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Solid-Phase, Pd-Catalyzed Silicon-Aryl Carbon Bond Formation. Synthesis of Sansalvamide A Peptide

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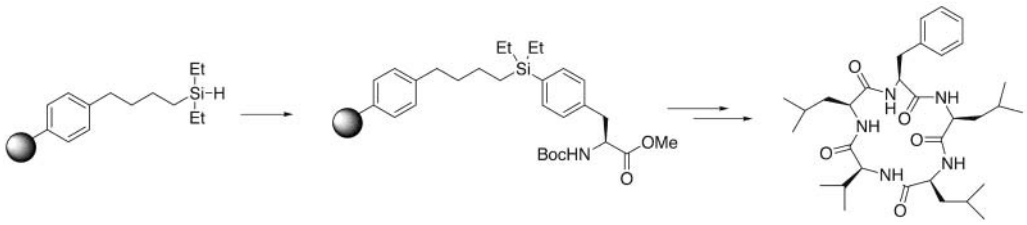
ABSTRACT



A palladium-catalyzed silicon–aryl carbon bond formation on solid-phase is reported. A phenylalanine silane resin was prepared directly from protected iodo-substituted phenylalanine with butyl diethylsilane polystyrene in one step. A rapid and high-yield solid-phase synthesis of sansalvamide A peptide was achieved from the phenylalanine silane resin.

Combinatorial chemistry plays an important role in drug discovery.[1,2] Vital to all solid-phase methodologies is the design and utilization of suitable linkers that allow facile attachment, functionalization, and release of the molecules of interest. Many novel linkers have recently been developed to facilitate solid-phase synthesis. An important approach is the use of a resin having a linker functional group that can be excised efficiently and quantitatively when desired, leaving behind no trace or "memory" of the solid-phase synthesis.[3] Recently, several novel strategies using a resin-bound arylsilane as a traceless linker have been developed for solid-phase synthesis of aromatics or heteroaromatic compounds.[3−7] An arylsilyl linker is compatible with a variety of reaction conditions and can be cleaved under several different conditions. Previously, we reported arylsilane-based traceless linker strategies for the attachment of the aromatic side chain of phenylalanine,[8] β-phenylalanine,[9] and other aromatic and heteroaromatic amino acid analogues[10] to a polystyrene resin, which were utilized for the efficient synthesis of small peptides[8−10] and a cyclic depsipeptide.[11] Unfortunately, the phenylalanine building block had to be constructed in six steps prior to being tethered to the resin (Scheme 1). Furthermore, every different arylsilane building block had to be synthesized in several steps before being tethered to the resin. A much more efficient method for the construction of these resin-bound building blocks would be to attach commercially available or readily synthesized amino acid analogues directly to the resin in one step.

Silicon−carbon bond formation has been reported to occur from the palladium-catalyzed reaction of an organosilane

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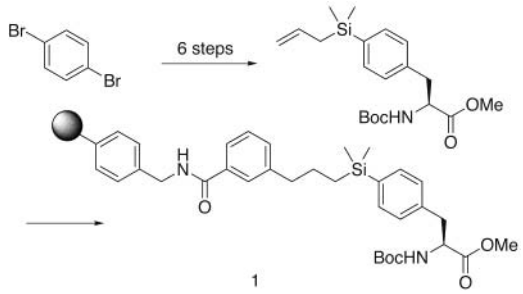
Scheme 1



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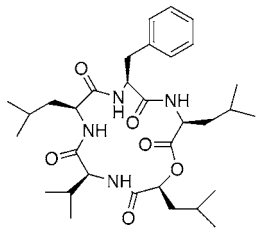
with an organic iodide.[12] A synthesis of arylsilanes via palladium-catalyzed silylation of aryl halides with triethoxysilane also was reported.[13] However, there has been no report of a palladium-catalyzed silicon−aryl carbon bond-forming reaction using polymeric hydrosilane derivatives. The traditional method of generating arylsilanes on a solid-phase is the reaction of chlorosilanes with aryllithium reagents, but this is restricted to substrates lacking sensitive functional groups. Here we report a novel and convenient method for the synthesis of a polymer-bound aryl building block. A silicon−aryl carbon bond was formed using the reaction of a polystyrene hydrosilane with iodophenylalanine under mild palladium-catalyzed reaction conditions. The resin-bound phenylalanine building block was then used for the synthesis of the first analogue of the natural cyclic depsipeptide, sansalvamide A, namely, the corresponding sansalvamide A cyclic peptide. This methodology is a convenient general approach for the generation of resin-bound arylsilanes directly from aryl halides.

The reaction of butyl silane polystyrene with Boc-4-iodophenylalanine methyl ester was investigated using different palladium catalysts in combination with different phosphines. As shown in Scheme 2, esterification of Boc-4-iodophenylalanine with iodomethane using sodium bicarbonate as a base afforded Boc-4-iodophenylalanine methyl ester (**4**). The palladium-catalyzed reaction of **4** and commercially available butyl diethylsilane polystyrene (**5**, PS-DES-SiH) under various reaction conditions afforded the phenylalanine silane linker (**2**), as described in Table 1. The loading level of **2** was determined by weighing the product of cleavage of **2** with bromine in methylene chloride. No reaction was observed using tetrakis-(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) as the catalyst, with either sodium carbonate or potassium acetate as the base both at room temperature and 105 °C. However, the reaction was catalyzed by tris-(dibenzyleneacetone) dipalladium(0) chloroform adduct ($Pd_2(dba)_3{\cdot}CHCl_3$). In the presence of an added bulky phosphine ($P(o\text{-}Tol)_3$), the reaction occurred, but only poorly (entries 4−6). KOAc proved to be a more effective base than the tertiary amine DIPEA. The use of amide solvents such as NMP and DMF also is essential for the success of this silylation reaction. The most effective base that we tried for this catalytic reaction was KOAc in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$.



Sansalvamide A

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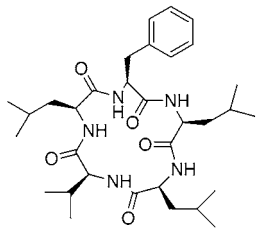

Sansalvamide A Peptide

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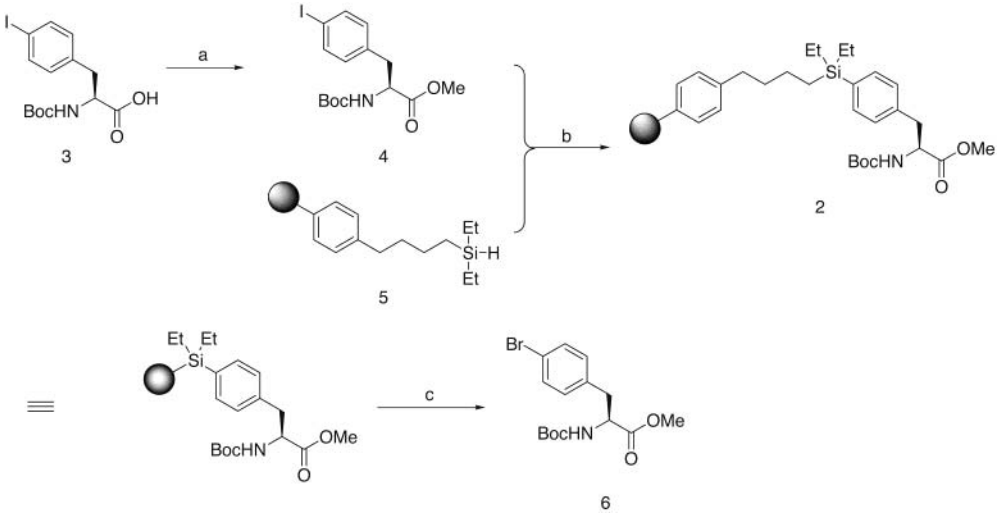
We recently reported the solid-phase synthesis of the natural depsipeptide sansalvamide A (**7**) from the polymer bound phenylalanine building block **1**, which was prepared in seven steps from *p*-dibromobenzene.[11] This highly lipo-

Scheme 2. Synthesis of Phenylalanine Silane Linker[a]



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[a] Reagents and conditions: (a) MeI, $NaHCO_3$, DMF, rt, 98%; (b) Pd catalyst, phosphine ligand, base, solvent; (c) Br_2 in CH_2Cl_2, 15 min.

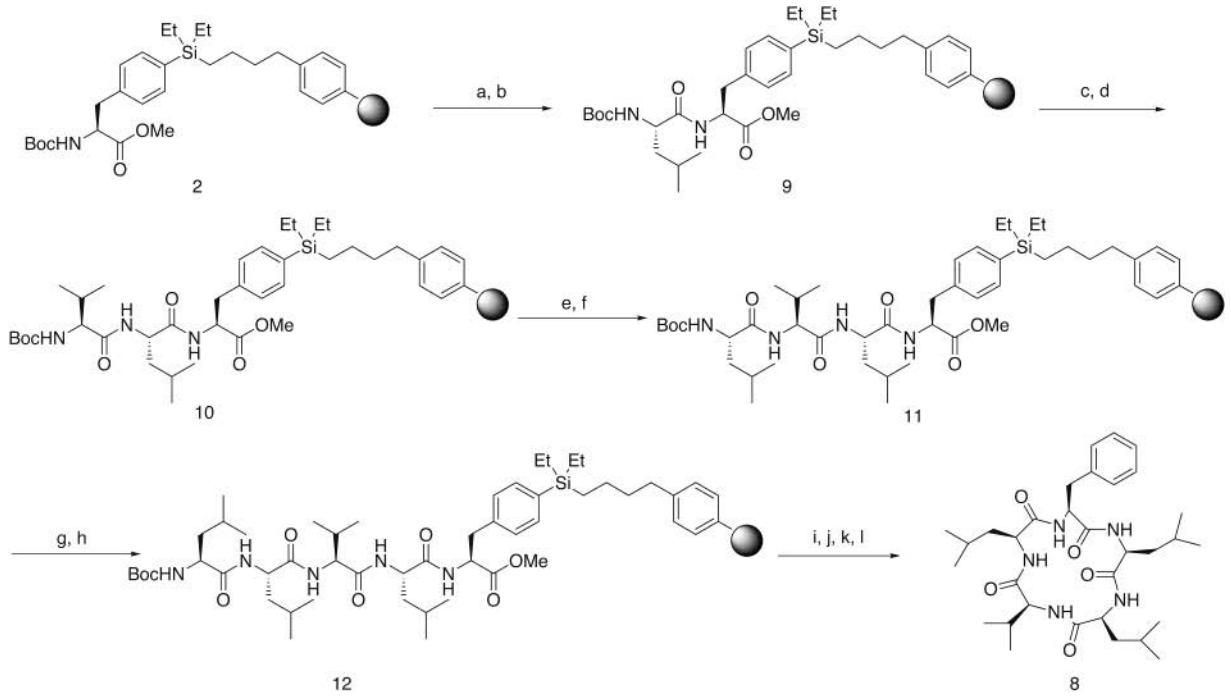
Table 1. Reaction Conditions of Butyl Diethylsilane Polystyrene (PS-DES) (Loading Level 1.45 mmol/g) with Boc-4-Iodophenylalanine Methyl Ester

entry	Pd catalyst	ligand	base	solvent	temperature (°C)	loading level (mmol/g)
1	$Pd(PPh_3)_4$		Na_2CO_3	NMP	25	
2	$Pd(PPh_3)_4$		Na_2CO_3	NMP	105	
3	$Pd(PPh_3)_4$		KOAc	NMP	105	
4	$Pd_2(dba)_3{\cdot}CHCl_3$	P(*o*-tol)$_3$	DIPEA	NMP	25	0.1
5	$Pd_2(dba)_3{\cdot}CHCl_3$	P(*o*-tol)$_3$	DIPEA	NMP	105	0.2
6	$Pd_2(dba)_3{\cdot}CHCl_3$	P(*o*-tol)$_3$	KOAc	NMP	105	0.3
7	$Pd_2(dba)_3{\cdot}CHCl_3$		KOAc	DMF	105	0.7
8	$Pd_2(dba)_3{\cdot}CHCl_3$		KOAc	NMP	105	0.8

philic natural product was found to have significant cancer cell cytotoxicity with a mean IC_{50} value of 27.4 μg/mL against the National Cancer Institute's 60 cell-line panel, and an in vitro value of 9.8 μg/mL toward HCT-116 colon carcinona.[14] We wondered if the lactone linkage of the depsipeptide was important for the activity of this compound and decided to apply the new methodology developed here for the synthesis of polymer bound phenylalanine building block **2** and use that in the synthesis of sansalvamide A peptide (**8**).

As shown in Scheme 3, the solid-phase synthesis of **8** was initiated from the N-terminus of phenylalanine silane linker **2**. A low loading level (0.09 mmol/g) of **2** was selected to avoid problems of oligomer formation during the final cyclization step. Boc protecting groups were employed for peptide chain extensions to reduce the possibility of diketopiperazine formation,[15−17] which is prevalent when Fmoc deprotection is used. Although oxazolone or oxazolonium ion formation occurs when acylating amine groups, and Boc-oxazolonium ions can decompose to *N*-carboxyanhydride derivatives much more readily than the corresponding Cbz- or Fmoc-protected derivatives,[18] the undesired byproducts can be washed out after every coupling reaction. Deprotection of the Boc group of **2** followed by reaction of the resulting amine with Boc-Leu-OH and DIPEA, in the presence of a highly effective activating reagent HATU[19] in NMP as a solvent, afforded polymer-bound dipeptide **9**. Elongation of the peptide chain to the linear peptide **12** was accomplished

Scheme 3. Synthesis of Sansalvamide A Peptide[a]



[a] Reagents and conditions: (a) 50% TFA in CH_2Cl_2, rt, 15 min; (b) Boc-Leu-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), NMP, 6 h; (c) 50% TFA in CH_2Cl_2, rt, 15 min; (d) Boc-Val-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), NMP, 6 h; (e) 50% TFA in CH_2Cl_2, rt, 15 min; (f) Boc-Leu-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), NMP, 6 h; (g) 50% TFA in CH_2Cl_2, rt, 15 min; (h) Boc-Leu-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), NMP, 6 h; (i) LiOH (5 equiv), THF/H_2O (7:1); (j) 50% TFA in CH_2Cl_2, rt, 15 min; (k) PyBOP (5 equiv), DIPEA (15 equiv), NMP, 24 h; (l) neat TFA, 24 h, rt.

by stepwise coupling of the appropriate Boc-protected amino acids under the same conditions. Deprotection of the methyl ester and Boc protecting groups of **12** gave the resin-bound linear peptide. To avoid guanidine formation when employing an excess of the uronium salt HATU during the activation of the carboxylate acid group of the linear pentapeptide,[20] the phosphonium salt PyBOP was substituted for HATU in the cyclization step. Sansalvamide A peptide **8** was released from the resin in an overall 66% yield (based on the loading level of **2**) using neat TFA for 24 h. HPLC analysis proved the cyclic peptide to be 94.1% pure. The target molecule was characterized with ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrum.

Sansalvamide A peptide (**8**) was found to be 10 times (0.98 μg/mL) more potent than sansalvamide A as a cytotoxic agent against HCT-116 human colon carcinoma.

In conclusion, the first palladium-catalyzed silane−aryl carbon bond-forming reaction was carried out on a solid support to afford a phenylalanine silane linker (**2**) from butyl diethylsilane polystyrene and Boc-4-iodophenylalanine methyl ester in one step. Various catalyst systems were tried, and $Pd_2(dba)_3$·$CHCl_3$ with KOAc was found to be the most effective catalyst for this reaction. Resin **2** was used to synthesize the first analogue of sansalvamide A (**7**), namely, the corresponding cyclic peptide **8**, which was found to be 10 times more potent than sansalvamide A against the growth of HCT-116 colon cancer cells. This synthetic methodology should be applicable to the one-step synthesis of a variety of traceless resin-bound arylsilanes from a commercially available silane resin and aryl iodides.

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Supporting Information Available: Complete experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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