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Combinatorial chemistry. Preparation of phenoxypropanolamines

William M. Bryan,* William F. Huffman and Pradip K. Bhatnagar

Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, PO Box 5089, 1250 South Collegeville Road, Collegeville, PA 19426, USA

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Abstract

An efficient solid-phase parallel synthesis of aryloxypropanolamines is described. Mitsunobu coupling was used to attach (*R*)-(+)- and (*S*)-(–)-glycidol to resin-bound phenols, then the epoxide ring was opened with amines. A 25-member array was synthesized on Wang resin with a sarcosine handle. The overall yield was about 70%. A 'split and mix' approach was used to prepare a 5800-member bead bound combinatorial library on Rink amide resin. Magic angle NMR was used to monitor the reaction progress on the resin. Analysis by LC–MS revealed that >70% of the beads examined contained an identifiable product that was >70% pure by HPLC.

Keywords: combinatorial chemistry; Mitsunobu reaction, epoxide ring opening.

Recently, there has been considerable interest in expanding the scope of polymer-supported chemistry for the preparation of organic molecules.[1] This powerful technique has been used to rapidly produce large numbers of potentially biologically relevant compounds both in a combinatorial fashion and by multiple simultaneous syntheses.[2] Aryloxypropanolamines are a pharmacologically important class of compounds and have been useful as adrenergic blockers (alpha and beta), cognition enhancers, vasodilators, antiarrhythmic, and calcilytics.[3,4] We were interested in efficiently synthesizing a large number of novel compounds in a combinatorial fashion on solid support based upon this key aryloxypropanolamine template. Recent reports of the polymer-supported ring opening of epoxides[5] has prompted us to report our own findings on the preparation of aryloxypropanolamines on solid support.

As shown in Scheme 1, we chose to immobilize the phenol on resin by way of a sarcosine handle. This strategy allowed us to take advantage of the large number of commercially available amines to introduce diversity. We initiated synthesis by attaching *N*-(9-fluorenylmethoxycarbonyl)sarcosine via its acyl fluoride to Wang resin to provide **1**. The *N*-protecting group was removed and the amine was acylated with 4-hydroxyphenylacetic acid. The resin-bound phenol **2**

* Corresponding author.

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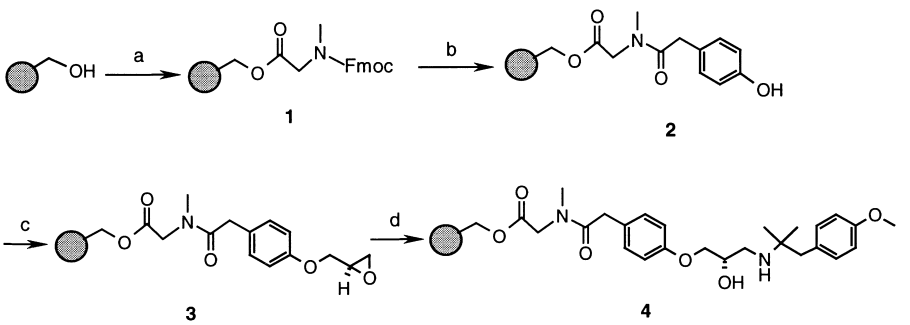
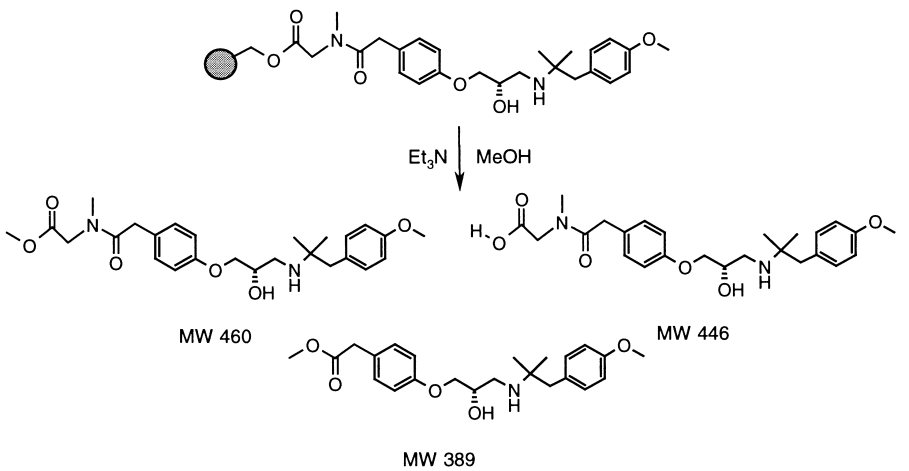


Scheme 1. (a) Fmoc-Sar-F, CH_2Cl_2, Et_3N, rt, 18 h; (b) (i) 20% piperdine/DMF; (ii) HOOC-CH_2-Ph-OH, HBTU, HOBt, DMF, 18 h; (c) (*R*)-(+)-glycidol, PPh_3, DIAD, THF, rt, 18 h; (d) 2-(4-methoxyphenyl)-1,1-dimethylethylamine, MeCN, 80°C, 18 h

was then reacted with (*R*)-(+)-glycidol under Mitsunobu reaction conditions[6] to give **3**. The epoxide of **3** was then reacted with 2-(4-methoxyphenyl)-1,1-dimethylethylamine to provide **4**.

This reaction sequence was used to prepare a 5×5-member array employing five different 2-aryl-1,1-dialkylethylamines, three 4-hydroxyphenylacetic and two 4-hydroxyphenylpropionic acids. The products were cleaved from the resin via transesterification with Et_3N/MeOH for 48 h and analyzed by LC–MS.[7] As shown in Scheme 2 and Fig. 1, along with the desired methyl esters, we also observed the corresponding acid as well as the corresponding des-sarcosine methyl ester. In most cases (22 out of 25) the sum of these products accounted for about 70% of the total cleaved product.To avoid obtaining the mixture of esters and acid after cleavage, we initiated solid-phase chemistry on Rink amide resin[7] as shown in Scheme 3. Rink amide resin was acylated with 4-hydroxybenzoic acid in DMF to give **5**. Because we desired a synthesis which would provide both the *R*- and *S*-enantiomer of the hydroxyl, the resin-bound phenol was reacted with either (*R*)-(+)- or (*S*)-(–)-glycidol under Mitsunobu reaction conditions to give **6**. The resulting aryloxyepoxide was then reacted with benzylamine to yield phenyloxypropanolamine **7**. All of the reactions were characterized on solid-phase using magic angle spinning ^{1}H NMR (MAS NMR).



Scheme 2. (a) HOOC-Ph-OH, DIC, HOBt, DMF, rt, 18 h; (b) (*R*)-(+) or (*S*)-(–)-glycidol, PPh_3, DIAD, THF, rt, 18 h; (c) benzyl amine, MeCN, 80°C, 18 h

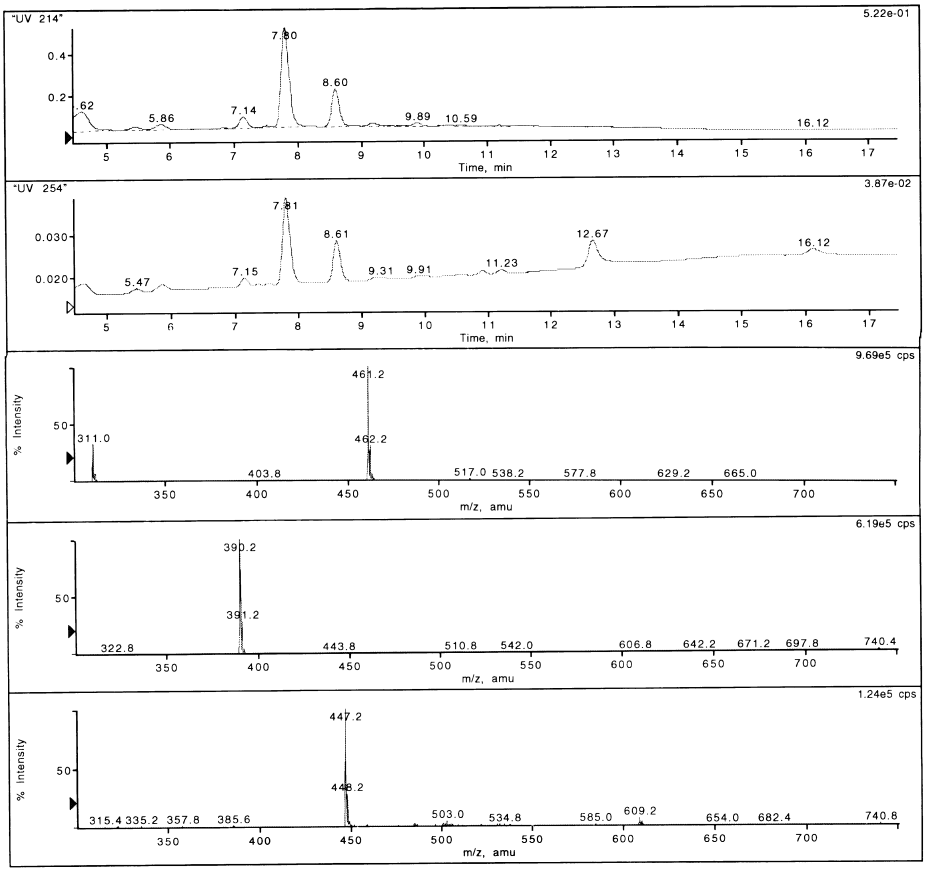
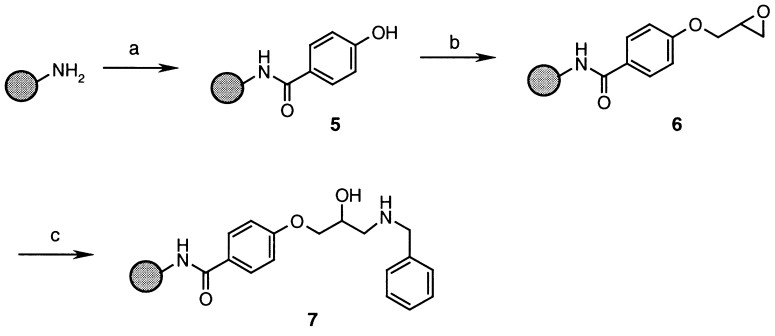


Figure 1. The LC–MS results of one member of the 5×5 sarcosine aryloxypropanolamine array showing the presence of the methyl ester at 7.80 min, the des-sarcosine methyl ester at 8.60 min and the acid at 7.14 min



Scheme 3.

Having validated the chemistry, this reaction sequence was used in a 'split and mix' fashion to prepare a 29×100-member aryloxypropanolamine combinatorial library containing the *R*-enantiomer and a 29×100-member aryloxypropanolamine library containing the *S*-enantiomer.[8] In this manner, we prepared 200 29-member sublibraries containing a total of 5800 unique members.

We selected 315 beads at random from the final 200 sublibraries and reacted them individually with 5% water in TFA.[9] Analysis of the resin-cleaved material by LC–MS revealed that >70% of the beads examined contained material with the expected molecular weight and was of >70% purity.[10]

In conclusion, we have developed an efficient solid-phase synthesis of phenyloxypropanolamines, which was used to prepare a 25-member array and a combinatorial library theoretically containing 5800 unique members. The chemistry proceeded well for the range of substrates chosen yielding the final compounds free from major impurities.

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7. Chiral HPLC analysis (Chiralpak AD column, 4.6×250 mm, with an ethanol/0.1 % diethylamine mobile phase running at 0.8 ml/min and monitoring the absorbance at 220 nm) of compounds prepared via similar chemistry has routinely indicated an ee of about 95% for the final product.
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9. Each of the two libraries (containing either the *R*- or *S*-enantiomer of the hydroxyl) consisted of 29 different hydroxybenzamides, hydroxyphenylacetamides and hydroxyphenylpropionamides and 100 different arylalkyl amines. Each amine comprises a separate sublibrary.
10. Single beads were treated with 200 µl of 5% water in TFA for 18 h at room temperature and filtered. The filtrates were then evaporated and analyzed.