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

Thomas A. Dineen and William R. Roush*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

roush@umich.edu

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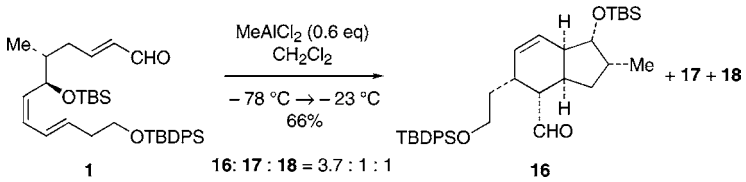
ABSTRACT



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.[1,2] Acyclic (*Z*)-1,3-dienes are substantially less reactive than (*E*)-dienes in the thermal Diels−Alder reaction[3,4] and are subject to thermal olefin isomerization.[5−9] As a result, their use in Diels−Alder reactions has been limited.[10] 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.[1,2]

In connection with ongoing studies on the synthesis of macquarimicin A and cochleamycin A,[11−13] 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.[5,14] 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).[15,16] In fact, thermal intramolecular Diels−Alder reactions of trienes similar to **3** have

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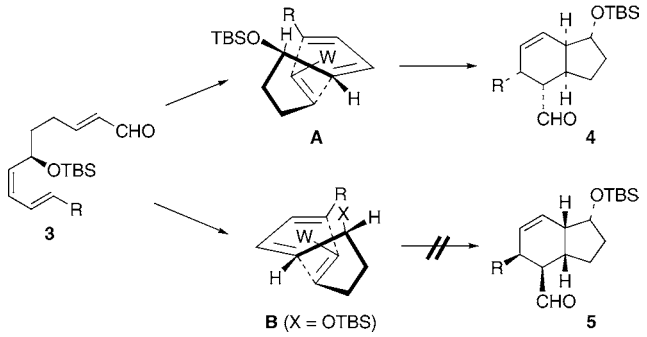
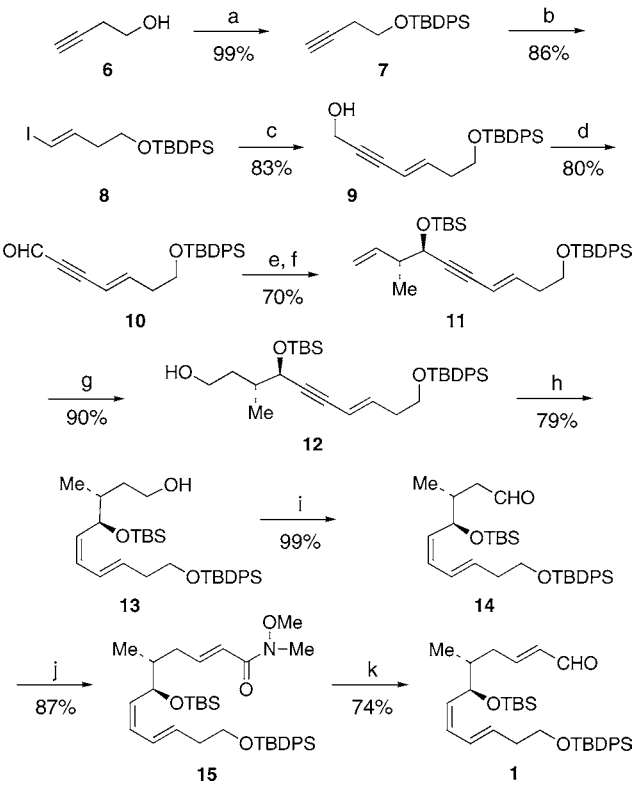


Figure 1. Diastereoselectivity in the IMDA of alkoxy-substituted (*Z*)-1,3-dienes.

recently been accomplished with excellent success by the Tadano[17] and Paquette[18] 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.[19] In contrast, dienylic alkoxy-substituted trienes with carboalkoxy dienophile activation tend to give only decomposition products under Lewis acid-promoted cycloaddition conditions.[20] Thus, the question we wished to address was if carboxaldehyde-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-butyn-1-ol to give the TBDPS ether **7** in 99% yield. Treatment of **7** with Schwartz's reagent followed by addition of I_2 gave vinyl iodide **8** in 86% yield.[21] Sonogashira coupling[22] of **8** with propargyl alcohol gave alcohol **9** in 83% yield, which was oxidized with MnO_2 to give aldehyde **10** in 80% yield. Treatment of the aldehyde with diisopropyl (*S*,*S*)-tartrate (*E*)-crotylboronate,[23] 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.[24,25] This reaction provided

Scheme 1[a]



[a] Reagents and conditions: (a) TBDPS−Cl, imidazole, DMAP, CH_2Cl_2:DMF (2:1); (b) $Cp_2Zr(H)Cl$, CH_2Cl_2, then I_2; (c) propargyl alcohol, $Pd(PPh_3)_2Cl_2$, CuI, Et_2N; (d) MnO_2, CH_2Cl_2; (e) diisopropyl (*S*,*S*)-tartrate (*E*)-crotylboronate, $PhCH_3$, −78 °C; (f) TBS−Cl, imidazole, CH_2Cl_2−DMF (2:1); (g) 9-BBN, THF, 0 °C, then H_2O_2, aqueous NaOH, 0 °C; (h) Zn, $Cu(OAc)_2 \cdot H_2O$, $AgNO_3$, MeOH:H_2O (1:1); (i) Dess−Martin periodinane, pyridine, wet CH_2Cl_2; (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.[26,27] 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 $MeAlCl_2$ in CH_2Cl_2 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 ^1H 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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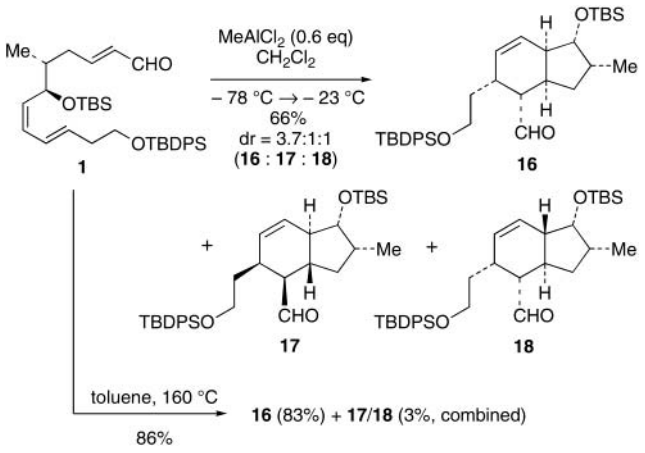
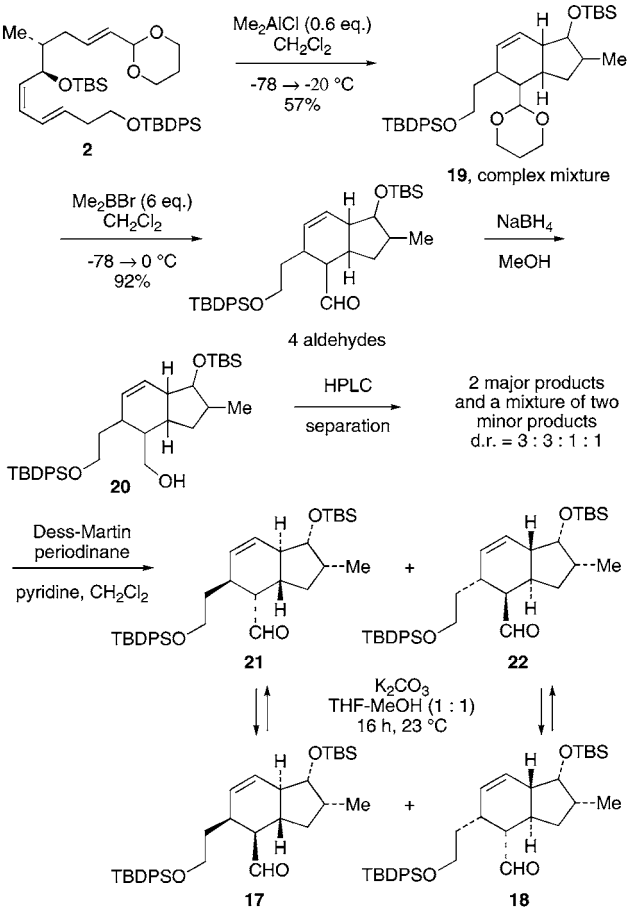
Scheme 2. Lewis Acid-Catalyzed and Thermal IMDA Cyclizations of (*E*,*Z*,*E*)-Triene **1**



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



spectroscopic correlation with the products of cyclization of acetal **2** (vide infra). Use of alternative Lewis acids (BF_3·OEt, $SnCl_4$, $TiCl_4$, and (menthyloxy)$AlCl_2$) for the IMDA cyclization of **1** gave very low yields of products, while attempted use of Me_2AlCl and 4 M $LiClO_4$ in CH_3NO_2 failed to promote any cycloaddition, and only returned unchanged starting triene. In contrast, heating a solution of **1** at 160 °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.[5,14] 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 $MeAlCl_2$-promoted cyclization of **1** was faster than decomposition pathways involving ionization of the pentadienyl ether,[19,20] 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 α,β-unsaturated acetal provides a vinyl dioxolenium ion, a very potent dienophile.[28,29] 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 catalytic amount of TsOH in THF.[30] Treatment of **2** with 0.6 equiv of Me_2AlCl in CH_2Cl_2 at −78 °C and immediately warming the mixture to −20 °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 $LiClO_4$ in CH_3NO_2 at room temperature overnight.[31,32] This mixture could not be separated by HPLC, so product separation was postponed following subsequent chemical manipulations. Treatment of the cycloadduct mixture with Me_2BBr (6 equiv) at −78 to 0 °C gave a mixture of four aldehydes (^{1}H NMR analysis) in 92% yield.[33] This mixture also could not be separated, so the aldehydes were reduced by treatment with $NaBH_4$ in MeOH at 0 °C.

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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).

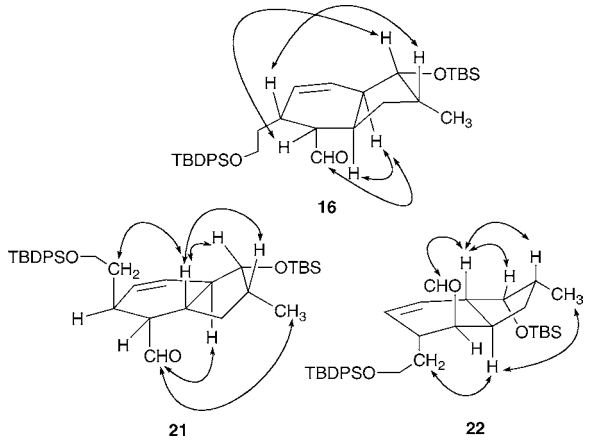
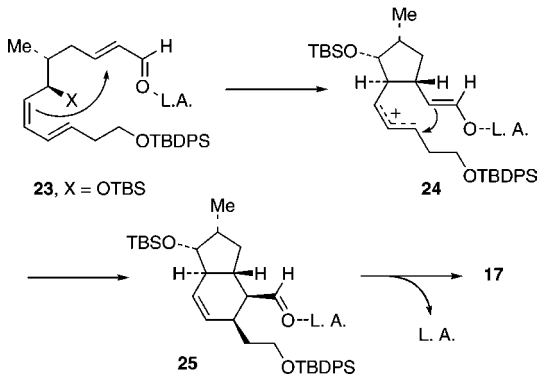


Figure 2. ^{1}H NOESY data for cycloadducts **16**, **21**, and **22.**

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 (aldehyde < 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.

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



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

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Supporting Information Available: Experimental procedures and spectroscopic characterization (^{1}H and ^{13}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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