Bangladesh J. Sci. Ind. Res. **42**(2), 135-146, 2007

Synthesis of Biologically Important Chiral Morpholine Derivatives

Mohammad Nurnabi and Mohammad Ismail

Department of Applied Chemistry and Chemical Technology,
University of Dhaka, Dhaka-1000, Bangladesh

Abstract

Electrophile (Br_2) induced cyclization of optically pure *N*-allyl-*β*-aminoalcohols **1a, 1b, 1c** and **2a, 2b** gave chiral morpholines (2*R*, 5*S*)-**3a, 3b, 3c** and (2*S*, 5*R*)-**4a, 4b** respectively. Quenching of the reaction with Na_2CO_3 after 5 min afforded 60 % conversion with 100 % *de*, whilst a 2:1 mixture of two diastereomers was obtained upon complete conversion. However, electron donating substituent (OMe) on the para position of the *C*-2 aryl moiety (substrates **1b** and **2b**) accelerates the reaction to give 80 % conversion and 50 % isolated yield of single diastereomer after 5 min and 8:1 mixture of diastereomers on complete conversion after 10 min.

Introduction

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mamalian nervous system (Wood *et al.*, 2000), which is activated by a class of receptor, known as GABA receptor. The subclass $GABA_B$ receptor is already identified (Bowery *et al.*, 1980; Hill and Bowery, 1981; Bowery and Hill, 1983) and the activation of this receptor causes prolonged synaptic inhibition through restriction of pre-synaptic calcium channel activity and activation of post synaptic potassium channels (Couve *et al.*, 2000; Bettler *et al.*, 1998; Kerr and Ong, 1995; Bowery *et al.*, 2000). The unbalanced pre-synaptic and post-synaptic neurotrans-mission triggers a lot of physiological processes and diseases including nocicep-tion, cognition, epilepsy, depression and drug addiction (Couve *et al.*, 2000; Bettler *et al.*, 1998) where $GABA_B$ plays the major roles. Thus activation (by agonists) of $GABA_B$ causes depression and absence seizure symptom, while blockade (by anta-gonists) causes excessive locomotor activities. It was documented that the blockade of $GABA_B$ stimulates the locomotor activities and ethanol withdrawal syndrome in mice (Colombo *et al.*, 2001; Carai *et al.*, 2002). $GABA_B$ Antagonists are thus used in the treatment of absence seizures (Snead, 1992), memory deficits (Mondadori *et al.*, 1992) and countering the respiratory depression caused by excessive doses of $GABA_B$ agonists (Blythin *et al.*, 1996). It was previously found that chiral morpholine **SCH5091** and its non-chiral derivatives are effective antagonists for $GABA_B$ receptor (Colombo *et al.*, 2001; Carai *et al.*, 2002; Blythin *et al.*, 1996; Ong *et al.*, 1999). Many more researches should have been devoted to the synthesis of morpholine derivatives having $GABA_B$ antagonizing properties as only a few methods are so far disclosed (Kelley *et al.*, 1996; Largeron *et al.*, 2002). Herein, we like

to report the synthetic methodology for highly substituted chiral morpholines from optically pure *N*-allyl-*β*-amino alcohols using bromine. *N*-allyl-*β*-amino alcohol contains a *δ*-hydroxy alkene moiety and the cyclization of *γ*-, *δ*- and *ω*-alkenyl alcohols can be achieved by acid catalysis (Miura *et al.*, 2000), ring closure metathesis (Nicolaou *et al.*, 1980) and halocyclisation (Corey, 1987; Jung and Lew, 1991; Jung *et al.*, 1993). Cyclizations of *γ*-hydroxy alkenes by iodine (Saksena *et al.*, 1996; Baldwin and Mclver, 1987; Reitz *et al.*, 1987; Bennet *et al.*, 1992) and cyclization of *γ*- and *δ*-hydroxy alkenes using phenylselenenyl bromide (Ezquerra *et al.*, 1990) have also been reported.

Materials and Methods

General technical data: Commercially available reagents were used without further purification. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo-Erba Model 1106 instrument. Proton nuclear magnetic resonance (^{1}H NMR) spectra and nuclear Overhauser effect (n.O.e) experiments were conducted at 300 MHz. on a Bruker DPX300 instrument and at 500 MHz. on a Bruker DRX500 spectometer as specified. Chemical shifts are reported in parts per million (*δ*) downfield from tetramethylsilane as internal standard reference and coupling constants are given in Hertz (Hz). ^{13}C NMR spectra were recorded with a Bruker DPX300 (75 MHz) and chemical shift values are reported in parts per million (ppm) relative to $CDCl_3$ (δ=77.0). Mass spectra were obtained on a VG Autospec mass spectrometer at 70 eV using electron impact (EI) or electron spray (ES) ionisation techniques. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer either by a film technique on sodium chloride discs by spreading dichloromethane (DCM) solution on the discs. The samples for the film technique were prepared by dissolving a small amount of compounds in dichloromethane and the solutions were poured on to sodium chloride disc and the dichloromethane was allowed to evaporate. Specific rotations were measured at ambient temperature with an Optical Activity Ltd., AA-1000 polarimeter. The $[\alpha]_D$ is given in deg per dm at 20^O C, and the concentration (*c*) is expressed in g 100 mL^{-1}. X-Ray crystallographic structures were determined on a Stoe STADI 4-circle machine.

General procedure for the cyclisation of *δ*-alkenols using Br_2

All reactions were performed under nitrogen atmosphere. *N*-Allyl-*β*-amino alcohols **1a**, **1b**, **1c** or **2a**, **2b** (0.5 mmol) were dissolved in freshly distilled dichloromethane (2-3 ml) in a round bottom flask. The flask was closed with a septum and the solution was

cooled to –78^{O} C by immersing the flask in a mixture of acetone-dry ice. A 10 % (w/v) solution of bromine in dichloromethane (0.8 ml, 1.0 mol eq.) was added dropwise over 5 min. After the addition was complete, the mixture removed from the cooling bath (acetone-dry ice) and immediately quenched with saturated aq. Na_2CO_3 solution (5 ml). The dichloromethane layer was separated, the aq. layer was further extracted with dichloromethane (2x5 ml) and the combined organic layer was dried ($MgSO_4$), filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether-diethylether solvent system.

(2*R*,5*S*)-2-(Bromomethyl)-5-isopropyl-2-phenylmorpholine (3a):

As a colourless oil (0.05 g, 31 %); $[\alpha]_D$ + 4 (*c* 1.00 in $CHCl_3$) (HRMS: 300.0974 (M^++H) (^{81}Br); $C_{14}H_{20}NOBr$ requires 300.0963 (M^++H) (^{81}Br); δ_H (300 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8, Me), 1.0 (3H, d, *J* 6.8, Me), 1.55-1.7 (1H, m, C<u>H</u>{Me}$_2$), 2.75-2.85 (1H, m, 5-H^{ax}), 3.25 (1H, t, *J* 10.7, 6-H,^{ax} apparent triplet instead of a double doublet), 3.47 (1H, d, *J* 11.5, CH_2Br), 3.77 (1H, d, *J* 11.5, CH_2Br), 3.95 (1H, dd, *J* 10.7 and 3.3, 6-H^{eq}), 3.96 (1H, d, *J* 10.8, 3-H^{eq}), 4.52 (1H, d, *J* 10.8, 3-H^{ax}), 7.25-7.4 (3H, m, ArH), 7.53 (2H, d, *J* 8.2, ArH); δ_C (75 MHz, $CDCl_3$) 18.9 (Me), 19.3 (Me), 31.0 (CH), 39.5 (CH_2), 54.4 (CH), 58.3, 71.3 (CH_2), 74.3 (CH_2), 77.9, 126.2, 128.0, 128.8 and 142.3; m/z (ES) 300 and 298 (100 %, M^++H); υ_{max}/cm^{-1}(film) 2918, 2714, 2433, 1741, 1654, 1550, 1449, 1353, 1276, 1179, 1111, 1051, 941, 906, 849, 762, 749, 698, 563 and 524.

(2*R*,5*S*) –2-(Bromomethyl)- 5 -isopropyl-2(4-methoxyphenyl) morpholine (3b) :

As a colourless oil (0.09 g, 52 %); $[\alpha]_D$ +8 (*c* 1.00 in $CHCl_3$) (Found: C, 54.65; H, 6.70; N, 4.15; Br, 24.1; $C_{15}H_{22}NO_2Br$ requires C, 54.9; H, 6.75; N, 4.25; Br, 24.30 %); δ_H (300 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.8, Me), 0.99 (3H, d, *J* 6.8, Me), 1.7-1.75 (1H, m, C<u>H</u>{Me}$_2$), 2.45-2.5 (1H, m, 5-H^{ax}), 3.05 (1H, d, *J* 11.5, CH_2Br), 3.4 (1H, d, *J* 11.5, CH_2Br), 3.65 (1H, dd, *J* 11.7 and 9.6, 6-H^{ax}), 3.75 (1H, d, *J* 11.1, 3-H^{eq}), 3.8 (3H, s, OMe), 3.9(1H, dd, *J* 11.7 and 3.5, 6-H^{eq}), 4.28 (1H, d, *J* 11.1, 3-H^{ax}), 6.9 (2H, d, *J* 9.0, ArH), 7.34 (2H, d, *J* 9.0, ArH); δ_C (75 MHz, $CDCl_3$) 19.3 (Me), 19.4 (Me), 29.9 (CH), 37.6 (CH_2), 52.9 (CH), 55.6 (OMe), 60.4, 65.0 (CH_2), 74.6 (CH_2), 114.0, 128.0, 128.8 and 142.3; m/z (ES) 330 and 328 (100 %, M^++H), υ_{max}/cm^{-1}(film) 3318, 2958, 2899, 2829, 2800, 1614, 1583, 1515, 1464, 1448, 1275, 1261, 1180, 1081, 1032, 831, 809, 764, 750, 612 and 547.

Methyl – 4 - [(2*R*,5*S*) -2 - (bromomethyl) – 5 - isopropyl – 2 – phenylmorpholin – 2 - yl]benzoate (3c):

As a colourless oil (0.07 g, 32 %); $[\alpha]_D$ +10 (*c* 1.00 in $CHCl_3$). A small portion of the oily product was converted to the hydrobromide salt by treating with ethereal HBr in ether. The product precipitated as a colourless solid which crystallized from EtOH as colourless plates, m. p. 154-156^{O} C

(HRMS : 438.0115 (M^+) (^{79,81}Br); $C_{16}H_{22}NO_3Br$ (HBr) requires 438.0102 (M^+) (^{79,81} Br); δ_H (300 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8, Me), 1.03 (3H, d, *J* 6.8, Me), 1.6-1.7 (1H, m, C<u>H</u>{Me}$_2$), 2.75-2.85 (1H, m, 5-H^{ax}), 3.25 (1H, t, *J* 10.8, 6-H,^{ax} apparent triplet instead of a double doublet), 3.45 (1H, d, *J* 11.5, CH_2Br), 3.88 (1H, d, *J* 11.5, CH_2Br), 3.9 (3H, s, CO_2Me), 3.94 (1H, dd, *J* 10.8 and 7.3, 6-H^{eq}), 3.95 (1H, d, *J* 11.0, 3-H^{eq}), 4.52 (1H, d, *J* 11.0, 3-H^{ax}), 7.62 (2H, d, *J* 8.7, ArH), 8.0 (2H, d, *J* 8.7, ArH); δ_C (75 MHz, $CDCl_3$) 18.9 (Me), 19.2 (Me), 31.0 (CH), 39.0 (CH_2), 52.5 (CH), 54.4 (OMe ester), 58.7, 71.3 (CH_2), 74.0 (CH_2), 126.3, 129.8, 130.1, 147.5 and 167.2 (CO ester); m/z (ES) 438 and 436 (M^++H); υ_{max}/cm^{-1}(film) 3326, 3029, 2961, 2914, 2861, 1703, 1667, 1493, 1452, 1265, 1245, 1082, 1064, 1031, 851, 757, 736 and 700.

(2*S*,5*R*)-2-(Bromomethyl)-2,5-diphenyl morpholine (4a):

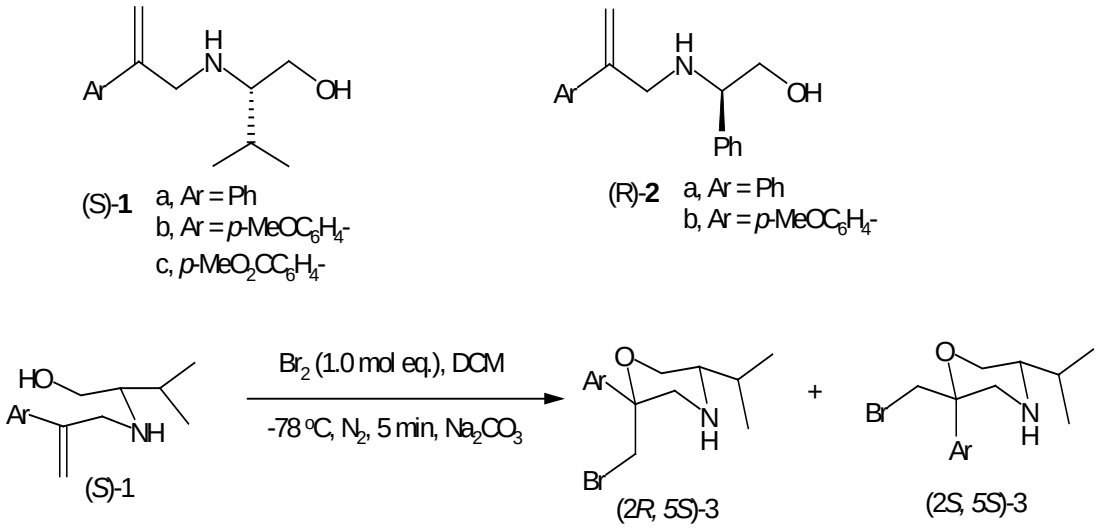
As a cplourless oil (0.05 g, 30 %); $[\alpha]_D$ -34 (*c* 1.00 in $CHCl_3$) (HRMS: 334.0605 (M^++H) (^{81}Br); $C_{17}H_{18}NOBr$ requires 334.0630 (M^++H) (^{81}Br); δ_H (300 MHz, $CDCl_3$-CF_3COOD) 3.79 (1H, d, *J* 13.8, CH_2Br), 3.88 (1H, d, *J* 13.8, CH_2Br), 4.00 (1H, dd, *J* 12.8 and 4.1, 6-H), 4.16 (1H, d, *J* 11.8, 3-H), 4.25 (1H, dd, *J* 12.8 and 4.6, 6-H), 4.38 (1H, d, *J* 11.8, 3-H), 4.60-4.65 (1H, m, 5-H), 7.30-7.60 (10H, m, ArH); δ_C (75 MHz, $CDCl_3$) 40.1 (CH_2), 54.0 (CH_2), 62.1 (CH_2), 65.8, 67.3 (CH), 113.7, 117.5, 127.5, 129.7, 129.9, 130.4, 130.6, 131.4, 136.2 and 136.7; m/z (ES) 334 and 332 (M^++H); υ_{max}/cm^{-1}(film) 2961, 2879, 2741, 2456, 1612, 1577, 1555, 1514, 1437, 1273, 1258, 1179, 1086, 1031, 909, 826, 790, 763, 697 and 559.

(2*S*,5*R*)-2-(Bromomethyl)–2-(4-methoxy-phenyl)-5-phenylmorpholine (4b) :

As a colourless oil (0.11 g, 50 %); $[\alpha]_D$ -26 (*c* 1.00 in $CHCl_3$). A small portion of the oily product was converted to the hydrobromide salt by treating with ethereal HBr in ether. The product precipitated as colourless solid which crystallized from EtOH as colourless plates, m. p. 141-143 ^oC (Found: C, 48.6; H, 4.75; N, 2.95; Br, 35.85; $C_{18}H_{20}NO_2Br$(HBr) requires C, 48.8; H, 4.75; N, 3.15; Br, 36.05 %); δ_H (500 MHz, $CDCl_3$-CF_3COOD) 3.55 (1H, d, *J* 11.7, CH_2Br), 3.7 (1H, d, *J* 11.7, CH_2Br), 3.8 (1H, d, *J* 11.2, 3-H), 3.83 (1H, d, *J* 11.2, 3-H), 3.84 (3H, s, OMe), 4.33 (1H, dd, *J* 13.6 and 3.9, 6-H), 4.4 (1H, dd, *J* 13.6 and 2.7 6-H), 4.45-4.47 (1H, m, 5-H), 7.0 (2H, d, *J* 8.8, ArH), 7.37 (2H, d, *J* 8.8, ArH), 7.48-7.5 (3H, m, ArH), 7.75-7.76 (2H, m, ArH); δ_C (75 MHz, $CDCl_3$) 46.4 (CH_2), 53.9 (CH_2), 55.6 (CH), 60.4 (OMe), 68.3, 74.8, 113.9, 126.7, 127.7, 128.1, 128.4, 129.0, 134.8, 140.5 and 159.3; m/z (ES) 444 and 442 (M^++H); υ_{max}/cm^{-1}(film) 3308 (NH), 3066, 2967, 2912, 2802, 1719 (CO ester), 1609, 1578, 1548, 1474, 1436, 1410, 1326, 1275, 1223, 1206, 1118, 1040, 1017, 967, 940, 854, 822, 773, 700 and 590.

Results and Discussion

The optically pure *N*-allyl-*β*-amino alcohols were synthesized by employing a palladium catalyzed three component cascade reactions (Gai *et al.*, 2001) and were subjected to various electrophile mediated cyclization



Scheme 1

conditions (Table I). A brief investigation revealed that the best result is achievable by using Br_2 solution in dichloromethane (1.0 mol eq.) at -78^{O} C for 5 min. The cyclization of the *δ*-hydroxy alkene moiety could give rise to two diastereomers (Scheme 1). However, the diastereoselectivity is dependent to the reaction conditions (Table I). Substrates were dissolved in dry dichloromethane (DCM), cooled to -78^{O} C and 10 % Br_2 solution (1.0 mol eq.) was added drop wise under nitrogen, the mixture was left for 5 min at the same temperature and then quenched with saturated aq. solution of Na_2CO_3. Monitoring the reaction by NMR showed that after 5 min the reaction had proceeded to 60 % to afford a single diastereomer in 30-32 % isolated yield (Table I, entry 5). Substrate **1b** undergoes 80% conversion over a 5 min reaction time with the production of a single diastereomer of the respective product in 50 % yield (Table I, entry 9). However, after a reaction time of 10 min, substrate **(*S*)-1a** underwent complete conversion giving a 2:1 mixture of diastereomeric products (Table I, entry 3). Extending the reaction period to 4h did not alter the diastereomeric ratio (*dr*) beyond 2:1 (Table I, entry 4). Furthermore, substrate (*S*)-**1b**, over a 10 min reaction time, underwent complete conversion giving a *dr* of 8:1 and 68% isolated yield (Table I, entry 8). *N*-bromosuccinimide (NBS) /dichloromethane /rt reaction condition required 3h for complete conversion and gave a 2:1 mixture of diastereomers (Table I, entry 1). It was also observed with *N*-bromosuccinimide (NBS) that there was a 30 min induction period (Table I, entry 2). Both I_2 and PhSeBr failed to effect cyclization (Table 1, entries 6 and 7). Substrate **(*S*)-1c** gave a similar result to **(*S*)-1a** with Br_2/dichloromethane/-78^{O} C. Substrates **(*R*)-2a, 2b** were then subjected to the best conditions achieved and comparable

Table I. Cyclisation of δ-hydroxy alkene moiety in (*S*)-1a,1b,1c and (*R*)-2a,2b[a]

Entry	Substrate	Conditions	Conver. (%)[b]	*dr*[c]	Yield (%)[d]
1	(*S*)-1a	NBS / DCM / rt / 3 h	100	2:1	50
2	(*S*)-1a	NBS / DCM /-78 ^{o}C / rt / 30 min	0	-	-
3	(*S*)-1a	Br_2 / DCM /-78 ^{o}C / 10 min	100	2:1	-
4	(*S*)-1a	Br_2 / DCM / -78 ^{o}C to rt / 4 h	100	2:1	-
5	(*S*)-1a	Br_2 / DCM /-78 ^{o}C / 5 min / Na_2CO_3	60	100 : 0	32
6	(*S*)-1a	I_2 / Py / MeCN / rt/ 20 h	-	-	-
7	(*S*)-1a	PhSeBr / MeCN / rt / 2 h / K_2CO_3	-	-	-
8	(*S*)-1b	Br_2 / DCM /-78 ^{o}C / 10 min /	100	8 : 1	68
9	(*S*)-1b	Na_2CO_3	80	100 : 0	50
10	(*S*)-1c	Br_2 / DCM /-78 ^{o}C / 5 min / Na_2CO_3	60	100 : 0	30
11	(*R*)-2a	Br_2 / DCM /-78 ^{o}C / 5 min / Na_2CO_3	60	100 : 0	30
12	(*R*)-2b	Br_2 / DCM /-78 ^{o}C / 5 min / Na_2CO_3	80	100 : 0	52
		Br_2 / DCM /-78 ^{o}C / 5 min / Na_2CO_3			

[a] All reactions employed **1a,1b,1c** or **2a,2b** (0.50 mmol) and Br_2 (1.0 mol eq.) (10% w/v solution in DCM) under nitrogen. [b] Conversion by NMR. [c] Ratio was determined from the proton NMR of the crude reaction mixture. [d] Isolated combined yield. DCM means dichloromethane and NBS means *N*-bromosuccinimide.

yields and diastereoselectivities were obtained (Table I, entries 11 and 12).

The relative stereochemistry of morpholine derivatives **3a, 3b, 3c** was assigned from the experimental data of nuclear Overhauser effect (Fig. 1). Based on the known absolute configuration of starting materials **(*S*)-1a-1c**, the absolute configuration of the new *C*-2 chiral centre in **3a, 3b, c** was established as (*R*). In the case of **3a**, there was a 6.2% enhancement of one of the CH_2Br (δ 3.47) proton when the axial proton at C(6) (δ 3.2) was irradiated. This confirms that the CH_2Br group at *C*(2) is in the axial position and the configuration of *C*(2) chiral centre is (*R*). The observed 3.1% enhancement of the proton at C(5) (δ 2.78-2.82, m) when the

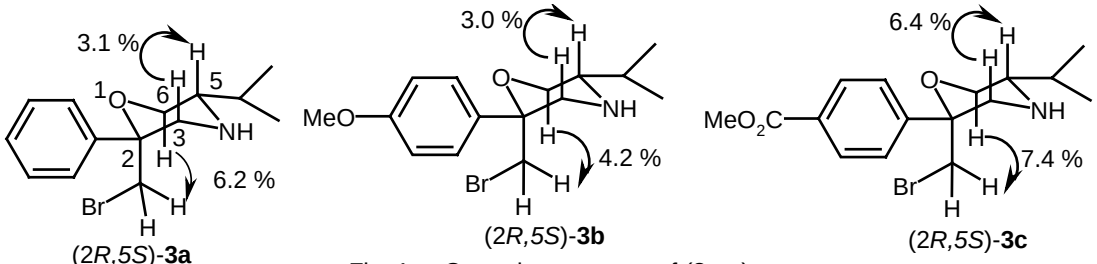
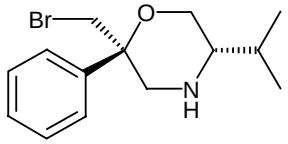
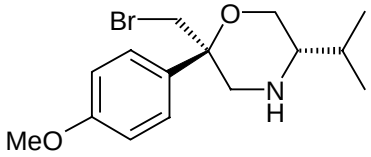
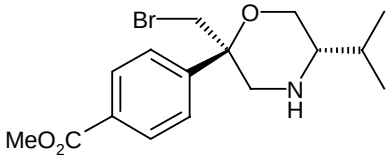
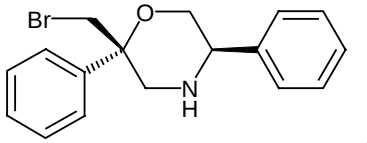
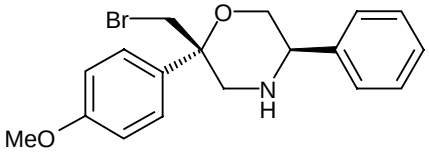


Fig. 1. n.O.e enhancements of (**3a-c**)

Table II. Diastereoselective synthesis of chiral morpholines (3a-c) and (4a, b)[a]

Entry	Substrate	Product	Yield (%)[b]
1	**(*S*)-1a**	 **3a**	30
2	**(*S*)-1b**	 **3b**	50
3	**(*S*)-1c**	 **3c**	32
4	**(*R*)-2a**	 **4a**	30
5	**(*R*)-2b**	 **4b**	52

[a] All reactions employed **1a,1b,1c** or **2a, 2b** (0.50 mmol) and Br_2 (1.0 mol eq.) (10 % w/v solution in DCM) under nitrogen at -78 ^oC for 5 min and afforded a single diastereomer. [b]Isolated yield.

axial proton at C(3) (δ 4.5) was irradiated confirms that C(5) proton is axial and the isopropyl group at C(5) is equatorial. Nuclear Overhauser effect (n.O.e) experiments showed similar enhancements for **3b**, **3c** (Fig.1). Nuclear Overhauser effect experiments on compounds **4a, 4b** were not conclusive. The stereochemistry of **4b** (as the hydrobromide salt) was determined by X-ray crystallography as (2*S,5R*) (Fig. 2). The stereochemistry of **4a** was assigned by an analogy with **4b**.

Presumably the reaction proceeds through the formation of bromonium ion followed by the intramolecular nucleophilic attack by OH to give the product. For substrates **(*S*)- 1a,**

1b,1c two chair-like transition states **5a** and **5b** (Scheme 2) are possible and it seems likely that the low energy transition state is **5a** as both the sterically demanding phenyl and isopropyl group are in equatorial positions whereas in **5b** the phenyl group is in the axial position, and thus energetically less favourable. For substrates **(*R*)-2a, 2b** two analogous chair-like transition states **6a** and **2b** (Scheme 3) are possible and the transition state **6a** is energetically favoured as both the bulky phenyl groups are equatorial whereas in **6b** one of the phenyl groups is axial and thus energetically less favourable.

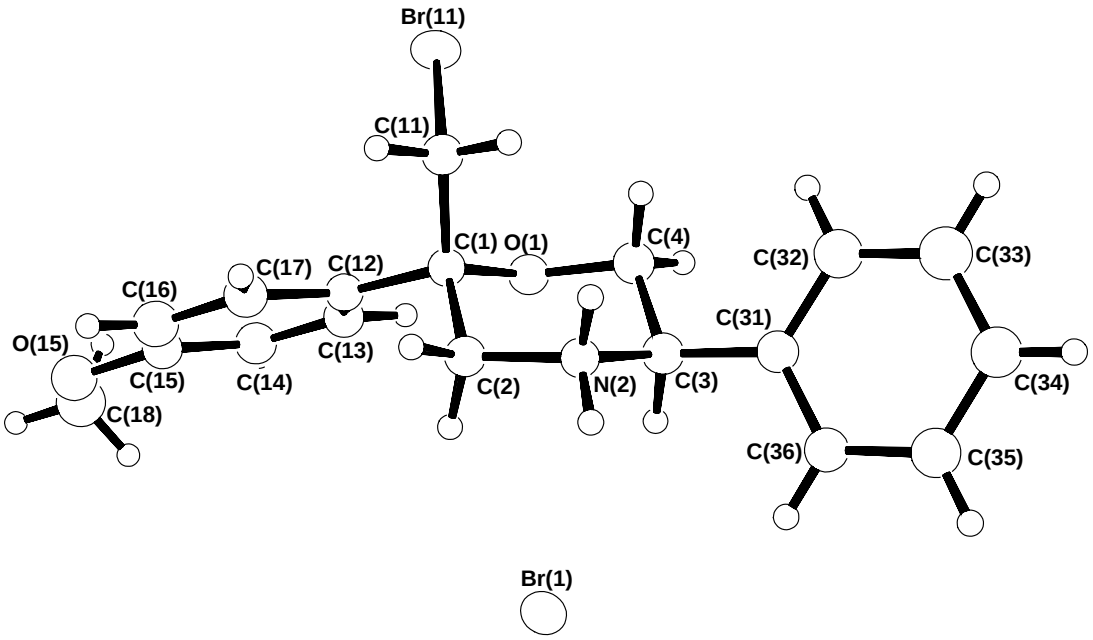
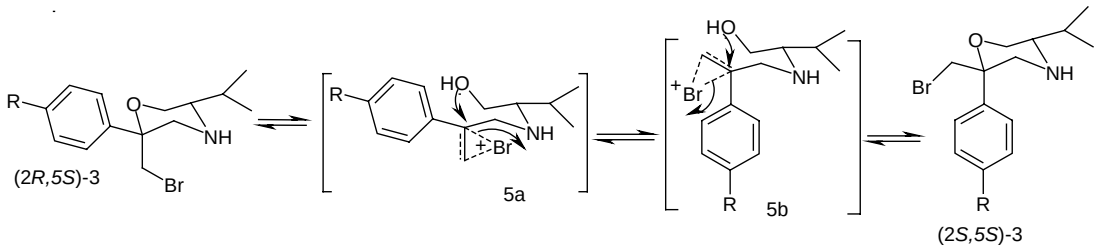
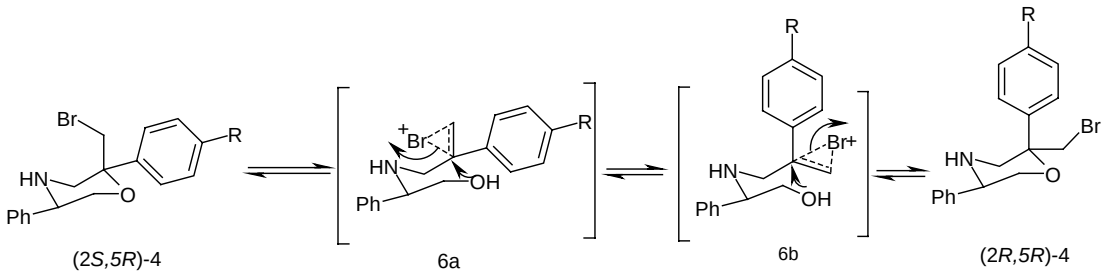


Fig.2. X-ray crystal structure of 4b



Scheme 2

This theory predicts the preferred formation of (2*R,5S*)-**3a, 3b, 3c** and (2*S,5R*)-**4a, 4b** over (2*S, 5S*)-**3a, 3b, 3c** and (2*R,5R*)-**4a, 4b** respectively over a short reaction time (5 min) in a kinetically controlled process. However, a reaction time of 10 min gives rise to an inseparable 2:1 mixture of diastereomers in almost all cases except for **(*S*)-1b** and **(*R*)-2b** which gave 8:1 mixtures of diastereomers. The electron donating group of the styryl moiety can stabilize the bromonium ion and leads to a faster reaction affording better diastereoselectivities. This theory requires that a long reaction time and increased temperature (rt, 4h) results in formation of the thermodynamic mixture.



Scheme 3

Conclusion

Optically pure *N*-allyl-*α*-amino alcohols 1a-c and **(*R*)-2a, (*R*)-2b** were subjected to electrophile induced cyclization using bromine to give chiral morpholines (2*R*, 5*S*)-**3a-c** and (2*S*,5*R*)-**3a, 3b** respectively. It is noteworthy that if the reaction is quenched after 5 min it gives 60% conversion and 30-32% isolated yield of single diastereomer, whilst a 2:1 mixture of two diastereomers were obtained if the reaction is allowed to go to complete conversion. However, electron donating substituent (OMe) on the para position of the C-2 aryl moiety (substrates **(*S*)-1b** and **(*R*)-2b**) accelerates the reaction to give 80% conversion and 50% isolated yield of single diastereomer after 5 min and an 8:1 mixture of diastereomers on complete conversion after 10 min.

Acknowledgement

We thank the Department of Applied Chemistry and Chemical Technology of Dhaka University for support.

References

Baldwin, S.W. Mclver, J. M. (1987**)** Stereoselective Synthesis of (±) Methyl Nonacetate. *J. Org. Chem.* **52**(2): 320-322.

Bennet, F. Bedford, S.B. Bell, K.E. Fenton, G. Knight, D.W. Shaw, D. (1992) Iodine-Induced Cyclizations of (E)- and (Z)-S-Hydroxy-5-Alkenoates: Stereoselective Approaches to Trisubstituted Tetrahydro-furans. *Tetrahedron Lett.* **33**(43): 6507-6510.

Bettler, B. Kaupmann, K. Bowery, N.G. (1998) $GABA_B$ receptors: drugs meet clones. *Curr. Opin. Neurobiol*. **8** : 345-350.

Blythin, D.J. Kuo, S.–C. Shue, H. –J. McPhail, A.T. (1996) Substituted Morpholine-2*S*-Acetic Acid Derivatives: SCH 50911 and Related Compounds as Novel $GABA_B$ Antagonists. *Bioorg. Med. Chem. Lett*. **6**(13) : 1529-1534.

Bowery, N.G. Enna, S.J. (2000) Gamma-aminobutyric acid (B) receptors: first of the functional metabotropic heterodimers. *J. Pharmacol. Exp. Ther*. **292**(1) : 2-7.

Bowery, N.G. Hill, D.R. Hudson, A.L. (1983) Characterisation of $GABA_B$ receptor binding sites on rat whole brain synaptic membranes. *Br. J. Pharmacol*. **78**(2) : 191-206.

Bowery, N.G. Hill, D.R. Hudson, A.L. Doble, A. (1980) (-) Baclofen decreases neuro-transmitter release in a mamalian CNS by an action at a novel GABA receptor. *Nature*. **283** : 92-94.

Carai, M.A.M. Brunetti, G. Lobina, C. Serra, S. Vacca, G. Minardi, G. Colombo, G. Gessa, G.L. (2002) Proconvulsive effect of the $GABA_B$ receptor antagonist, SCH 50911, in rats undergoing ethanol withdrawal syndrome. *Eur. J. Pharmacol*. **445** (3): 195-199.

Colombo, G. Melis, S. Brunetti, G. Serra, S. Vacca, G. Carai, M.A.M. Gessa, G.L. (2001) $GABA_B$ receptor inhibition causes locomotor stimulation in mice. *Eur. J. Pharmacol*. **433**(1) : 101-104.

Corey, P. F. (1987) Asymmetric Bromolactoniza-tion Reaction: Synthesis of Optically Active 2-Hydroxy-Methylalkanoic Acid from 2-Methylenealkanoic Acid. *Tetrahedron Lett.* **28**(25) : 2801-2804.

Couve, A. Moss, S.J. Pangalos, M.N. (2000) $GABA_B$ receptors: a new paradigm in G protein signaling. *Mol. Cell. Neurosci*. **16** : 296-312.

Ezquerra, J. He, W. Paquette, L.A. (1990) Enantiospecific Synthesis of the Tricyclic Nucleus of Acetoxycrenulide by Claisen Ring Expansion. *Tetrahedron Lett.* **31**(48) : 6979-6982.

Gai, X. Grigg, R. Collard, S. Muir, J.E. (2001) Palladium catalysed 3-component cascade synthesis of bis(2-arylallyl)tertiary amines from aryl iodides, allene and primary

amines. *J. Chem. Soc., Chem. Commun.* 1712-1713.

Hill, D.R. Bowery, N.G. (1981) ^{3}H-Baclofen and ^{3}H-GABA bind to bicuculline-insensitive $GABA_B$ sites in rat brain. *Nature.* **290** : 149-152.

Jung, M.E. D'Amico, D.C. Lew, W. (1993) Efficient Total Synthesis of the Cytotoxic Halogenated Monoterpene Aplysiapyranoid A. *Tetrahedron Lett.* **34** (6): 923-926.

Jung, M.E. Lew, W. (1991) Efficient Total Synthesis of the Cytotoxic Halogenated Monoterpene Aplysiapyranoid D. *J. Org. Chem.* **56**(4): 1347-1349.

Kelley, J.L. Musso, D.L. Boswell, G.E. Soroko, F.E. Cooper, B.R. (1996) (2S,3S,5R)-2-(3,5-Difluorophenyl)-3,5-dimethyl-2-morpholinol: A Novel Antidepressant Agent and Selective Inhibitor of Norepinephrine Uptake. *J. Med. Chem*. **39** (2) : 347-349.

Kerr, D.I. Ong, J. (1995) $GABA_B$ receptors. *Pharmacol. Ther*. **67**(2) : 187-246.

Largeron, M. Neudorffer, A. Vuilhorgne, M. Blattes, E. Fleury, M. (2002) –B. Regiospecific Inverse-Electron-Demand Diels-Alder Reaction of Simultaneously Electrogenerated Diene and Dienophile: An Expeditious Route to Polyfunctionalized 1,4-Benzoxazine Derivatives. *Angew. Chem. Int. Ed*. **41** : 824-827.

Miura, K. Okajima, S. Hondo, T. Nakagawa, T. Takahashi, T. Hosomi, A. (2000) Acid-Catalyzed Cyclization of Vinylsilanes Bearing a Hydroxy Group: A New Method for Stereoselective Synthesis of Disubstituted Tetrahydrofurans. *J. Am. Chem. Soc.* **122**(46) : 11348-11357.

Mondadori, C. Preiswerk, G. Jaekel, J. (1992) Treatment with a $GABA_B$ receptor blocker improves the cognitive performance of mice, rats and rhesus monkeys. *Pharmacol. Commun*. **2** : 93-97.

Nicolaou, K.C. Magolda, R.L. Sipi, W.J. Bernette, W.E. Lysenko, Z. Jullie, M.M. (1980) Phenylselenoetherification. A Highly Efficient Cyclization Process for the Synthesis of O- and S-Heterocycles. *J. Am. Chem. Soc.* **102**(11) : 3784-3793.

Ong, J. Marino, V. Parker, D.A.S. Kerr, D.I.B. Blythin, D.J. (1999) Antagonism of $GABA_B$ receptors by morpholino-2-acetic acid derivatives Sch 54679 and Sch 51324 in rat brain. *Eur. J. Pharmacol*. **369**(1) : 33-37.

Reitz, A.B. Nortey, S.O. Maryanoff, B.E. Liotta, D. Monahan, I.R. (1987) Stereoselectivity of Electrophile-Promoted Cyclizations of γ-Hydroxyalkenes. An Investigation of Carbohydrate- Derived and Model

Substrates. *J. Org. Chem.* **52**(19) : 4191-4202.

Saksena, A. K. Girijavallabhan, V. M. Wang, H. C. Liu, Y. –T. Pike, R. E. Ganguly, A. K. (1996) Concise Asymmetric Routes to 2,2,4-Trisubstituted tetrahydrofurans via Chiral Titaniumimide Enolates: Key Intermediates Towards Synthesis of Highly Active Azole Antifungals SCH 51048 and SCH 56592. *Tetrahedron Lett.* **37**(32) : 5657-5660.

Snead, O.C. (1992) Evidence for $GABA_B$–mediated mechanisms in experimental generalized absence seizures. *Eur. J. Pharmacol*. **213**(3) : 343-349.

Wood, M.D. Murkitt, K.L. Rice, S.Q. Testa, T. Punia, P.K. Stammers, M. Jenkins, O. Elshourbagy, N.A. Shabon, U. Taylor, S.J. Gager, T.L. Minton, J. Hirst, W.D. Price, G.W. Pangalos. M. (2000) The human $GABA_{B1b}$ and $GABA_{B2}$ heterodimeric recombinant receptor shows low sensitivity to phaclofen and saclofen. *Br. J. Pharmacol*. **131**(6) : 1050-1054.

Received : August 28, 2006;

Accepted : April 19, 2007