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Asymmetric synthesis of triacetyl-D-*erythro*-sphingosine and D-1-deoxyallonojirimycin via Miyashita C2 selective *endo*-mode azide opening of 2,3-epoxy alcohol

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Dedicated to Dr. K. Nagarajan on the occasion of his 79th birthday

ABSTRACT

An efficient protocol for the asymmetric synthesis of triacetyl-D-*erythro*-sphingosine and D-1-deoxyallonojirimycin has been developed starting from commercially available propargyl alcohol. The key steps involved Sharpless asymmetric epoxidation and Miyashita C2 selective *endo*-mode azide opening of the 2,3-epoxy alcohol.

1. Introduction

Advances in organic synthesis, especially of chiral intermediates, have been facilitated by many novel methodologies developed over the decades. Amongst them, the combination of Sharpless asymmetric epoxidation and C2 selective *endo*-mode nucleophilic substitution reaction of 2,3-epoxy alcohol developed by Miyashita et al. [1] have acquired significance for the production of key intermediates in natural product synthesis.[2] This type of reaction proceeds via an intramolecular boron chelate through a novel *endo*-mode epoxide opening with extremely high C2 selectivity.[1] We have utilised this approach for the asymmetric synthesis of two biologically important compounds triacetyl-D-*erythro*-sphingosine and D-1-deoxyallonojirimycin and describe herein their significance.

Sphingolipids are long chain amino alcohols, which are found in the plasma membranes of eukaryotic cells. They play important role in many physiological processes, such as immune response, cell recognition, adhesion, apoptosis[3] and are implicated in a variety of diseases, such as cancer, Alzheimer's disease and an array of neurological syndromes.[4]

Although a number of structurally related sphingoid base structures are known, the most frequently encountered sphingoid base in nature is D-*erythro*-(2*S*,3*R*)-sphingosine **1**. D-*erythro*-sphingosine **1** and its derivatives (Fig. 1) are shown to be promising enzyme inhibitors.[5] This has led to growing interest in developing efficient methods for their synthesis.[6] Many of these syntheses start from various chiral pools, such as amino acids[7] and carbohydrates.[8] Thus, recent interest has increasingly focused on the enantioselective synthesis of D-*erythro*-sphingosine and its derivative from achiral sources.[9]

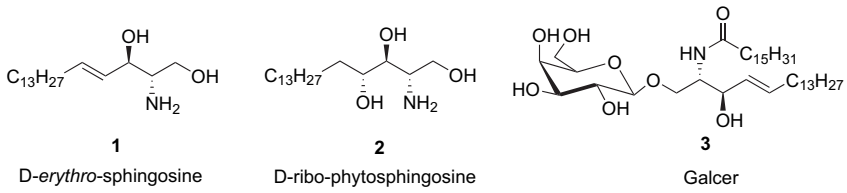

Figure 1.

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Another important class of biologically important compounds are alkaloid sugar mimics with nitrogen in the ring (commonly known as iminosugars, azasugars, or polyhydroxy piperidines),[10] which have become important tools in glycobiology due to their role as glycosidase inhibitors.[11] Glycosidase inhibitors have received great deal of attention because of their therapeutic potential in the treatment of cancer, viral infections including HIV, diabetes and other metabolic disorders.[12] Amongst various polyhydroxy piperidines, deoxynojirimycin (DNJ **4**) and its analogues (Fig. 2) have acquired significance due to their potential as drugs for treating a variety of carbohydrate mediated diseases.[13] Traditionally enantiopure azasugars were synthesised from the readily available chiral starting materials like carbohydrates, or aminoacid derivatives.[14] Amongst these azasugars, D-1-deoxyallonojirimycin **7** has become important due to its significant biological activity.[15] As a result much synthetic efforts have been directed towards the stereoselective synthesis D-1-deoxyallonojirimycin **7**.[16,26]

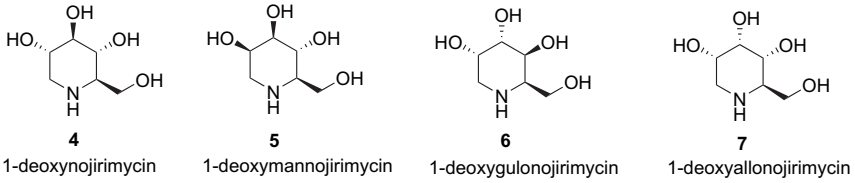


Figure 2.

We herein, disclose a simple and convenient approach for the asymmetric synthesis of triacetyl-D-*erythro*-sphingosine **19** and D-1-deoxyallonojirimycin **7** starting from the commercially available propargyl alcohol **8**.

2. Results and discussion

2.1. Synthesis of triacetyl-D-*erythro*-sphingosine (19)

The retrosynthetic analysis of **19** revealed an intermediate **17**, which can be synthesised conveniently from 2,3-epoxy alcohol **12** and cross-metathesis reaction could be utilised for establishing the *E*-double bond of the sphingosine backbone (Fig. 3).

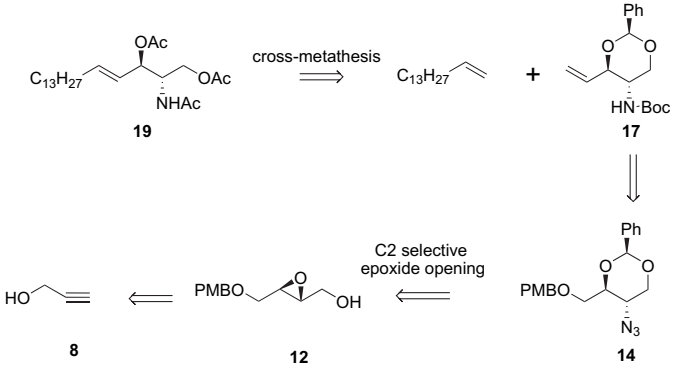


Figure 3. Retrosynthetic analysis of triacetyl-D-*erythro*-sphingosine **19**.

The propargyl alcohol **8** was protected as its PMB ether **9** using PMB-Br and NaH in THF with 93% yield. Homologation[17] of **9** was achieved using *n*-BuLi and formaldehyde resulting in **10** (93%), which was followed by stereoselective reduction of triple bond with $LiAlH_4$ in THF to give the desired *trans*-allylic alcohol **11** in 94% yield. The *E*-allylic alcohol **11** was subjected to Sharpless asymmetric epoxidation[18] by using D(−)-diethyl tartrate, $Ti(O^iPr)_4$ and TBHP to afford epoxyalcohol **12** in 79% yield.

The highly efficient C2 selective azide substitution reaction of **12** was accomplished by using NaN_3-$(CH_3O)_3B$ system developed by Miyashita et al.[1] This reaction proceeds via an intramolecular boron chelate through a novel *endo*-mode epoxide opening with extremely high C2 selectivity (Scheme 2). Under these conditions, the desired azido diol was produced in good yield and high diastereoselectively (C2/C3 opening, 14:1). The minor 1,2-diol that resulted from C3 opening was removed by treating the mixture with sodium periodate to give pure 2-azide-1,3-diol **13** in 83% yield.

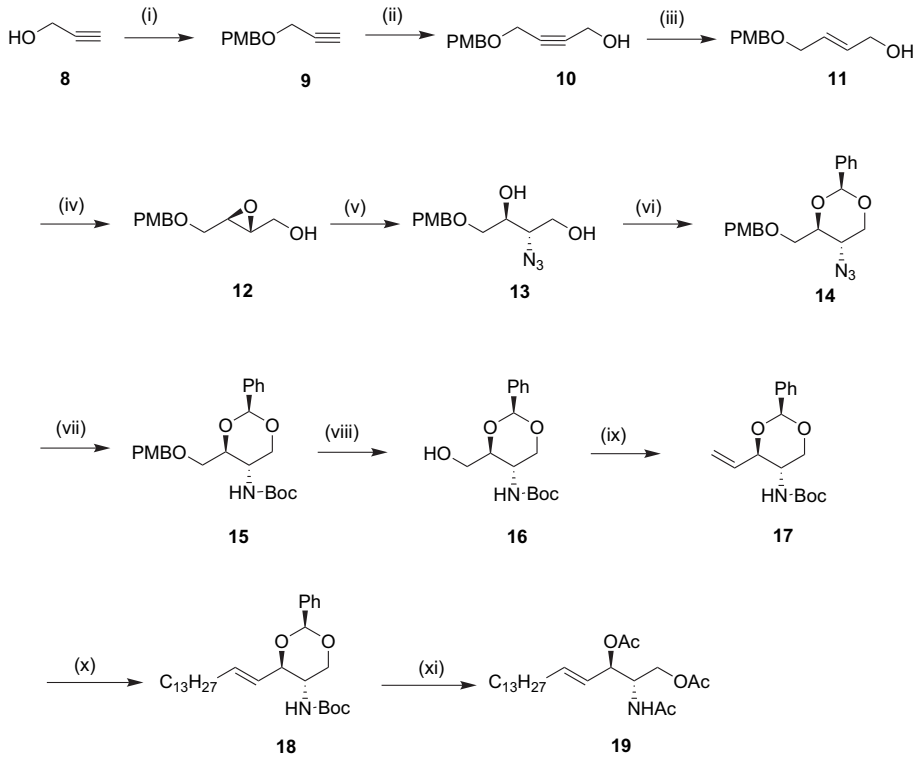
The resulting 1,3-diol **13** was protected as benzylidene acetal using benzaldehyde dimethyl acetal[19] in the presence of catalytic amount of PPTS in benzene to give the desired acetal **14** in good yield (92%). Reduction of azide with Lindlar catalyst[19] in methanol worked efficiently to give the amine, which was taken for the next step without purification. It was protected with $(Boc)_2O$ in the presence of β-cyclodextrin[20] in water to give **15** in good yield. Deprotection of PMB group using DDQ in DCM/pH 7 buffer gave alcohol **16** (92%), which upon oxidation under Swern conditions yielded the aldehyde. The resulting crude aldehyde was subjected to Wittig methylenation reaction using Ph_3PCH_3Br and ^tBuOK in THF at 0 °C to produce the desired olefin **17** in 85% yield.

With the key intermediate in hand, we proceeded with the olefin cross metathesis using 1-pentadecene in the presence of 10 mol % of Grubbs II generation catalyst, which provided the cross-coupled product **18** with complete *E*-stereo selectivity in 94%, yield.[9a] Finally, deprotection of **18** with 6 N HCl in MeOH, followed by reaction with Ac_2O in pyridine gave desired product **19** in 92% yield. The spectroscopic and analytical data of triacetyl-D-*erythro*-sphingosine **19** were in good agreement with the literature values.[21]

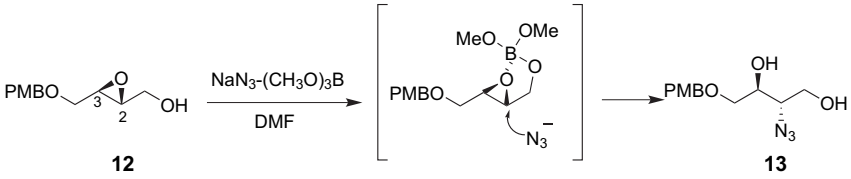
2.2. Synthesis of D-1-deoxyallonojirimycin (7)

After successful synthesis of **19**, we exploited the synthesis of D-1-deoxyallonojirimycin **7** from the same starting material **8** (Scheme 3). The (−)-enantiomer of **12** was prepared by using Sharpless asymmetric epoxidation of **11** by using L(+)-diethyl tartrate, $Ti(O^iPr)_4$ and TBHP. The same sequence of reactions (of Scheme 1) was carried out for the synthesis of (−)-enantiomer of **15** from **12**. Allylation of **15** with allyl bromide using NaH and catalytic amount of crown ether resulted in **20** (94%). Deprotection of PMB group using DDQ in DCM/pH 7 buffer gave alcohol **21** (95%), which upon oxidation under Swern conditions yielded aldehyde. The resulting crude aldehyde was subjected to olefination under modified Horner–Wadsworth–Emmons olefination[22] using triethylphosphono acetate and DBU in the presence of Lithium bromide to produce the desired α,β-unsaturated ester **22** in 94% yield.

The useful piperidine intermediate **23** was accomplished by ring-closing metathesis[23] using Grubbs I generation catalyst (10 mol %) at 90 °C in good yield (92%). The subsequent diol **24** was obtained as a single diastereomer in high yield (86%) by the



Scheme 1. Synthesis of triacetyl-D-erythro-sphingosine **19**. Reagents, conditions and yields: (i) PMBBr, NaH, THF, 0 °C-rt, 12 h, 93%; (ii) *n*-BuLi, $(CH_2O)_n$, THF, −78 °C-rt, 16 h, 93%; (iii) $LiAlH_4$, THF, 0 °C-rt, 12 h, 94%; (iv) D(−)-DET, $Ti(O^iPr)_4$, TBHP, 4 Å MS, DCM, −20 °C, 3 h, 79%; (v) $(MeO)_3B$, NaN_3, DMF, 50 °C, 3 h, 83%; (vi) $PhCH(OMe)_2$, PPTS, Benzene, reflux, 15 h, 92%; (vii) (a) H_2, Lindlar cat, MeOH, rt, 6 h; (b) $(Boc)_2O$, β-CD/H_2O, rt, 20 min, 90% for two steps; (viii) DDQ, DCM/pH 7 buffer (5:1), rt, 2 h, 92%; (ix) (a) oxalyl chloride, DMSO, TEA, DCM, −78 °C, 1 h; (b) Ph_3PCH_3Br, ^{t}BuOK, THF, 0 °C, 1 h, 85%; (x) 1-pentadecene, Grubbs II generation catalyst (10 mol %), CH_2Cl_2, reflux, overnight, 94%; (xi) 6 N HCl, MeOH, rt, overnight; then Ac_2O, pyridine, 92% for two steps.



Scheme 2. C2 selective azide substitution reaction.

stereoselective dihydroxylation of the double bond[24] of piperidine **23** using cat. OsO_4 and 4-methyl morpholine N-oxide at 0 °C. The formation of single diastereomer **24** can be explained by the approach of OsO_4 from the less hindered α-face of the olefin due to steric hindrance on the β-face by the bulky N-Boc group.[25] The structure of **24** was also further confirmed by conversion to D-1-deoxyallonojirimycin **7** of known stereochemical configuration. Deprotection of **24** with 6 N HCl in MeOH, followed by treatment with ion-exchange resin DOWEX 50Wx8 yielded **7** in 89%. The spectroscopic and analytical data of D-1-deoxyallonojirimycin **7** were in good agreement with the literature values.[14c]

3. Conclusion

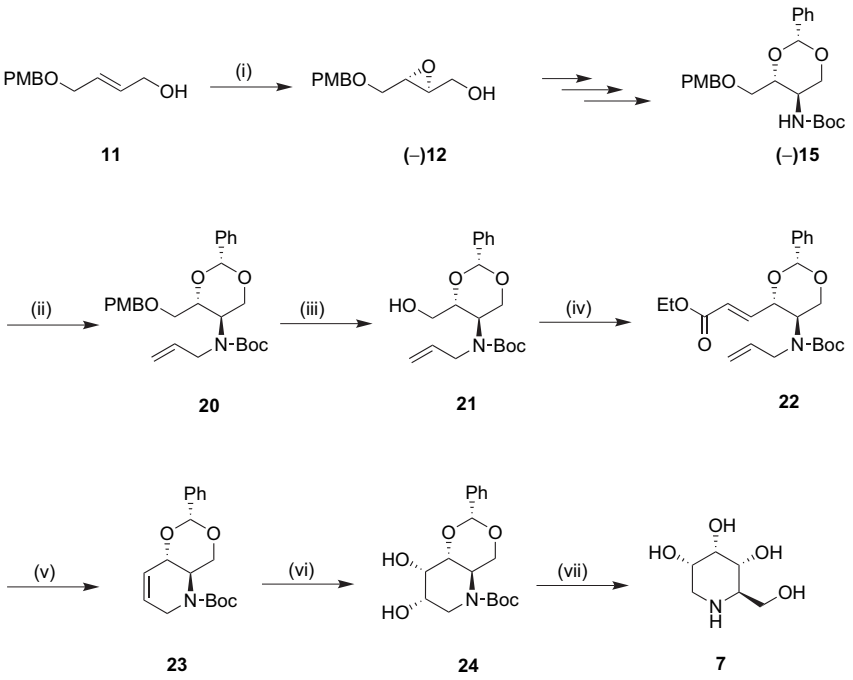
In summary, we have demonstrated a simple and highly efficient asymmetric synthesis for triacetyl-D-*erythro*-sphingosine and D-1-deoxyallonojirimycin. The stereogenic centres in the polar head group of triacetyl-D-*erythro*-sphingosine were installed by using Sharpless asymmetric epoxidation, *endo*-mode C2 selective azide substitution of 2,3-epoxy alcohol followed by cross-metathesis reaction to establish the *E*-double bond of the sphingosine backbone, whereas the asymmetric synthesis of D-1-deoxyallonojirimycin was obtained utilising Sharpless epoxidation, *endo*-mode C2 selective azide substitution of epoxide, Horner–Wadsworth–Emmons olefination, RCM with Grubbs catalyst and diastereoselective dihydroxylation as the key steps.

4. Experimental

4.1. General

Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Jasco Dip 360 digital polarimeter. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 mesh). Mass spectra were obtained on Finnigan MAT1020B or micromass VG 70–70H spectrometer operating at 70 eV using a direct inlet system. All high resolution spectra were recorded on QSTAR XL hybrid MS/MS system equipped with an ESI source (IICT, Hyderabad).

*4.1.1. 1-Methoxy-4-((prop-2-ynyloxy)methyl)benzene (**9**)*[26]. A round-bottom flask was charged with 60% dispersion of sodium hydride in mineral oil (1.66 g, 42.8 mmol) under nitrogen, the oil was removed by washing with hexane (20 mL), THF (50 mL) was then added and



Scheme 3. Synthesis of D-allo-DNJ **7**. Reagents, conditions and yields: (i) L(+)-DET, $Ti(O^iPr)_4$, TBHP, 4 Å MS, DCM, –20 °C, 3 h, 80%; (ii) NaH, allyl bromide, 18-crown-6-ether, THF, 0 °C-rt, 3 h, 94%; (iii) DDQ, DCM/pH 7 buffer (5:1), rt, 2 h, 95%; (iv) (a) oxalyl chloride, DMSO, TEA, DCM, −78 °C, 1 h; (b) LiBr, triethylphosphonoacetate, DBU, THF, rt, 1 h, 94% for two steps; (v) Grubbs I generation catalyst, Toluene, 90 °C, 2 h, 92%; (vi) 4% OsO_4, NMO, acetone:water, 0 °C, overnight, 86%; (vii) 6 N HCl, MeOH, rt, overnight; DOWEX 50wX8, 89%.

the resulting cloudy white suspension was cooled to 0 °C. A solution of propargyl alcohol **8** (2 g, 35.7 mmol) in THF (20 mL) was added via syringe, followed by *p*-methoxybenzyl bromide (8.6 g, 42.8 mmol). The reaction mixture was stirred at room temperature for 12 h. It was then carefully quenched with saturated aqueous NH_4Cl (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of crude compound by flash chromatography (10% EtOAc/hexane) afforded PMB ether **9** (5.8 g, 93%) as yellow liquid; R_f (5% EtOAc/hexane) 0.42; IR (neat): λ_{max} 3288, 3002, 2940, 1248, 1078 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.24 (2H, d, J=8.1 Hz, Ar-*H*), 6.84 (2H, d, J=8.1 Hz, Ar-*H*), 4.52 (2H, s, benzylic C*H*$_2$), 4.10 (2H, d, J=2.2 Hz, C*H*$_2$OPMB), 3.79 (3H, s, OC*H*$_3$), 2.4 (1H, t, J=2.2 Hz, triple bond C*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.2, 129.6, 129.1, 113.7, 79.6, 74.4, 70.9, 56.5, 55.1; MS (ESIMS): *m*/*z* 177 $[M+H]^+$; HRMS (ESI): $[MH]^+$, found 177.0822. $C_{11}H_{13}O_2$ requires 177.0837.

*4.1.2. 4-(4-Methoxybenzyloxy)but-2-yn-1-ol (**10**)*[26]. To a solution of alkyne **9** (4 g, 22.7 mmol) in THF (100 mL) was added at −78 °C a 1.6 M solution of *n*-BuLi in hexane (14.2 mL, 22.7 mmol) dropwise over 10 min under nitrogen atmosphere. The reaction mixture was stirred at −78 °C for 40 min, then dry paraformaldehyde (0.98 g, 34 mmol) was added, and the mixture was allowed to warm up to room temperature and stirred for 16 h. Saturated aqueous NH_4Cl solution (25 mL) was carefully added, the layers were separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (30% EtOAc/hexane) to afford **10** (4.36 g, 93%) as yellow liquid; R_f (15% EtOAc/hexane) 0.44; IR (neat): λ_{max} 3413, 2935, 2860, 1611, 1513, 1248, 1028 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.22 (2H, d, J=8.6 Hz, Ar-*H*), 6.81 (2H, d, J=8.4 Hz, Ar-*H*), 4.48 (2H, s, benzylic C*H*$_2$), 4.24 (2H, s, C*H*$_2$OPMB), 4.12 (2H, s, C*H*$_2$OH), 3.77 (3H, s, OC*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 129.5, 129.1, 128.3, 113.6, 84.8, 81.1, 71.1, 56.8, 55.0, 50.4; MS (ESIMS): *m*/*z* 229 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 229.0937. $C_{12}H_{14}O3Na$ requires 229.0946.

*4.1.3. (E)-4-(4-Methoxybenzyloxy)but-2-en-1-ol (**11**)*[26]. In a clean and dry round-bottom flask $LiAlH_4$ (1.29 g, 33.9 mmol) and dry THF (25 mL) were taken under nitrogen atmosphere and cooled to 0 °C. To this a solution, alcohol **10** (3.5 g, 16.9 mmol) dissolved in THF (30 mL) was added via syringe. The reaction mixture was stirred for 12 h at room temperature. It was cooled to 0 °C, then carefully quenched with saturated aq Na_2SO_4 (10 mL) and stirred for 3 h. Then it was filtered through Celite and washed with ethyl acetate (20 mL×2). The combined organic layers were washed with water (25 mL), brine (20 mL), dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue obtained was purified by column chromatography (30% EtOAc/hexane) to give the allylic alcohol **11** (3.3 g, 94%) as yellowish oily liquid; R_f (25% EtOAc/hexane) 0.45; IR (neat): λ_{max} 3400, 2932, 2855, 1611, 1513, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (2H, d, J=8.3 Hz, Ar-*H*), 6.82 (2H, d, J=9.0 Hz, Ar-*H*), 5.72–5.92 (2H, m, C*H*=C*H*), 4.42 (2H, s, benzylic C*H*$_2$), 4.12 (2H, d, J=3.7 Hz, C*H*$_2$OPMB), 3.96 (2H, d, J=4.5 Hz, C*H*$_2$OH), 3.79 (3H, s, OCH$_3$), 1.49 (1H, s, O*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 132.2, 130.1, 129.3, 127.7, 113.7, 71.8, 69.7, 62.8, 55.2; MS (ESIMS): *m*/*z* 226 $[M+NH_4]^+$; HRMS (ESI): $[M+H]^+$, found 209.1137. $C_{13}H_{16}O_3$ requires 209.1146.

*4.1.4. ((2R,3R)-3-((4-Methoxybenzyloxy)methyl)oxiran-2-yl)methanol (**12**).* To a cooled (–20 °C) suspension of activated, powdered 4 Å MS (7.5 g) in CH_2Cl_2 (100 mL) under nitrogen were added D (−)-DET (0.68 g, 3.3 mmol), $Ti(O^iPr)_4$ (0.87 g, 3 mmol), and TBHP (4 M in toluene, 3.3 mL, 13.2 mmol). After 20 min, a solution of alcohol **11** (2.3 g, 11 mmol) in CH_2Cl_2 (90 mL) was added at −20 °C over a period of 20 min. The resulting mixture was stirred at that temperature for 3 h, quenched with a cooled solution of ferrous sulfate and tartaric acid (stoichiometric amount) in distilled water, stirred vigorously for 30 min, and extracted with ether (50 mL×3). The combined organic layers were treated with a pre-cooled (0 °C)

solution of 30% NaOH (w/v) in brine and stirred for 1 h at room temperature. The two layers were separated and the aqueous layer was extracted with ether (30 mL×3). The combined ether layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed (40% EtOAc/hexane) to give epoxide **12** (1.95 g, 79%) as white solid; R_f (25% EtOAc/hexane) 0.56; Mp 84 °C; $[\alpha]_D^{25}$ +14.0 (*c* 1, $CHCl_3$); {$[\alpha]_D^{25}$ of compound (−)**12**=−13.9 (*c* 1, $CHCl_3$)}; IR (KBr): λ_{max} 3445, 3015, 2928, 1612, 1513, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (2H, d, *J*=8.3 Hz, Ar-*H*), 6.82 (2H, d, *J*=9.1 Hz, Ar-*H*), 4.47 (2H, dd, *J*=11.3, 7.5 Hz, benzylic CH_2), 3.85–3.92 (1H, m, CH_aH$_b$OPMB), 3.79 (3H, s, OCH_3), 3.56–3.68 (2H, m, CH$_a$$H_b$OPMB and C$H_aH_b$OH), 3.46 (1H, dd, *J*=5.3, 11.3 Hz, CH$_a$$H_b$OH), 3.13–3.17 (1H, m, epoxide), 2.99–3.03 (1H, m, epoxide), 1.81 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.9, 129.5, 129.1, 113.4, 72.5, 69.1, 61.04, 55.6, 54.9, 54.1; MS (ESIMS): *m*/*z* 247 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 247.0937. $C_{12}H_{16}O_4Na$ requires 247.0946.

*4.1.5. (2S,3S)-4-(4-Methoxybenzyloxy)-2-azidobutane-1,3-diol (**13**).* A mixture of epoxy alcohol **12** (1.6 g, 7.1 mmol), $(MeO)_3B$ (1.6 mL, 14 mmol), and NaN_3 (0.91 g, 14 mmol) in DMF (20 mL) was stirred at 50 °C for 3 h. After cooling to 0 °C, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the mixture was stirred for 30 min and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layer was successively washed with water (10 mL), saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get yellow oil. The residue was dissolved in MeOH (5 mL) and treated with a solution of NaIO4 (0.45 g, 2.1 mmol) in water (15 mL). The solution was stirred at room temperature for 20 min and then extracted with EtOAc (3×30 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (40% EtOAc/hexane) to give azide **13** (1.58 g, 83%) as a pale yellow oil; R_f (30% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ +18.1 (*c* 1, $CHCl_3$); {$[\alpha]_D^{25}$ of compound (−)**13**=−17.9 (*c* 1, $CHCl_3$)}; IR (neat): λ_{max} 3415, 2932, 2101, 1513, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (2H, d, *J*=8.0 Hz, Ar-*H*), 6.85 (2H, d, *J*=8.7 Hz, Ar-*H*), 4.47 (2H, s, benzylic CH_2), 3.81–3.87 (1H, m, CH_aH$_b$OPMB), 3.79 (3H, s, OCH_3), 3.77–3.78 (2H, m, CH$_a$$H_b$OPMB and C*H*OH), 3.45–3.61 (3H, m, CH_2OH and C*H*N$_3$), 2.92 (1H, br s, O*H*), 2.57 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.9, 129.1, 113.4, 72.6, 70.4, 69.6, 63.7, 61.73, 54.7; MS (ESIMS): *m*/*z* 290 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 290.1110. $C_{12}H_{17}N_3O_4Na$ requires 290.1116.

*4.1.6. (2S,4S,5S)-4-((4-Methoxybenzyloxy)methyl)-5-azido-2-phenyl-1,3-dioxane (**14**).* Benzaldehyde dimethyl acetal (0.51 g, 33 mmol) was added in one portion to a solution of diol **13** (0.9 g, 33 mmol) and PPTS (0.053 g, 0.21 mmol) in benzene (30 mL) at room temperature. The solution was heated at reflux for 15 h, cooled to room temperature and treated with a saturated aqueous solution of $NaHCO_3$ (10 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo to give yellow oil. The crude material was purified by column chromatography (10% EtOAc/hexane) to give azide **14** (1.1 g, 92%) as colourless oil; R_f (5% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ +17.5 (*c* 1, $CHCl_3$); {$[\alpha]_D^{25}$ of compound (−)**14**=−17.4 (*c* 1, $CHCl_3$)}; IR (neat): λ_{max} 2862, 2108, 1612, 1513, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.46 (2H, m, Ar-*H*), 7.31–7.37 (3H, m, Ar-*H*), 7.24 (2H, d, *J*=8.7 Hz, Ar-*H*), 6.83 (2H, d, *J*=8.7 Hz, Ar-*H*), 5.41 (1H, s, PhC*H*(O)$_2$), 4.54 (2H, dd, *J*=10.9, 19.0 Hz, benzylic CH_2), 4.36 (1H, dd, *J*=5.1, 10.9 Hz, C*H*CH$_2$OPMB), 3.66–3.68 (7H, m, CH_2OPMB, OCH_3 and CH_2CHN$_3$), 3.60 (1H, m, C*H*N$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.1, 137.1, 129.7, 129.1, 128.8, 128.0, 125.9, 113.5, 101.1, 79.6, 72.9, 68.9, 68.6, 54.9, 53.2; MS (ESIMS): *m*/*z* 378 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 378.1424. $C_{19}H_{21}N_3O_4Na$ requires 378.1429.

*4.1.7. tert-Butyl (2S,4S,5S)-4-((4-methoxybenzyloxy)methyl)-2-phenyl-1,3-dioxan-5-yl carbamate (**15**).* A solution of azide **14** (700 mg, 1.97 mmol) and Lindlar catalyst (70 mg, 10% by weight) in MeOH (25 mL) was stirred under H_2 atmosphere at room temperature for 6 h. The solution was filtered through Celite and concentrated in vacuo to give pale yellow oil. The crude amine was used for the further step without purification.

To a solution of β-cyclodextrin (220 mg, 0.19 mmol) in distilled water (5 mL) at room temperature was added crude amine in acetone (1 mL), then $(Boc)_2O$ (0.42 mL, 1.97 mmol) was added to the reaction mixture and stirring was continued for 20 min. The product was then extracted with ethyl acetate (2×25 mL) and washed with brine solution (10 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product thus obtained was purified by column chromatography (10% EtOAc/hexane) to afford compound **15** (760 mg, 90%) as a white solid. The aqueous layer was cooled to 5 °C to recover precipitated β-cyclodextrin by filtration (95%); R_f (5% EtOAc/hexane) 0.41; $[\alpha]_D^{25}$ +19.4 (*c* 1, $CHCl_3$); {$[\alpha]_D^{25}$ of compound (−) **15**=−19.1 (*c* 1, $CHCl_3$)}; mp 120 °C; IR (KBr): λ_{max} 3345, 2977, 2926, 1680, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.51 (2H, m, Ar-*H*), 7.32–7.39 (3H, m, Ar-*H*), 7.27 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.86 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.48 (1H, s, PhC*H*(O)$_2$), 4.46–4.57 (2H, m, benzylic CH_2), 4.38 (1H, dd, *J*=4.3, 6.2 Hz, C*H*CH$_2$OPMB), 3.8 (3H, s, OCH_3), 3.51–3.76 (5H, m, CH_2OPMB, CH_2CHNH and C*H*NHBoc), 1.43 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.1, 155.1, 137.5, 129.9, 129.4, 128.9, 128.1, 126.1, 113.7, 101.1, 80.1, 73.2, 70.5, 69.7, 68.9, 67.8, 55.2, 28.2; MS (ESIMS): *m*/*z* 452 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 452.2040. $C_{24}H_{31}NO_6Na$ requires 452.2049.

*4.1.8. tert-Butyl (2S,4S,5S)-4-(hydroxymethyl)-2-phenyl-1,3-dioxan-5-ylcarbamate (**16**).* To a solution of **15** (400 mg, 0.93 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added aqueous NaH_2PO_4/Na_2HPO_4 (pH 7) buffer (4 mL) and DDQ (250 mg, 1.1 mmol). The reaction was allowed to warm to room temperature. After 2 h the reaction mixture was filtered through a Celite pad, and layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting 15% EtOAc/hexane to afford alcohol **16** (265 mg, 92%) as a white solid; R_f (10% EtOAc/hexane) 0.45; mp 143 °C; $[\alpha]_D^{25}$ +8.43 (*c* 1, $CHCl_3$); IR (KBr): λ_{max} 3369, 3221, 3060, 2923, 1676, 1566 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.47 (2H, m, Ar-*H*), 7.29–7.35 (3H, m, Ar-*H*), 5.42 (1H, s, PhC*H*(O)$_2$), 4.25–4.41 (2H, m, C*H*CH$_2$OH and CH_aH$_b$CHNH), 3.70–3.94 (3H, m, CH$_a$$H_b$CHNH and C$H_2$OH), 3.51–3.57 (2H, m, C*H*NHBoc and N*H*), 1.45 (9H, s, C(CH_3)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.8, 137.3, 129.1, 128.1, 126.1, 101.2, 81.7, 80.5, 68.9, 62.4, 43.4, 28.1; MS (ESIMS): *m*/*z* 332 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 332.1472. $C_{16}H_{23}NO_5$ Na requires 332.1473.

*4.1.9. tert-Butyl (2S,4R,5S)-2-phenyl-4-vinyl-1,3-dioxan-5-ylcarbamate (**17**).* To a solution of oxalyl chloride (0.114 mL, 1.29 mmol) in dry DCM (15 mL) at −78 °C, DMSO (0.136 mL, 1.92 mmol) was added dropwise with stirring under nitrogen. After stirring for 15 min, alcohol **16** (200 mg, 0.64 mmol) in dry CH_2Cl_2 (10 mL) was added to the reaction mixture. After 1 h stirring at −78 °C, Et_3N (0.53 mL, 3.84 mmol) was added and stirred for another 0.5 h at −78 °C and 0.5 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (2×50 mL), brine (25 mL), dried on Na_2SO_4 and concentrated in vacuo. The crude compound was used in the next step without purification.

To methyltriphenylphosphonium iodide (2.58 g, 6.4 mmol) in dry THF (50 mL) under a nitrogen atmosphere at −78 °C was added

t-BuOK (0.53 g, 7.3 mmol) and stirred for 30 min at room temperature. Then the orange yellow ylide solution was added to the above crude aldehyde in dry THF (5 mL) via a cannula and stirring was continued for 1 h, allowing the temperature to warm to 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL). The mixture was filtered over a sintered funnel and the residue was washed with ether (3×15 mL). The combined organic filtrates were evaporated after washing with water (25 mL), drying over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (8% EtOAc in petroleum ether eluent) afforded **17** (167 mg, 85%) as a light yellow solid; R_f (5% EtOAc/hexane) 0.55; $[\alpha]_D^{25}$ +28.1 (*c* 1, $CHCl_3$); mp 92 °C; IR (KBr): λ_{max} 3353, 2977, 2928, 2858, 1685, 1529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.49 (2H, m, Ar-*H*), 7.29–7.36 (3H, m, Ar-*H*), 5.86–5.99 (1H, m, CH_2=C*H*), 5.46 (1H, s, PhC*H*$(O)_2$), 5.4 (1H, d, *J*=17.3 Hz, C$H_a$$H_b$=CH), 5.28 (1H, d, *J*=10.1 Hz, $CH_a$$H_b$=CH), 4.21–4.38 (2H, m, C=CHC*H* and C$H_a$$H_b$CHNH), 3.93–4.04 (1H, m, $CH_a$$H_b$CHNH), 3.48–3.72 (2H, m, C*H*NHBoc and N*H*), 1.43 (9H, s, C(CH_3)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.9, 137.4, 134.1, 128.9, 128.2, 126.1, 118.9, 100.1, 82.1, 69.9, 60.3, 43.1, 28.3; MS (ESIMS): *m*/*z* 328 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 328.1531. $C_{17}H_{23}NO_4Na$ requires 328.1524.

*4.1.10. tert-Butyl (2S,4R,5S)-4-((E)-pentadec-1-enyl)-2-phenyl-1,3-dioxan-5-yl carbamate (**18**).* Compound **17** (0.580 mg, 0.26 mmol) and 1-pentadecene (220 mg, 1.04 mmol) were dissolved in CH_2Cl_2 (25 mL) at room temperature. Grubbs II generation catalyst (10 mol %) was added to the solution and then the reaction mixture was refluxed under nitrogen for 14 h. After cooling the reaction mixture it was concentrated and purified by column chromatography with hexane:ethyl acetate (4:1) to afford compound **18** (120 mg, 94%) as a white solid; R_f (5% EtOAc/hexane) 0.45; $[\alpha]_D^{25}$ +10.7 (*c* 1, $CHCl_3$); mp 88 °C; IR (KBr): λ_{max} 3354, 2923, 2853, 1686, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.53 (2H, m, Ar-*H*), 7.31–7.41 (3H, m, Ar-*H*), 5.78–5.91 (1H, m, C*H*=CH), 5.47–5.61 (2H, m, PhC*H*$(O)_2$ and CH=C*H*), 4.19–4.35 (2H, m, OC*H*CH and C$H_a$$H_b$CHNH), 3.91–4.02 (1H, m, $CH_a$$H_b$CHNH), 3.49–3.79 (2H, m, C*H*NHBoc and N*H*), 1.98–2.13 (2H, m, CH_2CH=CH), 1.16–1.66 (31H, m, C(CH_3)$_3$ and CH_3(CH_2)$_{11}$), 0.87 (3H, t, *J*=6.7 Hz, CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.9, 137.6, 136.9, 128.9, 128.2, 126.2, 101.1, 82.3, 69.9, 60.3, 47.7, 32.3, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 28.8, 28.2, 22.6, 14.1; MS (ESIMS): *m*/*z* 510 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 510.3540. $C_{30}H_{49}NO_4Na$ requires 510.3559.

*4.1.11. (2S,3R,4E)-1,3-Diacetoxy-2-acetamido-octadec-4-ene [N,O,O-triacetyl sphingosine] (**19**).* To a solution of **18** (80 mg, 0.16 mmol) in MeOH (6 mL) was added 6 N HCl. The reaction mixture was stirred at room temperature for overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in pyridine (10 mL) and Ac_2O (0.1 mL excess) and DMAP (2 mg) were added sequentially. The reaction mixture was stirred for 10 h and quenched with H_2O (3 mL). The reaction mixture diluted with H_2O (8 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2×10 mL), and the combined organic layers were washed sequentially with satd aq $CuSO_4$ (2×5 mL), H_2O (10 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting with 15% EtOAc/hexane to afford **19** (64 mg, 92%) as a white solid;R_f (10% EtOAc/hexane) 0.45; $[\alpha]_D^{25}$ −12.1 (*c*1, $CHCl_3$); [lit.[21b] $[\alpha]^{24}_D$ −13.0 (*c*1.6 $CHCl_3$)]; mp 99–101 °C; IR (KBr):λ_{max} 3288, 2919, 2850, 1734, 1653, 1548, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ5.79 (1H, dd,*J*=15.3, 6.6 Hz, C(5)*H*), 5.65 (1H, d, *J*=8.8 Hz, N*H*), 5.39 (1H, dd, *J*=15.3, 7.9 Hz, C(4)*H*), 5.25–5.29 (1H, m, C(3)*H*), 4.39–4.47 (1H, m, C(2)*H*), 4.30 (1H, dd, *J*=11.7, 5.9 Hz, C(1)H_b), 4.04 (1H, dd, *J*=11.7, 4.4 Hz, C(1)*Ha*), 1.95–2.13 (11H, m, 3X COCH_3, C(6)H_2), 1.17–1.41 (22H, m, C(7)-C(17)H_2), 0.88 (3H, t, *J*=6.6 Hz, C(18)H_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.0, 170.0, 169.6, 137.5, 124.1, 73.8, 62.5, 60.4, 50.6, 32.2, 31.9, 29.7, 29.6, 29.4, 29.3, 29.1, 28.9, 23.3, 22.6, 21.1, 20.7, 14.1; MS (ESIMS): *m*/*z* 448 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 448.3032. $C_{24}H_{43}NO_5Na$ requires 448.3038.

*4.1.12. tert-Butyl (2R,4R,5S)-4-((4-methoxybenzyloxy)methyl)-2-phenyl-1,3-dioxan-5-ylallyl carbamate (**20**).* A round-bottom flask was charged with a 60% dispersion of sodium hydride in mineral oil (0.049 g, 1.2 mmol) and THF (10 mL) under nitrogen atmosphere and the resulting cloudy white suspension was cooled to 0 °C. A solution of carbamate (-) **15** (0.44 g, 1 mmol) in THF (10 mL) was added via syringe, followed by allyl bromide(0.1 mL, 1.2 mmol), 18-crown-6-ether (0.05 g, 0.2 mmol) and the resulting mixture was stirred at room temperature for 3 h. The mixture was quenched with saturated NH_4Cl (5 mL) and the whole mixture was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (7% EtOAc/hexane) to give **20** (0.45 g, 94%) as yellow oil; R_f (5% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ −33.5 (*c* 1, $CHCl_3$); IR (neat): λ_{max} 2973, 2931, 1693, 1612, 1152 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.44 (2H, d, *J*=6.5 Hz, Ar-*H*), 7.28–7.33 (3H, m, Ar-*H*), 7.21 (2H, d, *J*=8.0 Hz, Ar-*H*), 6.81 (2H, d, *J*=8.0 Hz, Ar-*H*), 5.67–5.83 (1H, s, PhC*H*$(O)_2$), 5.39–5.46 (1H, m, C*H*=CH2), 5.05–5.21 (2H, m, CH=CH_2), 4.42–4.67 (2H, m, benzylic CH_2), 3.87–4.11 (3H, m, C*H*CH_2O and CH_2OPMB), 3.77 (3H, s, OCH_3), 3.53–3.69 (5H, m, CH_2CHN, CH_2N and C*H*NBoc), 1.45 (9H, s, C(CH_3)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 154.6, 134.4, 131.6, 129.2, 128.7, 128.1, 126.1, 117.1, 113.6, 101.0, 78.2, 73.1, 69.5, 67.87, 67.81, 57.1, 55.4, 55.1, 28.2; MS (ESIMS): *m*/*z* 492 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 492.2355. $C_{27}H_{35}NO_6Na$ requires 492.2362.

*4.1.13. tert-Butylallyl (2R,4R,5S)-4-(hydroxymethyl)-2-phenyl-1,3-dioxan- 5-yl carbamate (**21**).* To a solution of **20** (418 mg, 0.89 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added aqueous NaH_2PO_4/Na_2HPO_4 (pH 7) buffer (4 mL) and DDQ (242 mg, 1 mmol). The reaction was allowed to warm to room temperature. After 2 h the reaction mixture was filtered through a Celite pad, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting with 15% EtOAc/hexane to afford alcohol **21** (295 mg, 95%) as a white solid; R_f (10% EtOAc/hexane) 0.45; $[\alpha]_D^{25}$ −32.1 (*c* 1, $CHCl_3$); mp 120 °C; IR (KBr): λ_{max} 3519, 2977, 1689, 1132 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.42–7.47 (2H, m, Ar-*H*), 7.31–7.37 (3H, m, Ar-*H*), 5.75–5.89 (1H, s, PhC*H*$(O)_2$), 5.43–5.59 (1H, m, C*H*=CH2), 5.14–5.31 (2H, m, CH=CH_2), 4.07–4.49 (3H, m, C*H*CH_2OH and CH_2OH), 3.59–3.98 (5H, m, CH_2CHN, CH_2N, C*H*NBoc), 1.47 (9H, s, C(CH_3)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.9, 134.5, 129.1, 128.2, 126.1, 117.19, 101.1, 78.2, 73.1, 67.8, 67.2, 62.1, 55.4, 28.2; MS (ESIMS): *m*/*z* 372 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 372.1798. $C_{19}H_{27}NO_5Na$ requires 372.1786.

*4.1.14. tert-Butyl (2R,4S,5S)-4-((E)-2-(ethoxycarbonyl)vinyl)-2-phenyl-1,3-dioxan-5-ylallyl carbamate (**22**).* To a solution of oxalyl chloride (0.137 mL, 1.54 mmol) in dry DCM (15 mL) at −78 °C, DMSO (0.164 mL, 2.32 mmol) was added dropwise with stirring under nitrogen. After stirring for 15 min, alcohol **21** (270 mg, 0.77 mmol) in dry DCM (10 mL) was added to the reaction mixture. After 1 h stirring at −78 °C, Et_3N (0.64 mL, 4.62 mmol) was added and stirred for another 0.5 h at −78 °C and 0.5 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (2×50 mL), brine (25 mL), dried on Na_2SO_4 and concentrated in vacuo. The crude compound thus obtained was used in the next step without further purification.

To a stirred solution of LiBr in dry THF under nitrogen atmosphere, at room temperature, was added triethylphosphonoacetate

(0.184 mL, 0.92 mmol), DBU (117 mg, 0.77 mmol) and finally aldehyde dissolved in THF (10 mL). After 1 h stirring saturated NH_4Cl (5 mL) was added and the whole mixture was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (10% EtOAc/hexane) to give the ester **22** (302 mg, 94%) as a colourless liquid; R_f (5% EtOAc/hexane) 0.47; $[\alpha]_D^{25}$ −62.1 (*c* 1, $CHCl_3$); IR (neat): λ_{max} 2977, 2930, 1721, 1694, 1149, 1025 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.27–7.48 (5H, m, Ar-*H*), 6.92 (1H, dd, *J*=15.8, 10.7 Hz, C*H*=CHCO), 6.08 (1H, d, *J*=15.8 Hz, CH=C*H*CO), 5.39–5.93 (2H, m, PhC*H*$(O)_2$ and C*H*=CH2), 5.11–5.34 (2H, m, CH=CH_2), 4.37–4.51 (1H, m, CH=CHC*H*), 4.01–4.25 (5H, m, CH_2CHN, CH_2N, C*H*NBoc), 3.57–3.96 (2H, m, OCH_2), 1.47 (9H, s, C(CH_3)$_3$), 1.29 (3H, t, *J*=6.98 Hz, CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.9, 154.5, 143.4, 134.1, 128.9, 128.8, 128.2, 125.9, 122.4, 117.6, 100.7, 78.2, 77.4, 68.2, 67.1, 60.4, 55.4, 28.3, 14.1; MS (ESIMS): *m*/*z* 440 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 440.2042. $C_{23}H_{31}NO_6Na$ requires 440.2049.

*4.1.15. (2R,4aS,8aS)-tert-Butyl4,4a-dihydro-2-phenyl-6H-[1,3]dioxino[5,4–b]pyridine-5 (**8a**H)-carboxylate (**23**).* Bis-(tricyclohexylphospine)benzylideneruthenium (IV) chloride (Grubbs' catalyst) (5 mg, 10 mol %) was added to a solution of **22** (250 mg, 0.6 mmol) in toluene (300 mL) and the mixture was stirred for 2 h at 90 °C. The solvent was evaporated under reduced pressure and the residue obtained was purified by chromatography (20% EtOAc/hexane) to afford **23** (175 mg, 92%) as a black solid; R_f (15% EtOAc/hexane) 0.44; mp 89 °C; $[\alpha]_D^{25}$ +16.5 (*c* 1, $CHCl_3$); IR (KBr): λ_{max} 3043, 2974, 2877, 1704, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.47 (2H, m, Ar-*H*), 7.29–7.35 (3H, m, Ar-*H*), 5.72–5.85 (2H, m, C*H*=C*H*), 5.57 (1H, s, PhC*H*$(O)_2$), 4.73 (1H, dd, *J*=4.8, 6.4 Hz, C=CHC*H*), 4.49 (1H, *apparent* t, *J*=11.2, 10.4 Hz, CH_aH$_b$CHN), 4.2–4.34 (2H, m, CH$_a$$H_b$CHN and C*H*NBoc), 3.68 (1H, dd, *J*=2.4, 16.1 Hz, CH_aH$_b$N), 3.17–3.25 (1H, m, CH$_a$$H_b$N), 1.47 (9H, s, C(C$H_3$)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.2, 137.6, 128.9, 128.2, 127.1, 126.1, 101.4, 80.6, 75.2, 70.1, 55.1, 45.9, 28.3; MS (ESIMS): *m*/*z* 340 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 340.1529. $C_{18}H_{23}NO_4Na$ requires 340.1524.

*4.1.16. (2R,4aS,7S,8S,8aR)-tert-Butylhexahydro-7,8-dihydroxy-2-phenyl-[1,3] dioxino [5,4-b] pyridine-5-carboxylate (**24**).* To a solution of compound **23** (150 mg, 0.47 mmol) in acetone (2 mL) was added aqueous 4% OsO_4 (65 μL, 0.01 mmol) solution at 0 °C. After 10 min, aqueous 50% NMO solution (0.23 mL, 1.41 mmol) was added and the mixture was stirred overnight at the same temperature. To the reaction mixture Na_2SO_3 and Na_2SO_4 were added, it was filtered through a pad of Celite and the solvent was evaporated. The residue was purified by column chromatography (50% EtOAc/hexane) to afford the diol **24** (142 mg, 86%) as a colourless liquid; R_f (40% EtOAc/hexane) 0.52; $[\alpha]_D^{25}$ +4.4 (*c* 1, $CHCl_3$); IR (neat): λ_{max} 3427, 2923, 1694, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.47 (2H, m, Ar-*H*), 7.32–7.37 (3H, m, Ar-*H*), 5.58 (1H, s, PhC*H*$(O)_2$), 4.74 (1H, dd, *J*=4.3, 7.3 Hz, C*H*CHN), 4.48 (1H, *apparent* t, *J*=11.7, 10.9 Hz, CH_aH$_b$CHN), 4.15 (1H, br s, CH$_a$$H_b$CHN), 4.01 (1H, dd, 5.1, 8.0 Hz, C*H*NBoc), 3.58–3.67 (2H, m, 2X C*H*OH), 3.45–3.53 (1H, m, CH_aH$_b$N), 2.88 (1H, t, *J*=12.4, 11.7 Hz, CH$_a$$H_b$N), 2.8 (1H, br s, O*H*), 2.71 (1H, br s, O*H*), 1.45 (9H, s, C(CH_3)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.2, 137.3, 129.1, 128.2, 126.1, 101.3, 80.7, 77.7, 69.8, 69.2, 66.7, 50.1, 46.9, 28.3; MS (ESIMS): *m*/*z* 374 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 374.1576. $C_{18}H_{25}NO_6Na$ requires 374.1579.

*4.1.17. D-1-Deoxyallonojirimycin (**7**).* To a solution of **24** (90 mg, 0.25 mmol) in MeOH (6 mL) was added 6 N HCl (5 mL) and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was treated with Dowex 50wX8 ion-exchange resin using a sequence of water and 5% NH_4OH as eluent to yield **7** (37 mg, 89%) as a white solid; R_f (MeOH) 0.2; mp 163 °C; $[\alpha]_D^{25}$ +35.1 (*c* 1, MeOH), [lit.[26] $[\alpha]_D^{25}$ +36.2 (*c* 0.83 MeOH)]; IR (neat): λ_{max} 3448, 2924, 2855, 1626, 1379, 1036, 763, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.0 (1H, br s, NCHCHC*H*), 3.71 (1H, dd, *J*=2.9, 11.7 Hz, NCHC*H*), 3.52–3.63 (2H, m, NCH2C*H* and CH_aH$_b$OH), 3.38 (1H, dd, *J*=10.3, 2.9 Hz, CH$_a$$H_b$OH), 2.75 (1H, dd, *J*=12.5, 5.1 Hz, NCH$_a$$H_e$), 2.55–2.67 (2H, m, NC*H*, NCH_aH$_e$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.3, 69.5, 69.0, 62.2, 55.3, 44.5; MS (ESIMS): *m*/*z* 164 $[M+H]^+$; HRMS (ESI): $[M+H]^+$, found 164.0925. $C_6H_{13}NO_4$ requires 164.0922.

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References and notes

1. Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789.
2. (a) Tomata, Y.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2003**, *44*, 8975; (b) Rogers, E. W.; Molinski, T. F. *Org. Lett.* **2007**, *9*, 437.
3. (a) Riethmuller, J.; Riehle, A.; Grassme, H.; Gulbins, E. *Biochim. Biophys. Acta* **2006**, *1758*, 2139; (b) Snook, C. F.; Jones, J. A.; Hannun, Y. A. *Biochim. Biophys. Acta* **2006**, *1761*, 927.
4. (a) Kester, M.; Kolesnick, R. *Pharm. Res.* **2003**, *47*, 365; (b) Rosen, H.; Liao, J. *Curr. Opin. Chem. Biol.* **2003**, *7*, 461; (c) Summers, S. A.; Nelson, D. H. *Diabetes* **2005**, *54*, 591; (d) Modrak, D. E.; Gold, D. V.; Goldenberg, D. M. *Mol. Cancer Ther.* **2006**, *5*, 200; (e) Zhou, S.; Zhou, H.; Walian, P. J.; Jap, B. K. *Biochemistry* **2007**, *46*, 2553; (f) Kolter, T.; Sandhoff, K. *Biochim. Biophys. Acta* **2006**, *1758*, 2057.
5. (a) Karlsson, K. A. *Trends Pharmacol. Sci.* **1991**, *12*, 265; (b) Hannun, Y.; Bell, R. M. *Science* **1989**, *243*, 500; (c) Hannun, Y. *Science* **1996**, *274*, 1855; (d) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532; (e) Sawatzki, P.; Kolter, T. *Eur. J. Org. Chem.* **2004**, 3693.
6. (a) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075; (b) Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365.
7. (a) Chun, J.; Lee, G.; Byun, H.-P.; Bittman, R. *Tetrahedron Lett.* **2002**, *43*, 375; (b) Yadav, J. S.; Geetha, V.; Raju, A. K.; Gnaneshwar, D.; Chandrasekhar, S. *Tetrahedron Lett.* **2003**, *44*, 2983; (c) Lombardo, M.; Capdevila, M. G.; Pasi, F.; Trombini, C. *Org. Lett.* **2006**, *8*, 3303; (d) Lee, J.-M.; Lim, H.-S.; Chung, S.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 343.
8. (a) Luo, S.-Y.; Thopate, S. R.; Hsu, C.-Y.; Hung, S.-C. *Tetrahedron Lett.* **2002**, *23*, 4889; (b) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805; (c) Lin, C.-C.; Fan, G.-T.; Fan, J.-M. *Tetrahedron Lett.* **2003**, *44*, 5281; (d) Chiu, H.-Y.; Tzou, D.-L. M.; Patkar, L. N.; Lin, C.-C. *J. Org. Chem.* **2003**, *68*, 5788; (e) Plettenburg, O.; Bodmer-Narkevich, V.; Wong, C.-H. *J. Org. Chem.* **2002**, *67*, 4559.
9. (a) Llaveria, J.; Diaz, Y.; Isabel Matheu, M.; Castillon, S. *Org. Lett.* **2009**, *11*, 205; (b) Yoon, H. J.; Kim, Y.-W.; Lee, B. K.; Lee, W. K.; Kim, Y.; Ha, Y.-J. *Chem. Commun.* **2007**, 79; (c) Righi, G.; Ciambrone, S.; D'Achille, C.; Leonelli, A.; Bonini, C. *Tetrahedron* **2006**, *62*, 11821; (d) Enders, D.; Palecek, J.; Grondal, C. *Chem. Commun.* **2006**, 655; (e) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618; (f) Cai, Y.; Ling, C.-C.; Bundle, D. R. *Org. Biomol. Chem.* **2006**, *4*, 1140.
10. Paulsen, H. *Iminosugars as Glycosidase Inhibitors*; Wiley-VCH: Germany, 2004; p. 1.
11. (a) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497; (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.
12. (a) Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anti- Cancer Agents Med. Chem.* **2008**, *8*, 77; (b) Yoshikuni, Y.; Ezure, Y.; Seto, T.; Mori, K.; Watanabe, M.; Enomoto, H. *Chem. Pharm. Bull.* **1989**, *37*, 106; (c) Kimura, M.; Chen, F.-J.; Nakashima, N.; Kimura, I.; Asano, N.; Koya, S. J. *Trad. Med.* **1995**, *12*, 214; (d) Robina, I.; Moreno-Vargas, A. J.; Carmona, A. T.; Vogel, P. *Curr. Drug Metab.* **2004**, *5*, 329; (e) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683; (f) Fan, J.-Q. *Trends Pharmacol. Sci.* **2003**, *24*, 355.
13. (a) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; (b) *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999.
14. For recent publications see: (a) Racine, E.; Bello, C.; Lemaire, S. G.; Vogel, P.; Sandrine, P. *J. Org. Chem.* **2009**, *74*, 1766; (b) Song, X.; Hollingsworth, R. I. *Tetrahedron Lett.* **2007**, *48*, 3115; (c) Takahata, H.; Banba, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199; (d) Saha, N. N.; Desai, V. N.; Dhavale, D. D. *Tetrahedron* **2001**, *57*, 39; (e) Comins, D. L.; Fulp, A. B. *Tetrahedron Lett.* **2001**, *42*, 6839; (f) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427.
15. Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701.
16. Previous synthesis of allo-DNJ. (a) Guaragna, A.; D'Errico, S.; D'Alonzo, D.; Pedatella, S.; Palumbo, G. *Org. Lett.* **2007**, *9*, 3473; (b) Hong, B.-C.; Chen, Z.-Y.; Nagarajan, A.; Kottani, R.; Chavan, V.; Chen, W.-H.; Jiang, Y.-F.; Zhang, S.-C.; Liao, J.-H.; Sarshar, S. *Carbohydr. Res.* **2005**, *340*, 2457; (c) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamato, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036; (d) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387; (e) Asano, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commun.* **1999**, 41.
17. (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5335; (b) Millar, J. G.; Oehlschlager, A. C. *J. Org. Chem.* **1984**, *49*, 2332.

18. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Pfenninger, A. *Synthesis* **1986**, 89; (c) Baker, S. R.; Boot, J. R.; Molgan, S. E.; Osborne, D. T.; Ross, W. J.; Shrubsall, P. R. *Tetrahedron Lett.* **1983**, *24*, 4469.
19. Hayes, C. J.; Sherlock, A. E.; Green, M. P.; Wilson, C.; Blake, A. J.; Selby, M. D.; Prodger, J. C. *J. Org. Chem.* **2008**, *73*, 2041.
20. Reddy, M. S.; Narender, M.; Nageswar, Y. V. D.; Rao, K. R. *Synlett* **2006**, 1110.
21. (a) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655; (b) Disadee, W.; Ishikawa, T. *J. Org. Chem.* **2005**, *70*, 9399; (c) Findeis, M. A.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2838.
22. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
23. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013; (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490; (e) Bhasker, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915.
24. (a) Ghosh, S.; Shashidar, J.; Kumar Dutta, S. *Tetrahedron Lett.* **2006**, *47*, 6041; (b) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761; (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943.
25. Guaragna, A.; D'Alonzo, D.; Paolella, C.; Palumbo, G. *Tetrahedron Lett.* **2009**, *50*, 2045.
26. Takemura, A.; Fujiwara, K.; Shimawaki, K.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron* **2005**, *61*, 7392.