Synthesis of (*S,S*)-Reboxetine

Hyeyeon Jun, Min Lee Yu, and Soo Y. Ko*

Department of Chemistry, Ewha Womans University, Seoul 03760, South Korea.
**E-mail: sooyko@ewha.ac.kr*
Received August 5, 2018, Accepted October 9, 2018

Keywords: Reboxetine, Diastereomer, Tandem reaction, One-pot

Advents of asymmetric reactions employing asymmetric reagents or catalysts are regarded as a paradigm shift in the field of stereoselective synthesis. In this paradigm, choices of the appropriate asymmetric reagents/catalysts control the configurations of newly created stereocenters (reagent-control).[1] This is in contrast to the traditional substrate-control, in which a pre-existing stereocenter in the starting material induces the configurations of newly created stereocenters in the product.[2] The archetype of the reagent-control strategy is probably the hexose synthesis by Sharpless–Masamune.[1b,c] Here, each of the diastereomeric hexose products was synthesized from a common starting material, following a common synthetic sequence.

In reality, asymmetric reagents/catalysts do not always grant an equal access to diastereomers. They are often effective in producing one diastereomer (in either enantiomeric form), but not so for other diastereomers, for which different and often lengthier synthetic sequences may have to be devised.[3] The syntheses of reboxetine offer a good example. Reboxetine is a potent selective norepinephrine reuptake inhibitor and is effective in treating depression and attention deficit/hyperactivity disorder (ADHD).[4] Initial interests were directed mainly on the *syn*-diastereomers [(*S,S*) and (*R,R*)], the racemic mixture of which is currently on the market. More recently, the *anti*-diastereomers [(*R,S*) and (*S,R*)] began to gain attentions as some *anti*-derivatives exhibited biological activities, which are comparable to, and at the same time, distinct from those of (*S,S*)-reboxetine (Figure 1).[5]

A survey of the synthetic sequences of reboxetines reveals that the pathways for reboxetine diastereomers are not parallel to each other, as in the hexose synthesis, but require different starting materials or different strategies.[6,7] For example, following the asymmetric dihydroxylation (AD) process, *syn*-reboxetine was synthesized via O–Aryl disconnection strategy, while *anti*-diastereomer required an O–Benzyl disconnection strategy. The latter is a contribution from our laboratories.[8] Having previously achieved a synthesis of (*R,S*)-reboxetine, we embarked on a synthetic study of (*S,S*)-reboxetine. Our aim was to develop a synthetic sequence for (*S,S*)-reboxetine, which would be parallel, as closely as possible, to our own synthetic pathway for the *anti*-diastereomer.

Our previous work on the synthesis of (*R,S*)-reboxetine started with Si-protected *trans*-cinnamyl alcohol. The AD was the asymmetric reagent and the resulting diol was simultaneously activated in the form of the cyclic sulfate. A series of tandem reactions transposed the activation, first to C-1 (via cyclic sulfate rearrangement),[9] then to C-3 (via epoxide ring-closure),[10] allowing the sequential introductions of nucleophiles there (Nu^1=N_3 at C-1, Nu^3=2-ethoxyphenoxide at C-3). During this process, an inversion of configuration at C-2 and a retention (double-inversion) of configuration at C-3 took place, so that the AD product, a *syn*-diol, was transformed to the *anti*-1-Nu^1-3-Nu^3-2-ol product. The whole sequence was conducted in a step- and pot-economic manner (Scheme 1, top).

In our efforts to develop a synthetic sequence for (*S,S*)-reboxetine, which would be comparable to our own synthetic pathway for the *anti*-diastereomer, we were prescribed to use the same starting material (*trans*-cinnamyl alcohol), same key processes (AD, cyclic sulfate activation, activation transfer, etc.), same disconnection strategy (Nu^1=N_3, Nu^3=2-ethoxyphenyloxy), and all these in a comparably efficient and economic process.[11]

The two synthetic pathways, one for (*R,S*)-reboxetine, and the other for (*S,S*)-reboxetine, must deviate from each other in the stereochemical courses, as the latter required the AD product, a *syn*-diol, to be transformed to the *syn*-1-Nu^1–3-Nu^3-2-ol product. In practice, it may be realized with one less (or one more) step of configurational inversion at C-2 or C-3 than in the (*R,S*)-reboxetine pathway. We envisaged that a simple change in the order of operations would accomplish the task. Thus, a Nu^3-substitution at C-3 *preceding* the activation transfer to C-1 would result in one less configurational inversion at C-3 and fulfill the stereochemical requirements needed for the synthesis of *syn*-reboxetine (Scheme 1, bottom).

Thus, *trans*-cinnamyl alcohol (**1**) was Si-protected (**2**), then subjected to the AD protocol. One less configurational inversion at C-3 meant that the (*R,R*)-*syn*-diol (**3**) was the right enantiomer leading to (*S,S*)-reboxetine, which dictated the use of AD-mix-β as the appropriate choice of the asymmetric reagent (Scheme 2).[12] The two hydroxyl groups of the AD product (**3**) were both activated in the form of cyclic sulfate (**4**). 2-Ethoxyphenoxide nucleophile was then

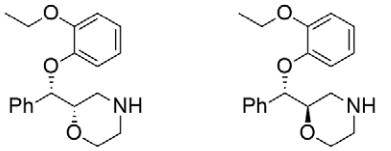


Figure 1. Reboxetine diastereomers.

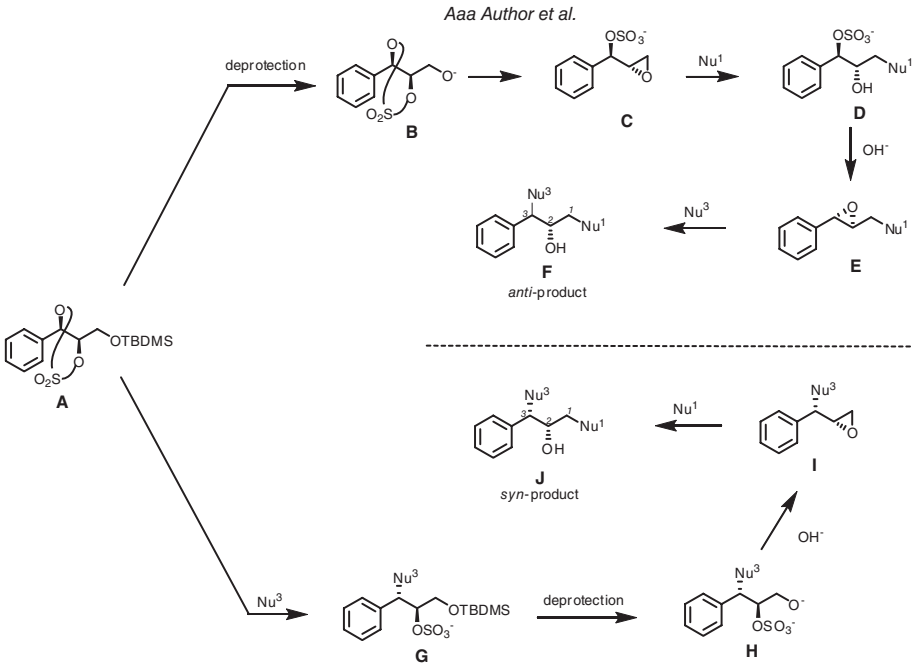
introduced at this stage (2-EtO-Ph-OH, DBU, THF), which took place selectively at C-3. The reaction mixture was then treated with TBAF in the same reaction vessel to execute the desilylation.

The Nu^3-substitution having taken place with an inversion of configuration at C-3, the remaining tasks were an inversion of configuration at C-2 and the Nu^1-substitution at C-1. The activation transfer in the form of 1,2-epoxidation would provide a solution for these tasks.

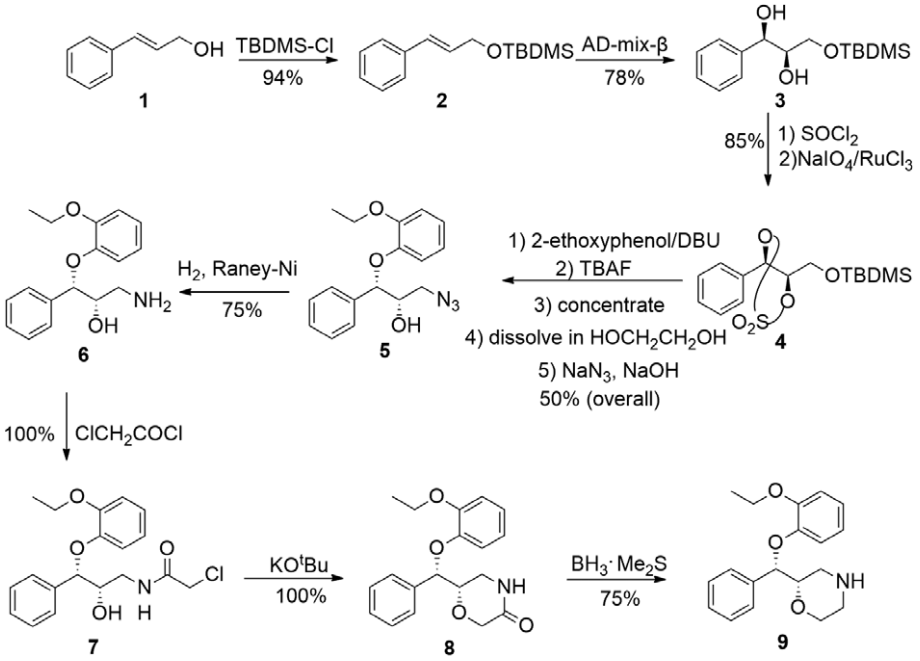
The 1,2-epoxidation in the present work (H → I, Scheme 1, bottom) seemingly corresponds to the first (B → C, Scheme 1, top) of the two epoxidation steps in our (*R,S*)-reboxetine pathway, but is more challenging than that as the leaving group is sulfate dianion, a poorer one than sulfate ester monoanion. In this sense, it resembles the second epoxidation in the tandem process (D → E, Scheme 1, top), but faces an obstacle as the reaction is to take place at a non-benzylic site.[13] Additional difficulties arose at a practical level as the Nu^1-reagent, NaN_3, was only sparingly soluble in many organic solvents.

Our work in (*R,S*)-reboxetine synthesis had revealed that the sulfate dianion displacement was best achieved under aqueous alkaline conditions. As the terminal epoxide intermediate was thought to be unstable under these conditions, we attempted an *in situ* epoxide opening by treating the desilylation reaction mixture with $NaOH/NaN_3/H_2O$.[14] The reaction mixture was heterogeneous, and no promising results were initially observed. When an alcoholic co-solvent (MeOH, EtOH, or iPrOH) was added, the solubility problem persisted, but varying amounts of the desired product **5** were obtained along with a major by-product, which was the C-1-alkoxy-substituted product. Further optimizations of the reaction conditions led to the following procedure: after the TBAF-desilylation, the reaction mixture was concentrated; the resulting residue was dissolved in ethylene glycol (10 mL/mmol substrate); the mixture was then treated with NaN_3 (5 M in H_2O, 10 equiv.) and NaOH (6 equiv.) at 130 °C for 2 days. Following an extractive work-up and chromatographic purification, the desired *syn*-product **5** was obtained in 50% overall yield from the cyclic sulfate **4**. The whole operation, encompassing four steps of reactions, was done in a single reaction vessel, with no isolation/purification of the intermediates, and one change of the reaction solvents. The stereochemical outcome of this one-pot tandem process is inversions of configuration at both C-2 and C-3, therefore, the *syn*-diol starting material was converted to *syn*-1-Nu^1-3-Nu^3-2-ol product. Note that a single activation of the both hydroxyl groups of the *syn*-diol was responsible for the introductions of the two different nucleophiles at C-3 and at C-1, regioselectively.

The *syn*-product **5** was spectroscopically distinct from the *anti*-diastereomer, and the structural proof came with the subsequent conversion to (*S,S*)-reboxetine, which followed the same sequence of reactions that had been



Scheme 1. Tandem processes for converting *syn*-diol cyclic sulfate (a) to *anti*-1-Nu^1-3-Nu^3-2-ol, F (top) and to *syn*-1-Nu^1-3-Nu^3-2-ol, J (bottom).



Scheme 2. Synthetic pathway for (S,S)-reboxetine.

employed for the synthesis of (*R,S*)-reboxetine.[8] Thus, azide reduction (H_2, Raney-Ni, to give **6**), amidation (**7**), cyclization (**8**), and lactam reduction (BH_3-Me_2S) all proceeded uneventfully to yield (*S,S*)-reboxetine (**9**).

In conclusion, (*S,S*)-reboxetine was synthesized. Following the AD on Si-protected *trans*-cinnamyl alcohol, a single, cyclic sulfate activation of the diol and a series of tandem reactions allowed the introductions of the two nucleophiles at C-3 and at C-1 in a one-pot operation. The present synthetic pathway is comparable to our previous route for the (*R,S*)-counterpart in terms of the common starting material, the common key processes, and the overall efficiencies and economies. A simple change in the order of reactions provided pathways for either diastereomer.

Experimental

Experimental procedure for the tandem process converting **4** to **5** (1S,2S)-3-azido-1-(2-ethoxyphenoxy)-1-phenylpropan-2-ol:

The cyclic sulfate **4** (1.467 g, 4.26 mmol) was dissolved in THF (10 mL). To this solution was added a solution of 2-ethoxyphenol (0.706 g, 5.11 mmol) and 1,8-diazabicyclo [5.4.0]undec-7-ene (0.778 g, 5.11 mmol) in THF (7 mL). The mixture was stirred at rt. overnight. TBAF (1 M in THF, 6.39 mL, 6.39 mmol) was added to reaction mixture and the mixture was stirred at rt. overnight. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethylene glycol (28.4 mL), and the solution was treated with a solution of NaN_3 (5 M in H_2O, 8.52 mL, 42.6 mmol) and NaOH (1.022 g, 25.56 mmol) in ethylene glycol (14.2 mL). The reaction mixture was stirred at 130 °C for 2 days. Extractive work-up ($CHCl_3$-brine) was followed by drying (Na_2SO_4) and concentration. Flash silica column chromatography (hexane-ethyl acetate 3:1, v/v) yielded the desired product **5** as a yellow liquid (0.674 g, 2.15 mmol, 50% from **4**). Chiral HPLC analysis (Chiralcel OD-H) indicated the product to be 97.42% ee; ^{1}H NMR($CDCl_3$) δ 7.42–7.32(5H, m, Ar), 7.01–6.83(2H, m, OAr), 6.70(1H, td, J = 7.6, 1.7 Hz, OAr), 6.63(1H, dd, J = 8.0, 1,7 Hz, OAr), 4.81(1H, d, J = 8.4 Hz, Ph-CH), 4.44(1H, s, OH) 4.18–4.08(3H, m, CH(OH)-CH_2, O-CH_2-CH_3), 3.42(1H, dd, J = 12.9, 3.0 Hz, $CH_AH_BN_3$), 2.89(1H, ddd, J = 13.1, 4.3, 1.4 Hz, $CH_AH_BN_3$), 1.53(3H, t, J = 7.1 Hz, O-CH_2-CH_3) ppm; $[\alpha]_D^{20}$ = + 37.4 (c 0.775, $CHCl_3$).

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2016R1D1A1B03930148).

Supporting Information. Experimental procedure for the reactions described in the paper.

References

1. (a) S. Masamune, W. Choy, J. S. Peterson, L. R. Sita, *Angew. Chem.* **1985**, *97*, 1. (b) S. Y. Ko, A. W. Lee, S. Masamune, L. A. Reed III. , K. B. Sharpless, F. J. Walker, *Science* **1983**, *220*, 949. (c) S. Y. Ko, A. W. Lee, S. Masamune, L. A. Reed III. , K. B. Sharpless, F. J. Walker, *Tetrahedron* **1990**, *46*, 245.
2. (a) P. A. Bartlett, *Tetrahedron* **1980**, *36*, 2. (b) K. B. Sharpless, *Chem. Scr.* **1985**, *25*, 71.

3. Asymmetric and diastereodivergent catalytic processes attract attentions. For recent reviews, see: (a) M. Bihani, J. G.-C. Zhao, *Adv. Synth. Catal.* **2017**, *359*, 534. (b) L. Lin, X. Feng, *Chem. Eur. J.* **2017**, *23*, 6464. (c) M. T. Oliveira, M. Luparia, D. Audisio, N. Maulide, *Angew. Chem. Int. Ed.* **2013**, *52*, 13149.
4. (a) P. Melloni, G. Carniel, A. Della Torre, A. Bensignon, A. Buonamici, O. Pozzi, S. Ricciardi, A. C. Rossi, *Eur. J. Med. Chem.* **1984**, *19*, 235. (b) M. Hajós, J. C. Fleishaker, J. K. Filipiak-Reisner, M. T. Brown, E. H. F. Wong, *CNS Drug Rev.* **2004**, *10*, 23.
5. (a) N. K. Jobson, R. Spike, A. R. Crawford, D. Dewar, S. L. Pimlott, A. Sutherland, *Org. Biol. Chem.* **2008**, *6*, 2369. (b) N. K. Jobson, A. R. Crawford, D. Dewar, S. L. Pimlott, A. Sutherland, *Bioorg. Med. Chem. Lett.* **2008**, *16*, 4940. (c) R. Bischoff, D. J. Hamilton, N. K. Jobson, A. Sutherland, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 523. (d) D. M. Aparicio, J. L. Terán, D. Gneco, A. Galindo, J. R. Juárez, M. L. Orea, A. Mendoza, *Tetrahedron Asymmetry* **2009**, *20*, 2764.
6. A recent review for the syntheses of reboxetines: D. Shahzad, M. Faisal, A. Rauf, J.-H. Huang, *Org. Process Res. & Dev.* **2017**, *21*, 1705.
7. (a) A recent report disclosed an asymmetric and diastereodivergent synthesis of reboxetine diastereomers in a reagent-control strategy. See: C. Lui, Z.-W. Lin, Z.-H. Zhou, H. B. Chen, *Org. Biomol. Chem.* **2017**, *15*, 5395. (b) The syntheses of the four reboxetine diastereomers in this case require two different starting materials (enantiomeric to each other).
8. J. Yu, S. Y. Ko, *Tetrahedron: Asymmetry* **2012**, *23*, 650.
9. (a) S. Y. Ko, M. Malik, *Tetrahedron Lett.* **1993**, *34*, 4675. (b) S. Y. Ko, M. Malik, A. F. Dickinson, *J. Org. Chem.* **1994**, *59*, 2570. (c) S. Y. Ko, *Tetrahedron Lett.* **1994**, *35*, 3601. (d) S. Y. Ko, J. Lerpiniere, *Tetrahedron Lett.* **1995**, *36*, 2101.
10. (a) N. Lee, H. Oh, S. Y. Ko, *Bull. Korean Chem. Soc.* **2015**, *36*, 715. (b) N. Lee, M. L. Yu, H. Jun, S. Y. Ko, *Bull. Korean Chem. Soc.* **2016**, *37*, 2091.
11. (a) L. Albrecht, H. Jiang, K. A. Jørgensen, *Ang. Chem. Int.* **2011**, *50*, 8492. (b) C. Vaxelaire, P. Winter, M. A. Christmann, *Chem. Int. Ed.* **2011**, *50*, 3605. (c) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, *1*, 1477. (d) P. A. Clarke, S. Santos, W. H. C. Martin, *Green Chem.* **2007**, *9*, 438.
12. The starting diol for (R,S)-reboxetine was the (S,S)-isomer (ent-**3**), the preparation of which required the use of AD-mix-α.
13. D. O. Jang, Y. H. Joo, D. H. Cho, *Synth. Commun.* **2000**, *30*, 4489.
14. (a) C. H. Behrens, S. Y. Ko, K. B. Sharpless, F. J. Walker, *J. Org. Chem.* **1985**, *50*, 5687. (b) G. B. Payne, *J. Org. Chem.* **1962**, *27*, 3819.

