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Enantioselective α-Silyl Amino Acid Synthesis by Reverse-Aza-Brook Rearrangement

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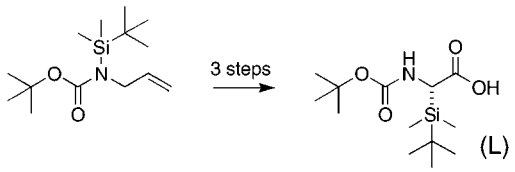
ABSTRACT



Asymmetric reverse-aza-Brook rearrangement of *N*-Boc-*N*-trialkylsilyl allylamine yields an enantiomerically enriched α-amino allylsilane. Oxidative cleavage of the alkene leads to a Boc-protected amino acid with the configuration of naturally occurring amino acids (L). Standard coupling protocols, including the use of trifluoroacetic acid for removal of the Boc group, yield a tripeptide with a central silane amino acid.

Unnatural amino acids are important tools for probing the interplay between amino acid structure and peptide conformation.[1] Introduction of unnatural amino acids into peptide sequences can also lead to enhanced stability in vivo.[2] In addition, they can be building blocks of catalysts and reagents designed for asymmetric synthesis.[3]

Derivatives and analogues of the natural amino acids that incorporate organosilanes, Figure 1, have been developed

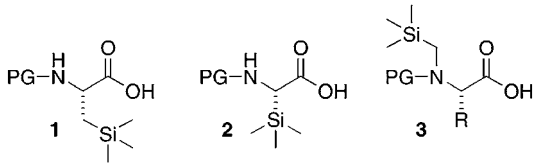


Figure 1. Trialkylsilane-substituted amino acids (PG = protecting group).

over nearly five decades.[4] Birkofer prepared the first examples of silylalanine (±)-**1**[4a] and several studies have found that peptides incorporating this amino acid can have potent biological activity.[5] Very recently, the first examples of **2** have been described in which the silicon is attached directly to the amino acid backbone.[6,7] Moeller has reported the synthesis of a third type, *N*-silylmethyl-substituted amino acids **3**, and their use in chemical transformations of polypeptides.[8]

α-Silyl amino acids related to **2** have been prepared only three times, as outlined in Scheme 1. Metalation between nitrogen and silicon to give **4** followed by addition to ethyl chloroformate gave **6**.[9] Rhodium acetate-mediated insertion of diazoester **7** into a nitrogen−hydrogen bond led to **9** in

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(2) Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963−978.

(3) Mori, A.; Abe, H.; Inoue, S. *Appl. Organomet. Chem.* **1995**, *9*, 189−197.

(4) (a) Birkofer, L.; Ritter, A. *Angew. Chem.* **1956**, *68*, 461−462. (b) Birkofer, L.; Ritter, A. *Liebigs Ann. Chem.* **1958**, *612*, 22−33. (c) See also: Tacke, R.; Handmann, V. I. *Organometallics* **2002**, *21*, 2619−2626 and references therein.

(5) For examples, see: Weidmann, B. *Chimia* **1992**, *46*, 312−313. Wienand, A.; Ehrhardt, C.; Metternich, R.; Tapparelli, C. *Bioorg. Med. Chem.* **1999**, *7*, 1295−1307. Tacke, R.; Merget, M.; Bertermann, R.; Bernd, M.; Beckers, T.; Reissmann, T. *Organometallics* **2000**, *19*, 3486-3497.

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(7) Chen, J.-X.; Tunge, J. A.; Norton, J. R. *J. Org. Chem.* **2002**, *67*, 4366−4369.

(8) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547−1550. Sun, H.; Moeller, K. D. *Org. Lett.* **2003**, *5*, 3189−3192.

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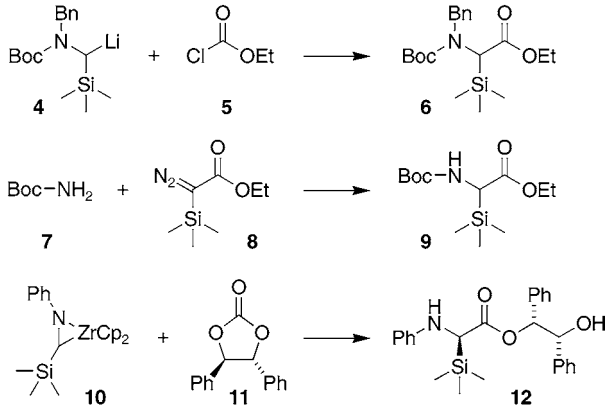
Scheme 1. Silane Amino Acid Syntheses



high yield.[6] The reactions leading to **6** and **9** result in racemic products and in the latter case were separated by chiral HPLC. Reaction of (*R*,*R*)-**11** with zirconium substrate **10** gave *N*-phenyl silyl ester **12** in good yield and with excellent diastereoselectivity.[7]

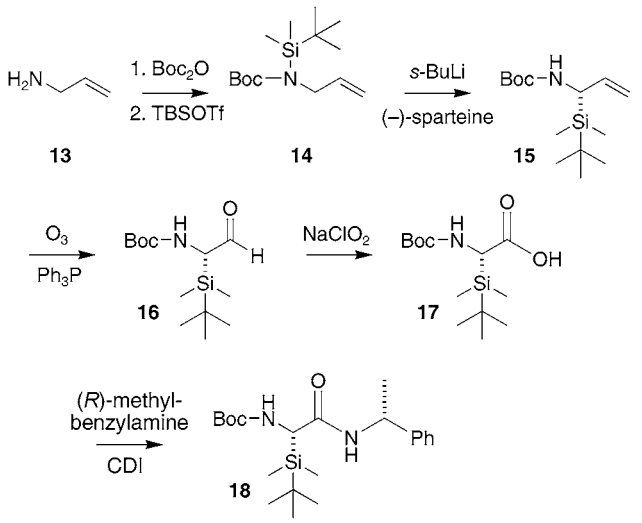
We recently reported an enantioselective rearrangement of compounds such as **14**, easily prepared in two steps from allylamine.[10] Metalation of **14** with a mixture of (−)-sparteine and *sec*-butyllithium gave **15** in high yield and with up to 95% enantiomeric excess. The (*S*) stereochemistry of the product was determined by X-ray crystallography of a derivative of a closely related structure (methyldiphenylsilyl instead of *tert*-butyldimethylsilyl).[10]

The stereochemistry of **15** appeared to be ideal for preparation of silane analogues of L-amino acids, through oxidative cleavage of the alkene.[11] When **15** was treated at −78 °C with ozone in methylene chloride followed by a triphenylphosphine workup, aldehyde **16** was produced. While the parent structure trimethylsilyl acetaldehyde is very unstable,[12,13] aldehyde **16** could be purified by flash chromatography in 80% yield. When the crude aldehyde **16** was subjected to Pinnick oxidation, chromatography gave acid **17** in 73% overall yield from **15**.

The stereochemical integrity of the transformation was evaluated by coupling acid **17** with (*R*)-α-methyl benzyl amine. Starting with a sample of silane **15** with an enantiomeric ratio of 4:1, the amide **18** was formed as a 4:1 mixture of diastereomers, indicating that the oxidation had proceeded with little or no epimerization.

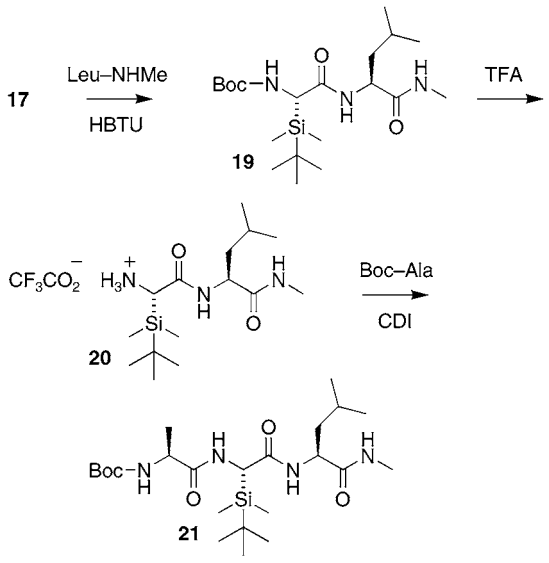
The robustness of this unnatural amino acid toward standard peptide coupling chemistry was also investigated. Coupling acid **17** with the *N*-methyl amide of leucine, using HBTU, gave **19** in 88% yield. The Boc protecting group of **19** was then removed with trifluoroacetic acid. While this

Scheme 2. Allyl Silane Oxidation



step has the potential for rearrangement of the α-silyl carbonyl,[12] no decomposition was observed. Coupling of **20** with Boc-protected alanine that had been activated with carbonyl diimidazole gave the tripeptide **21** in 50% yield for the two steps. This sequence was carried out with use of a sample of **17** that had an enantiomeric ratio of 2:1 and the diastereomers were carried through the sequence without change in their ratio, consistent with little or no epimerization. This is the first tripeptide incorporating an α-silyl amino acid, and its preparation demonstrates its compatibility with standard coupling procedures.

Scheme 3. Tripeptide Synthesis



The chemistry reported here is a practical method for asymmetric α-silyl amino acid synthesis.[14] The use of commercially available (−)-sparteine during the Brook

(9) Sieburth, S. McN.; Somers, J. J.; O'Hare, H. K. *Tetrahedron* **1996**, *52*, 5669−5682.

(10) Sieburth, S. McN.; O'Hare, H. K.; Xu, J.; Chen, Y.; Liu, G. *Org. Lett.* **2003**, *5*, 1859−1861.

(11) The examples of oxidative allylsilane cleavage to α-silyl aldehydes that we are aware of are those of Landais: Landais, Y.; Zekri, E. *Eur. J. Org. Chem.* **2002**, *23*, 4037−4053. Landais, Y.; Zekri, E. *Tetrahedron Lett.* **2001**, *42*, 6547−6551.

rearrangement step leads to the "natural" L-configuration of the amino acid **17**. The procedure yields a Boc-protected product that can be used directly in peptide chemistry. The availability of these silane amino acids provides opportunities for expanded evaluation of peptide conformation and novel pharmaceutical entities.

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Supporting Information Available: Detailed procedures and characterization data and proton NMR spectra for **16**−**19** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0358713

(12) Landais, Y. In *Organometallics; Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds*; Fleming, I., Ed.; Georg Thieme Verlag: New York, 2000; Vol. 4, pp 757−771.

(13) Hudrlik, P. F.; Hudrlik, A. M.; Misra, R. N.; Peterson, D.; Withers, G. P.; Kulkarni, A. K. *J. Org. Chem.* **1980**, *45*, 4444−4448. Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251−6253. Sato, T.; Matsumoto, K.; Abe, T.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2167−2170. Review: Larson, G. L. *Adv. Silicon Chem.* **1996**, *3*, 105−271.

(14) Use of this methodology with analogues of **15** in which the *tert*-butyldimethylsilyl group has been replaced with trimethylsilyl, dimethylphenylsilyl, or methyldiphenylsilyl has not resulted in acceptable yields of the corresponding amino acids. Efforts to optimize this chemistry for other substrates is continuing.