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A Versatile Access to Calystegine Analogues as Potential Glycosidases Inhibitors

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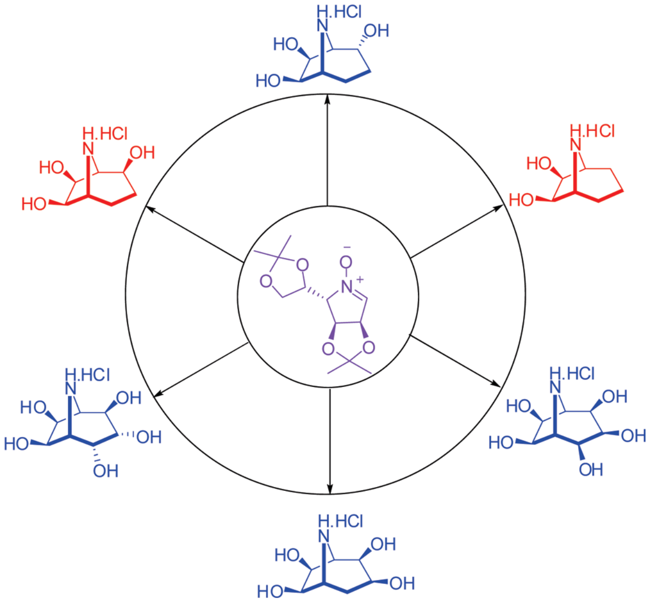

An efficient metathetic strategy and nitrone chemistry have been suitably tethered to construct 8-azabicyclo[3.2.1]octanes as versatile precursors for the synthesis of several calystegine analogues. This synthetic strategy relies on the ability of mannose-derived nitrone to undergo a highly stereoselective nucleophilic addition of various Grignard reagents to access *syn* orientation of alkenes, which then smoothly undergo ring-closing metathesis (RCM) to provide this framework. These RCM products **18** and **20** have been successfully used as advance precursors to synthesize many calystegine analogues (**27**, **36**, **38**, **40**, **43**, and **44**) either by *syn*-dihydroxylation or by hydrogenation and followed by global deprotection. Interestingly, both compounds **36** and **40** exhibited significant noncompetitive inhibition against α-mannosidase and *N*-acetyl-*β*-D-glucosaminidase.

Introduction

Calystegines belong to polyhydroxy bicyclic nortropane alkaloids which were first isolated from the roots and root extrudates of *calystegia sepium*[1] by Tefer et al. in 1988 as plant secondary metabolites and they are believed to function as nutritional mediators in the plant rhizosphere.[1,2] Since then their family members such as calystegine A (with three hydroxy groups), calystegine B (with four hydroxy groups), and calystegine C (with five hydroxy groups)

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have been found[3,4] in various fruits, vegetables (potatoes, egg plant, and sweet potato), moths, and butterflies, the larvae of which feed on solanam.[5] Like azasugars,[6] calystegines possessing an aza-bridged skeleton, which also may be viewed as a hybrid of pyrrolidine and piperidine, show potent and specific glycosidase inhibitory activity,[7] particularly glucosidases and galactosidases. They are lead compounds for chemotherapeutic drugs for the treatment of cancer,[8] viral infection,[9] and metabolic disorders such as diabetes.[10] However, in contrast to monocyclic (pyrrolidines and piperidines) and bicyclic (pyrrolizidines and indolizidines) polyhydroxyalkaloids which have been extensively exploited in the field of glycosidase inhibition,[6] calystegines have been less explored and only a handful of calystegines with ring-modified analogues have been reported so far.[11] Hitherto, in spite of a variable hydroxylation pattern, the synthesis of calystegines (Figure 1) with hydroxyl groups on both C6 and C7 has seldom been attempted.[11b] Furthermore, only a few unnatural calystegines have been synthesized and screened for biological activity.[11a] It was anticipated that an efficient strategy for the synthesis of unnatural analogues of calystegines could provide more possibilities for evaluating this class of compounds as glycosidase inhibitors. With these considerations, as well as in continuation of our interest in the synthesis of natural[12] and natural product like molecules,[13] herein we disclose a flexible synthetic route to several unnatural calystegine analogues as potential glycosidases inhibitors. After the completion of our synthesis of these analogues, during the investigation of their glycosidase inhibitory activity, Martin's group[11e] reported a stereodivergent synthesis of calystegine analogues namely polyhydroxylated 10-azabicyclo[4.3.1]decanes as glycosidase inhibitors, which prompted us to disclose our synthesis and glycosidase inhibitory activity of calystegine analogues. Their synthesis relied on a double benzotriazolyl/carbon nucleophilic exchange followed by a ring-closing metathesis. Some of their calystegine analogues have been evaluated as glucosidases and glucocerebrosidase.

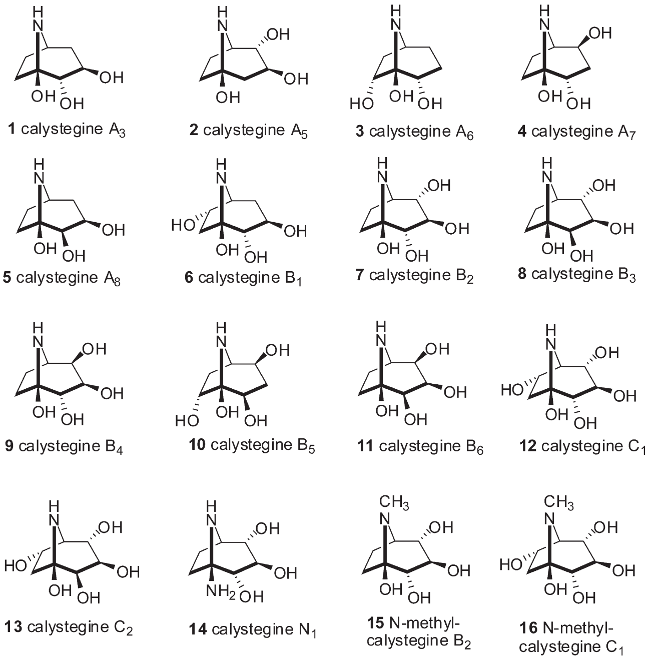
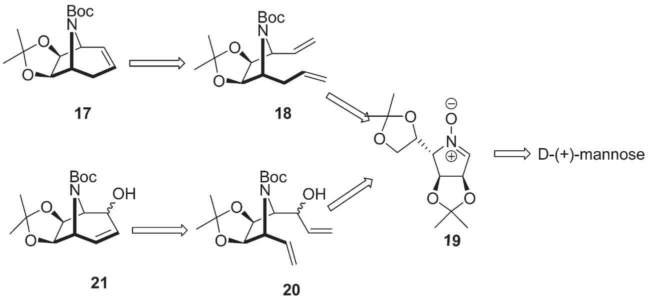


FIGURE 1. Calystegine family.

SCHEME 1. Retrosynthetic Analysis



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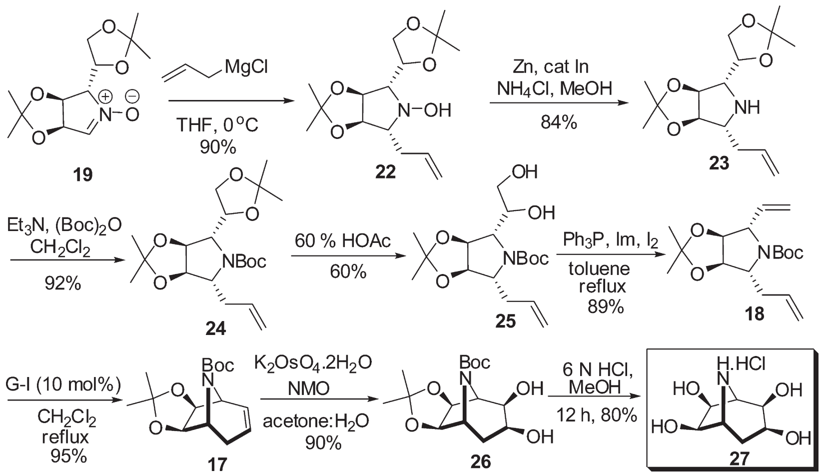
SCHEME 2. Synthesis of Aza-Bridged Polycyclitol



Results and Discussion

Chemistry. It has been quite a while since olefin metathesis[14] has emerged as one of the most powerful synthetic tools in organic synthesis and it is primarily due to the ready availability of many air-stable metathetic catalysts such as Grubbs' first generation catalyst,[15] Grubbs' second generation catalyst,[16] Hoveyda's catalyst,[17] etc., and also due to their high level of functional group tolerance. Among the various possible metathetic applications, the ring-closing metathesis (RCM) reaction has been extensively used for the syntheses of several monocyclic and bicyclic azasugars.[18] Likewise, nitrones have also been known for a long time as a versatile synthetic intermediate for the syntheses of several azasugars, owing to their ability to undergo numerous synthetically useful reactions such as 1,3-dipolar cycloadditions,[19] nucleophilic additions,[20] and pinacol-type coupling reactions.[21] Consequently, the enantiomerically pure and polyfunctional cyclic nitrones, in conjunction with various key reactions, have found applications in the total synthesis, asymmetric synthesis of polyhydroxylated pyrrolidine, indolizidine, and pyrrolizidine alkaloids.[22] On the basis of our ongoing efforts in exploiting the synthetic utility of nitrones[13f] as well as the RCM reaction,[12a,12b,13d] we initiated a program to develop a general and unified strategy for the syntheses of calystegine analogues.

Retrosynthesis. Our retrosynthetic analysis of these targets is outlined in Scheme 1. As indicated, the bicyclic tropane framework could be constructed by ring-closing metathesis. We then anticipated that the RCM products **17** and **21** would present themselves as potential and versatile intermediates for the syntheses of several calystegine analogues. The requisite *syn* dienes **18** and **20** could, in turn, be accessed from a stereoselective nucleophilic addition of various Grignard reagents to the known[23] nitrone **19**, derived from D-mannose in a few steps, and followed

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by functional group manipulation of the more exposed acetonide to alkene. This strategy, as a whole, provides an interesting challenge to assemble the tropane skeleton of calystegines easily from commercially available sugars. Apparently, most of the aforementioned synthesis of calystegine[24] involved lengthy routes to the synthesis of aminocycloheptanone followed by aminoketalization. However, our synthesis starts with a sugar-derived pyrrolidine ring and installation of a polyhydroxylated piperidine ring by taking the advantage of RCM. During the course of synthetic investigation, we envisioned that among the wide varieties of sugars, mannose-derived nitrone **19**, in particular, would be an ideal starting material keeping in mind the RCM as the key reaction.

Our synthetic endeavors commenced with a stereoselective nucleophilic addition[22c,25] of allyl magnesium chloride to nitrone **19** to afford the hydroxylamine **22** in 90% yield. It is worth noting that the product **22** is derived from an *anti* attack of the organometallic reagent with respect to 2,3-*O*-isopropylidine, as a result of a combination of steric and stereoelectronic effects. Therefore the allyl functionality and the more exposed acetonide group oriented themselves *syn* to each other. The N−O bond in **22** was successively cleaved according to the reported procedure,[26] with powdered Zn (4 equiv) and catalytic indium (18%) in the presence of saturated ammonium chloride solution. Subsequently, the resulting secondary amine **23** was protected as *N*-Boc **24** on treatment with $(Boc)_2O$ and Et_3N in CH_2Cl_2. The selective removal of the 5,6-*O*-isopropylidine group was successfully accomplished with 60% aqueous acetic acid to afford the vicinal diol **9** in 60% yield. The diol **25** was then converted into the desired RCM precursor diene **18** (89% yield) in a single step following Garegg's protocol.[27]

With a wealth of literature available for sterically crowded amines to undergo RCM,[28] we next submitted the diene **18** to 10 mol % of Grubbs' first generation catalyst in refluxing dichloromethane. As anticipated, the RCM proceeded smoothly to afford the expected 8-azabicyclo[3.2.1]octane derivative **17** in excellent yield as a colorless crystalline solid. As premeditated, the RCM product was further utilized as an advance precursor for the syntheses of several analogues of calystegine. To functionalize the double bond, catalytic *syn*-dihydroxylation of compound **17** in the presence of K_2OsO_4/NMO provided exclusively *exo*-diol **26** in 90% yield and with no evidence of *endo* product. The most favorable *exo*-attack was in accordance with the dihydroxylation reaction performed on related bicyclic systems such as 8-azabicyclo[3.2.1]octanes[29] and 9-azabicyclo[4.2.1]-nonenes.[11b] The deprotection of acetonide as well as *N*-Boc was simultaneously achieved with 6 N aq HCl in MeOH to afford the desired aza-bridged polycyclitol **27** in 80% yield (Scheme 2).

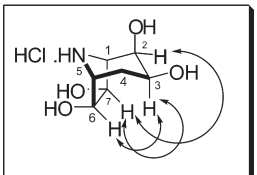

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FIGURE 2. NOE interaction.

Finally, the stereochemical assignment of hydroxyl groups was established on the basis of the NOESY spectrum. The distinct NOE interaction indicated strong cross peaks between C(2)H and C(7)H, C(3)H and C(7)H, and also C(3)H and C(6)H for compound **27**, which suggested the *exo*-product (Figure 2). In comparison to the naturally occurring calystegine, the resulting polyhydroxy aza-bridged compound **27** could be categorized as an analogue of calystegine B.

Having successfully accomplished the synthesis of calystegine analogue **27**, we then shifted our focus to investigate the general applicability of this strategy for the synthesis of more such analogues. This could be easily done by tethering a larger number of hydroxyl functionalities around the bicyclic core, which in turn could be obtained from different RCM products. To access the same, it was required to introduce a vinyl group instead of an allyl moiety to nitrone **19** as mentioned earlier in Scheme 2. As required, nitrone **19** was treated with 1.2 equiv of 1 M solution of vinyl magnesium bromide in THF at 0 °C to afford hydroxylamine **28** in 91% yield. As observed earlier (Scheme 2), the Grignard addition provided a single diastereomer as a result of *anti* attack of the organometallic reagent with respect to the vicinal 2,3-*O*-isopropylidine group. The formation of a single diastereomer **28** was further determined by ^1H as well as ^{13}C NMR. Subsequent reduction of resulting hydroxylamine **28** with powdered Zn (4 equiv) in the presence of catalytic indium (18%) afforded the pyrrolidine **29** in 72% yield. Protection of the resulting secondary amine **29** as its carbamate with $(Boc)_2O$ and Et_3N in CH_2Cl_2 at 0 °C afforded the alkene in 88% yield. The 5,6-*O*-isopropylidine group was then deprotected selectively by using 60% aqueous acetic acid to furnish the diol **31** in 61% yield. The diol **31** was then smoothly converted to its corresponding aldehyde **32**, which was directly treated with 3 equiv of vinyl magnesium bromide at room temperature to afford the allylic alcohol **20** as a mixture of diastereomers. Nonetheless, the diene **20** was subsequently subjected to RCM with Grubbs' first generation catalyst (10 mol %) in refluxing dichloromethane to afford a mixture of two products **33** and **34** in 31% and 53% yields, respectively, which were easily separated by silica gel column chromatography (Scheme 3).

The structures were tentatively assigned by ^1H and ^{13}C NMR. This observation concluded that the Grignard reaction provided inseparable diastereomeric mixtures **20**, which were separated easily after the RCM. However, we initially anticipated that the Grignard reaction to aldehyde would provide a single isomer in accordance with a report by Parson

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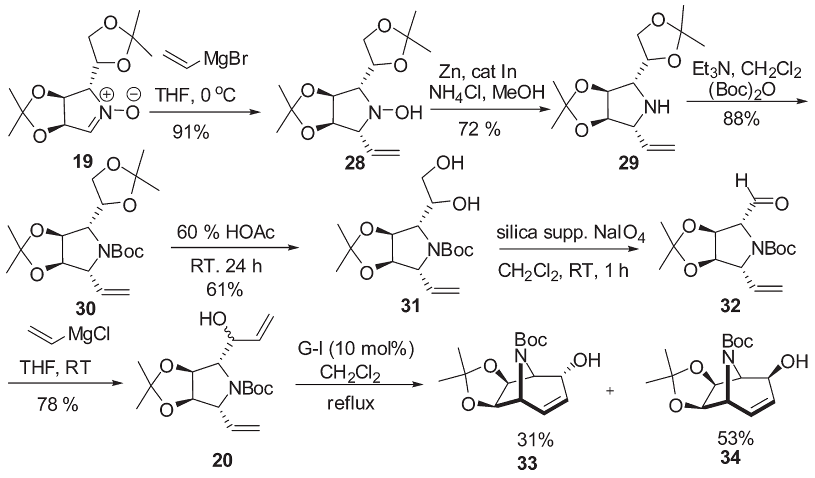
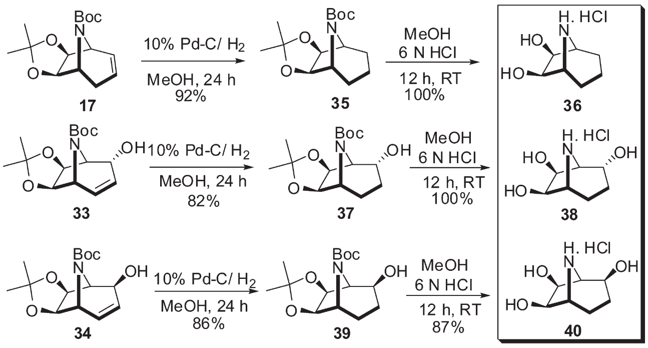
SCHEME 3. Synthesis of Aza-Bridged Polycyclitols



SCHEME 4. Synthesis of Aza-Bridged Polycyclitols



et al.[30] where Mg coordinated with both aldehyde and Boc carbonyl oxygen followed by Grignard addition from *exo*-attack provided exclusively one isomer. On the other hand, the formation of two diastereomers provided an opportunity to access an additional number of calystegine analogues.

These RCM products **17**, **33**, and **34** could be easily employed to synthesize a range of polyhydroxylated tropane derivatives. Hydrogenation of intermediate **17**, **33**, and **34** with 10% Pd/C under hydrogen atmosphere provided compounds **35**, **37**, and **39** in 92%, 82%, and 86% yields, respectively. Final removal of Boc as well as an acetonide group was achieved on treatment with 6 N aq. HCl in MeOH to afford calystegine analogues **36**, **38**, and **40** in excellent yields (Scheme 4). The stereochemical array of hydroxyl groups for compounds **38** and **40** was assigned by NOESY spectra. The observed NOE effects between C(2)H and C(7)H for compound **40** confirmed the *β*-orientation of C(2)OH. However the other isomer **38** did not show any such significant NOE effect, specifying the α-orientation of C(2)OH (Figure 3).

Having succeeded in the synthesis of calystegine analogues with two and three hydroxyl groups, we next focused our interest to incorporate more hydroxyl functionalities around the bicyclic ring in order to generate diverse calystegine analogues. With this view, the allylic alcohol **34** was subjected for *syn*-dihydroxylation in the presence of K_2OsO_4 and NMO. However, *syn*-dihydroxylation of **34** was nonselective and gave a separable mixture of diastereomeric triols **41** and **42** in 50% and 40% yields, respectively (Scheme 5). The products were characterized by ^1H, as well as ^{13}C, NMR. Presumably, the *exo* dihydroxylation led to the formation of the *meso* product, which showed zero specific rotation, whereas the *endo* product showed significant specific rotation $[\alpha]^{25}_{D}$ −9.7 (*c* 1.00, MeOH). These results tentatively supported our prediction of the formation of *exo* and *endo* dihydroxylated product. Both isomers were then separately treated with 6 N aq HCl in MeOH to provide compounds **43** and **44** in excellent yields (Scheme 5). Finally the stereochemical assignments of hydroxyl groups were assigned on the basis of extensive NOE interaction. The significant NOE interaction between C(3)H and C(6)H and also between C(3)H and C(7)H for compound **43** supported the *exo* product of dihydroxylation reaction, whereas the absence of such interactions in compound **44** (except C(2)H and C(7)H NOE interaction) supported the *endo* isomer (Figure 4).

Glycosidase Inhibitory Study. After the successful synthesis of these calystegine analogues, the inhibitory activities of compounds **27**, **36**, **38**, **40**, **43**, and **44** were studied against various glycosidases (α-galactosidase, *β*-galactosidase, α-amylase, *β*-glucosidase, α-mannosidase, and *N*-acetyl-*β*-D-glucosaminidase).

Unfortunately, none of the above compounds showed inhibition against α-galactosidase, *β*-galactosidase, α-amylase, and *β*-glucosidase, whereas compounds **36** and **40** exhibited noncompetitive inhibition against α-mannosidase and *N*-acetyl-*β*-D-glucosaminidase. IC_{50} and kinetic studies of compounds **36** and **40** were carried out, which exhibited inhibitory activity against α-mannosidase with K_i = 0.42 mM and K_i = 0.54 mM, respectively. Compouns **36** also exhibited inhibitory activity against *N*-acetyl-*β*-D-glucosaminidase (K_i = 0.83 mM), while compound **40** showed weak inhibition for *N*-acetyl-*β*-D-glucosaminidase (K_i = 1.6 mM). It is interesting to note that our synthetic calystegine analogues **36** and **40** show moderate activity against *N*-acetyl-*β*-D-glucosaminidase and α-mannosidases. This finding could be a potential lead to further chemotherapeutic applications.

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[30] Murray, A. J.; Parsons, P. J. *Synlett* **2006**, 1443–1445.

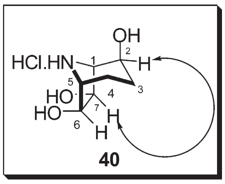

FIGURE 3. NOE interaction.

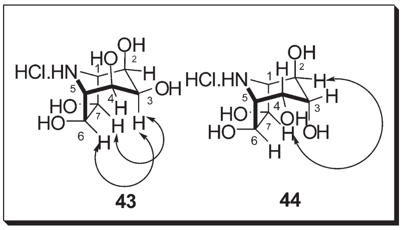

FIGURE 4. NOE interaction.

SCHEME 5. Synthesis of Aza-Bridged Polycyclitols

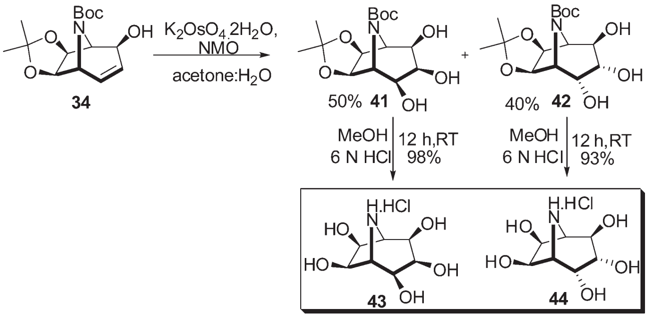

TABLE 1. IC$_{50}$ values for 36 and 44 (in mM)

compd	α-mannosidases	*N*-acetyl-*β*-D-glucosaminidase
36	1.5	1.4
40	0.75	0.68

Conclusion

In conclusion, we have demonstrated a rapid and efficient strategy for the facile construction of the 8-azabicyclo[3.2.1]octane framework of calystegine through a highly stereoselective Grignard addition followed by a RCM reaction. As a proof of this strategy, we have successfully synthesized a few calystegine analogues having two to five peripheral hydroxy groups and screened them against several glycosidases. Interestingly, compounds **36** and **40** exhibited significant noncompetitive inhibition against α-mannosidase and *N*-acetyl-*β*-D-glucosaminidase. This unified strategy has great potential to make more diverse analogues of calystegines with several peripheral functional groups, which could be easily introduced by using the double bond present in the intermediate formed by the RCM reaction and could be studied further.

Experimental Section

(3a*R*,4*R*,6*S*,6a*S*)-4-Allyl-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5(4*H*)-ol (22). To a stirred solution of **19** (2.13 g, 8.28 mmol) in THF (80 mL) was slowly added a 2 M solution of allyl magnesium chloride in THF (5 mL, 9.94 mmol) under nitrogen atmosphere at 0 °C. After stirring at 0 °C for 2 h, 30 mL of saturated aqueous $NaHCO_3$ was added. The precipitate was filtered and the mixture extracted with diethyl ether (3 × 40 mL). The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (10% ethyl acetate in hexanes) to afford the hydroxylamine **22** (2.2 g) as a pale yellow solid in 90% yield: R_f 0.57 (20% ethyl acetate/hexanes); mp 62−64 °C; $[\alpha]^{25}_D$ −37.8 (*c* 1.00, $CHCl_3$); IR (KBr) 3428, 3345, 2989, 2936, 2908, 2886, 1643, 1455, 1381, 1372, 1257, 1211, 1158, 1067, 913, 869, 842, 516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97−5.83 (m, 1H), 5.43 (br s, 1H, OH), 5.17 (ddd, J = 17.2, 4.7, 1.8 Hz, 1H), 5.12−5.08 (m, 1H), 4.30 (dd, J = 12.1, 6.6 Hz, 1H), 4.23−4.16 (m, 2H), 4.10 (dd, J = 8.4, 6.4 Hz, 1H), 3.94 (dd, J = 8.8, 5.5 Hz, 1H), 3.08−3.00 (m, 2H), 2.59−2.50 (m, 1H), 2.41−2.31 (m, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 117.3, 113.9, 110.0, 78.0, 77.6, 77.5, 74.5, 72.2, 66.4, 35.8, 27.4, 26.6, 25.5, 25.3; HRMS (ESI-TOF) calcd for $C_{15}H_{26}NO_5$ $(M+1)^+$ *m*/*z* 300.1811, found *m*/*z* 300.1800.

(3a*R*,4*R*,6*S*,6a*S*)-4-Allyl-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole (23). To a stirred solution of **22** (1.71 g, 5.72 mmol) in MeOH (68 mL) were added a saturated solution of NH_4Cl (102 mL), powdered Zn (1.5 g, 23 mmol), and a catalytic amount of indium dust (11 mg, 0.097 mmol) at 20 °C. The mixture was heated under reflux overnight. The solvent was evaporated in vacuo and a saturated aqueous solution of Na_2CO_3 (100 mL) was added. The mixture was extracted with diethyl ether (3 × 50 mL). The combined layers were washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (30% ethyl acetate in hexanes) to afford secondary amine **23** (1.36 g) as a brownish oil in 84% yield: R_f 0.56 (30% ethyl acetate in hexanes); $[\alpha]^{25}_D$ −0.76 (*c* 1.00, $CHCl_3$); IR (neat) 3594, 3341, 3077, 2986, 2934, 1642, 1456, 1381, 1372, 1260, 1211, 1159, 1069, 918, 868, 803, 663, 512 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91−5.77 (m, 1H), 5.19−5.08 (m, 2H), 4.30−4.23 (m, 2H), 4.17−4.06 (m, 2H), 3.9−3.83 (m, 1H), 3.17 (ddd, J = 6.9, 4.4 Hz, 1H), 3.10 (dd, J = 6.2, 5.1 Hz, 1H), 2.46−2.37 (m, 1H), 2.34−2.14 (m, 1H), 2.14 (br s, 1H, NH), 1.51 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 117.4, 114.0, 109.2, 84.3, 81.7, 77.4, 66.3, 66.0, 63.1, 38.1, 27.2, 26.5, 25.2, 25.1; HRMS (ESI-TOF) calcd for $C_{15}H_{26}NO_4$ $(M+1)^+$ *m*/*z* 284.1862, found *m*/*z* 284.1861.

(3a*R*,4*R*,6*S*,6a*S*)-*tert*-Butyl 4-Allyl-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (24). To a solution of **23** (2.7 g, 9.56 mmol) in CH_2Cl_2 (47 mL) at 0 °C was added Et_3N (4.8 mL, 34 mmol) with stirring for 30 min. After 30 min, a solution of Boc_2O (3.13 g, 14.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The resulting reaction mixture was then slowly allowed to warm to ambient temperature and stirred for an additional 24 h. The mixture was then treated with 1 N aqueous $KHSO_4$ (10 mL). The organic layer was separated and washed with 1 N aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography (20% ethyl acetate in hexanes) afforded **24** (3.31 g) in 92% yield: R_f 0.77 (20% ethyl acetate in hexanes); $[\alpha]^{25}_D$ 76.4 (*c* 1.00, $CHCl_3$); IR (neat) 3515, 3078, 2983, 2936, 1695, 1642, 1478, 1456, 1382, 1334,1242, 1215, 1165, 1070, 1053, 914, 887, 770, 513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.77 (m, 1H), 5.17−5.11 (m, 2H), 4.70 (d, J = 5.5 Hz, 1H), 4.47 (dd, J = 5.5, 2.2 Hz, 1H), 4.30−4.20 (m, 2H), 3.98 (br s, 1H), 3.54 (t, J = 8.8 Hz, 1H), 2.54 (unresolved br s, 1H), 2.38−2.32 (m, 1H), 1.46 (s, 12H), 1.43 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 134.6, 117.2, 111.5, 108.5, 84.2, 82.1, 80.1, 66.3, 65.6, 63.0, 38.1, 28.2, 27.3, 26.5, 25.7, 25.4; HRMS

(ESI-TOF) calcd for $C_{20}H_{33}NO_6Na$ $(M+Na)^+$ *m*/*z* 406.2206, found *m*/*z* 406.2210.

(3a*R*,4*R*,6*S*,6a*S*)-*tert*-Butyl 4-Allyl-6-((*S*)-1,2-dihydroxyethyl)-2,2-dimethyldihydro-3aH-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (25). Compound **24** (1 g, 2.6 mmol) was taken in 23 mL of 60% AcOH in water and the mixture was stirred for 24 h at rt. Then toluene (3×20 mL) was successively added and evaporated in vacuo to remove traces of water and acetic acid. The crude diol was purified by silica gel column chromatography (60% ethyl acetate in hexanes) and afforded the pure diol **25** (0.53 g) in 60% yield: R_f 0.30 (30% ethyl acetate in hexanes); mp 100−102 °C; $[\alpha]^{25}_{D}$ 33.9 (*c* 1, $CHCl_3$); IR (KBr) 3373, 3079, 2987, 2953, 2922, 2875, 1654, 1407, 1367, 1213, 1160, 1046, 919, 903, 874, 684, 515 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 5.87−5.77 (m, 1H), 5.16−5.11 (m, 2H), 4.66 (d, *J* = 5.5 Hz, 1H), 4.47 (d, *J* = 4.3 Hz, 1H), 4.32 (br s, 1H), 3.97 (unresolved br s, 2H), 3.80 (unresolved br s, 1H), 3.58−3.53 (m, 2H), 2.57 (d, *J* = 5.2 Hz, 1H), 2.48−2.45 (m, 1H), 2.38−2.31 (m, 1H), 1.48 (s, 9H), 1.46 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 134.8, 117.9, 111.7, 84.4, 82.8, 81.3, 72.9, 66.0, 65.4, 63.5, 38.0, 28.4, 27.6, 25.6; HRMS (ESI-TOF) calcd for $C_{17}H_{29}NO_6Na$ $(M + Na)^+$ *m*/*z* 366.1893, found *m*/*z* 366.1878.

(3a*R*,4*R*,6*S*,6a*S*)-*tert*-Butyl 4-Allyl-2,2-dimethyl-6-vinyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (18). To a refluxing solution of the crude diol **25** (0.080 g, 0.23 mmol), imidazole (0.064 g, 0.92 mmol), and triphenylphosphine (0.244 g, 0.92 mmol) in toluene (4 mL) was added iodine (0.177 g, 0.69 mmol) portion wise through the condenser. The reaction mixture was further refluxed for 5 h and cooled to rt. The organic layer was washed with saturated sodium thiosulfate solution (3×10 mL), water, and brine, dried (Na_2SO_4), and filtered. Removal of the solvent followed by silica gel column chromatography (10% ethyl acetate in hexanes) yielded **18** (0.063 g) in 89% yield: R_f 0.81 (30% ethyl acetate in hexanes); $[\alpha]^{25}_{D}$ −16.5 (*c* 1.16, $CHCl_3$); IR (neat) 3523, 3081, 2980, 2934, 1696, 1643, 1479, 1392, 1327, 1213, 1175, 1133, 1060, 920 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87−5.74 (m, 2H), 5.25−5.08 (m, 4H), 4.54 (dd, *J* = 5.8, 1.1 Hz, 2H), 4.55 (dd, *J* = 5.5, 1.1 Hz, 1H), 4.39−4.07 (m, 1H), 2.52−2.49 (m, 1H), 2.14−2.03 (m, 1H), 1.47 (s, 3H), 1.45 (s, 9H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 136.7, 134.4, 118.0, 116.1, 111.9, 84.5, 83.4, 79.9, 66.5, 64.1, 38.2, 29.8, 28.5, 27.3, 25.5; HRMS (ESI-TOF) calcd for $C_{17}H_{27}NO_4Na$ $(M + Na)^+$ *m*/*z* 332.1838, found *m*/*z* 332.1830.

Compound 17. To a stirred solution of **18** (0.05 g, 0.16 mmol) in 32 mL of CH_2Cl_2 was added G-I catalyst (0.014 g, 0.016 mmol). The solution turned yellow upon initial heating and then purple as the mixture was refluxed over 1.5 h. The reaction mixture was then cooled to rt and DMSO (0.02 mL, 0.15 mmol) was added and the mixture stirred overnight at rt. Then solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography to yield **17** (0.043 g) in 95% yield as a colorless solid: R_f 0.51 (20% ethyl acetate in hexanes); mp 93−94 °C; $[\alpha]^{25}_{D}$ 4.2 (*c* 1.00, $CHCl_3$); IR (KBr) 3042, 2984, 2936, 1697, 1379, 1368, 1347, 1169, 1051, 984, 857 cm^{-1}; (doubling of ^{1}H and ^{13}C NMR resonances due to Boc rotamers) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89−5.83 (m, 1H), 5.64−5.56 (m, 1H), 4.56 (dd, *J* = 5.8, 1.8 Hz, 1H), 4.46 (dd, *J* = 5.5, 2.2 Hz, 1H), 4.36 (d, *J* = 5.9 Hz, 1H), 4.20 (dd, *J* = 5.9, 1.1 Hz, 1H), 2.70−5.56 (m, 1H), 1.93−1.84 (m, 1H), 1.47 (s, 9H), 1.43 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 128.5, 127.7, 127.0, 126.3, 111.7, 85.6, 85.5, 85.2, 85.0, 79.7, 59.4, 58.4, 58.0, 57.0, 29.6, 29.4, 28.5, 26.4, 24.6; HRMS (ESI-TOF) calcd for $C_{15}H_{23}NO_4Na$ $(M + Na)^+$ *m*/*z* 304.1525, found *m*/*z* 304.1515.

Compound 26. To a solution of **17** (0.040 g, 0.14 mmol) in acetone (1 mL) and H_2O (0.7 mL) was added *N*-methylmorpholine *N*-oxide (0.041 mg, 0.31 mmol) followed by potassium osmate dihydrate (0.003 g, 0.007 mmol). The mixture was stirred at rt for 24 h and then all volatiles were evaporated in vacuo to give a dark oil. This was subsequently purified by a silica gel column chromatography (75% ethyl acetate in hexanes) to furnish compound **26** (0.039 g) in 90% yield: R_f 0.36 (100% ethyl acetate), mp 180−181 °C; $[\alpha]^{25}_{D}$ −10.8 (*c* 1.00, $CHCl_3$); IR (KBr) 3401, 2988, 2976, 2920, 1668, 1434, 1210, 1171, 1115, 1081, 1051, 874, 703 cm^{-1}; (doubling of ^{1}H and ^{13}C NMR resonances due to Boc rotamers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48−4.38 (m, 2H), 4.21 (s, 1H), 3.92 (t, *J* = 3.6 Hz, 1H), 3.82 (s, 1H), 3.42 (d, *J* = 4.3 Hz, 1H), 1.93−1.84 (m, 1H), 1.73−1.63 (m, 1H), 1.48 (s, 9H), 1.42 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.3, 111.5, 81.6, 81.5, 80.4, 80.3, 79.8, 79.3, 68.2, 68.1, 65.2, 65.1, 64.3, 62.9, 58.6, 57.4, 32.7, 32.4, 28.3, 25.9, 25.8, 24.0, 23.9; HRMS (ESI-TOF) calcd for $C_{15}H_{26}NO_6$ $(M+1)^+$ *m*/*z* 316.1760, found *m*/*z* 316.1746.

Compound 27. To a MeOH (2.5 mL) solution of compound **26** (0.035 g, 0.11 mmol) was added 2.5 mL of 6 N aq HCl then the reaction mixture was stirred for 12 h at rt. All volatiles were removed in vacuo to afford **27** (0.019 g) as its hydrochloride salt in 80% yield: R_f 0.48 (2:1 CH_2Cl_2/MeOH); $[\alpha]^{25}_{D}$ −17.0 (*c* 1.00, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 4.41 (dd, *J* = 9.8, 6.5 Hz, 2H), 4.14 (t, *J* = 3.6 Hz, 1H), 3.89 (d, *J* = 2.9 Hz, 2H), 3.67 (ddd, *J* = 11.4, 5.8, 3.7 Hz, 1H), 2.11−2.04 (m, 1H), 1.97−1.87 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 73.0, 70.2, 70.1, 68.6, 64.9, 64.7, 31.7; HRMS (ESI-TOF) calcd for $C_7H_{14}NO_4$ $(M + 1)^+$ *m*/*z* 176.0923, found *m*/*z* 176.0927.

(3a*S*,4*S*,6*R*,6a*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5(4*H*)-ol (28). To a stirred solution of nitrone **19** (8 g, 31.1 mmol) in THF (180 mL) was slowly added a 1 M solution of vinyl magnesium bromide in THF (93 mL, 93.3 mmol) under nitrogen atmosphere at 0 °C. After stirring at 0 °C for 4 h, 30 mL of saturated aqueous $NaHCO_3$ was added. The precipitate was filtered and the mixture extracted with diethyl ether (3×40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated in vacuo, and purified by silica gel column chromatography (12% ethyl acetate in hexanes) to afford the hydroxylamine **28** (8.01 g) as a pale yellow solid in 91% yield: R_f 0.63 (30% ethyl acetate in hexanes); mp 72−74 °C; $[\alpha]^{25}_{D}$ 2.4 (*c* 1.00, $CHCl_3$); IR (KBr) 3428, 3084, 2987, 2933, 1792, 1705, 1643, 1449, 1377, 1257, 1213, 1156, 1077, 922, 858, 757, 515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 17.2, 10.3, 6.6 Hz, 1H), 5.32 (ddd, *J* = 17.2, 1.5, 1.1 Hz, 1H), 5.16 (ddd, *J* = 10.3, 1.5, 1.1 Hz, 1H), 4.34−4.27 (m, 2H), 4.17−4.07 (m, 2H), 3.90−3.83 (m, 1H), 3.63−3.58 (m, 1H), 3.18−3.14 (m, 1H), 1.99 (br s, 1H, OH), 1.53 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 119.2, 113.9, 109.9, 80.3, 76.4, 75.9, 74.2, 66.3, 27.3, 26.5, 25.2, 25.1; HRMS (ESI-TOF) calcd for $C_{14}H_{24}NO_5$ $(M + 1)^+$ *m*/*z* 286.1654, found *m*/*z* 286.1657.

(3a*S*,4*S*,6*R*,6a*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole (29). To a stirred solution of hydroxylamine **28** (3.5 g 12.2 mmol) in MeOH (145 mL) were added a saturated solution of NH_4Cl (216 mL), powdered Zn (3.2 g, 48.9 mmol), and a catalytic amount of indium dust (0.024 g, 0.2 mmol) at 20 °C. The mixture was refluxed overnight. Then the solvent was evaporated in vacuo and a saturated aqueous solution of Na_2CO_3 (100 mL) was added. The mixture was extracted with diethyl ether (3 × 50 mL). The combined layers were washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (30% ethyl acetate in hexanes) to afford pyrrolidine **29** (4.84 g) in 72% yield as a brownish liquid: R_f 0.50 (50% ethyl acetate in hexanes); $[\alpha]^{25}_{D}$ 6.2 (*c* 1.00, $CHCl_3$); IR (neat) 3342, 3082, 2987, 2931, 1644, 1448, 1377, 1258, 1213, 1156, 1074, 923, 859, 757, 515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.6, 10.6, 7.6 Hz, 1H), 5.40 (ddd, *J* = 17.2, 2.6, 1.5 Hz, 1H), 5.35 (br s, 1H, NH), 5.29 (ddd, *J* = 10.3, 1.5, 0.7 Hz, 1H), 4.36 (dd, *J* = 11.7, 6.6 Hz, 1H), 4.29−4.20

(m, 2H), 4.10 (dd, J = 8.8, 6.6 Hz, 1H), 3.95 (dd, J = 8.8, 5.5 Hz, 1H), 3.43 (t, J = 6.9 Hz, 1H), 3.13 (dd. J = 6.2, 4.7 Hz, 1H), 1.54 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 137.6, 116.6, 114.3, 109.4, 85.0, 81.7, 77.6, 66.6, 66.5, 66.3, 27.3, 26.7, 25.3, 25.2; HRMS (ESI-TOF) calcd for $C_{14}H_{24}NO_4$ (M + 1)$^+$ *m*/*z* 270.1705, found *m*/*z* 270.1716.

(3a*S*,4*S*,6*R*,6a*R*)-*tert*-Butyl 4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (30). To a solution of pyrrolidine **29** (4.84 g, 17.97 mmol) in CH$_2$Cl$_2$ (88 mL) at 0 °C was added Et$_3$N (9 mL, 64.7 mmol) then the mixture was stirred for 30 min at 0 °C. After 30 min, a solution of Boc$_2$O (5.8 g, 27 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added dropwise. The resulting reaction mixture was then allowed to warm to ambient temperature and stirred for an additional 24 h. The mixture was then treated with 1 N aqueous KHSO$_4$ (20 mL). The organic layer was separated and washed with 1 N aqueous KHSO$_4$, saturated aqueous NaHCO$_3$, and brine, dried (Na$_2$SO$_4$), and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (6% ethyl acetate in hexanes) to afford **30** (5.84 g) in 88% yield as a brownish liquid: R_f 0.64 (2:1 hexanes/ethyl acetate); $[\alpha]^{25}{}_{D}$ 91.5 (*c* 1, CHCl$_3$); IR (neat) 3082, 2985, 2937, 1694, 1479, 1457, 1382, 1242, 1174, 1128, 1050, 968, 922, 884, 859, 738, 514 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.92 (ddd, J = 17.4, 10.4, 7.3 Hz, 1H), 5.24 (d, J = 16.5 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 4.66 (d, J = 5.5 Hz, 1H), 4.54 (dd, J = 5.5, 2.4 Hz, 1H), 4.43−4.33 (br m, 2H), 4.19 (br s, 1H), 3.97 (dd, J = 8.2, 5.8 Hz, 1H), 3.57 (t, J = 8.5 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 9H), 1.41 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.4, 137.6, 116.5, 111.9, 108.9, 85.3, 82.3, 80.5, 77.6, 69.0, 66.6, 63.4, 28.5, 27.6, 26.7, 25.8, 25.7; HRMS (ESI-TOF) calcd for $C_{19}H_{32}NO_6$ (M + 1)$^+$ *m*/*z* 370.2230, found *m*/*z* 370.2225.

(3a*S*,4*S*,6*R*,6a*R*)-*tert*-Butyl 4-((*S*)-1,2-Dihydroxyethyl)-2,2-dimethyl-6-vinyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (31). The diacetonide **30** (5.82 g, 15.7 mmol) was taken in 95 mL of 60% AcOH in water then the mixture was stirred for 24 h at rt. Next toluene (3 × 20 mL) was successively added and evaporated in vacuo to remove traces of water and acetic acid. The crude diol was purified by silica gel column chromatography (30% ethyl acetate in hexanes) to afford the diol **31** (3.18 g) in 61% yield as a crystalline solid: R_f 0.41 (50% ethyl acetate in hexanes); mp 76 °C; $[\alpha]^{25}{}_{D}$ 61.0 (*c* 1.00, CHCl$_3$); IR (KBr) 3349, 2937, 2985, 2958, 1657, 1598, 1410, 1367, 1243, 1213, 1171, 1135, 1020, 905, 771 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.94 (ddd, J = 16.8, 10.3, 5.8 Hz, 1H), 5.30−5.26 (m, 1H), 5.19 (ddd, J = 10.6, 2.9, 1.5 Hz, 1H), 4.65 (d, J = 5.5 Hz, 1H), 4.57 (dd, J = 5.8, 2.2 Hz, 1H), 4.48−4.36 (br m, 2H), 4.13−3.99 (br m, 1H), 3.79−3.74 (m, 1H), 3.63−3.55 (m, 1H), 2.31 (d, J = 7.3 Hz, 1H, OH), 1.48 (s, 3H), 1.45 (s, 9H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.9, 137.1, 116.1, 111.4, 85.1, 82.5, 81.0, 77.3, 72.6, 69.1, 64.8, 63.0, 29.5, 28.1, 27.2, 25.2; HRMS (ESI-TOF) calcd for $C_{16}H_{27}NO_6Na$ (M + Na)$^+$ *m*/*z* 352.1736, found *m*/*z* 352.1739.

(3a*S*,4*R*,6*R*,6a*R*)-*tert*-Butyl 4-Formyl-2,2-dimethyl-6-vinyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (32). To a vigorously stirred suspension of silica supported NaIO$_4$ reagent (15 g) in CH$_2$Cl$_2$ (150 mL) was added a solution of vicinal diol **31** (1.86 g, 5.64 mmol) in CH$_2$Cl$_2$ (5 mL). The reaction was monitored by TLC until disappearance of the starting material (1 h). The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with CHCl$_3$ (3 × 20 mL). Evaporation of the solvent afforded the aldehyde **32** (1.59 g) as a colorless oil, which was used as such for the next step without further purification: R_f 0.58 (50%, ethyl acetate in hexanes); IR (neat) 3032, 2996, 1744, 1077 cm^{-1}.

(3a*S*,4*S*,6*R*,6a*R*)-*tert*-Butyl 4-(1-Hydroxyallyl)-2,2-dimethyl-6-vinyldihydro-3a*H* [1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (20). To a solution of aldehyde **32** (1.59 g, 5.34 mmol) in THF (46 mL) was added a 1 M solution of vinyl magnesium bromide in THF (16 mL, 16 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 24 h at rt. Then the reaction mixture was quenched with saturated NH$_4$Cl solution, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and filtered. The filtrate was then evaporated under reduced pressure and purified by silica gel column chromatography (14% ethyl acetate in hexanes) to afford allylic alcohol **20** (1.36 g) in 78% yield as an inseparable mixture of diastereomers: R_f 0.58 (2:1 hexanes/ethyl acetate); $[\alpha]^{25}{}_{D}$ 44.5 (*c* 1, CHCl$_3$); IR (neat) 3454, 3081, 2981, 2933, 1682, 1478, 1456, 1393, 1238, 1215, 1172, 1139, 1061, 991, 923, 871, 769, 515 cm^{-1}; (doubling of ^{1}H and ^{13}C NMR resonances due to Boc rotamers) ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.99−5.86 (m, 2H), 5.42−5.18 (m, 4H), 4.62 (dd, J = 14.6, 5.1 Hz, 1H), 4.52−4.47 (m, 3H), 4.17−4.14 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.8, 137.6, 137.3, 137.1, 116.4, 116.1, 115.9, 111.7, 111.5, 84.5, 84.1, 80.8, 80.3, 79.6, 77.2, 72.5, 68.9, 68.7, 67.6, 28.2, 28.1, 27.2, 27.1, 25.3, 25.2; HRMS (ESI-TOF) calcd for $C_{17}H_{27}NO_5Na$ (M + Na)$^+$ *m*/*z* 348.1787, found *m*/*z* 348.1770.

Compounds 33 and 34. To a stirred solution of diene **20** (0.5 g, 1.54 mmol) in 308 mL of CH$_2$Cl$_2$ was added Grubbs' (I) catalyst (0.130 g, 10 mol %). The solution turned yellow upon initial heating and then purple as the mixture was refluxed over 1.5 h. The reaction mixture was cooled to rt, DMSO (0.02 mL, 0.15 mmol) was added, and the mixture was stirred overnight at rt. Then solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (32% ethyl acetate in hexanes) to yield **33** (0.14 g, 31%) and **34** (0.24 g, 53%), respectively: Compound **33**: R_f 0.65 (2:1 ethyl acetate:hexanes); $[\alpha]^{25}{}_{D}$ −51.4 (*c* 1.00, CHCl$_3$); IR (neat) 3435, 2980, 2934, 2873, 1678, 1478, 1420, 1369, 1212, 1164, 1118, 1057, 874, 757 cm^{-1}; (doubling of ^{1}H and ^{13}C NMR resonances due to Boc rotamers) ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.95 and 5.89 (2ddd, J = 9.8, 5.2, 1.8 Hz, 1H), 5.62−5.56 (m, 1H), 4.99 (dd, J = 5.5, 4.3 Hz, 1H), 4.62−4.58 (m, 1H), 4.52 (d, J = 5.5 Hz, 1H), 4.44 (dd, J = 5.5, 1.3 Hz, 1H), 4.36 and 4.29 (2d, J = 5.2 and 5.5 Hz, 1H), 1.44 (s, 9H), 1.40 (s. 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.5, 154.1, 131.4, 130.9, 128.8, 127.8, 111.6, 111.5, 83.1, 82.8, 80.2, 79.8, 79.3, 77.2, 65.5, 65.4, 64.5, 63.6, 57.8, 56.6, 28.2, 28.0, 26.1, 24.3; HRMS (ESI-TOF) calcd for $C_{15}H_{24}NO_5$ (M + 1)$^+$ *m*/*z* 298.1654, found *m*/*z* 298.1660. Compound **34**: R_f 0.47 (2:1 ethyl acetate:hexanes); $[\alpha]^{25}{}_{D}$ 58.8 (*c* 1.00, CHCl$_3$); IR (neat) 3334, 3063, 3026, 2927, 2878, 1650, 1606, 1496, 1453, 1362, 1140, 1124, 1102, 1028, 986, 922, 864, 730, 693 cm^{-1}; (doubling of ^{1}H and ^{13}C NMR resonances due to Boc rotamers) ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.08 (ddd, J = 17.9, 9.5, 5.5 Hz, 1H), 5.78−5.69 (m, 1H), 4.65−4.39 (m, 4H), 3.8 (br s, 1H), 1.49 (s, 3H), 1.47 (s, 6H), 1.44 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 15.1, 154.6, 131.4, 130.3, 129.2, 128.4, 112.8, 112.7, 83.0, 82.9, 81.3, 81.1, 80.4, 80.2, 77.5, 77.3, 77.1, 76.7, 66.9, 66.5, 66.4, 65.1, 58.3, 56.8, 28.3, 26.1, 24.4, 24.3; HRMS (ESI-TOF) calcd for $C_{15}H_{23}NO_5Na$ (M + Na)$^+$ *m*/*z* 320.1474, found *m*/*z* 320.1462.

Compound 35. To a solution of compound **17** (0.27 g, 0.96 mmol) in MeOH (5 mL) was added 10% Pd−C (0.1 g) under H$_2$ atmosphere then the mixture was stirred for 24 h at rt. Next Pd−C was filtered through a short pad of Celite and washed with MeOH (3 × 20 mL) and the filtrate was evaporated under reduced pressure. Purification by a silica gel column chromatography (16% ethyl acetate in hexanes) afforded the reduced product **35** (0.25 g) in 92% yield as a white solid: R_f 0.54 (2:1 hexanes/ethyl acetate); mp 93−94 °C; IR (KBr) 2998, 2979, 2937, 1693, 1594, 1394, 1335, 1173, 1101, 856 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.27 (s, 2H), 4.14 (s, 2H), 1.73−1.25 (m, 21H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.2, 110.7, 82.8, 82.4, 79.1, 60.1, 58.9, 28.4, 27.0, 26.6, 26.0, 24.1, 18.1; HRMS

(ESI-TOF) calcd for $C_{15}H_{25}NO_4Na$ $(M + Na)^+$ *m*/*z* 306.1681, found *m*/*z* 306.1672.

(6*R*,7*S*)-8-Azabicyclo[3.2.1]octane-6,7-diol Hydrochloride (36). To a solution of compound **35** (0.22 g, 0.77 mmol) in MeOH (5 mL) was added 2.5 mL of 6 N aq HCl then the mixture was stirred for 12 h. Next solvent was removed under reduced pressure to afford compound **36** (0.138 g) in quantitative yield as its hydrochloride salt: ^{1}H NMR (400 MHz, D_2O) δ 4.42 (s, 2H), 3.88 (s, 2H), 1.86−1.84 (m, 4H), 1.69−1.65 (m, 1H), 1.42−1.35 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 74.4, 66.6, 28.1, 18.5; HRMS (ESI-TOF) calcd for $C_7H_{14}NO_2$ $(M + 1)^+$ *m*/*z* 144.1025, found *m*/*z* 144.1021.

Compound 37. To a solution of allylic alcohol **33** (0.27 g, 0.9 mmol) in MeOH (5 mL) was added 10% Pd−C (0.1 g) under H_2 atmosphere then the mixture was stirred for 24 h. Next Pd−C was filtered through a short pad of Celite and washed with MeOH (3 × 25 mL) and the filtrate was evaporated under reduced pressure to afford crude product. Purification over silica gel column chromatography (40% ethyl acetate in hexanes) afforded pure reduced product **37** (0.22 g) in 82% yield as crystalline solid: R_f 0.44 (2:1 ethyl acetate/hexanes); mp 58 °C; $[\alpha]^{25}_D$ −13.5 (*c* 1, $CHCl_3$); IR (neat) 3434, 2978, 2939, 2873, 1695, 1674, 1422, 1275, 1210, 1173, 1046, 984, 876, 762 cm^{-1}; (doubling of ^{1}H and ^{13}C NMR resonances due to Boc rotamers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (t, *J* = 5.5 Hz, 1H), 4.41 (t, *J* = 5.5 Hz, 1H), 4.25−4.21 (m, 1H), 4.11 (s, 1H), 3.78 (ddd, *J* = 16.2, 10.7, 4.6 Hz, 1H), 1.95−1.90 (m, 1H), 1.70−1.48 (m, 2H), 1.45 (s, 3H), 1.43 (s, 6H), 1.40 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 110.8, 110.7, 82.68, 82.3, 79.8, 79.6, 79.1, 78.6, 66.6, 65.9, 64.7, 63.8, 59.0, 57.8, 28.3, 27.4, 26.8, 26.0, 25.9, 25.5, 25.1, 24.03, 24.04; HRMS (ESI-TOF) calcd for $C_{15}H_{26}NO_5$ $(M + 1)^+$ *m*/*z* 300.1811, found *m*/*z* 300.1822.

(2*R*,6*R*,7*S*)-8-Azabicyclo[3.2.1]octane-2,6,7-triol Hydrochloride (38). To a solution of compound **37** (0.17 g, 0.57 mmol) in MeOH (5 mL) was added 2.5 mL of 6 N aq HCl then the mixture was stirred for 12 h at rt. Next solvent was removed in a rotary evaporator to afford aza-bridged polycyclitol **38** (0.11 g) as its hydrochloride salt in quantitative yield: $[\alpha]^{25}_D$ 8.0 (*c* 1, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 4.48 (d, *J* = 6.6 Hz, 1H), 4.33 (d, *J* = 6.6 Hz, 1H), 4.00 (ddd, *J* = 11.7, 5.8, 3.9 Hz, 1H), 3.88 (br s, 1H), 3.78−3.77 (m, 1H), 2.03−1.97 (m, 1H), 1.92−1.87 (m, 1H), 1.83−1.73 (m, 1H), 1.26−1.15 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 74.4, 70.5, 69.2, 67.3, 27.7, 25.2; HRMS (ESI-TOF) calcd for $C_7H_{14}NO_3$ $(M + 1)^+$ *m*/*z* 160.0974, found *m*/*z* 160.0981.

Compound 39. To a solution of compound **34** (0.24 g, 0.8 mmol) in MeOH (5 mL), was added 10% Pd−C (0.09 g) under H_2 atmosphere and the mixture was stirred for 24 h at rt. Then Pd−C was filtered through a short pad of Celite and washed with MeOH (3 × 25 mL) and the filtrate was evaporated under reduced pressure. Purification over silica gel column chromatography (40% ethyl acetate in hexanes) afforded the product **39** (0.205 g) in 86% yield: R_f 0.43 (2:1 ethyl actetate:hexanes); $[\alpha]^{25}_D$ −7.3 (*c* 1.00, $CHCl_3$); IR (neat) 3431, 2979, 2934, 1680, 1431, 1367, 1276, 1211, 1173, 1121, 1055, 1004, 864, 760 cm^{-1}; (doubling of ^{1}H and ^{13}C NMR resonances due to Boc rotamers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (t, *J* = 5.2 Hz, 1H), 4.43 (t, *J* = 5.5 Hz, 1H), 4.39 and 4.36 (2 br s, 1H), 4.28 and 4.20 (2 br s, 1H), 3.87and 3.79 (2 br s, 1H), 2.05−1.89 (m, 3H), 1.73−1.63 (m, 1H), 1.47 (S, 9H), 1.41 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 155.3, 111.2, 111.1, 82.0, 81.7, 80.6, 80.1, 79.9, 79.8, 77.1, 66.0, 65.6, 65.5, 63.8, 60.0, 58.7, 28.3, 28.2, 25.9, 25.8, 25.7, 25.5, 23.9, 23.8, 22.9, 22.8; HRMS (ESI-TOF) calcd for $C_{15}H_{26}NO_5$ $(M + 1)^+$ *m*/*z* 300.1811, found *m*/*z* 300.1819.

(2*S*,6*R*,7*S*)-8-Azabicyclo[3.2.1]octane-2,6,7-triol Hydrochloride (40). To a solution of compound **39** (0.16 g, 0.53 mmol) in MeOH (5 mL) was added 2.5 mL of 6 N aq HCl then the mixture was stirred for 12 h at rt. Next solvent was removed under reduced pressure to afford compound **40** (0.9 g) in 87% yield as its hydrochloride salt: $[\alpha]^{25}_D$ −7.6 (*c* 1, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 4.43 (d, *J* = 6.2 Hz, 1H), 4.36 (d, *J* = 6.6 Hz, 1H), 4.18 (br s, 1H), 3.88 (s, 1H), 3.78 (s, 1H), 2.10−2.04 (m, 1H), 1.78−1.74 (m, 1H), 1.69−1.65 (m, 1H), 1.59−1.56 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 73.6, 71.5, 70.5, 66.7, 66.5, 25.6, 24.1; HRMS (ESI-TOF) calcd for $C_7H_{14}NO_3$ $(M + 1)^+$ *m*/*z* 160.0974, found *m*/*z* 160.0967.

Compounds 41 and 42. To a solution of **34** (0.5 g, 1.68 mmol) in acetone (10 mL) and H_2O (7 mL) was added 4-methylmorpholine *N*-oxide (0.5 g, 3.69 mmol) followed by potassium osmate dihydrate (0.03 g, 0.081 mmol). The mixture was stirred at rt for 24 h and then all volatiles were evaporated in vacuo to give a dark oil. The TLC analysis showed formation of two products. Purification over silica gel column chromatography (80% ethyl acetate in hexanes) afforded 0.22 g of **42** (40%) and 0.28 g of **41** (50%). Compound **41**: R_f 0.20 (100% ethyl acetate); IR (neat) 3544, 3419, 2930, 1965, 1679, 1426, 1216, 1165, 1049, 912, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (dd, *J* = 3.7, 1.8 Hz, 1H), 4.49 (dd, *J* = 3.7, 1.8 Hz, 1H), 4.42 (s, 2H), 3.94 (br m, 1H), 3.80 (br m, 1H), 3.16 (t, *J* = 3.9 Hz, 1H), 1.48 (s, 9H), 1.42 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 112.1, 80.9, 79.8, 79.5, 69.3, 69.2, 65.9, 64.4, 62.9, 28.4, 26.0, 23.9; HRMS (ESI-TOF) calcd for $C_{15}H_{25}NO_7Na$ $(M + Na)^+$ *m*/*z* 354.1529, found *m*/*z* 354.1537. Compound **42**: R_f 0.33 (100% ethyl acetate); $[\alpha]^{25}_D$ −9.7 (*c* 1, MeOH); IR (neat) 3403, 2979, 2921, 2851, 1965, 1667, 1435, 1164, 1041, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, *J* = 5.5 Hz, OH), 4.87 (d, *J*=5.5 Hz, OH), 4.83 (d, *J* = 5.5 Hz, OH), 4.35 (br m, 1H), 4.27 (d, *J* = 4.0 Hz, 1H), 4.18 (d, *J* = 4.0 Hz, 1H), 4.06 (br m, 2H), 3.92−3.90 (m, 2H), 1.47 (s, 9H), 1.41 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.2, 156.9, 112.0, 81.5, 81.2, 81.1, 80.3, 80.0, 72.2, 67.2, 66.9, 65.9, 65.5, 64.6, 64.2, 28.8, 26.6, 24.4; HRMS (ESI-TOF) calcd for $C_{15}H_{25}NO_7Na$ $(M + Na)^+$ *m*/*z* 354.1529, found *m*/*z* 354.1534.

(2*R*,3*S*,4*S*,6*R*,7*S*)-8-Azabicyclo[3.2.1]octane-2,3,4,6,7-pentaol Hydrochloride (43). To a solution of compound **41** (0.18 g, 0.54 mmol) in MeOH (5 mL) was added 2.5 mL of 6 N aq HCl then the solution was stirred for 12 h at rt. Next solvent was removed in a rotary evaporator to afford aza-bridged polycyclitols **43** (0.12 g) in 98% yield as its hydrochloride salt: ^{1}H NMR (300 MHz, D_2O) δ 4.41 (br m, 2H), 4.17 (t, *J* = 3.2 Hz, 2H), 3.95 (d, *J* = 2.4 Hz, 2H), 3.52 (t, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 70.4, 69.8, 69.6, 65.6; HRMS (ESI-TOF) calcd for $C_7H_{14}NO_5$ $(M + 1)^+$ *m*/*z* 192.0872, found *m*/*z* 192.0869.

(2*R*,3*S*,4*R*,6*R*,7*S*)-8-Azabicyclo[3.2.1]octane-2,3,4,6,7-pentaol Hydrochloride (44). To a solution of compound **42** (0.11 g, 0.33 mmol) in MeOH (5 mL) was added 2.5 mL of 6 N aq HCl then the mixture was stirred for 12 h at rt. Next solvent was removed under reduced pressure to afford compound **44** (0.07 g) in 93% yield as a crystalline solid: $[\alpha]^{25}_D$ −17.1 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.75 (d, *J* = 2.5 Hz, 1H), 4.74 (d, *J* = 2.9 Hz, 1H), 4.15 (t, *J* = 2.9 Hz, 1H), 4.11 (t, *J* = 4.4 Hz, 1H), 3.89−3.87 (m, 1H), 3.84 (br m, 1H), 3.75 (br d, *J* = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 71.3, 70.4, 70.1, 69.7, 69.3, 68.3, 66.7; HRMS (ESI-TOF) calcd for $C_7H_{14}NO_5$ $(M+1)^+$ *m*/*z* 192.0872, found *m*/*z* 192.0872.

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