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Investigation of a novel sequential 1,5 O→O silyl migration/Horner–Wadsworth–Emmons reaction

M. C. Hillier and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

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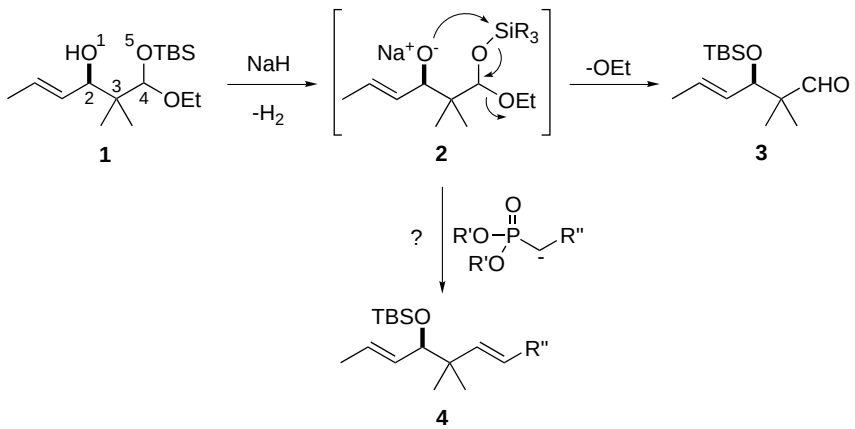
Abstract—A study and application of a sequential 1,5 O→O silyl migration/Horner–Wadsworth–Emmons reaction is presented.

The migration of trialkylsilyl protecting groups from oxygen to oxygen (O→O) is a well-known phenomenon in organic chemistry.[1] Usually, these rearrangements occur in a 1,4 and 1,5 O→O fashion, and a 1,11 O→O type silyl migration[2] has also been observed. However, these O→O rearrangements are generally considered to be undesired side reactions and have been put to use only in a few cases.[3] We became interested in this process during our study on the total synthesis of the natural product disorazole C_1,[4] wherein one of the requisite moieties containing the *tert*-butyldimethylsilyl (TBS) acetal **1** was readily converted to the β-silyloxy dimethyl aldehyde **3** upon treatment with base (Scheme 1). Presumably, this product may arise from a base induced 1,5 O→O silyl migration followed by elimination of ethoxide to give the aldehyde **3**, resulting in a one-pot two-step transformation. In light of this result, we considered the idea of treating the aldehyde **3** in situ with a phosphonate anion under Horner–Wadsworth–Emmons conditions to provide the more advanced intermediate in disorazole C_1, namely the substituted 1,5-diene **4**. In addition we were also concerned with the effect of changing the silyl group on the acetal, and how this may affect the course of the reaction.

Our investigation began by preparing a number of acetal substrates **6**–**10a**,**b** following the procedure of Kiyooka and co-workers.[5] Addition of a series of aldehydes to a solution of BH_3·THF and racemic *N*-tosyl valine in CH_2Cl_2 at −78°C followed by the addition of *tert*-butyldimethylsilyl ketene acetal **5a**[6] furnished the hydroxy silylated acetals **6**–**10** (Scheme 2).[7] The purified acetals were treated with excess NaH or NaHMDS (2.1 equiv.) in the presence of triethylphosphonoacetate in



Scheme 1.

* Corresponding author.

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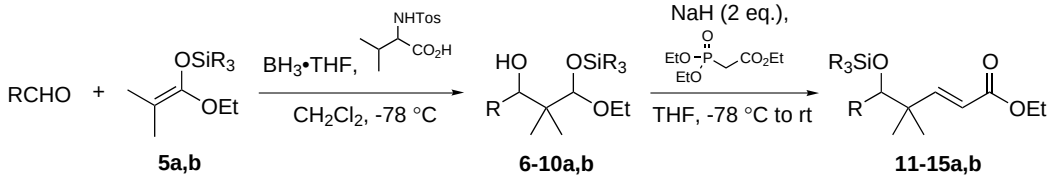
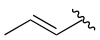
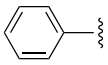
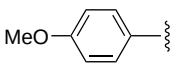
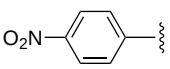
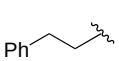


Scheme 2.

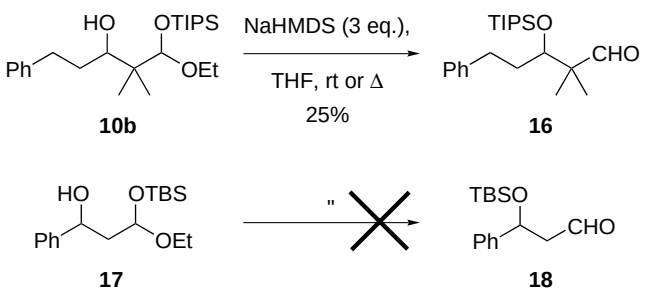
THF at −78°C followed by warming to room temperature to provide the α,β-unsaturated esters **11**–**15**. Interestingly, repetition of this process using the TIPS ketene acetals **5b** gave better yields of **6**–**10**. The results of these experiments are shown in the Table 1, and compare the yields of the TBS and TIPS acetals obtained after workup and purification by column chromatography. These reactions were not optimized and diastereomeric ratios of the acetal products **6**–**10a**,**b** was not determined.

Examination of Table 1 reveals a number of interesting results. For example, the aldol reaction was successful in all cases providing the desired acetal products **6**–**10a**,**b** in good to excellent yields (67–89%). The higher yields using TIPS ketene acetals (**5b**) may be due, in part, to the less stable nature of the TBS group under the Lewis acidic reaction conditions employed when compared to the TIPS group. The subsequent O→O rearrangement elimination was successful only with the unsaturated- and aromatic-substituted substrates **6**–**9a**,**b** to give the intermediate aldehyde, which then gave the α,β-unsaturated esters **11**–**14a**,**b** in moderate to good yield (54–82%). Furthermore, the differing electronic nature of aromatic rings in **7**–**9a**,**b** did not seem to have much effect on the course of the reaction. The effect of the silyl group of the acetal moiety (e.g. TBS versus TIPS) during the latter reaction leading to **11**–**15** was also not very pronounced. On the other hand, hydrocinnamaldehyde acetals **10a**,**b** did not provide appreciable amounts of either **15a** or **15b**, respectively, even at elevated temperatures and in the presence of excess base. We initially assumed that this was due to the failure of the initial 1,5 O→O silyl migration during the formation of the presumed aldehyde intermediate (**6**–**10**→**11**–**15**). This notion was confirmed when the acetal **10b** was stirred in the presence of excess NaHMDS (3 equiv.) in THF for 3 days at room temperature and only a small amount of the aldehyde **16** (25%) was recovered along with an appreciable amount of starting material (62%). The addition of excess base, and elevated reaction temperatures led only to decomposition.[8] It is, therefore, reasonable to assume that the proximity of the oxygen substituents (i.e. ONa and $OSiR_3$) has been altered due to the β-phenethyl group adjacent to the hydroxyl in **10b** so as not to allow the O→O silyl shift to occur. Conformational requirements for O→O silyl migrations have been previously observed.[1,9] We were also curious as to the importance of the *gem*-dimethyl substituents in this rearrangement and therefore the nor-methyl derivative **17** was synthesized[3a] and subjected to the same reaction conditions. Interestingly, based-catalyzed rearrangement failed, and none of the aldehyde **18** could be isolated. This suggests that the dimethyl substituents were required for the silyl migration to occur, perhaps due to the presence of *gem*-dimethyl (Thorpe–Ingold),[10] which also play a role in placing the two oxygen atoms in a conformationally favorable position, so that O→O shift may occur (Scheme 3).

Table 1. Synthesis of **6**–**10a**,**b** and **11**–**15a**,**b**

R	SiR_3	Yield (%)	
	**a**: TBS	**6a**: 81	**11a**: 72
	b: TIPS	**6b**: 87	**11b**: 80
	**a**: TBS	**7a**: 67	**12a**: 63
	b: TIPS	**7b**: 87	**12b**: 59
	**a**: TBS	**8a**: 73	**13a**: 54
	b: TIPS	**8b**: 89	**13b**: 82
	**a**: TBS	**9a**: 67	**14a**: 67
	b: TIPS	**9b**: 85	**14b**: 82
	**a**: TBS	**10a**: 69	**15a**: nd[a]
	b: TIPS	**10b**: 79	**15b**: trace[b]

[a] No product was isolated.
[b] NaHMDS was used as base and the reaction was heated to 55°C for 24 h.



Scheme 3.

In conclusion, we have examined some parameters in this novel sequential 1,5 O→O silyl migration/Horner–Wadsworth–Emmons reaction. The results reveal that

the R substituent (Table 1) must be either unsaturated or aromatic in nature. The presence of a methylene group α to the carbinol center in **6**–**10** appears to inhibit the initial silyl migration, as demonstrated by the poor conversion of **10b** to the corresponding aldehyde **15**. This may be due to conformational changes prior to the O→O shift. In addition the presence of the *gem*-dimethyl group also appears to be required to assume the proper conformation, as seen by the failure of **17** to provide any of the aldehyde **18**. It is possible that substrates such as **10a**,**b** and **17** may yet undergo the 1,5 O→O silyl migration, if proper conditions are found, but this has not yet been observed.

Acknowledgements

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7. Prepared in the same manner as **5a** (Ref. 6), except TIPSCl was substituted for TBSCl in the procedure.
8. When NaH was employed as the base, no difference was observed and the use of toluene as solvent led to no detectable reaction.
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