

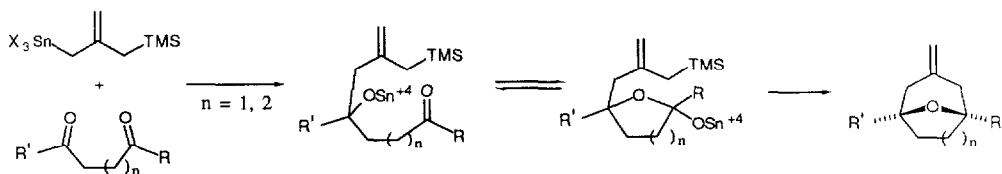
BIS(TRIMETHYLSILYL) ENOL ETHERS AS 1,3-DIANION EQUIVALENTS: REGIOCONTROLLED [3+4] AND [3+5] ANNULATION REACTIONS

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Abstract: In the presence of titanium tetrachloride, 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-butadiene (1) undergoes facile [3 + n] annulation reactions with 1,4- and 1,5-dielectrophiles to generate seven- and eight-membered bicyclic ether adducts. The annulations occur in good yields (49-83%) and are also highly regioselective for substrates containing two distinct electrophilic groups.

Cycloaddition reactions represent the most efficient method for the generation of complex ring systems. Current efforts to develop cycloaddition approaches to stereodefined seven-² and eight-membered³ carbocycles have been stimulated by the ever-increasing number of important natural products which contain these ring systems. Cyclization reactions leading to seven- and particularly eight-membered rings often proceed in low yields due to entropic factors and developing transannular interactions.⁴ Recently, we reported efficient [3 + 4] and [3 + 5] annulations between trimethylenemethane dianionic synthons and dicarbonyl partners.⁵ This strategy circumvents problems normally encountered in construction of medium-sized rings by relying on *in situ* formation of a five- or six-membered hemiketal template which facilitates subsequent cyclization to the desired carbocycles.^{5,6}

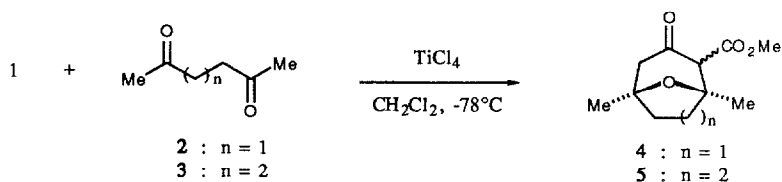


Although use of the trimethylenemethane dianionic synthon provides a convenient approach to simple bicyclic ethers, initial attempts to develop a substituted, unsymmetrical variant of the synthon failed. We now report that the bis(trimethylsilyl) enol ether of methyl acetoacetate (1)⁷ is an effective 1,3-dianionic synthon for these annulation

processes, and permits complete regioselectivity in the synthesis of functionalized, unsymmetrical seven- and eight-membered carbocycles.



While bis(trimethylsilyl) enol ethers of this type have been extensively employed in [3+3]⁸ and [4+2]⁹ annulation reactions, the corresponding [3+4] and [3+5] annulation processes have not been fully developed. Precedents for such a sequence were established by Chan and coworkers, who report that treatment of 2,4-hexanedione (**2**) with titanium tetrachloride and bis(trimethylsilyl) enol ether **1** generates bicyclic ether **4** in an unspecified yield.¹⁰



We initiated our study by re-examining this simple case. Optimal conditions for the annulation were achieved by treatment of bis(trimethylsilyl) enol ether **1** (0.2 M in CH₂Cl₂) with 1.0 eq of titanium tetrachloride (0.2 M in CH₂Cl₂), followed by addition of 2,5-hexanedione **2** (0.1 M in CH₂Cl₂). At -78° C, these conditions resulted in a rapid [3 + 4] annulation, generating the desired bicyclic ether product **4** in an 83% isolated yield. Homologous 1,5-dicarbonyl species were also suitable substrates for this annulation process. Treatment of 2,5-heptanedione (**3**)¹¹ with bis(trimethylsilyl) enol ether **1** under the standard reaction conditions generated the corresponding eight-membered cycloadduct **5** in 68% isolated yield. The cycloadducts (**4** and **5**) were generated as a 1 : 1 mixture of diastereomers at the carboxylate stereocenter.

The discrete reactivity of the two nucleophilic centers of bis(trimethylsilyl) enol ethers is well documented.¹² We envisioned that the differential reactivity between these sites would translate into high regioselectivity if the annulation process was applied to substrates containing two distinct electrophilic groups. To test this hypothesis, we subjected 1,4-ketoaldehydes **6**¹³ to the standard annulation conditions. The desired annulation did indeed occur, generating the expected cycloadducts **8** in good yields (Table I, entries 1-3). Homologous 1,5-ketoaldehyde substrates **7**¹⁴ were likewise cyclized to provide the corresponding eight-membered ring cycloadducts **9** (Table I, entries 4-6). In each case, the crude reaction mixtures were uncontaminated by regioisomeric cycloadducts.

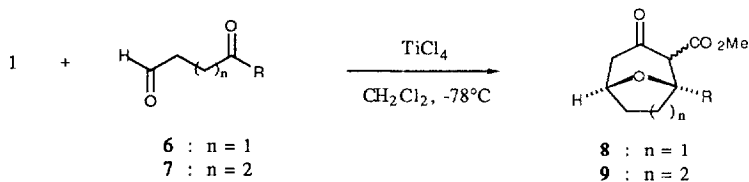
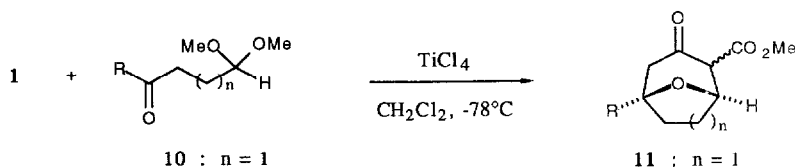


Table I. [3 + 4] and [3 + 5] Annulation Reactions with 1,4- and 1,5-Dielectrophilic Substrates.

entry	substrate	R	n	% isolated yield ^a
1	6a	Me	1	66
2	6b	<i>t</i> -Bu	1	72
3	6c	Ph	1	49
4	7a	Me	2	77
5	7b	<i>t</i> -Bu	2	71
6	7c	Ph	2	63
7	10a	Me	1	79
8	10b	<i>t</i> -Bu	1	82
9	10c	Ph	1	63

^a Satisfactory ¹H NMR, ¹³C NMR, IR, and exact mass spectral data were obtained for all compounds

Cycloadducts possessing complementary regiochemistry could be accessed by employing ketoacetal substrates. For example, treatment of bis(trimethylsilyl) enol ether **1** with 1,4-ketoacetal substrates **10**¹³ generates cycloadducts **11** in good yield (Table I, entries 7-9). Again, annulation with these substrates occurred with complete regioselectivity. Attempts to extend this methodology to 1,5-ketoacetal dielectrophiles (n = 2) were unsuccessful.



These preliminary examples delineate a simple, highly efficient entry to stereo- and regiodefined seven- and eight-membered carbocycles. The diversity of functionality incorporated within the ring system makes this approach especially attractive. Furthermore, by taking advantage of various alkylation procedures and the steric biases inherent in the system, additional sites can be functionalized selectively with excellent control of stereochemistry. At present we are continuing to explore the generality of this process and its application to the synthesis of natural products.

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