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A Short Synthesis of (±) - Methylenolactocin

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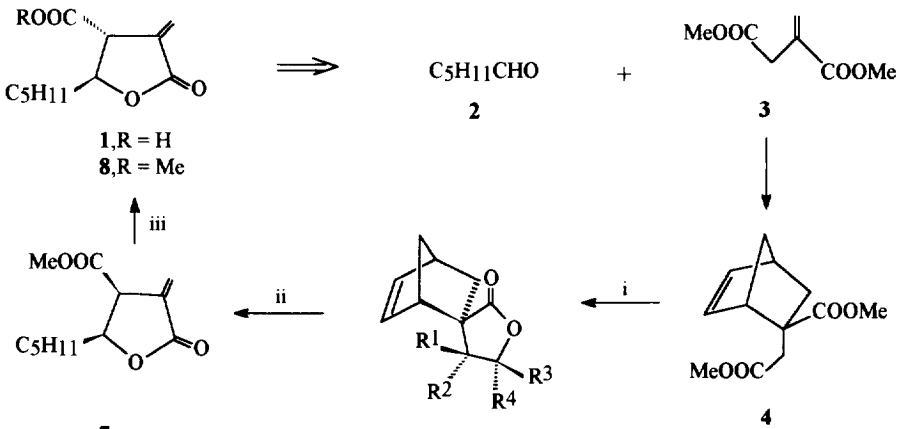
Abstract : *A short synthesis of the antitumor antibiotic methylenolactocin 1 and the first synthesis of the methyl ester of its cis analogue 7 are described.* Copyright © 1996 Elsevier Science Ltd

Methylenolactocin **1** , isolated from the culture filtrate of *Penicillium sp*[1] , is an antitumor antibiotic.It contains a highly isomerisation prone α - methylene - γ - butyro lactone as the basic structural unit. The pharmacological importance and isomerisation prone nature of this compound made it an attractive synthetic target. Several multistep syntheses have recently been accomplished both in enantioselective[2] and racemic[3] forms. We here report a short facile synthesis of (±) - methylenolactocin and the first synthesis of the methyl ester of its cis analogue.

We envisaged that coupling of the ester enolate derived from dimethyl itaconate **3** with hexanal **2** might offer a direct approach to **1** .However, such an attempt resulted in a complicated mixture of products probably arising from all the possible carbanionic intermediates available through isomerisation of the initially formed



5, R^1 = COOMe, R^2 = R^4 = H, R^3 = C_5H_{11}

6, R^1 = COOMe, R^2 = R^3 = H, R^4 = C_5H_{11}

Reagents : i,LDA, THF , -78 ° C, $C_5H_{11}CHO$, 79 % ; ii, FVT at 550 ° C (0.005 mm),92 %; iii, 6N HCl, butanone, reflux, 3h, 71%.

carbanion from **3.** We , thus , considered the possibility of using the cyclopentadiene-dimethyl itaconate adduct **4**,[4] for coupling and finally removing cyclopentadiene to generate the methylene unit. Treatment of the dimethyl ester **4** with 1.5 equivalent of LDA in THF at -78^0 C followed by exposure of the resulting enolate to hexanal **2** effected smooth C-C bond formation with spontaneous lactonisation to afford a solid (mp 91^{0}C;IR 1780, 1740 cm^{-1}) in 79% yield as a mixture of two components (ca.2:1) from ^{1}H NMR.[5] These lactones are resistant to equilibriation with DBU . The stereochemical assignment to the major and minor lactones as cis - **5** and trans - **6** respectively is based on their transformation to methylenolactocin as follows . Flash vacuum thermolysis of this mixture afforded a mixture of two exo methylene lactones **7** and **8**(IR 1770, 1740 cm^{-1}) in 92% yield in the ratio (ca. 2:1) identical to that of the lactones **5** and **6** . The identity of the minor component **8** with the methyl ester [2e] of methylenolactocin as indicated by comparison of ^{1}H NMR spectral data confirmed **6**, the precursor of **8**, to be the structure of the minor lactone . Hydrolysis of the mixture of the exo methylene lactones **7** and **8** in refluxing butanone with 6N HCl according to Weavers[2e] effected, as expected, epimerisation [3] of the cis isomer **7** to afford methylenolactocin [6] in 71% yield as a liquid. The major cis-lactone **5** could be separated by repeated fractional crystallisation of the mixture of **5** and **6** and was converted on thermolysis to the methyl ester of the cis- analogue of methylenolactocin **7** in 90 % yield.

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4. The exclusive exo adduct **4** can be prepared from Diels- Alder reaction of itaconic anhydride with cyclopentadiene followed by hydrolysis and esterification (Fotiadu, F. ; Michel, F.; Buono, G. *Tetrahedron Lett.* **1990,** *31,* 4863.).
5. ^{1}H NMR spectral data : **5** and **6** (as mixture), δ(60 MHz,CCl_4) 0.91(br s, 3H),1.38(br, 10H), 1.83-2.30(m, 2H) ,2.58 and 2.73 (both d, J = 3Hz, 1H), 2.93 (br s, 2H), 3.63 and 3.76 (both s, 3H), 4.0-4.63(m, 1H) and 5.83 - 6.53(m, 2H).7 , δ(200MHz) 0.88(t, J = 6 Hz, 6H),1.29(m, 6H), 1.58(m,2H), 3.75 (s, 3H), 4.59 (m,1H), 5.81 (d, J = 2Hz ,1H) and 6.40(d ,J = 2Hz, 1H). **1,**δ (200 MHz) 0.89(brs, 3H), 1.20-1.75 (m, 8H),3.60(m, 1H), 4.80(q, J = 6.4Hz), 6.00 (d, J = 2.6Hz) and 6.44 (d, J = 2.6Hz, 1H).
6. ^{1}H NMR spectrum of methylenolactocin thus obtained was compared and found identical with ^{1}H NMR reported (ref . 3) by Roy et al of this laboratory.

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