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

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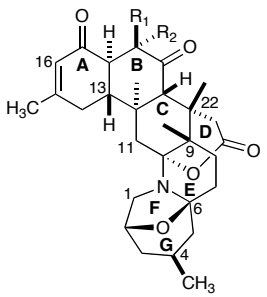
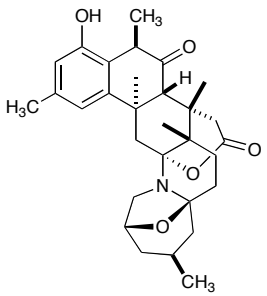
Abstract – Studies have provided an efficient preparation of 8-oxa-6-azabicyclo[3.2.1]octanes. These functionalized hemi-aminal systems are readily incorporated into a variety of structures which exhibit the pharmacophore characteristics found in the zoanthamine alkaloids.

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



1 zoanthamine $R_1 = CH_3$, $R_2 = H$
2 norzoanthamine $R_1 = H$, $R_2 = H$



3 zoanthenol

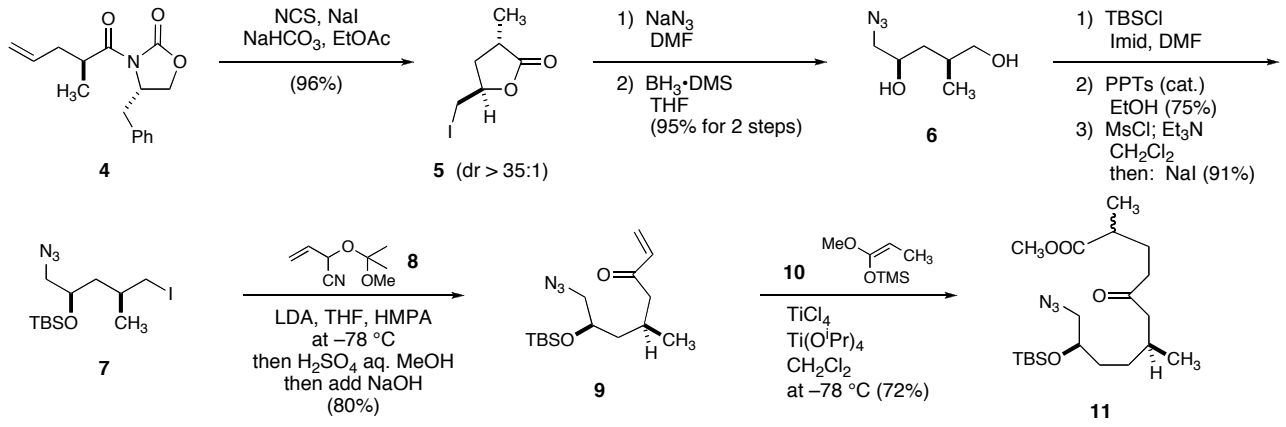
approaches toward zoanthenol (**3**) which illustrate a substituted aromatic A-ring within this interesting alkaloid framework.[6] For the most part, investigators have theorized that the enamine-aminal heterocyclic core which is identified as the highly condensed DEFG ring system of **1**, is responsible for

† *Dedicated to Professor Yoshito Kishi in celebration of his 70th birthday.*

the bioactivity.[7] In fact, early studies toward **1** and **2** have focused on the construction of the cyclic hemi-aminal system.[8] 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.

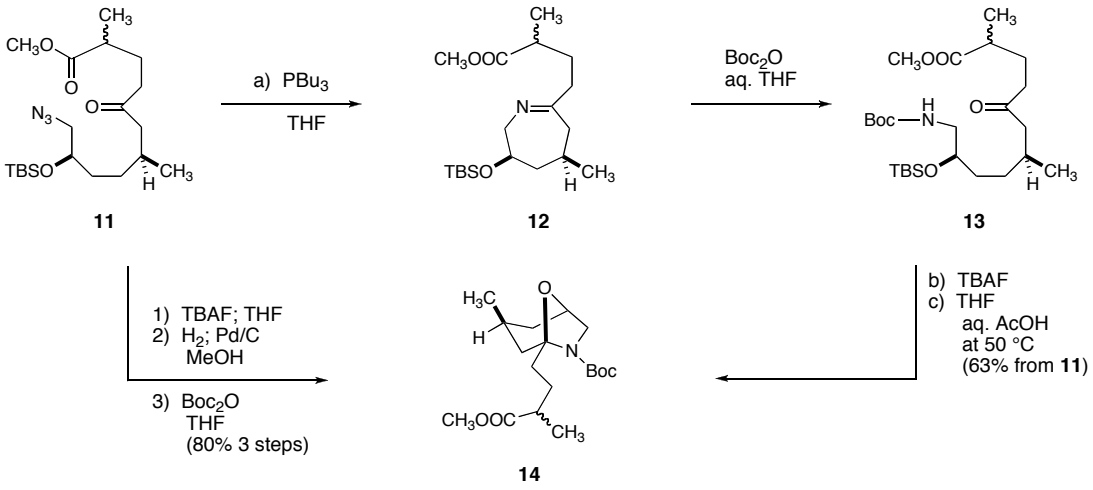
Our synthetic pathway for efficient formation of the nonracemic bicyclic hemi-aminal system has utilized the Evans oxazolidinone **4** for direct iodolactonization yielding *trans*-**5** (Scheme 1).[8a] Azide displacement and borane reduction leads to the chiral primary iodide **7** for α-alkylation 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

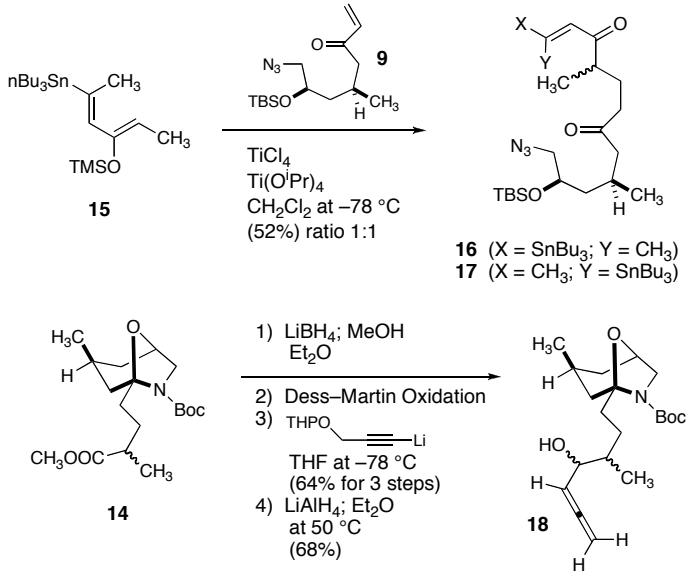


Formation of the hemi-aminal system was examined from **11** utilizing tri-n-butylphosphine which led to a Staudinger reduction of azide followed by an internal aza-Wittig reaction to give imine **12** (Scheme 2).[9] Direct treatment with Boc_2O in wet THF led to the isolation of the acyclic hydrolysis 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 Boc_2O to yield **14** (80% overall).

Scheme 2



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 reduction[12] of the N,N-dimethylamide afforded

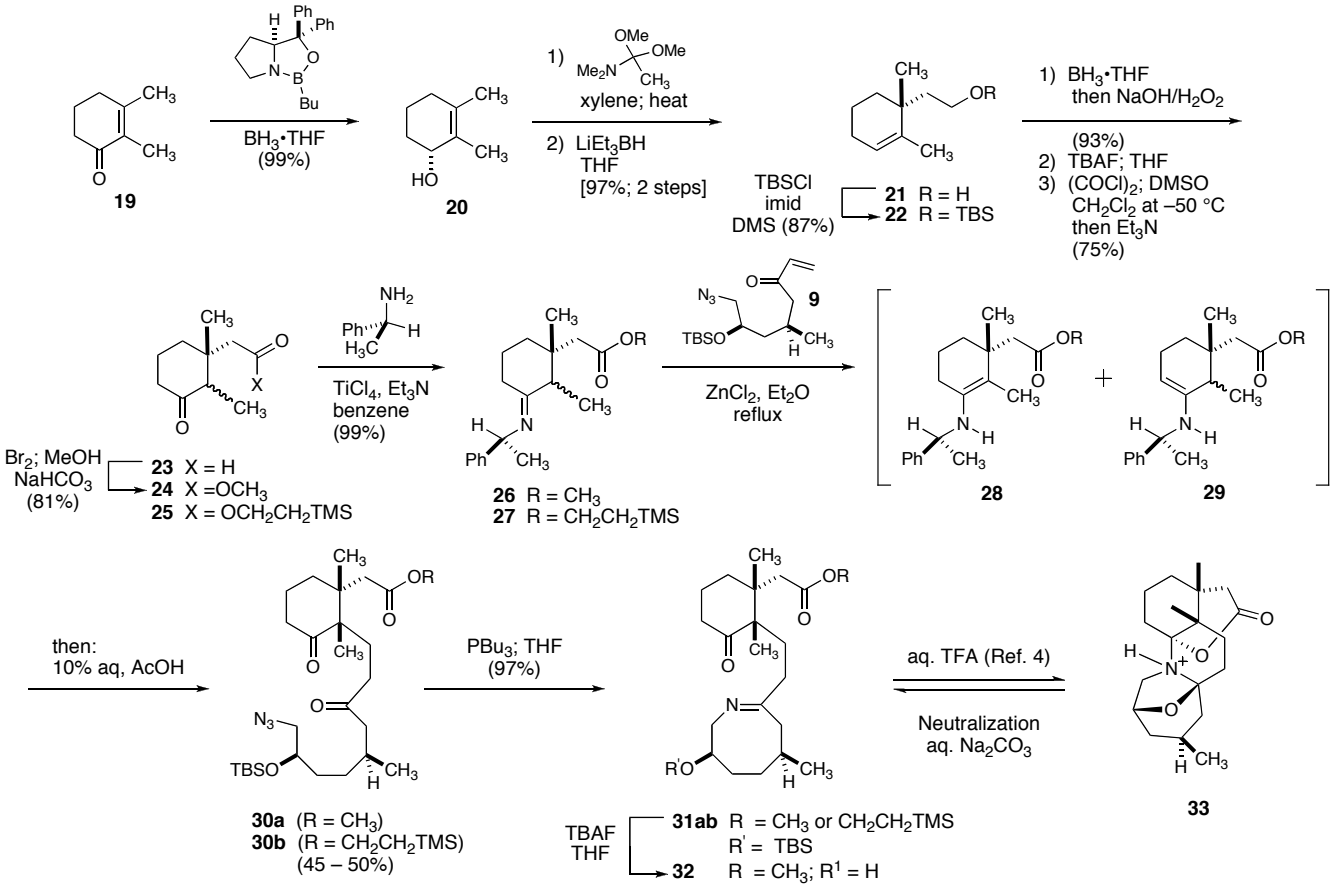
primary alcohol **21** (97% for 2 steps from **20**). Hydroboration of **21** and oxidative quench proceeded in high yield after silyl ether formation,[13] and the subsequent Swern oxidation of a mixture of diastereomeric diols gave the keto-aldehyde **23**. Transformation of **23** to the methyl ester **24** proceeded directly upon treatment with bromine in methanol (81% yield).[14] 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-trimethylsilylethyl ester **25** under Mitsunobu conditions (DIAD, Ph_3P, CH_2Cl_2, 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.[15] Thus, quantitative formation of imines **26** and **27** occurred at 22 °C using (*S*)-(–)-α-methylbenzylamine in the presence of $TiCl_4$ (4.0 equivalents) which served as a Lewis acid catalyst and as a water scavenger needed to drive these reactions to completion.[16] 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**.[17] Upon quenching with 10% aqueous acetic acid, the diketones **30ab** were isolated in yields of 45 to 50%. Diagnostic signals in the ^{13}C 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 ^{1}H 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).[18]

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,[4] 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-azabicyclo[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



ACKNOWLEDGEMENTS

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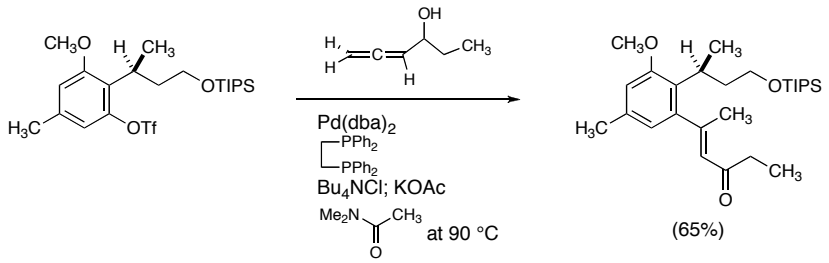
10. Previously we have shown that allenic alcohols are excellent substrates for Heck cross-coupling reactions with aryl triflates as illustrated below:



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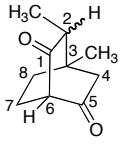
17. Allylic ($A^{1,3}$) interactions are minimized in enamine **28**. Thus, diastereofacial selectivity in the transition state for conjugate addition with **11** avoids nonbonded interactions with the phenyl of the chiral controller. Secondly, the concerted asynchronous transfer of the N-hydrogen of **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 C_2 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.



i