Accepted Manuscript

Lewis Acid Mediated Intramolecular C-O Bond Formation of Alkanol-Epoxide Leading to Substituted Morpholine Derivatives: Total Synthesis of (±) - Viloxazine

Priya Ghosh, Manash J. Deka, Anil K. Saikia

PII: S0040-4020(15)30265-9

DOI: 10.1016/j.tet.2015.12.015

Reference: TET 27341

To appear in: *Tetrahedron*

Received Date: 19 October 2015

Revised Date: 21 November 2015

Accepted Date: 7 December 2015

Please cite this article as: Ghosh P, Deka MJ, Saikia AK, Lewis Acid Mediated Intramolecular C-O Bond Formation of Alkanol-Epoxide Leading to Substituted Morpholine Derivatives: Total Synthesis of (±) - Viloxazine, *Tetrahedron* (2016), doi: 10.1016/j.tet.2015.12.015.

Graphical Abstract

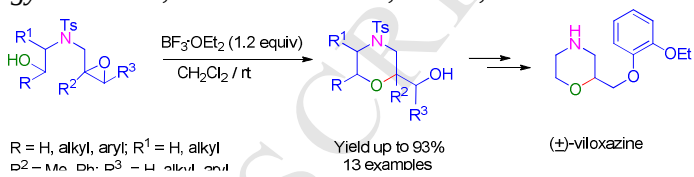
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Lewis acid mediated intramolecular C-O bond formation of alkanol-epoxide leading to substituted morpholine and 1,4-oxazepane derivatives: Total synthesis of (±) -viloxazine

Leave this area blank for abstract info.

Priya Ghosh, Manash J. Deka and Anil K. Saikia*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, Assam, India



ELSEVIER

Tetrahedron
journal homepage: www.elsevier.com

Lewis acid mediated intramolecular C-O bond formation of alkanol-epoxide leading to substituted morpholine and 1,4-oxazepane derivatives: Total synthesis of (±) -viloxazine

Priya Ghosh, Manash J. Deka and Anil K. Saikia*

[a]*Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, Assam, India*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Lewis acid
Intramolecular
Alkanol-epoxide
Morpholine
Viloxazine

ABSTRACT

Intramolecular cyclization of nitrogen tethered alkanols and epoxides mediated by boron trifluoride etherate leads to substituted morpholines and 1,4-oxazepanes in good yields. The methodology has been used for the total synthesis of (±)-viloxazine.

1. Introduction

Of the various nitrogen heterocyles known, morpholine derivatives are of particular importance. Substituted morpholine derivatives are widely distributed in many naturally occurring and biologically active molecules.[1] Many compounds of this class have shown notable biological properties, for example, viloxazine (**1**), reboxetine (**2**) and edivoxetine (**3**) show antidepressant properties.[2] Similarly, the compounds **4** and **5** containing morpholine unit have anti-inflammatory and $GABA_B$ receptor-antagonist properties.[3] Morpholines are not only used in organic synthesis as bases or *N*-alkylating agents[4] but also used as versatile synthetic units in organic synthesis particularly for the construction of agrochemical, fungicides and bactericides.[5] They are also used as chiral auxiliary in some chemical transformations.[6]

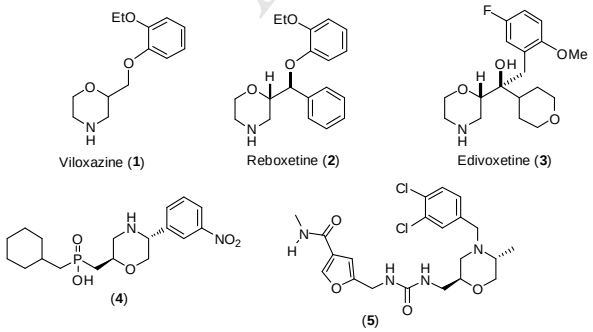


Fig. 1. Biologically important morpholines

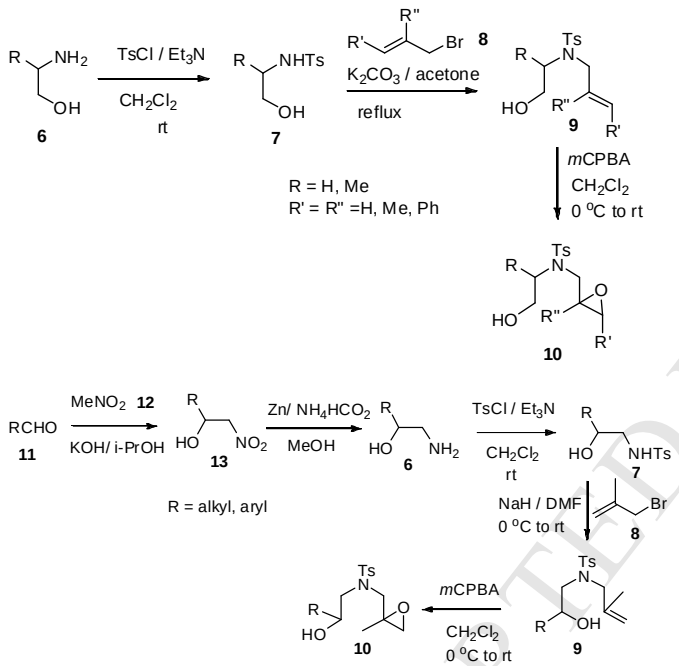
Over the years, several synthetic approaches have been developed for the preparation of morpholines such as ring closure of amino diols,[7] amino alcohols and sulfonium salts,[8] double allylic substitution by amino alcohols,[9] cyclization of *N*-tethered haloalcohols,[10] reductive amination of diketones,[11] reductive etherification of *N*-tethered ketoalcohols,[12] cyclization of *O*-protected amino alcohols,[13] oxirane ring opening by tosylamide and subsequent cyclization,[14] ring opening of aziridines,[15] palladium catalyzed coupling of *O*-allylethanolamines and aryl and alkenyl halide[16] and intramolecular cyclization of *N*-tethered alkene-alkanol.[17] Moreover, there are also reports of intramolecular cyclization of alkanol epoxide using strong bases such as NaOMe,[18] KOH/NaOH[19] and Lewis acid like $Cu(OTf)_2$.[20] Although, many synthetic methodologies have been developed, some of them suffer from serious problems of low yields[10c,11,14] strong bases,[18,19] long reaction time,[18] metal triflates[20] and harsh reaction conditions.[17a] Therefore, there is a need for the protocol which facilitates the preparation in good yields, mild reaction condition and with a choice of wide variety of substrates.

Recently, we have developed a methodology for the synthesis of oxygen and nitrogen heterocyclic compounds *via* intramolecular C-C bond formation of alkyne-epoxide mediated by boron trifluoride etherate.[21] This paper presents a methodology for the synthesis of morpholines, using intramolecular C-O bond formation of alkanol-epoxide mediated by boron trifluoride etherate at ambient temperature in moderate to good yields. Furthermore, to demonstrate the scope of the reaction we have also prepared (±)-viloxazine, an anti-depressant agent in a very good yield.

2. Results and discussion

To start with, alkanol epoxide **10a** was treated with 1.2 equivalents of boron trifluoride etherate in dichloromethane at room temperature for 1.5 h and (4-Tosylmorpholin-2-yl) methanol **14a** was obtained in 78% yield. The reaction was also performed using different Lewis acids and Brønsted acids and the results are shown in Table 1. The reaction with metal triflates such as $Zn(OTf)_2$, $Cu(OTf)_2$ and $In(OTf)_3$ (entries 3-5) gave 30, 15 and19% yields, respectively. $Bi(OTf)_3$ produced 40% of the product, $Sc(OTf)_3$ was found to be poor for the reaction resulting only trace amount of the desired product (entry 10). On the other hand, metal salts $InCl_3$ (entry 2) gave 46%, whereas $FeCl_3$ produced only trace amount (entry 11). Brønsted acids such as camphor sulfonic acid (CSA) and triflic acid (TfOH) gave 33% and 52% yields, respectively. Strong Lewis acid Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (entry 8) failed to produce the desired product, instead starting material was found to be decomposed.

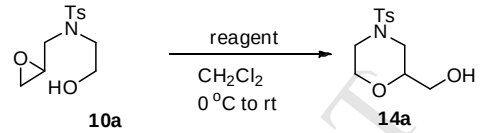
Scheme 1. Synthesis of starting materials



Once optimized conditions were obtained, we further examined the scope of the reaction with variety of substrates **10a-10m**, which were prepared as per literature methods (Scheme 1). For the synthesis of *N*-tethered primary alkenol, commercially available ethanol amine was treated with tosyl chloride in dichloromethane to afford corresponding *N*-tosylated ethanol amine, which was coupled with allyl bromide using potassium carbonate as base.[22] On the other hand, the secondary alcohol was synthesized using Henry reaction and subsequent reduction of nitro group to amine, which was then coupled with allyl bromide using sodium hydride as base. The *N*-tethered alkenol was then treated with *m*-chloroperbenzoic acid to give corresponding epoxide.[23] It was observed from the Table 2 that terminal epoxides (entries 1-10) gave the desired morpholines whereas 1,2-disubstituted epoxides (entries 11-13) produced 1,4-oxazepanes in good yields. It has been observed that yield is determined by the nature of the substituent present in the substrates. Alkanol epoxides **10a-c** gave single isomer in **14a-c** in 78, 80 and 72% yields, respectively. The relative stereochemistry of compound **14c** was determined from the NOE experiment (Figure 2). The compound hydrogen C-5H and hydrogens of methyl substituent at C-2 **14c** showed a clear characteristic NOE correlation between the position. There is another NOE correlation between the hydrogens of C-5Me and two hydrogens of -CH_2OH at C-2 position of **7c**. Substrate **10d**

Table 1

Optimization of the reaction condition

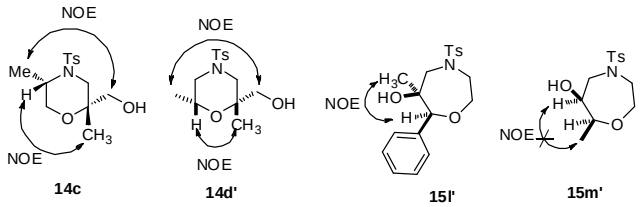


10a **14a**

entry	reagent (mmol)	yield (%)[a]
1	**$BF_3{\cdot}OEt_2$ (1.2)**	**78**
2	$InCl_3$ (1.0)	46
3	$Zn(OTf)_2$ (1.0)	30
4	$Cu(OTf)_2$ (1.0)	15
5	$In(OTf)_3$ (1.0)	19
6	CSA (1.2)	33
7	TfOH (1.2)	52
8	TMSOTf (1.0)	--[b]
9	$Bi(OTf)_3$ (1.0)	40
10	$Sc(OTf)_3$ (1.0)	trace
11	$FeCl_3$ (1.0)	trace

[a]Yield refers to isolated yield. [b]Decomposed.

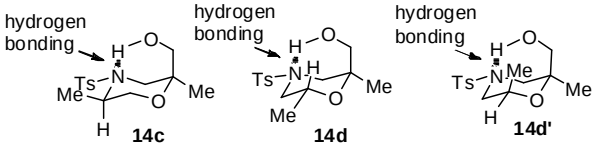
gave two separable diastereomers **14d** and **14d'** in 40 and 42% yields, respectively. The stereochemistry of the two diastereomers was determined by NOE experiment. There is a NOE correlation between hydrogen C-6H and hydrogens of methyl (-$\underline{CH_3}$) substituent at C-2 position of compound **14d´** (Figure 2). Again there is a NOE correlation between two hydrogens of C-2$\underline{CH_2}$OH and hydrogens of C-6Me of **14d´**.



14c **14d'** **15l'** **15m'**

Fig. 2. NOE of compounds **14c**, **14d´, 15l** and **15m**'

The formation of compounds **14c**, **14d** and **14d'** may be due to the stability imparted by hydrogen bonding between the hydroxyl group and the tertiary amine group (Figure 3). The starting material for the synthesis of **14c** is a chiral compound **10c** and therefore, it produces only single diastereomer **14c**, whereas diastereomeric mixture **10d** produces both the diastereomers



14c **14d** **14d'**

Fig. 3. NOE of compounds **14c**, **14d** and **14d´**

14d and **14d'** (Figure 3). On the other hand, substrates **10e-i** furnished two inseparable diastereomers each with varied ratios. Substrate **10j** gave single isomer **14j** with very good yield (95%). Epoxide **10k-m** having terminal groups produced seven membered 1,4- oxazepanes. Epoxide **10k** furnished only *anti* diasteromer **15k** with 48% yield

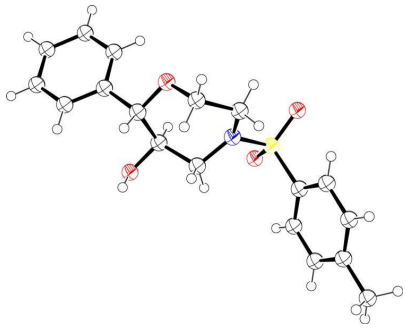
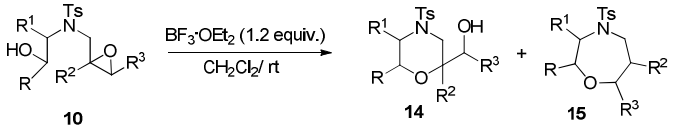
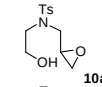
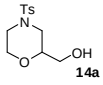
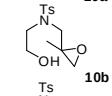
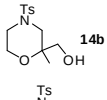
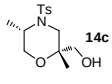
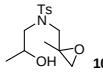
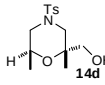
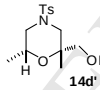
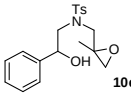
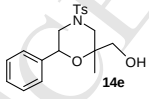
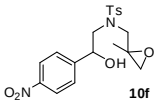
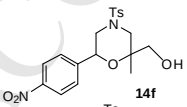
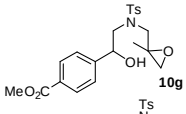
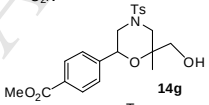
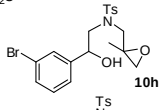
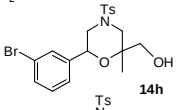
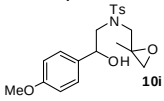
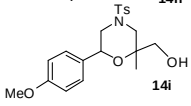
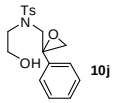
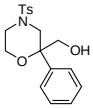


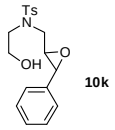
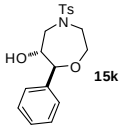
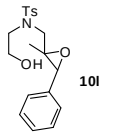
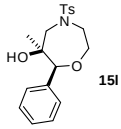
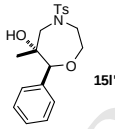
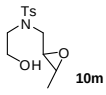
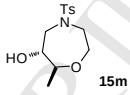
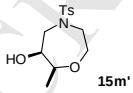
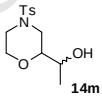
Fig. 4. ORTEP diagram of compound **15k** with 45% probability ellipsoid

Table 2

Synthesis of morpholines



Sl.No.	Substrate **10**	Product **14/15**	Yield (%)[a]	dr
1	 **10a**	 **14a**	78	—
2	 **10b**	 **14b**	80	—
3	 **10c**	 **14c**	72	—
4	 **10d**	 **14d**	40	—
		 **14d'**	42	—
5	 **10e**	 **14e**	75	1:1
6	 **10f**	 **14f**	70	3:2
7	 **10g**	 **14g**	68	1:1
8	 **10h**	 **14h**	61	1:1
9	 **10i**	 **14i**	65	3:2
10	 **10j**	 **14j**	95	---

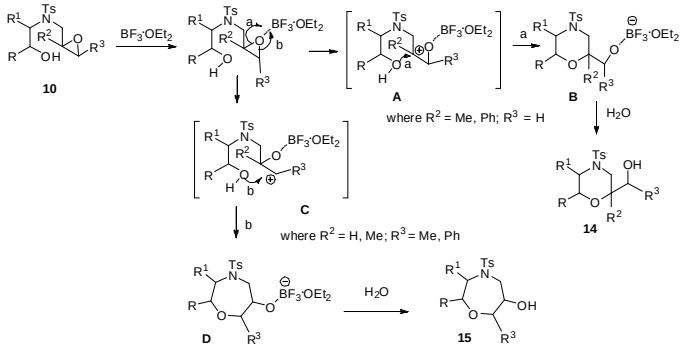
Sl.No.	Substrate **10**	Product **14/15**	Yield (%)[a]	dr
11	 **10k**	 **15k**	48	—
12	 **10l**	 **15l**	48	—
		 **15l'**	35	—
13	 **10m**	 **15m**	15	—
		 **15m'**	51	—
		 **14m**	25	9:1

[a] Yield refers to isolated yield. All the products were characterized by ^{1}H, ^{13}C NMR and Mass spectrometry. [b] Inseparable mixture of diastereomers. Ratio was determined by ^{1}H NMR.

and **10l** gave separable diastereomers **15l** and **15l'** with 48% and 35% yields, respectively. The relative stereochemistry of **15k** was determined from coupling constant (C-7H, 4.43ppm, J = 7.8 Hz) and X-ray crystallographic analysis (Figure 4).[24] The relative stereochemistry of compounds **15l** and **15l'** was determined from NOE experiment of **15l'**. There is a NOE correlation between hydrogen C-7H and hydrogens of methyl (-$\underline{CH_3}$) substituent at C-6 position of compound **15l'** (Figure 2). The compound **10m** having terminal methyl group gave three isolable compounds, two of which are diastereomeric oxazepanes **15m** and **15m´** with 15% and 51% yields, respectively, and six membered diastereomeric mixture **14m** with a ratio of 9:1 and 25% overall yield. The relative stereochemistry of these two compounds is determined from NOE experiment of **15m´** (Figure 2). There was no NOE between C-6H proton and protons of methyl group at C-7Me, which indicates that OH group at C-6 and Me at C-7 are *cis* to each other.

The mechanism of formation of morpholine and oxazepanes can be rationalized by considering the formation of different stable carbocations. The boron trifluoride etherate opens the monosubstituted terminal epoxide ring of **10** to give more stable

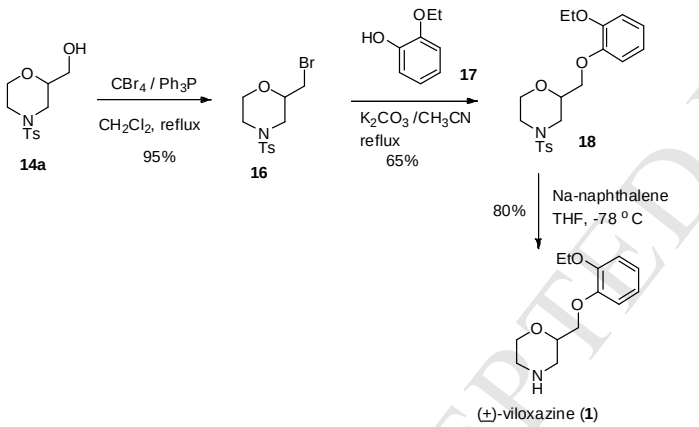
Scheme 2. Plausible mechanism of the reaction



either secondary or tertiary carbocation **A**, where R^2 = Me, Ph; R^3 = H (entries 1-10, path a), which is attacked by alkanol to give six membered intermediate **B**. The intermediate **B** is then hydrolyzed to form morpholine **14.** On the other hand, disubstituted epoxide **10k,l** opens under the same reaction conditions to give more stable benzylic carbocation **C,** where R^2 = H, Me; R^3 = Me, Ph (entries 11,12, path b), or secondary carbocation **A** or **C,** R^2 = H; R^3 = Me (entry 13, in this case both carbocations **A** and **C** are secondary). The carbocation C is subsequently attacked by alkanol to give seven membered intermaediate **D** (entries 11, 12). Similarly, secondary carbocations **A** and **C** are attacked by alkanol to produce **B** and **D** (entry 13), respectively. The intermediates **B** and **D** are then hydrolysed to give morpholine **14** and oxazepane **15**, respectively (Scheme2).

The strategy is successfully applied for the synthesis of (±)-viloxazine **1**. The compound is considered as an anti depression agent. Only a few protocols have been introduced for total synthesis of viloxazine till date.[1b,25] The synthesis started with the bromination of alcohol **14a** with carbon tetrabromide and triphenyl phosphine in dichloromethane at room temperature to give bromide **16**, which was then treated with 2-ethoxyphenol **17** to provide *N*-tosyl protected (±)-viloxazine **18**. Deprotection of **11** with sodium naphthalide gave the final product (±)-viloxazine **1** in 80% yield (Scheme 3).

Scheme 3. Total synthesis of (±)-viloxazine 1



3. Conclusions

In conclusion, we have developed a mild and efficient method for the synthesis of substituted morpholines *via* intramolecular cyclization reaction of *N*-tethered alkanols-epoxides in good yields. The reaction is compatible with a wide range of functional groups such as ester, ether, -NO_2, and bromo. The major advantage of this reaction is that it generates alcohols in side chain of the morpholine ring, which is used for the synthesis of biologically active molecule (±)-viloxazine **1**.

4. Experimental section

General Information: All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in open capillary tubes and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

4.1. General Procedure for the Synthesis of *N*-Tethered Alkanol-Epoxide:

The alkenols **10a-10m** (1equiv) was treated with metachloroperbenzoic acid (*m*CPBA) (1.5 equiv) in dicholomethane (15 ml) at 0 ^{0}C. The reaction mixture was brought to room temperature and stirred for a specific time. After completion of the reaction, as determined by TLC, a saturated aqueous solution of Na_2SO_3 was added to quench excess *m*CPBA. Dichloromethane was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solutions, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by neutral alumina using ethyl acetate and hexane as eluents.

4.2.1. *Synthesis of N-(2-hydroxyethyl)-4-methyl-N-(oxiran-2ylmethyl)benzene-sulfonamide (**10a**).* To a stirred solution of *N*-allyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (254 mg, 1.0 mmol) in dichlorormethane (6.0 mL), was added *m*-chloroperbenzoic acid (258.0 mg, 1.49 mmol) at 0 ^{0}C. The reaction mixture was brought to room temperature and stirred for 12 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, a saturated aqueous solution of Na_2SO_3 was added to quench excess *m*CPBA. Dichloromethane was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solution. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over neutral alumina using ethyl acetate and hexane as eluents to give *N*-(2-hydroxyethyl)-4-methyl-*N*-(oxiran-2-ylmethyl)benzenesulfonamide as a colourless oil. R_f (hexane/ EtOAc 3:2) 0.50; yield 203 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.18 (t, *J* = 10.2 Hz, 1 H), 2.33 (t, *J* = 11.4 Hz, 1 H), 2.37 (s, 3 H), 3.44-3.48 (m, 2 H), 3.50-3.64 (m, 4 H), 3.86 (d, *J* = 11.4 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 45.5, 47.1, 63.2, 65.8, 75.5, 127.8, 129.9, 131.9, 144.1; IR (KBr, neat) 3508, 2923, 2866, 1453, 1339, 1166, 1048, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{18}NO_4S$ $(M + H)^+$ 272.0951, found 272.0950.

*4.2.2 N-(2-Hydroxyethyl)-4-methyl-N-((2-methyloxiran-2-yl)methyl)benzenesulfonamide (**10b**).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.47; yield 271 mg, 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 2.41 (s, 3 H), 2.69 (d, *J* = 4.2 Hz, 1 H), 2.94 (d, *J* = 4.2 Hz, 1 H), 3.01-3.07 (m, 1 H), 3.24 (d, *J* = 15.0 Hz, 1 H), 3.32 (t, *J* = 6.0 Hz, 1 H), 3.34-3.38 (m, 1 H), 3.40 (d, *J* = 15.0 Hz, 1 H), 3.69-3.72 (m, 1 H), 3.73-3.78 (m, 1 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.67 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.3, 21.7, 52.0, 53.5, 54.5, 57.2, 61.4, 127.5, 130.1, 135.7, 144.0; IR (KBr, neat) 3454, 2927, 1598, 1338, 1162, 1090, 1029, 816, 706 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108, found 286.1108.

*4.2.3. N-(1-Hydroxypropan-2-yl)-4-methyl-N-((2-methyloxiran-2-yl)methyl)benzenesulfonamide (diastereomeric mixture, 7:3: **10c**).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 230 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.4 Hz, 3 H, major), 0.83 (d, *J* = 6.8 Hz, 3 H, minor), 1.41 (s, 3 H, major), 1.49 (s, 3 H, minor), 2.43 (s, 3 H), 2.71-2.84 (m, 2 H), 3.24-3.28 (m, 1 H), 3.36-3.41 (m, 1 H), 3.48-3.61 (m, 2 H), 3.72-3.94 (m, 2 H), 7.30-7.33 (m, 2 H), 7.68-7.72 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 13.3, 18.9, 20.0, 21.7, 45.9, 49.9, 52.9, 53.2, 55.8, 56.8, 58.4, 64.9, 65.1, 127.2, 127.5, 129.9, 130.0,

137.2, 137.4, 143.8, 144.0; IR (KBr, neat) 3522, 2928, 2876, 1598, 1453, 1337, 1216, 1153, 1091, 1025, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264, found 300.1263.

4.2.4. N-(2-hydroxypropyl)-4-methyl-N-((2-methyloxiran-2-yl)methyl)benzenesulfonamide (diastereomeric mixture, 3:2, ***10d****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 278 mg, 93%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.4 Hz, 3 H, major), 1.16 (d, *J* = 6.8 Hz, 3 H, minor), 1.37 (s, 3 H, minor), 1.42 (s, 3 H, major), 2.44 (s, 3 H), 2.71-2.74 (m, 1 H, major), 2.77-2.87 (m, 1 H, minor), 3.14-3.18 (m, 1 H), 3.20-3.23 (m, 1 H), 3.45 (d, *J* = 15.2 Hz, 1 H), 3.57 (d, *J* = 15.2 Hz, 1 H), 3.90-3.98 (m, 1 H), 4.04-4.12 (m, 1 H), 7.34 (d, *J* = 7.6 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2, 19.3, 19.5, 20.5, 20.7, 21.7, 52.0, 52.2, 53.6, 55.9, 57.0, 57.3, 58.4, 59.4, 65.2, 67.2, 127.4, 127.5, 129.9, 130.0, 135.4, 135.5, 144.0, 144.1; IR (KBr, neat) 3450, 2925, 1598, 1494, 1339, 1161, 1020, 908, 729 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264, found 300.1267.

4.2.5. N-(2-Hydroxy-2-phenylethyl)-4-methyl-N-((2-methyloxiran-2-yl)methyl)benzenesulfonamide (diastereomeric mixture, 5:4, ***10e****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 339 mg, 94%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3 H, minor), 1.45 (s, 3 H, major), 2.40 (s, 3 H), 2.70 (d, *J* = 4.0 Hz, 1 H, minor), 2.76 (d, *J* = 4.0 Hz, 1 H, major), 2.97-3.04 (m, 3 H, major), 3.06-3.15 (m, 3 H, minor), 3.28-3.35 (m, 1 H), 3.44-3.48 (m, 1 H, major), 3.68 (d, *J* = 15.6 Hz, 1 H, minor), 4.89 (d, *J* = 9.2 Hz, 1 H, major), 5.08 (d, *J* = 9.2 Hz, 1 H, minor), 7.26-7.43 (m, 6 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 19.3, 21.6, 52.0, 52.1, 52.5, 56.2, 56.7, 57.3, 58.4, 60.3, 71.4, 73.6, 126.0, 126.1, 127.4, 127.5, 127.7, 128.0, 128.5, 128.6, 129.9, 130.0, 135.4, 135.6, 141.4, 141.7, 144.0, 144.2; IR (KBr, neat) 3485, 2924, 1495, 1334, 1161, 1091, 1024, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 362.1423.

4.2.6. *N-(2-hydroxy-2-(4-nitrophenyl)ethyl)-4-methyl-N-((2-methyl-oxiran-2-yl)methyl)benzene-sulfonamide (diasteromeric mixture 4:3,* ***10f****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 292 mg, 72%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.35 (s, 3 H, minor), 1.49 (s, 3 H, major), 2.42 (s, 3 H, major), 2.43 (s, 3 H, minor), 2.75 (d, *J* = 4.2 Hz, 1 H, minor), 2.81 (d, *J* = 4.2 Hz, 1 H, major), 3.00-3.09 (m, 3 H), 3.29 (dd, *J* = 15.0 and 1.2 Hz, 1 H, minor), 3.41 (dd, *J* = 15.0 and 5.4 Hz, 1 H, major), 3.48 (d, *J* = 15.0 Hz, 1 H, minor), 3.76 (d, *J* = 15.0 Hz, 1 H, major), 5.06 (d, *J* = 8.4 Hz, 1 H, minor), 5.23 (d, *J* = 8.4 Hz, 1 H, major), 7.30-7.34 (m, 2 H), 7.51-7.60 (m, 2 H), 7.64-7.71 (m, 2 H), 8.19 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 36.0, 49.5, 62.2, 62.4, 116.3, 126.8, 126.9, 127.8, 128.5, 128.8, 128.83, 129.2, 130.0, 137.5, 138.0, 138.6, 143.9, 145.4; IR (KBr, neat) 3499, 2923, 2852, 1521, 1453, 1347, 1161, 1090, 853, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}N_2O_6S$ $(M + H)^+$ 407.1271, found 407.1275.

4.2.7. *Methyl 4-(1-hydroxy-2-(4-methyl-N-((2-methyloxiran-2-yl)methyl)phenylsulfonamido)ethyl)-benzoate (diastereomeric mixture, 1:1,* ***10g****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 306 mg, 73%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.24 (s, 3 H), 2.39 (s, 1.5 H), 2.41 (s, 1.5 H), 2.70 (s, 0.5 H), 2.77 (s, 0.5 H), 2.97 (s, 1 H), 3.01-3.10 (m, 2 H), 3.28 (d, *J* = 15.0 Hz, 0.5 H), 3.26-3.42 (m, 1 H), 3.69 (d, *J* = 15.0 Hz, 0.5 H), 3.89 (s, 3 H), 4.96 (d, *J* = 10.2 Hz, 0.5 H), 5.14 (d, *J* = 12.0 Hz, 0.5 H), 7.29 (d, *J* = 7.2 Hz, 2 H), 7.43-7.50 (m, 2 H), 7.65 (d, *J* = 7.8 Hz, 2 H), 7.98 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 19.3, 21.7, 22.8, 51.9, 52.0, 52.2, 53.6, 56.4, 56.8, 57.4, 58.3, 60.3, 71.2, 73.5, 126.0, 126.1, 127.4, 127.5, 129.9, 129.93, 130.1, 130.2, 135.3, 135.7, 144.2, 144.3, 146.6, 146.9, 167.0, 167.1; IR (KBr, neat) 3498, 2925, 2854, 1722, 1612, 1437, 1339, 1282, 1159, 1089, 1019, 987, 816, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{26}NO_6S$ $(M + H)^+$ 420.1481, found 420.1478.

4.2.8. *N-(2-(3-Bromophenyl)-2-hydroxyethyl)-4-methyl-N-((2-methyloxiran-2-yl)methyl)benzene-sulfonamide (diastereomeric mixture, 1:1,* ***10h****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.39; yield 312mg, 71%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.34 (s, 1.5 H), 1.46 (s, 1.5 H), 2.40 (s, 3 H), 2.71 (d, *J* = 3.0 Hz, 0.5 H), 2.77 (d, *J* = 3.6 Hz, 0.5 H), 2.96-3.02 (m, 1.5 H), 3.06-3.10 (m, 1 H), 3.26 (d, *J* = 15.0 Hz, 0.5 H), 3.35-3.44 (m, 1.5 H), 3.70 (d, *J* = 15.0 Hz, 0.5 H), 4.87 (d, *J* = 9.6 Hz, 0.5 H), 5.05 (d, *J* = 9.6 Hz, 0.5 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.28-7.39 (m, 4 H), 7.52 (s, 0.5 H), 7.59 (s, 0.5 H), 7.65-7.68 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 19.3, 21.6, 51.9, 52.0, 53.5, 56.4, 56.7, 57.3, 58.3, 60.2, 70.8, 73.1, 122.7, 124.7, 124.8, 127.4, 127.5, 129.1, 129.2, 130.0, 130.1, 130.16, 130.2, 130.8, 130.9, 135.3, 135.5, 143.8, 144.1, 144.2, 144.3; IR (KBr, neat) 3492, 2925, 2855, 1597, 1428, 1338, 1159, 1090, 804, 762 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0526.

4.2.9. *N-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)-4-methyl-N-((2-methyloxiran-2-yl)methyl)benzene-sulfonamide (diastereomeric mixture, 1:1,* ***10i****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 301 mg, 77%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.33 (s, 1.5 H), 1.43 (s, 1.5 H), 2.39 (s, 3 H), 2.68 (d, *J* = 3.0 Hz, 0.5 H), 2.74 (d, *J* = 3.0 Hz, 0.5 H), 2.93-3.01 (m, 1.5 H), 3.06-3.13 (m, 1 H), 3.26 (d, *J* = 15.0 Hz, 0.5 H), 3.33 (d, *J* = 15.6 Hz, 0.5 H), 3.41-3.47 (m, 1 H), 3.66 (d, *J* = 15.0 Hz, 0.5 H), 3.77 (s, 3 H), 4.84 (d, *J* = 9.6 Hz, 0.5 H), 5.02 (d, *J* = 9.0 Hz, 0.5 H), 6.85 (d, *J* = 7.8 Hz, 2 H), 7.21-7.67 (m, 4 H), 7.65-7.70 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.0, 19.2, 21.6, 51.9, 52.0, 53.4, 53.6, 55.3, 56.1, 56.6, 57.2, 58.2, 60.0, 70.9, 72.1, 73.1, 113.8, 114.0, 127.1, 127.2, 127.3, 127.4, 129.9, 130.0, 133.5, 133.9, 135.5, 135.7, 143.9, 144.1, 159.2, 159.3; IR (KBr, neat) 3508, 2978, 1598, 1455, 1341, 1162, 1092, 815, 770 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_5S$ $(M + H)^+$ 392.1526, found 392.1527.

*4.2.10. N-(2-Hydroxyethyl)-4-methyl-N-((2-phenyloxiran-2-yl)methyl)benzenesulfonamide (****10j****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 336 mg, 97%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.87 (d, *J* = 6.6 Hz, 1 H), 2.93 (dt, *J* = 9.6 and 4.4 Hz, 1 H), 3.41 (d, *J* = 6.6 Hz, 1 H), 3.46 (dt, *J* = 9.6 and 4.8 Hz, 1 H), 3.69-3.81 (m, 4 H), 7.29-7.39 (m, 5 H), 7.43 (d, *J* = 7.6 Hz, 2 H), 7.65 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 53.1, 53.5, 53.6, 60.7, 61.3, 126.3, 127.6, 128.5, 128.8, 130.1, 135.1, 137.3, 144.2; IR (KBr, neat) 3508, 2977, 2876, 1598, 1452, 1336, 1153, 1091, 1024, 815, 679 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264, found 348.1262.

*4.2.11. N-(2-hydroxyethyl)-4-methyl-N-((3-phenyloxiran-2-yl)methyl)benzenesulfonamide (****10k****).* Colourles oil, R_f (hexane/ EtOAc 3:2) 0.50; yield 330 mg, 95%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.25-3.30 (m, 2 H), 3.32-3.34 (m, 2 H), (dd, *J* = 16.8 and 4.8 Hz, 1 H), 3.82 (t, *J* = 4.8 Hz, 2 H), 3.86 (d, *J* = 1.8 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.29-7.35 (m, 5 H), 7.71 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 51.2, 52.6, 57.6, 61.6, 61.7, 125.9, 127.4, 128.6, 128.7, 130.1, 135.7, 136.0, 144.1; IR (KBr, neat) 3499, 2923, 2873, 1598, 1451, 1337, 1160, 1089, 978, 815, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264, found 414.1359.

4.2.12. N-(2-Hydroxyethyl)-4-methyl-N-((2-methyl-3-phenyloxiran-2-yl)methyl)benzenesulfonamide (diastereomeric mixture, 4:1, ***10l****).* Colourless oil, R_f (hexane/ EtOAc 3:2) 0.48 yield; 332 mg, 92%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.13 (s, 3 H,

major), 1.58 (s, 3 H, minor), 2.38 (s, 3 H, minor), 2.44 (s, 3 H, major), 3.03-3.08 (m, 1 H), 3.46 (d, *J* = 6.0 Hz, 2 H), 3.49-3.54 (m, 1 H), 3.66 (t, *J* = 4.8 Hz, 1 H), 3.77-3.81 (m, 1 H), 3.83-3.87 (m, 1 H), 3.99 (s, 1 H, minor), 4.32 (s, 1 H, major), 7.23-7.37 (m, 7 H), 7.53 (d, *J* = 7.8 Hz, 2 H, minor), 7.72 (d, *J* = 7.8 Hz, 2 H, major); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.5, 21.6, 21.7, 51.4, 51.7, 53.4, 55.4, 61.1, 61.6, 61.7, 62.3, 63.7, 63.9, 126.5, 126.6, 127.4, 127.6, 127.9, 128.2, 128.3, 128.6, 130.0, 130.1, 135.0, 135.1, 135.5, 136.0, 143.8, 144.1; IR (KBr, neat) 3520, 2928, 1598, 1450, 1339, 1161, 1089, 751, 656 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 380.1323.

4.2.13. *N-(2-Hydroxyethyl)-4-methyl-N-((3-methyloxiran-2-yl)methyl)benzenesulfonamide (diastereomeric mixture, 1:2, **10m**).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.46; yield 257 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J* = 5.2 Hz, 3 H, minor), 1.29 (d, *J* = 5.2 Hz, 3 H, major), 2.39 (s, 3 H), 2.93-3.00 (m, 2 H, major) 3.01-3.09 (m, 2 H, minor), 3.10-3.15 (m, 1 H, major), 3.16-3.19 (m, 1 H, minor), 3.20-3.30 (m, 2 H), 3.45-3.51 (m, 1 H, minor), 3.57-3.63 (m, 1 H, major), 3.74 (t, *J* = 5.2 Hz, 2 H, major), 3.77-3.80 (m, 2 H, minor), 7.29 (d, *J* = 7.6 Hz, 2 H), 7.69 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 18.7, 20.0, 21.5, 51.1, 51.6, 52.4, 52.7, 53.7, 55.7, 58.6, 61.4, 65.9, 68.0, 127.2, 129.8, 129.9, 135.5, 143.8; IR (KBr, neat) 3518, 2926, 2854, 1625, 1598, 1452, 1337, 1161, 1090, 1020, 802, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108, found 328.1219.

4.3. General Procedure for Lewis Acid Catalyzed Intramolecular C−O Bond Formation of Alkanol-Epoxide.

To a corresponding hydroxyl-epoxide substrates (1.0 equiv) in CH_2Cl_2 (5.0 mL) at 0 °C was added $BF_3 \cdot Et_2O$ (1equiv) dropwise, and the reaction mixture was brought to room temperature. The reaction was continued for a specified time and monitored by TLC. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5.0 mL). The product was extracted with CH_2Cl_2 (2 × 10.0 mL) and washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the cyclic compounds.

*4.3.1. Synthesis of (4-Tosylmorpholin-2-yl)methanol (**14a**).* To a stirred solution of *N*-(2-hydroxyethyl)-4-methyl-*N*-(oxiran-2-ylmethyl)benzenesulfonamide (270 mg, 1.0 mmol) in dichloromethane(5.0 mL), was adeed boron triflouride etherate (0.15 mL, 1.2 mmol) dropwise at 0 ^{0}C. The reaction mixture was brought to room temperature and stirred for 1.5 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was washed with saturated sodium bicarbonate solution and brine solution. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel using ethyl acetate and hexane as eluents to give (4-tosylmorpholin-2-yl)methanol as a white solid; mp 120-121 ^{o}C; R_f (hexane/ EtOAc 3:2) 0.47; yield 211 mg, 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (dd, *J* = 11.6 and 10.4 Hz, 1 H), 2.39 (dt, *J* = 11.6 and 3.6 Hz, 1 H), 2.45 (s, 3 H), 3.52-3.59 (m, 3 H), 3.64-3.70 (m, 2 H), 3.74 (dd, *J* = 11.2 and 2.8 Hz, 1 H), 3.92-3.97 (m, 1 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.63 (t, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 21.6, 45.6, 47.1, 63.3, 65.9, 75.5, 128.0, 129.9, 132.1, 144.2; IR (KBr, neat) 3498, 2921, 2863, 1597, 1344, 1168, 1097, 974, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{18}NO_4S$ $(M + H)^+$ 272.0951 found 272.0951.

*4.3.2. (2-Methyl-4-tosylmorpholin-2-yl)methanol (**14b**).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.47; yield 228 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25 (s, 3 H), 2.42 (s, 3 H), 2.64-2.68 (m, 1 H), 2.77 (d, *J* = 12.0 Hz, 1 H), 2.95 (d, *J* = 12.0 Hz, 1 H), 3.19 (dt, *J* = 11.4 and 2.4 Hz, 1 H), 3.50 (dd, *J* = 11.4 and 5.4 Hz, 1 H), 3.55 (d, *J* = 10.8 Hz, 1 H), 3.75 (dt, *J* = 12.0 and 4.2 Hz, 1 H), 3.84-3.88 (m, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.60 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 19.2, 21.7, 45.8, 50.6, 60.5, 66.8, 73.5, 127.9, 130.0, 132.4, 144.1; IR (KBr, neat) 3509, 2925, 2879, 1598, 1455, 1350, 1166, 1090, 1057, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108 found 286.1111.

4.3.3. ((2R,5S*)-2,5-dimethyl-4-tosylmorpholin-2-yl)methanol (**14c**).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 215 mg, 72%; $[\alpha]_D^{25}$ +13.6 (c 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 5.2 Hz, 3 H), 1.22 (s, 3 H), 2.43 (s, 3 H), 2.96 (d, *J* = 13.6 Hz, 1 H), 3.37 (m, 2 H), 3.60 (d, *J* = 10. 8 Hz, 1 H), 3.73 (d, *J* = 11. 6 Hz, 1 H), 3.86-3.94 (m, 2 H), 7.26 (d, *J* = 6.8 Hz, 2 H), 7.67 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8 21.7, 22.4 22.9 (minor), 45.2, 48.6, 62.3, 66.0, 73.2, 127.2, 130.0, 137.1, 143.8; IR (KBr, neat) 3434, 29 24, 2854, 1454, 1337, 1161, 1037, 953, 815, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264 found 300.1278.

4.3.4. ((2R,6S*)-2,6-Dimethyl-4-tosylmorpholin-2-yl)methanol (**14d**).* White solid, mp 127-128 ^{o}C; R_f (hexane/ EtOAc 3:2) 0.45; yield 120 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, *J* = 6.0 Hz, 3 H), 1.16 (s, 3 H), 1.92 (t, *J* = 10.8 Hz, 1 H), 2.05 (d, *J* = 11.6 Hz, 1 H), 2.45 (s, 3 H), 3.52-3.60 (m, 2 H), 3.69 (d, *J* = 11.2 Hz, 1 H), 3.91 (d, *J* = 11.2 Hz, 1 H), 3.94-3.98 (m, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 19.2, 21.7, 23.3, 50.4, 51.3, 62.5, 65.6, 73.7, 127.9, 130.0, 132.5, 144.2; IR (KBr, neat) 3463, 2925, 2852, 1598, 1493, 1342, 1166, 1094, 1030, 814, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264 found 300.1271.

4.3.5. ((2S,6S*)-2,6-Dimethyl-4-tosylmorpholin-2-yl)methanol (**14d'**).* White solid, mp 125-126 ^{o}C; R_f (hexane/ EtOAc 3:2) 0.48; yield 126 mg, 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.4 Hz, 3 H), 1.29 (s, 3 H), 1.82 (t, *J* = 10.4 Hz, 1 H), 2.38 (d, *J* = 11.2 Hz, 1 H), 2.42 (s, 3 H), 3.27-3.33 (m, 2 H), 3.50 (d, *J* = 7.2 Hz, 1 H), 3.55 (dt, *J* = 11.2 and 3.0 Hz, 1 H), 3.96-4.05 (m, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 18.3, 19.0, 21.7, 49.8, 51.6, 65.4, 68.8, 74.0, 127.9, 130.0, 132.6, 144.0; IR (KBr, neat) 3463, 2925, 2852, 1598, 1493, 1342, 1166, 1094, 1030, 814, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264 found 300.1271.

*4.3.6. (2-Methyl-6-phenyl-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 1:1, **14e**).* White solid, M. P. 133-136 0 ^{o}C; R_f (hexane/ EtOAc 3:2) 0.40; yield 271 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (s, 1.5 H), 1.43 (s, 1.5 H), 2.07-2.17 (m, 1.5 H), 2.40 (s, 1.5 H), 2.42 (s, 1.5 H), 2.53 (d, 11.2 Hz, 0.5 H), 3.44 (dd, *J* = 10.8 and 3.2 Hz, 1 H), 3.60 (d, *J* = 11.6 Hz, 0.5 H), 3.67 (d, *J* = 11.6 Hz, 0.5 H), 3.76 (dd, *J* = 11.6 and 1.6 Hz, 1 H), 3.81 (d, *J* = 11.6 Hz, 0.5 H), 3.94 (d, *J* = 11.2 Hz, 0.5 H), 4.88 (dd, *J* = 10.8 and 2.8 Hz, 0.5 H,), 4.94 (d, *J* = 10.4 Hz, 0.5 H), 7.28-7.32 (m, 7 H), 7.58 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 18.0, 21.6, 23.2, 50.0, 50.4, 51.8, 51.9, 62.2, 68.8, 71.5, 71.6, 74.1, 74.5, 126.3, 126.4, 127.7, 127.8, 128.4, 128.5, 128.57, 128.6, 129.9, 130.0, 132.2, 132.4, 138.7, 138.8, 144.0, 144.1; IR (KBr, neat) 3531, 2925, 1598, 1454, 1342, 1160, 1092, 1021, 816, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421 found 362.1418.

*4.3.7. (2-Methyl-6-(4-nitrophenyl)-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 3:2, **14f**).* White solid, mp

142-144 °C; R_f (hexane/ EtOAc 3:2) 0.45; yield 284 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (s, 3 H, major), 1.46 (s, 3 H, minor), 2.05-2.10 (m 1 H), 2.19 (d, *J* = 12.0 Hz, 1 H, major), 2.42 (s, 3 H, minor), 2.43 (s, 3 H, major), 2.55 (d, *J* = 11.5 Hz, 1 H, minor), 3.50 (t, *J* = 12.0 Hz, 1 H), 3.67 (d, *J* = 11.4 Hz, 1 H, minor), 3.71 (dd, *J* = 11.4 and 1.2 Hz, 1 H, major), 3.82 (d, *J* = 12.0 Hz, 1 H), 3.86 (d, *J* = 11.4 Hz, 1 H, major), 3.99 (d, *J* = 11.4 Hz, 1 H, minor), 5.05 (dd, *J* = 10.8 and 2.4 Hz, 1 H, major), 5.08 (dd, *J* = 10.8 and 2.4 Hz, 1 H, minor), 7.32 (t, *J* = 8.4 Hz, 2 H), 7.49-7.53 (m, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 8.18 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 21.7, 22.9, 23.2, 50.1, 50.5, 51.5, 51.7, 62.4, 68.9, 70.8, 71.0, 74.7, 75.2, 123.8, 123.9, 126.5, 127.2, 127.8, 127.9, 128.1, 128.5, 130.1, 130.2, 132.3, 144.4, 144.5, 146.0, 148.0; IR (KBr, neat) 3528, 2925, 1600, 1522, 1454, 1349, 1166, 1092, 1022, 759, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}N_2O_6S$ $(M + H)^+$ 407.1271 found 407.1277.

4.3.8. *Methyl 4-(6-(hydroxymethyl)-6-methyl-4-tosylmorpholin-2-yl)benzoate (diastereomeric mixture, 1:1,* ***14g****).* White solid, mp 150-152 °C; R_f (hexane/ EtOAc 3:2) 0.40; yield 285 mg, 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (s, 1.5 H), 1.44 (s, 1.5 H), 2.05-2.10 (m, 1 H), 2.18 (d, *J* = 12.0 Hz, 0.5 H), 2.40 (s, 1.5 H), 2.41 (s, 1.5 H), 2.54 (d, *J* = 11.4 Hz, 0.5 H), 3.46 (t, *J* = 12.0 Hz, 1 H), 3.64 (d, *J* = 11.4 Hz, 0.5 H), 3.67 (d, *J* = 11.4 Hz, 0.5 H), 3.78 (dd, *J* = 12.0 and 1.2 Hz, 1 H), 3.81 (d, *J* = 11.4 Hz, 0.5 H), 3.89 (s, 1.5 H), 3.90 (s, 1.5 H), 4.00 (d, *J* = 11.4 Hz, 0.5 H), 4.95 (d, *J* = 10.2 Hz, 0.5 H), 4.98 (d, *J* = 10.8 Hz, 0.5 H), 7.30 (t, *J* = 8.4 Hz, 2 H), 7.36-7.40 (m, 2 H), 7.57 (d, *J* = 7.8 Hz, 2 H), 8.98 (dd, *J* = 8.4 and 3.6 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.1, 21.7, 22.9, 23.3, 50.0, 50.5, 51.7, 51.8, 52.4, 62.4, 68.9, 71.3, 71.4, 74.4, 74.8, 126.3, 126.32, 127.8, 127.9, 129.9, 130.0, 130.1, 130.2, 130.3, 132.4, 143.7, 143.8, 144.2, 144.3, 166.8, 166.9; IR (KBr, neat) 3492, 2925, 2854, 1721, 1455, 1342, 1282, 1166, 1091, 1020, 779, 705 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{26}NO_6S$ $(M + H)^+$ 420.1475, found 420.1480.

4.3.9. (6-(3-Bromophenyl)-2-methyl-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 1:1, ***14h****).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.48; yield 268 mg, 61%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (s, 1.5 H), 1.42 (s, 1.5 H), 2.02-2.07 (m, 1 H), 2.14 (d, *J* = 12.0 Hz, 0.5 H), 2.40 (s, 1.5 H), 2.42 (s, 1.5 H), 2.50 (d, *J* = 11.4 Hz, 0.5 H), 3.45 (dd, *J* = 11.4 and 6.0 Hz, 1 H), 3.61 (d, *J* = 11.4 Hz, 0.5 H), 3.66 (d, *J* = 12.0 Hz, 0.5 H), 3.74 (d, *J* = 11.4Hz, 1 H), 3.81 (d, *J* = 11.4 Hz, 0.5 H), 3.92 (d, *J* = 11.4 Hz, 0.5 H), 4.87 (dd, *J* = 10.2 and 3.0 Hz, 0.5 H), 4.90 (d, *J* = 10.8 Hz, 0.5 H), 7.16-7.23 (m, 2 H), 7.30 (t, *J* = 9.0 Hz, 2 H), 7.40 (t, *J* = 6.0 Hz, 1 H), 7.45 (s, 0.5 H), 7.47 (s, 0.5 H), 7.57 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.0, 21.2, 23.2, 50.4, 51.7, 51.8, 62.3, 68.8, 70.9, 71.0, 72.1, 74.4, 74.8, 122.8, 125.0, 125.1, 127.8, 129.3, 129.9, 130.1, 130.2, 130.3, 131.5, 131.6, 132.1, 132.3, 141.1, 141.2, 144.2, 144.3; IR (KBr, neat) 3509, 2925, 2853, 1597, 1341, 1165, 1071, 808, 774, 682 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0527.

4.3.10. (6-(4-Methoxyphenyl)-2-methyl-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 3:2, ***14i****).* Colourless oil; R_f (hexane/ EtOAc 3:2) 0.38; yield 254 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25 (s, 3 H, major), 1.43 (s, 3 H, minor), 2.04-2.14 (m, 1 H), 2.18 (d, *J* = 12.0 Hz, 1 H, minor), 2.42 (s, 3 H, major), 2.43 (s, 3 H, minor), 2.55 (d, *J* = 11.4 Hz, 1 H, major), 3.41-3.44 (m, 1 H), 3.61 (d, *J* = 11.4 Hz, 1 H, major), 3.65 (dd, *J* = 11.4 and 1.2 Hz, 1 H, minor), 3.72 (d, *J* = 11.4 Hz, 1 H), 3.76 (d, *J* = 11.4 Hz, 1 H, major), 3.78 (s, 3 H), 4.02 (dd, *J* = 11.4 and 2.4 Hz, 1 H, minor), 4.83 (dd, *J* = 10.2 and 2.4 Hz, 1 H, minor), 4.90 (d, *J* = 10.2 and 2.4 Hz, 1 H, major), 6.83-6.87 (m, 2 H), 7.20-7.26 (m, 2 H), 7.32 (t, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.2, 21.7, 23.4, 49.9, 50.5, 52.0, 55.5, 62.5, 68.9, 71.3, 71.5, 74.2, 74.4, 114.1, 114.2, 127.7, 127.8, 127.86, 127.9, 128.4, 128.7, 130.0, 131.0, 132.5, 144.1, 144.2, 159.8, 159.9; IR (KBr, neat) 3527, 2925, 2853, 1613, 1456, 1341, 1249, 1165, 1092, 1033, 815, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_5S$ $(M + H)^+$ 392.1526, found 392.1525.

*4.3.11. (2-Phenyl-4-tosylmorpholin-2-yl)methanol (****14j****).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 330 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 2.50-2.57 (m, 1 H), 2.88 (d, *J* = 12.4 Hz, 1 H), 3.33 (d, *J* = 11.6 Hz, 1 H), 3.50 (d, *J* = 11.6 Hz, 1 H), 3.67 (d, *J* = 12.4 Hz, 1 H), 3.72 (d, *J* = 7.6 Hz, 2 H), 4.17 (d, *J* = 12.4 Hz, 1 H), 7.32-7.37 (m, 3 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.51 (d, *J* = 7.6 Hz, 2 H), 7.66 ((d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 45.7, 47.9, 60.8, 69.3, 78.2, 127.3, 127.9, 128.1, 128.8, 129.9, 131.9, 138.3, 144.1; IR (KBr, neat) 3509, 2925, 2854, 1598, 1450, 1350, 1166, 1092, 1017, 816, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264, found 348.1267.

4.3.12. (6S,7R*)-7-Phenyl-4-tosyl-1,4-oxazepan-6-ol (****14k****).* White solid, mp 132-134 °C; R_f (hexane/ EtOAc 3:2) 0.37; yield 167 mg, 48%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 3.05-3.10 (m, 1 H), 3.40 (dd, *J* = 15.0 and 3.6 Hz, 1 H), 3.73 (dd, *J* = 15.0 and 1.2 Hz, 1 H), 3.88 (d, 3.0 Hz, 1 H), 3.89 (d, 3.0 Hz, 1 H), 3.91-3.95 (m, 1 H), 4.19 (dd, *J* = 12.6 and 3.0 Hz, 1 H), 4.43 (d, *J* = 7.8 Hz, 1 H), 7.28 (t, *J* = 7.2 Hz, 1 H), 7.33-7.36 (m, 4 H), 7.40 (d, *J* = 7.8 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 52.6, 54.5, 73.5, 76.2, 88.3, 126.6, 127.2, 128.0, 128.6, 130.1, 136.0, 141.2, 144.0; IR (KBr, neat) 3508, 2923, 1597, 1494, 1336, 1161, 1089, 1029, 816, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264 found 348.1268.

4.3.13. (6R,7S*)-6-Methyl-7-phenyl-4-tosyl-1,4-oxazepan-6-ol (****15l****).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 173 mg, 48%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 2.44 (s, 3 H), 3.00 (dt, *J* = 12.6 and 4.2 Hz, 1 H), 3.10 (d, *J* = 15.6 Hz, 1 H), 3.64 (d, *J* = 15.0 Hz, 1 H), 3.88 (dt, *J* = 12.0 and 3.6 Hz, 1 H), 3.98 (dd, *J* = 13.8 and 3.6 Hz, 1 H), 4.17 (dd, *J* = 12.6 and 4.2 Hz, 1 H), 4.68 (s, 1 H), 7.23-7.26 (m, 1 H), 7.31 (t, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.41 (d, *J* = 7.2 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 21.7, 53.3, 61.6, 74.0, 76.4, 89.2, 126.9, 127.0, 127.2, 127.7, 130.1, 136.0, 139.3, 144.0; IR (KBr, neat) 3507, 2929, 2872, 1595, 1451, 1335, 1157, 1024, 815, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421 found 362.1431.

4.3.14. (6R,7R*)-6-Methyl-7-phenyl-4-tosyl-1,4-oxazepan-6-ol (****15l'****).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 126 mg, 35%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 2.44 (s, 3 H), 3.24 (d, *J* = 13.8 Hz, 1 H), 3.27-3.31 (m, 1 H), 3.45 (d, *J* = 14.4 Hz, 1 H), 3.53 (dt, *J* = 13.8 and 3.6 Hz, 1 H), 3.77-3.82 (m, 1 H), 4.10-4.15 (m, 1 H), 4.41 (s, 1 H), 7.29-7.35 (m, 7 H), 7.70 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 24.4, 51.9, 60.8, 71.4, 74.8, 88.0, 127.4, 128.1, 128.2, 128.3, 130.1, 135.5, 138.1, 143.9; IR (KBr, neat) 3507, 2929, 2872, 1595, 1451, 1335, 1157, 1024, 815, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421 found 362.1431.

4.3.15. (6R,7S*)-7-Methyl-4-tosyl-1,4-oxazepan-6-ol (****15m****).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 43 mg, 15%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 3 H), 2.43 (s, 3 H), 3.28 (d, *J* = 13.8 and 4.2 Hz, 1 H), 3.31-3.34 (m, 1 H), 3.44 (dt, *J* = 13.8 and 4.2 Hz, 1 H), 3.49 (dd, *J* = 14.4 and 4.2 Hz, 1 H), 3.64 (dt, *J* = 12.6 and 3.0 Hz, 1 H), 3.78-3.83 (m, 2 H), 3.97 (dt, *J* = 12.0 and 4.2 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.67 (d,

J = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 18.5, 21.7, 51.2, 54.1, 70.0, 72.2, 79.2, 127.0, 130.0, 135.9, 143.8; IR (KBr, neat) 3508, 2973, 2925, 1598, 1495, 1337, 1163, 1089, 1039, 763, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ (M + H)$^+$ 286.1108 found 332.1318.

4.3.16. (6S,7S*)-7-Methyl-4-tosyl-1,4-oxazepan-6-ol (**15m'**).* Pale yellow oil; R_f (hexane/ EtOAc 4:1) 0.38; yield 145 mg, 51%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.0 Hz, 3 H), 2.42 (s, 3 H), 2.87-2.92 (m, 1 H), 3.02 (d, *J* = 8.4 Hz, 1 H), 3.22 (d, *J* = 15.0 Hz, 1 H), 3.53-3.56 (m, 2 H), 3.64 (d, *J* = 15.0 Hz, 1 H), 3.74 (ddd, *J* = 12.0, 9.0 and 3.0 Hz, 1 H), 4.04 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.1, 21.7, 52.8, 54.5, 73.1 76.6, 83.1, 127.0, 130.0, 136.0, 143.9; IR (KBr, neat) 3508, 2973, 2925, 1598, 1495, 1337, 1163, 1089, 1039, 763, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ (M + H)$^+$ 286.1108 found 332.1318.

*4.3.17. 1-(4-Tosylmorpholin-2-yl)ethanol (diastereomeric mixture, 9:1, **14m**).* Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 75 mg, 25%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.0 Hz, 3 H), 2.21 (t, *J* = 10.8 Hz, 1 H), 2.30 (brs, 1 H), 2.38 (dd, *J* = 10.8 and 1.8 Hz, 1 H), 2.45 (s, 3 H), 3.35 (dd, *J* = 7.8 and 7.2 Hz, 1 H), 3.53-3.62 (m, 3 H), 3.69 (t, *J* = 12.0 Hz, 1 H), 3.96 (d, *J* = 11.4 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 2 H, minor), 7.35 (d, *J* = 8.4 Hz, 2 H, major), 7.63 (d, *J* = 7.8 Hz, 2 H, major), 7.67 (d, *J* = 8.4 Hz, 2 H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) 18.9, 20.2, 21.7, 22.8, 45.6, 47.2, 52.8, 54.6, 66.0, 68.2, 73.2, 76.7, 79.2, 83.2, 127.0, 128.0, 130.0, 130.1, 132.3, 143.9, 144.2; IR (KBr, neat) 3508, 2973, 2925, 1598, 1495, 1337, 1163, 1089, 1039, 763, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ (M + H)$^+$ 286.1108 found 332.1318.

4.4. Synthesis of (±)-viloxazine 1

*4.4.1. 2-(Bromomethyl)- 4-tosylmorpholine (**9**).* Carbon tetrabromide (671 mg, 2.0 mmol) was added in one portion to a solution of **7a** (500 mg, 1.84 mmol) in dry CH_2Cl_2 (3.5 mL) at 0 °C, and the reaction was stirred at 0 °C. After 10 minutes, a solution of Ph_3P (530 mg, 2.0 mmol) in CH_2Cl_2 (1.5 mL) was added via cannula and stirred at 0 °C for 10 min. Then the reaction mixture was allowed to warm to room temperature and further stirred for 2 h. After reaction completed, the mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography to give the bromide **9** as white solid M.P. 81-82 °C; R_f (hexane) 0.80; yield 583 mg, 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.24 (t, *J* = 10.2 Hz, 1 H), 2.42-2.47 (m, 1 H), 2.45 (s, 3 H), 3.31 (dd, *J* = 10.8 and 5.4 Hz, 1 H), 3.35 (dd, *J* = 10.2 and 5.4 Hz, 1 H), 3.51 (d, *J* = 11.4 Hz, 1 H), 3.69-3.77 (m, 3 H), 3.95 (d, *J* = 10.2 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 31.5, 45.4, 49.0, 66.2, 74.3, 128.0, 130.0, 132.2, 144.3; IR (KBr, neat) 2920, 2862, 1597, 1452, 1344, 1167, 1097, 974, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{17}BrNO_3S$ (M + H)$^+$ 334.0107, found 334.0115.

*4.4.2. 2-((2-Ethoxyphenoxy)methyl)-4-tosylmorpholine (**11**).* To a solution 2-ethoxyphenol **10** (414 mg, 3 mmol) in CH_3CN (10 mL) was added K_2CO_3 (620 mg, 4.5 mmol) at room temperature, followed by a solution of **9** (1200 mg, 4.5 mmol) in CH_3CN (1 mL). The reaction mixture was heated to reflux overnight. After cooling to rt, silica gel was added to the reaction mixture and the solvent was removed on the vacuum. The residue was purified by column chromatography to give **11** as a white solid, M.P. 90-92 °C; R_f (hexane/ EtOAc 4:2) 0.40; yield 381 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3 H), 2.36 (t, *J* = 5.4 Hz, 1 H), 2.43 (s, 3 H), 2.45 (dt, *J* = 11.4 and 3.6 Hz, 1 H), 3.55 (d, *J* = 11.4 Hz, 1 H), 3.72 (dt, *J* = 11.4 and 2.4 Hz, 1 H), 3.80 (d, *J* = 11.4 Hz, 1 H), 3.93-3.97 (m, 3 H), 4.02-4.05 (m, 3 H), 6.84-6.89 (m, 3 H), 6.92-6.96 (m, 1 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.0. 21.7, 45.7, 48.0, 64.6, 66.1, 70.5, 73.8, 114.0, 116.1, 121.1, 122.7, 128.0, 129.9, 132.3, 144.1, 148.4, 149.6; IR (KBr, neat) 2924, 2854, 1596, 1504, 1453, 1346, 1256, 1167, 1122, 1041, 961, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_5S$ (M + H)$^+$ 392.1526, found 392.1536.

4.4.3. *2-((2-Ethoxyphenoxy)methyl)morpholine, (±)-viloxazine (**1**).* To a cooled (-78 °C) green suspension of sodium metal (33 mg, 1.44 mmol) and naphthalene (208 mg, 1.62 mmol) in dry THF (4.0 mL) was added the corresponding *N*-tosyl protected (±)-viloxazine **11** (140 mg, 0.36 mmol) under argon, and the mixture wasstirred for 45 min at the same temperature. Then, the reactionwas hydrolyzed with brine (10.0 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried overanhydrous $MgSO_4$ and evaporated. The resulting residue was purified by flash chromatography (deactivated silica gel, ether/acetone) to yield the corresponding pure product as colourless solid, M.P. 177-179 °C; R_f (MeOH/ $CHCl_3$, 9:1) 0.40; yield 145 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3 H), 2.81 (t, *J* = 11.4 Hz, 1 H), 2.89 (d, *J* = 9.0 Hz, 1 H), 2.95 (dd, *J* = 12.6 and 6.6 Hz, 1 H), 3.15 (d, *J* = 12.0 Hz, 1 H), 3.70 (t, *J* = 11.4 Hz, 1 H), 3.75 (t, *J* = 6.0 Hz, 1 H), 3.91-3.97 (m, 3 H), 4.04-4.08 (m, 3 H), 6.87-6.89 (m, 2 H), 6.91-6.93 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.1, 45.7, 48.3, 64.7, 67.8, 71.0, 74.9, 114.1, 115.4, 121.2, 122.2, 148.8, 149.5; IR (KBr, neat) 3440, 2924, 1503, 1453, 1255, 1125, 1039, 1002, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_3$ (M + H)$^+$ 238.1438, found 238.1437.

Acknowledgements

PG is thankful to Council of Scientific and Industrial Research (CSIR), New Delhi, for her fellowship. Authors are also grateful to CSIR, New Delhi, for financial support (Grant No. 02/0159/13/EMR-II). Authors are also grateful to Central Instruments Facility (CIF) of Indian Institute of Technology Guwahati for NMR facilities.

Supplementary data

Supplementary data related to this article can be found online at doi:10.

References and notes

1. (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641-662; (b) Audouze, K.; Nielson, E. Ø.; Peters, D. *J. Med. Chem*. **2004**, *47*, 3089-3104; (c) Sharma, G.; Park, J. Y.; Park, M. S. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 3188-3191; (d) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8333-8336; (e) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett*. **1994**, *35*, 8337-8340.
2. (a) Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev*. **2004**, *10*, 23-44; (b) Versiani, M.; Cassano, G.; Perugi, G.; Benedetti, A.; Mastalli, L.; Nardi, A.; Savino M. J. *Clin. Psychiatry* **2002**, *63*, 31-37; (c) Wong, E. H. F.; Sonders, M. S.; Amara, S. G.; Tinholt, P.

M.; Piercey, M. F. P.; Hoffmann, W. P.; Hyslop, D. K.; Franklin, S.; Porsolt, R. D.; Bonsignori, A.; Carfagna, N.; McArthur, R. A. *Biol. Psychiatry* **2000**, *47*, 818-829; (d) Audouze, K.; Nielsen, O.; Peters, D. *J. Med. Chem*. **2004**, *47*, 3089-3104.

3. (a) Ancliff, R. A.; Cook, C. M.; Eldred, C. D.; Gore, P. M.; Harrison, L. A.; Hayes, M. A.; Hodgson, S. T.; Judd, D. B.; Keeling, S. E.; Lewell, X. Q.; Mills, G.; Robertson, G. M.; Swanson, S.; Walker, A. J.; Wilkinson, M. 2003, PCT Int. Appl. WO 03082861; (b) Ong, J.; Kerr, D. I. B.; Bittiger, H.; Waldmeier, P. C.; Baumann, P. A.; Cooke, Mickel, N. G.; S. J.; Froestl, W. *Eur. J. Pharmacol.* **1998**, *362*, 27-34; (c) Kuo, S.-C.; Blythin, D. J.; Kreutner, W. 1999, U.S.Patent 5929236.
4. (a) Eisenhut, M.; Brandau, Missfeldt, W.; M. *Nuclear Medicine and Biology* **1989**, *16*, 805-811; (b) Kenneth, B.; Sloan, K. G. S. *Tetrahedron* **1984**, *40*, 3997-4001; (c) Han, Y.; Tang, W.-Q.; Yan, C.-G. *Tetrahedron Lett*. **2014**, *55*, 1441-1443; (d) Liang, S.; Jasinski, J.; Hammond, G. B.; Xu, B. *Org. Lett*. **2015**, *17*, 162-165.
5. (a) Bowers, W. S.; Ebing, W.; Fukuto, T. R.; Martin, D. In *Chemistry of Plant Protection*; Springer: Berlin, 1986; Vol. 1, pp 55-56; (b) Worthing, C. R.; *The Pesticide Manual*, 7th ed.; British Crop Protection Council: 1983; pp 265, 550.
6. (a) Licandro, E.; Maiorana, S.; Papagni, A.; Pryce, M.; Zanotti-Gerosa, A.; Rivaa, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1891-1894; (b) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, S.; Zanotti-Gerosa, A. *J. Organomet. Chem*. **1995**, *486*, 279-282; (c) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 66-72.
7. (a) Ritzen, B.; Hoekman, S.; Verdasco, E. D.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem*. **2010**, *75*, 3461-3464; (b) Lanman, B. A.; Myers, A. G. *Org. Lett*. **2004**, *6*, 1045-1047.
8. (a) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett*. **2009**, *11*, 257-260; (b) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2008**, ***47***, 3784-3786.
9. Wilkinson, M. C. *Tetrahedron Lett*., 2005, **46**, 4773-4775.
10. (a) Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett*. **2005**, *7*, 937-939; (b) Jagtap, R. S.; Joshi, N. N. *Tetrahedron: Asymmetry* **2011**, *22*, 1861-1864; (c) O'Reilly, M. C.; Lindsley, C. W. *Tetrahedron Lett*. **2012**, *53*, 1539-1542.
11. Burland, P. A.; Osborn, H. M.; Turkson, A. *Bioorg. Med. Chem*. **2011**, *19*, 5679-5692.
12. Gharpure, S. J.; Prasad, J. V. K. *J. Org. Chem*. **2011**, *76*, 10325-10331.
13. Dave, R.; Sasaki, N. A. *Org. Lett*. **2004**, *6*, 15-18.
14. (a) Lupi, V.; Albanese, D.; Landini, D.; Scaletti, D.; Penso, M. *Tetrahedron* **2004**, *60*, 11709-11718; (b) Zhou, J. Z.; Zhou, L.; Yeung, Y.-Y. *Org. Lett*. **2012**, *14*, 5250-5253.
15. (a) D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem*. **2006**, *71*, 4678-4681; (b) Ghorai, M. K.; Shukla, Das, D.; K. *J. Org. Chem*. **2009**, *74*, 7013-7022; *(c)* Bornholdt, J.; Felding, J.; Kristensen, j. L. *J. Org. Chem*. **2010**, *75*, 7454-7457.
16. Leathen, L. M.; Rosen, R. B.; Wolfe, P. J. *J. Org. Chem*. **2009**, *74*, 5107-5110.
17. (a) Sequeira, F. C.; Chemler, S. R. *Org. Lett*. **2012**, *14*, 4482-4485; (b) Deka, M. J.; Indukuri, K.; Sultana, S.; Borah, M.; Saikia, A. K. *J. Org. Chem*. **2015**, *80*, 4349-4359.
18. Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem*. **2007**, 2100-2106.
19. Buriks, R. S.; Lovett, E. G. *J. Org. Chem*. **1987**, *52*, 5247-5254.
20. Aparicio, D. M.; Terán, J. L.; Roa, L. F.; Gnecco, D.; Juárez, J. R.; Orea, M. L.; Mendoza, A.; Flores-Alamo, M.; Micouin, L. *Synthesis* **2011**, 2310-2313.
21. Ghosh, P.; Saha, P.; Bondalapati, S.; Indukuri, K.; Saikia, A. K. *J. Org. Chem*. **2014**, *79*, 4119-4124.
22. Liu, H.; Qiao, Z.; Jiang, X. *Org. Biomol. Chem*. **2012**, *10*, 7274-7277.
23. Gudla, V.; Balamurugan, R. *J. Org. Chem*. **2011**, 76, 9919-9933.
24. The crystallographic data for compounds **8k** has been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication numbers CCDC 1419078.
25. (a) Balsamo, A.; Giorgi, I.; Lapucci, A.; Lucacchini, A.; Macchia, B.; Macchia, F.; Martini, C.; Rossi, A. *J. Med. Chem*. **1987**, *30*, 222-225; (b) Liang, L.; Bhatt, P. P.; Dain, D.; Taquet, J.-P.; Pechenov, A.; Tchesnokov, A.; Mariaux, R. U.S. Pat. Appl. Publ. 2011, US 20110251198 A1.