

## Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

### A Rapid and Efficient Synthesis of a Bifunctional $\beta$ -Silylketone, Precursor for a Solid Supported $\beta$ -Silylethanol Anchoring Group

Sonali M. Date <sup>a</sup>, Prema Iyer <sup>a</sup> & Sunil K. Ghosh <sup>a</sup>

<sup>a</sup> Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai, 400 085, India

Published online: 16 Aug 2006.

To cite this article: Sonali M. Date, Prema Iyer & Sunil K. Ghosh (2004) A Rapid and Efficient Synthesis of a Bifunctional  $\beta$ -Silylketone, Precursor for a Solid Supported  $\beta$ -Silylethanol Anchoring Group, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 34:3, 405-411, DOI: [10.1081/SCC-120027279](https://doi.org/10.1081/SCC-120027279)

To link to this article: <http://dx.doi.org/10.1081/SCC-120027279>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

## A Rapid and Efficient Synthesis of a Bifunctional $\beta$ -Silylketone, Precursor for a Solid Supported $\beta$ -Silylethanol Anchoring Group

Sonali M. Date, Prema Iyer, and Sunil K. Ghosh\*

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai, India

### ABSTRACT

A concise synthesis of 3-dimethyl(phenyl)silyl-5-oxo-hexanoic acid **1**, the precursor for a solid supported  $\beta$ -silylethanol anchoring group has been achieved from ethyl 2-ethoxycarbonyl-3-dimethyl(phenyl)silyl-2-propenoate **2** featuring amino acid catalysed Michael addition of acetone as the key step.

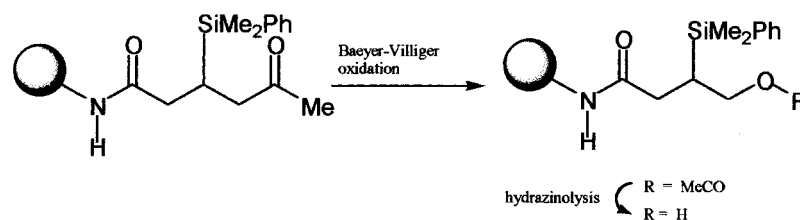
*Key Words:*  $\beta$ -Silylketone; Michael addition; Amino acid; Catalysis.

---

\*Correspondence: Sunil K. Ghosh, Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India; Fax: +91-22-25505151; E-mail: ghsunil@magnum.barc.ernet.in.

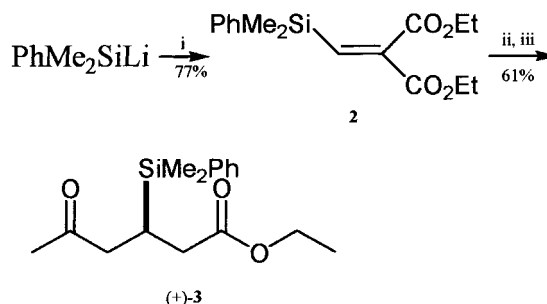
Development of novel linkers between the solid support and the substrates cleavable under mild/specific conditions is an essential attribute of combinatorial chemistry. In this perspective, organosilicon chemistry plays a vital role with the development of many specific linkers.<sup>[1–3]</sup> The  $\beta$ -(trimethylsilyl)ethyl ester functionality is a popular protecting group largely due to its chemical stability to the hydrolytic, oxidative, or reductive conditions that are commonly used to cleave other ester protecting groups.<sup>[4]</sup>  $\beta$ -Silylethanol linker could also be transformed into secondary linkers like  $\beta$ -silylethoxymethyl chloride<sup>[5]</sup> which then, could be used for the attachment of functionalized molecules such as alcohols, thiols, amines, carboxylic acids and phenolic compounds on to the resin. Silicon linkers based on the trimethylsilylethanol group have, therefore, been designed to be cleaved by a  $\beta$ -elimination mechanism.  $\beta$ -Silylethanol linkers are usually made by multi-step synthesis of a bifunctionalized silane containing the  $\beta$ -silylethanol moiety and a second functional group in solution phase. Subsequently, they are attached to the resin via the latter functionality.<sup>[6–8]</sup> We<sup>[9]</sup> have recently applied the regio-directing effect of a silicon group in the Baeyer-Villiger oxidation<sup>[10]</sup> of a resin bound  $\beta$ -silyl ketone to get exclusively the  $\beta$ -silylethyl acetate which was subsequently hydrazinolized to provide the resin bound  $\beta$ -silylethanol as depicted in Sch. 1. Herein, we report, a rapid synthesis of 3-dimethyl(phenyl)silyl-5-oxo-hexanoic acid **1**, the bifunctional precursor for the solid supported  $\beta$ -silylethanol anchoring group.

We began our synthesis with the silyl substituted alkylidene malonate **2**.<sup>[11]</sup> A low yielding (40%) synthesis of this compound was reported by Knochel<sup>[12]</sup> using diethyl phenylsulfonylmethylene malonate and a bimetallic silicon reagent. We have prepared it by a conjugate addition-elimination reaction starting from the commercially available diethyl ethoxymethylene malonate as shown in Sch. 2. Addition of dimethyl(phenyl)silyllithium<sup>[13]</sup> to it gave the silyl substituted unsaturated diester **2** in 77% yield. Michael addition of ethyl acetoacetate in the presence of a catalytic amount of diethylamine gave the intermediate triester which on Krapcho deethoxycarbonylation



Scheme 1.





**Scheme 2.** Reagents and conditions: (i) (EtO)HC=C(CO<sub>2</sub>Et)<sub>2</sub>, THF, −78 to 0°C; (ii) EtO<sub>2</sub>CCH<sub>2</sub>COCH<sub>3</sub>, Et<sub>2</sub>NH, room temperature; and (iii) NaCl, DMSO, H<sub>2</sub>O, 125–160°C.

furnished the keto ester **3**. However the last step was tricky and required great care to get the desired keto ester **3** in appreciable yield and purity. Best yield (61%) of **3** could be obtained by sequential heating the intermediate triester at 125°C/24 h, at 140°C/7 h and finally at 160°C for 7 h. An alternative and more efficient protocol was therefore developed involving direct addition of acetone on the alkylidene malonate **2** using amino acids as catalysts to give the ketodiester **4**. The conjugate addition of ketones to Michael acceptors has been known<sup>[14]</sup> to be catalysed by proline and cyclic imines. In the present endeavour, we studied a number of amino acids and different solvent systems for the conjugate addition of acetone to compound **2** and the results are presented in Table 1. Amongst the solvent and amino acid combinations chosen, racemic tryptophan in dimethyl sulfoxide gave the best result (Table 1; entry 7). The ketodiester **4** then easily underwent deethoxycarbonylation (170°C, 4 h) to give the keto ester **3** in 82% yield. The desired keto-acid **1**, in turn, was obtained in high yield by its alkaline hydrolysis (Sch. 3).

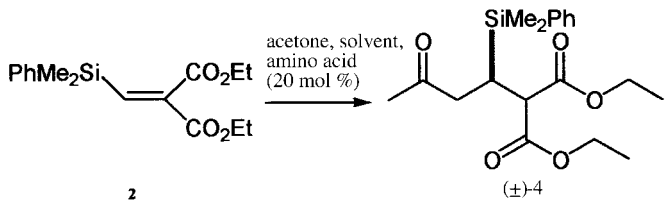
In conclusion, we have developed a method for the preparation of the bifunctional  $\beta$ -silylketone **1** in a rapid and efficient fashion from commercially available cheap starting materials such as diethyl ethoxymethylene malonate and racemic amino acids. This would facilitate the preparation of  $\beta$ -silylethanol anchoring group<sup>[9]</sup> for use in solid phase organic synthesis and combinatorial chemistry.

## EXPERIMENTAL

All reactions were performed in oven-dried (120°C) or flame-dried glass apparatus under dry N<sub>2</sub> or argon atmosphere. THF was dried with sodium/



**Table 1.** Effect of solvent and amino acid on the conjugate addition of acetone to **2**.



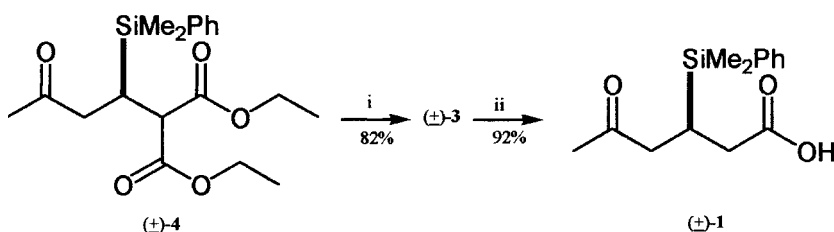
**2** (±)-4

Entry	Amino acid <sup>a</sup>	Solvent/time in days	Yield (%)
1	proline	DMSO/2	89
2	proline	DMSO/2.5	85
3	proline	NMP/2.5	84
4	phenylalanine	DMSO/2	70 <sup>b</sup>
5	tyrosine	DMSO/3.5	57 <sup>b</sup>
6	valine	DMSO/3.5	62 <sup>b</sup>
7	tryptophan	DMSO/2	98

<sup>a</sup>All reactions were conducted at room temperature using DL-amino acids.

<sup>b</sup>Incomplete reaction.

benzophenone and DMSO with  $\text{CaH}_2$ . Ethyl acetoacetate acetate and diethylamine were freshly distilled before use. Diethyl ethoxymethylene-malonate was obtained from Spectrochem (India).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker 200 MHz spectrometer. Mass spectra were recorded on a Fissons VG Quatro II mass spectrometer or HP GCD G1800A mass spectrometer. Infrared spectra (IR) were recorded on a Nicolet Impact 410 FT IR spectrophotometer.



**Scheme 3.** Reagents and conditions: (i) NaCl, DMSO,  $\text{H}_2\text{O}$ ,  $170^\circ\text{C}$ , 4 h; and (ii) NaOH, MeOH,  $\text{H}_2\text{O}$ .



**Ethyl 2-ethoxycarbonyl-3-dimethyl(phenyl)silyl-2-propenoate (2).** Dimethyl(phenyl)silyllithium<sup>[13]</sup> (0.85 M solution in THF) (105 mL, 89 mmol) was added dropwise to a stirred solution of diethyl ethoxymethylenemalonate (18 mL, 89 mmol) in THF (200 mL) at  $-78^{\circ}\text{C}$  over 0.5 h. After the addition was over, the reaction mixture was stirred for 5 min and the cold bath was removed. The reaction mixture was allowed to attain room temperature ( $\sim 25$  min), poured into saturated ammonium chloride solution and extracted with  $\text{Et}_2\text{O}$ . The organic extract was washed with water and brine, dried ( $\text{MgSO}_4$ ) and evaporated. The residue was purified by chromatography to give the diester **2** as a colorless oil.<sup>[12]</sup>

Yield: 21 g, 77%.  $R_f$ : 0.6 (hexane :  $\text{EtOAc}$ ; 95 : 5). IR (film): 1731, 1600, 1237,  $1115\text{ cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ) 0.45 (s, 6H), 1.19 (t,  $J = 7.1$  Hz, 3H), 1.29 (t,  $J = 7.1$  Hz, 3H), 4.00 (q,  $J = 7.1$  Hz, 2H), 4.24 (q,  $J = 7.1$  Hz, 2H), 7.32 (s, 1H), 7.34–7.38 (m, 3H), 7.50–7.55 (m, 2H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ) 165.94, 163.57, 147.38, 141.52, 136.12, 133.75, 129.33, 127.74, 61.42, 61.08, 13.91, 13.69,  $-2.75$ . MS (ESI):  $m/z$  329 ( $\text{M} + \text{Na}$ , 15), 307 ( $\text{M} + \text{H}$ , 5), 229 ( $\text{M} - \text{Ph}$ , 100), 201 (82), 173 (41), 155 (37).

**Ethyl (3*RS*)-3-dimethyl(phenyl)silyl-5-oxo-hexanoate [( $\pm$ )-3].** Diethylamine (0.25 mL, 2.42 mmol) was added to a mixture of ethyl acetoacetate (4.2 mL, 33.1 mmol) and ester **2** (5.08 g, 16.55 mmol) at  $0^{\circ}\text{C}$ . After stirring for 1.5 h at room temperature, the reaction mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$ . The organic extract was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The residue was subjected to Kugelrohr distillation to remove the excess ethyl acetoacetate furnishes the intermediate keto-triester. A stirred solution of this triester, sodium chloride (2.4 g) and water (0.9 mL) in DMSO (86 mL) was heated at  $125^{\circ}\text{C}$  under nitrogen for 24 h. The bath temperature was raised to  $140^{\circ}\text{C}$  and heated further for 7 h and at  $160^{\circ}\text{C}$  for 7 h. The reaction mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$ . The organic extract was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The residue was purified by chromatography to give ( $\pm$ )-**3** as a colorless oil. Yield: 3.02 g, 61%.  $R_f$ : 0.4 (hexane :  $\text{EtOAc}$ ; 10 : 90) IR(film): 1731, 1251,  $1112\text{ cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ) 0.30 (s, 6H), 1.21 (t,  $J = 7.1$  Hz, 3H), 1.83–2.08 (m, 1H), 2.05 (s, 3H), 2.17 (dd,  $J = 8.9, 15.2$  Hz, 1H), 2.39 (dd,  $J = 5, 15.2$  Hz, 1H), 2.45 (d,  $J = 6.42$  Hz, 1H), 4.02 (q,  $J = 7.1$  Hz, 2H), 7.34–7.38 (m, 3H), 7.45–7.52 (m, 2H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ) 208.10, 173.53, 136.92, 133.97, 129.29, 127.88, 60.35, 43.78, 34.70, 29.72, 17.46, 14.13,  $-4.31$ ,  $-4.57$ . MS (ESI):  $m/z$  292 ( $\text{M}^+$ , 1.8), 277 (22), 247 (10.7), 215 ( $\text{M} - \text{Ph}$ , 100), 135 (24). Anal. Calcd for  $\text{C}_{16}\text{H}_{24}\text{O}_3\text{Si}$  (292.456): C, 65.71; H, 8.27%. Found: C, 65.44; H, 8.50%.



**(3RS)-3-Dimethyl(phenyl)silyl-5-oxo-hexanoic acid [(±)-1].** Sodium hydroxide (2 M in water, 5 mL, 10 mmol) was added portionwise to a stirred solution of the ketoester (±)-3 (1.7 g, 5.82 mmol) in MeOH (20 mL) in 4 h. The solvent was evaporated and the residue was diluted with water, extracted with ether. The aqueous phase was acidified with dil HCl and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the acid (±)-1 as a thick gum. Yield: 1.27 g, 92%. IR (film): 3500–2500 (br), 1720, 1251, 1112 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) 0.32 (s, 6H), 1.86–2.01 (m, 1H), 2.05 (s, 3H), 2.22 (dd, *J* = 8.8, 15.6 Hz, 1H), 2.39–2.50 (m, 3H), 6.62 (s-br, 1H), 7.34–7.38 (m, 3H), 7.46–7.52 (m, 2H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) 208.48, 179.14, 136.66, 133.92, 129.36, 127.92, 43.63, 34.37, 29.74, 17.20, –4.34, –4.62.

**Amino acid catalysed Michael addition of acetone to 2; General Procedure.** A mixture of the diester 2 (1 mmol), amino acid (0.2 mmol) and acetone (2 mL) in DMSO or DMF or NMP (8 mL) was stirred at r.t. for appropriate time mentioned in Table 1. The contents were diluted with water (30 mL) and extracted with Et<sub>2</sub>O (3 × 30 mL). The organic extract was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by chromatography to give (±)-4 as a thick oil.

**Ethyl (3RS)-3-dimethyl(phenyl)silyl-2-ethoxycarbonyl-5-oxo-hexanoate [(±)-4].** Following the general procedure, diester 2 (11.3 g, 36.99 mmol), (DL)-tryptophan (1.634 g, 7.4 mmol) and acetone (76 mL) in DMSO after 2 days gave (±)-4. Yield: 13.16 g (98%). *R*<sub>f</sub>: 0.37 (hexane : EtOAc; 10 : 90). IR (film): 1746, 1728, 1250, 1112 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) 0.33 (s, 3H), 0.34 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.97 (s, 3H), 2.30 (q, *J* = 5.9 Hz, 1H), 2.60 (dd, *J* = 5.8, 18.7 Hz, 1H), 2.78 (dd, *J* = 6.5, 18.7 Hz, 1H), 3.48 (d, *J* = 5.6 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 4H), 7.30–7.40 (m, 3H), 7.45–7.55 (m, 2H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) 207.49, 169.78, 169.39, 137.11, 134.15, 129.11, 127.64, 61.25, 61.08, 51.66, 41.66, 29.56, 20.52, 13.87, –3.31, –3.54. MS (EI): *m/z* 349 (M – Me, 3), 287 (12), 189 (15), 135 (Me<sub>2</sub>PhSi, 100), 127 (41), 111 (26), 105 (15), 75 (32). Anal. Calcd for C<sub>19</sub>H<sub>28</sub>O<sub>5</sub>Si (364.516): C, 62.61; H, 7.74%. Found: C, 62.50; H, 7.96%.

**Preparation of Ethyl (3RS)-3-dimethyl(phenyl)silyl-5-oxo-hexanoate [(±)-3] from diester (±)-4.** A stirred mixture of diester (±)-4 (13 g, 35.714 mmol), sodium chloride (4.48 g, 76.58 mmol) and water (1.5 mL) in DMSO (150 mL) was heated at 170°C under nitrogen for 4 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether. The organic extract was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by chromatography to give (±)-3 (8.5 g, 82%) as a colorless oil.



# ACKNOWLEDGMENT

We thank Shreenivas Shreenath and D. P. Mondal of IIT, Kharagpur, for some help.

# REFERENCES

1. Comely, A.C.; Gibson, S.E. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1012 (recent reviews).
2. Guiller, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091 (recent reviews).
3. Brase, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899 (recent reviews).
4. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999 (references cited therein).
5. Kim, K.; Wang, B. *Chem. Commun.* **2001**, 2268.
6. Chao, H.-G.; Bernatowicz, M.S.; Reiss, P.D.; Klimas, C.E.; Matsueda, G.R. *J. Am. Chem. Soc.* **1994**, *116*, 1746.
7. Weigelt, D.; Magnusson, G. *Tetrahedron Lett.* **1998**, *39*, 2839.
8. Wagner, M.; Kunz, H. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 317.
9. Iyer, P.; Ghosh, S.K. *Tetrahedron Lett.* **2002**, *43*, 9437.
10. Hudrlik, P.F.; Hudrlik, A.M.; Nagendrappa, G.; Yimenu, T.; Zellers, E.T.; Chin, E. *J. Am. Chem. Soc.* **1980**, *102*, 6894.
11. Ghosh, S.K.; Singh, R.; Date, S.M. *Chem. Commun.* **2003**, 636.
12. Tucker, C.E.; Knochel, P. *Synthesis* **1993**, 530.
13. Fleming, I.; Newton, T.W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
14. Betancort, J.M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C.F. *Tetrahedron Lett.* **2001**, *42*, 2839.

Received in India July 31, 2003





## **Request Permission or Order Reprints Instantly!**

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Order Reprints" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

### **Request Permission/Order Reprints**

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081SCC120027279>