Model Studies on the Synthesis of Milbemycin β_3

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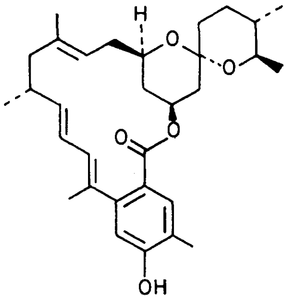
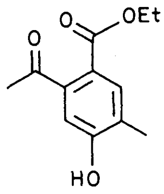
Summary 2,4-Di(lithio-oxy)penta-1,3-diene and 2,4-di(lithio-oxy)-3-methylpenta-1,3-diene condensed with tetrahydropyran-2-one to give 2-methyl- and 2,3-dimethyl-1,7-dioxaspiro[5.5]undec-2-en-4-one; subsequent reduction gave the derived alcohols ($LiAlH_4$) and 2,3-dimethyl-1,7-dioxaspiro[5.5]undec-3-ene ($LiAlH_4$–$AlCl_3$); the milbemycin β_3 unit ethyl 2-acetyl-4-hydroxy-5-methylbenzoate was prepared from ethyl 2-(4-chlorophenylthio)-4-oxopent-2-enoate and (*E*)-1-methoxy-2-methyl-3-trimethylsilyloxy-buta-1,3-diene *via* a Diels–Alder reaction.



(1)



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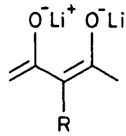
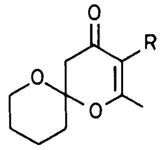


(3)
a; R = H
b; R = Me



(4)
a; R = H
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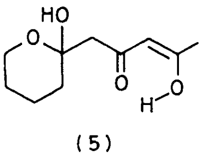

(5)

The avermectins[1] are noted for their most potent anthelmintic properties. The milbemycins,[2] including milbemycin β_3 (**1**) are structurally related pesticidal antibacterials. Herein we report model studies directed towards the construction of the spiro-acetal system and the synthesis of the milbemycin β_3 unit (**2**).

We considered that a concise novel route to the spiro-acetal unit should be available by the condensation of a lactone and β-dione dianion. As a model study, tetrahydropyran-2-one was condensed with the dianion (**3a**)[3] in tetrahydrofuran (THF) at -78 to 0 °C to give the β-dione (**5**)† (95%) or the spiro-dihydropyrone (**4a**) (88%), m.p. 56—57 °C, on acetic or toluene-4-sulphonic acid work-up respectively. In the same way, tetrahydropyran-2-one and the dianion (**3b**) gave the spiro-dihydropyrone (**4b**) (68%). Both adducts (**4a** and **b**)† were unambiguously spiro-cyclic; for example, (**4a**) exhibited ν_{max} (film) 1720w, 1670s, and 1620s cm^{-1}, λ_{max} (MeOH) 260 nm (ϵ 11,000) [2,3-dihydro-2,2,6-trimethylpyran-4-one 266 nm (11,800)[4]], δ (^1H) ($CDCl_3$) 5·37 (1H, s, 3-H), 3·72 (2H, m, 8-CH_2), 2·6 and 2·5 (2H, ABq, *J* 15 Hz, 5-CH_2), and 2·03 (3H, s, 2-Me), *m/e* 182 (M^+), 167, and 98 (retro-Diels–Alder).

Both spiro-compounds (**4a** and **b**) were reduced with lithium aluminium hydride in THF at 0 °C to give the expected alcohols (**6a**, 2:1 mixture of epimers) (90%) and (**6b**, 5·8:1 mixture of epimers) (88%). Alternatively, addition of the spiro-compound (**4b**) to lithium aluminium hydride in THF at 0 °C followed by inverse addition to lithium aluminium hydride and aluminium chloride (1:4)

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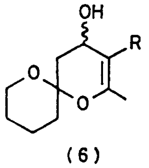
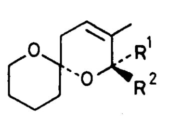
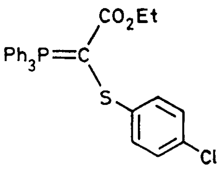
† All new compounds were fully characterised by spectral data and microanalyses. The alcohol (**6b**) and olefin (**7b**) were not obtained microanalytically pure although all other data were consistent with the structural assignments.



(6)
a; R = H
b; R = Me



(7)
a; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H



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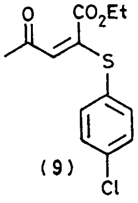

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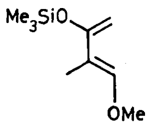

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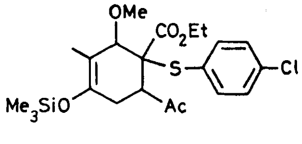

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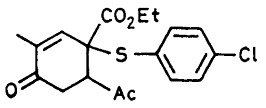

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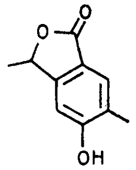

(13)

in THF at − 78 to 0 °C gave the spiro-acetals (**7a**) (22%) and (**7b**) (7%) (yields unoptimised). Using boron trifluoride–diethyl ether and diborane (2 : 1), instead of lithium aluminium hydride–aluminium chloride, the same products (**7a** and **b**) (40%, 1 : 1) were obtained. The two epimers were readily distinguished by nuclear Overhauser effect experiments. Clearly spiro-acetals are now readily available from the highly versatile β-diones.

The milbemycin β_3 unit (**2**) was prepared *via* a Diels–Alder reaction. Condensation of the ylide (**8**), m.p. 198—201 °C, with pyruvaldehyde in refluxing benzene for 24 h gave the enone (**9**)‡ (72%). This reacted with the Danishefsky diene (**10**)[5] in refluxing benzene for 6 h to give the adduct (**11**). Although not characterized, the crude product (**11**) gave the enone (**12**) (64%), m.p. 116·5—119·5 °C, with ethanolic hydrogen chloride and, subsequently, unit (**2**) (75%), m.p. 128·5—129·5 °C, with ethanolic sodium ethoxide. The regioselectivity of the Diels–Alder reaction was unequivocal since unit (**2**) was formed *via* (**12**). In addition, sodium borohydride reduction of (**2**) gave the derived phthalide (**13**) (100%), m.p. 182·5—184 °C, with the expected bathochromic shift in the u.v. spectrum on deprotonation.

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‡ Compounds (**9**) and (**12**) [and presumably (**11**)] were single isomers.

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[3] T. M. Harris and C. M. Harris, *Tetrahedron*, 1977, **33**, 2159, and references therein.

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