Asymmetric Synthesis of the Spiroacetal Fragment of Milbemycin E

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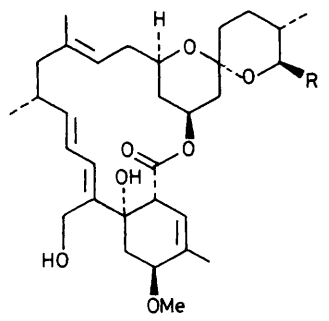
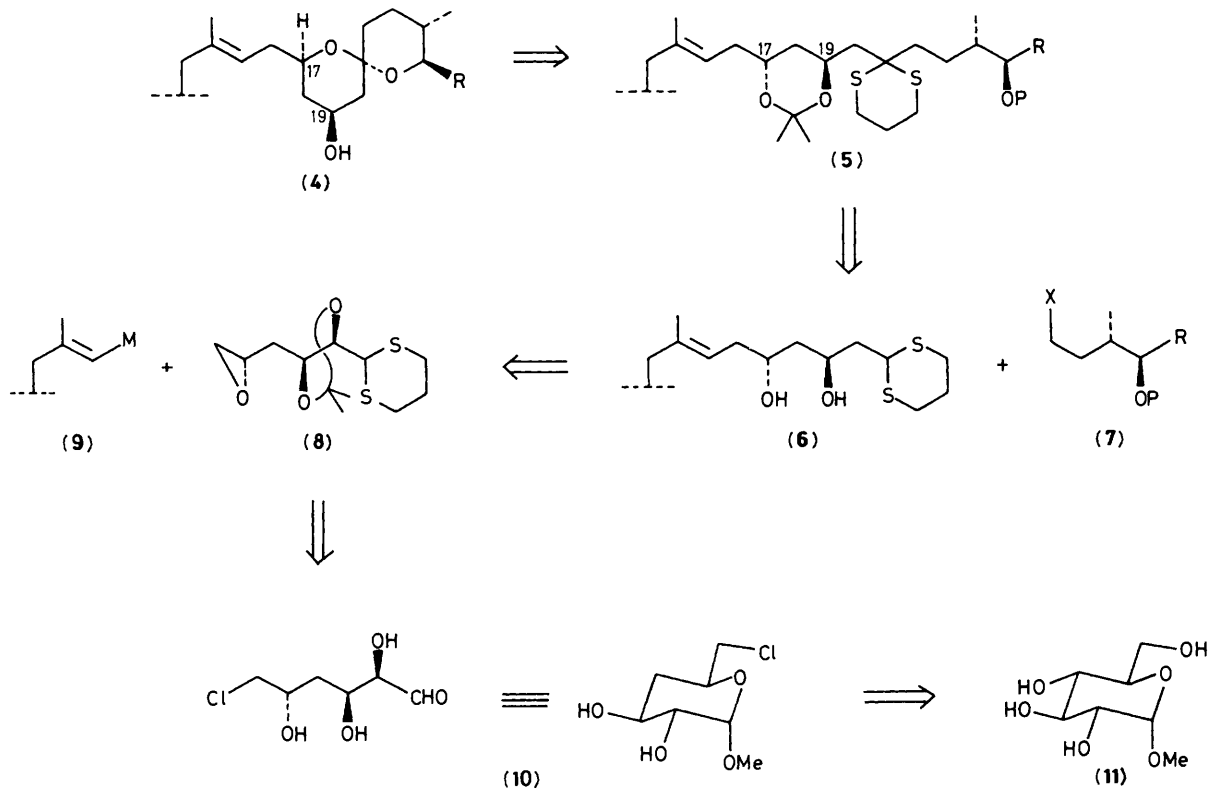
Spiro-acetals (**17**) and (**21**) have been synthesized from methyl α-D-glucopyranoside (**11**), *via* the 6-chloro-4,6-dideoxygalactopyranoside (**10**), the epoxy-dithiane (**8**), and the open-chain dithianes (**16**) and (**20**).

Total synthesis of the milbemycins and avermectins is of considerable interest at present because of their potent biological activity and potential commercial importance.[1] To date several syntheses of the spiroacetal and 'lower hemisphere' fragments of these compounds have been described, together with syntheses of the aromatic milbemycin β_3 and a synthesis of avermectin B_{1a}.[2,3] We have been interested in developing syntheses of the non-aromatic β-milbemycins, *i.e.*, β_1, β_2, and E (**1**)—(**3**), and now report a convergent and flexible asymmetric synthesis of the spiroacetal fragment of milbemycin E (**3**).

Our synthetic strategy is outlined in Scheme 1. The key intermediate is epoxy-dithiane (**8**) which it was thought would be available from methyl α-D-glucopyranoside (**11**) *via* the 6-chloro-4,6-dideoxygalactopyranoside (**10**). Cleavage of this epoxide with a vinyl organometallic reagent (**9**) followed by



(**1**) R = Me
(**2**) R = Et
(**3**) R = Pr^i



Scheme 1

acetonide fragmentation and ketenethioacetal reduction would give the dihydroxy-dithiane (**6**). Diol protection and dithiane alkylation with a suitable alkyl halide (**7**) would then provide the dialkyldithiane (**5**), which on deprotection should cyclize to spiroacetal (**4**).

Syntheses of spiroacetals (**17**) and (**21**) based on this approach are summarized in Scheme 2. Methyl α-D-glucopyranoside (**11**) was treated with sulphuryl chloride and KI to give methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside which was conveniently purified as its diacetate (**12**).[4] Selective hydrogenolysis of the secondary C–Cl bond was achieved using a Pd–C catalyst in ethanol in the presence of KOH, and was accompanied by ester cleavage, giving an excellent yield (>90%) of the 6-chloro-4,6-dideoxygalactopyranoside (**10**).† Alternative procedures for the selective reduction of this secondary chloride, *e.g.*, by using a trialkyltin hydride,[5] or by hydrogenolysis in the presence of a Raney nickel catalyst,[6] were either less regioselective or less convenient. The 6-chloro-4,6-dideoxygalactopyranoside was then converted into the epoxy-dithiane (**8**) by treatment with propane-1,3-dithiol,[7] diol protection, and cyclization.

The epoxy-dithiane was found to be reactive towards organometallic reagents at two sites. Treatment with vinylmagnesium bromide in the presence of a copper(I) catalyst caused epoxide ring opening and gave a good yield (82%) of the homoallylic alcohol (**14**). In contrast the more basic n-butyl-lithium removed the dithiane proton, initiating acetonide fragmentation, and gave the epoxy-hydroxy-ketenethioacetal (**22**), also in good yield (87%).

For the synthesis of spiroacetal (**17**), the homoallylic alcohol (**14**) was treated with n-butyl-lithium and $LiAlH_4$, which gave the acetonide-dithiane (**15**) after diol protection. This was alkylated using the optically active alkyl iodide (**27**) conveniently prepared from 2-methylpropanal in four steps. Thus treatment of 2-methylpropanal with *trans*-but-2-enyldi-(+)-isopinocamphenylborane (**23**) according to the procedure reported by Brown[8] gave a 60—70% isolated yield of the *anti*-alcohol (**24**) together with *ca.* 10% of its separable *syn*-diastereoisomer. The alcohol (**24**) was estimated to have an enantiomeric excess of >90% (Mosher's derivative), and was converted through to the required iodide (**27**) by protection, hydroboration, and treatment with triphenylphosphine, imidazole, and iodine. Alkylation of dithiane (**15**) with iodide (**27**) gave the dialkyldithiane (**16**) which on deprotection underwent spontaneous cyclization to give spiroacetal (**17**).

For the synthesis of spiroacetal (**21**), epoxide (**8**) was treated with an excess of *p*-methoxybenzyl alcohol and base to give the dihydroxyketenethioacetal (**18**) *via* simultaneous epoxide cleavage and acetonide fragmentation. Reduction and diol protection then gave the acetonide-dithiane (**19**) which was alkylated, in this case using bromide (**28**), to give the target spiroacetal (**21**) after deprotection.

This work has developed a reasonably short [13 linear steps from methyl α-D-glucopyranoside (**11**)], convergent, and flexible synthesis of milbemycin spiroacetals. Moreover, the readily available epoxydithiane (**8**) and derivatives, *e.g.*, the epoxy-hydroxy-ketenethioacetal (**22**), should be generally useful for the synthesis of optically active *anti*-1,3-diols.

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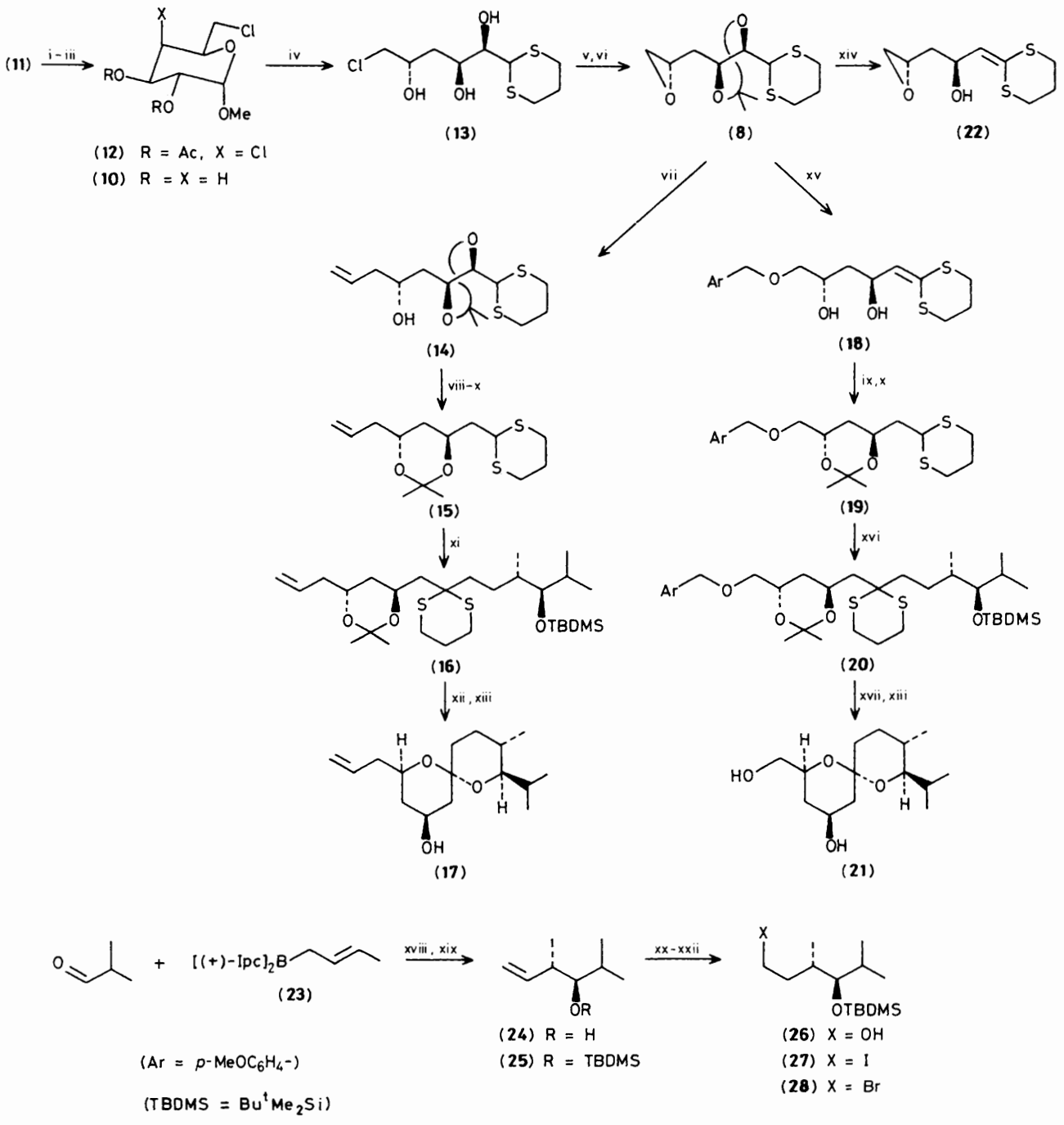

Scheme 2. *Reagents:* i, SO_2Cl_2, pyridine (py), −78 °C, 2 h, then KI; ii, Ac_2O, py [40% from (**11**)]; iii, H_2, Pd–C, KOH, EtOH, 150 p.s.i., 6 h (95%); iv, $HS[CH_2]_3SH$, HCl, room temp. (r.t.), 16 h (93%, crude); v, acetone, $CuSO_4$, *p*-$MeC_6H_4SO_3H$ (PTSA), r.t., 17 h (91%); vi, powdered NaOH, EtOH, r.t., 30 min (75%); vii, vinylmagnesium bromide, CuI, −40 to −30 °C, 4 h (82%); viii, Bu^nLi tetrahydrofuran (THF), −78 °C, 2 h; ix, $LiAlH_4$, THF, r.t., 16 h [65% from (**14**), 85% from (**18**)]; x, acetone, 2,2-dimethoxypropane, PTSA, r.t., 12 h (90%); xi, Bu^tLi, hexamethylphosphoramide (HMPA)–THF, −22 °C, 2 h, then add (**27**) in THF, −22 °C, 16 h (75%); xii, 1 M-HCl, MeOH, r.t., 12 h (85%); xiii, $HgCl_2$, THF, r.t., 12—24 h (70%); xiv, Bu^nLi, THF, −78 °C, 30 min (87%); xv, *p*-$MeOC_6H_4CH_2OH$, NaH, dimethylformamide (DMF), 2 h, r.t. (70%); xvi, Bu^tLi, THF, −70 to −40 °C, then add HMPA and (**28**) at −70 °C (40%); xvii, HOAc, THF, H_2O, 40 °C, 16 h (65%); xviii, −78 °C, 3 h, then NaOH, H_2O_2, 0 °C then heat under reflux, 1 h [60—70% of (**24**)]; xix, CF_3SO_3-$SiMe_2Bu^t$, 2,6-lutidine, CH_2Cl_2, 0 °C to r.t., 2 h (quant.); xx, borane–THF, 0 °C to r.t., then H_2O_2, NaOH, 1 h, heat under reflux (70%); xxi, Ph_3P, imidazole, I_2, benzene, 80 °C, 2 h (90%); xxii, CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 30 min (82%).

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