Synthesis of Enantiopure 3-Substituted Pyrroline *N*-Oxides by Highly Regioselective Oxidation of the Parent Hydroxylamines: A Mechanistic Rationale

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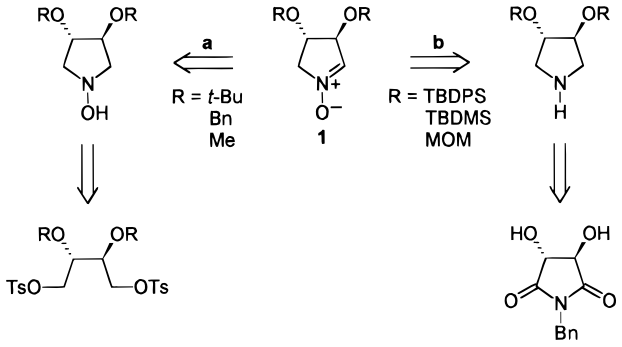
The syntheses of four new, differently *O*-substituted 3-hydroxypyrroline *N*-oxides and the first 3-amino analogue have been performed by the use of a strategy involving double nucleophilic displacement of the corresponding dimesylates by hydroxylamine and oxidation of the resulting 1-hydroxypyrrolidines. The regioselectivity data of the oxidation reactions nicely confirm the mechanistic hypothesis, which explains the dependence on the electronic nature of the substituent. The trend of the regioselectivity ratio has useful predictive value. Practical complete regioselection has been obtained by substitution with a benzoyloxy functionality. The *O*-allyl-substituted nitrone is not stable in the reaction conditions, undergoing immediately an intramolecular cycloaddition reaction with complete stereocontrol and inversion of regio- and stereoselectivity with respect to the intermolecular case.

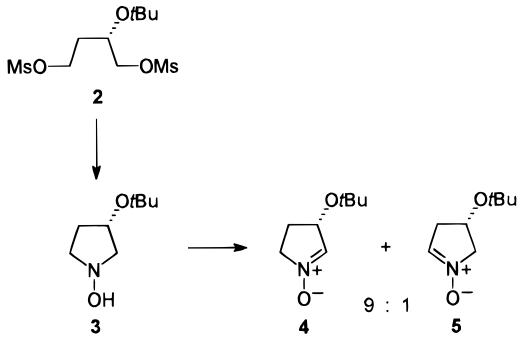
Introduction

Enantiomerically pure five-membered cyclic nitrones substituted with protected hydroxy functionalities[1] have been recently used as new chiral building blocks for the synthesis of natural and unnatural polyhydroxyindolizidines,[1d,2] potential glycosidase inhibitors.[3] Disubstituted nitrones **1** (Scheme 1), derived from unexpensive L-tartaric acid, and the corresponding enantiomers, have been applied quite extensively.[1b,c,2] Nitrones **1** were obtained from the starting acid by two alternative strategies (Scheme 1),[1a−c] whose convenience depends on the choice of the protecting groups. Route a requires immediate protection of the secondary hydroxyl groups, followed by reduction of the ester, tosylation, and ring-closure with hydroxylamine.[1a] In our hands, this route proved to be more efficient and reproducible when the nature of the protecting groups is compatible with the reaction conditions. This was not the case of silyl protecting groups, which have the tendency to migrate to the primary hydroxy groups in the reduction step. When protection by silyl groups is desired, route b, which consists of initial ring-closure to a pyrrolindione and successive reduction and protection,[1b,c] should be used instead. Both strategies require in the last step an oxidation to nitrone, of a hydroxylamine[4] and of an amine,[5] respectively. However, no matter of selectivity arises in these oxidations, since the nitrone precursors possess a C_2 symmetry.

Scheme 1



Scheme 2



On the contrary, the question of regioselectivity arose in the oxidation of hydroxylamine **3**, synthesized by a modification of route a starting from L-malic acid.[1d] However, a practicable 9:1 ratio in favor of nitrone **4**, with respect to its regioisomer **5**, was obtained in the first example of this strategy (Scheme 2).[1d] The high regioisomeric ratio of the hydroxylamine to nitrone oxidation

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(3) Reviews: (a) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497. (b) Vogel, P. *Chim. Oggi* **1992**, *10*, 9. (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (d) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (e) Fellows, L. E. *Chem. Br.* **1987**, *23*, 842. (f) Fellows, L. E. *New Sci.* **1989**, *123*, 45.

(4) (a) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473. (b) Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571.

(5) (a) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383. (b) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736. (c) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett.* **1995**, *36*, 3561. (d) Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025.

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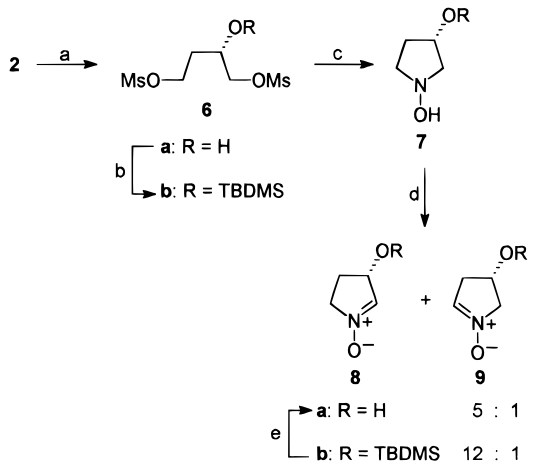
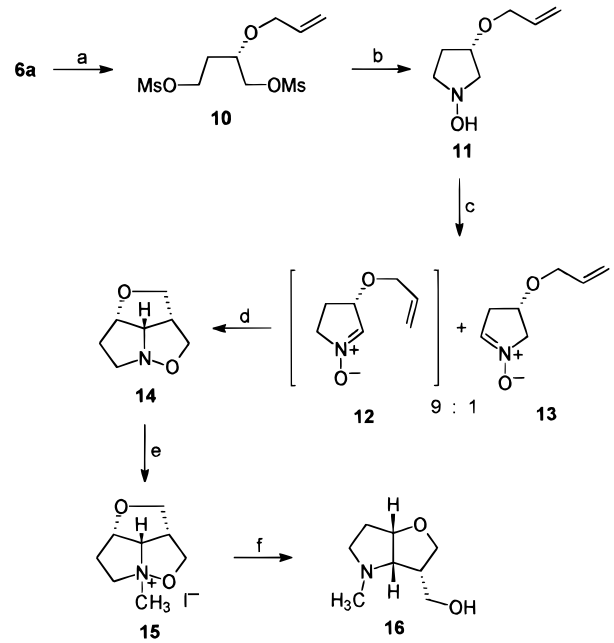
Scheme 3[a]



[a](a) CF_3COOH, rt, 1 h, 84%;
(b) TBDMSCl (1.2 equiv.), imidazole (1 equiv.), DMF, rt, 1 d, 84%;
(c) $NH_2OH{\cdot}HCl$ (4 equiv.), NEt_3, reflux, 2 h;
(d) yellow HgO (4 equiv.), CH_2Cl_2, rt, 2 h; **a**: 24%, **b**: 64% (from **6**);
(e) CsF (1.3 equiv.), abs. EtOH, rt, 18 h; **8a**: 90%, **9a**: 76%.

Scheme 4[a]



[a](a) $CH_2{=}CHCH_2OC(=NH)CCl_3$ (2 equiv.), CF_3SO_3H, CH_2Cl_2, rt, 7 d, 58%;
(b) $NH_2OH{\cdot}HCl$ (4 equiv.), NEt_3, reflux, 2 h, 46%;
(c) yellow HgO (4 equiv.), CH_2Cl_2, rt, 2 h;
(d) CH_2Cl_2, rt, 14 h; **14**: 90%; **13**: 10%;
(e) CH_3I (13 equiv.), C_6H_6, rt, 12 h;
(f) H_2 (70 psi), 10% Pd/C, CH_3OH, rt, 12 h, 65% (from **14**).

has been related to the electron-withdrawing properties of the O*t*Bu group, which stabilizes a developing negative charge on the α-carbon atom. Consistently with this interpretation, alkyl groups at C-3 gave a scarce 1.8–2:1 selectivity.[1d] Meanwhile, Murahashi has obtained a somewhat lower 6.8:1 ratio in the direct oxidation of the 3(*R*)-OTBDMS-substituted pyrrolidine to the corresponding nitrones.[6]

In this Article we report the synthesis of a series of 3-hydroxypyrroline *N*-oxides substituted at the oxygen with a variety of different groups and also of a related 3-amino-substituted nitrone. The results of the oxidation reactions furnish a tool to predict the selectivity of the oxidation and to choose the appropriate protecting group in order to obtain synthetically useful selectivities.

Results and Discussion

As already pointed out, the synthesis of silylated nitrones of type **1** by route a is prevented by scrambling of the silicon moiety when primary hydroxy groups are present. In order to avoid this drawback, the direct deprotection of dimesylate **2** with trifluoroacetic acid was attempted with success (Scheme 3). The alcohol **6a** was then protected with chloro-*tert*-butyldimethylsilane to give the corresponding silyl ether **6b**. Both dimesylates **6** were converted into a mixture of the regioisomeric nitrones **8** and **9** by a one-pot, two-step procedure via the corresponding hydroxylamines **7** (Scheme 3). The latter compounds are difficult to purify and were only characterized spectroscopically by ^{1}H NMR and oxidized *in situ* with yellow HgO.[4a] Structural assignment to nitrones **8** and **9** could be easily made on the basis of the different shape and chemical shifts of the proton signals for hydrogen atoms on C-2 and C-3 in **8** with respect to the corresponding on C-2 and C-4 in **9**. Both protons gave less-coupled signals in **8** than in **9**, and the proton attached at the substituted carbon atom was significantly more deshielded in **8** ($\Delta\delta$ > 0.5 ppm). The structural assignment was finally confirmed by comparison of physical data of **8b** and **9b** with those previously reported for the enantiomeric nitrones.[6] The measured **8/9** ratio was 5:1 for the nitrones having the free hydroxy groups and 12:1 for the OTBDMS substituted ones. It is noteworthy that this ratio is almost double than the one obtained by Murahashi and co-workers for formation of the enantiomeric nitrones by direct oxidation of the corresponding pyrrolidine,[6] suggesting a higher selectivity for the HgO oxidation of hydroxylamines.

While the major nitrone **8b** was easily separated from its regioisomer **9b**, analogous separation failed in the case of **8a**. Moreover, all the compounds **7a**, **8a**, and **9a** are very polar and hardly recoverable from the reaction mixtures, which might partly account for the low yields of nitrones obtained. However, nitrone **8a** was obtained as a pure solid in good overall yield by desilylation of **8b** with fluoride ions (Scheme 3), while direct deprotection of nitrone **4** failed. Use of CsF in absolute EtOH[7] gave the best results in the deprotection of **8b**, whereas TBAF in THF made the nitrone purification difficult by the presence of ammonium salts as side-products. The same procedure on nitrone **9b** gave the hydroxy nitrone **9a**.

The allyl protecting group was interesting in both mechanistic and synthetic aspects, as it is slightly less electron-donating and encumbered than *t*-Bu and, at the same time, contains a dipolarophile for internal trapping of the nitrone moiety (Scheme 4).

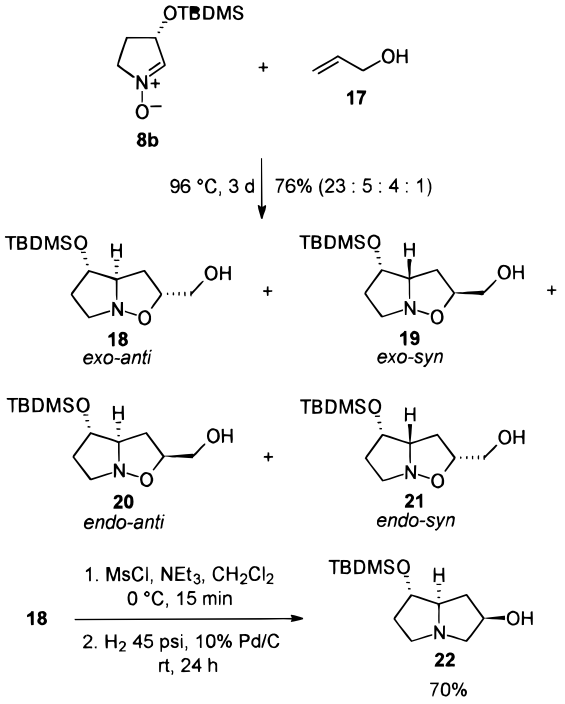
Allyl derivatization of the hydroxy group of **6a** was only possible through allyl trichloroacetimidate,[8] which avoids basic conditions. Double nucleophilic displacement of the mesylate **10** and oxidation gave a mixture of nitrone **13**

(6) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170.

(7) Desilylation with CsF in THF failed due to the low solubility of the cesium salt, which, on the contrary, is the most soluble alkaline fluoride in absolute EtOH: Rand, L.; Swisher, J. V.; Cronin, C. J. *J. Org. Chem.* **1962**, *27*, 3505.

(8) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

Scheme 5



and cycloadduct **14** in 1:9 ratio (Scheme 4). The nitrone **12** was not even observed in the reaction mixture after oxidation, since it underwent completely intramolecular trapping to **14**, while its regioisomer **13** was unreactive in the same conditions. Complete regio- and stereoselectivity was attained in the intramolecular cycloaddition to furnish exclusively the cycloadduct **14**, a result that is reverse and complementary with the analogous intermolecular cycloaddition. Indeed, cycloaddition of nitrone **8b** to allyl alcohol **17** gave a mixture of four cycloadducts **18**−**21** in a 23:5:4:1 ratio, independently on the reaction temperature (Scheme 5). Assignment of the relative stereochemistry to all the adducts **18**−**21** was possible on the basis of 2D NOESY spectra and comparison with analogous cycloaddition products.[1c,d,2] All the adducts **18**−**21** derived from the regiochemical approach opposite to the intramolecular version and the major one was the *exo-anti* adduct (Figure 1).[1c,d,2,9] The cycloaddition of nitrone **8a** to allyl alcohol gave the related adducts in a 23:4:2:1 ratio,[10] showing that the protecting group has virtually no influence on the diastereoselective approaches of the reactants.[11]

Formation of the adduct **14** in the intramolecular version is ascribed to a high preference for an *endo-syn* transition state, due to the constraint imposed by the short three-atom connecting chain (Figure 1).[12]

The synthetic utility of both intra- and intermolecular processes has been exemplified by the conversion of cycloadducts **14** and **18** to the novel nitrogen heterocycles **16** and **22**. Methylation and reductive isoxazolidine ring-opening of **14** gave the bicyclic amino alcohol **16** having

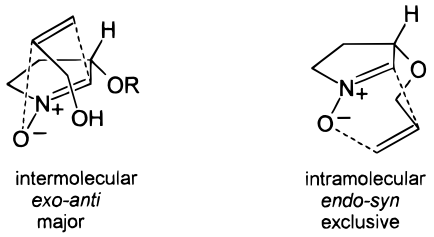
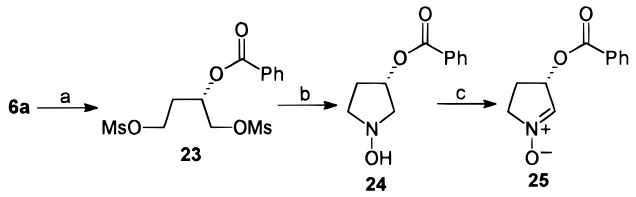


Figure 1. Preferred transition states for the inter- and intramolecular cycloadditions to 3-OR-substituted nitrones.

Scheme 6[a]



[a](a) PhCOCl (1.2 equiv.), NEt_3 (1.2 equiv.), DMAP (0.05 equiv.), THF, rt, 3.5 h, 100%; (b) $NH_2OH{\cdot}HCl$ (4 equiv.), NEt_3, reflux, 3 h; (c) yellow HgO (4 equiv.), CH_2Cl_2, rt, 3 h, 50% (from **23**).

the furo[2,3-*b*]pyrrole skeleton (Scheme 4).[13] Mesylation and hydrogenation of the major cycloadduct **18** afforded the hydroxypyrrolizidine **22** (Scheme 5).[1d,2c,e,14]

Finally, the benzoyl protecting group was considered as a candidate to further stabilize an incipient α-anion in the pyrrolidine ring. Standard benzoylation of **6a** gave the ester **23** which was cyclized and oxidized as usual (Scheme 6). Oxidation of hydroxylamine **24** gave selectively the nitrone **25**, no trace of its regioisomer being detectable by ^1H NMR in the crude reaction mixture.

In order to achieve a more complete picture of dependence on substituents of the regiochemistry of oxidation, extension of the same process to the nitrogen-substituted diol **26** was attempted (Scheme 7). Diol **26**[15] was obtained in two steps from L-aspartic acid as previously reported.[16] The subsequent reactions were complicated by formation of several side products, probably due to the reported equilibrium of dimesylate **27** with aziridinium ion **28**, prone to undergo several different transformations,[17] and no intermediate **27** or **29** could be isolated in pure form (Scheme 7). However, completion of the three-step process *in situ* allowed the isolation and characterization of the expected nitrones **30** and **31**, although in very low yield, which were formed in a 4:1 ratio (Scheme 7).

The same nitrone **30** was synthesized from diol **26** by a different route, according to Scheme 8. Monomesylation occurred mainly at the less encumbered position to give the intermediate **32**, as previously reported.[18] This monomesylate was directly oxidized *in situ* by the Swern procedure to afford the aldehyde **33**, which was obtained chemically pure in 25% yield from **26** by flash column chromatography on silica. The following oximation gave

(9) *Syn* and *anti* refer to the approaches of dipolarophile from the same or the opposite face of the substituent at C-3 of the nitrone, respectively.

(10) Nannelli, L. Tesi di Laurea, Università di Firenze, 1996.

(11) However, the cycloaddition of but-3-en-1-ol to nitrone **4** gave only the *exo* adducts in 8:1 ratio,[1d] suggesting that selectivity strongly depends on minor changes in dipolarophiles.

(12) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley: New York, 1984; Vol. 2, p 277.

(13) (a) Fraser, R. R.; Lin, Y. S. *Can. J. Chem.* **1968**, *46*, 801. (b) Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4004.

(14) (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866.

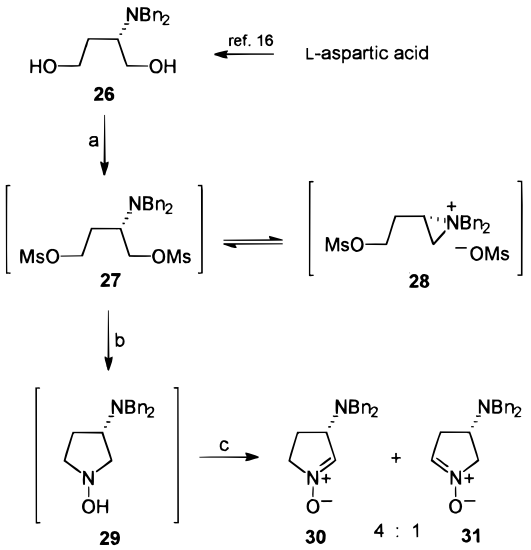
(15) (a) Gmeiner, P. *Arch. Pharm. (Weinheim)* **1991**, *324*, 551. (b) Pedrocchi-Fantoni, G.; Servi, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1029.

(16) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766.

(17) Gmeiner, P.; Orecher, F.; Thomas, C.; Weber, K. *Tetrahedron Lett.* **1995**, *36*, 381.

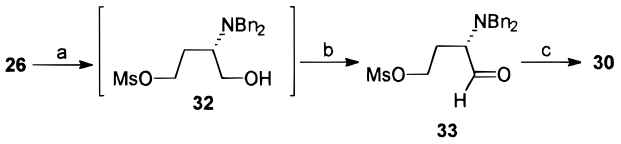
(18) Gmeiner, P.; Kärtner, A. *Synthesis* **1995**, 83.

Scheme 7[a]



[a](a) CH_3SO_2Cl (2.2 equiv.), NEt_3 (2.4 equiv.), CH_2Cl_2, -10 °C, 1 h; (b) $NH_2OH{\cdot}HCl$ (4 equiv.), NEt_3, reflux, 2 h; (c) yellow HgO (4 equiv.), CH_2Cl_2, rt, 3 h, 12 % (from **26**).

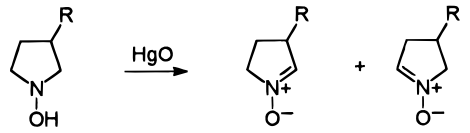
Scheme 8[a]



[a](a) CH_3SO_2Cl (1.1 equiv.), NEt_3 (1.2 equiv.), CH_2Cl_2, -15 °C, 1 h; (b) i. $(COCl)_2$ (1.1 equiv.), DMSO (2.2 equiv.), CH_2Cl_2, -60 °C, 20 min; ii. NEt_3 (4.4 equiv.), 10 min; 25 % (from **26**); (c) $NH_2OH{\cdot}HCl$ (1.1 equiv.), K_2CO_3 (2.2 equiv.), CH_3OH, rt, 30 min, 100%.

directly the nitrone **30** in quantitative yield by nucleophilic attack of the intermediate oxime nitrogen to the carbon atom bearing the mesylate moiety.[19] However, the obtained nitrone was largely racemized, as proved by the lower specific optical rotation with respect to the nitrone obtained by oxidation of the hydroxylamine **29**. The observed partial racemization might have occurred at the level of the intermediate aldehyde, since α-amino aldehydes are known to suffer of configurational lability.[20] Proof of this hypothesis derived from ^{1}H NMR spectra of the aldehyde **33** in the presence of the shift reagent Yb(hfc)$_3$, which showed the splitting of the H—C═O signals. On the other hand, Reetz and coworkers have reported the obtainment of configurationally stable (at room temperature) α-dibenzylamino aldehydes by Swern oxidation of the corresponding alcohols, but the aldehydes were used without purification and no mention about configurational instability on purification was made.[21] Indeed, when the crude aldehyde **33** was treated directly with hydroxylamine without purification, the nitrone **30** was obtained enantiomerically pure, proving that racemization had occurred during chromatography of **33**. The three-step *in situ* conversion of diol **26** afforded nitrone **30** in 24% overall yield (Scheme 8).

Table 1. Regioselective Ratios in the HgO Oxidation of 3-Substituted 1-Hydroxypyrrolidines



R	hydroxylamine	nitrones	ratio	yield (%)	reference
Me	**34**	**35**, **36**	1.8	90	1d
Ph	**37**	**38**, **39**	2	95	1d
(*S*)-NBn_2	**29**	**30**, **31**	4	12[a]	this work
(*S*)-OH	**7a**	**8a**, **9a**	5	24[b]	this work
(*S*)-O*t*Bu	**3**	**4**, **5**	9	80	1d
(*S*)-O-allyl	**11**	**12**,[c] **13**	9	100	this work
(*S*)-OTBDMS	**7b**	**8b**, **9b**	12	64[b]	this work
(*S*)-OCOPh	**24**	**25**	>20	50[b]	this work

[a] On a three-step reaction from the diol. [b] On a two-step reaction from the dimesylate. [c] Calculated as the intramolecular cycloadduct.

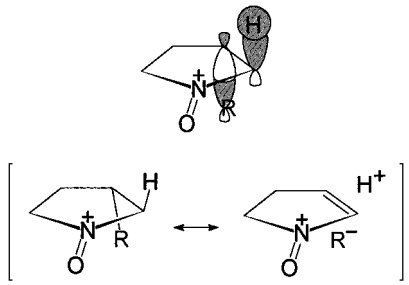
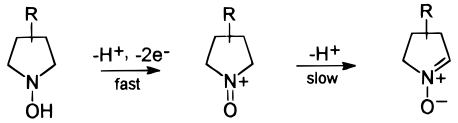


Figure 2. Representation of orbital interaction of the 3-substituent with the *trans* hydrogen atom.

Scheme 9



The results of the regioselectivity of oxidation of 3-substituted *N*-hydroxypyrrolidines are summarized in Table 1.

Examination of these data shows a direct correlation of the regioselectivity with the electronegativity of the substituent. Steric effects seem to play only a minor role,[22] *e.g.* in enhancing the regioselectivity ratio from hydroxylamine **3** with respect to the unprotected **7a**. These findings reinforce our reported mechanistic hypothesis for the oxidation of hydroxylamines in a two-step process (Scheme 9).[1d,23] The substituents might play their role in the second, rate-determining step by stabilizing the incipient negative charge on the α carbon atom by $\sigma_{C-H} \rightarrow \sigma^*_{C-R}$ donation (Figure 2). The greater is the ability of the substituent in stabilizing the negative charge, the higher the regioselectivity in the oxidation reaction. The importance of the stereoelectronic effects on the proton *trans* to the substituent, represented in Figure 2 in both MO and VB notations, has already been demonstrated by isotopic labeling.[1d]

(19) (a) Stork, G.; Darling, S. D.; Harrison, I. T.; Wharton, P. S. *J. Am. Chem. Soc.* **1962**, *84*, 2018. (b) Stempel, A.; Douvan, I.; Sternbach, L. H. *J. Org. Chem.* **1968**, *33*, 2963.

(20) See for example: (a) Hanson, G. H.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399. (b) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 1983. (c) Garner, P. *J. Org. Chem.* **1986**, *51*, 2609. (d) Fehrens, J. A.; Castro, B. *Synthesis* **1983**, 676. (e) Coj, D. H.; Hocart, S. J.; Sasaki, Y. *Tetrahedron* **1988**, *44*, 835.

(21) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.

(22) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373.

(23) (a) LeBel, N. A.; Post, M. E.; Hwang, D. *J. Org. Chem.* **1979**, *44*, 1819. (b) Asrof Ali, Sk.; Wazeer, M. I. M. *Tetrahedron Lett.* **1992**, *33*, 3219. (c) Asrof Ali, Sk. *Tetrahedron Lett.* **1993**, *34*, 5325. (d) Asrof Ali, Sk. *J. Chem. Res. (M)* **1994**, 301.

Conclusions

From the synthetic point of view, very useful levels of regioselectivity have been achieved for the synthesis of the oxygen substituted nitrones, up to a complete selectivity with the benzoate substituted one. The scale in Table 1 also has a useful predictive value for the selectivity to be expected in presence of a certain substituent. The obtainment of the amino-substituted nitrone **30** might prove useful for the construction of amino indolizidinols and pyrrolizidinols related to the parent polyhydroxy derivatives.[1d,2] Finally, the facile and straightforward assembly of a polycyclic skeleton as in **14** and **16** by the intramolecular version of cycloaddition to this family of nitrones has been demonstrated. Application of the inter- and intramolecular cycloaddition methodologies to this family of enantiopure cyclic nitrones[24] for the synthesis of natural products is underway in our group.

Experimental Section

For instruments and generalities see ref 1d.

General Procedure for the Synthesis of *N*-Hydroxypyrrolidines by Nucleophilic Displacement of Dimesylates. A suspension of the dimesylate and hydroxylamine hydrochloride (4 equiv) in triethylamine (8 mL/mmol) was heated at reflux for 2−3 h. Triethylamine was then evaporated off, and the resulting white solid was washed thoroughly with diethyl ether. Ethereal extracts were then concentrated to give the crude *N*-hydroxypyrrolidines.

General Procedure for the Synthesis of 2*H*-Pyrroline *N*-Oxides by Oxidation of *N*-Hydroxypyrrolidines. Yellow mercury oxide (4 equiv) was added in portions to an ice-cooled solution of the *N*-hydroxypyrrolidine in CH_2Cl_2 (10 mL/mmol). The suspension was then stirred at room temperature for 2−3 h. The reaction mixture was filtered through Celite and concentrated to give the crude regioisomeric nitrones.

(2*S*)-2-Hydroxy-1,4-bis[(methansulfonyl)oxy]butane (6a). A solution of (2*S*)-2-*tert*-butoxy-1,4-bis[(methansulfonyl)-oxy]butane[1d] (**2**, 4.0 g, 12.5 mmol) in trifluoroacetic acid (4.6 mL, 60 mmol) was stirred at room temperature for 1 h. The acid was distilled off at reduced pressure, and the residue was recrystallized from CH_2Cl_2/Et_2O 1:1 to give the pure title compound **6a** (2.77 g, 10.5 mmol, 84%). Mp 65−66 °C. $[\alpha]^{20}_D = -17.9$ (*c* 1.82, CH_2Cl_2); ^{1}H NMR: δ 4.54−4.06 (m, 5H), 3.09 (s, 3H), 3.05 (s, 3H), 2.57 (br, 1H), 2.10−1.80 (m, 2H); ^{13}C NMR: δ 73.0 (d), 66.1 (t), 65.6 (t), 37.5 (q), 37.3 (q), 32.1 (t); IR: 3615, 3410 (br), 3015, 1200 cm^{-1}; MS: *m*/*z* (rel intensity) 262 (M^+, 2), 97 (92), 79 (100), 57 (100). Anal. Calcd for $C_6H_{14}O_7S_2$: C, 27.47; H, 5.38. Found: C, 27.12, H, 5.30.

(2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1,4-bis[(methansulfonyl)oxy]butane (6b). *tert*-Butyldimethylchlorosilane (1.57 g, 10.4 mmol) was added at 0 °C to a solution of **6a** (2.15 g, 8.2 mmol) and imidazole (562 mg, 8.2 mmol) in DMF (10 mL). The mixture was stirred at rt for 1 d and then diluted with water and extracted repeatedly with diethyl ether. The collected organic phases were dried over Na_2SO_4 and then filtered and concentrated. The residue was purified by flash column chromatography, eluent ethyl acetate, to give the protected dimesylate **6b** (2.61 g, 6.9 mmol, 84%) which crystallized on standing. Mp 41−42 °C. R_f 0.44; $[\alpha]^{22}_D = -13.3$ (*c* 1.54, $CHCl_3$); ^{1}H NMR: δ 4.45−4.25 (m, 2H), 4.13 (m, 3H), 3.05 (s, 3H), 3.03 (s, 3H), 2.10 (m, 2H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR: δ 72.3 (d), 67.1 (t), 66.1 (t), 38.0 (q, 2C), 34.1 (t), 26.2 (q, 3C), 17.8 (s), −4.0 (q), −4.5 (q); IR: 3029, 1171 cm^{-1}; MS: *m*/*z* (rel intensity) 376 (M^+, 0.02), 249 (3), 153 (100). Anal. Calcd for $C_{12}H_{28}O_7S_2Si$: C, 38.28; H, 7.49. Found: C, 38.70, H, 7.40.

3(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-*N*-hydroxypyrrolidine (7b) was obtained from **6b** (520 mg, 1.38 mmol) according to the general procedure and pure enough to be used for the following step. A sample purified by chromatography on silica, eluent ethyl acetate, afforded an analytically pure oil. R_f 0.54; $[\alpha]^{20}_D = -0.1$ (*c* 1.58, $CHCl_3$); ^{1}H NMR: δ 4.47 (m, 1H), 3.32−3.14 (m, 2H), 3.02 (m, 1H), 2.97 (dd, J = 12.0, 4.0 Hz, 1H), 2.20 (m, 1H), 1.75 (m, 1H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR: δ 70.9 (d), 67.2 (t), 57.4 (t), 33.2 (t), 25.7 (q, 3C), 18.0 (s), −4.8 (q), −4.9 (q); IR: 3157, 1462 cm^{-1}; MS: *m*/*z* (rel intensity) 215 ($M^+ - H_2$, 7), 83 (60), 75 (100), 73 (83). Anal. Calcd for $C_{10}H_{23}NO_2Si$: C, 55.25; H,10.66; N, 6.44. Found: C, 55.65; H, 10.99; N, 6.02.

(3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-pyrroline *N*-Oxide (8b) and (4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-pyrroline *N*-Oxide (9b). A 12:1 mixture of nitrones **8b** and **9b** was obtained by the oxidation of **7b** (256 mg, 1.18 mmol) according to the general procedure. Separation of the regioisomeric nitrones by flash column chromatography, eluent ethyl acetate, gave **8b** (174 mg, 59%) and **9b** (14 mg, 5%) as pure solid compounds, which were recrystallized from petroleum ether. **8b**: mp 74−75 °C. R_f 0.21; $[\alpha]^{21}_D = -62.3$ (*c* 1.04, $CHCl_3$); $[\alpha]^{22}_D = -59.8$ (*c* 1.03, CH_3OH) [lit. for the (*R*)-enantiomer:[6] mp 73.8−75.5 °C; $[\alpha]^{28}_D = +55.9$ (*c* 1.14, CH_3OH)]; ^{1}H NMR: δ 6.83 (q, J = 1.7 Hz, 1H), 5.01 (m, 1H), 4.15 (m, 1H), 3.86 (m, 1H), 2.56 (m, 1H), 2.08 (m, 1H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR: δ 135.5 (d), 72.1 (d), 61.3 (t), 30.9 (t), 25.6 (q, 3C), 18.0 (s), −4.7 (q), −4.8 (q); IR: 1586, 1251 cm^{-1}; MS: *m*/*z* (rel intensity) 215 (M^+, 16), 75 (100). Anal. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50. Found: C, 55.67; H, 9.70; N, 6.20. **9b**: mp 67.5−68.5 °C. R_f 0.06; $[\alpha]^{23}_D = +46.5$ (*c* 0.92, CH_3OH) [lit. for the (*R*)-enantiomer:[6] mp 72.1−72.9 °C; $[\alpha]^{28}_D = -50.9$ (*c* 1.14, CH_3OH)]; ^{1}H NMR: δ 6.88 (m, 1H), 4.64 (m, 1H), 4.12 (m, 1H), 3.80 (m, 1H), 3.01 (ddd, J = 18.8, 4.4, 2.1 Hz, 1H), 2.62 (d, J = 18.8 Hz, 1H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR: δ 133.7 (d), 70.5 (d), 66.4 (t), 40.0 (t), 25.6 (q, 3C), 17.9 (s), −4.9 (q, 2C); IR: 1595, 1255 cm^{-1}; MS: *m*/*z* (rel intensity) 215 (M^+, 1), 101 (74), 75 (100). Anal. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50. Found: C, 56.07; H, 10.00; N, 6.39.

(3*S*)-3-Hydroxy-1-pyrroline *N*-Oxide (8a) and (4*S*)-4-Hydroxy-1-pyrroline *N*-Oxide (9a). A 5:1 mixture of nitrones **8a** and **9a** (24 mg, 24%) was obtained according to the general procedures by treatment of dimesylate **6a** (262 mg, 1 mmol) with hydroxylamine and direct oxidation of the resulting mixture.

Synthesis of (3*S*)-3-Hydroxy-1-pyrroline *N*-Oxide (8a) by Deprotection of 8b. A solution of **8b** (800 mg, 3.71 mmol) and cesium fluoride (733 mg, 4.83 mmol) in absolute EtOH (41 mL) was stirred at rt for 18 h. The solvent was removed *in vacuo*, and flash chromatography of the resulting mixture, eluent AcOEt/MeOH 1:1, afforded the desired nitrone **8a** (333 mg, 3.3 mmol, 90%) as a solid, which was recrystallized from ethyl acetate. **8a**: mp 105−107 °C. R_f 0.36; $[\alpha]^{21}_D = -136.4$ (*c* 0.94, $CHCl_3$); ^{1}H NMR: δ 7.01 (m, 1H), 4.98 (m, 1H), 4.31−4.17 (m, 1H), 3.94−3.80 (m, 1H), 3.60−3.20 (br, 1H), 2.72−2.54 (m, 1H), 2.25−2.10 (m, 1H); ^{13}C NMR: δ 137.7 (d), 71.4 (d), 61.4 (t), 30.1 (t); IR: 3317 (br), 1586, 1245 cm^{-1}; MS: *m*/*z* (rel intensity) 101 (M^+, 37), 85 (62), 83 (100), 71 (64). Anal. Calcd for $C_4H_7NO_2$: C, 47.57; H, 6.98; N, 13.86. Found: C, 47.22; H, 7.05; N, 13.48.

Synthesis of (4*S*)-4-Hydroxy-1-pyrroline *N*-Oxide (9a) by Deprotection of 9b. The same procedure as above on nitrone **9b** (14 mg, 0.065 mmol) with cesium fluoride (20 mg, 0.13 mmol) afforded nitrone **9a** (5 mg, 0.049 mmol, 76%) as a

(24) For some recent examples on the synthesis and use of different chiral, enantiomerically pure, cyclic nitrones, see: (a) Golik, J.; Wong, H.; Krishnan, B.; Vyas, D. M.; Doyle, T. W. *Tetrahedron Lett.* **1991**, *32*, 1851. (b) Tronchet, J. M. J.; Zosimo-Landolfo, G.; Balkadjian, M.; Ricca, A.; Zsély, M.; Barbalat-Rey, F.; Cabrini, D.; Lichtle, P.; Geoffroy, M. *Tetrahedron Lett.* **1991**, *32*, 4129. (c) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929. (d) Herczegh, P.; Kovács, I.; Szilágyi, L.; Varga, T.; Dinya, T.; Sztaricskai, F. *Tetrahedron Lett.* **1993**, *34*, 1211. (e) Berranger, T.; Langlois, Y. *J. Org. Chem.* **1995**, *60*, 1720. (f) de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *J. Chem. Soc., Chem. Commun.* **1995**, 2097. (g) van den Broek, L. A. G. M. *Tetrahedron* **1996**, *52*, 4467. (h) Katagiri, N.; Okada, M.; Kaneko, C.; Furuya, T. *Tetrahedron Lett.* **1996**, *37*, 1801. (i) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1863. (j) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *J. Chem. Soc., Chem. Commun.* **1996**, 1861.

white solid. **9a**: mp 115−116 °C. R_f 0.18; $[\alpha]^{20}_D = +87.7$ (*c* 0.18, $CHCl_3$); ^{1}H NMR: δ 6.93 (q, J = 1.9 Hz, 1H), 4.66 (t, J = 6.0 Hz, 1H), 4.30 (br, 1H), 4.20 (m, 1H), 3.88 (d, J = 15.1 Hz, 1H), 3.09 (m, 1H), 2.73 (d, J = 18.7 Hz, 1H); ^{13}C NMR: δ 134.3 (d), 70.5 (d), 65.7 (t), 39.6 (t); IR: 3275 (br) cm^{-1}; MS: *m*/*z* (rel intensity) 101 (M^+, 81), 83 (10), 72 (100). Anal. Calcd for $C_4H_7NO_2$: C, 47.57; H, 6.98; N, 13.86. Found: C, 47.32; H, 7.06; N, 13.50.

(2*S*)-2-(Allyloxy)-1,4-bis[(methansulfonyl)oxy]butane (10). Trifluoromethanesulfonic acid (5 mL) was added portionwise during 2 d to a solution of dimesylate **6a** (2.25 g, 8.6 mmol) and allyltrichloroacetimidate[8] (5.2 g, 17.2 mmol) in CH_2Cl_2 (80 mL). The solution was stirred at rt for additional 5 d and then washed with H_2O and saturated $NaHCO_3$. After removal of the solvent, the crude product was purified by passage over a short pad of silica gel, eluent ethyl acetate/petroleum ether 1:1, to give the desired allyloxy dimesylate **10** (1.5 g, 5.0 mmol, 58%) as a liquid. R_f 0.32; $[\alpha]^{22}_D = -29.4$ (*c* 0.97, $CHCl_3$); ^{1}H NMR: δ 5.90 (ddt, J = 16.7, 10.8, 5.7 Hz, 1H), 5.35−5.17 (m, 2H), 4.46−4.28 (m, 3H), 4.28−3.98 (m, 3H), 3.85−3.73 (m, 1H), 3.05 (s, 3H), 3.02 (s, 3H), 2.05−1.93 (m, 2H); ^{13}C NMR: δ 133.9 (d), 117.9 (t), 72.5 (d), 71.3 (t), 69.9 (t), 65.9 (t), 37.6 (q), 37.3 (q), 31.2 (t); IR: 3015, 1358, 1171 cm^{-1}; MS: *m*/*z* (rel intensity) 245 ($M^+ - OCH_2CH{=}CH_2$, 3), 97 (100), 79 (100). Anal. Calcd for $C_9H_{18}O_7S_2$: C, 35.75; H, 6.00. Found: C, 35.40, H, 6.02.

(3*S*)-3-(Allyloxy)-*N*-hydroxypyrrolidine (11). The hydroxylamine **11** was synthesized from **10** (1.5 g, 5.0 mmol) under standard conditions. Purification by passage over a short pad of silica, eluent ethyl acetate, gave **11** (330 mg, 2.28 mmol, 46%) as a pure oil. R_f 0.35; $[\alpha]^{26}_D = +8.6$ (*c* 0.74, $CHCl_3$); ^{1}H NMR: δ 8.36 (br, 1H), 5.88 (ddt, J = 17.2, 10.2, 5.2 Hz, 1H), 5.30−5.12 (m, 2H) 4.18 (m, 1H), 4.05−3.90 (m, 2H), 3.29−2.97 (m, 4H), 2.25−2.00 (m, 1H), 2.00−1.70 (m, 1H); ^{13}C NMR: δ 134.6 (d), 116.9 (t), 77.2 (d), 70.2 (t), 64.3 (t), 57.2 (t), 29.6 (t); IR: 3001, 1346, 1205 cm^{-1}. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.84; H, 9.24; N, 9.78.

(4*S*)-4-(Allyloxy)-1-pyrroline *N*-Oxide (13) and (2a*R*,6a*S*,6b*S*)-Perhydro-1,4-dioxa-4a-azacyclopenta[*cd*]pentalene (14). Oxidation of the hydroxylamine **11** was accomplished in standard conditions, but the reaction mixture was then stirred at rt for additional 14 h. After removal of the solvent, the crude product was passed over a short pad of silica, eluent ethyl acetate, to afford the pure cycloadduct **14** (240 mg, 1.7 mmol, 90%) and, by elution with methanol, the nitrone **13** (27 mg, 0.18 mmol, 10%). **14**: $[\alpha]^{20}_D = +58.5$ (*c* 0.37, CH_2Cl_2); ^{1}H NMR: δ 4.36 (dt, J = 1.6, 4.8 Hz, 1H), 4.18 (dd, J = 8.4, 4.8 Hz, 1H), 4.09 (t, J = 8.4 Hz, 1H), 3.89 (dd, J = 9.4, 1.5 Hz, 1H), 3.75 (dd, J = 9.4, 5.1 Hz, 1H), 3.70 (dd, J = 8.8, 7.3 Hz, 1H), 3.30−3.10 (m, 3H), 2.10 (dddd, J = 13.7, 5.9, 3.7, 1.6 Hz, 1H), 1.85 (dddd, J = 13.7, 9.4, 7.6, 4.6 Hz, 1H); ^{13}C NMR: δ 83.1 (d), 75.8 (d), 71.6 (t), 70.5 (t), 52.4 (t), 51.0 (d), 30.0 (t); IR (CH_2Cl_2): 3043, 1096 cm^{-1}; MS: *m*/*z* (rel intensity) 141 (M^+, 89), 68 (93), 55 (100). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.57; H, 7.72; N, 9.46. **13**: ^{1}H NMR: δ 6.86 (m, 1H), 6.00−5.80 (m, 1H), 5.36−5.20 (m, 2H), 4.44−4.33 (m, 1H), 4.20−4.08 (m, 1H), 4.04−3.90 (m, 3H), 3.12−2.92 (m, 1H), 2.86−2.70 (m, 1H); ^{13}C NMR: δ 133.5 (d), 133.0 (d), 117.8 (t), 72.0 (d), 69.9 (t), 67.6 (t), 36.4 (t); MS: *m*/*z* (rel intensity) 141 (M^+, 100), 83 (24). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.43; H, 7.90; N, 9.54.

(3*S*,3a*S*,6a*S*)-3-(Hydroxymethyl)-4-methyl-hexahydrofuro[2,3-*b*]pyrrole (16). The adduct **14** (240 mg, 1.7 mmol) was reacted with methyl iodide (1.37 mL, 22 mmol) in C_6H_6 (3 mL) at rt for 12 h. After removal of the solvent, the crude ammonium salt **15** was obtained and subjected to hydrogenation without any further purification. ^{1}H NMR: δ 6.05 (t, J = 6.7 Hz, 1H), 5.18 (dt, J = 3.7, 6.7 Hz, 1H), 4.81 (dd, J = 9.6, 6.6 Hz, 1H), 4.57 (dt, J = 12.4, 8.3 Hz, 1H), 4.36 (dd, J = 9.6, 2.7 Hz, 1H), 4.22−3.96 (m, 4H), 4.01 (s, 3H), 2.92−2.77 (m, 1H), 2.50−2.35 (m, 1H); ^{13}C NMR: δ 87.3 (d), 83.2 (d), 76.9 (t), 73.4 (t), 68.1 (t), 52.3 (d), 48.9 (q), 29.5 (t).

The crude salt **15** was dissolved in CH_3OH (15 mL) and added with 10% Pd on charcoal (100 mg). The suspension was then hydrogenated under pressure (70 psi) at rt for 12 h. The crude reaction mixture was filtered over Celite and passed in a column filled with Amberlyst-A26. After removal of the solvent *in vacuo*, the product was purified on silica, eluent CH_2Cl_2/CH_3OH 20:1, to afford the pure amino alcohol **16** (141 mg, 1.12 mmol, 65%) as an oil. R_f 0.15; $[\alpha]^{20}_D = -45.7$ (*c* 1.07, $CHCl_3$); ^{1}H NMR: δ 4.67 (q, J = 7.0 Hz, 1H), 4.06 (dd, J = 11.7, 2.9 Hz, 1H), 4.03−3.76 (AB part of an ABX system, 2H), 3.75 (dd, J = 11.7, 4.0 Hz, 1H), 3.17 (t, J = 7.1 Hz, 1H), 3.05 (ddd, J = 10.2, 6.7, 3.4 Hz, 1H), 2.41 (s, 3H), 2.28 (dt, J = 5.8, 10.2 Hz, 1H), 2.20−1.93 (m, 2H), 1.88−1.70 (m, 1H); ^{13}C NMR: δ 84.2 (d), 77.2 (d), 72.6 (d), 68.0 (t), 59.8 (t), 56.3 (t), 43.7 (q), 31.3 (t); IR: 1213 cm^{-1}; MS: *m*/*z* (rel intensity) 157 (M^+, 11), 156 (16), 98 (100). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.00; H, 9.67; N, 9.37.

Cycloaddition of Nitrone 8b to Allyl Alcohol (17). A mixture of nitrone **8b** (174 mg, 0.81 mmol) and allyl alcohol (**17**, 1.5 mL) was heated at reflux for 3 d. Excess alcohol was distilled off under reduced pressure to leave a crude mixture of adducts **18**−**21** in a 23:5:4:1 ratio (by ^{1}H NMR). Separation by flash column chromatography, eluent ethyl acetate/petroleum ether 8:1, gave the major adduct **18** (111 mg, 0.41 mmol, 50%) as a pure oil, adduct **19** containing some impurities of **18** (33 mg), and an inseparable mixture of adducts **20** and **21** (24 mg), for a 76% total yield in recovered cycloadducts. A reaction run at 27 °C for 10 d gave a mixture of the adducts **18**−**21** (64% yield) in roughly the same ratio.

(2*R*,3a*R*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(hydroxymethyl)hexahydropyrrolo[1,2-*b*]isoxazole (18). R_f 0.24; $[\alpha]^{21}_D = -17.2$ (*c* 1.27, $CHCl_3$); ^{1}H NMR: δ 4.17 (m, 1H), 4.07 (dt, J = 5.8, 3.0 Hz, 1H), 3.70 (dd, J = 11.8, 2.9 Hz, 1H), 3.60−3.52 (m, 1H), 3.56 (dd, J = 11.8, 5.2 Hz, 1H), 3.32 (m, 2H), 2.43 (m, 1H), 2.27−2.05 (m, 2H), 1.80−1.60 (br, 1H), 1.73−1.62 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR: δ 79.1 (d), 77.7 (d), 74.6 (t), 64.4 (d), 55.1 (t), 35.9 (t), 33.9 (t), 25.7 (q, 3C), 17.9 (s), −4.7 (q), −4.8 (q); IR (CCl_4): 3447, 1248 cm^{-1}; MS: *m*/*z* (rel intensity) 273 (M^+, 1), 216 (13), 149 (18), 71 (48), 57 (100). Anal. Calcd for $C_{13}H_{27}NO_3Si$: C, 57.10; H, 9.95; N, 5.12. Found: C, 57.37; H, 9.92; N, 4.78.

(2*S*,3a*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(hydroxymethyl)hexahydropyrrolo[1,2-*b*]isoxazole (19). R_f 0.22; ^{1}H NMR: δ 4.13−4.07 (m, 2H), 3.88−3.81 (m, 1H), 3.76−3.53 (m, 2H), 3.44−3.24 (m, 2H), 2.60−2.42 (m, 1H), 2.31−2.14 (m, 2H), 1.92−1.60 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR: δ 79.5 (d), 78.1 (d), 75.6 (t), 62.3 (d), 55.0 (t), 36.0 (t), 33.4 (t), 25.7 (q, 3C), 18.0 (s), −4.7 (q), −4.8 (q). **(2*S*,3a*R*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(hydroxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (20)**. R_f 0.08; ^{1}H NMR: δ 4.50−4.18 (m, 2H), 3.83−3.68 (m, 2H), 3.57 (dd, J = 11.7, 5.1 Hz, 1H), 3.23−3.10 (m, 2H), 2.90−2.80 (br, 1H), 2.45−2.37 (m, 1H), 2.11−2.03 (m, 2H), 1.95−1.85 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR: δ 78.6 (d), 72.1 (d), 69.2 (t), 63.5 (d), 53.4 (t), 34.1 (t), 31.2 (t), 25.7 (q, 3C), 18.0 (s), −4.7 (q), −4.8 (q). **(2*R*,3a*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(hydroxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (21)**. R_f 0.08; ^{1}H NMR: δ 4.48−4.15 (m, 2H), 3.88−3.63 (m, 3H), 3.47−3.35 (m, 1H), 3.02−2.85 (m, 1H), 2.90−2.80 (br, 1H), 2.52−2.48 (m, 1H), 2.15−1.98 (m, 2H), 1.91−1.83 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR: δ 79.2 (d), 73.3 (d), 69.0 (t), 63.0 (d), 52.8 (t), 34.1 (t), 30.6 (t), 25.8 (q, 3C), 18.0 (s), −4.7 (q), −4.8 (q).

(1*S*,6*R*,7a*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-hydroxy-1*H*-hexahydropyrrolizine (22). Triethylamine (72 μL, 0.51 mmol) and methanesulfonyl chloride (29 μL, 0.38 mmol) were added at 0 °C to a solution of cycloadduct **18** (94 mg, 0.34 mmol) in CH_2Cl_2 (2 mL). The mixture was reacted at rt for 15 min under stirring and then concentrated. The resulting crude product was dissolved in CH_3OH (18 mL) and poured into a Parr bottle. 10% Palladium on charcoal (50 mg) was added, and the mixture was hydrogenated at a Parr apparatus at 45 psi. After 1 d the suspension was filtered over Celite and Amberlyst A-26 and the filter washed thoroughly with CH_3OH. Removal of the solvent *in vacuo* gave an oil which was purified by flash column chromatography, eluent CH_3OH + 5% NH_4OH, to afford the desired pyrrolizidine **22** (62 mg, 70%) as an oil. $[\alpha]^{21}_D = +33.0$ (*c* 0.74, $CHCl_3$); ^{1}H NMR: δ

4.44 (quint, J = 5.4 Hz, 1H), 4.15 (q, J = 4.7 Hz, 1H), 3.35−3.18 (m, 3H), 2.90−2.75 (m, 1H), 2.60−2.50 (m, 1H), 2.31−2.00 (m, 3H), 1.82−1.69 (m, 1H), 1.64−1.51 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR: 78.3 (d), 72.5 (d), 71.3 (d), 62.0 (t), 53.2 (t), 38.5 (t), 34.1 (t), 25.8 (q, 3C), 18.0 (s), −4.6 (q), −4.7 (q); IR (CCl_4): 3352, 1248 cm^{-1}. Anal. Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65; H, 10.57; N, 5.44. Found: C, 60.20; H, 10.70; N, 5.22.

(2*S*)-2-(Benzoyloxy)-1,4-bis[(methansulfonyl)oxy]-butane (23). Benzoyl chloride (921 μL, 7.94 mmol) was added dropwise at 0 °C to a solution of dimesylate **6a** (1.73 g, 6.61 mmol), triethylamine (1.1 mL, 7.94 mmol), and 4-(dimethylamino)pyridine (40.4 mg, 0.33 mmol) in THF (15 mL). The mixture was reacted at rt for 3.5 h and then diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Separation of the crude product by flash column chromatography, eluent CH_2Cl_2/CH_3OH 25:1, gave the ester **23** (2.42 g, 100%) as a white solid which was recrystallized from AcOEt/(iPr)$_2$O. Mp 68−69 °C. R_f 0.43; $[\alpha]^{25}_D$ = −29.6 (c 1.00, $CHCl_3$); ^{1}H NMR: δ 8.08−8.03 (m, 2H), 7.65−7.58 (m, 1H), 7.51−7.44 (m, 2H), 5.51 (m, 1H), 4.57−4.32 (m, 4H), 3.04 (s, 3H), 3.01 (s, 3H), 2.33−2.24 (m, 2H); ^{13}C NMR: δ 165.7 (s), 133.6 (d), 129.7 (d, 2C), 129.0 (s), 128.6 (d, 2C), 69.2 (t), 68.2 (d), 65.2 (t), 37.7 (q), 37.4 (q), 30.3 (t); IR: 3014, 1721, 1265 cm^{-1}; MS: m/z (rel intensity) 271 (M^+ − OSO_2CH_3, 2), 105 (100), 77 (57). Anal. Calcd for $C_{13}H_{18}O_8S_2$: C, 42.62; H, 4.95. Found: C, 42.45; H, 5.03.

3(*S*)-3-(Benzoyloxy)-*N*-hydroxypyrrolidine (24). The hydroxylamine **24** was prepared from dimesylate **23** (366 mg, 1 mmol) according to the general procedure. A portion of the crude product, purified by flash column chromatographhy, eluent ethyl acetate, afforded **24** as a white solid, which was recrystallized from ethyl acetate/pentane. Mp 125 °C dec. R_f 0.35; $[\alpha]^{25}_D$ = +3.7 (c 0.77, CH_3OH); ^{1}H NMR: δ 8.06−8.02 (m, 2H), 7.60−7.39 (m, 3H), 6.35 (br, 1H), 5.53 (m, 1H), 3.53−3.03 (m, 4H), 2.56−2.34 (m, 1H), 2.14−1.96 (m, 1H); ^{13}C NMR: δ 166.2 (s), 132.1 (d), 129.6 (d, 2C), 128.6 (s), 128.3 (d, 2C), 73.5 (d), 64.1 (t), 57.0 (t), 30.0 (t); IR: 3585, 1274 cm^{-1}; MS: m/z (rel intensity) 207 (M^+, 1), 105 (100), 85 (56), 77 (80). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.37; H, 6.33; N, 6.30.

(3*S*)-3-(Benzoyloxy)-1-pyrroline *N*-Oxide (25). Oxidation of **24** according to the general procedure furnished exclusively the nitrone **25** (103 mg, 0.50 mmol, 50% from **23**) as a pure solid after flash column chromatography, eluent ethyl acetate/methanol 20:1. Mp 100−101 °C. R_f 0.25; $[\alpha]^{25}_D$ = −147.7 (c 1.04, $CHCl_3$); ^{1}H NMR: δ 8.03−7.99 (m, 2H), 7.63−7.41 (m, 3H), 7.09 (d, J = 1.8 Hz, 1H), 6.02 (dd, J = 7.7, 1.8 Hz, 1H), 4.35−4.20 (m, 1H), 4.06−3.92 (m, 1H), 2.91−2.71 (m, 1H), 2.47−2.33 (m, 1H); ^{13}C NMR: δ 165.8 (s), 133.5 (d), 131.8 (d), 129.6 (d, 2C), 129.0 (s), 128.5 (d, 2C), 74.3 (d), 61.4 (t), 27.0 (t); IR: 1719, 1578, 1256 cm^{-1}; MS: m/z (rel intensity) 205 (M^+, 19), 122 (89), 105 (100), 84 (93), 83 (74), 77 (49). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.14; H, 5.54; N, 6.93.

(3*S*)-3-(*N*,*N*-Dibenzylamino)-1-pyrroline *N*-Oxide (30) and (4*S*)-4-(*N*,*N*-Dibenzylamino)-1-pyrroline *N*-Oxide (31). Methanesulfonyl chloride (0.895 mL, 11.6 mmol) was added dropwise to an ice-cooled solution of the diol **26**[15,16] (1.50 g, 5.2 mmol) and triethylamine (1.76 mL, 12.6 mmol) in CH_2Cl_2 (45 mL). The mixture was reacted at −10 °C for 1 h and then allowed to warm to rt. After removal of the solvent *in vacuo*, the crude mixture was treated according to the general procedure for formation of the cyclic hydroxylamine. The resulting crude yellow oil was then oxidized under standard conditions to the crude regioisomeric nitrones **30** and **31**. Separation by flash column chromatography, eluent CH_2Cl_2/CH_3OH 30:1, afforded pure **30** (129 mg, 0.46 mmol, 9%) and **31** still contaminated with some of the major nitrone (43 mg, 0.15 mmol, 3%). **30**: mp 127−128 °C. R_f 0.08; $[\alpha]^{21}_D$ = −87.4 (c 0.73, $CHCl_3$); ^{1}H NMR: δ 7.36−7.24 (m, 10H), 6.87 (q, J = 1.8 Hz, 1H), 4.38−4.26 (m, 1H), 4.12−3.85 (m, 2H), 3.64 (A_2B_2 system, J = 13.7 Hz, 4H), 2.45−2.13 (m, 2H); ^{13}C NMR: δ 139.0 (s, 2C), 136.6 (d), 129.0 (d, 8C), 127.9 (d, 2C), 62.4 (d), 62.2 (t), 55.1 (t, 2C), 21.9 (t); IR (CCl_4): 3029, 2955, 1575, 1236 cm^{-1}; MS: m/z (rel intensity) 280 (M^+, 2), 263 (8), 91 (100). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.16; H, 7.39; N, 9.59. **31**: R_f 0.03; ^{1}H NMR: δ 7.38−7.21 (m, 10H), 6.90−6.85 (m, 1H), 4.02−3.83 (m, 3H), 3.60 (A_2B_2 system, J = 13.6 Hz, 4H), 2.79 (m, 2H); ^{13}C NMR: δ 138.2 (s, 2C), 134.7 (d), 128.6 (d, 4C), 128.5 (d, 4C), 127.4 (d, 2C), 63.5 (d), 53.9 (t, 2C), 53.6 (t), 31.8 (t); IR: 3032, 1595, 1263 cm^{-1}; MS: m/z (rel intensity) 280 (M^+, 3), 279 (4), 223 (16), 196 (18), 132 (28), 106 (88), 91 (100), 65 (80).

(2*S*)-2-(*N*,*N*-Dibenzylamino)-4-[(methansulfonyl)oxy]-butan-1-al (33). Triethylamine (167 μL, 1.2 mmol) and methanesulfonyl chloride (85 μL, 1.1 mmol) were added to a solution of the diol **26** (285 mg, 1 mmol) in CH_2Cl_2 (5 mL) cooled at −15 °C, and the mixture was reacted at this temperature for 1 h. The solution was then concentrated to complete precipitation of the formed salt. The supernatant was added at −60 °C to a solution previously prepared by addition of DMSO (156 μL, 2.2 mmol) dissolved in CH_2Cl_2 (1 mL) to a solution of $(COCl)_2$ (94 μL, 1.1 mmol) in CH_2Cl_2 (1 mL) at −60 °C. After 20 min, triethylamine (613 μL, 4.4 mmol) has been added and the mixture stirred for additional 10 min. Saturated $NaHCO_3$ has been added, and the product was extracted with diethyl ether. The organic phase was dried over Na_2SO_4 and concentrated to give the crude aldehyde **33**. Purification by flash column chromatography on silica, eluent CH_2Cl_2, gave the pure aldehyde **33** (90 mg, 0.25 mmol, 25%) partially racemized (23% ee measured by integration of the aldehydic proton signals in the ^{1}H NMR spectrum recorded in presence of 0.65 equiv of Yb(hfc)$_3$). R_f 0.47; $[\alpha]^{18}_D$ = −44.2 (c 0.74, $CHCl_3$); ^{1}H NMR: δ 9.73 (s, 1H), 7.41−7.25 (m, 10H), 4.41−4.33 (m, 1H), 4.30−4.16 (m, 1H), 3.74 (A_2B_2 system, J = 13.5 Hz, 4H), 3.39 (dd, J = 7.7, 5.5 Hz, 1H), 2.86 (s, 3H), 2.21−2.03 (m, 2H); ^{13}C NMR: δ 202.9 (d), 138.4 (s, 2C), 128.9 (d, 4C), 128.6 (d, 4C), 127.6 (d, 2C), 67.1 (t), 63.0 (d), 55.0 (t, 2C), 37.2 (q), 23.7 (t); IR: 3031, 1728 cm^{-1}; MS: m/z (rel intensity) 332 (M^+ − CHO, 65), 236 (57), 149 (67), 91 (100), 65 (74). Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41; N, 3.88. Found: C, 63.23; H, 6.70; N, 3.41.

(3*S*)-3-(*N*,*N*-Dibenzylamino)-1-pyrroline *N*-Oxide (30) by Reaction of Aldehyde 33 with Hydroxylamine. NH_2-OH·HCl (10 mg, 0.14 mmol) and K_2CO_3 (39 mg, 0.28 mmol) were added to a solution of the aldehyde **33** (47 mg, 0.13 mmol) in CH_3OH (4 mL). The mixture was stirred at rt for 30 min, H_2O and CH_2Cl_2 were added, and the organic phase was separated and dried over Na_2SO_4. The crude product (36 mg, 0.13 mmol, 100%) was chemically pure by comparison of its NMR spectra with those of the nitrone **30** obtained by the alternative procedure (see above), and its specific optical rotation ($[\alpha]^{22}_D$ = −24.2 (c 0.85, $CHCl_3$)) confirmed the occurred partial racemization.

The same reaction carried out on the crude aldehyde **33** gave, after removal of the solvent *in vacuo*, a crude product which was purified by flash column chromatography, eluent CH_2Cl_2/CH_3OH 30:1. Nitrone **30** (66 mg, 0.24 mmol, 24% from diol **26**) was collected chemically and enantiomerically pure. Mp 127−128 °C; $[\alpha]^{21}_D$ = −88.5 (c 0.79, $CHCl_3$). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.82; H, 7.18; N, 9.64.

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