JOC*Note*

Concise Synthesis of (*S*)-N-BOC-2-Hydroxymethylmorpholine and (*S*)-N-BOC-Morpholine-2-carboxylic Acid

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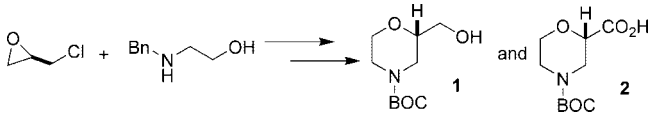

An operationally simple synthesis of *N*-BOC-2-hydroxymethylmorpholine (**1**) and *N*-BOC-morpholine-2-carboxylic acid (**2**) from epichlorohydrin has been developed. No chromatography is required in the processing, which allows high process throughput.

N-BOC-2-Hydroxymethylmorpholine (**1**) and the closely related *N*-BOC-morpholine-2-carboxylic acid (**2**) have been used extensively in the preparation of pharmacologically active compounds, both as the racemates and as single enantiomers. These include a number of CNS compounds such as reboxetine and related norepinephrine and norepinephrine-serotonin reuptake inhibitors (NRI and NSRI, respectively),[1] NRI and NSRI indazoles,[2] and other CNS structural classes.[3] In addition, **1** and **2** have been used to prepare a wide variety of other pharmaceutically active compounds.[4]

Despite their widespread use, synthetic routes to these valuable compounds, either racemic or single enantiomer, are limited by expensive starting materials, processing issues, and lengthy and/or inefficient routes. For example, a 4-step synthesis of (*S*)-**1** starting with (*S*)-3-amino-1,2-propanediol was recently reported as part of a synthesis of reboxetine.[5] Although the starting material is commercially available, its high cost makes this route economically unattractive.[6] In addition, the poor solubility properties of the intermediates and the need for multiple chromatographies make scale-up of this synthesis problematic. Another short route uses the reaction of (*S*)-benzylglycidyl ether with 2-aminoethyl hydrogen sulfate and base to generate the morpholine in a one-pot sequence.[7] BOC protection and debenzylation yields **1**. Unfortunately, tars are formed in this process which are difficult to remove. On a kilogram scale, the overall yield of **1** was 38%, but two distillations and three chromatographies were required to give material of acceptable quality, which seriously detracts from the chemical brevity of this synthesis. A more straightforward route also starting from (*S*)-benzylglycidyl ether has been described.[8] This route has also been scaled but has seven isolated intermediates, three chromatographies, and a distillation, which limit throughput. A similar but even longer route starting with D-mannitol has also been described.[9]

Given the utility of **1** and **2**, there remains a need for a more efficient and scalable route to these valuable compounds. We describe herein a concise synthesis that can be used to make either enantiomer starting from inexpensive chiral epichlorohydrin. The basic synthetic approach is shown in Scheme 1.

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10.1021/jo800356q CCC: $40.75
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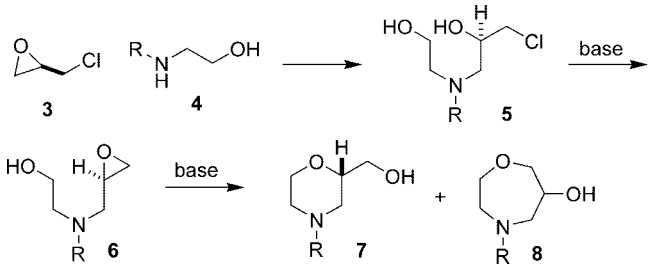
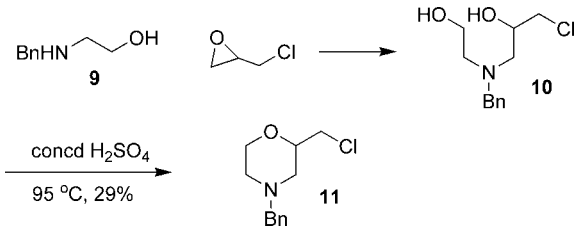
SCHEME 1



SCHEME 2



Reaction of chiral epichlorohydrin **3**[10] with a protected ethanolamine **4** would yield the chlorohydrin **5**. Epoxide formation (**6**) from the chlorohydrin was expected to be facile, and then further reaction of the epoxide would induce cyclization to the morpholine−oxazepine mixture (**7** and **8**).

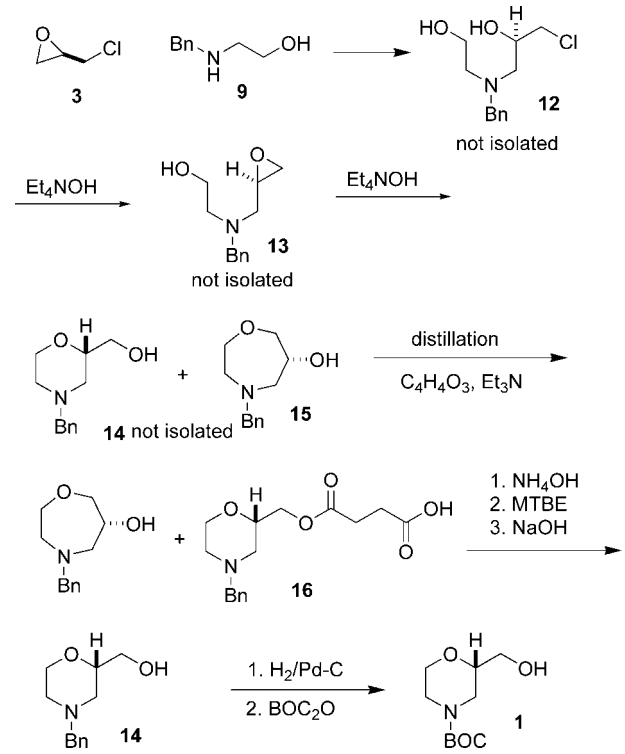
We are aware of a single example of this type of base-promoted cyclization in the literature, which claimed a 9:1 ratio of morpholine to oxazepine for the *N*-methyl compounds derived from racemic epichlorohydrin and *N*-methylethanolamine (Scheme 1, R = CH_3). These results are hard to interpret since the ratio appears to be reported for a purified sample and the actual yield is unclear.[11]

N-Benzylethanolamine **9** is also known to react with racemic epichlorohydrin to give the racemic chlorohydrin **10**, which has been cyclized to give **11** (Scheme 2). The cyclization was done in concentrated sulfuric acid at 95–150 °C and the stereochemical outcome of this cyclization is unknown.[12]

N-Benzylethanolamine (**9**) was chosen for this process since removal of the benzyl group should be facile and the benzyl group provides a convenient chromophore for reaction monitoring. Reaction of *N*-benzylethanolamine with (*S*)-epichlorohydrin **3** cleanly yielded the chlorohydrin **12** (Scheme 3). In contrast to the reported reaction with racemic epichlorohydrin,[12] which used a large excess of epichlorohydrin, we ran the reaction with a 1:1 molar ratio of *N*-benzylethanolamine:epichlorohydrin to minimize consumption of the chiral epichlorohydrin. This reaction proceeded only in protic solvents and gave essentially no product in solvents such as DMF, THF, CH_3CN, or toluene. The reaction ran well in alcohols such as methanol or IPA and was substantially accelerated by addition of water. In addition, reaction in aqueous alcohols minimized impurity formation. The chlorohydrin was relatively unstable; isolated samples lost HPLC potency and degraded so it is not normally isolated.

Conversion of the chlorohydrin **12** to the epoxide **13** was facile. Epoxide **13** underwent further reaction readily and for

SCHEME 3



isolation the epoxide, formation was best done under phase transfer conditions. The epoxide was also relatively unstable and was not normally isolated; purified samples cyclized in a few months when stored in a refrigerator and faster at ambient conditions.

A survey of Lewis acid conditions for the conversion of **13** to **14** and **15** showed slow and very messy reaction with LiOTf in CH_3CN or *t*-BuOH, no reaction with $LiClO_4$ in CH_3CN, *t*-BuOH, or Et_2O, very messy reaction with trifluoroacetic acid, and no reaction with methanesulfonic acid. Exposure of the epoxide to lanthanide triflates ($La(OTf)_3$, $Yb(OTf)_3$, $Nd(OTf)_3$) in 2-propanol or CH_3CN gave no reaction.

Cyclization of **13** to **14** and **15** was promoted by hydroxide. Concentrated NaOH or KOH worked but the reactions were nonhomogeneous and became unstirrable due to salt precipitation. LiOH was ineffective and CsOH also worked but was no different than NaOH or KOH. Aqueous tetraalkylammonium hydroxide solutions gave mixtures that were homogeneous throughout the reaction. No difference was seen in the ratio of **14** to **15** with various hydroxides (Me_4NOH, Et_4NOH, *n*-Pr_4NOH, *n*-Bu_4NOH, and $BnNMe_3NOH$ were examined). The ratio of **14** to **15** was invariably about 70:30. There was minimal temperature effect on this ratio and the reaction was run at about 20–25 °C. *n*-Bu_4NOH was originally used but extraction of the product was inefficient and there was carryover of tetrabutylammonium residues into the organic phase. The more hydrophilic Et_4NOH was chosen to overcome these issues.

Stereochemical correlation was done starting with (*R*)-epichlorohydrin **3**. This yielded the (*S*)-enantiomer of **1** with no detectable enantiomer by chiral HPLC analysis, demonstrating that the epoxide opening proceeded with complete inversion. However, when chlorohydrin **12** was used that had been held as a concentrated oil for about a week before use, the **1** obtained had about 15% of the wrong enantiomer. Racemization is presumably proceeding through intermediacy of the azetidinium

(10) (*R*)-Epichlorohydrin used for this study was purchased for $470/kg in 5 kg lots. Both enantiomers of epichlorohydrin are available in bulk for <$40/kg.

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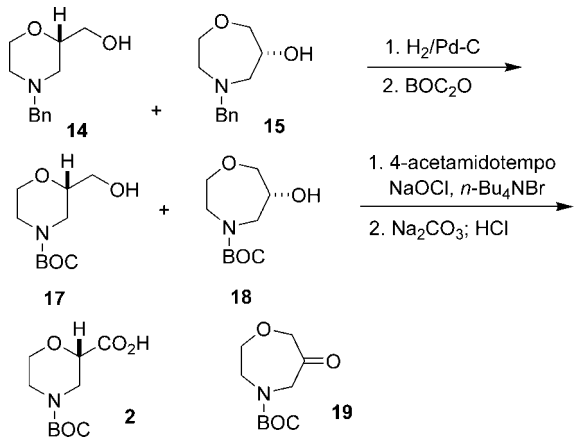
SCHEME 4



species.[13,14] Reaction starting with (*S*)-epichlorohydrin predictably yielded the (*R*)-enantiomer of **1**.

Stereochemical analysis of the oxazepine **15** derived from (*R*)-epichlorohydrin was done. Chiral HPLC assay showed it to be essentially a single enantiomer, indicating it is formed by a competing 7-endo cyclization and not via an azetidinium species, which would have given racemic oxazepine product.

In the final optimized conditions, chlorohydrin formation, epoxidation, and cyclization were run in one pot without isolation of the intermediates **12** and **13**. The reaction to form **12** was done in 1:1 2-propanol−water at 20–25 °C. When this reaction was done, 1.2 equiv of 35% aqueous Et_4NOH was added. Formation of epoxide **13** was rapid and cyclization to **14** and **15** required about 2 h.

Selective succinoylation[15] of the morpholine primary alcohol to hemisuccinate **16** allowed nonchromatographic separation of the mixture of **14** and **15**. Selectivity for the primary vs secondary alcohol was about 6:1 at rt but increased at lower temperatures. Reaction at –25 °C gave rapid reaction with the primary alcohol and good selectivity. Simple distillation of the crude mixture of **14** and **15** to remove high-boiling impurities gave better control over succinic anhydride stoichiometry and gave cleaner final product. Succinoylation was fast and selective in CH_2Cl_2 with triethylamine or other nonhindered bases such as dimethylethylamine or *N*-methylpyrrolidine, and was sluggish with diisopropylethylamine as the base or in ethyl acetate or methyl *tert*-butyl ether. One equivalent of succinic anhydride based on the morpholine HPLC area percent of **14** was added in 2 or 3 portions. After 30 min, dilute aqueous ammonia was added to extract the hemisuccinate into the aqueous phase. Use of aqueous Na_2CO_3 or K_2CO_3 for the extractions led to serious emulsions. The succinate **16** was readily hydrolyzed by addition of NaOH. The isolated purified **14** contained <1% oxazepine **15**. Hydrogenation and BOC protection yielded **1** with >99% ee in 41% overall yield from (*R*)-epichlorohydrin.

Conversion of this mixture to the carboxylic acid (**2**) was straightforward (Scheme 4). The undistilled mixture of **14** and **15** was hydrogenated to remove the benzyl groups and the nitrogens protected to give the BOC derivatives **17** and **18**. Tempo oxidation converted the primary alcohol of the morpholine **14** to the carboxylic acid **2** and the secondary alcohol of **15** to the ketone **19**. These products were easily separated by simple acid–base extractions. Overall yield of **2** from epichlorohydrin was 39%, with no chromatography or distillation. The product assayed at >99% ee by chiral HPLC.

Experimental Section

(*S*)-*N*-BOC-2-Hydroxymethylmorpholine (1). *N*-Benzylethanolamine **9** (151.2 g, 1.0 mol), water (100 mL), and 2-propanol (100 mL) were charged to a jacketed 2 L reactor with a 20 °C circulating jacket. (*R*)-Epichlorohydrin **3** (97.15 g, 1.05 mol) was added and the solution was stirred overnight. A 35 wt % aqueous solution of Et_4NOH (495 mL, 1.3 mol) was added over <5 min. The mixture exothermed to +29 °C in about 30 min, and then the temperature returned to ambient. After 4 h, the reaction was quenched with 1 M HCl (150 mL, final pH: 9). Water (350 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 500 mL). The extracts were combined and evaporated to an oil, which was distilled through a short path under vacuum (0.5 mm, bath 175–190 °C, bp 150–180 °C) to yield a clear colorless distillate (169.9 g) and about 20 g of clear amber still bottoms. The distillate was 67.7:32.3 **14**:**15** by HPLC; the still bottoms were a gross mixture containing little **14**.

The distillate (**14** and **15**, 169.9 g) and triethylamine (115 mL, 0.81 mol) were dissolved in 1500 mL of CH_2Cl_2 and cooled to –25 °C (±3 °C). Succinic anhydride (49.0 g, 0.49 mol) was added in two portions over 45 min and then stirred for 2 h. Dilute aqueous ammonia (40 mL of 28% diluted to 440 mL volume) was added and the mixture was warmed to rt and stirred for 30 min. The organic phase was extracted with dilute aqueous ammonia (2 × 40 mL of 28% diluted to 440 mL volume). The combined aqueous phases were extracted with CH_2Cl_2 (1 × 400 mL). The aqueous phase was basified with 50% NaOH (40 mL) and stirred overnight. The solution was extracted with CH_2Cl_2 (3 × 400 mL), dried briefly over Na_2SO_4, filtered, and evaporated to yield 91.2 g (44% overall) of **14** as a colorless oil.

The product was hydrogenated over Pd/C (50 psi, 10% Pd/C, 50% water wet) in methanol. The solution in methanol (750 mL volume) after catalyst filtration was stirred at rt and BOC_2O (96 g, 0.44 mol) in 100 mL of methanol was added in portions over 90 min. The solution was stirred for 30 min after completion of the addition. An additional 5 g of BOC_2O dissolved in 10 mL of methanol was added and the solution was stirred for 30 min. *N*,*N*-Dimethylethylenediamine (66 mmol, 7.2 mL) was added and the mixture was stirred for 30 min. The solution was concentrated on a rotovap to an oil. The oil was partitioned between CH_2Cl_2 (1L) and 100 mL of 1 M HCl and 100 mL of water. The CH_2Cl_2 phase was extracted again with 100 mL of 1 M HCl and 100 mL of water. The combined aqueous phases were back extracted with 500 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with 200 mL of 1 M Na_2CO_3. The CH_2Cl_2 solution was evaporated to an oil and then heptane (2 × 1 L) was added and evaporated. The resulting oil solidified on standing to yield a white solid **1** (90.2 g, 41.8% overall from (*R*)-epichlorohydrin): mp 61–64 °C (lit.[5] mp 60–62 °C); $[\alpha]^{25.3}_D$ + 18.97° (*c* 0.2, $CHCl_3$); (lit.[5] $[\alpha]^{20}_D$ +20.7 (*c* 1.01, $CHCl_3$)); ^{1}H NMR (399.76 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.19 (br s, 1H), 2.64–2.79 (m, 1H), 2.82–2.99 (m, 1H), 3.42–3.60 (m, 3H), 3.60–3.67 (m, 1H), 3.73–3.94 (m, 3H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 28.5, 42.5–46.1 (br), 63.6, 66.5, 76.0, 80.3, 154.9; Chiral HPLC, Chirapak AD 4.6 mm × 250 mm, 10 μm, 92:8:0.1 hexane: IPA:TFA, 1.0 mL/min, 215 nm; *S*, 8.7 min; *R*, 9.8 min; ROI < 0.1%. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.43; H, 8.90; N, 6.44.

(*S*)-2,4-Morpholinedicarboxylic Acid, 4-(1,1-Dimethylethyl) Ester 2. *N*-Benzylethanolamine **9** (12.6 g, 83.3 mmol) and (*R*)-

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(14) The HPLC purity of the isolated chlorohydrin had dropped from about 90 area % to less than 60% during storage.

(15) Formation of the hemisuccinate **16** was confirmed by mass spectral data. Other anhydrides examined either gave sluggish reaction and poor selectivity (phthalic anhydride, glutaric anhydride) or poor partitioning during the aqueous base extractions (hexahydrophthalic anhydride).

epichlorohydrin **3** (8.09 g, 87.5 mmol) were stirred in a 35 °C oil bath with 12 mL of 2-propanol. The solution was cooled to rt. Et_4NOH (35% aqueous; 43 mL, 99 mmol) was added and the mixture was allowed to stir overnight at toom temperature. The pH was adjusted to 9–10 with concd HCl. Water (50 mL) and MTBE (50 mL) were added. The phases separated and the aqueous phase was extracted with 50 mL of methyl *tert*-butyl ether. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to yield the crude product (**14** and **15**, 15.28 g). The material was hydrogenated in methanol with Pd/C (50 psi, 10% Pd/C, 50% water wet). Yield 8.16 g of a slightly yellow oil.

The oil was stirred with THF (100 mL). A small amount of white solids formed which were removed by filtration. BOC_2O (69 mmol, 14.6 g) was added in portions as a solid. The solution was stirred overnight a rt and then evaporated to an oil. Methyl *tert*-butyl ether (2 × 100 mL) was added and evaporated to yield a mixture of **17** and **18**. The oil was dissolved in CH_2Cl_2 (67 mL). Water (33 mL), Bu_4NBr (0.93 g, 2.9 mmol), and 4-acetamidotempo (0.06 g, 0.28 mmol) were added and the two-phase mixture was stirred at 0 °C. A solution of 70 mL of 12.5% NaOCl and 0.3 g of $NaHCO_3$ and 20 mL of water was added over 1 h. The excess NaOCl was quenched with sodium sulfite and the pH (about 7) was adjusted to >12 with 50% NaOH. The phases were separated and the aqueous phase was extracted with 20 mL of CH_2Cl_2. The pH of the aqueous phase was adjusted to <2 with concd HCl and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The organic solutions were combined, dried over Na_2SO_4, and evaporated to yield **2** as a white solid (7.65 g, 39% overall): mp 127–134 °C dec; $[\alpha]^{20}_D$ +30.58 (*c* 0.5, EtOH); ^{1}H NMR (399.76 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.99–3.15 (m, 2H), 3.52–3.60 (m, 1H), 3.71–3.80 (m, 1H), 3.93–4.02 (m, 1H), 4.04–4.17 (m, 2H), 6.83 (br s, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 28.5, 43.0 (br), 45.6 (br), 66.2, 73.7, 81.2, 154.8, 172.2; low resolution mass spec, nominal *m*/*e* calcd for $C_{17}H_{21}O_4$ $(M + H)^+$ 289, found *m*/*z* 289 $[M + 1]^+$ (Ion Mode: APCI); Chiral HPLC, Chirapak AD 4.6 × 250 mm, 10 μm; 95:5:0.1 hexane:ethanol:TFA; 0.5 mL/min; 215nm; *R*, 29.8 min; *S*, 27.6 min; ROI < 0.1%. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.95; H, 7.40; N, 6.01.

Acknowledgment. Anne Akin and Eric Nord developed the chiral and achiral HPLC methods and provided expert analytical support.

Supporting Information Available: Experimental procedures and spectral data for intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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