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

Jose L. Chiara,* Ángela García, Esther Sesmilo, and Tatiana Vacas

Instituto de Química Orgánica General, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain

jl.chiara@iqog.csic.es

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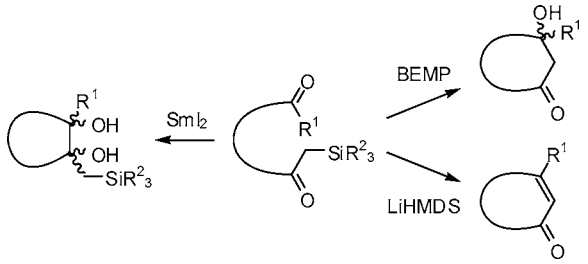
ABSTRACT



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 olefins[3] 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 protiodesilylation and thermal rearrangement.

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(2) (a) Brook, A. G.; MacRae, D. M.; Limburg, W. W. *J. Am. Chem. Soc.* **1967**, *89*, 5493−5. (b) Lutsenko, I. F.; Baukov, Y. I.; Dudukina, O. V.; Kramarova, E. N. *J. Organomet. Chem.* **1968**, *11*, 35−48. For a recent theoretical study on this rearrangement, see: (c) Takahashi, M.; Kira, M. *J. Am. Chem. Soc.* **1999**, *121*, 8597−8603.

(3) (a) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464−1468. (b) Utimoto, K.; Obayashi, M.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2940−2941. (c) Hudrlik, P. F.; Hudrlik, A. M.; Misra, R. N.; Peterson, D.; Withers, G. P.; Kulkarni, A. K. *J. Org. Chem.* **1980**, *45*, 4444−4448. (d) Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251−6253. (e) Fürstner, A.; Kollegger, G.; Weidmann, H. *J. Organomet. Chem.* **1991**, *414*, 295−305. (f) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M. *J. Org. Chem.* **1992**, *57*, 386-389. (g) Trost, B. M.; Ball, Z. T.; Kang, E.-J. *Org. Lett.* **2005**, *7*, 4911−4913.

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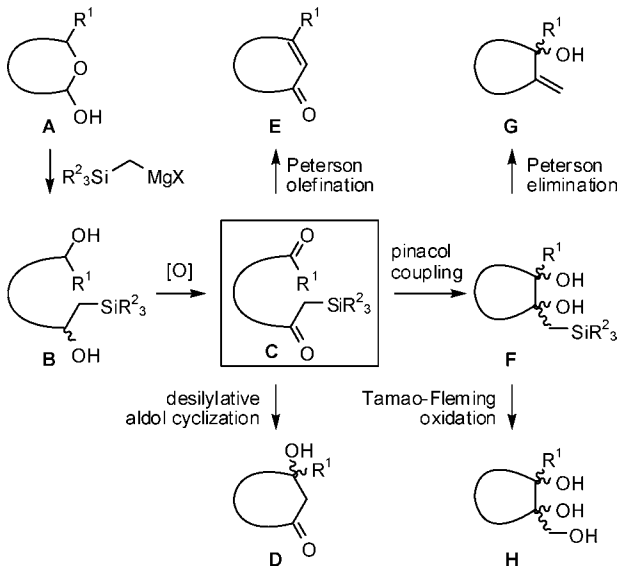
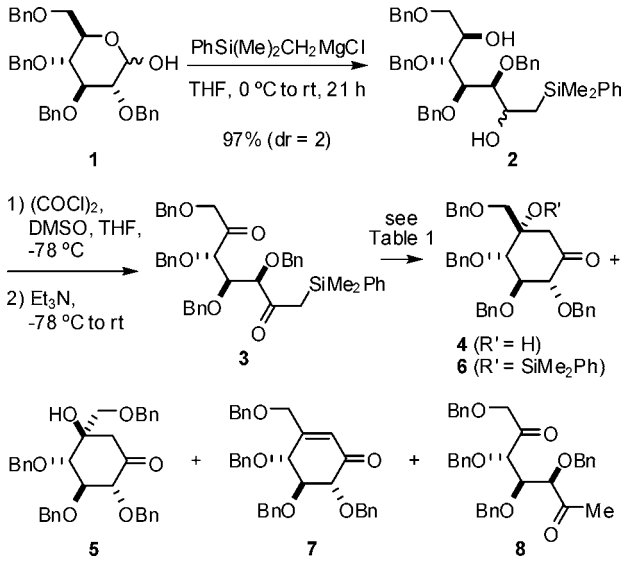
Due to our interest in the synthesis of carbocyclic polyhydroxylated natural products and analogues,[5] we decided to explore the potential and versatility of 1-silyl-2,6-diketones in carbocyclization reactions performed under anionic and radical conditions. To our knowledge, α-silyl ketones have never 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 C_7 aminocyclitol ring.[6] The general synthetic plan is depicted in Scheme 1. Alicyclic

Scheme 1



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

Scheme 2



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 $PhMe_2SiCH_2MgCl$ 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	$BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, −78 °C, 7 h	**4** (20), **8** (80)
4	$SnCl_4$, (1.2 equiv), CH_2Cl_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)

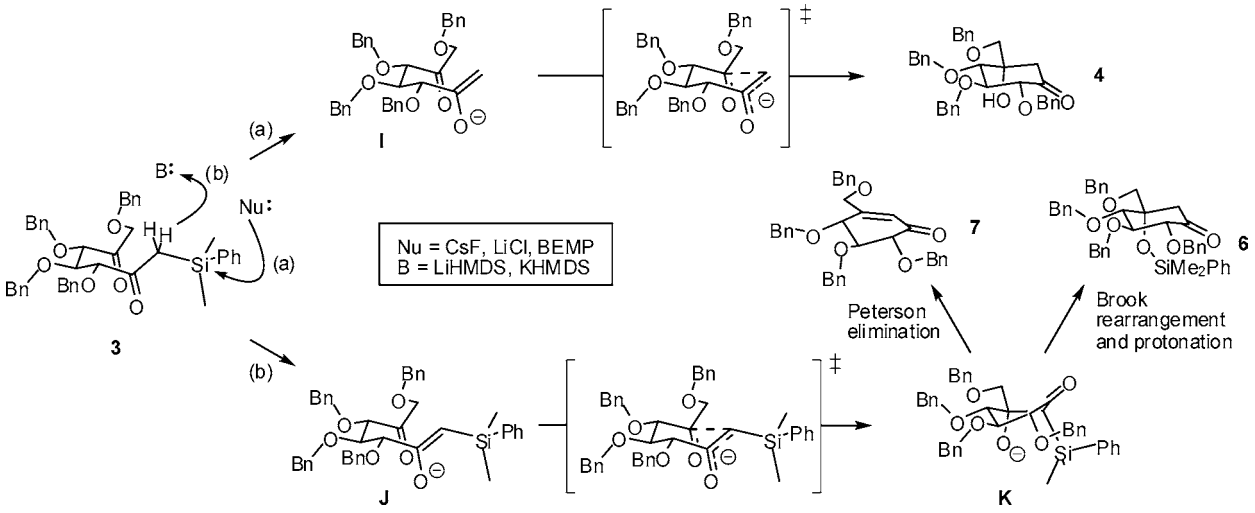
[a] Overall isolated yield from diol **2**.

(4) (a) Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887−4890. (b) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371−7372. (c) Inoue, T.; Sato, T.; Kuwajima, I. *J. Org. Chem.* **1984**, *49*, 4671−4674. (d) Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588−7591. (e) Fiorenza, M.; Mordini, A.; Papaleo, S.; Pastorelli, S.; Ricci, A. *Tetrahedron Lett.* **1985**, *26*, 787−788. (f) Matsuda, I.; Sato, S. *J. Organomet. Chem.* **1986**, *314*, 47−52. (g) Enders, D.; Adam, J.; Klein, D.; Otten, T. *Synlett* **2000**, 1371−1384.

(5) (a) Chiara, J. L.; Storch de Gracia, I.; Garcia, A.; Bastida, A.; Bobo, S.; Martin-Ortega, M. D. *ChemBioChem* **2005**, *6*, 186−191. (b) Chiara, J. L.; Garcia, A.; Cristobal-Lumbroso, G. *J. Org. Chem.* **2005**, *70*, 4142−4151. (c) Chiara, J. L.; Garcia, A. *Synlett* **2005**, 2607−2610. (d) Chiara, J. L.; Storch de Gracia, I.; Bastida, A. *Chem. Commun.* **2003**, 1874−1875. (e) Storch de Gracia, I.; Bobo, S.; Martin-Ortega, M. D.; Chiara, J. L. *Org. Lett.* **1999**, *1*, 1705−1708. (f) Bobo, S.; Storch de Gracia, I.; Chiara, J. L. *Synlett* **1999**, 1551−1554. (g) Storch de Gracia, I.; Dietrich, H.; Bobo, S.; Chiara, J. L. *J. Org. Chem.* **1998**, *63*, 5883−5889. (h) Chiara, J. L. In *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: New York, 1998; Chapter 7, pp 123−156 and references cited therin.

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

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 $BF_3{\cdot}OEt_2$, however, the major product was the protiodesilylated diketone **8**.[12] No other carbocyclic regioisomeric aldol products could be detected in any of the crude reaction mixtures (^{1}H NMR analysis).[13] More interesting results were obtained under basic reaction conditions. Thus, treatment of **3** with substoichiometric amounts of the phosphazene base BEMP[14] 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 group[16] 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 partitions[18] 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 C_7 aminocyclitol natural products[6,11,15b] including valiolamine, valienamine and its derivatives, such as acarbose, the validamycins, salvostatin, 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 Et_3N) of crude **3** afforded only a 42% yield of **3** along with protiodesilylated 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*-Bu_4NF, $BF_3{\cdot}OEt_2$, $TiCl_4$, or $SnCl_4$, 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 ^{1}H 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 elimation 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.

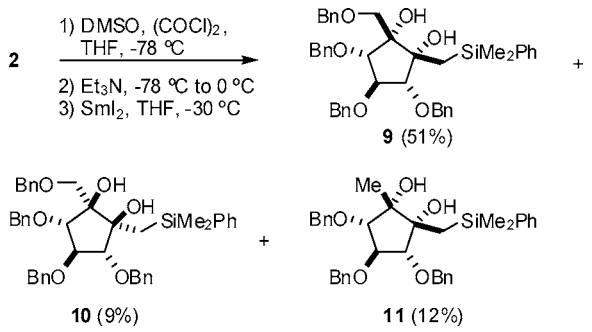
(18) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084.

(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.

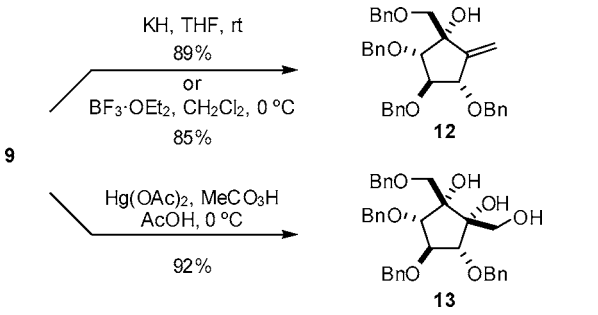
We studied next the preparation of five-membered cyclitols from diketone **3** via an intramolecular pinacol coupling reaction (Scheme 4). This transformation was more efficiently performed starting from diol **2** and using our previously developed[5d,g,h] one-pot methodology of Swern oxidation followed by reductive coupling promoted by SmI_2. Under these conditions, a chromatographically separable 5.7:1 mixture of diastereoisomeric *cis*-cyclopentanediols **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]

Scheme 4



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 conditions[21] afforded the asymmetrically protected polyhydroxylated meso cyclopentane **13** in excellent yield.

Scheme 5



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]

Acknowledgment. Financial support from the Ministry of Science and Technology of Spain (project BQU2000-1501-C02-01), Fundación Ramón Areces, and Comunidad de Madrid (predoctoral fellowships to A.G and E.S., respectively) are gratefully acknowledged.

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.