Total Synthesis of an Antitumour Antibiotic, (±)-Reductiomycin

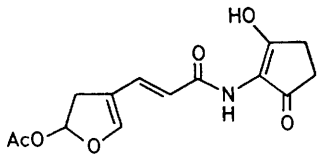
Makoto Ojika, Haruki Niwa, Yoshikazu Shizuri, and Kiyoyuki Yamada*

Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

The title synthesis has been achieved starting from 3-hydroxymethylfuran.

Reductiomycin (**1**) is an antibiotic, which shows activity against tumours,[1] gram-positive bacteria,[2] fungi,[2] and Newcastle disease virus.[2] While the structure of reductiomycin has been reported to be (**12**), based on *X*-ray crystallography,[3] we have shown by chemical and spectroscopic data that the structure is (**1**),[4] and we have now confirmed this by synthesis.

Oxidation of 3-hydroxymethylfuran (**2**)[5] with lead(IV) acetate (AcOH, room temperature, 14 h) gave a mixture of



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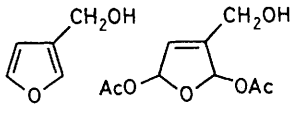
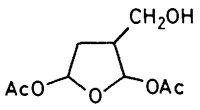


(2) (3)



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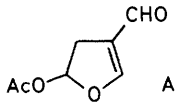
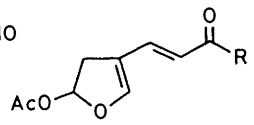


(5)



(6) R = OCH_2CCl_3
(7) R = OH
(8) R = Cl

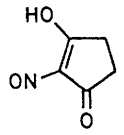
stereoisomeric diacetoxy-compounds (**3**)†‡ [colourless oil, 90% after purification by chromatography over silica gel with EtOAc–benzene (1 : 2)]. The mixture of stereoisomers (**3**) was hydrogenated (5% Rh–Al_2O_3, EtOAc, room temperature, 14 h) to afford a mixture of the stereoisomeric tetrahydrofuran (THF) derivatives (**4**)†§ [colourless oil, 62% after purification by chromatography over silica gel with EtOAc–benzene (1 : 1)]. Subsequently a mixture of the stereoisomers (**4**) was oxidized (CrO_3·2py, CH_2Cl_2, room temperature, 10 min), yielding a conjugated aldehyde (**5**)†‡ as a colourless oil, which was employed in the next reaction without purification.

The Wittig reaction of (**5**) with a phosphorane (**11**)[6] (benzene, reflux, 14 h) gave a conjugated ester (**6**)†‡ [colourless oil, 48% from (**4**) after purification by chromatography over silica gel with EtOAc–hexane (1 : 4)], which was converted by reduction with powdered zinc [AcOH–H_2O (9 : 1), room temperature, 4 h] into the corresponding carboxylic acid (**7**),†‡ m.p. 182—183 °C (57% after recrystallization from benzene–$CHCl_3$). The carboxylic acid (**7**) was converted on treatment with oxalyl chloride (40 °C, 5 min) into the acid chloride (**8**) (oil), which was used immediately in the next reaction.

† The i.r., n.m.r. and mass spectral data for the new racemic compound(s) were in accord with the structure(s) assigned.

‡ Satisfactory microanalyses or high resolution mass spectral data were obtained.

§ During the catalytic hydrogenation, a conjugated aldehyde (**5**) was found to be formed, though in low yield (2—5%), by Rh-catalysed isomerization of the double bond of (**3**) and subsequent elimination of AcOH; however, (**5**) was further reduced to a saturated aldehyde at the end of the hydrogenation reaction.



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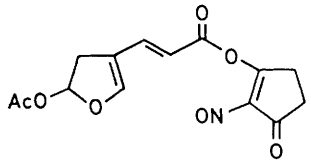
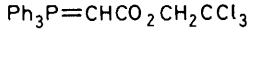
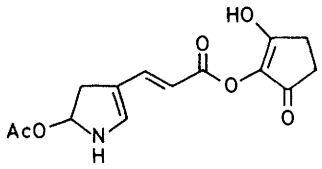


(10)



(11)



(12)

3-Hydroxy-2-nitrosocyclopent-2-en-1-one (**9**)[7] was allowed to react with the acid chloride (**8**) (*ca.* 4 mol. equiv.) [pyridine (*ca.* 4 molar equiv.)–THF, −30 °C to 0 °C, 20 min] to give an enol ester (**10**),¶ which, without isolation, was subsequently reduced with powdered zinc (−30 °C to room temperature, 1.5 h and room temperature, 1.5 h) and further treated with powdered zinc in acetic acid containing a trace amount of conc. hydrochloric acid (room temperature, 3 h), affording, through intramolecular O → N acyl migration, (±)-reductiomycin (**1**),† m.p. 211—213 °C (from MeOH) [*ca.* 20% based on (**9**) after purification by preparative t.l.c. on silica gel with benzene–acetone (2 : 1)], spectroscopically (i.r., n.m.r., and mass) and chromatographically identical with natural reductiomycin.

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¶ Assuming that the nitroso-compound (**9**) exists as a β-hydroxy-α,β-unsaturated keto-form, acylation of (**9**) using (**8**) would result in the formation of the enol ester (**10**); unambiguous structural assignment for this intermediate (**10**) based on the spectral data could not be made owing to its instability.