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Preparation of novel 2-(trialkylsilyl)ethyl linkers and first synthesis of Tryprostatin B on solid phase

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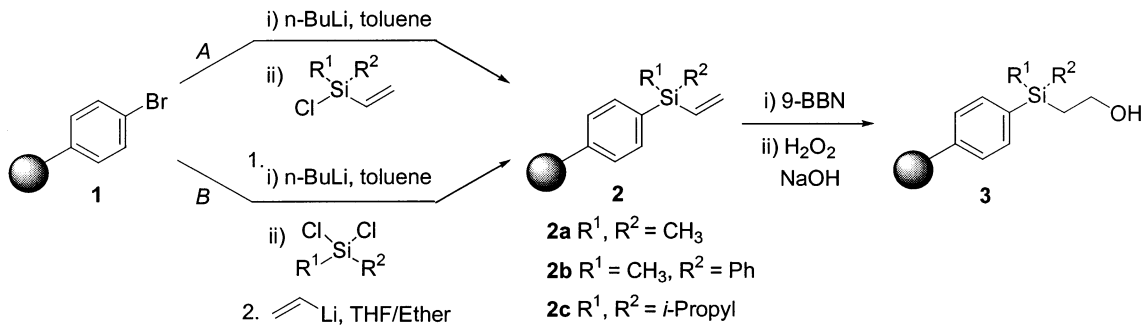
Abstract—Two synthetic methods for novel polymer-supported 2-(trialkylsilyl)ethanol linkers **3** are described. The new silyl linker has been examined as a C-terminal linkage to provide several diketopiperazines. Using this synthetic method, the first solid phase synthesis of Tryprostatin B was accomplished. Several functionalized 2-(trialkylsilyl)ethyl linkers **12**–**17** are synthesized from 2-(trialkylsilyl)ethanol linkers. During the course of preparations, the new silyl linkers proved resistant to various reaction conditions such as basic and moderately acidic media, oxidation, and elevated thermal conditions.

Solid phase synthetic methodologies have played an important role in the successful application of high-throughput chemistry to accelerate the pharmaceutical lead generation and lead optimization process.[1] In order to expand the scope of functional groups and chemistries that can be adapted to solid phase, there is a continuing need for the development of new linkers.[2] A representative linker is Si-based, where the corresponding substituted silicon commonly serves as a protecting group in solution phase. While several applications using Si on solid phase have been reported as a traceless linker or silyl-based spacer, our interest in developing new silicon-based linkers has led us to explore more diverse polymeric silyl linkers and their facile applications to library synthesis.[3] Herein, we report a series of convenient methods to prepare polymer-supported 2-(trialkylsilyl)ethyl linkers and describe their application for solid phase synthesis.[4]

Several preparative methods of 2-(trialkylsilyl)ethanols and their applications for the protection of carboxylic acids and alcohols have been reported.[5] Based on the preliminary results in solution phase, we designed the polymer-bound 2-(trialkylsilyl)ethanol resins with careful consideration of the possibility of 'protodesilation' or 'Peterson olefination'.[6] The silyl linker synthesis outlined in Scheme 1 starts with direct lithiation[7] of commercially available 4-bromopolystyrene resin **1**. Chlorodimethylvinylsilane or methyl-phenyl-vinylchlorosilane was added to 4-lithiated polystyrene resin in a THF solution to provide the corresponding polymer-bound vinylsilane **2a** or **2b** in high yield



Scheme 1.

Keywords: combinatorial chemistry; protecting group; solid-supported reagent.

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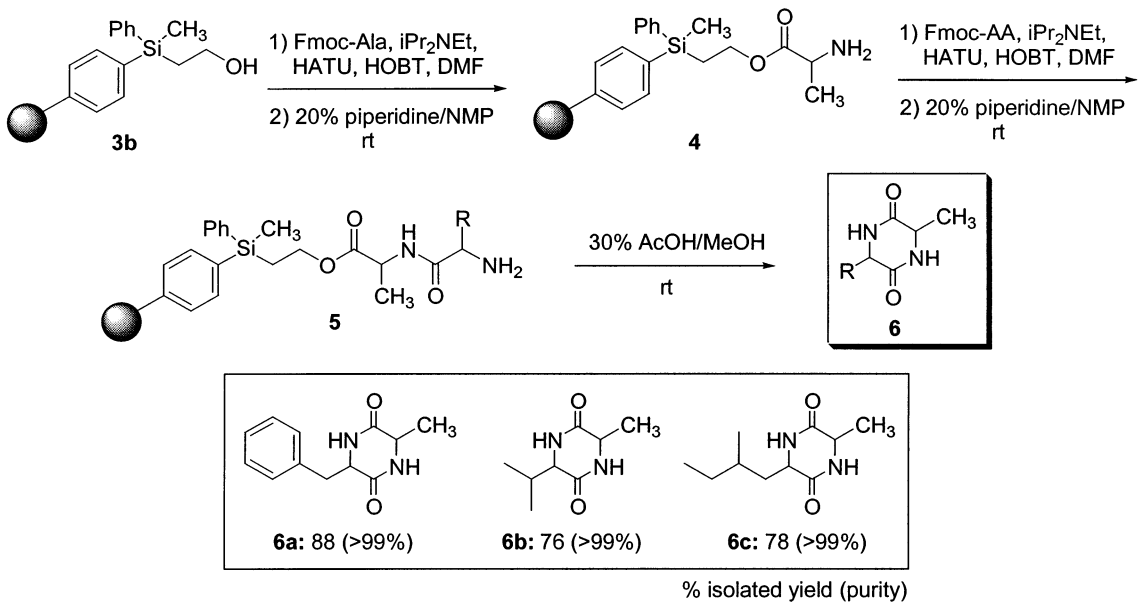
(>90%) (method A). Following hydroboration of the vinylsilanes **2** with 9-BBN and subsequent oxidation, the desired polymer-bound 2-(trialkylsilyl)ethanol linker **3a** or **3b** was successfully prepared in 67–85% yield.[8] However, due to a lack of commercially available chlorodialkylvinylsilanes, a different synthetic route was explored. To this end, dialkyldichlorosilanes were employed to introduce various polymer-supported vinylsilanes. Diisopropyldichlorosilane addition to the 4-lithiated polystyrene resin in a THF solution followed by the addition of vinyllithium provided diisopropylvinylsilane **2c** in 71% yield (method B).[9] It is important that vinyllithium should be prepared immediately before use to get a good yield. The sequential hydroboration and oxidation of polymer-bound diisopropylvinylsilane **2c** provided the corresponding silyl ethanol resin **3c** in 58–70% yield. The polymeric 2-(trialkylsilyl)ethanol linkers **3** can be successfully prepared in 15–25 g scale. The final resin loadings were determined to be 0.9–1.3 mmol/g.[10]

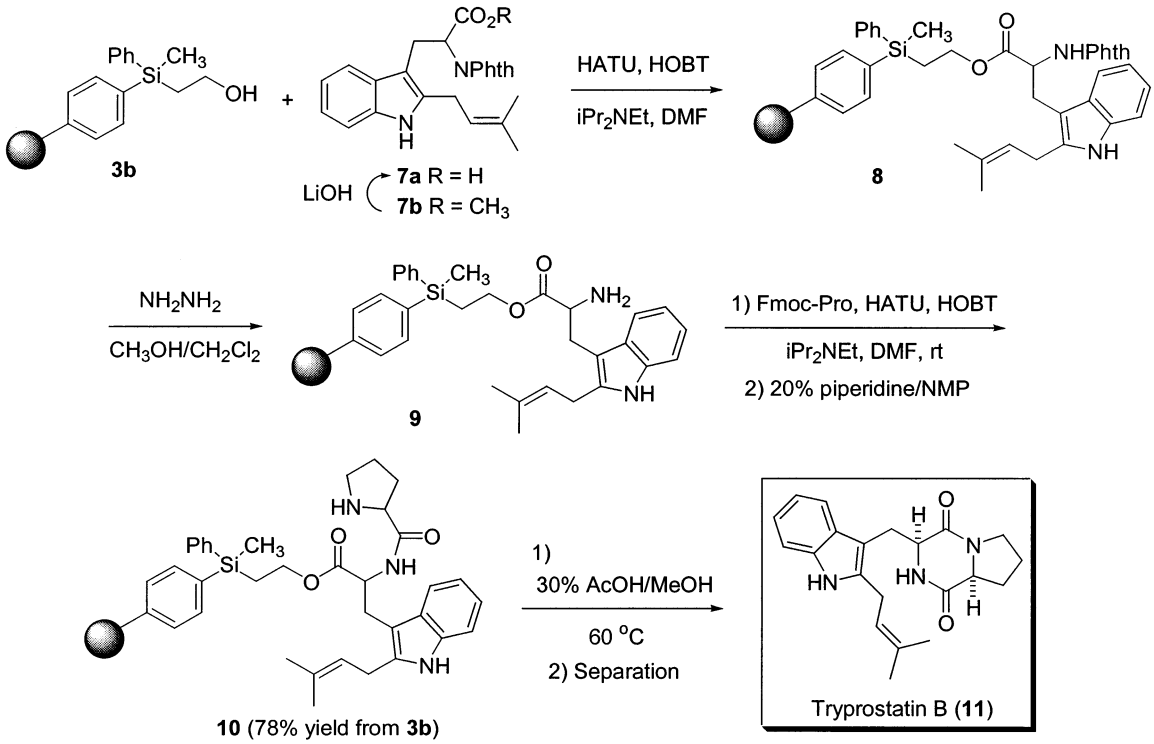
After synthesizing diverse silyl linkers, we investigated their application in solid phase synthesis. The acylation of polymeric 2-(diphenylmethylsilyl)ethanol linker **3b** with Fmoc-Ala using standard coupling conditions followed by subsequent amino acid coupling and Fmoc deprotection yielded dipeptide **5** (Scheme 2). Cleavage of the silyl linker in acidic media induced cyclization to provide diketopiperizines **6** in high yield (76–88%) and purity (>99%).[11] This silyl linker application directed toward the synthesis of diketopiperazines proved efficient and convenient at the final cleavage step when compared with the approach derived from Wang resin.[12] The isolated yield and purity of some diketopiperizines are given in Scheme 2.

Further application of our new silyl linkers was examined for a more complicated diketopiperazine, Tryprostatin B (**11**) (Scheme 3). This natural product isolated from *Aspergillus fumingatus* prevents the interaction between microtubule-associated proteins with the carboxy-terminal domain of tubulin.[13] The coupling of prenyltryptophan derivative **7a** prepared from the corresponding methyl ester **7b**[14] and silyl resin **3b** was successfully conducted to provide **8**. Hydrazinolysis of **8** followed by Fmoc-Pro coupling and deprotection of Fmoc afforded **10** in 78% yield from **3b**. The loading capacity of **10** was determined to be 0.43 mmol/g based on quantitation of the Fmoc chromophore. Subsequent acid-induced cyclization provided the desired Tryprostatin B (**11**) and the corresponding diastereoisomer in 76% yield with 100% purity. The physical and spectral data of **11** are consistent with those of Tryprostatin B synthesized by Danishefsky and colleagues.[14,15]

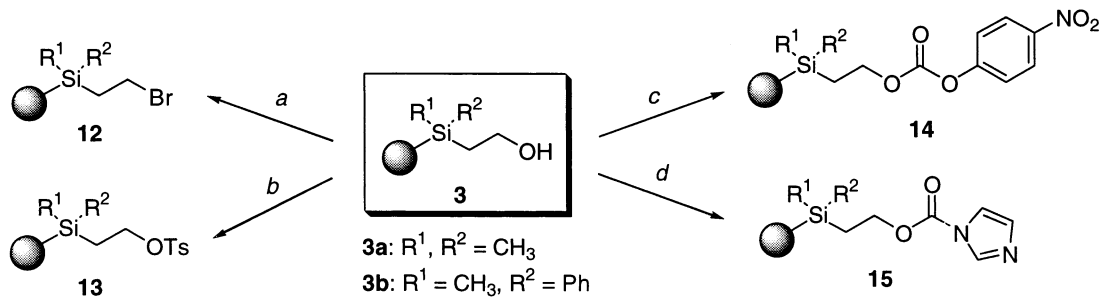
We next turned our attention to the modifications of 2-(trialkylsilyl)ethanol linker **3** to explore various functionalized 2-(trialkylsilyl)ethyl linkers. Our initial efforts were directed toward the preparation of polymer-supported 2-(trialkylsilyl)ethyl bromide **12**, tosylate **13**, 4-nitrophenyl carbonate **14**, and imidazolide carbamate **15** (Scheme 4). Similar applications have frequently been utilized in solution phase as protection groups for 2-(trimethylsilyl)ethyl carbamate (Teoc-NR_2), carbonate (TMSEC), and glycoside (TMSEt-glycoside).[16] Mild bromination conditions were chosen to prepare silyl bromide linker **12** using the preformed adducts of triphenylphosphine with carbon tetrabromide. For the tosylation, a solution of 2-(trialkylsilyl)ethanol resin **3**, *p*-toluenesulfonyl chloride, and pyridine in CH_2Cl_2 was shaken overnight to afford tosylate **13**. In order to verify the progress of both bromination and tosylation, the disappearance of the O–H stretch at 3428 cm^{-1} was monitored by FT-IR spectroscopy. Carbonate **14** and imidazolide carbamate **15** resins were successfully prepared from the standard coupling conditions. After acylation of **3** with either 4-nitrophenyl chloroformate or 1,1′-dicarbonylimida-



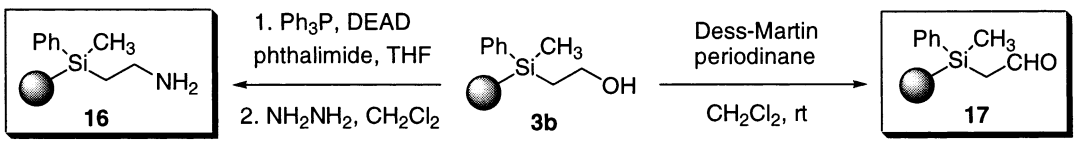
Scheme 2.



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) PPh_3 (5.0 equiv.), CBr_4 (5.0 equiv.), THF, overnight, rt. (b) *p*-toluenesulfonyl chloride (5.0 equiv.), pyridine (10 equiv.), CH_2Cl_2, rt. (c) 4-nitrophenyl chloroformate (2.5 equiv.), NMM (5.0 equiv.), CH_2Cl_2, 0°C→rt. (d) 1,1′-dicarbonylimidazole (5.0 equiv.), THF, rt.



Scheme 5.

zole, the O–H stretch at 3428 cm^{-1} disappeared and a new C=O stretch was observed at 1761 and at 1762 cm^{-1}, respectively. These silyl-based linkers are resistant to the described reaction conditions and are envisioned to serve as precursors that can be easily attached to various scaffolds possessing an amine or alcohol functional group. The final loading capacity of each linker was determined by bromine (**12**), sulfur (**13**), and nitrogen (**14** and **15**) elementary analysis.[17]

Further modifications were explored to provide more diverse Si-based linkers (Scheme 5). A Mitsunobu reaction of **3b** with phthalimide followed by hydrazinolysis was carried out to obtain amino-substituted silyl linker **16** in two steps with a 71% yield overall. The loading capacity of **16** was determined to be 1.05 mmol/g by quantitation of the Fmoc chromophore after acylation with Fmoc-Ala and was confirmed by nitrogen analysis. Several oxidation conditions were examined for the

preparation of silyl aldehyde **17**. We determined that Dess–Martin periodinane proved to be most efficient oxidant to provide the desired silyl aldehyde **17**. The progress of oxidation was monitored by FT-IR spectroscopy. The O–H stretch of **3b** disappeared and simultaneously the C=O stretch of aldehyde at 1703 cm^{-1} and the corresponding H–C stretch at 2721 cm^{-1} were observed.

In conclusion, several polymer-supported 2-(trialkylsilyl)ethanol linkers **3** were prepared using two different synthetic pathways. Because the novel silyl-based resins are found to be resistant to various reaction conditions used in peptide synthesis, our initial efforts were directed toward application of the silyl linker as a C-terminal linkage. Using the silyl linker, diketopiperazine synthesis on solid phase was successfully carried out with high yield and purity. In addition, the first solid phase synthesis of Tryprostatin B was accomplished. Polymer-supported 2-(trialkylsilyl)ethyl bromide **12**, tosylate **13**, 4-nitrophenyl carbonate **14**, imidazolide carbamate **15**, amine **16**, and aldehyde **17** were also prepared from 2-(trialkylsilyl)ethanol linkers **3**. The new synthetic silyl linkers can be applied as protecting groups, traceless linkers, and polymer-supported reagents. Additional details and applications of silyl linkers will be reported in a full account of this work.

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8. β-Dimethylphenylsilylethyl linker **3a** was independently prepared by M. Kurth and his colleagues: *Tetrahedron Lett.* **2000**, *41*, 5617–5622.
9. The yield and loading of **2** determined by silicon elementary analysis: **2a** ($R^1=CH_3$, $R^2=CH_3$; 95%, 1.85 mmol/g), **2b** ($R^1=CH_3$, $R^2=$Ph; 90%, 1.77 mmol/g), **2c** ($R^1=$*iso*-propyl, $R^2=$*iso*-propyl; 71%, 1.38 mmol/g).
10. The respective yield and loading was determined by silicon elementary analysis and confirmed by quantitation of the Fmoc chromophore after acylation with Fmoc-alanine. General procedures for the preparation of 2-(trialkylsilyl)ethanol linkers **3** are described as follows: to a stirred solution of vinylsilane **2** (1.0 equiv.) in dry THF (0.2 M) solution at 0°C was added slowly 9-BBN in THF (0.5 M, 3.0 equiv.) and the mixture was allowed to warm to room temperature. After shaking overnight, the mixture was cooled to 0°C and water was cautiously added followed by the dropwise addition of equal volumes of 3 M NaOH and 30% hydrogen peroxide, respectively (volume equal to volume of 9-BBN solution). After stirring overnight at 40°C, the resin was filtered, washed and dried in vacuo at 40°C overnight to provide **3**.
11. The purity was determined by a C18 reverse phase HPLC column, WR-C18 3u 120A (30×3.2 mm) of ES Industries in 10–90% CH_3CN/H_2O containing 0.02% TFA and monitored at 215 nm using a UV detector and by SEDEX 55 Evaporative Light Scattering Detector (ELSD). The purity scores reported herein are based on ELSD.
12. We examined the diketopiperazines synthesis using Wang resin. Numerous cleavage conditions were attempted such as acid- or base-induced cyclization and elevated reaction temperature. However, only moderate results were achieved in refluxing toluene to yield **6a–c** in high purity (87–97%), but poor isolated yield (8–23%).
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15. Tryprostatin B **(11)** synthesized on solid phase: $[\alpha]_D^{25}=-74$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.47 (d, $J=7.7$ Hz, 1H), 7.32 (d, $J=8.1$ Hz, 1H), 7.15 (t, $J=8.1$ Hz, 1H), 7.11 (t, $J=8.1$ Hz, 1H), 6.10 (s, 1H), 5.4–5.21 (br s, 1H), 5.31 (t, $J=7.3$ Hz, 1H), 4.42 (br d, $J=8.1$ Hz, 1H), 4.08 (t, $J=7.3$ Hz, 1H), 3.71–3.40 (m, 4H), 3.0 (dd, $J=15$ Hz, 11 Hz, 1H), 2.39–2.27 (m, 1H), 2.05–1.85 (m, 3H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 165.9, 136.7, 135.5, 135.4, 127.9, 121.9, 119.9, 119.6, 117.7, 110.8, 104.1, 59.2, 54.7, 45.5, 28.3, 25.7, 25.1, 22.5, 17.9; HRMS (FAB) calculated for $C_{21}H_{25}N_3O_2$ $(M)^+$ 351.1947, found 351.1954.
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17. The yield and loading determined by elementary analysis follow: **12** (42% yield, loading: 0.5 mmol/g), **13** (94% yield, loading: 1.13 mmol/g), **14** (72%, loading: 0.86 mmol/g), **15** (quantitative yield, loading: 1.28 mmol/g).