Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7365

www.rsc.org/obc

PAPER

One pot synthesis of amino acid derived chiral disubstituted morpholines and 1,4-oxazepanes *via* tandem aziridine/epoxide ring opening sequences†

Krishnananda Samanta and Gautam Panda*

Received 23rd March 2011, Accepted 22nd June 2011
DOI: 10.1039/c1ob05462g

A new one-pot synthetic strategy is described for the synthesis of enantiomerically pure *cis*-3,5-disubstituted morpholines and 3,6-disubstituted 1,4-oxazepanes *via* tandem aziridine/epoxide ring opening sequences. This new strategy describes how epoxy alcohols could act as both a nucleophile and an electrophile in a tandem fashion and undergo intermolecular regioselective ring opening of chiral aziridines for the first time.

Introduction

The design and synthesis of chiral heterocycles has received a lot of attention in synthetic organic chemistry due to their diverse applications as drug candidates,[1] materials,[2] and for catalysis.[3] Among them, morpholine structural units are generally used in pharmaceutical industry, the World Drug Index cites 100 drugs containing a morpholine core. Morpholine containing structural units exhibit a wide range of biological activites,[4] including antidepressant,[5] **1**, antioxidant,[6] serotonin agonist, NK-1 and NK-2 receptor antagonist, and antifungal,[7b] **2** and $GABA_B$ receptor antagonist[7c,d] **3**, Fig. 1. Furthermore, heterocycles containing nitrogen and oxygen, such as oxazepanes have been important synthetic targets for synthetic and medicinal chemists,[8] because of their diverse biological properties.[9] 1,4-Oxazepane structural frameworks can be found in natural products such as neurotoxin batrachotoxin.[10] Recently, Shankaran and coworkers reported the synthesis and biological evaluation of oxazepane, diazepane, and thiazepane derivatives as nitric oxide synthase inhibitor.[11] The amino acids derived oxazepane units are also important building blocks for the synthesis of peptide nucleic acids (PNAs) to control the biological function in the desired manner.[12]

We have been working on the synthesis and biology of *S*-amino acid–base chiral heterocyles and natural product-like molecules.[13] We are interested in developing new methodology to construct chiral heterocycles for biological evaluation.[13h,i] Towards this objective, we chose to synthesize enantiomerically pure amino acids derived morpholines and 1,4-oxazepanes for which not many practical methods are known.[11,14,15] Moreover, one pot synthetic approaches towards chiral morpholine and oxazepane derivatives are still not reported. Very recently, our group reported a new route to 1,4-oxazepanes and 1,4-diazepanes from Garner aldehyde.[15b] Herein, we disclosed base promoted one pot synthesis of *cis*-3,5-disubstituted morpholines and 3,6-disubstituted 1,4-oxazepanes *via* tandem aziridine/epoxide ring opening sequences.

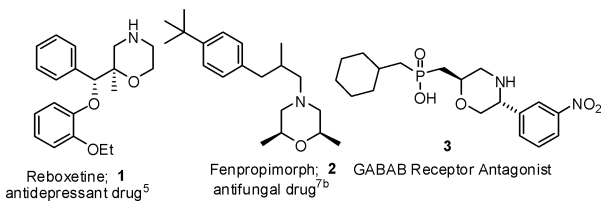
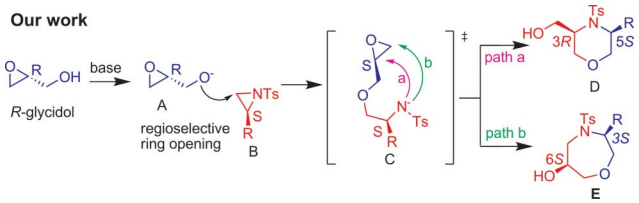


Fig. 1 Some bioactive morpholines derivatives.

As a three-member-ring heterocycle, both aziridine and epoxide have ring strain and readily undergo ring opening reaction with different types of nucleophiles.[16] In the present paper we shown that chiral epoxy alcohols could act as both a nucleophile and an electrophile in tandem fashion and undergo regioselective ring opening of chiral aziridines.

In our work, we reasoned that initial base mediated conversion of epoxy alcohol to alkoxide anion (Scheme 1) itself could act as the nucleophile **A** and might undergo regioselective ring opening of aziridine **B** to yield **C** as a fleeting intermediate. Next, sulfonamide anion of the intermediate **C** might proceed nucleophilic ring opening of epoxide (either path **a** or **b**, or both) to give either product **D** or **E** or mixture of both **D** and **E**.



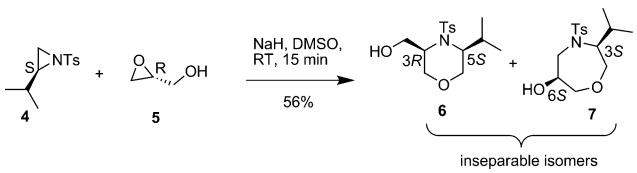
Scheme 1 Our hypothesis.

Medicinal and Process Chemistry Division, CSIR, Central Drug Research Institute, Lucknow, 226001, UP, India. E-mail: gautam.panda@gmail.com, gautam_panda@cdri.res.in; Fax: +91-522-2623405; Tel: +91-522-2612411-18, Ext. 4385, 4603

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05462g

Results and discussion

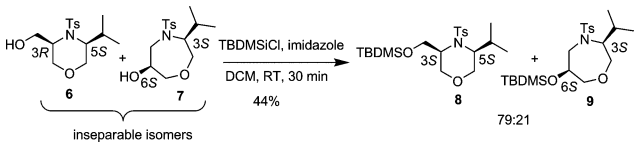
To test our hypothesis, first NaH promoted ring opening of N-Ts aziridine **4** with *R*-glycidol **5** was carried out in DMSO at room temperature (Scheme 2). Aziridine **4** was prepared according to our reported procedure.[16] To our delight, the starting materials were fully consumed within 15 min, as confirmed by TLC monitoring, and a new spot was detected. From ^{1}H NMR analysis, ratio of 2.1 : 1 mixture of two products was found which were inseparable on silica gel column chromatography. Next, our expected product was assigned by mass spectroscopy analysis. From MS (ESI) spectrum, one peak was found at *m*/*z* 314 (M + H)$^+$ ion that indicates that the reaction proceeded smoothly *via* one pot tandem aziridine/epoxide ring opening sequences because, the exact mass of the compounds **6** and **7** are found to be 313.13 amu.



Scheme 2 One pot synthesis of disubstituted morpholine and 1,4-oxazepane derivatives.

Our next objective was to optimize the reaction conditions (Table 1) in order to improve the yield and regioselectivity. Chiral aziridine **4** and *R*-glycidol **5** were chosen as model substrates. The best result was obtained when the reaction was performed in the presence of 1.2 equiv ^{t}BuOK in DMSO with 70% yield (Table 1, Entry 6). It is noted that the yield of the product was improved, but the regioselectivity remained unchanged. There was no formation of product when the reaction was carried out at 0 °C in THF, DMF or DMSO. Again, when the reaction was performed in THF, promoted by NaH or ^{t}BuOK, no desired product was detected (Table 1, Entry 2 & 7). In THF, it is probable that the alkoxide anion of *R*-glycidol is bound to potassium as a tight ion pair (supported by literature precedent[17]) that did not allow intermolecular nucleophilic attack on the aziridine ring. In polar solvent like DMSO, DMF the reaction facilitates because the anion is more naked than that complexed to the potassium. This observation suggested that a polar solvent was necessary for the reaction.

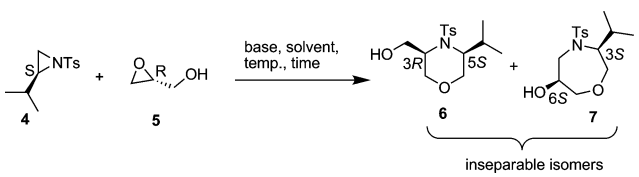
Next, our challenge was to separate the two isomers. On the basis of the above aforementioned results, we confirmed that the initial ring opening of aziridine with alkoxide anion **A** of *R*-glycidol was highly regioselective. The reaction occurred at the least hindered carbon due to the steric bulk of the epoxide ring. However, final intramolecular epoxide ring opening by sulfonamide anion gave possibility of two isomers (path **a** & **b**, Scheme 1). According to our hypothesis (Scheme 1), a mixture of primary and secondary carbinol bearing substituted morpholines and oxazepanes were formed, respectively. In an effort to separate the compounds, the mixture was treated with TBDMSiCl (1 equiv), imidazole in dry DCM for 30 min at room temperature (Scheme 3).



Scheme 3 Separation of inseparable isomers.

We were delighted to find that more reactive primary carbinol of **6** was readily protected with TBDMS group and easily separated using silica gel column chromatography with 44% yield. From ^{1}H NMR spectrum analysis, formation of 3.8 : 1 mixture of **8** and **9** was found. Under this condition secondary carbinol of **7** was also prone to react with TBDMSiCl. Pure compound **7** was isolated with 48% yield at room temperature based on **4**. Next, we decided to optimize the reaction temperature to avoid the unwanted TBDMS protection of **7**. After several attempts, (Table 2) a reproducible result was obtained, when the inseparable mixture was treated with TBDMSiCl at 0 °C for 20 min. When the reaction was performed at –10 °C, 100% pure morpholine **8** (13%) was obtained along with 56% recovery of starting materials **6** & **7** (Table 2, entry 2). Using this optimized condition (entry 3), two isomers were separated that were confirmed by ^{1}H and ^{13}C NMR analysis.

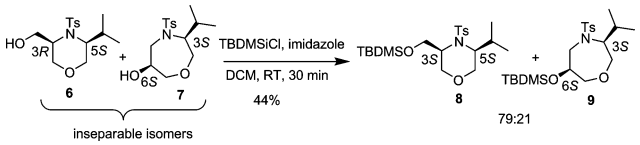
Table 1 Optimization of the reaction conditions[a]



Entry	Base (equiv)	Solvent	*T*/°C	Time	%Yield[b]	dr[c]
1	NaH (4)	DMSO	RT	15 min	56	2.1 : 1
2	NaH (4)	THF	RT	180 min	0	
3	K_2CO_3 (1.5)	THF	RT	180 min	0	
4	K_2CO_3 (1.5)	DMSO	RT	45 min	Trace	
5	^{t}BuOK (1.2)	DMSO	0 °C	60 min	0	
6	^{t}BuOK (1.2)	DMSO	RT	10 min	70	2.1 : 1
7	^{t}BuOK (1.2)	THF	RT	60 min	0	
8	^{t}BuOK (1.2)	DMF	0 °C	40 min	0	
9	^{t}BuOK (1.2)	DMF	RT	20 min	63	2.1 : 1

[a] Reaction conditions: **4** (1 equiv), **5** (1 equiv). [b] Combined yield of **6** & **7** based on **4**. [c] dr values determined by ^{1}H NMR analysis of the crude product.

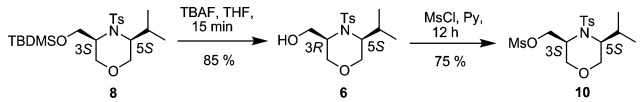
Table 2 Optimization of the reaction temperature



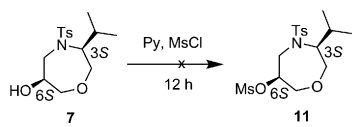
Entry	T/°C	Time	Ratio **8** : **9**[a]	**8**, %yield[b]
1	–20	120 Min	0 : 0	0
2	–10	60 Min	100 : 0	13[c]
3	0	20 Min	100 : 0	25.7[d]

[a] Ratio was determined by ^{1}H NMR analysis. [b] Isolated yield based on **4**. [c] recovery of starting materials **6** & **7** (56%). [d] isolated yield of pure **7** at 0 °C (46.6%) based on **4** (See exp. section).

To further ensure the formation of **6** and **7**, some functional group manipulation was carried out on the compounds (Scheme 4 and Scheme 5). TBDMS group of the separated compound **8** was deprotected by TBAF to afford primary carbinol **6** in 85% yield. Next, carbinol **6** was protected with a mesyl group using standard conditions to obtain **10**, which gives scope for further structural diversification.



Scheme 4 Synthesis of **10**.



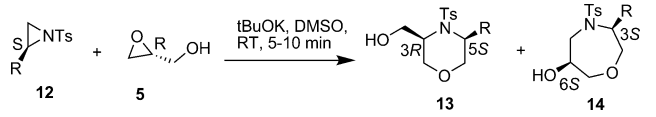
Scheme 5 Synthesis of **11**.

Similarly, compound **7** was treated with mesyl chloride in the presence of a minimum volume of pyridine, but did not furnish **11**, giving recovery of starting material which indicates the presence of less reactive secondary carbinol group. This above experiment proves the formation of primary (CH_2OH) and secondary carbinol (CHOH) bearing six and seven member morpholine and 1,4-oxazepane derivatives which was also supported by DEPT spectrum analysis (see ESI†).

Next, the scope of this tandem aziridine/epoxide ring opening reactions was then explored. A wide range of chiral monosubstituted aziridines were investigated (Table 3).

All aziridines reacted well in the tandem process to furnish products with moderate to good yield as revealed in Table 3. Surprisingly, *sec*-butyl, *iso*-butyl and indole-substituted aziridines gave only seven member oxazepane derivatives that were confirmed from ^{1}H and ^{13}C NMR spectroscopy analysis. It was further confirmed through treatment with TBDMSiCl at 0 °C (Table 2, entry 3) and no TBDMS protected product was detected. However, mixture of both isomers was obtained for methyl, benzyl-substituted aziridines. Methyl substituted aziridine afforded an inseparable mixture of isomers on silica gel column chromatography which was separated

Table 3 Ring opening reaction of aziridines (**12**) with *R*-glycidol promoted by ^{t}BuOK[a]



Entry	Aziridine	*R*	**13**(%)[b]	**14**(%)[b]
1	**12a**	$CH_2CH(CH_3)_2$	NF[c]	**14a** (74)
2	**12b**	$CH(CH_3)CH_2CH_3$	NF	**14b** (65)
3	**12c**	CH_2-indole	NF	**14c** (63)
4	**12d**	CH_3[d]	**13a** (22.7)	**14d** (43.7)
5	**12e**	$CH_2C_6H_5(OMe)$[e]	**13b** (25)	**14e** (39)

[a] Reaction conditions: **12** (1 equiv), **5** (1 equiv). [b] Isolated yield based on **12**. [c] NF means not formed. [d] Inseparable mixtures were formed. Yields are given after separation based on **12d** (see exp. section.). [e] Compounds are separated on silica gel column chromatography.

in accordance with the above mentioned optimized condition (Table 2, entry 3).

However, to confirm the stereochemistry of those products, a 2D NMR experiment was carried out (see ESI†). In compound **14d** (Fig. 2), the locations of all the protons were confirmed on the basis of the COSY spectrum. The *cis* relationship between Hα-3/Hα-2 (J_{cis} = 4.2 Hz), Hα-6/Hα-5 (J_{cis} = 4.3 Hz) and *trans* relationship between Hα-6/Hβ-7 (J_{trans} = 8.7 Hz) was deduced from the vicinal coupling constant value. The absolute configuration of C-6 was determined on the basis of the NOESY correlations between Hα-2/Hα-7, Hβ-2/Hβ-7, Hα-5/Hα-3, Hβ-7/Hβ-5, Hβ-2/CH_3-3, Hβ-5/CH_3-3 and Hβ-7/CH_3-3. The absolute configuration of **14d** is (3*S*, 6*S*) which was also supported by our proposed hypothesis.

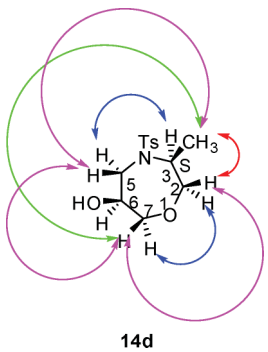
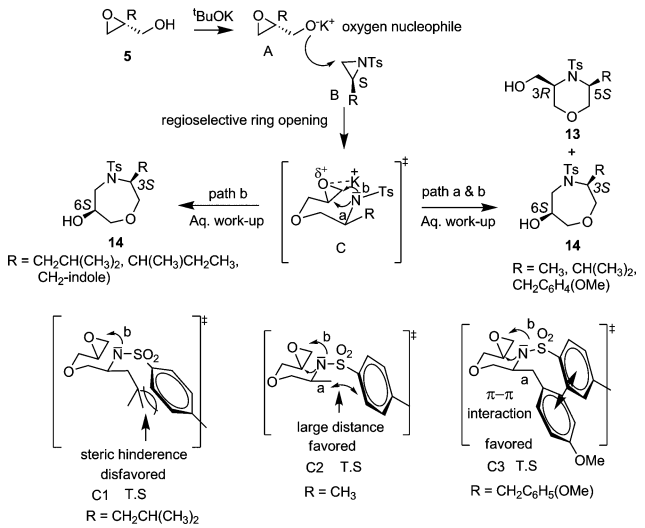


Fig. 2 Confirmation of stereochemistry by NOE contacts from NOESY Experiment of **14d** (400 MHz, $CDCl_3$).

Based on the above results, a plausible mechanism was proposed (Scheme 6). First, ^{t}BuOK mediated conversion of *R*-glycidol to oxygen nucleophile **A**, which underwent highly regioselective aziridine ring opening to produce another nitrogen nucleophile **C** as a fleeting intermediate. Afterwards, there would be two probable pathways (path **a** & **b**) to form the desired molecules. Interestingly, aziridines **12a–c** showed a similar kind of reactivity to follow path **b**, giving 1,4-oxazepane derivatives **14a–c**.

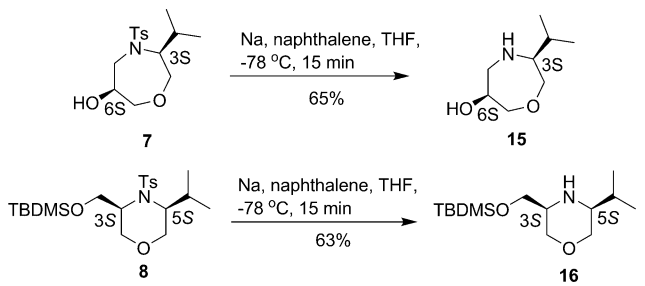
However, aziridines **12d–e** followed path **a** & **b**, leading to the formation of mixture of isomers. To rationalize the formation of six and seven member chiral heterocycles, we focused our attention on the intermediate **C**. Probably, depending on the stability of **C** and activation of the epoxide ring due to non covalent interaction with



Scheme 6 Proposed plausible mechanism.

potassium ion, the above results could be explained. For aziridines **12a–c**, large steric interaction between tosyl and alkyl groups disfavored six members T.S (see **C1**, Scheme 6) that allowed path **b** to provide 1,4-oxepane derivatives. In case of **12d** & **4**, probably, the large distance between tosyl and alkyl groups minimized the steric interaction (see **C2**) in comparison to **14a–c** that helps to stabilize **C** and high reactivity of epoxide ring follows path **a** & **b** giving the mixture of isomers. For benzyl substituted aziridines **12e**, probably, π–π stacking interaction and epoxide reactivity is the driving force to follow the path **a** & **b** to furnish separable isomers. It is worth noting that yield of formation of seven member oxazepane is more favored than six member morpholine.

The tosyl group of the selected molecules **7** & **8** were deprotected (Scheme 7) by using sodium naphthalenide [131] in dry THF with 65% & 63% yield, respectively.



Scheme 7 Tosyl group deprotection of **7** & **8**.

In conclusion, a new one pot synthetic strategy for the synthesis of enatiomerically pure *cis*-3,5-disubstituted morpholines and 3,6-disubstituted 1,4-oxazepanes is described from *S*-amino acids derived aziridines and *R*-glycidol *via* tandem aziridine/epoxide ring opening sequences. A plausible reaction mechanism was proposed and it was also rationalized that formation of six member morpholine and seven member 1,4-oxazepane derivatives depending on chiral aziridines. This new strategy describes how epoxy alcohols could act as both nucleophile and electrophile in a tandem process and undergo intermolecular regioselective ring opening of aziridines for the first time. Further scope of this methodology is being investigated in our laboratory.

Experimental

General methods

IR spectra were recorded on a Perkin-Elmer FT-IR RXI spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker DPX-200 (operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C) or DPX-300 (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25 °C. Coupling constants (*J* values) are given in hertz (Hz). Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded using electron spray ionization (ESMS). Glycerol or *m*-nitro benzyl alcohol was used as matrix. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel). Detecting agents used (for TLC) were iodine vapors and/or spraying with an aqueous solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (100–200 mesh) procured from Qualigens (India) using freshly distilled solvents. The diastereomeric excess was determined by LichroCART Chiradex column (250 × 4 mm), (*R*,*R*)-Whelk-01) column using *iso*-propanol/acetonitrile, flow rate 0.50 mL min^{-1} and for **14d** hexane/acetonitrile, flow rate 0.80 mL min^{-1} as eluent at 20 °C.

Experimental procedures and characterization data

Experimental procedure for the synthesis of chiral aziridines 4, 12a–d & 12e

The chiral aziridines are prepared in our previously reported procedure.[17]

(*S*)-2-*iso*-Propyl-1-tosylaziridine 4. Colorless solid; mp 78–82 °C; yield, 47% (four steps); R_f 0.50 (8.5/1.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ = +4.4 (c 0.1, $CHCl_3$); IR (neat, cm^{-1}): 3298, 3024, 2964, 1463, 1321, 1158, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79–7.75 (m, 2H), 7.30–7.26 (m, 2H), 2.55–2.43 (m, 5H), 2.02–2.00 (m, 1H), 1.46–1.30 (m, 1H), 0.89 (d, 3H, *J* = 6.6), 0.79 (d, 3H, *J* = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 135.8, 129.4, 128.2, 45.8, 32.4, 30.1, 21.6, 19.6, 19.2; MS (ESI): *m*/*z* 240 [M+H]$^+$.

(*S*)-2-*iso*-Butyl-1-tosylaziridine 12a. Colorless oil; yield, 45% (four steps); R_f 0.50 (8.5/1.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ = +24.1 (c 0.11, $CHCl_3$); IR (neat, cm^{-1}): 3291, 3021, 2958, 1462, 1159, 764; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83–7.80 (m, 2H), 7.34–7.32 (m, 2H), 2.82–2.74 (m, 1H), 2.63–2.61 (m, 1H), 2.44 (s, 3H), 2.03–2.01 (m, 1H), 1.67–1.56 (m, 1H), 1.35–1.30 (m, 2H), 0.889–0.885 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 135.0, 129.5, 127.8, 40.3, 38.9, 33.9, 26.6, 22.6, 21.8, 21.5; MS (ESI): *m*/*z* 254 [M+H]$^+$.

(*S*)-3-((1-Tosylaziridin-2-yl)methyl)-1*H*-indole 12c. Colorless oil; yield, 46% (four steps); R_f 0.50 (7.0/3.0, hexane/ethyl acetate); $[\alpha]_D^{25}$ = +8.6 (c 0.06, $CHCl_3$); IR (neat, cm^{-1}): 3408, 3021, 2923, 1320, 1218, 1158, 762; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (bs, 1H), 7.68–7.66 (m, 2H), 7.48 (d, 1H, *J* = 7.8), 7.32 (d, 1H, *J* = 8.1), 7.21–7.06 (m, 4H), 6.996–6.990 (m, 1H), 3.11–2.99 (m, 2H), 2.86 (dd, 1H, J_1 = 6.5, J_2 = 14.9), 2.72 (d, 1H, *J* = 6.6), 2.40 (s, 3H), 2.22–2.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 136.0,

134.6, 129.3, 127.6, 127.1, 122.3, 121.9, 119.3, 118.5, 111.1, 111.0, 40.6, 33.3, 27.1, 21.5; MS (ESI): *m/z* 327 $[M+H]^+$.

(*S*)-2-Methyl-1-tosylaziridine 12d. Colorless semi-solid; yield, 42% (four steps); R_f 0.51 (8.0/2.0, hexane/ethyl acetate); $[\alpha]_D^{25}$ –13.1 (*c* 0.1, $CHCl_3$); IR (neat, cm^{-1}): 3291, 3027, 2958, 1457, 1320, 1158, 759; ^1H NMR (200 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.34–7.30 (m, 2H), 2.88–2.74 (m, 1H), 2.61–2.57 (m, 1H), 2.43 (s, 3H), 2.02–1.99 (m, 1H), 1.23 (d, 3H, J = 5.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 135.3, 129.6, 127.7, 35.7, 34.6, 21.5, 16.7; MS (ESI): *m/z* 212 $[M+H]^+$.

(*S*)-2-(4-Methoxybenzyl)-1-tosylaziridine 12e. First, phenolic-OH group of L-tyrosine methyl ester hydrochloride was methylated and then aziridine was synthesized in accordance with our previously reported sequence.[17]

Experimental procedure for the synthesis of 6 & 7

To a stirred solution of chiral aziridine **4** (500 mg, 2.09 mmol) and *R*-glycidol (0.14 mL, 2.09 mmol) in anhydrous DMSO (10 mL) was added ^{t}BuOK (281 mg, 2.51 mmol) and then the mixture was stirred for 5–15 min at RT. After completion of reaction, the reaction mixture was diluted with water and aqueous layer was extracted with AcOEt (2 × 50 mL). Removal of solvent under vacuum and column chromatography of the crude product on silica gel with AcOEt-hexane (2.5 : 7.5) as eluent to furnish inseparable mixture of **6** & **7** (458 mg, 70% yield) as a colorless oil.

Separation of inseparable isomers (6 & 7). To a stirred solution of mixture compounds (**6** & **7**) (458 mg, 1.46 mmol) in anhydrous DCM (10 mL) were added TBDMSiCl (220 mg, 1.46 mmol) and imidazole (149 mg, 2.19 mmol) at 0 °C. The resulting solution was stirred for 20 min at the same temperature. The reaction mixture was diluted with water and then aqueous layer was extracted with DCM (2 × 50 mL). Removal of solvent under vacuum and column chromatography of the crude product on silica gel with AcOEt-hexane to furnish TBDMS-protected **8** (230 mg, 25.7% yield) based on **4** as colorless oil and **7** (305 mg, 46.6% yield) based on **4** as a colorless oil.

Next, to a stirred solution of **8** (230 mg, 0.54 mmol) in anhydrous THF (10 mL) under an atmosphere of N_2, was added TBAF (1 M) (0.64 mL) dropwise at 0 °C. The reaction mixture was stirred for 25 min at the room temperature The reaction mixture was diluted with water and extracted with ethyl acetate (2 × 50 mL). Removal of solvent under vacuum and column chromatography of the crude product on silica gel with AcOEt-hexane to furnish **6** (142 mg, 84.5% yield) as colorless oil and 21.7% yield based on **4**.

(3*S*,5*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl)-5-*iso*-propyl-4-tosylmorpholine 8. Colorless oil; yield, 25.7% (based on **4**); R_f 0.51 (9.0/1.0, hexane/ethyl acetate); IR (neat, cm^{-1}): 3431, 2958, 2863, 1638, 1218, 761; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.72 (m, 2H), 7.34–7.31 (m, 2H), 3.92–3.84 (m, 3H), 3.75 (dd, 1H, J_1 = 4.3, J_2 = 8.7), 3.56–3.50 (m, 1H), 3.32 (dd, 1H, J_1 = 3.3, J_2 = 10.7), 3.01 (dd, 1H, J_1 = 3.7, J_2 = 11.8), 2.88 (dd, 1H, J_1 = 3.5, J_2 = 11.8), 2.45 (s, 3H), 2.06–1.94 (m, 1H), 1.10 (d, 1H, J = 6.7), 0.98 (d, 1H, J = 6.4), 0.90 (s, 9H), 0.08 (s, 6H); MS (ESI): *m/z* 428 $[M+H]^+$.

(3*S*,6*S*)-3-*iso*-Propyl-4-tosyl-1,4-oxazepan-6-ol 7. Colorless oil; yield, 46.6% (based on **4**); R_f 0.51 (7.0./3.0, hexane/ethyl acetate); $[\alpha]_D^{25}$ = +6.8 (c 0.1, MeOH); HPLC analysis: de > 99 (t_R = 4.62 min, CH_3CN/*iso*-propanol); IR (neat, cm^{-1}): 3513, 3271, 2958, 1463, 1158, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76–7.73 (m, 2H), 7.27–7.24 (m, 2H), 5.14–5.12 (m, 1H), 3.54 (dd, 1H, J_1 = 2.7, J_2 = 11.5), 3.38 (dd, 1H, J_1 = 4.2, J_2 = 9.8), 3.25–3.07 (m, 3H), 2.98–2.95 (m, 1H), 2.72–2.69 (m, 1H), 2.49 (dd, 1H, J_1 = 2.7, J_2 = 5.0), 2.38 (s, 3H), 1.87–1.83 (m, 1H), 0.84–0.80 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 137.8, 129.5, 127.0, 78.1, 74.7, 71.1, 64.6, 47.4, 26.4, 21.4, 19.6, 19.5; MS (ESI): *m/z* 314 $[M+H]^+$, 336 $[M+Na]^+$.

(3*R*,5*S*)-5-*iso*-Propyl-4-tosylmorpholin-3-yl)methanol 6. Colorless oil; yield, 21.7% (based on **4**); R_f 0.50 (7.0/3.0, hexane/ethyl acetate); $[\alpha]_D^{25}$ = +25.61 (c 0.010, MeOH), IR (neat, cm^{-1}): 3421, 2922, 2857, 1463, 1218, 767; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.71 (m, 2H), 7.34–7.32 (m, 2H), 3.92–3.75 (m, 4H), 3.66–3.62 (m, 1H), 3.37 (dd, 1H, J_1 = 3.5, J_2 = 10.8), 3.03 (dd, 1H, J_1 = 3.7, J_2 = 11.9), 2.94 (dd, 1H, J_1 = 4.2, J_2 = 11.7), 2.45 (s, 3H), 2.31 (bs, 1H), 2.12–2.03 (m, 1H), 1.15 (d, 3H, J = 6.7), 0.98 (d, 3H, J = 6.5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.6, 138.0, 130.0, 126.8, 66.6, 65.2, 62.8, 59.1, 53.7, 29.5, 21.5, 20.6, 20.4; MS (ESI): *m/z* 314 $[M+H]^+$.

Experimental procedure for the synthesis of 10

The compound **6** (85 mg, 0.27 mmol) was dissolved in 1.5 mL anhydrous pyridine, and then it was cooled at 0 °C, followed by addition of methane sulfonyl chloride (0.06 mL, 0.81 mmol). Then it was continuous stirred for 12 h. The pyridine was quenched with dil HCl and then diluted with 30 mL water. The aqueous layer was extracted with ethyl acetate (2 × 50 mL) and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the crude product was then chromatographed over silica gel with eluent AcOEt-Hexane (3.5 : 6.5) to afford the title compound **10** (80 mg, 75%) as a colorless oil.

(3*S*,5*S*)-5-*iso*-Propyl-4-tosylmorpholin-3-yl)methylmethanesulfonate 10. Colorless oil; yield, 75%; R_f 0.52 (7.5/2.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ = +15.21 (c 0.098, MeOH), HPLC analysis: de > 99 (t_R = 4.63 min, CH_3CN/H_2O); IR (neat, cm^{-1}): 3421, 3028, 2922, 1635, 1349, 1170, 768; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.71 (m, 2H), 7.36–7.33 (m, 2H), 4.52–4.46 (m, 1H), 4.33 (dd, 1H, J_1 = 5.2, J_2 = 9.5), 3.95–3.76 (m, 3H), 3.37 (dd, 1H, J_1 = 3.4, J_2 = 11.2), 3.09 (s, 3H), 3.01–2.94 (m, 2H), 2.46 (m, 2H), 2.03–1.95 (m, 1H), 1.11 (dd, 1H, J = 6.8), 1.00 (d, 3H, J = 6.3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.8, 137.6, 130.0, 129.7, 127.0, 126.8, 67.4, 66.5, 64.6, 58.7, 50.5, 37.4, 29.7, 21.4, 20.5, 20.3; MS (ESI): *m/z* 348 $[M^+-CH(CH_3)_2]$, 392 $[M+H]^+$.

Experimental procedure for the synthesis of 14a–c

The procedure was followed as described for**6** & **7**.

(3*S*,6*S*)-3-*iso*-Butyl-4-tosyl-1,4-oxazepan-6-ol 14a. Colorless oil; yield, 74%; R_f 0.52 (7.5/2.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ –62.9 (*c* 0.105, MeOH); HPLC analysis: de > 99 (t_R = 4.66 min, CH_3CN/*iso*-propanol); IR (neat, cm^{-1}): 3510, 3276, 2957, 1461, 1328, 1157, 759; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2H), 7.33–7.30 (m, 2H), 4.95–4.91 (m, 1H), 3.66–3.59 (m, 1H), 3.39–3.18 (m, 4H), 3.08–3.00 (m, 1H), 2.82–2.75 (m, 1H), 2.57–2.53 (m, 1H), 2.44 (s, 3H), 1.66–1.53 (m, 1H), 1.39–1.33 (m, 2H), 0.85 (d, 3H, J = 6.6), 0.76 (d, 3H, J = 6.4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.1, 138.2, 129.5, 127.0, 72.9, 71.8, 51.8, 50.5, 44.0, 41.5, 24.2,

22.7, 21.8, 21.4; MS (ESI): *m/z* 254 [M$^+$-OH, $CH_2CH(CH_3)_2$], 310 [M$^+$-OH], 327.9 [M+H]$^+$, 344.9 [M+NH_4]$^+$.

(3*S*,6*S*)-3-*sec*-Butyl-4-tosyl-1,4-oxazepan-6-ol 14b. Colorless oil; yield, 65%; R_f 0.51 (7.5/2.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ −2.23 (*c* 0.101, MeOH); HPLC analysis: de > 99 (t_R = 4.67 min, CH_3CN/*iso*-propanol); IR (neat, cm^{-1}): 3431, 3290, 2965, 1328, 1217, 1159, 768; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.75 (m, 2H), 7.30–7.28 (m, 2H), 4.97–4.94 (d, 1H), 3.59–3.54 (m, 1H), 3.44–3.39 (m, 1H), 3.28–3.15 (m, 3H), 3.02–2.97 (m, 1H), 2.76–2.73 (m, 1H), 2.53–2.50 (m, 1H), 2.42 (s, 3H), 1.70–1.61 (m, 1H), 1.55–1.44 (m, 1H), 1.12–0.99 (m, 1H), 0.84 (d, 3H, *J* = 7.2), 0.82 (d, 3H, *J* = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.2, 129.5, 127.1, 71.8, 70.2, 57.6, 50.6, 44.1, 36.5, 25.3, 21.5, 15.1, 11.5; MS (ESI): *m/z* 254 [M$^+$-OH, $CH_2CH(CH_3)_2$], 310 [M$^+$-OH], 328 [M+H]$^+$, 345 [M+NH_4]$^+$.

(3*S*,6*S*)-3-((1*H*-Indol-3-yl)methyl)-4-tosyl-1,4-oxazepan-6-ol 14c. Colorless oil; yield, 63%; R_f 0.51 (6.5/3.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ −64.6 (*c* 0.105, MeOH); HPLC analysis: de > 99 (t_R = 4.74 min, CH_3CN/*iso*-propanol); IR (neat, cm^{-1}): 3413, 2985, 1700, 1429, 1226, 1155, 764; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (bs, 1H), 7.56–7.52 (m, 2H), 7.29–6.97 (m, 7H), 5.30–5.24 (m, 1H), 5.01–4.85 (m, 3H), 3.75–3.33 (m, 3H), 2.80 (bs, 2H), 2.36 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 136.2, 129.3, 127.2, 126.6, 123.3, 121.8, 119.3, 118.3, 111.2, 109.9, 77.2, 70.5, 69.7, 53.4, 52.2, 29.6, 21.9; MS (ESI): *m/z* 401 [M+H]$^+$.

Experimental procedure for the synthesis of 13a & 14d

To a stirred solution of chiral aziridine **12d** (580 mg, 2.74 mmol) and *R*-glycidol (0.18 mL, 2.74 mmol) in anhydrous DMSO (10 mL) was added ^{t}BuOK (369 mg, 3.29 mmol) and then the mixture was stirred for 5 min at RT. Same work-up procedure was followed as described for **6** & **7** and column chromatography of the crude product on silica gel with AcOEt-hexane (3.5 : 6.5) as eluent to furnish inseparable mixture (494 mg, 63% yield) as a colorless oil.

Separation of inseparable isomers

To a stirred solution of mixture compounds (494 mg, 1.73 mmol) in anhydrous DCM (10 mL) were added TBDMSiCl (260.7 mg, 1.73 mmol) and imidazole (176 mg, 2.59 mmol) at 0 °C. The resulting solution was stirred for 20 min at the same temperature. Same work-up procedure was followed as described for **6** & **7** and column chromatography of the crude product on silica gel with AcOEt-hexane to furnish TBDMS-protected morpholine (296 mg, 27% yield) based on **12d** as colorless oil and **14d** (342 mg, 43.7% yield) based on **12d** as a colorless oil.

Next, to a stirred solution of TBDMS-protected morpholine (296 mg, 0.74 mmol) in anhydrous THF (10 mL) under atmosphere of N_2, was added TBAF (1 M) (0.89 mL) dropwise at 0 °C. The reaction mixture was stirred for 30 min at the room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate (2 × 50 mL). Removal of solvent under vacuum and column chromatography of the crude product on silica gel with AcOEt-hexane to furnish **13a** (178 mg, 84.3% yield) as colorless oil and 22.7% yield based on **12d**.

(3*S*,5*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl)-5-methyl-4-tosylmorpholine. Colorless oil; yield, 27% (based on **12d**); R_f 0.53 (8.5/1.5, hexane/ethyl acetate); IR (neat, cm^{-1}): 3438, 2953, 2862, 1634, 1219, 1098, 768; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.70 (m, 2H), 7.32–7.29 (m, 2H), 4.04–3.81 (m, 4H), 3.68–3.59 (m, 2H), 3.23–3.18 (m, 1H), 3.11–3.06 (m, 1H), 2.43 (s, 3H), 1.33 (d, 3H, *J* = 7.0), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.3, 138.3, 129.8, 126.7, 70.5, 65.2, 62.7, 53.5, 47.6, 25.9, 21.5, 21.4, 18.2, −5.3, −5.5; MS (ESI): *m/z* 400 [M+H]$^+$, 421.7 [M+Na]$^+$.

(3*S*,6*S*)-3,6-Dimethyl-4-tosyl-1,4-oxazepane 14d. Colorless oil; yield, 43.7% (based on **12d**); R_f 0.51 (7.5/2.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ = +35.7 (c 0.101, MeOH); HPLC analysis: de > 99 (t_R = 17.75 min, hexane/CH_3CN); IR (neat, cm^{-1}): 3429, 3021, 2932, 2870, 1331, 1155, 764; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.70 (m, 2H), 7.32–7.29 (m, 2H), 4.16–4.11 (m, 2H), 3.93–3.78 (m, 2H), 3.75–3.69 (m, 2H), 3.56 (dd, 1H, J_1 = 4.1, J_2 = 12.7), 3.09 (dd, 1H, J_1 = 8.7, J_2 = 15.1), 2.43 (s, 3H), 2.28 (bs, 1H), 1.03 (d, 3H, *J* = 6.7); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.3, 137.8, 129.7, 126.8, 77.5, 77.4, 70.5, 53.6, 46.8, 21.4, 15.1; MS (ESI): *m/z* 272 [M+H$^+$-CH_3], 308 [M+Na]$^+$.

((3*R*,5*S*)-5-Methyl-4-tosylmorpholin-3-yl)methanol 13a. Colorless oil; yield, 22.7% (based on **12d**); R_f 0.51 (7.5/2.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ −12.46 (*c* 0.106, MeOH); HPLC analysis: de > 99 (t_R = 4.98 min, CH_3CN/*iso*-propanol); IR (neat, cm^{-1}): 3429, 2931, 2858, 1468, 1219, 764; ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.73–7.70 (m, 2H), 7.32–7.29 (m, 2H), 3.91–3.83 (m, 4H), 3.75–3.72 (m, 1H), 3.57–3.53 (m, 1H), 3.23–3.12 (m, 2H), 2.43 (s, 3H), 1.38 (d, 3H, *J* = 7.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 138.0, 129.9, 126.6, 70.4, 65.7, 63.0, 53.4, 47.8, 21.4, 21.0; MS (ESI): *m/z* 286 [M+H]$^+$.

Experimental procedure for the synthesis of 13b & 14e

To a stirred solution of chiral aziridine **12e** (480 mg, 1.51 mmol) and *R*-glycidol (0.10 mL, 1.51 mmol) in anhydrous DMSO (7 mL) was added ^{t}BuOK (203 mg, 1.81 mmol) and then the mixture was stirred for 5 min at RT. Same work-up procedure was followed as described for **6** & **7** and column chromatography of the crude product on silica gel with AcOEt-hexane furnished separable mixture of **13b** (147 mg, 25% yield) and **14e** (233 mg, 39% yield) as a colorless oil. Combine yield is 64%.

((3*R*,5*S*)-5-(4-Methoxybenzyl)-4-tosylmorpholin-3-yl) methanol 13b. R_f 0.51 (7.5/2.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ −21.6 (*c* 0.105, MeOH); HPLC analysis: de > 99 (t_R = 4.76 min, CH_3CN/*iso*-propanol); IR (neat, cm^{-1}): 3420, 2927, 2363, 1611, 1221, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H), 7.24–7.22 (m, 2H), 6.97–6.73 (m, 2H), 3.78 (s, 3H), 3.69–3.64 (m, 1H), 3.51–3.47 (m, 1H), 3.38–3.26 (m, 3H), 3.11–3.06 (m, 1H), 2.82–2.72 (m, 3H), 2.59–2.56 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 143.1, 137.5, 130.2, 129.5, 128.9, 126.9, 113.8, 71.7, 71.4, 55.1, 54.7, 50.5, 44.1, 37.1, 21.4; MS (ESI): *m/z* 414 [M+Na]$^+$, 430 [M+K]$^+$.

(3*S*,6*S*)-3-(4-Methoxybenzyl)-4-tosyl-1,4-oxazepan-6-ol 14e. R_f 0.49 (7.5/2.5, hexane/ethyl acetate); $[\alpha]_D^{25}$ −19.0 (*c* 0.109, MeOH); HPLC analysis: de > 99 (t_R = 4.95 min, CH_3CN/*iso*-propanol); IR (neat, cm^{-1}): 3445, 2362, 1631, 1220, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.56 (m, 2H), 7.24–7.21 (m, 2H), 6.97–6.94 (m, 2H), 6.75–6.72 (m, 2H), 4.19–4.10 (m, 2H), 3.88–3.76 (m, 7H), 3.58 (dd, 1H, J_1 = 3.6, J_2 = 12.7), 3.19 (dd, 1H,

J_1 = 6.9, J_2 = 15.0), 2.86 (dd, 1H, J_1 = 8.9, J_2 = 13.5), 2.65 (dd, 1H, J_1 = 6.0, J_2 = 13.6), 2.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.3, 143.2, 137.4, 130.1, 129.6, 129.2, 126.8, 113.9, 75.0, 71.1, 59.9, 55.1, 47.4, 35.0, 21.4; MS (ESI): *m/z* 121 $[CH_2C_6H_4OMe]^+$, 391.9 $[M+H]^+$ 414 $[M+Na]^+$, 433 $[M+2H+Na]^+$.

General experimental procedure for the synthesis of 15 & 16. Finely chopped sodium metal (12 equiv) and naphthalene (14 equiv) were dissolved in 7 mL dry THF. The reaction mixture was stirred for 2 h, until a dark green color was appeared. The desired THF solution of **7** & **8** were cooled to −78 °C and then Na-napthalenide solution was added dropwise to the reaction mixture *via* a syringe, until a dark green color was persisted. The reaction mixture was stirred for 15 min at −78 °C and then it was quenched by adding 1–2 drops water to discharge the green color. The reaction mixture was diluted with water and then extracted with EtOAc (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum and the column chromatography (eluent = MeOH/$CHCl_3$, 0.6 : 9.4) of crude product over silica gel furnished **15** & **16**.

(3*S*,6*S*)-3-*iso*-Propyl-1,4-oxazepan-6-ol 15. Brown oil; yield, 65%; R_f 0.25 (6.5/3.5, hexane/ethyl acetate); IR (neat, cm^{-1}): 3443, 2963, 1632, 1367, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03–4.01 (m, 2H), 3.93–3.84 (m, 1H), 3.68–3.53 (m, 2H), 3.17–3.14 (m, 1H), 2.41–2.37 (m, 1H), 2.09–2.02 (m, 1H), 1.07 (d, 3H, J = 6.8), 1.00 (d, 3H, J = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.3, 67.8, 57.3, 28.4, 18.9, 18.5; MS (ESI): *m/z* 144 $[M+2H-OH]^+$.

(3*S*,5*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl)-5-isopropyl-4-tosylmorpholine 16. Brown oil; yield, 63%; R_f 0.35 (6.5/3.5, hexane/ethyl acetate); IR (neat, cm^{-1}): 3402, 2366, 1584, 1261, 1131, 775; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85–3.79 (m, 2H), 3.74–3.69 (m, 3H), 3.62–3.54 (m, 3H), 2.00–1.94 (m, 1H), 0.96 (d, 3H, J = 7.3), 0.95 (d, 3H, J = 6.9); MS (ESI): *m/z* 274 $[M+H]^+$, 298 $[M+2H+Na]^+$.

Acknowledgements

This research project was supported by Department of Science and Technology (SR/S1/OC-74/2009), New Delhi, India. Krishnananda thanks Dr A. Ravishankar for helpful discussion about 2D NMR and CSIR for providing fellowship (NET-SRF). This has CDRI communication no 8086.

Notes and references

1 (*a*) J. Taunton, J. L. Collins and S. L. Schreiber, *J. Am. Chem. Soc.*, 1996, **118**, 10412; (*b*) P. J. Murray, M. Kranz, M. Ladlow, S. Taylor, F. Berst, A. B. Holmes, K. N. Keavey, A. Jaxa-Chamiec, P. W. Seale, P. Stead, R. J. Upton, S. L. Croft, W. Clegg and M. R. J. Elsegood, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 773.
2 (*a*) J. Sanchez-Quesada, M. R. Ghadiri, H. Bayley and O. Braha, *J. Am. Chem. Soc.*, 2000, **122**, 1175; (*b*) D. T. Bong, T. D. Clark, J. R. Granja and M. R. Ghadiri, *Angew. Chem., Int. Ed.*, 2001, **40**, 988.
3 E. R. Jarvo and S. J. Miller, *Tetrahedron*, 2002, **58**, 2481.
4 For a review on the synthesis and biological significance of C-substituted morpholines, see: (*a*) R. Wijtmans, M. K. S. Vink, H. E. Schoemaker, F. L. van Delft, R. H. Blaauw and F. P. J. T. Rutjes, *Synthesis*, 2004, 641.
5 E. H. F. Wong, M. S. Sonders, S. G. Amara, P. M. Tinholt, M. F. P. Piercey, W. P. Hoffmann, D. K. Hyslop, S. Franklin, R. D. Porsolt, A. Bonsignori, N. Carfagna and R. A. McArthur, *Biol. Psychiatry*, 2000, **47**, 818.
6 (*a*) M. C. Chrysselis, E. A. Rekka and P. N. Kourounakis, *J. Med. Chem.*, 2000, **43**, 609; (*b*) M. C. Chrysselis, E. A. Rekka, I. C. Siskou and P. N. Kourounakis, *J. Med. Chem.*, 2002, **45**, 5406; (*c*) C. Guilloneau, Y. Charton, Y. Ginot, M. Fouquier-d'Herouel, M. Bertrand, B. Lockhart, P. Lestage and S. Goldstein, *Eur. J. Med. Chem.*, 2003, **38**, 1.
7 (*a*) H. Dieckmann, M. Stockmaier, R. Kreuzig and M. Bahadir, *Fresenius' J. Anal. Chem.*, 1993, **345**, 784; (*b*) J. A. H. Lainton, M. C. Allen, M. Burton, S. Cameron, T. R. G. Edwards, G. Harden, R. Hogg, W. Leung, S. Miller, S. S. Morrish, S. M. Rooke and B. Wendt, *J. Comb. Chem.*, 2003, **5**, 400 and references cited therein; (*c*) D. Enders, O. Meyer, G. Raabe and J Runsink, *Synthesis*, 1994, 66–72; (*d*) R Dave and N. A. Sasaki, *Org. Lett.*, 2004, **6**, 15–18.
8 (*a*) H. Ohno, H. Hamaguchi, M. Ohata, S. Kosaka and T. Tanaka, *J. Am. Chem. Soc.*, 2004, **126**, 8744; (*b*) L. Banfi, A. Basso, G. Guanti, N. Kielland, C. Repetto and R. Riva, *J. Org. Chem.*, 2007, **72**, 2151.
9 (*a*) K. Ø. Audouze, E. Nielsen and D. Peters, *J. Med. Chem.*, 2004, **47**, 3089; (*b*) G. Sharma, J. Y. Park and M. S. Park, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3188; (*c*) S. Y. Ablordeppey, R. B. Altundas, X. Y. Zhu, E. V. K. S. Kumar, T. Jackson, A. Khan and B. L. Roth, *Bioorg. Med. Chem.*, 2008, **16**, 7291.
10 (*a*) T. J. Grinsteiner and Y. Kishi, *Tetrahedron Lett.*, 1994, **45**, 8333; (*b*) T. J. Grinsteiner and Y. Kishi, *Tetrahedron Lett.*, 1994, **45**, 8337.
11 K. Shankaran, K. L. Donnelly, S. K. Shah, C. G. Caldwell, P. Chen, W. K. Hagmann, M. MacCoss, J. L. Humes, S. G. Pacholok, T. M. Kelly, S. K. Grant and K. K. Wong, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5907.
12 (*a*) P. Wittung, P. E. Nielsen, O. Buchardt, M. Egholm and B. Nordén, *Nature*, 1994, **368**, 561; (*b*) K. E. Nelson, M. Levy and S. L. Miller, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 3868.
13 (*a*) J. K. Mishra and G. Panda, *Synthesis*, 2005, 1881; (*b*) J. K. Mishra, J. S. Rao, G. N. Sastry and G. Panda, *Tetrahedron Lett.*, 2006, **47**, 3357; (*c*) Shagufta and G. Panda, *Org. Biomol. Chem.*, 2007, **5**, 360; (*d*) J. K. Mishra and G. Panda, *J. Comb. Chem.*, 2007, **9**, 321; (*e*) J. K. Mishra, P. Garg, P. Dohare, A. Kumar, M. I. Siddiqi, M. Ray and G. Panda, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1326; (*f*) A. K. Srivastava and G. Panda, *Chem.–Eur. J.*, 2008, **14**, 4675; (*g*) A. K. Srivastava, S K. Das and G. Panda, *Tetrahedron*, 2009, **65**, 5322; (*h*) M. K. Parai and G. Panda, *Tetrahedron Lett.*, 2009, **50**, 4703; (*i*) K. Samanta, B. Chakravarti, J. K. Mishra, S. K. D. Dwivedi, L. V. Nayak, P. Choudhry, H. K. Bid, R. Konwar, N. Chattopadhyay and G. Panda, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 283; (*j*) J. K. Mishra, K. Samanta, M. Jain, M. Dikshit and G. Panda, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 244; (*k*) S K. Das, A. K. Srivastava and G. Panda, *Tetrahedron Lett.*, 2010, **51**, 1483; (*l*) k. Samanta and G. Panda, *Org. Biomol. Chem.*, 2010, **8**, 2823.
14 (*a*) M. L. Leathen, B. R. Rosen and J. P. Wolfe, *J. Org. Chem.*, 2009, **74**, 5107 and references cited therein; (*b*) L. Wang, Q. B. Liu, D. S. Wang, X. Li, H. W. Han, W. J. Xiao and Y. G. Zhou, *Org. Lett.*, 2009, **11**, 1119.
15 (*a*) S. M. Clark and H. M. I. Osborn, *Tetrahedron: Asymmetry*, 2004, **15**, 3643; (*b*) S K. Das, A. K. Srivastava and G. Panda, *Tetrahedron Lett.*, 2010, **51**, 1483.
16 K. Samanta and G. Panda, *Chem.–Asian J.*, 2011, **6**, 189 references cited therein.
17 G. B. Payne, *J. Org. Chem.*, 1962, **27**, 3819.