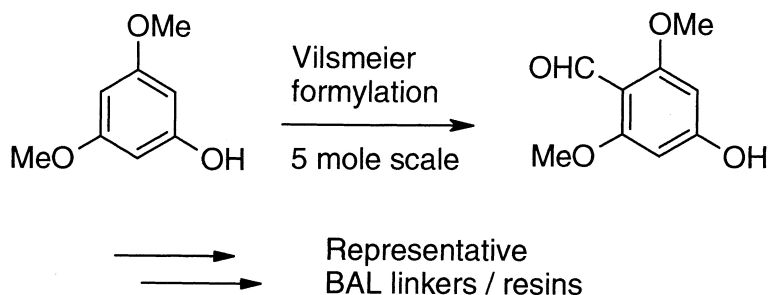Article

Convenient Preparation of 4-Formyl-3,5-dimethoxyphenol and Its Incorporation into Linkers and Resins for Solid-Phase Synthesis

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Convenient Preparation of 4-Formyl-3,5-dimethoxyphenol and Its Incorporation into Linkers and Resins for Solid-Phase Synthesis

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4-Formyl-3,5-dimethoxyphenol (**1**) is a key synthetic intermediate used to prepare the BAL family (backbone amide linker) of acid-labile linkers and resins. The utility of these linkers and resins for solid-phase synthesis of both peptides and non-peptides has been amply demonstrated. In this article we report a simple and scalable procedure for preparation of isomerically pure 4-formyl-3,5-dimethoxyphenol (**1**) and its subsequent incorporation into a representative BAL linker and functionalized resin: 4-(4-formyl-3,5-dimethoxyphenoxy)-butanoic acid and 4-formyl-3,5-dimethoxyphenoxy-polystyrene, respectively. The procedures are reproducible, are readily scalable, and require no chromatography.

Introduction

The backbone amide linking (BAL) approach is a broadly applicable anchoring strategy for solid-phase organic synthesis.[1−3] In peptide applications, the growing peptide is anchored to the solid-phase through a backbone amide nitrogen instead of through the C^{α}-carboxyl group. This acid-labile anchor point overcomes many of the limitations inherent in C-terminal and side-chain anchoring and facilitates the preparation of cyclic and C-terminal modified peptides (i.e., C-terminal carboxamides, alcohols, aldehydes, esters, *p*-nitroanilides).[2,3] While originally designed for solid-phase synthesis of peptides, this anchoring approach has now been extended to combinatorial synthesis of diverse amide,[4] sulfonamide,[4] urea,[4] hydroxamate,[5] and heterocyclic[6] small-molecule libraries. Today, the BAL approach is most commonly applied using a solid support that has been functionalized with a tris(alkoxy)benzaldehyde-based linker.[2,3] The structures of the most common linkers [4-formyl-3,5-dimethoxyphenol (**1**), 4-(4-formyl-3,5-dimethoxyphenoxy)-butanoic acid (**2**), and 5-(4-formyl-3,5-dimethoxyphenoxy)-pentanoic acid (**3**)] and functionalized resins (**4** and **5**) are shown in Figure 1.[7]

In addition to serving as a linker, 4-formyl-3,5-dimethoxy-phenol (**1**) is also a key synthetic intermediate in the preparation of linkers **2** and **3**. The reported Vilsmeier formylation of commercially available 3,5-dimethoxyphenol (**6**) typically provides a mixture of 4-formyl-3,5-dimethoxy-phenol (**1**), the isomeric 2-formyl-3,5-dimethoxyphenol (**7**), and 2,6-diformyl-3,5-dimethoxyphenol (**8**).[1] Isolation of **1** from this mixture of formylated reaction products is often problematic.[8] On the basis of this practical consideration and experimental observations by Barany,[9] commercially available BAL linkers and resins are frequently composed of both 4- and 2-formyl regioisomers as mixtures of 4-formyl-3,5-dimethoxyphenol (**1**) and the 2-formyl derivative **7**. However, we prefer to use BAL linkers and resins derived from single-
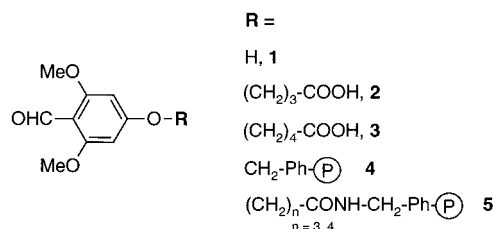

Figure 1. Structures of tris(alkoxy)benzaldehyde-based linkers and functionalized resins.

isomer **1** for chemistry optimization and library production. Use of regio-pure linkers and resins eliminates all risk of reactivity differences (during resin loading, elaboration, or cleavage) that could arise from the more sterically hindered 2-formyl isomer and can simplify interpretation of MAS NMR data during chemistry optimization.

Using the published procedure of Barany,[1] we also encountered difficulty isolating pure 4-formyl-3,5-dimethoxy-phenol (**1**) from the Vilsmeier product mixture especially at synthesis scales required to support library optimization and preparation. Therefore, a more reliable synthesis and purification method for multi-hundred-gram quantities of isomerically pure **1** was sought. In this article, we report a convenient, reliable preparation of isomerically pure 4-formyl-3,5-dimethoxyphenol (**1**) and methods for subsequent incorporation of **1** into a representative linker and functionalized resin: 4-(4-formyl-3,5-dimethoxyphenoxy)butanoic acid (**2**) and 4-formyl-3,5-dimethoxyphenoxy-polystyrene (**4**), respectively. The synthesis scale was selected to supply sufficient quantity of linker for optimization and preparation of a typical 10 000-member library.

Results and Discussion

Preparation of 4-Formyl-3,5-dimethoxyphenol (1). The large-scale procedure described here is an adaptation of the
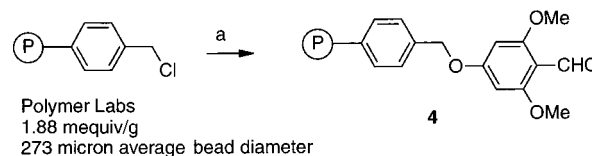
Scheme 1. Preparation of 4-Formyl-3,5-dimethoxyphenol (**1**)[a]
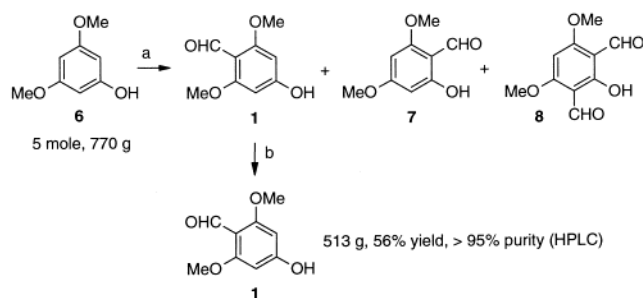
[a] Reagents and conditions: (a) POCl₃, DMF, 0 °C to room temperature, 16 h; (b) CHCl₃, 1 L, brief multiple treatments, 56% for two steps.

Vilsmeier formylation approach described by Barany et al.[1,10] In a typical 5 mol scale preparation, DMF (582 mL, 7.52 mol) is added dropwise to a stirred 0 °C solution of 3,5-dimethoxyphenol (**6**, 770 g, 5 mol) in POCl₃ (936 mL, 10.04 mol). After stirring at room temperature for 16 h, hydrolysis of the resulting α-chloroamine intermediate, and precipitation of crude product, 4-formyl-3,5-dimethoxyphenol (**1**) is obtained as the major product along with the reported byproducts 2-formyl regioisomer **7** and the bisformylated derivative **8** (Scheme 1). We found that during large-scale preparation, slow addition of DMF, temperature control, and vigorous mechanical stirring were essential to minimize the formation of these byproducts and to achieve consistent, reproducible results.

The convenient purification described here is effective owing to an earlier observation by Barany[1] that compounds **1**, **7**, and **8** have different solubility properties. During preliminary studies, sample preparation of the crude product mixture for NMR analysis revealed that the chloroform solubility of the byproducts **7** and **8** is much higher than that of the desired 4-formyl positional isomer **1**. This observation prompted us to pursue trituration as a simple and scalable method for large-scale purification of 4-formyl-3,5-dimethoxyphenol (**1**). In practice (5 mol scale), brief trituration of the crude Vilsmeier product mixture with chloroform (3 treatments, 1 L/treatment) followed by evaporation of excess solvent provides **1** as a pale orange powder (513 g, 56% overall yield) in greater than 95% purity (¹H NMR, HPLC). The progress of the purification can be followed easily by TLC, ¹H NMR, or HPLC analysis of either the residual solids or the chloroform solution during trituration. This simple, scalable trituration step eliminates the need for the large-scale aqueous/organic extraction and recrystallization steps employed in earlier procedures.[1,4c] Characterization data (¹H NMR, ¹³C NMR, MS, IR, CHN analysis, melting point) for **1** agree with those previously published.[1,4c] This rapid and reliable procedure is now used routinely in our labs for multi-hundred-gram preparation of 4-formyl-3,5-dimethoxyphenol (**1**).

With a reliable supply of 4-formyl-3,5-dimethoxyphenol (**1**) in hand, synthetic protocols were developed for incorporation of **1** into the related linker **2** and functionalized resins **4** and **5**. We report here representative procedures for large-scale preparation of (4-formyl-3,5-dimethoxyphenoxy)-methyl-polystyrene (**4**) and the linker 4-(4-formyl-3,5-dimethoxyphenoxy)butanoic acid (**2**).

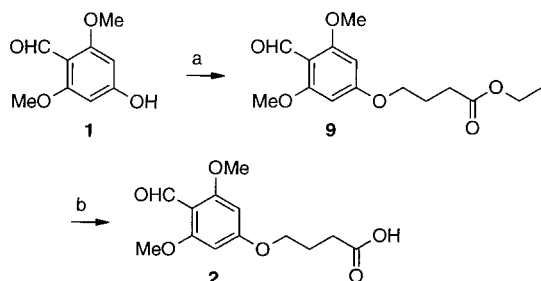**Scheme 2.** Preparation of (4-Formyl-3,5-dimethoxyphenoxy)methyl-polystyrene (**4**)[a]

[a] Reagents and conditions: (a) 4-formyl-3,5-dimethoxyphenol (**1**), Cs₂CO₃, anhydrous DMA, 85 °C, 36 h.

Preparation of (4-Formyl-3,5-dimethoxyphenoxy)-methyl-polystyrene (4). (4-Formyl-3,5-dimethoxyphenoxy)-methyl-polystyrene (**4**) was the anchoring resin in Ellman's solid-phase synthesis of heterocyclic 1,4-benzodiazepine-2,5-diones.[6a,b] Subsequently, others have also successfully applied this resin for synthesis of small-molecule combinatorial libraries.[4a,d] Ellman prepared resin **4** from chloromethylpoly-styrene (200−400 mesh, 1% cross-linked, 0.76 mequiv/g, Novabiochem, cat. # 01-64-0007) by treatment with the preformed sodium salt of 4-formyl-3,5-dimethoxyphenol (**1**) in DMF at 50 °C.

In our hands with larger-diameter, higher-loading chloromethylpolystyrene beads (average bead diameter 273 μm, 1.88 mequiv/g), however, the reported conditions only worked well on small scales (<25 mmol). Alkylation on a larger scale (150 mmol) consistently failed to go to completion.[11] Precipitation of the sodium salt at the higher concentration used for convenient preparative scale work is one plausible reason for incomplete reaction. In addition, the potential fire hazard of using sodium hydride in DMF on a large scale also prompted us to look for alternative alkylation conditions. The use of cesium carbonate in the loading of other functionalized phenols onto Merrifield resin was reported.[12] We therefore attempted the literature conditions and have found that reliable and complete alkylation was obtained on the 150 mmol scale by treating the resin with the more soluble cesium salt of **1** in dimethylacetamide at 85 °C (Scheme 2). Elemental analysis of resin **4** (chlorine content < 0.1% detection limit) and expected weight gain confirmed complete reaction. ¹H MAS NMR and IR spectra of resin **4** were consistent with the proposed structure and in good agreement with the literature.[6b] While not demonstrated herein, the complete alkylation might also be accomplished by using other bases such as potassium or sodium carbonate in combination with a phase transfer catalyst such as tetrabutylammonium iodide.

Preparation of 4-(4-Formyl-3,5-dimethoxyphenoxy)-butanoic Acid (2). Resins functionalized with linkers **2** and **3** are now often preferred over resin **4** for a number of practical reasons: (1) these linkers are attached to solid supports by reliable, high-yielding amide bond formation, (2) reaction rates and yields are reported to increase with increasing length of the spacer between the solid support and the tris(alkoxy)phenyl moiety,[13] and (3) resins derived from linkers **2** and **3** are less susceptible to the undesired release of the trioxygenated phenyl anchor point from the resin during TFA-mediated product cleavage.[14]

4-(4-Formyl-3,5-dimethoxyphenoxy)butanoic acid (**2**) is conveniently prepared from **1** using the two-step sequence described in Scheme 3. While this alkylation/saponification

Scheme 3. Preparation of
4-(4-Formyl-3,5-dimethoxyphenoxy)butanoic Acid (**2**)[a]

[a] Reagents and conditions: (a) ethyl 4-bromobutanoate, Cs$_2$CO$_3$, anhydrous DMA, 85 °C, 16 h, 98%; (b) 2 N NaOH, MeOH, 2 h, 100%.

sequence is similar to that originally described by Barany and co-workers[1] for preparation of 5-(4-formyl-3,5-dimethoxyphenoxy)pentanoic acid (**3**), a number of modifications have been made in order to better accommodate preparative-scale work.

Treatment of 4-formyl-3,5-dimethoxyphenol (**1**) (507 g, 2.8 mol) in DMA (4.6 L) with cesium carbonate and ethyl 4-bromobutanoate at 85 °C provides crude ethyl 4-(4-formyl-3,5-dimethoxyphenoxy)butanoate (**9**) as a white solid (807 g, 98% yield). Saponification of **9** (190 g, 0.642 mol) is smoothly accomplished using aqueous sodium hydroxide in methanol. Purification is achieved by a sequence of two precipitation steps during workup. With this protocol, 4-(4-formyl-3,5-dimethoxyphenoxy)butanoic acid (**2**) is obtained as a white solid (172 g, 100% yield). Analytical data (^{1}H NMR, ^{13}C NMR, MS, IR, CHN analysis) for **9** and **2** are consistent with the proposed structures.[15] Thus, an efficient, two-step procedure was identified for large-scale preparation of BAL linker 4-(4-formyl-3,5-dimethoxyphenoxy)butanoic acid (**2**) from 4-formyl-3,5-dimethoxyphenol (**1**). While not explicitly demonstrated herein, these methods are likely applicable for the large-scale preparation of 5-(4-formyl-3,5-dimethoxyphenoxy)pentanoic acid (**3**) as well.

In summary, we report here a convenient scalable synthesis of 4-formyl-3,5-dimethoxyphenol (**1**) and subsequent efficient incorporation of **1** into a representative BAL linker and functionalized resin: 4-(4-formyl-3,5-dimethoxyphenoxy)butanoic acid (**2**) and 4-formyl-3,5-dimethoxyphenoxy-polystyrene (**4**), respectively. Importantly, these procedures are reproducible, are readily scalable, and require no chromatographic purification steps. With these reliable procedures now available, one can anticipate broader application of these versatile linkers and resins for preparation of small-molecule and peptide combinatorial libraries.

Experimental Section

General. 3,5-Dimethoxyphenol (**6**) was purchased from Aldrich-Fluka Chemical Co. (Chloromethyl)polystyrene resin (Merrifield resin, average bead diameter 273 μm, 1% cross-linked, 1.88 mequiv/g, product no. 1461-6689) was purchased from Polymer Laboratories Inc. All other reagents were purchased from commercial sources. NMR spectra were recorded on Bruker AMX360 and Bruker AC400 spectrometers. Magic angle spinning (MAS) proton NMR was obtained on a Varian Inova300 spectrometer equipped with a magic angle spinning NANOPROBE. A Rainin Dynamax

HPLC system equipped with a Rainin Dynamax A1−1A automatic sample injector, a Rainin Dynamax UV-1 absorbance detector, and a Vydac C-18 protein column was used to determine the purity of **1**. A 25 min gradient from 20% to 80% of acetonitrile containing 0.1% of trifluoroacetic acid at flow rate of 1 mL/min was used as the analytical method.

4-Formyl-3,5-dimethoxyphenol (1). To a 4 L three-neck round-bottomed flask equipped with a mechanical stirrer, a 1 L addition funnel, and a thermometer were added 770 g (5.00 mol) of 3,5-dimethoxyphenol (**6**) and 936 mL (10.04 mol) of POCl$_3$ under argon. After being stirred for 10 min, the mixture was cooled to 0 °C and 582 mL (7.52 mol) of anhydrous DMF was added dropwise via the addition funnel over 4 h. It was crucial that the internal temperature remain below 10 °C during the entire addition period. After the addition, the mixture was allowed to warm to room temperature while stirring. As the reaction progressed, the reaction mixture became very viscous. Therefore, use of a mechanical stirrer rather than a magnetic stirrer is highly recommended. After being stirred at room temperature for an additional 16 h, the reaction mixture was poured into 11.5 kg of ice. Additional water was used to ensure quantitative transfer of the product out of the reaction flask (three 2 L portions). The combined aqueous mixture was allowed to warm to room temperature over 1 h while stirring. NaOH pellets (~1.2 kg) were added until a pH of 6.0 was reached. The resulting precipitate was then collected using a filter funnel and dried in a vacuum oven at 40 °C overnight. The collected precipitate was triturated three times with 950 mL portions of CHCl$_3$ to remove the CHCl$_3$-soluble byproducts (2-formyl-3,5-dimethoxyphenol (**7**) and the bisformylated derivative **8**). The remaining solid was then dried in a vacuum oven at 40 °C for 24 h to yield 4-formyl-3,5-dimethoxyphenol (**1**) as a pale orange powder (513 g, 56%). ^{1}H NMR, ^{13}C NMR, MS, IR spectra of the product were consistent with literature data.[1] Purity of the product was greater than 95% by HPLC. mp 223−225 °C (lit.[1] mp 224−226 °C). Anal. Calcd for C$_9$H$_{10}$O$_4$: C, 59.34; H, 5.53. Found: C, 59.29; H, 5.55.

(4-Formyl-3,5-dimethoxyphenoxy)methyl-polystyrene (4). To a 2 L bubbler with coarse frit were added Merrifield resin (80 g, average bead diameter 273 μm, 1% cross-linked, 1.88 mequiv/g, product no. 1461-6689) and 500 mL of anhydrous DMA under argon at room temperature. After argon was bubbled through the mixture for 10 min, the solvent was drained. 4-Formyl-3,5-dimethoxyphenol (**1**, 58.24 g, 320 mmol) and anhydrous DMA (1 L) were added to the swollen resin under argon. While argon was vigorously bubbled through the mixture, 125.1 g (384 mmol) of Cs$_2$CO$_3$ was added. The resulting mixture was heated to 85 °C. After bubbling at 85 °C for 36 h, the reaction mixture was cooled to room temperature and the solvent was drained. The resulting resin was washed with DMF (3 × 500 mL), 1:1 DMF/H$_2$O (3 × 500 mL), H$_2$O (3 × 500 mL), 1:1 DMF/H$_2$O (1 × 500 mL), DMF (3 × 500 mL), 1:1 DMF/1,4-dioxane (1 × 500 mL), 1,4-dioxane (3 × 500 mL), and MeOH (3 × 500 mL). The resulting resin was dried in a vacuum oven at 35 °C overnight to yield (4-formyl-3,5-dimethoxyphenoxy)methyl-polystyrene (**4**) as a light tan

colored resin (103 g). ^{1}H MAS NMR (300 MHz, CDCl$_3$) δ 1.24 (s), 1.44 (br s), 1.85 (br s), 3.77 (s, OCH$_3$), 4.90 (br s, OCH$_2$C), 6.08 (s), 6.54 (br s), 7.05 (s), 10.35 (s, CHO). elemental analysis Cl < 0.1%. IR spectrum is consistent with that reported.[6b]

Ethyl 4-(4-Formyl-3,5-dimethoxyphenoxy)butanoate (9). 4-Formyl-3,5-dimethoxyphenol (**1**, 507 g, 2.78 mol) was completely dissolved in dry DMA (4.6 L) in a dried 12 L round-bottomed flask. Cs$_2$CO$_3$ (1100 g, 3.38 mol) was then added in one portion followed by the addition of neat ethyl 4-bromobutyrate (442 mL, 3.09 mol). The temperature was then increased to 85 °C and heated overnight for 16 h. The reaction mixture was then cooled to room temperature and filtered. The filtrate was placed on a rotary evaporator (60 °C bath temperature) and concentrated to dryness under high vacuum (~3 Torr). The residue was dissolved in 1.5 L of dichloromethane. The organic layer was then washed with 300 mL of water (1×), 300 mL of 2 N NaOH (1×), and 300 mL of brine (2×). The organic layer was dried with Na$_2$SO$_4$, filtered, and concentrated to dryness. The resulting product was further dried overnight in a vacuum oven (40 °C) to provide ethyl 4-(4-formyl-3,5-dimethoxyphenoxy)-butanoate (**9**) as a white solid (807 g, 98%). mp 93−94 °C. IR (KBr disk) 3434, 2785, 1730, 1671 cm^{-1}. ^{1}H NMR (360 MHz, CDCl$_3$) δ 1.26 (t, 3H, $J = 7.1$ Hz), 2.15 (m, 2H), 2.52 (t, 2H, $J = 7.1$ Hz), 3.87 (s, 6H), 4.08 (t, 2H, $J = 6.2$ Hz), 4.16 (q, 2H, $J = 7.1$ Hz), 6.07 (s, 2H), 10.35 (s, 1H). ^{13}C NMR (CDCl$_3$) δ 14.21, 24.34, 30.44, 56.01, 60.55, 67.02, 90.69, 108.66, 164.09, 165.45, 172.93, 187.67. Anal. Calcd for C$_{15}$H$_{20}$O$_6$: C, 60.81; H, 6.80. Found: C, 60.89; H, 6.70.

4-(4-Formyl-3,5-dimethoxyphenoxy)butanoic Acid (2). A 2 N NaOH solution (1.5 L) was added to a 4 L round-bottomed flask containing a methanol solution (1.5 L) of crude ethyl 4-(4-formyl-3,5-dimethoxyphenoxy)butanoate (**9**) (190 g, 0.642 mol). The solution was stirred for 2 h at room temperature. The bulk of the solvent was then evaporated (rotavap, 40 °C bath temperature, water aspirator) to produce a heterogeneous suspension of product. The white precipitate was collected on a filter, dried under house vacuum for 1 h, and then washed with 2 L of dichloromethane. The remaining solid was then redissolved in about 3 L of water, and the solution was acidified with 3 N HCl (~1 L) to pH 1. The resulting precipitate was collected on a filter, washed with a portion of water, and dried (vacuum oven, 48 h, 40 °C) to produce 4-(4-formyl-3,5-dimethoxyphenoxy)butanoic acid (**2**) as a white solid (172 g, 100%). mp 170−171 °C. IR (KBr disk) 3585, 3413, 3100−3000, 1717, 1636 cm^{-1}. ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.95 (m, 2H), 2.39 (t, 2H, $J = 7.2$ Hz), 3.8 (s, 6H), 4.1 (t, 2H, $J = 6.5$ Hz), 6.24 (s, 2H), 10.18 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 23.98, 29.9, 56, 67.18, 91.11, 107.85, 163.39, 165.23, 173.99, 185.61; Anal Calcd for C$_{13}$H$_{16}$O$_6$: C, 58.21; H, 6.01. Found: C, 58.24; H, 5.85.

Supporting Information Available. ^{1}H and ^{13}C NMR spectra and HPLC chromatogram of **1** after trituration, ^{1}H NMR spectra and HPLC chromatograms of the crude products of Vilsmerier formylation before trituration, MAS ^{1}H NMR of resin **4**, and ^{1}H NMR of **9** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) These linkers are available from a number of commercial sources (e.g., 4-formyl-3,5-dimethoxyphenol (**1**) is available from Aldrich Chemical Co.). However, cost considerations, small lot size, supply variability, and regioisomer issues prompted our efforts reported herein.

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propylsiloxy-3,5-dimethoxybenzene. While this three-step synthesis provides regiopure **1** in quantities sufficient to prepare small combinatorial libraries (see Ellman et al. ref 6a,b), it was deemed less attractive for larger-scale work.

(9) Barany et al. have demonstrated that mixtures of 4-formyl and 2-formyl-3,5-dimethoxyphenol can be used to prepare linkers **2** and **3** (note: Figure 1 shows only the structure derived from 4-formyl-3,5-dimethoxyphenol) without significantly compromising yield and purity of peptidyl C-terminal-carboxamide products when cleaved under *optimized* conditions (reagent A or R, see ref 1). We are unaware of any subsequent comparative studies that confirm these observations when regioisomeric BAL linkers are employed for preparation of structurally diverse non-peptide libraries (particularly those obtained using less "optimal" cleavage conditions).

(10) Hansen et al. (see ref 4c) have since reported scaled up preparations of Barany's original synthesis of 4-formyl-3,5-dimethoxyphenol (**1**) and linker **3**. However, the preparations described herein offer improved yields at 10-fold larger scale.

(11) A total of 40% of the starting Merrifield resin was not converted to resin **4** based on the chlorine content (2.5%) of the dried product resin.

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(14) Unintended release of this electron-rich anchoring point is occasionally observed when functionalized supports such as resin **4** are treated with solutions of TFA during cleavage (acid lability of benzylic ether C–O bond).

(15) While compounds **9** and **2** are mentioned in the literature, no analytical data has been reported for these compounds.

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