Syntheses of (S,S)-Reboxetine via a Catalytic Stereospecific Rearrangement of β -Amino Alcohols

Thomas-Xavier Métro, Domingo Gomez Pardo, Janine Cossy

► To cite this version:

Thomas-Xavier Métro, Domingo Gomez Pardo, Janine Cossy. Syntheses of (S,S)-Reboxetine via a Catalytic Stereospecific Rearrangement of β -Amino Alcohols. *Journal of Organic Chemistry*, 2008, 73 (2), pp.707-710. 10.1021/jo701554h . hal-03232563

HAL Id: hal-03232563

<https://hal.science/hal-03232563>

Submitted on 21 May 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Syntheses of (*S,S*)-Reboxetine via a Catalytic Stereospecific Rearrangement of β -Amino Alcohols

Thomas-Xavier Métro, Domingo Gomez Pardo,* and Janine Cossy*

Laboratoire de Chimie Organique, ESPCI, CNRS,
10 rue Vauquelin, 75231 Paris Cedex 05, France

domingo.gomez-pardo@espci.fr; janine.cossy@espci.fr

Received July 16, 2007

SCHEME 1

SCHEME 2

The formal total synthesis of (*S,S*)-reboxetine has been realized by two different approaches using a stereospecific rearrangement of β -amino alcohols catalyzed by $(\text{CF}_3\text{CO})_2\text{O}$.

Recently, we have shown that *N,N*-dialkyl- β -amino alcohols of type **A** can be rearranged stereospecifically by using a catalytic amount of $(\text{CF}_3\text{CO})_2\text{O}$ followed by saponification with NaOH to produce β -amino alcohols of type **B** (Scheme 1).¹

Herein, we would like to report the application of this rearrangement to the synthesis of (*S,S*)-reboxetine. Reboxetine is a selective norepinephrine reuptake inhibitor (NRI) which has been widely studied for its pharmacological properties.² Commercially available under the name Edronax, Prolift, Vestra, and Norebox, reboxetine is indicated in the treatment of depressive disorder and is marketed as a racemic mixture of the (*R,R*)- and (*S,S*)-enantiomers. However, the latter enantiomer has a greater affinity and selectivity for the norepinephrine transporter (NET).³ So far, the methods reported to isolate the (*S,S*)-enantiomer of reboxetine and analogues include chemical resolution,⁴ capillary electrophoresis,⁵ and chiral HPLC.⁶ Asym-

metric syntheses via a chiral starting material^{4a,7} and by Sharpless epoxidation⁸ or dihydroxylation⁹ have also been reported.

The synthesis of (*S,S*)-reboxetine **1** was envisaged from morpholinone **2** that would arise from the β -amino alcohol **3**. The latter compound would be issued from the rearrangement of a *N,N*-dibenzylated amino alcohol obtained from the commercially available (–)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **4** (Scheme 2).

The synthesis of (*S,S*)-reboxetine started with the transformation of the commercially available (–)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **4** to the corresponding tertiary amine **5** by *N,N*-dibenylation in 98% yield. When **5** was treated with $(\text{CF}_3\text{CO})_2\text{O}$ (0.4 equiv) in refluxing toluene for 5 h followed by a NaOH treatment, the rearranged amino alcohol **3**¹ was isolated in 78% yield with an ee of 99%.¹⁰ Whereas in these

(1) (a) Métro, T.-X.; Appenzeller, J.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2006**, *8*, 3509–3512. (b) Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2007**, *72*, 6556–6561.

(2) (a) Melloni, P.; Carniel, G.; Della Torre, A.; Bonsignori, A.; Buonamici, A.; Pozzi, O.; Ricciardi, S.; Rossi, A. C. *Eur. J. Med. Chem.* **1984**, *19*, 235–242. (b) Hajós, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23–44.

(3) Wong, E. H. F.; Ahmed, S.; Marshall, R. C.; McArthur, R.; Taylor, D. P.; Birgerson, L.; Cetera, P. Patent WO 2001001973.

(4) (a) Melloni, P.; Della Torre, A.; Lazzari, E.; Mazzini, G.; Meroni, M. *Tetrahedron* **1985**, *41*, 1393–1399. (b) Prabhakaran, J.; Majo, V. J.; Mann, J. J.; Kumar, J. S. D. *Chirality* **2004**, *16*, 168–173.

(5) Raggi, M. A.; Mandrioli, R.; Sabbioni, C.; Parenti, C.; Cannazza, G.; Fanali, S. *Electrophoresis* **2002**, *23*, 1870–1877.

(6) (a) Boot, J.; Cases, M.; Clark, B. P.; Findlay, J.; Gallagher, P. T.; Hayhurst, L.; Man, T.; Montalbetti, C.; Rathmell, R. E.; Rudyk, H.; Walter, M. W.; Wharton, M.; Wood, V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 699–703. (b) Ficarra, R.; Calabro, M. L.; Tommasini, S.; Melardi, S.; Cutroneo, P.; Ficarra, P. *Chromatographia* **2001**, *53*, 261–265. (c) Lin, K.-S.; Ding, Y.-S. *Chirality* **2004**, *16*, 475–481.

(7) Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett.* **2005**, *7*, 937–939.

(8) (a) Henegar, K. E.; Cebula, M. *Org. Process Res. Dev.* **2007**, *11*, 354–358. (b) Harding, W. W.; Hodge, M.; Wang, Z.; Woolverton, W. L.; Parrish, D.; Deschamps, J. R.; Prisinzano, T. E. *Tetrahedron: Asymmetry* **2005**, *16*, 2249–2256.

(9) (a) Tamagnan, G. D.; Alagille, D. Patent WO 2007005935. (b) Siddiqui, S. A.; Narkhede, U. C.; Lahoti, R. J.; Srinivasan, K. V. *Synlett* **2006**, *11*, 1771–1773.

(10) Determined by SFC using a Daicel chiralcel OD-H column.

SCHEME 3

conditions the yield was slightly lower than in the previously reported conditions [(CF₃CO)₂O (0.2 equiv), THF, 100 °C, 18 h, microwaves irradiation, 83%],^{1b} using 0.4 equiv of (CF₃CO)₂O in refluxing toluene allowed us to reduce the reaction time, to perform the rearrangement on a bigger scale, and to avoid the use of the microwave apparatus. Removing the benzyl groups of the *N,N*-dibenzylamino alcohol **3** was initially attempted by hydrogenolysis under 1 or 4 atm of H₂ in the presence of Pd/C with and without formic acid, but under these conditions, the debenzylation did not go to completion and a mixture of the mono- and dibenzylated products was obtained. Additionally, using ammonium formate as a hydrogen source in the presence of Pd/C in refluxing MeOH or in MeOH under microwave irradiation¹¹ did not improve the conversion toward the dibenzylated amino alcohol **6**. However, the hydrogenolysis of **3** under 1 atm of H₂ in the presence of Pd(OH)₂ in MeOH at room temperature for 26 h led to the primary amine **6** with a yield of 71%. As the construction of the morpholine ring was conceived to be achievable by an intramolecular substitution of a chloroamide by an alkoxide, compound **6** was treated with chloroacetyl chloride, and chloroacetamide **7** was isolated in 89% yield. The latter compound was then transformed into morpholinone **2** in 62% yield by treatment with *t*BuOK (2.5 equiv) in *i*PrOH at room temperature for 2 h. As the stereogenic center at the benzylic position in morpholinone **2** has to be inverted, a Mitsunobu reaction¹² was applied directly on substrate **2**. As the introduction of the 2-ethoxyphenoxy group failed under these conditions, probably related to the presence of the secondary amide in **2**, it was decided to first reduce the morpholinone ring and then to protect the resulting secondary

amine as a *tert*-butylcarbamate. Therefore morpholinone **2** was reduced with Red-Al (4.0 equiv) in refluxing THF for 3 h, and the resulting secondary amine was directly transformed into *tert*-butylcarbamate **8** in 67% yield over two steps. The physical and spectroscopic data of **8** were in full agreement with the literature data, and the synthesis of (*S,S*)-reboxetine was completed as described by Tamagnan et al.⁷ The protected morpholine **8** was treated under Mitsunobu conditions [PPh₃ (2.0 equiv), 2-ethoxyphenol (2.0 equiv), DIAD (2.0 equiv), THF, rt, 22 h] to produce the desired compound **9** in modest yield (35%, lit. 53%). Deprotection of morpholine **9** using TFA (15 equiv, CH₂Cl₂, rt, 16 h then NaOH) afforded (*S,S*)-reboxetine in 88% yield (Scheme 3). Using this strategy, (*S,S*)-reboxetine was obtained in nine steps with an overall yield of 6.2%.

A second approach of (*S,S*)-reboxetine was envisioned from the (*S,S*)-*N*-benzylreboxetine **10**, as this compound had been previously transformed to (*S,S*)-reboxetine in 88% yield by treatment with 1-chloroethylchloroformate (5.0 equiv) and *i*Pr₂NEt (5.0 equiv) in refluxing CH₂Cl₂.^{9a} In order to shorten the reaction sequence, the construction of the morpholine ring present in **10** was planned by an intramolecular cyclization of the aminodiol **11** already possessing a hydroxyethyl chain on the nitrogen atom. The aminodiol **11** would arise from the rearrangement of aminodiol **12** which could be obtained from the dibenzoylated amino alcohol **13**. The latter would be prepared from the commercially available (–)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **4** (Scheme 4).

In order to perform a Mitsunobu reaction on the benzylic alcohol present in **4**, the primary amino and hydroxyl groups were benzoylated to provide compound **14** with a yield of 96%. After treatment of **14** with 2-ethoxyphenol (1.5 equiv), PPh₃ (2.0 equiv), and DIAD (2.0 equiv) in THF at room temperature for 1 h, compound **13** was not isolated, but aziridine **15** was

(11) Banik, B. K.; Barakat, K. J.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1999**, *64*, 5746–5753.

(12) Mitsunobu, O. *Synthesis* **1981**, 1–28.

SCHEME 4

SCHEME 5

obtained in 76% yield, resulting from the substitution of the benzylic position by the amide group. In order to avoid the formation of **15**, a large excess of 2-ethoxyphenol (20 equiv), PPh₃ (2.0 equiv), and DIAD (2.0 equiv) was stirred in THF during 30 min at room temperature before the addition of compound **14** (1.0 equiv) in one portion. The desired benzylic ether **13** was obtained as the major compound in 76% yield. The latter was then reduced by treatment with BH₃·THF (6.0 equiv) in refluxing THF for 3 h to afford *N*-benzylamino alcohol

16 in 92% yield. Diol **12**, which will be the substrate used for the rearrangement, was obtained in 70% yield (two steps from **16**) by *N*-alkylation using methyl bromoacetate (4.6 equiv) followed by reduction of the crude material by LiAlH₄. The *N,N*-dialkylamino alcohol **12** was then submitted to the rearrangement by treatment with (CF₃CO)₂O (0.4 equiv, THF, 120 °C, 18 h under microwave irradiation), and the rearranged aminodiol **11** was isolated in a modest yield of 36%, probably because of the sensitivity of the ether functionality in acidic

conditions. We have to point out that, when the rearrangement was performed with 1.1 equiv of $(\text{CF}_3\text{CO})_2\text{O}$ in the presence of Et_3N (2.0 equiv) in THF at 120 °C during 27 h under microwave irradiation,^{1a} the rearranged amino alcohol **11** could not be separated from byproducts. In order to obtain the morpholine ring, a solution of amino alcohol **11**, Et_3N (2.0 equiv), and DMAP (2.3 equiv) in CH_2Cl_2 was treated with TsCl (3.0 equiv) which was added in small portions until complete disappearance of aminodiol **11**. The reaction mixture was then treated under basic conditions (NaOH) to produce (S,S) -*N*-benzylreboxetine **10** in 57% yield (Scheme 5). As this product was previously transformed to (S,S) -reboxetine in 88% yield,^{9a} we have achieved a formal synthesis of (S,S) -reboxetine in eight steps from **4** with an overall yield of 8.5%. Even though the rearrangement of **12** to **11** proceeded with a modest yield, this strategy is better than the previous one considering the overall yield.

We have shown that the stereospecific rearrangement of *N,N*-dialkyl- β -amino alcohols in the presence of a catalytic amount of $(\text{CF}_3\text{CO})_2\text{O}$ could be successfully applied in total synthesis as we performed two different syntheses of the (S,S) -reboxetine using the rearrangement as a key step. The first approach allowed us to complete a total synthesis of (S,S) -reboxetine in nine steps with an overall yield of 6.2%, and in the second approach, a formal synthesis of (S,S) -reboxetine was achieved in eight steps with an improved overall yield of 8.5%.

Experimental Section

(–)-(1*R*,2*S*)-3-*N,N*-Dibenzylamino-1-phenylpropan-1,2-diol (**3**).¹ To a solution of the *N,N*-dibenzylamino alcohol **5** (4.23 g, 12.2 mmol, 1.0 equiv) in freshly distilled toluene (50 mL) at room temperature was added $(\text{CF}_3\text{CO})_2\text{O}$ (689 μL , 4.9 mmol, 0.4 equiv), and the solution was heated at reflux for 5 h. After addition at room temperature of an aqueous 3.75 M NaOH solution (15 mL), the mixture was stirred for 2 h, extracted with EtOAc (2×50 mL), and the combined organic extract was dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1) afforded 3.3 g (9.5 mmol, 78%) of **3** as a yellow oil: $\text{C}_{23}\text{H}_{25}\text{NO}_2$; MW = 347.45 $\text{g}\cdot\text{mol}^{-1}$; $[\alpha]_{\text{D}}^{20} = -84.0$ (*c* 0.3, CHCl_3); IR (neat) 3387, 3028,

2839, 1494, 1452, 1064, 1027, 733, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.23 (15H), 4.62 (d, *J* = 5.6 Hz, 1H), 3.82–3.75 (2H), 3.61 (d, *J* = 13.2 Hz, 2H), 3.56 (d, *J* = 13.2 Hz, 2H), 2.73 (dd, *J* = 12.8, 8.0 Hz, 1H), 2.46 (dd, *J* = 12.9, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.1 (s), 137.9 (s), 129.3 (d), 128.6 (d), 128.4 (d), 127.7 (d), 127.5 (d), 126.4 (d), 76.3 (d), 70.1 (d), 58.9 (t), 53.7 (t); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2 , 20% MeOH, 5 mL/min, λ = 220 nm, t_{R} (major) = 2.7 min, t_{R} (minor) = 3.4 min); HRMS (CI^+ , CH_4) calcd for $\text{C}_{23}\text{H}_{26}\text{NO}_2$ (*M* + H^+) 348.1964, found 348.1966.

(+)-(2*S*,3*S*)-1-[Benzyl-(2-hydroxyethyl)amino]-3-(2-ethoxyphenoxy)-3-phenylpropan-2-ol (**11**). To a solution of **12** (141 mg, 0.33 mmol, 1.0 equiv) in THF (2 mL) was added $(\text{CF}_3\text{CO})_2\text{O}$ (19 μL , 0.13 mmol, 0.4 equiv). After being stirred for 18 h at 120 °C under microwave irradiation, the reaction was quenched with a 3.75 M NaOH solution (2 mL) at room temperature and stirred for 2 h. The aqueous phase was extracted with AcOEt (2×25 mL), and the combined organic extract was dried over MgSO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10) afforded 51 mg (0.12 mmol, 36%) of **11** as a colorless oil: $\text{C}_{26}\text{H}_{31}\text{NO}_4$; MW = 421.53 $\text{g}\cdot\text{mol}^{-1}$; $[\alpha]_{\text{D}}^{20} = +38.0$ (*c* 0.55, CHCl_3); IR (neat) 3600–3100, 3050–2700, 1735, 1594, 1499, 1453, 1252, 1213, 1123, 1042, 742, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.28 (5H), 7.24–7.18 (3H), 7.17–7.14 (2H), 6.90 (m, 1H), 6.85 (ddd, *J* = 8.1, 8.1, 1.4 Hz, 1H), 6.66 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 6.59 (dd, *J* = 8.0, 1.4 Hz, 1H), 4.65 (d, *J* = 7.5 Hz, 1H), 4.13–4.04 (3H), 3.66 (d, *J* = 13.7 Hz, 1H), 3.59 (d, *J* = 13.7 Hz, 1H), 3.56–3.44 (4H), 2.74 (m, 1H), 2.61–2.54 (2H), 2.45 (dd, *J* = 13.8, 2.9 Hz, 1H), 1.46 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.0 (s), 148.0 (s), 138.6 (s), 129.0 (d), 128.6 (d), 128.4 (d), 128.3 (d), 127.4 (d), 127.0 (d), 123.2 (d), 120.9 (d), 119.2 (d), 113.2 (d), 87.1 (d), 73.8 (d), 64.4 (t), 59.7 (t), 59.5 (t), 56.4 (t), 55.3 (t), 14.9 (q); HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{32}\text{NO}_4$ (*M* + H^+) 422.2326, found 422.2317.

Acknowledgment. Sanofi-Aventis is greatly acknowledged for financial support (grant to T.-X.M.).

Supporting Information Available: Experimental procedures and characterization data of compounds **1–3** and **5–16**. This material is available free of charge via the Internet <http://pubs.acs.org>. JO701554H