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IODINE-INDUCED CYCLIZATIONS OF *N*-ALKOXYAMINOALKENES. A STEREOCONTROLLED APPROACH TO *trans*-2,6-DISUBSTITUTED PIPERIDINE ALKALOIDS†

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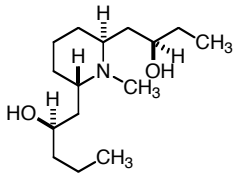
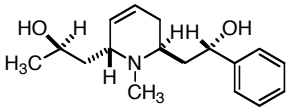
Abstract – Iodine-induced intramolecular cyclizations of γ-alkenyl-*N*-alkoxyamines preferentially produce 2,6-*trans*-disubstituted piperidines. Subsequent iodoetherifications of *N*-benzyloxypiperidines demonstrate the stereoselective transfer of oxygen to a proximate carbon *via* formation of bicyclic 1,3-*syn*-isoxazolidines. The strategy facilitates preparation of nonracemic piperidine diols from acyclic, optically active alcohols.

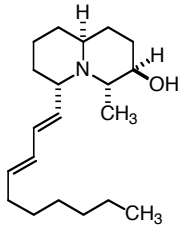
Piperidine alkaloids are among the most common heterocyclic natural products, and many studies have examined the development of stereoselective pathways for the preparation of functionalized examples of this family.[1,2] In part, these efforts have significantly contributed toward the stereocontrolled formation of amino alcohols as a central topic in medicinal chemistry.[3] Thus, examples such as dihydroandrachcine (**1**),[4] sedinine (**2**),[5] and clavepictine B (**3**)[6] continue to be topics for chemical studies. Herein, we describe the use of chiral, nonracemic *N*-alkoxyamines in iodine-induced cyclizations of acyclic alkenyl derivatives for the stereocontrolled construction of hydroxylated *trans*-2,6-disubstituted piperidines.



1 (Dihydroandrachcine)



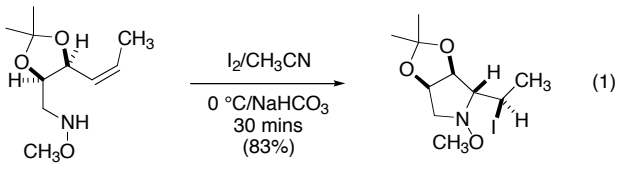
2 (Sedinine)



3 (Clavepictine B)

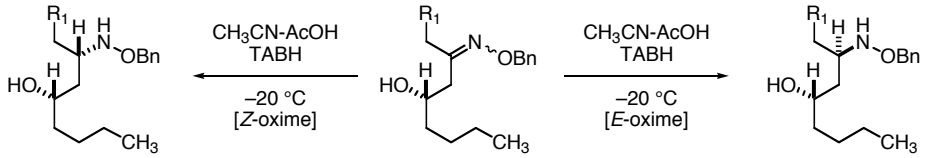
†*Dedicated to Dr. Pierre Potier in celebration of his 70th birthday.*

Intramolecular electrophilic cyclizations of olefinic precursors *via* amidomercuration or amidohalogenation are well known.[7] Amines are seldom used in this fashion owing to their increased nucleophilicity which leads directly to oxidation.[8] Previously, we have shown that *N*-alkoxyamines provide for efficient ring closures in the five-exo mode affording pyrrolidines.[9] As illustrated in Equation 1, high stereoselectivity may be achieved using *Z*-alkenes with a consideration for *anti* addition and minimization of A(1,3)-strain.[10]



(1)

To advance this chemistry of the synthesis of piperidines alkaloids, we prepared a series of 1,3-*syn*- and 1,3-*anti*-*N*-benzyloxyamino alcohols (**4**) and (**5**) *via* the development of stereoselective reductions of *E*- and *Z*-oximino ethers with the participation of a proximate hydroxyl group using tetramethylammonium triacetoxyborohydride (TABH) as summarized below.[11]

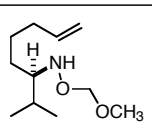
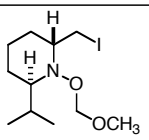
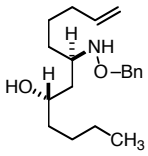
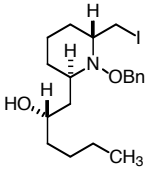
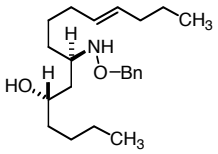
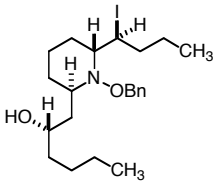
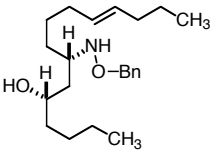
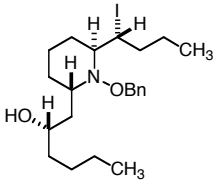
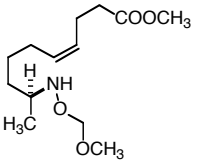
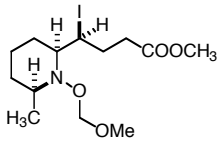
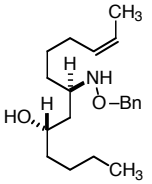
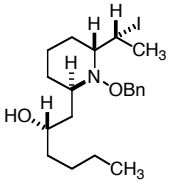
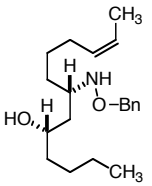
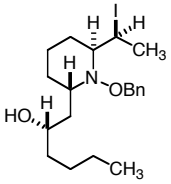
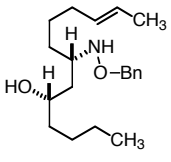
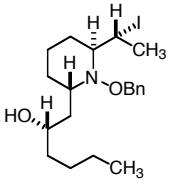
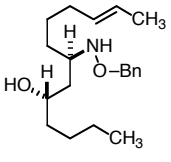
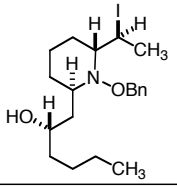


4 **5**

Table 1 summarizes the results of our iodine-induced cyclizations of γ-alkenylamines. General conditions utilized the dropwise addition of a CH_2Cl_2 solution of iodine (3 equivs) into a solution of starting *N*-alkoxyamine (CH_2Cl_2) containing a suspension of $NaHCO_3$ (10 equivs) with stirring at 0 °C. The use of solid $NaHCO_3$ neutralized HI and served to stabilize acid-labile protecting groups. Upon completion, reactions were quenched by the addition of saturated, aqueous $NaHSO_3$ and diluted with Et_2O leading to the isolation of the desired piperidines in good yields. Crude reaction mixtures were usually cleaned up by a rapid flash chromatography followed by NMR spectral assessment of diastereomeric mixtures of 2,6-*cis*- and 2,6-*trans*-piperidines. Subsequently careful chromatography separated pure *cis*- and *trans*-products for individual characterizations.

Cyclization of the amine of Entry 1, bearing a terminal alkene, was initially examined to evaluate the inherent diastereofacial selectivity. *trans*-2,6-Disubstituted piperidine was identified as the major product (approximately 2:1 *trans*/*cis* ratio). Owing to slow conformational isomerization and nitrogen inversion, ^{1}H NMR spectra of pure *trans*-2,6-piperidines are characterized by broad, poorly-defined signals for C2 and C6 methine hydrogens, while *cis*-isomers reveal the expected patterns for 2,6-diequatorial substitution. Eliel[12] has shown that C2 and C6 carbon resonances of *trans*-2,6-disubstituted piperidines

Table 1. Iodine Cyclizations of *N*-Alkoxyamines.

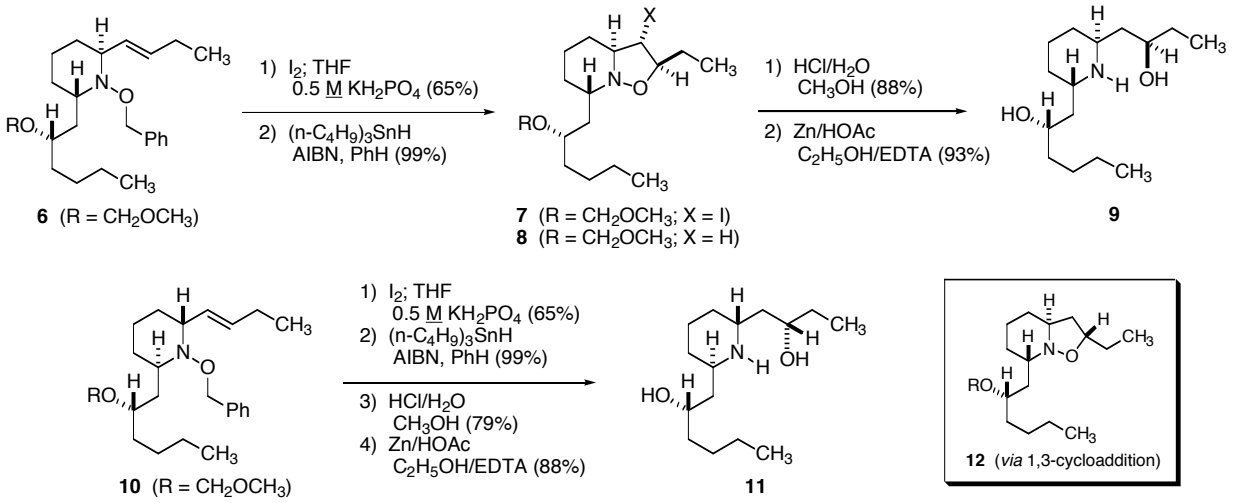
Entry	Starting Amine	Major Product	Isomer Ratio [*trans*/*cis*][a]	Total Yield
1.			63 : 37	81%[b]
2.			80 : 20	65%[b]
3.			81 : 19	94%[b]
4.			76 : 24	86%[b]
5.			33 : 67	80%[b,c]
6.			82 : 18	83%[b,c]
7.			55 : 45	74%[b,c]
8.			80 : 20	86%[b,c]
9.			80 : 20	87%[b,c]

[a] Ratios were determined by integration of selected ^{1}H NMR signals for product mixtures following silica gel flash chromatography. Careful flash silica gel chromatography or preparative TLC led to pure individual diastereomers for complete characterizations. [b] Reactions were not optimized: Iodine (3.0 equivs), CH_2Cl_2, solid $NaHCO_3$ (10 equivs), 0 °C. In some cases, methylene chloride/ether (2:1 by volume) was used as solvent. [c] Reactions were initiated at 0 °C and warmed to 20 °C.

appear upfield (Δδ ≅ 6.6 ppm) compared to the corresponding signals of *cis*-isomers. Additionally, the C4 carbon signal in *trans* compounds is also found upfield (Δδ ≅ 5.6 ppm) relative to the *cis*-isomer. These trends proved to be diagonistic throughout our series of compounds. The infusion of pure *cis*-product into reaction mixtures of Entry 1 failed to provide evidence for thermodynamic control. Thus, *trans*:*cis* ratios reflect products of kinetic nonequilibrating reactions. Finally, our previous efforts[9] leading to *N*-alkoxy-2,5-pyrrolidines included an X-Ray diffraction study which confirmed the *anti*-periplanar addition of nitrogen and iodide. The results of Table 1 do not suggest evidence of a change in mechanism. The incorporation of the β-hydroxyl substituent in Entry 2 coincides with enhanced production of *trans*-piperidine, and this trend remains intact throughout the series of starting *E*-olefins (Entries 3, 4, 8, 9). On the other hand, the interchange of O-methyl, O-benzyl and O-MOM protection in the starting hydroxylamines had a negligible effect on the observed stereoselectivity for these reactions. By comparison, the *Z*-alkene of Entry 5 led to a reversal of selectivity favoring the *cis*-isomer. In the case of the *syn*-1,3-*N*-benzyloxyamino alcohol of Entry 6, this was not observed. Moreover, the *anti*-isomer (Entry 7) underwent cyclization less efficiently producing nearly equal amounts of *cis*- and *trans*-product.[13] While our preliminary results have established a clear trend for cyclization to *trans*-2,6-disubstituted piperidines, the latter examples require further studies and perhaps suggest effects due to hydrogen bonding, which may lead to conformational preferences in the ring closure event.

Our *N*-alkoxypiperidines also allow an efficient, stereocontrolled transfer of oxygen along the carbon skeleton. For example, protection (MOMCl, (i-C_3H_9)/NC_2H_5, DMAP, CH_2Cl_2, 94%) and S_N2 elimination ($KOC(CH_3)_3$, $(C_2H_5)_3N$, DMF/THF (1:1 by volume) 65%) of the *trans*-product of Entry 4 gave the *E*-alkene (**6**) (Scheme 1). Iodine-induced cyclization led to a five-*endo* ring closure with dealkylation of the resulting oxonium species and formation of a single isoxazolidine (**7**) (65%).[14] Reduction quantitatively afforded the *syn*-1,3-disubstituted isoxazolidine (**8**) as confirmed by nOe studies.[15] Acid hydrolysis and

Scheme 1.



6 (R = CH_2OCH_3)

7 (R = CH_2OCH_3; X = I)
8 (R = CH_2OCH_3; X = H)

9

10 (R = CH_2OCH_3)

11

12 (*via* 1,3-cycloaddition)

N–O bond cleavage with zinc in acetic acid gave the piperidine diol (**9**). Similarly the isomeric *E*-alkene (**10**) yielded the chiral, nonracemic amino diol (**11**). Interestingly, these observations are in contrast to results obtained from dipolar cycloadditions of cyclic nitrones with terminal olefins, which exclusively provide bicyclic *anti*-3,5-disubstituted isoxazolidines, as exemplified by **12**.[16]

Overall, a synthesis strategy has been developed toward piperidine alkaloids, which utilizes nonracemic, acyclic alcohols as starting precursors for the transmission of functionality and stereochemistry along the carbon backbone. Our studies have described iodine-induced cyclizations of acyclic *N*-alkoxyamines yielding *trans*-2,6-disubstituted piperidines as major products. Dehydrohalogenations permit sequential iodine cyclizations in the five-*endo* mode to produce bicyclic *syn*-3,5-disubstituted isoxazolidines for reduction to 1,3-*syn*-amino alcohols.

ACKNOWLEDGEMENTS

We gratefully acknowledge the National Institutes of Health (GM-41560) for generous support.

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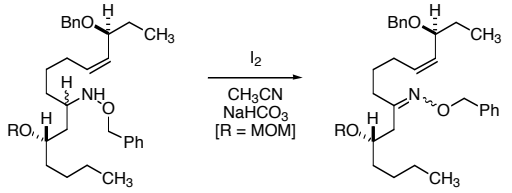
13. Less reactive alkenes failed to undergo cyclizations as shown by iodine oxidation of the example below.



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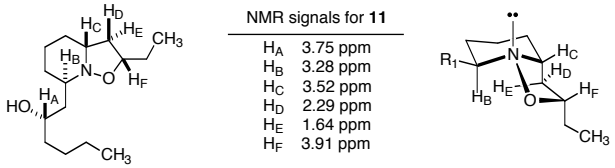
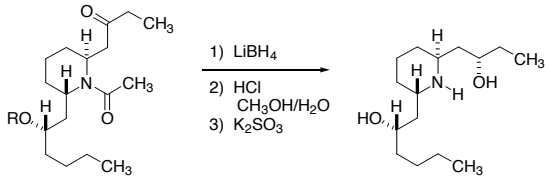
15. The nOe study of isoxazolidine (**11**) confirmed the 1,3-*syn* stereoassignment *via* irradiation at H_C revealing a 3.3% nOe of H_D and 1.3% of H_F. Irradiation of H_D gave 3.8% nOe of H_C and 6.5% nOe of H_F. No nOe was observed for H_C, H_D or H_F upon irradiation of H_B.



16. Carruthers and coworkers prepared bicyclic **12** by 1,3-dipolar cycloaddition en route to alleged andrachamine. However, their claim of a total synthesis was proven to be incorrect following our studies which conclusively demonstrated the misassignment of the natural product. These efforts demonstrated the conversion of **13** (from **8**) to the diastereomeric alcohol (**14**), which was shown to be identical to the product of N–O reduction from **12**. See: (a) W. Carruthers, P. Coggins, and J. B. Weston, *J. Chem. Soc., Perkin Trans. I,* 1990, 2323. (b) M. H. Osterhout, Ph.D. Thesis, Indiana University, Department of Chemistry, Bloomington, U.S.A., 1991.



13 (R = CH_2OCH_3) **14**