Published in final edited form as:

Tetrahedron Lett. 2011 September 21; 52(38): 4920–4923. doi:10.1016/j.tetlet.2011.07.054.

Intramolecular Cyclization Strategies Toward the Synthesis of Zoanthamine Alkaloids

Derek Fischer, Thong X. Nguyen, Lynnie Trzoss, Marianna Dakanali, and Emmanuel A. Theodorakis*

Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0358

Abstract

Stabilized 2-amino-1,3-dienes can participate in intramolecular Diels-Alder (IMDA) reactions with pendant dienophiles. We found that these dienes can be readily prepared via standard palladium-mediated coupling reactions and have comparable reactivity to 2-oxodienes. Application of these substrates to the synthesis of tetracyclic model systems representing the ABCE motif of the zoanthamines is presented.

Keywords

zoanthamine; cycloaddition; aminodiene; Stille coupling; Diels-Alder reaction

Isolated from colonial zoanthids of the genus *Zoanthus* sp.,¹ zoanthamine (**1**) has defined a new family of marine alkaloids that have impressive chemical structures, significant pharmacological potential and unknown biosynthesis.^{2,3} Common to all these metabolites is a fused polycyclic framework, exemplified by the structures norzoanthamine (**2**),⁴ zoanthenol (**3**)⁵ and zoanthamide (**4**),⁶ that is presumably accountable for a wide range of bioactivities (Figure 1). For example, compounds **1** and **4** were shown to inhibit phorbol myristate acetate (PMA)-induced inflammation in mouse ear,^{6,7} while **2** reportedly inhibits the growth of P-388 murine leukemia cells with an IC₅₀ value of 24 µg/ml.^{4b} More importantly, norzoanthamine (**2**) has been reported to suppress the loss of bone weight in ovariectomized mice and thus it represents a promising candidate for an antiosteoporotic drug.^{1,8}

The combination of challenging chemical structure and unexplored biology invited the development of chemical strategies toward the synthesis of these metabolites, culminating in the synthesis of norzoanthamine by the Miyashita⁹ and the Kobayashi groups.¹⁰ More recently, Miyashita and co-workers also reported the total synthesis of zoanthenol via oxidation of norzoanthamine hydrochloride.¹¹ In continuation of our synthetic efforts,¹² we sought to explore intramolecular cyclization strategies toward the zoanthamine motif. Inspiration for these studies rose from a biosynthetic scenario toward **1**, proposed by Uemura, in which an acyclic polyketide precursor **7** could undergo a polycyclization cascade to form **1** (Figure 2).^{4a,8b} Although there were no details provided for such a proposal, one could envision two cyclization scenarios. In the first case, condensation of the 1,2-aminoalcohol at the C6 and C10 carbonyl groups of **7** could form a 2-aminodiene

*Corresponding author. Tel.: +1-858-822-0456; fax: +1-858-822-0387; etheodor@ucsd.edu.

Supporting Information Available Experimental procedures, characterization data and copies of the ¹H and ¹³C NMR of new compounds, as well as X-ray data of compound **16**.

intermediate **5** that upon cycloaddition with the pendant C21–C22 dienophile would produce the C ring of **1**. Alternatively, a C9–C12 oxodiene could undergo cycloaddition with the C21–C22 dienophile (intermediate **8**) to form the C-ring of **6** and ultimately zoanthamine (**1**). With these considerations in mind, we sought to explore the intramolecular Diels-Alder (IMDA) reactions of 2-amino- and 2-oxo-dienes for the formation of the C ring in zoanthanol model systems. It should be noted that Miyashita et al. have successfully employed a similar oxodiene-based IMDA disconnection in their synthesis of norzoanthamine.⁹

Presumably due to their sensitivity toward hydrolysis,¹³ 2-aminodienes have not been evaluated as substrates in intramolecular cycloaddition reactions.¹⁴ The more stable 2-amido-1,3-dienes behave predictably as substrates both in intermolecular¹⁵ and IMDA cycloadditions.¹⁶ Along these lines, we chose to evaluate compound **15**, containing a 2-amido-1,3-diene motif, as the cyclization precursor (Scheme 1). The synthesis of **15** features a Stille coupling between aryl iodide **11** and vinyl stannane **13**. Fragment **11** was prepared in a two-step sequence from alcohol **9**,¹⁷ namely IBX oxidation followed by addition of vinyl Grignard **10** to the corresponding aldehyde (57% yield, 2 steps). On the other hand, *N*-methylglutarimide **12**¹⁸ was treated with LiHMDS and chlorodiethylphosphonate to form an intermediate vinyl phosphonate, which was then coupled with *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene to give vinyl stannane **13** in 35% overall yield. Stille coupling of fragments **11** and **13** led to the formation of allylic alcohol **14** that after oxidation produced 2-amido-1,3-diene **15** (49% yield, 2 steps/one pot).

The cyclization of **15** was initially evaluated by NMR in deuterated solvents, including 1,2-dichlorobenzene, bromobenzene and *m*-xylene. Best results were obtained upon heating the reaction at 200 °C (1,2-dichlorobenzene) where compound **16** was produced after 11 hours in 72% yield. It is worth noting that **16** was isolated as a single stereoisomer and its structure is reminiscent of zoanthamide (**4**). The observed coupling constant of 11.8 Hz between the protons at C12 and C21 indicated a *trans* junction between the BC rings, suggesting an *exo*-selective Diels-Alder cycloaddition. Furthermore, during this cycloaddition, the C10–C11 enamine was isomerized at the thermodynamically more stable C9–C10 position. The chemical structure of compound **16** was ultimately confirmed via a single crystal X-ray analysis.¹⁹

The *exo*-selectivity of this intramolecular Diels-Alder reaction deserves some additional comments. Figure 3 depicts the two transition structures (TS) of compound **15**. It is likely that the *trans*-TS is favored due to the π -conjugative interactions between the phenyl ring (A ring) and the diene which, in turn, bring carbons C9–C18 to an almost planar arrangement. The role of these π -conjugative interactions has been investigated in similar substrates and is reflected in the dihedral angle θ formed between the diene and the A ring.²⁰ The *cis*-TS shows a nearly perpendicular diene-arene dihedral angle whereas in the *trans*-TS the dihedral angle is smaller, allowing a significantly increased conjugation between the two groups.²⁰ It should be noted that the *exo* (*trans*) product was found to be the major product in the synthesis of norzoanthamine by Miyashita's group. In their case the preference for the *exo* transition state has been proposed to result primarily from steric effects due to the substitution at the C12 center.²¹

Overall, this strategy produced evidence that: (a) the ABCE ring motif of zoanthanol could be produced with high stereocontrol via an IMDA of an appropriately functionalized 2-aminodiene; and (b) that a fully functionalized C22 quaternary center can be incorporated prior to the cycloaddition. Thus, our studies further show the ability of these motifs to participate in a predictable manner in intramolecular cycloaddition reaction with pendant dienophiles.¹⁶

We then investigated the oxodiene cycloaddition pathway to form the ABC core structure. Along these lines, silylated propargyl alcohol **17** was converted to vinyl stannane **18**²² and upon coupling with iodide **9** produced compound **19** in 39% overall yield (Scheme 2). Oxidation of **19** followed by treatment of the resulting aldehyde with vinyl Grignard **10** under CeCl_3 ²³ led to the formation of allylic alcohol **20** (72% yield over 2 steps). Oxidation at the C20 hydroxyl group, gave rise to enone **21** in 91% yield. Methylation at C19, deprotection of the C10 TBS ether followed by oxidation of the resulting alcohol produced dienone **22** (70% over 3 steps). Selective silylation of **22** formed the cyclization precursor **23** in 80% yield. Upon heating in *m*-xylene, oxodiene **23** underwent the desired cycloaddition, producing, after desilylation, tricycle **24** (60% yield over two steps, 2:1 mixture of isomers at C19). The coupling constant of the protons at C12 and C21 was found to be approximately 12.0 Hz indicating an *exo*-selective Diels-Alder reaction.²⁴

In conclusion, inspired by biosynthetic hypotheses, we have explored intramolecular cycloaddition approaches toward the construction of the zoanthamine motif. We found that an amide-stabilized 2-aminodiene can efficiently react with a dienophile, in an *exo*-selective IMDA reaction, to produce model systems representing the ABCE ring scaffold of these natural products. Although 2-amido-1,3-diene **15** is somewhat less reactive than the 2-oxo diene **23**, it can yield the IMDA product at elevated temperatures. In turn, this provides support for the use of stabilized 2-aminodienes in cycloaddition reactions for the synthesis of polycyclic natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the National Institutes of Health (NIH) for financial support of this work through Grant Number R01 GM081484. We thank the National Science Foundation for instrumentation grants CHE9709183 and CHE0741968. We also thank Dr. Anthony Mrse (UCSD NMR Facility); Dr. Yongxuan Su (UCSD MS Facility) and Dr. Arnold L. Rheingold and Dr. Curtis E. Moore (UCSD X-Ray facility).

References and Notes

1. Rao CB, Anjaneyula ASR, Sarma NS, Venkateswarlu Y, Rosser RM, Faulkner DJ, Chen MHM, Clardy J. J. Am. Chem. Soc. 1984; 106:7983–7984.
2. For selected reviews on this topic, see: (a) Rahman AU, Choudhary MI. Alkaloids. 1999; Vol 52:233–260. Academic Press New York. (b) Kuramoto M, Yamaguchi K, Tsuji T, Uemura D. Fusetani N. Zoanthamines, Antiosteoporotic Alkaloids. Drugs from the Sea. 2000:98–106. Karger Basel. (c) Yamada K, Kuramoto M, Uemura D. Rec. Res. Devel. Pure Appl. Chem. 1999; 3:245–254. (d) Fernandez JJ, Souto ML, Daranas AH, Norte M. Curr. Topics Phytochem. 2000; 4:105–119.
3. For a comprehensive review of the chemistry and biology of zoanthamines see: Behenna DC, Stockdill JL, Stoltz BM. Angew. Chem., Int. Ed. 2008; 47:2365–2386.
4. (a) Kuramoto M, Hayashi K, Fujitani Y, Yamaguchi K, Tsuji T, Yamada K, Ijuin Y, Uemura D. Tetrahedron Lett. 1997; 38:5683–5686. (b) Fukuzawa S, Hayashi Y, Uemura D, Nagatsu A, Yamada K, Ijuin Y. Heterocycl. Commun. 1995; 1:207–214.
5. Villar RM, Gil-Longo J, Daranas AH, Souto ML, Fernandez JJ, Peixinho S, Barral MA, Santafe G, Rodriguez J, Jimenez C. Bioorg. Med. Chem. 2003; 11:2301–2306. [PubMed: 12713841]
6. Rao CB, Anjaneyulu ASR, Sarma NS, Venkateswarlu Y, Rosser RM, Faulkner DJ. J. Org. Chem. 1985; 50:3757–3760.
7. Rao CB, Rao DV, Raju VSN, Sullivan BW, Faulkner DJ. Heterocycles. 1989; 28:103–106.

8. (a) Yamaguchi K, Yada M, Tsuji T, Kuramoto M, Uemura D. *Biol. Pharm. Bull.* 1999; 22:920–928. [PubMed: 10513613] (b) Kuramoto M, Hayashi K, Yamaguchi K, Yada M, Tsuji T, Uemura D. *Bull. Chem. Soc. Jpn.* 1998; 71:771–779.
9. Miyashita M, Sasaki M, Hattori I, Sakai M, Tanino K. *Science*. 2004; 305:495–499. [PubMed: 15205476]
10. (a) Murata Y, Yamashita D, Kitahara K, Minasako Y, Nakazaki A, Kobayashi S. *Angew. Chem. Int. Ed.* 2009; 48:1400–1403. (b) Yamashita D, Murata Y, Hikage N, Takao KI, Nakazaki A, Kobayashi S. *Angew. Chem. Int. Ed.* 2009; 48:1404–1406.
11. Takahashi Y, Yoshimura F, Tanino K, Miyashita M. *Angew. Chem. Int. Ed.* 2009; 48:8905–8908.
12. (a) Rivas F, Ghosh S, Theodorakis EA. *Tetrahedron Lett.* 2005; 46:5281–5284. (b) Ghosh S, Rivas F, Fischer D, Gonzalez MA, Theodorakis EA. *Org. Lett.* 2004; 6:941–944. [PubMed: 15012070] (c) Nguyen TX, Dakanali M, Trzoss L, Theodorakis EA. *Org. Lett.* 2011; 13:3308–3311. [PubMed: 21615125]
13. (a) Enders D, Meyer O. *Lieb. Ann.* 1996:1023–1035. (b) Barluenga J, Suarez-Sobrinio A, Lopez LA. *Aldrichim. Acta.* 1999; 32:4–15. (c) Notz W, Tanaka F, Barbas CF III. *Acc. Chem. Res.* 2004; 37:580–591. [PubMed: 15311957]
14. For selected reports on intermolecular Diels-Alder reaction of 2-aminodienes see: (a) Pitacco G, Risaliti A, Trevisan ML, Valentin E. *Tetrahedron.* 1977; 33:3145–3148. (b) Marc G, Nitti P, Pitacco G, Pizzoli A, Valentin E. *J. Chem. Soc., Perkin Trans. 1.* 1997:223–228. (c) Barluenga J, Aznar F, Valdes C, Martin A, Garcia-Granda S, Martin E. *J. Am. Chem. Soc.* 1993; 115:4403–4404. (d) Kniep CS, Boese R, Sustmann R. *Tetrahedron.* 2000; 56:4157–4162. (e) Barluenga J, Mateos C, Aznar F, Valdes C. *Org. Lett.* 2002; 4:1971–1974. [PubMed: 12027660]
15. For selected reports on intermolecular Diels-Alder of 2-amidodienes see: (a) Occhiato EG, Trabocchi A, Guarna A. *Org. Lett.* 2000; 2:1241–1242. [PubMed: 10810717] (b) Galbo FL, Occhiato EG, Guarna A, Faggi C. *J. Org. Chem.* 2003; 68:6360–6368. [PubMed: 12895072] (c) Huang J, Xiong H, Hsung P, Rameshkumar C, Mulder JA, Grebe TP. *Org. Lett.* 2002; 4:2417–2420. [PubMed: 12098261] (d) Huang C-C, Chang N-C. *Org. Lett.* 2008; 10:673–676. [PubMed: 18205376] (e) Kobayashi S, Furuya T, Otani T, Saito T. *Tetrahedron.* 2008; 64:9705–9716. (f) Kobayashi S, Semba T, Takahashi T, Yoshida S, Dai K, Otani T, Saito T. *Tetrahedron.* 2009; 65:920–933.
16. (a) Movassaghi M, Hunt DK, Tjandra M. *J. Am. Chem. Soc.* 2006; 128:8126–8127. [PubMed: 16787063] (b) Chelliah MV, Chackalamannil S, Xia Y, Eagen K, Clasby MC, Gao X, Greenlee W, Ahn H-S, Agans-Fantuzzi J, Boykow G, Hsieh Y, Bryant M, Palamanda J, Chan T-M, Hesk D, Chintala M. *J. Med. Chem.* 2007; 50:5147–5160. [PubMed: 17854166] (c) Movassaghi M, Tjandra M, Qi J. *J. Am. Chem. Soc.* 2009; 131:9648–9650. [PubMed: 19555115]
17. Kataoka N, Shelby Q, Stambuli JP, Hartwig JF. *J. Org. Chem.* 2002; 67:5553–5556. [PubMed: 12153253]
18. Marson CM, Khan A, Porter RA. *J. Org. Chem.* 2001; 66:4771–4775. [PubMed: 11442402]
19. CCDC-812060 (16) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/const/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk). For clarity reasons only the C12 and C21 hydrogens are shown.
20. (a) Pearson EL, Kwan LCH, Turner CI, Jones GA, Willis AC, Paddon-Row MN, Sherburn MS. *J. Org. Chem.* 2006; 71:6099–6109. [PubMed: 16872192] (b) Pearson EL, Willis AC, Sherburn MS, Paddon-Row MN. *Org. Biomol. Chem.* 2008; 6:513–522. [PubMed: 18219422] (c) Pearson EL, Kanizaj N, Willis AC, Paddon-Row MN, Sherburn MS. *Chem. Eur. J.* 2010; 16:8280–8284.
21. (a) Yoshimura F, Sasaki M, Hattori I, Komatsu K, Sakai M, Tanino K, Miyashita M. *Chem. Eur. J.* 2009; 15:6626–6644. (b) Miyashita M. *Pure Appl. Chem.* 2007; 79:651–665. (c) Juhl M, Tanner D. *Chem. Soc. Rev.* 2009; 38:2983–2992. [PubMed: 19847335]
22. (a) Pinkerton DM, Banwell MG, Willis AC. *Org. Lett.* 2009; 11:4290–4293. [PubMed: 19743818] (b) Lumb J-P, Trauner D. *J. Am. Chem. Soc.* 2005; 127:2870–2871. [PubMed: 15740120]
23. Imamoto T, Takiyama N, Nakamura K, Hatajima T, Kamiya Y. *J. Am. Chem. Soc.* 1989; 111:4392–4398.

24. (a) Burke JP, Sabat M, Myers WH, Chruma JJ. *Tetrahedron, Asym.* 2011; 22:31–35.(b) Clarke PA, Davie RL, Peace S. *Tetrahedron.* 2005; 61:2335–2351.

Figure 1.
Structures of selected zoanthamine natural products

Figure 2.
Proposed biosynthesis pathways of zoanthamines

Figure 3.
Transition structures (TS) of compound **15**

Scheme 1.

Reagents and conditions: (a) 2.5 equiv. IBX, MeCN, reflux, 1 h; (b) 1.5 equiv. $\text{Me}_2\text{C}=\text{CHMgBr}$ (**10**), THF, 0 °C to r.t., 12 h, 57% (over 2 steps); (c) 1 equiv. LiHMDS, 0 °C, then 1 equiv. diethylchlorophosphate, THF, -78 °C; (d) 1.2 equiv. trans-1,2-bis(tri-*n*-butylstannyl)ethylene, 3 mol% $\text{Pd}(\text{PPh}_3)_4$, 10 equiv. LiCl, THF, 0 to 60 °C, 5 h, 35% (over 2 steps); (e) 1.2 equiv. **13**, 3 mol% of $\text{Pd}(\text{PPh}_3)_4$, 10 equiv. LiCl, THF, 25 to 95 °C, 2.5 h, 55%; (f) 4 equiv. IBX, EtOAc, reflux, 2.5 h, 89%; (g) 200 °C, 11 h, 72%.

Scheme 2.

Reagents and conditions: (a) 1.5 equiv. Bu_3SnH , 1 mol% AIBN, 130 °C, 2 h, 57%; (b) 1.5 equiv. 18, 10 mol% $\text{Pd}_2(\text{dba})_3$, 11 mol% $\text{P}(\text{tBu})_3$, toluene, 25 to 80 °C, 12 h, 68%; (c) 3 equiv. IBX, DCM:DMSO (2:1), 25 °C, 3 h, 98%; (d) 1.5 equiv. CeCl_3 , 1.5 equiv. $\text{Me}_2\text{C}=\text{CHMgBr}$ (10), THF, -78 to 25 °C, 5 h, 73%; (e) 2.5 equiv. IBX, DCM:DMSO (1:1), 25 °C, 12 h, 91%; (f) 2 equiv. KOH, 1.5 equiv. MeI, DME, 25 °C, 2 h, 94%, (g) AcOH:H₂O:THF (2:1:1), 25 °C, 12 h, 78%; (h) 3 equiv. IBX, DCM:DMSO (4:1), 25 °C, 2.5 h, 95%; (i) 2 equiv. TEA, 1.5 equiv. TBSOTf, DCM, -78 °C, 30 min, 80%; (j) 150 °C, 10 h, 91%; (k) 1M HCl, THF, 25 °C, 24 h, 65%.