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NOVEL ANTIPARASITIC AGENTS DERIVED BY MODIFICATION OF A NEW NATURAL PRODUCT SERIES

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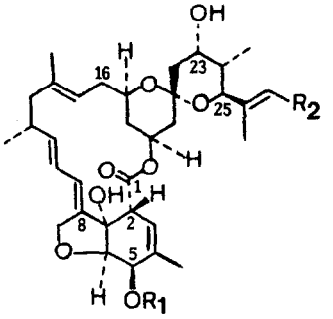
Summary: Regioselective reactions on the C5-, C7- and C23-hydroxyl groups of the macrocyclic lactones (1), (3) and (4) are described.

The recent report[1] by Cyanamid workers on the isolation and structure determination of the macrocyclic lactones LL-F28249α, λ, β and γ (1)-(4), elaborated by *S. cyanogriseus ssp noncyanogenus*, prompts us to disclose our own work in this area. We have independently obtained these compounds, which are related to the avermectins[2] and milbemycins,[3] from the fermentation broth of a different *Streptomyces* strain, *viz. S. thermoarchaensis*. The latter organism also furnished the metabolites (5) and (6). We established that the absolute configurations of (1), (3), (4) and (5) are analogous to that of milbemycin D[4] from a comparison of their circular dichroism spectra in methanol.



	R_1	R_2
(1) ...	H	Pr^i
(2) ...	Me	Pr^i
(3) ...	H	Me
(4) ...	Me	Me
(5) ...	H	Et
(6) ...	Me	Et

The C5-, C7-, and C23-hydroxy groups are ideal sites for chemical modification. The secondary C5-OH is allylic and pseudo-equatorial and should, threfore, be more easily functionalised than the axial-OH at C23. As anticipated, alkylation of (1) and (3) with excess MeI under standard conditions (Ag_2O, Et_2O, r.t., 2h, *ca.* 35%) afforded, almost exclusively, the 5-methoxy derivatives (2) and (4) respectively. Similarly reaction of (1) with Bu^tSiMe_2Cl (Im, DMF, r.t., 3h) provided the 5-silyl ether (7) (77%). Acylation of (1) with Ac_2O (1.2 eq) at ambient temperature (py, 16h) or with AcCl (1.4 eq) at 0-5°

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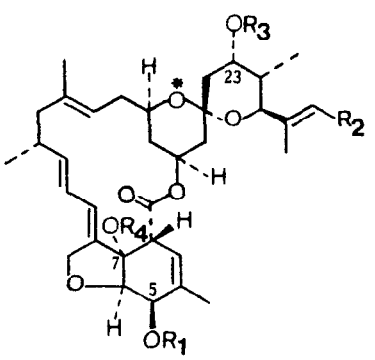
(py, 5 min) again selectively functionalised the C5-OH to provide the allylic acetate (8) (*ca.* 80%). Similarly, the 5-N-methylcarbamate (9) was the only major product isolated from the reaction of (1) with excess MeNCO (Et_3N, DMF, 80°, 7h, 36%).

More vigorous conditions were necessary to derivitize the C23-OH which not only has axial stereochemistry but is also hydrogen bonded to one of the spiroacetal oxygen atoms (*) (X-ray data on (4) and derivatives of (1) and (3) show that the distance between the C23-hydroxyl hydrogen atom and the proximal spiroacetal oxygen atom is *ca.* 2.0 Å). Thus the 23-methyl ether (10) was produced only after prolonged reaction of (8) with excess MeI, either in Et_2O (Ag_2CO_3, $AgClO_4$, r.t., 18h, 61%) or in the more polar HMPA (MeMgI, r.t., 24h, 41%). Preparation of the crystalline 5,23-diacetate (11) from compound (3) required an excess of acetic anhydride and a catalytic amount of dimethylaminopyridine (DMAP) (py, r.t., 24h, 51%). The structure and relative stereochemistry of (11) was confirmed by X-ray methods (Fig. 1). Treatment of (4) with excess $ClCH_2COCl$ and finely divided $CaCO_3$ in CH_2Cl_2 (r.t., 20h, 75%) afforded the crystalline 23-chloroacetate (12) which was readily transformed (excess KI, acetone, Δ, 3h, 80%) into the iodoacetate (13). The latter compound served as a precursor for the azidoacetate (14) (NaN_3, DMF, r.t., 16h, 52%) and the glycyl ester (15) ("880" NH_3, dioxan, r.t., 1½h, 22%). Trichloroethyl chloroformate (3 eq) reacted smoothly with (4) and (8) in CH_2Cl_2 (10 eq py, r.t., 3h) to give the corresponding carbonates (16) and (17) in >70%; reaction of these compounds with $MeNH_2$ in EtOH (2h at 0°, 1h at r.t., *ca.* 45%) then provided the urethanes (18) and (19) respectively. All attempts to introduce the methyl carbonate group at C23 by direct reaction of the 23-hydroxyl group with MeOCOCl have been unsuccessful (*vide infra*).



	R_1	R_2	R_3	R_4
(7)	$SiMe_2Bu^t$	Pr^i	H	H
(8)	Ac	Pr^i	H	H
(9)	CONHMe	Pr^i	H	H
(10)	Ac	Pr^i	Me	H
(11)	Ac	Me	Ac	H
(12)	Me	Me	$COCH_2Cl$	H
(13)	Me	Me	$COCH_2I$	H
(14)	Me	Me	$COCH_2N_3$	H
(15)	Me	Me	$COCH_2NH_2$	H
(16)	Me	Me	$CO_2CH_2CCl_3$	H
(17)	Ac	Pr^i	$CO_2CH_2CCl_3$	H
(18)	Me	Me	CONHMe	H
(19)	Ac	Pr^i	CONHMe	H
(20)	Ac	Me	Ac	$COCO_2Me$
(21)	Ac	Pr^i	H	$CH_2CO_2Bu^t$
(22)	Me	Me	H	CONHMe
(23)	H	Me	Ac	H
(24)	H	Pr^i	CONHMe	H
(25)	H	Pr^i	CO_2Me	H

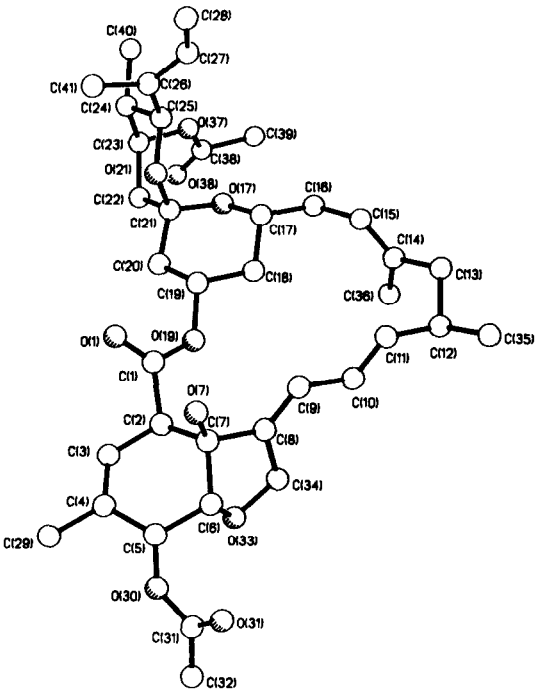


Figure 1. The molecular structure of (11). There are two crystallographically independent molecules (mol. 1 and mol. 2) which differ only slightly in the orientation of the C(23) acetate group. There are intermolecular hydrogen bonds between the two independent molecules, between the C(7) hydroxy and the C(5) ester carbonyl oxygen atom: O(7) H(7) .... O(80), 2.87 Å; H...O, 1.93 Å; O-H...O ∠159°; O(56)-H(56)...O(31), 2.75 Å; H...O, 1.95 Å; O-H...O ∠137°. N.B. O(80) in mol. 2 is equivalent to O(31) in mol. 1 and O(56) in mol. 2 is equivalent to O(7) in mol. 1.

The foregoing alkylation and acylation experiments suggest that the tertiary-OH at C7 is the most difficult hydroxyl group of the three to modify. However, acylation of the C-7 hydroxyl group can be achieved by employing highly electrophilic acid chlorides such as MeO_2CCOCl (excess pyridine, Et_2O, r.t., 16h); thus the 5,23-diacetate (11) was converted into the 7-hemi-oxalate ester (20) (57%) by this method. In contrast, when the 5-acetate (8) was alkylated in CH_3CN with the bulky electrophile $BrCH_2CO_2Bu^t$ using a sterically demanding base the tertiary hydroxyl group was functionalised preferentially: thus with KF/alumina[6] (r.t., 44h, 61%) or TlOEt (r.t., 20h, 41%) as the catalyst the 7-substituted derivative (21) was the only significant product. Moreover, when the 5-methyl ether (4) was exposed to excess MeNCO in the presence of DMAP (CH_2Cl_2, r.t., 24h) the major component (32%) of the reaction mixture, apart from recovered starting material (30%), was the crystalline 7-N-methylcarbamate (22). HPLC evidence suggested that very little, if any, of the isomeric compound (18) was formed in this reaction.

The preferential formation of the 7-t-butoxycarbonylmethyl ether (21) and the 7-N-methylcarbamate (22) is explained as follows. Moodie and Sansom[7] have studied the pyridine-catalysed reaction of MeOH with PhNCO in CCl_4, *i.e.* conditions which are similar to those used to prepare (22). Their kinetic results are consistent with a general base mechanism of catalysis which initially requires a loose association of base and alcohol followed by the generation of a transient termolecular species (Fig. 2). It is relatively easy to model such an

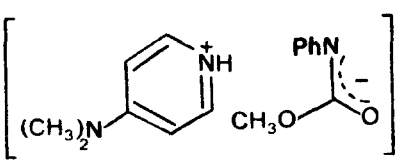


Figure 2

intermediate using the C7-OH and avoid unfavourable interactions with the substituents at C2 and C8. The hydrogen bonded spiroacetal system is a compact, fairly rigid structure. To accommodate the steric requirements of the C16-methylene group, the 25-axial hydrogen atom, and the C24-methyl group, molecular models suggest that the tertiary base must protrude directly over the lone pairs of electrons of the C23-hydroxyl group, blocking the approach of an incoming isocyanate molecule and preventing the formation of the termolecular transition state. It seems likely that a similar situation arises in the regioselective formation of compound (21).

Hydrolysis of (11) with NaOH (1eq) in MeOH-H_2O (9:1) at 0-5° selectively removed the C5-acetate to give the compound (23) in 60% yield; the urethane (24) was similarly prepared from the ester (19). When the trichloroethyl carbonate (17) was subjected to these conditions, concomitant replacement of the trichloroethoxy group by methoxide ion occurred and the 23-methylcarbonate (25) was obtained (64%) yield.

Acknowledgements

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5. Crystal data for (11): $C_{38}H_{52}O_{10}$, M = 668.8, triclinic, a = 11.580 (1), b = 14.368(3), c = 14.622(2)Å, space group α = 79.91 (1), β = 66.72 (1), γ = 66.71 (1)°, U = 2052 Å^3 $P\bar{1}$, Z = 2 (2 crystallographically independent molecules), D_c = 1.08 gcm^{-3}, μ(Cu-Kα) = 6 cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and refined anisotropically to give R = 0.063, R_w = 0.063 for 5281 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $\theta > 58°$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.
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