The Chemistry of Spiroacetals.[1] Preparation of a Chiral Disubstituted Lactone Derivative; a Key Intermediate for Synthesis of the Spiroacetal Moieties of the Avermectins and Milbemycins

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A synthesis of two diprotected (4*S*, 6*S*)-4-hydroxy-6-hydroxymethyltetrahydropyran-2-ones has been developed from laevoglucosan; reaction of these lactones with a substituted lithium acetylide derivative followed by hydrogenation and acid catalysed cyclisation has led to formation of the spiroacetal moiety of milbemycin β_1 and β_3.

The avermectins [A_{1b} is compound (**1**)] comprise a group of natural products isolated from the mycelia of *Streptomyces avermitilis*.[2] The increasing interest in these compounds has been stimulated by the discovery that they are effective against helminths and arthropods at very low concentrations. This activity is believed to be a result of interference with invertebrate neurotransmission. The combination of high toxicity and high specificity to invertebrates gives these compounds an enormous potential as broad spectrum antiparasitic agents. These compounds are structurally related to the milbemycins[3] [β_1 is compound (**2**)] which also exhibit activity against some insect pests.[4]

A feature common to the avermectins and milbemycins is the spiroacetal moiety, three carbons of which form part of the sixteen-membered macrolide ring. The synthesis of the spiroacetal fragment of each of the members of both these series of compounds could be achieved *via* the lactone (**3**). This in turn could form the basis of enantiospecific syntheses of the various macrolides. We report the synthesis of this lactone from laevoglucosan, and demonstrate its utility by converting it into (**4**), the spiroacetal fragment of milbemycins β_1 and β_3.

The starting material for this synthesis, laevoglucosan (**5**) (1,6-anhydro-β-D-glucopyranose), is readily available from pyrolysis of corn starch.[5] Tosylation of (**5**) (p-MeC$_6$H$_4$SO$_2$Cl–pyridine–acetone) afforded the bis(toluene-p-sulphonate) (**6**) which on reduction with lithium triethylborohydride gave a mixture of alcohols (**7a**), m.p. 87—90 °C† (EtOH), $[\alpha]_D^{25}$ −81°

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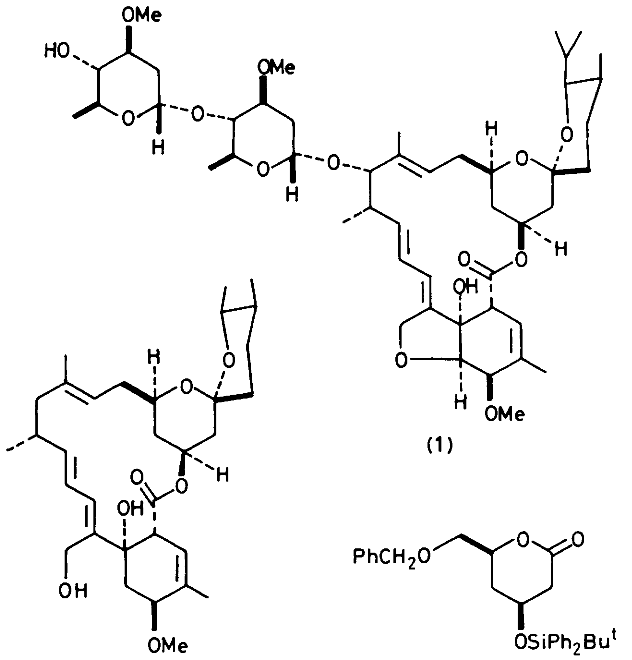
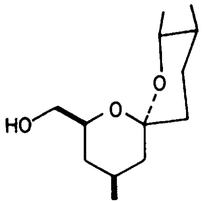
† This compound has been previously reported as a colourless oil (Ref. 6).



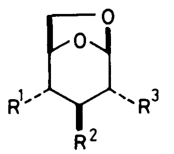
(1)

(2)

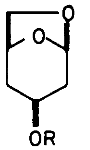
(3)



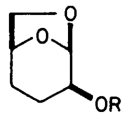
(4)



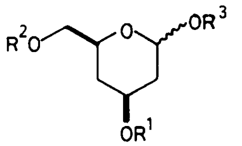
(5) $R^1 = R^2 = R^3 = OH$
(6) $R^1 = R^3 = OSO_2C_6H_4Me$-*p* $R^2 = OH$



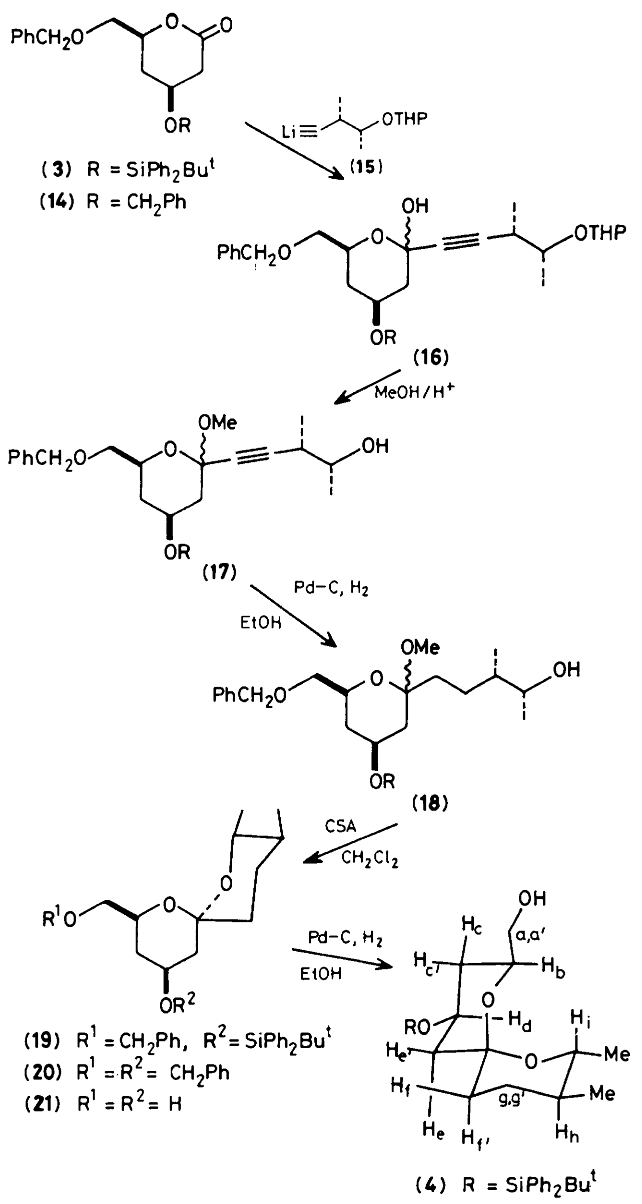
(7a) R = H
(8a) R =



(7b) R = H
(8b) R =



(9) $R^1 =$, $R^2 = H$, $R^3 = Me$
(10) $R^1 =$, $R^2 = CH_2Ph$, $R^3 = Me$
(11) $R^1 =$, $R^2 = CH_2Ph$, $R^3 = Me$
(12) $R^1 = H$, $R^2 = CH_2Ph$, $R^3 = Me$
(13) $R^1 = SiPh_2Bu^t$, $R^2 = CH_2Ph$, $R^3 = H$



(3) $R = SiPh_2Bu^t$
(14) $R = CH_2Ph$

(19) $R^1 = CH_2Ph$, $R^2 = SiPh_2Bu^t$
(20) $R^1 = R^2 = CH_2Ph$
(21) $R^1 = R^2 = H$

(4) $R = SiPh_2Bu^t$

THP = tetrahydropyranyl, CSA = camphorsulphonic acid.

(*c*, 1.0, H_2O) and (**7b**) in a combined yield of 70% in the ratio 10:1.[6] These isomers were not separated but were converted into the corresponding allyl ethers (**8**) by treatment with sodium hydride and alkylation with allyl bromide. The two ethers could then be separated easily by flash chromatography using 25% ethyl acetate–light petroleum (b.p. 40—60 °C) as eluant.

The anhydro bridge of (**8a**) was opened in methanol in the presence of Amberlite resin IR 118 to yield glycoside (**9**) in quantitative yield as a mixture of anomers. Treatment of the alkoxide, generated with sodium hydride, with benzyl bromide yielded the corresponding benzyl ether (**10**). Rearrangement of the allyl ether to the corresponding vinyl ether (**11**) was achieved using $Rh(PPh_3)_3Cl$[7] and methanolysis with Amberlite IR 118 in methanol yielded alcohol (**12**). Protection of the alcohol with chloro(t-butyl)diphenylsilane–KH[8] and hydrolysis with formic acid yielded the lactol (**13**). Oxidation of the lactol with Ag_2CO_3 on celite[9] gave the key lactone (**3**)‡ in an overall yield of 55% from (**10**); (**3**), colourless oil, $[\alpha]_D^{25}$ + 10.4 ° (*c*, 1.0, CH_2Cl_2); ^1H n.m.r. ($CDCl_3$) δ 1.07 (9H, s, Bu^t), 1.5—2.2 (2H, m, $-CH_2-$), 2.3—2.9 (2H, m, $-CH_2CO$), 3.58 (2H, d, *J* 5 Hz, $-CH_2O$), 3.8—4.4 (2H, m, 2 × CH), 4.55 (2H, s, CH_2Ph), and 7.0—7.8 (15H, m, Ar); ν_{max} ($CHCl_3$) 2 930, 1 740, 1 115, and 730 cm^{-1}.

Treatment of the lactone with the lithium acetylide (**15**)§

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‡ Satisfactory spectroscopic and microanalytical data have been obtained for all new compounds.

§ A sample of the required acetylene had previously been prepared as a 67:33 mixture of enantiomers by reaction of lithium acetylide with *cis*-butene epoxide, followed by partial resolution of the phthalate half ester as its α-methylbenzylamine salt. The absolute stereochemistry of the major acetylenic derivative was determined by conversion into (*S*)-(+)-3-methylpentan-2-one (Ref. 10).

gave the hemiacetal (**16**) which was stirred with Amberlite IR 118 in methanol overnight to effect cleavage of the tetrahydropyranyl ether and formation of the acetal (**17**) in essentially quantitative yield. Hydrogenation of the triple bond (10% Pd–C in EtOH for 1 h) gave (**18**) which on subsequent treatment with a catalytic amount of camphorsulphonic acid in CH_2Cl_2 yielded the spiroacetal (**19**). Hydrogenolysis of the benzyl ether using 10% Pd–C in ethanol overnight proceeded smoothly to yield the corresponding primary alcohol (**4**) in an overall yield of 30% from (**15**); (**4**), colourless oil, $[\alpha]_D^{25}$ + 23° (*c*, 1.0, CH_2Cl_2); ^1H n.m.r. (400 MHz, $CDCl_3$) δ 0.70 (3H, d, $J_{Me,h}$ 6 Hz, CH_3), 0.89 (3H, d, $J_{Me,i}$ 6, CH_3), 0.96 (9H, s, Bu^t), 1.07—1.12 (1H, m, H_h), 1.25 (1H, ddd, $J_{c',c}$ 12, $J_{c',b}$ 11, $J_{c',d}$ 11, $H_{c'}$), 1.35 (1H, dd, $J_{e',d}$ 11, $J_{e',e}$ 12.5, $H_{e'}$), 1.37—1.43 (3H, m, $H_g + H_{g'} + H_f$), 1.51 (1H, m, $J_{c,c'}$ 12, $J_{c,b}$ small, H_c), 1.57 (1H, m, $H_{f'}$), 1.85 (1H, ddd, $J_{e,e'}$ 12.5, $J_{e,d}$ 5, $J_{e,c}$ 2, H_e), 1.9 (1H, br. s, OH), 3.14 (1H, dq, $J_{i,Me}$ 6, $J_{i,h}$ 10, H_i), 3.35—3.45 (3H, m, $H_b + H_a + H_{a'}$), 4.14 (1H, dddd, $J_{d,c}$ 4.5 $J_{d,c'}$ 11, $J_{d,e}$ 5, $J_{d,e'}$ 11, H_d), and 7.25—7.6 (10H, m, Ar).

Formation of two diastereoisomers is possible from cyclisation of (**18**), each of which could exist in two conformations. The single major product¶ isolated can be explained by the preference for the desired spiroacetal to adopt the conformation in which the two vicinal methyl groups are equatorial and the ring oxygens are axial to the adjacent ring thus gaining stability from the anomeric effect.[11] The ^1H n.m.r. data, including the 2-dimensional n.m.r. spectrum, of (**4**) are fully consistent with the assigned structure. The signal at δ 4.14 results from the characteristic deshielding of this proton (H_d) due to the 1,3-diaxial interaction with the oxygen of the adjacent ring. This signal appears as seven evenly spaced lines, intensity ratios 1 : 2 : 3 : 4 : 3 : 2 : 1.[1b,12] The signal for H_i appears at δ 3.14 as a double quartet, J_{ih} 10 Hz, indicating that protons i and h are in a diaxial orientation.

In an analogous series of reactions the dibenzyl protected lactone (**14**) was converted into the corresponding spiroacetal (**20**) in 80% overall yield, colourless oil, $[\alpha]_D^{25}$ + 40° (*c*, 0.9, CH_2Cl_2). This was converted by overnight hydrogenation in the presence of Pd–C in EtOH into (**21**), m.p. 97—98 °C after crystallisation from methanol–ether. It is clear that (**3**) is an important and key precursor for the synthesis of the series of avermectins and milbemycins.

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¶ The minor enantiomer of (**15**) undoubtedly forms the equivalent adduct to (**16**) but following hydrogenation does not undergo cyclisation under the acid catalysed conditions employed. The reason for this is that the product cannot attain an anomerically stabilised conformation, with all four substituents equatorial.