Tetrahedron: *Asymmetry* 21 (2010) 494–499

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Total synthesis of (+) methyl β-D-vicenisaminide

Takeru Ehara [a,b], Mikio Fujii [a], Machiko Ono [c], Hiroyuki Akita [a,*]

[a] *Faculty of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan*
[b] *Research Institute, Novartis Pharma K.K.;8 Ohkubo, Tsukuba, Ibaraki 300-2611, Japan*
[c] *School of Pharmaceutical Sciences, International University of Health and Welfare, 2600-1 Kitakanemaru, Ohtawara, Tochigi 324-8501, Japan*

ARTICLE INFO

Article history:
Received 26 January 2010
Accepted 16 February 2010
Available online 16 March 2010

ABSTRACT

The total synthesis of methyl β-D-vicenisaminide **1** has been achieved. In this approach, the synthesis of enantiomerically pure methyl (4*R*,5*S*)- and (4*S*,5*R*)-4-azido-5-hydroxy-2(*E*)-hexenoates **2** was established by enzymatic resolution of (±)-*anti*-5-acetoxy -4-azido-2(*E*)-hexenoate **4**. Another stereogenic center was introduced by base-catalyzed intramolecular conjugate addition of a hemiacetal-derived alkoxide nucleophile obtained by the reaction of methyl (4*S*,5*R*)-*N*-4-*tert*-butoxycarbonyl-*N*-methylamino-5-hydroxyl-2(*E*)-hexenoate **8** and benzaldehyde in the presence of a base.

1. Introduction

Aminosugars are isolated from many antibiotics or natural products as constituents of these compounds, and the role of the whole structure has a close connection with their biological activities.[1] Hence, efficient and highly stereoselective synthetic methods have been investigated.[2] Vicenistatin was isolated from *Streptomyces* sp. HC34 as a novel antitumour antibiotics (Scheme 1),[3] while methyl β-D-vicenisaminide **1** was obtained by methanolysis of vicenistatin under acidic conditions over the course of the structural elucidation.[3] Fewer enantioselective syntheses of methyl β-D-vicenisaminide **1** have been reported. Ichikawa et al. reported the efficient synthesis of **1** from D-glucose utilizing an allyl cyanate-to-isocyanate rearrangement.[4] Matsushima et al. also reported the stereoselective total synthesis of **1** from 2-oxiranemethanol prepared from 2-butene-1-ol.[5] Herein, we report another approach towards β-D-vicenisaminide **1** starting from non-carbohydrate material without a carbon-chain homologation. We will report a chemoenzymatic synthesis of enantiopure multifunctional building blocks from commercially available methyl sorbate.

2. Results and discussion

2.1. Lipase mediated chemoenzymatic synthesis of methyl (4*S*,5*R*)- and (4*R*,5*S*)-*anti*-4-azido-5-hydroxy-2(*E*)-hexenoates 2

The retrosynthesis of β-D-vicenisaminide **1** from (4*S*,5*R*)-4-azido-5-hydroxy-2(*E*)-hexenoate **2** was shown in Scheme 1. The methyl glycoside **1** could be constructed from the lactone equivalent **A**, which would be obtained by lactonization of (3,5)-*syn*-dihydroxy hexanoate conger **B**. The enantiopure form of **B** could be obtained by stereoselective β-hydroxylation at the C_3-position of (4*S*,5*R*)-**2**, which could be prepared by enzyme assisted resolution of the corresponding acetate of (±)-**2**.

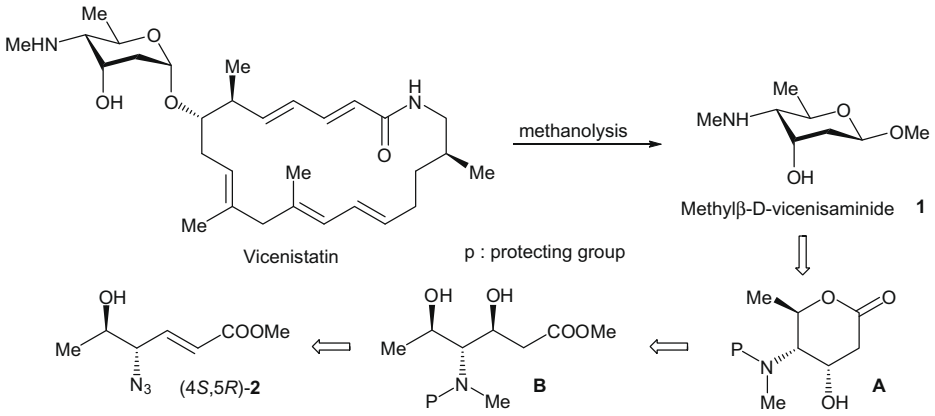
The reaction of (±)-(4,5)-*trans*-epoxy-2(*E*)-hexenoate **3** with sodium azide in the presence of acetic acid afforded (±)-**2** regioselectively in 88% yield. The *anti*-stereochemistry of (±)-**2** could be explained by taking into account the result of the $BF_3{\cdot}Et_2O$ assisted reaction of (±)-**3** and benzyl alcohol, which afforded (±)-(4,5)-*anti*-5-hydroxy-4-benzyloxy-2(*E*)-hexenoate.[6] Acetylation of (±)-**2** gave the corresponding acetate (±)-**4** in 76% yield, which was then subjected to enantioselective hydrolysis using the lipase 'Amano PS' from *Burkholderia cepacia* (EC 3.1.1.34) in phosphate buffer solution at pH 7.2 to give (4*S*,5*R*)-**2** {$[\alpha]_D$ = +52.9 (*c* 0.82, $CHCl_3$), >99% ee, 42% yield} and (4*R*,5*S*)-**4** {$[\alpha]_D$ = −44.1 (*c* 0.78, $CHCl_3$), >99% ee, 43% yield}, respectively. The enantiomeric excesses (ee) of the optically active compounds were determined by HPLC on a chiral column (see Section 4). Methanolysis of (4*R*,5*S*)-**4** with K_2CO_3 provided (4*R*,5*S*)-**2** {$[\alpha]_D$ = −55.6 (*c* 0.69, $CHCl_3$)} in 86% yield, whose absolute configuration was confirmed by comparison of the $[\alpha]_D$ of an authentic sample of (4*R*,5*S*)-**4** {$[\alpha]_D$ = −57.1 (*c* 0.54, $CHCl_3$)} prepared by the reaction of the known (4*S*,5*S*)-**3**[6] with sodium azide as described in Scheme 2.

2.2. Total synthesis of methyl β-D-vicenisaminide

The enantiomerically pure building block (4*S*,5*R*)-**2** obtained was further utilized for the reaction as shown in Scheme 3. Chemoselective transformation of azide (4*S*,5*R*)-**2** was performed by a Staudinger reduction using PPh_3 in THF/H_2O,[7] followed by in situ Boc protection of the amino group to give (4*S*,5*R*)-**5** {$[\alpha]_D$ = +19.3 (*c* 0.88, MeOH)} in 77% yield in order to avoid the manipulation of the very polar amino group. In this case, the formation of by-products due to the 3,3-sigmatropic rearrangement of allyl

* Corresponding author. Tel.: +81 047 472 1805; fax: +81 047 472 1825.
E-mail address: akita@phar.toho-u.ac.jp (H. Akita).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.02.014



Scheme 1.

azide (4*S*,5*R*)-**2** was not observed by NMR analysis of (4*S*,5*R*)-**5**. Protection of the hydroxyl group of **5** as a *tert*-butyldimethylsilyl (TBDMS) ether was accomplished using TBDMSCl and imidazole in DMF to afford (4*S*,5*R*)-**6** {$[\alpha]_D = -3.5$ (*c* 0.55, MeOH)} in 90% yield. The Boc-carbamate in (4*S*,5*R*)-**6** was subjected to methylation by using MeI and Ag_2O to give of the desired (4*S*,5*R*)-**7** as rotamers in 82% yield. Another stereogenic center was constructed by the intramolecular conjugate addition of a hemiacetal-derived alkoxide nucleophile obtained by the reaction of methyl (4*S*,5*R*)-*N*-4-*tert*-butoxycarbonyl-*N*-methylamino-5-hydroxyl-2(*E*)-hexenoate **8** and benzaldehyde in the presence of base to the α,β-unsaturated ester by using Evans' procedure.[8] In fact, deprotection of the silyl ether using tetrabutylammonium fluoride (TBAF) in the presence of acetic acid regenerated the secondary alcohol (4*S*,5*R*)-**8** in 92% yield. For the purpose of introduction of the hydroxyl moiety at the 3-position of (4*S*,5*R*)-**8**, treatment of (4*S*,5*R*)-**8** with PhCHO in the presence of KO^{t}Bu (THF, 0 °C) afforded **9** in 61% yield with high diastereoselectivity (>90:10) from the ^{1}H NMR measurement. This high diastereoselectivity could be explained via a chair-like intermediate as shown in Figure 1. We attempted to remove the benzylidene acetal **9** by hydrolysis under acidic conditions, although with only limited success. The reaction was slow and led to the formation of an unidentified by-product. Thus, Pd-catalyzed hydrogenation of acetal **9** was employed to give diol **10** in 78% yield as a single isomer, followed by the lactonization in the presence of acid catalyst to afford lactone **11** in 68% yield. Numerous procedures have been reported for the half-reduction of a lactone involving DIBAL-H reduction, however $LiAlH_4$ only worked to give the desired lactol in the present case. Lactone **11** was partially reduced to the lactol by using one equivalent of $LiAlH_4$ at 0 °C (Scheme 3). This lactol was immediately transformed to the methyl glycoside under acidic conditions (AcCl/MeOH) to give 32% of the slow eluting isomer **12** and 24% of the fast eluting isomer **13** in the column chromatography. Finally, deprotection of the Boc-group of isomer **12** using $ZnBr_2$ in CH_2Cl_2[9] provided methyl β-D-vicenisaminide **1** in 68% yield. Treatment of **1** with 4 M HCl in dioxane gave the methyl β-D-vicenisaminide **1** hydrocholride salt, whose spectroscopic data were identical with those previously reported.[4] Isomer **13** was also treated with $ZnBr_2$ to afford methyl α-D-vicenisaminide **14,** which was converted by heating with HCl in MeOH to give methyl β-D-vicenisaminide **1** (Scheme 4).[4]

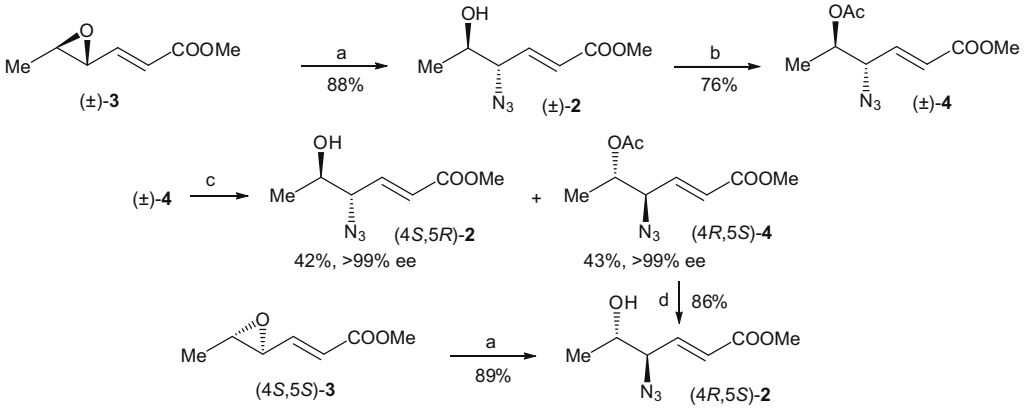
3. Conclusion

In conclusion, the total synthesis of methyl β-D-vicenisaminide **1** has been achieved. In our approach, synthesis of enantiomerically pure methyl (4*R*,5*S*)- and (4*S*,5*R*)-4-azido-5-hydroxy-2(*E*)-hexenoates **2** was established by enzymatic resolution of 5-acetate precursor (±)-**4**. Another stereogenic center was introduced by the intramolecular conjugate addition of a hemiacetal-derived alkoxide nucleophile to the α,β-unsaturated ester **8**.

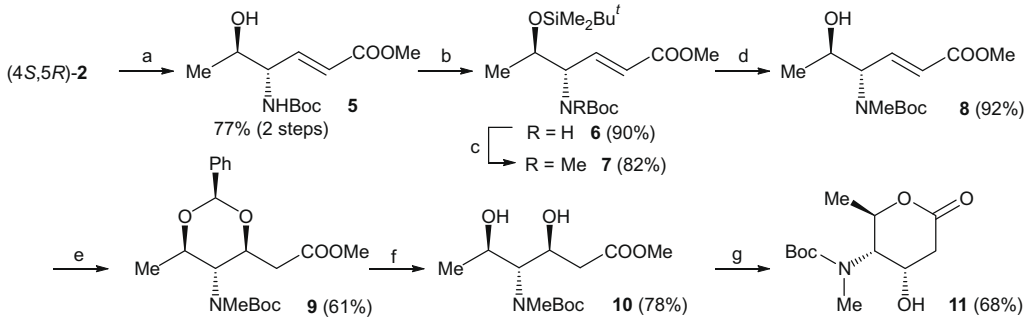
4. Experimental

4.1. General

All melting points were measured on a Mettler FP-62 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were



Scheme 2. Reagents: (a) (1) NaN_3/AcOH/H_2O; (b) Ac_2O/DMAP/pyridine (c) lipase 'Amano PS'/phosphate buffer (pH 7.2); (d) K_2CO_3/MeOH.



Scheme 3. Reagents: (a) (1) PPh_3/THF/H_2O, (2) Boc_2O/$NaHCO_3$/CH_2Cl_2/H_2O; (b) $^tBuMe_2SiCl$/imidazole/DMF; (c) MeI/Ag_2O/DMF; (d) $Bu_4N^+F^-$/AcOH/THF; (e) PhCHO/KO^{t}Bu/THF; (f) H_2/5% Pd–C/MeOH; (g) CSA/benzene.

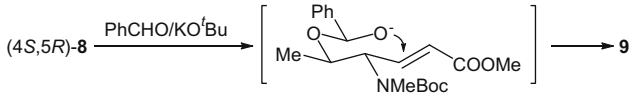


Figure 1.

recorded on JEOL AL 400 spectrometer or Bruker AV400 M digital spectrometer in $CDCl_3$, MeOH-d_4, and DMSO-d_6 with or without Me_4Si as an internal reference. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-600H (matrix; glycerol, *m*-nitrobenzyl alcohol) spectrometer. High-resolution FAB MS were obtained with a JEOL JMS-SX-102A or JMS-T100LP. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 or P-1020 digital polarimeter. All evaporations were performed under reduced pressure. All reagents were purchased from commercial sources and were used without purification. For column chromatography, silica gel (Kieselgel 60, Merck) or NH-silica gel (Chromatorex, DM1020, Fuji Silysia chemical) were employed.

4.2. (±) Methyl (4,5)-*anti*-4-azido-5-hydroxy-2(*E*)-hexenoate 2

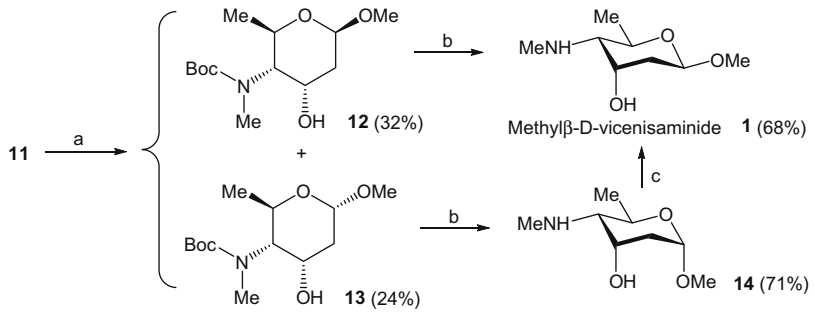
To a suspension of (±)-**3** (50 g, 352 mmol) and AcOH (44 mL, 769 mmol) in H_2O (800 mL) was added NaN_3 (50 g, 769 mmol) in H_2O (400 mL), then the mixture was stirred at room temperature for 12 h. The reaction was quenched by 5% aqueous $NaHCO_3$ and the basic media was extracted with Et_2O (2 × 1000 mL). The combined organic layer was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (500 g, hexane/EtOAc = 4:1) to afford (±)-**2** (57.4 g, 310 mmol, 88%) as a colorless oil. (±)-**2**: IR (neat): 1714, 2104, 2901, 2980, 3439 cm^{-1}. ^1H NMR: δ 1.20 (3H, d, J = 6.6 Hz), 1.86 (1H, d, J = 5.1 Hz), 3.78 (3H, s), 3.95 (1H, ddd, J= 1.3, 7.1, 7.3 Hz), 4.09 (1H, ddd, J = 1.0, 7.1, 7.3 Hz), 6.11 (1H, dd, J = 1.3, 15.7 Hz), 6.88 (1H, dd, J = 7.3, 15.7 Hz). ^{13}C NMR: δ 18.5, 51.8, 68.0, 69.2, 125.0, 140.9, 165.7. HRMS (FAB+) calcd for $C_7H_{12}N_3O_3$: 186.0879, found: 186.0874.

4.3. (±) Methyl (4,5)-*anti*-5-acetoxy-4-azido-2(*E*)-hexenoate 4

To a solution of (±)-**2** (30 g, 162 mmol) in Ac_2O (70 mL, 810 mmol) were added pyridine (30 mL) and DMAP (0.2 g, 1.6 mmol) at 0 °C, then the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into ice/H_2O and extracted with Et_2O (1000 mL). The organic layer was successively washed with 1 M aqueous HCl (2 × 300 mL), 5% $NaHCO_3$ (200 mL) and brine, dried over $MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (1000 g, hexane/EtOAc = 15:1–9:1) to afford (±)-**4** (28 g, 123 mmol, 76%) as a colorless syrup. (±)-**4**: IR (neat): 1731, 2107, 2950, 2989 cm^{-1}. ^1H NMR: δ 1.23 (3H, d, J = 6.6 Hz), 2.09 (3H, s), 3.78 (3H, s), 4.25 (1H, ddd, J = 1.4, 6.3, 6.3 Hz), 5.06 (1H, dq, J = 6.3, 6.6 Hz), 6.12 (1H, dd, J = 1.4, 15.6 Hz), 6.88 (1H, dd, J = 6.3, 15.6 Hz). ^{13}C NMR: δ 15.1, 21.0, 51.9, 65.0, 71.2, 125.0, 140.2, 165.7, 170.0. HRMS (FAB+) calcd for $C_9H_{14}N_3O_4$: 228.0984, found: 228.0990.

4.4. (+) Methyl (4*S*,5*R*)-4-azido-5-hydroxy-2(*E*)-hexenoate 2 and (−)-methyl (4*R*,5*S*)-5-acetoxy-4-azido-2(*E*)-hexenoate 4

A suspension of (±)-**4** (28 g, 122.8 mmol) and lipase 'Amano PS' (2.8 g) in phosphate buffer (0.1 M, pH 7.2, 1240 mL) was stirred at 33 °C for 48 h. The reaction mixture was diluted with Et_2O (500 mL) and solid materials were removed by filtration through a Celite pad. The reaction mixture was extracted with Et_2O (2 × 500 mL) and combined organic extracts were washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and filtered.



Scheme 4. Reagents: (a) (1) $LiAlH_4$/THF, (2) AcCl/MeOH; (b) $ZnBr_2/CH_2Cl_2$; (c) 2 M HCl/MeOH.

Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (500 g, hexane/EtOAc = 3:1–2:1) to afford (−)-**4** (12 g, 53 mmol, 43%) as a colorless syrup and (+)-**2** (9.5 g, 51 mmol, 42%) as a colorless oil. (−)-**4**; $[\alpha]_D^{23} = -44.1$ (*c* 0.78, $CHCl_3$). HPLC; CHIRALPAK OB-H (4.6 × 250 mm), eluents: hexane/EtOH = 99:1, t_R = 26.9 min, [(±)-**4**; t_R = 24.4 and 26.9 min]: (+)-**2**; $[\alpha]_D^{23} = +52.9$ (*c* 0.82, $CHCl_3$). HPLC; CHIRALPAK OD (4.6 × 250 mm), eluents: hexane/EtOH = 97:3, t_R = 16.5 min [(±)-**2**; t_R = 16.5 and 17.9 min].

4.5. (−) Methyl (4*R*,5*S*)-4-azido-5-hydroxy-2(*E*)-hexenoate 2

A mixture of (−)-**4** (570 mg, 2.51 mmol) and K_2CO_3 (416 mg, 3.0 mmol) in MeOH (10 mL) was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with Et_2O (50 mL) and solid materials were removed by filtration through a Celite pad. Evaporation of the organic solvent gave a crude product, which was purified by silica gel chromatography (10 g, hexane/EtOAc = 3:1) to give (−)-**2** (350 mg, 1.89 mmol, 86%) as a colorless oil. (−)-**2**: $[\alpha]_D^{21} = -55.6$ (*c* 0.69, $CHCl_3$). HPLC; CHIRALPAK OD (4.6 × 250 mm), hexane/EtOH = 97:3, t_R = 17.9 min.

4.6. Authentic sample of (−) methyl (4*R*,5*S*)-4-azido-5-hydroxy-2(*E*)-hexenoate 2

The authentic sample (4*R*,5*S*)-**2** was prepared by the reaction of (4*S*,5*S*)-**3** with sodium azide with a similar procedure as described in the synthesis of (±)-**2**. $[\alpha]_D^{24} = -57.1$ (*c* 0.54, $CHCl_3$). HPLC; OD (4.6 × 250 mm), hexane/EtOH = 97:3, t_R = 17.9 min.

4.7. Methyl (4*S*,5*R*)-4-*tert*-butoxycarbonylamino-5-hydroxy-2(*E*)-hexenoate 5

To a solution of (4*S*,5*R*)-**2** (8 g, 43.2 mmol) in THF/H_2O (140:70 mL) was added PPh_3, (22.7 g, 86.4 mmol), then the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc (500 mL) and extracted with 1 M aqueous HCl (2 × 50 mL). The aqueous layer was diluted with H_2O and basified by $NaHCO_3$ (33.6 g, 400 mmol) at 0 °C. To the suspension was added Boc_2O (47 g, 216 mmol) in CH_2Cl_2 (200 mL) at 0 °C, then the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with H_2O and brine, dried over $MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (300 g, hexane/EtOAc = 3:1–2:1) to afford (4*S*,5*R*)-**5** (8.6 g, 33.2 mmol, 77%) as white needles. (4*S*,5*R*)-**5**: mp = 85.8 °C. $[\alpha]_D^{23} = +19.3$ (*c* 0.88, MeOH). IR (KBr): 1518, 1693, 2977, 3373 cm^{-1}. ^1H NMR: δ 1.21 (3H, d, *J* = 6.6 Hz), 1.45 (9H, s), 1.87 (1H, br s), 3.75 (3H, s), 3.95–4.02 (1H, m), 4.27 (1H, br s), 5.03 (1H, br s), 6.02 (1H, dd, *J* = 1.3, 15.7 Hz), 6.93 (1H, dd, *J* = 6.1, 15.7 Hz). ^{13}C NMR: δ 19.8, 28.3, 51.7, 56.9, 69.7, 80.2, 123.2, 143.7, 155.4, 166.4. HRMS (FAB+) calcd for $C_{12}H_{22}NO_5$: 260.1498, found: 260.1462.

4.8. Methyl (4*S*,5*R*)-4-*tert*-butoxycarbonylamino-5-*tert*-butyldimethylsilanyloxy-2(*E*)-hexenoate 6

To a solution of (4*S*,5*R*)-**5** (8 g, 30.9 mmol) in DMF (62 mL) were added imidazole (4.2 g, 61.7 mmol) and TBDMSCl (9.3 g, 61.7 mmol) at 0 °C, then the mixture was stirred at room temperature for 2 h. The reaction was quenched by MeOH (10 mL) and diluted with H_2O (500 mL) and extracted with Et_2O (2 × 300 mL). The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (200 g, hexane/EtOAc = 15:1–9:1) to afford (4*S*,5*R*)-**6** (10.4 g, 27.8 mmol, 90%) as a colorless oil. (4*S*,5*R*)-**6**: $[\alpha]_D^{22} = +3.5$ (*c* 0.55, MeOH). IR (neat): 1714 (s), 2888 (s), 3363 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.13 (3H, d, *J* = 6.3 Hz), 1.43 (9H, s), 3.74 (3H, s), 3.93–3.99 (1H, m), 4.17 (1H, br s), 4.82 (1H, d, *J* = 7.1 Hz), 5.98 (1H, d, *J* = 15.7 Hz), 6.93 (1H, dd, *J* = 6.6, 15.7 Hz). ^{13}C NMR ($CDCl_3$): δ −5.0, −4.4, 18.0, 20.4, 25.7, 28.3, 51.6, 57.2, 70.1, 79.7, 122.7, 144.4, 155.0, 166.6. HRMS (FAB+) calcd for $C_{18}H_{36}NO_5Si$: 374.2363, found: 374.2365.

4.9. Methyl (4*S*,5*R*)-*N*-4-*tert*-butoxycarbonyl-*N*-methylamino-5-*tert*-butyldimethylsilanyloxy-2(*E*)-hexenoate 7

To a solution of (4*S*,5*R*)-**6** (10 g, 26.8 mmol) in DMF (54 mL) were added Ag_2O (12.4 g, 53.5 mmol) and MeI (3.3 mL, 53.5 mmol), then the mixture was stirred vigorously at 40 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with H_2O/Et_2O (400:600 mL) after which the solid materials were removed by filtration through a Celite pad. The organic layer was separated and washed with H_2O and brine, dried over $MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (600 g, hexane/EtOAc = 15:1) to afford (4*S*,5*R*)-**7** (8.5 g, 21.9 mmol, 82%) as a colorless oil. (4*S*,5*R*)-**7**: $[\alpha]_D^{21} = -18.1$ (*c* 0.72, MeOH). IR (neat): 1697, 1730, 2858, 2954 cm^{-1}. ^1H NMR (DMSO-d_6): δ (contain rotamers) 0.01 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.08 (3H, br s), 1.39 (9H, s), 2.71 (3H, s), 3.66 (3H, s), 4.01 and 4.25 (0.5H and 0.5H, br s), 4.07 (1H, dq, *J* = 6.1, 8.2 Hz), 5.83 (1H, dd, *J* = 1.0, 15.8 Hz), 7.01 (1H, dd, *J* = 6.2, 15.8 Hz). ^{13}C NMR ($CDCl_3$): δ (contain rotamers) −4.9, −4.2, 17.9, 21.1 and 21.2, 25.7, 28.4, 31.6 and 31.7, 51.5, 62.6 and 64.4, 68.7 and 68.9, 79.9 and 80.3, 122.4 and 123.1, 144.3 and 144.9, 155.4 and 155.8, 166.6. HRMS (FAB+) calcd for $C_{19}H_{38}NO_5Si$: 388.2519, found: 388.2501.

4.10. Methyl (4*S*,5*R*)-*N*-4-*tert*-butoxycarbonyl-*N*-methylamino-5-hydroxyl-2(*E*)-hexenoate 8

To a solution of (4*S*,5*R*)-**7** (3 g, 20.6 mmol) in THF (50 mL) were added AcOH (8.65 mL, 150 mmol) and TBAF (1 M in THF, 103 mmol), then the mixture was stirred at 40 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with H_2O (300 mL) and extracted with EtOAc (2 × 400 mL). The combined organic layer was washed with 5% aqueous $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (300 g, hexane/EtOAc = 2:1) to afford (4*S*,5*R*)-**8** (5.2 g, 19.0 mmol, 92%) as a colorless oil. (4*S*,5*R*)-**8**: $[\alpha]_D^{21} = +14.8$ (*c* 0.82, MeOH). IR (neat): 1695, 2977, 3442 cm^{-1}. ^1H NMR (DMSO-d_6): δ (contain rotamers) 1.06 (3H, d, *J* = 5.7 Hz), 1.40 (9H, s), 2.66 (3H, s), 3.31 (3H, s), 3.79 (1H, dq, *J* = 5.7, 6.6 Hz), 4.14 and 4.32 (0.5H and 0.5H, br s), 5.07 (1H, br s), 5.79 (1H, d, *J* = 16.1 Hz), 7.07 (1H, dd, *J* = 4.8, 16.1 Hz). ^{13}C NMR ($CDCl_3$): δ (contain rotamers) 20.9, 28.3, 32.8, 51.6, 63.8, 68.4, 80.5, 123.2, 143.4, 156.1, 166.5. HRMS (FAB+) calcd for $C_{13}H_{24}NO_5$: 274.1654, found: 274.1637.

4.11. Methyl [(4*S*,5*R*,6*R*)-5-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-6-methyl-2-phenyl-[1,3]dioxan-4-yl]-acetate 9

To a solution of (4*S*,5*R*)-**8** (3 g, 11.0 mmol) in THF (110 mL) at 0 °C was added fleshly distilled benzaldehyde (1.67 mL, 16.5 mmol), followed by KO^{t}Bu (123 mg, 1.1 mmol), then the orange solution was stirred at the same temperature for 15 min. This sequence (addition/stirring) was repeated twice, and the mixture stirred for 1 h. The reaction mixture was poured into phosphate buffer at pH 7.2. The reaction mixture was extracted with Et_2O and the organic layer was washed with H_2O and brine, dried over

$MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (500 g, hexane/EtOAc = 15:1) to afford the inseparable rotamers of **9** (2.55 g, 6.72 mmol, 61%) as a pale yellow oil, which was used in the next reaction without any further purification. Compound **9**: $[\alpha]_D^{21} = -1.1$ (*c* 0.69, MeOH). IR (neat): 1695, 1740, 2978 cm^{-1}. ^1H NMR (MeOH-d_4): δ (contain rotamers) 1.23 and 1.25 (3H, d, *J* = 6.3 Hz), 1.48 and 1.50 (9H, s), 2.57 (1H, dd, *J* = 7.5, 15.4 Hz), 2.65 (1H, dd, *J* = 5.2, 15.4 Hz), 2.76 and 2.78 (3H, s), 3.66 and 3.67 (3H, s), 3.76 and 3.84 (1H, t, *J* = 9.9 Hz), 4.11–4.18 (1H, m), 4.41–4.49 (1H, m), 5.62 and 5.63 (1H, s), 7.32–7.34 (3H, m), 7.43 (2H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ (contain rotamers) 18.0 and 18.3, 28.3 and 28.4, 28.5 and 28.6, 37.9 and 38.0, 51.8 and 51.9, 56.8, 58.5, 73.9 and 74.3, 80.2 and 80.7, 100.4 and 100.6, 126.0 and 126.2, 128.3 and 128.9, 137.5 and 137.7, 155.8 and 156.2, 171.0 and 171.6. HRMS (FAB+) calcd for $C_{20}H_{30}NO_6$: 380.2073, found: 380.2089.

4.12. Methyl (3*S*,4*R*,5*R*)-4-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-3,5-dihydroxy-hexanoate 10

A solution of **9** (2.5 g, 6.6 mmol) in MeOH (66 mL) was hydrogenated over 10% Pd/C (250 mg) at room temperature under an atmospheric pressure of hydrogen for 24 h. After removal of the catalyst by filtration through a Celite pad, evaporation of the organic solvent gave a crude product, which was purified by silica gel chromatography (25 g, gradient, hexane/EtOAc = 1:1 to EtOAc only) to afford (3*S*,4*R*,5*R*)-**10** (1.5 g, 5.2 mmol, 78%) as a colorless oil. (3*S*,4*R*,5*R*)-**10**: $[\alpha]_D^{23} = +24.4$ (*c* 0.50, MeOH). IR (neat): 1694, 1738, 2977, 3380 cm^{-1}. ^1H NMR (MeOH-d_4): δ (contains rotamers) 1.14 and 1.15 (3H, d, *J* = 6.1 Hz), 1.45 and 1.47 (9H, s), 2.42 and 2.44 (1H, dd, *J* = 8.1, 15.2 Hz), 2.51 and 2.52 (1H, dd, *J* = 4.6, 15.2 Hz), 2.65 and 2.73 (3H, s), 3.62 and 3.77 (1H, s), 3.67 (3H, s), 4.01–4.22 (1H, m), 4.28–4.48 (1H, m). ^{13}C NMR (MeOH-d_4): δ (contains rotamers) 21.3, 28.6 and 28.7, 29.9, 41.2, 52.1, 64.5, 81.4, 81.9, 157.9, 173.3, 173.6. HRMS (FAB+) calcd for $C_{13}H_{26}NO_6$: 292.1760, found: 292.1802.

4.13. ((2*R*,3*R*,4*S*)-4-Hydroxy-2-methyl-6-oxo-tetrahydropyran-3-yl)-*N*-methyl-carbamic acid *tert*-butyl ester 11

To a solution of (3*S*,4*R*,5*R*)-**10** (1.2 g, 4.1 mmol) in benzene (50 mL) was added CSA (186 mg, 0.8 mmol), then the mixture was stirred at 60 °C for 36 h. The reaction mixture was cooled down to room temperature and diluted with CH_2Cl_2. The organic layer was washed with 5% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a crude residue, which was subjected to crystallization from CH_3CN to afford **11** (722 mg, 2.78 mmol, 68%) as colorless needles. Compound **11**: mp = 173 °C, $[\alpha]_D^{22} = +59.7$ (*c* 0.60, $CHCl_3$), IR (KBr): 1644, 1748, 2977, 3361 cm^{-1}. ^1H NMR (MeOH-d_4): δ (contains rotamers) 1.32 (3H, d, *J* = 6.1 Hz), 1.48 (9H, s), 2.64 (1H, dd, *J* = 2.9, 17.8 Hz), 2.89 (1H, dd, *J* = 3.4, 17.8 Hz), 2.95 (3H, s), 4.03–4.19 (2H, m), 4.92–5.02 (1H, m). ^{13}C NMR (MeOH-d_4): δ (contains rotamers) 18.8, 28.3, 36.3, 40.2 and 40.3, 62.6 and 62.8, 66.5 and 66.6, 71.5, 81.4, 157.2, 169.4. HRMS (EI) calcd for $C_{12}H_{21}NO_5$: 259.1417, found: 259.1420.

4.14. ((2*R*,3*R*,4*S*,6*R*)-4-Hydroxy-6-methoxy-2-methyl-tetrahydropyran-3-yl)-*N*-methylcarbamic acid *tert*-butyl ester 12 and ((2*R*,3*R*,4*S*,6*S*)-4-hydroxy-6-methoxy-2-methyl-tetrahydropyran-3-yl)-*N*-methylcarbamic acid *tert*-butyl ester 13

(i) To a suspension of $LiAlH_4$ (61.5 mg, 1.62 mmol) in THF (4 mL) at −20 °C was added a THF solution of **11** [347.0 mg, 1.34 mmol in THF (10 mL)], then the mixture was stirred at 0 °C for 1 h. The reaction mixture was cooled to −20 °C and saturated with aqueous Rochelle salt, diluted with THF and the mixture was stirred at 0 °C for 1 h. The solid materials were removed by filtration through a Celite pad and the filtrate was washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the organic solvent gave a crude residue, which was used in the next reaction without any further purification. (ii) A solution of the above crude product in HCl in MeOH (prepared by an addition of AcCl (450 μL, 6.75 mmol) to MeOH (10 mL)) was stirred at 0 °C for 0.5 h. The mixture was quenched by 5% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the organic solvent gave a crude residue, which was purified by NH-silica gel column chromatography (5 g, gradient, hexane/EtOAc = 4:1–1:2) to afford **13** (87 mg, 0.316 mmol, 24%) as a colorless oil and **12** (120 mg, 0.436 mmol, 32%) as a colorless amorphous material, respectively, in elution order. Compound **13**: $[\alpha]_D^{23} = +120.2$ (*c* 0.50, $CHCl_3$), IR (NaCl): 1692, 2975, 2983, 3522 cm^{-1}. ^1H NMR (MeOH-d_4): δ (contain rotamers) 1.15 amd 1.16 (3H, d, *J* = 6.5 Hz), 1.45 and 1.46 (9H, s), 1.88–2.00 (2H, m), 2.88 and 2.89 (3H, s), 3.36 (3H, s), 3.65–3.75 (1H, m), 3.96–4.01 (1H, m), 4.26–4.33 (1H, m), 4.72–4.75 (1H, m). ^{13}C NMR (MeOH-d_4): δ (contain rotamers) 18.6 and 18.8, 28.7, 31.5 and 32.3, 37.9 and 38.0, 55.4, 60.6 and 61.5, 61.7, 69.6 and 69.9, 81.2 and 81.4, 99.7 and 99.8, 157.8 and 158.4. HRMS (EI) calcd for $C_{13}H_{25}NO_5$: 275.1733, found: 275.1729. Compound **12**: $[\alpha]_D^{23} = -15.1$ (*c* 0.65, $CHCl_3$), IR (NaCl): 1668, 2927, 2975, 3448 cm^{-1}. ^1H NMR (MeOH-d_4): δ (contains rotamers) 1.16 and 1.18 (3H, d, *J* = 6.0 Hz), 1.45 and 1.46 (9H, s), 1.54–1.71 (1H, m), 1.86–1.94 (1H, m), 2.84 and 2.87 (3H, s), 3.44 (3H, s), 3.55–3.68 (1H, m), 4.08–4.21 (2H, m), 4.73–4.77 (1H, m). ^{13}C NMR (MeOH-d_4): δ (contains rotamers) 18.8 and 19.1, 28.7, 31.6 and 32.8, 41.0 and 41.1, 56.6 and 56.7, 61.4 and 62.1, 68.2 and 68.3, 69.5 and 69.7, 81.3 and 81.4, 100.5 and 100.6, 157.9 and 158.4. HRMS (EI) calcd for $C_{13}H_{25}NO_5$: 275.1733, found: 275.1738.

4.15. Methyl β-D-vicenisaminide 1

To a solution of **12** (40 mg, 0.145 mmol) in CH_2Cl_2 (1 mL) was added $ZnBr_2$ (163 mg, 0.726 mmol), then the mixture was stirred at room temperature for 24 h. The suspension was dissolved by the addition of the minimum amount of MeOH, then NH-silica gel was added. Evaporation of the organic solvent gave a crude product, which was purified by NH-silica gel column chromatography (3 g, gradient, CH_2Cl_2 to CH_2Cl_2/MeOH = 19:1) to afford **1** as a pale yellow oil. The free form was dissolved in Et_2O (1 mL) and 4 M HCl in dioxane was added to the solution. The resulting white needles were collected by filtration to afford hydrochloride **1** (20.9 mg, 0.099 mmol, 68%) as colorless needles. Compound **1**: mp = 182 °C (hydrochloride), $[\alpha]_D^{22} = -3.7$ (*c* 0.40, MeOH, NH free form), ^1H NMR (hydrochloride, MeOH-d_4): δ 1.35 (3H, d, *J* = 6.3 Hz), 1.67 (1H, ddd, *J* = 2.8, 9.1, 14 Hz), 2.03 (1H, ddd, *J* = 2.3, 4.3, 14 Hz), 2.74 (3H, s), 2.92 (1H, dd, *J* = 3.2, 9.3 Hz), 3.44 (3H, s), 4.01 (1H, dq, *J* = 6.3, 9.3 Hz), 4.35 (1H), 4.75 (1H, dd, *J* = 2.3, 9.1 Hz). ^{13}C NMR (hydrochloride, MeOH-d_4): δ 18.6, 31.2, 38.8, 56.7, 62.4, 63.3, 67.9, 100.4. HRMS (FAB+) calcd for $C_8H_{18}NO_3$: 176.1287, found: 176.1286.

4.16. Deprotection of the Boc-group of 13

To a solution of **13** (40 mg, 0.145 mmol) in CH_2Cl_2 (1 mL) was added $ZnBr_2$ (163 mg, 0.726 mmol), then the mixture was stirred at room temperature for 24 h. The suspension was dissolved by an addition of a minimum amount of MeOH, then NH-silica gel was added. Evaporation of the organic solvent gave a crude product, which was purified by NH-silica gel column chromatography (3 g, gradient, CH_2Cl_2 to CH_2Cl_2/MeOH = 19:1) to afford **14**

(18 mg, 0.103 mmol, 71%) as a pale yellow oil. Compound **14**: $[\alpha]_D^{22} = +198.0$ (*c* 0.6, $CHCl_3$, NH free form), ^1H NMR ($CDCl_3$): δ 1.32 (3H, d, *J* = 6.3 Hz), 1.85 (1H, dt, *J* = 3.5, 14.4 Hz), 2.08 (1H, dd, *J* = 3.0, 9.9 Hz), 2.15 (1H, ddd, *J* = 1.3, 3.5, 14.4 Hz), 2.44 (3H, s), 3.37 (3H, s), 3.69 (1H, dq, *J* = 6.3, 9.9 Hz), 4.07 (1H, dq, *J* = 6.3, 9.3 Hz), 4.77 (1H, d, *J* = 3.5 Hz). ^{13}C NMR ($CDCl_3$): δ 18.7, 33.9, 35.3, 55.1, 62.9, 63.9, 64.1, 98.5. HRMS (FAB+) calcd for $C_8H_{18}NO_3$: 176.1287, found: 176.1300.

4.17. Transformation of 14 to 1

A mixture of **14** (12 mg, 0.068 mmol) and HCl in MeOH [prepared by the addition of AcCl (45 μL, 0.68 mmol) to MeOH (1 mL)] was stirred at 50 °C for 1 h. Evaporation of the organic solvent gave a crude product, which was purified by NH-silica gel column chromatography (100 mg, gradient, CH_2Cl_2 to CH_2Cl_2/MeOH = 19:1) to afford **1** as pale yellow oil. The free form was dissolved in Et_2O (1 mL) and 4 M HCl in dioxane was added to the solution. The resulting white needles were collected by filtration to afford hydrochloride **1** (12 mg, 0.057 mmol, 83%) as a white amorphous solid. The obtained compound from **14** was identical in respects (^1H NMR, ^{13}C NMR, and TLC) with **1**.

References

1. (a) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624; (b) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152; (c) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99–110; (d) Varki, A. *Glycobiology* **1993**, *3*, 97–130.
2. (a) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35–67; (b) Knapp, S. *Chem. Soc. Rev.* **1999**, *28*, 61–72.
3. Shido, K.; Kamishohara, M.; Odagawa, A.; Matsuoka, M.; Kawai, H. *J. Antibiot.* **1993**, *46*, 1076–1081.
4. Ichikawa, Y.; Osada, M.; Ohtani, I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449–1455.
5. Matsushima, Y.; Nakayama, T.; Tohyama, S.; Eguchi, T.; Kakimura, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 569–577.
6. Ono, M.; Saotome, C.; Akita, H. *Tetrahedron: Asymmetry* **1996**, *7*, 2595–2602.
7. Gololobov, Y. G. *Tetrahedron* **1992**, *48*, 1353–1406. and references cited therein.
8. Evans, D. A.; Gauchet-Prunet, J. A. *Journal. Org. Chem.* **1993**, *58*, 2446–2453.
9. Satish, N. C.; Andre, M.; Maurizio, T.; Camille-Georges, W. *Synth. Commun.* **1989**, *19*, 3139–3142.