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A new approach to (+)-anisomycin☆

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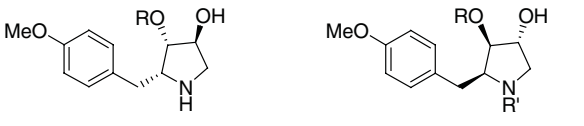
Abstract—An efficient approach to enantiomerically pure (+)-deacetylanisomycin **2a** and a formal synthesis of (+)-anisomycin **2** (11% overall yield in 10 steps) have been achieved through simple and good yielding reactions, starting from 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol **3**. Grignard reaction and intramolecular cyclisation reactions are key steps in the strategy.

1. Introduction

Anisomycin **1** is an antibiotic that was isolated from the fermentation broth filtrates of *Streptomyces griseolous* and *Streptomyces roseochromogens* by Sobin and Tanner at Pfizer, Inc. in 1954.[1] Its structure and relative stereochemistry were confirmed by chemical studies[2] and X-ray crystallographic analysis.[3] The absolute stereochemistry of this alkaloid (Fig. 1) were firmly established as (2*R*,3*S*,4*S*) by chemical correlation with L-tyrosine.[4]

Anisomycin **1** possesses a strong and selective activity against pathogenic protozoa and fungi, and has been used successfully in the clinics for the treatment of *Trichomonas vaginitis* and for amoebic dysentery.[5] Both anisomycin **1** and its deacetyl derivative **1a** have been used as fungicides in the eradication of bean mildew and for the inhibition of other pathogenic fungi in plants.[6] Anisomycin **1** was found to inhibit peptide bond formation on *eukaryotic ribosomes*.[7]



1 R=Ac
1a R=H

2 R=Ac, R'=H
2a R=R'=H
2b R=H, R'=Cbz

Figure 1. The structure of (−)-anisomycin **1** and (+)-anisomycin **2**.

2. Results and discussion

The diverse biological activity of anisomycin is due to the presence of a chiral pyrrolidine skeleton.[8] The activity and structural features of **1** has attracted the attention of several synthetic organic chemists.[9,10] Few routes have given good stereoselectivity, while others have an inherent problem in separating unwanted isomers. In continuation of our interest in the synthesis of biologically active chiral pyrrolidines,[11] we undertook the synthesis of the unnatural isomer, (+)-anisomycin **2**. Herein, we report a strategy where all the three centers of the (+)-anisomycin **2** were fixed from the inexpensive and readily available chiral pool starting material, D-mannitol. So far, three syntheses are reported for (+)-anisomycin **2**.[10] Two of the approaches[10a,b] are nonstereoselective and low yielding while the other[10c] prepared (+)-anisomycin, but with 88–90% ee. Previously, (+)-anisomycin **2** was synthesized from (+)-*N*-benzyloxycarbonyl deacetylanisomycin **2b** in three steps.[10c] Therefore, our approach mainly deals with the synthesis of (+)-(2*S*,3*R*,4*R*) deacetylanisomycin **2a** and its Cbz derivative **2b** as outlined below.

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-mannitol **3**, a fully protected form of D-mannitol was treated with H_5IO_6 to give aldehyde[12] **4** and immediate reduction of the resultant crude aldehyde **4** with $NaBH_4$ gave arabinitol derivative **5**. Treatment of **5** with benzyl bromide/NaH furnished benzyl ether derivative **6**. Selective hydrolysis of **6** with 50% aq AcOH gave diol **7**. Regioselective tosylation of **7** gave **8**, which on further treatment with K_2CO_3/MeOH yielded epoxide **9**. Reaction of **9** with *p*-methoxyphenylmagnesium bromide in the presence of a catalytic amount of I_2/CuI gave **10**. Compound

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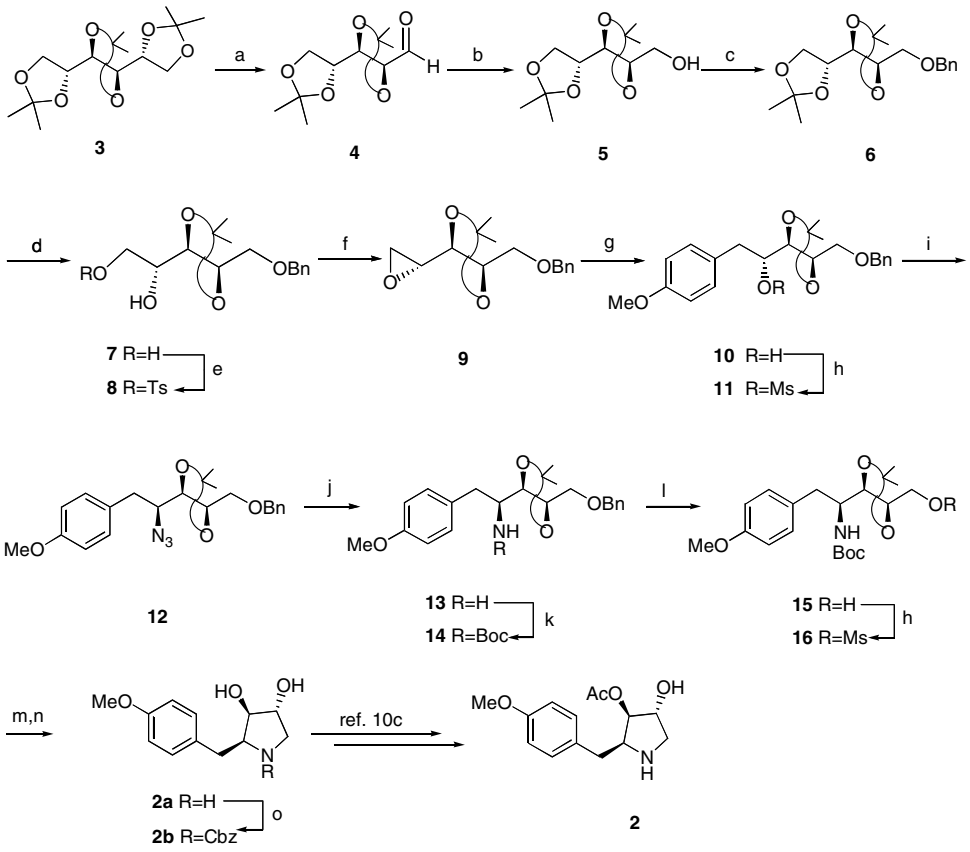

Reagents and conditions: (a) ref. 12; (b) $NaBH_4$, MeOH, rt, 3 h, 67% for two steps; (c) NaH, BnBr, DMF, 0 °C–rt, overnight, 84%; (d) 50% aq. AcOH, rt, overnight, 84%; (e) *p*-TsCl, Et_3N, DCM, 0 °C, 16 h; (f) K_2CO_3, MeOH, 30 min, 71% for two steps; (g) 4-Bromo anisole, Mg, I_2/CuI (cat.), 0 °C–rt, overnight, 86%; (h) MsCl, Et_3N, DCM, rt, 1 h; (i) NaN_3, [18-Crown-6], DMSO, 65 °C, 24 h, 83% for two steps; (j) $LiAlH_4$, THF, 0 °C– rt, overnight; (k) $(Boc)_2O$, Et_3N, THF, rt, 6 h, 81% for two steps; (l) Li/liq.NH_3, -78 °C, 30 min, 83%; (m) TFA, DCM, 0 °C–rt, 10 h; (n) Et_3N, MeOH, 0 °C– rt, 5 h; (o) Cbz-Cl, Na_2CO_3, THF, 2 h, 69% for four steps.

10 on treatment with MsCl/Et_3N gave **11**, which on further treatment with NaN_3/[18-crown-6] in DMSO[13] yielded azido derivative **12**. Reduction of the azido functionality with $LiAlH_4$/THF gave amine **13**, which on in situ treatment with $(Boc)_2O$/Et_3N afforded compound **14**. Removal of benzyl group in **14** was achieved using Li/liq. NH_3 to give **15**. Compound **15** was converted to corresponding mesyl derivative **16** with MsCl/Et_3N, which without purification treated with TFA followed by Et_3N to give (+)-deacetyl anisomycin **2a**. Further treatment of **2a** with Cbz–Cl gave (+)-*N*-benzyloxycarbonyl deacetylanisomycin **2b**,[9a,c,e,k] whose melting point, ^1H NMR and IR were in agreement with the reported values. The specific rotation of (+)-*N*-benzyloxycarbonyl deacetylanisomycin **2b** is $[\alpha]_D^{25} = +7.9$ (*c* 0.45, MeOH) {lit.[9e] for (−)-isomer is $[\alpha]_D^{25} = -8.2$ (*c* 5.97, MeOH)}.

3. Conclusion

Since **2b** had previously been transformed into (+)-anisomycin **2**,[10c] the present work offers an alternative route to the enantiomerically pure unnatural isomer **2**. A good yielding approach to the synthesis of (+)-deacetylanisomycin **2a**, has been achieved from D-mannitol, which also helps in making compound **2** in good quantities for the complete evaluation of its biological activity.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet nexus 670 FT-IR systems. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Avance-300 MHz spectrometer. ^1H NMR (400 MHz) spectra were recorded on a Varian Unity-400 MHz spectrometer. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. FABMS were recorded on a VG AUTOSPEC M251 (Micromass) at 70 eV using a direct inlet system. EI-mass spectrum was recorded on a VG 7070 H (Micromass) spectrometer. HRMS were recorded on a Q STAR XL HYBRID (PE SEIEX) spectrometer. Chiral

HPLC followed by LC–MS was carried out on AGILENT-1100 SERIES spectrometer.

4.1. 2,3:4,5-Di-*O*-isopropylidene-D-arabinitol 5

To a solution of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol **3** (12.5 g, 41.4 mmol) in dry ether (180 mL) was added periodic acid (12.26 g, 53.80 mmol) portionwise at 0 °C under a nitrogen atmosphere. After stirring for 6 h at room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate concentrated under reduced pressure to give crude arabinose derivative **4**, which was used in the next step without any purification.

To the above arabinose derivative **4** in dry MeOH (40 mL) was added $NaBH_4$ (1.81 g, 47.86 mmol) portionwise at 0 °C under a nitrogen atmosphere. After being stirred for 3 h at room temperature, saturated aq NH_4Cl was added to the reaction mixture, MeOH concentrated under reduced pressure and residue 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) (1:11) to afford **5** (4.5 g, 67% based on recovery of SM **3**) as a yellowish oil. $[\alpha]_D^{25} = -1.1$ (*c* 1.14, $CHCl_3$); IR ν_{max} (film, cm^{-1}): 845, 905, 1069, 1157, 1218, 1377, 1455, 2882, 2932, 2987, 3488; ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (dd, 1H, $J = 5.4$, 8.6 Hz), 3.91–4.03 (m, 3H), 3.63–3.79 (m, 3H), 2.25 (dd, 1H, $J = 4.7$, 8.6 Hz), 1.41 (s, 3H) 1.38 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 109.82, 109.39, 80.82, 78.68, 76.87, 67.88, 62.72, 26.92, 26.88, 26.60, 25.15; FABMS (M^++1): 233; HRMS calcd for $C_{11}H_{20}O_5Na^+$: 255.1208, found: 255.1220.

4.2. 1-*O*-Benzyl-2,3:4,5-di-*O*-isopropylidene-D-arabinitol 6

To a stirred suspension of NaH (1.03 g, 25.86 mmol) in dry DMF (20 mL) was added a solution of **5** (3 g, 12.93 mmol) in dry DMF (10 mL) dropwise at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 15 min, benzyl bromide was added and the reaction mixture stirred overnight, quenching with saturated aq NH_4Cl at 0 °C and extracted with ether (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) (1:24) to afford pure **6** (3.5 g, 84%) as a pale yellow oil. $[\alpha]_D^{25} = +6.1$ (*c* 0.95, $CHCl_3$); IR ν_{max} (film, cm^{-1}): 844, 1057, 1083, 1152, 1214, 1249, 1474, 1637, 2875, 2933, 2987; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18–7.34 (m, 5H), 4.60 (d, 1H, $J = 11.7$ Hz), 4.57 (d, 1H, $J = 11.7$ Hz), 4.07 (m, 2H), 3.94–4.02 (m, 1H), 3.89 (dd, 1H, $J = 4.7$, 7.8 Hz), 3.68–3.73 (m, 2H), 3.54 (dd, 1H, $J = 5.5$, 10.6 Hz), 1.39 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 138.18, 128.28, 127.67, 127.52, 109.76, 109.57, 79.75, 77.74, 77.17, 73.45, 70.68, 67.57, 27.05, 26.59, 25.23; FABMS (M^++1): 323; HRMS calcd for $C_{18}H_{26}O_5Na^+$: 345.1680, found: 345.1677.

4.3. 1-*O*-Benzyl-2,3-*O*-isopropylidene-D-arabinitol 7

The fully protected compound **6** (2.5 g, 7.76 mmol) was stirred at room temperature in 50% acetic acid (25 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 (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane) (1:1) to afford **7** (1.4 g, 84% based on SM recovery) as a pale yellow syrup. $[\alpha]_D^{25} = -1.4$ (*c* 1.065, $CHCl_3$) [>99% enantiomeric excess was determined from chiral HPLC using Chiralcel OB-H column (5% *i*-propanol/*n*-hexane, flow rate = 1 mL/min, $\lambda = 225$ nm)]; IR ν_{max} (KBr, cm^{-1}): 860, 1083, 1216, 1375, 1453, 1638, 2357, 2926, 2985, 3427; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.38 (m, 5H), 4.59 (s, 2H), 4.02 (dt, 1H, $J = 4.5$, 7.5 Hz), 3.68–3.78 (m, 3H), 3.58–3.67 (m, 2H), 3.53 (dd, 1H, $J = 7.5$, 9.0 Hz), 3.33 (br s, OH), 2.08 (br s, OH), 1.36 (s, 3H), 1.35 (s, 3H); FABMS (M^++1): 283; HRMS calcd for $C_{15}H_{22}O_5Na^+$: 305.1377, found: 305.1364.

4.4. 1-*O*-Benzyl-2,3-*O*-isopropylidene-4-oxiranyl-D-arabinitol 9

To a stirred solution of **7** in CH_2Cl_2 (1.3 g, 4.6 mmol) were added Et_3N (1.92 mL, 13.82 mmol) and *p*-toluenesulfonylchloride (0.87 g, 4.6 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 16 h at room temperature, the reaction mixture was extracted with $CHCl_3$ (150 mL). The organic extract was washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and then carried to the next step without any purification.

To a stirred solution of monotosylate derivative **8** in dry MeOH (8 mL) was added K_2CO_3 (1.14 g, 8.25 mmol) under a nitrogen atmosphere. After being stirred for 30 min at room temperature, the MeOH was evaporated under reduced pressure keeping the temperature below 30 °C. The residue was extracted with $CHCl_3$ (100 mL). The organic extract was washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane) (1:11) to give **9** (860 mg, 70%) as a colorless oil. $[\alpha]_D^{25} = -4.0$ (*c* 0.22, $CHCl_3$); IR ν_{max} (film, cm^{-1}): 858, 915, 1085, 1247, 1374, 1454, 1625, 2865, 2924, 2988; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.33 (m, 5H), 4.57 (s, 2H), 4.07–4.13 (m, 1H), 3.57–3.63 (m, 3H), 2.99–3.03 (m, 1H), 2.77 (t, 1H, $J = 4.5$ Hz), 2.62 (dd, 1H, $J = 3.0$, 5.2 Hz), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 137.92, 128.37, 127.66, 110.09, 78.09, 73.61, 70.52, 51.73, 44.93, 26.95, 26.69; FABMS (M^++1): 283; HRMS calcd for $C_{15}H_{20}O_4Na^+$: 287.1259, found: 287.1266.

4.5. (2*R*,3*R*,4*R*)-1-*O*-Benzyl-2,3-*O*-isopropylidene-5-(4-methoxyphenyl) pentane-1,2,3,4-tetrol 10

To a stirred solution of **9** (550 mg, 2.08 mmol) in dry THF (10 mL), CuI (10 mg) was added (*p*-methoxyphenyl)magnesium bromide {freshly prepared with Mg (252 mg, 10.4 mmol), *p*-bromo anisole (0.78 mL, 6.24 mmol) and I_2 (5 mg) in dry THF (5 mL)} dropwise at 0 °C under nitrogen atmosphere. After stirring overnight at room temperature, the reaction mixture was quenched with saturated aq NH_4Cl at 0 °C, THF was removed under reduced pressure and the residue 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) (1:9) to afford **10** (670 mg, 86%) as a pale brown oil. $[\alpha]_D^{25} = +13.2$ (*c* 0.68, $CHCl_3$); IR ν_{max} (film, cm^{-1}): 818, 1035, 1084, 1172, 1245, 1297, 1372, 1454, 1511, 1613, 2358, 2923, 2986, 3448; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.33 (m, 5H), 7.12 (d, 2H, $J = 8.7$ Hz), 6.78 (d, 2H, $J = 8.7$ Hz), 4.55 (s, 2H), 3.99–4.13 (m, 1H), 3.76 (s, 3H), 3.70–3.79 (m, 1H), 3.51–3.65 (m, 3H), 2.92 (dd, 1H, $J = 3.0$, 13.6 Hz), 2.6 (dd, 1H, $J = 7.5$, 13.6 Hz), 2.52 (br s, OH), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 158.21, 137.46, 130.46, 129.80, 128.34, 127.73, 113.81, 109.08, 80.87, 78.28, 73.50, 73.16, 70.79, 55.13, 38.88, 26.96, 26.86; FABMS (M^+): 372; HRMS calcd for $C_{22}H_{28}O_5Na^+$: 395.1834, found: 395.1828.

4.6. (2*R*,3*R*,4*S*)-4-Azido-1-*O*-benzyl-2,3-*O*-isopropylidene-5-(4-methoxyphenyl) pentane-1,2,3-triol 12

To a stirred solution of **10** (620 mg, 1.66 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (0.7 mL, 4.99 mmol) at 0 °C under a nitrogen atmosphere. After 5 min of stirring, methanesulfonylchloride (0.17 mL, 2.16 mmol) was added dropwise to the reaction mixture and allowed to stir at room temperature for 1 h, the reaction mixture was extracted with $CHCl_3$ (100 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 **11** as a yellow oil, which was carried to the next step without any purification.

To a stirred solution of above mesylate derivative **11** in dry DMSO (10 mL) were added [18-crown-6] (438 mg, 1.66 mmol) and NaN_3 (539 mg, 8.3 mmol) under nitrogen atmosphere at room temperature, the reaction was slowly heated to 65 °C, after being stirred for 24 h, the reaction mixture was allowed to room temperature, poured in to ice cold water (20 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane) (1:49) to afford **12** (550 mg, 83% from **10**) as a pale yellow oil. $[\alpha]_D^{25} = +16.9$ (*c* 0.69, $CHCl_3$); IR ν_{max} (film, cm^{-1}): 812, 852, 1036, 1092, 1172, 1246, 1299, 1373, 1454, 1511, 1612, 2109, 2924, 2989; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.3 (m, 5H), 7.11 (d, 2H, $J = 8.7$ Hz), 6.81 (d, 2H, $J = 8.7$ Hz), 4.5 (d, 1H, $J = 11.7$ Hz), 4.47 (d, 1H, $J = 11.7$ Hz), 4.19–4.24 (m, 1H), 3.83 (dd, 1H, $J = 2.1$, 8.0 Hz), 3.79 (s, 3H), 3.58 (dd, 1H, $J = 4.3$, 9.5 Hz), 3.42 (dd, 1H, $J = 5.8$, 9.5 Hz), 3.24 (dt, 1H, $J = 2.1$, 7.3, 14.6 Hz), 2.99 (dd, 2H, $J = 5.1$, 7.3 Hz), 1.49 (s, 3H), 1.377 (s, 3H); FABMS (M^+): 397; HRMS calcd for $C_{22}H_{27}O_4N_3Na^+$: 420.1899, found: 420.1919.

4.7. (2*R*,3*R*,4*S*)-1-*O*-Benzyl-4-(*tert*-butoxycarbonyl)-amino-2,3-*O*-isopropylidene-5-(4-methoxyphenyl) pentane-1,2,3-triol 14

To a suspension of $LiAlH_4$ (94 mg, 2.46 mmol) in dry THF (4 mL) was added compound **12** (490 mg, 1.23 mmol) in dry THF (6 mL) dropwise at 0 °C under a nitrogen atmosphere. After overnight stirring at room temperature, the reaction mixture was quenched with water (0.5 mL), 15% aq NaOH (0.5 mL) and water (1.5 mL) successively at 0 °C. After 10 min of stirring, $(Boc)_2O$ (0.85 mL, 3.70 mmol) was added and the reaction continued for 6 h at room temperature. The reaction mixture was then extracted with ethyl acetate (80 mL). The organic extract was washed with water (30 mL), brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (ethyl acetate/hexane) (1:15) to give **14** (450 mg, 81% based on recovery of SM **12**) as a pale yellow oil. $[\alpha]_D^{25} = -4.3$ (*c* 0.33, $CHCl_3$); IR ν_{max} (film, cm^{-1}): 818, 857, 1039, 1086, 1169, 1247, 1368, 1511, 1584, 1611, 1712, 2930, 2981, 3448; ^1H NMR (300 MHz, $CDCl_3$): δ 7.08–7.25 (m, 7H), 6.76 (d, 2H, $J = 9.0$ Hz), 4.79 (d, 1H, $J = 9.8$ Hz), 4.45 (s, 2H), 3.85 (m, 3H), 3.74 (s, 3H), 3.46 (d, 2H), 2.7–2.88 (m, 2H), 1.42 (s, 3H), 1.39 (s, 9H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 158.21, 155.63, 138.12, 130.26, 130.03, 128.27, 127.48, 113.83, 108.98, 79.36, 76.33, 73.32, 69.69, 55.18, 50.85, 38.90, 28.33, 27.01, 26.80; FABMS (M^++1): 472; HRMS calcd for $C_{27}H_{37}O_6N^+$: 472.2699, found: 472.2720.

4.8. (2*R*,3*R*,4*S*)-4-(*tert*-Butoxycarbonyl)amino-2,3-*O*-isopropylidene-5-(4-methoxyphenyl) pentane-1,2,3-triol 15

To a solution of lithium (14 mg, 2.01 mmol) in liquid NH_3 (50 mL) was added a solution of benzyl ether **14** (190 mg, 0.40 mmol) in dry THF (5 mL) at −78 °C. After stirring for 30 min at −78 °C, the reaction mixture was slowly warmed to room temperature for 2 h to evaporate the ammonia. The reaction mixture was neutralized with aq NH_4Cl, and concentrated under reduced pressure. The residue was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane) (1:3) to give **15** (128 mg, 83%) as a sticky syrup. $[\alpha]_D^{25} = -11.5$ (*c* 0.3, $CHCl_3$); IR ν_{max} (film, cm^{-1}): 816, 898, 1039, 1168, 1246, 1369, 1459, 1511, 1612, 1705, 2854, 2925, 3447; ^1H NMR (300 MHz, $CDCl_3$): δ 7.1 (d, 2H, $J = 8.8$ Hz), 6.77 (d, 2H, $J = 8.8$ Hz), 4.71 (d,

1H, $J = 9.6$ Hz), 3.78–3.94 (m, 2H), 3.79 (s, 3H), 3.58–3.66 (br s, 2H), 2.79 (d, 2H, $J = 8.0$ Hz), 2.1–2.2 (br s, 1H), 1.41 (s, 3H), 1.37 (s, 9H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 158.21, 155.94, 130.11, 129.71, 113.84, 108.77, 79.59, 77.94, 77.39, 61.80, 65.14, 50.83, 38.79, 28.24, 26.97, 26.89; FABMS (M^++1): 382; HRMS calcd for $C_{20}H_{31}O_6Na^+$: 404.2049, found: 404.2053.

4.9. (2*S*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-3,4-dihydroxy-2-(4-methoxybenzyl) pyrrolidine 2b

To a stirred solution of primary alcohol **15** (90 mg, 0.23 mmol) in dry CH_2Cl_2 (3 mL) was added Et_3N (0.1 mL, 0.70 mmol) at 0 °C under a nitrogen atmosphere. After 5 min stirring, methanesulfonylchloride (0.02 mL, 0.26 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 $CHCl_3$ (60 mL). The organic extract was washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford **16** as a pale yellow oil, which was carried to the next step without any purification.

To the above mesylate derivative **16** in CH_2Cl_2 (3 mL) were added trifluoroacetic acid (0.5 mL) and H_2O (0.25 mL) and the reaction mixture was stirred at room temperature for 10 h. After concentration of the solvent under reduced pressure, benzene (10 mL) was added to the residue and solvents were removed under reduced pressure. The crude residue was dissolved in MeOH (3 mL) and Et_3N (0.08 mL, 0.05 mmol) was added dropwise at 0 °C under nitrogen atmosphere. After stirring for 5 h at room temperature, removal of the solvent under reduced pressure afforded compound **2a** as a solid, which was carried to the next step without any purification.

To the above deactylanisomycin **2a** in dry THF (4 mL) was added Na_2CO_3 (36.5 mg, 0.34 mmol) at 0 °C under nitrogen atmosphere. After 5 min stirring, Cbz–Cl (0.07 mL, 0.46 mmol) was added dropwise to the reaction mixture and allowed to stir at room temperature for 2 h and the reaction mixture extracted with $CHCl_3$ (50 mL). The organic extract was washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane) (1:1) to afford **2b** (58 mg, 69% from **15**) as a white solid. Mp: 125–126 °C [(lit.[9e] mp 127–129 °C for (−)-isomer)]; $[\alpha]_D^{25} = +7.9$ (*c* 0.45, MeOH) {lit.[9e] for (−) isomer is $[\alpha]_D^{25} = -8.2$ (*c* 5.97, MeOH)}; IR[9c] (KBr, cm^{-1}): 816, 966, 1033, 1101, 1178, 1245, 1302, 1357, 1423, 1511, 1611, 1673, 2854, 2925, 3030, 3050, 3600–3150; ^{1}H NMR[9e] (400 MHz, $CDCl_3$): δ 7.30–7.52 (5H, m), 7.01–7.24 (2H, unresolved), 6.79 (2H, br s), 5.16 (2H, br s), 4.23 (1H, br s), 4.03 (1H, br s), 3.95 (1H, br s), 3.78 (3H, s), 3.60 (1H, dd, $J = 11.4$, 5.7 Hz), 2.99–3.51 (2H, unresolved), 2.89 (1H, dd, $J = 13.6$, 9.3 Hz), 1.79–2.02 (2H, unresolved); EIMS[9e] (M^+−121): 236; HRMS calcd for $C_{27}H_{37}O_6Na^+$: 380.1473, found: 380.1471.

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