Stereoselective Synthesis of (−)-Deacetylanisomycin

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Dedicated to Prof. E. Meléndez on the occasion of his retirement

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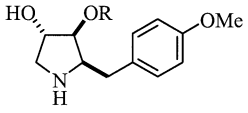
A stereoselective synthesis of (–)-deacetylanisomycin has been achieved from a nitrone derived from L-threose in 6 steps and 53.7% overall yield. The key step of the synthesis is the nucleophilic addition of a Grignard derivative with complete diastereofacial selectivity.

Introduction

Anisomycin (**1**) is a dihydroxylated pyrrolidine originally isolated from various species of *Streptomyces*.[1] Since its initial isolation **1** has aroused considerable interest due to its potent and specific antibiotic activity[2] against several microorganisms. It also inhibits the ribosomal peptide synthesis[3] and exhibits high antitumor activity.[4] In light of these diverse biological activities, it is not surprising that anisomycin has received considerable attention as a synthetic target, with no less than 20 total syntheses of the molecule having been reported to date.[5−8] These syntheses include preparation of (−)-deacetylanisomycin **2** since it is well documented that anisomycin **1** can be easily prepared from **2**.[9]

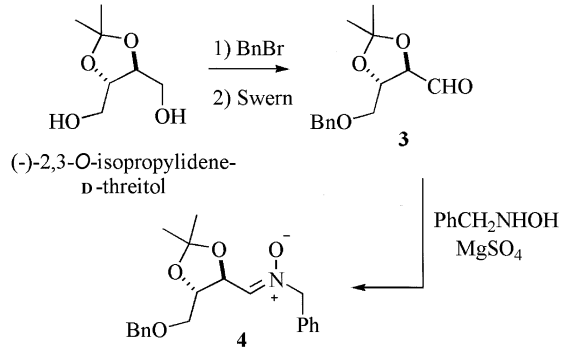


1 R = COMe anisomycin
2 R = H deacetylanisomycin

In light of the high interest in anisomycin and its deacetyl derivative **2**, we undertook a study designed to provide a highly stereoselective synthesis of **2**. Specifically, we envisaged the use of a nucleophilic addition to an L-threose-derived nitrone for the introduction of the (4-methoxyphenyl)methyl moiety. Nucleophilic addition to a cyclic nitrone has previously been used for synthesizing **2** by Petrini et al.[10] However, the reaction showed poor selectivity (*dr* = 3:2).

Results and Discussion

Our synthesis starts with nitrone **4**, which can be easily obtained from commercially available (−)-2,3-*O*-isopropylidene-D-threitol in three steps and in a 51.6% overall yield (Scheme 1). Nucleophilic additions to acyclic α-alkoxy nitrones have been used previously for highly stereoselective syntheses of a variety of nitrogen-containing compounds in our laboratory.[11]



Scheme 1

Nitrone **4** was treated with *p*-methoxybenzylmagnesium chloride or bromide under several different reaction conditions and in the presence or absence of additives in order to achieve the best selectivity (Scheme 2, Table 1). The absence of an additive, the use of THF as solvent, and addition of excess *p*-methoxybenzylmagnesium chloride (3.0

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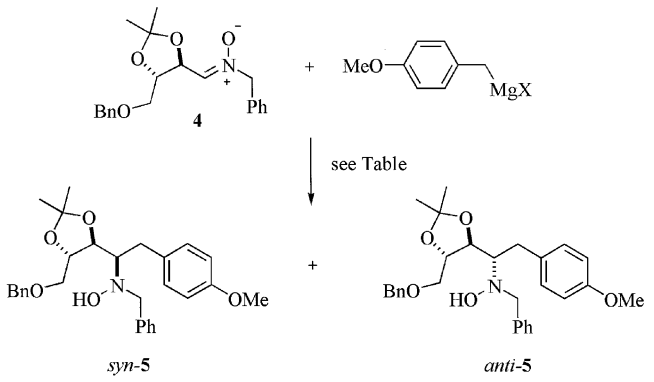


Scheme 2

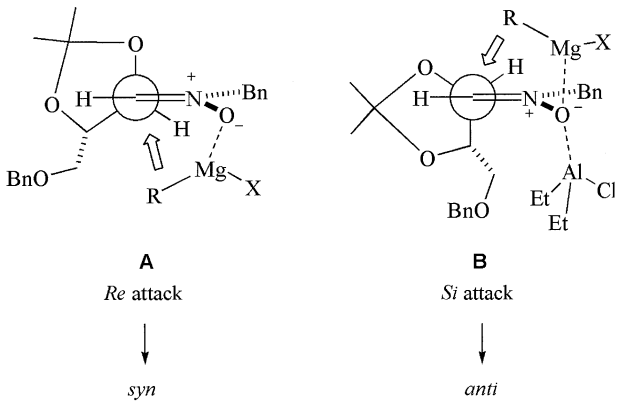


Figure 1. Preferential attacks for the nucleophilic addition to **4**

equiv.) at −20 °C (Entry 4) afforded a single isomer (by NMR) with the required configuration, isolated in an 84% yield.

The configuration of the newly generated chiral center in *syn*-**5a** could not be deduced from the NMR spectra but we anticipated a *syn* configuration on the basis of previous nucleophilic additions to α-alkoxy nitrones[12] The unambiguous assignment of the configuration was possible after the total synthesis of the target compound as discussed below.

The stereochemical course of the reaction in the absence of any additive can be rationalized by invoking a Houk model **A** (Figure 1). Coordination of the Grignard compound favours attack at the less-hindered *Re* face leading to the *syn* adduct. This coordination (prior to the transference of R) has been studied by us theoretically for α-amino nitrones[13] and it can also be invoked in the case of α-alkoxy nitrones. We have also experimentally demonstrated (NMR spectroscopy) that Et_2AlCl coordinates to the nitrone oxygen, as can be inferred from the displacement of the chemical shift corresponding to the azomethine proton.[14] Moreover, in that study it was also shown that addition of a second equivalent of coordinating agent led to additional deshielding of the azomethine proton, thus indicating an additional coordination at the nitrone oxygen. The theoretical study of the process is in complete agreement with the experimental observations.[14]

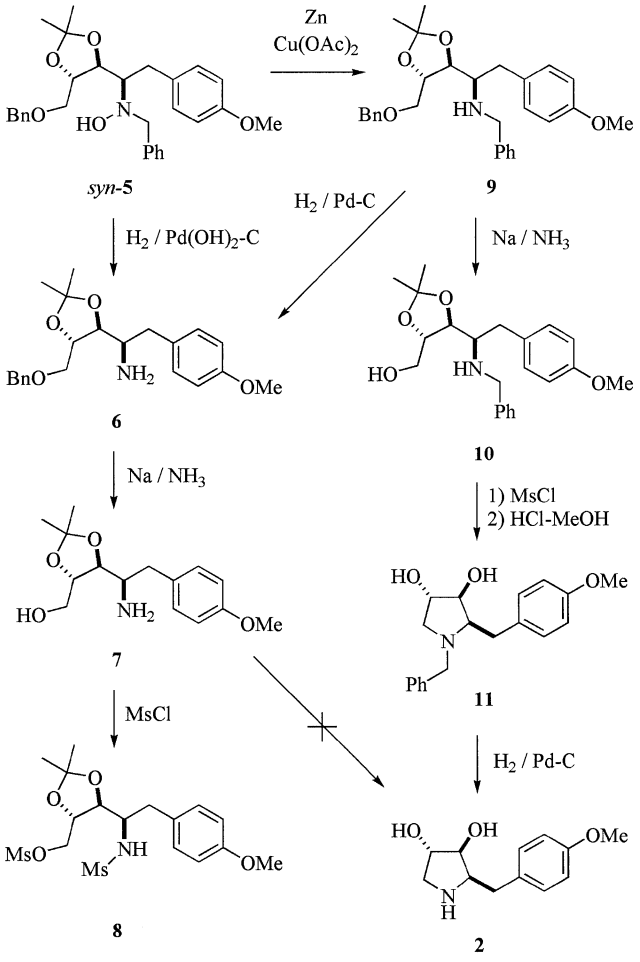
Thus, for the addition in the presence of Lewis acids an initial coordination of the Lewis acid leads to a structure similar to **A**. Further addition of Grignard reagent can only occur on the other face leading to structure **B**, which gives rise to the *anti* adduct. Obviously, one should consider the conformational equilibrium due to rotation around the N−O bond and, in fact, such a possibility may explain the only moderate degree of selectivity observed for additions in the presence of Lewis acids, in contrast to the complete selectivity observed for the reaction without additive.

With *syn*-**5** accessible in a totally diastereoselective way, we investigated the necessary transformations towards the target compound (Scheme 3). Attempts at *O*-debenzylation and subsequent complete reduction of the hydroxyamino moiety by hydrogenolytic methods failed and free amino **6** was obtained. It has been observed in our laboratory that *O*-benzyl groups cannot be easily eliminated by hydrogenolysis in the presence of a free amino group.[15] Debenzylation of the hydroxy group was achieved in quantitative yield with sodium in liquid ammonia. Unfortunately, mesylation of compound **7** followed by acidic treatment did not afford the target compound **2**, probably because compound **7** was also mesylated at the amino moiety to a great extent, as was evident from the NMR spectra of some isolated by-products. Among these, dimesylated derivative **8** could be completely characterized.

Table 1. Nucleophilic additions of *p*-methoxybenzylmagnesium halides to nitrone **4**

Entry[a]	X	Solvent	Time (h)	Temp. (°C)	Additive	*syn*:*anti*	Yield (%)[b]
1	Cl	Et_2O	12	−80	none	−	< 10[c]
2	Cl	Et_2O	12	−50	none	>95:5	36[c]
3	Cl	THF	12	−80	none	>95:5	45[c]
4	Cl	THF	4	−20	none	>95:5	84
5	Br	THF	4	−20	none	>95:5	66
6	Cl	THF	6	−20	Et_2AlCl	30:70	68
7	Cl	THF	6	−20	$BF_3{\cdot}Et_2O$	40:60	52

[a] All reactions were carried out with excess Grignard reagent (3.0 equiv.). [b] Isolated yields. [c] considerable amounts of nitrone **4** were found in the crude product indicating low conversion.



Scheme 3

On the other hand, chemical reduction of hydroxylamine *syn*-**5** using Zn/Cu couple afforded compound **9**, which was chemoselectively *O*-debenzylated with sodium in liquid ammonia to give compound **10** in quantitative yield. Hydrogenolysis of **9** was only effective on the *N*-benzyl group and compound **6** was again obtained. Compound **10** has been used successfully by Larcheveque and co-workers[7] for the synthesis of (−)-deacetylanisomycin, so at this point we had achieved the formal synthesis of the target compound. However, we decided to study some modifications to the procedure described by Larcheveque in order to improve the overall yield of the synthesis. Thus, treatment of **10** with mesyl chloride and in situ acid-mediated cleavage (HCl/MeOH) of the acetonide moiety afforded cyclic compound **11** in good chemical yield (78%). Finally, *N*-debenzylation of **11** by catalytic hydrogenation provided (−)-deacetylanisomycin **2** as a white crystalline compound in quantitative yield. The physical and spectroscopic properties of compound **2** were fully consistent with those reported in the literature (see Exp. Sect.).

Conclusion

We have presented a short (nine steps) and highly efficient (27.7% overall yield) synthesis of (−)-deacetylanisomycin (**2**) from commercially available (−)-2,3-*O*-isopropylidene-D-threitol. The synthesis is an extension of our previously disclosed methodology for the stereocontrolled addition of nucleophiles to α-alkoxy[11] and demonstrates once again the usefulness of our nitrone-based methodology for the synthesis of nitrogenated compounds. The high yields obtained in all steps and the mild conditions used make this approach amenable to large scale synthesis.

The practicality of this route to deacetylanisomycin **2** compares favourably with that of previous syntheses also based on nucleophilic additions to C=N bonds in which moderate selectivities were obtained.[7,10] Our synthesis shows complete diastereoselectivity (only one isomer is detected by NMR spectroscopy) in the key nucleophilic addition step. The reversal of the selectivity by precomplexing the nitrone with diethylaluminium chloride is of particular value, which should see use in the concise synthesis of the epimer at C-2 of both deacetylanisomycin (**2**) and anisomycin (**1**). Further studies in this direction are underway and will be reported in due course.

Experimental Section

General Remarks: The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the positions of the spots were detected with 254 nm UV light or by spraying with ethanolic phosphomolybdic acid. Flash chromatography was performed with a Buchi MPLC system using solvents that were distilled prior to use. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Unity (300 MHz) or on a Bruker (300 MHz) instrument. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ_H = 7.26 and δ_C = 77.0 for ^{1}H and ^{13}C, respectively) in $CDCl_3$. Optical rotations were recorded at 25 °C with a Perkin−Elmer 241 polarimeter. Elemental analysis were performed on a Perkin−Elmer 240B microanalyzer. 4-*O*-Benzyl-2,3-*O*-isopropylidene-L-threose was prepared from (−)-2,3-*O*-isopropylidene-D-threitol as described previously.[16]

Nitrone 4: A well-stirred solution of freshly prepared aldehyde **3** (10.0 g, 40 mmol) in dry dichloromethane (200 mL) was treated with *N*-benzylhydroxylamine (4.92 g, 40 mmol) and anhydrous magnesium sulfate (4.82 g, 40 mmol). The resulting mixture was vigorously stirred at room temperature for 4 h. The reaction mixture was filtered and the filtrate evaporated under reduced pressure to yield a residue which was applied to a short pad of silica gel and eluted with ethyl acetate. Evaporation of the solvent gave the pure nitrone **4** (12.23 g, 86%) as a white solid. M.p. 68−70 °C. $[\alpha]_D$ = +20 (*c* = 0.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 3 H), 1.43 (s, 3 H), 3.72 (d, *J* = 6.6 Hz, 1 H, 10.5 Hz), 3.89 (dd, *J* = 2.8, 10.5 Hz, 1 H), 4.15 (ddd, *J* = 2.8, 6.6, 7.3 Hz, 1 H), 4.57 (s, 2 H), 4.85 (s, 2 H), 4.99 (dd, *J* = 5.6, 7.3 Hz, 1 H), 6.78 (d, *J* = 5.6 Hz, 1 H), 7.21−7.40 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.3, 26.8, 69.5, 71.5, 73.2, 73.6, 79.8, 110.7, 127.4, 127.7, 128.2, 129.0, 129.2, 129.3, 132.2, 137.2, 138.2 ppm. $C_{21}H_{25}NO_4$ (335.43): calcd. C 70.96, H 7.09, N 3.94; found C 71.10, H 7.21, N 3.81.

(2*S*,3*S*,4*R*)-1-*O*-Benzyl-4-(benzylhydroxyamino)-2,3-*O*-isopropylidene-5-(4-methoxyphenyl)pentan-1,2,3-triol (*syn*-5): A freshly prepared solution of *p*-methoxyphenylmethylmagnesium chloride

(16.89 mmol, 5.63 mL of a 3.0 M solution in tetrahydrofuran) was added dropwise to a cooled (−20 °C) solution of nitrone **4** (2 g, 5.63 mmol) in dry tetrahydrofuran (60 mL). During the addition the temperature of the reaction mixture was not allowed to rise above −20 °C. The mixture was stirred for 4 h at −20 °C, quenched with saturated aqueous ammonium chloride (30 mL), stirred again at ambient temperature for 15 min and diluted with diethyl ether (50 mL) and saturated aqueous ammonium chloride (50 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 4:1) to afford 2.26 g (84%) of *syn*-**5** as a colourless oil. $[\alpha]_D = -10$ ($c = 0.27$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.21 (s, 3 H), 1.46 (s, 3 H), 2.96 (dd, J = 2.9, 11.4 Hz, 1 H), 3.01 (dd, J = 2.9, 11.7 Hz, 1 H), 3.16−3.22 (m, 1 H), 3.29 (dd, J = 5.1, 10.3 Hz, 1 H), 3.38 (dd, J = 5.1, 10.3 Hz, 1 H), 3.76 (s, 3 H), 3.8 (d, J = 13.0 Hz, 1 H), 3.93 (dd, J = 1.8, 8.1 Hz, 1 H), 4.14 (d, J = 13.2 Hz, 1 H), 4.36 (s, 2 H), 4.33−4.40 (m, 1 H), 5.3 (br. s, 1 H, exch. with D_2O), 6.76−6.82 (m, 2 H), 7.06−7.11 (m, 4 H), 7.18−7.30 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.8, 27.0, 29.5, 55.2, 61.0, 65.0, 70.4, 73.6, 76.0, 79.4, 108.8, 114.0, 127.2, 127.4, 127.6, 128.3 (2C), 129.0, 130.2, 137.8, 138.1 (2C), 158.0 ppm. $C_{29}H_{35}NO_5$ (477.59): calcd. C 72.93, H 7.39, N 2.93; found C 73.05, H 7.50, N 2.71.

(2*S*,3*S*,4*R*)-4-Amino1-*O*-benzyl-2,3-*O*-isopropylidene-5-(4-methoxyphenyl)pentane-1,2,3-triol (6): A solution of *syn*-**5** (478 mg, 1 mmol) in methanol (15 mL) was treated with Pearlman's catalyst (13 mg) and the resulting suspension was stirred under a hydrogen atmosphere at 1500 psi for 24 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate, 1:9) to give 345 mg (93%) of amine **6** as an oil. $[\alpha]_D = -12$ ($c = 0.12$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.31 (br. s, 2 H, exch. with D_2O), 1.43 (s, 3 H), 1.47 (s, 3 H,) 2.51 (dd, J = 9.3, 13.2 Hz, 1 H), 2.80 (dd, J = 4.9, 13.2 Hz, 1 H), 2.93−3.1 (m, 1 H), 3.57 (dd, J = 4.4, 10.2 Hz, 1 H), 3.63 (dd, J = 5.4, 10.2 Hz, 1 H), 3.81 (s, 3 H), 3.78−3.85 (m, 1 H), 4.23−4.30 (m, 1 H), 4.57 (s, 2 H), 6.83−6.89 (m, 2 H), 7.09−7.15 (m, 2 H), 7.27−7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.2, 27.3, 41.0, 53.6, 55.2, 70.9, 73.5, 81.2, 91.0, 109.1, 113.9, 127.6, 128.0, 128.4, 130.2, 131.0, 138.1, 158.2 ppm. $C_{22}H_{29}NO_4$ (371.47): calcd. C 71.13, H 7.87, N 3.77; found C 71.29, H 7.61, N 3.59.

(2*S*,3*S*,4*R*)-4-Amino-2,3-*O*-isopropylidene-5-(4-methoxyphenyl)-pentane-1,2,3-triol (7): A solution of compound **6** (279 mg, 0.75 mmol) in diethyl ether (3 mL) was added to a solution of sodium (75 mg, 3 mmol) in liquid ammonia (10 mL) cooled to −50 °C. The mixture was stirred for 15 min and then treated with solid ammonium chloride until the solution became colourless. The ammonia was allowed to evaporate at ambient temperature and water (5 mL) was then added. The aqueous solution was extracted with dichloromethane (3 × 10 mL), dried ($MgSO_4$) and the solvents evaporated under reduced pressure. The residue was filtered through a short pad of silica gel and eluted with ethyl acetate. Evaporation of the solvent afforded essentially pure **7** (211 mg, 100%) as an oil. $[\alpha]_D = +20$ ($c = 0.12$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.23 (br. s, 2 H, exch. with D_2O), 1.40 (s, 3 H), 1.42 (s, 3 H,) 2.36−2.51 (m, 1 H), 2.45 (br. s, 1 H, exch. with D_2O) 2.98 (dd, J = 2.44, 13.6 Hz, 1 H), 3.23 (dt, J = 3.7, 10.6 Hz, 1 H), 3.61 (dd, J = 6.6, 11.0 Hz, 1 H), 3.72−3.80 (m, 2 H), 3.76 (s, 3 H), 4.05−4.13 (m, 1 H), 6.80−6.86 (m, 2 H), 6.98−7.13 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.0, 27.1, 37.8, 52.6, 55.2, 62.5, 77.2, 82.4, 108.5, 114.0, 130.0, 130.4, 158.2 ppm. $C_{15}H_{23}NO_4$ (281.35): calcd. C 64.03, H 8.24, N 4.98; found C 63.89, H 8.43, N 5.12.

(2*S*,3*S*,4*R*)-2,3-*O*-Isopropylidene-1-*O*-mesyl-4-(mesylamino)-5-(4-methoxyphenyl)pentane-1,2,3-triol (8): A cooled (0 °C) solution of amino alcohol **7** (141 mg, 0.5 mmol) in dichloromethane (10 mL) was treated sequentially with DMAP (6 mg, 48 μmol), triethylamine (40 μL) and mesyl chloride (60 μL, 0.39 mmol). The resulting solution was stirred at ambient temperature for 4 h at which time additional mesyl chloride (30 μL, 0.20 mmol) was added. The reaction mixture was stirred for a further 12 h and then treated with water (15 mL). The crude mixture was extracted with dichloromethane (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvents evaporated under reduced pressure. After flash chromatography of the residue, dimesylated compound **8** was isolated (118 mg, 54%) as an oil. $[\alpha]_D = -24$ ($c = 0.25$, EtOH). ^1H NMR ($CDCl_3$): δ = 1.40 (s, 3 H), 1.41 (s, 3 H), 2.88 (s, 3 H), 3.06 (dd, 1 H, J = 11.03, 12.5 Hz), 3.19 (s, 3 H), 3.24−3.40 (m, 3 H), 3.64 (dd, J = 3.3, 12.5 Hz, 1 H), 3.74 (s, 3 H), 3.76−3.81 (m, 2 H), 3.95 (br. s, 1 H, exch. with D_2O), 6.80−6.84 (m, 2 H), 7.22−7.26 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.1, 27.2, 34.7, 35.0, 40.0, 55.6, 56.2, 66.5, 75.5, 76.5, 109.2, 114.6, 131.5, 132.3, 159.6 ppm. $C_{17}H_{27}NO_8S_2$ (437.50): calcd. C 46.67, H 6.22, N 3.20; found C 46.73, H 6.04, N 3.53.

(2*S*,3*S*,4*R*)-1-*O*-Benzyl-4-(benzylamino)-2,3-*O*-isopropylidene-5-(4-methoxyphenyl)pentane-1,2,3-triol (9): Zn dust (1.0 g, 15.3 mmol) was added to a solution of copper(II) acetate (45 mg, 0.30 mmol) in acetic acid (4 mL) and the mixture was stirred at ambient temperature for 15 min under argon. A solution of *syn*-**5** (1.43 g, 3.0 mmol) in acetic acid (4 mL) and water (1.5 mL) was added and the mixture was heated at 70 °C for 1 h. After cooling to 20 °C the disodium salt of EDTA (3.0 g) was added and the solution was basified (pH 10) by addition of aqueous NaOH (3 M). The solution was extracted with ethyl acetate (3 × 30 mL), the combined organic extracts were washed with saturated aqueous EDTA (30 mL) and brine (30 mL). The organic layer was separated, dried ($MgSO_4$) and the solvents evaporated under reduced pressure to give the crude product which was purified by flash chromatography (silica gel, hexane/ethyl acetate, 4:1) to provide pure **9** (1.14 g, 82%) as an oil. $[\alpha]_D = -8$ ($c = 0.20$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.37 (s, 3 H), 1.42 (s, 3 H), 1.85 (br. s, 1 H, exch. with D_2O) 2.72 (dd, J = 5.2, 9.4 Hz, 1 H), 2.75−2.81 (m, 1 H), 2.84 (dd, J = 5.2, 9.4 Hz, 1 H), 3.42−3.45 (m, 2 H), 3.70 (d, J = 13.2 Hz, 1 H), 3.77 (s, 3 H), 3.82 (d, J = 13.2 Hz, 1 H), 3.81−3.86 (m, 1 H), 4.33 (dt, J = 8.0, 4.8 Hz, 1 H), 4.46 (s, 2 H), 6.76−6.84 (m, 2 H), 7.02−7.07 (m, 2 H), 7.15−7.35 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.0, 27.2, 36.8, 51.6, 55.2, 58.1, 71.0, 73.4, 76.3, 78.8, 108.8, 113.9, 126.8, 127.4, 128.1, 128.3, 128.4, 130.1, 131.0, 138.1 (2C), 138.2, 158.2 ppm. $C_{29}H_{35}NO_4$ (461.59): calcd. C 75.46, H 7.64, N 3.03; found C 75.36, H 7.81, N 3.15.

(2*S*,3*S*,4*R*)-4-(Benzylamino)-2,3-*O*-isopropylidene-5-(4-methoxyphenyl)pentane-1,2,3-triol (10): A solution of compound **9** (923 mg, 2.0 mmol) in diethyl ether (8 mL) was added to a solution of sodium (200 mg, 8 mmol) in liquid ammonia (25 mL) cooled to −50 °C. The mixture was stirred for 15 min and then treated with solid ammonium chloride until the solution became colourless. The ammonia was allowed to evaporate at ambient temperature and water (10 mL) was then added. The aqueous solution was extracted with dichloromethane (3 × 25 mL), dried ($MgSO_4$) and the solvents evaporated under reduced pressure. The residue was filtered through a short pad of silica gel and eluted with hexane/ethyl acetate (7:3). Evaporation of the solvent afforded **10** (743 mg, 100%) as a white solid. M.p. 80−82 °C; ref.[7] m.p. 82−83 °C. $[\alpha]_D = +47$ ($c = 0.96$,

$CHCl_3$), ref.[7] $[\alpha]_D$ = +46 (*c* = 0.96, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.42 (s, 3 H), 1.44 (s, 3 H), 2.10 (br. s, 2 H, exch. with D_2O), 2.43 (dd, *J* = 11.6, 14.5 Hz, 1 H), 3.10−3.20 (m, 2 H), 3.52 (d, *J* = 13.0 Hz, 1 H), 3.55 (dd, *J* = 8.7, 11.0 Hz, 1 H), 3.78 (d, *J* = 13.0 Hz, 1 H), 3.79 (s, 3 H), 3.86 (dd, *J* = 3.4, 11.0 Hz, 1 H), 3.98 (dd, *J* = 3.4, 8.7 Hz, 1 H), 4.07 (dt, *J* = 3.4, 8.7 Hz, 1 H), 6.79 (m, 2 H), 6.9−7.04 (m, 4 H), 7.13−7.21 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.9, 27.0, 34.5, 52.7, 55.0, 58.0, 62.8, 76.1, 81.0, 108.4, 114.0, 127.3, 128.0, 128.4, 129.7, 129.8, 138.5, 158.3 ppm. $C_{22}H_{29}NO_4$ (371.47): calcd. C 71.13, H 7.87, N 3.77; found C 71.32, H 7.76, N 3.97.

(2*R*,3*S*,4*S*)-1-Benzyl-2-(4-methoxybenzyl)pyrrolidine-3,4-diol (11): A cooled (0 °C) solution of compound **10** (500 mg, 1.35 mmol) in dichloromethane (30 mL) was treated sequentially with DMAP (16 mg, 0.128 mmol), triethylamine (107 μL) and mesyl chloride (160 μL, 1.04 mmol). The resulting solution was stirred at ambient temperature for 4 h after which time additional mesyl chloride (80 μL, 0.53 mmol) was added. The reaction mixture was stirred for an additional 12 h and then treated with water (30 mL). The crude mixture was extracted with dichloromethane (3 × 40 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and the solvents evaporated under reduced pressure. The residue was taken up with a saturated (ca. 10%) solution of HCl in MeOH (25 mL) and the resulting solution was stirred for an additional 4 h. The reaction mixture was filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:4 hexane/ethyl acetate) to afford pyrrolidine **11** (330 mg, 78%) as a white solid; m.p. 80−82 °C; ref.[7] m.p. 81−82 °C. $[\alpha]_D$ = −80 (*c* = 0.40, $CHCl_3$), ref.[7] $[\alpha]_D$ = −82.1 (*c* = 1.13, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 2.14 (dd, *J* = 3.7, 11.0 Hz, 1 H), 2.80−3.00 (m, 3 H), 3.30 (d, *J* = 13.0 Hz, 1 H), 3.36 (dd, *J* = 6.0, 11.0 Hz, 1 H), 3.63 (m, 1 H), 3.75 (s, 3 H), 4.00 (m, 1 H), 4.10 (d, *J* = 13.0 Hz, 1 H), 6.80 (m, 2 H), 7.20 (m, 2 H), 7.26 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 2.14 ppm. $C_{19}H_{23}NO_3$ (313.39): calcd. C 72.82, H 7.40, N 4.47; found C 72.91, H 7.29, N 4.60.

(−)-Deacetylanisomycin (2): A solution of **11** (157 mg, 0.5 mmol) in methanol (10 mL) was treated with 10% Pd-C (25 mg) and the resulting suspension was stirred under hydrogen at 70 psi for 8 h (Parr hydrogenation apparatus). The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by a short flash chromatography (silica gel, chloroform/methanol, 9:1) to afford pure **2** (112 mg, 100%) as a white solid. M.p. 172−174 °C; ref.[7] m.p. 173−174 °C. $[\alpha]_D$ = −24 (*c* = 0.20, MeOH), ref.[6] $[\alpha]_D$ = −22.5 (*c* = 1.00, MeOH). ^1H NMR (CD_3OD): δ = 2.54 (dd, *J* = 2.0, 12.2 Hz, 1 H), 2.70 (dd, *J* = 6.5, 13.5 Hz, 1 H), 2.91 (dd, *J* = 8.0, 13.5 Hz, 1 H), 3.21 (m, 1 H), 3.30 (dd, *J* = 6.0, 12.5 Hz, 1 H), 3.72 (d, *J* = 3.0 Hz, 1 H), 3.75 (s, 3 H), 4.10 (d, *J* = 5.0 Hz, 1 H), 5.20 (br. s, 3 H), 6.76 (m, 2 H), 7.12 (m, 2 H) ppm. ^{13}C NMR (CD_3OD): δ = 34.3, 53.2, 55.5, 64.2, 78.0, 79.0, 14.6, 131.0, 133.0, 159.8 ppm. $C_{12}H_{17}NO_3$ (223.27): calcd. C 64.55, H 7.67, N 6.27; found C 64.40, H 7.81, N 6.08.

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