The Chemistry of Spiroacetals. An Enantiospecific Synthesis of the Spiroacetal Moiety of Milbemycins α_7 and α_8

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An enantiospecific synthesis of the dioxygenated spiroacetal moiety of milbemycins α_7 and α_8 has been developed from the appropriate epoxide and regioselective acylation of the C-23 alcohol.

The milbemycins [(**1a**) is milbemycin α_7, (**1b**) is milbemycin α_8]‡ comprise a group of natural products isolated from cultures of Streptomyces B-41-146.[1] Interest in these compounds has increased since the isolation and identification of a structurally related series of macrolides, the avermectins.[2] The avermectins are effective against helminths and arthropods at very low concentrations, giving these compounds enormous potential as anti-parasitic agents.[3] In addition, the milbemycins have shown important activity against a wide variety of insect pests.[4] Several total syntheses of milbemycin β_3 have been reported to date[5,6] and several reports on the spiroacetal portions of some of the more complex milbemycins and avermectins have appeared.[7,8] Previously we have described the synthesis of the chiral lactone (**2**)[9] and demonstrated its utility in an enantiospecific synthesis of the spiroacetal subunit of milbemycin β_3 (**3**) and, subsequently, incorporation into a total synthesis of milbemycin β_3.[6] We have also reported the use of this lactone in the synthesis of the spiroacetal moiety of avermectin B_{1b} (**4a**)[8] and its subsequent elaboration into the spiroacetal of avermectin B_{2b} (**5**).[8] We now report the use of the chiral lactone (**2**) in the enantiospecific synthesis of the dioxygenated spiroacetal of milbemycins α_7 and α_8.

The starting point for our synthesis was *cis*-pent-2-ene-1-ol (**6**) which was epoxidised using the protocol developed by Sharpless[10] to yield the epoxy alcohol (**7**) in 60% yield and in 80% enantiomeric excess (e.e.), [calculated by the preparation of the methoxy(trifluoromethyl)phenylacetyl (MTPA) ester], $[\alpha]_D$ −11.8° (*c* 1.7, CH_2Cl_2). Lithium acetylide opening of the epoxide yielded a mixture of 1,3- and 1,2-diols but the undesired latter compound could easily be removed by periodate cleavage. The required diol (**8**) was obtained in 52% yield and, conveniently, recrystallisation from diethyl ether yielded material of ≥95% e.e. (m.p. 72—74 °C).

Preparation of the primary toluene-*p*-sulphonate and protection of the secondary alcohol as its tetrahydropyran-2-yl (THP) ether proceeded smoothly in 72% overall yield. Reductive removal of the toluene-*p*-sulphonate with lithium triethylborohydride gave the required alkyne (**9**) in 80% yield, $[\alpha]_D$ +6.8 (*c* 1.5, CH_2Cl_2) (1 : 1 mixture of THP diastereoisomers); b.p. 85 °C at 20 mmHg; $\lambda_{max.}$ 2950 (≡CH), 2115 (C≡), 1133, and 1079 cm^{-1}; δ_H (360 MHz, $CDCl_3$), 4.7 (0.5H, dd, *J* 3.8 and 3.6 Hz, OCHO), 4.65 (0.5H, dd, *J* 3.1 and 4.5

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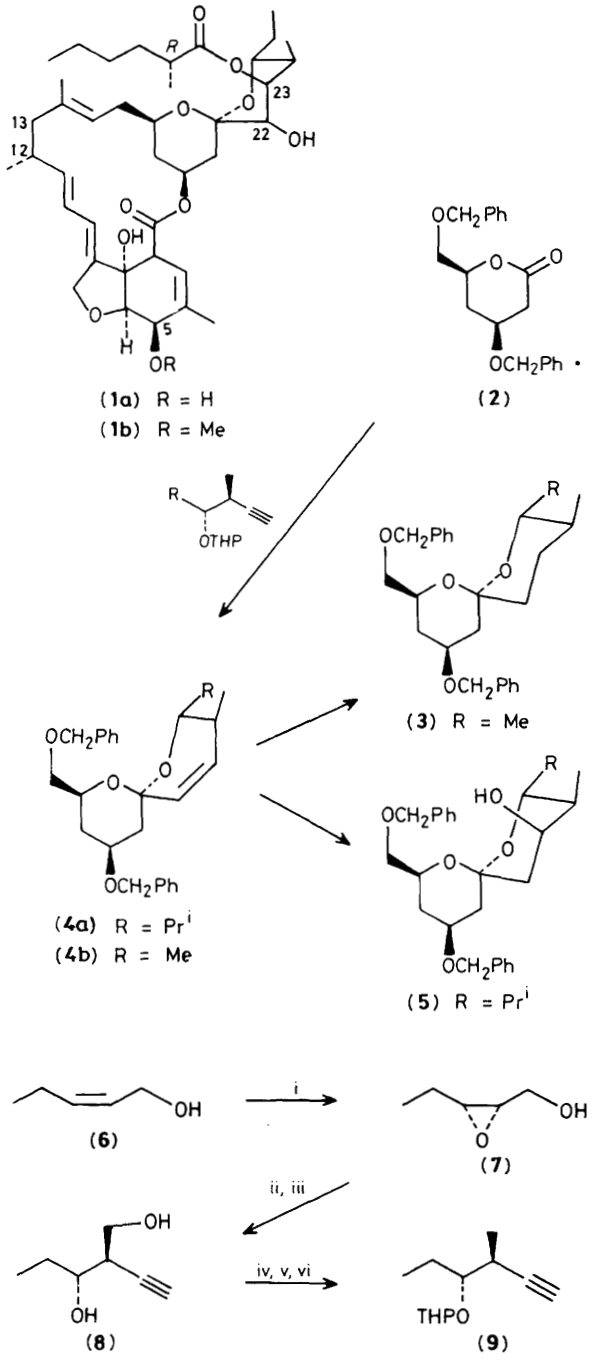
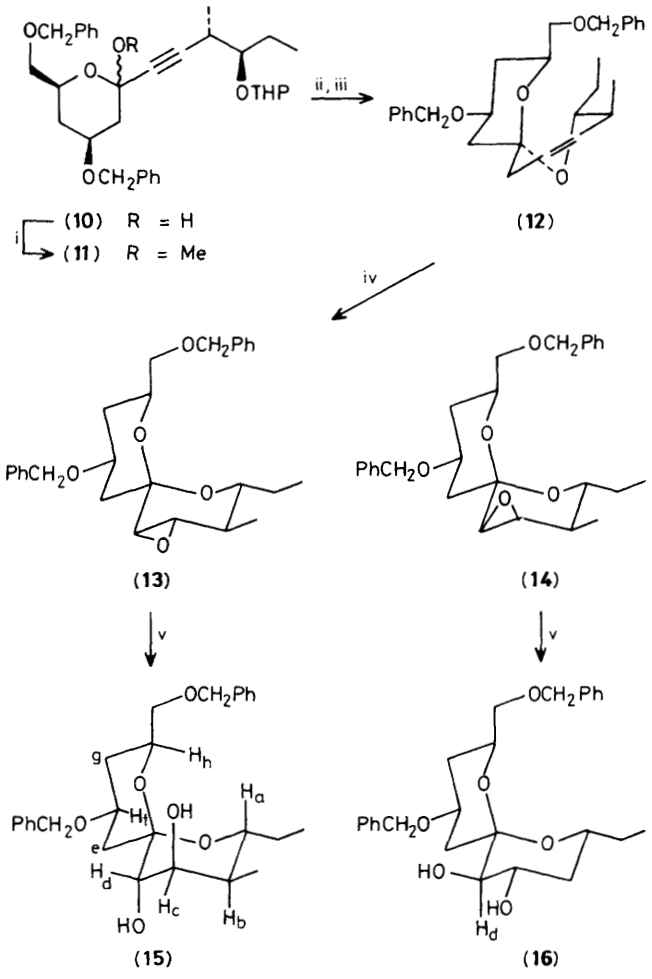
‡ The absolute configuration of the acyl group of the natural isomer is not known but we have prepared the *R*-isomer.



Reagents: i, $Ti(OPr^i)_4$, (+)-diethyl tartrate, Bu^tOOH; ii, LiC≡CH·ethylenediamine complex, dimethyl sulphoxide; iii, $NaIO_4$–H_2O; iv, *p*-$MeC_6H_4SO_2Cl$–pyridine; v, dihydropyran–Et_2O–CSA; vi, $LiEt_3BH$–THF.



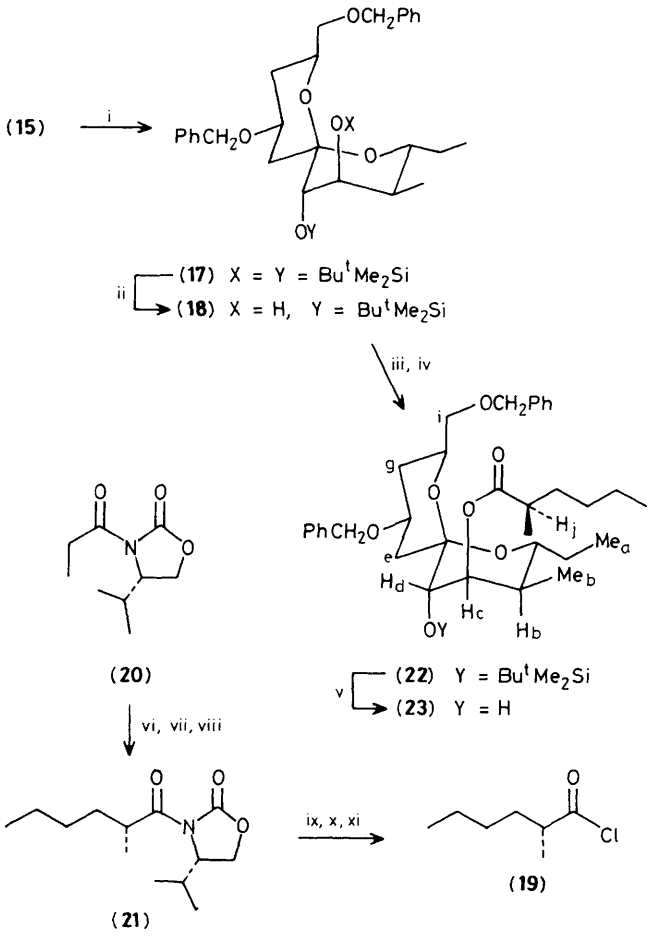
Reagents: i, MeOH–H^+; ii, Lindlar catalyst–MeOH–H_2; iii, CSA–CH_2Cl_2; iv, MCPBA; v, $HClO_4$.

Hz, OCHO), 3.92 (1H, m, –C*H*HO), 3.6—3.45 (2H, m, –CH*H*O and >CH–O), 2.9 (0.5H, m, –CHC≡), 2.73 (0.5H, m, –CHC≡), 2.06 (0.5H, d, *J* 2.6 Hz, HC≡), 2.04 (0.5H, d, *J* 2.6 Hz, HC≡), 1.9—1.4 (8H, m, 4 × CH_2), 1.22 (1.5H, d, *J* 7 Hz, >CH*Me*), 1.14 (1.5H, d, *J* 7 Hz, –CH*Me*), 0.99 (1.5H, d, *J* 7.4 Hz, CH_2*Me*), 0.93 (1.5H, d, *J* 7.4 Hz, CH_2*Me*); *m/z* M^+ − H, 195.1398, $C_{12}H_{19}O_2$ requires M^+ − H 195.1385.

Treatment of the alkyne (**9**) with Bu^nLi [1 equiv. tetrahydrofuran (THF), −78 °C] followed by reaction with the lactone (**2**) yielded the hemiacetal (**10**), which exists as a mixture of cyclised and open chain forms, in 80% yield. This was stirred in methanol in the presence of Amberlite IR-118 to yield the methoxyacetal (**11**) in a yield of 84%. Partial hydrogenation over Lindlar catalyst and subsequent acid-catalysed cyclisation yielded the unsaturated spiroacetal (**12**) in 87% yield $[\alpha]_D$ +73.4 (*c* 0.9, CH_2Cl_2) as a colourless oil.

Epoxidation with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 at room temperature yielded a mixture of two epoxides (ratio 2 : 1). These could easily be separated by flash chromatography eluting with 30% diethyl ether in light petroleum (b.p. 40—60 °C) (ΔR_f 0.1) to yield the desired β-epoxide (**13**), $[\alpha]_D$ +64.5° (*c* 0.8, CH_2Cl_2) as the major product in 60% yield, and the α-epoxide (**14**), $[\alpha]_D$ +79.8° (*c* 0.37, CH_2Cl_2). These assignments were confirmed by the subsequent conversion into the corresponding diols *vide infra*.

Base hydrolysis of the epoxides proved very difficult; however acid hydrolysis was a very rapid process giving the required diols in excellent yields (>70%). Thus the β-epoxide (**13**) yielded the desired diaxial diol (**15**) exclusively and α-epoxide (**14**) gave only the diequatorial diol (**16**). At this point the relative stereochemistry of the diaxial diol of spiroacetal (**15**), a very viscous oil, was confirmed by ^1H n.m.r. spectroscopy, $[\alpha]_D$ +73.5 (*c* 1.07, CH_2Cl_2); $\lambda_{max.}$ 3500, 1600, 1580, 1500 cm^{-1}; δ_H 7.3—7.4 (10H, m, Ar), 4.5 (4H, m, 2 × CH_2), 3.9 (1H, m, H_f), 3.85 (1H, m, H_h), 3.55 (2H, m, H_c



Reagents: i, Bu^tMe_2SiTf–2,6-lutidine; ii, MeOH–CSA; iii, Bu^nLi; iv, (**19**); v, Bu_4NF; vi, lithium di-isopropylamide; vii, $CH_3CH{=}CHCH_2I$; viii, H_2–Pd–C–MeOH; ix, $PhCH_2OLi$; x, H_2–Pd–C–MeOH; xi, $(COCl)_2$–C_6H_6, 0 °C.

and OH), 3.45 (1H, d, *J* 3 Hz, H_d), 3.3—3.5 (3H, m, H_a and $-CH_2O$), 2.6 (1H, d, OH), 2.45 (1H, dd, $H_{e,eq.}$), 2.0 (1H, dd, $H_{g,eq.}$), 1.78 (1H, m, $H_{e,ax.}$), 1.65 (1H, m, H_b), 1.1—1.3 (3H, m, $H_{g,ax.}$ and CH_2Me), 0.9—1.0 (6H, m, 2 × Me); *m/z* 456.2524, $C_{27}H_{36}O_6$ requires 456.2512. The small coupling (*J* 3 Hz) displayed by H_d confirms the diaxial disposition of the alcohols. The stereochemistry of the diequatorial diol (**16**) was also confirmed by ^1H n.m.r. spectroscopy in particular the large coupling (*J* 12 Hz) displayed by H_d. The unusual diequatorial opening is undoubtedly due to the influence of the anomeric oxygens on the adjacent carbon, hindering nucleophilic attack.

Treatment of the diol (**15**) with t-butyldimethylsilyl trifluoromethanesulphonate (Bu^tMe_2SiTf) in the presence of 2,6-lutidine gave the corresponding disilylated spiroacetal (**17**), $[\alpha]_D$ +45° (*c* 0.1, CH_2Cl_2). Removal of the benzyl protecting groups would now allow further elaboration towards a total synthesis of milbemycins α_7 and α_8. A requirement of any synthetic strategy would be that it must allow for the selective acylation of the C-23 alcohol. Consequently we turned our attention to devising methodology to achieve this transformation. Earlier work on the spiroacetal diol (**15**) had shown that preferential acylation of the C-22 alcohol took place under various acylation conditions, and that attempted selective silylation (Bu^tMe_2SiCl, imidazole, dimethylformamide) yielded a mixture of both di- and mono-silyl products. However, treatment of the disilylspiroacetal (Bu^tMe_2SiTf–lutidine) (**17**) with camphorsulphonic acid (CSA) in methanol allowed selective deprotection to the C-23 alcohol (**18**). The origin of this effect might be a consequence of a directing effect on protonation by the axial oxygen of the adjacent ring. This assignment was confirmed by i.r. and ^1H n.m.r. spectroscopy, in particular the presence of a sharp peak at 3500 cm^{-1} indicating strong intramolecular hydrogen bonding and a signal at δ 3.54 (1H, ddd, $J_{c,OH}$ 10, $J_{cb} = J_{cd}$ = 2.8 Hz).

The chiral acid chloride (**19**) was prepared *via* the enantiospecific alkylation of the acyl oxazolidone (**20**),[11] hydrogenation and cleavage of the chiral auxiliary yielded the (*R*)-carboxylic acid derivative (**21**), $[\alpha]_D$ −19.7° (lit. −15.9).[12] Overnight treatment with oxalyl chloride in benzene at 4 °C yielded the required acid chloride (**19**). Treatment of the alcohol (**18**) with Bu^nLi (1 equiv. THF, −60 °C) and addition of the acid chloride (**19**) gave the acylated spiroacetal (**22**), subsequent treatment with tetrabutylammonium fluoride gave the hydroxyacylspiroacetal (**23**), $[\alpha]_D$ +30° (*c* 0.1, CH_2Cl_2); $\lambda_{max.}$ 3500, 1730 cm^{-1}; δ_H (360 MHz), 7.4 (10H, m, Ar), 4.8 (1H, dd, $J_{cb} = J_{cd}$ = 3 Hz, H_c), 4.5 (4H, m, 2 × CH_2O), 3.9 (2H, m, H_f, H_h), 3.6 (3H, m, H_a, H_d, H_i), 3.4 (1H, H_i), 2.45 (1H, dd, $H_{e,eq.}$), 2.38 (1H, m, H_j), 2.15 (1H, m, $H_{g,eq.}$), 2.0 (1H, m, H_b), 1.1—1.7 (10H, m), 1.1 (3H, d, *J* 7 Hz, Me_j), 0.95 (3H, Me_a), 0.85 (6H, Me_b, $MeCH_2$).

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