Tetrahedron 67 (2011) 9426–9432

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient and stereoselective syntheses of DAB-1 and D-fagomine via chiral 1,3-oxazine

Ji-Yeon Kim [a], Yu Mu [a], Xiangdan Jin [a], Seok-Hwi Park [a], Van-Thoai Pham [a], Dong-Keun Song [a], Kee-Young Lee [b], Won-Hun Ham [a,*]

[a] School of Pharmacy, SungKyunKwan University, Suwonsi 440-746, Republic of Korea
[b] Yonsung Fine Chemicals Co., Ltd., 129-9 Suchon-ri, Jangan-myeon, Hwaseong-si, Gyeonggi-do 445-944, Republic of Korea

ARTICLE INFO

Article history:
Received 4 August 2011
Received in revised form 19 September 2011
Accepted 20 September 2011
Available online 25 September 2011

Keywords:
Natural product
DAB-1
D-Fagomine
Oxazine
Pd(0) catalyst
Catalytic hydrogenation

ABSTRACT

The concise, stereocontrolled syntheses of DAB-1 and D-fagomine were achieved utilizing chiral oxazine. The key features in these strategies are the stereoselective intramolecular oxazine formation catalyzed by palladium(0), and pyrrolidine and piperidine formation by catalytic hydrogenation of oxazine.

1. Introduction

1,4-Dideoxy-1,4-imido-D-arabinitol (**1**, known as DAB-1; see Fig. 1), a potent glucosidase inhibitor and potential anti-HIV agent, was isolated from *Angylocalyx boutiqueanus* and *Arachniodes standishii* in 1985.[1,2] (2*R*,3*R*,4*R*)-2-Hydroxymethylpiperidine-3,4-diol (**2**, known as D-fagomine) was first isolated from Japanese buckwheat seeds of *Fagopyrum esculentum* Moeneh in 1974 and more recently from *Xanthocercis zambesiaca* in a southern African dry forest.[3] **2** has inhibitory activity against mammalian α-glucosidase and β-galactosidase.[4] Recently, **2** has also been shown to exhibit a potent antihyperglycemic effect in streptozocin-induced diabetic mice and the potentiation of glucose-induced insulin secretion.[5]

A number of their synthetic approaches have been reported due to their three contiguous stereocenters and their promising biological activity.[6,7]

Recently, we have described a new Pd(0)-catalyzed procedure for the stereoselective formation of an oxazine ring from a γ-allylic benzamide having a benzoyl substituent as an N-protection group in the presence of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI (Scheme 1).

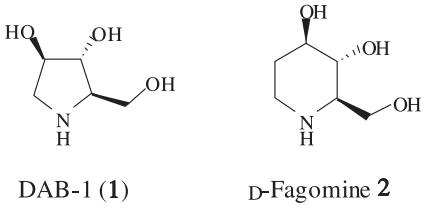
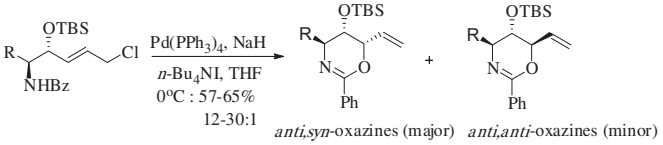


Fig. 1. Structures of DAB-1, D-fagomine.



R= (a) C_6H_5, (b) $C_6H_5CH_2$, (c) $(CH_3)_2CH$, (d) $(CH_3)_2CHCH_2$

Scheme 1. Oxazine formation from 1,2-*anti*-amino alcohol derivatives.

2. Results and discussion

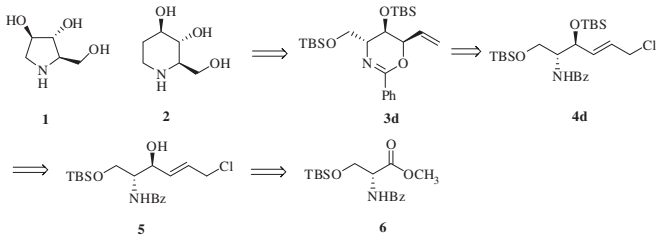
As part of a program directed at expanding the synthetic utility of oxazine as a chiral building block for the syntheses of natural

* Corresponding author. E-mail address: whham@skku.edu (W.-H. Ham).

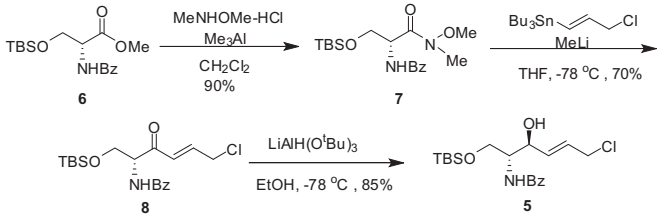
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.084

products, we report herein our synthetic efforts, which led to a concise and highly stereocontrolled total syntheses of **1** and **2** using oxazine **3d**. We envisioned that this method could be utilized to set the three contiguous stereocenters of DAB-1 (**1**) and D-fagomine **2**. The pendent vinyl group of oxazine **3d** could be converted to the corresponding aldehyde, which could be employed in formation of the pyrrolidine ring by catalytic hydrogenation of oxazine. Also one carbon elongation from this pendent vinyl group of oxazine, which could be used in preparation of the piperidine as the same reaction (hydrogenolysis). The oxazine **3d** could be prepared from **4d** by our newly developed palladium(0) catalyzed oxazine formation reaction.[8] This process efficiently adjusted stereochemistry and provided simultaneous protection for the newly generated hydroxyl group. In the proposed retrosynthesis, compound **1** and **2** can be obtained from a common intermediate **3d**.

We now report enantioselective syntheses of **1** and **2** in accordance with these strategies. Our retrosynthetic analysis is displayed in Scheme 2. The synthesis of **5** is made from *N*-benzoyl-D-serine methyl ester **6** according to the known procedure (Scheme 3).[9]



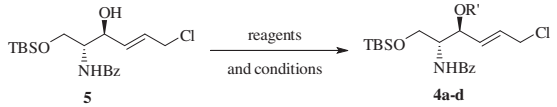
Scheme 2. Retrosyntheses of DAB-1 and D-fagomine.



Scheme 3. Synthesis of **5** from D-serine.

On the basis of our previous research, we anticipated that the palladium(0)-catalyzed oxazine formation of γ-allylbenzamide with various alcohol protection substituents might proceed with high stereoselectivity.[8] In order to investigate the influence of the bulkiness of the protective group, these reaction conditions were extended to other substrates used to investigate the influence of the R group on selectivity. These substrates were simply prepared under the reaction conditions shown in Table 1.

Table 1
Preparation of various alcohol protection of cyclization precursors

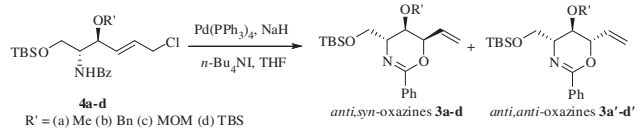


Substrate	R′	Reagents	Temp (°C)	Time (h)	Yield[a] (%)
4a	Me	MeI, NaH, THF	0	2	73
4b	Bn	BnBr, NaH, THF	rt	2	70
4c	$MeOCH_2$	MOMCl, TEA, CH_2Cl_2	0-rt	24	80
4d	TBS	TBSCl, Imid, DMF	rt	2	95

[a] Yield refer to the isolated products.

The reaction of **4a**–**d**, which had methyl, benzyl, methoxymethyl, and *tert*-butyldimethylsilyl as the protective groups with NaH and *n*-Bu_4NI in the presence of $Pd(PPh_3)_4$ in THF at 0 °C afforded the *anti*,*syn*-oxazines **3a**–**d** as the major products along with minor amounts of the *anti*,*anti*-oxazines **3a′**–**d′**. The results are summarized in Table 2.

Table 2
Oxazine formation catalyzed by Pd(0)



Entry	Substrate	Temp (°C)	Time (h)	Yield[a] (%)	Ratio[b](*anti*,*syn*/*anti*,*anti*)
1	**4a**	0	5	51	2:1
2	**4b**	0	5	70	3:1
3	**4c**	0	5	76	3:1
4	**4d**	0	5	65	>30:1

[a] Yield refers to the isolated and mixed products.
[b] Ratio was determined by ^1H NMR of *anti*,*syn*-oxazines and *anti*,*anti*-oxazines.

The diastereoselectivity was decreased with sterically less bulky groups, such as methyl, benzyl, and methoxymethyl (entries 1–3, Table 2). The diastereoselectivity was improved to >30:1 when R′ was the TBS group (entry 4). It is clear from these experiments that steric bulkiness at the R′ groups highly influences the level of diastereoselectivity (Table 2). The diastereoselectivity of oxazine ring formation is dominantly controlled by the bulkiness of R′. This result verified that the bulky TBS group plays an important role in determining the stereoselectivity during oxazine formation. Upon extensive examination of R′, we found that reaction using TBS as the protection group gave the desired diastereomer as the major compound with high diastereoselectivity and in good yield.

To verify the stereochemical outcome at the newly generated stereocenter C-6, the NOE spectra of the oxazine were studied under the assumption that there must be a NOE difference between the two isomers **A** and **B**.[†]

The stereochemistries of the oxazines obtained above were elucidated by ^1H NMR, as shown in Table 3. The relative configuration of each diastereomer of the oxazine products obtained after the silica gel column separation was determined by comparing their coupling constants (Table 3). Small coupling constants of $J_{5,6}$=3.5–4.5 Hz, as in *anti*,*syn*-oxazine (**A**), are caused by the axial–equatorial relationship between the two adjacent protons in six-membered rings. The large coupling constants of $J_{5,6}$=8.3–9.0 Hz, as in *anti*,*anti*-oxazine (**B**), are typically due to the

[†] The assignment of relative configuration was confirmed by observation of the larger NOE enhancement for *anti*,*syn*-oxazines **3d**, and *anti*,*anti*-oxazine **3d′** as shown below: in the *anti*,*syn*-oxazines case, for compound **3d**: there are 6.10% NOE between H-5 and H-6, 2.83% between H-5 and H-4, but no NOE effective between H-4 and H-6.; in the *anti*,*anti*-oxazine case, for compound **3d′**: there are 4.72% between H-4 and H-6, 0.72% between H-5 and H-4, 1.16% between H-5 and H-6.

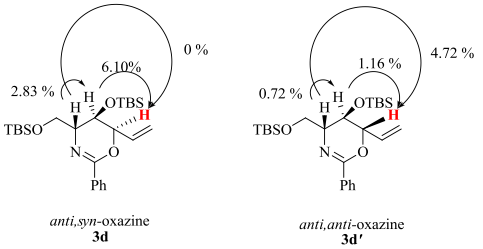
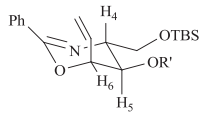
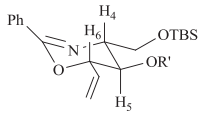


Table 3
^{1}H NMR ($CDCl_3$) coupling constants of oxazines



anti,syn-oxazines (**A**)



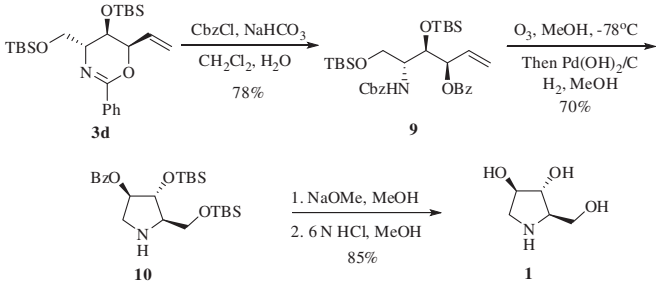
anti,anti-oxazines (**B**)

Substrate	R′	Isomer	$J_{4,5}$	$J_{5,6}$
3a	Me	A	6.5	4.5
3a′	Me	B	8.5	8.3
3b	Bn	A	6.5	3.5
3b′	Bn	B	8.4	9.0
3c	MOM	A	6.5	3.5
3c′	MOM	B	7.5	8.5
3d	TBS	A	6.0	4.0
3d′	TBS	B	8.0	8.8

diaxial relationship between the two adjacent protons in six-membered rings.[10]

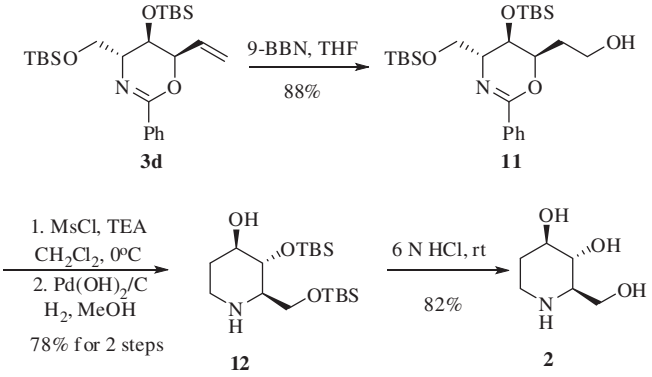
In addition, the coupling constants of the newly generated chiral center (H_5–H_6) of **A** have similar values of 2.5–4.0 Hz compared to those previously reported for *syn,syn*-oxazine compounds. In contrast, the coupling constants of the newly generated chiral center (H_5–H_6) of **B** have the same values of 7.5–9.0 Hz as the *syn,anti*-isomer.[9]

As showed in Scheme 4, the oxazine **3d** was treated with benzyl chloroformate in the presence of aqueous sodium bicarbonate (Schotten–Baumann conditions), affording the carbamate **9** in 78% yield. Ozonolysis of the terminal olefin gave the corresponding aldehyde. Hydrogenolysis (70 psi of H_2 gas) of aldehyde in MeOH afforded the protected DAB-1 (**10**) as a single isomer in 70% yield. Finally, removal of benzoyl group and disilyl group by treatment of **10** with NaOMe in MeOH followed by 6 N HCl yielded the DAB-1 salt, which was purified by ion-exchange chromatography through a DOWEX 50WX8-100(H^+) to give DAB-1 (**1**). The optical rotation of **1**, $[\alpha]_D^{25}$ +6.2 (*c* 1.0, H_2O), compared to the reported valve, $[\alpha]_D^{25}$ +7.8 (*c* 1.0, H_2O),[6f] confirms the identity of the absolute configuration.



Scheme 4. Synthesis of DAB-1 (**1**).

Terminal olefin of the oxazine **3d** was converted into the primary alcohol **11** by hydroboration of **3d** with 9-BBN in THF at room temperature (88% yield) (Scheme 5). Mesylation of **11** ($MeSO_2Cl$, Et_3N, 0 °C) gave mesylate in excellent yield (97%). Hydrogenolysis of mesylate afforded the protected D-fagomine **12**. Under these conditions, we achieved not only hydrogenolysis of oxazine moiety but also cyclization of the intramolecular amino mesylate to piperidine **12** in 78% yield. Finally, TBS protecting groups were removed by treatment with 6 N HCl in methanol, afforded D-fagomine **2** in 82% yield after DOWEX 50WX8-100(H^+) ion-exchange chromatography. The optical rotation of **2**, $[\alpha]_D^{25}$ +14.9 (*c* 0.9, H_2O), compared to the reported valves, $[\alpha]_D^{25}$ +13.4 (*c* 0.86, H_2O),[7d] $[\alpha]_D^{25}$ +18.0 (*c* 0.92, H_2O),[7f] confirms the identity of the absolute configuration.



Scheme 5. Synthesis of D-fagomine **2**.

The spectroscopic (^{1}H and ^{13}C NMR) data for synthetic **1** and **2** were fully identical with those of synthetic compounds and the properties of **1** and **2** showed good agreement with those reported.[6b,7f]

3. Conclusion

We have described a Pd(0)-catalyzed procedure for the stereoselective formation of an oxazine ring, the diastereoselectivity of oxazine ring formation is predominantly controlled by the bulkiness of alcohol protecting groups. On the basis of these results, we applied to the asymmetric synthetic method for DAB-1 (**1**) and D-fagomine **2** utilizing chiral oxazine **3d**. The key features in these strategies are the stereoselective intramolecular oxazine formation catalyzed by palladium(0), and pyrrolidine and piperidine formation by catalytic hydrogenation of oxazine. The net results were syntheses from a linear sequence of 6 steps from **5** in 24% overall yield for DAB-1, and 7 steps in 23% overall yield for D-fagomine.

4. Experimental section

4.1. General methods and materials

Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained from Cooperative Center for Research Facilities in Sungkyunkwan University on FT-NMR 125, 300 or 500 MHz spectrometers. Chemical shifts are reported as δ values in parts per million relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on a Bruker FT-IR spectrometer. Mass spectral data were measured on Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer. Flash chromatography was executed with Merck Kiesegel 60 (230–400 mesh) using mixtures of ethyl acetate and hexane as eluants. Ethyl acetate and hexane were dried and purified by distillation prior to use. Tetrahydrofuran (THF) and diethylether (Et_2O) was distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

4.2. Experimental procedures

*4.2.1. (R)-Methyl-2-benzamido-3-(tert-butyldimethylsilyloxy)propanoate (**6**).* Thionyl chloride (5.17 mL, 71.03 mmol) was added dropwise to methanol (47.4 mL) at 0 °C. Then D-serine (5 g, 47.35 mmol) was added to the solution. The mixture was heated to reflux for 5 h. Concentration under reduced pressure provided hydrochloride salt as a white solid. To a solution of D-serine methyl ester hydrochloride (7.52 g, 48.68 mmol) in methanol (48.6 mL) was added dropwise triethylamine (6.22 mL, 53.55 mmol) and

benzoyl chloride (20.36 mL, 146.06 mmol) at 0 °C. The residue was extracted with ethyl acetate. The ethyl acetate extracts were washed with saturated ammonium chloride, saturated sodium bicarbonate and brine, dried with $MgSO_4$. The filtrate was concentrated in vacuo. The crude compound was immediately employed in the next step without further purification. Imidazole (4.0 g, 58.83 mmol) and *tert*-butyldimethyl chlorosilane (8.87 g, 58.83 mmol) were added to a stirred solution of *N*-benzoyl-D-serine methyl ester (10.9 g, 49.02 mmol) in CH_2Cl_2 (98.0 mL) at room temperature. The mixture was stirred for 2 h at room temperature. The mixture was washed with saturated ammonium chloride, saturated sodium bicarbonate and brine, dried with $MgSO_4$. The filtrate was concentrated in vacuo to give the crude product, which upon purification by column chromatography on silica gel gave the *N*-benzoyl-*O*-TBS-D-serine methyl ester **6** (14.9 g, 93% yield for 3 steps) as a colorless oil, R_f=0.6 (ethyl acetate/hexane=1/2); $[\alpha]_D^{25}$ −56.7 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3865, 3335, 2954, 2886, 2858, 1748, 1665, 1523, 1486, 1439, 1352, 1253, 1209, 1164, 1110, 839, 780, 715, 670, 504, 451 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.02–0.05 (m, 6H), 0.92 (s, 9H), 3.78 (s, 3H), 3.95–3.98 (dd, *J*=3.0, 10.0 Hz, 1H), 4.14–4.18 (dd, *J*=3.0, 10.0 Hz, 1H), 4.99 (dt, *J*=2.5, 8.0 Hz, 1H), 6.99 (d, *J*=7.5 Hz, 1H), 7.44–7.52 (m, 3H), 7.83–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.40, −5.25, 18.40, 25.90, 52.70, 54.95, 63.80, 127.30, 128.95, 132.0, 134.30, 167.20, 171.20; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{17}H_{27}NO_4Si$ 338.1788 found 338.1788.

*4.2.2. (R)-N-(3,8,8,9,9-Pentamethyl-4-oxo-2,7-dioxa-3-aza-8-siladecan-5-yl)benzamide (**7**).* To a solution of *N*,*O*-dimethyl-hydroxylamine hydrochloride (867 mg, 8.89 mmol) in CH_2Cl_2 (10 mL) was added trimethylaluminum (4.45 mL of a 2 M solution in hexane, 8.89 mmol) at 0 °C (Caution: CH_4-evolution). The mixture was stirred for 30 min at room temperature. Subsequently, a solution of *N*-benzoyl-*O*-TBS-D-serine methyl ester **6** (1.00 g, 2.96 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at room temperature for 1 h, after which time TLC analysis indicated complete reaction. The reaction mixture was cooled to 0 °C and carefully quenched with 10% sodium potassium tartrate (2.20 mL). After being stirred for 1 h at room temperature, the resulting suspension was filtered through Celite pad, washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give the crude product, which upon purification by column chromatography on silica gel gave the Weinreb amide **7** (987 mg, 91% yield) as a colorless oil, R_f=0.30; $[\alpha]_D^{25}$ −4.28 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3325, 2930, 2856, 2359, 1640, 1110, 873 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.02–0.05 (m, 6H), 0.92 (s, 9H), 3.29 (s, 3H), 3.83 (s, 3H), 3.96 (dd, *J*=4.5, 10.0 Hz, 1H), 4.06 (dd, *J*=4.5, 10.0 Hz, 1H), 5.25 (m, 1H), 7.09 (d, *J*=7.5 Hz, 1H), 7.44–7.52 (m, 3H), 7.83–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.02, 0.05, 23.76, 31.31, 57.48, 67.06, 68.73, 132.62, 134.07, 137.13, 139.26, 172.43; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{18}H_{31}N_2O_4Si$ 367.2053 found 367.2050.

*4.2.3. (R,E)-N-(1-(tert-Butyldimethylsilyloxy)-6-chloro-3-oxohex-4-en-2-yl)benzamide (**8**).* Vinyltin (1.50 g, 4.09 mmol) was dissolved in dry THF (10 mL) and cooled to −78 °C. MeLi (1.6 M solution in hexane, 2.60 mL, 4.09 mmol) was added dropwise. The mixture was stirred for 30 min at same temperature. Subsequently, a solution of Weinreb amide **7** (0.50 g, 1.36 mmol) in dry THF (5 mL) was added dropwise and stirring was allowed to continue for 30 min, after which time TLC analysis indicated complete reaction. The reaction was quenched by aqueous saturated NH_4Cl (10 mL) then warmed to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (20 mL×2). The combined organic layer washed with saturated $NaHCO_3$ solution (20 mL), brine (20 mL), dried with $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting substance was purified by silica gel column chromatography gave the amino ketone **8** (447 mg, 1.12 mmol, 86% yield) as a colorless oil; R_f=0.6 (ethyl acetate/hexane=1/2); $[\alpha]_D^{25}$ −6.11 (*c*=1.3, $CHCl_3$); IR (neat) ν_{max}: 3422, 2929, 2857, 1703, 1657, 1515, 1109, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.034–0.089 (m, 6H), 0.87–0.91 (m, 9H), 4.02 (dd, *J*=4.5, 10.2 Hz, 1H), 4.26 (dd, *J*=3.0, 4.5 Hz, 1H), 4.27 (dd, *J*=1.8, 5.7 Hz, 2H), 5.06–5.11 (m, 1H), 6.67 (ddd, *J*=1.5, 1.8, 15.3 Hz, 1H), 7.03–7.08 (m, 1H), 7.11 (d, *J*=3.0 Hz, 1H), 7.47–7.60 (m, 3H), 7.86–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.34, −5.32, 18.28, 25.95, 42.97, 59.67, 63.28, 127.29, 127.46, 128.36, 128.88, 132.02, 134.16, 141.50, 167.13, 195.89; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{19}H_{29}NO_3SiCl$ 382.1605 found 382.1606.

*4.2.4. N-((2R,3S,E)-1-(tert-Butyldimethylsilyloxy)-6-chloro-3-hydroxyhex-4-en-2-yl)benzamide (**5**).* To a solution of amino ketone **8** (365 mg, 0.96 mmol) in ethanol (10 mL) was added lithium tri-*tert*-butoxyaluminohydride (1 M solution in THF, 1.92 mL, 1.92 mmol) at −78 °C. After the reaction mixture was stirred at the same temperature for 2 h, 10% aqueous solution of citric acid (10 mL) was added. The resulting mixture was warmed to room temperature and extracted with ethyl acetate (10 mL×3). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. The column chromatography on silica gel gave amino alcohol **5** (323 mg, 87% yield, ratio *anti*/*syn*=10:1 by ^1H NMR) as a colorless oil; R_f=0.36 (ethyl acetate/hexane=1/2) $[\alpha]_D^{25}$ −4.22 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3425, 3064, 2953, 2856, 1644, 1521, 1255, 1112, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08–0.13 (m, 6H), 0.92–0.95 (m, 9H), 3.91 (dd, *J*=3.0, 10.5 Hz, 1H), 3.99–4.03 (m, 1H), 4.05 (d, *J*=3.0, 5.4 Hz, 1H), 4.12 (d, *J*=6.0 Hz, 2H), 4.15–4.25 (m, 1H), 4.47–4.44 (m, 2H), 5.87–6.10 (m, 2H), 6.97 (d, *J*=8.1 Hz, 1H), 7.42–7.59 (m, 3H), 7.78–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.38, −5.35, 18.30, 54.03, 63.38, 73.74, 127.17, 127.99, 128.80, 128.91, 131.98, 134.32, 134.41, 167.86; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{19}H_{30}NO_3SiCl$ 384.1762 found 384.1764.

*4.2.5. N-((5S,6R)-5-((E)-3-Chloroprop-1-enyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)benzamide (**4d**).* Imidazole (64 mg, 0.94 mmol) and *tert*-butyldimethyl chlorosilane (141 mg, 0.94 mmol) were added to a stirred solution of **5** (300 mg, 0.78 mmol) in DMF (8.0 mL) at room temperature. And stirring was allowed to continue for 2 h. The reaction mixture was quenched with H_2O then extracted twice with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and evaporated in vacuo. Purification by silica gel chromatography gave **4d** (363 mg, 95%) as a white solid, mp: 79–80 °C; R_f=0.3 (ethyl acetate/hexane=1/8); $[\alpha]_D^{25}$ −5.49 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3324, 2954, 2857, 2360, 1643, 1515, 1254, 1058, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.06–0.11 (m, 12H), 0.91–0.93 (m, 18H), 3.71 (dd, *J*=4.9, 10.2 Hz, 1H), 3.98–4.07 (m, 2H), 4.17–4.20 (m, 1H), 4.44 (t, *J*=6.4 Hz, 1H), 5.83–5.87 (m, 1H), 5.92 (dd, *J*=6.5, 15.3 Hz, 1H), 6.34 (d, *J*=8.6 Hz, 1H), 7.42–7.45 (m, 2H), 7.49–7.52 (m, 1H), 7.72–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.29, −5.09, −4.70, −3.84, 18.32, 18.42, 25.88, 26.05, 26.10, 44.44, 55.46, 61.25, 72.20, 126.94, 128.18, 128.81, 131.63, 135.05, 135.45, 167.24; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{25}H_{45}NO_3Si_2Cl$ 498.2627 found 498.2630.

4.3. General procedure for oxazine formation

NaH (60% in mineral oil, 2.0 equiv) and *n*-Bu_4NI (1.0 equiv) were added to a stirred solution of methyl ether, benzyl ether, methoxymethyl ether or silyl ether (1.0 equiv) in dry THF (0.05 M) at 0 °C. After being stirred for 5 min, $Pd(PPh_3)_4$ (0.2 equiv) was added to a mixture and stirring was allowed to continue for 5 h at same temperature. The reaction mixture was filtered through a pad of silica and then evaporated under reduced pressure to give the

crude product. Purification of this material by silica gel chromatography gave mixtures of *anti,syn*/*anti,anti*-oxazines.

*4.3.1. (4R,5R,6R)-4-((tert-Butyldimethylsilyloxy)methyl)-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3a**).* Colorless oil; R_f=0.51 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ +35.2 (*c* 0.9, $CHCl_3$); IR (neat) ν_{max}: 3867, 3356, 2946, 2834, 1659, 1454, 1114, 1028, 838, 780, 672, 498, 453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 3.44 (s, 3H), 3.64–3.74 (m, 3H), 3.99 (dd, *J*=3.5, 10.5 Hz, 1H), 4.84 (ddd, *J*=3.0, 4.5, 7.0 Hz, 1H), 5.36 (dt, *J*=1.5, 11.0 Hz, 1H), 5.43 (dt, *J*=1.5, 17.0 Hz, 1H), 6.10 (ddd, *J*=5.5, 10.5, 17.5 Hz, 1H), 7.33–7.43 (m, 3H), 7.95–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.06, −4.30, 18.45, 26.05, 56.60, 57.89, 64.70, 74.26, 74.52, 116.40, 116.54, 117.94, 125.06, 127.61, 128.16, 130.65, 133.61, 133.76, 155.13; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{20}H_{31}NO_3Si$ 362.2151 found 362.2147.

*4.3.2. (4R,5R,6S)-4-((tert-Butyldimethylsilyloxy)methyl)-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3a′**).* Colorless oil; R_f=0.63 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ +15.1 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3867, 3357, 2946, 2834, 1666, 1453, 1115, 1028, 671, 497, 453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 3.39 (t, *J*=8.0, 8.5 Hz, 1H), 3.47 (m, 1H), 3.51 (s, 1H), 3.96 (ddd, *J*=3.3, 10.3, 18.5 Hz, 2H), 4.48 (ddt, *J*=1.0, 4.5, 7.5 Hz, 1H), 5.38 (dt, *J*=1.0, 9.5 Hz, 1H), 5.55 (dt, *J*=1.5, 17.5 Hz, 1H), 6.07 (ddd, *J*=5.8, 10.8, 17.3 Hz, 1H), 7.34–7.43 (m, 3H), 7.95–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.06, −4.89, 0.20, 18.52, 31.15, 60.17, 60.66, 63.95, 75.29, 77.79, 118.42, 127.70, 128.16, 130.66, 133.29, 134.76, 154.65; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{20}H_{31}NO_3Si$ 362.2151 found 362.2155.

*4.3.3. (4R,5R,6R)-5-(Benzyloxy)-4-((tert-dimethylsilyloxy)methyl)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3b**).* Colorless oil; R_f=0.53 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ +38.1 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max}: 3841, 3381, 2948, 2835, 1660, 1452, 1112, 1029, 837, 780, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 3.67 (q, *J*=5.0, 8.5 Hz, 1H), 3.76 (dd, *J*=5.5, 10.0 Hz, 1H), 3.92 (dd, *J*=4.0, 5.0 Hz, 1H), 4.00 (dd, *J*=3.5, 10.5 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 4.70 (d, *J*=12.0 Hz, 1H), 6.10 (ddd, *J*=1.5, 3.5, 3.5 Hz, 1H), 5.33 (dt, *J*=1.5, 10.5 Hz, 1H), 5.38 (dt, *J*=1.5, 17.5 Hz, 1H), 6.10 (ddd, *J*=5.5, 11.0, 17.5 Hz, 1H), 7.27–7.43 (m, 8H), 7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.07, −5.02, 0.20, 18.49, 26.10, 56.96, 64.62, 71.91, 72.07, 74.51, 76.96, 117.86, 127.62, 128.00, 128.16, 128.18, 128.59, 130.65, 133.61, 133.76, 138.32, 154.92; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{26}H_{35}NO_3Si$ 438.2464 found 438.2466.

*4.3.4. (4R,5R,6S)-5-(Benzyloxy)-4-((tert-dimethylsilyloxy)methyl)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3b′**).* Colorless oil; R_f=0.57 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ +5.0 (*c* 0.7, $CHCl_3$); IR (neat) ν_{max}: 3841, 3381, 2947, 2834, 1662, 1452, 1039, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 3.56 (dt, *J*=3.0, 8.0 Hz, 1H), 3.70 (t, *J*=8.5, 9.0 Hz, 1H), 3.97 (dd, *J*=3.0, 5.0 Hz, 1H), 4.02 (dd *J*=3.0, 5.0 Hz, 1H), 4.55 (ddt, *J*=1.0, 6.0, 9.0 Hz, 1H), 4.66 (d, *J*=6.0 Hz, 1H), 4.70 (d, *J*=6.0 Hz, 1H), 5.38 (dt, *J*=1.3, 10.5 Hz, 1H), 5.57 (dt, *J*=1.5, 17.0 Hz, 1H), 6.07 (ddd, *J*=1.0, 5.5, 6.5 Hz, 1H), 7.29–7.44 (m, 8H), 7.96–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.01, −4.84, 0.21, 18.55, 26.11, 50.83, 63.83, 73.40, 74.52, 78.05, 118.76, 127.72, 128.12, 128.17, 128.30, 128.66, 130.67, 133.24, 134.83, 138.23, 154.72; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{26}H_{35}NO_3Si$ 438.2464 found 438.2461.

*4.3.5. (4R,5R,6R)-4-((tert-Butyldimethylsilyloxy)methyl)-5-(methoxymethoxy)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3c**).* Colorless oil; R_f=0.38 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ +18.6 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3357, 2946, 2833, 1655, 1452, 1113, 1029, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 3.39 (s, 3H), 3.64 (q, *J*=4.0, 6.5 Hz, 1H), 3.78 (dd, *J*=5.5, 10.5 Hz, 1H), 3.99 (dd, *J*=3.5, 10.5 Hz, 1H), 4.11 (t, *J*=3.5, 4.5 Hz, 1H), 4.68 (d, *J*=7.0 Hz, 1H), 4.77 (d, *J*=7.0 Hz, 1H), 4.91 (ddd, *J*=2.0, 3.5, 3.5 Hz, 1H), 5.36 (dt, *J*=1.5, 11.0 Hz, 1H), 5.45 (dt, *J*=1.5, 17.0 Hz, 1H), 6.10 (ddd, *J*=5.0, 10.5, 17.5 Hz, 1H), 7.34–7.43 (m, 3H), 7.96–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.13, −5.05, 18.43, 26.03, 56.06, 57.58, 64.59, 70.85, 74.89, 76.96, 96.36, 117.99, 127.61, 128.17, 130.68, 133.59, 133.76, 155.10; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{21}H_{33}NO_3Si$ 392.2257 found 392.2261.

*4.3.6. (4R,5R,6S)-4-((tert-Butyldimethylsilyloxy)methyl)-5-(methoxymethoxy)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3c′**).* Colorless oil; R_f=0.45 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ −1.7 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3358, 2947, 2834, 1664, 1454, 1111, 1030, 836, 780, 672, 498, 453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 3.41 (s, 3H), 3.54 (q, *J*=4.0 Hz, 1H), 3.84 (t, *J*=7.5, 8.0 Hz, 1H), 3.92 (dd, *J*=4.0, 6.0 Hz, 1H), 3.97 (dd, *J*=4.0, 6.0 Hz, 1H), 4.53 (dd, *J*=6.5, 8.0 Hz, 1H), 4.71 (d, *J*=6.5 Hz, 1H), 4.77 (d, *J*=6.5 Hz, 1H), 5.38 (dt, *J*=1.0, 10.5 Hz, 1H), 5.52 (dt, *J*=1.5, 17.0 Hz, 1H), 6.05 (ddd, *J*=6.5, 10.5, 17.0 Hz, 1H), 7.34–7.43 (m, 3H), 7.95–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.08, −4.93, 18.50, 26.06, 58.43, 60.81, 63.69, 71.71, 77.96, 97.53, 119.04, 127.70, 128.19, 130.72, 133.21, 134.75, 154.80; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{21}H_{33}NO_3Si$ 392.2257 found 392.2259.

*4.3.7. (4R,5R,6R)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3d**).* Colorless oil; R_f=0.5 (ethyl acetate/hexane=1/30); $[\alpha]_D^{25}$ +3.84 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2929, 2360, 1661, 1471, 1254, 1115, 836, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08–0.20 (m, 12H), 0.88–0.96 (m, 18H), 3.47 (dd, *J*=3.0, 5.0, 8.0 Hz, 1H), 3.83 (dd, *J*=5.0, 10.0 Hz, 1H), 4.02 (dd, *J*=3.0, 10.0 Hz, 1H), 4.21 (dd, *J*=4.0, 7.0 Hz, 1H), 4.80 (ddd, *J*=2.0, 4.0, 7.0 Hz, 1H), 5.35 (ddd, *J*=1.0, 2.0, 7.0 Hz, 1H), 5.40 (ddd, *J*=1.0, 2.0, 13.0 Hz, 1H), 6.10 (ddd, *J*=5.0, 10.5, 17.0 Hz, 1H), 7.38–7.47 (m, 3H), 8.01–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.04, −4.99, −4.51, −4.35, 18.27, 18.55, 26.00, 26.13, 26.27, 59.62, 64.13, 65.35, 75.93, 117.54, 127.62, 128.21, 130.59, 133.72, 133.79, 154.43; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{25}H_{44}NO_3Si_2$ 462.2860 found 462.2857.

*4.3.8. (4R,5R,6S)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**3d′**).* Colorless oil; R_f=0.5 (ethyl acetate/hexane=1/20); $[\alpha]_D^{25}$ −5.3 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3356, 2946, 2833, 1663, 1451, 1030, 836, 780, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 3H), 0.11 (s, 3H), 0.12 (s, 3H), 0.17 (s, 3H), 0.87 (s, 9H), 0.93 (s, 9H), 3.43 (dd, *J*=2.85, 2.85, 8.55 Hz, 1H), 3.90 (t, *J*=8.55 Hz, 1H), 3.94–4.02 (m, 2H), 4.40 (dd, *J*=6.5, 8.5 Hz, 1H), 5.38 (dt, *J*=1.5, 10.5 Hz, 1H), 5.53 (dt, *J*=1.5, 17.5 Hz, 1H), 6.03 (ddd, *J*=6.5, 10.5, 17.5 Hz, 1H), 7.33–7.42 (m, 3H), 7.97–8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.05, −4.90, −4.20, −3.40, 18.39, 18.15, 26.05, 26.20, 62.80, 63.10, 66.28, 79.39, 119.10, 127.70, 128.19, 130.60, 133.21, 135.19, 154.70; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{25}H_{44}NO_3Si_2$ 462.2860 found 462.2861.

*4.3.9. (3R,4R,5R)-5-(Benzyloxycarbonylamino)-4,6-bis(tert-butyldimethylsilyloxy)hex-1-en-3-ylbenzoate (**9**).* To a solution of oxazine **3d** (71 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of $NaHCO_3$ (52 mg, 0.62 mmol) in water (1.0 mL), and the mixture was cooled in an ice bath. To this solution was added dropwise a solution of benzyl chloroformate (0.044 mL, 0.31 mmol). The mixture was stirred at room temperature for 24 h. Then benzyl chloroformate (0.044 mL, 0.31 mmol) was added. The mixture was continued stirring (24 h) until TLC indicate that complete reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×2 mL). The combined organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo.

Purification by silica gel chromatography (ethyl acetate/hexane=1/15) gave alkene **9** (74 mg, 78%) as a colorless oil; R_f=0.67 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ +39.58 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3455, 2952, 2857, 1724, 1260, 1103, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03–0.10 (m, 12H), 0.86 (s, 9H), 0.88 (s, 9H), 3.75 (dd, *J*=4.7, 10.0 Hz, 2H), 3.92 (dd, *J*=5.4, 10.0 Hz, 1H), 4.16 (t, *J*=5.1 Hz, 1H), 5.04–5.14 (m, 2H), 5.29–5.43 (m, 2H), 5.64 (t, *J*=5.6 Hz, 1H), 6.04 (ddd, *J*=6.2, 10.7, 17.2 Hz, 1H), 7.32–7.41 (m, 7H), 7.52–7.57 (m, 1H), 8.05 (d, *J*=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.26, −5.16, −4.46, −4.13, 0.21, 18.39, 26.09, 54.92, 61.42, 66.81, 72.67, 76.57, 118.82, 128.17, 128.21, 128.67, 129.89, 130.47, 133.89, 133.27, 136.94, 156.64, 165.61; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{33}H_{52}NO_6Si_2$ 614.3333 found 614.3328.

*4.3.10. (3R,4R,5R)-4-(tert-Butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)pyrrolidin-3-ylbenzoate (**10**).* Alkene **9** (749 mg, 1.22 mmol) was dissolved in dry methanol (30 mL) and cooled to −78 °C. Ozone was passed through the solution until the reaction is complete. The reaction mixture was quenched with $(CH_3)_2S$ (0.1 mL) and allowed to warm to room temperature. The solvents were evaporated under reduced pressure. The crude aldehyde was immediately employed in the next step without further purification. A solution of aldehyde in MeOH (10 mL), to which was added 350 mg of 20% $Pd(OH)_2/C$, was vigorously shaken under 75 psi H_2 for 24 h at ambient temperature. The mixture was then filtered through a pad of silica and concentrated in vacuo. Purification by column chromatography over silica gel (ethyl acetate/hexane=1/10) gave the pyrrolidine **10** (398 mg, 70% for 2 steps); R_f=0.38 (ethyl acetate/hexanes=1/2); $[\alpha]_D^{25}$ −39.17 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2941, 2859, 1722, 1462, 1388, 1263, 1107, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04–0.14 (m, 12H), 0.93–0.96 (m, 18H), 2.14 (s, br, 1H-NH), 3.02–3.14 (m, 2H), 3.45 (dd, *J*=5.7, 13.2 Hz, 1H), 3.78 (dd, *J*=4.5, 10.0 Hz, 1H), 3.86 (dd, *J*=4.5, 10.2 Hz, 1H), 4.34–4.37 (m, 1H), 5.19–5.23 (m, 1H), 7.30–7.49 (m, 2H), 7.57–7.63 (m, 1H), 8.05–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.27, −5.22, −4.73, −4.33, 18.17, 18.53, 25.97, 26.12, 51.92, 62.14, 68.13, 78.21, 83.67, 128.58, 129.86, 130.32, 133.26, 166.27; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{24}H_{44}NO_4Si_2$ 466.2809 found 466.2805.

*4.3.11. (2R,3R,4R)-2-(Hydroxymethyl)pyrrolidine-3,4-diol:[1,4-dideoxy-1,4-imino-D-arabinitol: DAB-1] (**1**).* A solution of compound **10** (166 mg, 0.36 mmol) in MeOH (3 mL) was added 0.4 mL of solution NaOMe in methanol. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was acidified with 6 N HCl (5 mL) then continues stirring for 12 h before evaporation to remove methanol. The aqueous solution was extracted with dichloromethane. The aqueous layer was evaporated to dryness to give the **1** (51 mg, 85%). Further purification by treatment of resulting salt with ion-exchange resin afforded the known 1,4-dideoxy-1,4-imino-D-arabinitol; R_f=0.1 (chloroform/methanol=1/1); $[\alpha]_D^{25}$ +6.2 (*c* 1.0, H_2O); IR (neat) ν_{max}: 3336, 2944, 2832, 1451, 1030, 793, 671 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 2.84 (dd, *J*=3.5, 12.0 Hz, 1H), 3.07 (d, *J*=4.5 Hz, 1H), 3.11 (dd, *J*=6.0, 12.0 Hz, 1H), 3.60 (dd, *J*=7.0, 12.0 Hz, 1H), 3.68 (dd, *J*=5.0, 11.5 Hz, 1H), 3.79 (t, *J*=4.0 Hz, 1H), 4.08 (dd, *J*=3.5, 9.0 Hz, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 50.61, 61.57, 65.66, 76.96, 78.52; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_5H_{12}NO_3$ 134.0817 found 134.0819.

*4.3.12. 2-((4R,5R,6R)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazine-6-yl) ethanol (**11**).* A 0.5 M 9-BBN solution in THF (35.69 mL, 17.85 mmol) was added a THF(60.0 mL) solution of oxazine **3d** (2.75 g, 5.95 mmol). The resulting mixture was stirred at 25 °C for 20 h under a nitrogen atmosphere, and (10.88 mL) of ethanol, (3.64 mL) of 6 N aqueous solution of sodium hydroxide, and (7.22 mL) of 30% aqueous hydrogen peroxide were successively added to the above mixture. The resulting product was stirred for a further 30 min and extracted with ethyl acetate. The combined organic layer was washed with water, dried with $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane=1/10) gave alcohol **11** (2.46 g, 88%) as a colorless oil; R_f=0.22 (ethyl acetate/hexane=1/6); $[\alpha]_D^{25}$ +37.82 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2938, 2861, 2358, 1651, 1111, 1065, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05–0.23 (m, 12H), 0.88–1.02 (m, 18H), 1.78 (br, 1H, OH), 1.85–1.98 (m, 1H), 2.07–2.21 (m, 1H), 3.59–3.63 (m, 1H), 3.66–3.71 (m, 1H), 3.96–4.03 (m, 3H), 4.15 (t, *J*=3.0 Hz, 1H), 4.44–4.49 (m, 1H), 7.37–7.47 (m, 3H), 7.93–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.11, −5.08, −4.39, −4.29, 18.27, 18.49, 26.01, 26.10, 31.11, 33.70, 59.78, 60.64, 64.65, 65.49, 72.33, 127.48, 128.22, 130.57, 134.01, 155.26; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{25}H_{46}NO_4Si_2$ 480.2965 found 480.2969.

*4.3.13. (2R,3R,4R)-3-(tert-Butyldimethylsilyloxy)-2-((tert-butyldimethylsilyloxy)methyl)piperidin-4-ol (**12**).* To a solution of **11** (1.47 g, 3.12 mmol) in dichloromethane (40 mL) at 0 °C were added triethylamine (0.66 mL, 4.71 mmol), and MsCl (0.29 mL, 3.76 mmol) successively. The reaction mixture was then stirred at 0 °C for 2 h. Water was added. The aqueous layer was extracted with dichloromethane. The dichloromethane extracts were washed with saturated ammonium chloride, saturated sodium bicarbonate, and brine, dried, and evaporated. Flash column chromatography on silica gel (ethyl acetate/hexane=1/8) gave mesylate compound (1.69 g, 97%) as a colorless oil; R_f=0.2 (ethyl acetate/hexane=1/10); $[\alpha]_D^{25}$ +63.54 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2940, 2859, 1657, 1464, 1354, 1254, 1174, 1110, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.12 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.87–1.92 (m, 1H), 2.02–2.22 (m, 1H), 3.02 (s, 3H), 3.55–3.58 (m, 1H), 3.61–3.68 (m, 1H), 3.94–3.99 (m, 2H), 3.10 (t, *J*=2.85 Hz, 1H), 4.38–4.43 (m, 1H), 4.49–4.56 (m, 1H), 7.36–7.40 (m, 3H), 7.88–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.41, −4.28, 18.24, 18.50, 25.98, 26.10, 30.75, 37.65, 60.52, 64.58, 65.23, 66.49, 70.83, 127.47, 128.28, 130.72, 133.74, 154.76; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{26}H_{47}NO_6SSi_2$ 558.2741 found 558.2739. A suspension of above mesylate compound (500 mg, 0.89 mmol) in MeOH (8 mL) in the presence of 20% $Pd(OH)_2/C$ (200 mg) at room temperature was hydrogenated at atmospheric pressure overnight. The catalyst was removed by filtration through Celite pad. The filtrate was evaporated to dryness. The residue was purified by a flash column chromatography (silica gel, chloroform/methanol=9/1) to give compound **12** (269 mg, 80%) as a colorless oil, R_f=0.4 (chloroform/methanol=9/1); $[\alpha]_D^{25}$ −5.7 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3348, 2945, 2832, 1452, 1030, 836, 779, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (s, 6H), 0.13 (s, 3H), 0.14 (s, 3H), 0.93 (s, 9H), 0.94 (s, 4H), 1.52 (ddd, *J*=4.2, 8.4, 12.0 Hz, 1H), 1.84 (dt, *J*=2.4, 4.8 Hz, 1H), 1.88 (dt, *J*=2.4, 4.8 Hz, 1H), 2.56 (ddd, *J*=3.0, 6.0, 12.0 Hz, 1H), 2.67 (td, *J*=2.7, 12.6 Hz, 1H), 3.06 (ddd, *J*=2.4, 4.8, 13.2 Hz, 1H), 3.20 (t, *J*=9.0 Hz, 1H), 3.48–3.56 (m, 1H), 3.73 (dd, *J*=6.6, 9.6 Hz, 1H), 3.92 (dd, *J*=3.5, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.20, −4.37, −3.86, 18.26, 18.55, 26.04, 26.18, 35.21, 43.94, 61.29, 64.17, 74.96, 76.37; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{18}H_{41}NO_3Si_2$ 376.2703 found 376.2700.

*4.3.14. (2R,3R,4R)-2-(Hydroxymethyl)piperidine-3,4-diol [D-fagomine] (**2**).* A solution of compound **12** (100 mg, 0.27 mmol) in 6 N HCl (3 mL) was stirred at room temperature for 24 h. To the reaction mixture was added dichloromethane then aqueous solution was extracted with dichloromethane. The aqueous layer was evaporated to dryness to give the **2** (40 mg, 82%). Further purification by treatment of resulting salt with ion-exchange resin afforded the known D-fagomine; R_f=0.15 (chloroform/methanol=1/1); $[\alpha]_D^{25}$ +14.9 (*c* 0.9, H_2O); IR (neat) ν_{max}: 3357, 2946, 2833, 1451, 1030, 671 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 1.36 (ddd, *J*=4.5, 13.0, 24.5 Hz, 1H), 1.88–1.92 (m, 1H), 2.45 (ddd, *J*=3.0, 6.5, 9.5 Hz, 1H), 2.53 (td, *J*=2.5, 12.5 Hz, 1H),

2.90–2.94 (m, 1H), 3.08 (t, J=9.5 Hz, 1H), 3.45 (ddd, J=5.0, 7.8, 12.8 Hz, 1H), 3.55 (dd, J=6.5, 11.5 Hz, 1H) 3.76 (dd, J=3.0, 11.5 Hz, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 32.67, 42.73, 61.03, 61.68, 73.25, 73.30; HRMS (FAB$^+$) (M^++H) m/z calcd for $C_6H_{13}NO_3$ 148.0974 found 148.0974.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (S-2010-1110-000) and Yonsung Fine Chemicals Coperations. The Global Ph.D. Fellowship grants to S.H.P. is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.084.

References and notes

1. (a) Jones, D. W. C.; Nash, R. J.; Bell, E. A.; William, J. M. *Tetrahedron Lett.* **1985**, *26*, 3125; (b) Nash, R. J.; Bell, E. A.; Williams, J. M. *Phytochemistry* **1985**, *24*, 1620; (c) Furukawa, J.; Okuda, S.; Saito, K.; Hatatanaka, S. I. *Phytochemistry* **1985**, *24*, 593.
2. (a) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F. X.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128; (b) Behling, J. R.; Campbell, A. L.; Babiak, K. A.; Ng, J. S.; Medich, J.; Farid, P.; Fleet, G. W. J. *Tetrahedron* **1993**, *49*, 3359; (c) Asano, N.; Kizu, H.; Oseki, K.; Tomioka, E.; Matsui, K.; Okamoto, M.; Baba, M. *J. Med. Chem.* **1995**, *38*, 2349; (d) Legler, G. In *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999; p 50.
3. (a) Koyama, M.; Sakamura, S. *Agric. Biol. Chem.* **1974**, *38*, 1111; (b) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; price, D. A. *Tetrahedron* **1999**, *55*, 8931; (c) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.
4. (a) Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G. W. J. *Life Sci.* **1986**, *39*, 645; (b) Kato, A. .; Asano, N.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 312.
5. (a) Nojima, H.; Kimura, I.; Fu-Jin, C.; Sugiura, Y.; Haruno, M. .; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397; (b) Taniguchi, S.; Asano, N.; Tomino, F.; Miwa, I. *Horm. Metab. Res.* **1998**, *30*, 679.
6. For the syntheses of DAB-1(**1**), see: (a) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929; (b) Kim, I. S.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2006**, *8*, 4101; (c) Lauritsen, A.; Madsen, R. *Org. Biomol. Chem.* **2006**, *4*, 2898; (d) Ayad, T.; Génisson, Y.; Broussy, S.; Baltas, M.; Gorrichon, L. *Eur. J. Org. Chem.* **2003**, 2903; (e) Hulme, A. N.; Montgomery, C. H.; Henderson, D. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1837; (f) Kim, J. H.; Yang, M. S.; Lee, W. S.; Park, K. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2877; (g) Ahn, K. H.; Shin, Y. S. *Bull. Korean Chem. Soc.* **1997**, *18*, 1192; (h) Kim, Y. J.; Kido, M.; Bando, M.; Kitahara, T. *Tetrahedron* **1997**, *53*, 7501; (i) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61; (j) Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215; (k) Griffat-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 2889; (l) Hung, R. R.; Straub, J. A.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 3849; (m) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119; (n) von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F., III; Pederson, R. L.; Wang, Y. F.; Wong, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 3924; (o) Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 716; (p) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1986**, *42*, 5685.
7. For the syntheses of D-fagomine **2**, see: (a) Bartali, L.; Casini, A.; Guarana, A.; Occhiato, E. G.; Scarpi, D. *Eur. J. Org. Chem.* **2010**, 5831; (b) Bartali, L.; Scarpi, D.; Guarna, A.; Prandi, C.; Occhiato, E. G. *Synlett* **2009**, 913; (c) Kumari, N.; Reddy, B. G.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 160; (d) Yokoyama, H.; Ejiri, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 852; (e) Castillo, J. A.; Calveras, J.; Casas, J.; Mitjans, M.; Vinardell, M. P.; Parella, T.; Inoue, T.; Sprenger, G. A.; Joglar, J.; Clapés, P. *Org. Lett.* **2006**, *8*, 6067; (f) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603; (g) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774; (h) Désiré, J.; Dransfield, P. J.; Gore, P. M.; Shipman, M. *Synlett* **2001**, 1329; (i) Banba, Y.; Abe, C.; Nemoto, H.; Kato, A.; Adachi, I. .; Takahata, H. *Tetrahedron: Asymmetry* **2001**, *12*, 817; (j) Degiorgis, F.; Lombardo, M.; Trombini, C. *Synthesis* **1997**, 1243; (k) Fleet, G. W. J.; Smith, P. W. *Tetrahedron Lett.* **1985**, *26*, 1469.
8. Pham, V. T.; Joo, J. E.; Lee, K. Y.; Kim, T. W.; Mu, Y.; Ham, W. H. *Tetrahedron* **2010**, *66*, 2123.
9. (a) Joo, J. E.; Pham, V. T.; Tian, Y. S.; Chung, Y. S.; Lee, K. Y.; Ham, W. H. *Org. Biomol. Chem.* **2008**, *6*, 1498; (b) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Ham, W. H. *Eur. J. Org. Chem.* **2007**, 1586; (c) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Tian, Y. S.; Ham, W. H. *Org. Lett.* **2007**, *9*, 3627.
10. Compound **3d** has almost similar TLC and ^{1}H NMR patterns to a previously reported *anti*,*syn*-oxazines. Protons of the terminal olefin and ^{1}H have peaks at 6.0 and 4.2 ppm. In addition, the coupling constant of the newly generated chiral center (H_5–H_6) of compound **3d** has the similar value 4.0 Hz, compared to all *anti*,*syn*-oxazines previously reported.