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ScienceDirect
Tetrahedron 62 (2006) 10162–10170
Tetrahedron

Synthesis of enantiopure bis-aziridines, bis-epoxides, and aziridino-epoxides from D-mannitol

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Received 26 April 2006; revised 26 July 2006; accepted 10 August 2006
Available online 6 September 2006

Abstract—A practical synthesis of enantiopure bis-aziridines **11** and **15**, bis-epoxides **12** and **17**, and aziridino-epoxides **27** and **30** is reported using inexpensive D-mannitol as the starting material. The key transformation involves the reductive cleavage of bis-benzylidene acetal **3** to form dimesylate **4**, which was further converted to monoazides and diazides followed by reduction, mesylation, and cyclization to furnish the required compounds in good yields.

1. Introduction

D-Mannitol is a naturally occurring inexpensive chiral building block used for the synthesis of many biologically active and pharmaceutically important natural products.[1,2] In general the bis-aziridines, bis-epoxides, and aziridino-epoxides derived from mannitol are key intermediates in the synthesis of various nitrogen, sulfur, and selenium heterocycles with potential biological activity.[4–8] Though Depezay et al.[3] reported the first synthesis of enantiopure 1,5-bis-aziridine and 1,5-bis-epoxide from D-mannitol in 1986, there are no alternate synthetic procedures available for the synthesis of chirally pure 1,5-bis-aziridines, 1,5-bis-epoxides, and 2,4-bis-epoxides. Additionally there are no reports on the synthesis of 2,4-bis-aziridines, 1,5-aziridino-epoxides, and 2,4-aziridino-epoxides from D-mannitol in the literature. The main problem with Depezay's procedure is the difficulty in the removal of triphenyl phosphine oxide byproduct. Herein, we report simple alternative procedures for the synthesis of optically pure 1,5-bis-aziridine, 1,5-bis-epoxide, 2,4-bis-aziridine, 2,4-bis-epoxide, 1,5-aziridino-epoxide, and 2,4-aziridino-epoxide starting from the same intermediate, bis-benzylidene acetal **2**, derived from D-mannitol.

2. Results and discussion

2.1. Synthesis of 2,4-bis-aziridine 11

The bis-benzylidene acetal **2**[9] derived from D-mannitol was converted to the dimesylate **3**[10] (Scheme 1; Fig. 1) in 71% yield in two steps. Using a procedure developed by Baskaran et al.,[11] a highly regio- and chemoselective reductive cleavage of bis-benzylidene acetal **3** with $BF_3\cdot Et_2O/Et_3SiH$ in dry CH_2Cl_2 furnished C_2-symmetric diol **4** (78%), which was then converted to the acetonide **5** in 80% yield. Nucleophilic substitution of the dimesylate **5** with NaN_3 afforded the corresponding diazide[11b] **6**, which was subjected to chemoselective reduction using Lindlar's catalyst to furnish the bis-amine **7**. Compound **7** was converted to the ditosylate **8** followed by deprotection using $FeCl_3\cdot 6H_2O$[12] in dry CH_2Cl_2 to give the diol **9**. Finally, mesylation of diol **9** and intramolecular cyclization using NaH in THF afforded enantiopure C_2-symmetric 2,4-bis-aziridine **11** in 23% overall yield from D-mannitol. The structure of compound **11**[13] was confirmed by single crystal X-ray analysis (Fig. 2).

2.2. Synthesis of 2,4-bis-epoxide 12

In order to synthesize the 2,4-bis-epoxide **12** from D-mannitol, dimesylate **4** was directly treated with NaH in THF. It underwent cyclization to afford the required enantiopure 2,4-bis-epoxide[14] **12** in 47% overall yield from D-mannitol (Scheme 2). Bis-epoxide **12** is a useful starting material for the synthesis of C_2-symmetric, diol-based HIV-1 protease inhibitors.[15]

2.3. Synthesis of 1,5-bis-aziridine 15

In order to synthesize the 1,5-bis-aziridine **15**, the intermediate ditosylate **8** (from Scheme 1) was subjected to hydrogenolysis (10% Pd/C, H_2, 1 atm, MeOH) to furnish diol **13** in 90% yield. Treatment of **13** with methane sulfonyl chloride followed by intramolecular cyclization using NaH in dry THF gave C_2-symmetric bis-aziridine[3] **15** in 24% overall yield from D-mannitol (Scheme 3).

Keywords: Bis-benzylidene acetal; Bis-aziridines; Bis-epoxides; Aziridino-epoxides.
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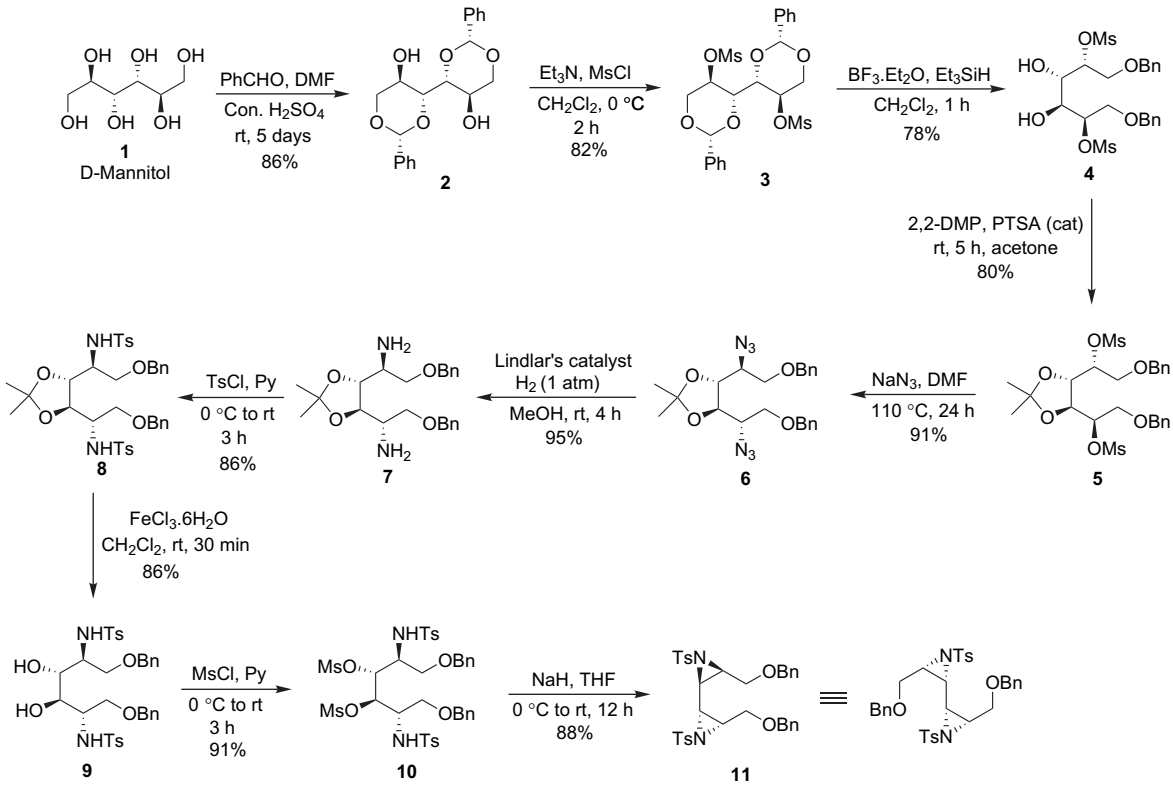
doi:10.1016/j.tet.2006.08.035



Scheme 1. Synthesis of C_2-symmetric *N*-tosyl-2,4-bis-aziridine **11**.

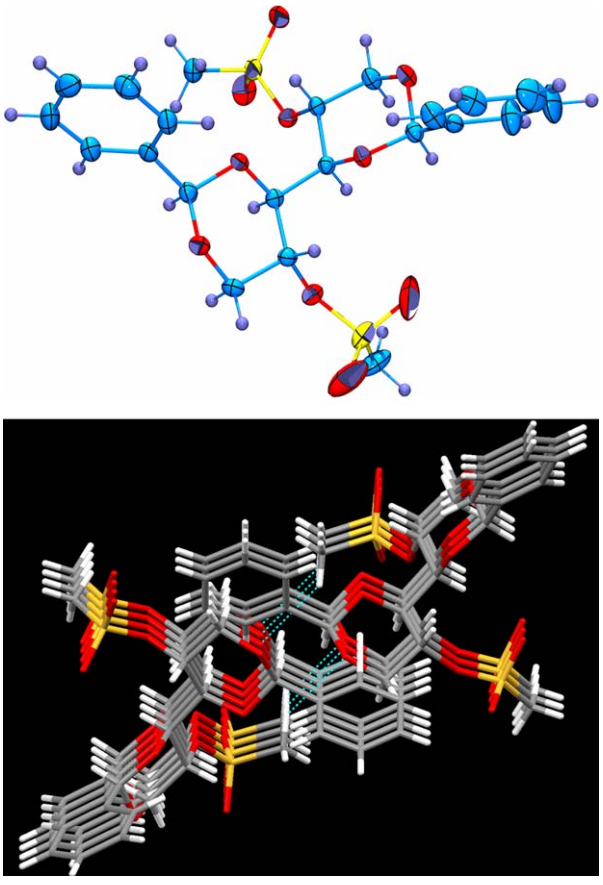


Figure 1. Solid state structure of compound **3** and C–H···O (C9–H9B···O: 2.485 Å; 140.08°) interactions that form chain like structure through '*b*' axis.

2.4. Synthesis of 1,5-bis-epoxide 17

The synthesis of 1,5-bis-epoxide **17** utilizes dimesylate **5** as the starting material, which upon hydrogenolysis (10% Pd/C, H_2, 1 atm, MeOH) afforded diol **16** in 86% yield. Subsequent intramolecular cyclization using NaH in THF gave the bis-epoxide[3] **17** in 32% overall yield from D-mannitol (Scheme 4). The bis-aziridine **15** and bis-epoxide **17** are the key intermediates in the synthesis of thiepane derivatives, which are potential glycosidase[7a] and HIV protease[8] inhibitors. The structure of bis-epoxide **17**[16] was confirmed by X-ray analysis (Fig. 3).

2.5. Synthesis of 2,4-aziridino-epoxide 27

In order to synthesize the aziridino-epoxide **27**, bis-benzylidene acetal **2** was reacted with 1 equiv TsCl in pyridine to furnish the monotosylate **18** in 62% yield. Compound **18** was converted to acetate **19**, which on reductive cleavage with $BF_3 \cdot Et_2O/Et_3SiH$ in dry CH_2Cl_2 gave the diol **20** in 78% yield. Next, diol **20** was protected as the corresponding acetonide **21**. Formation of the corresponding azide **22** and reduction using Lindlar's catalyst provided amine **23** in 91% yield. Amine **23** was converted to the tosylate **24**, which on hydrolysis resulted in the formation of diol **25**. Finally, diol **25** was converted into dimesylate **26** and intramolecular cyclization using NaOMe in MeOH afforded the 2,4-aziridino-epoxide **27** in 15% overall yield from D-mannitol (Scheme 5).

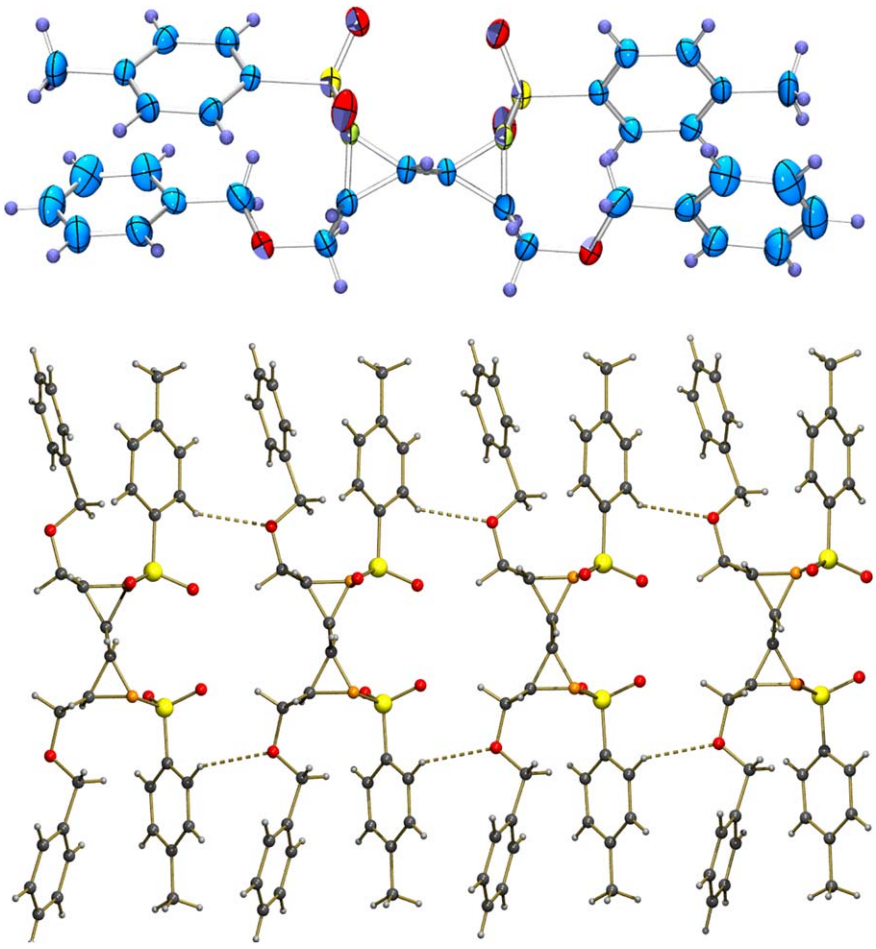
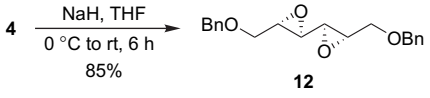
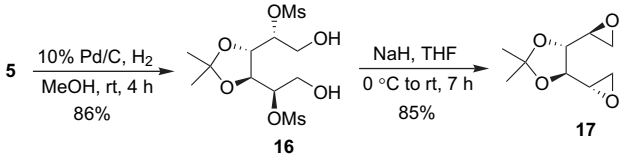


Figure 2. Solid state structure of compound **11** and C–H···O (C33–H33···O6: 2.570 Å; 137.44°) interactions that form chain like structure through '*a*' axis.



Scheme 2. Synthesis of C_2-symmetric 2,4-bis-epoxide **12**.



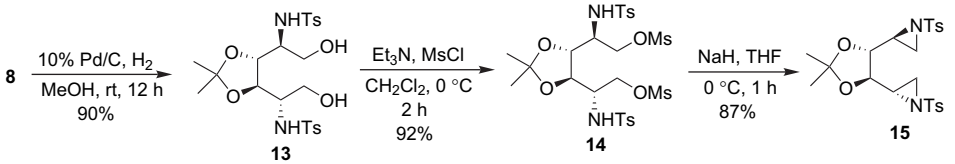
Scheme 4. Synthesis of C_2-symmetric 1,5-bis-epoxide **17**.

2.6. Synthesis of 1,5-aziridino-epoxide 30

To synthesize the unsymmetrical 1,5-aziridino-epoxide **30**, acetate **24** was subjected to hydrogenolysis (10% Pd/C, H_2, 1 atm, MeOH) to afford the diol **28** in 83% yield. Compound **28** on treatment with methane sulfonyl chloride gave the dimesylate **29**, which upon intramolecular cyclization using NaOMe in MeOH (0 °C, 1 h) furnished the 1,5-aziridino-epoxide **30** in 15% overall yield from D-mannitol (Scheme 6).

3. Conclusion

In conclusion, we have demonstrated here the development of simple but efficient synthesis of enantiopure bis-aziridines **11** and **15**, bis-epoxides **12** and **17**, and aziridino-epoxides **27** and **30** from readily available and inexpensive D-mannitol.



Scheme 3. Synthesis of C_2-symmetric 1,5-bis-aziridine **15**.

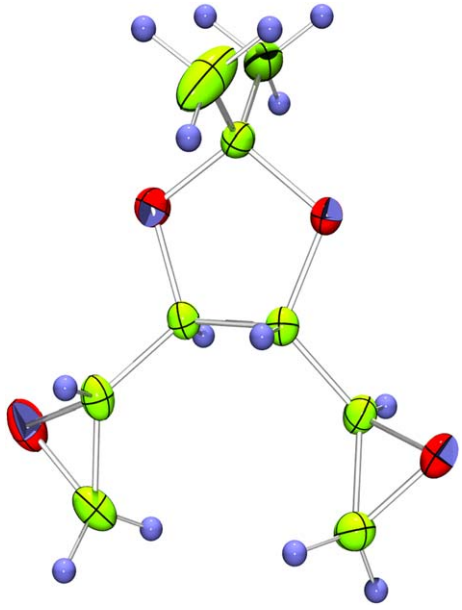


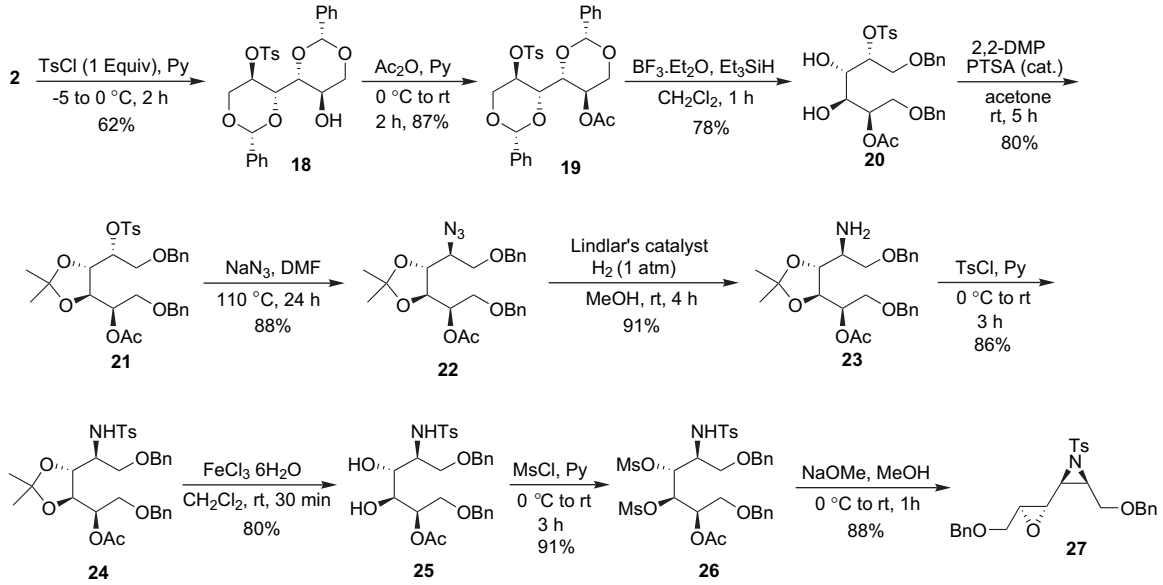
Figure 3. Solid state structure of compound **17**.

4. Experimental

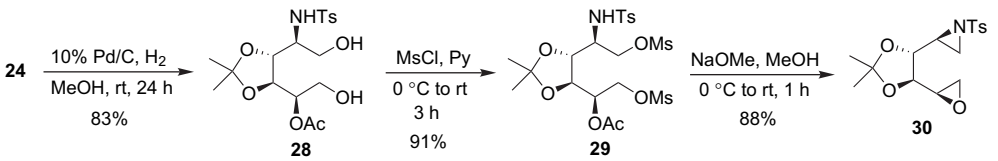
4.1. General methods

All reactions were carried out in oven-dried apparatus using dry solvents under anhydrous conditions. Commercial grade solvents were distilled and dried according to literature procedures. Analytical TLC was performed on commercial plates coated with silica gel GF_{254} (0.25 mm). Silica gel (230–400 mesh) was used for column chromatography. Melting points determined are uncorrected. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. NMR spectra were recorded on 300 or 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations explain the multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. IR spectra were recorded on a FTIR spectrometer.

4.1.1. (*S*)-2-(Benzyloxy)-1-((4*R*,5*R*)-5-((*S*)-2-(benzyloxy)-1-(tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-tosylethanamine 8. The azide **6** was synthesized from D-mannitol according to the literature procedure.[11] Lindlar's catalyst (0.115 g, 20 wt %) was added to the stirred solution of azide **6** (1 g, 2.2 mmol) in methanol (20 mL). The reaction flask was evacuated and flushed with H_2 gas. The resultant mixture was stirred under hydrogen atmosphere (balloon) at room temperature (28 °C) for 4 h. After completion of the reaction, the catalyst was filtered through a pad of Celite, washed with methanol (50 mL) and the filtrate was concentrated under reduced pressure. To the crude residue (0.84 g, 2.1 mmol) in pyridine (15 mL) at 0 °C was added tosyl chloride (0.88 g, 4.5 mmol) slowly. After 3 h stirring at room temperature, the reaction mixture was poured into ice cold solution of 1 M HCl and extracted with diethyl ether thrice (100 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave a yellow residue. The residue was purified



Scheme 5. Synthesis of 2,4-aziridino-epoxide **27**.



Scheme 6. Synthesis of 1,5-aziridino-epoxide **30**.

over silica gel (230–400 mesh) using 10–20% EtOAc in hexane solvent as eluent to afford pure compound **8** (1.28 g, 86%) as a colorless liquid. R_f=0.80 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ +16.00 (*c* 1.0, $CHCl_3$); IR (neat): 3281, 1328, 1160, 1092, 814, 738, 699, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.1 Hz, 2H), 7.32–7.26 (m, 3H), 7.17–7.13 (m, 4H), 4.87 (d, *J*=9.3 Hz, 1H), 4.29 (s, 2H), 4.05 (s, 1H), 3.69–3.62 (m, 1H), 3.39–3.29 (m, 2H), 2.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 138.1, 137.7, 129.4, 128.2, 127.6, 127.5, 127.1, 109.1, 76.7, 72.9, 70.5, 52.2, 26.9, 21.5; HRMS *m/z* calcd for $C_{37}H_{44}N_2O_8S_2$ [M+Na^+]: 731.2437; found: 731.2462.

4.1.2. (2*S*,3*R*,4*R*,5*S*)-1,6-Bis(benzyloxy)-2,5-bis(tosylamino)hexane-3,4-diol 9. To a solution of **8** (1 g, 1.41 mmol) in CH_2Cl_2 (20 mL) at room temperature was added $FeCl_3\cdot 6H_2O$[11] (1.33 g, 4.94 mmol). The resulting yellow to amber colored suspension was stirred for 30 min and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography of the resulting oil on silica gel (230–400 mesh) and elute with 20% EtOAc/hexanes yielded amino diol **9** (0.811 g, 86%). R_f=0.15 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −23.00 (*c* 1.0, $CHCl_3$); IR (neat): 3469, 3278, 1317, 1160, 813, 659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.1 Hz, 2H), 7.34–7.24 (m, 3H), 7.21–7.15 (m, 4H), 4.31 (dd, *J*=28.50, 12.0 Hz, 2H), 3.85 (s, 1H), 3.66 (t, *J*=4.2 Hz, 1H), 3.37 (dd, *J*=9.9, 4.5 Hz, 1H), 3.28 (dd, *J*=9.9, 5.4 Hz, 1H), 2.54 (br s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 137.8, 137.3, 129.5, 128.3, 127.7, 127.6, 126.9, 73.1, 70.9, 70.2, 53.4, 21.4; HRMS *m/z* calcd for $C_{34}H_{40}N_2O_8S_2$ [M+Na^+]: 691.2124; found: 691.2124.

4.1.3. (2*R*,3*S*,4*S*,5*R*)-1,6-Bis(benzyloxy)-3,4-bis((methylsulfonyl)methyl)-*N*2,*N*5-ditosylhexane-2,5-diamine 10. To a solution of diol **9** (0.80 g, 1.19 mmol) in dry CH_2Cl_2 (10 mL), pyridine (0.3 mL, 3.65 mmol) followed by mesyl chloride (0.24 mL, 2.98 mmol) were slowly added at 0 °C. The mixture was stirred at 20 °C for 3 h. The reaction mixture was diluted with Et_2O followed by washing with cold HCl (1 N). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) dimesylate **10** (0.923 g, 91%) as a colorless liquid. R_f=0.50 (EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ +18.00 (*c* 1.0, $CHCl_3$); IR (neat): 3280, 1454, 1334, 1162, 1091, 815, 738, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.1 Hz, 2H), 7.30–7.26 (m, 3H), 7.19 (d, *J*=8.1 Hz, 2H), 7.13–7.09 (m, 2H), 5.13 (d, *J*=9.9 Hz, 1H), 5.06 (d, *J*=6.0 Hz, 1H), 4.31 (d, *J*=11.7 Hz, 1H), 4.20 (d, *J*=11.7 Hz, 1H), 4.02–3.95 (m, 1H), 3.43 (dd, *J*=10.5, 2.1 Hz, 1H), 3.24 (s, 3H), 2.87 (dd, *J*=10.5, 3.9 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 137.2, 136.9, 129.9, 128.5, 127.9, 127.8, 126.9, 76.7, 73.2, 67.2, 53.7, 39.2, 21.5; HRMS *m/z* calcd for $C_{36}H_{44}N_2O_{12}S_4$ [M+Na^+]: 847.1675; found: 847.1695.

4.1.4. (2*R*,3*R*)-2-((Benzyloxy)methyl)-3-((2*R*,3*R*)-3-((benzyloxy)methyl)-1-tosylaziridin-2-yl)-1-tosylaziridine 11. To a solution of dimesylate **10** (0.90 g, 1.09 mmol) in dry THF (10 mL), NaH (0.08 g, 3.18 mmol) was slowly added at 0 °C. The mixture was stirred at 20 °C for 12 h, and then slowly water (1 mL) was added drop wise at 0 °C to quench the excess of NaH. The reaction mixture was diluted with water and extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) the bis-aziridine **11** (0.59 g, 88%) as a colorless solid. R_f=0.80 (EtOAc/hexanes, 1:1); mp: 121 °C; $[\alpha]_D^{27}$ +38.00 (*c* 1.0, $CHCl_3$); IR (neat): 1596, 1328, 1160, 1090, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J*=8.4 Hz, 2H), 7.35–7.17 (m, 7H), 4.39 (s, 2H), 3.67–3.57 (m, 2H), 3.08–2.99 (m, 1H), 2.89–2.84 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 137.5, 134.4, 129.6, 128.3, 127.9, 127.8, 127.6, 72.9, 66.4, 41.9, 39.3, 21.6; HRMS *m/z* calcd for $C_{34}H_{36}N_2O_6S_2$ [M+Na^+]: 655.1912; found: 655.1914.

4.1.5. (2*S*,3*R*)-2-((Benzyloxy)methyl)-3-((2*R*,3*S*)-3-((benzyloxy)methyl)oxiran-2-yl)oxirane 12. Bis-epoxide **12** (0.267 g, 85%) was synthesized from the dimesylate **4** (0.50 g, 0.97 mmol) as a colorless liquid by using the procedure described for compound **11** (see Section 4). R_f=0.80 (EtOAc/hexanes, 1:1); $[\alpha]_D^{27}$ +68.00 (*c* 1.0, $CHCl_3$); IR (neat): 1454, 1274, 1099, 892, 748, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.21 (m, 5H), 4.55 (dd, *J*=15.3, 12.0 Hz, 2H), 3.72 (dd, *J*=11.7, 3.0 Hz, 1H), 3.49 (dd, *J*=11.7, 5.1 Hz, 1H), 3.17–3.15 (m, 1H), 2.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 128.3, 127.6, 127.5, 73.1, 68.9, 54.4, 53.4; HRMS *m/z* calcd for $C_{20}H_{22}O_4$ [M+Na^+]: 349.1416; found: 349.1424.

4.1.6. (*S*)-2-((4*R*,5*R*)-5-((*S*)-1-(Tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-tosyl ethanamine 13. A solution of ditosylate **8** (0.50 g, 0.71 mmol) in MeOH (10 mL) was treated with H_2 over 10% Pd/C (0.05 mg) at atmospheric pressure for 12 h. The mixture was filtered through Celite and the solvent was evaporated in vacuo. The crude residue was purified by chromatography on silica gel (230–400 mesh) using 30–50% EtOAc in hexane solvent as eluent to afford pure compound **13** (0.336 g, 90%) as a colorless liquid. R_f=0.20 (EtOAc/hexanes, 7:3); $[\alpha]_D^{25}$ −42.00 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 3281, 1324, 1158, 816, 658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 5.36 (d, *J*=9.3 Hz, 1H), 4.17 (s, 1H), 3.64 (dd, *J*=11.4, 2.7 Hz, 1H), 3.46–3.42 (m, 1H), 3.17–3.14 (m, 1H), 2.43 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 137.4, 129.9, 126.9, 109.7, 79.1, 63.9, 51.4, 26.9, 21.5; HRMS *m/z* calcd for $C_{23}H_{32}N_2O_8S_2$ [M+Na^+]: 551.1498; found: 551.1501.

4.1.7. (1*S*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-(1*S*)-1-[(4-methylphenyl)sulfonyl]oxy-2-[(methylsulfonyl)oxy]ethyl-1,3-dioxolan-4-yl)-2-[(methylsulfonyl)oxy]ethyl 4-methyl-1-benzenesulfonate 14. The dimesylate **14** (0.358 g, 92%) was synthesized from the diol **13** (0.30 g, 0.57 mmol) as a colorless liquid by using the procedure described for compound **10** (see Section 4). R_f=0.20 (EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ −28 (*c* 1.0, $CHCl_3$); IR (neat): 3278, 1451, 1336, 1171, 1094, 821, 744, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 5.08 (d, *J*=9.6 Hz, 1H), 4.07–3.97 (m, 3H), 3.82–3.76 (m, 1H), 2.84 (s, 3H), 2.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$): δ 144.1, 137.5, 129.9, 127.0, 110.1, 75.1, 67.3, 50.7, 37.2, 26.8, 21.5; HRMS *m/z* calcd for $C_{25}H_{36}N_2O_{12}S_4$ [M+Na$^+$]: 707.1049; found: 707.1062.

4.1.8. (*S*)-2-((4*R*,5*R*)-2,2-Dimethyl-5-((*S*)-1-tosylaziridin-2-yl)-1,3-dioxolan-4-yl)-1-tosyl aziridine 15. The bis-aziridine **15** (0.22 g, 87%) was synthesized from the dimesylate **14** (0.35 g, 0.51 mmol) as a colorless solid by using the procedure described earlier for compound **11** (see Section 4). R_f=0.30 (EtOAc/hexanes, 2:8); mp: 68 °C; $[\alpha]_D^{27}$ −34.00 (*c* 1.0, $CHCl_3$); IR (neat): 1930, 1596, 1325, 1162, 678 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 3.83 (dd, *J*=2.7, 1.5 Hz, 1H), 2.77–2.73 (m, 1H), 2.60 (d, *J*=7.2 Hz, 1H), 2.45 (s, 3H), 2.38 (d, *J*=4.2 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9, 134.6, 129.8, 128.0, 110.4, 75.9, 37.8, 30.9, 26.6, 21.6; HRMS *m/z* calcd for $C_{23}H_{28}N_2O_6S_2$ [M+Na$^+$]: 515.1287; found: 515.1304.

4.1.9. (1*R*)-2-Hydroxy-1-((4*S*,5*S*)-5-(1*R*)-2-hydroxy-1-[(methylsulfonyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl methanesulfonate 16. The diol **16** (0.175 g, 86%) was synthesized from the dimesylate **5** (0.30 g, 0.54 mmol) as a colorless liquid by using the procedure described earlier for compound **13**. R_f=0.20 (EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ +84.00 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 1317, 1158, 814, 658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81–4.79 (m, 1H), 4.37 (dd, *J*=3.9, 1.5 Hz, 1H), 4.03 (dd, *J*=12.9, 3.3 Hz, 1H), 3.89 (dd, *J*=12.9, 6.0 Hz, 1H), 3.19 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.3, 82.0, 61.4, 38.7, 26.9; HRMS *m/z* calcd for $C_{11}H_{22}O_{10}S_2$ [M+Na$^+$]: 401.0552; found: 401.0546.

4.1.10. (4*R*,5*R*)-2,2-Dimethyl-4,5-di((*S*)-oxiran-2-yl)-1,3-dioxolane 17. The bis-epoxide **17** (0.063 g, 85%) was synthesized from the diol **16** (0.15 g, 0.40 mmol) as colorless crystals by using the procedure described for compound **11** (see Section 4). R_f=0.70 (EtOAc/hexanes, 3:7); mp: 74 °C; $[\alpha]_D^{27}$ −19.00 (*c* 1.0, $CHCl_3$); IR (neat): 1460, 1360, 1276, 1096, 890, 752, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (dd, *J*=3.3, 1.5 Hz, 1H), 3.10–3.06 (m, 1H), 2.85 (dd, *J*=5.4, 4.2 Hz, 1H), 2.75 (dd, *J*=5.4, 2.4 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.7, 77.9, 51.1, 43.8, 26.6; HRMS *m/z* calcd for $C_9H_{14}O_4$ [M+Na$^+$]: 209.0790; found: 209.0798.

4.1.11. (2*R*,4*S*,5*R*)-4-((2*R*,4*R*,5*R*)-5-Hydroxy-2-phenyl-1,3-dioxan-4-yl)-2-phenyl-1,3-dioxan-5-yl-4-methylbenzenesulfonate 18. To a solution of diol **2** (3 g, 8.38 mmol) in dry pyridine (30 mL), tosyl chloride (1.75 g, 9.22 mmol) was slowly added at −5 °C. Then the reaction mixture was stirred for 2 h at 20 °C. The reaction mixture was diluted with Et_2O followed by washing with cold HCl (1 N). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) monotosylate **18** (2.66 g, 62%) as a colorless liquid. R_f=0.20 (EtOAc/hexanes, 4:6); $[\alpha]_D^{25}$ −22.00 (*c* 1.0, $CHCl_3$); IR (neat): 3464, 1338, 1154, 821, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J*=8.1 Hz, 2H), 7.45–7.31 (m, 10H), 7.09 (d, *J*=8.1 Hz, 2H), 5.48 (s, 1H), 4.96 (s, 1H), 4.82 (m, 1H), 4.41 (dd, *J*=11.1, 5.4 Hz, 1H), 4.26–4.16 (m, 2H), 4.03 (m, 1H), 3.82 (t, *J*=10.5 Hz, 1H), 3.61 (dd, *J*=9.3, 1.5 Hz, 1H), 3.47 (t, *J*=10.5 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 137.3, 136.8, 132.5, 129.9, 129.1, 128.8, 128.2, 127.9, 127.8, 126.2, 126.0, 101.3, 100.4, 77.3, 74.9, 71.0, 68.6, 67.2, 59.7, 21.5; HRMS *m/z* calcd for $C_{27}H_{28}O_8S$ [M+Na$^+$]: 535.1403; found: 535.1416.

4.1.12. (2*R*,3*S*,4*R*,5*R*)-5-Acetoxy-1,6-bis(benzyloxy)-3,4-dihydroxy-2-yl-4-methylbenzene sulfonate 20. To a solution of monotosylate **18** (2.5 g, 4.88 mmol) in dry pyridine (20 mL), Ac_2O (0.51 mL, 5.34 mmol) was slowly added at 0 °C. The reaction mixture was stirred at 20 °C for 2 h and it was diluted with Et_2O followed by washing with cold HCl (1 N). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated to afford crude acetate **19** (silica gel; EtOAc/hexanes, 80:20) as a colorless liquid, which was used in the next step without purification. To a crude solution of **19** in dry CH_2Cl_2 (40 mL) at 0 °C was added Et_3SiH (1.3 mL, 7.94 mmol) followed by $BF_3\cdot Et_2O$ (1.5 mL, 11.6 mmol). After stirring the reaction mixture at 0 °C for 1 h, it was quenched with saturated $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the product, which was purified by flash chromatography to give pure diol **20** (1.85 g, 68% overall yield). R_f=0.20 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −104.00 (*c* 1.0, $CHCl_3$); IR (neat): 3462, 1740, 1374, 1236, 1092, 736, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.1 Hz, 2H), 7.36–7.18 (m, 12H), 5.00 (q, *J*=4.2 Hz, 1H), 4.70 (q, *J*=3.9 Hz, 1H), 4.57 (dd, *J*=22.2, 12.0 Hz, 2H), 4.41 (s, 2H), 3.98 (d, *J*=8.4 Hz, 1H), 3.83 (d, *J*=7.8 Hz, 1H), 3.75 (d, *J*=4.5 Hz, 2H), 3.69 (dd, *J*=6.0, 4.2 Hz, 2H), 2.38 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 144.9, 137.7, 137.5, 133.4, 129.7, 128.4, 128.3, 127.9, 127.7, 127.6, 79.3, 73.4, 71.8, 68.7, 68.4, 68.1, 67.7, 21.6, 21.1; HRMS *m/z* calcd for $C_{29}H_{34}O_9S$ [M+Na$^+$]: 581.1821; found: 581.1833.

4.1.13. (*R*)-1-((4*S*,5*R*)-5-((*S*)-1-Azido-2-(benzyloxy)-ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(benzyloxy)-ethyl acetate 22. The diol **20** (1.8 g, 3.23 mmol) was dissolved in dry acetone (15 mL) and then treated with 2,2-dimethoxypropane (1.2 mL, 9.68 mmol) followed by a solution of *p*TSA in dry acetone (4 mL). The resultant mixture was allowed to stir for 5 h at room temperature. The mixture was then diluted with EtOAc (15 mL), washed with a saturated solution of $NaHCO_3$ (2×5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield a crude product, which was purified by flash chromatography to give pure acetonide **21** (1.53 g, 80% yield). A suspension of acetonide **21** (1.5 g, 2.54 mmol) and sodium azide (0.198 g, 3.05 mmol) in dry DMF (30 mL) was stirred at 110 °C for 24 h. After evaporation of DMF, 15 mL of water was added to the residue, which was then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and evaporated to give a syrupy liquid, which was purified by flash column chromatography to give pure azide **22** (1.05 g, 88%). R_f=0.80 (EtOAc/hexanes, 2:8); $[\alpha]_D^{25}$ +53.00 (*c* 1.0, $CHCl_3$); IR (neat): 2105, 1743, 1454, 1371, 1232, 1097, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 10H), 5.17–5.12 (m, 1H), 4.55

(d, J=5.1 Hz, 2H), 4.51 (d, J=3.0 Hz, 2H), 4.29 (dd, J=7.8, 5.2 Hz, 1H), 4.10 (dd, J=7.8, 2.7 Hz, 1H), 3.81–3.61 (m, 4H), 3.53–3.48 (m, 1H), 2.05 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 137.6, 137.5, 128.4, 128.3, 127.7, 127.6, 127.5, 110.4, 77.8, 76.1, 73.3, 73.2, 69.9, 68.4, 60.7, 26.9, 26.7, 20.9; HRMS m/z calcd for $C_{25}H_{31}N_3O_6$ [M+Na$^+$]: 492.2111; found: 492.2104.

4.1.14. (*R*)-2-(Benzyloxy)-1-((4*S*,5*R*)-5-((*S*)-2-(benzyloxy)-1-(tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate 24. The tosylate **24** (0.993 g, 78% overall yield) was synthesized from the azide **22** (1 g, 2.13 mmol) as a colorless liquid by using the procedure described for compound **8**. R_f=0.40 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −30.00 (c 1.0, $CHCl_3$); IR (neat): 3295, 1743, 1454, 1371, 1332, 1232, 1160, 1091, 815, 738, 698, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J=8.1 Hz, 2H), 7.32–7.25 (m, 10H), 7.17 (d, J=8.1 Hz, 2H), 5.20–5.15 (m, 1H), 4.98 (d, J=9.3 Hz, 1H), 4.52 (dd, J=18.6, 12.0 Hz, 2H), 4.32 (s, 2H), 4.25 (dd, J=8.1, 1.5 Hz, 1H), 3.86 (dd, J=8.1, 6.0 Hz, 1H), 3.65 (dd, J=11.4, 3.6 Hz, 2H), 3.48 (dd, J=11.4, 6.0 Hz, 1H), 3.40 (dd, J=9.3, 5.1 Hz, 1H), 3.33 (dd, J=17.1, 9.0 Hz, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 143.2, 137.9, 137.7, 137.6, 129.5, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 126.9, 109.6, 76.6, 75.9, 72.9, 72.8, 72.1, 69.9, 68.7, 52.6, 26.9, 26.7, 21.4, 20.9; HRMS m/z calcd for $C_{32}H_{39}NO_8S$ [M+Na$^+$]: 620.2294; found: 620.2267.

4.1.15. (2*R*,3*S*,4*R*,5*S*)-1,6-Bis(benzyloxy)-3,4-dihydroxy-5-(tosylamino)hexan-2-yl acetate 25. Diol **25** (0.672 g, 80%) was synthesized from acetonide **24** (0.90 g, 1.51 mmol) as a colorless liquid by using the procedure described for compound **9**. R_f=0.20 (EtOAc/hexanes, 4:8); $[\alpha]_D^{25}$ +21.00 (c 1.0, $CHCl_3$); IR (neat): 3502, 3272, 1733, 1454, 1240, 1160, 1093, 815, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J=8.1 Hz, 2H), 7.33–7.17 (m, 12H), 5.47 (d, J=6.9 Hz, 1H), 5.02–4.97 (m, 1H), 4.52 (d, J=3.6 Hz, 2H), 4.33 (s, 2H), 3.80–3.71 (m, 4H), 3.46 (d, J=7.2 Hz, 2H), 3.34–3.29 (m, 3H), 2.37 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 143.4, 137.6, 137.2, 136.9, 129.6, 128.4, 128.3, 127.8, 127.7, 127.6, 127.1, 73.3, 73.2, 72.2, 69.6, 68.7, 68.6, 68.5, 55.7, 21.5, 20.9; HRMS m/z calcd for $C_{29}H_{35}NO_8S$ [M+Na$^+$]: 580.1981; found: 580.1993.

4.1.16. (2*R*,3*S*,4*R*,5*S*)-1,6-Bis(benzyloxy)-3,4-dimethanesulfono-5-(tosylamino)hexan-2-yl acetate 26. The dimesylate **26** (0.70 g, 91%) was synthesized from the diol **25** (0.60 g, 1.08 mmol) as a colorless liquid by using the procedure described for compound **10**. R_f=0.40 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ +29.00 (c 1.0, $CHCl_3$); IR (neat): 3280, 1749, 1596, 1454, 1353, 1228, 1178, 1093, 954, 738, 700, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J=8.1 Hz, 2H), 7.30–7.24 (m, 8H), 7.21 (d, J=8.1 Hz, 2H), 7.08–7.04 (m, 2H), 5.49 (dd, J=7.8, 2.4 Hz, 1H), 5.33–5.26 (m, 2H), 5.18 (d, J=9.9 Hz, 1H), 4.55 (dd, J=13.8, 11.4 Hz, 2H), 4.07 (d, J=11.4 Hz, 1H), 3.95–3.88 (m, 2H), 3.84 (dd, J=10.2, 5.4 Hz, 1H), 3.69–3.62 (m, 1H), 3.23 (s, 3H), 3.09 (s, 3H), 2.95 (dd, J=9.9, 3.0 Hz, 1H), 2.67 (dd, J=9.9, 4.8 Hz, 1H), 2.41 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 143.9, 137.3, 136.8, 129.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 126.9, 79.6, 73.8, 73.3, 70.3, 68.4, 67.4, 52.6, 39.1, 38.2, 21.6, 20.8; HRMS m/z calcd for $C_{31}H_{39}NO_{12}S_3$ [M+Na$^+$]: 736.1532; found: 736.1533.

4.1.17. (2*R*,3*S*)-2-((Benzyloxy)methyl)-3-((2*S*,3*S*)-3-((benzyloxy)methyl)oxiran-2-yl)-1-tosyl aziridine 27. To a solution of dimesylate **26** (0.50 g, 0.70 mmol) in dry MeOH (10 mL), NaOMe (0.151 g, 2.8 mmol) was slowly added at 0 °C. The mixture was stirred at 20 °C for 1 h, and then MeOH was evaporated under reduced pressure. The reaction mixture was diluted with water and extracted with Et_2O (3×10 mL). The combined organic extract was dried (Na_2SO_4) and evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) the aziridinoepoxide **27** (0.296 g, 88%) as a colorless liquid. R_f=0.80 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ +20.00 (c 1.0, CH_2Cl_2); IR (neat): 1361, 1336, 1176, 1162, 923, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J=8.1 Hz, 2H), 7.33–7.18 (m, 12H), 4.50 (s, 2H), 4.43 (d, J=2.4 Hz, 2H), 3.70 (d, J=1.8 Hz, 1H), 3.68 (s, 1H), 3.65 (d, J=2.7 Hz, 1H), 3.44 (dd, J=11.7, 4.8 Hz, 1H), 3.17 (dd, J=11.7, 6.0 Hz, 1H), 3.07–3.04 (m, 1H), 2.99 (dd, J=7.2, 2.1 Hz, 1H), 2.91 (dd, J=7.2, 4.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 137.6, 134.5, 129.7, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 73.3, 73.0, 68.6, 66.7, 55.2, 50.7, 42.9, 41.8, 21.6; HRMS m/z calcd for $C_{27}H_{29}NO_5S$ [M+Na$^+$]: 502.1664; found: 502.1664.

4.1.18. (*R*)-2-Hydroxy-1-((4*S*,5*R*)-5-((*S*)-2-hydroxy-1-(tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate 28. The diol **28** (0.29 g, 83%) was synthesized from the tosylate **24** (0.50 g, 0.84 mmol) as a colorless liquid by using the hydrogenolysis procedure described earlier for compound **13**. R_f=0.40 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −16.00 (c 1.0, $CHCl_3$); IR (neat): 3523, 3297, 1739, 1598, 1454, 1367, 1243, 1176, 1093, 983, 815, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J=8.1 Hz, 2H), 7.32 (d, J=8.1 Hz, 2H), 5.17 (d, J=8.1 Hz, 1H), 4.28 (dd, J=9.9, 2.4 Hz, 1H), 3.99–3.88 (m, 5H), 3.72–3.68 (m, 2H), 2.43 (s, 3H), 2.12 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 143.9, 137.3, 129.8, 127.0, 109.7, 78.1, 74.9, 71.9, 68.8, 66.1, 51.9, 26.8, 21.6, 21.5, 20.7; HRMS m/z calcd for $C_{18}H_{27}NO_8S$ [M+Na$^+$]: 440.1355; found: 440.1362.

4.1.19. (1*R*)-2-Hydroxy-1-[(4*S*,5*R*)-5-((1*S*)-2-hydroxy-1-[(4-methylphenyl)sulfonyl]amino ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl acetate 29. The dimesylate **29** (0.312 g, 91%) was synthesized from the diol **28** (0.25 g, 0.60 mmol) as a colorless liquid by using the procedure described earlier for compound **10**. R_f=0.80 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −18.00 (c 1.0, $CHCl_3$); IR (neat): 3303, 1749, 1596, 1355, 1226, 1089, 970, 815 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J=8.1 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 5.04 (d, J=9.6 Hz, 1H), 4.86–4.81 (m, 1H), 4.56 (dd, J=12.6, 2.1 Hz, 1H), 4.23 (dd, J=7.8, 1.2 Hz, 1H), 4.11–3.84 (m, 5H), 3.14 (s, 3H), 2.90 (s, 3H), 2.44 (s, 3H), 2.12 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 144.1, 137.5, 129.9, 127.1, 110.9, 79.0, 73.9, 67.4, 63.0, 51.9, 38.8, 37.2, 26.8, 26.6, 21.5, 20.7; HRMS m/z calcd for $C_{20}H_{31}NO_{12}S_3$ [M+Na$^+$]: 596.0906; found: 596.0922.

4.1.20. (*S*)-2-((4*R*,5*S*)-2,2-Dimethyl-5-((*R*)-oxiran-2-yl)-1,3-dioxolan-4-yl)-1-tosylaziridine 30. Dimesylate **29** was subjected to cyclization using the procedure described earlier for compound **27** to furnish aziridino-epoxide **30** (0.163 g, 80% overall yield). R_f=0.60 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −59.00 (*c* 1.0, CH_2Cl_2); IR (neat): 1939, 1598, 1325, 1163, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 4.02 (dd, *J*=7.8, 3.9 Hz, 1H), 3.35 (t, *J*=7.8 Hz, 1H), 2.99–2.95 (m, 1H), 2.91–2.85 (m, 1H), 2.81 (dd, *J*=8.7, 5.1 Hz, 1H), 2.66 (d, *J*=7.5 Hz, 1H), 2.47–2.45 (m, 1H), 2.46 (s, 3H), 2.41 (d, *J*=4.8 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 134.5, 129.7, 128.3, 110.8, 79.3, 76.6, 51.4, 45.9, 39.7, 30.4, 26.9, 26.4, 21.6; HRMS *m*/*z* calcd for $C_{16}H_{21}NO_5S$ [M+Na^+]: 362.1038; found: 362.1040.

Acknowledgements

We thank CSIR, New Delhi for senior research fellowships to S.M. and D.S., and DST, New Delhi for CCD X-ray facility and J. C. Bose National Fellowship to S.C.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.035.

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10. Crystal data for compound **3**: structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P2_1/c$, cell parameters: a=11.256(4), b=9.278(4), c=12.614(5) Å, α=90.00°, β=112.461(6)°, γ=90.00°, V=1217.41 Å^3, Z=2, ρ_{calcd}=1.40 g cm^{-3}, $F(000)$=340, μ=0.272 mm^{-1}, λ=0.71073 Å. Total number l.s. parameters=309. $R1$=0.053 for 4240 $F_o>4\sigma(F_o)$ and 0.071 for all 8862 data. $wR2$=0.104, GOF=1.035, restrained GOF=1.035 for all data. (CCDC no. 612123).
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13. Crystal data for compound **11**: structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P2_1$, cell parameters: a=22.752(3), b=7.383(7), c=22.459(2) Å, α=90.00°, β=118.819(3)°,

γ=90.00°, V=3305.49 Å^3, Z=4, ρ_{calcd}=1.27 g cm^{-3}, $F(000)$=1336, μ=0.207 mm^{-1}, λ=0.71073 Å. Total number l.s. parameters=399. $R1$=0.049 for 5710 $F_o>4\sigma(F_o)$ and 0.060 for all 11973 data. $wR2$=0.107, GOF=1.134, restrained GOF=1.134 for all data. (CCDC no. 292270).

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16. Crystal data for compound **17**: structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P2_1$, cell parameters: a=5.434(6), b=11.272(9), c=8.406(9) Å, α=90.00°, β=105.842(2)°, γ=90.00°, V=495.35 Å^3, Z=2, ρ_{calcd}=1.25 g cm^{-3}, $F(000)$=200, μ=0.098 mm^{-1}, λ=0.71073 Å. Total number l.s. parameters=120. $R1$=0.045 for 1673 $F_o>4\sigma(F_o)$ and 0.060 for all 3523 data. $wR2$=0.085, GOF=1.079, restrained GOF=1.079 for all data. (CCDC no. 292059). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html.