An Efficient Synthesis of (–)-Deacetylanisomycin Starting from D-Tyrosine[1]

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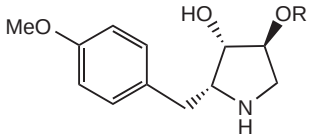
Abstract: The antibiotic (–)-deacetylanisomycin was synthesized starting from D-tyrosine using Sharpless asymmetric dihydroxylation as a key reaction.

Key words: anisomycin, (–)-deacetylanisomycin, D-tyrosine, Sharpless asymmetric dihydroxylation

Anisomycin (**1**) is an antibiotic that has been isolated from fermentation broth filtrates of various species of *Streptomyces*.[2] X-ray crystallographic analysis[3] and chemical studies[4] reveal the structure and relative stereochemistry of anisomycin to be that depicted in structure **1** (Figure 1). The absolute stereochemistry was established as 2*R*,3*S*,4*S* by chemical correlation studies.[5] Anisomycin possesses strong and selective activity against pathogenic protozoa and fungi and has been proved successful clinically in the treatment of amoebic dysentry and trichomonas vaginitis.[6] It has been shown to block ribosomal peptide synthesis.[6]



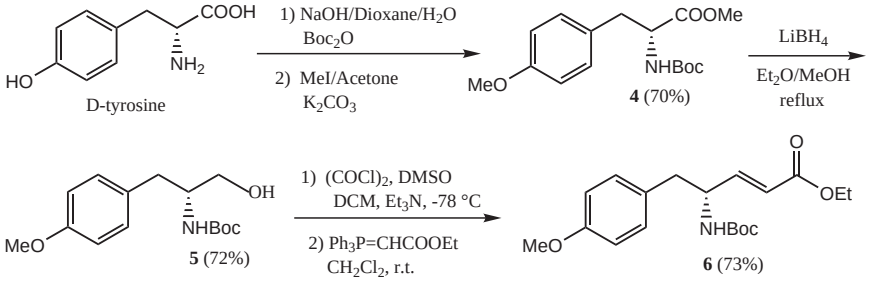
1 R = $COCH_3$
2 R = H

Figure 1 The structure of Anisomycin (**1**)

Although a few total synthesis of (–)-anisomycin have been reported[7] previously, the molecule still continues to attract the attention of synthetic organic chemists owing to its high biological profile. Our continued interest in the development of new and efficient synthetic routes to clinically significant amino compounds prompted us to investigate the total synthesis of (–)-deacetylanisomycin (**2**).[8] We wish to report herein the synthesis of **2** from D-tyrosine, which also constitutes a formal total synthesis of **1**. It appeared to us that an expedient approach to **2** from D-tyrosine would involve a reaction sequence outlined as below (Scheme 1).

Compound **4** was obtained in 70% yield from D-tyrosine by protecting the amino functionality using di-*tert*-butyl dicarbonate, followed by methylation of the acid and phenolic hydroxyl group with MeI/K_2CO_3. Reduction of ester **4** with lithium borohydride[9] furnished the alcohol **5** (72%). A Swern oxidation[10] followed by Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane in CH_2Cl_2 yielded the *trans* α,β-unsaturated ester **6** (73%). In order to avoid or minimize any possible racemization at the chiral centre, the aldehyde was used immediately without purification.

Our strategy required that the olefination product **6** contained the desired *trans* geometry at the double bond for the subsequent creation of chiral diol via Sharpless asymmetric dihydroxylation. Upon reacting the *N*-Boc-protected γ-amino-α,β-unsaturated ester **6** with the modified Sharpless asymmetric dihydroxylation conditions using AD-mix-α,[11] the expected (2*R*,3*S*,4*R*) configured ester **7** (60%) was obtained with high stereoselectivity (Scheme 2). This result has precedence.[12,13]



Scheme 1

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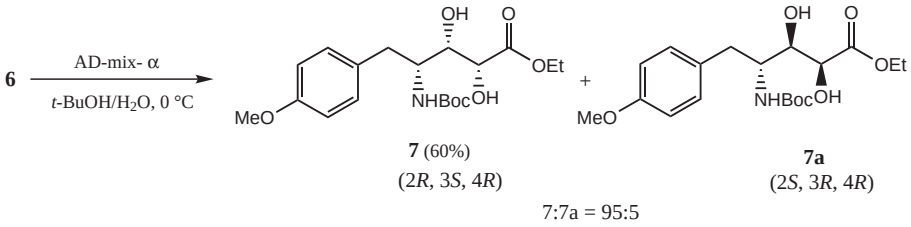


Scheme 2

Then diol **7** was subjected to acetonation with 2,2-dimethoxypropane (2,2-DMP) in the presence of a catalytic amount of camphorsulfonic acid (CSA) in anhydrous CH_2Cl_2 to afford the acetonide **8** (72%). Then **8** was reduced to the corresponding alcohol **9** (68%) with $LiBH_4$ (Scheme 3).

The alcohol **9** was converted to its corresponding bromide **10** (65%) via the tosylate (TsCl/Py) using LiBr/DMF. The above obtained Boc-amine **10** was subjected to acidolysis using TFA and the resulting amine was in situ treated with triethylamine, thereby facilitating cyclisation to the desired (–)-deacetylanisomycin **2** (70%). The sample had identical spectral data, to that previously reported in the literature[14] (Scheme 3).

The present work offers an alternative route to the antibiotic in enantiomerically pure form. It is to be noted that a completely different approach to the synthesis of (–)-deacetylanisomycin has been achieved starting from the chiral pool D-tyrosine. Further work on the synthesis of anisomycin analogues utilizing the above method is in progress and will be reported in due course.

Crude products were purified by column chromatography on silica gel (60–120 mesh). ^{1}H NMR were obtained in $CDCl_3$ at 200 MHz. Chemical shifts are given in ppm, with respect to internal TMS; *J* values are quoted in Hz. DMSO, Et_3N and CH_2Cl_2 were distilled from CaH_2 and stored over molecular sieves. Benzene and Et_2O were dried over sodium and benzophenone. All reactions were carried out under N_2 using dry glassware.

Methyl (2*R*)-2-(*tert*-Butoxycarbonyl)amino-3-(4-methoxyphenyl)propanoate (4)

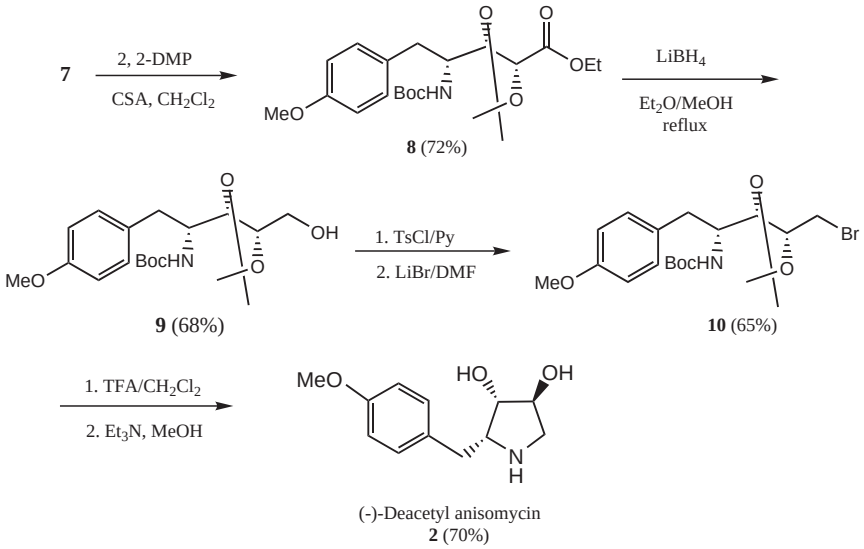
A solution of D-tyrosine (3 g, 16.5 mmol) in a mixture of dioxane (30 mL), H_2O (20 mL) and aq 1 M NaOH (20 mL) was stirred and cooled in an ice-water bath. Di-*tert*-butyl dicarbonate (3.97 g, 18.2 mmol) was added and stirring was continued at r.t. for 30 min. The solution was concentrated in vacuo to about 10–15 mL, cooled in an ice-water bath, covered with a layer of EtOAc (30 mL) and acidified with dilute aq $KHSO_4$ solution to pH 2–3. The aqueous phase was extracted with EtOAc (2 × 50 mL). The EtOAc extracts were pooled, washed with H_2O (2 × 30 mL), dried (Na_2SO_4) and evaporated in vacuo. To a solution of this crude *N*-Boc protected amino acid (3 g, 10.6 mmol) in acetone (100 mL) were added anhyd K_2CO_3 (7.35 g, 53.3 mmol) and MeI (4.55 g, 32 mmol). The resulting mixture was refluxed for 8 h, cooled to r.t. and filtered. The filtrate was concentrated and purified by column chromatography (hexane–EtOAc, 7:3) to give **4** (2.3 g, 70%) as a colorless viscous oil; $[\alpha]_D^{25}$ –58.4 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H), 3.05 (d, *J* = 4.65 Hz, 2 H), 3.7 (s, 3 H), 3.8 (s, 2 H), 4.05 (m, 1 H), 4.9 (br d, 1 H, NH), 6.8 (d, *J* = 8.3 Hz, 2 H), 7.05 (d, *J* = 8.3 Hz, 2 H).

EIMS: *m*/*z* = 192 (M^+ – 117), 121, 57.

(2*R*)-2-(*tert*-Butoxycarbonyl)amino-3-(4-methoxyphenyl)propan-1-ol (5)

To a stirred solution of ester **4** (2 g, 6.4 mmol) in anhyd Et_2O (100 mL) were added $LiBH_4$ (0.57 g, 25.5 mmol) and MeOH (10 mL) at



Scheme 3

0 °C. The reaction mixture was then refluxed for 5 h and quenched by adding an aq sat. NH_4Cl solution. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (2 × 25 mL), and dried (Na_2SO_4). The volatiles were removed under reduced pressure and the residue purified by column chromatography (hexane–EtOAc, 6.5:3.5) to afford **5** (1.3 g, 72%) as a syrupy liquid; $[\alpha]_D^{25}$ +12.58 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H), 2.48 (m, 1 H), 2.78 (d, *J* = 4.55 Hz, 2 H), 3.55 (m, 2 H), 3.8 (s, 3 H), 4.75 (br d, 1 H, NH), 6.8 (d, *J* = 6.8 Hz, 2 H), 7.1 (d, *J* = 6.8 Hz, 2 H).

HRMS: *m*/*z* calcd for $C_{15}H_{23}NO_4$: 281.1627 (M^+), observed: 281.1628 (M^+).

Ethyl (2*E*,4*R*)-4-(*tert*-Butoxycarbonyl)amino-5-(4-methoxyphenyl)pent-2-enoate (6)

To a stirred solution of oxalyl chloride (1.2 g, 9.6 mmol) in CH_2Cl_2 (15 mL) at –78 °C under N_2 was added DMSO (0.75 mL, 10 mmol) dropwise. After stirring for 30 min, a solution of the amino alcohol **5** (1.5 g, 5.33 mmol) in CH_2Cl_2 (25 mL) was added over 15 min. The mixture was warmed to –45 °C and stirring was continued for 1 h at this temperature, then Et_3N (2.7 g, 26.6 mmol) was added. The reaction mixture was brought to 0 °C and maintained at this temperature for 15 min, then a solution of (ethoxycarbonylmethylene)triphenylphosphorane (2.2 g, 6.4 mmol) in benzene (15 mL) was added and the resulting solution was stirred for 15 h at r.t. The solvent was removed under vacuum; the residue was washed with H_2O, brine and dried (Na_2SO_4). The residue was purified by column chromatography (hexane–EtOAc, 8:2) to yield the amino α,β-unsaturated ester **6** (1.35 g, 73%) as a pale yellow viscous liquid; $[\alpha]_D^{25}$ –5.25 (*c* = 2, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.3 (t, *J* = 5.1 Hz, 3 H), 1.4 (s, 9 H), 2.85 (d, *J* = 4.0 Hz, 2 H), 3.8 (s, 3 H), 4.2 (q, *J* = 5.1 Hz, 2 H), 4.45 (m, 1 H), 4.55 (br d, 1 H, NH), 5.82 (d, *J* = 13.5 Hz, 1 H), 6.85 (m, 3 H), 7.08 (d, *J* = 6.2 Hz, 2 H).

FABMS: *m*/*z* = 372 (M^+ + 23).

Ethyl (2*R*,3*S*,4*R*)-4-(*tert*-Butoxycarbonyl)amino-2,3-dihydroxy-5-(4-methoxyphenyl)pentanoate (7)

A mixture of **6** (0.4 g, 1.15 mmol) and the Sharpless AD-mix-α (1.6 g) modified by additional $(DHQ)_2PHAL$ (35.65 mg) and potassium osmate (3.45 mg) in *tert*-butyl alcohol (11.5 mL) and H_2O (11.5 mL) was stirred at r.t. for 18 h. The mixture was treated with Na_2SO_3 (2.3 g). After 0.5 h, EtOAc (100 mL) was added and the organic phase separated and washed twice with aq 1 M $KHSO_4$ (100 mL) and aq 5% $NaHCO_3$. The organic phase was filtered through silica gel and dried ($MgSO_4$). The residue was purified by column chromatography (hexane–EtOAc, 6:4) to yield **7** (0.26 g, 60%) as a semi-solid; $[\alpha]_D^{25}$ +9.12 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.3 (t, *J* = 3.1 Hz, 3 H), 1.4 (s, 9 H), 2.85 (m, 2 H), 3.35 (m, 2 H), 3.68 (m, 1 H), 3.75 (s, 3 H), 3.92 (m, 1 H), 4.2 (m, 3 H), 4.9 (m, 1 H, NH), 6.8 (d, *J* = 6.1 Hz, 2 H), 7.1 (d, *J* = 6.1 Hz, 2 H).

HRMS *m*/*z* calcd for $C_{19}H_{29}NO_7$: 383.1944 (M^+), observed: 383.1946 (M^+).

Ethyl (1*R*,4*R*,5*R*)-5-[1-(*tert*-Butoxycarbonyl)amino-2-(4-methoxyphenyl)ethyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate (8)

To a stirred solution of **7** (0.25 g, 2.4 mmol) in CH_2Cl_2 (10 mL) were added 2,2-dimethoxypropane (1.25 g, 12 mmol) and a catalytic amount of camphorsulfonic acid (15 mg) at 0 °C. The mixture was left stirring at r.t. for 2–3 h under N_2. The progress of the reaction was monitored by TLC. The solvent was removed under vacuo and the residue was purified by column chromatography (hexane–EtOAc, 8:2) to give the desired compound **8** (0.2 g, 72%) as a yellow viscous oil; $[\alpha]_D^{25}$ +14.22 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.12 (t, *J* = 4.75 Hz, 3 H), 1.30 (s, 6 H), 1.35 (s, 9 H), 2.8 (m, 3 H), 3.7 (s, 3 H), 4.1 (m, 4 H), 4.7 (br d, 1 H, NH), 6.75 (d, *J* = 7.1 Hz, 2 H), 7.1 (d, *J* = 7.1 Hz, 2 H).

FABMS: *m*/*z* = 424 (M+1).

(1*R*,4*S*,5*R*)-5-[1-(*tert*-Butoxycarbonyl)amino-2-(4-methoxyphenyl)ethyl]-2,2-dimethyl-1,3-dioxolan-4-ylmethanol (9)

To a stirred solution of the protected ester **8** (0.5 g, 1.18 mmol) in anhyd Et_2O (50 mL) were added $LiBH_4$ (0.1 g, 4.72 mmol) and MeOH (5 mL) at 0 °C. The reaction mixture was then refluxed for 5 h and quenched by the addition of aq sat. NH_4Cl solution. The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine (2 × 10 mL), dried (Na_2SO_4). The volatiles were removed under reduced pressure and the residue was purified by column chromatography (hexane–EtOAc, 7:3) to afford **9** (0.375 g, 68%) as a syrupy liquid; $[\alpha]_D^{25}$ +7.75 (*c* = 1.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.4 (2 s, 9 H + 6 H), 2.65 (m, 1 H), 2.8 (d, *J* = 5.1 Hz, 2 H), 3.68 (m, 2 H), 3.78 (s, 3 H), 3.88 (m, 2 H), 4.86 (br d, 1 H, NH), 6.85 (d, *J* = 5.5 Hz, 2 H), 7.17 (d, *J* = 5.5 Hz, 2 H).

FABMS: *m*/*z* = 382 (M + 1).

(1*R*,4*R*,5*R*)-1-[*N*-(*tert*-Butoxycarbonyl)]-1-(5-bromomethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxyphenyl)ethan-1-amine (10)

To a solution of compound **9** (0.2 g, 5.3 mmol) in anhyd CH_2Cl_2 (15 mL) containing anhyd pyridine (0.062 g, 7.9 mmol) at 0 °C under N_2 was added a solution of tosyl chloride (0.12 g, 6.3 mmol) in CH_2Cl_2 (5 mL) and the reaction mixture was stirred for 10 h at r.t.. The mixture was washed with aq sat. $CuSO_4$ solution (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. To the above obtained crude tosyl compound (0.2 g, 0.37 mmol) in anhyd DMF (15 mL) was added LiBr (0.1 g, 1.12 mmol) and the reaction mixture was stirred for 10 h at 80 °C. The mixture was cooled to r.t. and diluted with H_2O (20 mL), the resulting mixture was extracted with Et_2O (2 × 25 mL) and dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (hexane–EtOAc, 8.5:1.5) to afford the bromo compound **10** (0.107 g, 65%) as a yellow liquid; $[\alpha]_D^{25}$ +6.65 (*c* = 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.35 (2 s, 9 H + 6 H), 2.85 (m, 3 H), 3.38 (d, *J* = 2.9 Hz, 2 H), 3.76 (s, 3 H), 3.95 (m, 2 H), 4.8 (br d, 1 H, NH), 6.8 (d, *J* = 7.2 Hz, 2 H), 7.15 (d, *J* = 7.2 Hz, 2 H).

FABMS: *m*/*z* = 467 (M + 23).

(–)-Deacetylanisomycin (2)

To a solution of compound **10** (0.23 g, 0.6 mmol) in CH_2Cl_2 (5 mL) were added trifluoroacetic acid (1 mL) and H_2O (0.5 mL) and the reaction mixture was stirred at r.t. for 10 h. After concentration of the solvent under reduced pressure, benzene (5 mL) was added to the residue and the solvents were removed under vacuo. The crude residue was dissolved in MeOH (5 mL) and cooled to 0 °C. Et_3N (0.15 g, 1.5 mmol) was added slowly to the mixture and it was stirred at r.t. for 5 h. Removal of solvent under reduced pressure, followed by purification of the crude residue by column chromatography (CH_2Cl_2–MeOH, 9:1) afforded compound **2** (0.07 g, 70%) as a solid; $[\alpha]_D^{25}$ –22.5 (*c* = 1, MeOH).[13]

^{1}H NMR (DMSO-d_6): δ = 2.36 (dd, 1 H, *J* = 2.1, 11.8 Hz, H-5), 2.52 (dd, 1 H, *J* = 6.5, 13.2 Hz, C*H*$_2$Ar), 2.71 (dd, 1 H, *J* = 7.4, 13.2 Hz, C*H*$_2$Ar), 2.96 (ddd, 1 H, *J* = 3.5, 6.8, 7.6 Hz, H-2), 3.15 (dd, 1 H, *J* = 5.5, 11.8 Hz, H-5), 3.45–3.47 (m, 1 H, H-3), 3.70 (s, 3 H, OCH_3), 3.82–3.85 (m, 1 H, H-4), 4.56 (br s, 1 H, OH), 4.61 (br s, 1 H, OH), 6.81 (d, 2 H_{arom}, *J* = 8.3 Hz), 7.16 (d, 2 H_{arom}, *J* = 8.3 Hz).

HRMS: *m*/*z* calcd for $C_{12}H_{17}NO_3$: 224.1286 (M + 1), observed: 224.1286 (M + 1).

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