Synthesis of Azasugars via Lanthanide-Promoted Aza Diels−Alder Reactions in Aqueous Solution

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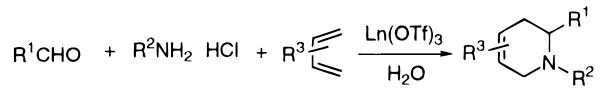
Aqueous aza Diels−Alder reactions of chiral aldehydes, prepared from carbohydrates, with benzylamine hydrochloride and cyclopentadiene, were promoted by lanthanide triflates. The *exo*/*endo* selectivities and diastereoselectivities of the reactions were elucidated by NMR, CD spectroscopy, and X-ray crystallography. The nitrogen-containing heterocyclic products were further transformed to azasugars, which are potential inhibitors against glycoprocessing enzymes.

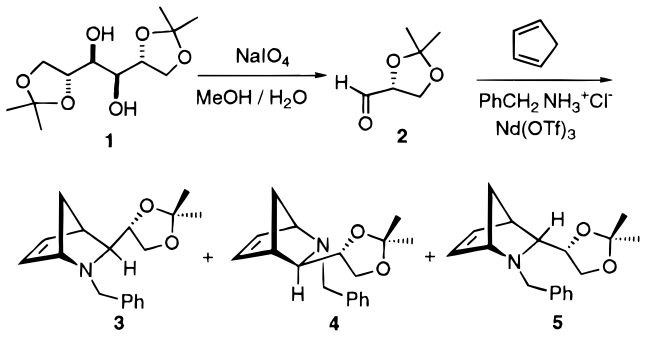
Introduction

The aqueous aza Diels−Alder (DA) reaction combines three components (an aldehyde, an amine salt, and a diene) to produce heterocyclic products which are useful synthetic intermediates.[1] Although chiral amines such as amino acids have been used as the amine part to prepare optically pure heterocyclic compounds, the reactions were largely limited to formaldehyde and activated aldehydes such as glyoxylate.[2] Recently, we found[3] that lanthanide triflates can promote the aqueous aza Diels−Alder reaction (Scheme 1), and this has allowed us to employ larger inactivated aldehydes to prepare heterocyclic compounds efficiently. Since reactions in aqueous media allow the use of unprotected carbohydrates or their derivatives as one of the components, application of the lanthanide-promoted aqueous aza DA reaction in carbohydrate chemistry promises to provide a novel entry to numerous carbohydrate-derived nitrogen-containing heterocycles (Scheme 1). Currently, we are especially interested in utilizing this methodology to synthesize azasugars and their analogs, which are potential inhibitors against glycoprocessing enzymes.[4] Here, we describe lanthanide-promoted reactions of two chiral aldehydes, prepared from D-mannitol and D-glucosamine, with benzylamine hydrochloride and cyclopentadiene, and subsequent transformations to azasugars from the adducts.

Scheme 1



Scheme 2



Results and Discussion

We started with glyceraldehyde acetonide **2** prepared from D-mannose derivative **1**.[5] The reaction of **2** with benzylamine hydrochloride and cyclopentadiene was carried out in water, in the presence of lanthanide triflates (Scheme 2). Three products (**3**, **4**, and **5**) were isolated. Table 1 lists the yields of the reaction with different lanthanides. It was found that the lanthanides of medium sizes gave better yields than smaller or larger ones. Among the seven lanthanides tested, $Nd(OTf)_3$ exhibited the best catalytic effect and gave 44% yield when 10% equiv of lanthanide triflate, based on benzylamine hydrochloride, was used. Different lanthanides did not significantly change the product distributions, and the ratios of **3**/**4**/**5** were around 1/8/3. When the amount of $Nd(OTf)_3$ was increased to 40% equiv, the reaction yield was increased to 72%.

We prepared another chiral aldehyde **7** via the diazotization of D-glucosamime hydrochloride **6**, followed by a ring contraction rearrangement.[6] The resultant aqueous solution of **7** was then combined with benzylamine hydrochloride and cyclopentadiene, followed by the addition of $Nd(OTf)_3$. The aza DA reaction produced only one major product **8**, which was acetylated to give **9** in a combined yield of 35% for the three steps (Scheme 3).

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(2) (a) Waldman, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 274−275. (b) Waldmann, H. *Liebigs Ann. Chem.* **1989**, 231. (c) Walmann, H. Braun, M. *Liebigs Ann. Chem.* **1991**, 1045. (d) Pombo-Villar, E.; Boelsterli, J.; Cid, M. M.; France, J.; Fuchs, B.; Walkinshaw, M.; Weber, H.-P. *Helv. Chim. Acta* **1992**, *76*, 1203−1215. (f) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263−1282. (g) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1337. (h) Stella, L.; Abraham, H.; Feneau-Dupont, J.; Tinant, B.; Decercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603. (i) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707.

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(4) (a) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (b) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195. (c) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, 182.

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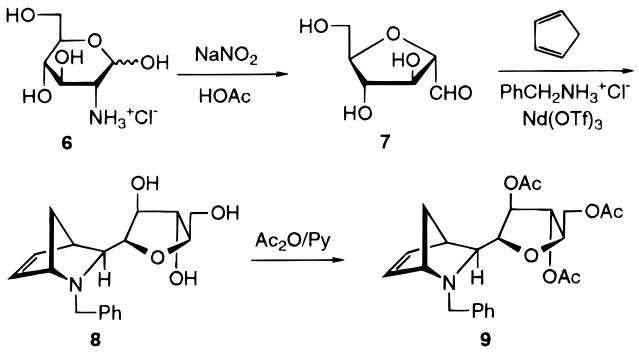
Table 1. Reaction[a] of 2 with $BnNH_2$·HCl and C_5H_5 promoted by Lanthanides Triflates

$Ln(OTf)_3$	yield (%)[b]	$Ln(OTf)_3$	yield (%)[b]
La	7	Dy	10
Pr	14	Er	15
Nd	44	Yb	8
Gd	32		

[a] The reaction was run with 1 mmol of $BnNH_2$·HCl, 1 mmol of **2**, and 170 μL of cyclopentadiene in the presence of 0.1 mmol of lanthanide triflate in 4 mL of water for 48 h. [b] Isolated yields.

Scheme 3



Scheme 4

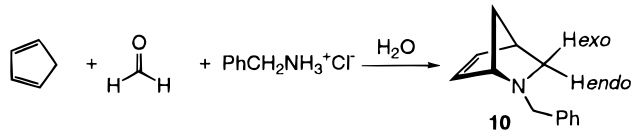


Table 2. Selected Chemical Shifts (δ) and Coupling Constants (J) of 3-H in compounds 3, 4, 5, 8 and 10[a]

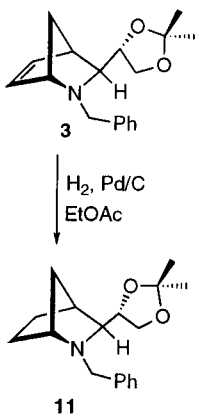
compd	δ[b]	J[c]
10	3.18	8.8, 3.2
	1.52	8.8, 1.6
3	1.80	8.0
4	1.89	7.6
8	2.03	6.0
5	2.76	6.4, 3.2

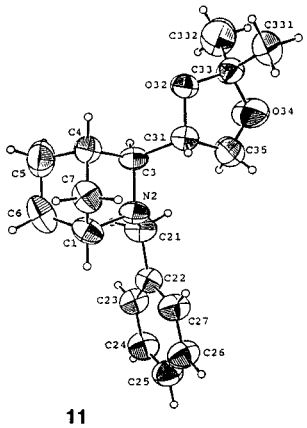
[a] All ^{1}H NMR spectra were recorded in $CDCl_3$. [b] In ppm. [c] In hertz.

To determine the structures of the above products, we studied the NMR spectra of a simple model compound **10**, which was prepared by an aza DA reaction of formaldehyde, benzylamine hydrochloride and cyclopentadiene (Scheme 4).[1b] The ^{1}H NMR peaks were assigned by 2D COSY NMR. Table 2 lists chemical shifts and coupling constants of 3-H in compound **3**, **4**, **5**, **8**, and **10**. For **10**, the peak at 3.18 ppm with coupling constants of 8.8 and 3.2 Hz was assigned to the 3-*exo*-H; the peak at 1.52 ppm with coupling constants of 8.8 and 1.60 Hz was assigned to the 3-*endo*-H. Thus, the *exo* and *endo* hydrogens at the 3-position have quite different chemical shifts, and this was used to characterize **3**, **4**, **5**, and **8**. Since chemical shifts of 3-H in **3**, **4**, and **8** are 1.80, 1.89, and 2.03 ppm, respectively, products **3**, **4**, and **8** were assigned to *exo* isomers. In contrast, product **5** was assigned to the *endo* isomer due to the chemical shift of 2.76 ppm and the coupling mode (dd, J = 6.4, 3.2 Hz) for its 3-H.

The absolute configurations of the azanorbornene products were determined by CD spectroscopy. For the 2-aza-*N*-benzyl-bicyclo[2.2.1]-5-heptene system without substitution at the 3-position, it was reported that the double bond and the benzyl group served as two exitons in CD measurement to deduce the absolute configurations of the enantiomers.[7] For our system, the benzyl group was *trans* to the bulky substituent at the 3-position. Thus, the benzyl group was downward in *exo* compounds **3**, **4**, and **8** and upward in the *endo* compound **5** (Figure 1). On the basis of the direction of rotation from the benzyl group to the double bond in these four compounds, the negative Cotton effect of **3** and **8** indicated their configurations shown in Scheme 2 and 3, respectively, and the positive Cotton effect of **4** and **5** indicated their configurations shown in Scheme 2.

Scheme 5





The assigned structures were further verified by X-ray crystallography and NOE study of their derivatives. Firstly, the double bond of product **3** was hydrogenated in ethyl acetate in the presence of Pd/C catalyst to give **11**,[11] which was recrystallized in hexane to give single crystals. The X-ray crystallography of **11** confirmed the structure of **3** (Scheme 5).[8] Secondly, we studied 2D NOESY of **9**, since ^{1}H NMR of **9** displayed well-resolved and separated peaks. The 2D NOESY NMR exhibited a cross peak between a-H and d-H, which supported the *exo* structure (Figure 2). The cross peaks between b-H and e-H, c-H and e-H suggested that the three hydrogens were spatially close, which was compatible to the configuration assigned to **8**.

The explanation of the stereoselectivity of the two aza DA reactions is depicted in Scheme 6. We assume that the lanthanide(III) coordinates the nitrogen of the Schiff base and the adjacent oxygen to form a 5-membered ring intermediate. The formation of the ring may require a lanthanide(III) with a suitable atomic radius. This may explain why the reaction of **2** with benzylamine hydrochloride and cyclopentadiene achieved the best yields with medium-sized lanthanides. On the basis of this 5-membered ring intermediate, *si* attack for the formation of **3** would be unfavorable due to stereohindrance. Between the two choices of *re* attacks, the pathway to produce compound **4** should be more favorable. This rationalization is consistent with our experimental results (e.g., **3/4/5** = 1/8/3). Similarly, sterically favored *si* attack to a 5-membered ring intermediate produces compound 8.

Finally, products **4** and **9** were converted into azasugars. In order to work out general procedures, we started with the model compoud **10**. Dihydroxylation of **10** by

(7) Pombo-Villar, E.; Boelsterli, J.; Cid, M. M.; France, J.; Fuchs, B.; Walkinshaw, M.; Weber, H.-P. *Helv. Chim. Acta* **1993**, *76*, 1203.

(8) X-ray data for **11**: $C_{18}H_{23}NO_2$; FW = 287.41; monoclinic $P2_1$; a = 9.7557(7) Å, $b \simeq$ 6.4260(6) Å, c = 13.4426(9) Å; β = 104.465(6)°, Σ = 0.710 73 Å, V = 816.0(1) Å; R = 0.0427, R_w = 0.0423, S = 1.76 based on 2872 observed reflections.

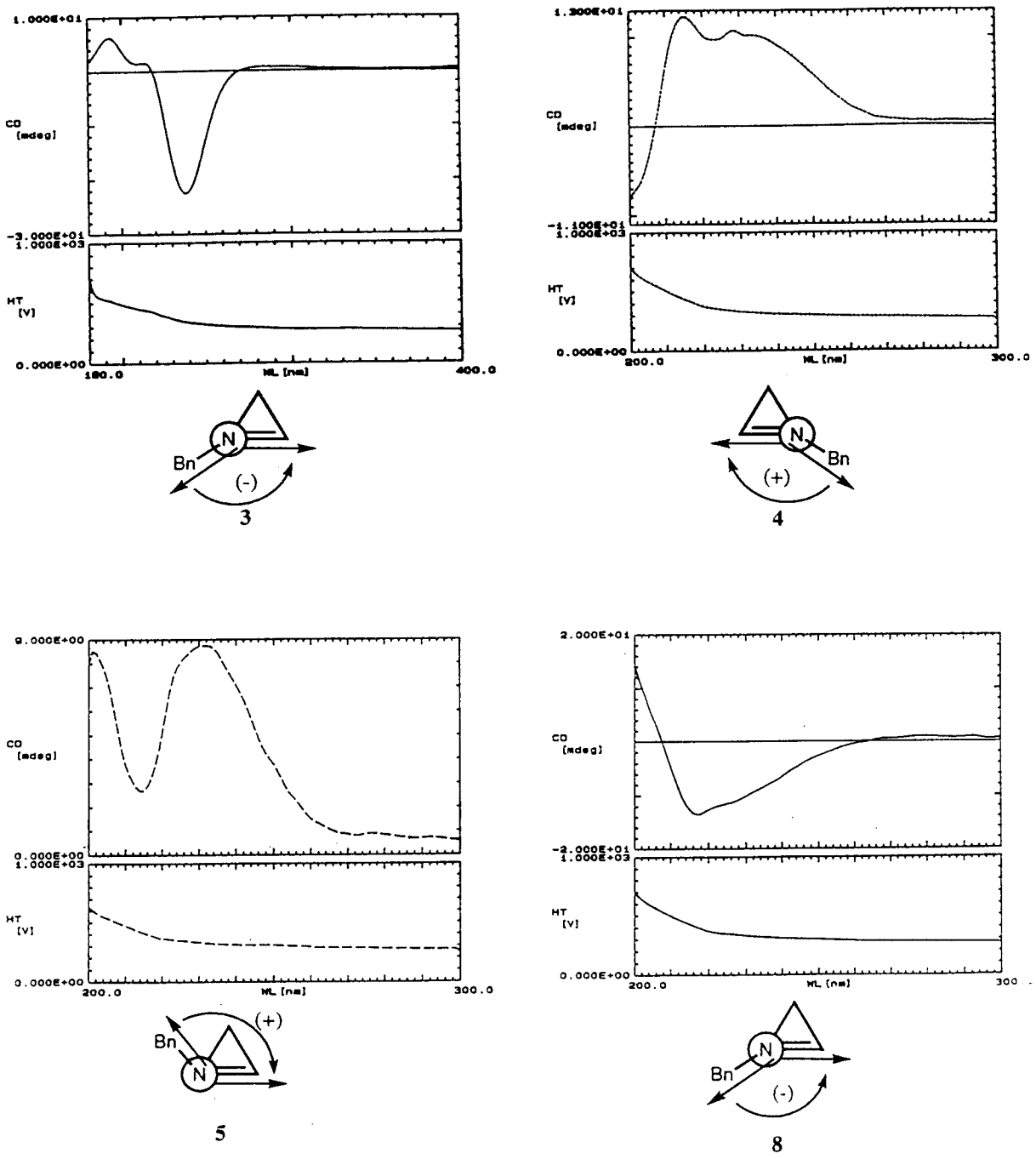
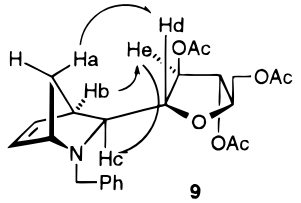


Figure 1. CD spectra of **3**, **4**, **5**, and **8** measured in methanol at 25 °C.



9

Figure 2. Illustration of NOE interactions of **9**.

OsO_4/Me_3NO/pyridine[9] in 2-propanol gave **12,** which was characterized as the *exo* diol because no vicinal couplings between 1-H and 6-H, 4-H and 5-H were observed.[10] Catalytic hydrogenation of **12** in methanol gave racemic azasugar **13** (Scheme 7). Similarly, dihydroxylation of **4** by OsO_4/Me_3NO in acetone and water afforded diol **14**, which was converted to the polyhydroxy compound **15** by acid-catalyzed deketalization in acetic acid and water (8/2). The azasugar **16** was synthesized through Pd-catalyzed debenzylation of **15** in methanol (Scheme 8). Further, compound **9** was dihydroxylated to afford compound **17**, which was deacetylated to afford compound **18** by NaOMe/MeOH. The aza disaccharide **19** was prepared through debenzylation of **18** (Scheme 9).

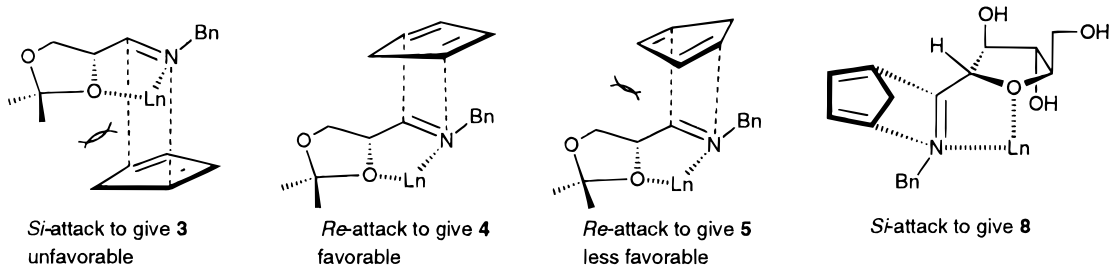
In summary, lanthanide-catalyzed aza DA reactions of two chiral aldehydes, prepared from carbohydrates,

(9) (a) Larsen, S. D.; Monti, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 8015. (b) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.

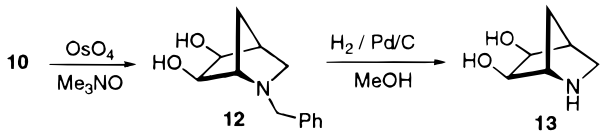
(10) Jäger, M.; Polborn, K.; Steglich, W. *Tetrahedron Lett.* **1995**, *36*, 861.

(11) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

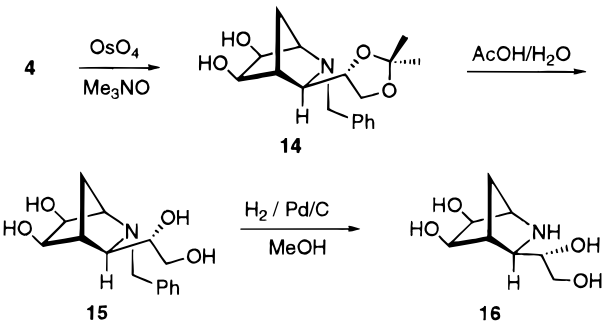
Scheme 6



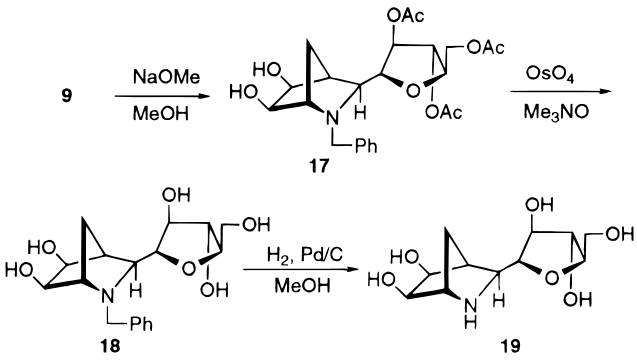
Scheme 7



Scheme 8



Scheme 9



stereoselectively produced chiral heterocyclic compounds, two of which were converted to the constrained azasugars. Work is in progress to study the inhibition of these coumpounds against a variety of glycoprocessing enzymes and to apply this methodology for the synthesis of bioactive carbohydrate analogs.

Experimental Section

General. ^{1}H and ^{13}C spectra were recorded on a 400 MHz NMR spectrometer. Mass spectra were run on the mass spectrometry facility at the University of California, Riverside. Thin-layer chromatography was conducted on Baker Si_{250F} silica gel TLC plates with a fluorescent indicator. Column chromatography was conducted with silica gel, grade 62, 60−200 mesh, 150 Å.

(1*S*,4*R*)-2-Aza-*N*-benzyl-3(*S*)-(1′(*S*), 2′-di-*O*-isopropylideneethyl)bicyclo[2.2.1]-5-heptene (3) and (1*R*,4*S*)-2-Aza-*N*-benzyl-3(*R*)-(1′(*S*),2′-di-*O*-isopropylideneethyl)-bicyclo[2.2.1]-5-heptene (4), and (1*S*,4*R*)-2-Aza-*N*-benzyl-3(*R*)-(1′(*S*),2′-di-*O*-isopropylideneethyl)bicyclo[2.2.1]-5-heptene (5). To a solution of benzylamine hydrochloride (144 mg, 1 mmol) and lanthanide triflate (0.1 mmol) in water (2 mL) were added 2, 3-di-*O*-isopropylidene glyceraldehyde (130 mg, 1 mmol) and cyclopentadiene (0.17 mL, 2 mmol). The reaction flask was sealed tightly, and the reaction mixture was allowed to stir vigorously for 48 h. The resulting solution was extracted with chloroform (10 mL × 3). The combined organic phase was washed with 1 N NaOH solution and brine and then dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure, and the residue was chromatographed to give **3**, **4**, and **5** sequentially, eluting with a mixture of ethyl acetate and hexane (1/9, 2/8, and 6/4). **3**: ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 8.40 Hz, 1 H), 1.36 (s, 3 H), 1.40 (s, 3 H), 1.73 (d, J = 8.40 Hz, 1 H), 1.80 (d, J = 8.0 Hz, 1 H), 3.02 (s, 1 H), 3.32 (d, J = 13.2 Hz, 1 H), 3.48 (d, J = 13.2 Hz, 1 H), 3.65 (m, 2 H), 3.93 (m, 2 H), 4.06 (dd, J = 8.0, 6.0 Hz, 1 H), 6.16 (dd, J = 5.60, 1.60 Hz, 1 H), 6.47 (m, 1 H), 7.25−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.9, 45.0, 46.4, 59.0, 63.3, 65.7, 68.3, 80.0, 108.6, 127.0, 128.3, 128.3, 133.0, 137.1; MS *m/e* 285 (M^+); HRMS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1732. **4**: ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 8.40 Hz, 1 H), 1.41 (s, 3 H), 1.45 (s, 3 H), 1.73 (d, J = 8.40 Hz, 1 H), 1.89 (d, J = 7.6 Hz, 1 H), 2.57 (s, 1 H), 3.18 (d, J = 13.8 Hz, 1 H), 3.70 (m, 2 H), 3.83 (m, 1 H), 4.11 (m, 2 H), 6.14 (d, J = 5.60, 2.0 Hz, 1 H), 6.46 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.9, 45.6, 45.8, 58.8, 62.4, 66.3, 67.2, 80.5, 108.9, 126.7, 128.2, 129.1, 132.5, 136.8; MS *m/e* 285 (M^+); HRMS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1738. **5**: ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.41 (s, 3 H), 1.47 (d, J = 8.80 Hz, 1 H), 1.71 (d, J = 8.80 Hz, 1 H), 2.77 (dd, J = 6.4, 3.6 Hz, 1 H), 2.87 (d, J = 3.6 Hz, 1 H), 3.60 (s, 1 H), 3.61 (d, J = 13.4 Hz, 1 H), 3.66 (m, 1 H), 3.77 (m, 1 H), 3.99 (m, 1 H), 4.15 (d, J = 13.4 Hz, 1 H), 6.04 (dd, J = 5.6, 2.8 Hz, 1 H), 6.32 (dd, J = 5.6, 3.0 Hz, 1 H), 7.32 (m, 5 H); MS *m/e* 285 (M^+); HRMS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1734.

1-Deoxy-*C*-(1 → 3)-((1*S*,3*S*,4*R*)-2-aza-*N*-benzylbicyclo-[2.2.1]-3-hept-5-enyl)-α-D-arabinofuranose (8) and 2,3,5-Tri-*O*-acetyl-1-deoxy-*C*-(1 → 3)-((1*S*,3*S*,4*R*)-2-aza-*N*-benzyl-bicyclo[2.2.1]hept-5-enyl)-D-α-arabinofuranose (9). A solution of glucosamine hydrochloride (11 g, 50 mmol) in water (80 mL) was stirred at room temperature for 6 h to reach mutarotational equilibrium. After the solution was cooled to 0 °C with an ice−salt bath, sodium nitrite (3.5 g, 55 mmol) was added. When acetic acid (9 mL, 150 mmol) in water (5 mL) was added dropwise, the reaction solution generated bubbles. After 1 h of stirring at 0 °C, TLC (^{i}PrOH/MeOH/H_2O, 8/2/1) showed the disappearance of the starting material. The cooling bath was removed, and then the reaction mixture was allowed to warm to room temperature. To the solution were added benzylamine hydrochloride (7.2 g, 50 mmol) and Nd(OTf)$_3$ (20 mmol) followed by the addition of cyclopentadiene (6.2 mL, 75 mmol). The reaction flask was sealed tightly, and the reaction mixture was stirred vigorously for 60 h. The reaction mixture was extracted with chloroform (50 mL × 3). The combined organic phases were washed with 1 N NaOH and brine and dried over anhydrous magnesium sulfate. Removal of solvents *in vacuo* gave a residue, half of which was chromatographed to afford **8** using chloroform and methanol (7/3, v/v) as eluents. The other half was mixed with 100 mL of a solution of dry pyridine and acetic anhydride (5/4). The resulting solution was stirred overnight. After the evaporation of solvents *in vacuo*, chloroform was added and the solution was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give an oil. Product **9** was obtained by silica gel flash

chromatography eluting with a mixture of ethyl acetate and hexane (3/7, 1/1, and 8/2 sequentially). **8**: ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 8.2 Hz, 1 H), 1.81 (d, J = 8.2 Hz, 1 H), 2.03 (d, J = 6.0 Hz, 1 H), 2.96 (s, 1 H), 3.07 (d, J = 12.4 Hz, 1 H), 3.59 (s, 1 H), 3.71 (dd, J = 11.6, 1.7 Hz, 1 H), 3.78 (dd, J = 11.6, 2.4 Hz, 1 H), 3.86 (d, J = 8.4 Hz, 1 H), 3.98 (m, 1 H), 4.16−4.21 (m, 3 H), 6.12 (m, 1 H), 6.53 (m, 1 H), 7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 45.9, 59.9, 62.5, 62.8, 66.0, 78.8, 79.6, 86.6, 88.2, 127.5, 128.5, 129.5, 132.5, 137.4, 138.7; MS *m/e* 318 (M + 1); HRMS calcd for $C_{18}H_{24}NO_4$ 318.1705, found 318.1699. **9**: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 8.20 Hz, 1 H), 1.67 (d, J = 8.20 Hz, 1 H), 1.90 (d, J = 8.0 Hz, 1 H), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 2.73 (s, 1 H), 3.13 (d, J = 12.8 Hz, 1 H), 3.59 (s, 1 H), 3.71 (d, J = 12.8 Hz, 1 H), 3.98 (dd, J = 8.0, 3.60 Hz, 1 H), 4.16 (m, 3 H), 5.06 (m, 1 H), 5.21 (m, 1 H), 6.11 (dd, J = 5.60, 2.0 Hz, 1 H), 6.41 (m, 1 H), 7.16−7.33 (m, 5 H); MS *m/e* 444 (M + 1); HRMS calcd for $C_{24}H_{29}NO_7$ 444.2022, found 4434.2033.

(1*S*,4*R*)-2-Aza-*N*-benzyl-3(*S*)-(1′(*S*),2′-di-*O*-isopropylideneethyl)bicyclo[2.2.1]heptane (11). To a solution of **3** (300 mg) in ethyl acetate was added 5% Pd/C (30 mg). The reaction mixture was hydrogenated under a hydrogen pressure of 40 lb/cm^2. The reaction was complete in 3 h. The reaction mixture was filtered, and the filtrate was condensed, followed by flash chromatography to give a solid **11** (272 mg) in 91% yield. The compound **11** was recrystallized in hexane to prepare single crystals for X-ray crystallography. **11**: mp 62−63 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 9.6 Hz, 1 H), 1.19−1.30 (m, 2 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 1.65 (m, 1 H), 1.75 (d, J = 9.6 Hz, 1 H), 2.01 (m, 1 H), 2.17 (d, J = 7.2 Hz, 1 H), 2.40 (d, J = 4.4 Hz, 1 H), 3.08 (s, 1 H), 3.65 (d, J = 13.6 Hz, 1 H), 3.68 (t, J = 8.0 Hz, 1 H), 3.75 (d, J = 13.6 Hz, 1 H), 3.82 (m, 1 H), 3.93 (dd, J = 8.0, 5.6 Hz, 1 H), 7.22−7.32 (m, 5 H); MS *m/e* 287 (M$^+$).

2-Aza-5,6-*exo*-dihydroxy-*N*-benzylbicyclo[2.2.1]heptane (12). To the solution of **10** (0.93 g, 5 mmol) in 50 mL of 2-propanol and water (3/1, v/v) were added trimethylamine oxide (1.4 g, 12 mmol), pyridine (0.5 mL), and osmium tetraoxide (75 mg, 0.3 mmol). The reaction mixture was refluxed overnight. After the mixture was cooled to room temperature, sodium sulfite was added. Water (50 mL) was added, and the resulting solution was extracted with chloroform. The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. Evaporation of solvents afforded the residue which was purified by chromatography (ethyl acetate/hexane, 1:1) to give **12** in 85% yield. **12**: ^{1}H NMR ($CDCl_3$) δ 1.55 (d, J = 10.8 Hz, 1 H), 1.74 (d, J = 10.8 Hz, 1 H), 2.31 (d, J =3.6 Hz, 1 H), 2.40 (d, J = 10.0 Hz, 1 H), 2.51 (dd, J = 10.0, 4.0 Hz, 1 H), 3.05 (s, 1 H), 3.30 (br, OH), 3.69 (s, 2 H), 3.83 (d, J = 6.0 Hz, 1 H), 4.01 (d, J = 6.0 Hz, 1 H), 7.31 (m, 5 H); MS *m/e* 219 (M$^+$); HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1268.

2-Aza-5,6-*exo*-dihydroxybicyclo[2.2.1]heptane (13). To a solution of **12** (660 mg, 3 mmol) in methanol (50 mL) was added 10% Pd/C (100 mg). The resulting black suspension was charged with hydrogen overnight, with a pressure of 40 lb/in.^{2}, through a Parr hydrogenation apparatus. The suspension was filtered, and the filtrate was concentrated to give the product **13** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J = 8.4 Hz, 1 H), 1.88 (d, J = 8.4 Hz, 1 H), 2.33 (d, 1 H), 2.42 (d, J = 8.0 Hz, 1 H), 2.78 (dd, J = 10.0, 3.6 Hz, 1 H), 2.98 (br, OH), 3.22 (s, 1 H), 3.71 (d, J = 5.6 Hz, 1 H), 3.81 (d, J = 5.6 Hz, 1 H); MS *m/e* 130 (M$^+$); HRMS cacld for $C_6H_{12}NO_2$ 130.0868, found 130.0867.

(1*R*,4*R*)-2-Aza-*N*-benzyl-3(*R*)-(1′(*S*),2′-di-*O*-isopropylideneethyl)-5(*R*),6(*S*)-*exo*-dihydroxybicyclo[2.2.1]heptane (14). Following the same procedure for preparation of **12**, **14** was prepared in 84% yield from **4**: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.40 (s, 3 H), 1.53 (d, J = 10.8 Hz, 1 H), 1.65 (d, J = 10.8 Hz, 1 H), 2.05 (s, 1 H), 2.12 (s, J = 6.80 Hz, 1 H), 2.93 (s, 1 H), 3.65 (m, 2 H), 3.83 (d, J = 5.80 Hz, 1 H), 3.98 (m, 3 H), 4.28 (d, J = 5.80 Hz, 1 H), 7.22−7.38 (m, 5 H); MS *m/e* 320 (M + 1); HRMS calcd for $C_{18}H_{26}NO_4$ 320.1862, found 320.1858.

(1*R*,4*R*)-2-Aza-*N*-benzyl-3(*R*)-(1′(S),2′-hydroxyethyl)-5(*R*),6(*S*)-*exo*-dihydroxybicyclo[2.2.1]heptane (15). A solution of **14** (200 mg) in acetic acid and water (8/2,v/v) was stirred in a bath of 55 °C for 10 h. The solvents were evaporated *in vacuo* to give a residue, which was purified via flash chromatography using chloroform and methanol (8/2, v/v) as eluents to give **15** in 90% yield: ^{1}H NMR (CD_3OD) δ 1.58 (d, J = 10.6 Hz, 1 H), 1.79 (d, J = 10.6 Hz, 1 H), 2.26 (s, 1 H), 2.39 (d, J = 6.40 Hz, 1 H), 2.97 (s, 1 H), 3.52 (m, 2 H), 3.64 (dd, J = 13.2, 7.2 Hz, 1 H), 3.82 (d, J = 13.2 Hz, 1 H), 3.85 (dd, J = 4.80, 1.60 Hz, 1 H), 4.07 (d, J = 13.2 Hz, 1 H), 4.38 (dd, J = 4.80, 1.60 Hz, 1 H), 7.30−7.45 (m, 5 H); MS *m/e* 280 (M + 1); HRMS calcd for $C_{15}H_{21}NO_4$ 280.1549, found 280.1543.

(1*R*,4*R*)-2-Aza-3(*R*)-(1′(*S*),2′-hydroxyethyl)-5(*R*),6(*S*)-*exo*-dihydroxybicyclo[2.2.1]heptane Hydrochloride (16). **16** was prepared in 90% yield from **15** by Pd/C-catalyzed hydrogenolysis in methanol: ^{1}H NMR (CD_3OD) δ 1.87 (d, J = 12.0 Hz, 1 H), 2.12 (d, J =12.0 Hz, 1 H), 2.50 (s, 1 H), 3.17 (d, J = 7.20 Hz, 1 H), 3.63 (m, 2 H), 3.68 (m, 2 H), 3.94 (d, J = 5.4 Hz, 1 H), 4.02 (d, J = 5.4 Hz, 1 H); MS *m/e* 190 (M + 1); HRMS for $C_8H_{15}NO_4$ 190.1079, found 190.1077.

2,3,5-Tri-*O*-acetyl-1-deoxy-*C*-(1 → 3)-((1*S*,3*S*,4*S*)-2-aza-*N*-benzyl-5(*S*),6(*R*)-*exo*-dihydroxybicyclo[2.2.1]heptyl)-α-D-arabinofuranose (17). Following the same procedure for preparation of **12**, **17** was prepared in 80% yield from **9**: ^{1}H NMR ($CDCl_3$) δ 1.59 (d, J = 10.4 Hz, 1 H), 1.65 (d, J = 10.4 Hz, 1 H), 2.04 (s, 3 H), 2.10 (s, 6 H), 2.23 (m, 2 H), 2.92 (s, 1 H), 3.63 (d, J = 12.8 Hz, 1 H), 3.81 (d, J = 5.60 Hz, 1 H), 3.95 (m, 2 H), 4.16 (m, 3 H), 4.27 (d, J = 5.6 Hz, 1 H), 5.07 (dd, J = 3.6, 2.8 Hz, 1 H), 5.18 (dd, J = 3.6, 2.4 Hz, 1 H), 7.25−7.38 (m, 5 H); MS *m/e* 478 (M + 1); HRMS calcd for $C_{24}H_{32}NO_9$ 478.2077, found 478.2057.

1-Deoxy-1-*C*-(1 → 3)-((3*S*,1*S*,4*S*)-2-aza-*N*-benzyl-5(*S*),6-(*R*)-*exo*-dihydroxybicyclo[2.2.2]heptyl)-α-D-arabinofuranose (18). To a solution of **9** (200 mg, 0.42 mmol) in 5 mL of anhydrous methanol was added sodium methoxide (20 mg). After 2 h of stirring, Dowex resin (H$^+$ form) was added to neutralize the reaction solution until a pH of 7−7.5, and then the resin was filtered. The filtrate was concentrated *in vacuo* to give **18** (140 mg) in 97% yield: ^{1}H NMR (CD_3CD) δ 1.55 (d, J = 10.0 Hz, 1 H), 1.67 (d, J = 10.0 Hz, 1 H), 2.23 (d, J = 9.60 Hz, 1 H), 2.32 (s, 1 H), 2.82 (s, 1 H), 3.60 (m, 2 H), 3.67 (m, 2 H), 3.78 (m, 2 H), 3.86 (m, 1 H), 3.94 (m, 1 H), 4.07 (d, J = 12.4 Hz, 1 H), 4.35 (d, J = 5.2 Hz, 1 H), 7.22−7.48 (m, 5 H); MS *m/e* 352 (M + 1); HRMS calcd for $C_{18}H_{26}NO_6$ 352.1760, found 352.1766.

1-Deoxy-*C*-(1 → 3)-((3*S*,1*S*,4*S*)-2-aza-5(*S*),6(*R*)-*exo*-dihydroxybicyclo[2.2.1]heptyl)-α-D-arabinofuranose (19). 19 was prepared from **18** in 92% by Pd/C catalyzed hydrogenolysis in methanol: ^{1}H NMR (CD_3OD) 1.78 (d, J = 10.8 Hz, 1 H), 2.03 (d, J = 10.8 Hz, 1 H), 2.55 (s, 1 H), 3.58 (m, 2 H), 3.64 (m, 1 H), 3.76 (m, 2 H), 3.82 (m, 1 H), 3.98 (m, 4 H); MS *m/e* 262 (M$^+$); HRMS calcd for $C_{11}H_{20}NO_6$ 262.1291, found 262.1303.

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Supporting Information Available: NMR spectra including 2D COSY and NOESY (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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