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The Design and Synthesis of Substituted Biphenyl Libraries

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Abstract—A novel scaffold system for the generation of diversity libraries has been designed which allows for rapid modification not only of functional groups, but their spatial arrangements as well. The biphenyl scaffold allows for display of three or four diverse functional groups in a wide variety of spatial arrangements depending on the substitution pattern selected. The libraries are generated by a combination of solution and solid-phase chemistries and are cleaved off the solid-support for screening.

The rapid chemical generation of molecular diversity libraries, followed by their evaluation using high-throughput screening systems, represents a major paradigm shift for identifying and optimizing new lead structures for the pharmaceutical industry.[1–4] The preparation of the first non-peptide, 'drug-like' libraries took place just 3 years ago.[5,6] Since that time we have seen the steady development of new chemistries applied to library generation to the point where it is now possible to synthesize an almost endless variety of non-peptide libraries using these methodologies.

Such libraries will be useful for lead optimization, as well as for new lead discovery. Already, these technologies have proven immensely useful in carrying out *rapid structure–activity studies* for optimization of known leads.[7] The question remains as to what structural classes of molecule(s) will be most useful in a *new lead discovery library*?

A number of scaffolding approaches, where functional groups postulated to be important for interaction with a biological target are held in a rigid alignment, have been reported.[8–14]

We also have been very active in preparing a large number of rigid or semi-rigid scaffolds to which a wide variety of functional groups could be attached and have reported one example.[15]

In these examples, rigid scaffolds with fixed display orientations have been used to generate large libraries. However, for effective lead discovery a facile method to functionalize a small molecule scaffold with not only a wide variety of functional groups but also in a wide variety of spatial configurations would be ideal. This approach represents a more difficult design challenge.

At Sphinx, we have been developing just such a system.

The universal library concept

Biological macromolecules (receptor, enzyme, antibody, etc.) recognize ligands through a number of precisely oriented physicochemical interactions described by parameters such as size, hydrogen bonding ability, hydrophobic interactions, etc. We are attempting to explore this multi-parameter space by designing libraries which orient a collection of groups responsible for these binding interactions at large numbers of unique locations in space through a scaffolding approach. Each scaffold has the ability to display three or four diverse functional groups in a large number of spatial orientations, and furthermore, the scaffolds are easily modified to change their size, shape, and physical properties. Each unique, but related scaffold will explore a collection of functional groups in unique sizes, shapes, and volumes. A collection of such libraries should rapidly explore multi-parameter space and consequently identify a chemical lead for any biological target of interest.

To prepare such a library rapidly using the smallest number of building blocks, the Sphinx double combinatorial approach has been utilized. In this scheme (Figure 1), functional groups, representing various physicochemical properties (and include for example alkyl, aryl, alcohol, amino, and heterocyclic containing side chains), are introduced onto the first scaffold building block. The second scaffold building block is then added, followed by additional rounds of

Key words: library, biphenyl, solid-phase synthesis, multiple simultaneous synthesis.

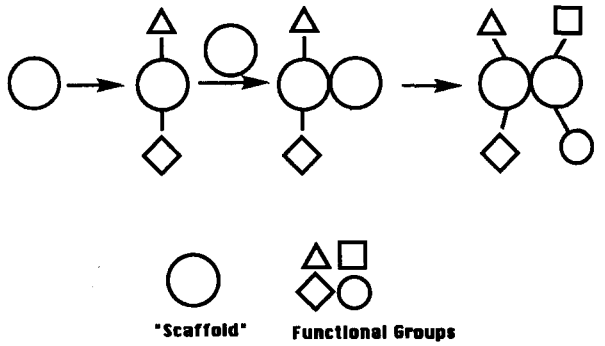


Figure 1. The double combinatorial approach.

functional group introduction on solid support. The completed target molecule is then cleaved from the solid support to afford the desired product in solution and ready for screening. By applying the double combinatorial approach, a very large number of highly functionalized low molecular weight target molecules can be rapidly produced from a small collection of building blocks.

A major challenge was to select a general structural class of 'drug-like' target molecules of sufficient generality to allow a wide variation in substitution patterns, as well as a method to readily effect changes in overall size, shape, and physical properties. The biphenyl scaffold (Fig. 2) was selected as our initial class of target molecules. This drug-like scaffold allows for facile introduction of three or four functional groups in a large number of spatial arrangements by simply altering the substitution pattern on each aromatic ring. Furthermore, we have built into our design a simple method of changing the biphenyl scaffold to easily change the size, shape, and physical properties of the final products.

We have chosen to prepare individual molecules of known structural identity using a parallel synthesis approach. The individual chemical reactions are carried out by a multi-step organic synthesis procedure in a spatially addressable and parallel format so that one single and well defined compound is prepared at each site of the solid support and multiple syntheses are carried out simultaneously in sufficient quantities for use in multiple screens.

A simple, useful apparatus for multiple simultaneous synthesis has been constructed and utilized for rapid preparation of organic molecules via multi-step resin-based procedures.[15] A 96-well format was chosen, the format used routinely for automated high throughput screens. Plate synthesis was carried out on resin placed in sterile polypropylene deepwell plates which were modified for filtration by drilling a small hole in the bottom of each well, then placing a porous polyethylene frit into the bottom of each well. An aluminum plate clamp was made as a two-piece assembly, consisting of a solid base clamp fitted with four removable corner stainless steel studs, and a frame clamp which fits atop the plate and is secured with wing nuts. A gasket was utilized on the base clamp to prevent leakage of well contents. The inexpensive equipment and limited human resources required for this effort illustrates the economic and productivity advantages of this technology.

The biphenyl molecules described herein are synthesized through a solution coupling reaction. The scaffold is functionalized with appropriate side chains on the solid support using the Mitsunobu reaction and the final products are cleaved from the solid support for subsequent modification and testing. It is important to note that the final products contain a pendant methyl group. This is significant since we desired not to have an invariant hydroxyl or carboxyl group in our final product. We wish to display important functional groups in space and do not wish to be biased by a strongly interacting invariant functional group. Production chemistries for library generation are now operational, and we are preparing the desired libraries.

Results and Discussion

The preparation of the biphenyl targets was accomplished as shown in Schemes 1 and 2. For the preparation of the stannylated 'A-ring', iodophenol **1** was alkylated with a series of halides to give a collection of arylalkyl ethers (these halides contain the required functional groups; these functional groups where selected to represent various physicochemical properties and include for example alkyl, aryl, alcohol, amino, and heterocyclic containing side chains). These alkylated products were directly stannylated under standard conditions with hexamethylditin in the presence of tetrakis-(triphenylphosphine)palladium(0) to afford the stannylated aryl ethers **2**.

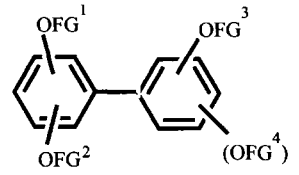
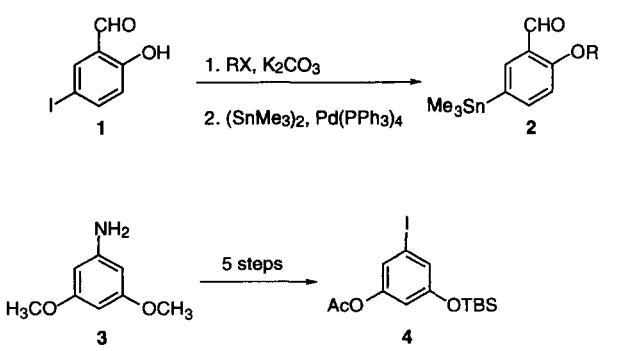
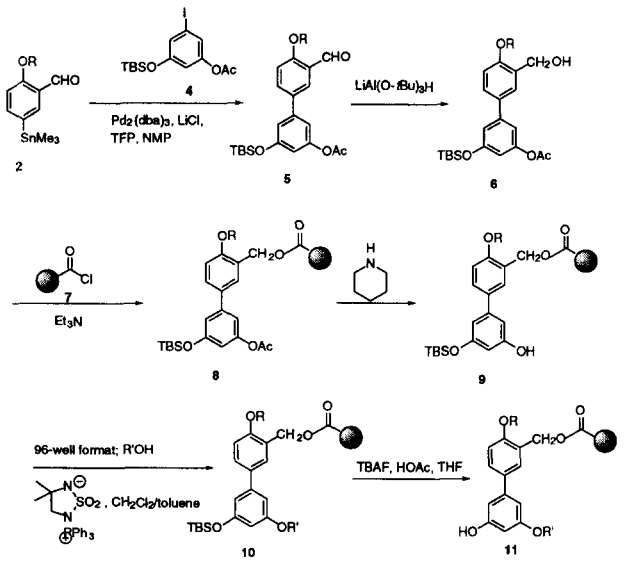


Figure 2. Generic structure of the biphenyl library.



Scheme 1. Preparation of 'A-ring' and 'B-ring'.



Scheme 2. Preparation of biphenyl products.

The differentially protected 'B-ring' was prepared by diazotization of dimethoxyaniline followed by treatment with potassium iodide to afford the aryl iodide. Removal of both methyl groups with boron tribromide was followed by exhaustive acetylation. Selective monosaponification of this diester gave the phenolic acetate. This material was readily converted to the desired *t*-butyldimethylsilyl ether **4** under standard conditions.

The formation of the doubly protected biphenyl scaffold **5** was accomplished utilizing modified Stille conditions.[16,17] By this route, multi-gram quantities of each unique biphenyl could be obtained after silica gel chromatography. The unoptimized yield of the coupling reaction was 35% due to loss of a protecting group. If desired, this deprotected material could be recovered and converted into **5**.

Prior to attaching the doubly protected biphenyl scaffolds to the solid support, reduction of the aldehyde functionality was necessary. Treatment of the biphenyl aldehydes **5** with a slight excess of LiAlH(O-*t*-Bu)$_3$ in THF cleanly afforded the corresponding benzyl alcohol derivatives **6** in near quantitative yield.

Polystyrene resin (100–200 mesh, 1% cross-linked) was carboxylated as previously described.[18] The resulting carboxylated resin was efficiently converted to its corresponding acid chloride derivative **6** using oxalyl chloride in benzene with mild heating for 12 h. The extent of derivatization corresponded to a loading capacity of 2.2 mmol/g of resin as determined by chlorine analysis. Although the acid chloride resin is stable for weeks under an atmosphere of argon, it is best to use immediately after preparation.

Attachment of the benzyl alcohol biphenyls **6** to the functionalized acid chloride resin **7** was accomplished using a slight excess of benzyl alcohol (1.05 equiv.) in the presence of triethylamine in methylene chloride at room temperature for 12 h. The coupling yields were in every case greater than 90% based on percent weight increase of the polystyrene resin. At this point, each unique biphenyl bound resin **8** was ready for selective phenolic acetate removal.

Phenolic acetate removal from the series of resin-bound biphenyls was accomplished with a solution of 20% piperidine in methylene chloride for 12 h. The resulting resins **9** were thoroughly washed and dried to constant weight. These resin-bound deprotected biphenyl phenols were loaded into modified 96-well plates.[15]

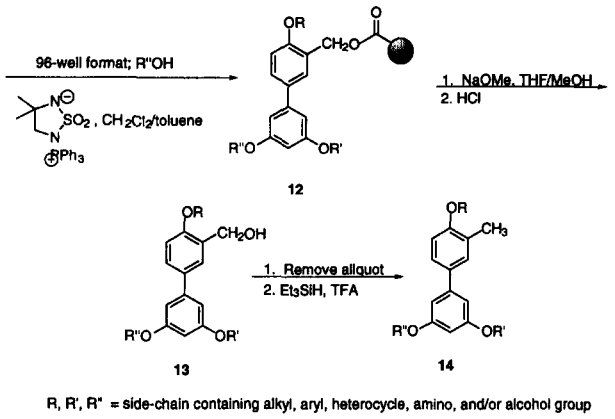
Functionalization of the free phenolic hydroxyl was accomplished using Castro conditions.[19] Mitsunobu reactions were conducted by addition of a suspension of the preformed betaine in methylene chloride and a solution of the appropriate alcohol in toluene. Excess reagents (10 equiv.) were used to drive these alkylations to completion. As the reactions proceeded, the solid betaine-phosphine complex dissolved to give a homogeneous solution (excluding the resin). Functionalization of this hydroxyl group was completed in three days at ambient temperature. Following this reaction, the resin **10** was thoroughly washed.

Removal of the phenolic *t*-butyldimethylsilyl ether was accomplished with an acetic acid/tetrabutylammonium fluoride solution. After 12 h of treatment, the resin **11** was thoroughly washed, including an acidic wash with HCl in DMF, and carried forward for further functionalization.

Functionalization of the remaining free phenolic hydroxyl group was accomplished with a mixed suspension of the preformed betaine complex and appropriate alcohols described above. These reactions were allowed to proceed for one week at ambient temperature. Following this second cycle of Mitsunobu chemistry, the resin **12** was washed and the functionalized biphenyls were ready to be removed from the solid support.

The benzyl ester linker proved to be remarkably robust, surviving conditions such as piperidine/methylene chloride (transformation **8** to **9**), Mitsunobu reaction (transformation **9** to **10**), an an excess of fluoride/acetic acid in tetrahydrofuran (transformation **10** to **11**). Stability of the linker was demonstrated by tlc analysis of products of the individual reactions and the >90% recovery of product in a number of analyzed wells. Data gathered during reaction optimization studies offered no evidence (NMR or unaccounted for UV active components in reaction solutions) of premature cleavage of biphenyl methanol scaffold at any steps prior to saponification of the desired product.

Cleavage of the biphenyl library from the solid support was accomplished by saponification. The wells were treated with a solution of sodium methoxide in methanol/THF for 12 h. The resulting solutions were acidified, and the free biphenyl methanols **13** were collected by gravity filtration into an indexed 96-well



Scheme 3.

plate. Samples were removed for quality control, and the volatile components in each well were removed under reduced pressure.

Post cleavage modification of the library's benzylic alcohol stub was accomplished by redissolving the product biphenyl methanols **13** and transferring aliquots to a second indexed 96-well plate. Volatile components were removed, and the free benzylic alcohols were reduced with a solution of triethylsilane and TFA in methylene chloride for 12 h. Volatile components were removed to afford the free biphenyl methanes **14**.

HPLC analysis of crude compound **14**, which was selected as a representative example, gave a purity of approximately 90%. This compound was *fully characterized* to demonstrate that the chemical route for preparation of the library afforded the desired product. This characterization can be found in the experimental section. To assess the purity and structure of the remaining members of the library, random sampling of both the biphenyl benzyl alcohols and the biphenyl methyl derivatives was performed and quantified by TLC, HPLC, ^{1}H NMR, and MS. Based on these analyses, average purity of the desired compounds within the library was estimated to be $>50\%$.

The Experimental section contains general synthetic protocols for the generation of the biphenyl library. For the sake of simplicity, the experimentals describe the preparation and characterization of the hydroxymethyl derivative **13** and its conversion to biphenylmethane, **14** (Fig. 3).

Conclusion

A versatile class of molecules which allows the rapid display of multiple functional groups in large numbers of spatial arrangements has been designed. Fundamental design considerations allow simple modifications to significantly change the size, shape, and physical properties of the target molecules. Described herein is an example of the synthesis of one such

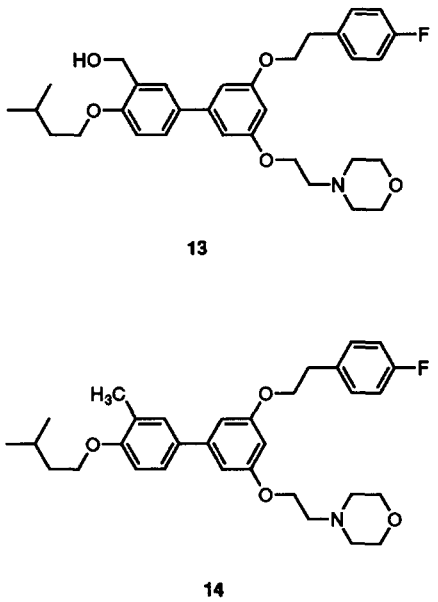


Figure 3. Structures of compounds **13** and **14**.

substitution pattern. The biphenyl targets have been synthesized by a combination of solution and solid-phase chemistries. These refined methods are now being used to produce related libraries.

The double combinatorial approach described for the biphenyl libraries can easily be used to prepare extremely large numbers of target molecules. This represents a formidable challenge in materials and labor (and is probably unnecessary to explore the relevant volumes). Therefore, we are now using computational tools to design a subset of molecules that will most effectively explore multi-parameter space.

Experimental

The experimental section contains synthetic protocols for the generation of the biphenyl library. For the sake of simplicity, the experimentals describe the preparation and characterization of the hydroxymethyl derivative **13** and the biphenylmethane, **14**.

Preparation of compound 1. In a dry 1-L round-bottom flask fitted with a dropping funnel was placed salicylaldehyde (87 mL, 100 g, 0.82 mol) and CH_2Cl_2 (500 mL). A solution of ICl (132 g, 0.82 mol) in CH_2Cl_2 (250 mL) was added dropwise over 2 h. The soln was stirred overnight at ambient temperature. An aq soln of Na_2SO_3 was added to the reaction mixture, and the layers sepd. The pooled organic frs were washed with H_2O, dried over $MgSO_4$, filtered, and concd. Recrystallization from benzene afforded 70 g (34% for 2 crops) of the desired iodophenol as a greyish solid: IR (KBr pellet): 3175, 2852, 1668, 1651, 1611, 1570, 1466, 1365, 1279, 1225, 1177 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.93 (s, 1H), 9.83 (s, 1H), 7.84 (d, 1H, $J = 2.2$), 7.76 (dd, 1H, $J = 8.7, 2.2$), 6.80 (d, 1H,

$J = 8.7$); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 196.33, 161.21, 145.25, 141.83, 122.56, 120.16, 80.31; HRMS calcd for $C_7H_5O_2I$ [M^+]: 247.9334; Found: 247.9347.

General procedure for the preparation of stanylated and alkylated phenols (2) illustrated with the specific example of R = 3-methylbutyl

In a dry 250-mL round-bottomed flask fitted with a reflux condensor was placed 5-iodosalicylaldehyde (10.0 g, 40 mmol), K_2CO_3 (16.6 g, 120 mmol) and 18-crown-6 (0.1 g, 0.4 mmol). Dimethylformamide (80 mL) was added followed by isoamyl bromide (14.5 mL, 18.3 g, 120 mmol). The suspension was heated (100 °C) with stirring overnight. The reaction mixture was cooled, dild with H_2O, and partitioned between Et_2O and H_2SO_4 (0.5 M). The pooled organic frs were extracted with aqs NaOH (1.0 M, 3×), satd aq bicarbonate solution, brine, and dried over $MgSO_4$. After filtration and concn, the phenolic ether was purified by chromatography using 10% EtOAc in hexanes to give 11.8 g (93%) of a pale yellow oil. Yields for the alkylation ranged from 80 to 95%. Analytical characterizations of the alkylated iodosalicaldehyde intermediate: IR (thin film): 2961, 2873, 1683, 1586, 1470, 1385, 1275, 1245, 1180, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.3 (s, 1H), 8.08 (d, 1H, $J = 2.1$), 7.77 (dd, 1H, $J = 8.7$, 2.1), 6.77 (d, 1H, $J = 8.7$), 4.08 (t, 2H, $J = 6.4$), 1.79 (m, 3H), 0.96 (d, 6H, $J = 6.4$); ^{13}C NMR (74.55 MHz, $CDCl_3$): δ 188.2, 161.03, 144.00, 136.78, 126.59, 114.94, 82.68, 67.25, 37.58, 25.07, 22.47; HRMS calcd for $C_{12}H_{15}O_2I$ [M^+] 318.0117; Found: 318.0107.

A dry 250-mL round-bottomed flask fitted with a reflux condensor was charged with aryl iodide **1** (7.91 g, 24.9 mmol) and toluene (150 mL) under an Ar atmosphere. Tetrakis(triphenylphosphine)palladium(0) (1.43 g, 1.24 mmol) was added followed by hexamethylditin (9.75 g, 29.8 mmol). The reaction mixture was heated to reflux for 12 h and cooled to room temperature. The product mixture was diluted with Et_2O (50 mL) and filtered through a Celite pad. After concentration, the aryl stannane **2** was purified by chromatography using 10% Et_2O in hexanes to afford 6.65 g (75%) of **2** as a colorless oil. IR (thin film): 2958, 1682, 1583, 1473, 1378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.90 (d, 1H, $J = 1.5$), 7.61 (dd, 1H, $J = 8.2$, 1.5), 6.96 (d, 1H, $J = 8.2$), 4.09 (t, 2H, $J = 6.5$), 1.75 (m, 3H), 0.96 (d, 6H, $J = 6.5$), 0.27 (s, 9H); ^{13}C NMR (74.55 MHz, $CDCl_3$): δ 189.88, 161.64, 143.12, 135.09, 132.46, 124.40, 112.20, 66.57, 37.57, 24.94, 22.34, –9.63; HRMS calcd for $C_{15}H_{24}O_2Sn$ [$M-CH_3$]: 341.0564; Found: 341.0565.

Preparation of 3. In a 1-L, 3-necked, round-bottomed flask equiped with a thermometer, a mechanical stirrer, and an addition funnel was placed HCl (12 M, 200 mL, 2.4 mol) and crushed ice (200 g). The flask was immersed in an ice–Me_2CO cooling bath, and 3,5-dimethoxyaniline (50 g, 326 mmol) was added portionwise with stirring. To this cold suspension was added dropwise a soln of $NaNO_2$ (27g, 390 mmol) in 125 mL H_2O at such a rate as to maintain the temperature of the reaction mixture between -5 °C and +2 °C throughout the addition. The soln was stirred at 0 °C for 30 min, and then transfered to a jacketed addition funnel maintained at −5 °C. The dark soln of the diazonium salt was added in a rapid dropwise fashion to a well-stirred room temperature solution of KI (550 g, 3.3 mol) in water (750 mL) in a 4-L flask. The mixture was stirred for 1 h, and then allowed to stand overnight. The resulting solution was partitioned against a 1:1 mixture of Et_2O–hexanes (700 mL, 2×) then Et_2O. The pooled organic extracts were washed with H_2O (700 mL, 2×), an aq satd Na_2SO_3 soln (500 mL, 2×), dried over Na_2SO_4, filtered, and concd to *ca.* 1 L. Silica gel was added, and the mixture evapd to dryness. This preloaded silica gel was placed on a pad of silica gel and eluted with 5% EtOAc in hexanes to give 55 g (64%) of a colorless solid, 3,5-dimethoxyiodobenzene. IR ($CDCl_3$): 3008, 2941, 1596, 1568, 1456, 1421, 1205, 1152, 1061, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.85 (2H, s), 6.40 (1H, s), 3.76 (6H, s); ^{13}C NMR (75.44 MHz, $CDCl_3$): δ 161.51, 116.24, 101.06, 94.57, 55.90.

Methyl group removal. In a dry 3-L, 3-necked, round-bottomed flask was placed a solution of BBr_3 in methylene chloride (1.0 M, 1.6 L, 1.6 mol) under Ar. The reaction mixture was cooled to −20 °C, and solid 3,5-dimethoxyiodobenzene (170 g, 0.65 mol) was added portionwise under a stream of Ar. The reaction mixture was allowed to warm with stirring overnight. The resulting solution was slowly poured into a soln of CH_2CL_2 and MeOH. Aqueous NaOH (2 M) was carefully added until a pH of 8.5 was acheived, and the two phase mixture was the re-acidified (3 M HCl) to pH 1. Extraction with Et_2O followed by evapn gave a pale-brown solid. Purification by silica gel chromatography using 40% EtOAc in hexanes afforded a quantitative yield of a colorless solid. IR (acetone): 3225, 1481, 1344, 1294, 1167 cm^{-1}; ^1H NMR (300 MHz, d_6-Me_2CO): δ 8.5 (2H, br s), 6.73 (2H, s), 6.34 (1H, s), 6.20–6.23 (2H, m); ^{13}C NMR (75.44 MHz, d_6-Me_2CO): δ 160.15, 117.05, 103.51, 94.42; HRMS: calcd for $C_6H_5O_2I$ [M^+]: 235.9334; Found: 235.9339.

Differential protection to afford compound 4

A dry 2-L round-bottomed flask was charged with 3,5-dihydroxyiodobenzene (132 g, 0.56 mol) and sealed. CH_2Cl_2 (600 mL) and Et_3N (390 mL, 283 g, 2.8 mol) were sequentially added and the resulting soln was cooled (ice–Me_2EO bath). Acetic anhydride (172 mL, 1.69 mol) was added dropwise over 30 min. The reaction mixture was allowed to warm with stirring overnight. Water (500 mL) was added to the flask, and the biphasic mixture was vigorously stirred for 2 h. The two phases were sepd, and the aq phase was extracted once with Et_2O. The crude product was concd on silica gel and purified by chromatrography using a 30% EtOAc in hexanes soln as eluant to give 173 g (96%) of a colorless solid. IR ($CDCl_3$): 3086, 29026, 1770,

1584, 1429, 1370, 1197, 1125, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35(2H, two s), 6.90 (1H, s), 2.26 (6H, s); ^{13}C NMR (75.44 MHz, $CDCl_3$): δ 168.46, 151.11, 128.17, 115.39, 92.37, 20.91; Microanalysis for $C_{10}H_9O_4I$: calcd: C, 37.15; H, 2.80; I, 39.29; Found: C, 37.47; H, 2.75; I, 39.74.

A 1.0 M solution of KOH (33 g, 576 mmol) in EtOH was added dropwise to a cooled (0 °C) soln of 3,5-diacetoxyiodobenzene (185 g, 576 mmol) in a 1:1 mixture of benzene and EtOH (500 mL). The reaction mixture was stirred for 30 min at 0 °C then carefully quenched with a 10% HCl aq soln (the pH was set around 6). The reaction mixture was extracted with a 1:1 mixture of Et_2O and hexanes. The pooled organic extracts were washed with H_2O (2×) and concd. The solid residue was recrystallized from a mixture of benzene (200 mL) and hexanes (200 mL). The first crop yield 115 g (72%) of pure product as a very pale-yellow solid. IR ($CDCl_3$): 3588, 1769, 1599, 1584, 1207,1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.04 (1H, s), 7.03 (1H, s), 6.54 (1H, s), 6.11 (1H, s), 2.32 (3H, s); ^{13}C NMR (75.44 MHz, $CDCl_3$): δ 170.58, 157.36, 151.60, 123.15, 123.12, 109.59, 93.65, 21.46; Microanalysis for $C_8H_7O_3I$: calcd: C, 34.54; H, 2.53; I, 45.65; Found: C, 34.83; H, 2.46; I, 45.53.

To a solution of imidazole (1.1 g, 16.0 mmol) in CH_2Cl_2 (25 mL) in a dry 50 mL round-bottomed flask was added at −5 °C solid *tert*-butyldimethylchlorosilane (2.2 g, 15.2 mmol) portionwise. The white suspension was stirred 15 min then treated with a solution of 3-hydroxy-5-acetoxy iodobenzene (4.0 g, 14.4 mmol) in the same solvent (20 mL). The mixture was allowed to warm with stirring overnight and then quenched with H_2O. The reaction mixture was extracted with Et_2O, the pooled organic phases were dried over Na_2SO_4, filtered, and concd. Purification by chromatography on silica gel using 30% CH_2Cl_2 in hexanes afforded 5.1 g (91%) of **4** as a colorless oil. IR (neat): 3076, 2955, 2930, 2858, 1770, 1588, 1568, 1471, 1367, 1285, 1255, 1199, 1139, 1021, 1001, 912, 866, 837, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (1H, s), 7.07 (1H, s), 6.55 (1H, s), 2.25 (3H, s), 0.96 (9H, s), 0.2 (6H, s); ^{13}C NMR (75.44 MHz, $CDCl_3$): δ 168.70, 156.76, 151.44, 126.89, 123.79, 113.61, 92.87, 25.5, 20.97, 18.08, −4.56; Microanalysis for $C_{14}H_{21}O_3ISi$: Calc: C, 42.84; H, 5.39; Found: C, 42.83; H, 5.43.

Preparation of biphenyl 5. Compound **2** (4.64 g, 9.52 mmol) was taken up in 40 mL dry *N*-MP under argon and compound **4** (2.92 g, 8.64 mmol) was added followed by LiCl (2.93 g, 69.12 mmol), trifurylphosphine (0.60 g, 2.60 mmol), and Pd_2dba_3 (1.18 g, 0.80 mmol). The reaction mixture was heated to 65 °C for 12 h and cooled to room temperature. After diluting the reaction mixture with 250 mL Et_2O and filtering the soln through a pad of Celite, the filtrate was transferred to a 500 mL separatory funnel and the Et_2O layer was washed with distilled H_2O (3 × 50 mL) and brine (3 × 50 mL). The Et_2O layer was dried over $MgSO_4$, filtered, and concd to give a brown viscous oil which was purified by flash chromatography on silica gel with 50% EtOAc in hexanes to afford 1.52 g of compound **5** as a colorless oil in 35% yield. IR (thin film): 2955 , 1768, 1685, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.53 (s, 1H), 8.01 (d, 1H, J = 2.5 Hz), 7.71 (dd, 1H, J = 8.7, 2.5 Hz), 7.03 (d, 1H, J = 8.7 Hz), 6.90 (br s, 2H), 6.55–6.57 (m, 1H), 4.14 (t, 2H, J = 6.5 Hz), 2.30 (s, 3H), 1.83–1.90 (m, 1H), 1.73–1.79 (m, 2H), 0.99 (s, 9H), 0.98 (d, 6H, J = 5.36 Hz), 0.23 (s, 6H); ^{13}C NMR (74.55 MHz, $CDCl_3$): δ 189.60, 169.15, 161.15, 156.71, 151.74, 141.53, 134.19, 132.43, 126.39, 124.87, 115.89, 112.94, 112.89, 112.40, 67.16, 37.69, 25.59, 25.10, 22.49, 21.06, 18.13, −4.45.

Preparation of compound 6. Compound **5** (8.24 g, 18.08 mmol) was taken up in 100 mL dry THF under Ar and cooled to 0 °C. $LiAlH(O\text{-}t\text{-}Bu)_3$ was then added in small portions over a 5 min period. Once the evolution of gas had subsided, the reaction mixture was gradually warmed to room temperature and stirred an additional 3 h. The reaction mixture was then quenched with 50 g of silica gel and concd. The resulting free flowing powder was loaded atop a column of silica gel and chromatographed with Et_2O to give 7.86 g of compound **6** as a colorless oil in 95% yield. IR (thin film): 3440, 2956, 1769, 1742, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.47 (m, 2H), 6.94 (d, 1H, J = 8.4 Hz), 6.90 (br s, 2H), 6.54–6.56 (m, 1H), 4.74 (s, 2H), 4.10 (t, 2H, J = 6.5 Hz), 2.31 (s, 3H), 1.85–1.87 (m, 1H), 1.72–1.78 (m, 2H), 1.01 (s, 9H), 0.99 (d, 6H, J = 6.5 Hz) 0.24 (s, 6H); ^{13}C NMR (74.55 MHz, $CDCl_3$): δ 169.23, 156.72, 156.53, 151.60, 142.74, 132.50, 129.46, 127.31, 115.99, 112.99, 111.91, 111.23, 66.55, 62.22, 37.95, 25.61, 25.19, 22.52, 21.13, 18.15, −4.44.

Preparation of resin 7. To a gently stirring suspension of carboxylated polystyrene[18] (20.0 g, 60.0 mmol, 3.0 mmol/g) in 200 mL dry benzene under Ar was added 4.0 equiv. of oxalyl chloride (20.0 mL, 240.0 mmol) dropwise over a 10 min period. After the addition was complete, the reaction flask was fitted with a water-cooled condenser and the mixture was gradually warmed to 70 °C for 12 h. After cooling to room temperature, the resin was allowed to settle without stirring and the supernatant was withdrawn and discarded. The remaining slurry was washed with dry benzene (3 × 100 mL) and dried under high vacuum at 35 °C for 10 h to give 22.0 g of resin **7** as a tan colored solid. Chlorine analysis of this resin gave 8.90% chlorine which corresponds to a loading capacity of 2.5 mmol/g of resin. IR (KBr pellet): 1743, 1598 cm^{-1}.

Preparation of compound 8. Compound **6** (7.86 g, 17.16 mmol) was taken up in 60 mL dry CH_2Cl_2 under argon and Et_3N (3.59 mL, 25.74 mmol) was added followed by resin **7** (6.33 g, 16.34 mmol, 2.5 mmol/g loading). The reaction mixture was stirred for 12 h and then filtered followed by washing with CH_2Cl_2 (3 × 50 mL), MeOH (3 × 50 mL), DMF (3 × 50 mL), and THF (3 × 50 mL). The resulting light-tan resin was dried

under high vacuum to give 12.00 g of resin **8** as a light-tan colored resin. Based on the percent weight gain, the new loading of resin **8** was assumed to be 1.4 mmol/g.

Preparation of compound 9. A dry 100-mL shaker vessel was charged with resin **8** (2.8 mmol, 2.0 g). The vessel was sealed under an Ar atmosphere and CH_2Cl_2 (30 mL) added. Piperidine (6.0 mL) was added, and the reaction mixture was gently shaken for 12 h. The resin was washed (sequentially with CH_2Cl_2, MeOH, THF, CH_2Cl_2), and dried under high vacuum to yield 2.0 g of yellow resin.

Parallel synthesis

At this stage the synthesis was changed from a bulk preparation of unique A-ring substituted resins to a 96-well format for parallel synthesis. A drilled 96-well microtiter plate fitted with polyethylene frits was charged with a series of unique A-ring substituted resins (ca. 20 mg/well). The charged plate was clamped in an aluminum frame fitted with a Viton seal.

Preparation of compound 10. Mitsunobu functionalization of the resin-bound biphenyl phenols was accomplished by addition of the alcohol of choice (10 equiv) in toluene (0.4 mL/well) followed by a suspension of the sulfonamide–betaine[19] in CH_2Cl (11.9 g in 53 mL, 10 equiv, 0.5 mL/well). The wells were sealed, and the charged plates were agitated by rotation for 3 days. During the course of the reaction, the contents of each well became homogeneous with the exception of the resin particles. The plates were transfered to a filtration manifold and the resins washed (sequentially with CH_2Cl_2, THF, MeOH, CH_2Cl_2, THF, CH_2Cl_2, THF; 3–5 × with each solvent). The plates were placed in a vacuum desicator and dried.

Preparation of compound 11. For treatment of a single plate, a solution of TBAF (1.0 M in THF, 31.2 mL) containing HOAc (1.8 mL) in THF (72 mL) was prepared. Deprotection of the silyl ethers was accomplished by addition of 0.9 mL of this cocktail to each well. The plates were sealed, and rotated overnight. The resins were washed (sequentially with THF, CH_2Cl_2, 1% 1.0 M HCl in DMF, THF, CH_2Cl_2, THF; 3–5 × with each solvent) and dried under vacuum.

Preparation of compound 12. The second round of Mitsunobu functionalization of the resins was accomplished as outlined above for the preparation of **9** with a different set of alcohols. Once sealed, the plates were rotated for 7 days. The resins were washed and dried as described.

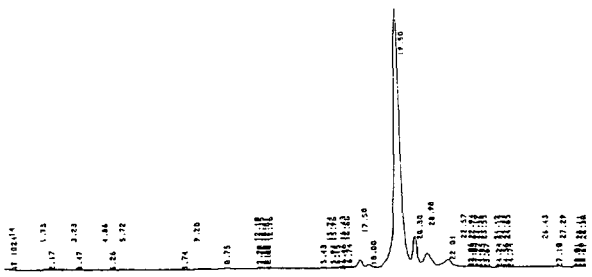
Preparation of compound 13. The resin-bound biphenyls were released by treatment with a soln of NaOMe. A stock soln of NaOMe (0.2 M) in THF:MeOH (4:1) was prepared. Each well was charged with this soln (0.8 mL) and the sealed plates rotated overnight. The wells were opened and HCl (1.0 M in Et_2O, 0.13 mL) added. The plates were resealed, and rotated to mix. The sealed plates were removed from the clamps, stacked over unmodified 96-well plates, and the seals removed. Gravity filtration provided solutions of the target biphenyls in the unmodified plate. Samples were removed for analysis and the solvents removed in vacuo.

Biphenyl 13. The crude product was removed from the well and analyzed without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.50 (m, 2H), 7.15–7.30 (m, 2H), 6.80–7.05 (m, 3H), 6.65–6.70 (m, 2H), 6.40–6.45 (m, 1H), 4.73 (s, 2H), 3.95–4.20 (m, 6H), 3.74 (dd, 4H, J = 4.6, 4.6), 3.07 (t, 2H, J = 6.8), 3.21 (t, 2H, J = 5.7), 2.55–2.60 (m, 4H), 2.36 (br s, 1H), 1.68–1.90 (m, 3H), 0.98 (d, 6H, J = 6.5); HRMS calcd for $C_{32}H_{40}O_5NF$: 538.2969; Found: 538.2980.

Preparation of compound 14. The biphenyl methanols were redissolved and aliquots transfered to a second 96-well plate. Following solvent evapn, solns of TFA in CH_2Cl_2 (2.0 M, 0.4 mL) and triethylsilane in CH_2Cl_2 (0.01 M, 0.4 mL) were sequentially added to each well. The wells were sealed and the plates vortexed to effect solution. After 12 h, volatile components were removed under high vacuum to afford the desired products.

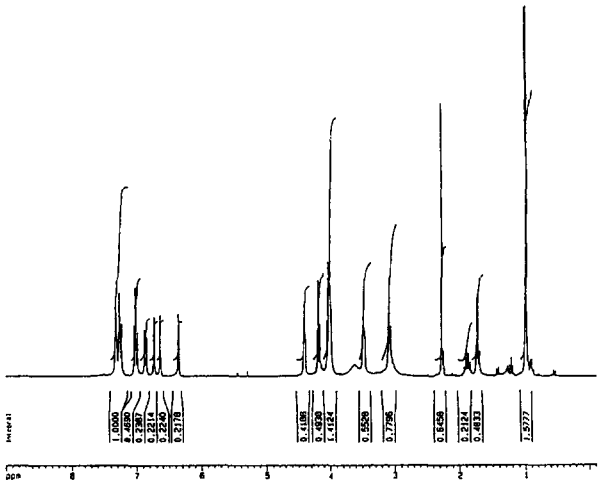
Biphenyl 14. The crude product was removed from the well and analyzed without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.40 (m, 4H), 7.02 (t, 2H, J = 8.7), 6.87 (m, 1H), 6.74 (m, 1H), 6.64 (m, 1H), 6.36 (m, 1H), 4.39–4.43 (m, 2H), 4.19, (t, 2H, J = 6.8), 3.87–4.07 (m, 6H), 3.45–3.50 (m, 4H), 3.09 (t, 4H, J = 6.7), 2.28 (s, 3H), 1.89 (m, 1H), 1.69–1.77 (m, 2H), 0.99 (d, 6H, 6.5); HRMS Calcd for $C_{32}H_{40}O_4NF$: 522.3020; Found: 522.3008.

HPLC trace of crude 14



Waters Radial-Pak cartridge, type 8MBC 18, 10 μm, 2.0 mL/min; solvent A: 0.1% trifluoroacetic acid in water; solvent B: acetonitrile; gradient elution 95:5–5:95 A:B over 27 min.

NMR Spectrum of Crude 14



$CDCl_3$, 300 MHz.

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