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Utilization of 1-Oxa-2,2-(dimesityl)silacyclopentane Acetals in the Stereoselective Synthesis of Polyols

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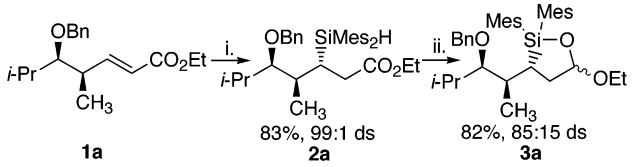
Cyclic silanes have been the targets of recent synthetic methods because these heterocycles can be readily converted into alcohols after oxidation of a carbon−silicon bond.[1−4] The 1-oxa-2-silacyclopentane moiety, in particular, is a useful intermediate for the stereoselective formation of 1,3-diols.[5−11] We have shown that oxasilacyclopentane acetals undergo substitution reactions with a range of nucleophiles to provide highly substituted oxasilacyclopentane products.[12] In this communication, we report a stereoselective and high-yielding synthesis of 1-oxa-2,2-(dimesityl)-silacyclopentane acetals from readily available starting materials. Subsequent Lewis acid-mediated nucleophilic substitution further functionalizes the oxasilacyclopentane, and oxidation of the C−Si bond reveals the 1,3-diol.

Formation of the oxasilacyclopentane acetal was achieved by conjugate addition of a hydrosilyl anion to an α,β-unsaturated ester followed by an intramolecular hydrosilylation reaction.[13] While conjugate addition of a hydrosilyl anion has not been previously demonstrated, conditions developed by Lipshutz for the conjugate addition of phenyldimethylsilyllithium enabled the stable silyllithium complex $Mes_2SiHLi\cdot(THF)_2$ (**4**)[14,15] to add in a 1,4-fashion to chiral α,β-unsaturated ester **1a** to provide β-silyl ester **2a** in high yield and 99:1 diastereoselectivity (Scheme 1).[16,17] The 1-oxa-2-silacyclopentane acetal **3a** was then formed as an 85:15 mixture of acetal epimers in good yield by an intramolecular hydrosilylation of β-silyl ester **2a** using conditions similar to those developed by Davis for the hydrosilylation of β-siloxy esters (Scheme 1).[13]

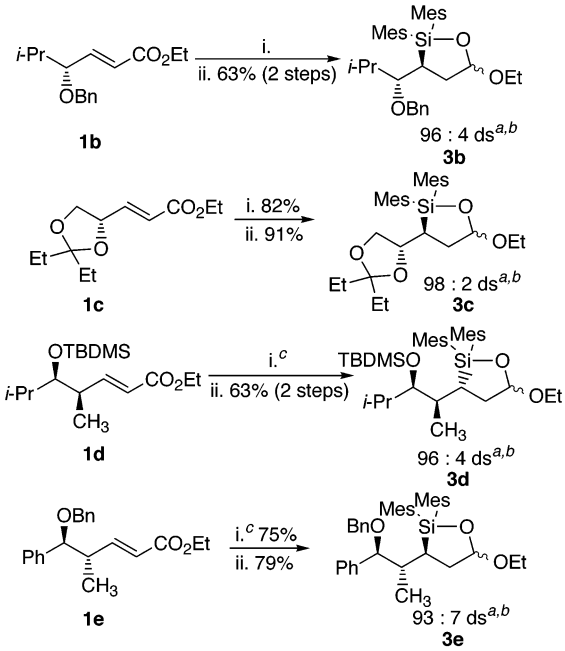
Scheme 1[a]



[a] Key: (i) **4**, Me_2Zn, 5 mol % $Me_2CuLi\cdot LiCN$, 3 equiv of $(CH_3)_3SiCl$, −78 °C. (ii) 10 mol % *n*-Bu_4NF, 0 °C.

The conjugate addition of silyl anion **4** to α,β-unsaturated esters containing stereogenic centers proceeded with high selectivity for a variety of substrates. Conjugate addition to enoates possessing an alkoxy group at the γ-position afforded products with high selectivity.[7,18,19] Addition to enoate **1b** resulted in 96:4 selectivity; selectivity increased to 98:2 for conjugate addition to enoate **1c**, derived from D-mannitol (Scheme 2).[20] Conjugate additions to esters containing the γ-methyl-δ-alkoxy substitution pattern resulted in even higher selectivities.[7] The choice of hydroxyl protecting group had little effect on the outcome of the conjugate addition (cf., **1a** and **1d**, Schemes 1 and 2).[21] Addition to enoate **1e**[22] demonstrated that the selectivity of the addition is unaffected by the orientation of the δ-stereocenter (Scheme 2).[7,23]

Scheme 2[a]



[a] Key: (i) **4**, Me_2Zn, 5 mol % $Me_2CuLi\cdot LiCN$. (ii) 10 mol % *n*-Bu_4NF, 0 °C. (a) Diastereoselectivities refer to conjugate addition. Diastereoselectivities of the hydrosilylation ranged between 80:20 and 85:15. (b) Selectivities determined by GCMS or ^1H NMR spectroscopy. (c) 3 equiv of $(CH_3)_3SiCl$ added.

Conversion of the β-silyl esters to the oxasilacyclopentanes highlighted the mild conditions and functional group tolerance of the hydrosilylation reaction. Hydrosilylation of β-silyl esters **2b**−**e** afforded oxasilacyclopentane acetals **3b**−**e** in high yield (Scheme 2). Even a β-silyl ester bearing a hydroxyl group protected as a TBDMS ether could be converted to the oxasilacyclopentane acetal **(**Scheme 2).

The β-silyl esters can be further functionalized by installing an alkyl group at the α-position with a high degree of stereocontrol. A representative alkylation of β-silyl ester **2a** was carried out with MeI. Under optimized conditions, the desired α-methyl-β-silyl ester **5a** was obtained with 97:3 diastereoselectivity (eq 1). As expected, alkylation occurs trans to the large β-silyl substituent,[24−26] providing the framework for the synthetically challenging *anti,anti* dipropionate stereotriad.[27−29] Ester **5a** undergoes hydrosilylation to afford oxasilacyclopentane **6a** in a similar manner as β-silyl ester **2a**.

The efficiency of this route can be greatly increased because conjugate addition, enolate alkylation, and hydrosilylation can be conducted in one flask without isolation of intermediates. For example, after conjugate addition of silyllithium **4** to **1f**, the resulting enolate was alkylated stereoselectively with MeI. After being stirred

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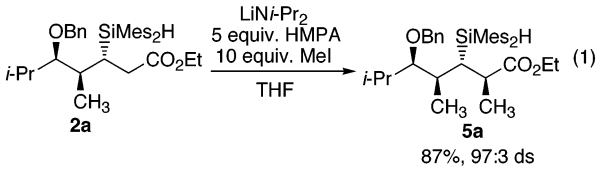
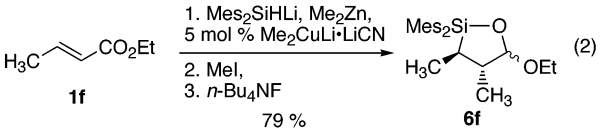
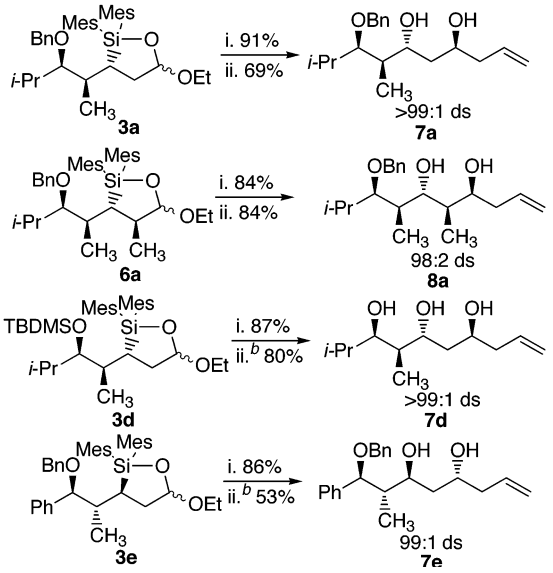


overnight, the reaction mixture was treated with *n*-Bu_4NF (eq 2), leading directly to the oxasilacyclopentane acetal **6f**.



Lewis acid-mediated nucleophilic substitution followed by oxidation of the carbon−silicon bond[1,2] revealed the 1,3-diol moiety (Scheme 3). Allyltrimethylsilane was employed as the representative nucleophile.[30] In accordance with our studies of five-membered ring oxocarbenium ions,[30,31] nucleophilic substitution provided the 1,3-trans products with high stereoselectivity (Scheme 3). Oxidation of the resulting oxasilacyclopentanes with alkyl hydroperoxides[32] provided 1,3-diols, including polyol **8a** containing the desired *anti,anti* stereotriad (Scheme 3).

Scheme 3[a]



[a] Key: (i) $CH_2CHCH_2Si(CH_3)_3$, $BF_3{\cdot}OEt_2$, −78 °C to 0 °C. (ii) 10 equiv of $CsOH{\cdot}H_2O$, 5.5 equiv of CsF, 8 equiv of *t*-BuOOH, NMP. (a) Diastereoselectivity determined by GCMS or ^1H NMR spectroscopy. (b) 8 equiv of cumene hydroperoxide was used.

In conclusion, we have developed a route for the stereoselective synthesis of 1-oxa-2,2-(dimesityl)silacyclopentane acetals, intermediates for the formation of highly functionalized 1,3-diols. This route involves a diastereoselective conjugate addition reaction of a silyllithium reagent, subsequent diastereoselective enolate alkylation, and a fluoride-catalyzed hydrosilylation reaction to afford the oxasilacyclopentane acetal. A highly selective nucleophilic substitution reaction, followed by oxidation of the C−Si bond, leads to the desired polyol. This method provides a general approach to acyclic polyols because substitution can be independently installed in a modular manner at each step in the synthetic pathway with high selectivity.

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Supporting Information Available: Full experimental and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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