Synthesis of the Spiroacetal Unit Related to the Avermectins and Milbemycins

José Godoy, Steven V. Ley,* and Barry Lygo

Department of Chemistry, Imperial College, London SW7 2AY, U.K.

A route to enantiomerically pure 1,7-dioxaspiro[5.5]undecanes as important building blocks for milbemycin/avermectin synthesis is described, involving the Wittig reaction of a substituted cyclic ether with aldehydes, followed by spiroacetalisation.

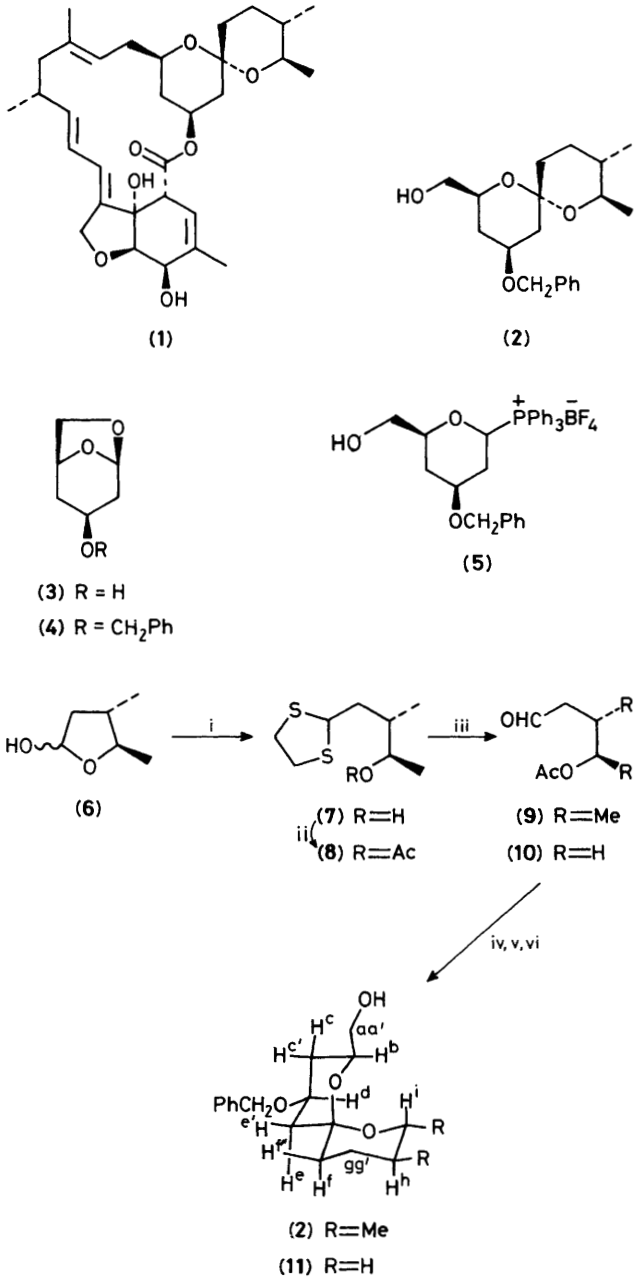
As part of a programme directed at the total synthesis of the potent antiparasitic agents, the milbemycins[1] and avermectins,[2] we have developed a new route to the inherent 1,7-dioxaspiro[5.5]undecane[3] (spiroacetal) unit the details of which are reported here.

We required a concise method which would be capable of producing material in its optically pure natural form by a process which was also amenable to larger scale production. For a projected synthesis of milbemycin α_1 (**1**) we constructed the spiroacetal (**2**) suitably protected by a benzyl group, which would allow further chemical modification of the primary hydroxy group.

Benzylation of the known alcohol[4] (**3**) using benzyl bromide and a catalytic quantity of tetra-*N*-butylammonium iodide readily affords (**4**) in 71% yield.† Treatment of the strained anhydro-derivative (**4**) with triphenylphosphonium tetrafluoroborate[5] $[Ph_3PH]^+[BF_4]^-$ at room temperature in acetonitrile solution provided a quantitative yield of the phosphonium salt (**5**). Preparation of the other partner for the proposed Wittig reaction with (**5**) was achieved from the enantiomerically pure lactol (**6**).‡

† All new compounds gave satisfactory spectral, microanalytical and/or accurate mass data.

‡ Various routes to this simple chiral lactol have been studied the full details of which will appear later.



Scheme 1. *Reagents and conditions:* i, $HSCH_2CH_2SH$ (4 equiv.), $TiCl_4$ (1 equiv.), CH_2Cl_2, −78 °C → room temp. 1 h; ii, AcCl, pyridine, 4-*N*,*N*-dimethylaminopyridine, 1 h; iii, $Tl(OCOCF_3)_3$ (2 equiv.), tetrahydrofuran (THF), 30 min; iv, (**5**)/Bu^nLi (2 equiv.), THF, −78 °C → room temp., 12 h; v, NaOMe, MeOH, room temp., 30 min; vi, 3M HCl, 30 min.

Opening of the lactol (**6**) with ethanedithiol and titanium(IV) chloride[6] afforded the 1,3-dithiolane (**7**) in 67% yield. Acetylation of (**7**) to give (**8**) was achieved in 91% yield, and removal of the dithiolane group with thallium(III) trifluoroacetate,[7] gave the desired aldehyde (**9**), (75%) (Scheme 1). After formation of the phosphorane from (**5**) using two equivalents of butyl-lithium at −78 °C, it was treated with (**9**).§ The crude product was then treated with sodium methoxide, to remove the acetate group, followed by aqueous hydrochloric acid to effect spiroacetalation giving (**2**) in 36% overall yield. This Wittig reaction using a chiral substituted cyclic ether[8] constitutes an excellent general method for the construction of spiroacetals. The structure of (**2**) is in accord with its spectral parameters;¶ {$\nu_{max.}$ (film) 3453 cm^{-1}; $[\alpha]_D^{22}$ +46.7° (*c* 2.5, $CHCl_3$); δ (400 MHz, $CDCl_3$) 7.35—7.25 (5H, m, ArH), 4.56 (2H, d, *J* 1.0 Hz, $-CH_2Ph$), 4.00 (1H, tt, *J* 4.7, 11.0 Hz, H_d), 3.75—3.68 (1H, m, H_b), 3.67 (1H, dd, *J* 3.2, 11.3 Hz, H_a), 3.59 (1H, dd, *J* 7.0, 11.3 Hz, $H_{a'}$), 3.30 (1H, dq, *J* 6.0, 9.8 Hz, H_i), 2.16 (1H, ddd, *J* 1.7, 4.7, 12.5 Hz, $H_{e'}$), 2.05 (1H, br. s, OH), 2.01 (1H, sym. m, 10 lines, *J* 1.7, 4.7, 12.1 Hz, $H_{c'}$), 1.75—1.69 (1H, m, H_f), 1.63—1.49 (3H, m, $H_{f'}$, H_g, $H_{g'}$), 1.38 (1H, dd, *J* 11.0, 12.5 Hz, H_e), 1.30 (1H, dd, *J* 11.0, 12.1 Hz, H_c), 1.27 (1H, m, H_h), 1.13 (3H, d, *J* 6.0 Hz, Me_i), and 0.85 (3H, d, *J* 6.0 Hz, Me_h)}.

We have also investigated the reaction of the phosphorane from (**5**) with the unsubstituted aldehyde (**10**) which upon similar work-up provided the spiroacetal (**11**) in 40% yield {$\nu_{max.}$ (film) 3458 cm^{-1}; $[\alpha]_D^{22}$ +57.1° (*c* 5.0, $CHCl_3$); δ (400 MHz, $CDCl_3$) 7.36—7.24 (5H, m, ArH), 5.55 (2H, s, $-CH_2Ph$), 3.95 (1H, tt, *J* 4.7, 11.0 Hz, H_d), 3.76 (1H, m, H_b), 3.70—3.53 (4H, m, H_a, $H_{a'}$, H_i, $H_{i'}$), 2.18 (1H, br. s, OH), 2.16 (1H, ddd, *J* 1.7, 4.7, 12.0 Hz, $H_{e'}$), 1.99 (1H, sym. m, 10 lines, *J* 1.7, 4.7, 12.0 Hz, $H_{c'}$), 1.85 (1H, m), 1.70 (1H, m), 1.66—1.48 (4H, m), 1.36 (1H, dd, *J* 11.0, 12.5 Hz, H_e), and 1.31 (1H, dd, *J* 11.0, 12.0 Hz, H_c)}.

We acknowledge financial support from the S.E.R.C., the Wolfson Foundation, and Pfizer Central Research, U.K. and the Royal Society for a European Science Exchange Programme Grant (to J. G.).

Received, 16th July 1984; Com. 1018

References

1 H. Mishima, M. Kurabayashi, C. Tamura, S. Sato, H. Kuwano, and A. Saito, *Tetrahedron Lett.*, 1975, 711; H. Mishima, J. Ide, S. Muramatsu, and M. Ono, *J. Antibiotics*, 1983, **36**, 980 and references therein.
2 G. Albers-Schönberg, B. H. Arison, J. C. Chabala, A. W. Douglas, P. Eskola, M. H. Fisher, A. Lusi, H. Mrozik, J. L. Smith, and R. L. Tolman, *J. Am. Chem. Soc.*, 1981, **103**, 4216.
3 For related studies in this area see S. V. Attwood, A. G. M. Barrett, and J. C. Florent, *J. Chem. Soc., Chem. Commun.*, 1981, 556; A. B. Smith, III, S. R. Schow, J. D. Bloom, A. S. Thompson, and K. N. Winzenberg, *J. Am. Chem. Soc.*, 1982, **104**, 4015; D. R. Williams, B. A. Barner, K. Nishitani, and J. G. Phillips, *ibid.*, 4708; D. R. Williams and B. A. Barner, *Tetrahedron Lett.*, 1983, **24**, 427; S. J. Danishefsky and W. H. Pearson, *J. Org. Chem.*, 1983, **48**, 3865; R. Baker, R. H. O. Boyes, D. M. P. Broom, J. A. Devlin, and C. J. Swain, *J. Chem. Soc., Chem. Commun.*, 1983, 829; S. Hanessian, A. Ugolini, and M. Therien, *J. Org. Chem.*, 1983, **48**, 4427; M. T. Crimmins and D. M. Bankaitis, *Tetrahedron Lett.*, 1983, **24**, 4551; I. T. Kay and E. G. Williams *ibid.*, 5915; P. Kocienski and S. D. A. Street, *J. Chem. Soc., Chem. Commun.*, 1984, 571.
4 A. G. Kelly and J. S. Roberts, *Carbohydr. Res.*, 1979, **77**, 231.
5 C. G. Kruse, E. K. Poels, and A. van der Gen, *J. Org. Chem.*, 1979, **44**, 2911.
6 P. C. Bulman-Page, R. A. Roberts, and L. A. Paquette, *Tetrahedron Lett.*, 1983, **24**, 3555.
7 T-L. Ho and C. M. Wong, *Can. J. Chem.*, 1972, **50**, 3740.
8 For related Wittig–Horner reactions see T. Shono, Y. Matsumura, and T. Kanazawa, *Tetrahedron Lett.*, 1983, **24**, 4577; S. V. Ley, and B. Lygo, *Tetrahedron Lett.*, 1984, **25**, 113.

§ All attempts to react the phosphorane directly with lactol (**6**) (or its anion) failed.

¶ We thank Professor R. Baker for providing a spectrum of a related derivative for comparison.