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Diene-Transmissive Cycloadditions: Control of Monocycloaddition by Self-Assembly on a Lewis Acid Template

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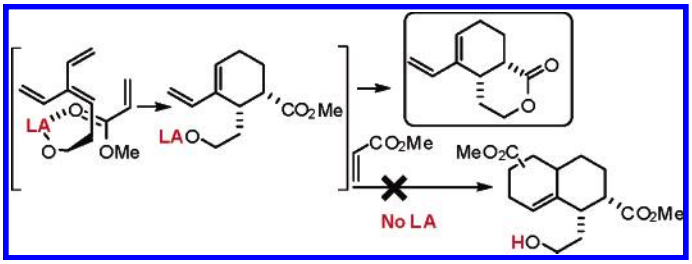
ABSTRACT

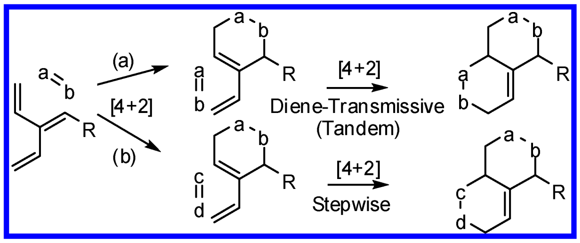


The sequential control of diene-transmissive Diels–Alder reactions to expand their versatility for natural product synthesis and the preparation of diversity oriented libraries is described. Self-assembly of the components (trienol 5 and methyl acrylate) via a Lewis acid template proceeds with regio-, diastereo-, and enantioselective [(*S*)-BINOL added] control to the monoadduct. In contrast, no cycloaddition reaction occurred at 22 °C in the absence of catalyst. This protocol obliterates the necessity of tether installation for an intramolecular cyclization.

Cross-conjugated trienes ([3]dendralenes) are versatile precursors for diene-transmissive (tandem) intermolecular Diels−Alder cycloadditions. Sequential cycloadditions can afford eight rings directly (quinone, cyclopentadiene).[1] Substituted [3]dendralenes can be prepared readily from the exclusive γ addition to carbonyl groups followed by elimination of water.[1a,2] With reactive dienophiles, the tandem reaction predominates (Scheme 1, eq a).

Consequently, it is a challenge to control the monoaddition of different dienophiles in a selective manner when both cyclizations are intermolecular. One solution is to employ an intramolecular cycloaddition initially followed by an intermolecular reaction.[3] Another possibility employs dienophiles in which the cycloaddition rates differ significantly (Scheme 1, eq b). Schreiber et al. [4] employed a triene approach for a library of 29 000 molecules and noted that chlorine and methyl substitution on the dienophile encouraged single cycloadditions.

Scheme 1. Reaction Pathway for Cross-Conjugated Trienes ([3]Dendralenes)



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(1) (a) Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573−575. (b) For [4]dendralene, see: Payne, A. D.; Willis, A. C.; Sherburn, S. *J. Am. Chem. Soc.* **2005**, *127*, 12188−12189. For related examples, see: Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: New York, 2000; pp 253−260. (c) Miller, N. A; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2006**, Early View.

(2) Hirashita, T.; Inoue, S.; Yamamura, H.; Kawai, M.; Araki, S. *J. Organomet. Chem.* **1997**, *549*, 305−309.

10.1021/ol062869d CCC: $37.00

The trienes **4** and **5** required for our study were generated from the protected aldehyde **2**[5] followed by pentadienyl indium addition and elimination of water as illustrated in Scheme 2.[16]

Scheme 2. Synthesis of Cross-Conjugated Trienol **5** from Pentadienyl Indium Condensation with **2**

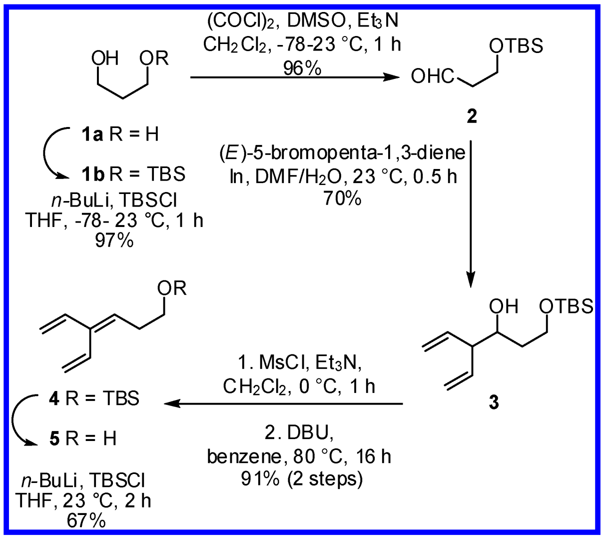
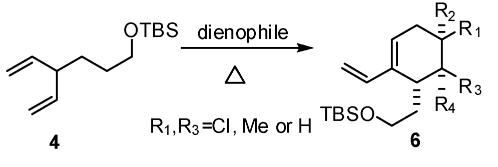
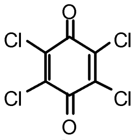
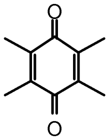
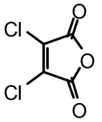
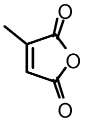
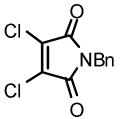


Table 1 summarizes our results with the silyl-protected triene **4**; however, the yields are low to nonexistent (entries 2 and 5),[6] and the substitution pattern in the best example with tetrachloroquinone (entry 1) is not very synthetically useful.

A significant improvement would be to develop a temporary tether which could also introduce useful functionality for subsequent transformations and provide a general solution to eq b in Scheme 1. An attractive possibility involved a Lewis acid catalyzed and self-assembled Diels−Alder cycloaddition (LACASA-DA) in which magnesium, aluminum, or a related metal could complex with the unprotected triene alcohol and the ester dienophile to provide a temporary template to control the in situ intramolecular Diels−Alder reaction.[7] In addition, this protocol holds promise to control the chemo-, regio- stereo-, and enantioselectivity of the reaction.

Table 1. Thermal Diels−Alder Reactions of **4** with Chlorine and Methyl-Substituted Dienophiles



entry	dienophile	conditions	yield (%)[a]
1		75 °C, 2 d	66
2		75 °C, 2 d	0
3		100 °C, 2 d	16
4		200 °C, 16 h	33[b]
5		110 °C, 2 d	0

[a] Isolated yields. [b] Isolated as a mixture of regioisomers.

For silyl ether **4** (Table 2), *n*-pentanol was added to mimic the presence of an alkoxide−Lewis acid intermediate and create conditions similar to the successful cycloadditions below. The first two examples (entries 1 and 2) in Table 2 demonstrate, as anticipated, that the reactions of the silyl-protected trienol **4** and methyl acrylate were unsatisfactory with Et_2AlCl/*n*-pentanol or MeMgBr/*n*-pentanol and there was no reaction in the absence of Lewis acid. A blank reaction (entry 3) with **5** and methyl acrylate at 23 °C also failed.

In contrast, the reaction of alcohol **5** with diethylaluminum chloride and methylmagnesium bromide/*n*-pentanol[7,8] afforded yields of 74% and 85%, respectively (entries 4 and 5). These latter results demonstrated the utility of this approach.

It was also of interest to examine some related dienophiles to ascertain the selectivity that could be achieved. Examples of sequential cycloadditions under LACASA conditions with one equivalent of dienophile afforded concomitant generation of the lactone **8** or **9** in the case of dimethyl fumarate and maleic anhydride (Table 3, entries 1 and 2).

Consistent with the examples above, DA reaction of **5** with dimethyl fumarate afforded lactone **8** with complete chemo-

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(3) (a) Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 1013−1016. (b) Clay, M. D.; Riber, D.; Fallis, A. G. *Can. J. Chem.* **2005**, *83*, 559−568.

(4) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402.

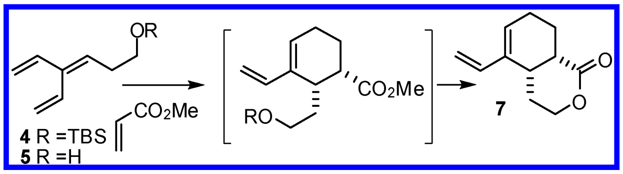
(5) Smith, A. B., III; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099−3102.

(6) Cebrowski, P., unpublished results.

(7) For key references on Lewis acid catalyzed and self-assembled Diels−Alder reactions (LACASA-DA), see: (a) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937−3940. (b) Ward, D. E.; Souweha, M. S. *Org. Lett.* **2005**, *7*, 3533−3536. (c) For a templated copper dimerization, see: Heuft, M. A.; Fallis, A. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4520−4523.

(8) Addition of *n*-pentanol has been shown to facilitate cycloadditions involving dienols, presumably due to the speciation of the Mg(II) salts formed. See: (a) Coates, G. E.; Ridley, D. *J. Chem. Soc., Chem. Commun.* **1966**, 560−561. (b) Moseley, P. T.; Shearer, H. M. M. *J. Chem. Soc., Chem. Commun.* **1968**, 279−280.

Table 2. Trial Diels−Alder Reactions of **4** or **5** with Methyl Acrylate



entry	diene	conditions	yield (%)[a]
1	**4**	Et$_2$AlCl, *n*-pentanol 23 °C, 2 d	10
2	**4**	MeMgBr, *n*-pentanol 23 °C, 2 d	0
3	**5**	23 °C, 2 d	0[b]
4	**5**	Et$_2$AlCl 23 °C, 1 d	74
5	**5**	MeMgBr, *n*-pentanol 23 °C, 1 d	85

[a] Isolated yields. [b] Only starting material detected in the crude ^{1}H NMR spectrum.

and stereoselectivity. The yield with maleic anhydride is poor, but the cycloaddition afforded a single adduct. The reversal in chemoselectivity (i.e., **10**:**11**) observed for entries 3 and 4 was not anticipated but provides additional experimental support for the importance of the Lewis acid complex and its promotion of the initial cycloaddition. Consequently, minor variation of the experimental conditions expands the synthetic utility of this protocol. The tetracyclic structure of adduct **11** was confirmed by X-ray analysis (Figure 1).[9]

The scope of this procedure would be enhanced if the LACASA-DA reaction of **5** with methyl acrylate could be rendered enantioselective. These results are summarized in Scheme 2, and clearly, trimethyl aluminum by itself is not a suitable catalyst. The cycloaddition became enantioselective with the addition of (*S*)-BINOL (1 equiv) in the presence of Me$_3$Al to afford 80% yield of **7** with a modest ee of 75% (Scheme 3). The presence of (*S*)-BINOL accelerates the reaction, but the factors responsible are still unclear.

Recently, several synthetic examples or studies toward a target utilized a stereoselective Lewis acid tethered Diels−Alder reaction as an important step for natural product construction. These include Abyssomicin C,[10] Penostatin F,[11]

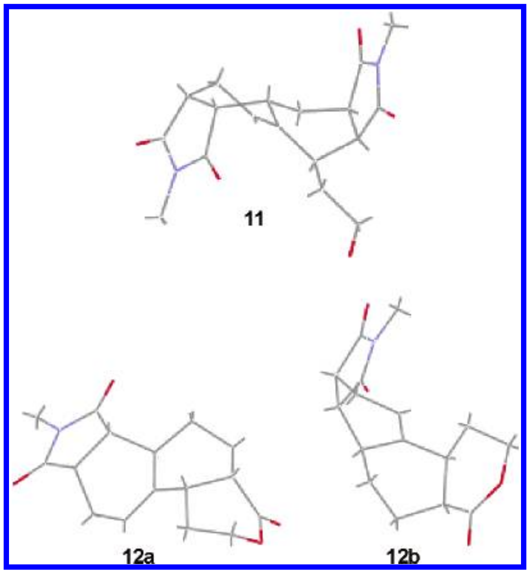
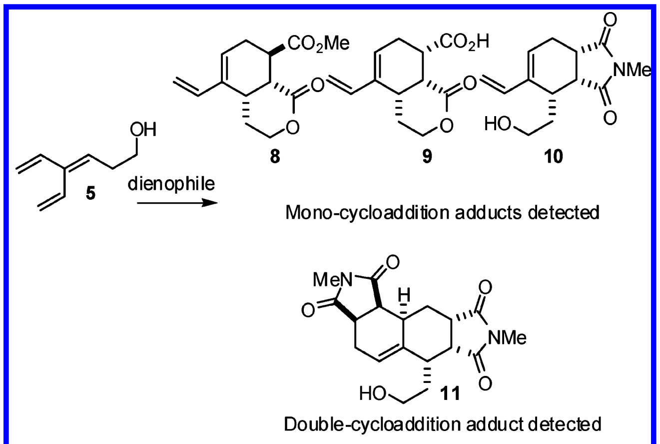
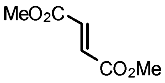
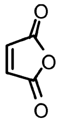
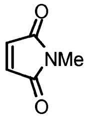
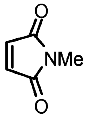


Figure 1. X-ray structures of adducts **11**, **12a**, and **12b**.

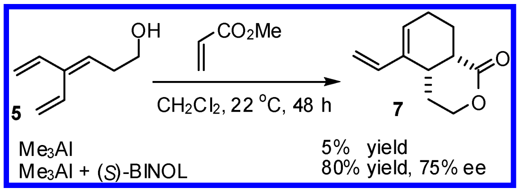
Table 3. Monocyclization via LACASA Reactions of **5** with Various Dienophiles



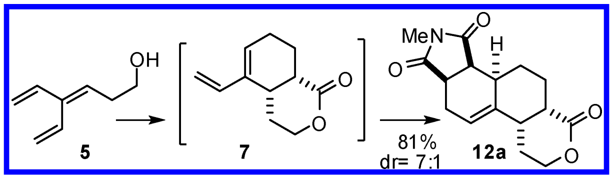
entry	dienophile	conditions	adduct, yield (%)[a]
1		MeMgBr, *n*-pentanol 23 °C, 1 d	**8**, 80
2		23 °C, 1 d	**9**, 19
3		23 °C, 1 d	**10**, 17 **11**, 36
4		MeMgBr, *n*-pentanol 23 °C, 1 d	**10**, 61 **11**, 17

[a] Isolated yields.

Scheme 3. Enantioselective LACASA-DA Reaction of **5** with Methyl Acrylate to Lactone **7**



Scheme 4. Sequential Double Diels−Alder of Cross-Conjugated Trienol **5** with Methyl Acrylate and *N*-Methylmaleimide



and Vinigrol.[12] Another interesting and synthetically useful variant is to follow the initial mono-LACASA-DA reaction with a second intramolecular [4+2] cycloaddition for a more complex natural product skeleton. In addition, the monocycloaddition adduct may now be employed in a double Diels−Alder reaction from the cross-conjugated triene **5** in a stepwise fashion. Thus, exposure of lactone **7** to *N*-methylmaleimide provided the tetracyclic heterocycle **12** in 93% yield with good diastereoselectivity (dr = 7:1) (Scheme 4). These results were confirmed by X-ray analysis (Figure 1)[9] and revealed the bowl-shaped motif of the minor isomer **12b**.

In summary, the application of an initial mono-LACASA-DA reaction in a controlled, stepwise, sequential cycloaddition sequence expands the potential of this triene chemistry for the preparation of complex polycyclic frameworks. Currently, we are applying this chemistry toward a variety of synthetic objectives.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support of this research and to I. Korobkov (University of Ottawa) for X-ray analysis.

Supporting Information Available: Experimental details, spectral characterization, and CIF data files for these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062869D

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(9) CCDC 633006−633008 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) (a) Nicolaou, K. C.; Harrison, S. T. *J. Am. Chem. Soc.* **2007**, *129*, 429−440. (b) Nicolaou, K. C.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3256−3260. (c) Zografos, A. L.; Yiotakis, A.; Georgiadis, D. *Org. Lett.* **2005**, *7*, 4515−4518. (d) Rath, J.-P.; Kinast, S.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3089−3092.

(11) Barriault, L.; Ang, P. J. A.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317−1319.

(12) Morency, L.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 8841−8853.