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Enantioselective Syntheses of (-)-Anisomycin and Its Propionate Derivative (3097-B1)

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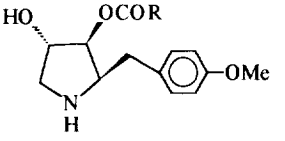
Abstract: Facile syntheses of (-)-anisomycin and 3097-B1 from divinylcarbinol **3** in an overall yield of 12.2% and 13.2%, respectively are described.

Anisomycin (**1**) was first isolated from two *Streptomyces* species (*S. grieolus* and *S. roseochromogenes*) by Sobin and Tanner in 1954[1] and was also found from two related strains: *Streptomyces* sp. No. 638[2] and *streptomyces* strain *SA 3097*.[3]

Anisomycin, as a valuable tool in molecular biology, exhibits selective action against protozoa and several strains of fungi due to the fact that it specifically blocks peptide bond formation on eukaryotic ribosomes.[4] It has been used successfully in the clinic for the treatment of both amebic dysentery[5] and trichomonas vaginitis[6], and as a fungicide to eradicate bean mildew.[7] Recently, Kameyama *et al.* reported that anisomycin and its relatives (3097-B1, 3097-B2 and 3097-C2) were isolated as antitumor substances showing cytotoxicity against human tumor cell lines *in vitro*. A structure-activity relationship was also discussed.[3]

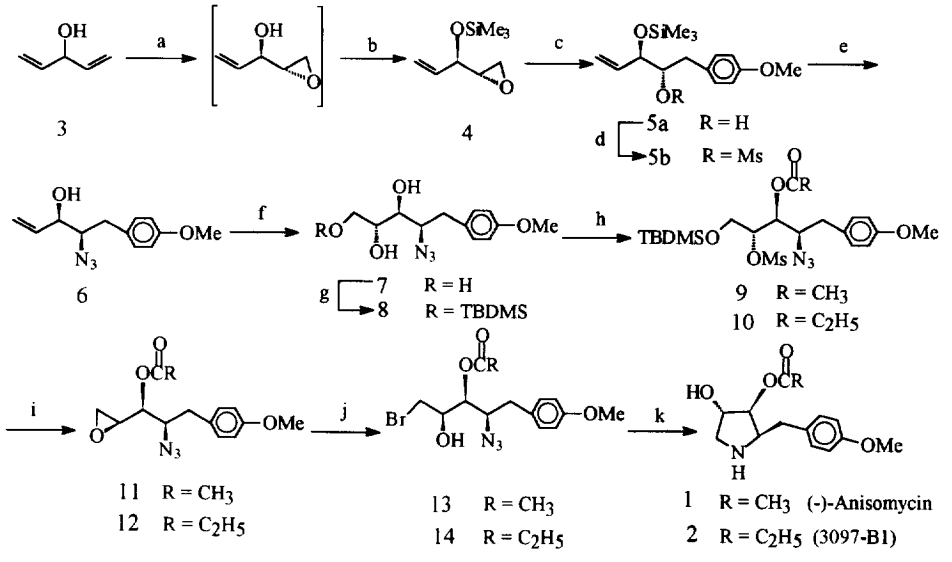


1 R=CH_3, (-)-Anisomycin
2 R=C_2H_5, 3097-B1

The diverse biological activities of **1** and its relatives have stimulated a great deal of interest in its chemical synthesis both in the racemic[8] and homochiral form.[9] However, many of them used 3,4-dihydroxy-2-(*p*-methoxybenzyl)pyrrolidine as the intermediate, in which the multisteps were required in order to differentiate the 3,4-dihydroxy by protection and deprotection[9f-l]. Therefore, there is a continued need to search for solution of this problem.

Here we wish to report a facile stereoselective synthesis of anisomycin (**1**) and 3097-B1 (**2**) by the combined application of Sharpless asymmetric epoxidation[10] [11] and Sharpless asymmetric dihydroxylation

reactions[12] as outlined in Scheme 1. The 4-hydroxy-3-acetyloxy or propionyloxy moiety was readily constituted without suffering from many steps of protection and deprotection.



Scheme 1

Reaction Conditions:

a: D-(-)-DIPT, TBHP, $Ti(OPr^i)_4$, CH_2Cl_2, -20°C. b: trimethylsilyl chloride, Et_3N, DMAP, CH_2Cl_2,. c: *p*-anisyl magenesium bromide, CuI (10%), THF, -10°C. d: methanesulfonyl chloride, pyridine, CH_2Cl_2, r.t.. e: NaN_3, DMF, 80°C, 7 hr then 2N aq. HCl, 30 min. f: OsO_4 (cat),$K_3Fe(CN)_6$, K_2CO_3, DHQ-CLB, t-BuOH/water, r.t.. g: *tert*-butyldimethylsilyl chloride, imidazole, DMF, 0°C. h: 1.1 eq acetyl chloride or pioponyl chloride, pyridine, CH_2Cl_2, r.t., 2 hr, then 1.5 eq methanesulfonyl chloride, 4 hr. i: 1.0 M $n\text{-}Bu_4N^+F^-$ THF solution, THF, 0°C, 1 hr. j: lithium bromide (10 eq), HOAc, THF, r.t., 24 hr. k: H_2, 10% Pd/C, r.t., 1atm, 2 hr., then NaOAc (1.5 eq), MeOH, reflux, 10 hr.

The (*3R, 4S*)-trimethylsilyloxy oxirane **4** was readily obtained in 65% yield from divinylcarbinol **3** using asymmetric epoxidation with 98% de and 97% ee.[10d, 11f-i] Regioselective ring opening of **4** with *p*-anisyl magnesium bromide in the presence of copper (I) iodide gave **5a** (85%), which was followed by mesylation to afford **5b** in 94% yield. Treatment of **5b** with sodium azide in DMF, and removal of the silyl group with 2N aq. HCl produced the azide **6** in 75% yield. Dihydroxylation of **6** using DHQD-CLB (Aldrich, No: 33648-3) or $(DHQD)_2PHAL$ (Aldrich, No: 39273-1) as the chiral ligand did not afford the desired product of the *2,3-threo*-triol.[13] The reason is probably due to the substrate-control induced by 3-ol in **6**[14]. After several attempts, finally, the 2,3-*erythro*-triol was constituted firstly through matched AD reaction (substrate control and chiral ligand), then the conversion of the stereochemistry of C-2. Thus, dihydroxylation of **6** using DHQ-CLB (Aldrich, No: 33649-1) as the chiral ligand and $K_3Fe(CN)_6$ as the cooxidant to furnish the triol **7** (no detectable diastereoisomer was found) (95%). Regioselective silylation of the primary alcohol in **7** with *tert*-butyldimethylsilyl chloride in DMF and imidazole at 0°C gave the diol **8** (89%). Treatment of **8** firstly by slowly

addition of 1.1 eq of acetyl chloride or propionyl chloride in pyridine followed by the second addition of 1.5 eq of methanesulfonyl chloride produced the silyl mesylate **9** or **10**. Now, the 2,3-dihydroxy corresponding the 3,4-dihydroxy in anisomycin were readily differentiated. The yield is **78%** (for **9**) and **85%** (for **10**), respectively. Then the silyl mesylate **9** or **10** was treated with 1.0 **M** n-$Bu_4N^+F^-$ (dried with 4ÅM.S.) to remove the silyl group. The resultant alkoxide anion, acting as the nucleophile, displaced spontaneously the mesyloxy group (S_N2) to produce the oxirane **11** or **12** in 91% and 98% yield, respectively.[15] The stereochemistry of C-2 was in *threo* position with C-3 as desired in the synthesis of anisomycin and 3097-B1. Hydrogenation of the oxirane **11** failed in the formation of the anisomycin due to the poor nucleophilic activity of amine in opening the oxirane. So, regioselective cleavage of the oxirane with lithium bromide (anhydrous) and HOAc in THF was conduct to give the bromohydrin[16] **13** and **14** in 90% and 89% yield respectively. Finally the bromohydrin was hydrogenated with 10% Pd/C under hydrogen for 2 hr followed by refluxing with NaOAc (1.5 eq) in MeOH to produce the (-)-anisomycin **1** and 3097-B1 **2** in 58% and 54% yield, respectively. The spectra data of **1** and **2** are consistent with the literature. [9b, 9g, 3][17]

In conclusion, we have synthesized the (-)-anisomycin and 3097-B1 *via* Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation reaction in 10 steps in 12.2% and 13.2% total yield, repectively.

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13. threo:erythro < 1:10 (DHQD CLB is used); threo:erythro = 1:5 ((DHQD)2PHAL is used)
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15. Spectra for **11**: $[\alpha]_D^{25}$ +40.1 (c, 0.1, $CHCl_3$). ν_{max}: 2100 ($-N_3$); 1740 (-OCO), 1240 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 7.16 (2H, d, J=8.61 Hz, 2H of phenyl); 6.88 (2H, d, 2H of phenyl); 4.34 (1H, dd, J=12.25 and 3.26 Hz, 3-H); 3.99 (1H, dd, J=12.49 and 5.97 Hz, 2-H); 3.81 (3H, s, -OMe); 3.68 (1H, m, 4-H); 3.28 (1H, m, 1-H); 3.01 (1H, dd, J=4.99 and 2.12 Hz, 1'-H); 2.93 (1H, dd, J=14.23 and 4.84 Hz, 5-H); 2.78 (1H, dd, J=14.15 and 8.10 Hz, 5'-H); 2.11 (3H, s, $COCH_3$) ppm. m/z (%): 291 (M^+, 1.54); 290 (M-1, 0.58); 121 (CH_2PhOMe, base). HRMS: Calcd for $C_{14}H_{17}N_3O_4$ 291.1219; Found: 291.1233. Spectra data for **12**: $[\alpha]_D^{25}$ +22.2 (c, 0.78, $CHCl_3$). ν_{max}: 2920; 2100 ($-N_3$); 1740; 1620 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.14 (2H, d, J=8.61 Hz, 2H of phenyl); 6.87 (2H ,d, J=8.64 Hz, 2H of phenyl); 4.33 (1H, dd, J=8.46 and 3.45 Hz, 3-H); 3.98 (1H, dd, J=12.42 and 5.86 Hz, 2-H); 3.80 (3H, s, -OMe); 3.63 (1H, m, 4-H); 3.24 (1H, m, 1-H); 2.98 (1H, dd, J=5.25 and 2.10 Hz, 1'-H); 2.91 (1H, dd, J=14.8 and 4.86 Hz, 5-H); 2.76 (1H, dd, J=14.91 and 8.05 Hz, 5'-H); 2.47 (2H, q, J=7.59 Hz, $C\underline{H}_2CH_3$); 1.16 (3H, t, J=7.54 Hz, $CH_2C\underline{H}_3$) ppm. m/z (%): 305 (M^+, 2.94); 121 (CH_2PhOMe, base). HRMS: Calcd for $C_{15}H_{19}N_3O_4$ 305.1376; Found: 305.1355.
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17. spectra data of 1: mp: 141-143°C (lit. [9g] mp: 144-145°C). $[\alpha]_D$ -29.1 (c, 0.1, MeOH), (lit. [9g], $[\alpha]_D$ -30.4 (c, 1.32, MeOH); ^1H NMR (CD_3OD, 300 MHz): 2.10 (3H, s); 2.65-2.81 (3H, m); 3.44(1H, dd, J=10.9 and 6.5 Hz); 3.52(1H, m); 3.75 (s, 3H); 4.18 (1H, m); 4.74 (1H, dd, J=5.0 and 1.6 Hz); 6.83 (2H, d, J=8.63 Hz); 7.11 (2H, d, J=8.63 Hz) ppm. m/z (%): 266 (M+1, 1.1), 222(0.6); 121 (base). spectra data of 2: mp: 145-147°C. $[\alpha]_D$ -10.2 (c, 0.1, MeOH). ^1H NMR (CD_3OD, 300 MHz): 1.16 (3H, t, J=7.5 Hz); 2.45 (2H, q, J=7.5 Hz); 2.90 (1H, J=13.5 Hz); 3.41 (1H, dd, J=13.5 and 5.0 Hz); 3.72 (3H, s); 3.78 (1H, m); 4.17 (1H, m); 4.82 (1H, d, J=4.1 Hz); 6.81 (2H, d, J=8.60 Hz); 7.13 (2H, d, J=8.60 Hz) ppm. m/z (%): 280 (M+1, 0.6). 121 (base).

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