



## 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.

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Isolated from colonial zoanthids of the genus *Zoanthus* sp.,<sup>1</sup> zoanthamine (**1**) has defined a new family of marine alkaloids that have impressive chemical structures, significant pharmacological potential and unknown biosynthesis.<sup>2,3</sup> Common to all these metabolites is a fused polycyclic framework, exemplified by the structures norzoanthamine (**2**),<sup>4</sup> zoanthenol (**3**)<sup>5</sup> and zoanthamide (**4**),<sup>6</sup> 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,<sup>6,7</sup> while **2** reportedly inhibits the growth of P-388

murine leukemia cells with an  $IC_{50}$  value of 24  $\mu\text{g/ml}$ .<sup>4b</sup> 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.<sup>1,8</sup>

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<sup>9</sup> and the Kobayashi groups.<sup>10</sup> More recently, Miyashita and co-workers also reported the total synthesis of zoanthenol via oxidation of norzoanthamine

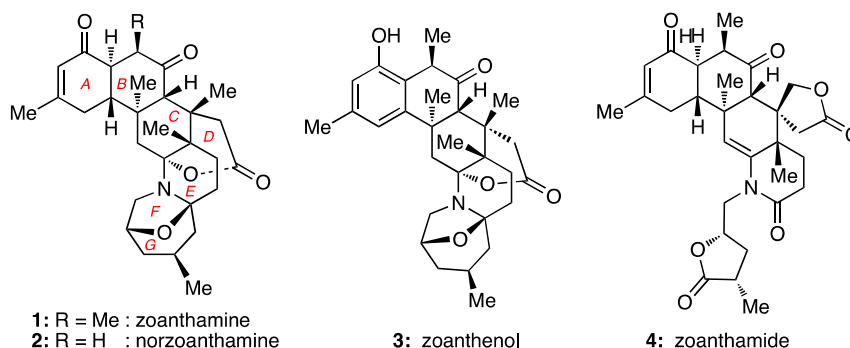


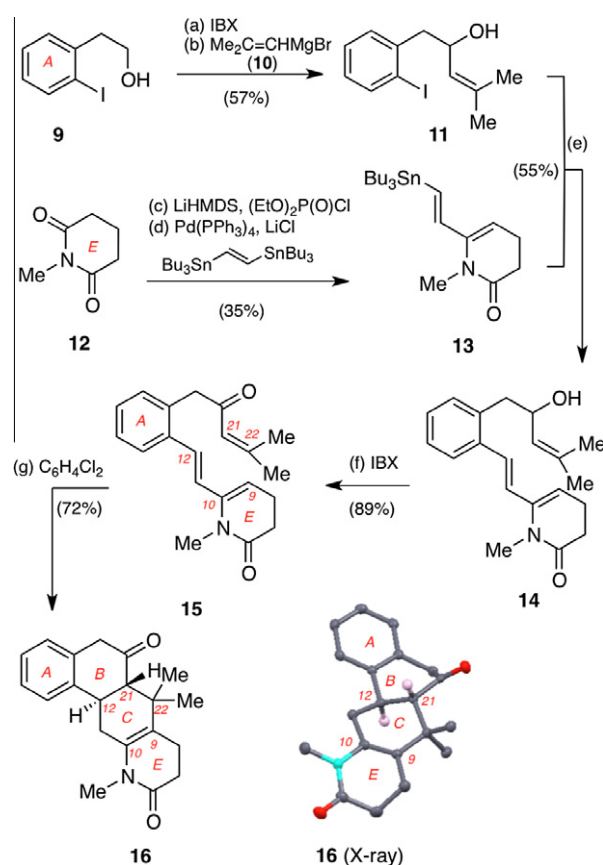
Figure 1. Structures of selected zoanthamine natural products.

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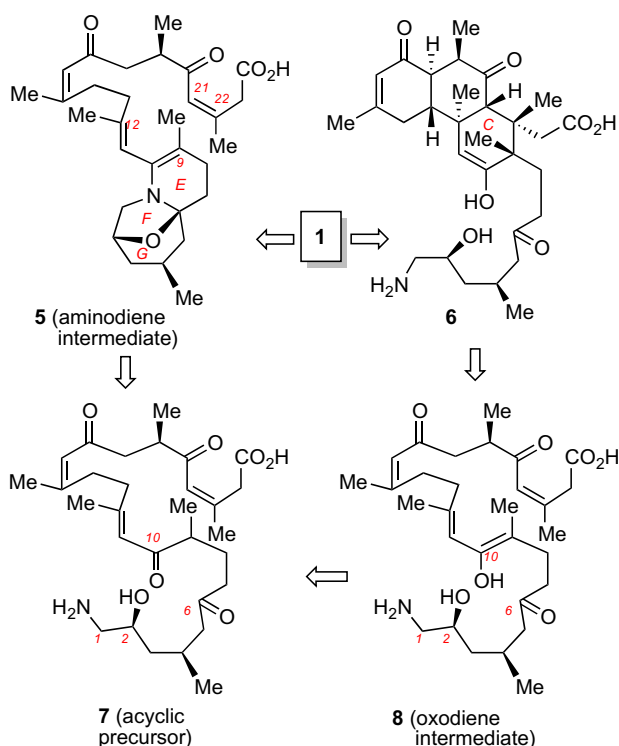
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hydrochloride.<sup>11</sup> In continuation of our synthetic efforts,<sup>12</sup> we sought to explore intramolecular cyclization strategies toward the zoanthamine motif. Inspiration for these studies rose from a biosynthetic scenario toward **1**, proposed by Uemura, in which an acyclic polyketide precursor **7** could undergo a polycyclization cascade to form **1** (Fig. 2).<sup>4a,8b</sup> 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 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.<sup>9</sup>

Presumably due to their sensitivity toward hydrolysis,<sup>13</sup> 2-aminodienes have not been evaluated as substrates in intramolecular cycloaddition reactions.<sup>14</sup> The more stable 2-amido-1,3-dienes behave predictably as substrates both in intermolecular<sup>15</sup> and IMDA cycloadditions.<sup>16</sup> 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**,<sup>17</sup> 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**<sup>18</sup> 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**



**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 rt, 12 h, 57% (over 2 steps); (c) 1 equiv LiHMDS, 0 °C, then 1 equiv diethylchlorophosphonate, 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, 0–60 °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, 25–95 °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.

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 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.<sup>19</sup>

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  $\pi$ -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  $\pi$ -conjugative interactions has been investigated in similar substrates and is reflected in the dihedral angle  $\theta$  formed between the diene and the A ring.<sup>20</sup> 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.<sup>20</sup> It should be noted that the *exo* (*trans*) product was found

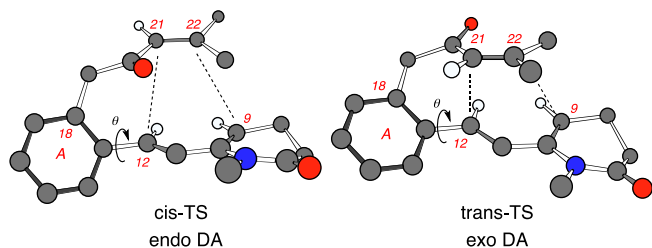


Figure 3. Transition structures (TS) of compound 15.

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.<sup>21</sup>

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.<sup>16</sup>

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**<sup>22</sup> 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  $\text{CeCl}_3$ <sup>23</sup> 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.<sup>24</sup>

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.

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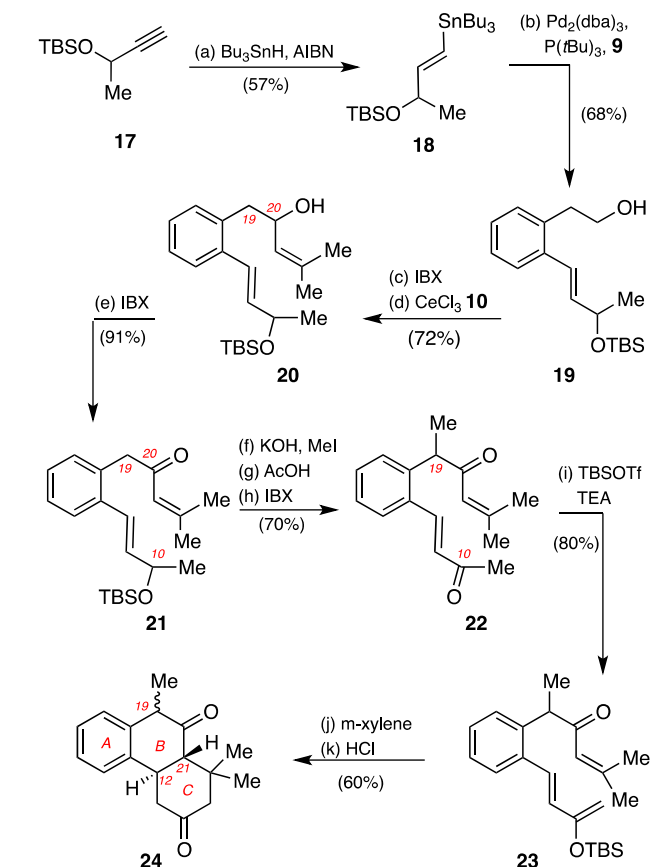
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## Supplementary data

Supplementary data (experimental procedures, characterization data and copies of the  $^1\text{H}$  and  $^{13}\text{C}$  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](https://doi.org/10.1016/j.tetlet.2011.07.054).

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

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