

# Probing the Lewis Acid-Catalyzed Intramolecular Diels–Alder Cyclizations of Allylic Alkoxy-Substituted (*Z*)-1,3-Dienes

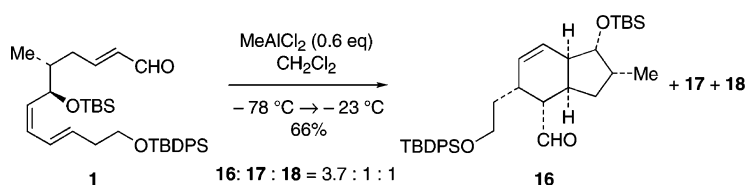
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## ABSTRACT



The Lewis acid-promoted Diels–Alder reaction of (*E,Z,E*)-trienal **1** provides not only the expected cis-fused cycloadduct **16** but also the trans-fused products **17** and **18**. Trans-fused cycloadducts **17** and **18** are also products of the Lewis acid-promoted cyclization of (*E,Z,E*)-trienyl acetal **2**. These products presumably derive from a stepwise cyclization pathway.

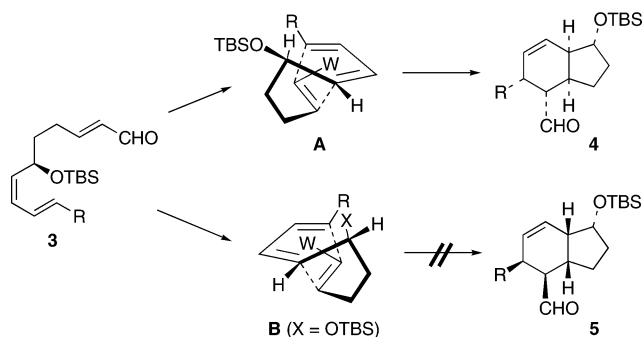
Previous work in this laboratory has explored the application of Lewis acid catalysis to the Diels–Alder reaction of (*Z*)-substituted 1,3-dienes.<sup>1,2</sup> Acyclic (*Z*)-1,3-dienes are substantially less reactive than (*E*)-dienes in the thermal Diels–Alder reaction<sup>3,4</sup> and are subject to thermal olefin isomerization.<sup>5–9</sup> As a result, their use in Diels–Alder reactions has been limited.<sup>10</sup> We have demonstrated that the synthetic utility of (*Z*)-1,3-dienes (and dienes with (*Z*)-substituents) is substantially enhanced by using Lewis acid catalysts, in both inter- and intramolecular Diels–Alder (IMDA) reaction

manifolds. These Lewis acid-promoted reactions proceed under mild conditions to give cycloadducts in good yield, generally with excellent stereoselectivity.<sup>1,2</sup>

In connection with ongoing studies on the synthesis of macquarimycin A and cochleamycin A,<sup>11–13</sup> we became interested in exploring the IMDA reactions of trienes that possess an alkoxy function allylic to the diene, as in **3** (Figure 1). Because of geometric constraints, substrates such as **3** react thermally only via endo transition states to give cis-fused products.<sup>5,14</sup> Minimization of allylic strain interactions involving the OTBS group should highly bias the IMDA reaction of **3** to proceed with high selectivity via the endo transition state **A** (see Figure 1).<sup>15,16</sup> In fact, thermal intramolecular Diels–Alder reactions of trienes similar to **3** have

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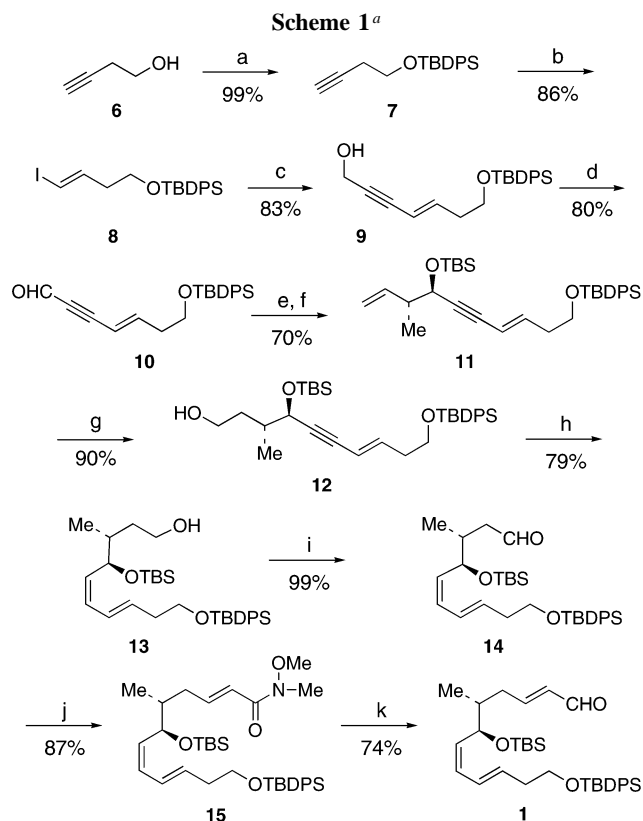
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**Figure 1.** Diastereoselectivity in the IMDA of alkoxy-substituted (*Z*)-1,3-dienes.

recently been accomplished with excellent success by the Tadano<sup>17</sup> and Paquette<sup>18</sup> groups in their studies toward the synthesis of macquarimicin A and cochleamycin A. Nevertheless, we were interested in determining if the IMDA reactions of substrates such as **3** could be successfully achieved with Lewis acid catalysis. Marshall has shown that the best results in Lewis acid-promoted IMDA reactions of trienes with dienylic ether substituents are obtained with substrates containing carboxyaldehyde dienophile activating groups.<sup>19</sup> In contrast, dienylic alkoxy-substituted trienes with carboalkoxy dienophile activation tend to give only decomposition products under Lewis acid-promoted cycloaddition conditions.<sup>20</sup> Thus, the question we wished to address was if carboxyaldehyde-activated, alkoxy-substituted (*Z*)-1,3-dienes such as **3** would be sufficiently reactive to undergo efficient Lewis acid-promoted IMDA reactions without competitive decomposition of the sensitive dienylic ether unit. Triene **1** (Scheme 1) served as the initial substrate for these investigations.

The synthesis of **1** (Scheme 1) began with protection of 3-butyne-1-ol to give the TBDPS ether **7** in 99% yield. Treatment of **7** with Schwartz's reagent followed by addition of I<sub>2</sub> gave vinyl iodide **8** in 86% yield.<sup>21</sup> Sonogashira coupling<sup>22</sup> of **8** with propargyl alcohol gave alcohol **9** in 83% yield, which was oxidized with MnO<sub>2</sub> to give aldehyde **10** in 80% yield. Treatment of the aldehyde with diisopropyl (*S,S*)-tartrate (*E*)-crotylboronate,<sup>23</sup> followed by protection of the resulting homoallylic alcohol as a TBS ether gave **11** in 70% yield over two steps. Subjection of **11** to a hydroboration/oxidation sequence then gave primary alcohol **12** in 90% yield. Cis-reduction of the alkyne was best accomplished by using a Zn/Ag couple.<sup>24,25</sup> This reaction provided



<sup>a</sup> Reagents and conditions: (a) TBDPS-Cl, imidazole, DMAP, CH<sub>2</sub>Cl<sub>2</sub>:DMF (2:1); (b) Cp<sub>2</sub>Zr(H)Cl, CH<sub>2</sub>Cl<sub>2</sub>, then I<sub>2</sub>; (c) propargyl alcohol, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, CuI, Et<sub>3</sub>N; (d) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (e) diisopropyl (*S,S*)-tartrate (*E*)-crotylboronate, PhCH<sub>3</sub>, -78 °C; (f) TBS-Cl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>-DMF (2:1); (g) 9-BBN, THF, 0 °C, then H<sub>2</sub>O<sub>2</sub>, aqueous NaOH, 0 °C; (h) Zn, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O, AgNO<sub>3</sub>, MeOH:H<sub>2</sub>O (1:1); (i) Dess-Martin periodinane, pyridine, wet CH<sub>2</sub>Cl<sub>2</sub>; (j) diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate, NaH, THF; (k) DIBAL-H, THF, -78 °C.

diene **13** in 79% yield, with excellent (*Z*) selectivity. The primary alcohol unit of **13** was then oxidized to aldehyde **14** in 99% yield with use of the Dess-Martin periodinane reagent.<sup>26,27</sup> Horner-Wadsworth-Emmons olefination of **14** yielded the α,β-unsaturated Weinreb amide **15** in 87% yield. Finally, DIBAL-H reduction of **15** at -78 °C furnished the targeted triene aldehyde **1** in 74% yield.

Treatment of **1** with 0.6 equiv of MeAlCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> initially at -78 °C and then for 2 h at -23 °C provided an ca. 3.7:1:1 mixture of diastereomeric cycloadducts **16**, **17**, and **18** in 66% combined yield, as determined by <sup>1</sup>H NMR analysis (Scheme 2). Cycloadduct **16** could be readily separated from the mixture by HPLC and characterized, but **17** and **18** were inseparable by HPLC. The structure of **16** was assigned as the expected cis-fused cycloadduct by using NOESY experiments (Figure 2). The structures of trans-fused cycloadducts **17** and **18** were determined subsequently by

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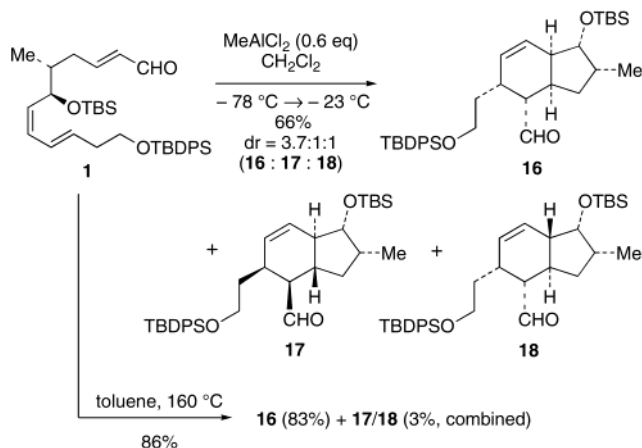
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**Scheme 2.** Lewis Acid-Catalyzed and Thermal IMDA Cyclizations of (*E,Z,E*)-Triene **1**

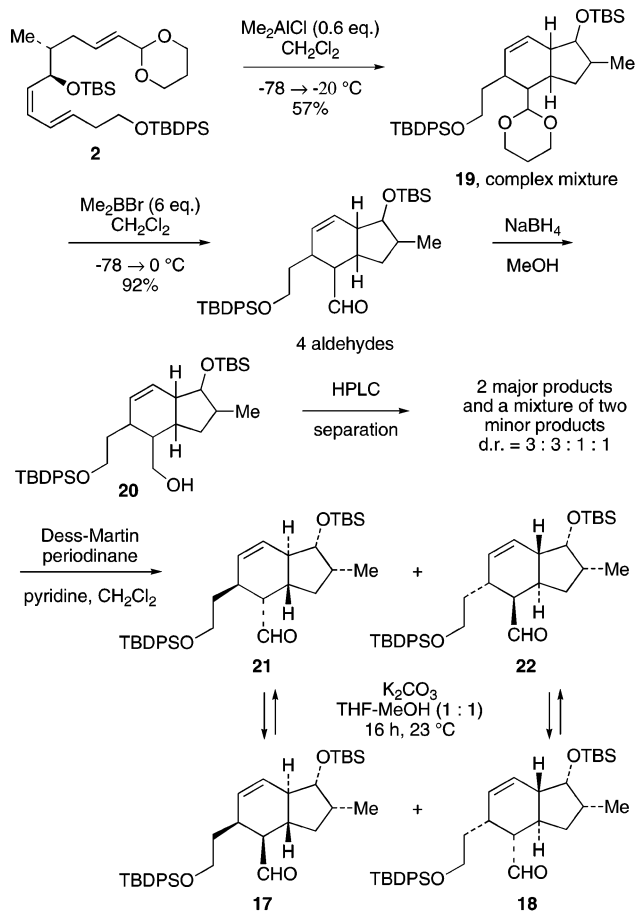


spectroscopic correlation with the products of cyclization of acetal **2** (vide infra). Use of alternative Lewis acids ( $\text{BF}_3 \cdot \text{OEt}$ ,  $\text{SnCl}_4$ ,  $\text{TiCl}_4$ , and (menthyloxy) $\text{AlCl}_2$ ) for the IMDA cyclization of **1** gave very low yields of products, while attempted use of  $\text{Me}_2\text{AlCl}$  and 4 M  $\text{LiClO}_4$  in  $\text{CH}_3\text{NO}_2$  failed to promote any cycloaddition, and only returned unchanged starting triene. In contrast, heating a solution of **1** at  $160^\circ\text{C}$  in toluene in a sealed tube in the presence of a small amount of BHT for 16 h gave **16** in 83% yield along with 3% of a mixture of **17** and **18**. It is assumed that the trans-fused products **17** and **18** arise from a stepwise cyclization pathway, because geometric constraints posed by the three-carbon tether should preclude access to the exo cyclization transition state necessary for concerted formation of these products from a (*Z*)-1,3-diene.<sup>5,14</sup> We consider it unlikely that **17** and **18** arise from IMDA cyclization of the (*E,E,E*)-isomer of **1**, since this species is not present in **1** recovered from experiments in which the Lewis acid-promoted cycloaddition does not go to completion.

While it was encouraging that the  $\text{Me}_2\text{AlCl}_2$ -promoted cyclization of **1** was faster than decomposition pathways involving ionization of the pentadienyl ether,<sup>19,20</sup> we were very surprised that substantial amounts of trans-fused **17** and **18** were also produced, suggesting a lack of concertedness under the IMDA reaction conditions. Accordingly we became interested in exploring alternative strategies for promoting the IMDA cyclizations of **1** and its derivatives. The Lewis acid-catalyzed cyclization of acetal **2** was of interest in this regard, because Lewis acid treatment of the  $\alpha,\beta$ -unsaturated acetal provides a vinyl dioxolenium ion, a very potent dienophile.<sup>28,29</sup> We hoped that implementation of this strategy would permit use of a less reactive Lewis acid (compared to the Lewis acids employed in the IMDA reaction of **1**), thereby enabling the cyclization of **2** to occur under milder conditions.

Cyclic acetal **2** was prepared in 83% yield by treatment of **1** with 2-methoxy-1,3-dioxane and 1,3-propanediol and a

**Scheme 3.** Lewis Acid-Promoted Cyclization of (*E,Z,E*)-Triene Acetal **2**



catalytic amount of  $\text{TsOH}$  in  $\text{THF}$ .<sup>30</sup> Treatment of **2** with 0.6 equiv of  $\text{Me}_2\text{AlCl}$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  and immediately warming the mixture to  $-20^\circ\text{C}$  for 45 min provided a mixture of products **19** in 57% yield. The same product mixture was obtained in 65% yield by treatment of the triene acetal **2** with 4 M  $\text{LiClO}_4$  in  $\text{CH}_3\text{NO}_2$  at room temperature overnight.<sup>31,32</sup> This mixture could not be separated by HPLC, so product separation was postponed following subsequent chemical manipulations. Treatment of the cycloadduct mixture with  $\text{Me}_2\text{BBr}$  (6 equiv) at  $-78$  to  $0^\circ\text{C}$  gave a mixture of four aldehydes ( $^1\text{H}$  NMR analysis) in 92% yield.<sup>33</sup> This mixture also could not be separated, so the aldehydes were reduced by treatment with  $\text{NaBH}_4$  in  $\text{MeOH}$  at  $0^\circ\text{C}$ .

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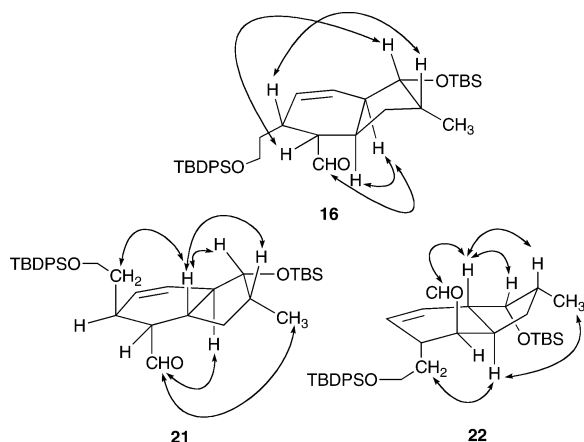
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Fortunately, the mixture of alcohols **20** could be fractionated at this stage by using HPLC. Pure samples of the two major stereoisomers were obtained, along with a mixture of two minor products. Oxidation of the two major alcohols with Dess–Martin periodinane gave trans-fused perhydroindenes **21** and **22**, the stereostructures of which were unambiguously assigned by using 1D and 2D NMR experiments (Figure 2).

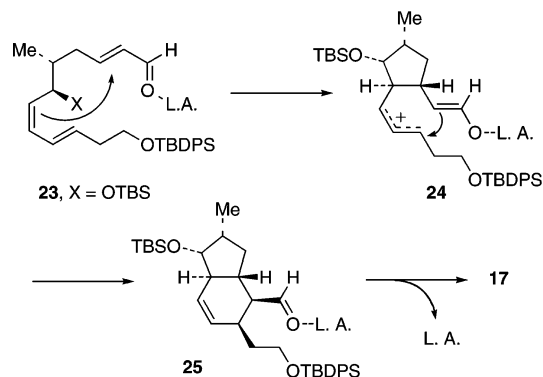


**Figure 2.**  $^1\text{H}$  NOESY data for cycloadducts **16**, **21**, and **22**.

Base-promoted epimerization of **21** and **22** provided authentic samples of **17** and **18**, which were identified as the minor products of the IMDA cyclization of **1** (vide supra). A mixture of **17** and **18** was similarly prepared by oxidation of the mixture of minor alcohols **20** (deriving from **19**).

The appearance of trans-fused products in the cyclizations of **1** and **2** implicates a stepwise cyclization mechanism, rather than a traditional concerted [4+2] transition state (see Scheme 4). Increasing the activation of the dienophile (alde-

**Scheme 4.** Proposed Stepwise Pathway for Formation of Trans-Fused Cycloadducts



hyde < Lewis acid-complexed aldehyde < dioxolenium ion) appears to increase the asynchronicity of the transition state to the point where a stepwise mechanism is by far the major pathway. Interestingly, the allylic strain arguments that have been advanced to rationalize the high asymmetric induction in the competing IMDA transition states A vs B do not apply to the nonconcerted cyclization leading to **17**, **18**, **21**, and **22**. Thus, for substrates such as **1**, a thermal IMDA cyclization protocol appears to be superior to the Lewis acid promoted alternative.

Further studies of the (*Z*)-diene Diels–Alder reaction in natural products synthesis will be reported in due course.

**Acknowledgment.** Financial support by the National Institutes of Health (GM26782) is gratefully acknowledged.

**Supporting Information Available:** Experimental procedures and spectroscopic characterization ( $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, and HRMS) of compounds **1**, **2**, **8–16**, **21**, and **22**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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