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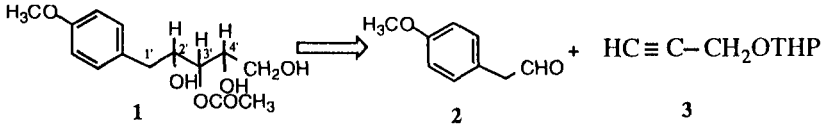
A STEREO FLEXIBLE TOTAL SYNTHESIS OF KARALICIN, AN ANTIVIRAL AGENT

T. Prabhakar Rao

Indian Institute of Chemical Technology, Hyderabad-500 007, India

Abstract: The first stereo flexible total synthesis of Karalicin, an antiviral agent recently isolated from a fermentation broth of the *Pseudomonas Fluoriscens/Putida* strain SS-3 (CCM 4430), from readily available starting materials is described.

In 1996, Lampis et al.[1-2] reported the isolation of Karalicin, a new biologically active compound, which showed a weak but specific and irreversible antiviral activity on herpes simplex viruses. It also exhibited some inhibitory activity on different species of yeast. The structure elucidation of Karalicin and the stereochemistry of active sites (C=2',3' and 4') were not mentioned in their communication[3]. Its biological activity prompted us to intiate total synthesis of



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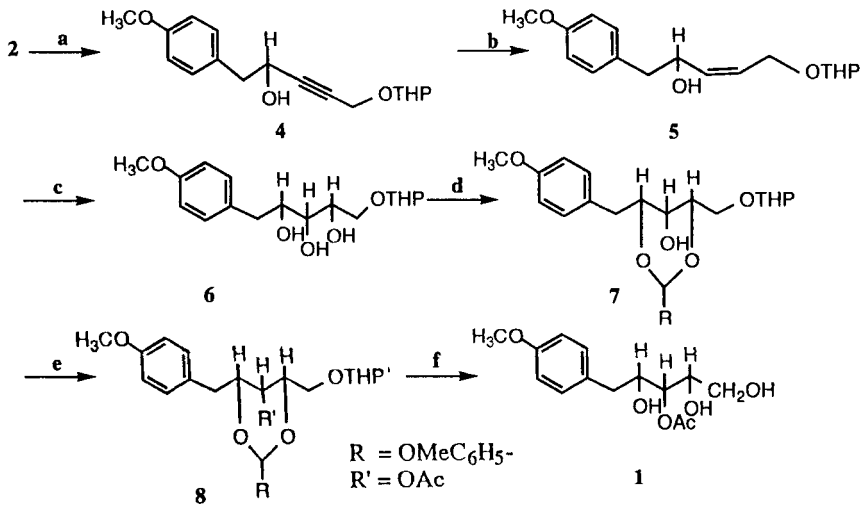
all its possible isomers. In this paper we describe the stereo flexible total synthesis of Karalicin from commercially available p-anisaldehyde.

Results and discussion

The synthesis began from p-methoxy-phenylacetaldehyde **2** which is easily accessible by a known procedure[4]. The aldehyde **2** was reacted with THP protected propargyl alcohol **3** to give **4**. This on stereospecific partial hydrogenation under Lindlar's conditions[5] afforded the olefin **5**.

Scheme



a. Propargyl alcohol/Bu-Li/THF/-78°C
b. H_2-Pd-$BaSO_4$/EtOH
c. OsO_4/NMO/t-BuOH:H_2O
d. p-Anisaldehyde dimethyl acetal/PTSA/CH_2Cl_2
e. Ac_2O/TEA/DMAP/CH_2Cl_2
f. MeOH/1% HCl

Dihydroxylation of **5** using OsO_4/NMO[6] gave triol **6**. At this stage the 1,3-diol was protected in the form of the PMB derivative[7] (p-methoxybenzylidene) **7**.

For operational simplicity, the secondary alcohol **7** was derivatised as acetate **8**, using Ac_2O/TEA. Final deprotection of THP ether and PMB derivative yielded the final molecule **1** whose spectral data including HRMS are in agreement with the reported data[1-2].

In conclusion a stereo flexible and first total synthesis of Karalicin is described starting from readily available precursers. The allyl alcohol intermediate **5** allows, in principle to utilise Sharpless asymmetric epoxidation[8] and dihydroxylation[9] techniques to provide all the possible stereoisomers for better understanding of SAR studies. Work in this direction is currently being undertaken.

Experimental Section

General Procedures: All reagent grade chemicals and solvents are purified with standard procedures and for all reactions using an extraction as a part of the work-up. The combined organic extracts were dried over Na_2SO_4 and the solvents removed in vacuo prior to chromatography, unless otherwise noted. Colum chromatography was performed on less than 0.08 mm, finer than 200 mesh silica gel and analytical thin layer chromatography was performed on precoated silica gel plates (60 F 254 Merck 595) and visualized with U.V. light. ^1H and ^{13}C NMR spectra were measured at 200 and 50 MHz (Varian Gemini) respectively in $CDCl_3$.

^1H chemical shifts are reported in δ (ppm) down field from TMS (0.0 ppm) as an internal standard. ^{13}C NMR shifts are reported in δ(ppm) measured relative to the centre resonance of $^{13}CDCl_3$ (77.00 ppm). J values are in Hertz, IR spectra were obtained as KBr pellets and the Mass spectra were obtained at VG auto spec-M- Mass spectrometer.

1-(4-Methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxy)-pent-3-yn-2-ol (4):

To a solution of THP ether **3** (0.924 g, 6.6 mmol) in dry THF (30 ml) was added 2.5N n-BuLi (2.9 ml, 2.5 M solution in hexane) at -78°C and stirred for 45 minutes. The aldehyde **2** (0.900 g, 6 mmol) was added slowly to the reaction mixture and stirred for further 2 h at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted wtih ethyl acetate (2 x 60 ml). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (4:1 hexane-ethyl acetate) to obtain acetylenic alcohol **4**.

^1H NMR ($CDCl_3$), δ (ppm): 1.40-1.90 (m, 6 H), 2.93 (d, 2 H, J = 6.9 Hz), 3.40-3.55 (m, 1 H), 3.8 (s, 3 H), 3.82-3.9 (m, 1 H), 4.21-4.3 (m, 2 H), 4.50-4.65 (m, 1 H), 4.75 (bs, 1 H), 6.83 (d, 2 H, J = 8.6 Hz), 7.19 (d, 2 H, J = 8.6 Hz).

^{13}C NMR ($CDCl_3$), δ (ppm): 18.82, 25.19, 30.04, 42.93, 54.04, 54.18, 55.08, 61.76, 63.10, 81.32, 86.50, 96.44, 113.64, 128.60, 130.61, 158.37.

1-(4-Methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxy)-pent-3(Z)-en-2-ol (5):

The mixture of acetylenic alcohol **4** (0.145 g, 0.5 mmol) catalytic amount of Pd-$BaSO_4$, quinolene (2 drops) and ethanol (1.5 ml) was stirred for 2 h at ambient temperature under H_2 atmosphere. The reaction mixture was filtered in ethanol was removed under vaccum and the residue was chromatographed on a silica gel column (4:1 hexane-ethyl acetate) to yield allyl alcohol **5**.

^{1}H NMR ($CDCl_3$), δ (ppm): 1.4-1.9 (m, 6 H), 2.7 (d, 2 H, J = 6.6 Hz), 3.4-3.55 (m, 1 H), 3.72 (s, 3 H), 3.79-3.82 (m, 1 H), 3.9-4.21 (m, 2 H), 4.5-4.65 (m, 2 H), 4.59 (d, 2 H, J = 2.36 Hz), 6.78 (d, 2 H, J = 8.6 Hz), 7.09 (d, 2 H, J = 8.6 Hz).

IR (KBr, cm^{-1}) : 3450

1-tetrahydropyranyl-5-(p-methoxyphenyl)-1,2,3,4-tetrahydroxy)-pentane-2,3,4-triol (6): To a solution of allyl alcohol **5** (0.090 g, 0.3 mmol) in t-BuOH:H_2O (1.5 ml 1:1) was added K_2CO_3 (0.127 g) and $K_3Fe(CN)_6$ (0.304 g) respectively and OsO_4 in water (0.02 ml) dropwise with the help of a microsyrange. Finally N-methyl morpholine N-oxide (0.03 g) was added to the reaction mixture and the stirred for 12 h at ambient temperature. The solvent from reaction mixture was removed under reduced pressure and the crude triol **6** was subjected to further transformation without purification.

m.p. 82°C, IR (KBr, cm^{-1}) : 3400-3600, E.A. calculated for $C_{17}H_{26}O_6$: C=62.55, H= 8.02; Found : C= 62.32, H= 7.90.

4-(4-methoxy-benzene)-2-(4-methoxy-phenyl)-6(tetrahydro-pyran-2-yloxymethyl)-[1,3]dioxan-5-ol (7): The triol **6** (0.080 g, 0.246 mmol) was dissolved in CH_2Cl_2 (1.5 ml) and catalytic amount of PTSA was added followed by the addition of benzaldehyde dimethyle acetal (1 ml). The reaction mixture was stirred for 12 h at ambient temperature. The solvent was removed under reduced pressure and the recidue was extracted with EtOAc (3x15 ml) the combined organic layers were washed with saturated solution of $NaHCO_3$, H_2O, brine and dried over Na_2SO_4 . The residue was chromatographed on a silica gel column (17:3 hexane-ethyl acetate) to afforded **7**. IR (KBr, cm^{-1}) : 3375.

4-(4-methoxy-benzene)-2-(4-methoxy-phenyl)-6(tetrahydro-pyran-2-yloxymethyl)-[1,3]dioxan-5-acetate (8):

To a solution of compound **7** (0.045 g, 0.101 mmol), Ac_2O (0.012 g, 0.01ml) and CH_2Cl_2 (2 ml) was added TEA (0.02 ml) and catalytic amount of DMAP, respectively. The reaction mixture stirred for 8 h at ambient temperature and diluted with CH_2Cl_2 (15 ml). The organic layer was washed twice with water, brine and dried over Na_2SO_4 . The solvent was evaporated and residue was chromatographed on a silica gel column (9:1 hexane-ethyl acetate) to afforded acetate **8**.

IR (KBr, cm^{-1}) : 1740

Mass calculated 486.5608 and ; Found : 486.4407

Karalicin 1: To a mixture of **11** (0.030 g, 0.06 mmol) and MeOH (1 ml) was added 1% HCl (0.6 ml). The reaction mixture was stirred for 11 h and neutralised with $NaHCO_3$. The reaction mixture was filtered through a small pad of celite and washed with MeOH. The filtrate was concentrated under reduced pressure and the residue was chromatographed on a silica gel column (3:1 hexane-ethyl acetate) to obtain **1**.

IR (KBr, cm^{-1}) : 1735, 3500 ; HRMS calculated : 284.1259; Found : 284.1272.

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3. The stereochemistry of the structure 1 is not mentioned intentionally to avoid ambiguities.

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