Stereocontrolled Synthesis of Tricyclic Fused Oxazolidinone as Antibacterial Agent

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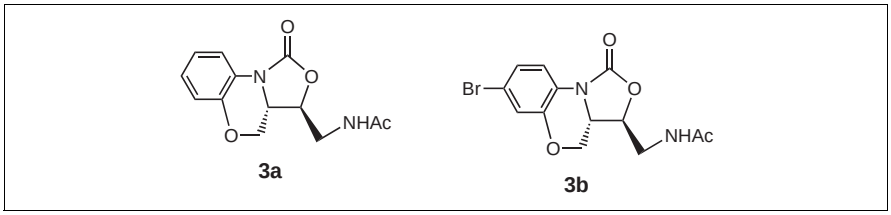

Tricyclic fused oxazolidinone **3a** and **3b** have been synthesized as antibacterial agents in 12 and 11 steps respectively. The key intermediates **10a** and **10b** have been developed via opening of epoxide 9a and 9b and cyclization by the resulting oxygen anion attack.

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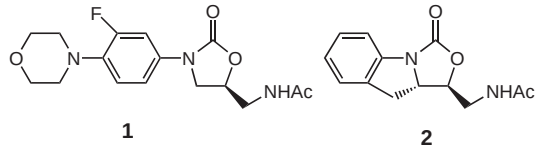
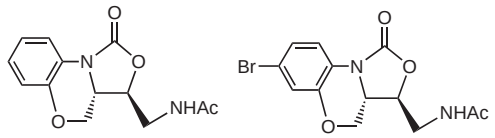
Introduction.

Oxazolidinones, a promising new class of synthetic antibacterial agents, exhibit excellent antibacterial activity against multi-drug resistant Gram-positive organisms [1,2]. Linezolid (zyvox^R, 1), the only oxazolidinone approved by the FDA, has already taken its place in the clinic for treatment of Gram-positive infections [3,4]. They have a novel mechanism of action that is shown to selectively and uniquely bind to the 50S ribosomal subunit, inhibiting bacterial translation at the initiation phase of protein synthesis. It appears that there is a lack of cross-resistance with any known antibiotics [5,6]. Many efforts are focused on oxazolidinone with potent activity and broad spectrum [7,8]. Researchers at Pharmacia corporation have synthesized tricyclic fused oxazolidinone **2**; it shows comparable antibacterial activity to Linezolid [9-11]. In the period of our research on oxazolidinone, we hope to investigate antibacterial activity of restricted conformation oxazolidinones. According to the structure of compound **2** and principle of isosters in medicinal chemistry, we have designed that the methylene group of compound **2** has been replaced by the heteroatom oxygen; in addition, the five-membered ring was enlarged to a six-membered ring. Thus the new tricyclic fused oxazolidinones **3a** and **3b** were prepared to investigate structure-activity relationship.



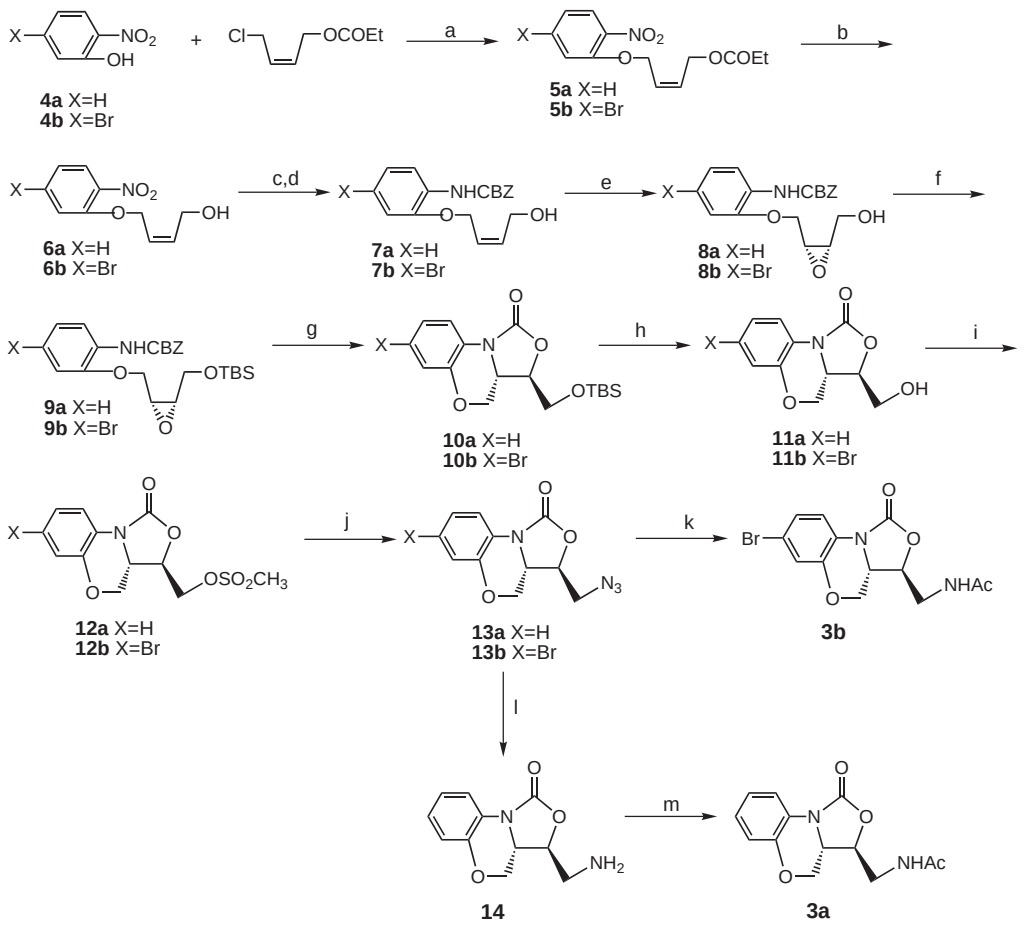


Results and Discussion.

The synthetic route is outlined in Scheme 1 on the base of reference [12]. Phenol 4 was condensated with (*Z*)-1-acetoxy-4-chloro-2-butene which was prepared from (*Z*)-2-butene-1,4-diol in two steps of acylation and chlorinate to give ether **5**. Ether **5** was then hydrolyzed, hydrogenated and protected with CBZ to yield alcohol **7**. Alcohol **7** was converted into epoxide **8** by the Sharpless asymmetric epoxidation with high enantiomeric excess (%ee > 99%, confirmed by HPLC analysis) [13]. Racemic epoxide 8 was prepared by *m*-CPBA oxidation of alcohol **7**. Epoxide **8** was protected with TBDMSCl to afford compound **9**. Compound **9** was treated with 1.6 *M n*-BuLi-cyclohexane at –78°C to afford tricyclic fused oxazolidinone **10**. Functional group manipulation of oxazolidinone **10** yielded the desired acetamide derivatives **3a** and **3b**. When compound **13b** was hydrogenated, loss of bromo gave rise to **14**. So thioacetic acid was used to reduce and acylate of azide **13b** to afford **3b**.

Antibacterial activity of Compounds **3a** and **3b** was tested *in vitro* against a panel of clinical isolates of Gram-positive species. Minimum inhibitory concentration (MIC) values were determined using Agar dilution methodology [14]. Linezolid was selected as reference compound. Compounds **3a** and **3b** exhibit weak antibacterial activity. Comparing with compound **2**, the

Scheme 1



Reagents and conditions: (a) Acetone, K_2CO_3, reflux; (b) 10% KOH; c. $SnCl_2.2H_2O$, EtOH; (d) CBZ-Cl, $NaHCO_3$, acetone:H_2O = 2:1; (e) L-(+)DET, TBHP, Ti(Oi-Pr)$_4$, 4Å; (f) TBDMSCl, imidazole, DMAP, dry DMF; (g) *n*-BuLi, dry THF, -78 °C to rt; (h) (*n*-Bu)$_4$NF, dry THF; (i) MsCl, Et_3N, CH_2Cl_2; (j) NaN_3, DMF, 70-80 °C; (k) CH_3COSH, rt; (l) 10% Pd/C, CH_3OH; (m) $(Ac)_2O$, Py, 0 °C.

ring of compounds **3a** and **3b** is enlarged and ethylene is replaced by oxygen, however, antibacterial activity of them is poor. We suspect that restricted conformation between aryl and oxazolidinone ring in the new oxazolidinone derivatives is not favorable for receptor.

EXPERIMENTAL

Melting points were determined on a MEL-TEMP melting point apparatus and were uncorrected. ^{1}H NMR spectral data were recorded using a Bruker AM-400 spectrometer. Chemical shifts are reported in δ units (ppm). Coupling contants (*J*) are reported in hertz (Hz). Mass spectra are recorded on a MAT-711. Elemental analysis was recorded on an Elemental vario 1106. Optical rotations were measured with a PERKIN-ELMER 241.

General Procedure for the Synthesis of Compounds (**5a**) and (**5b**).

A mixture of **4** (84.0 mmol), (*Z*)-1-acetoxy-4-chloro-2-butene (11.7 g, 84.0 mmol) and anhydrous K_2CO_3 (12.2 g, 88.0 mmol) in anhydrous acetone (100 mL) was heated to reflux overnight with stirring. After concentration *in vacuo*, the residue was poured into H_2O. The aqueous phase was extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum–AcOEt = 2:1) to give **5a** and **5b** in 70 and 67% yield, respectively.

(2*Z*)-4-(2-nitrophenoxy) but-2-enyl propionate (**5a**).

This compound was obtained as yellow oil. ^{1}H nmr (deuteriochloroform): **δ** 7.80(m, 1H), 7.45-7.50(m, 1H), 7.05(m, 1H), 7.00(m, 1H), 5.82-5.80(m, 1H), 5.70-5.80(m, 1H), 4.80(m, 2H), 4.70(m, 2H), 2.35(q, J= 7.7Hz, 2H), 1.10(t, J= 7.7Hz,1H; ms: m/z 265(M^+).

(2*Z*)-4-(5-bromo-2-nitrophenoxy)but-2-enyl propionate (**5b**).

This compound was obtained as yellow oil. ^{1}H nmr (deuteriochloroform): δ 7.98(d, J=9.0 Hz, 1H), 7.20(d, J=2.7 Hz, 1H), 6.90(dd, J=9.0 Hz, J=2.7 Hz, 1H), 5.78-5.85(m, 2H), 4.73(m, 2H), 4.67(m, 2H), 2.35(t, J=7.6 Hz, 2H), 1.80(t, J=17.6 Hz, 3H).

General Procedure for the Synthesis of Compounds (**6a**) and (**6b**).

To a stirred solution of 5 (59.1 mmol) in CH_3OH (50 mL) was added dropwise10% KOH in CH_3OH at rt. The mixture was stirred overnight. The reaction mixture was poured into H_2O. The aqueous phase was extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum– acetone = 2:1) to give **6a** and **6b** in 55 and 73% yield, respectively.

(2*Z*)-4-(2-Nitrophenoxy)but-2-en-1-ol (**6a**).

This compound was obtained as red oil. ^{1}H nmr (deuterio-chloroform): δ 7.80(m, 1H), 7.45(m, 1H), 7.05(m, 1H), 7.00(m, 1H), 5.85-5.95(m, 1H), 5.75-5.82(m, 1H), 4.78(m, 2H), 4.28(m, 2H); ms: m/z 209(M^+).

(2*Z*)-4-(5-Bromo-2-nitrophenoxy)but-2-en-1-ol (**6b**).

This compound was obtained as yellow solid, mp 80-82°C; ^{1}H nmr (deuteriochloroform): δ 7.75(d, J=8.5 Hz, 1H), 7.38(dd, J=8.5 Hz, J=2.8 Hz, 1H), 5.58-6.00(m, 1H), 5.60-5.75(m, 1H), 4.56(m, 2H), 4.35(m, 2H), 1.64(brs, 2H);ms: m/z 287,289(M^+).

Anal. Calcd. for $C_{10}H_{10}BrNO_4$: C, 41.67; H, 3.47; N, 4.86. Found: C, 42.30; H, 3.53; N, 4.60.

General Procedure for the Synthesis of Compounds (**7a**) and (**7b**).

A mixture of **6** (32.0 mmol) and $SnCl_2$ .2 H_2O (36.86 g, 163 mmol) in absolute C_2H_5OH (80 mL) was heated at 80-90°C for 2 h with stirring. The reaction mixture was poured into ice-H_2O, the aqueous phase was adjusted to pH 7-8 by NaOH and saturated $NaHCO_3$, the resulting mixture was filtered and the filtrate was extracted with AcOEt, dried over Na_2SO_4. The solution was concentrated *in vacuo* to give the amine as red oil, which was used for the next reaction without further purification.

The crude amine was dissolved in acetone (60 mL) and H_2O (30 mL). To the cooled solution was added $NaHCO_3$ (4.164 g, 50 mmol) and then benzyl chloroformate (5.79 g, 90% W/W, 30.6 mmol) over 10 min *via* syringe. The mixture was warmed to rt and stirred overnight. After concentration *in vacuo*, the residue was extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum– AcOEt = 2:1) to give **7a** and **7b** in 70 and 18% yield, respectively.

Benzyl 2-(((2*Z*)-4-hydroxybut-2-enyl)oxy)phenylcarbamate (**7a**).

This compound was obtained as orange oil. ^{1}H nmr (deuteriochloroform): δ 8.12 (brs, 1H), 7.30-7.50(m, 6H), 6.95-7.00(m, 2H), 6.85(m, 1H), 5.75-5.85(m, 2H), 5.19(s, 2H), 4.60-4.65(m, 2H), 4.50-4.55(m, 2H); ms: m/z 313(M^+).

Benzyl 4-bromo-2-(((2*Z*)-4-hydroxybut-2-enyl)oxy)phenyl-carbamate (**7b**).

This compound was obtained as yellow solid, mp 66-70 °C; ^{1}H nmr (deuteriochloroform): δ 8.00(brs, 1H), 7.28-7.44(m, 8H), 7.09(dd, J=8.5 Hz, J=1.9 Hz, 1H), 7.09(d, J=1.9 Hz, 1H), 5.84-5.96(m, 1H),5.74-5.82(m, 1H), 5.19(s, 2H), 4.70(m, 1H), 4.63(m, 2H),4.26(m, 2H), 1.83(brs, 2H);ms: m/z 391,393(M^+).

Anal. Calcd. for $C_{18}H_{18}BrNO_4$: C, 55.10; H, 4.59; N, 3.57. Found: C, 55.25; H, 4.54; N, 3.31.

General Procedure for the Synthesis of Compounds (**8a**) and (**8b**).

4Å Molecular sieves (1.2 g) was suspended in anhydrous CH_2Cl_2 (50 mL) at –40 to -20 °C. To the cooled mixture was added a solution of L-(+)DET (1.71 g, 8.3 mmol) in anhydrous CH_2Cl_2 (5 mL), a solution of Ti(Oi-Pr)$_4$ (1.9 g, 7.0 mmol) in anhydrous CH_2Cl_2 (5 mL) and TBHP (3.6 mL, 4.949 *M*, 18.0 mmol). After stirring for 1h at –40 to -20 °C, a solution of compound **7** (7.3 mmol) in anhydrous CH_2Cl_2 (12 mL) was added dropwise, and the reaction mixture was stirred for 20h at –40 to -20 °C. To cooled (0 °C) reaction mixture was added 10% L-Tartaric acid (20 mL). After stirring for 1h, the mixture was diluted with brine (60 mL) and extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was redissolved in Et_2O. To the cooled (0 °C) solution was added 1 *N* NaOH (20 mL). After stirring for 1h, the mixture was diluted with brine (60 mL) and extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum– acetone = 3:2) followed by recrystallization from Et_2O to give **8a** and **8b** in 67 and 53% yield, respectively.

Benzyl 2-(((2*R*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)methoxy)-phenylcarbamate (**8a**).

This compound was obtained as white solid, mp 57-60°C; $[\alpha]_D^{20}$ = +0.15 (c 0.52, DMSO); %ee > 99%; ^{1}H nmr (deuteriochloroform): δ 8.12 (brs, 1H), 7.30-7.43(m, 6H), 6.95-7.00(m, 2H), 6.85(m, 1H), 5.20(s, 2H), 4.26(dd, J=11.1 Hz, J=4.4 Hz, 1H), 4.20(dd, J=11.2 Hz, J=6.4 Hz, 1H), 3.90(dd, J=12.5 Hz, J=4.4 Hz, 1H), 3.82(dd, J=12.5 Hz, J=5.5 Hz, 1H), 3.43-3.51(m, 1H), 3.30-3.33(m, 1H), 1.90(brs, 1H); ms: m/z 329(M^+).

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.78; N, 4.26. Found: C, 65.41; H, 5.94; N, 4.59.

Benzyl 4-bromo-2-(((2*R*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)-methoxy)phenylcarbamate (**8b**).

This compound was obtained as white solid, mp 92-94 °C; $[\alpha]_D^{20}$ = -6.02 (c 0.42, DMSO); %ee > 99%; ^{1}H nmr (deuteriochloroform): δ 8.02(brs, 1H), 7.32-7.44(m, 5H), 7.12(dd, J=8.6 Hz, J=2.0 Hz, 1H), 6.99(d, J=2.0 Hz, 2H), 5.20(s, 2H),4.58(dd, J=11.3 Hz, J=3.6 Hz, 1H), 4.38(dd, J=11.3 Hz, J=6.6 Hz, 1H), 3.93(dd, J=12.4 Hz, J=4.4 Hz, 1H), 3.85(dd, J=12.5 Hz, J=5.4 Hz, 1H), 3.42-3.47(m, 1H), 3.30-3.35(m, 1H); ms: m/z 407, 409(M^+).

Anal. Calcd for $C_{18}H_{18}BrNO_5$: C, 52.94; H, 4.41; N, 3.43. Found: C, 52.67; H, 4.48; N, 3.21.

General Procedure for the Synthesis of Compounds (**9a**) and (**9b**).

To the cooled (0°C) solution of TBDMSCl (0.362 g, 2.41 mmol), imidazole (0.169 g, 2.49 mmol) and a catalytical amount of DMAP in anhydrous DMF (2 mL) was added a solution of compound **8** (1.57 mmol) in anhydrous DMF (2 mL). The reaction mixture was allowed to warm to rt and stirred overnight. The mixture was poured into ice-H_2O and extracted with CH_2Cl_2, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography

(petroleum– acetone = 10:1) to give **9a** and **9b** in 74 and 58% yield, respectively.

Benzyl 2-(((2*R*,3*S*)-3-((1,1-dimethylethyl)dimethylsilanemethyl)-oxiran-2-yl)methoxy)phenylcarbamate (**9a**).

This compound was obtained as colorless oil. ^{1}H nmr (deuteriochloroform): δ 8.12(brs, 1H), 7.30-7.43(m, 4H),6.95-7.00(m, 2H),6.85(m, 1H),5.22(s, 2H), 4.30(dd, J=11.4 Hz, J=3.7 Hz, 1H), 4.10(dd, J=11.4 Hz, J=6.9 Hz, 1H), 3.85(q, 2H), 3.40(q, 1H), 3.25(t, J=4.8 Hz, 1H), 0.90(s, 9H), 0.10(s, 3H).

Benzyl 4-bromo-2-(((2*R*,3*S*)-3-((1,1-dimethylethyl)dimethyl-silanemethyl)oxiran-2-yl)methoxy)phenylcarbamate (**9b**).

This compound was obtained as yellow oil. ^{1}H nmr (deuteriochloroform): δ 8.05(brs, 1H), 7.34-7.44(m, 5H), 7.25(brs, 1H), 7.11(dd, J=8.7 Hz, J=2.1 Hz, 1H), 6.98(d, J=2.1 Hz, 1H), 5.20(s, 2H), 4.30(dd, J=11.3 Hz, J=3.2 Hz, 1H), 4.08(q, 1H), 3.75(q, 2H), 3.38(m, 1H), 3.25(m, 1H), 0.92(s, 9H), 0.10(s, 3H).

General Procedure for the Synthesis of Compounds (**10a**) and (**10b**).

To a solution of compound **9** (4.0 mmol) in dry THF (30 mL) at -78 °C under Ar was added dropwise (4.0 mL 1.27 *M n*-butylithium-cyclohexane, 5.0 mmol). After stirring for 2h at –78 °C, the reaction mixture was allowed to warm to rt and overnight. To the cooled (0 °C) solution was added saturated NH_4Cl (20 mL) and extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum– acetone = 3:1) to give **10a** and **10b** in 76 and 89% yield, respectively.

(3*R*,3a*S*)-3-((1,1-Dimethylethyl)dimethylsilanemethyl)-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*][1,4]benzoxazin-1-one (**10a**).

This compound was obtained as white solid, mp 123-125 °C; $[\alpha]_D^{20}$ = -62.02 (c 1.0, DMSO); ^{1}H nmr (deuteriochloroform): δ 8.00(m, 1H), 6.95-7.05(m, 3H), 4.45(2×dd, J=10.6 Hz, J=3.2 Hz, 1H), 4.25-4.30(m, 1H), 4.09-4.15(m, 1H), 3.87-3.96(m, 3H), 0.90(s, 9H), 0.10(s, 3H); ms: m/z 335(M^+).

Anal. Calcd. for $C_{17}H_{26}NO_4Si$: C, 60.90; H, 7.46; N, 4.18. Found: C, 61.12; H, 7.37; N, 4.06.

(3*R*,3a*S*)-7-Bromo-3-((1,1-dimethylethyl)dimethylsilanemethyl)-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*][1,4]benzoxazin-1-one (**10b**).

This compound was obtained as white solid; mp 130-132°C; $[\alpha]_D^{20}$ = -45.2 (c 0.025, DMSO); ^{1}H nmr (deuteriochloroform): δ 7.88(dd, J=6.0 Hz, J=3.1 Hz, 1H), 7.10-7.13(m, 2H),4.45(dd, J=10.4 Hz, J=3.3 Hz, 1H), 4.26-4.30(m, 1H), 4.07-4.12(m, 1H), 3.86-3.96(m, 3H), 0.90(s, 9H), 0.10(s, 3H); ms: m/z 413,415(M^+).

Anal. Calcd. for $C_{17}H_{26}NO_4Si$: C, 49.28; H, 5.80; N, 3.38. Found: C, 49.27; H, 5.65; N, 3.08.

General Procedure for the Synthesis of Compounds (**11a**) and (**11b**).

To the cooled (0 °C) solution of compound **10** (3.0 mmol) in THF (15 mL) was added a solution of *n*- Bu_4NF. After stirring for 2h, the reaction mixture was diluted with H_2O and extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2– CH_3OH = 25:1) to give **11a** and **11b** in 62 and 88% yield, respectively.

(3*R*,3a*S*)-3-(hydroxymethyl)-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*]-[1,4]benzoxazin-1-one (**11a**).

This compound was obtained as white solid, mp 116-117°C; $[\alpha]_D^{20}$ = -45.04 (c 1.0, DMSO); ^{1}H nmr (deuteriochloroform): δ 7.98(m, 1H), 6.93-7.06(m, 3H), 4.48(dd, J=10.5 Hz, J=3.1 Hz, 1H), 4.34-4.38(m, 1H), 4.16-4.22(m, 1H), 4.02(dd, J=12.5 Hz, J=3.8 Hz, 1H), 3.94(t, J=10.4 Hz, 1H), 3.85(dd, J=12.6 Hz, J=4.0 Hz, 1H), 2.29(brs, 1H); ms: m/z 221(M^+).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.73; H, 4.98; N, 6.33. Found: C, 59.61; H, 5.02; N, 6.00.

(2R,3aS)-7-Bromo-3-(hydroxymethyl)-3a,4-dihydro-3*H*-[1,3]-oxazolo[4,3-*c*][1,4]benzoxazin-1-one (**11b**).

This compound was obtained as white solid, mp 130-132°C; $[\alpha]_D^{20}$ = -24.1 (c 0.22, DMSO); ^{1}H nmr (deuteriochlooform): δ 7.98(d×t, 1H), 7.10-7.12(m, 2H),4.49(dd, J=10.6 Hz, J=3.1 Hz, 1H),4.35-4.39(m, 1H), 4.14-4.20(m, 1H), 4.03(dd, J=12.4 Hz, J=3.8 Hz, 1H), 3.83-3.94(m, 2H), 2.05(brs, 2H); ms: m/z 299, 301(M^+).

Anal. Calcd. for $C_{11}H_{10}BrNO_4$: C, 44.00; H, 3.33; N, 4.67. Found: C, 43.97; H, 3.31; N, 4.39.

General Procedure for the Synthesis of Compounds (**12a**) and (**12b**).

To the cooled (0°C) solution of compound **11** (1.86 mmol) and Et_3N (0.6 mL, 4.33 mmol) in CH_2Cl_2 (25 mL) was added dropwise $MeSO_2Cl$ with stirring, the reaction mixture was allowed to warm to rt and stirred overnight. The mixture was diluted with H_2O and extracted with CH_2Cl_2, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2– CH_3OH = 25:1) followed by recrystallization from Et_2O to give **12a** and **12b** in 97 and 94% yield, respectively.

((3*R*,3a*S*)-1-Oxo-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*][1,4]benz-oxazin-3-yl)methyl methanesulfonate (**12a**).

This compound was obtained as white solid, mp 124-126 °C; $[\alpha]_D^{20}$ = -61.39 (c 0.54, DMSO); ^{1}H nmr (deuteriochloroform): δ 7.98(m, 1H), 6.95-7.09(m, 3H), 4.48-4.56(m, 4H), 4.12-4.16(m, 1H), 3.94(t, J=10.3 Hz, 1H), 3.18(s, 3H); ms: m/z 299(M^+).

Anal. Calcd. for $C_{12}H_{13}NO_6S$: C, 48.16; H, 4.35; N, 4.68. Found: C, 48.21; H, 4.41; N, 4.86.

((3*R*,3a*S*)-7-Bromo-1-oxo-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*]-[1,4]benzoxazin-3-yl)methyl methanesulfonate (**12b**).

This compound was obtained as white solid, mp 117-118 °C; $[\alpha]_D^{20}$ = -18.0(c 0.30, DMSO); ^{1}H nmr (deuteriochloroform): δ 7.85(m, 1H), 7.12(m, 2H), 4.48-4.55(m, 4H), 4.07-4.12(m, 1H), 3.95(t, J=10.3 Hz, 1H), 3.12(s, 3H); ms: m/z 377, 379(M^+).

Anal. Calcd. for $C_{12}H_{12}BrNO_6S$: C, 38.10; H, 3.17; N, 3.70. Found: C, 38.53; H, 3.00; N 3.56.

General Procedure for the Synthesis of Compounds (**13a**) and (**13b**).

A mixture of compound **12** (1.0 mmol) and NaN_3 (0.265 g, 4.0 mmol) in DMF (10 mL) was heated at 70-80 °C overnight with stirring. The mixture was diluted with H_2O and extracted with AcOEt, dried over Na_2SO_4, then concentrated *in vacuo* to give **13a** and **13b** respectively.

(3S,3aS)-3-(Azidomethyl)-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*]-[1,4]benzoxazin-1-one (**13a**).

This compound was obtained as yellow oil , which was used for the next reaction without further purification.

(3*S*,3a*S*)-3-(azidomethyl)-7-bromo-3a,4-dihydro-3*H*-[1,3]oxazolo-[4,3-*c*][1,4]benzoxazin-1-one (**13b**).

This compound was obtained 0.191 g (44%) as white solid, mp 116-117 °C; $[\alpha]_D^{20}$ = -48.67 (c 0.285, DMSO); ^{1}H nmr (deuteriochloroform): δ 7.85(m, 1H), 7.12(m, 2H), 4.49(dd, J=10.6 Hz, J=3.2 Hz, 1H), 4.36-4.41(m, 1H),4.01-4.06(m, 1H), 3.95(t, J=10.3 Hz, 1H), 3.76(dd, J=13.0 Hz, J=5.4 Hz, 1H), 3.76(dd, J=13.0 Hz, J=5.4 Hz, 1H); ms: m/z 324, 326(M^+).

Anal. Calcd. for $C_{11}H_9BrN_4O_3.1/4C_4H_8O_2$: C, 41.50; H,3.17; N, 16.14. Found: C, 41.50; H, 2.80; N, 16.48.

(3*S*,3a*S*)-3-(aminomethyl)-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*]-[1,4]benzoxazin-1-one (**14**).

A mixture of compound **13a** and 10% Pd/C (0.027 g, 4.0 mmol) in CH_3OH (10 mL) was stirred for 7h at rt under a H_2 atmosphere (1 atm). The resulting mixture was filtered and concentrated *in vacuo*, the residue was purified by silica gel column chromatography (CH_2Cl_2– CH_3OH = 10:1) followed by recrystallization from Et_2O to give **14** 0.200 g (97%) as white solid, mp 88-90°C; $[\alpha]_D^{20}$ = -62.39 (c 1.0, DMSO); ^{1}H nmr (deuteriochloroform): δ 8.00(m, 1H), 6.92-7.06(m, 3H), 4.48(dd, J=10.5 Hz, J=3.1 Hz, 1H), 4.26-4.31(m, 1H), 4.03-4.09(m, 1H), 3.92(t, J=10.4 Hz, 1H), 3.16(dd, J=13.6 Hz, J=4.6 Hz, 1H), 3.09(dd, J=13.6 Hz, J=5.5 Hz, 1H), 1.48(brs, 2H); ms: m/z 220(M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.45; N, 12.73. Found: C, 59.97; H, 5.55; N, 12.84.

N-(((3*S*,3a*S*)-1-oxo-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*][1,4]-benzoxazin-3-yl)methyl) acetamide (**3a**).

To the cooled (0 °C) solution of compound **14** (0.200 g, 0.91 mmol) and pyridine (0.4 mL, 2.5 mmol) in CH_2Cl_2 (15 mL) was added $(Ac)_2O$ with stirring, the reaction mixture was allowed to warm to rt and overnight. The mixture was washed with H_2O and brine respectively, then dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2– CH_3OH = 20:1) to give **3a** 0.15 g (63%) as white solid, mp 136-138°C; $[\alpha]_D^{20}$ = -38.45 (c 0.75, DMSO); ^{1}H nmr (deuteriochloroform): δ 7.96(m, 1H), 6.93-7.06(m, 3H), 6.33(brs, 1H), 4.53(dd, J=9.9 Hz, J=2.5 Hz, 1H), 4.38-4.44(m, 1H), 3.93-4.00(m, 1H), 3.89(t, J=10.2 Hz, 1H), 3.65-3.77(m, 2H),2.05(s, 3H); ms: m/z 262(M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_4.1/4C_4H_8O$: C, 58.53; H, 5.44; N, 10.51. Found: C, 58.92; H, 5.63; N, 10.43.

N-(((3S,3aS)-7-bromo-1-oxo-3a,4-dihydro-3*H*-[1,3]oxazolo[4,3-*c*][1,4]benzoxazin-3-yl)methyl) acetamide (**3b**).

The solution of compound **13b** (0.19 g, 0.58 mmol) in CH_3COSH (10 mL) was stirred at rt overnight. The mixture was diluted with AcOEt (20 mL), the organic layer was washed with saturated Na_2CO_3, H_2O and brine respectively then dried over Na_2SO_4 The resulting solution was then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2– CH_3OH = 25:1) to give **3b** 0.14 g (70.2%) as white solid, mp 184-186 °C; $[\alpha]_D^{20}$ = -3.81 (c 0.535, DMSO); ^{1}H nmr (deuteriochloroform): δ 8.28(t, J=5.5 Hz, 1H), 7.82(d, J=8.8 Hz, 3H), 7.18-7.22(m, 2H), 4.54(dd, J=10.0 Hz, J=2.7 Hz, 1H), 4.45-4.50(m, 1H), 4.04(t, J=10.0 Hz, 1H), 3.94-4.00(m, 1H), 3.46-3.58(m, 2H),1.86(s, 3H); ms: m/z 340, 342(M^+).

Anal. Calcd. for $C_{13}H_{13}BrN_2O_4.1/4C_4H_8O_2$: C, 46.28; H, 4.13; N 7.71. Found: C, 46.53; H, 3.70; N, 7.85.

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[14] National Committee for Clinical Laboratory Standards. NCCLS Document M7-A3 (ISBN 1-56238-209-8); NCCLs: 771 Lancaster Ave., Villanova, PA 19085, 1993.