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Synthesis of Reboxetine Intermediate and Carnitine Acetyltransferase Inhibitor via NBS-Induced Electrophilic Multicomponent Reaction

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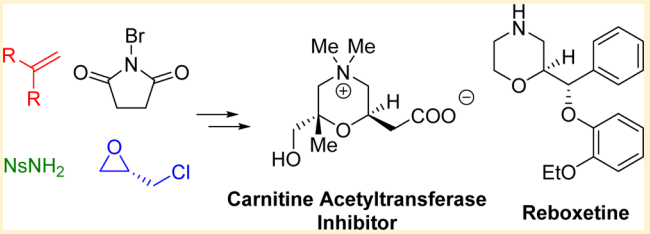
Supporting Information

ABSTRACT: *N*-Bromosuccinimide-induced electrophilic multicomponent reaction has been applied to the synthesis of Reboxetine intermediate, a highly potent selective norepinephrine reuptake inhibitor. By simply changing the olefinic partner, the synthesis of a carnitine acetyltransferase inhibitor, which contains a 2,6,6-trisubstituted morpholine system, can be accomplished.

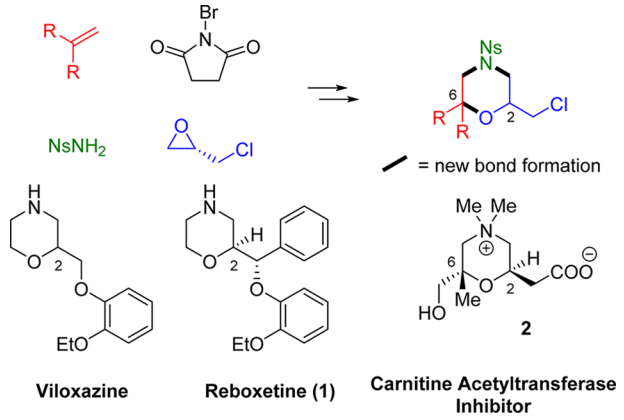


INTRODUCTION

The importance in ensuring the economic competitiveness of pharmaceutical industry while reducing the impact on environment has emerged in recent years.[1] Multicomponent reaction (MCR), in which three or more reactants are combined in a single chemical operation, is one of the ideal solutions for sustainable manufacture.[2] Recently, we have developed a number of electrophilic MCRs using *N*-bromosuccinimide (NBS) as the initiator.[3] Herein we are pleased to report the application of electrophilic MCR in the synthesis of bioactive 2-substituted morpholines Reboxetine (**1**) (a norepinephrine reuptake inhibitor, marketed as an antidepressant by Pfizer) and **2** (a potent carnitine acetyltransferase inhibitor) (Scheme 1).[4,5]

Morpholines with substitutions at the α-oxygen positions (2-substituted or 2,6-disubstituted morpholines) are a class of molecules that possess interesting biological activities.[6]

Scheme 1. NBS-Induced MCR in the Synthesis of 2-Substituted Morpholines



Comparing to other substituted morpholines (e.g., 3-subsituted morpholines) that can readily be constructed by using amino acid building blocks,[7] enantioselective syntheses of 2-substituted morpholine systems are less reported.[8] In one of our focuses on the electrophilic MCRs using epoxide as the nucleophilic partner, epichlorohydrin was found to be effective, which gave rise to the corresponding morpholine with a chloride handle (Scheme 1).[3e] We reasoned that this kind of functionalized scaffold is very useful as an advanced intermediate for pharmaceutically important morpholines.

RESULTS AND DISCUSSION

Racemic Reboxetine (**1**) is marketed currently. However, recently it was found that the pure enantiomer (+)-(*S*,*S*)-Reboxetine (**1**) is significantly more active, and a number of biologically studies are underway.[9] As a result, an efficient and enantioselective entry toward the synthesis of enantiopure Reboxetine (**1**) is highly desirable.[10]

Toward the formal synthesis of Reboxetine (**1**), we simply need to react ethylene with epichlorohydrin, NBS, and $NsNH_2$ at −30 °C for 16 h. Morpholine **3** with a methylene chloride handle at the 2-position could be achieved in 66% yield (Scheme 2). The structure of **3** was confirmed by an X-ray crystallographic study. Substitution of the chloride in **3** with acetate followed by hydrolysis allowed for the introduction of an oxygen functionality, providing morpholine **4**. Subsequently, conventional protecting group manipulation accomplished hydroxyl morpholine **5**, which is a key intermediate in the synthesis of Reboxetine (**1**).[10g] By using appropriate hands of epichlorohydrin, one can access both enantiomers of Reboxetine (**1**) efficiently.

Other than the synthesis of **1**, we also found that this type of electrophilic MCR can be applied to the total synthesis of the

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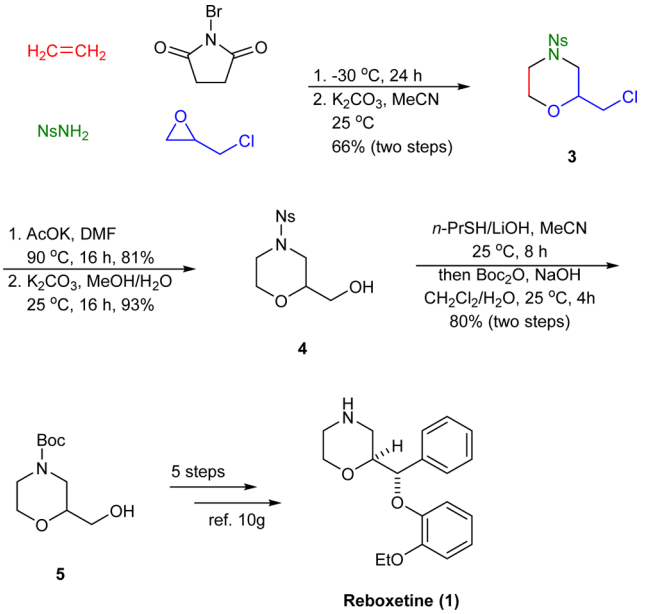
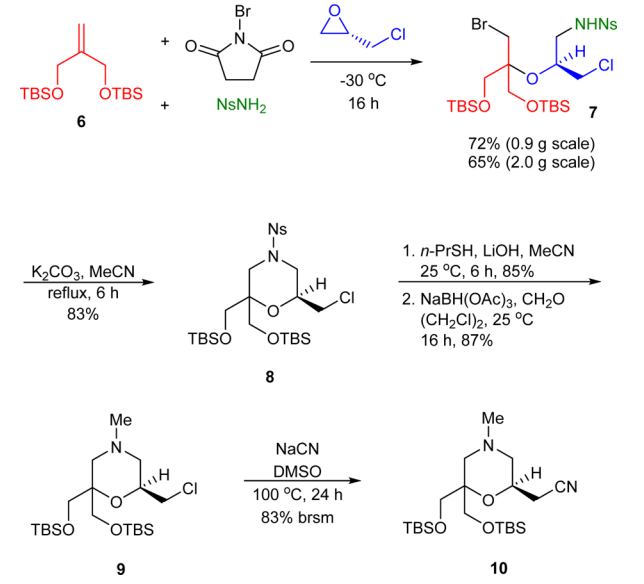
Scheme 2. Formal Synthesis of Reboxetine (1)



carnitine acetyltransferase inhibitor **2**. Toward the enantioselective synthesis of **2**, we first reacted the olefinic partner with enantiopure (*S*)-epichlorohydrin, NBS, and $NsNH_2$ to construct the morpholine core. After screening some olefins, it was found that **6** was suitable, which gave rise to **7** in 72% yield (6:1 regioselectivity) (Scheme 3). The unreacted (*S*)-

Scheme 3. NBS-Induced MCR in the Synthesis of 2-Substituted Morpholines

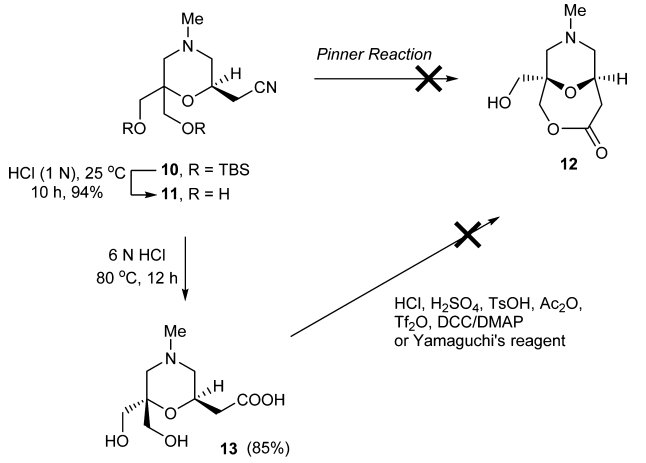


epichlorohydrin was recovered by a simple distillation. Attempt to scale up the reaction (using 2 g of olefin **6**) returned with comparable reaction yield of 65%. Subsequent treatment of **7** with base under reflux furnished the multifunctionalized morpholine **8** in 83% yield.

Next, we attempted to substitute the chloride with cyanide. However, it was found that chloride **8** was inert toward the substitution. The *N*-nosyl group in **8** was then removed to give the corresponding free amine, which was then methylated to give *N*-methyl morpholine **9**. Subsequent treatment of **9** with sodium cyanide in DMSO at 100 °C accomplished **10**. The cyanide group in **10** is a precursor for the introduction of carboxylate group at the later stage.

Global desilylation of **10** gave diol **11** in excellent yield (Scheme 4). The structure of **11** was confirmed by an X-ray

Scheme 4. Attempts to Synthesize 12



crystallographic study. Attempt to differentiate the two hydroxyl groups by transforming **11** into lactone **12** via Pinner reaction was not successful; carboxylic acid **13** was isolated in 85% yield when heating **11** in 6 N HCl for 12 h. Further trials to dehydrate **13** aiming to synthesize lactone **12** using various reagents were also fruitless. We suspected that the rigidity of the seven-membered ring lactone might disfavor the cyclization process.[11]

After extensive experimentations, it was found that treatment of **11** with 1.0 equiv of *n*-BuLi followed by 1.0 equiv of *p*-TsCl gave tosylate **14** (R = *p*-Ts) in 81% yield with the desired isomer **14a** as the major product (**14a**:**14b** = 9:1, R = *p*-Ts) (Scheme 5). Interestingly, when MsCl was used in the same reaction, isomer **14b** (R = Ms) was obtained as the major product (**14a**:**14b** = 1:4, R = Ms). We speculate that the *n*-butyl lithium might first coordinate to the nitrogen in **11** to give complex **A**. Because of the close proximity of the *n*-BuLi and the axial methylene OH, the deprotonation might proceed to give lithium alkoxide **B**.[5a,12] The relatively smaller size MsCl might be able to react with the axial alkoxide in **B** to yield **14b**. On the other hand, the reaction between **B** and the bulkier *p*-TsCl might be disfavored. Instead, **B** could isomerize to **C**, which contains an equatorial OLi, and then react with *p*-TsCl to yield **14a**. At this point, the two hydroxyl groups were differentiated, which is important for the subsequent functionalization.

After silylation of the hydroxyl group in **14a**, the OTs group in **15** was removed by heating it with sodium boronhydride in DMSO at 100 °C (Scheme 6). Treating **16** with MeI gave quaternary ammonium salt **17** in 91% yield. Finally, subjecting **17** in 6 N HCl at reflux transformed the cyanide into a carboxylic acid. The silyl protection was also removed under the same conditions. Workup of the reaction mixture with aqueous base accomplished the desired carnitine acetyltransferase inhibitor **2** in 72% yield.

In summary, we have successfully applied the NBS-induced electrophilic MCR in the formal synthesis of the antidepressant

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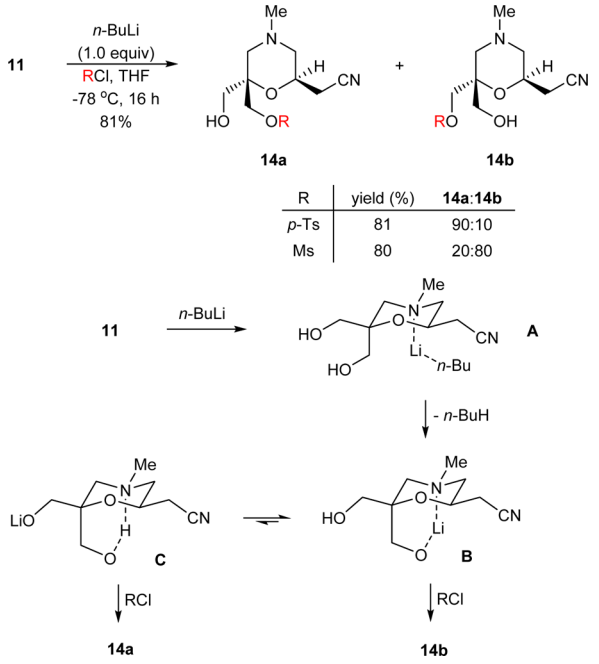
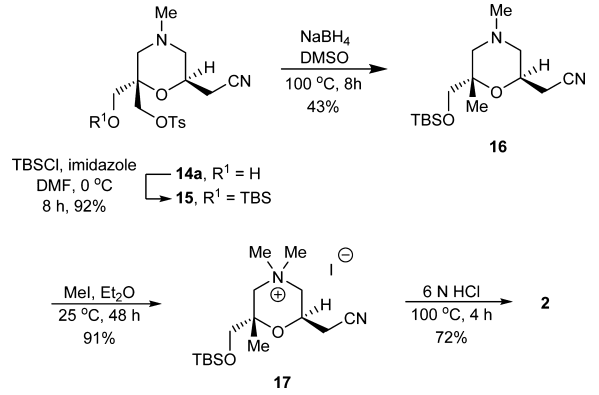
Scheme 5. Selective Tosylation of 11



Scheme 6. Enantioselective Synthesis of 2



drug Reboxetine (**1**) intermediate. In addition, the enantioselective synthesis of carnitine acetyltransferase inhibitor 2,6,6-trisubsituted morpholine **2** was accomplished by using (*S*)-epichlorohydrin as the nucleophilic partner. This approach not only provides an efficient approach toward biologically relevant 2-subsituted morpholine systems, but also offers flexibility in making drug analogues for further biological studies.

EXPERIMENTAL SECTION

Materials and Methods. All reactions that required anhydrous conditions were carried by standard procedures under nitrogen atmosphere. Commercially available reagents and solvents were used without further treatment. Tetrahydrofuran (THF) was freshly distilled prior to use from sodium/benzophenone ketyl under N_2. CH_2Cl_2 was freshly distilled from CaH_2. Thin-layer chromatography (TLC) was performed using precoated silica gel foils, and compounds were visualized with a spray of 5% (w/v) dodecamolybdophosphoric acid in ethanol and subsequent heating. Chromotographic purification was performed on silica gel (0.040−0.063 mm). ^{1}H and ^{13}C NMR spectra were either recorded on spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei or 500 MHz for proton and 125 MHz for carbon nuclei. Data for ^{1}H NMR spectra are reported as follows: chemical shift δ ppm (multiplicity, coupling constant (Hz), integration). Data for ^{1}H NMR spectra are referenced to the centerline of $CDCl_3$ δ 7.26) as the internal standard. Data for ^{13}C NMR spectra are referenced to the centerline of $CDCl_3$ (δ 77.0). High resolution mass spectra were obtained on spectrometer in ESI or EI mode using a TOF mass analyzer.

Formal Synthesis of Reboxetine (1) Intermediate. *2-Chloromethyl-4-nosylmorpholine (**3**).* Nosylamide (202 mg, 1.0 mmol) and NBS (214 mg, 1.2 mmol) were dissolved in epichlorohydrin (2 mL) at −30 °C. With the protection of N_2, ethylene gas was then bubbled into the solution for 2 h. After stirring at the same temperature for 24 h, the reaction was quenched by saturated sodium sulfite solution (1 mL). The mixture was then extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with brine (1 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude bromoether product was used in the next step without further purification.

To the crude bromoether product was added CH_3CN (10 mL) and K_2CO_3 (276 mg, 2.0 mmol) at 25 °C. The resultant mixture was then stirred for 16 h. Upon completion, the reaction was quenched by adding water (3 mL). The mixture was extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 5:1) to give compound morpholine **3** (211 mg, 66% for 2 steps) as solid: mp 132−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 4.05−3.93 (m, 1H), 3.87−3.77 (m, 2H), 3.73 (td, J = 11.5, 2.7 Hz, 1H), 3.67−3.58 (m, 1H), 3.55 (dd, J = 11.7, 4.7 Hz, 1H), 3.46 (dd, J = 11.7, 5.9 Hz, 1H), 2.53 (td, J = 11.5, 3.4 Hz, 1H), 2.34 (t, J = 11.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 141.4, 128.9, 124.5, 74.4, 66.0, 48.0, 45.2, 43.6; IR (KBr) 3108, 2992, 1528, 1352, 1177, 1107 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{13}ClN_2O_5S$ $[M]^+$ 320.0234, found 320.0226.

*2-Hydroxymethyl-4-nosylmorpholine (**4**).* To a solution of morpholine **3** (160 mg, 0.5 mmol) in DMF (5 mL) was added potassium acetate (490 mg, 5 mmol) at 25 °C. Under the protection of N_2, the reaction mixture was stirred at 90 °C for 16 h. Upon completion, the reaction was quenched by adding water (2 mL). The mixture was extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 3:1) to give 2-Acetoxymethyl-4-nosylmorpholine (139 mg, 81%) as a light-yellow solid: mp 95−97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 4.06 (qd, J = 11.8, 5.2 Hz, 2H), 3.98 (dd, J = 11.8, 1.9 Hz, 1H), 3.82−3.77 (m, 1H), 3.75−3.66 (m, 2H), 3.61 (d, J = 11.4 Hz, 1H), 2.51 (td, J = 11.5, 3.4 Hz, 1H), 2.26 (t, J = 10.9 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 150.4, 141.4, 128.9, 124.5, 73.0, 65.9, 64.0, 47.3, 45.3, 20.7; IR (KBr) 3111, 2980, 1749, 1542, 1351, 1248, 1167 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}N_2O_7S$ $[M]^+$:344.0678, found 344.0690.

2-Acetoxymethyl-4-nosylmorpholine (172 mg, 0.5 mmol) was dissolved in CH_3OH/H_2O (5 mL, 1:1 v/v) and K_2CO_3 (207 mg, 1.5 mmol) was added at 25 °C. The reaction mixture was stirred at the same temperature for 16 h. The mixture was then extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 1:1) to give **4** (140 mg, 93%) as a light-yellow powder: mp 173−174 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.47 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.9 Hz, 2H), 3.94 (ddd, J = 11.5, 3.2, 1.3 Hz, 1H), 3.72−3.67 (m, 1H), 3.64 (td, J = 11.5, 2.7 Hz, 1H), 3.61−3.46 (m, 4H), 2.47 (td, J = 11.5, 3.4 Hz, 1H), 2.26 (dd, J = 11.5, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, MeOD) δ 152.0, 142.6, 130.4, 125.6, 77.1, 67.0, 63.6, 46.9; IR (KBr) 3450, 3114, 2921, 1530, 1350, 1176 cm^{-1} HRMS (EI) calcd for $C_{11}H_{14}N_2O_6S$ $[M]^+$:302.0573, found 302.0575.

*2-Hydroxymethyl-4-bocmorpholine (**5**).* A mixture of compound **4** (121 mg, 0.4 mmol), lithium hydroxide monohydrate (84 mg, 2.0 mmol) and 1-propanethiol (18 μL, 2.0 mmol) was stirred at 25 °C in CH_3CN (4 mL) for 8 h. After the reaction was complete, the solvent

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was evaporated. The mixture was used in the next step without further purification.

The mixture was dissolved in CH_2Cl_2/H_2O (8 mL, 1:1 v/v). NaOH (32 mg, 0.8 mmol) and Boc_2O (174 mg, 0.8 mmol) were added subsequently. The resultant mixture was stirred at 25 °C for 4 h. The mixture was then extracted with EtOAc (10 mL × 3). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 1:1) to afford morpholine **5** (70 mg, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88−3.86 (m, 3H), 3.69−3.44 (m, 4H), 2.90 (bs, 1H), 2.72 (bs, 1H), 2.34 (t, J = 5.4 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 80.2, 75.8, 66.4, 63.5, 28.4; MS (EI) 217 m/z. (The physical data are in full accordance with the literature **10g**.)

Enantioselective Total Synthesis of 2. *3-tert-Butyldimethylsilyoxy-2-(tert-butyldimethylsilyoxy)methylpropene (**6**).* To a stirred solution of dihydroxyacetone dimer (2.0 g, 11.1 mmol) and imidazole (4.0 g, 58.8 mmol) in DMF (16 mL) was added *tert*-butyldimthylsilyl chloride (8.8 g, 58.4 mmol) portion-wise at 0 °C. After stirring at 25 °C for 6 h, the reaction was quenched by water (10 mL). The mixture was then extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4, and filtered. After filtration through a short plug of silica, ketone **S2** was used in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (s, 4H), 0.92 (s, 18H), 0.09 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 67.9, 25.8, 18.3, −5.6 ppm.

To a stirred solution of methyltriphenylphosphonium bromide (10.0 g, 28.1 mmol) in THF (300 mL), NaHMDS (2.0 M in THF, 26.2 mmol, 13.1 mL) was added dropwise at 0 °C. After stirring at the same temperature for 30 min, ketone **S2** obtained from the previous step was then added dropwise. The mixture was further stirred for 4 h at 25 °C, after which water (30 mL) was added to quench the reaction. The mixture was extracted with EtOAc (50 mL × 3). The combined organic extracts were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by passing through a short plug of silica eluted with Hexane:EtOAc (50:1) to give the desired product **6** (6.4 g, 91% for two steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (t, J = 1.3 Hz, 2H), 4.16 (t, J = 1.3 Hz, 4H), 0.91 (s, 18H), 0.07 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 109.0, 63.9, 25.9, 18.4, −5.4 ppm.

*(−)-(2S)-N-Nosylate-2-[1-bromo-2,2-bis((tert-butyldimethylsilyoxy)methyl)ethan-2-yloxy]-3-chloropropan-1-amine (**7**).* Into the mixture of nosylamide (505 mg, 2.5 mmol), NBS (534 mg, 3 mmol) and (*S*)-epichlorohydrin (5 mL) was added olefin **6** (948 mg, 3 mmol) at −30 °C. After stirring at the same temperature for 16 h, the reaction was quenched by saturated sodium sulfite solution (5 mL). After recovery of the excessive (*S*)-epichlorohydrin by distillation, the mixture was extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 10:1) to give **7** (1.3 g, 72%) as a semisolid: mp 84−88 °C; $[\alpha]_D^{26}$ −7.7 (c 1.0, $CHCl_3$, 99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 5.42 (t, J = 6.0 Hz, 1H), 4.20 (m, 1H), 3.73−3.32 (m, 9H), 3.21(m, 1H), 0.89 (s, 9H) 0.88(s, 9H), 0.09(s, 3H), 0.08(s, 3H), 0.07(s, 3H), 0.06(s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl3) δ 150.1, 145.8, 128.4, 124.4, 80.3, 71.6, 63.4, 63.1, 45.0, 43.3, 34.4, 25.8, 25.8, 18.2, 18.1, −5.6, −5.6 ppm; IR (KBr) 3287, 2956, 2858, 1528, 1346, 1169, 1091, 838 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{46}BrClN_2NaO_7SSi_2$ [M + Na]$^+$ 711.1328, found 711.1346. The enantiopurity of 4 was determined by HPLC analysis: Daicel Chiralpak IA, *i*-PrOH/hexane =5/95, 0.5 mL/min, 254 nm; t = 19.369 (major), t = 22.082 (minor).

*(+)-(6S)-2,2-Bis((tert-butyldimethylsilyloxy)methyl)-6-chloromethyl-4-nosylmorpholine (**8**).* The CH_3CN (15 mL) solution of compound 7 (1.0 g, 1.5 mmol) and K_2CO_3 (414 mg, 3.0 mmol) was heated under reflux for 6 h. After cooling to room temperature, the mixture was extracted with EtOAc (10 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 20:1) to give morpholine **8** (760 mg, 83%) as a semisolid: mp 116.1−118.3 °C; $[\alpha]_D^{26}$ +6.7 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 4.04 (m, 1H), 3.86 (d, J = 11.1 Hz, 1H), 3.80 (dd, J = 10.5, 15.2 Hz, 2H), 3.67(m, 2H), 3.49 (dd, J = 4.4, 11.4 Hz, 1H), 3.33 (m, 2H), 2.25 (d, J = 11.7 Hz, 1H), 2.12(t, J = 10.8 Hz, 1H), 0.91 (s, 9H), 0.84 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 141.5, 128.9, 124.4, 76.7, 68.8, 64.9, 58.5, 48.1, 47.0, 44.0, 25.79, 25.77, 18.20, 18.18, −5.41, −5.45, −5.49, −5.54 ppm; IR (KBr) 2957, 2858, 1528, 1356, 1172, 1102, 835 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{36}ClN_2O_7SSi_2$ [M − t-Bu]$^+$ 551.1470, found 551.1466.

*(+)-(6S)-2,2-Bis((tert-butyldimethylsilyloxy)methyl)-6-chloromethyl-4-methylmorpholine (**9**).* A mixture of compound **8** (1.0 g, 1.6 mmol), lithium hydroxide monohydrate (344 mg, 8.2 mmol) and 1-propanethiol (742 μL, 8.2 mmol) was stirred at 25 °C in CH_3CN (15 mL) for 6 h. The reaction was then quenched with water (5 mL), extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 5:1) to give 2,2-Bis((*tert*-butyldimethylsilyloxy)methyl)-6-chloromethylmorpholine (590 mg, 85%) as a clear oil: $[\alpha]_D^{26}$ +3.1 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (m, 1H), 3.93 (d, J = 10.4 Hz, 1H), 3.79 (d, J = 10.4 Hz, 1H), 3.55 (d, J = 9.8 Hz, 1H), 3.43 (dd, J = 5.1, 11.1 Hz, 1H), 3.33 (m, 2H), 3.07 (dd, J = 2.1, 12.2 Hz, 1H), 2.98 (d, J = 13.0 Hz, 1H), 2.60 (d, J = 13.0 Hz, 1H), 2.47 (t, J = 11.5 Hz, 1H), 0.90 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H), 0.03 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.4, 70.4, 66.1, 61.6, 48.9, 48.1, 45.3, 25.9, 25.8, 18.21, 18.18, −5.43, −5.46, −5.50, −5.52 ppm; IR (neat) 3319, 2956, 2858, 1472, 1257, 1216, 1105, 759 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{43}ClNO_3Si_2$ [M + H]$^+$ 424.2465, found 424.2466.

To a solution of 2,2-Bis((*tert*-butyldimethylsilyloxy)methyl)-6-chloromethylmorpholine (850 mg, 2.0 mmol) in 1,2-dichloroethane (20 mL) was added formaldehyde (37% aqueous solution, 0.17 mL, 2.2 mmol) and $NaBH(OAc)_3$ (466 mg, 2.2 mmol) at 25 °C. After stirring at the same temperature for 16 h, the mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduce pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 6:1) to give morpholine **9** (762 mg, 87%) as a clear oil: $[\alpha]_D^{26}$ +7.0 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.92 (d, J = 10.4 Hz, 1H), 3.72 (m, 2H), 3.49 (dd, J = 4.9, 11.0 Hz, 1H), 3.34 (m, 2H), 2.88 (d, J = 10.8 Hz, 1H), 2.70 (d, J = 11.6 Hz, 1H), 2.22 (s, 3H), 1.79 (d, J = 11.6 Hz, 1H), 1.71 (t, J = 10.8 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 76.9, 69.7, 65.4, 59.2, 58.2, 57.3, 46.6, 45.1, 25.9, 18.27, 18.24, −5.39, −5.42 ppm; IR (neat) 3020, 2956, 2857, 1216, 758 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{45}ClNO_3Si_2$ [M + H]$^+$ 438.2621, found 438.2621.

*(−)-(6R)-2,2-Bis((tert-butyldimethylsilyloxy)methyl)-6-cyanomethyl-4-methylmorpholine (**10**).* A mixture of compound **9** (1.0 g, 2.3 mmol) and NaCN (336 mg, 6.9 mmol) was stirred in DMSO (10 mL) at 110 °C for 24 h. The mixture was then extracted with EtOAc (5 mL × 5). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 5:1) to give the starting material compound **9** (635 mg, 64%) and cyanide **10** (296 mg, 30%, brsm 83%) as a clear oil: $[\alpha]_D^{26}$ −1.9 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (m, 1H), 3.90 (d, J = 10.3 Hz, 1H), 3.72 (d, J = 10.3 Hz, 1H), 3.68 (d, J = 9.7 Hz, 1H), 3.34 (d, J = 9.7 Hz, 1H), 2.79 (d, J = 10.8 Hz, 1H), 2.70 (d, J = 11.7 Hz, 1H), 2.46 (m, 2H), 2.22 (s, 3H), 1.79 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.8, 65.6, 65.2, 59.2, 59.0, 56.8, 46.4, 25.86, 25.84, 22.5, 18.25, 18.21, −5.42, −5.45 ppm; IR (neat) 2953, 2857, 2247, 1468, 1255, 1104, 838, 777

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cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{45}N_2O_3Si_2$ $[M + H]^+$ 429.2961, found 429.2963.

*(−)-(6R)-2,2-Bis(hydroxymethyl)-6-cyanomethyl-4-methylmorpholine (**11**).* Cyanide **10** (900 mg, 2.1 mmol) was added into 1 N HCl aqueous solution (10 mL) and stirred at 25 °C for 10 h. After the reaction was completed, the solution was neutralized by saturated $NaHCO_3$ solution to pH 7. The aqueous solution was concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2:CH_3OH = 10:1) to give the diol **11** (395 mg, 94%) as a white solid: mp 105−107 °C; $[\alpha]_D^{23}$ −12.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (m, 1H), 3.94 (d, *J* = 11.7 Hz, 1H), 3.84 (d, *J* = 11.7 Hz, 1H), 3.52 (d, *J* = 11.6 Hz, 1H), 3.45 (d, *J* = 11.6 Hz, 1H), 2.83 (m, 1H), 2.80 (d, *J* = 11.7 Hz, 1H), 2.59 (dd, *J* = 5.8, 16.8 Hz, 1H), 2.50 (dd, *J* = 5.3, 16.8 Hz, 1H), 2.29 (s, 3H), 2.21 (d, *J* = 11.7 Hz, 1H), 1.96 (t, *J* = 10.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.4, 76.0, 66.7, 66.3, 66.0, 58.4, 56.6, 46.0, 22.8 ppm; IR (KBr) 2951, 2857, 2252, 1469, 1249, 1102, 844 cm^{-1}; HRMS (ESI) calcd for $C_9H_{16}N_2NaO_3$ $[M + Na]^+$ 223.1053, found 223.1063.

*(−)-(2S,6R)-2-Hydroxymethyl-2-tosyloxymethyl-6-cyanomethyl-4-methylmorpholine (**14a**).* To a solution of diol **11** (400 mg, 2.0 mmol) in THF (10 mL) was added *n*-BuLi (1.6 M in hexane, 1.3 mL, 2 mmol) dropwise at −78 °C. After stirring the solution at the same temperature for 30 min, a solution of TsCl (382 mg, 2 mmol) in THF (2 mL) was added dropwise. The reaction was further stirred at −78 °C for 16 h. The temperature was then raised to 0 °C and water (3 mL) was added to quench the reaction. The mixture was then extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2:CH_3OH = 10:1, **14a** R_f = 0.30, **14b** R_f = 0.35) to give tosylate **14a** (517 mg, 73%) as a semisolid: mp 99−101 °C; $[\alpha]_D^{23}$ −2.8 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.25 (m, 1H), 3.99 (d, *J* = 12.0 Hz, 1H), 3.91 (d, *J* = 10.0 Hz, 1H), 3.82 (d, *J* = 10.0 Hz, 1H), 3.71 (d, *J* = 12.0 Hz, 1H), 2.81 (m, 2H), 2.45 (m, 5H), 2.25 (s, 3H), 2.01 (d, *J* = 11.7 Hz, 1H), 1.88 (t, *J* = 10.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 132.3, 130.0, 128.0, 116.3, 74.9, 71.0, 66.6, 63.0, 58.3, 56.7, 46.0, 22.5, 21.6 ppm; IR (KBr) 2947, 2828, 2247, 1598, 1465, 1355, 1172, 1073, 849 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}N_2NaO_5S$ $[M + Na]^+$ 377.1142, found 377.1150.

*(+)-(2S,6R)-2-tert-Butyldimethylsilyloxymethyl-2-tosyloxymethyl-6-cyanomethyl-4-methylmorpholine (**15**).* To a stirred solution of tosylate **14a** (350 mg, 1 mmol) and imidazole (204 mg, 3 mmol) in DMF (2 mL) was added *tert*-butyldimthylsilyl chloride (225 mg, 1.5 mmol) at 0 °C. After stirring at 25 °C for 8 h, the reaction was quenched by adding water (1 mL). The mixture was then extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 5:1) to give morpholine **15** (430 mg, 92%) as a clear oil: $[\alpha]_D^{23}$ + 3.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (*J* = 8.2 Hz, 2H), 3.99 (d, *J* = 9.7 Hz, 1H), 3.94 (m, 1H), 3.87 (d, *J* = 9.7 Hz, 1H), 3.80 (d, *J* = 10.2 Hz, 1H), 3.73 (d, *J* = 10.2 Hz, 1H), 2.73 (d, *J* = 10.8 Hz, 1H), 2.69 (d, *J* = 11.6 Hz, 1H), 2.43 (s, 3H), 2.37 (m, 2H), 2.21 (s, 3H), 1.84 (d, *J* = 11.6 Hz, 1H), 1.78 (t, *J* = 10.8 Hz, 1H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 132.7, 129.8, 128.0, 116.4, 75.7, 71.2, 66.1, 59.4, 58.5, 55.0, 46.1, 25.7, 22.3, 21.6, 18.0, −5.6, −5.7 ppm; IR (KBr) 2951, 2856, 2253, 1599, 1465, 1363, 1178, 1098, 839 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{36}N_2NaO_5SSi$ $[M + Na]^+$ 491.2006, found 491.2021.

*(+)-(2S,6R)-2-(−6-((tert-Butyldimethylsilyloxy)methyl)-4,6-dimethylmorpholin-2-yl)acetonitrile (**16**).* A mixture of morpholine **15** (200 mg, 0.43 mmol) and $NaBH_4$ (82 mg, 2.15 mmol) in DMSO (5 mL) was heated at 100 °C for 8 h. The reaction was then cooled to 25 °C and quenched by adding water (1 mL). The resultant mixture was extracted with EtOAc (5 mL × 4). The combined organic extracts were washed with brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane:EtOAc = 6:1) to give the morpholine **16** (55 mg, 43%) as a colorless oil: $[\alpha]_D^{25}$ + 11.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.99 (m, 1H), 3.89 (d, *J* = 9.3 Hz, 1H), 3.51 (d, *J* = 9.3 Hz, 1H), 2.77 (m, 2H), 2.48 (dd, *J* = 5.7, 16.7 Hz, 1H), 2.43 (dd, *J* = 6.3, 16.7 Hz, 1H), 2.22 (s, 3H), 1.77 (t, *J* = 10.8 Hz, 1H), 1.68 (d, *J* = 11.7 Hz, 1H), 1.13 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 116.9, 75.3, 66.0, 63.6, 59.6, 59.0, 46.1, 25.8, 23.6, 22.8, 18.2, −5.4, −5.5 ppm; IR (neat) 2932, 2856, 2360, 1462, 1255, 1100, 853, 777 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{31}N_2O_2Si$ $[M + 1]^+$ 299.2149, found 299.2152.

*(+)-(2S,6R)-2-((tert-Butyldimethylsilyloxy)methyl)-6-(cyanomethyl)-2,4,4-trimethylmorpholin-4-ium iodide (**17**).* Morpholine **16** (40 mg, 0.13 mmol) was dissolved in anhydrous Et_2O (5 mL) and MeI (185 mg, 1.3 mmol) was then added. The mixture was stirred at 25 °C for 2 d. The precipitate (54 mg, 91%) formed was then filtered, and washed with anhydrous Et_2O to give iodide salt **17** as a white solid: mp 193−195 °C; $[\alpha]_D^{25}$ + 13.6 (*c* 1.0, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.65 (m, 1H), 4.13 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 1.8, 13.5 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 3.60 (d, *J* = 10.9 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.25 (m, 1H), 3.18 (d, *J* = 13.5 Hz, 1H), 2.88 (dd, *J* = 4.6, 17.1 Hz, 1H), 2.78 (dd, *J* = 6.5, 17.1 Hz, 1H), 1.34 (s, 3H), 0.96 (s, 9H), 0.16 (s, 6H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 117.1, 75.4, 65.7, 63.4, 63.4, 59.5, 51.5, 27.3, 27.2, 26.3, 22.3, 19.0, −5.3, −5.5 ppm; IR (KBr) 2928, 2850, 2253, 1470, 1257, 1098, 849, 777 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{33}N_2O_2Si$ $[M - I]^+$ 313.2306, found 313.2316.

*(+)-(2S,6R)-6-(Hydroxymethyl)-4,4,6-trimethylmorpholin-4-ium-2-yl)acetate (**2**).* Compound **17** (50 mg, 0.11 mmol) in 6 N HCl (4 mL) was refluxed for 4 h. 5% aqueous NaOH was added to neutralize the mixture to pH 7. The product was purified following the same procedure reported. Compound **2** was obtained (18 mg, 72%): $[\alpha]_D^{23}$ +21.2 (*c* 0.05, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.55 (m, 1H), 3.85 (d, *J* = 11.9 Hz, 1H), 3.78 (dd, *J* = 1.8, 13.4 Hz, 1H), 3.68 (d, *J* = 11.8 Hz, 1H), 3.58 (ddd, *J* = 1.8, 1.9, 12.6 Hz, 1H), 3.33 (s, 3H), 3.27 (s, 3H), 3.13 (dd, *J* = 11.9, 13.6 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 2.45 (dd, *J* = 6.9, 15.5 Hz, 1H), 2.33 (dd, *J* = 6.1, 15.5 Hz, 1H), 1.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 177.2, 74.7, 65.0, 64.9, 63.8, 59.4, 51.4, 42.1, 26.8 ppm; HRMS (ESI) calcd for $C_{10}H_{20}NO_4$ $[M + 1]^+$ 218.1387, found 218.1386. (The physical data are in full accordance with the literature **5a**.)

■ ASSOCIATED CONTENT

Supporting Information

CIF files of **3** and **11**, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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