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Stereoselective Synthesis of Polyhydroxylated Quinolizidines from C-Glycosides by One-Pot Double-Conjugate Addition

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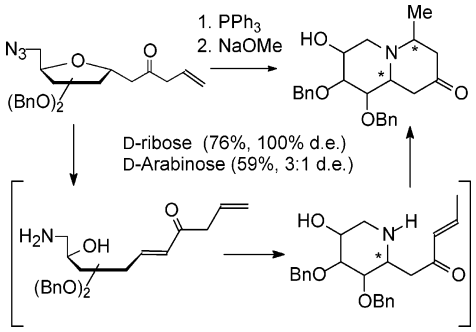

An effective one-pot synthesis of polyhydroxylated quinolizidines from 1-*C*-(2′-oxo-4′-pentenyl)-5-azido-*C*-glycofuranosides was developed. Reduction of the 5-azido group using triphenylphosphine followed by base treatment produced quinolizidines in good yield. The base-mediated ring-opening β-elimination produced an acyclic α,β-conjugated ketone as a Michael acceptor, which was followed by an intramolecular nitrogen conjugate addition to form an aza-*C*-glycopyranoside intermediate. Meanwhile, the β,γ-double bond of the aglycon migrated under the basic conditions to form another α,β-conjugated ketone. The subsequent intramolecular conjugate addition by the azasugar nitrogen led to the formation of the quinolizidines in a highly stereoselective manner. The stereoselectivity of the first conjugate addition giving azasugar is affected by the stereochemistry of the monosaccharide substrate, whereas the stereoselectivity in the second conjugate addition was likely directed entirely by steric repulsion from the azasugar.

Introduction

Quinozilidine and indolizidine alkaloids have provided a rich source of synthetic targets because of their potential pharmaceutical applications.[1] The construction of nitrogen bicycles has been achieved by ring-closing metathesis,[2] Diels−Alder reactions,[3] other inter- and intramolecular cycloadditions,[4] and reactions based on *N*-nitrones[5] and *N*-sulfinylimines.[6] Polyhydroxylated indolizidines have also been desirable synthetic targets because they are able to selectively inhibit glycoprocessing enzymes[7] and thus may be used as therapeutic agents for the treatment of diabetes, viral infections, and cancers.[8] The synthesis of polyhydroxylated indolizidines has been often accomplished in a stepwise approach via pyrrolidine and piperidine intermediates.[9] Few examples exist where the nitrogen bicyclic ring system was constructed by a one-pot reaction. They include an intramolecular 1,3-dipolar addition of azide to an

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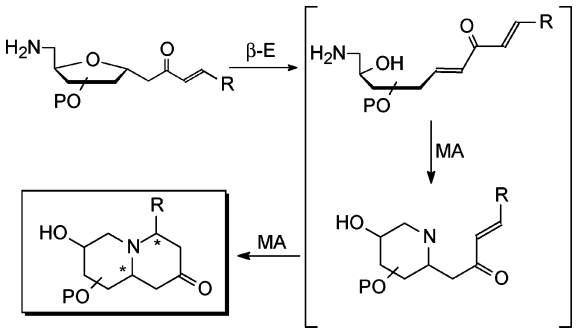
olefin followed by a nucleophilic substitution,[10] a double intramolecular N-alkylation involving an epoxide,[11] and a reductive double cyclization to bicyclic lactam.[12] The majority of these syntheses started from a carbohydrate, which takes advantage of pre-existing stereocenters.

Surprisingly, polyhydroxylated quinozilidines have so far not been discovered in Nature. Consequently, their synthesis has attracted much less interest and is only scarcely reported. The synthetic methods are based on those for quinozilidines/indolizidines and polyhydroxylated indozilidines, which include double-reductive amination,[13] hetero-Diels−Alder reaction,[14] intramolecular S_N2 reactions involving a mesyl leaving group[15] and an epoxide,[11] cycloaddition via nitrones[16] and sulfones,[17] ring-closure metathesis,[18] and ring expansion via an aziridinium intermediate.[19] Both carbohydrates and non-carbohydrates were used as starting material.

SCHEME 1. Nitrogen Bicycles by Double-Michael Addition



Ideally, one would like to construct the nitrogen bicyclic system in a single step in a highly stereoselective manner. Although double-reductive amination of an azido-α,ω-dialdehyde[13] and double-intramolecular N-alkylation[11] are two excellent examples, the synthesis of these intermediates itself was a challenge that required careful control of the stereochemistry during multistep manipulations. Our goal is to develop a more general method that does not require a sophisticated technique, uses common chemicals, and is applicable to different monosaccharides.

During the course of our synthetic work toward aza-*C*-glycosides[20] via a base-mediated intramolecular nitrogen Michael addition,[21] we envisioned that C-glycosides equipped with an amino group (e.g., at C5 of furanosides) may produce polyhydroxylated nitrogen bicycles (such as quinolizidines) as illustrated in Scheme 1. This double-conjugate addition synthetic pathway results in the creation of two stereocenters during the carbon−nitrogen bond formation. Thus, we are also interested in investigating the stereoselectivity of the reaction and how substrate chirality of the monosaccharide and conformation of the azasugar intermediate affect the stereochemical outcome.

Stereoselective conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds is widely used in organic synthesis,[22] e.g., as one of the most effective methods for the synthesis of β-amino acids and β-lactams,[23] and is often

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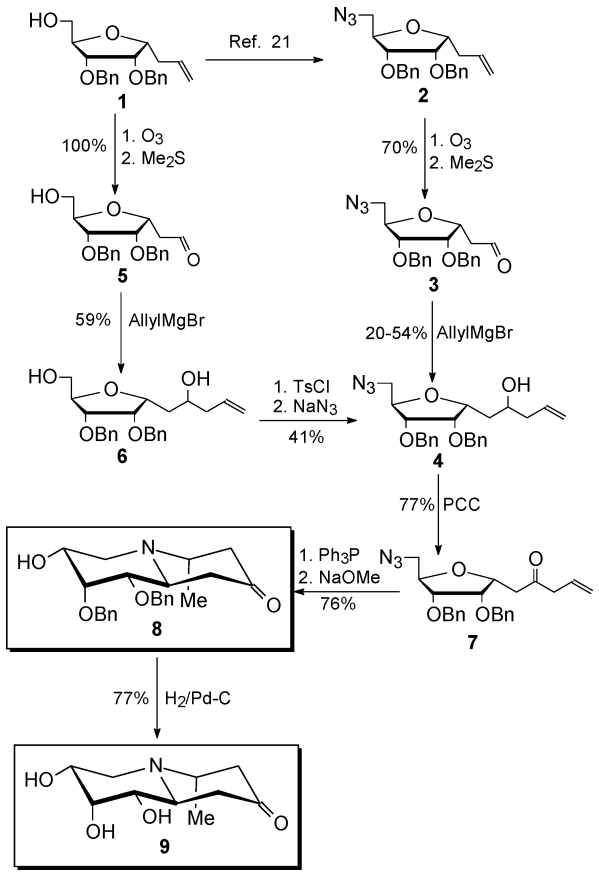
achieved using chiral acceptors,[24] chiral amines,[25] and chiral catalysts.[26] The α,β-unsaturated carbonyl generated by β-elimination from amino-C-glycoside (see Scheme 1) can be considered as both chiral amine and chiral Michael acceptor; therefore, one would expect the conjugate addition to be stereoselective. Using ribose- and arabinose-derived amino-C-glycosides as substrates, we describe here the feasibility of this double-Michael addition for the synthesis of nitrogen bicycles and the factors affecting the stereochemistry.

Synthesis of Polyhydroxylated Quinolizidines. Instead of an α,β-conjugated ketone as an aglycon, we decided to synthesize β,γ-conjugated ketones, namely 1-*C*-(2′-oxo-4′-pentenyl)-glycosides,[27] as substrates to further exploit our previous observation that the β,γ-double bond of a 2′-ketone C-glycoside migrated under basic conditions to form an α,β-conjugated ketone.[21b,c] Therefore, the first test substrate was the ribose derivative **7** (see Scheme 2) since we have previously obtained 5-azido-*C*-riboside **2** via allyl-1-*C*-riboside **1**.[21]

The allyl double bond of **2** was oxidized to aldehyde **3** by ozonolysis in good yield. The resultant aldehyde was reacted with allylmagnesium bromide (AllylMgBr) to afford a mixture of two diastereomers (**4**) in a ratio of ca. 5:1. No investigation on stereochemistry of the products was attempted. Instead, the mixture of alcohols was oxidized using PCC to ketone **7** in 77% yield. However, the Grignard reaction, which converts **3** to **4**, was somewhat unpredictable and often gave low yields (20−54%) likely due to a side reaction involving an azido group since we observed decomposition of azido-*C*-glycoside **2** when treated with AllylMgBr. One of the difficulties associated with the Grignard reaction was the adjustment of the amount of AllylMgBr to be used to compensate for deterioration of the commercial reagent. We often found either starting material remained or the product significantly decomposed.[28] In order to circumvent this problem, we modified the reaction sequence by introducing the azido group after Grignard reaction. Thus, C-glycoside **1** was converted quantitatively to aldehyde **5** by ozonolysis without chromatographic purification. The aldehyde

SCHEME 2. Synthesis of Polyhydroxylated Quinolizidines



was then reacted with AllylMgBr to give a diastereomeric mixture of 2′,5-diols (**6**) in 59% yield. After the 5-OH was converted to the 5-azido group by O-tosylation followed by treatment with sodium azide to give **4**, the 2′-OH was subsequently oxidized to obtain azidoketone **7**. Although this procedure gave a moderate yield, few chromatography purifications were required. Actually, we were able to just purify **6** in this synthetic pathway to **7**.

Nevertheless, with substrate **7** in hand, we performed a Staudinger reduction of the azido group to amine using Ph_3P.[29] After removal of solvent, the resulting amine, without further purification, was treated with base (4% NaOMe or 1% K_2CO_3 in methanol). The first Michael addition was complete within 4 h as indicated by the appearance of a faster moving spot on TLC, and this intermediate was then further converted overnight to an even less polar product **8**, a quinolizidine derivative isolated by chromatography (76% from **7**) as a single diastereomer.

This one-pot transformation from C-glycoside **7** to nitrogen bicyclic **8** likely starts with base-mediated β-elimination (see Scheme 3). The resultant α,β-conjugated ketone **11** in turn underwent an intramolecular nitrogen conjugate addition to form azasugar **12**. Meanwhile, as expected, the β,γ-double bond spontaneously migrated under the same conditions to produce **13** with an α,β-conjugated ketone functionality, which underwent a second intramolecular conjugate addition by azasugar nitrogen to afford **8**. In fact, the formation of only one diastereomer indicates both intramolecular conjugate additions

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(27) To avoid confusion in the assignment of NMR data the carbon numbering used in this paper corresponds to the numbering of the original carbohydrates.

(28) Better yield might be obtainable by stoicheiometric reaction of freshly prepared AllylMgBr with azidoaldehyde.

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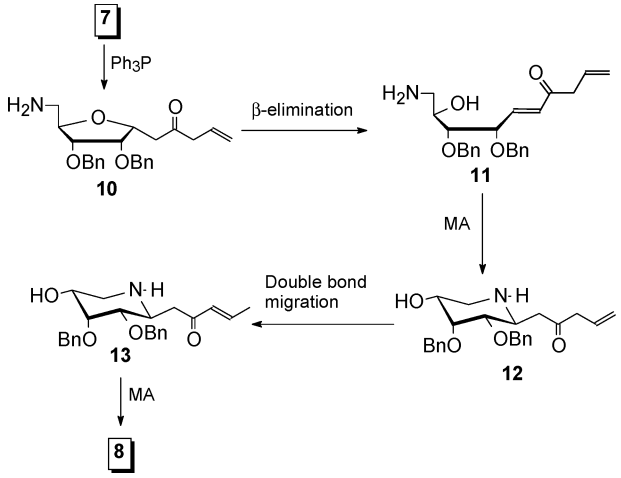
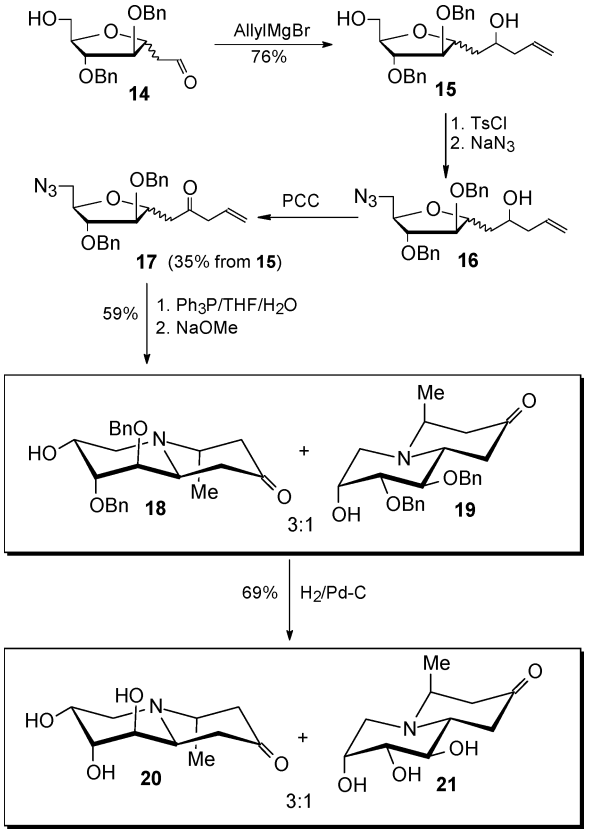
SCHEME 3. Proposed Pathway of the Base-Mediated One-Pot Reaction



SCHEME 4. Synthesis of Polyhydroxylated Quinolizidines



being highly stereoselective. Removal of *O*-benzyl groups by catalytic hydrogenation provided trihydroxylated quinolizidine derivative **9** in good yield.

In order to investigate the utility of this one-pot procedure, we selected C-arabinoside azidoketone **17** as the next test substrate. Using aldehyde **14**[30] as starting material, **17** was synthesized by the same procedure as described above for substrate **7** (see Scheme 4), which included (a) Grignard reaction to 2′,5-diol **15** (76%); (b) azido-substitution at C5 to azide **16**; and (c) PCC oxidation of 2′-OH to **17** (35% for two steps). We prepared an anomeric mixture of **17**α/β (α/β 1:1) from **14**α/β as well as an anomerically pure **17**α from **14**α to investigate the influence of the anomeric configuration, if any, on the stereoselectivity of the conjugate additions. After subjecting **17**α/β and **17**α to Staudinger reduction and base treatment, we isolated, from both reactions, a mixture of two diastereomers (**18** and **19)** in a ratio of 3:1, which were inseparable by silica gel chromatography, in 50−60% yield.

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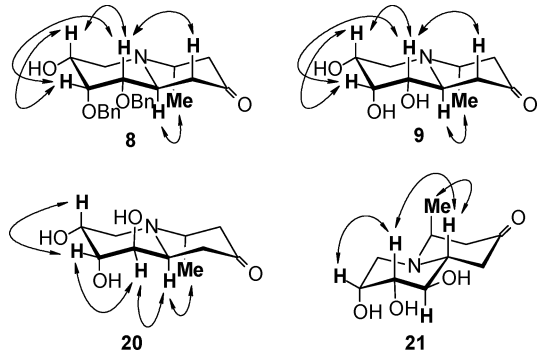


FIGURE 1. Major NOEs observed in compounds **8**, **9**, **20**, and **21**.

The Stereochemistry of Quinolizidines. It is apparent that the stereoselectivity of the conjugate additions can be affected by the substrate chirality but is independent of the anomeric configuration of azidoketone substrates. Double conjugate addition could produce four diastereoisomers; however, we obtained a single diastereomer **8** from **7** and a pair of stereoisomers (**18** and **19**) from **17**, indicating both intramolecular additions as being stereoselective. The stereochemistry of **8** and **18**/**19** was determined on the basis of various 1D- and 2D-NMR spectroscopic analyses and confirmed by the NMR analysis on their de-*O*-benzylated products, namely, **9** and **20**/**21**, respectively.

The proton spectrum of **8** revealed H1 resonance at 3.10 ppm with a coupling constant $J_{1,2} = 9.2$ Hz and small couplings between H2 and H3, and H3 and H4, which indicates the azasugar ring in **8** was in a $^4C_1$ conformation with an equatorial substitution at C1. The stereochemistry at C4′ was assigned on the basis of the observation of NOE between H1 and Me at C4′ (see Figure 1). After removal of the *O*-benzyl groups, the azasugar ring of quinolizidine **9** also adopts a $^4C_1$ conformation with 1,2-diaxial configuration clearly indicated by the coupling constants, $J_{1,2} = 9.6$ Hz, and the NOE between H2 and H4 (see Figure 1).

The structures of **18** and **19** in a mixture were also determined by various NMR analyses. The major compound **18** was assigned on the basis of proton−proton couplings (COSY and TOCSY) and NOEs. We observed small coupling constants between adjacent azasugar ring protons (H1, H2, and H3) and NOEs between H1 and H2, H2 and H3, and H3 and H4. These results indicate that the azasugar ring must adopt a $^4C_1$ conformation with an equatorial substitution at C1 (1,2-cis configuration).[31] In contrast, structural determination of the minor compound **19** was less straightforward because of many overlapping signals with **18**. However, we observed a doublet of doublet at 3.58 ($J = 8.8$ and 9.2 Hz), a characteristic signal of an axial proton that couples with two adjacent axial protons.

(31) In the previous report (ref 20), we presumed a similar L-arabinoazasugar adopting $^4C_1$ conformation (equatorial orientation at C2 and C3 and axial at C4) and thus made an error in the assignment of the anomeric stereochemistry.

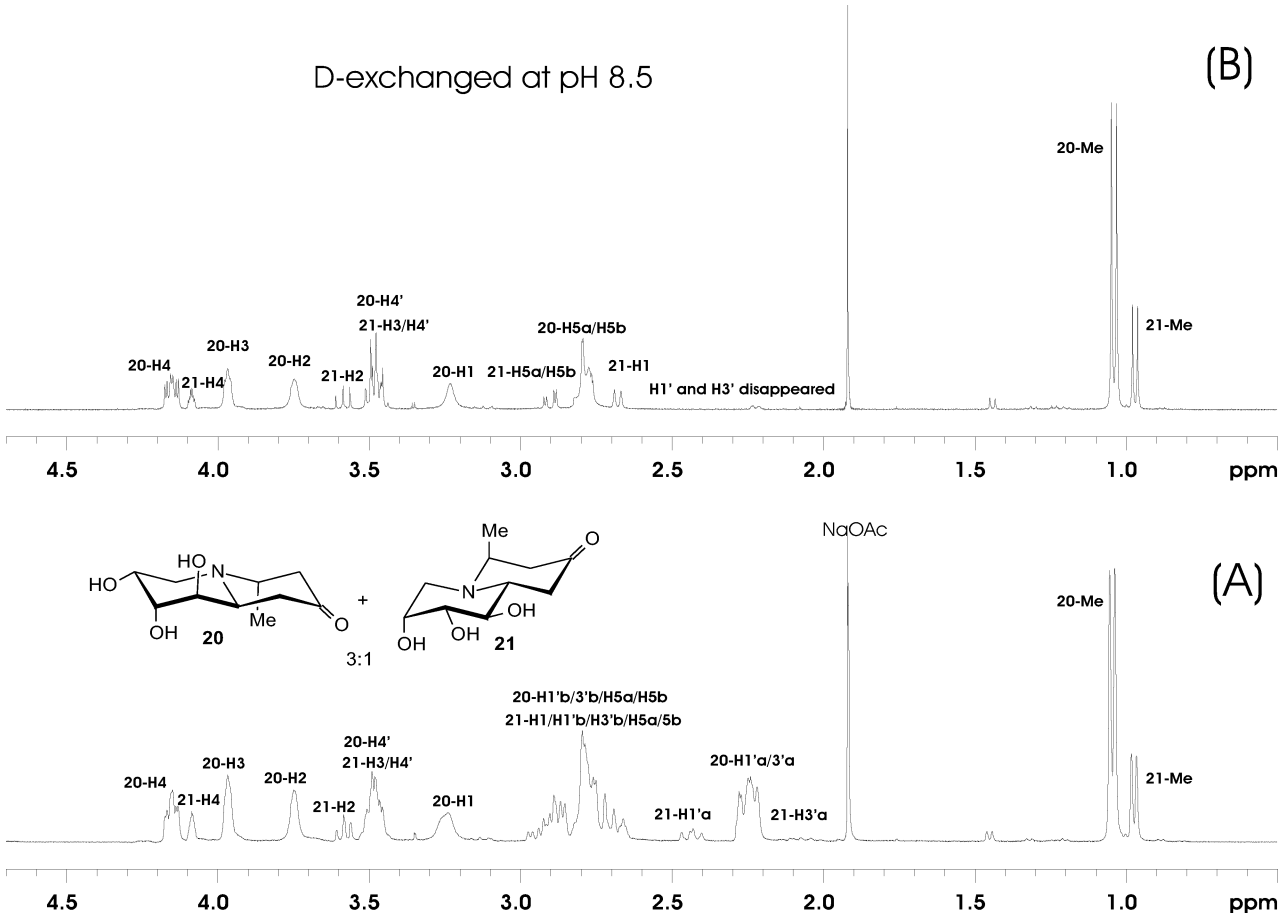


FIGURE 2. 400 MHz ^{1}H NMR spectra of a mixture of **20**/**21** recorded in D_2O at room temperature (A) and in D_2O (pH 8.5) with the same sample after 2 days at room temperature (B).

1D-TOCSY experiments provided evidence suggesting this proton as H2, and the structure of **19** was proposed in which the azasugar ring has a $^1C_4$ conformation with a 1,2-trans configuration as illustrated in Scheme 4. Both structures (**18** and **19**) were unambiguously confirmed by determination of the structures of their de-*O*-benzylated products **20** and **21**. Although they were still a mixture, removal of the *O*-benzyl groups provided a ^{1}H NMR spectrum which clearly indicated that the azasugar ring of the major compound (**20**) adopted $^4C_1$ conformation with a 1,2-cis configuration as evidenced by the small coupling constant between H1 and H2, H2 and H3, and H3 and H4 (actually broad singlets were obtained) due to their axial−equatorial and equatorial−equatorial relationships (Figure 2A). A simpler ^{1}H NMR spectrum was obtained by deuterium replacement of the α-protons adjacent to the ketone group at C1′ and C3′ (see Figure 2B); this transformation was completed by dissolving the compounds (**20**/**21**) in D_2O at pH 8.5 (adjusted by the addition of Na_2HPO_4). Thus, we were able to unambiguously assign all the protons of **20** and **21** based on various 2D-NMR spectra (COSY, TOCSY, NOESY). The axial−axial coupling constants of H1−H2 and H2−H3 ($J_{1,2}$ = 8.8 Hz and $J_{2,3}$ = 9.6 Hz) and NOEs observed in **21** (see Figure 1) not only revealed the structure of **21** but also confirmed the previous structural assignment of **19**. It is also noteworthy to mention that the α-protons at C1′ were more readily exchanged with deuterium than those at C3′ since we observed that the H1′ proton resonances had completely disappeared within 24 h while 25% of H3′ protons remained. Thus, regioselective modification at C1′ may be possible.

In contrast to the chair conformation of azasugar ring, the conformation of the ketone ring of **9**, **20**, and **21**[32] was less certain. Slow conformational interchange around nitrogen, especially in **20**, results in broadened ^{13}C NMR signals of C1′, C3′, and Me at C4′ (see the Supporting Information). Consequently, we were unable to detect these ^{13}C−^{1}H correlations by HSQC spectroscopic analysis.[33]

Stereochemistry of Conjugate Additions. The difference in diastereoselectivity resulting from the two substrates (ribose and arabinose) suggests the stereochemistry of the sugar played an important role, particularly in the first conjugate addition, where ribo-substrate **7** gave single product **8**, whereas arabino-substrate **17** produced two isomers (**18** and **19**). The effect of substrate chirality during the first conjugate addition is illustrated in Figure 3. Both thermodynamic and steric effects contribute to the stereoselectivity of azasugar formation. The thermody-

(32) It is noteworthy that the hydroxylated quinolizidines **9**, **20**, and **21** described here possess the same or similar skeleton as naturally occurring myrtine from plants and xestosin found from marine sponges. See: (a) Slosse, P.; Hootelé, C. *Tetrahedron* **1981**, *37*, 4287−4294. (b) Iwagawa, T.; Kaneko, M.; Okamura, H.; Nakatani, M.; van Soest, R. W. M.; Shiro, M. *J. Nat. Prod.* **2000**, *63*, 1310−1311.

(33) We attempted to record NMR spectra at 60 °C; unfortunately, epimerization at C4′ likely occurred in both **20** and **21**, as indicated by the proportional decrease of 4′-Me signals of **20** and **21** and by the appearance of a methyl resonance at 1.24 ppm (J = 5.9 Hz). See ref 32a.

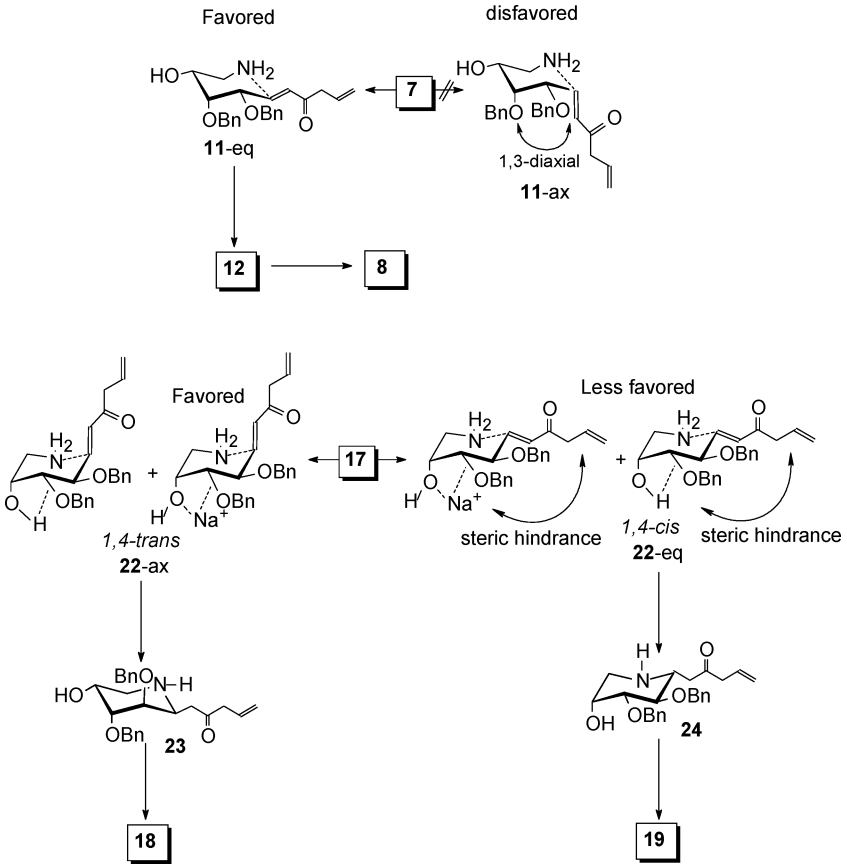
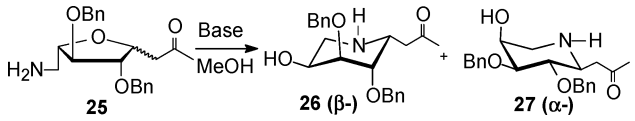


FIGURE 3. Stereoselectivity of the first Michael addition.

namic effect likely decides the initial conformation of the transition state, where ribose intermediate **11** adopts a more stable $^4C_1$ conformation and arabinose intermediate favors $^1C_4$ conformation, where both accommodate two equatorial substitutions and one axial substitution.[34] The key to the stereoselectivity is the orientation of the Michael acceptor. For example, **11** may lead to two transition states, **11**-eq and **11**-ax (see Figure 3), but **11**-eq which gave the equatorially substituted C-glycoside was favored thermodynamically and sterically, while **11**-ax with an axial Michael acceptor was disfavored due to 1,3-diaxial interactions. Consequently, aza-*β*-C-glycoside (**12**) was formed as a single distereomeric intermediate. Similarly, two transition states with $^1C_4$ conformation, **22**-ax and **22**-eq, were proposed (see Figure 3). Because we obtained **18** as the major product and **19** as the minor product from **17**, azasugars **23** and **24** were likely the intermediates. Therefore, the major transition state must be **22**-ax rather than **22**-eq. Although **22**-eq with an equatorial Michael acceptor is favored thermodynamically, the steric repulsion, likely resulting from metal ion chelation and/or hydrogen bonding between the vicinal axial 4-OH and amino groups in the transition state, acted in the opposite direction. This steric repulsion appears more critical than the thermodynamic effect to the transition state. In addition, the axial Michael acceptor was not interfered with by 1,3-diaxial interaction. Thus, the transition state **22**-ax became favored to give the major intermediate **23** with 1,4-trans configuration, while **22**-eq provided minor intermediate **24**. The metal chelation and/or hydrogen bonding were proposed because we observed, in a similar intramolecular conjugate addition using L-arabinose **25** as a substrate, the influence of base to the stereoselectivity (see Table 1). Apparently, because of the depleted chelation due to use of organic base, we were able to increase the ratio of α- to *β*-aza-C-glycosides (**27**/**26**). The significant amount of **26** produced with organic base was likely due to the role played by the intramolecular hydrogen-bonding effect (C−O−H···$^-$NH) that could not be suppressed using organic base. Additionally, it has also been reported in the literature that the axial 4-*O*-acyl substitution of a glycosyl donor favors 1,4-trans glycosylation as a result of remote participation that stabilizes the anomeric oxacarbenium ion.[35,36] However, there was no evidence to suggest such participation in our case other than

TABLE 1. Stereocontrol by Chelation



base	NaOMe	LiOH	DBU	2,6-lutidine	TEA
26/27	80:20	70:30	60:40	55:45	45:55

(34) The conformation should unlikely be affected by the stereoelectronic substituent effects which were observed upon protonation of azasugars. See: (a) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259−265. (b) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, *8*, 1218−1226.

(35) (a) De Meo, C.; Kamat, M. N.; Demchenko, A. V. *Eur. J. Org. Chem.* **2005**, 706−711. (b) Cheng, Y. P.; Chen, H. T.; Lin, C. C. *Tetrahedron Lett.* **2002,** *43*, 7721−7723. (c) Demchenko, A. V.; Rousson, E.; Boons, G. J. *Tetrahedron Lett.* **1999**, *40*, 6523 −6526.

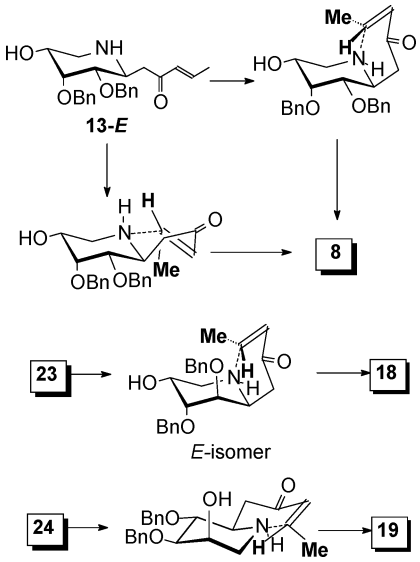


FIGURE 4. Stereoselectivity of the second Michael addition.

the steric repulsion. The mechanism proposed in Figure 3 is different from those in a typical Michael addition where the metal ion chelation occurs between carbonyl group and the nucleophile.[36]

The second conjugate addition was totally stereoselective because the existing azasugar ring likely directed the stereochemistry. The β,γ-double bond migration prior to the conjugate addition must have produced the thermodynamic stable *E*-isomers, e.g., **13-E** (see Figure 4). Subsequently, the steric repulsion between the methyl group and the azasugar ring dictated the transition-state topicity. Although the lone electron pair of nitrogen may approach the Michael acceptor from both axial and equatorial direction, regardless, both transition states afforded the same conjugation addition product. As a result, we were able to obtain complete diastereoselectivity in the conjugation addition.

In summary, we described here an effective method for the synthesis of polyhydroxylated quinolizidines by a double-conjugate addition. The evidence from our work suggests that the transition state of the first conjugate addition of nitrogen, which produces azasugar, is controlled by both the steric and thermodynamic effects, whereas the second conjugate addition is highly specific and entirely controlled by steric effect. This synthesis takes advantage of substrate chirality rather than use of chiral catalysts and is simple and easy to reproduce. In addition, the intermediates with hydroxyl and ketone functionalities should allow us to further modify these molecules to generate molecular diversities, which may provide critical value to lead discovery.

Experimental Section

2-*C*-(5-Azido-2,3-di-*O*-benzyl-5-deoxy-α-D-ribofuranosyl)acetaldehyde (3). A solution of **2** (1.0 g, 2.64 mmol) in CH_2Cl_2 (40 mL) was bubbled with ozone at −78 °C until a blue color appeared (10 min). The solution was concentrated to a residue, which was treated with dimethyl sulfide (5 mL) at room temperature overnight. The solvent was removed, and the crude was purified by chromatography (hexane−EtOAc 3:1) to give **3** as a syrup (0.7 g, 70%). ^{1}H NMR ($CDCl_3$) δ: 2.81 (bdd, 1H, 1′-CH_2, J = 6.0, 15.6 Hz), 2.89 (dd, 1H, 1′-CH_2, J = 6.4, 15.6 Hz), 3.17 (dd, 1H, H-5a, J = 4.0, 13.2 Hz), 3.55 (dd, 1H, H-5b, J = 3.6, 13.2 Hz), 4.02 (dd, 1H, H-3, J = 4.4, 7.6 Hz), 4.13 (dd, 1H, H-2, J = 4.4, 4.4 Hz), 4.18 (m, 1H, H-5), 4.50 (d 1H, CH_2Ph, J = 11.6 Hz), 4.53 (m, 1H, H-1), 4.53 (d 1H, CH_2Ph, J = 11.6 Hz), 4.68 (d 1H, CH_2Ph, J = 11.6 Hz), 4.78 (d 1H, CH_2Ph, J = 11.6 Hz), 9.74 (s, 1H, CHO).

5-*C*-(5-Azido-2,3-di-*O*-benzyl-5-deoxy-α-D-ribofuranosyl)-1-penten-4-ol (4). Method A. To a solution of aldehyde **3** (0.3 g, 0.79 mmol) in diethyl ether (10 mL) at −78 °C was dropwise added a solution of 1 M AllMgBr in diethyl ether (2 mL, 2 mmol). The mixture was stirred overnight at room temperature and diluted by the addition of saturated 0.5 M aqueous HCl/EtOAc (1:1, 100 mL). The organic phase was washed with water, dried, and concentrated. Purification by chromatography (EtOAc−hexanes 1:3) afforded a mixture of diastereomeric alcohols **4** (0.18 g, 54%) as a syrup.

Method B. To a solution of 1 M AllMgBr in diethyl ether (15 mL, 15 mmol) at −40 °C was dropwise added a solution of aldehyde **5** (0.9 g, 2.53 mmol) in anhydrous THF (5 mL). After 5 min at −40 °C, the mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of aqueous NH_4Cl, and the solution was extracted with dichloromethane. The organic phase was dried and concentrated. Purification by chromatography (EtOAc−hexanes 1:1) gave alcohol **6** (0.6 g, 59%) as a syrup.

To a solution of **6** (0.14 g) in dichloromethane (10 mL) was added a solution of TsCl (0.14 g) in pyridine (1.5 mL) at 0 °C. The mixture was kept at 4 °C for 2 days. The excess amount of TsCl was destroyed by the addition of MeOH, and the solution was washed with 0.5 M HCl and brine. The organic phase was dried and concentrated to a residue. To a solution of the residue in DMF (7 mL) was added NaN_3 (0.1 g), and the mixture was stirred at 80 °C for 4 h. Upon cooling, the mixture was diluted by the addition of water, and the aqueous solution was extracted with ethyl acetate. The combined organic solution was dried and concentrated. Purification by chromatography (EtOAc−hexanes 1:3) gave **4** as a syrup (60 mg, 41%). ^{1}H NMR ($CDCl_3$) δ: 1.72 (m, 1H), 1.92 (m, 1H), 2.23 (m, 2H), 3.14 (m, 1H), 3.54 (m, 1H), 3.77−3.85 (m, 1H), 3.99−4.03 (m, 2H), 4.19−4.32 (m, 2H), 4.47−4.82 (m, 4H, 2 × CH_2Ph), 5.08−5.14 (m, 2H), 5.75 (m, 1H), 7.29−7.37 (m, 10H).

5-*C*-(5-Azido-2,3-di-*O*-benzyl-5-deoxy-α-D-ribofuranosyl)-1-penten-4-one (7). To a mixture of alcohol **4** (0.13 g, 0.31 mmol), NaOAc (0.1 g), and 4 Å molecular sieves (0.2 g) in DCM (10 mL) was added PCC (0.15 g, 0.7 mmol) at room temperature. The mixture was stirred for 5 h, and the filtrate was washed and dried. Purification by chromatography (EtOAc−hexanes 1:3) afforded ketone **7** (0.1 g, 77%) as a syrup. $[\alpha]_D$: +36 (*c* 0.4, MeOH); ^{1}H NMR ($CDCl_3$) δ: 2.82 (dd, 1H, CH_2, J = 6.0, 17.6 Hz), 2.94 (dd, 1H, CH_2, J = 8.0, 17.6 Hz), 3.09 (bd, 1H, C*H*$_2$CH=CH_2, J = 6.8 Hz), 3.11 (bd, 1H, C*H*$_2$CH=CH_2, J = 6.8 Hz), 3.16 (dd, 1H, H-5a, J = 4.4, 13.2 Hz), 3.52 (dd, 1H, H-5b, J = 3.2, 13.2 Hz), 3.99 (dd, 1H, H-3, J = 4.0, 7.6 Hz), 4.14 (dd, 1H, H-4, J = 4.0, 7.6 Hz), 4.17 (dd, 1H, H-2, J = 3.6, 4.4 Hz), 4.49 (m, 1H, H-1), 4.44 and 4.79 (d and d, 1H each, CH_2Ph, J = 11.2 Hz), 4.51 and 4.68 (d and d, 1H each, CH_2Ph, J = 12.0 Hz), 5.07 (d, 1H, CH=C*H*$_2$, J = 16.4 Hz), 5.14 (d, 1H, CH=C*H*$_2$, J = 10.4 Hz), 5.84 (m, 1H, C*H*=CH_2), 7.28−7.36 (m, 10 H, 2 × Ph). ^{13}C NMR ($CDCl_3$) δ: 42.8 (C-1′), 48.4 (C-3′), 52.3 (C-5), 73.2 (*C*H$_2$Ph), 74.1 (*C*H$_2$Ph), 74.4 (C-1), 76.5 (C-2), 78.7 (C-4), 80.6 (C-3), 119.3 (C-5′), 128.0, 128.3, 128.6, 127.8, 130.4 (C-4′), 137.3 (Ph), 138.3 (Ph), 207.3 (C-2′). HRMS: calcd for $C_{24}H_{28}N_3O_4$ [M + H] 422.2084, found 422.2079.

Di-*O*-benzylquinolizidine 8. To a solution of azide **7** (55 mg, 0.131 mmol) in THF−H_2O (20:1, 6 mL) was added Ph_3P (60 mg), and the mixture was stirred at room temperature overnight. Complete reduction of the azide to amine was detected by TLC

(36) Gawley, R. E.; Aube, J. *Principles of asymmetric synthesis*, 1st ed.; Pergamon: Oxford, U.K., 1996.

(EtOAc−MeOH 5:1, R_f 0.15). The solvent was removed by evaporation under diminished pressure to a residue, to which was added 4% NaOMe (3.6 mL). After 2 h at room temperature, the starting material had disappeared and an intermediate with a slightly higher R_f was formed. The mixture was continuously stirred overnight to give a much less polar product. The mixture was diluted with water and extracted with ethyl acetate. The combined organic solution was dried and concentrated. Purification by chromatography (EtOAc to EtOAc/MeOH 5:1) gave compound **8** as a syrup (39 mg, 76%). $[\alpha]_D$: −19.2 (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.97 (d, 3H, CH_3, J = 6.8 Hz), 2.00 (dd, 1H, H-1′a, J = 10.8, 14.8 Hz), 2.18 (ddd, 1H, H-3′a, J = 2.0, 2.4, 14.0 Hz), 2.26 (bs, 1H, 4-OH), 2.60−2.75 (m, 4H, H-5a, 5b, 1′b, 3′b), 3.10 (ddd, 1H, H-1, J = 4.0, 9.2, 10.8 Hz), 3.23 (dd, 1H, H-2, J = 2.0, 9.2 Hz), 3.36 (m, 1H, H-4′), 3.75 (m, 1H, H-4), 4.05 (bs, 1H, H-3), 4.50 and 4.74 (d and d, 1H each, CH_2Ph, J = 11.6 Hz), 4.56 and 5.03 (d and d, 1H each, CH_2Ph, J = 11.6 Hz), 7.28−7.36 (m, 10 H, 2 × Ph). ^{13}C NMR ($CDCl_3$) δ: 11.7 (CH_3), 44.4 (C-1′), 48.6 (C-3′), 51.8 (C-1), 52.8 (C-5), 56.5 (C-4′), 67.8 (C-4), 72.8 (*C*H_2Ph), 74.6 (*C*H_2Ph), 74.9 (C-3), 83.5 (C-2), 128.0, 128.1, 128.3, 128.8, 137.5, 138.7, 209.2 (C-2′). HRMS: calcd for $C_{24}H_{30}$ NO_4 [M + H] 396.2174, found 396.2174.

Trihydroxyquinolizidine 9. A mixture of **8** (19 mg, 0.048 mmol) and 10% Pd−C (50% wet, 20 mg) in MeOH−HOAc (10:1, 5 mL) was subjected to hydrogenation (40 psi) overnight. The catalyst was removed by centrifugation, and the solvent was evaporated to a residue, which was dissolved in water. The product obtained by lyophilization was dissolved in water, and the solution was adjusted to pH 8 with 0.1 N NaOH before lyophilization. Purification by chromatography (EtOAc−MeOH 5:1) gave the final trihydroxylated quinolizidine **9** as a white solid (8 mg, 77%). $[\alpha]_D$: −6.5 (*c* 0.1, MeOH). ^{1}H NMR (D_2O) δ: 1.00 (d, 3H, CH_3, J = 6.8 Hz), 2.27 (m, 1H, H-1′a), 2.29 (m, 1H, H-3′a), 2.60 (m, 1H, H-5eq), 2.64 (m, 1H, H-3′b), 2.75 (dd, 1H, H-5ax, J = 10.8, 10.8 Hz), 2.82 (m, 1H, H-1′b), 2.92 (m, 1H, H-1), 3.44 (dd, 1H, H-2, J = 2.8, 9.6 Hz), 3.48 (m, 1H, H-4′), 3.87 (m, 1H, H-4), 4.02 (dd, 1H, H-3, J = 2.4, 2.8 Hz). ^{13}C NMR (D_2O) δ: 10.8 (CH_3), 43.2 (C-3′), 47.5 (C-1′), 49.3 (C-5), 52.0 (C-1), 55.9 (C-4′), 66.6 (C-4), 70.3 (C-3), 73.4 (C-2), 214.4 (C-2′). HRMS: calcd for $C_{10}H_{18}$ NO_4 [M + H] 216.1226, found 216.1235.

5-*C*-(5-Azido-2,3-di-*O*-benzyl-5-deoxy-α-D-arabinofuranosyl)-1-penten-4-one (17α). To a solution of aldehyde **14**α (0.45 g, 1.26 mmol) in anhydrous THF (5 mL) at −40 °C was dropwise added a solution of AllylMgBr in diethyl ether (7 mL, 7 mmol). After 5 min at −40 °C, the mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of 0.5 M HCl, and the solution was extracted with dichloromethane. The organic phase was dried and concentrated. Purification by chromatography (EtOAc−hexanes 1:3) afforded a diastereomeric mixture of **15**α (0.38 g, 76%) as a syrup.

To a solution of **15**α (0.35 g, 0.88 mmol) in dichloromethane (15 mL) was added a solution of TsCl (0.35 g, 1.8 mmol) in pyridine (1.5 mL) at 0 °C. The mixture was kept at 4 °C overnight and then at room temperature for additional 6 h. The excess amount of TsCl was destroyed by the addition of MeOH, and the solution was washed with 0.5 M HCl and brine. The organic phase was dried and concentrated to a residue. To a solution of above residue in DMF (15 mL) was added NaN_3 (0.3 g). The mixture was stirred at 80 °C for 6 h. Upon cooling, the mixture was diluted by the addition of water, and the aqueous solution was extracted with ethyl acetate. The combined organic phase was dried and concentrated to azide **16**α as a syrup.

To a solution of above syrupy **16**α in dichloromethane (20 mL) were added NaOAc (0.2 g), 4 Å molecular sieves (0.4 g), and PCC (0.4 g, 1.86 mmol) at room temperature. The mixture was stirred for 5 h, and the filtrate was washed and dried. Purification by chromatography (EtOAc−hexanes 1:3) afforded ketone **17**α as a wax (0.13 g, 35% over three steps). $[\alpha]_D$: +6 (*c* 4.0, MeOH). ^{1}H NMR ($CDCl_3$) δ: 2.75 (dd, 1H, H-1′a, J = 7.6, 16.8 Hz), 2.82 (dd, 1H, H-1′b, J = 6.4, 16.8 Hz), 3.17 (bd, 2H, 3′-CH_2, J = 7.2 Hz), 3.31 (dd, 1H, H-5a, J = 5.6, 12.8 Hz), 3.41 (dd, 1H, H-5b, J = 6.8, 12.8 Hz), 3.89 (bs, 1H, H-2), 3.91 (bs, 1H, H-3), 4.15 (m, 1H, H-4), 4.56 (m, 1H, H-1), 4.47 and 4.51 (d and d, 1H each, CH_2Ph, J = 13.2 Hz), 4.55 and 4.63 (d and d, 1H each, CH_2Ph, J = 11.8 Hz), 5.12 (d, 1H, H-5′a, J = 17.2 Hz), 5.18 (d, 1H, H-5′b, J = 10.4 Hz), 5.87 (m, 1H, H-4′), 7.28−7.36 (m, 10 H, 2 × Ph). ^{13}C NMR ($CDCl_3$) δ: 41.9 (C-1′), 48.4 (C-3′), 52.7 (C-5), 72.0 (*C*H_2Ph), 72.2 (*C*H_2Ph), 79.3 (C-1), 82.4 (C-4), 85.5 (C-2), 86.4 (C-3), 119.4 (C-4′), 127.8, 127.9, 128.2, 128.6, 127.7, 130.4 (C-5′), 137.5, 137.8, 206.6 (C-2′). HRMS: calcd for $C_{24}H_{28}$ N_3O_4 [M + H] 422.2084, found 422.2088.

The anomeric mixture, **17** with 1:1 α/β ratio, was prepared by same procedure and used for the one-pot reaction as well. For the NMR spectra, see the Supporting Information.

Protected Quinolizidines 18 and 19. To a solution of ketone **17**α (and **17**) (100 mg, 0.238 mmol) in THF−H_2O (20:1, 3 mL) was added Ph_3P (100 mg), and the solution was stirred at room temperature overnight. The solvent was evaporated to a residue, which was dissolved in 4% NaOMe (3 mL). The mixture was stirred at room temperature overnight, diluted with water, and extracted with ethyl acetate. The combined organic solution was dried and concentrated. Purification by chromatography (hexanes−EtOAc 1:4) afforded a mixture of **18** and **19** as a syrup in a ratio of 3:1 (55 mg, 59%). HRMS: calcd for $C_{24}H_{30}$ NO_4 [M + H] 396.2174, found 396.2152.

18 (Major). ^{1}H NMR ($CDCl_3$) δ: 0.97 (d, 3 H, Me, J = 6.8 Hz), 1.94 (bd, 1H, H-1′a, J = 14.0 Hz), 2.12−2.17 (m, 1H, H-3′a), 2.62−2.70 (m, 2H, H-1′b, 5a), 2.76−2.80 (m, 2H, H-3′b, 5b), 3.09 (bd, 1H, H-1, J = 10.8 Hz), 3.34 (bs, 1H, H-2), 3.44 (m, 1H, H-4′), 3.69 (dd, 1H, H-3, J = 4.0, 3.2 Hz), 4.12 (m, 1H, H-4), 4.45 and 4.51 (d and d, 1H each, CH_2Ph, J = 12.0 Hz), 4.48 and 4.57 (d and d, 1H each, CH_2Ph, J = 12.0 Hz), 7.24−7.60 (m, 10H, 2 × Ph). ^{13}C NMR ($CDCl_3$) δ:11.9 (CH_3), 41.7 (C-1′), 47.9 (C-3′), 52.2 (C-1), 52.5 (C-5), 56.7 (C-4′), 66.0 (C-4), 73.2 (*C*H_2Ph), 73.8 (*C*H_2-Ph), 75.3 (C-3), 75.8 (C-2), 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 137.3, 138.0, 210.1 (C-2′).

19 (Minor). ^{1}H NMR ($CDCl_3$, assigned based on 1D-TOCSY) δ: 0.93 (d, 3H, Me, J = 6.8 Hz), 2.20 (dd, 1H, H-1′a, J = 10.4, 14.0 Hz), 2.62−2.70 (m, 2H, H-1, 1′b, 5a), 2.76−2.80 (m, 2H, H-3′b, 5b), 3.09 (bd, 1H, H-1, J = 10.8 Hz), 3.42 (dd, 1H, H-3, J = 3.2, 9.2 Hz), 3.44 (m, 1H, H-4′), 3.58 (dd, 1H, H-2, J = 8.8, 9.2 Hz), 4.12 (m, 1H, H-4), 4.60 and 4.94 (d and d, 1H each, CH_2-Ph, J = 12.0 Hz), 4.69 and 4.74 (d and d, 1H each, CH_2Ph, J = 12.0 Hz), 7.24−7.60 (m, 10H, 2 × Ph). ^{13}C NMR ($CDCl_3$) δ: 11.2 (CH_3), 44.4 (C-1′), 48.5 (C-3′), 54.4 (C-1), 56.5 (C-5), 57.4 (C-4′), 65.8 (C-4), 72.0 (*C*H_2Ph), 75.3 (*C*H_2Ph), 81.4 (C-2), 82.7 (C-3), 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 138.0, 138.2, 208.7 (C-2′).

Trihydroxyquinolizidines 20 and 21. A mixture of **18**/**19** (24 mg, 0.06 mmol) and 10% Pd−C (50% wet, 20 mg) in MeOH−HOAc (10:1, 5 mL) was subjected to hydrogenation (40 psi) overnight. The catalyst was removed by centrifugation, and the solvent was evaporated. The residue was dissolved in water and lyophilized. The solid obtained was redissolved in water, and the solution was adjusted to pH 8 with 0.1 N NaOH and lyophilized again to give crude product. Purification by chromatography (EtOAc−MeOH 5:1) gave the final product **20**/**21** as a white solid (9 mg, 69%). HRMS: calcd for $C_{10}H_{18}$ NO_4 [M + H] 216.1235, found 216.1221.

20 (Major). ^{1}H NMR ($CDCl_3$) δ: 1.04 (d, 3H, Me, J = 6.8 Hz), 2.22−2.28 (m, 2H, H-1′a, 3′a), 2.64−2.90 (m, 4H, H-1′b, 3′b, 5a, 5b), 3.24 (bs, 1H, H-1), 3.48 (m, 1H, H-4′), 3.75 (bs, 1H, H-2), 3.96 (bs, 1H, H-3), 4.14 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ: 11.0

(Me), 49.8 (C-5), 52.1 (C-1), 56.3 (C-4′), 65.3 (C-4), 69.6 (C-3), 70.7 (C-2), 216.1 (C-2′).

21 (Minor). ^{1}H NMR ($CDCl_3$) δ: 0.97 (d, 3H, Me, J = 6.8 Hz), 2.45 (m, 1H, H-3′a), 2.46 (dd, 1H, H-1′a, J = 9.8, 14.4 Hz), 2.68 (m, 1H, H-1), 2.78−2.81 (m, 2H, H-3, 5a), 2.91 (dd, 1H, H-5b, J = 3.2, 13.2 Hz), 3.43−3.50 (m, 2H, H-3, 4′), 3.58 (dd, 1H, H-2, J = 8.8, 10.0 Hz), 4.08 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ: 10.2 (Me), 54.1 (C-5), 56.0 (C-4′), 57.6 (C-1), 67.9 (C-4), 73.29 (C-3), 73.32 (C-2), 215.2 (C-2′).

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Supporting Information Available: General methods and ^{1}H and ^{13}C NMR spectra of products **7**−**9** and **17**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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