Total synthesis of antidepressant drug (*S,S*)-reboxetine : A review

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Abstract:

Morpholine ring structures are amongst the biologically active heterocyclic compounds in organic chemistry because of their omnipresent structural motifs in natural and unnatural products with assorted range of biological activity. The review utilizes the various methodologies for the total synthesis of (S,S)-reboxetine from optically active starting materials, asymmetric epoxidation, chemical resolution, asymmetric transfer hydrogenation, hydrolytic kinetic resolution, and dihydroxylation.

Introduction:

Reboxetine is a selective norepinephrine reuptake inhibitor[1] (NRI) which has been extensively studied for its pharmaceutical importance and used as medicine for the treatment of hyperactivity disorder and depression (Figure 1). Reboxetine has been commercialized under the name of Vestra, Norebox, Prolift, Integrex, Edronax for the treatment of depression, narcolepsy and cocaine dependence disorder and as a racemic mixture of the (*S,S*)-**1** and (*R,R*)-**2** enantiomers. However, (*S,S*)-**1** enantiomer is by far the more effective one and highly selective for the norepinephrine transporter (NET).[2]

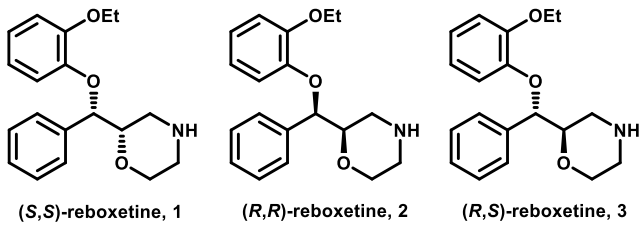


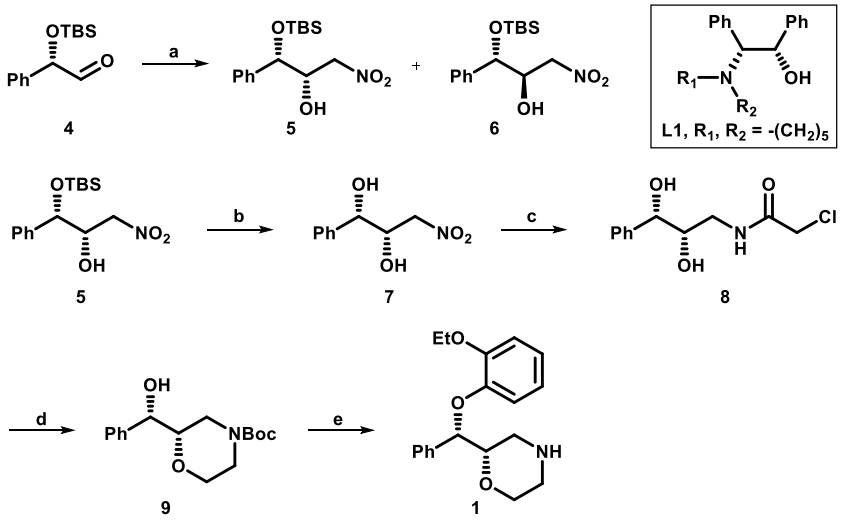
Figure 1. Structures of (*S,S*)-**1**, (*R,R*)-**2** and (*R,S*)-reboxetine **3**.

Synthesis of antidepressant drug (*S,S*)-reboxetine

The synthesis described in this review are based on optically active starting materials,[3] chemical resolution,[4] asymmetric epoxidation,[4] hydrolytic kinetic resolution,[5] asymmetric transfer hydrogenation[6] and dihydroxylation.[7]

Chen, H. B. (2017)[3]

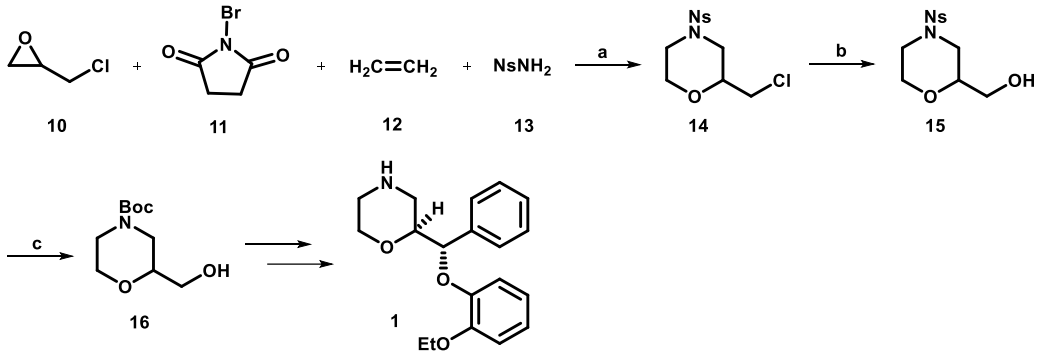
H. B. Chen and co-workers disclosed strereodivergent synthesis of reboxetine **1** from the readily available aldehyde **4** by using the chiral amino alcohol-copper (II) catalyzed diastereoselective nitroaldol reaction as the key step (Scheme 1). The aldehyde **4** on treatment with nitromethane in presence of catalyst **L1** furnished the nitroaldol adduct **5** and **6** (*syn*/*anti* 10.4:1) in 86% yield. The *O*-TBS protected compound **5** on deprotection with 3N HCl afforded the diol **7** which on hydrogenation using Pd/C and subsequent treatment with $ClCH_2COCl$ in the presence of base afforded the chloroacetamide derivative **8** in 71% yield. The amide derivative **8** was subjected to cyclization using *t*-BuOK followed by amide reduction with LAH followed by *N*-Boc protection afforded the morpholine derivative **9** in 70% yield. Finally, derivative **9** was transformed to reboxetine **1** in 85% yield by following the known literature method. [5,6]



Scheme 1. *Reagents and conditions*: (a) $CuOAc.H_2O$, **L1**, $MeNO_2$, rt, 3 d, 86%; (b) 3N HCl, MeOH, rt, 3 h, 84%; (c) i) 10% $Pd/C/H_2$, CH_3OH, rt, 12 h; ii) $ClCH_2COCl$, K_2CO_3, 0 ^oC, 1 h, 71%; (d) i) *t*-BuOK, *t*-BuOH, rt, 2 h; ii) LAH, THF, 0 ^oC-reflux, 6 h; iii) $(Boc)_2O$, THF, rt, 12 h, 70%; (e) i) CBr_4, PPh_3, imidazole, CH_2Cl_2, room temp., 2 h; ii) 2-ethoxyphenol, *t*-BuOK, *t*-BuOH, THF, heat, 12 h; iii) TFA, DCM, rt, 6 h, 85%.

Yeung, Y. Y. *et al.* (2014)[8]

Y. Y. Yeung and co-workers disclosed the formal synthesis of reboxetine **1** starting from commercially available epichlorohydrin **10** employed the *N*-bromosuccinimide induced electrophilic multicomponent reaction as key step (Scheme 2). The epichlorohydrin **10** on treatment with ethylene **12**, NBS **11** and $NsNH_2$ **13** at -30 ^oC and subsequent treatment with base afforded the morpholine derivative **14** in 66% yield. The compound **14** on substitution with acetate followed by hydrolysis furnished the alcohol derivative **15** in 93% yield.



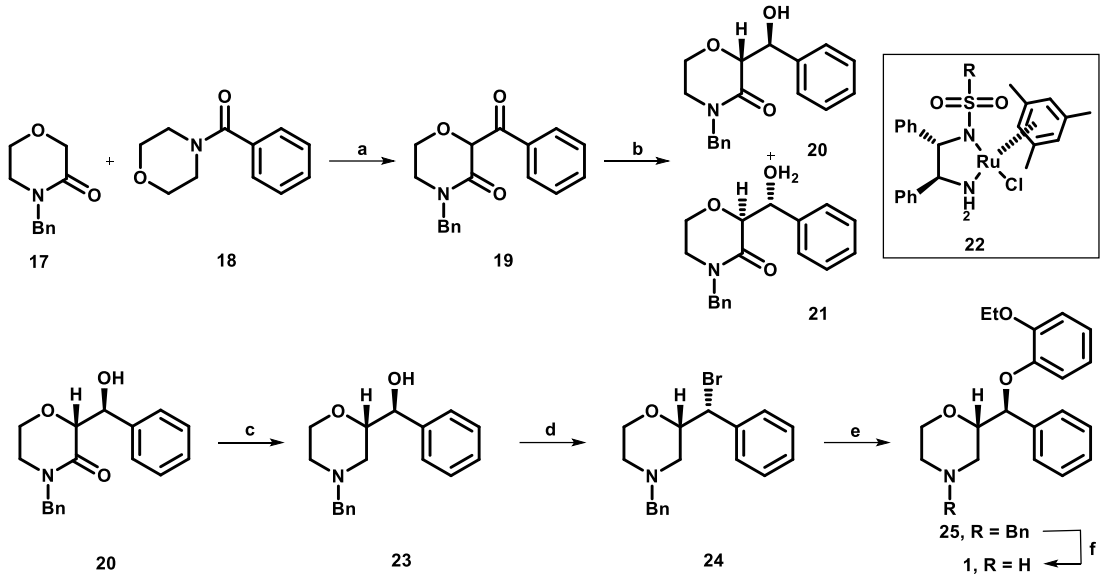
Scheme 2. *Reagents and conditions*: (a) i) -30 °C, 24 h; ii) K_2CO_3, MeCN, 25 °C, 66% (over two steps); (b) i) AcOK, DMF, 90 °C, 16 h, 81%; ii) K_2CO_3, MeOH/H_2O, 25 °C, 16 h, 93%; (c) i) *n*-PrSH/LiOH, CH_3CN, 25 °C, 8 h; ii) $(Boc)_2O$, NaOH, CH_2Cl_2/H_2O, 25 °C, 4 h, 80% (over two steps).

The alcohol **15** on deprotection of nosyl amide group and subsequent treatment with Boc anhydride furnished the *N*-Boc protected derivative **16** in 80% yield. Finally, the compound **16** was converted into final target compound reboxetine **1** by following the known literature method.[9]

Lee, H. K. *et al.* (2013)[6]

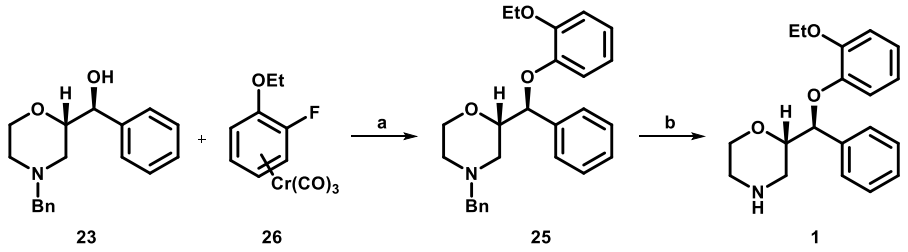
H. K. Lee and co-workers described the stereoselective synthesis of reboxtine **1** employed the dynamic kinetic resolution mediated asymmetric transfer hydrogenation reaction (ATH) of 2-benzoylmorpholin-3-ones as key step (Scheme 3). The *N*-benzyl-3-morpholinone **17** on condensation reaction with *N*-aroylmorpholines **18** in the presence of LDA furnished the *N*-benzyl-2-aroylmorpholin-3-one **19** in 93% yield. The dynamic kinetic resolution mediated ATH reaction of **19** with catalyst (*S*,*S*)-**22** afforded the alcohol (2*R*,3*S*)-**20** and (2*S*,3*R*)-**21** in 90% combined yield.

The lactam **20** on reduction with BH_3·THF delivered the morpholine benzyl alcohol **23** in 97% yield which on subsequent treatment with Ph_3PBr_2 synthesized the corresponding morpholine bromide derivative **24** in 95% yield. The compound **24** on bromide displacement with 2-ethoxyphenol in the presence of *t*-BuOK afforded the *N*-benzyl-protected derivative **25** in 91% yield. The compound **25** on treatment with *α*-chloroethyl chloroformate and subsequent methanolysis furnished the target molecule (*S*,*S*)-reboxetine **1** in 86% yield.



Scheme 3. *Reagents and conditions*: (a) LDA, THF, -78 to 10 °C, 93%; (b) **22**, HCOOH, Et_3N, CH_2Cl_2, 35 °C, 24 h, 99%; (c) BH_3.THF, THF, 60 °C, 2 h, then CH_3OH, 97%; (d) Ph_3PBr_2, DCM, 50 °C, 95%; (e) 2-EtO-phenol, *t*-BuOK, *t*-BuOH, THF (3:1), 80 °C, 24 h, 91%; (f) *α*-chloroethyl chloroformate, (*i*-Pr)$_2$NEt, DCM, 50 °C, 4 h, then CH_3OH, heat, 2 h, 86%.

In another approach, the 2-ethoxyphenyl group was directly incorporated in compound **23** with retention of configuration at the benzylic position (Scheme 4). The treatment of benzyl compound **23** with the tricarbonylchromium complex of 1-ethoxy-2-fluorobenzene **26** in the catalytic amount of NaH, which on oxidative dechromination with I_2 afforded the *N*-Benzyl protected reboxetine derivative **25** in 88% yield. The *N*-Bn derivative **25** on reaction with *α*-chloroethyl chloroformate and subsequent treatment with methanol furnished the target molecule (*S*,*S*)-reboxetine **1** in 86% yield.



Scheme 4. *Reagents and conditions*: (a) i) NaH, DMF, room temp., 2 h; ii) I_2, THF, 0 °C to room temp., 1 h, 88%; (b) *α*-chloroethyl chloroformate, (*i*-Pr)$_2$NEt, DCM, 50 °C, 4 h, then CH_3OH, heat, 2 h, 86%.

Conclusion:

In conclusion, a simple and flexible enantioselective total synthesis of (*S*,*S*)-reboxetine **1** has been disclosed employing the chiral amino alcohol-copper (II) catalyzed diastereoselective nitroaldol reaction, the *NBS* induced electrophilic multi-component reaction and the dynamic kinetic resolution mediated asymmetric transfer hydrogenation reaction (ATH) of 2-benzoylmorpholin-3-ones as the key steps.

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