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## Review Article

# Rearrangement of $\beta$ -Amino Alcohols and Application to the Synthesis of Biologically Active Compounds

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**ABSTRACT**  $\beta$ -Amino alcohols derived from natural amino acids have been used extensively as a powerful source of chirality. Transformation of the hydroxy group of these  $\beta$ -amino alcohols into a good leaving group, by using trifluoroacetic anhydride, led to rearranged  $\beta$ -amino alcohols in good yields and with high enantiomeric excesses. This rearrangement has allowed the transformation of substituted prolinols to substituted 3-hydroxypiperidines and linear  $\beta$ -amino alcohols, issued from natural amino acids, to rearranged  $\beta$ -amino alcohols.

**KEY WORDS:** rearrangement; aminoalcohols; trifluoroacetic anhydride

## INTRODUCTION

In biology, chirality is particularly important for drugs as two enantiomers can have different biological activities. One of the first chemists to be aware of the relationship between organic synthesis, stereochemistry, and biology was Emil Fisher who explained the specific action of a single substrate with an enzyme by using a lock-key analogy. In this analogy, the lock is the enzyme and the key is the substrate. Only the correct key (substrate) fits into the key hole (active site) of the lock (enzyme). When smaller or larger keys are used or, when they are not well-positioned in the enzyme, the substrate has no activity. However, it has been shown that all enzymatic reactions can not be described with this theory.

As enantiomerically pure substituted 3-hydroxypiperidines of type **A** and  $\beta$ -amino alcohols of type **B** are present in a great variety of biologically active compounds, and knowing that the biological activity is directly related to the absolute configuration of the stereogenic centers present in **A** and **B**, we tried to find methods that would allow access to these compounds through easily accessible  $\beta$ -amino alcohols of type **A'** and **B'**, respectively. These  $\beta$ -amino alcohols **A'** and **B'** can be derived from  $\alpha$ -amino acids after *N*-alkylation and reduction (Scheme 1).

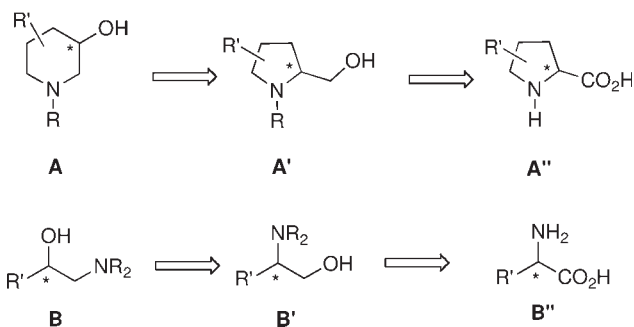
To begin, different conditions were assayed to transform **A'** to **A** and the best conditions, that we found, were trifluoroacetic anhydride (TFAA) and triethylamine ( $\text{Et}_3\text{N}$ ) in refluxing THF, followed by the addition of NaOH.<sup>1–12</sup> Under these conditions, a ring expansion of **A'** took place and 3-hydroxypiperidines of type **A** were isolated in good yields and with excellent enantiomeric excesses. For example, when *N*-benzylprolinol **1** was treated with TFAA and  $\text{Et}_3\text{N}$  in refluxing THF, then with NaOH, 3-hydroxypiperidine **11** was isolated in 63% yield and with an enantiomeric excess of 95%. This enantioselective ring expansion

of *N*-alkylated prolinols (**1–10**) is very general. No matter which *N*-alkyl group (compounds **1–3**), or substituents were present on the prolinols (compounds **4–10**), the rearrangement took place to produce the corresponding 3-hydroxypiperidines (**11–20**) in good yields and with good enantiomeric excesses<sup>3–6</sup> (Table 1).

Prolinols possessing either primary hydroxy groups (**1–6**), secondary hydroxy groups (**7, 8**) or quaternary centers such as compounds **9** and **10**, were transformed to 3-hydroxypiperidines in good yields (54–100%) and with excellent diastereo- and enantioselectivities (*ee* > 95%). We emphasize that unprotected hydroxy groups or acid-sensitive protecting groups were tolerated under these conditions.

In this transformation of prolinols to 3-hydroxypiperidines, the first step implies an esterification of prolinols by TFAA and the formation of the corresponding ammonium salts resulting in the obtention of intermediates **C**. By treatment of these ammonium salts with triethylamine, amino-esters **D** are formed and an  $\text{S}_{\text{N}}1$  process can take place to give tight ion-pairs **E** that reacts to produce the ring expanded products **F** in the form of esters. Finally, saponification of esters **F** using NaOH (2.5 M) leads to 3-hydroxypiperidines **A** (Scheme 2).

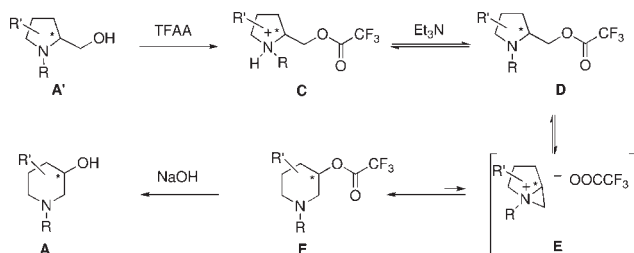
This ring expansion was utilized to synthesize a number of natural and non-natural products with biological activity,<sup>13–18</sup> in particular, this reaction was applied to the syn-



**Scheme 1.** Retrosynthetic analysis of  $\beta$ -amino alcohols of type **A** and **B** from  $\alpha$ -amino acids.

thesis of Ro 67-8867, a NMDA 2B receptor antagonist.<sup>19–21</sup> The first synthesis of this compound was achieved in nine steps, and the key step was a dynamic-kinetic reduction of *N*-benzyl-4-benzyl-3-oxopiperidine using an optically active ruthenium catalyst under hydrogenation in order to control the two stereogenic centers present in Ro 67-8867.<sup>22–25</sup> By using the ring expansion of substituted prolinols, we were able to shorten the synthesis of Ro 67-8867 to seven steps from the commercially available, optically active (*R*)-phenylethylamine **21**.<sup>26</sup> This compound was transformed to the desired prolinol **25** using a diastereo- and enantioselective amino-zinc-ene-enolate cyclization<sup>27–35</sup>/Negishi coupling,<sup>36,37</sup> an one-pot sequence as the key step.

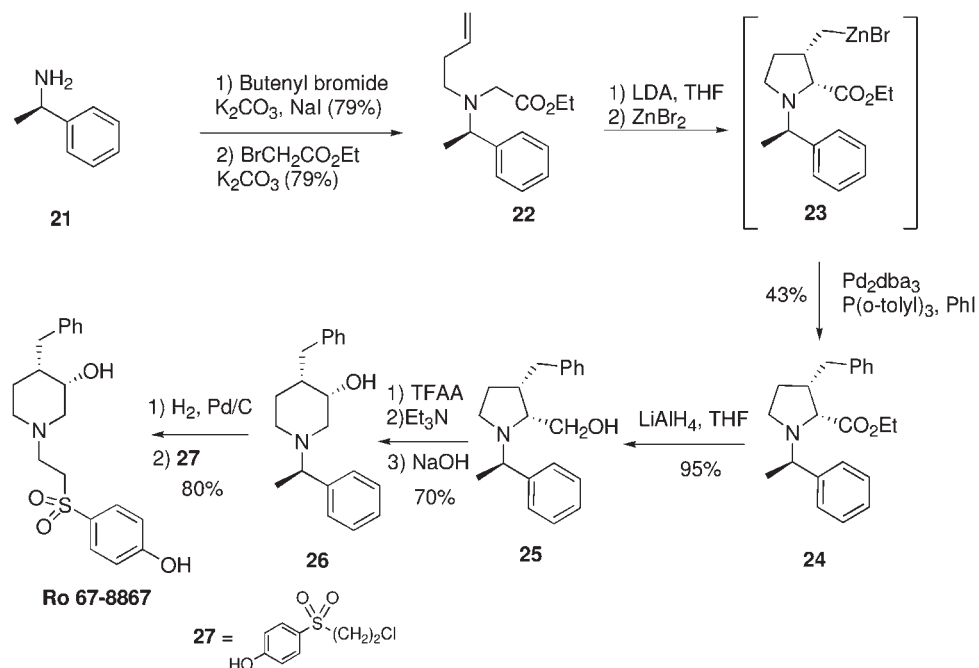
The synthesis of Ro 67-8867 started with *N,N*-alkylation of (*R*)-phenylethylamine under basic conditions to furnish the precursor of the amino-zinc-ene-enolate cyclization, compound **22**, in two steps (62% overall yield). After deprotonation of **22** with LDA (THF,  $-78^\circ\text{C}$ ), the lithium enolate was transmetalated with zinc bromide and the amino-zinc-ene cyclization took place at rt.<sup>34</sup> The resulting organozinc intermediate **23** was then treated with phenyl iodide in the presence of palladium(0) to produce, with excellent *cis*-diastereoselectivity, amino ester **24**.<sup>34</sup> In order to obtain the desired prolinol **25**, precursor of 3-hydroxypiperidine **26**, compound **24** was reduced by  $\text{LiAlH}_4$  (THF, rt, 95%). In agreement with our previous results treatment of prolinol **25** with TFAA in THF followed by the addition of  $\text{Et}_3\text{N}$  and then by the addition of NaOH, produced 3-hydroxypiperidine **26** (70% yield) with a diastereomeric excess superior to 95%. The hydrogenolysis of piperidine **26** ( $\text{Pd/C}$ ,  $\text{H}_2$ , EtOH) led to the desired 3-hydroxypiperidine (94%) which was then transformed to



**Scheme 2.** Mechanism for the rearrangement of prolinols to 3-hydroxypiperidines.

**TABLE 1.** Ring expansion of *N*-alkylated prolinols to 3-hydroxypiperidines.

Starting material	Product	Yield ( <i>ee</i> )
		63% (>95%)
		61% (>95%)
		70% (>97%)
		67% (>98%)
		54% (>98%)
		82% (>98%)
		100% (>98%)
		70% (>98%)
		82% (>97%)
		93% (>98%)

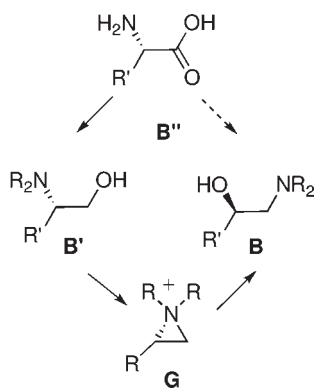


Scheme 3. Synthesis of Ro 67-8867.

Ro 67-8867 by treatment with sulfone **27** (85% yield)<sup>25</sup> (Scheme 3).

In addition to 3-hydroxypiperidines, linear  $\beta$ -amino alcohols of types **B** and **B'** are also encountered in a great variety of biologically active products.  $\beta$ -Amino alcohols of type **B'** can be obtained easily by *N,N*-alkylation and reduction of the corresponding natural amino acids **B''** on the contrary,  $\beta$ -amino alcohols of type **B** cannot be issued from  $\alpha$ -amino acids **B''** in a straightforward manner.

As it was previously demonstrated, the transformation of a hydroxy group present in  $\beta$ -amino alcohols of type **B'** into a good leaving group led to the formation of an aziridinium intermediate of type **G** which can be attacked by a nucleophile to produce rearranged compound.<sup>38-45</sup>



Scheme 4. Rearrangement of linear  $\beta$ -amino alcohols.

Because of the formation of aziridinium intermediates of type **G**, one can envisage the synthesis of  $\beta$ -amino alcohols of type **B** by the attack of **G** by oxygenated nucleophiles (Scheme 4).

In light of our previous success with the rearrangement of substituted prolinols to substituted 3-hydroxypiperidines, the same conditions, e.g. TFAA,  $\text{Et}_3\text{N}$  then treatment with NaOH, were applied to amino alcohols of type **B'**. Thus, when *N,N*-dibenzylamino alcohols **28-31** (compounds of type **B'**) were heated under microwave irradiation at 100°C for 2 h with TFAA (1.5 equiv) and  $\text{Et}_3\text{N}$  (2.0 equiv) in THF and then treated with NaOH,  $\beta$ -amino alcohols **32-35** were obtained in good yields and with high enantiomeric excesses. Even in the case of compound **31**, possessing a quaternary center, the rearrangement is very stereoselective, as it was transformed to **35** in good yield (63%) and with an excellent enantiomeric excess (88%) with practically no loss of chirality (Table 2). These results show that the rearrangement is very regio-, stereo-, and enantioselective.<sup>46</sup>

As for the rearrangement of prolinols, the stereoselectivity of the rearrangement of linear amino alcohols of type **B'** can be explained by the formation of an aziridinium intermediate of type **G** according to Scheme 5.

Later on, we discovered that the rearrangement can be performed with a catalytic amount of TFAA and without  $\text{Et}_3\text{N}$ , as the excess of amino alcohol **B'** can act as a tertiary amine. By using less than one equivalent of NaOH (10% in excess to TFAA), the residual ester was cleaved (Scheme 6). Under these new conditions, all of the amino alcohols of type **B'** were rearranged with excellent yields and enantiomeric excesses (Scheme 6).<sup>47</sup>

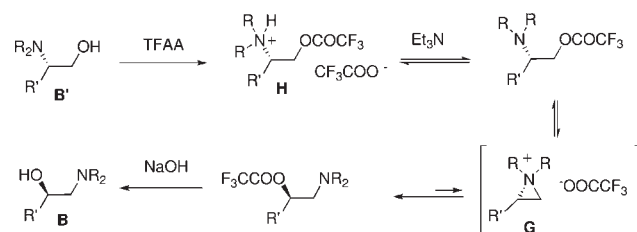
**TABLE 2. Rearrangement of  $\beta$ -amino alcohols of type B' to  $\beta$ -amino alcohols of type B.**

Starting materials ( <i>ee</i> )	Products	Yield ( <i>ee</i> )
 <b>28</b> (> 99%)	 <b>32</b>	97% (>95%)
 <b>29</b> (> 99%)	 <b>33</b>	93% (99%)
 <b>30</b> (> 99%)	 <b>34</b>	66% <sup>a</sup> (>98%)
 <b>31</b> (91%)	 <b>35</b>	63% <sup>b</sup> (88%)

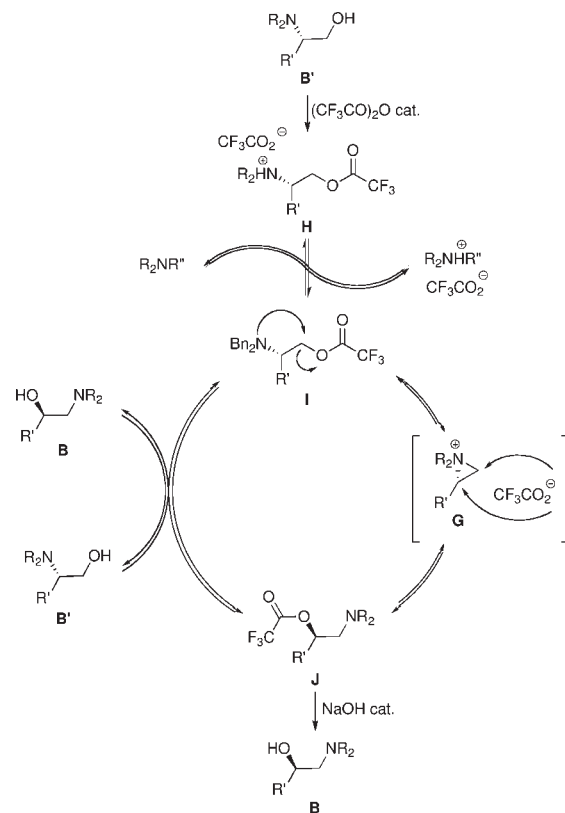
<sup>a</sup>TFAA (1.1 equiv), Et<sub>3</sub>N (1.5 equiv).

<sup>b</sup>TFAA (2.0 equiv), Et<sub>3</sub>N (3.0 equiv), rt, 48 h.

The application of this rearrangement, induced by a catalytic amount of TFAA, was applied to the synthesis of a biologically active compound, (*S,S*)-reboxetine. (*S,S*)-Reboxetine is a selective norepinephrine reuptake inhibitor (NRI) which has been widely studied for its pharmacological properties.<sup>48,49</sup> We have to point out that the (*S,S*)-reboxetine has a greater affinity and selectivity for the norepinephrine transporter than its (*R,R*)-enantiomer<sup>50</sup> and different methods have been developed to access the (*S,S*)-enantiomer such as chemical resolution,<sup>51,52</sup> capillary electrophoresis,<sup>53</sup> chiral HPLC,<sup>54–56</sup> and asymmetric syntheses.<sup>51,57–61</sup> As the rearrangement of linear  $\beta$ -amino alcohols was very selective under catalytic conditions, the synthesis of (*S,S*)-reboxetine was envisaged to pass through  $\beta$ -amino alcohol **K**. Rearrangement of compound **K** should lead to **L**, a known precursor of (*S,S*)-reboxetine (Scheme 7).

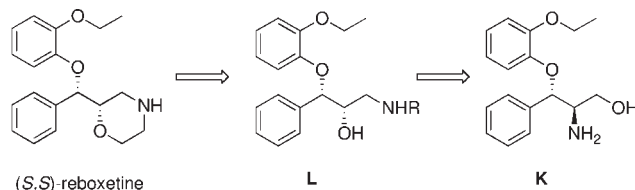


**Scheme 5.** Mechanism of the rearrangement of  $\beta$ -amino alcohols of type B' to  $\beta$ -amino alcohols of type B.

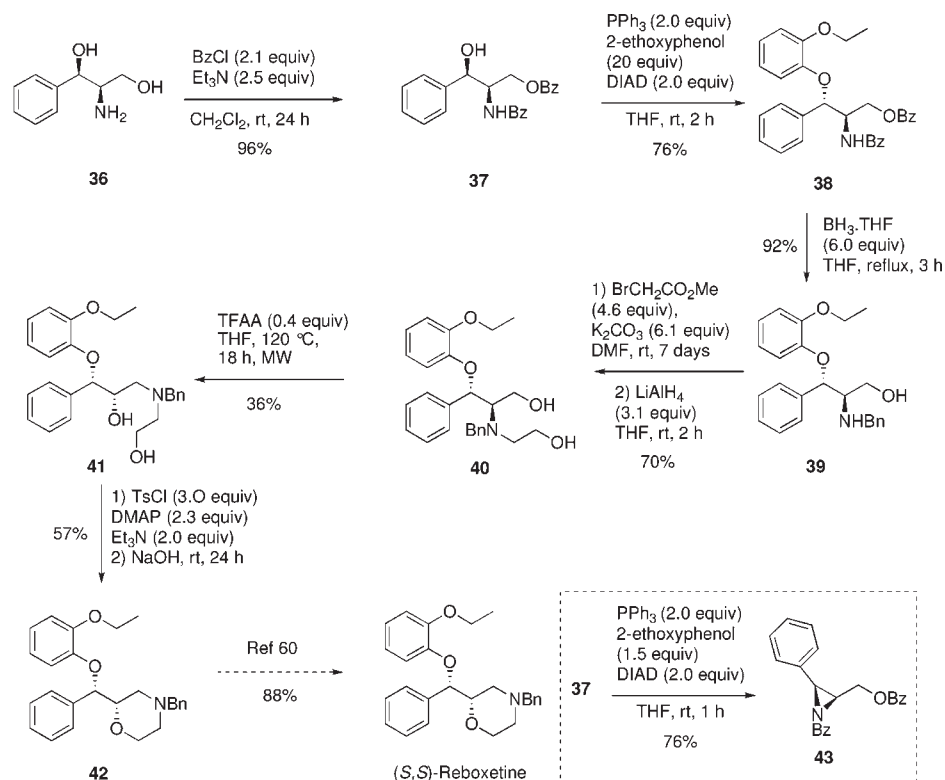


**Scheme 6.** Mechanism of rearrangement under catalytic conditions.

The synthesis of (*S,S*)-reboxetine started with the amino diol **36**. After protection of **36** to the corresponding amido benzoyl ester **37** (BzCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>) in 96% yield, this latter product was converted to **38** by using a large excess of 2-ethoxyphenol (20 equiv), PPh<sub>3</sub> (2.0 equiv) and DIAD (2.0 equiv) in order to avoid an intramolecular Mitsunobu reaction that led to an aziridine (aziridine **43** was obtained from **37** when 1.5 equiv of 2-ethoxyethanol was used).<sup>62</sup> After reduction of **38** (BH<sub>3</sub>•THF in refluxing THF), *N*-benzylamino alcohol **39** was isolated (92% yield). The *N*-alkylation of **39**, using methyl bromoacetate (K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 7 d) followed by reduction of the crude material utilizing LiAlH<sub>4</sub> (THF, rt, 2 h), led to amino alcohol **40** (70% yield). The conditions of the rearrangement (0.4 equiv of TFAA, then NaOH) were then applied to **40** and the expected rearranged  $\beta$ -amino alcohol **41** was isolated in a nonoptimal yield of 36%. The morpholine ring was built from



**Scheme 7.** Retrosynthetic analysis of (*S,S*)-reboxetine.



Scheme 8. Synthesis of (*S,S*)-reboxetine.

**41** in two steps. After treatment with TsCl (DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 48 h) and then with NaOH, morpholine **42** was isolated (57% yield). As this latter compound was transformed previously to (*S,S*)-reboxetine,<sup>60</sup> a formal synthesis of this biologically active product was achieved in eight steps from amino diol **36** with an overall yield of 8.5% (Scheme 8).<sup>62</sup>

By using the rearrangement of cyclic and linear  $\beta$ -amino alcohols induced by TFAA, Et<sub>3</sub>N, followed by treatment with NaOH, a great diversity of rearranged  $\beta$ -amino alcohols were obtained in good yields and enantiomeric excesses, producing useful building blocks that can be utilized to synthesize compounds with interesting biological activities.

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