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The Chemistry of Spiroacetals.[1] Enantiospecific Synthesis of the Spiroacetal Units of Avermectins B_{1b} and B_{2b}

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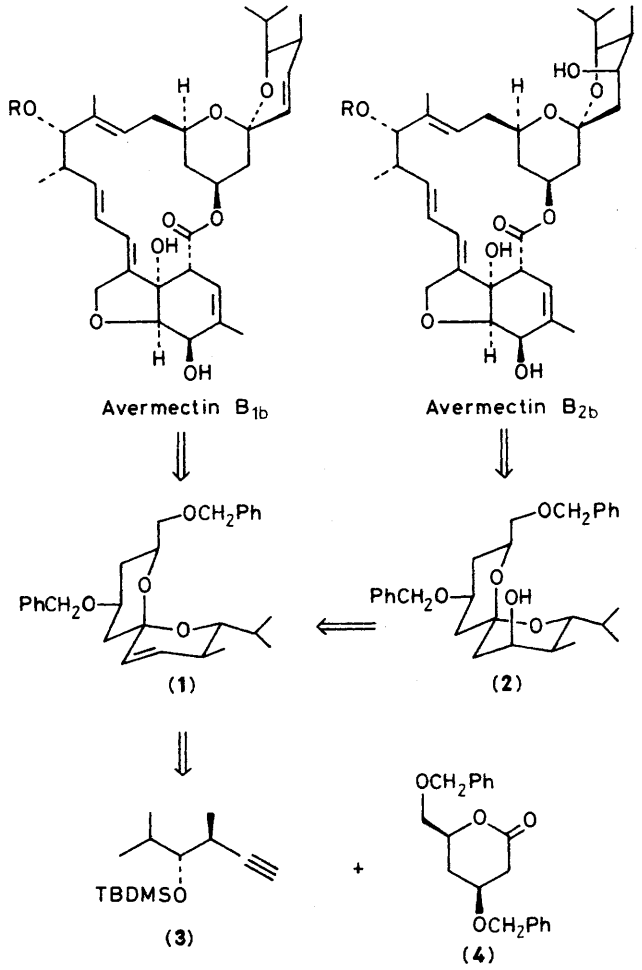
An enantiospecific synthesis of the spiroacetal sub-unit of avermectins B_{1b} and B_{2b} from the optically pure precursors acetylene (**3**) and lactone (**4**) is reported.

The spiroacetal moiety has received much attention in recent years owing to its unusual stereoelectronic properties[2] and its occurrence in a number of natural products.[3] One such group of compounds is the *avermectins*[4] which show highly specific toxicity towards arthropods and helminths at very low concentrations[5] and there is considerable interest in their potential as broad spectrum anti-parasitic agents. An important part in any total synthesis of these compounds would be the preparation of the spiroacetal portion.

In a previous publication we reported synthesis of the disubstituted lactone (**4**) from laevoglucosan[1] and its application to the formation of the spiroacetal moiety of milbemycin β_3. A synthesis of the spiroacetal unit of avermectin B_{1a} from carbohydrate precursors has been reported.[6] We now report a highly efficient enantiospecific synthesis of the unsaturated sub-unit of avermectin B_{1b} (**1**) and its subsequent elaboration into the hydroxylated sub-unit of avermectin B_{2b} (**2**) *via* formation of the appropriate chlorohydrin derivative.

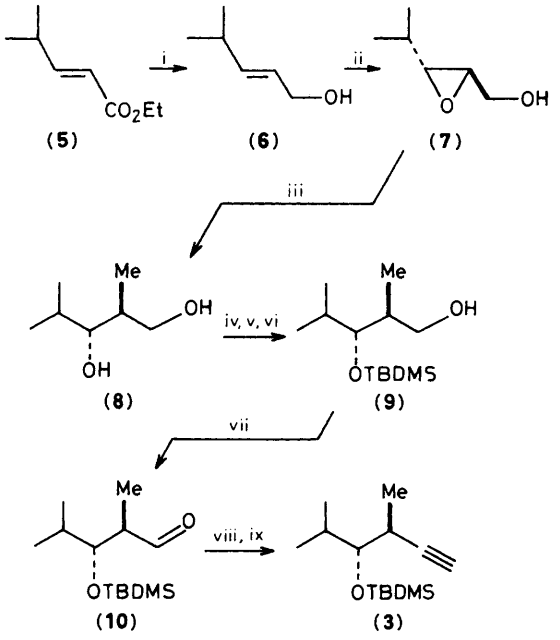
The methodology employed was reaction of the chiral lactone (**4**) with the optically pure acetylene (**3**) followed by selective reduction to an olefinic lactol and cyclisation to the required 1,7-dioxaspiro[5.5]undec-4-ene derivative (**1**). This sequence leads to formation of a single enantiomer identical to that in the natural product since both fragments (**3**) and (**4**) possess the correct absolute configuration while the spiro-centre is generated in a stereospecific manner because of the anomeric effect[2] (Scheme 1).

The optically pure acetylene (**3**) was prepared by a series of high yielding and stereoselective reactions (Scheme 2). Wittig reaction between iso-butyraldehyde and (carbethoxymethylene)triphenylphosphine gave the *trans*-enoate (**5**) in 86% yield; this underwent di-isobutylaluminium hydride (DIBAL-H) reduction to yield the allylic alcohol (**6**) (86%). Asymmetric epoxidation using Sharpless' method[7] [(−)diethyl tartrate (DET), Bu^tOOH, $Ti(OPr)_4$] gave the 2*R*,3*R*-*trans*-epoxyalcohol (**7**) (59%), $[\alpha]_D^{25}$ + 32.2° (*c* 2.7, CH_2Cl_2). Reaction of (**7**) with $Me_2CuCNLi_2$[8] (4 equiv.) showed a useful level of regioselectivity, giving a 6 : 1 ratio of the 1,3-diol (**8**) and the regioisomeric 1,2-diol. The latter could be simply removed by treatment with periodate to give pure (**8**) in 82% yield.



TBDMS = t-butyldimethylsilyl
R = disaccharide

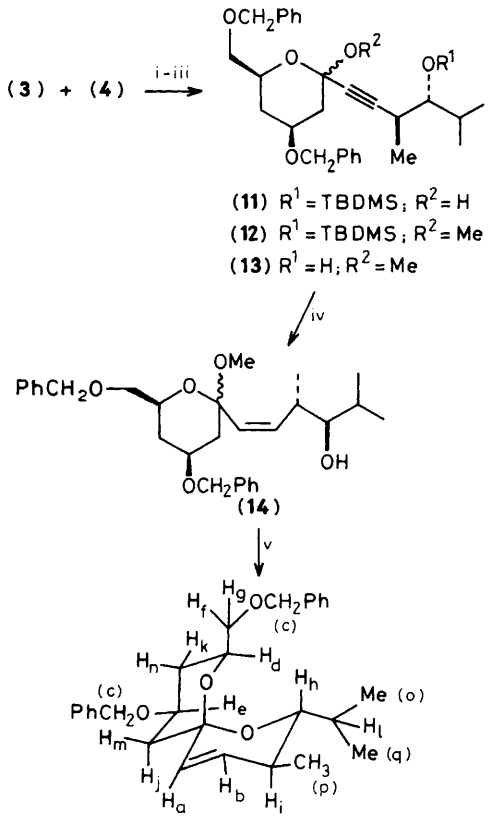
Scheme 1



Scheme 2. *Reagents:* i, 2 equivs. DIBAL-H, Et_2O, −78 °C; ii, (−)DET, Bu^tOOH, $Ti(OPr)_4$; iii, $Me_2CuCNLi_2$, Et_2O, −30 °C; aq. NH_4Cl; aq. $NaIO_4$, H^+; iv, 1 equiv. PhCOCl, pyridine; v, TBDMSCl, imidazole, 4-*N,N*-dimethylaminopyridine, *N,N*-dimethyformamide, 50 °C; vi, KOH, MeOH; vii, $(COCl)_2$, Me_2SO; Et_3N; viii, CBr_4, 2 PPh_3, CH_2Cl_2; ix, 2 equivs. BuLi, tetrahydrofuran (THF), −78 °C → room temperature.

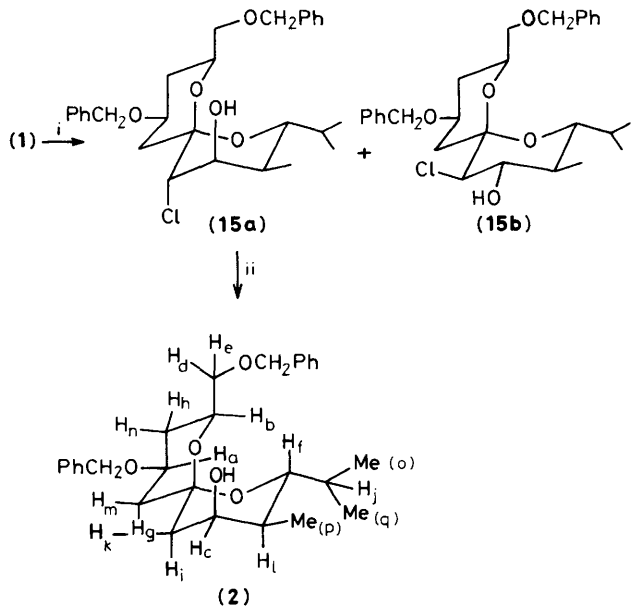
Sequential benzoylation, silylation, and saponification gave the t-butyldimethylsilyl (TBDMS) ether (**9**) in an overall yield of 72%. Swern oxidation [$(COCl)_2$, dimethyl sulphoxide, Et_3N] gave the aldehyde (**10**) in 84% yield. Conversion into the key acetylene was achieved by treatment with carbon tetrabromide and triphenylphosphine to give the 1,1-dibromoolefin; subsequent treatment with Bu^nLi furnished the acetylene (**3**) as a colourless oil (78%) b.p. (Kugelrohr) 75 °C @ 14 mmHg; $[\alpha]_D^{25}$ + 10.7° (*c* 1.57, CH_2Cl_2); $\nu_{max.}$ 3320 (HC≡), 2960, 2860, 2115 (C≡C), 1460, 1250 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.45 (1H,dd, *J* 4 and 5 Hz, O–CH), 2.9—2.4 (1H,m, H–CMe), 2.05 (1H,d, *J* 3 Hz, H–C≡), 2.0—1.6 (1H,m, $-CHMe_2$), 1.2 (3H,d, *J* 7 Hz, Me), 0.95 (6H,d, *J* 7 Hz, Me_2), 0.92 (9H,s,Bu^t), 0.08 (6H,s,Me_2); *m/z* (electron impact) 187(29%), 183(36), 141(12), 131(13), 111(37), 75(68), 73(100).

The acetylide anion of (**3**) was generated using Bu^nLi (−78 °C) in THF and reacted with the lactone (**4**) to yield the adduct (**11**) (54%) (Scheme 3). Subsequent treatment with Amberlyst H^+ in methanol yielded the methoxyacetal (**12**) and removal of the silyl protecting group (Bu^n_4NF) gave the acetylenic alcohol (**13**) (83% overall). Hydrogenation over poisoned 5% Lindlar catalyst in methanol provided the olefin (**14**) in quantitative yield. Subsequent treatment with camphorsulphonic acid (CSA) in diethyl ether caused a rapid and clean cyclisation to provide the desired spiroacetal (**1**) as a colourless oil (83% overall), $[\alpha]_D^{25}$ + 75.2° (*c* 1.17, CH_2Cl_2); $\nu_{max.}$ 3030, 2960, 1660 (C=C), 1600 (Ar); δ_H (400 MHz; $CDCl_3$) 7.3 (10H,br. s,2×Ph), 5.7 (1H,dd, J_{ab} 10, J_{ai} 1 Hz, H_a), 5.59 (1H,dd, J_{ba}10, J_{bi} 2 Hz, H_b), 4.55 (4H,s,H_c), 4.03 (1H,m,H_d), 3.96 (1H,m,H_e), 3.56 (1H,dd, *J* 10 and 5 Hz, $H_{f\ or\ g}$), 3.46 (1H,dd, *J* 10 and 5 Hz, $H_{f\ or\ g}$), 3.35 (1H,dd, J_{hi} 10, J_{hi} 2 Hz, H_h) 2.21(1H,m,H_i), 2.14(2H,m,H_j + H_k), 1.9(1H,m,H_l), 1.48(1H,dd, *J* 12 and 11 Hz, H_m), 1.34 (1H,ddd, J_{nk} = J_{ne} = J_{nd} = 12 Hz, H_n), 1.03(3H,d, J_{ol} 7 Hz, $Me_{o\ or\ q}$), 0.89 (3H,d, J_{pi} 7 Hz, Me), 0.87 (3H,d, J_{ql} 7 Hz, $Me_{o\ or\ q}$); *m/z* (electron impact) 364 (1%, loss of Me_2CH–CHO retro Diels–Alder), 315(8), 256(5), 207(4); *m/z* (chemical ionisation 437(M^+ + H). As anticipated, the favoured conformation is that which has all the substituents in equatorial or pseudoequatorial positions with the anomeric effect also providing additional stability.[2] Confirmation of the stereochemistry was available from examination of the 400 MHz spectra (assisted by COSY experiments). The signal at δ 3.35 assigned to H_h has a coupling of J_{hi} = 10 Hz which is consistent with the pseudodiaxial arrangement of protons H_h and H_i. Proton H_e (δ 3.96) shows the characteristic deshielding due to the 1,3-diaxial interaction with the oxygen of the adjacent ring.[1]



Scheme 3. *Reagents:* i, Bu^nLi, (**3**), THF; add lactone (**4**); ii, MeOH, Amberlyst H^+; iii, $Bu^n_4N^+F^-$, THF; iv, H_2, $Pd/CaCO_3/Pb$, quinoline, MeOH; v, CSA, Et_2O.

Elaboration of (**1**) to the spiroacetal unit of avermectin B_{2b} was achieved by a simple two step sequence (Scheme 4). Treatment of (**1**) with t-butyl hypochlorite proceeded with complete regiocontrol and moderate stereoselectivity[9] to provide the chlorohydrins (**15a**) and (**15b**) in a ratio of 2 : 1 in 85% yield, easily separable by flash chromatography [20% diethyl ether–light petroleum: (**15a**) R_f 0.5, (**15b**) R_f 0.33]. The regio- and stereo-chemistry of the diaxial chlorohydrin (**15a**) was confirmed by its 400 MHz n.m.r. spectrum. In particular, the equatorial proton next to chlorine (δ 3.90) appears as a narrow doublet (2.5 Hz) consistent with a diequatorial disposition of the protons adjacent to Cl and OH. Reduction of (**15a**) with tributyltin hydride yielded the desired spiroacetal (**2**) in 80% yield as a colourless crystalline solid m.p. 66—67 °C; $[\alpha]_D^{25}$ + 70.2° (*c* 0.49,CH_2Cl_2); $\nu_{max.}$ 3520(OH), 3040, 2980, 1590(Ar); δ_H (360 MHz; $CDCl_3$), 7.4 (10H,s,2×Ph), 4.57 (4H,s,2×ArCH_2), 3.94 (1H,m,H_a),



Scheme 4. *Reagents:* i, Bu^{t}OCl, H_2O, acetone, room temperature; ii, Bu$^n_3$SnH, toluene, azoisobutyronitrile, 110 °C.

3.90 (1H,m,H_b), 3.79 (2H,br.s,H_c+OH), 3.55—3.44 (3H,m,H_d+H_e+H_f), 2.13 (1H,dd, *J* 12 and 5 Hz,H_g), 2.05 (1H,m,H_h), 2.03 (1H,dd, *J* 13.5 and 2 Hz, $H_{i\ or\ k}$), 1.88 (1H,m,H_j), 1.69 (1H,dd, *J* 13.5 and 2 Hz, $H_{i\ or\ k}$), 1.58 (1H,m,H_l), 1.44 (1H,dd, *J* 12 and 11 Hz, H_m), 1.28 (1H,ddd, *J* 12, 12, and 12 Hz, H_n), 1.01 (3H,d, *J* 7 Hz, $Me_{o\ or\ q}$), 0.94 (3H,d, *J* 7 Hz, Me_p), 0.87 (3H,d, *J* 7 Hz, $Me_{o\ or\ q}$); *m/z* (electron impact) 333(2%), 328(2), 325(1), 315(1), 217(6), 94(17), 91(100).

It is evident that the described methodology can be used to prepare multigram quantities of the enantiomerically pure spiroacetals (**1**) and (**2**) and could be generally applied to the preparation of the spiroacetal unit of a series of avermectin and related milbemycin derivatives. In particular, the use of 2*S*-methylbutyraldehyde† would provide access to the s-butyl substituted spiroacetal unit found in the 'a' series of avermectins, with the likelihood of even higher regiocontrol in the cuprate opening of the epoxyalcohol in the synthesis of the required acetylene.

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† *S*-(−)-2-Methylbutan-1-ol is readily available.