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VINYLIC CARBANIONS IN SYNTHESIS. NOVEL SYNTHESES OF ISO-GREGATIN B, ISO-ASPERTETRONIN A AND RELATED O-METHYL TETRONIC ACIDS

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Summary: Reaction between the octadienone (8) and the vinylic carbanion (6) derived from (5) leads, in one step, to the O-methyl tetronic acid (9). Metallation of (9), followed by treatment of the resulting α-vinylic carbanion with methyl acetate and with methyl E-butenoate then gives the acylated O-methyl tetronic acids (12) and (14) respectively which are shown to be enol ether isomers of the natural products gregatin B and aspertetronin A found in Aspergillus sp. and Cephalosporium gregatum.

Demonstrations of the utility of vinylic carbanions in synthesis have burgeoned in the past two decades.[1] In the previous Letter we showed that lithium diisopropylamide (LDA) removes the α-proton from the O-methyl tetronic acid (1) in a totally regiospecific manner, giving the vinylic carbanion (2).[2] This anion was then found to react readily with a range of electrophiles (eg. MeI, Me_3SiCl, ArCHO, RCO_2Me) at -78° in tetrahydrofuran, to provide a preparatively useful procedure for the synthesis of the corresponding α-substituted O-methyl tetronic acids. In the specific case of methyl propenoate only the product of 1,2-addition (i.e. 3) was obtained. We have now combined this last result with the recent report[3] of a one-step synthesis of O-methyl 2-methyltetronic acids from metallated E-3-methoxy-2-methylpropenoate and aldehydes, to provide an exceptionally short synthesis of the substituted tetronic acid ring system (4). This ring system is found in aspertetronin A (14),[4] gregatin B (12)[5] and related compounds, isolated from Aspergillus sp. and from Cephalosporium gregatum. The overall design is shown in the Scheme.

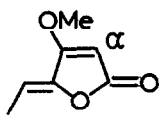
Studies by Schmidt et al[6] have shown that metallation of ethyl E-3-methoxypropenoate (5) with LDA at -90° is highly regioselective (>95%) leading to the vinylic carbanion (6) (2 mins); although within 2.5 h at -90° a 2:1 mixture of (6) and the corresponding vinylic carbanion (7) is established. Accordingly, metallation of (5) was carried out at -78° (LDA in THF), and the resulting vinylic carbanion (6) was treated with the E,E-octadienone (8) within one minute.

The mixture was kept at -78° for 1 h, then allowed to warm to 0° when it was quenched with dilute hydrochloric acid. The usual work up, followed by chromatography, then gave the O-methyl tetronic acid (9; 45%) as an oil, b.p. 110° (oven)/0.05 mm Hg, λ_{max} (EtOH) 224 nm, ν_{max} (film) 1758, 1638 cm^{-1}, τ3.56 - 4.3 (m, 3H), 4.49 (d, J 17, :CH.CMe), 5.08 (:CHCO), 6.16 (OMe), 7.95 (m, 2H), 8.49 (Me), 9.05 (t, J 7.5, CH_2CH_3) whose structure followed from its spectral data.[8] In some experiments, using excess LDA and longer periods for the metallation of (5) the yield of (9) was greatly reduced and significant amounts of the by-products (10) and (11) were separated by chromatography.

Metallation of (9) using LDA at -78°, followed by acylation of the resulting vinylic anion (CH_3CO_2Me,-78°), as expected from our previous investigations[2] led exclusively to the product (12) (19%), a pale yellow oil b.p. 110° (oven)/0.01 mm, λ_{max} 227 nm. ν_{max} 1755, 1685, 1660, 1612 cm^{-1}, τ3.5 - 4.3 (3H), 4.51 (d, J 17, :CHCMe), 5.88 (OMe), 7.47 (COMe), 7.93 (m 2H), 8.46 (Me), 9.05 (t, J 7, CH_2CH_3), δ(carbon) 13.2 q, 23.4 q, 25.7 t, 30.6 q, 63.7 q, 82.4, 103, 126.3 d, 127.6 d, 132.3 d, 139.9 d, 169.5, 183.9, 195.1 p.p.m. of α-substitution in (9). The same O-methyl tetronic acid (12) was also obtained from (9) in two stages following reaction of the desired anion with acetaldehyde (84%), and oxidation of the resulting carbinol (13), ν_{max} 3425, 1740, 1650 cm^{-1}, τ5.07 - 5.28 (CHOH), 6.35 (OH), 8.53 (d, J 6, CH_3CHOH) with pyridinium dichromate in DMF (48%).

In a parallel series of reactions, the (α-) vinylic anion produced from (9) and LDA was treated with methyl E-2-butenoate and with E-2-butenal leading to the O-methyl tetronic acids (14), [an oil λ_{max} 225 nm, ν_{max} 1762, 1750, 1675, 1655, 1625, 1603 cm^{-1}, τ 2.9 - 3.47 (m, 2H), 3.54 - 4.58 (m, 4H), 6.02 (OMe), 7.97 (m, 2H), 8.14 (d, J 6, :CHMe), 8.49 (Me), 9.09 (t, J 7.5, CH_2CH_3); δ(carbon) 13.2 q, 18.4 q, 23.4 q, 25.7 t, 62.8 q, 82.7, 102.5, 126.7 d, 127.7d, 131.4 d, 132.3d, 139.6 d, 145.6 d, 169.3, 183.3, 186.9 p.p.m.] and (15) respectively. Subsequent oxidation of (15), using pyridinium chlorochromate, did not however give (14), but instead led to the isomeric enone (16), λ_{max} (EtOH) 282 nm, τ 2.46 (d, J 15.5, CH:CHCOMe), 2.66 (d, J 15.5, CH:CHCOMe), 5.75 (OMe), 7.73 (COMe), resulting from oxidation of the transposed allylic alcohol corresponding to (15).

The O-methyl tetronic acids (12) and (14) are the structures proposed for two members of a family of biologically active metabolites known as aspertetronins, gregatins or graminins isolated from Aspergillus rugulosus, A.panamensis, Cephalosporium gregatum and C. gramineum.[4,5,9,10] Inspection and comparison of the spectral data (uv, ir, pmr) obtained for synthetic (12) and (14) with those reported for the corresponding natural products (i.e. gregatin B and aspertetronin A respectively) showed however that the natural products did not have the structures (12) and (14)! Indeed, correlation of the sets of spectral data, with those of model compounds, support the alternative enol ether formulation [i.e. 5-methoxy-3(2H)-furanone] for the natural compounds (see accompanying Letter).[11] We therefore propose the



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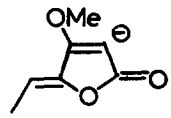

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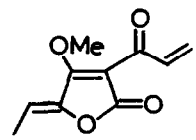

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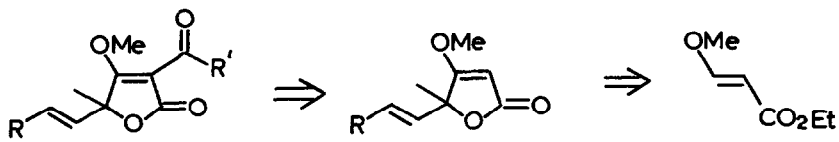
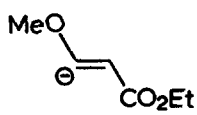


(4) (5)

Scheme



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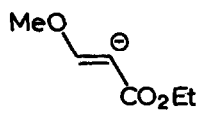

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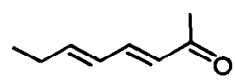

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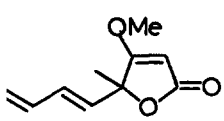

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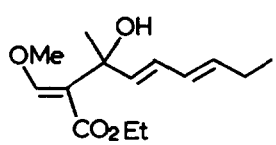

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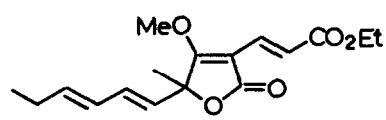

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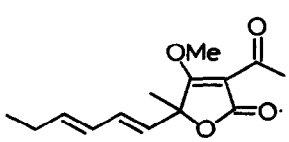

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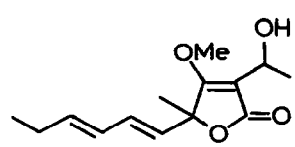

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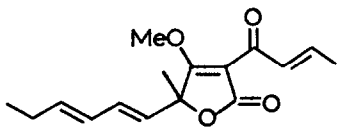

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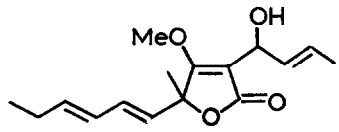

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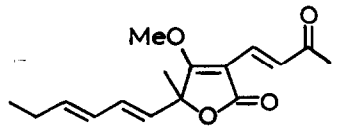

(16)

names iso-gregatin B and iso-aspertetronin A for the synthetic O-methyl tetronic acids (12) and (14) respectively.

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