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Diels-Alder Chemistry of Siloles and their Transformation into Cyclohex-2-ene-1,4-*cis*-diols

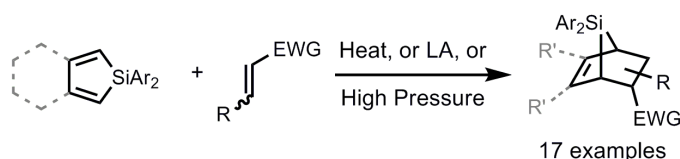
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ABSTRACT



In this report the synthesis of siloles with substitution patterns that are continuative towards natural product synthesis are described. Their reactivity in Diels-Alder chemistry was explored through thermal, Lewis acid, and high pressure reactions. Furthermore, bicyclic adducts were oxidatively cleaved to reveal a highly functionalized cyclohexene core.

Acyclic organosilanes have been heavily investigated for many years and have proven to be an invaluable tool in synthetic organic chemistry.¹ They have been applied in diverse reactions such as allylations,² annulations,³ crotylations,⁴ olefinations,⁵ oxidations,⁶ and as cross-coupling partners.⁷ Recently, silacycles have drawn synthetic interest as new reactivity patterns emerge. Kozmin has reported a route to acyclic polyol compounds via an asymmetric deprotonation of *meso*-

silacyclopentenoxides⁸ and have applied their methodology in the enantioselective synthesis of pinolidoxin.⁹ Steel has used silacyclohexenes in the Hosomi-Sakurai reaction to yield 1,4-diols with the potential to install up to four contiguous stereocenters.¹⁰ Leighton has introduced a chiral oxazasilolidine reagent that can be used for the asymmetric allylation of aldehydes¹¹ or as a Lewis acid in Diels-Alder chemistry.¹² Despite advances in silacycles, siloles remain a largely unexplored heterocycle in synthetic organic chemistry, despite being extensively studied for their intriguing electrochemical properties.¹³

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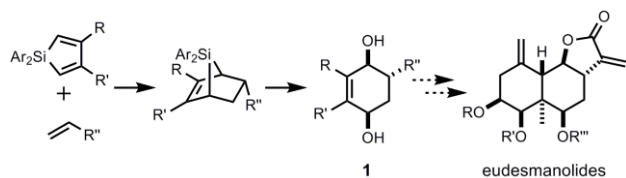
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Siloles have been shown to engage in Diels-Alder chemistry,¹⁴ but the scope and potential usefulness of the resulting adducts has yet to be thoroughly investigated. At the onset of this work we speculated that the bicyclic adduct of a silole Diels-Alder reaction could undergo silicon-carbon bond oxidation to form a highly functionalized cyclohex-2-ene-1,4-diol (Scheme 1). The structural features contained in **1** can potentially facilitate rapid access to a diverse range of compounds, which could lead to the synthesis of natural products such as the eudesmanolides. In this communication we describe the Diels-Alder reaction of several siloles with a variety of dienophiles, as well as a subsequent Tamao-Fleming oxidation to deliver highly functionalized cyclohex-2-ene-1,4-diols.

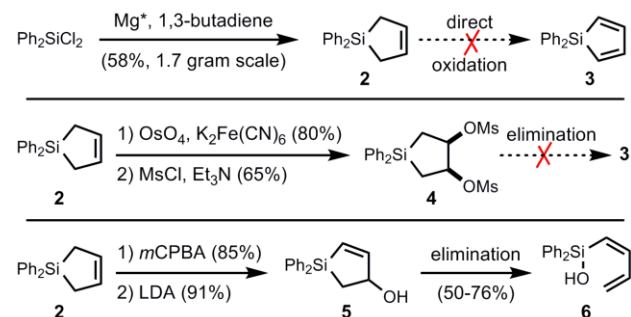
Scheme 1. Cyclohex-2-ene-1,4-diols from siloles and potential applications



The initial goal of this study was to examine the reactivity of a *C*-unsubstituted silole.¹⁵ We had envisioned preparing the desired siloles by either direct oxidation or through an oxidation-elimination sequence of the readily accessible dihydrosilole **2** (Scheme 2). Synthetic efforts began with formation of the dihydrosilole **2** through reductive cyclization of commercially available dichlorodiphenylsilane with butadiene and Rieke magnesium (Mg*¹⁶). Unfortunately, direct oxidation of **2** with DDQ, MnO₂, Pd/C or SeO₂ failed to deliver the silole, thus a stepwise reaction sequence was developed. Dihydroxylation and mesylation of **2** afforded the bis-mesylate **4**, but it failed to undergo double elimination with a variety of bases. Next, through a sequence similar to that employed by Kozmin,⁸ the allylic alcohol **5** was obtained by epoxidation of **2** followed by elimination with lithium diisopropylamide. Unfortunately, derivatives of

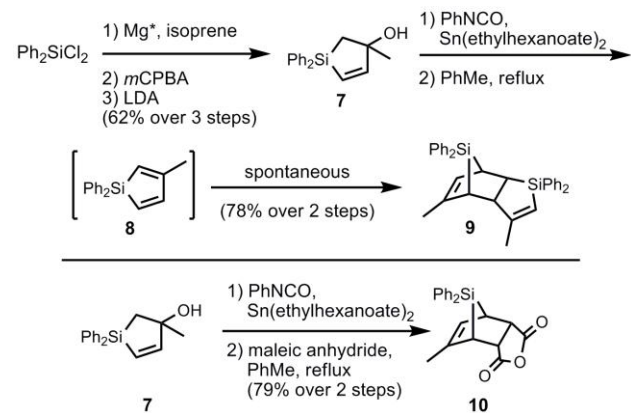
compound **5** were highly susceptible to silicon-carbon bond cleavage to give silanol **6**, even when relatively stable leaving groups (sulfonates) were introduced, as well as milder elimination protocols of Burgess¹⁷ or Grieco¹⁸.

Scheme 2. Problematic routes toward an unsubstituted silole



Faced with the difficulties encountered in forming **3**, we turned our attention to the more stable *C*-substituted siloles (i.e. **8**, Scheme 3).¹⁹ Additionally, since tertiary alcohols are more readily eliminated from dihydrosiloles than are secondary alcohols, milder reaction conditions should be compatible.¹⁹ The same three-step protocol was used to prepare tertiary alcohol **7** from isoprene and dichlorodiphenylsilane. Elimination of the tertiary alcohol in **7** was achieved through formation of a carbamate, followed by thermolysis; however, only the dimerization product **9** was obtained, and the monomeric silole was not

Scheme 3. Preparation of an alkyl silole dimer



observed. Introducing a reactive dienophile after carbamate formation but prior to thermolysis was successful at trapping the monomeric silole, and the

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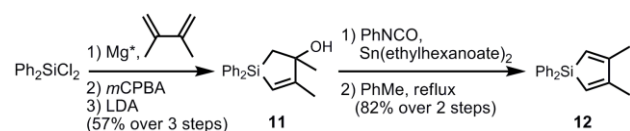
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Diels-Alder product **10** was obtained in 79% yield over two steps. Unfortunately, this interception strategy could not be extended to other dienophiles. Attempts to crack the dimer and trap it with maleic anhydride under prolonged high temperature conditions (refluxing xylenes) resulted only in slow decomposition of the dimer. Room temperature eliminations were investigated with the corresponding sulfonates, but again dimerization proved more facile than the desired Diels-Alder cycloaddition.

A stable monomeric silole was secured by installation of an additional methyl group about the silole ring (Scheme 4). Employment of the same three-step protocol afforded tertiary alcohol **11**. Formation of a carbamate followed by thermolysis succeeded in delivering silole **12** in 82% yield over two steps.

Scheme 4. Synthesis of silole **12**



Having secured a reliable route to a monomeric silole, the breadth of the Diels-Alder cycloaddition was investigated (Table 1). Reactions with highly reactive dienophiles such as maleic anhydride or maleimide (entries a and b) were complete after 16 h at room temperature while less reactive dienophiles, such as fumarates and quinones (entries c - e), required elevated temperatures to undergo cyclization.

Due to the sluggish nature of these silole Diels-Alder reactions, Lewis acidic conditions and high pressure experiments, both of which are known to facilitate Diels-Alder reactions, were explored (Table 2).²⁰ After screening several Lewis acids, it was found that diethylaluminum chloride catalyzed the reaction of dienophiles bearing a single activating group (e.g., acrylates, methylvinyl ketone, entries f - i) and the desired adducts could be obtained at ambient temperature in substantially reduced reaction times (from 16 h to 2 h). High pressure conditions also facilitated access to the desired products in yields comparable to those observed with diethylaluminum chloride. Furthermore, acrolein, which polymerized under both thermal and Lewis acidic conditions, was found to be an ammicable dienophile when subjected to high pressure (entry j).

Table 1. The thermal Diels-Alder reaction of siloles

entry	dienophile	product	yield (%)		
			thermal ^a	Lewis acid ^b	h.p. ^c
a			90 ^d	-	-
b			85 ^d	-	-
c			85 ^e	-	-
d			80	70	89
e			83	-	87
f			-	90	92
g			-	92	-
h			-	75	-
i			-	91	90
j			-	-	84

^a Xylenes, reflux, 16 h. ^b Et₂AlCl, PhMe, 2 h. ^c High Pressure, 160 000 psi, CH₂Cl₂, 16 h. ^d PhMe, 22 °C, 16 h. ^e PhMe, reflux, 16 h

Having successfully discovered complementary reaction conditions for the Diels-Alder reaction with siloles, more interesting silole substrates with greater potential utility in natural product synthesis were prepared. The cyclohexyl fused silole **14** (Table 3) was prepared from 1,2-dimethylenecyclohexane and Rieke magnesium using the same sequence of reactions described in Scheme 4, while the C-unsubstituted silole **15** was synthesized according to literature procedures.¹⁵ The cyclohexyl-fused silole **14** was found to undergo the cycloaddition with maleic anhydride, methyl fumarate, methylacrolein, and methylvinyl ketone (entries a - d) in yields comparable to those found with silole **12**. Likewise, C-unsubstituted silole **15** formed the desired cycloadducts with methacrolein, methylvinyl ketone, and benzoquinone (entries a - g); however, there was a

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noticeable increase in reaction times likely due to the buttressing affects of the mesityl groups a.²¹

Table 2. Additional substituted silole substrates.

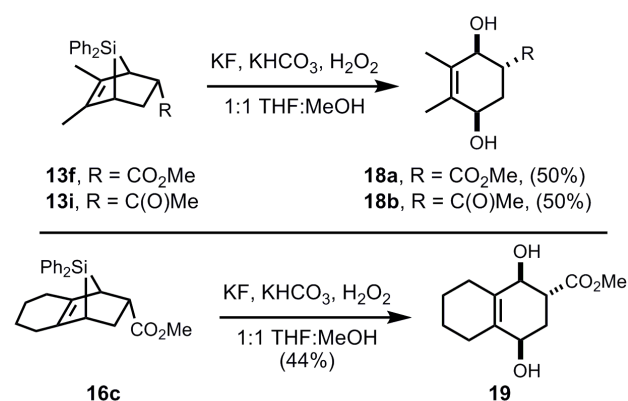
entry	dienophile	product	yield (%)
a			75 ^a
b			72 ^b
c			82 ^b
d			79 ^b
e			73 ^c
f			84 ^b
g			86 ^d

^a PhMe, 22 °C, 16 h. ^b PhMe, Et₂AlCl, 2 h. ^c PhMe, Et₂AlCl, 24 h. ^d CH₂Cl₂, 160 000 psi.

The relative stereochemistry of the Diels-Alder adducts was determined by observing nOe interactions between the methine proton alpha to the electron withdrawing group and one of the protons of the phenyl ring attached to the silicon atom.²² Furthermore, the typically diagnostic chemical shift difference between the axial and equatorial positions of all-carbon [2.2.1] bicyclic systems suggests that the *exo* products were never formed in quantity sufficient to be detected by NMR spectroscopy.²³

The 7-silabicyclo[2.2.1]hept-2-ene framework displays several functional groups that evoke opportunities for synthetic manipulation. To illustrate this point, oxidation of the carbon-silicon bond by the Tamao-Fleming reaction⁶ successfully converted representative silole Diels-Alder adducts **13f**, **13i**, and **16c** diastereoselectively to their respective *cis*-diols, in 44-50% isolated yield (which correlates to a 65-70% yield per oxidation).

Scheme 5. Tamao-Fleming oxidation of the Diels-Alder adducts



In summary, we have explored the reactivity of siloles in Diels-Alder chemistry. Various promoters, including elevated temperatures, Lewis acids, and ultra-high pressures were necessary to expand the reaction scope with less active dienophiles, and in all cases complete *endo* selectivity was observed. Furthermore, we have successfully cleaved the resulting bicyclic adducts to reveal a highly substituted cyclohex-2-ene-1,4-diol. We are currently investigating the single-step oxidation of dihydrosiloles to siloles and these results will be reported in due course.

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Supporting Information Available: General experimental procedures and characterization of all new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(21) Siloles **12** and **14** required 2 h for the Lewis acid Diels-Alder reaction (c.f., Table 1 entry f, Table 2, entry c) while silole **15** required 24 h for the reaction to complete in one instance (Table 2, entry e).

(22) See Supporting Information for nOe spectra.

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