Model Studies on the Synthesis of Milbemycin β_3

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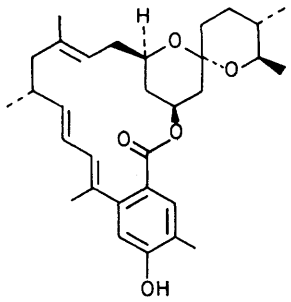
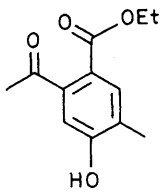
Summary 2,4-Di(lithio-oxy)penta-1,3-diene and 2,4-di(lithio-oxy)-3-methylpenta-1,3-diene condensed with tetrahydropyran-2-one to give 2-methyl- and 2,3-dimethyl-1,7-dioxaspiro[5.5]undec-2-en-4-one; subsequent reduction gave the derived alcohols ($LiAlH_4$) and 2,3-dimethyl-1,7-dioxaspiro[5.5]undec-3-ene ($LiAlH_4$–$AlCl_3$); 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.

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**).

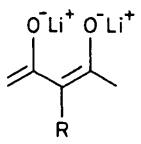
We considered that a concise novel route to the spiro-acetal unit should be available by the condensation of a lactone and β-dione dianion. As a model study, tetrahydropyran-2-one was condensed with the dianion (**3a**)[3] in tetrahydrofuran (THF) at − 78 to 0 °C to give the β-dione (**5**)† (95%) or 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).



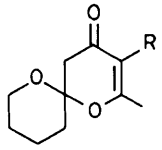
(1)



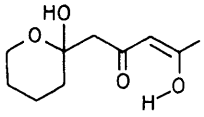
(2)



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



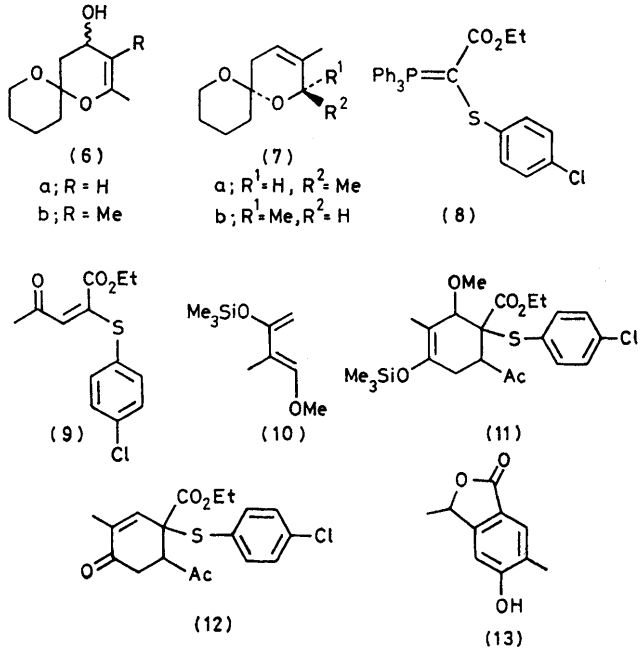
(4)
a; R = H
b; R = Me



(5)

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)

† 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.



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.

We thank the S.R.C. and the Royal Society for generous support, and Dr. M. R. G. Leeming and Dr. N. D. Walsh for helpful discussion and generosity.

(*Received, 27th February* 1981; *Com.* 226.)

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

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