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A Concise, Economical, and Diastereoselective Synthesis of Methyl DGJ Isopropylidene: An Iminocyclitol Molecule Core for Analogue Synthesis

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Abstract:

A six-step synthesis of the title compound starting from L-lyxonolactone 2,3-isopropylidene (6) is described. The synthesis is achieved by conversion of 6 to the C_5-triflate or C_5-mesylate 7a or 7b and their displacement by sodium azide to yield the C_5 azido compound 8. Addition of methylmagnesium bromide and catalytic hydrogenation during which the azide group is reduced to the amine followed by an intramolecular cyclization yields the imine 15. Concomitant reduction of the imine occurs stereoselectively to yield methyl DGJ isopropylidene (5) which is isolated *via* the succinic acid salt and its further neutralization with ammonia. It was found that changing the synthetic sequence, namely, instead of 7a → 8 → 9, the methylmagnesium bromide could be added first to the mesylate 7b, 7b → 11 followed by azide ion displacement 11 → 9. This modification proved advantageous from the viewpoint of cost, use of methanesulfonyl chloride rather than trifluoromethylsulfonyl chloride, ease of operation, and yield. Methyl DGJ isopropylidene (5) is an important azasugar precursor because it can undergo N-alkyl substitution *via* reductive amination and be derivatized at C_2 *via* the secondary hydroxyl group. The synthesis reported herein allows for the production of mutikilogram amounts of this important key iminocyclitol core.

Introduction

Over the last three decades, iminocyclitols (also known as azasugars) have emerged as an important class of compounds because of their anti-glycosidase activity.[1−3] Iminocyclitols are most commonly pyranoses or furanoses in which the ring oxygen has been replaced by a nitrogen atom. They are hydrolytically stable molecules but can still be recognized by glycosidases and other carbohydrate-recognizing proteins because of their resemblance to the intermediate oxonium ion assumed to occur during glycolytic cleavage (Figure 1).[1f] Glycosidases are key enzymes involved in the biosynthesis and processing of glycoproteins. The iminocyclitols inhibit the glycosidases by mimicking the pyranosyl and furanosyl moiety of the corresponding substrate. Thus, because these substances inhibit the enzymatic function of glycosidases, they have become important as potential drug candidates for the treatment of various diseases.[4−6] Included among the iminosugars of recent interest are 5-methyl-1-deoxygalactonojirimycin (C_5-methyl DGJ, **1**), 1-deoxygalactonojirimycin (DGJ, **2**), and their N-alkyl derivatives (**3**) (Figure 1). The iminosugar methyl-deoxygalactonojirimycin (**1**) is a potent inhibitor of galactosidases with promising medicinal applications in the treatment of various viral infections, such as hepatitis C,[4,5] HIV-1[4−6] (the virus responsible for AIDS), cancer,[5a] diabetes,[5b] and obesity.[5b] In recent years, the worldwide growth in the number of patients with hepatitis C (∼170 million)[6i−j] has resulted in an intensified search for drugs to treat this disease. A number of research laboratories have become involved in the synthesis and structural modifications of iminocyclitols.[6i−j]

The use of methyl DGJ (**1**) as an iminocyclitol core molecule in organic synthesis is well documented.[6] Recently in our laboratory, we pursued improvements in the synthesis of **UT-231B** (**4**, an analogue of methyl DGJ, **1**), and we required a large supply of the compound for clinical development (Figure 2). **UT-231B** is currently in phase II clinical trials as an antiviral agent for the treatment of hepatitis C.

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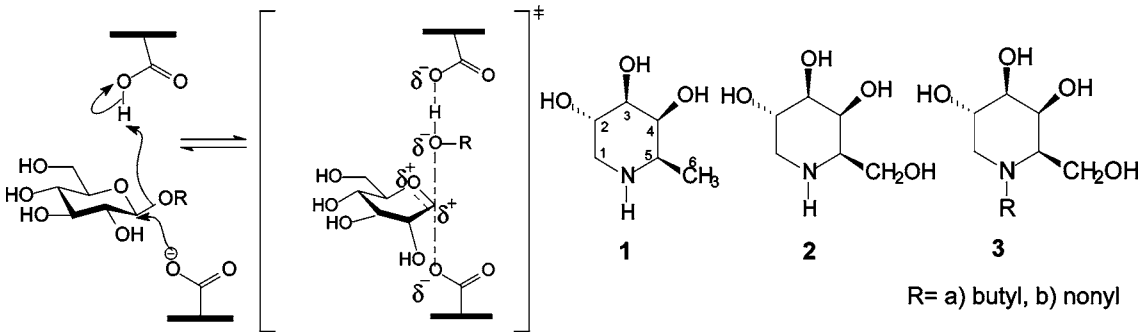

Figure 1. **Intermediate oxonium ion produced during glycolytic cleavage and structures of methyl DGJ (1) and DGJ analogues (2) and (3).**

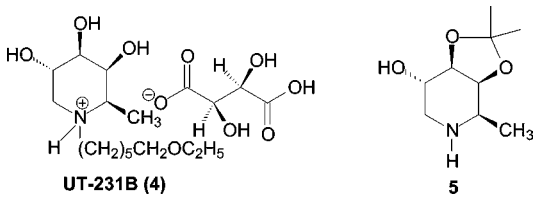

Figure 2. **Structures of UT-231B (4) and methyl DGJ isopropylidene (5).**

Results and Discussion

The present report focuses on the diastereoselective synthesis of a protected derivative of **1**, namely **5**.[7] Our synthetic method for producing **5** involved first the large-scale production of the key intermediate L-lyxonolactone (**6**)[8a] (Scheme 1). We envisioned that the ring nitrogen in compound **5** could be introduced by reductive cyclization of the azidolactol precursor **9**.[7,10] The synthesis of azidolactol **9** could be achieved by simple nucleophilic displacement upon triflate **7a** or mesylate **7b** using sodium azide, and the synthesis of **6** could be accomplished from the chiral sugar precursor, D-ribonolactone-2,3-*O*-isopropylidene using a literature procedure.[8]

Initially, to meet our requirement of **UT-231B** (**4**) for clinical studies, we synthesized **5** *via* the triflate route (**6** → **7a** → **8** → **9** → **10** → **5**) (Scheme 1). Treating **6** with triflic anhydride in the presence of pyridine in CH_2Cl_2 afforded triflate **7a**. Nucleophilic displacement of the triflate with sodium azide in DMF at 110−120 °C gave azide **8**. Attempts to synthesize azide **8** *via* the mesylate **7b** failed under similar conditions. Addition of methylmagnesium bromide to **8** gave hydroxylmethyl azide **9**. Catalytic hydrogenation of **9** in the presence of 10% palladium on activated carbon afforded piperidine derivative **5** stereoselectively.

This process was scaled to 200 kg with an overall yield of 40−42% starting from **6**. However, this process suffered from the following drawbacks: (a) triflate **7a** was not very stable and had to be used immediately in the subsequent step; (b) because of the instability of triflate **7a**, the subsequent steps were not clean, and intermediate **9** required purification by silica gel filtration using large amounts of solvents; (c) the isolation of pure **5** was difficult because of the carried over byproducts from the preceding steps. As crystallization was not a useful option, we converted crude **5** to its succinic acid salt form **10** and then converted it back to the free base with ammonia to obtain pure **5**; (d) the manufacturing cost for compound **5** *via* the triflate route (Scheme 1) was very expensive because of the cost of triflic anhydride; (e) finally, triflic anhydride was not readily commercially available in the quantities required.

At this point, after considering the drawbacks associated with this route, alternative approaches for the synthesis of compound **5** were sought. One approach was to achieve the azide displacement reaction on triflate **7a** at a lower temperature because of its thermal instability [investigation by an accelerated rate calorimeter test (ARC) of a 35% solution of **7a** in dichloromethane showed that the maximum safe handling temperature for triflate (**7a**) was 60 °C].

Following the first projected alternative approach, we conceived the idea of trying the displacement reaction in water as triflate **7a** was stable to hydrolysis. Fortunately, the displacement reaction in acetone/water worked very well at ambient temperature, and subsequent steps were also more easily performed. This procedure was implemented on a large scale (∼50 kg), and the results were encouraging. Using this approach, more than 100 kg of compound **5** were synthesized with an overall yield of 45% starting from **6** *via* **7a** using the acetone/water medium for azide ion displacement at room temperature.

Nonetheless, we continued our pursuit of a less expensive, alternative route as our demand for **UT-231B** grew. In early development, the displacement of mesylate **7b** was attempted in DMF at 110−120 °C, and we found that the reaction rate was very slow and the reaction did not go to completion. The yields were also relatively low. Displacement of the mesylate **7b** by sodium azide in solvents like butanone and DMSO was unsuccessful. The displacement of mesylate **7b** was expected to be slower than that of triflate **7a**,[9] but the cost of the mesylate route would be less expensive than the triflate route (Scheme 1, cost of mesyl chloride, $93/2.5 kg *versus* cost of triflic anhydride, $6000/2.5 kg). The synthesis of **5** using mesylate **7b** was reinvestigated with some modifications to our earlier attempts to obtain **8** *via* mesylate **7b** (Scheme 1). Mesylation of **6** with methanesulfonyl

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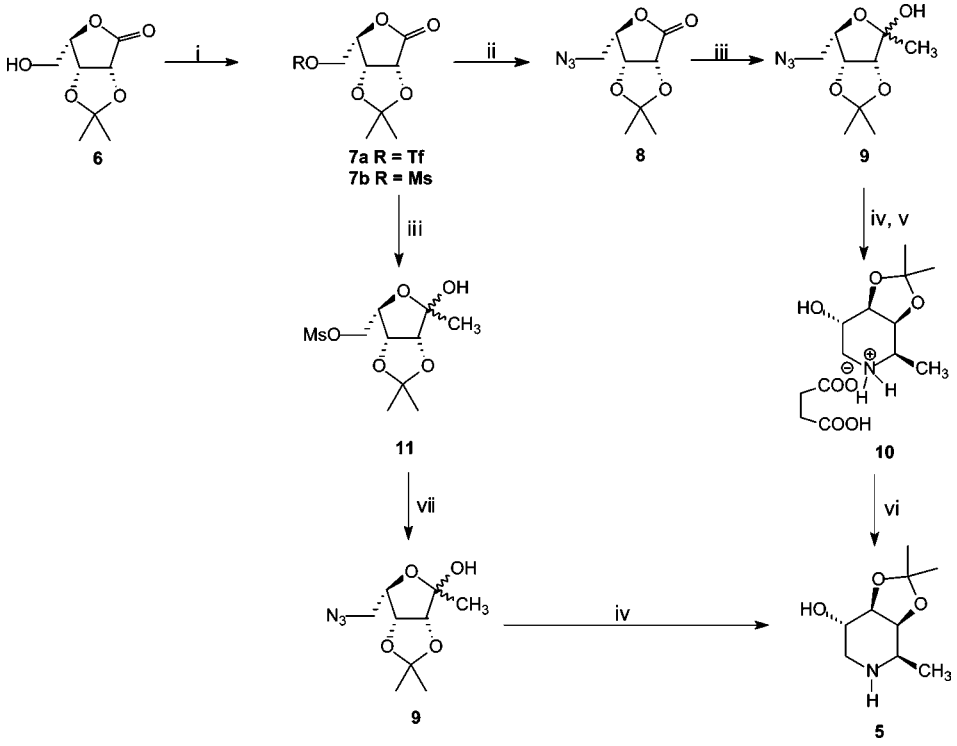
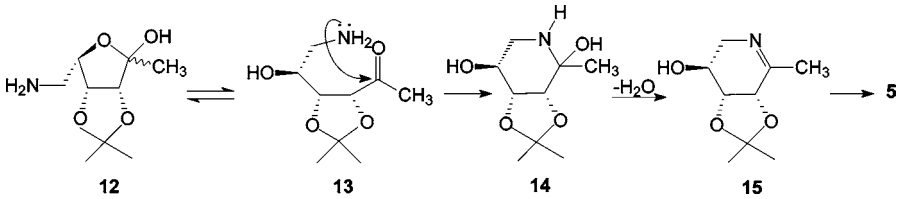
Scheme 1[a]



[a] Conditions: (i) $(CF_3SO_2)_2O$, Py, CH_2Cl_2 or MsCl, Et_3N, CH_2Cl_2; (ii) NaN_3, DMF, 110−120 °C or NaN_3, acetone, H_2O, rt; (iii) CH_3MgBr, THF; (iv) H_2, Pd/C, EtOH, 70−80 psi; (v) succinic acid; (vi) NH_3, EtOH; (vii) NaN_3, DMF, Bu_4NBr, 110−120 °C.

Scheme 2



chloride in the presence of triethylamine in methylene chloride gave mesylate **7b** in 93% yield. Initial efforts focused on conversion of **7b** to azidolactone **8** by nucleophilic displacement with sodium azide. Displacement of mesylate **7b** in a mixture of DMF and toluene gave a good yield of **8** on a 10-g scale, and the reaction was clean. When the reaction was performed on a 50-g scale, the reaction did not go to completion after 36 h at 100−110 °C.

The displacement of mesylate **7b** in DMF at 110−120 °C in the presence of various phase transfer catalysts (PTC) was attempted, and the results were promising, affording essentially quantitative conversion. Displacement in the presence of 10 mol % of tetrabutylammonium bromide gave the best results as compared to hexadecyltributylphosphonium bromide and tetrabutylammonium hydrogen sulfate that were other PTCs tried. Displacement of mesylate **7b** by sodium azide in the presence of tetrabutylammonium bromide followed by the addition of methylmagnesium bromide yielded hydroxylmethyl azide **9**.

The synthesis of compound **5** using mesylate **7b** was successful on a 10-g scale. However, when this route was scaled to 50 g, it was once again necessary to purify **5** *via* its succinic acid salt. The inherent instability of mesylate **7b**, as evidenced by a color change in **7b** if left standing at room temperature for an extended period of time, was seen as the cause of the relative impurity of both **8** and **9** and ultimately **5**. At this point reversing the sequence of the reactions for the addition of methylmagnesium bromide and mesylate displacement was attempted. We speculated that **11** might be more stable than its precursor **7b** and the displacement step with sodium azide on hydroxylmethyl mesylate **11** might be cleaner (Scheme 1). It was found that changing the synthetic sequence, namely, instead of **7b**→**8**, adding methylmagnesium bromide to **7b** (**7b** → **11**), followed by **11** → **9** → **5**, was advantageous from the viewpoint of cost, ease of operation, and yield.

The crude mesylate **7b**, upon addition of methylmagnesium bromide, afforded the desired lactol **11**. Treatment of **11** with sodium azide in DMF at 110−120 °C in the presence of tetrabutylammonium bromide provided hydroxymethyl azide **9** in 6 to 7 h. The hydroxymethyl azide **9** was used without purification for the reductive cyclization.

Catalytic hydrogenation of **9** gave iminosugar derivative **5** in 76% yield. This pathway involves the key intermediate **12**, which, once formed, cyclizes spontaneously to yield imine **15** probabaly *via* **14** (Scheme 2). The imine is further hydrogenated to give **5** with an overall yield of 55% from **6**.

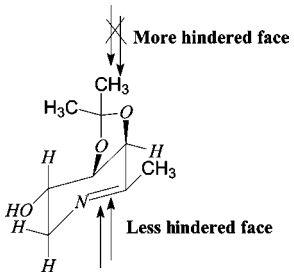


Figure 3. **Diastereoselective Hydrogenation of 15.**

The hydrogenation gave excellent diastereoselectivity. The selectivity of the hydrogenation, as depicted by Fleet,[7] can be rationalized as shown in Figure 3.

An axial attack of the hydrogen from the top face is hindered by the bulky isopropylidene group at C_3 and C_4. Therefore, the attack exclusively occurs from the bottom face leading to the desired stereochemistry in **5**.

In summary, the approach **7b** → **11** → **9** → **5** (Scheme 1) provides a simple and straightforward synthesis of methyl DGJ isopropylidene derivative (**5**) with an overall yield of 54−56%. This method is economical, gives reasonable yields, and is easily scaleable from laboratory to production scale. The key features of this synthesis are addition of the Grignard reagent to mesylate **7b** and the intramolecular reductive cyclization of azide **9** to afford the piperidine ring system of **5**. Iminocyclitol **5** is used for the synthesis of **UT-231B** (**4**), and work is in progress in our laboratory to demonstrate the use of this synthetic methodology on a multikilogram scale to meet our clinical demands of **UT-231B**. A detailed synthesis of **UT-231B** and some analogues will be the subject of a forthcoming report from our laboratory.

Experimental Section

Melting points were determined using a capillary tube melting point apparatus and are uncorrected. Air and moisture sensitive reactions were carried out under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol-300 spectrometer at 300 MHz. Tetramethylsilane (TMS) and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) were used as an internal standard for ^{1}H NMR. All chemical shifts are reported in parts per million (ppm), and the coupling constant (*J*) values were calculated in hertz (Hz) based on the chemical shifts. ^{13}C NMR spectra were recorded at 75 MHz. Deuteriochloroform ($CDCl_3$) was used as solvent for all NMR experiments with residual chloroform as an internal standard. IR spectra were recorded on a Thermo Nicolet Nexus-470 FT-IR spectrophotometer. All solvents were obtained commercially and used as received.

(3a*R*,6*S*,6a*R*)-Tetrahydro-6,2,2-dimethyl-6-oxofuro-[3,4-*d*]-1,3-dioxol-4-yl-methyltrifluoromethanesulfonate (7a). A 22-L, three-neck, round-bottom flask equipped with an air-driven mechanical stirrer, a thermometer, and an addition funnel was charged with **6** (500 g, 2.66 mol), dichloromethane (4500 mL), and pyridine (430 mL, 421 g, 5.32 mol) under argon. The clear solution was cooled to −10 °C, and a solution of trifluoromethanesulfonic anhydride (537 mL, 900 g, 3.19 mol) in dichloromethane (500 mL) was added slowly with stirring while maintaining the temperature of the solution between −10 and 0 °C. After complete addition, the reaction solution was stirred for 1 h below 0 °C. After completion of the reaction (NMR), the solution was washed successively with 10% hydrochloric acid (2000 mL), water (2000 mL), and brine (1000 mL), then dried over anhydrous sodium sulfate (200 g), and filtered. The filtrate was concentrated *in vacuo* to obtain (3a*R*,6*S*,6a*R*)-tetrahydro-6,2,2-dimethyl-6-oxofuro[3,4-*d*]-1,3-dioxol-4-yl-methyltrifluoromethanesulfonate (**7a**) (1066 g) as a pale-yellow solid. This crude triflate (**7a**) contained some solvent (NMR); the theoretical yield of **7a** should be 852 g; mp 65−67 °C (analytical sample); $[\alpha]^{25}_D = -63.3°$ (*c* 1.0, CH_2Cl_2); IR (KBr) 1791, 1415, 1380, 950 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95−4.91 (m, 2H), 4.87−4.82 (m, 2H), 4.76−4.69 (m, 1H), 1.48 and 1.40 (two s, 2 × 3H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.29, 115.15, 76.58, 75.81, 75.24, 72.91, 26.46, 25.55. The crude product was used immediately in the next step.

(3a*R*,6*S*,6a*R*)-Dihydro-6-(azidomethyl)-2,2-dimethylfuro-[3,4-*d*]-1,3-dioxol-4(3a*H*)-one (8). A 22-L, three-neck, round-bottom flask equipped with an air-driven mechanical stirrer, a thermometer, and an addition funnel was charged with a solution of crude **7a** (1066 g, calculated as 852 g, 2.66 mol) in acetone (4000 mL), sodium azide (260 g, 3.99 mol), and water (1000 mL). The clear solution was stirred at room temperature overnight. After 16 h, acetone was removed from the reaction mixture *in vacuo* below 40 °C, and the remaining aqueous layer that contained the product was diluted with water (1000 mL) and extracted with ethyl acetate (1 × 2000 mL, 2 × 1000 mL). The combined ethyl acetate extracts were washed with a saturated sodium chloride solution (1000 mL), dried over anhydrous sodium sulfate (100 g), and filtered, and the filtrate was concentrated *in vacuo* to obtain crude **8** (596 g) as a viscous liquid that solidified upon cooling to room temperature. The theoretical weight of **8** should be 567 g based on the amount of **6** used. An NMR analysis indicated that this product was of sufficient purity to be used in the next step. Recrystallization of the crude solid from a mixture of EtOAc and hexanes (1:1) provided an analytical sample; mp 54−56 °C; $[\alpha]^{25}_D = -74.0°$ (*c* 1.0, CH_2Cl_2); IR (KBr) 2130, 1782, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89−4.84 (m, 2H), 4.63−4.58 (m, 1H), 3.75−3.61 (m, 2H), 1.48 and 1.41 (two s, 2 × 3H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.86, 114.44, 77.15, 75.93, 75.67, 26.64, 25.64. Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.42; H, 5.26; N, 19.75. Found: C, 45.07; H, 5.16; N, 19.71.

(3a*R*,6*S*,6a*R*)-6-(Azidomethyl)tetrahydro-2,2,4-trimethylfuro[3,4-*d*]-1,3-dioxol-4-ol (9). A 22-L, three-neck, round-bottom flask equipped with an air-driven mechanical stirrer, thermometer, and addition funnel was charged with a solution of crude **8** (596 g, calculated as 567 g, 2.66 mol) in anhydrous tetrahydrofuran (4500 mL) under argon. The clear solution was cooled to −10 °C (ice/acetone or dry ice/acetone bath), and a solution of methylmagnesium bromide in tetrahydrofuran/toluene (50/50 ratio) (2.0 M, 1730 mL, 3.46 mol) was added slowly over a period of 1 h while maintain-

ing the temperature of the mixture between −10 and −5 °C. After complete addition, the mixture was stirred for 2 h between −10 and 0 °C. The mixture was quenched carefully by slow addition of a saturated ammonium chloride solution (600 mL), and a light-yellow, granular solid formed. The organic layer was decanted from the solid, and the solid was washed with ethyl acetate (1 × 1000 mL and 2 × 500 mL) and filtered. The combined organic filtrates were washed with a saturated sodium chloride solution (600 mL), dried over anhydrous sodium sulfate (∼120 g), and filtered. The filtrate was concentrated *in vacuo* to approximately 1000 mL and diluted with an equal volume of hexanes (1000 mL). The solution was then passed through a pad of silica gel (250−400 mesh, 500 g), and the silica gel was washed with 20% ethyl acetate in hexanes (5000 mL). The combined clear filtrates were concentrated *in vacuo* to give a white solid of **9** (474 g, 78%). According to an NMR analysis the product was of sufficient purity to go forward to the next step. Recrystallization of the crude solid from a mixture of EtOAc and hexanes (1:1) provided an analytical sample, mp 87−89 °C; IR (KBr) 3250, 2100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78−4.76 (m, 1H), 4.48−4.46 (m, 1H), 4.28−4.18 (m, 1H), 3.54−3.52 (m, 2H), 2.39 (s, 1H), 1.53 (s, 3H, CH_3), 1.47 and 1.33 (two s, 2 × 3H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.89, 105.35, 85.39, 80.49, 76.38, 49.89, 25.96, 24.71, 22.31. Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.10; H, 6.55; N, 18.34. Found: C, 46.93; H, 6.59; N, 18.16.

(3a*S*,4*R*,7*S*,7a*R*)-Hexahydro-2,2,4-trimethyl-1,3-dioxolo-[4,5*c*]pyridine-7-ol (5): A clean, 2-gal Parr reactor was charged with a solution of **9** (474 g, 2.06 mol) in ethyl alcohol (2200 mL) followed by addition of 10% palladium on activated carbon (50% wet, Degussa Type) (47 g). The reactor was evacuated under a house vacuum and then filled with argon and flushed out under a vacuum, and the process was repeated before being pressurized with hydrogen to 80 psi. The hydrogenation reaction was stirred for 2 h, and during that time the temperature of the mixture rose to 43 °C. At this stage, the reactor was evacuated, and fresh hydrogen was introduced to a pressure of 80 psi. The mixture was stirred, the temperature of the mixture rose to 62 °C, and then the temperature of the mixture dropped to ambient. The mixture was stirred for 18 h. The mixture was removed from the reactor under argon and filtered through a pad of Celite (∼100 g) to remove the catalyst and carbon. The filtrate was transferred to a 12-L, three-neck, round-bottom flask equipped with an air-driven mechanical stirrer, a thermometer, and an addition funnel and charged with succinic acid (244 g, 2.06 mol). The mixture was heated to a gentle reflux until a clear solution was obtained. The clear solution was heated at reflux for 1 h and then allowed to cool to ambient temperature overnight. After 16 h, the mixture was cooled to 5 °C (ice−water bath) with stirring for 1 h. The white succinate (**10**) was collected on a Buchner funnel, washed with *tert*-butyl methyl ether (800 mL), and dried to obtain **10** (365 g). The mother liquor was concentrated to dryness and triturated at 5 °C with 25% *tert*-butyl methyl ether in acetone (390 mL). The mixture was filtered to obtain an off-white solid as a second crop. The solid was washed with 25% *tert*-butyl methyl ether in acetone (300 mL) and dried to give a white solid (55 g); both of the crops were combined to obtain **10** (420 g); mp 188−189 C; $[\alpha]^{25}_D$ = −32.4° (*c* 1.0, H_2O); IR (KBr) 3419, 3217, 2816, 2714, 2556, 1671, 1621, 1106, 1066 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.55−4.52 (m, 1H), 4.32−4.28 (m, 1H), 4.02−3.97 (m, 1H), 3.89−3.82 (m, 1H), 3.72−3.42 (m, 1H), 3.12−3.05 (m, 1H), 2.52 (s, 4H 2 × CH_2COO), 1.43 (d, 3H, *J* = 6 Hz, CH_3), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). Anal. Calcd for $C_9H_{18}NO_3 \cdot C_4H_5O_4$: C, 51.14; H, 7.54; N, 4.59. Found: C, 51.17; H, 7.59; N, 4.55.

The combined succinate crops (**10**) (420 g) were dissolved in ethyl alcohol (4500 mL) by heating to gentle reflux, and then a stream of ammonia gas was introduced into the solution until the solution became basic (checked by litmus paper; approximately 1 h). During this process, a copious amount of ammonium succinate formed. After 1 h, the stirred mixture was cooled to room temperature. After stirring for 1 h, the mixture was filtered through a Buchner funnel, the filter cake (ammonium succinate) was washed with warm ethyl alcohol (65 °C, 2 × 500 mL), and the combined filtrates were concentrated *in vacuo* to give a pale-yellow solid. *tert*-Butyl methyl ether (2000 mL) was added to the solid, and the mixture was filtered to give **5** (233 g, 60.2%) as a white solid; mp 185−186 °C; $[\alpha]^{25}_D$ = +80.5° (*c* 1.0, H_2O); IR (KBr) 3424, 3286, 2731, 1131, 1091, 1051, 1027 cm^{-1}; ^1H NMR (300 MHz, MeOH-d_4) δ 4.08−4.05 (m, 1H), 3.84−3.80 (m, 1H), 3.65−3.57 (m, 1H), 3.02−2.91 (m, 2H), 2.36−2.28 (m, 1H), 1.49 and 1.33 (two s, 2 × 3H, 2 × CH_3), 1.21 (d, 3H, *J* = 6 Hz, CH_3); ^{13}C NMR (75 MHz, MeOH-d_4) δ 110.00, 81.49, 78.05, 71.30, 52.46, 49.94, 28.53, 26.65, 17.58. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.75; H, 9.15; N, 7.48. Found: C, 57.73; H, 9.11; N, 7.52.

(3a*R*,6*S*,6a*R*)-Tetrahydro-6,2,2-dimethyl-6-oxofuro-[3,4-*d*]-1,3-dioxol-4-yl-methanesulfonate (7b): A 1000 mL, three-necked, round-bottom flask equipped with a magnetic stir bar, thermometer, and argon inlet−outlet adapter connected to a bubbler was charged with **6** (50 g, 0.265 mol, 1.0 equiv), dichloromethane (400 mL), and triethylamine (33.3 g, 22.5 mL, 0.292 mol, 1.1 equiv) under argon. This mixture was stirred until it became clear, and then the solution was cooled below −10 °C. To this solution was added methanesulfonyl chloride (29.5 g, 41.0 mL, 0.292 mol, 1.1 equiv) dropwise, and the reaction mixture was stirred for 1 h below −10 °C. After stirring for 1 h at this temperature, the solution was allowed to warm to ambient temperature. After completion of the reaction (∼3−4 h, checked by NMR) the reaction was quenched with 1 N HCl (50 mL). The organic layer was separated and washed with a saturated $NaHCO_3$ solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo* to yield an off-white, crystalline mesylate **7b** (65.5 g, 93%), mp 124−127 °C (lit[8b] mp 122−124 °C). According to NMR analysis, this product was of sufficient purity to go forward in the synthesis. Recrystallization of crude **7b** from EtOAc provided an analytical sample; mp 133−134 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (m, 2H), 4.81−4.71 (m, 1H), 4.60−4.50 (m, 1H), 4.50−

4.41 (m, 1H), 3.08 (s, 3H, CH_3), 1.46 and 1.38 (two s, 2 × 3H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.73, 114.99, 76.33, 75.93, 75.48, 69.99, 37.82, 26.75, 25.84. Anal. Calcd for $C_9H_{14}O_7S$: C, 40.60; H, 5.30; S, 12.04. Found: C, 40.40; H, 5.25; S, 12.13.

(3a*R*,6*S*,6a*R*)-6-(Methanesulfonyl)tetrahydro-2,2,4-trimethylfuro[3,4-*d*]-1,3-dioxol-4-ol (11): A 1-L, three-neck, round-bottom flask equipped with an air-driven mechanical stirrer, a thermometer, and an addition funnel was charged with a solution of mesylate (**7b**) (60 g, 0.225 mol) in anhydrous tetrahydrofuran (360 mL) under argon. The clear solution was cooled to −10 °C (ice/acetone or dry ice/acetone bath), and then a solution of methylmagnesium bromide in tetrahydrofuran/toluene (1.4 M) (34.93 g, 209 mL, 0.292 mol, 1.3 equiv) was added slowly over a period of 30 min while the temperature of the mixture was monitored between −10 and −5 °C. After complete addition, the mixture was stirred for 2−3 h between −5 and 0 °C. After the reaction was complete (NMR), the reaction mixture was carefully quenched by slow addition of a saturated ammonium chloride solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo* to dryness to obtain crude **11** as an off-white solid (63 g, 99%). Crystallization of **11** from a mixture of EtOAc and hexanes (130 mL:260 mL) afforded pure **11** as a white solid; mp 83−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88−4.71 (m, 1H), 4.44−4.42 (m, 2H), 4.41−4.28 (m, 2H), 3.05 (s, 3H, CH_3), 1.52 and 1.45 (two s, 2 × 3H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.17, 105.76, 85.32, 80.50, 68.29, 35.56, 26.12, 24.76, 22.43. Anal. Calcd for $C_{10}H_{18}O_7S$: C, 42.55; H, 6.43; S, 11.36. Found: C, 42.53; H, 6.21; S, 11.28.

(3a*R*,6*S*,6a*R*)-6-(Azidomethyl)tetrahydro-2,2,4-trimethylfuro[3,4-*d*]-1,3-dioxol-4-ol (9): A 200-mL, three-necked, round-bottom flask equipped with a magnetic stir bar, oil bath, thermometer, and argon inlet−outlet adapter connected to a bubbler was charged with compound **11** (20 g, 0.070 mol, 1.0 equiv), sodium azide (8.35 g, 0.127 mol, ∼1.8 equiv), tetrabutylammonium bromide (3.42 g, 15 mol %), and DMF (120 mL) under argon. The mixture was stirred and heated to 110−120 °C (oil-bath temperature). After 6 h, the reaction mixture was cooled to ambient temperature and quenched with a saturated NH_4Cl solution (100 mL), and then toluene (200 mL) was added. The organic layer was separated, and the aqueous layer was extracted with toluene (2 × 75 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, and then filtered, and the filtrate was concentrated *in vacuo* to obtain crude azide **9** (16.2 g, ∼100% crude yield). An NMR analysis indicated that the product was of sufficient purity to go forward to the next step. Recrystallization of crude solid from EtOAc and hexanes (1:1) afforded an analytical sample, mp 87−89 °C with properties essentially identical to those of **9** obtained from the triflate route above **8**→**9**.

(3a*S*,4*R*,7*S*,7a*R*)-Hexahydro-2,2,4-trimethyl-1,3-dioxolo-[4,5*c*]pyridine-7-ol (5): A clean, 400-mL Parr reactor was charged with a solution of crude (3a*R*,6*S*,6a*R*)-6-(azidomethyl)tetrahydro-2,2,4-trimethylfuro[3,4-*d*]-1,3-dioxol-4-ol (**9**) (16.2 g) in ethyl alcohol (120 mL) followed by 10% palladium on activated carbon (50% wet, Degussa Type) (∼1.7 g) and acetic acid (0.5 mL). The reactor was evacuated under a house vacuum, then filled with argon, and flushed-out under a vacuum. The process was repeated before the reactor was pressurized with hydrogen to 80 psi. The hydrogenation reaction was stirred for 1 h, and during that time the temperature of the mixture rose to 37−38 °C and then dropped to 22 °C. At this stage, the reactor was evacuated and repressurized to 50 psi with fresh hydrogen. The mixture was stirred, and the temperature rose to 27 °C and then dropped to ambient temperature. After 6 h, the reaction was complete, as evidenced by a cessation of hydrogen uptake. The mixture was removed from the reactor under argon and filtered through a pad of Celite (∼100 g) to remove the catalyst. The filtrate was concentrated *in vacuo* to afford 14 g of an off-white solid mass. This product was crystallized by dissolving with 2 times the volume of 2-propanol at 78 °C and then cooling to −5 °C slowly. The solid in the flask was collected by filtration and dried to afford **5** (10 g, 76%); mp 183−184 °C; $[\alpha]^{25}_D = +82.9°$ (*c* 1.0, H_2O) with NMR spectra identical to those of **5** from the above route **9**→**10**→**5**. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.75; H, 9.15; N, 7.48. Found: C, 57.61; H, 9.13; N, 7.31.

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