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An unexpected migration of *O*-silyl group under Mitsunobu reaction conditions

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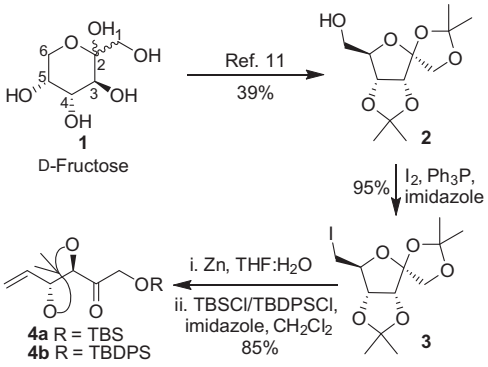
ABSTRACT

A 1,4 *O*→*O* silyl migration followed by nucleophilic substitution with phthalimide was observed under Mitsunobu reaction conditions. This one step secondary alcohol protection and primary alcohol substitution with *N*-nucleophiles was extended to a variety of 2-hydroxyethyl trialkylsilylether derivatives. A possible mechanism has been postulated based on the pK_a values of the alcohol and nucleophile. The present one-pot silyl migration and substitution reaction might find application in the stereoselective synthesis of novel iminosugar derived anti diabetic agents.

Mitsunobu reaction has been widely used in organic synthesis for the stereochemical inversion of a hydroxyl carbon with several nucleophiles.[1] A number of protective groups are found to be stable under this reaction conditions. Eventhough several reports were published for the hydroxyl group inversion with different carboxylic acids,[2] comparatively, fewer methods were discussed with nitrogen based nucleophiles.[1d] Trialkylsilyl group (R_3Si-) serves as an excellent protective group for alcohol function in total synthesis of natural products.[3] It is well documented that silyl protective groups are stable under a variety of reaction conditions.[4] However, a few unexpected deprotection of trialkylsilyl groups were observed in rare cases.[5] It has been shown that these silyl protective groups migrate to different nucleophilic centers in a molecule under anionic conditions.[6] These migrations are assumed to involve nucleophilic attack at Si generating a pentaco-ordinate Si intermediate or transition state.[7] Migrations involving 1,2-diol-1-trialkylsilyl ether→1,2-diol-2-trialkylsilyl ether (1,4 *O*→*O* migration) are very common under strong basic conditions[8] with retention of configuration at both the alcoholic carbon centers. However, in this Letter we report an unexpected 1,4 *O*→*O* silyl migration, for the first time under Mitsunobu reaction conditions.

In our investigations for the synthesis of phytosphingosines[9] from commercially inexpensive carbohydrate raw materials, we planned to synthesize D-ribo-phytosphingosine[10] from D-fructose **1**. Towards this, **1** was converted to the known 1,2:3,4-di-*O*-isopropylidene-D-psicofuranose **2** in an overall yield of 39% after four steps.[11] Substitution of the resulting primary hydroxyl group in **2** with iodine using I_2/Ph_3P/imidazole under reflux in toluene provided 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-D-psicofuranose **3** in 95% yield. Zinc mediated fragmentation of **3** gave α-hydroxy ketone in which the hydroxyl function was protected with TBS (*tert*-butyldimethylsilyl) or TBDPS (*tert*-butyldiphenylsilyl) without isolation to produce compound **4a** or **4b**, respectively, in good yield (85% after two steps) (Scheme 1).



Scheme 1. Preparation of key intermediates **4a** or **4b**.

Reduction of ketone **4a** with $NaBH_4$ at −78 °C in ethanol[12] provided 2,3-syn alcohol **5a**[13] and 2,3-anti alcohol **6a**[14] in a ratio of 1:24, respectively. When LAH was used as a reducing agent the ratio of **5a** and **6a** was found to be 1:1. Interestingly, when $LiAlH(O\text{-}^tBu)_3$[12] was employed for the reduction the ratio of **5a** and **6a** was 7:3, respectively, with 78% combined yield. Both the diastereomers

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can be isolated in pure form by conventional silica–gel column chromatography. No major difference in diastereomeric ratio was observed when the reduction was performed on TBDPS protected ketone **4b** to produce the corresponding 2,3-syn alcohol **5b** and 2,3-anti alcohol[15] **6b** (Scheme 2).

Having good amount of alcohol **5a** in hand we planned to introduce a protected amino group at C-2 position with inversion of configuration, to resemble the stereochemisry present in D-ribo-phytosphingosine, using Mitsunobu reaction. For the convenience we chose to use phthalimide as nucleophile. Accordingly, treatment of alcohol **5a** with Ph_3P/DIAD/phthalimide in dry THF at 0 °C followed by allowing it to 25 °C, surprisingly, we obtained olefin **8** as the sole product, instead of expected Mitsunobu substituted product **7**. The formation of compound **8** can be envisaged through a 1,4 *O*→*O* silyl migration followed by substitution at C-1 with phthalimide. (Scheme 3).

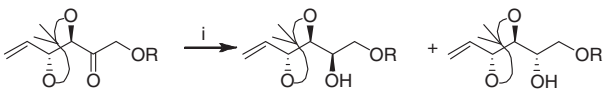
The structure of compound **8** was confirmed by an upfield shift of C-1 carbon and a down field shift of C-2 carbon in ^{13}C NMR spectra. It was also observed that the migration was occurred with retention of configuration at C-2 position. The structure of compound **8** was also confirmed by single crystal X-ray diffraction (Fig. 1).[16]

The probable reason for the formation of **8** could be explained based on the initial formation of ionpair (**9** and **10**) due to the lower pK_a value of the alcohol **5** compared to the nucleophile, phthalimide. As illustrated in the proposed mechanism (Scheme 4) oxyanion **10** could form the oxyphosphonium ion **11**[18] that could undergo an S_N2 substitution at C-2 to give the expected Mitsunobu product **7**. On the otherhand **10** may undergo a 1,4 *O*→*O* silyl migration giving oxyanion **12**[19] which will produce oxyphosphonium ion **13** followed by nucleophilic substitution at C-1 to produce the observed product **8**. As can be seen in the mechanism, the approach of the oxyanion **10** towards the phosphonium ion **9** to form the oxyphosphonium ion **11** is inhibited by more steric hindrance owing to the adjacent acetonide. Due to this reason, the facile formation of oxyphosphonium ion **13** leads to the formation of product **8**.

A similar kind of reaction was observed even with alcohol **6a** producing compound **14** and in both cases no trace amount of the expected Mitsunobu product was observed (Table 1, entry 1). We further investigated the migratory aptitude of more stable and bulky O-protective group TBDPS. Towards this, reaction of **5b** and **6b** with phthalimide under Mitsunobu reaction conditions again produced **15** and **16**, respectively, similar to what we observed for TBS derivatives (Table 1, entries 2 and 3). Similarly, reaction of sugar derived alcohol **17**[20] with phthalimide under Mitsunobu reaction conditions produced compound **18** as a single product (entry 4).

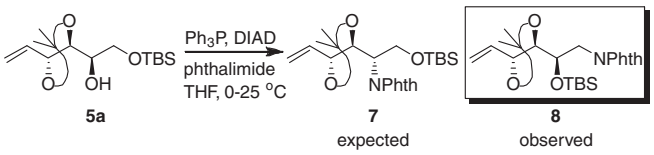
However, Mitsunobu reaction on simple TBS protected hydroxyacetonide **19**[21] gave a mixture of products **20** and **21** in a ratio of 4:6 which are derived from a 1,4 *O*→*O* silyl migration with retention of configuration and usual Mitsunobu inversion product, respectively (entry 5). The formation of **21** may be due to the presence of less hindered terminal acetonide in **19**. Finally, 1-(*tert*-butyldimethylsilyloxy)propan-2-ol **22**,[22] in which no steric hindrance is present adjacent to the secondary alcohol, upon reaction with Ph_3P/DIAD/phthalimide in dry THF at 0–25 °C produced a completely substituted product **23** without any migration of TBS (entry 6).

In conclusion, an interesting one-pot 1,4 *O*→*O* silyl migration followed by nucleophilic substitution with phthalimide was discussed. The probability of the reaction has been evaluated by applying the methodology to a number of substituted 2-hydroxyethyl trialkylsilyl ethers. A tentative mechanism is proposed. The application of this methodology towards the synthesis of 6-membered iminosugars[23] as anti diabetic agents is under progress. The present observation needs to be taken into account during the planning of any synthesis involving Mitsunobu reaction[24] at a



R = TBS (**5a**, **6a**)
R = TBDPS (**5b**, **6b**)
If (i) = $NaBH_4$, -78 °C, EtOH, yield 85%. **5a**:**6a** (1:24), **5b**:**6b** (0:100)
(i) = $LiAlH_4$, -78 °C, THF, yield 75%. **5a**:**6a** (1:1)
(i) = $LiAlH(O\text{-}^tBu)_3$, -78 °C, EtOH, yield 78%. **5a** or **5b**: **6a** or **6b** (7:3)

Scheme 2. Reduction of ketones **4a** and **4b**.



Scheme 3. Mitsunobu reaction on alcohol **5a**.

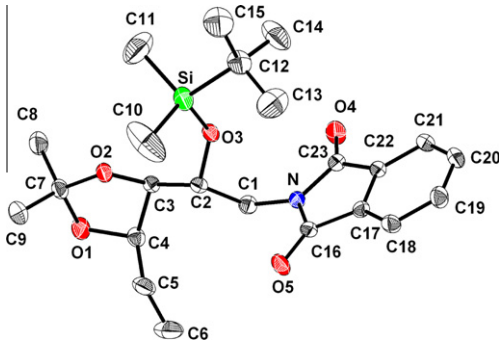
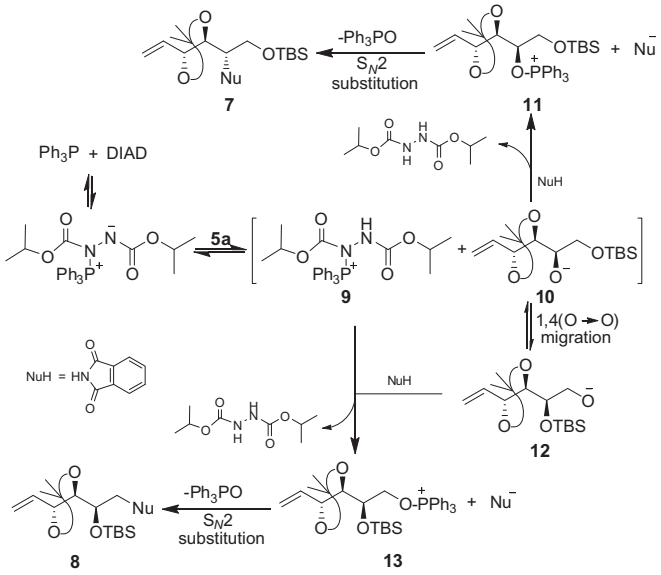
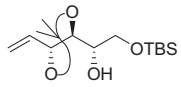
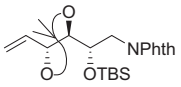
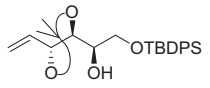
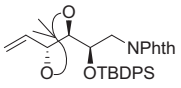
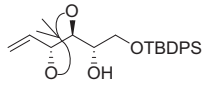
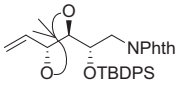
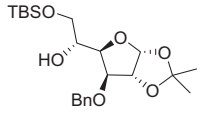
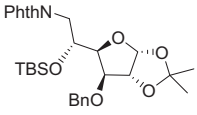
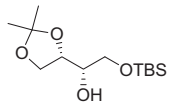
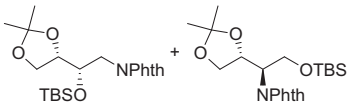
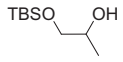
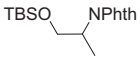


Figure 1. ORTEP diagram of compound **8**.[17]



Scheme 4. Proposed mechanism for the formation of **7** and **8**.

Table 1
Mitsunobu reaction products of differentially protected 2-hydroxyethyl trialkylsilyl ether derivatives

Entry	Alcohol[a]	Product after Mitsunobu reaction[b] (%)
1	 **6a**	 **14** (75)
2	 **5b**	 **15** (85)
3	 **6b**	 **16** (80)
4	 **17**	 **18** (75)
5	 **19**	 **20** (31) **21** (46)
6	 **22**	 **23** (82)

[a] No silyl-tropism was observed by stirring the alcohols in dry THF for 72 h at 25 °C.
[b] Yield represents to pure and isolated products.

sterically hindered secondary alcohol that is spatially oriented to a nearby silylether.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.015.

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15. The numbers were assigned based on the starting material fructose.
16. Crystal data for compound **8** ($C_{23}H_{33}NO_5Si$): Mr = 431.59, orthorhombic, space group P212121 a = 7.5487 Å, b = 15.382 Å, c = 21.659 Å, V = 2514.8(10) Å^3, Z = 4, Mo Kα radiation (λ = 0.71073 Å), T = 100(2) K; $R1$ = 0.0626, $wR2$ = 0.1556 ($I > 2\sigma(I)$); $R1$ = 0.0667, $wR2$ = 0.1589 (all data). The CIF file for the crystal data of compound **8** and **16** is available from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif under CCDC ref no. 801190 and 801191, respectively.
17. Hydrogen atoms were removed for clarity of the structure.
18. A similar kind of intermediate has been found in the azidation of 1,2 and 1,3-diols by azidotrimethylsilane via a Mitsunobu reaction to give C-2 and C-3 azides, respectively. It is also noticed that the selectivity depends on the surrounding sterichindrance of the C-2 or C-3 alcohol. (a) He, L.; Wanunu, M.; Byun, H.-S.; Bittmann, R. *J. Org. Chem.* **1999**, *64*, 6049; (b) Mathieu-Pelta, I.; Evans, S. A., Jr. *J. Org. Chem.* **1992**, *57*, 3409.
19. One of the intermediate similar to **12** has been isolated as an alcohol by quenching a stirred mixture of DIAD, Ph_3P and **6a** in THF with water. This intermediate was further confirmed by observing a downfield shift of C1 protons in the corresponding C1-O-acetylated derivative. Where as a downfield shift of C2 proton was observed in C2-O-acetylated derivative of compound **6a**.
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24. *General procedure for Mitsunobu reaction:* To a stirred solution of alcohol **5a** (300 mg, 0.99 mmol), Ph_3P (781.6 mg, 2.98 mmol) and phthalimide (175.3 mg, 1.19 mmol) in dry THF (8 mL) at 0 °C was injected DIAD (602 mg, 2.98 mmol) dropwise. The reaction mixture was allowed to stir at 25 °C for 6 h. After completion of reaction (by TLC) the mixture was concentrated and the product was purified by column chromatography using ethyl acetate: hexane (1:9) to give compound **8** (322 mg, 75%) as a colorless liquid.