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A versatile route to 2,4,6-trideoxy-4-aminohexoses: Stereoselective syntheses of D-vicenisamine and its epimers via iodocyclization of carbamate

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ABSTRACT

Stereoselective syntheses of the 2,4,6-trideoxy-4-amino sugar D-vicenisamine and its epimers 3-*epi*- and 4-*epi*-D-vicenisamine were accomplished via stereoselective nitrogen functional group introduction and iodocyclization of carbamate. This versatile synthetic route started from the enantiomerically pure diol obtained from ethyl sorbate by Sharpless asymmetric dihydroxylation.

1. Introduction

Sugar components, especially deoxy and deoxyamino sugars, are found in clinically important antibiotics, such as antimicrobial macrolides and antitumor antibiotics.[1] In most cases, the sugar components of these antibiotics are essential for biological activity; however, the functions of the sugar moieties have not been investigated thus far.[2] We envisaged that modification of the sugar moieties of these antibiotics could serve as a tool for investigating the significance of the corresponding sugars and their structure–activity relationships and for elucidating the biosynthetic route for antibiotics.[3] For this purpose, a versatile synthetic route for deoxy and deoxyamino sugars is highly desirable. Thus far, we have been interested in developing new synthetic routes, especially for deoxyamino sugars[4] and branched-chain sugars, such as noviose,[5] from non-sugar materials.

Vicenistatin (**1**), an antitumor antibiotic isolated from *Streptomyces* sp. HC-34, has a unique structure that includes a 20-membered macrocyclic lactam aglycone and an unprecedented deoxyamino sugar, D-vicenisamine Fig. 1.[6] A major biological characteristic of this compound is its significant inhibitory activity, especially against HL-60 (human leukemia) and COLO205 (human colon carcinoma) *in vitro* and Co-3 (human colon carcinoma) *in vivo*.[6] The entire structure of vicenistatin, including its absolute configuration, was proposed from degradation studies[6,7] and was confirmed during the course of synthetic studies toward the first total synthesis.[8]

Vicenistatin has received considerable attention because of its potential as a new anticancer drug. Similarly, the biosynthetic pathway of vicenistatin has been extensively studied.[9] Vicenistatin was also recently identified as a biologically active molecule from the National Cancer Institute (NCI) libraries using a high-throughput yeast halo assay.[10] In addition, a novel macrolactam antibiotic, sannastatin, whose structure is closely related to that of vicenistatin Fig. 1, i.e. it has the same deoxyamino sugar vicenisamine, was newly isolated, together with vicenistatin, as a growth inhibitor against brine shrimp (*Artemia salina*) larvae.[11] Recently, a total synthesis of vicenistatin was newly reported, along with its structure–activity relationship, especially for the macrolactam skeleton.[12] In this study, the vicenisamine sugar moiety was synthesized as a protected glycosyl donor using an intramolecular epoxide opening reaction via the carbamate. Further, the Tsukuba group very recently suggested that vicenistatin is a novel

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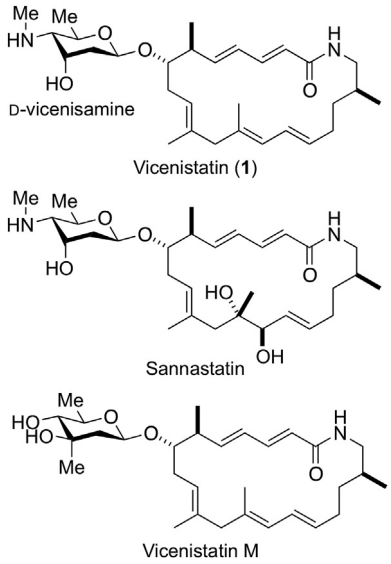


Fig. 1. Structures of vicenistatin and related compounds.

compound that induces the formation of early endosome-derived vacuole-like structures in cells by activating Rab5 and by increasing the fluidity of the membrane surface.[13]

Interestingly, instead of vicenisamine, a new congener, vicenistatin M, which contains a neutral sugar moiety, D-mycarose (2,6-dideoxy-3-*C*-methyl-D-*ribo*-hexose) Fig. 1 and shows no cytotoxicity, was isolated during the course of biosynthetic studies.[14] This finding strongly suggests that the vicenisamine amino sugar plays an important role in the cytotoxicity of vicenistatin.

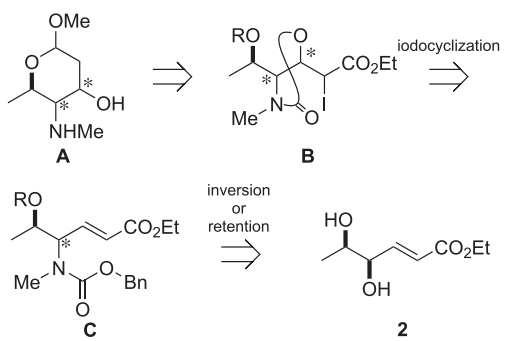
Methyl D-vicenisaminide has been previously synthesized from a sugar material,[15] a chiral epoxy alcohol,[8b] ethyl sorbate,[4a] and methyl sorbate.[16] However, practical and generic approaches for obtaining vicenisamine and its isomers are still desirable from the viewpoint of producing vicenistatin derivatives or biosynthetic tools. In our opinion, the previously reported synthetic routes are not fully satisfactory in all these respects. In this paper, we describe a versatile strategy for the synthesis of D-vicenisamine and its epimers (3-*epi*- and 4-*epi*-D-vicenisamine) starting from a chiral diol (**2**). The diol is afforded in both enantiomers by Sharpless asymmetric dihydroxylation (AD) of commercially available ethyl sorbate.

2. Results/discussion

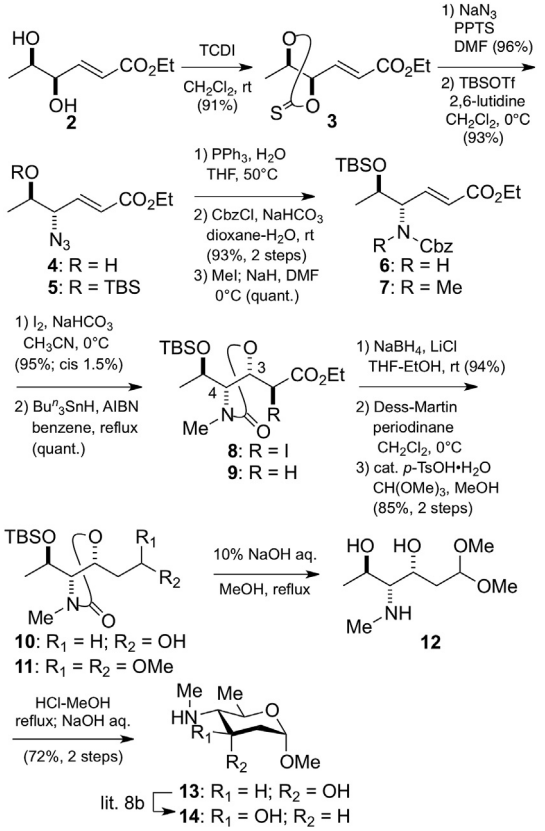
From the retrosynthetic analysis of vicenisamine and its isomers **A** Scheme 1, we assumed that oxazolidinones **B** would be a suitable precursor for deoxyamino sugars with a 3,4-aminoalcohol moiety, especially vicenisamine. Notably, oxazolidinone derivatives **B** could be prepared by iodocyclization of the carbamate based on the (*E*)-α,β-unsaturated ester moiety indigenous to the starting materials expectantly with 1,2-asymmetric induction. Moreover, carbamates **C** could be prepared, in turn, from chiral diol **2** via regioselective introduction of a nitrogen functional group with inversion or retention of the stereochemistry of the 4-hydroxy group. Evidently, both enantiomers of the starting chiral diol **2** are easily obtained by Sharpless AD.

Starting chiral diol **2**[17] was acquired in 88% yield from commercially available ethyl sorbate[18] by Sharpless AD (AD-mix β) using $(DHQD)_2PHAL$ (dihydroquinidine phthalazine) as a chiral ligand.[19] A similar chiral diol obtained from *tert*-butyl sorbate and its epimer were reported by the Kitasato group as chiral starting materials for macrosphelides.[20]

The first stage in this synthesis involved the introduction of the nitrogen functional group with inversion of the stereochemistry of the 4-hydroxy group of diol **2**. In our preliminary report,[4a] we conducted this transformation in 51% yield (three steps). Protection of the 5-hydroxy group of diol **2** with a *tert*-butyldimethylsilyl (TBS) group furnished the corresponding ether with moderate selectivity and 64% yield, along with substantial amounts of the starting diol (7%), its regioisomer (8%), and di-TBS ether (20%). Subsequent sulfonylation of the 4-hydroxy group was followed by azide ion nucleophilic displacement (80%, two steps). The enantiomeric purity of diol **2** was estimated as 93% ee by ^1H NMR analysis of the thus-obtained 5-OH mono-TBS-protected alcohol as its (+)/(−)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) ester, as described previously.[4a,4b] In this report, we successfully conducted selective transformation via a cyclic thionocarbonate in



Scheme 1. Retrosynthetic analysis of vicenisamine and its isomers.



Scheme 2. Synthesis of vicenisamine and 3-epimer from chiral diol **2**.

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excellent yield Scheme 2. Diol **2** was transformed to cyclic thionocarbonate **3** and selective nucleophilic attack by the azide ion was performed.[21] The resulting free 5-hydroxy group of compound **4** was then protected with a TBS group to afford compound **5** in 81% yield (three steps).

Among many methods for the heterofunctionalization of alkenes, iodocyclization of carbamates, so-called iodocyclocarbamation, is a well-documented method.[22] However, examples of reaction with the electron-deficient olefins are exceptional.[23] Usefully, iodocyclization of carbamates involving electron-deficient olefins has been reported to be greatly facilitated by silver triflate.[24] In an attempt to establish our strategy for synthesizing 2,4,6-trideoxy-4-amino sugars, we successfully used iodocyclization of the carbamate based on the (*E*)-α,β-unsaturated ester moiety indigenous to the starting materials Scheme 2. First, the azide group of compound **5** was effectively reduced to a primary amine by treatment with triphenylphosphine and water in THF with gentle warming (50 °C). The thus-obtained primary amine was subsequently immediately protected with a carbobenzoxy (Cbz) group, which could be used as the origin of an oxygen functional group, i.e. the 3-hydroxy group, to furnish compound **6** (93% yield, two steps). The methyl group on the amino nitrogen of vicenisamine was introduced at this point. Notably, reverse addition of sodium hydride to the substrate and excess methyl iodide afforded compound **7** in quantitative yield. Next is the iodocyclization of the carbamate to form key intermediate oxazolidinone **8** (= **B**). The reaction was performed with iodine in acetonitrile in the presence of sodium hydrogen bicarbonate, which was used to prevent removal of the TBS protecting group during the course of the reaction. However, in the absence of silver triflate, compound **7** underwent facile cyclization at 0 °C with extremely high diastereoselective formation of *trans*-product **8** in excellent yield (95%), along with a trace amount of *cis*-product **8′** (1.5%). For oxazolidinone rings, it has been reported that a large NMR coupling constant corresponds to the *cis* form and a small one to the *trans* form.[25] Therefore, the observation of a small coupling constant ($J_{H\text{-}3,4} = 2.8$ Hz) implied that compound **8** had *trans* stereochemistry. Further, the stereochemistry of *trans*-product **8** was also confirmed by a nuclear Overhauser enhancement (NOE) experiment as follows: irradiation of H-4 yielded an NOE of approximately 10% on H-2, whereas a relatively small NOE (3%) was observed on H-3. The stereoselectivity of this cyclization reaction can be explained using the transition state (TS) models Fig. 2. Owing to steric hindrance between the side chain R and the alkenyl group, the *cis*-TS model is obviously less favorable than the *trans*-TS model. Therefore, the cyclization reaction is thought to proceed through the *trans*-TS model to give the *trans*-oxazolidinone product, i.e. *trans*-product **8**.[25]

The final manipulation in this work was transformation to the intermediate compound for vicenisamine synthesis. For this purpose, reductive deiodination of compound **8** was conducted with tri-*n*-butyltin hydride in the presence of 2,2′-azobis(isobutyronitrile) (AIBN) in boiling benzene to afford compound **9** in quantitative yield. Next, reduction of the ester group of compound **9** was readily realized using sodium borohydride with lithium chloride to give alcohol **10** in 94% yield. Thus-obtained primary alcohol **10** was oxidized using Dess–Martin periodinane to furnish the corresponding aldehyde, which was subsequently treated with *p*-toluenesulfonic acid (*p*-TsOH) in MeOH in the presence of methyl orthoformate to afford crystalline dimethyl acetal **11** (85% yield, two steps). Finally, the TBS protective group and cyclic carbonate group of acetal **11** were removed by alkaline hydrolysis with refluxing NaOH in H_2O/MeOH to furnish corresponding aminodiol **12**. Compound **12** was subsequently reacted with HCl-MeOH to afford methyl 3-*epi*-D-vicenisaminide **13** (72% yield, two steps). The spectral data (^{1}H and ^{13}C NMR, IR) of **13** derived from chiral diol **2** were identical to those previously reported.[8b] Present synthetic scheme was started from the readily available chiral starting material **2** and, the total yield (41%) was satisfactorily improved than that of previous report (15%).[8b] The transformation of compound **13** to methyl D-vicenisaminide **14** was also reported.[8b]

After establishing a synthetic strategy for synthesizing D-vicenisamine and its 3-epimer, the synthesis of another diastereomer, 4-*epi*-D-vicenisamine, was performed Scheme 3. Starting chiral diol **2** was transformed to cyclic carbonate **15**[17c] in 93% yield and then submitted to a subsequent azide substitution reaction with retention of the stereochemistry. For this purpose, Pd(0)-catalyzed stereospecific azidation[26] was effectively carried out in the presence of tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, in degassed wet THF to give compound **16** in 77% yield. The mechanism involving S_N2 nucleophilic displacement of the leaving group (cyclic carbonate) by Pd(0) followed by a second displacement of Pd by the nucleophilic nitrogen of azide is commonly known as the palladium-mediated double inversion process. Silica gel chromatography afforded azide alcohol **16** as an approximately 10:1 mixture with its (4*S*,5*S*)-epimer **4**. As chromatographic separation of **16** and **4** was not possible at this stage, the subsequent reactions

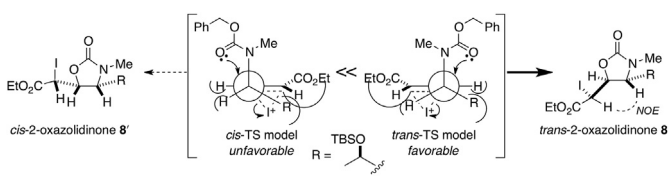
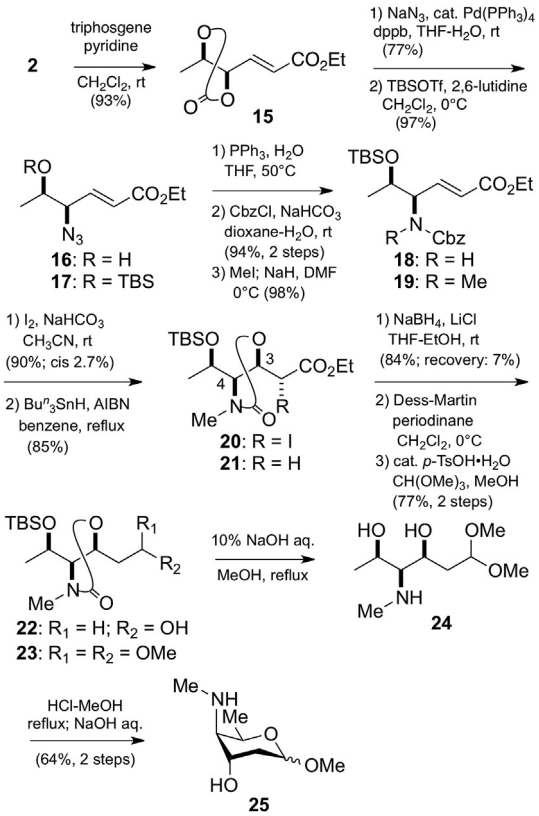


Fig. 2. Proposed transition state models for iodocyclization of carbamate **7**.



Scheme 3. Synthesis of 4-*epi*-vicenisamine from chiral diol **2**.

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were carried out using this mixture.

From intermediate azide alcohol **16**, the successive transformations to methyl 2,4,6-trideoxy-4-methylamino-D-*xylo*-hexopyranoside, i.e. methyl 4-*epi*-D-vicenisaminide **25** Scheme 3, were essentially the same as those used in the synthesis of D-vicenisamine and its 3-epimer Scheme 2. The hydroxy group of compound **16** was protected by a TBS group, and the azide group of resulting compound **17** was transformed to a Cbz-protected amino group to give compound **18** (94% yield, two steps). Subsequent *N*-methylation afforded compound **19** in 98% yield. The key iodocyclocarbamation reaction was also performed with iodine in acetonitrile in the presence of sodium hydrogen bicarbonate; however, unlike for compound **7**, in this case, the reaction did not proceed substantially at 0 °C. However, although addition of silver triflate[24] certainly hastened the reaction, it was not effective in this case because the reaction proceeded with substantial degradation. Instead, the reaction was performed at r.t. for several days to afford the cyclized product with high diastereoselectivity and excellent yield (*trans*-**20**: 90%; *cis*-**20**′: 2.7%). This reaction might have proceeded slowly because the steric hindrance between the side chain R and the alkenyl group in the *cis*-TS model of compound **19** is thought to be smaller than that in compound **7**.

Reductive deiodination of compound **19** afforded ethyl ester **21**, which was then reduced to alcohol **22** in 84% yield with recovery of the starting ester (7%). Chromatographic separation of the isomer derived from the Pd-catalyzed azidation was fully realized at this stage. Thus-obtained pure alcohol **22** was oxidized to the corresponding aldehyde, which was then transformed to crystalline dimethyl acetal **23** by treatment with a catalytic amount of *p*-TsOH in MeOH in the presence of methyl orthoformate (77% yield, two steps). Alkaline hydrolysis of the cyclic carbonate group and the TBS protective group of compound **23** gave corresponding aminodiol **24**, which is a previously unknown compound. Reaction with HCl-MeOH led to methyl 4-*epi*-D-vicenisaminide **25** as an anomeric mixture. Notably, before the isolation of vicenistatin, the synthesis of methyl 2,4,6-trideoxy-4-methylamino-L-*xylo*-hexopyranoside (methyl 4-*epi*-L-vicenisaminide, the antipode of **25**) from 3,4-di-*O*-Ac-L-rhamnal (3,4-di-*O*-acetyl-6-deoxy-L-glucal) was reported.[27] The spectral data (^{1}H and ^{13}C NMR) of **25** derived from chiral diol **2** were identical to those of this previously reported compound.[27]

3. Conclusion

In conclusion, we successfully realized the syntheses of D-vicenisamine and its epimers (3-*epi*- and 4-*epi*-D-vicenisamine) by using stereoselective nitrogen functional group introduction and iodocyclization of carbamates as the key reactions. Our synthetic strategy is simple and easy to operate and superior to the previous ones in accessibility to the isomers from the same starting material without using Mitsunobu inversion. Thus, our versatile synthetic strategy is generally applicable to the synthesis of 2,4,6-trideoxy-4-amino sugars. Furthermore, in addition to these types of amino sugars, our strategy also has the potential to be applicable to other types of molecules with amino alcohol moieties in the structure. For example, the importance of the 1,2-aminoalcohol motif in synthetic chemistry is illustrated by its occurrence in a vast range of natural products and other biologically active compounds.[28]

4. Experimental section

4.1. General

All mps are uncorrected. NMR spectra were recorded on a JEOL GSX-270 spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were reported in δ-values based on internal tetramethylsilane ($\delta_H = 0$), or solvent signal ($CDCl_3$ δ_C = 77.0) as reference. IR spectra were recorded on a HORIBA FT-720 Fourier-transform infrared spectrometer. Optical rotations were measured on a Rudolph Research Analytical AUTOPOL V polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured on a Shimadzu LCMS-IT-TOF mass spectrometer. Flash silica gel column chromatography was carried out on KANTO CHEMICAL CO., INC. Silica Gel 60 N (spherical, neutral, 40–50 mm).

4.2. Ethyl (2E,4R,5R)-4,5-dihydroxyhex-2-enoate *2*

The mixture of AD-mix-β {9.93 g, containing with $K_3Fe(CN)_6$ (6.95 g, 21.1 mmol), K_2CO_3 (2.92 g, 21.1 mmol), $(DHQD)_2$-PHAL (52.7 mg, 0.0676 mmol), and $K_2OsO_4 \cdot H_2O$ (10.9 mg, 0.0295 mmol)} and $MeSO_2NH_2$ (0.85 g, 8.9 mmol) in *t*-BuOH (36 mL) and H_2O (36 mL) was stirred at r.t. for 15 min. The resulting clear solution was then cooled to 0 °C. To this solution was added ethyl sorbate (1.00 g, 7.13 mmol) in *t*-BuOH (1 mL). The reaction mixture was stirred at 0 °C for ca. 24 hr. The reaction was quenched with sodium sulfite (4.77 g, 37.8 mmol) and the mixture was stirred at r.t. for 1 h. The mixture was extracted with EtOAc (150 mL, 2 × 50 mL) and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane: EtOAc = 3: 2 to 1: 1) to give the diol **2** (1.09 g; 88% yield) as a colorless oil. A small amount of less polar regioisomer **2**′(Ethyl (4*E*,2*S*,3*R*)-2,3-dihydroxyhex-4-enoate) was also obtained in pure form.

diol **2**: colorless oil; $[\alpha]_D^{27.2}$ + 64.7° (*c* 1.45, EtOH) {lit. 17(b) $[\alpha]_D^{24}$ + 64.0° (*c* 1.10, EtOH); lit. 17(c) $[\alpha]_D$ + 63.0° (*c* 1.0, EtOH)}; ν_{max} (neat)/cm^{-1} 3402, 2981, 1705, 1658, 1369, 1309, 1282, 1182, 1036 and 985; δ_H (270 MHz, $CDCl_3$) 6.92 (dd, *J* = 5.1, 15.8 Hz, 1 H), 6.15 (dd, *J* = 1.7, 15.8 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.07 (ddd, *J* = 1.4, 4.9, 6.3 Hz, 1 H), 3.73 (ddq, *J* = 4.2, 6.3, 6.3 Hz, 1 H), 2.70 (br. d, *J* = 4.7 Hz, 1 H), 2.41 (br. d, *J* = 4.1 Hz, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H) and 1.25 (d, *J* = 6.4 Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$) 166.4, 146.5, 122.5, 75.6, 70.2, 60.6, 19.0 and 14.1.

diol **2**′:colorless oil; $[\alpha]_D^{27.7}$ + 22.7° (*c* 1.57, EtOH); ν_{max} (neat)/cm^{-1} 3435, 2983, 1736, 1446, 1271, 1207, 1097, 1032 and 968; δ_H (270 MHz, $CDCl_3$) 5.82 (ddq, *J* = 1.0, 6.4, 15.4 Hz, 1 H), 5.64 (ddq, *J* = 1.5, 6.6, 15.4 Hz, 1 H), 4.40–4.32 (m, 1H), 4.29 (q, *J* = 7.2 Hz, 2 H), 4.13 (dd, *J* = 2.8, 5.8 Hz, 1 H), 3.13 (br. d, *J* = 6.0 Hz, 1 H), 2.28 (br. d, *J* = 7.1 Hz, 1 H), 1.74 (ddd, *J* = 0.6, 1.5, 6.4 Hz, 3 H) and 1.32 (t, *J* = 7.2 Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$) 172.9, 129.3, 129.2, 73.8, 73.4, 62.1, 17.8 and 14.1; Anal. Calcd for: $C_8H_{14}O_4$: C 55.16; H 8.10. Found: C 54.98; H 8.30%.

4.3. Ethyl (E)-3-((4R,5R)-5-methyl-2-thioxo-1,3-dioxolan-4-yl) acrylate *3*

To a solution of the diol **2** (217 mg, 1.25 mmol) in anhydrous CH_2Cl_2 (5.5 mL) was added 1,1′-thiocarbonyldiimidazole (TCDI) (362 mg, 2.03 mmol) and DMAP (25.3 mg, 0.207 mmol). The reaction mixture was stirred at r.t. for ca. 2.5 h. The mixture was directly purified by flash column chromatography on silica gel (hexane: EtOAc = 1: 1) to give the cyclic thionocarbonate **3** (243.9 mg; 91% yield).

Colorless oil; $[\alpha]_D^{22.6}$–7.97° (*c* 0.605, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2983, 1720, 1367, 1346, 1311, 1273, 1188, 1038 and 978; δ_H (270 MHz, $CDCl_3$) 6.84 (dd, *J* = 6.1, 15.7 Hz, 1 H), 6.22 (dd, *J* = 1.4, 15.7 Hz, 1 H), 4.96 (ddd, *J* = 1.4, 6.0, 8.0 Hz, 1 H), 4.71 (dq, *J* = 6.3, 8.0 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 1.59 (d, *J* = 6.2 Hz, 3 H) and 1.31 (t, *J* = 7.2 Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$) 190.4, 164.6, 137.4, 126.2, 85.5, 82.6, 61.3, 17.9 and 14.1; Anal. Calcd for: $C_9H_{12}O_4S$: C 49.99; H 5.59. Found: C 49.93; H 5.60%.

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4.4. Ethyl (2E,4S,5R)-4-azide-5-hydroxyhex-2-enoate **4**

To an ice-cooled solution of the cyclic thionocarbonate **3** (243.9 mg, 1.13 mmol) in anhydrous DMF (8.0 mL) was added sodium azide (248.7 mg, 3.83 mmol) and PPTS (579.5 mg, 2.31 mmol). The reaction mixture was allowed to warm to r.t. and stirred for ca. 5 hr. The mixture was poured into H_2O (20 mL) and extracted with EtOAc (2 × 50 mL) and the combined extracts were washed successively with sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 3: 2) to give the azide **4** (214.8 mg; 96% yield).

Colorless oil; $[\alpha]_D^{22.3}$ + 55.1° (*c* 0.950, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3450, 2981, 2104, 1718, 1658, 1369, 1269, 1180, 1038 and 984; δ_H (270 MHz, $CDCl_3$) 6.83 (dd, *J* = 7.4, 15.7 Hz, 1 H), 6.11 (dd, *J* = 1.2, 15.7 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.94 (ddd, *J* = 1.1, 6.4, 7.5 Hz, 1 H), 3.77 (dq, *J* = 4.5, 6.3 Hz, 1 H), 2.39 (br. d, *J* = 4.7 Hz, 1 H), 1.32 (t, *J* = 7.2 Hz, 3 H) and 1.23 (d, *J* = 6.4 Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$), 165.4, 141.0, 125.3, 69.3, 69.0, 60.9, 19.4 and 14.1; HRMS (ESI-TOF) calcd for: $C_8H_{14}N_3O_3$ $[M+H]^+$: 200.1029, found: 200.1055.

4.5. Ethyl (2E,4S,5R)-4-azide-5-tert-butyldimethylsilyloxyhex-2-enoate **5**

To an ice-cooled solution of the alcohol **4** (214.8 mg, 1.08 mmol) in anhydrous CH_2Cl_2 (7.0 mL) was sequentially added 2,6-lutidine (650 μL, 5.58 mmol) and TBSOTf (400 μL, 1.74 mmol). The reaction mixture was stirred at 0 °C for ca. 45 min. The mixture was poured into H_2O (20 mL) and extracted with EtOAc (50 mL) and the extract was washed successively with 0.5 M HCl, sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane: EtOAc = 20: 1) to give the TBS ether **5** (314.8 mg; 93% yield).

Colorless oil; $[\alpha]_D^{29.2}$ + 7.8° (*c* 0.44, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2956, 2931, 2104, 1724, 1658, 1257, 1178, 1097, 1041, 987, 837 and 777; δ_H (270 MHz, $CDCl_3$) 6.80 (dd, *J* = 6.2, 15.6 Hz, 1 H), 6.05 (dd, *J* = 1.3, 15.6 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.99 (ddd, *J* = 1.5, 4.5, 6.2 Hz, 1 H), 3.92 (dq, *J* = 4.6, 6.1 Hz, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H), 0.89 (s, 9 H) and 0.08 (s, 6 H); δ_C (67.8 MHz, $CDCl_3$) 166.5, 141.9, 124.3, 70.8, 68.1, 60.6, 25.7, 19.4, 17.9, 14.2, −4.6 and −4.9; Anal. Calcd for: $C_{14}H_{27}N_3O_3Si$: C 53.64; H 8.68; N 13.40. Found: C 53.91; H 8.64; N 13.32%.

4.6. Ethyl (2E,4S,5R)-4-N-benzyloxycarbonylamino-5-tert-butyldimethylsilyloxyhex-2-enoate **6**

To a solution of the azide **5** (247.1 mg, 0.788 mmol) in THF (9.0 mL) was added triphenylphosphine (531 mg, 2.02 mmol) and H_2O (3.0 mL). The reaction mixture was stirred at 55 °C for ca. 22 hr. The mixture was diluted with EtOAc and dried ($MgSO_4$) and concentrated *in vacuo*. To an ice-cooled solution of the residue in 1,4-dioxane (22 mL) and H_2O (4.5 mL) was added successively $NaHCO_3$ (1.13 g, 13.5 mmol) and CbzCl (281.4 μL, 1.97 mmol). The reaction mixture was stirred at 0 °C for ca. 1 hr. To the mixture was added ice water and the mixture was allowed to warm to r.t. The whole mixture was extracted with EtOAc (2 × 50 mL) and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 5: 1) to give the compound **6** (307.9 mg; 93% yield in 2 steps) as a colorless solid. Analytical pure sample was obtained by recrystallization from hexane.

Colorless prism; mp 65.3–66.0 °C; $[\alpha]_D^{24.0}$ + 2.59° (*c* 0.580, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3373, 2958, 2929, 1716, 1697, 1657, 1525, 1373, 1263, 1186, 1149, 1097, 1045, 1005, 993, 837, 773, 756, 696 and 500; δ_H (270 MHz, $CDCl_3$) 7.51–7.35 (m, 5H), 6.91 (dd, *J* = 6.7, 15.7 Hz, 1 H), 5.97 (d, *J* = 15.8 Hz, 1 H), 5.12 (d, *J* = 12.2 Hz, 1 H), 5.09 (d, *J* = 12.2 Hz, 1 H), 5.07 (br. s, 1H), 4.30–4.16 (m, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.97 (br. dq, *J* = 4.0, 6.1 Hz, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H) and 0.06 (s, 6 H); δ_C (67.8 MHz, $CDCl_3$) 166.0, 155.6, 143.6, 136.3, 128.5, 128.1, 128.0, 123.4, 70.0, 66.9, 60.4, 57.7, 25.7, 20.3, 17.9, 14.2, −4.4 and −5.0; Anal. Calcd for: $C_{22}H_{35}NO_5Si$: C 62.67; H 8.37; N 3.32. Found: C 62.92; H 8.40; N 3.42%.

4.7. Ethyl (2E,4S,5R)-4-N-benzyloxycarbonyl-N-methylamino-5-tert-butyldimethylsilyloxyhex-2-enoate **7**

To an ice-cooled solution of the compound **6** (280.7 mg, 1.08 mmol) in anhydrous DMF (17 mL) was added successively MeI (830 μL, 13.3 mmol) and NaH (55% mineral oil suspension; 35.4 mg, 0.811 mmol). The reaction mixture was stirred at 0 °C for ca. 45 min. The reaction was quenched by the addition of sat. aq NH_4Cl and crushed ice and the mixture was extracted with EtOAc (2 × 100 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 4: 1) to give the carbamate **7** (288.7 mg; quantitative yield).

Colorless oil; $[\alpha]_D^{24.4}$–12.4° (*c* 0.660, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2956, 2931, 1718, 1705, 1657, 1473, 1398, 1304, 1257, 1178, 1147, 1092, 1041, 985, 835, 777 and 698; δ_H (270 MHz, $CDCl_3$) for major rotamer 7.42–7.23 (m, 5H), 7.11 (dd, *J* = 6.0, 15.6 Hz, 1 H), 5.88 (d, *J* = 15.6 Hz, 1 H), 5.15 (s, 2H), 4.47 (br. dd, *J* = 6.7, 6.7 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.04 (br. dq, *J* = 6.5, 6.5 Hz, 1 H), 2.85 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 3H) and 0.05 (s, 3H); for minor rotamer 7.42–7.23 (m, 5H), 7.07 (dd, *J* = 6.0, 15.8 Hz, 1 H), 5.83 (d, *J* = 15.2 Hz, 1 H), 5.15 (s, 2H), 4.31 (br. dd, *J* = 6.6, 6.6 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.93 (br. dq, *J* = 6.6, 6.6 Hz, 1 H), 2.85 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 3H) and 0.02 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$) 166.1, 156.4, 156.2, 143.8, 143.4, 136.6, 136.4, 128.5, 128.0, 127.8, 123.7, 123.2, 68.6, 68.5, 67.5, 67.3, 63.8, 63.5, 60.4, 31.8, 31.6, 25.7, 21.2, 17.9, 14.2, −4.2 and −4.9; Anal. Calcd for: $C_{23}H_{37}NO_5Si$: C 63.41; H 8.56; N 3.22. Found: C 63.77; H 8.60; N 3.23%.

4.8. Ethyl (S)-2-((4S,5S)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-3-methyl-2-oxooxazolidin-5-yl)-2-iodoacetate trans-**8** and Ethyl (R)-2-((4S,5R)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-3-methyl-2-oxooxazolidin-5-yl)-2-iodoacetate cis-**8′**

To an ice-cooled solution of the carbamate **7** (288.7 mg, 0.663 mmol) and $NaHCO_3$ (7.03 g, 83.7 mmol) in anhydrous CH_3CN (34 mL) was added iodine (535 mg, 2.11 mmol). The reaction mixture was stirred at 0 °C for 2 days. The reaction was quenched by the addition of 10% aq $Na_2S_2O_3$ and the mixture was allowed to warm to r.t. The resulting mixture was extracted with EtOAc (2 × 100 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 3: 1) to give the cyclic carbamate *trans*-**8** (297.3 mg; 95% yield) along with a small amount of the less polar *cis*-**8′** (4.8 mg; 1.5% yield).

trans-**8**: colorless oil; $[\alpha]_D^{23.3}$–18.2° (*c* 0.695, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2956, 2929, 1766, 1745, 1435, 1375, 1255, 1236, 1120, 1020, 987, 837 and 777; δ_H (270 MHz, $CDCl_3$) 4.47 (dd, *J* = 2.8, 8.5 Hz, 1 H), 4.38 (d, *J* = 8.8 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 4.06 (dq, *J* = 1.6, 6.4 Hz, 1 H), 3.54 (dq, *J* = 1.9, 2.8 Hz, 1 H), 2.95 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.094 (s, 3 H) and 0.087 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$) 168.6, 156.8, 74.0, 67.9, 67.0, 62.5, 30.3, 25.6, 23.0, 18.2, 17.7, 13.7, −4.5 and −4.9; Anal. Calcd for: $C_{16}H_{30}INO_5Si$: C 40.77; H 6.41; N 2.97. Found: C 40.95; H 6.44; N

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2.81%.

cis-**8′**: colorless oil; δ_H (270 MHz, $CDCl_3$) 4.97 (dd, $J = 7.3, 12.0$ Hz, 1 H), 4.29 (q, $J = 6.1$ Hz, 1 H), 4.25 (q, $J = 7.0$ Hz, 2 H), 4.20 (d, $J = 12.0$ Hz, 1 H), 3.83 (d, $J = 7.3$ Hz, 1 H), 3.05 (s, 3 H), 1.29 (t, $J = 7.2$ Hz, 3 H), 1.19 (d, $J = 6.2$ Hz, 3 H), 0.90 (s, 9 H), 0.14 (s, 3 H) and 0.11 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 168.1, 157.1, 76.5, 67.3, 64.5, 62.7, 31.9, 25.6, 19.1, 17,7, 14.4, 13.6, −4.6 and −4.7.

4.9. Ethyl 2-((4S,5R)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-3-methyl-2-oxooxazolidin-5-yl)acetate **9**

To a solution of the compound **8** (480.9 mg, 1.02 mmol) in anhydrous benzene (28 mL) was added AIBN (188 mg, 1.14 mmol) and tri-*n*-butyltin hydride (560 μL, 2.08 mmol). The reaction mixture was refluxed for ca. 1.5 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 5: 2) to give the compound **9** (353.0 mg; quantitative yield).

Colorless oil; $[\alpha]_D^{22.4}$ + 16.5° (*c* 0.530, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2956, 2929, 1765, 1743, 1437, 1406, 1377, 1254, 1184, 1149, 1084, 1030, 837 and 777; δ_H (270 MHz, $CDCl_3$) 4.65 (ddd, $J = 3.9, 6.0, 6.7$ Hz, 1 H), 4.17 (q, $J = 7.1$ Hz, 2 H), 4.03 (dq, $J = 1.7, 6.4$ Hz, 1 H), 3.34 (dd, $J = 1.8, 3.7$ Hz, 1 H), 2.73 (dd, $J = 5.8, 16.0$ Hz, 1 H), 2.65 (dd, $J = 7.2, 15.9$ Hz, 1 H), 1.28 (t, $J = 7.2$ Hz, 3 H), 1.13 (d, $J = 6.4$ Hz, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H) and 0.06 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 169.3, 157.6, 70.3, 67.5, 66.8, 61.1, 40.1, 30.1, 25.6, 18.3, 17.7, 14.1, −4.4 and −5.1; Anal. Calcd for: $C_{16}H_{31}NO_5Si$: C 55.62; H 9.04; N 4.05. Found: C 55.48; H 8.98; N 4.17%.

4.10. (4S,5R)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-5-(2-hydroxyethyl)-3-methyloxazolidin-2-one **10**

To a solution of the compound **9** (333.0 mg, 1.08 mmol) in anhydrous THF (8.5 mL) and EtOH (17 mL) was added successively LiCl (240 mg, 5.66 mmol) and $NaBH_4$ (215 mg, 5.68 mmol). The reaction mixture was stirred at r.t. for ca. 4.5 h. The reaction was quenched by the addition of acetone (4.0 mL). The mixture was diluted with CH_2Cl_2 (250 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 1: 5) to give the alcohol **10** (273.8 mg; 94% yield). Analytical pure sample was obtained by recrystallization from hexane-EtOAc at 4 °C.

Colorless flake; mp 106.5–108.0 °C; $[\alpha]_D^{23.3}$ + 39.7° (*c* 0.540, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3410, 2954, 2929, 1726, 1471, 1464, 1441, 1414, 1373, 1362, 1255, 1225, 1142, 1090, 1070, 1045, 982, 951, 914, 841, 777, 764 and 501; δ_H (270 MHz, $CDCl_3$) 4.52 (ddd, $J = 4.4, 4.4, 8.8$ Hz, 1 H), 3.99 (dq, $J = 1.8, 6.4$ Hz, 1 H), 3.90–3.79 (m, 2 H), 3.26 (dd, $J = 1.7, 4.5$ Hz, 1 H), 2.90 (s, 3 H), 2.01–1.75 (m, 2 H), 1.71 (br. s, 1 H), 1.14 (d, $J = 6.4$ Hz, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H) and 0.06 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 158.0, 71.9, 68.2, 66.4, 58.7, 38.6, 29.9, 25.6, 18.5, 17.8, −4.3 and −5.0; Anal. Calcd for: $C_{14}H_{29}NO_4Si$: C 55.41; H 9.63; N4.62. Found: C 55.29; H 9.51; N 4.40%.

4.11. (4S,5R)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-5-(2,2-dimethoxyethyl)-3-methyloxazolidin-2-one **11**

To an ice-cooled solution of the alcohol **10** (153.7 mg, 0.506 mmol) in anhydrous CH_2Cl_2 (6.0 mL) was added Dess-Martin periodinane (520 mg, 1.22 mmol). The reaction mixture was stirred at r.t. for ca. 1.5 h. The reaction was quenched by the addition of 10% aq $Na_2S_2O_3$ and the mixture was allowed to warm to r.t. and stirred for 0.5 h. The resulting mixture was extracted with EtOAc (2 × 50 mL). The combined extracts were washed successively with sat. aq $NaHCO_3$ + 10% aq $Na_2S_2O_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. To the solution of the residual aldehyde in MeOH (9.0 mL) was added successively $CH(OMe)_3$ (560 μL, 5.11 mmol) and *p*-TsOH·H_2O (26.1 mg, 0.137 mmol). The reaction mixture was stirred at r.t. for ca. 2 hr. The reaction was quenched by the addition of $NaHCO_3$ (2.5 g, 30 mmol). The mixture was diluted with EtOAc (150 mL), filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 1: 1) to give the acetal **11** (149.2 mg; 85% yield in 2 steps). Analytical pure sample was obtained by recrystallization from hexane.

Colorless prism; mp 50.2–51.5 °C; $[\alpha]_D^{28.3}$ + 51.5° (*c* 0.710, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2958, 2925, 1755, 1736, 1450, 1408, 1261, 1157, 1124, 1099, 1061, 1039, 1011, 958, 945, 904, 837, 781 and 760; δ_H (270 MHz, $CDCl_3$) 4.56 (dd, $J = 3.8, 7.3$ Hz, 1 H), 4.43 (ddd, $J = 4.4, 4.4, 8.7$ Hz, 1 H), 3.96 (dq, $J = 1.9, 6.3$ Hz, 1 H), 3.41 (s, 3 H), 3.35 (s, 3 H), 3.27 (dd, $J = 1.8, 4.4$ Hz, 1 H), 2.90 (s, 3 H), 1.97 (ddd, $J = 3.8, 8.3, 14.1$ Hz, 1 H), 1.85 (ddd, $J = 4.9, 7.3, 14.2$ Hz, 1 H), 1.11 (d, $J = 6.2$ Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H) and 0.05 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 158.0, 101.9, 71.0, 68.0, 66.5, 54.7, 53.6, 39.6, 30.0, 25.6, 18.3, 17.8, −4.4 and −5.0; Anal. Calcd for: $C_{16}H_{33}NO_5Si$: C 55.30; H 9.57; N 4.03. Found: C 55.13; H 9.49; N 3.84%.

4.12. (2R,3R,4R)-6,6-dimethoxy-3-(methylamino)hexane-2,4-diol **12**

A solution of **11** (80.0 mg, 0.230 mmol) in MeOH (7 mL) and 10% aq. NaOH (4.2 mL, 10.5 mmol) was gently refluxed for 17 h. The reaction mixture was cooled, and concentrated *in vacuo*. The residue was dissolved in a minimum amount of water and extracted with EtOAc (5 × 10 mL). The combined organic extract was dried ($MgSO_4$), and concentrated *in vacuo*. Thus obtained amino diol **12** (47.7 mg, quantitative) was sufficiently pure for spectrometric analysis and the most part (41.3 mg) was used for the next reaction.

Colorless oil; $[\alpha]_D^{28.4}$–3.43° (*c* 0.530, $CHCl_3$) {lit. 8(b) $[\alpha]_D^{24}$ − 3.3° (*c* 1.06, $CHCl_3$)}; ν_{max} (neat)/cm^{-1} 3406, 3356, 2962, 2933, 1738, 1572, 1448, 1385, 1375, 1242, 1192, 1124, 1057, 966, 916 and 820; δ_H (270 MHz, $CDCl_3$) 4.60 (dd, $J = 5.0, 5.9$ Hz, 1 H), 4.12 (ddd, $J = 2.9, 2.9, 9.6$ Hz, 1 H), 4.02 (dq, $J = 4.0, 6.6$ Hz, 1 H), 3.45 (br. s, 3H), 3.38 (s, 6 H), 2.52 (s, 3 H), 2.21 (dd, $J = 2.9, 4.0$ Hz, 1 H), 1.98 (ddd, $J = 4.9, 9.5, 14.3$ Hz, 1 H), 1.74 (ddd, $J = 2.9, 6.0, 14.2$ Hz, 1 H) and 1.26 (d, $J = 6.4$ Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$)103.5, 67.3, 67.1, 66.9, 53.7, 53.4, 37.5, 35.5 and 19.9; HRMS (ESI-TOF) calcd for: $C_9H_{22}NO_4$ $[M+H]^+$: 208.15488, found: 208.1565.

4.13. Methyl 2,4,6-trideoxy-4-methylamino-α-D-arabino-hexopyranoside (methyl 3-epi-D-vicenisaminide) **13**

To an HCl-MeOH solution, which had been prepared by adding AcCl (0.120 mL, 1.69 mmol) to ice-cooled dry MeOH (1.2 mL), was added a solution of **12** (41.3 mg, 0.199 mmol) in anhydrous MeOH (1.2 mL) at 0 °C and the reaction mixture was refluxed for 2 h. After the addition of 2 M NaOH (1.25 mL, 2.50 mmol) at 0 °C, the mixture diluted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography (EtOAc-MeOH, 6: 1 to 4: 1) to afford **13** (25.2 mg, 72%, 2 steps).

Colorless oil; $[\alpha]_D^{27.1}$ + 122° (*c* 0.690, $CHCl_3$) {lit. 8(b) $[\alpha]_D^{19}$ + 123° (*c* 1.05, $CHCl_3$)}; ν_{max} (neat)/cm^{-1} 3333, 2933, 2900, 1446, 1379, 1215, 1192, 1126, 1105, 1049, 972, 908 and 756; δ_H (270 MHz, $CDCl_3$) 4.75 (br. d, $J = 3.4$ Hz, 1 H), 3.81 (ddd, $J = 5.1, 9.9, 11.3$ Hz, 1 H), 3.70 (dq, $J = 6.2, 9.8$ Hz, 1 H), 3.32 (s, 3 H), 2.48 (s, 3 H), 2.29 (br. s, 2 H), 2.19 (ddd, $J = 1.2, 5.0, 12.8$ Hz, 1 H), 2.06 (dd, $J = 9.8, 9.8$ Hz, 1 H), 1.66 (ddd, $J = 3.7, 11.4, 12.8$ Hz, 1 H), 1.30 (d, $J = 6.2$ Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$) 98.6, 67.8, 66.9, 65.5, 54.6, 37.9, 33.2 and 18.6.

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4.14. Ethyl (E)-3-((4R,5R)-5-methyl-2-oxo-1,3-dioxolan-4-yl) acrylate **15**

To an ice-cooled solution of the diol **2** (522 mg, 2.99 mmol) in anhydrous CH_2Cl_2 (4.5 mL) and pyridine (1.8 mL) was added dropwise triphosgene (451 mg, 1.52 mmol) in anhydrous CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at 0 °C for ca. 2 hr. The reaction mixture was poured into ice-cooled sat. aq NH_4Cl and the mixture was extracted with EtOAc (2 × 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 3: 2) to give the known cyclic carbonate **15** (556 mg; 93% yield).

Colorless oil; $[\alpha]_D^{29.9}$ + 18.2° (*c* 0.850, $CHCl_3$) {lit. 17(c) $[\alpha]_D^{23.8}$ + 23.8° (*c* 1.03, CH_2Cl_2)}; ν_{max} (neat)/cm^{-1} 2985, 1809, 1716, 1666, 1369, 1304, 1273, 1188, 1076, 1034, 980 and 773; δ_H (270 MHz, $CDCl_3$) 6.84 (dd, *J* = 5.7, 15.7 Hz, 1 H), 6.20 (dd, *J* = 1.4, 15.7 Hz, 1 H), 4.77 (ddd, *J* = 1.4, 5.8, 7.4 Hz, 1 H), 4.50 (dq, *J* = 6.2, 7.5 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 1.54 (d, *J* = 6.4 Hz, 3 H) and 1.31 (t, *J* = 7.2 Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$) 164.8, 153.5, 138.6, 125.2, 81.3, 77.8, 61.2, 18.4 and 14.1.

4.15. Ethyl (2E,4R,5R)-4-azide-5-hydroxyhex-2-enoate **16**

To a solution of the carbonate **15** (294.4 mg, 1.47 mmol) and sodium azide (161 mg, 2.48 mmol) in degassed THF (14 mL) and H_2O (1.4 mL) was added tris(triphenylphosphine)palladium (173 mg, 0.150 mmol). The reaction mixture was stirred at 45 °C for ca. 45 min. The reaction mixture was poured into H_2O and the mixture was extracted with EtOAc (2 × 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 5: 2) to give the azide alcohol **16** (225.9 mg; 77% yield), containing inseparable diastereomer **4** as by-product. This was used for the next reaction without further purification.

Colorless oil; ν_{max} (neat)/cm^{-1} 3450, 2981, 2104, 1718, 1658, 1369, 1269, 1180, 1038 and 984; δ_H (270 MHz, $CDCl_3$) 6.83 (dd, *J* = 7.4, 15.7 Hz, 1 H), 6.11 (dd, *J* = 1.2, 15.7 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.94 (ddd, *J* = 1.1, 6.4, 7.5 Hz, 1 H), 3.77 (dq, *J* = 4.5, 6.3 Hz, 1 H), 2.39 (br. d, *J* = 4.7 Hz, 1 H), 1.32 (t, *J* = 7.2 Hz, 3 H) and 1.23 (d, *J* = 6.4 Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$), 165.4, 141.0, 125.3, 69.3, 69.0, 60.9, 19.4 and 14.1.

4.16. Ethyl (2E,4R,5R)-4-azide-5-tert-butyldimethylsilyloxyhex-2-enoate **17**

In the same procedure as described in the synthesis of the TBS ether **5**, the alcohol **16** (365.2 mg, 1.83 mmol) was silylated in anhydrous CH_2Cl_2 to give the TBS ether **17** (556.2 mg, 97%) as a colorless oil.

Colorless oil; ν_{max} (neat)/cm^{-1} 2956, 2931, 2858, 2104, 1724, 1660, 1257, 1178, 1134, 1092, 837 and 777; δ_H (270 MHz, $CDCl_3$) 6.86 (dd, *J* = 6.3, 15.7 Hz, 1 H), 6.07 (dd, *J* = 1.4, 15.7 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.88 (dq, *J* = 5.6, 6.1 Hz, 1 H), 3.81 (ddd, *J* = 1.4, 5.4, 6.4 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.19 (d, *J* = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H) and 0.09 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 165.6, 142.2, 124.2, 70.8, 68.0, 60.6, 25.7, 20.3, 18.0, 14.2, −4.6 and −5.0.

4.17. Ethyl (2E,4R,5R)-4-N-benzyloxycarbonylamino-5-tert-butyldimethylsilyloxyhex-2-enoate **18**

In the same procedure as described in the synthesis of the carbamate **6**, the azide **17** (168.1 mg, 0.536 mmol) was reduced and the resulting amine was protected by Cbz group to give the carbamate **18** (213 mg, 94%) as a colorless oil.

Colorless oil; ν_{max} (neat)/cm^{-1} 3443, 3342, 2956, 2929, 1720, 1660, 1525, 1500, 1304, 1255, 1184, 1068, 1049, 837, 777 and 698; δ_H (270 MHz, $CDCl_3$) 7.43−7.26 (m, 5 H), 6.88 (dd, *J* = 5.1, 15.6 Hz, 1 H), 5.94 (dd, *J* = 1.7, 15.6 Hz, 1 H), 5.17 (br. d, *J* = 9.0 Hz, 1 H), 5.12 (s, 2 H), 4.33−4.21 (m, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.06−3.92 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.19 (d, *J* = 6.2 Hz, 3 H), 0.85 (s, 9 H), 0.04 (s, 3 H) and 0.01 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$) 165.9, 156.2, 147.1, 136.2, 128.6, 128.2, 121.9, 69.6, 67.1, 60.3, 57.6, 25.7, 20.9, 17.9, 14.2, − 4.5 and − 5.0.

4.18. Ethyl (2E,4R,5R)-4-N-benzyloxycarbonyl-N-methylamino-5-tert-butyldimethylsilyloxyhex-2-enoate **19**

In the same procedure as described in the synthesis of the compound **7**, the carbamate **18** (413 mg, 0.980 mmol) was methylated to give the compound **19** (419.9 mg, 98%) as a colorless oil.

Colorless oil; ν_{max} (neat)/cm^{-1} 2956, 2931, 1720, 1697, 1658, 1473, 1400, 1308, 1257, 1176, 1147, 1039, 837, 777 and 698; δ_H (270 MHz, $CDCl_3$) for major rotamer 7.41−7.25 (m, 5 H), 6.98 (dd, *J* = 5.6, 15.8 Hz, 1 H), 5.91 (d, *J* = 16.0 Hz, 1 H), 5.14 (s, 2H), 4.72 (br. dd, *J* = 4.8, 4.8 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.15 (br. dq, *J* = 6.1, 6.1 Hz, 1 H), 2.96 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.18 (br. d, *J* = 6.2 Hz, 3 H), 0.85 (s, 9 H) and 0.06 (s, 6 H); for minor romater 7.41−7.25 (m, 5 H), 6.92 (dd, *J* = 5.3, 16.0 Hz, 1 H), 5.88 (d, *J* = 16.0 Hz, 1 H), 5.14 (s, 2H), 4.60 (br. dd, *J* = 4.4, 4.4 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.06 (br. dq, *J* = 5.9, 5.9 Hz, 1 H), 2.96 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.14 (br. d, *J* = 6.6 Hz, 3 H), 0.85 (s, 9 H) and 0.05 (s, 6 H); δ_C (67.8 MHz, $CDCl_3$) 166.0, 156.9, 144.4, 144.2, 136.7, 136.6, 128.8, 128.4, 127.9, 127.7, 123.3, 123.2, 70.0, 69.8, 67.4, 67.3, 62.4, 60.4, 32.0, 25.6, 20.9, 17.8, 16.8, 14.2, − 4.3 and − 5.2.

4.19. Ethyl (R)-2-((4R,5R)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-3-methyl-2-oxooxazolidin-5-yl)-2-iodoacetate trans-**20** Ethyl (S)-2-((4R,5S)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-3-methyl-2-oxooxazolidin-5-yl)-2-iodoacetate cis-**20′**

In the same procedure as described in the synthesis of the cyclic carbamate **8**, the carbamate **19** (190.2 mg, 0.437 mmol) was treated with iodine to give the cyclic carbamate *trans*-**20** (184.3 mg, 90%) as a colorless oil along with a small amount of the more polar *cis*-**20′** (5.5 mg, 2.7%), however, in this case the reaction was need to perform at r.t. for 5 days.

trans-**20**: colorless oil; ν_{max} (neat)/cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.60 (dd, *J* = 2.4, 8.3 Hz, 1 H), 4.38 (d, *J* = 8.3 Hz, 1 H), 4.25 (dq, *J* = 7.2, 10.8 Hz, 1 H), 4.24 (dq, *J* = 7.1, 10.8 Hz, 1 H), 4.05 (dq, *J* = 3.8, 6.4 Hz, 1 H), 3.55 (dd, *J* = 2.4, 3.6 Hz, 1 H), 2.95 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.22 (d, *J* = 6.4 Hz, 3 H), 0.91 (s, 9 H) and 0.11 (s, 6 H); δ_C (67.8 MHz, $CDCl_3$), 168.6, 156.9, 75.2, 68.2, 66.0, 62.4, 31.1, 25.8, 22.0, 19.0, 18.0, 13.7, −4.4 and −4.7.

cis-**20′**: colorless oil; δ_H (270 MHz, $CDCl_3$) 4.95 (dd, *J* = 6.8, 11.5 Hz, 1 H), 4.45 (d, *J* = 11.5 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 1 H), 4.24 (dq, *J* = 7.2, 11.0 Hz, 1 H), 4.22 (dq, *J* = 7.1, 11.0 Hz, 1 H), 3.65 (dd, *J* = 0.6, 6.8 Hz, 1 H), 3.03 (s, 3 H), 1.38 (d, *J* = 6.6 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 0.89 (s, 9 H), 0.17 (s, 3 H) and 0.13 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 168.4, 157.7, 77.2, 65.9, 64.3, 62.4, 32.6, 25.6, 22.7, 17.7, 15.2, 13.6, −2.9 and −5.1.

4.20. Ethyl 2-((4R,5S)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-3-methyl-2-oxooxazolidin-5-yl)acetate **21**

In the same procedure as described in the synthesis of the compound **9**, the *trans*-**20** (404 mg, 0.857 mmol) was treated with AIBN and tri-*n*-butyltin hydride to afford the compound **21**

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(251 mg, 85%) as a colorless oil.

Colorless oil; ν_{max} (neat)/cm^{-1} 2956, 2931, 1766, 1433, 1398, 1254, 1184, 1111, 1038, 837 and 779; δ_H (270 MHz, $CDCl_3$) 4.72 (ddd, J = 4.6, 5.2, 6.3 Hz, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.08 (dq, J = 4.7, 6.3 Hz, 1 H), 3.43 (dd, J = 4.6, 4.6 Hz, 1 H), 2.89 (s, 3 H), 2.67 (dd, J = 5.3, 16.0 Hz, 1 H), 2.65 (dd, J = 6.5, 16.0 Hz, 1 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.15 (d, J = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H) and 0.08 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 169.2, 157.6, 70.9, 67.5, 65.8, 61.0, 40.3, 30.4, 25.7, 17.9, 17.5, 14.1, −4.5 and −5.0.

4.21. (4R,5S)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-5-(2-hydroxyethyl)-3-methyloxazolidin-2-one **22**

In the same procedure as described in the synthesis of the alcohol **10**, the compound **21** (227 mg, 0.658 mmol) was treated with LiCl and $NaBH_4$ to afford the compound **22** (168 mg, 84%) as a colorless oil along with the compound **21** (15.2 mg, 6.7%) as the recovery starting material. Separation from the isomer derived from the Pd-catalyzed azidation was fully conducted at this stage.

Colorless oil; $[\alpha]_D^{27.2}$−35.4° (c 0.780, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3437, 2954, 2929, 1747, 1473, 1439, 1408, 1255, 1113, 1057, 1041, 837 and 777; δ_H (270 MHz, $CDCl_3$) 4.56 (ddd, J = 4.4, 4.4, 8.5 Hz, 1 H), 4.08 (dq, J = 4.8, 6.3 Hz, 1 H), 3.82 (br. t, J = 5.8 Hz, 1 H), 3.37 (dd, J = 4.5, 4.5 Hz, 1 H), 2.88 (s, 3 H), 2.00−1.78 (m, 3 H including OH), 1.12 (d, J = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H) and 0.09 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 157.8, 72.4, 67.3, 66.5, 58.7, 38.6, 30.1, 25.7, 18.0, 17.2, −4.5 and −4.9; Anal. Calcd for: $C_{14}H_{29}NO_4Si$: C 55.41; H 9.63; N 4.62. Found: C 55.19; H 9.37; N 4.43%.

4.22. (4R,5S)-4-((R)-1-tert-butyldimethylsilyloxyethyl)-5-(2,2-dimethoxyethyl)-3-methyloxazolidin-2-one **23**

In the same procedure as described in the synthesis of the acetal **11**, the alcohol **22** (198 mg, 652 mmol) was oxidized by Dess-Martin periodinane, and the resulting aldehyde was transformed to afford the acetal **23** (175 mg, 77%) as a colorless solid. Analytical pure sample was obtained by recrystallization from hexane at 0 °C.

Colorless plate; mp 59.0−62.0 °C; $[\alpha]_D^{28.8}$−53.4° (c 0.785, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2958, 2933, 1766, 1759, 1738, 1473, 1437, 1390, 1261, 1248, 1138, 1103, 1078, 1039, 1007, 891, 775 and 758; δ_H (270 MHz, $CDCl_3$) 4.62 (dd, J = 5.4, 6.3 Hz, 1 H), 4.48 (ddd, J = 4.5, 6.2, 6.8 Hz, 1 H), 4.04 (dq, J = 4.9, 6.3 Hz, 1 H), 3.37 (s, 3 H), 3.34 (s, 3 H), 3.31 (dd, J = 4.6, 4.6 Hz, 1 H), 2.88 (s, 3 H), 1.92 (dd, J = 6.0, 14.3 Hz, 1 H), 1.88 (dd, J = 5.3, 14.1 Hz, 1 H), 1.12 (d, J = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.09 (s, 3 H) and 0.08 (s, 3 H); δ_C (67.8 MHz, $CDCl_3$), 157.9, 101.2, 71.6, 67.5, 66.6, 53.6, 53.5, 39.5, 30.3, 25.7, 18.0, 17.5, −4.5 and −4.9; Anal. Calcd for: $C_{16}H_{33}NO_5Si$: C 55.30; H 9.57; N 4.03. Found: C 55.09; H 9.34; N 3.97%.

4.23. (2R,3S,4S)-6,6-dimethoxy-3-(methylamino)hexane-2,4-diol **24**

In the same procedure as described in the synthesis of the diol **12**, the compound **23** (111.3 mg, 320 mmol) was treated with 10% aq. NaOH in MeOH to afford amino diol **24** (67.3 mg, quantitative) as a colorless oil, which was sufficiently pure for spectrometric analysis and used for the next reaction.

Colorless oil; $[\alpha]_D^{27.1}$−11.8° (c 0.730, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3406, 3354, 2964, 2933, 1736, 1448, 1408, 1375, 1192, 1126, 1057 and 966; δ_H (270 MHz, $CDCl_3$) 4.60 (dd, J = 5.4, 5.4 Hz, 1 H), 3.86 (ddd, J = 2.9, 2.9, 9.8 Hz, 1 H), 3.80 (dq, J = 4.6, 6.4 Hz, 1 H), 3.392 (s, 3 H), 3.386 (s, 3 H), 3.01 (br. s, 3 H), 2.58 (s, 3 H), 2.07 (dd, J = 3.0, 4.5 Hz, 1 H), 1.92 (ddd, J = 5.3, 9.8, 14.1 Hz, 1 H), 1.79 (dd, J = 2.8, 5.6, 14.1 Hz, 1 H), 1.24 (d, J = 6.4 Hz, 1 H); δ_C (67.8 MHz, $CDCl_3$) 103.8, 69.4, 68.9, 68.3, 53.9, 53.5, 38.2 and 20.8; HRMS (ESI-TOF) calcd for: $C_9H_{22}NO_4$ $[M+H]^+$: 208.15488, found: 208.1531.

4.24. Methyl 2,4,6-trideoxy-4-methylamino-D-xylo-hexopyranoside (methyl 4-epi-D-vicenisaminide) **25**

In the same procedure as described in the synthesis of methyl 3-*epi*-D-vicenisaminide **13**, the compound **24** (67.3 mg) was treated with HCl-MeOH solution to afford crude product. This was purified by flash silica gel chromatography (EtOAc-MeOH, 7: 1 to 3: 1) to afford **25** (35.5 mg, %, 2 steps) as a mixture of α- and β-anomer.

Colorless oil; $[\alpha]_D^{22.3}$−8.91° (c 0.550, $CHCl_3$); {lit.27 (L-isomer) α-anomer: $[\alpha]_D^{20}$ − 117° (c = 0.7, $CHCl_3$); β-anomer: $[\alpha]_D^{20}$ + 51° (c = 2, $CHCl_3$)}; ν_{max} (neat)/cm^{-1} 3354, 3321, 2933, 1448, 1389, 1192, 1169, 1130, 1090, 1082, 984, 891 and 727; δ_H (270 MHz, $CDCl_3$) for major = β-anomer 4.69 (dd, J = 3.0, 7.5 Hz, 1 H), 4.17 (dq, J = 2.9, 6.7 Hz, 1 H), 4.20−4.12 (m, 1 H), 3.46 (s, 3 H), 2.49 (s, 3 H), 2.33 (ddd, J = 0.64, 2.8, 5.1 Hz, 1 H), 2.36 (br. s, 2 H), 1.85 (ddd, J = 3.4, 7.5, 13.7 Hz, 1 H), 1.75 (dddd, J = 0.64, 3.0, 5.1, 13.7 Hz, 1 H) and 1.30 (d, J = 6.8 Hz, 3 H); for minor = α-anomer 4.76 (br. d, J = 3.2 Hz, 1 H), 4.32 (dq, J = 2.1, 6.6 Hz, 1 H), 4.10−3.96 (m, 1 H), 3.36 (s, 3 H), 2.51 (s, 3 H), 2.40−2.37 (m, 1H), 2.36 (br. s, 2 H), 1.80−1.72 (m, 1 H) and 1.25 (d, J = 6.6 Hz, 3 H); δ_C (67.8 MHz, $CDCl_3$), 99.7, 69.0, 66.2, 62.4, 56.0, 35.1, 35.0 and 16.7; 99.1, 66.2, 61.9, 61.4, 55.1, 35.6, 30.3 and 17.0; HRMS (ESI-TOF) calcd for: $C_8H_8NO_3$ $[M+H]^+$: 176.1281, found: 176.1298.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.10.009.

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