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CHEMOENZYMATIC APPROACH TO SYNTHESIS OF HYDROXYLATED PYRROLIDINES FROM BENZOIC ACID

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The authors dedicate this article to Victor Snieckus on the occasion of his 77th birthday and in recognition of his outstanding contributions to the art and craft of organic synthesis

Abstract – The fermentation of benzoic acid with *R. eutrophus* B9 provides the corresponding *ipso*-diol that serves as a convenient homochiral starting material for the synthesis of oxygenated compounds. In this paper we report the conversion of the *ipso*-diol to a hydroxylated pyrrolidine, which is found as a subunit in biologically active compounds. The key steps involve the enzymatic oxidation of benzoic acid, the subsequent hetero-Diels-Alder cycloaddition, and the oxidative cleavage, reductive cyclization to form the pyrrolizidine. Experimental and spectral data are provided for all new compounds.

INTRODUCTION

Polyhydroxylated pyrrolidines are found as major subunits of numerous biologically active molecules and natural products.[1] Structurally they are natural sugar mimics and have found clinical utility in a number of medicinally important molecules that span a range of diseases and disorders, including antidiabetic, antiviral, and anticancer activities.[2-4] Hydroxylated pyrrolidines **1** and **2** have been used to prepare compounds **4** (BCX-4208) and **5** (BCX-1777) (Figure 1) and represent a class of selective immunosuppressive agents that are currently in clinical trials as inhibitors of human purine nucleoside phosphorylase (PNP). More recently a series of aza sugar mimics containing the ribose configuration has been reported as part of efforts aimed at screening for more effective hepatitis C virus (HCV) agents.[5]

Compounds **6 – 8** represent a series of derivatives that contain a stereo defined methyl substituent in the 2'-β position that has been deemed crucial in HCV replication assays.[6]

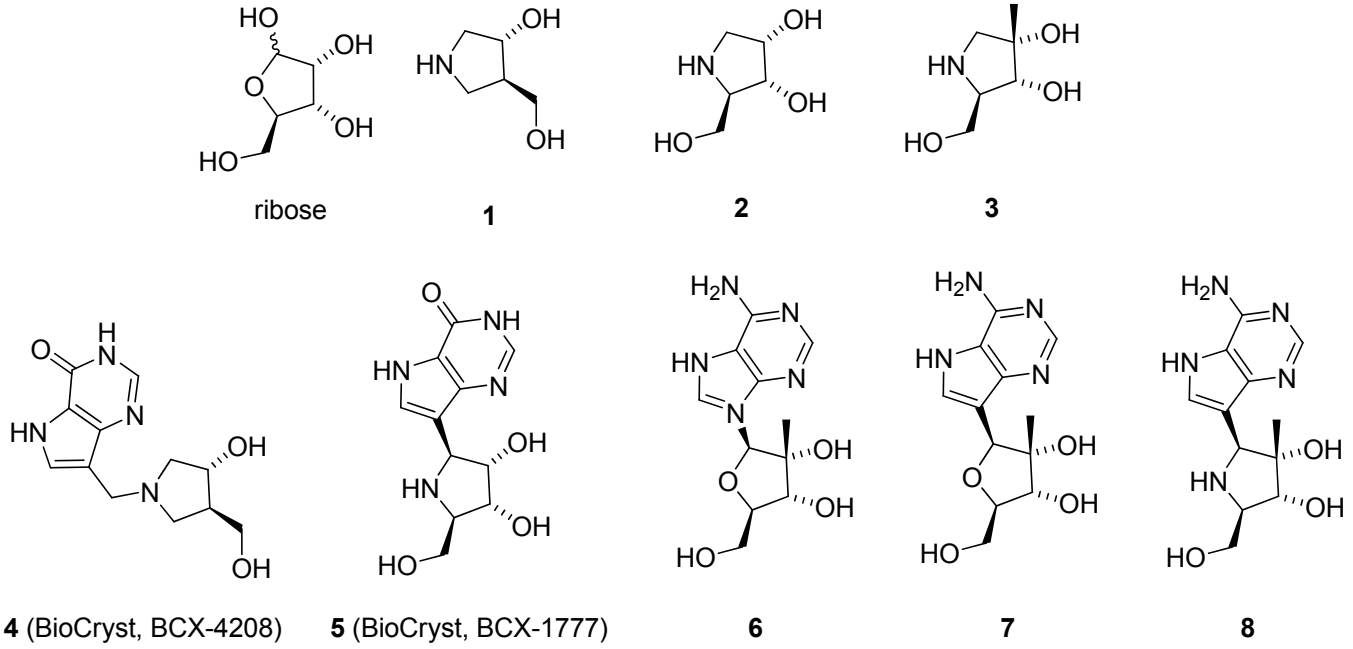


Figure 1. Examples of hydroxylated pyrrolidines

We have been involved for some time in the design and development of general methodology toward oxygenated compounds by employing a chemoenzymatic strategy depicted in Figure 2. Homochiral diols of type **9**, Figure 2, are accessible via the whole-cell fermentation of aromatic compounds with the recombinant strain JM109 (pDTG601A) that was developed by Gibson[7] and that over-expresses toluene dioxygenase. More than 400 of such metabolites are known[8] and many have been widely used in the total synthesis of natural products.[9] Our program was designed for a fully general approach to inositols,[10] aminocyclitols,[11] azasugars,[12] pseudosugars,[13] as well as their fluorinated[14] or deuterated analogues,[15] and extended to morphine[16] and Amaryllidaceae alkaloids.[17]

The metabolites derived from halobenzenes are ideally suited for further functionalization, such as dihydroxylation of the distal double bond followed by oxidative cleavage-reductive cyclization, a strategy that was shown to be useful in approaches to aza sugars, as demonstrated on the synthesis of mannojirimycin **10**[18] and kifunensine **11**,[19] as shown in Figure 2. Carbohydrates containing five-membered rings have also been synthesized.[20] Recently, we reported the total synthesis of idesolide[21] that originated in the *ipso*-diol **12** available by enzymatic oxidation of benzoic acid with the mutant strain *R.eutrophus* B9.[21] The *ipso*-diol is ideally suited for approaches to hydroxylated pyrrolidines containing the angular methyl, such as the recently reported pyrrolidine **3**, Figure 1.[5] In this report we present the synthesis of an aza sugar derivative **14b** from enantiomerically pure *ipso* diol **12** and indicate the potential

use of this compound to approaches to other five-membered polyhydroxylated pyrrolidines.

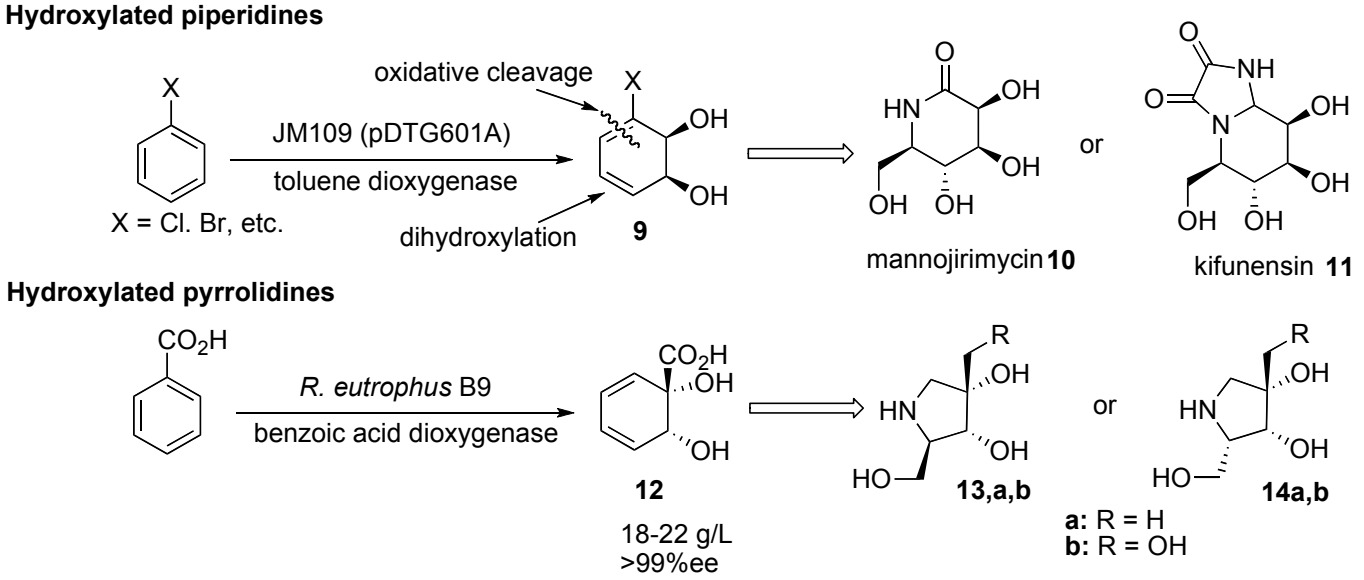


Figure 2. Design of hydroxylated piperidines and pyrrolidines from *cis*-dihydrodiols derived by enzymatic dihydroxylation

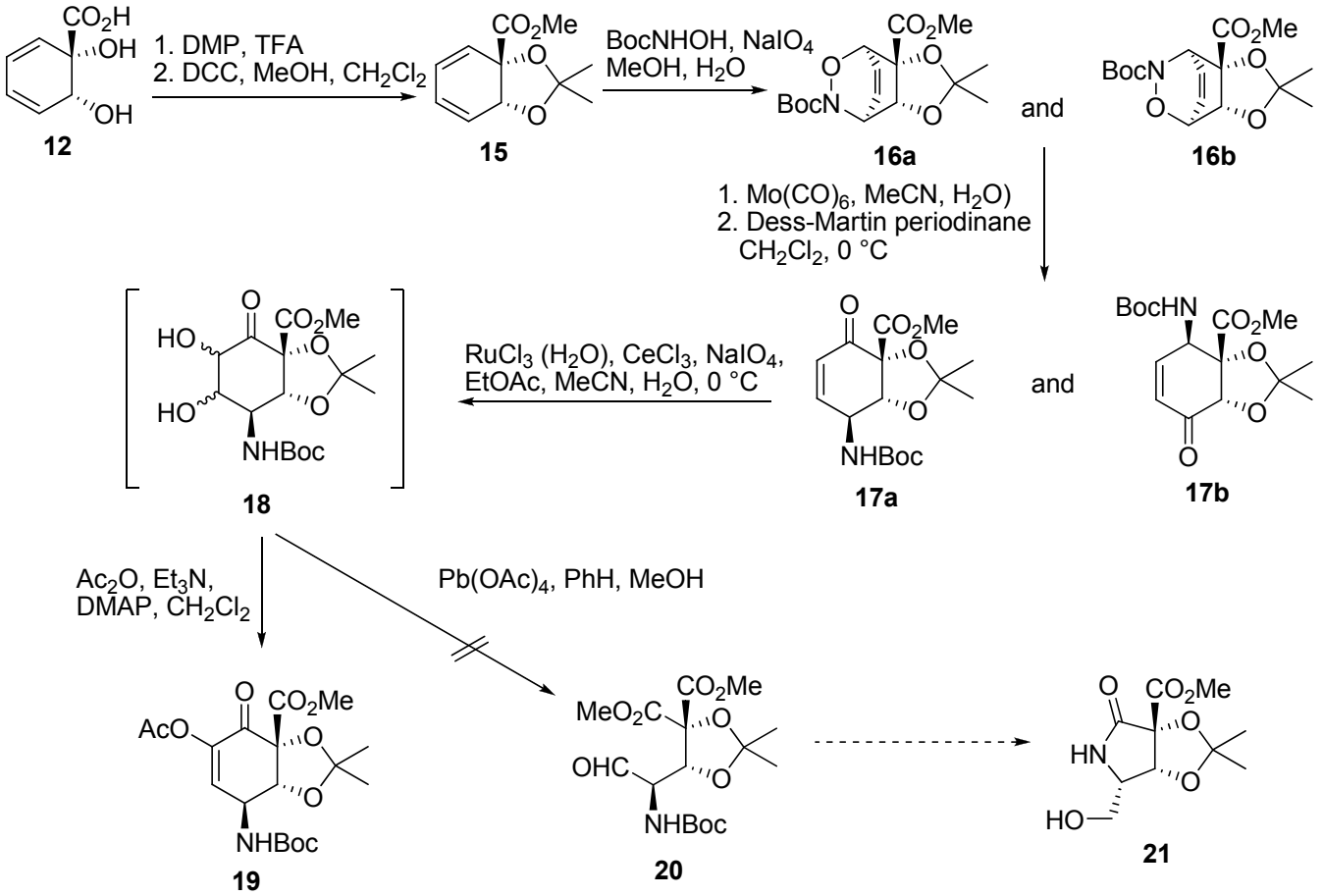
RESULTS AND DISCUSSION

While the biocatalytic dihydroxylation of halobenzenes to the *cis*-dihydrodiols **9**, Figure 2, has found utility in many synthetic strategies[8,9a,9b,10a,10c,22-58] the *ipso* dihydroxylation of benzoic acids using the mutant organism *R. eutrophus* B9[59] has not been exploited to the extent of usage of other mutant organisms, such as *E.coli* JM109 and organisms expressing other aromatic dioxygenases.[60-67] The synthesis of aza-sugar **14b** demonstrates the versatility of metabolite **12** as a chiral synthon.

In our initial approach to compounds **13** and **14**, both the angular methyl (**3**, or **13a**, and **14a**) and the hydroxymethyl derivatives (**13b** and **14b**), we assumed that the amino enones of type **17** could easily be cleaved oxidatively to esters of type **20** by methods such as those employed by Danishefsky in his synthesis of vernolepin.[68] The well-known oxidative cleavage of enones results in the loss of the α-carbon to furnish aldehyde-esters[69] and these were envisioned as intermediates for eventual transformation to pyrrolidones such as **20**, Scheme 1.

After successive methylation and acetalization of the *ipso* carboxylic acid **12**, the diene in methyl ester **15** was converted to the hetero Diels-Alder adducts **16a/b** (3:1 a/b) *via* the cycloaddition with *N*-acyl nitroso dienophile generated in situ by oxidation of *N*-Boc hydroxyl amine with sodium periodate, Scheme 1. The isolation of individual adducts **16a/b** could not be realized at this stage and the mixture of regioisomers was used in crude state after washing with aqueous base ($NaHCO_3$). The reduction of the N-O bond with molybdenum hexacarbonyl ($Mo(CO)_6$)[70] and subsequent oxidation of the amino alcohols

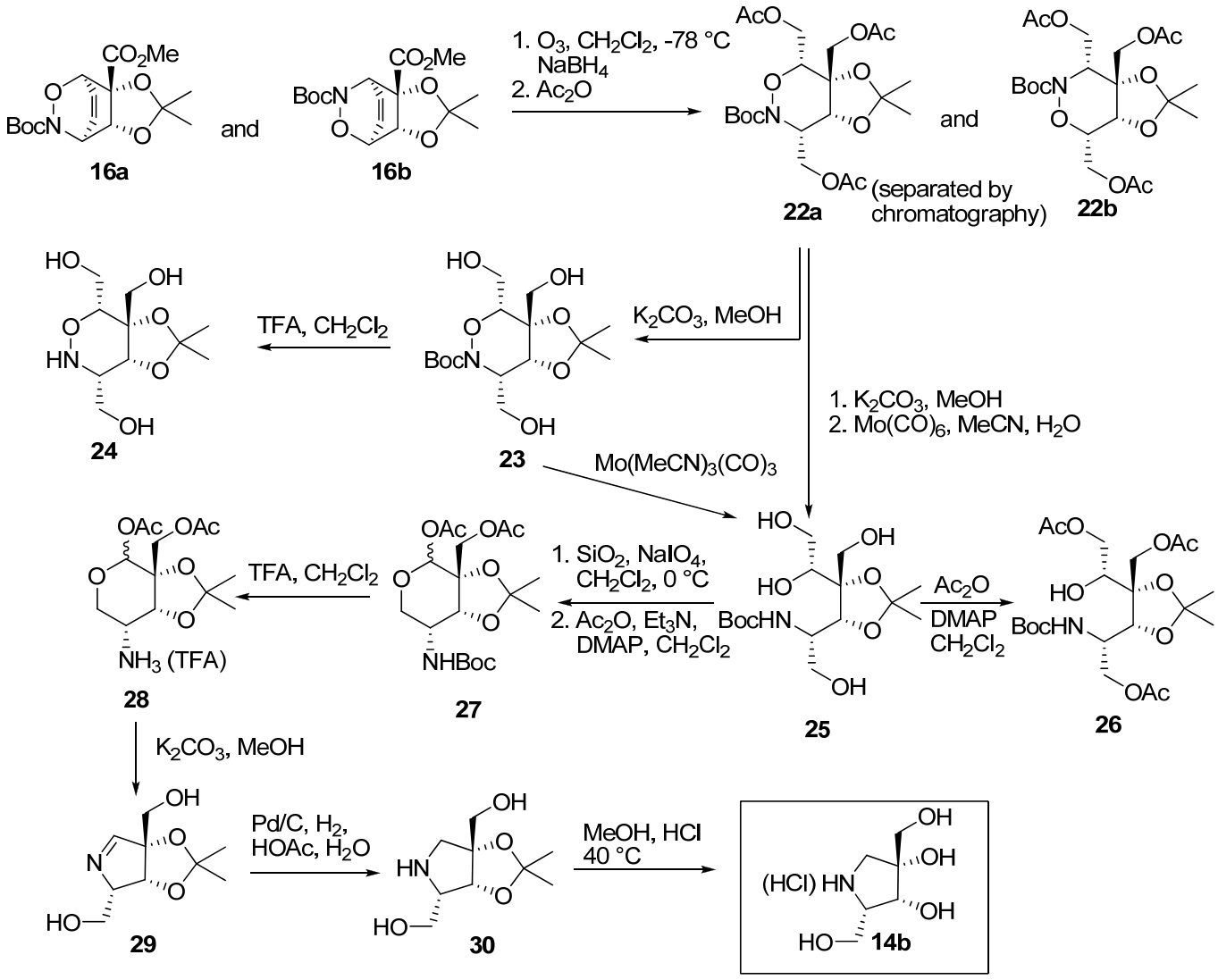
(not shown) with Dess-Martin periodinane (DMP) resulted in an isomeric mixture of enones **17a/b** that were separable at this point by flash chromatography on silica gel. The dihydroxylation of enone **17a** by the conditions reported in the literature[68,69] proved troublesome, probably because of the tendency of the electron deficient olefin to oxidatively cleave under standard Upjohn[71] reaction conditions (OsO_4/NMO) as reported by Plietker and substantiated by the complex mixtures obtained in our experiments. The ruthenium chloride/cesium chloride/sodium periodate redox system developed by Plietker and co-workers[72] established a level of oxidative control and diol **18** could be generated by this protocol. The active Ce(IV)-periodate complex was preformed by gently heating a mixture of cerium chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) and sodium periodate ($NaIO_4$) in water until a yellow suspension was formed. At this point an aqueous solution of ruthenium(III) chloride was added followed by addition of substrate. The diastereomeric mixture of diols **18** was used as such, after rapid chromatographic purification, and proved to be fairly sensitive to prolonged exposure to acidic environment. Upon acylation the distal hydroxy group was eliminated to form the α,β-unsaturated intermediate **19**. All attempts to oxidatively cleave diol **18** with lead tetraacetate ($Pb(OAc)_4$) with concomitant loss of the α-carbon atom of the ketone only resulted in complex mixtures of unidentifiable material.



Scheme 1

Having failed in the planned route to pyrrolidone **21** an alternative strategy to access pyrrolidines of type **14** was pursued. We envisioned that if acetal **27** could be prepared through a series consisting of a reduction, oxidative cleavage, and protecting group manipulations typical in sugar chemistry, that azomethine **29** could be attained and subsequently would yield pyrrolidine tetrol **14b**, Scheme 2. The polar nature of many of the intermediates depicted in Scheme 2 made their isolation difficult. The acylation of compound mixtures provided the means for isolation, characterization, and protection of functionality. The initial ozonolysis of isoxazolidines **16a/b** is a case in point. The ozonolysis of **16a/b** in methylene chloride was rapid but the reduction of the ozonide and methyl ester functionality by addition of solid sodium borohydride ($NaBH_4$) took several hours, even after reaching ambient temperature from -55 ˚C. The reaction mixture was quenched with water prior to concentration *in vacuo* and the crude ozonolysis reaction mixture was acylated using standard conditions (Ac_2O, Et_3N, DMAP, CH_2Cl_2). At this point the regioisomers were separable by silica gel chromatography and afforded the individual isoxazolidine acetates **22a** and **22b** in yields ranging from 22 – 37% of the desired **22a** (from **16a/b**). The [latent] *vic*-1,2-diol in **22a,** which would be liberated upon the hydrolysis of acetates and the reduction of the isoxazolidine, was to be oxidatively cleaved in order to furnish acetal **27** following the cyclization onto the aldehyde generated by the cleavage of **25**. To this end base hydrolysis was used to provide the corresponding isoxazolidine **23**, which was characterized more easily as the fully deprotected isoxazolidine **24** upon treatment with trifluoroacetic acid (TFA). The characterization of this compound was easier than that of isoxazolidine **23**, which consisted of a mixture of rotamers (Boc carbamate). Tetrol **25** was prepared from acetate **22a** by hydrolysis and immediate reduction after workup of the N-O bond by $Mo(CO)_6$. The reduction with $Mo(CO)_6$ to yield **25** proved moderately difficult and many experiments were performed in attempts to improve the reproducibility and yields. In order to establish a moderate level of reproducibility for the reduction of the N-O bond several details had to be addressed. The purity of the $Mo(CO)_6$ was critical and sublimation of the reagent was required to eliminate the batch variation in commercially available $Mo(CO)_6$. Also, the *in situ* formation of the chemically active $Mo(MeCN)_3(CO)_3$[73,74] species generated from ligand exchange between acetonitrile (MeCN) and carbon monoxide (CO) had to be monitored (visible by TLC) as the reaction progressed. It was observed that the reduction of **23** could proceed much faster if the active catalyst $Mo(MeCN)_3(CO)_3$ was generated separately, isolated, and then used in subsequent reactions. However, the lack of confidence in the purity and stability of $Mo(MeCN)_3(CO)_3$ prevented its usage in the direct transformation of **23** to **25** and $Mo(CO)_6$ was used instead. Another crucial aspect of this reaction pertained to the liberation of substrate **25** from the complexation with molybdenum. It was found that upon the completion of the reaction the mixture had to be treated with sodium bicarbonate and exposed to air with vigorous stirring for several hours (> 12 h) in order to allow for the decomplexation of the product-molybdenum species. Following

this protocol led to the isolation of **25** in yields up to 87%.



Scheme 2

The oxidative cleavage of the free vicinal diol in **25** with sodium periodate ($NaIO_4$) in a biphasic $NaHCO_3$(aq)/CH_2Cl_2 mixture provided an equilibrium mixture of a hemiacetal (not shown) and the corresponding hydroxy aldehyde isomer (as evidenced by NMR, not isolated). The oxidative cleavage of **25** was found to proceed much more smoothly and with better purity profile when a silica gel-supported periodate reagent was used.[76] After filtration of the periodate/silica gel support the hemiacetal was immediately subjected to acylation and the bis acetate **27** was isolated in 41% overall yield from isoxazolidine **22a**; the isolation of pure intermediates during this sequence was further detrimental to the yield. The Boc-protected amine **27** was treated with trifluoroacetic acid (TFA) to furnish **28** as a stable TFA salt. The hydrolysis of **28** under basic methanolic (anhydrous) conditions provided pyrroline **29** in 50% yield from **27**. The impurity profile consisted only of potassium acetate and potassium

trifluoroacetate salts and pyrroline **29** was obtained by trituration of the mixture with acetone. Hydrogenation of **29** proceeded smoothly under standard conditions (1 atm) to provide acetonide protected pyrrolidine **30** in quantitative yield. The hydrolysis of acetonide **30** proved to be sluggish at room temperature and required up to four days under these conditions to achieve full conversion. Alternatively, the use of trifluoroacetic acid in water provided pyrrolidine **14b** within 24 hours but the handling and increased solubility of the TFA salt made purification more difficult than that of the corresponding crystalline HCl salt of **14b**. Ultimately, treatment of acetonide **30** with HCl/MeOH at 40 ˚C provided pyrrolidine **14b** as an easily crystallizable HCl salt in 75% yield.

CONCLUSIONS

We have demonstrated that the *ipso*-diol **12**, derived enzymatically from benzoic acid, can be used for the synthesis of hydroxylated pyrrolidines by sequential hetero Diels-Alder cycloaddition followed by reductive cleavage and eventual recyclization. Future work in this area will examine the generality of this method as applicable to other targets.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

All non-aqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. All solvents were distilled unless otherwise noted. Analytical thin layer chromatography was performed on EMD Silica gel 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh). Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm. H^1 and C^{13} spectra were recorded on a 300 MHz and 600 MHz Bruker spectrometer. All chemical shift are referenced to TMS or residual non-deuterated solvent. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t),

quartet (q) and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (C) relative to TMS. Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University. Combustion analyses were performed by Atlantic Microlabs, Atlanta, GA.

(1*S*,2*R*)-1,2-Dihydroxycyclohexa-3,5-diene-1-carboxylic acid (**12**).

The whole-cell biotransformation of benzoic acid was performed based on a modified procedure established by Mihovilovic and co-workers.[63] LB(II) medium (100 mL) was inoculated with a single colony of *Ralstonia eutrophus* B9 that was grown on LB(II) agar plates at 30 ˚C for two days. The inoculated medium was incubated at 30 ˚C on an orbital shaker at 185 RPM until OD_{256} = 4.8 (1:10 dilution; ~ 24 h). At this point the cellular suspension (80 mL) was used as a preculture and added to a 15 L Sartorius Biostat C bioreactor that contained HMB medium (8.4 L) at pH = 7.4, aerated with sterile air at 3 L/min, agitation speed of 300 RPM, and D-fructose (50 mL of a 1.5 M aq. solution) concentration of 0.009 M. The culture was grown until an OD_{256} = 2.8 (1:10 dilution) was achieved (~ 20 h) and then induced with sodium benzoate (12 mL of a 1.5 M aq. solution; 18 mmol) and D-fructose (53 mL of a 1.5 M aq. solution; 80 mmol). After 6 h consumption of benzoate was observed by UV analysis (265 nm) and a repetitive feeding program was initiated at which 15 min feeding of an aq. solution of sodium benzoate (22 mL, 1.5 M; 1.5 mL/min feed rate) and aq. D-fructose (22 mL, 1.5 M; 1.5 mL/min feed rate) was performed every 3 h over the course of 4 days; a total of approximately 170 g of sodium benzoate was fed. After the feeding regime was completed the broth was drained and separated from cell matter by centrifugation at 5 ˚C (10,000 RPM). The dark brown ferment broth was concentrated *in vacuo* at 35 ˚C to dryness to obtain several lots of *ipso* diene diol carboxylate as the mixed potassium/sodium salts, was contaminated with other inorganic salts. NMR spectroscopy assay was used to establish a weight-weight percentage of the crude material with an internal standard (potassium benzoate). A total mass of 261.5 g of crude material was obtained and corresponded to 177 g of the salt of *ipso* diol **12** that could be stored at room temperature without any observable degradation (several months). ^{1}H NMR (600 MHz, D_2O) δ 6.03 (dd, *J* = 9.5, 5.2 Hz, 1H), 5.93 – 5.81 (m, 1H), 5.71 – 5.64 (m, 2H), 4.77 (s, 1H).[75] The free acid **12** was obtained by the acidification of a cold aqueous solution of the salts with 6M HCl and extraction with EtOAc.

12: ^{1}H NMR (300 MHz, D_2O) δ 6.12 (dd, *J* = 9.3, 5.1 Hz, 1H), 6.05 – 5.90 (m, 1H), 5.77 (d, *J* = 9.6 Hz, 2H), 4.86 (s, 1H).

(3a*S*,7a*R*)-Methyl 2,2-dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole-3a-carboxylate (**15**).

To a slurry of mixed sodium/potassium carboxylate of **12** (61.6 g (81.1 g at 76 wt% purity), 317 mmol) in

2,2-dimethoxypropane (790 mL, 0.4 m) at 0 ˚C with vigorous stirring was added trifluoroacetic acid (146 mL, 1.90 mol, 6.0 equiv.) dropwise over 6 min while the internal temperature was monitored; no significant exotherm observed. The reaction mixture was warmed up to room temperature and stirred until the consumption of **12** was observed by TLC (4:1 EtOAc/MeOH) and/or HPLC analysis (254 nm) at approximately 6 h. The reaction mixture was filtered over a pad of Celite and the filtrate concentrated *in vacuo* to a dark brown/black oil. The crude oily mixture was dissolved in H_2O (100 mL) and extracted twice with CH_2Cl_2. The organic phase was then extracted with an aqueous $NaHCO_3$ solution (sat'd, 3 x 100 mL) and concentrated to dryness *in vacuo* to provide, as a solid, the sodium salt of **(3a*S*,7a*R*)-2,2-Dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole-3a-carboxylate**, contaminated with other inorganic salts. The crude product was then dissolved in MeOH and the heterogeneous mixture containing undissolved inorganic salts was filtered. The filtrate was concentrated *in vacuo* to yield 62.08 g (90%) of sodium salt acetonide as a slightly off-white solid. The storage of the sodium carboxylate was convenient in that its shelf life at room temperature exceeded several months with no loss in purity as indicated by NMR analysis.

(3a*S*,7a*R*)-2,2-Dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole-3a-carboxylate, sodium salt: ^{1}H NMR (300 MHz, D_2O) δ 6.13 (dd, *J* = 5.6, 9.5 Hz, 1H), 6.06 (dd, *J* = 5.5, 9.6 Hz, 1H), 5.92 (dd, *J* = 4.3, 9.5 Hz, 1H), 5.71 (dd, *J* = 9.9, 4.5 Hz, 1H), 4.80 (d, *J* = 4.2 Hz, 1H), 1.33 (s, 3H), 1.33 (s, 3H).

The corresponding free acid was obtained by the acidification of a cold aqueous solution of the salts with 6M HCl and extraction with EtOAc.

(3a*S*,7a*R*)-2,2-Dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole-3a-carboxylic acid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (bs, 1H), 6.16 (m, *J* = 3.6 Hz, 1H), 6.04 (dd, *J* = 4.7, 9.6 Hz, 1H), 5.77 (q, *J* = 3.2 Hz, 1H), 4.93 (d, *J* = 4.2 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H).[60]

To a clear light brown solution of freshly extracted **(3a*S*,7a*R*)-2,2-dimethyl-3a,7a-dihydrobenzo-[*d*][1,3]dioxole-3a-carboxylic acid** (67 g, 341 mmol) in CH_2Cl_2 (1.7 L, 0.2 M) at 10 ˚C was added MeOH (34 mL, 853 mmol, 2.5 equiv.), dimethylaminopyridine (4.2 g, 34.1 mmol, 0.1 equiv.), and *N*,*N*'-dicyclohexylcarbodiimide (77.4 g, 375 mmol, 1.1 equiv.) under an atmosphere of argon and with vigorous stirring; almost immediately a white slurry was generated and the reaction was stirred to room temperature and monitored by TLC analysis (5:1 hexanes/EtOAc). After 12 h the reaction mixture was filtered and the filter cake rinsed with CH_2Cl_2 (2x). The filtrate was slightly concentrated, which allowed for additional precipitation of dicyclohexylurea and the material was filtered again. The filtrate was concentrated to dryness *in vacuo* and provided crude material (71.92 g) as a brown oil that was contaminated by dicyclohexylurea. The crude material was subjected to silica gel chromatography (5:1 → 4:1 hexanes/EtOAc) and yielded 42.2 g (67%) of known methyl ester **15** as a yellow oil that solidified to a low-melting, white crystalline solid at low temperature (5 ˚C).

15: R_f = 0.51 (hexanes/EtOAc 5:1); IR (film, cm^{-1}) 3043, 2989, 2934, 2846, 1753, 1735, 1454, 1434, 1380, 1371, 1254, 1209, 1168, 1036, 885, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (m, 2H), 6.04 (m, 1H), 5.84 (m, 1H), 4.99 (d, *J* = 4.1 Hz, 1H), 3.81 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 172.18, 124.75, 124.52, 124.07, 124.01, 106.81, 79.42, 72.74, 52.95, 26.89, 25.16.[60]

8-*tert*-Butyl 3a-methyl (3a*R*,4*R*,7*S*,7a*R*)-2,2-dimethyl-7,7a-dihydro-4,7-(epoxyimino)-1,3-benzodioxole-3a,8(4*H*)-dicarboxylate (16a/b).

To a solution of diene ester **15** (2.72 g, 12.9 mmol) in a mixture of MeOH/H_2O (4:1 v/v, 65 mL, 0.2 M) at 0 ˚C was added sodium periodate (3.60 g, 16.8 mmol, 1.3 equiv.) as a single portion. To this mixture was added a solution of *t*-butyl hydroxycarbamate (2.24 g, 16.8 mmol, 1.3 equiv.) in MeOH/H_2O (4:1 v/v, 10 mL, 1.7 M) dropwise over several minutes. The reaction mixture became a thick slurry upon addition of the hydroxy carbamate and progress was monitored by TLC analysis (4:1 hexanes/EtOAc, CAM). Upon consumption of **15** (approximately 2.5 h) the reaction was diluted with EtOAc and the thick slurry was filtered. The filter cake was rinsed with EtOAc and the filtrate was collected and rinsed with aqueous $NaHCO_3$ (saturated, 1x), H_2O (1x), and then brine (1x). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield an orange oil. The crude material was chromatographed on silica gel (2:1 hexanes/EtOAc) to yield a mixture regioisomers **16a** and **16b** (4.32 g, 96%; 3:1 **16a**/**16b** ratio determined by NMR). The purity of the crude material was sufficient enough to use without further purification.

16a/16b: R_f = 0.34 (4:1 hexanes/EtOAc); IR (film, cm^{-1}) *v* 2984, 2954, 2940, 2253, 1745, 1709, 1458, 1437, 1382, 1372, 1263, 1213, 1160, 1110, 1088, 1061, 1017, 877, 732; ^1H NMR (600 MHz, $CDCl_3$) δ 6.53 (m, *J* = 4.9 Hz, 1H), 6.49 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.17 (d, *J* = 4.4 Hz, 1H), 5.14 (dd, *J* = 1.4, 5.9 Hz, 1H), 5.09 (m, *J* = 2.9 Hz, 1H), 3.89 (s, 1H), 1.48 (s, 1H), 1.34 (s, 1H), 1.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 157.0, 131.0, 129.9, 128.7, 112.7, 82.7, 82.3, 74.4, 72.7, 53.5, 53.1, 28.1, 26.2, 26.1; MS (EI+) *m/z* (%) 341 (0.4), 159 (12), 158 (35), 151 (7), 143 (21), 124 (8), 109 (7), 105 (13), 93 (13), 83 (22), 73 (21), 65 (12), 61 (15), 59 (42), 58 (16), 57 (100), 56 (26), 55 (16), 45 (20), 44 (34), 43 (96), 42 (17), 41 (65); HRMS (+EI) calcd for $C_{12}H_{23}N_1O_7$: 341.1475. Found: 341.14759.

(3a*R*,7*S*,7a*R*)-Methyl-7-(*tert*-butoxycarbonylamino)-2,2-dimethyl-4-oxo-3a,4,7,7a-tetrahydrobenzo-[*d*][1,3]dioxole-3a-carboxylate (**17a**).

To a solution of isoxazolidines **16a/b** (773 mg, 2.26 mmol) in MeCN/H_2O (16 mL, 0.15 M, 15:1 *v*/*v*) at 80 ˚C was added molybdenum hexacarbonyl (897 mg, 3.39 mmol, 1.5 equiv.) with stirring. The reaction was monitored by TLC analysis ($CHCl_3$/MeOH 95:5) and deemed complete after 24 h. The reaction mixture was filtered through a plug of Celite and the filtrate concentrated to dryness *in vacuo*. The crude mixture

of amino alcohol regioisomers (3:1 ratio established by NMR analysis) was subjected to oxidative conditions by dissolution in CH_2Cl_2 (23 mL, 0.1 M), chilling the solution to 0 ˚C, and a single portion addition of Dess-Martin periodinane (1.44 g, 3.39 mmol, 1.5 equiv.) with stirring. The reaction was allowed to slowly warm to ambient temperature and was monitored by TLC analysis (hexanes/EtOAc 1:1). After 23 h the reaction was quenched with aq. $Na_2S_2O_3$ (sat'd, 2 mL) and diluted with CH_2Cl_2 (25 mL). Precipitation occurred and the solid was filtered. The organic filtrate was washed with aq. $NaHCO_3$ (sat'd, 1 x 6 mL), brine (1 x 8 mL), and then dried over $MgSO_4$ and filtered. The crude organic solution was concentrated *in vacuo* to a solid crude material (1.34 g) that was chromatographed on silica gel (two chromatographic processes) ($CHCl_3$/MeOH/hexanes 78:4:1) to yield **17a** (246 mg, 32% from **16a/b**) as a yellow-orange oil and **17b** (30 mg, 4% from **16a/b**) as a yellow oil.

17a: R_f = 0.60 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ 64.912 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) *v* 3029, 2986, 1710, 1692, 1496, 1299, 1226, 1162, 1101, 770; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 1.6, 5.0, 9.9 Hz, 1H), 6.86 (d, *J* = 1.7 Hz, 1H), 6.16 (d, *J* = 10.2 Hz, 1H), 5.41 (d, *J* = 9.3 Hz, 1H), 4.84 (dd, *J* = 5.0, 7.4 Hz, 1H), 4.43 (s, 1H), 3.83 (s, 1H), 1.44 (s, 1H), 1.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.30, 168.64, 154.73, 145.76, 127.45, 111.22, 81.98, 80.59, 79.44, 77.25, 53.56, 45.41, 28.30, 27.12, 25.59; MS (+EI) *m/z* (%) 285 (2), 270 (4), 248 (7), 228 (9), 159 (55), 143 (7), 127 (41), 96 (9), 83 (37), 73 (21), 59 (15), 57 (100), 43 (18), 41 (18); HRMS (+EI) calcd for $C_{16}H_{23}O_7N$: 341.1475. Found: 341.1481.

(3a*R*,7*S*,7a*R*)-Methyl-7-(*tert*-butoxycarbonylamino)-5,6-dihydroxy-2,2-dimethyl-4-oxohexahydro-benzo[*d*][1,3]dioxole-3a-carboxylate (**19**).

Step 1. To a solution of sodium periodate (904 mg, 4.22 mmol, 1.5 equiv.) in H_2O (0.85 mL, 3.3 M) at room temperature was added cerium (III) chloride heptahydrate (104 mg, 0.281 mmol, 10 mol%) and the white slurry was gently heated so that it became yellow in color. The yellow slurry was cooled in an ice-bath and a mixture of EtOAc/MeCN (1.2:1 v/v) was added. To this chilled mixture was added ruthenium (III) chloride hydrate ($RuCl_3 \cdot xH_2O$, 0.25 mol%) and the reaction mixture immediately turned to a dark brown color. A solution of enone **17a** (962 mg, 2.81 mmol, 1.0 equiv.) in EtOAc (6.5 mL, 0.43 M) was added to the reaction mixture and the reaction was stirred for approximately 23 h with gradual warming to room temperature over the first 1.5 h. The reaction was monitored by TLC analysis (EtOAc/hexanes 2:1). Once the reaction was deemed complete by TLC small portions of sodium sulfite were added until no more active oxidant was detectable by KI/starch paper. The reaction mixture was filtered and the filtered solid washed with small portions of EtOAc. The filtrate was concentrated to yield 1.00 g of crude material as a light yellow foam-like solid. Silica gel chromatography (EtOAc/hexanes 2:1) provided 647 mg of **18** (quant.).

Step 2. To a solution of reasonably pure **18** (26 mg, 0.081 mmol, 1.0 equiv.) in CH_2Cl_2 (0.8 mL, 0.1 M) at room temperature was added acetic anhydride (30 μL, 0.327 mmol, 4.0 equiv.), triethylamine (45 μL, 0.327 mmol, 4.0 equiv.), and dimethylaminopyridine (DMAP, cat.) in succession. Upon addition of triethylamine the clear and colorless mixture became clear and yellow and following the addition of DMAP the mixture lightened in color. The reaction was monitored by TLC analysis (hexanes/EtOAc 1:1) and starting material was consumed after 10 min. The reaction was quenched with an aqueous solution of ammonium chloride (sat'd, 0.2 mL) and followed by the addition of H_2O (0.4 mL). The phases were separated and the organic phase was washed with H_2O (2x), brine (1x), and then dried over $MgSO_4$. The organic phase was concentrated *in vacuo* to yield 28 mg of crude material as a white foam-like solid. The crude material was chromatographed on silica gel (hexanes/EtOAc 2:1) to yield 18 mg (52%) of acetate **19** as a white solid.

19: mp 103 – 105 ˚C (pentane); R_f = 0.54 (hexane/EtOAc 2:1); $[\alpha]_D^{20}$ +64.888 (*c* 0.90, $CHCl_3$); IR (film, cm^{-1}) *v* 3393, 2984, 1773, 1703, 1498, 1369, 1303, 1193, 1165, 1094, 1014, 875, 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d, *J* = 5.6 Hz, 1H), 5.48 (d, *J* = 9.6 Hz, 1H), 5.03 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.46 (s, 1H), 3.89 (s, 3H), 2.25 (s, 3H), 1.53 – 1.46 (m, 12H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.24, 168.05, 154.62, 143.94, 131.53, 111.93, 83.36, 80.74, 79.52, 77.44, 77.02, 76.59, 53.75, 44.90, 28.30, 26.97, 25.64, 22.32, 20.20, 14.04; HRMS (EI+ TOF) calcd for $C_{18}H_{25}NO_9$: 399.1529. Found: 399.1539.

[(3a*R*,4*R*,7*S*,7a*R*)-2,2-Dimethyldihydro-4*H*-[1,3]dioxolo[4,5-*d*][1,2]oxazine-3a,4,7-triyl]tri-(methylene) triacetate (**22a**).

To a clear and colorless solution of isoxazolidine **16a/b** (104 mg, 0.295 mmol, ~6:1 mixture of regioisomers) in CH_2Cl_2 (6 mL) at -70 °C was bubbled ozone until a blue color persisted (*ca*. 35 min) which corresponded to the consumption of **16a/b** by TLC analysis (hexanes/EtOAc 2:1). Oxygen was used to purge the reaction mixture and devoid it of excess ozone and its blue color. Sodium borohydride (21 mg) was added directly to the reaction mixture at -54 °C and the reaction was slowly warmed to room temperature and allowed to stir for a total of 23 h at room temperature. To the hazy, off-white reaction mixture was added H_2O (3 drops) and stirring was allowed for several minutes prior to concentration *in vacuo*. The crude mixture was then reconstituted in CH_2Cl_2 (3 mL) and acetic anhydride (140 μL, 1.47 mmol), triethylamine (205 μL, 1.47 mmol), and 4-dimethylaminopyridine (DMAP, cat.) was added in sequence and allowed to stir overnight at room temperature. After 17 h the reaction was quenched with aq. NH_4Cl (sat'd, 1 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 1 mL) and brine (1 x 1 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to provide an orange oil (119 mg). The crude material was chromatographed on silica gel (hexanes/EtOAc 2:1) to yield **22a** (31 mg, 22%) as a colorless oil.

22a: R_f = 0.41 (hexanes/EtOAc 2:1); $[\alpha]_D^{20}$ +37.47° (*c* 0.7, $CHCl_3$); IR (film, cm^{-1}) υ 2984, 2936, 1746, 1706, 1456, 1370, 1337, 1233, 1165, 1132, 1043, 930, 885, 854, 759; ^{1}H NMR (300 MHz, DMSO) δ 4.55 (d, *J* = 4.0 Hz, 1H), 4.38 – 4.23 (m, 3H), 4.20 (s, 2H), 4.14 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.01 (dd, *J* = 13.0, 8.4 Hz, 1H), 3.81 (dd, *J* = 8.3, 2.1 Hz, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.45 (s, 9H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 170.7, 170.5, 170.1, 155.9, 109.6, 81.9, 81.8, 78.3, 73.5, 64.8, 62.2, 62.0, 52.8, 28.3, 27.2, 26.0, 21.2, 21.1, 20.9; MS (+EI) *m/z* (%) 283 (M^+-CH_3, 1), 375 (11), 223 (21), 167 (20), 149 (100), 101 (15), 57 (87); HRMS (+EI) calcd for $C_{21}H_{33}O_{11}N$: 475.2054. Found 475.2054.

(3a*R*,4*R*,7*S*,7a*R*)-*tert*-Butyl 3a,4,7-tris(hydroxymethyl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*d*]-[1,2]oxazine-6(4*H*)-carboxylate (23).

To a solution of protected isoxazolidine **22a** (39 mg, 0.082 mmol) in MeOH (2 mL) at room temperature was added an aqueous solution of potassium carbonate (10%, 1.3 mL) with stirring. The consumption of **22a** was observed by TLC analysis (EtOAc) after 1.2 h and the reaction mixture was neutralized with aqueous HCl (1 M). The mixture was extracted with EtOAc (3 x 1.5 mL), the combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield **23** (31 mg, quant.) as a colorless oil. An analytical sample was obtained by silica gel chromatography (EtOAc).

23: R_f = 0.37 (EtOAc); $[\alpha]_D^{20}$ +56.68° (*c* 0.7, $CHCl_3$); IR (film, cm^{-1}) υ 3379, 2983, 2935, 1700, 1456, 1393, 1370, 1337, 1251, 1217, 1150, 1117, 1050, 1010, 904, 866, 844, 826, 756; ^{1}H NMR (600 MHz, DMSO) δ 5.18 (t, *J* = 5.2 Hz, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.52 (d, *J* = 3.6 Hz, 1H), 4.48 (t, *J* = 5.7 Hz, 1H), 3.79 (dt, *J* = 9.8, 4.2 Hz, 1H), 3.68 – 3.63 (m, *J* = 9.5, 4.7 Hz, 1H), 3.63 – 3.53 (m, 4H), 3.45 – 3.38 (m, 2H), 1.42 (s, 9H), 1.34 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 157.4, 108.3, 85.1, 81.1, 80.1, 74.5, 63.8, 60.4, 59.1, 57.5, 28.4, 27.5, 26.6; MS (FAB+) *m/z* (%) 350 (3), 294 (13), 250 (10), 192 (14), 136 (12), 109 (11), 107 (12), 97 (14), 95 (17), 57 (100), 43 (58), 41 (50), 39 (18), 29 (23); HRMS (FAB+) calcd for $C_{15}H_{28}O_8N$: 350.1815 [M^++1]. Found 350.1791.

***tert*-Butyl (*S*)-1-((4*R*,5*S*)-5-((*R*)-1,2-dihydroxyethyl)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethylcarbamate (25)**.

To a clear, light yellow and degassed solution of isoxazolidine **23** (152 mg, 0.435 mmol, 1.0 equiv.) in MeCN/H_2O (4.4 mL, 0.1 M, 15:1 *v*/*v*) at room temperature was added molybdenum hexacarbonyl (sublimed, 252 mg, 0.957 mmol, 2.2 equiv.) with stirring and under a blanket of argon. The reaction mixture slowly changed from a light yellow heterogeneous mixture of $Mo(CO)_6$ crystals and dissolved substrate to a darker homogeneous mixture and an eventual black mixture upon heating to reflux. The reaction was monitored by TLC analysis (4:1 EtOAc/MeOH, CAM) and stirred for *ca*. 20 h prior to

cooling to room temperature and spiking the reaction mixture with solid $NaHCO_3$ (two small spatula tips) and several drops of an aqueous $NaHCO_3$ (sat'd) solution and exposing to air for > 8 h. Celite (small scoop) was added to the reaction mixture with stirring and then passed over a short pad of Celite/SiO_2 (1:1 *w*/*w*) and eluted with EtOAc. Three fractions were collected and the main fraction that contained **25** was concentrated *in vacuo* to yield 133 mg (87%) of **25** as a slightly pink crude material that was used without further purification.

25: mp 61 – 63 ˚C; R_f = 0.58 (EtOAc/MeOH 4:1); $[\alpha]_D^{20}$ +2.1 (*c* 1.5, $CHCl_3$); IR (film, cm^{-1}) ν 3418, 2982, 2936, 1691, 1507, 1456, 1384, 1252, 1218, 1168, 1053, 894, 865, 615; ^1H NMR (300 MHz, MeOD) δ 4.38 (d, *J* = 4.6 Hz, 1H), 4.11 (dd, *J* = 11.0, 5.3 Hz, 1H), 3.88 (dd, *J* = 7.3, 3.5 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.72 – 3.57 (m, 5H), 1.51 (s, 3H), 1.47 (s, 8H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, MeOD) δ 156.7, 107.5, 84.2, 79.0, 78.4, 71.6, 63.6, 62.3, 62.2, 51.0, 27.3, 25.8, 25.1; MS (FAB+) *m*/*z* (%) 353 (12), 352 (67.5), 296 (17), 253 (12), 252 (99), 238 (15), 214 (21), 194 (33), 176 (10), 149 (29), 113 (12), 57 (100), 55 (13), 43 (28), 41 (24), 29 (12); HRMS (FAB+) calcd for $C_{15}H_{30}NO_8$: 352.1971 [M+1]. Found 352.1976; Anal. Calcd for $C_{15}H_{29}O_8N$: C, 51.27; H, 8.32. Found C, 51.37; H, 8.16.

((4*S*,5*R*)-5-((*S*)-2-Acetoxy-1-(*tert*-butoxycarbonylamino)ethyl)-4-((*R*)-2-acetoxy-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate (**26**).

To a clear and colorless solution of isoxazolidine triol **23** (52 mg, 0.148 mmol) in a mixture of MeCN/H_2O (1.5 mL, 15:1 v/v) at room temperature was added molybdenum hexacarbonyl (58 mg, 0.223 mmol) with stirring. The reaction was heated to reflux for *ca*. 24 h prior to an additional portion of molybdenum hexacarbonyl (39 mg, 0.148 mmol) was added. The reaction was stirred at reflux for another 12 h prior to cooling to room temperature and filtration through a pad of Celite. The filtrate was concentrated *in vacuo* to yield a crude black mass that was dissolved in CH_2Cl_2 (2.5 mL) and acetic anhydride (140 μL, 1.48 mmol), Et_3N (206 μL, 1.48 mmol), and 4-dimethylaminopyridine (cat.) was added sequentially at room temperature and with stirring. The reaction was stirred for 20 h and quenched with aq. NH_4Cl (sat'd, 0.5 mL). The phases were separated and the organic phase was washed with H_2O (2x) and brine (1x). The organic phase was dried over $MgSO_4$ and concentrated to provide crude material (25 mg) that was chromatographed on silica gel (hexanes/EtOAc 1:1) to yield **26** (6 mg, 8%) as a white foam.

26: R_f = 0.53 (hexanes/EtOAc 1:1); IR (film, cm^{-1}) υ 3368, 2981, 2930, 1747, 1715, 1497, 1454, 1369, 1226, 1165, 1046, 870, 603; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 (dd, *J* = 7.2, 3.4 Hz, 1H), 4.96 (d, *J* = 9.0 Hz, 1H), 4.34 – 4.23 (m, 2H), 4.21 (d, *J* = 4.2 Hz, 2H), 4.18 – 4.05 (m, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.50 (s, 3H), 1.46 (s, 8H), 1.36 (s, 3H); MS (EI+) *m/z* (%) 448 (2), 404 (3), 346 (10), 287 (14), 259 (15), 149 (11), 102 (36), 57 (64), 43 (100); HRMS (EI+) calcd for $C_{22}H_{34}O_{12}N$:

504.2081 [M^+-CH_3]. Found 504.2084.

((3a*R*,7*S*,7a*R*)-4-Acetoxy-7-(*tert*-butoxycarbonylamino)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo-[4,5-*c*]pyran-3a-yl)methyl acetate (**27**).

To a clear and red solution of tetrol **25** (2.37 g, 6.74 mmol; 3.70 g **25** with 64.1% *w*/*w* purity) in CH_2Cl_2 (70 mL, 0.1 M) at 0 ˚C was added a freshly prepared quantity of silica gel support $NaIO_4$ (15% *w*/*w*; 13.5 g, 9.43 mmol, 1.4 equiv.)[76] over 2 min; the color of the slurry immediately changed from red to light yellow and a small exotherm was detected. The reaction was monitored by TLC analysis (EtOAc, CAM) and **25** was consumed after 0.5 h. The reaction mixture was filtered and the solid support was rinsed thoroughly with CH_2Cl_2 and EtOAc until no chemical species was detectable by TLC [R_f = 0.61 (EtOAc)]. The clear and yellow filtrate was dried over Na_2SO_4 and quickly concentrated *in vacuo* prior to reconstitution in CH_2Cl_2 (70 mL, 0.1 M) and addition of acetic anhydride (4.5 mL, 47.1 mmol, 7 equiv.), triethylamine (6.6 mL, 47.1 mmol, 7 equiv.), and a catalytic amount of dimethylaminopyridine with stirring. The acylation was monitored by TLC analysis (EtOAc, CAM) and the intermediate lactol (R_f = 0.61) was consumed within 1 h. An aqueous solution of NH_4Cl (half sat'd, 25 mL) was added to the chilled (ice bath) reaction mixture. After warming to ambient temperature the phases were separated and the organic phase was washed with H_2O (1x), brine (1x), dried over Na_2SO_4, filtered and then concentrated *in vacuo* to an orange oil (4.03 g). The crude material was chromatographed on silica gel (3:1 → 2:1 hexanes/EtOAc) to yield 1.53 g (56%) of acetal **27** as a hygroscopic white foam.

27: mp (pentane) 53 – 56 ˚C; R_f = 0.39 (2:1 hexanes/EtOAc); IR (film, cm^{-1}) υ 3362, 2983, 2934, 1764, 1747, 1711, 1511, 1454, 1382, 1366, 1305, 1240, 1218, 1171, 1097, 1053, 1006, 899, 872, 757, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (s, 1H), 5.27 (d, *J* = 7.8 Hz, 1H), 4.48 – 4.31 (m, *J* = 4.0, 2.0 Hz, 3H), 4.09 (d, *J* = 12.1 Hz, 1H), 4.03 (s, 1H), 3.86 (d, *J* = 12.2 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 1.53 (s, 3H), 1.46 (s, 8H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.0, 154.9, 109.7, 95.5, 80.05, 66.6, 61.5, 46.8, 28.3, 27.8, 26.3, 20.9, 20.8; MS (EI+) *m/z* (%) 403 (< 1), 272 (19), 227 (20), 184 (18), 113 (45), 101 (12), 88 (29), 57 (76), 43 (100); HRMS (EI+) calcd for $C_{18}H_{29}O_9N$: 403.1842 [M^+]. Found 403.1842. Anal. Calcd for $C_{18}H_{29}O_9N$: C, 53.59; H, 7.25. Found C, 53.68; H, 7.26.

((3a*R*,7*S*,7a*R*)-4-Acetoxy-7-amino-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-3a-yl)-methyl acetate (**28**).

To a flamed dried flask a solution of acetal **27** (33 mg, 0.081 mmol) in CH_2Cl_2 (2 mL) at 0 ˚C was added trifluoroacetic acid (0.5 mL) as a single portion with stirring and under a blanket of argon. The reaction was allowed to warm to room temperature and monitored by TLC analysis (EtOAc/MeOH 4:1 (or) hexanes/EtOAc 2:1). The reaction was deemed complete after 50 min and concentrated *in vacuo* to

provide crude material (31 mg) that was passed through a plug of deactivated (20% wt/wt H_2O) silica gel and eluted with EtOAc. The mother liquor was concentrated to yield 15 mg (62%) of amine salt **28** as a white crystalline solid.

28: mp 163 – 165 ˚C (Et_2O); R_f = 0.13 (ethyl acetate); $[\alpha]_D^{20}$ -17.890 (*c* 0.60, $CHCl_3$); IR (KBr, cm^{-1}) *v* 3369, 2991, 2939, 1769, 1746, 1678, 1376, 1212, 1137, 1063, 907, 836, 799, 721, 665; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (bs, 2H), 5.68 (s, 1H), 4.68 (d, *J* = 12.8 Hz, 1H), 4.44 (s, 1H), 4.36 (d, *J* = 12.8 Hz, 1H), 4.20 – 3.90 (m, 2H), 3.60 (s, 1H), 2.15 (s, 2H), 2.14 (s, 2H), 1.54 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.18, 168.91, 110.07, 110.07, 95.45, 95.45, 77.82, 77.82, 77.43, 77.01, 76.59, 75.59, 65.56, 60.79, 47.59, 47.59, 27.75, 27.75, 26.08, 26.08, 20.77, 20.77, 20.70, 20.70; Anal. Calcd for $C_{15}H_{22}F_3NO_9$: C, 43.17; H, 5.31. Found C, 42.92; H, 5.34.

((3a*R*,6*S*,6a*R*)-2,2-Dimethyl-6,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-3a,6-diyl)dimethanol (**29**). To a flamed dried vessel that contained vacuum dried solid K_2CO_3 (31 mg, 0.229 mmol, 4.0 equiv.) was added a solution of trifluoroacetate salt **28** (23 mg, 0.057 mmol, 1.0 equiv.) in anhydrous MeOH-d_4 (0.50 mL, 0.11 M) with stirring. The reaction was stirred for 5.5 h at room temperature and was monitored by ^{1}H NMR [Note: R_f is identical to that of starting material **28**, R_f = 0.52 (4:1 EtOAc/MeOH)]. The reaction was filtered through a pad of Celite and washed with small volumes of MeOH (2 x 0.5 mL). The filtrate was concentrated *in vacuo* to provide an oily white crystalline material (32 mg) that was contaminated with KOAc and CF_3CO_2K. The crude material could be purified by trituration with acetone several times to yield 9 mg of **29** (81%).

29: R_f = 0.52 (4:1 EtOAc/MeOH); $[\alpha]^{20}_D$ -24.408 (*c* 0.45, MeOH); IR (KBr, cm^{-1}) ν 3306, 2987, 2930, 2846, 1626, 1572, 1454, 1373, 1240, 1215, 1182, 1090, 1049, 900, 863; ^{1}H NMR (600 MHz, MeOH-d_4) δ 4.62 (d, *J* = 4.1 Hz, 1H), 4.07 – 3.99 (m, 1H), 3.93 – 3.84 (m, 2H), 3.84 – 3.77 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (MeOH-d_4, 150 MHz) δ 169.2, 111.9, 97.7, 80.0, 75.6, 61.4, 59.9, 26.2, 25.5; HRMS (EI+) calcd for $C_9H_{16}NO_4$ (M+H): 202.1079. Found: 202.1071.

((3a*R*,6*S*,6a*R*)-2,2-Dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-3a,6-diyl)dimethanol (30).

To a round bottom flask that contained crude pyrroline **29** (22 mg, 0.109 mmol, 1.0 equiv.; contaminated with KOAc/CF_3CO_2K) was added HOAc (1.0 mL; aqueous, 3 M) followed by 10% Pd/C (2 mg, 10 wt%) and the reaction vessel was purged with H_2 (3x) and set to stir at room temperature for approximately 15 h under 1 atmosphere of hydrogen. The reaction mixture was filtered over a pad of Celite and rinsed with small amounts of H_2O. The filtrate was concentrated *in vacuo* to yield crude material that was crystalline in nature and was triturated with acetone (precipitating any KOAc/CF_3CO_2K). The mother liquor was concentrated *in vacuo* to yield a sticky white foam, 8 mg, **30** (quantative over 2 steps from TFA salt).

30: R_f = 0.30 (4:1 EtOAc/MeOH); $[\alpha]^{20}_D$ +17.312 (*c* 0.40, MeOH); IR (KBr, cm^{-1}) ν 3416, 2937, 1681, 1563, 1414, 1384, 1206, 1139, 1051, 803, 723; ^{1}H NMR (600 MHz, MeOH-d_4) δ 4.60 (d, *J* = 3.0 Hz, 1H), 3.92 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.80 (dd, *J* = 11.4, 7.6 Hz, 1H), 3.77 – 3.72 (m, 2H), 3.15 (dd, *J* = 12.8 Hz, 2H), 1.52 (s, 3H), 1.39 (s, 3H), signal (1H) under solvent peak; ^{13}C NMR (151 MHz, MeOH-d_4) δ 111.8, 91.4, 81.8, 65.0, 63.5, 58.3, 53.3, 48.0, 47.9, 47.7, 47.6, 47.5, 47.3, 47.2, 25.8, 24.8; HRMS (ESI) calcd for $C_9H_{17}NO_4$ (M+H): 204.1228. Found: 204.1236.

(2*S*,3*R*,4*R*)-3,4-Dihydroxy-2,4-bis(hydroxymethyl)pyrrolidinium chloride (**14b**).

To a light yellow solution of protected pyrrolidine **30** (165 mg, 0.811 mmol) in MeOH (4 mL, 0.2 M) at room temperature was added conc. HCl (0.7 mL) with stirring and under a blanket of argon. The reaction was heated to 40 ˚C and monitored by NMR. Starting acetonide **30** was consumed after approximately 5 h and the reaction mixture was concentrated *in vacuo* to dryness. The reaction was reconstituted in a minimal amount of MeOH and precipitated with the addition of Et_2O while stirring. The slightly off-white precipitate was dried under high vacuum to yield 121 mg (75%) of pyrrolidine tetrol **14b** as the hydrochloride salt. An analytical sample was obtained by recrystallization from boiling MeOH to give white crystalline solid.

14b: mp 141 – 143 ˚C (MeOH); R_f = 0.0 (EtOAc/MeOH 4:1); $[\alpha]_D^{20}$ -29.881 (*c* 0.95, MeOH); IR (film, cm^{-1}) *v* 3214, 1607, 1415, 1322, 1251, 1196, 1119, 1031, 696, 636, 524; ^{1}H NMR (600 MHz, MeOD) δ 4.26 (d, *J* = 6.7 Hz, 1H), 3.97 – 3.87 (m, 2H), 3.81 (dd, *J* = 12.7, 6.6 Hz, 1H), 3.61 (d, *J* = 11.6 Hz, 1H), 3.59 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR (150 MHz, MeOD) δ 78.92, 70.65, 63.37, 63.32, 58.16, 49.91;MS (FAB+) *m/z* (%) 223 (18), 164 (56), 131 (100), 75 (11), 61 (14), 57 (23), 43 (12), 39 (45), 29 (13); HRMS (FAB+) calcd for $C_{12}H_{14}O_4N$: 164.0917. Found: 164.09301.

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