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Synthesis of DMJ analogs with seven- and eight-membered iminocyclitols

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Abstract—A straightforward synthesis of new hydroxy azepane and azocane with an additional hydroxymethyl side arm (1-deoxymannojirimycin, DMJ analogs) has been achieved from *trans*-(2*S*,4*R*)-4-hydroxyproline via Grignard addition, ring-closing metathesis, and stereoselective osmylation as the key steps.

1. Introduction

The structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline possesses three functional groups that can be easily modified.[1] The skeleton represents the significant feature for producing a series of different carbon frameworks using an efficient modification technique. Recently we have introduced a straightforward approach toward anisomycin, epibatidine, pancracine, streptorubin B core, statine, and Vigabatrin® employing *trans*-(2*S*,4*R*)-4-hydroxyproline as the starting material.[2] To explore a new application, synthetic studies toward new hydroxy azepane **1** and azocane **2** with an additional hydroxymethyl side arm were further investigated as shown in Figure 1. According to the structural framework of 1-deoxymannojirimycin (DMJ, **3**), compounds **1** and **2** have the common configuration of hydroxyl group at the cyclic ring and their only difference is the extra methylene group (–CH_2–) between C2–C3 and C3–C4 positions.

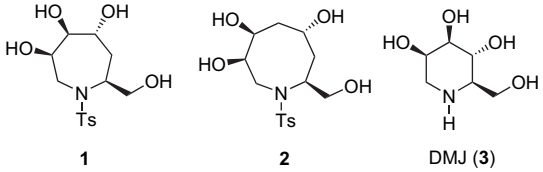

Figure 1. Structural characteristics of seven-, eight-, and six-membered iminocyclitols **1**, **2**, and DMJ (**3**).

Keywords: *trans*-(2*S*,4*R*)-4-Hydroxyproline; 1-Deoxymannojirimycin (DMJ); Azepane; Azocane; Grignard addition; Ring-closing metathesis; Stereoselective osmylation.
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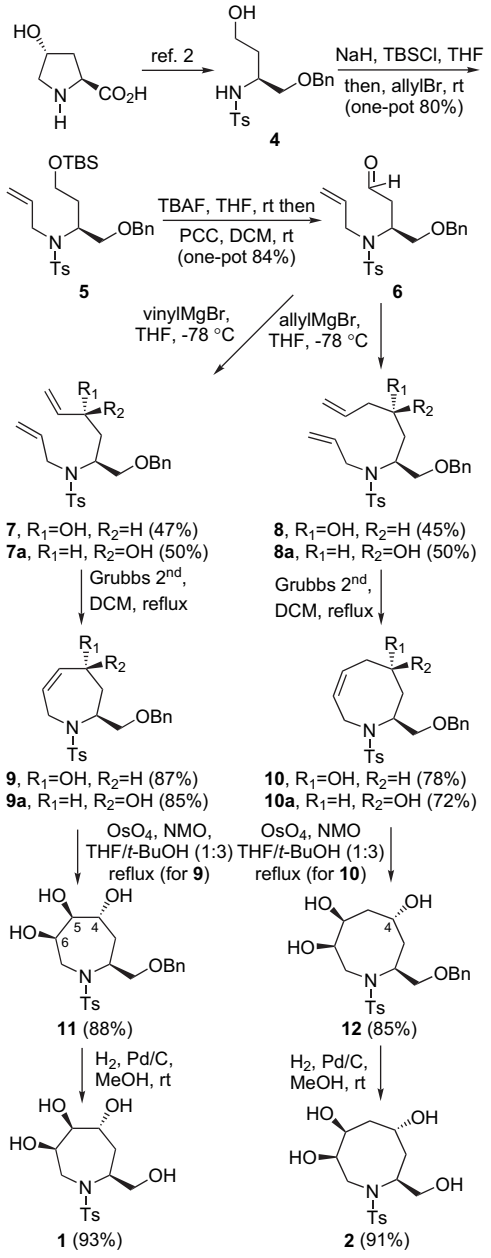
Glycosidases and glycosyltransferases are involved in the processing and synthesis of complex carbohydrates, which are essential in various biological recognition processes.[3,4] While deoxynojirimycin (DNJ) constitutes a well known example of a potent naturally occurring glycosidase inhibitor, DMJ has been found as a selective inhibitor of α-mannosidase I. Iminocyclitols based on seven- or eight-membered rings having the same carbon content as the azasugars but endowed with the conformational advantage of a more flexible azepane or azocane ring that could lead to favorable binding to the active site of the enzyme have been documented.[5–7] In connection with our studies on *trans*-(2*S*,4*R*)-4-hydroxyproline as the chiral material, we are interested in developing an easy and straightforward approach to two DMJ analogs **1** and **2** via Grignard addition, ring-closing metathesis, and stereoselective osmylation.

2. Results and discussion

The straightforward synthesis of compounds **1** and **2** began from alcohol **4** as illustrated in Scheme 1. The preparation of alcohol **4** was recently reported from *trans*-(2*S*,4*R*)-4-hydroxyproline.[2] First, compound **5** was synthesized via one-pot reaction by O-silylation with *tert*-butyldimethylsilyl chloride and sodium hydride, followed by N-allylation of the resultant product with allyl bromide in 80% yield. To this end, compound **5** was treated with tetra-*n*-butylammonium fluoride and subsequently oxidized with pyridinium chlorochromate and Celite to aldehyde **6** under the one-pot condition in 84% yield. Further, in order to achieve the synthesis of targets **1** and **2**, two dienes **7** and **7a** (47% and 50%) or **8** and **8a** (45% and 50%) were yielded in nearly 1:1 ratio by Grignard addition of aldehyde **6** with vinyl- or

allylmagnesium bromide. The yields of alcohols **7** and **7a** or **8** and **8a** were adjusted based on isolated products.



Scheme 1. Synthesis of DMJ analogs **1** and **2**.

The key ring-closing metathesis was examined in the following step. Ring-closing metathesis has been established as a powerful method for the elaboration of medium-sized rings, including carbohydrates, heterocycles, and alkaloids.[4b,8,9] To build up the azepane and azocane structural skeletons, dienes **7** and **7a** or **8** and **8a** were subjected to a ring-closing metathesis employing Grubbs' second generation catalyst and the expected compounds **9** and **9a** or **10** and **10a** were generated, respectively.

In order to increase the total yields of DMJ analogs **1** and **2**, alcohols **9a** and **10a** were successfully epimerized to the desired alcohols **9** and **10** by Mitsunobu reaction with diethyl azodicarboxylate, triphenylphosphine, and acetic acid and hydrolysis with potassium carbonate in methanol in 89% and 83% yields. The successful epimerizations of compounds **9a** and **10a** were determined by comparing their ^{1}H NMR spectra with those of compounds **9** and **10**. Stereoselective osmylation of allylic or homoallylic alcohols **9** and **10** on the azepane or azocane framework with osmium tetraoxide and *N*-methylmorpholine *N*-oxide afforded triol **11** or **12** as a single diastereomer.

According to the literature reports,[4b,6o] we envisioned that the hydroxyl group at C4 position is an important factor to cause steric hindrance and affects the stereoselective introduction of *cis*-dihydroxyl groups. Thus, this remarkably high diastereoselectivity of the hydroxylation would arise from the steric blocking of the concave face. On examining the steric hindrance factor of C4 substitutent during the osmylation procedure, reaction of compound **9** with acetoxy group was still afforded the sole product under the same reaction condition. During the osmylation process, the other stereoisomers of compounds **11** and **12** were not observed. The related trans–cis stereochemical structure of triol **11** with contiguous chiral centers at C4, C5, and C6 was determined by single-crystal X-ray analysis as shown in Diagram 1.[10]

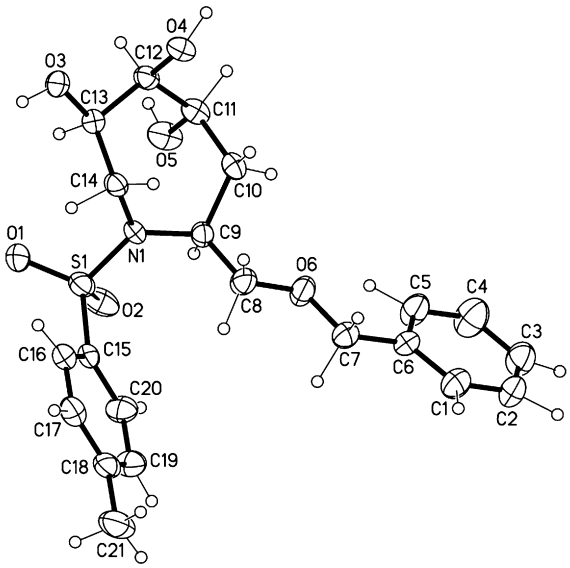


Diagram 1. X-ray crystallography of compound **11**.

According to the corresponding results of osmylated product **11**, we think that the similar manner should be also used to predict the stereochemical structure of triol **12** as a trans–cis conformation. Finally, synthesis of DMJ analogs **1** and **2** was achieved via hydrogenolysis with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon.

3. Conclusion

In summary, we succeeded in accomplishing the synthesis of DMJ analogs **1** and **2** in moderate yields via Grignard addition, ring-closing metathesis, and highly stereoselective

osmylation as the key steps. The synthesis of desulfonated DMJ analogs **1** and **2** and their structure–activity studies in the inhibition of glycosidases will also be investigated in succeeding works.

4. Experimental

4.1. General

Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. All reported melting temperatures are uncorrected.

4.1.1. *N*-Allyl-*N*-[1-benzyloxymethyl-3-(*tert*-butyldimethyl-silanyloxy)propyl]-4-methylbenzenesulfonamide (5). *tert*-Butyldimethylsilyl chloride (750 mg, 5.0 mmol) and sodium hydride (400 mg, 60%, 10.0 mmol) were added to a stirred solution of compound **4** (1.4 g, 4.0 mmol) in DMF (5 mL) at rt. The reaction mixture was stirred at rt for 10 h. The procedure was monitored by TLC until the reaction was complete. Allyl bromide (750 mg, 6.2 mmol) was added to the reaction mixture at rt for 5 h. The reaction mixture was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with AcOEt (3×50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield crude product. Purification on silica gel (hexane/AcOEt=5/1) afforded compound **5** (1.61 g, 80%). $[\alpha]_D^{31}$ −25.6 (*c* 0.025, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{42}NO_4SSi$ (M^++1) 504.2604, found 504.2608; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.0 Hz, 2H), 7.34–7.27 (m, 3H), 7.21–7.17 (m, 4H), 5.84–5.76 (m, 1H), 5.13 (dd, *J*=1.0, 17.0 Hz, 1H), 5.05 (dd, *J*=1.0, 10.0 Hz, 1H), 4.40 (d, *J*=12.0 Hz, 1H), 4.34 (d, *J*=12.0 Hz, 1H), 4.18–4.13 (m, 1H), 3.86 (d, *J*=6.5 Hz, 2H), 3.56–3.47 (m, 4H), 2.38 (s, 3H), 1.84–1.71 (m, 2H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.75, 138.29, 137.96, 136.06, 129.27 (2×), 128.27 (2×), 127.60 (2×), 127.56, 127.42 (2×), 117.07, 72.86, 71.36, 60.14, 55.09, 47.51, 33.69, 25.90 (3×), 21.47, 18.22, −5.38, −5.44. Anal. Calcd for $C_{27}H_{41}NO_4SSi$: C, 64.37; H, 8.20; N, 2.78. Found: C, 64.65; H, 8.45; N, 2.56.

4.1.2. *N*-Allyl-*N*-(1-benzyloxymethyl-3-oxopropyl)-4-methylbenzenesulfonamide (6). A solution of tetra-*n*-butylammonium fluoride (1.2 mL, 1.0 M in THF, 1.2 mmol) in THF (1 mL) was added to a solution of compound **5** (1.0 g, 2.0 mmol) in THF (5 mL) at rt for 1 h. The procedure was monitored by TLC until the reaction was complete. A mixture of pyridinium chlorochromate (1.0 g, 4.6 mmol), Celite (3.0 g), and DCM (50 mL) was added to the stirring reaction. After being stirred at rt for 10 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt=4/1) afforded compound **6** (650 mg, 84%). $[\alpha]_D^{30}$ −3.5 (*c* 0.018, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{26}NO_4S$ (M^++1) 388.1583, found 388.1588; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.70 (d, *J*=8.5 Hz, 2H), 7.34–7.28 (m, 3H), 7.23 (d, *J*=8.5 Hz, 2H), 7.18 (d, *J*=7.0 Hz, 2H), 5.82–5.74 (m, 1H), 5.16 (d, *J*=17.0 Hz, 1H), 5.11 (d, *J*=10.5 Hz, 1H), 4.57–4.52 (m, 1H), 4.39 (d, *J*=12.0 Hz, 1H), 4.34 (d, *J*=12.0 Hz, 1H), 3.89–3.82 (m, 2H), 3.56 (dd, *J*=6.5, 10.0 Hz, 1H), 3.47 (dd, *J*=6.5, 10.0 Hz, 1H), 2.78 (ddd, *J*=1.0, 7.5, 17.5 Hz, 1H), 2.69 (ddd, *J*=1.5, 6.5, 17.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.44, 143.35, 137.58, 137.46, 135.38, 129.56 (2×), 128.37 (2×), 127.79, 127.66 (2×), 127.27 (2×), 117.98, 73.03, 70.62, 52.55, 48.30, 45.31, 21.51. Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.45; H, 6.71; N, 3.84.

4.1.3. *N*-Allyl-*N*-(1-benzyloxymethyl-3-hydroxypent-4-enyl)-4-methylbenzenesulfonamide (7 and 7a). A solution of vinylmagnesium bromide (1.0 M in toluene, 1.5 mmol, 1.5 mL) was added to a stirred solution of compound **6** (500 mg, 1.29 mmol) in THF (20 mL) at −78 °C. The reaction mixture was stirred at rt for 2 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield crude product. Purification on silica gel (hexane/AcOEt=4/1) afforded compound **7** (252 mg, 47%) and **7a** (268 mg, 50%). For compound **7**: $[\alpha]_D^{30}$ −19.7 (*c* 0.1, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{30}NO_4S$ (M^++1) 416.1896, found 416.1899; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J*=8.0 Hz, 2H), 7.35–7.29 (m, 3H), 7.15 (d, *J*=8.0 Hz, 2H), 7.10–7.08 (m, 2H), 5.89–5.79 (m, 2H), 5.27 (tt, *J*=1.5, 17.5 Hz, 1H), 5.13–5.06 (m, 3H), 4.39–4.29 (m, 2H), 4.27 (d, *J*=12.0 Hz, 1H), 4.22 (d, *J*=12.0 Hz, 1H), 3.94 (dd, *J*=5.0, 16.0 Hz, 1H), 3.75 (dd, *J*=8.0, 16.0 Hz, 1H), 3.37 (dd, *J*=7.5, 10.0 Hz, 1H), 3.30 (dd, *J*=5.0, 10.0 Hz, 1H), 2.37 (s, 3H), 1.76 (ddd, *J*=2.5, 11.5, 14.5 Hz, 1H), 1.56 (br s, 1H), 1.47 (ddd, *J*=3.5, 10.5, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.07, 139.99, 137.51, 137.43, 135.91, 129.25 (2×), 128.30 (2×), 127.75 (2×), 127.73, 127.49 (2×), 117.57, 114.18, 72.94, 70.45, 67.85, 54.89, 46.79, 37.93, 21.52. Anal. Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.69; H, 7.32; N, 3.12. For compound **7a**: $[\alpha]_D^{30}$ −32.1 (*c* 0.1, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{30}NO_4S$ (M^++1) 416.1896, found 416.1895; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.5 Hz, 2H), 7.35–7.28 (m, 3H), 7.20–7.18 (m, 4H), 5.87–5.79 (m, 2H), 5.25 (tt, *J*=1.5, 17.5 Hz, 1H), 5.15 (dd, *J*=1.5, 17.5 Hz, 1H), 5.12 (tt, *J*=1.5, 10.0 Hz, 1H), 5.07 (dd, *J*=1.5, 10.0 Hz, 1H), 4.38 (d, *J*=12.0 Hz, 1H), 4.33 (d, *J*=12.0 Hz, 1H), 4.25–4.17 (m, 2H), 3.87 (d, *J*=6.5 Hz, 2H), 3.50 (dd, *J*=6.5, 10.0 Hz, 1H), 3.45 (dd, *J*=6.0, 10.0 Hz, 1H), 2.39 (s, 3H), 1.86 (ddd, *J*=5.0, 7.5, 14.5 Hz, 1H), 1.77 (br s, 1H), 1.76 (ddd, *J*=6.5, 7.5, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.01, 140.29, 137.90, 137.53, 135.91, 129.35 (2×), 128.35 (2×), 127.74, 127.70 (2×), 127.46 (2×), 117.34, 114.99, 72.98, 71.13, 70.19, 54.76, 47.51, 38.47, 21.49. Anal. Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.21; H, 7.15; N, 3.10.

4.1.4. *N*-Allyl-*N*-(1-benzyloxymethyl-3-hydroxyhex-5-enyl)-4-methylbenzenesulfonamide (8 and 8a). A solution of allylmagnesium bromide (1.0 M in toluene, 1.5 mmol,

1.5 mL) was added to a stirred solution of compound **6** (500 mg, 1.29 mmol) in THF (20 mL) at −78 °C. The reaction mixture was stirred at rt for 2 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield crude product. Purification on silica gel (hexane/AcOEt=4/1) afforded compound **8** (250 mg, 45%) and **8a** (277 mg, 50%). For compound **8**: $[\alpha]_D^{29}$ −10.2 (*c* 0.1, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{24}H_{32}NO_4S$ (M^++1) 430.2052, found 430.2057; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=8.0 Hz, 2H), 7.33–7.29 (m, 3H), 7.14 (d, *J*=8.0 Hz, 2H), 7.09–7.07 (m, 2H), 5.88–5.75 (m, 2H), 5.11–5.04 (m, 4H), 4.34–4.29 (m, 1H), 4.26 (d, *J*=12.0 Hz, 1H), 4.21 (d, *J*=12.0 Hz, 1H), 3.93–3.87 (m, 2H), 3.72 (dd, *J*=8.0, 16.0 Hz, 1H), 3.35 (dd, *J*=8.0, 10.0 Hz, 1H), 3.29 (dd, *J*=5.0, 10.0 Hz, 1H), 2.36 (s, 3H), 2.33–2.27 (m, 1H), 2.22–2.17 (m, 1H), 1.71 (ddd, *J*=2.0, 11.5, 14.5 Hz, 1H), 1.59 (br s, 1H), 1.37 (ddd, *J*=3.5, 10.5, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.00, 137.57, 137.44, 135.93, 135.04, 129.20 (2×), 128.29 (2×), 127.77 (2×), 127.71, 127.49 (2×), 117.48, 117.15, 72.91, 70.49, 66.29, 55.02, 46.68, 41.37, 37.36, 21.50. Anal. Calcd for $C_{24}H_{31}NO_4S$: C, 67.10; H, 7.27; N, 3.26. Found: C, 67.41; H, 7.48; N, 3.39. For compound **8a**: $[\alpha]_D^{29}$ −56.16 (*c* 0.1, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{24}H_{32}NO_4S$ (M^++1) 430.2052, found 430.2052; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.5 Hz, 2H), 7.34–7.29 (m, 3H), 7.20–7.17 (m, 4H), 5.84–5.73 (m, 2H), 5.14 (dd, *J*=1.0, 17.0 Hz, 1H), 5.11 (d, *J*=10.5 Hz, 1H), 5.11 (d, *J*=17.0 Hz, 1H), 5.07 (dd, *J*=1.0, 10.5 Hz, 1H), 4.38 (d, *J*=12.0 Hz, 1H), 4.32 (d, *J*=12.0 Hz, 1H), 4.26–4.21 (m, 1H), 3.87 (d, *J*=6.0 Hz, 2H), 3.72–3.67 (m, 1H), 3.50 (dd, *J*=6.5, 10.0 Hz, 1H), 3.44 (dd, *J*=5.0, 10.0 Hz, 1H), 2.39 (s, 3H), 2.30–2.25 (m, 1H), 2.16–2.12 (m, 1H), 1.79 (ddd, *J*=4.5, 7.5, 14.0 Hz, 1H), 1.67 (ddd, *J*=6.0, 8.0, 14.0 Hz, 1H), 1.58 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.97, 137.92, 137.63, 135.95, 135.48, 129.34 (2×), 128.34 (2×), 127.71, 127.69 (2×), 127.47 (2×), 118.16, 117.25, 72.97, 71.09, 68.20, 55.16, 47.43, 41.93, 37.89, 21.49. Anal. Calcd for $C_{24}H_{31}NO_4S$: C, 67.10; H, 7.27; N, 3.26. Found: C, 66.91; H, 7.12; N, 3.63.

4.1.5. 2-Benzyloxymethyl-1-(4-methylphenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepin-4-ol (9 and 9a). Grubbs' second generation catalyst (30 mg) was added to a solution of compound **7** or **7a** (100 mg, 0.24 mmol) in DCM (50 mL) at rt. The reaction mixture was refluxed for 2 h. The mixture was concentrated and purified by flash column chromatography (hexane/AcOEt=2/1) to yield compound **9** (81 mg, 87%) or **9a** (79 mg, 85%). For compound **9**: $[\alpha]_D^{27}$ −105.2 (*c* 0.01, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{21}H_{26}NO_4S$ (M^++1) 388.1583, found 388.1584; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J*=8.0 Hz, 2H), 7.36–7.26 (m, 5H), 7.20 (d, *J*=8.0 Hz, 2H), 5.55 (ddt, *J*=2.0, 6.5, 11.0 Hz, 1H), 5.48 (d, *J*=11.0 Hz, 1H), 4.49 (d, *J*=12.0 Hz, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 4.29 (dd, *J*=6.5, 18.5 Hz, 1H), 4.11–4.06 (m, 1H), 3.92 (ddd, *J*=2.0, 5.0, 18.5 Hz, 1H), 3.85 (br s, 1H), 3.59 (dd, *J*=4.5, 10.0 Hz, 1H), 3.52 (dd, *J*=6.0, 9.5 Hz, 1H), 2.39 (s, 3H), 2.15–2.11 (m, 2H), 1.82 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.16, 137.93, 137.54, 136.47, 129.25 (2×), 128.37 (2×), 127.66, 127.53 (2×), 127.39 (2×), 126.52, 73.29, 72.72, 69.22, 53.31, 42.19, 38.87, 21.51. Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.30; H, 6.68; N, 3.92. For compound **9a**: $[\alpha]_D^{27}$ −148.3 (*c* 0.01, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{21}H_{26}NO_4S$ (M^++1) 388.1583, found 388.1582; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.0 Hz, 2H), 7.35–7.28 (m, 3H), 7.26–7.21 (m, 4H), 5.89 (ddd, *J*=3.0, 6.5, 10.5 Hz, 1H), 5.79 (ddd, *J*=2.5, 6.0, 10.5 Hz, 1H), 4.39 (d, *J*=12.5 Hz, 1H), 4.38–4.32 (m, 1H), 4.34 (d, *J*=12.5 Hz, 1H), 4.27 (dd, *J*=7.0, 18.0 Hz, 1H), 4.23–4.19 (m, 1H), 3.98 (d, *J*=18.0 Hz, 1H), 3.33 (d, *J*=4.5 Hz, 2H), 2.39 (s, 3H), 2.27 (ddd, *J*=1.5, 11.5, 15.0 Hz, 1H), 2.20 (dt, *J*=5.5, 15.0 Hz, 1H), 2.01 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.57, 137.96, 137.34, 132.92, 130.95, 129.51 (2×), 128.33 (2×), 127.61 (3×), 127.42 (2×), 73.16, 72.57, 67.32, 51.67, 42.12, 35.50, 21.51. Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.24; H, 6.31; N, 3.49.

4.1.6. 2-Benzyloxymethyl-1-(4-methylphenylsulfonyl)-1,2,3,4,5,8-hexahydro-azocin-4-ol (10). Grubbs' second generation catalyst (30 mg) was added to a solution of compound **8** (100 mg, 0.23 mmol) in DCM (50 mL) at rt. The reaction mixture was refluxed for 2 h. The mixture was concentrated and purified by flash column chromatography (hexane/AcOEt=2/1) to yield compound **10** (73 mg, 78%). $[\alpha]_D^{27}$ +18.5 (*c* 0.01, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO_4S$ (M^++1) 402.1739, found 402.1741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.5 Hz, 2H), 7.33–7.28 (m, 3H), 7.19 (d, *J*=8.5 Hz, 2H), 7.10 (dd, *J*=2.0, 8.0 Hz, 2H), 5.64–5.59 (m, 1H), 5.51–5.48 (m, 1H), 4.60–4.55 (m, 1H), 4.40 (d, *J*=19.5 Hz, 1H), 4.22 (s, 2H), 4.07–4.02 (m, 1H), 3.82 (dd, *J*=2.5, 19.5 Hz, 1H), 3.28 (dd, *J*=5.0, 10.0 Hz, 1H), 3.24 (dd, *J*=5.5, 10.0 Hz, 1H), 3.11–3.04 (m, 1H), 2.38 (s, 3H), 2.39–2.31 (m, 1H), 2.11 (ddd, *J*=2.5, 12.5, 15.0 Hz, 1H), 1.81 (dt, *J*=3.5, 15.0 Hz, 1H), 1.68 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.70, 136.34, 135.55, 128.01, 127.16 (2×), 126.08 (2×), 125.39, 125.22 (2×), 124.67 (2×), 122.79, 70.70, 69.41, 66.85, 49.56, 42.87, 31.34, 29.88, 19.26. Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.38; H, 6.93; N, 3.55.

4.1.7. 7-Benzyloxymethyl-1-(4-methylphenylsulfonyl)-azepane-3,4,5-triol (11). A solution of osmium tetraoxide (5 mL, 2% in THF) in THF was added to a solution of compound **9** (50 mg, 0.13 mmol) in THF (5 mL) and *t*-BuOH (5 mL) and *N*-methylmorpholine-*N*-oxide (100 mg, 50% in water, 0.43 mmol) at refluxed temperature for 10 h. Sodium bisulfite solution (10%, 5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/AcOEt=1/3) afforded compound **11** (48 mg, 88%). $[\alpha]_D^{26}$ −60.5 (*c* 0.01, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{21}H_{28}NO_6S$ (M^++1) 422.1637, found 422.1639; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=8.0 Hz, 2H), 7.34–7.27 (m, 3H), 7.20 (d, *J*=8.0 Hz, 2H), 7.17 (d, *J*=7.0 Hz, 2H), 4.31 (s, 2H), 4.20–4.16 (m, 2H), 4.08 (br t, *J*=7.0 Hz, 1H), 3.83 (br s, 1H), 3.53 (dd, *J*=3.5, 15.0 Hz, 1H), 3.45 (dd, *J*=9.0, 15.0 Hz, 1H), 3.41 (dd, *J*=5.0, 10.0 Hz, 1H), 3.35 (dd, *J*=4.0, 10.0 Hz, 1H), 2.39 (s, 3H), 2.32 (dd, *J*=9.0, 15.0 Hz, 1H), 2.13 (br s, 3H), 1.97–1.91 (m, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 143.54, 137.57, 137.11, 129.59 (2×), 128.38 (2×), 127.77, 127.61 (2×), 127.29 (2×), 74.59, 73.21, 71.30, 69.74, 68.61, 52.29, 45.36, 31.67, 21.54. Single-crystal X-ray diagram: crystal of compound **11** was grown by slow diffusion of AcOEt into a solution of compound **11** in DCM to yield colorless prism. The compound crystallizes in the monoclinic crystal system. Space group $P2(1)$, a=5.4539(15) Å, b=9.571(3) Å, c=19.784(5) Å, V=1027.5(5) Å^3, Z=4, d_{calcd}=2.725 mg/m^3, $F(000)$=896, absorption coefficient 0.391 mm^{-1}, 2θ range (1.03°–28.36°).

4.1.8. 8-Benzyloxymethyl-1-(4-methylphenylsulfonyl)-azocane-3,4,6-triol (12). A solution of osmium tetraoxide (5 mL, 2% in THF) in THF was added to a solution of compound **10** (50 mg, 0.12 mmol) in THF (5 mL) and *t*-BuOH (5 mL) and *N*-methylmorpholine-*N*-oxide (100 mg, 50% in water, 0.43 mmol) at refluxed temperature for 10 h. Sodium bisulfite solution (10%, 5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/AcOEt=1/3) afforded compound **12** (46 mg, 85%). $[\alpha]_D^{26}$ −15.2 (*c* 0.01, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{30}NO_6S$ (M^++1) 436.1794, found 436.1798; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J=7.0 Hz, 2H), 7.30–7.21 (m, 5H), 7.06 (d, J=7.0 Hz, 2H), 4.36 (dd, J=3.0, 12.0 Hz, 1H), 4.27–4.18 (m, 2H), 4.18 (d, J=12.0 Hz, 1H), 4.10 (d, J=12.0 Hz, 1H), 3.87–3.76 (m, 2H), 3.50–3.46 (m, 1H), 3.13 (dd, J=3.5, 10.0 Hz, 1H), 3.07 (dd, J=3.5, 10.0 Hz, 1H), 2.54–2.47 (m, 1H), 2.42 (s, 3H), 2.05–1.94 (m, 2H), 1.88–1.86 (m, 1H), 1.83 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.07, 137.40, 136.52, 129.79 (2×), 128.40 (2×), 127.81, 127.52 (2×), 127.47 (2×), 73.20, 71.52, 70.69, 69.82, 66.76, 51.40, 38.28, 33.23, 30.92, 21.57. Anal. Calcd for $C_{22}H_{29}NO_6S$: C, 60.67; H, 6.71; N, 3.22. Found: C, 60.31; H, 6.89; N, 3.38.

4.1.9. 7-Hydroxymethyl-1-(4-methylphenylsulfonyl)-azepane-3,4,5-triol (1). Palladium on activated carbon (10%, 10 mg) was added to a solution of compound **11** (30 mg, 0.07 mmol) in MeOH (20 mL). Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 20 h. The reaction mixture was filtered and evaporated to yield crude product. Purification on silica gel (AcOEt/MeOH=9/1) afforded compound **1** (22 mg, 93%). $[\alpha]_D^{27}$ −20.6 (*c* 0.007, D_2O); HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NO_6S$ (M^++1) 332.1168, found 332.1174; ^{1}H NMR (300 MHz, D_2O) δ 7.80 (d, J=8.1 Hz, 2H), 7.45 (d, J=8.1 Hz, 2H), 4.10–4.01 (m, 2H), 3.78–3.68 (m, 3H), 3.62–3.43 (m, 3H), 2.44 (s, 3H), 2.22 (dd, J=11.4, 15.6 Hz, 1H), 1.95 (ddd, J=5.4, 7.5, 15.6 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 147.77, 138.84, 132.58 (2×), 129.85 (2×), 74.94, 71.28, 70.82, 67.05, 56.38, 46.92, 30.88, 23.38.

4.1.10. 8-Hydroxymethyl-1-(4-methylphenylsulfonyl)-azocane-3,4,6-triol (2). Palladium on activated carbon (10%, 10 mg) was added to a solution of compound **12** (30 mg, 0.07 mmol) in MeOH (20 mL). Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 20 h. The reaction mixture was filtered and evaporated to yield crude product. Purification on silica gel (AcOEt/MeOH=9/1) afforded compound **2** (22 mg, 91%). HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NO_6S$ (M^++1) 346.1324, found 346.1325; ^{1}H NMR (300 MHz, D_2O) δ 7.84 (d, J=8.1 Hz, 2H), 7.44 (d, J=8.1 Hz, 2H), 4.19–4.04 (m, 2H), 3.93 (dd, J=3.3, 16.2 Hz, 1H), 3.82 (br s, 1H), 3.72 (d, J=7.8 Hz, 1H), 3.52 (d, J=15.3 Hz, 1H), 3.44 (t, J=5.4 Hz, 2H), 2.43 (s, 3H), 2.15 (ddd, J=8.4, 11.4, 14.1 Hz, 1H), 1.92–1.88 (m, 2H), 1.54 (dd, J=6.9, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 147.79, 138.65, 132.44 (2×), 130.39 (2×), 73.67, 71.90, 68.90, 66.04, 56.33, 48.52, 37.94, 35.51, 23.41.

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Supplementary data

Photocopies of NMR (^{1}H and ^{13}C) spectral data for new compounds were supported. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.002.

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10. CCDC 623695 (compound **11**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).