Generating Diverse Skeletons of Small Molecules Combinatorially

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Supporting Online Material

1. Materials and methods

Materials. Commercially available reagents (*1*) were obtained from Aldrich Chemical Co. (Milwaukee, WI), Fluka Chemical Corp. (Milwaukee, WI), Bachem (Bubendorf, Switzerland), and MoscowMedChemLabs (Moscow, Russia) and used without further purification unless otherwise noted. All solvents were dispensed from a solvent purification system that passes solvents through packed columns (THF, Et_2O, CH_3CN, and CH_2Cl_2: dry neutral alumina; hexane, benzene, and toluene: dry neutral alumina and Q5 reactant; DMF: activated molecular sieves). Water was double distilled. Triethylamine, diisopropylethylamine, and 2,6-lutidine were distilled under nitrogen from CaH_2. Macrobeads **1** were prepared by Max Narovlyansky at Harvard's ICCB: Longwood as previously described (*2*).

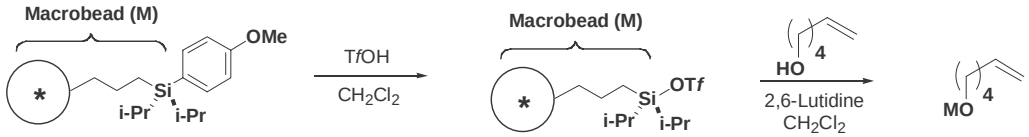
Solution phase reactions. All solution-phase reactions were performed in oven- or flame-dried glassware under positive argon pressure unless otherwise indicated. Reactions were monitored by analytical thin-layer chromatography performed using indicated solvent on E. Merck silica gel 60 F_{254} plates (0.25mm). Compounds were visualized with a UV lamp (λ_{254}) and/or staining with cerium ammonium molybdate.

Solid phase reactions. Solid-phase reaction were performed in oven- or flame-dried glassware (I-Chem vials or Wheaton vials, fitted with Teflon-coated caps) with gentle mixing provided by Thermoline Vari-Mix shaker or a Vortex Genie-2 vortexer (VWR 58815-178, setting V1-V2) fitted with a 60 microtube insert. After reactions were completed, resin was isolated by filtration in 10 ml Amersham columns on a Vac-Man laboratory Vacuum Manifold (Promega A7231) fitted with nylon 3-way stopcocks (Biorad 732-8107). Resin was then washed as indicated and solvent was removed *in vacuo*. All compounds were cleaved from the solid-support resin using the following standard procedure: To resin in a polypropylene eppendorf tube at rt under ambient was added a freshly prepared solution of 5% HF/Pyr in THF (10-100 μL per mg of resin). The resulting mixture was then agitated at rt for 2 h. The reaction was then quenched with the addition of neat

methoxytrimethylsilane or ethoxytrimethylsilane (2/1 v/v relative to 5% HF/Pyr in THF solution). The resulting mixture was then agitated at rt for 10 minutes, and the solution was then transferred to a Wheaton vial. Resin was washed twice with THF. The combined reaction solution and wash solutions were concentrated *in vacuo* and the cleaved product was then analyzed as indicated.

Purification and analysis. Flash chromatography was performed using the indicated solvent on E. Merck silica gel 60. All yields refer to compounds cleaved from 75-85 mg of macrobeads and purified by flash chromatography. Infrared spectra were recorded as a thin film on NaCl plates on a Nicolet 5PC FT-IR spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded on Varian Unity/Inova500 (500 MHz) spectrometer. ^{13}C NMR spectra were recorded on Varian Unity/Inova400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and referenced to $CDCl_3$. (^1H-NMR, 7.26; ^{13}C-NMR, 77.0, center line). Nanotube solid-phase MAS ^1HNMR were obtained in CD_2Cl_2 on a Varian Inova 600 instrument fitted with a magic-angle spinning nanoprobe. Reverse-phase LCMS data was obtained with a Gilson/Finnigan LCMS system. LCMS chromatography was performed on a SymmetryShield™ RP_8, 3.5 uM, 4.6 x 100mm column (Waters Corporation, Milford, MA, Batch #111) using a flow rate of 1 ml/min and a 10 min gradient of 20-80% CH_3CN in water, constant 0.1% formic acid, with UV detection at 214 and 280 nm. MS analysis was performed with a Finnigan Aqa MS detector with ES+ ionization. Chiral LC was performed on a Gilson LC system using a Chiralpak® AS™ 250 x 4.6 mm column (Amylose tris-[(*S*)-α-methylbenzyl carbamate] coated on 10 μm silica-gel substrate, Chiral Technologies Inc., Exton, PA) using a flow rate of 1 ml/min and an eluent of 4 % IPA in hexanes. High resolution mass spectra were obtained at the mass spectrometry facility at Harvard University using a Micromass LCT (ES) spectrometer.

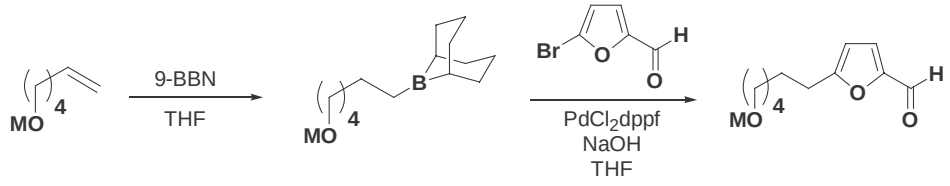
Synthetic conditions.



1 **2**

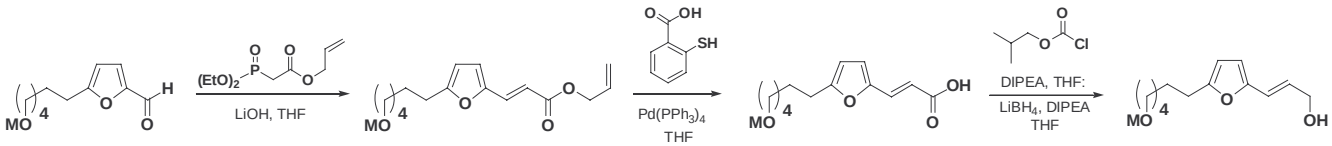
Macrobead-bound-5-hexen-1-ol (2). 3-[Diisopropyl(*p*-methoxyphenyl)silyl]propyl functionalized macrobeads **1** (400 mg, estimated loading ~1.3 meq Si/g, ~0.52 mmol) in a 20 mL polypropylene tube at rt under Ar were allowed to swell in CH_2Cl_2 (15 ml) for 10 min. The colorless beads were then filtered and again washed with CH_2Cl_2 (15 mL x 10 min.), and then resuspended in a 2.5% (v/v) solution of TMSCl in CH_2Cl_2 (15 mL) for 30 min. The beads were again filtered and washed thrice with CH_2Cl_2 (5 min each) and then suspended in a 3% (v/v) solution of trifluoromethanesulfonic acid in CH_2Cl_2 (9.2 mL, 3.12 mmol) for 20 min during which the reaction tube was shaken periodically and the beads turned orange. After filtration, the orange-colored beads were again thrice washed with CH_2Cl_2 and then resuspended in a minimum volume of CH_2Cl_2 (1 mL). Freshly distilled 2,6-lutidine was then added (485 uL, 4.2 mmol) resulting in bead discoloration followed by 5-hexen-1-ol (500 uL, 4.2 mmol). The resulting colorless reaction mixture was then shaken manually and let stand at rt for 12 h. The beads were then filtered, washed with CH_2Cl_2 (5 x 15 mL x 5 min. each), and the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield resin **2** (372 mg) loaded with 5-hexen-1-ol. MAS ^1H

NMR (600 MHz, CD_2Cl_2) selected peaks δ 5.81 (br s), 5.00 (d, *J* = 17.0 Hz), 4.93 (d, *J* = 8 Hz), 3.65 (br s).



2 **3**

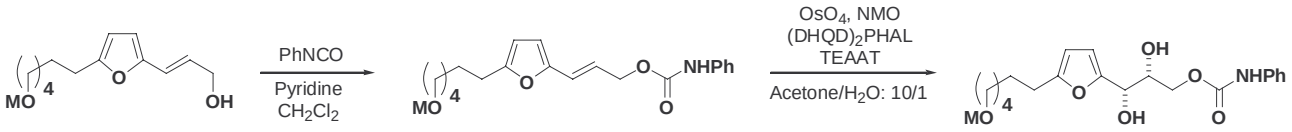
Macrobead-bound-5-(6-hydroxy-hexyl)-furan-2-carbaldehyde (3). Colorless beads **1** (500 mg, max theoretical loading 1.3 meq/g, 0.65 mmol) were washed with THF (2 x 10 mL x 10 min each) at rt and then resuspended in 15 mL THF. A 0.5M solution of 9-BBN in THF (10 mL, 5.0 mmol) was then added and the resulting mixture was manually agitated and let stand at rt for 5 h. The reaction solution was then removed via cannula and the colorless resin was washed thoroughly with THF (5 x 15 mL x 10 min each). To the resin was then added solid $PdCl_2$dppf (6.1 mg, 0.0075 mmol), 5-bromofuraldehyde (438 mg, 2.5 mmol) *via* cannula as a solution in THF (6.25 mL), and a 1M aq. solution of NaOH (1.25 mL, 1.25 mmol). The resulting orange reaction mixture was sealed under a cloud of Ar and heated at 65 ^oC with periodic manual agitation for 18 h (reaction mixture turned dark brown). The yellow/orange resin was then isolated by filtration and washed as follows, 4 x (5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 30 min), 5 x THF, THF x 30 min, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 30 min, and then the solvent was removed *in vacuo* to yield 535 mg of yellow/orange product resin **3**. 5 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{3_{M=H}}$ with LCMS purity >85% (λ_{214}), t_R 4.82 min. 75 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, hexane/EtOAc:1/2) to afford alcohol $\mathbf{3_{M=H}}$ as a yellow oil (10.0 mg, 0.679 meq./g, 58% over two steps based on estimated meq. Si/g). R_f = 0.27 (hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3426, 2932, 2859, 1674, 1518, 1399, 1024; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.23 (d, *J* = 4.0 Hz, 1H), 3.64 (t, *J* = 7.0 Hz, 2H), 2.73 (t, *J* = 7.5Hz, 2H), 1.72 (m, 2H), 1.57 (m, 2H), 1.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 163.9, 151.8, 123.6, 108.7, 62.8, 32.5, 28.9, 28.3, 27.5, 25.3; HRMS (ES^+) calculated for $C_{11}H_{16}O_3$ $(M+H)^+$: 197.1177, Found: 197.1177.



3 **4**

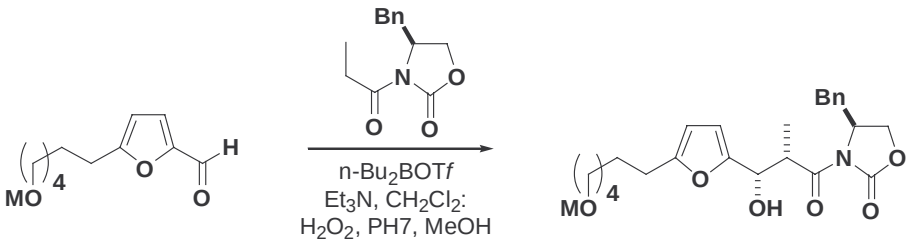
Macrobead-bound-*trans*-3-[5-(6-hydroxy-hexyl)-furan-2-yl]-prop-2-en-1-ol (4). To a stirred solution of allyldiethylphosphonoacetate (0.664 mL, 3.15 mmol) in THF (10.5 mL) at rt was added solid LiOH (151 mg. 6.29 mmol). The resulting mixture was stirred vigorously at rt for 4 h. The stir bar was then removed and resin **3** (315 mg, 0.679 meq/g, 0.214 mmol) was added. The resulting reaction mixture was sealed under a cloud of Ar and tumbled at rt for 25 h. Resin was then isolated by filtration and washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/dilute aq. NH_4Cl (sat. aq. NH_4Cl/H_2O : 1/2) : 1/1 x 1 h. 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 5 x THF, THF x 30 min, 5 x CH_2Cl_2, CH_2Cl_2 x 20 min, 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 10

min. Solvent was then removed *in vacuo* to yield 336 mg of yellow-orange resin. This resin (331 mg) was then added to a mixture of $Pd(PPh_3)_4$ (382 mg, 0.331 mmol) in THF (7.2 mL). To this mixture was then added solid thiosalicylic acid (510 mg, 3.31 mmol) and the resulting dark red mixture was sealed under a cloud of Ar, covered with aluminum foil, and tumbled at rt for 24 h. Resin was then isolated by filtration and washed as follows: 5 x (5 x THF, THF x 1 h), 5 x CH_2Cl_2, CH_2Cl_2 x 20 min, 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 10 min . Solvent was then removed *in vacuo* to yield 322 mg of yellow-orange resin. This resin (317 mg) was then washed twice with anhydrous THF and then resuspended in THF (29 mL). Diisopropylethylamine (2.75 mL, 15.8 mmol) was then added and the resulting mixture was cooled to 0 ^oC. To this mixture was added 4-methylmorpholine (0.035 mL, 0.317 mmol) and isobutylchloroformate (0.411 mL, 3.17 mmol). The resulting mixture was maintained at 0 ^oC for 2 h, with periodic manual agitation every 30 minutes. The reaction solution was removed via cannula and the resin was washed with 8.6% (v/v) diisopropylethylamine in THF (3 x 15 mL x 5 min each) at 0 ^oC. Resin was then resuspended in a solution of 8.6% (v/v) diisopropylethylamine in THF (40 mL) at 0 ^oC, and to this mixture was added solid $LiBH_4$ (21 mg, 0.95 mmol) . The resulting mixture was sealed under a cloud of Ar and tumbled at 4 ^oC for 24 h. The resin was then isolated by filtration at rt and washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/dilute aq. NH_4Cl (sat. aq. NH_4Cl/H_2O : 1/2) : 1/1 x 1 h. 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 30 min and then solvent was removed *in vacuo* to yield light yellow product resin **4** (320 mg). 5 mg of this product resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude diol $\mathbf{4_{M=H}}$ with LCMS purity 68% (λ_{214}), t_R 5.80 min. 75 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, hexane/EtOAc:1/2) to afford diol $\mathbf{4_{M=H}}$ as a colorless solid [8.1 mg, 0.482 meq./g, Theoretical yield 0.637 meq./g, 76% from **3**, E/Z : >20/1 (^{1}H NMR)]. R_f = 0.24 hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3349, 2928, 2857, 1661, 1588, 1532, 1463, 1380, 1254; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 16 Hz, 1 Hz, 1H), 6.21 (dt, *J* = 16 Hz, 6 Hz, 1H), 6.13 (d, *J* = 3.5 Hz, 1H), 5.95 (d, *J* = 3.5 Hz, 1H), 4.27 (d, *J* = 5.5 Hz, 2H), 3.64 (t, *J* = 7 Hz, 2H) 2.61 (t, *J* = 7.5Hz, 2H), 1.66 (m, 2H), 1.58 (m, 2H), 1.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 150.6, 125.5, 119.8, 109.1, 106.6, 63.5, 62.9, 32.6, 28.9, 28.0, 27.9, 25.4; HRMS (ES^+) calculated for $C_{13}H_{20}O_3$ $(M-H)^-$: 223.1334, Found: 223.1333.



Macrobead-bound-(2*R*,3*S*)-phenyl-carbamic acid 2,3-dihydroxy-3-[5-(6-hydroxy-hexyl)-furan-2-yl]-propyl ester (5). Light yellow beads **4** (220 mg, 0.482 meq./g, 0.106 mmol) were washed with CH_2Cl_2 (2 x 10 mL x 10 min each) at rt and then resuspended in CH_2Cl_2 (11 mL) . To this mixture at rt was added pyridine (0.356 mL, 4.41 mmol) and phenyl isocyanate (0.239 mL, 2.20 mmol). The resulting mixture was sealed under a cloud of Ar and tumbled at rt for 24 h. Resin was then isolated by filtration and washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/dil. aq. $NaHCO_3$ (sat. aq. $NaHCO_3/H_2O$: 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/dilute aq. NH_4Cl (sat. aq. NH_4Cl/H_2O : 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, and then residual solvent was removed *in vacuo* to yield 245 mg of yellow resin. A separate vessel was then charged with $(DHQD)_2PHAL$ (10.6 mg,

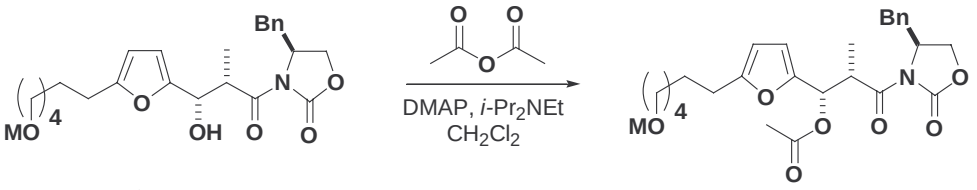
0.0135 mmol), tetraethylammonium acetate tetrahydrate (113 mg, 0.433 mmol) and 4-methylmorpholine *N*-oxide (76.2 mg, 0.650 mmol). This solid mixture was dissolved in a solution of acetone/water : 10/1 at rt under ambient and to this clear, slightly yellow-tinted solution was added OsO_4 as a 2.5 wt% solution in *tert*-butyl alcohol (0.060 ml, 0.00542 mmol). The resulting clear, yellow-tinted solution was let stand at rt with periodic manual agitation for 15 min and then cooled to 0 °C. The resin (217 mg) was then added and the resulting mixture was sealed and tumbled at 4 °C for 48 h. The reaction solution was then removed *via* syringe and quenched with excess sodium metabisulfite, and the resin was washed with acetone/water : 10/1 (1 x 5 mL x 10 min, 1 x 15 mL x 30 min) at 4 °C, and then isolated by filtration and washed as follows: 5 x THF, 10% pyridine in THF x 1 h, 5 x THF, 10% pyridine in THF x 12 h, 5 x THF, 10% pyridine in THF x 4 h, 5 x THF, 10% pyridine in THF x 4 h, 5 x THF, 5 x H_2O, 5 x THF, THF/dil. aq. $NaHCO_3$ (sat. aq. $NaHCO_3/H_2O$: 1/2) : 1/1 x 45 min, 5 x THF, 5 x H_2O, 5 x THF, THF/dilute aq. NH_4Cl (sat. aq. NH_4Cl/H_2O : 1/2) : 1/1 x 45 min, 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 5 x THF, THF x 45 min, 5 x DMF, DMF x 45 min, 5 x THF, THF x 45 min, 5 x anh. THF, anh. THF x 30 min, and then solvent was removed under Ar flow followed by residual solvent removal *in vacuo*. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude triol $\mathbf{5_{M=H}}$ with LCMS purity >90 % (λ_{214}), t_R 5.92 min. 75.2 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, EtOAc/MeOH: 100/0 → 90/10) to afford triol $\mathbf{5_{M=H}}$ as a yellow oil [8.3 mg, 0.292 meq./g, Theoretical yield 0.449 meq./g, 65% from **4**. The enantioselectivity obtained in this reaction was determined after converting **5** → **8** (*vide infra*). R_f = 0.33 (EtOAc/MeOH : 99/1); FTIR (film, cm^{-1}) 3322, 2932, 2858, 1711, 1601, 1547, 1501, 1445, 1315, 1224, 1055; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 4H), 7.07 (t, *J* = 7 Hz, 1H), 6.96 (br s, 1H), 6.27 (d, *J* = 3 Hz, 1H), 5.94 (d, *J* = 3 Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.27 (dd, *J* = 11.5, 3.5 Hz, 1H), 4.22-4.13 (m, 2H), 3.62 (t, *J* = 6.5 Hz, 2H), 3.26 (br s, 1H), 2.97 (br s, 1H), 2.60 (t, *J* = 7 Hz, 2H), 1.63 (m, 2H), 1.55 (m, 2H), 1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 153.7, 150.8, 137.5, 129.1, 123.7, 118.7, 108.9, 105.7, 72.0, 68.0, 66.0, 62.8, 32.4, 28.7, 27.8, 27.7, 25.3; HRMS (ES^+) calculated for $C_{20}H_{27}NO_6$ $(M+Na)^+$: 400.1736, Found: 400.1737.



3 **6**

Macrobead-bound-(4*S*)-4-benzyl-3-{(3*S*,2*S*)-3-hydroxy-3-[5-(6-hydroxy-hexyl)-furan-2-yl]-2-methyl-propionyl}-oxazolidin-2-one (6). Yellow-orange beads **3** (365 mg, 0.679 meq./ g, 0.248 mmol) were washed with CH_2Cl_2 (2 x 15 mL x 10 min each) at rt, and then cooled to –78 °C. In a separate vessel, to a stirred solution of (*S*)-(+)-4-benzyl-3-propionyl-2-oxazolidinone (426 mg, 1.83 mmol) in CH_2Cl_2 (7.3 mL) at 0 °C was added a 1M solution of dibutylboron triflate in CH_2Cl_2 (1.92 mL, 1.92 mmol, *nBu_2BOTf solution was obtained from Aldrich chemical company and stored at –26°C upon delivery*. ***Best results were obtained when this reagent was used within 2 weeks of shipping date***) followed by triethylamine (0.305 mL, 2.19 mmol). The resulting enolate solution was cooled to –78 °C and then transferred rapidly *via* cannula to the vessel containing **3**. The

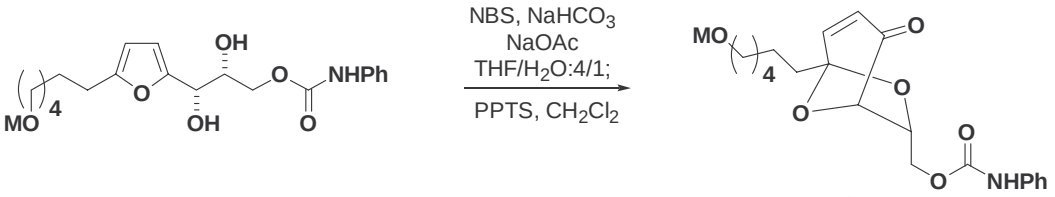
resulting mixture was sealed under a cloud of Ar and maintained at –78 °C for 48 h, -26 °C for 24 h, and 0 °C for 1 h (with periodic manual agitation about once every 8 h). The reaction was then quenched with the addition of pH7 phosphate buffer (7 mL), MeOH (7 mL), and 30% aq. H_2O_2 (4.7 mL), and the resulting mixture was tumbled at 4 °C for 12 h. Resin was then isolated by filtration and washed as follows: 5 x CH_2Cl_2, 5 x DMF, 5 x THF, 5 x CH_2Cl_2, CH_2Cl_2 x 1 h, 5 x DMF, DMF x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 30 min, and residual solvent was removed *in vacuo* to yield **6** as light yellow beads (431 mg). 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude diol $\mathbf{6_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 7.74 min. 75.2 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford diol $\mathbf{6_{M=H}}$ as a yellow oil [18.2 mg, 0.0424 mmol, 0.563 meq./g, Theoretical yield 0.586 meq./g, 96% from **3**, *dr* > 20:1 (^{1}H NMR)]. R_f = 0.30 hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3442, 2933, 2859, 1781, 1696, 1454, 1387, 1210, 1108, 1012; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 3H), 7.19 (app d, *J* = 6.5 Hz, 2H), 6.17 (d, *J* = 3 Hz, 1H), 5.90 (d, *J* = 3 Hz, 1H), 5.01 (m, 1H), 4.62 (m, 1H), 4.16 (m, 3H), 3.62 (t, *J* = 6 Hz, 2H), 3.24 (dd, *J* = 13 Hz, 3 Hz, 1H), 2.99 (br d, *J* = 4 Hz, 1H), 2.78 (dd, *J* = 13 Hz, 9 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.62 (m, 2H), 1.56 (m, 2H), 1.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 156.0, 152.8, 152.1, 135.0, 129.4, 128.9, 127.4, 107.3, 105.3, 68.7, 66.2, 62.8, 55.2, 42.5, 37.8, 32.5, 28.7, 27.8 (2 carbons), 25.3, 12.2; HRMS (ES$^+$) calculated for $C_{24}H_{31}NO_6$ $(M+NH_4)^+$: 447.2495, Found: 447.2497.



6 **7**

Macrobead-bound-(4*S*)-4-benzyl-3-{(3*S*,2*S*)-3-acetoxy-3-[5-(6-hydroxy-hexyl)-furan-2-yl]-2-methyl-propionyl}-oxazolidin-2-one (7). Light yellow beads **6** (0.180 g, 0.563 meq./g, 0.101 mmol) were washed with CH_2Cl_2 (2 x 9 mL x 5 min each) at rt and then resuspended in 9 mL CH_2Cl_2. To this mixture at rt was added diisopropylethylamine (0.627 mL, 3.6 mmol), DMAP (22 mg, 0.18 mmol), and acetic anhydride (0.170 mL, 1.8 mmol). The resulting mixture was sealed under a cloud of Ar and tumbled at rt for 28 h. Resin was then isolated by filtration and washed as follows: 5 x CH_2Cl_2, 5 x THF, 5 x CH_2Cl_2, CH_2Cl_2 x 45 min, 5 x THF, THF x 45 min, 5 x CH_2Cl_2, CH_2Cl_2 x 45 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 20 min. Solvent was then removed *in vacuo* to yield **13** as light yellow beads. 5.0 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{7_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 8.83 min. 75.2 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford alcohol $\mathbf{7_{M=H}}$ as a yellow oil [17.1 mg, 0.0363 mmol, 0.482 meq./g, Theoretical yield 0.550 meq./g, 88% from **6**). R_f = 0.17 hexane/EtOAc:1/1); FTIR (film, cm^{-1}) 3545, 2933, 2859, 1782, 1744, 1700, 1455, 1387, 1225, 1108, 1016; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 3H), 7.18 (d, *J* = 7 Hz, 2H), 6.22 (d, *J* = 3.5 Hz, 1H), 6.14 (d, *J* = 7 Hz, 1H), 5.89 (d, *J* = 3 Hz, 1H), 4.51 (m, 2H), 4.13 (m, 2H), 3.62 (t, *J* = 6 Hz, 2H), 3.23 (dd, *J* = 13, 3 Hz, 1H), 2.75 (dd, *J* = 13, 9.5 Hz, 1H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.09 (s, 3H), 1.60 (m, 2H), 1.56 (m, 2H), 1.39-1.30 (m, 4H), 1.33 (d, *J* = 7 Hz,

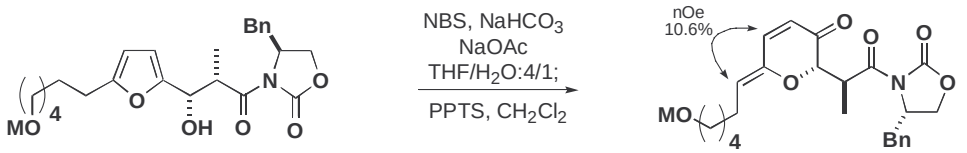
3H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.4, 170.1, 156.6, 153.1, 149.1, 135.1, 129.4, 128.9, 127.4, 109.6, 105.5, 69.2, 66.2, 62.8, 55.4, 40.8, 37.8, 32.5, 28.8, 27.8, 27.7, 25.3, 21.0, 13.3; HRMS (ES^+) calculated for $C_{26}H_{33}NO_7$ $(M+Na)^+$: 494.2155, Found: 494.2169.



5 **8**

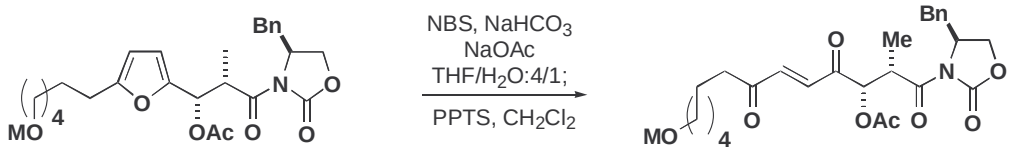
Macrobead-bound-phenyl-carbamic acid (1*S*,5*S*,7*R*)-5-(6-hydroxy-hexyl)-2-oxo-6,8-dioxabicyclo[3.2.1]-oct-3-en-7-ylmethyl ester (8). To a mixture of light yellow beads **5** (0.090 g, 0.292 meq./g, 0.026 mmol) in THF/water : 4/1 at rt under ambient was added $NaHCO_3$ (227 mg, 2.70 mmol), NaOAc (111 mg, 1.35 mmol), and *N*-bromosuccinimide (160 mg, 0.90 mmol). The resulting mixture was sealed, wrapped in foil, and tumbled at rt for 1 h. Resin was then isolated by filtration and washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/water : 3/1 x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 30 min, and then transferred to a separate vessel containing a 0.00075M solution of pyridinium *p*-toluenesulfonate in CH_2Cl_2 (20 mL). The resulting mixture was sealed under a cloud of argon and maintained at 40-45 ^oC (oil bath) for 20 h. Resin was then isolated by filtration and washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/dil. aq. $NaHCO_3$ (sat. aq. $NaHCO_3/H_2O$: 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/dilute aq. NH_4Cl (sat. aq. NH_4Cl/H_2O : 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 30 min. Solvent was then removed *in vacuo* to yield **8** as light yellow beads. 5.4 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{8_{M=H}}$ with LCMS purity 64%, t_R 7.04 min (an impurity at t_R=8.20 min which was ^{1}H NMR-silent and had an MS isotope pattern consistent with an osmium-containing substance was not included in purity calculation for this product; for additional purity information, see ^{1}H NMR of crude and purified product **8**). 80.8 mg of the product resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford alcohol $\mathbf{8_{M=H}}$ as a yellow oil [2.9 mg, 0.00773 mmol, 0.0.096 meq./g, Theoretical yield 0.0.292 meq./g, 33% from **5**). R_f = 0.31 (hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3323, 2932, 2859, 1705, 1599, 1537, 1491, 1445, 1400, 1309, 1220, 1075; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.26 (m, 4H), 7.08 (t, *J* = 7 Hz, 1H), 7.02 (d, *J* = 10 Hz, 1H), 6.82 (br m, 1H), 6.08 (dd, *J* = 10 Hz, 1 Hz, 1H), 4.59 (app d, *J* = 6.5 Hz, 1H), 4.30-4.26 (m, 2H), 4.06 (app q, *J* = 5 Hz, 1H), 3.64 (t, *J* = 6 Hz, 2H), 2.02-1.91 (m, 2H), 1.60-1.48 (m, 4H), 1.44-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 150.7 (2C), 132.1, 129.1, 126.5, 123.7, 120.2, 106.0, 94.4, 82.3, 73.2, 62.8, 34.5, 32.4, 29.1, 25.4, 22.3; HRMS (ES^+) calculated for $C_{20}H_{25}NO_6$ $(M+Na)^+$: 398.1580, Found: 398.1570. To determine the enantioselectivity achieved in the asymmetric dihydroxylation reaction (**4'** → **5**), this reaction was repeated using the pseudoenantiomeric ligand $(DHQ)_2PHAL$, and the enantiomeric diol was subjected to the same conditions described above. A ~1/1 mixture of the two purified, enantiomeric bicyclic ketals was then prepared, and separation was achieved on a Chiralpak® AS™ 250 x 4.6 mm column (Amylose tris-[(*S*)-α-methylbenzyl carbamate] coated on 10 μm silica-gel substrate, Chiral Technologies Inc., Exton, PA) using a flow rate of 1 ml/min and an eluent of 4% IPA in hexanes [t_R(**8**) = 3.13 min., t_R(enantiomeric **8**) = 4.09 min). Using this LC method, the enantiomeric ratio achieved in the transformation of **4'** → **5** was determined to be

major:minor 83:17 (66% ee), and the stereochemistry of the major isomer was assigned using the Sharpless mnemonic.



6 **9**

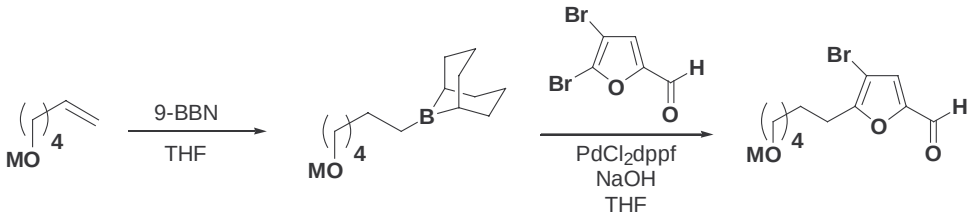
Macrobead-bound-(4*S*)-4-benzyl-3-{((2*S*)-2-[(2*S*)-6-(6-hydroxy-hexylidene)-3-oxo-3,6-dihydro-2*H*-pyran-2-yl]-propionyl}-oxazolidin-2-one (9). Light yellow beads **6** (0.090 g, 0.563 meq./g, 0.051 mmol) were treated with the same reaction conditions and washing protocols described above for the transformation of **5** → **8**. Solvent was then removed *in vacuo* to yield **9** as light yellow beads. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{9_{M=H}}$ with LCMS purity 86% (λ_{214}), t_R 8.15 min. 84.6 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford alcohol $\mathbf{9_{M=H}}$ as a yellow oil [7.2 mg, 0.0168 mmol, 0.199 meq./g, Theoretical yield 0.564 meq./g, 35% from **6**). R_f = 0.24 (hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3432, 2932, 2859, 1780, 1695, 1455, 1391, 1354, 1213, 1112, 1051; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 3H), 7.21 (app d, *J* = 7 Hz, 2H), 6.93 (d, *J* = 10 Hz, 1H), 5.94 (d, *J* = 10.5 Hz, 1H), 5.22 (t, *J* = 8 Hz, 1H), 4.77-4.70 (m, 1H), 4.73 (d, *J* = 8.5 Hz, 1H), 4.32-4.26 (m, 2H), 4.18 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 3.28 (dd, *J* = 13 Hz, 3.5 Hz, 1H), 2.81 (dd, *J* = 13 Hz, 10 Hz, 1H), 2.32-2.26 (m, 2H), 1.62-1.40 (m, 6H), 1.41 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 173.9, 153.3, 146.9, 141.9, 135.2, 129.4, 128.9, 127.3, 122.1, 121.6, 81.0, 66.3, 62.8, 55.5, 39.8, 38.0, 32.5, 28.7, 27.5, 25.5, 13.7; HRMS (ES^+) calculated for $C_{24}H_{29}NO_6$ $(M+H)^+$: 428.2073, Found: 428.2061.



7 **10**

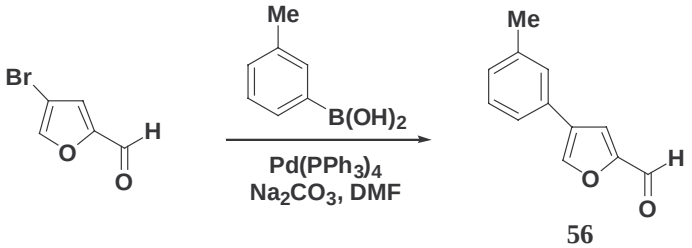
Macrobead-bound-1-((4*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-(2*S*,3*S*)-3-acetoxy-13-hydroxy-2-methyl-tridec-5-ene-1,4,7-trione (10). Light yellow beads **7** (0.090 g, 0.482 meq./g, 0.043 mmol) were treated with the same reaction conditions and washing protocols described above for the transformation of **5** → **8**. Solvent was then removed *in vacuo* to yield **10** as light yellow beads. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{10_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 8.12 min. 83.8 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford alcohol $\mathbf{10_{M=H}}$ as a yellow oil [15.8 mg, 0.0324 mmol, 0.387 meq./g, Theoretical yield 0.478 meq./g, 81% from **7**). R_f = 0.23 (hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3539, 2934, 2860, 1779, 1746, 1691, 1454, 1390, 1220, 1108, 1047; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 3H), 7.19 (app d, *J* = 6 Hz, 2H), 7.16 (d, *J* = 15.5 Hz, 1H), 7.03 (d, *J* = 15.5 Hz, 1H), 5.73 (d, *J* = 5 Hz, 1H), 4.67-4.61 (m, 1H), 4.33-4.27 (m, 2H), 4.21 (dd, *J* = 9 Hz, 2.5 Hz, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.24 (dd, *J* = 13 Hz, 3 Hz, 1H), 2.79 (dd, *J* = 13 Hz, 10 Hz, 1H), 2.66 (t, *J* = 7 Hz, 2H), 2.18 (s, 3H), 1.66 (m, 2H), 1.57 (m, 2H),

1.42-1.32 (m, 4H), 1.25 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 194.7, 172.7, 170.2, 153.3, 137.8, 134.9, 132.1, 129.4, 129.0, 127.4, 76.9, 66.5, 62.8, 55.4, 41.8, 39.5, 37.8, 32.5, 28.8, 25.4, 23.5, 20.6, 12.0; HRMS (ES^+) calculated for $C_{26}H_{33}NO_8$ $(M+H)^+$: 488.2284, Found: 488.2275.



2 **11**

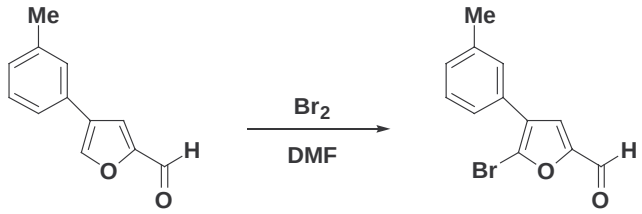
Macrobead-bound-4-Bromo-5-(6-hydroxy-hexyl)-furan-2-carbaldehyde (11) Colorless beads **2** (500 mg) were washed with THF (2 x 10 mL x 10 min each) at rt and then resuspended in 15 mL THF. A 0.5M solution of 9-BBN in THF (10 mL, 5.0 mmol) was then added and the resulting mixture was manually agitated and let stand at rt for 5 h. The reaction solution was then removed via cannula and the colorless resin was washed thoroughly with THF (5 x 15 mL x 10 min each). To the resin was then added solid $PdCl_2$dppf (10.2 mg, 0.0125 mmol), 4,5-dibromo-2-furaldehyde (635 mg, 2.5 mmol) *via* cannula as a solution in THF (6.25 mL), and a 1M aq. solution of NaOH (1.25 mL, 1.25 mmol). The resulting orange reaction mixture was sealed under a cloud of Ar and heated at 65 ^oC with periodic manual agitation for 18 h (reaction mixture turned dark brown). The dark orange resin was then isolated by filtration and washed as follows, 4 x (5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 30 min), 5 x THF, THF x 30 min, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 30 min, and then the solvent was removed *in vacuo* to yield 525 mg of dark orange product resin **11**. 5 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{11_{M=H}}$ with LCMS purity 88 % (λ_{214}), t_R 6.40 min. 75.4 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, hexane/EtOAc:1/2) to afford alcohol $\mathbf{11_{M=H}}$ as a yellow oil (3.9 mg, 0.188 meq./g, 19% over two steps based on estimated meq. Si/g). R_f = 0.26 (hexanes/EtOAc:1/1); FTIR (film, cm^{-1}) 3401, 2932, 2858, 1683, 1521, 1462, 1393, 1285, 1119; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.19 (s, 1H), 3.64 (t, *J* = 7.0 Hz, 2H), 2.76 (t, *J* = 7.5 Hz, 2H), 1.73 (m, 2H), 1.57 (m, 2H), 1.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 160.3, 150.9, 124.3, 99.3, 62.8, 32.5, 28.8, 27.2, 26.5, 25.3; HRMS (ES^+) calculated for $C_{11}H_{15}BrO_3$ $(M+H)^+$: 275.0283, Found: 275.0282.



56

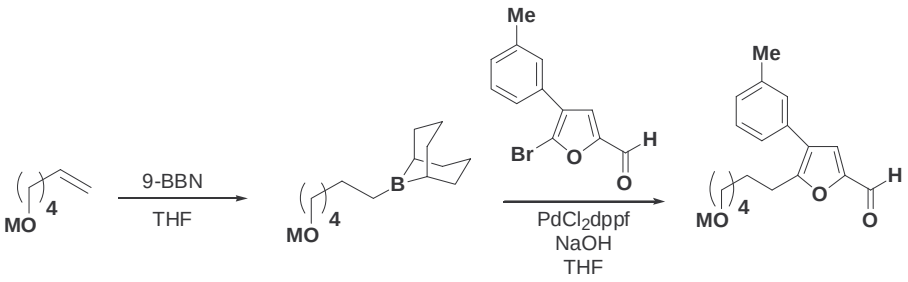
4-*m*-Tolyl-furan-2-carbaldehyde (**56**) To a stirred mixture of 4-bromo-2-furaldehyde (ABCR, 5.070 g, 29.0 mmol) and $Pd(PPh_3)_4$ (0.869 mmol, 1.004 g) in DMF (132 mL) at rt under Ar was added sodium carbonate (72.4 mmol, 7.68g) as a solution in a minimum amount of water (20 mL), followed by 3-methylbenzeneboronic acid (30.4 mmol, 4.14 g). The resulting light yellow reaction

mixture was fitted with a reflux condensor and heated to 105-110 ^{o}C with vigorous stirring for 22.5 h (reaction mixture became very dark as reaction progressed). The dark brown reaction mixture was then cooled to rt, filtered over a glass frit, diluted with water (100 mL) and Et_2O (150 mL) and transferred to a separatory funnel. The layers were then separated and the aqueous/DMF layer was extracted with Et_2O (3 x 100 mL). The combined organic fractions were washed with water (60 mL), brine/water : 1/1 (60 mL), and brine (60 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; hexanes/ethyl acetate : 50/1 → 30/1, column repeated on fractions containing Pd-discoloration) afforded the desired biaryl product **56** as a yellow/orange oil (4.5 g, 24.2 mmol, 83%). R_f = 0.27 (hexanes/EtOAc:20/1 x 3 cycles); FTIR (film, cm^{-1}) 3131, 3027, 2920, 2827, 1681, 1613, 1518, 1478, 1349, 1148; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.94 (s, 1H), 7.51 (d, *J* = 1 Hz, 1H), 7.31 (m, 3H), 7.16 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 153.5, 143.7, 138.8, 130.3, 129.4 ,129.0, 128.9, 126.7, 123.0, 119.0, 21.4; HRMS (ES^+) calculated for $C_{12}H_{10}O_2$ $(M+H)^+$: 187.0759, Found: 187.0753.



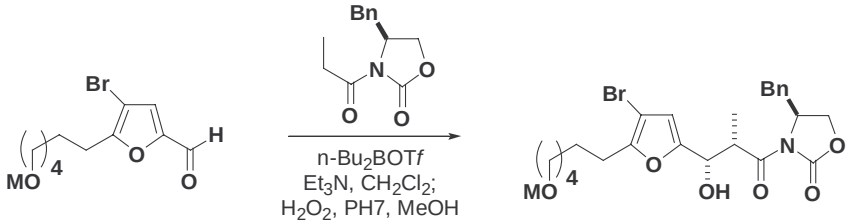
56 **57**

5-Bromo-4-*m*-tolyl-furan-2-carbaldehyde (**57**) To DMF (19.3 mL) stirred at –60 to –55 ^{o}C under Ar was added bromine (48.3 mmol, 2.48 ml) dropwise over 15 min. The resulting red/orange slurry (solidification occurred upon bromine addition) was warmed to –25 ^{o}C over 30 min to yield a bright orange solution (maintained at –25 ^{o}C). In a separate flask, 4-*m*-Tolyl-furan-2-carbaldehyde **56** was dissolved in DMF (19.3 mL) and stirred at rt under Ar. To this solution was added the Br_2/DMF solution dropwise *via* cannula over 45 min. The resulting dark orange/brown solution was stirred for an additional 15 min and then transferred to a separatory funnel and extracted with 8.5% ethyl acetate/hexanes (5 x 100 mL, 2 x 50 mL). The combined extracts were then concentrated *in vacuo* and the resulting orange DMF solution was dissolved in Et_2O (200 mL) and washed with water (1 x 40 mL, 1 x 20 mL) (ethereal layer turned light yellow) and brine (1 x 20 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude product was azeotropically dried (benzene 30 mL, rotary evaporation) to yield 4.3 g of an orange oil, which was purified by flash chromatography (SiO_2, hexanes/ethyl acetate : 100/1 → 50/1) to yield 3.9 g of the desired product **57** (14.7 mmol, 76%) R_f = 0.30 (hexanes/EtOAc:20/1 x 3 cycles); FTIR (film, cm^{-1}) 3106, 2921, 2824, 1684, 1611, 1578, 1512, 1473, 1370, 1342, 1302, 1167; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.42-7.33 (m, 4H), 7.21 (app d, *J* = 7.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 153.6, 138.6, 129.7, 129.2, 128.7, 128.1, 127.9, 127.8, 124.5, 121.8, 21.4; HRMS (ES^+) calculated for $C_{12}H_9BrO_2$ $(M+H)^+$: 264.9864, Found: 264.9871. For a related transformation see (Sessler and coworkers, *J. Org. Chem.* **1997**, *62*, 9251-9260).



2 **12**

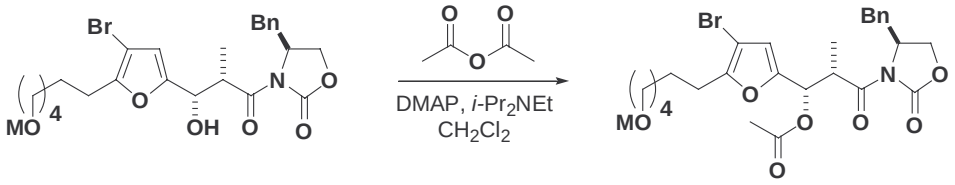
Macrobead-bound-5-(6-Hydroxy-hexyl)-4-*m*-tolyl-furan-2-carbaldehyde (12) Colorless beads **2** (667 mg, max theoretical loading 1.3 meq/g, 0.867 mmol) were washed with THF (1 x 30 mL x 10 min, 1 x 20 mL x 10 min) at rt and then resuspended in 20.1 mL THF. A 0.5M solution of 9-BBN in THF (13.3 mL, 6.67 mmol) was then added and the resulting mixture was manually agitated and let stand at rt for 5 h. The reaction solution was then removed via cannula and the colorless resin was washed thoroughly with THF (5 x 15 mL x 5-10 min each). To the resin was then added solid $PdCl_2$dppf (8.2 mg, 0.0075 mmol), 4-*m*-MePh-5-bromofuraldehyde **57** (884 mg, 3.34 mmol) *via* cannula as a solution in THF (8.3 mL), and a 1M aq. solution of NaOH (1.67 mL, 1.67 mmol). The resulting orange reaction mixture was sealed under a cloud of Ar and heated at 65 ^{o}C with periodic manual agitation for 22 h (reaction mixture turned dark brown). The yellow/orange resin was then isolated by filtration and washed as follows, 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 2 x (5 x THF, THF/H_2O : 3/1 x 1 h) , 5 x THF, THF x 20 min, 5 x CH_2Cl_2, CH_2Cl_2 x 20 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 20 min, and then the solvent was removed *in vacuo* to yield 761.2 mg of yellow/orange product resin **12**. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{12_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 8.07 min. 75 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, hexane/EtOAc:1/1) afforded alcohol $\mathbf{12_{M=H}}$ as a yellow oil (11.7 mg, 0.545 meq./g loading level). R_f = 0.29 (hexane/EtOAc:1/1); FTIR (film, cm^{-1}) 3433, 2931, 2858, 1678, 1611, 1526, 1483, 1333, 1122; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.34-7.30 (m, 2H), 7.19-7.14 (m, 3H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 1.77 (m, 2H), 1.54 (m, 2H), 1.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 159.2, 150.9, 138.6, 132.1, 128.7, 128.6, 128.3, 124.9, 124.8, 123.5, 62.8, 32.5, 29.0, 27.9, 27.1, 25.3, 21.5; HRMS (ES^+) calculated for $C_{18}H_{22}O_3$ $(M+H)^+$: 287.1647, Found: 287.1647.



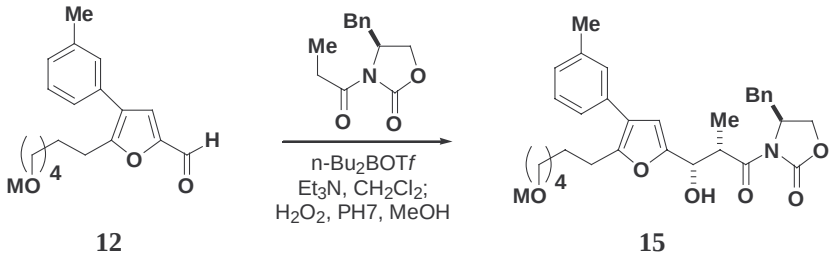
11 **13**

Macrobead-bound-(4S)-4-Benzyl-3-{(3*S*,2*S*)-3-[4-bromo-5-(6-hydroxy-hexyl)-furan-2-yl]-3-hydroxy-2-methyl-propionyl}-oxazolidin-2-one (13). Light yellow beads **11** (358 mg, 0.188 meq./g, 0.0673 meq.) were treated with the same reaction conditions used for the transformation of **3** → **6**. After washing, solvent was removed *in vacuo* to yield 381 mg of light yellow product resin **13**. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General

Methods) to yield crude diol $\mathbf{13_{M=H}}$ with LCMS purity >90 % (λ_{214}), t_R 8.56 min. 75.2 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford diol $\mathbf{13_{M=H}}$ as a light yellow oil [8.8 mg, 0.0173 mmol, 0.230 meq./g, Theoretical yield 0.180 meq./g, >95 % from **11**. R_f = 0.46 (hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3446, 2932, 2858, 1781, 1696, 1454, 1386, 1210, 1109, 1014; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 3H), 7.20 (d, *J* = 7 Hz, 2H), 6.28 (s, 1H), 5.0 (m, 1H), 4.67 (m, 1H), 4.20 (m, 2H), 4.13 (m, 1H), 3.62 (t, *J* = 6 Hz, 2H), 3.24 (dd, *J* = 13.5 Hz, 3 Hz, 1H), 3.12 (br d, *J* = 3.5 Hz, 1H), 2.79 (dd, *J* = 13 Hz, 9 Hz, 1H), 2.61 (t, *J* = 7.5Hz, 2H), 1.62 (m, 2H), 1.56 (m, 2H), 1.4-1.32 (m, 4H), 1.32 (d, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 152.8, 152.5, 152.3, 134.8, 129.4, 129.0, 127.5, 110.6, 96.4, 68.4, 66.3, 62.8, 55.1, 42.2, 37.8, 32.5, 28.5, 27.4, 25.8, 25.2, 11.9; HRMS (ES^+) calculated for $C_{24}H_{30}BrNO_6$ $(M+Na)^+$: 530.1154, Found: 530.1169.

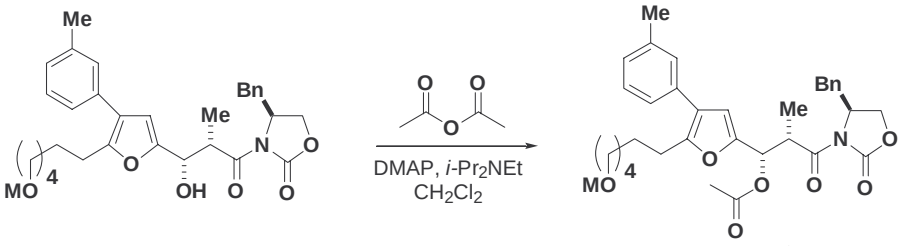


Macrobead-bound-(4*S*)-4-Benzyl-3-{(3*S*,2*S*)-3-[4-bromo-5-(6-hydroxy-hexyl)-furan-2-yl]-3-acetoxy-2-methyl-propionyl}-oxazolidin-2-one (14). Light yellow beads **13** (180 mg, 0.0414 meq.) were treated with the same reaction conditions used for the transformation of **6** → **7**. Solvent was removed *in vacuo* to yield 183 mg of light yellow product resin **14**. 5.0 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{14_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 8.94 min. 75.3 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford alcohol $\mathbf{14_{M=H}}$ as a yellow oil (8.5 mg, 0.0154 mmol, 0.205 meq./g, Theoretical yield 0.228 meq./g, 90% from **13**). R_f = 0.21 (hexane/EtOAc:1/1); FTIR (film, cm^{-1}) 3535, 2933, 2859, 1782, 1745, 1698, 1454, 1387, 1223, 1108, 1018; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 3H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.31 (s, 1H), 6.11 (d, *J* = 7.5 Hz, 1H), 4.55 (m, 1H), 4.47 (m, 1H), 4.16 (m, 2H), 3.62 (t, *J* = 6.5 Hz, 2H), 3.23 (dd, *J* = 13, 3 Hz, 1H), 2.76 (dd, *J* = 15, 9.5 Hz, 1H), 2.60 (t, *J* = 7 Hz, 2H), 2.09 (s, 3H), 1.64-1.53 (m, 4H), 1.40-1.30 (m, 4H), 1.32 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 173.1, 170.0, 153.1, 153.1, 149.4, 135.0, 129.4, 128.9, 127.4, 112.6, 96.4, 68.7, 66.3, 62.8, 55.3, 40.7, 37.8, 32.5, 28.6, 27.4, 25.9, 25.2, 20.9, 13.2; HRMS (ES^+) calculated for $C_{26}H_{32}BrNO_7$ $(M+Na)^+$: 572.1260, Found: 572.1277.



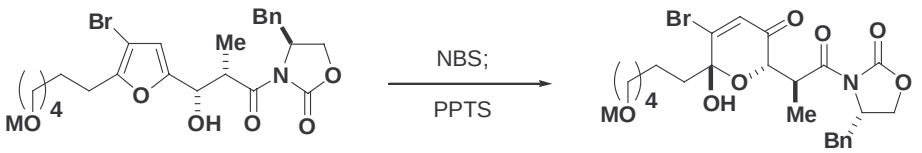
Macrobead-bound-(4*S*)-4-Benzyl-3-{(3*S*,2*S*)-3-hydroxy-3-[5-(6-hydroxy-hexyl)-4-*m*-tolyl-furan-2-yl]-2-methyl-propionyl}-oxazolidin-2-one (15). Light yellow beads **12** (400 mg, 0.218

meq.) were treated with the same reaction conditions used for the transformation of **3** → **6**. Solvent was removed *in vacuo* to yield 456 mg of light yellow product resin **15**. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude diol $\mathbf{15_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 9.47 min. 75.2 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford diol $\mathbf{15_{M=H}}$ as a yellow oil [18.0 mg, 0.0346 mmol, 0.460 meq./g, Theoretical yield 0.484 meq./g, 95% from **12**. R_f = 0.30 (hexane/EtOAc:1/1); FTIR (film, cm^{-1}) 3446, 2932, 2858, 1782, 1696, 1605, 1455, 1386, 1210, 1109, 1051, 1015; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.06 (m, 9H), 6.41 (s, 1H), 5.07 (d, *J* = 4 Hz, 1H), 4.65 (m, 1H), 4.25-4.10 (m, 3H), 3.60 (t, *J* = 7 Hz, 2H), 3.25 (dd, *J* = 13.5 Hz, 3 Hz, 1H), 3.10 (br s, 1H), 2.80 (dd, *J* = 13.5 Hz, 9.5 Hz, 1H), 2.75 (t, *J* = 8 Hz, 2H), 2.37 (s, 3H), 1.69 (m, 2H), 1.54 (m, 2H), 1.39 (d, *J* = 7 Hz, 3H, 1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 176.3, 152.9, 151.6, 151.2, 138.1, 134.9, 133.9, 129.4, 129.0, 128.4, 128.4, 127.5, 127.2, 124.7, 121.5, 108.5, 68.7, 66.2, 62.8, 55.2, 42.5, 37.8, 32.5, 28.8, 28.1, 26.7, 25.2, 21.5, 12.1; HRMS (ES^+) calculated for $C_{31}H_{37}NO_6$ $(M+NH_4)^+$: 537.2965, Found: 537.2977.



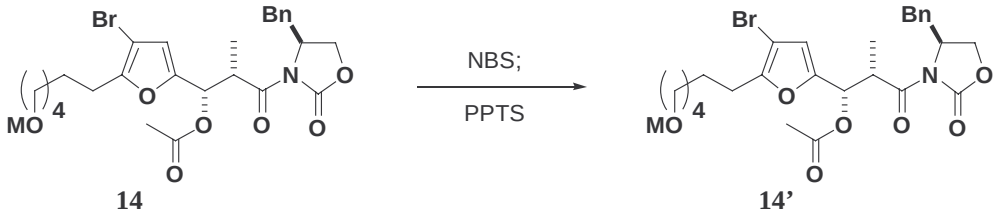
15 **16**

Macrobead-bound-(4*S*)-4-Benzyl-3-{(3*S*,2*S*)-3-acetoxy-3-[5-(6-hydroxy-hexyl)-4-*m*-tolyl-furan-2-yl]-2-methyl-propionyl}-oxazolidin-2-one (16). Light yellow beads **15** (180 mg, 0.460 meq/g, 0.083 meq.) were treated with the same reaction conditions used for the transformation of **6** → **7**. Solvent was removed *in vacuo* to yield light yellow product resin **16**. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{16_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 10.55 min. 75.2 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford alcohol $\mathbf{16_{M=H}}$ as a yellow oil (16.0 mg, 0.0285 mmol, 0.379 meq./g, Theoretical yield 0.451 meq./g, 84% from **15**). R_f = 0.26 (hexane/EtOAc:1/1); FTIR (film, cm^{-1}) 3538, 3028, 2932, 2859, 1782, 1744, 1700, 1606, 1455, 1386, 1227, 1108, 1018; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.06 (m, 9H), 6.44 (s, 1H), 6.19 (d, *J* = 8 Hz, 1H), 4.59-4.50 (m, 2H), 4.16-4.10 (m, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.24 (dd, *J* = 13, 3 Hz, 1H), 2.77 (dd, *J* = 13.5, 10 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H), 2.36 (s, 3H), 2.12 (s, 3H), 1.70-1.64 (m, 2H), 1.54 (m, 2H), 1.39-1.32 (m, 4H), 1.36 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 173.4, 170.1, 153.1, 151.7, 148.7, 138.1, 135.1, 133.6, 129.4, 128.9, 128.4, 128.4, 127.4, 127.3, 124.6, 121.6, 110.5, 69.1, 66.2, 62.8, 55.4, 40.8, 37.8, 32.6, 28.9, 28.1, 26.7, 25.3, 21.5, 21.0, 13.2; HRMS (ES^+) calculated for $C_{33}H_{39}NO_7$ $(M+Na)^+$: 584.2624, Found: 584.2609.



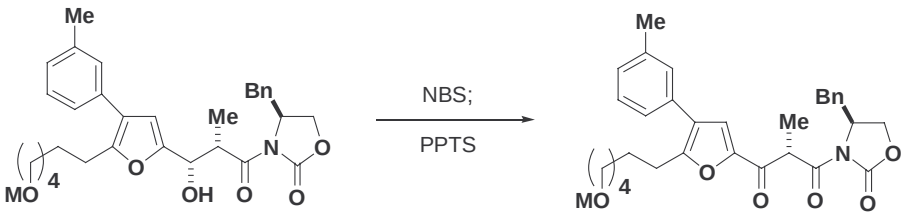
13 **17**

Macrobead-bound-(4*S*)-4-Benzyl-3-{(2*S*)-2-[(2*S*,6*R*)5-bromo-6-hydroxy-6-(6-hydroxy-hexyl)-3-oxo-3,6-dihydro-2*H*-pyran-2-yl]-propionyl}-oxazolidin-2-one (**17**). Light yellow beads **13** (0.090 g, 0.230 meq./g, 0.021 mmol) were treated with the same reaction conditions and washing protocol described above for the transformation of **5** → **8**. Solvent was then removed *in vacuo* to yield **17** as light yellow beads. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude diol $\mathbf{17_{M=H}}$ with LCMS purity 90% (λ_{214}), t_R 8.14 min, epimeric ratio = 9.4:1. 87.8 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford diol $\mathbf{17_{M=H}}$ as a yellow oil (8.6 mg, 0.0164 mmol, 0.187 meq./g, Theoretical yield 0.229 meq./g, 82% from **13,** the stereochemical assignment at the hemiketal center has been tentatively assigned. R_f = 0.3 (hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3452, 2933, 2860, 1781, 1695, 1605, 1455, 1392, 1352, 1208, 1110, 1050; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.25 (m, 3H), 7.22-7.18 (m, 2H), 6.50 (s, 1H), 4.92 (d, *J* = 8.5 Hz, 1H), 4.74 (m, 1H), 4.30 (app t, *J* = 8.5 Hz, 1H), 4.19 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.12 (dq, *J* = 8, 7 Hz, 1H), 3.65 (t, *J* = 7 Hz, 2H), 3.25 (dd, *J* = 13.5, 3 Hz, 1H), 2.81 (dd, *J* = 13, 10 Hz, 1H), 2.16 (m, 1H), 1.93 (m, 1H), 1.58 (m, 2H), 1.42-1.34 (m, 6H), 1.33 (d, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.2, 174.3, 153.2, 148.3, 135.1, 131.0, 129.5, 129.0, 127.4, 98.1, 74.5, 66.3, 62.9, 55.3, 40.5, 38.3, 38.0, 32.5, 29.0, 25.4, 23.2, 13.6; HRMS (ES^+) calculated for $C_{24}H_{30}BrNO_7$ $(M+Na)^+$: 546.1103, Found: 546.1086.



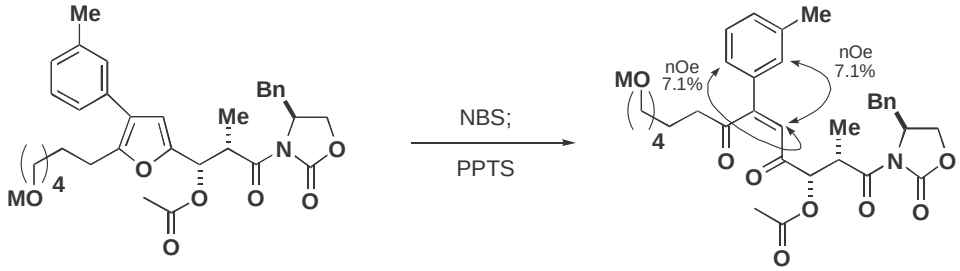
14 **14'**

Macrobead-bound-(4*S*)-4-Benzyl-3-{(3*S*,2*S*)-3-[4-bromo-5-(6-hydroxy-hexyl)-furan-2-yl]-3-acetoxy-2-methyl-propionyl}-oxazolidin-2-one (14'). Light yellow beads **14** (0.090 g, 0.205 meq./g, 0.018 mmol) were treated with the same reaction conditions and washing protocols described above for the transformation of **5** → **8**. Solvent was then removed *in vacuo* to yield unreacted **14'** as light yellow beads. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{14'_{M=H}}$ with LCMS purity >90% (λ_{214}), t_R 9.55 min. 84.2 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 1/1 → 1/2) to afford alcohol $\mathbf{14'_{M=H}}$ as a yellow oil (8.4 mg, 0.053 mmol, 0.181 meq./g, Theoretical yield 0.205 meq./g, 88% from **14**).



15 **18**

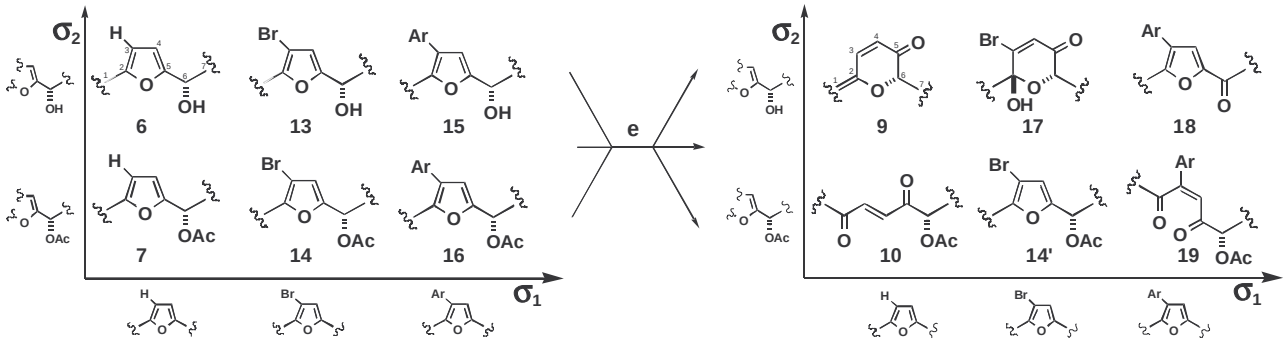
Macrobead-bound-1-((4*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-3-[5-(6-hydroxy-hexyl)-4-*m*-tolyl-furan-2-yl]-(2*S*)-2-methyl-propane-1,3-dione (**18**). Light yellow beads **15** (0.090 g, 0.460 meq./g, 0.041 mmol) were treated with the same reaction conditions and washing protocol described above for the transformation of **5** → **8**. Solvent was then removed *in vacuo* to yield **18** as light yellow beads. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{18_{M=H}}$ with LCMS purity 72% (λ_{214}), t_R 10.12 min. 86.1 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 2/1 → 1/2) to afford alcohol $\mathbf{18_{M=H}}$ as a yellow oil (15.2 mg, 0.0294 mmol, 0.341 meq./g, Theoretical yield 0.460 meq./g, 74% from **15**). R_f = 0.24 (hexane/EtOAc:1/1); FTIR (film, cm^{-1}) 3524, 2933, 2859, 1780, 1706, 1700, 1524, 1482, 1454, 1390, 1358, 1213, 1125, 1014; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.13 (m, 10H), 5.28 (q, *J* = 7.5 Hz, 1H), 4.77 (m, 1H), 4.25 (app t, *J* = 8.5 Hz, 1H), 4.18 (dd, *J* = 9, 2.5 Hz, 1H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.37 (dd, *J* = 13, 3 Hz, 1H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.79 (dd, *J* = 14, 10 Hz, 1H), 2.39 (s, 3H), 1.76 (m, 2H), 1.58 (d, *J* = 7 Hz, 3H), 1.53 (m, 2H), 1.40-1.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 170.4, 157.5, 153.9, 149.4, 138.7, 135.4, 132.6, 129.7, 129.2, 129.0, 128.9, 128.4, 127.6, 125.2, 125.0, 120.1, 66.8, 63.0, 55.7, 49.1, 38.2, 32.7, 29.1, 28.1, 27.4, 25.5, 21.7, 14.0; HRMS (ES^+) calculated for $C_{31}H_{35}NO_6$ $(M+H)^+$: 518.2542, Found: 518.2532.



16 **19**

Macrobead-bound-acetic acid (1*S*)-1-[2-((4*S*)-4-benzyl-2-oxo-oxazolidin-3-yl)-(1*S*)-1-methyl-2-oxo-ethyl]-11-hydroxy-2,5-dioxo-4-*m*-tolyl-undec-3-enyl ester (**19**). Light yellow beads **16** (0.090 g, 0.379 meq./g, 0.034 mmol) were treated with the same reaction conditions and washing protocol described above for the transformation of **5** → **8**. Solvent was then removed *in vacuo* to yield **19** as light yellow beads. 5.2 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) to yield crude alcohol $\mathbf{19_{M=H}}$ with LCMS purity 66% (λ_{214}), t_R 9.57 min. 84.4 mg of this resin was then treated with HF/Pyridine cleavage conditions and the crude product was purified by flash chromatography (SiO_2, Hexanes/EtOAc: 2/1 → 1/2) to afford alcohol $\mathbf{19_{M=H}}$ as a yellow oil (13.3 mg, 0.0230 mmol, 0.273 meq./g, Theoretical yield 0.377 meq./g, 72% from **16**). R_f = 0.29 (hexane/EtOAc:1/2); FTIR (film, cm^{-1}) 3537, 2934, 2859, 1779, 1746, 1702, 1577, 1454, 1388, 1223, 1106, 1048; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.24 (m, 7H), 7.20-7.17 (m, 2H), 6.81 (s, 1H), 5.74 (d, *J* = 5 Hz, 1H), 4.62 (m, 1H), 4.36-4.30 (m, 2H), 4.20

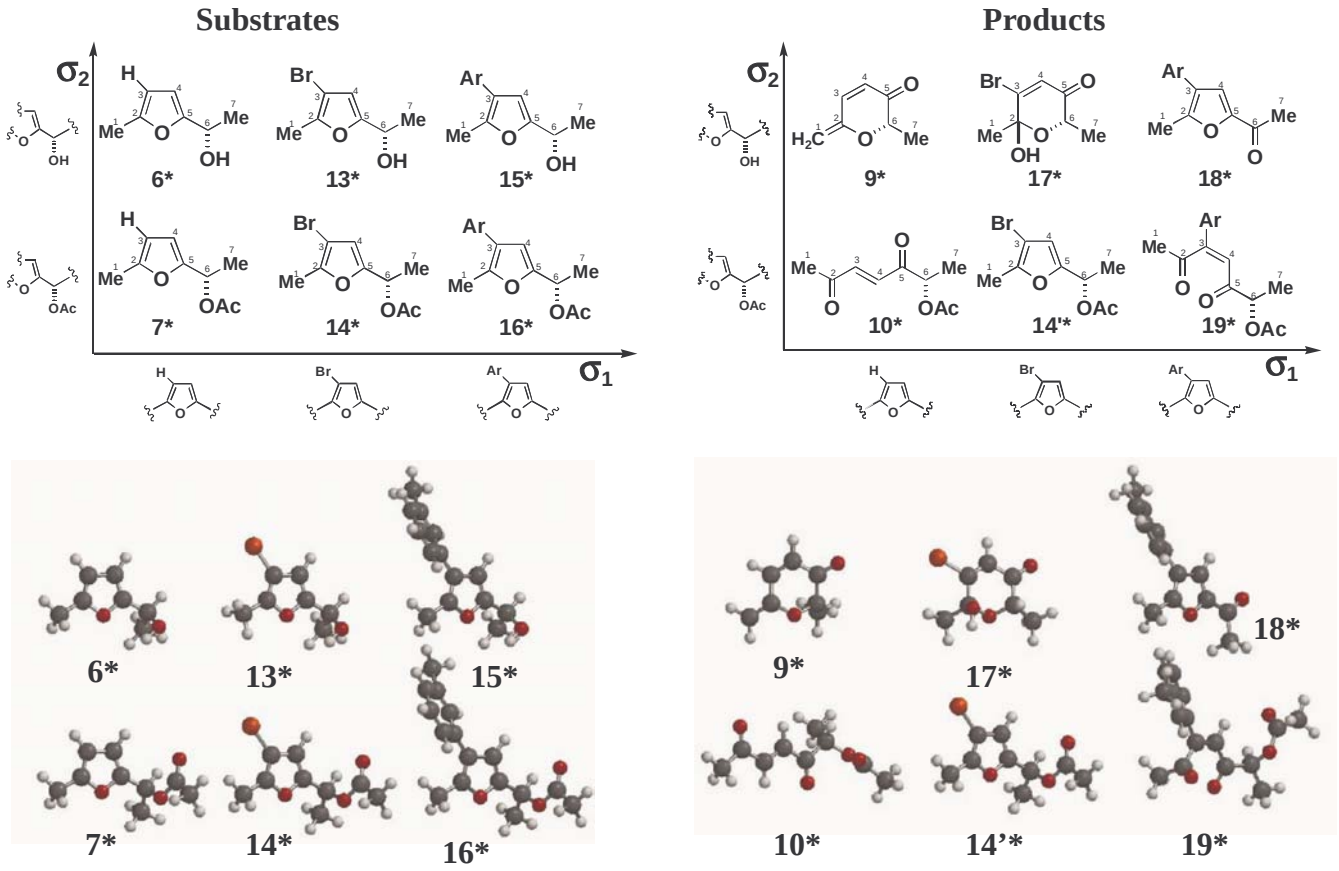
(dd, *J* = 9, 2 Hz, 1H), 3.61 (t, *J* = 7 Hz, 2H), 3.25 (dd, *J* = 13.5, 3 Hz, 1H), 2.80 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.61 (dt, *J* = 18, 7 Hz, 1H), 2.51 (dt, *J* = 18.5, 7.5 Hz, 1H), 2.37 (s, 3H), 2.18 (s, 3H), 1.72 (m, 2H), 1.54 (m, 2H), 1.39-1.33 (m, 4H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 192.9, 172.4, 170.4, 159.5, 153.5, 139.0, 135.0, 132.9, 131.9, 129.4, 129.1, 129.0, 127.7, 127.4, 124.3, 117.9, 77.11, 66.6, 62.8, 55.6, 41.9, 39.2, 37.8, 32.5, 28.4, 25.3, 22.8, 21.4, 20.7, 11.2; HRMS (ES^+) calculated for $C_{33}H_{39}NO_8$ $(M+NH_4)^+$: 595.3019, Found: 595.3034.



Common conditions (e): (The following experiment was performed in triplicate) A common reaction vessel was charged with 6 individual macrobeads **6**, **7**, **13**, **14**, **15**, and **16** and to this mixture at rt under ambient was added THF/water : 4/1 (1.5 mL), $NaHCO_3$ (56.7 mg, 0.675 mmol), NaOAc (27.7 mg, 0.338 mmol), and *N*-bromosuccinimide (40.0 mg, 0.23 mmol). The resulting mixture was sealed, wrapped in aluminum foil, and tumbled at rt for 1 h. The 6 macrobeads were then isolated from the reaction mixture by filtration and collectively washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/water : 3/1 x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 30 min. After removing the solvent *in vacuo*, the 6 macrobeads were transferred collectively to a new reaction vessel containing a 0.00075M solution of pyridinium *p*-toluenesulfonate in CH_2Cl_2 (2 mL). The resulting mixture was sealed under a cloud of argon and maintained at 40-45 ^oC (oil bath) for 20 h. The 6 macrobeads were then isolated from the reaction mixture by filtration and washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/dil. aq. $NaHCO_3$ (sat. aq. $NaHCO_3/H_2O$: 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/dilute aq. NH_4Cl (sat. aq. NH_4Cl/H_2O : 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 30 min. Solvent was then removed *in vacuo* to yield 6 product macrobeads, which were segregated into individual polypropylene eppendorf tubes and treated with HF/Pyridine cleavage conditions (see General Methods). The cleaved products were then analyzed by LCMS. In all 3 experiments, 6/6 (100%) of the anticipated compounds were identified as the major product (by t_R and mass) cleaved from an individual macrobead.

Skeletal diversity metric. The synthesis of diverse skeletons is critical to achieving diverse displays of chemical information in 3-dimensional space. To provide some form of quantification for this type of diversity found in the set of six skeletons shown in Fig 2B, we developed a *skeletal diversity metric* based on the distance, angle, and dihedral angle between common atoms in computationally derived 3-dimensional structures. Specifically, the missing bonds in both the substrates and products in Figure 2B of the text represent potential attachment sites to which building blocks could be appended. The six substrates, having a 3 x 2 matrix of different

appendages attached to a common α-alkoxy furan skeleton resemble the types of compounds typically derived from the one synthesis-one skeleton approach. Alternatively, the six products represent six distinct molecular skeletons generated combinatorially using the σ-element-based synthesis strategy. Comparing and contrasting these two collections (which are almost constitutionally isomeric) can provide a metric for the skeletal diversity generated in this one reaction using a common set of reagents. By replacing each of the missing bonds in the 12 structures shown in Fig 2B with methyl groups (or a methylene group for the 'left side' of structure **9**), we were able to generate a collection of 12 simplified structures: 6 substrates (**6***, **7***, **13***, **14***, **15***, and **16***) and 6 products **(9***, **10***, **17***, **14'***, **18***, and **19***), which all share in common the 7 contiguous carbon atoms labeled C_1 – C_7. Using the Spartan software package (Spartan '02, Wavefunction, Inc.) and a Gateway PC with an Intel Pentium 4 processor, we then performed the following two-step calculation on all 12 structures: The **equilibrium conformer** was determined reproducibly using the standard Spartan equilibrium conformer search with semiempirical AM1 calculations, followed by the determination of **equilibrium geometry** using the Hartree-Fock method with the 6-31G* split-valence basis set.

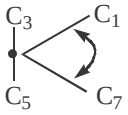


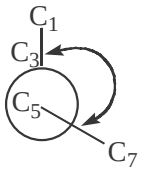
For each of these 12 computationally derived 3-dimensional structures, the positions of every other carbon in the common, contiguous 7-carbon atom stretch were then used to determine

the following three parameters (each parameter provides unique information regarding the relative positions of the building block attachment sites, C_1 and C_7, in 3-dimensional space:

1. the **distance** (in angstroms) between C_1 and C_7
2. the **angle** C_1 - the midpoint between C_3 and C_5 - C_7.
3. the **dihedral angle** comprising C_1, C_3, C_5, and C_7.

This analysis produced the following data



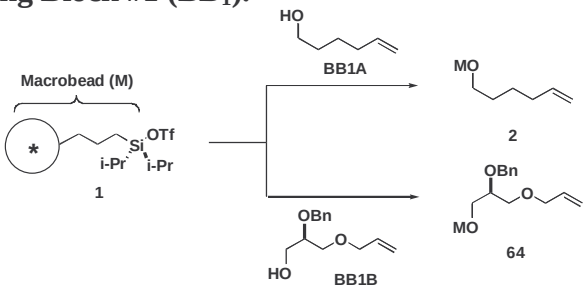


Substrates	distance (angstroms)	angle (degrees)	dihedral angle (degrees)
6*	5.30	110.6	76.5
7*	5.17	105.9	56.8
13*	5.30	110.6	75.2
14*	5.16	105.8	55.7
15*	5.27	109.6	74.9
16*	5.14	104.9	54.2
standard deviation	***0.07***	***2.4***	***10.0***
Products			
9*	4.04	83.7	39.4
10*	6.81	145.0	158.2
17*	4.64	91.0	14.9
14'*	5.16	105.8	55.7
18*	5.10	102.1	2.6
19*	5.90	123.1	128.5
standard deviation	***0.89***	***20.5***	***57.5***

Plotting these parameters for both substrates and products in a 3-dimensional plot using the Spotfire graphing package produced the 3-D plots shown in Figure 2C of the text. By this analysis, the 6 substrates, which represent a collection of products having a common skeleton similar to those derived from the one-synthesis-one skeleton approach, create a dense cluster (the two lobes of this dense cluster represent the acetylated and non-acetylated substrates). In contrast, the 6 products, which represent 6 distinct molecular skeletons generated combinatorially using the σ-element-based synthesis strategy, distribute broadly (both plots are drawn to the same scale) consistent with a diverse display of chemical information in 3-dimensional space.

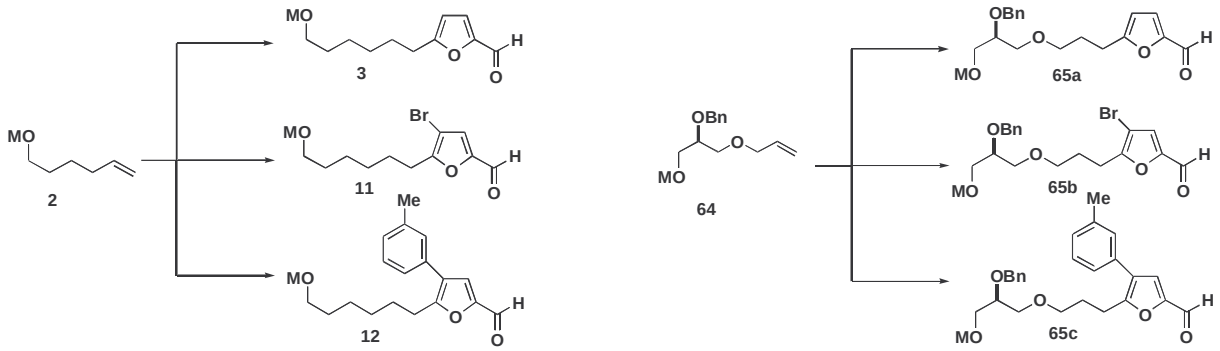
Parallel Library Synthesis

Step 1. Loading of Building Block #1 (BB_1).



1.2 g of 3-[Diisopropyl(*p*-methoxyphenyl)silyl]propyl functionalized macrobeads **1** was split into two portions (600 mg each) and each portion was subjected to a unique loading reaction with BB_1A or BB_1B, using the same protocol described previously for the transformation of **1** → **2** to yield **2** and **64**, which were carried on to step 2.

Step 2. Suzuki coupling of Skeletal Information Unit #1 (σ_1)

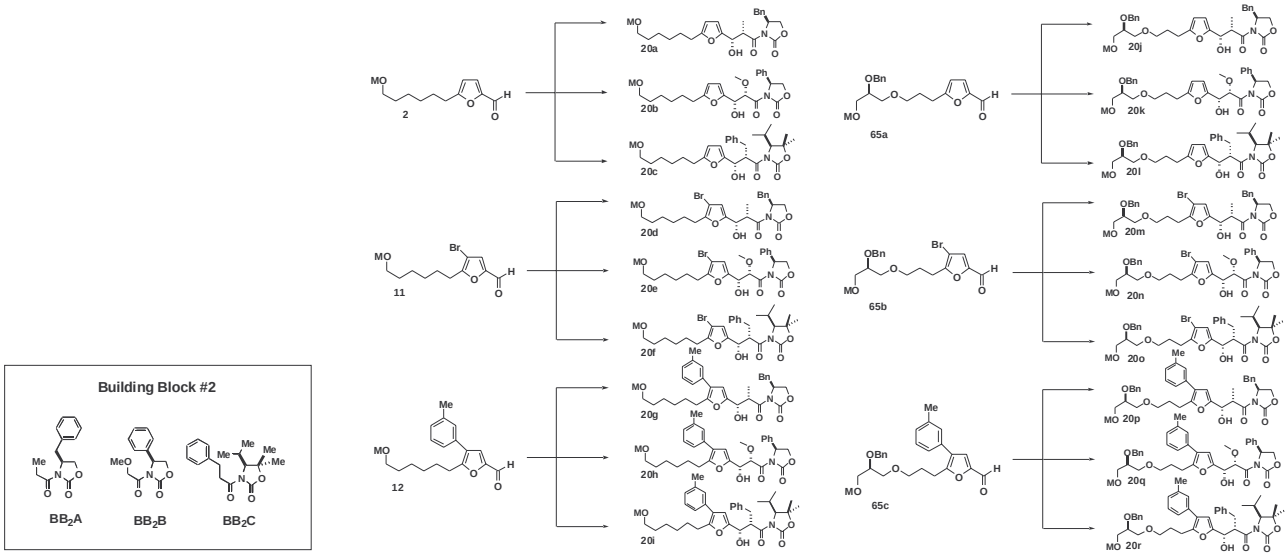


Suzuki coupling of Skeletal Information Unit #1 (σ_1) Colorless beads **2** (555 mg) and **64** (630 mg) were each split evenly by weight into three portions. Each of the three portions of **2** and **64** was then subjected to a B-alkyl Suzuki coupling with a unique 4-substituted-5-bromofuraldehyde (σ_1 = H, σ_2 = Br, or σ_3 = *m*-MePh, 6 parallel reactions) using the same protocols described previously for the transformation of **2** → **3**, **2** → **11**, and **2** → **12**.

						% Purity		HRMS	
No.	**BB_1**	**σ_1**	**BB_2**	**σ_2**	**^{1}H NMR**	**LCMS, 214 nm**	**Ionization**	**Calculated**	**Observed**
3	A	H	-	-	√	>85	ES+	$(M+H^+)$ 197.1177	197.1177
11	A	Br	-	-	√	>90	ES+	$(M+H^+)$ 275.0283	275.0282
12	A	*m*-MePh	-	-	√	>90	ES+	$(M+H^+)$ 287.1647	287.1647
65a	B	H	-	-	√	88 (280 nm, 92)	ES+	$(M+H^+)$ 319.1545	319.1536
65b	B	Br	-	-	√	71 (280 nm, 94)	ES+	$(M+H^+)$ 397.0650	397.0645
65c	B	*m*-MePh	-	-	√	>90	ES+	$(M+H^+)$ 409.2015	409.2015

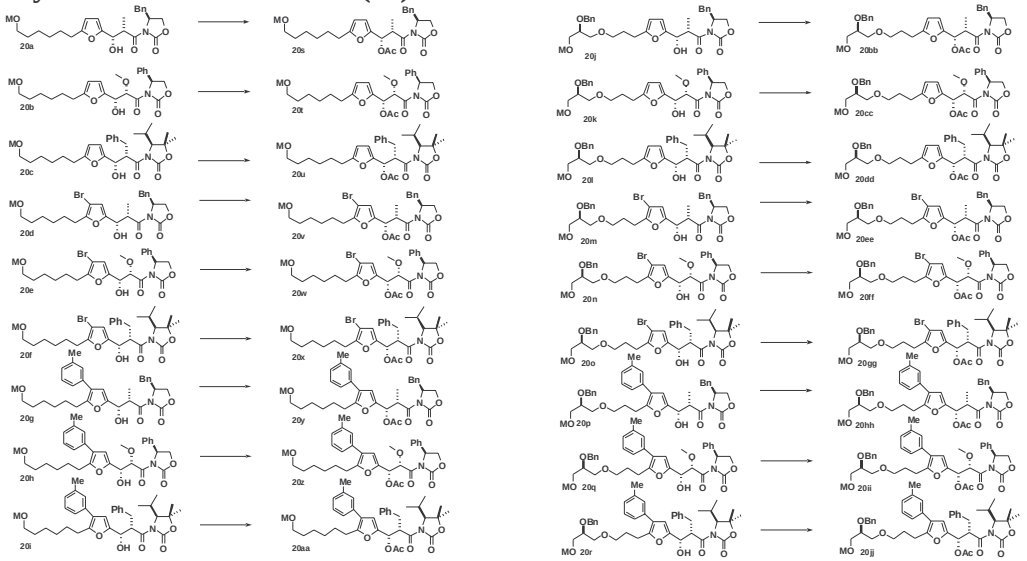
√: ^{1}H NMR spectrum consistent with anticipated structure, LCMS purities for **65a** and **65b** are reported with detection at both λ_{214} and λ_{280}; all other LCMS data reported with detection at λ_{214}.

Step 3. Evans aldol coupling of Building Block #2



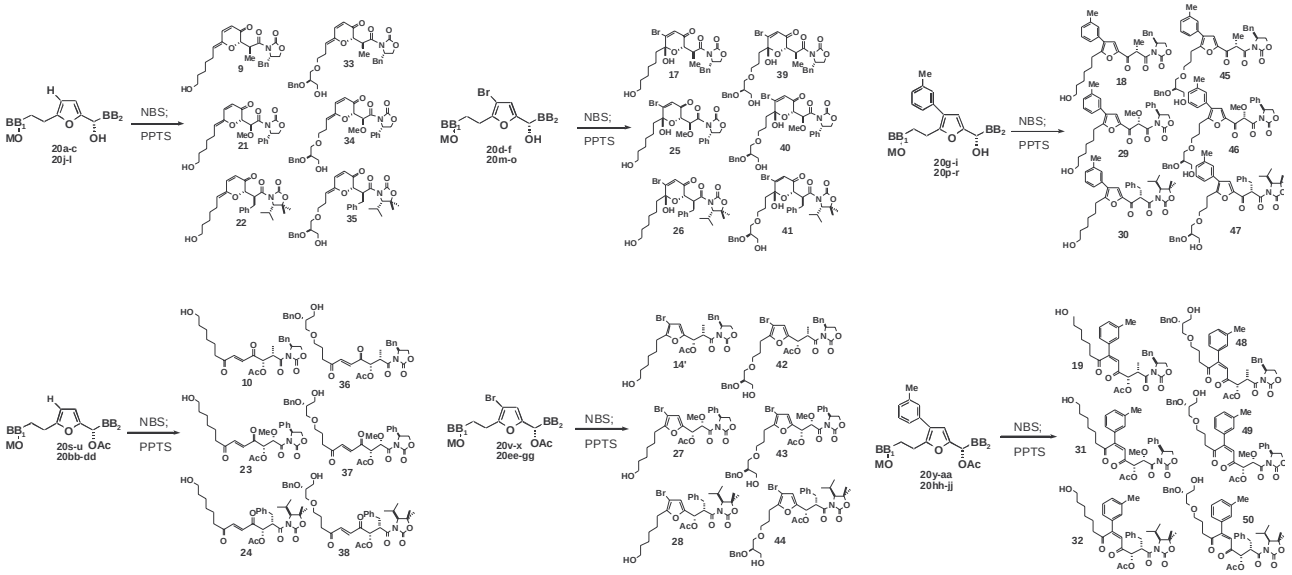
Aldol coupling of Building Block #2 (BB_2). The six pools of light yellow resin from Step 2 (**2**, **11**, **12**, and **65a-65c**) were then each split into 3 equal portions (18 pools of ~60 mg each). Each of these 18 portions was then subjected to an aldol coupling reaction with one of the three acyl oxazolidinones **BB_2A**, **BB_2B**, or **BB_2C**. Specifically, in 18 parallel reactions, **2**, **11**, **12**, and **65a-65c** were transformed to **20a-r** using the same protocols described previously for the transformation of **3** → **6**, **11** → **13**, and **12** → **15**. For the transformation of **65a-65c** → **20l**, **20n**, and **20r**, reactions were maintained at –78 °C for 72 h, -26 °C for 28 h, and 0 °C for 2 h to promote full conversion.

Step 4. Acetylation of aldol adducts (σ_2)



Step 4. 18 portions of light yellow resin from Step 3 (**20a-r**, ~60 mg each) were then each divided into two equal portions; one of these portions was subjected to an acetylation reaction using the same protocols described previously for the transformation of **6** → **7**, **13** → **14**, and **15** → **16**, and the other portion was not acetylated yielding **20a-jj**. Results are presented in Table 1.

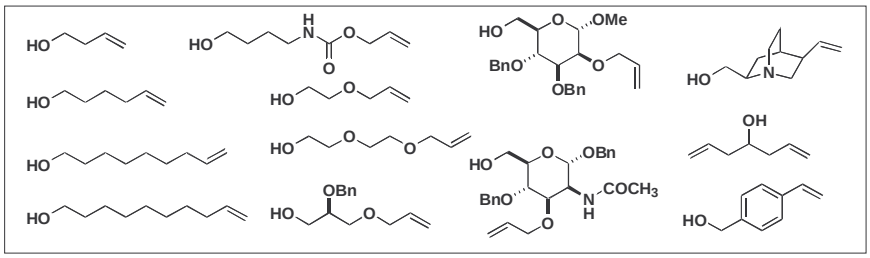
Step 5. NBS and PPTS-mediated transformation of 20a-jj into a complete, combinatorial matrix of molecular skeletons, each derivatized with a complete, combinatorial matrix of building blocks.

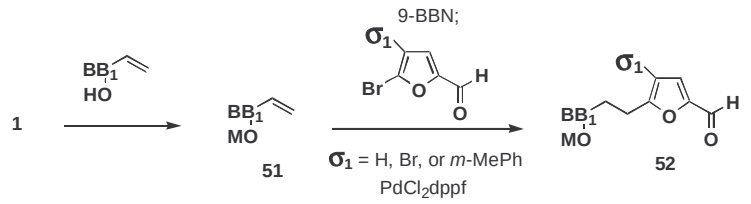


NBS and PPTS-mediated transformations. In 36 parallel reactions, each substrate **20a-jj** was subjected to the same reaction conditions **(**NBS/THF at rt for 1h; PPTS/CH_2Cl_2 at 40-45 ^oC for 20 h) using the protocol described previously for the transformation of **5** → **8**. Results are presented in Table 2.

Split-pool library synthesis (Text Fig. 4)

Screening for BB#1 (BB_1) The 13 commercially available compounds shown below, each containing both a hydroxyl group and a terminal olefin, were screened for both effective loading onto macrobeads and subsequent B-alkyl Suzuki coupling with one or more of the following: 5-bromofuraldehyde, 4,5-dibromofuraldehyde, and 4-*m*-MePh-5-bromofuraldehyde. All reactions were run on ~25 mg of macrobeads.



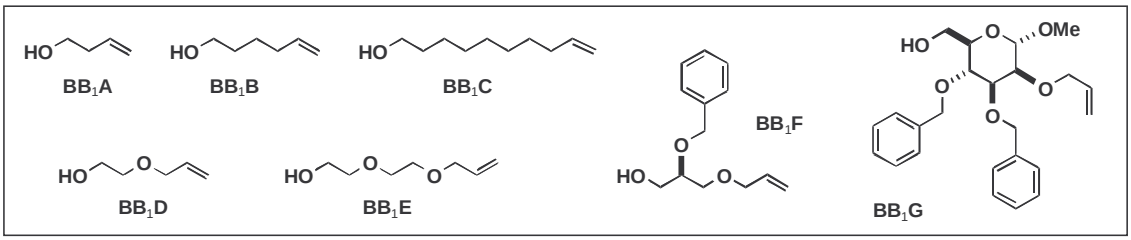


51 3-[Diisopropyl(*p*-methoxyphenyl)silyl]propyl functionalized beads **1** (25 mg, estimated loading ~1.3 meq Si/g, ~0.0325 meq.) in a 2 mL polypropylene tube at rt under Ar were allowed to swell in CH_2Cl_2 (~10 ml) for 10 min. The colorless beads were then filtered and again washed with CH_2Cl_2 (~10 mL x 10 min.), and then resuspended in a 2.5% (v/v) solution of TMSCl in CH_2Cl_2 (~10 mL) for 30 min. The beads were again filtered and washed thrice with CH_2Cl_2 (5 min each) and then suspended in a 3% (v/v) solution of trifluoromethanesulfonic acid in CH_2Cl_2 (0.575 mL, 0.195 mmol) for 20 min during which the reaction tube was shaken periodically and the beads turned orange. After filtration, the orange-colored beads were again thrice washed with CH_2Cl_2 and then resuspended in a minimum volume of CH_2Cl_2 (~0.2 mL). Freshly distilled 2,6-lutidine was then added (30.3 uL, 0.26 mmol) resulting in bead discoloration followed by building block #1 (0.26 mmol). The resulting colorless reaction mixture was then shaken manually and let stand at rt for 12 h. The beads were then filtered, washed with CH_2Cl_2 (5 x 5 mL x 5 min. each), and the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield resin **51** loaded with candidates for building block #1.

52 Macrobeads loaded with candidates for building block #1 **51** (~0.0325 meq.) were washed with THF (2 x 3 mL x 10 min each) at rt and then resuspended in THF (0.750 mL). A 0.5M solution of 9-BBN in THF (0.5 mL, 0.25 mmol) was then added and the resulting mixture was let stand at rt for 5 h (with periodic manual agitation every hour). The reaction solution was then removed *via* cannula and the colorless resin was washed thoroughly with THF (5 x 5 mL x 10 min each). To the resin was then added $PdCl_2$dppf (1 mg, 0.00125 mmol) *via* cannula as a suspension in THF (0.125 mL), one of the following three furaldehyde coupling partners: 5-bromofuraldehyde (21.9 mg, 0.125 mmol), 4,5-dibromofuraldehyde (31.7 mg, 0.125 mmol), or 4-*m*-MePh-5-bromofuraldehyde

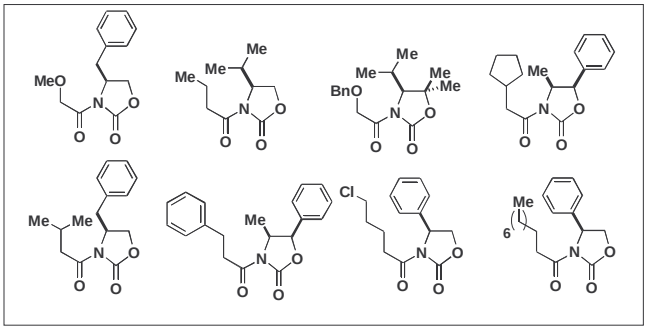
(33.1 mg, 0.125 mmol) *via* cannula as a solution in THF (0.188 mL), a 2M solution of NaOH (31 μL, 0.0625 mmol). The resulting orange reaction mixture was sealed under a cloud of Ar and heated at 60-65 ^{o}C with periodic manual agitation for 24-28 h (reaction mixture turned dark brown). The yellow/orange resin was then isolated by filtration and washed as follows, 4 x (5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 30 min), 5 x THF, THF x 30 min, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, and the residual solvent was removed *in vacuo* to yield product resin **52**. 5 mg of this resin was then treated with HF/Pyridine cleavage conditions (see General Methods) and the crude product residue was analyzed by ^{1}H NMR, LCMS, and HRMS.

This building block screen led to the identification of seven building blocks shown below. (abbreviated alphabetically **BB_1A**, **BB_1B**, **BB_1C**, etc.). The results for these building blocks are shown in Table 3.

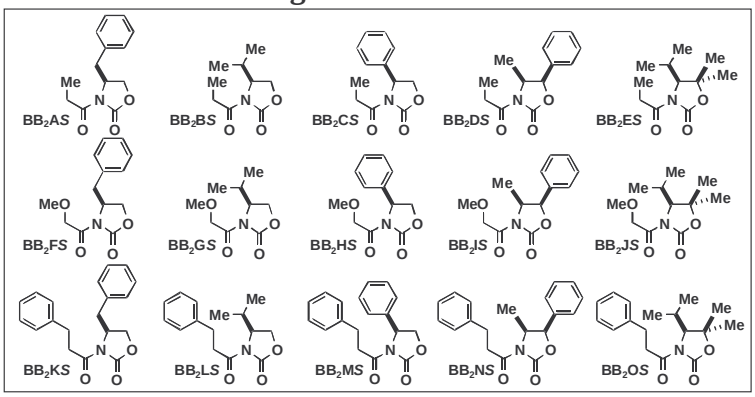


Screening for Building Block #2 (BB_2) We then screened a variety of commercially available, nonracemic chiral oxazolidinones combined with diverse acyl side chains for efficient coupling with macrobead-bound 5-(6-hydroxyhexyl)-furaldehyde. We first synthesized a diverse set of eight chiral oxazolidinones coupled to various acyl side chains, and tested them for efficient aldol coupling. Tolerance for diverse oxazolidinones was noted and the three most effective acyl side chains from those tested were identified and used in a second round of screening, in which a 5 x 3 matrix of commercially available oxazolidinones and acyl side chains were synthesized and tested. These 15 building blocks (**BB_2A*S*-BB_2O*S*)** were found to be effective coupling partners in the Evans aldol reaction. The 15 enantiomeric acyl oxazolidinones (**BB_2A*R*-BB_2O*R***) were also prepared, allowing us to take advantage of reagent-based stereocontrol to generate both sets of possible enantiomeric or diastereomeric (when **BB_1** is chiral) aldol adducts.

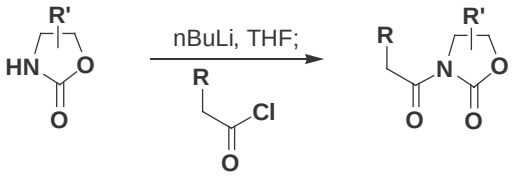
Collection of candidate building blocks included in first screen for BB#2



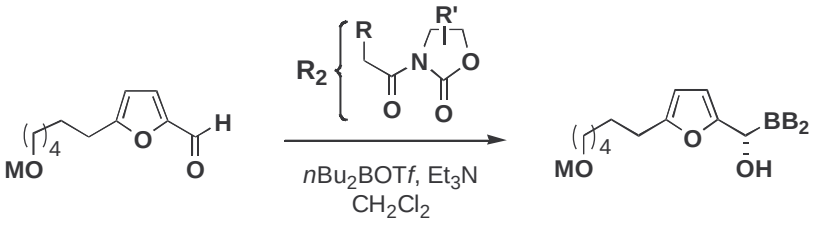
Collection of candidate building blocks included in second screen for BB#2



These building blocks are classified as *R* or *S* by the orientation of the 4'-substituent on the oxazolidinone ring.



Synthesis of acyl oxazolidinones. A stirred solution of oxazolidinone (1 g.) in anhydrous THF (0.2 M in oxazolidinone) was cooled to –78 °C for 15 minutes. nBu-Li (1.1 equiv.) was slowly added and the mixture was stirred for 15 minutes. The appropriate acid chloride (1.1 equiv.) was then added by syringe and the mixture stirred for another 30 minutes. The mixture was then warmed to rt over 45 minutes, quenched with NH_4Cl (4 mL), and the THF was removed with rotary evaporation. The resulting slurry was then extracted with CH_2Cl (2 x 5 mL), and the combined organic fractions were washed with 2 M NaOH (aq.) (5 mL) and brine (5 mL), dried over sodium sulfate, and concentrated *in vacuo*. The product was then purified *via* flash chromatography (SiO_2, hexanes/ethyl acetate), azeotropically dried with benzene, and stored under Argon for further use. The average chemical yield of the syntheses was roughly 85%.



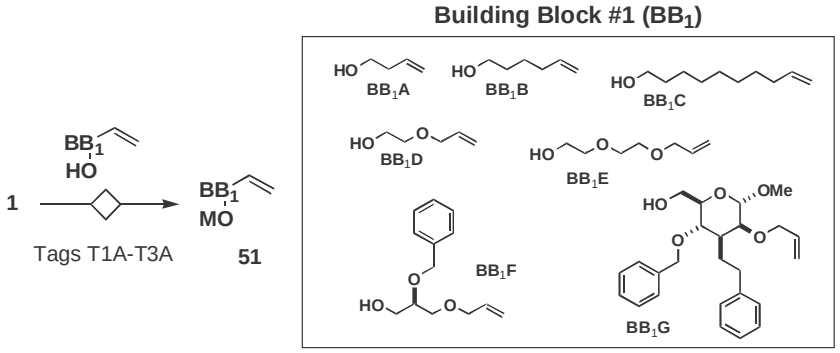
3

Screening of acyl oxazolidinones Yellow-orange macrobeads **3** (25 mg) were washed with CH_2Cl_2 (3 x 1 mL x 10 min each) at rt, and then cooled to –78 °C. In a separate vessel, to a stirred solution of acyl oxazolidinone (0.125 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added a 1M solution of dibutylboron triflate in CH_2Cl_2 (131 μL, 0.131 mmol) followed by triethylamine (21 μL, 0.150 mmol). The resulting enolate solution was cooled to –78 °C and then transferred rapidly *via* cannula to the vessel containing **3**. The resulting mixture was sealed under a cloud of Ar and maintained at –78 °C for 48 h, -26 °C for 24 h, and 0 °C for 1 h (with periodic manual agitation about once every 8 h). The reaction was then quenched with the addition of pH7 phosphate buffer

(500 μL), MeOH (500 μL), and 30% aq. H_2O_2 (333 μL), and the resulting mixture was tumbled at 4 ^oC for 12-15 h. Resin was then isolated by filtration and washed as follows: 5 x CH_2Cl_2, 5 x DMF, 5 x THF, 5 x CH_2Cl_2, CH_2Cl_2 x 1 h, 5 x DMF, DMF x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 30 min, and residual solvent was removed *in vacuo* to yield the product resin. 5 mg of this product resin was then treated with HF/Pyridine cleavage conditions (see General Methods), and the crude product residue was analyzed by ^1H NMR, LCMS, and HRMS. The results are summarized in Table 4.

Split-pool library synthesis

Step 1. Coupling of Building Block #1 (BB_1)



Coupling of Building Block #1 (BB_1). A single pool of 3-[Diisopropyl(*p*-methoxyphenyl)silyl]-propyl functionalized beads **1** (2 g) was split evenly into seven portions (286 mg each), and each was subjected to a loading reaction with a unique BB#1 as described below:

51 3-[Diisopropyl(*p*-methoxyphenyl)silyl]propyl functionalized beads **1** (286 mg per reaction) in a 10 mL polypropylene tube at rt under Ar were allowed to swell in CH_2Cl_2 (7 ml) for 10 min. The colorless beads were then filtered and again washed with CH_2Cl_2 (7 mL x 10 min.), and then resuspended in a 2.5% (v/v) solution of TMSCl in CH_2Cl_2 (7 mL) for 30 min. The beads were again filtered and washed thrice with CH_2Cl_2 (5 min each) and then suspended in a 3% (v/v) solution of trifluoromethanesulfonic acid in CH_2Cl_2 (6.6 mL) for 20 min during which time the reaction tube was shaken periodically and the beads turned orange. After filtration, the orange-colored beads were again thrice washed with CH_2Cl_2 and then resuspended in a minimum volume of CH_2Cl_2 (~1 mL). Freshly distilled 2,6-lutidine was then added (346 uL, addition resulted in bead discoloration) followed by building block #1:

BB#1 used in split-pool synthesis

Building Block	mol	formula weight (g/mol)	density (g/mL)	volume (uL)	mass (g)
BB_1A	0.002974	72.11	0.85	252	
BB_1B	0.002974	100.16	0.834	357	
BB_1C	0.002974	156.27	0.876	531	
BB_1D	0.002974	102.13	0.955	318	
BB_1E	0.002237	146.68	1.01	325	
BB_1F	0.002974	222.28	~1	661	0.661
BB_1G	0.002974	414.49	n/a		1.23*

*dissolved in 300 uL CH_2Cl_2

The resulting colorless reaction mixtures were then shaken manually and let stand at rt for 16 h. The beads were then filtered, washed with CH_2Cl_2 (5 x 7 mL x 20 min. each), and the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield seven portions of resin **51**, each loaded with a unique building block #1.

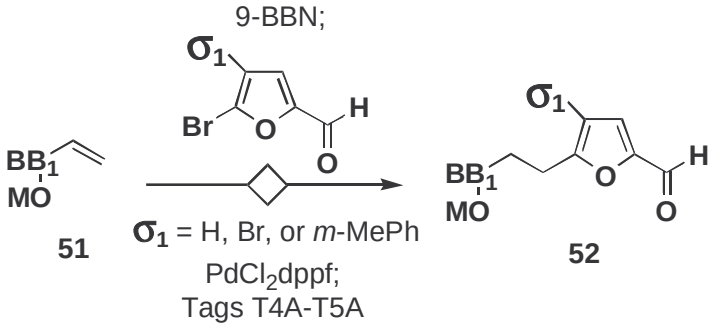
Tagging for Building Block #1 (BB_1). (*3*) Each of the seven portions of resin **51** loaded with BB#1 were then subjected to a unique encoding reaction. A freshly prepared solution of one or more tags (each tag 4.4 mM in 4.76 mL CH_2Cl_2) was individually prepared for each reaction. The resin **51** (~286 mg/rxn) was then added to the solution of tags, placed under an Argon cloud, capped and sealed with parafilm, and allowed to rotate gently for 1 h. To this mixture was then added a freshly prepared solution of rhodium triphenylacetate (4.4 mg/mL, 4.76 mL), and the vial was sealed under Ar, wrapped in aluminum foil to prevent exposure to light, and allowed to tumble gently for 15 h. The resin was then isolated by filtration and washed as follows: 2 x (5 x CH_2Cl_2, CH_2Cl_2 x 15 min.), 3 x (5 x THF, THF x 2 h), 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 15 min. The solvent was then removed under Ar flow for 1 h followed by residual solvent removal *in vacuo* to yield seven portions of resin **51** loaded with building block #1 and chemically encoded with polychlorinated aromatic tags T1A-T3A.

Encoding scheme for building block #1

	T1A	T2A	T3A	T4A	T5A	T6A	T7A	T8A	T9A	T10A	T11A	T13A
BB_1A			1									
BB_1B		1										
BB_1C		1	1									
BB_1D	1											
BB_1E	1		1									
BB_1F	1	1										
BB_1G	1	1	1									

Two macrobeads from each of the seven portions were removed and subjected to the standard HF-Pyridine-mediated compound cleavage conditions (see General Information), and the individual macrobeads and/or a portion of the solution of cleaved compounds were subsequently subjected to the standard CAN-mediated tag cleavage reaction. After confirming tagging scheme, the seven portions of dry resin **52** were then pooled together in a single polypropylene tube, swollen in anh. THF, tumbled for 30 min, and then the solvent was removed under Ar flow followed by residual solvent removel *in vacuo*.

Step 2. Suzuki coupling of Skeletal Information Element #1 (σ_1)



Suzuki coupling of Skeletal Information Element #1 (σ_1) A single pool of resin **51** was split evenly into three portions (672 mg each), and each was subjected to a coupling reaction with a unique σ_1 as described below:

Colorless beads **51** (672 mg) were washed with THF (2 x 15 mL x 10 min each) at rt and then resuspended in 20.2 mL THF. A 0.5M solution of 9-BBN in THF (13.4 mL, 6.72 mmol) was then added and the resulting mixture was manually agitated and let stand at rt for 5 h. The reaction solution was then removed via cannula and the colorless resin was washed thoroughly with THF (5 x 15 mL x 10 min each). To the resin was then added solid $PdCl_2$dppf (σ_1 H: 8.2 mg, 0.0101 mmol; σ_1 Br: 13.7 mg, 0.0168 mmol; σ_1 Ar: 8.2 mg, 0.0101 mmol), and one of the following three 5-bromofuraldehydes:

σ-elements #1 used in split-pool synthesis

Skeletal information element (σ)	mmol	formula weight (g/mol)	mass (g)
σ_1**A**, 5-Bromofuraldehyde	3.36	174.99	0.5880
σ_1**B**, 4,5-Dibromofuraldehyde	3.36	253.88	0.8530
σ_1**C**, 4-*m*-MePh-5-bromofuraldehyde	3.36	265.1	0.8907

via cannula as a solution in THF (8.4 mL), and a 1M solution of NaOH (1.68 mL, 1.68 mmol). The resulting orange reaction mixture was sealed under a cloud of Ar and heated at 65 ^{o}C with periodic manual agitation for 20 h (each reaction mixture turned dark brown). The yellow/orange resin was then isolated by filtration and washed as follows, 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 2 h, 5 x THF, 3 x H_2O, 5 x THF, THF/H_2O : 3/1 x 45min, 5 x THF, THF/H_2O : 3/1 x 45 min, 5 x THF, THF x 20 min, 5 x CH_2Cl_2, CH_2Cl_2 x 20 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 20 min, and then the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield three portions of yellow/orange product resin **52**.

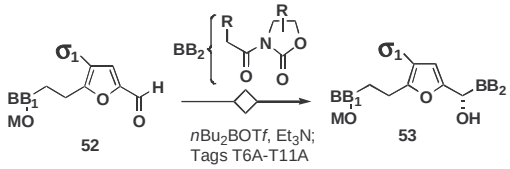
Tagging for Skeletal Information Element #1 (σ_1). Each of the three product portions **52** was then subjected to a unique encoding reaction. A freshly prepared solution of one or more tags (each tag 4.4 mM in 11.1 mL CH_2Cl_2) was individually prepared for each reaction. The resin **52** (>672 mg/rxn) was then added to the solution of tags, placed under an Argon cloud, capped and sealed with parafilm, and allowed to rotate gently for 1 h. To this mixture was then added a freshly prepared solution of rhodium triphenylacetate (4.4 mg./mL, 11.1 mL), and the vial was sealed under Ar, wrapped in aluminum foil to prevent exposure to light, and allowed to tumble gently for 15 h. The resin was then isolated by filtration and washed as follows: 2 x (5 x CH_2Cl_2, CH_2Cl_2 x 15 min.), 3 x (5 x THF, THF x 2 h), 5 x anh. THF, anh. THF x 1 h, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 20 min, and the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield three portions of resin **52**, collectively representing all combinations of building block #1 and σ-element #1, with each combination chemically encoded with polychlorinated aromatic tags.

Encoding scheme for skeletal information element #1 (σ_1)

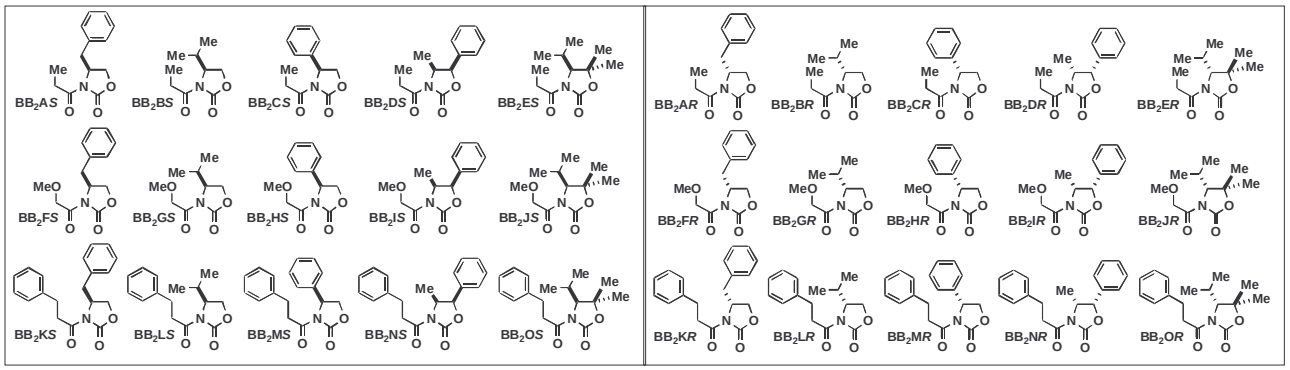
	T1A	T2A	T3A	T4A	T5A	T6A	T7A	T8A	T9A	T10A	T11A	T13A
σ_1A (H)					1							
σ_1B (Br)				1								
σ_1C (Ar)				1	1							

10 individual macrobeads were removed from each portion **52** and subjected to the standard HF-Pyridine cleavage conditions. The cleaved product from all 30 individual macrobeads was analyzed by LCMS, and the polychlorinated tags remaining on each macrobead were then cleaved and analyzed by GC (data not shown). The three pools of dry resin **52** were then pooled together in a single polypropylene tube, swollen in anh. CH_2Cl_2, tumbled for 30 min, and then the solvent was removed under Ar flow followed by residual solvent removal *in vacuo*.

Step 3. Evans aldol coupling of Building Block #2 (BB_2)



Building Block #2 (BB_2)



Aldol coupling of Building Block #2 (BB_2). The pooled resin **52** from Step 2 was then split into 30 equal portions (73.5 mg each) and each was subjected to an aldol coupling reaction with a unique BB#2. Resin **52** (73.5 mg) was washed with CH_2Cl_2 (2 x 3 mL x 10 min each) at rt, and then cooled to –78 °C. In a separate vessel, to a stirred solution of acyl oxazolidinone (0.75 mmol, each was azeotropically dried from benzene just prior to reaction):

BB#2 used in split-pool synthesis

BB#2	mmol	FW (g/mol)	mass (g)	BB#2	mmol	FW (g/mol)	mass (g)
BB_2A*S*	0.75	233.26	0.175	**BB_2A*R***	0.75	233.27	0.175
BB_2B*S*	0.75	185.22	0.1389	**BB_2B*R***	0.75	185.22	0.1389
BB_2C*S*	0.75	219.24	0.1644	**BB_2C*R***	0.75	219.24	0.1644
BB_2D*S*	0.75	233.26	0.175	**BB_2D*R***	0.75	233.26	0.175
BB_2E*S*	0.75	213.27	0.16	**BB_2E*R***	0.75	213.27	0.16
BB_2F*S*	0.75	249.26	0.1869	**BB_2F*R***	0.75	249.26	0.1869
BB_2G*S*	0.75	201.22	0.1509	**BB_2G*R***	0.75	201.22	0.1509
BB_2H*S*	0.75	235.24	0.1764	**BB_2H*R***	0.75	235.24	0.1764
BB_2I*S*	0.75	249.26	0.1869	**BB_2I*R***	0.75	249.26	0.1869
BB_2J*S*	0.75	229.27	0.172	**BB_2J*R***	0.75	229.27	0.172
BB_2K*S*	0.75	309.36	0.232	**BB_2K*R***	0.75	309.36	0.232
BB_2L*S*	0.75	261.32	0.196	**BB_2L*R***	0.75	261.32	0.196
BB_2M*S*	0.75	295.33	0.2215	**BB_2M*R***	0.75	295.33	0.2215
BB_2N*S*	0.75	309.36	0.232	**BB_2N*R***	0.75	309.36	0.232
BB_2O*S*	0.75	289.37	0.217	**BB_2O*R***	0.75	289.37	0.217

in CH_2Cl_2 (3 mL) at 0 °C was added a 1M solution of dibutylboron triflate in CH_2Cl_2 (0.788 mL, 0.788 mmol) followed by triethylamine (0.125 mL, 0.900 mmol). The resulting enolate solution was cooled to –78 °C and then transferred rapidly *via* cannula to the vessel containing **52**. The resulting mixture was sealed under a cloud of Ar and maintained at –78 °C for 48 h (72 h for

BB_2M*S*, **BB_2O*S***, **BB_2M*R***, **BB_2N*R***, and **BB_2O*R***) -26 ^oC for 24 h, and 0 ^oC for 2 h (with periodic manual agitation about once every 8 h). The reaction was then quenched with the addition of pH7 phosphate buffer (3 mL), MeOH (3 mL), and 30% aq. H_2O_2 (2 mL), and the resulting mixture was tumbled at 4 ^oC for 12-15 h. Resin was then isolated by filtration and washed as follows: 5 x CH_2Cl_2, 5 x DMF, 5 x THF, 5 x CH_2Cl_2, CH_2Cl_2 x 1 h, 5 x DMF, DMF x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 30 min, and the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield yellow product resin **53**.

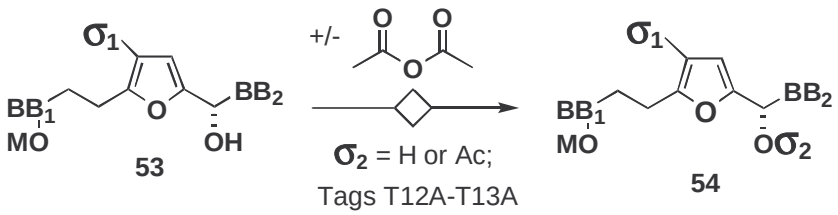
Tagging for building block #2. Each of the 30 portions of product resin **53** loaded with BB_2 was then subjected to a unique encoding reaction. A freshly prepared solution of one or more tags (each tag 4.4 mM in 1.1 mL CH_2Cl_2) was individually prepared for each reaction. The resin **53** (>73.5 mg/rxn) was then added to the solution of tags, placed under an Argon cloud, capped and sealed with parafilm, and allowed to rotate gently for 1 h. To this mixture was then added a freshly prepared solution of rhodium triphenylacetate (4.4 mg./mL, 1.1 mL), and the vial was sealed under Ar, wrapped in aluminum foil to prevent exposure to light, and allowed to tumble gently for 15 h. The resin was then isolated by filtration and washed as follows: 2 x (5 x CH_2Cl_2, CH_2Cl_2 x 15 min.), 3 x (5 x THF, THF x 2 h), 5 x anh. THF, anh. THF x 1 h, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 20 min, and the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield 30 portions of resin **53** representing all combinations of building block #1, σ-element #1, and building block #2, with each combination chemically encoded with polychlorinated aromatic tags.

Encoding scheme for building block #2

	T1A	T2A	T3A	T4A	T5A	T6A	T7A	T8A	T9A	T10A	T11A	T13A
BB_2A*S*									1	1		
BB_2B*S*								1		1		
BB_2C*S*								1	1	1		
BB_2D*S*							1			1		
BB_2E*S*							1		1	1		
BB_2F*S*							1	1		1		
BB_2G*S*							1	1	1	1		
BB_2H*S*						1				1		
BB_2I*S*						1			1	1		
BB_2J*S*						1		1		1		
BB_2K*S*						1		1	1	1		
BB_2L*S*						1	1			1		
BB_2M*S*						1	1		1	1		
BB_2N*S*						1	1	1		1		
BB_2O*S*						1	1	1	1	1		
BB_2A*R*									1		1	
BB_2B*R*								1			1	
BB_2C*R*								1	1		1	
BB_2D*R*							1				1	
BB_2E*R*							1		1		1	
BB_2F*R*							1	1			1	
BB_2G*R*							1	1	1		1	
BB_2H*R*						1					1	
BB_2I*R*						1			1		1	
BB_2J*R*						1		1			1	
BB_2K*R*						1		1	1		1	
BB_2L*R*						1	1				1	
BB_2M*R*						1	1		1		1	
BB_2N*R*						1	1	1			1	
BB_2O*R*						1	1	1	1		1	

Two individual macrobeads were removed from each portion of product resin 53 and subjected to the standard HF-Pyridine cleavage conditions. The cleaved product from each of these 60 individual macrobeads was analyzed by LCMS, and the polychlorinated tags remaining on each macrobead were then cleaved and analyzed by GC. The results are presented below in Table 5. The 30 portions of dry resin 53 were then pooled together in a single polypropylene tube and well-mixed.

Step 4. +/- Acetylation of aldol adducts (σ_2)



+/- Acetylation of aldol adducts (σ_2). The pooled collection of macrobeads **53** from Step 3 (2.157 g, ~0.19 mg/bead, ~11,170 beads) was then split evenly into two portions (1.08 g each). One portion was subjected to acetylation and the other portion was not. For the acetylation reaction, an oven-dried 120 mL sealed tube apparatus (ChemGlass) was charged with resin **53** and flushed with Ar stream for 10 minutes. The resin was then washed with anhydrous CH_2Cl_2 (2 x 50 mL x 10 min each) at rt under Ar (washings removed by cannula) and then resuspended in CH_2Cl_2 (55 mL). To this mixture was then added *i*-Pr_2NEt (3.8 mL, 0.022 mol), DMAP (134 mg, 0.0011 mol), and finally acetic anhydride (1.04 mL, 0.011 mol) with manual agitation of the reaction solution following each addition. The resulting mixture was sealed under a blanket of Ar, the sealed tube was covered with aluminum foil, and the reaction mixture was tumbled at rt for 28 h. Resin was then isolated by filtration into a 20 polypropylene tube and washed as follows: 5 x CH_2Cl_2, 5 x THF, 5 x CH_2Cl_2, CH_2Cl_2 x 45 min, 5 x THF, THF x 45 min, 5 x CH_2Cl_2, CH_2Cl_2x 45 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 20 min, and then the solvent was removed under argon flow followed by residual solvent removal *in vacuo*.

Tagging for +/- acetylation of aldol adducts (σ_2). The product resin from this acetylation reaction was then added to a freshly prepared solution of tag T13A in CH_2Cl_2 (16.7 mL, 4.4 mM). The resulting mixture was sealed under an argon cloud and allowed to rotate gently for 1 h. Then, a freshly prepared solution of rhodium triphenylphosphate (16.66 mL., 4.4 mg./mL.) was added to the mixture of tags and resin. This vial was then sealed under an argon cloud, capped and sealed with parafilm, wrapped in aluminum foil to prevent exposure to light, and allowed to rotate gently for 15 h. The resin was then isolated by filtration and washed as follows: 2 x (5 x CH_2Cl_2, CH_2Cl_2 x 15 min.), 3 x (5 x THF, THF x 2 h), 5 x anh. THF, anh. anh. THF x 45 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 20 min, and the solvent was removed under Ar flow followed by residual solvent removal *in vacuo* to yield two portions of resin **54** representing all combinations of building block #1, σ-element #1, and building block #2, and σ-element #2, with each combination chemically encoded with polychlorinated aromatic tags.

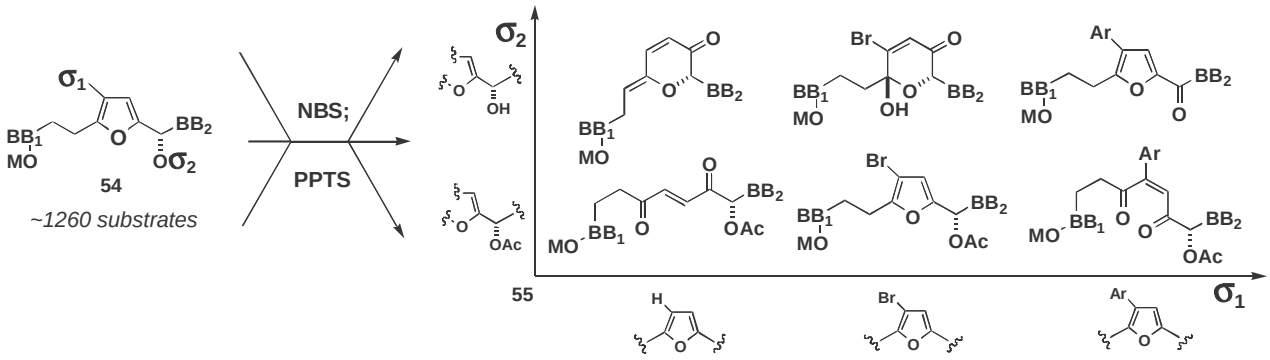
Encoding scheme for σ-element #2

	T1A	T2A	T3A	T4A	T5A	T6A	T7A	T8A	T9A	T10A	T11A	T13A
σ_2A (H)												
σ_2B (Ac)												1

The compound and chemical tags were then cleaved from 60 individual macrobeads 54 (30 from each portion) and analyzed by LCMS and GC, respectively. These data were found to be consistent for 60/60 (100%) of these macrobeads, and the compounds cleaved from 55/60 (92%) of these macrobeads were determined to be ≥ 70% pure by LCMS analysis. The results are presented in Table 6.

427 mg of each of the two portions of light brown product resin were then pooled together in a single polypropylene tube and well mixed to generate a collection **54** representing all possible combinations of **BB_1**, **σ_1**, **BB_2**, and **σ_2** in both enantiomeric and diasteromeric forms.

Step 5. NBS and PPTS-mediated transformation of pooled substrates 54 into ~1260 products 55 representing a complete, combinatorial matrix of molecular skeletons, each derivatized with a complete, combinatorial matrix of building blocks in both enantiomeric and diastereomeric forms.



~1260 products representing overlapping, combinatorial matrices of molecular skeletons and appended building blocks in both enantiomeric/diastereomeric forms.

Experimental: A 120 mL sealed tube apparatus (Chemglass) was charged with THF (64 mL), H_2O (16 mL, THF and H_2O were mixed to homogeneity), and macrobead-bound substrates **54** (853 mg, ~5.2 macrobeads/mg, ~4410 macrobeads, multiplicative factor = 3.5; substrate macrobeads were light brown) at rt under ambient. The resulting mixture was agitated manually for 2 min and then let stand at rt under ambient for 10 minutes. To this mixture was then added $NaHCO_3$ (3.06 g, 36 mmol) and NaOAc (1.48 g, 18 mmol) and the resulting mixture let stand at rt for 10 minutes with periodic manual agitation (2 layers formed). To this mixture was then added NBS (2.136 g, 12 mmol) and the resulting yellow tinted reaction mixture was sealed under ambient and manually agitated. The flask was immediately wrapped in aluminum foil and then tumbled at rt for 1 h (the reaction solution turned dark yellow/yellow-orange). The resin was then isolated by filtration into a 20 mL polypropylene tube using THF and H_2O (macrobeads were light yellow) and then washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 1 h, 5 x THF, THF x 1 h, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anhydrous CH_2Cl_2, anhydrous CH_2Cl_2 x 30 min, 5 x anhydrous CH_2Cl_2 x 2 min each, and then the solvent was removed under Ar flow followed by residual solvent removal *in*

vacuo (~1 h). An oven-dried, 350 mL sealed tube apparatus (Chemglass) was then charged at rt under a cloud of Ar with anh. CH_2Cl_2 (200 mL) and pyridinium *p*-toluenesulfonate (37.7 mg, 0.15 mmol, 0.00075M in CH_2Cl_2). The flask was then sealed and manually agitated to make a clear, colorless solution. The resin was added, the flask was sealed under a cloud of Ar, and the reaction mixture was warmed to 40-45 ^oC and maintained at that temperature for 20 h with periodic manual agitation every 4-8 h. Resin was then isolated by filtration into a 20 mL polypropylene tube (using THF and a glass funnel to transfer resin) and then washed as follows: 5 x THF, 5 x H_2O, 5 x THF, THF/dil. aq. $NaHCO_3$ (sat. aq. $NaHCO_3/H_2O$: 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/dilute aq. NH_4Cl (sat. aq. NH_4Cl/H_2O : 1/2) : 1/1 x 1 h, 5 x THF, 5 x H_2O, 5 x THF, THF/H_2O : 3/1 x 45 min, 5 x THF, THF x 45 min, 5 x CH_2Cl_2, CH_2Cl_2 x 30 min, 5 x anh. CH_2Cl_2, anh. CH_2Cl_2 x 30 min, and 5 x anhydrous CH_2Cl_2 x 2 min each. Solvent was then removed under Ar flow followed by residual solvent removal *in vacuo* to yield a collection of macrobead-bound products **55** representing a complete, combinatorial (3 x 2 = 6) matrix of molecular skeletons, each derivatized with a complete, combinatorial (7 x 15 = 105) matrix of building blocks in both enantiomeric/diastereomeric forms (6 x 15 x 2 = 1260). The compound and chemical tags were cleaved from 120 individual product macrobeads **55** and then analyzed by LCMS and GC, respectively. The LCMS data were consistent with the formation of the functionalized skeleton encoded by the corresponding chemical tags in 120 out of 120 cases (100%). Moreover, 84/120 (70%) of these compounds were determined to be $\geq$ 70% pure by LCMS analysis. These results are presented in Table 7.

2. Supporting tables

Table 1. Results of Steps 3 & 4 of parallel library synthesis

						% Purity		HRMS	
No.	**BB_1**	**σ_1**	**BB_2**	**σ_2**	**^{1}H NMR**	**LCMS, 214 nm**	**Ionization**	**Calculated**	**Observed**
20a	A	H	A	H	√	86	ES+	($M+NH_4^+$) 447.2495	447.2497
20b	A	H	B	H	√	89	ES+	($M+Na^+$) 454.1842	454.1857
20c	A	H	C	H	√	>90	ES+	($M+Na^+$) 508.2675	508.2670
20d	A	Br	A	H	√	>90	ES+	($M+Na^+$) 530.1154	530.1169
20e	A	Br	B	H	√	>90	ES+	($M+Na^+$) 532.0947	532.0940
20f	A	Br	C	H	√	90	ES+	($M+NH_4^+$) 581.2226	581.2242
20g	A	*m*-MePh	A	H	√	>90	ES+	($M+NH_4^+$) 537.2964	537.2972
20h	A	*m*-MePh	B	H	√	89	ES+	($M+NH_4^+$) 539.2757	539.2750
20i	A	*m*-MePh	C	H	√	72	ES+	($M+NH_4^+$) 594.3591	593.3590
20j	B	H	A	H	√	81	ES+	($M+Na^+$) 573.2417	574.2401
20k	B	H	B	H	√	81	ES+	($M+Na^+$) 576.2210	576.2219
20l	B	H	C	H	√	81	ES+	($M+Na^+$) 630.3043	630.3035
20m	B	Br	A	H	√	71	ES+	($M+Na^+$) 652.1522	652.1506
20n	B	Br	B	H	√	71	ES+	($M+Na^+$) 654.1315	654.1289
20o	B	Br	C	H	√	79	ES+	($M+Na^+$) 708.2148	708.2156
20p	B	*m*-MePh	A	H	√	76	ES+	($M+Na^+$) 664.2886	664.2890
20q	B	*m*-MePh	B	H	√	82	ES+	($M+Na^+$) 666.2757	666.2742
20r	B	*m*-MePh	C	H	√	>90	ES+	($M+Na^+$) 720.3512	720.3529
20s	A	H	A	Ac	√	>90	ES+	($M+Na^+$) 494.2155	494.2169
20t	A	H	B	Ac	√	86	ES+	($M+Na^+$) 496.1947	496.1951
20u	A	H	C	Ac	√	>90	ES+	($M+Na^+$) 550.2781	550.2798
20v	A	Br	A	Ac	√	>90	ES+	($M+Na^+$) 572.1260	572.1277
20w	A	Br	B	Ac	√	>90	ES+	($M+Na^+$) 574.1052	574.1057
20x	A	Br	C	Ac	√	>90	ES+	($M+Na^+$) 628.1886	628.1874
20y	A	*m*-MePh	A	Ac	√	>90	ES+	($M+Na^+$) 584.2624	584.2609
20z	A	*m*-MePh	B	Ac	√	>90	ES+	($M+Na^+$) 586.2417	586.2419
20aa	A	*m*-MePh	C	Ac	√	75	ES+	($M+Na^+$) 640.3250	640.3244
20bb	B	H	A	Ac	√	77	ES+	($M+Na^+$) 616.2523	616.2524
20cc	B	H	B	Ac	√	81	ES+	($M+Na^+$) 618.2315	618.2334
20dd	B	H	C	Ac	√	76	ES+	($M+Na^+$) 672.3149	672.3134
20ee	B	Br	A	Ac	√	71	ES+	($M+Na^+$) 694.1628	694.1645
20ff	B	Br	B	Ac	√	67	ES+	($M+Na^+$) 696.1420	696.1391
20gg	B	Br	C	Ac	√	73	ES+	($M+Na^+$) 750.2254	750.2261
20hh	B	*m*-MePh	A	Ac	√	87	ES+	($M+Na^+$) 706.2992	706.3015
20ii	B	*m*-MePh	B	Ac	√	>90	ES+	($M+Na^+$) 708.2785	708.2781
20jj	B	*m*-MePh	C	Ac	√	>90	ES+	($M+Na^+$) 762.3618	763.3609

√: ^{1}H NMR spectrum consistent with anticipated structure

Table 2. Results of Step 5 of parallel library synthesis.

						% Purity		HRMS	
No.	**BB_1**	**σ_1**	**BB_2**	**σ_2**	**^{1}H NMR**	**LCMS, 214 nm**	**Ionization**	**Calculated**	**Observed**
9	A	H	A	H	√	83	ES+	$(M+H^+)$ 428.2703	428.2061
21	A	H	B	H	√	>70	ES+	$(M+Na^+)$ 452.1685	452.1700
22	A	H	C	H	√	>80	ES+	$(M+H^+)$ 484.2699	484.2699
10	A	H	A	Ac	√	>90	ES+	$(M+H^+)$ 488.2284	488.2275
23	A	H	B	Ac	√	85	ES+	$(M+NH_4^+)$ 507. 2343	507.2358
24	A	H	C	Ac	√	78	ES+	$(M+NH_4^+)$ 561.3176	561.3162
17	A	Br	A	H	√	>90 (10:1 e.r.)	ES+	$(M+Na^+)$ 546.1103	546.1086
25	A	Br	B	H	√	>90 (1:1 e.r.)	ES+	$(M+Na^+)$ 548.0896	548.0895
26	A	Br	C	H	√	89 (8:1 e.r)	ES+	$(M+Na^+)$ 602.1729	602.1733
14'	A	Br	A	Ac	√	>90	ES+	$(M+Na^+)$ 572.1260	572.1288
27	A	Br	B	Ac	√	>90	ES+	$(M+Na^+)$ 574.1052	574.1038
28	A	Br	C	Ac	√	>90	ES+	$(M+NH_4^+)$ 623.2332	623.2353
18	A	*m*-MePh	A	H	√	80	ES+	$(M+H^+)$ 518.2542	518.2532
29	A	*m*-MePh	B	H	√	52	ES+	$(M+Na^+)$ 542.2155	542.2152
30	A	*m*-MePh	C	H	√	71	ES+	$(M+H^+)$ 574.3168	574.3163
19	A	*m*-MePh	A	Ac	√	76	ES+	$(M+NH_4^+)$ 595.3019	595.3034
31	A	*m*-MePh	B	Ac	√	44	ES+	$(M+NH_4^+)$ 597.2812	597.2803
32	A	*m*-MePh	C	Ac	√	56	ES+	$(M+Na^+)$ 656.3199	656.3177
33	B	H	A	H	√	27	ES+	$(M+H^+)$ 550.2441	550.2437
34	B	H	B	H	√	21	ES+	$(M+H^+)$ 552.2233	552.2233
35	B	H	C	H	√	28	ES+	$(M+H^+)$ 606.3067	606.3066
36	B	H	A	Ac	√	70	ES+	$(M+NH_4^+)$ 627.2918	627.2930
37	B	H	B	Ac	√	70	ES+	$(M+H^+)$ 612.2445	612.2455
38	B	H	C	Ac	√	59	ES+	$(M+H^+)$ 666.3278	666.3286
39	B	Br	A	H	√	74 (8:1 e.r)	ES+	$(M+NH_4^+)$ 663.1917	663.1911
40	B	Br	B	H	√	72 (3:1 e.r)	ES+	$(M+Na^+)$ 670.1264	670.1268
41	B	Br	C	H	√	68 (8:1 e.r)	ES+	$(M+NH_4^+$+) 719.2543	719.2547
42	B	Br	A	Ac	√	76	ES+	$(M+NH_4^+)$ 689.2074	689.2081
43	B	Br	B	Ac	√	>90	ES+	$(M+NH_4^+)$ 691.1866	691.1869
44	B	Br	C	Ac	√	>90	ES+	$(M+NH_4^+)$ 745.2700	745.2704
45	B	*m*-MePh	A	H	√	71	ES+	$(M+H^+)$ 640.2910	640.2911
46	B	*m*-MePh	B	H	√	74	ES+	$(M+H^+)$ 642.2703	642.2705
47	B	*m*-MePh	C	H	√	84	ES+	$(M+H^+)$ 696.3536	696.3550
48	B	*m*-MePh	A	Ac	√	33	ES+	$(M+NH_4^+)$ 717.3387	717.3383
49	B	*m*-MePh	B	Ac	√	27	ES+	$(M+NH_4^+)$ 719.3180	719.3179
50	B	*m*-MePh	C	Ac	√	86	ES+	$(M+NH_4^+)$ 773.4013	773.4014

√: ^{1}H NMR spectrum consistent with anticipated structure, e.r. = epimeric ratio

Table 3. Results of screening for building block #1

BB_1	σ_1	^{1}H NMR	% Purity LCMS, λ_{280}	% Purity LCMS, λ_{214}	Ionization	HRMS Calculated	HRMS Observed
BB_1A	H	√	>95	-	EI+	(m/z) 168.0786	168.0785
BB_1B	H	√	>85	-	ES+	($M+H^+$) 197.1177	197.1177
BB_1C	H	√	>95	-	EI+	(m/z) 252.1725	252.1723
BB_1D	H	√	>95	-	EI+	(m/z) 198.0892	198.0893
BB_1E	H	√	>95	-	EI+	(m/z) 242.1154	242.1152
BB_1F	H	√	93	-	EI+	(m/z) 318.1467	318.1464
BB_1G	H	√	>95	-	ES+	($M+Na^+$) 533.2151	533.2145
BB_1A	Br	√	>95	-	ES+	($M+H^+$) 246.9970	246.9969
BB_1B	Br	√	-	>95	ES+	($M+H^+$) 397.0650	397.0645
BB_1C	Br	√	>90	-	ES+	($M+H^+$) 331.0909	331.0906
BB_1D	Br	√	>95	-	ES+	($M+H^+$) 277.0075	277.0066
BB_1E	Br	√	>95	-	ES+	($M+H^+$) 321.0337	321.0326
BB_1F	Br	√	>95	-	ES+	($M+H^+$) 397.0650	387.0643
BB_1G	Br	√	84	-	ES+	($M+Na^+$) 611.1256	611.1246
BB_1A	*m*-MeAr	√	-	90	ES+	($M+H^+$) 259.1134	259.1340
BB_1B	*m*-MeAr	√	-	>95	ES+	($M+H^+$) 287.1647	287.1647
BB_1C	*m*-MeAr	√	-	>95	ES+	($M+H^+$) 343.2273	343.2272
BB_1D	*m*-MeAr	√	-	92	ES+	($M+H^+$) 289.1440	289.1430
BB_1E	*m*-MeAr	√	-	89	ES+	($M+H^+$) 333.1702	333.1709
BB_1F	*m*-MeAr	√	-	83	ES+	($M+H^+$) 409.2015	409.2009
BB_1G	*m*-MeAr	√	-	80	ES+	($M+Na^+$) 623.2621	623.2615

√ = ^{1}H NMR spectrum consistent with anticipated structure

Table 4. Results of screening for building block #2

	% Conversion	d.r.	% Purity		HRMS	
BB2	**^{1}H NMR**	**^{1}H NMR**	**LCMS, λ_{214}**	**Ionization**	**Calculated**	**Found**
BB$_2$A*S*	>95	20:1	86	ES+	(M+NH_4^+) 447.2495	447.2497
BB$_2$B*S*	>95	20:1	92	ES+	(M+Na^+) 404.2049	404.2049
BB$_2$C*S*	>95	20:1	91	ES+	(M+Na^+) 438.1893	438.1899
BB$_2$D*S*	>95	20:1	>95	ES+	(M+Na^+) 452.2049	452.2058
BB$_2$E*S*	>90	8:1	>95	ES+	(M+NH_4^+) 427.2808	427.2805
BB$_2$F*S*	>95	10:1	92	ES+	(M+Na^+) 468.1998	468.2001
BB$_2$G*S*	>95	12:1	86	ES+	(M+Na^+) 420.1998	420.2002
BB$_2$H*S*	>95	11:1	83	ES+	(M+Na^+) 454.1842	454.1857
BB$_2$I*S*	>95	16:1	77	ES+	(M+Na^+) 468.1998	468.1985
BB$_2$J*S*	>95	20:1	97	ES+	(M+Na^+) 448.2311	448.2314
BB$_2$K*S*	>95	20:1	97	ES+	(M+Na^+) 528.2362	528.2366
BB$_2$L*S*	>95	10:1	72	ES+	(M+Na^+) 480.2362	480.2371
BB$_2$M*S*	>85	7:1	90	ES+	(M+Na^+) 514.2206	514.2219
BB$_2$N*S*	>90	9:1	93	ES+	(M+NH_4^+) 523.2808	523.2816
BB$_2$O	>85	9:1	96	ES+	(M+Na^+) 508.2675	508.2670

Table 5. Results of Step 3 of split-pool library synthesis

	Structure encoded by chemical tags			% Purity by LCMS analysis	ES+ Mass spec			Mass spec consistent with tag-
Macrobead	**BB1**	**σ1**	**BB2**	**(λ = 214 nm)**	**Ion**	**Calculated**	**Observed**	**encoded structure**
53a	A	C	A*S*	>90	$M+Na^+$	514	514	√
53b	E	B	A*S*	>90	$M+Na^+$	576	576	√
53c	A	C	B*S*	>90	$M+Na^+$	466	466	√
53d	E	B	B*S*	>90	$M+Na^+$	528	528	√
53e	B	A	C*S*	>90	$M+Na^+$	438	438	√
53f	B	C	C*S*	90	$M+Na^+$	528	528	√
53g	D	A	D*S*	>90	$M+Na^+$	454	454	√
53h	A	C	D*S*	>90	$M+Na^+$	514	514	√
53i	G	A	E*S*	67	$M+Na^+$	746	746	√
53j	A	B	E*S*	>90	$M+Na^+$	482	482	√
53k	C	C	F*S*	88	$M+Na^+$	614	614	√
53l	G	B	F*S*	55	$M+NH_4^+$	855	855	√
53m	G	A	G*S*	56	$M+Na^+$	734	734	√
53n	A	A	G*S*	>90	$M+Na^+$	392	392	√
53o	C	A	H*S*	>90	$M+Na^+$	510	510	√
53p	B	C	H*S*	88	$M+Na^+$	544	544	√
53q	D	C	I*S*	87	$M+Na^+$	560	560	√
53r	F	C	I*S*	88	$M+Na^+$	680	680	√
53s	C	B	J*S*	>90	$M+Na^+$	582	582	√
53t	D	C	J*S*	>90	$M+Na^+$	540	540	√
53u	E	C	K*S*	>90	$M+Na^+$	664	664	√
53v	C	A	K*S*	>90	$M+Na^+$	584	584	√
53w	E	C	L*S*	85	$M+Na^+$	616	616	√
53x	C	A	L*S*	90	$M+Na^+$	536	536	√
53y	G	B	M*S*	58	$M+NH_4^+$	901	901	√
53z	G	A	M*S*	74	$M+NH_4^+$	823	823	√
53aa	G	C	N*S*	ND	$M+NH_4^+$	927	927	√
53bb	E	C	N*S*	82	$M+Na^+$	664	664	√
53cc	E	A	O*S*	91	$M+Na^+$	554	554	√
53dd	F	A	O*S*	66	$M+Na^+$	630	630	√
53ee	B	C	A*R*	86	$M+Na^+$	542	542	√
53ff	E	B	A*R*	>90	$M+Na^+$	576	576	√
53gg	F	C	B*R*	83	$M+Na^+$	616	616	√
53hh	G	A	B*R*	78	$M+Na^+$	718	718	√
53ii	E	A	C*R*	>90	$M+Na^+$	484	484	√
53jj	D	C	C*R*	84	$M+Na^+$	530	430	√
53kk	G	A	D*R*	86	$M+NH_4^+$	761	761	√
53ll	G	A	D*R*	81	$M+NH_4^+$	761	761	√
Macrobead	**BB1**	**σ1**	**BB2**	**(λ = 214 nm)**	**Ion**	**Calculated**	**Observed**	**encoded structure**
53mm	D	*C*	E*R*	71	$M+Na^+$	524	524	√

53nn	A	B	E*R*	75	$M+Na^+$	482	482	√
53oo	E	C	F*R*	89	$M+Na^+$	604	604	√
53pp	C	*A*	F*R*	>90	$M+Na^+$	524	524	√
53qq	ND	ND	ND	89	ND	ND	ND	-
53rr	C	A	G*R*	>90	$M+Na^+$	476	476	√
53ss	F	B	H*R*	>90	$M+Na^+$	654	654	√
53tt	ND	ND	ND	>90	ND	ND	ND	-
53uu	A	B	I*R*	>90	$M+Na^+$	518	518	√
53vv	F	B	I*R*	>90	$M+Na^+$	668	668	√
53ww	F	B	J*R*	90	$M+Na^+$	648	648	√
53xx	G	B	J*R*	61	$M+NH_4^+$	835	835	√
53yy	A	B	K*R*	>90	$M+Na^+$	578	578	√
53zz	B	C	K*R*	67	$M+Na^+$	618	618	√
53aaa	G	A	L*R*	56	$M+NH_4^+$	789	789	√
53bbb	C	C	L*R*	62	$M+Na^+$	626	626	√
53ccc	G	C	M*R*	69	$M+NH_4^+$	913	913	√
53ddd	C	C	M*R*	67	$M+Na^+$	660	660	√
53eee	B	B	N*R*	>90	$M+Na^+$	606	606	√
53fff	G	B	N*R*	63	$M+NH_4^+$	915	915	√
53ggg	G	B	O*R*	36	$M+NH_4^+$	895	895	√
53hhh	A	C	O*R*	58	$M+Na^+$	570	570	√

Table 6. Results of Step 4 of split-pool library synthesis.

	Structure encoded by chemical tags				LCMS analysis (λ = 214 nm)		ES+ Mass Spec			Mass spec consistent with tag-encoded structure
Macrobead	**BB1**	**σ1**	**BB2**	**σ2**	**Purity (%)**	**t_R (min)**	**Ion**	**Calculated**	**Observed**	
54a	F	C	H*S*	A	>90	9.36	$M+NH_4^+$	661	661	√
54b	G	B	K*S*	A	75	11.89	$M+NH_4^+$	915	915	√
54c	D	C	C*R*	A	84	8.15	$M+NH_4^+$	525	525	√
54d	F	C	E*S*	A	>90	10.10	$M+NH_4^+$	639	639	√
54e	A	C	O*S*	A	71	9.88	$M+NH_4^+$	565	565	√
54f	A	B	B*S*	A	87	6.98	$M+Na^+$	454	454	√
54g	C	C	J*S*	A	>90	9.12	$M+NH_4^+$	499	499	√
54h	C	B	K*R*	A	>70	11.54	$M+Na^+$	662	662	√
54i	C	A	A*S*	A	88	9.55	$M+Na^+$	508	508	√
54j	E	A	D*R*	A	90	6.70	$M+Na^+$	498	498	√
54k	F	A	L*S*	A	>90	9.08	$M+Na^+$	602	602	√
54l	E	A	J*R*	A	87	5.43	$M+NH_4^+$	489	489	√
54m	C	A	B*S*	A	89	9.14	$M+Na^+$	460	460	√
54n	F	A	G*S*	A	72	7.15	$M+NH_4^+$	537	537	√
54o	G	B	A*R*	A	76	11.06	$M+NH_4^+$	839	839	√
54p	F	B	H*R*	A	78	8.43	$M+Na^+$	654	654	√
54q	A	A	O*R*	A	>90	8.07	$M+Na^+$	480	480	√
54r	G	B	J*S*	A	87	10.37	$M+NH_4^+$	835	835	√
54s	B	A	D*S*	A	87	7.99	$M+Na^+$	452	452	√
54t	A	B	K*R*	A	86	8.97	$M+NH_4^+$	573	573	√
54u	D	B	B*R*	A	89	6.59	$M+Na^+$	484	484	√
54v	B	C	F*R*	A	91	8.79	$M+NH_4^+$	553	553	√
54w	F	B	B*R*	A	74	8.76	$M+Na^+$	604	604	√
54x	E	A	D*R*	A	>90	6.66	$M+NH_4^+$	493	493	√
54y	C	H	O*R*	A	>70	10.79	$M+Na^+$	564	564	√
54z	C	A	M*R*	A	<70	10.34	$M+Na^+$	570	570	√
54aa	B	C	K*R*	A	<70	10.44	$M+NH_4^+$	613	613	√
54bb	G	C	H*S*	A	88	10.74	$M+NH_4^+$	853	853	√
54cc	F	H	K*R*	A	80	9.48	$M+NH_4^+$	645	645	√
54dd	A	C	O*S*	A	68	9.83	$M+NH_4^+$	565	565	√
54ee	E	B	H*R*	B	>90	7.50	$M+NH_4^+$	615	615	√
54ff	F	C	N*R*	B	85	12.59	$M+NH_4^+$	777	777	√
54gg	C	A	K*S*	B	>90	11.76	$M+NH_4^+$	621	621	√
54hh	B	B	O*S*	B	>70	10.85	$M+NH_4^+$	623	623	√
54ii	E	B	O*R*	B	69	9.56	$M+NH_4^+$	669	669	√
54jj	D	B	M*S*	B	88	9.35	$M+NH_4^+$	631	631	√
54kk	C	A	J*R*	B	>90	10.28	$M+NH_4^+$	541	541	√
54ll	G	A	I*S*	B	>90	10.71	$M+NH_4^+$	819	819	√
Macrobead	**BB1**	**σ1**	**BB2**	**σ2**	**Purity (%)**	**t_R (min)**	**Ion**	**Calculated**	**Observed**	**tag-encoded structure**

54mm	B	*A*	M*S*	B	90	9.57	$M+NH_4^+$	551	551	√
54nn	G	B	J*R*	B	71	11.43	$M+NH_4^+$	877	877	√
54oo	A	B	A*R*	B	>90	8.95	$M+NH_4^+$	539	539	√
54pp	A	C	G*S*	B	77	8.78	$M+NH_4^+$	519	519	√
54qq	A	C	N*R*	B	88	11.27	$M+NH_4^+$	627	627	√
54rr	B	C	J*S*	B	>90	10.07	$M+NH_4^+$	575	575	√
54ss	B	A	J*S*	B	>90	8.27	$M+NH_4^+$	485	485	√
54tt	B	C	F*R*	B	>90	9.88	$M+NH_4^+$	595	595	√
54uu	A	B	M*R*	B	>90	9.66	$M+NH_4^+$	601	601	√
54vv	B	A	O*S*	B	>90	9.95	$M+NH_4^+$	545	545	√
54ww	C	A	M*S*	B	>90	11.31	$M+NH_4^+$	607	607	√
54xx	A	C	J*S*	B	>90	9.39	$M+NH_4^+$	547	547	√
54yy	D	A	J*S*	B	>90	7.01	$M+NH_4^+$	487	487	√
54zz	A	C	A*S*	B	>90	9.87	$M+NH_4^+$	551	551	√
54aaa	D	A	H*R*	B	>90	6.62	$M+NH_4^+$	493	493	√
54bbb	E	C	H*R*	B	>90	8.56	$M+NH_4^+$	627	627	√
54ccc	C	B	C*S*	B	<70	11.12	$M+Na^+$	614	614	√
54ddd	F	B	L*S*	B	73	10.83	$M+NH_4^+$	717	717	√
54eee	D	B	L*S*	B	>90	9.20	$M+NH_4^+$	597	597	√
54fff	A	A	E*S*	B	>90	8.06	$M+Na^+$	446	446	√
54ggg	D	A	E*S*	B	>90	7.71	$M+NH_4^+$	471	471	√
54hhh	D	C	J*R*	B	87	9.08	$M+NH_4^+$	577	577	√

Table 7. Results of step 5 of split-pool library synthesis

	Structure encoded by chemical tags				LCMS analysis (λ = 214 nm)		ES+ Mass Spec			Mass Spec consistent with tag-encoded structure
Macrobead	**BB1**	**σ1**	**BB2**	**σ2**	**Purity (%)**	**t_R (min)**	**Ion**	**Calculated**	**Observed**	
55a	F	B	D*R*	B	37	10.61	$M+NH_4^+$	689	689	√
55b	E	A	A*R*	B	>90	6.98	$M+NH_4^+$	551	551	√
55c	B	C	K*S*	B	65	10.39	$M+NH_4^+$	671	671	√
55d	D	A	J*R*	A	21	6.06	$M+H^+$	426	426	√
55e	E	A	F*R*	B	>90	6.38	$M+NH_4^+$	567	567	√
55f	G	B	D*S*	A	49	10.98	$M+NH_4^+$	855	855	√
55g	D	A	L*S*	B	>90	7.75	$M+NH_4^+$	535	535	√
55h	B	A	I*R*	B	>90	7.78	$M+NH_4^+$	521	521	√
55i	B	A	I*R*	A	>90	7.67	$M+H^+$	444	444	√
55j	F	C	O*R*	B	43	11.43	$M+NH_4^+$	773	773	√
55k	G	A	F*R*	A	82	9.91	$M+NH_4^+$	775	775	√
55l	D	B	M*R*	A	79	8.06	$M+NH_4^+$	605	605	√
55m	B	B	B*R*	A	>90	7.45	$M+Na^+$	498	498	√
55n	A	B	F*S*	B	>90	8.31	$M+Na^+$	560	560	√
55o	C	B	N*S*	A	<70	11.7	$M+Na^+$	678	678	√
55p	G	B	M*S*	A	47	11.32	$M+NH_4^+$	917	917	√
55q	F	B	N*R*	A	74	10.32	$M+NH_4^+$	739	739	√
55r	B	A	C*R*	A	>90	7.73	$M+H^+$	414	414	√
55s	B	A	F*S*	A	>90	7.26	$M+H^+$	444	444	√
55t	G	A	B*R*	A	68	10.10	$M+NH_4^+$	711	711	√
55u	D	C	H*S*	B	71	7.81	$M+H^+$	582	582	√
55v	D	C	E*R*	A	54	9.28	$M+H^+$	500	500	√
55w	A	B	K*S*	B	>90	9.99	$M+NH_4^+$	615	615	√
55x	A	C	H*S*	A	49	8.76	$M+H^+$	492	492	√
55y	B	C	L*R*	B	32	10.12	$M+NH_4^+$	623	623	√
55z	E	B	C*S*	A	>90	6.58	$M+NH_4^+$	573	573	√
55aa	B	B	K*R*	B	>90	10.63	$M+NH_4^+$	643	643	√
55bb	C	A	C*R*	A	>90	9.72	$M+H^+$	470	470	√
55cc	E	A	J*R*	A	51	6.06	$M+H^+$	470	470	√
55dd	F	A	G*S*	A	60	7.54	$M+H^+$	518	518	√
55ee	B	A	N*R*	A	>90	9.74	$M+H^+$	504	504	√
55ff	A	C	O*S*	A	3	10.73	$M+H^+$	546	546	√
55gg	B	A	L*S*	A	>90	8.81	$M+H^+$	456	456	√
55hh	C	A	F*R*	B	>90	9.26	$M+NH_4^+$	577	577	√
55ii	B	A	F*S*	A	>90	7.27	$M+H^+$	444	444	√
55jj	C	B	O*S*	A	>90	11.71	$M+Na^+$	658	658	√
55kk	G	B	F*R*	A	65	10.07	$M+NH_4^+$	871	871	√
55ll	A	C	N*S*	A	84	10.86	$M+H^+$	566	566	√
55mm	D	B	I*S*	A	78	6.69	$M+NH_4^+$	559	559	√
Macrobead	**BB1**	**σ1**	**BB2**	**σ2**	**Purity**	**t_R (min)**	**Ion**	**Calculated**	**Observed**	**Tag-encoded**

					(%)					**structure**
55nn	E	B	I*R*	B	<70	8.12	M+NH_4^+	629	629	√
55oo	A	B	N*R*	B	>90	10.36	M+NH_4^+	615	615	√
55pp	E	B	L*S*	A	87	7.75	M+NH_4^+	615	615	√
55qq	B	B	L*S*	B	>90	10.22	M+Na^+	600	600	√
55rr	F	B	B*S*	A	64	8.38	M+NH_4^+	615	615	√
55ss	C	A	D*S*	A	>90	10.54	M+H^+	484	484	√
55tt	C	A	E*R*	B	>70	10.14	M+H^+	524	524	√
55uu = 18	B	C	A*S*	A	>90	10.06	M+H^+	518	518	√
55vv	D	C	L*S*	A	>90	9.87	M+H^+	548	548	√
55ww	F	A	H*R*	B	>90	7.98	M+NH_4^+	629	629	√
55xx	G	C	L*S*	A	ND	>12.5	M+NH_4^+	878	878	√
55yy	C	C	J*S*	B	49	10.92	M+H^+	630	630	√
55zz	E	B	H*R*	B	>70	7.51	M+NH_4^+	615	615	√
55aaa	E	C	A*R*	A	79	8.96	M+H^+	564	564	√
55bbb	A	B	M*S*	A	>70	8.24	M+Na^+	580	580	√
55ccc	D	C	L*R*	A	61	9.83	M+H^+	548	548	√
55ddd	C	A	I*S*	A	>90	9.40	M+H^+	500	500	√
55eee	D	A	H*S*	B	>90	5.97	M+NH_4^+	509	509	√
55fff	B	A	L*R*	B	>70	8.69	M+Na^+	538	538	√
55ggg	A	C	G*R*	B	41	8.95	M+Na^+	540	540	√
55hhh	F	A	J*R*	A	43	8.38	M+H^+	546	546	√
55iii	A	C	N*R*	A	>90	10.95	M+H^+	566	566	√
55jjj	A	C	L*S*	A	>90	10.10	M+H^+	518	518	√
55kkk	B	A	A*R*	B	>90	8.04	M+NH_4^+	505	505	√
55lll	C	C	M*S*	B	ND	12.07	M+NH_4^+	713	713	√
55mmm	E	C	A*S*	A	78	8.97	M+H^+	564	564	√
55nnn	C	C	N*S*	A	ND	>12.5	M+H^+	650	650	√
55ooo	C	B	D*R*	A	>90	10.60	M+Na^+	602	602	√
55ppp	B	B	G*R*	B	>90	8.55	M+Na^+	540	540	√
55qqq	F	A	M*R*	A	70	9.63	M+H^+	612	612	√
55rrr	A	A	L*R*	A	>90	7.98	M+H^+	428	428	√
55sss	E	A	O*S*	A	81	8.30	M+H^+	530	530	√
55ttt	E	C	B*R*	A	72	8.41	M+H^+	516	516	√
55uuu	G	B	N*S*	A	37	12.08	M+NH_4^+	931	931	√
55vvv	F	C	K*R*	A	82	11.78	M+H^+	716	716	√
55www	A	B	M*S*	A	>90	8.24	M+Na^+	580	580	√
55xxx	A	C	A*R*	A	>90	8.61	M+H^+	476	476	√
55yyy	F	B	I*S*	B	79	9.96	M+Na^+	710	710	√
55zzz	A	C	G*S*	A	42	8.50	M+H^+	458	458	√
55aaaa	G	C	F*S*	A	38	11.78	M+NH_4^+	865	865	√
55bbbb	G	C	C*S*	B	85	11.21	M+NH_4^+	895	895	√
55cccc	D	A	O*R*	A	72	8.42	M+H^+	486	486	√
Macrobead	**BB1**	**σ1**	**BB2**	**σ2**	**Purity (%)**	**t_R (min)**	**Ion**	**Calculated**	**Observed**	**Tag-encoded structure**
55dddd	C	B	H*R*	A	>70	9.04	M+Na^+	604	604	√

55eeee	D	C	J*S*	B	80	8.29	$M+H^+$	576	576	√
55ffff	G	A	N*S*	A	75	11.43	$M+NH_4^+$	835	835	√
55gggg	F	A	F*S*	B	>90	8.30	$M+NH_4^+$	643	643	√
55hhhh	E	A	A*S*	B	>90	6.93	$M+H^+$	534	534	√
55iiii	E	C	H*S*	A	66	8.28	M+H++	566	566	√
55jjjj	F	C	A*S*	A	69	10.67	$M+H^+$	640	640	√
55kkkk	E	B	F*S*	A	81	6.28	$M+NH_4^+$	603	603	√
55llll	D	B	A*R*	A	90	7.00	$M+NH_4^+$	543	543	√
55mmmm	C	B	J*R*	A	>90	9.60	$M+Na^+$	598	598	√
55nnnn	C	A	C*S*	A	>90	9.71	$M+H^+$	470	470	√
55oooo	B	C	D*S*	B	73	9.87	$M+NH_4^+$	595	595	√
55pppp	B	A	O*R*	B	<70	9.4	$M+Na^+$	566	566	√
55qqqq	A	A	F*S*	A	>90	6.35	$M+H^+$	416	416	√
55rrrr	E	A	B*S*	A	>90	5.95	$M+H^+$	426	426	√
55ssss	C	B	F*S*	B	>90	10.90	$M+Na^+$	644	644	√
55tttt	F	C	K*R*	B	79	10.95	$M+NH_4^+$	793	793	√
55uuuu	C	C	H*R*	A	73	11.05	$M+H^+$	576	576	√
55vvvv	C	B	A*R*	B	>70	11.58	$M+Na^+$	628	628	√
55wwww	F	C	D*S*	B	>90	10.47	$M+NH_4^+$	717	717	√
55xxxx	C	B	B*S*	A	69	9.62	$M+Na^+$	554	554	√
55yyyy	F	A	M*R*	B	85	9.49	$M+NH_4^+$	689	689	√
55zzzz	F	A	D*R*	A	69	8.90	$M+H^+$	550	550	√
55aaaaa	E	B	L*S*	A	89	7.74	$M+NH_4^+$	615	615	√
55bbbbb	B	B	H*S*	B	>90	8.76	$M+Na^+$	574	574	√
55ccccc	F	B	M*S*	B	>90	10.79	$M+NH_4^+$	751	751	√
55ddddd	D	A	J*S*	B	>90	6.42	$M+NH_4^+$	503	503	√
55eeeee	G	A	H*R*	B	80	9.59	$M+NH_4^+$	821	821	√
55fffff	D	B	N*S*	A	>90	8.76	$M+Na^+$	624	624	√
55ggggg	C	C	K*R*	B	ND	>12.5	$M+Na^+$	732	732	√
55hhhhh	E	A	F*R*	B	>90	6.33	$M+NH_4^+$	567	567	√
55iiiii	C	C	L*R*	A	ND	>12.5	$M+H^+$	602	602	√
55jjjjj	D	A	N*R*	A	65	8.71	$M+H^+$	506	506	√
55kkkkk	D	C	O*S*	A	76	10.49	$M+H^+$	576	576	√
55llllll	A	A	E*R*	A	>90	7.48	$M+H^+$	380	380	√
55mmmmm	A	C	N*R*	B	35	11.80	$M+Na^+$	648	648	√
55nnnnn	C	C	I*S*	A	>90	11.86	$M+H^+$	590	590	√
55ooooo	F	A	K*R*	A	71	9.90	$M+H^+$	626	626	√
55ppppp	A	C	A*R*	A	>90	9.44	$M+H^+$	490	490	√

3. Supporting references and notes

1. List of abbreviations: **Ac** acetyl, **9-BBN** 9-borabicyclo [3.3.1] nonane, **CAN** ceric ammonium nitrate, **DCM** dichloromethane, **DMAP** 4-(dimethylamino)pyridine, **DMF** *N*,*N*-dimethylformamide, **dppf** 1,1'-bis(diphenylphosphino)ferrocene, **EtOAc** ethyl acetate, **LCMS** tandem liquid

chromatography and mass spectrometry, **MAS NMR** magic angle spinning nuclear magnetic resonance spectrometry, **MeOH** methanol, **NBS** *N*-bro0mosuccinimide, **NMM** *N*-methylmorpholine, **NMO** *N*-methylmorpholine *N*-oxide, **NMR**, nuclear magnetic resonance spectrometry, **PPTS** pyridinium *para*-toluenesulfonate, **TEAAT** tetraethylammonium acetate tetrahydrate, **T*f*OH** trifluoromethanesulfonic acid, **THF** tetrahydrofuran, **TLC** thin layer chromatography.

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