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A Stereoselective Approach to the Synthesis of γ-Silylated Amino Acids.

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Abstract: The synthesis of enantiomerically enriched silicon containing amino acids is described. Silylcupration of 2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine, easily derived from serine aldehyde, afforded regio- and stereoselectively γ–silylated ethenyloxazolidines of (*E*)-geometry as useful precursors of saturated and unsaturated γ-silylated amino acids.

Keywords: Addition reaction; Amino acids and derivatives; Copper and compounds; Regiocontrol; Stereocontrol; Silicon and compounds.

Stereoselective synthesis of unnatural α-amino acids has become an increasingly important field of research in recent years[1][2][3][4][5] and, in particular, attention has been devoted to introducing large and hydrophobic moieties on the lateral chains.[6] In this respect, trialkylsilyl groups are regarded as being very promising, as they are known to have non-polar hydrophobic properties which are relevant to biological activity.[7] The presence of such moieties on amino acids could result, after incorporation into peptides, in conformational restriction and increased rigidity, leading, for example, to enhanced resistance towards protease enzymes. Up to now, only a few reports on the synthesis of silicon-containing amino acids are known, mainly concerning trimethylsilylalanine (TMS-Ala). This amino acid has been prepared in both racemic[8] and enantiomerically enriched forms[6][9][10][11] and its N-Fmoc and N-Boc derivatives have been successfully used as phenylalanine bioisosteres in renin peptide inhibitors.[12]

Research in our laboratory has recently focused on the synthesis of enantiomerically enriched α-amino acids[13] using (*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine **1**, which can be easily obtained from naturally occurring *L*-serine,[14][15] as a chiral building block. Alkyne **1** proved to be a suitable substrate for the regio- and stereochemically controlled

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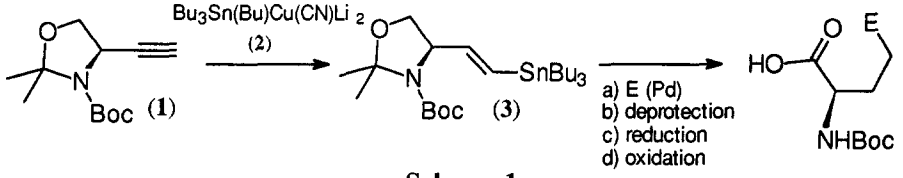
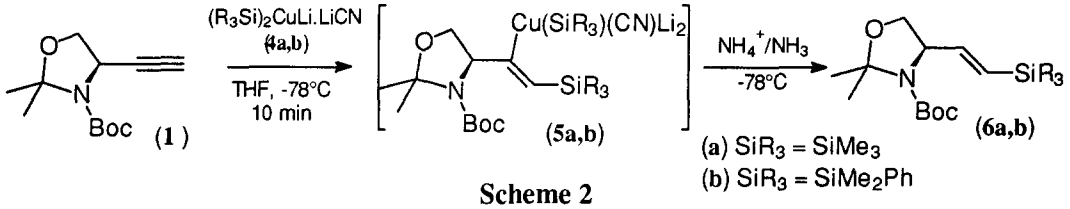
addition of tributylstannylcuprate **2** leading to stannylated oxazolidine **3**, a useful intermediate for the synthesis of γ-functionalized amino acids of (*R*)-configuration.[13] (Scheme 1).



Scheme 1

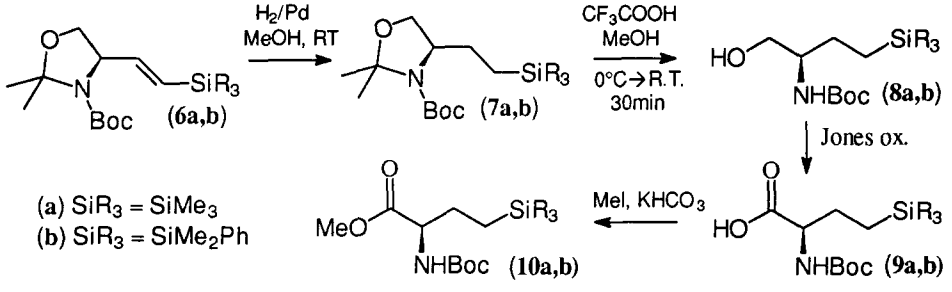
One of the most remarkable features of the stannylcupration protocol is that the resulting amino acids showed no loss of stereochemical information.[13][16] Analogous results were found when nucleophilic displacements were carried out with several silylcuprates on electrophilic alaninol synthons,[6] highlighting metallocuprates as suitable reagents to be used on chiral starting materials.

In consideration of these results, we reasoned that silylcupration of **1** could be an efficient method leading to vinylsilanes **6a,b** which are precursors of a new class of amino acids bearing different trialkylsilyl substituents on the γ-position of their lateral chain.



Scheme 2

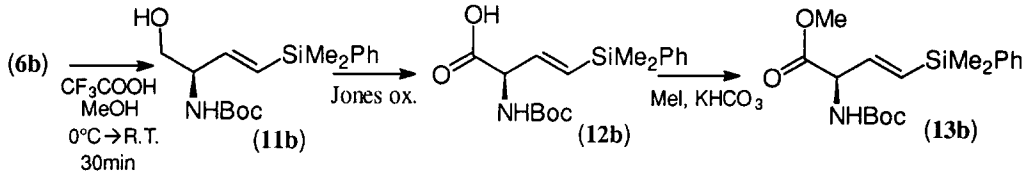
Oxazolidine **1** was reacted with both the trimethylsilylcuprate **4a**[17] and the dimethylphenylsilylcuprate **4b**[18] at low temperature affording a very fast regio- and stereoselective *syn* addition, as proved by ^{1}H NMR analysis of the crude mixture which was obtained after hydrolysis with an ammonia buffer. Only compounds **6a** or **6b** were isolated with *J* values of 18.6 and 18.8 Hz, respectively, being found for the coupling constants of their vinylic protons in good agreement with the proposed geometry. Flash chromatography allowed the isolation of pure **6a** and **6b** in 82% and 67% yield.



Scheme 3

Reduction of the double-bond of **6a** and **6b** gave the saturated products **7a** and **7b** quantitatively. These were deprotected to the corresponding amino alcohols **8a** and **8b** by carefully monitored treatment with CF_3COOH in MeOH. Oxidation to the corresponding amino acids was performed using Jones' reagent, applying the reverse addition procedure.[19] Compounds **9a** and **9b** were obtained in 66% and 57% overall yield from **6a** and **6b**. For characterisation purposes, the crude amino acids were converted directly into their methyl esters **10a** and **10b** which were isolated in pure form after flash chromatography (Scheme 3).

Our approach also offers the opportunity of accessing enantiomerically enriched β,γ-unsaturated α-amino acids of the kind of **12b**. Unsaturated amino acids are a class of compounds with interesting biological properties.[20][21][22] Some methods have been described for the preparation of this products,[23] but most suffer from either poor control of double-bond geometry or variable enantiomeric purity. However, Wittig condensations of phosphorous ylides with the Garner aldehyde[23] followed by deprotection and oxidation of the corresponding unsaturated amino alcohols has been shown to be a practical approach for preparing chiral β,γ–unsaturated amino acids with defined double-bond geometry. The most challenging step in this procedure is the oxidation of the amino alcohol, the efficiency of which is dependent on the substituent at the terminal vinylic position with the best results being obtained in the presence of electron donating groups. This observation led us to conceive that a trialkylsilyl group could be a suitable substituent permitting a successful oxidation step. Unsaturated amino alcohol **11b** was prepared by deprotection of **6b**. Oxidation under Jones' conditions gave amino acid **12b** in 64% overall yield. Pure ester **13b** was obtained after esterification and flash chromatography.



Scheme 4

In summary, we report here our approach to the synthesis of new silylated amino acids. Several aspects of this procedure are noteworthy. The yields of the overall process are satisfactory considering that all the steps can be carried out without purification of the intermediates.[24] The silylcupration technique employed opens the way to various ß-substituted γ-silylated amino acids by trapping the vinyl copper intermediates **5a,b** (see Scheme 1) with different electrophiles.[17] The vinylsilanes **6a,b** are very useful and we have shown they can be applied to the synthesis of silylated unsaturated aminoacids of (*E*) geometry. Due to the rich reactivity known for organosilanes[25] this class of molecules can also be regarded as interesting building blocks allowing further elaborations on the lateral chain of the amino acid precursor. The synthetic potential of this methodology is under current investigation in our laboratory.

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24. All the new compounds were fully characterized by ^{1}H NMR (200 MHz, $CDCl_3$),^{13}C NMR (75.45 Mhz, $CDCl_3$) and MS; selected data for **6a**, **6b**, **10a**, **10b** and **13b**. **6a**: ^{1}H-NMR δ: 5.91[dd, 1H, J=18.6, 6.2 Hz], 5.72 [d, 1H, J=18.6 Hz], 4.22 [m, 1H], 4.01 [dd, 1H, *J* = 8.8, 6.2 Hz], 3.72 [dd, 1H, *J* = 8.8, 2.2 Hz], 1.58 [s, 3H], 1.43 [s, 3H], 1.39 [s, 9H], 0.04 [s, 9H]. ^{13}C-NMR δ 151.95, 144.36, 130.85, 93.95, 79.45, 68.02, 61.63, 28.29, 26.40, 23.67, -1.41. MS *m/z:* 299(0.2), 284(12), 228(92), 73(78), 57(100). $[\alpha]_D^{25}$ = -30.7 (*c*=0.9, $CHCl_3$) **6b**: ^{1}H-NMR δ: 7.56-7.34 [m, 5H], 6.04 [dd, 1H, J=18.8, 6.6 Hz], 5.87 [d, 1H, J=18.8 Hz], 4.32-4.27 [m, 1H], 4.04 [dd, 1H, *J* = 8.8, 6.2 Hz], 3.76 [dd, 1H, *J* = 8.8, 2.2 Hz], 1.61-1.37 [m, 6H+9H], 0.34 [s, 6H]. ^{13}C-NMR δ: 151.94, 146.18, 138.53, 133.78, 128.98, 128.65, 127.94, 127.74, 94.06, 79.51, 67.98, 61.54, 28.27, 26.47, 23.67, -2.71. MS *m/z:* 346(41), 290(17), 135(53), 57(100). $[\alpha]_D^{26}$ = -36.8 (*c*=0.9, $CHCl_3$). **10a**: ^{1}H-NMR δ: 5.03 [bd, 1H, J=7.8 Hz], 4.31-4.24 [m, 1H], 3.73 [s, 3H], 1.78-1.62 [m, 2H], 1.44 [s, 9H], 0.51-0.39 [m, 2H], -0.03 [s, 9H]. ^{13}C-NMR δ: 173.31, 154.68, 79.76, 55.51, 52.13, 28.26, 27.20, 11.44, -2.02. MS *m/z*: 233(1), 205(20), 73(100), 57(100). $[\alpha]_D^{25}$ = -21.7 (*c*=1.05, $CHCl_3$). **10b**: ^{1}H-NMR δ: 7.49-7.33 [m, 5H], 5.01 [bd, 1H, J=7.2 Hz], 4.34-4.22 [m, 1H], 3.70 [s, 3H], 1.84-1.53 [m, 2H], 1.43 [s, 9H], 0.81-0.66 [m, 2H], 0.26 [s, 6H]. ^{13}C-NMR δ: 173.20, 156.61, 138.21, 133.53, 129.08, 127.86, 79.85, 55.47, 52.14, 28.27, 27.14, 10.65, -3.27. MS *m/z:* 352(2), 280(14), 135(100), 57(89). $[\alpha]_D^{25}$ = -20.2 (*c*=2, $CHCl_3$). **13b**: ^{1}H-NMR δ: 7.53-7.26 [m, 5H], 6.78-6.69 [m, 2H], 5.36-5.24 [m, 1H+1H], 3.73 [s, 3H], 1.44 [s, 9H], 0.34 [s, 6H]. MS *m/z* 249(1), 234(2), 135(100), 57(29).
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