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An expeditious synthesis of a β-silylethanol anchoring group by a silicon directed Baeyer–Villiger oxidation on solid-phase

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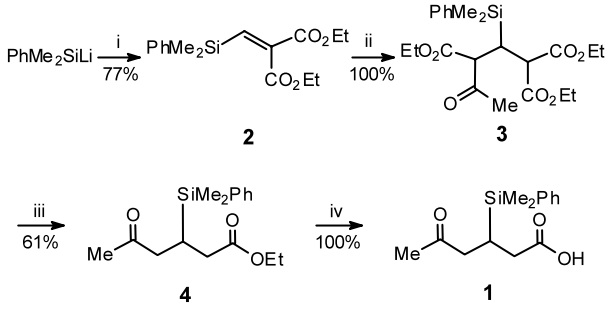
Abstract—A concise synthesis of a β-silylethanol anchoring group on an aminomethylated Merrifield resin has been achieved from 3-dimethyl(phenyl)silyl-5-oxohexanoic acid featuring a solid-phase silicon directed Baeyer–Villiger oxidation of a β-silylketone as the key step.

Organic transformations that can be successfully demonstrated on solid supports, development of novel linkers between the solid support and the substrates cleavable under mild/specific conditions, and the design of new solid phases which can provide favourable reaction surroundings are essential attributes of combinatorial chemistry.[1] In this arena, organosilicon chemistry plays a vital role and has already started showing its fruits with the development of many specific linkers.[2] It is well known that a silicon group exerts a strong β-effect[3] thus controlling the selectivity and the rate of many organic reactions.[4,5] The propensity of β-elimination of organosilicon compounds was first demonstrated by Peterson[6] for olefin synthesis and has subsequently been exploited for the development of β-silylethyl based protecting groups[7] for many functionalities. 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.[8] Silicon linkers based on the trimethylsilylethyl ester group have, therefore, been designed to be cleaved by a β-elimination mechanism. Polymer bound β-silylethanols are made either by hydroboration-oxidation of polymer bound vinyl silanes[9,10] or by multi-step synthesis of bifunctionalized silanes containing the β-silylethanol and a second functional group in solution phase and subsequent attachment to a resin via the latter functionality.[11–13] We envisaged that the regio-directing effect of a silicon group could possibly be used in solid-phase organic reactions. It is known that the Baeyer–Villiger (B–V) oxidation of a β-silyl ketone is controlled[14] by the silicon substituent and gives exclusively the β-silylethyl ester. Herein, we report a comprehensive method for the direct generation of the β-silylethanol linker on a Merrifield solid support with a good loading capacity.

The β-silyl-5-oxohexanoic acid **1** was prepared as shown in Scheme 1. Addition of dimethyl(phenyl)-silyllithium to diethyl ethoxymethylenemalonate 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 triester **3** which on Krapcho decarboxylation provided the ethyl 3-silyl-5-oxohexanoate **4** in 61% overall yield from **2**. Its hydrolysis gave the desired keto-acid **1** in quantitative yield.



Scheme 1. *Reagents and conditions*: i. diethyl ethoxymethylenemalonate, THF, −78 to 0°C; ii. $EtO_2CCH_2COCH_3$, Et_2NH, room temperature; iii. NaCl, DMSO, H_2O, 125–160°C; iv. NaOH, MeOH, H_2O.

Keywords: β-silylethanol; Baeyer–Villiger oxidation; silicon directed; solid-phase synthesis; anchoring group.

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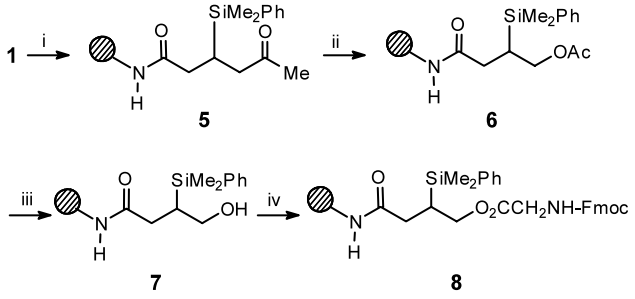
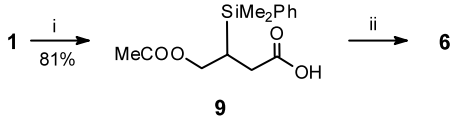
The Merrifield resin was first aminomethylated[15] (amine capacity 0.6 mmol/g) and reacted with the keto acid **1** to provide the resin bound methyl ketone **5** (Scheme 2). This, on B–V oxidation, gave the resin bound acetate **6**. The acetyl group was successfully removed by hydrazinolysis in *N*-methylpyrrolidone to give the resin bound alcohol **7**. For the determination of the OH capacity of this resin, it was coupled with *N*-Fmoc-Gly via the 1-hydroxybenzotriazolyl active ester to give **8**. The loading capacity was estimated† (0.52 mmol/g of resin; ca. overall 87% over five steps based on the initial loadings) after its deprotection and measurement of the UV for the Fmoc-derived chromophore liberated upon treatment with 20% piperidine–DMF.[16] The high loading value attests that all the reactions performed on the solid-phase must have taken place with high selectivity and conversions.

The selectivity and the efficacy of the silicon directed B–V oxidation on solid-phase is the key feature of the above strategy. For a critical assessment of these aspects, the acid **9** was first prepared in solution phase (in very good yield) from the keto acid **1** by a Si-directed B–V oxidation as shown in Scheme 3. The acid **9** on subsequent coupling with aminomethylated resin (amine capacity 0.6 mmol/g) provided the resin bound acetate **6**. Hydrazinolysis gave the resin bound β-silyl alcohol **7** which was coupled with *N*-Fmoc-Gly to give **8**. The loading capacity[16] of **7** prepared by this route was found† to be 0.54 mmol/g (overall 90% over four steps). This confirmed that the



Scheme 2. *Reagents and conditions*: i. aminomethylated Merrifield resin, DCCI, pentafluorophenol, DMAP, CH_2Cl_2, 0°C to room temperature; ii. MCPBA, Na_2HPO_4, CH_2Cl_2, 0°C to room temperature; iii. 15% N_2H_4 in NMP, room temperature; iv. Fmoc-Gly, DIC, 1-HOBt, DMAP, 0°C to room temperature. 2.5–3 equivalents of reagents with respect to resin amine capacity were used. Reactions on solid-phase were monitored by recording FT-IR of resin samples as KBr disks.



Scheme 3. *Reagents and conditions*: i. MCPBA, Na_2HPO_4, CH_2Cl_2, room temperature; ii. aminomethylated Merrifield resin, DIC, pentafluorophenol, DMAP, pyridine.

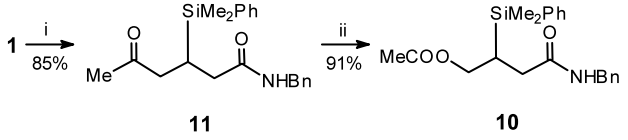
† Capacity based on capacity of the aminomethylated resin.

silicon-directed B–V oxidation on solid-phase had taken place with complete regiocontrol and in a quantitative manner.

To establish a suitable cleavage protocol for this β-silylethyl linker **7**, we first established the cleavage conditions using the acetate amide **10** in solution which was made from keto acid **1** via keto amide **11** as shown in Scheme 4. The best conditions for cleavage were $BF_3{\cdot}OEt_2$ (0.05 M) in dichloromethane or chloroform and the cleavage was complete within 15 min at room temperature.

The acetate resin **6** was subjected to cleavage under the above conditions which was completed within 1 h as monitored by IR of the cleaved resin. The cleavage of the Fmoc-Gly coupled resin **8** was slower than that of **6**, but proceeded smoothly with 0.1 M $BF_3.OEt_2$ in dichloromethane. After 6 h at room temperature, the amount of Fmoc-Gly recovered corresponded to 70–75% cleavage.

In order to evaluate further the scope of attaching different substrates onto the solid supported β-silylethyl linker **7**, different cleaving reagents/conditions and the possibility of the use of Merrifield aminomethylated resin with higher loading capacity (amine capacity 0.92 mmol/gm) were studied. For this, we coupled Fmoc-Gly and Fmoc-Phe to the linker **7** (OH capacity 0.81 mmol/g) and studied their cleavage using 0.1 M $BF_3{\cdot}OEt_2$ in dichloromethane. The time dependent cleavage of Fmoc-Gly‡ is presented in Fig. 1 which showed that the initial rate of cleavage was faster and became sluggish after 4.5 h. At this time, the amount of cleaved Fmoc-Gly corresponds to 74% cleavage based on initial loadings. The amount of Fmoc-Gly obtained



Scheme 4. *Reagents and conditions*: i. $BnNH_2$, DCCI, DMAP, CH_2Cl_2; ii. MCPBA, Na_2HPO_4, CH_2Cl_2, 0°C to room temperature.

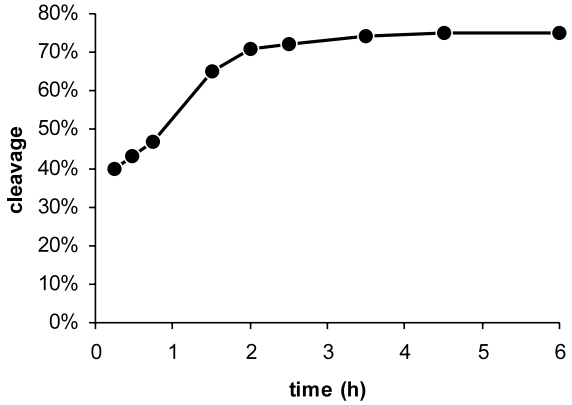
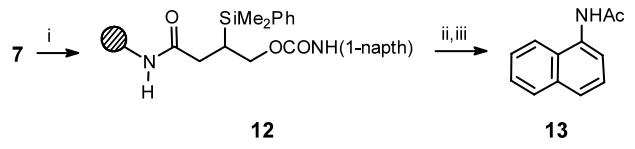


Figure 1. Course of cleavage of Fmoc-Gly from **8**.

‡ Cleavage was monitored by measurement of UV absorption at $\lambda = 300$ nm ($\varepsilon = 4636$).

after 12 h was quantified[§] which corresponds to 71% cleavage. Under the same conditions Fmoc-Phe was also quantified[§] and the amount also corresponded to 71%. The cleavage of Fmoc-Gly from the resin using TBAF in dichloromethane[13] was also carried out, but the Fmoc group was only partially cleaved.[¶] For the attachment of 1-naphthylamine onto the resin, the linker **7** (OH capacity 0.81 mmol/gm) was reacted with 1-naphthylisocyanate which provided the resin bound carbamate of 1-naphthylamine **12** as shown in Scheme 5. The cleavage of 1-naphthylamine from **12** was achieved using 0.1M TBAF in dichloromethane and was quantified[‖] (79% based on OH capacity) and characterized as its acetate **13**.

In conclusion, we have achieved the synthesis of a β-silylethanol anchoring group on an aminomethylated Merrifield resin from 3-silyl-5-oxohexanoic acid **1**. The present approach demonstrated a highly regioselective and efficient silicon directed B–V oxidation on solid-phase format for the first time, to the best of our knowledge. The versatility of this linker has been demonstrated using two different capacities of the resin, two functionality attachments and under two cleavage conditions. Similar to the preparation[17] of β-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl)[8] from β-trimethylsilylethanol, the resin bound β-silylethyl alcohol group linker can also be easily converted to a β-silylethoxymethyl chloride[18] which will broaden its use for the attachment of functionalized molecules such as alcohols, amines, carboxylic acids and phenolic compounds on the resin. The silylethanol linker can also be prepared in enantiomerically pure form using easily accessible optically pure



Scheme 5. *Reagents and conditions*: i. 1-naphthylisocyanate, DMAP, Et_3N, $CHCl_3$, reflux; ii. $TBAF{\cdot}3H_2O$, CH_2Cl_2; iii. Ac_2O, pyridine, CH_2Cl_2. 2.5–3 equivalents of reagents with respect to resin amine capacity were used. Reactions on solid-phase were monitored by recording FT-IR of resin samples as KBr disks.

β-silyl-keto acids.[19] This is expected to assist in carrying out asymmetric transformations on solid-phase. Therefore, the silicon based linkers which work on the principle of β-elimination[9–13] or otherwise[20] will enrich solid-phase library synthesis because of their specific advantages.

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References

1. For a few recent monographs, see: (a) *Combinatorial Peptide and Nonpeptide Libraries*; Jung, G., Ed., VCH: Weinheim, 1996; (b) *Combinatorial Libraries, Synthesis, Screening, and Application Potential*; Cortese, R. Ed., Walter de Gruyter & Co.: Berlin, 1996; (c) *Molecular Diversity and Combinatorial Chemistry, Libraries and Drug Discovery*; Chaiken, I. M.; Janda, K. D., Eds., ACS Books: Washington, 1996; (d) *Combinatorial Chemistry:Synthesis and Applications;* Wilson, S. H.; Czarnik, A. W., Eds., Wiley & Sons: New York, 1997; (e) *A Practical Guide to Combinatorial Chemistry;* Czarnik, A. W.; DeWitt, S. H., Eds., ACS Books: Washington, 1997; (f) *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Obrecht, D.; Villalgordo, J. M., Eds., Pergamon, 1998; (g) *Combinatorial Chemistry: A Practical Approach*; Bannwarth, W.; Felder,E., Eds., Wiley-VCH: Weinheim, 2000; (h) *Practical Solid-Phase Synthesis; A Book Companion*: Kates, S. A.; Albericio, F., Eds., Marcel Dekker: New York, 2000; (i) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies;* John Wiley & Sons: New York, 2001.
2. For a few recent reviews, see: (a) Comely, A. C.; Gibson, S. E. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1012–1032; (b) Guiller, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157; (c) Brase, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899–1905.
3. Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677–2689.
4. Verma, R.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2377–2381.
5. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192.
6. (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784; (b) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag, 1983; pp. 58–78.
7. (a) Sieber, P. *Helv. Chim. Acta.* **1977**, *60*, 2711–2716; (b) Gerlach, H. *Helv. Chim. Acta.* **1977**, *60*, 3039–3044.
8. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999 and references cited therein.
9. Alonso, C.; Nantz, M. H.; Kurth, M. J. *Tetrahedron Lett.* **2000**, *41*, 5617–5622.
10. Wang, B.; Chen, L.; Kim, K. *Tetrahedron Lett.* **2001**, *42*, 1463–1466.

[§] A suspension of resin bound Fmoc-Gly **8** (178 mg) in 0.1M $BF_3.OEt_2$ in dichloromethane (15 ml) was shaken for 12 h. The resin was filtered, washed with dichloromethane and methanol, and the filtrate was evaporated. The residue was esterified with diazomethane and Fmoc-Gly-OMe (26 mg) was isolated after chromatographic purification.

[¶] Partial cleavage of the Fmoc group took place to give Gly as monitired by TLC with ninhydrin.

[‖] A suspension of resin bound 1-naphthylamine **12** (211 mg) in 0.1M $TBAF{\cdot}3H_2O$ in dichloromethane (5 ml) was shaken for 12 h. The resin was filtered, washed with dichloromethane. The filtrate was washed with water and evaporated. The residue was acetylated with acetic anhydride in pyridine. Acetate **13** (22 mg) was isolated after chromatographic purification.

11. Chao, H.-G.; Bernatowicz, M. S.; Reiss, P. D.; Klimas, C. E.; Matsueda, G. R. *J. Am. Chem. Soc.* **1994**, *116*, 1746–1752.
12. Weigelt, D.; Magnusson, G. *Tetrahedron Lett.* **1998**, *39*, 2839–2842.
13. Wagner, M.; Kunz, H. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 317–321.
14. Hudrlik, P. F.; Hudrlik, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T.; Chin, E. *J. Am. Chem. Soc.* **1980**, *102*, 6894–6896.
15. (a) Mitchell, A. R.; Kent, S. B. H.; Erickson, B. W.; Merrifield, R. B. *Tetrahedron Lett.* **1976**, *17*, 3795–3798; (b) Sparrow, J. T. *J. Org. Chem.* **1976**, *41*, 1350–1353.
16. Chan, W. C.; Mellor, S. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1475–1477.
17. Corey, E. J.; Gras, J.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809–812.
18. Kim, K.; Wang, B. *Chem. Commun.* **2001**, 2268–2269.
19. (a) Singh, R.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 7711–7715; (b) Verma, R.; Mithran, S.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 257–264; (c) Verma, R.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 265–270; (d) Verma, R.; Ghosh, S. K. *Chem. Commun.* **1997**, 1601–1602.
20. (a) Ramage, R.; Barron, C. A.; Bielecki, S.; Holden, R.; Thomas, D. W. *Tetrahedron* **1992**, *48*, 499–514; (b) Ramage, R.; Barron, C. A.; Bielecki, S.; Thomas, D. W. *Tetrahedron Lett.* **1987**, *28*, 4105–4108; (c) Routledge, A.; Thijs Stock, H.; Flitsch, S. L.; Turner, N. J. *Tetrahedron Lett.* **1997**, *38*, 8287–8290; (d) Mullen, D. G.; Barany, G. *J. Org. Chem.* **1988**, *53*, 5240–5248.