Synthesis of 20-Dihydro-20-deoxy Derivatives of 16-Membered Macrolide Antibiotics

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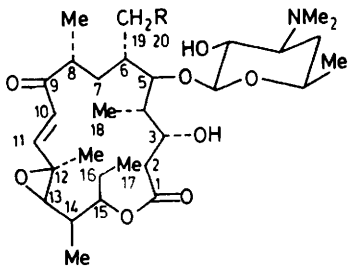
The use of bis(triphenylphosphine)copper(I) tetrahydroborate for selective reduction of aldehyde tosylhydrazones in the presence of other reducible and sensitive functions, as present in macrolide antibiotics, is described.

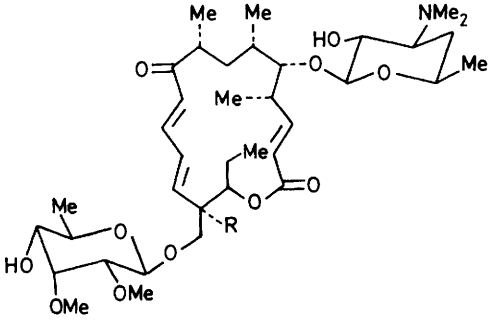
In recent publications[1-3] we have disclosed the structures of rosaramicin (**1**) and mycinamicins (**4**) and (**5**) and pointed out that rosaramicin (**1**)[4] possessed the broader spectrum of activity of the two antibiotics and mycinamicins (**4**) and (**5**) showed the more desirable absorption and pharmacokinetic properties. We have also described the mutasynthesis of a hybrid structure (**7**)[5] which possessed potent microbiological activity but did not show the desired absorption characteristics of mycinamicins. In this communication we describe the method of preparation and microbiological activity of a group of 20-dihydro-20-deoxy 16-membered macrolide antibiotics.

As in our previous work, tylosin (**8**)[6] and desmycosin (**9**)[7] have served as important starting materials for the preparation of the above mentioned class of compounds. The preparation of (**10**) and (**11**) from tylosin (**8**) and desmycosin (**9**) involves selective reduction of the aldehyde functions to the methyl group. Amongst the reagents considered, the use of bis(triphenylphosphine)copper(I) tetrahydroborate (**6**)[8] appeared to be most promising. It has been claimed[9] that tosylhydrazones of ketones and aldehydes are reduced with the reagent (**6**) to the corresponding alkanes in moderate yields under mild conditions. The reduction of the tosylhydrazones of α,β-unsaturated ketones with (**6**) proceeded in very poor yields.

To determine whether the above reaction sequence could be



(1) R = CHO
(2) R = Me
(3) R = CH=NNHSO$_2$C$_6$H$_4$Me-*p*



(4) R = H, Desepoxy-AR 5 no. 1 (Mycinamicin IV)
(5) R = OH, Desepoxy-AR 5 no. 2 (Mycinamicin V)

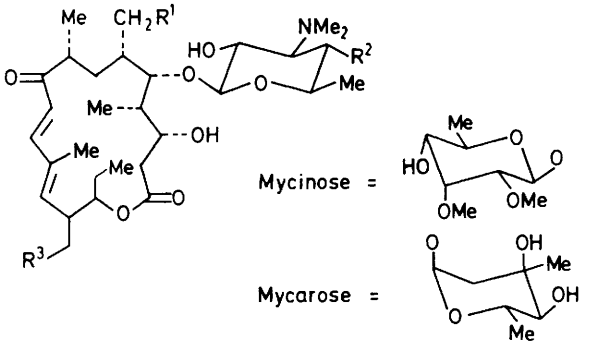
$(Ph_3P)_2CuBH_4$
(6)

applied successfully in a macrolide antibiotic possessing an epoxide, an α,β-unsaturated carbonyl group, a lactone function, and an aldehyde we have investigated the preparation of (**2**) from rosaramicin (**1**). Thus, reduction of rosaramicin tosylhydrazone (**3**)† {$C_{38}H_{59}N_3SO_{10}$, $[\alpha]_D^{26}$ −24.2° ($CHCl_3$)} with the reagent (**6**) in refluxing chloroform solution yielded (32%) (**2**) {$C_{31}H_{53}NO_8$, M^+ 567; $[\alpha]_D^{26}$ −21.7° (EtOH); u.v. λ_{max} 238 nm (ε 14 400)}. Compound (**2**) was found to be identical in all respects with an authentic sample of 20-dihydro-20-deoxy rosaramicin obtained from natural sources. We have demonstrated in an earlier publiction[10] that (**2**) is a biosynthetic precursor to rosaramicin (**1**).

Similarly, desepoxyrosaramicin (**12**) [prepared by chromium(II) chloride reduction[11] of rosaramicin], on treatment with tosylhydrazine yielded (85%) the hydrazone (**13**) {$C_{38}H_{59}N_3SO_9$, $[\alpha]_D^{26}$ −35.6° ($CHCl_3$)}. Reduction of (**13**) with the reagent (**6**) yielded (**14**) (35%) {$C_{31}H_{53}NO_7$, M^+ 551; $[\alpha]_D^{26}$ −3.9° ($CHCl_3$); u.v. λ_{max} 283 nm (ε 20 100)}.

Encouraged by the fact that the reduction of the tosylhydrazones of rosaramicin and desepoxyrosaramicin proceeded well we investigated the preparation of (**10**) and (**11**) from the corresponding tosylhydrazones (**15**) and (**16**). Tylosin (**8**) on treatment with tosylhydrazine yielded the hydrazone (**15**) (45%) {$C_{53}H_{85}N_3SO_{18}$, $[\alpha]_D^{26}$ −63.9° ($CHCl_3$)}. Refluxing

† In a typical experiment the tosylhydrazones were prepared as follows. An ethanolic solution (10 ml) of rosaramicin (2 mmol) and tosylhydrazine (2 mmol) was stirred for 24 h at room temperature and then the solvent was removed *in vacuo*. The crude reaction product was chromatographed on an alumina column (200 g; type IV Woelm superbasic) and the desired product eluted with 1% methanol in chloroform solution. The yield of the amorphous rosaramicin tosylhydrazone was 82%. Satisfactory analytical data were obtained for all new compounds reported. All u.v. data were measured in methanol solution.



(7) R^1 = CHO, R^2 = H, R^3 = Mycinose
(8) R^1 = CHO, R^2 = Mycarose, R^3 = Mycinose
(9) R^1 = CHO, R^2 = OH, R^3 = Mycinose
(10) R^1 = Me, R^2 = Mycarose, R^3 = Mycinose
(11) R^1 = Me, R^2 = OH, R^3 = Mycinose
(12) R^1 = CHO, R^2 = R^3 = H
(13) R^1 = CH=NNHSO$_2$C$_6$H$_4$Me-*p*, R^2 = R^3 = H
(14) R^1 = Me, R^2 = R^3 = H
(15) R^1 = CH=NNHSO$_2$C$_6$H$_4$Me-*p*, R^2 = Mycarose, R^3 = Mycinose
(16) R^1 = CH=NNHSO$_2$C$_6$H$_4$Me-*p*, R^2 = OH, R^3 = Mycinose

(**15**) in chloroform solution with (**6**) yielded (56%; after chromatographic purification) 20-dihydro-20-deoxytylosin (**10**) {$C_{46}H_{79}NO_{16}$, M^+ 901; $[\alpha]_D^{26}$ −45.2° ($CHCl_3$), u.v. λ_{max} 282 nm (ε 21 600)}. The ^{1}H n.m.r. spectrum of (**10**) showed the absence of an aldehyde function and the presence of the 20-methyl group (t, δ 0.82, *J* 7 Hz). The ^{13}C n.m.r. spectrum showed only two carbonyl carbons at δ 174.5 (C-1), and 203.9 (C-9), and 20-Me at 12.5 p.p.m. Similarly, desmycosin (**9**) was converted (56%) in two steps *via* (**16**) {$C_{46}H_{73}N_3SO_{15}$; $[\alpha]_D^{26}$ −35.1° ($CHCl_3$)} into (**11**) {$C_{39}H_{67}NO_{13}$, M^+ 757; $[\alpha]_D^{26}$ −10.0° ($CHCl_3$); u.v. λ_{max} 283 nm (ε 19 600); δ 174.6 (C-1) and 204 p.p.m. (C-9)}. The ^{1}H n.m.r. spectrum of (**16**) showed the presence of the 20-methyl group at δ 0.87 (t, *J* 7 Hz). Compound (**11**) was also obtained quantitatively by the acidic hydrolysis of (**10**).

In microbiological assay[12] the geometric mean of minimum inhibitory concentrations against sensitive Gram positive strains were 1.5 for (**2**), 0.65 for (**10**), 0.16 for (**11**), and 2.7 for (**14**). All the above geometric mean values refer to μcg ml^{-1}.

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