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The Facile Synthesis of Cyclopentanoid Antibiotic Kjellmanianone

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The synthesis of cyclopentanoid antibiotic Kjellmanianone is described in this study. The C-acylation of lithium enolates of 3-Methoxycyclopentenone by N-carbomethoxyimidazole or methylcyanoformate β-ketoester, which when oxidized with Mn(III) acetate produces kjellmanianone in good yield.

Introduction

The potential pharmacological importance of the cyclopentanone structure unit is the reactive functionality in a variety of structurally complex antitumor agents. Furthermore the number of natural products possessing α-hydroxymethyl-α,β-unsaturations having antitumor properties are known. Examples of these are glycalase 1 inhibitor 2- crotyloxylmethyl-4,5,6-trihydroxycyclohex-1-ene-3-one, the sesquiterpenoid lactone alliacol A, the diterpenoids[2] and kjellmanianone. Kjellmanianone, a member of the cyclopentanoid class of antibiotic, was isolated in 1980 by Nakayama et al[3] from the methanol extract of the marine algae *Sargassum kjellmanianum* and shows moderate activity against Gram-positive microorganisms such as *Esherichia coli* K12 and *Bacillus subtilisvar niger.* Structural assignments including the streochemistry were derived through spectroscopic measurements. Single crystal x-ray analysis elucidated the absolute configuration (R).

Experimental

All reagents were commerical quality solvents and were used without further purification. 1,3-cyclopentadione was purchased from the Aldrich Chemical Co, Ir spectra were recorded on a Philips model PU 9700 spectrometer. ^{1} H-NMR spectra were recorded on a Bruker AC 80 MHz-FT spectrometer. Melting points were determined by using a Buchi SMP-20 melting point apparatus and were left uncorrected.

(For the conversion of 1,3-cyclopentanedione to methoxycyclopentanedione a conventional procedure was used[4,5]).

5-Carbomethoxy-3-methoxy-2-cyclopenten-1-one(5)
To a solution of 11 mmol LDA in 40 ml THF at −78° C was added 896 mg (8 mmol) of 3-methoxy-2-cyclopentene-1-one **(4)** in 5 ml of THF. After the addition was complete the mixture was warmed to 0° C and stirred at this temperature for 30 min and then the reaction mixture was cooled to −78° C and a solution of N-carbomethoxyimidazole 883 mg (7 mmol) in 5 ml THF (or 10 mmol of methylcyanoformate in 5 ml of THF) was added, and stirred for 30 min. The mixture was poured into 1N HCI Solution and extracted with ether, washed with saturated NaCl solution and dried over magnesium sulfate. After removal of the solvent the crude product was purified by flash comlumn chromatography and the product **5** was obtained as a clorless solid, (829 mg % 61) (m.p. 53.0-55.5° C). The use of methylcyanoformate gave 63 % yield.

IR (KBr). 2980-3020, 1740, 1710, 1600 cm^{-1}.
^{1}H-NMR ($CDCl_3$) δ: 2.75-3.0 (m, 2H, CH_2), 3.56 (dd J=7 and 14 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.91 (s, 3H, CH_3) 5.32 (s, 1H, CH).
Anal. calc. for $C_8H_{10}O_4$: C, 56.47 H, 5.92, found: C, 56.67 H, 5.81.

5-Acetoxy-5-carbomethoxy-2-cyclopentene-1-one (Kjellmaniaone acetate) (6)
A mixture of 1.06 g (5 mmol) of manganese (III) acetate and 85 mg (0.5 mmol) of **5** in 30 ml of benzene was refluxed for 4 h under a Dean- Stark trap and examined by TLC. The mixture was cooled to 25° C, diluted with ethyl acetate, washed successively with 1 M aqueous HCI solution, saturated $NaHCO_3$ and $NaCl$ solution then dried over $MgSO_4$. The crude product was purified by PTLC using ether as a solvent. The product **6** was obtained (77 mg 68%) as a yellow solid m. p. 110- 113° C. (Lit. 113.0-115°)[6].

IR(KBr): 3010, 1710, 1590 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ: 2.18 (s, 3H, CH_3), 2.83-3.51(m, 2H, CH_2), 3.74(s, 3H, CH_3), 3.93 (s, 3H, CH_3), 5.96(s, 1H, CH).

5-Acetoxy-3-methoxy-2-cyclopentene-1-one (8)
A mixture of 2.12 g (10 mmol) of manganese (III) acetate and 224 mg (2 mmol) of **4** in 30 ml of benzene was refluxed for 3 h under a Dean- Stark trap and checked by TLC (EtoAc: hexane 1:3). The mixture was cooled to 25° C, diluted with ethyl acetate, washed successively with 1M aqueous HCl solution, saturated $NaHCO_3$ and NaCl solution then dried over $MgSO_4$. The crude product was purified by PTLC using EtOAc: hexane (1:3) as solvent. The evaportation of solvent afforded 285 mg (84%) of **8** as a yellow oil.

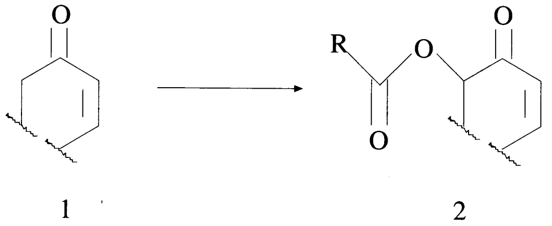
IR(neat): 1730, 1660, 1630 cm^{-1}
^{1}H NMR ($CDCl_3$) δ: 2.20 (s, 3H, CH_3), 2.39-2.41 (m, 2H, CH_2), 3.8 (s, 3H, OCH_3), 5.20(s, 1H, olef. H), 5.88 (dd, J=7 and 14 Hz, 1H, C-H).
Anal.calc.for $C_8H_{10}O_4$ (170.17) C, 56.47, H, 5.92; found: C, 56. 68, H, 5.77.

5-Carbomethoxy-5-hydroxy-2-cyclopentene-1-one (Kjellmanianone) (7)
0.5 gr K_2CO_3 in 15 ml of aqueous MeOH solution. 50 mg (0.2 mmol) of **6** was stirred with 0.5 gr K_2CO_3 in aqueous MeOH solution at room temperature for 50 min (TLC control). The mixture was extracted with EtOAc, dried over $MgSO_4$. The purification of crude product by PTLC afforded 27 mg (% 73) kjellmanianone **(7)** as a yellow solid. m. p.: 123-125° C (Lit. 126.0-128.0° C)[1,6].

IR (KBr): 3545, 3020, 2950 cm^{-1}.
^{1}H-NMR ($CDCl_2$) δ: 2.80-3.15 (m, 2H, CH_3), 3.76 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 5.36 (s, 1H, C-H).
^{13}C NMR ($CDCl_3$) δ: 41.1, 53.3, 58.9, 79.4, 101.3, 177.5, 191.7, 199.2.

Results and Discussion

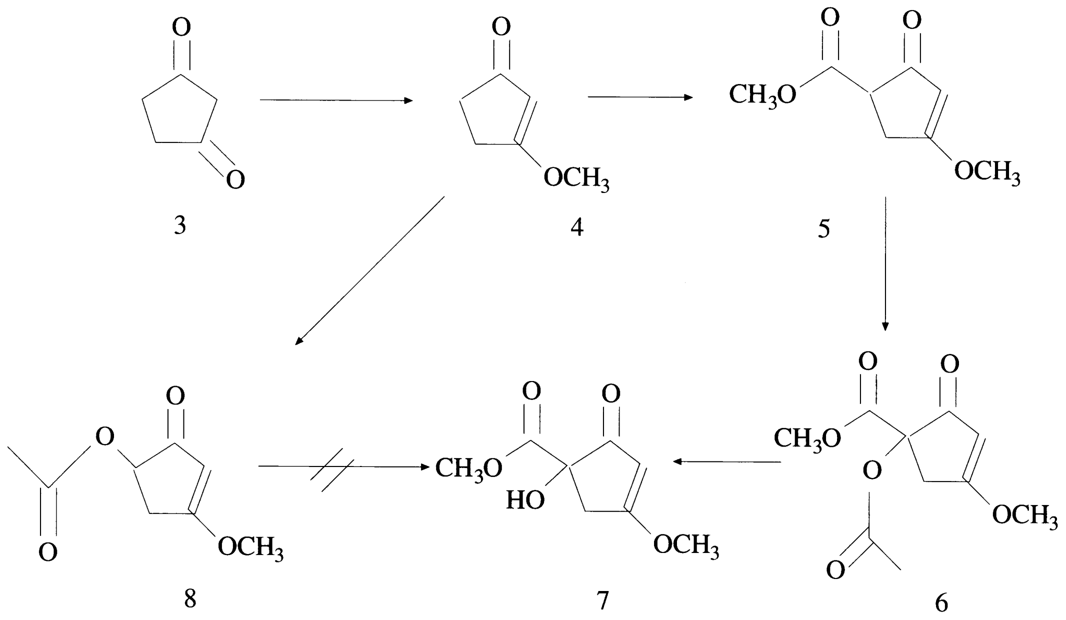
Kjellmanianone was synthesized from 1,3-cyclopentanedione. 1,3- cyclopentanedione, converted into its enolate and the acylation of the enolate with N-carbomethoxyimidazole gave the keto ester. The α- oxidation of the ketoester was carried out via the corresponding enolate with oxidizing agents m-CPBA and Davis' N-sulfonyl oxaziridines[6]. Irle et al used KF and molecular oxygen in dimethyl sulfoxide contaning 18- Crown-6 and triethylphosphite for the oxidation step[7]. The most important part of the procedures was the selective α-oxidation of enones. The procedure for the selective oxidation of common functional groups occupies a central position in the synthesis of complex natural products. Some years ago, in connection with our interest in the total synthesis of some terpenes, we required a procedure for the oxidation of an enone **1** to an α'-acetoxyenone **2** and due to unsatisfactory results to solve this problem (Scheme 1). This procedure was satisfactory for the preparation of α-acetoxyketones **2** ($R = CH_3$) and we subsequently investigated the extension of this oxidation procedure to a general synthesis of various α-acyloxyenones **2**[8].



Scheme 1.

This oxidation process exhibits the same regiochemical preference as that of the oxidation of β-alkoxy-$\alpha - \beta$-unsaturated ketones (α'-position) in good yield. We can now report the extension of this method to the synthesis of cyclopentanoid antibiotic kjellmanianone. From the retrosynthetic perspective 1,3-cyclopentanedione appears to be an ideal common intermediate. As shown in Scheme 2 the etherification of 1,3-cyclopentanedione **3** with trimethyl orthoformate in methanol gives 3-methoxy derivative **4** in 79% yield. This methoxycyclopentenone was also synthesized using the diketone **3** and HCl gas in methanol at 0° C[4,5]. This reaction gave **4** in 68% yield. For the acylation of enone **4** at α'-position lithium enolate was formed using LDA at $-78°$ C in THF[6]. The acylation of the formed Lienolate with N-carboxymethoxyimidazole afforded the acetyl enone **5** in 61% yield. The use of methyl cyanoformate as acylation reagent gives with Li-enolate acetyl enone **5** in 63% yield. The ^{1}H NMR spectrum shows the presence of only the keto form of **5** in $CDCl_3$ not the enol form. The proton at α'-position showed dd (J=7 and 14 Hz) and is equivalent to 1H. The oxidation of enone **4** at the α'-position using anhydrous manganese (III) acetate in benzene led to the desired acetyl kjellmaninone **6** in 73% yield This step was checked carefully by TLC (EtOAc: hexane 1:3) because long time reactions cause the polymerisation of the compounds. The mild saponification of acetate gave kjellmanianone in 78 % yield.

Another method for the synthesis of the target molecule is as follows enone **4** was first oxidized using manganese (III) acetate to obtain α'-acetoxyenone **8** in 84% yield. The acetylation reaction of this compound with N-carboxymethoxyimidazole and methyl cyanoformate in the presence of acid and base catalysts did not produce a reaction. Only the starting chemicals were isolated after the reaction.



Scheme 2.

Anhydrous manganese (III) acetate for oxidation was prepared from manganese (II) nitrate and acetic anhydride and dried over phosphorus (V) oxide prior to use. The mechanism of these oxidations remain uncertain. Several mechanisms are suggested for this oxidation. One might expect the formation of a metal enolate followed by acetate transfer to be analogous to the lead (IV) acetate oxidation proposed by Corey and Schaefer[9] for the acetoxylation reaction of ketones.

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