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Synthesis of a New Stable Conformationally Constrained 2,7-Anhydrosialic Acid Derivative

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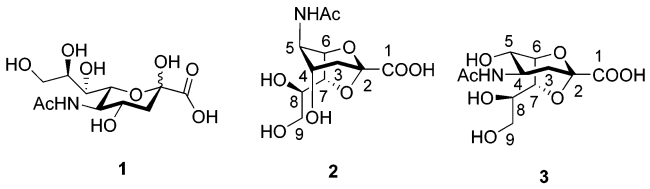
Abstract: A stereoseletive synthesis of 2,7-anhydrosialic acid derivative **18** was achieved from D-glucono-*δ*-lactone. A highly syn-selective addition of Grignard reagent to the *N*-benzylimine **8** served as a key step.

Sialic acids (e.g., *N*-acetylneuraminic acid, Neu5Ac, **1**) play significant biological roles in normal physiological processes and in disease states and microbial infections.[1−4] Due to the importance of sialic acids in biological investigations, many chemists have developed a number of efficient synthetic approaches[5,6] to these valuable compounds and their derivatives. Cornforth[7] completed the first synthesis of Neu5Ac in 1958. However, reports of sialic acids containing intramolecular glycosides are few. The first natural example, 2,7-anhydro-*N*-acetylneuraminic acid **2**, was isolated in a free form, cerumen of the wet type, by Suzuk[8] and synthesized from Neu5Ac (**1**) by Ogura and co-workers.[9,10] Due to the existence of an intramolecular acetal moiety in **2**, it offers an unusual rigid core that provides conformational constraint (Chart 1). Undoubtedly, the design and synthesis of additional sialic acid derivatives with stable and rigid conformations would provide valuable tools for the investigation of related biological questions. As mentioned above, the previously reported syntheses[9,10] of **2** are all from the sialic acid Neu5Ac, and therefore, most of the functional groups and their stereochemistries are fixed. To make more structurally diverse molecules, we are developing new stereoselective syntheses of these sialic acid derivatives from common sugars.[6k,11] Our considerations were based on a biomimetic [6 + 3] strategy (Scheme 1), which is commonly accepted as a biosynthetic route to sialic acids. The key point of our synthesis is that a three-carbon allylic bromide or propargyl bromide unit could be regarded as a synthetic precursor of pyruvate in the corresponding biosynthesis. One of the major advantages of such a strategy is that because lower carbon sugars are used as the starting materials, more diverse sialic acids can be generated via these new intermediates through various chemical reactions used during the synthesis. Herein, we present our recent results on the synthesis of a new sialic acid **3**, which contains an intramolecular glycoside prepared by the above-mentioned strategy. By comparison of **3** with **2**, the positional changes of functional groups on C-4 and C-5 are evident, as are their reversed stereochemistries which act as equatorial substitutions in **3**. Physically, the structure of **3** is kept rigid by the intramolecular glycoside, although a lower energy of **3** is theoretically possible determined by MM2 calculations[12] (see the Supporting Information). All of these structural characteristics were successfully established through a highly syn-selective addition of allylmagnesium bromide to the *N*-benzylimine, as well as further chemical transformations.

CHART 1



The synthesis of **3** was accomplished as shown in Scheme 2, Scheme 3, and Scheme 4. First, treatment of D-gluocono-*δ*-lactone with 2,2-dimethoxypropane in acetone and methanol in the presence of a catalytic amount of pTsOH hydrate afforded the methyl ester **4**[13] in high yield (83%) after simple distillation. Protection of the second alcohol with benzyl bromide in CH_2Cl_2 using silver

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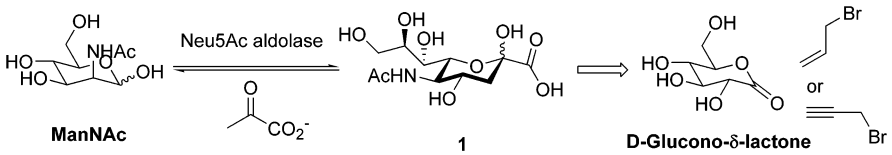
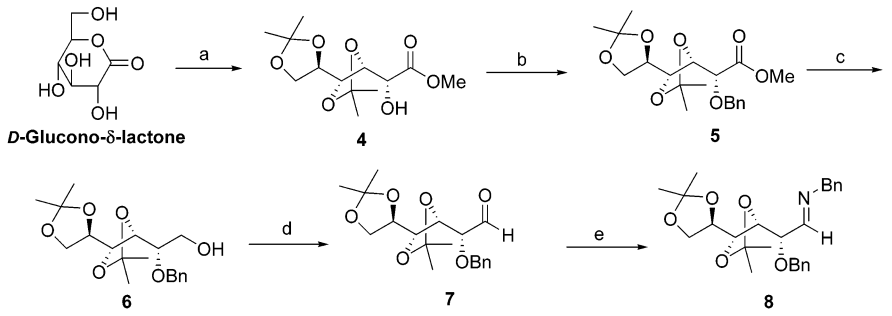
SCHEME 1

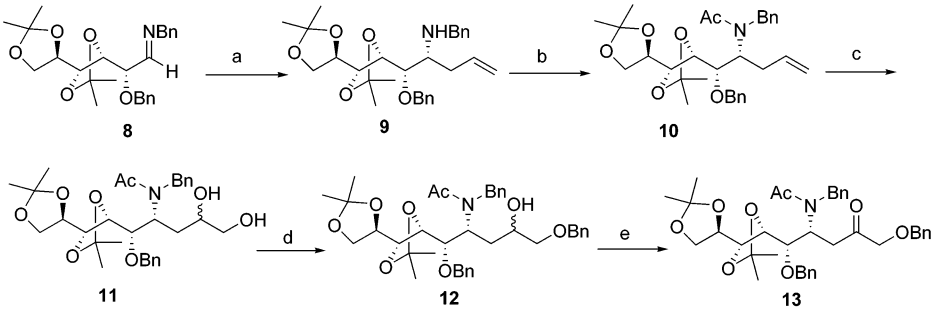


SCHEME 2[a]



[a] Reagents and conditions: (a) pTsOH, acetone, DMOP, MeOH, 83%; (b) Ag_2O, BnBr, CH_2Cl_2, 74%; (c) LAH, THF, 87%; (d) Dess−Martin periodinane, CH_2Cl_2, 83%; (e) Mg_2SO_4, 4 Å molecular sieves, $BnNH_2$, THF, 100%.

SCHEME 3[a]



[a] Reagents and conditions: (a) C_3H_5MgBr, Et_2O, 0−25 °C, two steps 56%; (b) Ac_2O, Et_3N, CH_2Cl_2, 88%; (c) OsO_4, NMO, acetone, H_2O, 76−83%; (d) Bu_2SnO, TBAB, BnBr, toluene, 98%; (e) Dess−Martin periodinane, CH_2Cl_2, 90%.

oxide as a base gave **5** in 74% yield.[14] The corresponding alcohol **6** was obtained by reduction of ester **5** with $LiAlH_4$ (87%). Treatment of alcohol **6** with Dess−Martin periodinane in CH_2Cl_2 gave the aldehyde **7** (83%), which was further converted into the imine **8** in quantitative yield.

The highly syn-selective addition of Grignard reagent to *N*-benzylimine **8** served as a key step in our synthesis (Scheme 3). The *N*-benzylimine **8** was treated with 3 equiv of allylmagnesium bromide in ether at room temperature to afford the syn adduct **9** (two steps in 56% yield) and minor anti adduct (syn/anti > 10:1 as measured by the ^1H NMR of crude product). The syn selectivity was finally confirmed by an X-ray study of a related derivative after five-step transformation from the major adduct **9** (unpublished results; see the Supporting Information), and the stereochemistry of addition could be explained well by Cram's rule.[15−19] The amine **9** was directly treated with Ac_2O and triethylamine in CH_2Cl_2 using DMAP as catalyst to give acetamide **10** in 88% yield. Dihydroxylation of alkene **10** with NMO and catalytic OsO_4 (2.5 wt % in ^{n}BuOH) in acetone and H_2O afforded diol **11** in 76% yield (as a mixture of two diastereomers). Selective protection of the primary hydroxyl group with Bu_2SnO and benzyl bromide yielded **12** in 98% yield. Subsequent oxidation of the free hydroxyl group with Dess−Martin periodinane gave ketone **13** (90%) as a single enantiomer.

Removal of the two acetonide protecting groups in **13** was carried out with hydrogen chloride in methanol (Scheme 4), and the 6,8-dioxabicyclo[3.2.1]octane core was formed in situ to provide the 2,7-anhydro sugar derivative **14** in 80% yield. The facile formation of acetal could be explained by the spatial proximity of the 2-hydroxyl and 7-hydroxyl groups during the reaction, allowing additional free space for the three benzyl groups in the same molecule. The remaining two hydroxyls of **14** were then protected with 2,2-dimethoxylproprane to afford **15** (82%), which was further treated with lithium in liquid ammonia to give diol **16** in 90% yield. The

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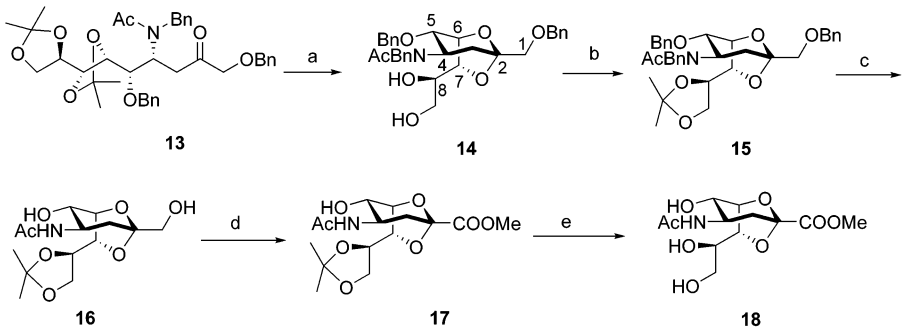
SCHEME 4[a]



[a] Reagents and conditions: (a) HCl, MeOH, 80%; (b) DMOP, pTsOH (cat.), 82%; (c) Li, liquid NH_3, 90%; (d) (1) KBr, TEMPO, TBAB, $Ca(ClO)_2$, (2) MeI, K_2CO_3, DMF, 60% in two steps; (e) HCl, MeOH, 89%.

primary alcohol of **16** was selectively oxidized by TEMPO and aqueous calcium hypochlorite to yield the corresponding acid, which was immediately trapped as its methyl ester by MeI in DMF to afford **17** (60% yield in two steps). Treatment of **17** with hydrogen chloride in methanol gave the final product **18** as a white solid in 89% yield. The structure of **18** was unambiguously confirmed by its physical data.

In summary, a new conformationally constrained 2,7-anhydrosialic acid derivative **18** was synthesized for the first time from readily available D-glucono-δ-lactone. The stereoselectivity, regioselectivity, and selective protection of free hydroxyls were controlled well in our synthesis. A highly syn-selective addition of allylmagnesium bromide to an α-alkoxyl imine served as a key step to introduce an essential three-carbon unit flowing a biomimetic [6 + 3] strategy. The strategy and methods described in this paper could be useful tools to obtain more diverse sialic acid derivatives for potential biological investigations.

Experimental Section

(4*R*,5*S*,6*R*,7*R*,8*R*)-*N*^{4}-Benzyl-5-benzyloxy-6,7:8,9-di-*O*-isopropylidene-1-nonene (9). To a stirred solution of Dess−Martin periodinane (0.72 g, 1.7 mmol) in dry CH_2Cl_2 (8 mL) was added **6**[14] (0.53 g, 1.5 mmol) in dry CH_2Cl_2 (13 mL) over 15 min. After 30 min, the homogeneous mixture was diluted with ether and poured into cooled saturated aq $NaHCO_3$ (15 mL) containing $Na_2S_2O_3$ (1.87 g). The combined organic layers were washed with saturated aq $NaHCO_3$ and brine and dried over $MgSO_4$. The solvents were evaporated to give compound **7** (0.44 g, 83%). The resultant yellow residue was used directly for the next step without further purification.

A mixture of **7** (1.73 g, 4.91 mmol), $MgSO_4$ (1.95 g), 4 Å MS (1.95 g), and benzylamine (0.67 mL) in dry THF (10 mL) was stirred at rt for 2 h. The solid was filtered and washed with dry THF (2 mL), and the filtrate was carried to the next step without further purification.

To the above THF solution of imine **8** was added allylmagnesium bromide (1 M in ether, 15 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 2 h until it was quenched with saturated aq NH_4Cl at 0 °C. The mixture was extracted with ether, and the combined organic layers were washed with saturated aq $NaHCO_3$, brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (hexane/ethyl acetate = 20:1) to give compound **9** (1.31 g, 56% yield based on crude **7**) as a yellowish oil. $[\alpha]_D = +4.4$ (*c* 1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.19 (m, 10H), 5.75 (m, 1H), 5.15−5.10 (m, 2H), 4.67 (AB, 2H, $J_{AB} = 11.4$ Hz), 4.29 (dd, 1H, $J = 7.5$, 3.3 Hz), 4.15−4.03 (m, 2H), 3.96 (dd, 1H, $J = 7.5$, 6.9 Hz), 3.88 (dd, 1H, $J = 7.5$, 5.7 Hz), 3.76 (AB, 2H, $J_{AB} = 12.8$ Hz), 3.65 (dd, 1H, $J = 4.8$, 3.3 Hz), 2.94 (m, 1H), 2.51 (m, 1H), 2.30 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H). EI-MS (*m*/*z*): 481 (M^+, 0.08), 466 ($M^+ - Me$, 3.08), 440 (10.76), 161 (12.59), 160 (100.0). IR (film): 3030, 2987, 2935, 1639, 1455, 1371, 1069 cm^{-1}. Anal. Calcd for $C_{29}H_{39}NO_5$: C, 72.32; H, 8.16; N, 2.91. Found: C, 72.82; H, 8.41; N, 2.91.

(4*R*,5*S*,6*R*,7*R*,8*R*)-*N*^{4}-Benzyl-*N*^{4}-acetyl-5-benzyloxy-6,7:8,9-di-*O*-isopropylidene-1-nonene (10). To a solution of **9** (1.31 g, 2.7 mmol) in dry CH_2Cl_2 (20 mL) were added Et_3N (1.1 mL, 8.2 mmol), DMAP (cat.), and acetic anhydride (0.55 mL, 5.46 mmol) at 0 °C. After the mixture was stirred for 8 h at room temperature, the reaction was quenched by water and the mixture was extracted with ether. The combined organic layers was washed with brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (hexane/EtOAc = 5:1) to give compound **10** (1.25 g, 88%) as a yellowish oil. $[\alpha]_D = +0.2$ (*c* 1.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.19 (m, 10H), 5.58 (m, 1H), 5.04−4.94 (m, 2H), 4.70 (AB, 2H, $J_{AB} = 11.4$ Hz), 4.47 (m, 1.14H), 4.27−4.11 (m, 2.86H), 4.04−3.83 (m, 4.58H), 3.60 (m, 0.42H), 2.43 (m, 2H), 2.21 (s, 1.19H), 2.00 (s, 1.81H), 1.43−1.25 (m, 12H). ESI-MS (*m*/*z*): 524 ($M^+ + 1$, 100), 546 ($M^+ + Na$, 10). IR (film): 3032, 2987, 2935, 1652, 1455, 1381, 1215, 1068 cm^{-1}. HRESIMS: calcd for $C_{31}H_{41}NO_6 + Na$ 546.2826, found 546.2808.

(2*RS*,4*R*,5*S*,6*R*,7*R*,8*R*)-*N*^{4}-Benzyl-*N*^{4}-acetyl-5-benzyloxy-6,7:8,9-di-*O*-isopropylidenenonane-1,2-diol (11). To a solution of **10** (0.52 g, 1 mmol) in acetone (5 mL) and water (1 mL) were added NMO monohydrate (202 mg, 1.5 mmol) and OsO_4 solution in *n*-BuOH (2.5 wt %, 508 mg, 0.05 mmol) at rt. After being stirred for 19 h at this temperature, the reaction was quenched by adding saturated aq Na_2SO_3. The mixture was filtered through a Celite pad and washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (hexane/EtOAc = 1:4) to afford **11** (0.38 g, 76%) as a yellowish oil. $[\alpha]_D = +22.9$ (*c* 1. 0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−7.18 (m, 10H), 5.29−4.30 (m, 4.50H), 4.17−3.80 m, 6.0H), 3.70−2.90 (m, 4.40H), 2.67−1.92 (m, 4.50H), 1.82−1.56 (m, 1.60H), 1.43−1.34 (m, 12H). ESI-MS (*m*/*z*): 580 ($M^+ + Na$, 100). IR (film): 3420, 3032, 2988, 2936, 1624, 1454, 1372, 1215, 1070 cm^{-1}.

(2*RS*,4*R*,5*S*,6*R*,7*R*,8R)-*N*^{4}-Benzyl-*N*^{4}-acetyl-1,5-bis(benzyloxy)-6,7:8,9,-di-*O*-isopropylidenenonan-2-ol (12) A mixture of compound **11** (403 mg, 0.7 mmol) and Bu_2SnO (200 mg, 0.8 mmol) in toluene (15 mL) and methanol (0.73 mL) was heated at 85 °C for 2 h. The solvents were evaporated under reduced pressure. TBAB (258 mg, 0.8 mmol), BnBr (0.26 mL), and toluene (11 mL) were then added. The mixture was heated at 80 °C for 10 h, and then the solvents were evaporated again under vacuum. The residue was directly purified by flash chromatography (hexane/EtOAc = 2:1) to give **12** (0.46 g, 98%) as a yellowish oil. $[\alpha]_D = +24.9$ (*c* 1.25, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.40−7.23 (m, 15H), 5.10−5.02 (m, 0.4H), 4.77−4.64 (m, 2.10H), 4.51−4.33 (m, 3.40H), 4.32−4.03 (m, 2.50H),

4.07−3.60 (m, 5.60H), 3.36−3.25 (m, 2H), 2.46 (d, 1H, J = 4.5 Hz), 2.13 (s, 1H), 1.98 (s, 2H), 1.92−1.78 (m, 2H), 1.43−1.25 (m, 12H). ESI-MS (m/z): 648 (M^+ + 1, 100), 670 (M^+ + Na, 25). IR (film): 3376, 3032, 2987, 2934, 1645, 1619, 1455, 1217, 1072 cm^{-1}. HRESIMS: calcd for $C_{38}H_{49}NO_8$ + Na 670.3350, found 670.3326.

(4*R*,5*S*,6*R*,7*R*,8R)-*N*^{4}-Benzyl-*N*^{4}-acetyl-1,5-bis(benzyloxy)-6,7:8,9-di-*O*-isopropylidene-2-oxononane (13). To a stirred solution of Dess−Martin periodinane (341 mg, 0.8 mmol) in dry CH_2Cl_2 (2 mL) was added **12** (461 mg, 0.7 mmol) in CH_2Cl_2 (4 mL) over 2 min. After 2 h, the homogeneous mixture was diluted with ether and poured into cooled saturated $NaHCO_3$ (7 mL) containing $Na_2S_2O_3$·$5H_2O$ (1.39 g). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 2:1) to give **13** (416 mg, 90%) as a yellowish oil. $[\alpha]_D$ = +42.3 (*c* 1.80, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.36−7.11 (m, 15H), 5.39−5.24 (m, 0.96H), 4.87−4.82 (m, 0.67H), 4.60−4.45 (m, 2.68H), 4.36−4.16 (m, 2.69H), 4.09−3.68 (m, 6.96H), 3.13 (d, 0.50H, J = 17.4 Hz), 3.01 (d, 0.54H, J = 16.8 Hz), 2.86 (m, 1.29H), 2.60 (dd, 0.71H, J = 16.9, 3.0 Hz), 2.38 (s, 2H), 2.02 (s, 1H), 1.45−1.32 (m, 12H). ESI-MS (m/z): 668 (M^+ + Na, 100.00). IR (film): 3065, 3032, 2988, 2935, 1728, 1646, 1619, 1454, 1372, 1215, 1069 cm^{-1}. HRESIMS: calcd for $C_{38}H_{47}NO_8$ + Na 668.3194, found 668.3187.

***N*-Benzyl-*N*-((2*S*,3*R*,5*S*,7*R*)-2-(benzyloxy)-5-((benzyloxy)-methyl)-7-((*R*)-2,2-dimethyl-1,3-dioxoxlan-4-yl)-6,8-dioxa-bicyclo[3.2.1]octan-3-yl)acetamide (15).** To a solution of **13** (130 mg, 0.2 mmol) in methanol (1 mL) was added HCl in methanol (1M, 4 mL). The mixture was stirred at room temperature for 14 h and then concentrated under reduced pressure. The residue was purified by flash chromatography (chloroform/methanol = 4:1) to give **14** (92 mg, 80%) as a syrup. The resultant diol **14** (85 mg) was then dissolved in 2,2-dimethoxylpropane (2 mL), and *p*-toluenesulfonic acid (cat.) was added. The reaction mixture was stirred at rt for 10 min and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 4:1−2:1) to give **15** (75 mg, 82% yield based on crude **14**) as a yellowish oil. $[\alpha]_D$ = −36.0 (*c* 0.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.16 (m, 15H), 4.70−4.18 (m, 8.3H), 4.07−3.88 (m, 4.10H), 3.63 (m, 0.6H), 3.48 (m, 2H), 2.37 (s, 1.8H), 2.0 (s, 1.2H), 1.95 (m, 2H), 1.47−1.29 (m, 6H). ESI-MS (m/z): 588 (M^+ + 1, 100.00), 610 (M^+ + Na, 38). IR (film): 3032, 2986, 2935, 1653, 1619, 1454, 1371, 1216, 1076 cm^{-1}. HRESIMS: calcd for $C_{35}H_{41}NO_7$ + Na 610.2775, found 610.2788.

***N*-((2*S*,3*R*,5*S*,7*R*)-2-Hydroxy-5-(hydroxymethyl)-7-((*R*)-2,2-dimethyl-1,3-dioxoxlan-4-yl)-6,8-dioxabicyclo[3.2.1]-octan-3-yl)acetamide (16).** To the precooled liquid ammonia (30 mL) was added lithium metal (189 mg, 27 mmol) until a dark blue color persisted, followed by the addition of a solution of **15** (1.6 g, 2.7 mmol) in anhydrous THF (15 mL). The mixture was stirred at the reflux temperature for 30 min, and solid NH_4-Cl was added to quench the reaction. The temperature was allowed to warm naturally, and ammonia was evaporated. The solid residue was purified by flash chromatography (chloroform/methanol = 20:1) to give **16** (0.778 g, 90%) as a white solid. $[\alpha]_D$ = +15.8 (*c* 0.50, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD): δ 4.34 (d, 1H, J = 3.9 Hz), 4.15 (d, 1H, J = 8.7 Hz), 4.06 (m, 2H), 3.94 (m, 2H), 3.68 (dd, 1H, J = 9.9, 4.2 Hz), 3.54 (s, 2H), 2.03 (dd, 1H, J = 12.8, 6.3 Hz), 1.94 (s, 3H), 1.53 (dd, 1H, J = 12.8, 11.4 Hz), 1.39 (s, 3H), 1.29 (s, 3H). ESI-MS (m/z): 318 (M^+ + 1, 100.00). IR (KBr): 3396, 3324, 2986, 2935, 1656, 1542, 1372, 1050, 850 cm^{-1}. HR-ESIMS: calcd for $C_{14}H_{23}NO_7$ + Na 340.1357, found 340.1367.

(2*S*,3*R*,5*S*,7*R*)-Methyl 3-Acetamido-2-hydroxy-7-((*R*)-2,2-dimethyl-1,3-dioxoxlan-4-yl)-6,8-dioxabicyclo[3.2.1]octane-5-carboxylate (17). To a stirred mixture of alcohol **16** (62 mg, 0.2 mmol), KBr (4 mg), and TBAB (4 mg) in saturated aq $NaHCO_3$ (2 mL) was added solid $Ca(ClO)_2$ (140 mg) at 15−18 °C. After 5 min, TEMPO (2 mg) was added in portions, and the mixture was vigorously stirred at 16−20 °C. After completion of the reaction monitored by TLC, solid $NaHSO_3$ was added to remove the excess $Ca(ClO)_2$. The solution was lyophilized, and the solid residue was suspended in DMF (2 mL) and treated with MeI (0.05 mL) for 4 h at rt. Water was added, and the mixture was extracted with chloroform. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (chloroform/methanol = 20:1) to give **17** (38 mg, 60%) as a white solid. $[\alpha]_D$ = +72.0 (*c* 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.57 (d, 1H, J = 5.7 Hz), 5.06 (s, 1H), 4.60 (d, 1H, J = 4.5 Hz), 4.38 (d, 1H, J = 8.4 Hz), 4.11−3.96 (m, 4H), 3.83 (s, 3H), 3.77 (dd, 1H, J = 9.0, 4.5 Hz), 2.42 (dd, 1H, J = 13.2, 6.6 Hz), 2.06 (s, 3H), 1.78 (dd, 1H, J = 13.2, 11.4 Hz), 1.44(s, 3H), 1.33(s, 3H). EI-MS (m/z): 330 (M^+ − Me, 59.09), 202(30.81), 193 (16.01), 173 (22.90), 142 (3.73), 101 (100.00). IR (KBr): 3438, 3323, 2988, 2957, 2881, 1756, 1636, 1562, 1293, 1084 cm^{-1}. HREIMS: calcd for $C_{14}H_{20}$-NO_8 (M^+ − Me) 330.1189, found 330.1181.

(2*S*,3*R*,5*S*,7*R*)-Methyl 3-Acetamido-2-hydroxy-7-((*R*)-1,2-dihydroxyethyl)-6,8-dioxabicyclo[3.2.1]octane-5-carboxylate (18). To a solution of **17** (38 mg, 0.11 mmol) in methanol (1 mL) was added HCl in methanol (1 M, 1 mL). The mixture was stirred at room temperature for 6 h and then concentrated under vacuum. The residue was purified by flash chromatography (chloroform/methanol = 6:1) to give **18** (30 mg, 89%) as a white solid. $[\alpha]_D$ = −4.5 (*c* 1.15, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 4.56 (d, 1H, J = 3.9 Hz), 4.32 (d, 1H, J = 8.4 Hz), 4.13 (m, 1H), 3.79 (s, 3H), 3.78−3.72 (m, 2H), 3.65 (dd, 1H, J = 11.4, 4.5 Hz), 3.54 (m, H), 2.30 (dd, 1H, J = 13.2, 6.0 Hz), 1.98 (s, 3H), 1.53 (dd, 1H, J = 13.2, 11.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 173.8, 169.1, 105.5, 79.9, 78.0, 72.3, 70.5, 63.4, 53.7, 49.2, 38.9, 22.9. ESI-MS (m/z): 306 (M^+ + 1, 100.00). IR (KBr): 3381, 2960, 1752, 1620, 1561, 1375, 1087, 992 cm^{-1}. HRESIMS: calcd for $C_{12}H_{19}NO_8$ + Na 328.1003, found 328.0999.

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Supporting Information Available: ^{1}H NMR spectra of compounds **9**, **13**, and **15**−**18** and the ^{13}C NMR spectrum of **18**, configuration confirmation of **9** by X-ray crystallography, and colored molecular presentations of **2** and **3** with lowest energies calculated by MM2. This material is available free of charge via the Internet at http://pubs.acs.org.

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