Synthesis of the Upper Fragment of Tetronolide

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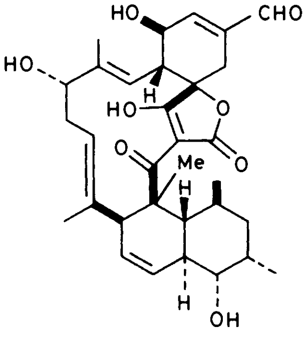
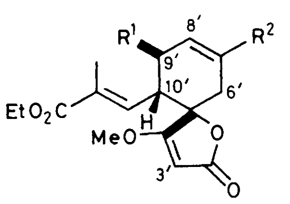
A stereoselective synthesis of the upper fragment (**4**) of tetronolide (**1**) was achieved *via* catalytic osmylation of the dienol acetate (**10**) derived from the spirotetronate (**3**).

We recently reported the synthesis of the upper fragment of the spirotetronate models (**2**) and (**3**) of tetronolide (**1**),[1] the aglycone of the novel macrolide antibiotic tetrocarcins.[2] Our continued efforts directed towards the total synthesis of (**1**) have now yielded the first synthesis of the actual upper fragment (**4**).



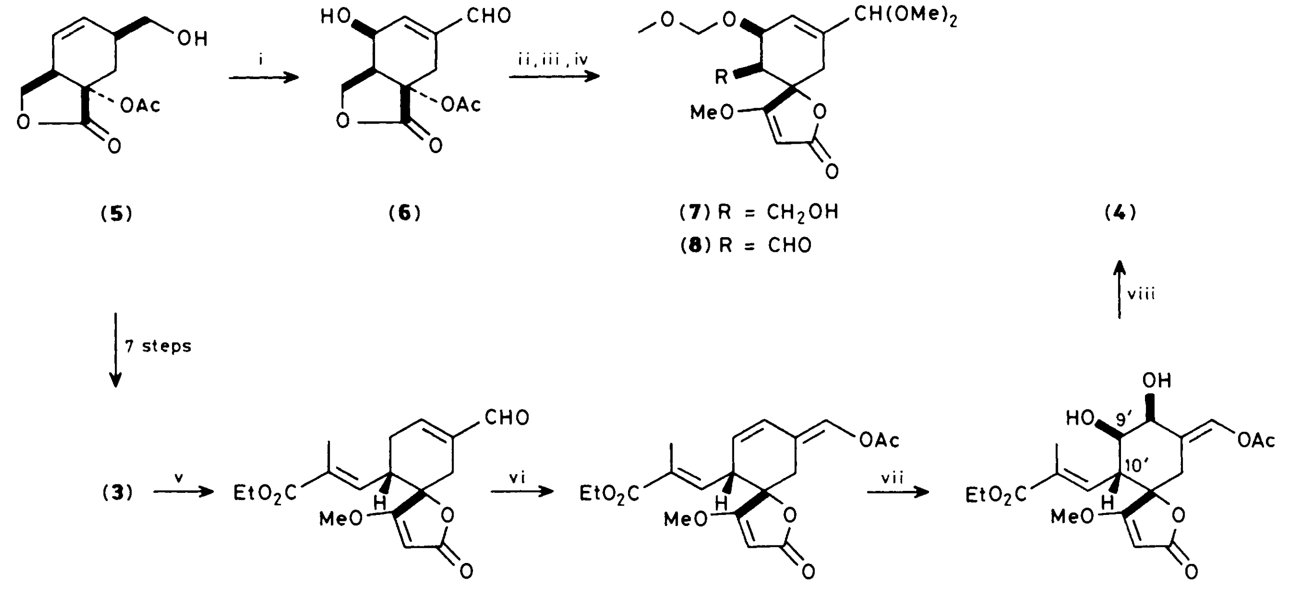
(**1**)



(**2**) $R^1 = R^2 = H$
(**3**) $R^1 = H$, $R^2 = CH_2OCH_2OMe$
(**4**) $R^1 = OH$, $R^2 = CHO$

The starting material in our initial plan for the synthesis of (**4**) was the bicyclic homoallyl alcohol (**5**) which had been previously employed as the precursor of (**3**).[1] The required γ-hydroxy-$\Delta^{\alpha,\beta}$-aldehyde system was readily established by stereoselective epoxidation with *m*-chloroperbenzoic acid (MCPBA) followed by Swern oxidation to provide compound (**6**), which was then transformed into the protected spirotetronate (**7**) by the sequence of reactions in Scheme 1 involving an intramolecular Claisen condensation of the α-acetoxy-γ-lactone group. Attempted oxidation of (**7**) to the aldehyde (**8**) by Swern's procedure[3] or with pyridinium chlorochromate (PCC),[4] the aldehyde being required for elongation of the side chain, resulted in concomitant loss of the $MeOCH_2O$ group presumably by β-elimination.

Since initial experiments indicated that the hydroxy group should be introduced after formation of the full skeleton of the upper fragment, we turned our attention to the spirotetronate (**3**)[1] for its stereoselective allylic hydroxylation leading to (**4**). Thus, the methoxymethyl protecting group in (**3**) was removed in the usual manner and the alcohol produced was subjected to Swern oxidation to give the aldehyde (**9**) in 55—60% yield. We envisaged here that regio- and stereoselective introduction of the hydroxy group to (**9**) could be achieved by peracid oxidation of the corresponding dienol



Scheme 1. All compounds are racemic. *Reagents:* i, MCPBA, $NaHCO_3$, CH_2Cl_2, then Me_2SO, $(COCl)_2$, Et_3N; ii, pyridinium toluene-*p*-sulphonate, MeOH, then $ClCH_2OMe$, Pr^i_2NEt, CH_2Cl_2, 68% from (**5**); iii, $KN(SiMe_3)$ tetrahydrofuran (THF), −80 °C to room temp., then Bu^n_4NOH, Me_2SO_4, 29%; iv, pyridinium toluene-*p*-sulphonate, MeOH, 89%; v, 1% aq. HCl–MeOH, reflux, 1 h, then Me_2SO, $(COCl)_2$, Et_3N, 55—60%; vi, Ac_2O (large excess), Me_3SiCl, NaI, 60 °C, 1 h, 99%; vii, OsO_4 (0.05 equiv.), *N*-methylmorpholine *N*-oxide (1 equiv.), Bu^tOH, H_2O–acetone, reflux, 1 h, 58%; viii, 5% HCl, EtOH–CH_2Cl_2 (1 : 3), 64%.

acetate (**10**).[5] Conversion of (**9**) into (**10**)† with acetic anhydride was achieved in quantitative yield in the presence of chlorotrimethylsilane and sodium iodide at 60 °C,[6] though the reaction was extremely sluggish with the standard procedure using protic acid[7] or 4-*N*,*N*-dimethylaminopyridine (DMAP)[8] as catalyst. Exposure of (**10**) to MCPBA or *p*-nitroperbenzoic acid under a variety of conditions resulted unexpectedly in either recovery of the substrate (**10**) or formation of a complex mixture of unidentifiable products. On the other hand, catalytic osmylation[9] was found to be more selective. Thus, under controlled conditions (step vii, Scheme 1) the diol (**11**)‡ was obtained in 58% yield based on recovered starting material (36%). Prolonged reaction was not beneficial, resulting merely in an increase in decomposition products. Finally, transformation of (**11**) into (**4**) was most readily achieved (64% yield) by treatment with 5% HCl in EtOH–CH_2Cl_2 (1 : 3) at room temperature for 1.5 h.§ The structure of compound (**4**), m.p. 159—160 °C, was fully characterized by spectral data and elemental analyses [^1H n.m.r. (270 MHz, $CDCl_3$) δ 1.29 (t, *J* 7.1 Hz, 3H, OCH_2Me), 1.90 (d, *J* 1.7 Hz, 3H, 2-Me), 2.22 (d, *J* 5.4 Hz, 1H, OH), 2.48 (d, *J* 18.6 Hz, 1H, H-6′), 2.78 (dt, *J* 18.6, 2.7 Hz, 1H, H-6′), 3.02 (dd, *J* 10.7, 9.8 Hz, 1H, H-10′), 3.85 (s, 3H, OMe), 4.19 (m, 2H, OCH_2Me), 4.74 (br. m, 1H, H-9′), 5.07 (s, 1H, H-3′), 6.45 (dm, *J* 10.7 Hz, 1H, H-3), 6.84 (d, *J* 0.7 Hz, 1H, H-8′), and 9.57 (s, 1H, CHO); i.r. (KBr) 3400, 1770, 1710, 1675, and 1635 cm^{-1}; *m/z* 336 (M^+), 318 ($M^+ - H_2O$), and 32 (100%)].

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† The (*E*) geometry of the acetoxymethylene group was deduced from ^1H n.m.r. spectroscopy by observation of a nuclear Overhauser enhancement of the H-8′ proton on irradiation of the vinyl proton (and *vice versa*).

‡ The *trans*-relationship of the C-9′ hydroxy group and the C-10′ side chain was determined by ^1H n.m.r. analysis ($J_{9',10'}$ 10.6 Hz).

§ Under alkaline conditions lower yields of (**4**) were obtained.

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