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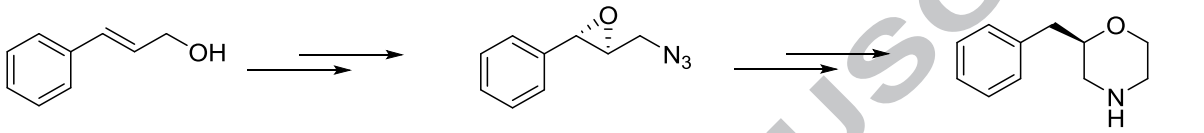

(R)-2-benzylmorpholine **1**
appetite suppressant

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ABSTRACT

Abstract: An alternate synthesis of (*R*)-2-benzylmorpholine **1**, an appetite suppressant agent has been accomplished starting from readily available *trans*-cinnamyl alcohol employing Sharpless asymmetric epoxidation strategy as a key step, with an overall yield 24%.

C-Substituted morpholine analogues, in particular the non-racemic ones are important structural scaffolds present in many pharmaceutically important compounds (Fig. 1).[1] They are potential therapeutic agents for wide variety of medical disorders such as depression (Reboxetine, Viloxesine),[2] anorectic (Phenmetrazine, Phendimetrazine),[3] chemotherapy induced nausea & vomiting (Aprepitant)[4] etc. In that series, (*R*)-2-benzyl morpholine is a classical example of chiral 2-morpholine analogues, known to be a potent appetite suppressant and widely studied for its pharmacological properties.[5] Further, its potential utility in treating diabetes mellitus and certain CNS disorders are also under investigation.[6] Despite their wide utility, synthetic routes to these valuable compounds especially the non-racemic ones are very limited.[7] So far, methods described in the literature to afford (*R*)-2-benzyl morpholine involve optical resolution,[5] chemoenzymatic route[8] or enantioselective method employing proline catalyzed α-aminooxylation strategy.[9]

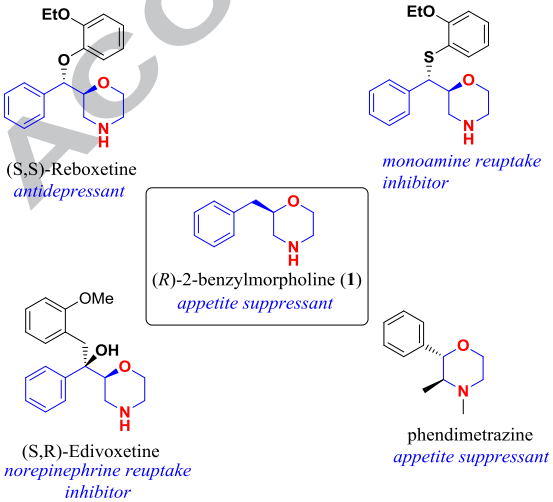
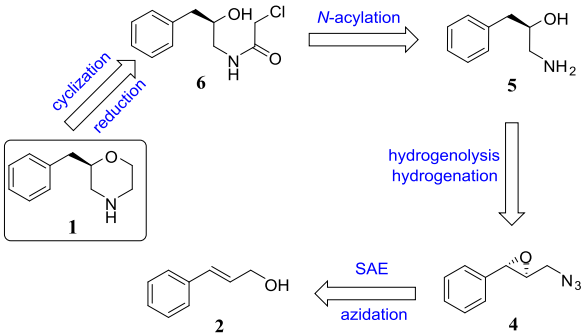


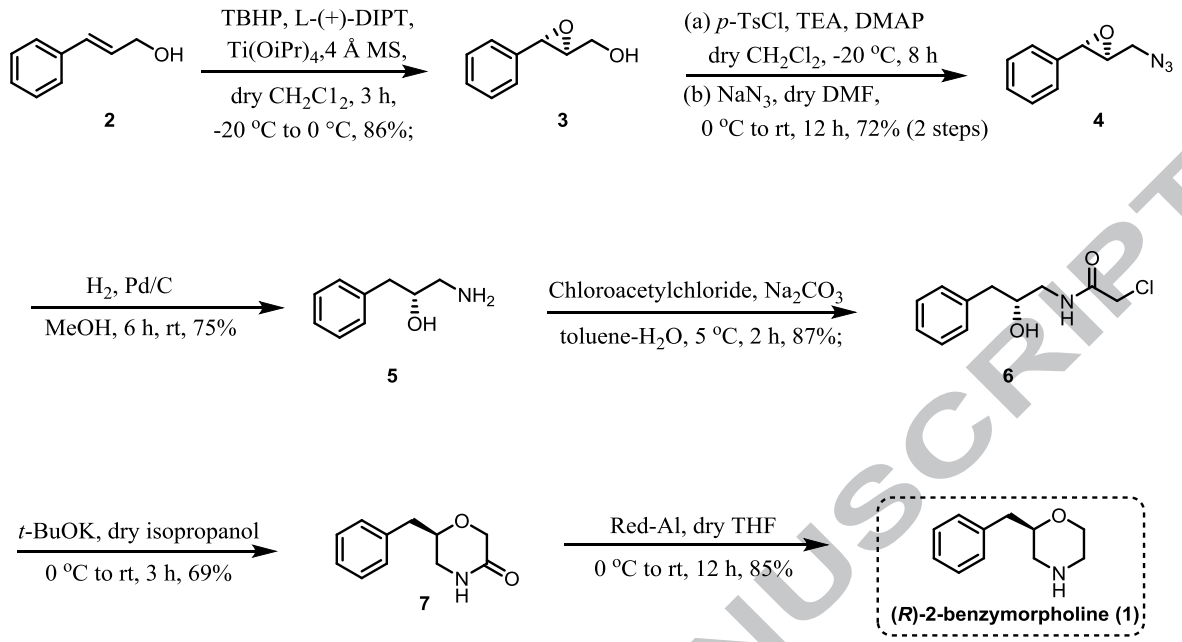
Figure 1 Few pharmaceutically important compounds possessing chiral C-2 substituted morpholine structure

As part of our ongoing programme on developing a new and improved process for the preparation of various pharmaceutically important compounds for industrial applications,[10,11] we herein report a simple and efficient approach towards the preparation of (*R*)-2-benzylmorpholine employing Sharpless asymmetric epoxidation (SAE)[12] strategy.

A retrosynthetic analysis of **1** is outlined in scheme 1. As shown in scheme 1, the amino alcohol **5** can be visualized as a key intermediate for the synthesis of (*R*)-2-benzylmorpholine (**1**) which can be elaborated to the amide derivative **6** by simple *N*-acylation. Further, compound **6** might be transformed to the target molecule **1** via cyclization followed by amide reduction.



Scheme 1 Retrosynthetic analysis of (*R*)-2-benzylmorpholine **1**



Scheme 2: Synthesis of (*R*)-2-benzylmorpholine

The amino alcohol **5** might, in turn, be prepared from readily available *trans*-cinnamyl alcohol **2** by means of SAE, azidation prior to concomitant hydrogenolysis and hydrogenation sequences.

Accordingly, our synthesis commenced with the readily available *trans*-cinnamyl alcohol **2**, which was subjected to Sharpless asymmetric epoxidation conditions ((+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 ^{0}C) to give enantiomerically pure epoxide alcohol **3** in 86% yield (ee >99%).[13] Subsequently, the epoxyalcohol **3** was converted into the corresponding azido epoxide **4** by carrying out *O*-tosylation at low temperature (-20 ^{0}C) followed by azidation using sodium azide in dry DMF. Next, the azido epoxide **4** was subjected to palladium carbon-catalyzed concomitant hydrogenolysis of epoxide and hydrogenation of azide moiety in a single step to provide aminoalcohol **5** in 75% yield. It is worth noting that although the regioselective ring opening of azido epoxide **4** with various nucleophiles have been studied, to our knowledge, the concomitant hydrogenolysis of epoxide and hydrogenation of azide in a single step to produce enantiopure β-amino alcohols have not been examined. Considering the significance of enantiopure β-amino alcohols as important structural elements present in many natural products as well as pharmaceuticals, this reaction represents the valuable alternative to prepare enantiopure β-amino alcohol, utilizing SAE strategy. Further, the aminoalcohol **5** on *N*-acylation with chloroacetyl chloride under basic condition provided compound **6** in 87% yield. Subsequent cyclization induced by *t*-BuOK in isopropanol gave the morpholinamide derivative **7** in 69% yield. Finally, the reduction of amide bond using Red-Al in THF completed the synthesis of (*R*)-2-benzylmorpholine, in overall 24% yield. The structure of (*R*)-2-benzylmorpholine (**1**) confirmed by means of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic analysis.

Conclusion

In conclusion, we have developed a new and alternative synthesis of (*R*)-2-benzylmorpholine **1**, an appetite suppressant agent employing SAE as a key step. Simple procedures, ready availability of the starting materials and high enantiopurity are some of the salient features of this approach. Further, this simple approach offers flexibility in making diverse lead like C-2 chiral morpholine scaffolds for application in a range of therapeutic areas.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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13. The enantiopurity purity was assessed by chiral HPLC analysis by reference to a racemic compound **3**. Racemic compound **3** was prepared using known procedure, see reference, Hashimoto, N.; Kanda, A. *Org. Process Res. Dev*. **2002**, *6*,405.

Spectral data for selected compounds:

(R)-2-chloro-N-(2-hydroxy-3-phenylpropyl)acetamide (**6**)*:* pale yellow oil**;** $[\alpha]_{25}^{D}$ = -6.3 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3423, 3022, 2928, 2403, 1741, 1594, 1532, 1423, 1216, 1030, 927, 765, 672; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.33 (bs, 1 H), 2.74 (dd, *J* = 13.7, 8.3 Hz, 1 H), 2.84 (dd, *J* = 13.6, 5.0 Hz, 1 H), 3.22-3.28 (m, 1 H), 3.60-3.66 (m, 1 H), 3.98-4.04 (m, 1 H), 4.07 (s, 2 H), 6.99 (bs, 1 H), 7.21-7.23 (m, 1 H), 7.26-7.36 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.7 (CO), 137.1 (C), 129.3 (CH, 2 carbons), 128.8 (CH, 2 carbons), 126.9 (CH), 71.6 (CH), 45.0 (CH_2), 42.6 (CH_2), 41.5 (CH_2); HRMS (ESI) calcd for $C_{11}H_{14}O_2NCl$ $[M+H]^+$ 228.0786, found 228.0784, $C_{11}H_{14}O_2NCl$ $[M+Na]^+$ 250.0605, found 250.0604.

(R)-6-benzylmorpholin-3-one (**7**): semi solid; $[\alpha]_{25}^{D}$ = -30.7 (*c* 1.81, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2400, 1681, 1496, 1455, 1427, 1341, 1215, 1114, 1027, 928, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.76 (dd, *J* = 13.9, 6.4 Hz, 1 H), 2.99 (dd, *J* = 13.9, 6.8 Hz, 1 H), 3.16-3.37 (m, 2 H), 3.84-3.97 (m, 1 H), 4.2 (dd, *J* = 31.5, 16.9 Hz, 2 H), 6.95 (bs, 1 H), 7.18-7.37 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 169.1 (CO), 136.7 (C), 129.1 (CH, 2 carbons), 128.6 (CH, 2 carbons), 126.8 (CH), 73.8 (CH), 67.6 (CH_2), 46.0 (CH_2), 39.2 (CH_2); HRMS (ESI) calcd for $C_{11}H_{13}O_2N$ $[M+H]^+$ 192.1019, found 192.1019, $C_{11}H_{13}O_2N$ $[M+Na]^+$ 214.0838, found 214.0838.

(R)-2-benzylmorpholine (**1**): colorless oil; $[\alpha]_{25}^{D}$ = +1.31 (*c* 5, $CHCl_3$); {lit.[8a] $[\alpha]_{25}^{D}$ = +1.28 (*c* 5, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2400, 1652, 1403, 1216, 1093, 925, 768, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.40 (bs, 1 H), 2.51-2.68 (m, 2 H), 2.75-2.93 (m, 4 H), 3.51-3.71 (m, 2 H), 3.83-3.89 (m, 1 H), 7.17-7.32 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 137.9 (C), 129.2 (CH, 2 carbons), 128.3 (CH, 2 carbons), 126.3 (CH), 77.6 (C), 68.2 (CH_2), 50.8 (CH_2), 45.7 (CH_2), 40.3 (CH_2); HRMS (ESI) calcd for $C_{11}H_{15}ON$ $[M+H]^+$ 178.1226, found 178.1226.