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Graphical Abstract

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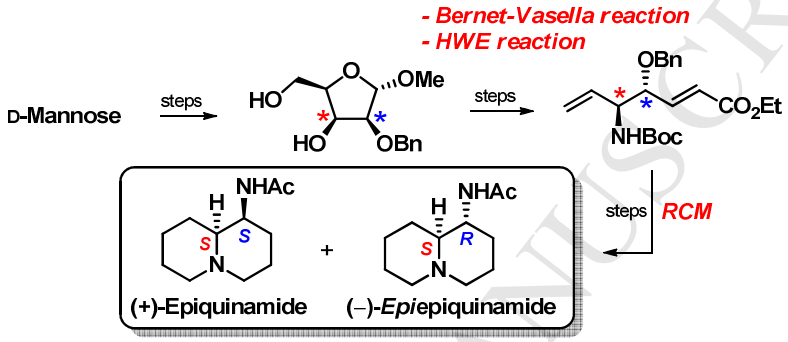

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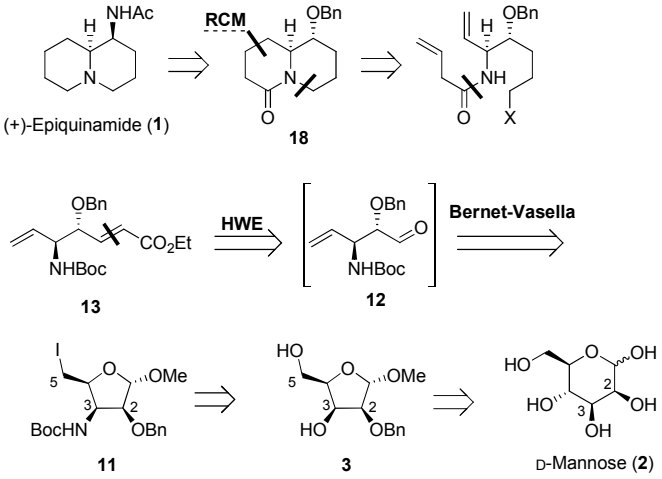
ABSTRACT

The total synthesis of (+)-epiquinamide and (−)-*epi*epiquinamide has been achieved starting from a 3,5-dihydroxyfuranoside synthon derived from D-mannose. The methods featured Bernet-Vasella reaction followed by Horner-Wadsworth-Emmons (HWE) reaction to provide a new chiral building block diene as the key steps. The bicyclic framework of this quinolizidine was constructed by using ring-closing metathesis, selective reduction of ester and intramolecular nucleophilic substitution-cyclization.

1. Introduction

(+)-Epiquinamide (**1**) is a quinolizidine alkaloid isolated from the skin extracts of an Ecuadorian poisonous frog, *Epipedobates tricolor*.[1] This compound has been reported to possess nicotinic agonistic activity and considered as a lead compound for a new nicotinic agent. Due to the low availability of the isolated product, many research groups have synthesized this alkaloid as a single enantiomer[2] and a racemic mixture[3] in order to identify its absolute configurations and examine the biological activities.[3a] Several asymmetric compounds including amino acids,[2a,2b] cyclic amines,[3a,2c] and a reduced monosaccharide[2e] were employed as chiral starting materials. In 2009, the reinvestigation of its biological activity revealed that (+)-epiquinamide and its stereoisomers are inactive to α4β2 nicotinic receptor subtypes up to 100 μM.[3a,4] The activity previously discovered is due to the contamination with epibatidine in the isolation steps. However, other biological activities have not yet to be examined.

Recently, a new method to synthesize oseltamivir phosphate (Tamiflu®), an anti-influenza drug, has been developed by our group.[5] Commercially available monosaccharides including, D-mannose[5b,5c] and D-glucose[5a,5d] were used as starting materials. The key features involved reductive ketal ring opening, Bernet-Vasella reaction, and ring-closing metathesis.



Scheme 1. Retrosynthesis of (+)-epiquinamide from D-mannose.

In this work, we have applied our reported key reactions for the asymmetric synthesis of (+)-epiquinamide (**1**) from D-mannose. An important core structure of (+)-epiquinamide would be useful for the modification in the synthesis of other bioactive alkaloids. The key reactions and synthetic methodologies could be a practical guideline for the application of monosaccharides in the synthesis of bioactive compounds which is very essential for drug development.

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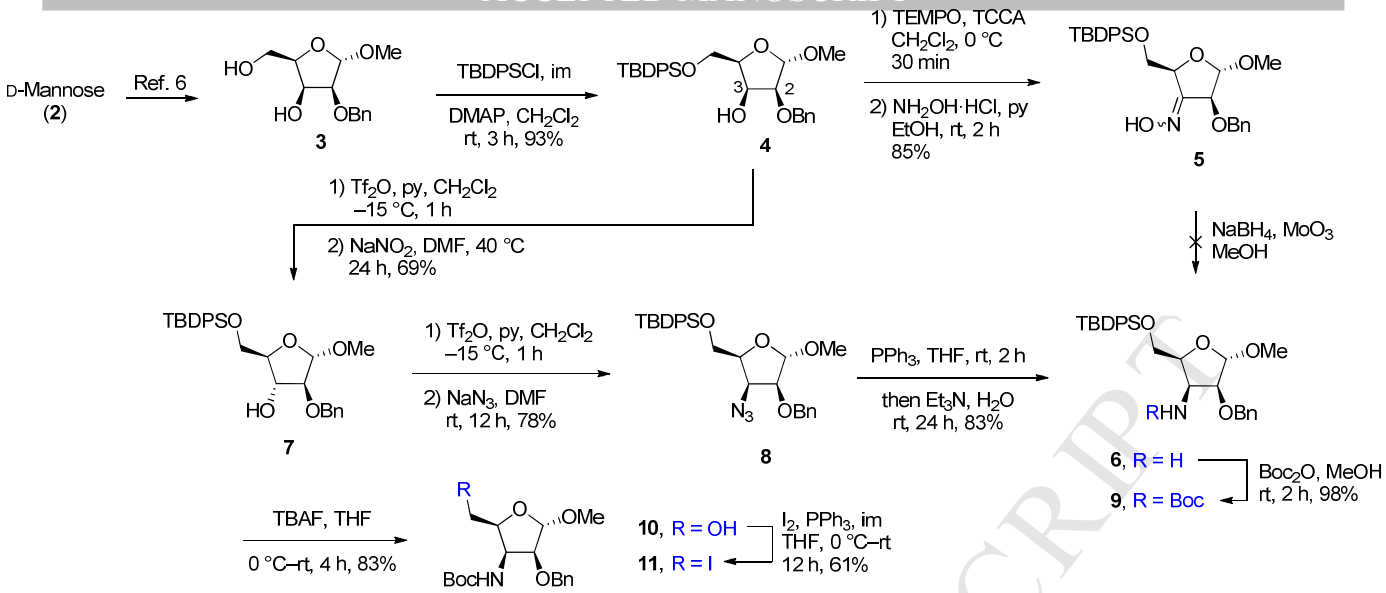


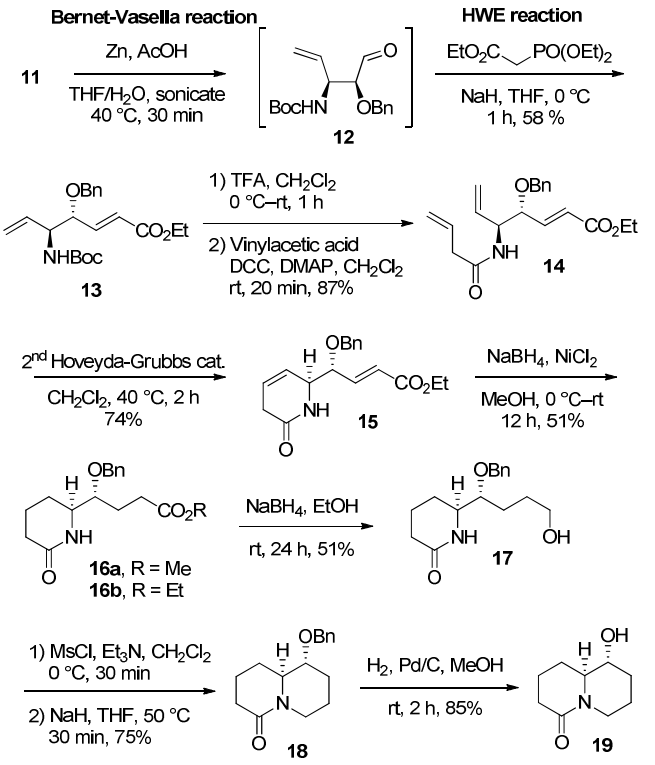
Scheme 2. Synthetic approach to 3-*N*-protected-5-iodo-β-aminofuranoside (**11**) from D-mannose.

2. Results and discussion

As depicted in Scheme 1, we envisaged to obtain epiquinamide from diene **13**. This key intermediate should provide a bicyclic skeleton after an intramolecular cyclization and ring-closing metathesis. For the synthesis of **13**, we relied on our recently developed strategy involving reductive benzylidene ring opening and Bernet-Vasella reaction followed by Horner-Wadsworth-Emmons (HWE) reaction of the 5-iodofuranoside **11**. The intermediate **11** could be obtained from diol **3**, which could be derived from D-mannose using a modified method previously reported by our group.[6]

The synthesis of **11** began with protection of the primary alcohol of **3** as TBDPS to provide furanoside **4** (Scheme 2). To replace the hydroxyl group at C-3 of **4** by amino group with retention configuration, oxidation of the hydroxyl group to a ketone, immediately followed by the conversion to oxime **5** were attempted. Unfortunately, a general reduction of oxime to amine using $NaBH_4/MoO_3$ provided only a trace amount of the desired amino product **6** along with an unidentified complex mixture. To overcome this problem, we decided to introduce the amino group *via* S_N2 substitutions with sodium azide. Firstly, the configuration of 3-OH of **4** was inverted by activating with Tf_2O followed by treating with sodium nitrite to afford **7** in moderate yield.[7] Once the 3-α-OH of **7** was activated again by the same manner, the resulting crude triflate was treated with NaN_3 to afford azide **8**, which established the 2,3-*cis*-stereochemistry. The corresponding azido group was mildly reduced to an amine by Staudinger reaction [PPh_3, THF then NEt_3, H_2O] and subsequently protected as NHBoc to give **9** in an excellent yield. After the removal of the silyl group, the corresponding hydroxyl group was converted to an iodide by using I_2/PPh_3/im in THF at room temperature to give **11** in modest yield.

Zn-mediated Bernet-Vasella reaction was employed for the opening of the furanoside ring of **11** as shown in scheme 3. This step was promoted by acetic acid. The crude aldehyde **12** was directly subjected to HWE reaction to afford α,β-unsaturated ester **13**. Boc protecting group was removed with TFA and the resulting amine was coupled with vinylacetic acid to provide triene **14** in good yield. Cyclization of **14** by ring-closing metathesis using the 2nd generation Hoveyda-Grubbs catalyst provided lactam **15** in good yield. Both double bonds of **15** were



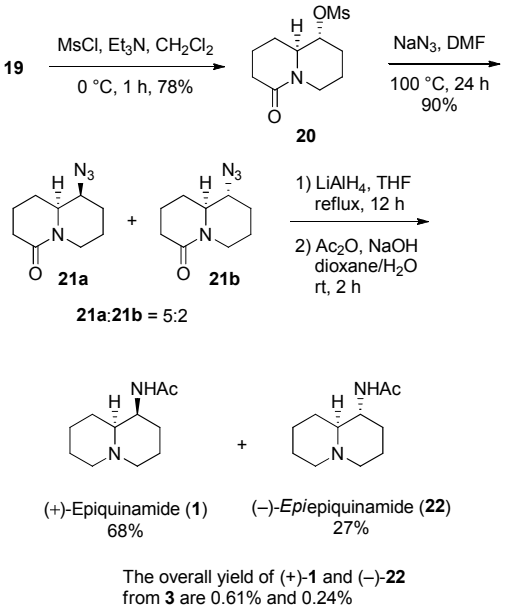
Scheme 3. Synthesis of bicycliclactam **19** via Bernet-Vasella reaction, Horner-Wadsworth-Emmons reaction, and ring-closing metathesis.

hydrogenated by $NaBH_4/NiCl_2$ in MeOH at room temperature. Transesterification occurred during the reduction to give a mixture of esters **16a** and **16b** (ratio = 1:1.8).

Selective reduction of the ester containing a lactam ring was investigated using various reducing agents and conditions including $NaBH_4$ in the presence of Lewis acids (LiCl and $CaCl_2$), DIBAL-H, $LiBH_4$, and $LiAlH_4$ at low temperature. None of the above mentioned reagents gave satisfactory results. Only

small amount of alcohol product was observed, along with a high polar complex mixture. The best result was obtained by using $NaBH_4$ in EtOH at room temperature for 24 h to give the alcohol product **17** in 51% yield.

The second ring of the quinolizidine skeleton was constructed by intramolecular nucleophilic substitution. Thus, the hydroxyl group of **17** was activated by converting to a mesylate, followed by treatment with NaH in THF to afford bicyclic compound **18**. The benzyl protecting group of **18** was easily cleaved by hydrogenolysis to give alcohol **19** (Scheme 3).

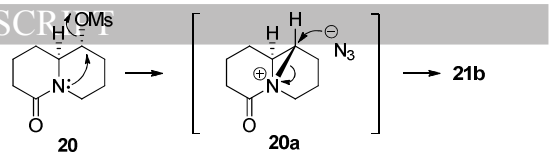


Scheme 4. Completion of the synthesis of (+)-epiquinamide (**1**) and (−)-*epi*epiquinamide (**22**).

For the synthesis of (+)-epiquinamide (**1**), **19** was mesylated to give **20**. The subsequent S_N2 reaction of **20** with sodium azide was carried out in DMF for 24 h to yield the desired azido product **21a**, along with **21b** as an inseparable diastereomeric mixture in 5:2 ratio. (determined by ^1H and ^{13}C NMR). The stereochemistry was ultimately proven by completion of the total synthesis and comparison of the spectra to the reported data of (+)-epiquinamide[2a] and (−)-*epi*epiquinamide[2d] (Scheme 4). This observation is in contrast to the previous publication in which the authors reported **21a** as a single isomer in 50% yield in the transformation from alcohol **19**.[2e]

In the course of our investigation on the azidation of **20**, DMSO was selected as a solvent due to improved solubility of sodium azide. The reaction at 80 °C for 12 h provided the same result as that of DMF.

We have proposed the mechanism for the transformation of **20** to **21a** and **21b**. The product **21a** was obtained via an S_N2 reaction; whereas the diastereomer **21b** was generated through the aziridinium ion intermediate **20a**, which was presumably formed upon the dissociation of the mesylate leaving group (Scheme 5). The latter mechanism is supported by the DFT calculations. Upon geometry optimization, the structure of the intermediate indicated a short distance between the nitrogen atom and the C1 carbon (1.54 Å in Figure 1), indicative of the formation of aziridinium ion (**20a**) through the neighboring group participation from the nitrogen lone pair electrons.



Scheme 5. A proposed mechanism for the azide substitution of **20** with retention of configuration.

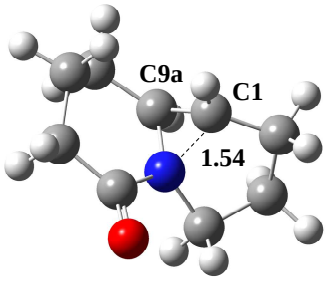


Figure 1. Optimized geometry (distance, Å) of the aziridinium ion intermediate **20a** for the substitution of **20** with NaN_3. The optimization was performed at DFT(B3LYP)/6-311G (d,p) level of theory.

Lithium aluminium hydride reduction of the azide mixture followed by acetylation provided the desired (+)-epiquinamide (**1**) in 68% along with the (−)-*epi*epiquinamide (**22**) in 27% yield after chromatographic separation. The physical and spectroscopic data of compound **1** and **22** are in full agreement with the literature.[8,2d,2b,2a]

3. Conclusion

We have developed a new asymmetric approach to access both (+)-epiquinamide and (−)-*epi*epiquinamide from the commercially available and inexpensive starting material, D-mannose. Bernet-Vasella and Horner-Wadsworth-Emmons (HWE) reactions were used as the key steps to provide a new chiral building block **13** from the intermediate compound **3**. Compound **13** from this synthetic pathway can be used as an important chiral building block for the total synthesis of iminosugars with potentially useful biological activities, which is currently under investigation in our laboratory.

4. Experimental

4.1. General

Starting materials and reagents were obtained from commercial sources and used without further purification. Solvents were dried by distillation from appropriate drying reagents immediately prior to use. Dry methanol, tetrahydrofuran and dichloromethane were distilled from magnesium, sodium/benzophenone and calcium hydride, respectively under nitrogen atmosphere. Moisture- and air-sensitive reactions were carried out under an atmosphere of nitrogen. Reaction flasks were oven dried overnight. Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator with water aspirator. Analytical thin-layer chromatography (TLC) was conducted using MERCK pre-coated TLC plates (silica gel 60 F-254). Compounds were visualized under ultraviolet light followed by heating the plate after dipping in 3% solution of vanillin in 0.1 M H_2SO_4 in EtOH and/or 1%

$KMnO_4$ in 0.4 M K_2CO_3 and 0.025 M NaOH. Flash column chromatography was carried out using SiliaFlash® irregular silica gels, F60, 40–63 µm (230–400 mesh). Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using Bruker Avance NanoBay 400 Mz spectrometer in $CDCl_3$. Chemical shifts were recorded as δ values in ppm. The peak due to residual $CHCl_3$ (7.26 ppm for ^1H and 77.16 ppm for ^{13}C) was used as the internal reference. Coupling constant (*J*) values were given in Hertz (Hz), and multiplicity was defined as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, dtd = doublet of triplet of doublets and m = multiplet. The specific rotations ($[\alpha]_D^T$) were measured with Polax-2L polarimeter and reported with the concentration in g/100 cm^3. Infrared (IR) spectra were recorded in cm^{-1} on Perkin-Elmer system 2000 FT-IR spectrometer. The high resolution mass spectra (HRMS) were recorded from Bruker, microTOF (Bruker Daltonics, Bremen, Germany) in the electrospray positive ionization mode (ESI^+). Melting points (mp) were determined on Electrothermal MelTemp® 1002 melting point apparatus and reported in degrees Celcius (^oC).

4.2. Experimental procedure

4.2.1. Methyl 2,3-O-benzylidene-α-D-mannofuranoside[6]

To a suspension of D-mannose (**2**) (1.0 g, 5.56 mmol) in dry MeOH (8 mL) was added benzaldehyde dimethylacetal (6 mL, 40 mmol) followed by *p*-TsOH (200 mg, 1.16 mmol). The mixture was stirred at room temperature for 20 min. Hexane (5 mL) was added and the reaction mixture was refluxed with Dean-Stark apparatus until the solvents were removed by azeotropic distillation. The reaction mixture was cooled and neutralized by satd aq $NaHCO_3$ (10 mL), extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was used in the next step without purification; R_f 0.30 (10% EtOAc/hexane).[9] A solution of crude methyl 2,3,5,6-di-*O*-benzylidene-α-D-mannofuranoside in MeOH (20 mL) was added 1.5% HCl (6 mL). The reaction mixture was stirred at room temperature for 3 h and then neutralized with ammonia solution. Solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2. The organic layer was collected, dried (Na_2SO_4) and concentrated to obtain a yellow oil. Purification by silica gel flash column chromatography (50% EtOAc/hexane) gave the diol product (Methyl 2,3-*O*-benzylidene-α-D-mannofuranoside) (1.2 g, 76%) as a colorless oil; a mixture of two isomers (ratio = 1:0.87); R_f 0.15 and 0.17 (40% EtOAc/hexane); FTIR (neat) ν_{max}, cm^{-1}: 3417, 3067, 2935, 1723, 1602, 1460; For the major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.34 (m, 5H), 5.75 (s, 1H), 5.06 (s, 1H), 4.87 (dd, *J* = 6.2, 3.6 Hz, 1H), 4.63 (d, *J* = 6.2 Hz, 1H), 4.06 (ddd, *J* = 8.3, 6.2, 3.3 Hz, 1H), 4.01 (dd, *J* = 8.3, 3.6 Hz, 1H), 3.85 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.71 (dd, *J* = 11.5, 6.2 Hz, 1H), 3.33 (s, 3H), 3.00 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 130.1, 128.6, 127.1, 106.9, 106.3, 85.3, 80.9, 79.2, 70.3, 64.6, 54.8; For the minor isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.34 (m, 5H), 5.92 (s, 1H), 5.05 (s, 1H), 4.92 (dd, *J* = 5.6, 3.6 Hz, 1H), 4.71 (d, *J* = 5.6 Hz, 1H), 4.07 (ddd, *J* = 8.3, 5.8, 3.2 Hz, 1H), 3.95 (dd, *J* = 8.3, 3.6 Hz, 1H), 3.88 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.70 (dd, *J* = 11.5, 5.8 Hz, 1H), 3.32 (s, 3H), 3.00 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 129.9, 128.6, 126.7, 107.4, 105.8, 84.5, 80.1, 79.7, 70.1, 64.5, 54.6; HRMS (ESI-TOF), *m/z* calcd for $C_{14}H_{18}NaO_6$ $[M+Na]^+$ 305.0996, found 305.1006.

4.2.2. Methyl 2,3-O-benzylidene-α-D-lyxofuranoside[6]

To a solution of methyl 2,3-*O*-benzylidene-α-D-mannofuranoside (1.83 g, 6.50 mmol) in MeOH (40 mL) was added a solution of $NaIO_4$ (1.53 g, 7.15 mmol) in water (10 mL). The reaction mixture was stirred at room temperature for 30 min. The white solid was filtered off through celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated to afford a crude aldehyde as a colorless oil. To a solution of the crude aldehyde in EtOH (38 mL) was added $NaBH_4$ (305 mg, 8.06 mmol) and then stirred at room temperature for 3 h. EtOAc (6 mL) was added and the reaction mixture was concentrated under reduced pressure. The residue was quenched with satd aq $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel flash column chromatography (30% EtOAc/hexane) to afford the alcohol product (Methyl 2,3-*O*-benzylidene-α-D-lyxofuranoside) (1.51 g, 92%) as a colorless oil; a mixture of two isomers (ratio 1:0.87); R_f 0.35 (40% EtOAc/hexane); FTIR (neat) ν_{max}, cm^{-1}: 3444, 3066, 2937, 1723, 1602, 1460; For the major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.36 (m, 5H), 5.75 (s, 1H), 5.12 (s, 1H), 4.84 (dd, *J* = 6.2, 3.7 Hz, 1H), 4.67 (d, *J* = 6.2 Hz, 1H), 4.16 (td, *J* = 5.4, 3.7 Hz, 1H), 4.05–3.93 (m, 2H), 3.38 (s, 3H), 2.26 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 130.1, 128.6, 127.1, 106.8, 106.5, 85.8, 81.1, 79.6, 61.1, 54.9; For the minor isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.36 (m, 5H), 5.94 (s, 1H), 5.10 (s, 1H), 4.87 (dd, *J* = 5.5, 3.7 Hz, 1H), 4.74 (d, *J* = 5.5 Hz, 1H), 4.14 (td, *J* = 5.4, 3.7 Hz, 1H), 4.02 (d, *J* = 5.4 Hz, 2H), 3.38 (s, 3H), 2.20 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 129.9, 128.6, 126.7, 107.3, 105.8, 84.9, 80.2, 80.1, 61.1, 54.8; HRMS (ESI-TOF), *m/z* calcd for $C_{13}H_{16}NaO_5$ $[M+Na]^+$ 275.0890, found 275.0894.

*4.2.3. Methyl 2-O-benzyl-α-D-lyxofuranoside (**3**)*[10,6]

$BH_3{\cdot}SMe_2$ (1.7 mL, 18.24 mmol) was added dropwise to a cooled solution of methyl 2,3-*O*-benzylidene-α-D-lyxofuranoside (1.51 g, 5.99 mmol) in dry THF (30 mL) under nitrogen atmosphere. The mixture was stirred for 30 min at room temperature. $Cu(OTf)_2$ (325 mg, 0.898 mmol) was added and the reaction mixture was stirred for 1 h. Satd aq $NaHCO_3$ was slowly added and the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, and purified by silica gel flash column chromatography (50% EtOAc/hexane) to give diol **3** (1.08 g, 71%) as a colorless oil; R_f 0.15 (40% EtOAc/hexane); $[\alpha]_D^{25}$ +33.3 (*c* 0.75, CH_2Cl_2); FTIR (neat) ν_{max}, cm^{-1}: 3434, 3063, 2932, 1606, 1454; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 4.94 (d, *J* = 1.5 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.47 (dt, *J* = 7.2, 5.5 Hz, 1H), 4.12 (dt, *J* = 5.5, 4.0 Hz, 1H), 3.91 (dd, *J* = 5.5, 1.5 Hz, 1H), 3.90–3.86 (m, 2H), 3.35 (s, 3H), 3.16 (d, *J* = 7.2 Hz, 1H,), 2.64 (t, *J* = 5.9 Hz, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 128.8, 128.4, 128.0, 105.9, 82.6, 79.2, 73.4, 72.0, 61.7, 55.4; HRMS (ESI-TOF), *m/z* calcd for $C_{13}H_{18}NaO_5$ $[M+Na]^+$ 277.1046, found 277.1061.

*4.2.4. Methyl 2-O-benzyl-5-O-(tert-butyldiphenyl)silyl-α-D-lyxofuranoside (**4**)*

TBDPSCl (0.94 mL, 3.61 mmol) was added to a solution of diol **3** (764 mg, 3.01 mmol), imidazole (408 mg, 6.01 mmol), and DMAP (36 mg, 0.30 mmol) in dry CH_2Cl_2 (30 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h and then quenched with satd aq NH_4Cl, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated under

reduced pressure. The crude product was purified by silica gel flash column chromatography (5–10% EtOAc/hexane) to give alcohol **4** (1.37 g, 93%) as a colorless oil; R_f 0.35 (10% EtOAc/hexane); $[\alpha]_D^{25}$ +86.5 (*c* 0.17, CH_2Cl_2); FTIR (neat) ν_{max}, cm^{-1}: 3520, 3069, 2930, 1777, 1589, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.64 (m, 4H), 7.50–7.32 (m, 11H), 4.98 (d, *J* = 2.7 Hz, 1H), 4.67 (s, 2H), 4.34 (td, *J* = 5.0, 3.8 Hz, 1H), 4.16 (td, *J* = 5.6, 3.8 Hz, 1H), 4.05 (dd, *J* = 10.6, 5.6 Hz, 1H), 3.96 (dd, *J* = 5.0, 2.7 Hz, 1H), 3.92 (dd, *J* = 10.6, 5.6 Hz, 1H), 3.38 (s, 3H), 2.82 (d, *J* = 5.0 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.8, 135.7, 133.6, 133.5, 129.8, 128.7, 128.2, 128.1, 127.8, 107.2, 84.3, 80.8, 73.0, 70.9, 62.5, 55.6, 26.9, 19.4; HRMS (ESI-TOF), *m/z* calcd for $C_{29}H_{36}NaO_5Si$ $[M+Na]^+$ 515.2224, found 515.2218.

*4.2.5. Methyl 2-O-benzyl-3-oxime-3-deoxy-5-O-(tert-butyldi phenyl)silyl-α-D-lyxofuranoside (**5**)*

To a cooled suspension of TCCA (188 mg, 0.81 mmol) in CH_2Cl_2 (2 mL) was added TEMPO (2.5 mg, 16 μmol). The solution of alcohol **4** (200 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 30 min. The white solid was removed by filtration through celite and the filtrate was concentrated under reduced pressure to provide a crude ketone as a yellow oil; R_f 0.42 (10% EtOAc/hexane). The crude ketone was dissolved in EtOH (1 mL), and $NH_2OH{\cdot}HCl$ (50 mg, 0.72 mmol) was then added, followed by pyridine (0.3 mL, 3.72 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated and purified by silica gel flash column chromatography (10% EtOAc/hexane) to provide two isomers of oximes (174 mg, 85%) as a colorless oil; R_f 0.25 (10% EtOAc/hexane); FTIR (neat) ν_{max}, cm^{-1}: 3354, 3070, 2931, 1589, 1472; **oxime isomer I**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.81–7.68 (m, 4H), 7.48–7.33 (m, 6H), 7.34–7.21 (m, 5H), 5.06 (s, 1H), 4.70–4.56 (m, 4H), 3.99 (dd, *J* = 11.0, 6.6 Hz, 1H), 3.92 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.39 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.9, 135.9, 135.8, 133.7, 133.5, 129.7, 128.4, 127.9, 127.8, 127.7, 106.5, 77.8, 75.8, 72.7, 66.3, 54.6, 26.9, 19.4; **oxime isomer II**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.87–7.65 (m, 4H), 7.47–7.34 (m, 6H), 7.32–7.17 (m, 5H), 5.10 (s, 1H), 4.97 (dd, *J* = 6.2, 2.9 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.21–4.07 (m, 2H), 4.03 (dd, *J* = 10.9, 6.2 Hz, 1H), 3.41 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.4, 135.9, 135.8, 133.7, 133.5, 129.7, 128.5, 128.1, 127.8, 127.7, 106.1, 79.7, 77.4, 70.3, 64.0, 54.8, 26.9, 19.4; HRMS (ESI-TOF), *m/z* calcd for $C_{29}H_{35}NNaO_5Si$ $[M+Na]^+$ 528.2177, found 528.2171.

*4.2.6. Methyl 2-O-benzyl-5-O-(tert-butyldiphenyl)silyl-α-D-arabinofuranoside (**7**)*[7]

To a −15 °C solution of alcohol **4** (1.46 g, 2.97 mmol) and pyridine (0.63 mL, 7.72 mmol) in dry CH_2Cl_2 (9 mL) was added Tf_2O (0.60 mL, 3.56 mmol). The reaction mixture was stirred at the same temperature for 1 h. A few drops of MeOH were added followed by water. The organic layer was combined, dried (Na_2SO_4) and concentrated under reduced pressure to give a crude triflate as a yellow oil. The crude triflate was dissolved in DMF (7.4 mL) and $NaNO_2$ (246 mg, 3.56 mmol) was added. The reaction mixture was stirred at 40 °C for 24 h. Water was added and the resulting mixture was extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10–20% EtOAc/hexane) to give alcohol **7** (1.02 g, 69%) as a colorless oil; R_f 0.20 (10% EtOAc/hexane); $[\alpha]_D^{25}$ −13.0 (*c* 0.39, CH_2Cl_2) (reported +34 (*c* 0.2, $CHCl_3$)); FTIR (neat) ν_{max}, cm^{-1}: 3452, 3070, 2955, 1589, 1427; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.63 (m, 4H), 7.51–7.26 (m, 11H), 4.92 (d, *J* = 1.1 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.18 (ddd, *J* = 7.5, 5.2, 2.7 Hz, 1H), 4.11 (dt, *J* = 6.9, 5.2 Hz, 1H), 3.91 (dd, *J* = 2.7, 1.1 Hz, 1H), 3.88 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.77 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.37 (s, 3H), 2.39 (d, *J* = 7.5 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.7, 133.4, 129.9, 128.6, 127.9, 127.8, 107.2, 88.4, 84.7, 76.9, 72.0, 64.5, 55.1, 27.0, 19.4; HRMS (ESI-TOF), *m/z* calcd for $C_{29}H_{36}NaO_5Si$ $[M+Na]^+$ 515.2224, found 515.2233.

*4.2.7. Methyl 2-O-benzyl-3-azido-3-deoxy-5-O-(tert-butyl diphenyl)silyl-α-D-lyxofuranoside (**8**)*

To a solution of alcohol **7** (261 mg, 0.53 mmol) and pyridine (0.09 mL, 1.14 mmol) in dry CH_2Cl_2 (1.32 mL) at −15 °C was added Tf_2O (0.1 mL, 0.58 mmol). After stirring for 1 h, a few drops of MeOH was added. The mixture was quenched with water, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated under reduced pressure to give a crude triflate as a yellow oil. The crude triflate was dissolved in DMF (0.88 mL). NaN_3 (171 mg, 2.63 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. Water was added and the resulting mixture was extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/hexane) to give azide **8** (214 mg, 78%) as a colorless oil; R_f 0.35 (5% EtOAc/hexane); $[\alpha]_D^{25}$ −34.5 (*c* 0.15, CH_2Cl_2); FTIR (neat) ν_{max}, cm^{-1}: 3070, 2955, 2108, 1589, 1427; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.63 (m, 4H), 7.52–7.29 (m, 11H), 4.96 (d, *J* = 3.8 Hz, 1H), 4.69 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.25 (ddd, *J* = 7.1, 6.0, 3.2 Hz, 1H), 4.14 (dd, *J* = 5.1, 3.8 Hz, 1H), 4.01 (dd, *J* = 5.1, 3.2 Hz, 1H), 3.92 (dd, *J* = 10.3, 7.1 Hz, 1H), 3.87 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.38 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.7, 133.4, 129.9, 128.6, 128.1, 127.9, 107.5, 85.6, 79.4, 73.0, 63.2, 62.3, 56.2, 26.9, 19.4; HRMS (ESI-TOF), *m/z* calcd for $C_{29}H_{35}N_3NaO_4Si$ $[M+Na]^+$ 540.2289, found 540.2296.

*4.2.8. Methyl 2-O-benzyl-3-amino-3-deoxy-5-O-(tert-butyldiphenyl)silyl-α-D-lyxofuranoside (**6**)*

*Method A: reduction of oxime **5**.* To a cooled solution of oxime **5** (100 mg, 0.20 mmol) and MoO_3 (40 mg, 0.28 mmol) in MeOH (2 mL) was added $NaBH_4$ (75 mg, 1.98 mmol) portionwise. After stirring at room temperature for 30 min, the starting material was completely consumed and a trace amount of the amine product was formed along with an unidentified complex mixture.

*Method B: Staudinger reduction of azide **8**.* To a solution of azide **8** (102 mg, 0.197 mmol) in THF (3.5 mL) was added PPh_3 (103 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 2 h. Et_3N (0.08 mL, 0.59 mmol) and water (0.3 mL) were added and the mixture was stirred at room temperature for 24 h and then poured into water and extracted with EtOAc. The organic layer was combined, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (50% EtOAc/hexane) to give amine **6** (80.1 mg, 83%) as a colorless oil; R_f 0.45 (50% EtOAc/hexane); $[\alpha]_D^{25}$ +21.3 (*c* 0.24, CH_2Cl_2);

FTIR (neat) ν_{max}, cm^{-1}: 3394, 3329, 3069, 2930, 1589, 1427; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4H), 7.47–7.27 (m, 11H), 4.94 (d, J = 2.6 Hz, 1H), 4.65 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 4.19 (ddd, J = 6.6, 5.9, 5.1 Hz, 1H), 3.95 (dd, J = 10.6, 6.6 Hz, 1H), 3.89 (dd, J = 10.6, 5.9 Hz, 1H), 3.88 (dd, J = 5.1, 2.6 Hz, 1H), 3.66 (t, J = 5.1 Hz, 1H), 3.38 (s, 3H), 1.36 (br s, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 135.7, 133.6, 133.5, 129.8, 128.5, 127.9, 127.8, 106.9, 84.8, 80.3, 72.7, 63.0, 55.7, 53.7, 27.0, 19.4; HRMS (ESI-TOF), *m/z* calcd for $C_{29}H_{38}NO_4Si$ $[M+H]^+$ 492.2565, found 492.2575.

*4.2.9. Methyl 2-O-benzyl-3-(tert-butoxycarbonyl)amino-3-deoxy-5-O-(tert-butyldiphenyl)silyl-α-D-lyxofuranoside (**9**)*

To a solution of amine **6** (623 mg, 1.26 mmol) in MeOH (5 mL) was added Boc_2O (412 mg, 1.89 mmol) at room temperature. After stirring for 2 h, the solvent was removed under reduced pressure. The residue was quenched with water, extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated and purified by silica gel flash column chromatography (10% EtOAc/hexane) to give **9** (735 mg, 98%) as a colorless oil; R_f 0.25 (10% EtOAc/hexane); $[\alpha]_D^{25}$ +26.3 (*c* 0.57, CH_2Cl_2); FTIR (neat) ν_{max}, cm^{-1}: 3420, 3070, 2958, 1715, 1504; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.67 (m, 4H), 7.48–7.26 (m, 11H), 5.50 (d, J = 8.9 Hz, 1H), 4.89 (s, 1H), 4.62–4.54 (m, 1H), 4.57 (s, 2H), 4.25 (dt, J = 6.6, 5.2 Hz, 1H), 3.95 (d, J = 5.7 Hz, 1H), 3.91 (dd, J = 11.1, 5.2 Hz, 1H), 3.75 (dd, J = 11.1, 5.2 Hz, 1H), 3.33 (s, 3H), 1.41 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 137.8, 135.8, 133.5, 133.3, 129.8, 129.7, 128.5, 127.9, 127.8, 106.1, 82.5, 79.5, 78.4, 73.0, 63.8, 55.1, 52.8, 28.5, 26.8, 19.3; HRMS (ESI-TOF), *m/z* calcd for $C_{34}H_{45}NNaO_6Si$ $[M+Na]^+$ 614.2908, found 614.2915.

*4.2.10. Methyl 2-O-benzyl-3-(tert-butoxycarbonyl)amino-3-deoxy-α-D-lyxofuranoside (**10**)*

TBAF solution (1 M in THF, 1.35 mL, 1.35 mmol) was added dropwise to a cooled solution of **9** (666 mg, 1.12 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 4 h. Satd aq NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20–40% EtOAc/hexane) to give alcohol **10** (330 mg, 83%) as a colorless oil; R_f 0.25 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −48.4 (*c* 0.10, CH_2Cl_2); FTIR (neat) ν_{max}, cm^{-1}: 3433, 3064, 3031, 2976, 1712, 1504; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 5.34 (d, J = 7.7 Hz, 1H), 4.87 (d, J = 0.9 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.51 (ddd, J = 7.7, 6.3, 5.5 Hz, 1H), 4.23 (ddd, J = 6.3, 5.2, 3.7 Hz, 1H), 3.96 (dd, J = 5.5, 0.9 Hz, 1H), 3.71 (dd, J = 12.0, 5.2 Hz, 1H), 3.62 (dd, J = 12.0, 3.7 Hz, 1H), 3.33 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 136.9, 128.7, 128.3, 128.0, 105.5, 81.8, 80.3, 78.8, 73.1, 60.9, 55.2, 52.5, 28.4; HRMS (ESI-TOF), *m/z* calcd for $C_{18}H_{27}NNaO_6$ $[M+Na]^+$ 376.1731, found 376.1754.

*4.2.11. Methyl 2-O-benzyl-3-(tert-butoxycarbonyl)amino-3-deoxy-5-iodo-5-deoxy-α-D-lyxofuranoside (**11**)*

To a cooled solution of alcohol **10** (281 mg, 0.79 mmol), PPh_3 (500 mg, 1.97 mmol), and imidazole (162 mg, 2.38 mmol) in dry THF (3.2 mL) was added portionwise I_2 (484 mg, 1.91 mmol). After stirring for 12 h, the reaction mixture was poured into satd aq $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/hexane) to give iodide **11** (227 mg, 61%) as a white solid (recrystallized from hexane; mp 83–84 °C); R_f 0.28 (10% EtOAc/hexane); $[\alpha]_D^{25}$ +185.2 (*c* 0.38, CH_2Cl_2); FTIR (film) ν_{max}, cm^{-1}: 3367, 3064, 2977, 1714, 1520; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5H), 5.03 (d, J = 8.5 Hz, 1H), 4.92 (d, J = 0.7 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.54–4.48 (m, 1H), 4.37 (ddd, J = 9.1, 6.1, 4.4 Hz, 1H), 3.98 (dd, J = 5.6, 0.7 Hz, 1H), 3.36 (s, 3H), 3.25 (dd, J = 10.2, 4.4 Hz, 1H), 3.16 (dd, J = 10.2, 9.1 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 137.0, 128.7, 128.2, 128.0, 104.9, 83.0, 80.1, 79.5, 72.9, 55.2, 53.2, 28.4, 3.6; HRMS (ESI-TOF), *m/z* calcd for $C_{18}H_{26}INNaO_5$ $[M+Na]^+$ 486.0748, found 486.0756.

*4.2.12. (4R,5S,E)-ethyl 4-(benzyloxy)-5-((tert-butoxycarbonyl)amino)hepta-2,6-dienoate (**13**)*

Iodide **11** (445 mg, 0.96 mmol) was dissolved in THF/H_2O (2:1 v/v, 7.3 mL). Activated zinc dust (630 mg, 9.63 mmol) was added followed by 50% acetic acid (0.15 mL, 1.31 mmol). The reaction mixture was sonicated for 30 min and then filtered through celite. The filtrate was extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4) and concentrated under reduced pressure to afford crude aldehyde **12** as a colorless oil; R_f 0.15 (10% EtOAc/hexane). To a suspension of NaH (60 % dispersion in mineral oil, 57 mg, 1.44 mmol) in dry THF (2 mL) at 0 °C was added triethyl phosphonoacetate (0.23 mL, 1.15 mmol) dropwise. After stirring for 15 min, a solution of crude aldehyde **12** in dry THF (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h. Water was slowly added and the mixture was extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/hexane) to give ester **13** (211.2 mg, 58 %) as a white solid (recrystallized from hexane; mp 78.0–78.5 °C); R_f 0.42 (20% EtOAc/hexane); $[\alpha]_D^{25}$ +47.1 (*c* 0.32, CH_2Cl_2); FTIR (film) ν_{max}, cm^{-1}: 3362, 3065, 2979, 1716, 1497; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 6.82 (dd, J = 15.8, 5.9 Hz, 1H), 6.09 (d, J = 15.8 Hz, 1H), 5.83 (ddd, J = 16.8, 10.5, 6.0 Hz, 1H), 5.26–5.19 (m, 2H), 4.84 (d, J = 6.3 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.41 (d, J = 11.9 Hz, 1H), 4.34 (br s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.17–4.11 (m, 1H), 1.42 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 155.3, 144.3, 137.7, 133.7, 128.6, 128.0, 127.9, 124.3, 117.6, 79.9, 71.6, 60.8, 55.7, 28.5, 14.3; HRMS (ESI-TOF), *m/z* calcd for $C_{21}H_{29}NNaO_5$ $[M+Na]^+$ 398.1938, found 398.1956.

*4.2.13. (4R,5S,E)-ethyl 4-(benzyloxy)-5-(but-3-enamido)hepta-2,6-dienoate (**14**)*

To a cooled solution of ester **13** (188 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added TFA (1 mL, 13.06 mmol). The reaction mixture was stirred at room temperature for 1 h. Satd aq $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4), concentrated under reduced pressure. The crude amine was dissolved in CH_2Cl_2 (5 mL). DCC (124 mg, 0.60 mmol) and DMAP (6 mg, 0.05 mmol) were added followed by vinylacetic acid (0.05 mL, 0.59 mmol). The reaction mixture was stirred at room temperature for 20 min. The white solid was filtered off through celite. The filtrate was quenched with satd aq $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (30% EtOAc/hexane) to give amide **14** (151 mg,

87%) as a white solid (recrystallized from hexane; mp 58.0–58.5 °C); R_f 0.27 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −99.3 (*c* 0.25, CH_2Cl_2); FTIR (film) ν_{max}, cm^{-1}: 3296, 3065, 2983, 1720, 1654, 1538; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 6.82 (dd, *J* = 15.8, 5.8 Hz, 1H), 6.10 (dd, *J* = 15.8, 1.4 Hz, 1H), 5.91–5.77 (m, 3H), 5.24–5.16 (m, 4H), 4.68–4.63 (m, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.34 (d, *J* = 11.9 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.15 (ddd, *J* = 5.8, 3.4, 1.4 Hz, 1H), 2.92 (d, *J* = 6.9 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 165.9, 144.0, 137.5, 132.8, 131.2, 128.7, 128.2, 128.1, 124.4, 120.1, 118.3, 79.4, 71.6, 60.8, 54.1, 41.7, 14.3; HRMS (ESI-TOF), *m/z* calcd for $C_{20}H_{25}NNaO_4$ $[M+Na]^+$ 366.1676, found 366.1697.

*4.2.14. (R,E)-ethyl 4-(benzyloxy)-4-((S)-6-oxo-1,2,5,6-tetrahydro-pyridin-2-yl)but-2-enoate (**15**)*

To a solution of amide **14** (45 mg, 0.13 mmol) in dry CH_2Cl_2 (4 mL) was added Hoveyda-Grubbs catalyst 2nd generation (4 mg, 6.7 µmol, 5 mol%). The reaction mixture was stirred at 40 °C for 2 h under argon atmosphere. The solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (3% MeOH/CH_2Cl_2) to give lactam **15** (31 mg, 74%) as a white solid (recrystallized from hexane; mp 109–110 °C); R_f 0.37 (3% MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ −122.4 (*c* 0.082, CH_2Cl_2); FTIR (film) ν_{max}, cm^{-1}: 3224, 3045, 2984, 1718, 1663, 1455; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.16 (m, 5H), 6.71 (dd, *J* = 15.8, 6.3 Hz, 1H), 6.32 (s, 1H), 6.02 (dd, *J* = 15.8, 1.2 Hz, 1H), 5.79 (dtd, *J* = 10.1, 3.5, 1.8 Hz, 1H), 5.69–5.48 (m, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 4.29–4.20 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.97 (ddd, *J* = 6.3, 3.9, 1.2 Hz, 1H), 2.90–2.75 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 165.5, 142.1, 137.2, 128.6, 128.1, 127.8, 125.9, 125.0, 120.6, 79.9, 71.5, 60.8, 57.1, 31.6, 14.2; HRMS (ESI-TOF), *m/z* calcd for $C_{18}H_{21}NNaO_4$ $[M+Na]^+$ 338.1363, found 338.1377.

*4.2.15. (R)-Methyl 4-(benzyloxy)-4-((S)-6-oxopiperidin-2-yl) butanoate (**16a**) and (R)-Ethyl 4-(benzyloxy)-4-((S)-6-oxo piperidin-2-yl)butanoate (**16b**)*

$NaBH_4$ (200 mg, 5.26 mmol) was added portionwise to a cooled solution of lactam **15** (210 mg, 0.66 mmol) and $NiCl_2$ (42 mg, 0.33 mmol) in MeOH (10 mL). Color gradually changed from yellow to brown and then black. The reaction mixture was stirred overnight at room temperature and then quenched with satd aq NH_4Cl. The solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated and purified by silica gel flash column chromatography (80% EtOAc/hexane) to give a mixture of lactam **16a** and **16b** (ratio 1:1.8, 109 mg, 51%) as a colorless oil; R_f 0.23 (80% EtOAc/hexane); FTIR (film, mixture) ν_{max}, cm^{-1}: 3394, 3031, 2950, 1731, 1660; ^1H NMR (400 MHz, $CDCl_3$, **16a**) δ 7.38–7.25 (m, 5H), 6.07 (s, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 3.77–3.70 (m, 1H), 3.61 (s, 3H), 3.46–3.40 (m, 1H), 2.52–2.21 (m, 4H), 1.98–1.43 (m, 6H); ^1H NMR (400 MHz, $CDCl_3$, **16b**) δ 7.38–7.25 (m, 5H), 6.07 (s, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.77–3.70 (m, 1H), 3.46–3.40 (m, 1H), 2.52–2.21 (m, 4H), 1.98–1.43 (m, 6H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, **16a** + **16b**) δ 174.0, 173.5, 172.5, 137.7, 137.6, 128.6, 128.0, 127.9, 79.4, 79.3, 72.0, 71.9, 60.6, 53.9, 51.7, 31.7, 30.1, 29.9, 24.4, 24.1, 20.2, 14.3; HRMS (ESI-TOF), *m/z* calcd for $C_{17}H_{24}NO_4$ $[M+H]^+$ 306.1702, found 306.1700 and $C_{18}H_{26}NO_4$ $[M+H]^+$ 320.1862, found 320.1856.

*4.2.16. (S)-6-((R)-1-(benzyloxy)-4-hydroxybutyl)piperidin-2-one (**17**)*

To a cooled solution of ester **16** (363 mg 1.15 mmol) in EtOH (10 mL) was added $NaBH_4$ (437 mg, 11.5 mmol) portionwise. The reaction mixture was stirred at room temperature for 12 h. NH_4Cl was added followed by a small amount of water and the solvent was removed under reduced pressure. The residue was dissolved with EtOAc, washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel flash column chromatography (5% MeOH/CH_2Cl_2) to provide alcohol **17** as a colorless oil (163 mg, 51%); R_f 0.35 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ +16.5 (*c* 2.42, $CHCl_3$); FTIR (neat) ν_{max}, cm^{-1}: 3298, 2948, 1651; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 6.81 (s, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 3.73–3.54 (m, 3H), 3.40 (q, *J* = 5.1 Hz, 1H), 2.66 (br s, 1H), 2.44–2.33 (m, 1H), 2.33–2.20 (m, 1H), 1.93–1.79 (m, 2H), 1.78–1.45 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 137.9, 128.6, 128.0, 80.4, 72.0, 62.6, 54.3, 31.5, 28.1, 25.6, 24.3, 19.7; HRMS (ESI-TOF), *m/z* calcd for $C_{16}H_{23}NNaO_3$ $[M+Na]^+$ 300.1570, found 300.1564.

*4.2.17. (9R,9aS)-9-(benzyloxy)hexahydro-1H-quinolizin-4(6H)-one (**18**)*

To a cooled solution of alcohol **17** (150 mg, 0.54 mmol) and Et_3N (0.15 mL, 1.07 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise MsCl (60 µL, 0.78 mmol). The white precipitate was formed and the reaction mixture was stirred at 0 °C for 30 min. Water was added and the organic layer was combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a yellow oil. To a cooled suspension of NaH (60%, 43 mg, 1.07 mmol) in dry THF (1.3 mL) was added dropwise a solution of the crude mesylate in dry THF (1.3 mL). The reaction mixture was stirred for 30 min at 50 °C. After cooling to 0 °C, water was added dropwise to destroy excess NaH. The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (1% MeOH/CH_2Cl_2) to afford **18** as a colorless oil (106 mg, 75%); R_f 0.60 (2% MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ −116.8 (*c* 1.67, $CHCl_3$); FTIR (neat) ν_{max}, cm^{-1}: 3030, 2938, 1644; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.77–4.70 (m, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.25–3.09 (m, 2H), 2.48–2.28 (m, 4H), 2.21–2.11 (m, 1H), 1.84–1.75 (m, 2H), 1.74–1.66 (m, 1H), 1.65–1.53 (m, 1H), 1.49–1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.2, 128.6, 128.0, 78.3, 71.1, 61.3, 42.6, 32.7, 30.2, 25.5, 23.4, 18.3; HRMS (ESI-TOF), *m/z* calcd for $C_{16}H_{21}NNaO_2$ $[M+Na]^+$ 282.1464, found 282.1464.

*4.2.18. (9R,9aS)-9-hydroxyhexahydro-1H-quinolizin-4(6H)-one (**19**)*

To a solution of lactam **18** (100 mg, 0.386 mmol) in MeOH (4 mL) was added 10% Pd/C (70 mg, 66 µmol). The reaction mixture was stirred at room temperature for 2 h under hydrogen atmosphere and then filtered through celite. The filtrate was concentrated and the crude product was purified by silica gel flash column chromatography (2% MeOH/CH_2Cl_2) to afford alcohol **19** (56 mg, 85%) as a white solid (recrystallized from hexane/CH_2Cl_2; mp 156–157 °C) (reported mp 156–157 °C, ent);[11] R_f 0.50 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ −73.3 (*c* 0.75, $CHCl_3$) (reported +73.7 (*c* 0.58, $CHCl_3$, ent));[11] FTIR (film) ν_{max}, cm^{-1}: 3282, 2947, 1598; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80–4.64 (m,

1H), 3.36 (td, *J* = 9.4, 4.4 Hz, 1H), 3.06 (dt, *J* = 9.4, 6.1 Hz, 1H), 2.43–2.32 (m, 3H), 2.30 (s, 1H), 2.21–2.06 (m, 2H), 1.90–1.78 (m, 2H), 1.77–1.71 (m, 1H), 1.70–1.60 (m, 1H), 1.55–1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 71.9, 62.6, 42.4, 34.3, 32.8, 25.4, 23.6, 18.4; HRMS (ESI-TOF), *m/z* calcd for $C_9H_{15}NNaO_2$ $[M+Na]^+$ 192.0995, found 192.0999.

*4.2.19. (1R,9aS)-6-oxooctahydro-1H-quinolizin-1-yl methane sulfonate (**20**)*[2e]

To a cooled solution of alcohol **19** (50 mg, 0.29 mmol) and Et_3N (0.12 mL, 0.85 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise MsCl (50 µL, 0.65 mmol). The white precipitate was formed and the reaction mixture was stirred at 0 °C for 1 h. Water was added and the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (0–2% MeOH/CH_2Cl_2) to afford mesylate **20** (57 mg, 78%) as a white solid (recrystallized from hexane/CH_2Cl_2; mp 108–109 °C); R_f 0.33 (2 % MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ −61.7 (*c* 0.95, $CHCl_3$); FTIR (film) ν_{max}, cm^{-1}: 2953, 1633, 1347; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82–4.68 (m, 1H), 4.40 (td, *J* = 10.4, 4.8 Hz, 1H), 3.31 (dt, *J* = 10.4, 6.1 Hz, 1H), 3.05 (s, 3H), 2.47–2.28 (m, 4H), 2.21–2.04 (m, 1H), 1.92–1.76 (m, 3H), 1.76–1.61 (m, 2H), 1.61–1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 80.0, 59.8, 42.0, 39.2, 32.7, 32.0, 25.4, 23.5, 18.1; HRMS (ESI-TOF), *m/z* calcd for $C_{10}H_{17}NNaO_4S$ $[M+Na]^+$ 270.0770, found 270.0766.

*4.2.20. (9S,9aS)-9-azidohexahydro-1H-quinolizin-4(6H)-one (**21a**)*[2e] *and its diastereoisomer (**21b**)*

To a solution of mesylate **20** (200 mg, 0.81 mmol) in DMF (8 mL) was added NaN_3 (263 mg, 4.05 mmol). The reaction mixture was stirred at 100 °C for 24 h under argon atmosphere. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with water. The organic layer was combined, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (2% MeOH/CH_2Cl_2) to give azide **21a** as the major product along with its diastereomer **21b** (colorless oil, 140 mg, 90%, ratio 1:0.4); R_f 0.35 (2% MeOH/CH_2Cl_2); FTIR (neat) ν_{max}, cm^{-1}: 2943, 2097, 1633; For **21a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84–4.73 (m, 1H), 3.68–3.59 (m, 1H), 3.38 (td, *J* = 7.5, 1.9 Hz, 1H), 2.48–2.24 (m, 3H), 2.18–2.10 (m, 1H), 1.97–1.82 (m, 3H), 1.78–1.67 (m, 2H), 1.65–1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 60.7, 58.2, 41.8, 32.8, 28.6, 26.6, 19.6, 19.0; For **21b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84–4.73 (m, 1H), 3.14–2.98 (m, 2H), 2.48–2.24 (m, 3H), 2.18–2.10 (m, 1H), 1.97–1.82 (m, 3H), 1.78–1.67 (m, 2H), 1.65–1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 62.7, 60.4, 41.9, 32.8, 30.2, 26.3, 23.6, 18.3.

*4.2.21. (+)-Epiquinamide (**1**)*[2b] *and (−)-epiepiquinamide (**22**)*[2d]

To a cooled suspension of $LiAlH_4$ (100 mg, 2.63 mmol) in dry THF (3 mL) was added dropwise a solution of azide **21a** and **21b** (73 mg, 0.38 mmol) in dry THF (3 mL) under nitrogen atmosphere. The reaction mixture was refluxed overnight. After cooling to 0 °C, water was carefully added followed by 10% NaOH and CH_2Cl_2. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure to provide a crude amine as a colorless oil. The crude amine was dissolved in dioxane (3 mL). 1 M NaOH (3 mL) was added followed by Ac_2O (0.2 mL, 2.11 mmol). The reaction mixture was stirred at room temperature for 2 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was combined, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (2% MeOH/CH_2Cl_2–6% MeOH/CH_2Cl_2 + 3% NH_3 sol.) to give (+)-epiquinamide (**1**) (50 mg, 68%) and (−)-*epi*epiquinamide (**22**) (20 mg, 27%); For (+)-**1**:[2b] white solid (recrystallized from hexane/CH_2Cl_2; mp 130–131 °C) (reported mp 130 °C); R_f 0.64 (6% MeOH/CH_2Cl_2 + 3% NH_3 sol.); $[\alpha]_D^{25}$ +26.8 (*c* 0.56, $CHCl_3$) (reported +24 (*c* 0.1, $CDCl_3$)); FTIR (film) ν_{max}, cm^{-1}: 3326, 2937, 1660; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (br s, 1H), 3.95–3.85 (m, 1H), 2.83–2.69 (m, 2H), 2.04–1.89 (m, 6H), 1.86–1.78 (m, 1H), 1.75–1.63 (m, 2H), 1.61–1.53 (m, 1H), 1.53–1.37 (m, 4H), 1.37–1.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 64.5, 56.9, 48.3, 29.8, 29.2, 25.7, 24.2, 23.6, 20.7; HRMS (ESI-TOF), *m/z* calcd for $C_{11}H_{21}N_2O$ $[M+H]^+$ 197.1648, found 197.1645;

For (−)-**22**:[2d] white solid; mp 190 °C (dec) (reported mp 190 ºC (dec)); R_f 0.28 (6% MeOH/CH_2Cl_2 + 3% NH_3 sol.); $[\alpha]_D^{25}$ −9.5 (*c* 0.11, $CHCl_3$) (reported −2.9 (c 0.6, CH_2Cl_2); FTIR (film) ν_{max}, cm^{-1}: 3422, 2931, 1635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (br s, 1H), 3.71 (dtd, *J* = 11.8, 9.5, 4.4 Hz, 1H), 2.84 (br d, *J* = 11.0 Hz, 1H), 2.76 (br d, *J* = 11.0 Hz, 1H), 2.03–1.94 (m, 3H), 1.96 (s, 3H), 1.85–1.47 (m, 7H), 1.35–1.03 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 67.5, 56.5, 55.8, 51.2, 32.0, 29.0, 25.4, 24.4, 23.8, 23.7; HRMS (ESI-TOF), *m/z* calcd for $C_{11}H_{21}N_2O$ $[M+H]^+$ 197.1648, found 197.1648.

4.3. Computational Details

The geometrical structure of aziridinium ion intermediate **20a** was optimized using the hybrid density functional B3LYP method. The basis set for all atoms was 6-311G (d,p), the charge was 1, and the spin state was singlet. The calculations were performed using the Gaussian03 package.[12]

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for all new and important known compounds, and atomic coordinates for optimized structure of **20a**) related to this article can be found at……

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