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Stereoselective Preparation of (*Z*)-2-(Trialkylsilyloxy)-2-alkenals by Retrocycloaddition Reactions of 4*H*-4-Alkyl-5-(trialkylsilyloxy)-1,3-dioxins. Useful Reactants for Lewis Acid Catalyzed [4 + 3] Cyclizations

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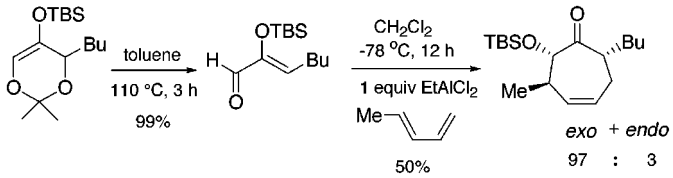
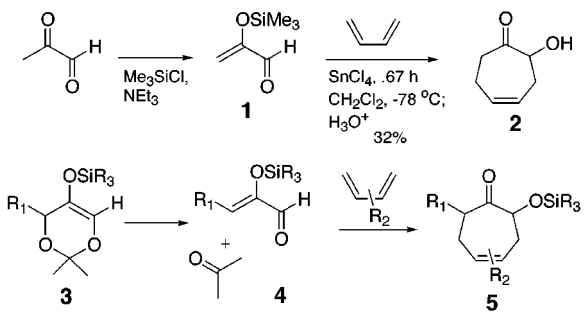
ABSTRACT



Retrocycloadditions of 4*H*-4-alkyl-5-(trialkylsilyloxy)-1,3-dioxins proceed smoothly in refluxing toluene to afford (*Z*)-2-(trialkylsilyloxy)-2-alkenals with complete stereoselectivity. These enals undergo Sasaki-type [4 + 3] cyclizations with dienes in the presence of Lewis acids, in many instances with excellent regio- and/or stereoselectivity.

The direct construction of seven-membered rings via [4 + 3] cyclization reactions is the most attractive strategy for preparing this frequently observed natural product substructure.[1] Accordingly, a great amount of effort has been focused on methods for generating the less accessible three-atom component of this reaction. One such method reported by Sasaki[2] involves the treatment of 2-(trimethylsilyloxy)-acrolein (**1**) with a Lewis acid in the presence of a diene to afford, after acidic workup, an α-hydroxycycloheptenone, e.g., **2** (Scheme 1). However, attempts to expand the scope of this reaction by employing β-substituted enals related to propenal **1** in both inter- and intramolecular [4 + 3] cycloaddition reactions was not reported.[3] We envisaged a convenient, stereoselective preparation of (*Z*)-2-(trialkylsilyoxy)-2-alkenals **4** by application of our 1,3-dioxin-based methodology.[4] Thus, based on this previous work it was anticipated that 4*H*-4-alkyl-5-(trialkylsilyloxy)-1,3-dioxins **3** would be available by silylation of the corresponding 1,3-

Scheme 1



(1) (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (b) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (c) Hosomi, A.; Tominaga. Y. *Comprehensive Organic Synthesis*; Trost, B. M, Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 593−615. (d) Rigby, J. *Org. React.* **1997**, *51*, 351. (e) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.

(2) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693.

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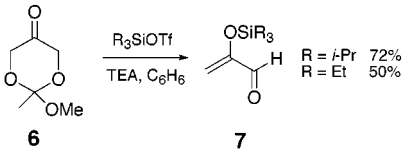
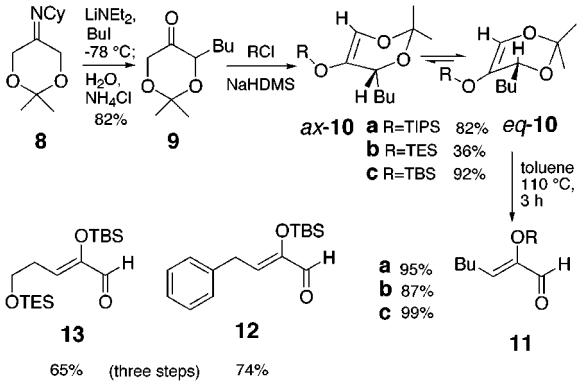
dioxin-5-ones and would undergo facile retrocycloadditions in refluxing toluene to provide the (*Z*)-enals **4** (Scheme 1). A stereoselective preparation of these enals was considered to be critical for investigating the regio- and stereoselectivity of the subsequent [4 + 3] cycloaddition reactions, thereby providing insight into the mechanism of this intriguing transformation. The recent report by Harmata[5] that 2-(trialkylsilyloxy)acroleins **7** also undergo [4 +3] cycloaddition reactions and can be prepared from dioxinone **6** via a 1,3-dioxin intermediate (Scheme 2) prompts us to disclose the results of our investigation at this time.

Scheme 2



The preparation of the 5-(silyloxy)dioxins **3** was easily accomplished. Thus, the aza-enolate[6] derivative of the imine **8** underwent efficient alkylation and upon hydrolytic workup afforded the desired butylated dioxinone **9**. Kinetic deprotonation of ketone **9** with sodium hexamethyldisilyl azide afforded the less-substituted enolate that could be *O*-silylated by several trialkylsilyl halides (Scheme 3). As expected, each

Scheme 3



of the resulting (trialkylsilyloxy)dioxins **10** was smoothly converted to only the *Z*-stereoisomer of the (silyloxy)enals **11** in nearly quantitative yields in refluxing toluene. The stereoselectivity is presumably a consequence of preferential retrocycloaddition through the boatlike conformer *eq*-**10** rather than boatlike conformer *ax*-**10** that is destabilized by a flagpole−flagpole interaction between the butyl group and axial lone pair. Thermodynamically controlled isomerization to (*Z*)-enals **11** was ruled out by heating a mixture of **11c** and its *E*-isomer (83:17), obtained by photoisomerization of **11c** (Hanovia 500 W, toluene), and observing no change in the ratio of isomers. Finally, the (*Z*)-2-(*tert*-butyldimethylsilyloxy)-2-enals **12** and **13** were also prepared by straightforward application of this protocol.

Table 1. [4 + 3] Cyclization Reactions of (*Z*)-2-(Trialkylsilyloxy)-2-enals

entry	reactants	conditions	products		
1[a]	**11c** + 5 equiv	CH_2Cl_2, -78 °C, 12 h; 1 equiv Me_2AlCl	*endo*	:	*exo*
		R = TBS 76%	77	:	23
2	**11b**	R = TES 78%	92	:	8
3[a]	**11c** + 5 equiv	CH_2Cl_2, -78 °C, 12 h; 1 equiv L.A.	*endo*	:	*exo*
		73% $SnCl_4$	80	:	20
		100% Me_2AlCl, R = TBS	100	:	0
4	**11a**	70% $SnCl_4$, R = TES	90	:	10
5	**12** + 5 equiv	CH_2Cl_2, -78 °C, 12 h; 1 equiv Me_2AlCl, 63%	*endo*		
6	**12** + 5 equiv	CH_2Cl_2, -78 °C, 12 h; 1 equiv $EtAlCl_2$, 65%			
7[b]	**11c** + 5 equiv	CH_2Cl_2, -78 °C, 12 h; 1 equiv $TiCl_4$			
		54% R = TBS	89	:	11
8	**11b**	40% R = TES	50	:	50
9[a]	**11c** + 5 equiv	CH_2Cl_2, -78 °C, 12 h; 1 equiv $EtAlCl_2$, 50%	*endo*	:	*exo*
			3	:	97
10[a]	OTBS	CH_2Cl_2, -78 °C, 12 h; 1 equiv Me_2AlCl	*endo*		*exo*
		74% R = TBS	79	:	21
11		80% R = TES	85	:	15

[a] Isomers separated by column chromatography. [b] Inseparable mixture of isomers.

We were pleased to discover that (*Z*)-2-(trialkylsilyloxy)-alkenals smoothly participated in Lewis acid catalyzed [4 + 3] cyclization reactions with a variety of dienes (Table 1). Several observations merit comment. In all cases the silyl group is cleanly transferred to the aldehyde oxygen. Moreover, all of the cycloadducts possess a *cis*-stereochemical relationship[7] between the β-alkyl substituent of the enal and the newly formed silyloxy substituent.[8] In addition, *endo*-

adducts are uniformly preferred over the *exo* counterparts and the stereoselectivity is better for smaller silyl substituents (compare entries 1 vs 2, 3 vs 4, and 10 vs 11). The *endo*/*exo* ratio can also be significantly improved by the choice of the Lewis acid catalyst (entry 3). Not surprisingly, acyclic dienes are not as reactive as the cyclic dienes, but acceptable yields were obtained with butadiene, isoprene, and *trans*-piperylene. It is of interest to note that the regioselectivity of the cyclization with isoprene is also sensitive to the substituents on the silyl group (entries 7 and 8) and that piperylene is the only diene which favors the *exo*-adduct in a highly regioselective and stereoselective cyclization (entry 9). Finally, the retrocycloaddition of 5-(trialkylsilyloxy)-1,3-dioxins can be catalyzed by a Lewis acid[9] with concomitant intramolecular [4 + 3] cyclization of the resulting 2-(trialkylsilyloxy)-2-enal to afford fused bicyclic adducts (entries 10 and 11), of potential value in natural product synthesis.

In conclusion, we have demonstrated that 2-(trialkylsilyloxy)-2-enals constitute another class of useful reactants that can be generated with high stereoselectivity by retrocycloaddition reactions of substituted 4*H*-1,3-dioxins. The [4 + 3] cyclizations of these enals documented herein substantially expand the scope and limitations of the original Sasaki account. Although the precise structure of the allyl cation intermediate generated in these reactions requires further clarification, the ability to control the regio- and stereoselectivity of these cyclization reactions by choice of the silyl substituents as well as the Lewis acid makes 2-(trialkylsilyloxy)-2-enals particularly attractive among the various three-atom components for [4 + 3] cycloadditions. Accordingly, additional studies and application of this methodology in natural product synthesis are underway in our laboratories.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) The methyl ketone analogous to aldehyde **1** was examined and gave only the Diels−Alder/[4 + 2] adducts ($SnCl_4$, −45 °C, 7 h, 29%). However, in a subsequent investigation a 1:1.5 mixture of the [4 + 3] and [4 + 2] adducts, respectively, was isolated using similar reaction conditions ($SnCl_4$, −78 °C, 6 h), see: Blackburn, C.; Childs, R. F.; Kennedy, R. A. *Can. J. Chem.* **1983**, *61*, 1981.

(4) For the preparation and cycloaddition reactions of (*E*)-2-alkenals, see: (a) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc*. **1988**, *110*, 1290. 2-(Acyloxy)acroleins, see: (b) Funk, R. L.; Yost, K. J., III. *J. Org. Chem.* **1996**, *61*, 2598. 2-Acylacroleins, see: (c) Funk, R. L.; Fearnley, S. P.; Gregg, R. *Tetrahedron* **2000**, *56*, 10275. 2-(Amido)acroleins, see: (d) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125. (e) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511. (f) (*Z*)-2-Acyl-2-enals, see: Aungst, R. A., Jr.; Funk, R. L. *J. Am. Chem. Soc*. **2001**, *123*, 9455.

(5) Harmata, M.; Sharma, U. *Org. Lett.* **2000**, *2*, 2703.

(6) We have been unable to efficiently alkylate the enolate derivative of 1,3-dioxin-5-one due to a competing aldol reaction. For similar problems, see: Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, *73*, 1616.

(7) Stereochemical assignments for all adducts were made using NOESY experiments. See the Supporting Information for the diagnostic observations. The regiochemistry for entries 7 and 9 was determined by 2D COSY NMR experiments. The methine proton on the silyloxy carbon of the major product of entry 7 was directly coupled to two allylic protons which were both coupled to one another as well as the vinylic proton. The methine proton on the silyloxy carbon of the major product of entry 9 was coupled to only one other proton which in turn was coupled to the methyl protons as well as one of the vinylic protons.

(8) A crossover experiment suggests that the silyl group is transferred both intra- and intermolecularly. Thus, when the cyclization shown in entry 2 was performed in the presence of an equivalent amount of enal **12**, the *endo* adduct shown in entry 2 was obtained accompanied by the *endo* adduct of entry 1 (86:14, respectively). Similarly, the *endo* cyclization product derived from enal **12** (TBS ether) was accompanied by the corresponding *endo* TES ether adduct (86:14, respectively).

(9) This protocol was necessary since thermolysis of the dioxin of entry 9 in refluxing toluene gave rise to the product derived from an intramolecular Diels−Alder reaction of the intermediate 2-(*tert*-butyldimethylsilyloxy)-2-enal.