STUDIES OF ZOANTHAMINE ALKALOIDS. A GENERAL SCHEME FOR THE PREPARATION OF FUNCTIONALIZED 8-OXA-6-AZABICYCLO[3.2.1]OCTANES†

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Abstract – Studies have provided an efficient preparation of 8-oxa-6-azabicyclo[3.2.1]octanes. These functionalized hemi-aminal systems are readily incorporated into a variety of structures which exhibit the pharmacophore characteristics found in the zoanthamine alkaloids.

The isolation and characterization of zoanthamine (1) as a metabolite of colonial species of the genus Zoanthus has led to the discovery of a unique class of marine alkaloids.1,2 The complex, polycyclic natural products of this family elicit a broad spectrum of biological activity, including anti-inflammatory and analgesic effects, antitumor activity, inhibition of platelet aggregation and anti-osteoporetic properties.3 Miyashita and coworkers have communicated the first synthesis of norzoanthamine (2),4 and several studies have reported synthetic routes for preparation of the trans-fused AB and ABC ring system of 1 and 2.5 Additional reports from our laboratories and Hirama and coworkers have explored approaches toward zoanthenol (3) which illustrate a substituted aromatic A-ring within this interesting alkaloid framework.6 For the most part, investigators have theorized that the enamine-aminal heterocyclic core which is identified as the highly condensed DEFG ring system of 1, is responsible for

† Dedicated to Professor Yoshito Kishi in celebration of his 70th birthday.
the bioactivity. In fact, early studies toward 1 and 2 have focused on the construction of the cyclic hemi-aminal system. Herein, we communicate our studies which have provided a general pathway for preparation of a fully elaborated aminal heterocyclic core as a basic pharmacophore with appropriate functionalization as a building block for direct incorporation in complex molecular architectures.

Our synthetic pathway for efficient formation of the nonracemic bicyclic hemi-aminal system has utilized the Evans oxazolidinone 4 for direct iodolactonization yielding trans-5 (Scheme 1). Azide displacement and borane reduction leads to the chiral primary iodide 7 for α-alkylation with the acyl anion equivalent generated upon low temperature deprotonation of 8. Upon stirring with aqueous acid and subsequent careful basification, the α,β-unsaturated ketone 9 is isolated without causing polymerization. This reactive enone is purified by flash chromatography and directly undergoes Lewis acid-mediated Mukaiyama-Michael reactions as illustrated with the ketene acetal 10 to provide 11 as a precursor for cyclization studies. The ease of conjugate additions to 9 under mild conditions is particularly advantageous for developing molecular complexity in this system.

### Scheme 1

![Scheme 1](image)

Formation of the hemi-aminal system was examined from 11 utilizing tri-n-butylphosphine which led to a Staudinger reduction of azide followed by an internal aza-Wittig reaction to give imine 12 (Scheme 2). Direct treatment with Boc₂O in wet THF led to the isolation of the acyclic hydrolysis product 13. Subsequent deprotonation and dehydration using aqueous acetic acid at 50 °C gave 14 in 63% overall yield from 11. An improved three-step sequence utilized 11 for O-desilation and catalytic hydrogenation under one atmosphere of hydrogen gas followed by direct treatment with Boc₂O to yield 14 (80% overall).
Efforts to explore the use of functionalized 8-oxa-6-azabicyclo[3.2.1]octanes in Pd-catalyzed cross-coupling processes led to the Mukaiyama-Michael reaction of 15 with 11. However, the reaction conditions promoted facile double bond isomerization resulting in a 1:1 mixture of E/Z-β-stannylated enones 16 and 17. To circumvent this problem, we have transformed the methyl ester 14 (Scheme 2) into the allenic alcohol 18 as a mixture of syn- and anti-diastereomers, for use as a reactive substrate in the analogous Heck cross couplings.10

Studies toward a fully functionalized pharmacophore of zoanthamine (1) are summarized in Scheme 3. Asymmetric CBS reduction of the cyclohexenone 19 gave 20 with high enantioselectivity.11 Although application of the Ireland-Claisen rearrangement from 20 was not successful, the use of the Eschenmoser variant of the Claisen procedure gave the desired amide resulting from [3,3]-sigmatropic rearrangement. The direct use of the amide under Rh-catalyzed hydroboration conditions led to the reisolation of unreacted alkene. However, the hydride reduction12 of the N,N-dimethylamide afforded
primary alcohol 21 (97% for 2 steps from 20). Hydroboration of 21 and oxidative quench proceeded in high yield after silyl ether formation, and the subsequent Swern oxidation of a mixture of diastereomeric diols gave the keto-aldehyde 23. Transformation of 23 to the methyl ester 24 proceeded directly upon treatment with bromine in methanol (81% yield). On the other hand, the use of the Jones oxidation in THF/acetone at 0 °C with Celite quantitatively gave the corresponding carboxylic acid which was immediately used for conversion to the β-trimethylsilyl ester 25 under Mitsunobu conditions (DIAD, Ph₃P, CH₂Cl₂, 55%).

A critical step in the synthesis of the heterocyclic hemi-aminal core of zoanthamine utilized the chiral imine methodology of Pfau and d’Angelo. Thus, quantitative formation of imines 26 and 27 occurred at 22 °C using (S)-(−)-α-methylbenzylamine in the presence of TiCl₄ (4.0 equivalents) which served as a Lewis acid catalyst and as a water scavenger needed to drive these reactions to completion. Condensations of imines 26 and 27 with the Michael acceptor 11 (from Scheme 1) utilized catalytic amounts of fused zinc chloride in ether. While the Lewis acid may facilitate reversible formation of the enamine regioisomers 28 and 29, the 1,4-conjugate addition provided for reactions from the more substituted 28. Upon quenching with 10% aqueous acetic acid, the diketones 30ab were isolated in yields of 45 to 50%. Diagnostic signals in the ¹³C NMR spectra at 215.8, 209.3 and 171.5 ppm (data for 30a), characterized the presence of the three carbonyl units, and the integration of signals in the ¹H NMR spectra for the methyl singlet of the newly-formed stereogenic center indicated high diastereofacial selectivity (dr 95:5). The chemoselectivity of the process is somewhat surprising since the equilibrium between 26 and enamine 28 and the less substituted 29 also dictates a divergent pathway for reactivity. In fact, enamine 29 does not lead to 1,4-conjugate addition, but undergoes intramolecular acylation to produce, upon hydrolysis, the [2.2.2]bicyclic diketone as a persistent minor product (approximately 10% yields).

The Staudinger-aza-Wittig reaction of 30 with tri-butylphosphine gave the seven-membered imines 31ab which were isolated in high yield after flash silica gel chromatography. However, the aminal ring closure process proved more challenging than anticipated. Deprotection of 31a or 31b with TBAF in THF led to desilylation, but the cascade of internal ketalizations did not take place as expected. In fact, removal of the TBS silyl ether in 31a (HF•pyridines) led to characterization of the secondary alcohol 32, and further saponification of the methyl ester with aqueous LiOH proceeded without evidence of the desired cyclization. On the other hand, treatment with aqueous TFA at 100 °C, as previously described by Miyashita and coworkers, led to the ammonium salt 33. This sample was not stable under mild conditions for neutralization with aqueous sodium carbonate providing hydrolysis to material tentatively characterized as the imine 32 (R; R’ = H) or the corresponding zwitterion.
Our studies have illustrated the effective preparation of functionalized 8-oxa-6-aza bicyclo[3.2.1]octanes. This heterocyclic hemi-aminal core is an important feature of the zoanthamine alkaloids, which may be broadly incorporated into a variety of structural motifs for biological studies. Most significantly, the chiral imine methodology for asymmetric conjugate addition has provided a solution to the formidable synthetic challenge of constructing two vicinal quaternary stereogenic carbon centers. Further efforts from these laboratories will be reported in due course.

Scheme 3

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REFERENCES AND NOTES


10. Previously we have shown that allenic alcohols are excellent substrates for Heck cross-coupling reactions with aryl triflates as illustrated below:


13. Formation of TBS ether 22 aided in the recovery of the diastereomeric alcohols from the hydroboration process. Omission of the silyl ether protection leads to the expected diols in significantly lower yields.


17. Allylic (A^{1,3}) interactions are minimized in enamine 28. Thus, diastereofacial selectivity in the transition state for conjugate addition with 11 avoids nonbonded interactions with the phenyl of the chiral controller. Secondly, the concerted asynchronous transfer of the N-hydrogen of 28 to the α-carbon of the Michael acceptor 11 suggests similarities to the Alder-Ene reaction. These conditions are not met in the case of less-substituted enamine 29.

18. Upon workup with aqueous acetic acid, an internal condensation product identified as the [2.2.2]bicyclic dione i was isolated in approximately 10% yield. This side product was characterized as a mixture of C2 diastereomers with two carbonyl signals in the $^{13}$C NMR spectrum (δ 209.9 and 206.9). The $^1$H NMR data display the bridgehead C$_6$ hydrogen as a multiplet (δ 3.12–3.16) and the quaternary C$_3$ methyl as a singlet (δ 1.09). A doublet pattern centered at δ 1.20 (J = 7.3 Hz) is assigned as the C$_2$ methyl isomers.

![Diagram](https://example.com/diagram.png)