dd, *J*=10.6, 5.4 Hz, 1H), 3.71 (dd, *J*=10.6, 6.0 Hz, 1H), 4.83–4.85 (m, 1H), 5.15–5.16 (m, 1H), 5.32–5.34 (m, 1H), 5.42–5.45 (m, 1H), 5.72–5.79 (m, 2H), 7.39–7.42 (m, 4H), 7.43–7.47 (m, 2H), 7.62–7.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 20.7, 26.8 (3C), 55.8, 64.9, 65.7, 75.5, 119.3, 128.0 (4C), 130.1, 130.2, 130.8, 132.2, 132.3, 135.5 (2C), 135.6 (2C), 153.0, 169.9; HRMS (FAB) calcd for $C_{25}H_{32}NO_5Si$: $[M+H]^+$, 454.2044; found: 454.2049.

4.12. *tert*-Butyl [(2*S*,3*S*,4*R*)-1,4-bis(*tert*-butyldiphenylsilyloxy)-3-hydroxyhex-5-en-2-yl]carbamate (19)

To a stirred solution of **7a** (2.50 g, 10.1 mmol) in CH_2Cl_2 (100 mL) were added imidazole (2.75 g, 40.4 mmol) and TBDPSCl (7.86 mL, 30.2 mmol) at −20 °C. After stirring for 19 h at this temperature, the mixture was quenched by addition of saturated NH_4Cl, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over NH silica gel with *n*-hexane–toluene (1:1) to give **19** as a colorless oil (6.86 g, 94% yield): $[\alpha]_D^{25}$ +11.5 (*c* 1.09, $CHCl_3$); IR (neat): 3445 (NH and OH), 1714 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.09 (s, 9H), 1.36 (s, 9H), 2.38 (d, *J*=3.4 Hz, 1H), 3.55 (m, 1H), 3.60–3.65 (m, 2H), 3.90 (m, 1H), 4.33 (m, 1H), 4.47 (d, *J*=9.7 Hz, 1H), 5.20–5.24 (m, 2H), 5.96 (ddd, *J*=17.2, 10.9, 6.3 Hz, 1H), 7.31–7.44 (m, 12H), 7.57–7.67 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3 (2C), 26.9 (3C), 27.0 (3C), 28.3 (3C), 52.1, 63.2, 74.0, 75.1, 79.1, 118.3, 127.5 (3C), 127.7 (3C), 129.7 (3C), 129.9 (3C), 133.1, 133.3, 133.4, 133.7, 135.1, 135.5 (2C), 135.6 (2C), 135.8 (2C), 135.9 (2C), 155.0. Anal. Calcd for $C_{43}H_{57}NO_5Si_2$: C, 71.33; H, 7.93; N, 1.93. Found: C, 71.59; H, 7.97; N, 1.98.

4.13. (4*S*,5*R*)-5-[(*R*)-1-(*tert*-Butyldiphenylsilyloxy)allyl]-4-[(*tert*-butyldiphenylsilyloxy)methyl]oxazolidin-2-one (20)

To a stirred solution of **19** (280 mg, 0.387 mmol) in THF (7.7 mL) was added $SOCl_2$ (140 μL, 1.93 mmol) at 0 °C, and the mixture was stirred for 16 h under reflux. The mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (7:1) to give **20** as a yellow oil (210 mg, 83% yield): $[\alpha]_D^{25}$ −9.5 (*c* 1.11, $CHCl_3$); IR (neat): 3280 (NH), 1759 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.03 (s, 9H), 3.47 (dd, *J*=10.3, 6.9 Hz, 1H), 3.56 (dd, *J*=10.3, 3.4 Hz, 1H), 3.82–3.84 (m, 1H), 3.99 (dd, *J*=4.9, 4.6 Hz, 1H), 4.37 (dd, *J*=6.0, 4.9 Hz, 1H), 5.05 (s, 1H), 5.18–5.25 (m, 2H), 6.00 (ddd, *J*=17.2, 10.9, 6.0 Hz, 1H), 7.27–7.46 (m, 12H), 7.56–7.61 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.3, 26.7 (3C), 27.0 (3C), 30.9, 54.0, 66.1, 73.4, 78.8, 119.0, 127.6 (2C), 127.8 (2C), 127.9 (2C), 129.9 (2C), 130.0 (2C), 130.1, 132.7 (2C), 132.8, 133.1, 134.0, 135.4 (2C), 135.5 (2C), 135.7 (2C), 135.8 (2C), 158.2; HRMS (FAB) calcd for $C_{39}H_{48}NO_4Si_2$: $[M+H]^+$ 650.3116; found: 650.3113.

4.14. (4*S*,5*R*)-5-[(*R*)-1-(*tert*-Butyldiphenylsilyloxy)allyl]-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-[(2-nitrophenyl)sulfonyl]oxazolidin-2-one (21)

To a stirred solution of **20** (460 mg, 0.708 mmol) in THF (3.5 mL) was added NaH (56 mg, 1.41 mmol) at 0 °C. After stirring for 30 min at room temperature, NsCl (312 mg, 1.41 mmol) was added. The mixture was stirred for 1 h at room temperature, and quenched by addition of saturated NH_4Cl at 0 °C. The whole was extracted with Et_2O. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–toluene (1:1) to give **21** as a colorless oil (502 mg, 85% yield): $[\alpha]_D^{25}$ +154.6 (*c* 0.63, $CHCl_3$); IR (neat): 1783 (C=O), 1371 (NO_2 and NSO_2), 1138 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.08 (s, 9H), 3.61 (dd, *J*=11.5, 1.7 Hz, 1H), 4.19–4.24 (m, 2H), 4.41 (dd, *J*=6.9, 2.9 Hz, 1H), 4.50–4.51 (m, 1H), 4.81–4.83 (m, 1H), 5.04–5.08 (m, 1H), 5.60 (ddd, *J*=17.8, 10.3, 7.4 Hz, 1H), 7.15–7.18 (m, 1H), 7.22–7.26 (m, 3H), 7.30–7.33 (m, 1H), 7.37–7.47 (m, 6H), 7.52–7.54 (m, 4H), 7.65–7.68 (m, 4H), 7.70–7.72 (m, 1H), 7.74–7.77 (m, 1H), 7.80–7.83 (m, 1H), 8.47 (dd, *J*=8.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.3, 26.7 (3C), 26.9 (3C), 59.4, 64.8, 74.2, 79.0, 121.0, 124.2, 127.4 (2C), 127.5 (2C), 127.8 (2C), 127.9 (2C), 129.7, 129.8, 130.0 (2C), 131.1, 132.0, 132.2, 132.7 (2C), 133.0, 133.3, 134.3, 134.9, 135.6 (2C), 135.8 (4C), 135.9 (2C), 147.8, 151.3; HRMS (FAB) calcd for $C_{45}H_{50}N_2NaO_8SSi_2$: $[M+H]^+$ 857.2724; found: 857.2729.

4.15. 2-Nitro-*N*-[(2*S*,3*R*,4*R*)-1,3,4-trihydroxyhex-5-en-2-yl] benzenesulfonamide (7c)

To a stirred solution of **21** (142 mg, 0.518 mmol) in THF (5.2 mL) was added TBAF (1.0 M in THF; 2.07 mL, 2.07 mmol) at 0 °C. After

stirring for 2 h at room temperature, 1 N KOH (5.2 mL, 5.20 mmol) was added. The mixture was stirred for 1 h at room temperature, and quenched by addition of saturated NH_4Cl at 0 °C. The mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The extract was dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with $CHCl_3$–MeOH (20:1) to give **7c** as a yellow solid (142 mg, 82% yield): mp 148–149 °C; $[\alpha]_D^{25}$ +13.8 (*c* 0.33, MeCN); IR (neat): 3370 (NH and OH), 1363 (NO_2 and NSO_2), 1168 (NSO_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 3.58–3.68 (m, 3H), 3.72–3.73 (m, 1H), 4.02–4.04 (m, 2H), 4.22–4.26 (m, 2H), 5.06–5.08 (m, 1H), 5.11–5.15 (m, 1H), 5.83 (ddd, *J*=17.2, 11.5, 5.8 Hz, 1H), 6.25 (br s, 1H), 7.88–7.93 (m, 2H), 7.98–8.02 (m, 1H), 8.15–8.20 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 57.3, 62.8, 73.1, 73.2, 117.0, 126.0, 131.2, 133.8, 134.7, 135.7, 138.6, 148.8. Anal. Calcd for $C_{12}H_{16}N_2O_7S$: C, 43.37; H, 4.85; N, 8.43. Found: C, 43.26; H, 4.67; N, 8.41.

4.16. (2*S*,3*R*,4*S*)-4-(2-Nitrobenzenesulfonylamido)-2-vinyltetrahydofuran-3-yl acetate (22)

To a stirred solution of **7c** (133 mg, 0.400 mmol) in CH_2Cl_2 (8.0 mL) were added $MeC(OMe)_3$ (300 μL, 2.40 mmol) and $BF_3\cdot OEt_2$ (9.9 μL, 0.0802 mmol) at room temperature, and the mixture was stirred for 18 h at this temperature. The mixture was quenched by addition of saturated $NaHCO_3$ at 0 °C, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to give **22** as a yellow oil (122 mg, 86% yield): $[\alpha]_D^{25}$ −101.1 (*c* 1.75, $CHCl_3$); IR (neat): 3334 (NH and OH), 1742 (C=O), 1365 (NO_2 and NSO_2), 1170 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.91 (dd, *J*=12.3, 4.9 Hz, 1H), 4.06–4.10 (m, 2H), 4.27–4.28 (m, 1H), 4.79–4.80 (m, 1H), 5.23 (dd, *J*=9.2, 1.7 Hz, 1H), 5.41 (dd, *J*=17.2, 1.7 Hz, 1H), 5.84–5.91 (m, 2H), 7.75–7.79 (m, 2H), 7.89–7.94 (m, 1H), 8.15–8.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 59.6, 72.1, 81.1, 83.5, 117.1, 125.5, 130.9, 133.0, 133.9, 134.1, 134.5, 147.8, 169.8; HRMS (FAB) calcd for $C_{14}H_{15}N_2O_7S$: $[M+H]^+$, 355.0605; found: 355.0603.

4.17. (2*S*,3*R*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (3a)

To a stirred solution of **22** (220 mg, 0.617 mmol) in CH_2Cl_2 (12 mL) were added tetradec-1-ene (1.56 mL, 6.16 mmol) and second generation Hoveyda–Grubbs catalyst (39 mg, 0.0622 mmol) at room temperature. After stirring for 10 h under reflux, the mixture was concentrated under reduced pressure followed by rapid filtration through a short pad of silica gel with *n*-hexane–EtOAc (4:1) to give a crude metathesis product, which was dissolved in MeCN (6.2 mL). To this solution were added PhSH (125 μL, 1.23 mmol) and Cs_2CO_3 (401 mg, 1.23 mmol) at room temperature. After stirring for 1 h at this temperature, 1 N KOH (6.2 mL, 6.20 mmol) was added. After stirring for 12 h at room temperature, MeCN was removed under reduced pressure. The residue was extracted with EtOAc, and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with $CHCl_3$–MeOH–28% NH_4OH (95:4:1) to give the corresponding amino alcohol as a white solid. To a stirred solution of this amino alcohol in EtOH (12 mL) was added 10% Pd/C (66 mg, 0.0620 mmol) at room temperature, and the mixture was stirred for 12 h at this temperature under H_2. The mixture was filtrated, and the filtrate was concentrated under reduced pressure to give a white solid, which was purified by column chromatography over silica gel with $CHCl_3$–MeOH–28% NH_4OH (100:3:1) to give **3a** as a white solid (109 mg 59% yield): mp 69–70 °C; $[\alpha]_D^{25}$ −2.66 (*c* 0.50, $CHCl_3$); IR (neat cm^{-1}): 3442 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.22–1.52 (m, 25H), 1.54–1.70 (m, 3H), 1.70–1.85 (br s, 3H), 3.30–3.33 (m, 1H), 3.57–3.62 (m, 3H), 4.01 (dd, *J*=9.2, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.3, 29.5, 29.6, 29.7 (6C), 31.9, 34.0, 60.3, 73.7, 83.7, 85.1. Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.08; H, 12.25; N, 4.76.

4.18. *tert*-Butyl (4*S*,5*R*)-5-[(*R*)-1-hydroxyallyl]-4-(hydroxymethyl)-2-oxooxazolidine-3-carboxylate (23)

To a stirred solution of **20** (1.91 g, 2.94 mmol) in THF (29 mL) were added Et_3N (407 μL, 2.94 mmol), Boc_2O (890 mg, 4.08 mmol), and DMAP (718 mg, 5.88 mmol) at 0 °C, and the mixture was warmed to room temperature. After stirring for 1 h at this temperature, the mixture was quenched by addition of saturated NH_4Cl at 0 °C, and the whole was extracted with Et_2O. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was dissolved in THF (29 mL). $3HF\cdot Et_3N$ (4.79 mL, 29.4 mmol) was added to this solution at room temperature, the mixture was stirred for 6 h under reflux. The mixture was quenched by addition of saturated $NaHCO_3$ at 0 °C and THF was removed under reduced pressure. The whole was extracted with EtOAc, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:2) to give **23** as a colorless oil (765 mg, 95% yield): $[\alpha]_D^{25}$ −6.6 (*c* 0.80, $CHCl_3$); IR (neat): 3442 (OH), 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.13–3.26 (m, 2H), 3.73 (dd, *J*=11.7, 3.2 Hz, 1H), 3.91 (dd, *J*=11.7, 4.3 Hz, 1H), 4.18–4.20 (m, 1H), 4.29 (dd, *J*=5.7, 4.6 Hz, 1H), 4.46 (dd, *J*=4.6, 4.0 Hz, 1H), 5.33–5.37 (m, 1H), 5.45–5.51 (m, 1H), 5.89 (ddd, *J*=17.2, 10.9, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9 (3C), 57.6, 61.9, 72.4, 77.3, 84.4, 119.1, 134.0, 149.4, 152.6; HRMS (FAB) calcd for $C_{12}H_{19}NNaO_6$: $[M+Na]^+$, 296.1110; found: 296.1115.

4.19. *tert*-Butyl [(3*S*,4*R*,5*R*)-4-hydroxy-5-vinyltetrahydrofuran-3-yl]carbamate (24)

To a stirred solution of **23** (146 mg, 0.534 mmol) and Et_3N (1.48 mL, 10.7 mmol) in CH_2Cl_2 (11 mL) were added TsCl (408 mg, 2.14 mmol) and $Me_3N\cdot HCl$ (51 mg, 0.534 mmol) at −78 °C. After stirring for 1 h at this temperature, the mixture was quenched by addition of saturated NH_4Cl, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a white solid, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give the corresponding tosylate as a white solid. To a stirred solution of the above tosylate in MeOH (11 mL) was added K_2CO_3 (149 mg, 1.08 mmol), and the mixture was stirred for 30 min at room temperature. The mixture was quenched by addition of saturated NH_4Cl, and concentrated under reduced pressure. The residue was extracted with EtOAc and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a white solid, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **24** as a white solid (81 mg, 66% yield): mp 120–121 °C; $[\alpha]_D^{25}$ −37.3 (*c* 0.81, $CHCl_3$); IR (neat): 3380 (NH and OH), 1684 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.34 (br s, 1H), 3.60 (dd, *J*=9.2, 3.4 Hz, 1H), 4.08–4.16 (m, 2H), 4.29 (dd, *J*=9.2, 6.0 Hz, 1H), 4.46–4.48 (m, 1H), 4.68 (br s 1H), 5.35–5.37 (m, 1H), 5.43–5.47 (m, 1H), 5.93 (ddd, *J*=17.8, 10.9, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (3C), 59.2, 70.8, 77.6, 80.2, 81.8, 118.4, 132.9, 155.5. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.38; H, 8.36; N, 5.97.

4.20. (2*R*,3*R*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (4a)

To a stirred solution of **24** (221 mg, 0.964 mmol) in CH_2Cl_2 (19 mL) were added tetradec-1-ene (2.44 mL, 9.64 mmol) and second generation Hoveyda–Grubbs catalyst (60 mg, 0.0964 mmol) at room temperature. After stirring for 6 h under reflux, the mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH silica gel with *n*-hexane–EtOAc (6:1) to give the *E*/*Z* mixture of corresponding metathesis product. To a stirred solution of the above metathesis product in EtOH (32 mL) was added 10% Pd/C (51 mg, 0.0479 mmol) at room temperature, and the mixture was stirred for 1 h at this temperature under H_2. The mixture was filtrated through a short pad of Celite, and the filtrate was concentrated under reduced pressure to give a white solid, which was dissolved in CH_2Cl_2 (19 mL). To this solution was added TFA (19 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with $CHCl_3$–MeOH–28% NH_4OH (95:4:1) to give **4a** as a white solid (153 mg, 53% yield): mp 80–81 °C; $[\alpha]_D^{25}$ −3.0 (*c* 0.98, $CHCl_3$); IR (neat): 3422 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.23–1.48 (m, 27H), 1.54–1.67 (m, 2H), 3.39 (dd, *J*=9.2, 3.4 Hz, 1H), 3.47–3.49 (m, 1H), 3.80 (dd, *J*=3.4, 1.1 Hz, 1H), 3.88–3.91 (m, 1H), 4.22 (dd, *J*=9.2, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.4, 28.5, 29.3, 29.6 (2C), 29.7 (5C), 29.8, 31.9, 59.9, 73.8, 79.8, 80.7. Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 71.90; H, 12.68; N, 4.87.

4.21. *tert*-Butyl [(3*R*,4*S*,5*S*)-4-hydroxy-5-vinyltetrahydrofuran-3-yl]carbamate (*ent*-24)

By a procedure identical with that described for the preparation of **24**, (*R*)-Garner's aldehyde was converted into *ent*-**24**: mp 120–121 °C; $[\alpha]_D^{25}$ +39.8 (*c* 0.30, $CHCl_3$) IR (neat): 3378 (NH and OH), 1685 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.59 (br s 1H), 3.60 (dd, *J*=9.2, 3.4 Hz, 1H), 4.08–4.16 (m, 2H), 4.29 (dd, *J*=9.5, 6.0 Hz, 1H), 4.46 (dd, *J*=5.7, 4.6 Hz, 1H), 4.75 (d, *J*=5.7 Hz, 1H), 5.35 (d, *J*=10.9 Hz, 1H), 5.44 (d, *J*=17.2 Hz, 1H), 5.93 (ddd, *J*=17.2, 10.9, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (3C), 59.2, 70.8, 77.6, 80.2, 81.8, 118.4, 132.9, 155.5. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.81; H, 8.65; N, 5.92.

4.22. (2*S*,3*S*,4*R*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (*ent*-4a)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (102 mg, 0.445 mmol) was reacted with tetradec-1-ene (1.13 mL, 4.46 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4a** (58 mg, 44% yield) as a white solid: mp 81–82 °C; $[\alpha]_D^{25}$ +3.6 (*c* 0.20, $CHCl_3$); IR (neat): 3350 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.24–1.48 (m, 27H), 1.54–1.66 (m, 2H), 3.39 (dd, *J*=9.2, 3.2 Hz, 1H), 3.47–3.49 (m, 1H), 3.80–3.81 (m, 1H), 3.88–3.91 (m, 1H), 4.22 (dd, *J*=9.2, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.4, 28.5, 29.3, 29.6 (2C), 29.7 (5C), 29.8, 31.9, 60.0, 73.8, 79.8, 80.7. Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.04; H, 12.57; N, 4.69.

4.23. (2*S*,3*S*,4*R*)-4-Amino-2-hexadecyltetrahydrofuran-3-ol (*ent*-4b)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (86 mg, 0.735 mmol) was reacted with hexadec-1-ene (1.07 mL, 3.73 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4b** (63 mg, 51% yield) as a white solid: mp 86–87 °C; $[\alpha]_D^{25}$ +2.7 (*c* 0.33, $CHCl_3$); IR (neat): 3312 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.24–1.48 (m, 31H), 1.54–1.67 (m, 2H), 3.39 (dd, *J*=9.2, 3.2 Hz, 1H), 3.47–3.49 (m, 1H), 3.80–3.81 (m, 1H), 3.88–3.91 (m, 1H), 4.22 (dd, *J*=9.2, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.4, 28.5, 29.3, 29.6 (2C), 29.7 (7C), 29.8, 31.9, 60.0, 73.7, 79.7, 80.8. Anal. Calcd for $C_{20}H_{41}NO_2\cdot 0.2H_2O$: C, 72.54; H, 12.60; N, 4.23. Found: C, 72.63; H, 12.51; N, 4.16.

4.24. (2*S*,3*S*,4*R*)-4-Amino-2-dodecyltetrahydrofuran-3-ol (*ent*-4c)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (122 mg, 0.532 mmol) was reacted with dodec-1-ene (1.18 mL, 5.31 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4c** (66 mg, 46% yield) as a white solid: mp 77–78 °C; $[\alpha]_D^{25}$ +3.3 (*c* 0.39, $CHCl_3$); IR (neat): 3364 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.24–1.48 (m, 21H), 1.54–1.67 (m, 2H), 3.39 (dd, *J*=9.2, 3.4 Hz, 1H), 3.47–3.49 (m, 1H), 3.80–3.81 (m, 1H), 3.88–3.91 (m, 1H), 4.22 (dd, *J*=9.2, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.4, 28.5, 29.3, 29.5, 29.6 (4C), 29.8, 31.9, 60.0, 73.8, 79.8, 80.7. Anal. Calcd for $C_{16}H_{33}NO_2$: C, 70.80; H, 12.25; N, 5.16. Found: C, 70.52; H, 12.40; N, 5.25.

4.25. (2*S*,3*S*,4*R*)-4-Amino-2-decyltetrahydrofuran-3-ol (*ent*-4d)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (146 mg, 0.637 mmol) was reacted with dec-1-ene (1.21 mL, 6.39 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4d** (81 mg, 52% yield) as a white solid: mp 70–71 °C; $[\alpha]_D^{25}$ +3.4 (*c* 0.39, $CHCl_3$); IR (neat): 3362 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.24–1.48 (m, 19H), 1.54–1.67 (m, 2H), 3.39 (dd, *J*=9.2, 3.2 Hz, 1H), 3.47–3.49 (m, 1H), 3.80–3.81 (m, 1H), 3.88–3.92 (m, 1H), 4.21 (dd, *J*=9.2, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.4, 28.5, 29.3, 29.5, 29.6 (2C), 29.8, 31.9, 60.0, 73.8, 79.8, 80.8. Anal. Calcd for $C_{14}H_{29}NO_2\cdot 0.2H_2O$: C, 68.08; H, 12.00; N, 5.67. Found: C, 68.03; H, 11.95; N, 5.54.

4.26. (2*S*,3*S*,4*R*)-4-Amino-2-octyltetrahydrofuran-3-ol (*ent*-4e)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (190 mg, 0.829 mmol) was reacted with oct-1-ene (1.29 mL, 8.29 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4e** (78 mg, 44% yield) as a white solid: mp 63–64 °C; $[\alpha]_D^{25}$ +3.2 (*c* 0.44, $CHCl_3$); IR (neat): 3356 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.21–1.68 (m, 17H), 3.39 (dd, *J*=9.2, 3.4 Hz, 1H), 3.47–3.49 (m, 1H), 3.81 (dd, *J*=3.4, 1.1 Hz, 1H), 3.88–3.92 (m, 1H), 4.21 (dd, *J*=9.2, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 26.4, 28.5, 29.2, 29.5, 29.8, 31.8, 60.0, 73.8, 79.7, 80.8. Anal. Calcd for $C_{12}H_{25}NO_2\cdot 0.2H_2O$: C, 65.83; H, 11.69; N, 6.40. Found: C, 65.96; H, 11.59; N, 6.27.

4.27. (2*S*,3*S*,4*R*)-4-Amino-2-vinyltetrahydrofuran-3-ol (*ent*-4f)

To a stirred solution of *ent*-**24** (120 mg, 0.523 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with $CHCl_3$–MeOH–28% NH_4OH (95:4:1) to give *ent*-**4f** (60 mg, 89% yield) as a white solid: mp 53–54 °C; $[\alpha]_D^{25}$ +23.6 (*c* 0.35, $CHCl_3$); IR (neat): 3355 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 3H), 3.53–3.57 (m, 2H), 3.88 (dd, *J*=3.7, 1.4 Hz, 1H), 4.25–4.28 (m, 1H), 4.59–4.61 (m, 1H), 5.37–5.40 (m, 1H), 5.48–5.52 (m, 1H), 5.91 (ddd, *J*=17.2, 10.5,

5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 59.2, 73.8, 79.5, 81.4, 118.4, 133.3. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.53; H, 8.76; N, 10.77.

4.28. (2*S*,3*S*,4*R*)-4-Amino-2-(4-octylphenethyl)tetrahydrofuran-3-ol (*ent*-4g)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (100 mg, 0.436 mmol) was reacted with 1-octyl-4-vinylbenzene (196 mg, 0.906 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4g** (37 mg, 20% yield) as a white solid: mp 93–94 °C; $[\alpha]_D^{25}$ −10.2 (*c* 0.23, $CHCl_3$); IR (neat): 3320 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.24–1.34 (m, 13H), 1.56–1.62 (m, 2H), 1.86–1.93 (m, 1H), 1.96–2.03 (m, 1H), 2.56 (t, *J*=7.7 Hz, 2H), 2.63–2.69 (m, 1H), 2.77–2.83 (m, 1H), 3.40 (dd, *J*=9.2, 3.4 Hz, 1H), 3.45–3.47 (m, 1H), 3.77–3.79 (m, 1H), 3.91–3.95 (m, 1H), 4.22 (dd, *J*=9.2, 5.7 Hz, 1H), 7.12 (dd, *J*=18.3, 8.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 29.3, 29.4, 29.5, 30.4, 31.6, 31.9, 32.1, 35.6, 60.1, 73.7, 79.8, 80.2, 128.2 (2C), 128.5 (2C), 138.9, 140.6. Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.02; H, 10.46; N, 4.40.

4.29. (2*S*,3*S*,4*R*)-4-Amino-2-(11-ethoxyundecyl)tetrahydrofuran-3-ol (*ent*-4h)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (100 mg, 0.436 mmol) was reacted with 11-ethoxyundec-1-ene (595 mg, 3.00 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4h** (67 mg, 56% yield) as a white solid: mp 59–60 °C; $[\alpha]_D^{25}$ +2.8 (*c* 0.70, $CHCl_3$); IR (neat): 3372 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, *J*=7.2 Hz, 3H), 1.25–1.47 (m, 19H), 1.54–1.67 (m, 4H), 3.38–3.41 (m, 3H), 3.45–3.49 (m, 3H), 3.80–3.81 (m, 1H), 3.90 (td, *J*=7.0, 2.7 Hz, 1H), 4.22 (dd, *J*=9.2, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 26.2, 26.4, 28.5, 29.5 (5C), 29.7, 29.8, 60.0, 66.0, 70.8, 73.7, 79.7, 80.7. Anal. Calcd for $C_{17}H_{35}NO_3$: C, 67.73; H, 11.70; N, 4.65. Found: C, 67.49; H, 11.81; N, 4.54.

4.30. (2*S*,3*S*,4*R*)-4-Amino-2-(10-propoxydecyl)tetrahydrofuran-3-ol (*ent*-4i)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (90 mg, 0.393 mmol) was reacted with 10-propoxydec-1-ene (350 mg, 1.76 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4i** (50 mg, 42% yield) as a white solid: mp 55–56 °C; $[\alpha]_D^{25}$ +1.6 (*c* 0.45, $CHCl_3$); IR (neat): 3361 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J*=7.4 Hz, 3H), 1.25–1.46 (m, 17H), 1.53–1.66 (m, 6H), 3.35–3.41 (m, 5H), 3.47–3.49 (m, 1H), 3.80–3.81 (m, 1H), 3.88–3.91 (m, 1H), 4.22 (dd, *J*=9.5, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.6, 22.9, 26.2, 26.4, 28.5, 29.5 (4C), 29.7, 29.8, 60.0, 70.9, 72.5, 73.8, 79.8, 80.7. Anal. Calcd for $C_{17}H_{35}NO_3 \cdot 0.25H_2O$: C, 66.73; H, 11.69; N, 4.58. Found: C, 66.47; H, 11.80; N, 4.52.

4.31. (2*S*,3*S*,4*R*)-4-Amino-2-[11-(cyclohexylmethoxy)undecyl] tetrahydrofuran-3-ol (*ent*-4j)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (80 mg, 0.349 mmol) was reacted with [(undec-10-en-1-yloxy)methyl]cyclohexane (595 mg, 3.00 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4j** (69 mg, 53% yield) as a white solid: mp 63–64 °C; $[\alpha]_D^{25}$ +1.8 (*c* 1.29, $CHCl_3$); IR (neat): 3365 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87–0.95 (m, 2H), 1.14–1.48 (m, 22H), 1.52–1.77 (m, 10H), 3.19 (d, *J*=6.3 Hz, 2H), 3.36–3.41 (m, 3H), 3.46–3.48 (m, 1H), 3.80–3.81 (m, 1H), 3.90 (td, *J*=6.7, 3.1 Hz, 1H), 4.22 (dd, *J*=9.2, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9 (2C), 26.2, 26.4, 26.7, 28.5, 29.5 (5C), 29.6, 29.7, 29.8, 30.2, 38.0, 60.0, 71.1, 73.8, 76.8, 79.8, 80.7. Anal. Calcd for $C_{22}H_{43}NO_3$: C, 71.50; H, 11.73; N, 3.79. Found: C, 71.22; H, 11.97; N, 3.75.

4.32. (2*S*,3*S*,4*R*)-4-Amino-2-(10-phenoxydecyl)tetrahydrofuran-3-ol (*ent*-4k)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (90 mg, 0.393 mmol) was reacted with (dec-9-en-1-yloxy)benzene (630 mg, 2.71 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4k** (65 mg, 49% yield) as a white solid: mp 62–63 °C; $[\alpha]_D^{25}$ +2.0 (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26–1.48 (m, 17H), 1.54–1.66 (m, 2H), 1.75–1.80 (m, 2H), 3.39 (dd, *J*=9.2, 3.4 Hz, 1H), 3.47–3.49 (m, 1H), 3.80–3.81 (m, 1H), 3.90 (td, *J*=6.7, 3.1 Hz, 1H), 3.95 (t, *J*=6.6 Hz, 2H), 4.22 (dd, *J*=9.2, 5.7 Hz, 1H), 6.89–6.94 (m, 3H), 7.26–7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 26.4, 28.5, 29.3, 29.4, 29.5 (3C), 29.8, 60.0, 67.9, 73.8, 79.9, 80.7, 114.5 (2C), 120.4, 129.4 (2C), 159.1. Anal. Calcd for $C_{20}H_{33}NO_3 \cdot 0.2H_2O$: C, 70.84; H, 9.93; N, 4.13. Found: C, 70.62; H, 10.06; N, 4.03.

4.33. (2*S*,3*S*,4*R*)-4-Amino-2-(11-phenoxyundecyl)tetrahydrofuran-3-ol (*ent*-4l)

By a procedure identical with that described for the preparation of **4a**, *ent*-**24** (80 mg, 0.349 mmol) was reacted with (undec-10-en-1-yloxy)benzene (667 mg, 2.71 mmol), followed by reduction and *N*-Boc deprotection to give *ent*-**4l** (64 mg, 52% yield) as a white solid: mp 74–75 °C; $[\alpha]_D^{25}$ +1.6 (*c* 0.70, $CHCl_3$); IR (neat): 3321 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27–1.48 (m, 16H), 1.52–1.66 (m, 5H), 1.75–1.80 (m, 2H), 3.39 (dd, *J*=9.2, 3.4 Hz, 1H), 3.47–3.49 (m, 1H), 3.80–3.82 (m, 1H), 3.90 (td, *J*=6.7, 2.7 Hz, 1H), 3.95 (t, *J*=6.6 Hz, 2H), 4.22 (dd, *J*=9.2, 5.7 Hz, 1H), 6.89–6.94 (m, 3H), 7.26–7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 26.4, 28.5, 29.3, 29.4, 29.5 (4C), 29.8, 60.0, 67.9, 73.8, 79.8, 80.7, 114.5 (2C), 120.4, 129.4 (2C), 159.1. Anal. Calcd for $C_{21}H_{35}NO_3 \cdot 0.2H_2O$: C, 71.43; H, 10.10; N, 3.97. Found: C, 71.34; H, 10.03; N, 3.87.

4.34. Sphingosine kinase assay

SphK inhibitory activities were evaluated by the off-chip mobility shift assay by the QuickScout® service from Carna Bioscience (Kobe, Japan). SphK1 (1–384) and SphK2 (1–618) were expressed as N-terminal GST-fusion proteins using a baculovirus expression system. They were purified using glutathione sepharose chromatography. Each chemical in DMSO at different concentrations was diluted fourfold with reaction buffer [20 mM HEPES (pH 7.5), 0.01% Triton X-100, 2 mM DTT]. For SphK reactions, a combination of the compound, 1 μM Sph, 5 mM $MgCl_2$, ATP (25 μM for SphK1; 600 μM for SphK2) in reaction buffer (20 μL) were incubated with each SphK in 384-well plates at room temperature for 1 h (*n*=2). The reaction was terminated by addition of 60 μL of termination buffer (Carna Biosciences). Substrate and product were separated by electrophoretic means using the LabChip3000 system. The kinase reaction was evaluated by the product ratio, which was calculated from the peak heights of the substrate (S) and product (P): [P/(P+S)]. Inhibition data were calculated by comparing with no-enzyme controls for 100% inhibition and no-inhibitor reactions for 0% inhibition. IC_{50} values were calculated using GraphPad Prism 4 software (GraphPad Software, Incorporated, La Jolla, CA, USA).

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