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Access to α,α-Disubstituted Disilylated Amino Acids and Their Use in Solid-Phase Peptide Synthesis

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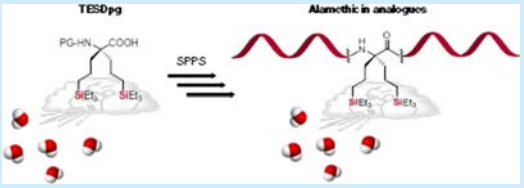
Supporting Information

ABSTRACT: A concise synthetic pathway yielding to hydrophobic α,α-disubstituted disilylated amino acids based on a hydrosilylation reaction is described. As a first example of utilization in solid-phase peptide synthesis, TESDpg was introduced in replacement of Aib in an alamethicin sequence, leading to analogues with modified physicochemical properties and conserved helical structures. This study highlights the potential of these new amino acids as tools for peptide modulation.



Unnatural amino acids (UAAs) are attractive tools for application in a large variety of areas such as biomaterials or bioactive compounds in medicinal chemistry.[1] Non-proteogenic amino acids are largely used for the synthesis of peptides with the aim of overcoming stability issues by preventing degradation by endogenous proteases and to improve their biological activities. In particular, the class of α,α-disubstituted α-amino acids has always been of great interest and has gained considerable attention in the past decades.[2] Their incorporation into peptides results in both the modulation of their physical and chemical properties and their secondary structural conformation.[2f] Silicon-containing molecules and amino acids are very attractive for the interesting properties of the silicon atom including its large covalent radius and electron density[3] and its high lipophilicity. On the other hand, when incorporated into peptides, silicon-containing amino acids increase their resistance to degradation[4] and stabilize their secondary structure.[5] Despite their attractiveness, they are still rare and limited in diversity (Figure 1). Some of them have been successfully used for the preparation of biological active compounds.[6]

We have previously described disubstituted amino acids bearing one silylated side chain and their incorporation into active peptides.[7] However, the synthesis of disubstituted disilylated amino acids still remained a challenge. Unsaturated amino acids have been proven to be good chemical precursors for the achievement of chemical diversity and are also useful starting materials for access to silicon-containing amino acids.[8]

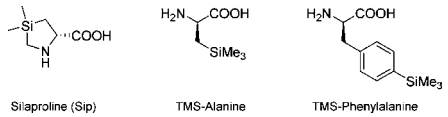


Figure 1. Examples of silicon-containing amino acids.

In this study, we present the first example of a new class of nonproteogenic α,α-dialkylated amino acids presenting a silicon moiety in both side chains. Due to their unique characteristics both in terms of bulkiness and lipophilicity, this new class of amino acids is very promising. We also describe in this paper their possible use in solid-phase peptide synthesis (SPPS).

The synthesis of disubstituted disilylated amino acid derivatives was performed in five steps starting from commercially available starting materials. The Schiff base benzophenone imine glycine ester was prepared in quantitative yield and then alkylated with allyl bromide using potassium *tert*-butoxide as base, leading to compound **2**. The reaction was quantitative and performed at room temperature within 30 min. The crude resulting product was hydrolyzed under mild acidic conditions with a solution of citric acid in water to yield the free amine **3**.[9] Compound **3** was treated with (benzyloxy)carbonyl chloride to afford the (benzyloxy)carbonyl (Z) N-protected dialkylated unsaturated amino ester **4** that provided the protected disilylated amino acids **5a−c** after hydrosilylation (Scheme 1). Orthogonal protection allows either coupling on the amino function or on the carboxylic acid.

Although silicon-containing amino acids can be prepared through alkylation with halomethylsilane,[10] the hydrosilylation reaction was exploited to avoid direct alkylation with bulkier reagent.[11] We chose to introduce the silicon moiety at the end of the synthesis in order to be able to modulate the steric hindrance and lipophilicity of the final compounds. To conserve the

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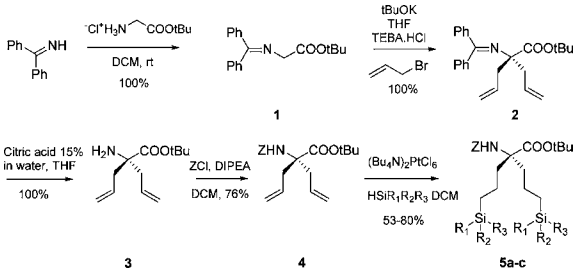
Scheme 1. Synthesis of Disilylated Amino Acids[a]



[a]R_1, R_2, and R_3 are defined in Table 1.

versatility of the synthesis, simple and commercially available silanes were used. Furthermore, the compounds were designed with side chains counting three methylene groups that facilitate the double addition of the silylated agent to the unsaturation and to obtain a constrained hindered new amino acid suitable for efficient coupling reactions. In addition, the resulting compounds are more stable than those in which the silicon is directly inserted at the α-position of the amino acid.[4b] We studied the hydrosilylation reaction conditions (Table 1). The reaction

Table 1. Optimization of Reaction Conditions

entry	$HSiR_1R_2R_3$	catalyst	cat. equiv	solvent	product	yield[a], (%)
1	$HSiEt_3$	$(Bu_4N)_2PtCl_6$	0.05	DCM	5a	38
2	$HSiEt_3$	$(Bu_4N)_2PtCl_6$	0.05	ACN	5a	0
3	$HSiEt_3$	$(Bu_4N)_2PtCl_6$	0.01	DCM	5a	53
4	$HSiEt_3$	$(Bu_4N)_2PtCl_6$	0.1	DCM	5a	41
5	$HSiEt_3$	$H_2PtCl_6{\cdot}H_2O$	0.05	DCM	5a	32
6	$HSiEt_3$	$H_2PtCl_6{\cdot}H_2O$	0.05	ACN	5a	19
7	$HSi(Me)_2tBu$	$(Bu_4N)_2PtCl_6$	0.01	DCM	5b	63
8	$HSi(Me)_2Ph$	$(Bu_4N)_2PtCl_6$	0.01	DCM	5c	80

[a]Yield of the isolated product.

proceeds with Pt^0 catalyst as already reported.[11] Speier's catalyst, $H_2PtCl_6{\cdot}6H_2O$, as well as the platinum complex analogue, tetrabutylammonium hexachloroplatinate $(Bu_4N)_2PtCl_6$, were tested. As demonstrated by Skoda-Földes, the regioselectivity of the hydrosilylation depends on the functionalities in the vicinity of the alkene, and the choice of a suitable catalyst allows insertion of the silicon to be oriented at the α or β position. Nevertheless, in our case, such a neighboring effect could not be expected and the reaction has a classic anti Markovnikov outcome.[12] A slight increase in the reaction yield was obtained with $(Bu_4N)_2PtCl_6$ (entries 1 and 5). The catalytic amount was reduced to 1% molar ratio (entry 4) in dichloromethane as solvent, while the reaction was ineffective in acetonitrile (entry 2). Despite our efforts to optimize the reaction conditions, the yield of compound **5a** (53%, entry 3) remained moderate albeit acceptable considering the steric hindrance of the bulky silicon group. We also observed formation of undesired side products such as the monosilylated derivative and of compounds where one or both unsaturated side chains were reduced by platinum-induced catalytic transfer hydrogenation with triethylsilane[13] (see the Supporting Information). The yields increased for compound **5b** (63%, entry 7) and for compound **5c** (80%, entry 8) bearing a dimethyl-*tert*-butyl and dimethylphenyl substitution on the silicon atom, respectively.

Crystals of compound **5a** were obtained by slow evaporation of a dichloromethane/*n*-hexane solution. The structure observed for compound **5a** could be attributed to the space group $P2_1$ with $Z = 4$. All atoms of the two independent molecules were connected by an inversion center with the exception of two terminal methyl groups of one silylated side chain. We have also considered the possibility that the space group could be $P2_1/c$ for this structure. The corresponding refinement, however, gave an unsatisfactory convergence with an R factor much higher (0.114) than that obtained in the space group $P2_1$ (0.071). Disilylated amino acid **5a** exhibited, as expected,[2e] a fully extended conformation ($\varphi = -179.9°$ and $\psi = 164.4°$) (see Supporting Information). This conformation, also called the C_5 conformation, is the basic unit of the 2.0_5-helix motif.[14] Both side chains also adopted an extended conformation, with the χ^{1L} and χ^{1D} values close to +60° (g^+) and −60° (g^-), respectively. Although homopeptides containing α,α-dialkylated amino acids like diethylglycine (Deg), di-*n*-propylglycine (Dpg), and di-*n*-butylglycine (Dbg) were usually observed in the C_5 conformation, several studies with heteromeric sequences revealed several examples of Dpg and Dbg containing peptides in helical conformations.[15]

To extend the possible use of these new amino acids, particularly in solid-phase peptide synthesis (SPPS), the Fmoc-protected amino esters were easily prepared (Scheme 2), yielding readily available Fmoc-building blocks after selective TFA ester removal (Table 2).

Scheme 2. Preparation of the Fmoc-Protected Disilylated Amino Esters

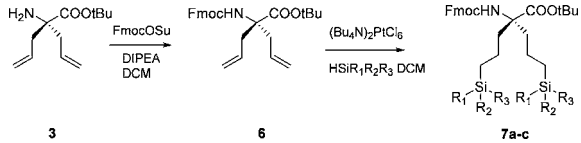


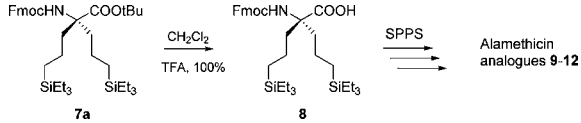
Table 2. Fmoc-Protected Derivatives

entry	$HSiR_1R_2R_3$	catalyst	cat. equiv	solvent	product	yield[a], (%)
1	$HSiEt_3$	$(Bu_4N)_2PtCl_6$	0.01	DCM	7a	52
2	$HSi(Me)_2tBu$	$(Bu_4N)_2PtCl_6$	0.01	DCM	7b	66
3	$HSi(Me)_2Ph$	$(Bu_4N)_2PtCl_6$	0.01	DCM	7c	94

[a]Yield of the isolated product after purification on silica gel.

To evaluate the reactivity of these derivatives in SPPS, as well as the effect on polarity and secondary structure conformation, compound **8** was prepared in quantitative yield by cleavage of the *tert*-butyl ester in a mixture of CH_2Cl_2 and TFA (Scheme 3). It

Scheme 3. Preparation of the Fmoc-amino Acid 8 Suitable for SPPS



was introduced in positions 1, 5, 10, and 13, respectively, in place of aminoisobutyric acid (Aib) into the highly hydrophobic amphipathic α helical peptide alamethicin F50/5 (Alm) (Table 3). The substitutions were carried out in the first half of the alamethicin helix corresponding to the well-organized one extending from Aib1 to Aib13. Peptides of the alamethicin family are one of the most studied peptaibols. They are rich in the

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Table 3. Alamethicin Analogues

compound	sequence	yield[a], (%)	Rt, (min), %, MeOH[b]	Log k′
Alm	AcUPUAUAQUVUGLUPV UUQQFol	35	3.2 82.6	-1.16
9	AcUPUA[TESDpg]AQUVU GLUPVUUQQFol	45	22 97.6	0.88
10	Ac[TESDpg]PUAUAQUVU GLUPVUUQQFol	8	20.2 96.2	0.87
11	AcUPUAUAQUVUGL[TES Dpg]PVUUQQFol	9	20 96	0.83
12	AcUPUAUAQUV[TESDpg] GLUPVUUQQFol	34	19.2 95.4	0.81

[a]After purification by semipreparative HPLC. [b]Final percentage of MeOH allowing the elution of peptide in a 25 min gradient from 80% methanol (eluent A)/20% H_2O (eluent B) to 100% eluent A.

helix promoter Aib, and the alamethicin structure has been extensively studied.[16]

Therefore, alamethicin constitutes a model of choice to investigate the impact of insertion of compound **8**, namely TESDpg, into secondary structured peptides. Although the incorporation of α,α-disubstituted amino acids via SPPS represents a challenge, this was achieved by applying an already reported procedure that was further optimized to spare compound **8**.[17] Indeed, for the stepwise microwave-assisted SPPS, the amount of amino acids was reduced to 3 equiv with respect to resin loading, without affecting the final yield. This synthetic strategy was then applied to derivatives **9**−**12** with moderate to good yields depending on the substitution position. The drop of the overall yield (compounds **10** and **11**) was observed for the coupling of the bulky silylated amino acid on the proline residue even after a double coupling procedure. On the other hand, coupling of compound **8** on a less hindered amino acid such as glycine or alanine proceeded without loss of efficacy (compounds **9** and **12**) (Table 3).

Purification of the final products was facilitated thanks to the exceptional decrease of the polarity of compound **9**−**12**, enabling us to discard secondary deletion products formed during the synthesis. RP-HPLC elution times of TESDpg-containing peptides **9**−**12** compared to native alamethicin perfectly reflect the drastic difference in their hydrophobicity (Table 3). The peptide analogues **9**−**12** differed from the natural compound by a single insertion of TESDpg that profoundly affected the polarity. After the drastic increase of hydrophobicity and the decrease of solubility in water induced by the replacement of one Aib by one TESDpg, the substitution was limited to one residue at a time. In order to more easily visualize the variation of hydrophobicity the retention factor log k' was used.[18] A negative value of log k' indicates a polar peptide, while a positive value reflects a highly hydrophobic compound. In agreement with this, the ratio of hydrophobicity of compounds **9**−**12** compared to the native form was almost of a factor of 100. Moreover, the overall hydrophobicity of TESDpg-containing peptides was not significantly affected, whether the TESDpg residue was inserted either on the polar (compounds **9**−**11**) or on the apolar (compound **12**) face of the helix, since they all share comparable log k' values.

The far-UV−CD spectra of the four TESDpg-containing alamethicin analogues were investigated to study the effect of the introduction of this new disilylated amino acid on the secondary structure. Different solvent systems were investigated, in particular, methanol, 2,2,2-trifluoroethanol ,and the more lipophilic 1-octanol. Studies were also performed in a SDS 100 mM solution in water as a membrane-mimicking environment (Figure 2).[19]

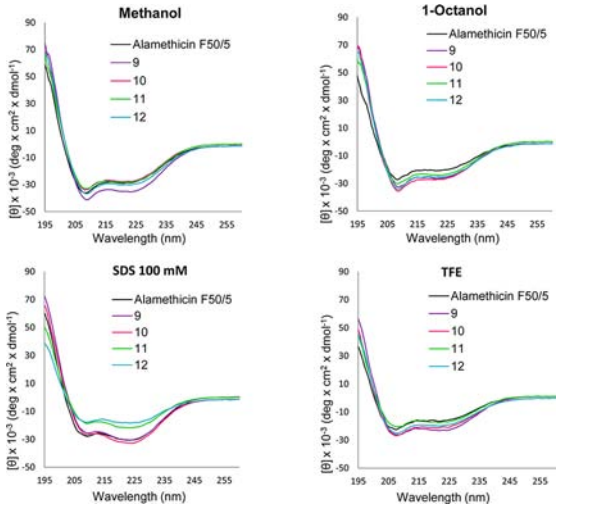

Figure 2. CD spectra of alamethicin F50/5 and compounds **9**−**12** (0.1 mM) in MeOH, 1-octanol, SDS (100 mM) in water, and TFE.

Under each of the four experimental conditions examined, the analogues exhibited a similar spectral shape with respect to the spectra of the reference compound alamethicin F50/5 at 0.1 mM concentration. All of the CD spectra were indicative of a right-handed, predominantly α-helical structure showing the three typical Cotton effects: the n−π transition at 222 nm (−) and the two π−π* bands at 208 nm (−) and 190 nm (+). The R ratio between θ222 and θ208 was calculated for each compound in all solvent systems. The results are summarized in Table 4. In all of

Table 4. R Ratios between the Intensities of the Two Negative Bands at 222 and 208 nm in Different Media

	R in			
compd	MeOH	1-Oct	TFE	SDS
Alm	0.79	0.77	0.76	1.13
9	0.87	0.82	0.89	1.24
10	0.82	0.77	0.79	1.26
11	0.87	0.80	0.86	1.23
12	0.82	0.75	0.80	1.04

the alcoholic environments, $R = 0.8 \pm 0.07$ indicating a typical monomeric α-helical structure (Figure 2). When the CD spectra of all compounds were recorded in the presence of SDS micelles, R was >1.0, typical for an aqueous solution. The major feature of these spectra was the large ellipticity excess of the band near 222 nm (n−π* transition) over the band around 208 nm (π−π*) characteristic of parallel helical coiled coils.[20] This observation may suggest the presence of supramolecular interactions and of a α-helical self-assembly (Figure 2).

The effect of temperature on the spectra of alamethicin analogues **9**−**12** was also investigated. The range of temperatures explored was from 5 to 75 °C. Notwithstanding the decrease of R for all compounds, they were revealed to be stable for temperatures up to 75 °C in methanol and TFE maintaining a ratio of $R > 0.7$. A pronounced decrease of R was observed in the

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strongly lipophilic solvent 1-octanol already at temperatures above 30 °C. This effect has already been reported for alamethicin (Supporting Information).[21] In order to confirm the hypothesis of parallel helical coiled coils, the CD spectra in a 1:1 100 mM mixture of TFE in SDS were recorded for all compounds at 0.1 mM concentration (see Supporting Information). TFE is known to enhance intramolecular α-helicity but to decrease intermolecular interactions.[22] A destruction of the homocoiled−coil binding motif results in a significant decrease in the θ222/θ208 ratio from SDS to 50% TFE in SDS.[19] For all compounds, the *R* decrease, confirmed the supramolecular organization of peptides in aqueous sodium dodecyl sulfate.

All of the synthesized analogues were tested in an agar bacterial growth assays at a dose of 20 μg/disk on Gram-positive *Bascillus subtilis*, and only the native alamethicin was found active. Therefore, we could suspect that due to steric hindrance the hexameric self-association of alamethicin needed to form the pore supramolecular structure is prevented.[23]

In conclusion, this study reports an easy access to α,α-disubstituted disilylated amino acids. These original amino acid derivatives are directly usable in SPPS and permit to conserve the helicoidal secondary structure of the peptide in which they are inserted. This amino acid surrogate of the Aib offers the possibility to strengthen the hydrophobicity of the peptide, and one can expect they would certainly reinforce their ability to cross membranes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02175.

Experimental procedures and characterization data (PDF)
X-ray data for **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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