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Studies of Zoanthamine Alkaloids. Enantiocontrolled Construction of the Tetracyclic Hemi-Aminal Core.

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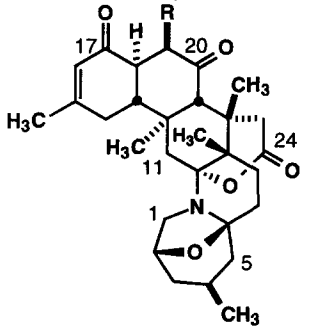
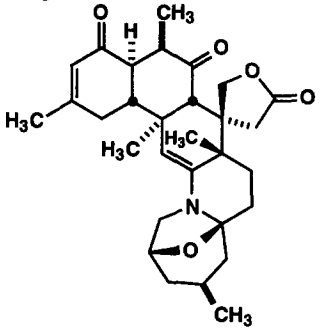
Abstract: *A concise enantiocontrolled synthesis of the enamine-aminal heterocyclic core found in the zoanthamine alkaloids is presented. Conjugate addition of a chiral imine provides for excellent diastereofacial selectivity in the generation of the quaternary C_9 asymmetry of* ***4****.*

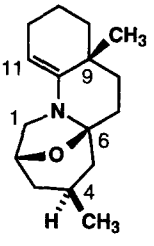
The zoanthamine alkaloids have been described as a family of marine metabolites with a unique array of structural and stereochemical complexity.[1] Zoanthamine (**1**) has displayed potent inhibitory activity toward phorbol myristate-induced inflammation in addition to powerful analgesic effects comparable to indomethacin. The inhibition of growth of P388 murine leukemia cell cultures has been reported,[2a] and very recently, norzoanthamine (**2**) has been shown to suppress the loss of bone weight and strength in ovariectomized mice.[2b] Recently, Tanner and coworkers have described model studies toward preparation of the A/B-*trans*-decalone ring system.[3] As a prelude to studies for total synthesis, our efforts have examined methodology for an enantiocontrolled pathway to the tetracyclic enamine **4**, which is a prominent feature of these natural products (**1**, **2**, and **3**). This communication demonstrates the effective use of an asymmetric Michael addition reaction followed by an intramolecular aza-Wittig condensation for construction of the novel hemi-aminal **4**.



1 (zoanthamine; R = CH_3)
2 (norzoanthamine; R = H)



3 (28-deoxyzoanthenamine)



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Our synthesis studies began with an enantioselective preparation of the requisite C_1-C_5 amino alcohol fragment as described in Scheme 1.[4] Evans methodology for asymmetric alkylation provided the known oxazolidinone **6** (98% de).[5] An efficient iodolactonization of **6** led to the *trans*-disubstituted butyrolactone **7** with outstanding diastereoselectivity (ratio >35:1). *In situ* generation of N-iodosuccinimide (NIS) under buffered conditions following the protocol described by Merck investigators,[6] apparently contributed to a significant improvement in the observed 1,3-asymmetric induction for this kinetic cyclization compared to results for iodine.[7]

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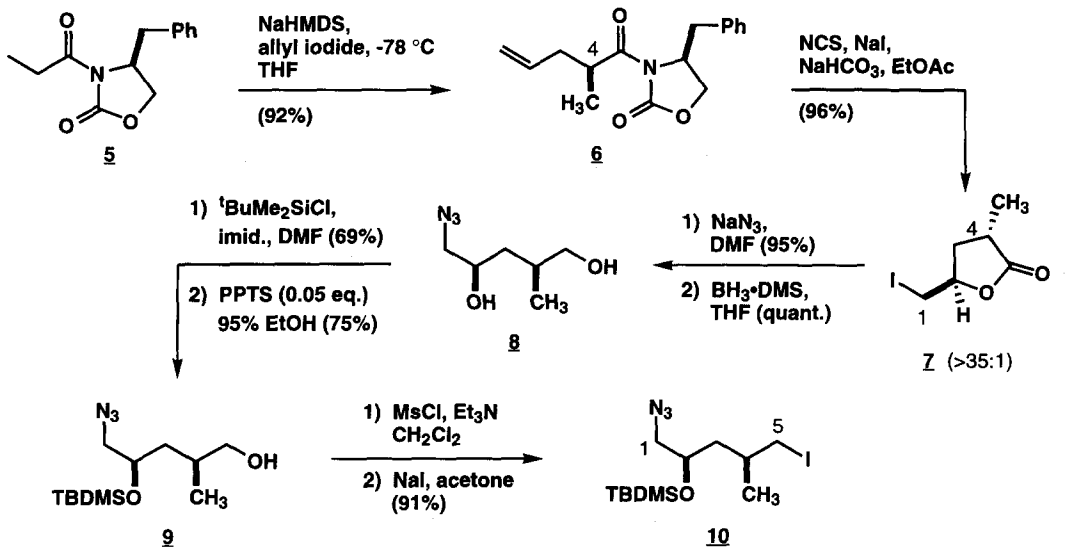
Scheme 1



The iodolactonization of 2-methyl-4-pentenoic acid has been reported to yield the corresponding *cis*-butyrolactone isomer with modest selectivity. However, the chiral auxiliary of **6** introduces the potential for A(1,3) strain in the transition state (Figure 1). Thus, nonbonded interactions are relieved in the iminium ion with placement of the C-4 methyl group in the pseudo-axial disposition. A minimization of 1,3-diaxial interactions results in a pseudo-equatorial orientation for the developing iodomethyl substituent.[8]

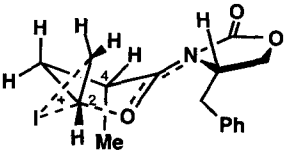


Figure 1

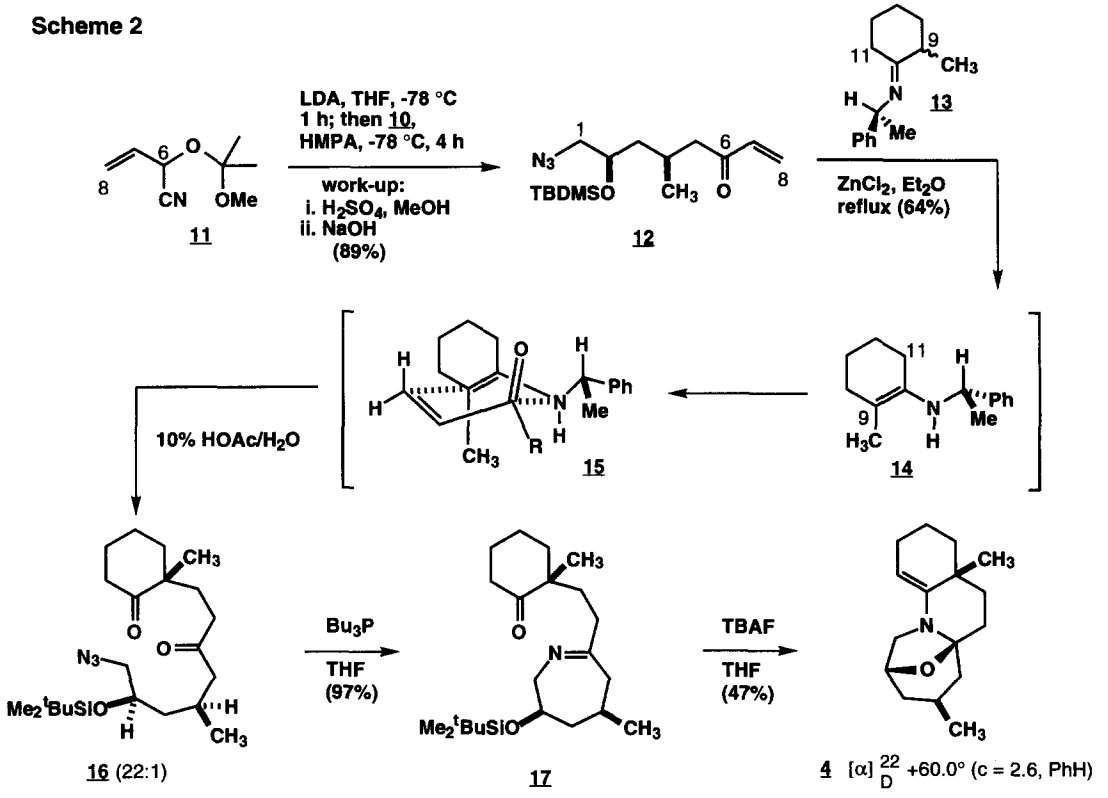
Azide displacement and the subsequent quantitative borane reduction of lactone **7** gave diol **8**. Silylation of the diol and selective deprotection[9] afforded the primary alcohol **9**, which was transformed into iodide **10** ($[\alpha]_D^{25}$ –8.8° (c = 0.02, $CHCl_3$)) via standard procedures.

Development of the stereogenic quaternary center at C-9, and cyclization to the hemi-aminal core **4** are described in Scheme 2. Low temperature deprotonation of the cyanohydrin **11**[10] afforded a reactive enolate for α-alkylation with iodide **10**. Subsequent mild hydrolysis of this acyl equivalent cleanly produced the vinyl ketone **12** (89% yield) without evidence of polymerization. The critical step in the formation of the C-8/C-9 bond of **4** was accomplished by utilizing the chiral imine methodology of Pfau and d'Angelo.[11a,11c] This deracemizing alkylation of 2-methylcyclohexanone occurred with initial preparation of chiral imine **13**.[11b] In the presence of fused zinc chloride (0.5 equiv.), rate-limiting isomerization to the more substituted enamine **14** triggers conjugate addition to the α,β-unsaturated ketone **12**. A minimization of nonbonded allylic interactions of the chiral controller unit of **14** with the neighboring C-11 methylene dictates facial approach (opposite to phenyl). It has been postulated that initial coordination of the enone may occur through the contact pair **15**.[12] In this manner, diketone **16** was obtained in 64% yield upon mild acidic hydrolysis (10% aqu. AcOH; 3 hrs). Remarkable diastereoselectivity was established (ratio 22:1) via ^1H NMR (500 MHz)

analysis of the C-9 methyl signals of product prior to purification. The C-9 stereoassignment of **16** is based upon the literature precedent.[11,12]

Finally, the amino functionality of **16** was released upon application of the Staudinger reaction of the primary azide with *tri*-n-butylphosphine. Direct intramolecular aza-Wittig condensation led to isolation of the desired tetrahydroazepine **17** in excellent yield (^{13}C NMR δ 205.1 and 99.4).[13] Hemi-aminal **4** was produced by desilylation of **17**, which resulted in ketalization, amination, and dehydration to the tetracyclic core of the zoanthamine alkaloids.[14]

Scheme 2



In summary, these studies have demonstrated the construction of a novel enamine-hemiaminal system. Enantiocontrol was established at a critical quaternary site via an asymmetric Michael addition, and the aza-Wittig process initiated the cascade of internal aminations. Further studies toward the synthesis of zoanthamine will be reported in due course.

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14. Characterization of the hemi-aminal **4** is provided as follows: R_f = 0.15 in 10% EtOAc/hexanes; $[\alpha]_D^{22}$ 60.0° (c = 2.6, PhH); IR ν_{max} 2942, 1645(m), 1475, 1367, 1228, 1073 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.45 (m, 1H), 4.43 (m, 1H), 3.03 (t, *J* = 6.6 Hz, 1H), 2.97 (d, *J* = 7.8 Hz, 1H), 2.04-2.30 (m, 4H), 1.93 (dd, *J* = 13.0 Hz, 5.3 Hz, 1H), 1.72-1.84 (m, 2H), 1.64-1.72 (m, 2H), 1.54-1.62 (m, 2H), 1.40-1.52 (m, 2H), 1.3-1.40 (m, 2H), 1.24 (s, 3H), 0.72 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 144.7, 97.6, 91.1, 73.9, 48.8, 42.7, 39.1, 39.0, 37.9, 36.3, 31.6, 26.5, 24.4, 23.2, 22.1, 18.8; MS (CI/NH_3), *m/z* (rel. int.) 247(9), 232(3); HRMS (CI/NH_3) calculated for $C_{16}H_{25}NO$ 247.1936, found 247.1943.