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# Biomimetic Macrocycle-Forming Diels–Alder Reaction of an Iminium Dienophile: Synthetic Studies Directed Toward Gymnodimine

**Jeffrey W. Johannes, Steve Wenglowsky, and Yoshito Kishi***

*Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138*

*kishi@chemistry.harvard.edu*

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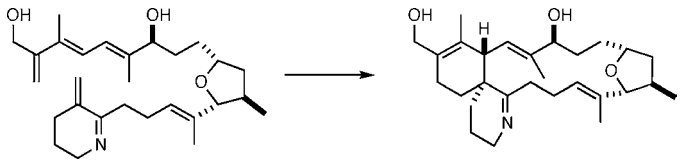
## ABSTRACT



**The macrocyclic core of gymnodimine has been constructed via an intramolecular Diels–Alder reaction of an α,β-unsaturated iminium dienophile in water. The cycloaddition furnished a single *exo*-product, along with two *endo*-products. Through X-ray analysis of a suitable derivative, the stereochemistry of the *exo*-product was established, thereby demonstrating that its stereochemistry matches that of gymnodimine. In contrast, macrocyclization of an analogous α,β-unsaturated ketone dienophile gave only undesired *endo*-products. Interestingly, the imine dienophile shows remarkable stability in water.**

Gymnodimine (**1**) was first isolated from oysters collected from the Foveaux Strait, South Island, New Zealand, by Yasumoto and co-workers in 1995 (Figure 1).[1] Blunt, Munro, and co-workers established the relative and absolute stereochemistry via single-crystal X-ray analysis.[2] Subsequently, Miles and co-workers isolated gymnodimines B and C.[3] Gymnodimine is a member of a large class of natural products bearing a cyclic imine fused to a cyclohexene ring and a macrocarbocycle. Members of this class of natural products include the pinnatoxins,[4] the pteriatoxins,[5] symbioimine,[6] the prorocentrolides,[7] the spirolides,[8] and spiroprorocentrimine.[9]

Upon isolation and structure elucidation of pinnaxtoxin A, Uemura proposed that the macrocarbocycle of the natural

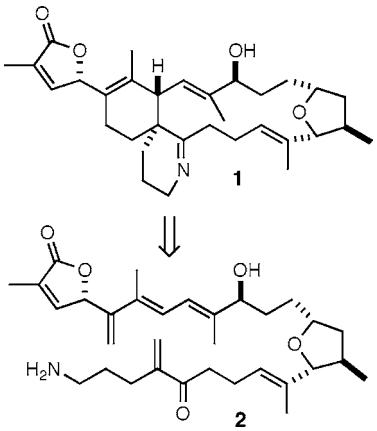


**Figure 1.** Structure of gymnodimine (**1**) and the hypothetical biosynthetic precursor **2**.

(1) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093−7096.
(2) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889−4890.
(3) Miles, C. O.; Wilkins, A. L.; Stirling, D. J.; MacKenzie, A. L. *J. Agric. Food Chem.* **2003**, *51*, 4838−4840.
(4) (a) Takada, N.; Umemura, N.; Suenaga, K.; Chou, T.; Nagatsu, A.; Haino, T.; Yamada, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3491−3494. (b) Chou, T.; Kamo, O.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023−4026. (c) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4027−4030. (d) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S. Z.; Chen, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 1155−1156.

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product might be biosynthesized via an intramolecular Diels−Alder reaction.[4d] Due to the structural similarities within this class of natural products, this biosynthetic hypothesis is applicable to gymnodimine and all other members of this class. The hypothetical linear biosynthetic precursor **2** of gymnodimine is depicted in Figure 1. In the synthetic direction, conversion of **2** to **1** requires two discrete steps: cyclic imine formation and a formal Diels−Alder reaction. This process could involve direct macrocyclization of ketone **2** followed by cyclic imine formation or, conversely, initial α,β-unsaturated imine formation (**16**, Scheme 3) followed by Diels−Alder macrocyclization. Close inspection of the stereochemistry of the resulting cyclohexene ring reveals that the Diels−Alder reaction must occur through the *exo*-mode, a common feature among most members of this class of natural products.

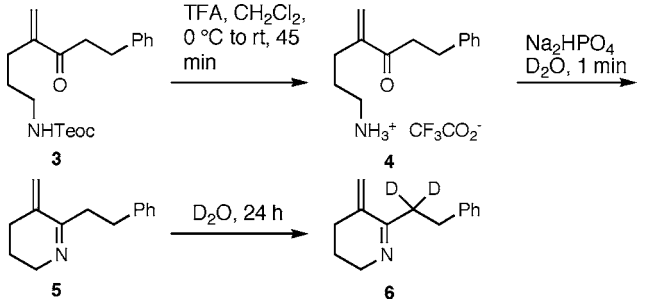
In the synthesis of pinnatoxin A, we mimicked the biosynthetic pathway suggested by Uemura.[10] In that work, the macrocarbocycle of pinnatoxin was constructed via an intramolecular Diels−Alder reaction using an α,β-unsaturated ketone as a dienophile followed by imine formation at high temperature. The cycloaddition occurred with a 5:1 *exo*/*endo*-selectivity at 70 °C. However, the facial selectivity of the *exo*-mode was close to 1:1. Overriding the inherent *endo*-selectivity known for Diels−Alder reactions and controlling the diastereofacial selectivity of the *exo* process are significant synthetic challenges. In the context of gymnodimine, several potential solutions to this problem have been disclosed.[11]

One might be tempted to hypothesize that an enzyme is required to form the macrocarbocycle present in these natural products. In recent years, several groups have reported isolation of an enzyme that catalyzes a Diels−Alder process.[12] The mechanistic details have also been examined from a theoretical perspective.[13] Most of these works have centered around α,β-unsaturated ketones as a dienophile.

While the Diels−Alder motif appears quite often in nature, this class of natural products is unique due to the intriguing possibility that the macrocyclization may be facilitated through the formation of an intramolecular α,β-unsaturated imine. MacMillan and co-workers have shown that formation of an α,β-unsaturated iminium ion formed via condensation of a secondary amine with a ketone creates a potent dienophile that is reactive toward a wide variety of dienes.[14] In the gymnodimine system, intramolecular condensation of the primary amine **2** with the ketone and subsequent protonation could provide a similar dienophile, cf. **16** in Scheme 3. In this letter, we report an intramolecular Diels−Alder reaction of an α,β-unsaturated iminium dienophile that allows us to construct the macrocyclic ring system of gymnodimine.

Our experimental efforts began by exploring the feasibility of intramolecular imine formation using compound **3** as a model (Scheme 1). Deprotection of the Teoc group afforded

**Scheme 1.** Imine Formation




amine salt **4**. Treatment of this salt in $D_2O$ with $Na_2HPO_4$ furnished α,β-unsaturated imine **5**. After standing for 24 h, complete deuterium incorporation was observed at the methylene α to the imine.[15]

Imine formation and stability were monitored by $^1H$ NMR (Figure 2). Spectrum **a** was taken 5 min after dissolving

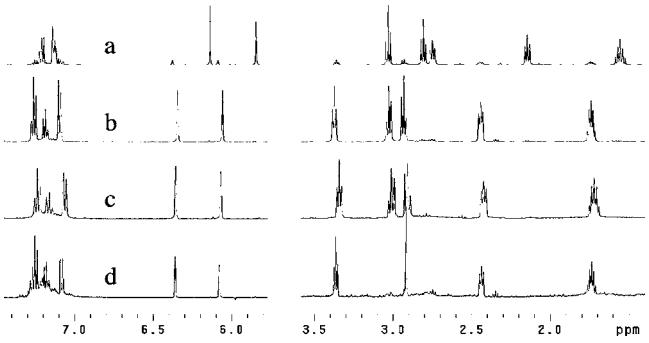



**Figure 2.** Imine formation and stability followed by $^1H$ NMR: (a) primary amine trifluoroacetate salt **4** dissolved in neutral $D_2O$, $t = 5$ min; (b) addition of $Na_2HPO_4$ to the NMR tube completed imine cyclization, $t = 20$ min; (c) acidification with trifluoroacetic acid, $t = 16$ h; (d) neutralization with $Na_2HPO_4$, $t = 30$ h, and observation of deuterium incorporation.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(6) Kita, M.; Kondo, M.; Koyama, T.; Yamada, K.; Matsumoto, T.; Lee, K. H.; Woo, J. T.; Uemura, D. *J. Am. Chem. Soc.* **2004**, *126*, 4794−4795. For a review of these macrocyclic iminium alkaloids, see: Kita, M.; Uemura, D. *Chem. Lett.* **2005**, *34*, 454−459.

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(8) (a) Hu, T. M.; Burton, I. W.; Cembella, A. D.; Curtis, J. M.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **2001**, *64*, 308−312. (b) Falk, M.; Burton, I. W.; Hu, T.; Walter, J. A.; Wright, J. L. C. *Tetrahedron* **2001**, *57*, 8659−8665. (c) Hu, T. M.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1996**, *37*, 7671−7674.

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(10) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647−7648.

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(12) (a) Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van den Heever, J. P.; Hutchinson, C. R.; Vederas, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11519−11520. (b) Ose, T.; Watanabe, K.; Mie, T.; Honma, M.; Watanabe, H.; Yao, M.; Oikawa, H.; Tanaka, I. *Nature* **2003**, *422*, 185−189. (c) Oikawa, H.; Katayama, K.; Suzuki, Y.; Ichihara, A. *Chem. Commun.* **1995**, 1321−1322.

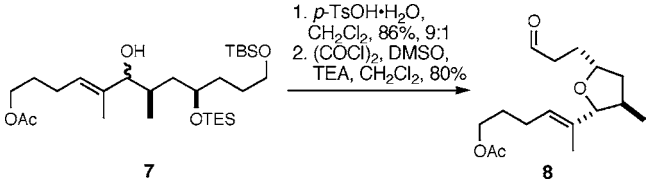
(13) Guimaraes, C. R. W.; Udier-Blagovic, M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2005**, *127*, 3577−3588.

amine salt **4** in $D_2O$. After addition of $Na_2HPO_4$, new resonances corresponding to imine **5** were observed immediately (spectrum **b**). To test the stability of this imine toward hydrolysis, the solution was reacidified with TFA and allowed to stand at room temperature for 16 h (spectrum **c**). Then, the solution was made neutral again through the addition of $Na_2HPO_4$ and allowed to stand for 24 h (spectrum **d**). These results imply that the imine is stable in water at acidic and neutral pH. Additionally, the reactivity of this imine was tested against *trans*-2-methyl-1,3-pentadiene in water at a slightly acidic pH. After approximately 4 h at room temperature, a Diels−Alder reaction was complete.

The ease of formation of the α,*β*-unsaturated imine system and its resistance to hydrolysis in water are remarkable. One potential complication might be a 1,4-addition of the primary amine to the unsaturated system; however, this has not been observed in the model system or the functionalized system. Once formed, imine **5** is surprisingly stable against hydrolysis.

Armed with this information, we designed and implemented a synthesis of Diels−Alder precursor **16** (Scheme 3). The first synthetic hurdle was the formation of the highly substituted tetrahydrofuran ring present in **16**.[16] To this end, compound **7** was prepared (Scheme 2). Acid-catalyzed

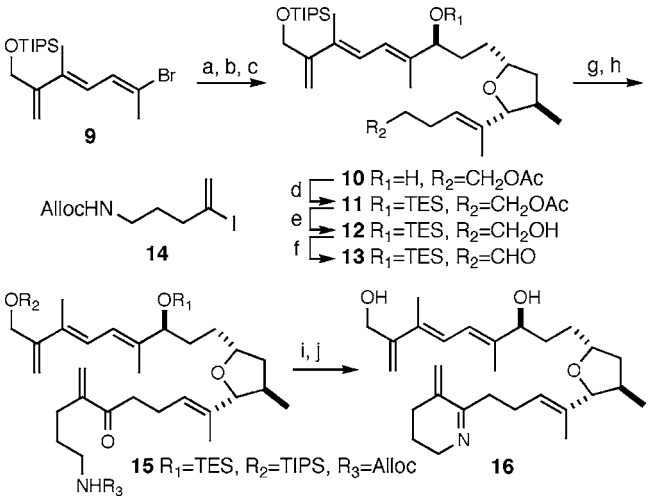
**Scheme 2.** Synthesis of the Tetrahydrofuran Moiety




cyclization of **7** occurred at room temperature to give a 9:1 mixture of cyclization products. The diastereomeric allylic alcohols behave identically under the cyclization conditions, supporting an $S_N1$ mechanism. Through direct chemical correlation and NOE analysis, the major product was shown to be the desired *syn*-product.[17] Under the acidic conditions employed, the primary TBS group was also cleaved. Oxidation of the resulting primary alcohol under Swern conditions gave aldehyde **8**.

The triene moiety present in **16** was introduced using a Ni(II)/Cr(II)-mediated coupling between aldehyde **8** and triene **9** (Scheme 3). Coupling of the trisubstituted vinyl bromide occurred using elevated temperature and a stoichiometric amount of Ni(II). Homocoupling was suppressed by

**Scheme 3.** Diels−Alder Precursor Synthesis[a]




[a] Reagents and conditions: (a) **8**, $NiCl_2$, $CrCl_2$, $Ni(COD)_2$, THF, DMF, *t*-BuPy, 50 °C, 70%, 1:1; (b) $MnO_2$, $CH_2Cl_2$, 50%; (c) (*R*)-2-methyl-CBS-oxazaborolidine, $BH_3$·DMS, tol, −10 °C, 80%, 6:1, *β*: α; (d) TESCl, $AgNO_3$, py, DMF, 99%; (e) DIBAL, $CH_2Cl_2$, −78 °C, 83%; (f) PCC, 4 Å MS, $CH_2Cl_2$, NaOAc, 71%; (g) 0.5% $NiCl_2$/$CrCl_2$, DMF, 56%; (h) $MnO_2$, $CH_2Cl_2$ reflux, 83%; (i) TBAF·$xH_2O$, AcOH, THF, 78%; (j) $(PPh_3)_4Pd$, tol (0.1% AcOH).

using a THF/DMF/*tert*-butylpyridine solvent system.[18] Oxidation of the resulting 1:1 mixture of allylic alcohols using $MnO_2$ and subsequent reduction of the resulting ketone using the CBS protocol[19] gave allylic alcohol **10** as a 6:1 mixture of diastereomers. The stereochemistry of the major product was tentatively assigned on the basis of the known preference of the CBS reduction and later proven through X-ray analysis. Protection of the secondary alcohol using TESCl/$AgNO_3$ followed by reductive removal of the acetate with DIBAL gave primary alcohol **12**.

Oxidation of this alcohol with PCC in the presence of molecular sieves and sodium acetate gave aldehyde **13**. Ni(II)/Cr(II)-mediated coupling of aldehyde **13** and vinyl iodide **14** and subsequent oxidation of the resulting mixture of allylic alcohols using $MnO_2$ gave enone **15**. Treatment of enone **15** with TBAF in the presence of 2 equiv of AcOH (relative to substrate) in THF cleanly removed the primary TIPS and secondary TES groups. Deprotection of the Alloc carbamate using $Pd(PPh_3)_4$ gave α,*β*-unsaturated imine **16**.

Diels−Alder macrocyclization of α,*β*-unsaturated imine **16** occurred in water at pH 6.5 under dilute conditions.[20] No starting material was observed after 30 h at 36 °C. The resulting cycloadducts were present as a mixture of one imine product and two keto-amine diastereomers wherein the imine

(14) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460.

(15) Deuterium incorporation was previously observed in a similar system: Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org. Lett.* **2001**, *3*, 751−754.

(16) For other approaches to the tetrahydrofuran system, see: (a) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417−1419. (b) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763−766. (c) White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4109−4112.

(17) Stereochemistry was assigned via an intermediate that had been assigned by NOE analysis similar to that of Murai. See ref 16a.

(18) Stamos, D. P.; Sheng, X. C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6355−6358.

(19) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987−2012.

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had been hydrolyzed. To simplify product analysis, the imines were reformed by treatment of the entire mixture with molecular sieves in benzene (Figure 3). The two major

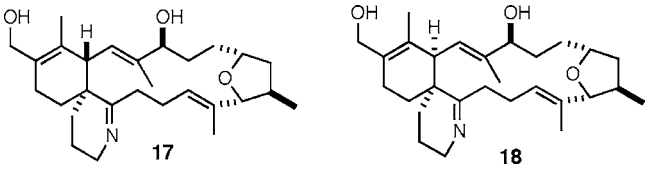


**Figure 3.** Imine Diels−Alder products. Cyclization conditions: (i) pH 6.5 sodium citrate/HCl buffer, $H_2O$, 36 °C, 48 h, concn = 60 $\mu$M; (ii) benzene, TEA, PivOH, 4 Å MS, 16 h. Derivatization conditions: (i) $NaCNBH_3$, MeOH, AcOH; (ii) *p*-bromobenzoyl chloride, $CH_2Cl_2$, $NaHCO_3$ (aq).

products thus isolated were *exo*-product **17** and *endo*-product **18** (about 1:1). A small amount of the second *endo*-product was also observed (not shown). Interestingly, it was found that the imine of the desired *exo*-product remained intact during the reaction in water. In contrast, the *endo*-products were observed as the keto-amines, which were presumably formed through an iminium-catalyzed Diels−Alder reaction followed by hydrolysis.

The structure of the *exo*-product **17** was established by derivatization and single-crystal X-ray crystallography. Reduction of the imine using $NaCNBH_3$ and acylation with *p*-bromobenzoyl chloride gave benzamide **19**. The X-ray structure of this compound is presented in Figure 4.

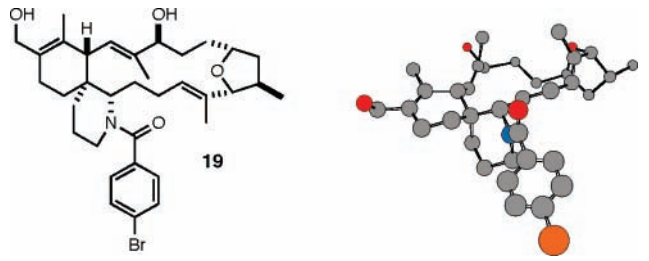


**Figure 4.** Crystal structure of compound **19**.

In contrast to the imine Diels−Alder, an α,*β*-unsaturated ketone dienophile gave only *endo*-products. Thermolysis of an α,*β*-unsaturated ketone (**15**, $R_1$, $R_2$ = TBS, $R_3$ = Teoc, Scheme 3)[21] at 185 °C in benzene in the presence of 4 Å molecular sieves and 4,4′-thiobis-(6-*tert*-butyl-3-methylphenol) (Sumilizer) gave two *endo*-products **20** and **21** in

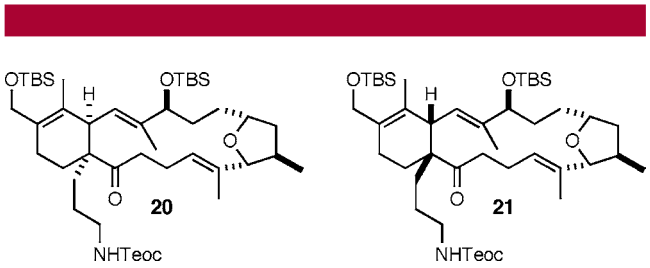


**Figure 5.** Ketone Diels−Alder products formed via thermolysis in benzene at 185 °C in the presence of 3 Å MS and Sumilizer for 48 h (60% yield, 2:1 selectivity).

60% yield but no detectable *exo*-product (Figure 5).[22] Interestingly, attempted macrocyclization of the intermediate diol derived from TBAF deprotection of ketone **15** under the aqueous conditions outlined in Figure 3 only resulted in decomposition of the triene moiety.

In summary, we have observed significant differences in rate and diastereoselectivity between the imine and ketone dienophiles. Under identical conditions in water, the imine dienophile reacts with the triene in 30 h, while the ketone fails to react before decomposition of the triene. The imine dienophile also allows access to the desired *exo*-product, while the ketone dienophile produces only *endo*-products. Moreover, in the *exo* manifold, the imine dienophile exhibits excellent facial selectivity.

The imine system exhibits several interesting properties. Cyclic imine formation from a linear carbon chain is facile and selective, and the resulting imine is stable in an aqueous environment. Moreover, the Diels−Alder reaction of the imine dienophile has been shown to occur in water at moderate temperatures. After cycloaddition under aqueous conditions at pH 6.5, the unnatural Diels−Alder diastereomers are hydrolyzed to keto-amines, while the natural diastereomer resists hydrolysis. In this context, it is intriguing to note that biologically inactive keto-amines have been isolated in the case of the spirolides.[8c] These experimental results suggest that the hypothetical biosynthesis outlined in Figure 1, wherein Diels−Alder precursor **2** reacts to form gymnodimine (**1**), could occur even without the aid of an enzyme.

**Acknowledgment.** J.W.J. thanks Eli Lilly and Co. for a predoctoral fellowship, and S.W. thanks the NIH/NIGMS for a postdoctoral fellowship (F32 NS10736). We also thank Dr. Richard Staples for performing the X-ray analysis experiments.

**Supporting Information Available:** Experimental details for the syntheses outlined in Schemes 1−3 and Figure 3, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This Diels−Alder precursor was prepared according to the synthetic route outlined in Scheme 3 using different protecting groups.

(22) Stereochemistry of the ketone Diels−Alder products was assigned via chemical correlation with the imine Diels−Alder products.