# Synthesis of Poly(aryl benzyl ether) Dendrimers on Solid Support

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ABSTRACT: Dendronized supports, combining core Wang resin and poly(aryl benzyl ether) dendrons, were prepared using a novel route. Employing a dimethyl 5-hydroxyisophthalate module and a Mitsunobu condensation/ester reduction iterative sequence, the dendrimer was cleanly and efficiently prepared to the third generation. The synthesis was monitored using gel-phase $^{13}C$ NMR and acidolytic cleavage, followed by $^{1}H$ NMR. Gel-phase NMR and swelling experiments demonstrated that the behavior of the dendronized resins in various solvents is strongly influenced by the peripheral functional groups. Synthesis of a cinnamate derivative (via Mitsunobu and Heck reactions) and of a tripeptide demonstrated suitability of the dendronized support for solid-phase synthesis.

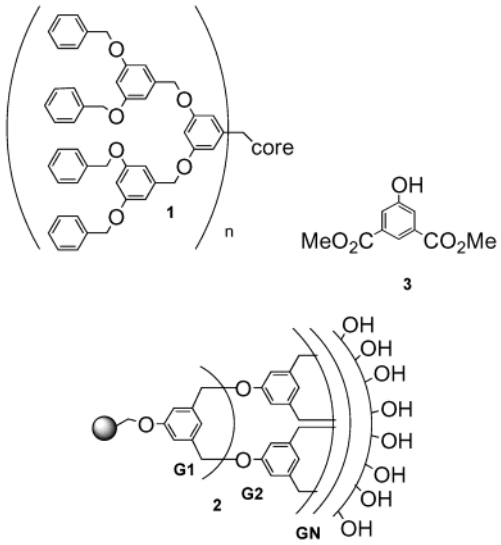
## Introduction

Dendrimers are branched, highly ordered oligomers, which are assembled in a modular fashion from polyfunctional building blocks and utilized for a surprisingly wide spectrum of applications.[1−3] While the majority of dendrimeric structures were prepared using orthodox solution chemistry, increasing attention has recently been diverted to dendrimer preparation on solid support.[4] Solid-phase synthesis can provide solutions to a number of problems associated with dendrimer preparation and, particularly, the time-consuming purifications.[5] Solid-phase synthesis can also markedly improve the yield and homogeneity of the formed dendrimer. Over the past decade, a number of dendrimers have been prepared on solid support. In addition to the polylysine dendrimers, used mainly as cores for MAP-induced antibody elicitation (MAP = multiple antigenic peptides),[6] a number of other polyamide dendrimeric systems have also been prepared on solid support.[5,7−9] These include the cornerstone work of Bradley and co-workers on poly(amidoamine) (PAMAM) and poly(amidourea) dendrimers.[5,7]

We recently became interested in generating chemically robust dendritic templates on solid support for catalytic studies. Unfortunately, all supported dendrimers known prior to the beginning of our work contained units (amides, amines, etc.) that are unstable during some synthetic transformations or that coordinate metallic catalytic centers.[10] Therefore, we decided to prepare a supported amine- and carbonyl-free dendrimer, based on ether linkage, between modules.

Poly(aryl benzyl ether) dendrimers (**1**) in solution were introduced by Fréchet[2] and extensively exploited.[11] Such dendrimers are assembled via a convergent route. On solid support, however, a divergent route must be adopted. Thus, we focused our attention on the on-resin assembly of "inverse" Fréchet-type dendrons **2**.

This modified Fréchet-type aryl benzyl ether dendrimer (**2**) was prepared to the third generation, with excellent results, using the Wang resin and the commercially available dimethyl 5-hydroxyisophthalate module **3**. While this report was being prepared, an alternative synthetic route to this dendrimer on related supports was reported.[12]




## Results and Discussion

Throughout our research, we used acidolytic cleavage (1:1 TFA/$CDCl_3$, TFA = trifluoroacetic acid) followed by $^{1}H$ and $^{13}C$ NMR measurements and a gel-phase $^{13}C$ NMR technique for monitoring the reactions and characterizing the products.

Initially, we planned to use the triol unit **4**, obtained by reduction of **3**, for the construction of the dendrons.[13] The obvious strategy for the assembly of dendrons from this monomer is repetitive Williamson etherification/bromodehydroxylation of the benzyl alcohol groups. Although **4** can be attached to solid support via selective phenol alkylation (eq 1), despite unprotected benzylic alcohols, we could not effectively brominate the benzylic alcohols and had to abandon this approach.

An alternate pathway was developed. According to this synthetic strategy, the Mitsunobu reaction was used to immobilize **3** onto the Wang resin. The immobilized diester was then reduced to form bis(benzyl) alcohol. This Mitsunobu/ester reduction iterative se-

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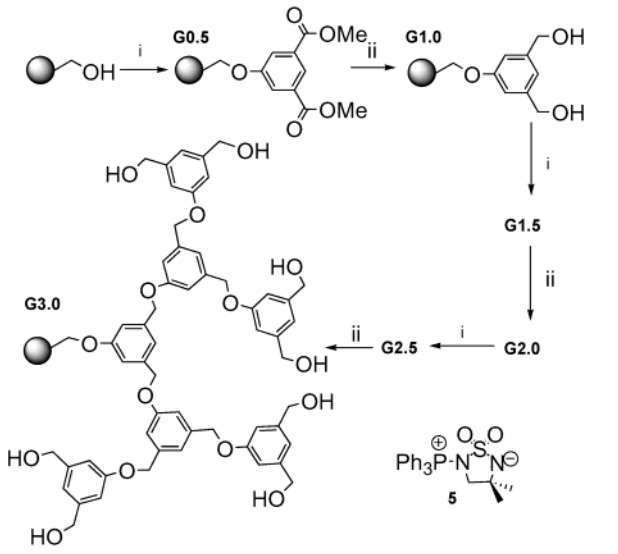
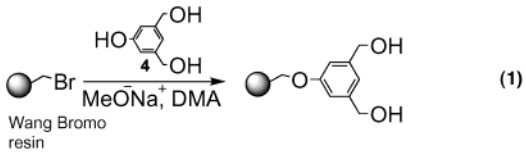
**Scheme 1**




(i) **3**, **5**, DCM; (ii) $LiBH_4$, $B(OMe)_3$, THF, 65 °C.

quence can be used for the preparation of the higher dendrimer generations.




(1)

The Mitsunobu coupling of **3** to the Wang resin was tested using standard conditions with diethyl azodicarboxylate (DEAD).[14] The reaction formed the desired resin **G0.5** with insufficient purity. The cleavage determined that the hydroxyisophthalate was contaminated by the reduced DEAD byproducts. Employing diisopropyl azodicarboxylate (DIAD), instead of DEAD, reduced the problem but still provided slightly impure material. Using the triphenylphosphine-sulfonamide betaine **5**,[15] however, yielded extremely gratifying results (Scheme 1). The best outcome was obtained when the procedure was repeated twice using 3 equiv (0.2 M) of the betaine and 3 equiv (0.2 M) of the diester in $CH_2Cl_2$ at room temperature for 24 h. Gel-phase $^{13}C$ NMR spectroscopy demonstrated complete conversion and a very clean resin **G0.5**. $^1H$ and $^{13}C$ NMR of a cleavage solution of **G0.5** exhibited only the signals of **3** and confirmed a perfect purity and quantitative yield.

$LiAlH_4$, diisobutylaluminum hydride (DIBAL-H), or sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) induced reduction of the diester resin **G0.5** to the diol resin **G1.0** proceeded to completion. However, deterioration of the resin quality usually occurred, presumably as a result of aluminate precipitation in the polystyrene matrix. The best outcome was achieved with $LiBH_4$ (Scheme 1). Using 10 equiv (0.77 M) of $LiBH_4$ and a catalytic amount of trimethylborate in refluxing THF overnight gave a quantitative yield and a very clean diol resin **G1.0**. $^1H$ and $^{13}C$ NMR spectra of a TFA/$CDCl_3$ cleavage solution of **G1.0** demonstrated complete conversion of the diester into the diol and perfect purity of the resin. $^{13}C$ gel-phase NMR spectrum exhibited solely the expected signals of **G1.0**. Using the internal standard of the cleavage solution, a 94% yield was determined.

Repetitive Mitsunobu coupling and an ester reduction sequence lead to the formation of second and third generation dendrimers (Scheme 1, resins **G2.0** and **G3.0**). Gel-phase $^{13}C$ NMR spectroscopy of the resins was used to monitor the synthetic transformations. The structure and purity of the dendrimers were determined via TFA-induced cleavage, followed by $^1H$ NMR, $^{13}C$ NMR, and MS analysis. Thus, $^1H$ NMR demonstrated that each reduction was accompanied by the disappearance of the carboxymethyl signal at 4.0 ppm and appearance of the $CH_2OH$ and $CH_2OCOCF_3$ signals at 4.8 and 5.4 ppm, respectively. Likewise, the distinct downfield aromatic signals of isophthalate (7.9 and 8.3 ppm) disappeared entirely. The Mitsunobu coupling steps were accompanied by the disappearance of the $CH_2OH$ and $CH_2OCOCF_3$ signals and appearance of the carboxymethyl and downfield aromatic signals of the isophthalate units. The same spectra also clearly demonstrated that neither **G1.5** nor **G2.5** contained any **G0.5**-like impurities since the aromatic signals of a simple hydroxy isophthalate are clearly distinct from those of isophthalates in higher generation dendrons (see the Experimental Section). The purity of each step is excellent as confirmed by the cleavage analysis. The absence of imperfect dendrons was likewise demonstrated for **G2.5** using MALDI−TOF. Besides the major signal ($(M + Na)^+$), no imperfect or lower generation dendrons were observed.[16] Moreover, according to the gel-phase $^{13}C$ NMR, there are no observable impurities on the support.[17]

According to the cleavage analysis and quantification, the overall yield of resin **G3.0** is 82%. Careful analysis of the outcome of each synthetic step en route to **G3.0** demonstrated that, while the Mitsunobu steps of the repetitive sequence are practically quantitative, the reduction step produces slightly lower yields.

An important observation was made during the dendrimer analysis using gel-phase $^{13}C$ NMR. Good gel-phase spectra were observed for Wang, **G0.5**, **G1.0**, **G1.5**, and **G2.5** resins swollen in benzene-$d_6$ (our regular conditions for polystyrene support). Under the same conditions, the only observable signal in the gel-phase $^{13}C$ NMR of the **G2.0** and **G3.0** resins was the residual benzene peak. For **G2.0**, traces of the polymeric matrix signals were observed as low broad hills while, for **G3.0**, these signals disappeared completely (Figure 1a). Remarkably, good gel-phase $^{13}C$ NMR spectra were obtained for both "problematic" resins in dioxane-$d_8$. The resolution improved upon addition of a small amount (ca. 10%) of methanol-$d_4$ (Figure 1b). This is probably due to the high density of the hydroxylic groups in the periphery of **G2.0** and, especially, that of **G3.0**. This high density of the hydroxy groups seems to generate a hydrogen-bonded hydrophilic "film" that prevents the proper swelling of the polystyrene core polymer in benzene.

As was revealed by the swelling studies, the size of the dry and swollen beads as well as the speed of the swelling are both affected by the dendronization. The average size of the beads of the hydroxy-terminated resins, in different solvents, was measured by optical microscopy (Table 1).[18] In general, the diameter of the dry resin steadily increases from Wang resin to **G3.0** (by 14%).[19] Likewise, there is a noteble drop in the swelling ability of the dendronized beads as compared to Wang resin. While the swelling of **G3.0** in DMF and dioxane is still very good (152% and 144% of the

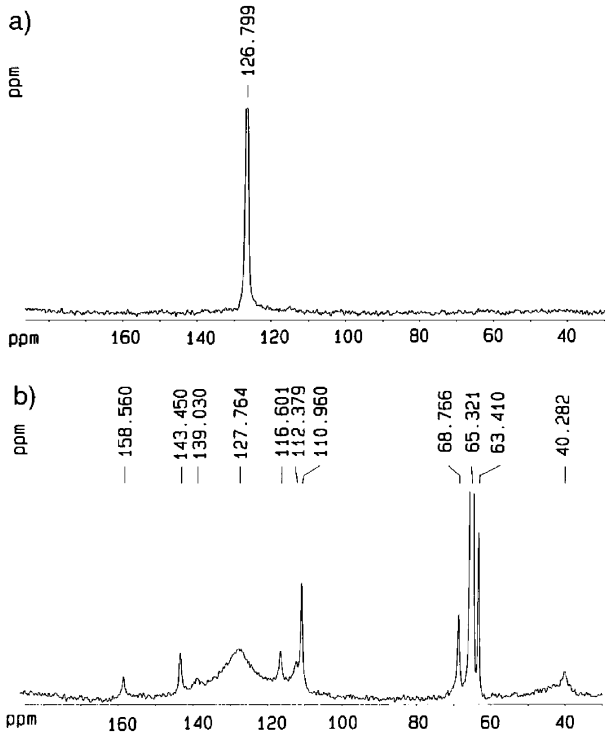



**Figure 1.** On-resin $^{13}C$ NMR of **G3.0** (a) in benzene and (b) in dioxane:MeOH (9:1).

**Table 1. Average Bead Size[a] of Resins Incubated in Different Solvents (Average of 13 Beads)[b]**

| | dry | benzene | dioxane | DMF | $^{i}$PrOH |
|---|---|---|---|---|---|
| Wang | 102 | 161 | 169 | 164 | 95 |
| **G1.0** | 103 | 134 | 158 | 134 | 96 |
| **G2.0** | 113 | 132 | 160 | 161 | 98 |
| **G3.0** | 116 | 113 | 167 | 176 | 114 |

[a] Diameter in $\mu$m. [b] Measured after 2 min (Wang resin in benzene, DMF, dioxane), 5 min (**G1.0** in dioxane, DMF), 10 min (**G2.0**, **G3.0** in dioxane, DMF), 20 min (**G1.0** in benzene), 40 min (**G2.0** in benzene), and 60 min (**G3.0** in benzene, all resins in $^{i}$PrOH).

diameter of the dry beads), it is somewhat lower than that of Wang resin (161% and 166%). The size of the beads in benzene, however, steadily decreases from the Wang resin to **G3.0**, indicating complete loss of the swelling ability in benzene by the latter.

The most striking effect of the resin structure is on the time it takes for the resins to swell. Thus, while the Wang resin swells instantaneously in DMF, dioxane and benzene (Figure 2b,d), the rate of swelling slows with each additional dendrimeric "layer". The behavior in various solvents is remarkably different, however, for the ester resins (**G0.5**, **G1.5**, **G2.5**) and the alcohol resins (**G1.0**, **G2.0**, **G3.0**). Thus, the hydroxy-terminated resins swell reasonably fast in dioxane (Figure 2e) and even better in DMF (less than a minute for **G1.0**, a matter of minutes even for **G3.0**). However, there is a significant increase in the swelling time of **G1.0** and even more of **G2.0** in benzene. As aforementioned, **G3.0** practically does not swell in benzene at all (Figure 2c). An opposite trend is observed for the ester-terminated resins. In benzene, the resins swell reasonably fast (minutes, even for **G2.5**). In dioxane and DMF the swelling is significantly slower. Thus, after an hour in DMF many of the **G2.5** beads still have a dry central area (Figure 2a). We measured the progress of the swelling of ester-terminated resins in DMF, counting

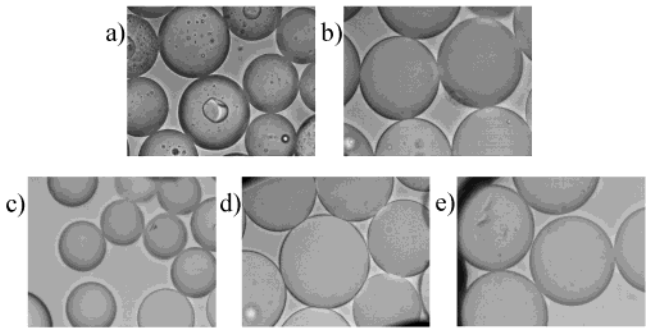



**Figure 2.** Swelling of (a) **G2.5** in DMF (after 1 h), (b) Wang in DMF (after 2 min),(c) **G3.0** in benzene (after 1 h), (d) Wang in benzene (after 2 min), and (e) **G3.0** in dioxane (after 10 min). Picture dimensions are 420 $\mu$m × 335 $\mu$m.

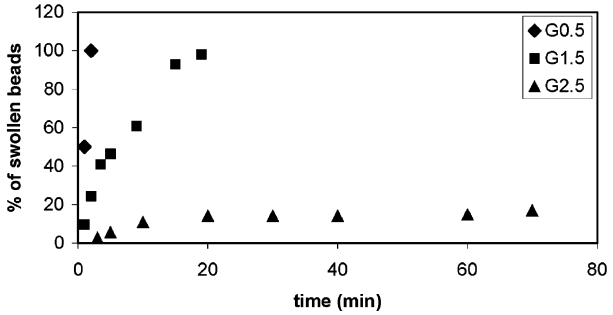
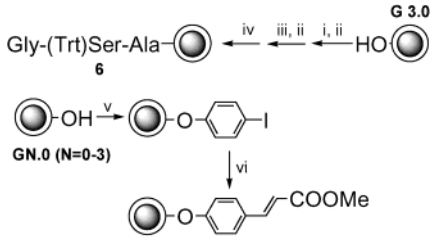



**Figure 3.** Percentage of fully swollen beads as a function of the incubation time for ester-terminated dendrimers in DMF.

**Scheme 2**




(i) DIC, DMAP, Fmoc-Ala-OH, DMF; (ii) Piperidine, DMF; (iii) HOBt, PyBOP, Fmoc-Ser(Trt)-OH, DMF; (iv) HOBt, PyBOP, Fmoc-Gly-OH, DMF; (v) 4-$IC_6H_4OH$, **5**, DCM; (vi) $Pd(OAc)_2$, P(*o*-tol)$_3$, $CH_2$=$CHCO_2Me$, $NEt_3$, DMF

fully swollen beads in a constant microscope viewfield as a function of time (Figure 3). These measurements clearly show the decrease in the swelling rate as the dendrimer generation increases. The observed phenomena, which must be taken into account when synthesis on dendrimeric support is planned, are in full accordance with those observed in gel-phase NMR measurements and, as before, are most likely connected to the high density of the peripheral dendrimer groups that "isolate" the polystyrene chains from the solvent.

To examine the potential of the dendronized support for solid-phase synthesis, we conducted a series of synthetic transformations on resins **G1.0**−**G3.0**. Thus, synthesis of a tripeptide Fmoc-Gly-Ser(Trt)-Ala (Fmoc = 9-fluorenylmethoxycarbonyl, Trt = triphenylmethyl) on the **G3.0** resin using Fmoc chemistry (resin **6**, Scheme 2) was demonstrated. Diisopropylcarbodiimide (DIC)/4-(*N*,*N*-dimethylamino)pyridine (DMAP) promoted attachment of the first amino acid was followed by benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP)/1-hydroxybenzotriazole (HOBt) coupling steps. The synthesis was monitored by gel-phase $^{13}C$ NMR and quantified using spectrophotomet-

ric determination of the terminal Fmoc groups. All steps demonstrated quantitative conversion. TFA-induced cleavage of **6** formed the crude dendrimer−peptide construct with 83% yield.[20] Similarly, a tripeptide FmocAla-Ser(Trt)-Val was assembled on **G2.0** resin with 85% yield.

In another experiment, we performed two successive synthetic steps: Mitsunobu condensation with iodophenol followed by Heck coupling with methyl acrylate,[21,22] on Wang, **G1.0**, **G2.0**, and **G3.0** resins (Scheme 2). According to the gel-phase $^{13}C$ NMR spectra, complete conversion was achieved for every resin. Fair yields were produced upon TFA-induced cleavage, without a substantial difference in the resin reactivities.[20]

In conclusion, we established a new synthetic route to aryl benzyl ether dendrimers on solid support. These dendronized supports exhibit intriguing swelling behavior. The experiments for exploring this behavior, as well as utilizing these resins for SPS and catalysis, are underway.

## Experimental Section

**General.** All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Dimethyl 5-hydroxyisophthalate, $LiAlH_4$ (1.0 M solution in THF), Red-Al (65% solution in toluene), DIBAL-H (1.0 M solution in hexanes), $LiBH_4$ (2.0 M solution in THF), $B(OMe)_3$, DIAD, DEAD, $PPh_3$, DMAP, TFA, 4-iodophenol, triethylamine, and methyl acrylate were purchased from Sigma-Aldrich at the highest available purity and used as received. Analytically pure DIC (Acros Organics), $Pd(OAc)_2$, and P(*o*-tol)$_3$ (Strem Chemicals) were used as received. The protected amino acids, HOBt, PyBOP, and Wang resin (0.72 mmol/g, 1% divinylbenzene, 100−200 mesh) were purchased from Novabiochem. THF was dried over, and distilled from, sodium/benzophenone ketyl. $CH_2Cl_2$ was dried over, and distilled from, $CaH_2$. Anhydrous DMF was purchased from Aldrich. Betaine **5** was prepared using a literature procedure.[23]

Solution $^1H$ (200 MHz) and $^{13}C$ NMR (100 MHz) spectra were recorded on Bruker AC-200 and AVANCE-400 spectrometers, respectively, in $CDCl_3$/TFA 1:1 with residual solvent peaks ($^1H$: 7.26 ppm; $^{13}C$: 77.16 ppm) as references. Gel-phase $^{13}C$ NMR spectra were recorded in benzene-$d_6$ or dioxane-$d_8$, using the Bruker AVANCE-400 instrument. MS and MALDI−TOF MS were recorded on Micromass VG-Autospec M250 and Bruker Reflex-3 mass spectrometers, respectively. A Zeiss Axiovert 25 microscope was used for the swelling studies, and the pictures were recorded using Pixera software.

Yields were determined using the $^1H$ NMR spectra of TFA:$CHCl_3$ (1:1) cleavage solutions with $C_6H_6$ (7.36 ppm) as an internal standard. Alcohols were partially converted to TFA esters under these conditions. An alternative yield-determining procedure (for OH-functionalized resins only) included the loading of an Fmoc-protected amino acid, piperidine-induced Fmoc release, and spectrophotometric analysis of a fluorenylmethylpiperidine adduct.[24]

**General Procedure for TFA Cleavage.** The dry resin (ca. 50 mg) is placed in a small vial, and 0.5 mL of the cleavage solution ($CDCl_3$:TFA 1:1 by volume), containing a known concentration of the internal standard (usually benzene, $5.5 \times 10^{-6}$ M), is added. After vigorous stirring for 1 h, the resin was filtered off and the solution analyzed.

**Typical Procedure for the Mitsunobu Step. Synthesis of G0.5.** Dimethyl 5-hydroxyisophthalate (0.45 g, 2.2 mmol, 3 equiv) and **5** (0.88 g, 2.2 mmol, 3 equiv) were added to a suspension of Wang resin (1.0 g, 0.72 mmol/g, 0.72 mmol, 1 equiv) in dry $CH_2Cl_2$ (10 mL). The suspension was mixed at room temperature for 24 h. The resin was washed with THF and $CH_2Cl_2$ and then dried under vacuum. For higher yield, the procedure was performed twice. Yield >99%,[25] purity >99%, loading 0.63 mmol/g.

Gel-phase $^{13}C$ NMR (100 MHz, $C_6D_6$): $\delta$ 165.8, 159.3, 158.0, 132.4, 129.5, 123.3, 120.4, 115.0, 70.0, 51.9.

Following TFA-induced cleavage: $^1H$ NMR (200 MHz, $CDCl_3$/TFA 1:1): $\delta$ 8.35 (t, $J = 1.3$ Hz, 1H), 7.86 (d, $J = 1.3$ Hz, 2H), 4.06 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$/TFA 1:1): $\delta$ 168.4, 154.8, 130.9, 123.8, 121.5, 53.1. HRMS (CI): $m/z$ ($MH^+$) Calcd 211.0606; found 211.0605.

**Typical Procedure for the Reduction Step. Synthesis of G1.0.** $LiBH_4$ (6.3 mL, 12.6 mmol, 20 equiv, 2 M THF) and $B(OMe)_3$ (0.071 mL, 0.63 mmol, 1 equiv) were added to a suspension of the resin **G0.5** (1.0 g, 0.63 mmol, 0.63 mmol/g, 1.26 mmol groups of ester) in dry THF (10 mL). The mixture was refluxed overnight. The resin was washed with water, a solution of ammonium chloride/THF (1:1), a solution of 10% HCl/THF (1:1), THF, and $CH_2Cl_2$ and then dried under vacuum. Yield 94%, purity >99%, loading 0.62 mmol/g.

Gel-phase $^{13}C$ NMR (100 MHz, $C_6D_6$): $\delta$ 159.5, 145.8, 143.4, 117.0, 115.0, 112.5, 70.2, 64.8.

Following TFA-induced cleavage: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 6.94−7.08 (m, 3H), 5.35 (s, 4H). $^{13}C$ NMR (100 MHz, $CDCl_3$/TFA 1:1): $\delta$ 154.2, 135.5, 121.3, 115.8, 68.6. HRMS (EI): $m/z$ ($M^+$) Calcd 154.0630; found 154.0626.

**G1.5.** Yield >99%, purity >95%, loading 0.49 mmol/g.

Gel-phase $^{13}C$ NMR (100 MHz, $C_6D_6$): $\delta$ 165.7, 158.9, 138.0, 132.3, 123.4, 120.2, 114.1, 69.8, 51.9.

Following TFA-induced cleavage: $^1H$ NMR (200 MHz, $CDCl_3$/TFA 1:1): $\delta$ 8.31 (t, $J = 1.3$ Hz, 2H), 7.91 (d, $J = 1.3$ Hz, 4H), 7.21 (s, 1H), 7.03 (s, 2H), 5.19 (s, 4H), 4.03 (s, 12H). $^{13}C$ NMR (100 MHz, $CDCl_3$/TFA 1:1): $\delta$ 168.6, 158.4, 157.0, 138.1, 130.7, 123.6, 121.0, 119.5, 114.0, 69.6, 53.1. HRMS (CI): $m/z$ ($MH^+$) Calcd 539.1553; found 539.1539.

**G2.0.** Yield >99%, purity >95%, loading 0.51 mmol/g.

Gel-phase $^{13}C$ NMR (100 MHz, $C_6D_6$): $\delta$ 158.6, 143.6, 139.5, 116.6, 114.2, 112.4, 110.0, 68.8, 63.4.

Following TFA-induced cleavage: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.03−7.20 (m, 9H), 5.39 (s, 8H), 5.16 (s, 4H). $^{13}C$ NMR (100 MHz, $CDCl_3$/TFA 1:1): $\delta$ 158.5, 154.9, 138.4, 135.2, 121.1, 119.8, 115.6, 114.0, 69.6, 68.8. HRMS (CI): $m/z$ ($M^+$) Calcd 810.0971; found 810.0973.

**G2.5.** Yield 94%, purity >95%, loading 0.34 mmol/g.

Gel-phase $^{13}C$ NMR (100 MHz, $C_6D_6$): $\delta$ 165.5, 158.9, 138.5, 132.2, 123.2, 120.0, 113.6, 69.7, 51.9.

Following TFA-induced cleavage: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.31 (s, 4H), 7.91 (s, 4H), 6.98−7.21 (m, 9H), 5.16 (s, 12H), 4.03 (s, 24H). $^{13}C$ NMR (100 MHz, $CDCl_3$/TFA 1:1): $\delta$ 168.5, 158.5, 158.4, 157.0, 138.5, 137.8, 130.7, 123.6, 120.9, 119.7, 119.4, 113.8, 114.0, 69.9, 69.7, 53.1. MS (MALDI): $m/z$ ($(M + Na)^+$) Calcd 1217; found 1217.

**Synthesis of G3.0.** Yield 93%, purity >95%, loading 0.32 mmol/g.

Gel-phase $^{13}C$ NMR (100 MHz, $C_6D_6$): $\delta$ 158.6, 143.5, 139.0, 116.6, 112.4, 111.0, 68.7, 63.4.

Following TFA-induced cleavage: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 6.98−7.20 (m, 21H), 5.36 (s, 16H), 5.13 (s, 12H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 158.5, 151.9, 138.0, 135.1, 121.0, 119.5, 115.4, 113.8, 69.8, 68.9.

**Typical Procedure for the Attachment of Iodophenol to Hydroxyl-Terminated Resins.** 4-Iodophenol (0.47 g, 2.2 mmol, 3 equiv) and **5** (0.88 g, 2.2 mmol, 3 equiv) were added to a suspension of the Wang resin (1.0 g, 0.72 mmol, 1 equiv) in dry $CH_2Cl_2$ (10 mL). The suspension was mixed at room temperature for 24 h. The resin was washed with THF and DCM and then dried under vacuum.

**Typical Procedure for the Heck Reaction on Iodophenyl-Terminated Resins.** $Pd(OAc)_2$ (0.070 g, 0.31 mmol, 0.5 equiv), P−(*o*-tol)$_3$ (0.38 g, 1.2 mmol, 2 equiv), $Et_3N$ (0.17 mL, 1.2 mmol, 2 equiv), and methyl acrylate (0.33 mL, 3.7 mmol, 6 equiv) were added to a suspension of the resin prepared at the previous step (1.0 g, 0.62 mmol, 1 equiv) in dry and degassed DMF (10 mL). The suspension was stirred at 100 °C for 20 h. The resin was washed with THF and $CH_2Cl_2$ and then dried under vacuum. At the end of the reaction, the resin became black, due to the precipitation of metal Pd. Yield 54%, purity 92%.

Following TFA-induced cleavage: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.73 (d, $J$ = 16.1 Hz, 1H), 7.50 (d, $J$ = 8.5 Hz, 2H), 6.93 (d, $J$ = 8.5 Hz, 2H), 6.39 (d, $J$ = 16.1 Hz, 1H), 3.89 (s, 3H).

On **G1.0**: Yield 52%, purity 90%.

Following TFA-induced cleavage: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.73 (d, $J$ = 16.1 Hz, 2H), 7.50 (d, $J$ = 8.5 Hz, 4H), 7.14 (s, 1H), 6.97 (s, 2H), 6.93 (d, $J$ = 8.5 Hz, 4H), 6.39 (d, $J$ = 16.1 Hz, 2H), 5.13 (s, 4H), 3.89 (s, 6H).

On **G2.0**: Yield 48%, purity 75%.

Following TFA-induced cleavage: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.74 (d, $J$ = 16.1 Hz, 4H), 7.50 (d, $J$ = 8.5 Hz, 8H), 7.08 (m, 17H), 6.39 (d, $J$ = 16.1 Hz, 4H), 5.14 (s, 12H), 3.90 (s, 12H).

On **G3.0**: Yield 57%, purity 90%.

Following TFA-induced cleavage: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.74 (d, $J$ = 16.1 Hz, 4H), 7.49 (d, $J$ = 8.5 Hz, 8H), 7.14 (s, 7H), 7.06 (m, 14H), 6.98 (d, $J$ = 8.5 Hz), 6.39 (d, $J$ = 16.1 Hz, 4H), 5.05 (s, 28H), 3.88 (s, 24H).

**Building Tripeptide on G3.0.** Fmoc-Ala-OH (2.0 g, 6.7 mmol, 80 equiv) was added to 30 mL of dry $CH_2Cl_2$ and 0.5 mL of dry DMF. The mixture was cooled to 0 °C. DIC (0.50 mL, 3.4 mmol, 40 equiv) was added and the mixture stirred for 20 min at 0 °C. The $CH_2Cl_2$ was evaporated and the mixture dissolved in dry DMF and then added to resin **G3.0** (200 mg, 0.42 mmol/g, 0.084 mmol, 0.67 mmol groups of alcohol, 1 equiv) with DMAP (1.0 mg, 0.0084 mmol, 0.1 equiv). The mixture was stirred at room temperature for 4 h, washed with THF and $CH_2Cl_2$, and then dried under vacuum.

Fmoc-Ser(Trt)OH (0.40 g, 1.1 mmol, ca. 16 equiv), HOBt (0.17 g, 1.1 mmol, ca. 16 equiv), PyBOP (0.58 g, 1.1 mmol, ca. 16 equiv), and diisopropylethylamine (DIPEA) (0.18 mL, 2.2 mmol, ca. 32 equiv) were added to the suspension of the resin (200 mg, 1 equiv) in 2 mL of dry DMF. The mixture was stirred at room temperature for 4 h, washed with THF and DCM, and then dried under vacuum.

Gly-Fmoc OH (0.17 g, 0.58 mmol, ca. 16 equiv), HOBt (0.087 g, 0.58 mmol, ca. 16 equiv), PyBOP (0.30 g, 0.58 mmol, ca. 16 equiv), and DIPEA (0.096 mL, 1.15 mmol, ca. 32 equiv) were added to the suspension of the resin (200 mg, 1 equiv) in 2 mL of dry DMF. The mixture was stirred at room temperature for 4 h, washed with THF and DCM, and dried under vacuum.

Following TFA-induced cleavage, crude **G3**−tipeptide construct was formed with 83% yield.

$^1$H NMR (200 MHz, $CDCl_3$/TFA 1:1): $\delta$ 7.72 (bs, 16H), 7.50 (bs, 16H), 7.30 (bs, 32H), 6.80−7.20 (bs, 21H), 4.90−5.50 (bs, 44H), 3.80−4.70 (bs, 56H), 1.40 (bs, 24H).

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**Supporting Information Available:** Gel-phase $^{13}$C NMR spectra of the resin-bound products, $^1$H NMR, $^{13}$C NMR, and MS spectra of the cleaved products, and table of increase of total resin volume upon swelling. This material is available free of charge via the Internet at http://pubs.acs.org.

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