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One-Pot Synthesis of Cyclic Nitrones and Their Conversion to Pyrrolizidines: 7a-*epi*-Crotanecine Inhibits α-Mannosidases

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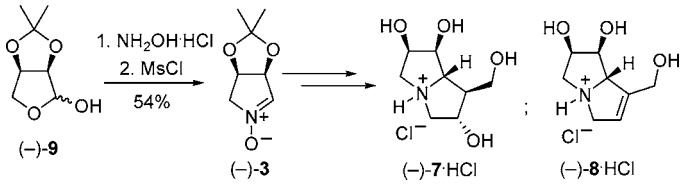

A new straightforward and inexpensive one-pot procedure is described for the preparation of enantiopure five-membered cyclic nitrones starting from the corresponding lactols. Its efficiency relies on the condensation of unprotected hydroxylamine with readily available lactols and on the chemoselectivity of the subsequent esterification with methanesulfonyl chloride. The targeted enantiomerically pure pyrroline *N*-oxides are versatile synthetic intermediates: one of the nitrones so-obtained has been converted into new polyhydroxypyrrolizidines, analogues of the alkaloids rosmarinecine and crotanecine, which were assayed for their inhibitory activities toward 22 commercially available glycosidase enzymes. One of them ((−)-7a-*epi*-crotanecine) is a potent and selective inhibitor of α-mannosidases from jack beans and almonds.

Introduction

Nitrones are useful synthetic intermediates as they undergo several synthetically useful reactions such as 1,3-dipolar cycloadditions,[1] nucleophilic additions,[1a,2] and pinacol-type coupling reactions.[3] Enantiomerically pure and polyfunctional cyclic nitrones such as **1**[4] and **2**,[5] derived from malic and tartaric acid, respectively, have found applications in the total, asymmetric synthesis of polyhydroxylated pyrrolidine, indolizidine, and pyrrolizidine alkaloids.[6] The latter compounds have shown interesting properties as glycosidase inhibitors[7] and as such are potential therapeutic agents.[8] Several glycosidase inhibitors are being currently tested or approved in the treatment of diabetes,[9]

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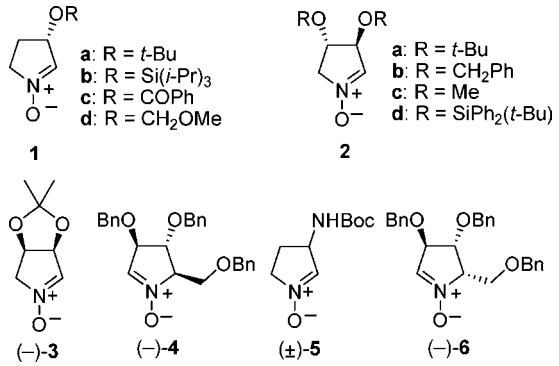
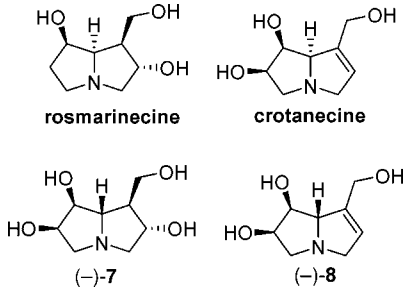
Gaucher's disease,[10] HIV infection,[11] viral infection,[12] or cancer.[13] Some of them have also been used as chemical probes, in combination with protein crystallography and kinetic studies, to provide new insights into glycosidase mechanisms.[14]



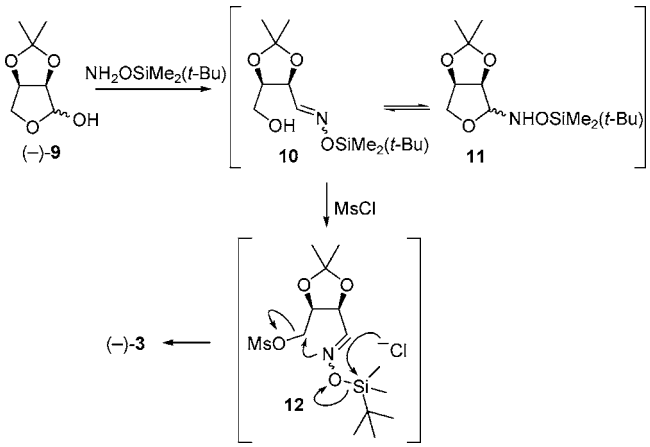
We describe, herein, efficient syntheses for the known cyclic nitrones (−)-**3** and (−)-**4** and for the yet unknown analogues (±)-**5** and (−)-**6**. Cycloaddition of (−)-**3** to dimethyl maleate has led us to prepare pyrrolizidinones. One of them has been converted into the new polyhydroxylated pyrrolizidines (−)-**7** and (−)-**8**, analogues of rosmarinecine and crotanecine, respectively. They have been tested as potential inhibitors toward 22 commercially available glycosidases. Interestingly, 7a-*epi*-crotanecine ((−)-**8**) has been found to be a potent and selective inhibitor of α-mannosidases from jack beans and almonds.



Results and Discussion

Racemic nitrone (±)-**3** has been obtained by Wightman and co-workers[6g] and by us[6a] through oxidation of the corresponding *meso*-pyrrolidine or *N*-hydroxypyrrolidine, respectively, derived from 2,3-*O*-isopropylidene-D-erythrose ((−)-**9**). Enantiomerically pure nitrone (−)-**3** was obtained by Closa and Wightman[15] according to a four-step process starting with (−)-**9**.[16] On our side, we reported that (−)-**3** can be derived from (−)-**9** in a one-pot process using $NH_2OSiMe_2(t\text{-Bu})$, as shown in Scheme 1.[17]

SCHEME 1



In the case of the preparation of enantiomerically pure (−)-**4**, we[18] first applied a similar approach to 2,3,5-*O*-tribenzyl-L-xylose and 2,3,5-*O*-tribenzyl-D-arabinose.[19,20] Both routes required three steps. As we shall show in this report, much more efficient one-pot processes have now been developed for the

(6) For leading references, see: (a) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633−3645 and references therein. (b) Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367−1369. (c) Cardona, F.; Goti, A.; Brandi, A. *Org. Lett.* **2003**, *5*, 1475−1478. (d) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235−4238. (e) Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem.* **2005**, *70*, 6552−6555. (f) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706−5707. (g) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429−9446. (h) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170−6172.

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(16) See also: Tamura, O.; Toyao, A.; Ishibashi, H. *Synlett* **2002**, 1344−1346.

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(18) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315−2318.

(19) Two other articles have then reported the preparation of (−)-**4** using similar procedures. From 2,3,5-*O*-tribenzyl-D-arabinose, see: (a) Carmona, A. T.; Wightman, R. H.; Robina, I.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 3066−3073. From 2,3,5-*O*-tribenzyl-L-xylose, see: (b) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459−1462.

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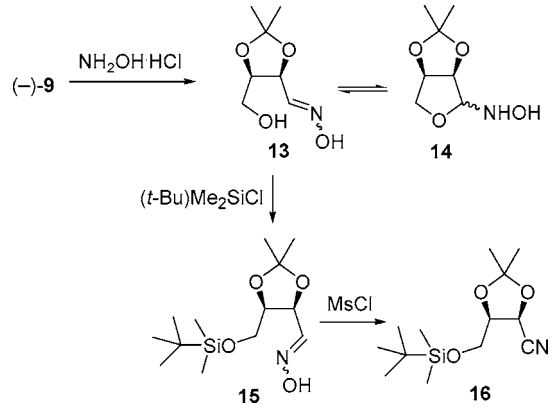
SCHEME 2



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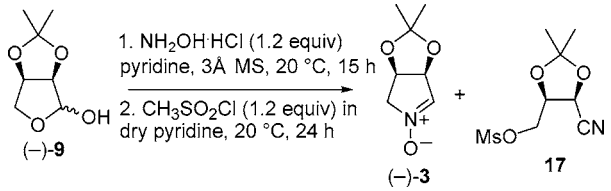
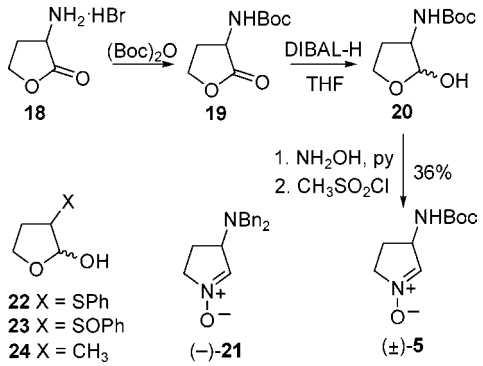


preparation of nitrones (−)-**3** and (−)-**4** and of the new analogues (±)-**5** and (−)-**6**.

In an exploratory study, we found that the reaction of lactol (−)-**9** with unprotected hydroxylamine·HCl generated the oxime **13**,[21] which reacted with (*t*-Bu)Me_2SiCl preferentially on the primary alcohol giving **15** (*Z*/*E* = 1:8). When the crude reaction mixture was treated with methanesulfonyl chloride, carbonitrile **16** was isolated as the main product (Scheme 2). These results suggested that esterification of **13** with a sulfonyl chloride might also occur preferentially at the primary alcohol moiety rather than at the oxime moiety. Indeed, the reaction of isolated oxime **13** with MsCl afforded nitrone (−)-**3**, but in a poor 25% yield. Unexpectedly, the same reaction was much more efficient when performed in a one-pot manner. When the crude mixture resulting from mixing (−)-**9** with NH_2OH·HCl in dry pyridine was reacted with CH_3SO_2Cl, (−)-**3** was obtained in a gratifying 54% yield, after purification by column chromatography on silica gel (Scheme 3). A secondary product was also isolated and identified as nitrile **17**.[21] Its amount could be limited by using only a slight excess of methanesulfonyl chloride (1.2 equiv), which was added rapidly to the reaction mixture as a solution in dry pyridine to avoid high local concentrations of CH_3SO_2Cl. The exchange of CH_3SO_2Cl for 2-nitrobenzenesulfonyl chloride and/or of pyridine for dichloromethane led to complex reaction mixtures. Attempts using stoichiometric amounts of bases were not met with more success.

To extend the scope of this one-pot procedure to the synthesis of other cyclic nitrones, we treated the racemic lactol **20**, (derived from lactone **18**,[22] Scheme 4) with NH_2OH·HCl and then with $MeSO_2Cl$ in pyridine. It led to nitrone (±)-**5**, which was isolated in 36% yield. Its structure was deduced from its ^1H and ^{13}C NMR spectra, which showed typical low field signals (δ_H 6.85 ppm, δ_C 135.0 ppm) for its sp^2-CH moiety. It is a close analogue of the already described nitrone (−)-**21**.[23]

SCHEME 4



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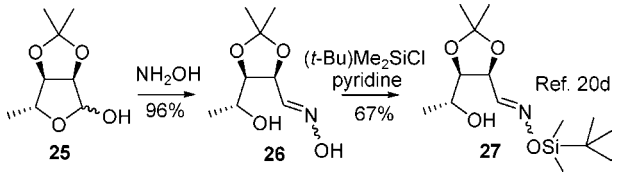

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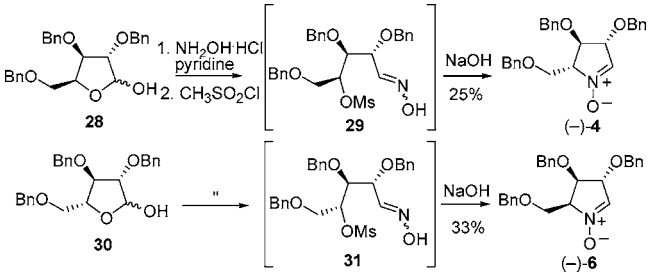

Unfortunately, when applied to lactols **22**−**24**, our one-pot method gave intractable mixtures of products.

The extension of our one-pot procedure to the synthesis of 5-substituted pyrroline *N*-oxides was not straightforward, as it was demonstrated in the case of oxime **26** derived from lactol **25** that its oxime moiety reacts with (*t*-Bu)Me_2SiCl in pyridine faster than its secondary alcohol moiety, giving selectively **27** (Scheme 5).[20d]

This did not impede us from running a reaction with lactol **28**, derived from L-xylose with NH_2OH·HCl first and then with CH_3SO_2Cl in pyridine. To our delight, after treatment of the crude reaction mixture so-obtained with aqueous NaOH at 0 °C,[24] nitrone (−)-**4** was isolated in 25% yield (Scheme 6) after column chromatography on silica gel. The same procedure applied to the D-arabinose derivative **30** produced nitrone (−)-**6** in 33% yield. Spectral data of (−)-**6** confirmed that it is the 5-epimer of (−)-**4**.[18,19]

Our previous, multistep synthesis of (−)-**4** from **28** gave yields ranging from 30 to 40%.[18,19] The moderate yields of the conversions of **28** and **30** to (−)-**4** and (−)-**6**, respectively, are balanced by the simplicity of the one-pot procedures and by the use of less-expensive reagents (NH_2OH instead of NH_2OSiR_3). Nitrone (−)-**4** is an important synthetic intermediate. It has been used in the syntheses of pyrrolizidine alkaloids such

(21) Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2377−2384.

(22) Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 379−385.

(23) Starting from L-aspartic acid, nitrone (−)-**21** had been obtained in a 12.6% overall yield after a much longer procedure; see ref 4c.

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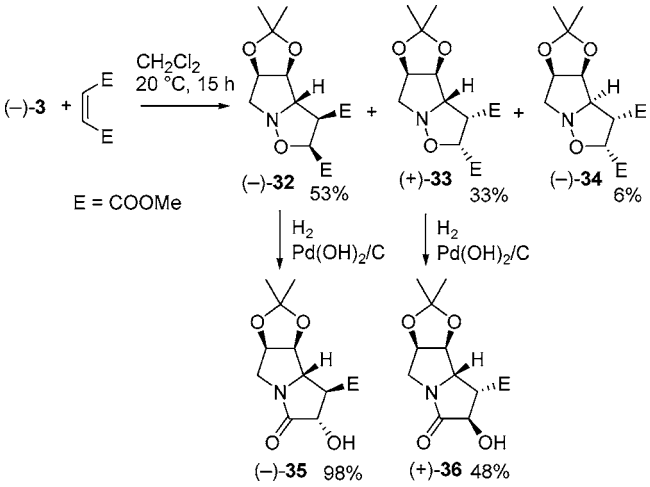
SCHEME 7



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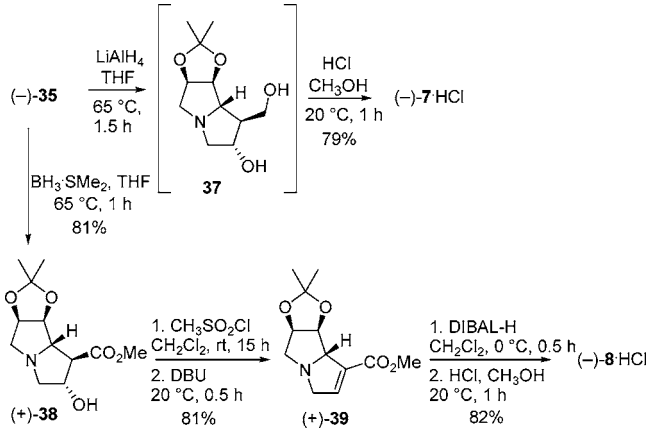


as hyacinthacine A_2.[18,19b] To illustrate further the usefulness of cyclic nitrones, we have converted (−)-**3** into rosmarinecine and crotanecine analogues.

The reaction of (−)-**3** with dimethyl maleate gave a 9.6:6:1 mixture of cycloadducts (−)-**32**, (+)-**33**, and (−)-**34**, which arise from anti-exo, anti-endo, and syn-exo approaches, respectively (Scheme 7). These products could be separated by column chromatography on silica gel. In the case of the reaction of racemic (±)-**3** with dimethyl maleate in benzene at room temperature for 1 d, the minor adduct (±)-**34** had not been detected.[6a] The structure of (−)-**34** was deduced from its spectral data. In particular, its ^{1}H NMR spectrum showed at δ_H 3.97 ppm a doublet of a doublet (J = 5.4, 2.2 Hz), typical of the bridgehead proton H-3a which is trans with respect to H-3 and cis with respect to H-4. The main cycloadducts (−)-**32** and (+)-**33** were converted into pyrrolizidinones (−)-**35** and (+)-**36**, respectively, upon hydrogenolysis in the presence of $Pd(OH)_2$ catalyst. The reduction of (−)-**32** and (+)-**33** with $Mo(CO)_6$/H_2O in acetonitrile[25] gave less satisfactory results.[6a]

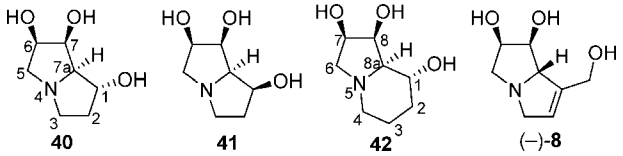
Pyrrolizidinone (−)-**35** has been converted (Scheme 8) into the new polyhydroxylated pyrrolizidines (−)-**7** ((6*R*)-hydroxy-7a-*epi*-rosmarinecine)[26] and (−)-**8**.[27−30] Treatment of (−)-**35** with $LiAlH_4$ in THF, followed by a workup with HCl in MeOH, provided the hydrochloride (−)-**7**·HCl in 79% yield (22% overall yield based on lactol (−)-**9**; 41% based on nitrone (−)-**3**). The selective reduction of lactam (−)-**35** with BH_3·SMe_2 in THF gave the β-hydroxyester (+)-**38** in 81% yield. After esterification of the alcohol (+)-**38** with methanesulfonyl chloride in CH_2Cl_2 and subsequent treatment with DBU at 20 °C, the α,β-unsaturated ester (+)-**39** was isolated in 81% yield. No alkene isomerization was observed under these conditions. The reduction of ester (+)-**39** with DIBAL-H ((*i*-Bu)$_2$AlH) in CH_2Cl_2, followed by a workup with HCl in MeOH, provided 7a-*epi*-crotanecine hydrochloride ((−)-**8**·HCl) in 82% yield (15% overall yield based on lactol (−)-**9**; 28% based on nitrone (−)-**3**).

TABLE 1. Inhibitory Activities of Pyrrolizidines (−)-7 and (−)-8[a]

enzyme	(−)-**7**·HCl	(−)-**8**·HCl
α-galactosidase from coffee beans	NI[b]	41
β-galactosidase from bovine liver	NI[b]	32
Amyloglucosidase from *Rhizopus* mold	NI[b]	23
β-glucosidase from almonds	NI[b]	33
α-mannosidase from jack beans	24	98
		IC_{50} = 7.4
α-mannosidase from almonds	NI[b]	99
		IC_{50} = 11.0

[a] Percentage of inhibition at 1 mM concentration, IC_{50} in μM, and optimal pH.[31] [b] NI = no inhibition.

The new analogues of pyrrolizidine alkaloids (−)-**7** and (−)-**8** were tested for their inhibitory activities toward 22 commercially available glycosidase enzymes.[31] At 1 mM concentration, compound (−)-**7** showed no significant inhibition of the tested glycosidases, apart from a weak inhibition of α-mannosidase from jack beans (Table 1). Compound (−)-**8** did not inhibit α-fucosidases from bovine epididymis and human placenta, α-galactosidase from *E. coli*, β-galactosidases from *E. coli*, *Aspergillus niger*, and *Aspergillus orizae*, α-glucosidases from yeast and rice, amyloglucosidase from *Aspergillus niger*, β-glucosidase from *caldocellum saccharolyticum*, β-mannosidase from *Helix pomatia*, β-xylosidase from *Aspergillus niger*, α-*N*-acetylgalactosaminidase from chicken liver, or β-*N*-acetylglucosaminidases from jack bean and bovine epididymis A and B. For six other enzymes, the results are shown in Table 1.



Data show that (−)-**8** is a selective inhibitor of α-mannosidases. Fleet and co-workers had shown that pyrrolizidines **40**

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(29) For the synthesis of crotanecine, see: (a) Yadav, V. K.; Rueger, H.; Benn, M. *Heterocycles* **1984**, *22*, 2735−2738. (b) See ref 21. (c) Bennett, R. B., III; Cha, J. K. *Tetrahedron Lett.* **1990**, *31*, 5337−5340. (d) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125−137.

and **41** that are "contracted" swainsonine analogues are very weak inhibitors of α-mannosidases (IC_{50} > 1000 μM).[30a] Swainsonine (**42**) inhibits α-mannosidases from jack beans and almonds with IC_{50} values of 0.2 and 0.4 μM, respectively.[7a] It is, thus, a surprise that (−)-**8** is only 1 order of magnitude less active than swainsonine toward these enzymes, although the structural changes between (−)-**8** and **42** appear to be more important than between **40** or **41** and **42**. The much higher inhibitory activity of (−)-**8** toward α-mannosidases compared with that of (−)-**7** is noteworthy. It suggests that other pyrrolidine and pyrrolizidine derivatives should be made because they might have interesting inhibitory activities toward α-mannosidases and/or other glycosidases. Unfortunately, the glycosidase inhibitory activities of crotanecine have not been reported yet. From the data available, it seems that the alkene moiety at C(2)−C(3) of (−)-**8** and its (7a*S*) configuration are crucial to render 1-hydroxymethylpyrrolizidines α-mannosidase inhibitors. Obviously, the 6*R*,7*S* configuration of the diol moiety at C(6,7) is also a requirement to make these systems capable of recognizing α-mannosidases. As simpler 3,4-dihydroxypyrrolidines have been found to inhibit the growth of cancer cells,[13c] derivatives of (−)-**8** and analogues should be prepared and assayed for their potential as antitumor agents.

Conclusions

In conclusion, we have developed and studied the scope of a novel variant for the formation of pyrroline *N*-oxides by intramolecular nucleophilic displacement, which is based on a simple one-pot procedure employing inexpensive hydroxylamine, methanesulfonyl chloride, and lactols. One cyclic nitrone obtained in this work has been used to prepare two new polyhydroxylated pyrrolizidines. One of them, (−)-**8**, is a good, selective inhibitor of α-mannosidases.

Experimental Section

The noncommercially available lactols, (−)-**9**,[32] 2-(*tert*-butoxycarbonylamino)-γ-butyrolactol (**20**),[22,33] 2,3,5-tri-*O*-benzyl-L-xylofuranose (**28**),[34] and 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**30**),[34] employed in this study were prepared according to published procedures.

General Procedure for the One-Pot Synthesis of Five-Membered Cyclic Nitrones (−)-3 and (±)-5. A 0.5 M solution of lactol (−)-**9** or (±)-**20** in dry pyridine (4 mL) was added with 3 Å molecular sieves (1.6 g) and hydroxylamine hydrochloride (1.2 equiv). The mixture was stirred overnight at room temperature, then a 0.6 M solution of methanesulfonyl chloride (1.2 equiv) in dry pyridine was added. The reaction mixture was stirred overnight at room temperature and then diluted with dichloromethane (4 mL), filtered through a Celite pad, concentrated, and purified by flash column chromatography (FCC).

(3*S*,4*R*)-3,4-Isopropylidenedioxypyrroline 1-Oxide ((−)-3). A 54% yield was obtained; spectroscopic and analytical data were in agreement with those previously reported.[17]

3-(*tert*-Butoxycarbonylamino)pyrroline *N*-Oxide ((±)-5). A colorless oil was obtained in a 36% yield (eluent, dichloromethane/ethyl acetate/methanol, 15:7:1; R_f = 0.13); ^{1}H NMR δ 6.85 (q, J = 1.8 Hz, 1H), 5.16 (m, 1H), 4.87 (br s, 1H), 4.71 (m, 1H), 3.92 (m, 1H), 2.70 (m, 1H), 2.02 (m, 1H), 1.44 (s, 9H); ^{13}C NMR δ 154.9 (s), 135.0 (d), 80.5 (s), 61.5 (t), 52.5 (d), 28.4 (t), 28.4 (3C, q). IR ($CHCl_3$) $\tilde{\nu}_{max}$ 3440, 3099, 1712, 1587, 1499, 1369 cm^{-1}. MS (%) *m*/z 144 (58), 127 (100), 115 (12), 84 (69), 57 (97). Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 53.68; H, 8.40; N, 14.15.

General Procedure for the Synthesis of Nitrones (−)-4 and (−)-6. A 0.5 M solution of lactol **28** or **30** in dry pyridine (2 mL) was added with 3 Å molecular sieves (800 mg) and hydroxylamine hydrochloride (1.2 equiv). The mixture was stirred overnight at room temperature, then a 0.6 M solution of methanesulfonyl chloride (1.2 equiv) in pyridine was added. The reaction mixture was stirred overnight at room temperature and then filtered through Celite. The filter was washed with dioxane (10 mL), and the collected solution was cooled at 0 °C. A cooled 2 M NaOH solution was added dropwise until pH = 10. The mixture was stirred at 0 °C for 2 h, maintaining the solution at pH > 9, then dioxane was removed in vacuo without heating. The solution was adjusted to pH = 7 by the dropwise addition of a cooled 2 M HCl solution. The resulting mixture was extracted with dichloromethane (3 × 50 mL). The collected organic phase was dried with Na_2SO_4, filtered, concentrated, and purified by FCC.

Nitrone (−)-4.[18,19] A white solid was obtained in a 25% yield (eluent, dichloromethane/ethyl acetate, 20:7; R_f = 0.40). Mp 92−93 °C. $[\alpha]^{19}_D$ −41.7 (*c* 1.00, $CHCl_3$) [lit.[19a] mp 88−90 °C, $[\alpha]^{20}_D$ −41.7 (*c* 1.00, $CHCl_3$); lit.[19b] mp 91−93 °C, $[\alpha]^{20}_D$ −42 (*c* 1.3, $CHCl_3$)]. ^{1}H NMR δ 7.38−7.26 (m, 15H), 6.91 (d, J = 1.9 Hz, 1H), 4.69−4.67 (m, 1H), 4.64−4.46 (m, 6H), 4.39 (dd, J = 3.2, 2.2 Hz, 1H), 4.10−4.04 (m, 2H), 3.78 (d, J = 7.3 Hz, 1H). ^{13}C NMR δ 137.7 (s), 137.2 (s), 137.1 (s), 132.9 (d), 128.6−127.7 (d, 15C), 82.7 (d), 80.3 (d), 77.4 (d), 73.9 (t), 71.9 (t), 71.6 (t), 66.1 (t). IR ($CHCl_3$) $\tilde{\nu}_{max}$ 3040, 2990, 2910, 1455, 1380, 1218 cm^{-1}. MS (%) *m*/z 285 (6), 234 (3), 132 (19), 91 (100), 77 (28). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.51; H, 6.78; N, 3.01.

Nitrone (−)-6. A dark yellow oil was obtained in a 33% yield; R_f = 0.38 (dichloromethane/ethyl acetate, 20:7). $[\alpha]^{23}_D$ −75.9 (*c* 0.54, CH_2Cl_2). ^{1}H NMR δ 7.40−7.20 (m, 15H), 6.80 (s, 1H), 4.72 (d, J = 2.9 Hz, 1H), 4.69−4.47 (m, 6H), 4.36 (dd, J = 7.7, 4.3 Hz, 1H), 4.16 (m, 1H), 3.98 (dd, J = 10.0, 4.3 Hz, 1H), 3.81 (dd, J = 10.0, 2.0 Hz, 1H).^{13}C NMR δ 137.8 (s), 137.2 (s), 137.1 (s), 133.7 (d), 128.5−127.5 (d, 15C), 83.1 (d), 80.5 (d), 74.0 (t), 73.5 (t), 73.1 (t), 72.4 (t), 64.3 (d). IR ($CHCl_3$) $\tilde{\nu}_{max}$ 3033, 2924, 2870, 1582, 1454, 1099 cm^{-1}. MS (%) *m*/z 326 (11), 218 (8), 181 (18),

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91 (100), 77 (20), 65 (27). FAB + 418. Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.91; H, 6.65; N, 3.57.

(6*R*)-Hydroxy-7a-*epi*-rosmarinecine Hydrochloride ((−)-7·HCl). A 1 M solution of $LiAlH_4$ in THF (1.5 mL) was slowly added to a solution of pyrrolizidinone (−)-**35** (135 mg, 0.5 mmol) in THF (5 mL) cooled to 0 °C. The mixture was heated at reflux for 1.5 h and then cooled to 0 °C. A saturated aq Na_2SO_4 solution was added to the stirred mixture. After filtration through Celite and washing with ethyl acetate, the solution was concentrated to give a solid residue that was directly dissolved in MeOH (5 mL). The resulting solution was treated at 0 °C with a 1 M HCl solution in MeOH (4 mL), stirred for 1 h at room temperature, and then concentrated in vacuo to give a pale yellow oil that was purified by crystallization from ethanol/ether to afford (−)-**7**·HCl as a white solid (75 mg, 79%). Mp 158−159 °C. $[\alpha]^{24}_D$ −23.1 (*c* 0.27, CH_3OH). ^{1}H NMR (D_2O, 400 MHz) δ 4.49−4.46 (m, 1H), 4.46−4.44 (m, 2H), 3.85 (dd, J = 7.0, 4.4 Hz, 1H), 3.72 (dd, J = 12.6, 2.2 Hz, 1H), 3.66 (dd, J = 13.0, 5.0 Hz, 1H), 3.63−3.56 (m, 2H), 3.50 (dd, J = 12.6, 3.3 Hz, 1H), 3.25 (dd, J = 13.0, 3.1 Hz, 1H), 2.51−2.46 (m, 1H). ^{13}C NMR (D_2O, 100 MHz) δ 76.3 (d), 72.8 (d), 70.4 (d), 69.8 (d), 59.4 (t), 59.3 (t), 58.5 (t), 50.4 (d). IR (KBr) $\tilde{\nu}_{max}$ 3483−3227 (br) cm^{-1}. MS (%) *m*/z 189 (1), 188 (2), 171 (9), 98 (50), 97 (100). Anal. Calcd for $C_8H_{16}NO_4Cl$: C, 42.58; H, 7.15; N, 6.21. Found: C, 42.49; H, 7.41; N, 5.96.

7a-*epi*-Crotanecine Hydrochloride ((−)-8·HCl). A 1 M solution of DIBAL-H (3.3 equiv) in dichloromethane was slowly added to a solution of (+)-**39** (120 mg, 0.5 mmol) in dichloromethane (5 mL) cooled to 0 °C. The reaction was stirred at 0 °C for 30 min and then quenched with methanol (2 mL). The suspension was diluted with CH_2Cl_2 (5 mL), and a saturated aq solution of sodium and potassium tartrate was added (1 mL). The mixture was stirred overnight and then quickly passed through a short pad of silica gel. The solution was concentrated to give a solid residue that was directly dissolved in MeOH (5 mL). The resulting solution was treated at 0 °C with a 1 M HCl solution in MeOH (2 mL), stirred for 1 h at room temperature, and then concentrated in vacuo to give a pale yellow oil, which was purified by crystallization from ethanol/ether to afford (−)-**8**·HCl (85 mg, 82%) as an extremely hygroscopic white solid. $[\alpha]^{23}_D$ −17.8 (*c* 0.04, CH_3OH). ^{1}H NMR (D_2O) δ 5.61 (br s, 1H), 4.87 (m, 1H), 4.32−4.22 (m, 3H), 4.17 (m, 2H), 3.82 (br d, J = 15.3 Hz, 1H), 3.68 (dd, J = 12.5, 2.2 Hz, 1H), 3.22 (dd, J = 12.5, 2.9 Hz, 1H). ^{13}C NMR (D_2O) δ 138.2 (s), 119.2 (d), 76.1 (d), 73.8 (d), 70.3 (d), 60.3 (t), 59.0 (t), 56.8 (t). MS (%) *m*/z 207 (M^+, 2), 172 (19), 112 (93), 94 (62), 82 (100), 80 (94), 69 (74). Anal. Calcd for $C_8H_{14}NO_3Cl·H_2O$: C, 42.58; H, 7.15; N, 6.21. Found: C, 42.34; H, 6.94; N, 6.54.

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Supporting Information Available: Experimental details, synthetic procedures, and characterization data for all newly synthesized compounds and ^{1}H and ^{13}C NMR spectra of compounds **5**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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