Pergamon

Tetrahedron, Vol. 53, No. 19, pp. 6595-6609, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00219-6

THE SOLID-PHASE COMBINATORIAL SYNTHESIS OF β-THIOKETONES.[1]

Chixu Chen, Lisa A. Ahlberg Randall, R. Bryan Miller,
A. Daniel Jones, and Mark J. Kurth*

Department of Chemistry
University of California, Davis
Davis, California 95616

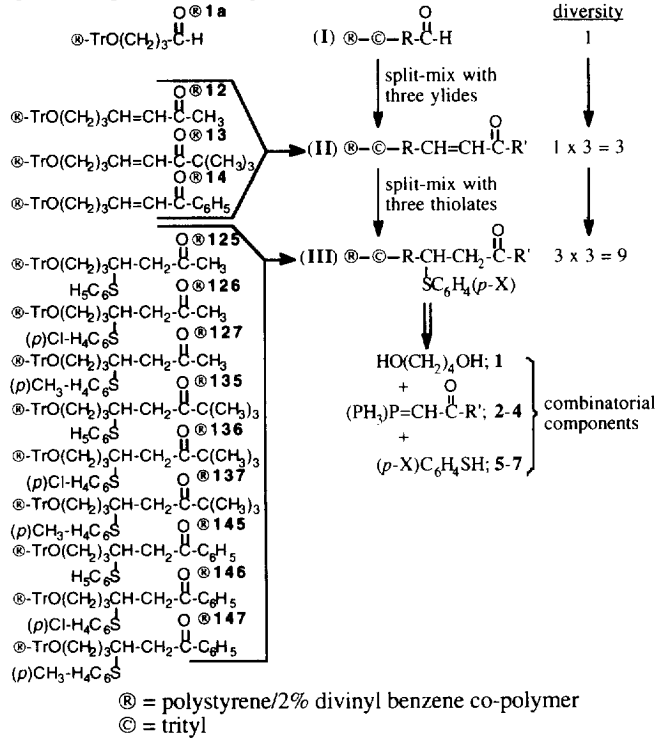
Abstract: A solid-phase split-mix organic synthesis method was developed which, by two synthetic steps, converts polymer-bound aldehyde **I** into resins **III**. Step one consists of dividing **I** into three equal portions in separate flasks, condensing each with a different ylide, and subsequently recombining to give **II**. This mixture of beads was again equally divided into three flasks, and each flask treated with a thiolate Michael donor. Prior to recombining the contents of each flask (i.e., sub-library), samples of each resin were removed and incubated with a THF/HCO_2H mixture to liberate the small molecule products. GC-MS established that each sub-library (A, B, and C) contained the three anticipated formate esters. In addition, GC analysis illustrates that, while there were no purification steps involved in this solid-phase analogous organic synthesis save bead washings between steps, the desired products are obtained in excellent purity. Single bead (200-400 mesh) selection from library D (combined sub-libraries A-C), solvolysis, and GC-MS analysis shows that compound identities can be established on a per bead basis.

Introduction:

The pioneering solid-phase[2] small-molecule work of Leznoff[3] and others[4] coupled with the more recent efforts of many academic and industrial chemists[5] have established three principal synthetic advantages of solid-phase synthetic techniques: (i) many solid-phase reactions can be driven to completion by addition of excess solution-phase reagents (removed by filtration and washing), (ii) solid-phase reaction products are "isolated" by filtration and washing, and (iii) multiple step synthesis terminating with a "selective" liberation step can deliver essentially pure product. However, when applied to oligomeric (peptides, oligosaccharides, and oligonucleotides) compounds, these advantages are restrained by limited reaction and reagent versatility.

These observations coupled with the importance of C—C-bond forming reactions in organic chemistry led us to explore the solid-phase "split-mix"[6] synthesis of β-mercaptoketones (**Figure 1**) as a preliminary probe of whether the essentially limitless diversity of solution-phase synthetic organic reactions and reagents can be adapted for

Figure 1. Split-mix solid-phase synthesis of nine β-mercaptoketones.

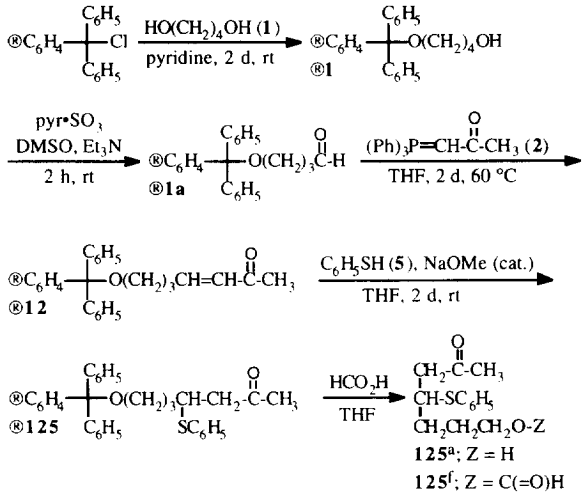


® = polystyrene/2% divinyl benzene co-polymer
© = trityl

combinatorial small-molecule synthesis. Herein we report the details of this study where solution-phase trityl protection, oxidation, Horner•Emmons condensation (reagent diversity consisting of three ylides), Michael addition (reagent diversity consisting of three thiolates), and trityl deprotection chemistry were adapted to deliver a nine-compound library where each component was held to the normal structural characterization (^{1}H- and ^{13}C-NMR, LR- and HR-MS) standards of organic chemistry.

The chemistry targeted for this study was first explored as a solid-phase serial synthesis to establish the validity of each synthetic step (**Scheme 1**). 1,4-Butanediol (**1**) was attached to the polystyrene support (® = polystyrene/2% divinyl benzene co-polymer) by trityl ether[7] mono-protection to give ®**1**. We initially assumed that polymer-based site isolation[4b] would effectively minimize bis-protection, but have since come to realize that kinetic site isolation is reaction dependent.[8] In a careful study of this issue as it pertains to mono-protection, Leznoff[9] has reported ≈40% of the diol is actually bis-protected. In our hands, deprotection (HCl gas, CH_2Cl_2) and capillary GC analysis established a butanediol loading of 0.9 ± 0.1 meq/g of resin.

Scheme 1. Serial solid-phase synthesis of β-mercaptoketone **125**.



Sulfur trioxide•pyridine mediated oxidation[10] of the free hydroxyl of ®**1** delivered polymer-bound aldehyde ®**1a** as evidenced by FTIR analysis[11] of the reaction mixture (KBr press: free -OH stretch at 3575 cm^{-1} and hydrogen bonded -OH stretch at 3452 cm^{-1} → C=O stretch at 1724 cm^{-1}). We have found that the reliability of FTIR-OH data is

improved when the KBr window is stored for 2-3 h at 110 °C prior to analysis (residual moisture is removed). Horner•Emmons condensation of THF-swollen resin ®**1a** with excess (5 meq/g of resin) 1-triphenylphosphoranylidene-2-propanone (**2**) delivered enone ®**12** [FTIR (KBr) 1674 cm^{-1}] with complete disappearance of the C=O stretch (1724 cm^{-1}) of ®**1a**. Having thus generated a resin-bound Michael acceptor, phenyl thiolate conjugate addition was effected by treating THF-swollen ®**12** with thiophenol (**5**; 9 meq/g of resin) and a catalytic amount of sodium methoxide. Michael adduct ®**125** was obtained as evidenced by an FTIR shift in the C=O stretch from 1674 to 1716 cm^{-1}. Moreover, trityl ether solvolysis with formic acid (THF:HCO_2H::1:3 v/v) delivered the targeted formate ester **125**^{f} (superscript f = formate, 0.42 meq/g of resin; 46% overall yield from ®**1**) and thus verified the success of each transformation depicted in **Scheme 1** (≈82% yield per step for these four steps). Based on a trityl chloride loading of 1.57 mmol/g of resin (determined by chloride titration),[12] the overall yield of **125**^{f} from ®$C_6H_4C(C_6H_5)Cl$ is 27% (≈77% yield per step for these five steps). This discrepancy in overall yield, -$O(CH_2)_4OH$ versus -Cl loading, may be a consequence of incomplete site isolation in the mono-protection step (**1** → ®**1**).

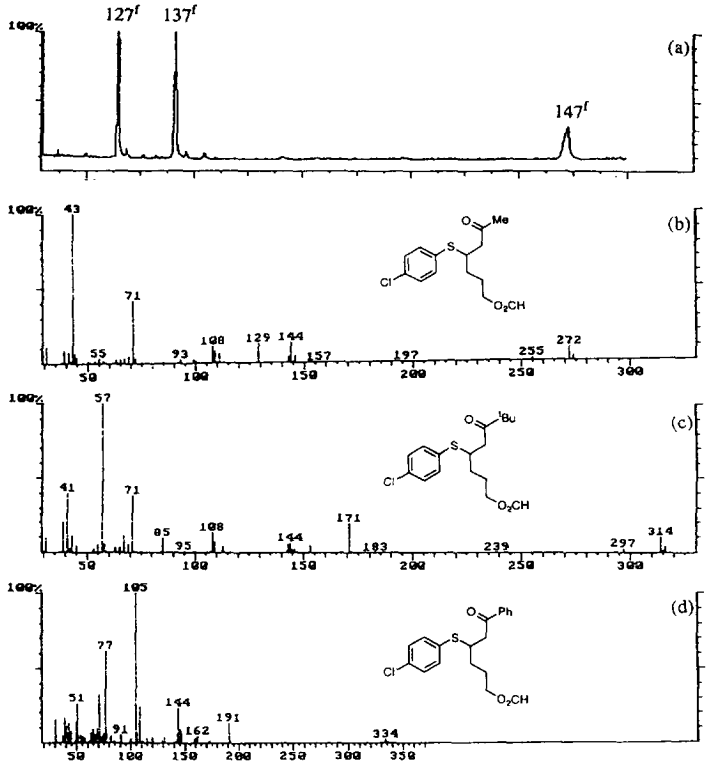
It is also noteworthy that variation in the trityl ether solvolysis reaction conditions can lead to either formate ester **125**^{f} (THF:HCO_2H::1:3 v/v; 12 h at room temperature) or the alcohol **125**^{a} (superscript a = alcohol, THF:HCO_2H::3:1 v/v; 10 min at room temperature). Intermediate conditions deliver formate ester and alcohol mixtures. This versatility can be exploited to deliver another level of library diversity.

The next objective was to adapt this chemistry to a "split-mix" organic synthesis method. To showcase this approach in small molecule chemistry, it was decided that polymer-bound aldehyde ®**1a** would be divided into equal portions and placed in three separate flasks. Subsequent condensation of ®**1a** with ylides **2-4** (R' = Me / ^{t}Bu / Ph, respectively; see **Figure 1**) delivered resin-bound enones ®**12** [flask #1; ®**1a** + **2** (R' = Me)], ®**13** [flask #2; ®**1a** + **3** (R' = ^{t}Bu)], and ®**14** [flask #3; ®**1a** + **4** (R' = Ph)]. Recombination, completing the split-mix cycle, gave an ≈1:1:1 mixture of these three resin-bound enones (mixture **II** in **Figure 1**).

This mixture of beads (**II**) was again equally divided into three flasks, the resin swollen with THF, and each flask treated with a Michael donor [**5**, **6**, or **7** where X = H / Me / Cl, respectively; see **Figure 1**] and catalytic sodium methoxide such that flask #4 received thiophenol (**II** + **5**), flask #5 received *p*-thiocresol (**II** + **6**), and flask #6 received 4-chlorothiophenol (**II** + **7**). Prior to recombining the contents of each flask to give mixture **III** (i.e., the nine β-mercaptoketone library), a small sample of each sub-library was removed and incubated with a THF/HCO_2H mixture (1:3, 12 h) to liberate the small

molecule products. The THF/HCO_2H solution was withdrawn from the beads, evaporated, and the residue taken up in benzene. We were pleased to find that capillary GC analysis of each sub-library mixture showed essentially only the three targeted formate esters. In this way, ®**1a** gave sub-library A (flask #4: **125**^{f} + **135**^{f} + **145**^{f}), sub-library B (flask #5: **126**^{f} + **136**^{f} + **146**^{f}), and sub-library C (flask #6: **127**^{f} + **137**^{f} + **147**^{f}). Each of these nine compounds were fully characterized by ^1H- and ^{13}C-NMR, HRMS, and low resolution GC-MS (see **Figure 2**; GC-MS trace and data for sub-library C).[13]

Figure 2. GC-MS trace and data for sub-library C (**127**^{f}, **137**^{f}, and **147**^{f}).

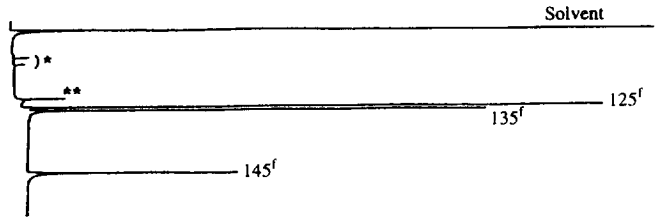


Data acquired with a Finnigan Mat ITD ion trap detector connected to a Varian 3400 GC (30m x 0.25μm DB5 fused silica column).

Sub-libraries A-C were also analyzed by capillary GC. The chromatogram for the mixture obtained from flask #4 (liberated by THF:HCO_2H::1:3 v/v, 12 h at room

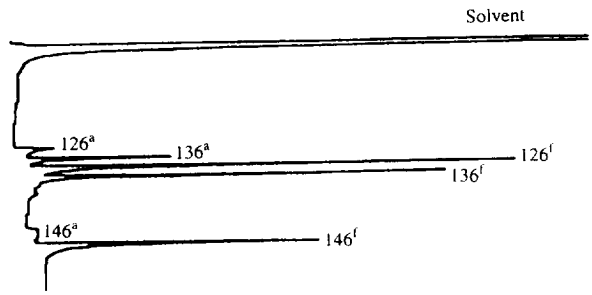
temperature) is shown in **Figure 3** and the chromatogram obtained from flask #5 (liberated by THF:HCO_2H::1:1 v/v; 1 h at room temperature) is shown in **Figure 4** (for flask #6 see **Figure 2**, THF:HCO_2H::1:3 v/v; 12 h at room temperature)). We were impressed to see that while there were no purification steps involved in the four-step conversion of **®1a** to these sub-libraries save bead washings between steps, the desired products were obtained in excellent purity. Clearly the Horner•Emmons condensation reactions and the Michael addition reactions all proceed nicely. The chemical reliability and product purity evident in these results also suggest that a deconvolutive assay (i.e., a strategy wherein the lead compound in a library is identified by successive analysis of the library and its predecessor sub-libraries)[14] requiring resin-free substrates could be utilized to screen these compounds.

Figure 3. Capillary GC trace for sub-library A (**125**^{f} + **135**^{f} + **145**^{f}).



Capillary GC analysis (Hewlett Packard 5890; 30m × 0.25μm DB210 fused silica column) of the sub-library from flask #4 (product\retention time): **125**^{f}\9.56 min, **135**^{f}\9.91 min, **145**^{f}\16.68 min [* = undetermined impurities; ** = $HCO_2CH_2CH_2CH_2CH{=}CHC(=O)C(CH_3)_3$].

Figure 4. Capillary GC trace for sub-library B (**126**^{a}/**126**^{f} + **136**^{a}/**136**^{f} + **146**^{a}/**146**^{f}).

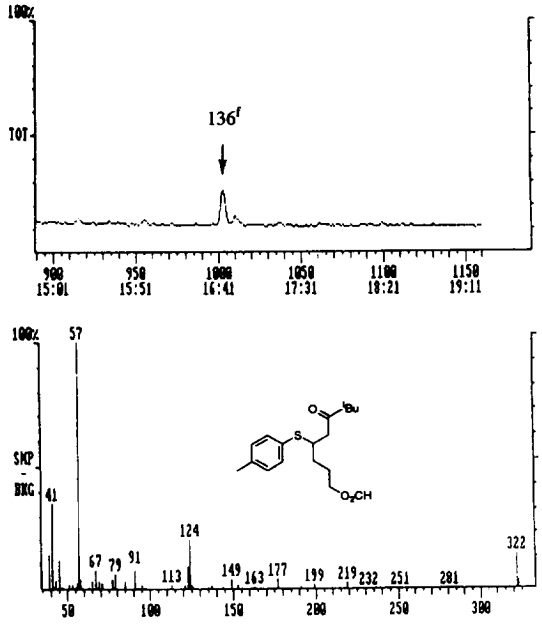


Capillary GC analysis (Hewlett Packard 5890; 15m × 0.25μm DB210 fused silica column) of the sub-library from flask #5 (product\retention time): **126**^{a}\4.60 min, **136**^{a}\4.98 min, **126**^{f}\5.33 min, **136**^{f}\5.65 min, **146**^{a}\8.40 min, **146**^{f}\8.99 min.

We were intrigued with the question of whether compound identity could be determined on a per bead basis and also confronted with the challenge of demonstrating the feasibility of characterizing product mixtures complicated by: (i) diversity of synthetic subunits (potentially far exceeding that encountered in peptide synthesis), (ii) the small amounts of material available ($\approx 10^{-10}$ mols/bead), and (iii) the potential for heterogeneity among modified polymer beads. Clean sample preparation and handling techniques coupled with sensitive GC-MS protocols were employed for this purpose. Because common substructures often yield characteristic mass spectral peaks, potential undesired side reactions as well as optimization of the analogous organic synthesis could be addressed by searching for the presence of these peaks by GC-MS.

To address this issue of per bead analysis, a single bead (200-400 mesh) was isolated with the aid of a microscope and placed in a glass melting point tube (1 mm diameter). Incubation with THF/HCO_2H (10 μL, overnight) followed by evaporation,

Figure 5. Single bead GC-MS analysis.



GC-MS analysis of a single bead liberating **136**[f]. Data acquired with a Finnigan Mat ITD ion trap detector connected to a Varian 3400 GC (30m × 0.25μm DB5 fused silica column).

residue dissolution in benzene (2 μL), and GC-MS analysis easily detected that single bead's formate ester product. Nine random single bead analyses of our nine-compound library [pooled library D (sub-libraries A + B + C)] detected formates **125**^{f} (detected in three analyses), **135**^{f}, **126**^{f}, **136**^{f}, **137**^{f} (detected in two analyses), and **147**^{f}. **Figure 5** shows the GC-MS chromatogram and the corresponding mass spectrum obtained in the single bead analysis of **136**^{f}. Clearly, single bead analysis of 200-400 mesh resin is straightforward, with the only difficulty being mechanical issues related to handling a single small bead (≈100 μm diameter).

As a final demonstration of the reliability of analogous organic synthesis, separate 800 mg samples of sub-libraries A, B, and C were incubated with THF/HCO_2H and the THF-soluble residues purified by preparative thin-layer chromatography. A UV-active band was observed for each formate ester which was subsequently isolated and fully characterized. By this process, sub-library A delivered the formate esters **125**^{f}, **135**^{f}, and **145**^{f} in 27%, 11%, and 25% (respectively) overall isolated yield based on 1.57 mmol trityl chloride/g resin (likewise, sub-library B delivered **126**^{f}, **136**^{f}, and **146**^{f} in 24%/17%/19% yield and sub-library C delivered **127**^{f}, **137**^{f}, and **147**^{f} in 24%/7%/20% yield).

Experimental:

General. Tetrahydrofuran (THF) was refluxed over and distilled from sodium-potassium immediately prior to use. Polystyrene-2% divinylbenzene (200-400 Mesh) was purchased from Kodak and used directly. Dimethylsulfoxide (DMSO) and triethylamine (Et_3N) were distilled and stored over 4 Å molecular sieves prior to use. All reactions were conducted under an argon atmosphere. Preparative TLC was performed on 0.25 × 200 × 200 mm general purpose, precoated silica gel glass plates. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz, respectively, and chemical shifts are reported in ppm downfield from internal tetramethylsilane. Mass spectra were obtained with Finnigan Mat ITD ion trap detector (low resolution) and VG TRIO2 (high resolution; VG-11-250 data system).

Polymer-bound 4-trityloxy-1-butanol (®1). Resin ®**1** was prepared according to the Fyles and Leznoff procedure.[9b] Determination of chloride content for the polymer bound tritylchloride employed Volhardt's procedure[12] modified as follows: three 0.2 g samples of ®$C_6H_4C(C_6H_5)Cl$ were swollen in THF (10 mL) for 15 min, 0.1 M aqueous $AgNO_3$ (10.00 mL) was added and the resulting mixtures were stirred 6 - 18 h. Three drops of saturated aqueous ferric alum, 1 N HNO_3 (1 mL), and a 1 cm layer of toluene were added and the resulting mixture titrated with 0.1 M NH_4SCN standard aqueous

solution to a red-brown endpoint. The average chloride content of the polymer was found to be 1.57 mmol Cl^-/g resin.

The 4-trityloxy-1-butanol loading was determined as follows. Resin ®**1** (1.0 g) was swollen in dichloromethane (50 mL) and a stream of hydrogen chloride gas, freshly generated from the reaction of sodium chloride and concentrated sulfuric acid, was passed through a calcium chloride drying tube and bubbled into the swollen resin for 4 h. The resin was filtered, washed with methanol (4 × 5 mL) and ether (4 × 5 mL) and the filtrate was concentrated.

The crude 1,4-butanediol obtained from the above experiment was dissolved in methanol (2.00 mL). A series of 1,4-butanediol standard methanol solutions with molar concentration of 0.1, 0.3, 0.5, 0.7, 0.9, and 1.1 M were prepared and used to construct a GC standard curve (straight line; percentage concentration from GC vs. standard molar concentration). The samples were analyzed by GC and from the percentage concentrations given by the GC, the molar concentrations were determined against the standard curve and the recovery of 1,4-butanediol was calculated to be 0.9 ± 0.1 meq/g ®**1**.

Polymer-bound 4-trityloxybutanal (®1a). Resin ®**1** (11.71 g), was purged with argon in a 500 mL round bottom flask for 1 h and dry DMSO (75 mL) was added. In another 500 mL round bottom flask, pyr•SO_3 complex (24.70 g, 155.2 mmol) was purged with argon for 30 min and DMSO (100 mL) and Et_3N (100 mL) were added via syringe. After stirring for 15 min, the pyr•SO_3 solution was canulated into the suspension of ®**1** in DMSO and the mixture stirred for 3 h at room temperature. The reaction mixture was filtered, and the resin washed with dry DMSO (3 × 50 mL), THF (6 × 100 mL), and ether (3 × 100 mL) to give ®**1a**. IR (KBr) 1724 cm^{-1} (s).

Polymer-bound 7-trityloxy-3-hepten-2-one (®12). A mixture of ®**1a** (1.67 g) and 1-triphenylphosphoranylidene-2-propanone (2.67 g, 8.4 mmol) was purged with argon and refluxed in THF (30 mL) for 4 d. The polymer was then filtered and washed with THF (6 × 50 mL), dichloromethane (6 × 50 mL), and ether (3 × 50 mL) to give ®**12**. IR (KBr) 1672, 1625 cm^{-1} (s).

Polymer-bound 7-trityloxy-2-thiophenoxy-2-heptanone (®125). A mixture of ®**12** (0.41 g) and sodium methoxide (0.06 g, 1.1 mmol) was purged with argon. THF (25 mL) was added followed by thiophenol (3.44 g, 31.2 mmol) and the reaction was stirred for 3 d at room temperature. The mixture was filtered and washed (3 × 20 mL each) with THF, methanol, THF, and ether to give ®**125**. IR (KBr) 1712 cm^{-1} (s).

2-Oxa-4-thiophenoxy-7-heptyl formate (125). Resin-bound β-mercaptoketone ®**125** (0.42 g) was placed into a 50 mL round bottom flask and purged with argon for 30

min. Dry THF (10 mL) was added to the flask followed by formic acid (30 mL). The resulting mixture was stirred for 2 d to insure complete cleavage of the targeted compound and the formation of the formate ester. The reaction mixture was concentrated and dried under vacuum (0.5 torr) overnight and the residue were taken up in dry THF (5 mL). Resin was removed by filtration and washed with dry THF (6 × 5 mL). The filtrate was collected into a 50 mL pear shape flask and concentrated to approximately 0.5 mL. The residue solution was purified by preparative TLC (3:17::EtOAc:Hex, R_f = 0.40) to give **125** as a pale yellow oil (42.9 mg, 0.42 meq/g). ^{1}H NMR δ 1.51-1.78 (2H, m), 1.80-2.01 (2H, m), 2.13 (3H, s), 2.63 (1H, dd, J = 7.6, 17.4 Hz), 2.77 (1H, dd, J = 5.9, 17.4 Hz), 3.54-3.62 (1H, m), 4.16 (2H, t, J = 6.3 Hz), 7.24-7.45 (5H, m), 8.04 (1H, s); ^{13}C NMR δ 25.89, 30.57, 30.94, 43.25,48.97, 63.43, 127.41, 128.99, 132.55, 133.85, 160.95, 206.30; LR GC-MS (EI) *m/z* (relative intensity) 266 (38), 221 (3), 157 (12), 110 (100), 65 (25); HRMS (FAB) calcd for $C_{14}H_{18}O_3S$ 266.0977, found 266.0985.

Split-mix synthesis of polymer-bound 7-trityloxy-3-hepten-2-one (®12), 8-trityloxy-2,2-dimethyl-4-octen-3-one (®13), and 5-trityloxy-1-penten-1-yl phenyl ketone (®14). These compounds were prepared in parallel according to the procedure described above for **®12**. Resin **®1a** was placed into three separate flasks (1.67 g **®1a** in each flask) and THF (30 mL) and ylide were added [flask #1 containing **®1a** + **2** (R' = Me; 2.67 g, 8.4 mmol), flask #2 containing **®1a** + **3** (R' = ^{t}Bu; 3.0 g, 8.3 mmol), and flask #3 containing **®1a** + **4** (R' = Ph; 3.2 g, 8.4 mmol)] and the contents intermittently stirred (to reduce polymer breakage) for 4, 11, and 4 d, respectively (reactions monitored by FTIR). Each mixture was filtered and the polymer washed as described above (for **®12**) to give **®12** (flask #1), **®13** (flask #2), and **®14** (flask #3). The contents of these three flasks were then combined and thoroughly mixed to give an ≈1:1:1 mixture of **®12** + **®13** + **®14**.

Split-mix synthesis of polymer-bound β-mercaptoketone mixtures ®125 + ®135 + ®145, ®126 + ®136 + ®146, and ®127 + ®137 + ®147. Following the procedure described above for the preparation of **®125**, the **®12** + **®13** + **®14** mixture (1.0 g/flask), sodium methoxide (0.015 g, 0.3 mmol), thiol [9 meq/g resin: flask #4 containing the **®12** + **®13** + **®14** mixture + **5** (X = H; 0.99 g, 9.0 mmol), flask #5 containing the **®12** + **®13** + **®14** mixture + **6** (X = Me; 1.12 g, 9.0 mmol), and flask #6 containing the **®12** + **®13** + **®14** mixture + **7** (X = Cl; 1.30 g, 9.0 mmol)], and THF (4 mL) were stirred intermittently for 4 d (reactions monitored by FTIR). Each mixture was filtered and washed (3 × 20 mL each) with THF, methanol, THF, and ether to give **®125** + **®135** + **®145** (flask #4), **®126** + **®136** + **®146** (flask #5), and **®127** +

®137 + ®147 (flask #6). A portion of resin (100 mg) from each flask was combined to give library D (Mixture **III**).

Liberations of formate esters 125, 135, 145, 126, 136, 146, 127, 137, 147. The resin sub-library containing **®125 + ®135 + ®145** (flask #4; 0.81 g), **®126 + ®136 + ®146** (flask #5; 0.80 g), and **®127 + ®137 + ®147** (flask #6; 0.82 g) were placed into three separate 50 mL round-bottom flasks and purged with argon for 30 min. To each flask was added dry THF (10 mL) followed by formic acid (30 mL) and the resulting mixtures were stirred intermittently for 2 d. Each reaction mixture was then concentrated and dried under vacuum (0.5 torr) overnight. Each resin was washed with dry THF (6 × 5 mL), the filtrates collected into 50 mL pear shape flasks (separately!), and concentrated to approximately 0.5 mL. Each residue was eluted on a preparative TLC plate with 3:7::EtOAc:Hex giving six UV active bands. Each band was removed from the prep-TLC plate, extracted with THF, concentrated, and dried under vacuum overnight. The resulting 9 formate esters were fully characterized.

125[f] (0.116 mmol); spectral data given above.

135[f] (0.047 mmol); ^{1}H NMR δ 1.10 (9H, s), 1.49-1.74 (2H, m), 1.76-2.00 (2H, m), 2.70 (1H, dd, *J* = 7.5, 17.6 Hz), 2.83 (1H, dd, *J* = 5.8, 17.6 Hz), 3.68 (1H, m), 4.15 (2H, t, *J* = 6.4 Hz), 7.20-7.44 (4H, m), 8.03 (1H, s); ^{13}C NMR δ 26.02, 26.22, 26.34, 31.11, 42.43, 43.25, 63.56, 128.52, 128.99, 131.86, 134.63, 160.98, 213.44; LR GC-MS (EI) m/z 308 (14), 263 (2), 199 (7), 109 (16), 85 (8), 57 (100); HRMS (FAB) calcd for $C_{17}H_{24}O_3S$ 308.1446, found 308.1450.

145[f] (0.114 mmol); ^{1}H NMR δ 1.53–2.08 (4H, m), 3.15 (1H, dd, *J* = 8.1, 17.2 Hz), 3.33 (1H, dd, *J* = 5.1, 17.2 Hz), 3.8 (1H, m), 4.16 (2H, t, *J* = 6.3 Hz), 7.17-7.91 (10H, m), 8.01 (1H, s); ^{13}C NMR δ 25.52, 30.52, 43.33, 43.72, 63.00, 126.88, 127.52, 128.14, 128.53, 132.00, 132.79, 133.58, 136.23, 160.49, 197.37; LR GC-MS (EI) m/z 328 (7), 219 (14), 109 (12), 105 (100), 77 (50); HRMS (FAB) calcd for $C_{19}H_{20}O_3S$ 328.1133, found 328.1141.

126[f] (0.100 mmol); ^{1}H NMR δ 1.48-1.73 (2H, m), 1.75-1.99 (2H, m), 2.12 (3H, s), 2.33 (3H, s), 2.69 (1H, dd, *J* = 7.6, 17.3 Hz), 2.77 (1H, dd, *J* = 6.0, 17.3 Hz), 3.49 (1H, m), 4.16 (2H, t, *J* = 7.4 Hz), 7.09-7.33 (4H, m), 8.04 (1H, s); ^{13}C NMR δ 21.01, 25.96, 30.49, 30.94, 43.76, 49.06, 63.48, 129.77, 129.95, 133.37, 137.77, 160.89, 206.19; LR GC-MS (EI) m/z 252 (30), 235 (3), 129 (15), 124 (100), 91 (55), 71 (53); HRMS (FAB) calcd for $C_{15}H_{20}O_3S$ 280.1133, found 280.1154.

136[f] (0.029 mmol); ^{1}H NMR δ 1.12 (9H, s), 1.49-1.72 (2H, m), 1.77-1.99 (2H, m), 2.35 (3H, s), 2.69 (1H, dd, *J* = 7.5, 17.9 Hz), 2.84 (1H, dd, *J* = 5.5, 17.9 Hz), 3.61 (1H, m), 4.17 (2H, t, *J* = 6.4 Hz), 7.09-7.35 (4H, m), 8.05 (1H, s); ^{13}C NMR δ 21.50,

26.05, 26.26, 31.05, 42.48, 43.72, 63.62, 93.80, 129.77, 131.90, 132.72, 137.50, 160.95, 203.40; LR GC-MS (EI) m/z 322 (15), 199 (2), 124 (22), 91 (10), 57 (100); HRMS (FAB) calcd for $C_{18}H_{26}O_3S$ 322.1603, found 322.1615.

146[f] (0.088 mmol); ^{1}H NMR δ 1.55–2.06 (4H, m), 2.32 (3H, s), 3.12 (1H, dd, *J* = 8.2, 17.1 Hz), 3.31 (1H, dd, *J* = 5.2, 17.1 Hz), 3.71 (1H, m), 4.18 (2H, t, *J* = 6.3 Hz), 7.09-7.90 (9H, m), 8.02 (1H, s); ^{13}C NMR δ 20.55, 25.51, 25.62, 30.40, 43.73, 63.05, 127.52, 128.09, 129.29, 129.53, 132.72, 132.86, 136.26, 137.23, 160.37, 197.44; LR GC-MS (EI) m/z 314 (7), 191 (12), 124 (24), 105 (100), 91 (44), 77 (74), 51 (30); HRMS (FAB) calcd for $C_{20}H_{22}O_3S$ 342.1290, found 342.1301.

127[f] (0.105 mmol); ^{1}H NMR δ 1.50-1.75 (2H, m), 1.76-1.97 (2H, m), 2.14 (3H, s), 2.63 (1H, dd, *J* = 7.4, 17.5 Hz), 2.75 (1H, dd, *J* = 6.1, 17.5 Hz), 3.55 (1H, m), 4.16 (2H, t, *J* = 6.4 Hz), 7.23-7.37 (4H, m) 8.03 (1H, s); ^{13}C NMR δ 26.36, 30.94, 31.52, 44.15, 49.29, 63.76, 129.60, 133.40, 134.10, 134.25, 161.24, 206.50; LR GC-MS (EI) m/z 302 (21), 300 (70), 146 (40), 144 (100), 129 (6), 111 (56), 108 (55), 93 (20), 71 (34); HRMS (FAB) calcd for $C_{14}H_{17}ClO_3S$ 300.0587, found 300.0591.

137[f] (0.073 mmol); ^{1}H NMR δ 1.11 (9H, s), 1.49-1.74 (2H, m), 1.76-1.94 (2H, m), 2.68 (1H, dd, *J* = 7.4, 17.8 Hz), 2.82 (1H, dd, *J* = 5.8, 17.8 Hz), 3.65 (1H, m), 4.16 (2H, t, *J* = 6.4 Hz), 7.23-7.37 (4H, m), 8.03 (1H, s); ^{13}C NMR δ 25.47, 25.67, 25.69, 30.67, 41.75, 43.17, 43.70, 62.94, 128.63, 132.60, 132.72, 132.75, 160.41, 212.69; LR GC-MS (EI) m/z 344 (3), 342 (9), 199 (7), 143 (7), 108 (11), 85 (4), 57 (100); HRMS (FAB) calcd for $C_{17}H_{23}ClO_3S$ 342.1056, found 342.1066.

147[f] (0.083 mmol); ^{1}H NMR δ 1.62-2.08 (4H, m), 3.16 (1H, dd, *J* = 7.9, 17.4 Hz), 3.30 (1H, dd, *J* = 5.6, 17.4 Hz), 4.20 (2H, t, *J* = 6.0 Hz), 7.23-7.93 (9H, m), 8.03 (1H, s); ^{13}C NMR δ 26.02, 31.15, 44.07, 44.19, 43.42, 128.01, 128.68, 129.20, 132.67, 133.40, 133.60, 136.66, 160.94, 197.65; LR GC-MS (EI) m/z 448 (4), 446 (22), 191 (18), 144 (26), 105 (100), 77 (76); HRMS (FAB) calcd for $C_{19}H_{19}ClO_3S$ 362.0743, found 362.0761.

Single bead GC–MS analysis. Single bead samples were prepared by the following means. Polymer beads were picked up by touching the closed end of fine capillary (≈0.2 mm diameter) against the inside wall of the library container. The excess beads were knocked back into the container by tapping the capillary against the mouth of the container. The bead(s) remaining on the capillary was (were) checked under a microscope and, if more then one bead remained on the capillary, the tapping was repeated until only one bead remained. The closed end of the capillary was inserted into a glass melting point tube (≈1 mm diameter) and approximately 10 μL 3:1 formic acid/THF solution was added. The single bead samples were incubated overnight and the solution

was evaporated under vacuum (0.5 mm, 4 h). Benzene (2.0 μL) was added to each sample by micro syringe rinsing from the open end of the melting point tube down to the close end. The sample was taken up by micro syringe and injected into the GC–MS [GC-MS parameters: Finnigan Mat ITD ion trap detector (low resolution) connected to a Varian 3400 GC with a 30 m × 0.25 mm DB5 fused silica column; column initial temperature, 50°C; hold time, 3 min; temperature ramping rate, 30°C/min; column final temperature, 240°C].

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-9108231) for financial support. Fellowship support was obtained for C.C. through a DOW Polymer Science Fellowship.

References and Notes.

1 Chen, C.; Ahlberg Randall, L. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661-2.

2 Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-54.

3 Literature reviews: (a) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327. (b) Leznoff, C. C. *Chem. Soc. Rev.* **1974**, *3*, 65.

4 Literature reviews: (a) Fréchet, J. M. J. *Tetrahedron*, **1981**, *37*, 663-83. (b) Crowley, J. I.; Rapoport, H. *Acc. Chem. Res.*, **1976**, *9*, 135-44.

5 Literature review: L.A. Thompson, J.A. Ellman, *Chem. Rev.* **1996**, *96*, 555.

6 Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Prot. Res.* **1991**, *37*, 487-93.

7 (a) Frechet, J. M. J.; Nuyens, L. J. *Can. J. Chem.* **1976**, *54*, 926-34. (b) Fyles, T. M.; Leznoff, C. C.; Weatherston, J. *Can. J. Chem.* **1978**, *56*, 1031-41.

8 For an example of effective site isolation, see: Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 10061-2.

9 (a) See reference 7b. (b) Fyles, T. M.; Leznoff, C. C. *Can. J. Chem.* **1976**, *54*, 935-42.

10 While oxalyl chloride/Et_3N/DMSO conditions resulted in acid-catalyzed deprotection of the trityl moiety, sulfur trioxide pyridine complex gave very satisfactory results: Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505-7.

11 Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492-6.

12 Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*; W. H. Freeman and Co.: San Francisco, 1969, pp. 55.

13 After submission of the communication of these results, the use of GC to characterize the products of a combinatorial synthesis was reported: Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci, U.S.A.* **1993**, *90*, 10922-6.

14 For a recent example of this strategy, see: Kurth, M. J.; Ahlberg Randall, L.; Chen, C.; Melander, C.; Miller, R. B.; McAlister, K.; Reitz, G.; Kang, R.; Nakatsu, T.; Green, C. *J. Org. Chem.* **1994**, *59*, 5862-4

(*Received* 31 *July* 1996; *accepted* 13 *January* 1997)