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Convenient Preparation and Use of a New Analytical Construct for the Analysis and Development of Solid-Phase Chemistries

Stephen P. Andrews and Mark Ladlow*

GlaxoSmithKline Cambridge Technology Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

mark.2.ladlow@gsk.com

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An expedient and scalable synthesis of a versatile new analytical construct intermediate **1** is described. The utility of the intermediate **1** is exemplified by the preparation of the construct resin **14** incorporating an acid-labile linker which is used to conveniently develop optimized conditions leading to the preparation of a small compound array **24**{*1*−*3*,*1*−*3*}. The optimized conditions are shown to work equally well on both the construct resin **14** and the corresponding base resin **15**.

Introduction

The solid-phase combinatorial synthesis of chemical compound libraries, coupled with the ability to efficiently screen large numbers of compounds utilizing high-throughput screening (HTS) techniques, has evolved into a powerful strategy for the identification of pharmacologically active lead molecules within the pharmaceutical industry.[1−3] However, although significant advances have been made in recent years,[4] the development and analysis of solid-phase chemistries may still prove to be difficult or unacceptably time-consuming, particularly for large numbers of compounds.

Recently, to help overcome this problem, the concept of "analytical constructs" has been introduced.[5] An analytical construct is a modified solid-phase dual linker[6] which is assembled from two orthogonal linkers connected through the intermediacy of an analytical enhancing group (Figure 1). The "analytical enhancer" is a small molecule which contains a "peak splitter" (mixture of isotopes) in order to produce readily identifiable ions with a characteristic splitting pattern in the mass spectrometer and a UV chromophore which absorbs at a remote wavelength to facilitate direct quantification.[7]

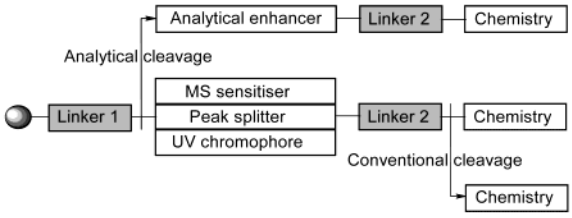

FIGURE 1. Generic analytical construct.

The analytical enhancer is attached to linker 1 (L1) in such a way that resin cleavage ("analytical cleavage") releases a fragment that is tagged with an amine and is thus sensitized to ESI+ mass spectrometric analysis. Alternatively, orthogonal cleavage ("conventional cleavage") at linker 2 (L2) releases only the desired substrate into solution. However, analytical constructs are not currently commercially available, and therefore, to facilitate their widespread adoption for the analysis and development of solid-phase chemistries, there is a need to establish convenient syntheses of generic construct components.[8]

Herein, we describe the efficient preparation of a new construct fragment **1** that may be used to assemble analytical constructs of the type shown in Figure 2. This analytical construct is particularly useful for the development and analysis of solid-phase chemistries employing widely used acid-labile linkers such as Rink,[9] Sasrin,[10] and BAL.[11] The new construct fragment **1** has been developed to be amenable to large scale synthesis without the need for extensive chromatography. In addition, removal of the *N*-BOC group reveals a primary amine (rather than the more hindered secondary amine present in previous constructs[12]) which facilitates the attachment

(1) Golebiowski, A.; Klopfenstein, S. R.; Portlock, D. E. *Curr. Opin. Chem. Biol.* **2001**, *5*, 273.
(2) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693−3716. Ganesan, A. *Drug Discovery Today* **2002**, *7* (1), 47.
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(6) For a general review of solid-phase linkers, see: Guillieri, F.; Orain, D.; Bradley, M. *Chem Rev.* **2000**, *100* (6), 2091.
(7) Williams, G. M.; Carr, R. A. E.; Congreve, M. S.; Kay, C.; McKeown, S. C.; Murray, P. J.; Scicinski, J. J.; Watson, S. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3293.
(8) Lorthioir, O.; McKeown, S. C.; Parr, N. J.; Washington, M.; Watson, S. P. *Tetrahedron Lett.* **2000**, *41*, 8609.
(9) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787.
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(11) Albericio, F.; Barany, G. *Int. J. Pept. Prot. Res.* **1987**, *30*, 206.

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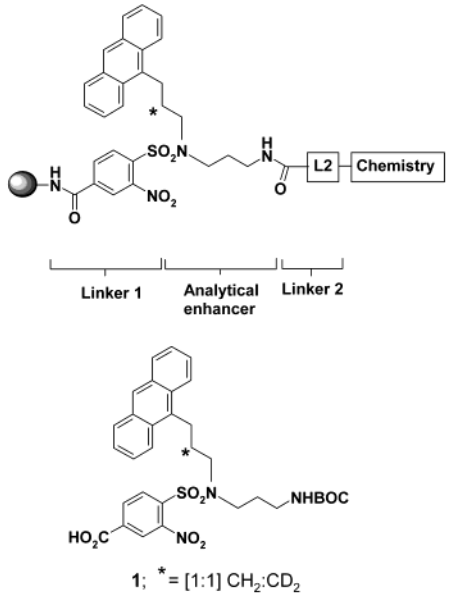


FIGURE 2.

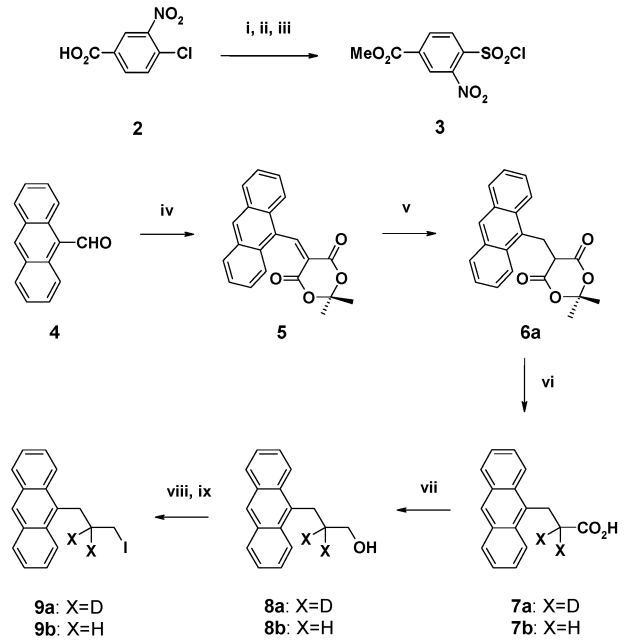
of L2 and, importantly, the incorporation of the deuterium mass tag is now performed more cost-effectively using D_2O. Further, the synthesis of the anthryl containing component in **1** may be readily modified to introduce different isotopic splitting patterns by using the appropriate combination of deuterated reducing agents sodium borohydride and lithium aluminum hydride in its preparation. The incorporation of the mass spectroscopic "peak splitter" is a versatile and useful feature inherent within the analytical construct approach. This facilitates the identification of construct derived fragments in the mass spectrum which may be performed automatically, without the precise knowledge of molecular weights, using commercial MS software to search the spectrum for peaks with the desired peak splitting. Although not reported herein, the ability to readily prepare constructs with different peak splittings also presents the opportunity to implement mass encoding of pooled resin beads.[13]

Results and Discussion

An acid-stable sulfonamide was chosen as linker L1 in order to establish the desired orthogonality to the acid-labile linker L2. The required sulfonyl chloride **3** was readily obtained in 64% overall yield starting from 4-chloro-3-nitrobenzoic acid **2** by modification of the reported procedure (Scheme 1).[14]

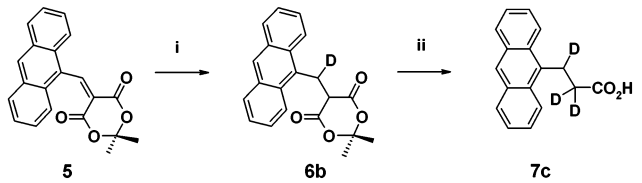
The anthracene fragment incorporating the isotopic mass splitter required for the analytical enhancer was prepared by condensation of Meldrum's acid with 9-anthraldehyde **4** to give the alkylidene **5**. Conjugate reduction of **5** in the presence of sodium borohydride afforded

SCHEME 1[a]



[a] Reagents and conditions: (i) $^cH_2SO_4$, MeOH, reflux, 94%; (ii) BnSH, DIPEA, MeOH, 0 °C to rt, 90%; (iii) Cl_2(g), AcOH−H_2O, rt, 76%; (iv) Meldrum's acid, py, rt, 95%; (v) $NaBH_4$, MeOH, 0 °C to rt, 97%; (vi) D_2O or H_2O, py, reflux, **7a** 99%, **7b** 94%; (vii) $LiAlH_4$, THF, rt, **8a** 94%, **8b** 97%; (viii) MsCl, DIPEA, CH_2Cl_2, 0 °C; (ix) NaI, Me_2CO, reflux, **9a** 85%, **9b** 94%.

SCHEME 2[a]



[a] Reagents and conditions: (i) $NaBD_4$, MeOH, 0 °C to rt, 72%; (ii) D_2O, py, reflux, quant.

the corresponding alkane **6a**. Both compounds were isolated in high purity and excellent yields by simple filtration. The required D_2 isotopic mass splitter was conveniently introduced upon hydrolysis/decarboxylation of **6a** in the presence of D_2O to afford **7a**.[15] Similarly, the H_2 analogue **7b** was obtained by hydrolysis/decarboxylation of **6a** in the presence of H_2O. The carboxylic acids **7a** and **7b** were reduced with lithium aluminum hydride to afford the alcohols **8a** and **8b**, which were then converted into the corresponding iodides **9a** and **9b**, respectively, following conversion to the intermediate methanesulfonate and subsequent displacement with sodium iodide in acetone.

This synthesis is both convenient and versatile and provides ready access to a range of alternative fragments incorporating different isotopic splitting patterns. For example, although not used in this study, the preparation of the corresponding D_3 acid **7c** (Scheme 2) was achieved following reduction of the Meldrum's acid adduct **5** with sodium borodeuteride to afford the D_1 alkane **6b**. This

(12) Congreve, M. S.; Ladlow, M.; Marshall, P.; Parr, N.; Scicinski, J. J.; Sheppard, T.; Vickerstaffe, E.; Carr, R. A. E. *Org. Lett.* **2001**, *3*, 507.

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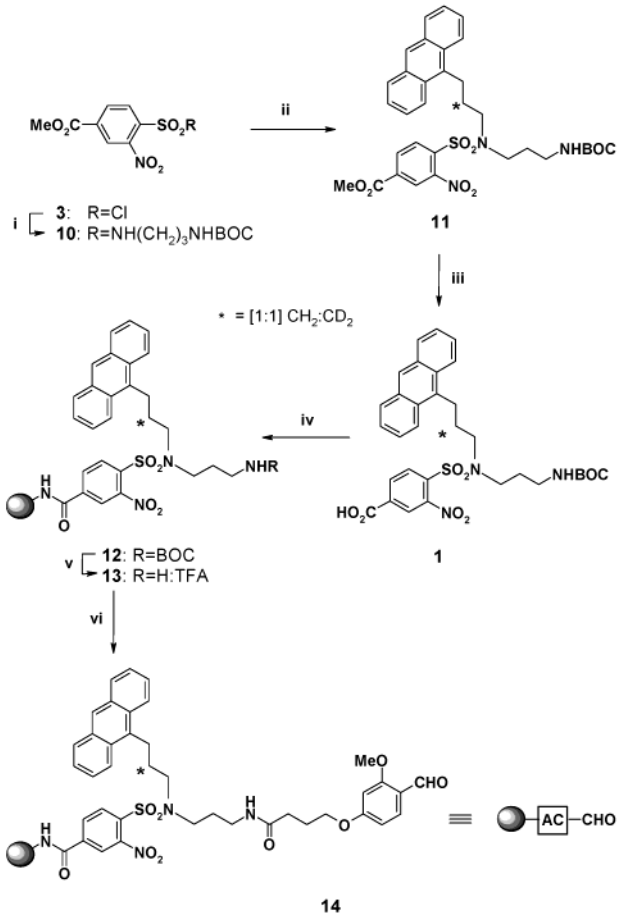
(14) Pattarawarapan, M.; Chen, J.; Steffensen, M.; Burgess, K. *J. Comb. Chem.* **2001**, *3*, 102.

(15) Kadam, A. J.; Desai, U. V.; Mane, R. B. *J. Labelled Cpd. Radiopharm.* **1999**, *42*, 835.

SCHEME 3[a]



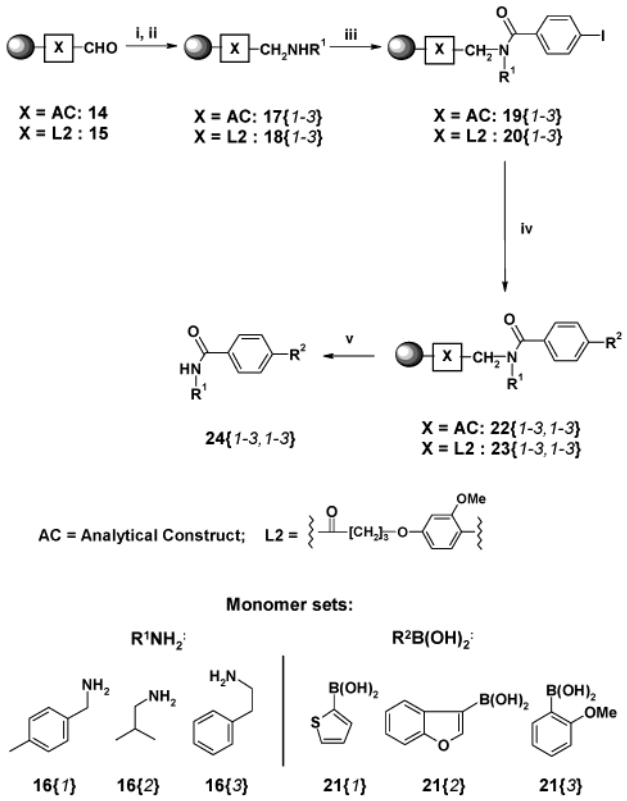
[a] Reagents and conditions: (i) $BOCHN(CH_2)_3NH_2$, DIPEA, CH_2Cl_2, 92%; (ii) (1:1) **9a**/**9b**, PS-BEMP, DMF, 89%; (iii) NaOH−H_2O, THF, 100%; (iv) ArgoGel-NH_2, DIC, HOBt, DIPEA, DMF; (v) (1:1) TFA−CH_2Cl_2, PhOH, H_2O; (vi) 4-[(4-formyl-3-methoxy)phenoxy]butyric acid, PyBOP, HOBt, DIPEA, DMF, rt.

was subsequently hydrolyzed and decarboxylated in the presence of D_2O to afford the D_3 acid **7c** in good overall yield. The acid may be converted into the corresponding alcohol or alkyl halide as required in an analogous manner to that outlined in Scheme 1.

Addition of the sulfonyl chloride **3** to mono *N*-BOC-1,3-diaminopropane gave the intermediate sulfonamide **10**, which was alkylated with a 1:1 mixture of the iodides **9a** and **9b** in the presence of BEMP on polystyrene[16] to give the mixed sulfonamide **11** (Scheme 3). The sulfonamide **11** was saponified to the versatile core analytical fragment **1** which was attached to ArgoGel amino resin to give the *N*-BOC resin **12**.

To demonstrate the utility of the analytical construct resin **12**, the *N*-BOC protecting group was removed with a solution of TFA in dichloromethane (1:1) to afford **13**, and the acid-labile linker L2, 4-[(4-formyl-3-methoxy)-phenoxy]butyric acid[17] was attached to provide the construct resin **14**. The resin **14** was used to optimize the conditions required to prepare a small compound

SCHEME 4[a]



[a] Reagents and conditions: (i) R^1NH_2 **16**{*1*−*3*}, AcOH, TMOF/NMP; (ii) $Me_4NBH(OAc)_3$, AcOH, CH_2Cl_2; (iii) 4-iodobenzoyl chloride, DIPEA, CH_2Cl_2; (iv) $R^2B(OH)_2$ **21**{*1*−*3*}, K_3PO_4, Pd-$(PPh_3)_4$, DMF/H_2O, 80 °C; (v) 90:5:5 TFA/TES/H_2O.

array using the commonly employed solid-phase reactions of reductive amination, acylation, and Suzuki coupling (Scheme 4).

For each step, a number of trial reactions were performed on small quantities of construct resin. A sample of beads (10−20) was removed in each case and subjected to analytical cleavage ($HS(CH_2)_2OH$/NaOMe/MeOH) followed by analysis of the cleavage solution by LC−MS. Based upon the interpretation of these results, reaction conditions (solvent, reagents, concentrations, equivalents) were modified, and the process was repeated in an iterative manner until optimized conditions were established.

In practice, for reasons of economy, it is conceivable that library chemistry would be developed on a construct derivatized resin but that subsequent library production would be performed on a non-derivatized base resin. Therefore, the compound array outlined in Scheme 4 was prepared in parallel on both the construct resin **14** and the corresponding base resin **15** derivatized with the acid-labile linker L2 but lacking the analytical construct fragment. The results were compared to determine if the construct was predictive of optimal conditions that were applicable to both resins. Thus, according to the conditions determined, the resins **14** and **15** were subjected to a two-step reductive amination procedure whereby the imine was first formed in the presence of trimethyl orthoformate (TMOF) and the appropriate amine **16**{*1*−*3*}. The resins were washed and the reducing agent tetramethylammonium triacetoxyborohydride was intro-

(16) BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) on polystyrene; commercially available from Sigma-Aldrich. Cf: Schwesinger, R. *Chimia* **1985**, *39*, 269.
(17) Ngu, K.; Patel, D. V. *J. Org. Chem*. **1997**, *62*, 7088.

TABLE 1. Comparison of Product Yields from Construct Derivatized and Nonderivatized Resins 22 and 23

	base resin		construct resin	
compd **24**{*x*,*y*}	% HPLC purity[a]	% yield[b]	% HPLC purity[a]	% yield[b]
{*1*,*1*}	>95	78	>95	70
{*2*,*1*}	>95	55	>95	63
{*3*,*1*}	>95	67	>95	66
{*1*,*2*}	>95	74	>95	74
{*2*,*2*}	95	79	>95	74
{*3*,*2*}	>95	73	>95	79
{*1*,*3*}	>95	81	91	81
{*2*,*3*}	>95	79	>95	81
{*3*,*3*}	>95	80	>95	82

[a] Determined at 254 nm. [b] Overall yields were calculated by ^{1}H NMR integration following cleavage from the resin and removal of solvents by preparing solutions in DMSO-d_6 previously calibrated with *p*-nitrophenol.

duced to afford the amino resins **17**{*1*−*3*} and **18**{*1*−*3*} respectively. Acylation with 4-iodobenzoyl chloride/DIPEA in dichloromethane then gave the iodo-resins **19**{*1*−*3*} and **20**{*1*−*3*}. Treatment of the resins **19**{*1*−*3*} and **20**{*1*−*3*} with the boronic acids **21**{*1*−*3*} in the presence of $Pd(PPh_3)_4/K_3PO_4$ at 80 °C for 1 h in 15% v/v aqueous DMF gave the resin-bound biaryls **22**{*1*−*3*,*1*−*3*} and **23**{*1*−*3*,*1*−*3*}.

The resins **22**{*1*−*3*,*1*−*3*}and **23**{*1*−*3*,*1*−*3*} were cleaved upon exposure to TFA/triethylsilane/H_2O (90:5:5; 2 × 1 h) to afford the carboxamides **24**{*1*−*3*,*1*−*3*}. The purities of the compounds obtained from both the construct and base resins were found to be excellent (Table 1). In addition, the yields of material from both resins were found to correlate well, within the limits of experimental deviation.

To illustrate the utility of analytical construct analysis in both reaction development and quality control analysis, some representative construct cleavage data obtained during early solid-phase studies is given in Figures 3−5.

An important prerequisite for successful solid-phase synthesis is to ensure that the initial resin loading step is both reliable and efficient. Failure in this respect leads at best to a reduced final cleavage yield and more typically to contaminated cleavage products that require further purification. When loading an acid-labile aldehyde linker such as that present on the resin **15** by reductive amination, the ability to adequately monitor this process can be problematic. For example, the direct acid-mediated cleavage of a sample of the product secondary amino-resin in the presence of a solution of 95% (v/v) TFA in dichloromethane typically fails.[18] An alternative is to monitor the resin beads by IR or MAS-^{1}H NMR and observe the disappearance of the aldehydic resonance. However, a competing reaction is the direct reduction of the aldehyde linker to the corresponding alcohol and this can be more difficult to observe by IR/NMR. In contrast, the use of the analytical construct resin **14** is particularly useful since direct cleavage of the BAL fragment in both the starting aldehyde and product resins can be readily achieved by an orthogonal, non-acid-mediated (thiolate) cleavage process. The analytical fragment obtained is then readily amenable to LC−MS

(18) Fivush, A. M.; Willson, T. M. *Tetrahedron Lett.* **1997**, *38*, 7151.

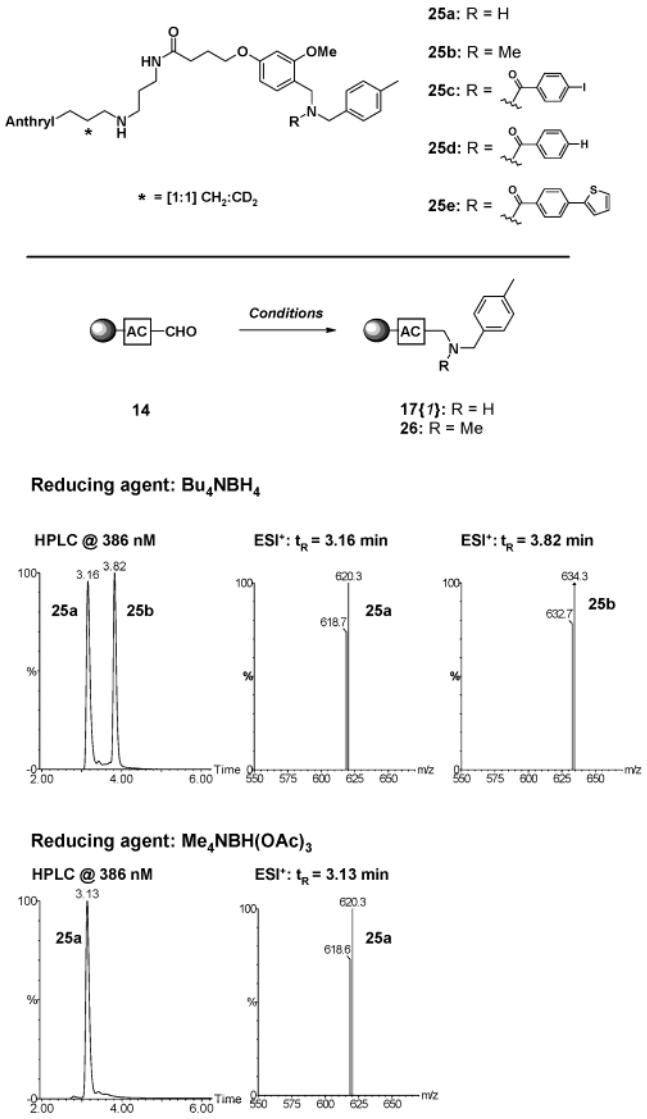


FIGURE 3. Analytical cleavage data obtained during optimization of the reductive amination of resin **14**.

analysis enabling the outcome of the reductive amination loading step to be determined with confidence.

This is illustrated in Figure 3 where we determined that the use of a two-stage reductive amination process—imine formation in the presence of TMOF followed by thorough washing of the resin and then introduction of the reducing agent tetramethylammonium triacetoxyborohydride—leads to the desired resin **17**{*1*} as evidenced by the isolation of the cleavage fragment **25a**. However, we were surprised to find that the use of the more powerful reducing agent tetrabutylammonium borohydride under identical conditions led to not only the desired resin-bound secondary amine but also approximately 40% of the corresponding *N*-methyl resin **26** (as evidenced by fragment **25b**). A similar result (not shown) was obtained when sodium borohydride was used as the reducing agent (approximately 20% **26**). The *N*-methyl-substituted resin **26** would remain unmodified in the subsequent synthetic transformations and lead to a reduced overall yield. However, it is unlikely that the reason for this would have been apparent without the use of the analytical construct. We examined the conse-

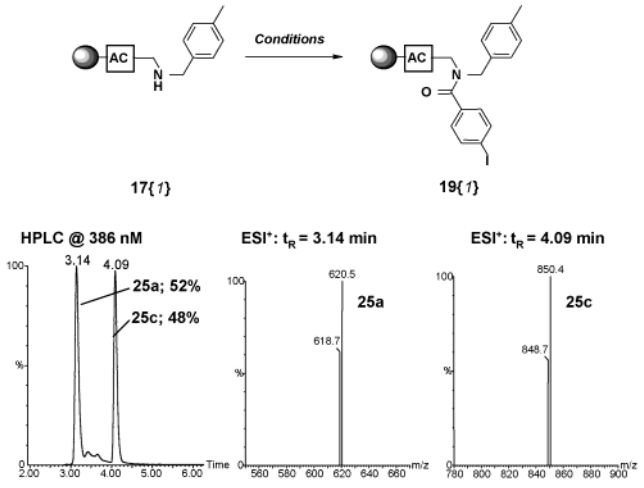


FIGURE 4. Analytical cleavage data obtained during acylation of resin **17**.

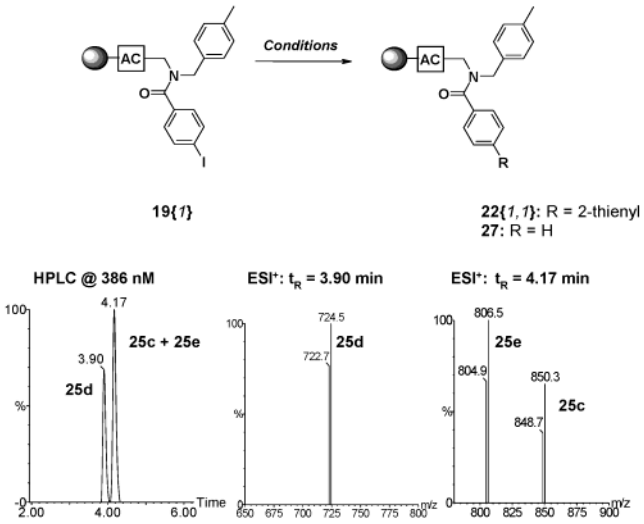


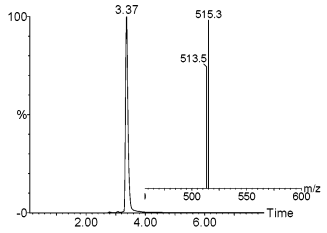
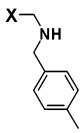
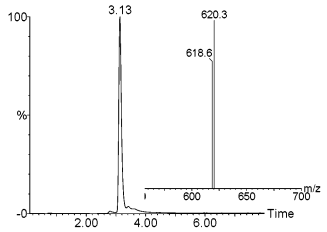
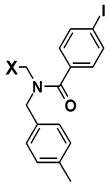
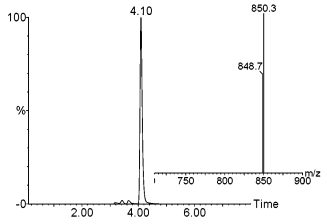
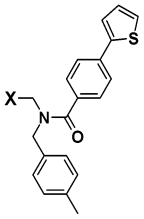
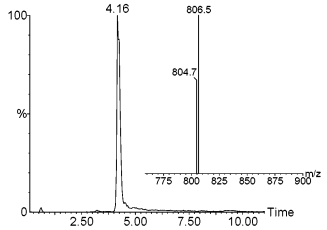
FIGURE 5. Analytical cleavage data obtained during optimization of the Suzuki coupling of resin **19**.

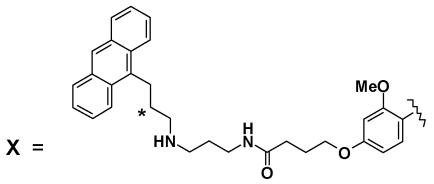
quences of changing the reductive amination conditions (alternative solvents, presence or absence of acetic acid as a catalyst) in an attempt to understand the origin of the *N*-methylation that was observed. These studies were not conclusive, but suggested that *N*-formylation (or formation of the corresponding dimethyl acetal) may occur in the presence of TMOF and that this intermediate is subsequently reduced in the presence of a "strong" reducing agent such as sodium borohydride, but undergoes hydrolysis in the presence of tetramethylammonium triacetoxyborohydride to afford the desired secondary amino-resin. In any event, these difficulties were circumvented by the use of tetramethylammonium borohydride as the reducing agent (see Table 2, entry 2).

A more straightforward outcome was encountered in the following acylation step. In an early experiment, the acylation of resin **17**{*1*} did not go to completion. While a simple Kaiser test[19] on the resulting resin indicated that free amino groups were still present, it was only

(19) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem*. **1970**, *200*, 803.

TABLE 2. Analytical Cleavage Data Leading to the Preparation of a Typical Array Member 24{*1,1*}

Resin	Analytical fragment[a]	LCMS data for analytical fragment
14{*1*}	X–CHO	
17{*1*}		
19{*1*}		
22{*1,1*}		



[a] Analytical cleavage fragments obtained by treatment of the parent construct resins with $HSCH_2CH_2OH$/NaOMe/MeOH at room temperature for 10 min. The resulting solutions were analyzed by LC–MS at 386 nm.

when the analytical cleavage data was obtained that the fragments **25a** and **25c** corresponding to the resin-bound starting amine and the desired acylated product, respectively, were shown to be the only compounds present on the resin in a ratio of 52:48 (Figure 4). As expected. increasing the number of equivalents of 4-iodobenzoyl chloride resulted in complete conversion to the desired acylated resin **19**{*1*} (see Table 2, entry 3).

Similarly, in an early attempt, the Suzuki coupling reaction of resin **19** did not proceed to completion. This was again clearly evident from the analytical cleavage data (Figure 5) where, in this case, the analytical fragments derived from the starting iodide **25c**, the dehalogenated analogue **25d**, and the desired biaryl product **25e** were all observed to be present on the resin. Unfortunately, relative quantification was not possible in the case of **25c** and **25e** which were observed to coelute under a range of HPLC conditions. By increasing the number of equivalents of boronic acid present, it was found that this transformation reliably went to completion to give only the desired resin-bound biaryl adduct **22**{*1,1*} (see Table 2, entry 4).

The analytical cleavage data for the optimized reaction conditions developed leading to the preparation of a representative array compound **24**{*1,1*} is shown in Table 2. For each step, the analytical resin cleavage and LC−MS analysis was conveniently performed in only 20−25 min, and it can readily be seen that, under the optimized reaction conditions, all the solid-phase transformations proceeded cleanly.

In conclusion, an expedient and scalable route to a versatile new analytical construct intermediate **1** is described. The utility of the intermediate **1** has been illustrated by the preparation of the analytical construct resin **14** incorporating the acid-labile linker 4-[(4-formyl-3-methoxy)phenoxy]butyric acid. The resin **14** has been used to optimize conditions for the preparation of a compound array **24**{*1−3,1−3*}. Data obtained using both the construct resin **14** and the analogous base resin **15** were found to be in good agreement, thereby demonstrating that this analytical construct may be used to determine optimized reaction conditions that are also applicable to the corresponding base resin.

Experimental Section

General Conditions for LC−MS Analysis. Routine LC−MS analyses were performed on an analytical HPLC equipped with a Supelcosil ABZ+PLUS column (3.3 cm, 4.6 mm ∅, 3 μm). Method: eluent, (A) water, 0.1% TFA, (B) acetonitrile 95%, water 5%, TFA 0.05%; gradient, 10−95% B in A (1 mL min^{-1}) over 8 min; detection, UV (215, 230, 254, 386 nm). The mass spectrometer was fitted with an electrospray ionization source, and mass spectra were obtained in both positive- and negative-ion modes (ESI±).

Methyl 4-Chloro-3-nitrobenzoate. Concentrated sulfuric acid (10 mL) was cautiously added to a chilled (0 °C) solution of 4-chloro-3-nitrobenzoic acid (50.0 g, 250 mmol) in methanol (200 mL) and the resulting mixture heated under reflux for 16 h. The reaction mixture was evaporated to dryness under reduced pressure, and the solid obtained was recrystallized from ethyl acetate/hexane mixture and washed successively with water (2 × 50 mL) and hexane (2 × 50 mL) to afford the title compound as white crystals (50.1 g, 94%). Mp: 78−79 °C. IR: ν_{max} (cm^{-1}) 1714, 1676, 1604, 1536. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.0 (3 H, s), 7.6 (1 H, d, J = 8 Hz), 8.15 (1 H, dd, J = 8, 2 Hz), 8.5 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 53.3, 127.0, 130.5, 132.1, 132.6, 134.0, 148.3, 164.6. HPLC (254 nm): t_R = 4.77 min (97%). MS (EI): m/z 215.1 (M^+, 55), 184.1 (100), 154.1 (20), 138.0 (55), 110.0 (30). HR-MS (EI): m/z calcd ($C_8H_6ClNO_4$) 214.9985, found 214.9987 M^+.

Methyl 4-Benzylsulfanyl-3-nitrobenzoate. A solution of benzyl mercaptan (11.4 mL, 97.0 mmol) in methanol (25 mL) was added at 0 °C to a stirring suspension of the methyl 4-chloro-3-nitrobenzoate (20.0 g, 93 mmol) and DIPEA (19.4 mL, 111 mmol) in methanol (225 mL). The resulting mixture was stirred at room temperature for 64 h and cooled to 0 °C, and the yellow precipitate obtained was collected by filtration. The solid was washed successively with cold methanol (50 mL), ethanol/water mixture (2:8, 2 × 50 mL), and hexane (50 mL) and dried in vacuo to yield the title compound as a yellow powder (25.5 g, 90%). Mp: 138−139 °C. IR: ν_{max} (cm^{-1}) 1710, 1669, 1606, 1520 and 1497. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.9 (3 H, s), 4.2 (2 H, s), 7.35 (3 H, m), 7.4 (2 H, m), 7.5 (1 H, d, J = 9 Hz), 8.1(1 H, dd, J = 9, 2 Hz), 8.8 (1 H, d, J = 2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 38.0, 53.0, 126.9, 127.1, 127.7, 128.4, 129.4, 129.5, 134.0, 134.6, 144.2, 145.5, 165.3. HPLC (254 nm): t_R = 5.89 min (100%). MS (EI): m/z 303.1 (M^+, 33), 272.1 (30), 238.2 (35), 197.1 (100), 164.1 (40), 121.1 (25). HR-MS (EI): m/z calcd ($C_{15}H_{13}NO_4S$) 303.0567, found 303.0567 M^+. Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62; S, 10.57. Found: C, 59.01; H, 4.31; N, 4.57; S, 10.50.

Methyl 4-Chlorosulfonyl-3-nitrobenzoate (3). Chlorine gas was bubbled through a suspension of methyl 4-benzylsulfanyl-3-nitrobenzoate (25.4 g, 83.7 mmol) in acetic acid/water (2:3, 500 mL) for 1.5 h. The mixture was stirred under the chlorine atmosphere for 19 h when the system was purged with nitrogen and the solvent was concentrated in vacuo. The resulting yellow precipitate was collected by filtration, washed with hexane (2 × 50 mL), and recrystallized from chloroform/hexane to afford **3** as white crystals (17.8 g, 76%). Mp: 101−102 °C. IR: ν_{max} (cm^{-1}) 1720, 1683, 1547. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.0 (3 H, s), 8.3 (1 H, d, J = 8 Hz), 8.45 (1 H, dd, J = 8, 2 Hz), 8.5 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 54.0, 126.5, 131.2, 133.8, 138.0, 139.0, 147.7, 163.4. HPLC (254 nm): t_R = 5.05 min, (94%). MS (EI): m/z 279.1 (M^+, 15), 244.1 (100), 154.0 (15), 138.0 (30), 119.1 (35). HR-MS (EI): m/z calcd ($C_8H_6ClNO_6S$) 278.9604, found 278.9611 M^+. Anal. Calcd for $C_8H_6ClNO_6S$: C, 34.36; H, 2.16; N, 5.01; S, 11.47; Cl, 12.68. Found: C, 34.59; H, 2.25; N, 4.45; S, 11.42; Cl, 12.64.

5-Anthracen-9-ylmethylene-2,2-dimethyl[1,3]dioxane-4,6-dione (5). A mixture of 9-anthraldehyde (20.0 g, 97.0 mmol) and Meldrum's acid (14.3 g, 99.0 mmol) in pyridine (80 mL) was stirred at room temperature for 6 h. The resulting mixture was concentrated in vacuo, and a mixture of ethyl acetate/hexane (1:4, 50 mL) was added. The solid obtained was collected by filtration, washed successively with ethyl acetate/hexane (1:4, 50 mL) and hexane (50 mL), and dried in vacuo to afford **5** as a white solid **(**31.7 g, 95%). Mp: 193−194 °C. IR: ν_{max} (cm^{-1}) 1765, 1731, 1621.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.9 (6 H, s), 7.5 (4 H, m), 7.8 (2 H, m), 8.1 (2 H, m), 8.5 (1 H, s), 9.5 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.5, 105.3, 121.4, 124.9, 125.9, 127.2, 127.5, 129.0, 129.7, 130.7, 131.3, 158.1, 158.3, 162.3. HPLC (386 nm): t_R = 5.72 min (100%). MS (ESI+): m/z 388.3 (50), 379.2 (15), 372.3 (25), 350.1 (MNH_4^+, 20), 344.2 (100), 328.2 (45). HR-MS (ESI+): m/z calcd ($C_{21}H_{20}NO_4$) 350.1392, found 350.1399 $(MNH_4)^+$. Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.80; H, 4.87.

5-Anthracen-9-ylmethyl-2,2-dimethyl[1,3]dioxane-4,6-dione (6a). Sodium borohydride (1.23 g, 32.0 mmol) was added gradually to a solution of the alkylidene **5** (9.97 g, 30.0 mmol) in methanol (200 mL) with external cooling so as to maintain the temperature below 20 °C. The resulting mixture was warmed to room temperature and stirred for 1 h before being recooled to 0 °C. The product was precipitated by dropwise addition of aqueous HCl (100 mL, 10%) and collected by filtration. The solid was washed with ice-cold water (3 × 50 mL) and dried in vacuo to afford **6a** as an orange powder (9.64 g, 96%). Mp: 168−169 °C. IR: ν_{max} (cm^{-1}) 1772, 1735, 1623, 1524. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.6 (3 H, s), 1.8 (3 H, s), 3.9 (1 H, t, J = 7 Hz), 4.5 (2 H, d, J = 7 Hz), 7.5 (2 H, m), 7.6 (2 H, m), 8.0 (2 H, d, J = 9 Hz), 8.4 (2 H, s), 8.5 (1 H, d, J = 9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.4, 26.8, 29.2, 49.6, 105.5, 124.8, 125.5, 126.7, 128.0, 129.9, 130.5, 131.0, 132.1, 165.7. HPLC (386 nm): t_R = 5.91 min (100%). MS (ESI+): m/z 388.3 (40), 368.1 (50), 352.2 (MNH_4^+, 85), 328.2 (30). HR-MS (ESI+): m/z calcd ($C_{21}H_{22}NO_4$) 352.1549, found 352.1562

$(MNH_4)^+$. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.41; H, 5.44.

5-Anthracen-9-yl-(*d*)-methyl-2,2-dimethyl[1,3]dioxane-4,6-dione (6b). The procedure for **6a** was repeated using sodium borodeuteride (1.23 g, 30.6 mmol) and the alkylidene **5** (10.1 g, 30.4 mmol) to afford **6b** as an orange solid (9.97 g, 98%). Mp: 164−165 °C. IR: ν_{max} (cm^{-1}) 1747, 1306. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.6 (3 H, s), 1.8 (3 H, s), 3.9 (1 H, m), 4.5 (2 H, m), 7.5 (2 H, m), 7.6 (2 H, m), 8.0 (2 H, d, J = 9 Hz), 8.4 (2 H, s), 8.5 (1 H, d, J = 9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.0 (m), 26.7, 29.2, 49.5, 105.5, 124.7, 124.7, 126.0, 127.9, 129.8, 130.4, 130.9, 132.0, 165.6. HPLC (386 nm): t_R = 5.97 min (100). MS (ESI+): m/z 388.2 (55), 379.2 (20), 369.2 (35), 353.2 (MNH_4^+, 60), 344.2 (100), 328.2 (40). HR-MS (ESI+): m/z calcd ($C_{21}H_{21}DNO_4$) 353.1612, found 353.1615 $(MNH_4)^+$.

3-Anthracen-9-yl-(2-d_2)-propionic Acid (7a). Deuterium oxide (30 mL) was added to a solution of the dione **6a** (30.1 g, 90.0 mmol) in pyridine (100 mL) and the mixture refluxed for 16 h. The resulting suspension was concentrated in vacuo and diluted with aqueous HCl (100 mL, 10%) and ethyl acetate (300 mL). The mixture was further diluted with water and the separated aqueous phase extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to yield the acid **7a** as a yellow solid (22.4 g, 99%). Mp: 192−193 °C. IR ν_{max} (cm^{-1}): 3053, 1720, 1690, 1043.^1H NMR: δ_H (400 MHz, DMSO-d_6) 3.82 (2 H, s), 7.5−7.6 (4 H, m), 8.07 (2 H, d, J = 9 Hz), 8.30 (2H, d, J = 9 Hz), 12.30 (1 H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 23.0, 36.0 (m), 124.4, 125.4, 126.3, 126.4, 129.4, 131.5, 133.3, 174.1. HPLC (386 nm): t_R = 5.82 min, (100%). MS (ESI+): m/z 270.2 (MNH_4^+, 30), 256.2 (85), 240.2 (15). HR-MS (ESI+): m/z calcd ($C_{17}H_{16}D_2NO_2$) 270.1463, found 270.1475 $(MNH_4)^+$.

3-Anthracen-9-ylpropionic Acid (7b). The procedure for **7a** was repeated using water (30 mL) and the dione **6a** (31.6 g, 94.0 mmol) to yield the acid **7b** as a yellow solid (22.0 g, 94%). Mp: 194−195 °C. IR ν_{max} (cm^{-1}): 3047, 1721, 1694, 1495. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.62 (2 H, t, J = 9 Hz), 3.84 (2 H, t, J = 9 Hz), 7.4−7.6 (4 H m), 8.08 (2 H, d, J = 8 Hz), 8.32 (2 H, d, J = 8 Hz), 8.50 (1 H, s), 12.20 (1 H, brs). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 23.5, 35.9, 124.8, 125.8, 126.6, 126.8, 129.7, 129.8, 131.8, 133.7, 174.4. HPLC (386 nm): t_R = 5.83 min, (100%). MS (ESI+): m/z 300.1 (30), 268.1 (MNH_4^+, 15), 256.2 (55), 212.1 (100). HR-MS (ESI+): m/z calcd ($C_{17}H_{18}NO_2$) 268.1338, found 268.1339 $(MNH_4)^+$.

3-Anthracen-9-yl-(1-*d*),(2-d_2)-propionic Acid (7c). The procedure for **7a** was repeated using deuterium oxide (1.0 mL) and the acid **6b** (991 mg, 2.95 mmol) in anhydrous pyridine (3.5 mL) to afford the acid **7c** as a pale yellow solid (745 mg, quant). Mp: 192−193 °C. IR ν_{max} (cm^{-1}): 3022, 1720, 1694, 1407. ^1H NMR (400 MHz, DMSO-d_6): δ_H 3.82 (1 H, m), 7.45−7.6 (4 H, m), 8.05 (2 H, d, J = 9 Hz), 8.28 (2 H, d, J = 9 Hz), 8.48 (1 H, s), 12.40 (1 H, brs). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 23.0 (m), 34.0 (m), 123.7, 124.8, 125.6, 125.7, 128.7, 130.8, 132.6, 173.4. HPLC (386 nm): t_R = 5.89 min (100%). MS (ESI+): m/z 271.2 (MNH_4^+, 35), 256.2 (85), 212.1 (100). HR-MS (ESI+): m/z calcd ($C_{17}H_{15}D_3NO_2$) 271.1526, found 271.1514 $(MNH_4)^+$.

3-Anthracen-9-yl-(2-d_2)-propan-1-ol (8a). A solution of lithium aluminum hydride in THF (1M, 100 mL, 100 mmol) was added steadily, dropwise to a solution of the propionic acid **7b** (22.2 g, 88.0 mmol) in THF (500 mL) with ice-bath cooling. The mixture was warmed to room temperature and stirred for 16 h before being quenched with aqueous HCl solution (250 mL, 10%) and then diluted with water (100 mL). The crude mixture was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford the alcohol **8a** (19.8 g, 94%). Mp: 99−100 °C. IR ν_{max} (cm^{-1}): 3650, 2885, 1043. ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.72 (2 H, s), 3.82 (2 H, s), 7.45−7.6 (4 H, m), 8.00 (2 H, d, J = 9 Hz), 8.30 (2 H, d, J = 9 Hz), 8.34 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.3, 33.8 (m), 62.9, 124.7, 125.2, 125.9, 126.2, 129.6, 130.1, 132.0, 134.7. HPLC (386 nm): t_R = 5.33 min (100%). MS (ESI+): m/z 239.1 (MH^+, 20), 221.1 (100), 191.1 (50). HR-MS (ESI+): m/z calcd ($C_{17}H_{14}D_2O$) 239.1405; found 239.1406 $(MH)^+$.

3-Anthracen-9-ylpropan-1-ol (8b). The procedure for the H_2 analogue **8a**, was repeated using the propionic acid **7b** (21.0 g, 84.0 mmol) in place of **7a**. The alcohol **8b** was obtained as sand-colored crystals (19.3 g, 97%). Mp: 100−101 °C. IR ν_{max} (cm^{-1}): 3669, 2926, 1621, 1408, 1039. ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.10 (2 H, m), 3.73 (2 H, t, J = 8 Hz), 3.85 (2 H, t, J = 6 Hz), 7.5−7.6 (4 H, m), 8.00 (2 H, d, J = 8 Hz), 8.32 (2 H, d, J = 8 Hz), 8.35 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.5, 34.4, 63.1, 124.7, 125.2, 125.9, 126.2, 129.6, 130.1, 132.0, 134.7. HPLC (386 nm): t_R = 5.77 min (100%). MS (ESI+): m/z 284.2 (20), 256.2 (80), 254.2 (MNH_4^+, 55), 235.1 (20). HR-MS (ESI+): m/z calcd ($C_{17}H_{20}NO$) 254.1544, found 254.1554 $(MNH_4)^+$.

9-(2-d_2-3-Iodopropyl)anthracene (9a). *Caution: handle with care; this compound is an alkylating agent and irritant!* A solution of methanesulfonyl chloride (88.0 mmol, 6.80 mL) in dichloromethane (30 mL) was added to a stirring mixture of the alcohol **8a** (19.3 g, 81.0 mmol) and DIPEA (20.7 mL, 119 mmol) in dichloromethane (300 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then washed successively with water (150 mL), aqueous HCl solution (100 mL, 10%), and saturated aqueous sodium bicarbonate solution (100 mL). The separated organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to afford the mesylate which was diluted with acetone (300 mL) and mixed with sodium iodide (56.2 g, 375 mmol). The mixture was heated under reflux for 0.5 h and then concentrated in vacuo. The residue was partitioned between water (450 mL) and ethyl acetate (450 mL) and the separated organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to yield the iodide **9a** as a beige solid (22.3 g, 85%). Mp: 99−100 °C. IR ν_{max} (cm^{-1}): 3048, 1622, 1446. ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.37 (2 H, s), 3.72 (2 H, s), 7.46 (2 H, m), 7.51 (2 H, m), 8.00 (2 H, d, J = 9 Hz), 8.29 (2 H, d, J = 9 Hz), 8.36 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 7.0, 29.0, 34.6 (m), 124.5, 125.3, 126.2, 126.6, 129.7, 130.1, 132.0, 133.2. HPLC (386 nm): t_R = 7.41 min (100%). MS (ESI+): m/z 433.1 (20), 349.0 (MH^+, 100), 221.1 (50), 191.0 (28). HR-MS (ESI+): m/z calcd ($C_{17}H_{13}D_2I$) 349.0422, found 349.0417 $(MH)^+$.

9-(3-Iodopropyl)anthracene (9b). *Caution: handle with care; this compound is an alkylating agent and irritant!* The procedure for the iodide **9a** was repeated using the H_2 analogue **8b** (18.8 g, 79.0 mmol) in place of **8a**. The crude product was recrystallized from ethyl acetate/hexane to afford the iodide **9b** as a beige solid (25.8 g, 94%). Mp: 95−96 °C. IR ν_{max} (cm^{-1}): 1622, 1492. ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.33 (2 H, m), 3.45 (2 H, t, J = 8 Hz), 3.75 (2 H, t, J = 8 Hz), 7.4−7.6 (4 H, m), 8.01 (2 H, d, J = 9 Hz), 8.28 (2 H, d, J = 9 Hz), 8.40 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 7.3, 29.2, 35.0, 124.5, 125.3, 126.2, 126.6, 129.7, 130.1, 132.0, 133.2. HPLC (386 nm): t_R = 7.37 min (100%). MS (ESI+): M^+, 346.1. Anal. Calcd for $C_{17}H_{15}I$: C, 58.98; H, 4.37. Found: C, 58.83; H, 4.30.

Methyl 4-(3-*tert*-Butoxycarbonylaminopropylsulfamoyl)-3-nitrobenzoate (10). A suspension of the sulfonyl chloride **3** (5.19 g, 19.4 mmol) in dichloromethane (10 mL) was added to a stirring solution of *N*-BOC-1,3-diaminopropane (3.72 mL, 21.3 mmol) and DIPEA (5.06 mL, 29.1 mmol) in dichloromethane (20 mL). After being stirred at room temperature for 16 h, the mixture was diluted with dichloromethane (100 mL) and washed successively with water, dilute aqueous HCl (10%), saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to afford the sulfonamide **10** as a yellow solid (7.43 g, 92%). Mp: 98−99 °C. IR ν_{max} (cm^{-1}): 3371, 1733, 1719, 1684, 1614, 1552, 1365. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (9 H, s), 1.67 (2 H, m), 3.18 (4 H, m), 4.01 (3 H, s), 4.60 (1 H, brs), 6.06 (1 H, brs), 8.19 (1 H, d, J = 8 Hz), 8.33 (1 H, dd, J = 2,

8 Hz), 8.40 (1 H, d, $J = 2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.7, 30.1, 36.4, 40.2, 52.6, 125.5, 130.5, 132.6, 134.4, 137.0, 147.4, 156.0, 163.1. HPLC (254 nm): $t_R = 4.90$ min (100%). MS (ESI+): *m/z* 344.2 (30), 318.2 ($MH^+ - BOC$, 15), 244.1 (65), 233.2 (30), 191.2 (30). Anal. Calcd for $C_{16}H_{23}N_3O_6S$: C, 46.04; H, 5.55; N, 10.07; S, 7.68. Found: C, 45.96; H, 5.22; N, 9.86; S, 7.57.

Methyl 4-[(3-Anthracen-9-ylpropyl)(3-*tert*-butoxycarbonylaminopropyl)sulfamoyl]-3-nitrobenzoate (11). A solution of the iodides **9a** and **9b** (1:1, 790 mg, 2.30 mmol) in DMF (5 mL) was added to a mixture of the sulfonamide **10** (860 mg, 2.10 mmol) and PS-BEMP (1.40 g, 3.10 mmol) in DMF (5 mL). The resulting mixture was stirred at room temperature for 64 h and filtered. The filtrate was evaporated in vacuo and purified by column chromatography eluting with ethyl acetate/hexane eluent (3:7) to give the mixed sulfonamide **(11)** as a pale yellow foam (1.17 g, 89%). IR ν_{max} (cm^{-1}): 3429, 1706, 1624, 1546, 1437. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.40 (9 H, s), 1.73 (2 H, m), 1.98 ($^1/_2 \times 2$ H, m), 3.09 (2 H, m), 3.36 (2 H, m), 3.50 (4 H, m), 3.98 (3 H, s), 4.70 (1H, brs), 7.40−7.50 (4 H, m), 7.78 (1 H, d, $J = 9$ Hz), 7.98 (2H, d, $J = 9$ Hz), 8.01 (1H, d, $J = 9$ Hz), 8.10 (2 H, d, $J = 9$ Hz), 8.13 (1 H, s), 8.32 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 22.7, 22.9, 27.4, 29.5, 35.6, 43.1, 45.0, 45.2, 51.4, 77.6, 122.1, 123.2, 123.4, 124.2, 124.5, 127.7, 127.8, 129.2, 129.8, 130.4, 131.0, 133.0, 135.0, 146.0, 154.8, 161.8. HPLC (386 nm): $t_R = 7.08$ min (100%). MS (ESI+): $(MH - BOC)^+$, 536.3, 538.3.

The H_2- and D_2-sulfonamides were also prepared separately using a similar procedure and gave the following analytical data:

H_2-Sulfonamide **(11)**. HPLC (386 nm): $t_R = 7.08$ min (100%). HR-MS (ESI+): *m/z* calcd ($C_{33}H_{37}N_3NaO_8S$) 658.2199, found 658.2211 $(MNa)^+$.

D_2-Sulfonamide **(11)**. HPLC (386 nm): $t_R = 7.07$ min (100%). HR-MS (ESI+): *m/z* calcd ($C_{33}H_{35}D_2N_3NaO_8S$) 660.2325, found 660.2341 $(MNa)^+$.

4-[(3-Anthracen-9-yl-propyl)(3-*tert*-butoxycarbonylaminopropyl)sulfamoyl]-3-nitrobenzoic Acid (1). Aqueous sodium hydroxide solution (5.0 mL × 2.0 M, 10.0 mmol) was added dropwise to a solution of the ester **11** (2.10 g, 3.40 mmol) in THF (20 mL) at 0 °C. The mixture was stirred at room temperature for 1.5 h and then acidified by addition of dilute aqueous HCl (10%) to pH 3. The resulting mixture was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to afford the acid **1** as a yellow foam (2.10 g, 100%). IR ν_{max} (cm^{-1}): 2937, 1704, 1365. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.29 (9 H, s), 1.63 (2 H, m), 1.80 ($^1/_2 \times 2$ H, m), 2.89 (2 H, m), 3.30 (2 H, m), 3.48 (2 H, m), 3.59 (2 H, m), 6.75 (1 H, brt), 7.4−7.50 (4 H, m), 8.0−8.10 (3 H, m), 8.21 (3 H, m), 8.37 (1 H, s), 8.48 (1 H, s). ^{13}C NMR, (100 MHz, DMSO-d_6): δ_C 22.3, 22.5, 26.3, 26.7, 27.6, 35.6, 43.5, 45.1, 45.2, 75.7, 122.2, 123.0, 123.2, 123.8, 124.0, 127.1, 127.2, 128.7, 129.3, 130.8, 131.7, 133.3, 134.3, 145.6, 153.7, 162.6. HPLC (386 nm): $t_R = 6.84$ min (100%). LC−MS (386 nm ESI-): $t_R = 5.90$ min (100%), MH^- 620.1, 622.2. HR-MS (ES+): *m/z* calcd ($C_{32}H_{35}N_3O_8NaS$, $C_{32}H_{33}D_2N_3O_8NaS$) 644.2043, 646.2168, found 644.2048, 646.2160 (MNa^+).

Standard Analytical Cleavage Procedure. A stock cleavage solution was prepared from 2-mercaptoethanol (40 μL, 600 mmol) and sodium methoxide solution (1.0 mL × 0.5 M in MeOH). A small sample of resin beads was removed (10−20 beads) and incubated with the cleavage solution (30 μL) for 10 min at room temperature and then filtered. The filtrate was diluted with CH_3CN (100 μL) and analyzed by LC-MS (ESI±) with UV detection at 386 nm.

Preparation of Construct Resins 12 and 13. ArgoGel-NH_2 resin (0.43 mmol g^{-1}, 500 mg, 0.22 mmol) was washed with piperidine/CH_2Cl_2/DMF (6:7:7, 10 mL), filtered, and washed extensively with DMF, CH_2Cl_2, and diethyl ether. The resin was pre-swollen with CH_2Cl_2 (2 mL) and then treated with a mixture of 1-hydroxybenzotriazole (60 mg, 440 μmol), DIC (69 μL, 440 μmol), and the carboxylic acid **1** (290 mg, 466 μmol) in DMF (2 mL). The mixture was shaken at room temperature for 18 h and then filtered, and the beads were washed extensively with DMF, CH_2Cl_2, and diethyl ether to afford the *N*-BOC resin **12**; Kaiser test negative.

The *N*-BOC protecting group was removed by treating the resin **12** with a mixture of DMF (1.25 mL) and CH_2Cl_2 (1.25 mL) containing water (125 μL) and phenol (250 mg). After 15 min, the resin was washed with CH_2Cl_2. This process was repeated to afford the amino-resin **13**; Kaiser test positive. Analytical cleavage data using standard cleavage conditions:

From Resin 12. LC−MS (386 nm): $t_R = 4.74$ min (100%); *m/z* (ESI+) MH^+ 393.1, 395.1.

From Resin 13. LC−MS (386 nm): $t_R = 4.10$ min (100%); *m/z* (ESI+) MH^+ 293.6, 295.6.

Preparation of the Analytical Construct Resin 14. The resin **13** (from 500 mg ArgoGel-NH_2) was pre-swollen with CH_2Cl_2 (2 mL) and treated with a mixture of PyBOP (220 mg, 420 μmol), HOBt (60 mg, 440 μmol), and 4-[(4-formyl-3-methoxy)phenoxy]butyric acid (94 mg, 400 μmol) in DMF (2 mL). DIPEA (140 μL, 880 μmol) was added, and the mixture was shaken at room temperature for 18 h, filtered, and washed extensively with DMF, CH_2Cl_2, and diethyl ether; Kaiser test negative.

Analytical cleavage data using standard conditions:

From Resin 14. LC−MS (386 nm): $t_R = 3.37$ min (100%); *m/z* (ESI+) MH^+ 513.5, 515.3.

Preparation of Base Resin 15. ArgoGel-NH_2 (500 mg, 0.22 mmol) was washed with piperidine/CH_2Cl_2/DMF (6:7:7, 10 mL), filtered, and washed extensively with DMF, CH_2Cl_2, and diethyl ether. The resin was pre-swollen with CH_2Cl_2 (2 mL) and treated with a mixture of PyBOP (220 mg, 420 μmol), HOBt (60 mg, 440 μmol), and 4-[(4-formyl-3-methoxy)phenoxy]-butyric acid (94 mg, 400 μmol) in DMF (2 mL). DIPEA (140 μL, 880 μmol) was added, and the mixture was shaken at room temperature for 18 h, filtered, and washed extensively with DMF, CH_2Cl_2, and diethyl ether; Kaiser test negative.

General Procedure for Formation of Fmoc Derivatives of Aldehyde Resins 14 and 15. A solution of 9-fluorenylmethyl carbazate (90 mg, 350 μmol) in DMF (2.2 mL) and AcOH (1.0 mL) was prepared. The resulting mixture (1.0 mL) was added to each of the aldehyde resins **14** and **15** (approx 35 μmol) pre-swollen in DMF (1.0 mL), and the resins were shaken for 16 h at room temperature. The resins were then filtered, washed extensively with DMF, CH_2Cl_2, and diethyl ether, and dried in vacuo to afford the corresponding resin-bound Fmoc hydrazones. Fmoc numbers were determined by cleavage of a known quantity of resin with piperidine/DMF mixture (1:1) and determination of the absorbance at 300 nm:

Construct resin **14** loading: 0.25 mmol g^{-1}.

Base resin **15** loading: 0.26 mmol g^{-1}.

General Procedure for Reductive Aminations of Aldehyde Resins: Preparation of Resins 17{*1*−*3*} and 18{*1*−*3*}. The aldehyde resins **14** and **15** (approximately 3 × 60 μmol each) were washed with trimethyl orthoformate and filtered. The resins were then pre-swollen with a mixture of TMOF/NMP (4:1 v/v, 1 mL) and shaken with an amine **16** (700 μmol) and AcOH (12 μL, 200 μmol) for 2 h at room temperature. The resins were filtered and washed with CH_2Cl_2, pre-swollen with CH_2Cl_2 (1 mL), and shaken with $Me_4NBH(OAc)_3$ (92 mg, 350 μmol) and AcOH (12 μL, 200 μmol) for 1 h.

The resins were again washed with CH_2Cl_2 and TMOF, pre-swollen with TMOF/NMP mixture (4:1 v/v, 1 mL), and shaken with the same amine **16** (700 μmol) and AcOH (12 μL, 200 μmol) for a further 2 h. Once more, the resins were filtered and washed with CH_2Cl_2, pre-swollen with CH_2Cl_2, and shaken with $Me_4NBH(OAc)_3$ (92 mg, 350 μmol) and AcOH (12 μL, 200 μmol) for 16 h. The resins were filtered and washed extensively with DMF, CH_2Cl_2, and diethyl ether to afford the amino-resins **17**{*1*−*3*} and **18**{*1*−*3*}.

Analytical cleavage data using standard cleavage conditions:

From Resin 17{*1*}. LC−MS (386 nm): t_R = 3.13 min (>95%); *m*/*z* (ESI+) MH^+ 618.6, 620.3.

From Resin 17{*2*}. LC−MS (386 nm): t_R = 3.10 min (91%); *m*/*z* (ESI+) MH^+ 570.4, 572.4.

From Resin 17{*3*}. LC−MS (386 nm): t_R = 3.20 min (93%); *m*/*z* (ESI+) MH^+ 618.5, 620.5.

General Procedure for Acylations of Amino-Resins with 4-Iodobenzoyl Chloride: Preparation of Resins 19-{*1*−*3*} and 20{*1*−*3*}. To the amino-resins **17**{*1*−*3*} and **18**{*1*−*3*} (approximately 3 × 60 μmol each), pre-swollen in DCM (1 mL), were added 4-iodobenzoyl chloride (48 mg, 180 μmol) and DIPEA (63 μL, 360 μmol). The suspensions were shaken at room temperature for 2 h, filtered, and washed extensively with DMF, CH_2Cl_2, and diethyl ether.

Analytical cleavage data using standard cleavage conditions:

From Resin 19{*1*}. LC−MS (386 nm): t_R = 4.10 min (>95%); *m*/*z* (ESI+) MH^+ 848.7, 850.3.

From Resin 19{*2*}. LC−MS (386 nm): t_R = 4.04 min (91%); *m*/*z* (ESI+) MH^+ 800.3, 802.3.

From Resin 19{*3*}. LC−MS (386 nm): t_R = 4.11 min (88%); *m*/*z* (ESI+) MH^+ 848.3, 850.3.

General Procedure for Suzuki Couplings: Preparation of Resins 22{*1*−*3*,*1*−*3*} and 23{*1*−*3*,*1*−*3*}. To the iodo-resins **19**{*1*−*3*} and **20**{*1*−*3*} (approximately 3 × 20 μmol each) were added solutions of the boronic acids **21**{*1*-*3*} (100 μmol) in DMF (350 μL), K_3PO_4 (50 μmol) in H_2O (150 μL), and $Pd(PPh_3)_4$ (4 μmol) in DMF (500 μL). The vessels were flushed with nitrogen gas and sealed. The suspensions were stirred and heated to 80 °C for 1.5 h, filtered, and washed extensively with DMF, CH_2Cl_2, and diethyl ether.

Analytical cleavage data using standard cleavage conditions:

From Resin 22{*1*,*1*}. LC−MS (386 nm): t_R = 4.16 min (>95%); *m*/*z* (ESI+) MH^+ 804.7, 806.5.

From Resin 22{*1*,*2*}. LC−MS (386 nm): t_R = 4.44 min (89%); *m*/*z* (ESI+) MH^+ 838.7, 840.5.

From Resin 22{*1*,*3*}. LC−MS (386 nm): t_R = 4.30 min (80%); *m*/*z* (ESI+) MH^+ 790.4, 792.4.

From Resin 22{*2*,*1*}. LC−MS (386 nm): t_R = 4.10 min (88%); *m*/*z* (ESI+) MH^+ 756.8, 758.4.

From Resin 22{*2*,*2*}. LC−MS (386 nm): t_R = 4.36 min (91%); *m*/*z* (ESI+) MH^+ 838.5, 840.5.

From Resin 22{*2*,*3*}. LC−MS (386 nm): t_R = 4.23 min (91%); *m*/*z* (ESI+) MH^+ 828.5, 830.5.

From Resin 22{*3*,*1*}. LC−MS (386 nm): t_R = 4.16 min (88%); *m*/*z* (ESI+) MH^+ 804.5, 806.5.

From Resin 22{*3*,*2*}. LC−MS (386 nm): t_R = 4.11 min (88%); *m*/*z* (ESI+) MH^+ 780.5, 782.5.

From Resin 22{*3*,*3*}. LC−MS (386 nm): t_R = 4.17 min (88%); *m*/*z* (ESI+) MH^+ 828.6, 830.6.

General Procedure for Resin Cleavage To Afford Carboxamides (24{*1*−*3*,*1*−*3*}). The resins **22**{*1*−*3*,*1*−*3*} and **23**{*1*−*3*,*1*−*3*} (approximately 9 × 20 μmol each) were shaken with TFA/TES/H_2O (500 μL, 90:5:5) at room temperature for 1 h, filtered, and washed with CH_2Cl_2 (2 × 1 mL). The procedure was repeated, and combined filtrates were evaporated under reduced pressure to afford the carboxamides **24**, which were quantified by ^1H NMR comparing peak areas relative to residual DMSO in DMSO-d_6 precalibrated with *p*-nitrophenol.

24{*1*,*1*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.24 (3 H, s), 4.41 (2 H, d *J* = 6 Hz), 7.10 (2 H, d, *J* = 8 Hz), 7.15 (1 H, m), 7.19 (2 H, d *J* = 8 Hz), 7.60 (2 H, m), 7.72 (2 H, m), 7.90 (2 H, m), 8.99 (1 H, t *J* = 6 Hz). LC−MS (254 nm): t_R = 5.61 min (>95%); *m*/*z* (ESI+) MH^+ 308.2.

24{*2*,*1*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 0.88 (6 H, d, *J* = 7 Hz), 1.83 (1 H, m), 3.07 (2 H, m), 7.15 (1 H, m), 7.59 (2 H, m), 7.70 (2 H, m), 7.86 (2 H, m), 8.45 (1 H, t, *J* = 6 Hz). LC−MS (254 nm): t_R = 5.09 min (>95%); *m*/*z* (ESI+) MH^+ 260.4.

24{*3*,*1*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.83 (2 H, t, *J* = 7 Hz), 3.45 (2 H, m), 7.1−7.3 (6 H, m), 7.60 (2 H, m), 7.70 (2 H, m), 7.83 (2 H, m), 8.57 (1 H, t, *J* = 6 Hz). LC−MS (254 nm): t_R = 5.46 min (>95%); *m*/*z* (ESI+) MH^+ 308.3.

24{*1*,*2*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.24 (3 H, s), 4.41 (2 H, d, *J* = 8 Hz), 7.12 (2 H, d, *J* = 8 Hz), 7.20 (2 H, d, *J* = 8 Hz), 7.27−7.33 (2 H, m), 7.57 (1 H, s), 7.65 (2 H, m), 8.0 (4 H, s), 9.10 (1 H, t, *J* = 8 Hz). LC−MS (254 nm): t_R = 6.28 min (>95%); *m*/*z* (ESI+) MH^+ 342.0.

24{*2*,*2*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 0.88 (6 H, d, *J* = 7 Hz), 1.84 (1 H, m), 3.08 (2 H, t, *J* = 6 Hz), 7.25−7.36 (2 H, m), 7.56 (1 H, m), 7.66 (2 H, m), 7.98 (4 H, m), 8.57 (1 H, t, *J* = 6 Hz). LC−MS (254 nm): t_R = 5.87 min (95%); *m*/*z* (ESI+) MH^+ 294.2.

24{*3*,*2*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.83 (2 H, t, *J* = 8 Hz), 3.46 (2 H, m), 7.16−7.36 (7 H, m), 7.56 (1 H, m), 7.66 (2 H, m), 7.92−8.0 (4 H, m), 8.69 (1 H, t, *J* = 6 Hz). LC−MS (254 nm): t_R = 6.14 min (>95%); *m*/*z* (ESI+) MH^+ 342.1.

24{*1*,*3*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.24 (3 H, s), 3.74 (3 H, s), 4.42 (2 H, d, *J* = 6 Hz), 7.01 (1H, m), 7.10 (2 H, m), 7.18 (3 H, m), 7.27−7.38 (2 H, m), 7.53 (2 H, m), 7.89 (2 H, m), 9.01 (1 H, t, *J* = 6 Hz). LC−MS (254 nm): t_R = 5.54 min (>95%); *m*/*z* (ESI+) MH^+ 332.2.

24{*2*,*3*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 0.88 (6 H, d, *J* = 8 Hz), 1.84 (1 H, m), 3.07 (2 H, m), 3.74 (3 H, s), 7.02 (1 H, m), 7.11 (1 H, m), 7.30 (1 H, m), 7.35 (1 H, m), 7.42 (2 H, m), 7.82 (2 H, m), 8.48 (1 H, t, *J* = 6 Hz). LC−MS (254 nm): t_R = 5.04 min (>95%); *m*/*z* (ESI+) MH^+ 284.4.

24{*3*,*3*}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.83 (2 H, m), 3.48 (2 H, m), 3.74 (3 H, s), 7.01 (1 H, m), 7.10 (1 H, m), 7.16−7.30 (7 H, m), 7.51 (2 H, m), 7.80 (2 H, m), 8.57 (1 H, t, *J* = 6 Hz). LC−MS (254 nm): t_R = 5.39 min (>95%); *m*/*z* (ESI+) MH^+ 332.2.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all compounds described that are not attached to resin or obtained following analytical cleavage. This material is available free of charge via the Internet at http://pubs.acs.org.

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