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An Aza-Achmatowicz Approach toward the Hydroxylated Piperidine Alkaloids (±)-Azimic Acid and (±)-Deoxocassine

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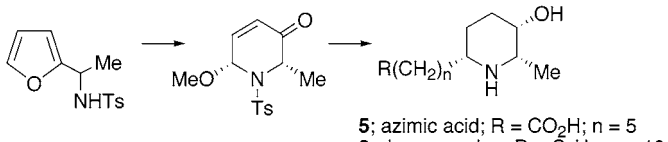
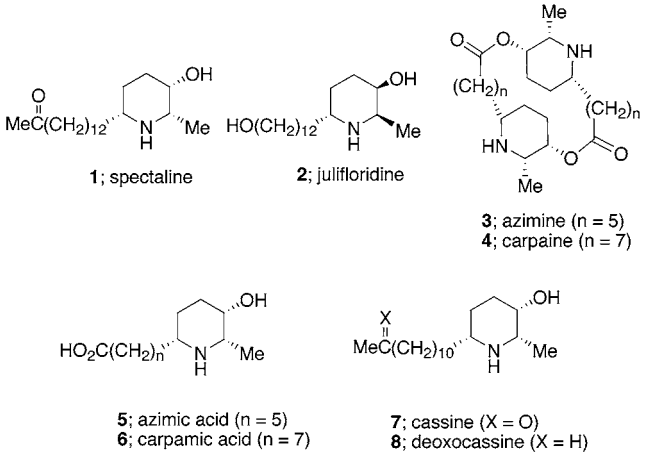
ABSTRACT



5; azimic acid; R = CO_2H; n = 5
8; deoxocassine; R = C_2H_5; n = 10

The synthesis of several *cis*-2,3,6-trisubstituted piperidines has been developed employing the aza-Achmatowicz oxidation as the key reaction step. Its usage is illustrated by the facile synthesis of the piperidin-3-ol alkaloids (±)-deoxocassine and (±)-azimic acid.

2,6-Disubstituted piperidin-3-ol alkaloids are abundantly found in nature and have attracted much attention in recent years from the synthetic community.[1] Typical representatives of this family include spectaline (**1**), julifloridine (**2**), azimine (**3**), and carpaine (**4**).[2,3] The latter two structures correspond to macrocyclic dilactones containing two molecules of the characteristic 2-methyl-3-piperidinol skeleton with a carboxyl group as a terminal substituent at the C-6 position.[4,5] They are readily hydrolyzed to azimic (**5**) and carpamic acid (**6**), which are presumably their biosynthetic precursors. Since their discovery in the 1960s, much effort has been directed to the synthesis of these and other related alkaloids such as cassine (**7**) and deoxocassine (**8**).[6] Besides the interesting



1; spectaline
2; julifloridine
3; azimine (n = 5)
4; carpaine (n = 7)
5; azimic acid (n = 5)
6; carpamic acid (n = 7)
7; cassine (X = O)
8; deoxocassine (X = H)

structural features, these compounds are also of pharmaceutical interest as they exhibit a wide range of biological activities.[7] The physiological effects stem from their ability to mimic carbohydrate substrates in a variety of enzymatic processes.

Despite the availability of many synthetic methods for this class of compounds,[8−10] there still exists a need to develop

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(7) (a) Fodor, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1985; Vol. 3, pp 1−90.

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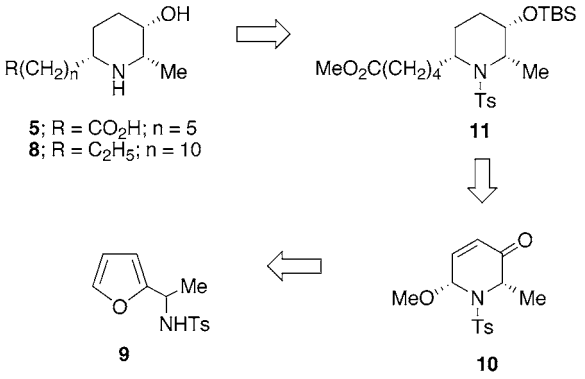
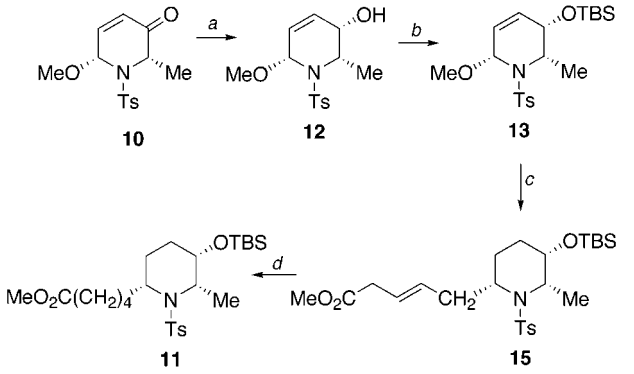
Scheme 1



Scheme 2 [a]



[a] Reagents: (a) $NaBH_4$, $CeCl_3$, MeOH, −40 °C; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 25 °C; (c) methyl 3-(trimethylsilyl)-4-pentenoate (**14**), $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (d) H_2, PtO_2, MeOH.

procedures more efficient than those currently in existence. As a result of our ongoing studies on natural product syntheses based on amidofuran chemistry,[11] we became interested in employing *N*-tosylaminofuran **9** for the synthesis of various *cis*-2,3,6-trisubstituted piperidine alkaloids. In this paper, we report a new approach to the total synthesis of azimic acid (**5**) and deoxocassine (**8**) based on the route shown in Scheme 1 which makes use of the aza-Achmatowicz oxidation[12] as a key reaction step in the overall sequence.

In an earlier study from our laboratory we had demonstrated the versatility of the aza-Achmatowicz oxidation for the synthesis of the putative indolizidine alkaloid 223A, which was isolated from the skin secretion of a neotropical frog.[13] Our retrosynthetic strategy for the present synthesis envisages initial construction of the functionalized piperidino ester **11** via a Lewis acid induced addition of a carbomethoxy-substituted allylsilane reagent to *N*-tosylaminal **10** (Scheme 1). The strategically placed carbomethoxy group of **11** can then be utilized toward formation of both piperidin-3-ols **5** and **8**. Accordingly, the readily available furyl sulfonamide **9**[14] was subjected to an oxidative ring expansion with *m*-MCPBA according to the conditions reported by Ciufolini.[15] The initially formed hemiaminal was immediately treated with trimethyl orthoformate and catalytic $BF_3{\cdot}OEt_2$ which furnished aminal **10** in 85% yield. Whereas the hemiaminal was difficult to purify, the resulting *N*-tosyl-*O*-methylaminal **10** is a stable crystalline solid that could be stored for extended periods of time. The exclusive *cis*-orientation of the substituent groups can be rationalized by assuming that $A^{1,3}$-strain of the tosyl group forces the methoxy and methyl groups to adopt a pseudoaxial orientation. Reduction of **10** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ (Luche conditions)[16] stereoselectively produced alcohol **12** (Scheme 2), whose configuration was elucidated by NMR studies. The reaction proved to be remarkably stereospecific, providing the desired *cis*-alcohol **12** in pure diastereomeric form and in 60% isolated yield. This result may be attributed to the steric hindrance between the pseudoaxially oriented 2,6-bulky substituents and an equatorially approaching hydride reagent which explains the exclusive formation of the *cis*-alcohol by axial approach of the hydride.[17]

Protection of the alcohol as the TBS ether (TBSCl, imidazole, DMAP, CH_2Cl_2, 82% yield) followed by reaction with methyl 3-(trimethylsilyl)-4-pentenoate (**14**) in the presence of $BF_3{\cdot}OEt_2$ led to the somewhat labile allylic ester **15**, which was immediately hydrogenated (H_2, PtO_2, MeOH) to give the key intermediate **11** in 57% yield. The choice of the hydrogenation catalyst proved to be crucial for the success of the reduction. Our first attempts used palladium

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(13) For the preparation of compound **10**, see: Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371.

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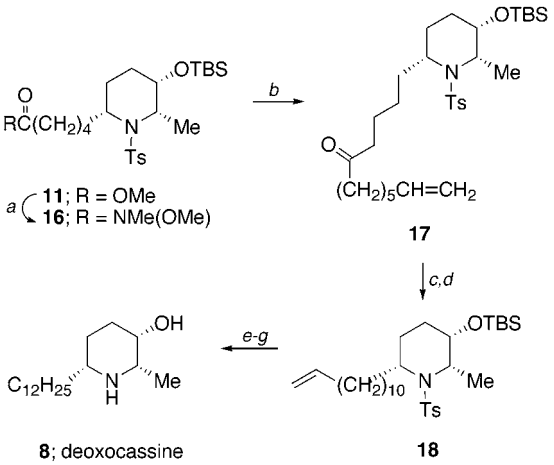
(17) For a related stereospecific reduction, see: Koulocheri, S. D.; Magiatis, P.; Skaltsounis, A.-L.; Haroutounian, S. A. *Tetrahedron* **2000**, *56*, 6135.

Scheme 3 [a]



[a] Reagents: (a) MeNH(OMe)·HCl, *i*-PrMgCl, THF, −20 °C; (b) CH_2═$CH(CH_2)_5I$, *t*-BuLi, heptane, −78 °C; (c) $TsNHNH_2$, EtOH, 25 °C; (d) DIBAH, NaOH, CH_2Cl_2, 0 °C; (e) H_2, PtO_2, MeOH; (f) TBAF, THF, 0 °C; (g) Li, NH_3,THF, −78 °C.

on carbon (Pd/C) as the catalyst in ethanol. The desired product was isolated in low yield with a nearly equal amount of the isomerized *N*-tosylenamine. On the other hand, the use of PtO_2 (Adams catalyst) afforded the desired saturated piperidine **11** as the exclusive product, with no evidence of epimerization at C-6. As suggested by others,[18] the preference for the *cis*-substitution pattern can be rationalized by assuming that the steric bulk associated with the tosyl group directs the attack of the allylsilane on the iminium ion to the side of the C_2-methyl group, thereby leading to the formation of the all *cis*-stereochemistry.

Having achieved a reliable synthesis of the key piperidine intermediate **11**, we proceeded to use this compound for the preparation of deoxocassine (**8**) as well as azimic acid (**5**). Accordingly, the ester functionality present in piperidine **11** was converted (85% yield) into the corresponding Weinreb amide **16** with methoxymethyl-amine hydrochloride and isopropylmagnesium chloride. Although *N*-methoxy-*N*-methylamides are generally prepared from the ester using an aluminum-based reagent,[19] we found that the use of *i*-PrMgCl[20] gave higher yields and resulted in a cleaner overall reaction. Treatment of **16** with 6-heptenyllithium in heptane at −78 °C provided the expected ketone **17** in 56% unoptimized yield (Scheme 3). The terminal π-bond present in **17** can be utilized for a synthesis of either cassine (**7**) or

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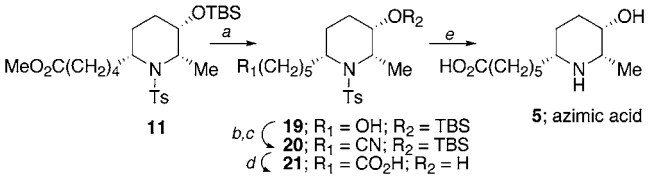
Scheme 4 [a]



[a] Reagents: (a) $LiAlH_4$, THF, 0 °C; (b) MsCl, Et_3N, CH_2Cl_2; 0 °C; (c) NaCN, DMF, 50 °C; (d) NaOH, MeOH, 70 °C; (e) Li, NH_3,THF, −78 °C.

deoxocassine (**8**) depending on the experimental conditions. Reduction of the carbonyl group in **17** proved more difficult than we originally anticipated. A Wolff−Kishner reduction of **17** provided a complex, intractable mixture of products. Instead, ketone **17** was converted to the corresponding tosylhydrazone and then treated with DIBAH/NaOH[21] which afforded **18** in reasonable yield. After hydrogenation of the double bond with PtO_2, the TBS protecting group was removed with TBAF and the tosyl group was cleaved using Li/NH_3 to furnish deoxocassine (**8**) in 92% yield for the three-step sequence.

Having successfully obtained deoxocassine (**8**) from piperidine **11**, we extended the above strategy to the synthesis of azimic acid (**5**). Our approach to **5** began with the LAH reduction of ester **11** which afforded the corresponding alcohol **19** in 97% yield (Scheme 4). Conversion of **19** to the mesylate in the normal fashion followed by cyanide displacement (NaCN, DMF) provided nitrile **20** which was hydrolyzed to carboxylic acid **21** in 89% yield. Deprotection of the TBS group occurred during the basic hydrolysis conditions used to convert **20** into **21** (NaOH, MeOH). Removal of the tosyl group with Li/NH_3 gave azimic acid (**5**) in 70% yield. The spectra data obtained were in good agreement with those reported in the literature.[8]

In conclusion, we have developed an efficient protocol for the preparation of hydroxylated piperidine alkaloids which employs an aza-Achmatowicz oxidation as the key reaction step. Its usage was illustrated by the facile synthesis of (±)-deoxocassine and (±)-azimic acid.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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