Asymmetric Synthesis of Milbemycin and Avermectin Spiroacetals

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Spiroacetals (**16**) and (**29**) have been synthesized from dimethyl (*S*)-malate (**9**) *via* convergent routes which use chiral boron reagents to control stereochemistry.

The milbemycins and avermectins are of considerable interest at present because of their potent anthelmintic activity and potential commercial importance.[1] Several syntheses of the spiroacetal and 'lower hemisphere' fragments of the milbemycins have been described,[2—5] together with syntheses of the aromatic milbemycin β_3 and avermectin B_{1a}.[6,7] We now report a convergent and stereoselective approach to the spiroacetal fragments of these compounds as exemplified by syntheses of the spiroacetals of milbemycin E (**1**) and avermectin A_{2a} (**2**). Our approach starts with the readily available (*S*)-dimethyl malate (**9**), and uses the recently developed allyl- and crotyl-borane chemistry of H. C. Brown to control stereochemistry.[8,9]

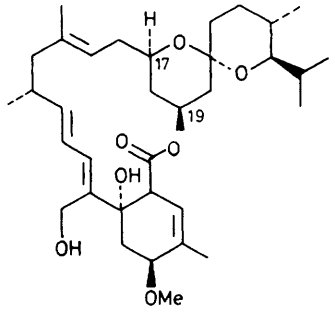
Our approach is outlined in Scheme 1. It was envisaged that the spiroacetals would be formed on deprotection of the open-chain dithianes (**3**) which should be accessible using dithiane anion chemistry from epoxide (**4**) and either epoxide (**5**) or iodide (**6**). Epoxide (**4**) was to be obtained from (*S*)-dimethyl malate (**9**) *via* aldehyde (**8**) and alcohol (**7**). Aldehyde (**8**) has been used before in milbemycin synthesis,[3] however its intrinsic diastereoface selectivity towards nucleophilic attack is rather weak, with the undesired adducts for milbemycin synthesis predominating. We hoped to get round this problem by using optically active allylborane reagents.

Thus treatment of aldehyde (**8**), readily available from (*S*)-dimethyl malate (**9**),[10] with the allyldi-isopinocampheylborane (**10**) derived from (−)-pinene followed by oxidation,[8] gave a mixture of the desired adduct (**7**) together with its diastereoisomer (**11**) (ratio 9 : 1, 60—65% yield). The configuration of the newly introduced chiral centre in the major adduct (**7**) was assigned by analogy[8] and was confirmed by synthesis of the known spiroacetal (**16**). Conversion of the alcohol-acetal (**7**) into the protected alcohol-epoxide (**12**) was achieved in four steps; SEM protection, acetal hydrolysis, selective tosylation, and cyclization; and the epoxide (**12**) was treated with an excess of the lithium salt of the dithiane (**14**), this dithiane having been obtained from 1,3-dithiane and the known iodide (**13**),[4] to provide the bisalkylated dithiane (**15**) (60% yield). Removal of the alcohol protecting groups and dithiane hydrolysis were achieved by treatment with dilute aqueous HF in acetonitrile to give the milbemycin E spiroacetal (**16**) (61% yield) identical with an authentic sample.[4]

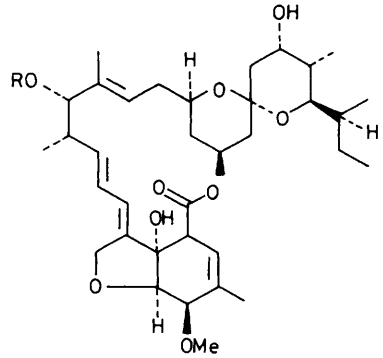
To apply this approach to a synthesis of the more complex avermectin A_{2a} spiroacetal, a stereoselective synthesis of the protected hydroxyepoxide (**5**; R = Bu^s) was required. The starting material for this synthesis was (*S*)-2-methylbutanal (**17**) obtained by chromic acid oxidation of commercially available (*S*)-2-methylbutanol.[11] We found that some racemization accompanied this oxidation, and the enantiomeric excess of the aldehyde was usually only *ca.* 70%. However treatment of this aldehyde with the crotyldi-isopinocampheylborane (**18**) derived from (+)-pinene[9] gave a mixture of adducts which contained >75% of the desired adduct (**19**), together with minor diastereoisomers including (**20**). Interestingly, the major adduct (**19**) now had an enantiomeric excess of >90% (Mosher's derivative), the increase in optical purity being due to the preferential formation of adduct (**20**), a diastereoisomer of (**19**), from the enantiomer of aldehyde (**17**). [The *enantiomer* of alcohol (**19**) could only have been formed if the enantiomer of (**17**) reacted with the boron reagent (**18**) *via* the reagent's less favourable mode.[9]]

Preliminary studies into the stereoselective iodolactonization of alcohol (**19**) were not encouraging,[12] however epoxidation using Bu^tO_2H–$VO(acac)_2$ (acac = pentane-2-4-dionato) was both efficient and stereoselective, giving an 80 : 20 mixture of epoxides (**21**) and (**22**) in which the desired isomer (**21**) was the major component (isolated by flash chromatography in 72% yield).[13] To test the usefulness of epoxide (**21**) in spiroacetal formation it was treated with an excess of the dithiane (**23**)–Bu^tLi which gave the bisalkylated dithiane (**24**) (60% yield). The t-butyldimethylsilyl group was then removed by treatment with tetra-n-butylammonium fluoride (78% yield), and the dithiane cleaved using mercuric chloride in tetrahydrofuran (THF) in the presence of calcium carbonate, to provide the spiroacetal (**25**) (85% yield) characterized as its acetate (**26**). In the absence of the calcium carbonate the dithiane cleavage was not clean and gave a mixture of products including the spiroacetal chloride (**31**).

To prepare the avermectin spiroacetal (**29**), the hydroxyepoxide (**21**) was treated with an excess of 1,3-dithiane–Bu^nLi to give the dithiane-acetal (**27**) after alcohol protection.

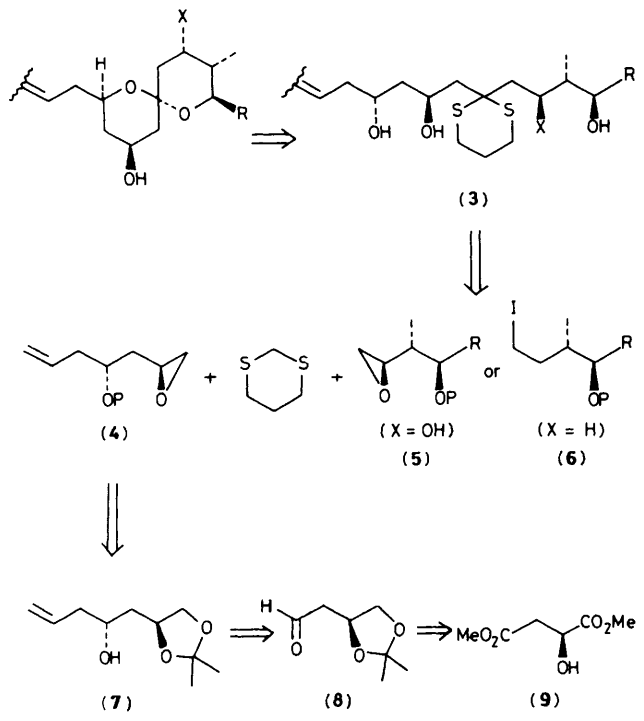


(**1**)

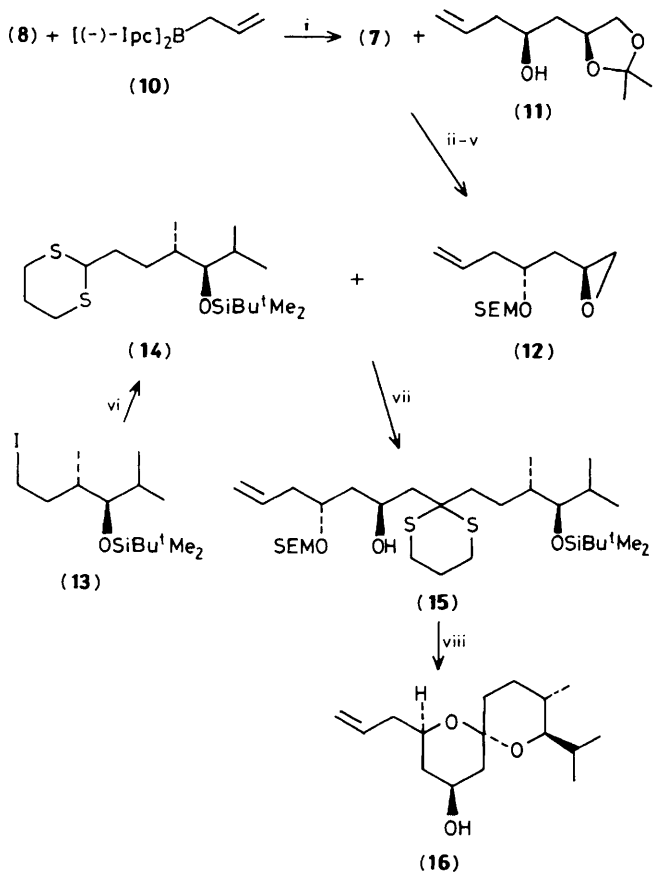


(**2**)

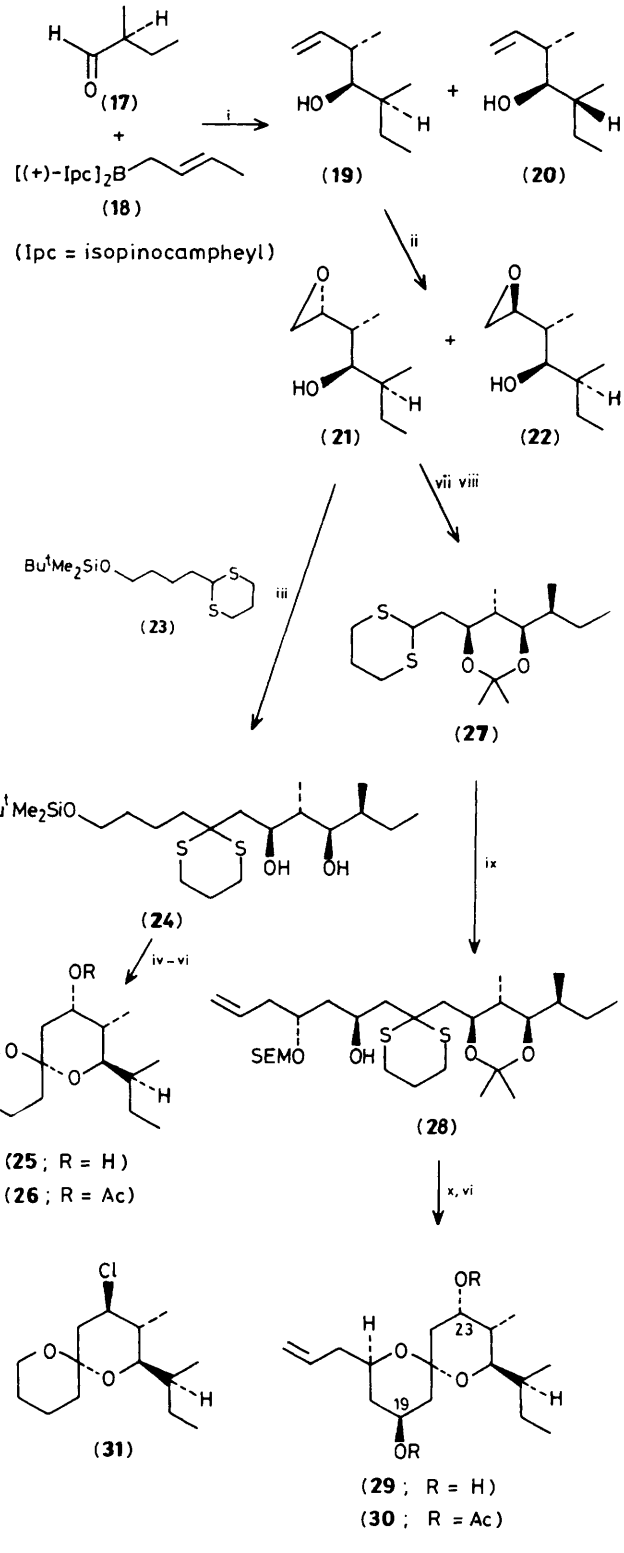
R = $(\alpha$-L-oleandrosyl$)_2$



Scheme 1



Scheme 2. *Reagents:* i, −70 °C then H_2O_2, OH^- (60—65%); ii, SEM–Cl, Pr^i_2NEt, CH_2Cl_2; iii, HCl, H_2O, THF; iv, TsCl, Et_3N, 4-dimethylaminopyridine, CH_2Cl_2; v, K_2CO_3, MeOH [40–50% from (7)]; vi, 1,3-dithiane, Bu^nLi, −40 °C then 24 h, −20 °C, 87% yield; vii, Bu^tLi, tetramethylethylendiamine, THF, −20 °C, 59% yield, viii, HF, H_2O, MeCN, room temp., 3 h, 61% yield.



Scheme 3. *Reagents:* i, −70 °C, 3 h then H_2O_2, OH^- [65% of isomer mixture, 41% of (**19**) after flash chromatography and preparative g.l.c.]; ii, Bu^tO_2H, $VO(acac)_2$ [72% of (**21**), 14% of (**22**) after flash chromatography]; iii, Bu^tLi, 0 °C, 60% yield; iv, Bu^n_4NF, THF, 78% yield; v, $HgCl_2$, $CaCO_3$, THF, 85% yield; vi, 4-dimethylaminopyridine, Et_3N, Ac_2O (100%); vii, 1,3-dithiane, Bu^nLi (50%); viii, 2,2-dimethoxypropane, acetone, TsOH (88%); ix, Bu^tLi, hexamethylphosphoramide, −20 °C then add (**12**), −15 °C (50—55%); x, HF–pyridine, CH_2Cl_2 (73%).

Deprotonation of this with Bu^{t}Li–HMPA (HMPA = hexamethylphosphoramide) and addition of epoxide (**12**) gave the doubly alkylated dithiane (**28**) which was deprotected and cyclized in a single step using HF–pyridine in dichloromethane, to provide the target spiroacetal (**29**) [73% yield in six steps from aldehyde (**17**)] characterized as its bisacetate (**30**). The structure and stereochemistry of spiroacetal (**29**) was confirmed by high field ^{1}H n.m.r. studies; in particular, the signal of the proton at C(23) (avermectin numbering[1]) was a quartet at δ 3.73, *J* 3.1 Hz, further split by coupling to the OH group, indicative of an equatorial proton, whereas the proton at C(19) showed a triplet of triplets at δ 4.1, *J* 11.2 and 4.9 Hz, characteristic of an axial proton *syn* to an axial acetal oxygen.

This work provides short and stereoselective access to milbemycin and avermectin spiroacetals, and demonstrates the potential of the chiral allyl- and crotyl-borane reagents for complex natural product synthesis.

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