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Traceless Solid-Phase Synthesis of Chiral 3-Aryl β-Amino Acid Containing Peptides Using a Side-Chain-Tethered β-Amino Acid Building Block

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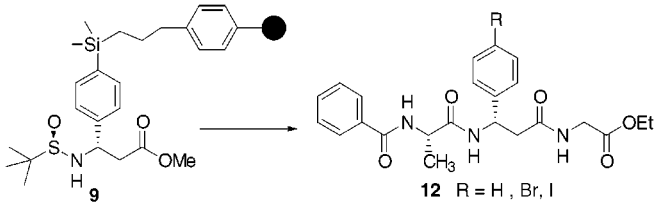
ABSTRACT



A general method for the attachment of a chiral aromatic side-chain-containing β-amino acid to a polymer support using a traceless silyl linkage strategy has been developed. Using this building block, solid-phase synthesis was carried out to obtain tripeptide analogues with the aromatic ring either unsubstituted or halogenated (Br, I) at the position of the silyl group. The building blocks could generate libraries of peptidomimetics or cyclic peptides containing β-amino acids with nonpolar side chains.

Since the introduction of the Merrifield resin,[1] libraries of peptides, nucleotides, and organic molecules have been generated on solid supports.[2] The application of combinatorial methods and high throughput screens have been powerful tools for the discovery of new leads and drug candidates. Because of poor oral bioavailability and enzymatic degradation of linear peptides, modified peptides, peptidomimetics, and cyclic peptides have become appealing targets for the design of therapeutic agents with increased pharmacological activities.[3] Conventional solid-phase peptide synthesis allows the elongation of the amino acid backbone unidirectionally (C to N or N to C). However, attachment of the amino acid side chain to the polymer permits chain elongation in both directions; thus, more diverse libraries can be prepared than with conventional methods. Furthermore, head-to-tail cyclization of peptides on the resin provides a facile route to cyclic compounds. Because the conventional linkers are mainly based on polar functional groups, this method has been applicable to amino acids which have polar side chains such as Asp, Glu (COOH), Ser, Tyr (OH), Lys, Arg (NH_2), or His (imidazole).[4]

Recent progress in linker technology has provided many novel linkages to facilitate both solution- and solid-phase reactions. Among them, a silicon-based linkage strategy to attach aromatic and heteroaromatic compounds to solid supports has received much attention.[5] This method allows

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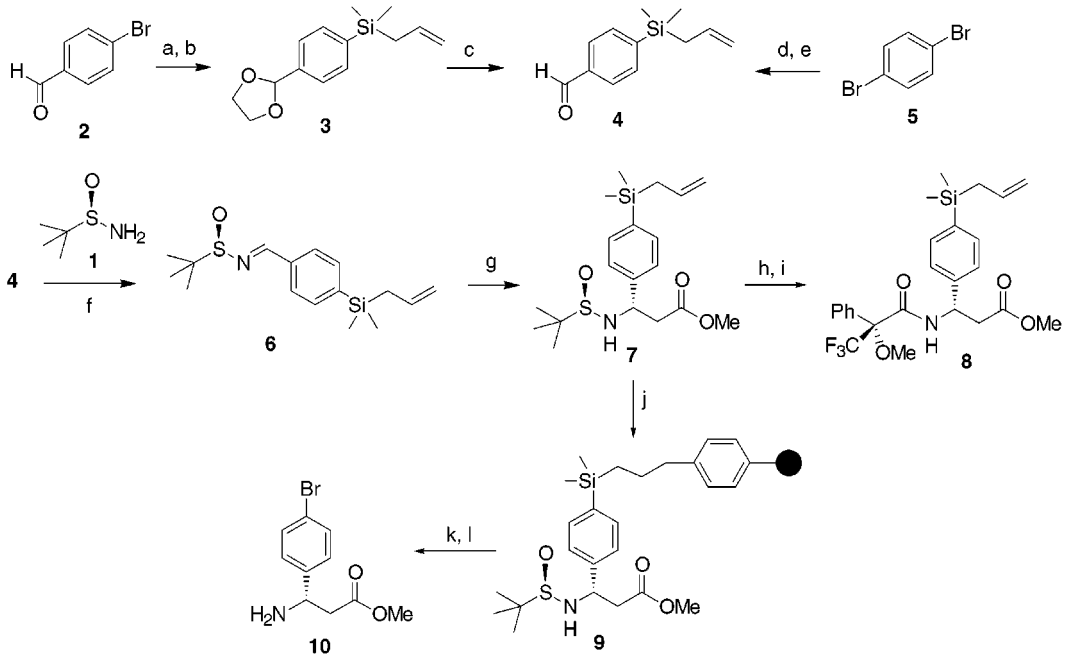
Scheme 1. Synthesis of Polymer-Bound Chiral 3-Phenyl-β-alanine Building Block[a]



[a] Conditions: (a) ethylene glycol, *p*-toluenesulfonic acid (cat.), benzene, reflux, 4 h; (b) *t*-BuLi, THF, −78 °C, then allylchlorodimethylsilane; (c) acetone, *p*-toluenesulfonic acid (cat)., reflux, 6 h; (d) *n*-BuLi, THF, −78 °C, then allylchlorodimethylsilane; (e) *t*-BuLi, THF, −78 °C, then DMF; (f) $Ti(OPr)_4$, THF, reflux, 1 h; (g) methyl acetate, LDA, THF, −78 °C, then chlorotitanium triisopropoxide (2.1 equiv); (h) 4 N HCl/dioxane, MeOH, 5 min; (i) (*R*)-MTPACl, pyridine, $CHCl_3$, 2 h; (j) 9-BBN, THF, 5 h, then bromopolystyrene, DMF, $Pd(PPh_3)_4$, Na_2CO_3, 75 °C, 48 h; (k) 50% TFA in CH_2Cl_2, 5 min; (l) Br_2 in CH_2Cl_2, 20 min.

the tethering of a substrate to the polymer at an inert site within the molecule. Upon completion of the desired solid-phase reactions, selective cleavage of the product at the position of the silyl group either by protiodesilylation or *ipso* substitution (with Br_2 or ICl) provided hydrogen- or halide-substituted compounds. To date, silicon-based linkages have been employed for solid-phase syntheses of only aromatic or heteroaromatic compounds.[6]

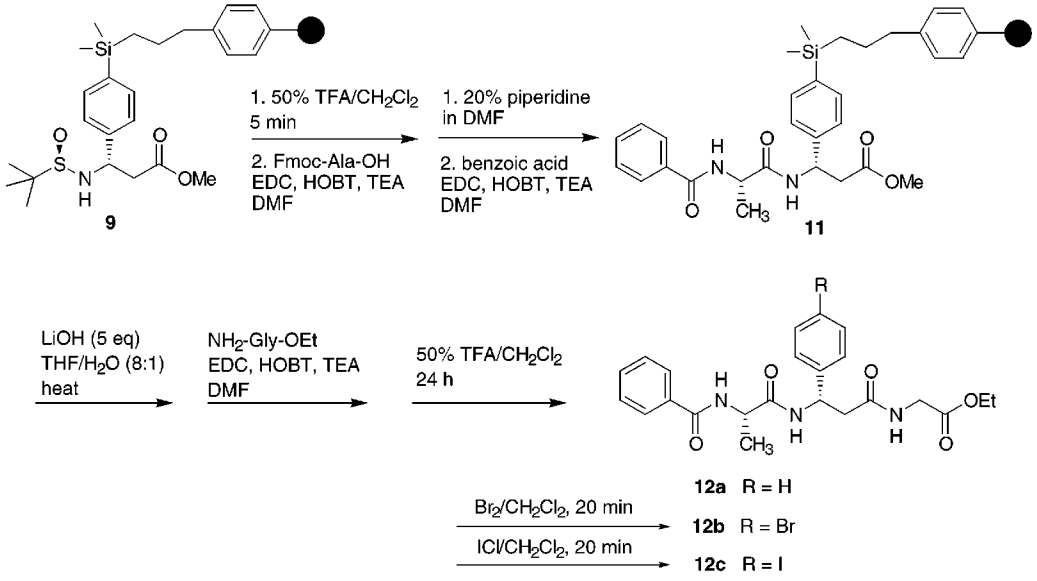
In an effort to synthesize libraries of phenylalanine-containing molecules on a solid support, we devised an arylsilane-based "traceless linker" strategy to attach the aromatic side chain of phenylalanine to bromopolystyrene and prepared phenylalanine- and halide-substituted-phenylalanine-containing dipeptide analogues in high yields and purities.[7] The side-chain-tethered phenylalanine building block may be used as a tool for the rapid synthesis of bioactive molecules in which the bulky nonpolar aromatic moiety plays a key role in the pharmacological effect. Using a similar strategy, α-amino acid building blocks derived from other aromatic rings can be constructed.

If libraries of target molecules require an aromatic side chain as an essential element for favorable interactions with the biological entity of interest, the α-amino acid can be replaced with other types of multifunctional units, such as β-amino acids. New amino acid building blocks can be designed to generate libraries of compounds containing the important aromatic side chain. As an example, the cyclo-β-tetrapeptide prepared by Seebach's group as a somatostatin analogue was found to display significant biological activity and affinity for human receptors.[8] This result suggests that the amino acid backbone can be replaced by other structures, supporting peptidomimetic approaches for peptide analogues.

β-Amino acids are frequently found in natural products and in therapeutic agents. Because of the enzymatic stability of β-peptides in biological systems, β-amino acids have become useful building blocks for the design of new peptidomimetics.[3] Although there are several known synthetic methods for β-amino acids, such as the Arndt−Eistert homologation of α-amino acids and catalytic hydrogenation of 3-aminoacrylate,[9] and a number of β-amino acids are commercially available, it is highly desirable to develop polymer-bound β-amino acid building blocks as a tool for the rapid synthesis and high diversification of compounds. Here we describe a synthetic route and applications of a side-chain-tethered β-homophenylalanine as an efficient tool to prepare β-amino acid analogues on a solid support.

Recently, a practical and highly enantioselective synthesis of *tert*-butanesulfinamide was reported by the Ellman group.[10] This chiral building block was used effectively for the asymmetric synthesis of α-branched amines[11] and β-amino acids.[12] It was also found that the *tert*-butanesulfinyl group acts as a Boc surrogate, which is advantageous for solid-phase reactions. This method for β-amino acid synthesis using *tert*-butanesulfinamide is generally applicable, and we found that it was well-adapted for the asymmetric synthesis of β-amino acid analogues with an aromatic side chain substituted with a silyl group, which was attached to a polymer support (Scheme 1).

Scheme 2. Synthesis of 3-Aryl-β-alanine-Containing Tripeptides from the Polymer-Bound β-Alanine Building Block



As illustrated in Scheme 1, commercially available 4-bromobenzaldehyde (**2**) was treated with ethylene glycol with a catalytic amount of *p*-toluenesulfonic acid to afford the 1,3-dioxolane derivative of **2**. Lithium−halogen exchange of the intermediate with *tert*-butyllithium at −78 °C followed by addition of allyldimethylsilyl chloride afforded **3** in an 86% yield from **2**. Refluxing of **3** in acetone in the presence of *p*-toluenesulfonic acid (cat) for 6 h provided 4-(allyldimethylsilyl)benzaldehyde (**4**) in an 86% yield. Alternatively, **4** was synthesized from 1,4-dibromobenzene (**5**) in a 67% yield by a two-step sequence: (1) replacement of one bromine with a silyl group and (2) replacement of the other bromine with a formylation reaction (*t*-BuLi, THF, −78 °C, then DMF). Condensation of **4** with (*R*)-(−)-*tert*-butanesulfinamide was performed in the presence of titanium propoxide in refluxing THF for 1 h to give the *tert*-butanesulfinyl imine **6** as an oil in a 68% yield. The titanium enolate generated by transmetalation of lithiated methyl acetate with $ClTi(O\text{-}i\text{-}Pr)_3$ in THF at −78 °C was allowed to react with **6** for 3 h to provide **7** in 79% yield. The diastereoselectivity of **7** was determined by the analysis of the Mosher amide **8**, prepared by deprotection of the *tert*-butanesulfinyl group (4 N HCl/dioxane, MeOH) followed by subsequent derivatization of the amino group with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MTPACl).[13] Analysis of both ^{1}H NMR and ^{19}F NMR spectra of **8** showed less than 1% of the minor diastereomer, which suggests that titanium enolate addition to the sulfinyl imine **6** proceeded in high stereoselectivity. Hydroboration of the terminal olefin of **7** with 9-BBN in THF followed by in situ Suzuki coupling[14] of the borane complex with bromopolystyrene resin[15] ($Pd(PPh_3)_4$, Na_2CO_3, in THF/DMF) resulted in the polymer-bound β-amino acid derivative **9**. The loading level (0.32 mequiv/g) of **9** was determined by mass balance of (3*R*)-methyl 3-amino-3-(4-bromophenyl)-butyrate (**10**), which was obtained by stirring an aliquot of resin **9** with 50% TFA in CH_2Cl_2 for 5 min followed by washing and then the cleavage reaction (Br_2, CH_2Cl_2, 20 min).

To demonstrate the suitability of building block **9** in solid-phase synthesis, we have prepared β-amino acid containing tripeptides **12** according to the procedure shown in Scheme 2.

Resin **9** was treated with 50% TFA in CH_2Cl_2 for 5 min to deprotect the amino group, which was treated with Fmoc-Ala-OH using standard EDC and HOBt coupling conditions in DMF; then the Fmoc group was deprotected with 20% piperidine in DMF for 30 min. After several washings of the resin, benzoic acid was coupled (EDC, HOBt, TEA in DMF) to the amine to construct the polymer-bound dipeptide anologue **11**. Hydrolysis of the ester group at the C-terminus

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(15) Farrall, M. J.; Frechet, J. M. *J. Org. Chem.* **1976**, *41*, 3877. The 4-bromopolystyrene resin (50−100 mesh, 1.97 mmol/g resin, produced by copolymerization of styrene, divinylbenzene (1%), and 4-bromostyrene) used in this study was purchased from Novabiochem Corp. (San Diego, CA).

of **11** was carried out with LiOH (5 equiv) in THF/H_2O (8:1) under refluxing conditions for 2.5 h, and the resulting carboxylic acid was coupled with Gly-OEt under the same conditions described above (EDC, HOBt, TEA in DMF). Upon completion of the synthesis, cleavage of the product with 50% TFA in CH_2Cl_2 at room temperature for 24 h yielded **12a** in 88% yield. Alternatively, cleavage of the tripeptide from the resin by *ipso* substitution of the silyl group with either Br_2 or ICl in CH_2Cl_2 for 20 min afforded **12b** and **12c**, respectively, in 95% yields. In all cases, the purity of **12**, as determined from the ^{1}H NMR spectra of the crude products, was greater than 95%. These results indicate the potential of building block **9** for the solid-phase synthesis of β-amino acid containing molecules and should be applicable to the generation of combinatorial libraries.

In conclusion, a side-chain-tethered β-amino acid building block has been developed as a tool for solid-phase synthesis of compounds in which the β-amino acid serves as an inert linker to facilitate maximal diversification of both the N- and C-termini. Cleavage of the product releases the aromatic linker moiety either with no substitution or with bromine or iodine at the *para* position under mild conditions. Because nonpolar aromatic rings play an important role as a pharmacophore in bioactive molecules, this building block may be used for the design of focused libraries containing a β-amino acid with a nonpolar aromatic side chain.

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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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