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Intramolecular reductive amination strategy to the synthesis of (*R*)-*N*-Boc-2-hydroxymethylmorpholine, *N*-(3,4-dichlorobenzyl)(*R*)-2-hydroxymethylmorpholine, and (*R*)-2-benzylmorpholine

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ABSTRACT

A concise high yielding enantioselective synthesis of (*R*)-*N*-Boc-2-hydroxymethylmorpholine, *N*-(3,4-dichlorobenzyl)(*R*)-2-hydroxymethylmorpholine, and (*R*)-benzylmorpholine has been achieved by employing proline-catalyzed asymmetric α-aminooxylation of aldehyde and palladium-catalyzed intramolecular reductive amination of azido aldehyde as the key steps.

1. Introduction

The 2-substituted chiral morpholine skeleton present in number of pharmacologically highly active molecules[1] such as, (*S*,*S*)-reboxetine **1**,[2] NAS-181 **2**,[3] urea **3**,[4] (*R*)-2-benzylmorpholine **4**[5] etc. (Fig. 1). These compounds exhibit wide range of application in the treatment of depression,[2] obesity,[5] asthma, and rhinitis[4] etc. Enantiomerically pure (*R*)-*N*-Boc-2-hydroxymethylmorpholine **5** and its enantiomer are attractive chiral building blocks for the synthesis of variety of pharmacologically active compounds.[7] (*R*)-*N*-Boc-2-hydroxymethylmorpholine **5** can be used as a useful chiral intermediate for the synthesis of 5-HT_{1B} receptor antagonist NAS-181 **2**, since (*R*)-*N*-trityl derivative of morpholine **5** is a known precursor of NAS-181 **2**.[3a] (*R*)-**5** has also been used in the preparation of 2-aryloxymethylmorpholine benzamide 5-HT4 stimulators[3b] and histamine H_3 antagonists,[3c] whereas the (*S*)-**5** is a versatile intermediate in the synthesis of (*S*,*S*)-reboxetine[6] and many other morpholines.[8] The urea based morpholine **3** and (*R*)-2-benzylmorpholine **4** are potent antagonist of CCR3 and appetite suppressant agent, respectively, which has potential therapeutic applications.[4,5]

Despite significant pharmacological activity and widespread utility of **4**–**6**, very few enantioselective synthesis of (*R*)-**4**, (*R*)-**5**, (*S*)-**5**, and (*R*)-**6** are known in the literature.[5,6,9–11] Tamagnan and co-workers and Henegar have reported synthesis of (*S*)-**5** from (*S*)-3-amino-1,2-propanediol[6] and (*S*)-epichlorohydrin,[10] respectively. Wilkinson and co-workers reported synthesis of **6** by using

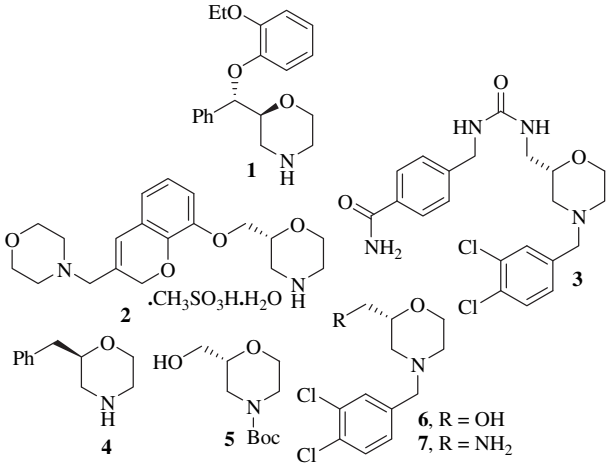

Figure 1. Pharmacologically active 2-substituted morpholines and their intermediate.

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palladium-catalyzed asymmetric allylic substitution as a part of a synthesis of aminomethylmorpholine **7**.[11a] Only two enantioselective synthesis of **4** have been reported, which involve resolution of racemic **4** using (−)-dibenzoyl tartaric acid[5a] and chemo-enzymatic reduction of (*Z*)-α-bromocinnamaldehyde using bakers yeast.[5b] Most of these methods for the synthesis of **4**–**6** involve either a lengthy chiral pool approach or use of expensive transition metal catalyst or chiral starting materials or low yielding and tedious classical or enzymatic resolution approach. Toward this end, a simple, inexpensive and eco-friendly practical route to the synthesis of enantiomerically pure **4**–**6** from achiral substrate is highly desirable.

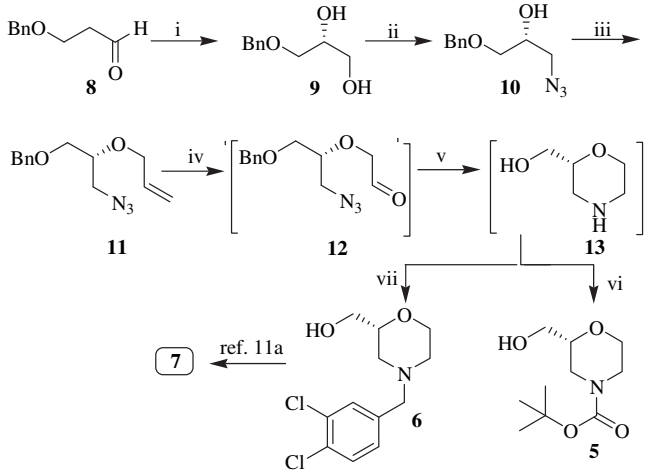
As part of our research program aimed toward the development of new strategy for the enantioselective synthesis of biologically active compounds and their chiral key intermediates[12] based on proline-catalyzed asymmetric α-aminooxylation of aldehydes,[13] we were encouraged to design a short and effective route to 2-substituted chiral morpholines. Herein we report a novel high yielding enantioselective synthesis of (*R*)-**4**–**6** by employing proline-catalyzed asymmetric α-aminooxylation of aldehyde and palladium-catalyzed intramolecular reductive cyclization of azido aldehyde as the key steps to introduce chirality and to generate morpholine ring (Scheme 1 and 2).

2. Result and discussion

2.1. Synthesis of 2-hydroxymethylmorpholine (*R*)-5 and (*R*)-6

The synthetic sequence for the enantioselective synthesis of (*R*)-**5** and (*R*)-**6** is started with aldehyde **8**,[14] which was prepared by IBX oxidation of 3-benzyloxypropanol (Scheme 1). We planned to prepare chiral building block **9**[15] by using eco-friendly organocatalytic method to demonstrate the utility of asymmetric α-aminooxylation reaction.[13a] Thus, aldehyde **8** was treated with nitrosobenzene in the presence of D-proline in CH_3CN at −20 °C followed by in situ reduction with $NaBH_4$ in methanol to afford aminoxy alcohol. The crude aminooxy intermediate was treated with 30 mol % $CuSO_4 \cdot 5H_2O$ in methanol to cleave the O–N bond to afford diol **9**[15] in 66% yield. Selective tosylation[16] of primary hydroxyl group was achieved using catalytic amount of dibutyltin oxide (2 mol %) and *p*-toluenesulfonyl chloride. The crude monotosylate was treated with sodium azide in dry DMF to afford azido alcohol **10**[17] in 88% yield (over two steps) and >95% *ee* (determined by ^1H NMR analysis of its Mosher's ester). The hydroxyl group of azido alcohol **10** was alkylated with allyl bromide in DMF using sodium hydride to afford azido allyl ether **11** in quantitative yield (97%), which on exposure to potassium osmate mediated dihydroxylation and subsequent oxidative cleavage of the ensuing diol using $NaIO_4$ resulted in a crucial azido aldehyde **12**.

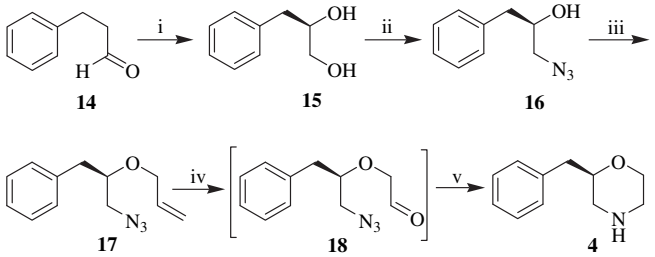
Our next aim was to construct morpholine skeleton through intramolecular reductive amination. The palladium-catalyzed intramolecular reductive amination of crude azido aldehyde **12** underwent smoothly in the presence of hydrogen atmosphere using Pd/C (10%) at 100 psi in MeOH to afford morpholine **13**, subsequent *N*-Boc-protection with $(Boc)_2O$ using $NaHCO_3$ in dioxane/water (3:1) gave *N*-Boc-morpholine (*R*)-**5** in 57% yield (over four steps) and >95% *ee*. Where as, synthesis of *N*-benzylmorpholine (*R*)-**6** was achieved by the treatment morpholine **12**, with 3,4-dichlorobenzyl bromide using K_2CO_3 in CH_3CN to afford (*R*)-**6** in 54% yield (over four steps) (Scheme 1). The synthesis of aminomethylmorpholine core **7** of CCR3 antagonist **3** from (*R*)-**6** has already been reported in the literature.[11a]



Scheme 1. Reagents and conditions: (i) (a) PhNO, D-proline (25 mol %), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$, 30 min, (b) $CuSO_4$ (30 mol %), MeOH, 0 °C, 12 h, 66% (over two steps); (ii) (a) dibutyltin oxide (2 mol %), *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, (b) NaN_3, DMF, 70 °C, 10 h, 89% (over two steps); (iii) allyl bromide, NaH, DMF, 0 °C 1.5 h, 97%; (iv) (a) $K_2OsO_4.H_2O$ (2 mol %), NMO, acetone:H_2O (8:2), rt, 12 h, (b) $NaIO_4$, acetone:H_2O (9:1), rt, 4 h, (v) H_2 (100 psi), Pd/C (10%), MeOH, rt, 24 h, (vi) $(Boc)_2O$, dioxane:H_2O (3:1), $NaHCO_3$, 0 °C to rt, 4.5 h, (57% over four steps), (vii) 3,4-dichlorobenzyl bromide, K_2CO_3, CH_3CN, rt, 5 h (54% over four steps).

2.2. Synthesis of (*R*)-2-benzylmorpholine 4

Similarly, enantioselective synthesis of (*R*)-2-benzylmorpholine **4** was completed with the same reaction sequence as described for the synthesis of morpholine (*R*)-**5** and (*R*)-**6** from readily available 3-phenylpropanaldehyde **14**. The L-proline catalyzed asymmetric α-aminooxylation of aldehyde **13** afforded diol **15** in 69% yield. Selective tosylation[16] of diol **15** followed by displacement of corresponding tosylate with sodium azide in dry DMF gave azido alcohol **16**[19] in 88% yield (over two steps) and >95% ee (determined by ^1H NMR analysis of its Mosher's ester). Allylation of alcohol **16** was accomplished using sodium hydride in dry DMF at 0 °C to afford azido allyl ether **17** in 98% yield. The dihydroxylation followed by subsequent oxidative cleavage of olefin **17** gave crucial azido aldehyde **18**, which on palladium-catalyzed intramolecular reductive amination using 10% Pd/C/H_2 (1 atm) in MeOH afforded (*R*)-2-benzylmorpholine **4** in 57% yield (over three steps) and >95% ee (Scheme 2). All the compounds **4**–**18** were fully characterized by spectroscopic technique. The spectral and analytical data of morpholine (*R*)-**4** and (*R*)-**5** were found to be in good agreement with literature data.[5b,6]



Scheme 2. Reagents and conditions: (i) (a) PhNO, L-proline (25 mol %), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$, 30 min, (b) H_2 (1 atm), Pd/C (10%), MeOH, 10 h, 69% (over two steps); (ii) (a) dibutyltin oxide (2 mol %), *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (b) NaN_3, DMF, 70 °C, 10 h, 88% (over two steps); (iii) allyl bromide, NaH, DMF, 0 °C, 1.5 h, 98%; (iv) (a) $K_2OsO_4.H_2O$(2 mol %), NMO, acetone:H_2O (8:2), rt, 10 h, (b) $NaIO_4$, acetone:H_2O (9:1), rt, 4 h; (v) H_2 (1 atm), Pd/C (10%), MeOH,12 h, 57% (over three steps).

3. Conclusion

In conclusion, a new and efficient enantioselective synthesis of (*R*)-*N*-Boc-2-hydroxymethylmorpholine, *N*-(3,4-dichlorobenzyl)-(*R*)-2-hydroxymethyl morpholine, and (*R*)-2-benzylmorpholine

has been achieved in 32%, 30%, and 33% overall yield, respectively. The proline-catalyzed asymmetric α-aminooxylation of aldehyde to introduce chirality and palladium-catalyzed intramolecular reductive cyclization of azido aldehyde to generate morpholine ring are the key steps involved in the present synthesis. Our strategy demonstrates the successful application of organocatalysis and reductive cyclization for the synthesis of chiral 2-substitituted morpholines and represent a good alternative to the known methods.

4. Experimental section

4.1. General experimental details

All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise noted, on Varian Mercury spectrometer at 300 and 75 MHz, respectively with TMS as an internal standard. IR spectra were recorded on Shimadzu FTIR 8400. Elemental analyses were carried out with Thermo-Electron Corporation CHNS analyzer, FLASH-EA 1112 at Shimadzu Analytical Centre, University of Pune. Thin layer chromatography was performed on Merck 60 F_{254} silica gel plates and column chromatography on silica gel of 100–200 mesh. Melting points were recorded with Thomas Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured on Jasco P-1020 digital polarimeter. Enantiomeric excesses were measured using either Mosher's ester or by comparison with specific rotation.

4.1.1. 3-Benzyloxypropionaldehyde ***8***[14]. A mixture of 3-benzyloxypropanol (3.0 g, 18.1 mmol) and IBX (6.5 g, 23.5 mmol) in DMSO (35 mL) was stirred for 3.5 h at room temperature, then water was added to the reaction mixture and 2-iodobenzoic acid was filtered off. The filtrate was extracted with ethyl acetate (3×25 mL), combined organic layer washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/hexane (10:90) afforded pure aldehyde **8** (2.57 g, 87%); as a colorless oil. [Found C, 73.34; H, 7.26%. $C_{10}H_{12}O_2$ required C, 73.15; H, 7.37%]; R_f (15% ethyl acetate/hexane) 0.50; ν_{max} (CH_2Cl_2) 2958, 2807, 2740, 1716, 1452, 1363, 1203, 1101, cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.67 (dt, 2H, J=1.8, 6.0 Hz), 3.79 (t, 2H, J=6.0 Hz), 4.51 (s, 2H), 7.28–7.32 (m, 5H), 9.75 (t, 1H, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$) 43.7, 63.7, 73.1, 127.5, 128.2, 137.5, 200.9.

4.1.2. (R)-3-(Benzyloxy)propane-1,2-diol ***9***. To a stirred solution of aldehyde **8** (2 g, 12.2 mmol) and nitrosobenzene (1 g, 9.34 mmol) in CH_3CN (25 mL) was added D-proline (0.27 mg, 2.33 mmol) at −20 °C. The reaction mixture was stirred for 24 h at the same temperature, then diluted with MeOH (15 mL) and to this solution was added $NaBH_4$ (1.06 g, 28 mmol). After 30 min, the reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3×30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The $CuSO_4 \cdot 5H_2O$ (0.7 g, 2.8 mmol) was added at 0 °C to the solution of crude product in MeOH (20 mL) and stirred for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×30 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography using ethyl acetate/hexane (35:65) to give pure diol **9** (0.73 g, 66%) as a viscous liquid. $[\alpha]_D^{25}$ +5.63 (*c* 20, $CHCl_3$), {lit.[15] $[\alpha]_D^{22}$ +5.5 (*c* 20, $CHCl_3$)}. [Found C, 65.83; H, 7.79%. $C_{10}H_{14}O_3$ required C, 65.91; H, 7.74%]; R_f (50% ethyl acetate/hexane) 0.20; ν_{max} ($CHCl_3$) 3414, 2928, 2872, 1082 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.15 (br s, 2H), 3.51–3.64 (m, 4H), 3.83–90 (m, 1H), 4.51 (s, 2H), 7.18–7.39 (m, 5H); δ_C (75 MHz, $CDCl_3$) 63.7, 70.7, 71.3, 73.7, 127.5, 128.2, 137.4.

4.1.3. (R)-1-Azido-3-(benzyloxy)propan-2-ol ***10***. To a stirred solution of diol **9** (0.7 g, 3.84 mmol) in dry CH_2Cl_2 (20 mL), dibutyltin oxide (18 mg, 0.08 mmol) was added Et_3N (0.54 mL, 3.91 mmol) at 0 °C. To this solution was added *p*-toluenesulfonyl chloride (0.75 g, 3.91 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. To a crude solution of tosylate (1.24 g, 3.69 mmol) in dry DMF (15 mL) was added sodium azide (0.53 g, 8.11 mmol) and stirred at 70 °C for 10 h, cooled to room temperature, diluted with water and extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate/hexane (10:90) to give pure azide **10** (0.7 g, 88%) as a colorless oil. $[\alpha]_D^{25}$ +11.7 (*c* 1.1, $CHCl_3$), {lit.[19] $[\alpha]_D^{25}$ +11.5 (*c* 1.1, $CHCl_3$)}. [Found C, 57.87; H, 6.54, N, 20.35%. $C_{10}H_{13}N_3O_2$ required C, 57.96; H, 6.32; N, 20.28%]; R_f (20% ethyl acetate/hexane) 0.25; ν_{max} ($CHCl_3$) 3433, 2104, 1267, 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.28 (br s, 1H), 3.30–3.39 (m, 2H), 3.45–3.54 (m, 2H), 3.91–3.98 (m, 1H), 4.54 (s, 2H), 7.29–7.36 (m, 5H); δ_C (75 MHz, $CDCl_3$) 53.4, 69.5, 71.2, 73.4, 127.6, 127.7, 128.3, 137.3.

4.1.4. General procedure for Mosher's ester preparation. To a stirred solution of alcohol (±)-**10**[20] or (+)-**10** (20 mg, 0.096 mmol), (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (24 mg, 0.106 mmol), and 4-dimethylaminopyridine (2 mg) in dry CH_2Cl_2 (3 mL) was added dropwise a solution of DCC (22 mg, 0.106 mmol) in CH_2Cl_2 (2 mL) at 0 °C under a nitrogen atmosphere and stirred at the same temperature for 30 min. Then reaction mixture was brought to room temperature and stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with saturated aqueous $NaHCO_3$ solution followed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate/hexane (4:96) to give Mosher's ester in 87% yield.

4.1.5. Mosher's ester of alcohol (±)- ***10***[20]. Colorless oil; R_f (10% ethyl acetate/hexane) 0.30; ^1H NMR (400 MHz, $CDCl_3$): δ 3.48–3.55 (m, 2H), 3.56 (s, 3H), 3.57 (s, 3H), 3.58–3.65 (m, 4H), 3.68–3.69 (m, 2H), 4.45 (AB quartet, 2H, J=12.0 Hz), 4.54 (AB quartet, 2H, J=12.0 Hz), 5.31–5.39 (m, 2H), 7.22–7.58 (m, 20H).

4.1.6. Mosher's ester of alcohol (+)- ***10***. Colorless oil; R_f (10% ethyl acetate/hexane) 0.30; ^1H NMR (400 MHz, $CDCl_3$): δ 3.50 (dd, 1H, J=6.4, 13.2 Hz), 3.54–3.58 (m, 1H), 3.56 (s, 3H), 3.68–3.69 (m, 2H), 4.54 (AB quartet, 2H, J=12.0 Hz), 5.35–5.38 (m, 1H), 7.29–7.57 (m, 10H).

4.1.7. 1-(((R)-2-(Allyloxy)-3-azidopropoxy)methyl)benzene ***11***. To a stirred suspension of NaH (0.15 g, 6.28 mmol) in dry DMF (15 mL) alcohol **10** (0.65 g, 3.14 mmol) in dry DMF (3 mL) was added at 0 °C, stirred for 5 min, followed by addition of allyl bromide (0.35 mL, 4.07 mmol). The resulting reaction mixture was stirred at same temperature for 1.5 h, quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using ethyl acetate/hexane (3:97) to give pure olefin **11** (0.75 g, 97%) as colorless oil. $[\alpha]_D^{25}$ −20.4 (*c* 1.2, $CHCl_3$). [Found C, 63.05; H, 6.84, N, 17.06%. $C_{13}H_{17}N_3O_2$ required C, 63.14; H, 6.93; N, 16.99%]; R_f (15% ethyl acetate/hexane) 0.50; ν_{max} ($CHCl_3$) 3030, 2924, 2858, 2100, 1278, 1101 cm^{-1}; δ_H (300 MHz, $CDCl_3$)

3.48–3.50 (d, 2H, J=5.7 Hz), 3.52–3.55, (m, 2H), 3.64–3.69 (m, 1H), 4.10–4.13 (m, 2H), 4.53 (s, 2H), 5.17 (bd, 1H, J=10.2 Hz), 5.27 (dd, 1H, J=1.5 and 17.1 Hz), 5.86–5.95 (m, 1H), 7.23–7.36 (m, 5H); δ_C (75 MHz, $CDCl_3$) 52.0, 69.4, 71.3, 73.4, 77.0, 117.2, 127.5, 127.6, 128.3, 134.3, 137.7.

4.1.8. (R)-N-Boc-2-hydroxymethyl morpholine ***5***. To a stirred solution of olefin **11** (0.5 g, 2.02 mmol) in acetone/water (10 mL, 9:1) was added NMO (0.47 g, 4.04 mmol) and potassium osmate ($K_2OSO_4 \cdot 5H_2O$) (15 mg, 0.04 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h, and then solid sodium sulfite (0.3 g) was added and stirred for 30 min. The solvent was removed under reduced pressure; residue was extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, to the crude solution of the diol in MeOH/H_2O (10 mL, 8:2), was added sodium metaperiodate (0.65 g, 3.03 mmol) at 0 °C and stirred at same temperature for 4 h. The reaction mixture was quenched with ethylene glycol (0.1 mL). The solvent was removed under reduced pressure; residue was extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give aldehyde **12**, which was used for next step without any purification. The crude aldehyde **12** (0.50 g, 2.02 mmol) and 10% Pd/C (40 mg) in MeOH (20 mL) was subjected to hydrogenation at room temperature at 100 psi. After 24 h the solution was filtered through a pad of Celite, washed with MeOH. The solvent was evaporated under reduced pressure to afford crude morpholine **13**, which was used for next step without any purification.

To a stirred solution of crude morpholine **13** (0.23 g, 2.02 mmol) in dioxane/H_2O (6 mL, 3:1) were added $NaHCO_3$ (0.20 g, 2.42 mmol) and $(Boc)_2O$ (0.46 mL, 2.02 mmol) at room temperature. After 4.5 h reaction mixture was diluted with water and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate/hexane (30:70) to give pure *N*-Boc-morpholine **5** (0.25 g, 57% over four steps) as a colorless solid, mp 59–61 °C $[\alpha]_D^{25}$ −20.5 (*c* 1.0, $CHCl_3$), {lit.[6] (for (*S*)-enantiomer) mp. 60–62 °C. $[\alpha]_D^{20}$ +20.7 (*c* 1.01, $CHCl_3$)}. [Found: C, 63.05; H, 6.98, Br, 17.08%. $C_{10}H_{19}NO_4$ required C, 63.14; H, 6.93; N, 16.99%]; R_f (30% ethyl acetate/hexane) 0.20; ν_{max} ($CHCl_3$) 3437, 2974, 2866, 1689, 1267, 1168, 1126 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.46 (s, 9H), 1.79 (br s, 1H), 2.70–2.96 (m, 2H), 3.48–3.69 (m, 4H), 3.83–3.91 (m, 3H); δ_C (75 MHz, $CDCl_3$) 28.4, 43.4, 44.9, 63.4, 66.3, 75.7, 80.1, 154.6.

4.1.9. N-(3,4-Dichlorobenzyl)(R)-2-hydroxymethylmorpholine ***6***. To a stirred solution of crude morpholine **13** (0.23 g, 2.02 mmol) in CH_3CN (5 mL) were added K_2CO_3 (0.31 g, 0.221 mmol) and 3,4-dichlorobenzyl bromide (0.48 g, 2.02 mmol) at room temperature and stirred for 5 h. The reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (3×20 mL) The combined organic extracts was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude *N*-benzylmorpholine, which was purified by silica gel chromatography using ethyl acetate/hexane (70:30) to give pure *N*-benzylmorpholine **6** (0.30 g, 54% over four steps) as a thick liquid. $[\alpha]_D^{25}$ −5.24 (*c* 0.4, $CHCl_3$). [Found: C, 52.34; H, 5.36; N, 5.19%. $C_{12}H_{15}Cl_2NO_2$ required C, 52.19; H, 5.47; N, 5.07%]; R_f (70% ethyl acetate/hexane) 0.30; ν_{max} ($CHCl_3$): 3443, 2928, 1456, 1288, 1184, 1041, 820, 667 cm^{-1}; δ_H NMR (300 MHz, $CDCl_3$) 2.12–2.33 (m, 2H), 2.74–2.83 (m, 3H), 3.52–3.66 (m, 3H), 3.75–3.93 (m, 3H), 7.22–7.46 (m, 3H); δ_C NMR (75 MHz, $CDCl_3$) 52.7, 54.3, 61.8, 63.8, 66.2, 75.7, 126.4, 130.2, 130.8, 131.2, 132.2, 137.6.

4.1.10. (R)-3-Phenyl propan-1,2-diol ***15***. Compound **15** (0.98 g, 69%) was obtained from aldehyde **14** (2.16 g, 12.1 mmol) using the same procedure for the preparation of **9** from **8**; colorless solid, mp: 46–47 °C, {lit.[18] 46–47 °C }. $[\alpha]_D^{25}$ +34.8 (*c* 1, EtOH); {lit.[18] $[\alpha]_D^{22}$ +35.4 (*c* 1, EtOH). [Found: C, 71.21; H, 7.89; N, 21.12%. $C_9H_{12}O_2$ required C, 71.03; H, 7.95; N, 21.03%]; R_f (40% ethyl acetate/hexane) 0.20; ν_{max} (CH_2Cl_2) 3417, 2928, 2864, 1496, 1452, 1273, 1078 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.54 (br s, 2H), 2.71–2.76 (m, 2H), 3.48 (dd, 1H, J=7.2, 11.1 Hz), 3.64 (dd, 1H, J=3.0, 11.4 Hz), 3.89–3.92 (m, 1H), 7.17–7.31 (m, 5H); δ_C (75 MHz, $CDCl_3$) 39.6, 65.6, 72.9, 126.2, 128.3, 137.8.

4.1.11. (R)-1-Azido-3-phenylpropan-2-ol ***16***. Compound **16** (0.92 g, 88%) was obtained from diol **15** (0.9 g, 5.92 mmol) using the same procedure for the preparation of **10** from **9**; colorless oil. $[\alpha]_D^{25}$ +2.71 (*c* 2.1, $CHCl_3$); {lit.[19] $[\alpha]_D^{24}$ +2.76 (*c* 2.1, $CHCl_3$)}. [Found: C, 61.16; H, 6.33; N, 23.67%. required $C_9H_{11}N_3O$ C, 61.00; H, 6.26; N, 23.71%]; R_f (20% ethyl acetate/hexane) 0.45; ν_{max} (CH_2Cl_2) 3416, 2924, 2102, 1494, 1452, 1282, 1084 cm^{-1}; δ_H NMR (300 MHz, $CDCl_3$): 2.0 (br s, 1H), 2.78–2.81 (m, 2H), 3.28 (dd, 1H, J=6.6, 12.6 Hz), 3.37 (dd, 1H, J=3.6, 12.3 Hz), 3.95–4.03 (m, 1H), 7.20–7.36 (m, 5H). δ_C (75 MHz, $CDCl_3$) 40.7, 55.7, 71.5, 126.5, 128.4, 129.1, 136.9.

*4.1.12. Mosher's ester of alcohol (±)-****16***[20]. Mosher ester of alcohol (±)-**16** was prepared by using the same procedure as described for the preparation of Mosher ester of (±)-**10**; colorless oil. R_f (10% ethyl acetate/hexane) 0.45; δ_H NMR (400 MHz, $CDCl_3$) 2.87 (dd, 1H, J=7.0, 14.0 Hz), 2.96–3.04 (m, 3H), 3.39–3.41 (m, 2H), 3.42 (s, 3H), 3.49–3.50 (m, 1H), 3.51 (s, 3H), 3.53–3.57 (m, 1H), 5.36–5.45 (m, 2H), 7.09–7.47 (m, 20H).

*4.1.13. Mosher's ester of alcohol (+)-****16***. Colorless oil. R_f (10% ethyl acetate/hexane) 0.45; δ_H NMR (500 MHz, $CDCl_3$) 2.87 (dd, 1H, J=7.1, 13.8 Hz), 2.98 (dd, 1H, J=7.13, 13.3 Hz), 3.39 (dd, 1H, J=4.0, 13.3 Hz), 3.51 (s, 3H), 3.55 (dd, 1H, J=7.3, 13.0 Hz), 5.35–5.41 (m, 1H), 7.09–7.41 (m, 10H).

4.1.14. 1-(R)-2-(Allyloxy-3-azidopropyl)benzene ***17***. Compound **17** (0.72 g, 98%) was obtained from alcohol **16** (0.6 g, 3.38 mmol) using the same procedure for the preparation of **11** from **10**; colorless oil. $[\alpha]_D^{25}$ +41.2 (*c* 1, $CHCl_3$). [Found C, 66.42; H, 6.83; N, 19.46%. $C_{12}H_{15}N_3O$ required C, 66.34; H, 6.96; N, 19.34%]; R_f (10% ethyl acetate/hexane) 0.45; ν_{max} (CH_2Cl_2) 3026, 2924, 2856, 2100, 1645, 1458, 1375, 1284, 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.77 (dd, 1H, J=6.9, 13.8 Hz), 2.90 (dd, 1H, J=6.3, 13.8 Hz), 3.15–3.27 (m, 2H), 3.65–3.71 (m, 1H), 4.01–4.03 (m, 2H), 5.16 (dd, 1H, J=1.2, 10.2 Hz), 5.25 (dd, 1H, J=1.5, 17.4 Hz), 5.79–5.92 (m, 1H), 7.16–7.30 (m, 5H); δ_C NMR (75 MHz, $CDCl_3$) 38.4, 53.2, 70.9, 79.2, 117.1, 126.3, 128.3, 129.2, 134.30, 137.3.

4.1.15. (R)-2-Benzyl morpholine ***4***. Compound **4** (0.23 g, 57%) was obtained from olefin **17** (0.5 g, 2.34 mmol) using the same procedure for the preparation of **13** from **11**; colorless oil. $[\alpha]_D^{25}$ +1.28 (c 5, $CHCl_3$), {lit.[5b] $[\alpha]_D^{20}$ +1.32 (*c* 5, $CHCl_3$)}. [Found C, 74.65; H, 8.60; N, 7.79%. $C_{11}H_{15}NO$ required C, 74.54; H, 8.53; N, 7.90%]; R_f (10% MeOH/$CHCl_3$) 0.30; ν_{max} (CH_2Cl_2) 3432, 2924, 2852, 1494, 1452, 1273, 1095 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.91 (br s, 1H), 2.53–2.66 (m, 2H), 2.75–2.91 (m, 4H), 3.53–3.66 (m, 2H), 3.84–3.88 (m, 1H), 7.16–7.28 (m, 5H). δ_C NMR (75 MHz, $CDCl_3$) 40.4, 45.8, 50.9, 68.1, 77.6, 126.1, 128.2, 129.1, 137.7.

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