

# Synthesis of polycyclic structures by Diels-Alder reaction using inner-outer-ring 1,3-bis[trimethylsilyloxy]dienes

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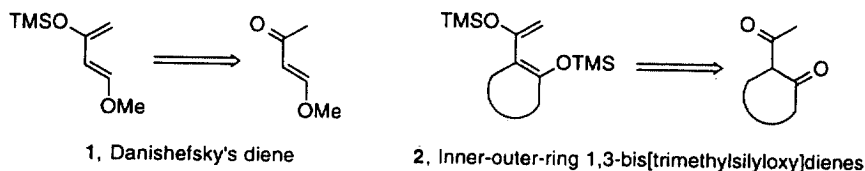
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**Abstract.** In this paper we describe regioselective one-pot preparations of inner-outer-ring 1,3-bis[trimethylsilyloxy]dienes and their Diels-Alder reactions with electron-deficient dienophiles. The dienes were prepared in quantitative yield, and the Diels-Alder reactions proceeded smoothly, regioselectively and with good yields, allowing efficient construction of highly functionalized polycyclic skeletons such as naphthofurans, benzofurans and various carbocycles present in natural and non-natural products. © 1999 Elsevier Science Ltd. All rights reserved.

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The Diels-Alder reaction is one of the most powerful C–C bond-forming reactions in natural product synthesis.[1] Over the years, intensive research has led to the preparation of a wide variety of dienes to which it can be applied.[2] In particular, cyclic dienes in which one of the double bonds is endocyclic (inner-outer-ring dienes) are highly valuable for the construction of polycyclic structures.[3,4] Dioxygenated 1,3-butadienes are also of great importance due to the abundance of natural polyoxygenated compounds, to the increased reactivity with dienophiles caused by the synergism between the two oxygen substituents, and to the ease with which the adducts may be selectively converted to enones and aromatic compounds;[5-8] the most important member of this group is undoubtedly the *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**, Danishefsky's diene, Scheme 1).[9-11]

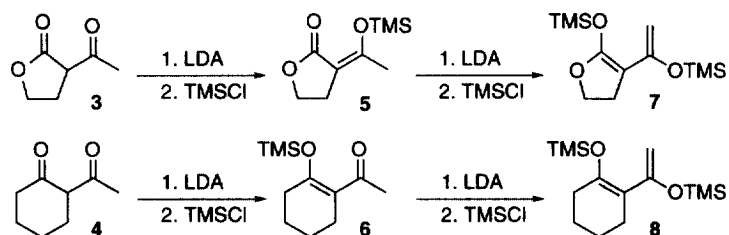
## Scheme 1



Despite their high synthetic potential, inner-outer-ring 1,3-bis[silyloxy]dienes (**2**) have found limited applications in Diels-Alder reactions.[12,13] We believe that this kind of diene will prove to be widely useful for the synthesis of highly functionalized polycyclic skeletons such as naphthofurans, benzofurans and various carbocycles present in natural and non-natural products. In this communication we report the use of inner-outer-ring 1,3-bis[trimethylsilyloxy]dienes (**2**), derived from 2-acetylcyclocompounds, in Diels-Alder reactions with various electron-deficient dienophiles.

Most 1,3-dioxygenated dienes have been prepared from linear  $\alpha,\beta$ -unsaturated compounds or 1,3-dicarbonylic acyclic structures and protected with the inexpensive trimethylsilyl group.[14] In the preparation of our 1,3-bis[trimethylsilyloxy]dienes we used commercially available 2-acetylbutyrolactone (**3**) and 2-acetylcyclohexenone (**4**). Starting from **3** (Scheme 2), the diene **7**[15] was prepared in quantitative yield as a distillable liquid in a one-pot reaction using two-step addition of LDA (1.2 equiv) and TMSCl (1.5 equiv) at low temperature ( $-78\text{ }^{\circ}\text{C}$ ).<sup>1</sup> When the reaction was interrupted after the first addition of LDA and TMSCl, the trimethylsilylenolether intermediate **5** was isolated, the structure of which was inferred from the observed homoallylic  $^1\text{H}$  NMR coupling constant ( $J = 2.0\text{ Hz}$ ) between the methyl group and the methylene carbon at the  $\beta$ -position.

Scheme 2



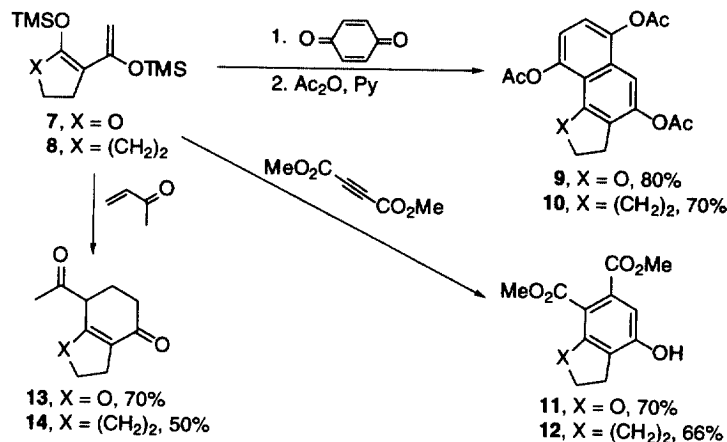
The efficient synthesis of inner-outer-ring 1,3-bis[silyloxy]dienes from carbocyclic compounds requires a regioselective deprotonation. Literature examples have reported experimental conditions where the desired diene **8** is the minor regioisomer.[16,17] In our hands, treatment of commercial 2-acetylcyclohexenone (**4**) with LDA (1.2 equiv) and TMSCl (1.5 equiv) at low temperature afforded a single product which the methyl singlet in the  $^1\text{H}$  NMR spectrum suggested was the necessary trimethylsilylenolether **6**, in which the double bond is endocyclic. Kinetic deprotonation of **6** led to the desired diene **8**[18] as the only regioisomer, in quantitative yield and as a distillable colorless oil.

<sup>1</sup> General experimental procedure for preparation of the dienes: To a cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of the 2-acetylcyclocompound (5 mmol) in THF (12 mL), under argon, a previously prepared solution of LDA in THF (1.2 equiv, 0.8–1.0 M) was slowly added dropwise via syringe. The mixture was stirred for 20 min and TMSCl (1.5 equiv) was added via syringe over 10 min. After stirring for 10 min, the cooling bath was removed and the reaction mixture allowed to reach room temperature. The reaction mixture was recooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of LDA in THF (1.2 equiv) was slowly added via syringe over 5 min. After 20 min, TMSCl (1.5 equiv) was added dropwise via syringe over 10 min, and the reaction mixture was left for 1 h to reach room temperature, and concentrated *in vacuo*. The residue was dissolved in  $\text{Et}_2\text{O}$  (25 mL), filtration and evaporation of the solvent *in vacuo* afforded the desired diene (99%).

In studying the reactivity of dienes **7** and **8** in the Diels-Alder reaction, and their usefulness for the synthesis of polycyclic structures,<sup>2</sup> we first explored the reaction with quinones, the reaction of which with acyclic oxygenated dienes is used in preparing a number of natural products.[12,14] Slow addition of *p*-benzoquinone to **7** and **8**, either neat or in solution, followed by treatment of the reaction mixture with Ac<sub>2</sub>O/Py at room temperature, afforded respectively the dihydronaphthofurane **9** and the tetrahydrophenanthrene **10**, in one pot and 70-80% yield. These transformations involve the exothermic Diels-Alder reaction, followed by elimination of the 1-OTMS group, trimethylsilylenolether hydrolysis and aromatization,[9] to give the corresponding naphthols which proved to be unstable to column chromatography or in air, and were protected *in situ* as the triacetylated derivatives **9** and **10**.

Encouraged by these results we studied the application of these dienes to the synthesis of benzofurans and naphthalenes. Benzofurans have previously been synthesized by Diels-Alder reaction with vinylfurans but the results are often unsatisfactory.[19] The Diels-Alder reaction of the acyclic dienophile dimethyl acetylenedicarboxylate (DMAD) with diene **7** at room temperature for 30 min afforded, after column chromatography, the desired dihydrobenzofurane **11** in good yield (70%). Likewise, reaction with **8** gave the functionalized tetrahydronaphthalene **12** in 66% yield. Curiously, a strongly acidic work-up was necessary to aromatize the corresponding cycloadduct.

Scheme 3



To study the regioselectivity of the reaction in this class of dienes we examined their Diels-Alder reaction with the asymmetric dienophile methylvinylketone (MVK). When MVK was added to the neat diene **7**, a slightly exothermic reaction took place, but the MVK was

<sup>2</sup> General experimental procedure for the Diels-Alder reaction. The dienophile (1.0 mmol) was added in portions at room temperature under argon, to the diene (1.5 mmol, neat or in benzene solution) and the mixture was stirred at room temperature (or heated), and monitored by TLC. The reaction mixture was worked up conveniently and the products were purified by flash column chromatography on silica gel.

only totally consumed after 12 h of stirring at room temperature. After elimination of the 1-OTMS group and trimethylsilylenolether hydrolysis in the reaction medium the enone **13** was obtained in 70% yield. With diene **8**, the reaction was slower but heating at 90 °C afforded the enone **14**, which proved to be unstable to work-up and could only be isolated in 50% yield. In both cases the only regioisomer detected by <sup>1</sup>H NMR was that expected for Danishefsky-type dienes.

In conclusion, inner-outer-ring 1,3-bis[trimethylsilyloxy]dienes can be prepared quantitatively starting from 2-acetyl cycloketones or lactones of various ring sizes. Their Diels-Alder reactions with electron-deficient dienophiles leads regioselectively to a variety of polycyclic structures of synthetic interest. Studies of the application of this methodology to other cyclocompounds and dienophiles, and to the synthesis of natural products of biological interest, are in progress and will be reported in due course.

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