

Intramolecular Diels–Alder Reactions of
Siloxacyclopentene Constrained Trienes

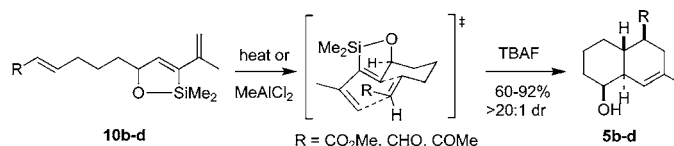
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ABSTRACT

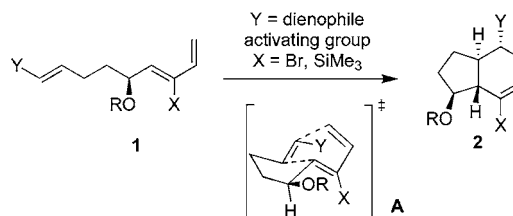


The synthesis of siloxacyclopentene-constrained trienes **7** and **10** and studies of their IMDA cycloadditions are described. The use of appropriately chosen thermal or Lewis acid conditions allows for cycloadducts **3–6** to be obtained with high levels of diastereoselectivity. These adducts possess *trans*-relationships between the hydroxyl group and the adjacent ring fusion proton, a stereochemical relationship not previously attainable in IMDA reactions.

Intramolecular Diels–Alder (IMDA) reactions of 1,3,8-nonatrienes and 1,3,9-decatrienes have been extensively applied to the synthesis of perhydroindene and octahydronaphthalene substructures found in a wide array of natural products.^{1–4} Temporary addition of stereochemical directing groups has been used to increase stereoselectivity in certain cases. Boeckman and our group developed the steric directing group strategy that allows for selective access to *trans*-fused cycloadducts where the ring fusion is flanked by a heteroatom functionality in a *cis*-relationship with the ring fusion proton (Scheme 1).^{5,6}

For example, by application of the steric directing group strategy, trienes **1** (X = –Br or –SiMe₃) react through transition state **A** to give cycloadducts **2** with excellent selectivity. Our group has applied this technology to the synthesis of chlorothricolide^{6–8} and spinosin A model systems.^{9,10} However, some natural products have the opposite

Scheme 1. Steric Directing Group Strategy



stereochemical arrangement, with a heteroatom substituent *trans* to the ring fusion proton as in cycloadducts **3–6** (e.g., FR182877),^{11–13} but this stereochemical relationship has proven difficult to achieve with consistently high levels of stereocontrol.

To access the *anti*-hydroxyl/ring fusion stereochemical relationship in *trans*-fused cycloadducts such as **3** and **5**, we

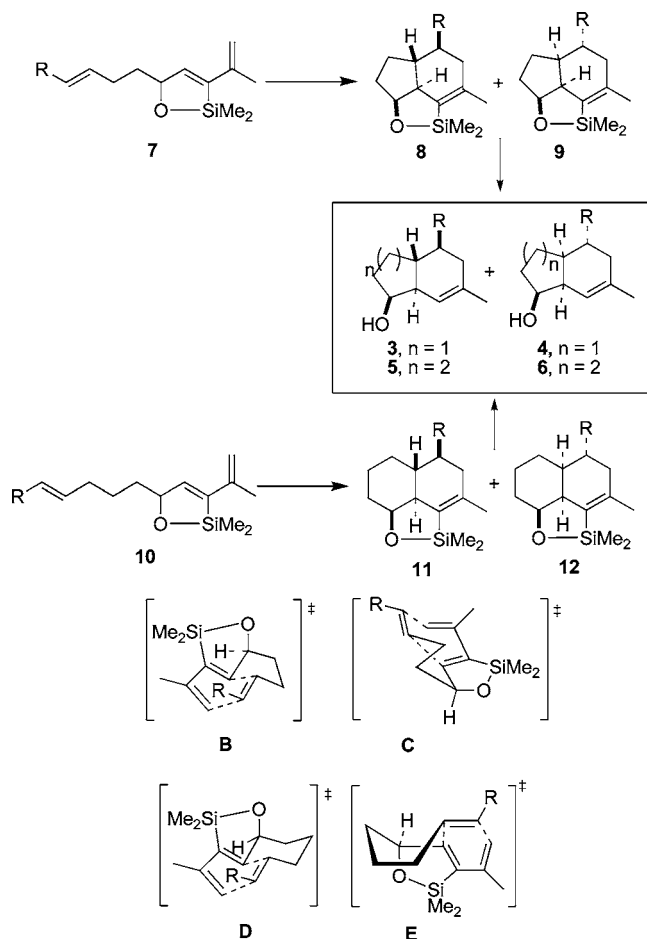
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sought to develop a strategy that would constrain the diene and adjacent hydroxyl functionality into coplanarity in the IMDA transition state(s). The diversity of methods for synthesizing five-membered siloxacycles,¹⁴ as well as the ease of their removal with fluoride ion sources, led us to explore the use of siloxacyclopentene units for this purpose. We report herein the successful development and implementation of the siloxacyclopentene-constrained strategy for IMDA reactions, which provides cycloadducts **3–6** in a manner complementary to the steric directing group strategy that has previously given access to cycloadducts such as **2**.

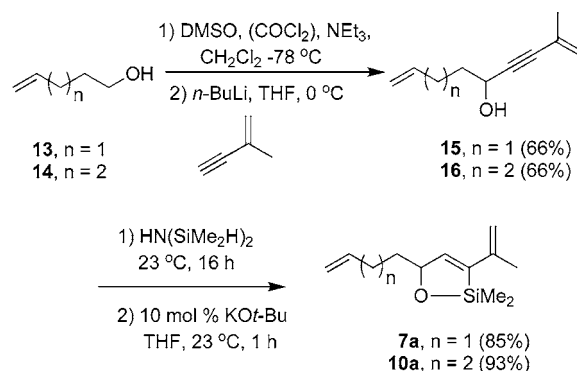
We targeted terminally active trienes **7a–e** and **10a–e** to illustrate this strategy. By virtue of the constaining siloxacyclopentene unit, trienes **7** would be forced to cyclize through the half-chair-like transition states *endo B* or *exo C* to give either *trans*-fused cycloadduct **8** or *cis*-fused cycloadduct **9**. Similarly, cyclization of the undecatriene homologues **10** would proceed either through chair-like transition state **D** or boat-like transition state **E** to give *trans*-fused **11** or *cis*-fused **12**, respectively (Scheme 2).

Scheme 2. Siloxacyclopentene Directing Group Strategy for IMDA Reactions



Synthesis of trienes **7a** and **10a** began with commercially available alcohols **13** and **14** (Scheme 3). Swern oxidation¹⁵ of **13** or **15** followed by addition of the lithium acetylide

Scheme 3. Synthesis of Trienes **7a** and **10a**



generated from 3-methylbutenyne gave propargyl alcohols **15** and **16**. Alcohols **15** and **16** were then treated with tetramethyldisilazane (neat), followed by 10 mol % of KOt-Bu according to Lee's hydrosilylation procedure.^{14e} This sequence provided trienes **7a** and **10a** in excellent yields, and could easily be preformed on multigram scale.

Trienes **7a** and **10a** were further functionalized via olefin cross metathesis¹⁶ by using the Hoveyda catalyst **17**¹⁷ to access terminally activated trienes **7b–e** and **10b–e**. Methyl esters **7b** and **10b** and methyl ketones **7d** and **10d** were obtained in 88–92% yield via cross metatheses, using methyl acrylate and methyl vinyl ketone, respectively. Similarly, cross metatheses of **7a** and **10a** with acrolein or acrolein acetals provided trienes **7c,e** and **10c,e**, in good yield when the reactions were performed in the presence of 1,4-benzoquinone (71–84%).¹⁸

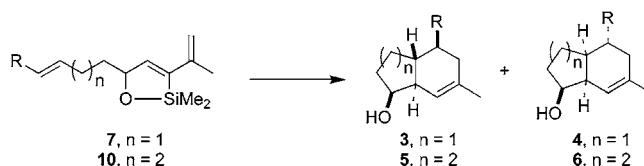
Table 1. Synthesis of Terminally Substituted Trienes **7b–e** and **10b–e**

Table 1 shows the synthesis of terminally substituted trienes **7b–e** and **10b–e** via cross metathesis of trienes **7a** and **10a** with various R groups using Hoveyda catalyst **17** (5 mol %, CH₂Cl₂, 40 °C, 16–18 h). The products are shown with their respective R groups and yields.

entry	$n =$	R =	yield (%) ^a	product
1	1	–CO ₂ Me	94	7b
2	2	–CO ₂ Me	94	10b
3	1	–CHO	84 ^b	7c
4	2	–CHO	83 ^b	10c
5	1	–COMe	92	7d
6	2	–COMe	88	10d
7	1	–CH(–OCH ₂ CH ₂ O–)	81 ^b	7e
8	2	–CH(–OCH ₂ CH ₂ O–)	71 ^b	10e

^a Yield of product after purification by silica gel chromatography.

^b Reaction performed with 10 mol % 1,4-benzoquinone.

Table 2. Thermal and Lewis Acid Promoted Intramolecular Diels–Alder Cycloadditions of Trienes **7** and **10**

entry	substrate	R	reaction conditions	product yield (%) ^a	products	ratio ^b
1	7a	–H	(1) ^c 180 °C, 24 h; (2) TBAF, THF, 60 °C, 1.5 h	75	3a:4a	<1:20
2	7b	–CO ₂ Me	(1) ^c 140 °C, 20 h; (2) TBAF, THF, 60 °C, 1.5 h	81	3b:4b	1:1
3	7b	–CO ₂ Me	MeAlCl ₂ , –78 to 23 °C, 16 h ^d	0		
4	7b	–CO ₂ Me	SnCl ₄ , –78 to 23 °C, 16 h ^e	0		
5	7c	–CHO	(1) ^c 100 °C, 20 h; (2) TBAF, THF, 12 h	60	3c:4c	2.5:1 ^f
6	7c	–CHO	(1) ^d MeAlCl ₂ , –78 to –20 °C, 3 h; (2) TBAF, THF, 12 h	55	3c:4c	>20:1 ^f
7	7d	–COMe	(1) ^c 100 °C, 20 h; (2) TBAF, THF, 60 °C, 1.5 h	85	3d:4d	2:1
8	7d	–COMe	(1) ^d MeAlCl ₂ , CH ₂ Cl ₂ , –78 to –20 °C, 3 h; (2) TBAF, THF, 60 °C, 1.5 h	75	3d:4d	94:6
9	7e	–CH(–OCH ₂ CH ₂ O–)	(1) ^c 160 °C, 36 h; (2) TBAF, THF, 60 °C, 1.5 h	74	3e:4e	<1:20
10	10a	–H	(1) ^c 190 °C, 72 h; (2) TBAF, THF, 60 °C, 1.5 h	65	5a:6a	1.25:1
11	10b	–CO ₂ Me	(1) ^c 140 °C, 20 h; (2) TBAF, THF, 60 °C, 1.5 h	92	5b:6b	>20:1
12	10b	–CO ₂ Me	MeAlCl ₂ , –78 to 23 °C, 16 h ^d	0		
13	10b	–CO ₂ Me	SnCl ₄ , –78 to 23 °C, 16 h ^e	0		
14	10c	–CHO	(1) ^c 120 °C, 24 h; (2) TBAF, THF, 12 h	57	5c:6c	>20:1 ^f
15	10c	–CHO	(1) ^d MeAlCl ₂ , –78 to –20 °C, 6 h; (2) TBAF, THF, 12 h	55	5c:6c	>20:1 ^f
16	10d	–COMe	(1) ^c 120 °C, 24 h; (2) TBAF, THF, 60 °C, 1.5 h	93	5d:6d	97:3
17	10d	–COMe	(1) ^d MeAlCl ₂ , –78 to 0 °C, 6 h; (2) TBAF, THF, 60 °C, 1.5 h	60	5d:6d	>20:1
18	10e	–CH(–OCH ₂ CH ₂ O–)	(1) ^c 190 °C, 72 h; (2) TBAF, THF, 60 °C, 1.5 h	57	5e:6e	1.8:1

^a Combined yield of products after purification by silica gel chromatography. ^b Product ratios determined by ¹H NMR analysis of crude reaction mixtures prior to protidesilylation. ^c 0.03–0.05 M PhMe solution in a sealed tube. ^d 0.01 M solution in CH₂Cl₂ with 1.0 equiv of MeAlCl₂. ^e 0.01 M solution in CH₂Cl₂ with 0.2 equiv of SnCl₄. ^f Ca. 10% epimerization α to the aldehyde occurred during protidesilylation and chromatography. Stereostructures were assigned by ¹H NOESY and *J* data (see the Supporting Information).

Results of the intramolecular Diels–Alder reactions of trienes **7** and **10** are summarized in Table 2. Thermal cycloadditions were performed at the indicated reaction temperatures in toluene (0.03 to 0.05 M) in a sealed tube. Lewis acid promoted cycloadditions were carried out in CH₂Cl₂

(0.01 M). A solution of the Lewis acid was added via syringe to the solution of triene at –78 °C, then the solution was warmed to the final reaction temperature. In both cases, the crude cycloadducts were immediately subjected to protidesilylation by treatment with TBAF (typically in THF at 60 °C) to aid in product isolation and purification.¹⁹ Stereochemistry of the cycloadducts was assigned by using ¹H NOESY and *J* data (see the Supporting Information).

The thermal cyclization of unactivated triene **7a** gave *cis*-fused cycloadduct **4a** with $\geq 20:1$ selectivity (entry 1). This result suggests that the siloxacyclopentene unit destabilizes the *trans*-fused transition state **B**, since it is known that thermal cycloadditions of conformationally unconstrained, unactivated nonatrienes provide the *cis*-fused cycloadducts with ca. 2–3:1 selectivity.²⁰

The high intrinsic selectivity preference for the *cis*-ring fusion exhibited in the IMDA reaction of **7a** proved difficult to overcome, as thermal cycloaddition of terminally activated trienes **7b–d** proved to be unselective (entries 2, 5, and 7). Thermal IMDA reactions of trienes analogous to **7b–d** but lacking the siloxacyclopentane unit generally display useful

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(18) Product yields in the absence of benzoquinone were typically <65%. For the use of quinones in metathesis see: Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

(19) The siloxacyclopentane units of some of the IMDA cycloadducts proved unstable to silica gel chromatography.

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selectivities for the *trans*-fused product (especially with terminal ketone or aldehyde dienophile activating groups).²¹

Attempts to effect the cycloaddition of trienoate **7b** by using Lewis acid catalysis gave no observable cycloadducts, with substrate decomposition occurring above 0 °C in the experiment performed with SnCl₄ (entries 3 and 4). However, Lewis acid promoted cycloadditions of trienal **7c** and trienone **7d** were highly selective for the *trans*-fused cycloadducts **3c** and **3d**, respectively (entries 6 and 8).

It proved necessary to use mild conditions for the protidesilylation of the siloxacyclopentane intermediate **8c** in the IMDA reactions of **7c**, as treatment of the crude cycloadduct with TBAF at 60 °C led to decomposition of the products (cf., **3c**), presumably due to competing reactions of the aldehyde function. Fortunately, decreasing the protidesilylation reaction temperature to 23 °C minimized side reactions, although a small amount of aldehyde epimerization was observed (ca. 10%).

Thermal cyclization of acetal **7e** was highly selective, giving the *cis*-fused cycloadduct **4e** as the only observable cycloadduct. This result is important, as this *exo*-selective cycloaddition provides access to a *cis*-fused cycloadduct series not previously obtainable with synthetically useful selectivity from intramolecular Diels–Alder reactions (entry 9).^{1–4}

A remarkably different trend of diastereoselectivity was found for IMDA reactions of decatrienenes **10**. Unlike **7a**, thermal cycloaddition of unactivated triene **10a** was sluggish and relatively nonselective, giving slightly more *trans*-fused cycloadduct **5a** than *cis*-fused **6a** (entry 10).

Thermal cycloadditions of terminally activated trienes **10b–d** gave primarily the *trans*-fused cycloadducts **5b–d** (entries 11, 14, and 16). Aldehyde cycloadduct **5c**, as with aldehyde **3c**, was prone to decomposition when exposed to TBAF at 60 °C, so here also the protidesilylation of the product mixture (**11c/12c**) obtained from the IMDA reactions of trienal **10c** was performed at ambient temperature (entries 14 and 15).

As with **7b**, attempts to promote the IMDA cyclization of trienoate **10b** with MeAlCl₂ failed to give any observable

cycloadducts, and use of SnCl₄ resulted in decomposition above 0 °C (entries 12 and 13). Lewis acid promoted cycloadditions of trienal **10c** and trienone **10d** gave exclusively the *trans*-fused cycloadducts **5c** and **5d**, respectively (entries 15 and 17), but in lower yields than under thermal conditions.

In contrast to the results obtained with **7e**, the thermal cycloaddition of acetal **10e** was unselective, exhibiting only a slight preference for the *trans*-fused cycloadduct **5e** (entry 18).

In summary, we have developed a strategy for the stereocontrolled synthesis of perhydroindene and octahydronaphthalene cycloadducts with *trans*-relationships between the ring fusion proton and an adjacent hydroxyl group, as in structures **3–6**, via the intramolecular Diels–Alder cyclizations of siloxacyclopentene-constrained trienes **7** and **10**. Cycloadducts **3–6** have not previously been accessible with synthetically useful levels of stereoselectivity from intramolecular Diels–Alder reactions. Moreover, this procedure is completely complementary to the stereochemical control achieved by application of the steric directing group strategy.^{5,6} Key to the successful demonstration of this new siloxacyclopentene-constraining strategy were the application of Lee's alkoxide-promoted intramolecular hydrosilylation of alkynes to the synthesis of the siloxacyclopentene-containing trienes **7a** and **10a**, and the utility of **7a** and **10a** as substrates for cross olefin metathesis leading to trienes **7b–e** and **10b–e**. Applications of this new strategy for stereochemical control of the intramolecular Diels–Alder reaction toward the synthesis of biologically active natural products synthesis will be reported in due course.

Acknowledgment. Financial support provided by the National Institutes of Health (GM 26782) is gratefully acknowledged.

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

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