A Synthesis of the Spiroacetal Moiety of Milbemycin β_3†

Philip Kocienski* and Stephen D. A. Street

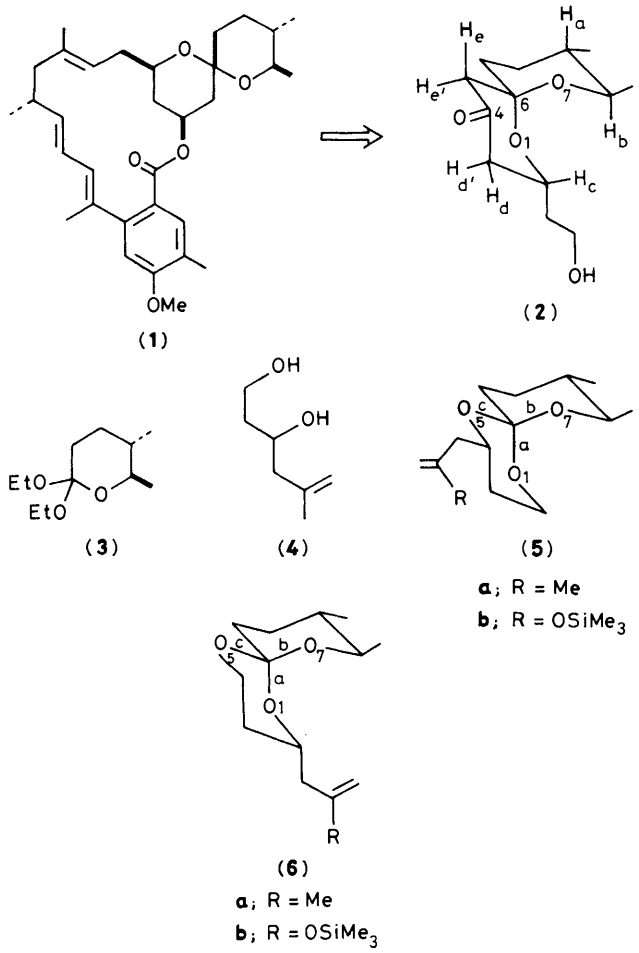
Department of Organic Chemistry, The University, Leeds LS2 9JT, U.K.

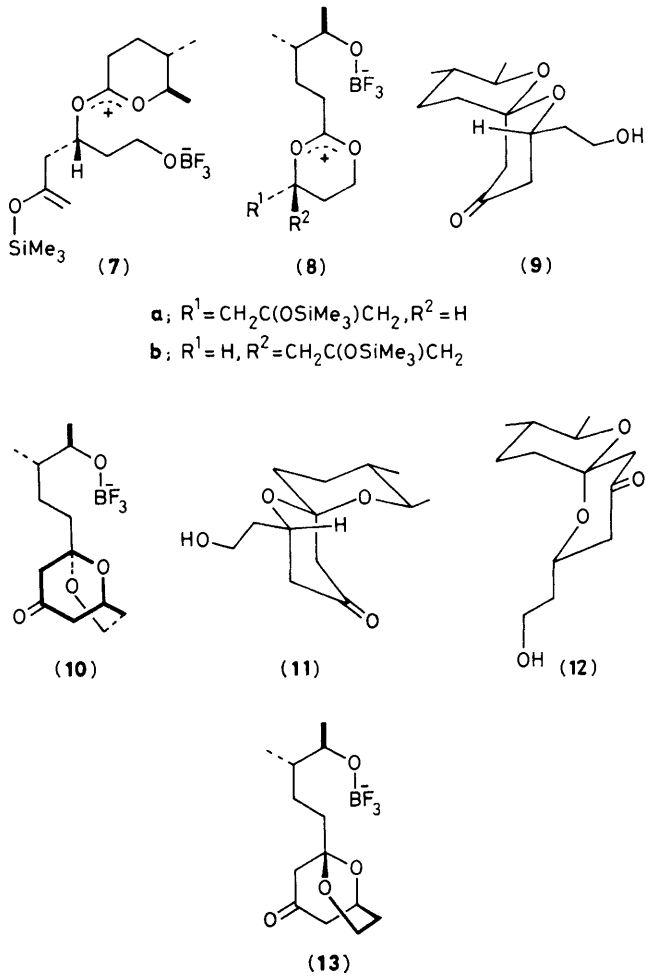
Intramolecular reaction of an enol silyl ether with a dioxonium ion generated by treatment of the 1,5,7-trioxaspiro[5.5]undecane (**5b**) with $BF_3{\cdot}Et_2O$ was the key step in a synthesis of the 1,7-dioxaspiro[5.5]undecane moiety (**2**) of Milbemycin β_3 (**1**).

We report a new synthesis of 1,7-dioxaspiro[5.5]undecan-4-ones in which the cardinal step involves intramolecular reaction of an enol silyl ether with a dioxonium ion generated by reaction of a spirocyclic ortholactone with a Lewis acid. This modification of the Mukaiyama directed aldol reaction[1] has been exemplified by a synthesis of the spiroacetal moiety (**2**) of Milbemycin β_3 (**1**).[2]

The spirocyclic ortholactone moiety was prepared by acid-catalysed exchange of ortholactone (**3**) and diol (**4**) to

† All compounds reported are racemic.





give approximately equal amounts of (**5a**) and (**6a**) in 70% yield. Isomers (**5a**) and (**6a**) were easily separated by chromatography on silica gel G (8% Et_2O in hexane) and converted into enol silyl ethers (**5b**) and (**6b**) by ozonolysis to the methyl ketones followed by trimethylsilylation (Me_3SiCl) of the lithium enolates generated with lithium di-isopropylamide in tetrahydrofuran at −78 °C. The overall yield of (**5b**) and (**6b**) from (**5a**) and (**6a**) was *ca.* 70%.

Treatment of (**5b**) with one equivalent of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C for 15 minutes gave the desired spiroacetal (**2**) in 35% yield after aqueous workup followed by chromatography on silica gel G eluting with 1:3 (v/v) EtOAc–hexane: $\nu_{max.}$ (film) 3 450 and 1 725 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.854 (3H, d, *J* 6.5 Hz, $CHCH_3$), 1.11 (3H, d, *J* 6 Hz, $OCHCH_3$), 1.24—1.32 (1H, m, $CHCH_3$), 1.42—1.65 (6H, m), 2.31 (1H, dd, $J_{d,d'}$ 14.5, $J_{d',c}$ 11 Hz, $H_{d'}$), 2.39 (1H, ddd, $J_{d,d'}$ 14.5, $J_{d,c}$ 3, $J_{d,e}$ 1.5 Hz, H_d), 2.40 (1H, br., OH), 2.40 (1H, A portion of AB system, $J_{e,e'}$ 15 Hz, $H_{e'}$), 2.43 (1H, B portion of AB system with further w-coupling, $J_{e,e'}$ 15, $J_{e,d}$ 1.5 Hz, H_e), 3.28 (1H, dq, $J_{b,a}$ 9, $J_{b,Me}$ 6.5 Hz, H_b), 3.85 (2H, t, *J* 5.75 Hz, CH_2OH), 4.105 (1H, dddd, $J_{c,d'}$ 11, $J_{c,d}$ 3, *J'* 8.5, *J''* 8.5 Hz, H_c); δ_C (22.6 MHz, $CDCl_3$) 17.9 (9-*Me*), 19.2 (8-*Me*), 27.9 (C-10), 35.1 (C-11), 35.8 (C-9), 38.0 (C-12), 46.8 (C-3 or C-5), 51.8 (C-3 or C-5), 60.5 (C-13), 68.2 (C-2), 72.3 (C-8), 99.3 (C-6), 205.4 p.p.m. (C-4) (found: M^+ 242.1517. $C_{13}H_{22}O_4$ requires *M*, 242.1518).

There are two indistinguishable pathways by which the spirocyclic ortholactone (**5b**) could have been converted into (**2**) corresponding to two modes of ortholactone cleavage. Lewis acid-catalysed scission of bond a in (**5b**) gives dioxonium ion (**7**) whereas scission of bond b gives dioxonium ion (**8a**). Both modes of cleavage should be favoured because bonds a and b both have two adjacent oxygen atoms with antiperiplanar lone pairs of electrons. Since bond c has only one adjacent oxygen atom with an antiperiplanar lone pair of electrons, its cleavage should not be favoured.[3]

The dioxonium ion (**7**) can suffer two modes of nucleophilic attack by the enol silyl ether to give the diastereoisomeric spiroacetals (**2**) and (**9**). Although none of the spiroacetal (**9**) was detected, a diastereoselective annulation cannot be inferred since (**9**), which is less stable than (**2**) by 4.8 kcal/mol[3]‡ could have equilibrated under the reaction conditions.

The conversion of dioxonium ion (**8a**) into (**2**) requires a more complex mechanism involving cyclisation of (**8a**) to give bicyclic acetal (**10**) followed by Lewis acid-catalysed acetal exchange. Support for this mechanism was derived by the conversion of spirocyclic ortholactone (**6b**) into a *ca.* 1:1 mixture of spiroacetals (**11**) and (**12**) in 30% yield under the conditions used for (**5b**) → (**2**). Again the products (**11**) and (**12**) can be explained by scission of bond b in (**6b**) to give dioxonium ion (**8b**) which then cyclised to give bicyclic acetal (**13**) before equilibrating to (**11**) and (**12**). The formation of two spiroacetals in equal amounts from a reaction under thermodynamic control was expected since (**11**) and (**12**) are equivalent in energy.[3]

‡ 1 kcal = 4.18 kJ.

The low yields of spiroacetals reflect the instability of the products to the reaction conditions; a problem which was not alleviated by the use of alternative Lewis acids such as $TiCl_4$ or $ZnBr_2$. Nonetheless, the above reactions do extend the scope of the intramolecular Mukaiyama reaction[4] which has not hitherto been used with orthoesters or ortholactones. The method is noteworthy for accomplishing the synthesis of a complex structure from simple starting materials and complements other recent approaches to spiroacetals.[5]

We thank the S.E.R.C. for financial support and Pfizer Central Research, U.K., for the Academic Award 1983—1984 (to P. K.) and a CASE studentship (to S. S.). We thank Dr. Brian Mann of the Sheffield High Field N.M.R. facility for 400 MHz ^1H n.m.r. spectra.

Received, 23rd January 1984; Com. 092

References

1 T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 817.
2 D. R. Williams, B. A. Barner, K. Nishitani, and J. G. Phillips, *J. Am. Chem. Soc.*, 1982, **104**, 4708; A. B. Smith, S. R. Schow, J. D. Bloom, A. S. Thompson, and K. N. Winzenberg, *ibid.*, p. 4015; R. Baker, R. H. O. Boyes, D. M. P. Broom, J. A. Devlin, and C. J. Swain, *J. Chem. Soc., Chem. Commun.*, 1983, 829.
3 P. Deslongchamps, D. D. Rowan, N. Pothier, T. Sauvé, and J. K. Saunders, *Can. J. Chem.*, 1981, **59**, 1105; P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry,' Pergamon, Oxford, 1983, pp. 4—53.
4 G. S. Cockerill and P. Kocienski, *J. Chem. Soc., Chem. Commun.*, 1983, 705, and references cited therein.
5 P. Kocienski and C. L. Yeates, *Tetrahedron Lett.*, 1983, **24**, 3905; I. T. Kay and E. G. Williams, *ibid.*, p. 5915; S. V. Ley and B. Lygo, *ibid.*, 1984, **25**, 113; S. L. Schreiber and T. J. Sommer, *ibid.*, 1983, **24**, 4781; M. T. Crimmins and D. M. Bankaitis, *ibid.*, p. 4551; S. J. Danishevsky and W. H. Pearson, *J. Org. Chem.*, 1983, **48**, 3865; S. Hanessian, A. Ugolini, and M. Therien, *ibid.*, p. 4427.