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A facile and stereoselective synthesis of the C-2 epimer of (+)-deacetylanisomycin

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ABSTRACT

A short, simple and efficient synthesis of the C-2 epimer of (+)-deacetylanisomycin starting from D-mannitol, utilizing an epoxide opening with a Grignard reagent and acid catalysed unusual intramolecular 5-*endo*-tet cyclization as key steps has been reported.

1. Introduction

Pyrrolidines are found in a number of biologically active natural and unnatural compounds.[1] Amongst them, polyhydroxylated pyrrolidines such as (−)-anisomycin **1** (Fig. 1) and its derivatives have drawn considerable interest over last three decades. Anisomycin **1** is an antibiotic and was first isolated from the fermentation broths of *Streptomyces griseolous* and *Streptomyces roseochromogens* by Sobin and Tanner in 1954.[2] Later it was also isolated from *Streptomyces* sp. SA3079 and No. 638.[3] The structure and relative stereochemistry of **1** were determined by chemical studies[4] and X-ray crystallographic analysis[5] and later the absolute stereochemistry of **1** was established as being (2*R*,3*S*,4*S*).[6]

Anisomycin **1** was found to exhibit selective and potent activities against pathogenic protozoa and certain strains of fungi[7] and it is currently being used in clinical trials for the treatment of amoebic dysentery and vaginitis. More recently it was reported that anisomycin **1** had been identified as an antitumor substance showing in vitro cytotoxicity against human tumour lines, such as mammalian cell lines HBL 100, RAS A and MCF 7 in the nanomolar region.[3,8] Both anisomycin **1** and its deacetylderivative **1a** have been used as fungicides in the eradication of bean mildew and for the inhibition of other pathogenic fungi in plants.[9] Recently some derivatives of **1** have also shown potent inhibitory activity against α-rhamnosidase and some other glycosidases.[10] Some chiral polyhydroxylated pyrrolidines have also been used as catalysts/ligands in asymmetric synthesis.[11]

2. Results and discussion

Due to promising biological activity and structural features of **1**, several strategies for the synthesis of (−)-anisomycin **1**[12,13f] and its analogues have been developed. Although several syntheses have been reported for **1** and its analogues, many of them have drawbacks, such as long reaction sequences and poor stereoselectivity. Therefore, any approach which gives enantiomerically pure compound is important for making analogues to evaluate their biological activity. In continuation of our efforts in the synthesis of polyhydroxylated pyrrolidine alkaloids and azasugars,[13] we herein report the stereoselective synthesis of a C-2 epimer of (+)-deacetylanisomycin **2a** whose absolute stereochemistry is (2*R*,3*R*,4*R*) from the inexpensive and readily available chiral pool starting material, D-mannitol. So far, one stereoselective synthesis has been reported for **2a**.[12d] However, the present method constitutes a novel approach for the synthesis of this compound (Schemes 1 and 2).

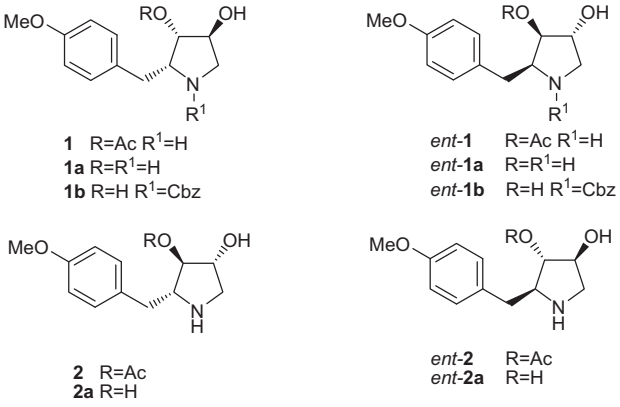

Figure 1. The structure of (−)-anisomycin **1** and its derivatives.

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-mannitol obtained from D-mannitol was treated with H_5IO_6 to give the corresponding aldehyde and immediate reduction of the resultant crude aldehyde with $NaBH_4$ gave arabinitol derivative **3**.[14] Treatment of **3** with MsCl/Et_3N gave **4**, which upon further treatment with NaN_3 in DMF

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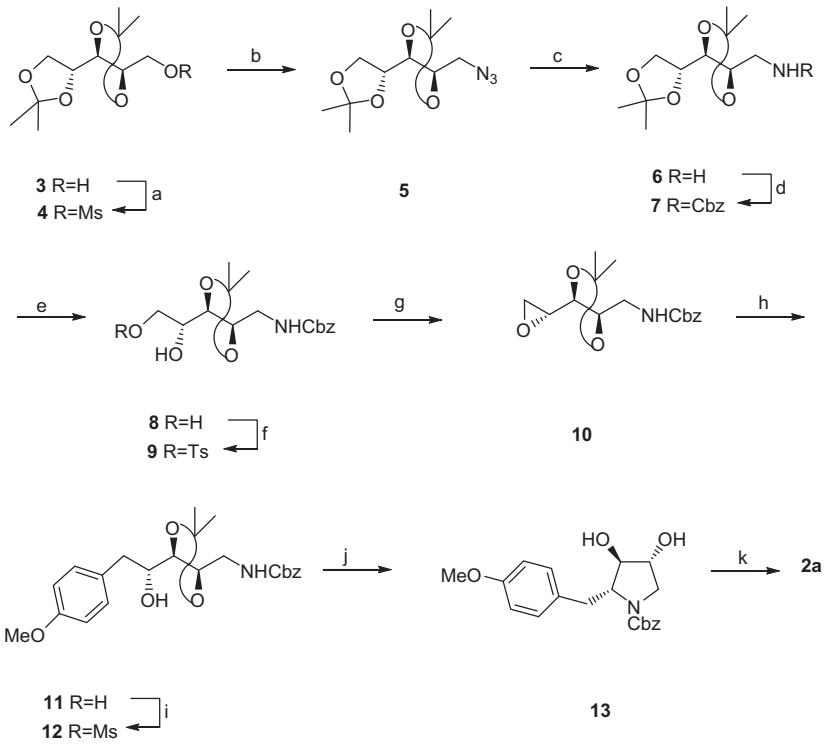
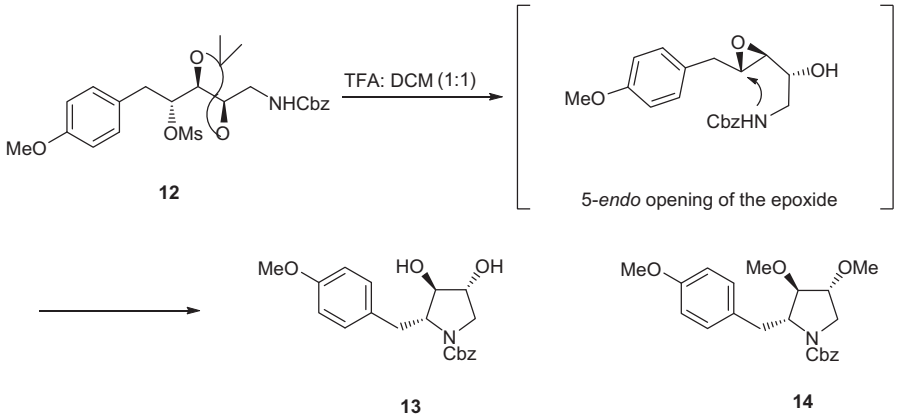


Scheme 1. Reagents and conditions: (a) MsCl, Et_3N, DCM, 0 °C to rt, 1 h; (b) NaN_3, DMF, 90 °C, 12 h, 83% for two steps; (c) Pd/C, MeOH, rt, 3 h; (d) CbzCl, Na_2CO_3, THF, 2 h, 81% for two steps; (e) 50% aq AcOH, rt, overnight, 84%; (f) *p*-TsCl, Et_3N, 10 mol % Bu_2SnO, DCM, 0 °C to rt, 1 h; 93%; (g) K_2CO_3, MeOH, 30 min, 90%; (h) 4-bromoanisole, Mg, I_2/CuCN (cat.), −78 °C, 2 h, 79%; (i) MsCl, Et_3N, DCM, rt, 1 h; (j) TFA, DCM, 0 °C to rt, 2 h, 79%; (k) Pd/C, MeOH, rt, overnight, 90%.



Scheme 2.

yielded azido derivative **5**. Reduction of the azido functionality with Pd/C in MeOH gave amine **6**, which upon in situ treatment with CbzCl/Na_2CO_3 afforded compound **7**. Selective hydrolysis of **7** with 50% aq AcOH gave diol **8**. The regioselective tosylation of **8** provided **9**, which upon further treatment with K_2CO_3/MeOH yielded epoxide **10**. The reaction of **10** with *p*-methoxyphenylmagnesium bromide in the presence of a catalytic amount of I_2/CuCN gave **11**. Compound **11** was converted into mesyl derivative **12**. It should be noted that the treatment of **12** with TFA gave the cyclised product **13** directly with double inversion of configuration, whose NMR did not match with (+)-*N*-benzyloxycarbonyl deacetylanisomycin *ent*-**1b** based on a comparison with the reported values.[13f] To further confirm the stereochemistry at the newly formed stereogenic centre the cyclised product **13** was converted into dimethoxy compound **14**, whose ^{1}H NMR spectra were in agreement with the reported values.[15] Compound **13** was subjected to hydrogenation in the presence of Pd/C, which resulted in the formation of **2a**. The specific rotation of the C-2 epimer of (+)-deacetylanisomycin **2a** was $[\alpha]_D^{25} = +18$ (*c* 0.8, MeOH), {lit[12d] $[\alpha]_D^{25} = +20$ (*c* 1, MeOH)}. The retention of configuration can be explained by the epoxide intermediate, which might have undergone cyclization via an unusual 5-*endo*-tet mode.[16]

3. Conclusion

In conclusion, we have developed a new, short and efficient synthetic approach for the C-2 epimer of (+)-deacetylanisomycin **2a** from D-mannitol, utilizing a stereoselective intramolecular in situ 5-*endo*-tet opening of an epoxide. The application of the above strategy for the synthesis of important pyrrolidine and piperidine molecules is currently in progress.

4. Experimental

Moisture and oxygen sensitive reactions were carried out under a nitrogen atmosphere. All the solvents and reagents were purified by standard techniques. TLC was performed on Merck Kiesel gel 60, F_{254} plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 and 100–200 mesh) using ethyl acetate, hexane chloroform and methanol as eluents. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR (400, 300 and 200 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded on the corresponding MHz. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s—singlet; d—doublet; t—triplet; q—quartet; m—multiplet), number of proton(s) and coupling constant(s) J (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with JASCO P-2000 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. ((4*S*,4′*R*,5*R*)-2,2,2′,2′-Tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)methanol 3

To a solution of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (10 g, 33.0 mmol) in dry ether (150 mL) was added periodic acid (9.8 g, 42.88 mmol) portion wise at 0 °C under a nitrogen atmosphere. After stirring for 6 h at room temperature, the reaction mixture was filtered and the filtrate concentrated under reduced pressure to give the aldehyde, which was used in the next step without any purification.

To the above aldehyde in dry MeOH (40 mL) was added $NaBH_4$ (1.44 g, 38.0 mmol) portionwise at 0 °C under a nitrogen atmosphere. After being stirred for 1 h at room temperature, satd aq NH_4Cl was added to the reaction mixture, followed by MeOH concentrated under reduced pressure and the residue was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:4) to afford **3** (5.2 g, 68%, based on recovery of starting material as a syrup. R_f (40% ethyl acetate/hexane) 0.5; $[\alpha]_D^{25} = -1.1$ (c 1.0, $CHCl_3$); IR (neat) ν_{max} 841, 1062, 1156, 1213, 1375, 2881, 2934, 2987, 3481 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (dd, 1H, J = 5.6, 8.1 Hz), 3.91–4.03 (m, 3H), 3.63–3.79 (m, 3H), 2.20 (br s, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 109.7, 109.3, 80.8, 78.4, 76.8, 67.7, 62.6, 26.8, 26.8, 26.5, 25.1; FABMS (m/z) 233 (M^++1); HRMS calcd for $C_{11}H_{20}O_5Na$ 233.1388, found 233.1398.

4.2. (4*S*,4′*R*,5*R*)-5-(Azidomethyl)-2,2,2′,2′-tetramethyl-4,4′-bis(1,3-dioxolane) 5

To a stirred solution of **3** (6.2 g, 26.6 mmol) in dry DCM (60 mL) was added Et_3N (3.5 mL, 26.6 mmol) at 0 °C under a nitrogen atmosphere. After 5 min of stirring, methanesulfonylchloride (2.1 mL, 26.6 mmol) was added dropwise to the reaction mixture and allowed to stir at room temperature for 1 h, then the reaction mixture was extracted with $CHCl_3$ (100 mL). The organic extract was washed with water (50 mL), brine (30 mL), dried over Na_2SO_4 and evaporation of the solvent under reduced pressure afforded **4** as a liquid, which was carried onto the next step without any purification.

To the above mesylate derivative **4** in dry DMF (30 mL) was added NaN_3 (2.6 g, 40.0 mmol) under a nitrogen atmosphere at room temperature. The reaction was slowly heated to 90 °C and stirred for 12 h, the reaction mixture was allowed to cool room temperature, poured into ice cold water (40 mL) and extracted with diethyl ether (3 × 80 mL). The combined organic extracts were washed with water (50 mL) brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:12) to afford **5** (5.5 g, 83% from **5**) as a liquid. R_f (20% ethyl acetate/hexane) 0.6; $[\alpha]_D^{25} = +63.4$ (c 1.5, $CHCl_3$); IR ν_{max} 666, 841, 917, 979, 1056, 1155, 1214, 1375, 1448, 1734, 2098, 2882, 2932, 2987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02–4.12 (m, 2H), 3.89–3.99 (m, 2H), 3.72 (t, 1H, J = 8.05 Hz), 3.63 (dd, 1H, J = 2.1, 13.1 Hz), 3.26 (dd, 1H, J = 4.7, 13.1 Hz), 1.43 (s, 3H), 1.37 (s, 6H), 1.30 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 109.8, 109.5, 79.7, 77.5, 77.1, 67.8, 51.7, 27.0, 26.8, 26.7, 25.2; ESI/MS (m/z) 230 ($M-N_2$).

4.3. Benzyl ((4*S*,4′*R*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl) methylcarbamate 7

To a solution of compound **5** (4.2 g, 16.3 mmol) in MeOH (30 mL) was added a catalytic amount of 10% Pd/C then the flask was purged with H_2 and the solution was hydrogenated for 24 h. The reaction mixture was filtered through a Celite bed, after which MeOH was removed from the reaction mixture in vacuo. The crude residue was dissolved in DCM (40 mL), and to it were added Na_2CO_3 (2.07 g, 19.5 mmol) and CbzCl (2.3 mL, 16.3 mmol) dropwise at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was diluted with $CHCl_3$ (50 mL). The organic layer was washed with water (30 mL), brine (20 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification by silica gel column chromatography (ethyl acetate/hexane 1:6) afforded **7** (4.83 g, 81%) as pale yellow liquid. R_f (30% ethylacetate/hexane) 0.5; $[\alpha]_D^{25} = -2.8$ (c 1.8, $CHCl_3$); IR ν_{max} 844, 1080, 1153, 1239, 1375, 1458, 1530, 1724, 2362, 2884, 2938, 2987, 3357 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.35 (m, 5H), 5.21 (br s, 1H), 5.02–5.12 (dd, J = 11.3, 2H), 4.06–4.14 (m, 1H), 3.87–4.01 (m, 3H), 3.44–3.57 (m, 3H), 1.39 (s, 3H) 1.36 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.3, 136.5, 128.4, 127.9, 109.8, 109.4, 79.4, 78.9, 76.7, 67.7, 66.6, 43.0, 26.9, 26.8, 26.5, 25.1; ESI/MS (m/z) 388 (M^++Na); HRMS calcd for $C_{19}H_{27}NO_6Na$ 388.1736, found 388.1730.

4.4. Benzyl ((4*R*,5*R*)-5-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl) methylcarbamate 8

Compound **7** (3.8 g, 10.3 mmol) was stirred at room temperature in 50% AcOH (38 mL). After stirring overnight at the same temperature, the reaction mixture was neutralized with aq $NaHCO_3$, and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:1.2) to afford **8** (2.84 g, 84% based on recovery of starting material) as white crystalline solid. R_f (80% ethyl acetate/hexane) 0.5; $[\alpha]_D^{25} = -17.5$ (c 1.0, $CHCl_3$); IR ν_{max} 698, 741, 883, 1049, 1158, 1245, 1374, 1457, 1531, 1695, 2855, 2924, 3357 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.40 (m, 5H), 5.39 (br s, 1H), 4.97–5.24 (dd, J = 12.6, 2H), 4.03–4.13 (m, 1H), 3.46–3.85 (m, 6H), 2.72 (br s, OH), 1.93 (br s, OH), 1.36 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.3, 136.1, 128.5, 128.2, 128.1, 109.0, 78.8, 77.2, 72.8, 67.1, 64.2, 42.6, 26.9, 26.8; ESI/MS (m/z) 348 (M^++Na); HRMS calcd for $C_{16}H_{23}NO_6Na$ 348.1423, found 348.1436.

4.5. (*R*)-2-((4*R*,5*R*)-5-((Benzyloxycarbonylamino)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl 4-methylbenzenesulfonate 9

To a stirred solution of **8** in DCM (2.2 g, 6.7 mmol) were added Et_3N (1.0 mL, 6.7 mmol), Bu_2SnO (168 mg, 0.67 mmol) and

p-toluenesulfonylchloride in DCM (1.38 g, 6.7 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 1 h at room temperature, the reaction mixture was extracted with $CHCl_3$ (100 mL). The organic extract was washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:8) to give **9** (3.0 g, 93%) as a liquid. R_f (20% ethyl acetate/hexane) 0.4; $[\alpha]_D^{25} = -32.3$ (*c* 1.2, $CHCl_3$); IR ν_{max} 699, 860, 1000, 1100, 1248, 1375, 1458, 1519, 1718, 2362, 2854, 2925, 3339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77–7.82 (m, 2H), 7.23–7.34 (m, 7H), 5.30 (br s, 1H), 5.02–5.14 (dd, *J* = 12.0, 2H), 4.15–4.22 (dd, 1H, *J* = 1.8, 10.1 Hz), 3.90–4.05 (m, 2H), 3.80 (br s, OH), 3.65–3.75 (m, 1H), 3.33–3.5 (m, 3H), 2.43 (s, 3H) 1.29 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.3, 136.1, 128.5, 128.2, 128.1, 128.0, 127.8, 109.0, 80.0, 78.7, 76.4 72.8, 67.1, 64.2, 50.9, 42.6, 29.7, 26.9, 26.8; ESI/MS (*m*/*z*) 480 (M^++1); HRMS calcd for $C_{23}H_{29}NO_8NaS$ 502.1511, found 502.1512.

4.6. Benzyl ((4*R*,5*S*)-2,2-dimethyl-5-((*R*)-oxiran-2-yl)-1,3-dioxolan-4-yl) methylcarbamate 10

To a stirred solution of monotosylate derivative **9** (2.8 g, 5.83 mmol) in dry MeOH (25 mL) was added K_2CO_3 (0.80 g, 5.83 mmol) under a nitrogen atmosphere. After being stirred for 30 min at room temperature, the MeOH was evaporated under reduced pressure while keeping the temperature of water bath below 30 °C. The residue was extracted with $CHCl_3$ (100 mL). The organic extract was washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:4) to give **10** (1.6 g, 90%) as a liquid. R_f (40% ethyl acetate/hexane) 0.5; $[\alpha]_D^{25} = -4.5$ (*c* 1.3, $CHCl_3$); IR ν_{max} 698, 744, 856, 986, 1081, 1155, 1242, 1375, 1455, 1528, 1711, 2361, 2934, 2987, 3343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.39 (m, 5H), 5.05–5.19 (m, 3H), 4.01–4.11 (m, 1H), 3.38–3.55 (m, 3H), 3.03–3.11 (m, 1H), 2.81–2.90 (m, 1H), 2.6–2.73 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.4, 136.3, 129.8, 128.4, 128.0, 109.9, 78.5, 77.4, 66.8, 51.3, 45.4, 42.7, 26.9, 26.5; ESI/MS (*m*/*z*) 308 (M^++1); HRMS calcd for $C_{16}H_{21}NO_5Na$ 330.1317, found 330.1328.

4.7. Benzyl ((4*R*,5*R*)-5-((*R*)-1-hydroxy-2-(4-methoxyphenyl)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl) methylcarbamate 11

To a stirred solution of **10** (1 g, 3.25 mmol) in dry THF (10 mL) were added CuCN (5 mg) and (*p*-methoxyphenyl) magnesium bromide {freshly prepared with Mg (312 mg, 13.0 mmol), *p*-bromo anisole (1.22 mL, 9.8 mmol) and I_2 (3 mg) in dry THF (5 mL)} dropwise at −78 °C under a nitrogen atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was quenched with satd aq NH_4Cl at 0 °C, concentrated under reduced pressure and the residue was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:4) to afford **11** (1.02 g, 76%) as a syrup. R_f (30% ethyl acetate/hexane) 0.5; $[\alpha]_D^{25} = -12.7$ (*c* 1.0, $CHCl_3$); IR ν_{max} 517, 699, 754, 1036, 1086, 1246, 1513, 1703, 2934, 2987, 3359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.37 (m, 5H), 7.13–7.30 (m, 2H), 6.82–6.87 (m, 2H), 5.25 (br s, 1H), 4.90–5.13 (dd, *J* = 12.2, 2H), 3.99–4.08 (m, 1H), 3.77 (m, 4H), 3.39–3.58 (m, 3H), 2.99 (dd, 1H, *J* = 2.2, 13.5 Hz), 2.63 (dd, 1H, *J* = 8.1, 13.7 Hz), 2.44 (br s, OH), 1.40 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.3, 156.8, 136.3, 130.5, 129.2, 128.4, 128.1, 128.0, 113.9, 108.8, 79.1, 78.8, 73.2, 66.9, 55.1, 42.9, 39.4, 27.0, 26.9; ESI/MS (*m*/*z*) 415.9 (M^++1); HRMS calcd for $C_{23}H_{29}NO_6Na$ 438.1892, found 438.1879.

4.8. (2*R*,3*R*,4*R*)-Benzyl 3,4-dihydroxy-2-(4-methoxybenzyl)-pyrrolidine-1-carboxylate 13

To a stirred solution of **11** (0.62 g, 1.49 mmol) in dry DCM (10 mL) was added Et_3N (0.24 mL, 1.79 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 5 min methanesulfonylchloride (0.12 mL, 1.64 mmol) was added dropwise to the reaction mixture and allowed to stir at room temperature for 1 h. The reaction mixture was then extracted with $CHCl_3$ (50 mL). The organic extract was washed with water (30 mL), brine (20 mL), dried over Na_2SO_4 and evaporation of the solvent under reduced pressure afforded **12** as a liquid, which was used in the next step without any purification.

To the above mesylate derivative **12** in DCM (5 mL) was added trifluoroacetic acid (5 mL) at 0 °C. After stirring for 1 h, the reaction mixture was concentrated under reduced pressure, after which benzene (10 mL) was added to the residue and the solvents were removed under reduced pressure. The crude residue was dissolved in ice cold water and extracted with ethyl acetate (40 mL). The organic extract was dried over Na_2SO_4, and the solvent evaporated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 3.5:1) to afford **13** (0.42 g, 79%) as a liquid. R_f (70% ethyl acetate/hexane) 0.4; $[\alpha]_D^{25} = +13.7$ (*c* 1.1, $CHCl_3$); IR ν_{max} 749, 815, 1032, 1178, 1244, 1511, 1611, 2928, 3326 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ 7.28–7.539 (m, 5H), 7.11–7.16 (m, 1H), 6.98–7.03 (m, 1H), 6.74–6.81 (m, 2H), 5.04–5.19 (m, 2H), 4.05–4.10 (m, 1H), 3.89–3.96 (m,1H), 3.79–3.87 (m, 2H), 3.74 (s, 3H), 3.05–3.33 (m, 2H), 2.89 (dd, 1H *J* = 13.1, 10.2 Hz), 2.24 (br s, 2H, 2OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.7, 157.9, 155.4, 155.2, 136.5, 136.2, 130.6, 130.4, 130.1, 128.4, 128.0, 127.9, 127.7, 113.9, 78.3, 77.6, 75.3, 74.9, 67.3, 66.8, 66.5, 66.4, 55.1, 52.6, 52.1, 36.8, 35.7; ESI/MS (*m*/*z*) 380 (M^++Na); HRMS calcd for $C_{20}H_{23}NO_5Na$ 380.1473, found 380.1489.

4.9. (2*R*,3*R*,4*R*)-2-(4-Methoxybenzyl)pyrrolidine-3,4-diol 2a

To a stirred solution of compound **13** (0.050 g, 0.13 mmol) in MeOH a catalytic amount Pd/C (10 mol %) was added, then the flask was purged with H_2 and the solution hydrogenated for 24 h. The reaction mixture was filtered through a Celite bed then the solution was concentrated under vacuum and purified by column chromatography (methanol/chloroform 1:19) to afford **2a** (0.026 g, 90%) as a syrup. R_f (5% Methanol/chloroform) 0.3.; $[\alpha]_D^{25} = +18$ (*c* 0.8, $CHCl_3$); {lit.[12d] $[\alpha]_D^{25} = +20$ (*c* 1, MeOH)} IR ν_{max} 752, 820, 1031, 1177, 1244, 1458, 1512, 1608, 2852, 2922, 3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.20 (2H, d, *J* = 8.3), 6.84 (2H, d, *J* = 8.3 Hz), 3.96–4.05 (m, 2H), 3.77 (s, 3H), 2.93–3.26 (m, 5H), 2.76–2.90 (m, 2H), 2.61 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.4, 130.3, 129.4, 114.2, 82.5, 75.6, 62.3, 55.2, 40.9, 36.5; ESI/MS (*m*/*z*) 224 (M^++1); HRMS calcd for $C_{12}H_{18}NO_3$ 224.1286, found 224.1278.

4.10. (2*R*,3*R*,4*R*)-Benzyl3,4-dimethoxy-2-(4-methoxybenzyl)-pyrrolidine-1-carboxylate 14

To a solution of the above diol (13 mg, 0.036 mmol) in THF (5 mL) was added NaH (2 mg, 95%, 0.08 mmol) and MeI in THF (0.4 v/v%, 1 mL) at 0 °C. After being stirred for 1 h at 0 °C and then for 40 min at rt and refluxed for 2 h, the reaction mixture was diluted with NH_4Cl solution (10 mL) and extracted with ethyl acetate (20 mL × 3). The extract was dried over $MgSO_4$, the solvent evaporated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:3) to afford **14** (12 mg, 87%) as a

liquid. R_f (50% ethyl acetate/hexane) 0.5; $[\alpha]_D^{25} = +30.2$ (c 1.3, $CHCl_3$); IR ν_{max} 841, 1062, 1155, 1212, 1375, 2880, 2934, 2987, 3480 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$): 7.46–7.28 (m, 5H), 7.20 (d, J = 7.5 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.83 (dd, J = 10.0, 4.6 Hz, 2H), 5.25–5.09 (m, 2H), 3.98 and 3.67 (rotamers, m, 1H), 3.80 (br s, 5H), 3.54 (s, 2H), 3.41 (s, 3H), 3.28 and 3.08 (rotamers, m, 1H), 3.03 (d, J = 6.7 Hz, 3H), 2.73 (q, J = 12.1 Hz, 1H); ESI/MS (m/z) 386 (M^++1).

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