A One-Pot Process toward 2-Hydroxy-1,3-diamino Compounds: A Synthetic Application to Dual Norepinephrine/Serotonin Reuptake Inhibitors

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Green chemistry, defined as the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products, is the chemists' efforts to achieve the society-wide goal of sustainable development.[1] In addition to chemical yields that have historically been the yardstick of successful reactions, "greenness" of reactions needs to be considered. Toward this end, the term E (environment) factor (kg waste per kg product) has been proposed as a measure for evaluating the environmental footprint of chemical reactions.[2]

In estimating the E factor, the waste is defined as everything but the desired product, and includes reagents, catalysts, and solvents. The greatest transgressors for a large E factor are probably organic solvents. An obvious strategy to decrease the E factor and increase the environmental friendliness of chemical reactions is to perform the reactions under solvent-free conditions. This approach of green chemistry is being actively pursued.[3]

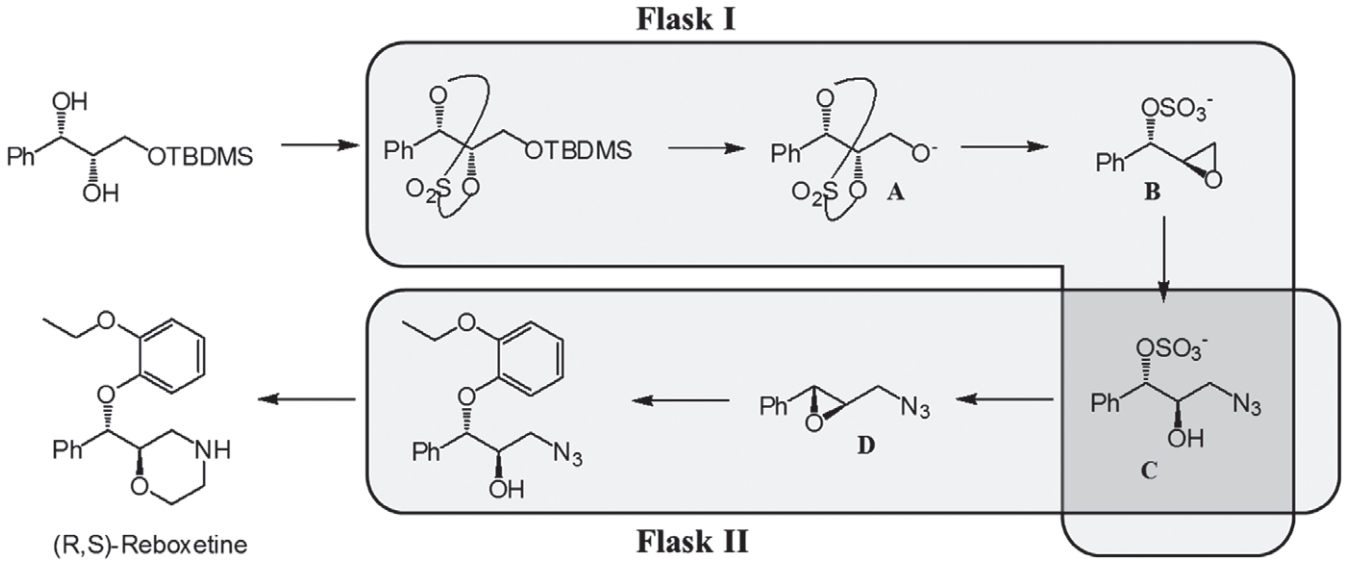
In a laboratory-scale organic synthesis, the step that consumes the largest amount of organic solvents is not the reaction itself, but the work-up and product isolation/purification steps. Organic solvents tens of times the weight of the starting material are commonly used in reactions, while in extractive work-up and in chromatographic purification steps, solvents several hundred times the weight are often used. Clearly, a more effective strategy to reduce the use of organic solvents would be to dispense with the work-up and product isolation/purification steps, *i.e.*, to perform as many sequential synthetic transformations as possible in the same reaction vessel without the need for work-up and isolations/purifications of the intermediates. Tandem reactions, domino reactions, multicomponent reactions, and cascade reactions are variations on the same theme that may simply be called as one-pot reactions.[4] The concept of pot-economy has been proposed to address this issue.[5]

Previously, we reported a synthesis of (*R*,*S*)-reboxetine starting from *trans*-cinnamyl alcohol, in which the key steps were a tandem cyclic sulfate rearrangement—epoxide opening and another tandem epoxide ring closure—epoxide opening processes (Scheme 1).[6] In the synthesis, it was not possible to execute the two key tandem processes in a completely one-pot operation, and an extractive work-up, but not a purification, was necessary at the intermediate stage (**C**). This was due to the fact that the first nucleophile (N_3^-) was employed in excess in the first tandem process, and the left-over anion needed to be removed through an extractive work-up before the second nucleophile (ArO^-) was added in the second tandem process.

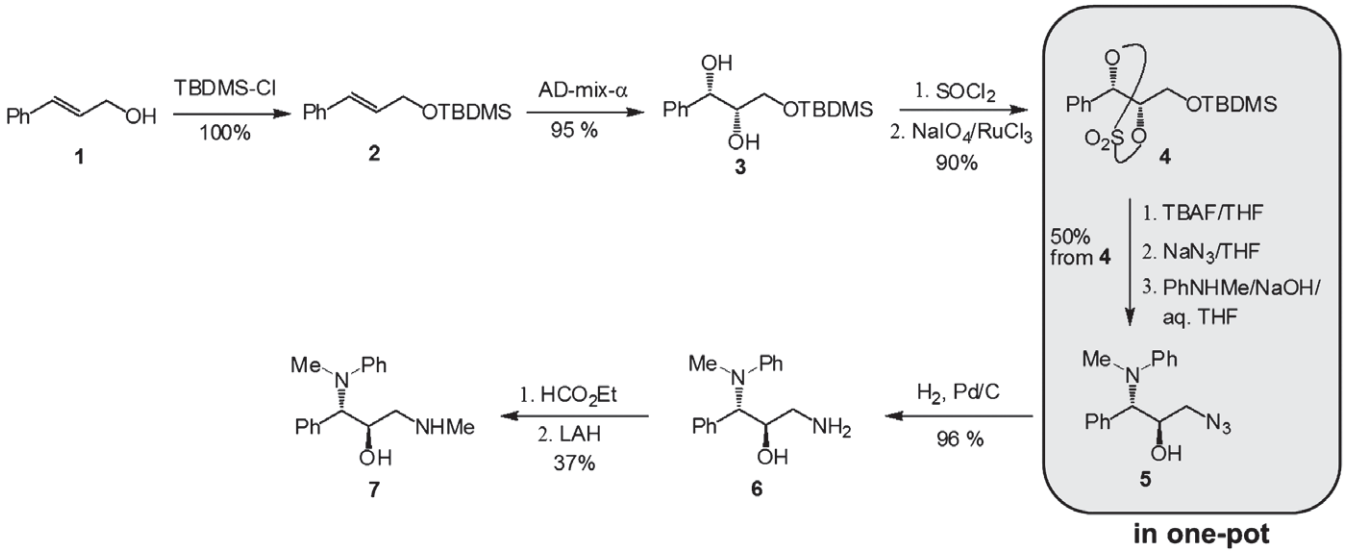
As a part of our efforts to expand the synthetic utility of the key tandem processes, we undertook a synthesis of a series of substituted phenylpropyl amino alcohol compounds in enantio-enriched forms. Many compounds acting on the central nervous system share this structural motif. In particular, 1-arylamino-substituted derivatives have been reported to represent a new series of dual norepinephrine and serotonin reuptake inhibitors, and as such, have received considerable attention for potential therapeutic agents treating depression and other CNS disorders.[7] Described here is a synthesis of 1-*N*-methyl-*N*-phenylamino-substituted 3-amino-1-phenylpropan-2-ol (**6**), the essential structural skeleton for the dual inhibitory activity in the series (Scheme 2).

trans-Cinnamyl alcohol (**1**) was *tert*-butyldimethylsilyl (TBDMS)-protected and the resulting product (**2**) was subjected to the Sharpless AD protocol.[8] The dual norepinephrine and serotonin reuptake inhibitory activity of the 1-arylamino-substituted series of compounds has been investigated with racemic mixtures, and at present it is not known which enantiomer, if either, has the desired biological activity.[7a] Considering the common stereochemical elements of other CNS-active compounds featuring the phenylpropyl backbone, such as fluoxetine, atomoxetine, nisoxetine, and reboxetine, we chose the (1*S*,2*R*)-stereoisomer (**6**) to be our target. Tracing the stereochemical courses of the tandem processes that we had observed in our earlier work led us to choose AD-mix-α as the right reagent for the present AD step.[6] The resulting (1*S*, 2*S*)-diol (**3**) was then converted to the cyclic sulfate (**4**) and the stage was set for the key tandem processes.

From the outset, we set the goal to execute the two key tandem processes in a completely one-pot operation. That



Scheme 1. Synthetic pathway for (*R*,*S*)-reboxetine employing two tandem processes.



Scheme 2. Synthetic pathway for (*R*,*S*)-**6** and **7**.

required the reaction conditions for the first part of this tandem process (the "Payne-type," cyclic sulfate rearrangement—terminal epoxide opening) to be optimized so that the epoxide opening step may be accomplished with just an equivalent amount of the first nucleophile (N_3^-).[9] In our earlier work of (*R,S*)-reboxetine synthesis, this part had been performed with 2 eq. of N_3^- in aqueous THF, the set of reaction conditions borrowed from the original cyclic sulfate rearrangement – epoxide opening process.[9a] Now our efforts to optimize this process led to the reaction conditions that allowed the epoxide opening step to be performed with just an equivalent amount of N_3^-. Thus, the cyclic sulfate was desilylated with TBAF in THF at rt then the mixture was treated with 1 eq. of NaN_3, still in the same solvent (neat THF) at reflux. NMR monitoring revealed that the cyclic sulfate rearrangement (to the terminal epoxide) was complete within 30 min after the TBAF-desilylation, then the azide-opening of the terminal epoxide required 96 hr when the reaction was performed in neat THF at reflux.

With the first part of the tandem process under control, we tackled the second part of the process so that the entire tandem sequence might be performed in a completely one-pot operation without any work-up at the intermediate stage. *N*-Methylaniline was the second nucleophile to be introduced at the C-1. Initially, we attempted to find the optimum reaction conditions for this second part using the isolated (but not purified) intermediate (**C**). Our strategy had been to optimize each tandem process separately, then combine the optimum reaction conditions in a one-pot operation. However, it turned out that some elements of the optimum reaction conditions that had been worked out in a traditional stop-and-go operation

were not directly transferable to a one-pot operation. Therefore, we had to perform the optimization study in a one-pot setting. The optimization study entailed the choice of co-solvent and its proportion (as THF, the reaction solvent for the first part, would still be present in a one-pot process), the choice of base and its amount, and the choices regarding the amount of PhNHMe, the concentration and the reaction time and temperature, etc. In the end, we established the following tandem, one-pot reaction conditions: (i) the cyclic sulfate in THF (0.2 M), TBAF (1 eq.), 30 min, rt; (ii) NaN_3 (1 eq.), 96 hr, reflux; (iii) NaOH (1 eq.), *N*-methylaniline (5 eq.) and H_2O (3.3 mL per mmol), overall concentration 0.12 M in THF-H_2O (3:2 v/v), 330 hr, reflux. The entire process, all together five steps including the desilylation, was performed in a single reaction vessel, and the desired product, (1*S*,2*R*)-3-azido-1-(*N*-methyl-*N*-phenylamino)-1-phenylpropan-2-ol (**5**), was isolated in ca. 50% yield after extractive work-up and chromatographic purification.[10]

Reduction of the 3-azido group (H_2, Pd/C, 96%) yielded the desired target, (1*S*,2*R*)-3-amino-1-(*N*-methyl-*N*-phenylamino)-1-phenylpropan-2-ol (**6**), the essential structure for the dual norepinephrine and serotonin reuptake inhibitors. Mono-*N*-methylation was achieved in two steps, *N*-formylation followed by lithium aluminium hydride (LAH) reduction (37%), to produce the (1*S*,2*R*)-lead structure (**7**), which had previously been reported as a racemic mixture.[11]

Thus, (1*S*,2*R*)-3-amino-1-(*N*-methyl-*N*-phenylamino)-1-phenylpropan-2-ol was synthesized starting from *trans*-cinnamyl alcohol. Following a silylation, the AD process brought the oxidation states at C-1 and C-2 to the levels of the target compound. The two hydroxyl groups were then simultaneously activated in a single operation to the cyclic sulfate. A series of tandem reactions initiated by desilylation transposed the activations to C-3, then to C-1, where N_3^- and *N*-methylaniline nucleophiles were introduced, respectively. In the process, the configuration at C-2 had been inverted and that at C-1 retained through a double inversion. These five steps of reactions were performed in a single reaction vessel. Five mL of THF (and 3.3 mL of H_2O) per mmol of the starting material was all the solvent that was required for this process, then some more for the work-up and purification at the end. The tandem, one-pot protocol is economical not only in terms of the number of reaction vessels and the amount of required solvents, but also in terms of the number of steps.[5] The "Payne-type," cyclic sulfate rearrangement – terminal epoxide opening process produced the intermediate (C) that contained a sulfate anion at C-1, which was exploited as a leaving group in the one-pot protocol. A traditional stop-and-go operation would require an acidic hydrolysis of the sulfate anion intermediate to yield the neutral *anti*-diol product.[9a] This would be a waste in terms of a valuable functional group at C-1, and add extra step(s) of re-activation in our synthetic sequence, which may cause further problems of regiochemistry (and subsequent stereochemistry).[12]

In conclusion, we have achieved an efficient synthesis of (1*S*,2*R*)-3-amino-1-(*N*-methyl-*N*-phenylamino)-1-phenylpropan-2-ol, a dual norepinephrine and serotonin reuptake inhibitory lead structure. The key steps were a tandem cyclic sulfate rearrangement – epoxide opening and another tandem epoxide ring closure – epoxide opening processes, all together five steps of reactions, executed in a one-pot operation.

Experimental

General Information. Reactions were monitored by TLC on silica gel glass-backed plates. Proton (250 or 300 MHz) and ^{13}C NMR (62.5 or 75 MHz) spectra were recorded in ppm relative to TMS as an internal standard. The following abbreviations designate splitting patterns: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of doublet), m (multiplet), br (broad). IR spectra were recorded as thin films on KRS-5 plates.

(1*S*,2*R*)-3-azido-1-(*N*-methyl-*N*-phenylamino)-1-phenylpropan-2-ol (5): Cyclic sulfate (**4**) (0.374 g, 1.086 mmol) was dissolved in THF (5.4 mL). Tetrabutylammonium fluoride (1 M in THF, 1.30 mL, 1.30 mmol) was added and the mixture was stirred at room temperature for 30 min. Then, NaN_3 (0.071 g, 1.086 mmol) was added and the mixture was stirred at 70 °C for 96 h. Next, the mixture was treated with NaOH (0.043 g, 1.086 mmol), *N*-methylaniline (0.59 mL, 5.430 mmol), and H_2O (3.5 mL) and heated at reflux for 330 h. Extractive work-up (EtOAc–brine) was followed by drying (Na_2SO_4) and concentration. Flash silica column chromatography (hexane:EtOAc = 3:1) yielded the desired product **5** as a yellow oil (0.156 g, 0.554 mmol, 51% from **4**). ^1H NMR ($CDCl_3$): δ 7.42–7.26 (7H, m), 6.93 (2H, d, J = 7.8 Hz), 6.84 (1H, t, J = 7.5 Hz), 4.96 (1H, d, J = 9.6 Hz), 4.60–4.53 (1H, m), 3.72 (1H, dd, J = 12.6, 3.0 Hz), 3.60 (1H, dd, J = 12.6, 6.3 Hz), 2.59 (3H, s). IR: 3442, 2104, 1598, 1512 cm^{-1}.

(1*S*,2*R*)-1-(methyl(phenyl)amino)-3-amino-1-phenylpropan-2-ol (6) and (1*S*,2*R*)-1-(methyl(phenyl)amino)-3-(methylamino)-1-phenylpropan-2-ol (7): The azide compound **5** (0.351 g, 1.244 mmol) was dissolved in EtOH (12 mL) and Pd/C 10% (0.035 g) was added. The mixture was subjected to a H_2 atmosphere for 14 h. The mixture was filtered through Celite, which was then washed with EtOH. The combined filtrate and washings were concentrated. Flash silica column chromatography (MeOH:EtOAc = 9:1) yielded the desired amine product **6** (0.307 g, 1.196 mmol, 96%). ^1H NMR ($CDCl_3$): δ 7.44–7.25 (7H, m), 6.90 (2H, d, J = 9.0 Hz), 6.77 (1H, t, J = 7.8 Hz), 4.92 (1H, d, J = 9.3 Hz), 4.34–4.28 (1H, m), 3.04 (1H, dd, J = 13.2, 3.3 Hz), 2.82 (1H, dd, J = 12.6, 6.9 Hz), 2.64 (3H, s). IR: 3397, 1976, 1598, 1505 cm^{-1}.

Ethyl formate (0.66 mL, 8.20 mmol) was added to the primary amine **6** (0.117 g, 1.456 mmol) and the mixture was stirred at 60 °C for 24 h. After concentration, the residue was dissolved in THF (2.3 mL) and the solution was cooled in an ice bath. LAH (1 M in THF, 0.68 mL, 0.683 mmol) was added slowly and the mixture was stirred at 5 °C for 30 min before it was heated at reflux for 21 h. The reaction mixture was cooled to room temperature, and was treated with aqueous

10% NaOH. Extractive work-up (EtOAc–brine) was followed by drying (Na_2SO_4) and concentration. Flash column chromatography (MeOH:EtOAc = 9:1) yielded the desired product **7** as a yellow oil (0.047 g, 0.172 mmol, 37%). ^{1}H NMR ($CDCl_3$): δ 7.42–7.25 (7H, m), 6.90 (2H, d, J = 8.1 Hz), 6.78 (1H, t, J = 7.2 Hz), 4.90 (1H, d, J = 9.0 Hz), 4.42 (1H, td, J = 8.7, 3.3 Hz), 2.88 (1H, dd, J = 12.3, 3.3 Hz), 2.74 (1H, dd, J = 8.4, 3.6 Hz), 2.69 (3H, s), 2.44 (3H, s). ^{13}C NMR ($CDCl_3$): δ 150.18, 138.34, 129.32, 128.38, 128.26, 127.40, 117.33, 113.48, 68.42, 65.40, 54.85, 36.17, 32.94. IR: 3317, 2931, 1959, 1597, 1499 cm^{-1}.

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12. A regioisomeric C-2 hydroxyl-activated by-product would lead to the (*S*,*S*)-epoxide intermediate (the antipode of D, Scheme 1), leading to a partial racemization.

