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Stereoselective transformations of polyhydroxyazepanes to piperidine and pyrrolidine derivatives—Efficient glycosidase inhibitors†

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N-Benzyl-4, 5-*O*-diprotected-3, 6-dihydroxyazepanes **1a** and **1b** prepared by the reaction of 1, 2 : 5, 6-dianhydro-3, 4-*O*-isopropylidene-L-iditol and benzylamine undergo a skeletal rearrangement to furnish the piperidine derivatives **3a** and **3b** under Mitsunobu condition. On the contrar*N*-benzyl-3, 6-diprotected-4, 5-dihydroxyazepane **5c** under identical conditions (Mitsunobu conditions) furnishes a pyrrolidine derivative **7**. Interestingly, azepane **1b** undergoes an intramolecular nucleophilic substitution in the absence of an external nucleophile (benzoic acid) under Mitsunobu condition to give the bicyclic compound **4a**.

Polyhydroxylated piperidines and pyrrolidines constitute a major class of glycosidase and glycosyl transferase inhibitors[1]. In recent years there has been increasing interest in the synthesis of these azasugars due to their chemotherapeutic utility in the treatment of diabetes[2], cancer[3], obesity[4] and AIDS[5,6]. Recently, the synthesis of six- and seven-membered azasugars in nearly 1:1 ratio has been reported by the reaction of dianhydrosugars with amines[7]. Some of the seven-membered polyhydroxylated heterocyclic compounds have been reported to undergo rearrangement to yield six-membered polyhydroxy heterocyclic compounds either *via* mesylation[8] of one of the hydroxy groups or by Mitsunobu reaction[9].

We have reported recently[10] the reaction of 1, 2 : 5, 6-dianhydro-3, 4-*O*-isopropylidenehexitols with benzylamine to furnish substituted azepane derivatives as the only isolable products in good yields (64-88%). Direct attempts to convert the appropriate dianhydrosugars selectively to polyhydroxylated piperidine or pyrrolidine derivatives were not encouraging. Therefore, we attempted a selective conversion of polyhydroxyazepanes prepared earlier[10] to either a six-membered piperidine or a five-membered pyrrolidine derivative. Here we report the transformation of polyhydroxyazepanes to deoxynojirimycin and pyrrolidine derivatives under Mitsunobu condition.

Results

1, 2:5, 6-Dianhydro-3, 4-*O*-isopropylidene-L-iditol was treated with benzylamine in refluxing THF to afford (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-3, 4, 5, 6-tetrahydroxy-4, 5-*O*-isopropylideneazepane **1a** in 64% yield[10]. Treatment of **1a** under Mitsunobu condition (1.5 equiv. PPh_3-DEAD-PhCOOH in THF at *ca* 25°C for 48 hr) provided a mixture of three products in 1:1:1 ratio, the structure of which has been established as dibenzoyl piperidine derivative **3a**, 3, 6-dibenzoylazepane derivative **5a** and monobenzoyl azepane **2a** based on spectral data. The structures of **2a, 3a** and **5a** were further confirmed by exhaustive benzoylation of **1a** and **2a** to **5a** using benzoyl chloride in pyridine in 85% yield at *ca* 0°C. In contrast, when azepane **1b** was treated with Ph_3P-DEAD-PhCOOH (Mitsunobu condition) only the piperidine derivative **3b** (25%) was obtained along with the unreacted azepane **1b** (Scheme I). Products were characterized by spectral data and by comparison with authentic material prepared through an independent route.

When the reaction of **1b** was performed with PPh_3-DEAD in the absence of benzoic acid, a 65% yield of the bicyclic compound **4a** was isolated as the only product. The structure of **4a** was established by spectral data and further transformation of **4a** to the corresponding known diol **4b** (40%) after removal of THP protecting group[11]. Further, the azepane **5a** was treated with 80% aqueous CF_3COOH to furnish *N*-benzyl-3, 6-dibenzoyl-4, 5-dihydroxyazepane **5c** in 97% yield. Treatment of azepane **5c** under Mitsunobu condi-

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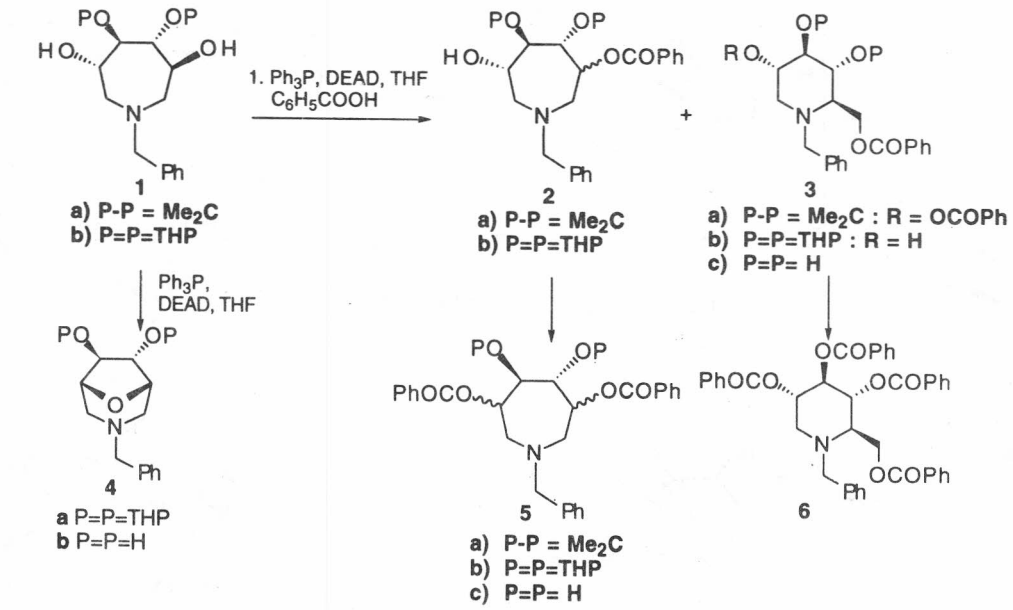
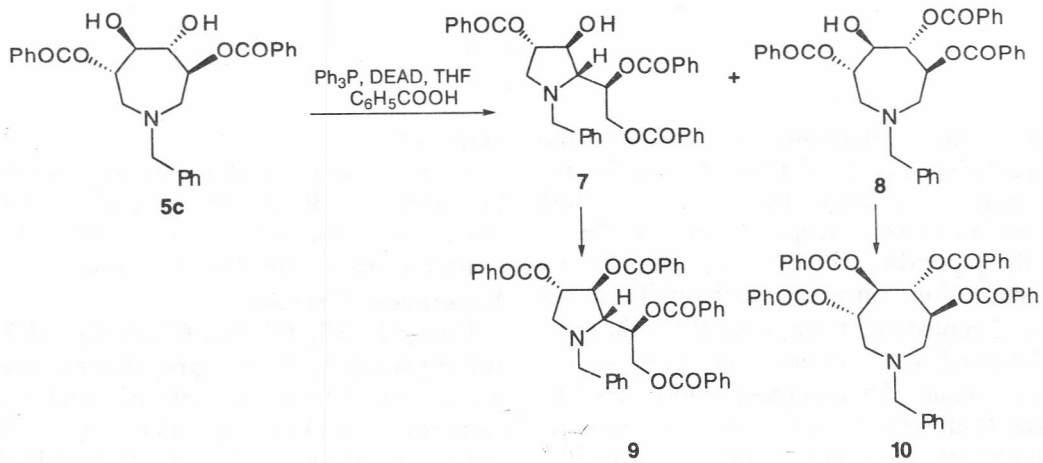


Scheme I



Scheme II

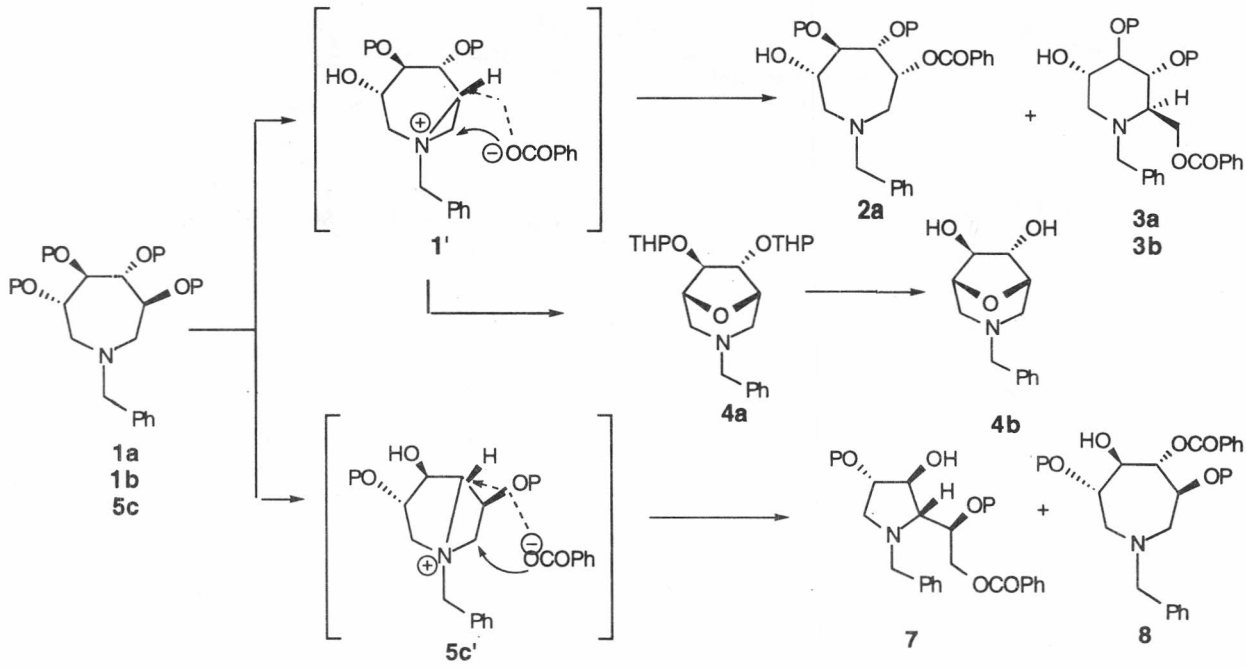
tion (1.5 eq, PPh_3-DEAD-PhCOOH in THF at room temperature for 48 hr) furnished a mixture of two products, characterized as the pyrrolidine derivative **7** and *N*-benzyl-3, 4, 6-tribenzoyl-5-hydroxyazepane **8** in 3:4 ratio based on analytical data (Scheme II).

The structures of **7** and **8** were further confirmed by converting them to the corresponding tetrabenzoyl derivatives **9** and **10** respectively and by comparison with authentic samples prepared by independent routes.

Discussion

Since the *trans*-acetonide, as the protecting group, played a crucial role in the selective transformation of 1, 2 : 5, 6-dianhydro-3, 4-O-isopropylidenehexitol[10] to azepane **1a**, further transformation of **1a** to piperidine **3a** under Mitsunobu condition was attempted. The possible transformations of azepane derivatives **1a, 1b** and **5c** are shown in Scheme III.

Under Mitsunobu condition, an intermediate aziridinium ion **1′** is formed. The nucleophilic $PhCOO^-$ ion attacked either at C-2 position leading to the formation of a piperidine derivative **3a** or at C-3 centre affording 3-benzoyl substituted azepane **2a** and 3, 6-dibenzoyl substituted azepane **5a**. The latter may arise by a double Mitsunobu reaction of **1a** or a further Mitsunobu reaction of **2a**. Although Mitsunobu reaction in this case is expected to proceed *via* a double inversion pathway leading ultimately to retention of the configuration at the reacting carbon centre (C-3), the azepanes **2a** and **5a** were found to undergo partial racemization. This may be due to the



Scheme III

formation of the aziridinium ion **1′** which may adopt a partial planar conformation and the nucleophile may react from either face to furnish partially the racemized azepanes **2a** and **5a**. In contrast, the piperidine derivative **3a** may not undergo racemization, since the nucleophilic attack occurs at C-2 centre which is not chiral. On the other hand, *N*-benzyl-4, 5-*O*-bistetrahydropyranyl-3, 6-dihydroxyazepane **1b** undergoes smooth skeletal rearrangement under Mitsunobu condition to furnish the piperidine derivative **3b** *via* a similar aziridinium intermediate **1′** as shown in Scheme III. Interestingly, when azepane **1b** is treated under identical conditions in the absence of benzoic acid, the intermediate aziridinium ion **1′** may undergo an intramolecular rearrangement in the absence of external nucleophile (benzoic acid), and the OH group present at C-3 centre in the molecule may act as an internal nucleophile to give **4a** as the sole product (Scheme III). Such an intramolecular rearrangement is not observed when 3, 4-hydroxy groups are protected as *trans*-acetonide as in the case of azepane **1a**.

In contrast, when hydroxy groups at C-4 and C-5 positions of azepane **5c** are unprotected and C-3 and C-6 positions are protected as dibenzoyl derivative, **5c** undergoes a rearrangement *via* an azetidinium intermediate **5c′** (Scheme III). The benzoic acid acts as a nucleophile and may react either at C-2 centre to furnish the pyrrolidine derivative **7** or at C-4 centre to give the azepane **8**, respectively.

Thus, we have been able to prepare deoxynojirimycin derivative **3b** and the pyrrolidine derivative **7** from a common starting material azepane, which is readily available from dianhydrosugar.

Experimental Section

General. (3*S*, 4*R*, 5*R*, 6*S*)-*N*-Benzyl-2, 4, 5, 6-tetrahydroxy-4, 5-*O*-isopropylidene azepane 1a was prepared from the corresponding 1, 2:5, 6-dianhydro-3, 4-*O*-isopropylidene-L-iditol by a reported procedure[10]. All the chemicals were distilled or recrystallised before use and anhydrous solvents were freshly prepared by standard procedure. TLC was performed on silica gel plates (60F254, Merck). Flash chromatography was performed on silica gel (SRL, 230-400 or 400-200 mesh). Melting points were recorded on a Veego melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and signals are reported in parts per million, ppm. IR spectra were recorded on a Perkin-Elmer FT IR-1600 spectrometer. Mass spectra were obtained on a HP 5989A mass spectrometer. Stereochemical assignments are based on the stereochemistry of the starting sugar derivative.

Mitsunobu reaction of (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-4, 5-*O*-isopropylidene-3, 6-dihydroxyazepane 1a. A mixture of azepane **1a** (586 mg, 2.0 mmoles), PPh_3 (786 mg, 3.0 mmoles), $PhCO_2H$

(366 mg, 3.0 mmoles), DEAD (472 μL, 5.22 mg, 3.0 mmoles) and THF (10 mL) was stirred at room temperature for 8 hr. The solvent was evaporated under reduced pressure and the residue flash chromatographed over silica gel using a mixture of pet. ether-ethyl acetate (3:1) to afford the dibenzoylazepane **5a** (250 mg, 25%); $[\alpha]_D^{25}$ + 8.0° (*c* 0.37, $CHCl_3$); IR (KBr) : 1709 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.44 (s, 6H), 2.88 (dd, *J*=6 and 12 Hz, 2H), 3.20 (dd, *J*=6 and 12 Hz, 2H), 3.70 (q, *J*=14 Hz, 2 H), 4.30-4.42 (m, 2H), 5.18-5.32 (m, 2H), 6.80-7.66 (m, 11H), 8.00 (d, *J*=6 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ26.9, 59.3, 63.5, 74.5, 77.8, 110.3, 127.1, 128.1, 128.6, 129.8, 132.9, 138.1, 165.7; MS (relative intensity): m/z 502 (M^+ + 1, 3%), 105 (90%), 91 (100%).

Further elution of the column with pet. ether-ethyl acetate (2:1) afforded the dibenzoylpyrrolidene derivative **3a** (200 mg, 20%); IR (KBr): 1718 cm^{-1}; ^1H NMR ($CDCl_3$) : 1.36 (s, 3H), 1.50 (s, 3H), 2.90 (dd, *J*=4 and 12 Hz, 2H), 3.06-3.30 (m, 2H), 3.76 (q, *J*=10 Hz, 2H), 4.22(d, *J*=6 Hz, 1H), 5.06 (t, *J*=6 Hz, 1H), 5.22 (brs, 1H), 5.62 (brs, 1H), 7.00-7.12 (m, 3H), 7.26-7.34 (m, 2H), 7.42-7.70 (m, 6H), 8.06 (d, *J*=6 Hz, 2H), 8.16 (d, *J*=6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 26.7, 27.1, 59.4, 59.8, 63.7, 69.6, 75.9, 76.3, 76.9, 110.1, 126.9, 128.1, 128.4, 129.6, 129.7, 132.9, 138.7, 165.6, 165.9; MS (relative intensity) : m/z 502 (M^+ + 1, 1%), 105(90%), 91 (100%).

Further elution of the column with pet. ether-ethyl acetate (1:1) afforded the monobenzoylazepane **2a** (250 mg, 30%); IR (Neat): 3454, 1718 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (s, 6H), 2.48-3.22 (m, 5H), 3.68 (q, *J*=10 Hz, 2H), 3.88 (d, *J*=6 Hz, 2H), 4.38 (t, *J*=6 Hz, 1H), 5.08-5.18 (m, 1H), 7.00-7.60 (m, 8H), 7.98 (d, *J*=6 Hz, 2H); MS (relative intensity) : m/z 398 (M^+ + 1, 1%) 105 (50%), 91 (100%).

Benzoylation of (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-4, 5-*O*-isopropylidene-3, 6-dihydroxyazepane 1a. To a solution of azepane **1a** (2.93 g, 10 mmoles) in dry pyridine (30 mL) was added benzoyl chloride (3.5 mL, 4.2 g, 30 mmoles) at *ca* 0°C under an argon atmosphere. The reaction mixture was stirred at room temperature for 12 hr followed by quenching with ice (50 g). The mixture was poured into 6*N* HCl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with brine (2 × 30 mL) dried, filtered and the filtrate evaporated under reduced pressure to give a residue which was flash chromatographed over silica gel using pet. ether-ethyl acetate (2:1) as eluent to afford **5a** (4.25 g, 85%) as a white solid, m.p. 160-62°; $[\alpha]_D^{25}$ + 43.3° (*c* 0.75, $CHCl_3$).

Benzoylation of (3*S, 4*R*, 5*R*, 6*S*)-*N*-benzyl-4, 5-*O*-isopropylidene-3-benzoyl- 6-hydroxyazepane 2a.** Following the above methodology, **2a** (216 mg, 0.5 mmole) was converted into **5a** (218 mg, 87%) as a white solid, m.p. 160-62°.

Preparation of (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-3, 6-*O*-dibenzoyl-4, 5-dihydroxyazepane 5c. An aqueous solution of CF_3CO_2H (80%, 25 mL) was added dropwise to a flask containing azepane **5a** (4.25 g, 8.5 mmoles) at *ca* 0°C and the reaction mixture stirred for 5 hr at room temperature. Trifluoroacetic acid was removed under reduced pressure and the syrupy material purified by silica gel column chromatography using pet. ether-ethyl acetate (1:1) as eluent to afford diol **5c** (3.8 g, 97%) as a white solid, m.p. 73-74°; $[\alpha]_D^{25}$ + 13.18° (c, 0.22, MeOH); IR (KBr) : 3411, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.30-3.54 (m, 4H), 3.98-4.32 (m, 4H), 5.14-5.40 (bs, 2H), 5.42-5.60 (bs, 2H), 7.20-7.64 (m, 11H), 8.00 (d, *J*=6 Hz, 4H); ^{13}C NMR ($CDCl_3$) : δ 52.7, 62.1, 71.5, 73.4, 128.4, 128.9, 129.1, 129.7, 129.9, 130.8, 133.5, 165.9; MS (relative intensity) : m/z 340 (M^+ + 1 − 122, 5%), 105 (56%), 91 (100%).

Preparation of (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-4, 5-*O*-bistetrahydropyranyl-3, 6-dihydroxyazepane 1b. To a solution of the azepane **5c** (3.8 g, 8.2 mmoles) in dry CH_2Cl_2 (20 mL) was added dihydropyran (2.2 mL, 2.02 g, 24 mmoles) and PPTS (1.0 g, 4 mmoles) and the mixture stirred for 6 hr at room temperature under an argon atmosphere. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using pet. ether-ethyl acetate (2:1) as eluent to afford (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-3, 6-*O*-dibenzoyl-4, 5-*O*-bistetrahydropyranylazepane **5b** (3.2 g, 62%) as a viscous oil; IR (Neat): 1721 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.20-1.80 (m, 12H), 2.80-3.20 (m, 4H), 3.22-3.52 (m, 2H), 3.62-3.98 (m, 4H), 4.10-4.42(m, 2H), 4.72-5.00 (m, 2H), 5.30-5.70 (m, 2H), 7.00-7.70 (m, 11H), 7.80-8.22 (m, 4H); MS (relative intensity): m/z 544 (M^+ − 85, 4%), 105 (80%), 91 (100%).

The azepane **5b** (3.14 g, 5 mmoles), obtained in the previous step, was dissolved in dry MeOH (20 mL) and anhydrous K_2CO_3 (3.45 g, 25 mmoles) was added to it. The mixture was stirred for 10 hr at room temperature under an argon atmosphere, filtered and the filtrate concentrated under

reduced pressure. The residue was purified by silica gel column chromatography using pet. ether-ethyl acetate (1:3) as eluent to afford azepane **1b** (1.1 g, 52%) as a viscous oil; IR (Neat): 3421, 1026 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42-1.92 (m, 12 H), 2.46-3.24 (m, 6 H), 3.32-3.84 (m, 10H), 3.9-4.16 (m, 1H), 4.50-4.80 (m, 1H), 7.20-7.42 (m, 5H); MS (relative intensity) : m/z 422 (M^+ + 1, 1%), 320 (43%), 91 (100%).

Mitsunobu reaction of (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-4, 5-*O*-bistetrahydropyranyl-3, 6-dihydroxyazepane 1b. The Mitsunobu reaction was carried out by the method as described for **1a** using the azepane **1b** (1g, 2.37 mmoles), PPh_3 (0.94 g, 3.55 mmoles), $PhCO_2H$ (0.44 g, 3.55 mmoles) and DEAD (0.6 mL, 0.62 g, 355 mmoles) in THF (10 mL) which afforded the piperidine derivative **3b** (290 mg, 25%) besides the unreacted **1b** (270 mg, 22%) after chromatographic separation. The piperidine derivative **3b** showed IR (KBr) : 3298, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.40-1.80 (m, 12 H), 2.70-3.10 (m, 3 H), 3.30-3.64 (m, 2 H), 3.70-3.96 (m, 2H), 4.00-4.24 (m, 6H), 4.42-4.56 (m, 2H), 4.60-4.40 (m, 1H), 4.88-5.00 (m, 1H), 7.26-7.62 (m, 8H), 8.00-8.18 (m, 2H); MS: (relative intensity) : m/z 526 (M^+ + 1, 1%), 390 (20%), 91 (100%).

Preparation of (2*R*, 3*R*, 4*R*, 5*S*)-*N*-benzyl-2-(benzoyloxymethyl)-3, 4, 5-tri-*O*-benzoylpiperidine 6. To a solution of the piperidine **3b** (220 mg, 0.4 mmole) in MeOH-H_2O (9:1, 2 mL) was added *p*-TsOH (63 mg, 0.25 mmole) and the mixture stirred for 10 hr at room temperature. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate-MeOH (1:1) as eluent to afford (2*R*, 3*R*, 4*R*, 5*S*)-*N*-benzyl-2-(benzoyloxymethyl)-3, 4, 5-trihydroxypiperidine **3c** (88 mg, 62%) as a syrup oil; IR (Neat) : 3404, 1717 cm^{-1}; ^1H NMR (CD_3OD) : δ 2.90-3.20 (m, 3H), 3.42-3.82 (m, 5H), 4.00-4.30 (m, 3H), 4.46 (d, *J*=6 Hz, 2H), 7.16-7.76(m, 8H), 8.06 (d, *J*=6 Hz, 2H); MS (relative intensity) : m/z 358 (M^+ + 1, 1%), 222, (10%), 91 (100%).

The piperidine derivative **3c**, obtained from the previous experiment (96 mg, 0.25 mmole), was benzoylated by the method described earlier, using benzoyl chloride (187 μl, 227 mg, 1.5 mmoles) in dry pyridine (2 mL) to afford **6** (80 mg, 50%) as a viscous oil; IR ($CHCl_3$) : 1688 cm^{-1}; ^1H NMR ($CDCl_3$) : δ2.84-3.30 (m, 3H), 3.42-3.70 (m, 2H), 4.68-4.82 (m, 2H), 5.44 (d, *J*=4 Hz, 1H), 5.68 (d, *J*=4Hz, 1H), 5.90 (d, *J*=4 Hz, 1H), 7.12-7.64 (m, 17H), 7.88-8.20 (m, 8H); MS (relative intensity) : m/z 670 (M^+, 0.5%), 105 (100%).

Mitsunobu reaction of (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-4, 5-*O*-bistetrahydropyranyl-5, 6-dihydroxyazepane 1b in the absence of benzoic acid. The Mitsunobu reaction was carried out by the method as described for **1a** using the azepane **1b** (295 mg, 0.7 mmole). DEAD (132 μL, 147 mg, 0.84 mmole) and PPh_3 (220 mg, 0.84 mmole) in dry THF (3 mL) to afford the bicyclic compound **4a** (182 mg, 65%) as viscous oil. Tetrahydropyranyl group was removed by the method described above using *p*-TsOH (20 mg, 0.1 mmole) and H_2O-MeOH (1:9, 5 mL) to give 8-oxa-3*N*-benzylbicyclo[3.2.1]octane-6, 7-diol **4b**[12] (48 mg, 40%) as a pale yellow solid (hygroscopic); IR (KBr) : 3378 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD) : δ3.08-3.42 (m, 4H), 3.56-3.90 (m, 2H), 4.10 (brs, 1H), 4.24 (brs, 1H), 4.30 (d, *J*=8 Hz, 1H), 4.42 (d, *J*=6 Hz, 1H), 4.54 (brs, 2H), 7.50 (brs, 5H); MS (relative intensity): m/z 235 (M^+, 6%), 91 (100%).

Mitsunobu reaction of (3*S*, 4*R*, 5*R*, 6*S*)-*N*-benzyl-3, 6-*O*-dibenzoyl-4, 5-dihydroxyazepane 5c. A mixture of azepane **5c** (235 mg, 0.5 mmole), PPh_3 (200 mg, 0.75 mmole), $PhCO_2H$ (90 mg, 0.75 mmole), DEAD (115 μL, 130 mg, 0.75 mmole) and THF (5 mL) was stirred at room temperature for 48 hr. The solvent was evaporated under reduced pressure and the residue flash chromatographed over silica gel using pet. ether-ethyl acetate (3:2) as cluent to afford (3*S*, 4*R**, 5*R*, 6*S*)-*N*-benzyl-3, 4, 6-*O*-tribenzoyl-5-hydroxyazepane **8** (110 mg, 40%) as a white solid, m.p. 119-20°; IR (Neat): 3415, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 2.90 (dd, *J*=6 and 12 Hz, 2H), 3.12 (dd, *J*=6 and 12 Hz, 2H), 3.30-3.50 (brs, 1H), 3.70 (q, *J*=12 Hz, 2H), 4.00-4.18 (m, 2H), 5.14-5.30 (m, 2H), 7.08-7.68 (m, 14H), 8.00 (d, *J*=6 Hz, 6H); ^{13}C NMR ($CDCl_3$) : δ 57.8, 63.2, 72.7, 75.9, 127.1, 127.5, 127.9 128.2, 128.7, 129.7, 133.1, 138.1, 166.2; MS (relative intensity): m/z 444 (M^+ −121, 5%), 105 (70%), 91 (100%).

Further elution of the column with pet. ether-ethyl acetate (1:3) as eluent afforded the pyrrolidine derivative **7** (60 mg, 30%) as a syrupy oil; IR (KBr): 3312, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) : δ2.80 (dd, *J*=6 and 10 Hz, 2H), 3.14 (q, *J*=12 Hz, 2H), 3.98-4.14 (m, 3H), 4.40 (d, *J*=10 Hz, 1H), 4.62 (d *J*=4 Hz, 1H), 5.12 (d, *J*=4 Hz, 1H), 5.10 (d, *J*=4 Hz, 1H), 7.22-7.72 (m, 16H), 7.92(d, *J*=6 Hz, 2H), 8.02 (d, *J*=6 Hz, 2H); ^{13}C NMR ($CDCl_3$) : δ56.61, 58.3

62.7, 70.9, 72.6, 77.6, 79.7, 127.1, 128.3, 128.8, 129.4, 129.6, 132.9, 133.2, 137.5, 166.1, 167.1; MS (relative intensity): m/z 444 ($M^+ - 122$, 4%), 91(70%), 105 (100%).

Benzoylation of azepane derivative 8. The azepane **8** was benzoylated by the method described earlier using **8** (113 mg, 0.2 mmole), dry pyridine (2 mL) and benzoyl chloride (47 μL, 0.4 mmole) to afford the tetrabenzoylazepane **10** (92 mg, 70%) as a white solid, m.p. 130-32°; $[\alpha]_D^{25}$ +25.0° (*c* 0.1, $CHCl_3$) [for authentic tetra-*O*-benzoyl compound $[\alpha]_D^{25}$ + 9.8° (*c* 0.1, $CHCl_3$)]; IR (KBr) : 1717 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.12 (dd, *J*=6 and 12 Hz, 2H), 3.36 (dd, *J*=4 and 10 Hz, 2H), 3.88-3.92 (q, J=12 Hz, 2H), 5.62-5.80 (m, 2H), 6.00-6.12 (m, 2H), 7.06-7.66 (m, 17 H), 7.82 (d, *J*=6 Hz, 4 H), 7.94 (d, *J*=6 Hz, 4 H); ^{13}C NMR ($CDCl_3$) : δ 56.7, 63.1, 72.2, 73.1, 127.3, 128.0, 129.2, 128.8, 129.5, 129.7, 130.1, 132.9, 133.1, 133.6, 137.7, 165.4.

Benzoylation of pyrrolidine derivative 7. Benzoylation of **7** (56.5 mg, 0.1 mmole) by the above method using dry pyridine (1 mL) and benzoyl chloride (35 μL, 0.3 mmole) afforded the tetra-*O*-benzoylpyrrolidine **9** (52 mg, 74%) as a white solid, m.p. 116-18°; $[\alpha]_D^{25}$ + 17.9° (*c* 0.15, $CHCl_3$); IR (KBr): 1721 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (dd, *J*=4 and 10 Hz, 2H), 3.40-3.76 (m, 2H), 4.40 (d, *J*=6 Hz, 1H), 4.70-4.92 (m, 2H), 5.42(d, *J*=4 Hz, 1H), 5.90 (d, *J*=4 Hz, 1H), 6.10 (d, *J*=4 Hz, 1H), 7.18-7.66 (m, 17H), 7.90-8.20 (m, 8H); ^{13}C NMR ($CDCl_3$) : δ57.7, 58.3, 63.6, 68.9, 69.5, 77.0, 78.7, 127.3, 128.3, 128.4, 128.9, 129.2, 129.6, 129.7, 130.0, 133.0, 133.4, 137.1, 165.2, 165.7, 166.1; MS (relative intensity) : m/z 670 (M^+ + 1, 5%), 105 (100%).

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