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PREPARATION OF SPIROKETALS BY REACTION OF ANIONS FROM 2-BENZENESULPHONYLTETRAHYDROPYRANS WITH EPOXIDES: SYNTHESIS OF THE C-11 TO C-25 FRAGMENT OF THE MILBEMYCINS

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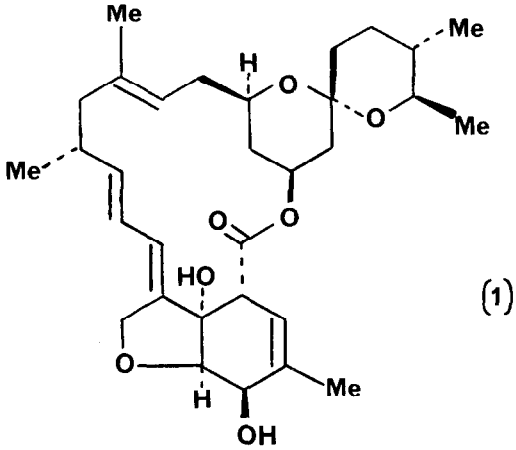
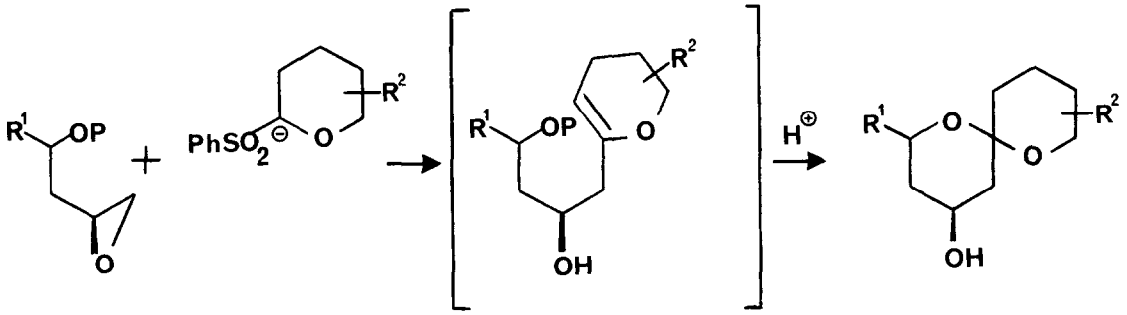
Abstract *Deprotonation of 2-benzenesulphonyltetrahydropyrans with n-butyllithium affords anions which react with substituted epoxides to give spiroketals upon acidification. Using this approach a highly convergent synthesis of the C-11 to C-25 fragment of the milbemycins was achieved.*

New methods for the preparation of the spiroketal unit are currently of great interest.[2] Undoubtedly the considerable activity in this area is due to synthetic efforts directed towards the potent antiparasitic agents the milbemycins and avermectins.[3,4] During studies on the synthesis of milbemycin α_1 (1) we have developed a new and very versatile approach to spiroketals, the details of which are reported here.



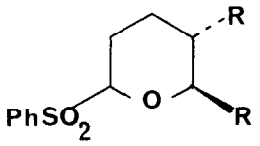
(1)

The method involves the addition of 2-benzenesulphonyltetrahydropyranyl anions[5] to epoxides which contain additional oxygen functionality to permit later spiroketal formation. (Scheme 1)



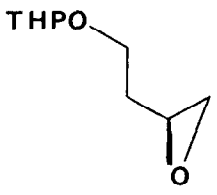
Scheme 1

In the first example the sulphone (2a) was deprotonated with n-butyllithium at -78° and reacted with the tetrahydropyranyl protected epoxy alcohol (3). Upon warming to room temperature spontaneous elimination of benzenesulphinic acid occurred to give an intermediate enol ether[6] which on treatment with camphorsulphonic acid in methanol, gave a 65% yield of the spiroketal (4). This compound is a minor component of the pheromone from the olive fly, Dacus oleae.[7]

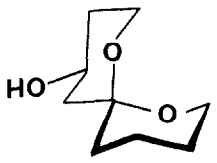


(2) a R= H

b R= Me

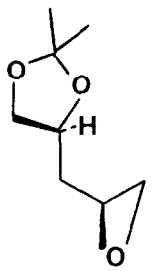


(3)

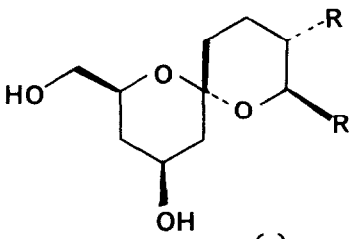


(4)

In a similar manner both the sulphones (2a) and (2b), after deprotonation, reacted with the acetal epoxide (5) $[\alpha]_D$ -15.6° (c = 1.8, $CHCl_3$) to afford the corresponding spiroketals (6a) and (6b) in 70% and 76% yield respectively.[8]



(5)



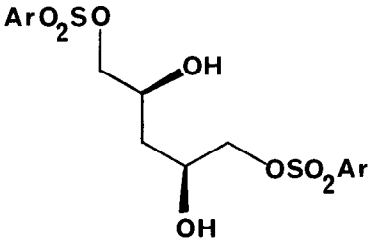
(6) a R= H

b R= Me

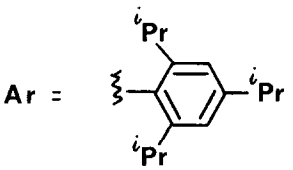
The whole process is therefore an extremely rapid and efficient entry to hydroxy substituted spiroketals. In these reactions the lithio-sulphone is behaving as an equivalent of a 2-lithiodihydropyran[9] but with the added advantage that the initial sulphones are stable, crystalline and easily handled materials.

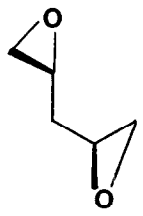
We are now in the position of using the new methodology in a highly convergent approach to the northern hemisphere of (1). Owing to the fact that the absolute configuration of the C-17 and C-19 centres are common to **all** avermectins and milbemycins we have chosen to assemble the key structural fragment for these systems by appropriate addition reactions to the symmetrical bis-epoxide (7). We[4c] and others[4e] have previously demonstrated the use of substituted vinyl metallic reagents with epoxides as the method of choice to introduce the 14,E-double bond of the milbemycins.

Preparation of (7)[10] from the known and readily available bis-sulphonate (8)[11] was achieved in 50% yield by treatment with a basic ion exchange resin (IR-400). This epoxide was then reacted at -65° with 1 equivalent of the homocuprate (9)[4c] to give the epoxy alcohol (10) (40%). Subsequent reaction of (10) with an excess of the anion from the sulphone (2b) in the presence of titanium [IV] isopropoxide and work-up with 5% sulphuric acid gave the C-11 to C-25 fragment of the milbemycins compound (11)[12] (80%). Alternatively the β-trimethylsilylethoxymethyl (SEM) derivative (12) with the anion from (2b) in the presence of borontrifluoride etherate followed by treatment with 5% hydrofluoric acid in acetonitrile also gave (11) in a comparible 72% yield.

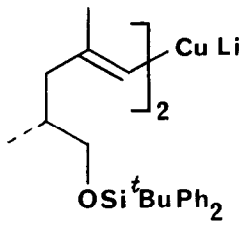


(8)

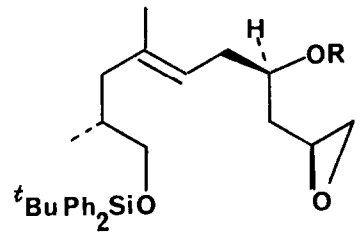




(7)

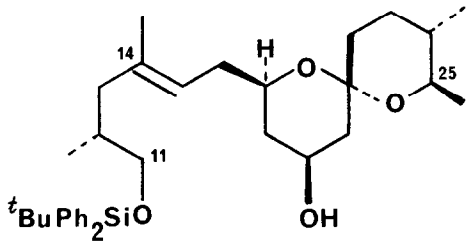


(9)



(10) R=H

(12) R=$CH_2OCH_2CH_2SiMe_3$



(11)

Conceptually the route reported above represents the most expedient and versatile preparatio to date of the northern hemisphere of the milbemycins and clearly may be readily adapted for th synthesis of the avermectins.

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REFERENCES AND FOOTNOTES

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8. R. Baker, R.H.O. Boyes, M.P. Broom, J.A. Devlin, and C.J. Swain, J. Chem. Soc., Chem. Commun., 1983, 829. Compound (6b) m.p. 152-4° $[\alpha]_D$ 14.3° (c = 0.17), $CHCl_3$) ^1H n.m.r. (250 MHz, $CDCl_3$): 0.85 (3H, d, J = 7.2 Hz, CH_3-9); 1.05 (3H, d, J = 6.6 Hz, CH_3-8); 1.30 (3H, m); 1.40-1.70 (4H, m); 1.85 (1H, dd, J = 2.0, 5.0, 12.3 Hz, H-3); 2.01 (1H, ddd, J = 2.0, 5.0, 12.3 Hz, H-5); 2.25 (2H, br.s, OH); 3.25 (1H, dq, J = 9.9, 6.6 Hz, H-8); 3.60 (3H, m); 4.15 (1H, tt, J = 5.0, 10.7 Hz, H-4).
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10. Compound (7) $[\alpha]_D$ -47° (c = 0.8, $CDCl_3$); ^1H n.m.r. (250 MHz, $CDCl_3$): 1.75 (2H, t, J = 5.6 Hz, H-3); 2.52 (2H, dd, J = 2.6, 5.0 Hz, H-1); 2.80 (2H, dd, J = 3.9, 5.0 Hz, H-1); 3.08 (2H, m, H-2) ^{13}C n.m.r. (22.51 MHz, $CDCl_3$): 35.6; 46.3; 48.9.
11. S.V. Attwood and A.G.M. Barrett, Perkin Trans. I, 1984, 1315.
12. Compound (11):- $[\alpha]_D$ 33° (c = 1.1, $CHCl_3$) ^1H n.m.r. (400 MHz, $CDCl_3$) Milbemycin numbering: 0.82 (3H, d, J = 6.5 Hz, CH_3-24); 0.89 (3H, d, J = 6.5 Hz, CH_3-12); 1.06 (9H, s, $C(CH_3)_3$); 1.10 (3H, d, J = 6.5 Hz, CH_3-25); 1.15-2.30 (17H, m); 3.26 (1H, dq, J = 10.0, 6.5 Hz, H-25); 3.44-3.54 (3H, m); 4.10 (1H, tt, J = 11.1, 5.0 Hz, H-19); 5.18 (1H, t, J = 6.9 Hz, H-15); 7.37-7.70 (10H, m, Ph).

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