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Intramolecular cyclization strategies toward the synthesis of zoanthamine alkaloids

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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.

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 (Fig. 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 IC_{50} 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 Miyashita[9] and the Kobayashi groups.[10] More recently, Miyashita and co-workers also reported the total synthesis of zoanthenol via oxidation of norzoanthamine

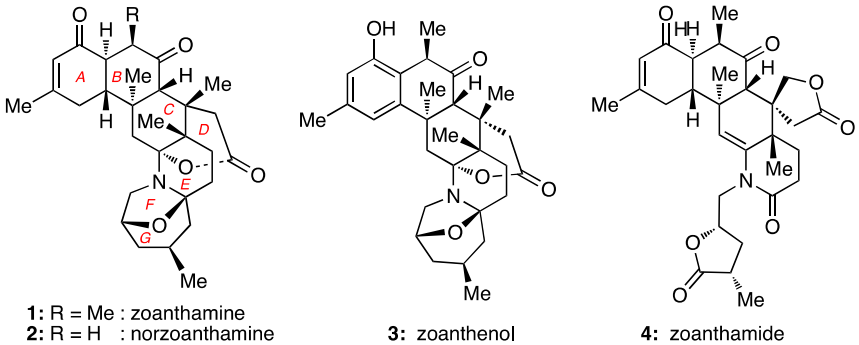

Figure 1. Structures of selected zoanthamine natural products.

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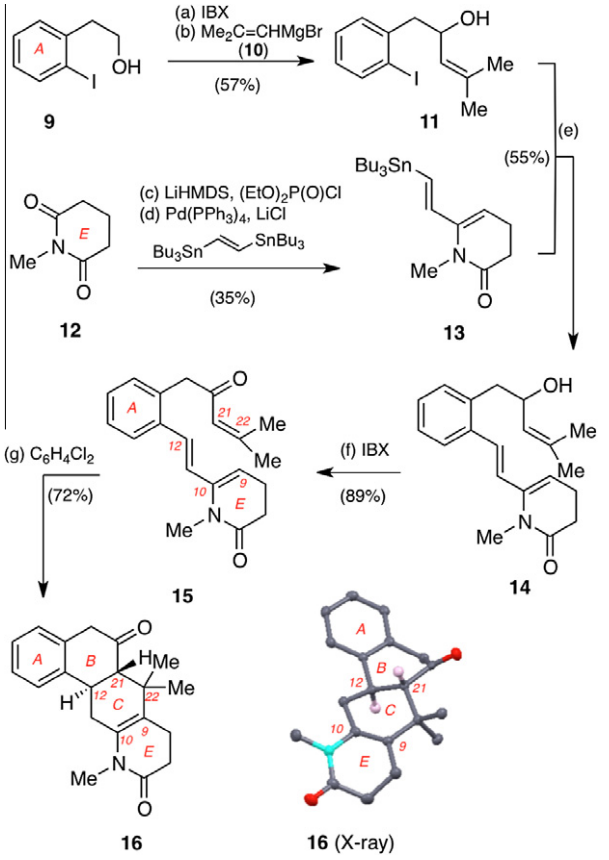
hydrochloride.[11] In continuation of our synthetic efforts,[12] we sought to explore intramolecular cyclization strategies toward the zoanthamine motif. Inspiration for these studies rose from a biosynthetic scenario toward **1**, proposed by Uemura, in which an acyclic polyketide precursor **7** could undergo a polycyclization cascade to form **1** (Fig. 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 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 zoanthenol 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 intermolecular[15] 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).



Scheme 1. Reagents and conditions: (a) 2.5 equiv IBX, MeCN, reflux, 1 h; (b) 1.5 equiv Me_2C = CHMgBr (**10**), THF, 0 °C to rt, 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 % $Pd(PPh_3)_4$, 10 equiv LiCl, THF, 0–60 °C, 5 h, 35% (over 2 steps); (e) 1.2 equiv **13**, 3 mol % of $Pd(PPh_3)_4$, 10 equiv LiCl, THF, 25–95 °C, 2.5 h, 55%; (f) 4 equiv IBX, EtOAc, reflux, 2.5 h, 89%; (g) 200 °C, 11 h, 72%.

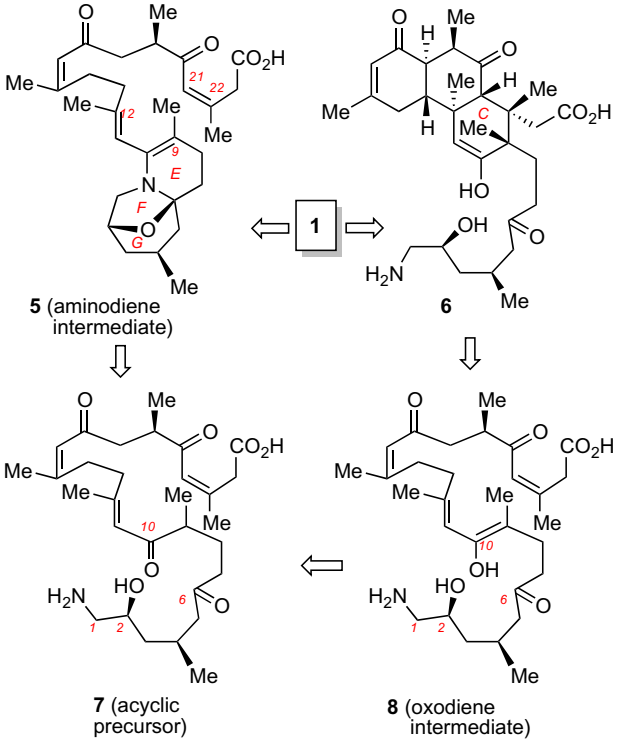


Figure 2. Proposed biosynthesis pathways of zoanthamines.

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 h 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 plannar 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

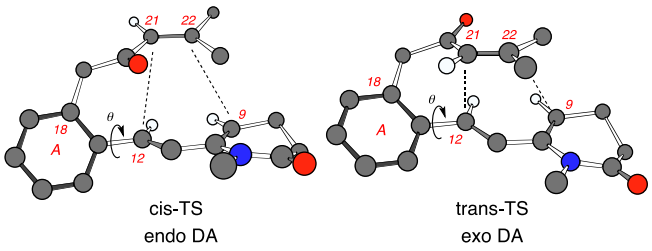
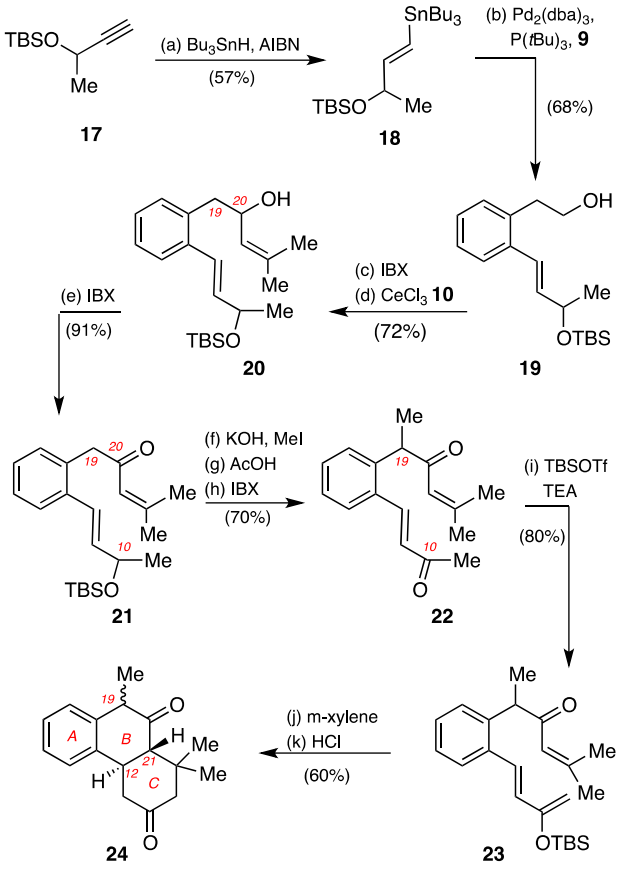


Figure 3. Transition structures (TS) of compound **15**.

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 zoanthenol 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]



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 % $Pd_2(dba)_3$, 11 mol % $P(tBu)_3$, toluene, 25–80 °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 $Me_2C=CHMgBr$ (10), THF, −78–25 °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:H_2O: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%.

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.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data and copies of the ^1H and ^{13}C NMR of new compounds, as well as X-ray data of compound **16**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.054.

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