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Asymmetric Synthesis of (+)-(*S*,*S*)-Reboxetine via a New (*S*)-2-(Hydroxymethyl)morpholine Preparation

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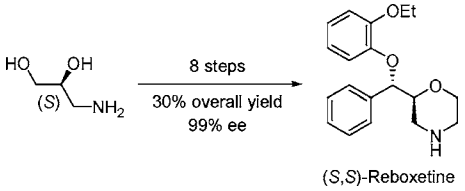
ABSTRACT



(*S*,*S*)-Reboxetine

(*S*,*S*)-Reboxetine was synthesized stereospecifically in 30% overall yield and 99% ee in eight steps. Key steps were selective oxidation of an N-protected hydroxymethylmorpholine and aryl-chromium-mediated aromatic nucleophilic substitution.

Reboxetine is the name given to the racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2-[α-(2-ethoxyphenoxy)phenylmethyl]-morpholine, known to be a potent selective norepinephrine reuptake inhibitor (NRI) and widely studied for its pharmacological properties.[1] Commercially sold as an antidepressant, reboxetine has comparable efficacy to that of imipramine, desipramine, and fluoxetine and has an improved side-effect profile.[2] Among reboxetine enantiomers, (2*S*,3*S*)-2-[α-(2-ethoxyphenoxy)phenylmethyl]morpholine, named (*S*,*S*)-reboxetine, presents the best affinity and selectivity for norepinephrine transporter (NET).[3] (*S*,*S*)-Reboxetine appeared to be an interesting lead compound for our research program, which is oriented toward drug development for depression and attention deficit hyperactivity disorder (ADHD), as well as radiotracer synthesis for in vivo imaging of NET. So far, methods described in the literature to afford (*S*,*S*)-reboxetine involve separation of reboxetine enantiomers by optical resolution,[4] capillary electrophoresis,[5] or chiral HPLC[6] and are specific to the reboxetine structure. A convenient route for the preparation of a variety of chiral aryl morpholine derivatives would be useful for generating targets that are

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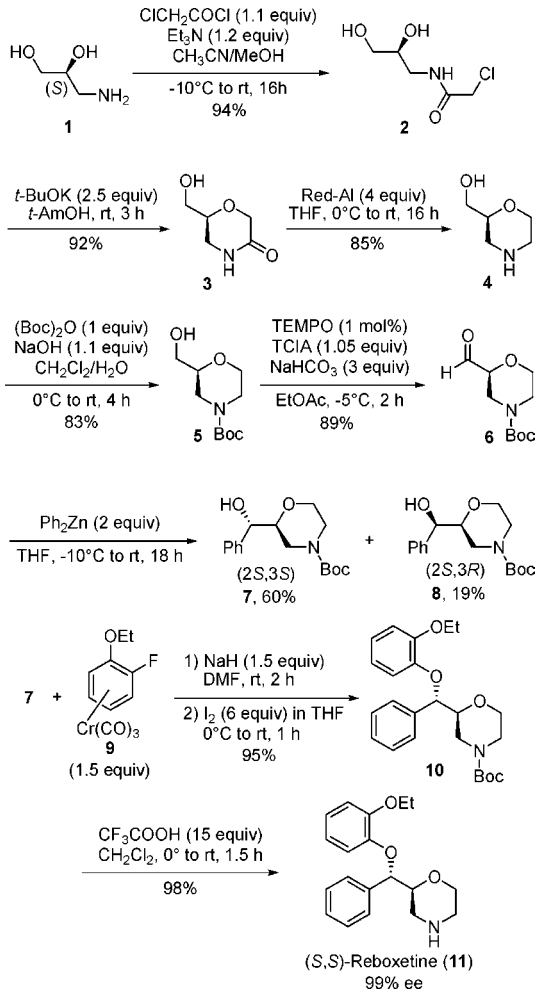
currently the object of intense development efforts toward new NRIs.[7] Here we report an efficient synthesis leading directly to (*S*,*S*)-reboxetine (**11**) starting from commercially available (*S*)-3-amino-1,2-propanediol (**1**).

Scheme 1. Synthesis of (*S*,*S*)-Reboxetine



Our approach was to build the chiral morpholine moiety first, before introducing the phenyl and aryloxy groups (Scheme 1). Reaction of **1** with chloroacetyl chloride in CH_3CN/MeOH provided amide **2** in 94% yield. Conversion to morpholinone **3** was realized directly (without protection of the primary alcohol) by addition of **2** to a solution of *t*-BuOK in *t*-AmOH, giving exclusively **3** with no detectable trace of seven-membered cyclization product. Conversion of alcohol **3** to the aldehyde was a key challenge in the synthesis. First, we attempted to oxidize **3** to the corresponding morpholinone aldehyde, an interesting intermediate itself, to introduce the phenyl moiety of (*S*,*S*)-reboxetine (**11**). Unfortunately, despite all our efforts to perform this oxidation, we were not able to obtain acceptable yields. Therefore, amide **3** was reduced and the resulting amine was protected before performing the oxidation. Hydride reduction of **3** afforded (*S*)-2-(hydroxymethyl)morpholine (**4**) in 85% yield. Red-Al was the best reducing agent; yields were 75% with BH_3[8] and <35% with $LiAlH_4$ in ether or THF. Intermediate **4** was thus synthesized in only three steps with 73% overall yield from **1**. This new route to key intermediate **4** is a clear improvement over those described in the literature.[9]

We chose the *tert*-butoxycarbonyl (Boc) group, easily cleaved in acidic conditions, to protect the amine function. Intermediate **5** was obtained in 83% yield by reaction of $(Boc)_2O$ with **4**. A side product of this reaction was identified as the expected N-protected carbonate resulting from condensation of alcohol **5** with $(Boc)_2O$. Oxidation of **5** to aldehyde **6** was first attempted under Swern conditions,[10] using diisopropylethylamine[11] or *N*-ethylpiperidine[12] as a base instead of triethylamine to avoid epimerization at the 2-position. Despite good yields, significant epimerization was observed in both cases. Consequently, oxoammonium oxidation using TEMPO[13] under catalytic conditions appeared to be a good alternative, since Leanna et al.[14] were able to prepare a large variety of α-amino and α-alkoxy aldehydes in high enantiomeric purity.

Our initial experiments under these biphasic conditions using bleach as a co-oxidizing agent gave only traces of aldehyde **6**. Only after modifications of the method described by De Luca et al.[15] were applied was the synthesis of **6** accomplished efficiently. Slow addition of trichloroisocyanuric acid (TCIA) in EtOAc to a mixture of TEMPO (1 mol %), alcohol **5**, and $NaHCO_3$ in EtOAc led to aldehyde **6** in 89% yield. The presence of $NaHCO_3$ is useful to neutralize HCl formed during the reduction of trichloroisocyanuric acid, thus avoiding partial loss of the Boc group. Use of EtOAc as a solvent instead of CH_2Cl_2 significantly increased yields of aldehyde by avoiding formation of chlorination side products.

Initial attempts to introduce the phenyl group of reboxetine directly with a Grignard reagent led to only partial conversion of the aldehyde to products **7** and **8**, because of the competing enolization that led to regeneration of the aldehyde (>50%) upon workup. The transformation was carried out successfully by treatment of **6** with excess Ph_2Zn. The best conversion was obtained by addition of **6** to Ph_2Zn in THF at −10 °C, generated in situ from PhMgBr in THF and anhydrous $ZnBr_2$.[16] Resulting diastereomers (2*S*,3*S*)-**7** and

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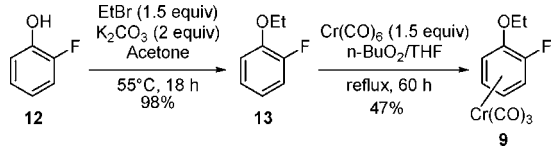
(2*S*,3*R*)-**8** were separated by flash chromatography on silica gel to give 60 and 19% yields, respectively. Reactions at lower temperatures or in less polar solvents such as Et_2O or toluene led to only a slight enhancement of the diastereomeric ratio in favor of **8**. Converting the main isomer (2*S*,3*S*)-**7** to ether **10** without affecting the stereochemistry was another challenge. The best way was via aromatic nucleophilic substitution. Sodium alkoxide of **7** in DMF reacted with aryl-chromium **9** to provide two chromium complexes, which led to **10** in 95% yield after oxidative dechromination with iodine.[17] Aryl-chromium complexes **9** were easily prepared from 2-fluorophenol (**12**) (Scheme 2).

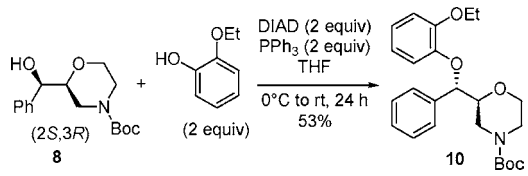
Scheme 2. Preparation of Chromium Complexes **9**



Alkylation of **12** afforded 1-ethoxy-2-fluorobenzene **13** in quasi quantitative yield.[18] Tricarbonylchromium complexes **9** were then obtained by heating **13** and $Cr(CO)_6$ in a mixture of dibutyl ether and THF under reflux.[19] Isomer (2*S*,3*R*)-**8** was also found to provide **10** by reaction with 2-ethoxy-phenol under Mitsunobu conditions,[20] but in this case isolated yields of **10** did not exceed 53% (Scheme 3).

Finally, treatment of Boc amide **10** with excess CF_3CO_2H provided (*S*,*S*)-reboxetine (**11**) in 98% yield.

Scheme 3. Preparation of **10** from Isomer **8**



Identification was established by comparison of spectral data and specific rotation with properties reported in the literature.[4a,b] Enantiomeric purity was determined by chiral HPLC to reveal an enantiomeric excess of 99%. These results confirm that oxidation of **5**, as well as the phenylation reaction, takes place without affecting the configurational integrity of the carbon in the 2-position.

In summary, we realized the synthesis of (*S*,*S*)-reboxetine via a new and particularly effective preparation of (*S*)-2-(hydroxymethyl)morpholine (**4**). The synthesis proceeded in 30% overall yield and 99% ee in eight linear steps starting from commercially available (*S*)-3-amino-1,2-propanediol (**1**). This work represents a convenient route to a wide variety of chiral α-aryloxybenzyl derivatives of morpholine. This route also allowed us to prepare the enantiomer (2*S*,3*R*)-**11** starting from either **7** or **8** in up to 90%. The synthesis of the two other isomers of reboxetine is possible starting with (*R*)-3-amino-1,2-propanediol.

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Supporting Information Available: Complete ref 1c, experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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