JOURNAL OF combinatorial CHEMISTRY

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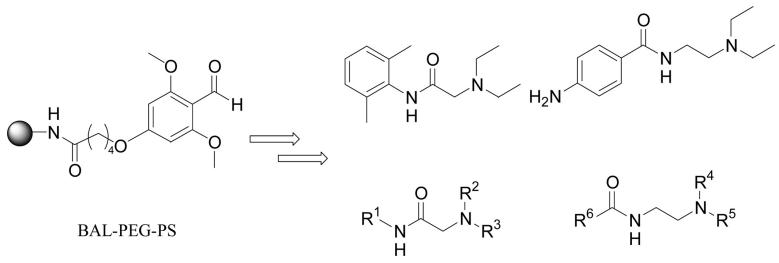
J. Comb. Chem., **2003**, 5 (6), 860-868• DOI: 10.1021/cc034014n • Publication Date (Web): 25 October 2003



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Solid-Phase Synthesis of Lidocaine and Procainamide Analogues Using Backbone Amide Linker (BAL) Anchoring[1]

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Received May 31, 2003

New solid-phase strategies have been developed for the synthesis of lidocaine (**1**) and procainamide (**2**) analogues, using backbone amide linker (BAL) anchoring. Both sets were prepared starting from a common resin-bound intermediate, followed by four general steps: (i) attachment of a primary aliphatic or aromatic amine to the solid support via reductive amination (as monitored by a novel test involving reaction of 2,4-dinitrophenylhydrazine with residual aldehyde groups); (ii) acylation of the resultant secondary amine; (iii) displacement of halide with an amine; and (iv) trifluoroacetic acid-mediated release from the support. A manual parallel strategy was followed to provide 60 novel compounds, of which two dozen have not been previously described. In most cases, initial crude purities were >80%, and overall isolated yields were in the 40−88% range.

Introduction

Backbone amide linkage (BAL)[3] has been established in several systems[4−9] and has proved to be compatible with a number of solid-phase organic transformations[10−13] that permit access to attractive molecular scaffolds. BAL anchoring was initially established for the solid-phase synthesis of C-terminal-modified/cyclic peptides,[3,14,15] including diketopiperazines,[16,17] as well as peptide aldehydes,[18] unprotected peptide *p*-nitroanilides and thioesters,[19] and peptides containing prolyl, *N*-alkylaminoacyl, and histidyl groups at the C-terminus.[20] The versatility of BAL anchoring extends to the solid-phase synthesis of oligosaccharides,[21,22] 1,4-benzodiazepine-2,5-diones,[23,24] hydroxamic acids,[25] 2,9-substituted purines,[26] modified amino sugars,[22] sulfamides,[27] aminopiperidines,[28] and peptidomimetics.[29,30] Other substituted benzaldehydes[31] have been used to access amine-bridged cyclic enkephalins,[32] constrained RGD ligands,[33] 1,3-bis(acylamino)-2-butanones (cysteine protease inhibitors),[34] benzimidazoles (important pharmacophores),[35,36] hapalosin mimetics,[37] quinoxalinones,[38,39] heterocyclic ethylenediamine-derivatized libraries,[40] *N*,*N*′-disubstituted ureas,[41] perhydroimidazo[1,5-*a*]pyrazines,[41] and other diazepines.[42,43]

Adding to the types of compounds accessible via BAL anchoring, the present paper describes simple methods to synthesize several analogues of lidocaine (**1**) and procainamide (**2**) (Figure 1). Over the past three decades, lidocaine and procainamide have been used as anesthetic[44−46] and antiarrhythmic[47−51] drugs. Lidocaine has also shown sedative,[46] analgesic,[52] anticonvulsant,[53] and depressant[54] activities and facilitates suppression/interaction with Na^+,[55,56] Ca^{2+}/K^+,[57] and rynodine receptors/Ca^{2+} releasing channels.[58] Similarly, procainamide affects biological systems interacting with Na^+ and K^+ channels[47,59−61] and has other functions of interest.[62−64]

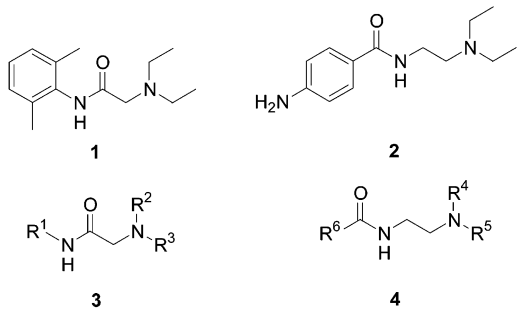

Figure 1. Lidocaine (**1**), procainamide (**2**), and analogues (**3** and **4**).

Since the first syntheses of lidocaine[65] and procainamide,[66] several groups have reported alternative solution routes[67−72] aimed at analogues that are more potent or more specific or that may be labeled for metabolic studies. To the best of our knowledge, solid-phase routes have not been described previously. The presence in both compounds of amide bonds suggests routes using BAL anchoring (Schemes 3 and 4); these could be readily conducted in parallel resulting in the creation of appropriate libraries.

Results and Discussion

Solution Synthesis of Lidocaine. Leading up to the solid-phase route, standards of lidocaine (**1**) and its propyl analogue (**8**) were prepared in solution (Scheme 1). 2,6-Dimethylaniline (**5**) (1 equiv) was condensed with bromoacetic acid (**6**) (1 equiv), as mediated by 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC) (1 equiv) in *N*,*N*-dimethylformamide (DMF). The resultant α-bromo amide **7** was subjected to displacement reactions using diethylamine and dipropylamine, respectively, as reactants/cosolvents with ethyl acetate (1:1).

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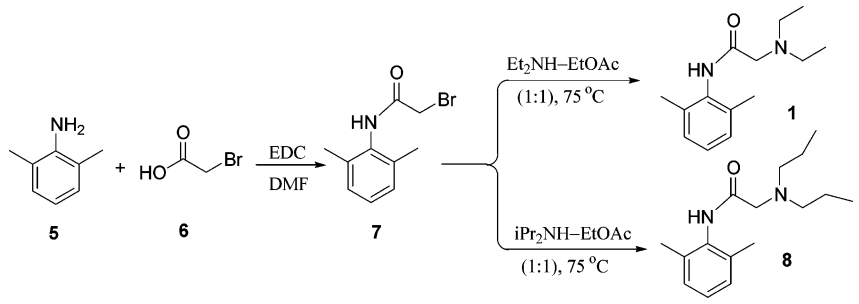
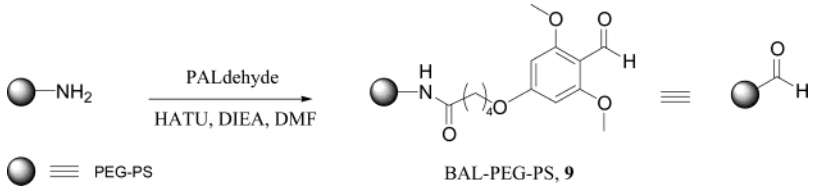
10.1021/cc034014n CCC: $25.00
Published on Web 10/25/2003

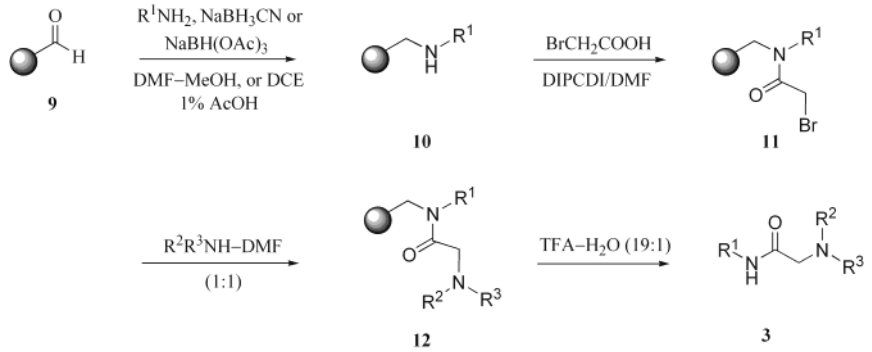
Scheme 1. Solution Synthesis of Lidocaine and Its Propyl Analogue



Scheme 2. Attachment of PALdehyde to PEG-PS



Scheme 3. Solid-Phase Synthesis of Lidocaine Analogues



Both **1** and **8** were exposed to trifluoroacetic acid (TFA)−H_2O (19:1); these are typical conditions to cleave nonpeptidic molecules from BAL. Reversed phase high-performance liquid chromatography (HPLC) monitoring confirmed that these compounds were entirely stable over a time period severalfold longer than what is required for quantitative cleavage (see Supporting Information, Table 1).

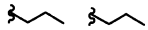
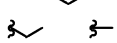
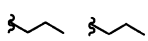
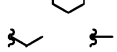
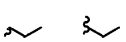
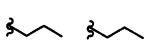
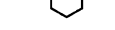
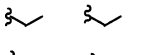
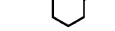
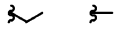
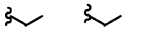
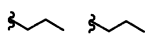
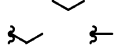
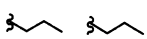
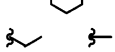
Solid-Phase Preparation of Lidocaine Analogues. Syntheses started with a common intermediate, resin-bound BAL linker **9**, which was prepared by coupling 4-formyl-(3,5-dimethoxyphenoxy)valeric acid (*p*-PALdehyde) (5 equiv) to PEG-PS (0.55 mmol NH_2 per g) in the presence of *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU) (4 equiv) and *N*,*N*-diisopropylethylamine (DIEA) (4 equiv) in DMF (Scheme 2). Small aliquots were removed and subjected to a Kaiser (ninhydrin) test[73] (negative upon completion of coupling) as well as a novel solid-phase 2,4-dinitrophenylhydrazine (DNPH) test (to confirm resin-bound aldehyde content; see Experimental Section).[74] The negative ninhydrin and positive DNPH verified the reaction course.

Conversion of **9** to secondary amines **10**, by reductive amination of primary amines (25 equiv), was mediated by sodium cyanoborohydride ($NaBH_3CN$, 25 equiv) in DMF or MeOH, in the presence of catalytic amounts of acetic acid (HOAc)[3] (Scheme 3). However, when amine hydrochloride salts were used, HOAc was not required. Both aniline and 2,6-dimethylaniline (R^1, series A/B, Table 1) reacted sluggishly when $NaBH_3CN$ was used as the reducing agent. Better results for anilines were obtained with sodium triacetoxyborohydride [$NaBH(OAc)_3$][75] in 1% HOAc/1,2-dichloroethane (DCE). The efficiency of each amination reaction was monitored by the chloranil[76] test for secondary amines, as well as the new DNPH test,[74] which at this stage confirmed the absence of free resin-bound aldehyde sites.

Next, α-bromo halides (**11**) were formed after *N*,*N*′-diisopropylcarbodiimide (DIPCDI)-mediated (10 equiv) coupling of bromoacetic acid (10 equiv) in DMF. There followed displacement of bromide, achieved upon agitation for 4 h at 75 °C with excess amine [cosolvent with DMF, i.e., amine−DMF (1:1, v/v)]. The elevated temperature and the high concentration of amine actually used were chosen based on the results of pilot studies under ambient conditions with lower excesses of amine. The *N*-alkylation reaction just described gave **12**, which upon exposure to TFA−H_2O (19:1) released **3** from its BAL linkage (see Supporting Information, Figure 1, for cleavage kinetics).

Purities of cleaved materials, monitored by HPLC analysis at 220 and 280 nm, ranged from 48 to 96%; isolated yields (gravimetric; calculated based on the initial substitution level of 0.55 mmol/g and ∼50 mg of resin) were between 40 and 88% (Table 1). Diversity at R^1 was introduced easily using a range of primary aliphatic and aromatic amines. Yields and purities improved as the amine (R^1) was changed from

Table 1. Lidocaine Analogues (**3**)[a]

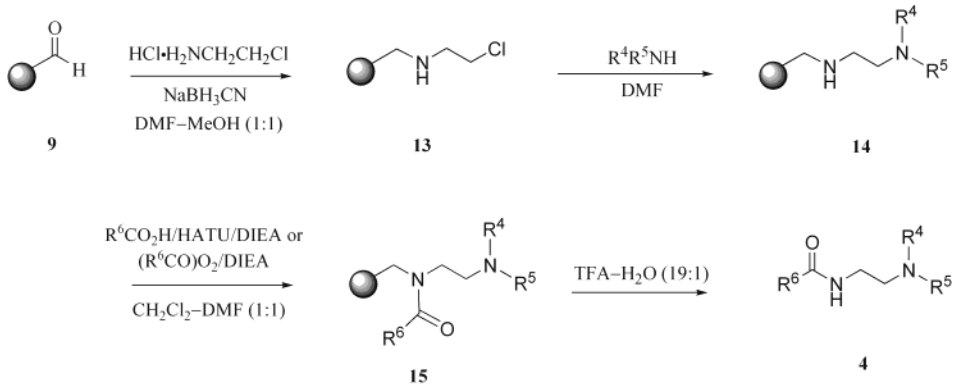
Series	R^1	R^2	R^3	Initial Purity (%)[b]	Yield (%)[c]	$[M + H]^+$ [d]
A1				77	45	235.1
A2	"			69	41	263.2
A3	"			88	43	247.2
A4	"			82	43	221.1
B1				80	65	207.2
B2	"			74	41	235.2
B3	"			91	63	219.2
B4*	"			84	60	193.2
C1				92	82	221.1
C2	"			89	74	249.1
C3	"			88	43	232.2
C4*	"			82	43	207.1
D1				77	55	187.1
D2	"			88	69	215.2
D3	"			79	63	199.1
D4*	"			72	43	173.1
E1*				95	37	215.1
E2*	"			90	56	243.1
E3*	"			90	67	227.2
E4*	"			91	45	201.1
F1				86	49	213.1
F2*	"			87	61	241.2
F3	"			81	50	225.2
F4*	"			83	52	199.2
G1*				68	54	187.1
G2*	"			58	48	215.1
G3*	"			69	53	199.1
G4*	"			55	41	173.2

[a] The overall chemistry is summarized in Scheme 3, and more detailed information about each specific compound appears in the Supporting Information. For series A and B, reductive aminations were mediated by $NaBH(OAc)_3$. For all other series in the table, reductive aminations were mediated by $NaBH_3CN$. An asterisk (*) next to the compound designation means that a recent (May 2003) search of the SciFinder and Beilstein databases did not show this analogue. [b] Determined by HPLC using relative peak areas with monitoring at 220 and 280 nm. [c] Isolated yields were calculated gravimetrically and based on the initial substitution level of 0.55 mmol/g and ~50 mg of resin. [d] The reported molecular ions in this column were all present upon CIMS examination of the isolated purified reaction products and in all cases agreed with the expected structure.

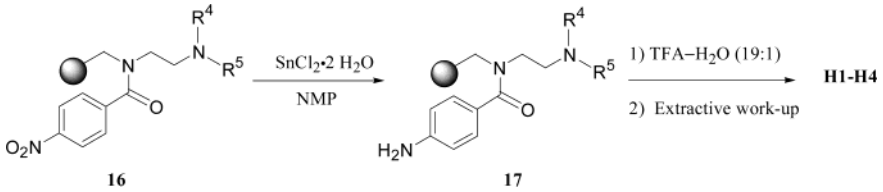
2,6-dimethylaniline (series A) to aniline (series B) to benzylamine (series C); this could be due to either steric or electronic effects. When starting with low molecular weight amines (introduced as solutions in tetrahydrofuran), yields and purities were lower than with the remaining examples tested (Table 1). R^2/R^3 diversity was achieved using four secondary amines [diethylamine (set 1), dipropylamine (set 2), piperidine (set 3), and *N*-ethylmethylamine (set 4)]. Yields, purities, and mass spectrometry results of the full lidocaine library are summarized in Table 1.

Solid-Phase Preparation of Procainamide Analogues. The solid-phase synthesis of procainamide (**4**) was accomplished using similar chemical manipulations (Scheme 4). Overnight reductive amination of resin-bound BAL linker

Scheme 4. Solid-Phase Synthesis of Procainamide Analogues



Scheme 5. Last Synthetic Steps Directed at Procainamide (**4**) and Its Close Analogues



9 (0.55 mmol/g) with chloroethylamine monohydrochloride (10 equiv) and $NaBH_3CN$ (10 equiv) in DMF−MeOH (1:1) provided **13**. Next, nucleophilic displacement of chloride to provide **14** occurred after treatment of **13** with amines (12 equiv, 2 × 48 h) in DMF at 25 °C. Note that this reaction sequence reverses the order of steps used in the earlier lidocaine synthesis, i.e., for procainamide, the *N*-alkylation (exogenous amine) precedes the *N*-acylation (modification of the BAL-anchored secondary amine; see next paragraph). Other trials showed that the preferred procainamide sequence when applied to lidocaine gave similar results, but the preferred lidocaine sequence when applied to procainamide gave rise to complex product mixtures.

The procainamide synthesis continued with acylations of **14** by either carboxylic acid/HATU/DIEA (10 equiv each) or symmetric anhydride (10 equiv)/DIEA (3 equiv) in solutions of CH_2Cl_2−DMF (1:1), providing **15**. The choice between alternative acylation conditions (including those involving activating agents such as DIPCDI other than the recommended HATU) was made experimentally; in most but not all cases, differences were relatively minor (details in Table 2). Finally, exposure of **15** to TFA−H_2O (19:1) released **4** from its BAL linkage.

To obtain the parent procainamide compound (**2**) and its close analogues (series H), an extra chemical step was required. Thus, *p*-aminobenzoic acid could not be used directly as a starting material, due to the possibility of competing reactions at the aromatic amino function. Rather, work was carried out starting with *p*-nitrobenzoic acid (series K) and then reducing the nitro group of intermediate **16** with $SnCl_2 \cdot 2H_2O$ (20 equiv) in NMP[77−80] (Scheme 5). There followed cleavage of resin-bound **17** upon treatment with TFA−H_2O (19:1). Finally, an extractive workup was carried out, which took advantage of the solubility of these aromatic amine products in aqueous acid and eliminated the need for chromatography.

Purities of cleaved materials ranged from 68 to 98%, and isolated yields were largely between 41 and 88% (Table 2). Diversity at R^6 was introduced by using substituted benzoic acids and symmetric anhydrides. R^4/R^5 diversity was achieved using three of the four secondary amines described for lidocaine and adding morpholine (set 4). Yields, purities, and mass spectrometry results of the full procainamide library are summarized in Table 2.

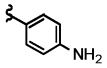
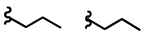
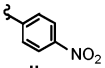
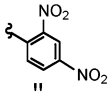
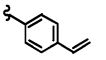
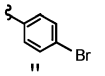
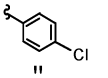
Conclusions

A simple and efficient four step BAL strategy has been described for the solid-phase syntheses of lidocaine, procainamide, and several analogues. The generalized methodology produced 60 compounds (24 of which were not in SciFinder or Beilstein databases) and could conceivably be automated to create diverse analogues with potentially improved anesthetic, antiarrhythmic, and other pharmaceutical properties. As a part of this work, a novel and sensitive DNPH test[74] for detecting resin-bound aldehydes has been introduced; its scope and limitations will be reported elsewhere soon.

Experimental Section

General Procedures. Solution and solid-phase organic transformations and resin washes were at 25 °C, unless indicated otherwise. Polymer-supported reactions were carried out using plastic syringes (3, 12, or 35 mL) fitted with polypropylene frits or in glass vials with Teflon-lined caps and rotated on an EStem Electrothermal Reacto-Station RS 6000 orbital shaker. Washes were typically 30−60 s, followed by draining under aspirator suction. Resin-bound intermediates were air-dried after the final CH_2Cl_2 washes, unless they needed to be reweighed in which case overnight drying under high vacuum (2 mm) in a desiccator was carried out. All starting materials and solvents were reagent grade from Aldrich (Milwaukee, WI), with the exception of PEGPS•HCl resin (0.55 mmol NH_2 per g) and PALdehyde, which were from PE Biosystems (Framingham, MA). CH_2Cl_2 was freshly distilled from anhydrous calcium hydride. All organic

Table 2. Procainamide Analogues (**4**)[a]

Series	R^6	R^5	R^4	Initial Purity (%)[b]	Yield (%)[c]	$[M + H]^+$ [d]
H1				> 98	57	236.2
H2	"			> 98	49	264.2
H3	"			> 98	44	248.2
H4	"			> 98	55	250.2
I1				68/69	53	221.1
I2*	"			66/63	41	249.2
I3	"			86/68	61	333.1
I4	"			91/83	77	235.2
J1				89	72	159.2
J2*	"			91	67	187.2
J3	"			96	88	171.2
J4	"			85	81	173.1
K1				69	66	266.1
K2*	"			71	51	294.2
K3	"			74	56	278.2
K4	"			78	66	280.2
L1*				86/82	73/84	311.1
L2*	"			88/85	64/83	339.2
L3*	"			91/92	66/71	323.1
L4	"			93/92	60/68	325.2
M1				93	65	247.2
M2*	"			93	62	275.2
M3*	"			95	74	259.2
M4*	"			98	54	261.1
N1				80	42	300.2
N2*	"			80	41	328.2
N3	"			76	26	312.1
N4	"			84	59	314.2
O1				70	63	255.1
O2*	"			72	54	283.2
O3	"			88	81	267.2
O4	"			88	82	269.2

[a] The overall chemistry is summarized in Scheme 4 (followed by Scheme 5 for series H), and more detailed information about each specific compound appears in the Supporting Information. A single entry means that acylation was carried out by HATU coupling. For series I, the first entry represents the result of anhydride coupling whereas the second entry represents HATU. For series L, the first entry represents results from DIPCDI activation and the second again represents HATU. An asterisk (*) next to the compound designation means that a recent (May 2003) search of the SciFinder and Beilstein databases did not show this analogue. [b] Determined by HPLC using relative peak areas with monitoring at 220 and 280 nm. [c] Isolated yields were calculated gravimetrically and based on the initial substitution level of 0.55 mmol/g and ~60−75 mg of resin. [d] The reported molecular ions in this column were all present upon ESIMS examination of the isolated purified reaction products and in all cases agreed with the expected structure.

phases after extractive workup were dried over Na_2SO_4, following which solvent removal was performed at reduced pressures and at temperatures less than 40 °C. Silica gel chromatography was performed with 60 mesh resin; further details are given with each individual compound. Melting points were taken on a Buchi 530 apparatus. ^{1}H NMR spectra were obtained at ambient temperature on Varian VXR-200 and 300 spectrometers. Chemical ionization mass spectrometry (CIMS) was performed on a Perkin-Elmer Sciex API III triple quadrupole mass spectrometer equipped with an ionspray interface. Electrospray ionization mass spectrometry (ESIMS) was performed on a Finnigan LQC mass spectrometer. Analytical HPLC was performed using a Vydac C_{18} reversed phase column (0.46 cm × 25 cm) on a Beckman instrument, configured with two 112 pumps and a 165 variable wavelength detector set at 220 and 280 nm. Linear gradients of 0.1% TFA in CH_3CN and 0.1% aqueous TFA were run at 1.0 mL/min flow rate from 3:97 to 1:1 over 30 min and then to 1:0 over the next 10 min.

Solid-Phase DNPH Test[74] for Aldehyde Content. The DNPH reagent solution was prepared by first dissolving 2,4-dinitrophenylhydrazine (100 mg) in concentrated H_2SO_4 (0.5 mL) and then adding this solution slowly, with stirring over 1 min, to H_2O−EtOH (1:10, 7.7 mL). This DNPH reagent solution can be stored under ambient conditions for several months. Approximately 2 mg of resin was transferred to a clean, dry test tube, and CH_2Cl_2 was added dropwise until the resin swelled and was immersed completely in CH_2Cl_2. Next, three drops of the DNPH solution were added to the test resin and the resulting red-orange suspension was agitated on a vortex mixer for 1 min at 25 °C. The suspension was then diluted with MeOH (2 mL) and decanted for several cycles (in each cycle, the resin sinks to the bottom) until the decanted MeOH solution was nearly colorless. In the presence of aldehydes, the resin immediately takes a dark red to orange appearance (positive test). Alternatively, resins that are free of aldehydes, or in which aldehyde functions have reacted completely, show no additional color (i.e., remaining pale yellow) by this test.

2-Diethylamino-*N*-(2,6-dimethyl-phenyl)acetamide (Lidocaine) (1). Compound **7** (30 mg, 0.124 mmol) was taken up in diethylamine−EtOAc (1:1, 2 mL), and the reaction mixture was stirred and heated at 75 °C for 18 h. The mixture was cooled, and then diluted with EtOAc (5 mL), washed with H_2O (3 × 1 mL) and brine (2 × 1 mL), dried (Na_2SO_4), and concentrated to give title compound **1** as white crystals; mp 67−70 °C; yield, 24 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (br s, 1H), 7.10 (br s, 3H), 3.24 (s, 2H), 2.71 (q, J = 7.2 Hz, 4H), 2.25 (s, 6H), 1.15 (t, J = 7.2 Hz, 6H). CIMS: m/z calcd for $C_{14}H_{22}N_2O$, 234.34; found, 235.1 $[M + H]^+$.

Isolation of 3: Cleavage of Lidocaine Analogues from BAL Support. Resins **12** (50 mg) were swollen in CH_2Cl_2 (1.5 mL, 5 min) and treated with TFA−H_2O (19:1, 2 mL) for 5 h. The filtrates were combined with washes of TFA (3 × 2 mL) and concentrated under a stream of N_2 to give crude analogues **3**, which were purified by silica gel column chromatography (see Supporting Information for elution conditions).

Isolation of 4: Cleavage of Procainamide Analogues from BAL Support. Resins **15** (75 mg) were swollen in CH_2Cl_2 (1.5 mL, 5 min) and treated with TFA−H_2O (19:1, 2 mL) for 3 h. The remainder of the procedure was exactly as described for compound **3**.

2-Bromo-*N*-(2,6-dimethyl-phenyl)acetamide (7). A solution of 2,6-dimethylaniline (**5**) (124 mg, 1.02 mmol), bromoacetic acid (142 mg, 1.03 mmol), and EDC (191 mg, 1.00 mmol) in dry DMF (3 mL) was stirred under N_2 for 1 h. After dilution with EtOAc (15 mL), the organic layer was separated and washed with 1 N aqueous HCl (3 × 15 mL), 5% aqueous $NaHCO_3$ (3 × 15 mL), and brine (2 × 15 mL) and then dried (Na_2SO_4). After concentration, the crude oil was purified by silica gel column chromatography ($CHCl_3$−MeOH, 10:1) to provide white crystals; mp 148−151 °C; yield, 194 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.1−7.2 (m, 3H), 4.25 (s, 2H), 2.41 (s, 6H). CIMS: m/z calcd for $C_{10}H_{12}NOBr$, 242.13; found, 243.0 $[M + H]^+$.

2-Diethylamino-*N*-(2,6-dimethyl-phenyl)acetamide (8). Compound **7** (32 mg, 0.132 mmol) was taken up in dipropylamine−EtOAc (1:1, 2 mL), and the remainder of the procedure was exactly as described for compound **1**, to provide **8** as white crystals; mp 52−54 °C; yield, 26 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (br s, 1H), 7.11 (br s, 3H), 3.25 (s, 2H), 2.57 (t, J = 7.5 Hz, 4H), 1.58 (s, 6H), 1.2−1.3 (m, 4H), 0.95 (t, J = 7.5 Hz, 6H). CIMS: m/z calcd for $C_{16}H_{26}N_2O$, 262.39; found, 263.2 $[M + H]^+$.

Preparation of 9: Resin-Bound BAL. PEG-PS (4.0 g, 0.55 mmol NH_2 per g, obtained as the amine hydrochloride) was swollen in CH_2Cl_2 (25 mL, 5 min) and washed thoroughly with DMF−DIEA (4:1, 5 × 25 mL). PALdehyde (12.2 mmol, 5 equiv), HATU (9.8 mmol, 4 equiv), and DIEA (9.8 mmol, 4 equiv) were dissolved in DMF (20 mL), and the resultant solution was added to the resin and rotated on an orbital shaker for 24 h to provide **9**. The resin was then washed with DMF (5 × 25 mL), MeOH (5 × 25 mL), and CH_2Cl_2 (5 × 25 mL) and dried (2 mm, overnight, desiccator). Completion of the reaction was verified by the Kaiser test[73] and the DNPH test.[74]

Preparation of 10: Method I. Reductive Amination Using Aromatic and Electron Deficient Amines (Table 1: Series A and B). Resin **9** (425 mg) was swollen in CH_2Cl_2 (8 mL, 5 min) and washed thoroughly with DCE (5 × 8 mL). A suspension was prepared involving $NaBH(OAc)_3$ (1.1 g, 5.21 mmol, 25 equiv) in DCE (8 mL), following which the amine (5.21 mmol, 25 equiv) and HOAc (80 μL, 1.40 mmol) were added, and finally the entire slurry was added to resin **9** and rotated on an orbital shaker for 24 h. The resultant secondary amine resin **10** was washed with DCE (5 × 8 mL), DMF (5 × 8 mL), and CH_2Cl_2 (5 × 8 mL) and then dried (2 mm, overnight, desiccator). The reaction was checked by the chloranil test[76] and the DNPH test.[74] The amines used were 2,6-dimethylaniline (series A) and aniline (series B).

Preparation of 10: Method II. Reductive Amination Using Aliphatic and Nonaromatic Amines (Table 1: Series C−G). Resin **9** (425 mg) was swollen in CH_2Cl_2 (8 mL, 5 min) and washed thoroughly with DMF (5 × 8 mL). A solution of $NaBH_3CN$ (327 mg, 5.21 mmol, 25 equiv)

and the amine (5.21 mmol, 25 equiv) in HOAc−DMF−MeOH (1:49:49, 8 mL) was added to resin **9** and rotated on an orbital shaker for 24 h. The resultant secondary amine resin **10** was washed with DMF (5 × 8 mL), MeOH (5 × 8 mL), and CH_2Cl_2 (5 × 8 mL) and then dried (2 mm, overnight, desiccator). The reaction was checked by the chloranil test[76] and the DNPH test.[74] The primary amines used were benzylamine (Table 1, series C), butylamine (series D), tetrahydrofurfurylamine (series E), cyclohexylamine (series F), and isopropylamine (series G).

Preparation of 11: Acylation of Secondary Amine. Resin **10** (425 mg) was swollen and washed as described for compound **10** (method II). A solution of bromoacetic acid (289 mg, 2.08 mmol, 10 equiv) and DIPCDI (262 mg, 2.08 mmol, 10 equiv) in DMF was added to resin **10** and rotated on an orbital shaker for 30 min. The resin was washed with DMF (5 × 8 mL), and the acylation was repeated for another 30 min. The remainder of the procedure (washing and drying) was exactly as described for compound **10** (method II). The reaction was checked by the chloranil test.[76]

Preparation of 12: *N*-Alkyl Substitution. Resin **11** (50 mg) was swollen in CH_2Cl_2 (1.5 mL, 5 min) and transferred to a 5 mL glass vial. A solution of amine−DMF (1:1, v/v, 3 mL) was added to the resin, sealed, and heated for 4 h at 75 °C on an orbital shaker. Resin **12** was then washed with DMF (5 × 1.5 mL), MeOH (5 × 1.5 mL), and CH_2Cl_2 (5 × 1.5 mL) and air-dried. The secondary amines used were diethylamine (Table 1, set 1), dipropylamine (set 2), piperidine (set 3), and *N*-methylethylamine (set 4).

Preparation of 13: Reductive Amination. Resin **9** (3.2 g) was swollen in CH_2Cl_2 (25 mL, 5 min) and washed thoroughly with DMF (5 × 25 mL). A suspension was prepared containing chloroethylamine monohydrochloride (2.0 g, 11.6 mmol, 10 equiv) and $NaBH_3CN$ (1.1 g, 11.6 mmol, 10 equiv each) in DMF−MeOH (1:1, 25 mL), and the entire slurry was added to resin **9** and rotated on an orbital shaker for 24 h resulting in secondary amine resin **13**. The remainder of the procedure (washing and drying) was exactly as described for compound **9**. The reaction was checked by the chloranil test[76] and the DNPH test.[74]

Preparation of 14: *N*-Alkyl Substitution. Resin **13** (775 mg) was swollen in CH_2Cl_2 (15 mL, 5 min) and washed thoroughly with DMF (5 × 15 mL). A solution of the secondary amine (3.43 mmol, 12 equiv) in DMF was added to the resin, and the mixture was rotated on an orbital shaker for 48 h. The resin was filtered and washed with DMF (5 × 25 mL), and the reaction was repeated for another 48 h. The resultant resin **14** was washed with DMF (5 × 15 mL), MeOH (5 × 15 mL), and CH_2Cl_2 (5 × 15 mL) and then dried (2 mm, overnight, desiccator). The secondary amines used were diethylamine (Table 2, set 1), dipropylamine (set 2), piperidine (set 3), and morpholine (set 4).

Preparation of 15: Method I. Acylation Using Acid Anhydrides (Table 2: Series I, J). Resin **14** (75 mg) was swollen in CH_2Cl_2 (1.5 mL, 5 min) and washed with DMF (5 × 1.5 mL). A solution of anhydride (0.413 mmol, 10 equiv) and DIEA (0.124 mmol, 3 equiv) in DMF−MeOH (1:1, 1.5 mL) was added to resin **14** and rotated on an orbital shaker for 24 h providing **15**. The remainder of the procedure (washing and drying) was exactly as described for compound **12**. The anhydrides used were benzoic anhydride (series I) and acetic anhydride (series J). The reaction was checked by the chloranil test.[76]

Preparation of 15: Method II. Acylation Using Acids (Table 2: Series H, I, K−O). Resin **14** (75 mg) was swollen and washed as described for compound **15** (method I). A solution of acid (0.562 mmol, 10 equiv), HATU (0.562 mmol, 10 equiv), and DIEA (0.562 mmol, 10 equiv) in DMF−MeOH (1:1, 1.5 mL) was added to resin **14** and rotated on an orbital shaker for 24 h to provide **15**. The remainder of the procedure (washing and drying) was exactly as described for compound **12**. The acids used were benzoic acid (series I), 4-nitrobenzioc acid (series H, K), 2,4-dinitrobenzoic acid (series L), 4-vinylbenzoic acid (series M), 4-bromobenzoic acid (series N), and 4-chlorobenzoic acid (series O).

Preparation of 17: Reduction of Nitro Group (toward Series H). Resin **16** (75 mg, from series K) was swollen in CH_2Cl_2 (1.5 mL, 5 min) and washed thoroughly with NMP (5 × 1.5 mL). A suspension of $SnCl_2 \cdot 2H_2O$ (1.13 mmol, 20 equiv) in NMP (2 mL) was added to resin **16** and rotated on an orbital shaker for 16 h. Resin **17** was then washed with NMP (5 × 1.5 mL), DMF (5 × 1.5 mL), MeOH (5 × 1.5 mL), and CH_2Cl_2 (5 × 1.5 mL), and then treated with TFA−H_2O (19:1, 2 mL) for 3 h. The filtrate was combined with washes of TFA (3 × 2 mL) and concentrated under a stream of N_2, and the crude residue was taken up in EtOAc−1 N aqueous HCl (1:1, 3 mL). The organic phase was removed, and the aqueous phase was washed with EtOAc (3 × 1 mL), adjusted to pH 12 using 1 N aqueous NaOH, and extracted with EtOAc (3 × 1 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to provide procainamide (**4**, H1) and related analogues in series H.

Acknowledgment. We thank Drs. Daniel G. Mullen, Christopher M. Gross, T. Scott Yokum, and Jordi Alsina for helpful discussions and the NIH for financial support (GM 42722).

Supporting Information Available. Crude purity, yield, ^{1}H NMR, and mass spectrometry and chromatographic data for all compounds in Tables 1 and 2, TFA exposure studies, cleavage kinetics, and a list of abbreviations. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC034014N