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SYNTHESIS OF CYCLOPENTANOID NATURAL PRODUCTS VIA VINYL PHOSPHONIUM SALTS

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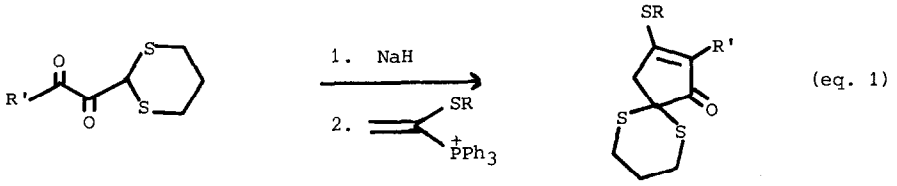
Cyclopentenones obtained from cyclisations involving phosphonium salts are converted to dihydrojasmone, dihydrojasmolone and known precursors of methylenomycins A and B.

We have recently described a method for the synthesis of highly functionalised cyclopentanes[1] (eq. 1) and the use of such a sequence in the preparation of prostaglandins.[2]



(eq. 1)

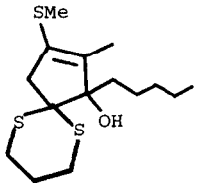
1; R = R' = Me

7; R = Me, R' = C_5H_{11}

This paper describes the use of the products of (eq. 1) as starting materials for a number of cyclopentanoid natural products and an extension of the method to prepare a precursor to methylenomycin A.

The carbonyl group of 1 was rather unreactive towards Grignard reagents but reacted with n-pentyl lithium giving the allylic alcohol 2 which was not isolated but immediately rearranged with acid to give the enone 3 (80%; m.p. 46-48 °C, IR (KBr) 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$)δ 0.4-1.7, m, 9H; 1.78, s, 3H; 1.9-2.5, m, 8H; 3.2, s, 2H). Reduction of the free carbonyl group in 3 with sodium borohydride gave 4 (85%; oil; IR (neat) 3300, 1670 cm^{-1}) which with N- chlorosuccinimide/silver nitrate[3] gave 5 (45%) whose IR and NMR

spectra corresponded to those described for dihydrojasmolone.[4]



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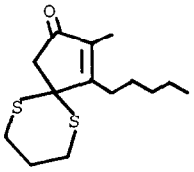

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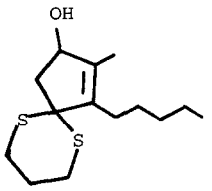

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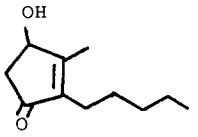

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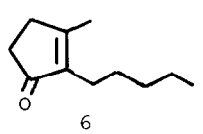
All attempts to reduce the free carbonyl group of 3 or the secondary hydroxyl group of 4 to methylene, to give a precursor to dihydrojasmone, 6, were unsuccessful. We therefore began our approach to dihydrojasmone from 7. This was obtained by alkylation of methyl dimethoxyacetate with 1-iodopentane[1,5] giving 8 (52%; oil; IR (neat) 1750 cm^{-1}) which was reacted with the anion of dithiane to give 9 (85%; oil; IR (neat) 2850, 1715 cm^{-1}). The ketal group of 9 was hydrolysed with moist trifluoroacetic acid to afford the diketodithiane 10 (89%; bright yellow oil; IR (neat) 1710 cm^{-1}). The anion of 10 (sodium hydride) reacted with our methylthiovinyl phosphonium salt[1] to give the cyclopentenone 7 (65%; oil; IR (neat)).

Reaction of 7 with methyl lithium followed by addition of aqueous acid gave the enone 11 (85%; m.p. 41-42 °C; IR (KBr) 1700, 1640 cm^{-1}) which was desulphurised with Raney nickel (acetone/ethanol, room temperature, 4 hours) to give dihydrojasmone, 6 (82%) whose spectra corresponded to those described.[6]



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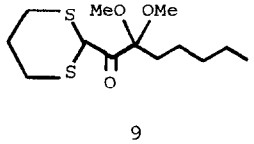

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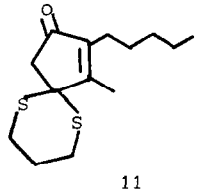

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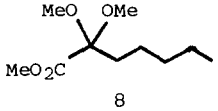

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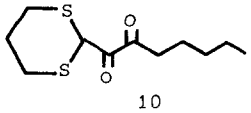

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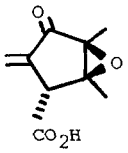
The antibiotics methylenomycins A and B, 12 and 13 have been obtained from the cyclopentenones 14 and 15 respectively.[7] We felt that 14 and 15 should be available from 1. Thus reaction of 1 with methyl lithium followed by addition of aqueous acid gave enone 16 (82%; m.p. 85-87 °C; (KBr) 1710, 1640 cm^{-1}) which



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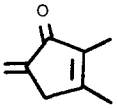

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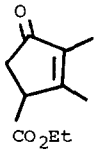

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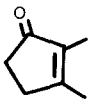

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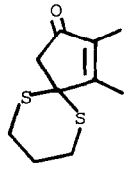
was desulphurised to afford 15 (78%). Alternatively reaction between 1 and Me_2CuLi (ether/dichloromethane, -78 °C) gave 17 (81%; oil; IR (neat) 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 , br s, 3H; 2.0, s, 3H; 2.1-2.7, m, 6H; 3.7-4.2, m, 2H) which could also be desulphurised to give 15 (83%). In order to obtain 14 we attempted to functionalise the methylene group of 1. Unfortunately, treatment of 1 with LDA, followed by addition of monomeric formaldehyde gave 18 (32%; m.p. 98-100 °C; ^1H NMR ($CDCl_3$) δ 1.3, s, 3H; 1.9-2.8, m, 4H; 3.4-3.9, m, 4H; 5.35, s, 1H), the result of reaction at the α-position of the anion, as the only isolated product.

However methylenomycin A has also been obtained from cyclopentenone 19[8] which we felt should also be obtainable from vinyl phosphonium salt methodology. A mixed Claisen condensation between methyl 2,2-dimethoxypropionate and methyl



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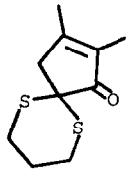

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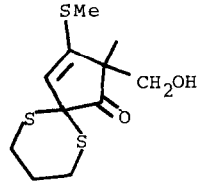

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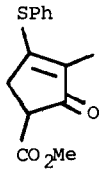
acetate[9] gave the ketal ester 20 which was hydrolysed with c. hydrochloric acid to give diketoester 21 (80% overall) whose ^1H NMR spectrum showed it to exist completely in the enol form in chloroform solution. (δ 2.4, s, 3H; 3.7, s, 3H; 5.9, s, 1H; 11.6, s, 1H). Formation of the anion of 21 (NaH/THF) followed by addition of our phenylthiovinyl phosphonium salt gave 19 (21%; m.p. 69-71 °C, lit[8] 69-71.5 °C).



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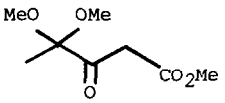

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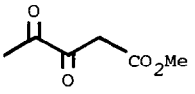

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The syntheses of 15 and 19 constitute formal total syntheses of methylenomycins A and B.

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