

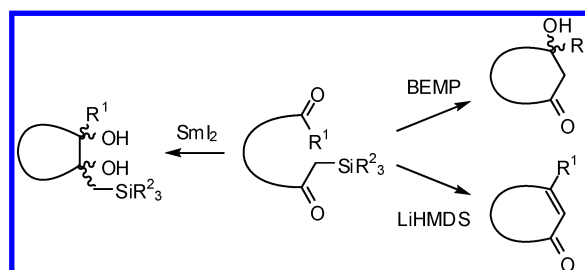
1-Silyl-2,6-diketones: Versatile Intermediates for the Divergent Synthesis of Five- and Six-Membered Carbocycles under Radical and Anionic Conditions

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ABSTRACT



1-Silyl-2,6-diketones, readily prepared by addition of (silylmethyl)metal reagents to 1,5-lactols followed by oxidation of the resultant diols, can be efficiently transformed into 3-hydroxycyclohexanones, cyclohex-2-enones, or 1-(silylmethyl)cyclopentane-1,2-diols under nucleophilic, basic, or single electron-transfer reduction conditions, respectively. The latter cyclitols can be further transformed into 2-methylenecyclopentanols or 1-(hydroxymethyl)cyclopentane-1,2-diols by Peterson elimination or Tamao–Fleming oxidation, respectively.

α -Silyl carbonyl compounds are highly versatile reagents that can be utilized in a wide range of useful synthetic transformations.¹ The particular reactivity of these compounds originates in the relative weakness of the C–Si bond, which is activated by the electron-withdrawing carbonyl group and the pronounced propensity of the silyl group to migrate to neighboring oxygen. Thus, α -silyl carbonyl compounds rearrange stereoselectively to silyl enol ethers under thermal conditions or in the presence of Lewis acids or metal catalysts.² α -Silyl aldehydes and α -silyl ketones are especially useful in the stereoselective synthesis of disubstituted and trisubstituted olefins³ and in a wide variety of regio-

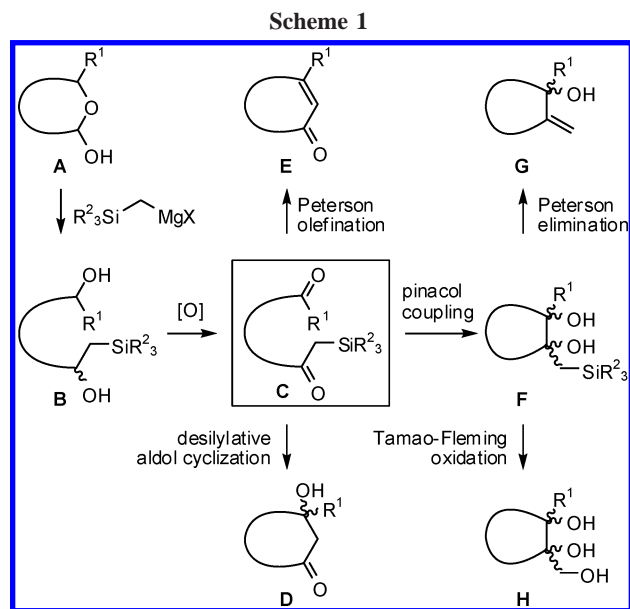
and diastereoselective electrophilic substitution reactions in which the silyl group acts as a “traceless” directing group.⁴ However, despite this synthetic potential, the widespread use of α -silyl carbonyl compounds has been limited by their high propensity to suffer protodesilylation and thermal rearrangement.

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Due to our interest in the synthesis of carbocyclic polyhydroxylated natural products and analogues,⁵ we decided to explore the potential and versatility of 1-silyl-2,6-diketones in carbocyclization reactions performed under anionic and radical conditions. To our knowledge, α -silyl ketones have never been used in intramolecular carbon-carbon bond-forming processes. With this study, we intended to develop a new synthetic strategy that could allow an efficient access to a series of key intermediates for the preparation of carbafuranoses, carbapyranoses, and natural inhibitors of glycosidases with a C₇ aminocyclitol ring.⁶ The general synthetic plan is depicted in Scheme 1. Alicyclic

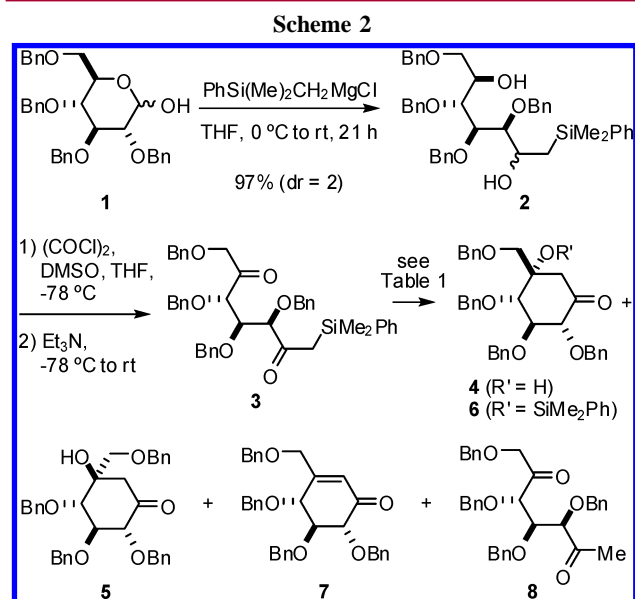


1-trialkylsilyl-2,*n*-diketones **C** could be readily accessed from cyclic hemiacetal **A** by reaction with a ((trialkylsilyl)methyl)-metal reagent and subsequent oxidation of the resultant diol. Desilylative aldol cyclization of **C**, promoted by an appropriate nucleophile, would produce β -hydroxy ketone **D** regioselectively. Treatment of **C** with an appropriate base instead would selectively remove a proton from the more acidic

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(6) For a recent review on this important family of compounds, see: Mahmud, T. *Nat. Prod. Rep.* **2003**, *20*, 137–166.



methylene (that flanked by the trialkylsilyl and carbonyl groups)^{4c} to form an intermediate α -trialkylsilyl enolate, which could participate in an intramolecular Peterson olefination reaction to afford cyclic enone **E**. Alternatively, the intramolecular reductive coupling reaction of diketone **C** would provide the cyclic pinacol **F** with a (trialkylsilyl)-methyl substituent. The functionality present in this compound endows it with a valuable synthetic versatility. Thus, **F** could be subjected to a Peterson elimination reaction to give allylic alcohol **G**, which can undergo a diversity of further synthetic transformations. Alternatively, oxidation of **F** under Tamao–Fleming conditions would afford branched triol **H**.

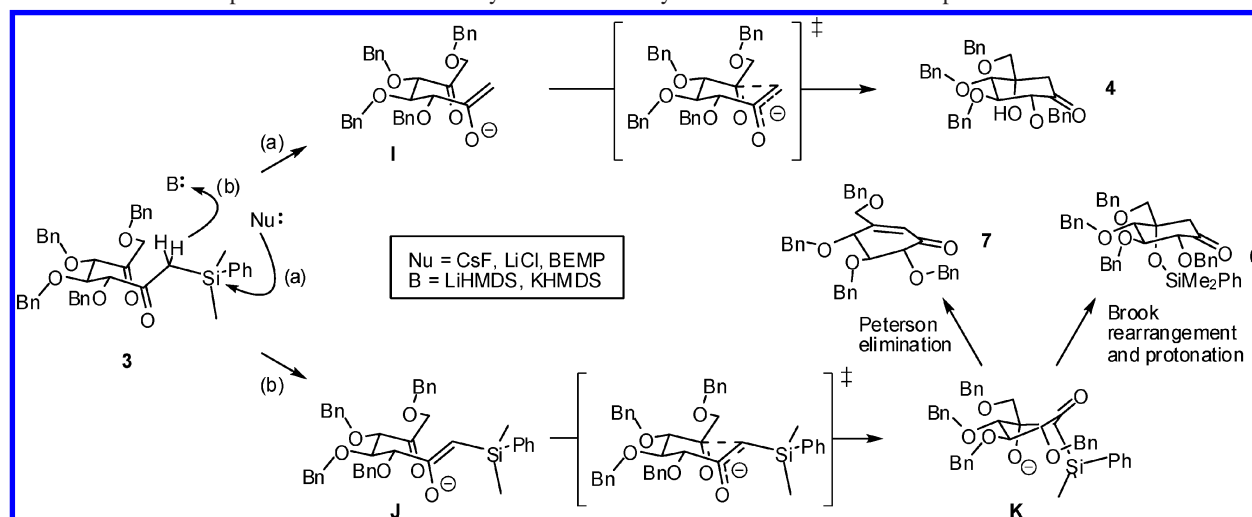
We have successfully reduced this plan to practice using the D-glucose-derived hemiacetal **1** as starting material. Thus, treatment of **1** with $\text{PhMe}_2\text{SiCH}_2\text{MgCl}$ afforded the open chain diol **2** as a 2:1 mixture of diastereoisomers in almost quantitative yield (Scheme 2).⁷ Swern oxidation of **2** cleanly gave diketone **3**, which, not surprisingly, proved to be

Table 1. Carbocyclization of Crude Diketone **3** under Anionic Conditions

entry	conditions	products (yield, %) ^a
1	CsF (3 equiv), MeCN, 0 °C, 4 h	4 (57), 5 (9), 7 (5), 8 (3)
2	LiCl (0.5 equiv), DMF, rt, 15 h	4 (50), 5 (6), 8 (5)
3	BF ₃ ·OEt ₂ (2 equiv), CH ₂ Cl ₂ , -78 °C, 7 h	4 (20), 8 (80)
4	SnCl ₄ (1.2 equiv), CH ₂ Cl ₂ , -78 °C, 2.5 h	4 (47), 5 (14), 8 (17)
5	BEMP (0.5 equiv), THF, 0 °C, 5 h	4 (75), 7 (6), 8 (5)
6	KHMDS (1 equiv), THF, -78 °C, 3.5 h	4 (7), 6 (25), 7 (55)
7	LiHMDS (1 equiv), THF, -78 °C, 24 h	6 (9), 7 (76), 8 (8)

^a Overall isolated yield from diol **2**.

Scheme 3. Proposed Mechanistic Pathways for the Carbocyclization of **3** under Nucleophilic and Basic Conditions



unstable on silica gel and, accordingly, was used for ensuing steps without purification.⁸ First, we tried to perform the carbocyclization of **3** under anionic conditions. For this purpose, we assayed the series of reagents and conditions shown in Table 1, some of which have been previously employed for intermolecular C–C bond forming processes of α -silyl ketones.⁹ Both nucleophilic (entries 1 and 2) and Lewis acidic conditions (entries 3 and 4) promoted the regioselective desilylative aldol carbocyclization of **3** affording a separable mixture of diastereoisomeric β -hydroxy cyclohexanones **4/5**^{10,11} in moderate yield and with moderate stereoselectivity (dr = 3.4–8.3). In the case of $\text{BF}_3 \cdot \text{OEt}_2$, however, the major product was the protidesilylated diketone **8**.¹² No other carbocyclic regioisomeric aldol products could be detected in any of the crude reaction mixtures (¹H NMR analysis).¹³ More interesting results were obtained under basic reaction conditions. Thus, treatment of **3** with substoichiometric amounts of the phosphazene base BEMP¹⁴ furnished β -hydroxy cyclohexanone **4** stereoselectively in

75% overall yield from **2** (entry 5). In contrast, deprotonation of **3** with KHMDS yielded a mixture of cyclohexenone **7**¹⁵ and *O*-silylated β -hydroxy cyclohexanone **6**¹⁰ as major products (entry 6). Treatment with LiHMDS instead maximized formation of **7** (76% overall yield from **2**) at the expense of **6**.

The distinct outcomes observed for the nonionic BEMP base and the metalated HMDS bases suggest different mechanistic scenarios in each case (Scheme 3). Thus, the BEMP-promoted aldol carbocyclization probably takes place through nucleophilic activation of the silyl group¹⁶ to afford enolate **I**, while the anionic bases are expected to produce the regioselective deprotonation of **3**, as previously explained, to give an α -trialkylsilyl *Z*-enolate (**J**).¹⁷ Both enolates cyclize stereoselectively via chairlike transition states. In the case of **J**, an intermediate aldol product **K** is produced containing a *cis*- β -silyl alkoxide, which partitions¹⁸ between Brook rearrangement followed by protonation of the ensuing enolate to give **6**, and Peterson elimination to afford **7**. As expected, the Brook rearrangement is more efficient for the potassium than for the lithium alkoxide.¹⁸

Compounds **4** and **7** are key intermediates for the preparation of carbapyranoses^{15a,19} and a number of important C₇ aminocyclitol natural products^{6,11,15b} including valioline, valienamine and its derivatives, such as acarbose, the validamycins, salvostatins, and the synthetic drug voglibose.

(7) For a similar transformation, see: Glanzer, B. I.; Gyorgydeak, Z.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 343–369.

(8) Flash chromatography (SiO_2 , EtOAc/hexanes 1:8 with 1% v/v Et₃N) of crude **3** afforded only a 42% yield of **3** along with protidesilylated diketone **8** (17%) and a 5:1 diastereoisomeric mixture of cyclohexanones **4** and **5**, respectively (27%).

(9) For intermolecular cross-aldol reactions of α -silyl ketones promoted by LDA, *n*-Bu₄NF, $\text{BF}_3 \cdot \text{OEt}_2$, TiCl₄, or SnCl₄, see: (a) Inoue, T.; Sato, T.; Kuwajima, I. *J. Org. Chem.* **1984**, *49*, 4671–4674. (b) Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887–4890. Promoted by CsF: (c) Fiorenza, M.; Mordini, A.; Papaleo, S.; Pastorelli, S.; Ricci, A. *Tetrahedron Lett.* **1985**, *26*, 787–788. For intermolecular cross-aldol reactions of α -silyl esters promoted by LiCl, see: (d) Miura, K.; Nakagawa, T.; Hosomi, A. *Synlett* **2005**, 1917–1921.

(10) The stereochemistry of the carbocyclic products was unambiguously established through ¹H NMR and 1D and 2D NOESY studies (see the Supporting Information for details).

(11) The structures of **4** and **5** were further confirmed by comparison of their physical and spectroscopic data with those described in the literature: (a) Fukase, H.; Horii, S. *J. Org. Chem.* **1992**, *57*, 3642–3650. (b) Mahmud, T.; Xu, J.; Choi, Y. U. *J. Org. Chem.* **2001**, *66*, 5066–5073.

(12) (a) Ohtake, H.; Ikegami, S. *Org. Lett.* **2000**, *2*, 457–460. (b) Ohtake, H.; Li, X.-L.; Shiro, M.; Ikegami, S. *Tetrahedron* **2000**, *56*, 7109–7122.

(13) Minor amounts (<10%) of three elimination products were isolated in some of the reactions included in Table 1 (see the Supporting Information for details).

(14) BEMP: 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine. (a) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167–1169. (b) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435–2454 and references therein.

(15) (a) Paulsen, H.; von Deyn, W. *Liebigs Ann. Chem.* **1987**, 125–131. (b) Fukase, H.; Horii, S. *J. Org. Chem.* **1992**, *57*, 3651–3658.

(16) For recent examples of nucleophilic activation of silylated nucleophiles by phosphazene bases, see: Ueno, M.; Hori, C.; Suzawa, K.; Ebisawa, M.; Kondo, Y. *Eur. J. Org. Chem.* **2005**, 1965–1968.

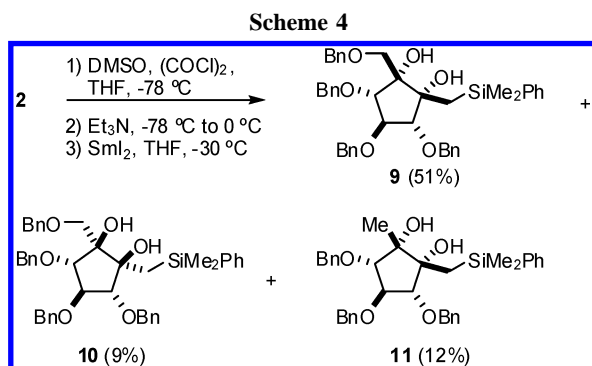
(17) Ketones with large substituents form preferentially *Z*-enolates under these conditions. See: Heathcock, C. H. *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: New York, 1992; Vol. 6, pp 1–102.

(18) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065–2084.

(19) For a review, see: Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21–90.

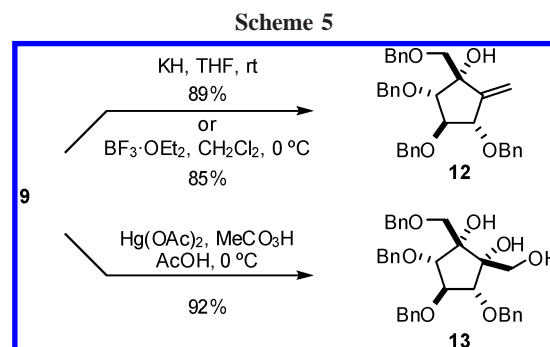
Compared to previous approaches^{11,12,15} to those key intermediates, our new method allows the divergent direct preparation of both compounds from a common intermediate in a shorter and more efficient route.

We studied next the preparation of five-membered cyclitols from diketone **3** via an intramolecular pinacol coupling reaction (Scheme 4). This transformation was more ef-



ficiently performed starting from diol **2** and using our previously developed^{5d,g,h} one-pot methodology of Swern oxidation followed by reductive coupling promoted by SmI₂. Under these conditions, a chromatographically separable 5.7:1 mixture of diastereoisomeric *cis*-cyclopentane diols **9**¹⁰ and **10**,¹⁰ respectively, was obtained in moderate overall yield together with a minor amount of diol **11**,¹⁰ a deoxy analogue of **9** resulting from the reductive elimination of the primary benzyloxy group prior to the pinacol coupling step. To our knowledge, this is the first example of a radical C–C bond forming reaction involving an α -silyl carbonyl compound. It is worth mentioning that this intramolecular diketone reductive coupling is astonishingly fast, taking less than 5 min at -30 °C to go to completion.²⁰

Compound **9** was further transformed into methylenecyclopentitol **12** via Peterson elimination reaction under either acidic or basic conditions (Scheme 5). In addition, oxidation



of **9** under Fleming conditions²¹ afforded the asymmetrically protected polyhydroxylated meso-cyclopentane **13** in excellent yield.

In conclusion, alicyclic 1-trialkylsilyl-2,6-diketones are versatile intermediates for the divergent preparation of a variety of saturated and unsaturated five- and six-membered cyclitols in a very efficient way, displaying a great potential for inclusion in synthetic schemes oriented to the generation of skeletal diversity.²²

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Supporting Information Available: Complete experimental procedures and characterization data for compounds **2–13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) This probably reflects a particularly facile single electron-transfer reduction of the β -silyl carbonyl group. It has been proposed that β -silyl alkyl radicals are stabilized by hyperconjugation involving the SOMO orbital of the radical center and the HOMO of the proximal C–Si bond: Bernardi, F.; Bottoni, A.; Fossey, J.; Sorba, J. *Tetrahedron* **1986**, *42*, 5567–5580.

(21) For a review, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662.

(22) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613–618.