Design and Synthesis of a G-Protein-Coupled Receptor Antagonist Library of Aryloxyalkanolamines Using a Polymer-Supported Acyclic Acetal Linker

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A G-Protein-coupled receptor-targeted library of aryloxypropanolamines and aryloxybutanolamines was efficiently executed using a novel, polymer-supported acyclic acetal linker, producing compounds in good yields and purities.

Introduction

G-Protein coupled receptors (GPCRs) have long been preferred targets of the pharmaceutical industry resulting in drugs that accounted for sales of more than US $30 billion worldwide in 2001.[1] The recent completion of the human genome project has resulted in the identification of additional GPCRs for which the function and ligands are unknown, providing a potential trove of new targets.[2] Aryloxypropanolamines are well-known as pharmaceutically useful pharmacophores for GPCRs with more than forty aryloxypropanolamine-derived drugs targeting GPCRs being described in the 13th edition of the Merck Index.[3] The interesting and varied biological activities of aryloxypropanolamines made this chemotype an attractive target for a lead discovery library focused on GPCRs. Preparation of smaller libraries of aryloxypropanolamines in solution via epoxide opening and scavenging of side products has been described previously.[4] However, to generate larger lead discovery libraries, a solid-phase approach which allowed for variation at multiple positions was needed.

In order to easily introduce a diverse set of inputs at both ends of the aryloxypropanolamine, an orthogonally protected core attached to a polymer support via the secondary hydroxyl group was envisioned. Sequential nucleophilic substitution would then allow incorporation of a variety of nucleophiles at both terminal positions (**1** and **2**, $n = 1$, Figure 1). Both enantiomers of the products could be easily accessed by starting with each of the optically pure precursor alcohols. In addition to the propyl cores, the route could be utilized to prepare enantiomeric aryloxybutanolamine analogs (**1** and **2,** $n = 2$). These latter compounds are not as well represented in the patent literature and could provide a greater opportunity for generating novel leads as tools to study GPCRs.

Hydroxyls have been attached to a polymer support via a variety of different linkers (Figure 2) including esters,[5] silyl ethers,[6] trityl ethers,[7] benzyl ethers **3,**[8] ethers using Wang's resin **4**,[9] and acetals **5**−**7**.[10] In this instance, only the acetal linkers, **5**−**7**, appeared to provide a suitable balance between chemical stability for the required synthetic manipulations envisioned and ease of cleavage under mild acidic conditions. The compounds were to be prepared using Irori NanoKans (NK), a technology allowing facile preparation of large libraries in milligram quantities. Thus, relatively large amounts of an inexpensive and high loading resin were desired. For this purpose, a novel low cost and high loading acyclic acetal linker of the type **8** was found to be very efficient for attaching the cores to the resin while allowing the synthesis to be easily executed. Selection of the various building blocks for the library from a set of amines and

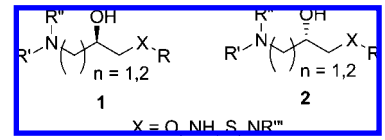

Figure 1. Generic aryloxyalkylamines.

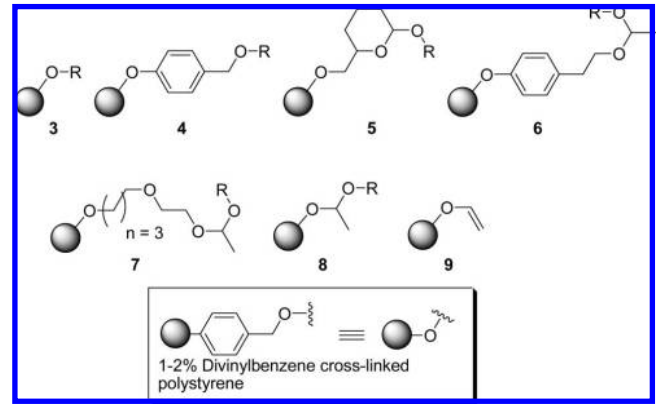

Figure 2. Ether and acetal linkers.

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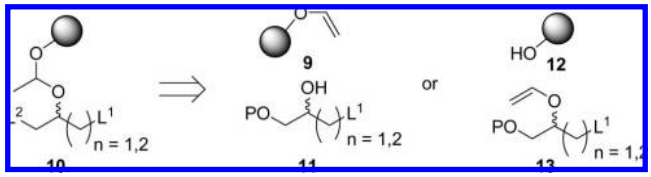
Scheme 1. Alternative Acetal Formation Strategies



phenols present in known GPCR ligands was aided using computational methods.

Results and Discussion

Linker Selection. At the time this work was executed, the only known polymer-linked acetal linker was the tetrahydropyranyl (THP) resin developed by Ellman and coworkers[10a] (**5**, Figure 2). Resins **6** and **7** were only recently reported.[10b,c] The loading of Ellman's THP resin was too low to provide the desired amount of material being targeted, and the precursor 3,4-dihydro-2*H*-pyran-2-carboxylic acid used to prepare the resin was viewed as undesirably expensive. A route was proposed that linked the core's alcohol to the readily available hydroxymethyl polystyrene via an acyclic acetal linker **8** derived from vinyl ether **9**. Acetal **10** (Scheme 1), having two differentiated functional groups L^1 and L^2, could be obtained by coupling secondary alcohol **11** with the polymer-supported vinyl ether **9** or by linking hydroxymethyl polystyrene **12** to the secondary vinyl ether **13**. Initial attempts at preparing the vinyl ether **9** were unsuccessful; however, vinyl ethers of the core secondary alcohol **13** were easily formed and were found to load on the resin with good efficiency.

Building Block Synthesis. *R*- or *S*-(2,2-Dimethyl-1,3-dioxolan-4-yl)methanol (**14*R*** and **14*S***) were readily available starting materials for the aryloxypropanolamine libraries (Scheme 2). The tosylates[11] derived from each of the alcohols **14*R*** and **14*S*** were silylated after cleavage of the acetonides with polymer-supported sulfonic acid to give alcohols **15*R*** and **15*S*** both in 99% overall yield. The alcohols **15*R*** and **15*S*** were converted to the unstable vinyl ethers **17*R*** and **17*S*** in 85% and 90% yield, respectively, by first making the acetals **16*R*** and **16*S*** with ethylvinyl ether[12] and then eliminating ethanol using trimethylsilyl triflate.[13] The vinyl ethers **17*R*** and **17*S*** were loaded on the hydroxymethylpolystyrene resin **12** (1.24 mmol/g) using a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). The loading for resin **18*S*** was ~0.74 mmol/g (91% loading) and for resin **18*R*** was ~0.61 mmol/g (~75% loading). Loadings were determined using four methods: resin weight increase, recovered vinyl ether, weight of product obtained by hydrogen chloride cleavage of an aliquot, and combustion analysis of the resin. The results for resin loading were consistent for all analyses. The resins were kept refrigerated over a desiccant (Drierite) until used.

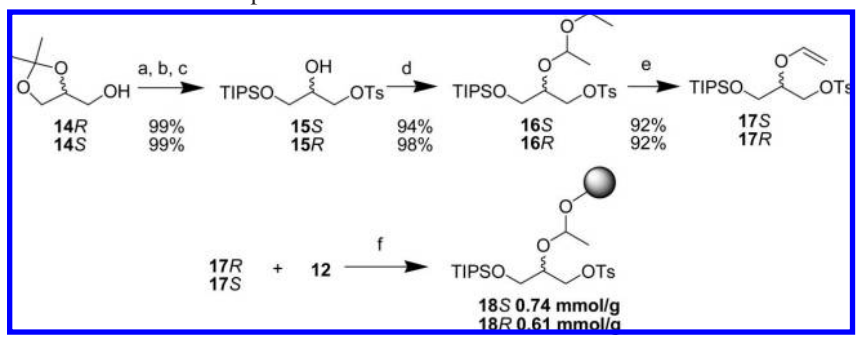
The (*S*)-aryloxybutanolamine precursor resin **21** (Scheme 3) was prepared from (*S*)-1,2,4-butanetriol (**19**), which was derived from (*S*)-malic acid.[14] Vinyl ether **20** was obtained in 15% overall yield from triol **19** via selective silylation (42% yield) of the less hindered primary alcohol with triisopropylsilyl chloride, tosylation of the other primary alcohol (58% yield), ethoxyethyl protection of the remaining secondary alcohol (94% yield), and finally, elimination of ethanol with trimethylsilyl trifluoromethanesulfonate to give the desired product (65% yield). This product was loaded onto the resin as described previously to give **21** (0.60 mmol/g, 92% loading).

The (*R*)-aryloxybutanolamine precursor resin **24** (Scheme 4) was prepared from vinyl ether **23**, which was derived from (*R*)-(+)-malic acid **22**[15,22] using a slightly modified sequence as compared to that utilized for the (*S*)-enantiomer resulting in a better overall yield. Malic acid **22** was reduced to the triol in quantitative yield using borane-dimethylsulfide complex. The less hindered primary alcohol was selectively protected using a kinetically controlled regiospecific silylation with dibutylstannanediyl acetal[23] and triisopropylsilyl chloride (89% yield). The resulting silyl diol was then converted to the desired resin **24** (0.59 mmol/g, 90% loading) using almost the same procedure as for **21** (see Experimental Section).

Development and Optimization of the Solid-Phase Sequence. A test library was prepared using free flowing resins initially in 40 mL vials (first step) and then in a 24-well Bohdan reactor.[16] The building blocks that were used are shown in Figure 3, and the conditions that were used are summarized in Scheme 5. Resins **18S** and **18R** (1.6 g each) in 40 mL vials were each treated with 1-phenylpiperazine (**25**) (1 M in NMP) or with 2-methylphenol (**26**), 4-cyanophenol (**27**) or 4-chloro-3-fluorophenol (**28**) in NMP (1.0 M) with potassium tert-butoxide (0.9 M) and a catalytic amount of 18-crown-6 in ether (0.01 M) at 95 °C for 20 h with gentle magnetic stirring. After the resins were cooled and thoroughly washed, they were distributed into the Bohdan reactors (100 mg/well). Eight extra reactions were run to allow sampling to monitor the progress of representative reactions. The TIPS group was cleaved with tetrabutylammonium fluoride (TBAF 0.5 M THF), and after washing, an aliquot of each resin from the duplicate reactions was cleaved using a solution of trifluoroacetic acid (TFA)/ethanol/DCM (5/16/4) and analyzed by LCMS. A few of these representative aliquots were also analyzed by ^{1}H NMR which showed that the desired product was the major component in all cases. The results of the diol formation are shown in Table 1. All of the alcohols were isolated by preparative HPLC and were analyzed by LCMS and ^{1}H NMR using a flow probe. The isolated yields ranged between 8−65% with the more hindered 2-methylphenol (entry 2) giving the lowest yield.

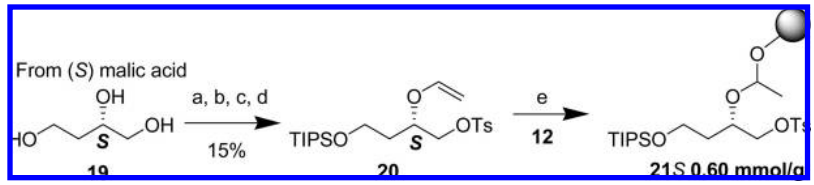
A primary alkyl iodide was selected as the leaving group for the final displacement. The iodide was formed using methyltriphenoxyphosphonium iodide[17] in DMF. The reagent was either freshly prepared[18] or purchased from Aldrich. An aliquot of each resin was cleaved and analyzed by LCMS. The iodide proved to be more unstable than the diol or the final product to the cleavage conditions and gave lower yields of isolated product (Table 1). Up to 39% of the starting alcohols were observed in some cases along with the iodide. More careful monitoring was used for the final library to prevent excessive diol formation. In all cases, the iodides

Scheme 2. Synthesis of the TIPS-Protected Propanetrioltoluenesulfonate Resins[a]



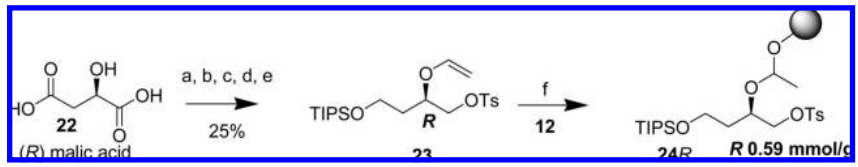
[a] Reagents and conditions: (a) *p*-toluenesufonyl chloride (TsCl), pyridine, 4 h; (b) AG 50W-XZ, MeOH/water 50:1, 2 d; (c) triisopropylsilyl chloride (TIPSCl), imidazole, 4-pyrrolidinopyridine, DMF, 1d; (d) ethylvinyl ether, pyridinium *p*-toluenesulfonate (PPTS) cat., dichloro methane (DCM), 2 h; (e) trimethyl silyl trifluoromethanesulfonate (TMSOTf), Et_3N, DCM, −78 °C; (f) PPTS cat., DCM, 42 h.

Scheme 3. Synthesis of the TIPS-Protected (*S*)-Butanetrioltoluenesulfonate Resin[a]



[a] Reagents and conditions: (a) TIPSCl, imidazole, DMF, −78 °C to rt, 6 h; (b) TsCl, pyridine, DCM, −78 °C to rt, 4 h; (c) ethylvinyl ether, PPTS cat., DCM, 1 h; (d) TMSOTf, Et_3N, DCM, −78 to 0 °C, 1 h; (e) PPTS cat., DCM, 42 h.

Scheme 4. Synthesis of the TIPS-Protected (*R*)-Butanetrioltoluenesulfonate Resin[a]



[a] Reagents and conditions: (a) H_3BSMe_2, THF, reflux 2.5 h; (b) (i) Bu_2SnO, MeOH, reflux 3 h, (ii) TIPSCl, chloroform, rt, overnight; (c) TsCl, pyridine, chloroform, −78 °C to rt, 24 h; (d) ethylvinyl ether, PPTS cat., DCM, 1 h; (e) TMSOTF, Et_3N, DCM, −78−0 °C, 2 h; (f) PPTS cat., DCM, 42 h.

were the major products, and crude ^{1}H NMR spectra of a few examples confirmed the LCMS results (entries 12−16).

Three amines were selected for the final displacement (**29**−**31**, Figure 3). The reactions were performed in NMP at 85 °C with a 1 M solution of the amine and a 0.5 M solution of *N,N*-diisopropyl-*N*-ethylamine. After cleavage with TFA/DCM/EtOH (5/16/4), the desired products were obtained in all cases. The main impurity was the diol that remains after incomplete iodination. No unreacted iodides or alkenes resulting from elimination were observed. Crude ^{1}H NMR spectra for **32**, **44**, **47**, **50**, **53**−**55** were obtained, and confirmed the results obtained by LCMS. The results are summarized in Table 2.

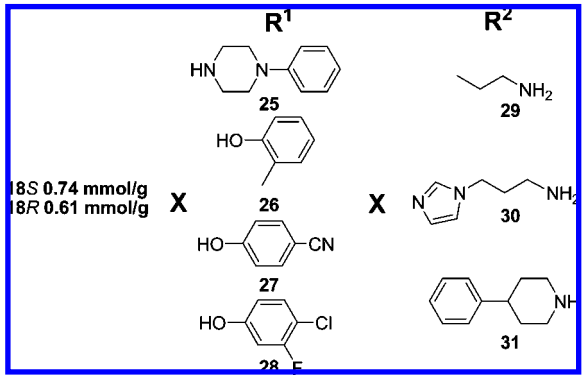


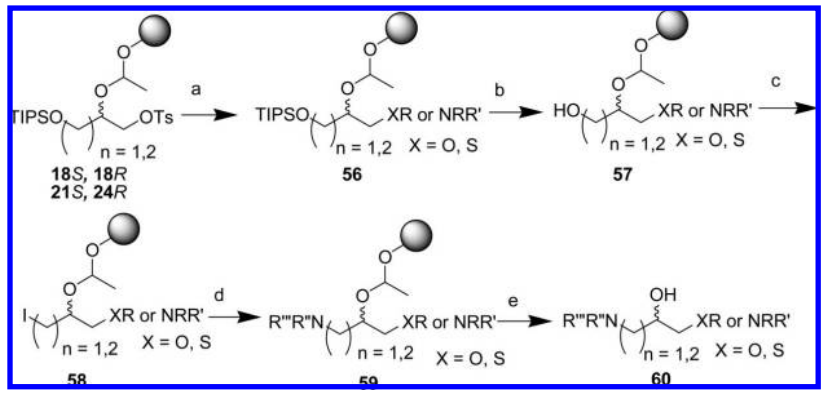
Figure 3. Building Blocks for the Test Library.

Compound **43** and **55** were more fully characterized, and in each case, the enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H). The enantiomeric excesses were found to be 98% (*S*-isomer **43**) and 99% (*R*-isomer **55**), indicating that no racemization had occurred during the reaction sequence.

Library Design. Reagents were selected from the ACD,[19] and those with undesirable functional groups (side reactivity, etc.) were filtered out. A set of Sybyl line notations (SLNs)[20] derived from a privileged substructure analysis[21] of the MDDR[22] database was used to sort each reagent list into sets of "GPCR-like", "non-GPCR-like", and "non-GPCR-like but interesting".[23] The last set consisted of reagents that provided small R-groups, such as halogens and small alkyl groups. In addition, molecular weight (<250) and cLogP[24] (<3.5) cutoffs were used to filter the reagent lists. All filtering was done using the Selector module of SYBYL6.7.[25] The "GPCR-like" and "interesting" lists were further reduced manually on the basis of reagent availability and reactivity considerations. CombiLibMaker[26] was used to generate a library whose members had molecular weights less than 800. Selector was then used to further filter the library using cLogP (<5) and MW <500 cutoffs.[27]

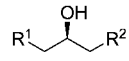
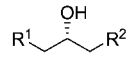
Library Execution. IRORI NanoKan (NK) technology was used for executing the large library[28] following the procedure illustrated in Scheme 5. Each barcoded NK

Scheme 5. Library Synthesis[a]



[a] Reagents and conditions: (a) 1.0 M HXR, 0.9 M tBuOK, 0.01 M 18-crown-6 or 1.0 M RR'NH, NMP, 95 °C, 18 h; (b) 0.5 M TBAF, THF, 18 h; (c) 0.5 M (PhO)3P+MeI⁻, 1.0 M pyridine, DMF, 18 h; (d) 1.0 M R″R‴NH, 0.5 M DIPEA, NMP, 85 °C, 20 h; (e) TFA/EtOH/DCM, (20%/16%/64%), 3 h.

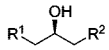
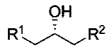
Table 1

Core	Nucleophile R[1]	R^2 = OH			R^2 = I		
		Entry	Crude Purity[a] (%)	Isolated Yield[b] (%)	Entry	Crude Purity (%) I (OH)[c]	Isolated Yield (%)
	**25**	1	89	36	9	42 (39)	26
	26	2	50	8	10	56 (0)	[d]
	27	3	74	55	11	60 (8)	44
	28	4	89[e]	65	12	78 (13)[e]	56
	**25**	5	92[e]	30	13	62 (29)[e]	25
	26	6	88[e]	36	14	81 (4)[e]	25
	27	7	74[e]	46	15	62 (7)[e]	54
	28	8	94[e]	50	16	68 (21)[e]	55

[a] As determined by LCMS coupled to a UV detector set at 220 nm. [b] Isolated by reversed-phase preparative HPLC. >90% pure. [c] Percent of the iodide (% of the remaining alcohol). [d] Lost in purification. [e] Crude ^{1}H NMR was obtained.

contained ~8 mg of resin (~5 μmol, expected yield of ~1.7 mg of product at an average MW of 350). The polymer-supported tosylates (**18***S*, **18***R*, **21***S* and **24***R*) were displaced with nucleophiles from a list of twenty one phenols, one thiol, fourteen thiophenols, two hydroxypyrimidines, seven secondary amines, and one sulfonamide to give products of the type **56**. As was done previously in the test library, extra NK were included so that aliquots could be removed during the sequence to allow monitoring of the progress of the reactions. Potassium *t*-butoxide with added 18-crown-6 was used as the base for the phenols, thiol, thiophenols, and hydroxypyrimidines, while no base was used for the secondary amines and the sulfonamide. This initial nucleophilic displacement was carried out in *N*-methylpyrrolidinone (NMP) at 90 °C for 18 h. The silyl group was then removed with tetrabutylammonium fluoride in THF for 18 h, and the free hydroxyls of **57** were converted to the primary iodides **58** using methyltriphenoxyphosphonium iodide.[25,29] Several of the extra NK were checked to ensure complete conversion of the alcohol. ***Caution****: The quality of the commercial methyltriphenoxyphosphonium iodide was highly variable. Better results were obtained when the phosphonium salt was not sticky and only lightly colored.* The iodides were displaced with a set of forty one primary amines, five anilines and seventeen secondary amines using *N,N*-diisopropyl-*N*-ethylamine (DIPEA) as a base in NMP at 85 °C for 20 h to give products of the type **59**.

Table 2

Core	Nucleophile R^1	Nucleophile R^2	#	Crude Purity[a] (%)	Isolated Yield[b] (%)
	**25**	**29**	**32**	67 (26)[c,h]	13[e]
		30	**33**	85[d]	27
		31	**34**	50 (34)	9
	26	**29**	**35**	54 (11)	9
		30	**36**	40 (9)	1[f]
		31	**37**	53 (11)	-[f,g]
	27	**29**	**38**	66[d]	33
		30	**39**	71 (10)	15
		31	**40**	66 (10)	40
	28	**29**	**41**	72 (12)	42
		30	**42**	72 (13)	34
		31	**43**	82 (10)	66
	**25**	**29**	**44**	62 (21)[h]	8[e]
		30	**45**	82[d]	20[f]
		31	**46**	59 (30)	25
	26	**29**	**47**	61[d,h]	22
		30	**48**	83 (6)	20
		31	**49**	50 (20)	27
	27	**29**	**50**	85[d,h]	39
		30	**51**	70 (10)	17
		31	**52**	76 (11)	43
	28	**29**	**53**	69 (20)[h]	41
		30	**54**	68 (16)[h]	35
		31	**55**	74 (12)[h]	76

[a] As determined by LCMS coupled to a UV detector set at 220 nm. [b] Isolated by reverse-phase preparative HPLC. >90% pure. [c] Percent of product (percent of the remaining alcohol). [d] Peak overlap. [e] Required three rounds of preparative HPLC to purify to >90% purity. [f] Required two rounds of preparative HPLC to purify to >90% purity. [g] Lost in purification. [h] Crude ^{1}H NMR was obtained.

The final alkanolamine products were released from the resin by adding a mixture of TFA and ethanol in dichloromethane (5:4:16) and soaking for 3 h to give the products **60**. The products were analyzed by HPLC (UV and ELSD [evaporative light scattering detector] detection) and the weights of the products were recorded. A small subset of the compounds was also analyzed by ^{1}H NMR. Comparison of the UV, ELSD, and proton NMR indicated that the ELSD data was most consistent with the ^{1}H NMR data (see **61**−**64**, Figure 4).[30]

In general, the reactions were very successful. Only four hundred compounds required purification (4%) using cationic solid phase extraction, and those were submitted as free bases. The rest of the compounds were submitted as TFA salts. Overall, based on the criteria of >0.4 μmol, correct mass by flow inject MS and >70% HPLC purity, 9966 compounds were submitted out of an attempted set of 10 800 representing a success rate of 93%. The average amount submitted was 4 μmol, which represented an average yield of 78%. The products were obtained with an average purity of 93%. Compounds with the butanolamine cores had a slightly lower submission rate than the propanolamine cores (85% versus 99%).

In conclusion, this work demonstrated that polymer-supported acetal linked alcohols could be used to efficiently generate libraries of compounds targeting GPCRs. The method is versatile, can accept many types of nucleophiles, and is amenable to synthetic strategies employing both free flowing resin and Irori's NK technology.

Experimental Section

Unless otherwise specified, most commercial reagents were purchased from Aldrich and used as is. Analytical high-pressure liquid chromatography (HPLC) and liquid chromatography/mass spectrometry (LC/MS) analyses were conducted using Shimadzu LC-10AS pumps and a SPD-10AV UV−vis detector using a Phenomenex column (Luna, C18, 50 × 4.6 mm) running a 4 min gradient from A to B (A 10% methanol, 90% water, 0.1% trifluoroacetic acid; B 90% methanol, 10% water, 0.1% trifluoroacetic acid) with a 1 min hold at 100% B at a flow rate of 4 mL/min. The peaks were detected using a UV detector at 220 nm. Preparative HPLC (prepHPLC) was performed using Shimadzu LC-10AS pumps and a SPD-10AV UV−vis detector using a Phenomenex column (Luna, C18, 50 × 30 mm) using a 12 min gradient from A to B (A 10% methanol, 90% water, 0.1% trifluoroacetic acid; B 90% methanol, 10% water, 0.1% trifluoroacetic acid) with a 2 min hold at 100% B at a flow rate of 40 mL/min. The peaks were detected using a UV detector at 220 nm. Chiral determinations were done on a Shimadzu HPLC using a Chiralpak AD column 10 μm, 4.6 mm × 250 mm, eluting with 2% isopropanol in heptane at 1 mL/min or a Chiralpak AD-H column with 40% heptane/60% (1:1) EtOH/MeOH (0.1% *N,N*-diethylamine) at a flow rate of 0.9 mL/min with UV detection at 227 nm. MS detection was performed with a Micromass Platform LC spectrometer. HPLC and LC/MS methods are detailed below. Preparative reverse-phase (RP) HPLC was performed using two Shimadzu LC-8A pumps and a SPD-10AV UV−vis detector set at 220 nm on C18 RP columns (YMC Pack ODSA S5 20 × 100 mm or 30 × 250 mm) using with methanol/water mixtures buffered with 0.1% trifluoroacetic acid. High-resolution mass spectra (HMRS) were recorded

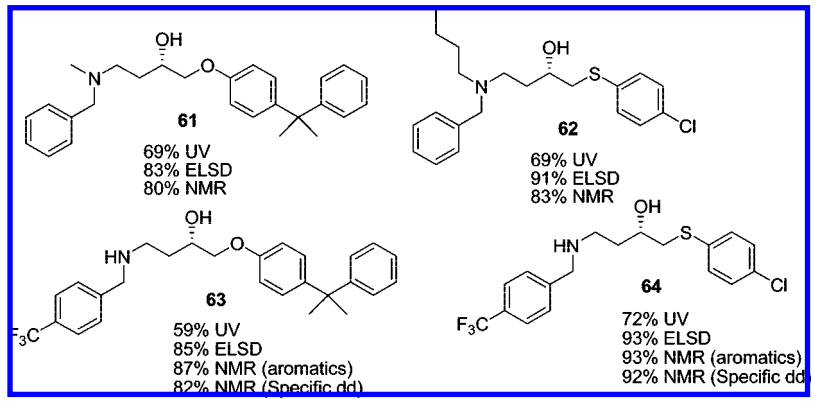


Figure 4. Comparison of purities determined by UV, ELS and ^{1}H NMR.

on a JEOL SX102 mass spectrometer. Optical rotations were determined on a Perkin-Elmer Model 241 polarimeter with a sodium lamp (589 nm) using a 100 mm cell. Elemental analyses were performed by Robertson Microlit Laboratories. Nuclear magnetic resonance spectra were run on Jeol (Eclipse-500) or Bruker (ARX-400, DPX-300B) spectrometers. The references for proton NMR spectra were either deuterochloroform (δ 7.25) or tetramethylsilane (δ 0.00), and for carbon NMR spectra was deuterochloroform (δ 77.0). FlowNMR spectra were obtained on a Varian Inova 400 spectrometer at 399.76 MHz using samples of approximately 7 mM concentration in DMSO-d_6/$CDCl_3$ (3/1) with $TMSSO_3$ as an internal standard in a 60 uL IFC flow probe. Thin layer chromatography (TLC) used EMD precoated plates with silica gel 60 F254 250 μM. The plates were visualized by UV at 254 nM and 20% phosphomolybdic acid in ethanol. Unless otherwise specified, all the reactions were performed under nitrogen using oven-dried glassware and were monitored by TLC, HPLC, or LCMS. Flash chromatography refers to the method of Still[31] using silica gel (EM Merck, 230−400 mesh).

(*S*)- and (*R*)-3-(Triisopropylsilyloxy)-2-(vinyloxy)propyl4-Methylbenzenesulfonate17*S* and17*R*. (a). (*S*)-2,2-Dimethyl-4-(toluenesulfonyloxymethyl)-1,3-dioxolane.[11] To a solution of (*R*)-2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane **14*R*** (Oakwood, 40 mL, 0.3 mol) in pyridine (120 mL) in an ice bath, was added *p*-toluenesulfonylchloride (61 g, 0.32 mmol) in one portion and the internal temperature rose to 44 °C. When the temperature started to drop, the ice bath was removed and the mixture was stirred for 3 h at room temperature. During that time, a white precipitate formed. The pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate (500 mL). The mixture was filtered and the filtrate was washed with ethyl acetate (100 mL). The combined ethyl acetate fractions were successively washed with aqueous citric acid (5%, 2 × 200 mL), saturated sodium bicarbonate (200 mL) and brine (200 mL). The organic layer was dried with sodium sulfate, filtered and concentrated to give a slightly colored oil that turned solid after pumping overnight (91 g, >100% yield). This product was used as is for the next step: ^{1}H NMR (Bruker 400 MHz, deuterochloroform): δ 7.76 (d, 2H, J = 8.6 Hz), 7.33 (d, 2H, J = 8.1 Hz), 4.25 (m, 1H), 3.98 (m, 3H), 3.74 (dd, 1H, J = 8.6, 5.0 Hz), 2.43 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H).

(*R*)-2,2-Dimethyl-4-(toluenesulfonyloxymethyl)-1,3-dioxolane (92 g, >100% yield): Prepared from (S)-2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane 14S (Fluka); ^{1}H NMR (Bruker 400 MHz, deuterochloroform) δ 7.77 (d, 2H, J = 8.1 Hz), 7.33 (d, 2H, J = 7.6 Hz), 4.25 (m, 1H), 3.98 (m, 3H), 3.74 (dd, 1H, J = 8.8, 5.3 Hz), 2.43 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H).

(b). (*S*)-2,3-Dihydroxypropyl 4-methylbenzenesulfonate. To a solution of (*S*)-2,2-dimethyl-4-(toluenesulfonyloxymethyl)-1,3-dioxolane (92 g, 0.3 mol) in methanol/water (3440:68 mL) was added sulfonic acid resin (84 g, DOWEX 50W-X2 resin prewashed with 500 mL water, followed by 500 mL of methanol) and the mixture was stirred for 24 h. After completion, the mixture was filtered and the resin was washed with methanol. The solvents were removed under reduced pressure to give colorless oil. The oil was dissolved in ether/DCM (1:1, 500 mL) and dried over magnesium sulfate, filtered, and concentrated to give 75 g of a colorless oil (>100% yield). This oil was used as is for the next step: ^{1}H NMR (Bruker 400 MHz, deuterochloroform) δ 7.77 (d, 2H, J = 8.3 Hz), 7.34 (d, 2H, J = 8.2 Hz), 4.05 (m, 2H), 3.92 (m, 1H), 3.67 (m, 1H), 3.58 (m, 1H), 2.83 (br, 2H), 2.43 (s, 3H); ^{13}C NMR (Bruker 100 MHz, deuterochloroform) δ 145.1, 132.2, 130.0, 128.0, 76.5, 69.7, 62.8, 21.6.

(*R*)-2,3-Dihydroxypropyl 4-methylbenzenesulfonate (79 g, >100%): ^{1}H NMR (Bruker 400 MHz, deuterochloroform) δ 7.77 (d, 2H, J = 8.1 Hz), 7.34 (d, 2H, J = 8.6 Hz), 4.04 (ddd, 2H, J = 13.2, 10.2, 5.3 Hz), 3.91 (m, 1H), 3.65 (m, 1H), 3.56 (m, 1H), 3.37 (d, 1H, J = 5.0 Hz), 2.82 (t, 1H, J = 6.0 Hz), 2.42 (s, 3H).

(c). (*S*)-2-Hydroxy-3-(triisopropylsilyloxy)propyl 4-Methylbenzenesulfonate 15*S*. To a cold (0 °C) solution of (*S*)-2,3-dihydroxypropyl 4-methylbenzenesulfonate (75 g, 0.3 mol), imidazole (40.8 g, 0.6 mol), and 4-pyrrolidinopyridine (1.9 g, 0.013 mol) in DMF (285 mL) was added triisopropylsilyl chloride (64 mL, 0.33 mol) dropwise via an addition funnel. After the addition was complete, the ice bath was removed, and the mixture was stirred for 24 h. The reaction was poured into hydrochloric acid (0.5 M, 600 mL) and was extracted with hexane (2 × 500 mL). The combined extracts were washed with water (2 × 500 mL) and brine (500 mL), dried with magnesium sulfate, filtered, and concentrated to give a colorless viscous oil (120 g, 99% yield). This product was used directly for the next step: ^{1}H NMR (Bruker 400

MHz, deuterochloroform) δ 7.77 (d, 2H, *J* = 8.6 Hz), 7.33 (d, 2H, *J* = 8.1 Hz), 4.10 (dd, 2H, *J* = 9.6, 5.0 Hz), 4.02 (dd, 2H, *J* = 10.0, 5.5 Hz), 3.85 (m, 1H), 3.70 (d, 2H, *J* = 5.0 Hz), 2.49 (2, 1H, *J* = 6.0 Hz), 2.43 (s, 3H), 1.01 (m, 21H); ^{13}C NMR (Bruker 100 MHz, deuterochloroform) δ 145.1, 132.8, 129.9, 128.0, 70.1, 69.5, 63.3, 21.6, 17.9, 11.9.

(*R*)-2-Hydroxy-3-(triisopropylsilyloxy)propyl 4-Methylbenzenesulfonate 15*R* (120 g, 99%): ^{1}H NMR (Bruker 400 MHz, deuterochloroform) δ 7.78 (d, 2H, *J* = 8.1 Hz), 7.34 (d, 2H, *J* = 8.1 Hz), 4.09 (dd, 2H, *J* = 10.1, 5.5 Hz), 4.03 (dd, 2H, *J* = 10.1, 5.5 Hz), 3.85 (m, 1H), 3.70 (d, 2H, *J* = 5.0 Hz), 2.49 (d, 1H, *J* = 6.0 Hz), 2.43 (s, 3H), 1.02 (m, 21H).

(d). (*S*)-2-(1-Ethoxyethoxy)-3-(triisopropylsilyloxy)propyl 4-Methylbenzenesulfonate 16*S*. To a cold (0 °C) solution of (*S*)-2-hydroxy-3-(triisopropylsilyloxy)propyl 4-methylbenzenesulfonate **15***S* (36 g, 90 mmol) and pyridinium *p*-toluene sulfonate (2.3 g, 9 mmol, dried by azeotropic distillation with toluene) in DCM (360 mL) was carefully added distilled ethylvinyl ether (90 mL, 900 mmol). The ice bath was removed and the mixture was stirred for 2 h at room temperature. The reaction was poured into saturated sodium bicarbonate (400 mL) and was extracted with hexane (2 × 900 mL). The combined organic layers were concentrated to ∼1000 mL, washed with brine (500 mL), and dried with magnesium sulfate. The drying agent was filtered, and the mixture was concentrated to give 42 g of an oil (94% yield). TLC: This product was used as is for the next step: ^{1}H NMR (Bruker 400 MHz, deuterochloroform) δ 7.77 (d, 2H, *J* = 8.1 Hz), 7.31 (d, 2H, *J* = 8.1 Hz), 4.75 (m, 1H) 4.19 (m, 1H), 4.03 (m, 1H), 3.69 (m, 4H), 3.42 (m, 1H), 2.41 (s, 3H), 1.24 (m, 3H), 1.12 (m, 3H), 0.99 (m, 21H); ^{13}C NMR (Bruker 100 MHz, deuterochloroform) δ 144.3, 132.9, 129.8, 128.0, (99.9, 99.5), (73.9, 73.6) (70.2, 69.9), (62.5, 62.4), (60.5, 60.1), 21.6, 20.2, 17.9, 15.2, 11.9.

(*R*)-2-(1-Ethoxyethoxy)-3-(triisopropylsilyloxy)propyl 4-Methylbenzenesulfonate 16*R* (49 g, 98%): ^{1}H NMR (Bruker 400 MHz, deuterochloroform) δ 7.77 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 4.75 (m, 1H) 4.19 (m, 1H), 4.04 (m, 1H), 3.70 (m, 4H), 3.42 (m, 1H), 2.41 (s, 3H), 1.23 (m, 3H), 1.13 (m, 3H), 1.01 (m, 21H).

(e). (*S*)-3-(Triisopropylsilyloxy)-2-(Vinyloxy)propyl 4-Methylbenzenesulfonate 17*S*. To a cold (−78 °C) mixture of (*S*)-2-(1-ethoxyethoxy)-3-(triisopropylsilyloxy)propyl 4-methylbenzenesulfonate **16***S* (42 g, 0.084 mol), triethylamine (EM Science, 17 mL, 0.125 mol) in DCM (600 mL) was added trimethylsilyl trifluoromethanesulfonate (19.2 mL, 0.108 mol) dropwise. The mixture was stirred at −78 °C for 20 min, 0 °C for 75 min, and at room temperature for 100 min. The reaction was poured into a mixture of saturated sodium bicarbonate (600 mL) and hexane (600 mL) and was extracted with hexane (2 × 50 mL). The hexane extracts were washed with brine (300 mL), dried with magnesium sulfate, filtered, and concentrated to give 33 g of a yellow oil (92% yield). The resulting oil was purified by passing through basic alumina (Brockman, 600 g) and was eluted with 9:1 hexane:ethyl acetate to give a colorless oil (32 g, 90% yield) after concentration: ^{1}H NMR (400 MHz, deuterochloroform) δ 7.78 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 6.23 (dd, 1H, *J* = 14.1, 6.6 Hz), 4.24 (m, 2H), 4.11 (dd, 1H, *J* = 10.6, 6.1 Hz), 4.00 (m, 2H), 3.77 (dd, 1H, *J* = 10.6, 5.0 Hz), 3.69 (dd, 1H, *J* = 10.1, 6.0 Hz), 2.44 (s, 3H), 1.00 (m, 21H); ^{13}C NMR (Bruker 100 MHz, deuterochloroform) δ 150.6, 144.8, 132.7, 129.8, 128.0, 89.2, 77.3, 68.6, 61.5, 21.6, 17.8, 11.7; $[\alpha]_D$ +7.9 ° (*c* = 1, chloroform); *ee* > 84% Chiralpak AD 5.7 min 1 mL/min 2% isopropanol in hexane; Anal. Calcd for $C_{21}H_{36}O_5SSi$ C 58.84, H 8.46, S 7.48, Si 6.55; Found C 58.92, H 8.45, S 7.28, Si 7.48; MS (CI) *m*/*z* 403.3 $[M + H]^+$.

(*R*)-3-(Triisopropylsilyloxy)-2-(vinyloxy)propyl 4-Methylbenzenesulfonate 17*R* (33 g, 92%): ^{1}H NMR (Bruker 400 MHz, deuterochloroform) δ 7.77 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 6.22 (dd, 1H, *J* = 14.1, 6.6 Hz), 4.24 (m, 2H), 4.11 (dd, 1H, *J* = 10.1, 5.5 Hz), 3.99 (m, 2H), 3.76 (dd, *J* = 10.6, 5.0 Hz), 3.69 (dd, *J* = 10.6, 6.0 Hz), 2.42 (s, 3H), 0.99 (m, 21H); ^{13}C NMR (Bruker 100 MHz, deuterochloroform) δ 151.0, 145.2, 133.1, 130.2, 128.4, 89.6, 77.3, 69.0, 61.9, 22.0, 18.2, 11.9; $[\alpha]_D$ −8.2 ° (*c* = 1, chloroform); *ee* > 86% Chiralpak AD 6.1 min 1 mL/min 2% isopropanol in hexane; Anal. Calcd for $C_{21}H_{36}O_5SSi$ C 58.84, H 8.46, S 7.48, Si 6.55; Found C 59.18, H 8.44, S 7.58, Si 6.82.

(*S*)-4-(Triisopropylsilyloxy)-2-(vinyloxy)butyl 4-Methylbenzenesulfonate 20. (a). (*S*)-4-(triisopropylsilyloxy)butane-1,2-diol. Trisopropylsilylchloride (96.4 g, 0.5 mol) was added to a cooled solution (−78 °C) of (*S*)-(-)-butane-1,2,4-triol **19** (50.0 g, 0.48 mol) and imidazole (64.7 g, 0.95 mol) in DMF (600 mL), and the mixture was stirred for 5 min. The cooling bath was removed and the mixture was stirred at room temperature for 6 h. The mixture was poured into water (3 L) and was extracted with hexane (1 L). The organic layer was separated, washed with brine (1 L), dried with sodium sulfate, and the solvents were evaporated. The residue was purified by flash chromatography over silica gel using a solvent gradient (5 to 50% of ethyl acetate in hexanes) to give 53 g (42% yield) of a colorless oil: ^{1}H NMR (300 MHz, deuterochloroform) δ 3.96−3.90 (m, 3H), 3.60−3.52 (m, 2H), 3.05 (br s, 2H), 1.85−1.60 (m, 2H), 1.20−1.03 (m, 21H); MS (ESI) *m*/*z* = 263 (MH^+).

(b). (*S*)-2-Hydroxy-4-(Triisopropylsilyloxy)butyl 4-Methylbenzenesulfonate. *p*-Toluenesulfonyl chloride (34.4 g, 0.18 mol) in DCM (50 mL) was added dropwise to a cooled solution (−78 °C) of (*S*)-4-(triisopropylsilyloxy)butane-1,2-diol (45.9 g, 0.17 mol) and pyridine (32.4 mL, 0.4 mol) in DCM (200 mL), over a 10 min period. The cooling bath was removed and the reaction was stirred at room temperature for 4 h. The mixture was poured into 0.5 M aqueous hydrochloric acid (500 mL) and was stirred for 5 min. The organic layer was separated, washed with aqueous sodium bicarbonate (500 mL), brine (500 mL), and dried over sodium sulfate, and the solvents were evaporated. The residue was purified by flash chromatography over silica gel using a solvent gradient (5 to 25% of ethyl acetate in hexanes) to give a pale yellow oil (42 g, 58% yield): ^{1}H NMR (300 MHz, deuterochloroform) δ 7.66 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.2 Hz), 4.15−3.80 (m, 5H), 3.18 (br s, 1H), 2.42 (s, 3H), 1.68 (m, 2H), 1.10− 0.90 (m, 21 H); MS (ESI) *m*/*z* = 417 (MH^+).

(c). (*S*)-2-(1-Ethoxyethoxy)-4-(Triisopropylsilyloxy)butyl 4-Methylbenzenesulfonate. Pyridinium *p*-toluenesufonate (100 mg) in DCM (5 mL) was added to a solution of (*S*)-2-hydroxy-4-(triisopropylsilyloxy)butyl 4-methylbenzenesulfonate (41.6 g, 100 mmol) and ethylvinyl ether (67.2 mL, 700 mmol) in DCM (350 mL), and the mixture was stirred for 1 h at room temperature. The solution was poured into saturated aqueous sodium bicarbonate (1 L) and stirred for 5 min. The organic layer was separated, washed with water (500 mL) and brine (500 mL), and dried over Na_2SO_4, and the solvents were evaporated to furnish a colorless oil (46 g, 94% yield), which was used in the next step without further purification. The product is unstable at room temperature in solvent: ^{1}H NMR (300 MHz, deuterochloroform) δ 7.79 (d, 2H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.2 Hz), 4.72 (m, 1H), 4.10−3.90 (m, 3H), 3.72−3.35 (m, 4H), 2.43 (s, 3H), 1.69 (m, 2H), 1.26− 0.90 (m, 27 H); MS (ESI) m/z = 489 (MH^+).

(d). (*S*)-4-(Triisopropylsilyloxy)-2-(Vinyloxy)butyl 4-Methylbenzenesulfonate 20. Trimethylsilyl triflate (22.6 mL, 0.12 mol) in DCM (10 mL) was added dropwise over 10 min to a cold solution (−78 °C) of (*S*)-2-(1-ethoxyethoxy)-4-(triisopropylsilyloxy)butyl 4-methylbenzenesulfonate (45.9 g, 0.94 mol) and triethylamine (27.9 mL, 0.2 mol) in DCM (300 mL). The reaction was stirred between 0−5 °C using an ice bath for 1 h. The mixture was poured into saturated aqueous sodium bicarbonate (1 L) and stirred for 5 min. The organic layer was separated, washed with water (500 mL) and brine (500 mL), and dried over sodium sulfate, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography over silica gel using a solvent gradient (0 to 5% of ethyl acetate in hexanes) to give a colorless oil (27 g, 65% yield). The product is unstable on silica and is better purified with basic alumina: ^{1}H NMR (300 MHz, deuterochloroform) δ 7.79 (d, 2H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.2 Hz), 6.25 (m, 1H), 4.30−3.70 (m, 7H), 2.42 (s, 3H), 1.72 (m, 1H), 1.01 (m, 21 H); MS (ESI) m/z = 443 (MH^+).

(*R*)-4-(Triisopropylsilyloxy)-2-(vinyloxy)butyl 4-Methylbenzenesulfonate 23. (a). (*R*)-Butane-1,2,4-triol. A solution of (*R*)-(+)-malic acid (**22**, 10 g, 74.6 mmol) in THF (100 mL) was added dropwise to a solution of borane-dimethylsulfide complex (22.4 mL, 236 mmol) in THF (90 mL), and after the addition was complete, the exothermic reaction was refluxed for 2.5 h. After all the starting material had been consumed, the mixture was cooled to 0 °C and methanol was carefully added until gas evolution ceased. The solvent were removed under removed pressure and azeotropic distillation with methanol (2 × 150 mL) provided (*R*)-butane-1,2,4-triol as a colorless oil (7.9 g, 100% yield): ^{1}H NMR (400 MHz, deuteromethanol) δ 3.8−3.6 (m, 3H), 3.4−3.5 (m, 2H), 1.9−1.65 (m, 1H), 1.6−1.5 (m, 1H); ^{13}C NMR (100 MHz, deuteromethanol) δ 71.2, 67.9, 60.3, 37.5.

(b). (*R*)-4-(Triisopropylsilyloxy)butane-1,2-diol. A solution of (*R*)-butane-1,2,4-triol (7.9 g, 74.4 mmol) in methanol was added to a suspension of dibutyltin oxide in methanol (300 mL). The mixture was refluxed for 3 h, and the clear solution was concentrated under reduced pressure. The residue was further concentrated under high vacuum for 2 h and was diluted with chloroform (370 mL). Triisopropylsilyl chloride (14.2 g, 89.3 mmol) was added, and the mixture was stirred at room temperature overnight. The clear suspension was concentrated under reduced pressure; the residue diluted in a small amount of ethanol, and the solid was filtered and rinsed with small amounts of ethanol. The filtrates were concentrated under reduced pressure to give a colorless oil (25 g). The oil was purified by flash chromatography eluting with ethyl acetate/heptane (15:85 then 3:7) to give (*R*)-4-(triisopropylsilyloxy)butane-1,2-diol as a colorless oil (17.4 g, 89% yield): ^{1}H NMR (500 MHz, deuterochloroform) δ 3.94 (m, 3H), 3.61 (dd, 1H, J = 3.8, 11 Hz), 3.51 (dd, 1H, J = 6.0, 11 Hz), 2.97 (br s, 2H), 1.78(m, 1H), 1.63 (m, 1H), 1.09 (m, 21H); ^{13}C NMR (100 MHz, deuterochloroform) δ 72.5, 67.0, 62.8, 35.3, 18.3, 12.4.

(c). (*R*)-2-Hydroxy-4-(Triisopropylsilyloxy)butyl 4-Methylbenzenesulfonate(15 g, 54%): ^{1}H NMR (500 MHz, deuterochloroform) δ 7.79 (d, 2H, J = 7.7 Hz), 7.33 (d, 2H, J = 8.2 Hz), 4.07(m, 1H), 3.95 (m, 3H), 3.85 (m, 1H) 2.43 (s, 3H), 1.70 (m, 2H), 1.10− 0.90 (m, 21 H); ^{13}C NMR (125 MHz, deuterochloroform) δ 145.3, 133.1, 130.3, 128.4, 73.5, 69.6, 62.2, 34.9, 22.0, 18.3, 12.3.

(d). (*R*)-2-(1-Ethoxyethoxy)-4-(triisopropylsilyloxy)butyl 4-Methylbenzenesulfonate (1.4 g, 80%), 1:1 Mixture of diastereomers: ^{1}H NMR (500 MHz, deuterochloroform) δ 7.77 (2d, 2H, J = 8.0 Hz), 7.32 (br d, 2H, J = 7.2 Hz), 4.71 (m, 1H), 4.02 (m, 3H), 3.70 (m, 2H), 3.56 (m, 1H), 3.41 (m, 1H), 2.43 (s, 3H), 1.70 (m, 2H), 1.24 (2d, 3H), 1.11 (2t, 3H), 0.99 (m, 21 H); ^{13}C NMR (125 MHz, deuterochloroform) δ 144.8, 144.7, 132.9, 129.9, 129.8, 128.0, 100.2, 100.1, 72.5, 71.1, 60.8, 60.2, 59.2, 58.8, 35.5, 34.9, 21.7, 20.2, 20.1, 18.0, 15.3, 15.2, 11.8, 11.7.

(e). (*R*)-4-(Triisopropylsilyloxy)-2-(vinyloxy)butyl 4-Methylbenzenesulfonate 2 (0.8 g, 64%): ^{1}H NMR (500 MHz, deuterochloroform) δ 7.79 (d, 2H, J = 8.3 Hz), 7.34 (d, 2H, J = 8.2 Hz), 6.23 (dd, 1H, J = 14.3, 6.6 Hz), 4.24 (m, 2H), 4.16 (dd, 1H, J = 10.5, 3.3), 4.07 (dd, 1H, J = 10.7, 6.3), 3.97 (m, 1H), 3.73 (m, 2H), 2.44 (s, 3H), 1.74 (m, 2H), 1.03 (m, 21 H); ^{13}C NMR (125 MHz, deuterochloroform) δ 151.1, 144.8, 132.8, 129.8, 128.0, 89.0, 74.1, 71.3, 58.5, 34.0, 21.6, 18.0, 11.8.

Loading of the Vinyl Ethers on Hydroxymethylpolystyrene (General Procedure). Hydroxymethyl polystyrene (25.0 g, 31.0 mmol, Novabiochem, 1.24 mmol/g, 100−200 mesh) in a 500 mL peptide synthesis vessel was washed with anhydrous DCM (2 × 300 mL). A solution of the vinyl ether (60 mmol) in anhydrous DCM (200 mL) was filtered through a pad of basic alumina (20 g), and the filtrate was added to the resin and shaken gently on a Mistral Multimixer for 30 min. Additional DCM was added (if necessary) to ensure that the volume of solvent was more than the volume of the swollen resin for efficient agitation. A solution of PPTS (0.75 g, 3 mmol) in DCM (10 mL) was added to the suspension and agitated for 42 h. The liquid was drained, and the resin was washed sequentially with 300 mL portions each of 1% triethylamine in anhydrous DCM (3×), anhydrous THF (3×), 1% triethylamine in anhydrous DCM (3 x), and anhydrous diethyl ether (3 x). The resin was dried under reduced pressure and kept refrigerated in the presence of a desiccant

until used. The resins were assumed to be sensitive to moisture and efforts were made to maintain anhydrous conditions or when water was used to ensure that the conditions were basic until the final cleavage.

Test Library. Nucleophilic Displacement of the Tosylate with Phenols and Secondary Amines. Resins **18S** and **18R** (1.60 g, 1.45 mmol, 0.91 mmol/g loading) were added to a solution of potassium *tert*-butoxide (1.47 g, 13.08 mmol), *o*-cresol (**26**, 1.50 mL, 14.53 mmol), and 18-crown-6 (0.04 g, 0.15 mmol) in NMP (25 mL) in a 40 mL vial under nitrogen, and the mixture was heated and very gently stirred with a magnetic stir bar for 18 h. The brown suspensions were cooled to room temperature, filtered into a 25 mL Varian polypropylene tube containing a polypropylene frit, washed with DMF (2 × 20 mL), DMF:water (2×) (3:2, 20 mL), DMF (3 × 20 mL), THF (3 × 20 mL), and 0.5% triethylamine in DCM (3 × 20 mL), and the brown resins were dried under reduced pressure. The resins were used as is for the next step. The *S*-resin gave (1.39 g, 1.34 mmol, 92% yield) of *R*-resin, while the *R*-resin gave (1.39 g, 1.34 mmol, 92% yield) of *S*-resin.

The same procedure was used with 4-hydroxybenzonitrile (**27**, 1.73 g, 14.5 mmol) except that a total of only 15 mL of NMP was required. The brown suspensions were cooled and treated as previously described to give the *R*-resin (1.55 g, 1.48 mmol, 102% yield) and the *S*-resin (1.53 g, 1.46 mmol, 101% yield).

The same procedure was used with 4-chloro-3-fluorophenol (**28**, 2.13 g, 14.5 mmol) except that a total of only 15 mL of NMP was required. The brown suspensions were cooled and treated as previously to give the *R*-resin (1.56 g, 1.45 mmol, 100% yield) and the *S*-resin (1.56 g, 1.48 mmol, 100% yield).

1-Phenylpiperazine (**25**, 2.22 mL, 14.5 mmol) was added to each resin (1.60 g, **18***S*, **18***R*, 0.91 mmol/g loading) suspended in 15 mL of NMP in a 40 mL vial under nitrogen, and the mixtures were heated and very gently stirred with a magnetic stir bar for 18 h. The yellow suspensions were cooled to room temperature, and were treated as previously described. The *S*-tosylate **18***S* gave 1.57 g of the *S*-resin, while the *R*-tosylate **18***R* gave 1.58 g of the *R*-resin.

Removal of the TIPS Protecting Group. The resins were arrayed in a 24-well Bohdan minireactor bloc (glass inserts) (115 mg of resin/well), and a solution of 0.5 M TBAF in THF (2 mL) was added to each reaction well. The tubes were stirred for 19 h using an platform orbital shaker (450 rpm, New Brunswick Scientific Innova 2100). Extra resins were distributed to provide sampling aliquots (eight samples derived from the **18***S*-resin and eight samples from the **18***R*-resin). The data and sample tracking was handled using proprietary software. At the end of the reaction time, the resins were filtered and washed with THF (2×), 3:2 DMF/H_2O (3×), DMF (3×), THF (3×), and DCM (3×), and then dried under reduced pressure for 48 h. An aliquot of each resin was cleaved with TFA/DCM/EtOH (5/16/4 ratio, 2 mL) for 2 h. The solvents were collected in pretared tubes, and the resins were washed with DCM (2 × 2 mL). Next, the combined washings were concentrated. Crude LCMS was obtained for all of the cleaved samples, and crude ^{1}H NMR's were obtained for the products of entries 4−8 of Table 1 and are included in the Supporting Information.

The aliquots were purified by prepHPLC (TFA/MeOH/water) to give the products with an isolated average yield of 41% and 99% purity (see Table 1). Flow NMR was obtained for all products.

Iodination. A solution of pyridine (1 mL, 2.0 M in DMF) was added to the resins in each well of the Bohdan 24 minireactor. The reactors were stirred for 5 min and stopped. A solution of methyltriphenoxyphosphonium iodide (1 mL, 1.0 M, 18 g in 32 mL of DMF) prepared according to the procedure of Hudson[26] was added and the mixture was stirred for 19 h. The pale yellow suspensions were filtered and washed with DMF (4×), THF (3×), and DCM (3×) [all containing 0.5% triethylamine], and the resins were dried under reduced pressure for 1 h. The resins were used as is for the next step.

An aliquot of each resin was cleaved with TFA/DCM/EtOH (5/16/4, 2 mL) for 2 h. The resins were drained and were washed with DCM (2 × 2 mL), and the combined filtrates were concentrated and analyzed by LCMS (see Table 1). Crude ^{1}H NMR values were obtained for entries 12−16 and showed the presence of the desired products. The samples were purified by prepHPLC (MeOH, TFA, water). The average yield was 36% and the average purity was 100%. The samples were analyzed by flowNMR except for entry 10 (Table 1) which was lost during purification.

Second Nucleophilic Displacement. A solution of the amine (1.0 M) and *N,N*-diisopropylethylamine (0.5 M) in NMP (2 mL) [the 1.0 M solutions were prepared from a stock solution of 5.0 mL of propylamine and 2.0 mL of *N,N*-diisopropylethylamine in 13 mL of NMP or 1-(3-aminopropyl)imidazole 3.0 mL, *N,N*-diisopropylethylamine 2 mL, and NMP 14 mL; 4-phenylpiperazine 3.22 g and 2 mL diisopropylethylamine in 15 mL NMP] was added to each reaction well (Bohdan 24). The mixtures were heated at 85 °C for 22 h. After cooling, the resins were washed with DMF (0.5% triethylamine) (4×), THF (0.5% triethylamine) (4×), and DCM (0.5% triethylamine) (3×). The resins were then used directly for the cleavage.

Cleavage. A solution of the cleavage solution (2 mL, EtOH/TFA/DCM 3/4/13) was added to each tube (2 mL each), and the resins were stirred at room temperature for 2 h. The samples were drained into tared test tubes (16 × 100 mm), and the resins were washed with DCM (2 × 2 mL). The combined solvents were removed under reduced pressure in a concentrator (Savant SpeedVac Plus SC250 DDA). The samples were weighed and were diluted in methanol (6 mL). An aliquot (70 uL) was taken from each sample and diluted to 300 uL and analyzed by LCMS (Phenominex, Luna C18, 4.6 × 50 mm, 4 min gradient from 10% MeOH, 90% water, 0.1% TFA to 90% MeOH, 10% water, 0.1% TFA). Crude ^{1}H NMR values were obtained for entries 33, 45, 48, 51, and 54−56 (Table 2). The average yield was 28% (six steps average 81% yield per step), and the average purity was 96%.

Enantiomeric Excess Determination. Samples from **43** and **55** (Table 2) were purified by preparative HPLC (MeCN, water, TFA). Compound **43** (TFA salt) gave 31 mg of a white solid, 66% yield, 100% pure, MH^+ 364.1; HRMS $C_{20}H_{24}ClFNO_2^+$ calcd 364.14741 obsd 364.14863; ^{1}H NMR (500 MHz, deuterochloroform) δ ppm 7.35 (t, J = 7.7 Hz, 2 H), 7.29 (t, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.2 Hz, 2 H), 6.71 (dd, J = 10.4, 2.7 Hz, 1 H), 6.64 (dd, J = 9.1, 1.9 Hz, 1 H), 4.56−4.65 (m, 1 H), 4.11 (dd, J = 9.3, 4.4 Hz, 1 H), 3.98 (d, J = 12.1 Hz, 1 H), 3.91 (t, J = 7.7 Hz, 1 H), 3.84 (d, J = 11.5 Hz, 1 H), 3.20−3.30 (m, 2 H), 2.87 − 2.98 (m, 2 H), 2.75 (tt, J = 12.3, 3.7, 3.6 Hz, 1 H), 2.29−2.44 (m, 2 H), 2.06 (t, J = 16.8 Hz, 2 H); ^{13}C NMR (126 MHz, deuterochloroform) δ ppm 157.64 (d, J = 10.2 Hz), 158.43 (d, J = 249.2 Hz), 142.62, 130.83 (2 C), 128.95, 127.33 (2 C), 126.64, 116.39 (d, J = 30.5 Hz), 110.85, 103.73 (d, J = 25.4 Hz), 70.15, 64.02, 61.94, 56.82, 54.41, 40.38, 30.31 (2 C); ^{19}F NMR (471 MHz, deuterochloroform) δ ppm −78.56 (s, 3 F, TFA), −115.30 (s, 1 F). The *ee* was determined using chiral HPLC and was determined to be 99%.

Compound **55** gave 36 mg of white solid, 76% yield, 100% pure MH+ 364.1; HRMS $C_{20}H_{24}ClFNO_2^+$ calcd. 364.14741 obs. 364.14836; ^{1}H NMR (500 MHz, deuterochloroform) δ ppm 7.35 (t, J = 7.4 Hz, 2 H), 7.29 (t, J = 8.8 Hz, 2 H), 7.24 (d, J = 7.1 Hz, 2 H), 6.71 (dd, J = 10.4, 2.7 Hz, 1 H), 6.64 (dd, J = 8.5, 2.5 Hz, 1 H), 4.61 (tt, J = 8.0, 4.1 Hz, 1 H), 4.11 (dd, J = 9.3, 4.4 Hz, 1 H), 3.98 (d, J = 11.5 Hz, 1 H), 3.91 (t, J = 7.7 Hz, 1 H), 3.84 (d, J = 12.1 Hz, 1 H), 3.21 − 3.29 (m, 2 H), 2.88−2.97 (m, 2 H), 2.71−2.79 (m, J = 12.2, 12.2, 3.6, 3.3 Hz, 1 H), 2.30−2.44 (m, 2 H), 2.06 (t, J = 16.8 Hz, 2 H); ^{13}C NMR (126 MHz, deuterochloroform) δ ppm 157.64 (d, J = 10.2 Hz), 158.43 (d, J = 249.2 Hz), 142.62, 130.83 (2 C), 128.95, 127.33 (2 C), 126.64, 116.39 (d, J = 30.5 Hz), 110.85, 103.73 (d, J = 25.4 Hz), 70.15, 64.02, 61.94, 56.82, 54.41, 40.38, 30.31 (2 C); ^{19}F NMR (471 MHz, deuterochloroform) δ ppm −78.50 (m, 3 F), −115.30 (s, 1 F). The *ee* was determined using chiral HPLC and was determined to be 97.5%

Nucleophilic Displacement of the Tosylate with Phenols, Thiophenols, or Secondary Amines: The NK were dry-loaded with the resins and were washed with DCM (0.3 mL/NK) for 2 h. The NK were dried under vacuum and were stored in dry plastic bags at room temperature. The NK were sorted into 48 bins for the tosylate displacement step. NMP solutions of each nucleophile (1.0 M, thiophenol or phenol), *t*-BuOK (0.9 M) and 18-crown-6 (0.01 M) in NMP were prepared (some nucleophiles required gentle heating to dissolve). The secondary amines did not require base or crown ether, and a solution of each in NMP (1.0 M) was prepared. The NK (∼8 mg/NK) were added to each solution of nucleophile, degassed, and heated with orbital shaking at 95 °C for 18 h. The NK were cooled, the solvent was drained, and each reaction batch was rinsed with DMF (2×). The NK were combined and washed with 3:2 DMF/H_2O (3×) and then washed in the IRORI autowasher. Each wash included two degas cycles where a vacuum was applied to remove air pockets from the NK and two cycles of stirring for 10−300 min. Finally, the NK were washed with DMF (4×), THF (3×), and DCM (3×) and dried under vacuum.

Removal of the TIPS Protecting Group. All of the NK were treated with 0.5 M TBAF (Aldrich, 1.0 M solution in THF) in reagent grade THF (NOT anhydrous). The NK were shaken for 18 h at room temperature. The NK were occasionally noted to have turned purple in color. This color change did not affect the outcome of the products with those NK. The NK were washed with THF (2×) and 3:2 DMF/H_2O (3×), then washed in the autowasher with DMF (3×), THF (3×), and DCM (3×), and dried under vacuum.

Iodination. The dry NK were suspended in 2.0 M pyridine in anhydrous DMF. To this suspension was added an equal volume of a solution of 1.0 M methyltriphenoxyphosphonium iodide in DMF. (The resultant concentration of pyridine was 1.0 M, and the resultant concentration of $Me(OPh)_3P^+I^-$ was 0.5 M.). Note: It is important that the pyridine is added before the $Me(OPh)_3P^+I^-$. The NK were then shaken at room temperature for 18 h. The solvent was drained, and the NK were washed in the autowasher with DMF (4×), THF (3×), and DCM (3×) and then dried under vacuum.

Second Nucleophilic Displacement. The NK were added to a solution of the nucleophile in NMP (1.0 M). Diisopropylethylamine was added to produce a 0.5 M final solution in each flask, and the mixture was heated at 85 °C for 20 h. The reactions were cooled to room temperature, the solvent was drained, and the NK were washed in the autowasher with DMF (4×), THF (3×), and DCM (3×) and dried under vacuum.

Final Cleavage. The NK were sorted into Clevap plates, and each plate was paired with a tared and barcoded Micronic plate (1.2 mL). The cleavage solution (450 μL, trifluoroacetic acid, ethanol in DCM 5:4:16) was added, and the NK were degassed and reacted for 2 h. The NK were drained into the tubes and additional cleavage solution was added (300 μL). The plates were then incubated for another hour before draining a second time. Finally, the NK were rinsed with methanol for 20 min, and the combined solutions were dried under reduced pressure.

SCX Purification. Four hundred compounds were purified by solid phase extraction using SCX (United ChemTech SCX100020X). The cartridges were washed with methanol (2 mL), and the sample was loaded in 500 μL of methanol. The sample was washed with methanol (2 mL) and was eluted with ammonia in methanol (1 mL) and concentrated.

In total, 9966 compounds were submitted (>0.4 μmol, correct mass, >70% HPLC purity) for a success rate of 93%. Average amount was 3.98 μmol. Average yield was 78.3%. Average purity was 92.7%.

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Supporting Information Available. Flow ^{1}H NMR data of purified compounds followed by LCMS data (UV absorbance, TIC and mass spectrum) and characterization of compounds **43** and **55**. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Klabunde, T.; Hessler, G. *ChemBioChem* **2002**, *3*, 928–944.

(2) Venter, J. C.; Adams, M. D.; Myers, E. W.; Li, P. W.; Mural, R. J.; Sutton, G. G.; Smith, H. O.; Yandell, M.; Evans, C. A.; Holt, R. A.; Gocayne, J. D.; Amanatides, P.; Ballew, R. M.; Huson, D. H.; Wortman, J. R.; Zhang, Q.; Kodira, C. D.; Zheng, X. H.; Chen, L.; Skupski, M.; G. Subramanian, G.; Thomas, P. D.; Zhang, J.; Gabor Miklos, G. L.; Nelson, C.; Broder, S.; Clark, A. G.; Nadeau, J.; McKusick, V. A.; Zinder, N.; Levine, A. J.; Roberts, R. J.; Simon, M.; Slayman, C.; Hunkapiller, M.; Bolanos, R.; Delcher, A.; Dew, I.; Fasulo, D.; Flanigan, M.; Florea, L.; Halpern, A.; Hannenhalli, S.; Kravitz, S.; Levy, S.; Mobarry, C.; Reinert, K.; Remington, K.; Abu-Threideh, J.; Beasley, E.; Biddick, K.; Bonazzi, V.; Brandon, R.; Cargill, M.; Chandramouliswaran, I.; Charlab, R.; Chaturvedi, K.; Deng, Z.; Di Francesco, V.; Dunn, P.; Eilbeck, K.; Evangelista, C.; Gabrielian, A. E.; Gan, W.; Ge, W.; Gong, F.; Gu, Z.; Guan, P.; Heiman, T. J.; Higgins, M. E.; Ji, R. R.; Ke, Z.; Ketchum, K. A.; Lai, Z.; Lei, Y.; Li, Z.; Li, J.; Liang, Y.; Lin, X.; Lu, F.; Merkulov, G. V.; Milshina, N.; Moore, H. M.; Naik, A. K.; Narayan, V. A.; Neelam, B.; Nusskern, D.; Rusch, D. B.; Salzberg, S.; Shao, W.; Shue, B.; Sun, J.; Wang, Z.; Wang, A.; Wang, X.; Wang, J.; Wei, M.; Wides, R.; Xiao, C.; Yan, C.; Yao, A.; Ye, J.; Zhan, M.; Zhang, W.; Zhang, H.; Zhao, Q.; Zheng, L.; Zhong, F.; Zhong, W.; Zhu, S.; Zhao, S.; Gilbert, D.; Baumhueter, S.; Spier, G.; Carter, C.; Cravchik, A.; Woodage, T.; Ali, F.; An, H.; Awe, A.; Baldwin, D.; Baden, H.; Barnstead, M.; Barrow, I.; Beeson, K.; Busam, D.; Carver, A.; Center, A.; Cheng, M. L.; Curry, L.; Danaher, S.; Davenport, L.; Desilets, R.; Dietz, S.; Dodson, K.; Doup, L.; Ferriera, S.; Garg, N.; Gluecksmann, A.; Hart, B.; Haynes, J.; Haynes, C.; Heiner, C.; Hladun, S.; Hostin, D.; Houck, J.; Howland, T.; Ibegwam, C.; Johnson, J.; Kalush, F.; Kline, L.; Koduru, S.; Love, A.; Mann, F.; May, D.; McCawley, S.; McIntosh, T.; McMullen, I.; Moy, M.; Moy, L.; Murphy, B.; Nelson, K.; Pfannkoch, C.; Pratts, E.; Puri, V.; Qureshi, H.; Reardon, M.; Rodriguez, R.; Rogers, Y. H.; Romblad, D.; Ruhfel, B.; Scott, R.; Sitter, C.; Smallwood, M.; Stewart, E.; Strong, R.; Suh, E.; Thomas, R.; Tint, N. N.; Tse, S.; Vech, C.; Wang, G.; Wetter, J.; Williams, S.; Williams, M.; Windsor, S.; Winn-Deen, E.; Wolfe, K.; Zaveri, J.; Zaveri, K.; Abril, J. F.; Guigo, R.; Campbell, M. J.; Sjolander, K. V.; Karlak, B.; Kejariwal, A.; Mi, H.; Lazareva, B.; Hatton, T.; Narechania, A.; Diemer, K.; Muruganujan, A.; Guo, N.; Sato, S.; Bafna, V.; Istrail, S.; Lippert, R.; Schwartz, R.; Walenz, B.; Yooseph, S.; Allen, D.; Basu, A.; Baxendale, J.; Blick, L.; Caminha, M.; Carnes-Stine, J.; Caulk, P.; Chiang, Y. H.; Coyne, M.; Dahlke, C.; Mays, A.; Dombroski, M.; Donnelly, M.; Ely, D.; Esparham, S.; Fosler, C.; Gire, H.; Glanowski, S.; Glasser, K.; Glodek, A.; Gorokhov, M.; Graham, K.; Gropman, B.; Harris, M.; Heil, J.; Henderson, S.; Hoover, J.; Jennings, D.; Jordan, C.; Jordan, J.; Kasha, J.; Kagan, L.; Kraft, C.; Levitsky, A.; Lewis, M.; Liu, X.; Lopez, J.; Ma, D.; Majoros, W.; McDaniel, J.; Murphy, S.; Newman, M.; Nguyen, T.; Nguyen, N.; Nodell, M. *Science* **2001**, *291*, 1304–1351.

(3) *The Merck Index*, 13th ed.; Merck: Whitehouse Station, NJ, 2001.

(4) Van Niel, M. B.; Beer, M. S.; Castro, J.; Cheng, S. K. F.; Evans, D. C.; Heald, A.; Hitzel, L.; Hunt, P.; Mortishire-Smith, R.; O'Connor, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3243–3248.

(5) Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1972**, *50*, 2892M–2893.

(6) (a) Farrall, M. J.; Frechet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877–3882. (b) Chan, T. H.; Huang, W. Q. *J. Chem. Soc., Chem. Comm.* **1985**, 909–911. (c) Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science* **1993**, *260*, 1307–1309.

(7) (a) Frechet, J. M. J.; Nuyens, L. J. *Can. J. Chem.* **1976**, *54*, 926–934. (b) Fyles, T. M.; Leznoff, C. C. *Can. J. Chem.* **1976**, *54*, 935–942.

(8) (a) Stones, D.; Miller, D. J.; Beaton, M. W.; Rutherford, T. J.; Gani, D. *Tetrahedron Lett.* **1998**, *39*, 4875–4878. (b) Craig, D.; Robson, M. J.; Shaw, S. J. *Synlett* **1998**, 1381–1383.

(9) (a) Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 733–736. (b) Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 737–740.

(10) (a) Thompson, L. A.; Ellman, Jonathan A. *Tetrahedron Lett.* **1994**, *35*, 9333–9336. (b) Yoo, S.-e.; Gong, Y.-D.; Choi, M.-Y.; Seo, J.-s.; Yang, Yi, K. *Tetrahedron Lett.* **2000**, *41*, 6415–6418. (c) Watanabe, Y.; Ishikawa, S.; Takao, G.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 3411–3414.

(11) Nicolaou, K. C.; Zipkin, R.; Tanner, D. *J. Chem. Soc., Chem. Commun.* **1984**, 349–350.

(12) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.

(13) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653–1656.

(14) Lei, P.-s.; Ogawa, Y.; Kovac, P. *J. Carbohydrate Chem.* **1996**, *15*, 485–500.

(15) Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc., Chem. Commun.* **1994**, *137*, 3–1374.

(16) Mettler-Toledo. http://us.mt.com/home (accessed May 2007).

(17) Landauer, S. R.; Rydon, H. N. *Chem. Ind.* **1951**, 313.

(18) Hudson, H. R.; Powroznyk, L. *ARKIVOC* **2004**, 19–33.

(19) MDL Available Chemicals Directory MDL. http://www.mdli.com/products/experiment/available_chem_dir/index.jsp (accessed March 2001).

(20) *21 Tripos Sybyl Line Notation*; TRIPOS: St Louis, MO; http://www.tripos.com (accessed March 2001).

(21) (a) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887–2893. (b) Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hulme, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251–3264. (c) Schnur, D.; Beno Brett, R.; Good, A.; Tebben, A. Approaches to target class combinatorial library design In *Methods in Molecular Biology*; Bajorath, J., Ed.; Humana Press: Clifton, NJ, 2004; Vol. 275, pp 355−378.

(22) MDL Drug Data Report. http://www.mdli.com/products/knowledge/drug_data_report/index.jsp (accessed March 2001).

(23) (a) Schnur, D. M.; Hermsmeier, M. Recent approaches to target class design. Presented at the 36th Mid Atlantic Regional Meeting of the American Chemical Society, Princeton, NJ, 2003. (b) Bondensgaard, K.; Ankersen, M.; Thogersen, H.; Hansen, B. S.; Wulff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 888–899.

(24) (a) Hansch, C.; Leo, A., Calculation of octanol-water partition coefficients by fragments In *Exploring QSAR: Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995; pp 125−168. (b) Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hulme, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251–3264. (c) *ClogP*; Biobyte Corp.: Mission Viejo, CA 1995, http://www.clogp@biobyte.com (accessed March 2001).

(25) *Sybyl*, 6.7; Tripos: St-Louis, MO, 2002.; http://www.tripos.com.

(26) *CombiLibMaker*; Tripos: St-Louis, MO; http://www.tripos.com (accessed March 2001).

(27) (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25. (b) Lipinski, C. A. *Drug Discovery Today: Technol.* **2004**, *1*, 337–341.

(28) Irori Nanokans. http://www.irori.com/Products/irori_tech_nanokan.html (accessed March 2001).

(29) Rydon, H. N. *Org. Synth.* **1971**, *51*, 44–47.

(30) Fang, L.; Wan, M.; Pennacchio, M.; Pan, J. *J. Comb. Chem.* **2000**, *2*, 254–257.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

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