Practical Synthesis of a Dithiane-Protected 3′,5′-Dialkoxybenzoin Photolabile Safety-Catch Linker for Solid-Phase Organic Synthesis

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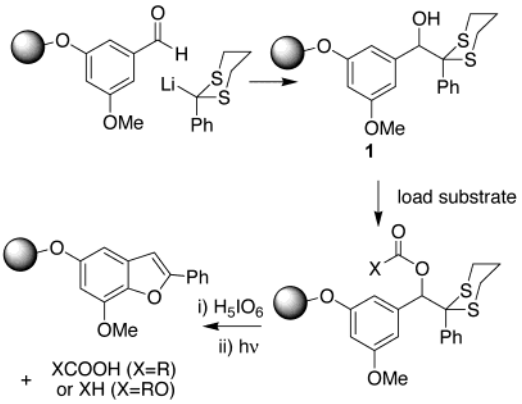
The solution-phase preparation of the 3′,5′-dialkoxybenzoin photolabile safety-catch linker **16** is described. Pivotal to this convenient synthesis is the selection of appropriate orthogonal protecting groups for the alkoxy functionalities present. The new linker can be readily loaded onto any standard amine-terminating resin under peptide-coupling conditions, without the need to protect the secondary alcohol functionality, and subsequently loaded with substrate. Alternatively, the loading efficiency of sterically hindered substrates can be enhanced by preloading the semiprotected linker variant **10** in solution prior to immobilization onto the resin. This second generation of benzoin photolabile safety-catch linkers provides greater control of both linker loading and resin attachment and should prove to be a more versatile and convenient form of the linker.

Introduction

Over the last 30 years solid-phase organic synthesis has matured into a valuable chemical technology, and many synthetic transformations have now been demonstrated on solid supports.[1] Linker molecules play a key role in any successful synthetic strategy on a solid phase.[2] Linkers must be stable to the wide variety of chemistries used in the library synthesis. Moreover, cleavage conditions should be compatible with the product released and should ideally not introduce impurities that are difficult to remove. Photocleavable linkers are particularly useful in this respect, offering a mild, neutral, and broadly orthogonal method of cleavage, without the need for exogenous reagents. The only widely used and commercially available photocleavable resins are based on the *o*-nitroveratryl linkers developed by Holmes.[3]

The benzoinyl photolinker **1** was recently reported by our group[4] as an example of a new class of photocleavable safety-catch linkers. As a first proof of concept, the linker was assembled on a resin in near-quantitative yield using Corey−Seebach dithiane addition.[5,6] The dithiane group that serves as a safety catch against premature photoreaction was removed by oxidation. The efficiency of the photoreaction has been shown[7] in solution to be highly dependent on the nature of the substituents on the phenyl ring, with the *m*-methoxy groups in the benzylalkoxy moiety giving the highest yield. Indeed, our kinetics studies on this system as a solid-phase linker confirmed, using an array of substituted benzoin derivatives, that the 3′-alkoxy- and 3′,5′-dialkoxybenzoin linker **1** both released a model substrate in high yield (80−90% for the photocleavage step) relatively quickly (2 h) upon irradiation at 350 nm in THF/MeOH (3:1). Furthermore, it was shown that a lower resin loading improved the cleavage kinetics for polystyrene and that TentaGel exhibits similar photocleavage kinetics in both organic and aqueous media. Derivatization of the benzoin linker to its ester[4] or carbonate[8] derivative has led to the efficient release of carboxylic acids and alcohols, respectively. Furthermore, on the basis of several studies, this system could be employed for the release of other functionalities which include the 5′-hydroxyl group of nucleosides,[9] secondary amines,[10] and thiols.[11]



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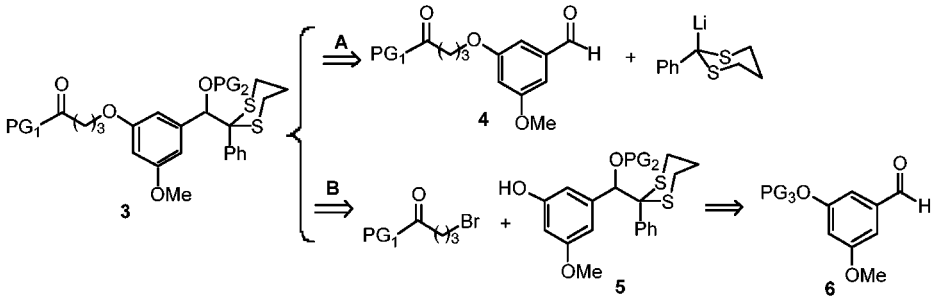
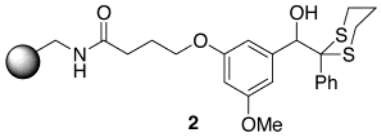
Scheme 1



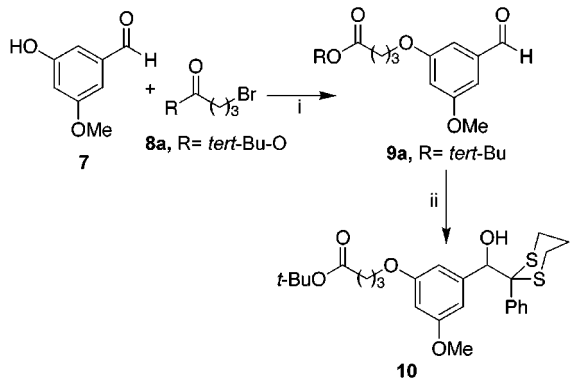
To follow these initial studies, we present herein a practical synthesis of the second generation benzoin linker **2**, which offers certain improvements to this class of photolinkers and should make them more accessible to researchers. The new linker is prepared in solution



with a carboxylic acid functionality as a point of attachment to the resin to exploit the wide range of commercially available amine-functionalized resins. Furthermore, a four-carbon tether anchoring the linker to the support is incorporated. The nature of such tethers has been shown to be important in solid-phase syntheses.[12] For example, a three-carbon tether for a nitroveratryl linker was found to be susceptible to β-elimination,[13] and a two-carbon tether[14] can undergo nucleophilic attack at the α-carbon. A four-carbon tether would not suffer from these problems, and in addition, the nitroveratryl linker was shown to exhibit faster photocleavage kinetics with a four-carbon rather than two-carbon tether.[3]

A common strategy for preparing photolabile supports is to anchor preformed linkers onto the support as carboxamides, thereby affording maximum control over the chemistry and level of substitution of the resin. Toward this end, we pursued the preparation of a fully protected preformed benzoinyl photolinker (**15**) (Scheme 4). The bis-deprotected linker **16** can then be attached to the solid support and subsequently loaded with the desired substrate. Alternatively, the linker may first be preloaded with substrate in solution prior to attachment to the resin. The latter may prove advantageous in the loading of sterically demanding starter monomers. As part of our aim to provide a useful linker for SPOC, the preformed derivative **16** has also provided the means for a chemical stability study and functional group compatibility profile of the benzoin photolabile safety-catch (BPSC) linker by assembling it as part of a dual-linker analytical construct system.[15]

Scheme 2[a]



[a] Reagents and conditions: (i) K_2CO_3 (1.5 equiv), **8a** (1.1 equiv), DMF, rt, overnight, 60%; (ii) 2-lithium-2-phenyl-1,3-dithiane (3.5 equiv), THF, −78 to 0 °C, 2 h, <5%.

Two retrosynthetic approaches to the fully protected linker **3** were considered (Scheme 1). The first approach is based on disconnection at the benzylic position and relies on dithiane addition to the protected aldehyde **4** (path A). The advantage of this strategy would be that it requires only one protecting group. Alternatively, path B involves the first disconnection at the ether linkage in **3**. This route entails a dithiane addition to the protected aldehyde **6** followed by subsequent deprotection of the phenol and *O*-alkylation with 4-bromobutyrate. This approach requires two orthogonal protecting groups for both hydroxyl functionalities in **5**.

Results and Discussion

Solution-Phase Synthesis of the Linker. Initially we chose to explore approach A (Scheme 2), involving *O*-alkylation of 3-hydroxy-5-methoxybenzaldehyde (**7**) with a protected 4-bromobutyric acid ester (**8**), followed by subsequent dithiane addition to aldehyde **9**. *O*-Alkylation of 3-hydroxy-5-methoxybenzaldehyde[16] with *tert*-butyl bromobutyrate ester[17] (**8a**) using K_2CO_3 in DMF as a base[3] proceeded in 60% isolated yield. The subsequent addition of the lithium salt of the dithiane resulted in a complex mixture which contained the desired product **10** in less than 5% yield according to ^{1}H NMR spectroscopic analysis. A major competing side reaction was found to be the dithiane anion addition to the protected ester functionality.

In an attempt to circumvent this problem, we investigated the alternative protection of the acid as an ortho

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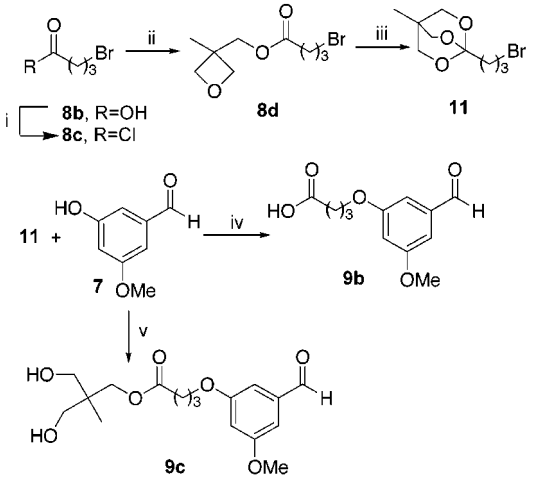
Scheme 3[a]



[a] Reagents and conditions: (i) $SOCl_2$ (1 equiv), 1 drop of DMF in DCM, 1 h at 40 °C; (ii) 3-methyl-3-hydroxymethyloxetane (1 equiv), pyr (2 equiv), 4 Å molecular sieves, THF, 0 °C, 1 h, 70% for two steps, i and ii; (iii) $BF_3{\cdot}Et_2O$ (0.25 equiv) in DCM, 0 °C, 1 h, 50%; (iv) **11** (1.5 equiv), K_2CO_3 (2.5 equiv), 18-crown-6 (0.5 equiv) in DMF at 70 °C overnight; (v) **11** (1.5 equiv), K_2CO_3 (2.5 equiv) in DMF at 50 °C for 2 days.

ester[18] (**11**; Scheme 3), which has been reported[19] to be stable toward strongly basic reagents and strong nucleophiles (such as Grignard reagents). In particular, bridged carboxylic ortho esters derived from 2,2-bishydroxymethyl-1-propanol have been obtained in high yields directly from the acid.[20] According to the literature method, 4-bromobutyroyl chloride (**8c**) was reacted in situ with commercially available 3-methyl-3-hydroxymethyloxetane in the presence of pyridine in methylene chloride solution at 0 °C to yield **8d** (70% overall yield). Treatment of the oxetane ester **8d** with 0.25 equiv of boron trifluoride etherate in dichloromethane furnished the ortho ester **11** in 50% yield. However, all attempts to alkylate 3-methoxy-5-hydroxybenzaldehyde (**7**) with the bromo derivative **11** failed. This was partly attributable to the instability of the ortho ester **11**, which was observed to undergo up to 50% hydrolysis upon storage at 4 °C for one week. The use of 2 equiv of DIPEA or K_2CO_3 at room temperature for 1−3 days gave no conversion. Alternatively, a stronger base such as NaH did not lead to the desired product, and under these conditions, decomposition of the ortho ester **11** was observed within only 3 h at room temperature. The use of a catalytic amount of a phase-transfer agent (18-crown-6) with 2 equiv of K_2CO_3 at 70 °C for 15 h in DMF furnished the *O*-alkylated product **9b** derived from concomitant loss of the ortho ester moiety. The use of 3 equiv of K_2CO_3 at 50 °C for 2 days gave partial conversion to product **9c** identified as the corresponding monoester between 2,2-bishydroxymethyl-1-propanol and **9b**. At this stage, this approach was abandoned in favor of the alternative strategy (disconnection B, Scheme 1).

3-Hydroxy-5-methoxybenzaldehyde (**7**) was protected as the trimethylsilylethoxy methyl ether (SEM)[21] derivative **12** and treated with a preformed solution of the lithium salt of 2-phenyl-1,3-dithiane, generated in situ with a stoichiometric amount of *n*-BuLi in dry THF at 0 °C (Scheme 4). After 1 h, the reaction was quenched with acetic anhydride in pyridine to give **13** in 80% isolated yield (for the two steps). However, the subsequent removal of the SEM group in **13** proved to be problematic. Five equivalents of TBAF in the presence of 4 Å molecular sieves cleaved the SEM derivative, but a concomitant retroaldol-type cleavage of the dithiane resulted in recovery of 3-hydroxy-5-methoxybenzaldehyde (**7**) as the only product. An alternative deprotection of the SEM group was attempted using nonaqueous acidic conditions. When either H_2SO_4 (10 equiv)[22] or $BF_3{\cdot}OEt_2$ (2 equiv)[23] was used, complete decomposition of the starting material to a complex mixture was observed by ^1H NMR spectroscopic analysis. The slow addition of an excess of TFA (up to 50 equiv) over 1 h while maintaining the temperature strictly below 0 °C throughout the reaction and workup gave the desired phenol **14** in up to 80% yield. However, this reaction proved not to be reproducible. The application of $MgBr_2$ in a $Et_2O/MeNO_2$ mixture[24] led to complete disappearance of starting derivative **13** to a complex mixture. Ultimately we were able to resolve this problem by using HF·pyr complex, an excellent desilylating agent in neutral conditions.[25] Slow addition of HF·pyr complex to a solution of the SEM ether **13** in THF at 0 °C reliably gave complete conversion to the alcohol **14** in high purity (80% isolated yield, 2 g scale). This reagent has previously been used for removal of the 2-(trimethylsilyl)ethyl group from homoallylic ethers[26] in a similar fashion. The *O*-alkylation of phenol **14** with *tert*-butyl 4-bromobutyrate was then effected using K_2CO_3 in combination with catalytic tetrabutylammonium iodide[10] in refluxing MeCN overnight to yield the ether **15** in 90% yield. The fully protected dithiane **15** is a versatile intermediate in that it can be selectively deprotected by removal of the *tert*-butyl ester with formic acid or removal of the acetoxy group with K_2CO_3. This approach allows either loading of the linker with substrate in solution prior to attachment to the resin (see Scheme 6) or, alternatively, loading the fully deprotected linker onto the resin as a first step (Scheme 5).

On-Resin Studies. The deprotected linker **16** (Scheme 5) was loaded onto TentaGel (TG) amino resin (Fmoc analysis, 0.2 mmol/g; see the Experimental Section) in the presence of TBTU/HOBt until a negative Kaiser test was obtained to afford resin **2**. Using these conditions, any self-condensation side product was not observed as shown in the Supporting Information submitted for the analytical construct study.[15] *N*-Fmoc-*β*-alanine was subsequently loaded under optimized[27] reaction conditions using DIC/DMAP (Fmoc analysis, 0.19−0.2 mmol/g).

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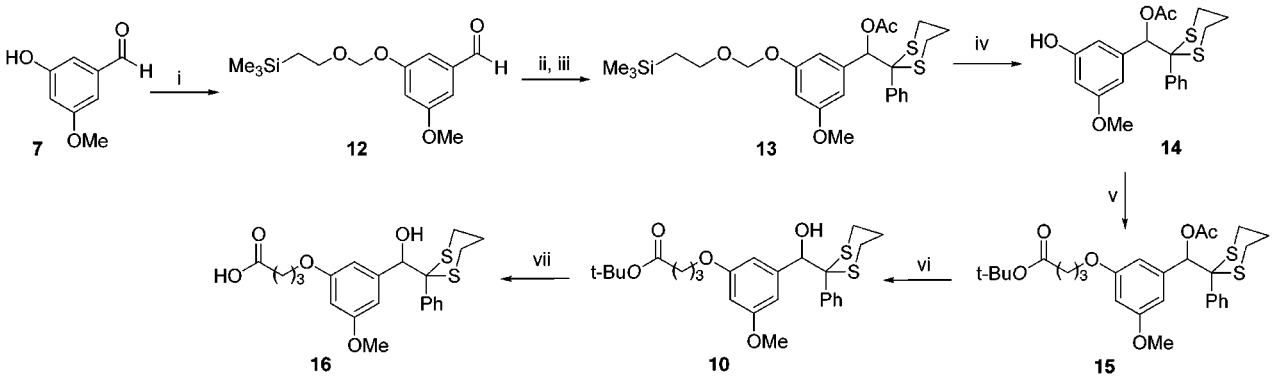
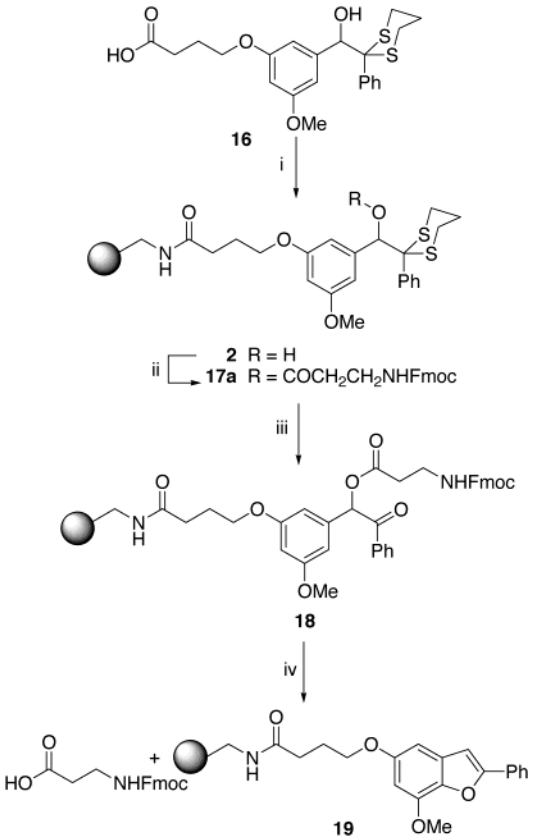
(27) Loading of the acid was attempted using Mitsunobu conditions (3 equiv of Ph_3P and DEAD), via the acyl chloride of the acid, and also using other coupling agents (3 equiv of PyBOP and DIPEA or 3 equiv of PyBrOP and DIPEA), furnishing resin **17a** in less than 20% yield. The mixture MSNT/MeIm proved as effective as the DIC/DMAP reported in the Experimental Section.

Scheme 4[a]



[a] Reagents and conditions: (i) SEM-Cl (1.1 equiv), DIPEA (2 equiv) in DCM, overnight, 93%; (ii) 2-lithium-2-phenyl-1,3-dithiane (3.5 equiv), THF, −78 to 0 °C, 2 h; (iii) Ac_2O (2 equiv), Et_3N (4 equiv), 30 min, 80% overall for b and c; (iv) HF·pyr (6000 mL/mol), slow addition for 1 h at 0 °C, 80%; (v) **8a** (1.2 equiv), K_2CO_3 (2.4 equiv), Bu_4NI (0.2 equiv) in acetonitrile under reflux, overnight, 90%; (vi) K_2CO_3 (2.1 equiv), Et_3N (30 equiv) in MeOH/H_2O (1:1) at 70 °C, 1 h, 95%; (vii) HCOOH (30 equiv), rt, 5 h, 95%.

Scheme 5[a]



[a] Reagents and conditions: (i) TentaGel amino resin (0.2 mmol/g, 1 equiv), TBTU (2.2 equiv), HOBt (2.5 equiv), *i*Pr_2NEt (4 equiv), **16** (2 equiv), CH_2Cl_2/DMF (1:1), overnight; (ii) $FmocNHCH_2CH_2COOH$ (4 equiv), DIC (4 equiv), DMAP (0.5 equiv), CH_2Cl_2, overnight; (iii) H_5IO_6 (2 equiv), THF, 30 min; (iv) irradiation at 350 nm in THF/MeOH (3:1), 1 h.

Resins **2**, **17a**, and **18** were characterized by FT-IR, gel-phase ^{13}C NMR, and MAS ^1H NMR spectroscopy. Indeed, the complete loading of the substrate onto the resin **2** can be readily monitored by MAS ^1H NMR spectroscopy following the singlet signal corresponding to the benzylic proton which shifts from δ 4.88 ppm in **2** to δ 6.05 ppm in **17a**. Removal of the dithiane group from resin **17a** was effected using just[28] 2 equiv of H_5IO_6 in dry THF for 1/2 h at room temperature (quantitative yield by ^{13}C NMR). Finally, irradiation of the resulting resin at 350 nm for 2 h afforded β-alanine amino acid in 70% yield (from **17a**, based on the initial resin loading), as indicated by residual Fmoc analysis of resin **19** and HPLC analysis (using Fmoc-serine as internal standard) of the supernatant solution. This synthetic sequence demonstrates efficient loading of the fully deprotected linker onto the resin, and a photocleavage efficiency comparable to that of our previously reported system.[4]

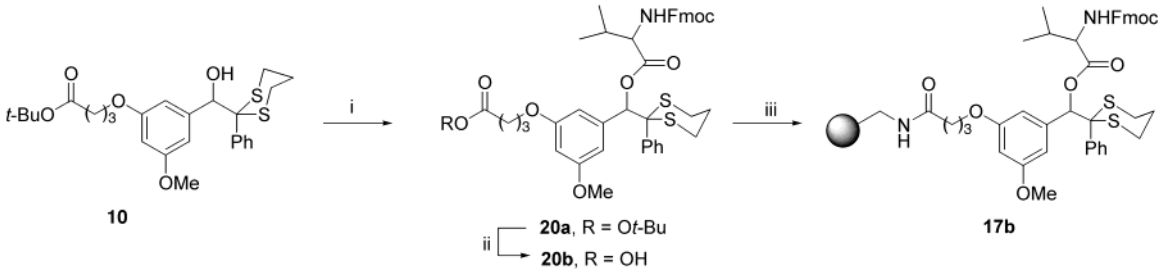
An advantage of this linker preparation is the option of preloading sterically hindered acids in solution prior to attachment to the resin. This can facilitate the preparation of resins loaded with substrates/starter monomers that would otherwise be difficult to obtain. In previous work[4] on the first generation BPSC linker, we reported difficulties in achieving high loadings for hindered substrates. For example, Fmoc-valine was loaded onto the solid supported linker in only 65% yield, in comparison to the less hindered substrate β-alanine, which was loaded quantitatively[4]. We preloaded Fmoc-valine onto the *tert*-butyl-protected derivative **10** in solution using polymer-supported carbodiimide/DMAP to afford derivative **20a** in 90% isolated yield (Scheme 6). Subsequently the *tert*-butyl protecting group was removed with formic acid, leading to the desired loaded linker **20b**. Immobilization of this derivative on TentaGel amino resin (TBTU/HOBt) furnished fully loaded resin **17b** as indicated by a negative Kaiser test. This sequence suggests that the problem of loading hindered substrate is likely to have been attributable to the resin environment rather than simply an intrinsic property of the BPSC linker construct.

Conclusion

A high-yielding and reliable route to a preformed benzoinyl safety-catch photolinker (**16**) is described. This BPSC linker is more versatile than the previous generation. The linker may be either immobilized directly onto a resin and subsequently loaded with substrate or preloaded in solution prior to resin attachment, as shown with compound **20b**. Furthermore, this form of the linker

(28) Optimized conditions from a study using different oxidizing reagents such as Chloramine-T, $NOHSO_4$, $(CF_3CO_2)IPH$, or $PhOPOCl_2$/NaI/DMF. Data not included.

Scheme 6[a]



[a] Reagents and conditions: (i) Fmoc-Val-OH (1.5 equiv), PS-carbodiimide (1.5 equiv), DMAP (0.1 equiv), DCM, overnight; (ii) HCOOH, rt, 3 h; (iii) TentaGel amino resin (0.2 mmol/g), TBTU (2.2 equiv), HOBt (2.5 equiv), Et_3N (4 equiv), **20b** (2 equiv), CH_2Cl_2/DMF (1:1), 5 h.

can be readily immobilized to the many commercially available amino-terminating resins. We believe that the BPSC linker should now be more accessible and widely applicable for solid-phase chemistry.

Experimental Section

General Methods. The chemicals were purchased from Aldrich Chemical Co. and used without further purification. NovaSyn TG amino resin (0.2 mmol/g) and Fmoc-protected amino acid were purchased from Novabiochem and used without further purification. The loading of the commercial resin was photochemically determined from the amount of Fmoc chromophore released upon treatment of the corresponding Fmoc-β-Ala-resin with piperidine/DMF, prior to use. Fmoc analysis was performed on a known quantity of resin sample (2−3 mg) in 5 mL of 20% piperidine in DMF, measuring the absorbance of the sample at 290 nm using the piperidine solution as baseline. All anhydrous solvents were purchased from Fluka or were distilled in house (THF from $LiAlH_4$/CaH_2 with triphenylmethane as indicator; DCM, MeOH, and MeCN from CaH_2). Infrared spectra of solution samples were obtained from a film on NaCl. FTIR spectra of resin samples were obtained from dry single beads. Gel-phase ^{13}C NMR spectroscopic data were acquired in $CDCl_3$ with an acquisition time of 0.1 s, 10 ns delay between pulses, and 3.5×10^5 to 7.0×10^5 scans. LC−MS analyses were carried out with a 0.1% formic acid/10 mmol solution of ammonium acetate in Milli-Q water, 0.05% formic acid/95% MeCN/5% Milli-Q water, and detection by UV at 215 nm. Photolysis was carried out in a Rayonet photochemical reactor fitted with eight 8 W RMR 350 nm lamps.

General Procedures. All solution-phase anhydrous experiments were performed under a positive pressure of argon in dried glassware equipped with a rubber septum cap. Anhydrous solvents and other liquid reagents were transferred by syringe or cannulation. Solid-phase reactions were typically carried out in fritted polyethylene filtration tubes fitted with a Teflon cap at the outlet and a rubber septum seal, under a positive pressure of nitrogen with gentle magnetic stirring. General washing procedure for resin samples: for every 100 mg of resin, three aliquots of 2 mL of DMF, THF, MeOH, THF, and DCM were used in succession. Column chromatography was performed using Merck silica gel (230−400 mesh silica kieselgel) under positive pressure, using hexane and ethyl acetate in increasing polarity.

3-Methoxy-5-(2-trimethylsilanylethoxymethoxy)-benzaldehyde (12). To a solution of 3-hydroxy-5-methoxybenzaldehyde (0.5 g, 3.3×10^{-3} mol) in DCM/ether (12 mL/5 mL) under argon was added 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) (0.64 mL, 3.63×10^{-3} mol, 1.1 equiv) and DIPEA (1.1 mL, 6.6×10^{-3} mol, 2 equiv). The mixture was stirred for 24h, diluted with 20 mL of ether, and washed three times with brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford an oil. Purification by flash chromatography yielded **12** (0.87 g, 93%) as a pale oil. ^1H NMR (400 MHz, δ, ppm): 9.89 (s, 1H), 7.14−7.13 (m, 1H), 7.04−7.05 (m, 1H), 6.84−6.85 (m, 1H), 5.24 (s, 2H), 3.83 (s, 3H), 3.73−3.77 (m, 2H), 0.93−0.97 (m, 2H), −0.01 (s, 9H). ^{13}C NMR (100 MHz, δ, ppm): 191.78, 161.19, 158.99, 138.39, 110.5, 109.2, 106.82, 92.94, 66.53, 55.62, 18.26, −1.46. FTIR (film, ν, cm^{-1}): 2954, 1703, 1595. HPLC: $R_t = 5.6$ min. HRMS (ESI + ve): [MNa^+] calcd for $C_{14}H_{22}O_4Si$ 305.1185, found 305.1183. Anal. Calcd for $C_{14}H_{22}O_4Si$: C, 59.54; H, 7.85. Found: C, 59.54; H, 7.89.

(±)-Acetic Acid [3-Methoxy-5-(2-trimethylsilanyl-ethoxymethoxy)phenyl](2-phenyl[1,3]dithian-2-yl)methyl Ester (13). To a stirred solution of 2-phenyl-1,3-dithiane (0.7 g, 3.6×10^{-3} mol, 1.3 equiv) in anhydrous THF (6 mL) under argon at 0 °C was added *n*-butyllithium (2.8 mL, 3.1×10^{-3} mol, 1.1 equiv). After 1 h at 0 °C the aldehyde **12** (0.78 g, 2.77×10^{-3} mol, 1 equiv) was added, and the mixture was stirred at room temperature for 2.5 h. This solution was then quenched by adding very slowly acetyl chloride (0.22 mL, 3.1×10^{-3} mol, 1.2 equiv) and pyridine (0.45 mL, 5.6×10^{-3} mol, 2 equiv). After 0.5 h, the mixture was washed with HCl (1 M) solution and the aqueous layer extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification by chromatography yielded **13** (1.1 g, 80%). ^1H NMR (400 MHz, δ, ppm): 7.75−7.77 (m, 2H), 7.28−7.32 (m, 3H), 6.47 (s, 1H), 6.20 (s, 1H), 6.05 (s, 1H), 6.10 (s, 1H), 5.01 (s, 2H), 3.66−3.70 (m, 2H), 3.59 (s, 3H), 2.62−2.68 (m, 4H), 2.11 (s, 3H), 1.9−1.95 (m, 2H), 0.91−0.93 (m, 2H), −0.01 (s, 9H). ^{13}C NMR (100 MHz, δ, ppm): 169.38, 159.34, 157.37, 137.15, 136.95, 130.92, 127.96, 127.55, 109.20, 107.45, 102.9, 92.96, 80.11, 66.15, 63.29, 55.15, 27.33, 27.18, 24.63, 20.92, 18.01, −1.40. FTIR (film, ν, cm^{-1}): 2952, 2904, 1751, 1599, 1496, 1224, 1159, 1034, 835. HPLC: $R_t = 6.0$ min. MS (ESI + ve, *m*/*z*, rel intens): 520.5 (10, M), 538.7 (30, M + 18), 461.6 (100, M − OAc). HRMS (ESI + ve): [MNa^+] calcd for $C_{26}H_{36}O_5SiS_2$ 543.1671, found 543.1652. Anal. Calcd for $C_{26}H_{36}O_5S_2Si$: C, 59.54; H, 6.97; S, 12.31. Found: C, 59.92; H, 6.95; S, 12.14.

(±)-Acetic Acid (3-Hydroxy-5-methoxyphenyl)(2-phenyl-[1,3]dithian-2-yl)methyl Ester (14). To the SEM-protected phenol **13** (0.745 g, 1.43×10^{-3} mol) azeotropically dried with benzene, in 30 mL of dry THF at 0 °C, was added dropwise HF·pyr complex (70% HF, 9 mL, 6000 mL/mol) until complete disappearance of starting material by TLC. The crude mixture was diluted with EtOAc at 0 °C and carefully neutralized by addition of a saturated solution of $NaHCO_3$. The organic layer was then washed with brine, dried over Na_2SO_4, and concentrated in vacuo, toluene was added, and the solution was again evaporated to remove any traces of pyridine. Immediate purification by flash chromatography yielded **14** (0.45 g, 81%). ^1H NMR (400 MHz, δ, ppm): 7.75−7.77 (m, 2H), 7.25−7.32 (m, 3H), 6.26 (s, 1H), 6.14 (s, 1H), 6.04 (s, 1H), 5.83 (s, 1H), 3.51 (s, 3H), 2.61−2.72 (m, 4H), 2.07 (s, 3H), 1.85−1.89 (m, 2H). ^{13}C NMR (100 MHz, δ, ppm): 169.87, 159.46, 155.86, 138.84, 136.97, 130.78, 128.33, 127.55, 108.6, 106.6, 102.5, 80.35, 63.25, 55.0, 27.24, 27.09, 24.48, 14.06. FTIR (film, ν, cm^{-1}): 3417, 2906, 1747, 1599, 1464, 1224, 1151, 1034, 702. HPLC: $R_t = 5.17$ min. MS (ESI + ve, *m*/*z*, rel intens): 408.53 (15, M + 18), 331.4 (100, M − OAc). HRMS (ESI + ve): [MNa^+]

calcd for $C_{20}H_{22}O_4S_2$ 413.0857, found 413.0847. Anal. Calcd for $C_{20}H_{22}O_4S_2$: C, 61.51; H, 5.68; S, 16.42. Found: C, 61.61; H, 5.22; S, 16.22.

(±)-4-{3-[Acetoxy-(2-phenyl[1,3]dithian-2-yl)methyl]-5-methoxyphenoxy}butyric Acid *tert*-Butyl Ester (15). A solution of phenol **14** (0.45 g, 1.15×10^{-3} mol), *tert*-butyl 4-bromobutanoate (0.3 g, 1.38×10^{-3} mol, 1.2 equiv), potassium carbonate (0.38 g, 2.76×10^{-3} mol, 2.4 equiv), and catalytic tetrabutylammonium iodide (85 mg, 2.3×10^{-4} mol, 0.2 equiv) in 65 mL of MeCN was heated at 90 °C for 20 h under argon. Then the mixture was allowed to cool and washed with brine. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to leave 0.97 g. Purification by flash chromatography afforded compound **15** (0.408 g, 75% isolated yield) and recovered **14** (40 mg). ^{1}H NMR (400 MHz, δ, ppm): 7.74−7.77 (m, 2H), 7.25−7.33 (m, 3H), 6.29 (s, 1H), 6.00 (s, 1H), 6.07 (s, 1H), 5.99 (s, 1H), 3.73 (t, $J = 6$, 2H), 3.56 (s, 3H), 2.61−2.69 (m, 4H), 2.34 (t, $J = 7$, 2H), 2.09 (s, 3H), 1.95 (q, $J = 7$, 4H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, δ, ppm): 172.47, 169.33, 159.41, 158.78, 138.13, 136.88, 130.94, 127.94, 127.51, 107.12, 106.64, 101.44, 80.22, 66.75, 63.26, 55.08, 31.99, 28.66, 27.29, 27.16, 24.64, 24.61, 20.88. FTIR (film, ν, cm^{-1}): 2975, 1751, 1729, 1599, 1467, 1367, 1226, 1151, 1034, 908, 732. HPLC: $R_t = 5.84$ min. MS (ESI + ve, *m*/*z*, rel intes): 550.72 (30, M + 18), 474.6 (100, M − *t*Bu). HRMS (ESI + ve): [MNa$^+$] calcd for $C_{28}H_{36}O_6S_2$ 555.1851, found 555.1847. Anal. Calcd for $C_{28}H_{36}O_6S_2$: C, 63.13; H, 6.81; S, 12.04. Found: C, 62.81; H, 6.91; S, 11.76.

(±)-4-{3-[Hydroxy(2-phenyl[1,3]dithian-2-yl)methyl]-5-methoxyphenoxy}butyric Acid *tert*-Butyl Ester (10). A solution of **15** (0.95 gm $1{,}78 \times 10^{-3}$ mol), potassium carbonate (1.52 g, 3.75×10^{-3} mol, 2.1 equiv), and triethylamine (7.4 mL, 5.34×10^{-2} mol, 30 equiv) in 80 mL of MeOH/water (1:1) was heated at 70 °C for 3 h, when TLC showed complete conversion. The mixture was concentrated in vacuo and the aqueous residue extracted with EtOAc. The aqueous layer was neutralized with HCl (1 M) and re-extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford product **10** (0.83 g, 95%) in 99% purity. ^{1}H NMR (400 MHz, δ, ppm): 7.69−7.72 (m, 2H), 7.23−7.31 (m, 3H), 6.27 (s, 1H), 5.98 (s, 1H), 4.90 (s, 1H), 5.95 (s, 1H), 3.71 (t, $J = 6$, 2H), 3.54 (s, 3H), 2.64−2.73 (m, 4H), 2.33 (t, $J = 6$, 2H), 1.88−1.95 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, δ, ppm): 172.5, 159.41, 158.77, 139.37, 137.57, 130.69, 128.14, 127.51, 107.12, 106.66, 106.09, 101.38, 80.29, 66.78, 66.30, 55.12, 32.05, 28.13, 27.34, 27.07, 24.79, 24.68. FTIR (film, ν, cm^{-1}): 3500, 2933, 1728, 1597, 1467, 1367, 1226, 1153, 1059. HPLC: $R_t = 5.68$ min. MS (ESI + ve, *m*/*z*, rel intens): 508.76 (50, M + 18), 473 (100, M − 17). HRMS (ESI + ve): [MNa$^+$] calcd for $C_{26}H_{34}O_5S_2$ 513.1745, found 513.1750.

(±)-4-{3-[Hydroxy(2-phenyl[1,3]dithian-2-yl)methyl]-5-methoxyphenoxy}butyric Acid (16). A solution of **10** (0.83 g, 1.69×10^{-3} mol) in formic acid (35 mL) was stirred at room temperature for 5 h,[29] when complete disappearance of **10** was detected by TLC. The solvent was removed under reduced pressure, and the crude product was redissolved in EtOAc and washed with saturated $NaHCO_3$ solution and brine. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to afford 0.76 g. Purification by column chromatography gave deprotected linker **16** (0.70 g, 90%) in high purity. ^{1}H NMR (400 MHz, δ, ppm): 7.69−7.71 (m, 2H), 7.31−7.24 (m, 3H), 6.27 (s, 1H), 5.98 (s, 1H), 4.91 (s, 1H), 5.95 (s, 1H), 3.73 (t, $J = 6$, 2H), 3.55 (s, 3H), 2.71−2.63 (m, 4H), 2.51 (t, $J = 5$ Hz, 2H), 1.99 (q, $J = 6$, 2H), 1.98−1.88 (m, 2H). ^{13}C NMR (100 MHz, δ, ppm): 178.8, 159.1, 158.14, 138.98, 137.09, 130.30, 127.73, 127.09, 106.05, 105.81, 100.91, 80.57, 65.94, 52.06, 54.72, 30.10, 26.91, 26.55, 24.36, 23.83. FTIR (film, ν, cm^{-1}): 3415, 2917, 1732, 1608. HPLC: $R_t = 5.68$ min. MS (ESI + ve, *m*/*z*, rel intens): 417.4 (100, M − OH), 452 (30, M + 18). HRMS (ESI + ve): [MNa$^+$] calcd for $C_{22}H_{26}O_5S_2$ 457.1119, found 457.1110.

(29) A longer reaction time (up to overnight) produced the formate ester of the alcohol **16** in addition to free alcohol **16**.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-methylbutyric Acid [3-(3-*tert*-butoxycarbonylpropoxy)-5-methoxyphenyl](2-phenyl[1,3]dithian-2-yl)methyl Ester (20a). Into a dry round-bottom flask were placed PS-carbodiimide resin (2.13 g, 2×10^{-3} mol, 4 equiv, 0.94 mmol/g) and *N*-α-Fmoc-L-valine (0.52 g, 1.53×10^{-4} mol, 3 equiv). The system was purged with argon/vacuum and dissolved in DCM. The mixture was stirred for 10 min prior to addition of a solution of the alcohol linker **10** (0.250 g, 1.53×10^{-4} mol, 1 equiv) and DMAP (6.2 mg, 5.1×10^{-5} mol, 0.1 equiv) in DCM. The reaction was shaken at room temperature for 5 h, when monitoring by LCMS showed no alcohol **10** left. The DMAP was scavenged using Dowex (H$^+$) resin. The two resins were removed by filtration, and the evaporation of the filtrate yielded the desired ester. The product was finally purified by column chromatography eluting with hexane/ethyl acetate (7:3) to give product **20a** as a white solid (0.41 g, 90%). ^{1}H NMR (400 MHz, δ, ppm): 7.79−7.72 (m, 6H), 7.56−7.60 (m, 2H), 7.39−7.23 (m, 5H), 6.29 (s, 1H), 6.09, 6.06 (s, 1H), 6.02 (s, 1H), 5.95 (s, 1H), 5.31 (t, $J = 11$, 1H), 4.42−4.33 (m, 3H), 4.25, 4.21 (t, $J = 7$, 1H), 3.76 (t, 7 Hz, 2H), 3.55 (s, 3H), 2.67−2.61 (m, 4H), 2.36−2.32 (m, 2H), 2.15−2.16 (m, 1H), 1.95−1.94 (m, 2H), 1.88−1.87 (m, 2H), 1.44 (s, 9H), 0.99, 0.89, 0.74 (d, $J = 7$ Hz, 6H). ^{13}C NMR (100 MHz, δ, ppm) (most of the signals are doublets because of the mixture of diastereomers): 170.36, 170.46, 172.46, 158.83, 159.48, 156.14, 141.24, 143.94, 143.77, 136.20, 136.28, 136.58, 136.66, 119.89, 125.08, 127.05, 127.63, 127.68, 128.00, 128.06, 131.07, 106.39, 106.45, 107.18, 101.83, 81.79, 81.63, 67.01, 67.09, 66.74, 63.08, 62.94, 59.18, 58.88, 55.02, 55.08, 47.19, 31.99, 31.27, 31.35, 28.10, 27.20, 27.14, 24.62, 19.37, 19.02, 17.20, 17.33. HPLC: $R_t = 6.37$ min. MS (ESI + ve, *m*/*z*, rel intens): 829 (30, M + 18), 473 (100, M − valine). HRMS (ESI + ve): [MNa$^+$] calcd for $C_{46}H_{53}NO_8S_2$ 834.3110, found 834.30940.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-methylbutyric Acid [3-(3-Carboxypropoxy)-5-methoxyphenyl]-(2-phenyl[1,3]dithian-2-yl)methyl Ester (20b). **20b** was prepared by the same procedure as that for the synthesis of **16**. *tert*-Butyl derivative **20a** (0.2 g, 2.5×10^{-4} mol) was stirred in 10 mL of HCOOH for 6 h, when the crude mixture was worked up following the former procedure to leave 0.206 g. This was purified by column chromatography to give **20b** as an oil (0.13 g, 70%). ^{1}H NMR (500 MHz, δ, ppm): 7.79−7.72 (m, 5H), 7.63−7.60 (m, 2H), 7.57−7.55 (m,1H), 7.4−7.29 (m, 5H), 6.30 (s, 1H), 6.06, 6.04 (s, 1H), 6.02, (s, 1H), 5.97 (s, 1H), 5.34, 5.28 (1H, d, $J = 9$, 2H), 4.58−4.36 (m, 2H), 4.32, 4.26 (t, $J = 7$, 1H), 3.79−3.75 (m, 2H), 3.57, 3.55 (s, 3H), 2.66−2.65 (m, 4H), 2.50−2.47 (m, 2H), 2.21−2.16 (m, 1H), 2.00−1.96 (m, 2H), 1.88−1.87 (m, 2H), 1.02, 0.92, 0.75 (d, $J = 7$ Hz, 6H). ^{13}C NMR (100 MHz, δ, ppm) (most of the signals are doublets because of the mixture of diastereomers): 182.34, 175.44, 170.49, 157.83, 159.03, 156.26, 141.26, 143.94, 143.82, 136.70, 136.37, 127.04, 127.29, 127.66, 128.02, 131.03, 119.91, 125.04, 106.59, 106.86, 107.09, 101.77, 101.96, 81.79, 81.65, 66.43, 67.15, 63.06, 59.07, 58.92, 55.09, 55.02, 47.20, 47.12, 31.13, 29.64, 29.84, 27.23, 27.13, 24.28, 23.56, 19.38, 19.02, 17.05, 17.27. FTIR (film, ν, cm^{-1}): 2963, 1714, 1598, 1514, 1468, 1265, 1159, 1066, 738. HPLC: $R_t = 5.91$ min. MS (ESI + ve, *m*/*z*, rel intens): 773.7 (10, M + 18), 417.4 (100, M − valine). HRMS (ESI + ve): [MNa$^+$] calcd for $C_{42}H_{45}NO_8S_2$ 778.2484, found 778.2474.

General Procedure for the Loading of Linker 16 (Leading to Resin 2) or 20b (Leading to Resin 17b) onto TG Amino Resin. TG amino resin (0.100 g, 0.2 mmol/g) was treated with 2 mL of 20% piperidine in DMF for 10 min. The resin was drained, washed with DMF and DCM, and dried under vacuum for 1 h. A solution under argon of HOBt (9.5 mg, 2.2 equiv) and TBTU (19.7 mg, 2.5 equiv) in 0.5 mL of DMF was added to the resin. Triethylamine (19.7 μL, 4 equiv) and then linker (2 equiv) in DCM (0.5 mL) were syringed into the previous solution, and the mixture was gently stirred for 24 h, by which time a negative Kaiser test was obtained. The resin was filtered, washed, and dried under vacuum to yield yellow beads.

Characterization of resin 2. MAS ^{1}H NMR (400 MHz, δ, ppm): 7.71−7.69 (m, 2H), 7.33−7.25 (m, 3H), 6.23 (s, 1H), 5.99 (s, 1H), 4.88 (s, 1H), 5.92 (s, 1H), 3.51 (s, 3H), 3.42−3.39 (m, 2H), 2.65−2.59 (m, 4H), 2.28 (t, J = 6 Hz, 2H), 1.99−1.94 (m, 2H), 1.82−1.81 (m, 2H). Gel ^{13}C NMR (100 MHz, δ, ppm): 173, 159.1, 158, 139.98, 137.01, 130.20, 127.23, 126.09, 106.10, 105.31, 100.61, 80.11, 66.24, 52.06, 54.32, 39.21, 32.10, 26.51, 26.55, 24.36, 24.21. FTIR (film, ν, cm^{-1}): 3508, 2874, 1669, 1601, 1542, 1454, 1346, 1283, 1100, 953, 845.

Characterization of resin 17b. Loading: 0.17 mmol/g (85% yield) obtained by Fmoc analysis. MAS ^{1}H NMR (400 MHz, δ, ppm): 7.75−7.70 (m, 5H), 7.59−7.55 (m, 3H), 7.34−7.29 (m, 5H), 6.27 (s, 1H), 6.02 (br s, 2H), 5.91 (s, 1H), 5.28 (s, 1H), 4.41−4.34 (m, 2H), 4.17, 4.23 (∼t, 1H, J = 7), 3.63 (vbr s from TG resin backbone), 2.99−2.97 (m, 4H), 2.76 (br s, 2H), 2.63 (br s, 1H), 2.29 (br s, 2H), 1.98 (br s, 2H), 0.99−0.77 (m, 6H). Gel ^{13}C NMR (100 MHz, δ, ppm): 172.41, 171, 143.97, 141.24, 136.68, 136.41, 131.11, 128.12, 127.76, 127.14, 125.15, 119.99, 107.28, 106.36, 101.92, 81.79, 66.99, 60.31, 59.33, 59.09, 55.11, 47.23, 45.05, 39.91, 39.27, 32.71, 31.22, 27.27, 25.14, 24.67, 19.83, 19.15, 17.51, 17.38. FTIR (film, ν, cm^{-1}): 3527, 2862, 1720, 1650, 1601, 1541, 1493.

Loading of Fmoc-Protected *β*-Alanine onto Resin 2 To Afford TG Resin 17a. Diisopropylcarbodiimide (DIC; 17.5 μL, 1.12×10^{-4} mol, 4 equiv) was syringed into a solution of resin **2** (0.100 g, 2.8×10^{-5} mol, 0.20 mmol/g), Fmoc-β-alanine (35 mg, 1.1×10^{-4} mol, 4 equiv), and DMAP (1.7 mg, 1.4×10^{-5} mol, 0.5 equiv) in dry DCM (1 mL) under argon at room temperature. The mixture was gently stirred for 24 h, when the resin was drained, washed, and dried under high vacuum for 6 h. The final loading was determined to be 0.20 mmol/g by Fmoc analysis. MAS ^{1}H NMR (400 MHz, δ, ppm): 7.82 (d, J = 8, 4H), 7.60−7.58 (br s, 2H), 7.39−7.35 (m, 2H), 7.33−7.28 (m, 5H), 6.29 (s, 1H), 6.05 (s, 1H), 5.99 (s, 1H), 5.92 (s, 1H), 4.39−4.38 (m, 2H), 4.17 (br s, 1H), 3.52 (s, 3H), 3.44−3.42 (m, 2H), 2.67 (br s, 2H), 2.61 (br s, 4H), 2.31−2.29 (m, 2H), 2.10−1.98 (m, 2H), 1.84−1.77 (m, 2H). Gel ^{13}C NMR (100 MHz, δ, ppm): 172, 169, 159.1, 158, 140, 143, 137, 130.1, 127.5, 127.0, 126.4, 125.8, 125.4, 125.2, 124.4, 119.2, 106.30, 105.7, 100.81, 79.91, 66.24, 65.8, 52.06, 54.42, 46.6, 39.51, 36.61, 34.31, 31.9, 26.61, 24.42, 24.91. FTIR (film, ν, cm^{-1}): 3571, 2885, 1721, 1671, 1601, 1536, 1453, 1160, 955, 845.

Dithiane Deprotection of 17a (18). Resin **17a** (50 mg, 1.15×10^{-5} mol, 0.20 mmol/g) and H_5IO_6 (5.24 mg, 2.3×10^{-5} mol, 2 equiv) were purged under vacuum/argon and dissolved in 1 mL of anhydrous THF. The mixture was gently stirred for 0.5 h, changing the color to orange. The suspension was drained, and the resin was washed with a saturated solution of Na_2SO_3 in water followed by a general washing procedure and then dried under vacuum for 5 h to afford orange beads. MAS ^{1}H NMR (400 MHz, δ, ppm): 7.74−7.72 (m, 4H), 7.64−7.62 (m, 2H), 7.44−7.24 (7H, t, 8.5 Hz, Fmoc), 6.81 (s, 1H), 6.57 (s, 2H), 6.48 (s, 1H), 4.35 (br s, 2H), 4.24−4.22 (m, 1H), 3.53 (s, 3H), 3.51−3.42 (m, 2H), 2.71−2.69 (m, 2H), 2.32 (br s, 2H), 2.02−2.06 (m, 2H). Gel ^{13}C NMR (100 MHz, δ, ppm): 171.5, 172, 159.9, 160.5, 140.5, 143.3, 133.2, 128.1, 126.9, 126.4, 124.6, 124.5, 119.2, 107.39, 107.04, 101.61, 77.91, 67.33, 66.7, 55.5, 47.23, 40.57, 37.01, 34.61, 32.5, 25.1. FTIR (film, ν, cm^{-1}): 3571, 2885, 1721, 1671, 1601, 1536, 1453, 1160, 955, 845.

Photolysis of Benzoyl Resin 18. Resin **18** (47 mg, 1.08×10^{-5} mol) and Fmoc-serine (internal standard, 1.5 mg) were dissolved in 3:1 distilled THF/MeOH (4 mL, degassed by passing argon through the mixture of solvents for 15 min) in a quartz test tube. The suspension was irradiated for 2 h with constant argon bubbling to yield the corresponding mixture of benzofuranyl resin **19** and Fmoc-protected β-alanine in solution. HPLC analysis of the solution indicated the presence of Fmoc-β-alanine in 70% yield. This was confirmed by Fmoc analysis of the residual resin.

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Supporting Information Available: Experimental part with all NMR peak assignments, plus full characterization data for compounds **10**, **16**, **20a**, and **20b** (^{1}H and ^{13}C NMR, LC, HRMS, IR) and resins **2**, **17a**, and **17b** (MAS ^{1}H NMR, gel ^{13}C NMR, IR). This material is available free of charge via the Internet at http://pubs.acs.org.

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