JOC*Note*

Stereoselective Route to the Ezoaminuroic Acid Core of the Ezomycins†

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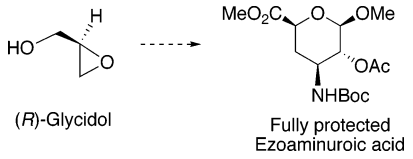
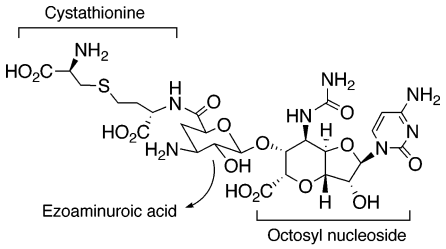


Starting from readily available (*R*)-glycidol, an efficient pathway to a strategically functionalized ezoaminuroic acid derivative of the antifungal ezomycins has been developed. A key transformation in the synthesis involves regio- and stereoselective conversion of the olefinic functionality of a 5,6-dihydropyran-2-one to the C-2, C-3 *trans*-1,2-amino alcohol moiety as present in ezoaminuroic acid.

The ezomycins are *Streptomyces*-derived natural products with specific activity against phytopathogenic fungi such as *Sclerotina* and *Botritus*.[1] The unique structural features and biological activity of the ezomycins are representative of the complex peptidyl nucleoside family of antibiotics.[2] Structurally, the ezomycins (Figure 1) include (i) an octosyl nucleoside core, (ii) ezoaminuroic acid component, and (iii) an *N*-linked pseudopeptide (cystathionine). While some of the ezomycins contain the cytosine nucleobase, others are of the pseudouridine type.

The complex structural features and antifungal potential of the ezomycins represents an attractive target for total synthesis and structure−activity relationship related studies. Although the syntheses of various structural fragments of ezomycins have been reported,[3,4] the total synthesis of this family of compounds has not yet been achieved. In continuation of our studies on complex peptidyl nucleoside antibiotics,[5] we report herein an efficient route to a strategically protected, masked ezoaminuroic acid structural core.



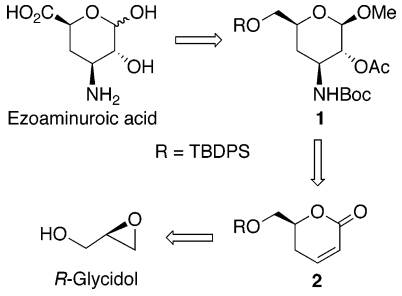
Ezomycin A_1

FIGURE 1. Representative structure of an ezomycin.

Ezoaminuroic acid is the first example of a naturally occurring 3-amino-3-deoxyhexuronic acid. Unlike the previously reported carbohydrate starting material based syntheses of ezoaminuroic acid derivaties,[4] we decided to investigate a more flexible non-carbohydrate approach toward de novo construction of the strategically functionalized carbohydrate core of the target compound (Scheme 1).

Our strategy involved utilization of commercially available (*R*)-glycidol toward initial formation of the enantiopure lactone **2**, followed by its subsequent transformation to the strategically functionalized masked ezoaminuroic acid derivative **1**.

SCHEME 1



Accordingly, following a known sequence of reactions,[6] silyl protection of the hydroxy group of (*R*)-glycidol, regioselective opening of the epoxide with vinylcuprate, conversion of the resulting secondary hydroxy group to its acrylate derivative, and subsequent ring closing metathesis with Grubbs' first-generation catalyst provided the functionalized lactone **2**[6] (Scheme 2) in 73% overall yield. Osmium tetroxide catalyzed stereoselec-

† This paper is dedicated to Professor Hiriyakkanavar Junjappa on the occasion of his 70th birthday.

(1) (a) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1974**, *38*, 1883−1890. (b) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1975**, *39*, 885−892. (c) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1977**, *41*, 2027−2032. (d) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1977**, *41*, 2033−2039. (e) Sakata, K.; Sakurai, A.; Tamura, S. *Tetrahedron Lett*. **1974**, *15*, 1533−1536.

(2) For reviews, see: (a) Zhang, D.; Miller, M. J. *Curr. Pharm. Design* **1999**, *5*, 73−99. (b) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859−1876. (c) Isono, K. Current progress on nucleoside antibiotics. *Pharmacol. Ther.* **1991**, *52*, 269−286. (d) Garner, P. Synthetic approaches to complex nucleoside antibiotics. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Stereoselective synthesis (Part A), Vol. 1, pp 397−435. (e) Isono, K. *J. Antibiot.* **1988**, *41*, 1711−1739.

(3) For some recent studies related to the octosyl nucleoside of the ezomycins, see: (a) Knapp, S.; Gore, V. K. *Org. Lett*. **2000**, *2*, 1391−1393 and references therein. (b) Haraguchi, K.; Hosoe, M.; Tanaka, H.; Tsuruoka, S.; Kanmuri, K.; Miyaska, T. *Tetrahedron Lett*. **1998**, *39*, 5517−5520. (c) Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nandan, S. R. *J. Org. Chem*. **1994**, *59*, 946−948. (d) Maier, S.; Preuss, R.; Schmidt, R. R. *Liebigs Ann. Chem*. **1990**, 483−489. (e) Danishefsky, S. J.; Hungate, R.; Schulte, G. *J. Am. Chem. Soc*. **1988**, *110*, 7434−7440 and references therein.

(4) For previous syntheses of the ezoaminuroic acid component, see: (a) Reference 3a above. (b) Knapp, S.; Jaramillo, C.; Freeman, B. *J. Org. Chem*. **1994**, *59*, 4800−4804. (c) Knapp, S.; Levorse, A. T.; Potenza, J. A. *J. Org. Chem*. **1988**, *53*, 4773−4779. (d) Ogawa, T.; Akatsu, M.; Matsui, M. *Carbohydr. Res.* **1975**, *44*, C22−24. (e) Mieczkowski, J.; Zamojski, A. *Bull. Acad. Pol. Sci*. **1975**, *23*, 581−583.

(5) Bhaket, P.; Stauffer, C. S.; Datta, A. *J. Org. Chem*. **2004**, 69, 8594−8601.

(6) Hansen, T. V. *Tetrahedron: Assymetry* **2002**, *13*, 547−550.

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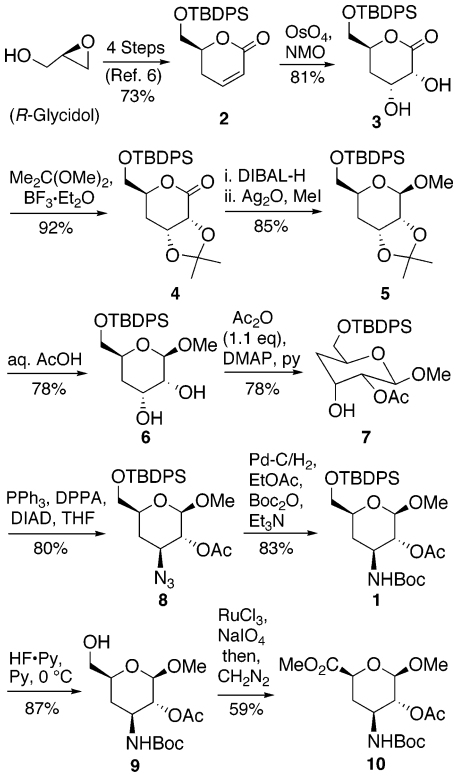
SCHEME 2



tive dihydroxylation of **2** (from the less hindered α-face)[5] yielded the corresponding diol **3** as the only product. Protection of the diol as the corresponding acetonide **4**, followed by partial reduction of the lactone to lactol and subsequent *O*-alkylation resulted in the stereoselective formation of the methyl glycoside **5** in good overall yield. In ^{1}H NMR studies, chemical shift (δ 4.45) and coupling constant of the anomeric proton (J = 5.6 Hz) confirmed the assigned β-stereochemistry of the methyl glycoside **5**. Hydrolysis of the acetonide linkage of **5** under mild conditions yielded the diol **6** in 78% yield. It was envisioned that stereochemical orientation of the hydroxy groups of **6** should allow differentiation between the C-2 and C-3 hydroxy groups. Gratifyingly, when the diol **6** was subjected to acylation in the presence of 1.1 equivalent of acetic anhydride, selective acetylation of the equatorial hydroxyl group (more favored)[7] resulted in the C-2 acetylated product **7** in good yield. The assigned structure of **7** was ascertained by high-resolution NMR studies (COSY and NOE). Following a modified Mitsunobu procedure,[8] the C-3 hydroxy group was then converted to the corresponding azido derivative **8**, with simultaneous inversion of the stereocenter involved. Subsequent reduction of the azido group to the corresponding amine and in situ Boc-protection afforded the amino sugar derivative **1** in good overall yield. Finally, selective unmasking of the primary hydroxy group to form **9** and its further conversion to the corresponding methyl carboxylate culminated in an efficient synthesis

(7) For a similar observation, see: Bhatt, R. K.; Chauhan, K.; Wheelan, P.; Murphy, R. C.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 5050−5056.

(8) (a) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235−4237. (b) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977−1979.

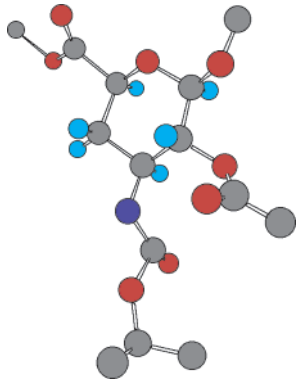


FIGURE 2. Ball and stick model of compound **10** (adapted from the X-ray crystal structure). Hydrogen atoms (except on the pyranose ring) have been omitted for clarity.

of the fully protected ezoaminuroic acid derivative **10** as a colorless crystalline solid.

At this stage, the assigned structure and absolute stereochemistry of **10** could be unamibigously confirmed by its X-ray crystallographic analysis (Figure 2). The strategically protected functionalities of both the intermediate **1** and the further oxidized product **10** render them as suitable ezoaminuroic acid glycosyl donors for eventual synthesis of the ezomycin nucleoside disaccharide component.

In terms of efficiency and brevity, the present route compares favorably with the other reported synthesis of ezoaminuroic acid derivatives.[4] Ready availability of the starting glycidol in both the enantiomerically pure forms, a simple and practical sequence of reactions, and the amenability of the method toward easy scale-up is expected to make the present synthetic route a method of choice in the total synthesis and structure−activity relationship investigations involving the ezomycin family of antifungal antibiotics.

Experimental Section

(3*R*,4*R*,6*S*)-6-[(*tert*-Butyldiphenylsilyloxy)methyl]-3,4-dihydroxytetrahydropyran-2-one (3). Lactone **2**[6] (1.76 g, 4.81 mmol) was dissolved in acetone/water (4:1, 30 mL), and to this was added NMO (1.63 g, 12.0 mmol), followed by OsO_4 (5% in toluene, 1.47 mL, 6 mol %). The resulting solution was stirred at room temperature for 50 min. After completion of the reaction (TLC monitoring), 10% aqueous $NaHSO_3$ (4 mL) was added to the reaction mixture, which was stirred for 5 min and diluted by addition of EtOAc (25 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Flash chromatography (hexane/EtOAc = 3:2) afforded the diol **3** as a colorless oil (1.55 g, 81%): $[\alpha]^{25}_D$ + 18.6 (*c* 1.04, $CHCl_3$); IR (NaCl) 3421, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 2.18−2.36 (m, 2H), 2.97 (br s, 1H, exchangeable with D_2O), 3.65 (br s, 1H, exchangeable with D_2O), 3.72 (dd, J = 3.1, 11.4 Hz, 1H), 3.96 (dd, J = 3.6, 11.4 Hz, 1H), 4.15 (s, 1H), 4.41 (br s, 1H), 4.81−4.87 (m, 1H), 7.42−7.45 (m, 6H), 7.66−7.69 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.7, 27.2, 30.0, 65.4, 66.5, 70.9, 78.6, 128.2, 130.3, 133.0, 133.4, 136.0, 174.4; HRMS (ES+) calcd for $C_{22}H_{29}O_5Si$ *m/z* (M + H)$^+$ 401.1784, found 401.1787.

(3a*R*,6*S*,7a*R*)-6-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4(6*H*)-one (4). The diol **3** (1.67 g, 4.18 mmol) was dissolved in a mixture of acetone (26 mL) and 2,2-dimethoxypropane (8 mL), and a catalytic amount of BF_3·Et_2O (0.1 mL) was added to it. The

resulting solution was stirred at room temperature for 2 h. The reaction was quenched with NEt_3 (0.2 mL), and the solvent was removed under vacuum. Purification of the residue by flash chromatography (hexane/EtOAc = 9:1) yielded the acetonide **4** as a colorless oil (1.69 g, 92%): $[\alpha]^{25}_D$ + 18.4 (*c* 1.25, $CHCl_3$); IR (NaCl) 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.41 (s, 3H), 1.52 (s, 3H), 2.02−2.16 (m, 2H), 3.79 (dd, *J* = 3.9, 11.2 Hz, 1H), 3.89 (dd, *J* = 4.3, 11.2 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.66−4.73 (m, 2H), 7.42−7.47 (m, 6H), 7.68−7.71 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.7, 24.5, 26.5, 27.2, 30.8, 65.4, 72.1, 73.3, 75.6, 111.1, 128.2, 130.3, 133.1, 133.4, 136.1, 168.5; HRMS (ES+) calcd for $C_{25}H_{33}O_5Si$ *m/z* $(M + H)^+$ 441.2097, found 441.2095.

***tert*-Butyl[{(3a*R*,4*R*,6*S*,7a*R*)-4-methoxy-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl}methoxy]diphenylsilane (5).** (Step 1) The acetonide **4** (1.52 g, 3.45 mmol) was dissolved in toluene (40 mL) and cooled to −78 °C. To this stirring solution was added DIBAL-H (1 M in toluene, 5.2 mL, 5.2 mmol) dropwise. The reaction was stirred at −78 °C for 1.5 h and then quenched by careful addition of MeOH (1.0 mL). The reaction mixture was brought to room temperature and diluted with EtOAc (50 mL), and saturated aqueous sodium potassium tartrate (50 mL) was added to it. The resulting mixture was stirred until two clear layers were seen. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated, and the crude lactol (1.40 g) was carried onto the next step without further purification.

(*Step 2*). The lactol (1.40 g, 3.17 mmol) from the above reaction was dissolved in anhydrous CH_2Cl_2 (30 mL), and to this solution was added freshly prepared Ag_2O (4.80 g, 20.7 mmol), followed by MeI (4.28 mL, 69.0 mmol) under N_2 and in the dark. The reaction mixture was stirred at room temperature for 3 h under N_2. The reaction mixture was filtered, and the residue washed with CH_2Cl_2 thoroughly. The combined filtrate was concentrated under vacuum to afford the crude product. Purification by flash chromatography (hexane/EtOAc = 4:1) afforded the methyl glycoside **5** (1.34 g, 85% over two steps) as a colorless oil: $[\alpha]^{25}_D$ − 49.8 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.40 (s, 3H), 1.56 (s, 3H), 1.85−1.92 (m, 1H), 2.04−2.08 (br m, 1H), 3.51 (s, 3H), 3.67−3.79 (m, 2H), 3.89−3.95 (m, 2H), 4.45 (d, *J* = 5.7 Hz, 1H), 4.95 (br s, 1H), 7.39−7.47 (m, 6H), 7.71−7.73 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.7, 25.9, 27.2, 28.1, 29.5, 56.8, 66.9, 70.9, 72.5, 75.4, 102.9, 109.5, 128.1, 130.1, 133.8, 136.0; HRMS (ES+) calcd for $C_{26}H_{36}O_5SiNa$ *m/z* $(M + Na)^+$ 479.2230, found 479.2228.

(2*R*,3*R*,4*R*,6*S*)-6-[(*tert*-Butyldiphenylsilyloxy)methyl]-2-methoxytetrahydro-2*H*-pyran-3,4-diol (6). The methyl glycoside **5** (1.25 g, 2.74 mmol) was dissolved in a mixture of AcOH/H_2O (3:1, 20 mL) and stirred at room temperature for 17 h. Excess solvent was removed in vacuo, and the residual product was purified by flash chromatography (hexane/EtOAc = 3:2), affording the diol **6** as a colorless oil (0.889 g, 78%): $[\alpha]^{25}_D$ −34.8 (*c* 1.00, $CHCl_3$); IR (NaCl) 3448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.62−1.68 (m, 1H), 1.95−2.00 (m, 1H), 2.61 (s, 2H, exchangeable with D_2O), 3.41−3.44 (m, 1H), 3.56 (s, 3H), 3.65−3.69 (m, 1H), 3.77−3.81 (m, 1H), 4.06−4.08 (m, 1H), 4.24−4.25 (br s, 1H), 4.56 (d, *J* = 7.9 Hz, 1H), 7.40−7.43 (m, 6H), 7.71−7.72 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.7, 27.2, 33.8, 57.1, 66.6, 67.7, 71.6, 72.3, 101.7, 128.1, 130.0, 133.9, 136.1; HRMS (ES+) calcd for $C_{23}H_{32}O_5SiNa$ *m/z* $(M + Na)^+$ 439.1917, found 439.1916.

(2*R*,3*R*,4*R*,6*S*)-3-Acetoxy-6-[(*tert*-butyldiphenylsilyloxy)-methyl]-4-hydroxy-2-methoxytetrahydro-2*H*-pyran (7). The diol **6** (0.13 g, 0.311 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL), and to this solution were added anhydrous pyridine (0.05 mL, 0.622 mmol), DMAP (10 mg, catalytic), followed by Ac_2O (0.035 mL, 0.374 mmol). The reaction mixture was allowed to stir at room temperature for 2 h and then quenched by addition of ice-cooled water (1 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and brine (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 4:1−7:3) to afford the acetate **7** as a white semisolid (0.111 g, 78%): $[\alpha]^{25}_D$ −51.4 (*c* 1.36, $CHCl_3$); IR (NaCl) 3485, 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.74−1.78 (m, 1H), 1.93−1.98 (m, 1H), 2.10 (br s, 1H, exchangeable with D_2O), 2.17 (s, 3H), 3.50 (s, 3H), 3.67−3.81 (m, 2H), 4.09−4.12 (m, 1H), 4.29 (br s, 1H), 4.74 (s, 2H), 7.40−7.43 (m, 6H), 7.70−7.72 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.7, 21.6, 27.2, 34.0, 56.7, 66.5, 67.1, 71.3, 73.4, 99.4, 128.1, 130.1, 133.9, 136.0, 170.2; HRMS (ES+) calcd for $C_{25}H_{34}O_6SiNa$ *m/z* $(M + Na)^+$ 481.2022, found 481.2011.

(2*R*,3*R*,4*S*,6*S*)-3-Acetoxy-4-azido-6-[(*tert*-butyldiphenylsilyloxy)methyl]-2-methoxytetrahydro-2*H*-pyran (8). To an ice-cooled solution of the acetate **7** (0.120 g, 0.262 mmol) in anhydrous THF (6 mL) were added diisopropyl azodiacarboxylate (0.072 mL, 0.367 mmol) and triphenylphosphine (0.096 mg, 0.367 mmol), followed by dropwise addition of diphenylphosphoryl azide (0.080 mL, 0.367 mmol). After completion of addition, the reaction mixture was brought to room temperature and then heated to 50 °C overnight. Excess solvent was removed under vacuum, and the residue was purified by flash chromatography (hexane/EtOAc = 6:1) to give the azide **8** as colorless oil (0.1 g, 80%): $[\alpha]^{25}_D$ −19.6 (*c* 1.00, $CHCl_3$); IR (NaCl) 2100, 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.50−1.56 (m, 1H), 2.10−2.16 (m, 4H), 3.48 (s, 3H), 3.56−3.70 (m, 3H), 3.81−3.85 (m, 1H), 4.30 (d, *J* = 7.8 Hz, 1H), 4.78−4.83 (m, 1H), 7.39−7.48 (m, 6H), 7.70 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.6, 21.3, 27.2, 33.2, 56.8, 60.6, 66.1, 73.3, 73.6, 102.2, 128.2, 130.2, 133.5, 136.0, 170.2; HRMS (ES+) calcd for $C_{25}H_{33}N_3O_6SiNa$ *m/z* $(M + Na)^+$ 506.2087, found 506.2089.

(2*R*,3*R*,4*S*,6*S*)-3-Acetoxy-4-(*tert*-butoxycarbonylamino)-6-[(*tert*-butyldiphenylsilyloxy)methyl]-2-methoxytetrahydro-2*H*-pyran (1). The azide **8** (0.087 g. 0.18 mmol) was dissolved in anhydrous EtOAc (5 mL) to which 10% Pd−C (26 mg) was added followed by di-*tert*-butyl dicarbonate (0.055 g, 0.252 mmol) and Et_3N (20 μL, catalytic). The reaction was allowed to stir under H_2 atmosphere at room temperature for 3 h. The mixture was then filtered and the residue washed thoroughly with EtOAc (3 × 10 mL). The combined filtrate was concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 9:1) to afford the protected ezoaminuroic acid **1** (0.083 g, 83%) as a white semisolid: $[\alpha]^{25}_D$ −17.3 (*c* 1.00, $CHCl_3$); IR (NaCl) 3352, 1744, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.34−1.44 (m, 10H), 2.07−2.16 (m, 4H), 3.49 (s, 3H), 3.65−3.89 (m, 4H), 4.36 (d, *J* = 7.7 Hz, 1H), 4.57−4.66 (m, 2H), 7.40−7.45 (m, 6H), 7.69−7.70 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.7, 21.4, 27.2, 28.7, 34.8, 51.2, 56.9, 66.3, 73.8, 74.2, 80.1, 102.4, 128.1, 130.1, 133.7, 136.0, 155.8, 171.4; HRMS (ES+) calcd for $C_{30}H_{44}NO_7Si$ *m/z* $(M + H)^+$ 558.2887, found 558.2877.

(2*R*,3*R*,4*S*,6*S*)-3-Acetoxy-4-(*tert*-butoxycarbonylamino)-6-(hydroxymethyl)-2-methoxytetrahydro-2*H*-pyran (9). The fully protected methylglycoside derivative **1** (0.208 g, 0.375 mmol) was dissolved in anhydrous pyridine (2 mL) and cooled to 0 °C, followed by addition of HF−pyridine solution (0.5 mL). The resulting solution was stirred at 0 °C for 1 h, after which the reaction was quenched with saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 3:7) to afford the alcohol **9** as a white solid (0.122 g, 87%): mp = 132−135 °C; $[\alpha]^{25}_D$ −27.7 (c 1.20, $CHCl_3$); IR (NaCl) 3358, 1740, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (br s, 10H), 2.03 (dd, *J* = 3.4 and 12.4 Hz, 1H), 2.10 (s, 3H), 2.12 (br s, 1H, exchangeable with D_2O), 3.52 (s, 3H), 3.56−3.73 (m, 3H), 3.86−3.89 (m, 1H), 4.39 (d, *J* = 7.7 Hz, 1H), 4.59 (dd, *J* = 2.6 and 10.4 Hz, 1H), 4.74 (br d, *J* = 8.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.3, 28.7, 33.8, 51.1, 57.3, 65.2, 70.9, 73.7, 80.1, 102.7, 155.8, 171.5; HRMS (ES+) calcd for $C_{14}H_{26}NO_7$ *m/z* $(M + H)^+$ 320.1709, found 320.1698.

(2*S*,4*S*,5*R*,6*R*)-Methyl 5-Acetoxy-4-(*tert*-butoxycarbonylamino)-6-methoxytetrahydro-2*H*-pyran-2-carboxylate (10). (Step 1) To a mixture of CH_3CN−CCl_4−H_2O (1.1 mL;

1:1:10) were added $NaIO_4$ (0.098 g, 0.46 mmol) and $RuCl_3 \cdot 3H_2O$ (0.005 g, 0.023 mmol) sequentially. The mixture was stirred at room temperature for 45 min and then added into an ice-cooled solution of the alcohol **9** (0.073 g, 0.23 mmol) in CH_3CN (1 mL), followed by addition of a second portion of $NaIO_4$ (0.048 g, 0.23 mmol). The resulting mixture was stirred at 0 °C for 1 h and filtered through Celite, and the Celite layer was then washed with EtOAc. The combined organic filtrate was washed once with water, and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude acid (~0.05 g) thus obtained was carried to the next step without further purification.

(Step 2) [**CAUTION**: Diazomethane (CH_2N_2) is an explosive and a highly toxic gas. Explosions may occur if the substance is dried and undiluted. All operations involving diazomethane should be carried out in an efficient fume hood following appropriate precautions.] To a biphasic solution of KOH (0.60 g) in H_2O (6 mL) and ether (6 mL) at 0 °C was added *N*-methyl-*N*′-nitro-*N*-nitrosoguandine (MNNG, 0.20 g) in one lot. The organic layer turned bright yellow. The ethereal layer was decanted into an ice-cooled Erlenmeyer flask containing KOH pellets. The aqueous layer was washed with ether (3 × 5 mL), and the ethereal layers were combined. The CH_2N_2 thus prepared was added to a stirred solution of the crude acid (0.05 g in 2 mL of ether) from step 1, and stirred for 30 min. Excess CH_2N_2 was removed by bubbling nitrogen into the reaction mixture for 15 min, followed by removal of solvent under vacuum. Purification by flash chromatography (hexane/EtOAc 7:3) yielded the protected ezoaminuroic acid **1** as a colorless crystalline solid (0.047 g, 59% over two steps): mp = 158−160 °C; $[\alpha]^{25}_D$ −26.2 (c 0.65, $CHCl_3$); IR (NaCl) 3362, 1749, 1742, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.58−1.68 (m, 1H), 2.10 (s, 3H), 2.45 (br d, J = 10.9 Hz, 1H), 3.53 (s, 3H), 3.79 (s, 3H), 3.85−3.96 (m, 1H), 4.15 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 7.5 Hz, 1H), 4.65 (dd, J = 2.6 and 10.1 Hz, 1H), 4.75 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.3, 28.7, 30.1, 34.8, 50.9, 52.9, 57.5, 71.8, 73.0, 80.3, 102.6, 155.7, 170, 171.3; HRMS (ES+) calcd for $C_{15}H_{26}NO_8$ *m/z* $(M + H)^+$ 348.1658, found 348.1661.

Supporting Information Available: General experimental methods and copies of ^1H and ^{13}C NMR spectra for all new compounds and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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