A Soluble Polymer Approach to the "Fishing Out" Principle: Synthesis and Purification of β-Amino Alcohols

Manabu Hori Kim D. Janda*

Department of Chemistry, The Scripps Research Institute, and The Skaggs Institute for Chemical Biology, 10550 North Torrey Pines Road, La Jolla, California 92037

Received September 16, 1997

Introduction

High through-put organic synthesis has become a paradigm for the production of small-molecule libraries.[1] Countless examples now exist on the solid-phase synthesis of these libraries, but relatively few examples of libraries generated by solution syntheses have been published.[2] Reasons for such trends have been mainly due to the difficulties in driving these reactions to completion and/or isolating pure products, yet solution-phase synthesis is the foundation upon which synthetic chemists are trained and in which synthetic methodology is developed.

Recently, several groups have developed strategies that allow solution-phase synthesis to be conducted in a library format. Techniques termed covalent scavenger and polymer-supported quench have been applied for the removal of unreacted starting materials, excess reagents, and unwanted byproducts.[3] Resin capture, on the other hand, initiates library synthesis in solution followed by material transfer to a solid support for further transformation.[4] Described herein is a method for library synthesis in solution and subsequent purification of the desired products via a soluble polymer-supported reagent. The strategy is based on the "fishing out" principle[5] and offers an alternative to solid-phase synthesis and resin capture/scavenger techniques. Using the "fishing out" technique, we have synthesized a set of structures displaying the classic β-amino alcohol pharmacophore.[6] The methodology provides a simple route to the high through-put solution synthesis of novel potential adrenergic agents.

Results and Discussion

"Fishing out" is a technique involving polymer-supported reactions or reagents. In this scenario, the desired product is formed as a component in a complex mixture and the polymer is, in effect, used to extract the desired component from a mixture. Thus, the mixture containing the compound of interest is treated with an appropriate polymer-supported reagent to selectively extract the desired product. The other components of the mixture are removed, and the desired compound is released from the polymer. To investigate the "fishing out" technique in a liquid-phase format, we turned to the soluble polymer support poly(ethylene glycol).[7] We have previously shown how this homopolymer can by applied in a number of settings from combinatorial synthesis to ligand accelerated catalysis.[8] The exemplary reaction sequence that we undertook involved the synthesis of propranolol (**1**) (Scheme 1), a well-known β-adrenergic blocking agent containing a β-amino alcohol core structure.[6,9] The reaction sequence shown in Scheme 1 generates propranolol in a 40% yield. The impurities from this route besides starting reagents include the bis-naphthol **4**. It was our contention that by utilizing a polymer-supported reagent, propranolol could be synthesized and then "fished out" from a sequential homogeneous reaction sequence that required no column-supported purification of intermediate **2**, byproduct **4**, or any of the starting materials. Demonstration of this reaction sequence, we hoped, could then be generalized for the synthesis and purification of a variety of molecules containing the β-amino alcohol moiety.[10]

It has been reported that boranes can react with structures displaying the β-amino alcohol subunit to generate 1,3,2-oxazaborolidines.[11] Such compounds can then be reversibly decomposed to give a β-amino alcohol in the presence of acid. On the basis of these studies, we set out to find suitable boranes for attachment to poly(ethylene glycol). Scheme 2 shows a select series of

* To whom correspondence should be addressed.

(1) (a) Chaiken, I. M., Janda, K. D., Eds. *Molecular Diversity and Combinatorial Chemistry Libraries and Drug Discovery*; American Chemical Society: Washington, DC, 1996. (b) Wilson, S. R., Czarnik, A. W., Eds. *Combinatorial Chemistry Synthesis and Application*; John Wiley & Sons: New York, 1997. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* (Washington, D.C.) **1996**, *96*, 555. (d) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. M. *Acc. Chem. Res.* **1996**, *20*, 123. (e) Balkenhohl, F.; Vondem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2289.

(2) (a) Smith, P. W.; Lai, J. Y. Q.; Whittington, A. R.; Cox, B.; Houston, J. G.; Stylli, C. H.; Banks, M. N.; Tiller, P. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2821. (b) Carell, T.; Winter, E. A.; Sutherland, A.; Rebek, J.; Dunayevskiy, Y. M.; Vouros, P. *Chem. Biol.* **1995**, *2*, 171. (c) Pirrung, M. C.; Chen, J. *J. Am. Chem. Soc.* **1995**, *117*, 1240. (d) Chen, S.; Commer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567. (e) Chen, S.; Tarby, C. M.; Commer, D. D.; Williams, J. P.; Caporale, L. H.; Myers, P. L.; Boger, D. L. *Bioorg. Med. Chem.* **1996**, *4*, 727. (f) Boger, D. L.; Ozer, R. S.; Anderson, C.-M. *Bioorg. Med. Chem.* **1997**, *7*, 1903.

(3) (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. (b) Kaldor, S. W.; Fritz, J. E.; Tang, J.; McKinney, E. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041. (c) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 513. (d) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (e) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.

(4) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.

(5) (a) Hodge, P. In *Synthesis and Separations Using Functional Polymers*; Sherrington, D. C., Hodge, D., Eds.; Wiley: New York, 1988; pp 43−123. (b) Hodge, P.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2319. (c) Seymour, E.; Frechet, J. M. S. *Tetrahedron Lett.* **1976**, *17*, 3699. (d) Cheminat, A.; Benezra, C.; Farrall, M. J.; Frechet, J. *Tetrahedron Lett.* **1980**, *21*, 617.

(6) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1984; Vol. 3, pp 19−37.

(7) Harris, M. J., Ed. *Poly(Ethylene Glycol) Chemistry Biotechnical and Biomedical Applications*; Plenum: New York, 1992.

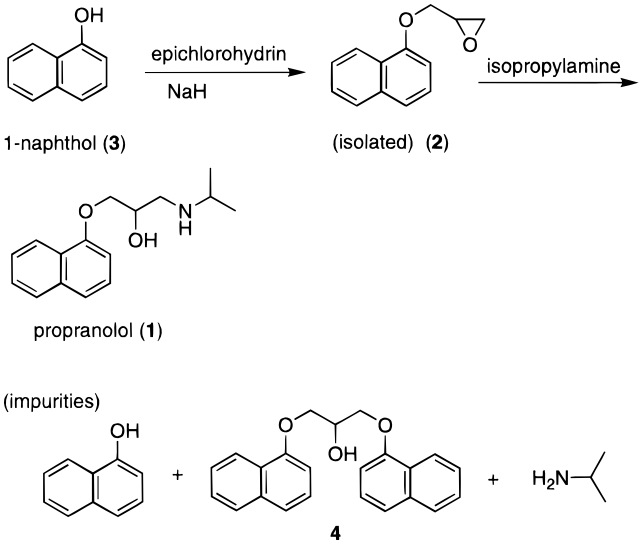
(8) (a) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419. (b) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539. (c) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632. (d) Zhao, X.-Y.; Jung, K. W.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 977. (e) Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527. (f) Jung, K. W.; Zhao, X.-Y.; Janda, K. D. *Tetrahedron* **1997**, *53*, 6645. (g) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.

(9) Crowther, A. F.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1009.

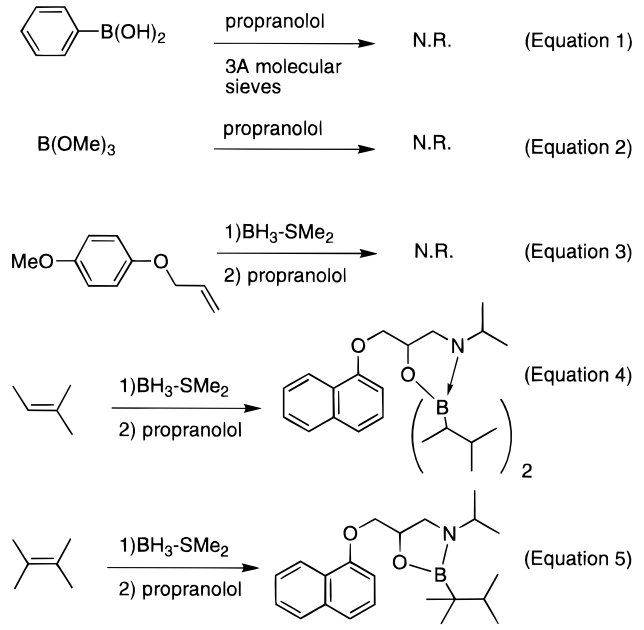
(10) Recently a β-amino alcohol library has been reported: Chng, B.-L.; Ganesan, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1511.

S0022-3263(97)01732-5 CCC: $15.00
Published on Web 01/22/1998

Scheme 1. Synthetic Route to Propranolol and Impurities Generated during Reaction Sequence



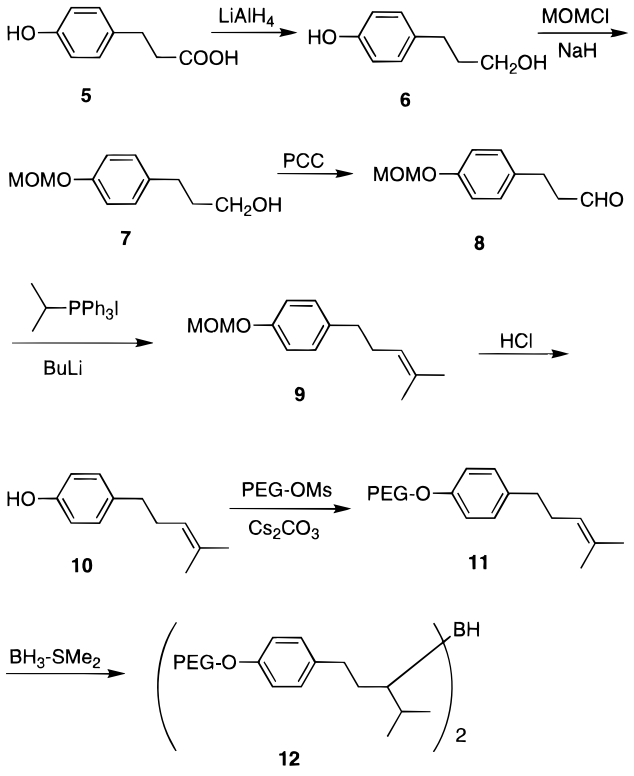
Scheme 2. Reactivity of Propranolol and Selected Borane Reagents



compounds that were examined in the presence of propranolol. The most promising results occurred when 2-methyl-2-butene or 2,3-dimethyl-2-butene was reacted with borane dimethyl sulfide producing either disiamylborane (Scheme 2, eq 4) or thexyborane (Scheme 2, eq 5). Both of these alkylboranes reacted with propranolol generating the desired 1,3,2-oxazaborilidinone. However, due to chromatographic instability these complexes could only be qualitatively identified by NMR.

Keeping these findings in mind, we synthesized the MeO-PEG-dialkylborane reagent **12** (Scheme 3). Starting from 3-(4-hydroxphenyl)propionic acid (**5**), **12** was rapidly obtained in seven steps. The key transformations in this sequence were (1) reaction of phenol **10** with monomethyl ether poly(ethyene glycol) mesylate[12] providing **11** and (2) addition of borane−methyl sulfide to **11** yielding the borane "fishing out" reagent **12**. The borane polymer **12** could be isolated as a solid; however, this borane was found to be moisture-sensitive, and hence it was found to be more convenient not to isolate this material but rather to utilize it as a toluene solution.[13] Our hope then was that this PEG-bound dialkylborane would display similar chemical reactivity to propranolol and other β-amino alcohols as was observed with the small molecule disiamylborane (vide supra). We anticipated that the disubstituted poly(ethylene glycol) "label" would ensure that all materials complexed to it would exhibit similar physical properties to that of the homopolymer poly(ethylene glycol), this latter point being of utmost importance if selective separation of the desired β-amino alcohol from unwanted starting materials and byproducts was to occur.

Scheme 3. Synthetic Route to the Dialkylborane "Fishing Out" Reagent 12



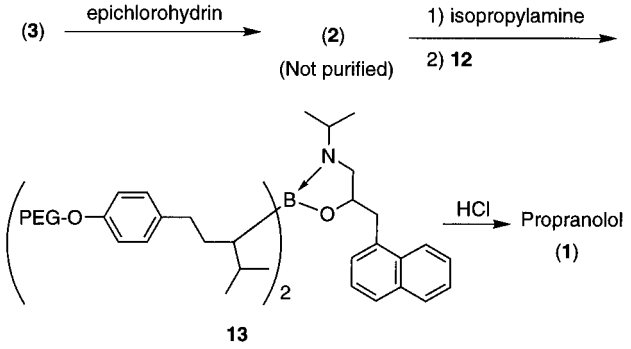
Application of **12** for the "fishing out" of propranolol was performed in the following manner (Scheme 4). In the first step a mixture of 1-naphthol (1.0 equiv), epichlorohydrin (1.2 equiv), and sodium hydride was reacted in DMF overnight at 50 °C. This was followed by an extraction/concentration to remove excess base and the reaction solvent *N,N*-dimethylformamide (concentration percentage by HPLC: **2**, 46%; **3**, 37%; **4**, 10%). This resultant mixture of the desired epoxide **2** and unwanted

(11) (a) Masamune, S.; Kim, B.; Petersen, J. S.; Sato, T.; Veenstra, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4549. (b) Masamune, S.; Short, R. P. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (d) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868. (e) Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron Asymmetry* **1994**, *5*, 165. (f) Matteson, D. S. In *Reactivity and Structure Concept in Organic Chemistry*; Hafner, K., Rees, C. W., Trost, B. M., Lehn, J.-M., Schleyer, P., Von Rague′, Zahradnik, R., Eds.; Springer: Berlin; Vol. 32, pp 353−361.

(12) Zhao, X.-Y.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 5437.

(13) It should be noted that while this approach negates the moisture-sensitivity problem in isolating the reagent **12**, it can compromise the yield of the desired product. This is due to the excess borane−methyl sulfide complex that is needed in forming **12**. Borane−methyl sulfide can compete with **12** in the formation oxazaborolidines.

Scheme 4. Sequence Used To Synthesize and Purify Propranolol



starting material/byproduct was reacted with isopropylamine (0.8 equiv) at 70 °C for 1.5 h (concentration percentage by HPLC: **1**, 36%; **2**, 24%; **4**, 10%). Propranolol was selectively "labeled" by the addition of the polymer borane reagent **12** granting the polymer oxazaborolidine complex **13**. Diethyl ether precipitation allowed purification of **13** from all starting materials and byproducts. Subsequent addition of HCl to a CH_2Cl_2/MeOH solution of **13** provided propranolol after simple precipitation of the spent polymer support in 58% yield, this based on the ratio of isolated mass over theoretical yield of compound **12** (see Table 1) and greater than 92% purity (Scheme 4).

The scope of this procedure (vide supra) has been expanded to the parallel synthesis (Scheme 5) of discrete β-amino alcohols on a multimilligram scale (Table 1). The building blocks were broken up into three categories: (1) aromatic phenols or sulfonamides, (2) epichlorohydrin, and (3) primary or secondary aliphatic or aromatic amines. While we have only attempted the synthesis of 20 compounds, clearly the potential to construct libraries of β-amino alcohols exists. All isolated β-amino alcohols were characterized by ^{1}H NMR, ^{13}C NMR, HPLC, and MS. The mass recovery and purity of these β-amino alcohols was good to excellent in view of the simplicity of our isolation procedure. The most problematic building block was *p*-anisidine; its poor nucleophilicity led to low reactivity as seen in several of the cases shown in Table 1. However, even when poor yields of the final β-amino alcohols were observed, the purity of the desired compound was still excellent.

In summary, a general reagent has been developed for the selective "fishing out" of β-amino alcohols. The β-amino alcohol moiety is a pharmacophore structure found in β-adrenergic blockers that is of significant interest to the pharmaceutical industry. The methodology we have described supports at least a two-step synthetic strategy and an isolation procedure less laborious than column chromatography. The procedure could undoubtedly be automated and adapted to create new reagents for the "fishing out" of other classes of molecules possessing interesting pharmacophores.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification. Analytical TLC (thin-layer chromatography) was carried out on precoated plates (Merck silica gel 60, F_{254}). Column chromatography was performed with silica gel (Merck, 70−230 mesh). HPLC analysis was performed with a VYDAC reverse-phase C_{18} column (25 cm × 4.6 mm); mobile phase, acetonitrile−water (contains 0.1% TFA, ratio between 25:75 and 35:65); flow rate, 1.0 mL; UV detection, 254 nm. ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, in $CDCl_3$. High-resolution mass spectra (HRMS) were performed in the analytical department of The Scripps Research Institute.

3-(4-Hydroxyphenyl)-1-propanol (6). This compound is available from Aldrich (19,741-6); however, its quoted price (1 g = $16.15) makes it more economical to synthesize the material from 3-(4-hydroxphenyl)propionic acid, **5** (39,353-3, 10 g = $13.80). Thus to a suspension of $LiAlH_4$ (8.0 g, 210 mmol, 1.0 equiv) in THF (300 mL) was added a solution of 3-(4-hydroxyphenyl)propionic acid (25.0 g, 150 mmol, 1.0 equiv) in THF (200 mL) dropwise at rt, and the mixture was stirred at 60 °C for 2 h. The reaction mixture was acidified with 1 M HCl, diluted with water, and extracted with AcOEt (ethyl acetate). The extract was washed with water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to give **5** (20 g, 88%) as a colorless oil: ^{1}H NMR δ 1.85 (2H, m), 2.26 (2H, t, J = 7.3 Hz), 3.66 (2H, t, J = 6.4 Hz), 3.75 (1H), 5.15 (1H), 6.74 (2H, d, J = 8.5 Hz), 7.04 (2H, d, J = 8.5 Hz).

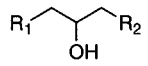
3-[4-(Methoxymethoxy)phenyl]-1-propanol (7). To a mixture of compound **6** (15.0 g, 99 mmol, 1.0 equiv) and DMF (500 mL) was added NaH (60% dispersion, 4.0 g, 100 mmol, 1.0 equiv) at rt, and the resulting mixture was stirred for 15 min. Chloromethyl methyl ether (8.0 g, 99 mmol, 1.0 equiv) was added dropwise to the mixture at rt, and the mixture was stirred for 2 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt = 2:1) to give **7** (11.5 g, 59%) as a colorless oil: ^{1}H NMR δ 1.85 (2H, m), 2.65 (2H, t, J = 7.4 Hz), 3.47 (3H, s), 3.64 (2H, td, m), 5.14 (2H, s), 6.95 (2H, d, J = 6.6 Hz), 7.11 (2H, d, J = 6.6 Hz); ^{13}C NMR δ 31.10, 34.25, 55.83, 62.02, 94.47, 116.17, 134.75, 192.25, 155.27; HRMS calcd for 196.1099 $C_{11}H_{16}O_3$ (M^+), found 196.1093.

3-[4-(Methoxymethoxy)phenyl]propional (8). A solution of compound **7** (23.0 g, 120 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added to a mixture of pyridinium chlorochromate (38.0 g, 180 mmol, 1.5 equiv) in CH_2Cl_2 (1000 mL) at rt, and the mixture was stirred for 3.5 h. The reaction mixture was washed with hexane (400 mL) and filtered through silica gel (60 g). The silica gel was eluted with a mixture of hexane and AcOEt (1:1, 250 mL). The collected filtrate was combined and concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt = 2:1) to give **8** (20.0 g, 88%) as a colorless oil: ^{1}H NMR δ 2.74 (2H, td, J = 7.3, 1.3 Hz), 2.90 (2H, t, J = 7.3 Hz), 3.46 (3H, s), 5.14 (2H, s), 6.95 (2H, d, J = 8.5 Hz), 7.10 (2H, d, J = 8.5 Hz), 9.80 (1H, J = 1.3 Hz); ^{13}C NMR δ 27.17, 45.34, 55.80, 94.34, 116.28, 129.16, 133.58, 155.56, 201.63; HRMS calcd for $C_{11}H_{16}O_3$ 194.0943 (M^+), found 194.0936.

1-(Methoxymethoxy)-4-(4-methyl-3-pentenyl)benzene (9). To a mixture of isopropyltriphenylphosphonium iodide (75.0 g, 170 mmol, 1.8 equiv) and THF (800 mL) was added butyllithium (2.5 M in hexane, 75 mL) at −70 °C dropwise, and the mixture was stirred at rt for 20 min. To the mixture was added a solution of compound **8** (18.0 g, 93 mmol, 1.0 equiv) in THF (80 mL) dropwise at −70 °C, and the mixture was stirred at rt for 2 h. The reaction mixture was diluted with hexane (500 mL) and filtered through silica gel (60 g). The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexane:AcOEt = 20:1) to give **9** (16.0 g, 78%) as a colorless oil: ^{1}H NMR δ 1.56 (3H, s), 1.67 (3H, s), 2.28 (2H, m), 2.56 (2H, t, J = 6.6 Hz), 3.47 (3H, s), 5.15 (2H, s), 5.12−5.18 (1H, pseudo-t), 6.94 (2H, d, J = 6.6 Hz), 7.10 (2H, d, J = 6.6 Hz); ^{13}C NMR δ 17.64, 25.67, 30.21, 35.26, 55.86, 94.56, 116.08, 123.73, 129.31, 135.86, 155.27; HRMS calcd for 220.1463 $C_{14}H_{20}O_2$ (M^+), found 220.1468.

4-(4-Methyl-3-pentenyl)phenol (10). A mixture of **9** (16.0 g, 73 mmol, 1.0 equiv), 12 M HCl (30 mL), and THF (250 mL) was stirred at rt for 2 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt = 6:1) to give **10** (12.0 g, 94%) as a colorless oil: bp 110 °C (0.02 mmHg); ^{1}H NMR δ 1.55 (3H, s), 1.67 (3H, s), 2.28 (2H, m), 2.55 (2H, t, J = 7.3 Hz), 4.67 (1H, OH), 5.17−5.11 (1H, t-like), 6.74 (2H, d, J = 8.4 Hz), 7.04 (2H,

Table 1. β-Amino Alcohols



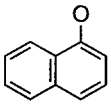
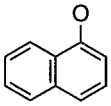
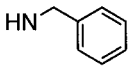
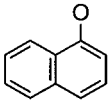
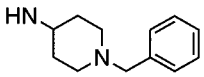
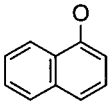
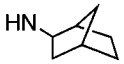
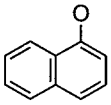
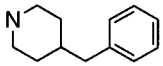
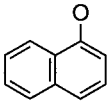
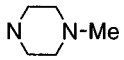
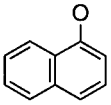
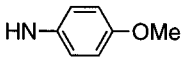
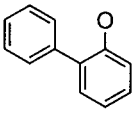
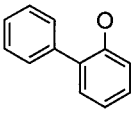
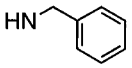
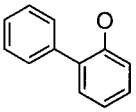
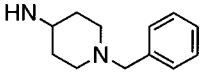
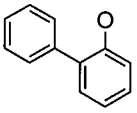
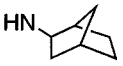
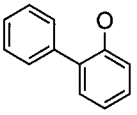
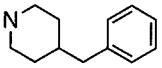
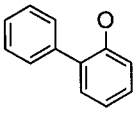
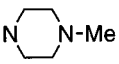
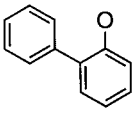
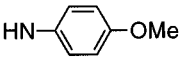
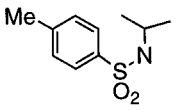
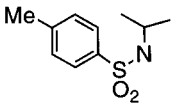
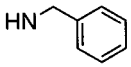
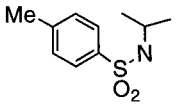
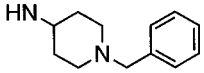
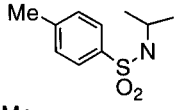
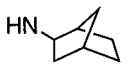
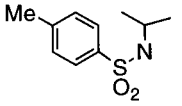
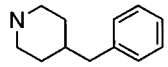
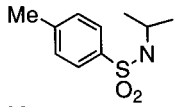
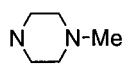
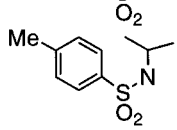
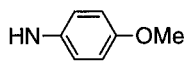
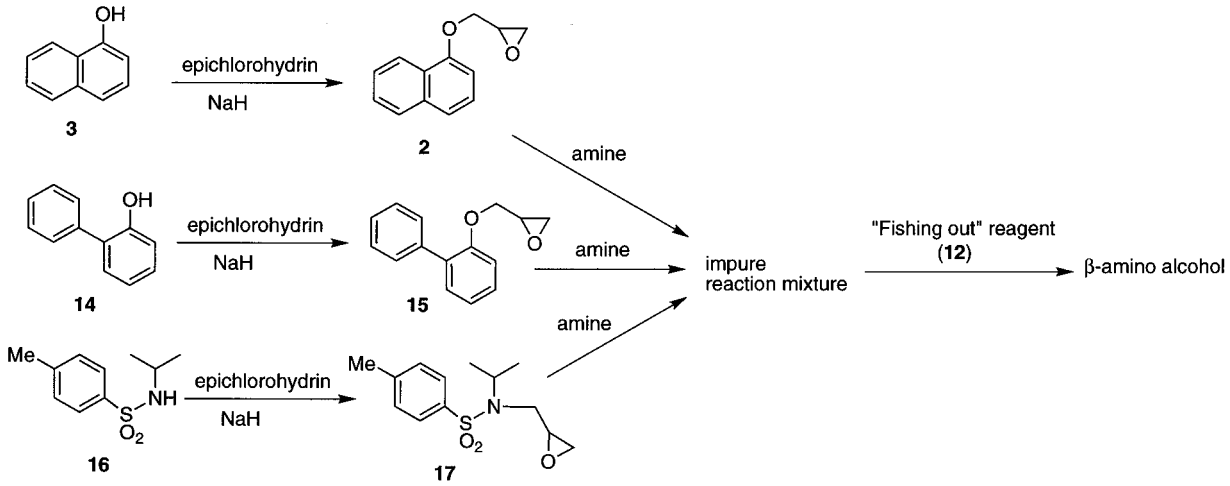
No.	R_1	R_2	Yield(%)[a]	Purity (%)[b]
1			58	92
18			49	91
19			38	93
20			64	96
21			77	94
22			40	92
23[c]			-	-
24			89	96
25			75	93
26			66	96
27			75	95
28			74	96
29			55	90
30			34	88
31			91	99

Table 1 (Continued)

No.	R_1	R_2	Yield(%)[a]	Purity (%)[b]
32			61	96
33			60	89
34			105	99
35			102	98
36			27	98
37			39	55[d]

[a] The yield was calculated as the ratio of isolated mass over theoretical yield of compound **12** and is expressed as a percentage. [b]Purity was determined by HPLC. [c] Compound **23** was not isolated due to low reactivity of *p*-anisole. [d] Greater than 80% purity was confirmed by ^{1}H NMR spectrum.

Scheme 5. Parallel Approach Used To Create *β*-Amino Alcohols



d, J = 8.4 Hz); ^{13}C NMR δ 17.64, 25.67, 30.24, 35.17, 115.01, 115.07, 123.71, 129.48, 132.08, 134.62, 153.42; HRMS calcd for 176.1201 $C_{12}H_{16}O$ (M^+), found 176.1198.

[[4-(4-Methyl-3-pentenyl)phenyl]oxy]poly(ethylene glycol) Methyl Ether (11). A mixture of MeO-PEG_{5000} mesylate[12] (50.0 g, 10.0 mmol, 1.0 equiv), compound **10** (7.0 g, 40 mmol, 4.0 equiv), Cs_2CO_3 (13.0 g, 40 mmol, 4.0 equiv), and DMF (400 mL) was stirred at 80 °C overnight. To the reaction mixture was added 1 M HCl−MeOH (60 mL), and the mixture was concentrated in vacuo. The residue was suspended in CH_2Cl_2 (300 mL), and any insoluble material was removed via filtration. The filtrate was concentrated to about half-volume and diluted with ether (900 mL). The resulting solid was collected by filtration to give **11** as a colorless powder (50 g, 98%): ^{1}H NMR δ 1.48 (3H, s), 1.59 (3H, s), 2.16 (2H, m), 2.51 (2H, t, J = 4.5 Hz), 3.3−4.1 (MeO-PEG), 4.97−5.10 (1H, t-like), 6.78 (2H, d, J = 7.5 Hz), 7.0 (2H, d, J = 7.5 Hz); ^{13}C NMR δ 17.31, 25.34, 29.88, 34.80, 58.65, 61.20, 67.03, 69.40, 70.18, 71.39, 114.00, 123.39, 128.88, 131.57, 134.25, 134.25, 156.49.

Bis[5-[4-(MeO-PEG-oxy)phenyl]-2-methylpentan-3-yl]-borane (12). To a mixture of **11** (1.0 g, 0.2 mmol, 1.0 equiv) and toluene (3 mL) was added BH_3−SMe_2 (1 M in CH_2Cl_2, 0.6 mL, 0.6 mmol, 3.0 equiv). This solution was stirred at 70 °C for 20 min (toluene solution of **12**, see general procedure). The reaction mixture was diluted with ether (80 mL), and the resulting solid was collected by filtration to give **12** (970 mg, 97%) as a colorless powder (Note: this material is moisture-sensitive): ^{1}H NMR 0.7−0.9 (12H), 1.0−1.8 (8H), 2.2−2.7 (4H), 3.3−4.1 (MeO-PEG),6.7−6.8 (4H), 6.9−7.1 (4H); ^{13}C NMR δ 58.94, 67.32, 69.69, 70.61, 71.60, 114.37, 129.18, 135.50, 156.75.

***N*-Isopropyl-4-toluenesulfonamide (16).** To a mixture of *p*-toluenesulfonyl chloride (5.1 g, 27 mmol, 1.0 equiv) and CH_2Cl_2 (70 mL) was added isopropylamine (5.0 g, 85 mmol, 3.1 equiv) at 0 °C, and the mixture was stirred at rt for 30 min. The reaction mixture was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give **16** (5.5 g, 96%) as a colorless oil: ^{1}H NMR δ 1.05 (6H, d, J = 6.5 Hz), 2.41 (3H, s), 3.39−3.47 (1H, m), 4.40 (1H, b), 7.28 (1H, d, J = 8.0

Hz), 7.75 (2H, d, J = 8.0 Hz); ^{13}C NMR δ 21.48, 23.65, 126.98, 129.60, 138.03, 143.14; HRMS calcd for 214.0902 $C_{10}H_{15}NO_2S$ ($M + H^+$), found 214.0897.

General Procedure for *β*-Amino Alcohol Synthesis and Purification. A mixture of NaH (60% dispersion, 33 mmol, 1.0 equiv) was washed with hexane (2 × 10 mL). This was added to a flask containing the phenol or sulfonamide (33 mmol, 1.0 equiv), epichlorohydrin (40 mmol, 1.2 equiv), and DMF (60 mL) which was stirred overnight at 50 °C. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. (The excess epichlorohydrin should be removed in this procedure.) This impure reaction mixture was diluted with toluene to make approximately a 0.5 M solution of the epoxide. To 1 mL of this were added an amine (0.4 M in toluene, 1 mL) and $LiClO_4$ (40 mg, 38 mmol, 0.8 equiv), and the solution was stirred overnight at 70 °C. Upon completion of the reaction all soluble material was added to a toluene solution of **12** (vide supra), and this was stirred at 70 °C for 1.5 h. This reaction mixture was diluted with ether (80 mL), and the resulting solid was collected by filtration followed by addition to CH_2Cl_2 (2 mL)/MeOH (2 mL). The mixture was added to 1 M HCl−MeOH (0.5 mL), and this was stirred at rt for 10 min. To this solution was added *t*-BuOK (200 mg, 1.8 mmol, 3.6 equiv), and the mixture was stirred at rt for 10 min before dilution with ether (80 mL). The resulting solid was filtered, and the filtrate was concentrated in vacuo. The residue was suspended in ether (10 mL), and any insoluble material was removed by filtration. The filtrate was concentrated in vacuo to give the *β*-amino alcohol.

1,2-Epoxy-3-(1-naphthoxy)propane (2): see general procedure up to addition of amine; ^{1}H NMR δ 2.84−2.88 (1H, m), 2.95−3.00 (1H, m), 3.49−3.50 (1H, m), 4.11−4.17 (1H, m), 4.37−4.39 (1H, m), 6.80 (1H, d, J = 7.5 Hz), 7.25−7.50 (4H), 7.78−7.81 (1H, m), 7.28−7.30 (1H, m); ^{13}C NMR δ 44.68, 50.21, 69.15, 102.81, 104.96, 121.68, 121.94, 125.27, 125.66, 126.45, 127.40, 134.42, 154.03; HRMS calcd for 200.0837 $C_{13}H_{12}O_2$ (M^+), found 200.0843.

1,2-Epoxy-3-(2-biphenylyloxy)propane (15): see general procedure up to addition of amine; ^{1}H NMR δ 2.65−2.68 (1H, m), 2.75−2.82 (1H, m), 3.24−3.27 (1H, m), 3.94−4.00 (1H, m), 4.14−4.23 (1H, m), 6.96−7.56 (9H); ^{13}C NMR δ 44.59, 50.23, 68.92, 113.10, 121.64, 126.91, 127.95, 128.59, 129.42, 129.51, 131.01, 138.26, 155.41; HRMS calcd for 226.0994 $C_{15}H_{14}O_2$ (M^+), found 226.0988.

***N*-(2,3-Epoxypropyl)-*N*-isopropyl-4-toluenesulfonamide (17)**: see general procedure up to addition of amine; ^{1}H NMR δ 0.95 (3H, d, J = 8.1 Hz), 1.14 (3H, d, J = 8.1 Hz), 2.40 (3H, s), 2.59−2.62 (1H, m), 2.83−2.85 (1H, m), 3.05 (1H, dd, J = 12.0, 5.2 Hz), 3.17−3.21 (1H, m), 3.47 (1H, dd, J = 12.0, 4.6 Hz), 4.11 (1H, m), 7.27 (2H, d, J = 8.3 Hz), 7.69 (2H, d, J = 8.3 Hz); ^{13}C NMR δ 19.99, 21.46, 21.60, 44.90, 46.96, 49.16, 51.98, 126.94, 129.68, 137.68, 143.20; HRMS calcd for 270.1164 $C_{13}H_{19}NO_3S$ (M^+), found 270.1172.

MeO-PEG-borane−Propranolol Complex (13): see general procedure up to addition of HCl−MeOH; ^{1}H NMR δ 0.8−1.0 (12H), 1.0−1.8 (10H), 2.2−3.2 (7H), 3.2−4.1 (MeO-PEG), 6.7−6.8 (5H), 6.9−7.0 (4H), 7.2−7.5 (4H), 7.1−7.1 (1H), 8.1−8.2 (1H).

Propranolol (1): see general procedure; ^{1}H NMR δ 1.09 (6H, d, J = 6.2 Hz), 2.79−3.00 (3H), 4.10−4.19 (3H), 6.81 (1H, d, J = 7.4 Hz), 7.32−7.50 (3H), 7.78 (1H), 8.23 (1H); ^{13}C NMR δ 22.88, 22.92, 48.87, 49.55, 68.39, 70.67, 104.79, 120.50, 121.77, 125.15, 125.44, 125.76, 126.34, 127.44, 134.39, 154.23; HRMS calcd for 260.1651 $C_{16}H_{21}NO_2$ ($M + H^+$), found 260.1643.

3-(2-Biphenylyl)-2-hydroxy-1-(isopropylamino)propane (24): see general procedure; ^{1}H NMR δ 0.83 (3H, d, J = 6.3 Hz), 0.84 (3H, d, J = 6.3 Hz), 2.38−2.61 (3H), 3.71−3.83 (3H), 6.90−7.38 (9H); ^{13}C NMR δ 22.87, 22.99, 48.72, 49.16, 68.39, 71.39, 112.96, 121.41, 126.93, 127.95, 128.64, 129.45, 130.84, 138.38, 155.44; HRMS calcd for 286.1807 $C_{18}H_{23}NO_2$ ($M + H^+$), found 286.1800.

***N*-[2-Hydroxy-3-(isopropylamino)propyl]-*N*-isopropyl-4-toluenesulfonylamide (31)**: see general procedure; ^{1}H NMR δ 0.96−1.05 (12H), 2.38 (3H, s), 2.59−2.80 (4H), 3.02−3.18 (2H), 3.84 (1H, m), 4.04 (1H, m), 7.26 (2H, d, J = 8.0 Hz), 6.68 (2H, d, J = 8.0 Hz); ^{13}C NMR δ 20.68, 21.11, 21.47, 23.01, 23.08, 46.99, 48.84, 49.92, 69.81, 127.11, 129.68, 137.16, 143.29; HRMS calcd for 329.1899 $C_{16}H_{28}N_2O_3S$ ($M + H^+$), found 329.1908.

Acknowledgment. This work was supported by The Skaggs Institute for Chemical Biology. We thank Dr. P. Wentworth, Jr., for helpful discussions.

Supporting Information Available: Compound characterization data and copies of HPLC, ^{1}H NMR, and ^{13}C NMR spectra for **1**, **18**−**22**, and **24**−**37**; high-resolution mass spectra for **18**−**22**, **25**−**30**, and **32**−**37**; copies of ^{1}H and ^{13}C NMR spectra for **7**−**12** and **15**−**17**; and copies of ^{1}H NMR spectra for **2**, **4**, **5**, and **13** (86 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971732L