A Five-Membered Enantiopure Cyclic Nitrone from Malic Acid by Regioselective Oxidation of Cyclic Hydroxylamine. Synthesis of (1S,7S,8aR)-Octahydro-1,7-dihydroxyindolizine

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The chiral optically pure five-membered 3-*tert*-butoxy-1-pyrroline *N*-oxide (**1**) was synthesized by a convenient five-step procedure from diethyl L-malate. The key step is the regioselective HgO dehydrogenation of the *N*-hydroxypyrrolidine **6** obtained by double-nucleophilic displacement of a (bis)mesylate with hydroxylamine. A rationalization of the observed regioselectivity of the oxidation by studying the oxidation of a deuterated *N*-hydroxypyrrolidine **20** is reported. Nitrone **1** has been applied to the synthesis of a new (1*S*,7*S*,8a*R*)-1,7-dihydroxyindolizidine (**28**) via 1,3-dipolar cycloaddition strategies.

The construction of highly functionalized nitrogen heterocycles in a stereoselective manner is an important focus of medicinal and natural product chemistry. In particular, substituted pyrrolidines, pyrrolizidines, and indolizidines have seen much synthetic attention because of the important role of these ring systems in many natural compounds with physiological activity. The 1,3-dipolar cycloaddition of nitrones derived from pyrrolidine compounds to different dipolarophiles has been an essential transformation in the synthesis of these classes of compounds, providing the stereoselective formation of carbon–carbon bonds together with the selective introduction of useful functionalities.[1]

Recently, syntheses of 3,4-alkoxy-substituted pyrroline *N*-oxides from tartaric acid, performed by the Petrini[2] laboratory and by our[3] laboratory, have offered access to structurally differentiated nitrogen heterocycles containing a pyrrolidine nucleus. Nucleophilic attack of an organometallic reagent on a MOM-protected nitrone was the basis of a straightforward synthesis of antibiotic anisomycin,[2] and the methylenecyclopropane cycloaddition–rearrangement process[4] with a TBDPS-protected nitrone permitted the first synthesis of enantiopure lentiginosine, a selective amyloglucosidase inhibitor.[1h]

We now report the synthesis and synthetic applications of novel, optically pure pyrroline *N*-oxide **1**, derived from L-malic acid.

Results and Discussion

For the synthesis of nitrone **1**, the strategy previously applied to tartaric acid derived nitrones protected with the *tert*-butyl groups was chosen.[3] The key *tert*-butoxyhydroxylamine **6** was obtained in high overall yield (45%) in four steps, consisting of the protection of the L-malate with 2-methylpropene, reduction with lithium aluminum hydride, mesylation, and cyclization of the (bis)mesylate **5** with hydroxylamine[5] (Scheme 1). It is worth noting that, in contrast to the previous synthesis of cyclic hydroxylamines from tartaric acid,[3] (bis)tosylates in this case gave more complex reaction mixtures and poor yields. The crucial step of the synthesis is the oxidation of the hydroxylamine **6**, which is able to afford two regioisomeric nitrones. By treatment with HgO in CH_2Cl_2, the two nitrones **1** and **7** were obtained with high 9:1 selectivity. The assignment of the structure to the two nitrones was easily made on the basis of the coupling pattern of the HC=N proton in the ^{1}H NMR spectra (δ 6.79, quartet, J = 1.8 Hz for **1**, and δ 6.83, multiplet for **7**).

The regioselectivity observed in the oxidation is essential to nitrone **1**'s synthetic utility and raises the question of its origin and its possible extension to other 3-substituted *N*-hydroxypyrrolidines. To study this aspect, we prepared 3-methyl- and 3-phenyl-*N*-hydroxypyrrolidine (**12** and **13**, respectively) using the same procedure (Scheme 2). When subjected to oxidation with HgO under the same conditions, both *N*-hydroxypyrrolidines **12** and **13** gave mixtures of two regioisomeric nitrones **14,15** and **16,17** in ratios of 1.8:1 and 2:1, respectively. The alkoxy group, and to a lesser extent an alkyl or aryl group, seems to steer the regioselectivity of the dehydrogenation.

To achieve better selectivity, we studied the dehydrogenation with other oxidants, such as Cu^{2+}/O_2 and TPAP/NMO.[6] The yields of recovered nitrone were generally lower than those from HgO, and, despite a slight increase of selectivity for oxidation of methyl-substituted *N*-hydroxypyrrolidine **12**, the choice of the oxidant did not affect the regioselectivity of the dehydrogenation. Therefore, the same mechanism for the dehydrogenation seems to operate in all of these cases. In contrast, oxidation of **6** by MCPBA gave a less clean reaction mixture, with a much poorer **1:7** ratio, based on the ^{1}H NMR spectrum

[⊗] Abstract published in *Advance ACS Abstracts*, June 15, 1995.

(1) For leading references on the use of pyrroline *N*-oxides 1,3-dipolar cycloadditions in natural product syntheses see: (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373. (c) Otomasu, H.; Takatsu, N.; Honda, T.; Kametani, T. *Tetrahedron* **1982**, *38*, 2627. (d) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1983**, 271. (e) Iida, H.; Watanabe, Y.; Kibayashi, C. *Chem. Lett.* **1983**, 1195. (f) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1265. (g) Brandi, A.; Cordero, F. M.; Querci, C. *J. Org. Chem.* **1989**, *54*, 1748. (h) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949.

(2) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316.

(3) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274.

(4) (a) Brandi, A.; Cordero, F. M.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1. (b) Brandi, A.; Dürüst, Y.; Cordero, F. M.; De Sarlo, F. *J. Org. Chem.* **1992**, *57*, 5666. (c) Brandi, A.; Cordero, F. M.; De Sarlo, F.; Gandolfi, R.; Rastelli, A.; Bagatti, M. *Tetrahedron* **1992**, *48*, 3323.

(5) Strasser, M.; Cooper, P.; Dewald, B.; Payne, T. *Helv. Chim. Acta* **1988**, *71*, 1156.

(6) Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571.

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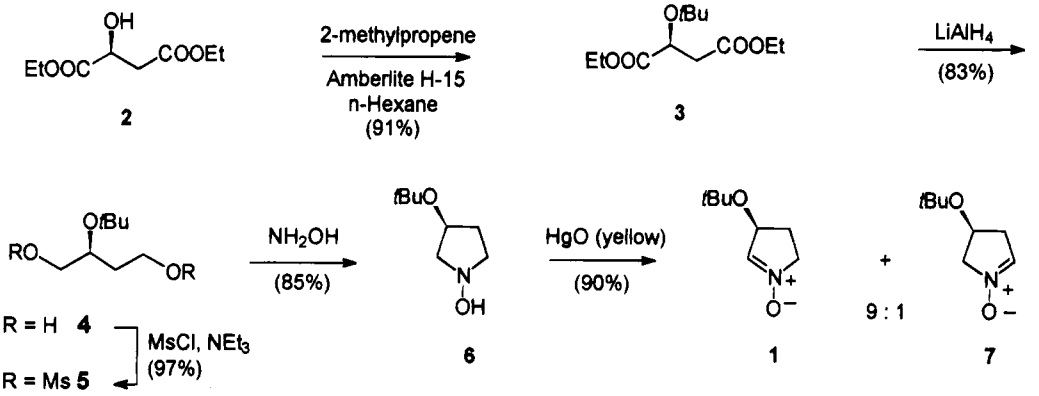
Scheme 1



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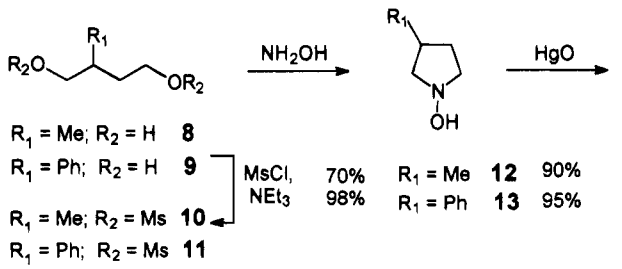
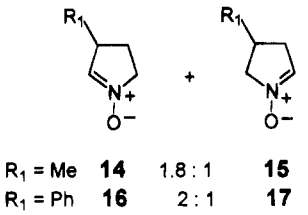
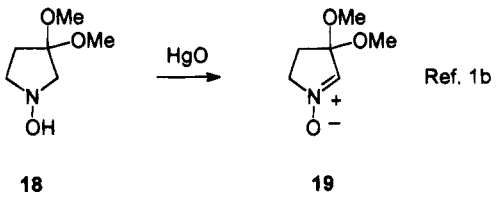
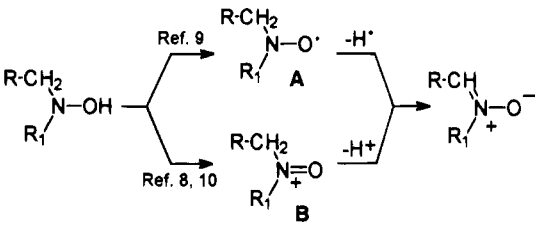




Scheme 3



Scheme 4



of the reaction mixture itself. The workup of the mixture resulted in a substantial increase of the isomeric ratio, but a loss of product.

The mechanism of the dehydrogenation of *N,N*-disubstituted hydroxylamines to nitrones has seen limited study, despite numerous reports on this reaction, and a clear-cut picture is lacking. Recently Carruthers[7] and Asrof Ali[8] studied the regioselectivity of the dehydrogenation of *N,N*-disubstituted hydroxylamines, but they used 2-substituted *N*-hydroxypyrrolidines or piperidines, where the formations of an aldonitrone and a ketonitrone compete. The only close example in the literature refers to the regioselective oxidation of hydroxylamine **18** to nitrone **19** (Scheme 3).[1b] Tufariello justifies the high selectivity observed in this case with "a diminution of eclipsing interactions, i.e. a more favorable dihedral angle relationship",[1b] which is difficult to transfer to our case,[1b] because steric effects alone cannot explain the different regioselectivities shown by hydroxylamines **6**, **12**, and **13**.

The dehydrogenation of *N,N*-disubstituted hydroxylamines is considered to be a two-step reaction. The first step is an oxidation of the −OH group; the second step is hydrogen abstraction from the α-carbon atom. Lacking detailed studies, two alternative mechanisms have been proposed for the first step, one involving a nitroxyl radical **A**,[9] derived from a hydrogen abstraction or a one-electron loss, and the second invoking a nitrosium ion **B**,[10,8] derived from the loss of a hydride equivalent (Scheme 4).

The formation of nitrosonium ion **B** is more consistent with our results and permits an explanation of the effect of the alkoxy group on the second step of the dehydrogenation. The polarization of the CH bond is the rate-determining step of the reaction and should be influenced by substituents on the 3-position of the cyclic hydroxylamine.[11] An electronegative substituent on C3 favors the C−H bond cleavage by stabilizing the incipient negative charge on C2. It follows that the proton *anti* to the alkoxy group is the one kinetically removed by the base. To prove this hypothesis, we synthesized C2 deuterated hydroxylamine **20** by reduction of nitrone **1** with lithium aluminum deuteride (Scheme 5).

The assignment of structure **20** with deuterium *anti* to the *tert*-butoxy group derives from the preferred attack of the deuteride on the face of the nitrone opposite the *tert*-butoxy group and has been confirmed unequivocally by comparison of the ^{1}H NMR spectrum with that of hydroxylamine **6**. In compound **20**, there is no signal corresponding to the most deshielded proton on the C2 methylene of **6** (at δ 3.24) which has a *cis* relationship

(7) (a) Carruthers, W.; Coggins, P.; Weston, J. B. *J. Chem. Soc., Chem. Commun.* **1990**, 91. (b) Carruthers, W.; Coggins, P.; Weston, J. B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2323.

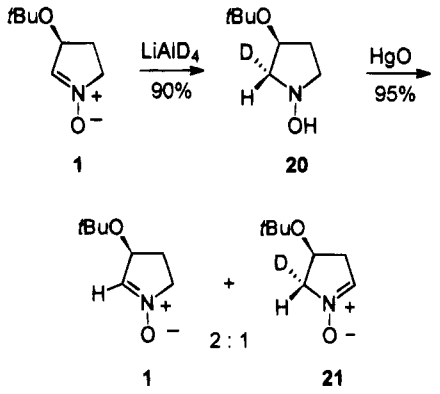
(8) (a) Asrof Ali, Sk.; Wazeer, M. I. M. *Tetrahedron Lett.* **1992**, *33*, 3219. (b) Asrof Ali, Sk. *Tetrahedron Lett.* **1993**, *34*, 5325. (c) Asrof Ali, Sk. *J. Chem. Res. (M)* **1994**, 301.

(9) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988; p 88 and references cited therein.

(10) LeBel, N. A.; Post, M. E.; Hwang, D. *J. Org. Chem.* **1979**, *44*, 1819.

(11) (a) Thesing, J.; Mayer, H. *Chem. Ber.* **1957**, *90*, 46. (b) Thesing, J.; Sirrenberg, W. *Chem. Ber.* **1959**, *92*, 1748.

Scheme 5



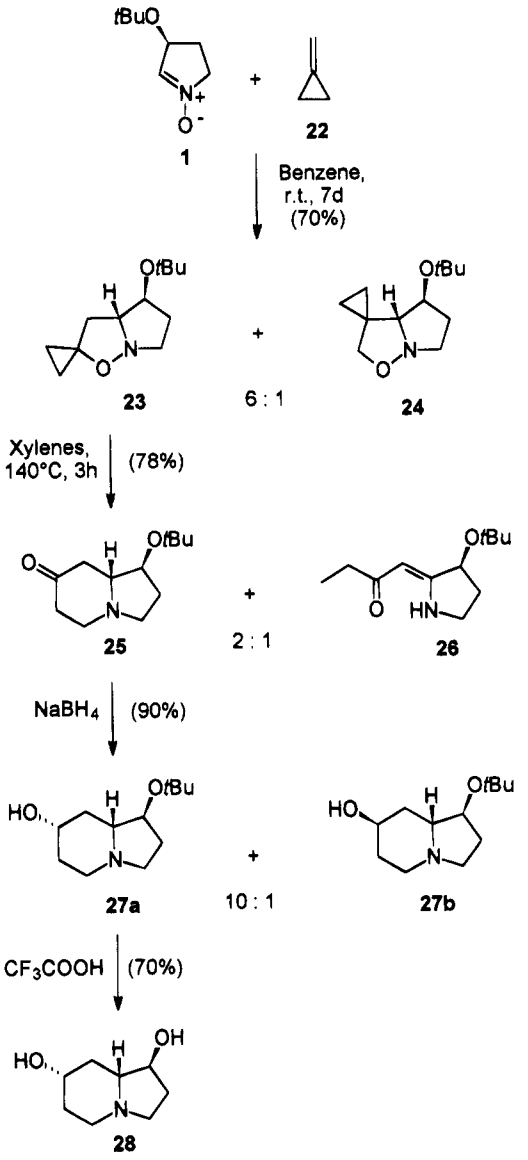
(J = 7 Hz) to the C3 proton. Dehydrogenation of the hydroxylamine **20** with HgO again gives a mixture of regioisomeric nitrones **1** and **21**, but with only 2:1 selectivity. This result indicates that the deuterium is selectively abstracted to give nitrone **1**, because it is *anti* to the *tert*-butoxy group, but a deuterium primary kinetic isotopic effect, lowering its rate of abstraction, favors abstraction of protons from the C5 methylene, reducing the selectivity from 9:1 to 2:1.

We can, then, conclude that the regioselectivity observed in the dehydrogenation of hydroxylamine **6** with HgO arises from a kinetic preference for the cleavage of the C−H bond *anti* to the *tert*-butoxy group, caused by a possible $\sigma_{C-H}-\sigma^*_{C-O}$ interaction that polarizes specifically the *anti* C−H bond α to nitrogen. This explanation is in agreement with the result of Tufariello,[1b] in that when two alkoxy groups are present at the 3-position, a doubling of the effect should be expected. The poor regioselectivity observed with hydroxylamines **12** and **13** can be, conversely, explained by the lack of any strong stabilization of the negative charge and by steric effects present at the transition state.[1b,11,12]

During our synthetic studies of natural and unnatural polyhydroxyindolizidines,[13,1h] potential inhibitors of glycosidases, we utilized the nitrone **1** for the synthesis of a new (1S,7S,8aR)-1,7-dihydroxyindolizidine (**28**) via the cycloaddition to methylenecyclopropane and thermal rearrangement of 5-spirocyclopropane isoxazolidine.[4]

The cycloaddition of nitrone **1** to methylenecyclopropane **22**, at room temperature for 7 days, gave a mixture of two regioisomers **23** and **24** in 70% yield and a 6:1 ratio.[4c] The assignment of the structures was easily made by ^{1}H NMR spectroscopy. The regioisomer **24** showed the diagnostic AB system at δ 3.59 and 3.80 (J = 7.6 Hz) for the C5 methylene protons (isoxazolidine numberings). Both regioisomers **23** and **24** derived from a highly preferred approach of the methylenecyclopropane *anti* to the *tert*-butoxy group at the transition state. The thermal rearrangement of **23** in xylene at reflux temperature afforded the indolizidinone **25** and the open-chain isomer[4] **26** in a 2:1 ratio and 78% yield. Reduction of **25** with $NaBH_4$ gave selectively the two monoprotected diols **27a** and **27b** in a 10:1 ratio and 90% yield. The major isomer **27a** has been assigned as the 7α-OH isomer

Scheme 6



on the basis of the ^{1}H NMR spectrum. The C7 proton resonates at δ 3.71 as a triplet of triplets, while the minor isomer **27b** shows, for the same proton, a more deshielded quintuplet (δ 4.16, J = 3 Hz). This is in agreement with previous literature data on analogous compounds.[14,1g] Product **27a** derives from the preferred axial attack of the hydride on the *trans*-fused indolizidinone **25**. The alcohol **27a** was, then, deprotected by treatment with CF_3COOH to obtain the diol **28** (Scheme 6).[15]

As a confirmation of the structure of alcohol **27a**, the same compound was obtained by a different cycloaddition strategy that affords the alcohol **27a** stereoselectively. The cycloaddition of nitrone **1** to 3-buten-1-ol (**29**) gives two diastereomeric pairs **30a** and **30b** in an 8:1 ratio (Scheme 7). As a consequence of the high exoselectivity of the cycloaddition,[16,1g] the two isomers were assigned as those derived from the approach to the two diastereo-

(12) After the completion of the present work, alternative syntheses of OTBDMS-substituted nitrones with *R* configuration analogous to **1** and **7** have appeared: Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170. The nitrone related to **1** has been obtained with a lower regioisomeric ratio (6.8:1) by oxidation of the corresponding pyrrolidine with H_2O_2/Na_2WO_4.

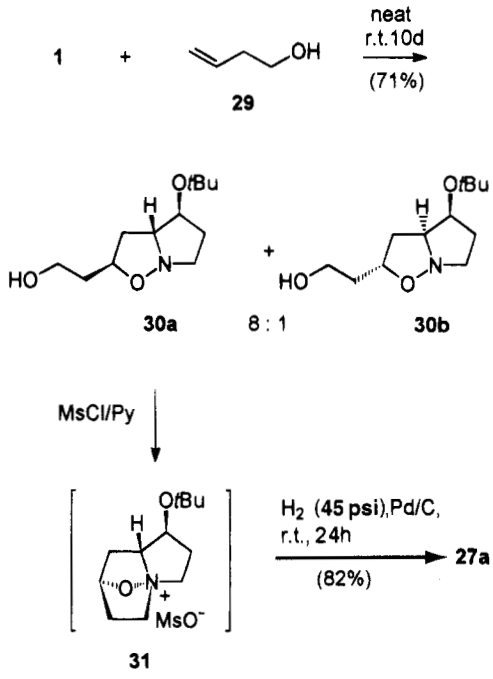
(13) Cossy, J.; Vogel, P. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1993; Vol. 12, p 275.

(14) (a) Rader, P. C.; Young, L. R.; Aaron, H. S. *J. Org. Chem.* **1965**, *30*, 1536. (b) Aaron, H. S.; Rader, P. C.; Wicks, G. E. *J. Org. Chem.* **1966**, *31*, 3502.

(15) For the synthesis of a diastereomeric racemic (1S*,7R*,8aS*)-octahydro-1,7-dihydroxyindolizine see: Maggini, M.; Prato, M.; Ranelli, M.; Scorrano, G. *Tetrahedron Lett.* **1992**, *33*, 6537.

(16) McCaig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939.

Scheme 7



faces of the nitrone, with the approach *syn* to the *tert*-butoxy group being disfavored. The cycloaddition with olefin **29** occurs, therefore, with less diastereoselectivity but with more regioselectivity than with methylenecyclopropane **22**.

The major isomer **30a** has a configuration at the C5 carbon (isoxazolidine numbering) identical to that of alcohol **27a**. The formation of the indolizidine ring was achieved by mesylation of the alcohol with spontaneous cyclization to the isoxazolidinium salt **31**.[17] Reductive cleavage of the N–O bond with H_2/Pd on carbon afforded the monoprotected indolizidinediol identical to **27a**.

The new indolizidinediol **28** will be biologically evaluated against glycosidases, considering that hydroxylated positions 1 and 7 in indolizidines play a crucial role in biological activity.[18] Further work is currently in progress to extend the use of nitrone **1** and its enantiomer to the synthesis of other natural and unnatural bioactive compounds.[19]

Experimental Section

All of the reactions were run under nitrogen atmosphere using anhydrous solvents. ^{1}H and ^{13}C NMR ($CDCl_3$, unless otherwise stated) spectra were recorded at 200 and 50 MHz, respectively. The coupling constants J are given in hertz. IR spectra were recorded in $CHCl_3$ solutions, unless otherwise stated. Mass spectra (MS) were recorded by GC inlet (70 eV).

Diethyl (2*S*)-*O*-*tert*-Butylmalate (3). 2-Methylpropene was bubbled through a suspension of diethyl malate (20.0 g, 0.11 mol) and Amberlite H-15 (4.0 g) in 200 mL of hexane for 6 h. The suspension was then filtered and 200 mg of K_2CO_3 added to the solution. The solution was washed with water, dried over Na_2SO_4, and concentrated. The residue was distilled (4×10^{-2} mbar, 110 °C) to give 24.5 g (91% yield) of **3**: $[\alpha]^{25}_D$ −38.9 (*c* 2.07, CH_2Cl_2); ^{1}H NMR δ 4.44 (dd, J = 7.4, 5.9, 1H), 4.47–4.09 (m, 4H), 2.67–2.62 (m, 2H), 1.26 (t, J = 7.0, 3H), 1.25 (t, J = 7.3, 3H), 1.18 (s, 9H); ^{13}C NMR δ 173.1 (s), 170.2 (s), 75.5 (s), 68.5 (d), 61.0 (t), 60.7 (t), 39.4 (t), 27.7 (q, 3C), 14.1 (q), 14.0 (q). Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found C, 58.70; H, 9.10.

(2*S*)-2-*tert*-Butoxy-1,4-butanediol (4). A solution of diethyl (2*S*)-*O*-*tert*-butylmalate (**3**) (22.4 g, 91 mmol) in ether (100 mL) was added dropwise to a suspension of $LiAlH_4$ (8.15 g, 215 mmol) in ether (300 mL). The suspension was refluxed for 6 h and then cooled in an ice bath. Saturated Na_2SO_4 solution (80 mL) was added dropwise, and the suspension was filtered and concentrated. The residue was distilled (7×10^{-2} mbar, 100 °C) to give 12.0 g (83% yield) of **4**: $[\alpha]^{25}_D$ +1.4 (*c* 1.37, CH_2Cl_2); ^{1}H NMR δ 3.86 (q, J = 5.0, 1H), 3.91–3.74 (m, 2H), 3.61–3.56 (m, 2H), 2.70 (s, 1H), 2.24 (s, 1H), 1.82 (q, J = 5.5, 2H), 1.23 (s, 9H); ^{13}C NMR δ 74.6 (s), 70.1 (t), 65.3 (t), 59.6 (d), 35.7 (t), 28.4 (q, 3C); IR 3510, 2976, 1463, 1366, 1186, 1061 cm^{-1}. Anal. Calcd for $C_8H_{18}O_3$: C, 59.21; H, 11.19. Found: C, 58.77; H, 11.52.

Synthesis of 2-Substituted-1,4-bis[(methylsulfonyloxy)]butanes. General Procedure. Methanesulfonyl chloride (1.2 mL, 14.8 mmol) was added dropwise to an ice-cooled solution of the diol (6 mmol) and triethylamine (2.5 mL, 18 mmol) in CH_2Cl_2. The solution was stirred at rt for 15 min; ice was then added, and the organic phase was washed with 1 M HCl solution, saturated Na_2CO_3, and brine. The organic phase was dried with Na_2SO_4 and concentrated to give the crude product, sufficiently pure to be used for the next reaction. Pure compounds for combustion analysis were obtained by elution on a short pad of silica gel.

2-Methyl-1,4-bis[(methylsulfonyloxy)]butane (10): yield 70%; ^{1}H NMR δ 4.32 (m, 2H), 4.11 (m, 2H), 3.03 (s, 6H), 2.10 (m, 2H), 1.68 (m, 1H), 1.06 (d, J = 6.6, 3H); ^{13}C NMR δ 73.4 (t), 67.3 (t), 37.4 (q), 37.3 (q), 32.1 (d), 29.8 (t), 16.1 (q); IR 2960, 1355, 1170 cm^{-1}. Anal. Calcd for $C_7H_{16}O_6S_2$: C, 32.30; H, 6.20. Found: C, 32.60; H, 6.22.

2-Phenyl-1,4-bis[(methylsulfonyloxy)]butane (11): yield 84%; ^{1}H NMR δ 7.42–7.20 (m, 5H), 4.42–4.30 (m, 2H), 4.27–4.17 (m, 1H), 4.09–3.97 (m, 1H), 3.30–3.16 (m, 1H), 2.92 (s, 3H), 2.86 (s, 3H), 2.40–2.26 (m, 1H), 2.17–2.02 (m, 1H); ^{13}C NMR δ 138.8 (s), 129.6 (d, 2C), 128.4 (d, 3C), 73.2 (t), 67.7 (t), 42.1 (d), 37.8 (q, 2C), 31.7 (t); IR 3089, 3068, 2962, 1352, 1173 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_6S_2$: C, 44.71; H, 5.63. Found: C, 45.10; H, 5.34.

(2*S*)-2-*tert*-Butoxy-1,4-bis[(methylsulfonyloxy)]butane (5): yield 97%; mp 63 °C (absolute ethanol); $[\alpha]^{25}_D$ −15.4 (*c* 1.02, CH_2Cl_2); ^{1}H NMR δ 4.36 (m, 2H), 4.18 (m, 2H), 3.88 (m, 1H), 3.07 (s, 3H), 3.04 (s, 3H), 2.00 (m, 2H), 1.24 (s, 9H); ^{13}C NMR δ 75.0 (s), 71.6 (d), 66.1 (t), 65.3 (t), 37.6 (q), 37.3 (q), 32.7 (t), 28.2 (q, 3C). Anal. Calcd for $C_{10}H_{22}O_7S_2$: C, 37.72; H, 6.96. Found: C, 37.71; H, 7.13.

Synthesis of *N*-Hydroxypyrrolidines. General Procedure. A suspension of the dimesylates (3.16 mmol) and hydroxylamine hydrochloride (0.973 g, 14 mmol) in triethylamine (10 mL) was heated at reflux for 4 h. Triethylamine was then evaporated off, and the remaining white solid was washed with ether. The ethereal extracts were concentrated to give the *N*-hydroxypyrrolidines.

3-Methyl-*N*-hydroxypyrrolidine (12): yield 70%; ^{1}H NMR δ 3.30–3.00 (m, 3H), 2.45–2.20 (m, 1H), 2.15–1.95 (m, 1H), 1.50–1.20 (m, 2H), 1.18 (d, J = 6.6, 3H); ^{13}C NMR 65.9 (t), 30.1 (t), 21.8 (d), 20.2 (t), 14.8 (q). Repeated analyses gave unsatisfactory results, probably because of the volatility of the compound.

3-Phenyl-*N*-hydroxypyrrolidine (13): yield 98%; ^{1}H NMR δ 7.36–7.17 (m, 5H), 3.55–3.49 (m, 2H), 3.27 (t, J = 7.0, 2H), 3.03 (dd, J = 12.1, 9.1, 1H), 2.40 (m, 1H), 1.95 (m, 1H); ^{13}C NMR δ 144.7 (s), 129.1 (d, 2C), 127.8 (d, 2C), 126.8 (d), 66.8 (t), 59.8 (t), 42.4 (d), 32.4 (t); IR 3224, 3065, 2953, 1599, 1491, 1448, 1228 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.69; H, 8.29; N, 8.57.

(3*S*)-3-*tert*-Butoxy-*N*-hydroxypyrrolidine (6): yield 85%; $[\alpha]^{25}_D$ +1.7 (*c* 4.41, CH_2Cl_2); ^{1}H NMR δ 4.32 (m, 1H), 3.24 (dd, J = 12.0, 7.0, 1H), 3.22 (m, 1H) 3.00 (m, 1H), 2.89 (dd, J = 12.0, 5.0, 1H), 2.20 (m, 1H), 1.70 (m, 1H) 1.18 (s, 9H); ^{13}C NMR δ 73.5 (s), 69.8 (d), 66.2 (t), 57.6 (t), 32.3 (t), 28.3 (q, 3C); IR 3575, 3180, 2972, 1455, 1380, 1360, 1185 cm^{-1}. Anal. Calcd

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for $C_8H_{17}NO_2$: C, 60.32; H, 10.76; N, 8.83. Found: C, 60.11; H, 10.51; N, 8.46.

Synthesis of 2*H*-Pyrroline *N*-Oxides. General Procedure. Yellow mercury oxide (9 mmol) was added in portions to an ice-cooled solution of *N*-hydroxypyrrolidines (6 mmol) in CH_2Cl_2 (30 mL). The reaction was stirred for an additional 2 h. The solution was then filtered through Celite and concentrated. The nitrones were obtained with a high degree of purity as mixtures of regioisomers very difficult to separate. A simple elution through a short pad of silica gel gave pure compounds for combustion analysis.

3-Methyl-1-pyrroline *N*-Oxide (14) and 4-Methyl-1-pyrroline *N*-Oxide (15): yield 90%. Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.12. Found: C, 60.70; H, 9.30; N, 14.02. IR 2940, 1715, 1490, 1360, 1220 cm^{-1}. **14:** ^1H NMR δ 6.83 (q, J = 1.9, 1H), 4.02–3.90 (m, 2H), 3.13 (m, 1H), 2.46 (ddt, J = 14.3, 5.6, 8.9, 1H), 1.80 (dddd, J = 16.5, 9.5, 7.8, 6.0, 1H), 1.18 (d, J = 7.0, 3H); ^{13}C NMR δ 140.2 (d), 61.6 (t), 36.0 (d), 27.6 (t), 18.1 (q). **15:** ^1H NMR δ 6.88 (m, 1H), 4.08 (m, 1H), 3.60 (m, 1H), 2.90 (m, 1H), 2.71 (m, 1H), 2.32 (m, 1H), 1.18 (d, J = 7.0, 3H); ^{13}C NMR δ 136.2 (d), 68.3 (t), 36.6 (t), 21.4 (d), 19.7 (q).

3-Phenyl-1-pyrroline *N*-Oxide (16) and 4-Phenyl-1-pyrroline *N*-Oxide (17): yield 95%. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.25; H, 7.12; N, 8.30. IR 3046, 2946, 1728, 1447, 1331, 1246 cm^{-1}. **16**: ^1H NMR δ 7.41–7.18 (m, 5H), 6.96 (m, 1H), 4.28–4.05 (m, 2H), 3.25–3.13 (m, 1H), 2.86–2.68 (m, 2H); ^{13}C NMR δ (aromatic signals not reported) 137.8 (d), 62.7 (t), 47.8 (d), 30.4 (t). **17**: ^1H NMR δ 7.41–7.18 (m, 5H), 6.96 (m, 1H), 4.28–4.05 (m, 2H), 3.86–3.73 (m, 1H), 2.25–2.07 (m, 2H); ^{13}C NMR δ (aromatic signals not reported) 134.8 (d), 69.1 (t), 39.2 (d), 38.1 (t).

(3*S*)-*tert*-Butoxy-1-pyrroline *N*-Oxide (1): yield 90% (mixture of **1** and **7**); mp 70–72 °C; $[\alpha]^{25}_D$ −84.3 (*c* 1.35, CH_2Cl_2); ^1H NMR δ 6.79 (q, J = 1.8, 1H), 4.80 (m, 1H), 4.14–4.00 (m, 1H), 3.83 (m, 1H), 2.49 (dddd, J = 13.3, 9.6, 6.0, 3.8, 1H), 2.09 (dddd, J = 13.2, 9.4, 5.9, 3.7, 1H), 1.18 (s, 9H); ^{13}C NMR δ 135.6 (d), 74.5 (d), 71.2 (s), 61.0 (t), 29.9 (t), 28.0 (q, 3C); IR 3600, 3406, 2972, 1711, 1583, 1460, 1365, 1180, 1066 cm^{-1}. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.10; H, 9.61; N, 8.94. Found: C, 61.35; H, 9.35; N, 9.24.

(4*S*)-4-*tert*-Butoxy-1-pyrroline *N*-Oxide (7): ^1H NMR δ 6.83 (m, 1H), 4.49 (dq, J = 3.3, 7.0, 1H), 4.10 (m, 1H), 3.72 (m, 1H), 3.02 (m, 1H), 2.65 (m, 1H), 1.17 (s, 9H); ^{13}C NMR δ 133.4 (d), 71.2 (s), 69.1 (t), 65.3 (d), 38.9 (t), 28.1 (q, 3C).

Oxidation of Hydroxylamine 6 with Other Oxidizing Agents. Oxidation with Cu^{2+}/O_2. Air was bubbled for 2 h through a suspension of cupric acetate (18 mg, 0.1 mmol) and hydroxylamine **6** (200 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath. The suspension was concentrated. The ^1H NMR spectrum of the crude mixture revealed the presence of the two nitrones **1** and **7** in a 9:1 ratio. The residue was purified by passage through a short pad of silica gel (eluent CH_2Cl_2–CH_3OH 20:1) to give 158 mg (80% yield) of the mixture of the two nitrones as a white solid.

Oxidation with Tetra-*n*-propylammonium Perruthenate (TPAP)/*N*-Methyl-morpholine *N*-Oxide (NMO). A solution of TPAP (9 mg, 0.025 mmol), NMO (88 mg, 0.75 mmol), and hydroxylamine **6** (80 mg, 0.5 mmol) in 2.5 mL of acetonitrile was stirred in the presence of powdered 4 Å molecular sieves at rt for 4 days. The suspension was concentrated, and the residue was purified by passage through a short pad of silica gel (eluent ethyl acetate, then methanol) to give 63 mg (81% yield) of the two nitrones **1** and **7** in a 9:1 ratio.

Oxidation with *m*-Chloroperbenzoic Acid. A solution of MCPBA (255 mg, 1.3 mmol, 85% pure) in 2 mL of CH_2Cl_2 was added dropwise over a period of 0.5 h to a solution of hydroxylamine **6** (200 mg, 1.3 mmol) in 3 mL of CH_2Cl_2 cooled in an ice bath.

Workup A. The solution was washed with a saturated solution of $NaHCO_3$ and then brine. The organic phase was dried over Na_2SO_4 and concentrated to give 40 mg (20% yield) of impure nitrone **1**.

Workup B. The solution was concentrated, and a ^1H NMR spectrum of the residue revealed the presence of the two nitrones **1** and **7** in a 1.5:1 ratio. The residue was dissolved in 5 mL of CH_3OH, and Na_2CO_3 (160 mg, 1.5 mmol) was added. The suspension was stirred for 1 h and then concentrated, and the residue was washed with ether. The ether washings were concentrated to give 150 mg (76% yield) of an impure mixture of the two nitrones **1** and **7** in a 3:1 ratio.

Reduction of 1 with $LiAlD_4$. A solution of **1** (200 mg, 1.3 mmol) in 3 mL of ether was added dropwise to a suspension of $LiAlD_4$ (42 mg, 2 mmol) in 5 mL of ether. The suspension was refluxed for 6 h and then cooled with ice, and a saturated solution of Na_2SO_4 (1 mL) was added. The white precipitate was filtered off and the solution concentrated to afford 180 mg (90% yield) of a colorless oil.

(3*S*,2*R*) 2-Deuterio-3-*tert*-butoxy-*N*-hydroxypyrrolidine (20): ^1H NMR δ 6.2–5.4 (bs, 1H), 4.30 (m, 1H), 3.14 (m, 1H), 2.96 (ddd, J = 11.4, 7.7, 5.4, 1H), 2.79 (bd, J = 5.2, 1H), 2.20 (m, 1H), 1.70 (m, 1H), 1.14 (s, 9H); ^{13}C NMR δ 73.5 (s), 69.7 (d), 65.8 (d) (t, J_{C-D} = 21.6), 57.5 (t), 32.3 (t), 28.3 (q, 3C); IR 3580, 3183, 2972, 1461, 1388, 1363, 1185, 1076 cm^{-1}.

Dehydrogenation of Hydroxylamine 20. Dehydrogenation of hydroxylamine **20** with mercury oxide was carried out as previously reported. Two regioisomeric nitrones **1** and **21** were obtained in 2:1 ratio and 95% yield.

(4*S*,5*R*)-4-*tert*-Butoxy-5-deuterio-1-pyrroline *N*-Oxide (21): ^1H NMR δ 6.83 (m, 1H), 4.49 (m, 1H), 3.83 (m, 1H), 3.02 (ddt, J = 18.9, 7.7, 2.5, 1H), 2.65 (dd, J = 18.9, 1.2, 1H), 1.17 (s, 9H); ^{13}C NMR δ 133.4 (d), 71.2 (s), 69.1 (d) (t, J_{C-D} = 22.3), 65.3 (d), 38.9 (t), 28.1 (q, 3C).

Cycloaddition of 1 to Methylenecyclopropane (22). A solution of **1** (400 mg, 2.5 mmol) and methylenecyclopropane (1.450 g, 26 mmol) in benzene was stirred in a sealed tube for 7 days. The crude reaction mixture was purified by flash column chromatography (eluent petroleum ether–ethyl acetate 1:2) to afford 380 mg of a colorless oil (70% yield) as a mixture of 4- and 5-substituted isoxazolidines (R_f 0.25).

(4′*S*,3a′*R*)-Hexahydro-4′-*tert*-butoxyspiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole] (23): $[\alpha]^{25}_D$ −6.1 (*c* 0.80, CH_2Cl_2); ^1H NMR δ 4.02 (dt, J = 6.5, 3.5, 1H), 3.68 (dt, J = 6.5, 4.0, 1H), 3.32 (dd, J = 6.3, 3.0, 1H), 3.30 (d, J = 6.6, 1H), 2.53 (dd, J = 12.2, 8.6, 1H), 2.28 (m, 1H), 2.15 (dd, J = 12.2, 3.8, 1H), 1.8–1.6 (m, 1H), 1.19 (s, 9H), 1.0–0.8 (m, 2H), 0.74–0.50 (m, 2H); ^{13}C NMR δ 78.3 (d), 74.3 (d), 73.5 (s), 61.8 (s), 55.4 (t), 40.2 (t), 33.5 (t), 28.4 (q, 3C), 10.4 (t), 9.5 (t). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.19; H, 10.01; N, 6.66. Found: C, 68.07; H, 10.20; N, 6.36.

(4′*S*,3a′*R*)-Hexahydro-4′-*tert*-butoxyspiro[cyclopropane-1,3′-pyrrolo[1,2-*b*]isoxazole] (24): ^1H NMR δ 4.03 (dt, J = 6.8, 3.7, 1H), 3.80 (d, J = 7.6, 1H), 3.59 (d, J = 7.6, 1H), 3.44 (m, 1H), 3.32 (dt, J = 7.1, 9.8, 1H), 3.10 (d, J = 3.9, 1H), 1.88 (m, 1H), 1.67 (m, 1H), 1.17 (s, 9H), 1.02–0.65 (m, 4H); ^{13}C NMR δ 78.3 (t), 74.4 (t), 73.9 (s), 73.2 (d), 55.6 (t), 40.5 (s), 34.3 (t), 28.7 (q, 3C), 12.9 (t), 5.7 (t).

Thermal Rearrangement of 23. A solution of **23** (200 mg, 1 mmol) in 10 mL of xylenes was refluxed under nitrogen for 3 h. The solution was then concentrated, and the crude reaction mixture was purified by flash chromatography (eluent petroleum ether–ethyl acetate 1:2) to afford 106 mg (53% yield) of **25** (R_f 0.10) and 50 mg (25% yield) of **26** (R_f 0.38).

(1*S*,8a*R*)-Octahydro-1-*tert*-butoxyindolizin-7-one (25): $[\alpha]^{25}_D$ +91.2 (*c* 1.24, CH_2Cl_2); ^1H NMR δ 3.82 (ddd, J = 9.0, 7.0, 4.4, 1H), 3.24 (m, 1H), 3.07 (dt, J = 2.1, 8.2, 1H), 2.72–2.12 (m, 8H), 1.68 (dddd, J = 13.7, 9.2, 4.4, 2.4, 1H), 1.16 (s, 9H); ^{13}C NMR δ 208.7 (s), 76.7 (d), 73.5 (s), 68.9 (d), 51.9 (t), 50.6 (t), 45.2 (t), 40.4 (t), 33.7 (t), 28.4 (q, 3C); IR 2971, 2808, 1711, 1389, 1363, 1225, 1191, 1112, 1086 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.19; H, 10.01; N, 6.66. Found: C, 67.93; H, 10.14; N, 6.50.

(3*S*)-2-(2-Oxobutylidene)-3-*tert*-butoxypyrrolidine (26): $[\alpha]^{25}_D$ −45.5 (*c* 0.34, CH_2Cl_2); ^1H NMR δ 9.60 (bs, 1H), 5.19 (s, 1H), 4.58 (t, J = 8.0, 1H), 3.60 (ddd, J = 11.4, 6.6, 2.6, 1H), 3.43 (ddd, J = 10.4, 8.8, 7.0, 1H), 2.33 (q, J = 7.7, 2H), 2.30 (m, 1H), 1.83 (m, 1H), 1.28 (s, 9H), 1.11 (t, J = 7.7, 3H); ^{13}C NMR δ 199.9 (s), 166.9 (s), 88.3 (d), 74.6 (s), 73.6 (d), 44.6 (t), 34.9 (t), 32.3 (t), 28.4 (q, 3C), 9.9 (q); IR 3687, 2975, 1629, 1546, 1217, 1185, 1114 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.19; H, 10.01; N, 6.66. Found: C, 67.80; H, 10.30; N, 6.38.

Reduction of Ketone 25 with $NaBH_4$. To a solution of 50 mg (0.24 mmol) of ketone **25** in 2 mL of absolute ethanol at 0 °C was added 18 mg (0.48 mmol) of $NaBH_4$. The solution was stirred for 1 h at rt and then concentrated. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4 and concentrated to give 45 mg (90% yield) of monoprotected diols **27a** and **27b** in a 10:1 ratio.

(1*S*,7*S*,8a*R*)-Octahydro-1-*tert*-butoxy-7-hydroxyindolizine (27a): $[\alpha]^{25}_D$ +50.8 (*c* 0.85, CH_2Cl_2); ^1H NMR δ 3.96 (dt, J = 4.4, 8.6, 1H), 3.71 (tt, J = 10.2, 4.6, 1H), 3.08–3.16 (m, 2H), 2.50–1.92 (m, 7H), 1.78–1.53 (m, 2H), 1.50–1.39 (m, 1H), 1.18 (s, 9H); ^{13}C NMR δ 73.7 (d), 73.6 (s), 67.5 (d), 67.4 (d), 51.3 (t), 49.8 (t), 35.8 (t), 33.0 (t), 32.1 (t), 28.5 (q, 3C); IR 3891, 2971, 2810 (Bohlmann band), 2743 (Bohlmann band), 1585, 1461, 1389, 1188, 1078 cm^{-1}; MS (rel abund), *m/z* 213 ($M^{\bullet+}$, 3), 156 (100), 138 (28), 112 (26), 96 (11), 84 (11), 70 (7), 57 (19), 43 (20), 42 (19), 41 (44). Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.24; H, 11.04; N, 6.71.

(1*S*,7*R*,8a*R*)-Octahydro-1-*tert*-butoxy-7-hydroxyindolizine (27b): ^1H NMR (only discerned signals) δ 4.16 (quintet, J = 3.0, 1H), 2.78 (dt, J = 11.0, 4.0, 1H), 1.14 (s, 9H).

(1*S*,7*S*,8a*R*)-Octahydro-1,7-dihydroxyindolizine (28). The *tert*-butyl ether **27a** (50 mg, 0.44 mmol) was added to distilled CF_3COOH (1 mL, 13 mmol) and stirred for 12 h. The TFA was removed under reduced pressure, and the product was dissolved in methanol and passed through a column of IRA 900 (2 g). The methanol solution was then concentrated, and flash chromatography of the residue (eluent CH_2Cl_2–methanol–NH_4OH conc 100:10:1) gave 27 mg (70% yield) of diol **28**: R_f 0.20; $[\alpha]^{25}_D$ +26.7 (*c* 0.85, MeOH); ^1H NMR (D_2O) δ 3.90 (ddd, J = 8.5, 6.6, 4.3, 1H), 3.60 (tt, J = 11.1, 4.7, 1H), 2.90–2.55 (m, 2H), 2.30–1.70 (m, 6H), 1.50–1.15 (m, 2H), 1.06 (q, J = 11.0, 1H). By adding traces of alcoholic solvent to the D_2O solution the ^1H NMR spectrum modifies: δ 4.01 (ddd, J = 8.5, 6.6, 4.3, 1H), 3.78 (tt, J = 11.1, 4.7, 1H), 3.24–3.10 (m, 2H), 2.77 (q, J = 9.2, 1H), 2.69–2.51 (m, 2H), 2.40–2.10 (m, 2H), 1.96 (ddd, J = 13.1, 4.7, 2.2, 1H), 1.80–1.60 (m, 1H), 1.60–1.40 (m, 1H), 1.25 (q, J = 11.0, 1H); ^{13}C NMR (D_2O) δ 76.3 (d), 71.0 (d), 69.7 (d), 52.6 (t), 51.2 (t), 37.1 (t), 33.6 (t), 33.3 (t). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.13; H, 9.71; N, 9.12.

Cycloaddition of 1 to 3-Buten-1-ol (29). A mixture of nitrone **1** (0.5 g, 3.18 mmol) and 3-buten-1-ol (**29**) (2 mL) was stirred at rt for 10 days. Excess butenol was distilled off under reduced pressure and the residue purified by flash column chromatography (eluent CH_2Cl_2–methanol 10:1) to give 518 mg (71% yield) of a mixture of two diastereomeric products **30a** and **30b** in an 8:1 ratio.

(2*S*,3a*R*,4*S*)-Hexahydro-4-*tert*-butoxy-2-(2-hydroxyethyl)pyrrolo[1,2-*b*]isoxazole (30a): R_f 0.25; $[\alpha]^{25}_D$ −26.7 (*c* 0.51, CH_2Cl_2); ^1H NMR δ 4.28 (dq, J = 4.3, 6.5, 1H), 3.86 (dt, J = 6.6, 4.0, 1H), 3.74 (m, 2H), 3.44 (dt, J = 7.3, 4.0, 1H), 3.35 (dt, J = 12.8, 7.3, 1H), 3.20 (ddd, J = 12.8, 7.3, 5.5, 1H), 2.36–2.02 (m, 3H), 1.94–1.58 (m, 4H), 1.18 (s, 9H); ^{13}C NMR δ 77.7 (d), 75.0 (s), 73.5 (d), 72.5 (d), 59.4 (t), 55.0 (t), 39.5 (t), 36.6 (t), 33.4 (t), 28.4 (q, 3C); IR 3231, 2971, 1677, 1445, 1389, 1363, 1188, 1066 cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.63; H, 10.32; N, 5.87.

(2*R*,3a*S*,4*S*)-Hexahydro-4-*tert*-butoxy-2-(2-hydroxyethyl)pyrrolo[1,2-*b*]isoxazole (30b): ^1H NMR δ 1.15 (s, 9H).

(1*S*,7*S*,8a*R*)-Octahydro-1-*tert*-butoxy-7-hydroxyindolizine (27a). To a solution of the alcohol **30a** (318 mg, 1.39 mmol) in dry pyridine (4 mL) stirred in an ice bath was added dropwise methanesulfonyl chloride (0.25 mL, 3.12 mmol). The solution was left for 4 h at −10 °C, and then the pyridine was distilled off under reduced pressure. The crude mixture was dissolved in 15 mL of ethanol, and 150 mg of 10% Pd/C was added. The suspension was transferred in a Parr apparatus and shaken under hydrogen (45 psi) for 24 h. The suspension was then filtered through Celite and the methanolic solution passed through a short column of strongly basic IRA 900 and concentrated. The crude material was purified by flash column chromatography (eluent CH_2Cl_2–MeOH 10:1) to give 242 mg (82% yield) of a compound (R_f 0.45) identical to the major isomer **27a** obtained by reduction of the ketone **25**.

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