

The highly diastereoselective addition of organometallic derivatives of trimethylsilylacetylen to *N*-Boc-*O*-Me-L-tyrosinal – synthesis directed towards anisomycin

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Dedicated to Professor Mieczysław Mąkosza on the occasion of his 70th birthday

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Abstract

Anisomycin analogue precursor was synthesised starting from a suitably protected α -amino aldehyde - tyrosine. The crucial step involves the addition of acetylenic reagent to *N*-Boc-*O*-methyl-L-tyrosinal in the presence of zinc(II) bromide, affording a *syn*-acetylenic adduct with high diastereoselectivity.

Keywords: Anisomycin, α -amino aldehydes, acetylenic addition, asymmetric synthesis

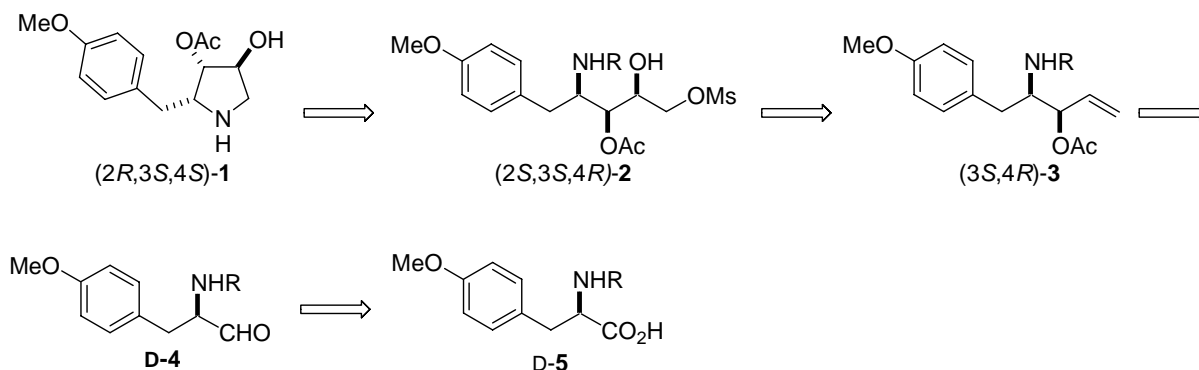
Introduction

Polyhydroxylated pyrrolidines and piperidines have received much attention since many representatives have been reported to exhibit interesting physiological effects. Anisomycin (**1**) is an antibiotic which was first isolated from the fermentation broths of *streptomyces* by Sobin and Tanner in 1954.¹ Since its isolation, this alkaloid has attracted much interest due to its potent and specific antibiotic activity² against several microorganisms. These properties have been successfully used in the clinical treatment of amoebic dysentery and *trichomonas vaginitis*.² Anisomycin (**1**) and its derivatives have also been employed as fungicides in plant infections.³ Renewed interest in this antibiotic and its derivatives has arisen when high anti-tumor activity in vitro was reported.⁴ The structure and relative stereochemistry of anisomycin (**1**) were studied chemically⁵ and then determined by X-ray crystallographic analysis.⁶ The absolute stereochemistry being (2*R*,3*S*,4*S*) was established on the basis of chemical correlation studies.⁷ As a result, many approaches have been developed for the asymmetric synthesis of anisomycin (**1**)⁸⁻¹⁵ but there is still a need for more efficient and elegant procedure. In the continuation of our efforts on the application of a methodology with the use of α -amino aldehydes to the synthesis of

natural compounds,¹⁶⁻²⁴ we have undertaken an effort directed towards the synthesis of the title alkaloid.

Results and Discussion

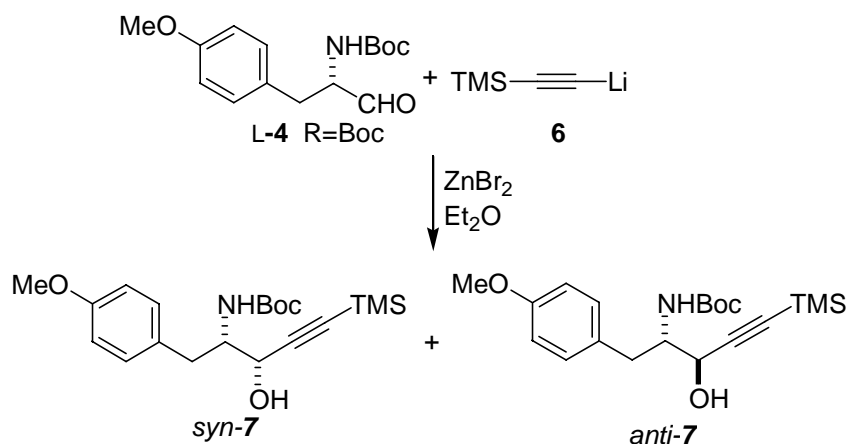
The retrosynthetic analysis, shown in Scheme 1, suggested that *N,O*-protected-D-tyrosinal of type **4** could serve as a starting material. Following our successful studies concerning the addition of various organometallic compounds^{16,25-28} to α -amino aldehydes, we envisaged that a propargylic addition to a suitably protected D-tyrosinal would be a key step. On the basis of earlier investigations²⁵ we assumed that the use of *N*-monoprotected-*O*-methyl derivative of D-tyrosinal (D-**4**) in the addition reaction should give desired *syn*-adduct predominantly. Among several possible *N*-protecting groups, the Boc group was selected since it can be easily removed under mild conditions.



Scheme 1

Recently we have reported the highly diastereoselective addition of the lithium derivative of *tert*-butyldimethylsilyl propargyl ether to *N*-Boc-*N,O*-isopropylidene-L-serinal.²⁸ It was found that the *syn*-selectivity was observed when the propargylic addition was carried out in the presence of most of the commonly used Lewis acid whereas *anti*-isomer predominated when HMPA or anhydrous CeCl₃ was used as an additive. Moreover, it has recently been reported¹³ that the addition of ethynylmagnesium bromide to *N*-monoprotected-D-tyrosinal gave *syn*-diastereoisomer predominantly. Having in mind our synthetic goal, we selected *N*-monoprotected α -amino aldehyde and because it is known that the *N*-protecting groups strongly influences the stereochemical course of the nucleophilic addition to the carbonyl group,²⁵ we extended our model studies to *N*-Boc-*O*-Me-L-tyrosinal (L-**4**).²⁹ Addition of lithium derivative of trimethylsilylacetylen (**6**) proceeded with moderate *anti*-stereoselectivity (82:18) and in a good yield (Scheme 2, Table 1, Entry 1). When the same reaction was carried out in the presence of HMPA as an additive, only *anti*-diastereoisomer **7** was isolated in 92% yield (Entry 2). The

direction of asymmetric induction was the same as for the addition of an acetylenic reagent to the Garner's aldehyde²⁸ and it can be explained by the Felkin-Anh model **A** (Figure 1).^{30, 31} Then the addition reaction of **6** to **L-4** was carried out in the presence of various Lewis acids. It was found that when anhydrous CeCl_3 was used, *anti*-isomer **7** predominated (Entry 3) whereas the use of ZnCl_2 afforded *syn*-isomer **7** as the major product in 68% yield. *syn*-Selectivity as well as the yield was further improved when the reaction was catalysed by ZnBr_2 instead of ZnCl_2 (Entries 4, 5). In this case the etynyl reagent attacks carbonyl group from the less hindered side of the chelation-controlled cyclic Cram model **B** (Fig. 1).³²



Scheme 2

Table 1. Addition of acetylenic reagent to tyrosinal **L-4**

Entry	Additive	Yield [%]	Ratio <i>anti</i> : <i>syn</i>
1	none	87	82:18
2	CeCl_3	90	>95:5
3	HMPA	92	>95:5
4	ZnCl_2	68	10:90
5	ZnBr_2	90	>5:95

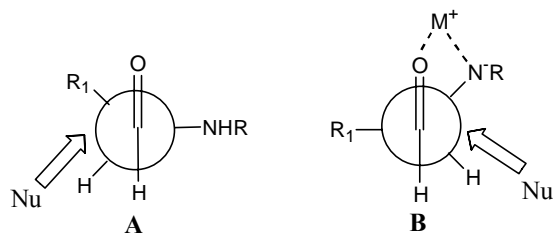
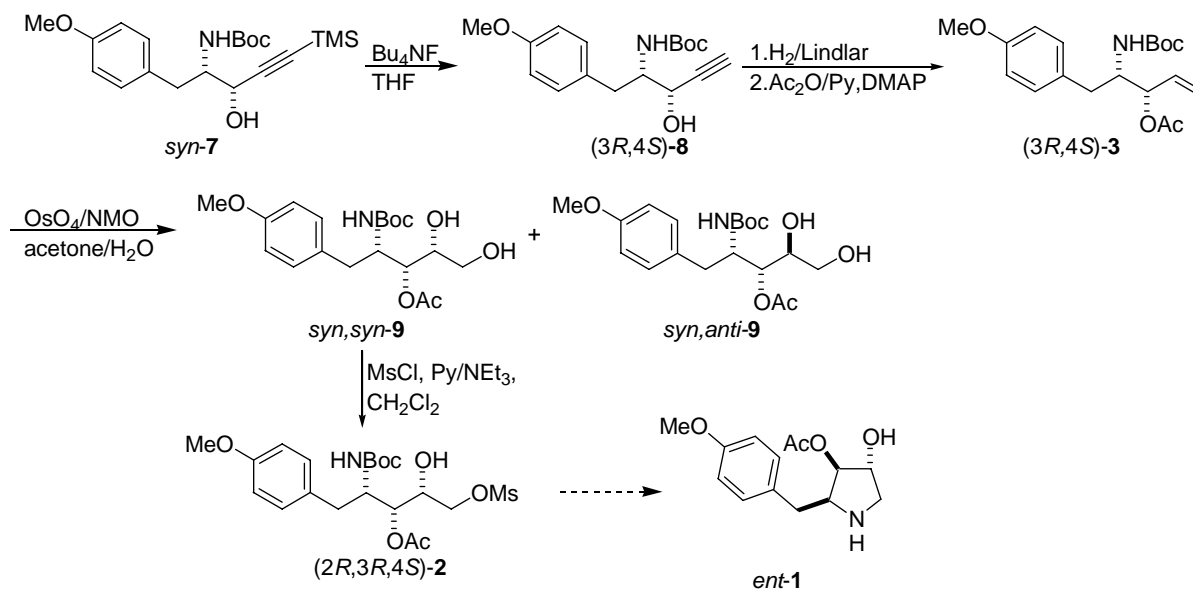


Figure 1

Having in hand highly stereoselective method for the preparation of *syn*-**7** and *anti*-**7** acetylenic adduct derivatives of *N*-Boc-*O*-Me-L-tyrosinal L-**4** we directed our efforts towards the synthesis of unnatural anisomycin *ent*-**1**. We pursued our studies exploiting compound *syn*-**7** (Scheme 3).



Scheme 3

syn-Adduct **7** was treated with crystalline $\text{Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$ ³³ giving desilylated compound $(3R,4S)$ -**8** in 88% yield. Subsequent hydrogenation, in the presence of a Lindlar catalyst,³⁴ yielded the vinyl adduct which was treated with acetic anhydride³⁵ affording $(3R,4S)$ -**3**. This compound could be obtained by the direct addition of a vinyl organometallic reagent to *N,O*-diprotected-L-tyrosinal L-**4** but there is no highly effective procedure for this transformation. *syn*-Dihydroxylation of $(3R,4S)$ -**3** with NMO and OsO_4 ³⁶ gave a mixture of diastereoisomeric polyhydroxylated amines **9**. The diastereoisomeric ratio was 4:1 in favour of the desired isomer *syn,syn*-**9**. After the chromatographic separation the primary hydroxy group of *syn,syn*-**9** was mesylated³⁷ in order to facilitate five-membered ring formation but unfortunately all attempts to do so failed to afford the desired antibiotic *ent*-**1**. Similar transformation was successfully accomplished using the Appel procedure by Jäger *et al.*³⁸ In his case, a polyhydroxylated amine with the neighbouring *N*-Bn and *O*-Bn triol, was used as pyrrolidine precursor. In this situation we did not further investigate our approach to the synthesis of anisomycin **1**.

In summary, we have presented highly diastereoselective addition of lithium trimethylsilylacetylen (**6**) to *N*-Boc-*O*-Me-L-tyrosinal (L-**4**), affording *anti*- or *syn*-adduct **7** depending on the conditions used. The synthetic interest of these transformations was illustrated by the preparation of the anisomycin precursor $(2R,3R,4S)$ -**2**.

Experimental Section

General Procedures. All chemicals were used as received unless otherwise noted. Reagent grade solvents (CHCl_3 , CH_2Cl_2 , hexanes, AcOEt) were distilled prior use. All reported NMR spectra were recorded with a Bruker spectrometer at 500 (^1H NMR) and 125 (^{13}C NMR) MHz or with a Varian Gemini spectrometer at 200 (^1H NMR) and 50 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS signal defined at $\delta = 0.00$ (^1H NMR) or $\delta = 0.0$ (^{13}C NMR). IR spectra were obtained on a Perkin-Elmer 1640 FTIR unit. Mass spectra were obtained on an AMD-604 Intectra instrument using the EI or LSIMS technique. Chromatography was performed on silica (Kieselgel 60, 200-400 mesh). Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell.

Compound L-4. ²⁹ Yield 90%, ^1H NMR (500 MHz, DMSO-d_6) 1.34 (s, 9H), 2.65 (dd, $J = 13.0$ Hz, $J = 10.0$ Hz, 1H), 3.00 (dd, $J = 13.0$ Hz, $J = 4.8$, 1H), 3.70 (s, 3H), 4.00 (m, 1H), 6.8-7.1 (m, 4H), 7.2-7.3 (m, 1H), 9.49 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) 28.1, 32.5, 61.0, 78.3, 113.6, 129.5, 130.1, 155.5, 157.8, 201.3; IR (KBr) 770, 835, 1034, 1164, 1248, 1367, 1514, 1613, 1701, 2978, 3364; HR EIMS $\text{C}_{15}\text{H}_{21}\text{NO}_4$ (M^+) calcd 279.1471, found 279.1470.

Compound *syn*-7. To the precooled to -50°C solution of trimethylsilylacetylen (12.3 mmol) in dry toluene (30 ml) the solution of *n*-BuLi in hexane (12 mmol, 7.5 ml, 1.6M) was added dropwise. The resulted mixture was stirred for 45 min during which time the temperature was raised to -30°C and then ZnBr_2 (1 mmol) was added. After 1 h, the reaction mixture was cooled to -78°C and the precooled solution of L-tyrosinal derivative L-4 (6 mmol) in toluene (5 ml) was added. When the reaction was completed (TLC) the reaction mixture was allowed to warm to room temperature and after an additional 1 h of stirring it was poured into aqueous $\text{NH}_4\text{Cl}_{\text{sat}}$. It was then extracted three times with AcOEt and the organic layer was worked up in the usual manner. The column chromatography (silica, hexanes/AcOEt) afforded adduct *syn*-7 as an amorphous solid, in the yield shown in Table 1. ^1H NMR (200 MHz, CDCl_3) 0.22 (s, 9H), 1.40 (s, 9H), 2.7-2.9 (m, 2H), 3.12 (d, $J = 6.0$ Hz, 1H), 3.71 (s, 3H), 3.9-4.1 (m, 1H), 4.38 (dd, $J = 3.0$ Hz, $J = 7.2$ Hz, 1H), 4.7 (d, $J = 8.0$ Hz, 1H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3) -0.13 , 28.3, 36.6, 55.3, 56.8, 65.4, 77.5, 80.1, 103.1, 114.0, 129.3, 130.1, 130.3, 158.4; IR (KBr) 849, 1014, 1177, 1247, 1527, 1692, 2180, 2835, 2959, 3373; Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_4\text{Si}$: C, 63.61; H, 8.29; N, 3.71. Found: C, 63.59; H, 8.39; N, 3.51; $[\alpha]_{\text{D}}^{20} -1.8$ (*c* 1, CHCl_3).

Compound *anti*-7. To the precooled to -50°C solution of trimethylsilylacetylen (12.3 mmol) in dry toluene (30 ml), the solution of *n*-BuLi in hexane (12 mmol, 7.5 ml, 1.6M) was added dropwise. The resulted mixture was stirred for 45 min during which time the temperature was raised to -30°C . Then it was cooled to -78°C and HMPA (0.1 mmol) was added. After 0.5 h, the precooled solution of L-tyrosinal derivative L-4 (6 mmol) in toluene (5 ml) was added. When the reaction was completed (TLC) the reaction mixture was allowed to warm to room temperature and after an additional 1 h of stirring it was poured into aqueous $\text{NH}_4\text{Cl}_{\text{sat}}$. It was then extracted three times with AcOEt, and the organic layer was worked up in the usual

manner. The column chromatography (silica, hexanes/AcOEt) afforded adduct *anti-7* as an amorphous solid, in the yield shown in Table 1. ^1H NMR (200 MHz, CDCl_3) 0.19 (s, 9H), 1.44 (s, 9H), 2.7-2.9 (m, 2H), 3.21 (d, $J = 6.2$ Hz, 1H), 3.68 (s, 3H), 3.9-4.1 (m, 1H), 4.31 (dd, $J = 3.2$ Hz, $J = 7.2$ Hz, 1H), 4.75 (d, $J = 7.8$ Hz, 1H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3) -0.09, 28.3, 36.3, 55.2, 57.7, 66.3, 77.0, 8.21, 100.1, 113.3, 129.0, 130.3, 130.5, 158.9; IR (KBr) 760, 840, 1038, 1066, 1176, 1246, 1300, 1368, 1455, 1626, 1611, 1678, 2177, 2835, 2980, 3388; HR EIMS $\text{C}_{20}\text{H}_{31}\text{NO}_4\text{Si}$ (M) $^+$ calcd 377.2022, found 377.2022. $[\alpha]_{\text{D}}^{20}$ -2.6 (c 1, CHCl_3).

Compound 8. To the solution of *syn-7* (700 mg, 1.86 mmol) in dry THF (10 ml), Bu_4NF (50 mg) was added. After 5 min, the reaction mixture was extracted twice with Et_2O . The organic layer was washed with water and brine. Filtration through the silica pad gave 645 mg (yield 88%) of desilylated compound **8** as a viscous oil. ^1H NMR (200 MHz, CDCl_3) 1.40 (s, 9H), 2.5-2.8 (m, 3H), 3.78 (s, 3H), 4.00 (m, 1H), 4.38 (m, 1H), 4.80 (brs, 2H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3) 28.2, 36.6, 55.2, 56.9, 62.5, 77.5, 80.1, 83.3, 114.0, 129.3, 130.1, 130.6, 158.9; IR (KBr) 1054, 1177, 1237, 1537, 1612, 1698, 2187, 2836, 2987, 3350; EIMS (m/z) $\text{C}_{17}\text{H}_{23}\text{NO}_4$ 306 ($\text{M}+\text{H}$) $^+$, 248, 150, 121, 86, 57; $[\alpha]_{\text{D}}^{20}$ -5.4 (c 1, CHCl_3).

Compound (3R,4S)-3. Hydrogenation of compound **8** (610 mg, 2 mmol) in the mixture of toluene and quinoline (1:1, 14 ml) in the presence of Lindlar catalyst for 2 h at room temperature. After filtration, the reaction mixture was washed with water and brine. Column chromatography (silica, hexanes/AcOEt) afforded 530 mg of vinyl alcohol derivative which was treated with a mixture of Ac_2O and pyridine (1:1) in the presence of catalytic amount of DMAP. Standard workup, followed by filtration through a silica pad, gave (3R,4S)-**3** (600 mg, 97%) as a viscous oil. ^1H NMR (200 MHz, CDCl_3) 1.36 (s, 9H), 2.10 (s, 3H), 2.6-2.9 (m, 2H), 3.20 (brs, 1H), 3.74 (s, 3H), 3.8-4.0 (m, 1H), 4.20 (brs, 1H), 5.2-5.4 (m, 2H), 5.93 (ddd, $J = 5.5$ Hz, $J = 10.4$ Hz, $J = 16.2$ Hz, 1H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3) 20.9, 29.3, 37.5, 50.6, 54.3, 55.1, 74.4, 79.4, 113.8, 118.0, 129.2, 130.1, 133.6, 155.3, 158.2, 169.6; IR (KBr) 840, 1053, 1176, 1300, 1357, 1445, 1606, 1611, 1678, 1704, 2838, 2987, 3388; ; HR EIMS $\text{C}_{19}\text{H}_{27}\text{NO}_5$ (M) $^+$ calcd 349.1892, found 349.1896; $[\alpha]_{\text{D}}^{20}$ +6.5 (c 1.3, CHCl_3).

Compound *syn, syn-9*. To a solution of (3R,4S)-**3** (52 mg, 0.15 mmol) in a mixture of acetone/ H_2O (7:1, 2.4 ml), were added subsequently *N*-methylmorpholine (170 mg, 1.26 mmol) and the solution of OsO_4 (0.01 mmol) in *tert*-BuOH (0.2 ml). The reaction mixture was stirred until the disappearance of the starting material (TLC) then saturated $\text{NaHSO}_{3\text{aq}}$ (20 ml) and Et_2O were added. The organic layer was washed with saturated solution of $\text{NaH}_2\text{PO}_{4\text{aq}}$ and brine. Column chromatography (silica, hexanes/AcOEt, 2:8) gave both oily diastereoisomers *syn, syn-9* (38 mg) and *syn, anti-9* (10 mg). ^1H NMR (200 MHz, CDCl_3) 1.40 (s, 9H), 2.10 (s, 3H), 2.50 (dd, $J = 1.7$ Hz, $J = 6.9$ Hz, 1H), 2.9-3.1 (m, 2H), 3.55 (dd, $J = 10.1$ Hz, $J = 14.3$ Hz, 1H), 3.76 (s, 3H), 4.1-4.3 (m, 2H), 4.6-4.8 (m, 1H), 5.20 (s, 1H), 6.8-7.2 (m, 4H); IR (KBr) 816, 1132, 1276, 1543, 1619, 1711, 2878, 2995, 3069, 3500; HR LSIMS $\text{C}_{19}\text{H}_{29}\text{NO}_7$ (M) $^+$ calcd 383.1944, found 383.1952; $[\alpha]_{\text{D}}^{20}$ +4.5 (c 1.0, CHCl_3).

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