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Siloxacyclopentenes as Dienophile-Linked Directing Groups in Intramolecular Diels−Alder Reactions

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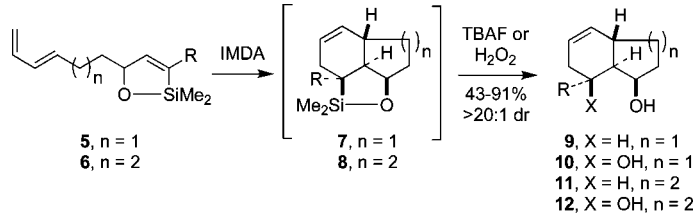
ABSTRACT



The synthesis and intramolecular Diels−Alder reactions of trienes 5 and 6 with a siloxacyclopentene-constrained dienophile are described. These reactions provide the primary cycloadducts 7 and 8 with high diastereoselectivity. These cycloadducts possess *trans*-relationships between the ring fusion proton and the adjacent C(1) alkoxy group and can be further elaborated to alcohols 9 and 11 (via protiodesilylation) or to 10 and 12 (via Fleming−Tamao oxidation) depending on the substitutent R.

Intramolecular Diels−Alder (IMDA) reactions of 1,3,8-nonatrienes and 1,3,9-decatrienes have been extensively applied to the synthesis of hexahydroindene and octahydronaphthalene substructures found in a wide array of natural products.[1−4] Addition of temporary stereochemical directing groups has been used to increase stereoselectivity of certain IMDA reactions.[5,6]

Boeckman and our group introduced the steric directing group strategy for diastereocontrol of IMDA reactions of trienes with alkoxy substituents at the internal dienylic position (e.g., **1**). Introduction of the diene substituent "X" in triene substrates allows for selective access to cycloadducts in which the alkoxy substituent of the product is in a *cis*-relationship with the adjacent ring fusion proton.[5,6] For example, trienes **1** (X = Br or $SiMe_3$) react through transition state **A** to give cycloadducts **2** with excellent diastereoselectivity. Our group has applied this methodology to the synthesis of chlorothricolide[6−8] and spinosyn A model systems.[9,10]

Complementary stereochemical control can be achieved by locking the diene and an adjacent hydroxyl group by way of a conformationally constraining siloxacyclopentene unit.[11] For example, trienes **3** react through transition state **B** to give cycloadducts **4** in which the heteroatom is in a *trans*-relationship with the adjacent ring fusion proton (Scheme 1).

In connection with an ongoing effort in natural product synthesis, we became interested in the possibility that use of a dienophile-tethered siloxacyclopentene unit could pro-

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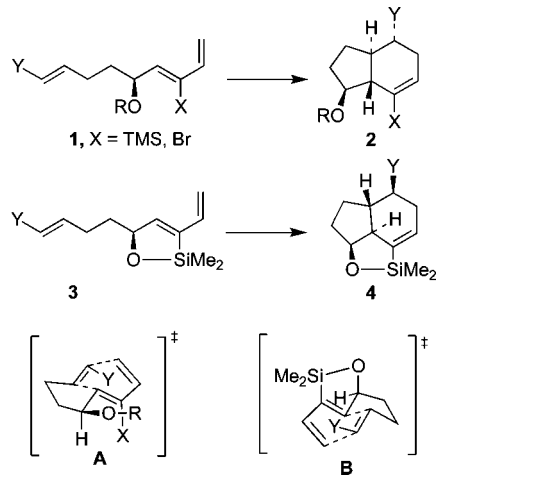
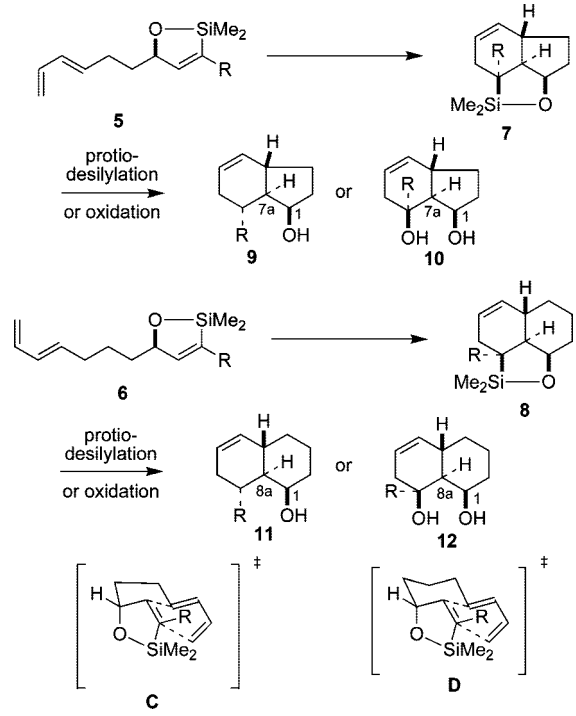
Scheme 1. Stereochemical Directing Group Strategies for IMDA Reactions



vide a general strategy for control of the stereochemistry of bicycles **9**−**12** (Scheme 2). On the basis of the limited number of literature examples of IMDA reactions of trienes with unconstrained alkoxy units allylic to the dienophile,[1−4] it appears that synthetically useful control of the stereochemistry of the alkoxy group relative to the ring fusion in cycloadducts analogous to **9** and **11** cannot always be achieved.[12] In contrast, it was anticipated that IMDA cyclizations of **5** and **6** should proceed via transition states **C** and **D** to give *trans*-fused cycloadducts **7** and **8**, respectively, with excellent stereochemical control. The constraint imposed by the siloxacyclopentene unit makes it impossible for these reactions to proceed with pseudoequatorial placement of the alkoxyl group, which would lead to the C(1)-epimers of **9**−**12**. Moreover, it was anticipated that the IMDA cyclizations of **5** and **6** should show excellent control for *trans*-ring-fused cycloadducts, as the alternative *cis*-fused transition states (not shown) suffer from nonbonded interactions between the diene and the dimethylsilyl unit. Elaboration of the primary cycloadducts **7** and **8**, either by protiodesilylation[13] or Fleming−Tamao oxidation,[14] would then lead to **9**−**12**. Cycloadducts **10** and **12** are of considerable interest as they are the formal products of intramolecular Diels−Alder reactions of enol-containing dienophiles.

Scheme 2. Strategy for Intramolecular Diels−Alder Cyclizations of Siloxacyclopentene-Constrained Trienes **5** and **6**

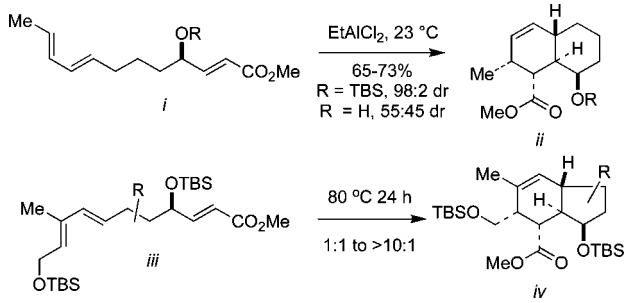


We report herein the synthesis and IMDA reactions of siloxacyclopentene-constrained trienes **5a**−**c** and **6a**−**c** to illustrate this strategy. The ethylene glycol acetal units in **5c** and **6c** serve as excellent dienophiles under Lewis acidic conditions.[15]

Synthesis of nonatrienes **5a**−**c** began with the known Claisen rearrangement[16] of commercially available 1,4-pentadien-3-ol (**13**) (Scheme 3). Aldehyde **14** was then treated with the lithium acetylides generated from either phenylacetylene, 2-furylacetylene, or propionaldehyde acetal **16**[17] to give alcohols **15a**−**c** respectively. These intermediates were then elaborated to trienes **5a**−**c** in good yield by treatment with tetramethyldisilazane, followed by catalytic potassium *tert*-butoxide in THF to effect intramolecular hydrosilylation (Scheme 3).[18]

Syntheses of decatrienes **6a**−**c** were performed by using similar procedures (Scheme 4). Commercially available

(12) (a) Funk has shown that decatriene ***i*** undergoes a highly stereoselective cycloaddition under Lewis acid promoted conditions to give cycloadducts ***ii***, as a result of a presumed hyperconjugation of the C—O bond with the dienophile in the transition state. However, lower selectivity is observed in the thermal cyclization and with the substrate lacking a TBS protecting group: Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (b) The IMDA cyclizations of nonatrienes ***iii*** display a less pronounced preference for cycloadducts ***iv***, and selectivity in this series is strongly influenced by substituents on the tether: Suzuki, T.; Tanaka, N.; Matsumura, T.; Hosoya, Y., Nakada, M. *Tetrahedron Lett.* **2006**, *47*, 1593.



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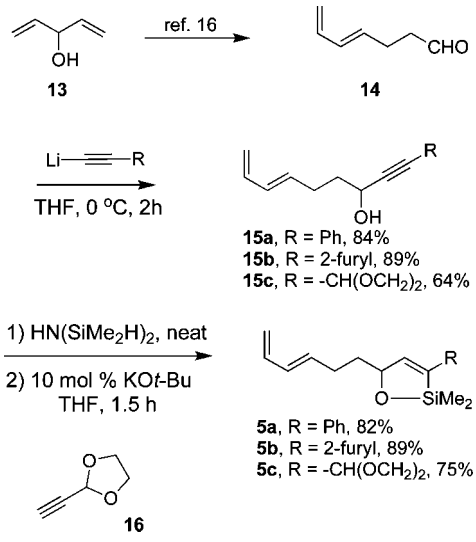
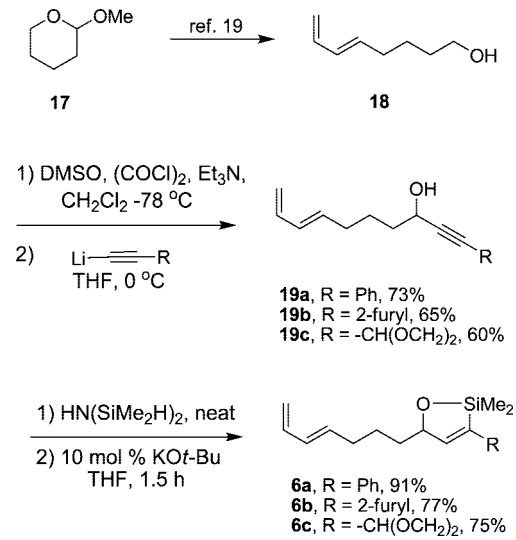
2-methoxytetrahydropyran (**17**) was converted into dienol **18** via the known procedure.[19] Alcohol **18** was oxidized using the Swern protocol,[20] and the resulting aldehyde was treated with the lithium acetylide generated from either phenylacetylene, 2-furylacetylene or **16** to give alcohols **19a**−**c**. Propargyl alcohols **19a**−**c** were then converted to the trienes **6a**−**c** by treatment with $HN(SiMe_2H)_2$ followed by catalytic KO*t*Bu in THF.[18]

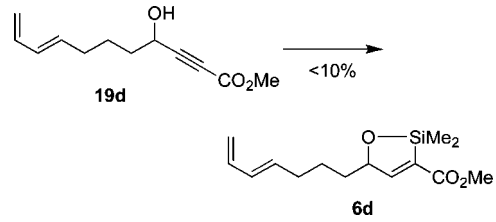
Scheme 3. Synthesis of Nonatrienes **5a**−**c**



Scheme 4. Synthesis of Decatrienes **6a**−**c**



Scheme 5. Attempted Hydrosilylation of **19d**



Although the results summarized in Schemes 3 and 4 (as well as those in our previous study[11]) demonstrate that the intramolecular hydrosilylation procedure, originally developed by Lee,[18] works well for a range of substrates, one limitation is for substrates like **19d** (Scheme 5). Attempted hydrosilylation of **19d** under a variety of conditions gave only small amounts (<10%) of **6d**, which proved to be highly unstable to attempted chromatographic purification, as well as to acidic, basic, and thermal (e.g., Diels−Alder) reaction conditions. Consequently, acetals **5c** and **6c** serve as surrogates for conventional dienophile-activated trienes in this study.

The results of intramolecular Diels−Alder reactions of trienes **5** and **6** are summarized in Table 1. Thermal cycloadditions were performed in toluene (0.03 M) in a sealed tube in the presence of a catalytic amount of BHT. Lewis acid promoted cycloadditions were carried out by addition of the reagent to a solution of triene in CH_2Cl_2 (0.02 M) at −78 °C, and then the solution was warmed to the final reaction temperature. In both sets of reactions, the crude cycloadducts were subjected either to protiodesilylation (TBAF in THF, 60 °C)[13] or to Fleming−Tamao oxidation (H_2O_2, KF, $KHCO_3$ in 1:1 THF/MeOH),[14] as indicated.[21,22] Remarkably, all cycloadditions were highly stereoselective for the *trans*-fused cycloadducts, with no observable *cis*-fused cycloadducts by ^{1}H NMR analysis of the crude reaction mixtures (≥20:1 dr).

The intramolecular cycloaddition of phenyl-substituted triene **5a** required 7 days at 190 °C to proceed to completion but nevertheless gave a single diastereomeric cycloadduct according to ^{1}H NMR analysis of the reaction mixture. Oxidation of crude **7a** under standard Fleming−Tamao conditions gave diol **10a** in 72% overall yield. The stereochemistry of **10a** (as with all isolated cycloadducts in this study) was assigned by NMR methods (see Supporting Information). Thermal cycloaddition of 2-furyl-substituted triene **5b** was also sluggish and required three days at 170 °C to go to completion. Again, standard Fleming−Tamao oxidation of the crude cycloadduct **7b** gave a single diol **10b** in 43% yield.

Attempted thermal cycloaddition of triene **5c** led only to decomposition. Fortunately, TMS-OTf promoted cycload-

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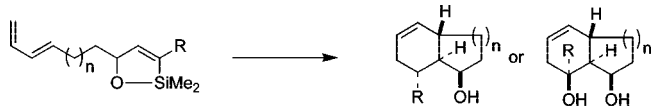
(21) The siloxacyclopentane units of the primary cycloadducts **7** and **8**, and especially those of ethylene glycol acetals **7c** and **8c**, are unstable. Therefore, all cycloadditions were processed as described in text to give **9**−**12** as the isolated reaction products.
(22) Protiodesilylation of cycloadduct **7a** with TBAF was unselective, giving a ca. 1.5:1 mixture of benzylic epimers.

Table 1. Thermal and Lewis Acid Promoted Intramolecular Diels−Alder Reactions of Trienes **5** and **6**



5, n = 1
6, n = 2

9, n = 1
11, n = 2

10, n = 1
12, n = 2

entry	substrate	R	Diels−Alder conditions	workup conditions	product[a]	product yield (%)[b]
1	**5a**	Ph	190 °C, 7 days	KF, $KHCO_3$, H_2O_2	**10a**	72
2	**5b**	2-furyl	170 °C, 72 h	KF, $KHCO_3$, H_2O_2	**10b**	43
3	**5c**	-$CH(OCH_2)_2$	170 °C, 72 h		**10c**	0
4	**5c**	-$CH(OCH_2)_2$	0.4 equiv TMS-OTf, −78 to 0 °C, 2 h	TBAF, THF, 60 °C, 2 h	**9c**	85
5	**6a**	Ph	190 °C, 5 days	KF, $KHCO_3$, H_2O_2	**12a**	64
6	**6b**	2-furyl	170 °C, 48 h	KF, $KHCO_3$, H_2O_2	**12b**	45
7	**6c**	-$CH(OCH_2)_2$	170 °C, 72 h		**11c**	0
8	**6c**	-$CH(OCH_2)_2$	0.4 equiv TMS-OTf, −78 to 0 °C, 2 h	TBAF, THF, 60 °C, 2 h	**11c**	91

[a] Each cycloaddition was highly diastereoselective (≥20:1 by ^{1}H NMR analysis of the crude reaction mixtures.) [b] Yield of cycloadducts after purification by silica gel column chromatography.

dition of **5c** proceeded smoothly at −78 to 0 °C. The resulting cycloadduct **7c** was converted to alcohol **9c** (85% yield) by treatment with TBAF in THF. Again **9c** was obtained as a single isomer by ^{1}H NMR analysis of the crude reaction mixture. Unfortunately, all attempts to oxidize the carbon−silicon bond of **7c** under a variety of conditions failed to give diol **10c**. All attempted oxidations of **7c** under conditions containing a fluoride source or a strong base led only to desilylated **9c** (H_2O_2, KF, $KHCO_3$ in 1:1 THF/MeOH or *t*-BuOOH, NaH in THF), while no reaction was observed under milder conditions (Me_3NO in DMF).

Decatrienes **6a**−**c** behaved analogously to their nonatriene counterparts. Thermal cycloaddition of **6a** required 5 days at 190 °C. Fleming−Tamao oxidation of the primary cycloadduct **8a** gave diol **12a** in 64% yield. Thermal cycloaddition of **6b** was complete after 2 days at 170 °C. Fleming−Tamao oxidation of **8b** provided the diol **12b** in 45% yield. Finally, treatment of decatriene **6c** with TMS-OTf at −78 °C with warming to 0 °C led to smooth cycloaddition. Protiodesilylation of the primary cycloadduct **8c** by treatment with TBAF in THF at 60 °C then provided alcohol **11c** in 91% yield and as a single diastereomer. All attempts to effect Fleming−Tamao oxidation of **8c** were unsuccessful.

In summary, we have developed a strategy for the stereocontrolled synthesis of hexahydroindene and octahydronaphthalene cycloadducts **9**−**12** via the intramolecular Diels−Alder cyclizations of siloxacyclopentene-constrained trienes **5** and **6**. The silacyclopentene units of **5** and **6** permit the stereochemistry of the C(1) hydroxyl group of the cycloadducts to be controlled relative to the ring fusion and also serve as a handle for subsequent Fleming−Tamao oxidation (in the case of cycloadducts **7a**,**b** and **8a**,**b**). Also of interest is the ability of triene acetals **5c** and **6c** to undergo TMS-OTf promoted cycloadditions to give cycloadducts **9c** and **11c** after protiodesilylation of the initial products, **7c** and **8c**. Applications of this new strategy for stereochemical control of the intramolecular Diels−Alder reaction in the synthesis of biologically active natural products synthesis will be reported in due course.

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Supporting Information Available: Experimental procedures and full charactization data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) for all new compounds, as well as summaries of stereochemical assignments for cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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