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LETTER

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Solid-Phase Synthesis of Tris-Benzamides as α-Helix Mimetics

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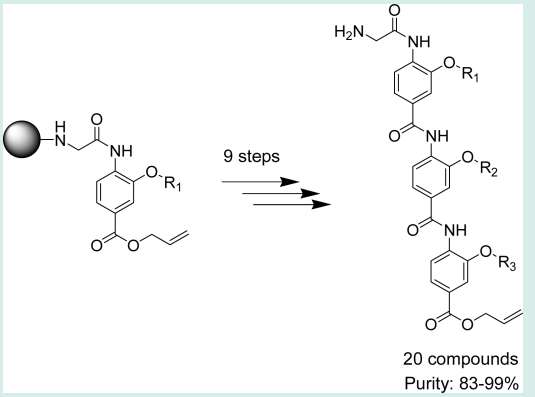
Supporting Information

ABSTRACT: Small molecules mimicking α-helices are of great interest since numerous protein−protein interactions use helical structures at the interface. With a goal of generating libraries of α-helix mimetics, an efficient solid-phase synthetic method was developed to produce tris-benzamides. The tris-benzamide scaffold was designed to place three side-chain functional groups found at the *i*, *i* + 4, and *i* + 7 positions of an α-helix, emulating one helical face. The synthetic strategy involves simple and iterative reactions of removal of an allyl ester, formation of an amide bond via an O → N acyl migration, and an O-alkylation. A small library of twenty tris-benzamides containing a variety of functional groups was prepared in high purity (83−99%) to demonstrate the versatility of the synthetic approach. This methodology allowed the facile and rapid construction of α-helix mimetics that would facilitate the identification of small molecules for target proteins.



KEYWORDS: α-helix mimetics, tris-benzamide scaffold, solid-phase synthesis, protein−protein interaction

At the interface of protein−protein interactions (PPI), α-helical structures are frequently found and mediate numerous key cellular functions, such as enzyme activity, protein synthesis, transcription, DNA binding, immune response, and signal transduction.[1] PPI through α-helices is thus recognized as attractive targets to intervene for treating diverse human diseases including cancer, neurological disorder, and viral infection.[2,3] This indicates that helical peptides are of high interest in developing new therapeutic candidates. However, short peptides often lose their well-defined structures or adopt less organized conformations in solution, resulting in decreased binding affinities to their targets.[4,5] In addition, short peptides are prone to be proteolytically degraded, especially in an extended conformation, and have difficulty in penetrating cellular membranes.[6,7] These factors severely compromise effective use of short peptides as PPI modulators.

Several strategies have been developed to stabilize helical conformations in short peptides. In addition to restricting torsional rotations in peptide backbones by incorporating non-natural amino acids like Aib,[8] arranging side chains in close proximity by forming a covalent bond or noncovalent interaction was found to enhance helicity of peptides.[9−15] Furthermore, foldamers like *β*-peptides have demonstrated stable helical conformations, as well as a resistance to proteases.[16]

As an alternative approach, nonpeptidic α-helix mimetics have been developed to reproduce side chain functional groups found in α-helical segments.[3,17] They are composed of rigid and preorganized scaffolds that are designed to place their substituents in the same spatial arrangement as an α-helix does. Due to their nonpeptidic structures, α-helix mimetics acquire high resistance to proteolytic cleavages and effective cell permeability. To date, a number of α-helix mimetics have been reported based on scaffolds like indanes,[18] terphenyls,[19] tris-pyridylamides,[20] trans-fused polycyclic ethers,[21] tris-benzamides,[22] pyridazines,[23] dipiperazinobenzenes,[24] and 2,5-terpyrimidinylenes.[25] Most of these scaffolds project three functional groups corresponding to the side chains of amino acids found at the *i*, *i* + 4 (or *i* + 3), and *i* + 7 positions of an α-helix, constituting one helical face. The utility of α-helix mimetics was well demonstrated by studies of disrupting various protein−protein interactions including Bcl-x_L/Bak[19b] and MDM2/p53.[22d] Recently, amphiphilic α-helix mimetics were also designed based on a bis-benzamide scaffold to present the functional groups found on two opposing helical sides.[26]

Primary sequences of α-helical segments in peptides and proteins can guide initial design of suitable α-helix mimetics. However, generating a number of α-helix mimetics has been frequently practiced to rapidly identify compounds with high potency in disrupting protein complex formations by exploring diverse functional groups as substituents for increasing their binding affinity to target proteins. In addition, fine-tuning of the substituents is often required to optimize initial leads because α-helix mimetics may have slightly different spatial arrangements of functional groups from an ideal helix, or a helical segment corresponding to α-helix mimetics may adopt a slightly altered helical structure from an ideal one. Therefore, constructing libraries of α-helix mimetics are of great use and solid-phase technique will be a suitable synthetic platform because of its facile achievement of complete conversion of reactions through the use

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of excessive reagents and easy separation of unreacted reagents from products bound on solid supports.

Among many α-helix mimetics reported to date, the tris-benzamides[22a] that we recently developed appear to be ideal to build combinatorial libraries because of its straightforward and high-yielding reactions involved in the synthesis. The tris-benzamide scaffold can easily place three functional groups corresponding to the side chains of the *i*th, $i + 4$th (or $i + 3$rd), and $i + 7$th residues of an α-helix, and these three substituents organize one side of two helical turns. Solution-phase synthesis of tris-benzamides can be achieved by using simple amide bond formation and *O*-alkylation reactions that are compatible for solid-phase strategy. With readily available starting materials, we have thus developed a parallel solid-phase synthetic method for efficient and rapid construction of tris-benzamides as α-helix mimetics.

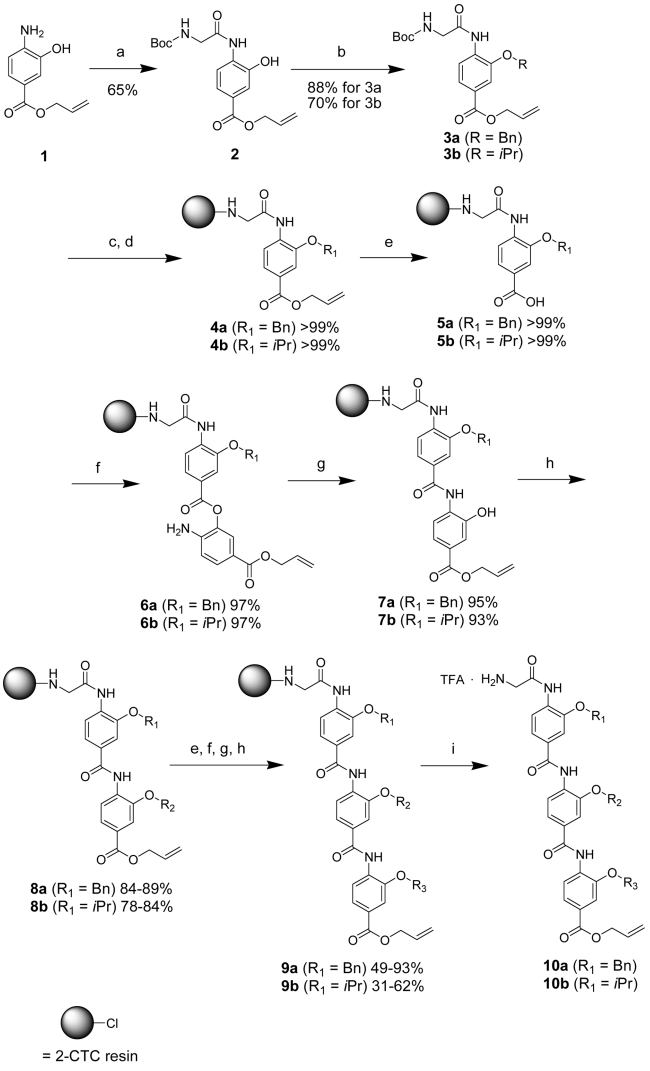
The solution-phase synthesis of tris-benzamides started from a commercially available 4-amino-3-hydroxybenzoic acid and proceeded in the N → C direction by carrying out iterative amide bond formation and O-alkylation reactions. The construction of tris-benzamides in the opposite C → N direction by using two 3-alkoxy-4-aminobenzoates has not been successful because of the significantly lowered nucleophilicity of the 4-amino group and electrophilicity of the 1-benzoic acid group, as well as a potential steric hindrance from a 3-alkoxy substituent (Scheme S1 in Supporting Information).[22a] Thus, a solid-phase synthetic route was also sought in the same N → C direction with the N-terminus of a tris-benzamide anchored to a solid support. Since the weak nucleophilicity of the 4-amino-3-hydroxybenzoate **1** also resulted in a poor loading yield to 2-chlorotritylchloride (2-CTC) resin, a glycine was introduced as a spacer to achieve efficient loading. In addition, the ammonium group of the glycine moiety was found to improve the solubility of tris-benzamides in water.

To demonstrate the synthetic feasibility of tris-benzamides containing a glycine at the N-terminus and optimize reaction conditions that would be later applied to solid-phase synthesis, a Boc-Gly-tris-benzamide bearing three benzyl groups **S6** was synthesized in solution-phase (Scheme S1 in Supporting Information). Instead of the methyl ester used in the previously reported synthesis of tris-benzamides,[22a] an allyl ester was employed as a protecting group for the 1-benzoic acid group since saponification with a hydroxide unexpectedly brought in cleavage of glycine anilides. In contrast, selective removal of an allyl ester was easily accomplished in a mild condition by using Pd^0 in both solution- and solid-phase without affecting the anilide bond.[10c]

An allyl 4-amino-3-hydroxybenzoate **1** was prepared from a 4-amino-3-hydroxybenzoic acid by acid-catalyzed esterification and used as a submonomer in the synthesis of tris-benzamides (Scheme 1). After the benzoate **2** was prepared by coupling Boc-Gly to **1**, it was treated with benzyl bromide and NaH yielding the monobenzamide **3a** with the first benzyl group that represents a side chain at the *i* position in high yield (Scheme 1). The synthesis of the tris-benzamide **S6** was completed from the monobenzamide **3a** in 22% yield over 8 steps by iterating the steps of the allyl ester removal, O-acylation, O → N acyl migration,[27] and O-alkylation, placing three benzyl groups that correspond to the side chains at the *i*, $i + 4$ (or $i + 3$), and $i + 7$ positions of a helix (Scheme S1 in Supporting Information).

Optimization of these reaction steps in solid-phase started with choosing an adequate solid support/linker system. As a widely used polymer support, polystyrene-based 2-chlorotritylchloride (2-CTC) resin has several advantages.[28] First, efficient attachment

Scheme 1. Solid-Phase Synthesis of Tris-Benzamides 10[a]



[a] Reagents and conditions: (a) Boc-Gly, PyBOP, DIEA, DCM, rt, 12 h; (b) NaH, Bn-Br, DMF, rt, 3 h for **3a**, NaH, *i*Pr−Br, DMF, rt, 12 h for **3b**; (c) 50% TFA/DCM, rt, 4 h; (d) (1) 2-CTC resin, DIEA, DMF, rt, 4 h, (2) 10% DIEA/MeOH, DMF, rt, 4 h; (e) $Pd(PPh_3)_4$, $PhSiH_3$, $CHCl_3$, rt, 1 h; (f) **1**, PyBOP, DIEA, DMF, rt, 20 h; (g) NaH, TBAB, DMF, rt, 1 h; (h) R_2-X (or R_3-X), Cs_2CO_3, TBAB, DMF, rt, 12 h (or 24 h); (i) 10% TFA/DCM, rt, 10 min for **10a**, (1) 1% TFA/DCM, rt, 5 min, (2) TFA/TIS/H_2O (95:2.5:2.5), rt, 1 h for **10b**.

to the resin can be achieved without an activating or coupling step. Second, final products can be released from the resin with a weak acid in a fully protected form that may contain even acid-labile protecting groups like Boc and *t*Bu. This allows that released and protected products can be readily used for further reactions if necessary. Third, the sterically bulky trityl linker makes a secondary amine formed by reacting the resin with a glycinylbenzoate unreactive during the construction of tris-benzamides.

With the 2-CTC resin as a polymer support, each reaction step was examined in solid-phase (Scheme 1 and Scheme S2 and Table S1 in Supporting Information). As the first residue, a glycinylbenzoate **3** that already bears an alkyl group was used because the 3-hydroxyl group of an unalkylated glycinylbenzoate (e.g., **2** or **S7**) underwent an O-capping reaction with the

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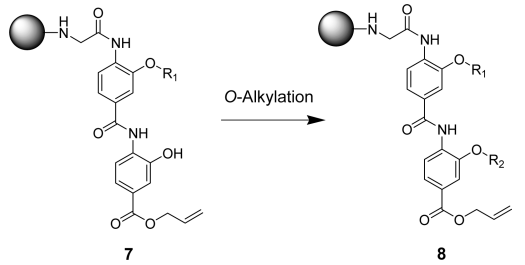
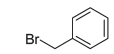
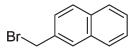
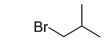
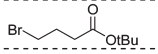
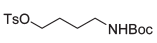
Table 1. O-Alkylation of the Resin-Bound Phenol 7[a]



Entry	R_1	R_2-X (equiv)	Cs_2CO_3 (equiv)	TBAB (equiv)	Reaction Time (h)	Purity (%)[b]
1	Bn		(10)	5	5	12	80
2	Bn		(5)	2	2	12	76 (84[c])
3	Bn		(5)	2	0	12	78
4	Bn		(10)	5	5	12	84
5	Bn		(5)	2	2	12	79 (86[c])
6	Bn		(5)	2	0	12	74
7	Bn		(10)	5	5	24	82 (84[c])
8	Bn		(10)	2	2	24	67 (89[c])
9	Bn		(10)	2	0	24	63 (75[c])
10	Bn		(10)	5	5	24	69 (78[c])
11	Bn		(10)	2	2	24	43 (88[c])
12	Bn		(10)	2	0	24	39 (61[c])
13	*i*Pr		(10)	2	2	24	78[c]
14	*i*Pr		(10)	2	2	24	84[c]

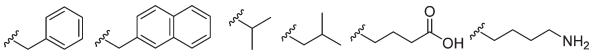
[a] Reaction conditions: the phenol **7**, an alkyl halide, Cs_2CO_3, TBAB, DMF, rt. [b] Purity was determined by analytical RP-HPLC. [c] O-Alkylation reaction was repeated twice.

2-chlorotrityl linker during the loading step, lowering yields of the subsequent O-alkylation reactions (Scheme S2 and Table S1 in Supporting Information). After removing the Boc protecting group, the glycinylbenzoate containing a 3-alkyloxy substituent was reacted with the 2-CTC resin yielding the resin-bound 3-alkyoxybenzoate **4**.

The subsequent removal of the allyl ester with $Pd(PPh_3)_4$ and coupling of the resulting carboxylic acid **5** with the submonomer **1** then led to the production of a mixture of the *O*- and *N*-acyl products (**6** and **7**, respectively) although the former was the major product. Because of the poor reactivity of the 4-amino group, the O-acyl product **6** was formed along with the desired N-acyl products **7**. To convert the O-acyl product **6** into the N-acyl product **7**, several bases (e.g., Cs_2CO_3, $NaOCH_3$, and NaH) were examined for the O → N acyl migration[27] in solid-phase, and NaH was found to be the most efficient despite its heterogeneous reaction condition (see Supporting Information for the solid-phase O → N acyl migration).

With the resin-bound phenol **7**, O-alkylation reactions with a variety of alkyl halides were examined (Table 1). Hydrophobic functional groups, such as benzyl, 2-naphthylmethyl (NAP), isopropyl, and isobutyl groups, were installed on the 3-hydroxyl group of **7a** to represent the side chains of Phe, Trp, Val, and Leu, respectively (Chart 1). In the beginning, O-alkylation reactions were carried out by using Cs_2CO_3 (5 equiv) and an alkyl bromide (10 equiv) in the presence of tetrabutylammonium bromide (TBAB, 5 equiv) in DMF for 12 h at room temperature. Although the reactions with reactive alkyl halides, in particular benzyl bromide and 2-naphthylmethyl bromide, showed complete consumption of the phenol **7a** and gave products with high yields

Chart 1. Substituents Placed on Tris-Benzamides to Represent the Side Chains of Amino Acids in an α-Helix



(**8a**{*1*} and **8a**{*2*} in 80% and 84% purity, respectively; entry 1 and 4 in Table 1), this reaction condition brought in the formation of a small amount of byproducts.

To carry out the reaction with minimal formation of the byproducts and in turn to achieve a higher purity, stoichiometry of the reactants, and additive was varied. The alkylation reaction with 2 equiv of a base and 5 equiv of an alkyl bromide in the presence of 2 equiv of TBAB was found to be the most effective and resulted in products without the byproduct formation in comparable yields (76% with benzyl bromide and 79% for 2-naphthylmethyl bromide; entry 2 and 5, respectively). The yield of the O-alkylation reaction was further increased by repeating the reactions twice (84−86%; entries 2 and 5). The reactive alkyl halides do not appear to need TBAB since comparable yields were obtained without it (entries 3 and 6).

Other alkyl substituents like isopropyl and isobutyl groups were introduced to the phenol **7a** in a similar manner by using 2-bromopropane and 1-bromo-2-methylpropane. These alkylation reactions were found to be substantially slower than those with the reactive alkyl halides, requiring 24 h even for lower conversions. However, repeating the alkylation reactions twice again resulted in acceptable yields in the production of **8a**{*3*} and **8a**{*4*} (89% and 88%, respectively; entries 8 and 11). Unlike the alkylation reactions with the reactive alkyl bromides, TBAB clearly assisted to obtain higher conversions with the less reactive alkyl bromides (entry 9 and 12). Accordingly, chemset **8a**{*1*−*4*} containing two hydrophobic functional groups (R_1 and R_2) that represent the side chains at the *i* and *i*+*4* positions of a helix was efficiently prepared on the 2-CTC resin.

In addition to the hydrophobic functional groups, hydrophilic ones like 3-carboxypropyl (CPr) and 4-aminobutyl (ABu) groups were also introduced as R_2 to represent the side chains of Glu and Lys, respectively. The optimized reaction condition for less reactive alkyl halides allowed to the preparation of chemset **8b**{*5*−*6*} in 78% and 84% purities, respectively (entry 13 and 14) with *t*-butyl 4-bromobutyrate[29] and 4-(*t*-butoxycarbonylamino)butyl tosylate.[30] The *t*-butyl protecting groups of the hydrophilic substituents can be easily removed with TFA at high concentrations at the end of the synthesis.

Starting from the resin-bound benzoate **4**, the synthesis of the bis-benzamide **8** that contains two substituents was carried out over the four steps of the ally ester removal, O-acylation with the submonomer **1**, O → N acyl migration, and O-alkylation. Iteration of these reactions with various alkyl halides finished the construction of the tris-benzamide **9** that has three functional groups to mimic amino acids at the *i*, *i* + 4, and *i* + 7 positions of a helix. As already demonstrated with the benzoate **4**, these steps proceeded in high efficiency with the bis-benzamide **8** resulting in the crude tris-benzamide **9** in overall purity of 31−93%.

Upon completion of the solid-phase synthesis, the resin-bound tris-benzamide **9a** was treated with 10% TFA in DCM releasing chemset **10a**{*1*−*4*,*1*−*4*} that contains a benzyl group as R_1 and

Table 2. Characterization of the Synthesized Tris-Benzamide 10

compound	R_1	R_2	R_3	purity (%)[a]	yield (%)[b]
10a{*1,1*}	Bn	Bn	Bn	93	12
10a{*1,2*}	Bn	Bn	NAP[c]	88	43
10a{*1,3*}	Bn	Bn	*i*Pr	84	14
10a{*1,4*}	Bn	Bn	*i*Bu	96	22
10a{*2,1*}	Bn	NAP	Bn	93	82
10a{*2,2*}	Bn	NAP	NAP	88	79
10a{*2,3*}	Bn	NAP	*i*Pr	88	43
10a{*2,4*}	Bn	NAP	*i*Bu	98	8
10a{*3,1*}	Bn	*i*Pr	Bn	87	47
10a{*3,2*}	Bn	*i*Pr	NAP	83	31
10a{*3,3*}	Bn	*i*Pr	*i*Pr	86	30
10a{*3,4*}	Bn	*i*Pr	*i*Bu	98	8
10a{*4,1*}	Bn	*i*Bu	Bn	83	8
10a{*4,2*}	Bn	*i*Bu	NAP	97	66
10a{*4,3*}	Bn	*i*Bu	*i*Pr	98	26
10a{*4,4*}	Bn	*i*Bu	*i*Bu	93	26
10b{*5,5*}	*i*Pr	CPr[d]	CPr	95	6
10b{*5,6*}	*i*Pr	CPr	ABu[e]	83	17
10b{*6,5*}	*i*Pr	ABu	CPr	95	6
10b{*6,6*}	*i*Pr	ABu	ABu	99	13

[a] Purity was determined by analytical RP-HPLC. [b] Isolation yield after precipitation. [c] NAP, 2-naphthylmethyl. [d] CPr, 3-carboxypropyl. [e] ABu, 4-aminobutyl.

hydrophobic substituents (Bn, NAP, *i*Pr, and *i*Bu) as R_2 and R_3. Whereas the purity of the crude products **10a**{*1*−*4,1*−*4*} was found to be outstanding over ten steps (49−93%), it was further improved (83−98%) by a simple purification step of precipitation in THF/H_2O. Final products were obtained in quantity of 4−36 mg in high purity (83−98%) with overall yields ranging from 8% to 82% (Table 2). To obtain tris-benzamides containing hydrophilic substituents, the tris-benzamide **9b** was treated with 1% TFA in DCM, and the resulting TFA salts were precipitated with water. This allowed the preparation of *t*Bu-protected tris-benzamides that can be readily used for further reactions if desired. The *t*Bu-protected tris-benzamides was treated with TFA/TIS/H_2O (95:2.5:2.5), producing chemset **10b**{*5*−*6,5*−*6*} bearing the hydrophilic side chains (CPr and ABu) as R_2 and R_3 in high purity (83−99%).

In summary, we have developed a solid-phase strategy for the synthesis of α-helix mimetics by using a tris-benzamide scaffold that was designed to place three side chain functional groups of amino acids found at the *i*, *i* + 4, and *i* + 7 position of an α-helix. The solid-phase synthesis involves four iterative steps of allyl ester removal, O-acylation, O → N acyl migration, and O-alkylation. After optimizing each reaction step, a small library of tris-benzamides containing a variety of substituents was efficiently constructed on 2-CTC resin. Both hydrophobic (benzyl, 2-naphthylmethyl, isopropyl, and isobutyl) and hydrophilic (3-carboxypropyl and 4-aminobutyl) functional groups were introduced as substituents to make structurally diverse α-helix mimetics. To demonstrate proof of concept, twenty tris-benzamides were synthesized in high purity with moderate to outstanding yields. This solid-phase synthetic route offers rapid access to a library of α-helix mimetics as an effective tool for identifying potent inhibitors of protein−protein interactions involving α-helices at the interface.

EXPERIMENTAL PROCEDURES

General Procedure for Solid-Phase Removal of an Allyl Ester. A resin-bound allyl ester (0.05 mmol) was swollen in $CHCl_3$ (6 mL) for 30 min and treated with $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol) and phenylsilane (0.062 mL, 0.50 mmol). After the reaction mixture was manually stirred for 1 h at room temperature, the resin was filtered, washed with DMF (6 mL × 3) and DCM (6 mL × 3), and dried in vacuo.

General Procedure for Solid-Phase Coupling of the Submonomer 1. A resin-bound carboxylic acid (0.05 mmol) was swollen in DMF (6 mL) for 30 min and reacted with the submonomer **1** (48 mg, 0.25 mmol), PyBOP (130 mg, 0.25 mmol), and DIEA (0.086 mL, 0.50 mmol). After the reaction mixture was shaken at room temperature for 20 h, the resin was filtered, washed with DMF (6 mL × 3) and DCM (6 mL × 3), and dried in vacuo.

General Procedure for Solid-Phase O → N Acyl Migration. A resin-bound O-acyl intermediate (0.05 mmol) was swollen in DMF (6 mL) for 30 min and treated with NaH (60% suspension in oil, 8.0 mg, 0.20 mmol) and TBAB (66 mg, 0.20 mmol). After the reaction mixture was manually stirred for 1 h at room temperature, the resin was filtered and washed with DMF (6 mL × 5), DMF/H_2O (4:1, 6 mL × 5), DMF (6 mL × 5) and DCM (6 mL × 5), and dried in vacuo.

General Procedure for Solid-Phase O-Alkylation. A resin-bound phenol (0.05 mmol) was swollen in DMF (6 mL) for 30 min and treated with Cs_2CO_3 (33 mg, 0.10 mmol), TBAB (33 mg 0.10 mmol), and an alkyl halide (0.25 or 0.50 mmol). After the reaction mixture was shaken at room temperature for 12 h (or 24 h), the resin was filtered and washed with DMF (6 mL × 3). This procedure was repeated, then the resin was filtered, washed with DMF/H_2O (4:1, 6 mL × 5), DMF (6 mL × 5), and DCM (6 mL × 5), and dried in vacuo.

ASSOCIATED CONTENT

Supporting Information. Experimental details, HRMS, ^1H and ^{13}C NMR spectra of compounds **1**−**3**, **S1**−**S7**, **S11**−**S12** and HRMS, ^1H NMR spectra, and HPLC chromatograms of **10a**{*1*−*4,1*−*4*} and **10b**{*5*−*6,5*−*6*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

T.K.L and J.M.A. conceived and designed the experiments. T.K.L. performed the experiments. T.K.L. and J.M.A. cowrote the manuscript and Supporting Information.

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ABBREVIATIONS:

ABu, 4-aminobutyl; CPr, 3-carboxypropyl; CTC, chlorotritylchloride; DCM, dichloromethane; DIEA, *N*,*N*-diisopropylethylamine;

DMF, *N*,*N*-dimethylformamide; NAP, naphthylmethyl; PPI, protein−protein interaction; PyBOP, benzotriazol-1-yloxytri-(pyrrolidino)phosphonium hexafluorophosphate; TBAB, tetrabutylammonium bromide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIS, triisopropylsilane

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