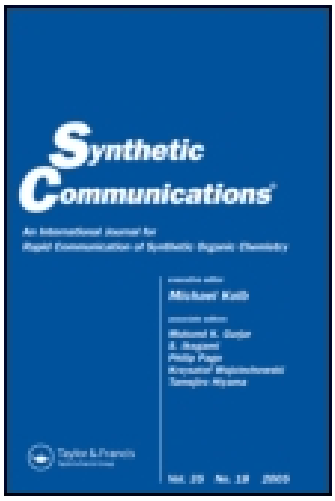

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A Rapid and Efficient Synthesis of a Bifunctional β-Silylketone, Precursor for a Solid Supported β-Silylethanol Anchoring Group

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ABSTRACT

A concise synthesis of 3-dimethyl(phenyl)silyl-5-oxo-hexanoic acid **1**, the precursor for a solid supported β-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: β-Silylketone; Michael addition; Amino acid; Catalysis.

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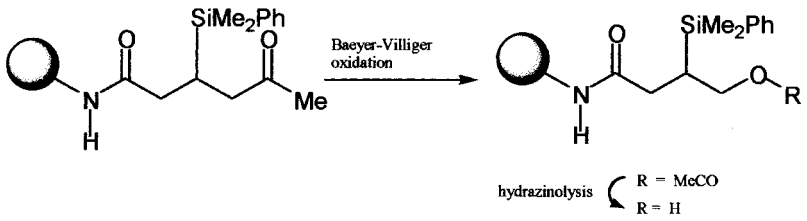
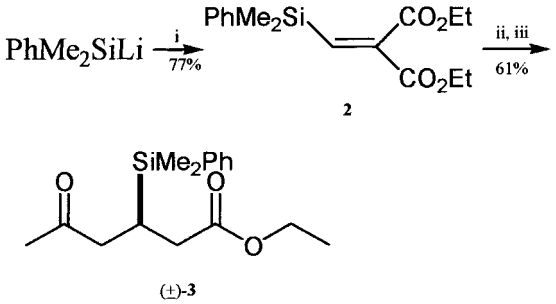
Development of novel linkers between the solid support and the substrates cleavable under mild/specific conditions is an essential attribute of combinatorial chemistry. In this perspective, organosilicon chemistry plays a vital role with the development of many specific linkers.[1–3] The β-(trimethylsilyl)ethyl 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.[4] β-Silylethanol linker could also be transformed into secondary linkers like β-silylethoxymethyl chloride[5] 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 β-elimination mechanism. β-Silylethanol linkers are usually made by multi-step synthesis of a bifunctionalized silane containing the β-silylethanol moiety and a second functional group in solution phase. Subsequently, they are attached to the resin via the latter functionality.[6–8] We[9] have recently applied the regio-directing effect of a silicon group in the Baeyer-Villiger (B-V) oxidation[10] of a resin bound β-silyl ketone to get exclusively the β-silylethyl acetate which was subsequently hydrazinolyzed to provide the resin bound β-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 β-silylethanol anchoring group.

We began our synthesis with the silyl substituted alkylidene malonate **2**.[11] A low yielding (40%) synthesis of this compound was reported by Knochel[12] 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[13] 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) $(EtO)HC{=}C(CO_2Et)_2$, THF, −78 to 0°C; (ii) $EtO_2CCH_2COCH_3$, Et_2NH, room temperature; and (iii) NaCl, DMSO, H_2O, 125–160°C.

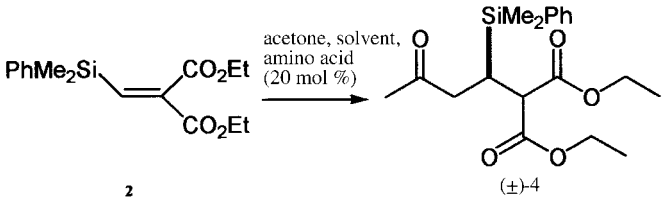
furnished the keto ester **3**. However the last step was tricky and required great care to get the desired keto ester **3** in appreciable yield and purity. Best yield (61%) of **3** could be obtained by sequential heating the intermediate triester at 125°C/24 h, at 140°C/7 h and finally at 160°C for 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[14] 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 β-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 β-silylethanol anchoring group[9] 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_2 or argon atmosphere. THF was dried with sodium/

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

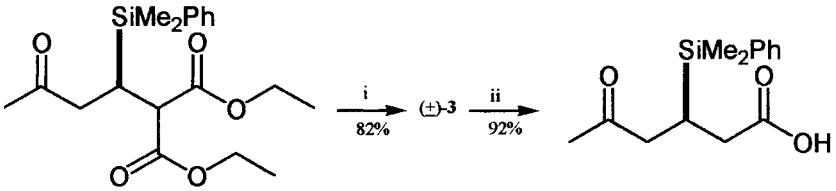


2 (±)-4

Entry	Amino acid[a]	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[b]
5	tyrosine	DMSO/3.5	57[b]
6	valine	DMSO/3.5	62[b]
7	tryptophan	DMSO/2	98

[a]All reactions were conducted at room temperature using DL-amino acids.
[b]Incomplete reaction.

benzophenone and DMSO with CaH_2. Ethyl acetoacetate acetate and diethylamine were freshly distilled before use. Diethyl ethoxymethylene-malonate was obtained from Spectrochem (India). ^1H NMR and ^{13}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.



(±)-4 (±)-1

Scheme 3. Reagents and conditions: (i) NaCl, DMSO, H_2O, 170°C, 4 h; and (ii) NaOH, MeOH, H_2O.

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Ethyl 2-ethoxycarbonyl-3-dimethyl(phenyl)silyl-2-propenoate (2). Dimethyl(phenyl)silyllithium[13] (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°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 (∼25 min), poured into saturated ammonium chloride solution and extracted with Et_2O. The organic extract was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography to give the diester **2** as an colorless oil.[12]

Yield: 21 g, 77%. R_f: 0.6 (hexane : EtOAc; 95 : 5). IR (film): 1731, 1600, 1237, 1115 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 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}C NMR (50 MHz, $CDCl_3$) 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 (M + Na, 15), 307 (M + H, 5), 229 (M − Ph, 100), 201 (82), 173 (41), 155 (37).

Ethyl (*3RS*)-3-dimethyl(phenyl)silyl-5-oxo-hexanoate [(±)-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°C. After stirring for 1.5 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. The organic extract was washed with water and brine, dried (Na_2SO_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°C under nitrogen for 24 h. The bath temperature was raised to 140°C and heated further for 7 h and at 160°C for 7 h. The reaction mixture was diluted with water and extracted with Et_2O. The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by chromatography to give **(±)-3** as an colorless oil. Yield: 3.02 g, 61%. R_f: 0.4 (hexane : EtOAc; 10 : 90) IR(film): 1731, 1251, 1112 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 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, $J = 6.42$ H), 4.02 (q, $J = 7.1$ Hz, 2H), 7.34–7.38 (m, 3H), 7.45–7.52 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) 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 (M^+, 1.8), 277 (22), 247 (10.7), 215 (M − Ph, 100), 135 (24). Anal. Calcd for $C_{16}H_{24}O_3Si$ (292.456): C, 65.71; H, 8.27%. Found: C, 65.44; H, 8.50%.

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(*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_2SO_4) 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^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 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). ^{13}C NMR (50 MHz, $CDCl_3$) 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_2O (3 × 30 mL). The organic extract was washed with water and brine, dried (Na_2SO_4) 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_f: 0.37 (hexane : EtOAc; 10 : 90). IR (film): 1746, 1728, 1250, 1112 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 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). ^{13}C NMR (50 MHz, $CDCl_3$) 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_2PhSi, 100), 127 (41), 111 (26), 105 (15), 75 (32). Anal. Calcd for $C_{19}H_{28}O_5Si$ (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_2SO_4) and evaporated under reduced pressure. The residue was purified by chromatography to give **(±)-3** (8.5 g, 82%) as a colorless oil.

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