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Chirality extension of an oxazine building block en route to total syntheses of (+)-hyacinthacine A_2 and sphingofungin B†

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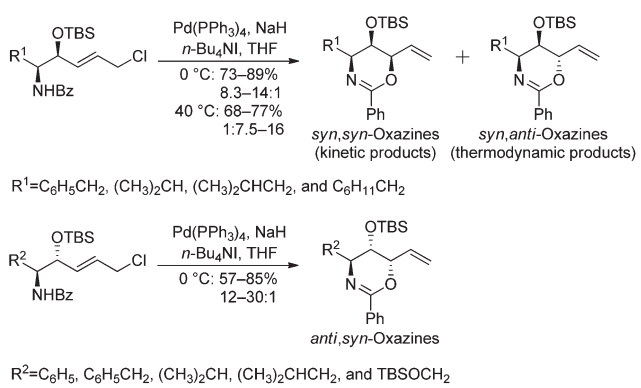
Concise and stereocontrolled syntheses of (+)-hyacinthacine A_2 and sphingofungin B were achieved *via* a diastereomerically enriched oxazine intermediate. The key strategies include palladium(0)-catalyzed intramolecular oxazine formation and diastereoselective nucleophilic addition to an aldehyde. (+)-Hyacinthacine A_2 was synthesized in 13 steps and 10.2% overall yield and the synthesis of sphingofungin B proceeded in a linear sequence over 15 steps and 6.9% overall yield from (*R*)-methyl 2-benzamido-3-((*tert*-butyldimethylsilyl)oxy)propanoate.

Introduction

As part of an ongoing research program aimed at developing total syntheses of biologically active compounds, we recently described a facile strategy towards the preparation of *syn*,*syn*-, *syn*,*anti*-,[1] and *anti*,*syn*-oxazines[2] *via* a stereoselective palladium(0)-catalyzed reaction (Scheme 1). The diastereoselectivity of *syn*,*syn*- and *syn*,*anti*- cyclizations can be critically dependent upon whether the reaction temperature results in kinetic or thermodynamic control of the products. Meanwhile, the diastereoselectivity of *anti*,*syn*-oxazine ring formation is predominantly controlled by the bulky OTBS group. Based on the oxazine library, piperidine alkaloid D-fagomine,[2d] pyrrolidine alkaloid DAB-1,[2d] indolizidine alkaloid (−)-lentiginosine,[2b] phytosphingosines,[1a,2c] and other natural products bearing three contiguous chiral centers were successfully synthesized.



Scheme 1 Oxazine library generated *via* a stereoselective palladium(0)-catalyzed reaction.

Polyhydroxylated alkaloids (or aminopolyols) isolated from plants and microorganisms should be thoroughly investigated because they can act as glycosidase inhibitors by mimicking natural monosaccharide substrates, which may allow for the development of new antiviral, antidiabetic, and anticancer agents.[3] More than two hundred of these naturally-occurring and water-soluble compounds have been isolated and classified structurally as piperidines, pyrrolidines, pyrrolizidines, indolizidines, and nortropanes. (+)-Hyacinthacine A_2 (**1**), which is a representative pyrrolizidine alkaloid, was first isolated from *Muscari armeniacum* bulbs and is a good inhibitor of both amyloglucosidase and lactase (Fig. 1).[4]

Its promising biological properties and the existence of four contiguous stereogenic centers in its structure have prompted the development of numerous synthetic approaches.[5,6] For example, in 2011, Fox *et al.* described the concise synthesis of (+)-hyacinthacine A_2, which relied on a novel transannular hydroamination of 5-aza-cyclooctene.[5a] Zheng and Huang's approach for the synthesis of **1** was SmI_2-mediated radical coupling reaction of an activated amide from (*R*,*R*)-tartarimide.[5b] Bonaccini *et al.* reported a stereocontrolled cyclic nitrone cycloaddition for the synthesis of **1**.[5c] Another previous result by Goti and Merino started from a nitrone, which is

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†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of **1**, **2**, and all new compounds; and NOESY spectra of *trans*-**6** and *cis*-**6**. See DOI: 10.1039/c5ob00251f
‡These authors contributed equally.

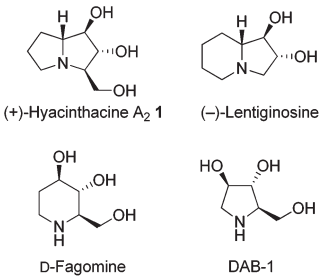


Fig. 1 The structures of several polyhydroxylated alkaloids.

readily prepared from D-arabinose.[5e] Marco *et al.* demonstrated a stereoselective synthesis of **1** *via* a double cyclization with the one-pot formation of two C–N bonds.[5f]

Sphingofungins isolated from fungi are also of significant interest owing to their biological activities as immunosuppressants and potential antifungal agents *via* the inhibition of serine palmitoyl-CoA transferase (SPT).[7] In addition to sphingofungins, congeners such as myriocin, sulfamisterin, and mycestericins exhibit similar functions.[7] Sphingofungin B (**2**), having a polar polyhydroxy amino acid head group and a long lipid chain containing an (*R*)-hydroxy group at C-14, was isolated from the fermentation broth of *Aspergillus fumigatus* and its structure was elucidated by Merck group in 1992 (Fig. 2).[8]

The promising biological activities and more than three contiguous chiral centers present in these compounds also have prompted the development of numerous synthetic approaches.[9–15] For example, the first total synthesis of sphingofungin B was successfully achieved by Kobayashi *et al.* in 1996 making use of catalytic asymmetric aldol reactions.[9] Meanwhile, the first total synthesis of sphingofungin D was

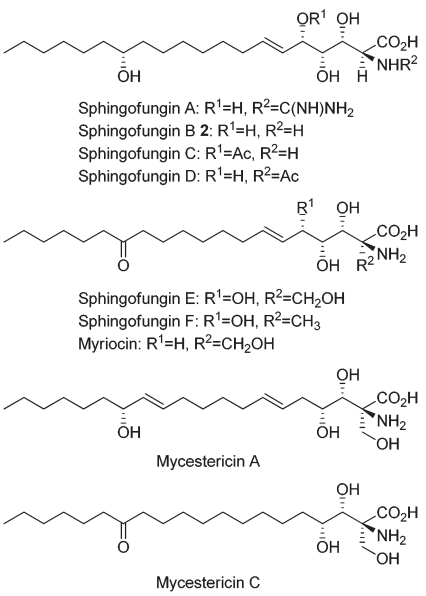


Fig. 2 The structures of several sphingolipids.

reported by Mori *et al.* in 1994 using a polar building block derived from *N*-acetyl-D-mannoside.[10a,c] Shortly thereafter, Chida *et al.* accomplished the synthesis of sphingofungin D starting from *myo*-inositol.[10b]

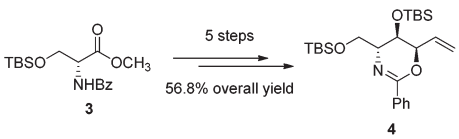
Herein we report the highly stereocontrolled total syntheses of (+)-hyacinthacine A_2 and sphingofungin B *via* straightforward procedures that rely on a chiral *anti*,*syn*-oxazine building block.

Results and discussion

Chirality extension of a chiral *anti*,*syn*-oxazine

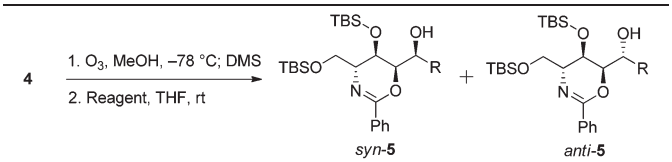
The first step in the syntheses, the preparation of the known chiral 1,3-oxazine **4** beginning with (*R*)-methyl 2-benzamido-3-((*tert*-butyldimethylsilyl)oxy)propanoate **3**, proceeded in 56.8% yield after five steps (Scheme 2).[2b,d]

We envisioned that a stereocontrolled Grignard reaction or Grignard-like nucleophilic addition[16] to the oxazine-derived aldehyde could generate the desired fourth contiguous stereocenter. In most cases, the chelation-control product of a Grignard reaction is produced *via* the chelation of organomagnesium nucleophiles rather than bisligation of Lewis acids; this is why ethers, which are the universal solvents of Grignard reactions, coordinate to Lewis acids to form octahedral complexes.[16e,17] Therefore, it is uncertain whether Lewis acid additives such as $ZnCl_2$,[18,19] $ZnBr_2$,[18–21] ZnI_2,[22,23]



Scheme 2 Synthesis of *anti*,*syn*-oxazine **4**.

Table 1 Grignard reaction with the prepared aldehyde



R=vinyl (**5a**), methyl (**5b**), ethyl (**5c**), allyl (**5d**), homoallyl (**5e**), and phenyl (**5f**)

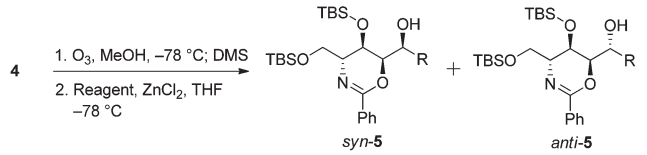
Entry	Reagent	Time (h)	Product	Ratio[a] (*syn*/*anti*)	Yield[b] (%)
1	$CH_2CHMgBr$	0.5	**5a**	1.3 : 1	78
2	MeMgBr	0.5	**5b**	1 : 1.5	71
3	EtMgBr	0.5	**5c**	1.5 : 1	70
4	CH_2CHCH_2MgBr	0.5	**5d**	2.0 : 1	70
5	$CH_2CH(CH_2)_2MgBr$	0.5	**5e**	1.5 : 1	70
6	PhMgBr	0.5	**5f**	4 : 1	70

[a] Ratios were determined by ^{1}H NMR peak intensities. [b] Yields refer to isolated yields over the two steps.

$MgBr_2{\cdot}OEt_2$,[20,23,24] $CdCl_2$,[18] and $Ti(OiPr)_4$[20] act as bidentate ligands, although stereoselective addition should be possible *via* a chelated transition state.[25] Hence, $ZnCl_2$ was tested in the following reaction to optimize the diastereomeric enrichment.

The results of the introduction of Grignard reagents are shown in Table 1. Unfortunately, in the absence of additives, organomagnesiums cannot chelate. Meanwhile, Table 2 summarizes the results of reactions in which $ZnCl_2$ was added to the reaction mixture; in each case, 1.1 equivalents of the Lewis acid were added dropwise followed by the addition of 3.0 equivalents of each Grignard reagent. Surprisingly, reactions favored the *syn*-product, indicating the occurrence of α-chelation with the oxygen inside the 1,3-oxazine moiety.

Table 2 $ZnCl_2$-mediated Grignard reaction with the prepared aldehyde



R=vinyl (**5a**), methyl (**5b**), ethyl (**5c**), allyl (**5d**), homoallyl (**5e**), and phenyl (**5f**)

Entry	Reagent	Time (h)	Product	Ratio[a] (*syn*/*anti*)	Yield[b] (%)
1	$CH_2CHMgBr$	1	**5a**	10 : 1	62
2	MeMgBr	1	**5b**	2.2 : 1	59
3	EtMgBr	1	**5c**	14 : 1	60
4	CH_2CHCH_2MgBr	1	**5d**	>20 : 1	60
5	$CH_2CH(CH_2)_2MgBr$	1	**5e**	>20 : 1	62
6	PhMgBr	1	**5f**	8 : 1	65

[a] Ratios were determined by ^{1}H NMR peak intensities. [b] Yields refer to isolated yields over the two steps.

Further experiments for using other organometallic compounds were conducted (Table 3). Replacing magnesium with lithium, which is less prone to chelation, shifted the product composition slightly to favor the Felkin–Anh variant (entry 1). Vinylation using vinylzinc chloride and divinylzinc, which were prepared *in situ* from zinc chloride and vinylmagnesium bromide,[26] generated the *syn*-alcohol exclusively (entries 2–4). Unfortunately, these conditions have limited applications; reactions using Me_2Zn, Et_2Zn, and other reagents proceeded sluggishly (entries 5–8), while that involving Ph_2Zn proceeded much more quickly (entry 9).

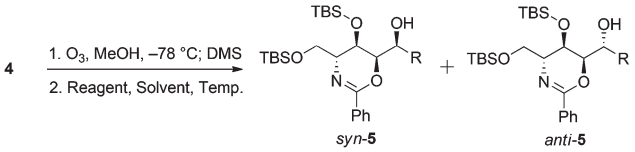
To determine the relative stereochemistry of *syn*-**5a**, diastereoisomer *anti*-**5a** was prepared (Table 1, entry 1). Oxazine rings of *syn*-**5a** and *anti*-**5a** were cleaved by hydrogenolysis. Two secondary alcohols gave the corresponding acetals, respectively. Unfortunately, the coupling constants between H_4 and H_5 of *trans*-**6** and *cis*-**6** were not in good agreement with theoretical values [$J_{4,5}$(*trans*-**6**) = 8.0 Hz and $J_{4,5}$(*cis*-**6**) = 5.4 Hz]. Therefore, NOESY spectra of *trans*-**6** and *cis*-**6**, representing the correlations between H_4 or H_5 and acetal methyl protons, confirm the identification of the diastereoisomers (Scheme 3).

Total synthesis of (+)-hyacinthacine A_2

Our retrosynthesis (Scheme 4) suggests that the bicyclic structure of **1** could be synthesized from tertiary amine **7**, which could in turn be prepared from secondary mesylate **8** *via* intramolecular S_N2 substitution. Conveniently, mesylate **8** could be obtained from the pentenyl alcohol *syn*-**5e**. The synthesis of *syn*-**5e** could be accomplished by nucleophilic addition to the corresponding aldehyde, which could be derived from conversion of the exomethylene moiety of *anti*,*syn*-oxazine **4**.

Pentenyl alcohol *syn*-**5e** was consecutively treated with MsCl and benzyl chloroformate under biphasic conditions to afford carbamate **8** in 69% yield over 2 steps. The room temperature exposure of **8** to sodium hydride led to the formation of ter-

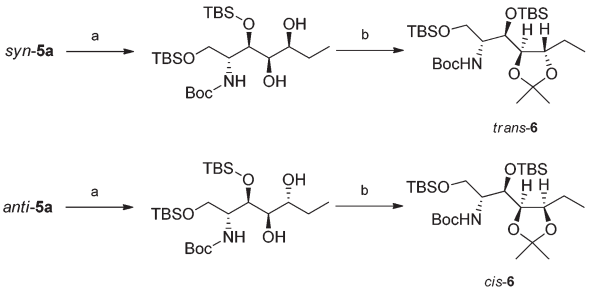
Table 3 Organometallic nucleophilic addition with the prepared aldehyde



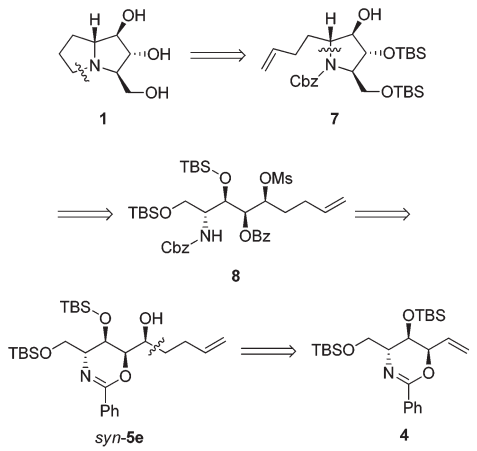
R=vinyl (**5a**), methyl (**5b**), ethyl (**5c**), allyl (**5d**), homoallyl (**5e**), and phenyl (**5f**)

Entry	Reagent	Solvent	Temp.	Time (h)	Product	Ratio[a] (*syn*/*anti*)	Yield[b] (%)
1	CH_2CHLi	Et_2O	−78 °C	1	**5a**	1 : 2.0	58
2	$CH_2CHZnCl$	THF	−78 °C to rt	3	**5a**	>20 : 1	75
3	$(CH_2CH)_2Zn$	THF	−78 °C to rt	3	**5a**	>20 : 1	85
4	$(CH_2CH)_2Zn/ZnCl_2$	THF	−78 °C to rt	3	**5a**	>20 : 1	80
5	Me_2Zn	THF	−78 °C to rt	3	**5b**	trace	
6	Et_2Zn	THF	−78 °C to rt	3	**5c**	trace	
7	$(CH_2CHCH_2)_2Zn$	THF	−78 °C to rt	3	**5d**	trace	
8	$(CH_2CH(CH_2)_2)_2Zn$	THF	−78 °C to rt	3	**5e**	trace	
9	Ph_2Zn	THF	−78 °C to rt	3	**5f**	>20 : 1	85

[a] Ratios were determined by ^{1}H NMR peak intensities. [b] Yields refer to isolated yields over the two steps.



Scheme 3 Determination of the relative stereochemistry of *trans*-**6** and *cis*-**6**.



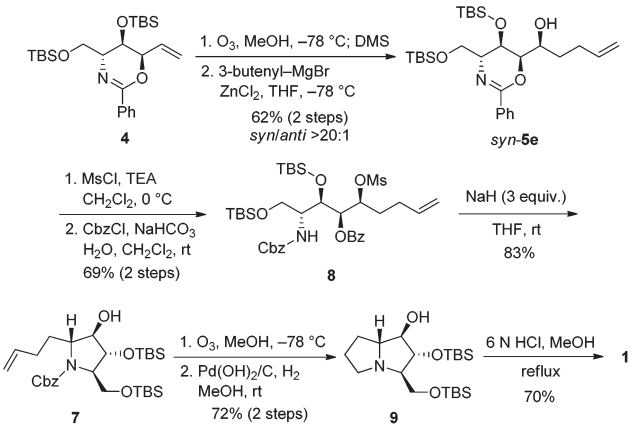
Scheme 4 Retrosynthesis of **1**.

tiary amine **7** (mixture of rotamers) in 83% yield *via* intramolecular cyclization as well as *O*-benzoyl hydrolysis. Next, ozonolysis and hydrogenolysis of **7** gave protected **9** in 72% yield over 2 steps. Finally, removal of TBS-protecting groups by treatment of **9** with concentrated acid yielded the **1**·HCl salt, which was neutralized with an ion-exchange resin to give **1** in 70% yield (Scheme 5). Our $[\alpha]_D$ +15.3 (*c* 0.1, H_2O) compared to the reported $[\alpha]_D$ +20.1 (*c* 0.44, H_2O),[4] $[\alpha]_D$ +12 (*c* 0.40, H_2O),[5a] $[\alpha]_D$ +10.6 (*c* 1.64, H_2O),[5b] and $[\alpha]_D$ +10.5 (*c* 0.6, H_2O)[5i] confirms the identity of the absolute configuration. We could also confirm the relative stereochemistry of chromatographically separable *syn*-**5e** after comparing spectroscopic data of **1** with those of 7a-epimer, 7-deoxyalexine.[27]

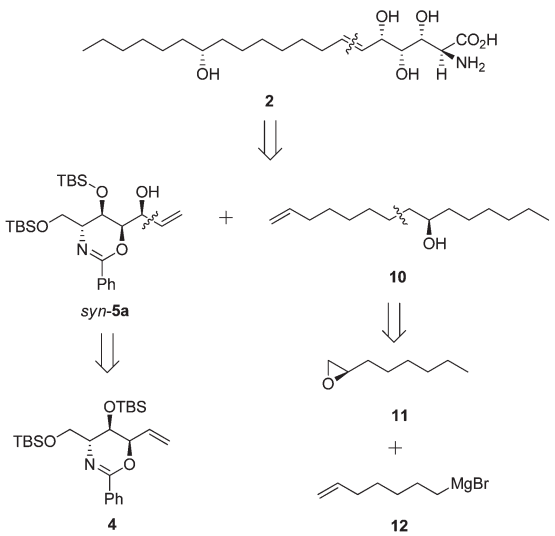
Total synthesis of sphingofungin B

Our retrosynthesis (Scheme 6) suggested that **2** could be generated from allylic alcohol *syn*-**5a** and lipid chain **10** by an olefin cross-metathesis reaction. Chiral alcohol **10** could be obtained from (*R*)-epoxyoctane **11** and 6-heptenylmagnesium bromide **12**.

Subsequent acetylation of the hydroxyl group of *syn*-**5a** yielded secondary allylic acetate **13** in 94% yield. Meanwhile, the nucleophilic addition reaction between (*R*)-epoxyoctane **11**

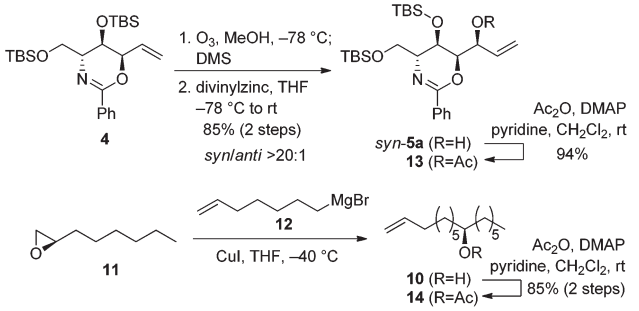


Scheme 5 Synthesis of **1**.

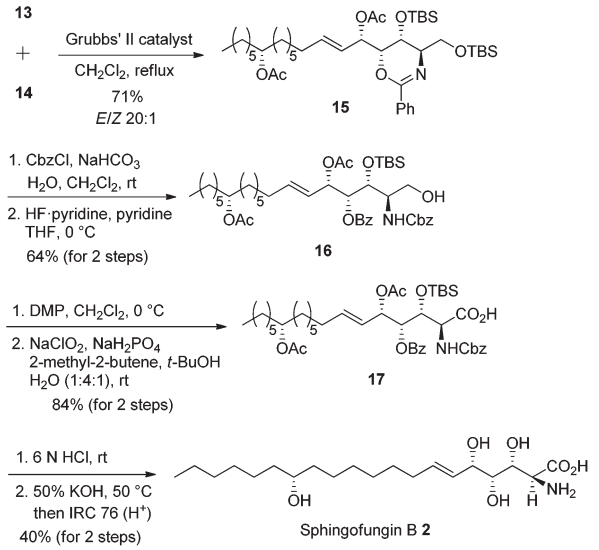


Scheme 6 Retrosynthesis of **2**.

and 6-heptenylmagnesium bromide **12**, which are both commercially available, and the subsequent acetylation provided the lipid chain subunit **14** in 85% yield over two steps (Scheme 7).



Scheme 7 Syntheses of subunits **13** and **14**.



Scheme 8 Synthesis of **2**.

Intermolecular olefin cross-metathesis between **13** and **14** resulted in compound **15** in 71% yield (E/Z > 20 : 1 ratio). 1,3-Oxazine **15** was treated with benzyl chloroformate under biphasic conditions followed by primary OTBS deprotection affording carbamate **16** in 64% yield over two steps. Primary alcohol **16** was oxidized to carboxylic acid **17** in 84% yield over two steps. Finally, acid- and base-promoted hydrolysis cleaved all protecting groups, and subsequent neutralization afforded sphingofungin B **2** in 40% yield over two steps (Scheme 8). The synthetic compound was spectroscopically in good agreement with the reported sphingofungin B.[9]

Conclusions

We described new procedures for stereoselective nucleophilic addition to *anti*,*syn*-oxazine. The diastereoselectivity of the Grignard reaction was predominantly controlled by zinc chloride. Furthermore, the reactions that used divinylzinc and diphenylzinc also favored the *syn*-adducts. We took advantage of these reactions and various other available transformations to synthesize (+)-hyacinthacine A_2 (**1**) and sphingofungin B (**2**) from a common source *via* chiral alcohol *syn*-**5e** and *syn*-**5a**. In addition to the diastereoselective reactions, these syntheses rely on a palladium(0)-catalyzed intramolecular oxazine formation reaction. Starting from readily available **3**, **1** was obtained in 13 steps and 10.2% overall yield, whereas starting from oxazine chiral building block **4**, **1** was afforded in 8 steps and 17.9% overall yield. Meanwhile, the synthesis of **2** proceeded in a linear sequence beginning from **3** over 15 steps and 6.9% overall yield and from the chiral oxazine **4** over 10 steps and 12.2% overall yield. The main advantage of this strategy is its high versatility, which allows the synthesis of not only **1** and **2**, but also a range of structural analogs. Using this protocol, we are in the process of synthesizing castanospermines, australine, broussonetines, and other natural products; the results will be reported in due course.

Experimental

General methods

Flash chromatography was executed using a Merck Kieselgel 60 (230–400 mesh) stationary phase and mixtures of ethyl acetate and hexanes as the eluents. Ethyl acetate and hexanes were dried and purified by distillation prior to use. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone (indicator). Dichloromethane was mixed with concentrated sulfuric acid (**Caution**), dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at the Center for Cooperative Research Facility at Sungkyunkwan University on FT-NMR 500 and 700 MHz spectrometers. Chemical shifts are reported as δ values in ppm relative to the $CHCl_3$ residual peak (7.26 ppm in $CDCl_3$). IR spectra were recorded on a Bruker FT-IR spectrometer. Optical rotation was measured on a Jasco Dip 1020 digital polarimeter. Mass spectral data were recorded at the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer.

(*S*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)prop-2-en-1-ol (*syn*-5a). Oxazine **4** (50 mg, 0.108 mmol) was dissolved in dry methanol (2.16 mL) and cooled to −78 °C. Ozone was then passed through the solution until the reaction was complete. The reaction mixture was quenched with methyl sulfide (0.08 mL) and allowed to warm to rt. The solvent was evaporated under reduced pressure, and the crude aldehyde was immediately employed in the next step without further purification. Vinylmagnesium bromide (1.0 M solution in diethyl ether, 0.32 mL, 0.324 mmol) was added to a solution of zinc chloride (1.0 M solution in diethyl ether, 0.32 mL, 0.324 mmol) in THF (0.76 mL) at rt and stirred for 0.5 h. A solution of the crude aldehyde in THF (0.32 mL) was added to this white suspension at −78 °C and allowed to warm to rt. After 3 h, the reaction was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography gave *syn*-**5a** (44.6 mg, 0.091 mmol); yield 85%; ratio *syn*/*anti* = >20 : 1; white solid; mp 115–132 °C; R_f = 0.50 (1 : 6 ethyl acetate/hexanes); $[\alpha]_D^{25}$ +40.1 (*c* 1.0, $CHCl_3$); IR (neat) 698, 777, 836, 937, 1110, 1161, 1256, 1279, 1638, 2855, 2928, 2955, 3387 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.02–0.03 (m, 3H), 0.06–0.07 (m, 3H), 0.12–0.15 (m, 6H), 0.86–0.88 (m, 18H), 3.04 (d, J = 2.1 Hz, 1H), 3.45 (dd, J = 10.8, 8.2 Hz, 1H), 3.71 (m, 1H), 3.97 (dd, J = 10.3, 3.9 Hz, 1H), 4.05 (dd, J = 5.6, 2.2 Hz, 1H), 4.30 (t, J = 2.0 Hz, 1H), 4.57 (d, J = 1.7 Hz, 1H), 5.36 (dt, J = 10.6, 1.3 Hz, 1H), 5.53 (dt, J = 17.2, 1.3 Hz, 1H), 5.97–6.02 (m,

1H), 7.38 (t, J = 7.5 Hz, 2H), 7.42–7.45 (m, 1H), 7.91–7.93 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ –5.5, –5.4, –4.5, –4.1, 18.0, 18.2, 25.7, 25.7, 25.8, 25.9, 61.1, 64.7, 65.5, 72.6, 76.1, 118.0, 127.3, 128.1, 130.5, 133.6, 135.4, 155.5; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{26}H_{46}O_4NSi_2$ 492.2965, found 492.2962.

(*R*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)prop-2-en-1-ol (*anti*-5a). Yield 85%; ratio *syn*/*anti* = >20 : 1; white solid; mp 106–110 °C; R_f = 0.53 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +21.6 (c 0.6, $CHCl_3$); IR (neat) 699, 778, 836, 937, 1033, 1118, 1256, 1280, 1651, 2934, 2951, 3358 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.16 (s, 3H), 0.17 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 2.74 (d, J = 5.0 Hz, 1H), 3.58 (dd, J = 10.5, 7.0 Hz, 1H), 3.67–3.70 (m, 1H), 3.96 (dd, J = 10.5, 3.5 Hz, 1H), 4.05 (dd, J = 8.0, 2.5 Hz, 1H), 4.47 (t, J = 2.5 Hz, 1H), 4.51–4.56 (m, 1H), 5.33 (dt, J = 12.0, 1.5 Hz, 1H), 5.45 (dt, J = 19.0, 1.5 Hz, 1H), 7.23–7.43 (m, 3H), 7.90–7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.2, –4.3, –4.2, 18.2, 18.4, 26.0, 26.1, 60.8, 64.6, 71.6, 75.1, 75.4, 77.4, 117.1, 127.6, 128.2, 130.7, 133.7, 137.8, 155.4; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{26}H_{46}O_4NSi_2$ 492.2965, found 492.2963.

(*S*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)ethanol (*syn*-5b). Oxazine **4** (50 mg, 0.108 mmol) was dissolved in dry methanol (2.16 mL) and cooled to –78 °C. Ozone was then passed through the solution until the reaction was complete. The reaction mixture was quenched with methyl sulfide (0.08 mL) and allowed to warm to rt. The solvent was evaporated under reduced pressure, and the crude aldehyde was immediately employed in the next step without further purification. Zinc chloride (1.0 M solution in diethyl ether, 0.11 mL, 0.119 mmol) was slowly added to a solution of the aldehyde in THF (1.08 mL) at –78 °C and stirred for 0.5 h. Methylmagnesium bromide (3.0 M solution in diethyl ether, 0.11 mL, 0.324 mmol) was added to this solution at –78 °C and allowed to react for 1 h. The reaction was quenched with saturated NH_4Cl, and warmed to rt. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography gave *syn*-**5b** (21.0 mg, 0.044 mmol): yield 59%; ratio *syn*/*anti* = 2.2 : 1; colorless liquid; R_f = 0.4 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +3.7 (c 1.0, $CHCl_3$); IR (neat) 667, 777, 837, 1071, 1111, 1141, 1257, 1653, 2858, 2930, 2955, 3385 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.13 (s, 6H), 0.81–0.94 (m, 18H), 2.94 (s, 1H), 3.44 (dd, J = 10.5, 8.4 Hz, 1H), 3.70 (m, 1H), 3.92 (dd, J = 6.0, 0.9 Hz, 1H), 3.98 (dd, J = 10.5, 4.0 Hz, 1H), 4.20 (t, J = 6.2 Hz, 1H), 4.28 (t, J = 1.6 Hz, 1H), 7.36–7.39 (m, 2H), 7.41–7.43 (m, 1H), 7.91–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.3, –5.2, –3.9, 18.2, 18.3, 18.4, 61.4, 65.1, 65.8, 67.9, 127.5, 128.2, 130.7, 134.0, 155.8; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{25}H_{46}O_4NSi_2$ 480.2965, found 480.2964.

(*R*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)ethanol (*anti*-5b). Yield 59%; ratio *syn*/*anti* = 2.2 : 1; white solid; mp 122–124 °C; R_f = 0.45 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +2.8 (c 1.0, $CHCl_3$); IR (neat) 702, 777, 838, 1103, 1140, 1363, 1648, 2856, 2929, 2978, 3193 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.04 (s, 3H), 0.09 (s, 3H), 0.17 (s, 6H), 0.87–0.90 (m, 18H), 1.40 (d, J = 6.2 Hz, 3H), 2.53 (s, 1H), 3.63–3.69 (m, 2H), 3.92 (dd, J = 8.1, 2.5 Hz, 1H), 3.97 (dd, J = 10.1, 3.0 Hz, 1H), 4.15–4.18 (m, 1H), 4.63 (dd, J = 3.2, 2.9 Hz, 1H), 7.33–7.38 (m, 2H), 7.40–7.43 (m, 1H), 7.91–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.1, –4.4, –4.3, 18.2, 18.5, 20.6, 26.0, 60.6, 64.5, 66.6, 127.6, 128.2, 130.6, 133.8, 155.2; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{25}H_{46}O_4NSi_2$ 480.2965, found 480.2961.

(*S*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)propan-1-ol (*syn*-5c). Yield 60%; ratio *syn*/*anti* = 14 : 1; colorless liquid; R_f = 0.5 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +3.9 (c 1.0, $CHCl_3$); IR (neat) 698, 777, 836, 1112, 1257, 1653, 2858, 2930, 2956, 3385 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.04–0.15 (m, 12H), 0.81–0.94 (m, 18H), 1.07 (t, J = 7.4 Hz, 3H), 1.63–1.68 (m, 1H), 1.71–1.74 (m, 1H), 3.02 (s, 1H), 3.47 (dd, J = 10.5, 8.3 Hz, 1H), 3.68–3.71 (m, 1H), 3.93–3.99 (m, 2H), 4.04 (dd, J = 5.2, 0.4 Hz, 1H), 4.30 (t, J = 1.7 Hz, 1H), 7.35–7.38 (m, 2H), 7.41–7.43 (m, 1H), 7.91–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.3, –5.2, –4.7, –3.9, 9.9, 10.1, 18.2, 25.5, 26.1, 61.5, 65.1, 66.3, 73.1, 75.6, 127.5, 128.2, 130.7, 134.0, 155.9; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{26}H_{48}O_4NSi_2$ 494.3122, found 494.3120.

(*R*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)propan-1-ol (*anti*-5c). Yield 60%; ratio *syn*/*anti* = 14 : 1; colorless liquid; R_f = 0.55 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +3.2 (c 1.0, $CHCl_3$); IR (neat) 697, 778, 836, 1140, 1256, 1655, 2858, 2930, 2956, 3385 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.16–0.17 (m, 6H), 0.87–0.90 (m, 18H), 1.07 (t, J = 7.4 Hz, 3H), 1.60–1.64 (m, 1H), 1.87–1.91 (m, 1H), 2.53 (s, 1H), 3.63–3.65 (m, 1H), 3.67–3.69 (m, 1H), 3.96–3.98 (m, 2H), 4.00–4.03 (m, 1H), 4.45 (dd, J = 3.3, 2.6 Hz, 1H), 7.35–7.38 (m, 2H), 7.40–7.42 (m, 1H), 7.90–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.1, –4.3, –4.2, 9.5, 18.2, 18.5, 64.6, 71.4, 75.3, 127.6, 128.2, 130.6, 133.8, 155.3; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{26}H_{48}O_4NSi_2$ 494.3122, found 494.3120.

(*S*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)but-3-en-1-ol (*syn*-5d). Yield 60%; ratio *syn*/*anti* = >20 : 1; colorless liquid; R_f = 0.5 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +4.6 (c 1.0, $CHCl_3$); IR (neat) 777, 837, 1007, 1033, 1057, 1110, 1257, 1655, 2859, 2930, 2955, 3419 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.03–0.08 (m, 6H), 0.15 (s, 6H), 0.80–0.95 (m, 18H), 2.42–2.45 (m, 1H), 2.50–2.53 (m, 1H), 3.12 (s, 1H), 3.47 (dd, J = 10.4, 8.2 Hz, 1H), 3.69–3.71 (m, 1H), 3.97 (dd, J = 10.5, 3.8 Hz, 1H), 4.08–4.13 (m, 2H), 4.32 (s, 1H), 5.14–5.19 (m, 1H), 5.21 (d, J = 1.61 Hz, 1H), 5.92–6.00 (m, 1H), 7.35–7.39 (m, 2H), 7.41–7.44 (m, 1H), 7.92–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.3, –5.2, –4.4, –3.9, 18.2, 18.4, 25.9, 26.1, 37.3,

61.3, 66.5, 71.4, 74.8, 118.2, 127.6, 128.2, 128.4, 130.7, 134.0, 134.3, 155.9; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{48}O_4NSi_2$ 506.3122, found 506.3121.

(*R*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)but-3-en-1-ol (*anti*-5d). Yield 60%; ratio *syn*/*anti* = >20 : 1; colorless liquid; R_f = 0.55 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +4.0 (*c* 1.0, $CHCl_3$); IR (neat) 697, 778, 837, 1072, 1119, 1257, 1656, 2858, 2929, 2955, 3356 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.15 (s, 6H), 0.80–0.98 (m, 18H), 2.37–2.41 (m, 2H), 2.67–2.69 (m, 1H), 3.60 (dd, *J* = 10.4, 7.1 Hz, 1H), 3.67–3.90 (m, 1H), 3.97 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.01 (dd, *J* = 8.3, 1.9 Hz, 1H), 4.05–4.08 (m, 1H), 4.45 (t, *J* = 2.4 Hz, 1H), 5.20–5.26 (m, 2H), 5.90–6.00 (m, 1H), 7.35–7.39 (m, 2H), 7.40–7.43 (m, 1H), 7.91–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.2, –4.4, –4.3, 9.7, 13.9, 18.2, 18.4, 26.2, 38.4, 61.0, 64.4, 64.7, 68.7, 75.2, 119.0, 127.5, 128.2, 130.6, 133.9, 134.3, 155.2; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{48}O_4NSi_2$ 506.3122, found 506.3120.

(*S*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)pent-4-en-1-ol (*syn*-5e). Yield 62%; ratio *syn*/*anti* = >20 : 1; colorless liquid; R_f = 0.5 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +10.0 (*c* 1.0, $CHCl_3$); IR (neat) 698, 778, 837, 1071, 1111, 1257, 1655, 2858, 2930, 2954, 3423 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ –0.07 (s, 2H), –0.03 (s, 2H), 0.00 (s, 2H), 0.67 (d, *J* = 5.2 Hz, 6H), 0.79 (s, 9H), 0.81 (s, 9H), 1.65–1.67 (m, 2H), 2.14–2.17 (m, 1H), 2.27–2.31 (m, 1H), 3.02 (s, 1H), 3.62–3.63 (m, 1H), 3.90 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.97 (s, 2H), 4.23 (s, 1H), 4.94 (d, *J* = 11.3 Hz, 1H), 5.02 (d, *J* = 20.4 Hz, 1H), 5.79–5.84 (m, 1H), 7.30 (t, *J* = 9.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.5, –5.4, –4.7, –4.1, 17.9, 18.2, 25.6, 25.7, 29.6, 31.7, 61.1, 64.8, 66.1, 71.1, 75.5, 115.0, 127.3, 128.1, 130.5, 133.7, 138.2, 155.7; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{50}O_4NSi_2$ 520.3278, found 520.3275.

(*R*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)pent-4-en-1-ol (*anti*-5e). Yield 62%; ratio *syn*/*anti* = >20 : 1; colorless liquid; R_f = 0.55 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +3.8 (*c* 1.0, $CHCl_3$); IR (neat) 698, 778, 836, 1117, 1256, 1654, 2858, 2930, 2954, 3384 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.16 (s, 6H), 0.80–0.94 (s, 18H), 1.65–1.71 (m, 1H), 1.95–1.99 (m, 1H), 2.22–2.27 (m, 1H), 2.34–2.38 (m, 1H), 2.51 (s, 1H), 3.62 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.68 (6, *J* = 3.4 Hz, 1H), 3.97 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.99–4.01 (m, 1H), 4.01–4.06 (m, 1H), 4.45 (s, 1H), 5.00 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.08 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.88–5.91 (m, 1H), 7.35–7.37 (m, 2H), 7.37–7.40 (m, 1H), 7.90–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.2, –5.1, –4.4, –4.3, 18.2, 18.5, 26.0, 29.6, 33.1, 60.7, 64.6, 69.7, 75.7, 115.2, 127.6, 128.2, 130.7, 133.8, 138.7, 155.3; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{50}O_4NSi_2$ 520.3278, found 520.3282.

(*S*)-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)(phenyl)methanol (*syn*-5f). Yield 65%; ratio *syn*/*anti* = 8 : 1; colorless liquid; R_f = 0.57 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +5.5 (*c* 1.0, $CHCl_3$); IR (neat) 699, 778, 837, 1112, 1134, 1256, 1472, 1648, 2857, 2929, 2955, 3284 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ –0.07 (s, 3H), 0.00 (s, 3H), 0.12 (s, 6H), 0.80 (s, 9H), 0.90 (s, 9H), 3.37–3.41 (m, 2H), 3.73 (dd, *J* = 8.1, 3.7 Hz, 1H), 3.93 (dd, *J* = 10.4, 3.9 Hz, 1H), 4.16 (d, J = 1.3 Hz, 1H), 4.28 (d, *J* = 5.4 Hz, 1H), 5.11 (d, *J* = 5.5 Hz, 1H), 7.33–7.44 (m, 6H), 7.50–7.53 (m, 2H), 7.88–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.7, –5.5, –4.4, –3.9, 18.1, 25.8, 61.1, 64.7, 65.9, 74.3, 126.0, 127.4, 128.1, 128.3, 128.4, 128.5, 130.5, 133.7, 139.7, 155.7; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{48}O_4NSi_2$ 542.3122, found 542.3121.

(*R*)-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)(phenyl)methanol (*anti*-5f). Yield 65%; ratio *syn*/*anti* = 8 : 1; white solid; mp 145–155 °C; R_f = 0.48 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +2.5 (*c* 1.0, $CHCl_3$); IR (neat) 699, 775, 830, 1016, 1033, 1057, 2858, 2925, 2950, 3211 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ –0.06 (s, 3H), 0.00 (s, 3H), 0.10–0.25 (m, 6H), 0.70–0.95 (m, 18H), 3.09 (s, 1H), 3.53 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.65–3.69 (m, 1H), 3.90 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.17 (dd, *J* = 7.9, 2.1 Hz, 1H), 4.44 (t, *J* = 2.7 Hz, 1H), 5.00 (dd, *J* = 7.9, 2.8 Hz, 1H), 7.20–7.40 (m, 8H), 7.61–7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.3, –5.0, –4.5, –4.3, 18.5, 26.0, 60.8, 64.6, 64.8, 73.00, 76.4, 127.1, 127.4, 127.6, 127.7, 127.9, 128.1, 128.2, 128.5, 128.6, 130.5, 133.5, 141.6, 155.3; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{48}O_4NSi_2$ 542.3122, found 542.3124.

(5*S*,6*S*,7*R*,8*R*)-6-(Benzoyloxy)-8-(((benzyloxy)carbonyl)amino)-7,9-bis((*tert*-butyldimethylsilyl)oxy)non-1-en-5-yl methanesulfonate (8). Triethylamine (74 μL, 0.533 mmol) and MsCl (56 μL, 0.727 mmol) were successively added to a solution of pentenyl alcohol *syn*-5e (126 mg, 0.242 mmol) in dichloromethane (4.84 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then distilled water was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography gave the secondary mesylate intermediate (133 mg, 0.223 mmol); colorless liquid; R_f = 0.48 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +19.3 (*c* 1.0, $CHCl_3$); IR (neat) 699, 778, 837, 926, 1110, 1178, 1256, 1359, 1658, 2858, 2930, 2954, 3423 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ –0.07 (s, 2H), –0.04 (s, 2H), 0.00 (s, 2H), 0.04 (d, *J* = 5.2 Hz, 6H), 0.78 (s, 9H), 0.80 (s, 9H), 1.71–1.74 (m, 1H), 1.88–1.92 (m, 1H), 2.21–2.25 (m, 2H), 2.98 (s, 3H), 3.42 (dd, *J* = 10.5, 7.9 Hz, 1H), 3.63–3.65 (m, 1H), 3.90 (dd, *J* = 10.6, 3.8 Hz, 1H), 4.17 (s, 1H), 4.26 (dd, *J* = 8.5, 0.7 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 5.00–5.04 (m, 2H), 5.75–5.79 (m, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.5, –5.4, –4.6, –3.9, 18.0, 18.1, 25.6, 25.8, 28.4, 29.6, 38.8, 60.6, 64.0, 64.5, 74.9, 82.4, 115.7, 127.4, 128.2, 130.5, 133.8, 136.8, 155.9; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{52}O_6NSi_2S$ 598.3054, found 598.3055. A solution of $NaHCO_3$ (0.6 M in distilled water, 1.5 mL, 0.892 mmol) and benzyl chloroformate (0.127 mL,

0.892 mmol) was successively added to a solution of this mesylate (133 mg, 0.223 mmol) in dichloromethane (1.5 mL). The reaction mixture was stirred at rt for 48 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with distilled water and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography gave **8** (125 mg, 0.167 mmol); yield 69% for two steps; rotamer ratio >20 : 1; colorless liquid; R_f = 0.35 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ −6.3 (*c* 1.0, $CHCl_3$); IR (neat) 712, 778, 836, 914, 1033, 1056, 1099, 1175, 1258, 1345, 1722, 2858, 2931, 2954, 3453 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.00 (s, 3H), 0.03 (d, J = 6.8 Hz, 3H), 0.10 (d, J = 15.5 Hz, 6H), 0.82 (s, 9H), 0.87 (s, 9H), 1.88–1.90 (m, 1H), 2.00–2.02 (m, 1H), 2.26–2.29 (m, 2H), 2.89 (s, 3H), 3.66 (dd, J = 10.3, 5.8 Hz, 1H), 3.80–3.83 (m, 1H), 3.89–3.91 (m, 1H), 4.23–4.25 (m, 1H), 5.01 (d, J = 10.4 Hz, 1H), 5.05 (d, J = 12.2 Hz, 1H), 5.09–5.12 (m, 2H), 5.45 (t, J = 5.6 Hz, 1H), 5.81–5.83 (m, 1H), 7.30–7.37 (m, 6H), 7.54–7.56 (m, 2H), 8.07 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ −5.7, −5.5, −4.8, −4.3, 18.0, 18.2, 25.9, 29.1, 31.2, 38.7, 54.6, 61.4, 66.8, 69.4, 74.1, 80.6, 115.7, 127.9, 128.4, 128.6, 129.9, 133.4, 136.5, 136.9, 155.9, 165.4; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{37}H_{60}O_9NSi_2S$ 750.3527, found 750.3528.

(2*R*,3*R*,4*R*,5*R*)-Benzyl 2-(but-3-en-1-yl)-4-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxypyrrolidine-1-carboxylate (7). NaH (21.4 mg, 0.892 mmol) was added to a solution of mesylate **8** (223 mg, 0.297 mmol) in THF (6 mL) at rt. The reaction mixture was stirred for 12 h, and then distilled water was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with distilled water and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography gave pyrrolidine **7** (135 mg, 0.246 mmol); yield 83%; rotamer ratio 3 : 1; colorless liquid; R_f = 0.5 (1 : 6 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +2.8 (*c* 0.1, $CHCl_3$); IR (neat) 474, 1012, 1032, 1055, 1656, 2825, 2936, 2953, 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.04–0.10 (m, 12H), 0.84–0.90 (m, 18H), 1.85–1.88 (m, 2H), 2.00–2.15 (m, 2H), 3.61 (dd, J = 10.6, 1.3 Hz, 1H), 3.70–3.85 (m, 2H), 3.86 (d, J = 2.1 Hz, 1H), 4.05–4.12 (m, 2H), 4.49 (dd, J = 10.6, 3.0 Hz, 0.75H), 4.57 (d, J = 11.3 Hz, 0.25H), 4.87 (dd, J = 11.9 Hz, 0.75H), 4.90–4.92 (m, 0.25H), 4.97 (d, J = 15.9 Hz, 0.75H), 5.07 (d, J = 15.9 Hz, 0.25H), 5.10–5.16 (m, 2H), 5.65–5.75 (m, 0.75H), 5.80–5.88 (m, 0.25H), 7.30–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ −5.8, −5.0, 17.9, 18.3, 25.7, 30.7, 31.1, 61.4, 62.8, 66.7, 68.5, 68.7, 114.7, 127.9, 128.2, 128.3, 128.5, 128.6, 136.5, 136.7, 137.9, 138.0, 154.2, 154.7; HRMS (FAB) *m*/*z*: $[M + H]^+$ $C_{29}H_{52}O_5NSi_2$ calcd for 550.3384, found 550.3383.

(1*R*,2*R*,3*R*,7a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)hexahydro-1*H*-pyrrolizin-1-ol (9). Pyrrolidine **7** (81 mg, 0.147 mmol) was dissolved in dry methanol (2 mL) and cooled to −78 °C. Ozone was passed through the solution until the reaction was complete. The reaction mixture was quenched with methyl sulfide (0.1 mL) and allowed to warm to rt. The solvent was evaporated under reduced pressure. The crude aldehyde was immediately employed in the next step without further purification. A solution of the aldehyde in MeOH (2 mL) was hydrogenated overnight in the presence of 20% $Pd(OH)_2/C$ (0.1 g) at rt. The catalyst was removed by filtration through Celite, and the filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography gave protected **9** (43 mg, 0.106 mmol); yield 72% for two steps; colorless liquid; R_f = 0.5 (1 : 2 ethyl acetate–hexanes); $[\alpha]_D^{25}$ +12.5 (*c* 1.0, $CHCl_3$); IR (neat) 663, 672, 775, 837, 1016, 1058, 1089, 2855, 2926, 2957 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.05–0.12 (m, 12H), 0.88–0.95 (m, 18H), 1.68–1.73 (m, 2H), 1.82–1.84 (m, 1H), 1.95–2.10 (m, 1H), 2.30–2.40 (br, s, 1H), 2.66–2.74 (m, 1H), 2.80–2.86 (m, 1H), 3.00–3.08 (m, 1H), 3.28–3.32 (m, 1H), 3.60–3.63 (m, 1H), 3.70–3.92 (m, 2H), 3.91 (t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ −5.2, −5.1, −4.7, −4.1, 18.1, 18.6, 25.4, 25.9, 26.2, 30.3, 56.3, 65.9, 70.9, 74.0, 80.7, 82.5; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{44}O_3NSi_2$ 402.2860, found 402.2861.

(1*R*,2*R*,3*R*,7*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2-diol [(+)-hyacinthacine A_2] (1). The solution of protected **9** (15.3 mg, 0.038 mmol) in 6 N HCl (2 mL) was refluxed for 12 h. The reaction mixture was then cooled to rt and evaporated to dryness to give **1**·HCl; ^1H NMR (D_2O, 700 MHz) δ 1.76–1.81 (m, 2H), 1.82–1.90 (m, 1H), 1.91–1.99 (m, 1H), 2.80–2.87 (m, 2H), 2.96–3.01 (m, 1H), 3.27–3.30 (m, 2H), 3.64 (dd, J = 12.0, 6.2 Hz, 1H), 3.73 (t, J = 7.9 Hz, 1H), 3.74–3.80 (m, 1H); ^{13}C NMR (D_2O, 175 MHz) δ 24.4, 29.5, 54.9, 61.6, 66.7, 69.3, 76.5, 79.6. Further purification by treatment of the salt with ion-exchange resin (Dowex 50W × 8) afforded **1** (4.6 mg, 0.026 mmol); yield 70%; yellow liquid; R_f = 0.1 (1 : 1 methanol–chloroform); $[\alpha]_D^{25}$ +10.4 (*c* 0.1, CH_3OH) and +15.3 (*c* 0.1, H_2O); IR (neat) 1033, 1391, 1642, 2923, 3385 cm^{-1}; ^1H NMR (D_2O, 700 MHz) δ 1.85–1.93 (m, 2H), 1.95–2.00 (m, 1H), 2.00–2.06 (m, 1H), 2.88–2.96 (m, 2H), 3.05–3.10 (m, 1H), 3.36–3.40 (m, 1H), 3.71–3.75 (m, 1H), 3.80–3.88 (m, 3H); ^{13}C NMR (D_2O, 175 MHz) δ 24.4, 29.4, 55.0, 61.2, 66.9, 69.3, 76.3, 79.4; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{16}O_3N$ 174.1130, found 174.1128.

(*S*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)allyl acetate (13). Acetic anhydride (0.863 mL, 9.15 mmol) and 4-DMAP (224 mg, 1.83 mmol) were added to a stirred solution of alcohol *syn*-**5a** (900 mg, 1.83 mmol) in CH_2Cl_2 (18.3 mL) and pyridine (1.83 mL). After stirring for 2 h, the reaction mixture was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution, and brine, dried with $MgSO_4$, and evaporated *in vacuo*. The resulting substance was purified by silica gel column chromatography to give allyl acetate **13** (918 mg, 1.72 mmol); yield 94%; colorless oil; $[\alpha]_D^{25}$ −64.0 (*c* 1.0, $CHCl_3$); IR (neat) 697, 777, 836, 1016, 1033, 1056, 1113, 1233, 1255, 1370, 1470, 1655, 1749, 2859, 2931, 2955, 3732 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.03 (s, 3H), 0.06–0.07 (m, 3H), 0.10–0.11 (m, 6H), 0.86–0.89 (m, 18H), 2.15 (s, 3H), 3.47 (dd, J = 10.5, 8.0 Hz, 1H), 3.66–3.69 (m, 1H), 3.97 (dd, J = 10.3, 3.9 Hz, 1H), 4.18 (dd, J = 8.2, 2.2 Hz, 1H), 4.23–4.25 (m, 1H), 5.39 (d, J = 10.8 Hz, 1H), 5.49 (d, J = 17.2 Hz,

1H), 5.74–5.78 (m, 1H), 5.91 (ddd, J = 17.1, 10.4, 6.4 Hz, 1H), 7.35–7.37 (m, 2H), 7.40–7.43 (m, 1H), 7.86–7.88 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.5, −5.4, −4.4, −4.0, 18.0, 18.1, 21.2, 25.8, 60.6, 63.3, 64.6, 73.1, 75.1, 120.1, 127.2, 128.0, 130.4, 131.7, 133.6, 155.4, 169.8; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{28}H_{48}O_5NSi_2$ 534.3071, found 534.3069.

(*R*)-Pentadec-14-en-7-yl acetate (14). 6-Heptenylmagnesium bromide **11** (0.5 M solution in tetrahydrofuran, 5.53 mL, 2.77 mmol) was added to a dry flask under argon gas. After cooling the mixture to −40 °C, copper(I) iodide (0.070 g, 0.37 mmol) was added to the mixture and stirred for 0.5 h. A solution of (*R*)-epoxyoctane **12** (0.23 g, 1.84 mmol) in THF (5.1 mL) was added to the mixture and stirred for 3 h. The reaction mixture was treated with MTBE (50 mL) and saturated NH_4Cl solution and allowed to warm to rt. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography gave unstable secondary alcohol. Acetic anhydride (0.37 mL, 3.88 mmol) and 4-DMAP (0.034 g, 0.277 mmol) were added to the solution of secondary alcohol in pyridine (0.32 mL) and stirred for 12 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$ and the filtrate was concentrated *in vacuo*. The resulting substance was purified by silica gel column chromatography gave acetate **14** (0.42 g, 1.56 mmol); yield 85% (for 2 steps); colorless oil; $[\alpha]_D^{25}$ +3.0 (c 1.0, $CHCl_3$); IR (neat) 990, 995, 1243, 1373, 1464, 1730, 2858, 2929 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86–0.89 (m, 3H), 1.26–1.38 (m, 16H), 1.50–1.52 (m, 4H), 2.00–2.10 (m, 5H), 4.80–4.90 (m, 1H), 4.92 (dd, J = 10.5, 2.0 Hz, 1H), 4.97 (dd, J = 17.0, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 21.4, 22.8, 25.4, 29.0, 29.2, 29.4, 29.6, 31.9, 33.9, 34.3, 74.6, 114.4, 139.3, 171.0; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{17}H_{33}O_2$ 269.2481, found 269.2477.

(1*S*,10*R*,*E*)-1-((4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)hexadec-2-ene-1,10-diyl diacetate (15). (*R*)-Pentadec-14-en-7-yl acetate **14** (1.24 g, 6.14 mmol) and Grubbs' second-generation catalyst (130 mg, 0.154 mmol) were subsequently added to a solution of allyl acetate **13** (1.87 g, 3.51 mmol) in CH_2Cl_2 (35 mL) at rt. The reaction mixture was stirred and heated to reflux for 8 h and then the solvent was removed *in vacuo* to give the crude products. The resulting substance purified by silica gel column chromatography gave alkene **15** (3.37 g, 4.36 mmol); yield 71%; colorless oil; $[\alpha]_D^{25}$ +31.6 (c 1.0, $CHCl_3$); IR (neat) 697, 778, 837, 1022, 1071, 1113, 1137, 1239, 1656, 1749, 2858, 2930, 2954 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.02–0.04 (m, 12H), 0.76–0.84 (m, 21H), 1.19–1.22 (m, 14H), 1.31 (br, s, 2H), 1.44 (br, s, 4H), 1.95 (s, 3H), 1.97–2.00 (m, 2H), 2.04 (s, 3H), 3.36 (t, J = 9.4 Hz, 1H), 3.60 (br, s, 1H), 3.91 (dd, J = 10.4, 3.9 Hz, 1H), 4.07 (d, J = 8.5 Hz, 1H), 4.14 (s, 1H), 4.75–4.84 (m, 1H), 5.39 (dd, J = 15.4, 7.7 Hz, 1H), 5.65 (t, J = 8.1 Hz, 1H), 5.88 (dt, J = 15.4, 6.0 Hz, 1H), 7.19–7.28 (m, 2H), 7.31–7.33 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.5, −5.4, −4.4, −4.0, 14.1, 18.0, 21.3, 22.6, 25.2, 25.3, 25.8, 25.9, 28.7, 29.2, 29.4, 31.8, 32.4, 32.5, 34.1, 60.8, 63.4, 64.7, 73.3, 74.3, 74.4, 74.9, 123.2, 123.3, 127.2, 128.0, 130.4, 133.7, 138.2, 138.4, 155.6, 169.9, 170.9; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{43}H_{76}O_7NSi_2$ 774.5160, found 774.5162.

(2*R*,3*R*,4*R*,5*S*,14*R*,*E*)-4-(Benzoyloxy)-2-(((benzyloxy)carbonyl)-amino)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyicos-6-ene-5,14-diyl diacetate (16). Benzyl chloroformate (0.2 mL, 1.40 mmol) and a solution of sodium bicarbonate (0.118 g, 1.40 mmol) in H_2O (2 mL) were subsequently added to a solution of alkene **15** (0.258 g, 0.334 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 24 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography (1 : 15 ethyl acetate–hexanes) gave the carbamate intermediate; colorless oil; $[\alpha]_D^{25}$ +6.1 (c 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.05–0.07 (m, 12H), 0.87–0.88 (m, 21H), 1.20–1.26 (m, 16H), 1.48–1.50 (m, 4H), 1.94 (s, 5H), 2.03 (s, 3H), 3.70–3.75 (m, 1H), 3.75–3.80 (m, 1H), 3.90–4.00 (m, 1H), 4.25 (s, 1H), 4.84 (m, 1H), 5.02–5.10 (m, 3H), 5.42 (dd, J = 15.4, 7.2 Hz, 1H), 5.48 (dd, J = 6.5, 4.2 Hz, 1H), 5.76 (t, J = 6.9 Hz, 1H), 5.87 (m, 1H), 7.26–7.31 (m, 5H), 7.35–7.40 (m, 2H), 7.50–7.60 (m, 1H), 8.02 (d, J = 8.1 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.6, −4.6, −4.5, 14.0, 18.0, 18.1, 21.0, 21.2, 22.5, 25.2, 25.7, 25.8, 28.6, 29.0, 29.1, 31.7, 32.3, 34.0, 54.6, 61.2, 66.4, 69.8, 72.8, 74.2, 74.3, 74.6, 124.0, 124.1, 127.8, 128.3, 128.4, 129.6, 129.7, 129.9, 133.0, 136.6, 137.2, 137.3, 155.7, 165.6, 169.9, 170.8. Pyridine (1.7 mL) buffered HF-pyridine (0.5 mL, 0.497 mmol) was added to a solution of carbamate (0.24 g, 0.257 mmol) in THF (5 mL) at 0 °C and then stirred at rt. After 3 h, the reaction mixture was quenched by saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated $CuSO_4$ and brine, dried with $MgSO_4$, and the filtrate was concentrated *in vacuo*. The resulting substance purified by silica gel column chromatography (1 : 15 ethyl acetate–hexanes) gave primary alcohol **16** (0.173 g, 0.213 mmol); yield 64% (for 2 steps); rotamer ratio >20 : 1; colorless oil; $[\alpha]_D^{25}$ +8.9 (c 1.0, $CHCl_3$); IR (neat) 713, 778, 838, 1026, 1068, 1108, 1243, 1727, 2857, 2930, 3451 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ −0.06 (s, 3H), 0.00 (s, 3H), 0.75 (s, 9H), 0.82 (m, 3H), 1.12–1.24 (m, 16H), 1.35–1.50 (m, 4H), 1.85–1.95 (m, 2H), 1.96–2.05 (m, 6H), 3.69 (dd, J = 11.6, 3.7 Hz, 1H), 3.73 (d, J = 3.7 Hz, 1H), 3.96 (d, J = 3.0 Hz, 1H), 4.23 (br, s, 1H), 4.73–4.82 (m, 1H), 4.99 (d, J = 12.2 Hz, 1H), 5.05 (d, J = 12.1 Hz, 1H), 5.30–5.40 (m, 2H), 5.46 (d, J = 6.9 Hz, 1H), 5.51–5.59 (m, 1H), 5.72–5.80 (m, 1H), 7.25–7.29 (m, 5H), 7.32–7.38 (m, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.97 (d, J = 7.2 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −4.6, 0.0, 8.3, 14.1, 18.0, 21.1, 21.3, 22.6, 25.2, 25.3, 25.8, 28.6, 29.0, 29.2, 29.3, 31.8, 32.3, 34.1, 53.7, 58.9, 60.4, 62.2, 66.8, 72.2, 72.6, 74.4, 74.8, 123.7, 128.1, 128.5, 129.8, 133.3, 136.4, 137.3, 156.0, 165.8, 170.0, 171.0; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{45}H_{70}O_{10}NSi$ 812.4769, found 812.4773.

(2*S*,3*R*,4*R*,5*S*,14*R*,*E*)-5,14-Diacetoxy-4-(benzoyloxy)-2-(((benzyloxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)icos-6-enoic acid (17). Dess–Martin periodinane (29 mg, 0.069 mmol) was added to a solution of primary alcohol **16** (37.4 mg, 0.046 mmol) in CH_2Cl_2 (0.15 mL) at rt. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was diluted with Et_2O, then saturated $NaHCO_3$ (27 mg, 0.322 mmol) and $Na_2S_2O_3$ (88 mg, 0.354 mmol) were added and then the heterogeneous mixture was stirred at rt. The transparent liquid was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was immediately used without further purification. 2-Methyl-2-butene (0.33 mL), NaH_2PO_4 (33.11 mg, 0.276 mmol), and $NaClO_2$ (24.98 mg, 0.276 mmol) were subsequently added to a solution of the aldehyde in *t*-BuOH (1.31 ml) and H_2O (0.33 ml) at rt (2-methyl-2-butene–*t*-BuOH–H_2O = 1 : 4 : 1). After 2 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and the filtrate was concentrated *in vacuo*. The resulting substance purified by silica gel column chromatography (1 : 20 methanol–chloroform) gave carboxylic acid **17** (32 mg, 0.039 mmol); yield 84% (for two steps); rotamer ratio >20 : 1; colorless oil; R_f = 0.2 (1 : 20 methanol–chloroform); $[\alpha]_D^{25}$ +4.7 (*c* 1.0, CH_3OH); IR (neat) 713, 778, 838, 1055, 1067, 1119, 1230, 1248, 1728, 2857, 2930, 3434 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ −0.16 (s, 3H), 0.00 (s, 3H), 0.67–0.74 (m, 9H), 0.86–0.88 (m, 3H), 1.14–1.28 (m, 18H), 1.40–1.50 (m, 4H), 1.90 (br, s, 2H), 2.00–2.10 (m, 3H), 2.12 (s, 3H), 4.41 (s, 1H), 4.52 (br, s, 1H), 4.80–4.91 (m, 1H), 5.00–5.10 (m, 3H), 5.13 (d, *J* = 11.6 Hz, 1H), 5.41 (br, s, 1H), 5.69–5.78 (m, 4H), 7.25–7.31 (m, 5H), 7.33–7.45 (m, 2H), 7.50–7.60 (m, 1H), 8.02 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −4.6, −4.5, 0.0, 14.1, 18.0, 21.3, 22.6, 25.1, 25.3, 25.7, 28.6, 28.8, 29.2, 29.7, 31.8, 32.1, 34.1, 56.7, 66.8, 72.6, 72.9, 74.8, 75.5, 124.2, 128.1, 128.4, 129.9, 130.2, 133.1, 136.0, 136.5, 155.3, 165.9, 170.8, 171.7; HRMS (FAB) *m*/*z*: $[M + Na]^+$ calcd for $C_{45}H_{67}O_{11}NSiNa$ 848.4381, found 848.4386.

(2*S*,3*R*,4*R*,5*S*,14*R*,*E*)-2-Amino-3,4,5,14-tetrahydroxyicos-6-enoic acid [sphingofungin B] (2). 6 N HCl (5 mL) was added to a solution of carboxylic acid **17** (76 mg, 0.092 mmol) in MeOH (5 mL) and then the mixture was stirred at rt for 7 h followed by concentration *in vacuo*. 50% KOH (10 mL) was added to the solution of the residue in MeOH (10 mL) and then the reaction mixture was heated at 50 °C for 24 h. The reaction mixture was cooled to rt, and then Amberlite IRC-76 resin was added to the solution until the pH value of the solution reached approximately 7.0. The resin was filtered and the filtrate was concentrated *in vacuo*. Further purification by silica gel column chromatography gave sphingofungin B **2** (14 mg, 0.037 mmol); yield 40% (for two steps); white solid; mp 145–155 °C; $[\alpha]_D^{25}$ −13.6 (*c* 1.0, CH_3OH); IR (neat) 1014, 1033, 1055, 1409, 1465, 1635, 2855, 2926, 3318 cm^{-1}; ^1H NMR (700 MHz, CD_3OD) δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.32–1.46 (m, 20H), 2.08–2.10 (m, 2H), 3.52 (br, s, 1H), 3.64 (dd, *J* = 6.5, 1.7 Hz, 1H), 3.78 (d, *J* = 4.9 Hz, 1H), 4.17–4.19 (m, 2H), 5.51 (dd, *J* = 15.4, 7.4 Hz, 1H), 5.80 (dt, *J* = 14.6, 6.1 Hz, 1H); ^{13}C NMR (175 MHz, CD_3OD) δ 14.5, 23.8, 26.9, 30.4, 30.5, 30.7, 30.8, 33.2, 33.6, 38.6, 61.0, 69.7, 72.6, 75.3, 76.1, 130.4, 135.7, 171.9; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{40}O_6N$ 390.2856, found 390.2854.

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Notes and references

1 (*a*) Y. Mu, T. Jin, G.-W. Kim, J.-S. Kim, S.-S. Kim, Y.-S. Tian, C.-Y. Oh and W.-H. Ham, *Eur. J. Org. Chem.*, 2012, 2614–2620; (*b*) J.-E. Joo, V.-T. Pham, Y.-S. Tian, Y.-S. Chung, C.-Y. Oh, K.-Y. Lee and W.-H. Ham, *Org. Biomol. Chem.*, 2008, **6**, 1498–1501; (*c*) J.-E. Joo, K.-Y. Lee, V.-T. Pham and W.-H. Ham, *Eur. J. Org. Chem.*, 2007, 1586–1593; (*d*) J.-E. Joo, K.-Y. Lee, V.-T. Pham, Y.-S. Tian and W.-H. Ham, *Org. Lett.*, 2007, **9**, 3627–3630.

2 (*a*) T. Jin, J.-S. Kim, Y. Mu, S.-H. Park, X. Jin, J.-C. Kang, C.-Y. Oh and W.-H. Ham, *Tetrahedron*, 2014, **70**, 2570–2575; (*b*) G.-W. Kim, T. Jin, J.-S. Kim, S.-H. Park, K.-H. Lee, S.-S. Kim, I.-S. Myeong and W.-H. Ham, *Tetrahedron: Asymmetry*, 2014, **25**, 87–91; (*c*) Y. Mu, J.-Y. Kim, X. Jin, S.-H. Park, J.-E. Joo and W.-H. Ham, *Synthesis*, 2012, 2340–2346; (*d*) J.-Y. Kim, Y. Mu, X. Jin, S.-H. Park, V.-T. Pham, D.-K. Song, K.-Y. Lee and W.-H. Ham, *Tetrahedron*, 2011, **67**, 9426–9432; (*e*) V.-T. Pham, J.-E. Joo, K.-Y. Lee, T.-W. Kim, Y. Mu and W.-H. Ham, *Tetrahedron*, 2010, **66**, 2123–2131.

3 For recent reviews, see: (*a*) P. Compain and O. R. Martin, *Iminosugar: From Synthesis to Therapeutic Applications*, Wiley, Chichester, 2007; (*b*) W. Zou, *Curr. Top. Med. Chem.*, 2005, **5**, 1363–1391; (*c*) Y. Nishimura, *Curr. Top. Med. Chem.*, 2003, **3**, 575–591; (*d*) P. Compain and O. R. Martin, *Curr. Top. Med. Chem.*, 2003, **3**, 541–560; (*e*) T. M. Wrodnigg, *Monatsh. Chem.*, 2002, **133**, 393–426; (*f*) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux and R. J. Nash, *Phytochemistry*, 2001, **56**, 265–295; (*g*) A. E. Stütz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, 1999.

4 N. Asano, H. Kuroi, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, I. Adachi, A. A. Watson, R. J. Nash and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1–8.

5 For previous syntheses of (+)-hyacinthacine A_2, see: (*a*) M. Royzen, M. T. Taylor, A. DeAngelis and J. M. Fox, *Chem. Sci.*, 2011, **2**, 2162–2165; (*b*) X.-K. Liu, S. Qiu, Y.-G. Xiang, Y.-P. Ruan, X. Zheng and P.-Q. Huang, *J. Org. Chem.*, 2011, **76**, 4952–4963; (*c*) C. Bonaccini, M. Chioccioli, C. Parmeggiani, F. Cardona, D. Lo Re, G. Soldaini, P. Vogel,

C. Bello, A. Goti and P. Gratteri, *Eur. J. Org. Chem.*, 2010, 5574–5585; (*d*) W.-J. Liu, J.-L. Ye and P.-Q. Huang, *Org. Biomol. Chem.*, 2010, **8**, 2085–2091; (*e*) I. Delso, T. Tejero, A. Goti and P. Merino, *Tetrahedron*, 2010, **66**, 1220–1227; (*f*) C. Ribes, E. Falomir, M. Carda and J. A. Marco, *Tetrahedron*, 2009, **65**, 6965–6971; (*g*) P. Dewi-Wülfing and S. Blechert, *Eur. J. Org. Chem.*, 2006, 1852–1856; (*h*) S. Desvergnes, S. Py and Y. Vallée, *J. Org. Chem.*, 2005, **70**, 1459–1462; (*i*) I. Izquierdo, M. T. Plaza and F. Franco, *Tetrahedron: Asymmetry*, 2003, **14**, 3933–3935; (*j*) F. Cardona, E. Faggi, F. Liguori, M. Cacciarini and A. Goti, *Tetrahedron Lett.*, 2003, **44**, 2315–2318; (*k*) L. Rambaud, P. Compain and O. R. Martin, *Tetrahedron: Asymmetry*, 2001, **12**, 1807–1809.

6 For previous syntheses of (−)-hyacinthacine A_2, see: (*a*) E. A. Brock, S. G. Davies, J. A. Lee, P. M. Roberts and J. E. Thomson, *Org. Biomol. Chem.*, 2013, **11**, 3187–3202; (*b*) J. Calveras, J. Casas, T. Parella, J. Joglar and P. Clapés, *Adv. Synth. Catal.*, 2007, **349**, 1661–1666.

7 For recent reviews, see: (*a*) H.-S. Byun, X. Lu and R. Bittman, *Synthesis*, 2006, 2447–2474; (*b*) J. Liao, J. Tao, G. Lin and D. Liu, *Tetrahedron*, 2005, **61**, 4715–4733; (*c*) S. H. Kang, S. Y. Kang, H.-S. Lee and A. J. Buglass, *Chem. Rev.*, 2005, **105**, 4537–4558; (*d*) Y. Ohfune and T. Shinada, *Eur. J. Org. Chem.*, 2005, 5127–5143; (*e*) M. Brunner and A. M. P. Koskinen, *Curr. Org. Chem.*, 2004, **8**, 1629–1645.

8 (*a*) F. VanMiddlesworth, R. A. Giacobbe, M. Lopez, G. Garrity, J. A. Bland, K. Bartizal, R. A. Fromtling, J. Polishook, M. Zweerink, A. M. Edison, W. Rozdilsky, K. E. Wilson and R. L. Monaghan, *J. Antibiot.*, 1992, **45**, 861; (*b*) F. VanMiddlesworth, C. Dufresne, F. E. Wincott, R. T. Mosley and K. E. Wilson, *Tetrahedron Lett.*, 1992, **33**, 297–300.

9 For previous syntheses of sphingofungin B, see: (*a*) S. Kobayashi and T. Furuta, *Tetrahedron*, 1998, **54**, 10275–10294; (*b*) S. Kobayashi, T. Furuta, T. Hayashi, M. Nishijima and K. Hanada, *J. Am. Chem. Soc.*, 1998, **120**, 908–919; (*c*) S. Kobayashi, T. Hayashi, S. Iwamoto, T. Furuta and M. Matsumura, *Synlett*, 1996, 672–674.

10 For previous syntheses of sphingofungin D, see: (*a*) K. Otaka and K. Mori, *Eur. J. Org. Chem.*, 1999, 1795–1802; (*b*) N. Chida, H. Ikemoto, A. Noguchi, S. Amano and S. Ogawa, *Nat. Prod. Lett.*, 1995, **6**, 295–302; (*c*) K. Mori and K. Otaka, *Tetrahedron Lett.*, 1994, **35**, 9207–9210.

11 For previous syntheses of sphingofungin E, see: (*a*) K. Ikeuchi, M. Hayashi, T. Yamamoto, M. Inai, T. Asakawa, Y. Hamashima and T. Kan, *Eur. J. Org. Chem.*, 2013, 6789–6792; (*b*) M. Martinková, J. Gonda, J. Š. Raschmanová, M. Slaninková and J. Kuchár, *Carbohydr. Res.*, 2010, **345**, 2427–2437; (*c*) B. Wang and G.-Q. Lin, *Eur. J. Org. Chem.*, 2009, 5038–5046; (*d*) C. J. Hayes, D. M. Bradley and N. M. Thomson, *J. Org. Chem.*, 2006, **71**, 2661–2665; (*e*) T. Oishi, K. Ando, K. Inomiya, H. Sato, M. Iida and N. Chida, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1927–1947; (*f*) T. Oishi, K. Ando, K. Inomiya, H. Sato, M. Iida and N. Chida, *Org. Lett.*, 2002, **4**, 151–154; (*g*) T. Nakamura and M. Shiozaki, *Tetrahedron*, 2002, **58**, 8779–8791; (*h*) B. M. Trost and C. Lee, *J. Am. Chem. Soc.*, 2001, **123**, 12191–12201; (*i*) T. Nakamura and M. Shiozaki, *Tetrahedron Lett.*, 2001, **42**, 2701–2704; (*j*) B. Wang, X.-M. Yu and G.-Q. Lin, *Synlett*, 2001, 904–906.

12 For previous syntheses of sphingofungin F, see: (*a*) Y.-C. Luo, H.-H. Zhang, Y. Wang and P.-F. Xu, *Acc. Chem. Res.*, 2010, **43**, 1317–1330; (*b*) F.-F. Gan, S.-B. Yang, Y.-C. Luo, W.-B. Yang and P.-F. Xu, *J. Org. Chem.*, 2010, **75**, 2737–2740; (*c*) See ref. 11*c*; (*d*) M. Li and A. Wu, *Synlett*, 2006, 2985–2988; (*e*) K.-Y. Lee, C.-Y. Oh and W.-H. Ham, *Org. Lett.*, 2002, **4**, 4403–4405; (*f*) See ref. 11*h*; (*g*) D.-G. Liu, B. Wang and G.-Q. Lin, *J. Org. Chem.*, 2000, **65**, 9114–9119; (*h*) See ref. 9*a*; (*i*) B. M. Trost and C. B. Lee, *J. Am. Chem. Soc.*, 1998, **120**, 6818–6819; (*j*) S. Kobayashi, M. Matsumura, T. Furuta, T. Hayashi and S. Iwamoto, *Synlett*, 1997, 301–303.

13 For previous syntheses of myriocin, see: (*a*) M. Inai, T. Goto, T. Furuta, T. Wakimoto and T. Kan, *Tetrahedron: Asymmetry*, 2008, **19**, 2771–2773; (*b*) M. C. Jones and S. P. Marsden, *Org. Lett.*, 2008, **10**, 4125–4128; (*c*) K.-Y. Lee, C.-Y. Oh, Y.-H. Kim, J.-E. Joo and W.-H. Ham, *Tetrahedron Lett.*, 2002, **43**, 9361–9363 and references cited therein; (*d*) See ref. 11*e*; (*e*) T. Oishi, K. Ando and N. Chida, *Chem. Commun.*, 2001, 1932–1933.

14 For previous syntheses of mycestericin A, see: (*a*) H. Yamanaka, K. Sato, H. Sato, M. Iida, T. Oishi and N. Chida, *Tetrahedron*, 2009, **65**, 9188–9201; (*b*) H. Sato, K. Sato, M. Iida, H. Yamanaka, T. Oishi and N. Chida, *Tetrahedron Lett.*, 2008, **49**, 1943–1947.

15 For previous synthesis of mycestericin C, see: S. Sakamoto, N. Kazumi, Y. Kobayashi, C. Tsukano and Y. Takemoto, *Org. Lett.*, 2014, **16**, 4758–4761.

16 For reviews, see: (*a*) A. Mengel and O. Reiser, *Chem. Rev.*, 1999, **99**, 1191–1223; (*b*) M. T. Reetz, *Chem. Rev.*, 1999, **99**, 1121–1162; (*c*) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1531–1546; (*d*) J. Jurczak and A. Gołębiowski, *Chem. Rev.*, 1989, **89**, 149–164; (*e*) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 556–569.

17 R. S. Coleman and A. J. Carpenter, *Tetrahedron Lett.*, 1992, **33**, 1697–1700.

18 T. Fujisawa, Y. Ukaji, M. Funabora, M. Yamashita and T. Sato, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1894–1897.

19 G. Boireau, A. Deberly and D. Abenhaïm, *Tetrahedron*, 1989, **45**, 5837–5844.

20 S. Kobayashi, P. Das, G. X. Wang, T. Mita, M. J. Lear and M. Hirama, *Chem. Lett.*, 2002, 300–301.

21 (*a*) M. Asami and R. Kimura, *Chem. Lett.*, 1985, 1221–1222; (*b*) M. Asami and T. Mukaiyama, *Chem. Lett.*, 1983, 93–96.

22 R. Bloch and L. Gilbert, *Tetrahedron Lett.*, 1987, **28**, 423–426.

23 G. E. Keck, M. B. Andrus and D. R. Romer, *J. Org. Chem.*, 1991, **56**, 417–420.

24 J. Mulzer and C. Pietschmann, *J. Org. Chem.*, 1997, **62**, 3938–3943.

25 "Although the actual role of $ZnBr_2$ is not clear at present" by Asami (ref. 21*a*, p. 1222), "its generality is unknown" by

Reetz (ref. 16*e*, p. 562), "although the actual stereochemical course is still an open question" by Fujisawa (ref. 18, p. 1895), "argues further against simple chelation model" by Coleman (ref. 17, p. 1698), and "the actual role of Ti $(OiPr)_4$ in our case... in THF is still a matter of debate" by Hirama (ref. 20, p. 301).

26 (*a*) J. L. von dem Bussche-Hünnefeld and D. Seebach, *Tetrahedron*, 1992, **48**, 5719–5730; (*b*) D. Seebach, L. Behrendt and D. Felix, *Angew. Chem. Int., Ed. Engl.*, 1991, **30**, 1008–1009.

27 I. Izquierdo, M. T. Plaza, R. Robles and F. Franco, *Tetrahedron: Asymmetry*, 2001, **12**, 2481–2487.