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

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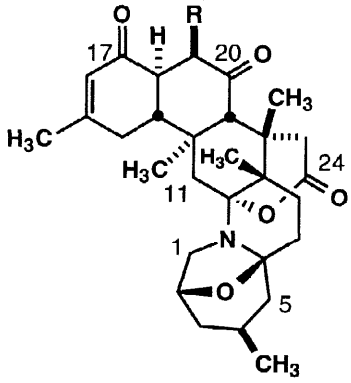
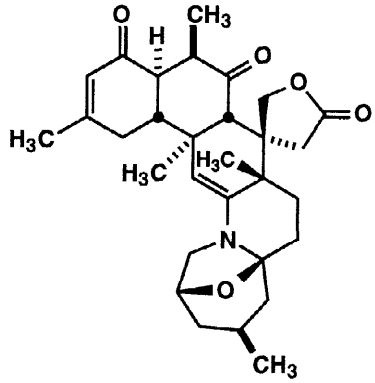
Abstract: *A concise enantiocontrolled synthesis of the enamine-aminal heterocyclic core found in the zoanthamine alkaloids is presented. Conjugate addition of a chiral imine provides for excellent diastereofacial selectivity in the generation of the quaternary C_9 asymmetry of* ***4****.*

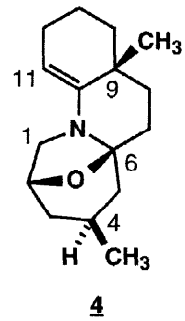
The zoanthamine alkaloids have been described as a family of marine metabolites with a unique array of structural and stereochemical complexity.[1] Zoanthamine (**1**) has displayed potent inhibitory activity toward phorbol myristate-induced inflammation in addition to powerful analgesic effects comparable 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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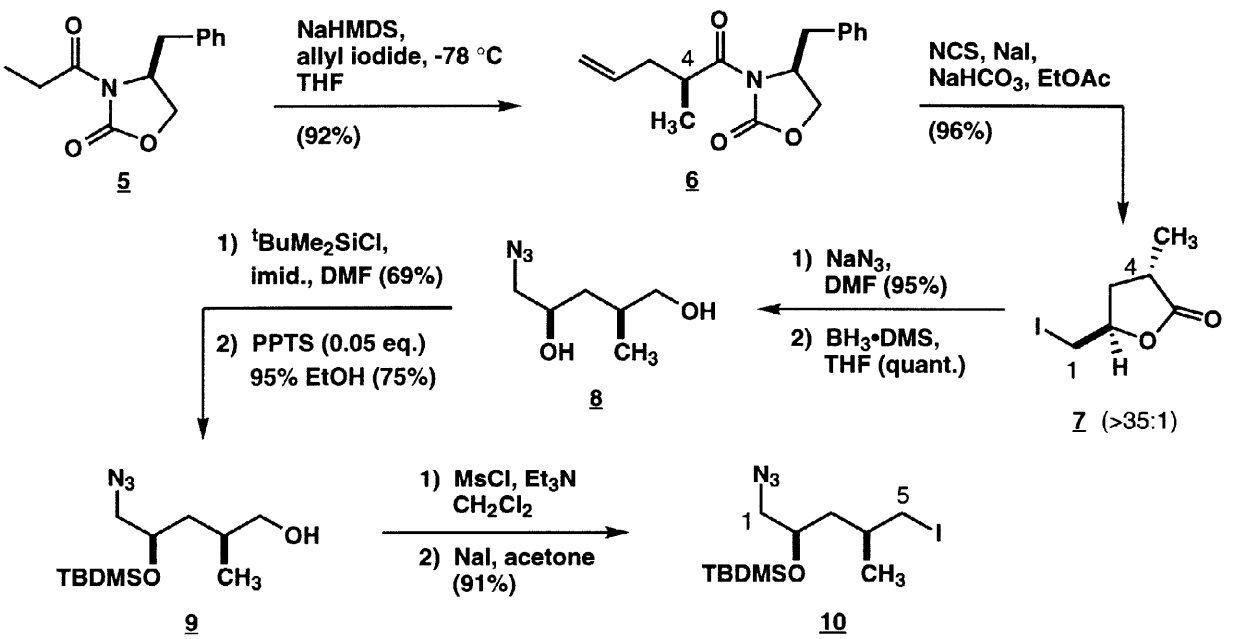
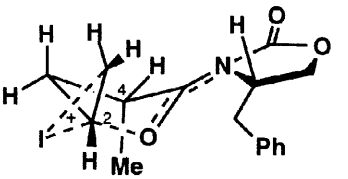
Scheme 1



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



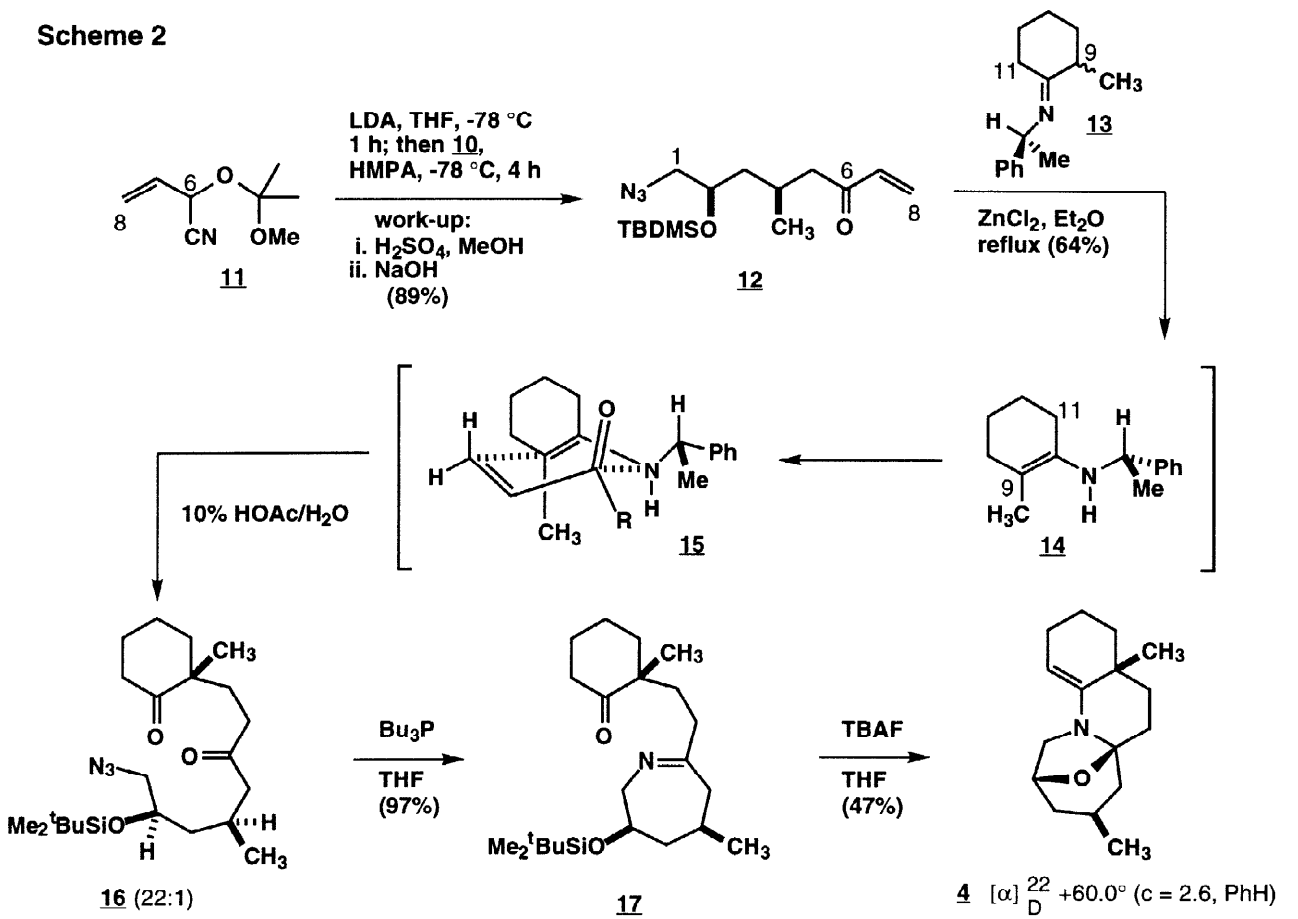
Azide displacement and the subsequent quantitative borane reduction of lactone **7** gave diol **8**. Silylation of the diol and selective deprotection[9] afforded the primary alcohol **9**, which was transformed into iodide **10** ($[\alpha]_D^{25}$ –8.8° (c = 0.02, $CHCl_3$)) via standard procedures.

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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References:

1. a) Rao, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkateswarlu, Y.; Rosser, R. M.; Faulkner, D. J.; Chen, M. H. M.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 7984. b) Rao, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkateswarlu, Y.; Rosser, R. M.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 3757. c) Rao, C. B.; Rao, D. V.; Naju, V. S. N.; Sullivan, B. W.; Faulkner, D. J. *Heterocycles* **1989**, *28*, 103. d) Rahman, A. -U.; Alui, K. A.; Abbar, S. A.; Choudhary, M. I.; Clardy, J. *Tetrahedron* **1989**, *30*, 6825.
2. a) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocycl. Commun.* **1995**, *1*, 207. b) Kuramoto, M.; Hayashi, K.; Fujitani, Y.; Yamaguchi, K.; Tsuji, T.; Yamada, K.; Ijuin, Y.; Uemura, D. *Tetrahedron Lett.* **1997**, *38*, 5863.
3. a) Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand.* **1997**, *51*, 1217. b) Tanner, D.; Andersson, P. G.; Tedenborg, L.; Somfai, P. *Tetrahedron* **1994**, *50*, 9135.
4. All new compounds were purified by silica gel chromatography and fully characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and HRMS data.
5. a) Ho, G., -J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271. b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
6. a) Maligres, P.E.; Upadhyay, V.; Rossen, K.; Cianciosi, S.J.; Purick, R.M.; Eng, K.K.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 2195. b) Vankar, Y.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233.
7. Moon, H.-S.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504.
8. Tamura, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079.
9. Isoe, S.; Katsumura, S.; Okada, T.; Yamamoto, K. *Tetrahedron Lett.* **1987**, *28*, 5865.
10. a) Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, *100*, 8272. b) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395.
11. a) For a review; d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459. b) Revial, G.; Pfau, M. *Org. Synth.* **1991**, *70*, 35. c) d'Angelo, J.; Guingant, A. *Tetrahedron Lett.* **1988**, *29*, 2667.
12. For a mechanistic presentation: Hickmott, P.W. in *The Chemistry of Enamines*, Part 1; Rappoport, Z. Ed.; John Wiley & Sons: New York, 1994 pp. 843-871. The initial complex **15** may progress along the reaction coordinate through an aza-ene mechanism for concerted proton transfer, or via formation of the hetero-Diels-Alder dihydropyran with subsequent isomerization.
13. For examples of aza-Wittig cyclizations: a) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 1923. b) White, J.D.; Cammack, J.H.; Sakuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 8970. c) Tanner, D.; Almario, A.; Högberg, T. *Tetrahedron* **1995**, *51*, 6061. d) Molina, P.; Fresneda, P.M., Almendros, P. *Heterocycles*, **1993**, *36*, 2255.
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.