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A Flexible Stereospecific Synthesis of Polyhydroxylated Pyrrolizidines from Commercially Available Pyranosides

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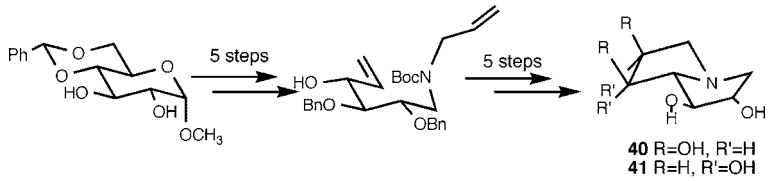
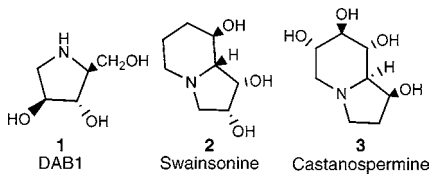


Nitrogen-containing sugar analogues, known as azasugars or iminosugars, such as polyhydroxylated piperdines, pyrrolidines, pyrrolizidines, and indolizidines, have the potential to become important therapeutic agents due to their ability to inhibit glycosidases. Synthetic pathways that are able to systematically produce a variety of these azasugars are eagerly sought after, since even minute structural or stereochemical changes often significantly alter the degree of inhibition. The synthesis of tetrahydroxylated pyrrolizidines **40** and **41** starting from methyl α-D-glucopyranoside is described and will be used as a template to develop syntheses of all the stereoisomers of polyhydroxylated pyrrolizidine **9** as well as other analogous bicyclic polyhydroxylated iminosugars. The key steps in this synthesis involve a one-pot conversion of a halopyranoside to a divinylamine by employing a simultaneous Zn reduction and reductive amination of the resulting aldehyde. After protection of the amine, a ring-closing metathesis results in a multifunctional eight-membered ring that then undergoes an internal S_N2 cyclization to form an alkene-containing pyrrolizidine **33**. Dihydroxylation of the alkene followed by hydrogenolysis of the benzyl protecting groups results in tetrahydroxylated pyrrolizidines **40** and **41**.

Introduction

Iminosugars or azasugars such as polyhydroxylated indolizidines, pyrrolizidines, piperidines, and pyrrolidines have increasingly gained attention due to their ability to inhibit glycosidases. This class of inhibitors was first discovered in plants in which azasugars such as DAB1 **1**, swainsonine **2**, and castanospermine **3** were found to protect the plants by inhibiting predators' sugar-



1 DAB1 **2** Swainsonine **3** Castanospermine

processing enzymes.[1] Since the discovery of these nitrogen-containing inhibitors, many medical studies have been performed to determine if their inhibitory nature could be used in therapeutic applications. Swainsonine **2** is one of the most widely studied polyhydroxylated alkaloids. Clinical trials have shown that it prevents tumor formation at new invasion sites, enhances antibody response to cancerous tumors, and improves stem cell formation in bone marrow.[2] Other studies have shown azasugars to aid in the treatment of diabetes and HIV/AIDS.[1,3,4] Consequently, these inhibitors have enormous medical potential; however, only about 25 naturally occurring iminosugars have been isolated,[5] which represent only a small fraction of the possible azasugars that could be potent medical agents. To test the entire chemical space occupied by these azasugars, syntheses of these compounds have been and must continue to be developed. In addition, naturally occurring azasugars are often difficult to purify from their natural sources,[6] and therefore, synthetic pathways to the naturally occurring iminosugars are also desirable.

(1) Fellows, L. E. *Chem. Br.* **1987**, *Sept.*, 842−844.

(2) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935−944.

(3) Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471−484.

(4) Meng, Q.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 445−450.

(5) Winchester, B.; Al Daher, S.; Carpenter, N. C.; Cenci di Bello, I.; Chio, S. S.; Fairbanks, A. J.; Fleet, G. W. J. *Biochem. J.* **1993**, *290*, 743−749.

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Due to the complexity and vast number of sugar processing enzymes, the inhibitory effects of polyhydroxylated alkaloids can only be fully determined through experimentation.[1] While numerous isomers of these iminosugars have shown inhibition against various types of glycosidases, these results are still ineffective in predicting enzyme inhibition. Furthermore, slight changes such as stereochemistry, ring size, and hydroxyl group location in these sugar analogues produce considerable differences in inhibition.[7] To fully study the inhibitory ability of this important class of compounds, syntheses that can both systematically produce all stereoisomers of these sugar analogues and allow for straightforward derivatization are highly sought after. It is only when a complete set of stereoisomers of an iminosugar are synthesized and tested that hypotheses can begin to be made on the structure−bioactivity relationship between the azasugar and enzyme.[8]

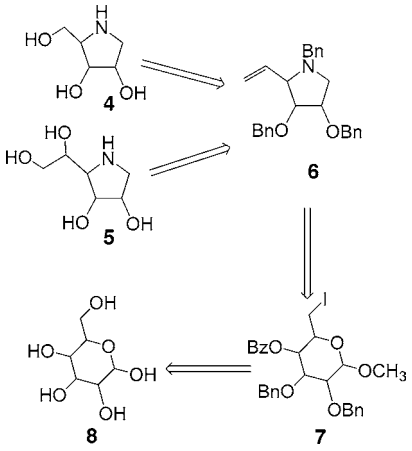
To date, there are many syntheses that lead to specific azasugars; however, syntheses that can produce every stereoisomer of a specific analogue are rare. Additionally, many of the syntheses that lead to every stereroisomer do not allow for the specific synthesis of only one isomer; that is, the multiple stereoisomers are synthesized simultaneously.[9] If large quantities of just one isomer were necessary, syntheses such as these would not be efficient.

The majority of synthetic pathways to these iminosugars begin with their carbohydrate analogues, taking advantage of the carbohydrates' many stereocenters. However, non-carbohydrate pathways such as ring closing metathesis,[10] cuprate chemistry,[11] cyclization of acetylenic sulfones with chloroamines,[12] and consecutive reductive aminations[13] are becoming more popular. Developers of non-carbohydrate synthetic plans claim that these pathways are superior because they exhibit increased stereoselectivity and are more efficient at introducing the amine moiety.[13] Ideally, a flexible and stereospecific synthesis that takes advantage of the stereocenters of a carbohydrate and efficiently introduces the amine is desired.

We have been developing a stereospecific synthesis of the eight different stereoisomers of trihydroxypyrrolidine **4** and the 16 different stereoisomers of tetrahydroxypyrrolidine **5** (Scheme 1). While this synthesis was being developed it was proposed that bicyclic pyrrolizidines and indolizidines are more potent inhibitors than monocyclic pyrrolidines due to their rigid structures.[13] We have altered the polyhydroxylated pyrrolidine synthetic methodology to prepare bicyclic polyhydroxylated pyrrolizidines. This altered methodology can also potentially be extended to the synthesis of other polyhydroxylated pyrrolizidines and to polyhydroxylated indolizidines.

The 2,3,5,6-tetrahydroxylated pyrrolizidines **9** were chosen as the targets for the development of this new method of synthesizing pyrrolizidines. Various stereoisomers of **9** have been shown in enzymatic studies to inhibit α-mannosidases, α-L-frucosidase, and α- and *β*-D-galactosidase.[5,14] There are 28

SCHEME 1



stereoisomers of this pyrrolizidine, all of which can theoretically be synthesized by adapting the approach we used for the synthesis of polyhydroxylated pyrrolidines **4** and **5**.

Scheme 2 illustrates our retrosynthetic plan for this class of pyrrolizidines. The synthesis begins with 4,6-*O*-benzylidine protected glycopyranoside **15**, but also employs the newer chemical techniques that are found in non-carbohydrate-based syntheses. The synthesis is flexible and allows for derivatization. The benzylidine protected glycopyranoside **15** can be converted to the 6-iodoglycopyranoside **14** through standard carbohydrate chemistry techniques.[15] As we have shown in the synthesis of pyrrolidines **4** and **5**, starting the synthesis with different glycopyranosides will lead to the different stereoisomers of the pyrrolizidine. The amine moiety is added by a Zn reduction followed by a reductive amination. In this case the amine used for the reductive amination was allylamine **13**; the use of other amines allows for derivatization of the final pyrrolizidine or for the synthesis of indolizidines. The amine is immediately protected as a carbamate, which solves the problem of inefficient amino protection when utilizing carbohydrate starting materials. A ring-closing metathesis is applied to form an eight-membered multifunctional ring that then undergoes an internal cyclization by an S_N2 mechanism to produce a double bond containing pyrrolizidine **10**, which upon dihydroxylation and deprotection results in the tetrahydroxylated pyrrolizidine **9**.

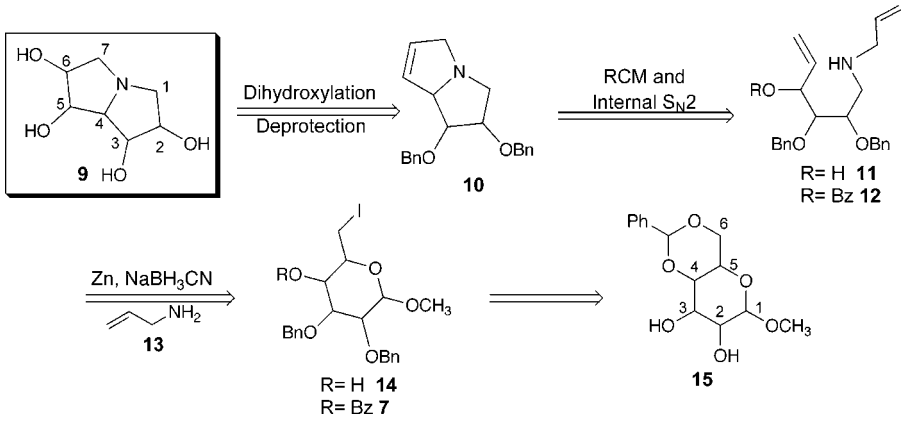
This paper presents our synthesis of two isomers of tetrahydroxylated pyrrolizidine **9**, the 2(*S*),3(*S*),4(*R*),5(*R*),6(*S*)-isomer **40** and the 2(*S*),3(*S*),4(*R*),5(*S*),6(*R*)-isomer **41**, starting form the 4,6-*O*-benzylidene of methyl α,D-glucopyranoside. (To avoid confusion the carbon numbering used throughout this paper corresponds to the numbering of the original glucopyranoside.)

Results and Discussion

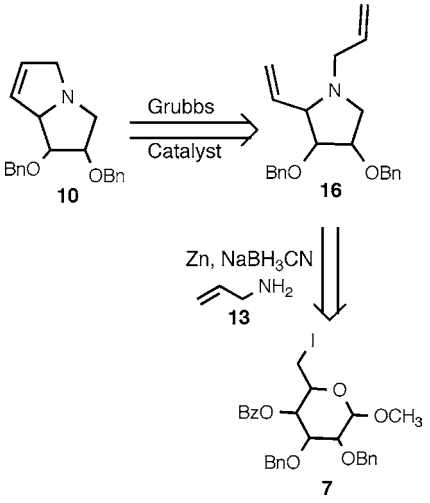
In the synthesis of polyhydroxylated pyrrolidines **4** and **5** only the internal S_N2 cyclization was necessary, not the ring-closing metathesis. Initial attempts to synthesize the pyrrolizidines involved first performing the same internal cyclization but substituting allylamine for the benzylamine, resulting in divinyl pyrrolidine **16**. Formation of the second ring was then attempted by a ring-closing metathesis (Scheme 3).

(6) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199−210.
(7) Paolucci, C.; Mattioli, L. *J. Org. Chem.* **2001**, *66*, 4787−4794.
(8) Hosaka, A.; Ichikawa, S.; Shindo, H.; Sato, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 797−799.
(9) Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 372−376.
(10) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359−7360.
(11) Dieter, K. R.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847−855.
(12) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543−4552.
(13) Zhao, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761−1767.
(14) Collin, W. F.; Fleet, G. W.; Haraldsson, M.; Cenci di Bello, I.; Winchester, B. *Carbohydr. Res.* **1990**, *202*, 105−116.
(15) Dechaux, E.; Savy, P.; Bouyain, S.; Monneret, C.; Florent, J.-C. *J. Carbohydr. Chem.* **2000**, *19*, 485−501.

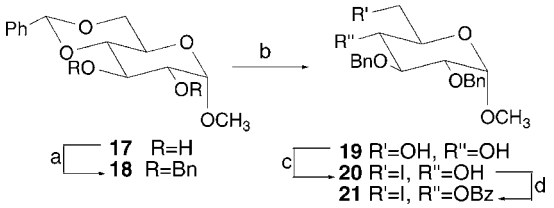
SCHEME 2



SCHEME 3



SCHEME 4 [a]



[a] Reagents: (a) BnBr, KOH; (b) (1) I_2, MeOH, (2) sodium thiosulfate; (c) Ph_3P, I_2, imidazole; (d) BzCl, pyridine.

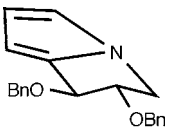
Iodobenzoate **21** was synthesized in 63.4% yield from methyl-4,6-*O*-benzylidine-α,D-glucopyranoside **17**, using a procedure previously reported for the conversion of methyl-4,6-*O*-benzylidine-α,D-altropyranoside into the corresponding iodobenzoate, Scheme 4.[15]

Iodobenzoate **21** was subjected to Zn, $NaBH_3CN$, and allylamine. In this reaction, the Zn reduced the iodide resulting in the pyranoside ring opening to form aldehyde **22**. The aldehyde underwent reductive amination to produce the divinylamine **24**,[16] which then spontaneously cyclized by an internal S_N2 reaction to form divinyl pyrrolidine **27** with inversion of the stereochemistry at C4 and retention of stereochemistry at C2 and C3 (Scheme 5).[17]

(16) When old $NaBH_3CN$ that has degraded due to moisture is used, a divinyl pyrrolidine missing the 3-*O*-benzyl is isolated.

(17) Liotta, L. J.; Ganem, B. *Synlett* **1990**, 503−504.

It had previously been reported that ring-closing metathesis with use of Grubbs catalyst could be performed on a hydrochloride salt of an amine with no decrease in yield.[18] However, these results could not be duplicated on divinylamine **27**. Despite the use of multiple catalysts under various reaction conditions,[19] the only product that could be isolated was aromatic product **28** in low yields (13%). Under the forcing conditions necessary for the metathesis, it appears that the catalyst led to immediate oxidation of any cyclized product that formed. A vast majority of successful ring-closing metatheses on nitrogen-containing compounds have nonbasic nitrogens (amide or carbamates).[20,21] The failure of this cyclization could therefore be due to the amine, even when protonated, deactivating the catalyst.



To circumvent this problem the order of the cyclizations was changed; the ring-closing metathesis was performed while the amine was protected, and before forming a tertiary amine through the S_N2 reaction. We reasoned that if the Zn reduction/reductive amination reaction was performed on the 6-iodoglucopyranoside **20** without the benzoate at C4 then no S_N2 cyclization could occur after the reductive amination of aldehyde **23**. When this was attempted, the desired acyclic divinylamine **25** was produced; however, purification was difficult and yields were low because of its high affinity for silica gel. Therefore, the crude reaction product was immediately treated with di-*tert*-butylpyrocarbonate, which resulted in the Boc-protected divinyl compound **26** in 70% yield after purification on silica gel (Scheme 5).

The Grubbs cyclization of **26** to tetrahydroazocine **29** (Scheme 6) proved to be much more successful than the olefin metathesis of **27**. Three different metathesis catalysts were tried for this reaction (Grubbs 1st generation, Grubbs 2nd generation, and Hoveyda−Grubbs 2nd generation)[22] in both toluene and CH_2Cl_2 at various temperatures. The best yield (99%) was

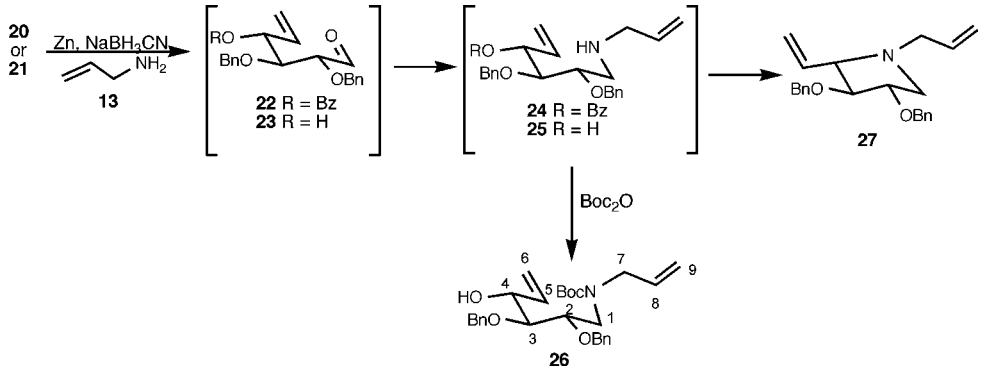
(18) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.

(19) Deprotonated divinylamine **27** subjected to Grubbs 2nd generation catalyst (20 mol % added in two intervals) refluxed in toluene for 2 h resulted in aromatic product **28**.

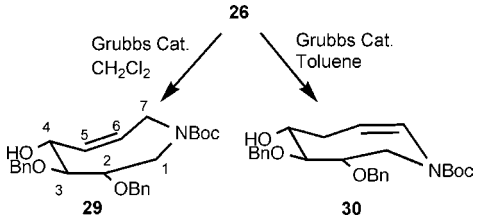
(20) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75−89.

(21) Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *36*, 93−105.

SCHEME 5



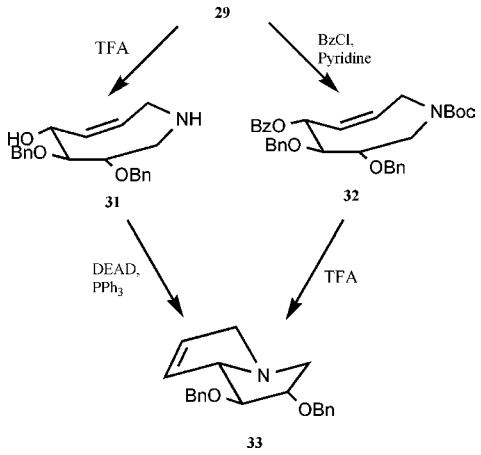
SCHEME 6



obtained using Grubbs 2nd generation catalyst (8 mol %) in CH_2Cl_2 at 40 °C. Interestingly, when the cyclization was performed with either Grubbs 2nd generation or Hoveyda−Grubbs 2nd generation catalyst in toluene, the reaction proceeded faster, but the location of the double bond isomerized resulting in the formation of tetrahydroazocine **30**. The isomerization was independent of temperature, occurring both at 40 °C and at reflux. This isomerization was consistent with other ring-closing metathesis results.[23] No isomerized product was observed when using CH_2Cl_2 as the solvent. In dicholoromethane, Grubbs 2nd generation catalyst resulted in the quickest ring-closing metatheses while Grubbs 1st generation catalyst did not exhibit any catalytic activity. Hoveyda−Grubbs 2nd generation catalyst did catalyze the ring-closing metathesis, but the reaction did not proceed as rapidly as the reaction with Grubbs 2nd generation catalyst. Since Hoveyda−Grubbs 2nd generation catalyst is recyclable,[24] it would be advantageous to use it when performing this reaction on larger scales.

We envisioned two potential approaches to obtain pyrrolizidine **33** from tetrahydroazocine **29** (Scheme 7): a Mitsunobu cyclization,[25] and the addition of a benzoate to the C4 hydroxyl group followed by refluxing in ethanol as used in the original synthesis (Scheme 3).

SCHEME 7

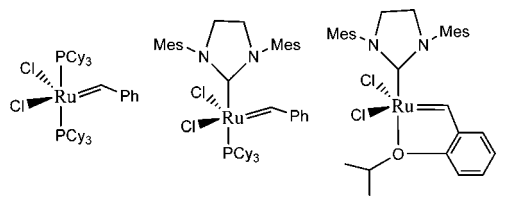


After quantitative removal of the Boc protecting group with trifluoroacetic acid (TFA), the Mitsunobu cyclization was attempted and by TLC appeared to produce reasonable yields of pyrrolizidine **33**; however, reproducibility was a problem and the triphenylphosphine oxide byproduct was difficult to remove. Only 34% of the pyrrolizidine could be cleanly isolated. In addition, an excess of diethyl azodicarboxylate (DEAD) resulted in the formation of the previously observed aromatic product **28** as the major product of the reaction. A possible mechanism for this oxidation of pyrrolizidine **33** by the DEAD is provided in the Supporting Information.

The benzoate approach proved to be simpler, cleaner, and more efficient (Scheme 7). While the tetrahydroazocine **29** was still Boc-protected, the benzoate was added by a standard procedure (BzCl, pyridine). The Boc-protecting group was then removed from compound **32** by treatment with TFA. The planned reflux in ethanol proved unnecessary since the free amine spontaneously attacked C4 and displaced the benzoate resulting in pyrrolizidine **33** in 93% yield.

The double bond of pyrrolizidine **33** was unreactive toward many oxidizing agents ($RuCl_3/NaIO_4$,[26] $KMnO_4$,[27] $KMnO_4$/18-crown-6,[28] $I_2/AgOAc/H_2O$,[29] $I_2/KIO_3/AcOH$,[30] and mCPBA[31]),

(22) Structures of the three Grubbs metathesis catalysts:



(23) Furstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207.

(24) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(25) Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161−164.

(26) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312−2313.

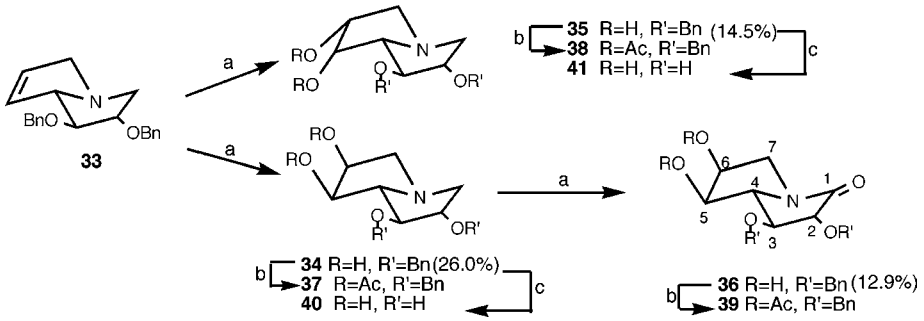
(27) Angermann, J.; Homann, K.; Reissig, H.-U. R.; Zimmer, R. *Synlett* **1995**, 1014−1016.

(28) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265−276.

(29) Woodward, R. B.; Brutcher, F. V., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 209−211.

(30) Mangoni, L.; Adinolfi, M.; Barone, G.; Parrilli, M. *Gaz. Chim. Ital.* **1975**, *105*, 377−383.

SCHEME 8 [a]



[a] Reagents: (a) OsO_4, NMO; (b) Ac_2O, pyridine; (c) H_2, 10% Pd/carbon.

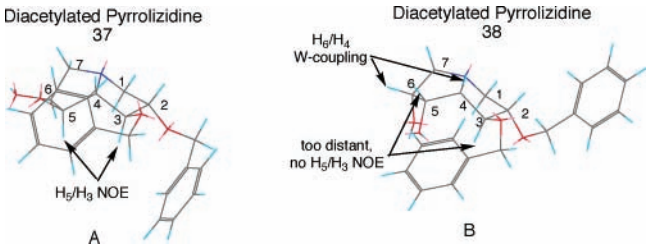


FIGURE 1. Verification of the stereochemistry of the dihydroxylation products **37** and **38**. (A) Proximity of H5 and H3 produces an NOE. (B) No NOE is observed between H5 and H3 but W coupling is observed between H6 and H4.

which made the dihydroxylation of the vinyl group more problematic than was expected. The alkene was oxidized by catalytic OsO_4 with *N*-methylmorpholine *N*-oxide[31] resulting in the desired dihydroxylation; however, lactam byproduct **36** was obtained along with the desired dihydroxylated pyrrolizidines **34** and **35** (Scheme 8). Formation of **36** could not be prevented, although it could be suppressed by lowering the reaction temperature to 0 °C resulting in a 40.5% yield of dihydroxypyrrolidines **34** and **35** in a 1.8:1 ratio and a 13% yield of the lactam byproduct **36**.

To identify the byproduct and determine the stereochemistries of the two diols, all three products were acetylated under standard conditions (Ac_2O, pyridine) to produce compounds **37**, **38**, and **39**, respectively. The acetylation allowed for H5 and H6 to be separated from H2 and H3 in the ^{1}H NMR and, therefore, to be positively identified. The carbonyl of byproduct **36** was identified by using ^{13}C NMR, and the location of the carbonyl either at C1 or C7 was confirmed through the observation of proton−proton coupling between the hydrogen on C6 and the two hydrogens on C7 in the ^{1}H-COSY NMR. The stereochemistries of the hydroxyl groups on **34** and **35** were assigned by using the ^{1}H-COSY and ^{1}H-NOESY spectra of compounds **37** and **38** (Figure 1). An ^{1}H-NOE between H5 and H3 in **37** but not in **38** confirmed the *R* stereochemistry of C5 and *S* stereochemistry of C6 for the major diol **34**. The expected *S* stereochemistry of C5 and *R* stereochemistry of C6 for the minor isomer **35** was further supported by the observed W coupling between H4 and H6 in the ^{1}H-COSY spectrum of **38**.

While the oxidation of tertiary amines to amides and lactams has been reported for reagents such as RuO_4,[32] $(batho)_2Cu$,[33] MnO_2,[34] $KMnO_4$,[35] and $Hg(OAc)_2$[36] such an oxidation by OsO_4 has not previously been reported. A possible mechanism for this oxidation is depicted in Scheme 9. This mechanism is based on the mechanistic proposals for the oxidation of amines by $(batho)_2Cu$,[33] $Hg(OAc)_2$,[36] CuCl/pyridine/O_2,[37] and CuCl/AcOH/O_2.[37] The oxidation steps in Scheme 9 (the conversion of **42** to **43** and **45** to **46**) are depicted as two-electron processes; however, they may very well be a combination of single-electron transfers and deprotonation. Due to the similarities between OsO_4 and RuO_4 we also considered the proposed concerted mechanism by which RuO_4 oxidizes ethers to esters,[38] but this mechanism did not explain the regiochemistry and compound selectivity observed in the OsO_4 oxidation.

A thorough mechanistic study of amine oxidation by $(batho)_2Cu$ indicated that pyrrolidines are particularly susceptible to oxidation to lactams (four times more likely than acyclic tertiary amines).[33] This study also indicated that, for stereoelectronic reasons, having electron donating groups antiperiplanar to the nitrogen results in an acceleration of the oxidation. These two aspects of the oxidation may explain why a mild oxidizing agent like OsO_4 was able to carry out this transformation and also why pyrrolizidine **37** was oxidized preferentially to pyrrolizidine **38**. In pyrrolizidine **37** both the new hydroxyl group at C6 and the benzyl ether at C2 are antiperiplanar to the nitrogen while in pyrrolizidine **38** only the benzyl ether at C2 is antiperiplanar; thus, **37** is doubly activated while **38** is only singly activated.

The observation that the C1-carbon is oxidized preferentially over the almost equivalent C7-carbon can be explained by requiring an anti relationship between the complexed OsO_4 and the proton being eliminated. Assuming that the OsO_4 is complexed to the lone pair of the nitrogen only the C1 carbon has a hydrogen in the correct orientation (Figure 2). This same phenomenon is observed for the $Hg(OAc)_2$ oxidation of amines.[36]

The final catalytic hydrogenolysis with H_2 and Pd/C quantitatively converted **37** and **38** to tetrahydroxylated pyrrolizidines

(31) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5537−5545.

(32) Yoshifuji, S.; Tanaka, K.-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5515−5521. Tanaka, K.-I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3879−3884. Yoshifuji, S.; Tanaka, K.-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873−3878.

(33) Wang, F.; Sayre, L. M. *J. Am. Chem. Soc.* **1992**, *114*, 248−255.

(34) Henbest, H. B.; Thomas, A. *J. Chem. Soc.* **1957**, 3032−3039.

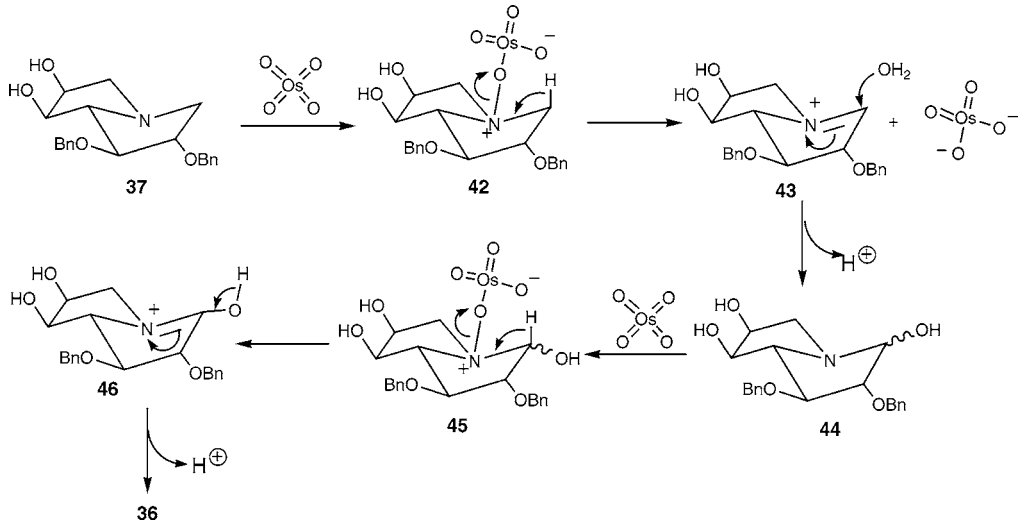
(35) Forrest, J.; Tucker, S. H.; Whalley, M. *J. Chem. Soc.* **1951**, 303−305. Schmidt, H. J.; Schafer, H. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 109. Wei, M.-M.; Stewart, R. *J. Am. Chem. Soc.* **1966**, *88*, 1974−1979. Shechter, H.; Rawalay, S. S. *J. Am. Chem. Soc.* **1964**, *86*, 1706−1709.

(36) Leonard, N. J.; Morrow, D. F. *J. Am. Chem. Soc.* **1958**, *80*, 371−375.

(37) Capdevielle, P.; Lavigne, A.; Maumy, M. *Tetrahedron* **1990**, *46*, 2835−2844.

(38) Bakke, J. M.; Froehaug, A. E. *Acta Chem. Scand.* **1995**, *49*, 615−622.

SCHEME 9



40 and **41** as their hydrochloride salts.[39] Pyrrolizidines **40** and **41** are currently being evaluated for their abilities to inhibit carbohydrate-processing enzymes.

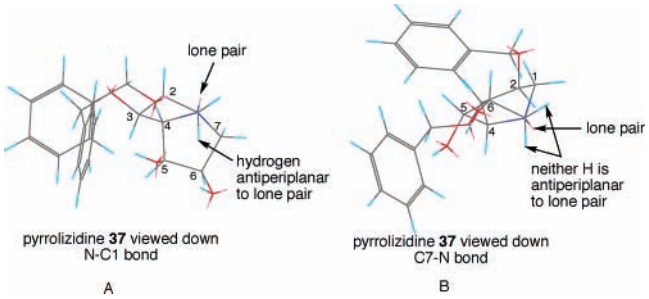


FIGURE 2. Only C1 (view A) has a hydrogen antiperiplanar to the nitrogen lone pair of electrons. With respect to C7 (view B), C6 is antiperiplanar to the nitrogen lone pair of electrons.

Conclusion

Two of the 28 possible stereoisomers of tetrahydroxylated pyrrolizidine **9** have been successfully synthesized in 10 steps starting from 4,6-*O*-benzylidine-α,D-glucopyranoside in 10% and 6% overall yields of isomers **40** and **41**, respectively. While pyrrolizidine **40** has previously been synthesized, this is the first reported synthesis of pyrrolizidine **41**.[40] The synthesis is both flexible, allowing for derivatization, and, with the exception of the penultimate dihydroxylation step, stereospecific. The synthetic pathway can easily be altered by changing either the starting pyranoside or the amine used in the reductive amination to produce various other bicyclic azasugars in a stereospecific manner. Although the dihydroxylation of the alkene was not as stereospecific or efficient as the proceeding steps, the overall yields are still respectable for a 10-step synthesis. Other methods of dihydroxylating are being attempted, including Sharpless dihydroxylations[41] and *anti*-dihydroxylation by the opening of an epoxide.

(39) The free amine form of **40** can be produced by adsorbing it onto a strongly acidic ion-exchange resin and then eluting the free amine with 6 M NH_4OH. The spectra for the free amine are identical with those previously published for this compound in ref 41.

(40) Carmona, A. T.; Fuentes, J.; Vogel, P.; Robina, I. *Tetrahedron*: *Asymmetry* **2004**, *15*, 323−333.

(41) Reetz, M. T.; Strack, T. J.; Mutulis, F.; Goddard, R. *Tetrahedron Lett.* **1996**, *37*, 9293−9296.

Experimental Section

***tert*-Butyl (2*S*,3*S*,4*R*)-Allyl[2,3-bis(benzyloxy)-4-hydroxyhex-5-en-1-yl]carbamate (26).** Methyl-2,3-di-*O*-benzyl-6-deoxy-6-iodo-α,D-glucopyranoside **20** (1.63 g, 3.35 mmol) was dissolved in 19:1 1-propanol/H_2O (96 mL) and Zn (8.56 g, 131 mmol, powdered, acid treated), $NaBH_3CN$ (10.8 mL, 1 M solution in THF, 10.8 mmol), and allylamine (5.8 mL, 77.4 mmol) were added and then the reaction was heated to reflux. The reaction was monitored by TLC (20:1 CH_2Cl_2/CH_3CN) until there was no more **20** present (R_f 0.72) at which point (approximately 2 h) the reaction was cooled to room temperature and filtered through Celite. The filtrate was evaporated to dryness. The resulting residue was dissolved in 6:4:1 CH_3OH/CH_2Cl_2/1.3 M HCl (60 mL), stirred for 45 min, and basified with 20% NaOH, then H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5 × 60 mL). The organic layers were combined, dried with $MgSO_4$, decanted, and evaporated to dryness to result in crude divinylamine. The crude divinylamine was dissolved in dioxane (20 mL) and di-*tert*-butyl dicarbonate (0.801 g, 3.67 mmol) was added. The reaction was monitored by TLC (2:1 ethyl acetate/hexane) for the disappearance of the crude divinylamine (R_f 0.42, approximately 30 min). The completed reaction was filtered though Celite. The filtrate was evaporated to dryness and chromatographed through silica gel with CH_2Cl_2/CH_3CN in a sequential gradient from 35:1 to 15:1. Fractions were analyzed by TLC in 20:1 CH_2Cl_2/CH_3CN. This procedure resulted in the isolation of pure **26** as a clear oil (R_f 0.60, 1.09 g, 2.34 mmol, 70%). $[\alpha]^{26}_D$ −25.0 (*c* 3.27, CH_2Cl_2). ^{1}H NMR δ 7.31−7.23 (m, 10 × Ar−H), 5.88 (ddd, J = 15.9, 10.5, 5.3 Hz, C5−H), 5.74 (ddd, J = 22.2, 10.6, 5.6 Hz, C8−H), 5.31 (dt, J = 17.2, 1.5 Hz, C6−H), 5.15 (dt, J = 10.5, 1.3 Hz, C6−H′), 5.08−5.01 (m, 2 × C9−H), 4.71 (d, J = 11.4 Hz, OBn-H), 4.61 (d, J = 11.4 Hz, OBn-H), 4.59 (m, 2, 2 × OBn-H), 4.34 (m, C4−H), 3.97−3.92 (m, C7−H, C1−H), 3.76 (dd, J = 15.9, 5.9 Hz, C7−H′), 3.54 (dd, J = 14.6, 3.3 Hz, C2−H), 3.44 (dd, J = 3.6, 5.4 Hz, C3−H), 3.37 (dd, J = 8.1, 14.6 Hz, C1−H), 1.45 (s, 9 × Boc-H). ^{13}C NMR δ 26.8 (CH_3), 46.4 (CH_2), 49.3 (CH_2), 69.9 (CH), 72.0 (CH_2), 72.5 (CH_2), 76.9 (CH), 78.0 (C), 79.7 (CH), 113.7 (CH_2), 114.3 (CH_2), 125.9 (CH), 126.1 (CH), 126.2 (CH), 126.4 (CH), 126.6 (CH), 126.8 (CH), 132.4 (CH), 136.5 (C), 136.6 (C), 137.2 (CH), 154.0 (C). IR 3454 (br), 3065, 3031, 3006, 2977, 2930, 1692, 1678, 1407, 1365, 1284, 1153 cm^{-1}. HRMS calculated for $C_{28}H_{38}NO_5$ ($M^+ + H$) 468.2750, found 468.2733.

(2*S*,3*S*,4*S*)-1-Allyl-3,4-bis(benzyloxy)-2-vinylpyrrolidine (27). Methyl-4-benzoate-2,3-di-*O*-benzyl-6-deoxy-6-iodo- α,D-glucopyranoside **21** (0.912 g, 1.55 mmol) was dissolved in 19:1 1-propanol/H_2O (53 mL). Zinc (5.06 g, 77.5 mmol, powdered, acid treated), $NaBH_3CN$ (6.5 mL of 1 M solution in THF, 6.5 mmol),

and allylamine (3.5 mL, 46 mmol) were added, and then the reaction was heated to reflux. The reaction was monitored by TLC (4:1 hexane/ethyl acetate) until there was no more **27** present (R_f 0.43) at which point (approximately 2 h) the reaction was cooled to room temperature and filtered through Celite. The filtrate was evaporated to dryness. The resulting residue was dissolved in 6:4:1 CH_3OH/CH_2Cl_2/1.3 M HCl (30 mL) and stirred for 30 min, basified with 20% NaOH, and extracted with CH_2Cl_2 (3 × 60 mL). The organic layers were combined, dried with Na_2SO_4, decanted, and evaporated to dryness to result in crude divinylamine, which was chromatographed through silica gel sequentially with hexane/ethyl acetate in ratios of 7:1, 6:1, 5:1, and 4:1. Fractions were analyzed by TLC in 4:1 hexane/ethyl acetate. This procedure resulted in the isolation of pure **27** as a slightly yellow oil that darkened upon exposure to air at room temperature (R_f 0.50, 0.294 g, 0.84 mmol, 54%). $[\alpha]^{26}_D$ +77.1 (*c* 7.94, CH_2Cl_2). ^{1}H NMR δ 7.35−7.09 (m, 10 × Ar−H), 5.90−5.78 (m, C5−H, C8−H), 5.35−5.08 (m, 2 × C9−H, 2 × C6−H), 4.59−4.49 (m, 4 × OBn-H), 3.92 (ddd, J = 7.8, 2.3, 1.4 Hz, C2−H), 3.85 (dd, J = 6.7, 2.3 Hz, C3−H), 3.43 (ddd, J = 13.5, 3.4, 1.5 Hz, C7−H), 3.16 (d, J = 10.8 Hz, C1−H), 2.80 (dd, J = 8.3, 7.0 Hz, C4−H), 2.63 (dd, J = 13.5, 8.1 Hz, C7−H′), 4.90 (dd, J = 10.8, 6.3 Hz, C1−H′). ^{13}C NMR δ 56.2 (CH_2), 56.9 (CH_2), 71.2 (CH), 72.1 (CH), 73.3 (CH), 81.9 (CH_2), 89.4 (CH_2), 117.4 (CH_2), 119.1 (CH_2), 128.3 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 135.2 (CH), 138.1 (C), 138.5 (CH). IR 3066, 3031, 2904, 2793, 1644, 1497, 1454, 1361 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.55; H, 7.70; N, 4.14.

***tert*-Butyl (3*S*,4*S*,5*R*,6*Z*)-3,4-Bis(benzyloxy)-5-hydroxy-3,4,5,8-tetrahydroazocine-1(2*H*)-carboxylate (29).** Boc-protected divinylamine **26** (0.300 g, 0.618 mmol) and Grubbs 2nd generation catalyst (0.040 g, 0.047 mmol) were combined in CH_2Cl_2 (50 mL) and heated to reflux. The reaction was monitored by TLC (10:1:0.1:1 CH_2Cl_2/CH_3CN/CH_3OH/hexane) until there was no more **26** present (R_f 0.69, approximately 40 min). The completed reaction was cooled to room temperature, then filtered through Celite, and the filtrate was evaporated to dryness. The crude product was chromatographed through silica gel with CH_2Cl_2/CH_3CN starting with a 30:1 ratio and decreasing to a 10:1 ratio. Fractions were analyzed by TLC in 20:1 CH_2Cl_2/CH_3CN. This procedure resulted in pure **29** as clear oil (R_f 0.60, 0.280 g, 0.623 mmol, 99%). $[\alpha]^{26}_D$ −89.8 (*c* 0.325, CH_2Cl_2). ^{1}H NMR δ 7.35−7.25 (m, 10 × Ar−H), 5.61 (ddd, J = 11.9, 6.6, 2.7 Hz, C5−H), 4.50 (m, C6−H), 4.91 (d, J = 10.9 Hz, OBn-H), 4.80 (d, J = 11.4 Hz, OBn-H), 4.70 (d, J = 11.2 Hz, OBn-H), 4.62 (d, J = 11.0 Hz, OBn-H), 4.54−4.49 (m, C7−H, C4−H), 3.95−3.83 (m, C2−H, C1−H), 3.51 (dd, J = 17.6, 5.6 Hz, C7−H′), 3.34 (dd, J = 9.4, 7.7 Hz, C3−H), 3.14 (s, OH), 3.01 (dd, J = 14.3, 10.2, C1−H′), 1.50 (s, 9 × Boc-H). ^{13}C NMR δ 28.5 (CH_3), 46.0 (CH_2), 47.0 (CH_2), 67.1 (CH), 72.6 (CH_2), 76.0 (CH_2), 77.1 (C), 84.7 (CH), 125.0 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 134.1 (CH), 135.8 (C), 136.3 (C), 153.1 (C). IR 3515, 3064, 3030, 2975, 2902, 1691, 1678, 1454, 1397, 1367, 1248, 1166, 1097 cm^{-1}. Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19. Found: C, 70.80; H, 7.87; N, 2.98.

(1*S*,2*S*,7a*S*)-1,2-Bis(benzyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (33) by Mitsunobu Chemistry. To a solution of macrocyle **29** (0.105 g, 0.234 mmol) in CH_2Cl_2 (4 mL) was added trifluoracetic acid (1 mL, 13.41 mmol). The reaction mixture was monitored by TLC (20:1 CH_2Cl_2/CH_3CN) for the disappearance of **29** (R_f 0.60) at which point the reaction was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ (2 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the organic layers were combined, dried with $MgSO_4$, decanted, and evaporated to dryness to result in crude **31**. The crude **31** (0.0283 g, 0.0811 mmol) was combined in CH_2Cl_2 with PPh_3 (40.1 mg, 0.153 mmol) and diethyl azodicarboxylate (22 μL, 0.14 mmol) was added dropwise. The mixture was monitored by TLC (1:1 CH_2Cl_2/CH_3CN) for the disappearance of **31** (R_f 0.28) at which point (less than 1 h) the reaction was quenched with H_2O (2 mL). The product was extracted with CH_2Cl_2 (4 × 3 mL). The organic layers were combined, dried with $MgSO_4$, decanted, and evaporated to dryness. The PPh_3O was precipitated with anhydrous diethyl ether. The mixture was decanted and evaporated to dryness. This crude product was chromatographed through silica gel with CH_2Cl_2/CH_3CN with ratios of 15:1, 10:1, 7:1, 6:1, and 5:1 with 0.5% triethylamine in each solvent. Fractions were analyzed by TLC in 1:1 CH_2Cl_2/CH_3CN. This procedure resulted in the isolation of pure **33** as a clear oil that darkened upon exposure to air at room temperature (R_f 0.13, 0.0092 g, 0.029 mmol, 35%). $[\alpha]^{26}_D$ −39.0 (*c* 0.47, CH_2Cl_2). ^{1}H NMR δ 7.35−7.25 (m, 10 × Ar−H), 5.73 (s, C5−H, C6−H), 4.63 (s, 2 × OBn-H), 4.60 (d, J = 11.9 Hz, OBn-H), 4.53 (d, J = 11.9 Hz, OBn-H), 4.19−4.13 (m, C4−H, C2−H), 3.87−3.80 (m, C7−H, C3−H), 3.47 (ddm, J = 15.3, 4.8 Hz, C7−H′), 3.38 (dd, J = 10.4, 5.5 Hz, C1−H), 2.70 (dd, J = 10.3, 6.9 Hz, C1−H′). ^{13}C NMR δ 58.2 (CH_2), 62.6 (CH_2), 71.96 (CH_2), 72.01 (CH_2), 76.2 (CH), 83.4 (CH), 86.1 (CH), 127.5 (CH), 127.60 (CH), 127.63 (CH), 127.7 (CH), 128.0 (CH), 128.38 (CH), 128.42 (CH), 128.6 (CH), 128.9 (CH), 138.2 (C), 138.3 (C). IR 3063, 3030, 1678, 1605, 1496,1453, 1365, 1111, 1073 cm^{-1}. HRMS calculated for $C_{21}H_{24}NO_2$ (M^+ + H) 322.1807, found 322.1778.

***tert*-Butyl (3*S*,4*S*,5*R*,6*Z*)-5-Benzoyloxy-3,4-bis(benzyloxy)-3,4,5,8-tetrahydroazocine-1(2*H*)-carboxylate (32).** A solution of **29** (2.00 g, 4.54 mmol) in pyridine (35 mL) was cooled to 0 °C and to it was added benzoyl chloride (0.76 mL, 6.5 mmol) dropwise. The reaction was warmed to room temperature and after 24 h the reaction mixture was poured over ice. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and washed with 6 M HCl (2 × 40 mL), saturated Na_2CO_3 (1 × 40 mL), and H_2O (4 × 40 mL). The organic layers were combined, dried with Na_2SO_4, decanted, and evaporated to dryness. The crude product was chromatographed through silica gel with CH_2Cl_2/hexane/CH_3CN first in a 45:60:1 ratio followed by 45:55:1, 45:20:1, and 45:10:0 ratios. All fractions were analyzed by TLC in 20:1 CH_2Cl_2/CH_3CN. This procedure resulted in the isolation of pure **32** as a clear oil (R_f 0.68, 2.39 g, 4.40 mmol, 97%). $[\alpha]^{26}_D$ −5.0 (*c* 0.72, CH_2Cl_2). ^{1}H NMR δ 7.99 (dd, J = 7.1, 1.4 Hz, 2 × *o*-Bz-H), 7.71 (tt, J = 7.4, 1.3 Hz, *p*-Bz-H), 7.38 (t, J = 7.5 Hz, 2 × *m*-Bz-H), 7.30−7.22 (m, 5 × Ar−H), 7.14−7.08 (m, 5 × Ar−H), 6.14 (dd, J = 8.9, 5.4 Hz, C6−H), 5.67−5.27 (m, C4−H, C5−H), 4.73−4.64 (m, 4 × OBn-H), 4.40 (br m, C7−H), 3.99−3.93 (m, C1−H, C2−H), 3.67 (m, C3−H, C7−H′), 3.22 (br s, C1−H′), 1.52 (s, 9 × Boc-H). ^{13}C NMR δ 28.6 (CH_3), 45.7 (CH_2), 47.0 (CH_2), 71.9 (CH), 73.0 (CH_2), 75.1 (CH_2), 76.6 (C), 80.2 (CH), 83.2 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 129.7 (CH), 130.8 (C), 132.7 (CH), 138.3 (C), 138.7 (C), 155.5 (C), 165.5 (C). IR 3089, 3063, 3030, 2975, 2931, 1726, 1710, 1692, 1678, 1602, 1585, 1545, 1494 cm^{-1}. Anal. Calcd for $C_{33}H_{37}NO_3$: C, 72.91; H, 6.86; N, 2.58. Found: C, 72.77; H, 7.12; N, 2.53.

(1*S*,2*S*,7a*S*)-1,2-Bis(benzyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine by Benzoate Displacement (33). Trifluoroacetic acid (3 mL, 40.25 mmol) was added to a solution of **32** (2.38 g, 4.30 mmol) in CH_2Cl_2 (10 mL). The reaction was monitored by TLC (20:1 CH_2Cl_2) for the disappearance of **32** (R_f 0.68) at which point (approximately 40 min) the mixture was evaporated to dryness. The resulting residue was dissolved in CH_2Cl_2 (30 mL) and washed with saturated Na_2CO_3 (2 × 30 mL), and the aqueous layers were extracted with CH_2Cl_2 (4 × 30 mL). The organic layers were combined, dried with $MgSO_4$, decanted, and evaporated to dryness to yield pure **33** (1.30 g, 4.02 mmol, 94%).

(1*R*,2*S*,6*S*,7*S*,7a*S*)-6,7-Bis(benzyloxy)hexahydro-1*H*-pyrrolizine-1,2-diol (34), (1*S*,2*R*,6*S*,7*S*,7a*S*)-6,7-Bis(benzyloxy)hexahydro-1*H*-pyrrolizine-1,2-diol (35), and (1*S*,2*R*,6*S*,7*R*,7a*S*)-1,2-Bis(benzyloxy)-6,7-dihydroxyhexahydro-3*H*-pyrrolizin-3-one (36). Vinyl pyrrolizidine **33** (0.044 g, 0.139 mmol) was suspended in acetone (1 mL) and cooled to 0 °C. *N*-Methylmorpholine *N*-oxide (0.0207 mg, 0.153 mmol) was added followed by OsO_4 (70 μL of

2.5% OsO_4 in *tert*-butyl alcohol, 0.0055 mmol). The reaction was kept at 0 °C and monitored by TLC (1:2:3:1 CH_2Cl_2/CH_3CN/MeOH/hexane) for the disappearance of **33** (R_f 0.54). Upon completion of the reaction (approximately 1 h), Na_2SO_3 (0.215 g, 2.09 mmol) was added and the solution was stirred at 0 °C. After 1.5 h, H_2O (3 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried with $MgSO_4$, decanted, evaporated to dryness, and chromatographed through silica gel with CH_2Cl_2/CH_3CN/MeOH/hexane starting with a 6:6:3:8 ratio and gradually decreasing to 6:6:3:0, while carefully monitoring by TLC in 6:6:3:1 CH_2Cl_2/CH_3CN/MeOH/hexane. This procedure resulted in the isolation of three diols, all as clear oils, that darkened upon exposure to air at room temperature: **34** (R_f 0.08, 0.0127 g, 0.0357 mmol, 26%), **35** (R_f 0.25, 0.0071 g, 0.0200 mmol, 15%), and **36** (R_f 0.83, 0.0066 g, 0.0187 mmol, 13%). **34:** $[\alpha]^{27}_D$ +24.4 (*c* 0.515, CH_2Cl_2) ^{1}H NMR δ 7.36−7.23 (m, 10 × Ar−H), 4.64 (d, J = 12.0 Hz, 1 × OBn-H), 4.57−4.50 (m, 3 × OBn-H), 4.14 (m, C6−H), 4.10−4.04 (m, C5−H, C3−H, C2−H), 3.43 (dd, J = 7.1, 2.1 Hz, C4−H), 3.25 (m, C7−H, C1−H), 2.99 (dd, J = 11.2, 3.8 Hz, C7−H′), 2.81 (dd, J = 12.3, 2.9 Hz, C1−H′). ^{13}C NMR δ 57.4 (CH_2), 60.5 (CH_2), 71.4 (CH_2), 71.6 (CH_2), 73.2 (CH), 73.8 (CH), 76.3 (CH), 84.7 (CH), 85.0 (CH), 127.5 (CH), 127.70 (CH), 127.73 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 137.4 (C), 137.6 (C). IR 3331 (br), 3031, 2922, 1605, 1453, 1094 cm^{-1}. HRMS calculated for $C_{21}H_{26}NO_4$ (M^+ + H) 356.1862, found 356.1843. **35:** $[\alpha]^{27}_D$ +10.1 (*c* 0.14, CH_2Cl_2). ^{1}H NMR δ 7.40−7.23 (m, 10 × Ar−H), 4.57 (s, 2 × OBn-H), 4.56 (s, 2 × OBn-H), 4.32 (m, C3−H), 4.18 (ddd, J = 10.5, 6.3, 4.2 Hz, C6−H), 4.09 (dt, J = 3.9, 2.6 Hz, C2−H), 4.00 (t, J = 4.6 Hz, C5−H), 3.64 (dd, J = 4.9, 2.8 Hz, C4−H), 3.37 (dd, J = 9.2, 6.5 Hz, C7−H), 3.22 (dd, J = 12.4, 4.1 Hz, C1−H), 2.94 (dd, J = 12.2, 2.4 Hz, C1−H′), 2.59 (t, J = 9.1 Hz, C7−H′). ^{13}C NMR δ 56.0 (CH_2), 57.5 (CH_2), 71.0 (CH_2), 71.0 (CH_2), 71.4 (CH), 76.5 (CH), 80.6 (CH), 83.2 (CH), 127.0 (CH), 127.3 (CH), 127.3 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 136.0 (C), 137.0 (C). IR 3406 (br), 3063, 3031, 2922, 2867, 1954, 1692, 1606, 1454, 1368, 1109 cm^{-1}. HRMS calculated for $C_{21}H_{26}NO_4$ (M^+ + H) 356.1862, found 356.1883. **36:** $[\alpha]^{25.5}_D$ +15.7 (*c* 0.42, CH_2Cl_2). ^{1}H NMR δ 7.40−7.23 (m, 10 × Ar−H), 5.07 (d, J = 11.7 Hz, OBn-H), 4.79 (d, J = 11.7 Hz, OBn-H), 4.64 (d, J = 11.6 Hz, OBn-H), 4.60 (dd, J = 8.0, 6.4 Hz, C3−H), 4.53 (d, J = 11.8 Hz, OBn-H), 4.44 (d, J = 8.1 Hz, C2−H), 4.37 (td, J = 8.1, 3.8 Hz, C6−H), 3.78 (t, J = 3.5 Hz, C5−H), 3.57 (dd, J = 3.3, 6.3 Hz, C4−H), 3.40 (m, 2 × C7−H). ^{13}C NMR δ 45.7 (CH_2), 64.8 (CH), 69.6 (CH), 72.7 (CH_2), 73.1 (CH_2), 73.9 (CH), 79.4 (CH), 82.7 (CH), 127.8 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 137.3 (C), 137.8 (C), 171.7 (C). IR 3388 (br), 3031, 2924, 1709, 1453, 1364, 1109 cm^{-1}. HRMS calculated for $C_{21}H_{24}NO_5$ (M^+ + H) 370.1654, found 370.1649.

(1*R*,2*S*,6*S*,7*S*,7a*R*)-6,7-Bis(benzyloxy)hexahydro-1*H*-pyrrolizine-1,2-diyl diacetate (37). Diol **34** (5.9 mg, 0.017 mmol) was dissolved in pyridine (0.3 mL) and cooled to 0 °C. Acetic anhydride (100 μL, 1.05 mmol) was added dropwise. The reaction was placed in a sonicating bath for 3 h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 (3 mL) and washed with saturated $NaHCO_3$ (1 × 3 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL). The organic layers were combined, dried with $MgSO_4$ decanted, evaporated to dryness, and chromatographed through silica gel with CH_2Cl_2/CH_3CN first in a 3:1 ratio followed by 2:1 and 1:1 ratios. Fractions were analyzed by TLC in 3:1 CH_2Cl_2/CH_3CN. This procedure resulted in the isolation of pure **37** as a clear oil that darkened upon exposure to air at room temperature (R_f 0.25, 7.3 mg, 0.0066 mmol, 100%). $[\alpha]^{26}_D$ 19.6 (*c* 0.33, CH_2Cl_2). ^{1}H NMR δ 7.34−7.19 (m, 10 × Ar−H), 5.38 (m, C6−H), 5.26 (dd, J = 4.5, 7.5 Hz, C5-H), 4.59 (d, J = 12.0 Hz, 1 × OBn-H), 4.56 (d, J = 11.7 Hz, 1 × OBn-H), 4.50 (d, J = 11.8 Hz, 1 × OBn-H), 4.48 (d, J = 11.8 Hz, 1 × OBn-H), 4.07 (m, C3−H, C2−H), 3.60 (dd, J = 7.5, 1.8 Hz, C4−H), 3.31−3.25 (m, C1−H, C7−H), 3.17 (dd, J = 11.5, 4.2 Hz, C7−H′), 2.88 (dd, J = 2.2, 12.5 Hz, C1−H′), 2.10 (s, 3 × Ac H), 2.07 (s, 3 × Ac H). ^{13}C NMR δ 19.8 (CH_3), 19.9 (CH_3), 56.9 (CH_2), 57.0 (CH_2), 70.1 (CH), 70.50 (CH_2), 70.54 (CH_2), 72.5 (CH), 73.9 (CH), 83.3 (CH), 83.6 (CH), 126.5 (CH), 126.6 (CH), 126.7 (CH), 126.8 (CH), 127.4 (CH), 127.5 (CH), 136.8 (C), 136.9 (C), 169.3 (C), 169.4 (C). IR 3031, 2922, 1744, 1453, 1370, 1247 cm^{-1}. HRMS calculated for $C_{25}H_{30}NO_6$ (M^+ + H) 440.2073, found 440.2050.

(1*S*,2*R*,6*S*,7*S*,7a*R*)-6,7-Bis(benzyloxy)hexahydro-1*H*-pyrrolizine-1,2-diyl Diacetate (38). The same procedure was used as for the synthesis of **37** above but starting with pyrrolizidine diol **35** (3.4 mg, 0.0096 mmol). This procedure resulted in the isolation of pure **38** as a clear oil that darkened upon exposure to air at room temperature (R_f 0.30, 3.5 mg, 0.0080 mmol, 83%). $[\alpha]^{26}_D$ 14.1 (*c* 0.20, CH_2Cl_2). ^{1}H NMR δ 7.36−7.16 (m, 10 × Ar−H), 5.39 (t, J = 4.1 Hz, C5−H), 5.27 (ddd, J = 10.5, 6.9, 3.8 Hz, C6−H), 4.72−4.51 (m, 4 × OBn-H), 4.30 (dt, J = 9.2, 6.5 Hz, C2−H), 4.13 (t, J = 6.6 Hz, C3−H), 3.56 (dd, J = 6.3, 4.4 Hz, C4−H), 3.40 (dd, J = 8.7, 6.3 Hz, C1−H), 3.29 (dd, J = 9.2, 6.9 Hz, C7−H), 2.63 (t, J = 9.3 Hz, C1−H′), 2.61 (t, J = 9.0 Hz, C7−H′), 2.00 (s, 3 × Ac−H), 1.98 (s, 3 × Ac−H). ^{13}C NMR δ 20.6 (CH_3), 20.7 (CH_3), 54.7 (CH_2), 58.2 (CH_2), 68.0 (CH), 71.7 (CH), 72.1 (CH_2), 72.7 (CH_2), 73.6 (CH), 80.6 (CH), 84.6 (CH), 127.6 (CH), 127.8 (CH), 127.8 (CH), 128.4 (CH), 129.1 (CH), 136.6 (C), 138.1 (C), 169.6 (C), 169.9 (C). IR 3063, 2923, 1754, 1744, 1453, 1370, 1246 cm^{-1}. HRMS calculated for $C_{25}H_{30}NO_6$ (M^+ + H) 440.2073, found 440.2109.

(1*R*,2*S*,6*R*,7*S*,7a*R*)-6,7-Bis(benzyloxy)-5-oxohexahydro-1*H*-pyrrolizine-1,2-diyl Diacetate (39). The same procedure was used as for the synthesis of **37** above but starting with lactam pyrrolizidone diol **36** (5.7 mg, 0.016 mmol). After chromatography through silica gel with CH_2Cl_2/CH_3CN first in a 5:1 ratio followed by a 3:1 ratio, this procedure resulted in the isolation of pure **39** as a clear oil that darkened upon exposure to air at room temperature (R_f 0.45, 4.7 mg, 0.011 mmol, 66%). $[\alpha]^{26}_D$ 27.4 (*c* 0.20, CH_2Cl_2). ^{1}H NMR δ 7.45−7.24 (m, 10 × Ar−H), 5.44−5.38 (m, C5−H, C6−H), 5.12 (d, J = 11.6 Hz, OBn-H), 4.82 (d, J = 11.6 Hz, OBn-H), 4.56 (s, 2 × OBn-H), 4.47 (d, J = 7.9 Hz, C2−H), 4.21 (t, J = 6.6 Hz, C3−H), 3.83 (dd, J = 3.5, 6.4 Hz, C4−H), 3.48 (d, J = 7.3 Hz, 2 × C7−H), 2.01 (s, 3 × Ac−H), 1.95 (s, 3 × Ac−H). ^{13}C NMR δ 20.5 (2 × CH_3), 43.5 (CH_2), 62.4 (CH), 69.4 (CH), 72.2 (CH_2), 72.3 (CH), 72.8 (CH_2), 78.7 (CH), 82.5 (CH), 127.7 (CH), 128.0 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 137.2 (C), 137.5 (C), 169.5 (C), 169.8 (C), 171.2.8 (C). IR 3031, 2925, 1754, 1745, 1722, 1710, 1370, 1239 cm^{-1}. HRMS calculated for $C_{25}H_{28}NO_6$ (M^+ + H) 454.1866, found 454.1824. Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 59.73; H, 5.10; N, 2.19.

(1*R*,2*S*,6*S*,7*S*,7a*S*)-Hexahydro-1*H*-pyrrolizine-1,2,6,7-tetrol (40). Ten percent Pd/C (ca. 5 mg) was added to a solution of diol **34** (11.1 mg, 0.031 mmol) in ethanol (2 mL). Once the metal catalyst was added, a drop of 6 M HCl was added to the solution and the reaction was placed under a hydrogen atmosphere delivered by a balloon. The reaction was monitored by TLC (1:1:3 CH_2Cl_2/CH_3CN/CH_3OH) for the disappearance of **34** (R_f 0.264). Once **34** was no longer present, the mixture was filtered through Celite and evaporated to dryness. The residue was dissolved in H_2O, washed with CH_2Cl_2, and lyophilized to a very hydroscopic solid (6.5 mg, 0.031 mmol, 99%). Mp ∼210 °C dec. $[\alpha]^{26}_D$ 23.1 (*c* 0.23, H_2O). ^{1}H NMR δ 4.28 (dd, J = 8.9, 3.6 Hz, C5−H), 4.15 (m, C2−H, C3−H), 4.08 (m, C6−H), 3.57 (d, J = 8.9 Hz, C4−H), 3.51 (d, J = 12.6 Hz, C7−H), 3.41 (dd, J = 13.2, 3.2 Hz, C1−H), 3.20 (dd, J = 12.6, 2.6 Hz, C1−H′), 3.12 (d, J = 13.1 Hz, C7−H′). ^{13}C NMR δ 57.9 (CH_2), 60.9 (CH_2), 71.4 (CH), 73.7 (CH), 75.5 (CH), 76.1 (CH), 77.0 (CH). IR 3378, 3301, 2943, 2726, 1136 cm^{-1}. HRMS calculated for $C_7H_{15}NO_4Cl$ (M^+ + H) 176.0923, found 176.0931.

(1*S*,2*R*,6*S*,7*S*,7a*S*)-Hexahydro-1*H*-pyrrolizine-1,2,6,7-tetrol (41). The same procedure used as for the synthesis of **40** above but starting with pyrrolizidone diol **35** (11.7 mg, 0.033 mmol) yielded **41** (7.3 mg, 0.034 mmol, 103%) as a very hydroscopic solid, mp

~210 °C dec. ^{1}H NMR δ 4.52 (t, J = 5.9 Hz, C5−H), 4.38 (dd, J = 5.7, 4.1 Hz, C3−H), 4.30 (ddd J = 9.7, 7.4, 5.8 Hz, C2−H), 4.19 (dt, J = 8.3, 6.1 Hz, C6−H), 3.94 (t, J = 5.6 Hz, C4−H), 3.79 (dd, J = 11.8, 6.1 Hz, C7−H), 3.65 (dd, J = 12.0, 5.7 Hz, C1−H), 3.22−3.09 (m, C7−H′, C1−H′). ^{13}C NMR δ 55.9 (CH_2), 57.8 (CH_2), 69.0 (CH), 71.2 (CH), 71.6 (CH), 73.4 (CH), 75.0 (CH). IR 3330 (br), 2928, 1461, 1126 cm^{-1}. HRMS calculated for $C_7H_{15}NO_4Cl$ (M^+ + H) 176.0923, found 176.0938.

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Supporting Information Available: Mechanistic proposal for DEAD oxidation of **33**, general experimental procedures, and procedures and product characterization data for compounds **18**, **19**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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